Allylic alcohol **5** underwent Simmons–Smith cyclopropanation[6] in 80% yield to the cyclopropylcarbinol **6** (contaminated with 15% of the biscyclopropyl compound). The stereochemistry of the cyclopropanation can be assigned on the basis of the well-established directing influence on such reactions by allylic alcohol substituents.[7] The stereochemistry of alcohol **5**, in turn, depends upon the analogous directing effect on epoxidation by the secondary allylic alcohol grouping[8] of the precursor to epoxide **3**. The stereochemistry of this allylic alcohol grouping is based on the known preference for metal hydride reductions of enones such as **2** to give equatorial alcohols.[9]

Ozonolysis of the allyl substituted tricyclic **6** followed by workup with silver oxide afforded acid **7** which readily and stereospecifically rearranged upon treatment with aqueous perchloric acid to the hydroazulene lactone **8** (80% overall yield).[10] Conversion to the butenolide **9** was achieved by subsequent treatment with diphenyl diselenide and lithium diisopropylamide followed by hydrogen peroxide.[11] Catalytic hydrogenation (Pd/C, ethyl acetate) then gave the crystalline *cis*-lactone **10** in 70% yield. Earlier synthetic studies have shown that hydrogenations involving positions 1, 7, and 10 of the pseudoguaiane ring system are strongly directed by the proximate C-5 quaternary methyl grouping.[12]

Introduction of the α-methylene moiety by the Minato–Horibe sequence[13] involving formylation, reduction, tosylation, and elimination, although successful for damsin-type pseudoguaianolides,[12] could not be effectively accomplished with the regioisomeric lactone **10**. Therefore an alternative method was examined.[14] To that end, the crystalline carbomethoxy derivative **11** obtained from lactone **10** with dimethyl carbonate–potassium hydride was converted to the enolate and reduced with lithium aluminum hydride to yield the diol **12**. Oxidation with manganese dioxide afforded the desired α-methylene-γ-butyrolactone **13**. Cleavage of the *tert*-butyl ether with trifluoroacetic acid led to the trifluoroacetate **14** which was saponified in isopropyl alcohol to minimize addition to the conjugated double bond by solvent-derived alkoxide.[15] Oxidation of the resulting alcohol **15** by the modified Collin's procedure[16] yielded (±)-confertin (**16**) whose spectral properties were identical with those of the natural product.[1,17]

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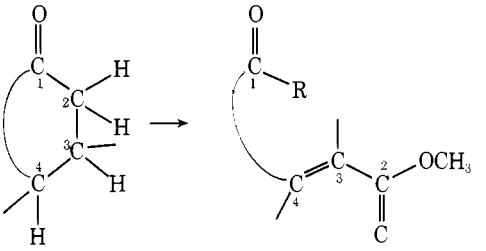
New Synthetic Reactions. Oxidative Seco Rearrangement

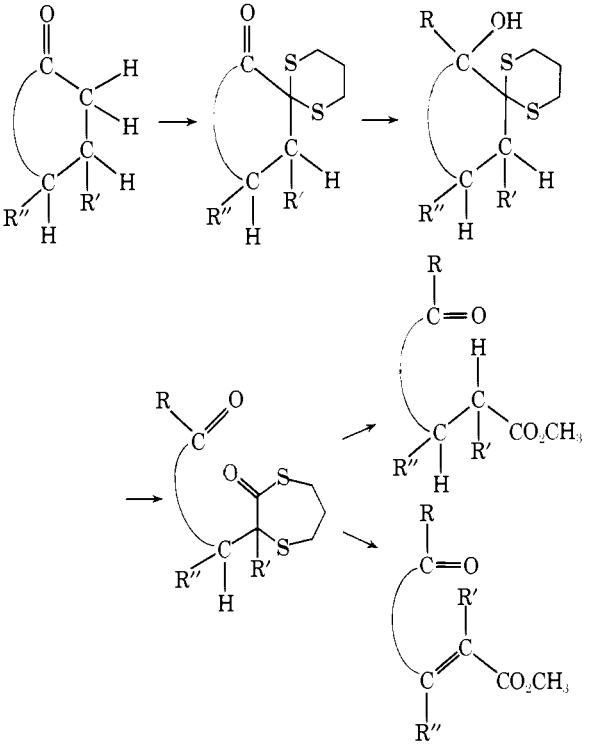
Sir:

We wish to report a new type of ring cleavage method that allows selective functionalization of C-1, -2, -3, and -4 of a cycloalkanone as illustrated in eq 1. The key step involves an intriguing oxidative cleavage that is accompanied by rearrangement of a 2,2-dithiocycloalkan-1-ol. The cleavage of functionalized rings serves as a major approach in the design of the total synthesis of many natural products.[1] Marshall developed an elegant approach to ring fission based upon the hydroxide induced cleavage of α,α-trimethylenedithiocycloalkanones;[2] however, the method is restricted to use of "naked" hydroxide and to ketone cleavages (i.e., the hydroxyl derivatives do not cleave). We developed an alternative approach based upon 1-hydroxy-2-phenylthiocycloalkanes;[3] however, this method is restricted to rings possessing some strain energy such as those of four or five members. The approach reported herein, as summarized in eq 2, further overcomes the limitations of these two methods and is applied to the synthesis of the queen's substance that is found in several species of insects.

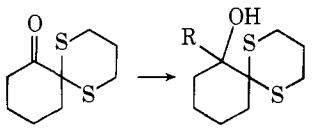


(1)

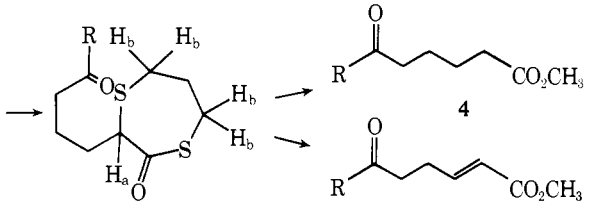
The carbonyl group of dithiane **1**[2a] can be reduced ($NaBH_4$, ethanol, room temperature) or undergo addition of an organometallic (CH_3Li, ether–THF, 0°) to produce the hydroxy dithianes **2**.[4] Subjection of **2** to 2.6 equiv of lead tetraacetate (PhH, 50–55°, 15 h) leads to the ring cleaved and rearranged products **3**[4] in excellent yields (**3a**, mp 61°, 80%; **3b**, mp 62°, 95%). The structures of **3** were indicated by their elemental compositions, spectral properties, and further conversions. In addition to the aldehyde (1728 cm^{-1}) and ketone (1718 cm^{-1}) carbonyl groups of **3a** and **b**, respectively, a thioester carbonyl



(2)



1 2



3 4 5

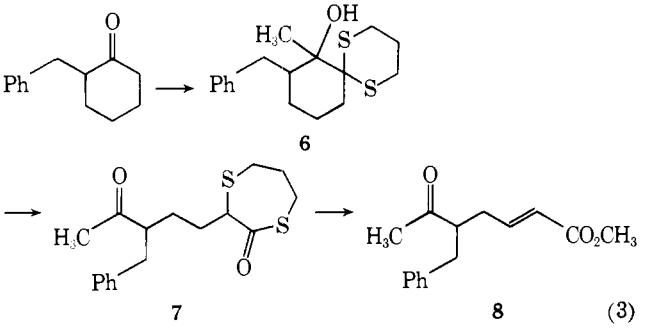
a, R = H
b, R = CH_3

absorption appeared at 1669 ± 3 cm^{-1}.[5] The NMR spectra showed a distorted triplet at δ 3.68 ± 0.05 for H_a, a ddd (J = 16, 11, 2 Hz) at δ 3.24 ± 0.02 for one of H_b, and a multiplet at approximately δ 3 for the remaining $3H_b$. In addition the appropriate aldehyde (δ 9.76, t, J = 2 Hz, 1 H, and 2.48, distorted t, 2 H) and ketone absorptions (δ 2.14, S, 3 H, and 2.49, distorted t, 2 H) were present. The 1,4-dithiacycloheptan-2-one ring system is characterized by loss of $CO(M^+ - CO)$ and by formation of ions of m/e 119 (dithanyl) and 106

in the mass spectrometer.

These α-thio-thioesters are potentially very versatile synthetic intermediates. In this way, C-1, -2, and -3 of the original cycloalkanone have been differentially functionalized. If simple cleavage to the keto ester is desired, methanolysis (1.0 equiv of iodine, methanol, reflux, 3 h) followed by addition of Raney nickel (reflux, 5 h) produces the keto ester **4** in 68% yield. More exciting is the employment of this selectively sulfenylated carbonyl system[6] for further specific strucutral modification. For example, transesterification as above followed by oxidation (2.0 equiv of $NaIO_4$, methanol, room temperature) and pyrolysis of the resultant sulfoxide[6a,7] ($PhCH_3$, reflux, 4 h) without isolation of any intermediates gives the trans enoates **5**[4] (**a**, ir 1720 and 1662 cm^{-1}; NMR δ 9.74 (1 H), 6.80 (dt, J = 14, 7 Hz, 1 H), 5.74 (d, J = 15 Hz, 1 H); **b**, ir 1716 and 1659 cm^{-1}; NMR δ 6.74 (dt, J = 15, 7 Hz, 1 H), 5.66 (d, J = 15 Hz, 1 H)) in 51–55% overall yield. The compatibility of the aldehyde function through this series of transformations demonstrates the mildness of this approach.

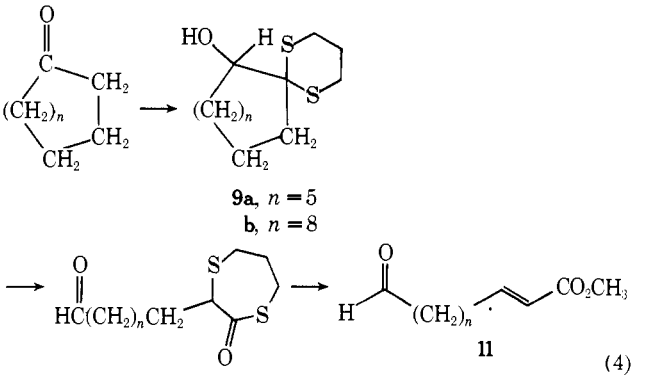
This method allows regiospecific ring cleavage of an unsymmetrical ketone as has been illustrated in the case of 2-benzylcyclohexanone (eq 3). Formation of the requisite sub-



6 7 8 (3)

strate **6** (mp 130–131°)[4] from 2-benzylcyclohexanone in the normal way proceeded in 69% isolated yield. Cleavage with lead tetraacetate at 55–60° for 19 h gave an 80% yield of oxidative seco-rearranged product **7**.[4] As before transesterification and pyrolysis produced the keto enoate **8**[4] (ir 1725 and 1619 cm^{-1}; NMR δ 6.79 (dt, J = 16, 7 Hz, 1 H), 5.77 (d, J = 16 Hz, 1 H), 3.65 (s, 3 H), 1.92 (s, 3 H)).

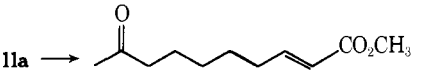
This approach applies equally well to larger ring ketones. Cyclononanone and cyclododecanone have been converted to the hydroxy dithianes **9a**[4] and **b** (mp 104–105°)[4,8] and cleaved in 66 and 65% yields, respectively, to **10a**[4] and **b** (mp 115–116°)[4] under the standard ring cleavage conditions which in turn were converted to the enoates **11a** and **b**.[4] The aldehydo



9a, n = 5
b, n = 8

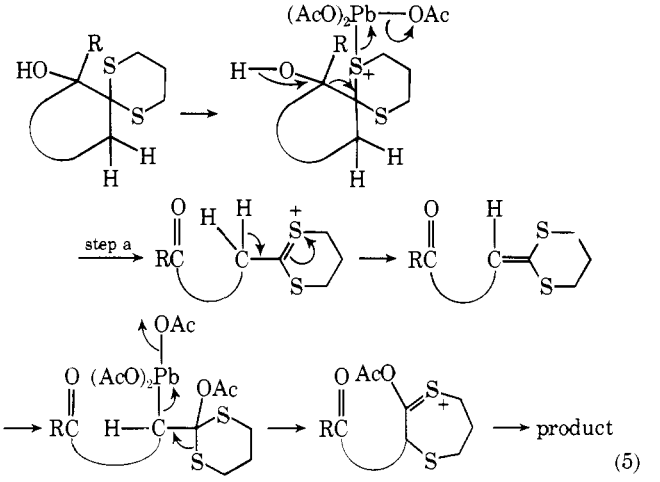
10 11 (4)

ester **11a** was converted to the methyl ester of the queen's substance[9] by chemospecific addition of methylmagnesium chloride (ether, −40°, 3 h) to the aldehyde and Jones oxidation (0°, 15 min) to give **12** (53% overall yield) which was identical with an authentic sample.[9a]



11a → **12**

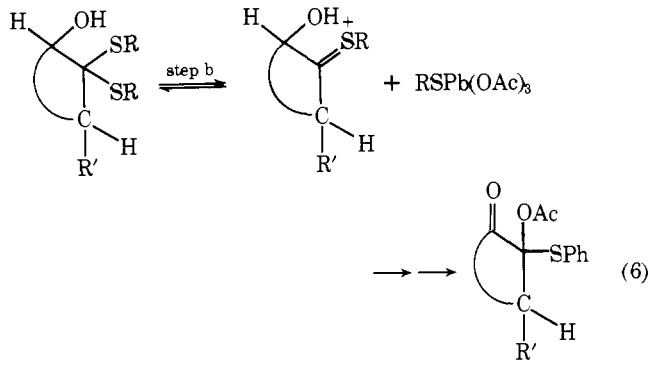
The pathway for this fascinating ring cleavage process which is accompanied by rearrangement[10] (thus the term oxidative seco-rearrangement) can only be speculative at this time (see eq 5). It is pertinent to point out that 2,2-bis(methylthio)- or



(5)

2,2-bis(phenylthio)cyclohexan-1-ol is oxidized to 2-acetoxy-2-methyl(or phenyl)thiocyclohexanone and no ring cleavage is observed. This implies that the ring cleavage (step a) is probably slow relative to sulfur serving as a leaving group. To make step b of eq 6 reversible under the reaction conditions, it is necessary to ensure an intramolecularity for recapture of the carbonium ion by the sulfur nucleophile—thus the requirement for the dithiane unit.

With this method and the previously reported ones, sulfenylated carbonyl systems and their carbonyl-modified derivatives of all ring sizes can now be selectively cleaved. More pertinent, the approach reported herein has several unique features. (1) It maintains a differentiation between the two carbonyl groups in the product. (2) It allows the carbonyl group



to serve its normal useful role as a key group for structural elaboration by addition of nucleophiles. (3) It selectively sulfenylates (oxidizes) C(3) of the original cycloalkanone. Sulfenylated carbonyl systems have proved to be versatile directing groups for structural elaboration.[3,6a,11] (4) It selectively dehydrogenates C(3)-C(4) of the original ketone. Thus, this method allows selective oxidation at C(1) and C(2), or C(1), C(2), and C(3), or C(1), C(2), C(3), and C(4). The structural flexibility provided by this new ring cleavage reaction should prove useful in synthetic elaborations.

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for their generous support of our programs.

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(8) (a) Addition of methyllithium to the dithianes derived from cyclononanone and cyclododecanone led to recovered starting material—presumably because of enolization. (b) In the cyclononanone case, reduction of the keto dithiane with diisobutylaluminum hydride ($PhCH_3$, −78°, 90% yield) was preferred.
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Acid–Base Catalysis and Autocatalysis of a Dehydrochlorination

Sir:

Interest in the concertedness of base-catalyzed elimination reactions continues to be very strong.[1] The dependence of rate on pH and base concentration in buffer solutions is an essential criterion for multistep mechanisms, though more thorough comparison of compounds and standardization of the properties of the non-aqueous buffers are needed than our single published example furnishes.[2] Investigating the elimination of HCl from β-chloro-β-phenylpropiophenone in methanol at 25°, we found the reaction to be catalyzed not only by base, as expected, but also by acid.

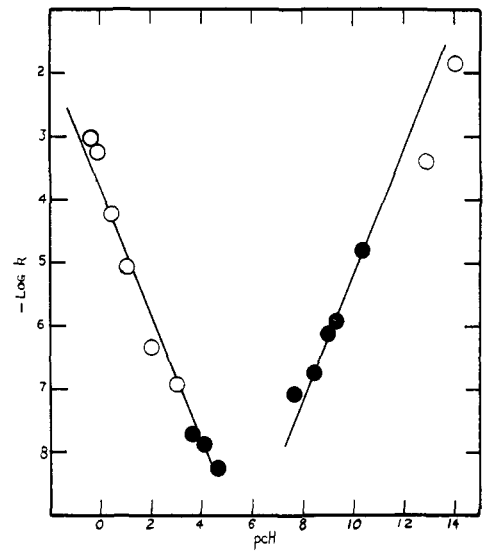

Figure 1. pcH-rate profile for the elimination of HCl from β-chloro-β-phenylpropiophenone in methanol. Lines drawn with slopes ±1, k in s^{-1}: dark circles, buffer solutions extrapolated to zero concentration; open circles, HCl or CH_3ONa.

$$C_6H_5COCH_2CHClC_6H_5 \rightarrow C_6H_5COCH{=}CHC_6H_5 + HCl \quad (1)$$

Since the most comprehensive reviews[2b] mention no acid-catalyzed dehydrochlorinations (we know of no others except that of camphene hydrochloride in ether[3]) and since the substrate is a type used in studies of E1cB reactions, it seems timely to show the pcH-rate profile for reaction 1.

General base catalysis was observed in acetate buffers (pcH 7.6–10.4) and general catalysis at pcH 3.6 in trichloroacetate buffers. Pseudo-first-order rate constants from the buffered runs were extrapolated to zero concentration to give the dark circles in Figure 1. The open circles represent pcH values controlled by anhydrous hydrogen chloride or sodium methoxide. The product is *trans*-chalcone above pcH 8 but contains 12% cis below pcH 4. The elimination is immeasurably slow in the pcH range 5–7. Unfortunately another, very slow acid-forming reaction, presumably displacement, complicates attempts to complete this portion of Figure 1.

The reaction is obviously catalyzed by $CH_3OH_2^+$; the rate constant, 1.3×10^{-4} M^{-1} s^{-1}, is insensitive to ionic strength. Acid catalysis implies that this elimination should be autocatalytic and in fact Vorlander[4] noted that the product accelerated the reaction, though he attributed it to a solvent effect. However, an unbuffered reaction mixture containing 0.015 M substrate and 0.001 M hydrogen chloride shows the initial acceleration and long period of nearly constant rate characteristic of reactions with rate equation $dx/dt = k(a + x)(s - x)$.

A mechanism consistent with these observations is rate-controlling, acid-catalyzed enolization followed by loss of chloride ion from the enol or its anion. Noyce and Reed[5] assigned an enolization mechanism to the acid-catalyzed dehydration of a β-ketol, $CH_3COCH_2CHOHC_6H_5$, structurally analogous to our β-chloroketone.

At high pcH the kinetics are consistent with an E2 or an