Reactions of Umpolung Reagents with Enol Ethers of β-Diketones: Sterically Induced Selectivity of the Dithiane Anion[1]

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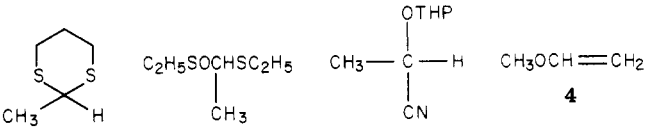
In work on the synthesis of a tricyclic analogue of daunomycinone, the reactions of several umpolung equivalents of acetaldehyde with enol ether esters of 3,5-dioxocyclohexanecarboxylic acid have been examined. The dithiane reagent **1** and the sulfoxide **2** give 1,2 attack on the carbonyl group of the vinylogous ester system and also react at a similar rate with ester groups. The latter reaction can be retarded by using esters formed with isobutyl rather than methyl alcohol. In order to get selective attack on the carbonyl of the vinylogous ester in preference to that of the ester, it is best to use reverse addition at low temperature.

Although reactions involving the reversal of carbonyl reactivity (e.g., the benzoin condensation) have been known for a long time, it is only recently that systematic studies have been made on the development of nucleophilic acylating, or "umpolung", reagents.[2] The main umpolung equivalents of acetaldehyde are the anions derived from the dithiane **1**,[3,4] the sulfoxide **2**,[5,6] the protected cyanohydrin **3**,[7] the vinyl ether **4**,[8] and acetylene.

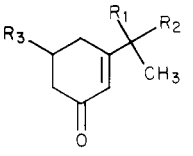
For work on the synthesis of **10**, a tricyclic analogue of daunomycinone,[9] we needed the diketo acid **5a** (with the ketone in the acetyl group in a protected form) to serve as a precursor for ring A. Compound **5a** could be approached through the addition of an acetyl equivalent to an enol ether ester of 3,5-dioxocyclohexanecarboxylic acid (**6a**). Both 1,2- and 1,4-addition to the carbonyl at C_3 will give, after acidification, the same unsaturated ketone related to **5a**. We now report a study of the addition of the umpolung reagents **1**–**4** to derivatives of **6a** and describe how steric factors can produce a selective reaction at an enol ether of a β-diketone, rather than at a hindered ester group.

We were not able to reproduce the yield obtained by Birch and his co-workers[10a] for the conversion of 3,4,5-trimethoxybenzoic acid (**7**) into **6a**. However, modification (described in the Experimental Section) of their procedure gave a yield of more than 90% of **6a**. The methyl and isobutyl enol ether esters **6b** and **6c** were prepared in excellent yields by the standard method of refluxing a solution of the acid **6a** with the appropriate alcohol in benzene with *p*-toluenesulfonic acid in a Dean–Stark apparatus.[10bc]

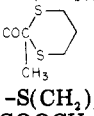
Sulfoxide Reagent 2. As the sulfoxide reagent **2**, which was developed by Tsuchihashi[5] and Schlessinger,[6] adds 1,4 to unsaturated ketones,[11a] it was of interest to examine the reaction of **2** with **6b**.



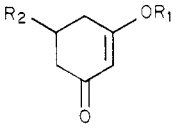
1 **2** **3** **4**



5a, R_1R_2 = =O; R_3 = COOH
b, R_1R_2 = =O; R_3 = $COOCH_3$
c, R_1R_2 = =O; R_3 = $COOCH_2CH(CH_3)_2$
d, R_1R_2 = $-S(CH_2)_3S-$; R_3 = H
e, R_1R_2 = $-S(CH_2)_5S-$; R_3 = COOiBu
f, R_1R_2 = $-S(CH_2)_3S-$; R_3 =



g, R_1R_2 = $-S(CH_2)_3S-$; R_3 = $COOCH_3$
h, R_1R_2 = $-S(CH_2)_3S-$; R_3 = COOH
i, R_1 = OTHP; R_2 = CN; R_3 = $COOCH_3$



6a, R_1 = H; R_2 = COOH
b, R_1 = CH_3; R_2 = $COOCH_3$
c, R_1 = $CH_2CH(CH_3)_2$; R_2 = $COOCH_2CH(CH_3)_2$
d, R_1 = $CH_2CH(CH_3)_2$; R_2 = H
e, R_1 = H; R_2 = $COOCH_2CH(CH_3)_2$
f, R_1 = $Si(CH_3)_3$; R_2 = $COOSi(CH_3)_3$

Addition of **6b** to a solution of the anion of **2** gave, after chromatography on silica gel, the diketo ester **5b** in 10% yield. In another experiment, crystallization of the crude reaction product (without chromatography) yielded the 1,2-adduct **8a** which, after treatment with perchloric acid in ether,[6] gave **5b**. These results show that the addition of the anion **2** to the enol ether of a β-diketone is 1,2 rather than 1,4 and that the initial adduct **8a** is converted to **5b** during chromatography on silica gel. Hydrolysis of a thioketal monosulfoxide on silica gel has not been observed before (compare ref 2, 6, and 11) but provides another mild way of generating the carbonyl compound. The poor yield of **5b** from the reaction of **6b** and **2** was apparently due

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(3) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975); E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075, 1077 (1965).
(4) E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968).
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(9) D. M. S. Wheeler, *Cancer Chemother. Rep. Part I*, **59**, 158 (1973).
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(11) (a) J. L. Herrmann, J. E. Richmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973); (b) J. L. Herrmann, J. E. Richman, P. J. Wepplo, and R. H. Schlessinger, *ibid.*, 4707 (1973).

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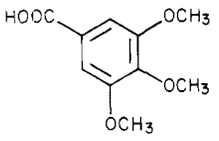

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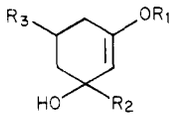
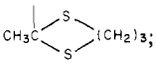
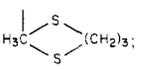


8a, $R_1 = CH_3$; $R_2 = -C(CH_3)(SC_2H_5)SOC_2H_5$; $R_3 = COOCH_3$

b, $R_1 = -CH_2CH(CH_3)_2$; R_2 =  ; $R_3 = COO\text{-}i\text{-}Bu$

c, $R_1 = CH_2CH(CH_3)_2$; R_2 =  ; $R_3 = H$

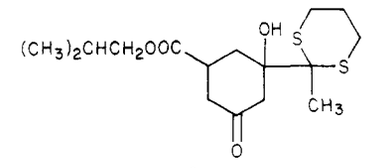
to reaction of the anion with the ester group[11b] as well as the enol ether. This is not surprising: as the enol ether of a β-diketone is the vinylogue of an ester, the reactivities of the two systems should be comparable. We decided to differentiate between the two groups by forming the isobutyl enol ether ester **6c**; as the addition of **2** to the carbonyl of the vinylogous ester is 1,2, it should not be as subject to steric hindrance by the isobutyl group as in its addition to the ester. In fact addition of the anion from **2** to the isobutyl compound **6c** gave a 38% yield of the keto ester **5c** after chromatography on silica gel. The ease with which the oxide of the thioketal is converted to the ketone during chromatography on silica gel is a disadvantage for further synthetic efforts, and so work with this reagent was abandoned.

Thioacetal Reagent 1. The dithiane reagent, **1**, was developed by Corey and Seebach,[3] who found that it reacts with esters. Later Corey and Crouse[4] found that **1** adds 1,2 to unsaturated ketones, and with the isobutyl enol ether **6d** gave the unsaturated ketone **5d** even when the reaction was worked up under nonacidic conditions.

We tried the reaction of **1** with the isobutyl ester **6c** using two different ways of combining the reactants. In the direct addition of **6c** to the anion from **1**, the diadduct **5f** (easily detectable in the crude reaction mixture by the appearance of a singlet at δ 1.72 as well as at δ 1.59 in the NMR) was formed to a large extent, especially when the reaction was done at −20 °C rather than −78 °C. By contrast, with reverse addition, when the anion of **1** is added to **6c** at −78 °C, the NMR spectrum of the crude product showed little of the diadduct; workup of the reaction mixture gave a 40% yield of the unsaturated ester **5e** and 7% of the diadduct **5f**. The remaining compounds obtained by chromatography from the reaction were the starting material **6c**, the β-diketo ester **6e**, the acid **5h**, and the reagent **1**. In our original work both reactants were dissolved in tetrahydrofuran; in later work we used toluene as the solvent for **6c** and found that the use of a less polar medium did increase slightly the selectivity of the reaction; the ratio of the combined yield of the ester **5e** and the related acid **5h** to the yield of **5f** was about 7.8:1.

The selectivity shown in this reaction is not merely the result of the reverse addition: addition of the dithiane **1** to the methyl ester enol ether **6b** gave 18% of the mono adduct **5g** and 10% of the diadduct **5f**; this confirms the importance of the larger ester group in **6c** in helping the selectivity of the reaction. Reaction of **1** with the trimethylsilyl enol ether ester **6f** yielded the unsaturated acid **5h** in 31% yield and the diadduct **5f** in 18% yield. Apart from the disappointing selectivity of this reaction, the yield of the enol ester **6f** from **6a** was poor.

Our results show that a combination of reverse addition and increasing the size of the alkyl group used to form the ester both contribute to the selectivity of the reaction. After our preliminary communication[1] Heathcock and co-workers[12] reported a similar selectivity of a dithiane reaction with a system containing a *tert*-butyl enol ether ester; their product was **11**.



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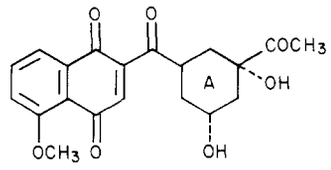

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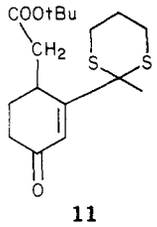

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When the reaction from **1** and **6c** was worked up under acidic conditions (even with very dilute acid), the NMR spectrum of the crude product did not show any evidence of the presence of the 1,2-adduct **8b** or the β-hydroxy ketone **9**. This is not surprising: Stiles and Langroy[13] showed that hydroxy enol ethers are converted with very dilute acid to the corresponding α,β-unsaturated ketone by a mechanism that does not involve a β-hydroxy ketone as an intermediate. Workup of the dithiane reaction under nonacidic conditions gave a crude product which, on the basis of its NMR, probably contains **8b** (new peak at δ 5.75) as well as **5e**, **5f**, and **6c**. Corey and Crouse[4] did not observe the 1,2-adduct **8c** in the reaction **1** and **6d**.

The structure of the monoadduct **5e** was confirmed by its spectral properties and its reactions. The monoketone **5e** with silver nitrate and *N*-chlorosuccinimide in acetonitrile[4] was converted smoothly to the diketone **5c**. This result contrasts with Heathcock's experience with a similar compound **11** in which the dithiane group was not convertible to a ketone.[12] Hydrolysis of **5e** gave the acid **5h** (also obtained from **1** and **6f**; vide supra); this hydrolysis is best done in methanolic sodium hydroxide and tetrahydrofuran at room temperature for 6 h; in the absence of tetrahydrofuran, starting material was recovered.[14] The keto acid **5h** is a promising precursor for ring A of **10**, a tricyclic analogue of daunomycinone.[16]

Other Reactions. Other methods[16] of adding the acyl group were not satisfactory. The anion from **4**[8] reacted with **6b** to give a small yield of **5b**. The reaction of the Stork reagent, **3**,[7] with **6b** gave after an acidic workup a product which on the basis of its spectral data was **5i**, but attempts to convert the cyanohydrin group to a carbonyl group led to aromatic products and the reaction was abandoned.[17]

(12) P. D. Wege, R. D. Clark, and C. H. Heathcock, *J. Org. Chem.*, **41**, 3144 (1976).

(13) M. Stiles and A. C. Langroy, *Tetrahedron Lett.*, 337 (1961).

(14) Our observation of the effect of tetrahydrofuran came in the course of unsuccessful experiments on the epoxidation of **5e**, when we attempted to use Grieco's result[15] that addition of tetrahydrofuran to the reaction accelerated epoxidations with *tert*-butyl hydroperoxide.

(15) P. A. Grieco, M. Nishizawa, S. D. Barbe, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).

(16) P. S. Tobin, Ph.D. Thesis, University of Nebraska, 1976.

Experimental Section

Melting points are uncorrected and were determined with the Mel-Temp instrument. Infrared spectra were recorded on Perkin-Elmer Models 137 and 237 spectrometers; ultraviolet spectra were recorded on a Cary Model 14 spectrometer; ^1H and ^{13}C NMR spectra were recorded on a Varian A-60D spectrometer and a Varian XL-100-15 spectrometer, respectively. Mass spectra were obtained from Hitachi RMU-6D and AEI MS 50 mass spectrometers. Tetrahydrofuran was dried by refluxing over calcium hydride, followed by distillation from lithium aluminum hydride.

3,5-Dioxocyclohexanecarboxylic Acid (6a). 3,5-Dioxocyclohexanecarboxylic acid (**6a**) was prepared according to the method of Birch, Hextall, and Sternhell,[10a] but with Li as the reducing metal in ammonia, *tert*-butyl alcohol, and tetrahydrofuran. Lithium wire (24.8 g, 3.14 mol) was added with good stirring over 15 min to a solution of 3,4,5-trimethoxybenzoic acid (150 g, 0.708 mol) in *tert*-butyl alcohol (1 L), tetahydrofuran (450 mL), and ammonia (4–5 L). The resulting blue solution was stirred for another 30 min. The reaction was quenched by adding ammonium chloride (375 g) over a period of 15 min and the excess ammonia was removed under reduced pressure (water aspirator) overnight. The reaction mixture was acidified with stirring to pH 1 with 6 N HCl, the *tert*-butyl alcohol removed, and the aqueous layer extracted twice with *tert*-butyl alcohol (1 L). The combined *tert*-butyl alcohol solutions were washed with saturated brine, dried ($MgSO_4$), and evaporated under reduced pressure to yield **6a** (100 g) which crystallized from ethyl acetate (90% yield): mp 178–180 °C (lit.[10a] 180 °C); NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.50–3.22 (m, 5 H, saturated H), 5.41 (br s, 1 H, vinyl H).

3-Methoxy-5-(carbomethoxy)-2-cyclohexen-1-one (6b). A mixture of **6a** (12 g, 0.0770 mol), methanol (50 mL), benzene (300 mL), and *p*-toluenesulfonic acid monohydrate (0.25 g) was refluxed in a Dean–Stark apparatus for 48 h (removing the benzene/water azeotrope approximately every 12 h), allowed to cool, and then washed with aqueous sodium bicarbonate (1 M) and aqueous sodium chloride. Concentration of the benzene layer yielded crystals which recrystallized from ethyl acetate/petroleum ether to give 3-methoxy-5-(carbomethoxy)-2-cyclohexen-1-one (**6b**) (10.8 g, 76%): mp 78–80 °C; IR (Nujol mull) ν_{max} 1640, 1720 cm^{-1}; ^1H NMR (CCl_4) δ 2.30–2.75 (m, 5 H), 3.68 and 3.72 (s, 3 H, OCH_3 and $COOCH_3$), 5.30 (s, 1 H, vinyl H); mass spectrum, *m/e* (relative intensity) 184.0739 (10, M^+), 153.0552 (14, $M^+ - OCH_3$), 125.0600 (100, $M^+ - COOCH_3$); *m/e* calcd for $C_9H_{12}O_4$, 184.0741; $C_8H_9O_3$, 153.0552; $C_7H_9O_2$, 125.0597.

3-Isobutoxy-5-(carboisobutoxy)-2-cyclohexen-1-one (6c). **6c** was made in the same way as **6b** from **6a** (40 g, 0.256 mol), isobutyl alcohol (300 mL), benzene (500 mL), and *p*-toluenesulfonic acid monohydrate (2 g). The crude product was obtained as an oil which was distilled. The fraction containing the 3-isobutoxy-5-(carboisobutoxy)-2-cyclohexen-1-one (**6c**) was collected at 136–8 °C (0.2 mm) (63 g, 92%): IR (neat) ν_{max} 1655, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 and 1.00 (d, J = 6 Hz, 12 H, CH_3), 1.59–2.29 (m, 2 H, $CH(CH_3)_2$), 2.29–3.23 (m, 5 H), 3.63 and 3.87 (d, J = 6 Hz, 4 H, OCH_2), 5.25 (s, 1 H, vinyl H); ^{13}C NMR ($CDCl_3$) δ 18.2 (4-CH_3), 26.3 (2-CH_2CH), 30.3, 37.7, 37.9 (ring CH_2, CH), 71.0 and 74.0 (-OCH_2), 101.6 (C=C—C=O), 171.5 (C=C—C=O), 174.5 (COO-*i*-Bu), 195.1 (ketone C). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.16, H, 8.96. Found: C, 66.64; H, 9.03.

Reaction of 3-Methoxy-5-(carbomethoxy)-2-cyclohexen-1-one (6b) and the Monosulfoxide of Acetaldehyde Diethyl Thioacetal (2). (a) A solution of *n*-BuLi (1.25 mL, 2.4 M, 0.00300 mol) in hexane was added to a solution of the monosulfoxide of acetaldehyde diethyl thioacetal (0.501 g, 0.00301 mol) in dry tetrahydrofuran (50 mL) at 0 °C and the solution was stirred for 15 min and cooled to −20 °C. A solution of 3-methoxy-5-(carbomethoxy)-2-cyclohexen-1-one (**6b**, 0.589 g, 0.00311 mol) in dry THF (5 mL) was then added dropwise. The color of the solution became yellow-green within 1 min and red-orange within 5 min. After 1 h at −20 °C the reaction mixture was added to saturated aqueous sodium chloride (30 mL). The water/THF mixture was extracted three times with ether; the combined ethereal extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated to yield an oil (0.759 g) which was chromatographed on silica gel. Elution with 25% ethyl acetate/carbon tetrachloride gave 0.060 g (9.8%) of 3-acetyl-5-(carbomethoxy)-2-cyclohexen-1-one (**5b**): mp 63.5 °C; IR (neat, crude oil) ν_{max} 1690, 1730 cm^{-1}; NMR ($CDCl_3$) δ 2.44 (s, 3 H, $C(O)CH_3$), 2.52–3.27 (m, 5 H), 3.73 (s, 3 H, $COOCH_3$), 6.60 (t, J = 1 Hz, 1 H, vinyl H); mass spectrum, *m/e* (relative intensity) 196.0736 (24, M^+), 165.0554 (7, $M^+ - OCH_3$), 153.0546 (10, $M^+ - COCH_3$), 137.0603 (100, $M^+ - COOCH_3$); *m/e* calcd for $C_{10}H_{12}O_4$, 196.0736; $C_9H_9O_3$, 165.0557; $C_8H_9O_3$, 153.0540; $C_8H_9O_2$, 137.0603.

(b) In a subsequent experiment, starting with 0.550 g of **6b** the same procedure was followed except that, after removal of the ether, the crude product was crystallized from ethyl acetate/petroleum ether to give **8a** (0.0491 g, 5.0%): mp 98–100 °C; IR (KBr) ν_{max} 1670, 1740, 3220 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.07–1.62 (m, 9 H, CH_2CH_3 and CCH_3), 1.90–3.42 (m, 9 H), 3.57 and 3.72 (s, 6 H, OCH_3), 4.27 (s, 1 H, OH, exchangeable with D_2O), 5.17 (m, 1 H, vinyl H).

A solution of the 1,2-adduct (**8a**, 0.0491 g) in 10 mL of ether and one drop of 70% perchloric acid (added at 0 °C) was stirred at 0 °C for 20 min and 20 mL of water was added. The aqueous layer was extracted three times with ether, and the combined ethereal solutions were washed with aqueous sodium chloride, dried ($MgSO_4$), and evaporated to yield 0.0466 g of an oil which possessed a proton NMR spectrum containing the same peaks as those for 3-acetyl-5-(carbomethoxy)-2-cyclohexen-1-one (**5b** see (a)) in addition to some peaks arising from the sulfoxide.

Reaction of 6b and 2-Methyl-1,3-dithiane (1). *n*-Butyllithium in hexane (11.9 mL, 1.6 M, 0.019 mol) was slowly added to a solution of the dithiane (**1**, 2.54 g, 0.019 mol) in dry tetrahydrofuran (40 mL) under N_2 at −40 °C. The solution was kept at a temperature of −20 °C for 70 min and then added at −78 °C over 1 h to a stirred solution of **6b** (3.50 g, 0.019 mol) in dry tetrahydrofuran (30 mL) at −78 °C. The mixture was stirred for an additional 10 min, diluted with water (50 mL), acidified to pH 1 with hydrochloric acid, and then extracted with ether (3 × 300 mL). The combined ethereal layers were washed with saturated sodium chloride, dried (magnesium sulfate), and evaporated in vacuo to give a yellow oil. The oil was chromatographed on a silica gel column. Elution with benzene/ethyl acetate (19:1) gave the disubstituted product **5f** (0.7 g, 9.8%): NMR ($CDCl_3$) δ 1.62 and 1.77 (s, 3 H, $SCCH_3$), 1.80–2.42 (m, 4 H, SCH_2CH_2), 2.48–3.30 (m, 13 H), 6.67 (s, 1 H, vinyl proton). Further elution resulted in the monosubstituted product **5g** (18%): NMR ($CDCl_3$) δ 1.61 (s, 3 H, $SCCH_3$), 1.68–2.38 (m, 2 H, SCH_2CH_2), 2.42–3.34 (m, 9 H), 3.74 (s, 3 H, OCH_3), 6.64 (s, 1 H, vinyl H).

Reaction of 6c and 2-Methyl-1,3-dithiane (1). A solution of 2-lithio-2-methyl-1,3-dithiane (**1**) (0.0367 mol, prepared according to the method of Corey and Crouse[4]) in 60 mL of dry tetrahydrofuran at −40 °C was added over 1 h to a well-stirred solution of **6c** (9.82 g, 0.0366 mol) in dry THF (15 mL) at −78 °C under nitrogen. The reaction mixture was added to saturated aqueous sodium chloride and extracted three times with ether. The combined ethereal extracts were washed thoroughly with water, dried ($MgSO_4$), and evaporated to yield a yellow oil (10.4 g). A solution of this oil in methanol (75 mL) and HCl (1 mL, 1 N) was stirred for 10 min at room temperature. Extraction three times with ether, drying ($MgSO_4$), and evaporation of the ether yielded a yellow oil, which was chromatographed on silica gel. Elution with 5% ethyl acetate/95% benzene gave **6c** (1.25 g, 12.7%), **1** (0.35 g, 7.2%), and a mixture of **5e** and **5f** which were separated by Kugelrohr distillation to give **5e** (4.23 g, 35%): bp 175–190 °C (0.2 mm); IR ($CHCl_3$) ν_{max} 1675, 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (d, J = 6.5 Hz, 6 H, $CH(CH_3)_2$), 1.63 (s, 3 H, $SCCH_3$), 1.68–2.30 (m, 3 H, SCH_2CH_2 and $CH(CH_3)_2$), 2.52–3.28 (m, 9 H), 3.92 (br d, 2 H, OCH_2), 6.64 (m, 1 H, vinyl H); mass spectrum, *m/e* (relative intensity) 328 (M^+, 18), 133 (12), 115 (21), 98 (100), 91 (12), 78 (43).

Crystallization from ethyl acetate/petroleum ether of the residue (0.89 g crude **5f**) from this distillation gave the diadduct (**5f**, 0.44 g, 3.1%), mp 143–146 C° Further recrystallization raised the melting point to 147.5–149 °C; IR ($CHCl_3$) ν_{max} 1660, 1695

(17) Unsuccessful experiments[16] included the following: reaction of nitroethane with **6b**, photochemical addition of acetaldehyde and acetaldehyde ethylene ketal to **6b** (cf. ref 18), addition of acetylide to **6b**, and the Wittig reaction with **6b** (cf. ref 12).

(18) B. Fraser-Reid, D. R. Hicks, D. L. Walker, D. E. Iley, M. B. Yunkers, S. Yik-Kai Tam, and R. C Anderson, *Tetrahedron Lett.*, 297 (1975).

cm^{-1}; NMR ($CDCl_3$) δ 1.59 and 1.72 (s, 6 H, CH_3), 1.80–2.28 (m, 4 H, SCH_2CH_2), 2.38–3.25 (m, 13 H), 6.62 (m, 1 H, vinyl H). Anal. Calcd for $C_{17}H_{24}O_2S_4$: C, 52.58; H, 6.19. Found: C, 52.64; H, 6.35.

When 30 g of crude reaction mixture was chromatographed on silica gel, **5e** (12.37 g), **5h** (1.88 g), and **5f** (2.24 g) were obtained. The remaining material consisted of the starting ester **6c**, the β-diketo ester **6e**, and the dithiane **1**. In this work the separation of **5e** and **5f** was effected through the insolubility of **5f** in ethanol and ether.

3-Acetyl-5-(carboisobutoxy)-2-cyclohexen-1-one (5c). (a) A solution of **5e** (0.297 g, 0.000905 mol) in acetonitrile (3 mL) was added dropwise over 1 min to a solution of *N*-chlorosuccinimide (0.483 g, 0.00362 mol) and silver nitrate (0.691 g, 0.00407 mol) in acetonitrile (5 mL) and water (2 mL) at 0 °C under nitrogen. The mixture was stirred for 25 min at 0 °C and allowed to warm to room temperature over 30 min. The grayish solid was filtered off and the filtrate was diluted with aqueous sodium chloride and then extracted with chloroform. The chloroform extract was washed with aqueous ammonium acetate, water, and aqueous sodium chloride and dried (Na_2CO_3). It was concentrated to yield a light yellow oil which was chromatographed on silica gel. Elution with 5% ethyl acetate/95% benzene yielded an oil (0.215 g, 50%) which crystallized from methanol/petroleum ether to give **5c**: mp 52–52.5 °C; IR (KBr) ν_{max} 1675, 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, 6 H, $CHCH_3$), 1.77–2.19 (m, 1 H, CH_3CH), 2.43 (s, 3 H, O=CCH_3), 2.57–3.03 (m, 5 H), 3.91 (d, J = 7 Hz, 2 H, OCH_2), 6.64 (t, J = 1 Hz, 1 H, vinyl H); mass spectrum, m/e (relative intensity) 238 (M^+, 2), 165 (19), 137 (88), 110 (19), 105 (32), 95 (33), 77 (11), 67 (20), 57 (31), 56 (17), 43 (100). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56. Found: C, 65.56; H. 7.67.

(b) *n*-Butyllithium (1.2 mL, 1.6 M, 0.00192 mol) was added to a solution of the sulfoxide (**2**, 309 mg, 0.00186 mol) in dry tetrahydrofuran (10 mL) under N_2 at −20 °C. The solution was kept at −20 to −10 °C for 1 h, and after cooling to −78 °C was added over a period of 1 h to a stirred solution of 1-isobutoxy-5-(carboisobutoxy)-1-cyclohexen-3-one (**6c**, 494 mg, 0.00184 mol) at −78 °C. The mixture was then poured into water (50 mL) which was extracted three times with ether. The combined ethereal layers (200 mL) were washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated overnight under N_2 to give a yellow oil (684 mg). The oil was chromatographed on a silica gel column (40 g of silica gel); elution with benzene/ethyl acetate (9:1) gave 1-acetyl-5-(carboisobutoxy)-1-cyclohexen-3-one (**5c**, 167 mg, 38%) as a yellow oil, identity established by spectral comparison with material from (a). Further elution with benzene/ethyl acetate (9:1) resulted in the recovery of **6c** (71 mg). Elution with chloroform resulted in the recovery of **2** (77 mg).

3-(Trimethylsiloxy)-5-(carbotrimethylsiloxy)-2-cyclohexen-1-one (6f). Trimethylchlorosilane (20.9 g, 0.1926 mol) was added over 1 min by syringe to **6a** (5 g, 0.0321 mol) and triethylamine (100 mL, dried over molecular sieves) under nitrogen. The mixture was stirred for 3 h and filtered by gravity in a nitrogen atmosphere. Distillation of the filtrate under water aspirator vacuum (connected to the distillation apparatus through a $CaSO_4$ drying tube) removed excess triethylamine. The silyl product **6f** (1.32 g, 14%) had bp 125–8 °C (0.2 mm); NMR ($CDCl_3$) δ 0.30 and 0.32 (s, 18 H, CH_3), 2.39–2.76 (m, 5 H, saturated cyclohexane H), 5.39 (m, 1 H, vinyl H).

2-Methyl-2-(5-carboxy-3-oxo-1-cyclohexen-1-yl)-1,3-dithiacyclohexane (5h). (a) Aqueous sodium hydroxide (50 mL, 0.2 M) was added over 15 min to a mixture of **5e** (2.6777 g), methanol (30 mL), and tetrahydrofuran (100 mL). The reaction mixture was stirred under nitrogen at room temperature for 6 h; ether was added and the organic layer was separated and extracted twice with 1 M sodium hydroxide. The combined alkaline extracts were washed twice with ether, acidified to pH 1 with 6 M HCl, and extracted five times with ether. The combined ethereal extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated to yield an oil which crystallized from ethyl acetate/petroleum ether to give **5h** (2.45 g, 70%): mp 165–7 °C; IR (KBr) 1645, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3 H, CH_3), 1.71–2.25 (m, 2 H, SCH_2CH_2), 2.50–3.15 (m, 9 H), 6.62 (br m, 1 H, vinyl H), 10.5 (1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 24.1, 28.0 (2, br), 29.0, 38.7, 40.0, 53.2 (CH_3 and saturated ring C except SCS), 95.8 (SCS), 128.3 (C=**C**—C=O), 162.4 (**C**=C—O), 178.0 (O—C=O), 190.3 (C=C—**C**=O); mass spectrum, m/e (relative intensity) 272 (M^+, 100), 230 (12), 200 (10), 198 (12), 166 (11), 153 (21), 133 (17), 125 (18), 106 (11), 91 (11), 74 (30). Anal. Calcd for $C_{12}H_{16}O_3S_2$: C, 52.94; H, 5.88. Found: C, 52.79; H, 6.00.

(b) A solution of the anion of **1** (0.00303 mol) [from **1** (406 mg) and *n*-BuLi (1.6 M) in hexane (2.0 mL)] in dry tetrahydrofuran (10 mL) under nitrogen at −78 °C was added over 1 h to 3-(trimethylsiloxy)-5-(carbotrimethylsiloxy)-2-cyclohexen-1-one (**6f**, 909 mg, 0.00303 mol) in dry tetrahydrofuran (15 mL) at −78 °C. The reaction mixture was then added to a mixture of methanol (25 mL), water (20 mL), and HCl (2 M, 2 mL) and stirred for 15 min at room temperature. After the addition of sodium hydroxide (6 M, 5 mL) and aqueous sodium chloride (50 mL), the basic reaction mixture was washed with ether. The aqueous layer was then acidified and extracted three times with ether. The combined ethereal extracts were washed with aqueous sodium chloride, dried ($MgSO_4$), and evaporated to yield an oil which crystallized from ethyl acetate/petroleum ether to yield **5h** (253 mg, 31%), mp 157–162 °C.

The disubstituted compound (**5f**, 216 mg, 18%, mp 137–142 °C, crystallized from ethyl acetate/petroleum ether) was obtained from the original ethereal extract of the basic solution. The identity of both compounds was confirmed by spectral comparison with samples previously obtained.

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Registry No. **1**, 6007-26-7; **1**, lithium salt, 27969-97-7; **2**, 72796-28-2; **5b**, 72796-29-3; **5c**, 60891-24-9; **5e**, 60891-21-6; **5f**, 60891-22-7; **5h**, 60891-23-8; **6a**, 56066-20-7; **6b**, 60891-25-0; **6c**, 60891-20-5; **6f**, 72796-30-6; **8a**, 72796-31-7; 3,4,5-trimethoxybenzoic acid, 118-41-2.