New Synthetic Reactions. Geminal Alkylation via α-Trimethylenedithiocyclobutanones[1]

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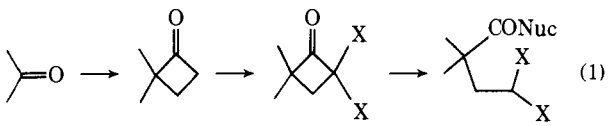
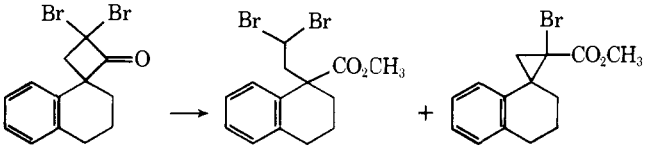
Abstract: A new geminal alkylation procedure based upon cyclobutanone spiroannelation with diphenylsulfonium cyclopropylide and 1-lithiocyclopropyl phenyl sulfide followed by cyclobutane ring cleavage replaces the C–O bonds of a carbonyl group by C–C bonds. Facilitation of ring cleavage by introduction of sulfur substituents α to the carbonyl group of the cyclobutanone is required. The nucleophiles that initiated ring cleavage include hydroxide, methoxide, and methyllithium. In this way, a carboxylic acid or ester or ketone possessing the dithiane derivative of CH_2CHO in the α position is created. While the versatility of this type of functionality is broad, it has been specifically demonstrated for the creation of α-methyl carboxylic esters and a novel cyclopentenone synthesis. Since the cyclobutanone spiroannelation is highly stereoselective, this geminal alkylation procedure is highly stereoselective. Thus, syntheses of methyl deoxypodocarpate from 4aβ-methyl-1,2,3,4,4a,9,10,10a-octahydro-1-phenanthrene and of 3-carbomethoxy-6,10-dimethylspiro[4.5]dec-6-en-1-one, a potential precursor of hinesol, from 2,6-dimethylcyclohex-2-enone are described.

The overall transformation represented by eq 1 involves the net replacement of the carbon–oxygen bonds of a carbonyl group with carbon–carbon bonds, a geminal alkyla-



(1)

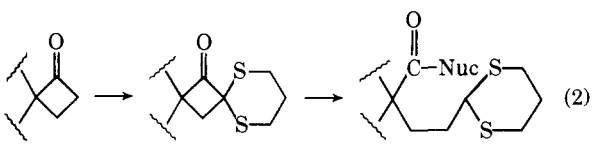
tion. In the preceding paper, the cleavage is accomplished utilizing X = Br.[3] Several limitations of the method are obvious. For example, the rigorousness required to achieve geminal bromination would eliminate the presence of isolated double bonds in the substrate. Cyclobutanones obtained by spiroannelation of aldehydes would brominate preferentially at the more substituted rather than less substituted side. A further complication involves the competition between ring cleavage and ring regression (semibenzylic acid rearrangement) with **1.** Methods to overcome these prob-



1

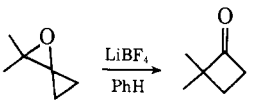
lems become even more important since cyclobutanones are also easily available from olefins as well as carbonyl partners.[4] These procedures can become stereospecific olefinic alkylations. In this paper, we wish to report in detail our results which attack this problem.

Sulfur, like bromine, is an anion-stabilizing group but, unlike bromine, is a poor leaving group. Introduction of a geminal sulfur grouping should facilitate ring cleavage but preclude the reaction of ring regression. Equation 2 outlines the approach.



(2)

The cyclobutanones employed in this study, **2–6,** were prepared as previously reported utilizing diphenylsulfonium cyclopropylide[5] or 1-lithiocyclopropyl phenyl sulfide[6] followed by rearrangement of the initial adducts. We have recently discovered that lithium fluoroborate[7] is a superior acid catalyst for the rearrangement of oxaspiropentanes to cyclobutanones. Its advantages lie in its greater reproducibility, its faster rates, and its higher solubility in hydrocarbon solvents compared with lithium perchlorate.[8,9] Although rearrangements were normally effected in refluxing benzene, room temperature also suffices with increased reaction times. Special note must be made of spiroannelation of 2,6-dimethylcyclohexanone and tricyclic ketone **7.** While these ketones are mixtures of *E* and *Z* isomers, only a single cyclobutanone is obtained. Three conclusions can be reached as a result of these observations. Under conditions of reversible ylide generation, geometrical isomerization is fast relative to ylide addition to the carbonyl group.[10] Of the two isomers in each series, (*Z*)-2,6-dimethylcyclohexanone and (*E*)-**7** react selectively to produce presumably the single oxaspiropentane from attack on the less hindered face. Rearrangement proceeds stereospecifically to generate the stereohomogeneous cyclobutanones. The bases for the stereochemical assignments have been previously discussed.[5,6b] In ketone **5,** the subsequent conversion to the



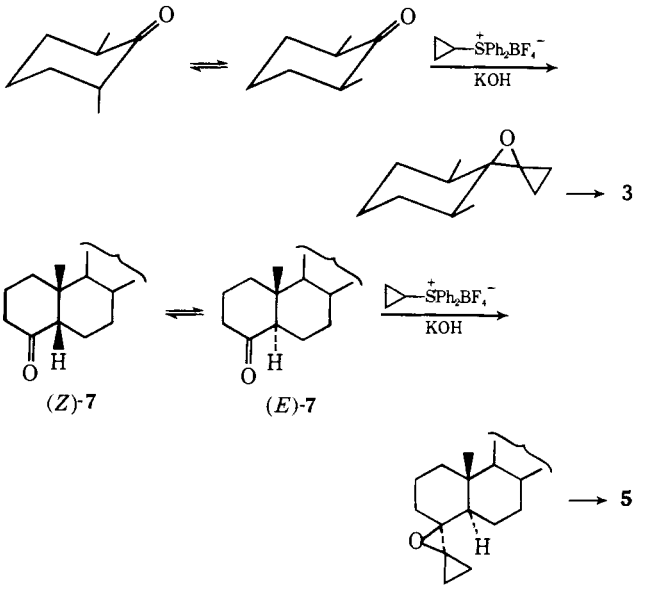
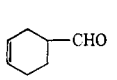
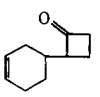
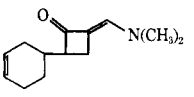
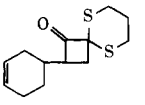
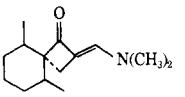
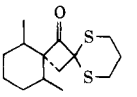
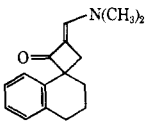
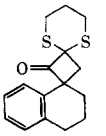
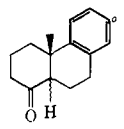
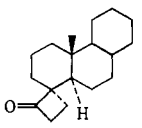
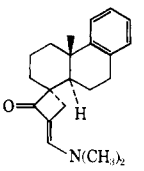
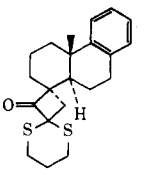
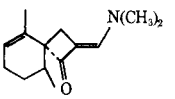
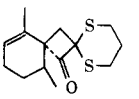


Table I. Syntheses of α,α-Trimethylenedithiocyclobutanones

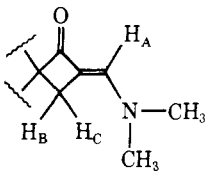
Aldehyde or ketone	Method of spiro-annel-ation[c]	Cyclobutanone	(% yield)[d]	Enamide	(% yield)[e]	Trimethylene-dithiocyclo-butanone	(% yield)[d]
	A	 2	(70)[f,g]	 10	(98)	 15	(19)
	A	 3	(88)[f]	 11	(87)	 16	(37)
1-Tetralone	A	 4	(99)[f,g]	 13	(95)	 17	(62)
 7	A	 5	(99)[f,g]	 13	(100)	 18	(91)
	B	 6	(72)[h]	 14	(97)	 19	(53)

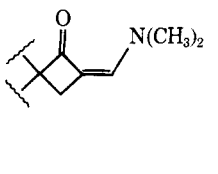
[a] G. Stork and A. Burgstahler, *J. Am. Chem. Soc.*, 73, 3544 (1951). [b] R. K. Smith, M.S. Thesis, University of Wisconsin, 1972. [c] Method A: diphenylsulfonium cyclopropylide, reversible conditions. Method B: 1-lithiocyclopropyl phenyl sulfide. [d] Yield of isolated pure product. [e] Yield of solid before recrystallization. Recrystallization unnecessary for further transformation. [f] This work. [g] See also reference 5. [h] Reference 6.

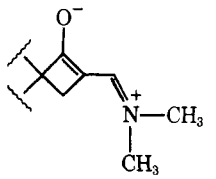
podocarpate series confirms the assignment.

The introduction of a trimethylenedithio group required the activation of the methylene group of the cyclobutanone since attempts to condense directly the enolate of a cyclobutanone with trimethylenedithiotosylate or the cyclobutanone with a bis(sulfenyl) chloride failed. Activation was achieved by the condensation of *tert*-butoxybis(dimethylamino)methane[11] with the cyclobutanone at 50–70° without solvent. Reaction times were determined by the disappearance of the infrared carbonyl absorption of the starting material. As listed in Table I, yields of the initially formed solids were normally in excess of 95%. Recrystallization from hexane or cyclohexane effected further purification. Nevertheless, since the spectral properties of the recrystallized and unrecrystallized products were superimposable, the unrecrystallized products were normally used for further transformations.

Infrared spectra show common absorptions at 1700 ± 10, 1608 ± 8, 1406 ± 4, 1361 ± 1, and 1102 ± 3 cm^{-1} which can be associated with the vinylogous amide unit as shown in **8.** The low energy of the carbonyl absorption indicates

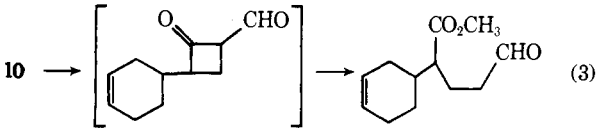

8a


8b


8c

substantial contributions from the dipolar resonance form **8c.** The NMR spectra show the olefinic proton (**8a,** H_A) as an ill-defined triplet (J = 1.4 ± 0.3 Hz) at δ 6.93 ± 0.12 and the *N*-methyl groups at δ 3.00 ± 0.05. In many cases, a second small singlet appears approximately 15 Hz downfield from the large N-CH_3 absorption (ratio 1:33). This singlet may be associated with the N-CH_3 absorption for the minor geometrical isomers. On the basis of the chemical shifts of the N-CH_3 groups, the major isomers (>97%) may be assigned the *E* configuration (i.e., **8a**). Since the absorptions for the *N*-methyl groups appear as sharp singlets, the barrier to rotation about the C–N bond is less than that of a typical amide.

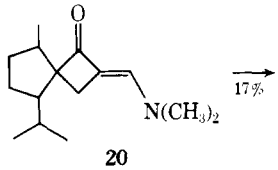
Solvolysis of the vinylogous amides in the presence of trimethylenedithiotosylate (**9**) in buffered ethanol leads to replacement of the dimethylaminomethylene unit with the trimethylenedithio unit.[12] The yields appear to correlate with molecular size, i.e., the higher the molecular weight, the higher the yield. This correlation arises from the fact that the vinylogous amides of the smaller substrates (i.e., **10, 11,** and **14**) are more sensitive to decomposition under the reaction conditions than the larger ones (i.e., **12** and **13**). In an examination of the by-products in the reaction of **10,** a compound tentatively identified as an aldehyde ester (see eq 3)


(3)

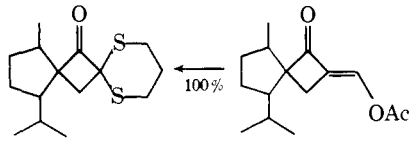
was isolated. The infrared spectrum showed absorptions at 2700, 1730, 1720, and 1650 cm^{-1}, and the NMR spectrum showed characteristic absorptions at δ 9.05 (CHO), 5.74

(=CH), and 3.77 (CO_2CH_3). Such a product would arise by hydrolysis of the enamide to the aldehyde followed by base-catalyzed 1,3-dicarbonyl cleavage. Since the lower yields appeared associated with the reactivity of the vinylogous amides to the reaction conditions, nonalcoholic solvents were examined, however, to no avail. Increasing the concentration of the dithiotosylate by utilizing decreased volumes of solvent and increased molar ratios with respect to the vinylogous amides does have a beneficial effect. For example, increasing the ratio of **9** to **14** from approximately 2:1 to 3:1 increased the yield of **19** from 35 to 53%. Similar changes in the cases of **10** → **15** and **11** → **16** would be expected to increase their yields substantially.

An alternative approach to increase the yields with the lower molecular weight compounds would utilize a more reactive activating group. For example, vinylogous amide **20** was transformed to **21** in 17% yield under the standard con-



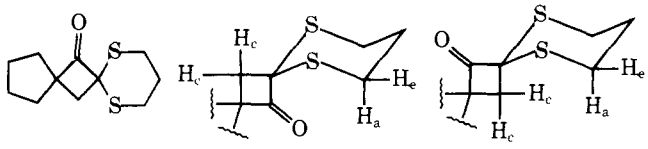
20



21 22

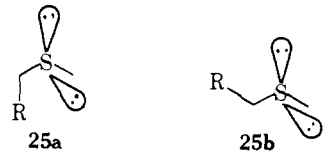
ditions; whereas, the enol acetate **22**[13] was converted to **21** in quantitative yield under the same conditions. Clearly, the utilization of the acetoxymethylene derivatives can be recommended.

Examination of the infrared spectra of dithianes **15–19, 21,** and **23** reveals common absorptions at 1757 ± 5, 1430



23 24a 24b

± 1, 1425 ± 1, 1275 ± 5, 1060 ± 10, and 901 ± 1 cm^{-1}. The methylene groups of the cyclobutanone (H_c, **24**) appear as singlets at δ 2.04, 1.91, and 1.92 for **16, 21,** and **23,** respectively, and AB quartets ($J \approx 14$ Hz) centered at δ 2.22 and 2.03 for **18** and **19** in the proton NMR spectra. Most interestingly, these spectra reveal the dithiane ring to be conformationally rigid.[14] The methylene group adjacent to sulfur shows H_a to be at δ 3.54 ± 0.06 and H_e to be at δ 2.57 ± 0.08 in the NMR spectrum. The assignment of these protons to H_a and H_e, respectively, rests on the coupling constants which are readily interpreted in the cases of **16, 21,** and **23.** For example, in the case of **16,** the absorption at δ 3.57 appears as a doublet of doublets of doublets, J = 15.2, 12.0, and 3.2 Hz, which is consistent with an axial hydrogen. The absorption at δ 2.64 appears as a doublet of triplets, J = 15.2 and 3.8 Hz, which is consistent with an equatorial hydrogen. Not only do the data indicate conformational rigidity (on the NMR time scale) but also suggest conformer **24a** rather than conformer **24b** because of the anticipated deshielding of H_a by the carbonyl group in **24a** but not in **24b.** The preferential existence of the sterically more crowded isomer indicates an electronic factor may be responsible. Deslongchamps pointed out that orientation **25a** is preferred over **25b,** when R is an electronegative substituent as a result of the interaction of the antiparallel lone

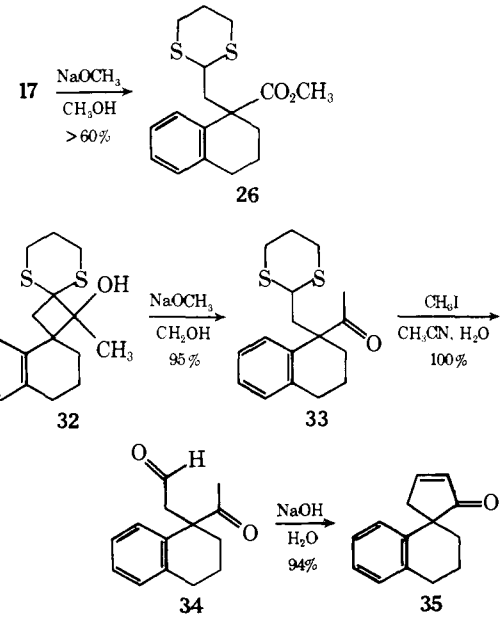


25a 25b

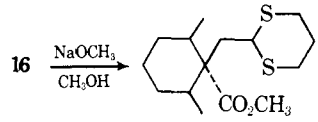
pair with the C-R bond.[15] Alternatively, there may be a through-space interaction (spiroconjugation)[16] that stabilizes **24a** over **24b.** The fact that the infrared carbonyl stretching frequencies occur 15–20 cm^{-1} to lower energy than the parent cyclobutanones (**2–6**) supports such a view.

Cleavage occurs cleanly by treatment with nucleophiles in hydroxylic solvents. Methanolic sodium methoxide cleaves **17** (to **26**) in 1.5 hr at reflux temperature (see Scheme I), but the highly sterically congested **16** (to **27**)

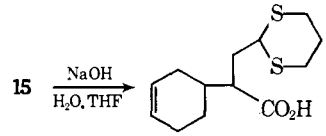
Scheme I



was only half complete after 65 hr. Aqueous sodium hydroxide smoothly cleaves **15** quantitatively to the carboxylic



27
(57%)

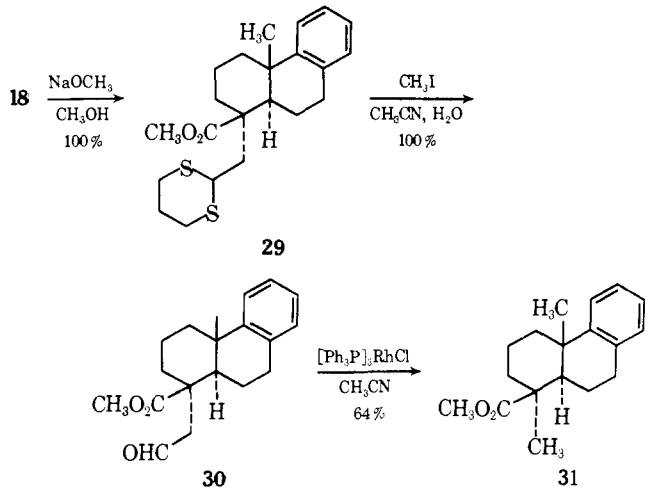


28
(100%)

acid **28** in only 18 hr. It is interesting to note that **28** appears to be stereohomogeneous on the basis of its chromatographic behavior, sharp melting point, and spectral properties. Thus, the method may have application in the creation of acyclic geometry as well, such as in the case of juvabione synthesis.[17] It is clear that the α,α-trimethylenedithiocyclobutanones cleave more slowly than the corresponding α,α-dibromocyclobutanones presumably as a result of both inductive and steric effects.

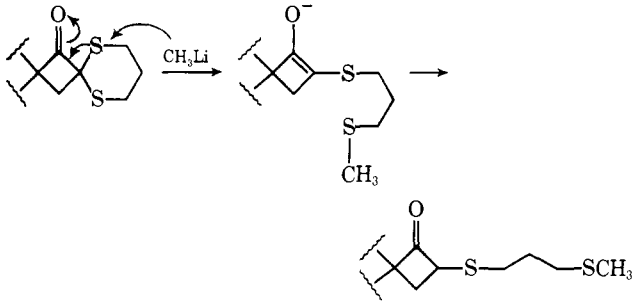
This reaction has been utilized to generate an α-methyl carboxylic acid unit, an important structural unit in many natural products, in a highly stereoselective fashion as illustrated in Scheme II. In this case, cleavage of **18** to **29** was

Scheme II

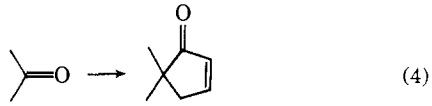


complete in 21 hr. Completion of the sequence to methyl deoxypodocarpate (**31**) was achieved by hydrolysis of the dithiane (to **30**)[18] and decarbonylation utilizing Wilkinson's catalyst.[19] This approach constitutes the first efficient use of the *Z,E* mixture of isomers at the A/B ring juncture of tricyclic ketone **7** in resin acid synthesis.[20-22]

Carbon nucleophiles may replace the heteroatom nucleophiles. Methyllithium addition to **17** generates **32** in high yield (see Scheme I). Examination of the crude product by ir reveals a very small cyclobutanone carbonyl absorption (not starting material), even with very large excesses of organolithium. A possible explanation for the presence of a cyclobutanone is that methyllithium may attack at sulfur as well as add to the carbonyl group. The enolate produced



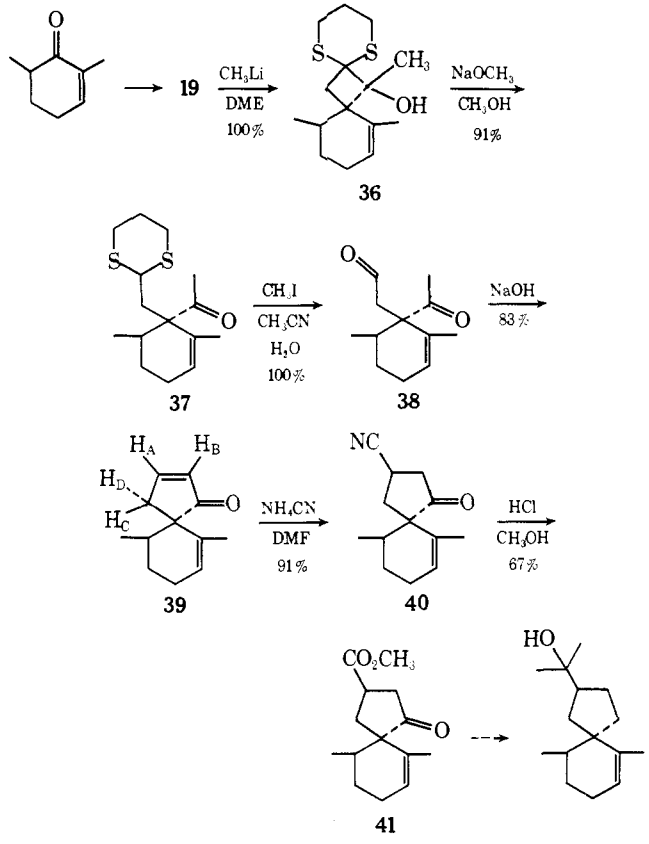
would be resistant to methyllithium addition and upon work-up generate a cyclobutanone. However, this side reaction is not a serious factor. The methyl group of **32** occurs at extraordinarily low field (δ 1.78) in the ^{1}H NMR spectrum. Cleavage to **33** occurs slowly (~60 hr) but cleanly with refluxing methanolic sodium methoxide. The utility of this sequence lies in the nature of the functionality available in the carbon chains, an acetyl group and a protected acetaldehyde. For example, unmasking of the aldehyde (**34**) followed by base-catalyzed aldol condensation[23] produces the cyclopentenone **35.** Thus, we have a method to annelate a cyclopentenone ring onto a carbonyl group (see eq 4).



(4)

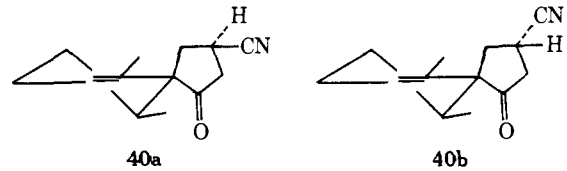
Scheme III illustrates a potential application of such a sequence. Dithiane **19,** available stereoselectively from 2,6-dimethylcyclohexenone, undergoes methyllithium addition to generate mainly a single stereoisomer as determined by the presence of a singlet at δ 1.64 for the tertiary methyl group. A smaller singlet at δ 1.71 may be due to the minor isomer. On the basis of the approach of methyllithium from

Scheme III



the least hindered face, the stereochemistry depicted in **36** is assigned. Methanolic sodium methoxide required 4 days at reflux for ring cleavage; however, the yield is excellent (91%). Hydrolysis (to **38**) and aldol condensation generates a single cyclopentenone **39.** The ^{1}H NMR spectrum exhibits a first-order pattern for the cyclopentenone protons. H_A (J = 6, 3 Hz) and H_B (J = 6, 2 Hz) appear as doublets of triplets at δ 7.64 and 6.13, respectively; H_C and H_D appear as doublets of doublets of doublets, J = 20, 3, 2 Hz, at δ 2.64 and 2.36, respectively.

Introduction of an 2-propanol group at C-3 and removal of the carbonyl group would effect a synthesis of hinesol, a key member of the spirosesquiterpenes.[24] Similar compounds have also been used as precursors to cedrenes.[25] A logical precursor to hinesol is **41.** Such a precursor is readily accessible from the cyclopentenone. Conjugate addition of cyanide utilizing ammonium cyanide generated in situ from ammonium chloride and potassium cyanide proceeds nearly quantitatively.[27] The NMR spectrum indicates a 2:1 isomeric mixture with the major isomer exhibiting methyl resonances at δ 0.78 and 1.55 and the minor isomer at δ 0.92 and 1.48. Deshielding by the nitrile group suggests **40a** rather than **40b** represents the major isomer. Models indi-

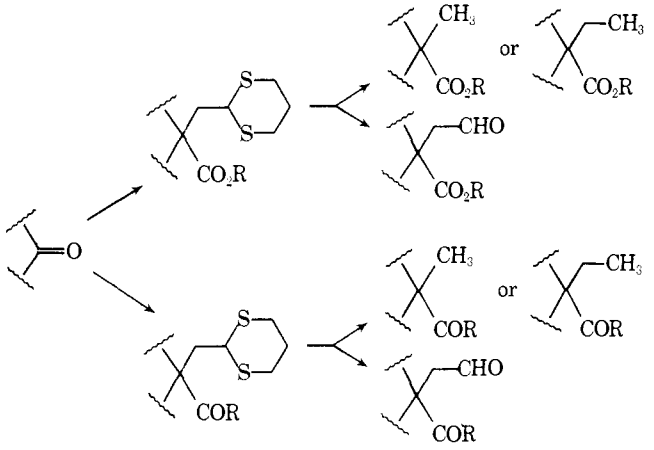


40a **40b**

cate that this product arises by addition of cyanide ion from the least hindered face. The stereochemistry of **40a** corresponds to the stereochemistry of hinesol. Treatment of **40** with dry hydrogen chloride in methanol completes the sequence.

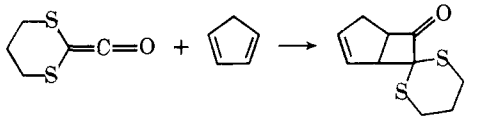
These synthetic approaches represent a net replacement

of a carbonyl group by differentially functionalized alkyl chains. The versatility of the dithiane group as an acyl



anion equivalent allows great modification.[28] Alternatively, desulfurization or a sequence of hydrolysis and decarbonylation effects an α-ethyl or α-methyl carbonyl (carboxylic acid, carboxylic ester, aldehyde, or ketone) synthesis in a highly stereoselective fashion. While only three nucleophiles have been explored (methoxide, hydroxide, and methyllithium), additional nucleophiles can be easily envisioned. For example, hydride ion addition followed by cleavage produces carboxaldehyde derivatives. The creation of alkyl chains by ring formation followed by ring cleavage may be termed secoalkylation. Thus, this method of geminal alkylation is a special case of the broader phenomenon of secoalkylation.

An alternative approach to the synthesis of α,α-trimethylenedithiocyclobutanones by a ketene cycloaddition has been reported.[29] This methodology extends our approach to stereospecific alkylations of reactive olefinic systems.



That these derivatives of cyclobutanones are special is clearly indicated by the excellent work of Marshall et al. with larger ring ketone systems.[30] He finds a highly reactive form of hydroxide is required to cleave the acyl dithianes, and that the corresponding alcohols do not cleave. He also noted a marked steric effect. In contrast to these results, cleavage of both the ketones and the related alcohols occurred in all cyclobutanone cases, although the rate of cleavage depended upon the steric congestion around the carbonyl group. The difference must relate to the relief of the approximately 26 kcal/mol of ring strain accompanying our cleavages. The use of the strain energy of small rings to provide the driving force for creation of carbon skeletons is a very useful approach to the synthesis of organic compounds.[31]

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Beckman IR-8 spectrometer in CCl_4 solutions unless otherwise noted. NMR spectra were determined with Varian A-60 or A-60-A or Jeolco MH-100 instruments in $CDCl_3$ or CCl_4 solutions unless otherwise stated. Chemical shifts are given in parts per million relative to internal Me_4Si. The abbreviations for multiplicity employed are s = singlet, d = doublet, t = triplet, qr = quartet, qt = quintet, ps = pseudosinglet, m = multiplet. Mass spectra were determined with an AEI MS-902 mass spectrometer at an ionizing current of 98 μA and an ionizing voltage of 70 eV. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

TLC was done with silica gel PF-254 (Merck, Darmstadt) on microscope slides for analysis and on 20 × 20 or 20 × 40 cm plates (~2-mm thick) for preparative work. Ether was employed to extract the products from the TLC silica gel. For column chromatography, Matheson Coleman and Bell silica gel, grade 62, was employed. All reactions were performed under nitrogen. When dry solvents are required, benzene and DMSO were distilled from calcium hydride, alcohols were distilled from magnesium, and DME, THF, and ether were distilled from sodium benzophenone ketyl. All glassware was dried by flaming under a stream of nitrogen. Anhydrous sodium or magnesium sulfate was employed as drying agents.

Synthesis of Starting Cyclobutanones. 4,5-Benzospiro[3.5]nonan-6-one (4). From 3.94 g (12.55 mmol) of cyclopropyldiphenylsulfonium fluoroborate (**42**), 1.60 g (10.9 mmol) of commercial 1-tetralone, and 1.22 g (21.8 mmol) of powdered potassium hydroxide, there was obtained 2.01 g (99% yield) of spirocyclobutanone identical by ir and NMR with the previously obtained sample.[5]

2-(Cyclohex-3′-ene)cyclobutanone (2). The oxaspiropentane from 3-cyclohexene-1-carboxaldehyde was prepared as previously described from 6.82 g (22.0 mmol) of **42**, 2.20 g (20.0 mmol) of freshly purified aldehyde,[31] and 2.24 g (40.0 mmol) of powdered potassium hydroxide. The crude mixture of oxaspiropentane and diphenyl sulfide was refluxed with 157 mg of anhydrous lithium fluoroborate in 50 ml of benzene for 4.25 hr. An additional 133 mg of lithium fluoroborate was added and the reflux continued for 1 hr. Addition of 350 ml of hexane precipitated inorganic salts which were removed by filtration. Evaporation of the solvent and distillation at 65° (0.2 mm) gave 2.09 g (13.9 mmol, 70%) of cyclobutanone which was identical with the previously obtained compound.[5]

Cyclobutanone 5. As previously described, 1.94 g (9.03 mmol) of 4aβ-methyl-1,2,3,4,4a,9,10,10a-octahydro-1-phenanthrene,[20] 2.90 g (9.23 mmol) of **42**, and 1.02 g (18.2 mmol) of powdered potassium hydroxide generated a mixture of the oxaspiropentane and diphenyl sulfide. Rearrangement in benzene as described above with 83 mg of anhydrous lithium fluoroborate for 2.3 hr gave an oil. Chromatography of this oil on 25 g of silica gel in a 1.8 × 27 cm column separated diphenyl sulfide by elution with 100 ml of hexane and the product (2.27 g, 8.95 mmol, 99%) by elution with 400 ml of ether. Further purification on preparative TLC (20% ether in hexane, $R_f \sim 0.5$) gave 1.86 g of spirocyclobutanone **5**, mp 55.5-56.5° (lit.[5] mp 55.5-56°).

(*Z*)-1,5-Dimethylspiro[3.5]nonan-(*Z*)-7-one (3). From 16.0 g (51.0 mmol) of **42**, 5.14 g (40.8 mmol) of an *E,Z* mixture of 2,6-dimethylcyclohexanone, and 4.58 g (81.7 mmol) of powdered potassium hydroxide in 120 ml of DMSO for 27.5 hr was obtained 15.69 g of a mixture of oxaspiropentane and diphenyl sulfide. Distillation of a 13.88-g aliquot of this mixture at 29-39° (0.4-0.04 mm) gave 6.154 g (100%) of pure 2,6-dimethyl-8-oxadispiro-[2.0.5]decane: mp 15°; ir 3090 (w), 1460 (m), 1410 (w), 1370 (m), 1185 (w), 1140 (w), 1050 (s), 1010 (m), 978 (m), 943 (w); NMR δ 0.89 (6 H, d, J = 6.3 Hz, CH_3), 0.8-1.1 (4 H, m, cyclopropyl H, 1.3-2.2 (8 H, m, methylene and methine H).

Rearrangement of 6.06 g (36.5 mmol) of the oxaspiropentane by 587 mg of anhydrous lithium fluoroborate in 180 ml of refluxing benzene (1 hr) was carried out as described above. Distillation at 33-41° (0.1-0.08 mm) gave 5.30 g (31.9 mmol, 88%) of pure **3**: mp −5 to −4°; ir 1765 cm^{-1}; NMR δ 2.75 (2 H, t, J = 8 Hz, CH_2CO), 2.01 (2 H, t, J = 8 Hz, CH_2CH_2CO), 1.3-1.9 (8 H, m, methylene and methine), 1.07 (6 H, virtually coupled multiplet, CH_3); MS *m/e* (rel %) 166 (23), 138 (100), 123 (77), 110 (29), 109 (72), 95 (100), 82 (72), 81 (43), 68 (61), 67 (40), 55 (31), 41 (48).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.50; H, 11.01.

Preparation of Vinylogous Amides. To the pure cyclobutanone was added slightly more than 1 equiv of *tert*-butoxybis(dimethylamino)methane (**43**).[11] The neat mixture was heated at 50-70°. After a period of time, an additional amount of **43** was added and heating continued at 50-70° for an additional interval (see Table II) determined by the disappearance of starting cyclobutanone (TLC). All volatiles were removed under reduced pressure (1-2 mm) at room temperature to give the enamides as yellow solids. Alternatively, the reaction was diluted with methylene chloride

Table II. Preparation of Vinylogous Amides

Cyclobutanone (g, mmol)	43, g (mmol) 1st portion	43, g (mmol) 2nd portion	Temp, °C	Time, hr 1st interval	Time, hr 2nd interval	Enamide (wt, %)	Mp, °C Initial	Mp, °C Recryst
2 (1.31, 8.72)	1.65 (9.50)	1.63 (9.37)	50	18	25	10 (1.91, 98)	55–58	64–65[a]
3 (0.315, 1.90)	0.434 (2.49)	0.350 (**2**.01)	70	1.75	17.5	11 (0.360, 87)	88–94	95–95.5[a]
4 (2.97, 16.0)	**2**.97 (17.1)		50	18		12 (3.67, 95)	160–165	173–175[a]
5 (1.70, 6.69)	1.42 (8.15)	0.365 (2.**12**)	50	16.5	71.5	13 (2.17, 100)	174–178	178–179[a]
6 (4.49, 27.0)	5.**52** (37.0)	4.24 (**28**.0)	70	4	18	14 (5.71, 97)	ND	ND[b]
44 (2.00, 11.1)[c,e]	2.54 (15.8)	2.05 (**12**.7)	75	2	22	**20** (**2**.30, 88)		*d*

[a] Recrystallized from cyclohexane. [b] Recrystallized from hexane. [c] 1-Isopropyl-4-methylspiro[3.4]octan-6-one. [d] Only obtained as a crude oil. [e] Experiment performed by Dr. N. C. Holy.

Table III. Preparation of Dithianes

Vinylogous amide (g, mmol)	Thiotosylate (g, mmol)	KOAc (g, mmol)	Solvent[a] (ml)	Time, hr	Dithiane (g, mmol, % yield)	Mp, °C	Analytical R_f
10 (0.878, 4.28)	1.96 (4.71)	1.68 (17.15)	A (25)	4	**15** (0.210, 0.83, 19)[b]	69–70	0.70[k]
11 (0.424, 1.92)	0.880 (**2**.12)	0.880 (8.90)	B (8)	65	16 (0.190, 0.71, 37)[b]	95–96	0.55[b]
12 (0.250, 1.04)	0.480 (1.15)	0.392 (4.0)	A (6)	25.5	**17** (0.186, 0.64, 62)[c]	100.5–102[i]	0.74[k]
13 (0.354, 1.15)	0.597 (1.43)	0.454 (4.63)	B (8)	43.5	18 (0.248, 0.69, 91)[d,e]	163.0–163.5[i]	0.75[k]
14 (5.3, 24)	28.5 (68)	13.4 (137)	B (60)	72	19 (3.45, **12**.8, 53)[f]	84–86[j]	0.74[f]
20 (1.5, 6.4)	4.6 (11)	3.4 (35)	B (100)	70	**21** (0.296, 1.1, 17)[g,h]	101–101.5[j]	0.55[b]

[a] Solvent A = methanol. Solvent B = ethanol. [b] Chromatographed utilizing 5% ether in hexane (v/v). [c] Chromatographed utilizing **2**% ether in hexane (v/v). [d] Chromatographed utilizing 2:1 hexane–ethyl acetate (v/v). [e] Also 160 mg of **13** recovered from column. Thus, the yield given is based on starting material consumed. [f] Chromatographed utilizing 10% ether in hexane (v/v). [g] Chromatographed utilizing 5% ether in pentane (v/v). [h] Experiment performed by Dr. Norman Holy. [i] Recrystallized from methanol. [j] Recrystallized from hexane. [k] Chromatographed utilizing 1:1 ether:hexane (v/v).

and washed with water. After drying and evaporation (ultimately with a vacuum pump), the solid enamides suitable for further reaction were obtained. Recrystallization from hexane or cyclohexane provided further purification.

10: ir 1710, 1620 cm^{-1}; NMR δ 6.96 (1 H, t, J = 1.4 Hz, =CHN), 5.67 (2 H, m, vinyl), 3.00 (6 H, s, NCH_3), 1.2–3.3 (10 H, m); MS *m/e* (rel %) 205 (59), 125 (55), 98 (96), 97 (100), 84 (99), 82 (45), 69 (100), 68 (49), 44 (39), 43 (70); mol wt 205.1467 (calcd for $C_{13}H_{19}NO$, 205.1470).

11: ir 1700, 1615 cm^{-1}; NMR δ 6.90 (1 H, t, J = 1.2 Hz, =CHN), 3.00 (6 H, s, N-CH_3), 2.52 (2 H, d, J = 1.2 Hz, cyclobutane CH_2), 1.3–1.8 (8 H, m), 1.00 (6 H, virtually coupled doublet, J = 4 Hz, CH_3); MS 221 (54), 138 (88), 123 (72), 110 (33), 109 (78), 98 (69), 97 (88), 95 (100), 82 (99), 81 (50), 69 (91), 68 (75), 67 (63), 55 (52), 46 (42); mol wt 221.1784 (calcd for $C_{14}H_{23}NO$, 221.1780).

12: ir 1690, 1605 cm^{-1}; NMR δ 7.05–7.30 (4 H, m, aryl), 7.04 (1 H, s, =CHN), 3.04 (6 H, s, NCH_3), 2.65–2.95 (4 H, m), 1.8–2.2 (4 H, m); MS *m/e* (rel %) 241 (42), 196 (44), 144 (57), 98 (70), 97 (49), 83 (53), 69 (100), 57 (40), 43 (63), 42 (86).

13: ir 1698, 1615 cm^{-1}; NMR δ 7.05–7.35 (4 H, m, aryl), 6.97 (1 H, t, J = 1.6 Hz, =CHN), 2.98 (6 H, s, NCH_3), 1.5–3.1 (17 H, m), 1.43 (3 H, s, CCH_3); MS *m/e* (rel %) 309 (44), 254 (39), 239 (34), 212 (47), 198 (34), 197 (100), 183 (57), 155 (30), 141 (47), 129 (36), 84 (48), 69 (35), 56 (88), 55 (42); mol wt 309.2093 (calcd for $C_{21}H_{27}NO$, 309.2099).

14: NMR δ 6.81 (1 H, t, J = 1.7 Hz, =CHN), 5.31 (1 H, m, =CH), 3.04 (6 H, s, NCH_3), 2.56 (2 H, bs, cyclobutane CH_2), 1.5–2.3 (5 H, m), 1.61 (3 H, d, J = 1.8 Hz, vinyl CH_3), 0.90 (3 H, d, J = 6 Hz, CCH_3).

20: ir 1695, 1615 cm^{-1}; NMR δ 6.80 (1 H, t, J = 1.5 Hz, =CHN), 3.03 (6 H, s, NCH_3), 2.74 (1 H, d, J = 13 Hz) and 2.46 (1 H, d, J = 13 Hz) (cyclobutane CH_2), 1.4–2.0 (7 H, m), 1.2 (3 H, d, J = 7 Hz, CCH_3), 0.96 (3 H, d, J = 7 Hz, CCH_3), 0.89 (3 H, d, J = 7 Hz, CCH_3).

Preparation of Dithianes. The vinylogous amide, trimethylene dithiotosylate,[12] and potassium acetate [recrystallized from glacial acetic acid, then from ethanol–water, and dried overnight at 100° (0.5 mm)] in anhydrous ethanol or methanol were refluxed. After the specified time (see Table III) the reaction was cooled and partitioned between ether and water. The aqueous layer was extracted with several additional volumes of ether. The combined ether solutions were dried and evaporated in vacuo. Chromatography (either column or preparative TLC) utilizing 2–10% ether in hexane (for **18** hexane:ethyl acetate 2:1) provided pure dithianes. The details for each of the runs are summarized in Table III.

15: ir 1762 cm^{-1}; NMR δ 5.64 (2 H, bs, vinyl), 3.60 (2 H, m, CHS), 3.3 (1 H, m, CHCO), 2.56 (2 H, m, CHS), 1.5–2.5 (11 H, m); MS *m/e* (rel %) 254 (16), 226 (24), 145 (57), 132 (100), 118 (20), 41 (29).

Anal. Calcd for $C_{13}H_{18}OS_2$ (254.0799): C, 61.41; H, 7.14; S, 25.16. Found (254.0808): C, 61.74; H, 6.81; S, 25.35.

16: ir 1752 cm^{-1}; NMR δ 3.57 (2 H, ddd, J = 15.2, 12.0, 3.2 Hz, CHS), 2.64 (2 H, dt, J = 15.2, 3.8 Hz, CHS), 2.04 (2 H, s, cyclobutane CH_2), 1.5–2.2 (8 H, m), 1.20 (6 H, virtually coupled doublet, J = 6 Hz, CH_3); MS *m/e* (rel %) 270 (1), 242 (14), 134 (10), 133 (17), 132 (100), 123 (10), 41 (16); mol wt 270.1114 (calcd for $C_{14}H_{22}OS_2$, 270.1112).

17: ir 1762 cm^{-1}; NMR δ 7.0–7.7 (4 H, m, aryl), 3.58 (2 H, m, CHS), 2.74 (2 H, m, benzylic), 2.60 (2 H, m, CHS), 1.6–2.5 (6 H, m); MS *m/e* (rel %) 290 (2), 262 (47), 158 (48), 130 (100), 129 (32), 128 (40).

Anal. Calcd for $C_{16}H_{18}OS_2$: C, 66.17; H, 6.25; S, 22.08. Found: C, 66.03; H, 6.20; S, 22.09.

18: ir 1758 cm^{-1}; NMR δ 7.0–7.4 (4 H, m, aryl), 3.57 (2 H, m, CHS), 3.01 (2 H, m, benzylic), 2.59 (2 H, m, CHS), 2.35 (1 H, d, J = 13.6 Hz) and 2.09 (1 H, d, J = 13.6 Hz) (cyclobutane CH_2), 1.4–2.6 (11 H, m), 1.34 (3 H, s, CH_3); MS *m/e* (rel %) 358 (0.5), 330 (20), 133 (27), 132 (100), 28 (27); mol wt 358.1425 (calcd for $C_{21}H_{26}OS_2$, 358.1444).

19: ir 1752 cm^{-1}; NMR δ 5.52 (1 H, m, vinyl), 3.48 (2 H, m, CHS), 2.16 (1 H, d, J = 14 Hz) and 1.90 (1 H, d, J = 14 Hz) (cyclobutane CH_2), 1.80 (3 H, bs, vinyl CH_3), 1.3–2.7 (7 H, m), 0.96 (3 H, d, J = 7 Hz, CCH_3); MS *m/e* (rel %) 268 (5), 240 (92), 198 (60), 136 (100), 133 (35), 132 (85), 124 (43), 119 (52); mol wt 268.0953 (calcd for $C_{14}H_{20}OS_2$, 268.0955).

21: ir 1760 cm^{-1}; NMR δ 3.56 (2 H, ddd, J = 14.8, 12.0, 3.2 Hz, CHS), 2.56 (2 H, dt, J = 14.8, 3.8 Hz, CHS), 1.91 (2 H, s, cyclobutane CH_2), 1.4–2.5 (9 H, m), 1.10 (3 H, d, J = 7 Hz, CCH_3), 1.01 (3 H, d, J = 7 Hz, CCH_3), 0.89 (3 H, d, J = 7 Hz, CCH_3); MS *m/e* (rel %) 284 (6), 256 (6), 133 (26), 132 (100), 109 (36).

Anal. Calcd for $C_{15}H_{24}OS_2$ (284.1269): C, 63.35; H, 8.51; S, 22.51. Found (284.1268): C, 63.32; H, 8.48; S, 22.52.

Preparation of Dithiane 21 from Enol Acetate 22. To a solution of 82.1 mg (0.328 mmol) of 2-acetoxymethylene-5-isopropyl-8-methyl-1-spiro[3.4]octanone (**22**) in 0.5 ml of absolute ethanol were added 0.163 g (1.66 mmol) of potassium acetate and 0.286 g

(0.688 mmol) of trimethylene dithiotosylate. The mixture was refluxed for 44 hr after which TLC examination (10% ether in hexane) showed the reaction to be complete. The orange solution was cooled and partitioned between 10 ml of water and 20 ml of ether. The water layer was extracted with additional portions of ether. After drying and evaporation in vacuo of the combined ether layers, 249.3 mg of crude product was obtained. Purification by chromatography on 10 g of silica gel utilizing 5% ether in hexane gave 110.7 mg (100%) of dithiane **21** identical with the previously obtained sample.

1-Carbomethoxy-1-(2′,2′-trimethylenedithioethyl)tetralin (26). Sodium (17 mg, 0.74 mmol) was dissolved in 3.3 ml of anhydrous methanol and the solution added to 100 mg (0.344 mmol) of dithiane **17**. After refluxing for 1.5 hr, the solution was evaporated in vacuo and the residue taken up in 2 ml of water, 0.5 g of solid carbon dioxide, and 10 ml of methylene chloride. The aqueous layer was washed with two additional portions of methylene chloride. Drying and evaporation in vacuo gave 126 mg (quantitative yield) of product **26**. Further purification on 3 g of silica gel (1.5 × 5 cm column) utilizing 2% and then 10% ether in hexane gave 69 mg (60%) of pure **26**, mp 65–66°. Because of an accidental loss of some of the column fractions, this yield must be considered a minimum: ir 1720 cm^{-1}; NMR δ 7.60 (1 H, m, aryl), 7.15–7.50 (3 H, m, aryl), 4.09 (1 H, dd, J = 7.2, 5.8 Hz, SCHS), 3.80 (3 H, s, CO_2CH_3), 2.7–3.1 (8 H, m), 1.7–2.7 (8 H, m); MS *m/e* (rel %) 322 (16), 190 (65), 158 (23), 155 (14), 135 (10), 133 (100), 131 (10), 130 (14), 129 (54), 128 (22), 119 (43), 115 (13), 73 (10), 45 (13).

Anal. Calcd for $C_{17}H_{22}O_2S_2$: C, 63.32; H, 6.88; S, 19.89. Found: C, 63.11; H, 6.88; S, 19.79.

(*Z,Z*)-2-Carbomethoxy-2-(2′,2′-trimethylenedithioethyl)-1,3-dimethylcyclohexane (27). To 111 mg (0.412 mmol) of dithiane **16** in 4.0 ml of anhydrous methanol was added 75.4 mg (1.40 mmol) of commercial sodium methoxide. After refluxing for 64.5 hr, the solution was reduced to a small volume in vacuo and the residue taken up in 10 ml of methylene chloride and 5 ml of water. The water layer was acidified with hydrochloric acid and extracted twice with methylene chloride. After drying and evaporating in vacuo, the crude product was applied to a preparative TLC plate and eluted twice with 1% ether in hexane (v/v). From the band of R_f 0.31, 54.5 mg of starting material was recovered. From the band of R_f 0.16, 36.1 mg (57% based on recovered starting material) of product, mp 91.0–91.5°, was obtained after recrystallization from cyclohexane–pentane: ir 1725 cm^{-1}; NMR δ 4.02 (1 H, t, J = 5 Hz, SCHS), 3.68 (3 H, s, OCH_3), 2.87 (4 H, m, SCH_2), 2.19 (2 H, d, J = 5 Hz, CH_2CH-dithiane), 1.2–2.2 (10 H, m), 0.88 (6 H, d, J = 6 Hz, CH_3); MS *m/e* (rel %) 302 (9), 170 (24), 155 (38), 133 (100), 132 (20), 119 (48), 109 (24), 67 (27), 55 (35), 41 (69); mol wt 302.1383 (calcd for $C_{15}H_{26}O_2S_2$, 302.1374).

2-(3′-Cyclohexen-1-yl)-3,3-trimethylenedithiopropanoic Acid (28). Dithiane **15** (116 mg, 0.464 mmol) was refluxed in a solution of 1 ml of THF and 4 ml of 1 *M* aqueous sodium hydroxide for 18.25 hr. TLC (ether–hexane 1:1) indicated the disappearance of starting material. The solution was acidified with 1 *M* aqueous hydrochloric acid and extracted with five 10-ml portions of methylene chloride. After drying and evaporating of the solvent in vacuo, 146 mg (100% yield) of product was obtained. Recrystallization from cyclohexane gave 111 mg (88%) of acid **28**: mp 89.0–89.5°; ir 2500–3500, 1700, 1645 cm^{-1}; NMR δ 10.85 (1 H, b, CO_2H), 5.65 (2 H, s, vinyl), 4.05 (1 H, dd, J = 9, 5 Hz, SCHS), 2.6–3.0 (6 H, m), 1.6–2.6 (8 H, m), 1.2–1.6 (2 H, m); MS *m/e* (rel %) 272 (1), 197 (8), 164 (4), 133 (8), 132 (5), 119 (15), 84 (80), 69 (25), 56 (100), 42 (33), 41 (82); mol wt 272.0915 (calcd for $C_{13}H_{20}O_2S_2$, 272.0905).

Cyclopentenone Annelation from Dithiane 17. Preparation of Dithiane Alcohol 32. A solution of 157 mg (0.541 mmol) of dithiane ketone **17** in 2.0 ml of dry ether was cooled to −78°. A commercial solution of methyllithium in ether (1.30 ml of 0.95 *M*, 1.24 mmol) was added. The reaction was allowed to warm to room temperature (15 min) and was stirred at that temperature for 30 min. TLC (hexane–ether 1:1) indicated the absence of starting ketone (R_f 0.77) and the presence of a more polar product (R_f 0.68). After addition of saturated aqueous ammonium chloride, the mixture was extracted four times with ether. The ether solution was dried and evaporated in vacuo to give 173 mg (100% yield) of product (**32**). Final purification was effected by preparative TLC eluting five times with 5% ether in hexane from which 128 mg was recovered: ir 3530, 1375, 1345 cm^{-1}; NMR δ 7.60 (1 H, m, aryl), 7.16 (3 H, m, aryl), 3.17 (1 H, s, OH), 1.4–3.2 (12 H, m), 2.16 (1 H, d, J = 16 Hz) and 1.92 (1 H, d, J = 16 Hz) (cyclobutane CH_2), 1.78 (3 H, s); MS *m/e* (rel %) 306 (0.2), 175 (13), 174 (91), 162 (100), 144 (30), 133 (36), 132 (19), 131 (73), 129 (47), 128 (29), 119 (33), 115 (22), 91 (19), 43 (50).

Anal. Calcd for $C_{17}H_{22}OS_2$: C, 66.65; H, 7.24; S, 20.89. Found: C, 66.35; H, 6.86; S, 20.85.

Preparation of Acetyl Dithiane 33. To 128 mg (0.418 mmol) of the above dithiane alcohol **32** in 20 ml of anhydrous methanol was added 126 mg (2.33 mmol) of commercial sodium methoxide. After refluxing for 7.25 hr, the reaction mixture was partitioned between 50 ml of ether and 50 ml of water. The aqueous layer was extracted with two additional 50-ml portions of the combined ether extracts and dried. After evaporation of solvent, ir and NMR indicated incomplete reaction. The oil was redissolved in 20 ml of methanol and 119 mg (2.20 mmol) of sodium methoxide added. After refluxing an additional 50 hr, it was worked up as before to give 122 mg (95% yield) of **33**. Further purification by preparative TLC (10% ether in hexane) allowed recovery of 88 mg, mp 84.5–85.0°, after recrystallization from cyclohexane: ir 1700 cm^{-1}; NMR δ 7.20 (4 H, m, aryl), 3.96 (1 H, t, J = 6 Hz, SCHS), 2.94 (6 H, m, benzylic and CH_2S), 2.48 (1 H, dd, J = 16, 6 Hz) and 2.24 (1 H, dd, J = 16, 6 Hz) (CH_2CH-dithiane), 2.00 (3 H, s, CH_3CO), 1.6–2.3 (6 H, m); MS *m/e* (rel %) 306 (0.8), 265 (5), 231 (8), 174 (52), 133 (37), 119 (100), 84 (36), 69 (14), 56 (60), 55 (25), 43 (42), 42 (22); mol wt 306.1123 (calcd for $C_{17}H_{22}OS_2$, 306.1112).

Preparation of Cyclopentenone 35. To 71.5 mg (0.234 mmol) of **33** in 0.5 ml of acetonitrile, 2 ml of THF, and 4.5 ml of water were added 300 mg (3.00 mmol) of calcium carbonate and 115 mg (0.811 mmol) of freshly distilled methyl iodide. The mixture was refluxed 45.5 hr. It was cooled and added to 80 ml of ether. The ether layer was washed with aqueous sodium bicarbonate, dried, and evaporated to give 60.3 mg (100% yield) of keto aldehyde: ir 2740, 1700 cm^{-1}; NMR δ 9.82 (1 H, t, J = 2.5 Hz, CHO), 7.18 (4 H, m, aryl), 2.83 (4 H, m, benzylic and CH_2CO), 2.02 (3 H, s, CH_3CO), 1.7–2.3 (4 H, m).

To 60 mg (0.277 mmol) of the keto aldehyde **34** in 2.5 ml of ethanol was added 5.0 ml of 1% aqueous sodium hydroxide solution, and nitrogen was bubbled through the solution for 5 min. It was then refluxed for 1 hr and cooled and the volume of solvent reduced in vacuo. The aqueous mixture was extracted with three 25-ml portions of ether and the ether extracted with 10 ml of saturated aqueous sodium chloride. After drying and evaporation, 51.4 mg (94%) of product, whose spectral data indicated it to be pure, was obtained. Further purification was achieved by preparative TLC (2% ether in benzene): ir 1710, 1598 cm^{-1}; NMR δ 7.85 (1 H, dt, J = 6, 3 Hz, CH=CHCO), 7.14 (3 H, m, aryl), 6.82 (1 H, m, aryl), 6.37 (1 H, dt, J = 6, 1.5 Hz, =CHCO), 2.92 (4 H, m), 1.5–2.5 (4 H, m); MS *m/e* (rel %) 198 (100), 169 (45), 142 (52), 141 (60), 130 (33), 129 (68), 128 (73), 115 (53), 84 (32), 79 (60), 69 (25), 56 (40), 43 (47), 42 (93); mol wt 198.1050 (calcd for $C_{14}H_{14}O$, 198.1045).

1β-Carbomethoxy-1α-(2′,2′-trimethylenedithioethyl)-4aβ-methyl-10aα-*H*-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (29). To a suspension of 79 mg (0.220 mmol) of dithiane **18** in 5 ml of methanol was added a solution of methanolic sodium methoxide prepared by reacting 80 mg (3.5 mg-atom) of sodium with 2 ml of methanol. After refluxing 21 hr, TLC (2:1 chloroform–hexane) indicated the disappearance of starting material (R_f 0.49) and the appearance of a product R_f 0.12. Work-up in the usual fashion gave 94 mg (100% yield) of **29** recrystallized from cyclohexane, mp 135.0–135.5°: ir 1725 cm^{-1}; NMR δ 7.02 (4 H, m, aryl), 4.06 (1 H, dd, J = 7, 3 Hz, SCHS), 3.62 (3 H, s, OCH_3), 1.2–3.0 (19 H, m), 1.02 (3 H, s, CCH_3); MS *m/e* (rel %) 390 (10), 258 (45), 183 (24), 133 (100), 85 (75), 69 (29), 56 (99), 55 (40), 43 (15).

Anal. Calcd for $C_{22}H_{30}O_2S_2$ (390.1687): C, 67.67; H, 7.74; S, 16.38. Found (390.1695): C, 67.76; H, 7.66; S, 16.32.

β-Carbomethoxy-4aβ-methyl-1α-(2′-oxoethyl)-10aα-*H*-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (30). A sample of 215 mg (0.552 mmol) of **29** was hydrolyzed as previously described utilizing 1 ml of acetonitrile, 7 ml of THF, 9 ml of water, 825 mg of calcium carbonate, and 1.567 g (1.103 mmol) of freshly distilled methyl iodide. The normal work-up gave 181 mg (100% yield).

Further purification by recrystallization from cyclohexane allowed recovery of 109 mg, mp 152.0–153.5°: ir 2720, 1725 cm^{-1}; NMR δ 9.85 (1 H, dd, J = 3.5, 1.4 Hz, CHO), 7.1 (4 H, m, aryl), 7.06 (3 H, s, CO_2CH_3), 1.2–3.0 (13 H, m), 1.08 (3 H, s, CCH_3); MS *m/e* (rel %) 300 (12), 285 (7), 257 (19), 256 (25), 241 (100), 225 (33), 207 (30), 197 (60), 183 (46), 181 (67), 155 (30), 143 (36), 142 (54), 141 (49), 131 (30), 129 (61), 128 (51), 127 (28), 117 (43), 115 (41), 91 (74), 78 (29); mol wt 300.1745 (calcd for $C_{19}H_{24}O_3$, 300.1725).

Racemic Methyl Deoxypodocarpate (31). Acetonitrile was dried by stirring over 4A Linde molecular sieves and distilling from calcium hydride. A solution of 109 mg (0.363 mmol) of **30** in 10 ml of dry acetonitrile was deoxygenated by bubbling nitrogen through the solution. Tris(triphenylphosphine)rhodium chloride (339 mg, 0.367 mmol) was added and the solution refluxed 3.25 hr. During this time, the deep-red solution became pale yellow, and a yellow solid separated. The solution was cooled and added to 30 ml of ethanol. Filtration removed the solid rhodium complex. The filtrate was evaporated in vacuo and the residue taken up in 10 ml of carbon tetrachloride. The undissolved solids (mainly additional rhodium salts) were removed by filtration, and the product was purified by TLC (10% ether in hexane) to give 58 mg (64%) of **31**, mp 126.5–127.0°, identical by ir and NMR with an authentic sample of optically pure methyl deoxypodocarpate.[21]

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.34; H, 8.89.

Cyclopentenone Annelation from Dithiane 19. A solution of 3.05 g (11.0 mmol) of keto dithiane **19** in 250 ml of dry THF was cooled to −78°. A commercial solution of methyllithium in hexane (62.4 ml of 1.82 *M*, 114 mmol) was added over 30 min. After stirring at −78° for 30 min, it was stirred at room temperature for 2.5 hr. Water was added by syringe *very slowly* to contain the frothing. The two-phase mixture was diluted with 1 l. of ether and washed twice with 75 ml of water. After drying of the solution and evaporation of the solvent, 3.30 g (quantitative yield) of alcohol was obtained: ir 3540, 3450 cm^{-1}; NMR δ 5.6 and 5.4 (1 H, m, vinyl), 1.96 (3 H, s, $=CCH_3$), 1.58 and 1.64 (3 H, s, $HOCCH_3$), 1.2–3.2 (13 H, m), 0.66 (3 H, d, J = 7 Hz, $CHCH_3$).

A solution of 3.01 g (57 mmol) of commercial sodium methoxide and the entire sample of crude alcohol from above was refluxed in 110 ml of anhydrous methanol. After 4 days at reflux, TLC (20% ether in hexane) indicated the absence of starting material. Upon cooling, the reaction mixture was diluted with 500 ml of ether and washed three times with 50 ml of water, and the water layers were reextracted twice with 50 ml of ether. The combined ether layers were dried and evaporated in vacuo to give 2.93 g (91% yield) of keto dithiane. A small sample was further purified by distillation: bp 60° (0.05 mm); ir 1704 cm^{-1}; NMR δ 5.78 (1 H, m, vinyl), 3.79 (1 H, t, J = 4.5 Hz, SCHS), 2.76 (5 H, m, SCH_2), 1.98 (3 H, s, CH_3CO), 1.63 (3 H, d, J = 1.5 Hz), 1.48–2.36 (9 H, m), 0.85 (3 H, d, J = 6 Hz, $CHCH_3$); MS *m/e* (rel %) 284 (15), 180 (26), 152 (60), 133 (45), 119 (100), 107 (71), and 91 (26); mol wt 284.1267 (calcd for $C_{15}H_{24}OS_2$, 284.1268).

Hydrolysis of 2.93 g (10.3 mmol) of dithiane was accomplished in the usual manner utilizing 212 ml of a 10% acetonitrile solution in water, 140 ml of THF, 51.6 g (364 mmol) of methyl iodide, and 21.2 g (212 mmol) of calcium carbonate. After the standard workup, 2.19 g (quantitative yield) of **38** was obtained: ir 2730, 1705, 1650 cm^{-1}; NMR δ 9.68 (1 H, dd, J = 4.4, 2.3 Hz, CHO), 5.76 (1 H, m, vinyl), 2.64 (1 H, dd, J = 15.8, 2.3 Hz) and 2.38 (1 H, dd, J = 15.8, 4.4 Hz) (CH_2CHO), 2.05 (3 H, s, CH_3CO), 1.62 (3 H, bs, vinyl CH_3), 0.89 (3 H, d, J = 7 Hz, $CHCH_3$).

The crude keto aldehyde **38** was dissolved in 100 ml of ethanol and 200 ml of a 1% aqueous sodium hydroxide solution. After deoxygenating the solution by bubbling nitrogen through it, it was heated to 80° for 1 hr. Upon cooling, it was diluted with 700 ml of ether and the aqueous layer separated. The water layer was extracted with additional ether. The aqueous layer was then concentrated in vacuo and extracted an additional time with 100 ml of ether. The combined ether layers were dried and evaporated in vacuo to give 1.51 g (83%) of cyclopentenone. Additional purification by distillation [50° (0.05 mm)] allowed recovery of 1.16 g (58% overall from **37**) of enone **39** as a colorless oil: ir 1700, 1665, 1590 cm^{-1}; NMR δ 7.64 (1 H, dt, J = 6, 3 Hz, $=CHCO$), 6.13 (1 H, dt, J = 6, 2 Hz, $CHCHCO$), 5.41 (1 H, m, $=CHCH_2$), 2.64 (1 H, ddd, J = 20, 3, 2 Hz) and 2.36 (1 H, ddd, J = 20, 3, 2 Hz) ($CH_2CH=CHCO$), 1.7–2.2 (3 H, m), 1.38 (3 H, bs, vinyl CH_3), 1.1–1.7 (2 H, m), 0.67 (3 H, d, J = 7 Hz); MS *m/e* (rel %) 176 (100), 145 (26), 133 (40), 105 (25), 93 (30), 91 (50), and 77 (25).

Anal. Calcd for $C_{12}H_{16}O$ (176.1201): C, 81.77; H, 9.15. Found (176.1201): C, 81.86; H, 8.99.

Preparation of Cyano Ketone 40. A solution of ammonium cyanide was generated by mixing 391 mg (6.00 mmol) of potassium cyanide and 241 mg (4.50 mmol) of ammonium chloride in 20 ml of DMF and 3.0 ml of water. A solution of 529 mg (3.00 mmol) of **39** in 4 ml of DMF was added at room temperature and subsequently the mixture heated at 100° for 18 hr. TLC (30% ether in hexane) indicated completion of reaction. Upon cooling, the mixture was poured in 250 ml of ether. The organic layer was washed with water and the water layer extracted with additional ether. After drying and removal of solvents in vacuo, 557 mg (91% yield) of white crystals was obtained. Recrystallization from hexane gave white needles: mp 79–82°; ir 2247, 1745 cm^{-1}; NMR δ 5.44 (1 H, m, vinyl), 1.6–3.2 (10 H, m), 1.55 and 1.48 (3 H, bs each, vinyl CH_3), 0.92 and 0.78 (3 H, d each, J = 6 Hz, $CHCH_3$); MS *m/e* (rel %) 203 (40), 188 (34), 185 (35), 167 (45), 160 (51), 122 (50), 107 (100), 93 (52), 91 (36), 68 (34); mol wt 203.1309 (calcd for $C_{13}H_{17}ON$, 203.1310).

Preparation of Keto Ester 41. A solution of 557 mg (2.74 mmol) of nitrile **40** in 10 ml of ether was added to 40 ml of ether containing 5 ml of freshly distilled methanol. After cooling to 0°, dry hydrogen chloride gas was bubbled through the solution for 1.5 hr. To remove some of the excess hydrogen chloride, nitrogen was bubbled through the solution for 20 min. The crude reaction mixture was poured onto 100 g of cracked ice, stirred for 20 min, and diluted with 100 ml of ether. After separation of layers, the aqueous layer was extracted three times with ether. After evaporation of solvent, 219 mg of ester was obtained. The aqueous layer was neutralized with cold 5% aqueous sodium hydroxide and extracted three times with 150 ml of ether. After drying and evaporation, an additional 286 mg of product was obtained. Final purification by preparative TLC (3:1 hexane–ether) gave 412 mg in the band R_f 0.1–0.3 and 23 mg in the band R_f 0.0–0.1 for a total yield of 435 mg (67% yield): ir 1740, 1670 cm^{-1}; NMR δ 5.36 (1 H, m, vinyl), 3.61 (3 H, s, CO_2CH_3), 2.6–3.1 (1 H, m), 1.7–2.6 (9 H, m), 1.47 (3 H, bs, vinyl CH_3), 0.79 and 0.76 (3 H, d each, J = 7 Hz, CH_3); MS *m/e* (rel %) 236 (28), 122 (99), 107 (100), 94 (56), 91 (35), 79 (26), 77 (21), 55 (32), 41 (40); mol wt 236.1414 (calcd for $C_{14}H_{20}O_3$, 236.1412).

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Polymeric Reagents. III. Synthesis of an Insoluble Polymeric Thioanisole and Its Utilization for the Oxidation of Alcohols

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Abstract: Macroreticular cross-linked polystyrene (Ⓟ-C_6H_5) has been functionalized by substituting varying percentages of the aromatic rings with *p*-methyl sulfide groups. This polymer is an effective coreactant for the sulfide-based oxidation of primary and secondary alcohols. The reaction has also been extended to the selective monooxidation of 1,7-heptanediol.

Insoluble polymers as supports for reagents useful in organic synthesis have been receiving considerable attention since R. B. Merrifield[2] first reported the synthesis of polypeptides on a cross-linked polystyrene support. The advantages of the use of polymeric reagents in general organic syntheses have been described and exploited in a number of papers[3] and recently summarized by Overberger.[4]

Major advantages of this approach that have not previously been stressed are: (a) the possibility of reducing the potential of pollution stemming from chemical research and industrial chemical processes; and (b) the production of recyclable polymeric reagents, which would be of value to an industry facing inevitable scarcity of products.

Taking into account the above factors, we investigated the application of a polymeric thioanisole in the new Corey[5] oxidation method. Although many new and efficient methods to oxidize alcohols to aldehydes or ketones have been developed, the sulfide-based method is significant for its ease of operation, mildness of conditions, and low cost of reagents. However, a number of major disadvantages arise, particularly when one might want to apply this approach to an industrial process. These disadvantages include the noxious odor associated with dimethyl sulfide or thioanisole and the difficulty involved in removing thioanisole from many products. It is anticipated that a polymeric reagent, equivalent in function to the monomeric sulfides, could solve these disadvantages in addition to being reusable and simple to apply.

Our efforts have been directed toward the synthesis of the cross-linked polymeric sulfide **3.** Soluble *p*-methylmercaptostyrene has been prepared via the direct polymerization of the monomer.[6] Although this polymer would probably function in the oxidation process, it does not have all the desired properties that a cross-linked chain would provide. We chose to concentrate on the functionalization of macroreticular polystyrene.[7,8] A major consideration in use of a macroreticular resin is the macroporosity and rigidity[8] of the beads that give certain advantages over the ordinary gel-type polymers: its easy filtration, its nominal shrinking and swelling properties in the reaction solvents even with changing temperatures, and its more accessible reactive sites.