SYNTHETIC APPLICATIONS
OF
CARBANIONS STABILIZED BY SULFUR

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This thesis is dedicated
to my mother, Hideko Oshima
and my uncle, Kazo Kadowaki
and to my wife
Shigeko Oshima

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ABBREVIATIONS

Brine = saturated aqueous sodium chloride, ether = diethyl ether, DMF = dimethylformamide, DMSO = dimethylsulfoxide, HMPA = hexamethylphosphoric triamide, THF = tetrahydrofuran, rel = relative.

Mp = melting point, bp = boiling point, tlc = thin layer chromatography (R_f = mobility relative to solvent front), glpc = gas-liquid phase chromatography (t_r = retention time).

Nmr = nuclear magnetic resonance (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and dt = doublet of triplets, etc), ir = infrared (s = strong, m = moderate, w = weak, and sh = shoulder), ms = mass spectrum, anal = elemental microanalysis.

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Chapter 1

Introduction and General Summary

The recent developments in organic synthesis have
been as dramatic as any that have occurred in other
laboratory sciences. One needs only mention a few terms to
understand that chemical systems that did not exist twenty
years ago have become as much a part of the repertoire of the
synthetic organic chemist as borosilicate glassware. The
list of such terms in organic reactions, for example, would
include the Wittig reaction, carbene reaction, hydroboration,
hydride reduction, homogeneous catalysis, and so on.
However, as compared with naturally proceeding biochemical
processes, we have to recognize that our artificial means in
synthetic chemistry are still too much unskillful. In the
biological realm, every enzyme catalysis is fast and
quantitative at room temperature and, in addition, each
biological process has its own tailor-made enzyme. Syntheses
in vitro up to 1950 approximately could be understood by
learning not more than 20 basic organic reactions. It
should be noted that all of the successful cases of synthesis
in these days have been characterized by a strong dependence
on creating one or more key synthetic means of novelity.
Thus, a big challenge to organic chemists today lies in
discovering more and more useful, highly specific reactions,
which are particularly suitable to the intended preparative
scheme, and also thus innovating in the actual synthetic
activities.

This thesis deals with the new roles of sulfur and phosphorus reagents in the organic synthesis. In order to place the present study into its proper perspective, it should be appropriate to review briefly some of the history of these reagents in synthetic methodology. Among the new reactive species developed in the last few decades, there is one which is of outstanding interest particularly to the synthetic organic chemists: that is an "ylide." The term "Ylid" was first coined in the German language by Georg Wittig in 1944.[1] It was derived by combination of the ending -yl to imply a covalency (i.e., Meth<u>yl</u>) and the ending -id to imply anionicity (i.e., Acety<u>lid</u>) both on a single carbon atom. Thus, an ylide is defined as a substance in which a carbanion is attached directly to a heteroatom carrying a high degree of positive charge and is represented by the general formula I.

$$\begin{array}{c} > \overset{-}{\underset{}{C}} - \overset{+}{X} \qquad I \end{array}$$
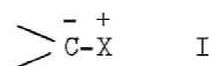
This definition is intended to include those resonance hybrid molecules in which there is at least one contributing structure which meets the original definition. Therefore, ylides may have an enolate structure (II). They also include

$$\underset{II}{\overset{O}{\underset{\|}{-C}}-\overset{-}{C}H-\overset{+}{X}} \quad \longleftrightarrow \quad \underset{III}{\overset{\overset{-}{O}}{\underset{|}{-C}}=CH-\overset{+}{X}} \qquad \overset{-}{C}-\overset{+}{X}-\overset{-}{O}$$
$$\qquad\qquad II \qquad\qquad\qquad\qquad\qquad III$$
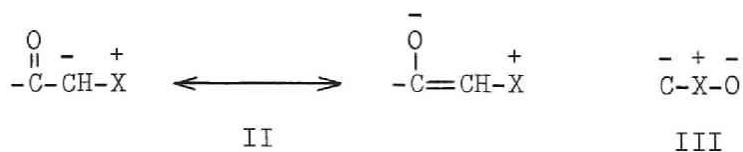
those molecular systems whose heteroatoms carry less than a full formal positive charge or the structure such as III. Accordingly an ylide is but a special type of zwitterion or betaine. However, these latter terms should be reserved for those doubly and oppositely charged species, in which the formal charges are not on adjacent atoms as this is the case with the zwitterionic form of α-amino acids.

Typical compounds of ylide structure are the diazoalkanes, the phosphorus ylides, and the sulfur ylides of Fig IV. To the extent that the structures in the lower line of Fig IV contribute to the resonance hybrids, these compounds are nucleophilic at the respective ylide carbon.

$$R_2C\overset{+}{=}\overset{-}{N}=N \quad\longleftrightarrow\quad R_2\overset{-}{C}-\overset{+}{N}-N$$

$$R_2C=P(C_6H_5)_3 \quad\longleftrightarrow\quad R_2\overset{-}{C}-\overset{+}{P}(C_6H_5)_3$$

$$R_2C=S(CH_3)_2 \quad\longleftrightarrow\quad R_2\overset{-}{C}-\overset{+}{S}(CH_3)_2$$

$$R_2C=\overset{O}{\overset{\uparrow}{S}}(CH_3)_2 \quad\longleftrightarrow\quad R_2\overset{-}{C}-\underset{+}{\overset{O}{\overset{\uparrow}{S}}}(CH_3)_2$$

diazoalkanes phosphorus ylides sulfur ylides (sulfonium type) sulfur ylides (oxosulfonium type)
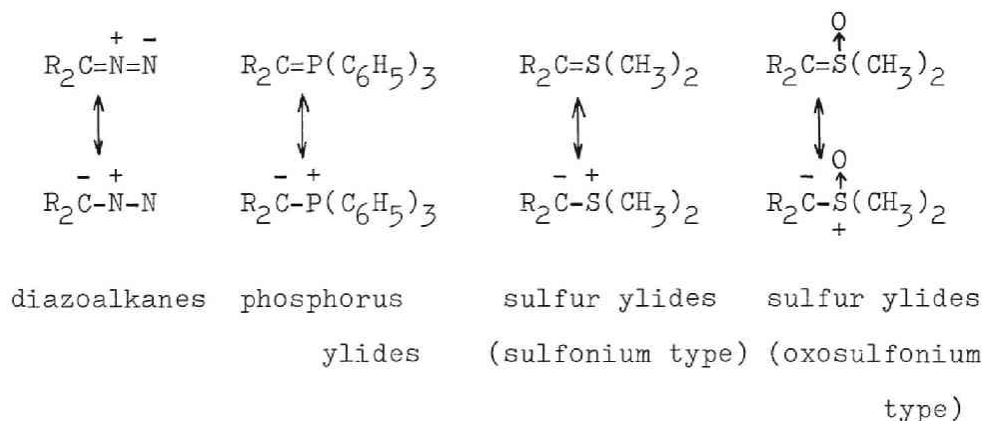
Fig IV. Strongly polarized (or polarizable) compounds which act as carbon nucleophiles (type $R_2C=Z$ carbon nucleophiles).

They undergo direct addition to carbonyl compounds to give intermediates which can collapse in three different ways, as shown in Fig V. Pathways a and b are examples of   the

addition-elimination [2] proceeding in virtue of good "leaving groups" (i.e., N_2 of diazoalkanes and $(CH_3)_2S$ of sulfur ylide, respectively). With diazoalkanes, both pathways a and b are frequently encountered, although the path b usually predominates; with the sulfur ylides, the path a is preferred. On the other hand, phosphorus ylides usually follow the path c, which represents a reorganization reaction (i.e., oxygen and a formal carbene carbon trade places). The phosphorus ylide reaction, often referred to as the "Wittig reaction," is particularly versatile in its applicability to the synthesis of a wide variety of olefins of the desired structures.
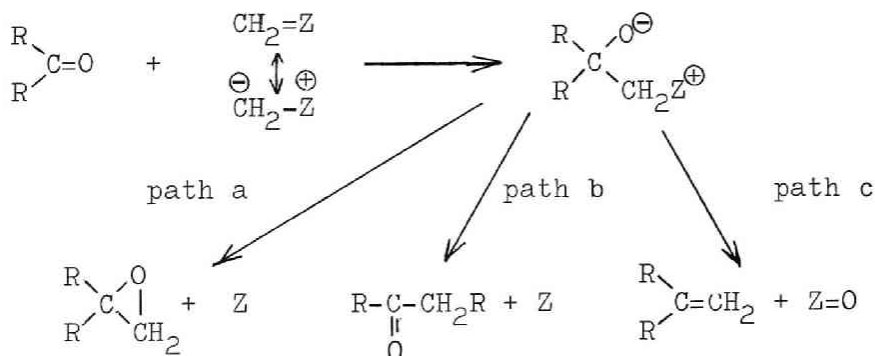

Fig V.   Reactions of $R_2C=Z$ type carbon nucleophiles with carbonyl compounds.

The "Wittig reagent" is prepared by allowing the appropriate alkyl halide to interact with triphenylphosphine, followed by treatment of the resulting phosphonium salt with

a strong base, as illustrated in Fig VI.

$$(C_6H_5)_3P \;+\; XC\overset{R^1}{\underset{R^2}{H}} \longrightarrow (C_6H_5)_3\overset{+}{P}-C\overset{R^1}{\underset{R^2}{H}} \;\;\underset{}{\overset{C_6H_5Li}{\longrightarrow}}\;\; (C_6H_5)_3P=C\overset{R^1}{\underset{R^2}{}}$$
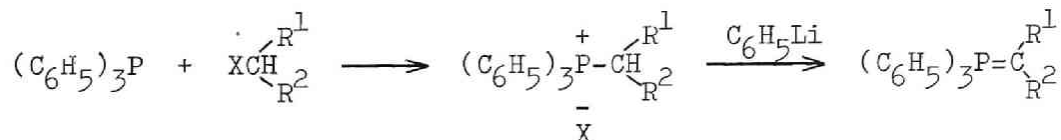$$\overset{-}{X}$$

Fig VI.   Preparation of phosphorus ylides

("Wittig reagents").

Despite the extensive scope of the Wittig method for olefination of ketones and aldehydes with alkylidenephosphoranes, this olefin synthesis does have certain limitation: (1) Highly hindered ketones are often inert even to methylene-triphenylphosphoranes[3] (2) Proton abstraction by the ylide from the substrate may occur faster than the desired carbonyl addition with consequent loss of the carbonyl component by isomerization and/or enolate condensation reactions. Unfortunately, such side reactions can not be suppressed by suitable choice of conditions. One of the possible approaches in overcoming these limitations of Wittig reactions consists in the use of a group of various carbanions $Z-C^-$ or Z_2C^- substituted directly by neutral heteroatom having vacant 3d orbital, as this is the case with Si, P, S etc.

The reactions of such heteroatom-substituted carbanions were virtually unknown prior to the 1950's, but since then this field of organic chemistry has developed quite rapidly. Perhaps the most significant factor responsible for this widespread attention seems to be the recognition of their

potentials of synthetic utility.

In classical organic chemistry, the carbanion reactions of carbonyl compounds having one or more acidic α-hydrogens have constituted an important chapter. More generally structures H-C-Y are acidic if the Y group delocalizes a negative charge developing on the carbon. In addition to the carbonyl group, other Y's known are NO_2, CN, $-N\equiv C:$, C=N, pyridyl etc. Compounds of the type listed in Table I are acidic enough to yield anions, when treated with sufficiently strong bases such as alkoxide ions, and are often referred to as "active methylene compounds." The basicity of these active methylene compounds are intermediate between alkyl anions of Grignard-type organometallic reagents (pKa of RH: 40-45) and cyanide ion (pKa of HCN: 9.1).

Table I. C-H Acidity Scale of Active Methylene Compounds [4]

| Compound	pKa	Compound	pKa
$C_6H_5CH_3$	35	CH_3OH	16
$CH_2=CH-CH_3$	35	H_2O	15.7
$(C_6H_5)_3CH$	32	$CH_2(COOC_2H_5)_2$	13
$C_6H_5NH_2$	27	$CH_2(CN)_2$	11
CH_3COCH_3	20	$CH_3COCH_2COOC_2H_5$	10

These traditional carbanions are stabilized by groups containing nitrogen and/or oxygen. In remarkable contrast, the new carbanions $Z-C\overset{\ominus}{\diagdown}$, $-\overset{\ominus}{C}Z_2$ aforementioned are characterized in the following points: (a) The conjugate acids $H-\overset{|}{\underset{|}{C}}-Z$ and $H\overset{|}{C}Z_2$ are relatively week acids; the pKa of $CH_3SO_2CH_3$ is 23-27 and that of CH_3SOCH_3 is 35.[5] Accordingly the anions have become accessible by the advent of routine employment of very strong bases such as alkali metal hydrides or lithium alkyls. (b) Some of the carbanion (or the organometallic $Mtl-C-Z$, $Mtl-CZ_2$) solutions are stable only at very low temperatures (-78° (Dry Ice-MeOH), -95° (liq. N_2-$C_6H_5CH_3$), etc). (c) The new carbanions do undergo nucleophilic attack on a carbonyl group and an oxirane ring as well as S_N2 reaction on alkyl halide similarly as the well-acquainted C, H, N, O carbanions. (d) The carbanion activity is often greatly enhanced by trapping the counter ion with polar aprotic solvents such as hexamethylphosphoric triamide (HMPA), dimethylsulfoxide (DMSO), dimethylformamide (DMF) or alternatively with suitable ligands such as tetramethyl-ethylenediamine (TMEDA), 1,4-diazabicyclo[2.2.2]octane (DABCO). (e) In the resulting products C-C-Z or C-CZ$_2$, the heteroatom Z provides a means of generating the desired functional group in various kinds of transformation. In other cases Z is eliminated simultaneously with the C-C bond formation to afford the C$=$C linkage.

The new carbanion chemistry has experienced a tremendous

growth and wide interest in the past decade. This chemistry
has outgrown from the pioneering work of Prof. Corey on
1,3-dithiane chemistry.

The 1,3-dithiane ring is a versatile synthon of a
carbonyl group.[6] This functional group has been invented
in order to perform several important operations of organic
chemistry including (a) the extension of carbon chains(1 → 3),
(b) the masking and unmasking of carbonyl groups (2 ⇌ 3),
(c) the blocking and unblocking of activated methylene groups
(4 ⇌ 3), (d) the reduction of carbonyl groups to methylene
groups (2 → 4), (e) the conversion of activated methylene
groups to carbonyl groups (4 → 2), and (f) the nucleophilic
acylation of carboxylic acid derivatives (1 → 2).
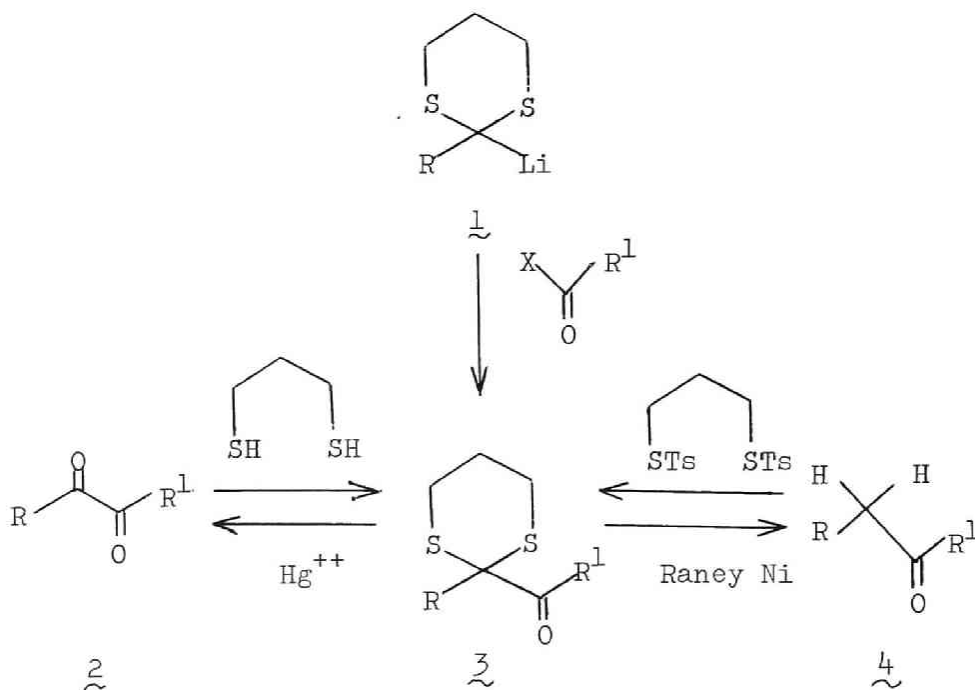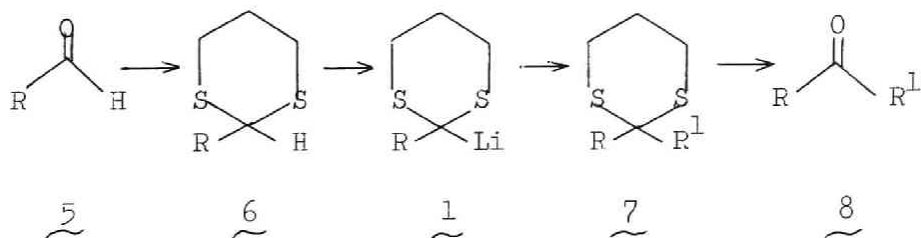
In 1965 Corey and Seebach [7] described an efficient four-step sequence for the conversion of aldehydes to ketones that uses lithiodithiane 1 as the key intermediate. The masking of aldehyde 5 as its dithiane derivative 6 renders the former aldehyde proton sufficiently acidic to undergo metalation with n-butyllithium in tetrahydrofuran to form lithiodithiane 1. [7-21] This is a nucleophilic acylating agent [9] instead of the conventional electrophilic one and reacts readily with most of the electron-seeking functional groups that normally combine with the Grignard reagents to furnish masked ketones of type 7. The final step of the lithiodithiane route to the ketone 8 is hydrolysis of the dithiane 7.

Typical known examples demonstrating the synthetic utility of heteroatom-substituted organometallic compounds are shown below.

$$C_6H_5C(O)D \quad \text{(ref. 11)}$$
$$(90\%)$$

$$\text{(dithiane)}C_6H_5,CH_3,Li \quad + \quad \alpha\text{-Np}(C_6H_5)(CH_3)\overset{*}{Si}Cl$$

$$\xrightarrow{\quad} \xrightarrow[H_2O]{Hg^{2+}} \quad C_6H_5C(O)\overset{*}{Si}(CH_3)\text{-}\alpha\text{-Np}$$

$$(55\%) \quad (\text{ref. 16a})$$

$$\text{(bis-dithiane-Li)} \quad + \quad \text{(CH}_2\text{Br)}_2\text{-benzene} \quad \xrightarrow{\quad} \xrightarrow[CH_3OH]{Hg^{2+}} \quad \text{(diketone)}$$

$$(12\%) \quad (\text{ref. 14})$$

$$\text{(dithiane-H,Li)} \quad + \quad I(CH_2)_3Cl \quad \xrightarrow{\quad} \quad \text{(dithiane-(CH}_2)_3Cl,H)$$

$$\xrightarrow{n\text{-BuLi}} \xrightarrow{Hg^{2+}} \quad \text{(cyclobutanone)}$$

$$(30\%) \quad (\text{ref. 12})$$

$$\text{(dithiane-H,Li)} \quad + \quad (C_2H_5O)_2CHCH\text{-}CH_2 \text{(epoxide)} \quad \xrightarrow{\quad} \quad \xrightarrow{(CH_3CO)_2O} \xrightarrow[BF_3]{HgO}$$

$$(C_2H_5O)_2CHCH(OH)CH_2CHO \quad \xrightarrow{Base} \quad (C_2H_5O)_2CHCH\!=\!CHCHO$$

$$(55\%) \quad (\text{ref. 22})$$

$(C_6H_5S)_3CLi \xrightarrow{C_6H_5CHO} \xrightarrow[H_2O]{HgCl_2} C_6H_5CH(OH)COOH$

(60%) (ref. 19)

$\underline{n}\text{-}C_5H_{11}Br + CH_3SCHLiCH=CHSCH_3 \longrightarrow \xrightarrow[H_2O]{Hg^{2+}}$ n-C$_5$H$_{11}$, H / C=C / H, CHO

(75%) (ref. 23)

NaCH(SOCH$_3$)(SCH$_3$) $\xrightarrow{RX} \xrightarrow{H^+}$ RCHO

(90%) (ref. 24)

$(CH_3O)_2\underset{O}{\overset{\|}{P}}CH_2SCH_3 \xrightarrow[\substack{R^1 \\ R^2}C=O]{\underline{n}\text{-}BuLi} \substack{R^1 \\ R^2}C=CHSCH_3 \xrightarrow[H_2O]{Hg^{2+}} \substack{R^1 \\ R^2}CHCHO$

(75%) (ref. 25)

(70%) (ref. 26)

$H\text{-}CH_2SC_6H_5 \xrightarrow[RCH_2X]{\underline{n}\text{-}BuLi/Dabco} RCH_2CH_2SC_6H_5 \xrightarrow[NaI/DMF]{CH_3I} RCH_2CH_2I$

(93%) (ref. 27)

$$(CH_3)_3SiCH_2SCH_3 \xrightarrow[\;(C_6H_5)_2C=O\;]{n-BuLi} \underset{C_6H_5}{\overset{C_6H_5}{>}}C=C\overset{H}{\underset{SCH_3}{<}} \quad \text{(ref. 28)}$$

(56%)

$$(CH_3)_3SiCH_2P(O)(OC_2H_5)_2 \xrightarrow[\;(C_6H_5)_2C=O\;]{n-BuLi} \underset{C_6H_5}{\overset{C_6H_5}{>}}C=C\overset{H}{\underset{P(O)(OC_2H_5)_2}{<}}$$

(83%) (ref. 29)

Under the circumstances, the author decided to devote himself to innovating in new carbanion chemistry and its synthetic application. The results are summarized below.

Chapter 2 is concerned with new synthetic reactions utilizing the carbanions derived from allylic sulfides. Although several reports describe selective alkylation of α-alkylthio allylic carbanions at the α-position, very few were known about the behavior of the carbanion derived from simple allylic sulfide. After careful re-examination of alkylthioallyllithium, the unprecedented introduction of a five-carbon chain having <u>trans</u>-olefinic linkage at the point of junction and terminating at an aldehyde function has been achieved by means of allyl vinyl sulfide as shown by the scheme.
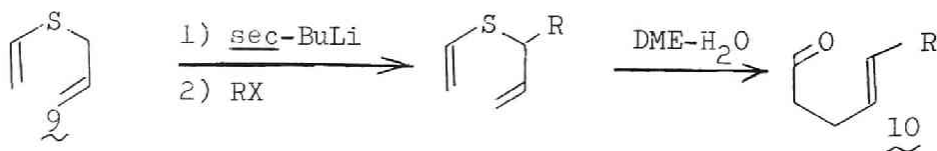
The novel conversion of allyl vinyl sulfide 9 to γ,δ-unsaturated aldehydes 10 consists of the α-selective metallation of allyl vinyl sulfide 9 in the presence of sec-butyllithium, the S_N reaction with a suitable alkyl halide, the thio-Claisen rearrangement and the final desulfurization of the resulting thioaldehyde, both proceeding smoothly in refluxing dimethoxyethane—water system.

The stereochemical outcome of the resulting olefinic aldehyde 10 being pure (E) isomer agreed with our original prediction. Assuming the chair-type conformation for the transition state of thio-Claisen (3,3)-sigmatropic rearrangement in the same manner as Cope and Claisen rearrangement, the alkyl substituent is placed in an equatorial position. As shown below, the conformer 11 should give rise to (E) olefinic aldehyde. An alternative conformer 12 leading to the (Z) isomer is regarded less favorable because of the indicated nonbonding interactions of the axial R group and olefinic hydrogens.

11   12
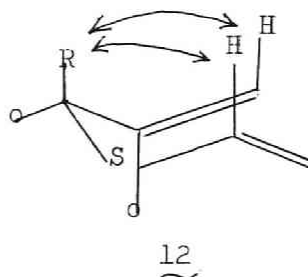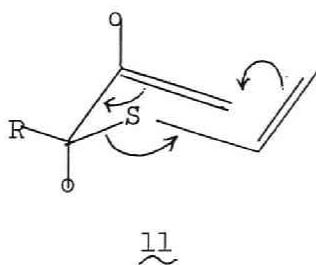
A useful extension of our chain elongation process was disclosed and this constitutes the content of Chapter 3. The synthesis involves 2-ethoxyallyl vinyl sulfide as a starting material which was subjected to the same sequence consisting of metallation—alkylation—thio-Claisen rearrangement—desulfurization to yield γ-ethoxy-substituted γ,δ-unsaturated aldehydes as shown below. The vinyl ether moiety is easily converted into γ-keto group. Therefore the sequence opened a new route to δ-ketoaldehydes.
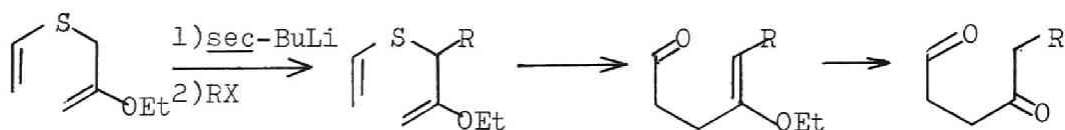
This method was used successfully in our total synthesis of dihydrojasmone 13, cis-jasmone 14, and allylrethrone 15.

13   14   15
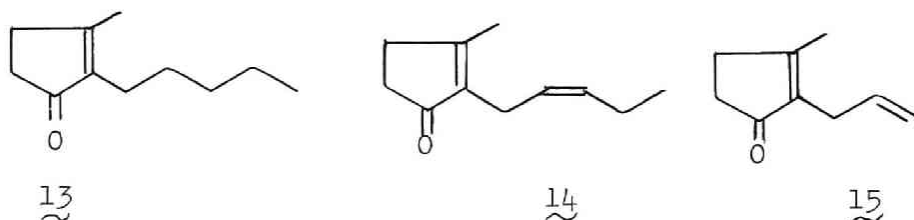
It should be pointed out that the δ-ketoaldehydes thus obtained are useful as synthetic intermediate of heteroaromatic compounds such as pyrrole and furan derivatives.

An attempted preparation of (E) trisubstituted olefins by means of methallyl vinyl sulfide failed to proceed in an expected way. The resulting olefins were found to be a mixture of geometrical isomers of trisubstituted ethylenes in an E/Z= 7:1 ratio. A logical approach to improve the

stereoselectivity should be the introduction of another
additional substituent, e.g. SMe, to the hypothetical
transition state of thio-Claisen rearrangement. Both the
newly introduced substituent and the alkyl group must have
a severe 1,3-diaxial interaction in the conformer 17 leading
to a (Z) olefin. In contrast, such repulsion is absent in
the alternative conformer 16.
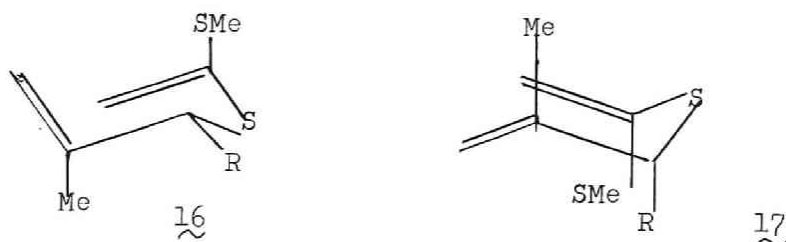
In chapter 4, the author describes the effort along
this line: the synthesis of γ,δ-unsaturated ester using the
dianion derived from methallyl dithioacetate as shown below.
Treatment of the sithioester with 2 equiv sec-
butyllithium in tetrahydrofuran provided a new type of
dianion which was first alkylated at α-position with an
appropriate alkyl halide and further S-methylated with methyl
iodide to produce the ketenedithiol 18. The thio-Claisen
rearrangement proceeded in the expected way to afford
stereoselectively an (E) trisubstituted olefin.
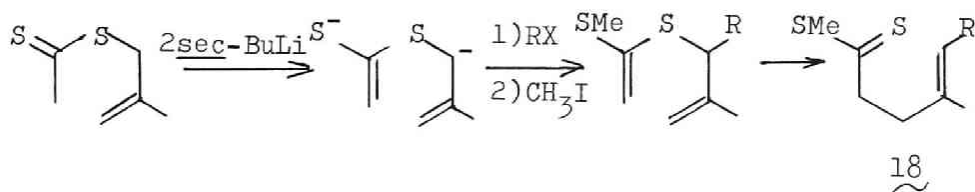
Chapter 5 features the discovery of a novel method of γ-selective alkylation of the carbanions derived from allylic sulfides. The selectivity expected in this synthesis is extremely difficult to achieve as compared with the alkylation at α and still such transformation would result a new three carbon chain extension method as depicted below. Such difficulty might partly be explained by the high electron deinsity of α-carbon of the allylic anion 19 due to d_π-p_π overlap effect.

$$RS\overset{-}{C}H\text{-}\overset{-}{C}H\text{-}CH_2 \xrightarrow{R^1X} RSCH{=}CHCH_2R^1 \longrightarrow R^1CH_2CH_2CHO$$

19
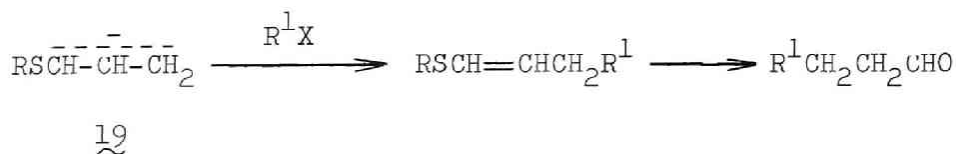
We examined thoroughly this process by changing the counter metal ion of allylic carbanion. An alkylthioallyl-copper reagent was eventually found to be attacked by allylic bromides at γ position with surprisingly high selectivity. In addition to this remarkable positional selectivity on the organometallic reagent side, the attack on the substrate took place exclusively at C-3 position of the allylic bromide or in the mode of S_N2' reaction as shown below. The whole process provided a completely new fashion of highly selective carbon-carbon bond formation and thus opened a new entry of sulfur chemistry.
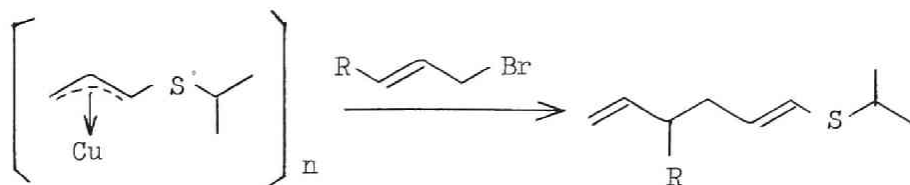
Chapter 6 comprises a new synthesis of ketones using 1-(alkylthio)vinyllithium. As early as 1966 Corey[30] pointed that the anions 20 derived from vinylic sulfides could be a versatile synthetic equivalent of acyl anions because vinyl sulfides should be converted to carbonyl derivatives under acidic or in the presence of mercury ion in neutral conditions. However, the ketone synthesis based on these possibility had not been realized due to the lack of a satisfactory base-solvent system to produce the anion 20 from vinylic sulfides efficiently. We found the very favorable system consisting of sec-butyllithium and tetrahydrofuran--hexamethylphosphoric triamide (9:1) for the convertion of vinylic sulfides into their corresponding anions and succeeded in elaborating a new ketone synthesis of practical utility.
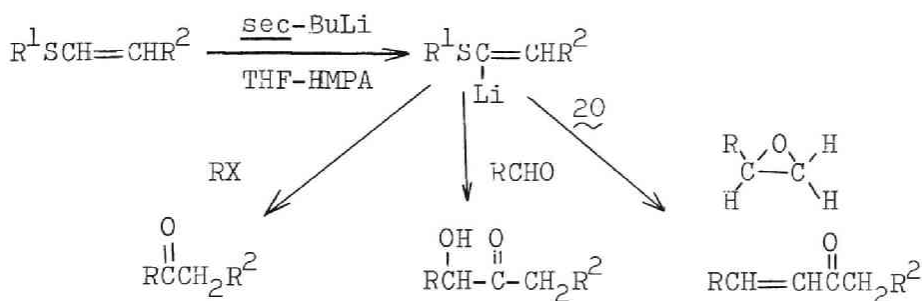
In conclusion, the author summarizes his contributions as follows: (a) Several masked nucleophiles, i.e., $\ominus CH=CHCH_2CH_2CHO$, $\ominus CH_2C(O)CH_2CH_2CHO$, and $\ominus CH=CH(Me)CH_2CH_2COOEt$, are developed by means of allylic sulfides and methallyl dithioester. The procedure consists of the α-selective metallation of allyl sulfide, the S_N reaction with a suitable alkyl halide, the thio-Claisen rearrangement and the final desulfurization. (b) A 1-alkylthioallylcopper reagent reacts with allylic bromides at γ position with high selectivity and affords the S_N2' type substitution products in excellent yields. (c) 1-(Alkylthio)vinyllithium ($R^1SC(Li)=CHR^2$) functions as the equivalent of acyl anion; thus it reacts with halides, aldehydes, and epoxides to yield, after hydrolysis with mercuric ion, ketones, acyloins, and α,β-unsaturated ketones.

Appendix A is concerned with a new reaction of α-lithio diethyl methylphosphonate with organic halides, specifically with gem-dibromocyclopropanes which have been converted to the monobromocyclopropane products by this reagent. Meanwhile, treatment of the dibromides with Cr^{II} acetate in dimethyl-sulfoxide gave rise to the semireduction product with different stereochemistry which was described in Appendix B. Whereas the reaction of α-lithiomethylphosphonate gave the exo-monobromides 21 predominantly, those obtained in the Cr(II) reduction were mainly the endo isomer 22.
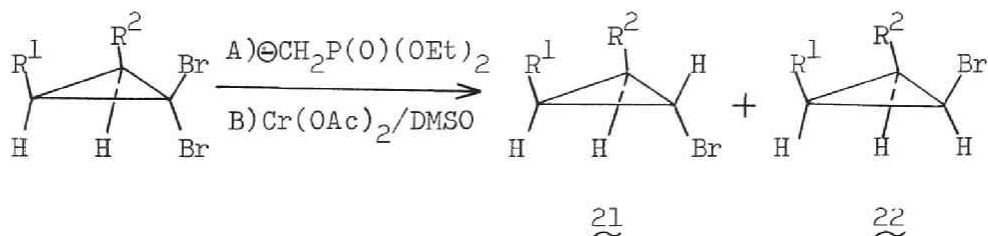
Incidentally, the reaction of gem-dibromocyclopropanes with Cr^{II} acetate in aqueous dimethylformamide afforded cyclopropyl acetate 23 as the major products in addition to 21 and 22. A substitution on cyclopropane carbon was also observed in the reduction of gem-dihalides with potassium pentacyanocobaltate in dimethylsulfoxide, furnishing cyclopropyl cyanides 24. Possible mechanisms accounting for these observations are discussed.
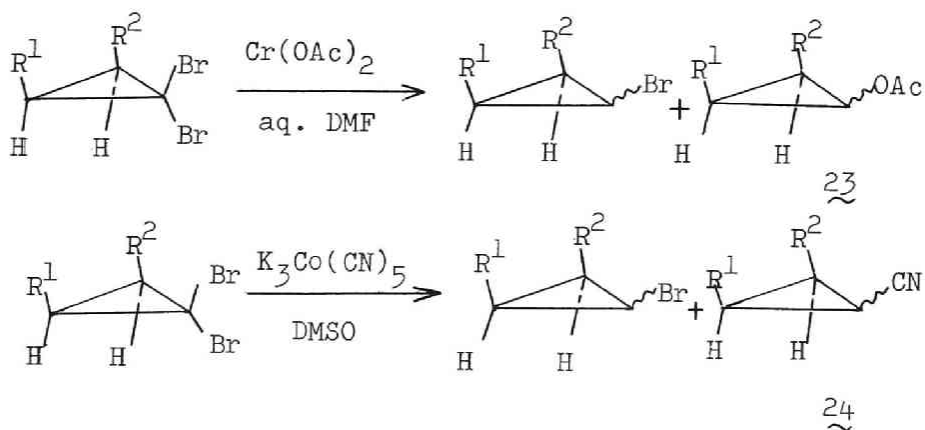
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CHAPTER 2

A New Synthesis of Aldehydes Using 1-Vinylthioallyllithium. A Facile Route to Propylure.

Abstract—— Reaction of allyl vinyl sulfide with sec-butyllithium in tetrahydrofuran produces 1-vinylthioallyllithium, viz. $CH_2=CH-S-CH(Li)-CH=CH_2$. The reagent so generated has been shown to react smoothly with a primary halide (RX). The subsequent thio-Claisen rearrangement in dimethoxyethane-water gives the five carbon homologated trans- γ,δ - unsaturated aldehyde ($RCH=CHCH_2CH_2CHO$) in 56-62% yield. The sex attractant of Pectinophora gossypiella Saunders (propylure) is synthesized effectively by means of this new technique starting from 1-iodo-4-(2'-tetrahydropyranyloxy)- butane.

For synthetic purposes, a 1-alkylthioallyl carbanion (I) is potentially equivalent to either $CH_3CH_2CO^{\ominus}$ or $^{\ominus}CH_2CH_2CHO$, depending on the terminus (α or γ) of the allylic reagent being coupled with the electron-deficient center of the substrate.

$$
\begin{array}{ccccc}
\underset{\displaystyle E-\overset{\displaystyle RS}{\underset{|}{C}H}-CH=CH_2}{} & \xleftarrow{\;E^+\;} & RS-\bar{C}H\text{-}\bar{C}H\text{-}\bar{C}H_2 & \xrightarrow{\;E^+\;} & \underset{\displaystyle H-\overset{\displaystyle RS}{\underset{|}{C}}=CH-CH_2-E}{}
\end{array}
$$

(I)

$$
\underset{\displaystyle E-\overset{\displaystyle RS}{\underset{|}{C}}=CH-CH_3}{} \qquad\qquad \overset{O}{\underset{\|}{H-C}}-CH_2-\bar{C}H_2 \xrightarrow{\;E^+\;} \overset{O}{\underset{\|}{H-C}}-CH_2-CH_2-E
$$

$$
\overset{O}{\underset{\|}{E-C}}-CH_2-CH_3 \xleftarrow{\;E^+\;} O=\bar{C}-CH_2-CH_3
$$
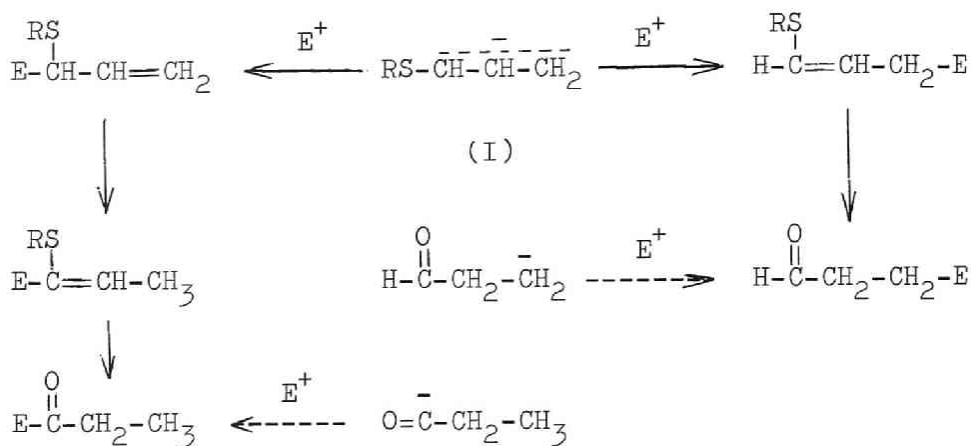
Biellmann and Ducep [1] generated 1-phenylthioallyl-lithium using a system consisting of n-butyllithium and diaza-1,4-bicyclo[2.2.2]octane (DABCO), with which iodomethane reacted to furnish the methylated products in a ratio of $\alpha/\gamma = 76{:}24$.

$$
PhS-\bar{C}H\text{-}\bar{C}H\text{-}\bar{C}H_2Li^+ \xrightarrow{\;CH_3I\;} \underset{\displaystyle \quad\overset{|}{CH_3}}{PhS-CH-CH=CH_2} \; + \; \underset{\displaystyle \qquad\overset{|}{CH_3}}{PhS-CH=CH-CH_2}
$$
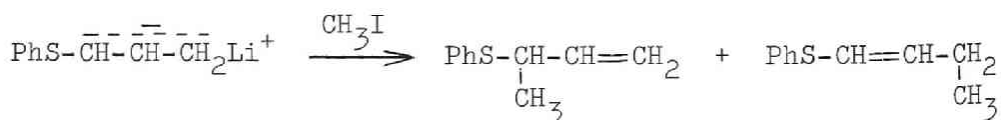
In contrast, we have observed that sec-butyllithium without DABCO in tetrahydrofuran is an efficient reagent and the reaction with allyl phenyl sulfide gives the α-alkylated product almost exclusively. Thus, 1-phenylthio-allyllithium prepared from allyl phenyl sulfide and sec-butyllithium in tetrahydrofuran at -78° was converted on treatment with iodomethane into the methylated product in quantitative yield. The composition of this product was analysed by the nmr spectrum and shown to be >95% the α alkylated product accompanying with <5% the γ alkylated isomer.

These observations prompted the author to investigate the possibility of a new aldehyde synthesis, the basic idea of which was shown below. A priori, this method consists of two steps. The first one requires the regioselective α-alkylation of allyl vinyl sulfide and the second one consists in thio-Claisen rearrangement of the resulting sulfide. The above-described alkylation process, thus, appeared to provide a hopeful answer to this idea.
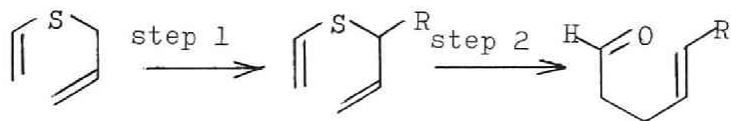
2.1. Regioselective Alkylation of Allyl Sulfide

Treatment of allyl vinyl sulfide 1 in dry THF at
-78° with 1 equivalent of sec-butyllithium in pentane gave
a yellow solution containing the anion 2 which was stable
at that temperature but decomposed slowly at 0°. The
formation of the anion 2 was verified by treatment with
1 equivalent of benzyl bromide at low temperature to give
the sulfide 3, as shown by nmr analysis to be >85% pure.
Additional proof of selective alkylation was obtained from
the reaction of methylthioallyllithium with benzyl bromide
to afford a mixture of three components in the ratio
4/5/6= 88:6:6.
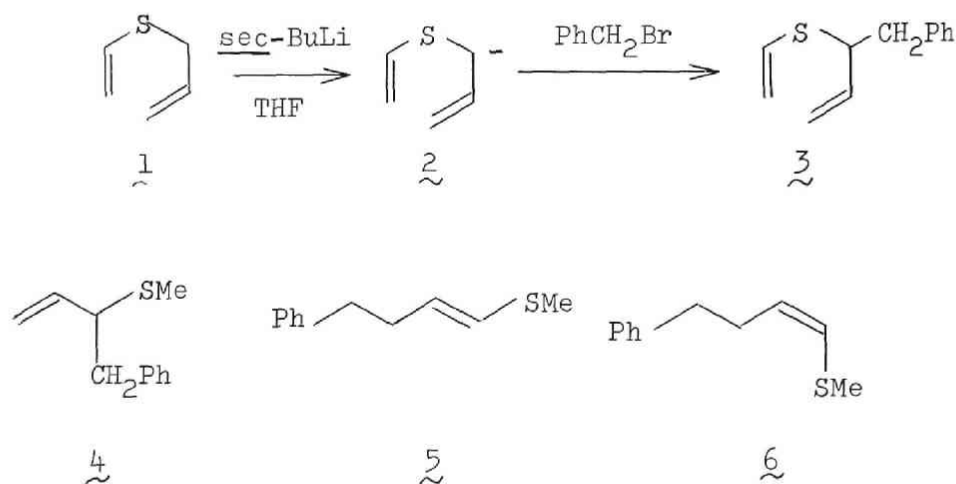
The association degree of alkyllithium varies with
both the solvent and the structure of alkyl group and,
in general, is higher for straight chain than for branched
chain alkyl compounds. Thus n-butyllithium is usually

hexamer in cyclohexane, benzene, and ether,[2,3] whereas
sec-butyllithium is tetramer in n-hexane and benzene.[4]
This difference would account for the higher reactivity
of sec-butyllithium. The factor governing the ratio of
α/γ alkylation is not clear yet. Possibly the kinetically
controlled alkylation is responsible to the present system,
because we can perform all the operations at very low
temperature by virtue of sufficiently high nucleophilicity
of sec-butyllithium which abstracts the α proton of 1.

 After the publication of our preliminary results,[5]
Scotter and Hornish [6] reported the metalation of 1-methyl-4-
thiacyclohexene-1 by means of sec-butyllithium-tetramethyl-
ethylenediamine (TMEDA). The complete anion formation
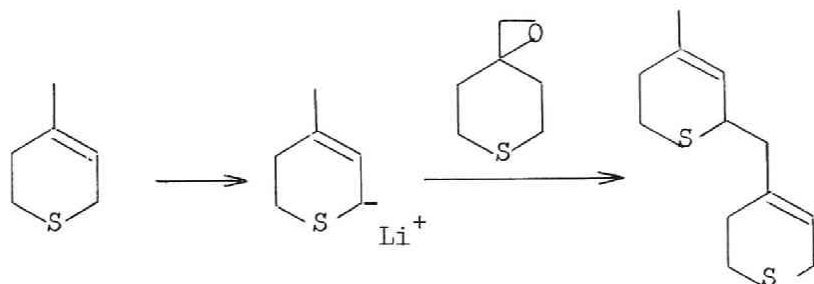
having occurred was proved by quenching with D_2O, allowing
almost quantitative isolation of 3-deuterio-1-methyl-4-
thiacyclohexene-1 containing a small amount of the
γ-deuterated isomer. No δ-alkylation products were
observed upon inspecting the nmr of the reaction product
with oxiranes as evidenced by the absence of high field
singlet for quaternary saturated methyl group. With

methyl iodide and with several different primary allylic
chlorides and bromides, the anion gave α-alkylated products
in good yields which usually contained varying amounts
(3-15%) of γ-alkylation isomers, as they reported.

2.2. Thio-Claisen Rearrangement

The Claisen rearrangement consists in a thermal
reaction of allyl vinyl ether to form the isomeric γ,δ-
unsaturated carbonyl system.[7] The role of the Claisen
rearrangement has been established recently in the arsenal
of synthetic organic chemistry as an important tool for
the preparation of unsaturated carbonyl compounds.[8]
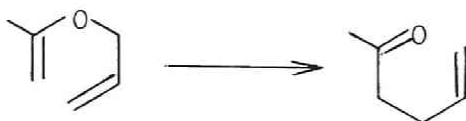
The sulfur analog is the "thio-Claisen rearrangement,"
on which very few have previously been reported.[9,10,11]
A recent paper by Corey and Shulman [12] has indicated the
utility of thio-Claisen rearrangement for the construction
of spiro ring derivatives. They reported that an attempted
thermal thio-Claisen rearrangement of allyl vinyl sulfide
7 at 160°-180° furnished only starting material and
intractable tars, and that heating 7 at 190° for 10 min
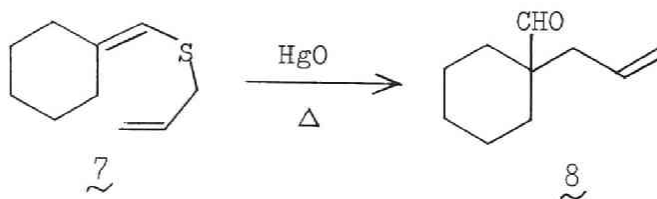
in the presence of 3 equiv of red mercuric oxide
afforded the desired aldehyde 8 in satisfactory yields.
This result has been based on the working hypothesis that
mercuric oxide might promote the rapid conversion of an
intermediary thioaldehyde to the corresponding aldehyde
and thereby exclude complex side reactions. This neat
synthesis of the aldehyde 8 was the only reported case
which could be applicable for our systems. Attempted
application of the Corey's HgO method to 9a, 9b, and 9c
proved to be disappointing. Heating 9a at 180°-200° with
or without red mercuric oxide afforded only an intractable
tar but no trace of the aldehyde 10a.

The crude sulfide 9a was then dissolved in dimethoxy-
ethane and water (3:1) (v/v) in the presence of excess
calcium carbonate (3 equivalent), and the mixture was
heated at reflux for 12 hr. After purification by thin
layer chromatography, the desired aldehyde 10a was obtained
very cleanly and efficiently (62% over-all yield from
benzyl bromide). The chromatographic analyses showed the
absence of any detectable amounts (⟨1%) of the geometrically
isomeric olefin. Similarly, the thio-Claisen rearrangement
of allyl vinyl sulfide 9b and 9c gave the corresponding
aldehydes 10b (57% over-all yield from n-octyl bromide)
and 10c (62% over-all yield from geranyl bromide),
respectively, both of which represented ⟩99% purity of the
trans olefins by gas chromatography and tlc assay on
silver nitrate-silica gel. This new method should serve

to broaden the scope and utility of the thio-Claisen
rearrangement.

The basis for the observed high stereoselectivity
in this reaction can be explained by essentially the same
arguments used to rationalize the stereochemical outcome of
Claisen rearrangement; the conformer 11 is a precursor to
the trans olefin and is favored over 12 leading to the cis
isomer, because the alkyl substituent has preference for
occupying an equatorial position.

(a) R=CH₂Ph

(b) R=n-C₈H₁₇

(c) R=geranyl
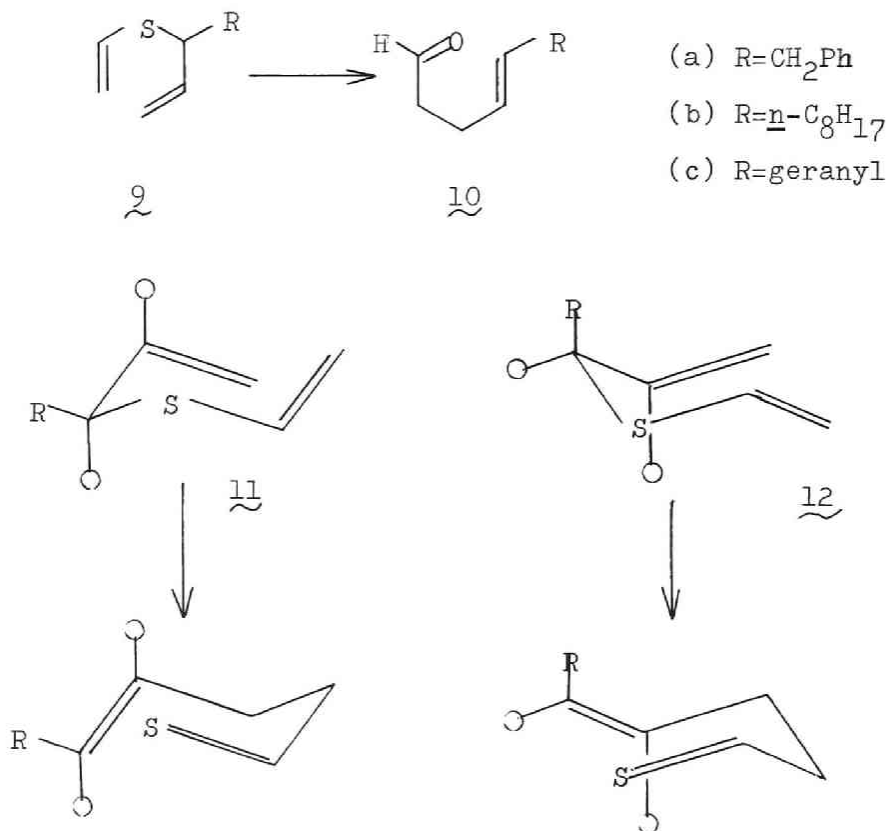
2.3. Application to the Synthesis of Propylure

The efficacy of the remarkably stereoselective and simple procedure for γ,δ-unsaturated aldehyde described above has been demonstrated by the synthesis of propylure, which is known as an insect hormone.[13] The structure of propylure had been identified by Jacobson [14] as 1-acetoxy-10-propyltrideca-trans-5,9-diene 13.

13
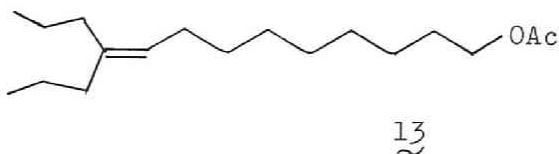
In analogy to the preparation of 6-phenyl-trans-2-hexenal 10a, we envisaged that alkylation of 1-vinylthio-allyllithium 2 with the iodide 14 [15] to give the sulfide 15, which on thio-Claisen rearrangement promised to give the aldehyde 16.
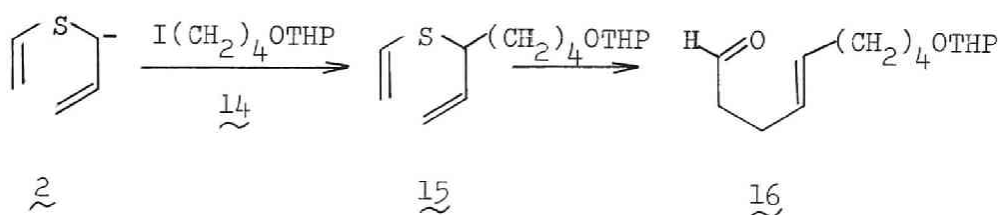
Treatment of allyl vinyl sulfide in dry THF at -78° with 1 equivalent of sec-butyllithium in pentane furnished a yellow solution of the anion 2, which was treated with iodide 14 to give the sulfide 15. A mixture of the crude sulfide 15 and calcium carbonate (3 equiv) in

dimethoxyethane-water (3:1) was heated at reflux for 13 hr.
Purification by preparative tlc afforded 9-(2'-tetrahydro-
pyranyloxy)-trans-4-nonenal cleanly in 55% yield, which
was spectrometrically identical with the reported data.[16]

In view of the recorded synthesis of propylure from
16 (simple Wittig reaction [16]), the route described above
constitutes a formal total synthesis of this hormone.
This is apparently more advantageous than the previous
ones [16,17] requiring a lengthy sequence of conventional
chain-extension reactions and giving low yields of the
final product.

2.4. Experimental Part

2.4.1. Instrumentation, Materials, and Methods— The
following details (Section 2.4.2 through 2.4.5) apply to
all experimental parts of this thesis.

2.4.2. General Reaction Procedures— Liquid reagents
were transferred via dry hypodermic syringe and added
through a rubber septum wired onto a neck of the reaction
flask. Solid reagents were added through a neck of the
reaction flask from which a steady stream of inert gas
was flowing.

Solvent mixtures are described in parts by volume.
Organic extracts of the reaction mixture were dried over
anhydrous magnesium or sodium sulfate unless noted otherwise.
The dried extracts were "freed of the solvent" by
evaporation at 20-60° with a Tokyo Rikakikai rotary

evaporator evacuated at 10-30 Torr by a water aspirator.
Yields are based on spectrometrically pure compounds which
were obtained by extraction or subsequent purification.
Those were characterized by infrared and nmr spectrometry.

2.4.3 Preparation and Purification of Reagents and
Solvents— Reagent-grade chemicals and solvents were used
without purification unless stated otherwise. Oil free
sodium hydride was prepared by trituration of the commercial
dispersion in mineral oil at least three times with
petroleum ether. The commercial products listed below
were distilled before use: HMPA (from calcium hydride),
THF (from lithium aluminum hydride), DMSO (from calcium
hydride).

Solutions of n-butyllithium in hexane and sec-
butyllithium in pentane were periodically assayed for active
alkyl by titration with 2-butanol in benzene using 1,10-
phenanthroline as indicator.[18]

2.4.4. Analytical Procedures and Instrumentation—
Analytical tlc was performed on commercial glass plates
bearing a 0.25 mm layer of Merck silica gel PF254.
Preparative tlc plates were prepared as follows: a free-
flowing slurry of Merck silica gel PF254 (25 g) in water
(60 ml) was spread on a clean glass plate (20x20 cm) to
an even depth of 1.5 mm; the plate was air-dried at room
temperature for at least two days before use.

Analytical glpc was performed with a Yanagimoto
Gas Chromatograph, Model GCG-550-F using flame ionization

detectors and nitrogen as carrier gas. Product percentages were calculated from peak area ratios without correction for detector response. Preparative gas-liquid phase chromatography was performed with a Yanagimoto Gas Chromatograph, Model GCG-3D and JEOL-JGC-20K using thermal conductivity detectors and helium as carrier gas. The individual columns are described below in Table 2-1.

Unless stated otherwise, ir samples were neat and nmr samples were dissolved in tetrachloromethane. Ir data were obtained on a Shimadzu IR-27G and calibrated against the 1028, 1495, and 1601 cm^{-1} bands of polystyrene. Nmr spectra were recorded with JEOL spectrometer c-60-H and Varian Associates spectrometers, Models T-60, EM-360, and HA-100. Ms data were measured with a Hitachi RMU 6D spectrometer. Elemental microanalyses were performed by Mrs. K. Fujimoto at the Laboratory of Prof. Sisido (now Prof. Kawanisi) and by the Elemental Analyses Center of Kyoto University.

2.4.5. Data Presentation— Mp and bp data are given in ^{o}C and are uncorrected. The tlc mobility of a given component is described by its $\underline{R}_f$ value, the ratio of the distance moved by that component to the distance moved by the solvent front. The glpc retention time ($\underline{t}_r$) of a component denotes the time (in minutes) at which the maximum concentration of that component reached the detector.

The nmr signals are expressed in δ units, parts per million downfield from internal tetramethylsilane ($\delta=0$). Nmr data are compiled in the form: δ-value of signal (peak

Table 2-1. Gas-Liquid Phase Chromatography Columns.

Column Code	Length (m)	Wt %	Composition	Mesh	Composition
			— Liquid Phase —		Solid Support
Analytical Columns (stainless steel tubing, 3 mm diameter):					
A	3	10	PEG-AgNO$_3$	60-80	Celite 545
B	0.75	5	SE-30	60-80	Chromosorb W
C	2	10	HVSG	60-80	Celite 545
D	1	5	OV-1	80-100	Chromosorb WAW
E	2	7	PEG	100-120	Celite 545
Preparative Columns (stainless steel tubing, 5 mm diameter):					
F	2	30	SE-30	60-80	Chromosorb W
G	2	30	HVSG	60-80	Celite 545

multiplicity, integrated number of protons, coupling constants
(if any), structural assignment). Major bands in the ir
spectrum are listed thus: wavelength of band maximum in cm^{-1}
(relative band intensity, structural of vibrational assignment).

Designations of the type "NMR 10" and "IR 15" refer
to nmr and ir spectra reproduced in the last Section. Regular
ms data and exact-mass measurement of the molecular ion
are presented in units of m/e, the ratio of the mass of
the observed ion to the mass of the electron. Analytical
data are given in weight percent.

2.4.6. Allyl Vinyl Sulfide (1)— Liquid ammonia was transferred in a 500 ml flask cooled with a dry ice-methanol bath. When 200 ml of liquid had been collected, the flask was flashed with dry nitrogen via the three-way stopcock and lithium wire (1.6 g, 0.23 atm) was added with stirring. After 30 min, ethyl vinyl sulfide (10.0 g, 0.14 mol) was introduced dropwise. Stirring was continued at -78° for 15 min, the resulting lithium amide was quenched by addition of solid ammonium chloride (6.1 g, 0.12 mol), and the mixture was stirred for 15 min. Allyl bromide (9.5 ml, 0.11 mol) was added and the mixture was allowed to stand at 0° to evaporate ammonia. The residue was washed with saturated aqueous ammonium chloride. The organic phase was dried and distilled to provide the sulfide 1 (7.0 g, 62% yield) as a colorless liquid: bp 37° (38 mmHg); ir (neat), 1640 (m), 1590 (s), 1430 (w), 1225 (m), 915 (s), 860 (m), and 745 cm^{-1} (m); nmr (NMR 1), 3.3 (d, 2H, J=7 Hz, S-C$\underline{H}_2$), 4.90-5.37 (m, 4H, =C$\underline{H}_2$), 5.70 (ddt, 1H, SCH$_2$-C$\underline{H}$=CH$_2$), 6.23 (dd, 1H, S-C$\underline{H}$=CH$_2$); MS ($\underline{m/e}$), 100 (25), 85 (39), 67 (62), and 41 (100).

2.4.7. Determination of α/γ Ratios of the Methylation Products of Thioallyllithium— sec-Butyllithium (1.6 ml of a 1.3 $\underline{M}$ pentane solution, 2.0 mmol) was added to a solution of allyl phenyl sulfide (0.30 g, 2.0 mmol) in dry THF (10 ml) stirring under nitrogen at -78°. The solution was kept at -78° for 30 min, warmed to -26° and stored there for 30 min. The resulting dark brown solution

was cooled to -78°, treated with methyl iodide (0.43 g, 3.0 mmol) and kept at -78° for 1 hr. The composition of the methylated product (0.33 g, 100%) obtained on extractive workup was analysed by the nmr. The spectrum exhibited a doublet methyl signal and a triplet signal in the ratio of >20:1 at δ1.37 and 1.03 ppm accounting for a total of three protons. Additional proof of α selective alkylation was obtained from the reaction of methylthioallyllithium with benzyl bromide. A solution of allyl methyl sulfide (0.19 g, 2.2 mmol) in dry THF (10 ml) was stirred at -78° under nitrogen and treated with 1.3 M sec-butyllithium in pentane (1.7 ml, 2.2 mmol). The solution was stirred for 30 min at -78° and at -26° for 30 min. The resulting solution, which was cooled to -78°, was treated dropwise with benzyl bromide (0.34 g, 2.0 mmol) in dry THF (2 ml) and kept at -78° for 1 hr. Extractive workup afforded an oily mixture of three components. The nmr spectrum of this mixture showed singlet absorptions at δ1.91, 2.11, and 2.17 ppm in a ratio of 88:6:6. The positions of these signals are in agreement with those expected for the respective methyl groups of the α-alkylated desired product 4, the γ-alkylated methyl sulfide (E) 5, and the isomer 6.

2.4.8. 6-Phenyl-trans-4-hexenal (10a)— sec-Butyllithium (1.7 ml of a 1.3 M pentane solution, 2.2 mmol) was added to a solution of allyl vinyl sulfide (0.22 g, 2.2 mmol) in dry THF (10 ml) stirring under nitrogen at -78°. The yellow solution was stored at -78° for 30 min and at -26°

for 30 min. The anion formation was determined by reaction
with benzyl bromide (0.34 g, 2.0 mmol) followed by usual
workup to give the sulfide shown by nmr analysis to be >85%
pure. The mixture of the crude sulfide and calcium carbonate
(0.60 g, 6.0 mmol) in 3:1 dimethoxyethane (DME)-water (40 ml)
was heated at reflux overnight. Extractive workup furnished
a liquid which was submitted to preparative tlc on silica
gel with 1:1 benzene-hexane as an eluant. The band at
R_f 0.35-0.60 afforded the γ,δ-unsaturated aldehyde 10a
(0.22 g, 62% yield) as a pale-yellow liquid: tlc, R_f 0.67
(CH_2Cl_2); glpc t_r 4.50 (column D, 130°); nmr, 2.45 (m, 4H,
$-CH_2CH_2CHO$), 3.34 (m, 2H, $C_6H_5CH_2CH=$), 5.53 (m, 2H, $-CH=CH-$),
7.20 (m, 5H, C_6H_5), and 9.77 (s, 1H, CHO); ir (neat), 2730
(w), 1730 (s, C=O), and 970 cm^{-1} (s, trans C=C); MS (m/e),
174 (2), 130 (100), 115 (27), and 91 (67). The gas
chromatographic analysis and silver nitrate-silica gel tlc
showed the absence of detectable amounts (<1%) of the
geometrically isomeric olefin. The analytical oily sample
was prepared by evaporative distillation at 120° (bath temp,
3 mmHg).

Found: C, 82.9; H, 8.03. Calcd for $C_{12}H_{14}O$: C, 82.7;
H, 8.10.

2.4.9. 4-(E)-Tridecenal (10b)— A solution of allyl vinyl
sulfide (0.22 g, 2.2 mmol) in dry THF (10 ml) was stirred
at -78° under nitrogen and treated with a 1.3 M solution
of sec-butyllithium in pentane (1.7 ml, 2.2 mmol). The
mixture was stirred at -78° for 30 min, warmed to -26° and

kept for 30 min. The resulting solution, which was cooled to -78°, was treated dropwise with 1-bromooctane (0.39 g, 2.0 mmol) in dry THF (2 ml) and kept at -78° for 1 hr. The oil obtained on extractive workup was dissolved in DME and water (3:1 40 ml) in the presence of calcium carbonate (0.60 g, 6.0 mmol), and the suspension was heated at reflux for 12 hr. The mixture was freed of the organic solvent and the residue was extracted with ether. The ethereal solution was filtered, washed with water, dried and concentrated. The residual liquid was submitted to preparative tlc on silica gel with 1:1 hexane-benzene as an eluant. The aldehyde 10b (R_f 0.3-0.6; 0.22 g, 57% yield) was isolated as a colorless liquid: silver nitrate-silica gel tlc, R_f 0.55 (CH_2Cl_2); glpc, t_r 5.0 (column B, 130°); ir (neat), 2725 (w), 1730 (s, C=O), and 970 cm^{-1} (s, trans C=C); nmr (NMR 3), 0.90-1.55 (m, 17H, $C_8\underline{H}_{17}$), 2.15-2.35 (m, 4H, -$C\underline{H}_2C\underline{H}_2$CHO), 5.30-5.55 (m, 2H, -$C\underline{H}$=$C\underline{H}$-), and 9.60 (s, 1H, $C\underline{H}$O); MS (m/e), 196 (3), 178 (9), 152 (23), 85 (68), and 55 (100);

Found: C, 79.7; H, 12.4. Calcd for $C_{13}H_{24}O$: C, 79.5; H, 12.3.

2.4.10. 5-Geranyl-trans-4-pentenal (10c)[*]— sec-Butyllithium in pentane (1.3 M, 1.7 ml, 2.2 mmol) was added to a solution of allyl vinyl sulfide (0.22 g, 2.2 mmol) in dry THF (15 ml) stirring at -78° under nitrogen. After 30 min at -78°,

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[*]Named after the IUPAC 1957 rule A-75-1.

then 30 min at -26°, the resulting yellow solution was
cooled to -78° and treated with geranyl bromide (0.43 g,
2.0 mmol). The mixture was stirred for 1 hr at -78° and
at 25° for 30 min and diluted with ether, and the ethereal
extract was washed with water, dried, and freed of the
solvent. The residual liquid was dissolved in DME and water
(3:1, 40 ml) in the presence of calcium carbonate (0.60 g,
6.0 mmol) and the mixture was heated at reflux overnight.
The liquid obtained on extractive workup was submitted to
preparative tlc on silica gel with 1:1 hexane-benzene as
an eluant. The aldehyde 10c (R_f 0.4-0.65; 0.27 g, 62%
yield) was isolated as a pale yellow liquid: silver nitrate-
silica gel tlc, R_f 0.58 (CH_2Cl_2); glpc, t_r 7.0 (column B,
140°); ir (neat) (IR 2), 2720 (w), 1728 (s, C=O), and
970 cm^{-1} (s, trans, C=C); nmr (NMR 4), 1.63 (bs, 6H,
=C(C$\underline{H}_3$)$_2$), 1.73 (bs, 3H, =CHC$\underline{H}_3$), 2.10 (m, 4H,
(CH_3)$_2$C=CHC$\underline{H}_2$C$\underline{H}_2$C(CH_3)=), 2.30-2.80 (m, 6H, 3 methylenes),
4.90-5.60 (m, 4H, olefinic protons), and 9.63 (s, 1H, C$\underline{H}$O);
MS (m/e), 220 (2), 195 (3), 177 (7), 123 (50), and 69 (100).

2.4.11. 4-(2'-tetrahydropyranyloxy)-butyl Iodide (14)—

A solution of 1,4-butanediol (7.2 g, 50 mmol) and 2,3-
dihydropyran (1.7 g, 20 mmol) in dry ether (30 ml) was
treated with p-toluenesulfonic acid monohydrate (0.10 g)
at room temp. After stirring for 3 hr at room temp, the
reaction mixture was washed with saturated sodium
bicarbonate and brine, and the ethereal phase was dried,
and freed of the solvent. The residue was purified on

silica gel (80 g) column chromatography with dichloro-
methane as an eluant. The obtained 1,4-butanediol mono-
tetrahydropyranyl. ether (2.6 g, 15 mmol) was dissolved in
pyridine (20 ml) and the solution of p-toluenesulfonyl
chloride (3.4 g, 18 mmol) in pyridine (5 ml) was added
solwly at 0°. The mixture was kept at 0° for 1 hr and
diluted with ether, and the ethereal extract was washed with
aqueous cupric sulfate and water, dried, and freed of the
solvent. The mixture of residual crude tosylate (4.5 g,
14 mmol) and sodium iodide (4.2 g, 28 mmol) in acetone (25 ml)
was stirred for 12 hr at room temp in dark. The solution
was diluted with hexane (50 ml) and filtered through a
pad of Celite 545, and freed of the solvent. Purification
by silica gel (80 g) column chromatography with dichloro-
methane as an eluant gave 4-(2'-tetrahydropyranyloxy)-butyl
iodide 14 (3.8 g) as a colorless liquid: tlc, R_f 0.4 (CH_2Cl_2);
ir (neat), 1440 (m), 1350 (m), 1220 (m), 1125 (s), 1110 (s),
1070 (s), 1060 (sh), 1025 (s), 920 (m), 860 (m), and 805
cm^{-1} (s); nmr, 1.2-2.2 (m, 10H), 3.0-4.0 (m, 6H), and
4.43 (t, 1H).

2.4.12. 9-(2'-tetrahydropyranyloxy)-trans-4-nonen-1-al (16)—
sec-Butyllithium in pentane (1.3 M, 1.7 ml, 2.2 mmol) was
added to a solution of allyl vinyl sulfide (0.22 g, 2.2 mmol)
in dry THF (15 ml) at -78° under nitrogen. The solution
was kept at -78° for 30 min, then at -26° for 30 min.
The resulting solution was treated at -78° with a solution
of the iodide 14 (0.57 g, 2.0 mmol) in THF (2 ml) and kept

at -78° for 30 min. Extractive workup furnished a liquid
that was heated at reflux in DME-water (3:1, 40 ml) with
calcium carbonate (0.60 g, 6.0 mmol). The solution was
diluted with ether, filtered off calcium carbonate, and
the ethereal extract was washed with water, dried, and freed
of the solvent. The residual liquid was submitted to
preparative tlc on silica gel with benzene as an eluant.
The band at R_f 0.2-0.4 afforded the aldehyde 16 (0.26 g,
55% yield). This material was identical in all respects
with the reported one.[16] Silver nitrate-silica gel tlc,
R_f 0.2 (CH_2Cl_2); ir (neat), 2710 (sh, CHO), 1722 (s, C=O),
and 963 cm^{-1} (m, trans C=C); nmr, 1.30-2.20 (m, 12H),
2.44 (m, 4H, -CH$_2$CH$_2$CHO), 3.20-4.10 (m, 4H, OCH$_2$), 4.60
(bt, 1H, -O-CH-O-), 5.48 (m, 2H, olefinic protons), and
9.83 (s, 1H, CHO).

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CHAPTER 3

A Facile Route to γ-Ketoaldehydes.
Synthesis of <u>cis</u>-Jasmone.

Abstract—— Treatment of 2-ethoxyallyl vinyl
sulfide with <u>sec</u>-butyllithium in tetrahydrofuran
produces the corresponding lithiation product,
$CH_2=CH-S-CH(Li)-C(OEt)=CH_2$. The novel reagent
thus obtained has been shown to react smoothly
with a primary halide (RX) to afford
$CH_2=CH-S-CHR-C(OEt)=CH_2$. The subsequent thio-
Claisen rearrangement in aqueous dimethoxyethane
gives the 5 carbon homologated γ-ketoaldehyde
($RCH_2C(O)CH_2CH_2CHO$) in 56 to 70% yield.
<u>cis</u>-Jasmone, dihydrojasmone, and allylrethrone
are synthesized efficiently by virtue of this
novel technique.

3.1. Synthesis of ɣ-Ketoaldehydes

The investigations described herein originate from the hypothesis that 2-ethoxy-1-vinylthioallyllithium 2 might react regioselectively with an alkyl halide to yield the sulfide 3 which in turn should give rise to the aldehyde 4 via thio-Claisen rearrangement. We can easily anticipate that the resulting 5-alkyl-4-ethoxy-4-pentenals 4 should be converted smoothly into ɣ-ketoaldehydes 5 and therefore into the corresponding 2-substituted 2-cyclopentenones.
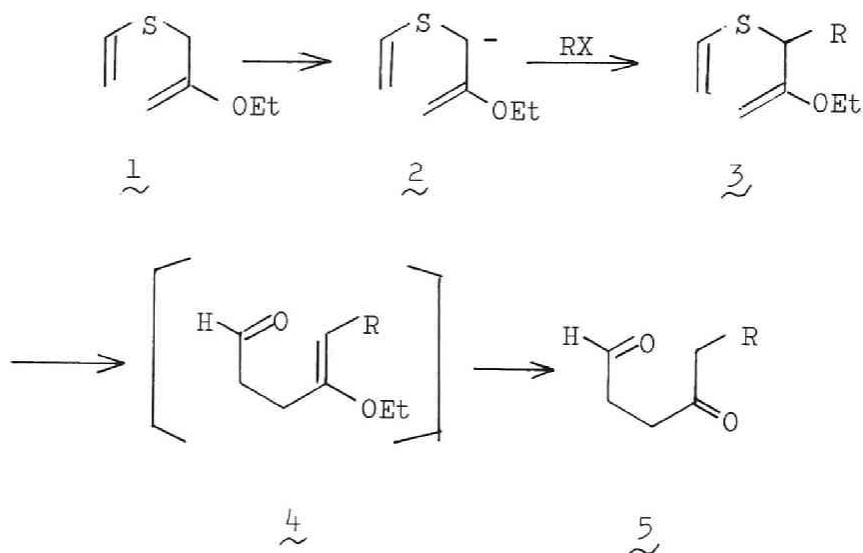
The starting 2-ethoxyallyl vinyl sulfide 1 was
obtained as follows. On treatment with sodio-phosphonate
6,[1] paraformaldehyde was converted into ethyl propenoate 7
in 30% yield. The ester 7 was transformed into the alcohol
8 on treatment with lithium aluminum hydride. Unlike the
higher homolog, 2-cyclohexylidend-2-ethoxyethanol,[2] this
new alcohol could not be distilled because of its thermal
lability. The crude alcohol was treated with n-butyl-
lithium and then with methanesulfonyl chloride and anhydrous
lithium bromide[3] to yield the ethoxyallyl bromide 9,
which was converted by treatment with lithium ethenethiolate[4]
into the sulfide 1 in 34% over-all yield on the basis of 7.

HCHO + EtO-C-P(OEt)$_2$ (with Na$^+$, O, COOEt) ⟶ H$_2$C=C(OEt)(COOEt) ⟶ H$_2$C=C(OEt)(CH$_2$OH)

6   7   8

⟶ H$_2$C=C(OEt)(CH$_2$Br) ⊖SCH=CH$_2$ ⟶ (ring structure with S and OEt)

9   1
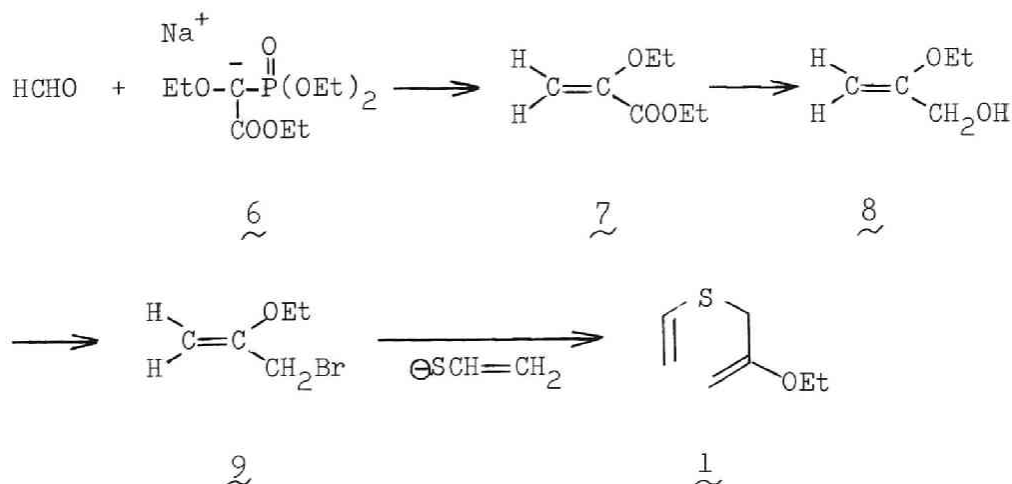
Addition of sec-butyllithium (1.1 equiv in
pentane) to the tetrahydrofuran solution of 2-ethoxyallyl
vinyl sulfide (1.2 equiv) under nitrogen at -78°
produced a straw yellow solution of the anion 2, which
was stable at this temperature. This anion was alkylated

at -78° by the addition of n-amyl bromide (1.0 equiv)
to produce high yields of the corresponding sulfide 3a.
The crude sulfide thus obtained after extractive workup
was found to be suitable for the thio-Claisen rearrangement,
which was actually carried out by dissolving in dimethoxy-
ethane-water (3:1) and heating at reflux for 12 hr in
analogous way as the preparation of γ,δ-unsaturated
aldehyde described in section 2.2. After preparative
layer chromatography on silica gel, the desired 4-oxodecanal
5a was obtained in 66% over-all yield. The complete
scheme is therefore a two-step operation requiring no
purification of intermediates. In a similar experiment,
allyl bromide and 1-bromo-cis-2-pentene gave the
corresponding γ-ketoaldehyde 5b (70% over-all yield) and
5c (56% over-all yield), respectively. The undesirable
byproduct, α-vinylthioketone, might be expected from the
direct hydrolysis of the sulfide 3 prior to the thio-Claisen
rearrangement, but no product originating therefrom was
detected among the crude reaction mixture.

2

3

5

(a) R=n-C$_5$H$_{11}$

(b) R=CH$_2$CH=CH$_2$

(c) R=CH$_2$C=C CH$_2$CH$_3$
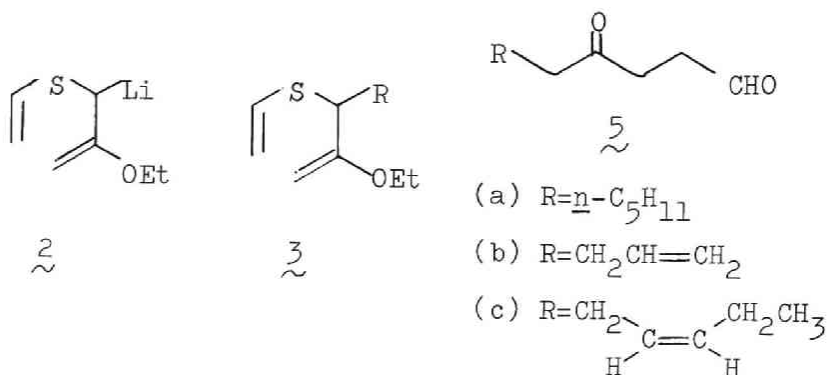
One of the advantages of the present synthetic
scheme is that it permits the introduction of a carbonyl
group into a molecule simultaneously with a carbon chain
extension operation. In other words, the carbon skeleton
of a molecule can be elaborated and a functional group
introduced in a single step. The γ-ketoaldehydes so
obtained are important synthetic intermediates since the
-CO-C-C-CHO unit can be transformed into several important
organic functionality including (a) cyclization to cyclo-
pentenone derivatives, (b) transformation to furan
derivatives, and (c) reaction to give pyrrole derivatives.

3.2. Synthesis of cis-Jasmone

In section 3.1 we established the efficient synthesis
of γ-ketoaldehydes starting from simple alkyl halides.
This unique process provides us with simple synthesis of
rethrone derivatives. γ-Ketoaldehydes must easily be
cyclized to cyclopentenone derivatives via intramolecular
aldol condensation as shown below.
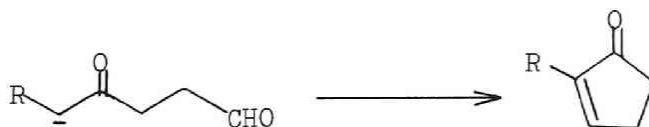
The actual execution of this scheme soon turned
out to be not so simple. Although Hunsdiecker's method [5]
has frequently been utilized in the cyclization of 1,4-
diketone,[6-11] but the reaction condition requires heating

with 2% aqueous potassium hydroxide at reflux. The same
process was found not to be applicable to the γ-ketoaldehydes. .
Success was attained, however, by stirring the ketoaldehydes
very vigorously for 2 hr at 25° in aqueous methanol
containing 10% sodium hydroxide. Cyclopentenone derivative
10c could thus be obtained from 5c in 60% yield.
Transformation of this cyclopentenone 10c to cis-jasmone
12c has been well-established [12] and involves condensation
with methyllithium and oxidation of the resulting carbinol
11c with chromium trioxide.

10a-c   11a-c   12a-c

(a) R=$\underline{n}$-C$_5$H$_{11}$

(b) R=CH$_2$CH=CH$_2$

(c) R=CH$_2$\C=C/CH$_2$CH$_3$
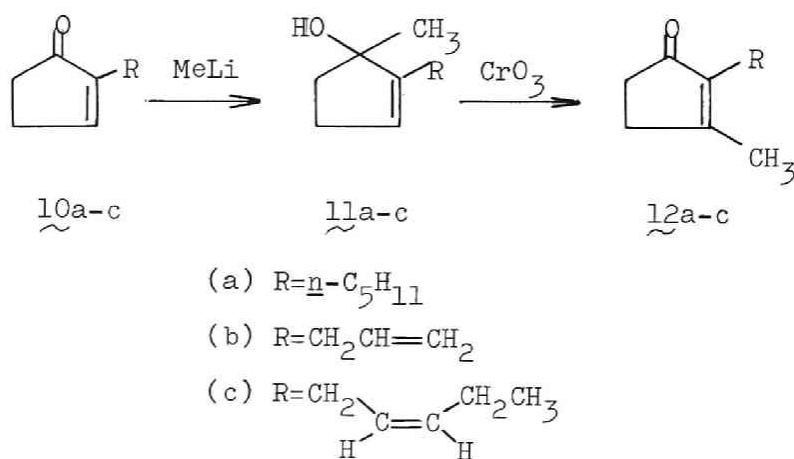
Applying this sequence, we were able to convert
the γ-ketoaldehyde 5a and 5b to 10a (71%) and 10b (71%),
respectively, each of which was transformed to dihydro-
jasmone 12a [11,13] or allylrethrone 12b,[14] respectively.

3.3. Experimental Part

3.3.1. Ethyl 2-Ethoxypropenoate (7)— According to

the method of Grell,[1] 7 was obtained from paraformaldehyde
as follows. Ethyl diethylphosphonoethoxyacetate [1] (26.8 g,
0.1 mol) was added dropwise with stirring under nitrogen
over a period of 30 min to a slurry of oil-free sodium
hydride (2.4 g, 0.1 mol) in dry dioxane (100 ml) at 50-60°.
The mixture was stirred at 50-60° until hydrogen evolution
had ceased (30 min), and treated with paraformaldehyde
(6.0 g, 0.2 mol) at room temp. After being stirred at
50° for 30 min, the resulting mixture was diluted with
ether, and the ethereal solution was washed with water,
dried, and freed of the solvent. Fractional distillation
of the residual liquid provided ethyl 2-ethoxypropenoate
7 (5.7 g, 40% yield) as a colorless liquid: bp 71-73°
(18 mmHg); ir (neat) (IR 3), 1730 (s, C=O), 1620 (s, C=C),
1190 (s), and 860 cm^{-1} (m, C=CH$_2$); nmr (NMR 5), 1.30
(t, 3H, -OCH$_2$CH$_3$), 1.35 (t, 3H, -COOCH$_2$CH$_3$), 3.70 (q, 2H,
-OCH$_2$CH$_3$), 4.13 (q, 2H, -COOCH$_2$CH$_3$), 4.40 (d, 1H, $\underset{H}{\overset{H}{>}}C=C\overset{COOEt}{\underset{OEt}{<}}$),

and 5.15 (d, 1H, $\underset{H}{\overset{H}{>}}C=C\overset{COOEt}{\underset{OEt}{<}}$); MS (m/e), 144 (49), 129
(47), 88 (78), and 60 (100).

3.3.2. 2-Ethoxy-2-propen-1-ol (8)— A suspension of

lithium aluminum hydride (1.6 g, 42 mmol) in absolute ether
(100 ml) was cooled to -78°. A solution of the ester 7
(5.0 g, 35 mmol) in ether (10 ml) was added during 30 min,

and the mixture was kept at -78° for 30 min and then at -26° for 30 min. The resulting solution was treated with ethyl acetate (1.0 g) and saturated aqueous ammonium chloride. The organic phase was separated and dried. Concentration of the solvent gave the crude alcohol 8 (2.8 g, 77% yield) as a colorless oil: ir (neat), 3450 (m, OH) and 1070 cm^{-1} (m). As attempted purification by fractional distillation failed (decomposition), the crude product was subjected immediately to the next step without further purification.

3.3.3. 3-Bromo-2-ethoxypropene (9)-- According to the method of Corey,[3] a mixture of the crude alcohol 8 (2.8 g, 27 mmol) and anhydrous lithium bromide (8.7 g, 0.1 mol) in dry ether (20 ml) at -78° was treated with n-butyllithium in hexane (1.5 M, 18 ml, 27 mmol) and methanesulfonyl chloride (2.3 ml, 29 mmol) and the suspension was allowed to warm to 0° over a 30 min period. After being stirred for an additional 30 min at 0° and 6 hr at 25°, the mixture was poured into cold sodium bicarbonate solution, and the product was extracted with ether and dried. Concentration in vacuo gave a quantitative yield of the desired bromide 9 (4.1 g). Further purification by chromatography or distillation was not effective according to the extreme lability of the bromide 9. Nmr: 1.35 (t, 3H, -OCH$_2$CH$_3$), 3.75 (q, 2H, -OCH$_2$CH$_3$), 3.78 (s, 2H, -CH$_2$Br), 4.02 (d, 1H,

$$\underset{H}{\overset{\underline{H}}{>}}C=C\underset{OEt}{\overset{CH_2Br}{<}}$$), and 4.23 (d, 1H, $$\underset{\underline{H}}{\overset{H}{>}}C=C\underset{OEt}{\overset{CH_2Br}{<}}$$).

3.3.4. 2-Ethoxyallyl Vinyl Sulfide (1)— Liquid ammonia
was poured in a 25 ml flask under cooling with a dry ice-
methanol bath. When 20 ml of the liquid had been collected,
dry nitrogen was introduced through a three-way stopcock
and then lithium (0.35 g, 50 mg-atom) was added with
stirring. After 30 min, ethyl vinyl sulfide (2.2 g, 25 mmol)
was introduced dropwise. Stirring was continued at -78°
for 15 min; then the resulting lithium amide was quenched
by the addition of solid ammonium chloride (1.3 g, 25 mmol).
After 15 min, crude bromide (4.1 g, 25 mmol) was added
and the mixture was allowed to stand at 0° to evaporate
ammonia. The residue was diluted with ether, and the
ethereal phase was washed with saturated aqueous ammonium
chloride solution, dried, and freed of the solvent. The
clear yellow oil thus obtained was distilled to furnish
the sulfide 1 (1.5 g, 34% yield from 7) as a colorless
liquid: bp 67° (16 mmHg); ir (neat), 1620 (m), 1580 (s),
1070 (s), and 800 cm^{-1} (m); nmr (NMR 7), 1.35 (t, 3H,
-OCH$_2$CH$_3$), 3.25 (s, 2H, S-CH$_2$), 3.75 (q, 2H, -OCH$_2$CH$_3$),

3.95 (d, 1H, $\overset{H}{\underset{H}{>}}C=C\overset{<}{_{OEt}}$), 4.07 (d, 1H, $\overset{H}{\underset{\underline{H}}{>}}C=C\overset{<}{_{OEt}}$),

5.10 (d, 1H, $\overset{H}{\underset{H}{>}}C=C\overset{S}{_{H}}$, J=16 Hz), 5.15 (d, 1H, $\overset{H}{\underset{\underline{H}}{>}}C=C\overset{S}{_{H}}$,

J=10 Hz), and 6.35 (dd, 1H, S-CH=CH$_2$); MS (m/e), 144 (M$^+$).

3.3.5. 4-Oxodecanal (5a)— sec-Butyllithium in pentane
(1.3 M, 0.85 ml, 1.1 mmol) was added with stirring under
nitrogen to a solution of 2-ethoxyallyl vinyl sulfide

(175 mg, 1.2 mmol) in dry THF (10 ml) at -78°. The solution was kept at -78° for 30 min, treated with n-amyl bromide (151 mg, 1.0 mmol), and kept at -78° for 1 hr. The reaction mixture was partitioned between ether and water. The organic phase was washed with water, dried and freed of the solvent. The remaining liquid was dissolved in DME-water (3:1, 20 ml) and heated at 110° for 12 hr. Extractive workup furnished a liquid which was submitted to preparative tlc on silica gel with 1:1 benzene-dichloromethane as an eluant. The band of R_f 0.3-0.5 provided the γ-ketoaldehyde 5a (112 mg, 66% yield): tlc, R_f 0.25 (CH_2Cl_2); ir (neat), 2735 (w), 1735 (sh, CHO), and 1710 cm^{-1} (s, C=O of ketone); nmr, 9.80 (s, 1H, CHO), MS (m/e), 170 (M$^+$).

3.3.6. 4-Oxo-6-octenal (5b)— A solution of 2-ethoxyallyl vinyl sulfide (175 mg, 1.2 mmol) in dry THF (10 ml) was treated with sec-butyllithium in pentane (1.3 M, 0.85 ml, 1.1 mmol) under nitrogen at -78°. After the mixture was stirred for 30 min at -78°, allyl bromide (85 μl, 1.0 mmol) was added. The mixture was stirred for 1 hr at -78° and at 25° for 10 min and extracted with ether. The ethereal phase was dried and freed of the solvent to yield the pale yellow liquid which was diluted with DME-water (3:1, 30 ml) and heated at reflux for 13 hr. The mixture was cooled, diluted with ether, and the ethereal extract was washed with water, dried, and freed of the solvent. The remaining liquid was submitted to preparative tlc on silica gel

·with 1:1 benzene-dichloromethane as an eluant. The band of R_f 0.25-0.45 furnished the aldehyde 5b (0.10 g, 70% yield) as a pale yellow liquid: tlc, R_f 0.20 (CH_2Cl_2); ir (neat), 2720 (sh, CHO) and 1710 cm^{-1} (s, C=O); nmr, 9.80 (s, 1H, CHO); MS (m/e), 140 (M^+).

3.3.7. 4-Oxo-cis-7-decenal (5c)— sec-Butyllithium in pentane (1.3 M, 1.4 ml, 1.8 mmol) was added to a solution of 2-ethoxyallyl vinyl sulfide (0.29 g, 2.0 mmol) in dry THF (10 ml) stirring under nitrogen at -78°. The solution was kept there for 30 min and treated with 1-bromo-cis-2-pentene (0.25 g, 1.67 mmol). The reaction mixture was kept at -78° for 1 hr and 25° for 30 min, and poured into water. The ethereal extracts were concentrated in vacuo to give a colorless liquid which was dissolved in a mixture of DME (15 ml)-water (5 ml), and the solution was heated at reflux overnight. Extractive workup furnished a liquid that was submitted to preparative tlc on silica gel with 1:1 benzene-dichloromethane as an eluant. The band of R_f 0.2-0.4 provided the desired aldehyde (0.14 g, 56% yield): tlc, R_f 0.25 (CH_2Cl_2); ir (neat), 2720 (sh, CHO) and 1710 cm^{-1} (s, C=O); MS (m/e), 168 (M^+).

3.3.8. Dihydrojasmone (12a)— A solution of sodium hydroxide (0.80 g, 20 mmol) in 1:1 methanol-water (20 ml) was added to the 4-oxodecanal (0.10 g, 0.6 mmol). The mixture was stirred vigorously at room temp for 2 hr. Ethyl acetate extracts of this mixture were washed with

water, dried, and freed of the solvent. The residual
liquid was submitted to preparative tlc with dichloro-
methane as an eluant. The strongly uv-active band ($\underline{R}_f$ 0.3-
0.5) affored a liquid identified as 2-$\underline{n}$-amylcyclopentenone
$\underset{\sim}{10}$a (65 mg, 71% yield): tlc, $\underline{R}_f$ 0.30 (CH_2Cl_2); ir (neat)
(IR 5), 1700 (s, C=O), 1000 (w), and 920 cm^{-1} (w); nmr
(NMR 8), 0.67-1.60 (m, 9H), 1.70-2.65 (m, 6H), and 7.17
(m, 1H, olefinic proton); MS ($\underline{m}/\underline{e}$), 152 (39), 123 (35),
97 (82), and 96 (100). According to the method of Grieco,[13]
ketone $\underset{\sim}{10}$a was converted to dihydrojasmone as follows:
A solution of ketone $\underset{\sim}{10}$a (65 mg, 0.4 mmol) in absolute
ether (2 ml) was stirred at 0°, treated with 0.8 $\underline{M}$
methyllithium in ether (1.0 ml, 0.8 mmol) and stirred at
room temp for 15 min. The solution was diluted with
ether and the ethereal extract was washed with water, and
concentrated $\underline{in\ vacuo}$ to give the alcohol $\underset{\sim}{11}$a (60 mg).
The crude carbinol $\underset{\sim}{11}$a was dissolved in ether (2 ml) and
a solution of chromium trioxide (80 mg) in aqueous 5%
sulfuric acid (0.8 ml) was added dropwise at 0°. The
mixture was stirred for 15 min at 0°, diluted with ether,
and the ethereal extract was washed with water. The
organic phase was dried and freed of the solvent. The
remaining oil was submitted to preparative tlc on silica
gel with dichloromethane as an eluant. The uv-active
band ($\underline{R}_f$ 0.3-0.5) furnished dihydrojasmone $\underset{\sim}{12}$a (40 mg)
which was identified by comparison with the reported data[11]:
tlc, $\underline{R}_f$ 0.3 (CH_2Cl_2); ir (neat) (IR 6), 1698 (s, C=O),

1645 (m, C=C), 1175 (m), and 1070 cm^{-1} (m); nmr (nmr 9),
0.67-1.60 (m, 9H), 1.70-2.65 (m, 6H), and 2.06 (s, 3H,
=CC$\underline{H}_3$); MS ($\underline{m}/\underline{e}$), 166 (18), 151 (50), 123 (20), and 110
(100).

3.3.9. Allylrethrone (12b)— A mixture of the γ-ketoaldehyde
$\underset{\sim}{5}$b (0.11 g, 0.79 mmol), sodium hydroxide (0.8 g, 20 mmol),
methanol (10 ml), and water (10 ml) was stirred at room
temp for 2 hr. The crude product obtained on extractive
workup was submitted to preparative tlc with dichloro-
methane as an eluant. The enone $\underset{\sim}{10}$b ($\underline{R}_f$ 0.25-0.40, 70 mg,
70% yield) was isolated as a colorless liquid: tlc, $\underline{R}_f$
0.25 (CH$_2$Cl$_2$); ir (neat) (IR 7), 1698 (s, C=O), 1638
(m, C=C), 1350 (m), 1000 (m), 910 (m), and 780 cm^{-1} (m);
nmr (NMR 10), 2.40-3.10 (m, 6H), 4.95-5.25 (m, 2H, -CH=C$\underline{H}_2$),
5.65 (m, 1H, -C$\underline{H}$=CH$_2$), and 7.25 (m, 1H, =C$\underline{H}$-); MS ($\underline{m}/\underline{e}$),
122 (85), 107 (20), 101 (10), 93 (20), and 79 (100).
Methyllithium in ether (0.8 $\underline{M}$, 1.5 ml, 1.2 mmol) was added
to a solution of ketone $\underset{\sim}{10}$b (70 mg, 0.55 mmol) in absolute
ether (2 ml) stirring under nitrogen at 0°. The mixture
was kept at room temp for 15 min and partitioned between
ether and aqueous ammonium chloride; the organic phase was
washed with water, dried, and freed of the solvent.
The residual crude alcohol $\underline{11}$b was dissolved in ether
(2 ml) and treated with a solution of chromium trioxide
(80 mg) in aqueous 5% sulfuric acid (0.8 ml) at 0°.
The solution was stirred for 15 min at 0°. Extractive
workup furnished a pale-yellow liquid that was submitted

to preparative tlc on silica gel with dichloromethane as
an eluant. The uv-active band (R_f 0.3-0.5) afforded the
desired enone 12b (50 mg). This material was identical
in all respects with the reported one.[14] tlc, R_f 0.25
(CH_2Cl_2); ir (neat) (IR 8), 1699 (s, C=O), 1640 (s, C=C),
1385 (m), 1180 (m), 998 (m), 910 (m), and 745 cm^{-1} (m);
nmr (NMR 11), 1.97 (s, 3H, CH_3), 2.20-3.00 (m, 6H), 4.65-
5.10 (m, 2H, -CH=CH_2), and 5.30 (m, 1H, -CH=CH_2); MS (m/e),
136 (100), 121 (76), 101 (15), and 93 (60).

3.3.10. cis-Jasmone (12c)— A solution of the aldehyde 5c
(0.14 g, 0.86 mmol) in aqueous methanol 10% sodium hydroxide
(20 ml) was stirred at room temp for 2 hr. Extractive
workup furnished a liquid that was submitted to preparative
tlc on silica gel with dichloromethane as an eluant.
The strongly uv-active band (R_f 0.3-0.5) provided the
enone 10c (75 mg, 60% yield): tlc, R_f 0.30 (CH_2Cl_2);
ir (neat) (IR 9), 1700 (s, C=O), 1630 (m, C=C), 1350 (m),
1000 (w), 970 (w), and 790 cm^{-1} (m); nmr (NMR 12), 1.00
(t, 3H, CH_3), 1.75-3.00 (m, 8H), 5.40 (m, 2H, -CH=CH-),
and 7.15 (m, 1H, =CH-); MS (m/e), 150 (36), 135 (18),
121 (36), 113 (20), 101 (22), 95 (31), and 55 (100).
Methyllithium in ether (0.8 M, 1.5 ml, 1.2 mmol) was added
to a solution of ketone 10c (75 mg, 0.52 mmol) in ether
(2 ml) stirring under nitrogen at 0°. After 15 min, the
solution contained only the uv-innactive alcohol 11c by
tlc assay. The crude alcohol obtained on extractive
workup was dissolved in ether (2 ml), and a solution of

chromium trioxide (80 mg) in aqueous 5% sulfuric acid (0.8 ml) was added at 0°. Ethereal extracts were dried and freed of the solvent. The remaining liquid was submitted to preparative tlc with dichloromethane as an eluant. The band at $\underline{R}_f$ 0.3-0.5 furnished a liquid that was identified as cis-jasmone 12c (45 mg) by the comparison of the following data with the reported ones [13]: tlc $\underline{R}_f$ 0.31 (CH_2Cl_2); ir (neat) (IR 10), 1700 (s, C=O), 1645 (m, C=C), 1385 (m), 1350 (m), 1180 (w), 1070 (w), and 965 cm^{-1} (w); nmr (NMR 13), 1.00 (t, 3H, $-CH_2C\underline{H}_3$), 1.98 (s, 3H, $C\underline{H}_3$), 2.00-3.00 (m, 8H), and 5.25 (m, 2H, $-C\underline{H}=C\underline{H}-$); MS ($\underline{m}/\underline{e}$), 164 (100), 149 (50), 135 (45), 122 (49), 110 (67), 93 (40), and 79 (61).

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CHAPTER 4

A Simple Stereoselective Version of the
Dithio Ester Thio-Claisen Rearrangement
Leading to ($\underline{E}$) Trisubstituted Ethylenes

Abstract—— Treatment of methallyl dithioacetate
with 2 equiv of $\underline{sec}$-butyllithium produces the
dianion, $CH_2=C(SLi)-S-CH(Li)-C(Me)=CH_2$. It
affords the dithioester, ($\underline{E}$) $RCH=C(Me)CH_2CH_2CSSMe$,
upon successive treatment with an alkyl halide
(RX) and methyl iodide followed by thio-Claisen
rearrangement. The transformation of the
dithioesters to the corresponding ethyl esters is
achieved by the action of cupric chloride-
cupric oxide in ethanol. The sequence furnishes
a useful method producing ethyl $4(\underline{E})$-alkenoates,
$RCH=C(Me)CH_2CH_2COOEt$, with high stereoselectivity.

4.1. Stereoselective Olefin Synthesis

The pursuit of rigorous stereoselectivity in the preparation of trisubstituted ethylenes has been a subject of considerable attention in recent years as an essential key in the synthesis of C_{18} _Cecropia_ juvenile hormone, for example.[1] The biological activity of various insect hormones and synthetic mimics is governed principally by the (E), (Z) geometry of the olefinic bonds.[2] The Johnson's biomimetic polyolefin cyclization,[3] on the other hand, does provide a new, practical route to steroids.[4] The ring junction stereochemistry has been shown to be dependent on the configuration of the olefinic precursor.[5] In both aspects of olefin chemistry, the stereochemical requirements are of paramount importance.

Many naturally occurring isoprenoids contain (E) trisubstituted ethylene bonds having a 1,5 arrangement with respect to the other. A prerequisite to the general synthetic route to this system must therefore be a combination of high stereoselectivity in the formation of each olefinic bond and the performance in effectively linking many isopreniod chains together by repetition of the synthetic procedure. While several investigators had adequately solved one or the other of the problems, the Cornforth's squalene synthesis[6] had been a single, exceptional case providing a solution to both of them simultaneously.

The Claisen rearrangement had already been employed in the preparation of isoprenoids by Faulkner and Petersen.[7] They treated an allylic alcohol 1 with isopropenyl methyl

ether in the presence of catalytic quantities of oxalic acid and hydroquinone to obtain a δ,δ-unsaturated ketone 2. The stereochemistry about the newly formed olefinic bond was shown to be $>$99% (E) and $<$1% (Z).
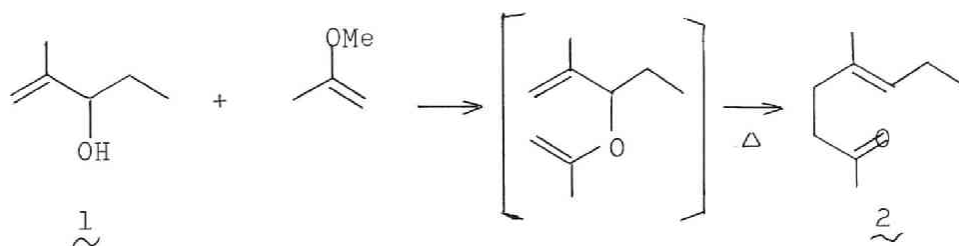
This section describes the exploitation of a highly stereoselective version of the thio-Claisen rearrangement providing a convenient route to (E) trisubstituted ethylenes which should serve as a convenient tool building up an isoprenoid chain.

At first sight the sequence described in Section 3.2 appeared to be extendible to the trisubstituted ethylene synthesis, but soon it turned out to be not the case. Thus, the stereochemistry about the newly formed olefinic linkage was shown to be ca. 80% (E) and 20% (Z) by glpc and nmr analyses in the following reaction.
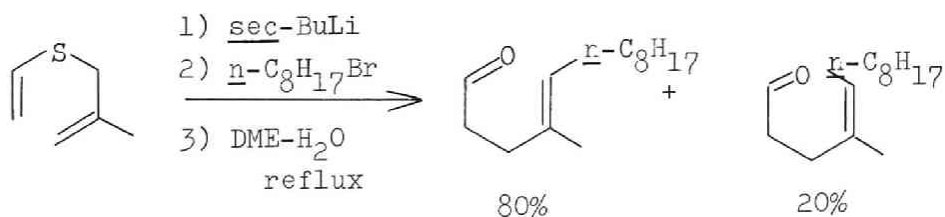
We had to reexamine the problem much more carefully. As discussed previously, the stereochemical outcome of thio-Claisen rearrangement is similar to that of the regular rearrangement of allyl ethers, which was studied extensively by Faulkner et al.[8] They have investigated factors determining the stereoselectivity of the rearrangement to find out that the cis/trans ratio of each product (Table 4-1, on the next page) reflected closely the one of axial/ equatorial conformers of the correspondingly substituted cyclohexane at the temperature of the Claisen rearrangement. By means of the recommended values of ΔG^{O}, i.e., the free-energy change for the conversion of a substituent from the equatorial to the axial position on a cyclohexane ring, they succeeded to predict accurately the cis/trans ratio in the Claisen rearrangement. Thus, the proportion of the trans product increased with increasing bulkiness of the substituent R^2 and decreased with increasing reaction temperature.
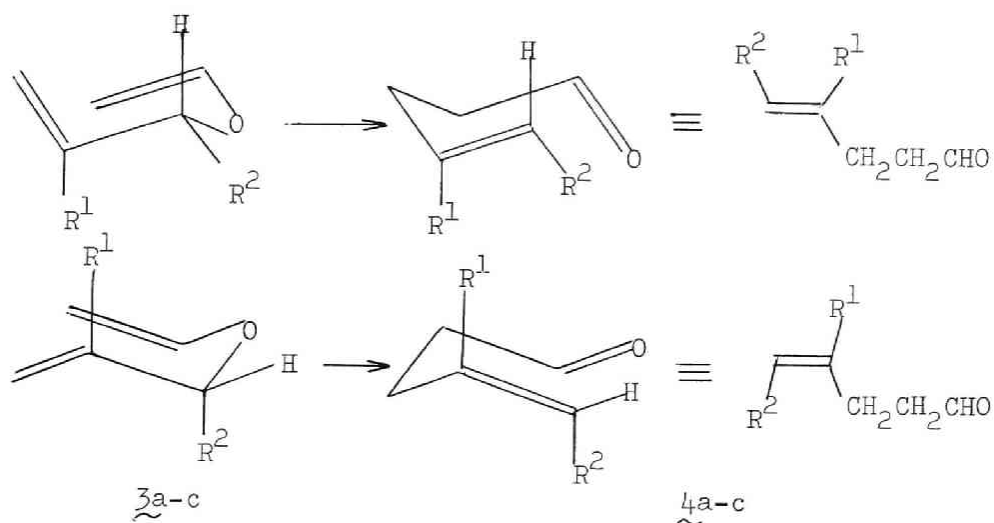
Table 4-1. Correlation of the cis/trans ratio of thio-
   Claisen rearrangement to axial/equatorial ratio of the
corresponding cyclohexane.

Reaction	R^1	R^2	Temp. °C	cis/trans ratio	Predicted axial/equatorial ratio
3a →4a	Me	Et	110	10:90	9:91
3a →4a	Me	Et	205	14:86	14:86
3b →4b	Me	i-Pr	110	7:93	6:94
3c →4c	Et	Et	110	10:90	9:91

On the basis of the cyclohexane-like transition state
of the chair form, we can predict that the increasing
bulkiness of the <u>axial</u> substituent R^3 would result in the
larger 1,3 diaxial interaction in the conformer A. This
must favor the conformer B in the transition state to
increase the proportion of the ($\underline{E}$) product. Several
reports [10,11] have provided evidence for this hypothesis
so that we can reasonably expect the severer 1,3 diaxial
interaction favoring the more stereoselective reaction
leading to the ($\underline{E}$) ethylenes.
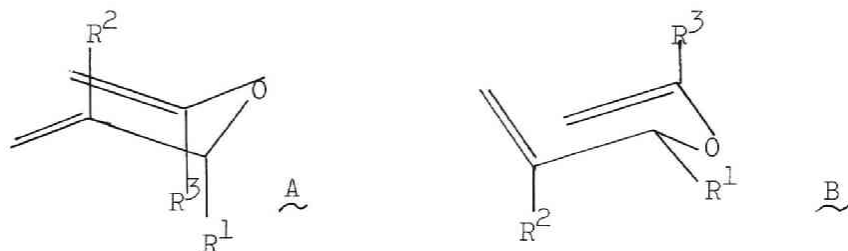
One known example is the acid-catalyzed thermal
reaction of allylic alcohols with triethyl orthoacetate.[10]
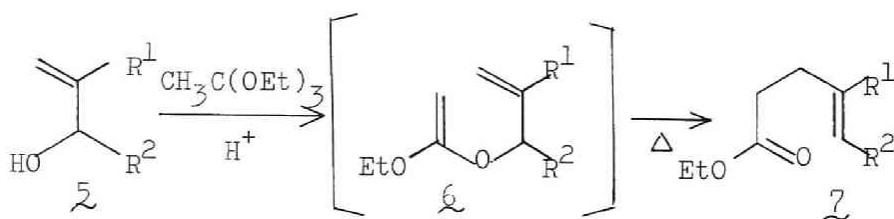
The alcohol 5 (R^1=Me, R^2=CH_2CH_2C(Me)=CH_2), on heating with
7 equiv of ethyl orthoacetate and 0.06 equiv of propionic
acid at 138° for 1 hr under distillative removal of ethanol,
was converted into the diene ester 7 (R^1=Me, R^2=CH_2CH_2-
C(Me)=CH_2) which consisted of $\rangle$98% ($\underline{E}$) and $\langle$2% ($\underline{Z}$) isomer.

The rigorous stereoselectivity was attributed to nonbonded interactions between the ethoxyl and R^2 group $\underset{\sim}{6}$ that developed only in the transition state leading to the ($\underline{Z}$) product. This method has proven to be valuable in ester synthesis under two-carbon homologation. The Eschenmoser's version [11] using 1-methoxy-1-dimethylaminoethylene is also known.
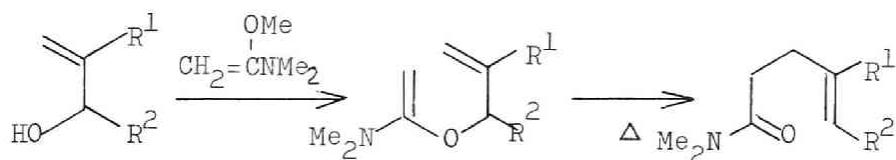

The facility of thio-Claisen rearrangement was first demonstrated by Brandsma and Schuijl.[12] They have described that the compounds $\underset{\sim}{9}$, prepared by metallation and subsequent reaction with $R^2R^3C{=}CHCH_2Br$, rearrange very smoothly into the thiocarbonyl compounds $\underset{\sim}{10}$. In a number of cases this rearrangement proceeded so easily that it was not possible to detect $\underset{\sim}{9}$ among the reaction mixture. On the other hand, the conversion of $CH_2{=}CH{-}O{-}CH_2{-}CH{=}CH_2$ or of $CH_2{=}CH{-}S{-}CH_2{-}CH{=}CH_2$ into $CH_2{=}CH{-}CH_2CH_2CHO$ required heating at 190-200° [13] and at 70-80°, [14] respectively. Meanwhile, the presence of a hetero-substituent on the vinyl α-carbon atom considerably facilitated the rearrangement.[15]
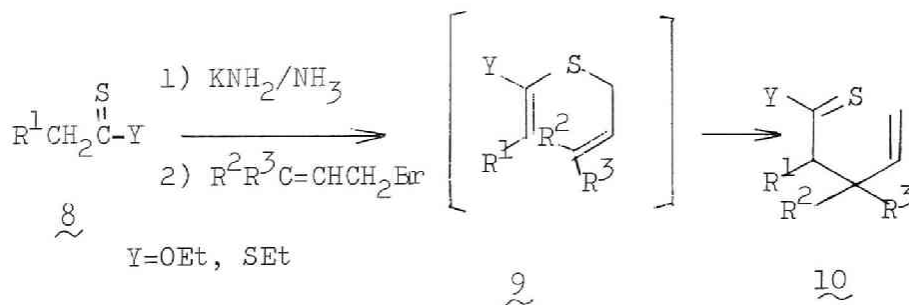
Clearly a ketene dithioacetal 9 is not a convenient starting substance due to its extreme lability. To avoid the difficulty we looked for the possibility of preparation of the dianion 12, which should provide us with the chance of success in the desired synthesis as shown below.
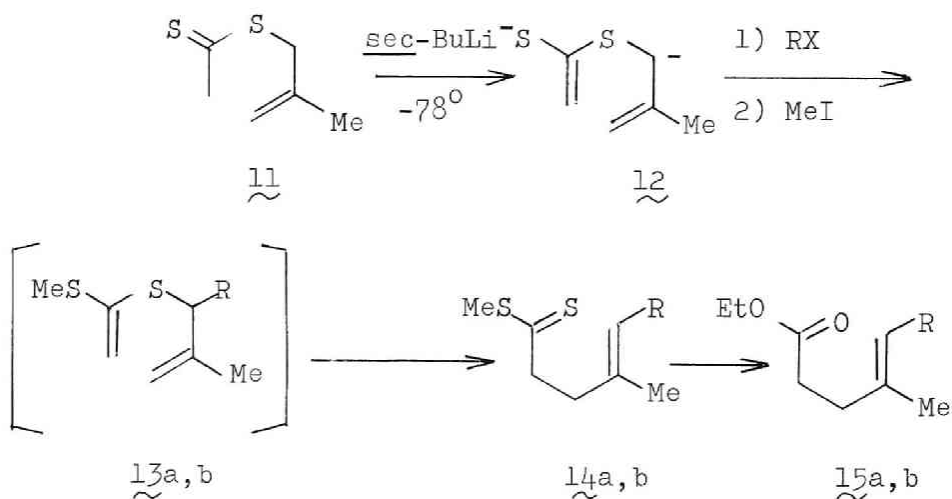
(a) $R = n\text{-}C_8H_{17}$

(b) $R = CH_2Ph$

Thus, the now established method simply involves the treatment of the dithioester 11 with 2 equiv of sec-butyllithium, followed by successive addition of an alkyl halide and methyl iodide. Evidently a dianion 12 was first formed, which, on stepwise alkylation followed by thio-Claisen rearrangement, afforded the dithioester 14 via the ketene thioacetal 13.

The transformation of the dithioesters to the respective esters has usually been effected under rather drastic conditions.[16] Seeking a milder procedure, we investigated the use of cupric chloride-cupric oxide in ethanol [17] and found that this system afforded almost quantitative yields of the desired esters under extremely mild conditions.

Detailed procedures of the sequence are as follows. The preparation of methallyl thioacetate 11 was accomplished, following the procedure of Schmidt,[18] by treatment of a mixture of methallyl thiol and acetonitrile with hydrogen chloride gas to obtain a salt, which was in turn decomposed with hydrogen sulfide in pyridine to yield 11 in 68% yield.

On treatment with sec-butyllithium (2 equiv) at -78° in tetrahydrofuran, the dithioester 11 was converted into a light-yellow solution of the dianion 12. Metalated dithioester 12 is apparently stable in the indicated solvent system at least upto -26°. The success of metalation can be attributed in large measure to the use of sec-butyl-lithium which, among other factors, possesses favorable

basicity. Notably, n-butyllithium or lithium diisopropyl-
amide as a base proved to be completely dissatisfactory.
After 30 min at -78°, 1-bromooctane (1 equiv) was added at
the same low temperature. The solution was kept there for
45 min and then at -26° for 1 hr to complete the first
C-alkylation process. Most of the color was discharged
after 10 min at -78°. The second S-methylation was performed
by the addition of methyl iodide (1 equiv) at -26° and the
resulting solution was stirred at -26° for 3 hr, during
which period the thio-Claisen rearrangement took place
spontaneously to give the yellow dithioester 14a.

Every dithioester itself is an important synthetic
intermediate [19] and the following transformation to the
ethyl carboxylate represents its versatile preparative
applicability. After examining the reaction with several
metal ions (Hg^+, Ag^+, and so on), halonium ions (NCS, NBS)
and methyl iodide, we found that the copper (II) ion
promoted the reaction quite effectively and cleanly. The
crude dithioester 14a, after extractive workup, was dissolved
in ethanol and added with three-fold excess of cupric chloride
and cupric oxide (1:1). The suspension was stirred at 25°
for 5 hr to afford the ester 15a in 63% over-all yield
after preparative layer chromatography on silica gel.
Similarly benzyl bromide gave the ester 15b in 70% over-all
yield.

The 100 MHz nmr spectrum of 15a (in CCl_4, TMS
internal standard) showed a sharp singlet at $\delta 1.60$ ppm

(3H) corresponding to the methyl group of (E) olefinic bond.[20] The rigorous stereoselectivity is probably attributable to the nonbonding interaction between the thiomethyl and n-C$_8$H$_{17}$ group 17 that develops only in the transition state leading to the (Z) isomer. The high stereoselectivity in the present reaction is in sharp contrast to the results obtained by Faulkner and Petersen[8]
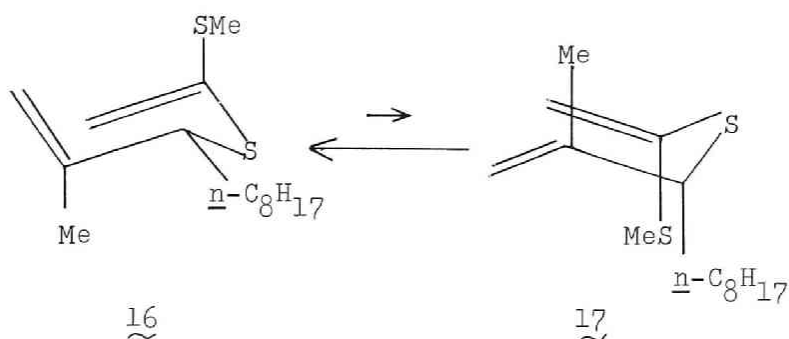
who claimed that substitution with S for CH$_2$ in the six membered ring transition state had caused a decrease in stereoselectivity of olefin formation. The low reaction temperature (-26°), at which our thio-Claisen rearrangement took place, may explain the observed selectivity.

This process is also applicable to the stereoselective production of trans disubstituted ethylenes. Starting from allyl dithioacetate 18, we could convert 1-bromooctane and benzyl bromide into trans alkenic ester 20a and 20b in 70% and 69% over-all yield, respectively.

The recently developed orthoester process [10] consisted in the addition of an _acetic acid unit_ to the γ-carbon of an allylic alcohol. The present, novel dianion method introduces $\ominus CH=C(Y)-CH_2CH_2COOEt$ (Y=Me, H) moiety with rigorous (E) geometry in a single synthetic operation in the reaction with a simple halide.

4.2. Experimental Part

4.2.1. Allyl Dithioacetate (18)—

Hydrogen chloride gas (4.3 g, 0.12 mol) was bubbled to a solution of acetonitrile (5.0 g, 0.12 mol) and 3-propenethiol (8.8 g, 0.12 mol) in petroleum ether (bp 30-70°, 10 ml) with stirring at 0°. White suspension immediately formed, and the solvent was removed by decantation. The resulting white solid was treated with pyridine (20 ml), saturated with hydrogen sulfide gas, at 0° and hydrogen sulfide gas was introduced to the solution for an additional 15 min. The mixture was diluted

with ether, washed with dilute hydrochloric acid three times
and water. Ethereal extracts were dried and freed of the
solvent. The residual yellow liquid was evaporatively
distillated through a 20 cm Vigreux column at 100° (bath
temp, 16 mmHg) to provide allyl dithioacetate (15.0 g,
95% yield) as a yellow liquid: tlc, R_f 0.55 (hexane); nmr
(NMR 14), 2.76 (s, 3H, CH_3), 3.83 (d, 2H, SCH_2), and
5.0-6.1 (m, 3H, $CH=CH_2$);

Found: C, 45.5; H, 6.10. Calcd for $C_5H_8S_2$: C, 45.5;
H, 6.10.

4.2.2. Methallyl Dithioacetate (11)— Methallyl dithio-
acetate (9.9 g, 68% yield) was obtained using the same
procedure described above from methallyl mercaptane (8.8 g,
0.10 mol). Physical data for 11: bp 120° (bath temp,
20 mmHg); tlc, R_f 0.55 (hexane); ir (neat), 1650 (m, S-C=C),
1195 (s), 1100 (s), 900 (s), and 860 cm^{-1} (s); nmr (NMR 15),
1.74 (d, 3H, J=1 Hz, $=CCH_3$), 2.75 (s, 3H, $CH_3C=S$), 3.75
(s, 2H, SCH_2), 4.74 and 4.85 (two bs, 1H each);

Found: C, 49.4; H, 7.07. Calcd for $C_6H_{10}S_2$: C, 49.3;
H, 6.90.

4.2.3. Methyl Dithio-trans-4-tridecenoate (19a)— sec-
Butyllithium in pentane (1.1 M, 3.8 ml, 4.2 mmol) was added
dropwise to a solution of allyl dithioacetate (0.29 g,
2.2 mmol) in dry THF (15 ml) with stirring under nitrogen
at -78°. The solution was kept at -78° for 30 min, treated
with 1-bromooctane (0.39 g, 2.0 mmol) in THF (2 ml), and
stirred at -78° for 45 min, then at -26° for 1 hr. Methyl

iodide (0.14 ml, 2.2 mmol) was added; after 2 hr at -26°, the reaction was terminated by the addition of water at -26°. Extractive workup afforded a yellow liquid that was submitted to preparative tlc on silica gel with hexane as an eluant. The band at $\underline{R}_f$ 0.60-0.80 provided the dithioester $\underset{\sim}{19a}$ (0.39 g, 76% yield): tlc, $\underline{R}_f$ 0.60 (hexane); ir (neat) (IR 11), 1210 (m), 965 (m), and 910 cm^{-1} (m); nmr (NMR 16), 0.90-1.60 (m, 17H), 1.80-2.30 (m, 2H, =CHC$\underline{H}_2$CH$_2$-), 2.60 (s, 3H, SC$\underline{H}_3$), 2.90-3.30 (m, 2H, C$\underline{H}_2$C=S), and 5.15-5.60 (m, 2H, C$\underline{H}$=C$\underline{H}$); MS ($\underline{m}/\underline{e}$), 258 (M$^+$).

4.2.4. Methyl Dithio-6-phenyl-trans-4-hexenoate (19b)—

sec-Butyllithium in pentane (1.1 $\underline{M}$, 3.8 ml, 4.2 mmol) was added to a solution of allyl dithioacetate (0.29 g, 2.2 mmol) in dry THF (15 ml) with stirring under nitrogen at -78°. Benzyl bromide (0.34 g, 2.0 mmol) was added; after 45 min at -78°, then 1 hr at -26°, the deep orange solution was treated at -26° with methyl iodide (0.14 ml, 2.2 mmol) and stirred at -26° for 2 hr. Water was added and ethereal extracts were dried, and freed of the solvent. The residual liquid was submitted to preparative tlc on silica gel with hexane as an eluant. The yellow-colored band ($\underline{R}_f$ 0.65-0.80) furnished the dithioester $\underset{\sim}{19b}$ as a yellow liquid (0.38 g, 80% yield): tlc, $\underline{R}_f$ 0.65 (hexane); ir (neat) (IR 11), 1600 (w), 1490 (s), 1210 (w), 965 (s, trans C=C), 905 (m), and 690 cm^{-1} (s); nmr, 2.23 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$), 2.57 (s, 3H, SC$\underline{H}_3$), 3.30 (d, 2H, C$\underline{H}_2$Ph), and 5.25-5.80 (m, 2H, C$\underline{H}$=C$\underline{H}$); MS ($\underline{m}/\underline{e}$), 236 (M$^+$).

4.2.5. Methyl Dithio-4-methyl-(E)-4-tridecenoate (14a)—
A solution of methallyl dithioacetate (0.32 g, 2.2 mmol)
in dry THF (15 ml) was stirred at -78° under nitrogen,
treated with 1.1 M sec-butyllithium in pentane (3.8 ml,
4.2 mmol) and the whole was stirred at -78° for 30 min. The
deep yellow solution was treated with 1-bromooctane (0.39 g,
2.0 mmol), and stirred at -78° for 45 min and at -26° for
1 hr. Methyl iodide (0.14 ml, 2.2 mmol) was added and the
mixture was kept at -26° for 2 hr. Extractive workup
furnished a yellow liquid which was submitted to preparative
tlc on silica gel with hexane as an eluant. The band at R_f
0.6-0.8 afforded the methyl dithioester 14a (0.41 g, 75%
yield): tlc, R_f 0.60 (hexane); ir (neat), 1210 (m) and
1140 cm^{-1} (w); nmr, 1.62 (s, 3H, =CCH$_3$), 2.57 (s, 3H, SCH$_3$),
and 5.19 (t, 1H, J=7 Hz, CH=); MS (m/e), 272 (M$^+$).

4.2.6. Methyl Dithio-4-methyl-6-phenyl-(E)-4-hexenoate (14b)
— sec-Butyllithium in pentane (1.1 M, 3.8 ml, 4.2 mmol) was
added to a solution of methallyl dithioacetate (0.32 g,
2.2 mmol) in dry THF (15 ml) with stirring under nitrogen
at -78°. Benzyl bromide (0.34 g, 2.0 mmol) was added;
after 45 min at -78°, then 1 hr at -26°, the resulting
solution was treated at -26° with methyl iodide (0.14 ml,
2.2 mmol) and kept at -26° for 2 hr. The reaction mixture
was diluted with ether and the ethereal extract was washed
with water and dried. The remaining liquid was submitted to
preparative tlc on silica gel with hexane as an eluant.
The band at R_f 0.65-0.80 afforded the dithioester 14b (0.35 g,

70% yield): tlc, $\underline{R}_f$ 0.65 (hexane); MS ($\underline{m}/\underline{e}$), 250 ($M^+$).

4.2.7. Ethyl trans-4-Tridecenoate (20a)— sec-Butyllithium in pentane (1.1 $\underline{M}$, 3.8 ml, 4.2 mmol) was added to a solution of allyl dithioacetate (0.29 g, 2.2 mmol) in dry THF (15 ml) with stirring under nitrogen at -78°. The solution was kept at -78° for 30 min and treated with a solution of 1-bromo-octane (0.39 g, 2.0 mmol) in THF (2 ml), and stirred at -78° for 45 min, then at -26° for 1 hr. Methyl iodide (0.14 ml, 2.2 mmol) was added and the mixture was kept at -26° for 2 hr, and treated with water. A mixture of the extracted liquid, anhydrous cupric chloride (0.81 g, 6.0 mmol), and cupric oxide (0.48 g, 6.0 mmol) in absolute ethanol (20 ml) was stirred under nitrogen at 25° for 5 hr. The black suspension was filtered through a pad of Celite and using ether to wash the filter cake. The filtrate and washings were combined, washed with water, dried, and freed of the solvent. The residual liquid was submitted to preparative tlc with benzene as an eluant. The major band ($\underline{R}_f$ 0.60-0.75) provided the trans ester 20a (0.34 g, 70% yield) as a colorless liquid: tlc, $\underline{R}_f$ 0.70 (benzene); ir (neat) (IR 12), 1735 (s, C=O), 1175 (m), and 975 cm^{-1} (m, trans, C=C); nmr (NMR 17), 2.27 (s, 3H, C=CC$\underline{H}_3$), 4.10 (q, 2H, OC$\underline{H}_2$CH$_3$), and 5.42 (t, 2H, C$\underline{H}$=C$\underline{H}$); MS ($\underline{m}/\underline{e}$), 240 ($M^+$). The analytical sample was prepared by evaporative distillation at 130° (bath temp, 18 mmHg).

Found: C, 74.8; H, 12.0. Calcd for $C_{15}H_{28}O_2$: C, 75.0; H, 11.7.

4.2.8. <u>Ethyl 6-Phenyl-trans-4-hexenoate (20b)</u>— A solution
of allyl dithioacetate (0.29 g, 2.2 mmol) in dry THF (15 ml)
was stirred under nitrogen at -78°, treated with 1.1 <u>M</u>
<u>sec</u>-butyllithium in pentane (3.8 ml, 4.2 mmol), and kept at
-78° for 30 min. The deep yellow solution was treated with
benzyl bromide (0.34 g, 2.0 mmol), and stirred at -78°
for 45 min and then at -26° for 1 hr. Methyl iodide (0.14 ml,
2.2 mmol) was added and the mixture was kept at -26° for
2 hr. Extractive workup furnished a liquid (0.48 g) that
consisted of the crude dithioester 19b. A solution of
crude dithioester 19b in absolute ethanol (20 ml) was
treated with cupric chloride (0.91 g, 6.0 mmol) and cupric
oxide (0.48 g, 6.0 mmol) at 25° for 5 hr. The product
obtained on extractive workup was submitted to preparative
tlc with benzene as an eluant. The ester 20b (R_f 0.60-
0.80, 0.30 g, 69% yield) was isolated as a colorless liquid:
bp 110° (bath temp, 2 mmHg); tlc, R_f 0.75 (benzene); ir
(neat) (IR 13), 1735 (s, C=O), 1260 (m), 970 (m, <u>trans</u> C=C),
and 700 cm^{-1} (s); nmr (NMR 18), 1.25 (t, 3H, C$\underline{H}_3$), 2.40
(m, 4H, C$\underline{H}_2$C$\underline{H}_2$), 3.35 (m, 2H, C$\underline{H}_2$Ph), 4.10 (q, 2H, OC$\underline{H}_2$CH$_3$),
5.40-5.80 (m, 2H, C$\underline{H}$=C$\underline{H}$), and 7.15 (s, 5H, C$_6\underline{H}_5$); MS ($\underline{m}/\underline{e}$),
218.1286 (calcd for C$_{14}$H$_{18}$O$_2$: 218.1423).

4.2.9. <u>Ethyl 4-Methyl-(E)-4-tridecenoate (15a)</u>— <u>sec</u>-
Butyllithium in pentane (1.1 <u>M</u>, 3.8 ml, 4.2 mmol) was added
to a solution of methallyl dithioacetate (0.32 g, 2.2 mmol)
in dry THF (15 ml) with stirring under nitrogen at -78°.
1-Bromooctane (0.39 g, 2.0 mmol) was added; after 45 min

at -78°, then 1 hr at -26°, the solution was treated at -26° with methyl iodide (0.14 ml, 2.2 mmol) and kept at -26° for 2 hr. The reaction mixture was diluted with ether. Ethereal extracts were washed with water, dried, and freed of the solvent. The remaining liquid (0.50 g) afforded the crude dithioester 14a. Powdered cupric chloride (0.81 g, 6.0 mmol) and cupric oxide (0.48 g, 6.0 mmol) were sequentially added to a solution of the liquid 14a (0.50 g) in absolute ethanol (20 ml). The heterogeneous reaction mixture was stirred under nitrogen at 25° for 5 hr and filtered through a pad of Celite 545 using ether to wash the filter cake. The organic phase was washed with water, dried, and freed of the solvent to give a yellow liquid which was submitted to preparative tlc with benzene as an eluant. The major band (R_f 0.55-0.70) provided the ester 15a (0.32 g, 63% yield) as a colorless liquid: bp 150° (bath temp, 18 mmHg); tlc, R_f 0.65 (benzene); ir (neat) (IR 14), 1730 (s, C=O), and 1160 cm^{-1} (m); nmr (NMR 19), 0.89 (t, 3H, J=7 Hz), 1.22 (t, 3H, J=7 Hz), 1.27 (bs), 1.60 (s, 3H, E-olefinic methyl), 1.85-2.35 (m, 6H), 4.05 (q, 2H, J=7 Hz), and 5.10 (t, 1H, J=7 Hz); MS (m/e), 254 (14), 208 (8), 166 (23), 142 (38), 83 (52), and 69 (100).

Found: C, 75.7; H, 12.1. Calcd for $C_{16}H_{30}O_2$: C, 75.5; H, 11.9.

4.2.10. Ethyl 4-Methyl-6-phenyl-(E)-4-hexenoate (15b)—
A solution of methallyl dithioacetate (0.32 g, 2.2 mmol) in dry THF (15 ml) was stirred under nitrogen at -78°,

treated with sec-butyllithium in pentane (1.1 M, 3.8 ml, 4.2 mmol), and kept at -78° for 30 min. The mixture was treated with benzyl bromide (0.34 g, 2.0 mmol) and stirred at -78° for 30 min, and then at -26° for 1 hr. Methyl iodide (0.14 ml, 2.2 mmol) was added and the resulting mixture was stirred at -26° for an additional 2 hr and treated with water. Ethereal extracts were washed with water, dried, and freed of the solvent. A mixture of the residual liquid, cupric chloride (0.81 g, 6.0 mmol), and cupric oxide (0.48 g, 6.0 mmol) in absolute ethanol (20 ml) was stirred under nitrogen at 25° for 5 hr. Extractive workup furnished a liquid which was submitted to preparative tlc with benzene as an eluant. The band at R_f 0.60-0.75 provided the ethyl ester 15b (0.33 g, 70% yield) as a colorless liquid: bp 125° (bath temp, 2 mmHg); tlc, R_f 0.70 (benzene); ir (neat) (IR 15), 1730 (s, C=O), 1600 (w), 1155 (m), 1105 (m), and 1055 cm^{-1} (m); nmr (NMR 20), 1.71 (s, 3H), 5.30 (t, 1H, J=7 Hz); MS (m/e), 232 (11), 186 (13), 194 (72), 129 (66), 103 (58), and 91 (100).

Found: C, 77.4; H, 8.84. Calcd for $C_{15}H_{20}O_2$: C, 77.6; H, 8.68.

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CHAPTER 5

Carbon-Carbon Bond Formation by
Selective Coupling of Alkylthioallyl-
copper Reagent with Allylic Halides

Abstract—— The reaction of 1-alkylthioallyl-
copper reagents with allylic halides affords the
S_N2' type substitution products in excellent
yields. The more synthetically useful reagent
1,3-bis(methylthio)allylcopper reagent behaves
in the same fashion. Attempts to hydrolyze the
vinyl sulfide moiety to an aldehyde unit is
successful only in the latter case. Yomogi
alcohol is synthesized stereospecifically in
the light of these results.

5.1. Coupling Reaction of Alkylthioallylcopper Reagent with Allylic Halides [1]

The remarkable regio- and stereospecificity of simple organocopper derivatives, e.g., CuR or $LiCuR_2$ where R= alkyl, vinyl, or aryl, to form carbon-carbon bond with organic halides [2] raises the question whether the specific reactivity of more stable carbanionic intermediates could be enhanced by copper(I) ion. [3] The answer to the question is of particular interest for the l-alkylthioallyl anions since the reaction of these systems has substantial synthetic utility. Moreover, the recent development of effective methods for converting allylic sulfides to l-alkylthioallyllithium species [4] has made l-alkylthioallylcopper(I) derivatives readily available for synthetic studies.

l-Alkylthioallyl anion is synthetically equivalent to either the l-oxopropyl anion ($\ominus COCH_2CH_3$) or 3-oxopropyl anion ($\ominus CH_2CH_2CHO$). It was already known that aryl- or
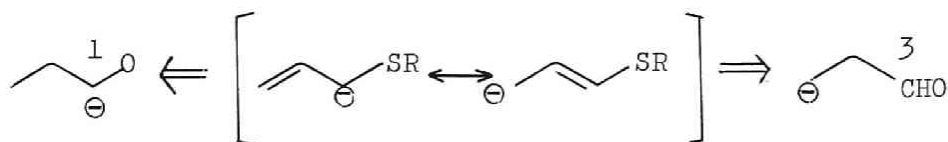
alkylthioallyllithium undergoes reaction with organic halides to introduce an alkyl group specifically on the carbon alpha to the alkylthio group and not gamma to the sulfur atom. [4] In this study we have synthesized alkylthioallylcopper(I) derivatives and have examined their behavior as potential

synthon of 3-oxopropyl anion. We have also examined 1,3-
bis(methylthio)allylcopper(I) as a synthon of 3-oxopropenyl
anion ($\ominus$CH=CHCHO).

A solution of 1-alkylthioallyllithium 1-3 in ether or
tetrahydrofuran was prepared from the corresponding alkyl
sulfide and sec-butyllithium at -26° for 30 min. Treatment
of the ethereal solution of organolithium derivative 1 or
2 with slightly excess cuprous iodide (CuI) at -78° for 15
min furnished a gray to white suspension which by analogy with
the previous work [5] probably due to the polymeric organocopper
derivatives 4 and 5, respectively.
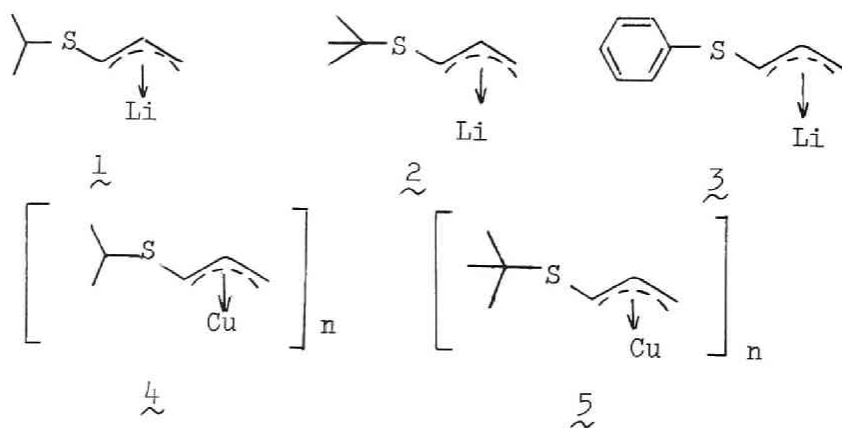
These suspensions were stable at -78° for 1 hr but
decompose gradually at -26° to form a black precipitate.[6]
Although the similar complex could be formed in tetrahydrofuran,
the resulting complex was found to decompose much faster.
Thus, alkylthioallylcopper derivatives should be prepared
in ether at -78° in a period of 15-30 min. It is noteworthy,
however, that similar treatment of 3 with CuI failed to

produce analogous monoalkylcopper derivatives but only a
black tar.

Attempted preparation of lithium di(alkylthioallyl)-
cuprate derivatives failed. After addition of a half equiv
of CuI to the lithium derivative 1 a black precipitate
formed, the behavior of which was quite similar to that of 1.
From the previous observation,[6b] it would appear that the
tendency of metal cuprate species to undergo specific reaction
is retarded by the presence of carbon ligand which could
form reasonably stable anions.

$$R_2Cu \rightleftharpoons RCu \cdot + R^-$$
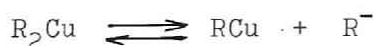
The reaction of 2-cyclohexylideneethyl bromide (1.0
equiv) with isopropylthioallylcopper (2.0 equiv) in ether at
-78° for 4 hr produced the substitution product 6 in 92%
yield: $\rangle$96% pure by glpc and nmr assay.
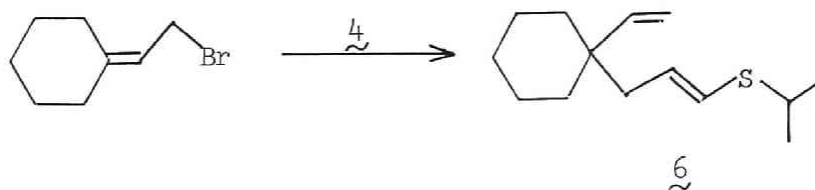
The reaction appears to be a pure S_N2' type displacement
of bromine by isopropylthioallyl group. In addition this
ambident anion undergoes alkylation exclusively gamma to
sulfur atom in high yield: thus, the alkylthioallylcopper
reagent did behave as a synthon of 3-oxopropyl anion.

Although the S_N2' type displacement of allylic or acetylenic acetate by metal dialkylcuprate reagent have been shown previously,[7] the present reaction offers the advantage of high regioselectivity to a unique degree.

In a similar experiment, allyl bromide and 1-cyclohexenylmethyl bromide gave the sulfide 7 and 8 in 88% and 87% yields, respectively.
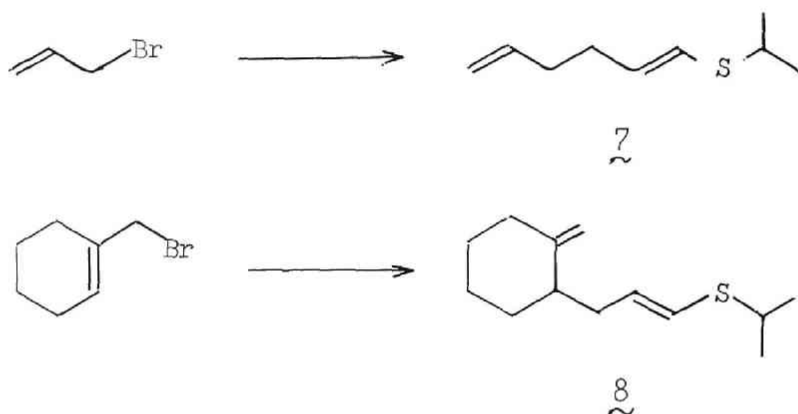
Futher study is required before the stereochemical and mechanistic details of these reactions can be understood. However, we could assume the involvement of a radical type intermediate for this reaction on the basis of the following results. Treatment of benzyl bromide with the copper complex 4 at -78° for 2 hr produced bibenzyl in a moderate yield. Similarly benzhydryl chloride gave 1,1,2,2-tetraphenylethane as a major product. These observations are possibly indicative of the presence of benzyl radical or benzhydryl radical in the course of the reaction, since both of which are known to be dimerized easily to form the isolated

coupling products.[8]

Alkylthioallylcopper also reacts with substances other
than allylic halides. The isopropylthio complex 4 reacts
with acetone in ether at -78° to yield 9 as a major product.
Thus, the behavior of carbonyl compounds toward the copper
derivative 4 contrasts sharply with that of allylic halides
as those appearing above.

9
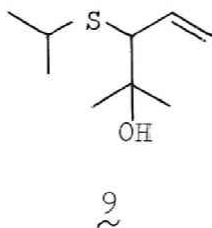
Finally, we examine the possibility of Michael reactions
including the addition of 4 or 5 to mesityl oxide. In no
case, however, did the presence of excess copper(I) derivatives
in the reaction mixture have any substantial effect on the
rate or product distribution of the Michael reaction.

The experimental procedure generally used for hydrolysis
of vinyl sulfides with mercuric chloride [9] was applied to
the product 6 without any success. Only minimal conversion
to the corresponding aldehyde was observed, and the major
products constitute a complex mixture, possibly as a result
of acid-catalyzed cyclization followed by rearrangements.
The relative difficulties associated with δ,ε-unsaturated
aldehyde synthesis led us to explore the following route
starting from 1,3-bis(methylthio)propene.

1,3-Bis(methylthio)allyllithium 10 was readily
prepared by metallation of 1,3-bis(methylthio)propene with
sec-butyllithium in ether at -26°, a procedure superior to
previous methods [10] for our present purpose in that 10 is
formed in high yield in the absence of secondary amine.
Although a solution of the lithio derivative 10 was reported
to be purple, a pale yellow solution was obtained in the
absence of diisopropylamine. Treatment of this solution with
CuI at -78° and stirring for 15 min produced the corresponding
copper derivative 11 which behaved similarly as isopropylthio-
allylcopper in the following reaction with allylic halides.

10   11
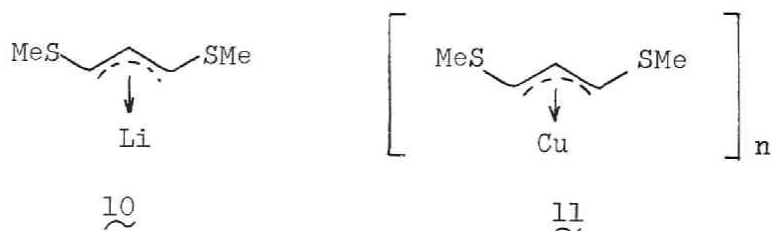
Thus, 2-cyclohexylideneethyl bromide was treated with the
copper reagent 11 at -78° to furnish the expected S_N2' type
substitution product 12 in almost quantitative yield.

12
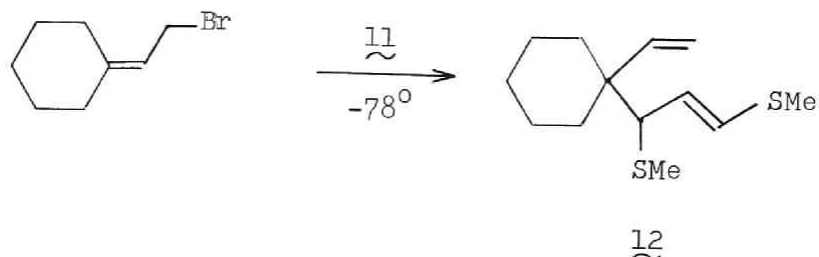
Previously, the hydrolysis of 1,3-bis(methylthio)propene
derivatives to α,β-unsaturated carbonyl compounds has been
effected by mercury(II) ion.[10]   Seeking a milder hydrolysis

procedure, we investigated the use of cupric ion in ethanol[11] and found that this ion afforded very high yields of pure aldehydes. The process is devoid of the cationic cyclization of 11 as well as other side reactions.
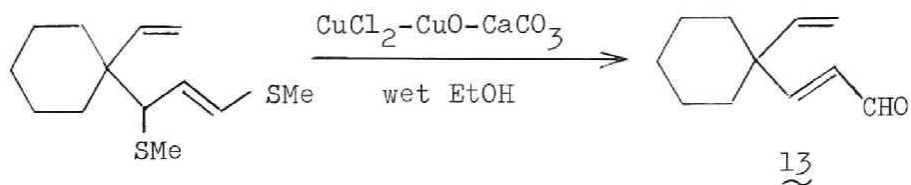
The δ,ε-unsaturated aldehyde 13 was obtained in 92% over-all yield from the cyclohexylideneethyl bromide. Similarly, the reaction of 1,3-bis(methylthio)allylcopper with several allylic halides in ether as solvent, followed by cupric ion catalyzed hydrolysis, led to efficient cross coupling as indicated below.
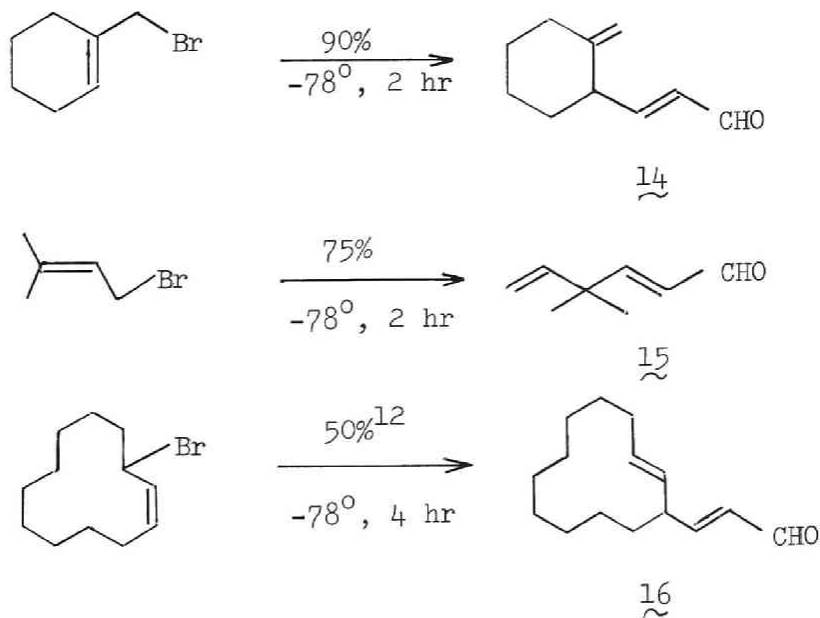
The observed regio- and stereoselectivity of our new reaction portends its broad synthetic application in the field of natural product chemistry. As an example, Yomogi alcohol, (E)-5,5,6-trimethyl-3,6-heptadien-2-ol 17,[13] was prepared regio- and stereoselectively when the aldehyde 15 was subjected to the following two-step sequence.
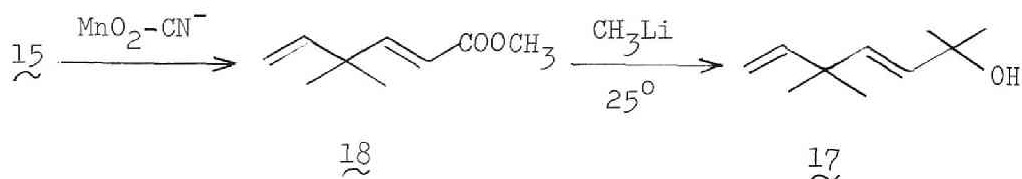
The aldehyde 15 was converted to the unsaturated carboxylic ester 18 stereospecifically in 76% yield by manganese dioxide-cyanide ion method.[14] The homogeneity of the ester 18 was indicated by tlc and glpc analysis. In addition, the nmr and infrared spectra of 18 were entirely analogous to those of the corresponding ethyl ester.[13] The ester so obtained was alkylated by the treatment of excess methyllithium [13] at 25° for 30 min to yield Yomogi alcohol 17 in 75% yield. The nmr, infrared, and mass spectra of 17 were identical with those of the natural alcohol 17.[13]

5.2. Experimental Part

5.2.1. Preparation of Allyl Isopropyl Sulfide— A mixture of propane-2-thiol (25 ml, 0.27 mol), sodium ethoxide (20 g, 0.30 mol), and ethanol (200 ml) was heated at reflux and treated with a solution of allyl bromide (37 g, 0.30 mol) in ethanol (20 ml) dropwise over 30 min. The mixture was heated at reflux for 1 hr, and allowed to cool to room temp. The reaction was quenched by the addition of water and the separated organic layer was dried. Fractional distillation through a 20 cm Vigreux column afforded nmr-pure allyl isopropyl sulfide: bp 127-128° (760 mmHg); ir (neat), 1640 (m), 1250 (m), 1230 (m), 990 (m), and 910 cm^{-1} (s); nmr, 1.20 (d, J=7 Hz), 2.82 (dq, J=7, 1H), 3.12 (d, J=8, 2H), 4.85-5.27 (m, 2H), 5.45-6.10 (m, 1H); MS (m/e), 116 (38), 74 (80), 59 (35), 43 (42), and 41 (100).

5.2.2. Preparation of Allyl Phenyl Sulfide and Allyl tert-Butyl Sulfide— These sulfides were prepared using the same procedure described above from benzenethiol (or 2-methyl-2-propanethiol) and allyl bromide.[*]

5.2.3. Generation of isopropylthioallylcopper 4 and 1,3-bis(methylthio)propenylcopper 11— Allyl isopropyl sulfide (or 1,3-bis(methylthio)propene) (2.0 mmol) was dissolved in dry ether (15 ml). The solution was cooled to -78° and

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[*] B. W. Erickson, Ph. D. Thesis, Harvard University, 1970, pp 190 and 194.

treated with sec-butyllithium in pentane (2.0 ml of 1.02 M
solution). After stirring for 30 min at -26°, the resulting
orange solution was recooled to -78°. Solid cuprous iodide
(2.4 mmol) was added. A white precipitate formed immediately
and the mixture was stirred at the same temp for 15 min before
subsequent described below.

5.1.4. Reaction of 4 with cyclohexylideneethyl bromide— A
solution of cyclohexylideneethyl bromide (1.9 g, 10 mmol)
in ether (10 ml) was added at -78° to a solution of 4
prepared from allyl isopropyl sulfide (2.4 g, 20 mmol), ether
(70 ml), sec-butyllithium (20 ml of 1.02 M solution in pentane),
and cuprous iodide (5.0 g, 26 mmol). The mixture was kept at
-78° for 4 hr. The resulting black mixture was filtered
through a pad of Celite 545 and the filter cake was washed
with ether. The filtrate and washings were combined, washed
with water, dried, and freed of the solvent. The residual
liquid was separated through a column chromatography on
silica gel (100 g) with hexane-benzene as an eluant. The
less polar fraction (tlc R_f 0.50 (hexane)) provided the
sulfide 6 (2.1 g, 92% yield): bp 145° (bath temp, 3 mmHg);
ir (neat)(IR 16), 1640 (m), 1242 (s), 945 (m), and 912 cm^{-1}
(s); nmr (NMR 22), 1.25 (d, J=7 Hz, 6H), 1.40 (bs, 10H),
2.03 (d, J=7 Hz), 3.00 (dq, J=7 Hz, 1H), 4.96 (dd, J=2 Hz
and 7 Hz, 1H), 5.09 (dd, J=12 and 2 Hz, 1H), 5.60 (dt, J=7
and 15 Hz, 1H), 5.70 (dd, J=12 and 17 Hz, 1H), and 6.02
(d, J=15 Hz, 1H); MS (m/e), 224 (5), 181 (16), 116 (20),
115 (100), and 73 (70);

Found: C, 75.2; H, 11.0. Calcd for $C_{14}H_{24}S$: C, 74.9; H, 10.8.

The more polar fraction (tlc $\underline{R}_f$ 0.15 (hexane)) afforded the dimer of allyl isopropyl sulfide (0.48 g) which was not identified completely.

5.2.5. Reaction of 4 with 1-cyclohexenylmethyl bromide— A solution of 4 prepared from allyl isopropyl sulfide (0.23 g, 2.0 mmol) was treated with 1-cyclohexenylmethyl bromide (0.18 g, 1.0 mmol) at -78° and stirred at -78° for additional 4 hr. The orange liquid obtained on extractive workup was submitted to preparative tlc on silica gel with hexane as an eluant. The band at $\underline{R}_f$ 0.4-0.6 provided the sulfide 8 (0.18 g, 87% yield) as a colorless liquid: bp 130° (bath temp, 3 mmHg); ir (neat) (IR 17), 1645 (m), 1240 (m), 945 (s), 905 (w), and 890 cm^{-1} (s); nmr (NMR 23), 1.25 (d, J=7 Hz, 6H), 2.95 (dq, J=7 Hz, 1H), 4.58 (bd, J=7 Hz, 2H), 5.63 (dt, J=7 and 15 Hz, 1H), 5.90 (d, J=15 Hz, 1H); MS ($\underline{m}/\underline{e}$), 210 (24), 167 (92), 134 (44), 116 (76), and 115 (100).

Found: C, 73.9; H, 10.4. Calcd for $C_{13}H_{22}S$: C, 74.2; H, 10.5.

5.2.6. Reaction of 4 with allyl bromide— A solution of 4 prepared from allyl isopropyl sulfide (0.23 g, 2.0 mmol) was treated with allyl bromide (86 μl, 1.0 mmol) at -78°. The resulting solution was kept at -78° for 4 hr, and the color of the solution was turned black at the end of the period. Tetralin (100 μl, 97 mg) was injected and the entire mixture was filtered through a pad of Celite 545 and

washed through with ether. The filtrate was washed with dilute hydrochloric acid, water and dried. The resulting organic phase was submitted directly to glpc to obtain the yield 88% of the sulfide 7 using tetralin as the internal standard. The analytical sample was prepared by preparative tlc and bulb to bulb distillation: bp 110° (bath temp, 45 mmHg);;;;;; ir (neat) (IR 18), 1640 (s), 1240 (s), 990 (m), 940 (s), and 910 cm^{-1} (s); nmr (NMR 24), 1.30 (d, J=7 Hz, 6H), 2.02-2.38 (m, 4H), 2.98 (dq, J=7 Hz, 1H), 4.75-5.16 (m, 2H), 5.40-6.05 (m, 3H); MS (m/e), 156 (8), 115 (51), 113 (18), 84 (14), and 73 (100).

Found: C, 69.2; H, 10.2. Calcd for $C_9H_{16}S$: C, 69.2; H, 10.3.

5.2.7. Reaction of 4 with benzyl bromide— Benzyl bromide (0.17 g, 1.0 mmol) was treated with the complex 4 (2.0 mmol) in ether (13 ml) at -78° for 2 hr. The preparative tlc separation of the crude reaction mixture gave bibenzyl (71 mg, 78% yield) as the major product; it was identical in all respects with an authentic sample.

5.2.8. Reaction of 4 with benzhydryl chloride— Benzhydryl chloride (0.20 g, 1.0 mmol) was treated with the emulsion 4 (2.0 mmol) in ether (10 ml) at -78° for 2 hr. After the concentration of the dried extracts in vacuo, a white solid was obtained. Recrystallization from benzene-hexane (1:1) gave pure 1,1,2,2-tetraphenylethane (0.12 g, 70% yield) as colorless crystals; the product was identical in all respects with an authentic sample.

5.2.9. Reaction of 11 with cyclohexylideneethyl bromide—
A solution of 11 derived from 0.27 g (2.0 mmol) of 1,3-
bis(methylthio)propene was treated with cyclohexylideneethyl
bromide (0.19 g, 1.0 mmol) at -78°. The color of the solution
turned brown rapidly and black after stirring for an additional
2 hr. The liquid (0.35 g) obtained on extractive workup
was treated with cupric chloride (0.44 g, 3.0 mmol) and
cupric oxide (0.24 g, 3.0 mmol) in ethanol (20 ml) at 25°
for 1 hr. The mixture was filtered through a pad of Celite
545 and the filter cake was washed with ether. The ethereal
solutions were washed with dilute hydrochloric acid and water
and concentrated. The residual liquid was submitted to
preparative tlc with benzene as an eluant. The band at R_f
0.5-0.6 provided the δ,ε-unsaturated aldehyde 13 (0.15 g,
92% yield) as a colorless liquid: bp 120° (bath temp, 18
mmHg); ir (neat), 1685 (s), 1625 (s), 1110 (m), 980 (m),
915 (m), and 850 cm^{-1} (m); nmr, 9.45 (d, J=7 Hz, 1H), 6.6
(d, J=15 Hz, 1H), 5.95 (dd, J=7 and 15 Hz, 1H), 4.7-5.8 (m,
2H), 1.2-2.1 (m, 10H); MS (m/e), 164 (12), 135 (67), 121 (24),
107 (36), 79 (70), and 67 (100).

5.2.10. Reaction of 11 with 1-cyclohexenylmethyl bromide—
A solution of 11 derived from 1,3-bis(methylthio)propene
(0.27 g, 2.0 mmol) was treated with 1-cyclohexenylmethyl
bromide (0.18 g, 1.0 mmol) at -78° and kept there for 2 hr.
After extractive workup, a mixture of residual liquid,
cupric chloride (0.40 g, 3.0 mmol), and cupric oxide (0.24 g,
3.0 mmol) in ethanol (20 ml) was stirred under nitrogen at

25° for 1 hr. The black suspension was filtered through a pad of Celite 545 and the filter cake was washed with ether. The ethereal solutions were washed with water, dried, and freed of the solvent. The remaining oil was submitted to preparative tlc on silica gel with benzene as an eluant. The band at $\underline{R}_f$ 0.45-0.6 provided the aldehyde $\underset{\sim}{14}$ (0.14 g, 90% yield) as a colorless liquid: bp 100° (bath temp, 18 mmHg); ir (neat), 1690 (s), 1645 (m), 1150 (s), 1120 (s), 980 (s), and 890 cm^{-1} (s); nmr, 10.1 (d, J=7 Hz, 1H), 6.8 (dd, J=8 and 15 Hz, 1H), 6.0 (dd, J=7 and 15 Hz, 1H), and 4.5-4.65 (bd, 2H); MS ($\underline{m}/\underline{e}$), 150 (21), 135 (35), 121 (62), 107 (65), 93 (39), 81 (94), and 79 (100).

Found: C, 79.8; H, 9.65. Calcd for $C_{10}H_{14}O$: C, 80.0; H, 9.39.

5.2.11. Reaction of 11 with 4-bromo-2-methyl-2-butene— A solution of $\underset{\sim}{11}$ prepared from 1,3-bis(methylthio)propene (0.27 g, 1.0 mmol) was treated with 4-bromo-2-methyl-2-butene (0.15 g, 1.0 mmol) at -78° for 2 hr. Ethereal extracts were washed with water, dried, and freed of the solvent. Powdered cupric chloride (0.40 g, 3.0 mmol) and cupric oxide (0.24 g, 3.0 mmol) were sequentially added to a solution of the remaining liquid (0.25 g) in ethanol (20 ml). The heterogeneous reaction mixture was stirred under nitrogen at 25° for 1 hr. Extractive workup furnished a liquid which was submitted to preparative tlc with benzene as an eluant. The band at $\underline{R}_f$ 0.5-0.65 provided the aldehyde $\underset{\sim}{15}$ (0.18 g, 72% yield) as a colorless liquid: ir (neat), 1690 (s), 1625 (m), 1110 (m),

985 (m), 920 (m), and 785 (w) cm^{-1}; nmr, 9.50 (d, J=7 Hz, 1H), 6.7 (d, J=16 Hz, 1H), 5.95 (dd, J=7 Hz and 16 Hz, 1H), 5.80 (dd, J=10 and 20 Hz, 1H), 5.02 (dd, J=2 and 10 Hz, 1H), 4.95 (dd, J=2 and 20 Hz, 1H), and 1.25 (s, 6H); MS (m/e), 124 (13), 109 (85), 81 (90), 79 (64), and 67 (100).

5.2.12. Reaction of 11 with 2-cyclododecenyl bromide—— A solution of 11 prepared from 1,3-bis(methylthio)propene (0.27 g, 2.0 mmol) was treated with 2-cyclododecenyl bromide (0.24 g, 1.0 mmol) at -78°. The color of the solution changed very slowly to brown and then the solution was maintained at -78° for 4 hr. The similar procedure afforded the aldehyde 16 (0.11 g, 50% yield) as a colorless liquid: bp 140° (bath temp, 0.1 mmHg); ir (neat), 1690 (s), 1630 (m), 1130 (s), and 975 cm^{-1} (s); nmr, 9.41 (d, J=8 Hz, 1H), 7.65 (dd, J=7 and 16 Hz), 6.95 (ddd, J=16, 7, and 1.5 Hz, 1H), 5.1-5.7 (m, 2H), 1.2-2.2 (m, 19H); MS (m/e), 220 (25), 135 (17), 121 (28), 107 (50), 95 (70), and 81 (100).

5.2.13. Generation of Yomogi alcohol from the aldehyde 15—— The aldehyde 15 (0.26 g, 2.1 mmol) was stirred with a mixture of sodium cyanide (0.40 g), acetic acid (0.16 g), and manganese dioxide (5.0 g) in methanol (25 ml) for 12 hr at 25°. The remaining liquid on extractive workup was submitted to preparative tlc with benzene as an eluant. The band at R_f 0.6-0.8 provided the ester 18 (0.24 g, 76 % yield) as a colorless liquid: ir (neat), 1725 (s), 1655 (m), 1190(s), 1165 (s), 1010 (m), and 985 cm^{-1} (m); MS (m/e), 154 (6), 139 (12), 125 (10), 123 (12), 111 (16), 95 (100), 79 (44), and

67 (38). The ester $\underset{\sim}{18}$ (0.15 g, 1.0 mmol) was treated with methyllithium (5 ml of 1.5 $\underline{M}$ solution in ether) in ether (5 ml) at 0° and kept at 25° for an additional 1 hr. The ethereal extracts were washed with water, dried, and freed of the solvent. . The residual liquid was submitted to preparative tlc on silica gel with dichloromethane as an eluant. The band at $\underline{R}_f$ 0.3-0.5 afforded the alcohol $\underset{\sim}{17}$ (0.12 g, 75 % yield) which was identified by comparison with the authentic sample.

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CHAPTER 6

A New Synthesis of Ketones Using
1-(Alkylthio)vinyllithium

Abstract—— Treatment of vinyl sulfide with
sec-butyllithium in THF-HMPA (9:1) at -78°
affords 1-(alkylthio)vinyllithium, $R^1SC(Li)=CHR^2$,
which reacts with halides, aldehydes, and
epoxides to yield, after hydrolysis with mercuric
ion, ketones, acyloins, and α,β-unsaturated
ketones. This process represents a simple,
mild and broadly applicable method for ketone
synthesis.

6.1. Examination of Base-Solvent Systems for the Anion Formation of Ethyl Vinyl Sulfide

Allenic ether can be metalated by n-butyllithium in ether [1] and this is based on the enhanced acidity of sp^2 hydrogen relative to sp^3 one.

$$CH_2=C=C\underset{H}{\overset{OMe}{\diagdown}} \quad \xrightarrow{\underline{n}-BuLi} \quad CH_2=C=C\underset{Li}{\overset{OMe}{\diagdown}} \quad \xrightarrow{RX} \quad CH_2=C=C\underset{R}{\overset{OMe}{\diagdown}}$$

On the other hand, although the potentiality of 1-(alkylthio)vinyllithium as a synthetic equivalent of acyl anion was proposed earlier by Corey,[2] the actual execution utilizing this type of reagent for ketone synthesis

$$R^1S\overset{-}{C}=CHR^2 \quad \xrightarrow{E^+} \quad R^1S\overset{\overset{E}{|}}{C}=CHR^2$$

$$\overset{-}{\underset{O}{\overset{\|}{C}}}CH_2R^2 \quad \dashrightarrow{E^+} \quad E-\underset{O}{\overset{\|}{C}}CH_2R^2$$

has never been developed to a useful level due to the lack of a satisfactory base-solvent system for converting a vinyl sulfide into a reactive anion 2; the competing addition of Li compounds to form 3 could not be entirely suppressed.[3]

$$CH_2=C\underset{H}{\overset{SR^1}{\diagdown}} \; + \; R^2Li \quad \longrightarrow \quad CH_2=C\underset{Li}{\overset{SR^1}{\diagdown}} \; + \; R^2-CH_2-\overset{\overset{Li}{|}}{C}H-SR^1$$

$$\underset{\underset{\sim}{1}}{} \qquad\qquad\qquad\qquad\quad \underset{\underset{\sim}{2}}{} \qquad\qquad\qquad \underset{\underset{\sim}{3}}{}$$

Looking for a good base-solvent system of the conversion of $\underset{\sim}{1}$ to $\underset{\sim}{2}$, we examined several base-solvent systems with respect to the reaction of ethyl vinyl sulfide and 1-bromooctane. The yields of 2-decanone were determined after hydrolysis and some of the results were shown in Table 6-1.

Table 6-1. 2-Decanone Synthesis

$$CH_2 = C\underset{H}{\overset{SEt}{\diagup}} \xrightarrow[\substack{2) \ \underline{n}\text{-}C_8H_{17}Br \\ 3) \ HgCl_2}]{1) \ base} \underline{n}\text{-}C_8H_{17}\underset{\underset{O}{\|}}{C}CH_3$$
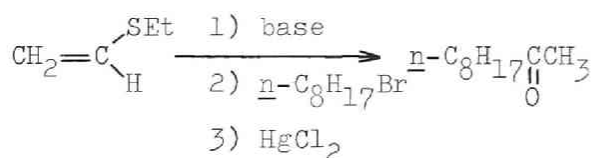
	base-solvent systems				
	$\underline{n}$-BuLi THF	$\underline{n}$-BuLi TMEDA-THF	$\underline{n}$-BuLi THF-HMPA	$\underline{sec}$-BuLi THF	$\underline{sec}$-BuLi THF-HMPA
Yields of 2-decanone (%)	2-3	10-20	68	72	90

Hydrogen-metal exchange reactions lead to the formation of a salt or another organometallic compound:

$$AH \ + \ MR \ \rightleftharpoons \ RH \ + \ MA \ (or \ M^+ \ + \ A^-)$$
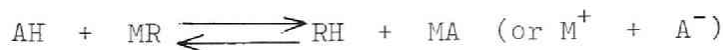
The equilibrium lies to the right-hand side when AH is more acidic than RH or when the conjugate base R^- is stronger than the base A^-. The solvent plays an important role in

exchange reactions of this type. Solvents possessing electron donor properties favor ionization, solvation, and dissociation of AH and MR. This is particularly true of HMPA, which is the best Lewis base of all the common aprotic solvents, and also has excellent solvation properties. For example, it causes strong solvation of the alkali metal cations and formation of highly reactive anions.

6.2. Synthesis of Carbonyl Compounds

Treatment of ethyl vinyl sulfide with equiv sec-butyllithium in THF-HMPA (9:1) at -78° furnished an orange solution of 1-(ethylthio)vinyllithium which was stable at this temperature for at least 6 hr. The reaction of this vinyllithium reagent with added electrophilic substrates demonstrated that the lithiation of ethyl vinyl sulfide had proceeded to completion. The reactivity of this new reagent was found to be very similar to that of 1,3-dithiane anion. Thus, it reacted with alkyl iodides and bromides smoothly at -78°, but proved much less reactive toward chlorides. For example, cyclohexyl chloride was almost inert and the yield of the corresponding α-hydroxyketone was less than 10%. At -78°, the anion 4 reacted with halides, aldehydes, and epoxides smoothly in the expected way and the following hydrolysis gave good yields of the corresponding ketones, acyloins, and α,β-unsaturated ketones, respectively, as depicted on the next page (Table 6-2).

Table 6-2. Reactions of 1-(Alkylthio)vinyllithium with Electrophile.

$R^1SCH{=}CHR^2$		Electrophile		Product[a]	Yield[b] (%)
R^1	R^2				
C_2H_5	H	n-Octyl bromide	7	$n\text{-}C_8H_{17}COCH_3$	90
CH_3	$n\text{-}C_8H_{17}$	n-Octyl bromide	8	$n\text{-}C_8H_{17}CO\text{-}n\text{-}C_9H_{19}$	82
CH_3	C_6H_5	n-Octyl bromide	9	$n\text{-}C_8H_{17}COCH_2C_6H_5$	65
C_2H_5	H	1,4-Dibromobutane	6	$CH_3CO(CH_2)_4COCH_3$	60
C_2H_5	H	1,3-Dibromopropane	10	3-Methyl-2-cyclo-hexenone	52
C_2H_5	H	Benzaldehyde	11	$C_6H_5CHOHCOCH_3$	64
C_2H_5	H	Nonanal	12	$n\text{-}C_8H_{17}CHOHCOCH_3$	58
CH_3	C_6H_5	Benzaldehyde	13	$C_6H_5CHOHCOCH_2C_6H_5$	54
CH_3	C_6H_5	Nonanal	14	$n\text{-}C_8H_{17}CHOHCOCH_2C_6H_5$	45
CH_3	$n\text{-}C_8H_{17}$	Benzaldehyde	15	$C_6H_5CHOHCO\text{-}n\text{-}C_9H_{19}$	51
CH_3	$n\text{-}C_8H_{17}$	Nonanal	16	$n\text{-}C_8H_{17}CHOHCO\text{-}n\text{-}C_9H_{19}$	35
C_2H_5	H	Styrene oxide	17	$C_6H_5CH{=}CHCOCH_3$	71
CH_3	C_6H_5	Propylene oxide	18	$CH_3CH{=}CHCOCH_2C_6H_5$	69
CH_3	C_6H_5	Styrene oxide	19	$C_6H_5CH{=}CHCOCH_2C_6H_5$	62

a) Product code numbers are provided for reference to the Experimental Part.
b) Yield of product after isolation by preparative tlc.

The over-all process is quite simple: Treatment of
1,4-dibromobutane with 1-(ethylthio)vinyllithium 4 for 2 hr
at -78° furnished the alkylated sulfide 5. The crude sulfide
was isolated and characterized in pure state, but it was
found that this delay of sequence was unnecessary and the
crude product was hydrolyzed directly with 6 equiv of
mercuric chloride in aqueous acetonitrile for 12 hr at
reflux to form 2,7-octadione 6 in 60% over-all yield. This
sequence is simpler and potentially more versatile than the
recently developed methods of ketone synthesis.[4]

$$Br(CH_2)_4Br \xrightarrow[\underset{4}{}]{CH_2=\overset{\overset{Li}{|}}{C}-SEt} H_2C=\overset{\overset{SEt}{|}}{C}(CH_2)_4\overset{\overset{SEt}{|}}{C}=CH_2 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}(CH_2)_4\overset{\overset{O}{\|}}{C}CH_3$$

$$\underset{5}{} \qquad \underset{6}{}$$
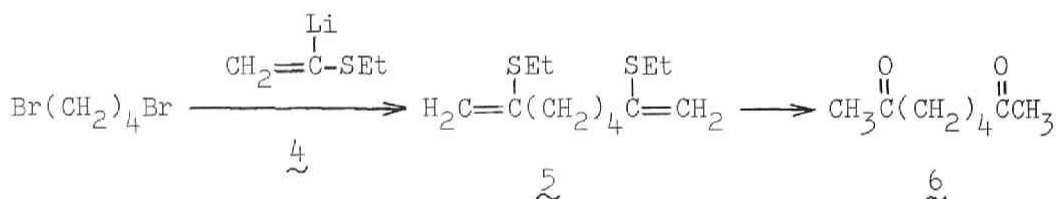
The use of mercuric chloride to promote the hydrolysis
of dithioacetals was introduced by Fisher in an 1894 paper
on the hydrolysis of sugar dithioacetals.[5] This method has
been widely employed with saccharides [6] and steroids.[7]
Hydrolysis with mercuric chloride received scant attention [8]
before the 1,3-dithiane method to ketones was introduced
in 1965. Since that time this method of hydrolysis has
become quite popular in many publications.[9]

An equilibrium between a dithiane 20 and a ketone 21
is established by Lewis acid catalysts in the presence of
1,3-propanedithiol and water. Use of relatively hard
Lewis acids (hydrogen chloride, zinc chloride, boron

trifluoride) strongly favors formation of the dithioacetal.
Relatively soft, thiophilic Lewis acids (mercuric chloride,
mercuric acetate, silver nitrate) displace the equilibrium
in favor of the ketone, for they form insoluble metal
complexes with 1,3-propanedithiol.

$$\underset{\underset{\sim}{20}}{} \qquad\qquad \underset{\underset{\sim}{21}}{}$$
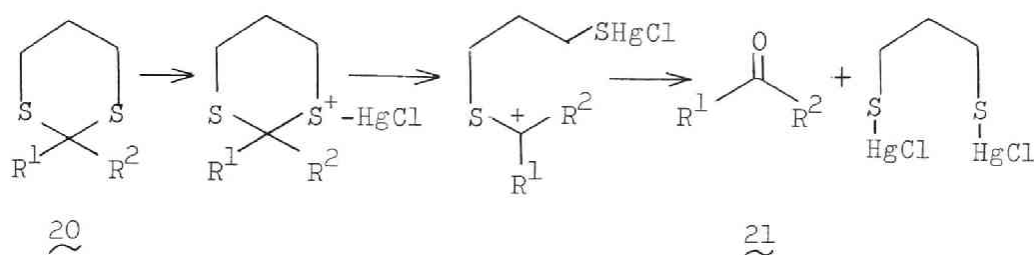
The probable mechanism of the mercuric chloride-
promoted hydrolysis of vinyl sulfide might involve a
different pathway. The over-all reaction is obviously
irreversible, as the thiol precipitates as the mercuric
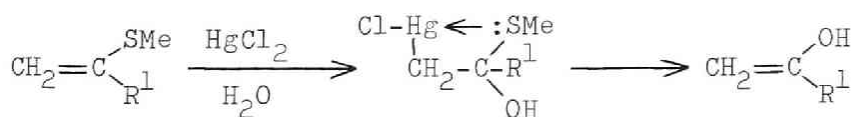
chloride complex. When hydrolysis was complete, the cooled
reaction mixture was filtered through Celite 545 to remove
mercury(II) salts from the organic layers.

The reaction of 1-(alkylthio)vinyllithium with an
aldehyde followed by the hydrolysis of 1-(alkylthio)-1-
alkene moiety furnishes an acyloin. For example, the
addition of benzaldehyde to the vinyllithium reagent $\underset{\sim}{22}$
in THF-HMPA (9:1) formed the hydroxyvinyl sulfide $\underset{\sim}{23}$, which

was hydrolyzed to 1-hydroxy-1-phenylundecan-2-one in 55%
yield using mercuric chloride as a trap of liberated
methanethiol.

$$CH_3(CH_2)_8 \underset{H}{\overset{}{\diagdown}} C = C \overset{}{\underset{SMe}{\diagup}} \quad \xrightarrow{PhCHO} \quad CH_3(CH_2)_8 \underset{H}{\overset{}{\diagdown}} C = C \overset{H-\overset{Ph}{\underset{}{C}}-OH}{\underset{SMe}{\diagup}} \quad \xrightarrow{HgCl_2} \quad CH_3(CH_2)_9 \overset{H}{\underset{O \ OH}{C-C-Ph}}$$

$$\underset{\sim}{22} \qquad\qquad\qquad \underset{\sim}{23} \qquad\qquad \underset{\sim}{15}$$
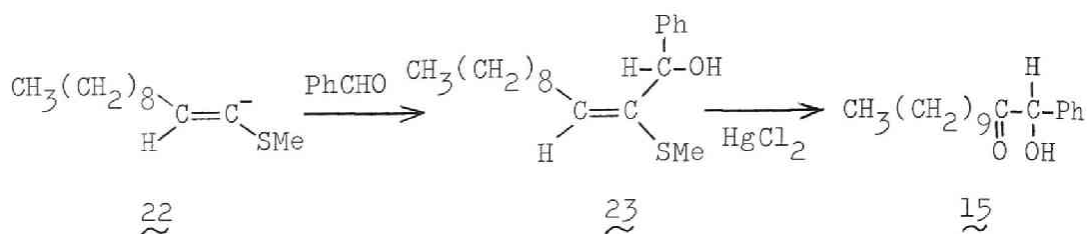
Finally, treatment of 1-(alkylthio)vinyllithium with
epoxides and subsequent hydrolysis affords a α,β-unsaturated
ketones. A solution of vinyllithium 24 in THF-HMPA (9:1)
was treated with propylene oxide to give the alcohol 25,
which was hydrolyzed to benzyl propenyl ketone 18 in 69%
yield on treatment with 3 equiv of mercuric chloride in
acetonitrile-water (3:1).

$$Ph \underset{H}{\overset{}{\diagdown}} C = C \overset{}{\underset{SMe}{\diagup}} \quad \xrightarrow{\triangle O} \quad Ph \underset{H}{\overset{}{\diagdown}} C = C \overset{CH_2\overset{OH}{\overset{|}{C}}HCH_3}{\underset{SMe}{\diagup}} \quad \xrightarrow{HgCl_2} \quad PhCH_2\overset{}{\underset{O}{C}}CH = CHCH_3$$

$$\underset{\sim}{24} \qquad\qquad \underset{\sim}{25} \qquad\qquad \underset{\sim}{18}$$
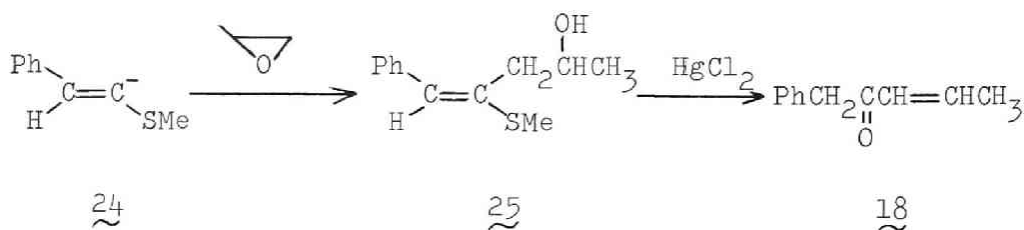
After the publication of these data, Carlson and
Isidor [10] have reported the utilization of the allenic
carbanion 26 derived from 1-thiomethyl-3,3-diethoxypropyne
for the introduction of an acylacetate unit. The carbanion
26 is synthetically equivalent to $\ominus COCH_2COOEt$.

CH$_3$SC≡C-CH(OEt)(OEt) $\longrightarrow$ CH$_3$-S$^-$-C=C=C(OEt)(OEt)

$\underset{\sim}{26}$

$\xrightarrow{RX}$ CH$_3$S-C=C=C(OEt)(OEt) $\longrightarrow$ RĊ-CH$_2$COOEt
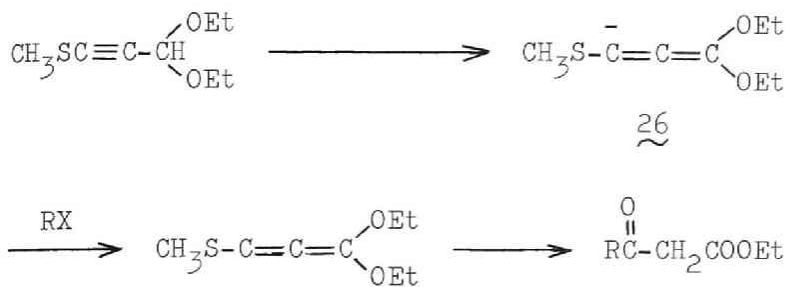
6.3. Experimental Part

6.3.1. Preparation of 1-(alkylthio)vinyllithium— Five combinations of bases and solvents were studied: (1) n-BuLi, THF, (2) n-BuLi, TMEDA-THF, (3) n-BuLi, THF-HMPA, (4) sec-BuLi, THF, (5) sec-BuLi, THF-HMPA. A solution of n-butyllithium or sec-butyllithium in hexane or pentane (1.0-1.5 M, 1.1 mol) was added to ethyl vinyl sulfide [11] (1.1 mol) dissolved in the above described solvent at -78° under stirring in nitrogen atmosphere and the mixture was kept at -78° for 30 min. Anion formation was determined by the addition of 1-bromooctane (1.0 mol) as a substrate and by the measurement of the isolated yield of 2-decanone after the usual treatment of mercuric chloride in acetonitrile at room temperature for 12 hr. The yields were (1) 2-3%, (2) 10-20%, (3) 68%, (4) 72%, (5) 90%, respectively.

6.3.2. 3-Ethylthio-2-methyl-3-buten-2-ol (27)— sec-Butyllithium in pentane (1.2 M, 0.95 ml, 1.1 mmol) was added to a solution of ethyl vinyl sulfide (0.11 g, 1.2 mmol) in 1:9 HMPA-THF (10 ml) at -78° with stirring under nitrogen. Dry acetone (1 ml) was added and after 30 min

at -78° the clear solution was poured into water. Ethereal
extracts were washed with water five times, dried and freed
of the solvent. The residual liquid was submitted to
preparative tlc on silica gel with benzene as an eluant.
The main band at R_f 0.25-0.45 provided the corresponding
alcohol 27 (88 mg, 60% yield): tlc, R_f 0.2 (benzene); nmr
(NMR 24), 1.30 (t, 3H, CH_2CH_3), 1.43 (s, 6H, CH_3), 2.12
(bs, 1H, OH), 2.76 (q, 2H, CH_2CH_3), 4.78 and 5.40 (s, 1H
for each).

6.3.3. Methyl Styryl Sulfide (28)— n-Butyllithium in
hexane (1.6 M, 15.6 ml, 25 mmol) was added to a solution of
diethyl methylthiomethylphosphonate [12,13] (5.0 g, 25 mmol)
in dry THF (40 ml) with stirring under nitrogen at -78°.
The clear orange solution was treated at -78° with
benzaldehyde (2.6 g, 25 mmol) and stirred at -78° for 1 hr,
at room temp for 2 hr. The resulting mixture was diluted
with water and the ethereal extracts of this solution were
dried and freed of the solvent. The residual liquid was
evaporatively distilled at 90-92° (4 mmHg) to provide
nmr-pure trans sulfide 28 (1.8 g, 48% yield) as a colorless
liquid: nmr, 2.35 (s, 3H, CH_3), 6.23 (d, J=16 Hz, 1H,
$CH-SCH_3$), 6.78 (d, J=16 Hz, 1H, CHPh), and 7.25 (bs, 5H,
C_6H_5).

6.3.4. 1-Decenyl Methyl Sulfide (29)— n-Butyllithium in
hexane (1.6 M, 15.6 ml, 25 mmol) was added to a solution
of diethyl methylthiomethylphosphonate (5.0 g, 25 mmol)
in dry THF (50 ml) with stirring under nitrogen at -78°.

The reaction solution was kept at -78° for 1 hr, treated with n-nonylaldehyde (3.6 g, 25 mmol), and kept at -78° for 1 hr and at room temp for 2 hr. Extractive workup furnished a liquid which was chromatographed over silica gel (50 g) using first with hexane and then benzene as an eluant to afford the sulfide 29 (1.7 g, 37% yield): nmr, 0.93 (m, 3H, CH₃), 1.05-2.10 (m, 14H, (CH₂)₇), 2.23 (s, 3H, SCH₃), 5.30 (dt, 1H, CH=CHS), and 5.90 (d, 1H, J=15 Hz, CH=CHS).

6.3.5. 2-Decanone (7)— sec-Butyllithium in pentane (1.1 M, 2.0 ml, 2.2 mmol) was added to a solution of ethyl vinyl sulfide (0.21 g, 2.4 mmol) in 1:9 HMPA-THF (15 ml) with stirring under nitrogen at -78°. After being stored at -78° for 30 min, the deep yellow solution was treated with 1-bromo-octane (0.39 g, 2.0 mmol), and the whole was kept at -78° for 30 min. Extractive workup afforded a yellow liquid which was treated with solid mercuric chloride (1.6 g, 6.0 mmol) in 3:1 acetonitrile-water (20 ml) at room temp. The heterogeneous reaction mixture was stirred under nitrogen at 110° for 5 hr and filtered through a pad of Celite 545 and filter cake was washed with dichloromethane. The organic phase of the filtrate was washed with water, dried, and freed of the solvent. The major band at R_f 0.8-0.9 provided the ketone 7 (0.28 g, 90% yield) as an oil: ir (neat) (IR 19), 1715 (s, C=O), 1155 (m), and 715 cm⁻¹ (w); nmr (NMR 25), 0.90 (t, 3H, CH₂CH₃), 1.30 (bs, 12H), 2.07 (s, 3H, COCH₃), and 2.40 (m, 2H, CH₂CO); MS (m/e), 156 (16),

142 (6), 113 (4), 98 (15), and 71 (100).

6.3.6. n-Nonyl n-Octyl Ketone (8)— sec-Butyllithium in
pentane (1.1 M, 1.0 ml, 1.1 mmol) was added to a solution
of 1-decenyl methyl sulfide (0.22 g, 1.2 mmol) in 1:9
HMPA-THF (10 ml) with stirring under nitrogen at -78°.
1-Bromooctane (0.19 g, 1.0 mmol) was added and the solution
was kept at -78° for 30 min. Extractive workup furnished
a liquid which was used to the next step without further
purification. A solution of mercuric chloride (0.82 g, 3.0
mmol) in 3:1 acetonitrile-water (20 ml) was added to a
solution of the crude product in the same solvent mixture
(5 ml) with stirring at 25°. A voluminous white precipitate
formed immediately. The mixture was stirred at 110° for
10 hr and filtered through a pad of Celite 545 and the
filter cake was washed with dichloromethane. The organic
phase of filtrate was washed with water, dried, and freed
of the solvent. The residual liquid was submitted to
preparative tlc with benzene as an eluant. The band at R_f
0.7-0.8 afforded the ketone 8 (0.23 g, 82% yield) as an oil
which crystallized on standing. Recrystallization from
benzene-hexane afforded colorless needles: mp 46.5-47.5^O;
ir (neat), 1724 (s, C=O), 1460 (m), and 1370 cm^{-1} (w); nmr
(NMR 26), 0.85 (t, 6H, C$\underline{H}_3$), 1.25 (bs, 26H), and 2.30 (m, 4H,
-C$\underline{H}_2$COC$\underline{H}_2$-); MS (m/e), 268 (23), 224 (14), 132 (50), 170 (50),
154 (78), 141 (81), and 71 (100).

Found: C, 80.4; H, 13.4. Calcd for $C_{18}H_{36}O$: C, 80.5;
H, 13.5.

6.3.7. 2,7-Octadione (6)— sec-Butyllithium in pentane
(1.1 M, 4.0 ml, 4.4 mmol) was added to a solution of ethyl
vinyl sulfide (0.42 g, 4.8 mmol) in 1:9 HMPA-THF (20 ml)
with stirring under nitrogen at -78° for 30 min. The mixture
was then treated with a solution of 1,4-dibromobutane (0.43 g,
2.0 mmol) in dry THF (2 ml). The resulting solution was
stirred at -78° for 30 min and treated with water. Ethereal
extracts were washed with water, dried, and freed of the
solvent. The remaining liquid was treated with a solution
of mercuric chloride (2.4 g, 8.0 mmol) in·3:1 acetonitrile-
water (20 ml). The opaque white mixture was heated at
reflux for 5 hr. The crude product obtained on extractive
workup was submitted to preparative tlc with dichloromethane
as an eluant. The major band at R_f 0.3-0.5 provided the
2,7-octadione 6 (0.17 g, 60% yield) as a colorless semisolid:
tlc R_f 0.25 (CH_2Cl_2); ir (neat), 1705 (s, C=O), 1350 (m),
1150 (m), 985 (w), and 708 cm^{-1} (w); nmr (NMR 27), 1.56
(m, 4H, CH_2CH_2), 2.13 (s, 6H, $COCH_3$), and 2.45 (m, 4H, CH_2CO);
MS (m/e), 142 (18), 124 (20), 109 (45), and 84 (100).

6.3.8. 3-Methyl-2-cyclohexenone (10)— A solution of ethyl
vinyl sulfide (0.42 g, 4.8 mmol) in 1:9 HMPA-THF (20 ml)
was treated under nitrogen at -78° with sec-butyllithium in
pentane (1.1 M, 4.0 ml, 4.4 mmol) and the whole was kept at
-78° for 30 min. 1,3-Dibromopropane (0.40 g, 2.0 mmol) was
added and the reaction mixture was stirred at -78° for 30
min. Extractive workup furnished a liquid (0.41 g) which
was dissolved in 3:1 acetonitrile-water (20 ml) and the

solution was stirred at 110° for 10 hr in the presence of added solid mercuric chloride (2.4 g, 8.0 mmol). The reaction mixture was filtered through a pad of Celite 545 and the filter cake was washed with dichloromethane. The filtrate was washed with water, dried, and freed of the solvent. The residual liquid was submitted to preparative tlc on silica gel with dichloromethane as an eluant. The strongly uv-active band at R_f 0.3-0.4 provided a liquid (0.11 g, 52% yield) which was identified as 3-methyl-2-cyclohexenone: tlc R_f 0.20 (CH_2Cl_2); ir (neat) (IR 22), 1660 (s, C=O), 1245 (m), 1190 (m), 1135 (w), and 880 cm^{-1} (m); nmr (NMR 28), 1.30 (s, 3H, CH_3), 2.05 (m, 6H), and 5.80 (bs, 1H, $CH=$); MS (m/e), 110 (M^+).

6.3.9. Benzyl n-Octyl Ketone (9)— sec-Butyllithium in pentane (1.1 M, 2.0 ml, 2.2 mmol) was added to a solution of methyl styryl sulfide (0.36 g, 2.4 mmol) in 1:9 HMPA-THF (15 ml) with stirring at -78° under nitrogen. The deep purple solution was stirred at -78° for 30 min, treated with 1-bromooctane (0.39 g, 2.0 mmol), and the whole was stirred at -78° for 30 min. The solution was diluted with ether, and the ethereal extracts were washed with water, dried, and freed of the solvent. The residual liquid (0.51 g) was treated with a solution of mercuric chloride (1.1 g, 4.1 mmol) in 3:1 acetonitrile-water (20 ml). The mixture was heated at reflux for 12 hr, cooled, filtered through a pad of Celite 545 and the solid was washed thoroughly with dichloromethane. The organic phase of the filtrate was

washed with water, dried, and freed of the solvent. The
residual liquid was submitted to preparative tlc with 1:1
benzene-hexane as an eluant. The major band at R_f 0.4-0.5
furnished the ketone 9 (0.30 g, 65% yield) as a liquid:
tlc R_f 0.51 (benzene); ir (neat) (IR 23), 1710 (s, C=O),
1600 (w), 1495 (m), 1350 (m), 1065 (m), and 692 cm^{-1} (s);
nmr (NMR 29), 0.90 (t, 3H, CH$_2$CH$_3$), 1.23 (bs, 12H), 2.4 (q,
2H, COCH$_2$CH$_3$), 3.6 (s, 2H, CH$_2$Ph), and 7.25 (m, 5H); MS (m/e),
232 (10) and 141 (100). The analytical sample was prepared
by evaporative distillation at 160° (bath temp, 1 mmHg).

   Found: C, 82.4; H, 10.3. Calcd for C$_{16}$H$_{24}$O: C, 82.7;
H, 10.4.

6.3.10. 1-Hydroxy-1-phenyl-2-propanone (11)— sec-

Butyllithium in pentane (1.1 M, 3.0 ml, 3.3 mmol) was added
to a solution of ethyl vinyl sulfide (0.32 g, 3.6 mmol) in
1:9 HMPA-THF (25 ml) with stirring at -78° under nitrogen.
The deep yellow solution was stirred at -78° for 30 min,
treated with benzaldehyde (0.32 g, 3.0 mmol) and the whole
was stirred at -78° for 30 min and poured into water.
Ethereal extracts of this mixture were washed with water,
dried, and freed of the solvent. A solution of the remaining
oil (0.63 g) in 3:1 acetonitrile-water (5 ml) was treated
with a solution of mercuric chloride (1.6 g, 6.0 mmol) in
the same solvent mixture (15 ml). The mixture was stirred
at 110° for 12 hr and filtered through a pad of Celite 545
and the solid was washed with dichloromethane. The organic
phase of the filtrate was washed with water, dried, and

freed of the solvent. The residual liquid was submitted to preparative tlc with trichloromethane as an eluant. Dichloromethane extracts of the major band (R_f 0.4-0.5) were freed of the solvent and the remaining liquid (0.29 g, 64% yield) was identified as 1-hydroxy-1-phenyl-2-propanone: tlc R_f 0.2 (CH_2Cl_2); ir (neat) (IR 24), 3400 (s, OH), 1710 (s, C=O), 1600 (w), 1490 (m), 1345 (m), 1065 (s), 960 (w), and 740 cm^{-1} (s); nmr (NMR 30), 2.06 (s, 3H, C$\underline{H}_3$), 4.23 (bs, 1H, O$\underline{H}$), 5.10 (s, 1H, C$\underline{H}$Ph), and 7.30 (s, 5H, C$_6\underline{H}_5$); MS ($\underline{m}/\underline{e}$), 150 (2), 132 (1), 144 (2), 116 (20), and 115 (100).

6.3.11. 3-Hydroxy-2-undecanone (12)— A solution of ethyl vinyl sulfide (0.32 g, 3.6 mmol) in 1:9 HMPA-THF (20 ml) was stirred under nitrogen at -78° and treated with sec-butyllithium in pentane (1.1 $\underline{M}$, 3.0 ml, 3.3 mmol). The resulting solution was treated with nonanal (0.43 g, 3.0 mmol) and kept at -78° for 30 min. Extractive workup afforded a yellow oil (0.57 g), which was dissolved in a solution of mercuric chloride (1.6 g, 6.0 mmol) in 3:1 acetonitrile-water (30 ml). The solution was heated at 110° for 7 hr, cooled, and diluted with dichloromethane. The liquid obtained on extractive workup was submitted to preparative tlc with trichloromethane as an eluant. The major band at R_f 0.2-0.4 provided the acyloin 12 (0.32 g, 58% yield) as a pale-yellow liquid: tlc R_f 0.23 (CH_2Cl_2); ir (neat), 3400 (m, OH), 1710 (s, C=O), 1120 (w), 1080 (m), 905 (w), and 730 cm^{-1} (s); nmr (NMR 31), 0.87 (t, 3H, CH$_2$C$\underline{H}_3$), 1.25 (bs, 12H), 2.13 (s, 3H, COC$\underline{H}_3$), 3.40 (s, 1H, O$\underline{H}$), and 4.2 (t, 1H,

C$\underline{H}$OH); MS ($\underline{m}$/$\underline{e}$), 186 (10), 144 (34), 143 (65), 142 (43), and 141 (100). The analytical sample was prepared by distillation at 110° (bath temp, 2 mmHg).

Found: C, 71.0; H, 11.8. Calcd for $C_{11}H_{22}O_2$: C, 70.9; H, 11.9.

6.3.12. <u>1-Hydroxy-1,3-diphenyl-2-propane (13)</u>— sec-Butyllithium in pentane (1.1 $\underline{M}$, 1.0 ml, 1.1 mmol) was added to a solution of methyl styryl sulfide (0.18 g, 1.2 mmol) in 1:9 HMPA-THF (10 ml) with stirring under nitrogen at -78°. The solution was kept at -78° for 30 min, treated with benzaldehyde (0.11 g, 1.0 mmol), and kept at -78° for 30 min. The reaction mixture was diluted with ether, and the ethereal extract was dried and freed of the solvent. The residual crude carbinol (0.31 g) was treated with a solution of mercuric chloride (0.82 g, 3.0 mmol) in 3:1 acetonitrile-water (20 ml). The solution was stirred at 110° for 5 hr, cooled, and diluted with dichloromethane; the entire mixture was filtered through a pad of Celite 545. The organic phase of the filtrate was washed with water, and the extract was dried and freed of the solvent. The residual liquid was submitted to preparative tlc with dichloromethane as an eluant. The major band at $\underline{R}_f$ 0.4-0.6 furnished the acyloin 13 (0.13 g, 55% yield) as a viscous oil: tlc $\underline{R}_f$ 0.42 (CH_2Cl_2); ir (KBr) (IR 26), 3440, 3400 (s, OH), 1710 (s, C=O), 1605 (w), 1040 (m), and 692 cm^{-1} (s); nmr (NMR 32), 3.60 (s, 2H, C$\underline{H}_2$Ph), 5.15 (s, 1H, O$\underline{H}$), 6.95 (m, 1H, C$\underline{H}$OHPh), and 7.25 (m, 10H, Ph); MS ($\underline{m}$/$\underline{e}$), 226 (1), 208 (19), 186 (18), 121 (20), and 105 (100).

6.3.13. 1-Phenyl-3-hydroxy-2-undecanone (14)— sec-
Butyllithium in pentane (1.1 $\underline{M}$, 2.0 ml, 2.2 mmol) was added
to a solution of methyl styryl sulfide (0.36 g, 2.4 mmol)
in 1:9 HMPA-THF (15 ml) with stirring under nitrogen at -78°.
After the solution was kept at -78° for 30 min, nonanal
(0.28 g, 2.0 mmol) was added and the mixture was stirred at
-78° for 30 min. Extractive workup afforded a liquid which
contained the crude alcohol (0.55 g). The crude carbinol
was dissolved in 3:1 acetonitrile-water (5 ml) and treated
with a solution of mercuric chloride (1.1 g, 4.0 mmol) in
the same solvent mixture (30 ml). The heterogeneous reaction
mixture was stirred at 110° for 13 hr and filtered through
a pad of Celite 545 and the filter cake was washed with
dichloromethane. The organic phase of the filtrate was
washed with water, dried, and freed of the solvent. The
remaining liquid was submitted to preparative tlc with
dichloromethane as an eluant. The band at $\underline{R}_f$ 0.4-0.65
provided the acyloin 14 (0.24 g, 45% yield) as a pale-yellow
oil: tlc $\underline{R}_f$ 0.35 (CH_2Cl_2); ir (neat), 3350 (m, OH), 1705
(s, C=O), and 697 cm^{-1} (m); MS ($\underline{m/e}$), 262 (5), 244 (4),
155 (51), and 107 (100). The analytical sample was obtained
by evaporative distillation at 110° (bath temp, 0.03 mmHg).

Found: C, 77.7; H, 10.0. Calcd for $C_{17}H_{26}O_2$: C, 77.8;
H, 10.0.

6.3.14. 1-Hydroxy-1-phenyl-2-undecanone (15)— sec-
Butyllithium in pentane (1.1 $\underline{M}$, 2.0 ml, 2.2 mmol) was added
to a solution of 1-decenyl methyl sulfide (0.46 g, 2.4 mmol)

in 1:9 HMPA-THF (15 ml) with stirring under nitrogen at -78°.
The mixture was stirred at -78° for 30 min, and then treated
with benzaldehyde (0.21 g, 2.0 mmol) and the whole was
stirred at -78° for 30 min, and poured into water. Ethereal
extracts of this mixture were washed with water, dried, and
freed of the solvent. The residual liquid furnished the
crude alcohol (0.57 g). A mixture of the crude carbinol,
mercuric chloride (1.1 g, 4.0 mmol), acetonitrile (15 ml),
and water (5 ml) was heated at reflux (near 100°) for 10 hr.
The crude product obtained on extractive workup was submitted
to preparative tlc with dichloromethane as an eluant. The
acyloin 15 (R_f 0.25-0.50; 0.27 g, 51% yield) was isolated
as a viscous oil. This material solidified on standing,
and the analytical sample was prepared by recrystallization
from hexane-benzene: mp 46.5-47.5°; tlc R_f 0.35 (CH_2Cl_2);
ir (neat), 3400 (m, OH), 1710 (s, C=O), 1605 (w), 1492 (w),
1185 (w), 1050 (w), 1020 (w), and 690 cm^{-1} (s); nmr, 0.85
(t, 3H, $CH_2C\underline{H}_3$), 1.20 (bs, 14H), 2.25 (m, 2H, $C\underline{H}_2CO$), 3.50
(m, 1H, O$\underline{H}$), 4.15 (m, 1H, C$\underline{H}$OH), and 7.20 (m, 5H, $C_6\underline{H}_5$).

Found: C, 77.6; H, 9.78. Calcd for $C_{17}H_{26}O_2$: C, 77.8;
H, 9.99.

6.3.15. 11-Hydroxy-10-nonadecanone (16)— A solution of
1-decenyl methyl sulfide (0.46 g, 2.4 mmol) in 1:9 HMPA-
THF (15 ml) was treated at -78° with sec-butyllithium (1.1 $\underline{M}$,
2.0 ml, 2.2 mmol). The mixture was stirred at -78° for 30 min,
and treated with nonanal (0.28 g, 2.0 mmol), and kept at -78°
for 30 min. Extractive workup furnished an alcohol (0.70 g).

Solid mercuric chloride (1.1 g, 4.0 mmol) was added to a
solution of the alcohol in 3:1 acetonitrile-water (20 ml)
The heterogeneous reaction mixture was stirred at 110° for
6 hr and filtered through a pad of Celite 545 and the filter
cake was washed thoroughly with dichloromethane. The organic
phase of the filtrate was washed with water, dried, and freed
of the solvent. The residual liquid was submitted to
preparative tlc with dichloromethane as an eluant. The major
band at R_f 0.4-0.7 afforded a liquid 16 (0.21 g, 35% yield)
which crystallized on standing. Recrystallization from
hexane-benzene provided colorless needles: mp 49-50°; tlc
R_f 0.45 (CH_2Cl_2); ir (neat), 3300 (m, OH), 1705 (s, C=O), and
1090 cm^{-1} (s); nmr, 0.95 (t, 6H, $CH_2C\underline{H}_3$), 1.30 (bs, 28H), 2.50
(m, 2H, $C\underline{H}_2CO$), 2.75 (bs, 1H, O$\underline{H}$), and 4.20 (m, 1H, C$\underline{H}$OH);
MS ($m/\underline{e}$), 298 (6), 269 (4), 186 (18), and 129 (100).

6.3.16. Methyl Styryl Ketone (17)— sec-Butyllithium in
pentane (1.1 M, 2.0 ml, 2.2 mmol) was added to a solution of
ethyl vinyl sulfide (0.21 g, 2.4 mmol) in 1:9 HMPA-THF (15 ml)
with stirring under nitrogen at -78°. The deep yellow solution
was stirred at -78° for 30 min, treated with styrene oxide
(0.24 g, 2.0 mmol), and the whole was stirred at -78° for
30 min. Extractive workup furnished the alcohol (0.39 g)
which was dissolved in 3:1 acetonitrile-water (10 ml) and
the solution was treated with a solution of mercuric chloride
(1.6 g, 6.0 mmol) in the same solvent mixture (10 ml). The
resulting mixture was heated at reflux (ca. 110°) for 10 hr,
cooled, and filtered through a pad of Celite 545 and the

solid was washed with dichloromethane. The filtrate was washed with water, dried, and freed of the solvent. The residue was submitted to preparative tlc with dichloromethane as an eluant. The strongly uv-active band at R_f 0.55-0.75 furnished the enone 17 (0.21 g, 71% yield) as a colorless liquid: tlc R_f 0.50 (CH_2Cl_2); ir (neat) (IR 30), 1655 (s, C=O), 1605 (s), 1490 (w), 1255 (m), 965 (s), and 740 cm^{-1} (s); nmr (NMR 36), 2.35 (s, 3H, CH_3), 6.60 (d, 1H, J=15 Hz, =CHCOCH$_3$), and 7.25-7.55 (m, 6H, C_6H_5 and PhCH=); MS (m/e), 146 (68), 131 (100), and 103 (97).

6.3.17. Benzyl Propenyl Ketone (18)— sec-Butyllithium in pentane (1.1 M, 1.0 ml, 1.1 mmol) was added to a solution of methyl styryl sulfide (0.18 g, 1.2 mmol) in 1:9 HMPA-THF (10 ml) with stirring under nitrogen at -78°. After the solution was kept at -78° for 30 min, propylene oxide (68 μl, 1.0 mmol) was injected and the entire mixture was kept at -78° for 30 min. A mixture of the crude carbinol obtained on extractive workup, mercuric chloride (0.82 g, 3.0 mmol), acetonitrile (15 ml), and water (5 ml) was heated at reflux for 10 hr. The crude oil obtained on extractive workup was submitted to preparative tlc with dichloromethane as an eluant. The enone 18 (R_f 0.7-0.8; 0.11 g, 69% yield) was isolated as a colorless liquid: tlc R_f 0.65 (CH_2Cl_2); nmr (NMR 37), 1.30 (d, 3H, =CHCH$_3$), 6.75 (m, 1H, COCH=), 3.60 (s, 2H, PhCH$_2$), 6.10 (dq, 1H, =CHCH$_3$), and 7.20 (bs, 5H, C_6H_5); MS (m/e), 160 (24), 105 (11), 91 (48), and 69 (100). The analytical sample was prepared by evaporative distillation at 120°

(bath temp, 3 mmHg).

Found: C, 82.3; H, 7.38. Calcd for $C_{11}H_{12}O$: C, 82.5; H, 7.55.

6.3.18. Benzyl Styryl Ketone (19)-- sec-Butyllithium in pentane (1.1 $\underline{M}$, 1.4 ml, 1.5 mmol) was added to a solution of methyl styryl sulfide (0.25 g, 1.7 mmol) in 1:9 HMPA-THF (10 ml) with stirring under nitrogen at -78°. The solution was kept at -78° for 30 min, treated with styrene oxide (0.17 g, 1.4 mmol), and the whole was kept at -78° for 30 min. The solution was diluted with ether, and the ethereal extract was washed with water, dried, and freed of the solvent. A solution of mercuric chloride (0.82 g, 3.0 mmol) in 3:1 acetonitrile-water (20 ml) was added to a solution of the residual crude alcohol (0.35 g) in the same solvent mixture (6 ml). The opaque white suspension was stirred at 110° for 13 hr. The resulting mixture was filtered through a pad of Celite 545 and the filter cake was washed with dichloromethane. . . The filtrate was washed with water, dried, and freed of the solvent. The remaining liquid was submitted to preparative tlc with trichloromethane as an eluant. The strongly uv-active band at $\underline{R}_f$ 0.60-0.80 provided the enone 19 (0.19 g, 62% yield) as a colorless liquid: tlc $\underline{R}_f$ 0.55 (CH_2Cl_2); ir (neat), 1685 (s, C=C), 1610 (s), 1492 (m), 1205 (m), 750 (m), and 700 cm^{-1} (s); nmr, 3.80 (s, 2H, PhC$\underline{H}_2$), 6.70 (d, 1H, J=16 Hz, =C$\underline{H}$Ph), and 7.25 (m, 11H, $C_6\underline{H}_5$ and =C$\underline{H}$CO); MS ($\underline{m}/\underline{e}$), 222 ($M^+$).

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APPENDIX A

The Reaction of O,O'-Diethyl α-Lithio-methylphosphonate with Organic Dihalides
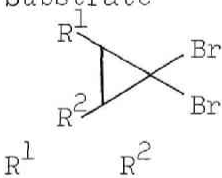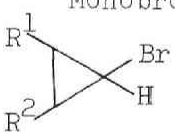
Abstract—— The reactions of the α-lithio derivative of diethyl methylphosphonate with various organic halides are described. The half-reduction of <u>gem</u>-dihalocyclopropanes has been achieved with this reagent. The same reagent gives bibenzyl and tetraphenylethane from benzyl bromide and benzhydryl chloride respectively. The deprotonation-metallation process is observed in the reactions of cinnamyl chloride and of <u>trans</u>-β-bromostyrene, in which 3-chloro-1,6-diphenyl-1,5-hexadiene and 1,4-diphenyl-3-buten-1-yne are produced respectively.

The half-reduction of olefin-dihalocarbene adducts
by organometallic reagents [1] is a useful method for obtaining
monohalocyclopropanes, but it has been limited in scope due
to competing reactions arising from the intermediary α-
halocyclopropylmetal compounds. The author has found that
the α-lithio derivative of diethyl methylphosphonate appears
to be an excellent reagent for the half-reduction of dihalo-
cyclopropanes under mild conditions. The present reagent
showed promise of largely circumventing the side reactions
encountered with other organometallic reagents.

O,O'-Diethyl α-lithiomethylphosphonate 1, prepared
simply from O,O'-diethyl methylphosphonate and n-butyllithium
at -78°,[2] reacted with 1,1-dibromo-2-phenylcyclopropane 2
to give the expected 1-bromo-2-phenylcyclopropane 8 as a
predominant product (68%). In contrast, the reaction of
methylsulfinylcarbanion [3] with the dibromide 2 resulted
in a polymeric mixture in which the desired bromide 8 was
absent. The anion produced 9-bromo-cis-bicyclo[6.1.0]nonane
11 from 9,9-dibromo-cis-bicyclo[6.1.0]nonane 5 in 66% yield,
while with n-butyllithium the latter afforded 1,2-cyclonona-
diene as a major product.[4]

A variety of gem-dibromocyclopropanes have been
successfully reduced to the respective monobromides using
the phosphonate reagent as is indicated in Table A-1.
Most noteworthy is the preferential formation of thermo-
dynamically more stable trans or exo-monobromocyclopropanes,
which might originate from endo-exo isomerization of the

Table A-1. Reaction of gem-Dibromocyclopropanes with
0,0'-Diethyl α-Lithiomethylphosphonate $\underset{\sim}{1}$ in THF.

Substrate		Monobromocyclopropane				
R^1, R^2 (structure with Br, Br) R^1, R^2		(structure with Br, H) R^1, R^2		Ratio of isomers		
				exo	:	endo
		Yield (%)[a]		(trans	:	cis)
$\underset{\sim}{2}$	Ph, H	$\underset{\sim}{8}$	68	79	:	21
$\underset{\sim}{3}$	$-(CH_2)_4-$	$\underset{\sim}{9}$	82	90	:	10
$\underset{\sim}{4}$	$-CH_2-CH=CH-CH_2-$	$\underset{\sim}{10}$	75	84	:	16
$\underset{\sim}{5}$	$-(CH_2)_6-$	$\underset{\sim}{11}$	66	80	:	20
$\underset{\sim}{6}$	$-(CH_2)_{10}-$	$\underset{\sim}{12}$	70	83	:	17[b]
$\underset{\sim}{7}$	n-hexyl, H	$\underset{\sim}{13}$	68	79	:	21

a) Yields were based on the consumed gem-dibromocyclopropanes.

b) Allene was also obtained in 9% yield and it was identified
   by comparison with an authentic sample.

initially formed halocyclopropyllithium.[5]

An unambiguous assignment of structure to the two monobromocyclopropane isomers, which could be separated by gas chromatography, the cyclopropane hydrogens gave an A_2X system in the nmr spectrum with differing values of $J_{AX}=$ 3-4 Hz for the isomers obtained in larger yield and 7-8 Hz for the other isomers. In most known cases the cis coupling constants in cyclopropane systems are larger than the trans coupling constants.[6,7] This would lead to an assignment of the exo or trans structure to the isomers formed in larger yield (J_{AX}=3-4 Hz) and of the endo or cis structure to the other isomers with J_{AX}=7-8 Hz.

The preparation of the totally reduced cyclopropane derivative was also attained with this reagent. When ca. 3 equiv of the anion 1 was allowed to react with 1,1-dibromo-2,2-diphenylcyclopropane 14, a mixture of 1-bromo-2,2-diphenylcyclopropane 15 and 1,1-diphenylcyclopropane 16 was obtained. The cyclopropane 16 was obtained as a sole product when a large excess of the anion 1 was used for this reaction (6 equiv).

14   15   16
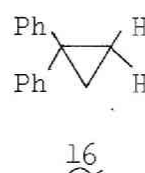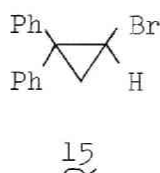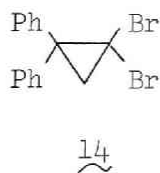
The similarity of the anion $\underset{\sim}{1}$ to methylsulfinyl-carbanion prompted the author to examine the reaction of $\underset{\sim}{1}$ with other organic halides. Corey and Chaykovski have reported [8] that the treatment of benzyl chloride and benzhydryl chloride with methylsulfinylcarbanion furnished stilbene and tetraphenylethylene, respectively. In contrast to these results, the anion $\underset{\sim}{1}$ gave bibenzyl $\underset{\sim}{17}$ and tetraphenylethane $\underset{\sim}{18}$ from benzyl bromide and benzhydryl chloride, respectively. The author supposes that this novel condensation reaction involves an unstable arylated carbanion which affords the final product upon reaction with another halide.

Although the above mentioned reactions are to be ascribed to the dehalogenation-metallation process, the deprotonation-metallation process has also been observed in some cases. Cinnamyl chloride gave 3-chloro-1,6-diphenyl-hexadiene-1,5 $\underset{\sim}{19}$, whereas trans-β-bromostyrene afforded 1,4-diphenyl-3-buten-1-yne $\underset{\sim}{23}$. The latter reaction might involve an intermediary vinylcarbenoid
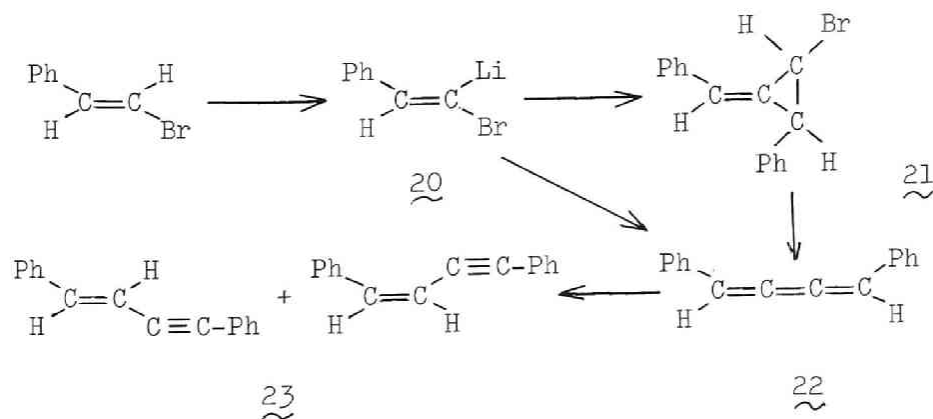
20, which reacts with β-bromostyrene to form the methylene-cyclopropane 21 followed by the isomerization to 23 through the cumulene derivative 22. Alternative pathway might be the direct dimerization of the vinylcarbenoid 20 to form the cumulene.[9] Possible formation of phenylacetylene as an intermediate was excluded by the following experiment. When the solution of 1 was successively treated with phenylacetylene at -78° and then with β-bromostyrene, no trace of 23 could be detected among the products.

Experimental Part

A.1. 1-Bromo-2-phenylcyclopropane (8)— n-Butyllithium in hexane (1.0 M, 3.0 ml, 3.0 mmol) was added to a solution of diethyl methylphosphonate (0.46 g, 3.0 mmol) in dry THF (15 ml) with stirring under nitrogen at -78°. The solution was kept at -78° for 15 min; 1,1-dibromo-2-phenylcyclopropane (0.28 g, 1.0 mmol) was added and the mixture was stirred at -78° for 30 min, then at 25° for 1 hr. Extractive workup furnished a liquid (0.29 g) which consisted of trans monobromocyclopropane 8a (53% yield) and the isomeric cis monobromide 8b (15% yield) by glpc assay. Physical data for the trans cyclopropane 8a: glpc, t_r 5.5 (column C, 160°); ir (neat), 1600 (s), 1500 (s), 1455 (m), 1370 (w), 1225 (s), 1030 (m), 930 (m), 755 (s), and 695 cm^{-1} (s); nmr, 1.3-1.6 (m, 2H, C$\underline{H}_2$), 2.35 (m, 1H, PhC$\underline{H}$), 3.00 (m, BrC$\underline{H}$), and 7.15 (m, 5H, C$_6\underline{H}_5$). 8b: glpc, t_r 6.5 (column C, 160°); ir (neat), 1600 (s), 1500 (s), 1450 (s), 1250 (s), 1020 (m), 755 (s), and 690 cm^{-1} (s); nmr, 1.1-1.6 (m, 2H, C$\underline{H}_2$), 2.27 (m, 1H,

PhC$\underline{H}$), 3.25 (m, 1H, BrC$\underline{H}$), and 7.20 (s, 5H, C$_6\underline{H}_5$).

A.2. 7-Bromonorcarane (9)— A solution of O,O'-diethyl α-lithiomethylphosphonate (3.0 mmol) in hexane-THF (1:5, 15 ml) was treated with 7,7-dibromonorcarane (0.25 g, 1.0 mmol) and kept at -78° for 30 min, then at 25° for 1 hr. The liquid (0.19 g) obtained on extractive workup consisted of exo-7-bromonorcarane 9a (74% yield) and endo isomer 9b (8% yield) by glpc assay. Physical data for the exo isomer 9a: glpc, $\underline{t}_r$ 4.2 (column C, 135°); ir (neat), 1215 (s) and 680 cm^{-1} (s); nmr, 0.8-2.2 (bm, 10H) and 2.55 (t, 1H, $J_{\underline{trans}}$=3.5 Hz). 9b: glpc, $\underline{t}_r$ 5.0 (column C, 135°); ir (neat), 1260 (s) and 725 cm^{-1} (m); nmr, 0.8-2.2 (bm, 10H) and 3.21 (t, 1H, $J_{\underline{cis}}$=7.9 Hz).

A.3. 7-Bromobicyclo[4.1.0]heptene-3 (10)— A solution of O,O'-diethyl α-lithiomethylphosphonate (6.0 mmol) in 1:5 hexane-THF (15 ml) was treated at -78° with 7,7-dibromo-bicyclo[4.1.0]heptene-3 (0.85 g, 3.4 mmol) and stirred at -78° for 30 min, at 25° for 1 hr. Extractive workup provided a liquid that was separated by preparative glpc (column F). The faster component ($\underline{t}_r$ 4.5) furnished the exo-monobromide 10a (0.44 g, 63% yield) and the slower component ($\underline{t}_r$ 6.0) afforded the endo isomer 10b (70 mg, 12% yield). Physical data for the exo isomer 10a: ir (neat), 3050 (m), 1655 (m, C=C), and 1220 cm^{-1} (s); nmr, 5.47 (b, 2H, C$\underline{H}$=C$\underline{H}$), 2.74 (t, 1H, $J_{\underline{trans}}$=3.1 Hz, C$\underline{H}$Br), 2.37 (b, 4H, C$\underline{H}_2$C$\underline{H}_2$), and 1.45 (b, 2H); MS ($\underline{m}/\underline{e}$), 172 and 174 (M$^+$). The analytical sample was obtained by evaporative distillation at 60°

(bath temp, 18 mmHg).

Found: C, 48.9; H, 5.46. Calcd for C_7H_9Br: C, 49.2; H, 5.24.

endo isomer 10b: ir (neat), 3050 (m), 1668 (m, C=C), and 1252 cm^{-1} (s); nmr, 3.29 (t, 1H, J_{cis}=7.4 Hz, CHBr).

A.4. 9-Bromobicyclo[6.1.0]nonane (11)— n-Butyllithium in hexane (1.0 M, 3.0 ml, 3.0 mmol) was added to a solution of diethyl methylphosphonate (0.46 g, 3.0 mmol) in dry THF with stirring under nitrogen at -78°. The resulting solution was treated with 9,9-dibromobicyclo[6.1.0]nonane (0.28 g, 1.6 mmol). Extractive workup afforded a liquid (0.12 g, 66% yield) consisted of the exo monohalide 11a and the endo isomer 11b in the ratio exo/endo= 80:20 (glpc). Preparative glpc (t_r 4.0 (11a) and 6.0 (11b) (column B, 120°)) provided the monohalide as a colorless liquid: 11a: ir (neat) (IR 33), 1225 cm^{-1} (s); nmr, 0.8-2.2 (m, 14H), 2.25 (t, 1H). 11b: ir (neat) (IR 34), 1245 cm^{-1} (s); nmr, 0.6-2.0 (m, 14H) and 3.17 (t, 1H, J_{cis}=7 Hz).

A.5. 13-Bromo-cis-bicyclo[10.1.0]tridecane (12)— n-Butyllithium in hexane (1.0 M, 3.0 ml, 3.0 mmol) was added to a solution of diethyl methylphosphonate (0.46 g, 3.0 mmol) in dry THF (15 ml) with stirring under nitrogen at -78°. The solution was treated with 13,13-dibromo[10.1.0]tridecane (0.60 g, 1.75 mmol) and kept at -78° for 30 min. Extractive workup afforded a 3 component mixture (12a, 12b, and 24) that was submitted to preparative glpc (t_r 3.0 (24), 11.2 (12a), and 13.4 (12b) (column F, 140°)). The faster

component $\underset{\sim}{24}$ was obtained as a liquid that was identified as
1,2-cyclotridecadiene (9% yield). The slower components
$\underset{\sim}{12}$a (0.27 g, 58% yield) and $\underset{\sim}{12}$b (11% yield) were separated.
Physical data for $\underset{\sim}{12}$a: bp 100° (bath temp, 0.05 mmHg);
ir (neat), 1469 (s), 1447 (m), 1250 (m), 1238 (m), and
1225 cm^{-1} (s). The nmr analysis did not reveal the methine
proton absorption.

Found: C, 60.5; H, 8.94. Calcd for $C_{13}H_{23}Br$: C, 60.2;
H, 8.94.

A.6. 13-Bromo-trans-bicyclo[10.1.0]tridecane (25)— A
solution of O,O'-diethyl α-lithiomethylphosphonate (3.0 mmol)
in 1:5 hexane-THF (15 ml) was treated at -78° with 13,13-
dibromobicyclo[10.1.0]tridecane (0.60 g, 1.75 mmol) and
kept at -78° for 30 min. Ethereal extracts of this reaction
mixture were washed with water, dried and freed of the
solvent. The residual liquid gave monobromide $\underset{\sim}{25}$ (72%
yield) and 1,2-cyclotridecadiene (8% yield) by glpc assay.
Physical data for $\underset{\sim}{25}$: ir (neat), 1465 (s), 1443 (m), 1270
(m), 1248 (m), 1237 (w), and 1222 cm^{-1} (m); nmr, 0.85
(b, 2H), 1.42 (b, 2H), 2.72 (q, 1H, $J_{cis}=7.2$ Hz, $J_{trans}=3.5$
Hz). The analytical sample was prepared by preparative
glpc (column F, 160°) and distillation at 100° (bath temp,
0.05 mmHg).

Found: C, 60.2; H, 9.14. Calcd for $C_{13}H_{23}Br$: C, 60.2;
H, 8.94.

A.7. 1-Bromo-2-n-hexylcyclopropane (13)— A solution of
0,0'-diethyl α-lithiomethylphosphonate (3.0 mmol) in hexane-
THF (15 ml) was treated at -78° with 1,1-dibromo-2-n-hexyl-
cyclopropane (0.28 g, 1.0 mmol) and kept at -78° for 30 min.
The liquid obtained on extractive workup consisted of trans
bromocyclopropane 13a (54% yield) and the cis isomer (14%
yield) by glpc assay. The analytical pure samples were
prepared by preparative glpc (t_r 7.2 (13a) and 13.0 (13b)
(column B, 100°)) and distillation at 80° (bath temp, 18
mmHg). 13a: glpc, t_r 6.5 (column C, 180°); ir (neat),
1470 (s), 1373 (m), 1234 (s), 1030 (s), and 920 cm^{-1} (m);
nmr, 2.48 (m, 1H, J_{trans}=3.3 Hz, CHBr), 1.32 (m, 11H,
methylenes and methine), and 0.87 (m, 5H, methyl and CH$_2$CHBr).

Found: C, 52.7; H, 8.28. Calcd for C$_9$H$_{17}$Br: C, 52.7;
H, 8.35.

A.8. Reaction of 1,1-Dibromo-2,2-diphenylcyclopropane (14)—
n-Butyllithium in hexane (1.0 M, 3.0 ml, 3.0 mmol) was
added to a solution of 0,0'-diethyl methylphosphonate
(0.46 g, 3.0 mmol) in THF with stirring under nitrogen
at -78°. The solution was treated with 1,1-dibromo-2,2-
diphenylcyclopropane (0.70 g, 2.0 mmol) and kept at -78°
for 30 min. Extractive workup afforded a liquid that was
separated by preparative glpc (column F, 130°). 1-Bromo-
2,2-diphenylcyclopropane 15 (0.40 g, 73% yield) was obtained
as a·liquid: bp, 140° (bath temp, 0.05 mmHg); ir (neat),
1252 cm^{-1} (s); nmr, 7.15 (d, 1H), 3.56 (t, 1H, J=6.5 Hz),
1.73 (d, 2H); MS (m/e), 272 and 274 (M$^+$). When 1,1-dibromo-

2,2-diphenylcyclopropane 14 (0.35 g, 1.0 mmol) was treated
with diethyl α-lithiomethylphosphonate (3.0 mmol), 1,1-
diphenylcyclopropane 16 (78 mg, 40% yield) was obtained in
addition to 15 (75 mg, 28% yield) by glpc. When 14 (60 mg,
0.17 mmol) was treated with diethyl α-lithiomethylphosphonate
(1.0 mmol), the cyclopropane 16 (62% yield) was provided
as a sole product by glpc assay.

A.9. Bibenzyl (17)— n-Butyllithium in hexane (1.0 $\underline{M}$, 3.0
ml, 3.0 mmol) was added to a solution of diethyl methyl-
phosphonate (0.46 g, 3.0 mmol) in dry THF with stirring
under nitrogen at -78°. After the solution was kept at
-78° for 30 min, benzyl bromide (0.34 g, 2.0 mmol) was added
and stirred at -78° for 30 min, at 25° for 1 hr. Extractive
workup provided a liquid that was submitted to preparative
tlc with hexane as an eluant. The band at $\underline{R}_f$ 0.6-0.8
afforded bibenzyl 17 (0.12 g, 70% yield) as a needle crystal:
mp 48-50.5^O (lit[10] 52-52.5^O).

A.10. Tetraphenylethane (18)— n-Butyllithium in hexane
(1.0 $\underline{M}$, 3.0 ml, 3.0 mmol) was added to a solution of diethyl
methylphosphonate (0.46 g, 3.0 mmol) in dry THF (15 ml) with
stirring under nitrogen at -78°. The solution was treated
with benzhydryl chloride (0.41 g, 2.0 mmol) and kept at
-78° for 30 min. The liquid obtained on extractive workup
was submitted to preparative tlc with hexane as an eluant.
The major band at $\underline{R}_f$ 0.7-0.85 provided tetraphenylethane
18 (0.14 g, 75% yield) as crystal: mp, 207-208° (lit[11] 209°).

A.11. 3-Chloro-1,6-diphenyl-1,5-diene (19)— Cinnamyl chloride (0.50 g, 3.3 mmol) was added to a solution of 0,0'-diethyl α-lithiomethylphosphonate (5.0 mmol) in 1:4 hexane-THF (20 ml) at -78°. After 30 min, the mixture was diluted with ether and the ethereal extracts were washed with water, dried, and freed of the solvent. The residual liquid afforded 3-chloro-1,6-diphenyl-1,5-diene 19 (71% yield) by preparative glpc separation (column F, 160°). The physical data for 19: bp, 160° (bath temp, 0.08 mmHg); ir (neat), 1624 (m), 1594 (m), 959 (s), 740 (m), and 692 cm^{-1} (m); nmr, 7.13 (b, 10H), 6.0 (m, 5H), and 2.55 (t, 2H).

Found: C, 80.3; H, 6.59. Calcd for $C_{18}H_{17}Cl$: C, 80.4; H, 6.38.

A.12. 1,4-Diphenyl-cis-3-buten-1-yne (23a) and 1,4-Diphenyl-trans-3-buten-1-yne (23b)— trans-β-Bromostyrene (0.60 g, 3.3 mmol) was added to a solution of 0,0'-diethyl α-lithio-methylphosphonate (4.9 mmol) in 1:4 hexane-THF (20 ml) at -78° and kept at -78° for 30 min. The colorless liquid obtained on extractive workup was separated by preparative glpc (column F, 165°) to afford cis-butene 23a (78 mg, 39% yield) and trans isomer 23b (15 mg, 3% yield). The physical data for 23a: bp, 80° (bath temp, 0.05 mmHg); ir (neat), 2200 (m) and 780 cm^{-1} (s); nmr, 7.73 (m, 2H), 7.21 (m, 8H), 6.56 and 5.76 (ABq, 1H each, J_{AB}=15 Hz). 23b: mp, 94-95° (lit[12] 95.5-96°); ir (KBr), 945 cm^{-1} (s); nmr, 7.23 (m, 5H), 6.96 and 6.26 (ABq, 1H each, J_{AB}=12 Hz).

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APPENDIX B

The Reduction of gem-Dibromocyclopropanes
by Means of Chromium(II) Acetate or
Potassium Pentacyanocobaltate

Abstract—— The reduction of gem-dibromocyclo-
propane with Cr^{II} acetate in DMSO gives mono-
bromocyclopropanes exclusively, whereas the
same components in aq. DMF afford cyclopropyl
acetates as the major products in addition to
monobromides. A similar substitution on
cyclopropane carbon is observed in the reduction
of gem-dibromide with $K_3Co(CN)_5$ in DMSO,
furnishing cyclopropyl cyanides mainly. The
stereochemistry of monobromides and cyclopropyl
acetates is determined by the NMR coupling
constants and chemical shifts, and that of
cyclopropyl cyanides by transformation to the
corresponding cyclopropyl methyl ketones derived
from cyclopropanecarboxylic acids of known
configurations. The reaction of monobromo-
cyclopropanes with $K_3Co(CN)_5$ is also described.

B.1. Reaction of gem-Dibromocyclopropanes with Cr[II] Acetate
and Potassium Pentacyanocobaltate

In previous work from our laboratory it was shown
that gem-dibromocyclopropanes, on treatment with chromium(II)
(Cr[II]) sulfate affords endo-monobromocyclopropanes along
with allenes and completely reduced cyclopropanes.[1] The
process appears to proceed via organochromium or chromim(III)-
carbene complex intermediate.
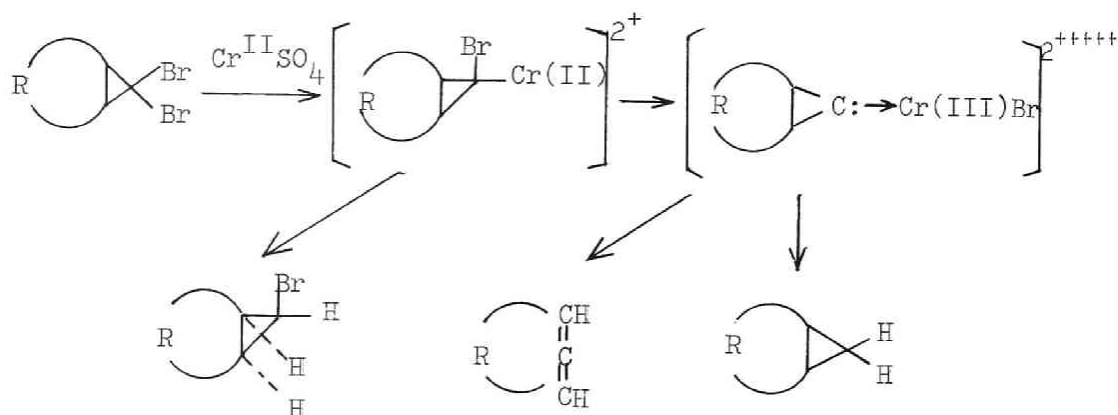
The author has now extended our study to include an
examination of the behavior of gem-dibromocyclopropanes
toword Cr[II] acetate[2] or potassium pentacyanocobaltate
$(K_3Co(CN)_5)$[3] in polar solvents.

The reaction of gem-dibromocyclopropanes with Cr[II]
acetate in dimethylsulfoxide (DMSO) formed the exo- and
endo-monobromocyclopropanes in ratios quite similar to
those observed with other reductants[4]; thus the predominance
of endo product over the stereoisomer exo monohalide (see
Table B-1 on the next page). For example, the reaction of

Table B-1. Reduction of <u>gem</u>-Dibromocyclopropanes with Cr^{II} Acetate in DMSO.
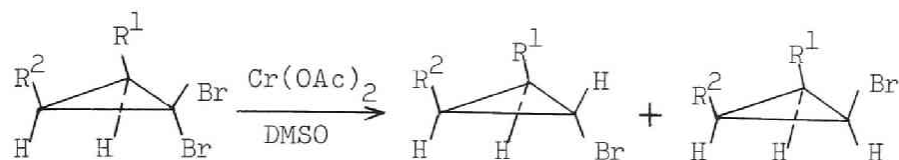
Substrate[a]		Monobromocyclopropane[a]				
R^1	R^2	<u>exo</u> (<u>trans</u>)	<u>endo</u> (<u>cis</u>)	Yield(%)	<u>exo</u> : <u>endo</u> Ratio[b]	
<u>1</u>	Ph, H	5a	5b	75	17 : 83	
<u>2</u>	-(CH$_2$)$_4$-	6a	6b	82	9 : 91	
<u>3</u>	-(CH$_2$)$_6$-	7a	7b	75	24 : 76	
<u>4</u>	<u>n</u>-hexyl, H	8a	8b	73	63 : 37	

a) Substrate and product code numbers are provided for reference to the Experimental Part.

b) <u>exo</u>/<u>endo</u> Ratios by glpc assay.

7,7-dibromonorcarane $\underset{\sim}{2}$ with Cr^{II} acetate gave the <u>endo-</u>
monohalide $\underset{\sim}{6b}$ and the exo isomer $\underset{\sim}{6a}$ in the ratio 91:9.
The products were isolated by preparative glpc and
characterized by nmr and infrared spectrometry.

$$\underset{\underset{\sim}{6b}}{}\qquad\qquad\underset{\underset{\sim}{6a}}{}$$

Treatment of 1,1-dibromo-2,2-diphenylcyclopropane $\underset{\sim}{9}$
with Cr^{II} acetate in DMSO afforded 1,1-diphenylallene $\underset{\sim}{10}$
as a sole product. This is the only case where an allene
is obtained.
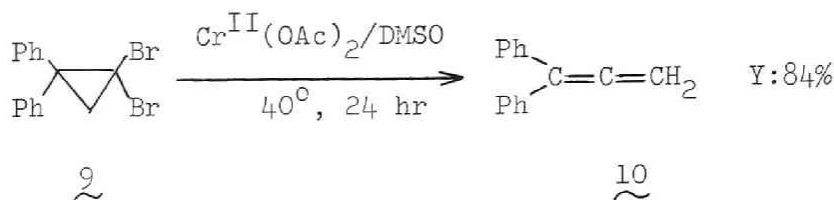
In contrast to the reaction with Cr^{II} salt in DMSO
described above, the reaction of <u>gem</u>-dibromocyclopropanes
in aqueous dimethylformamide (DMF) could form cyclopropyl
acetates in addition to monobromocyclopropanes (see Table
B-2). The stereochemistry of acetates was determined by
means of the nmr chemical shifts and coupling constants of
the acetoxy methyl protons and the acetoxy-substituted
methine protons.[5] The reaction of these dibromide with
$K_3Co(CN)_5$ in DMSO furnished the monohalides and cyclopropyl
cyanides as shown on Table B-3.[6] As the nmr spectra of

Table B-2. Reduction of <u>gem</u>-Dibromocyclopropanes with Cr^{II}
Acetate in Aqueous DMF.

Substrate		Product (Yield in %)[a]					
		monobromo-cyclopropane		cyclopropyl-acetate			
R^1	R^2	<u>exo</u> (<u>trans</u>)	<u>endo</u> (<u>cis</u>)	<u>exo</u> (<u>trans</u>)		<u>endo</u> (<u>cis</u>)	
<u>1</u>	Ph, H	7	34	<u>11a</u>	11	<u>11b</u>	1
<u>2</u>	-(CH$_2$)$_4$-	1	5	<u>12a</u>	53	<u>12b</u>	15
<u>3</u>	-(CH$_2$)$_6$-	0	25	<u>13a</u>	45	<u>13b</u>	4
<u>4</u>	<u>n</u>-hexyl, H	20	12	<u>14a</u>	27	<u>14b</u>	4

a) Yields were based on the consumed <u>gem</u>-dibromocyclopropanes.

Table B-3. Reduction of gem-Dibromocyclopropanes with
$K_3Co(CN)_5$ in DMSO.

| Substrate | | Product (Yiels in %)[a] | | | |
| | | monobromo-cyclopropane | | cyclopropyl cyanide | |
R^1	R^2	exo (trans)	endo (cis)	exo (trans)	endo (cis)
1	Ph, H	9	27	15a 26	15b 7[b]
2	-(CH$_2$)$_4$-	1	11	16a 46	16b 20
3	-(CH$_2$)$_6$-	nil[c]	nil[c]	17a 44	17b 30[d]
4	n-hexyl, H	32	27	18a 8	18b 6

a) Yields were based on the consumed gem-dibromocyclopropanes. . . .

b) Phenylallene was also obtained in a 17% yield.

c) Not isolated.

d) As the stereochemistry of 17a and 17b could not be
   determined because of the absence of the corresponding
   cyclopropanecarboxylic acid of known configuration, the
   assignment was made on the basis of glpc retention times
   and NMR chemical shifts of acetyl methyl protons of the
   corresponding cyclopropyl methyl ketones derived from
   17a and 17b as shown in Table B-4.

these cyclopropyl cyanides provided no information about the stereochemistry, the author tried to transform the cyanide into the corresponding cyclopropyl methyl ketones by treatment with methylmagnesium iodide (see Table B-4), and identified with an authentic samples obtained by the reaction of methyllithium with cyclopropanecarboxylic acids of known configurations (see Table B-5).[7] This method to determine the stereochemistry of cyclopropyl cyanides based on the hypothesis that these two reactions proceeds with retention of stereochemistry.

The reaction of $\underset{\sim}{3}$ with $K_3Co(CN)_5$ in DMSO was monitored by means of glpc. The results, shown in Fig-1, indicated the initial formation of monohalide from $\underset{\sim}{3}$ followed by the subsequent transformation of monobromide $\underset{\sim}{7}a$ and $\underset{\sim}{7}b$ into cyclopropyl cyanides, $\underset{\sim}{17}a$ and $\underset{\sim}{17}b$. In fact, the treatment of isolated exo- or endo-monobromide with $K_3Co(CN)_5$ in DMSO afforded a mixture of exo- and endo-cyclopropyl cyanide (see Table B-6). The observed formation of a mixture, exo- and endo-cyclopropyl cyanide, from either exo- or endo-monobromide possibly involves an S_N-type reaction on a cyclopropane ring, accompanied by no ring-cleavage.[8] The author may point out that the isomer ratios in this kind of S_N reactions are largely controlled thermodynamically, but a full explanation must await further investigations in the future.

Table B-4. Transformation of Cyclopropyl Cyanides to Cyclopropyl Methyl Ketones.

$$R^2 \underset{H}{\overset{R^1}{\diagup}} CN \xrightarrow[\text{ether}]{\text{MeMgI}} R^2 \underset{H}{\overset{R^1}{\diagup}} COCH_3$$

cyclopropyl cyanide Ratio exo : endo		R^1	R^2	cyclopropyl methyl ketone Ratio exo : endo		Yield(%)[a]
15	100 : 0	Ph,	H	19	100 : 0	67
16	70 : 30	$-(CH_2)_4-$		20	81 : 19	62
17	60 : 40	$-(CH_2)_6-$		21	85 : 15	65
18	57 : 43	n-hexyl,	H	22	60 : 40	67

a) Yields were based on the consumed cyclopropyl cyanides.

Table B-5.   Transformation of Cyclopropanecarboxylic Acids
to Cyclopropyl Methyl Ketones.
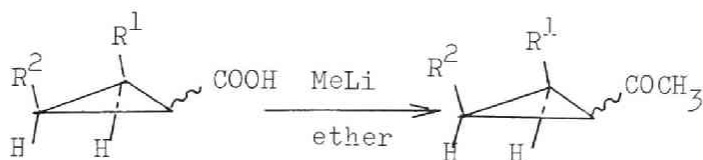
| cyclopropanecarboxylic acid | | | | cyclopropyl methyl ketone | | |
Ratio exo : endo		R^1	R^2	Ratio exo : endo		Yield(%)[a]
23	57 : 43	Ph,	H	19	60 : 40	75
24	88 : 12	-(CH$_2$)$_4$-		20	85 : 15	48
25	68 : 32	n-hexyl, H		22	66 : 34	65

a) Yields were based on the consumed cyclopropanecarboxylic
acids.
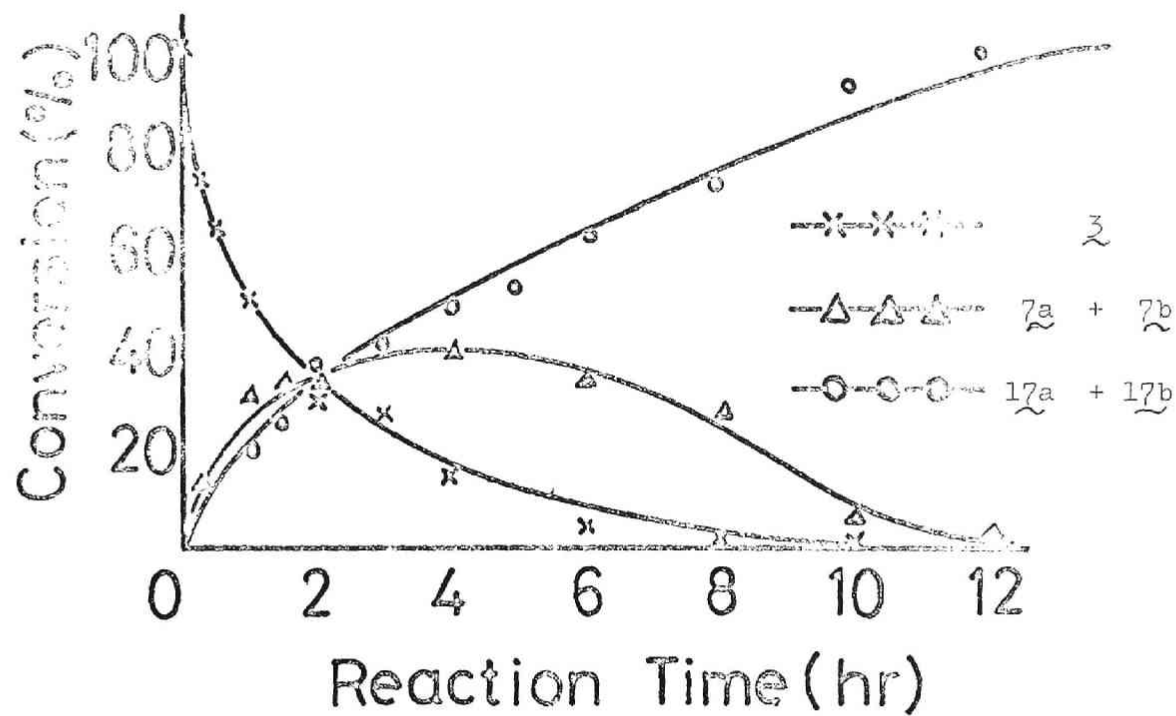
Figure 1. Reduction of 3 with $K_3\underline{Co(CN)}_5$ in DMSO followed by GLPC (HVSG 10%, 1.5 m, 130°)

Table B-6. Transformation of Monobromocyclopropanes to Cyclopropyl Cyanides with $K_3Co(CN)_5$ in DMSO.[a]
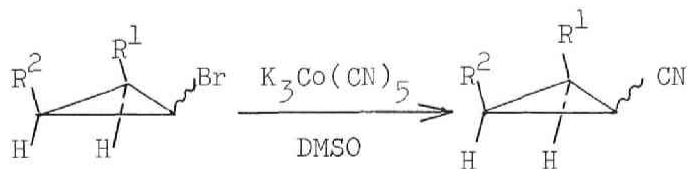
Monobromo-cyclopropane	R^1	R^2	Cyclopropyl Cyanide Ratio exo : endo (trans) (cis)		Yield (%)[b]
5a	Ph,	H	68 : 32		70
5b	Ph,	H	61 : 39		60
6a	$-(CH_2)_4-$		77 : 23		67
6b	$-(CH_2)_4-$		83 : 17		88
7a	$-(CH_2)_6-$		43 : 57		65
7b	$-(CH_2)_6-$		56 : 44		60
8a	n-hexyl,	H	42 : 58		78
8b	n-hexyl,	H	63 : 37		62

a) All reaction were performed at 70-80° for 15-20 hr.

b) Yields were based on the consumed amount of monobromo-cyclopropanes.

B.2. Mechanism of Reduction of gem-Dibromocyclopropanes

with Metal Salts

Seyferth [4a] have examined the stepwise reduction of
gem-dihalocyclopropanes with tri-n-butyltin hydride. The
reduction of 7,7-dibromobicyclo[4.1.0]heptane 2 resulted
in a mixture of both possible isomers, endo- and exo-
monobromide in a ratio of 2.5:1. They have pictured their
reaction in the following manner on the basis of the
structure assingnnents. Attack by the bulky tri-n-butyltin
radical would be expected to occur at the less hindered
C-Br bond, which is cis with respect to the two cyclopropane
hydrogens of 7,7-dibromonorcarane. Attack by tri-n-butyltin
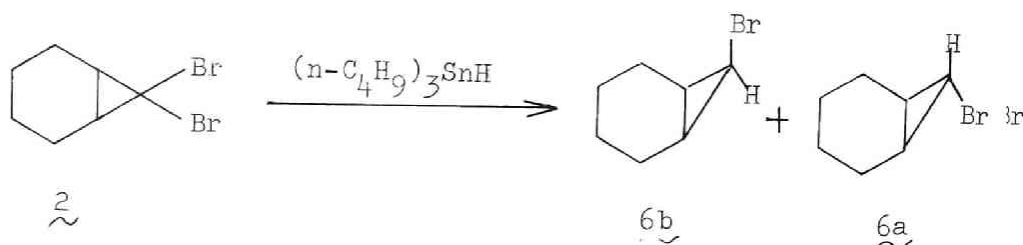
hydride on the resulting radical then would occur, with the
hydride having the possibility of attacking on either side
of the cyclopropane ring. In terms of either a planar or
a rapidly inverting radical center, steric factors hindering
approach of the bulky tri-n-butyltin hydride seem to outweigh
all other considerations in view of the observed endo-exo
ratio in the product.

The half reduction of gem-dibromocyclopropanes by
Cr^{II} acetate-DMSO system (Table B-1) resulted in a similar
isomer ratios to the above mentioned tin hydride-organic

halide reaction, and radical process may explain the isomer distribution. The hydrogen source might be solvent, DMSO. The reaction of gem-dibromocyclopropanes with Cr^{II} salts would probably proceed according to Scheme I (on the next page). Several remarkable points of difference have been observed between the two system, Cr^{II} sulfate in aqueous DMF (A) and Cr^{II} acetate in DMSO (B). (1) A more rigorous preference of endo monohalide over exo isomer is observed with the system A. (2) Better yields of allenes are obtained in the system A with the exception of the case of 1,1-dibromo-2,2-diphenylcyclopropane. (3) Totally-reduced cyclopropanes are obtained only in the system A. Rapidly flipping radicals 26 may be responsible, in part at least, for the formation of endo- and exo-monobromide in the system B, whereas organochromium intermediates 27 probably account for the exclusive formation of endo monohalide in the system A. Allenes and cyclopropanes may originate from the postulated inverse ylides 28, which can not be important in the system B. The author is tempted to assume that cyclopropyl acetate produced in the reaction of Cr^{II} acetate in aqueous DMF (system C) originate from chromium carbenoids 27 or from chromium inverse ylides 28, since the reaction of isolated monobromocyclopropanes with Cr^{II} or Cr^{III} acetate in DMSO or in aqueous DMF afforded no cyclopropyl acetate but only complex mixture, which could not be investigated further.

$R^1 \cdot CH=C=CHR^2$

Cr^{II}

A, B, C

26

A, B, C

B, C

S_N

A, B, C

27

A, C

$\rightarrow Cr^{III}Br(OAc)_2$

C

28

X=OAc or CN

X=OAc or CN

A: $Cr^{II}SO_4$/aq.DMF

B: $Cr^{II}(OAc)_2$/DMSO

C: $Cr^{II}(OAc)_2$/aq.DMF

Scheme I

B.3. Experimental Part

B.3.1. General Procedure of the Reactions of gem-Dibromo-
cyclopropane Derivatives with Chromium(II) Acetate or
Potassium Pentacyanocobaltate in DMSO or Aqueous DMF—
A solution of chromium(II) acetate (Cr^{II} acetate) (3.0-
4.0 mol) or potassium pentacyanocobaltate (K$_3$Co(CN)$_5$)
(3.0-4.0 mol, from potassium cyanide and cobalt(II) chloride)
in absolute DMSO or 1:1 DMF-water was heated under nitrogen
at 60-70° for 30 min. The solution was maintained at an
appropriate reaction temp, and treated with gem-dibromo-
cyclopropanes (1.0 mol). The mixture was heated and stirred
until the reddish-brown solution (or blue solution) turned
green (or colorless), cooled, and treated with water.
Ethereal extracts were washed with water, dried, and freed
of the solvent. The residual liquid was separated by
preparative tlc or preparative glpc and identified with an
authentic sample. Since the attempted isolation of stereo-
isomers of the substitution products: acetoxycyclopropanes
and cyanocyclopropanes gave unsatisfactory results, the
mixture was obtained by preparative tlc, and the ratio of
the isomers was calculated from the high-sensitive glpc and
nmr analyses.

B.3.2. Reaction of 1,1-Dibromo-2-n-hexylcyclopropane with
Cr^{II} Acetate in DMSO— A solution of Cr^{II} acetate (4.9 g,
28.8 mmol) in DMSO (100 ml) was treated at 50° with 1,1-
dibromo-2-n-hexylcyclopropane 4 (2.0 g, 7.1 mmol), and kept
at 50° for 17 hr. Extractive workup provided the isomers of

monobromide $\underset{\sim}{8a}$ and $\underset{\sim}{8b}$ (73% yield, $\underset{\sim}{8a}/\underset{\sim}{8b}$= 63:37 by glpc

assay).

B.3.3. 1,1-Diphenylallene (10)— A solution of Cr^{II} acetate

(2.9 g, 17 mmol) in DMSO (70 ml) was stirred under nitrogen

at 35° for 30 min. The solution was treated with 1,1-

dibromo-2,2-diphenylcyclopropane $\underset{\sim}{9}$ (1.5 g, 4.3 mmol) and

stirred at 35° for 24 hr. The crude liquid (0.69 g, 84%

yield) obtained on extractive workup consisted of 1,1-

diphenylallene as a sole component by glpc analysis (column

C, 160°): ir (neat), 1940 (m) and 850 cm^{-1} (s), nmr, 5.17

(s, 2H) and 7.1 (m, 5H, $C_{6}\underline{H}_{5}$).

B.3.4. Reaction of 1,1-Dibromo-2-phenylcyclopropane 1 with

Cr^{II} acetate in DMSO— A solution of Cr^{II} acetate (5.3 g,

31 mmol) in DMSO (100 ml) was stirred under nitrogen for

30 min at 25°. The resulting reddish-brown solution was

treated with 1,1-dibromo-2-phenylcyclopropane (2.8 g, 10 mmol),

and stirred at 25° for 20 hr, and diluted with water.

Extractive workup furnished the isomers of monobromide $\underset{\sim}{5a}$

and $\underset{\sim}{5b}$: $\underset{\sim}{5a}/\underset{\sim}{5b}$= 18:82 (13% and 62% yield, respectively) by

glpc assay (column C, 160°). Each isomer revealed the

identical physical properties with the samples obtained from

the reaction of diethyl α-lithiomethylphosphonate with

1,1-dibromo-2-phenylcyclopropane $\underset{\sim}{1}$.

B.3.5. Reaction of 7,7-Dibromonorcarane 2 with Cr^{II} acetate

in DMSO— A solution of Cr^{II} acetate (4.1 g, 24 mmol) in

DMSO (70 ml) was stirred under nitrogen for 30 min at 30°.

The solution was treated with 7,7-dibromonorcarane $\underset{\sim}{2}$ (2.0 g,

7.9 mmol) and kept at 45° for 15 hr. The crude liquid obtained on extractive workup contained 2-components in addition to the starting dibromide that was submitted to preparative glpc ($\underline{t}_r$ 4.8 and 5.6; column C, 140°). The monobromide 6 (6a/6b= 10:90, 82% yield) was afforded as a liquid. The spectrometric properties (ir and nmr) were identical with the authentic samples obtained in the reaction described before.

B.3.6. Reaction of 9,9-Dibromobicyclo[6.1.0]nonane 3 with Cr^{II} acetate in DMSO— A mixture of Cr^{II} acetate (5.4 g, 32 mmol), DMSO (70 ml), and dibromide 3 (2.8 g, 10 mmol) was heated at 50° for 16 hr. The resulting mixture was cooled, diluted with ether and the ethereal extract was washed with water, dried, and freed of the solvent. The residual liquid contained 3-components by glpc assay (column C, 160°): compound ($\underline{t}_r$, rel mol%), exo-monobromide 7a (6.0, 18%), endo isomer 7b (7.5, 55%), recovered dibromide (16.0, 27%): 7a/7b= 24:76.

B.3.7. 1-Acetoxy-2-phenylcyclopropane (11)— A solution of Cr^{II} acetate (5.0 g, 29 mmol) in 1:1 DMF-water (60 ml) was treated under nitrogen with dibromide 1 (1.8 g, 6.5 mmol) at 25°. The mixture was heated at 70° for 17 hr, cooled, and treated with water. Ethereal extracts of this mixture were washed with water, dried, and freed of the solvent. The residual liquid was submitted to preparative tlc with benzene as an eluant. The faster-moving band ($\underline{R}_f$ 0.8-0.95; 0.53 g, 41% yield) consisted of a mixture of the trans

monobromide 5a and the isomer 5b (trans/cis= 15:85 by glpc
assay, column C, 150°). The slower-moving band (R_f 0.4-0.55,
0.14 g, 12% yield) consisted of two isomers of the acetoxy-
cyclopropane 11a and 11b: 11a/11b= 92:8 by glpc assay
(column C, 150°). Physical data for 11: glpc, t_r 8.6 (11b)
and 9.5 (11a) (column C, 150°); bp, 80° (bath temp, 2 mmHg);
ir (neat), 1746 (s, C=O) and 1235 cm^{-1} (m); nmr, 7.12 (m,
C_6H_5), 4.15 (m), 2.30-2.15 (m), 1.21 (m), 2.00 (s, trans
OCOCH$_3$), and 1.70 (s, cis OCOCH$_3$); MS (m/e), 176 (M$^+$).

Found: C, 75.1; H, 6.80. Calcd for $C_{11}H_{12}O_2$: C, 75.0;
H, 6.86.

B.3.8. 7-Acetoxynorcarane (12)— A solution of Cr^{II} acetate
(1.6 g, 9.5 mmol) in DMF-water (50 ml) was treated under
nitrogen with a solution of 7,7-dibromonorcarane 2 (0.60 g,
2.4 mmol) in DMF (2 ml) at 25°. The mixture was heated at
80° for 12 hr, cooled, and treated with water. Ethereal
extracts of this solution were washed with water, dried,
and freed of the solvent. By glpc assay (column C, 155°)
the residual liquid (0.30 g) contained the five components
in the ratio 6a/6b/12b/12a/2= 1:5:15:53:8 (t_r 4.2, 5.2, 6.7
7.7, and 13.5, respectively). The analytically pure sample
of 12 as the mixture of exo and endo isomers was prepared by
preparative tlc with benzene as an eluant followed by
evaporative distillation at 60° (bath temp, 2 mmHg).
Physical data for 12: tlc, R_f 0.45 (benzene); ir (neat)
(IR 35), 1741 (s, C=O) and 1230 cm^{-1} (s); nmr, 3.93 (t,
J_{cis}=7.5 Hz), 3.68 (t, J_{trans}=2.8 Hz), 2.04 (s, endo OCOCH$_3$),

1.94 (s, <u>exo</u> OCOC$\underline{H}_3$), and 1.77-1.20 (m, methylenes and methines).

Found: C, 69.9; H, 9.08. Calcd for $C_9H_{14}O_2$: 70.1; H, 9.15.

B.3.9. 9-Acetoxybicyclo[6.1.0]nonane (13)— A mixture of Cr^{II} acetate (2.9 g, 17.0 mmol), DMF (40 ml), and water (40 ml) was stirred under nitrogen at 25°. The resulting reddish-brown solution was treated with dibromide 3 (0.88 g, 3.2 mmol) and kept at 80° for 15 hr. Extractive workup furnished the monobromide 7b ($\underline{R}_f$ 0.8-0.95, 0.16 g, 25% yield) and the mixture of acetoxycyclopropane 13 ($\underline{R}_f$ 0.4-0.6, 0.26 g, 45% yield, 13a/13b=64:36 by glpc and nmr assay) by preparative tlc with benzene as an eluant. Physical data for 13: bp, 75° (bath temp, 1 mmHg); tlc, $\underline{R}_f$ 0.50 (benzene); glpc, $\underline{t}_r$ 6.0 (13b) and 6.6 (13a) (column C, 165°); ir (neat), 1748 (s, C=O) and 1225 cm^{-1} (s); nmr (NMR 39), 3.99 (t, $J_{\underline{cis}}$=7.6 Hz), 3.42 (t, $J_{\underline{trans}}$=3.0 Hz), 1.99 (s, <u>endo</u> OCOC$\underline{H}_3$), 1.94 (s, <u>exo</u> OCOC$\underline{H}_3$), and 1.50-0.89 (m, methylenes and methines).

Found: C, 72.7; H, 9.76. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 9.96.

B.3.10. 1-Acetoxy-2-n-hexylcyclopropane (14)— A solution of Cr^{II} acetate (3.8 g, 23 mmol) in 1:1 DMF-water (90 ml) was treated under nitrogen with dibromide 4 (1.6 g, 5.6 mmol) at 25°, and stirred at 75° for 18 hr. The resulting green solution was diluted with ether. The crude liquid (0.69 g, 63% yield) obtained on extractive workup contained the

three components in the ratio $\underline{8a}/\underline{8b}/\underline{14}= 24:27:49$ by glpc assay ($\underline{t}_r$ 11.0, 14.0, and 21.0, respectively, column D, $90°$). The isomeric ratio of $\underline{14}$ was calculated by careful glpc assay ($\underline{14a}/\underline{14b}= 87:13$, column A, $100°$). The analytical sample of $\underline{14}$ was obtained by preparative glpc (column F, $120°$) followed by distillation at $65°$ (bath temp, 1 mmHg). The physical data for $\underline{14}$: glpc, $\underline{t}_r$ 6.0 (column C, $155°$); ir (neat) (IR 38), 1748 (s, C=O) and 1232 cm^{-1} (m); nmr, 4.06 (m, $J_{\underline{cis}}$=6.3 Hz), 3.72 (m, $J_{\underline{trans}}$=3.8 Hz), 1.99 (s, $\underline{cis}$ OCOC$\underline{H}_3$), 1.97 (s, $\underline{trans}$ OCOC$\underline{H}_3$), and 1.34-0.10 (m, methylenes and methines).

Found: C, 71.7; H, 11.1. Calcd for $C_{11}H_{20}O_2$: C, 71.7; H, 10.9.

B.3.11. 1-Cyano-2-phenylcyclopropane (15)— A solution of Co^{II} chloride (10.0 g, 77 mmol) and potassium cyanide (30 g, 0.46 mol) in dry DMSO (200 ml) was stirred at $25°$ under nitrogen and treated with $\underline{gem}$-dibromocyclopropane $\underline{1}$ (5.0 g, 18 mmol). The solution was stirred at $70°$ for 16 hr, cooled, poured into water, and extracted with ether. The extracts were washed with water, dried and freed of the solvent. The residual liquid (2.7 g, 86% yield) consisted of phenyl-allene (18 rel%), the $\underline{trans}$-monobromide $\underline{5a}$ (10 rel%), $\underline{cis}$-monobromide $\underline{5b}$ (31 rel%), and the cyanocyclopropane $\underline{15}$ (41 rel%). Physical data for the mixture of $\underline{15a}$ and $\underline{15b}$ ($\underline{15a}/\underline{15b}= 81:19$ by glpc assay): bp, $75°$ (bath temp, 2 mmHg).

Found: C, 83.8; H, 6.09; N, 9.52. Calcd for $C_{10}H_9N$: C, 83.9; H, 6.34; N, 9.78.

B.3.12. 7-Cyanonorcarane (16)— A mixture of Co^{II} chloride
(1.6 g, 12 mmol), potassium cyanide (5.0 g, 77 mmol), and
DMSO (150 ml) was stirred under nitrogen at 25° for 30 min.
The solution was treated with dibromide 2 (0.80 g, 3.2 mmol)
and stirred at 70° for 16 hr, cooled, and diluted with ether.
The ethereal extracts were washed with water, dried, and
freed of the solvent. The residual liquid (0.40 g, 74%
yield) consisted of the isomers of monohalide 6a and 6b
(6a/6b= 1:5) and the isomers of cyanocyclopropane 16a and
16b (16a/16b= 80:20) by glpc assay (column C, 150°). The
mixture of cyanide was separated by preparative glpc (column
G, 150°) as a colorless liquid: glpc, t_r 11.0 (16b) and
12.7 (16a) (column G, 150°); bp, 85° (bath temp, 4 mmHg);
ir (neat) (IR 36), 2235 (16a), 2210 (16b) cm^{-1}; nmr, 2.30-
1.03 (m, methylenes and methines).

   Found: C, 79.2; H, 9.13; N, 11.4. Calcd for $C_8H_{11}N$:
C, 79.3; H, 9.15; N, 11.6.

B.3.13. 9-Cyanobicyclo[6.1.0]nonane (17)— A mixture of
Co^{II} chloride (1.4 g, 0.11 mol), potassium cyanide (4.5 g,
69 mmol), and DMSO (200 ml) was stirred under nitrogen at
25° for 30 min. The blue solution was treated with dibromide
3 (0.80 g, 2.8 mmol) and kept at 80° for 16 hr. Extractive
workup furnished a liquid that was submitted to preparative
tlc with benzene-hexane (1:1) as an eluant. The main band
(R_f 0.5-0.7) afforded the cyanocyclopropane (0.33 g, 74%
yield, 17a/17b= 60:40 by glpc assay) as a colorless liquid:
t_r 16.0 (17b) and 19.5 (17a) (column C, 172°); bp, 90°

(bath temp, 3 mmHg); ir (neat), 2245 (17a) and 2215 cm^{-1} (17b); nmr, 2.11 (m, methines), 1.46 (m, methylenes), and 0.70 (m, methine).

Found: C, 80.9; H, 9.94; N, 9.36. Calcd for $C_{10}H_{15}N$: C, 80.5; H, 10.1; N, 9.39.

B.3.14. 1-Cyano-2-n-hexylcyclopropane (18)— A mixture of Co^{II} chloride (7.7 g, 60 mmol), potassium cyanide (23 g, 0.37 mol), and DMSO (200 ml) was stirred under nitrogen at 25°. The resulting mixture was treated with dibromide 4 (4.5 g, 16 mmol), heated at 75° for 16 hr and diluted with ether. The ethereal extracts were washed with water, dried, and freed of the solvent. The resulting yellow liquid contained two isomers of monobromide 8a and 8b (8a/8b= 54:46 by glpc assay) and two isomers of cyanocyclopropane 18a and 18b (18a/18b= 57:43 by glpc assay). It was separated into two fractions by preparative tlc with 1:1 benzene-hexane as an eluant. The faster-moving liquid (R_f 0.65-0.85; 1.9 g, 58% yield) was a mixture of 8a and 8b. The slower-moving liquid (R_f 0.3-0.5; 0.35 g, 15% yield) consisted of two isomers of the cyanocyclopropane 18. Physical data for 18: bp, 75° (bath temp, 1 mmHg); ir (neat) (IR 39), 2245 (18a) and 2225 cm^{-1} (18b); nmr, 2.08 (m, methine), 1.33 (m, methyl, methylenes and methine), and 0.90 (m, methine).

Found: C, 79.6; H, 11.3; N, 9.06. Calcd for $C_{10}H_{17}N$: C, 79.4; H, 11.3; N, 9.26.

B.3.15. General Procedure for the Transformation of Monobromocyclopropanes to Cyanocyclopropanes— A solution of Co^{II} chloride (2 mol) and potassium cyanide (12 mol) in dry DMSO was stirred under nitrogen at 25° for 30 min. The mixture was treated with *cis* or *trans* pure monobromide (1 mol) separately, stirred at 70-80° for 15 hr, cooled and poured into water. The obtained liquid on extractive workup furnished the mixture of cyanocyclopropane, the isomeric ratio which is determined by glpc analysis (column C). The result is shown in Table B-6.

B.3.16. General Procedure for the Transformation of Cyclopropyl Cyanides to the Corresponding Cyclopropyl Methyl Ketones— A solution of cyclopropyl cyanides (1.0 mol, the ratio of the isomers had been determined by glpc (column C)) in absolute ether was added to a solution of methylmagnesium iodide in ether (2.0 mol). The reaction mixture was treated with saturated aqueous ammonium chloride, and the organic phase was washed with water, dried, and freed of the solvent. The isomeric ratio of the crude methyl ketone was determined by glpc assay (column C). The analytical sample was prepared by preparative glpc (column B) and distillation.

B.3.17. (2-Phenyl)-cyclopropyl Methyl Ketone (19)— A solution of (2-phenyl)cyclopropyl cyanide 15 (0.18 g, 1.26 mmol, *trans* pure) in ether (5 ml) was added to a solution of methylmagnesium iodide in ether (3.0 mmol) at 45°, and the mixture was heated at 45° for 13 hr. The crude liquid on extractive workup afforded the ketone 19a (0.14 g, 67%

yield, <u>trans</u> pure).

<u>B.3.18. Methyl 7-Norcaranyl Ketone (20)</u>— A solution of
norcaranyl cyanide 16 (0.35 g, 2.9 mmol, 16a/16b= 7:3) in
ether (10 ml) was added to a solution of methylmagnesium
iodide (6.0 mmol) at 25°, and kept for 30 min. Extractive
workup furnished the ketone (0.25 g, 62% yield, 20a/20b=
81:19 by glpc assay) as a colorless liquid: bp 54° (bath temp,
0.5 mmHg); ir (neat), 1689 cm^{-1} (s, C=O); nmr (NMR 40), 2.17
(s, <u>endo</u> $COCH_3$), 2.14 (s, <u>exo</u> $COCH_3$), and 1.95-1.05 (m,
methylenes and methines);

Found: C, 78.1; H, 10.3. Calcd for $C_9H_{14}O$: C, 78.2;
H, 10.2.

<u>B.3.19. 9-Acetylbicyclo[6.1.0]nonane (21)</u>— A solution of
9-cyanobicyclo[6.1.0]nonane 17 (1.8 g, 12 mmol, 17a/17b=
60:40) in ether (15 ml) was added to a solution of methyl-
magnesium iodide (20 mmol) at 25° and the mixture was stirred
at 45° for 10 hr. Short-pass distillation of the residual
liquid afforded the glpc pure ketone 21 (1.1 g, 65% yield,
21a/21b= 85:15) as a colorless liquid: bp 64° (bath temp,
0.5 mmHg); ir (neat) (IR 37), 1689 cm^{-1} (s, C=O); nmr, 2.17
(s, <u>endo</u> $COCH_3$), 2.14 (s, <u>exo</u> $COCH_3$), and 2.00-0.70 (m,
methylenes and methines);

Found: C, 79.2; H, 11.1. Calcd for $C_{11}H_{18}O$: C, 79.5;
H, 10.9.

<u>B.3.20. (2-n-Hexyl)-cyclopropyl Methyl Ketone (22)</u>—
Methylmagnesium iodide (30 mmol) was treated with a solution
of 2-<u>n</u>-hexyl-cyclopropyl cyanide (0.20 g, 1.3 mmol, 18a/18b=

57:43) in ether at 45°, and the solution was kept at 45° for 2 hr, cooled, and treated with saturated aqueous ammonium chloride. Ethereal extracts were washed with water, dried, and freed of the solvent. The liquid remaining was evaporatively distilled at 50-60° (bath temp, 0.5 mmHg) to provide the ketone 22 (0.15 g, 68% yield, 22a/22b= 60:40) as a colorless liquid: bp 52° (bath temp, 0.5 mmHg); ir (neat) (IR 40), 1700 cm^{-1} (s, C=O); nmr, 2.18 (s, cis COCH$_3$), 2.14 (s, trans COCH$_3$), and 1.98-0.91 (m, methylenes and methines);

Found: C, 78.4; H, 11.9. Calcd for C$_{11}$H$_{20}$O: C, 78.5; H, 12.0.

B.3.21. General Procedure for the Transformation of Cyclo-propanecarboxylic Acids to the Corresponding Cyclopropyl Methyl Ketones— A solution of cyclopropanecarboxylic acids (cis, trans mixture, the ratio of cis/trans had been determined) in absolute ether was treated with excess amounts of methyl-lithium (3 equiv) in ether under gentle refluxing. The reaction mixture was treated with saturated aqueous ammonium chloride. Ethereal extracts of the reaction mixture was washed with water, dried, and freed of the solvent. A cis, trans mixture of cyclopropyl methyl ketone was obtained by preparative glpc (column G). The ratio of cis, trans isomers was determined by glpc (column C) and nmr signal of methyl protons.

B.3.22. Transformation of Norcarane-7-carboxylic Acid 24 to Methyl Norcaranyl Ketone (20)— A solution of carboxylic acid 24 (0.83 g, 5.9 mmol, exo/endo= 88:12) in absolute

ether (0.8 $\underline{M}$, 25 ml, 20 mmol) under refluxing. Extractive workup afforded a liquid (0.61 g) which was submitted to preparative glpc. The mixture of ketone 20 (0.38 g, 48% yield, 20a/20b= 85:15) was obtained as a liquid. Physical data was identified with the sample obtained from the corresponding cyanocyclopropane.

Found: C, 78.3; H, 10.2. Calcd for $C_9H_{14}O$: C, 78.2; H, 10.2.

B.3.23. Transformation of 2,3-Methylenencnanoic Acid 25 to Corresponding Methyl Ketone (22)— A solution of carboxylic acid 25 (2.1 g, 12.0 mmol, $\underline{trans}/\underline{cis}$= 32:68) in ether (30 ml) was treated with methyllithium in ether (0.8 $\underline{M}$, 40 ml, 32 mmol) under gentle refluxing and stirred at 26° for 30 min. The mixture was diluted with ether, and the ethereal extracts were washed with saturated aqueous ammonium chloride and water, dried, and freed of the solvent. The residual liquid (1.8 g) was submitted to preparative glpc. The mixture of ketone 22 (1.3 g, 65% yield, 22a/22b= 66:34) was obtained as a liquid which was identified with sample obtained in the reaction of cyanocyclopropane with methylmagnesium iodide.

Found: C, 78.5; H, 12.0. Calcd for $C_{11}H_{20}O$: C, 78.5; H, 12.0.

B.3.24. Transformation of 2-Phenylcyclopropanecarboxylic Acid 23 to (2-Phenyl)-cyclopropyl Methyl Ketone (19)— A solution of carboxylic acid 23 (0.7 g, 4.3 mmol, $\underline{trans}/\underline{cis}$= 57:43) in ether (10 ml) was treated under nitrogen with methyllithium in ether (0.8 $\underline{M}$, 15 ml, 12 mmol) at room temp.

The reaction mixture was stirred at 25° for 2 hr, treated with saturated aqueous ammonium chloride. Ethereal extracts of this entire mixture were washed with water, dried, and freed of the solvent. Short-pass distillation of the residual liquid provided the glpc pure ketone 19 (0.54 g, 75% yield, 19a/19b= 60:40) as a colorless liquid: bp 83° (bath temp, 1 mmHg).

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SPECTRA

(1) Nuclear Magnetic Resonance Spectra

(2) Infrared Spectra

1

2

CHART S-601

5

THPO～～CHO

500   400   300   200   100   0 Hz

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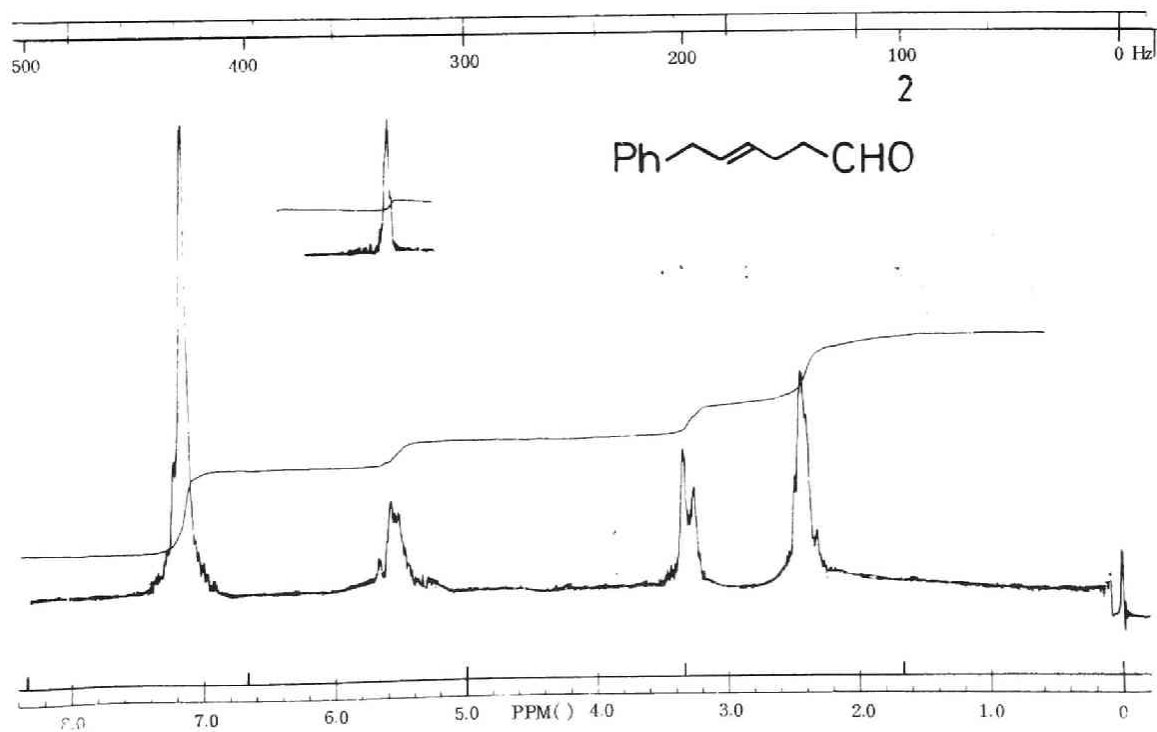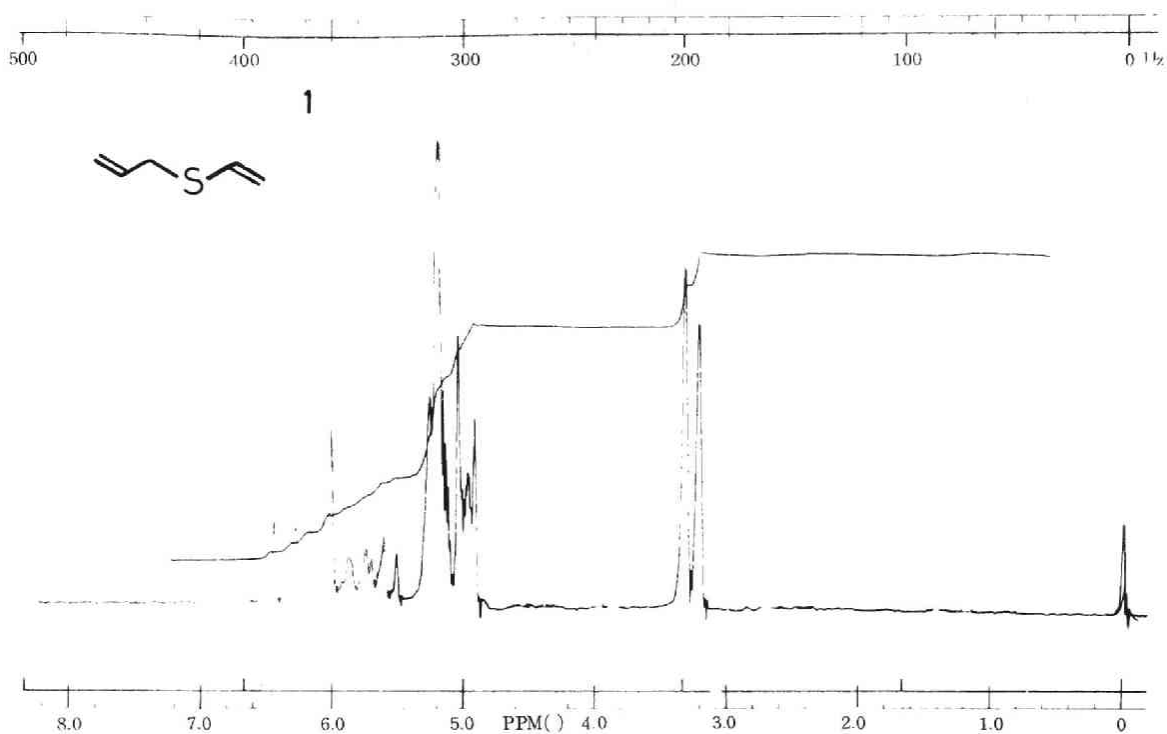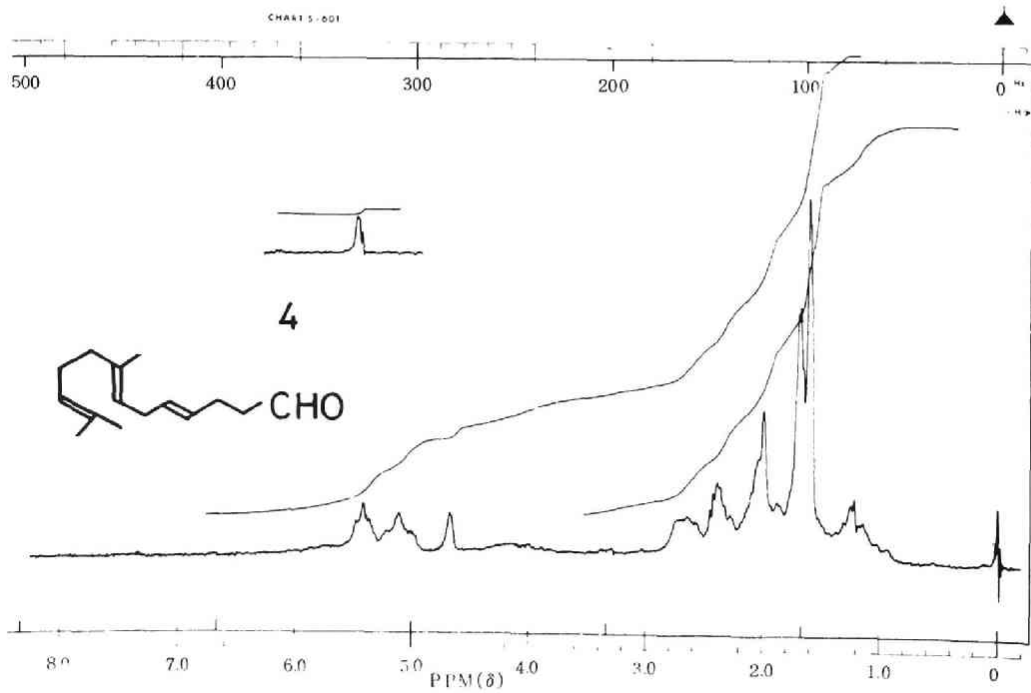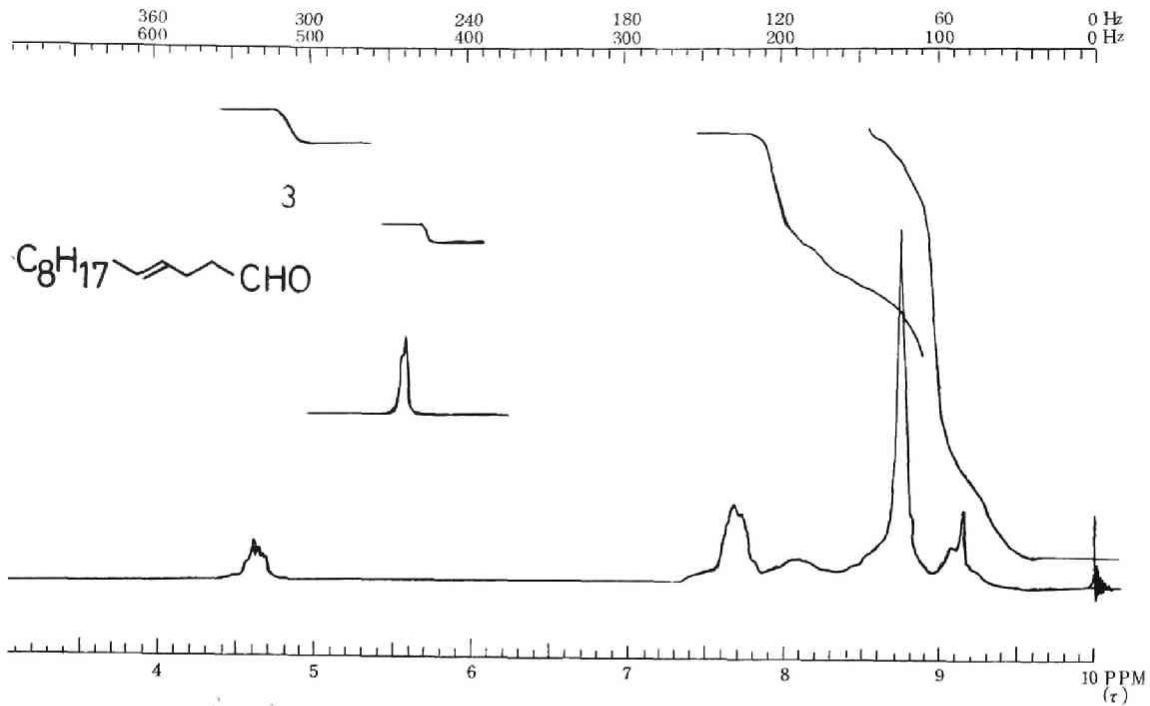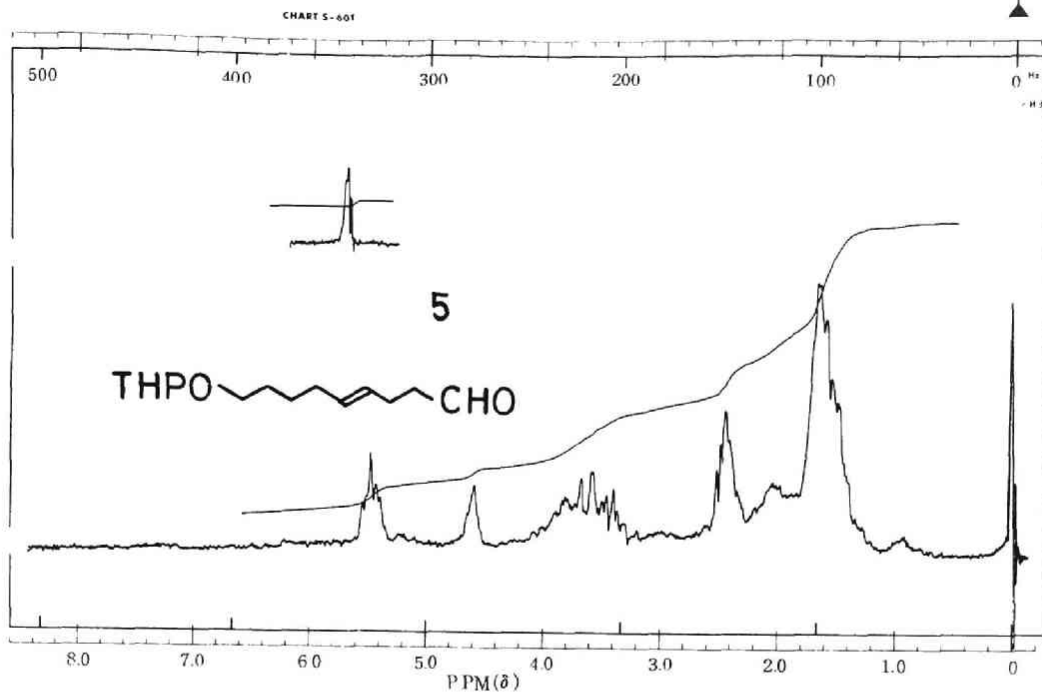
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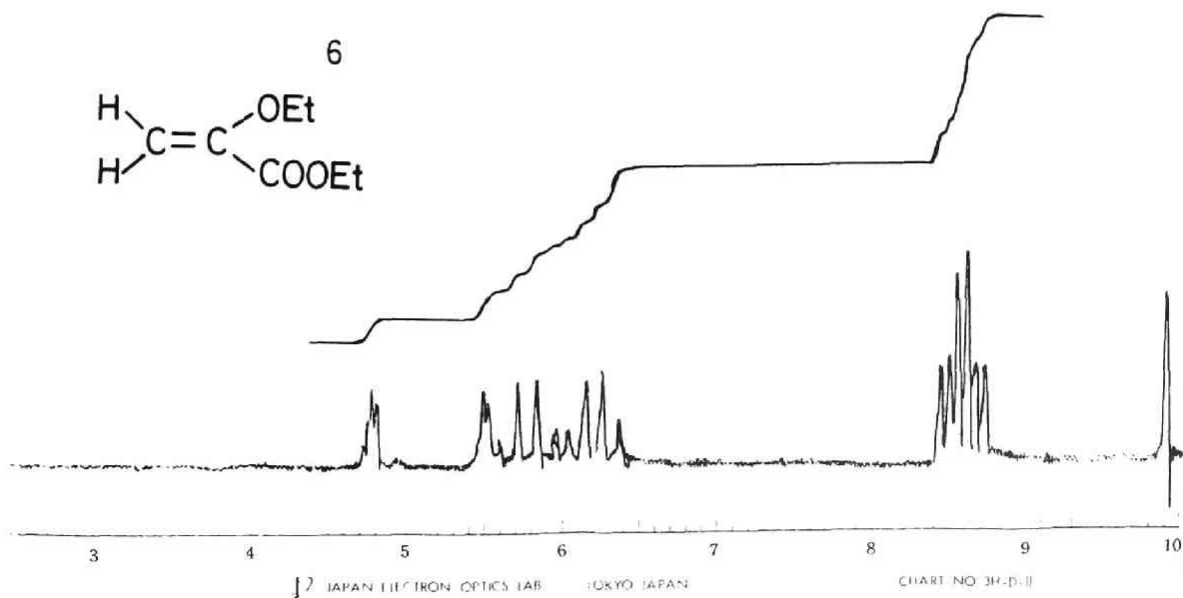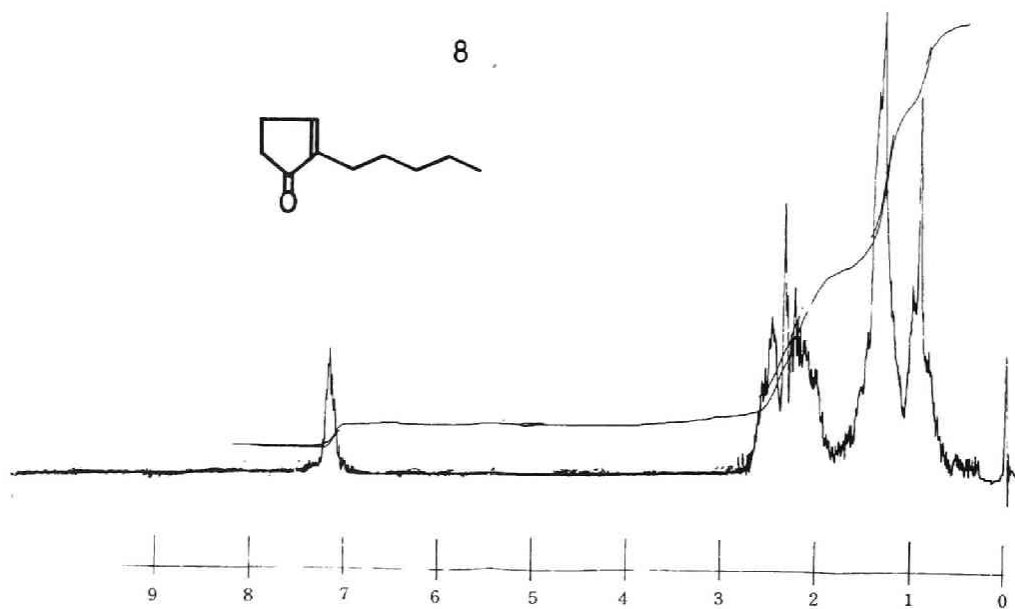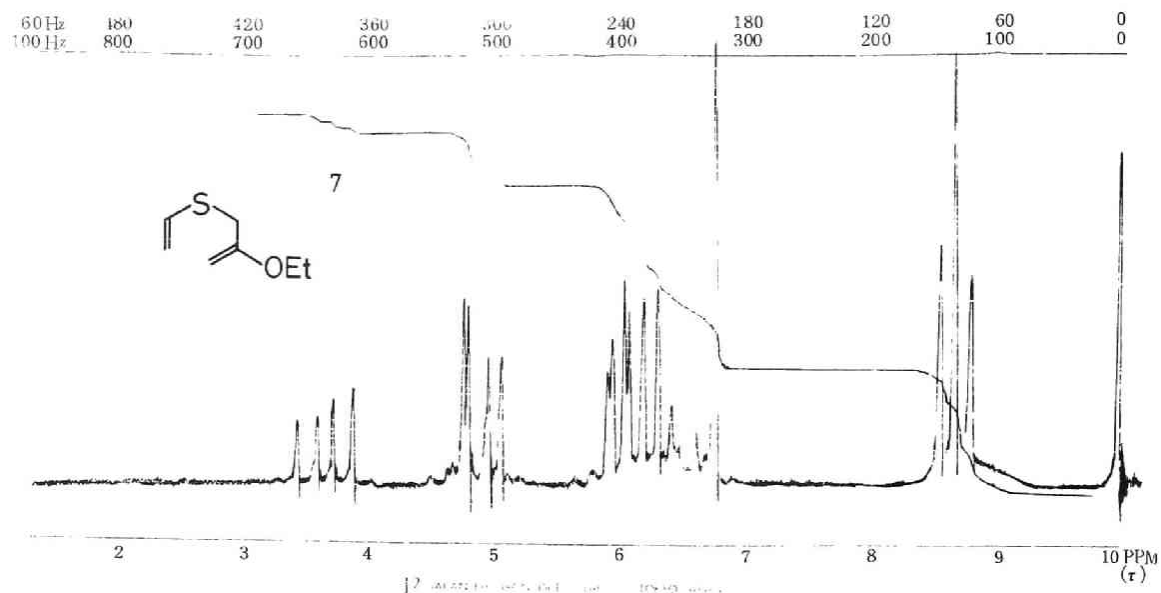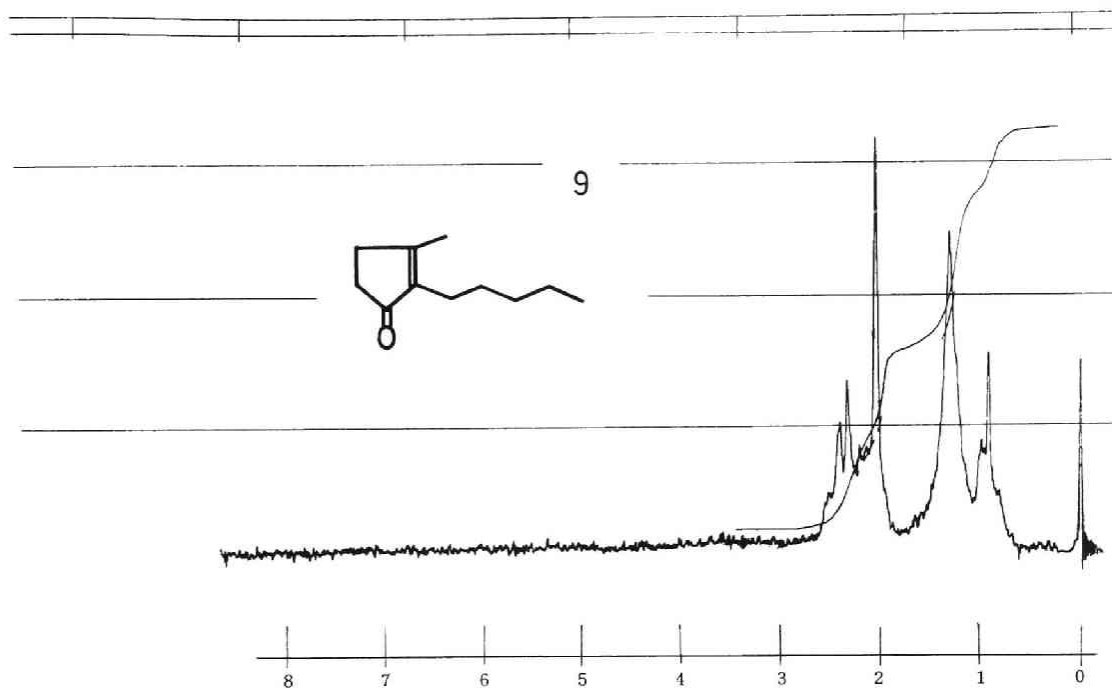
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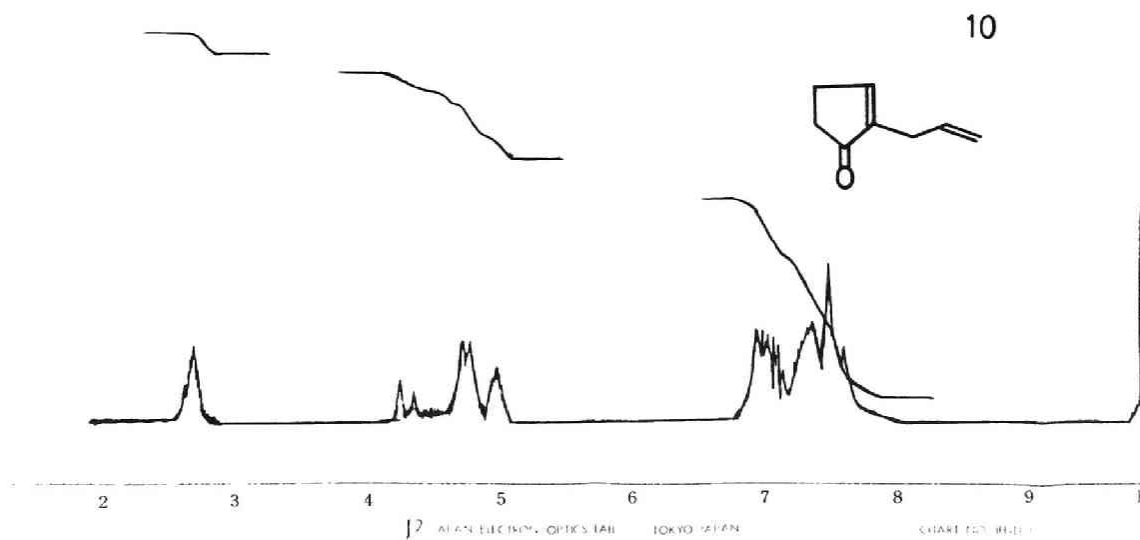
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　C=C
H　　COOEt

3   4   5   6   7   8   9   10

JAPAN ELECTRON OPTICS LAB   TOKYO JAPAN   CHART NO 3R-D-II

7

8

9

60 MHz	480	420	360	300	240	180	120	60
100 MHz	800	700	600	500	400	300	200	100

10

J2 AEAN ELECTRON OPTICS LAB   TOKYO JAPAN   CHART

13

14

15

16

17

EtO—O—n-C$_8$H$_{17}$

| 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 |

| 60MHz: | 480 | 420 | 360 | 300 | 240 | 180 | 120 | 60 | 0 Hz |
| 100MHz: | 800 | 700 | 600 | 500 | 400 | 300 | 200 | 100 | 0 Hz |

18

EtO—O—CH$_2$Ph

| 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

JAPAN ELECTRON OPTICS LAB   TOKYO JAPAN   CHART NO 3H-D-II   PPM(τ)

CHART 5-60T

20

MeS–S–n-C₈H₁₇

21

MeS–S–n-C₈H₁₇

22

23

24

25

CHART S-60T

26

n-C$_8$H$_{17}$C CH$_3$
||
O

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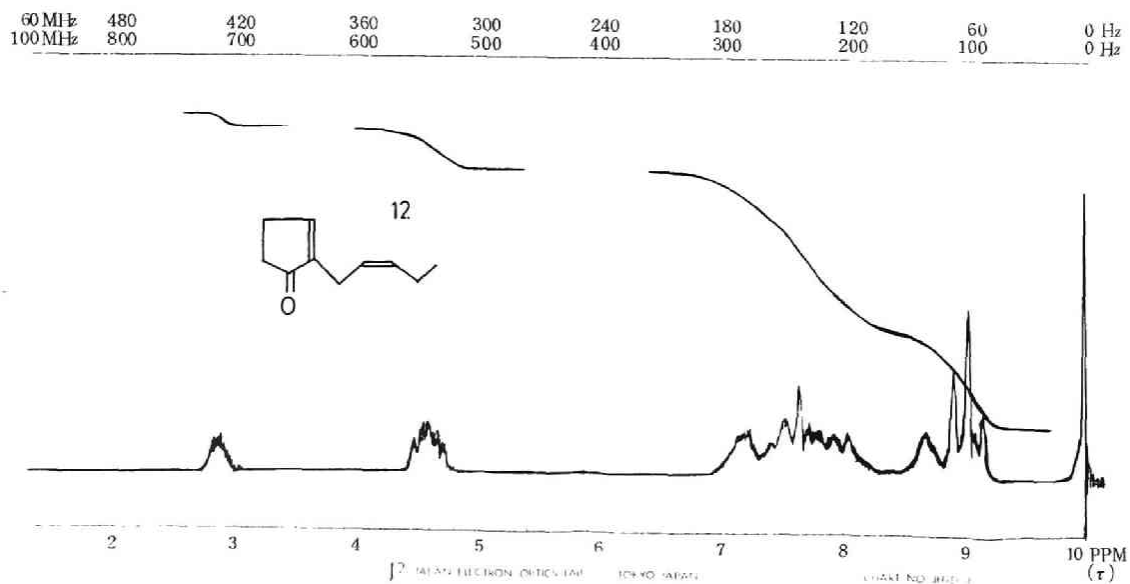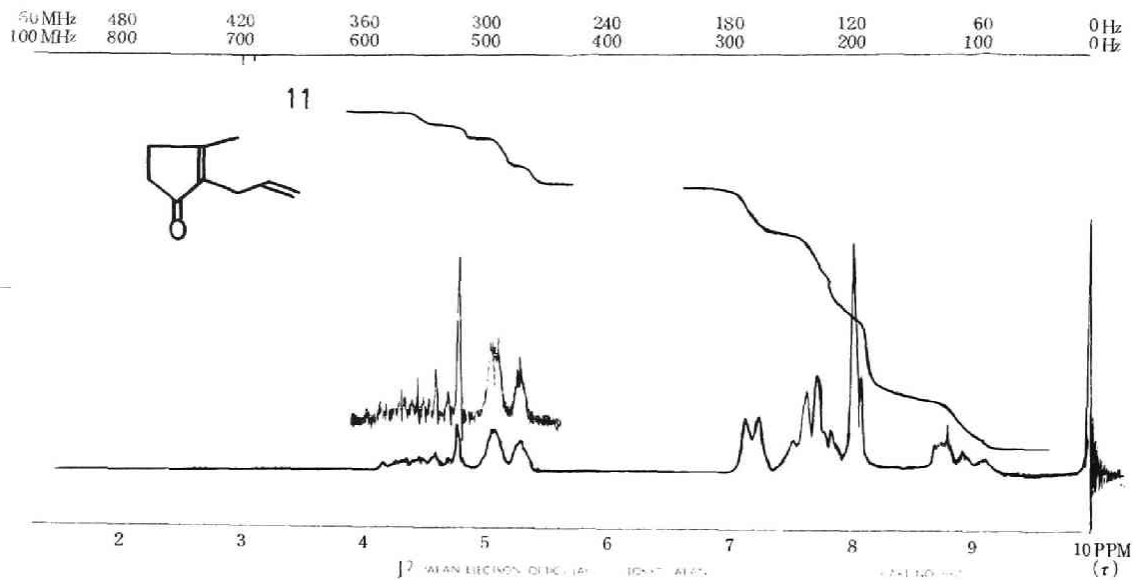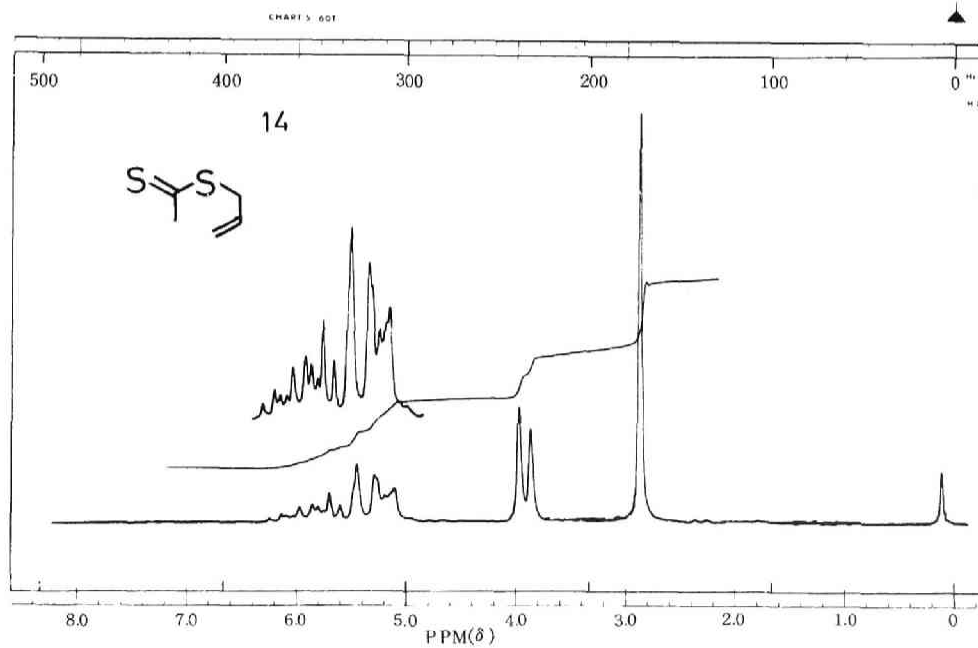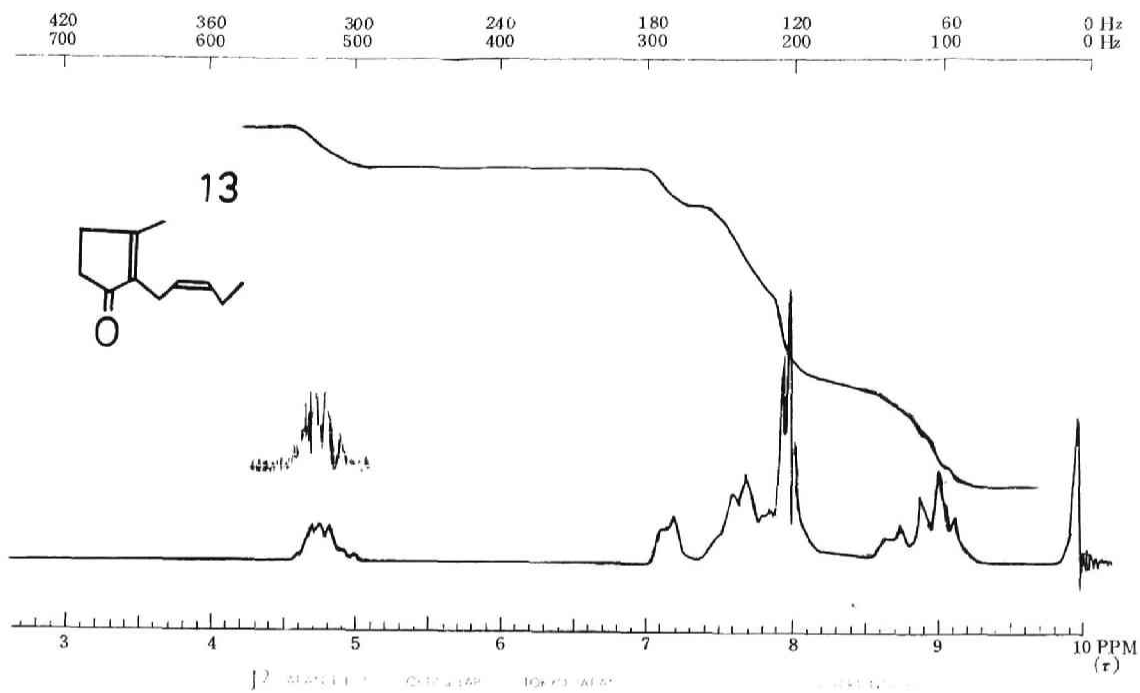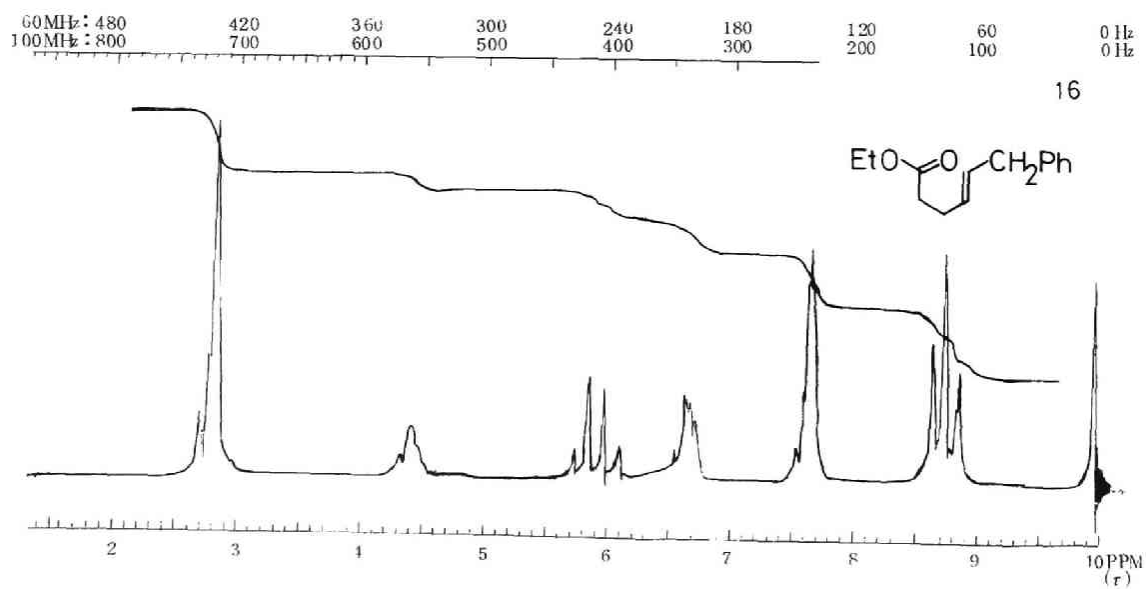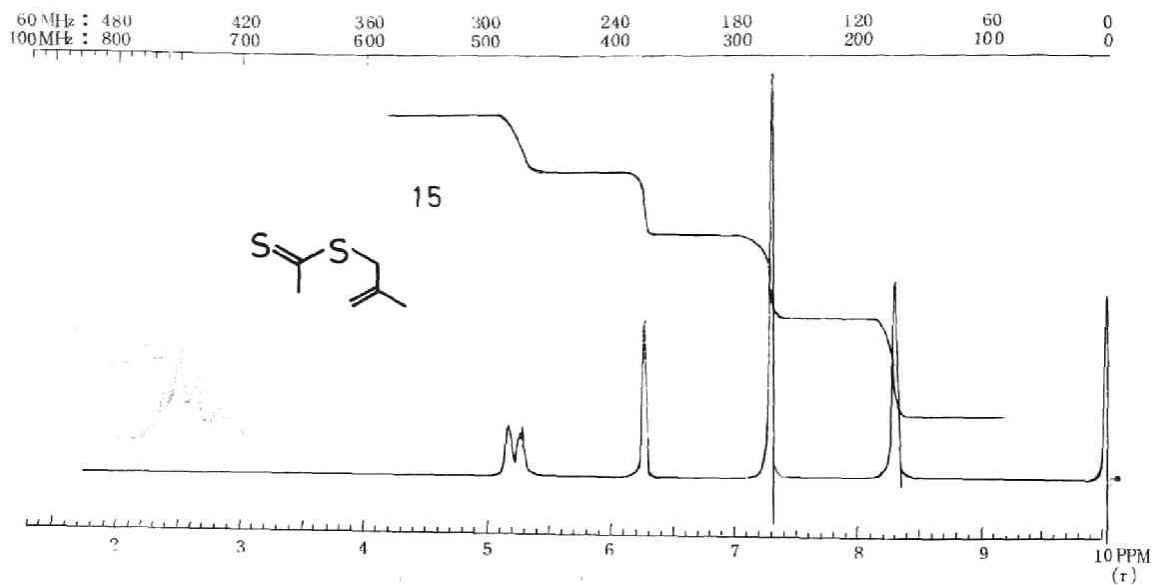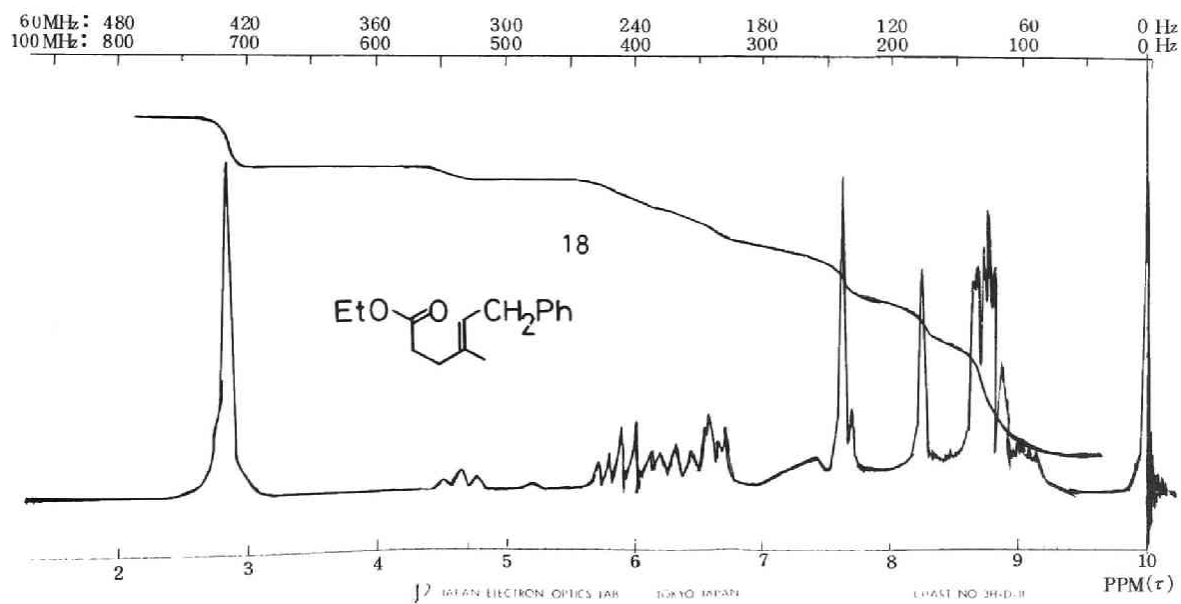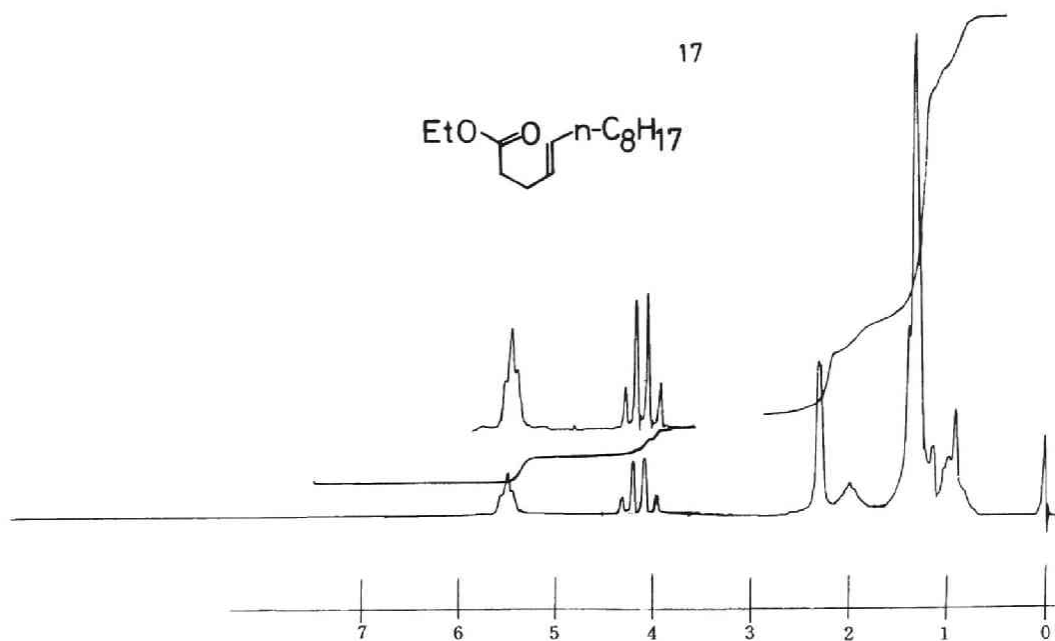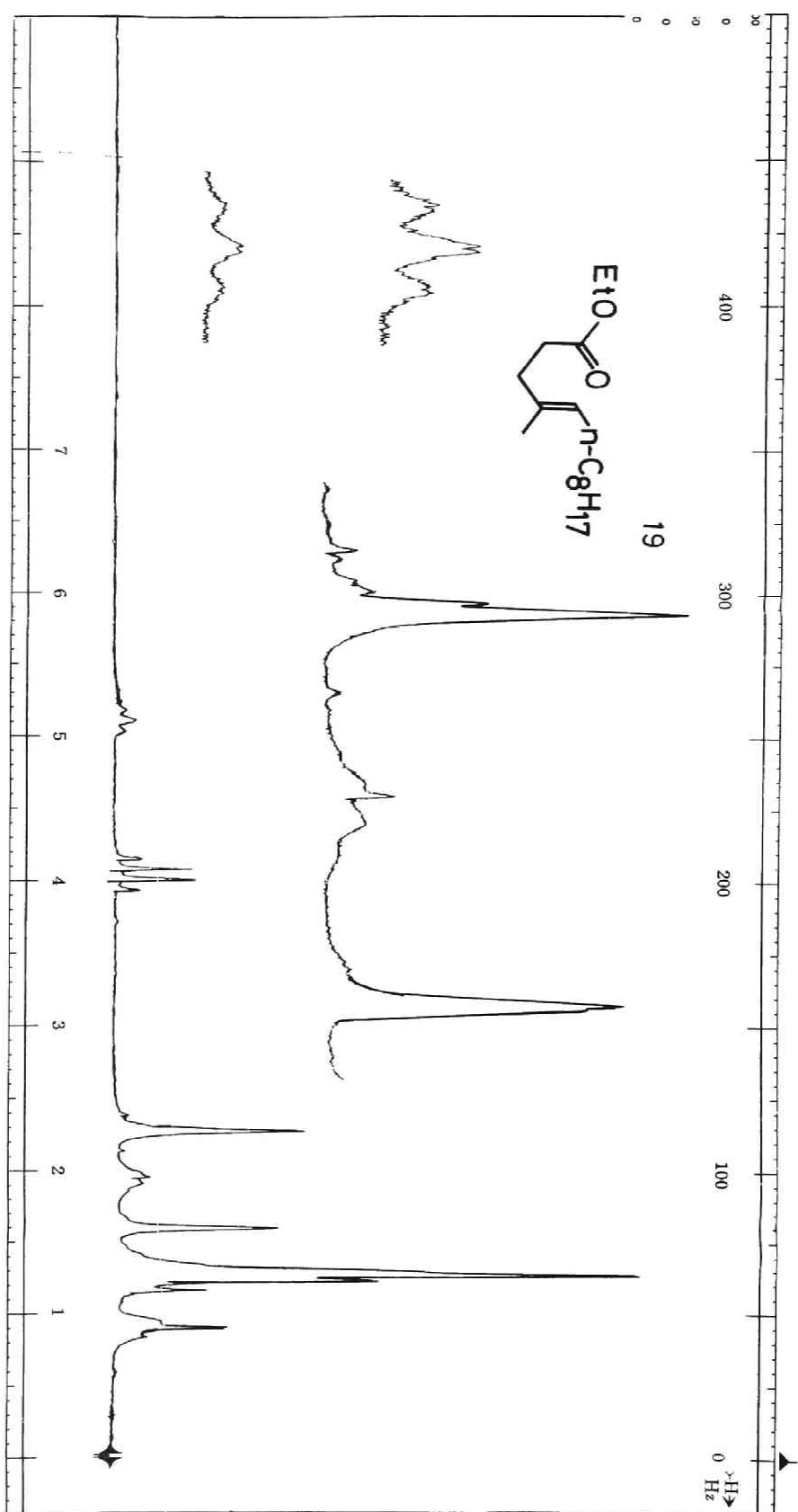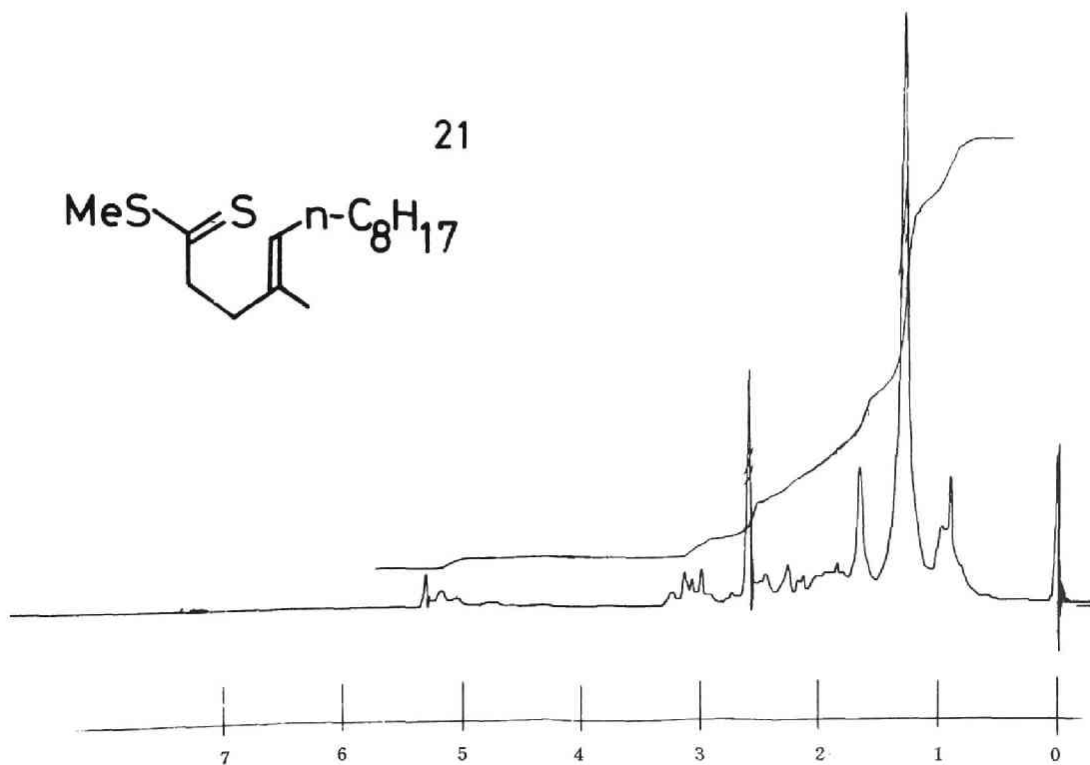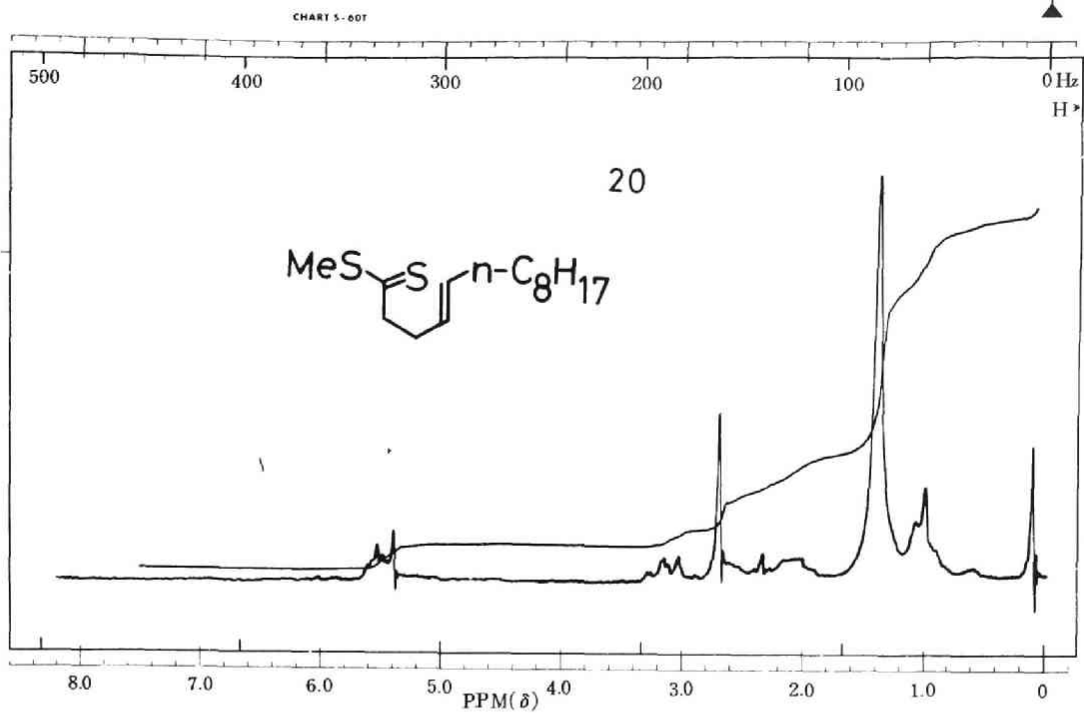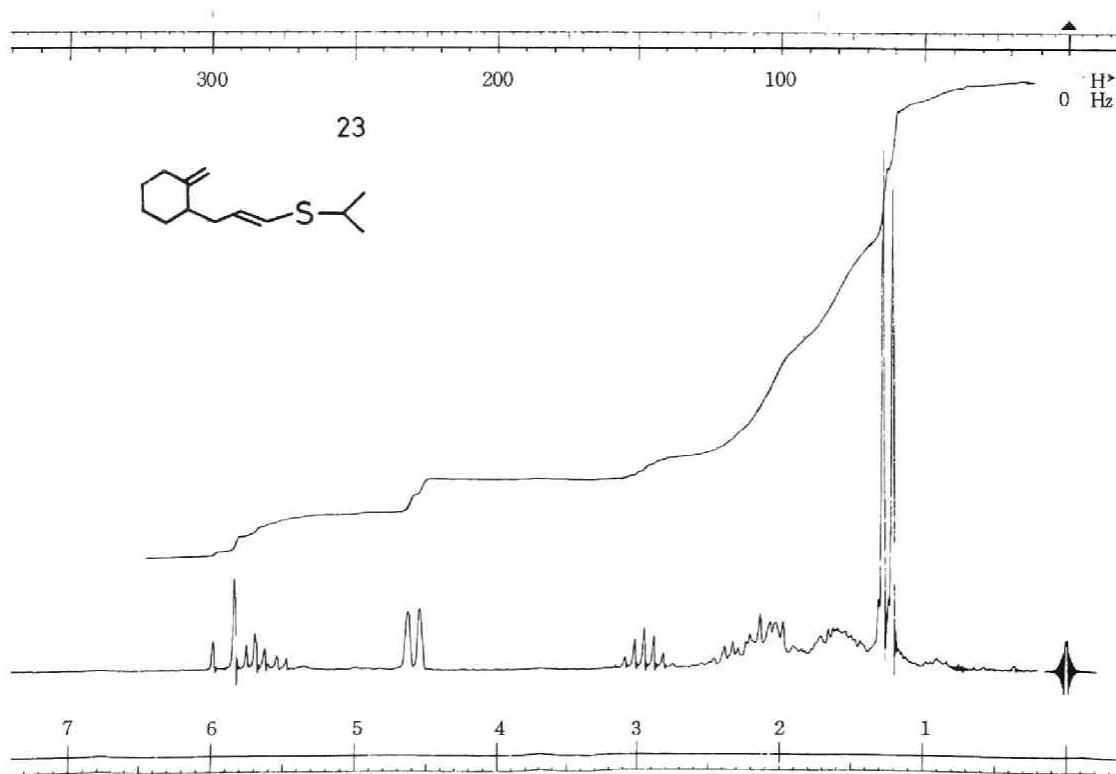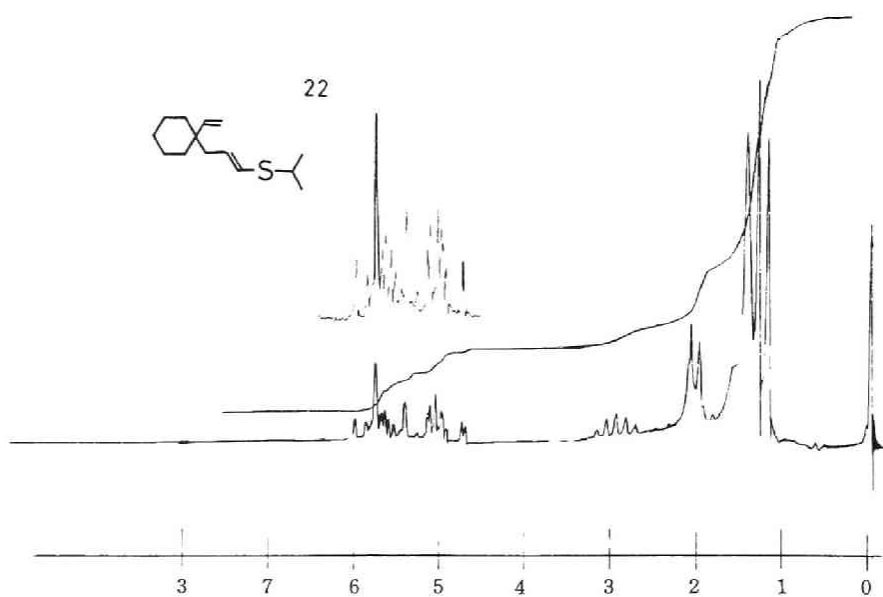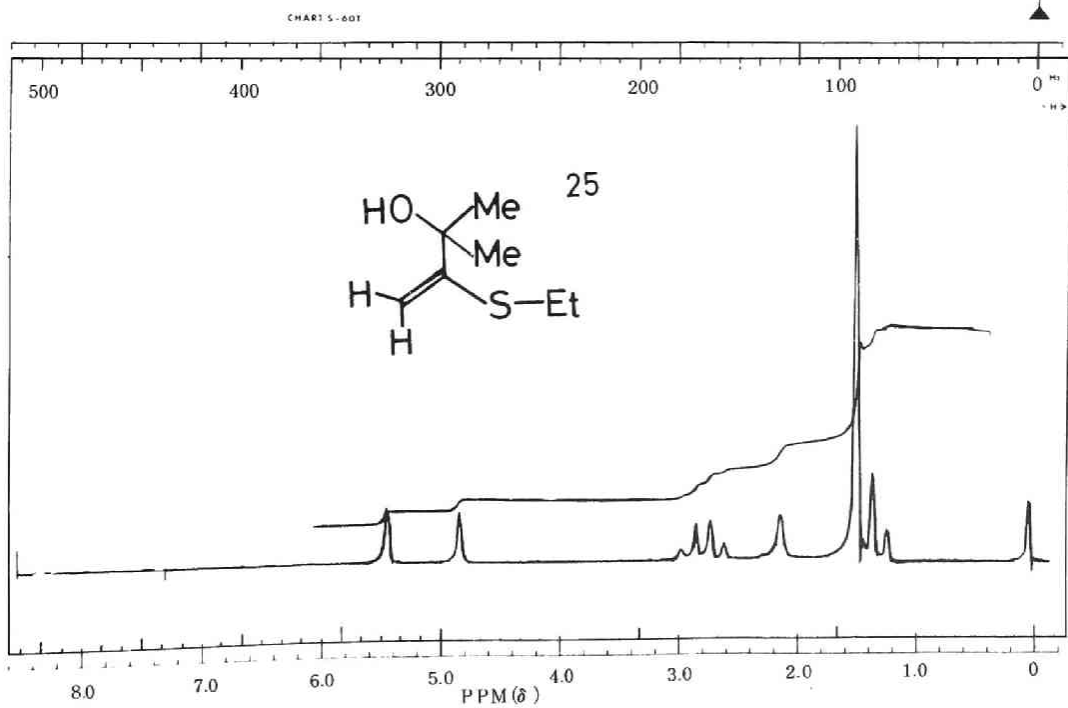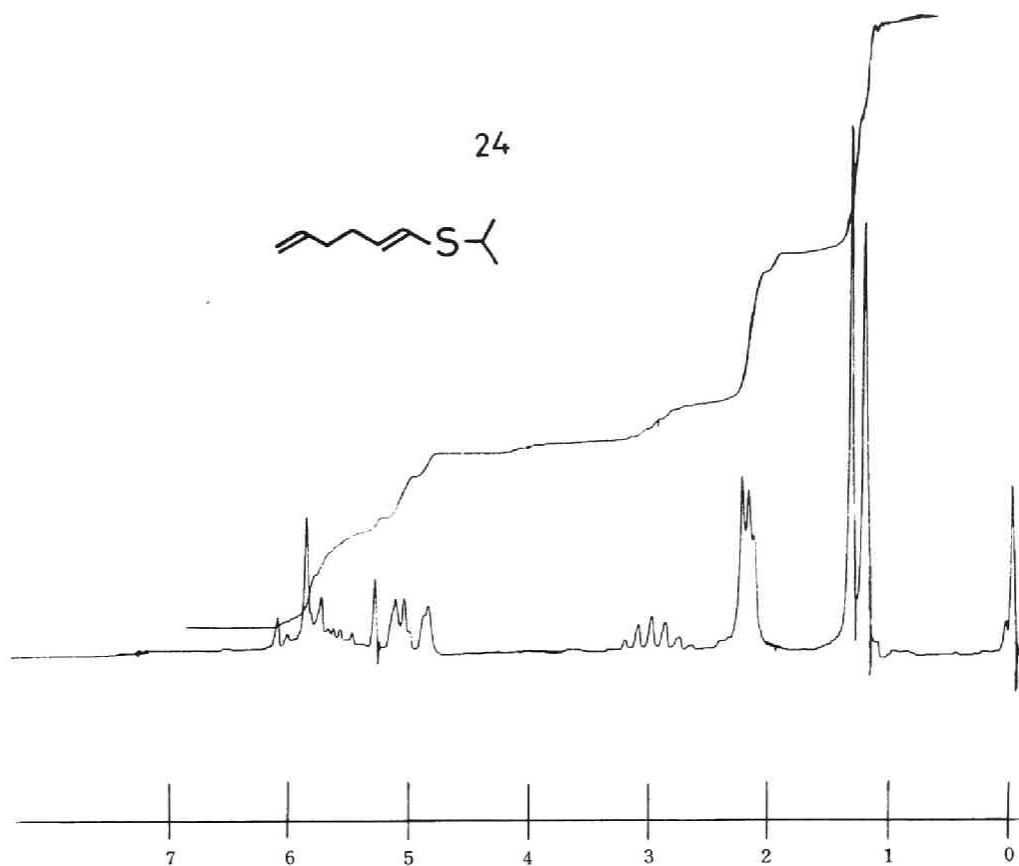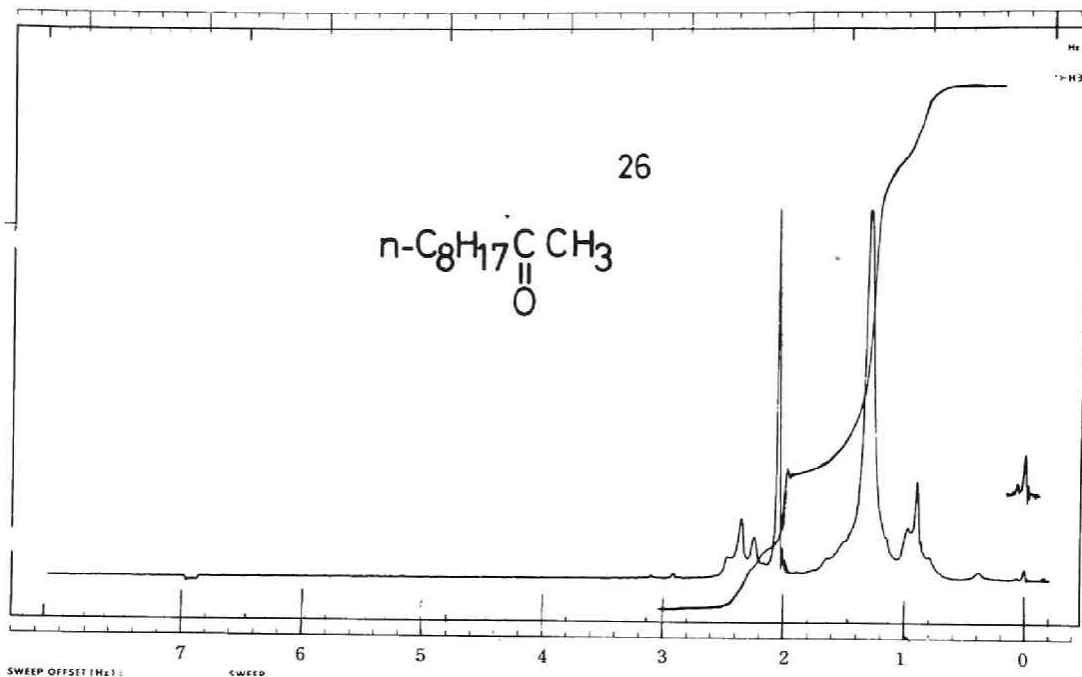
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| 600 | 500 | 400 | 300 | 200 | 100 | 0 Hz |

7   6   5   4   3   2   1   0

27

n-C$_9$H$_{19}$C-n-C$_8$H$_{17}$
||
O

4   5   6   7   8   9   10 PPM
(τ)

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28

29

$PhCH_2 \overset{\displaystyle C}{\underset{\displaystyle O}{\|}} -n-C_8H_{17}$

CHART S-60T

31

$$Ph-\overset{\displaystyle OH}{\underset{}{C}}H-\overset{\displaystyle }{\underset{\displaystyle O}{C}}-CH_3$$

32

$$CH_3(CH_2)_7\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-\underset{\underset{O}{||}}{C}CH_3$$

| 60 MHz | 480 | 420 | 360 | 300 | 240 | 180 | 120 | 60 |
| 100 MHz | 800 | 700 | 600 | 500 | 400 | 300 | 200 | 100 |

33

Ph — C(=O) — CH(OH) — Ph

34

$CH_3(CH_2)_7CH_2\underset{\underset{OOH}{||}}{C}CHPh$

35

$CH_3(CH_2)_7CH_2\underset{\underset{OOH}{||}}{C}CH(CH_2)_7CH_3$

60 MHz:	480	420	360	300	240	180	120	60
100 MHz:	800	700	600	500	400	300	200	100

36

60 MHz:	480	420	360	300	240	180	120	60
100 MHz:	800	700	600	500	400	300	200	100

37

PhCH₂-C-CH=CHMe

38

$PhCH_2CCH=CHPh$

(O below C)

39

(cyclooctyl)–OCCH₃ with O below C

120   360   300   240   180   120   60   ocps
'00   600   500   400   300   200   100   ocps

$\mathcal{V}$ JAPAN ELECTRON OPTICS LAB   TOKYO JAPAN   CHART NO. 3H-D

10

11

MeS—⟨S⟩—n-C₈H₁₇

12

EtO—⟨O⟩—n-C₈H₁₇

16

17

18

19

0173

n-C₈H₁₇CCH₃
‖
O

20

0212

21

0324

PhCH₂C-n-C₈H₁₇
‖
O

(cm⁻¹)

22

Ph—CH(OH)—C(=O)—CH₃

23

Ph—CH₂—C(=O)—CH(OH)—Ph

24

Ph—CH=CH—C(=O)—CH₃

25

PhCH₂CCH=CHPh
       ‖
       O

26

27

28

29

30

31

n-C₆H₁₃ OCOCH₃
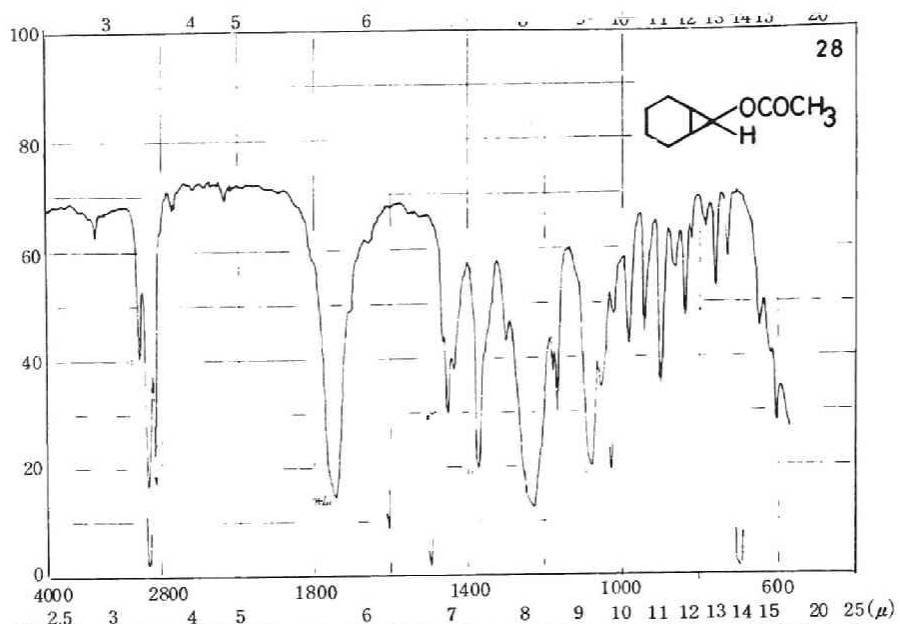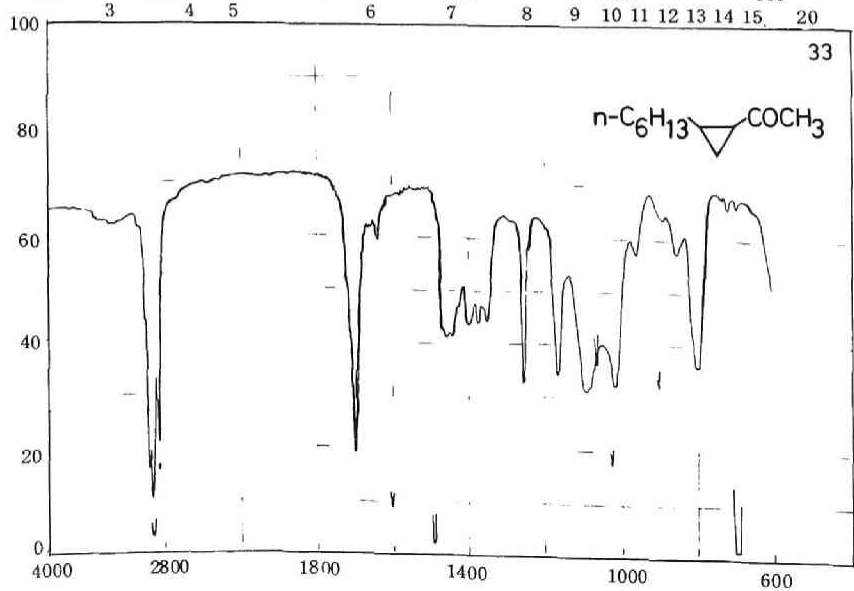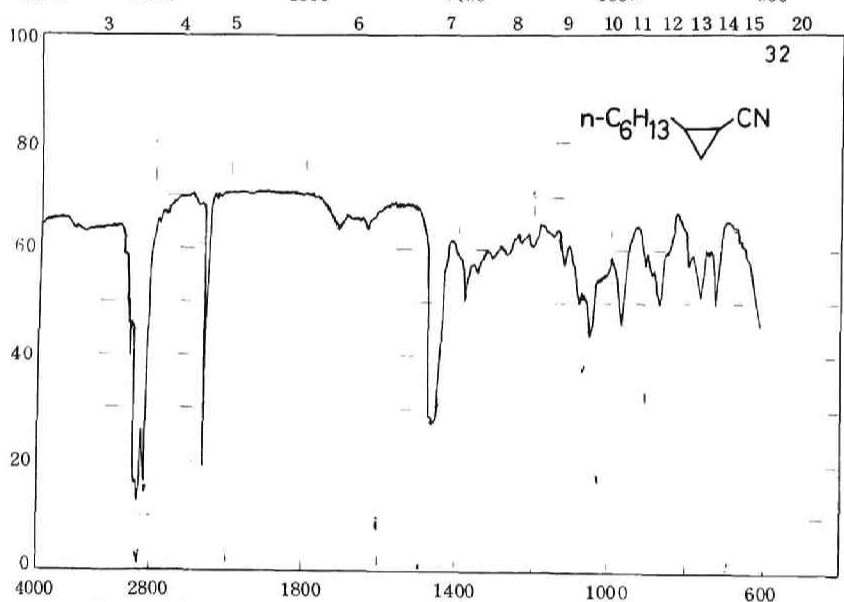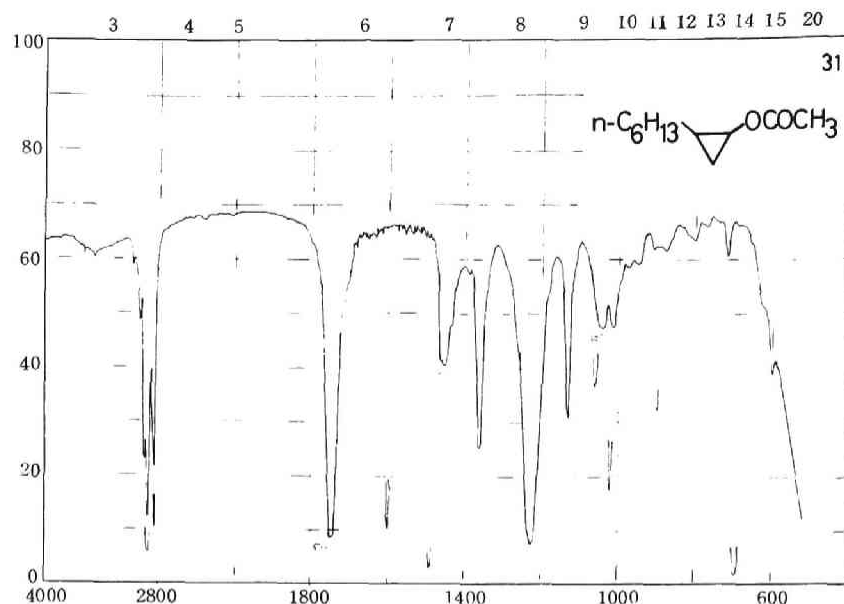
32

n-C₆H₁₃ CN

33

n-C₆H₁₃ COCH₃

PUBLICATION LIST

Parts of the present thesis have been published in the following journals.

Chapter 2.   J. Amer. Chem. Soc., 95, 2693 (1973).

Chapter 3.   J. Amer. Chem. Soc., 95, 4446 (1973).

Chapter 4.   J. Amer. Chem. Soc., 95, 5803 (1973).

Chapter 5.   J. Amer. Chem. Soc., 95, 7926 (1973);

Bull. Chem. Soc. Japan in press.

Chapter 6.   J. Amer. Chem. Soc., 95, 2694 (1973).

Appendix A.   Bull. Chem. Soc. Japan, 46, 1233 (1973).

Appendix B.   Bull. Chem. Soc. Japan, 44, 3161 (1971).

Other publications not included in this thesis.

The Determination of the Enantiomeric Purity of Methyl p-Tolyl Sulfoxide by Means of an NMR Shift Reagent. H. Nozaki, K. Yoshino, K. Oshima, and Y. Yamamoto, Bull. Chem. Soc. Japan, 45, 3495 (1972).

A New Synthesis of α,β-Unsaturated Carboxylic Esters. K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, J. Amer. Chem. Soc., 96, 1620 (1974).

Organoaluminun Reagents of Type $R^1R^2NAlEt_2$ Which Allow Regiospecific Isomerization of Epoxides to Allylic Alcohols. A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, J. Amer. Chem. Soc., in press.