New Synthetic Reactions. Oxidative Decarboxylation of α-Methylthiocarboxylic Acids, New Approach to Acyl Anion and Ketene Synthons

Barry M. Trost* and Yoshinao Tamaru

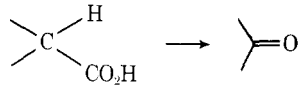
Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received September 9, 1976*

Abstract: α-Methylthiocarboxylic acids, available by the direct sulfenylation of the dianions of carboxylic acids or hydrolysis of sulfenylated esters, are rapidly transformed to the acetal or ketal of the noraldehyde or ketone. The effect of solvent on this reaction is substantial with methanol or ethanol preferred. The application to a fatty acid and 3-oxobisnorcholen-22-al illustrates some of the potential of the method in natural products. This approach allows the dianions of carboxylic acids or, more directly, the dianions of α-methylthiocarboxylic acids to serve as acyl anion equivalents. A synthesis of the insect hormone mimic, juvabione, illustrates an application of this sequence. The use of malonic ester as a carbonyl dianion equivalent is demonstrated in the synthesis of cyclobutanone diethyl ketal. The use of acrylic acid as a ketene equivalent in cycloadditions is highlighted by a synthesis of 7-*anti*-methoxymethylnorborn-5-en-2-one, the Corey prostaglandin intermediate.

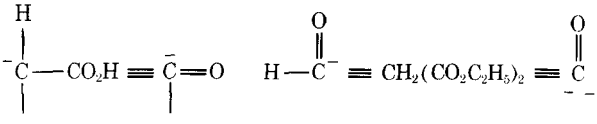
The degradation of carboxylic acids has played a pivotal role in the structural elucidation of natural products.[1] In other cases, carboxylic acids may be readily available but the norketone or aldehyde is the desired compound, e.g., from the Wolff rearrangement of α-diazo ketones. Degradation of fatty acids and subsequent reconstitution for introduction of radiolabels is important in biosynthetic studies.[1c,d] One of the classic sequences to achieve such a transformation, the Barbier–Weiland degradation, suffers from low yields and the use of several steps that are incompatible with other functionality such as olefins and ketones or aldehydes.[2] An alternative approach utilizes a Curtius or Hoffman rearrangement of a carboxylic acid derivative to generate an amine which is subsequently converted to a ketone.[3] The conversion of a carboxylic acid to a methyl ketone followed by a Baeyer–Villager oxidation also has found application.[4] These approaches suffer from their length.[5]

The successful oxidative decyanation of nitriles suggests that initial conversion of a carboxylic acid to a nitrile may be a feasible method.[6] The direct oxidation of the anions of carboxylic acids with molecular oxygen[7] opens several avenues which heretofore did not exist.[8,9] However, this method is limited to tertiary carboxylic acids.

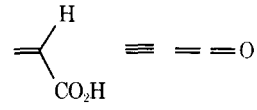
The desire to find an efficient method for such conversions is enhanced by consideration of the potential of various carboxylic acids in synthesis. The transformation replaces a geminal hydrogen and carboxylic acid with a carbonyl group.



Thus, the ability to directly alkylate carboxylic acids[10] translates these compounds into acyl anion equivalents. Since the alkylation of malonic esters is a general route into carboxylic

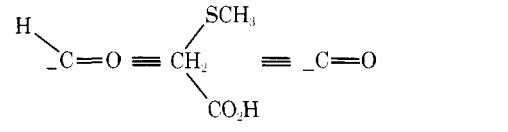


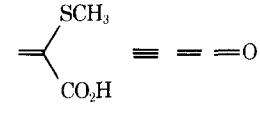
acids, these readily available building blocks are formyl anion or carbonyl dianion equivalents. A procedure does exist for the direct oxidation of geminal dicarboxylic acids to ketones utilizing lead tetraacetate; however, it does not appear to be general nor applicable to the formation of aldehydes.[11] The development of ketene equivalents, especially with respect to the net result of ketene participating in a formal [4 + 2] cycloaddition, has great synthetic utility.[12] This type of procedure would allow acrylic acid to serve in such a role.

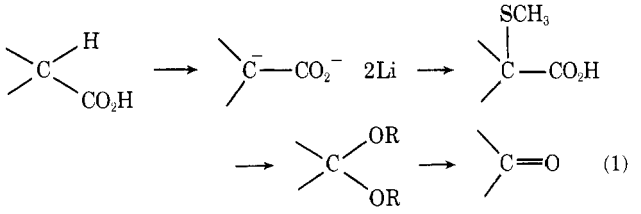


In considering various approaches involving oxidations, it is common to explore reagents which introduce oxygen directly. The difficulty with controlling such reactions, especially in polyfunctional molecules, diminishes their attractiveness. The replacement of a C–H bond by a C–S bond provides a potential alternative because of the mildness (and consequently selectivity) of the conditions for introduction of sulfur, especially α to a carbonyl group; i.e, these reactions tend to be chemoselective. To complete the sequence, the sulfur must ultimately be replaced with oxygen or eliminated. Indeed, sulfenylation–dehydrosulfenylation constitutes a useful approach to dehydrogenation.[13,14] Initiating various net oxidative sequences with a sulfenylation appears to hold promise for *selective* oxidations.[15,16]

Such an approach is particularly attractive for the problem at hand. Our previous work suggested that α-sulfenylated carboxylic acids should be readily available either by hydrolysis of the sulfenylated carboxylic esters or by direct sulfenylation of dianions of carboxylic acids. Furthermore, simple sulfenylated building blocks could be used in the types of synthetic manipulations mentioned above. For example, 2-methylthioacetic acid may be considered as a formyl anion or carbonyl dianion equivalent. 2-Methylthioacrylic acid[17] may be considered as a ketene equivalent. Obviously, the choice of whether the sulfenylated building block or the carboxylic acid would be used depends on the availability of the former. In this paper, we wish to report the successful realizations of these goals as illustrated in eq 1.[18,19] As will be shown, the method has the further advantage that the incipient carbonyl group is initially generated in a protected form as a ketal or acetal.







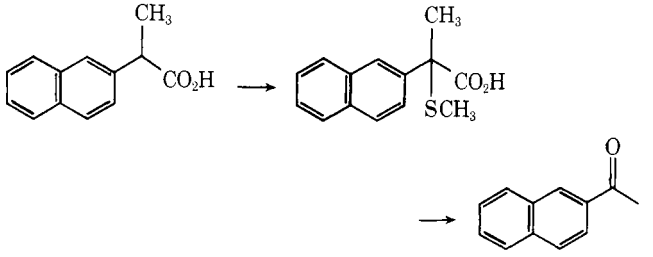
(1)

Results

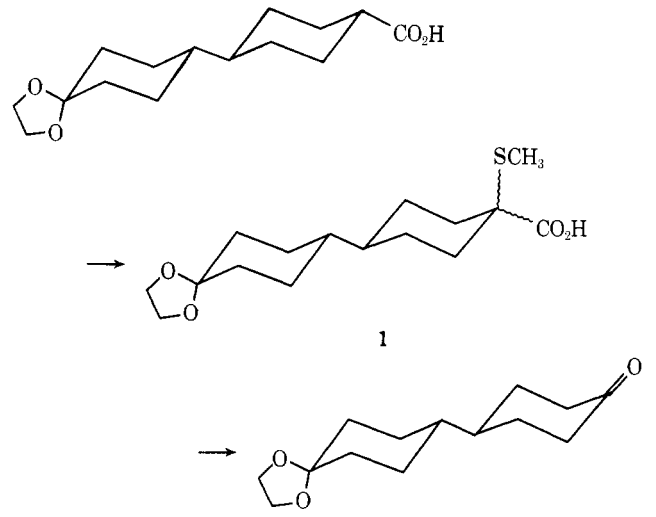
Utilizing the method of Creger,[10] we converted a number of carboxylic acids to their dianions as illustrated by cases 1-6. For the aryl cases (1 and 3) the use of THF was satisfactory for dianion formation; however, for most examples, THF-HMPA mixtures were employed. These solutions are then quenched by addition of freshly distilled dimethyl disulfide. The conversion to the sulfenylated carboxylic acids is normally quantitative and the material is generally utilized in the next step without further purification. Furthermore, the presence of any unreacted carboxylic acid does not interfere with nor is affected by the oxidative decarboxylation. It can be easily recovered at that stage by a simple base extraction since the product from the sulfenylated acid is neutral. In case 6, the direct quench procedure gave ~10% of the bisulfenylated acid. This by-product could be eliminated by adding the dianion to excess dimethyl disulfide.

The limitation of this approach resides mainly in the ability to generate the dianions. For example, attempts to form the dianion from **2a** or the trianion from **6a** failed. In both cases,

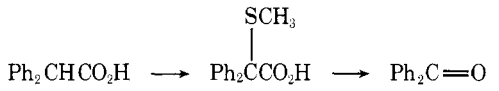
Case 1



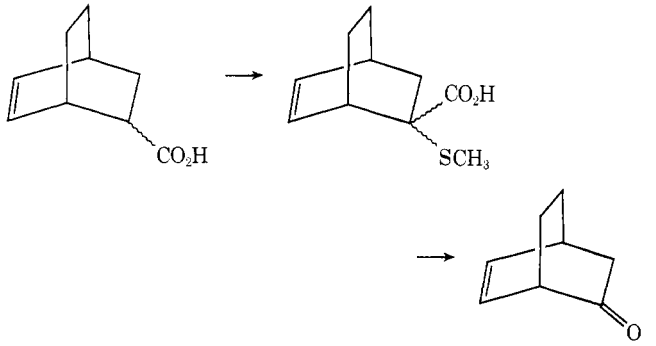
Case 2



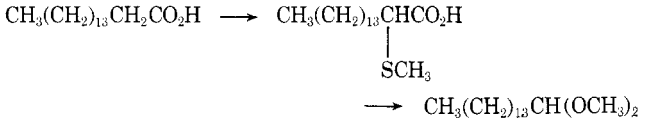
Case 3



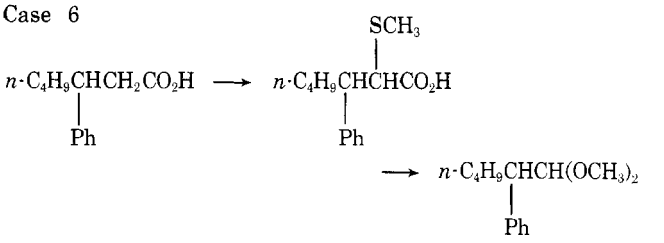
Case 4

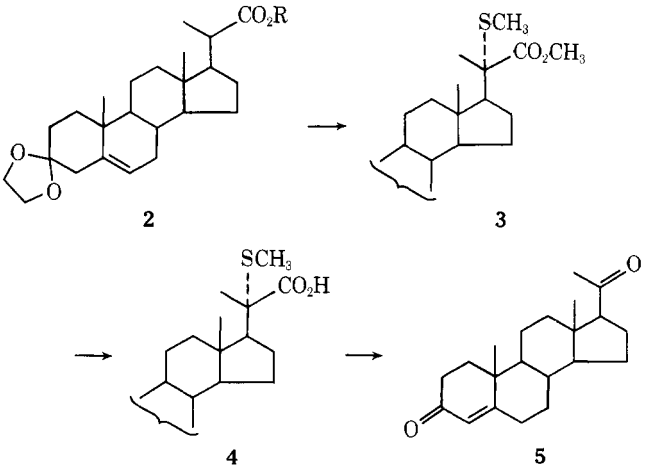


Case 5

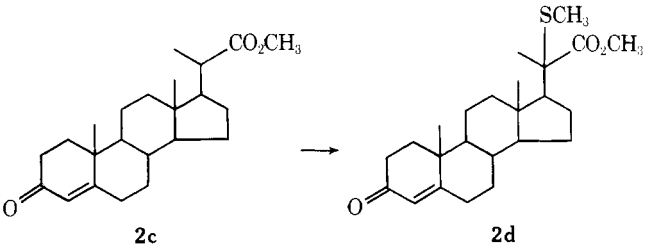


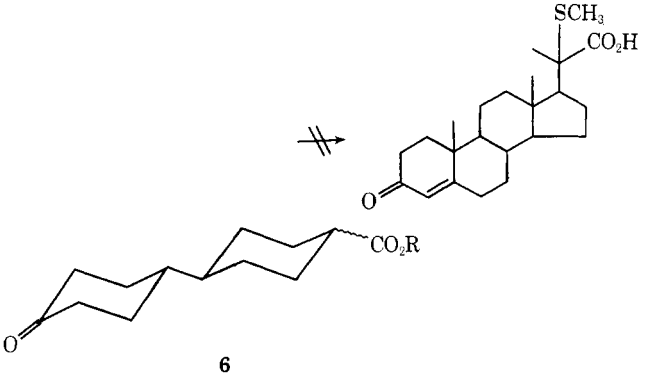
Case 6

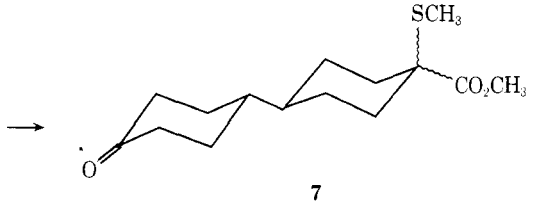




a, R = H
b, R = CH_3







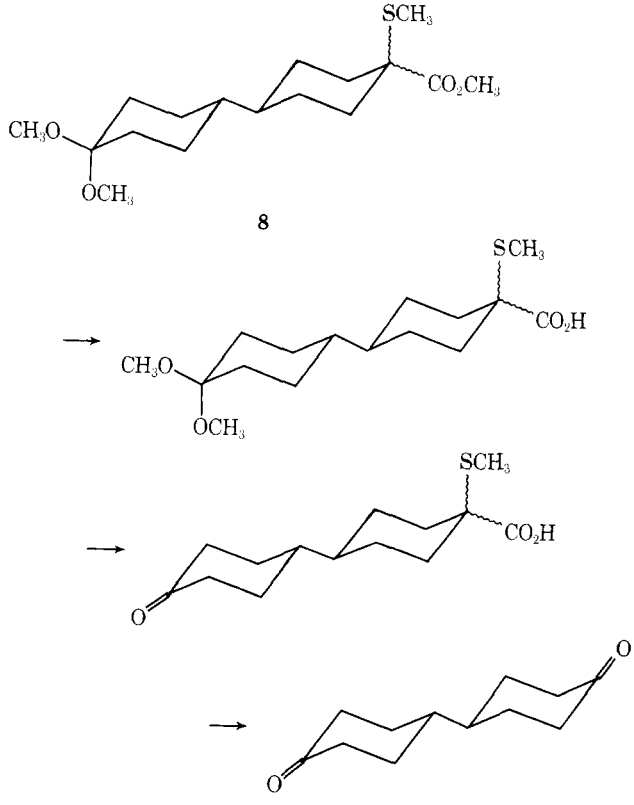
7

a, R = H
b, R = CH_3

the problem can be easily resolved by conversion to the ester. Keto esters **2c** and **6b** represent additional illustrations of the chemoselectivity of the sulfenylation reaction. Hydrolysis of the sulfenylated esters is accomplished with potassium hydroxide in hot ethylene glycol. Attempts to hydrolyze **2d** or **7** led to substantial decomposition. That the decomposition arose from the instability of the ketone function under the hydrolysis conditions is illustrated by the nearly quantitative hydrolysis of the ketal derivatives **3** and **8.** For **6a,** the problem can also be solved by ketalizing so that only a dianion is being generated (see case 2).

Normally, sulfenylation gave a stereoisomeric mixture of α-methylthiocarboxylic acids as determined by a pair of singlets for the SCH_3 groups in the ^1H NMR spectra (see Experimental Section). In the bicyclo[2.2.2]octene and bicyclo[2.2.1]heptene cases, the ^1H NMR spectra shows evidence for the presence of essentially one isomer. On the basis of steric approach control, the methylthio group is assigned the syn and anti configurations, respectively. In the steroid series, **3** also appears to be a single isomer as determined by its sharp melting point and more particularly the appearance of the NMR spectrum, which shows only one sharp *S*-methyl (δ 1.97) and three sharp *C*-methyl groups (δ 1.40, 0.98, and 0.76 for protons on C(21), C(19), and C(18), respectively). Alkylation at C(20) of a 22-keto steroid occurs on the α face[20] which in this case would produce the *S* isomer at C(20).

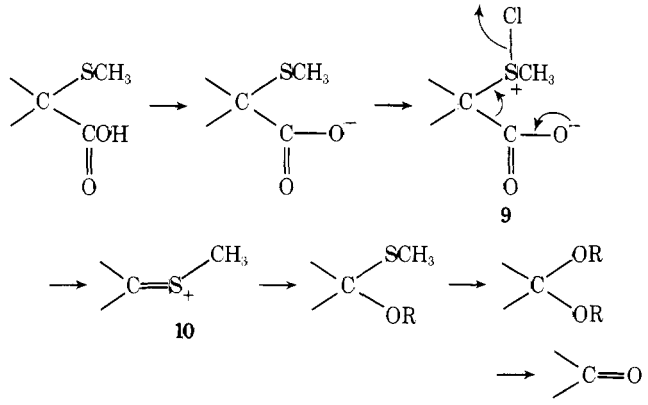
For the oxidative decarboxylation, a mild oxidizing agent that would be compatible with other functionality and that avoids oxidation to the sulfoxide, which appears to be inert



8

toward oxidative decarboxylation (vide infra), is required. We found that *N*-chlorosuccinimide (NCS) in anhydrous solvents served the role admirably for α-dialkyl-α-methylthiocarboxylic acids. Presumably, other positive halogenating agents also would work. Anhydrous alcoholic solvents are employed. The choice of alcohol appears to be important and depends somewhat on the structure of the substrate. For simple dialkyl examples (cases 2 and 4), ethanol was the preferred solvent; however, if steric congestion exists such as in the case of thio acid **4,** methanol was preferred.

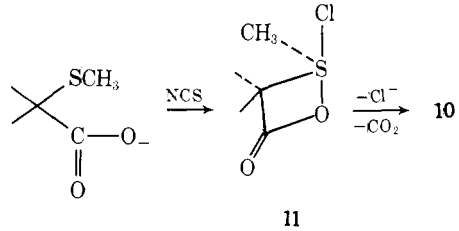
The critical choice of alcohol in such reactions can be understood by considering the possible mechanism of the reaction. The acid, which is initially converted to its salt by anhydrous sodium bicarbonate, is treated with NCS in the alcohol at room temperature. The known tendency[21] of sulfides to form chlorosulfonium salts such as **9** triggers the decarboxylation to form the key alkylthiononium ion **10,** which is analogous to the intermediate postulated in the Pummerer reaction.[22]



9

10

Considering the tendency of sulfur to form hypervalent states which are particularly favored by small rings and electronegative substituents,[23] an alternative intermediate **11** can

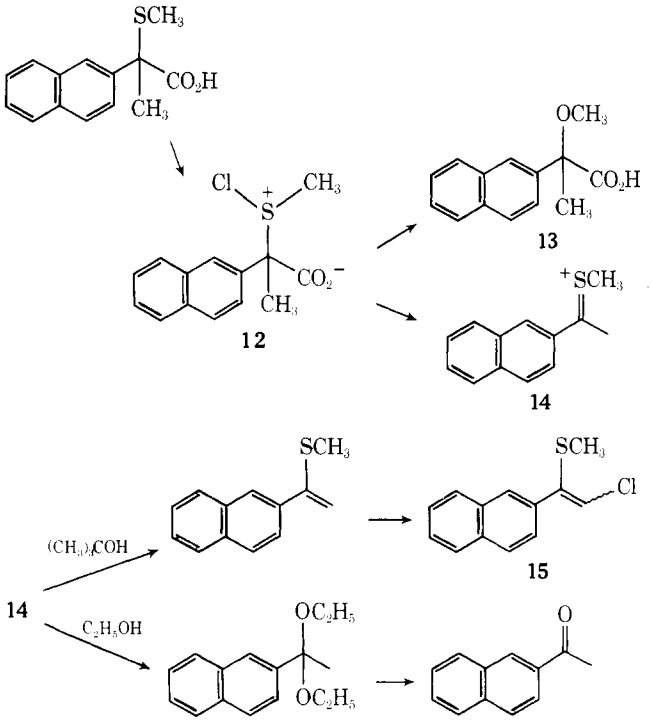


11

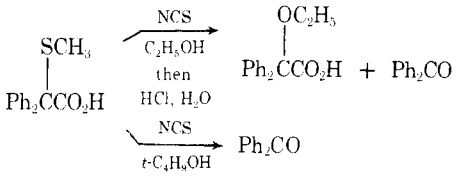
be considered as the precursor of **10.** Support for this suggestion arises in the facility of β-sultine formation in the oxidation of β-hydroxy-*tert*-butyl sulfoxides with sulfuryl chloride.[24]

In the case of **9,** sulfur is also a leaving group. When an activating group such as aryl is present at the α carbon (such as in **12**), solvolysis appears to compete with elimination. In methanol, a small amount of the solvolysis product, methoxy acid **13,** was isolated. This process is totally suppressed in ethanol, from which β-acetonaphthone could be isolated in 79% yield after hydrolysis. On the other hand, 2,2-diphenyl-2-methylthioacetic acid undergoes solvolysis and decarboxylation (about 1:1) in ethanol but produces only benzophenone (68% yield) in the poorer solvolysis solvent, *tert*-butyl alcohol. The formation of progesterone (**5**) from the bisnorcholenic acid was best performed in methanol, presumably because of steric hindrance. This approach serves as an effective means for this degradation.[5b]

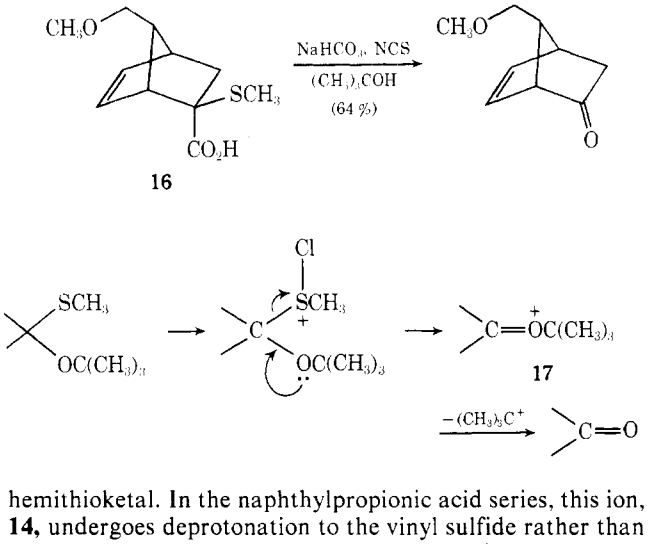
The direct formation of the ketone in *tert*-butyl alcohol is interesting. A similar observation was made for **16** (vide infra). A rationalization invokes the intermediacy of **17** which would be expected to extrude a *tert*-butyl carbonium ion with formation of the carbonyl group. Trapping of **17** by a second mole of *tert*-butyl alcohol to form the ketal is unlikely considering



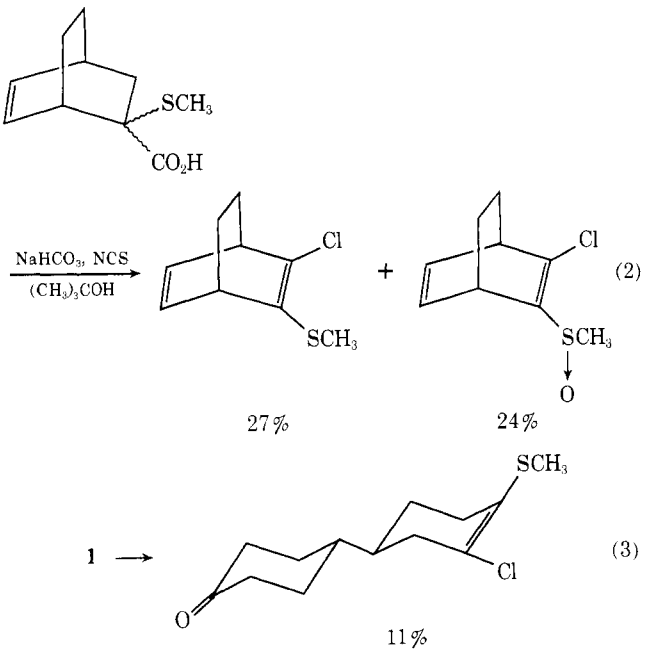
steric congestion. However, the use of *tert*-butyl alcohol in such a fashion is not general. The bulk of the *tert*-butyl group not



only hinders ketal formation but also would be expected to hamper trapping of the alkylthiononium ion to form the



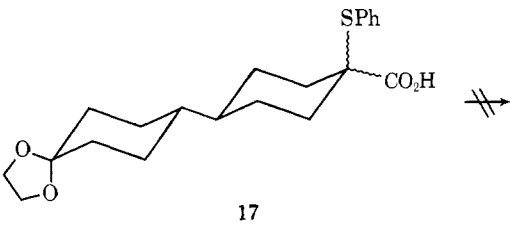
hemithioketal. In the naphthylpropionic acid series, this ion, **14,** undergoes deprotonation to the vinyl sulfide rather than hemithioketal formation. Since the vinyl sulfide is more reactive toward NCS than the starting α-methylthiocarboxylic acid, it undergoes chlorination to allow isolation of the chloro vinyl sulfide **15** in 62% yield. In the benzophenone case, such a possibility does not exist. For **16,** the high strain energy for introduction of a second double bond in a norbornene system apparently inhibits the deprotonation and thereby allows the "normal" course to proceed. That such an explanation is reasonable is shown by the fact that enol thioether formation does proceed in the bicyclo[2.2.2]octane series (see eq 2). A similar result was obtained in a simple cyclohexyl system although only in poor yield (eq 3). Such a reaction also could have an interesting synthetic application which, however, remains to be established.



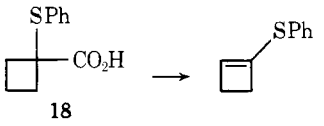
Utilization of NCS as the oxidizing agent in cases **5** and **6** led to complex mixtures. The ease of enolization of such sulfenylated acids suggested oxidation at the α position as the cause. We subsequently found that sodium metaperiodate in anhydrous methanol allows easy isolation of the corresponding acetals in good yields. Because sodium metaperiodate is not very soluble under these conditions, it is ground into a fine powder before using. The virtually total insolubility of sodium metaperiodate in anhydrous ethanol precludes the use of the latter as a solvent. Reaction times tend to be longer (~20–25 h) than for the NCS reactions. Sodium metaperiodate may also be employed in the α,α-dialkyl cases to generate ketals. Thus **1** is converted into the methyl ketal in 75% yield. Only starting

material was recovered when sodium metaperiodate in ethanol or lead tetraacetate in benzene was employed. However, the greater cost of sodium metaperiodate relative to NCS makes it less attractive for the formation of ketals and ketones.

We also examined the α-phenylthiocarboxylic acids which are readily available by the direct sulfenylation procedure. The



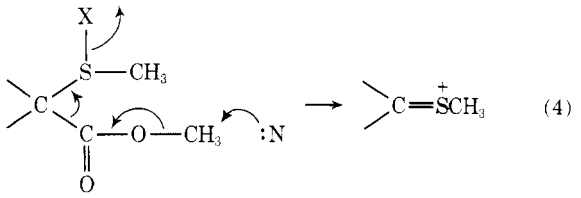
acid **17** was unreactive toward NCS and sodium metaperiodate when conditions paralleled those for the methylthio series. Upon prolonged treatment with the oxidizing agents or raising the temperature of the reaction, decomposition occurred; but the formation of the desired products could be, at most, a very minor pathway as determined by TLC comparison with authentic samples. In the cyclobutyl case **18,** a low yield of 1-



18

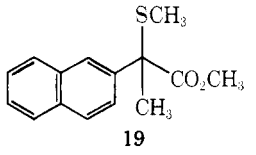
phenylthiocyclobutene could be isolated; nevertheless, the presence of many by-products was evident from inspection of the crude product by TLC and NMR.

Attempts to employ the sulfenylated ester by introducing a leaving group at sulfur in the presence of a nucleophile (see eq 4) were examined. Treatment of **8** or **19** with iodine and

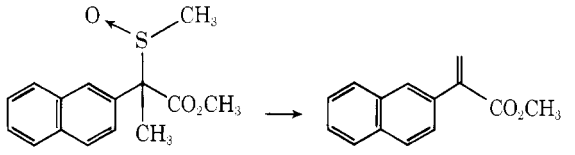


(4)

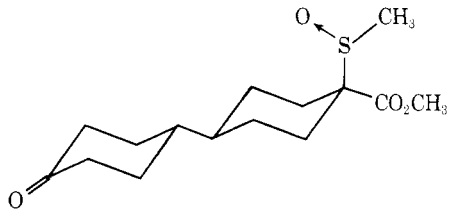
sodium iodide in DMF at various temperatures led only to recovered starting material. Initial conversion to the sulfoxides,



19



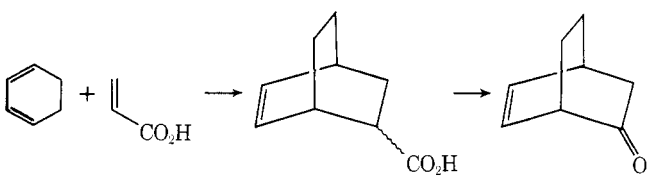
20



21

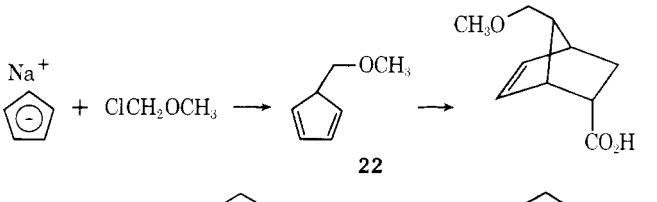
20 and **21**, and then treatment with acetic anhydride–sodium acetate in the presence of sodium iodide in hot DMF led only to elimination.[13] Thus direct dealkylative[25] decarboxylative elimination from the sulfide esters appears unpromising.

Synthons. With the establishment of the sequence, attention was turned to the use of various carboxylic acids as synthetic equivalents of carbonyl groups. A simple case is the utilization of acrylic acid as a synthon for ketene. In fact the bicyclo[2.2.2.2]oct-2-ene-5-carboxylic acid, case 4, is available

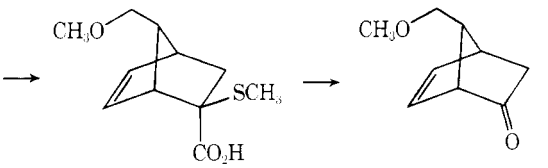


by the Diels–Alder reaction of acrylic acid with cyclohexadiene or by hydrolysis of the Diels–Alder adduct between ethyl acrylate and the same diene. The successful oxidative decarboxylation of this acid under standard conditions to bicyclo[2.2.2]oct-5-en-2-one constitutes the equivalent of the cycloaddition of ketene to cyclohexadiene. Because examination of the crude product shows only the desired ketone, we suspect that the somewhat reduced yield, in this case, is a reflection of the volatility of the compound when operating on a small scale.

The preparation of a Corey prostaglandin intermediate[12h] from simple and inexpensive building blocks without the need for thallium salts illustrates one advantage of this approach. The monoalkylcyclopentadiene **22** is able to undergo either

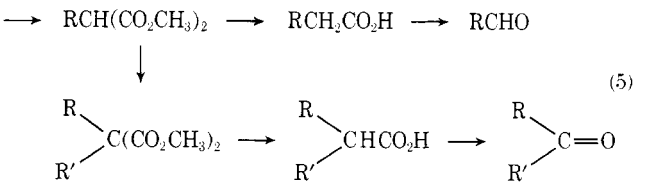


22



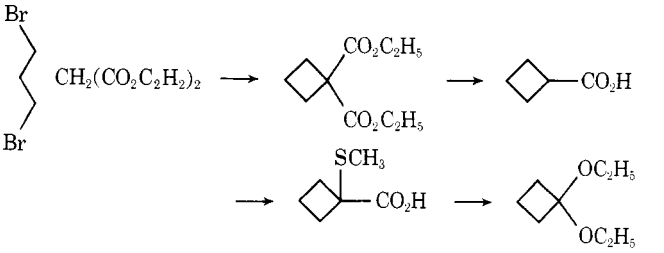
thermal or base-catalyzed prototropy with the result of loss of positional identity of the alkyl substituent. Since below 0 °C the thermal reaction is not rapid, the use of a buffer to minimize or eliminate the base reaction suggests that acrylic acid could serve a dual role. Indeed, reaction of **22** with excess acrylic acid at −7 °C led to the desired adduct. The compound was analyzed as its corresponding methyl ester which showed two methyl ester singlets at δ 3.56 and 3.66 in a ratio of 92:8 which we assign to the endo and exo isomers, respectively. Sulfenylation of the acid proceeds to give essentially one isomer as indicated by one SCH_3 signal at δ 2.18 (vide supra). Normally the sulfenylated acid was taken directly onto the next step without purification. The product norbornenone had spectral properties identical with those of an authentic sample. VPC analysis indicated less than 3% contamination by isomers.

The use of malonate as an acyl anion equivalent (eq 5) is straightforward since the alkylations of malonic ester are classic reactions. Thus, the preparation of simple carboxylic acids such as in cases 5 and 6 by such alkylation procedures is



(5)

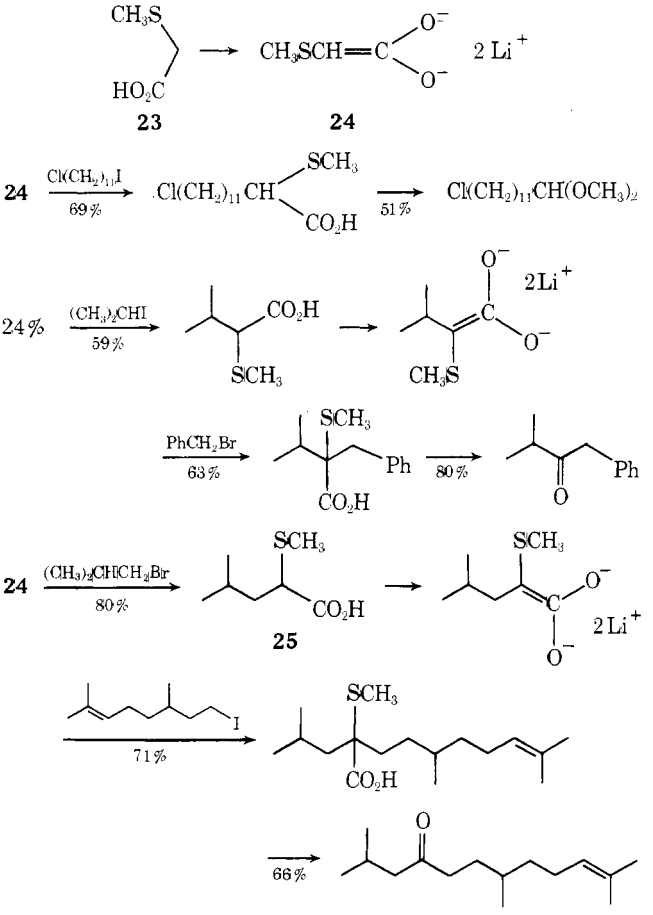
easily envisioned. Dialkylation with the subsequent preparation of ketones is equally straightforward. To illustrate the latter explicitly as well as the utility of this procedure in strained cases, a preparation of cyclobutanone was developed. The dialkylation of malonic ester with 1,3-dibromopropane to form diethyl 1,1-cyclobutanedicarboxylate followed by hydrolysis and decarboxylation provides cyclobutanecarboxylic acid in



large quantities.[26] The sulfenylation proceeded smoothly to give 1-methylthiocyclobutanecarboxylic acid in 81% distilled yield. Because of the water solubility of cyclobutanone, the oxidative decarboxylation was worked up under neutral conditions to allow isolation as the diethyl ketal in 50% distilled yield. Spectroscopic and chromatographic examination of the crude product showed only the desired ketal. Thus, volatility may again have played a role in determining the isolated yield. Since the ketal should be convertible to the ketone under nonaqueous conditions by ketal exchange, this route provides ready access to cyclobutanone on a laboratory scale.[27]

A more direct method for the preparation of ketones employs methylthioacetic acid (**23**), available from methanethiol and chloroacetic acid, in this sequence. Dianion formation succeeds upon treatment of acid **23** with 2 equiv of lithium dialkylamides in a THF–HMPA mixture at 0 °C (see Scheme I).[28] Alkylations with primary, secondary, and benzylic halides

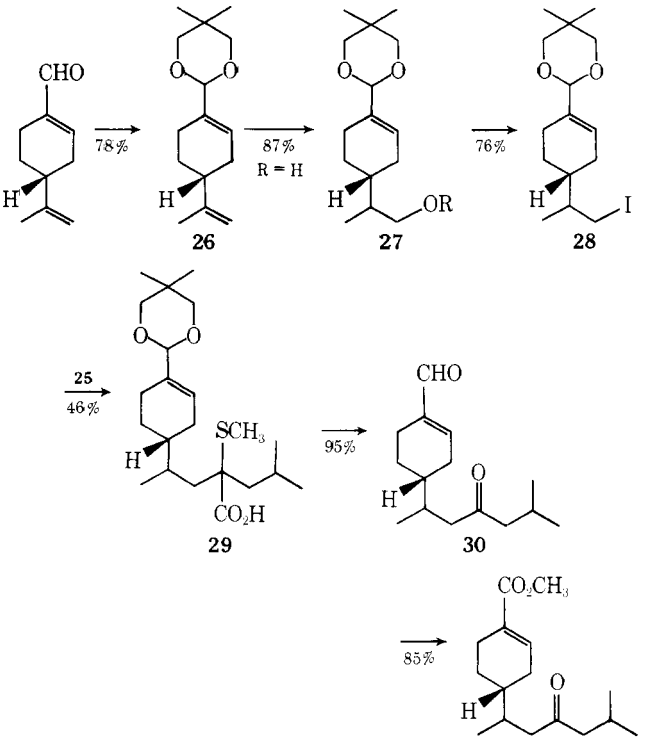
Scheme I. Dianion of Methylthioacetic Acid as Acyl Anion Equivalent



have been performed. Thus, addition of 1 equiv of 1-chloro-11-iodoundecane leads to the monoalkylated product which can be oxidatively decarboxylated to the aldehyde, isolated as its methyl acetal, utilizing the sodium metaperiodate method. The monoalkylated α-methylthiocarboxylic acid can be converted to its dianion and alkylated a second time. Thus, alkylation of **23** with isopropyl iodide followed by benzyl bromide gives 3-methyl-1-phenyl-2-butanone after oxidative decarboxylation with NCS. A similar series utilizing, sequentially, isobutyl bromide and citronellyl iodide gave the nonisoprenoid sesquiterpene type structure 2,7,11-trimethyldodec-10-en-4-one.

Scheme II outlines a synthesis of juvabione, a species specific juvenile hormone mimic, embodying this approach.[29] Thus, perillaldehyde can be converted to its 2,2-dimethylpropylene ketal.[26] Hydroboration of the less hindered double bond with

Scheme II. Synthesis of Juvabione



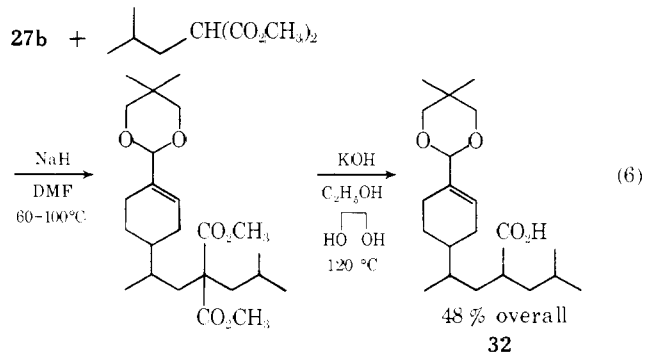
a, R = H
b, R = Ts

disiamylborane followed by oxidation gives the primary alcohol **27a.** At this time, a mixture of diastereomers, about 3:2, results as determined by the methyl group on C-8 which appears as two doublets at δ 0.90 and 0.92, J = 7 Hz. Since in the case of the methenols derived from (*R*)-(+)-limonene, the 4*R*,8*R* isomer showed this methyl group at higher field (δ 0.87) than the 4*R*,8*S* isomer (δ 0.90), we assign the major isomer as the desired 4*R*,8*R* configuration.[29c] Conversion of the alcohol to the iodide via the intermediacy of the tosylate[27b] proceeded without complications. Attempts to alkylate the anion of **25** with the tosylate **27b** were unsuccessful. On the other hand, the iodide **28** served well to give the desired α-methylthiocarboxylic acid **29.** Careful acidification of the aqueous layer with sodium bisulfate was necessary to avoid hydrolysis of the acetal. The main by-product in this reaction was **26** arising by simple dehydrohalogenation. The introduction of an additional asymmetric center complicates analysis of **29.** Since the asymmetry at this carbon is destroyed in the next reaction, no attempt was made to analyze the isomers.

The choice of conditions for the oxidative decarboxylation of **29** turned out to be surprisingly important. Use of sodium metaperiodate was ineffectual. NCS in ethanol followed by hydrolytic workup led to a 23% yield of desired products, **30** and **31,** the latter simply the result of incomplete hydrolysis. This yield increased to 96% when methanol was employed. Completion of the synthesis employed the procedure of Corey which allows the direct oxidation of aldehydes to methyl esters.[30]

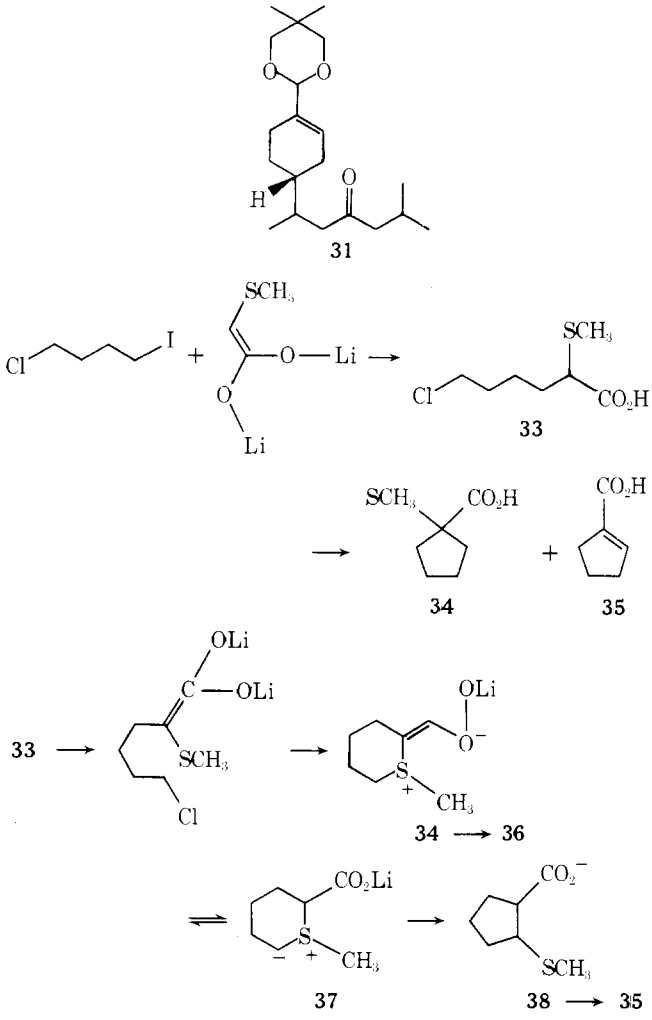
An alternative approach to **29** involves the sulfenylation of the acid **32.** The latter is readily available as shown in eq 6. The dianion of **32** could not be generated. Thus, the use of the dianion of α-methylthiocarboxylic acids rather than malonate anions as the acyl anion equivalent is preferable in this case.

On the other hand, in some cyclizations, the use of malonate rather than α-methylthiocarboxylic acids may be preferred. We briefly examined the alkylation of methylthioacetic acid with 1-chloro-4-iodobutane. Alkylation under the usual conditions led to the sensitive chloro acid **33.** We attribute its in-



(6)

stability to formation of a sulfonium salt by intramolecular alkylation. In any event, treatment of freshly prepared **33** with 2 equiv of lithium diisopropylamide led to the desired cyclization product **34** in 60% and to cyclopentene-1-carboxylic acid (**35**) in 20% yield. The direct formation of the unsaturated acid



was startling. The α-methylthio acid does not serve as a precursor to **35.** A possible rationalization envisions the initial alkylation to occur at sulfur rather than carbon to give ylide **36** which can serve as a precursor to **34** via a Stevens rearrangement.[31] Alternatively, the ylide **36** can equilibrate with a second ylide **37** which should undergo a Stevens rearrangement even more facilely to give the β-methylthiocarboxylic acid **38.** Under the strong basic conditions of the reaction, elimination of the elements of methanethiol from the latter would be reasonable. Support for such an interpretation arises in the cycloalkylation of the monosulfoxides of thioacetals which also appears to be initiated by attack at sulfur.[27g,32] Considering the potential implications of these results in connection with the question of the structural features that lead to stabilization of negative charge by sulfur heightens interest in further exploring these reactions. Nevertheless, the apparent complications offered by the presence of sulfur suggest that simple malonates may be preferable in these cases.

Experimental Section

General. All reactions were run under a positive pressure of dry nitrogen in an apparatus flame dried in a nitrogen stream. In experiments requiring dry solvents, ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. HMPA was distilled from calcium hydride. Dimethyl disulfide was freshly distilled from calcium hydride before using. The usual preparation of lithium diisopropylamide involved addition by syringe of 1.0 equiv of a hexane solution of *n*-butyllithium to a cold (0 or −78 °C) solution of 1.0 equiv of diisopropylamine in THF. Diisopropylamine was distilled from potassium hydroxide pellets. Thin layer or preparative thick layer (~1.5 mm) plates were made of E. Merck AG (Darmstadt) silica gel PF-254 activated by drying at 140 °C for 2 h. Column chromatography employed W. R. Grace silica gel, grade 62, 60–200 mesh. Melting points (obtained on a Thomas-Hoover apparatus) and boiling points are uncorrected. Micronanalyses were obtained from Spang Microanalytical Laboratories, Ann Arbor, Mich.

Infrared spectra were obtained as solutions in the indicated solvent on a Perkin-Elmer 267 spectrophotometer. Only significant peaks are reported. NMR spectra were determined on a Varian T-60 or Jeolco MH-100 spectrometer. Chemical shifts are given in parts per million downfield from Me_4Si and splitting patterns are designated b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. 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 100 mA.

Sulfenylation of Dianions of Carboxylic Acids. Preparation of 2-Methylthiohexadecanoic Acid (α-Methylthiopalmitic Acid). Into a solution of 11.5 mmol of lithium diisopropylamide (LDA) in 30 mL of dry THF at 0 °C was added over a 10-min period a solution of 1.28 g (5.0 mmol) of hexadecanoic acid (palmitic acid) in 6 mL of dry THF and 3 mL of dry HMPA. After a reaction time of 30 min at 0 °C, the cooling bath was removed and the mixture stirred for an additional 40 min. During this time, the precipitate that formed at the lower temperature usually dissolved. The reaction mixture was cooled to 0 °C and then 0.884 g (~0.90 mL, 9.4 mmol) of dimethyl disulfide was added all at once. After 30 min at 0 °C, the reaction was quenched with water and extracted with ether. The ether extracts were washed with additional water and 2 N aqueous sodium carbonate solution and these water washings combined with the original aqueous phase. The combined water layers were cooled to 0 °C and acidified to pH 1 with concentrated hydrochloric acid. After saturation of the water with sodium chloride, the mixture was extracted with ether several times. Drying ($MgSO_4$) and concentration in vacuo gave a solid. Recrystallization of this solid from *n*-hexane gave 1.45 g (90%), mp 65–67 °C, of the desired product: IR (CCl_4) 2400–3400 broad, 1705, 1420, 1290 cm^{-1}; NMR (CCl_4) δ 11.8 (bs, 1 H), 3.03 (m, 1 H), 2.15 (s, 3 H), 1.23 (bs, 26 H), and 0.88 (t, J = 5 Hz, 3 H); mass spectrum *m/e* (rel %) 302 (32), 257 (90), 241 (100), 105 (66), 83 (26), 73 (38), and 69 (34). Calcd for $C_{17}H_{34}O_2S$: 302.2280. Found: 302.2259.

Preparation of 2-Methylthio-2-(2′-naphthyl)propionic Acid. In similar fashion, 6.00 mmol of LDA in 10 mL of THF was reacted with 525 mg (2.5 mmol) of 2-(2′-napthyl)propionic acid in THF–HMPA at −78 °C for 45 min and −25 °C for 15 min. After addition of 0.395 mg (0.40 mL, 4.2 mmol) of dimethyl disulfide at −25 °C, stirring continued at −25 °C for 20 min and at 0 °C for 30 min. Chloroform was used as the extracting solvent to give 590 mg (92%) of the desired sulfenylated acid: mp 109–114 °C; IR (CCl_4) 2400–3400, 1710, 1608, 1512, and 1280 cm^{-1}; NMR (CCl_4) δ 7.4–8.0 (m, 7 H), 2.03 (s, 3 H), 1.90 (s, 3 H); mass spectrum *m/e* (rel %) 246 (26), 201 (20), 199 (87), 198 (34), 171 (15), 153 (100), 152 (68), and 43 (78). Calcd for $C_{14}H_{14}O_2S$: 246.0715. Found: 246.0718.

Preparation of 1. In similar fashion, 4.0 mmol of LDA in 10 mL of THF was reacted with 447 mg (1.67 mmol) of the ethylene ketal of 4-(4′-carboxycyclohexyl)cyclohexanone[33] in THF–HMPA at 0 °C for 1.5 h. After addition of 0.263 g (0.27 mL, 2.8 mmol) of dimethyl disulfide at 0 °C and stirring for 30 min, workup (extraction with chloroform) and purification (PLC, 2:1 hexane–acetone) gave 511 mg (98%) of **1:** mp 149–150 °C (recrystallized from benzene–

hexane); IR (CCl_4) 2400–3300, 1692, and 1280 cm^{-1}; NMR ($CDCl_3$) δ 10.1 (b, 1 H), 3.96 (s, 4 H), 2.04 and 2.12 (two s, 3 H) superimposed upon 0.9–2.5 (m, 18 H); mass spectrum *m/e* (rel %) 314 (<1), 267 (6), 179 (8), 136 (7), 135 (24), 99 (100), 86 (15), and 78 (21). Calcd for $C_{16}H_{26}O_4S$: 314.1552. Found: 314.1550.

Preparation of 17. In similar fashion, 14.1 mmol of LDA in 20 mL of dry THF was reacted with 1.576 g (5.01 mmol) of the ethylene ketal of 4-(4′-carboxycyclohexyl)cyclohexanone in THF–HMPA at 0 °C for 2 h. After addition of 1.984 g (9.1 mmol) of diphenyldisulfide in 4 mL of dry THF and stirring at 0 °C for 45 min, workup (extraction with chloroform) and purification gave the desired product **17**, mp 117–130 °C, as a mixture of isomers: IR (CCl_4) 2400–3400 and 1700 cm^{-1}; NMR (CCl_4) δ 10.71 (b, 1 H), 7.1–7.6 (m, 5 H), 3.86 (s, 4 H), 0.9–2.5 (m, 18 H); mass spectrum *m/e* (rel %) 376 (12), 276 (80), 99 (100), and 86 (19). Calcd for $C_{21}H_{28}O_4S$: 376.17.08. Found: 376.1710.

Preparation of 2,2-Diphenyl-2-methylthioacetic Acid. In similar fashion, 6.0 mmol of LDA in 10 mL of THF was reacted with 530 mg (2.50 mmol) of diphenylacetic acid at −78 °C for 10 min and −25 °C for 35 min. After addition of 0.395 g (0.40 mL, 4.2 mmol) of dimethyl disulfide at −25 °C and stirring for 30 min at −25 °C and 25 min at 0 °C, there was isolated 628 mg (quantitative yield) of sulfenylated acid. Recrystallization from carbon tetrachloride gave 543 mg: mp 178–179 °C; IR (CCl_4) 2400–3600, 1698, 1592, 1495, and 1265 cm^{-1}; NMR ($CDCl_3$) δ 9.9 (b, 1 H), 7.1–7.6 (m, 10 H), 1.97 (s, 3 H); mass spectrum *m/e* (rel %) 258 (3), 213 (16), 212 (45), 167 (60), 166 (26), 165 (100), 119 (50), 117 (55), and 105 (47). Calcd for $C_{15}H_{14}O_2S$: 258.0715. Found: 258.0715.

Preparation of 2-Carboxy-2-methylthiobicyclo[2.2.2]oct-5-ene. In similar fashion, 6.0 mmol of LDA was reacted with 380 mg (2.50 mmol) of 2-carboxybicyclo[2.2.2]oct-5-ene in THF–HMPA at 0 °C for 2.5 h. After addition of 0.348 g (0.35 mL, 3.7 mmol) of dimethyl disulfide and stirring at 0 °C for 40 min, workup (extraction with ether) and purification (PLC, 4:1 hexane–acetone) gave 414 mg (84%) of desired product: mp 104–113 °C; IR (CCl_4) 2300–3400, 1708, 1295 cm^{-1}; NMR (CCl_4) δ 6.3 (m, 2 H), 2.90 (m, 1 H), 2.10 (s, 3 H), 1.1–2.7 (m, 7 H); mass spectrum *m/e* (rel %) 198 (15), 150 (5), 105 (10), 80 (100), and 79 (78). Calcd for $C_{10}H_{14}O_2S$: 198.0715. Found: 198.0706.

Preparation of 2-Methylthio-3-phenylheptanoic Acid. In similar fashion, 21 mmol of LDA in 50 mL of dry THF was reacted with 2.06 g (10.0 mL) of 3-phenylheptanoic acid in 5 mL of THF and 5 mL of HMPA at 0 °C for 2.5 h. In this case an inverse quench was preferred because of some polysulfenylation product by the direct quench procedure. This solution was transferred by cannula into ~5 g (5.0 mL, 53.2 mmol) of dimethyl disulfide at −25 °C over a 30-min period and stirring continued for 1 h at −25 °C. Addition of ice quenched the reaction and it was worked up in the usual way to give after purification by column chromatography (elution gradient beginning with hexane and ending with 5:1 hexane–acetone) 2.48 g (99%) of the desired product: IR (CCl_4) 2500–3400, 1705, and 1290 cm^{-1}; NMR (CCl_4) δ 11.18 (b, 1 H), 7.0–7.4 (m, 5 H), 3.28 and 3.22 (two d, J = 11 Hz, 1 H), 2.88 (m, 1 H) and 1.89 (two s, 3 H), 0.7–1.8 (m, 9 H); mass spectrum *m/e* (rel %) 252 (1), 206 (<1), 147 (20), 106 (23), 91 (100), and 77 (8). Calcd for $C_{14}H_{20}O_2S$: 252.1184. Found: 252.1184.

Preparation of α-Methylthiocyclobutanecarboxylic Acid. In similar fashion, 120 mmol of LDA in 200 mL of THF was reacted with 5.0 g (50 mmol) of cyclobutanecarboxylic acid[26] in 10 mL of HMPA and 20 ml of THF at 0 °C for 2 h. After addition of 6.6 g (~7 mL, 70 mmol) of dimethyl disulfide and stirring at 0 ° for 30 min, workup and distillation at 125 °C (10 mm) gave 5.90 g (81%) of the desired sulfenylated acid: IR (CCl_4) 2400–3400, 1703, and 1299 cm^{-1}; NMR (CCl_4) δ 12.3 (b, 1 H), 2.65 (m, 2 H), 2.15 (m, 4 H), 2.14 (o, 3 H); mass spectrum *m/e* (rel %) 146 (50), 131 (55), 118 (100), 100 (19), and 73 (94). Calcd for $C_6H_{10}O_2S$: 146.0402. Found: 146.0401.

Preparation of α-Phenylthiocyclobutanecarboxylic Acid. In similar fashion, 60 mmol of LDA in 90 mL of THF was reacted with 2.5 g (25 mmol) of cyclobutanecarboxylic acid in 6.5 mL of HMPA for 2 h at 0 °C. After addition of a solution of 7.6 g (35 mmol) of diphenyl disulfide in 10 mL of THF and stirring at 0 °C for 45 min, workup and purification by column chromatography (solvent gradient from hexane to 5:1 hexane–acetone) gave 4.81 g (93%) of needles: mp 65.0–65.2 °C (from *n*-hexane); IR (CCl_4) 2400–3500, 1700, 1580, 1483, and 1295 cm^{-1}; NMR (CCl_4) δ 11.9 (b, 1 H), 7.2–7.4 (m, 5 H), 2.5–3.0 (m, 2 H), 1.8–2.5 (m, 4 H); mass spectrum *m/e* (rel %) 208 (22), 180 (28), 163 (15), 135 (100), 110 (34), and 91 (38). Calcd for $C_{11}H_{12}O_2S$: 208.0558. Found: 208.0561.

Preparation of Sulfenylated Ester 3. In similar fashion 0.95 mmol of LDA in 10 mL of THF was reacted with 180 mg (0.45 mmol) of ketal ester **2b** (vide infra) in 2 mL of THF at −25 °C for 2 h. After addition of 0.103 g (1.1 mmol) of dimethyl disulfide and stirring for 30 min at −25 °C and 45 min at 0 °C, workup gave 191 mg (98%) of product: mp 167.5–168.5 °C (from hexane); IR (CCl_4) 3060, 1725, and 1250 cm^{-1}; NMR (CCl_4) δ 5.18 (m, 1 H), 3.83 (s, 4 H), 3.67 (s, 3 H), singlets at δ 1.97, 1.40, 0.98, and 0.76 (3 H each) superimposed on m, 0.7–2.5 (20 H); mass spectrum *m/e* (rel %) 448 (4), 389 (1), 122 (6), 121 (7), 99 (100), 91 (12), and 55 (12). Calcd for $C_{26}H_{40}O_4S$: 448.2647. Found: 448.2664. Anal. ($C_{26}H_{40}O_4S$): C, H, S.

Preparation of Sulfenylated Acid 4. A solution of 140 mg (0.323 mmol) of the crude sulfenylated ester **3** and 170 mg (3.0 mmol) of potassium hydroxide in 3 mL of ethylene glycol was refluxed for 9 h. The reaction mixture was poured into water and washed with ether. The ether extract was discarded and chloroform added. The two-phase system was cooled to 0 °C and carefully acidified with 1 N sodium bisulfate with vigorous mixing. The water layer was extracted with additional chloroform, and the combined chloroform layers were dried, evaporated, and purified by PLC (2:1 hexane–acetone) to give 104 mg (77%) of desired acid: mp 129–134 °C, IR ($CHCl_3$) 2500–3500, 1697, and 1269 cm^{-1}; NMR ($CDCl_3$) δ 7.62 (b, 1 H), 5.32 (m, 1 H), 3.95 (s, 4 H), singlets at 2.11, 1.47, 1.00, 0.81 (3 H each) superimposed on multiplet 0.7–2.7 (20 H); mass spectrum *m/e* (rel %) 4.34 (<1), 386 (1), 249 (1), 99 (100), 94 (14), 91 (10), 57 (32), 56 (48), and 55 (20). Calcd for $C_{25}H_{38}O_4S$: 434.2491. Found: 434.2509. Anal. ($C_{25}H_{38}O_4S$): C, H, S.

Preparation of Sulfenylated Ester 8. In similar fashion, 3.0 mmol of LDA in 10 mL of dry THF was reacted with 710 mg (2.5 mmol) of methyl 4-(4′,4′-dimethoxycyclohexyl)cyclohexylcarboxylate[33] in 2 mL of dry THF at −78 °C for 30 min. After addition of 282 mg (3.0 mmol) of dimethyl disulfide at −25 °C and stirring for 30 min at −25 °C and 30 min at 0 °C, workup (extraction with chloroform) and recrystallization from ether gave 417 mg (51%) of **8**: mp 133–140 °C; IR (CCl_4) 1724 and 1279 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 3 H), 3.20 (s, 3 H), 3.13 (s, 3 H), 2.07 (s, 3 H), 0.9–2.8 (m, 18 H), mass spectrum *m/e* (rel %) 330 (<1), 300 (4), 299 (5), 284 (4), 283 (15), 251 (12), 250 (20), 158 (18), 149 (10), 111 (13), and 101 (100). Calcd for $C_{17}H_{30}O_4S$: 330.1845. Found: 330.1865.

Preparation of 4-(4′-Carboxy-4′-methylthiocyclohexyl)cyclohexanone. A solution of 200 mg (0.606 mmol) of **8** and 80 mg of potassium hydroxide in 5 mL of ethylene glycol was refluxed for 3 h. The solution was poured into ether and extracted with ether. The aqueous layer was then acidified to pH 1 with 1 N aqueous hydrochloric acid and extracted with chloroform. After drying and evaporation in vacuo, PLC (10:1 chloroform–methanol) purification gave 164 mg (quantitative) of desired keto acid as a mixture of stereoisomers: mp 139–140 and 167–169 °C; IR (KBr) 2300–3600, 1720, 1690, and 1298 cm^{-1}; NMR ($CDCl_3$) δ 2.03 and 2.10 (two s, 3 H), 0.9–2.6 (m, 18 H); mass spectrum *m/e* (rel %) 270 (7), 216 (11), 215 (17), 206 (40), 178 (16), 177 (27), 160 (15), 159 (19), 135 (14), 109 (20), 107 (25), 97 (28), and 81 (100). Calcd for $C_{14}H_{22}O_3S$: 270.1290. Found: 270.1290.

Oxidative Decarboxylations with *N*-Chlorosuccinimide (NCS). Of 2-Methylthio-2-(2′-naphthyl)propionic Acid. Preparation of β-Acetonaphthone. A mixture of 246 mg (1 mmol) of 2-methylthio-2-(2′-naphthyl)propionic acid and 103 mg (1.23 mmol) of anhydrous sodium bicarbonate in 2 mL of absolute ethanol was stirred for 10 min. Solid *N*-chlorosuccinimide (NCS, 295 mg, 2.20 mmol) was added in four portions and the reaction mixture stirred for 2 h at room temperature. A few drops of saturated aqueous sodium sulfite were added and this was followed by 2 mL of 1 N aqueous hydrochloric acid. Stirring continued for 30 min. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with saturated aqueous sodium bicarbonate solution, dried, evaporated in vacuo, and purified by PLC (chloroform) to give 135 mg (79%) of β-acetonaphthone, mp 55–56 °C (from hexane) (lit.[34] mp 56 °C).

A similar reaction in methanol from 100 mg (0.41 mmol) of sulfenylated acid and 120.9 mg (0.902 mmol) of NCS gave 51 mg (73%) of β-acetonaphthone. The basic water extract was acidified with 1 N aqueous hydrochloric acid and extracted with chloroform to give 9 mg (10%) of 2-methoxy-2-(2′-naphthyl)propionic acid; ir (CCl_4) 2500–3500, 2850, and 1715 cm^{-1}; NMR ($CDCl_3$) δ 7.85 and 7.50 (two m, 7 H), 3.31 (s, 3 H), 1.96 (s, 3 H); mass spectrum *m/e* (rel %)

186 (20), 171 (24), 170 (37), 155 (100), 127 (87), 99 (99), 77 (16), and 56 (86).

A similar reaction in 1 mL of *tert*-butyl alcohol from 52 mg (0.21 mmol) of sulfenylated acid, 30 mg (0.35 mmol) of sodium bicarbonate, and 60 mg (0.45 mmol) of NCS for 3 h gave 32 mg (62%) of a 1:1 mixture of (*E*)- and (*Z*)-2-chloro-1-methylthio-1-(2′-napthyl)ethylene: IR (CCl_4) 3090, 3020, 2950, 1600, 1565, and 1605 cm^{-1}; NMR (CCl_4) δ 7.33–7.90 (m, 7 H), 6.27 and 6.33 (two s, 1 H), 1.97 and 2.05 (two s, 3 H). Anal. ($C_{13}H_{11}ClS$): C, H.

Of Diphenylmethylthioacetic Acid. Preparation of Benzophenone. A similar reaction in 2 mL of dry *tert*-butyl alcohol utilizing 129 mg (0.50 mmol) of diphenylmethylthioacetic acid, 126 mg (3.0 mmol) of sodium bicarbonate, and 147 mg (1.7 mmol) of NCS at room temperature overnight gave, after the usual workup and purification, 62 mg (68%) of benzophenone whose IR and NMR spectra are identical with those of an authentic sample.

A similar reaction in 2 mL of absolute ethanol utilizing 100 mg (0.39 mmol) of diphenylmethylthioacetic acid, 100 mg (1.2 mmol) of sodium bicarbonate, and 150 mg (1.12 mmol) of NCS gave, after the usual workup and purification, 24.1 mg (34%) of benzophenone and 31.6 mg (34%) of diphenylethoxyacetic acid: IR (CCl_4) 1720, 1498, and 698 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (b, 10 H), 3.23 (q, J = 6.8 Hz, 2 H), 1.20 (t, J = 6.8 Hz, 3 H); mass spectrum *m/e* (rel %) 212 (5), 211 (30), 183 (28), 182 (14), 165 (15), 105 (100), and 77 (62).

Of Acid 1. Preparation of 4-(4′,4′-Ethylenedioxycyclohexyl)cyclohexanone. A similar reaction in 2 mL of absolute ethanol utilizing 100 mg (0.32 mmol) of **1**, 84 mg (0.96 mmol) of sodium bicarbonate, and 100 mg (0.70 mmol) of NCS for 1.5 h at room temperature gave after workup and PLC purification (3:1 chloroform–ethyl acetate) 59 mg (78%) of the desired monoketal ketone: mp 93–96 °C; IR (CCl_4) 1720 and 852 cm^{-1}; NMR (CCl_4) 3.84 (s, 4 H), 1.1–2.4 (m, 18 H); mass spectrum (rel %) 238 (6), 167 (20), 141 (6) 99 (100), 86 (40), 55 (37). Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1561.

A similar reaction in 2 mL of *tert*-butyl alcohol utilizing 100 mg (0.315 mmol) of **1**, 79.4 mg (0.95 mmol) of sodium bicarbonate, and 89.6 mg (0.662 mmol) of NCS for 2 h at room temperature gave after the usual workup and PLC purification (2:1) (hexane–acetone) 9.0 mg (11%) of 4-(3′-chloro-4′-methylthiocyclohex-3′-enyl)cyclohexanone in the neutral fraction: IR (CCl_4) 1725 and 1625 cm^{-1}; NMR (CCl_4) δ 2.27 (s, 3 H) superimposed on m, 1.2–2.5 (16 H); mass spectrum *m/e* (rel %) 260 (10), 258 (27), 222 (14), 209 (11), 194 (11), 193 (13), 175 (24), 160 (20), 158 (46), 136 (25), 134 (65), 119 (95), 117 (100), 99 (78), and 91 (83). Calcd for $C_{13}H_{19}OClS$:[35] 258.0845. Found: 258.0856.

Of 4-(4′-Carboxy-4′-methylthiocyclohexyl)cyclohexanone. Preparation of 4,4′-Bicyclohexanone. A similar reaction in 3 mL of absolute ethanol utilizing 110 mg (0.42 mmol) of sulfenylated acid, 50 mg (0.60 mmol) of sodium bicarbonate, and 110 mg (0.88 mmol) of NCS for 3 h at room temperature gave after the usual workup and PLC purification (3:1 chloroform and ethyl acetate) 61 mg (75%) of product, mp 113–114 °C (lit.[35] mp 114–115 °C). IR and NMR spectra were identical with those of an authentic sample.

Of Sulfenylated Acid 4. Preparation of Progesterone. A similar reaction in 2 mL of absolute methanol utilizing 43 mg (0.10 mmol) of acid **4**, 25 mg (0.30 mmol) of sodium bicarbonate, and 32 mg (0.24 mmol) of NCS was allowed to proceed for 4 h at room temperature. After addition of 0.5 mL of 1 N aqueous sodium sulfite solution, 2 mL of 2 N aqueous hydrochloric acid solution, and 5 mL of THF, the mixture was allowed to stir for 18 h to ensure hydrolysis of both ketals. Normal workup and PLC purification (2:1 hexane–acetone) gave 19 mg (60%) of progesterone, mp 123.0–123.5 °C (from hexane, lit.[36] mp 121–122 °C), whose IR and NMR spectra were identical with those of an authentic sample.

Of α-Methylthiocyclobutanecarboxylic acid. Preparation of Cyclobutanone Diethyl Ketal. A mixture of 3.70 g (25.3 mmol) of the sulfenylated acid and 6.39 g (76.1 mmol) of anhydrous sodium bicarbonate was vigorously stirred for 30 min and then 8.14 g (60.7 mmol) of NCS was added in ten portions at room temperature. After 18 h, the reaction mixture was quenched by addition of 20 mL of 1 N aqueous sodium sulfite solution, poured into 200 mL of water, and extracted with 3:1 pentane–ether. After drying ($MgSO_4$) the solvents were removed by distillation through a Vigreux column and the residue vacuum distilled at 62–63 °C (62 mm) (lit.[37] bp 138–141 °C) to give 1.80 g (50%) of 1,1-diethoxycyclobutane: NMR (CCl_4) δ 3.28 (q, J = 8 Hz, 4 H), 2.04 (~t, J = 8 Hz, 8 H), 1.67 (~quint, J = 8 Hz, 2 H), 1.13 (t, J = 8 Hz, 6 H).

Of 2-Benzyl-3-methyl-2-methylthiobutanoic Acid. Preparation of Benzyl Isopropyl Ketone. A similar reaction in 3 mL of absolute methanol utilizing 100 mg (0.42 mmol) of α-sulfenylated acid (vide infra), 105 mg (1.26 mmol) of anhydrous sodium bicarbonate, and 135 mg (1.01 mmol) of NCS at room temperature for 16 h gave, after the usual workup and PLC purification (chloroform), 54.3 mg (80%) of benzyl isopropyl ketone: IR (CCl_4) 1712, 1600, 1490, 1383, 1365, and 693 cm^{-1}; NMR (CCl_4) δ 7.0–7.3 (m, 5 H), 3.60 (s, 2 H), 2.60 (heptet, J = 7 Hz, 1 H), 1.04 (d, J = 7 Hz, 6 H); mass spectrum *m/e* (rel %) 162 (6), 91 (53), 71 (54), and 43 (100). Calcd for $C_{11}H_{14}O$: 162.1045. Found: 162.1047.

Of 2-Isobutyl-5,9-dimethyl-2-methylthiodec-8-enoic Acid. Preparation of 2,7,11-Trimethyldodec-10-en-4-one. A similar reaction in 15 mL of absolute methanol utilizing 399 mg (1.33 mmol) of α-sulfenylated acid (vide infra), 335 mg (3.99 mmol) of anhydrous sodium bicarbonate, and 427 mg (3.18 mmol) of NCS for 2 h at room temperature gave, after the usual workup and PLC purification (2:1 hexane–acetone), 194 mg (66%) of the desired enone: IR (CCl_4) 1720, 1650, 1382, and 1372 cm^{-1}; NMR (CCl_4) δ 5.12 (t, J = 7 Hz, 1 H), 2.1–2.4 (m, 4 H), 1.8–2.1 (m, 2 H), 1.68 (s, 3 H), 1.62 (s, 3 H), 1.1–1.5 (m, 6 H), 0.91 (d, J = 6 Hz, 6 H), 0.89 (d, J = 6 Hz, 3 H); mass spectrum *m/e* (rel %) 224 (21), 122 (24), 113 (32), 109 (20), 107 (22), 85 (77), 81 (40), 69 (90), and 57 (100). Calcd for $C_{15}H_{28}O$: 224.2140. Found: 224.2143.

Preparation of 7-*anti*-Methoxymethylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid. Freshly distilled cyclopentadiene (16.4 mL, 0.20 mol) was added via a dry ice jacketed dropping funnel into 4.6 g (0.20 mol) of sodium dispersion in 80 mL of dry THF at 0 °C over a 30-min period under nitrogen. After 4 h at 0 °C, the solution of cyclopentadienylsodium was decanted via a cannula into a solution of 16 mL (0.2 mol) of chloromethyl methyl ether in 16 mL of THF over 1.5 h at −55° to −60 °C. Unreacted sodium (0.53 g) was recovered. After stirring for an additional 40 min, 80 mL of freshly distilled acrylic acid was added to this solution over a 2–3-min period at −55 °C. The reaction continued at this temperature for 40 min and the mixture was left to stand for 18 h in a freezer (−7 °C). It was poured into saturated aqueous sodium chloride (150 mL) and extracted twice with ether (100 and 50 mL) and twice with chloroform (50 and 50 mL). The combined organic layers were dried over $MgSO_4$ and distilled in vacuo to give two fractions, bp 122–129 °C (0.05 mm) (2.1 g, 6.6%) and bp 129–135 °C(0.05–1.0 mm) (24.8 g, 77.5%), for a total yield of 84%. The yields are based upon the amount of sodium consumed. NMR ($CDCl_3$) δ ~10 (1 H, s), 6.1 (2 H, m), 2.7–3.5 (5 H, m) with 3 H, s, superimposed at 3.3, 2.1 (2 H, m), 1.5 (1 H, m); mass spectrum *m/e* (rel %) 182 (4), 164 (3), 150 (24), 110 (60), 109 (30), 105 (22), 95 (24), 91 (25), 84 (23), 80 (35), 79 (50), 78 (47), 77 (25) and 45 (100). Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0942. It was converted to the methyl ester with diazomethane for further characterization. IR (CCl_4) 1735 (s), 1455 (m), 1435 (m), 1350 (m), 1330 (m), 1270 (m), 1190 (s), 1175 (s), 1125 (s), 1095 (s), and 855 cm^{-1} (s); NMR δ 6.00 (m, pseudo dd, J = 6, 3 Hz), 5.75 (m, pseudo dd, J = 6, 3 Hz), 3.76 (s, 3 H), 3.19 (s, 3 H), 3.15 (d, J = 8 Hz, 2 H), 2.92 (dd, J = 8, 4 Hz), 1 H), 2.77 (m, 2 H), 1.8–2.1 (m, 2 H), 1.4 (dd, J = 12, 4 Hz, 1 H).

Direct Sulfenylation and Oxidative Decarboxylation. Preparation of 2-*anti*-Methoxymethylbicyclo[2.2.1]hept-5-en-2-one. Part A. Sulfenylation. Into a well-stirred and cooled (0 °C) mixture of 6.06 g (60 mmol) of diisopropylamine in 100 mL of dry THF under nitrogen was syringed 41.4 mL (60 mmol) of a 1.45 N solution of *n*-butyllithium in hexane over 10 min. After stirring for 30 min, 4.55 g (25 mmol) of 7-*anti*-methoxymethylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid in 30 mL of dry THF containing 5.38 g (30 mmol) of HMPA was added over a 10-min period and the resultant solution was stirred for 3.5 h at 0 °C. The reaction mixture was poured into ice water and extracted with ether. The water layer was acidified to pH 1 with 1 N hydrochloric acid in the cold (0 °C), saturated with sodium chloride, and extracted with ether. Evaporation of solvent left the crude product which was utilized directly in the next step.

An aliquot from one run was further purified by PLC (2:1 hexane–acetone) to give an 80% yield of pure sulfenylated acid: IR (CCl_4) 2500–3300, 1695, 1290, 1270, 1210, 1127, and 1100 cm^{-1}; NMR (CCl_4) δ 6.10 (m, 1 H), 5.99 (m, 1 H), 3.24 (s, 3 H), 3.2 (d, J = 8 Hz, 2 H), 2.99 (bs, 1 H), 2.76 (m, 2 H), 2.16 (s, 3 H), 2.02 (m, 2 H), 1.82 (dd, J = 13, 3 Hz); mass spectrum *m/e* (rel %) 228 (2), 196 (4), 148 (12), 118 (11), 110 (70), 109 (20), 80 (30), 79 (37), 78 (32), 77 (22),

and 45 (100). Calcd for $C_{11}H_{16}O_3S$: 228.0820. Found: 228.0806.

Part B. Oxidative Decarboxylation. The crude sulfenylated acid from the above reaction was neutralized with 6.3 g (75 mmol) of sodium bicarbonate in 60 mL of anhydrous ethanol under nitrogen. Solid *N*-chlorosuccinimide (7.04 g, 52.5 mmol) was added in six portions while cooling with a water bath. After stirring for an additional 2 h at room temperature, 5 mL of saturated aqueous sodium sulfite, 70 mL of 1.2 N hydrochloric acid, and 20 mL of ether were added and stirring continued for 5 h. The reaction mixture was poured into 200 mL of water and, after saturation with sodium chloride, extracted with three protions (100, 50, and 50 mL) of ether and three portions (50, 20, and 20 mL) of chloroform. After drying ($MgSO_4$), the organic layer was distilled to remove solvent and subsequently to give 2.883 g (76.2% overall yield) of product, bp 72–87 °C (2 mm). Redistillation gave 2.30 g (81.2% recovery) of colorless oil, bp 82–83 °C (2.4 mm), which consisted of >97% of desired product by VPC analysis. The IR and NMR spectra are identical with those of an authentic sample.[12h,38]

Oxidative Decarboxylation of 16 in *tert*-Butyl Alcohol. In usual fashion, a mixture of 415 mg (1.82 mmol) of **16,** 336 mg (4.00 mmol) of anhydrous sodium bicarbonate, and 537 mg (4.00 mmol) of NCS in 12 mL of anhydrous *tert*-butyl alcohol upon reaction for 21 h gave, after quenching with 2 mL of 1 N aqueous sodium sulfite solution and immediate extraction with ether, 168 mg (64%) of 7-*anti*-methoxymethylbicyclo[2.2.1]hept-5-en-2-one after PLC purification (2:1 hexane–acetone). The reaction mixture remained basic throughout.

Preparation of Bicyclo[2.2.2]oct-5-en-2-one. Following the direct sulfenylation–oxidative decarboxylation procedure, 3.20 g of crude sulfenylated acid (from 15.9 mmol of 2-carboxybicyclo[2.2.2]oct-5-ene), 4.03 g (48 mmol) of anhydrous sodium bicarbonate, and 4.70 g (35.2 mmol) of NCS gave after a reaction time of 25 min and the usual workup (pentane for extraction) and distillation at 70 °C (10 mm) (lit.[12a] bp 84–86 °C (13 mm)) 852 mg (44% overall from 2-carboxybicyclo[2.2.2]oct-5-ene) desired enone as a waxy solid.

Oxidative Decarboxylations with Sodium Metaperiodate. Of 2-Methylthiopalmitic Acid. Preparation of Pentadecanal Dimethyl Acetal. Sodium metaperiodate was ground into a fine powder utilizing a mortar and pestle. A mixture of 500 mg (1.65 mmol) of the sulfenylated acid and 530 mg (2.50 mmol) of finely ground sodium metaperiodate in 30 mL of anhydrous methanol was stirred at room temperature for 21 h. During this time, a sticky precipitate appeared on the wall of the reaction vessel. Addition of 3 mL of 1 N aqueous sodium sulfite solution quenched the reaction mixture which was then poured into 150 mL of saturated aqueous sodium chloride solution. Extraction with three portions of ether, followed by drying ($MgSO_4$), concentration in vacuo, and distillation (bath temperature 120–130 °C (0.3 mm)) gave 242 mg (54%) of 1,1-dimethoxypentadecane: IR (CCl_4) 2855, 1460, 1245, 1120, and 860 cm^{-1}; NMR (CCl_4) δ 4.22 (t, J = 6 Hz, 1 H), 3.20 (s, 6 H), 1.28 (m, 26 H), and 0.88 (t, J = 5 Hz, 3 H); mass spectrum *m/e* (rel %) 272 (<1), 241 (8), 97 (7), 83 (9), 75 (100), 71 (21), and 57 (17).

Of 2-Methylthio-3-phenylheptanoic Acid. Preparation of 2-Phenylhexanal Dimethyl Acetal. A similar reaction utilizing 770 mg (3.06 mmol) of sulfenylated acid and 980 mg (4.58 mmol) of sodium metaperiodate in 50 mL of absolute methanol at room temperature for 21 h gave, after the usual workup and PLC purification (2:1 hexane–acetone), 323 mg (53%) of the desired acetal: IR (CCl_4) 2820, 1600, 1495, 1110, 1080, 1060, and 693 cm^{-1}; NMR (CCl_4) δ 7.16 (ps, 5 H), 4.29 (d, J = 7 Hz, 1 H), 3.28 (s, 3 H), 3.11 (s, 3 H), 2.76 (m, 1 H), 0.9–2.0 (m, 6 H), 0.81 (t, J = 7 Hz, 3 H); mass spectrum *m/e* (rel %) 222 (<1), 191 (17), 147 (10), 105 (12), 92 (60), 76 (21), and 75 (100). Calcd for $C_{14}H_{22}O_2$: 22.1620. Found: 22.1625.

Of Sulfenylated Acid 1. Preparation of 4-(4′,4′-Dimethoxycyclohexyl)cyclohexanone Ethylenedioxy Ketal. A similar reaction utilizing 50 mg (0.16 mmol) of **1** and 40.9 mg (0.192 mmol) of finely ground sodium metaperiodate in 2 mL of absolute methanol for 18 h at room temperature gave after the usual workup and PLC purification (2:1 hexane–acetone) 34 mg (75%) of 4,4-dimethoxy-4′,4′-ethylenedioxy-1,1′-bicyclohexane: IR (CCl_4) 2960, 1445, 1375, 1110, 1065, and 920 cm^{-1}; NMR (CCl_4) δ 3.84 (s, 4 H), 3.10 (s, 3 H), 3.05 (s, 3 H), 1.1–2.1 (m, 18 H); mass spectrum *m/e* (rel %) 284 (<1), 237 (2), 194 (2), 167 (4), 141 (2), 99 (100), 86 (15), and 55 (17). Calcd for $C_{16}H_{28}O_4$: 284.1988. Found: 284.1986.

Of 13-Chloro-2-methylthiotridecanoic Acid. Preparation of 12-Chlorododecanal Dimethyl Acetal. A similar reaction utilizing 50 mg (0.17 mmol) of 13-chloro-2-methylthiotridecanoic acid (vide infra) and 55 mg (0.25 mmol) of powdered sodium metaperiodate in 4 mL of absolute methanol at room temperature for 18 h gave, after the usual workup and PLC purification (benzene), 23.1 mg (51%) of the desired acetal: IR (CCl_4) 2960, 2890, 1460, 1200, 1140, and 1070 cm^{-1}; NMR (CCl_4) δ 4.20 (t, J = 6 Hz, 1 H), 3.42 (t, J = 7 Hz, 2 H), 3.21 (s, 6 H), 1.7 (m) and 1.30 (b, 20 H); mass spectrum *m/e* (rel %) 264 (<1), 174 (8), 129 (8), 109 (9), 97 (20), 95 (20), 83 (32), 82 (34), 81 (24), 73 (33), 69 (47), and 55 (100). Calcd for $C_{14}H_{29}O_2Cl$: 264.1856. Found: 264.1849.

Alkylations of the Dianion of α-Methylthiocarboxylic Acids. Preparation of 2-Methylthio-4-methylpentanoic Acid. To a solution of 57.6 mmol of LDA in 30 mL of dry THF at 0 °C was added dropwise and rather slowly (about 15 min) 2.64 g (25.0 mmol) of 2-methylthioacetic acid[39] in 30 mL of dry HMPA. After 2.5 h at 0 °C, the reaction mixture was cooled to −20 °C and then 4.6 g (33.5 mmol) of isobutyl bromide was added all at once. After 4 h at −20 °C and 16 h at room temperature, the reaction mixture was poured into water and diluted with 30 mL of saturated aqueous sodium carbonate solution. The aqueous layer was extracted with ether and the ether washing discarded. The water layer was acidified to pH 1 with concentrated hydrochloric acid and extracted three times with ether. After addition of *n*-hexane to the ether layer resulting in about a 5:1 ether–hexane mixture, the organic phase was washed twice with water to remove HMPA. After drying ($MgSO_4$), concentration in vacuo, and distillation at 110–114 °C (22 mm), 3.21 g (80%) of the desired acid was obtained: IR (CCl_4) 2400–3400, 1709, 1375, 1392, and 1288 cm^{-1}; NMR (CCl_4) δ 12.07 (b, 1 H), 3.10 (dd, J = 8.0, 6.5 Hz, 1 H), 2.14 (s, 3 H), 1.3–2.0 (m, 3 H), 0.95 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), mass spectrum *m/e* (rel %) 162 (35), 114 (25), 106 (100), 105 (54), and 69 (59). Calcd for $C_7H_{14}O_2S$: 162.0715. Found: 162.0711.

Preparation of 2-Methylthio-13-chlorotridecanoic Acid. Into a solution of 11.0 mmol of the dianion of methylthioacetic acid in 17 mL of THF and 20 mL of HMPA generated in the usual way, 4.20 g (13.2 mmol) of 1-chloro-11-iodoundecane in 3 mL of HMPA was added over a 5-min period at −78 °C. After stirring at −78 °C for 2 h and 0 °C for 1 h, it was worked up in the usual way and purified by recrystallization from *n*-hexane to give 2.24 g (69%) of desired acid: mp 57–58 °C; IR (CCl_4) 2500–3400 and 1706 cm^{-1}; NMR (CCl_4) δ 12.01 (b, 1 H), 3.47 (t, J = 7 Hz, 2 H), 3.09 (bt, J = 7 Hz, 1 H), 2.18 (bs, 3 H), 1.8 (m, 4 H), 1.32 (b, 16 H). The signals at δ 3.09 and 2.18 showed a strong dependence upon conditions for recording the NMR spectrum. At times, these signals became very broad indicating some type of exchange process. Mass spectrum *m/e* (rel %) 294 (23), 251 (29), 249 (79), 235 (25), 233 (66), 122 (11), 106 (100), 83 (39), 81 (29), 73 (61), 69 (49), 67 (30), and 61 (72). Calcd for $C_{14}H_{27}O_2SCl$: 294.1400. Found: 294.1400.

Preparation of 3-Methyl-2-methylthiobutanoic Acid. Into a solution of 24 mmol of the dianion of methylthioacetic acid (generated utilizing 57.6 mmol of LDA) in 30 mL of dry THF and 30 mL of dry HMPA, was added at −30 °C 5.71 g (33.6 mmol) of 2-iodopropane. After 30 min at −30 °C and 30 min at room temperature, the usual workup and distillation at 107 °C (2.0 mm) gave 2.14 g (58%) of desired product: IR (CCl_4) 2400–3400, 1710, 1399, and 1379 cm^{-1}; NMR (CCl_4) δ 11.75 (b, 1 H), 2.81 (d, J = 9.5 Hz), 2.16 (s, 3 H), 2.1 (m, 1 H), 1.12 (d, J = 6.5 Hz, 3 H), 1.09 (d, J = 6.5 Hz, 3 H); mass spectrum *m/e* (rel %) 148 (91), 106 (95), 103 (100), 101 (30), 88 (99), 69 (46), 62 (46), and 57 (97). Calcd for $C_6H_{12}O_2S$: 148.0558. Found: 148.0559.

Preparation of 6-Chloro-2-methylthiohexanoic Acid. Into a solution of 15 mmol of the dianion of methylthioacetic acid in 18 mL of THF and 24 mL of HMPA cooled to −78 °C was added 3.94 g (18 mmol) of 1-chloro-4-iodobutane. After 2 h at −78 °C and 1 h at 0 °C, the usual workup and column chromatography (hexane to 5:2 hexane–acetone) gave 2.88 g (97%) of the desired acid which is very unstable and utilized immediately: IR (CCl_4) 2400–3400, 1710, and 1290 cm^{-1}; NMR (CCl_4) δ 11.12 (b, 1 H), 3.51 (t, J = 6 Hz, 2 H), 3.12 (t, J = 6 Hz, 1 H), 2.19 (s, 3 H), 1.8 (m, 6 H).

Cyclization of 6-Chloro-2-methylthiohexanoic Acid. A solution of 196 mg (1 mmol) of 6-chloro-2-methylthiohexanoic acid in 2 mL of HMPA was added over a 30-min period to a solution of 2.4 mmol of LDA in 2 mL of THF at 0 °C. After an additional 2.5 h at 0 °C and 2 h at room temperature, the usual workup and PLC purification (2:1 hexane–acetone) gave 96 mg (60%) of 1-methylthiocyclopentane-1-carboxylic acid and 22 mg (20%) of cyclopentene-1-carboxylic acid,

mp 119.5–119.8 °C (lit.[40] mp 123–124 °C).

Preparation of 2-Benzyl-2-methylthio-3-methylbutanoic Acid. To a solution of 5.0 mmol of the dianion of 3-methyl-2-methylthiobutanoic acid generated in the usual way with 12.0 mmol of LDA in 10 mL of THF and 6 mL of HMPA at 0 °C and then cooled to −78 °C was added 886 mg (7.0 mmol) of benzyl chloride in 1 mL of HMPA. After stirring at −78 °C for 1 h and −25 °C for 2 h, normal workup and PLC purification (2:1 hexane–acetone) gave 744 mg (63%) of crystalline product: mp 101.5–102 °C (hexane); IR (CCl_4) 2400–3400, 1690, 1600, 1495, 1275, and 710 cm^{-1}; NMR (CCl_4) δ 11.89 (b, 1 H), 7.1–7.4 (m, 5 H), 3.24 (d, J = 15 Hz, 1 H), 3.06 (d, J = 15 Hz, 1 H), 2.10 (heptet, J = 7 Hz, 1 H), 1.97 (s, 3 H), 1.08 (d, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H); mass spectrum *m/e* (rel %) 238 (10), 147 (100), 103 (43), 101 (38), 91 (73), and 55 (24). Calcd for $C_{13}H_{18}O_2S$: 238.1028. Found: 238.1035.

Preparation of 2-Isobutyl-5,9-dimethyl-2-methylthiododec-8-enoic Acid. To a solution of 2.51 mmol of the dianion of 2-methylthio-4-methylpentanoic acid (generated utilizing 6.02 mmol of LDA) in 4 mL of THF and 5 mL of HMPA cooled to −25 °C was added 935 mg (3.51 mmol) of citronellyl iodide in 1 mL of HMPA. After 1.5 h at −25 °C and 2.5 h at room temperature, the usual workup and PLC purification (2:1 hexane–acetone) gave 536 mg (71%) of the desired acid: IR (CCl_4) 2400–3400, 1697, and 1660 cm^{-1}; NMR (CCl_4) δ 11.8 (b, 1 H), 5.09 (t, J = 7 Hz, 1 H), 2.04 (s, 3 H), 1.70 (s, 3 H), 1.63 (s, 3 H), 1.0–2.0 (m, 12 H), 1.0 (d, J = 7 Hz), 0.94 (d, J = 7 Hz, 6 H); mass spectrum *m/e* (rel %) 300 (8), 209 (10), 162 (11), 124 (11), 109 (76), 82 (20), 81 (33), 69 (100), and 55 (32). Calcd for $C_{17}H_{32}O_2S$: 300.2123. Found: 300.2133.

Synthesis of Juvabione. Ketalization of Perillaldehyde. A solution of 10 g (66.7 mmol) of perillaldehyde and 8.32 g (80.0 mmol) of 2,2-dimethyl-1,3-propanediol in 200 mL of benzene containing 50 mg of *p*-toluenesulfonic acid was refluxed with azeotropic removal of water for 2.5 h. The reaction mixture was poured into an aqueous solution of sodium bicarbonate and sodium chloride. After extraction with ether, the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo, and the residue was distilled at 95–98 °C (0.4 mm) to give 12.3 g (78%) of **26:** IR (CCl_4) 1645, 1395, 1373, 1365, and 885 cm^{-1}; NMR (CCl_4) δ 5.72 (m, 1 H), 4.68 (s, 2 H), 4.56 (s, 1 H), 3.58 (d, J = 10 Hz, 2 H), 3.38 (d, J = 10 Hz, 2 H), 1.76 (s, 3 H), 1.5–2.3 (m, 7 H), 1.20 (s, 3 H), 0.74 (s, 3 H); mass spectrum *m/e* (rel %) 236 (61), 208 (38), 167 (41), 151 (20), 150 (23), 141 (23), 121 (30), 115 (100), and 107 (46). Calcd for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1778.

Preparation of Alcohol 27a. Disiamylborane was prepared in situ by addition of 33.5 mL (33.5 mmol) of a 1 M borane solution in THF to 4.69 g (67.0 mmol) of 2-methyl-2-butene in 10 mL of dry THF at 0 °C. Ketal **26** (6.08 g, 25.8 mmol) in 3 mL of dry THF was added in one portion. After 15 h at 0 °C, 10.1 mL of 3 N aqueous sodium hydroxide solution and 10.1 mL of 30% aqueous hydrogen peroxide solution were added during which time the temperature was maintained under 45 °C. Upon completion of the addition, the reaction mixture was kept at 40–45 °C for 1.5 h, poured into an aqueous solution of sodium bicarbonate and sodium chloride, and thoroughly extracted with ether. After drying ($MgSO_4$) and concentration in vacuo, the residue distilled at 130 °C (bath temperature) at 0.02 mm (Kugelrohr) to give 5.70 g (87%) of alcohol **27a:** IR (CCl_4) 3630, 3450, 1394, and 1366 cm^{-1}; NMR (CCl_4) δ 5.86 (m, 1 H), 4.70 (s, 1 H), 3.57 (d, J = 12 Hz, 2 H), 3.37 (d, J = 12 Hz, 2 H), 3.3–3.5 (m, 3 H), 1.3–2.3 (m, 8 H), 1.24 (s, 3 H), 0.94 and 0.92 (two d, J = 6 Hz, 3 H), 0.76 (s, 3 H); mass spectrum *m/e* (rel %) 254 (56), 195 (24), 159 (13), 158 (16), 157 (15), 141 (23), 115 (56), 109 (64), 107 (22), 93 (23), 81 (40), and 69 (100). Calcd for $C_{15}H_{28}O_3$: 254.1882. Found: 254.1895.

Preparation of Tosylate 27b. A solution of 7.0 g (27.6 mmol) of acetal alcohol **27a** in 100 mL of dry THF was treated with 20.9 mL (30.4 mmol) of a 1.45 N solution of *n*-butyllithium in hexane at −78 °C. After 30 min, 5.78 g (30.4 mmol) of *p*-toluenesulfonyl chloride in 12 mL of dry THF was added over a 30-min period. The dry ice bath was replaced with an ice bath and stirring continued for 2 h. The reaction mixture was poured into an aqueous solution of sodium bicarbonate and sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give an oil. Purification by column chromatography eluting a solvent gradient beginning with hexane and terminating with 5:2 hexane in ether gave 9.41 g (84%) of tosylate **27b:** IR (CCl_4) 1600, 1500, 1395, 1375, 1190, 1180, and 1103 cm^{-1}; NMR (CCl_4) δ 7.78 (d, J = 8 Hz, 2 H), 7.34 (d, J = 8 Hz, 2 H), 5.84 (b, 1 H), 4.68 (s, 1 H), 3.94 (bd, $J \sim 4$ Hz, 2 H), 3.65 (d, J = 11 Hz, 2 H), 3.47 (d, J = 11 Hz, 2 H), 2.48 (s, 3 H), 1.4–2.2 (m, 8 H), 1.22 (s, 3 H), 0.87 and 0.85 (two d, J = 6 Hz, 3 H), 0.76 (s, 3 H). Calcd for $C_{22}H_{32}O_5S$: 408.1970. Found: 408.1976.

Preparation of Iodide 28. A mixture of 1.00 g (2.45 mmol) of tosylate **27b** and 4.00 g (26.7 mmol) of anhydrous sodium iodide in 20 mL of acetone (freshly distilled over anhydrous potassium carbonate) containing a small amount of calcium carbonate was stirred for 17 h at room temperature. After pouring into an aqueous solution of sodium bicarbonate and sodium chloride, extraction with ether, drying ($MgSO_4$) of the ethereal extract, and concentration in vacuo, 873 (97%) of an oil was obtained and subsequently distilled in a Kugelrohr apparatus (90–98 °C, 0.03 mm) to give 800 mg of pure iodide: IR (CCl_4) 2950, 2840, 1460, 1390, 1380, 1363, and 1100 cm^{-1}; NMR (CCl_4) δ 5.74 (b, 1 H), 4.56 (s, 1 H), 3.53 (d, J = 11 Hz, 2 H), 3.35 (d, J = 11 Hz, 2 H), 3.24 (m, 2 H), 1–2.3 (m, 8 H), 1.18 (s, 3 H), 0.99 and 0.97 (two d, J = 7 Hz, 3 H), 0.72 (s, 3 H); mass spectrum *m/e* (rel %) 364 (2), 363 (4), 237 (100), 127 (40), 123 (21), 115 (19), 109 (17), 107 (15), 81 (42), and 69 (56). Calcd for $C_{15}H_{25}O_2I$: 364.0901. Found: 364.0901.

Preparation of Acid 29. As described above in alkylations, a solution of 1.56 mmol of the dianion of 2-methylthio-4-methylpentanoic acid (generated utilizing 3.12 mmol of LDA) and 473 mg (1.30 mmol) of iodide **28** in 5 mL of THF and 5 mL of HMPA was reacted for 15 h at room temperature. After the usual workup except utilizing 1 N aqueous sodium bisulfate at 0 °C for acidification, PLC purification (2:1 hexane–acetone) gave 197 mg (46%) of pure acid **29:** IR (CCl_4) 2400–3500, 1690, 1390, 1365, and 1100 cm^{-1}; NMR (CCl_4) δ 11.3 (b, 1 H), 5.80 (b, 1 H), 4.62 (s, 1 H), 3.58 (d, J = 11 Hz 2 H), 3.39 (d, J = 11 Hz, 2 H), 2.01 and 1.97 (two s, 3 H), 1–2.4 (m, 13 H), 1.17 (s, 3 H), 0.97 (d, J = 6 Hz, 9 H), 0.72 (s, 3 H); mass spectrum *m/e* (rel %) 398 (41), 351 (30), 195 (100), 193 (55), 136 (74), 115 (48), 109 (100), 107 (61), and 69 (81). Calcd for $C_{22}H_{38}O_4S$: 398.2490. Found: 398.2488.

Preparation of Keto Aldehyde 30. In the usual way for oxidative decarboxylations, 57 mg (0.14 mmol) of acid **29,** 50 mg (0.60 mmol) of anhydrous sodium bicarbonate, and 48 mg (0.36 mmol) of NCS in 3 mL of aboslute methanol at room temperature for 3 h gave, after normal workup and PLC purification (2:1 hexane–acetone), 20 mg of aldehyde **30** and 19 mg of its acetal, the latter being converted to **30** upon further reaction with aqueous hydrochloric acid (total yield 96%). **30:** IR (CCl_4) 2700, 1720, 1695, 1650, 1385, and 1372 cm^{-1}; NMR (CCl_4) δ 9.42 (s, 1 H), 6.72 (m, 1 H), 1–2.6 (m, 13 H), 0.93 (d, J = 7 Hz, 6 H), 0.89 (d, J = 8 Hz, 3 H); mass spectrum *m/e* (rel %) 236 (<1), 235 (<1), 179 (4), 136 (100), 127 (16), 109 (16), 107 (14), 85 (28), 79 (18), 58 (20) and 57 (48). Acetal of **30:** IR (CCl_4) 1720, 1390, 1360, 1100 and 860 cm^{-1}; NMR (CCl_4) δ 5.72 (m, 1 H), 4.55 (s, 1 H), 3.55 (d, J = 11 Hz, 2 H), 3.35 (d, J = 11 Hz, 2 H), 1–2.4 (m, 13 H), 1.16 (s, 3 H), 0.9 (m, 9 H), 0.69 (s, 3 H); mass spectrum *m/e* (rel %) 322 (1), 222 (41), 136 (100), 109 (46), 107 (28), 101 (20), 85 (28), 81 (30), and 69 (46). Calcd for $C_{20}H_{34}O_3$: 322.2508. Found: 322.2501.

Preparation of Juvabione. To a solution of 24.9 mg (0.101 mmol) of aldehyde **30** in 3 mL of absolute methanol were added 36.9 mg (0.75 mmol) of sodium cyanide, 260 mg (2.92 mmol) of manganese dioxide, and 14 mL of acetic acid sequentially. After stirring at room temperature for 5 h, the reaction mixture was filtered through super cel and the latter washed with ether. The combined organic solutions were washed with an aqueous solution of sodium chloride containing 240 mg of potassium hydroxide. After drying ($MgSO_4$) and concentration, the oil was treated with 0.5 mL of 2% aqueous hydrochloric acid solution and 2 mL of THF for 40 min at room temperature. The reaction mixture was diluted with ether and washed with an aqueous solution of sodium chloride and sodium bicarbonate. Purification by TLC (2:1 hexane–acetone) gave 23.8 mg (85%) of pure juvabione and epijuvabione. The spectral data agree perfectly with the published data.[29]

Preparation of Acid 32. Neat dimethyl isobutylmalonate (609 mg, 3.24 mmol) was added dropwise over a 10-min period to a suspension of 136 mg (3.24 mmol) of 57% mineral oil dispersion of sodium hydride in 2 mL of freshly distilled DMF. After 1.5 h, 1.10 g (2.7 mmol) of tosylate **27b** dissovled in 1.5 mL of dry DMF was added at room temperature and stirring continued for 16 h at 60 °C and 15 h at 100 °C. The reaction mixture was poured into 50 mL of an aqueous solution of sodium chloride and sodium bicarbonate, extracted with ether, dried ($MgSo_4$), and concentrated in vacuo to give 1.029 g of oil:

IR (CCl_4) 1740, 1390, and 1369 cm^{-1}; NMR (CCl_4) δ 5.88 (b, 1 H), 4.68 (s, 1 H), 3.69 (s, 6 H), 3.64 (d, J = 10 Hz, 2 H), 3.47 (d, J = 10 Hz, 2 H), 1.2–2.3 (m, 13 H), 1.20 (s, 3 H), 0.93 (d, J = 7 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H), 0.83 (d, J = 7 Hz, 3 H), 0.74 (s, 3 H). A 1.68-g aliquot of the crude oil was dissolved in a solution of 10 mL of ethylene glycol and 3 mL of ethanol containing 565 mg (10 mmol) of potassium hydroxide. This solution was heated at 120 °C for 17 h. It was poured into water and the water layer extracted with chloroform. The chloroform layer was discarded. The water layer was carefully acidified with 1 N aqueous sodium bisulfate and extracted with ether. After drying ($MgSO_4$) and concentration in vacuo, PLC purification (2:1 hexane–acetone) gave 356 mg (48% from **27b**) of desired acid: IR (CCl_4) 2300–3500, 1700, 1385, and 1365 cm^{-1}; NMR (CCl_4) δ 10.9 (b, 1 H), 5.76 (b, 1 H), 4.58 (s, 1 H), 3.58 (d, J = 11 Hz, 2 H), 3.36 (d, J = 11 Hz, 2 H), 1–2.6 (m, 14 H), 1.18 (s, 3 H), 0.92 (d, J = 6 Hz, 9 H), 0.72 (s, 3 H). Further characterization was performed as its methyl ester: IR (CCl_4) 1740, 1300, 1370, and 1100 cm^{-1}; NMR (CCl_4) δ 5.72 (b, 1 H), 4.52 (s, 1 H), 3.62 (s, 3 H), 3.52 (d, J = 11 Hz, 2 H), 3.36 (d, J = 11 Hz, 2 H), 1–2.6 (m, 13 H), 1.16 (s, 3 H), 0.86 (bd, J = 6 Hz, 9 H), 0.72 (s, 3 H); mass spectrum *m/e* (rel %) 366 (12), 237 (26), 195 (55), 115 (48), 109 (100), 87 (48), and 73 (54). Calcd for $C_{22}H_{38}O_4$: 366.2770. Found: 366.2766.

Preparation of 1-Chloro-11-iodoundecane. Methyl 10-undecenoate (40 g, 0.2 mol) was reduced under standard conditions by 7.6 g (0.2 mol) of lithium aluminum hydride in 400 mL of dry ether to give 39 g of crude alcohol. A solution of 10 g (59.5 mmol) of crude 10-undecenyl alcohol, 7.1 g (89.3 mmol) of pyridine, and 19.2 g (79.1 mmol) of thionyl chloride in 150 mL of dry chloroform gave under standard conditions 8.01 g (81%) of 10-undecenyl chloride: bp 68–71 °C (0.25 mm) (lit.[40] bp 111–113 °C); IR 3070, 2930, 2860, 1640, 990, 910, and 860 cm^{-1}; NMR (CCl_4) δ 5.70 (ddt, J = 17, 10, 7 Hz, 1 H), 4.94 (bd, J = 17 Hz, 1 H), 4.88 (bd, J = 10 Hz, 1 H), 3.45 (t, J = 7 Hz, 2 H), 2.0 (m, 2 H), 1.76 (m, 2 H), 1.33 (pseudo s, 12 H). Into a solution of 4.70 g (24.9 mmol) of 10-undecenyl chloride in 10 mL of THF was added dropwise 9.96 mL of a 1 M tetrahydrofuran solution (29.9 mmol) of borane over a period of 10 min. After stirring for 2 h at room temperature, a few drops of absolute methanol were added to quench the excess hydride. In one portion, 4.67 g (18.4 mmol) of iodine was added and the addition was followed by 5.92 mL of a 30% methanolic solution of sodium hydroxide. After an additional 2 h at room temperature, the reaction mixture was poured into 1 N aqueous sodium sulfite and extracted with ether. The ether layers were dried ($MgSO_4$) and concentrated in vacuo to give an oily solid. This residue was taken up in hexane and filtered, and the solid was discarded. The hexane solution was concentrated in vacuo and distilled in a Kugelrohr apparatus (160 °C, 0.08 mm) to give 4.30 g (54.5%) of desired product: IR (CCl_4) 2980, 2960, 1470, and 670 cm^{-1}; NMR (CCl_4) δ 3.51 (t, J = 6 Hz, 2 H), 3.18 (t, J = 7 Hz, 2 H), 1.8 (m, 4 H), 1.32 (pseudo s, 14 H).

Preparation of Ketal Ester 2b. To a solution of 3.00 g (9.15 mmol) of 3-oxopregn-4-ene-20α-carboxaldehyde[41] in 150 mL of *freshly distilled* acetone was added 2.55 mL (10.2 mmol) of *freshly prepared* Jones reagent at 0 °C over a 2–3-min period.[42] Substantially inferior results were obtained if solvent and reagent were not fresh. After a reaction time of 10 min, excess oxidizing reagent was destroyed by addition of 2-propanol and then 150 mL of THF and 1 L of water containing 15 g of sodium bicarbonate added. Evaporation of the THF and acetone and removal of the precipitate by filtration gives a transparent green aqueous solution. Acidification with concentrated aqueous hydrochloric acid, extraction with chloroform, drying ($MgSO_4$), and concentration in vacuo gave after recrystallization from ethanol 2.27 g (72%) of 3-oxopregn-4-ene-20α-carboxylic acid as colorless prisms, mp 272–276 °C (lit.[5b] mp 268–270 °C). Fisher esterification gave an 88% yield of methyl 3-oxopregn-4-ene-20α-carboxylate as prisms from benzene–hexane, mp 170–172 °C (lit.[5b] mp 178 °C). Normal ketalization utilizing 1.28 g (3.58 mmol) of ester enone and 9.10 mmol of ethylene glycol in refluxing benzene containing anhydrous calcium sulfate as a drying agent gave 1.10 g (77%) of **2b**: mp 170–172 °C from benzene–hexane; IR (CCl_4) 1740, 1370, 1260, 1200, 1170, and 1100 cm^{-1}; NMR ($CDCl_3$) δ 5.30 (m, 1 H), 3.92 (s, 4 H), 3.64 (s, 3 H), 1–2.6 (m, 21 H), 1.17 (d, J = 7 Hz, 3 H), 1.05 (s, 3 H), and 0.72 (s, 3 H). Calcd for $C_{25}H_{38}O_4$: 402.2770. Found: 402.2763.

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We also want to thank Professor E. J. Corey for copies of the spectra of 7-*anti*-methoxy methylnorborn-5-en-2-one and Dr. V. Van Rheenan for a generous gift of 3-oxobisnorcholen-22-al.

References and Notes

(1) (a) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959; (b) E. H. Rodd, "Chemistry of Carbon Compounds", Vol. Ic, Elsevier, Amsterdam, 1965, p 129 (c) J. M. Osbond *Prog. Chem. Fats Other Lipids*, **9**, 121 (1966); (d) F. Gunstone, C. Scrimgeour, and S. Vedanayagam, *J. Chem. Soc., Chem. Commun*, 916 (1974).
(2) P. Barbier and R. Locgrun, *C. R. Acad. Sci.*, **156**, 1443 (1913); H. Wieland, *Hoppe-Seyler's Z. Physiol. Chem.*, **161**, 80 (1926); W. M. Hoehm and H. L. Mason, *J. Am. Chem. Soc.*, **60**, 1493, (1938); C. Meystre, H. Frey, A. Wattstein, and K. Mrischer, *Helv. Chim. Acta*, **27**, 1815 (1944); G. Lehman, L. Koppe, and G. Hilgetag, *J. Prakt. Chem.*, **304**, 217 (1966); M. Fetizon, F. J. Kakis, and V. Ignatiadu-Ragoussis, *J. Org. Chem.*, **38**, 1732 (1973).
(3) M. S. Newman, *J. Am. Chem. Soc.*, **57**, 734 (1935); J. Von Braun, *Chem. Ber.*, **67**, 218 (1934). For a review of the Curtiss reaction see P. A. S. Smith, *Org. React.*, **3**, 337 (1946); for a review of the Hofmann reaction, see E. S. Wallis and J. E. Lane, *Ibid.*, **3**, 267 (1946). For a review of deamination of amines to ketones see R. J. Baumgarten, *J. Chem. Educ.*, **43**, 398 (1966). For some pertinent references for this transformation see K. Kahr and C. Berther, *Chem. Ber.*, **93**, 132 (1960); V. Cato, L. Lopez, and P. E. Todeseo, *J. Chem. Soc., Perkin Trans. 1*, 1652 (1972); E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.*, **91**, 1429 (1969); S. E. Dinizo and D. S. Watt, *ibid.*, **97**, 6900 (1975); D. St. C. Black and N. A. Blackman, *Aust. J. Chem.*, **28**, 2547 (1975).
(4) For an example see J. Meinwald, A. Lewis, and P. G. Gassman, *J. Am. Chem. Soc.*, **84**, 977 (1962).
(5) (a) For alternative approaches, see Y. Yanuka, R. Katz, and S. Sarel, *Tetrahedron Lett.*, 1725 (1968); *Chem. Commun.*, 851 (1968); N. L. Allinger, T. J. Walters, and M. G. Newton, *J. Am. Chem. Soc.*, **96**, 4588 (1974). (b) For conversion of 3-oxobisnor-4-cholen-22-al to progesterone see V. Van Rheenan, *Tetrahedron Lett.*, 985 (1969); M. E. Hen and F. W. Heyl, *J. Am. Chem. Soc.*, **74**, 3627 (1952).
(6) S. J. Selikson and D. S. Watt, *J. Org. Chem.*, **40**, 267 (1975).
(7) G. W. Moersch and M. L. Zwiesher, *Synthesis*, 647 (1971); D. A. Konen, L. S. Silbert, and P. E. Pfeffer, *J. Org. Chem.*, **40**, 3253 (1975); H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 1731 (1975). Also see E. C. Taylor, H. W. Altland, and G. McGillivray, *ibid.*, 5285 (1970).
(8) G. V. Bakore and S. Narain, *J. Chem. Soc.*, 3419 (1963); Y. Pocker and B. C. Davis, *J. Am. Chem. Soc.*, **95**, 6216 (1973); H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 4611 (1975); E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, **97**, 6908 (1975).
(9) R. M. Purkayastha and R. C. Ghosh, *Z. Phys. Chem. (Leipzig)*, **7**, 285 (1930); B. Perlmutter-Hayman and Y. Weissmann, *J. Am. Chem. Soc.*, **91**, 668 (1969); M. Caplow, *ibid.*, **93**, 230 (1971); J. M. Pink and R. Stewart, *Can. J. Chem.*, **49**, 649, 654 (1971); P. Ankett and I. R. L. Barker, *J. Chem. Soc., Perkin Trans. 2*, 965 (1972); Y. Ogata and K. Nagura, *J. Org. Chem.*, **40**, 318 (1975).
(10) P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); *J. Org. Chem.*, **37**, 1907 (1972); P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., *ibid.*, **37**, 451 (1972).
(11) J. J. Tufariello and W. J. Kissel, *Tetrahedron Lett.*, 6145 (1966).
(12) (a) W. C. Wildman and D. R. Saunders, *J. Org. Chem.*, **19**, 381 (1954); (b) P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 2473 (1956); (c) J. Paasivirta and H. Krieger, *Suom. Kemistil. B*, **38**, 182 (1965); (d) J. Paasivirta, *Suom. Kemistil. A*, **39**, 120 (1966); (e) H. Krieger and S. E. Masar, *ibid.*, **39**, 119 (1966); (f) P. S. Wharton and B. T. Au, *J. Org. Chem.*, **31**, 3787 (1966); (g) P. K. Freeman, D. M. Bales, and D. J. Brown, *ibid.*, **33**, 2211 (1968); (h) E. J. Corey, T. Ravindranathan, and S. Terashima, *J. Am. Chem. Soc.*, **93**, 4326 (1971); (i) D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 121 (1972); (j) S. Ranganathan, D. Ranganathan, and R. Iyengar, *Tetrahedron*, **32**, 961 (1976).
(13) B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973); *J. Org. Chem.*, **40**, 148 (1975); B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
(14) For an independent investigation on the direct sulfenylation of enolates see D. Seebach and M. Teschner, *Chem. Ber.*, **109**, 1601 (1976).
(15) A. W. P. Jarvie and D. Skeleton, *J. Organomet. Chem.*, **30**, 145 (1971); R. A. Ellison, *J. Org. Chem.*, **37**, 2757 (1972); D. Seebach and H. Neumann, *Chem. Ber.*, **107**, 847 (1974); D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974); N. Finch and C. W. Gemenden, *J. Org. Chem.*, **40**, 569 (1975); B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, **97**, 4018 (1975).
(16) B. M. Trost, K. Hiroi, and S. Kurozumi, *J. Am. Chem. Soc.*, **97**, 438 (1975); B. M. Trost and K. Hiroi, *ibid.*, **97**, 6911 (1975).
(17) K. D. Gundermann and H. Schulze, *Chem. Ber.*, **94**, 3254 (1961). For other applications of this compound see R. L. Cregge, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 2603 (1973).
(18) For preliminary reports of portions of this work see B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **97**, 3528 (1975); *Tetrahedron Lett.*, 3797 (1975).
(19) An interesting multistep approach for converting an α-phenylthio acid to the norcarbonyl derivative has recently appeared. See B. Lythgoe, J. R. Milner, and J. Tideswell, *Tetrahedron Lett.*, 2593 (1975).
(20) Y. Letourneux, G. Bujuktur, M. T. Ryzlak, A. K. Banerjee, and M. Gut, *J. Org. Chem.*, **41**, 2288 (1976).
(21) C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *Tetrahedron Lett.*, 501

(1972); E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972). Also see E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Vol. II, Chemical Publishing Co., New York, N.Y. 1975.
(22) C. R. Johnson and W. G. Phillips, *J. Am. Chem. Soc.*, **91**, 682 (1969).
(23) J. C. Martin and E. F. Perozzi, *J. Am. Chem. Soc.*, **96**, 3155 (1974), and earlier references cited therein.
(24) F. Jung, N. K. Sharma, and T. Durst, *J. Am. Chem. Soc.*, **95**, 3420 (1973).
(25) For a review see J. McMurry, *Org. React.* in press.
(26) G. B. Heisig and F. H. Stodola, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 213.
(27) For alternative cyclobutanone preparations see (a) P. Lipp and R. Köster, *Chem. Ber.*, **64**, 2823 (1931); (b) J. D. Roberts and C. W. Sauer, *J. Am. Chem. Soc.*, **71**, 3925 (1949); (c) J. M. Conia, P. Lerivérend, and J. L. Ripoll, *Bull. Soc. Chim. Fr.*, 1803 (1961); (d) D. Seebach and A. K. Beck, *Org. Synth.*, **51**, 76 (1971); (e) J. R. Salaun and J. M. Conia, *Chem. Commun.*, 1579 (1971); (f) M. M. Martin, F. T. Hammer, and E. Zader, *J. Org. Chem.*, **38**, 3422 (1973); (g) K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 3653 (1974).
(28) The dianion of phenylthioacetic acid has been reported: K. Iwai, M. Kawai, H. Kosugi, and H. Uda, *Chem. Lett.*, 385 (1974); H. Kosugi, H. Uda, and S. Yamigawa, *J. Chem. Soc., Chem. Commun.*, 192 (1975).
(29) (a) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968); (b) K. S. Ayyar and G. S. K. Rao, *Can. J. Chem.*, **46**, 1467 (1968); (c) B. A. Pawson, H. C. Cheung, S. Gurbaxani, and G. Saucy, *J. Am. Chem. Soc.*, **92**, 336 (1970); (d) A. J. Birch, P. L. Macdonald, and V. H. Powell, *J. Chem. Soc. C*, 1469 (1970); (e) A. A. Drabkina and Y. S. Tsizin, *J. Gen. Chem. USSR (Engl. Transl.)*, **43**, 422, 691 (1973); (f) R. J. Crawford, U.S. Patent 3 676 506; *Chem. Abstr.*, **77**, 113889e (1972); (g) J. Ficini, J. d'Angelo, and J. Noire, *J. Am. Chem. Soc.*, **96**, 1213 (1974); (h) E. Negishi, M. Sabinski, J. J. Katz, and H. C. Brown, *Tetrahedron*, **32**, 925 (1976). For a recorrection of the stereochemical assignment, see J. F. Manville, *Can. J. Chem.*, **53**, 1579 (1975).
(30) E. J. Corey, N. W. Gilman, and B. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).
(31) For a recent review see B. M. Trost and L. S. Melvin, Jr., "Sulfur Ylides. Emerging Synthetic Intermediates", Academic Press, New York, N.Y., 1975, Chapter 7; A. R. Lepley and A. G. Guimanini, "Mechanisms of Molecular Migrations", Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1971, pp 297–440.
(32) K. Ogura, M. Yamashita, S. Furukawa, M. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 2767 (1975). S- rather than C-alkylation of a sulfur stabilized vinyl organometallic has also been reported. See H. Westmijze, J. Meijer, and P. Vermeer, *Tetrahedron Lett.*, 2923 (1975).
(33) Obtained by standard ketalization procedures on 4-(4′-carboxycyclohexyl)cyclohexanone or its methyl ester: W. G. Dauben and M. Tanabe, *J. Am. Chem. Soc.*, **75**, 4969 (1953); A. L. Wilds and C. H. Shunk, *ibid.*, **72**, 2388 (1950).
(34) H. Stobbe and A. Lenzner, *Justus Liebigs Ann. Chem.*, **380**, 95 (1911).
(35) A. L. Wilds, C. H. Shunk, and C. H. Hoffman, *J. Am. Chem. Soc.*, **76**, 1733 (1954).
(36) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949).
(37) M. M. Kreevoy, C. R. Morgan, and R. W. Taft, *J. Am. Chem. Soc.*, **82**, 3064 (1960).
(38) We express our thanks to Professor E. J. Corey for making these data available to us.
(39) Prepared from chloroacetic acid, methyl mercaptan, and potassium hydroxide in ethanol: K. S. Bonstarry, *J. Chem. U.A.R.*, **9**, 317 (1966); V. E. Kuvenchik and V. E. Petrun'kin, *Zh. Org. Khim.*, **6**, 2227 (1970).
(40) F. Pueschel and C. Kaiser, *Chem. Ber.*, **97**, 2903 (1964).
(41) We wish to thank Dr. V. Van Rheenan of the Upjohn Co. for a very generous gift of this compound.
(42) Freshly prepared solvents and reagents are crucial for a high yield oxidation.

Oxyfunctionalization of Hydrocarbons. 7.[1a] Oxygenation of 2,2-Dimethylpropane and 2,2,3,3-Tetramethylbutane with Ozone or Hydrogen Peroxide in Superacid Media

Norihiko Yoneda[1b] and George A. Olah*

Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. *Received October 8, 1976*

Abstract: The reaction of ozone and hydrogen peroxide with neoalkanes, i.e., 2,2-dimethylpropane and 2,2,3,3-tetramethylbutane, in various superacid solutions has been investigated. Results indicate that the reactions proceed via electrophilic attack by protonated ozone, $^{+}O_3H$, into the involved σ bonds in alkanes through two-electron three-center bonded pentacoordinated carbonium ions. It was also observed that the electrophilic hydroxylation of alkanes with hydrogen peroxide and/or trioxide, which are formed as by-products in the cleavage of the pentacoordinated carbonium ions $[R_3C(H)OOOH]^+$, gives alcohols with no skeletal rearrangement (i.e., neopentyl alcohol from neopentane) again indicative of direct electrophilic hydroxylation with *no* trivalent carbenium ion formation.

We have previously reported the electrophilic oxygenation of alkanes with ozone[2] or hydrogen peroxide[3] in superacid media. In both cases the reactions proceed via electrophilic insertion of protonated ozone, i.e., $^{+}O_3H$, and protonated hydrogen peroxide, i.e., $H_3O_2^+ \equiv OH^+(H_2O)$, respectively, into the involved single σ bonds of the alkanes, similarly to such electrophilic reaction as protolysis,[4] chlorolysis,[5] and nitrolysis[6] of alkanes. In continuation of our work on electrophilic oxygenation of alkanes, we considered it to be of interest to extend our investigation to the electrophilic oxygenation of neoalkanes. These systems are expected to provide a fuller understanding of electrophilic oxygenations, particularly their steric requirements, as well as of the question of the involvement of pentacoordinated carbonium ion vs. trivalent carbenium ion intermediates, as the latter would inevitably lead to skeletal rearrangements.

Results and Discussion

2,2-Dimethylpropane (Neopentane). A stream of ~5% ozone containing oxygen was passed through a solution of neopentane (10 mmol) in FSO_3H–SbF_5–SO_2ClF (fourfold excess) held at −78 °C. Because of the limited solubility of neopentane in this acid solution, the reaction is initially carried out in a heterogeneous system. However, upon introduction of ozone, the brownish colored reaction medium becomes homogeneous. ^1H and ^{13}C NMR spectra of the resultant solution (after 40 mmol of ozone was passed through) showed formation of the dimethylethoxy carbenium ion (**1**) as the major product together with dimethylmethoxy carbenium ion (**2**) and protonated neopentyl alcohol (**3**). The conversion of the alkane was found to be almost 100%. The results under varying reaction conditions are summarized in Table I together with those of the reaction of 2,2,3,3-tetramethylbutane.

As discussed previously, the reaction of alkanes with ozone in FSO_3H–SbF_5–SO_2ClF solution can be best described by the electrophilic attack of protonated ozone into the C–C or C–H σ bonds of the alkanes (Scheme I).

Since ozone has a strong 1,3 dipole, or at least is strongly polarizable, it is not unexpected that it is readily protonated in superacids. Protonated ozone, $^{+}O_3H$, once formed seems