OXY ANION-ACCELERATED REARRANGEMENTS

Thesis by

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To My Parents

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Finally, a special word of thanks is extended to Dot Lloyd for a superb job in constructing this thesis.

ABSTRACT

The alkali metal salts of 1,5-hexadien-3-ols undergo accelerated Cope rearrangements to the enolates of δ,ε-unsaturated carbonyl compounds. The generality of the rearrangement was investigated in numerous systems, particularly acyclic cases, and the effect of changes in substituents, counterions, solvents, and geometrical structures were noted and discussed. Applications of this methodology in synthesis included the synthesis of the insect pheromone frontalin, the preparation of selectively monoprotected 1,6-dicarbonyl compounds from 4-methoxy- and 4-phenylthio-1,5-hexadien-3-ols, and the construction of complex ring structures such as a D-homo-estratetraenone derivative.

Thermochemical estimates of the energetics of anion-promoted alkoxide fragmentations were made, and in all cases heterolytic cleavage was favored over homolytic cleavage by 8.5-53 kcal/mol. The implication of these and other thermochemical estimates is that the anionic oxy-Cope rearrangement occurs *via* a concerted mechanism rather than a dissociation-recombination process. The concepts of anion-induced bond weakening were successfully applied to an accelerated [1,3]-shift of a dithiane fragment in a cyclohexenyl system. Trapping experiments demonstrated that > 85% of the [1,3]-shift occurred within

a solvent cage. Attempts at promoting an intramolecular ene reaction using the potassium salts of 2,7-octadien-1-ol and 2,8-nonadien-1-ol were unsuccessful. A general review of anion-promoted bond reorganizations and anion substituent effects is also presented.

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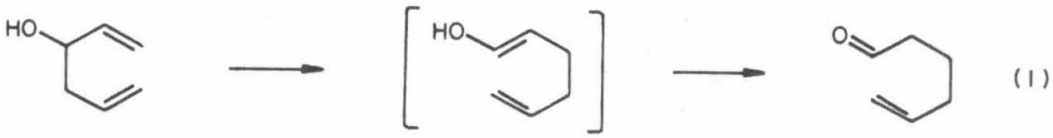
CHAPTER I

Accelerated [3,3]-Sigmatropic Rearrangements. Scope and Synthetic Utility of Base-Catalyzed Oxy-Cope Rearrangements.

Introduction

An important variation of [3,3]-sigmatropic rearrangements is the "oxy-Cope" rearrangement[1] of 1,5-hexadien-3-ols to δ,ε-unsaturated carbonyl compounds (eq 1). Modern



(1)

investigations into the nature of the oxy-Cope rearrangement began in 1964-65 with the work of Berson[2] and Viola.[3] Numerous chemical systems have since been examined: acyclic,[4,5] alicyclic,[6] and bicyclic[7] dienes, 1,5-enynes,[8] and 3,4-diols.[9,10] These rearrangements are characteristically high temperature reactions, and consequently are often susceptible to various side reactions, such as β-hydroxy olefin cleavage[3] and aldol condensations.[9,10]

Several years ago, a significant observation by Evans and Golob[11] was made concerning the reactivity of 1,5-diene alkoxides in [3,3]-sigmatropic rearrangements (eq 2). These anionic species exhibited dramatic rate accelerations which increased as the donor properties of the oxygen substituent increased (M = H → M = K). Performing other anionic oxy-Cope rearrangements under much milder conditions than the corresponding neutral dienol rearrange-

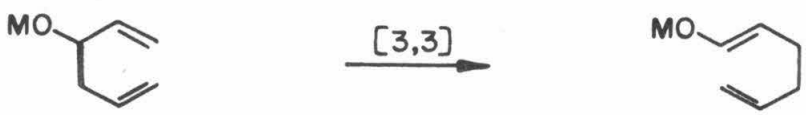
ments therefore appeared feasible.

(2)

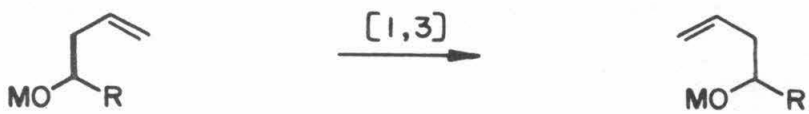
R = H, OMe
M = H, K

$\frac{k_M}{k_H} = 10^{12}-10^{17}$

Since the original report[11] from our laboratories, we[12] and several other researchers[13-15] have indeed extended the concept of alkoxide-accelerated [3,3]-sigmatropic rearrangements (eq 3) in a number of different chemical systems. This has stimulated other studies[16] aimed at exploring the possibility of promoting related [1,3]-sigmatropic processes (eq 4). Coincident with the above, Franzus[17] and Krow[18] have independently reported examples of facile [1,3]-sigmatropic rearrangements which are strongly promoted by charged heteroatom substituents (eq 5, eq 6 respectively).



(3)



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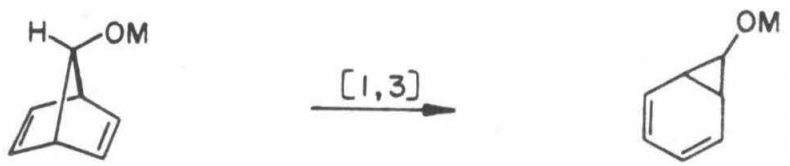

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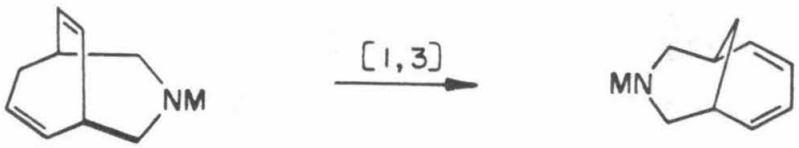
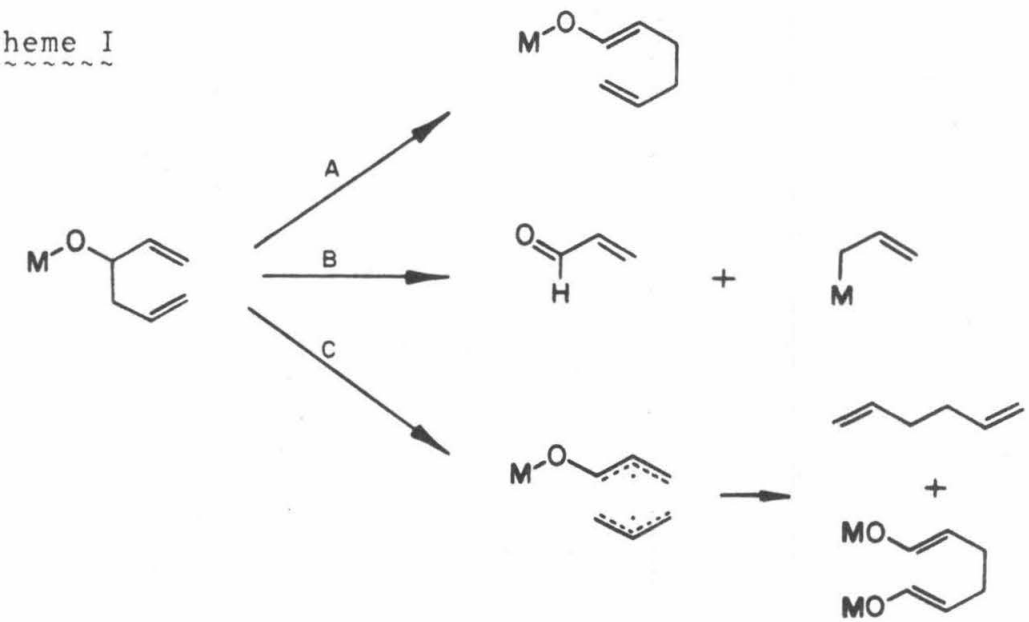


(6)

Before our investigations began, the scope of the base-catalyzed oxy-Cope rearrangement was unknown. Diene alkoxides, particularly acyclic substrates, could undergo several possible reactions other than the desired rearrangement (Scheme I). Fundamental questions concerning sub-

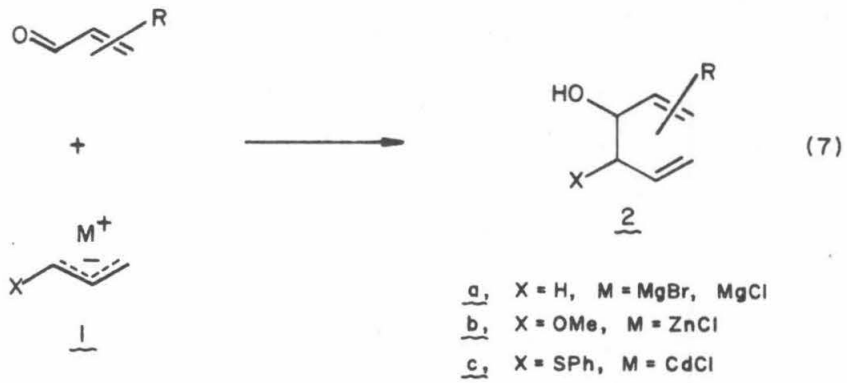
Scheme I



stituent effects, geometrical constraints, and experimental reaction parameters remained to be answered. This report summarizes the results of our work to define the scope of the rearrangement and those factors which limit it. In addition, the synthetic utility of the rearrangement is examined, and several promising applications are discussed.

Preparation of 1,5-Hexadien-3-ols

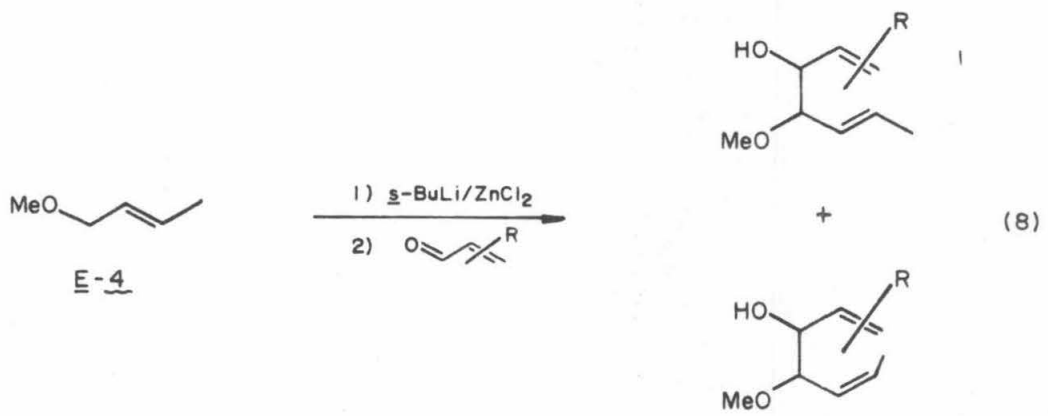
Oxy-Cope substrates, all 1,5-hexadien-3-ols, were prepared *via* organometallic additions to α,β-unsaturated enones (eq 7). Allylic Grignard reagents 1a were added to



(7)

enones according to established procedures to give the alkyl-substituted substrates 2a. The C-4 heteroatom-substituted substrates were prepared using methodology previously developed in our laboratory involving the additions of metallated allylic ethers 1b and thioethers 1c to electrophiles.[19] Highly regioselective 1,2-addition of 1-methoxy-2-propene (3), 1-methoxy-2-butene (4), and

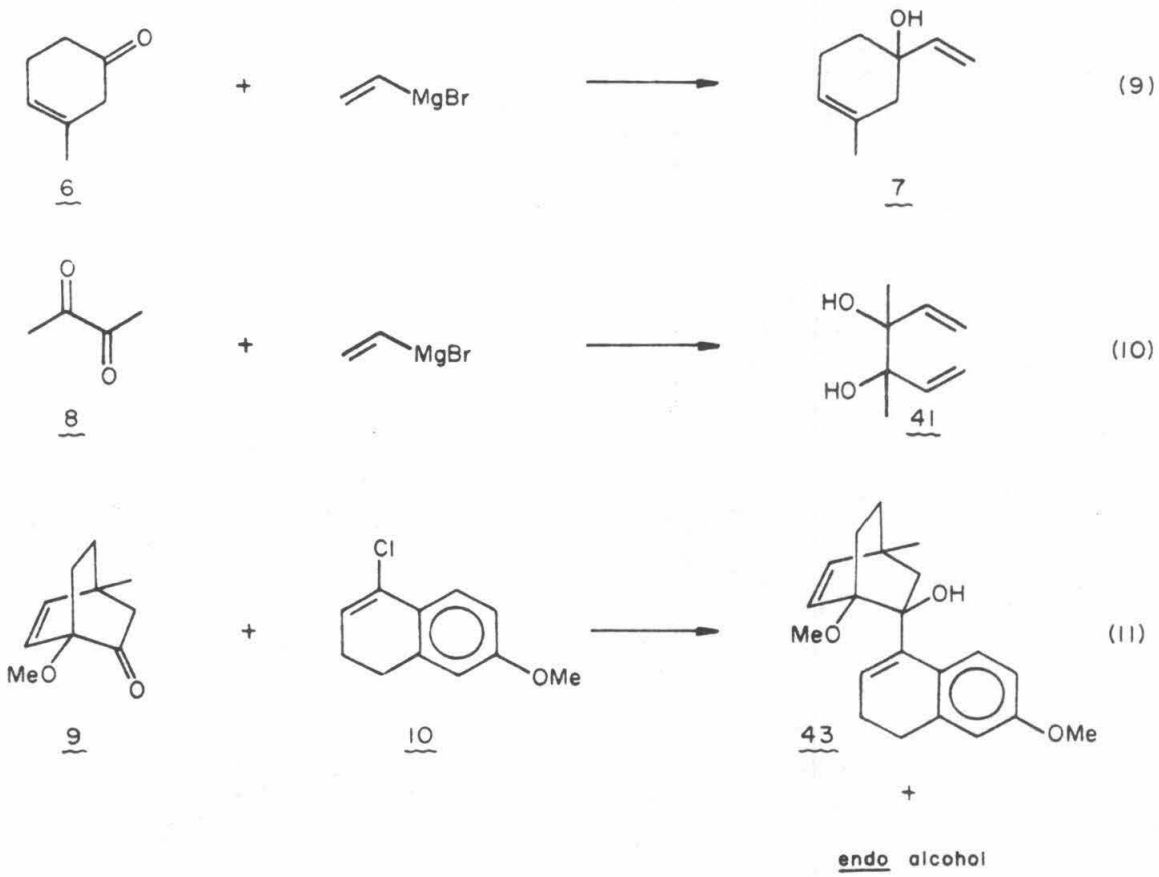
1-phenylthio-2-propene (5) to various enones afforded the dienols 2b and 2c in good yields. In the case of ether 4, scrambling of the olefin geometry occurred during the metallation-addition reaction (eq 8) to give both E and Z



(8)

isomers of the product.[20] Neither the olefin isomers nor the diastereomers obtained in these reactions were separated before undergoing oxy-Cope rearrangement.

Several other substrates were prepared by treating ketones with vinyl Grignard reagents (eq 9-11). The unconjugated cyclohexenone 6 was readily obtained by careful hydrolysis (aqueous oxalic acid/ether) of the Birch reduction product 2,5-dihydro-3-methylanisole.[21] Addition of vinylmagnesium bromide to 2,3-butanedione (8) led cleanly to the diol 41 with virtually no detectable formation of 2,7-octanedione, 42, the [3,3]-rearrangement product of the intermediate magnesium dialkoxide. The bicyclic ketone 9 was prepared by Diels-Alder cycloaddition



of the ketene equivalent, α-chloroacrylonitirle, and the Birch reduction product 2,5-dihydro-4-methylanisole, followed by alkaline hydrolysis.[22] Vinyl chloride 10 was obtained in high yield by treating 6-methoxy-1-tetralone with excess oxalyl chloride; the subsequent Grignard reagent was prepared according to the Rieke procedure.[23] Only in the case of the bicyclic alcohols were diastereomers

separated because the exo alcohol 43, not the endo alcohol, possessed the required geometry for the proposed [3,3]-rearrangement.[11]

[3,3]-Rearrangement of Diene Alkoxides

The results of our attempts to rearrange the alkali metal salts of 1,5-hexadien-3-ols are shown in Tables I and II. The success of these rearrangements convincingly proves that the alkoxide accelerated oxy-Cope rearrangement is indeed a general phenomenon. In conjunction with the initial allylic organometallic addition to an enone, the diene alkoxide rearrangement provides an efficient method for preparing δ,ε-unsaturated carbonyl compounds. Overall, the procedure is equivalent to the controlled 1,4-addition of an allyl anion to an enone (Scheme II), which may often

Scheme II

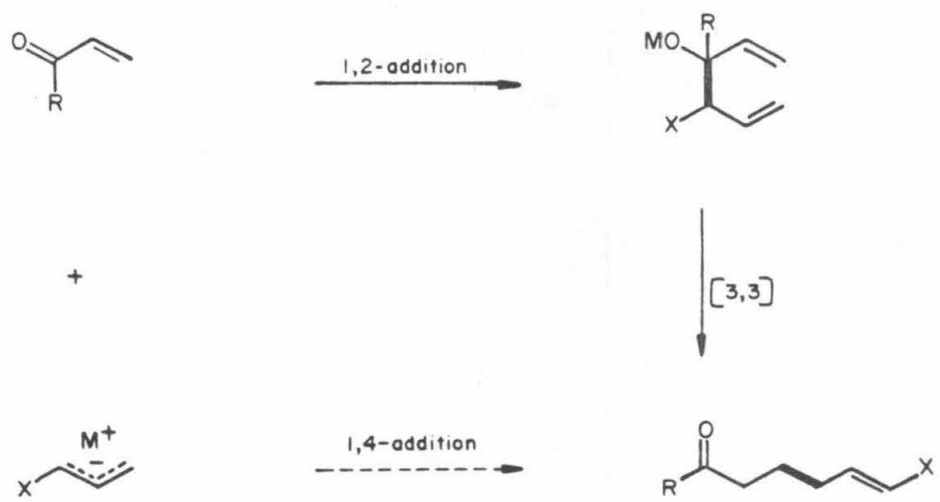


Table I. Cope Rearrangement of 1,5-Hexadien-3-ols.

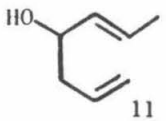
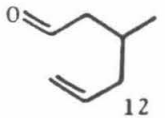
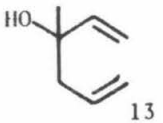
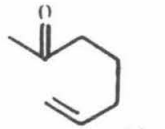
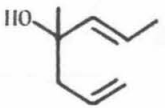
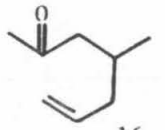
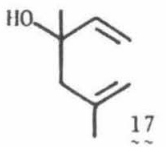
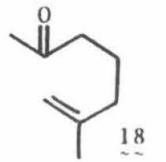
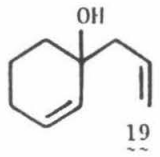
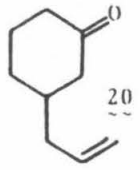
Entry	Alcohol	Conditions[a]	Yield, %[b]	Product
1	 11	KH, DME, 85°C, 12 h	(92)	 12
2	 13	KH, THF, 66°C, 5 h	(97)	 14
3	 15	KH, HMPA, 35°C, 9 h	80	 16
4	 17	KH, THF, 66°C, 12 h	88	 18

Table I (continued)

Entry	Alcohol	Conditions[a]	Yield, %[b]	Product
5	 19	KH, DME, 85°C, 18 h	76	 20

[a]All rearrangements were carried out under argon.

[b]Values refer to isolated yields; values in parentheses refer to glpc yields.

Table II. Cope Rearrangements of C-4 Substituted 1,5-Hexadien-3-ols.

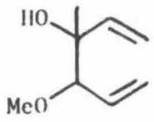
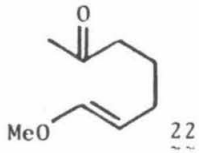
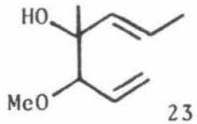
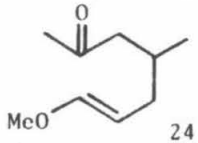
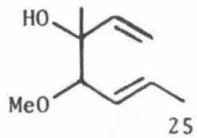
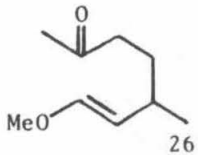
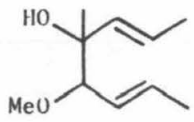
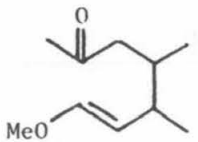
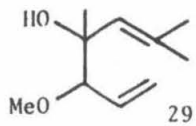
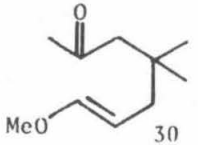
Entry	Alcohol[a]	Conditions[b]	Yield, %[c]	Product[d]
1	 21	KH, THF, 66°C, 9 h	85	 22
2	 23	KH, 85°C, 6 h Δ, 230°C, 8 h	79 (93)	 24
3	 25 [e]	KH, 85°C, 10.5 h	81	 26
4	 27 [e]	KH, 85°C, 12.5 h	81	 28
5	 29	KH, 85°C, 24 h	11	 30

Table II. (continued)

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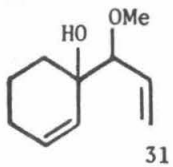
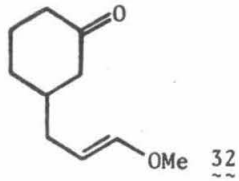
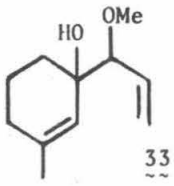
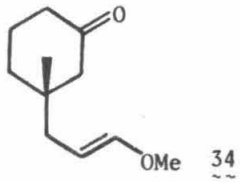
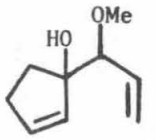
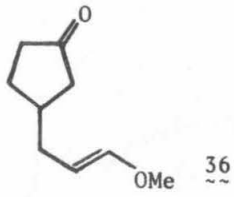
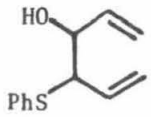
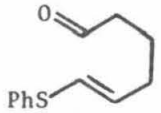
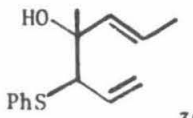
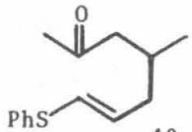
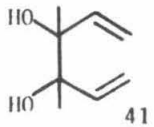
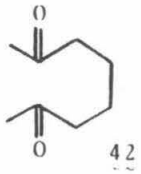
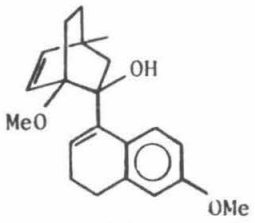
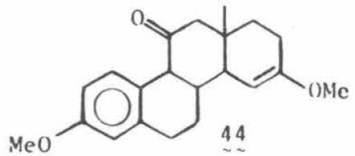
6	 31	KH, 85°C, 30 h Δ, 270°C, 8 h	70 (24)	 32
7	 33	KH, 85°C, 30 h	10	 34
8	 35	KH, 85°C, 9 h	64	 36
9	 37	KH, 25°C, THF, 1 h	42	 38
10	 39	NaH, 25°C, Et_2O, 6 h NaH, 25°C, THF, < 2 h	71 0	 40

Table II. (continued)

Entry	Alcohol[a]	Conditions[b]	Yield, %[c]	Product[d]
11	 41	MeLi, HMPA/ether (10:90), 25°C, 2.5 h	43 (62)	 42
12	 43	KH, 25°C, THF, 1 h	68	 44

[a]All alcohols were prepared as a mixture of diastereomers and rearranged as such.

[b]Unless specified all rearrangements were carried out in dimethoxyethane (DME) under argon.

[c]Values refer to isolated yields; values in parentheses refer to glpc yields.

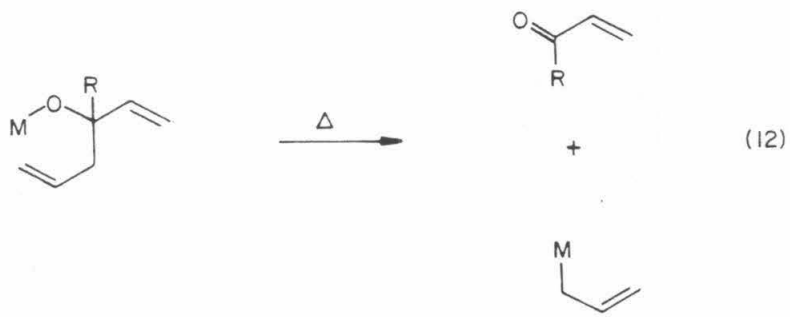
[d]Products (entries 1-10) exist as a mixture of E and Z olefin isomers.

[e]The Δ^5 olefin (entry 3) and Δ^6 olefin (entry 4) exist as a mixture of E and Z isomers.

be difficult to effect directly because of the ambident reactivity of both the electrophile and nucleophile.

Typical reaction conditions for the [3,3]-rearrangements are shown in Tables I and II. Several sets of reaction conditions were investigated, and reagents such as hexamethylphosphoric triamide (HMPA) and 18-crown-6 were sometimes employed. With respect to ease, simplicity, and effectiveness in promoting the desired transformations, the combination of potassium hydride in 1,2-dimethoxyethane (DME) at reflux proved to be most widely applicable. Depending on the reactivity of the particular alkoxide, three parameters, counterion, solvent, and reaction temperature, were altered to increase or decrease the severity of the rearrangement conditions (*vide infra*). With respect to the most commonly used base, potassium hydride, the best results were obtained when the hydride was fresh and had been scrupulously protected from moisture; any exposure of the hydride to air during repeated manipulation resulted in slowly decreasing yields of the rearrangement products.

A possible difficulty anticipated in the [3,3]-rearrangement of diene alkoxides was competitive cleavage to enone and allylic organometallic species via a retro-ene reaction (eq 12, M = alkali metal). Fragmentation of analogous dienols (eq 12, M = H) *via* this mechanism, β-



(12)

hydroxy olefin cleavage, occurred to a significant extent in similar reactions.[4,24] In addition, alkoxides of homoallylic alcohols were known to dissociate readily in the sense of reversible Grignard additions to ketones.[25] Despite the possibility of such side reactions, the majority of rearranging diene alkoxides displayed little apparent tendency to undergo similar cleavage processes. Exceptions to this observation were those cases (entries 5 and 7, Table II) where a quaternary center was generated as a consequence of the [3,3]-rearrangement. In the latter case, the predominant product (70%) was 3-methylcyclohexenone. Other exceptions were the phenylthio-substituted substrates, 37 and 39; if reaction conditions were not carefully selected and controlled, cleavage was easily competitive with rearrangement.

For comparative purposes, two methoxy-substituted alcohols, 23 and 31, were rearranged at 230°C and 270°C, respectively, in sealed glass tubes. Unexpectedly, the yield of the neutral rearrangement (93%) of the acyclic substrate 23 was higher than that of the anionic rearrange-

ment (79%). Considering, however, that the alcohol yield was determined by glpc and the alkoxide yield was determined by isolation, the net results are essentially comparable. Thermal rearrangement of alcohol 31 (24%) was significantly poorer than that of its potassium alkoxide (70%). Apparently, base-catalyzed oxy-Cope rearrangements are more effective than neutral rearrangements in more highly substituted and functionalized dienol systems.[26] The much lower reaction temperatures required in the anionic reactions definitely contribute to the stability of both reactants and products, and help minimize the occurrence of undesired side reactions.

Reaction and Substituent Parameters

Solvent and Counterion Effects. Ethereal solvents were most generally useful as reaction solvents; the particular choice was usually dictated by its solvating capabilities and by the temperature to be maintained during the rearrangement. Dimethoxyethane (DME) and tetrahydrofuran (THF) were especially suitable for most of the oxy-Cope substrates examined. Under many circumstances, DME was superior to THF because of its greater solvating power, and because of its greater stability toward metal hydrides and alkoxides at reflux temperatures. The higher boiling point of DME also allowed higher reaction temperatures and faster reaction rates.

The rate of diene alkoxide rearrangement exhibited an unusual concentration dependence. An increase in the concentration of the reacting alkoxide produced a marked decrease in the rate of the rearrangement. Typical large-scale preparatory reactions (0.1-1.0 M) often proceeded approximately 1.5-3.0 times slower than the corresponding small-scale investigatory reactions (<0.1 M) under otherwise identical experimental conditions. Perhaps limited solubility of the alkoxide was a contributing factor.

The initial work of Evans and Golob[11] clearly illustrated the dependence of the rate of rearrangement on the nature of the solvent and counterion. Control of the reaction rate fundamentally depends on controlling the ionic character of the metal-alkoxide bond which is experimentally equivalent to controlling the degree of ion pair dissociation of the alkoxide. Rates can be increased by using increasingly electropositive counterions (MgX^+ < Li^+ < Na^+ < K^+)[11,27] and increasingly powerful cation-solvating solvents (Et_2O < THF < DME < HMPA). An inherent limitation to these trends in acyclic systems was the tendency for irreversible alkoxide cleavage to occur under forcing conditions. A delicate balance between rearrangement and fragmentation often existed in these systems (path A vs paths B and C, Scheme I), and the same parameters used in controlling rates were used to control these two competing reaction pathways. Several

examples of these solvent and counterion effects were evident in the acyclic oxy-Cope rearrangements.

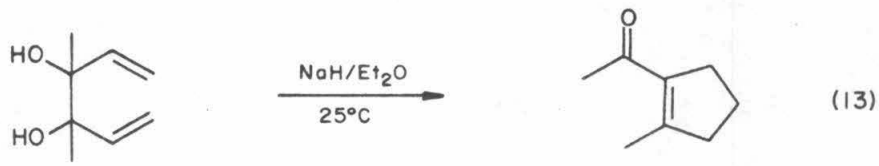
The phenylthio-substituted dienols, 37 and 39, were prone to undergo facile cleavage if the nature of the solvent and counterion were not carefully controlled. The extent of fragmentation could be minimized through the use of less electropositive counterions (Na^+ vs K^+) and less strongly cation-solvating solvents (Et_2O vs THF). The balance between rearrangement and cleavage is illustrated by 39. In ether, the sodium salt of 39 rearranged in 71% isolated yield; in THF under identical conditions, the alkoxide underwent cleavage nearly exclusively.

Rearrangement of the diol 41 was similarly counterion and solvent dependent. The dialkoxide was so reactive that use of K^+ counterion led only to degradation under all conditions, even if the reactant were carefully warmed from -78°C to room temperature. The reactivity of the dilithium salt, however, was sufficiently attenuated that rearrangement was the predominant reaction. Interestingly, the $MgBr^+$ counterion is so tightly bound to the oxygen anion that no rearrangement occurs at all; recall that the diol was originally made via a Grignard reaction.

Solvents had a considerable effect on the competition between rearrangement and cleavage of diol 41. For example, with 10% HMPA in ether as the reaction solvent, all starting material had disappeared in 2.5 h and the glpc yield

was 62%. When 100% HMPA was used as the solvent and other conditions were kept constant, all starting material had disappeared in less than 5 min and the glpc yield had dropped to 23%. In the latter case, the powerfully solvating HMPA simultaneously promoted the rate of rearrangement as well as the apparent cleavage of the dialkoxide. Thus, optimum reaction parameters must maintain a balance between maximum rate and yield, and minimum cleavage.

Another unexpected result was obtained during the search for the appropriate combination of conditions for rearranging diol 41. Treatment of 41 with sodium hydride in ether at room temperature resulted in the exclusive



(13)

41 45

formation of enone 45 (eq 13), the condensation product[51] of octanediol, 42; no trace of 42 was observed by glpc. Formation of 45 could only have occurred if some proton source were readily available in the reaction medium. The most obvious source of protons was the diol itself immediately upon addition to the hydride suspension. Perhaps rates of deprotonation, rates of rearrangement, solubility of salts, and other factors combined to produce

(1) a monoalkoxide which rearranged to the keto enolate which then suffered intramolecular condensation, and/or (2) a dialkoxide which rapidly rearranged to the dienolate which then scavanged a proton from as yet unreacted diol and underwent condensation. At this point, the reasons for obtaining such a product are speculative.

Substituent Effects. Alkyl substituents affected the ease of the diene alkoxide rearrangement primarily via steric interactions. In general, the observed alkyl substituent effects corresponded with those reported by Viola and coworkers[4] in the analogous dienol rearrangements. Substituents at C-3 and C-4 of the 1,5-hexadiene system facilitated the [3,3]-shift, while those at C-1 and C-6 hindered it (compare 11 vs 13, and 21 vs 23, 25). A methyl substituent at C-5 seemed to have minimal effect on the rearrangement (13 vs 17).

Heteroatom substituents were expected to exhibit an electronic component as well as a steric component to the overall substituent effect. Both alkoxy and alkylthio groups are capable of stabilizing adjacent radicals and carbanions. The presence of an alkoxy group adjacent to the site of bond cleavage in molecular reorganizations was found to lower activation energies by varying amounts, from 2 kcal/mol to 15 kcal/mol or more.[28,29] Although this effect is commonly attributed to stabilization of inter-

mediate radicals, Kirmse and Murawski[29] recently suggested that more subtle orbital interactions could be operating to raise the ground state energy or to weaken specific carbon-carbon bonds. Alkylthio groups, which are more powerful radical and anion stabilizers than alkoxy groups,[30] could function in the same manner. By analogy, heteroatom substituents at the C-4 position of the oxy-Cope substrate (2b, 2c) were expected to promote the rearrangement and/or cleavage of the diene alkoxides.

Comparison of the methoxy-substituted substrates (Table II) to the corresponding hydrocarbon substrates (Table I) reveals that the methoxy group had little if any effect in accelerating the [3,3]-rearrangement. Contrary to expectations, methoxy seemed to slow the rate of reaction in a number of cases. Many of these differences could be definitely attributed to minor changes in experimental conditions, especially concentration of reactants (vide supra). The phenylthio group, however, had a large substituent effect, and substrates 37 and 39 were rearranged under very mild conditions. The ease of rearrangement may reflect a significant degree of ionic character developed in the transition state due to the sulfur substituent. This is consistent with the observation that the phenylthio group promoted cleavage over rearrangement when the alkoxide reactivity was insufficiently attenuated.

Of all the examples of acyclic rearrangements, the dialkoxide of 41 was the most reactive. With the double activation of two oxy anions, the substrate was extremely susceptible to fragmentation. As the dilithium salt in ether, however, the dialkoxide very slowly rearranged to the dienolate of 42. A small amount of HMPA (approx. 10%) was added to speed up the rearrangement to a more reasonable rate.

Heteroatom substituents at C-4 can therefore further promote rearrangement/cleavage of the oxy-Cope substrates. The effectiveness of such promotion seems to depend on the ease with which the electron lone-pair orbitals of the heteroatom can interact with the orbitals of the rearranging 1,5-hexadiene system. High electron density ($-O^-$), high polarizability (S vs O), and low electronegativity (S vs O) of atoms positioned adjacent to the site of formal bond cleavage all seem to contribute toward facilitating the bond reorganization.

Structural and Geometrical Effects. Certain molecular structures and geometries were found to significantly modify the effectiveness of the [3,3]-rearrangement of diene alkoxides. In general, terminal substituents on the 1,5-hexadiene slowed the rate of rearrangement (vide supra). Geminal disubstitution of one terminal vinyl carbon not only slowed the reaction but also forced cleavage to largely predominate over rearrangement. As a

result, alcohols 29 and 33 (Table II; entries 5, 7) rearranged under standard conditions to ketones 30 and 34 in poor yield (11% and 10%, respectively). Yet, if the same two substituents were positioned at each end of the hexadiene framework as in alcohol 27 (Table II; entry 4) rearrangement again proceeded smoothly and in respectable yield.[26] Evidently, an unfavorably high degree of steric crowding occurs due to two substituents on a single terminal carbon. Examination of the expected chair-like transition state for the rearrangement of the acyclic substrate 29 revealed an unfavorable and unavoidable 1,3-diaxial interaction between one terminal methyl and either the methyl or oxido group at C-3; such an interaction does not exist in the 1,6-disubstituted substrate 27. Analysis of the cyclohexenyl case 33 is not nearly as clear-cut. Other than the increased steric congestion about one terminus of the 1,5-hexadiene system, specific steric interactions of the added methyl group are difficult to pinpoint. Whatever the rationale, formation of quaternary carbon centers *via* [3,3]-rearrangement is a disfavored process in acyclic and alicyclic systems.

The effect of another structural feature, that of ring size, can be examined in certain alicyclic oxy-Cope substrates. Ring size affected the ease with which 31 and 35 underwent rearrangement. Compared to the moderately flexible cyclohexenyl ring of 31, the cyclopentenyl ring of 35 is more rigid and the ensuing rearrangement transition

state is more strained. The result is a slightly lower yield of the cyclopentanone 36 compared to that of the cyclohexanone 32.

Geometrical constraints played a major role in the outcome of the attempted rearrangement of vinylcyclohexenol 7 to cyclohexanone 46 (eq 14). This tranformation was an

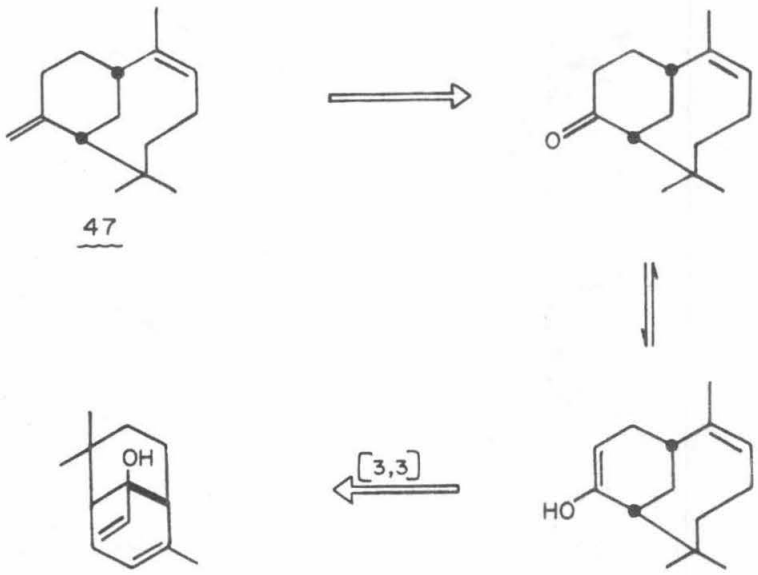
7 46 (14)

important one because of the potential applications in terpene synthesis. One such application was the proposed total synthesis of the unusual sesquiterpene bazzanene, 47;[31,32] retrosynthetic analysis of the last few steps including the crucial oxy-Cope rearrangement is outlined in Scheme III. Previous attempts at rearranging the dienol 48 at high temperatures had been completely unsuccessful.[33]

Two other dienes analogous to 7 had been successfully rearranged, albeit at high temperatures, by other investigators. Büchi and Powell[34] reported the Claisen rearrangement of 49 at 410°C in a flow system; Doering and

49 50

Scheme III



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48

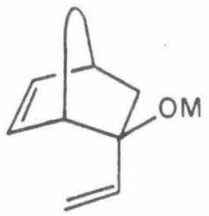
coworkers[35] studied the degenerate rearrangement of 4-vinylcyclohexene, 50, at temperatures above 335°C and reported an activation energy of 52 kcal/mol. Examination of molecular models confirmed the poor geometrical orientation of the interacting olefins. Obviously, the high energy requirements for the contemplated rearrangement (eq 14) would severely test the activation capabilities of the oxy anion.

Attempts at rearranging the potassium alkoxide of 7 were totally unsuccessful, even under reaction conditions chosen to maximize the anion substituent effect. The starting material remained unchanged over 24 h in

the presence of two equivalents of 18-crown-6 at temperatures ranging from 85°C in DME to 150°C in triglyme. In HMPA at elevated temperatures, the alkoxide only suffered degradation; at 80°C degradation was slow, but at 150°C degradation was complete in less than 1 h. Therefore, even the activation of an oxy anion was inadequate in lowering the activation energy of 7 enough to allow rearrangement at lower and more convenient temperatures.

With regard to the proposed bazzanene synthesis, additional work by Andrews[36] showed that an analogue of 48, one without the gem-dimethyl group, also resisted the desired [3,3]-shift. The potassium salt of this analogue and 18-crown-6 were heated in DME at reflux; the alkoxide was stable for long periods of time under these conditions. Thus, even in this more strained bicyclic molecule, the geometrical constraints are still too severe to be easily overcome.

Rearrangement of 1-vinyl-3-cyclohexen-1-ols can be effected, however, in a different geometrically constrained system, ie when C-2 and C-5 of the cyclohexene ring are bridged (51).[11,13c] For example, bicyclic oxy-Cope substrates such as 43 are cleanly and efficiently rearranged under mild reaction conditions. Several factors probably contribute to this ease of rearrangement. The olefins of the hexadiene framework are held physically close to one another in a geometry appropriate for easy



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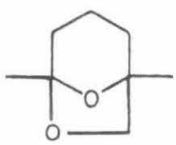
orbital interaction. Relief of strain in the bicyclic structure provides added driving force to the reaction. Finally, any cleavage reaction is probably reversible since the two cleavage species are physically connected and consequently cannot diffuse out of the reactant solvent cage.

Significance in Synthetic Methodology

Synthesis of Frontalin. An interesting and important class of natural products is one whose members possess a 6,8-dioxabicyclo[3.2.1]octane structure. Several of these



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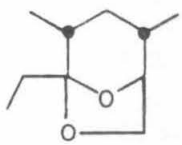

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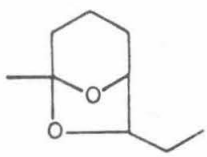

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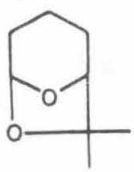
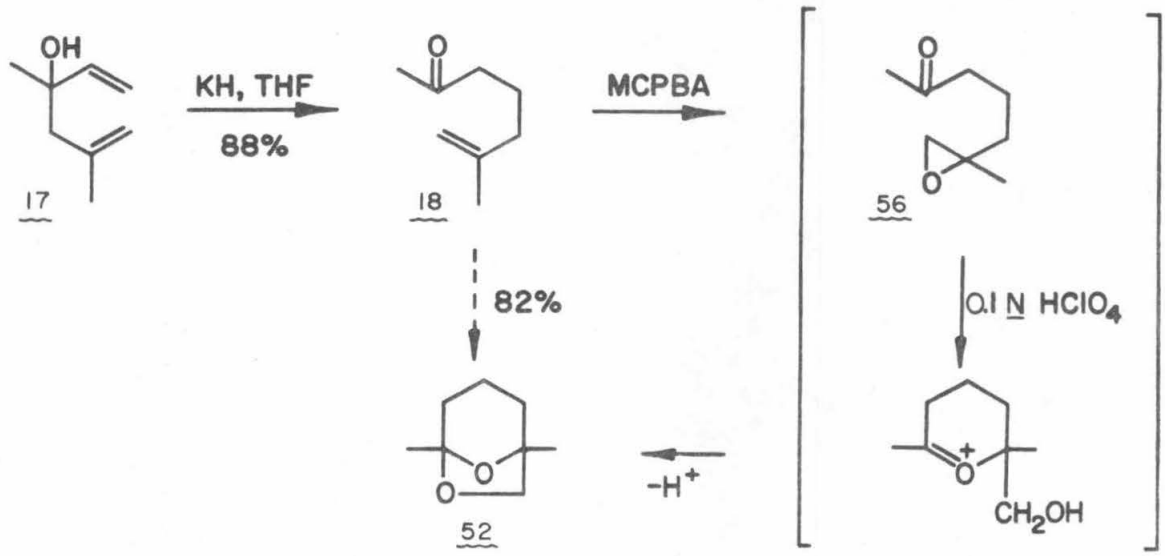


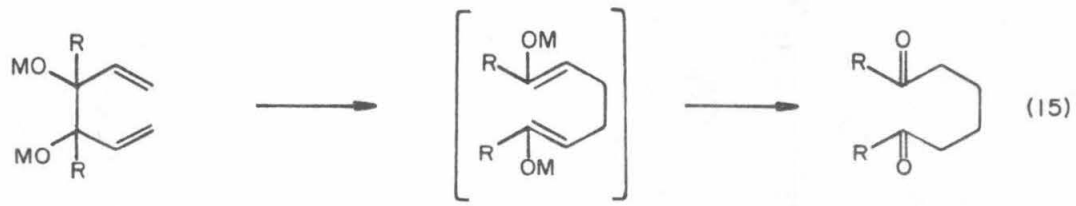
55

bicyclic ketals are insect pheromones for various species of beetle of the genera Dendroctonus and Scolytus: frontalin (52), brevicomin (53), and α-multistriatin (54). Another member of the class, 55,[37] is a constituent of hop oil. Several syntheses of the insect pheromones 52,[38-40], 53,[41,42] and 54[43] have been reported, and a number of them[41-43] depend on the preparation and use of a δ,ε-unsaturated carbonyl compound as a key intermediate. The Cope rearrangement of diene alkoxides provides a convenient and general method of preparing these keto olefins. In principle, each one of these bicyclic ketal natural products could be synthesized via an approach in which the oxy-Cope rearrangement is a crucial step. To demonstrate this procedure, the insect pheromone frontalin (52) was synthesized (Scheme IV). The Grignard adduct 17 was rearranged as the potassium salt to the keto olefin 18. Epoxidation of the double bond with m-chloroperbenzoic acid (MCPBA) gave intermediate 56 which was not isolated. Treatment of the reaction mixture containing 56 with dilute perchloric acid effected the internal ketalization of the carbonyl. Frontalin (52) was obtained in 82% yield from the keto olefin 18. The primary advantages of this route via the anionic oxy-Cope rearrangement are its simplicity and its inherent flexibility toward the preparation of analogous bicyclic ketals.

Scheme IV



Diol Rearrangements and Pinacol Reductions. Rearrangements of 1,5-hexadien-3,4-diols (M = H, eq 15) have been extensively examined with respect to structural and mechanistic properties, and applications in synthesis.[9,10] The most common problem encountered in these systems was the



(15)

57

intramolecular aldol condensation of the dione subsequent to the rearrangement.

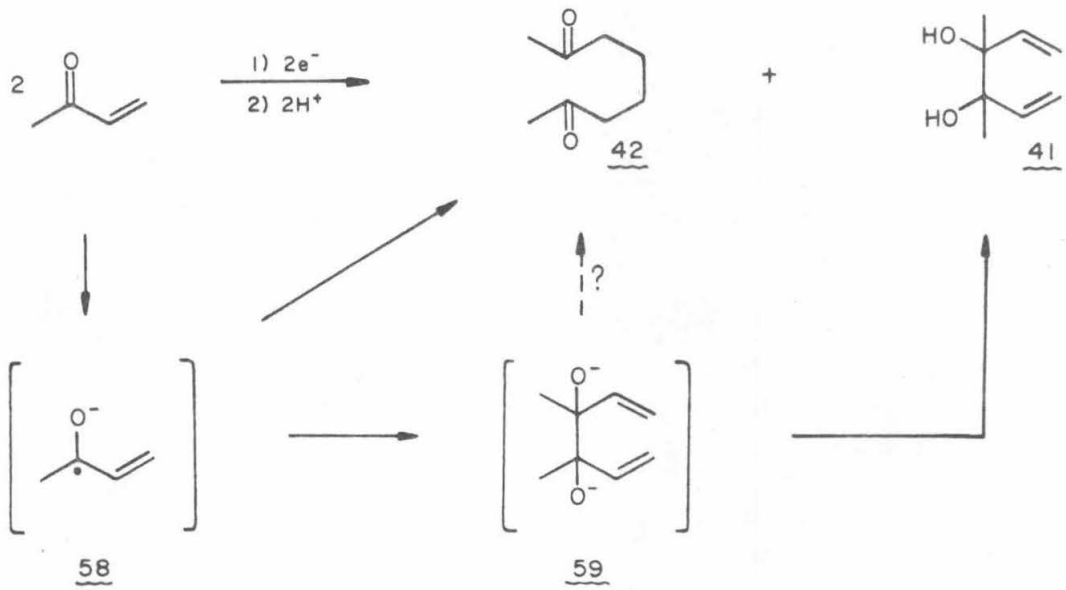
In the attempted accelerated rearrangement of such a dialkoxide (M = Li, eq 15), condensation of the product

dienolate (57) was not a problem. The dimethyl-substituted diol 41 (entry 11, Table II) was successfully rearranged to the dione 42 as the dilithium salt in a 10% HMPA/ether solvent at 25°C. These particular experimental conditions are remarkably mild due to the double activation of two oxy anions on the rearranging carbon framework.

The successful and facile anionic rearrangement of diol 41 takes on added significance in view of the numerous studies[44-48] on the pinacol reduction of α,β-unsaturated ketones and aldehydes. Mixtures of products (1,2-diols, 1,6-dicarbonyl compounds, and cross-coupled materials) were typically obtained in these reductions. Pinacol reduction of methyl vinyl ketone, for example, was accomplished both electrochemically[48] and with active metals[45] *via* the coupling of radical anion 58 or its corresponding protonated form (Scheme V). The possibility of a "hidden" anionic oxy-Cope rearrangement (59 → 42) in the reductive coupling of this and analogous α,β-unsaturated enones has received little recognition. Only Chuche and Wiemann[50] have suggested such a possibility; they recognized that the 1,6-dione from the reductive coupling of cinnamaldehyde could have occurred indirectly *via* [3,3]-shift of the diol. Independent rearrangement of 41 to 42 *via* the anionic intermediate 59 (*vide supra*) illustrates the feasibility of such a mechanistic pathway in pinacol reductions. Thus, the dialkoxide intermediate 59 could be

a precurser to both the diol 41 and the dione 42 in these reactions.

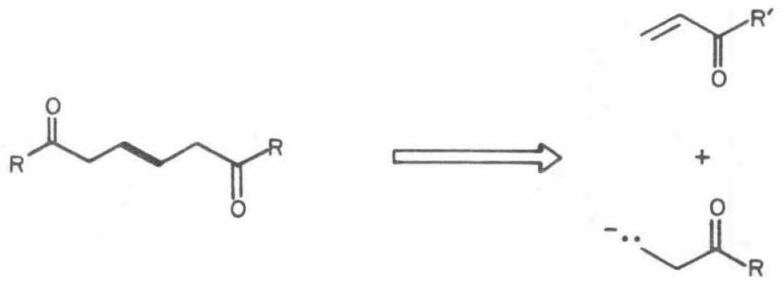
Scheme V



Reduction	Dione	Diol
Electrolysis (-1.4 V)	40-70%	1-13%
Zn, HOAc	trace	56%

Synthesis and Utility of 1,6-Dicarbonyl Substrates. Synthesis of symmetrical 1,6-diketones and related derivatives is readily achieved via the reductive coupling of α,β-unsaturated ketones with active metals[44,45] and by electrolysis.[46-48] Such methods, however, have thus far proven unsatisfactory for the synthesis of unsymmetrical dicarbonyl substrates. The bondpath construction which we envisaged to be most useful in preparing 1,6-dicarbonyl

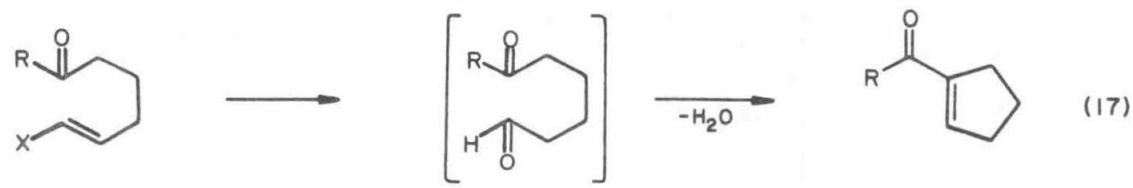
compounds is illustrated in equation 16.[49] With the use



(16)

of previously developed allylic ether anion chemistry[19] and the base-accelerated oxy-Cope rearrangement in sequence (Scheme II, X = OR, SR), this unsymmetrical bond construction has been accomplished. The final products (entries 1-10, Table II) have one of the two carbonyl groups in the molecule selectively protected as enol ethers or enol thioethers.

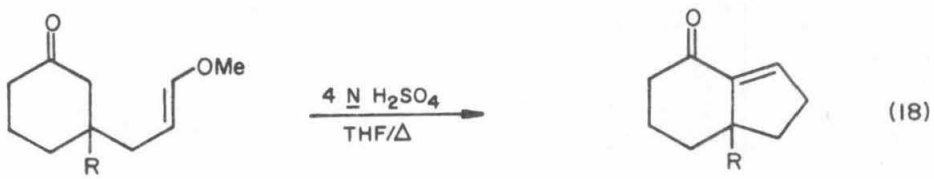
The ready availability of these substrates makes them valuable in subsequent ring constructions via acid-catalyzed intramolecular aldol condensation (eq 17). For instance,



(17)

X = OR, SR

treatment of the substituted cyclohexanones 32 and 34 with dilute aqueous H_2SO_4 in THF leads to the formation of tetrahydroindenones 60 and 61, respectively (eq 18).



(18)

32, R = H
34, R = Me

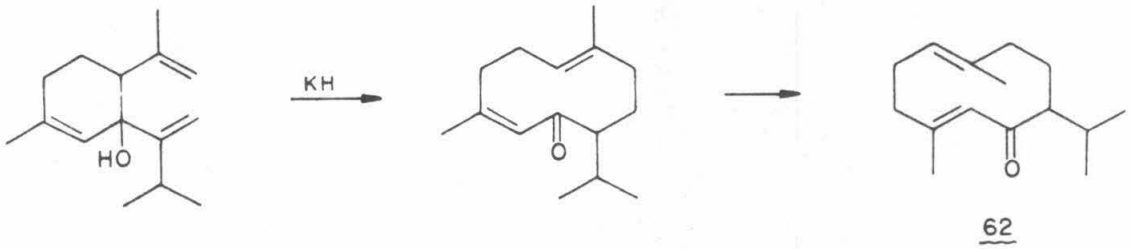
60, R = H, 80%
61, R = Me, 47%

The overall sequence of allylic ether anion addition, [3,3]-rearrangement, and aldol condensation represents a convenient five-membered ring annulation procedure, especially for cyclic α,β-unsaturated enones (eq 19).

(19)

Ring Construction. Perhaps one of the most valuable areas of application of base-catalyzed oxy-Cope rearrangement is the construction of complex cyclic and polycyclic rings; such structures are particularly important in natural product synthesis. This methodology of building complex ring structures has been employed recently in several cases. W. C. Still[14] has developed a short, efficient route to members of the germacrene class of sesquiterpenes. One example is the preparation of (±)-

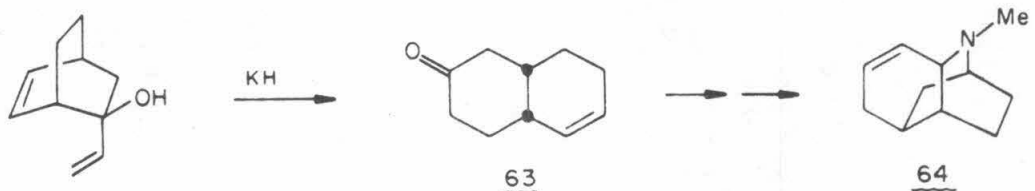
acoragermacrone (62) shown in equation 20. Bicyclic oxy-



(20)

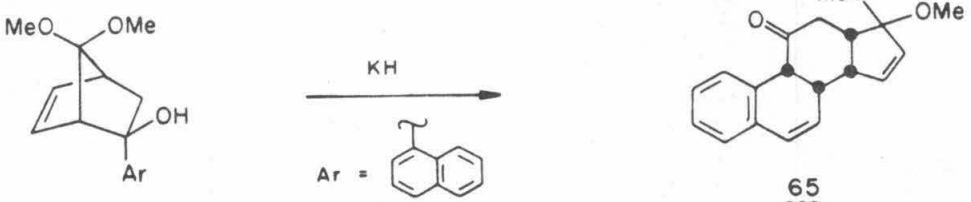
62

Cope substrates are particularly advantageous in constructing fused polycyclic molecules. Evans and Golob



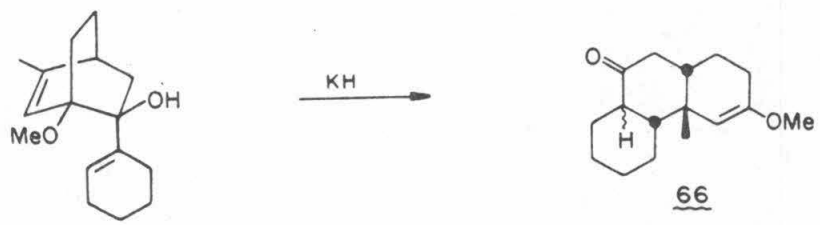
(21)

63 64



(22)

65

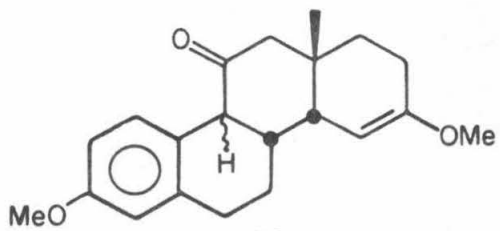


(23)

66

used the Cope product 63[11] to prepare the novel alkaloid cannivonine, 64, in a structure proof of the natural product.[52] Jung and Hudspeth[15] rearranged aromatically substituted norbornenyl systems to obtain cis-hydrindanone derivatives, including 65 which possesses a basic steroid skeleton (eq 22). Ireland and O'Neill[53] have used the oxy-Cope rearrangement to prepare 66 (eq 23) in studies directed toward the total synthesis of the macrolide antibiotic chlorothricolide.

Generally, base-catalyzed [3,3]-rearrangements of bicyclic 1,5-hexadien-3-ols such as those above are efficient and high yield processes. Rearrangement of the highly functionalized dienol 43 was no exception. Under mild conditions (KH, THF, 25°C, 1 h), 43 was easily converted to the fused tetracyclic molecule, 44, a D-homo



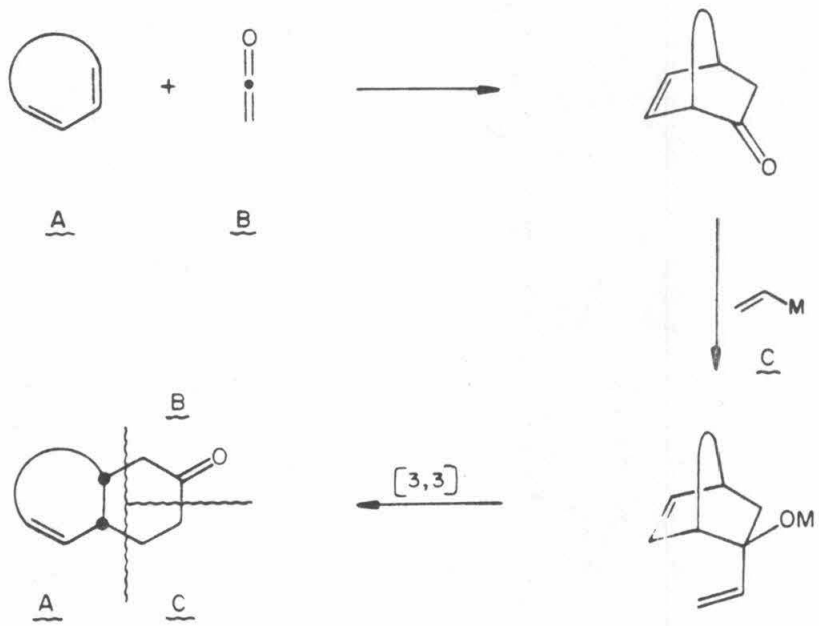
44

steroid. Both diastereomers, 9α and 9β, were obtained in a ratio of 1:2.2, respectively; thus, protonation of the intermediate enolate occurred primarily on the convex face of the molecule. Some of the major isomer crystallized from the product mixture, and it was assigned as the 9β

isomer based on the nmr coupling constant, J = 6 Hz, of the benzylic methine proton. Furthermore, 9β could be converted to 9α by treatment with sodium methoxide/methanol; assignment of the trans ring fusion was based on the large coupling constant, J = 12.5 Hz, of the benzylic methine proton. The stereochemistry at C-8 and C-14 was assigned as syn based on our previous experience with simpler decalin systems (eq 2).[11] Analogous to the steroid model 65, 44 could be a valuable precursor to a number of classes of medicinally important steroids: the estrogens which possess a 3-hydroxy aromatic A-ring, and the adrenocortical hormones which possess an α,β-unsaturated ketone in the A-ring and an oxygen functional group at C-11.

The concept of multiple ring construction utilizing the anionic oxy-Cope rearrangement as one of the key reactions is very powerful synthetically. A generalized strategy used in the previous examples of accelerated bicyclic [3,3]-rearrangements is illustrated in Scheme VI. The exact structure of the essential components A, B, and C could be varied over a wide range without affecting the fundamental nature of the ring-building procedure. Several synthetically important ring systems which are found in a multitude of natural products could be prepared by the strategy in Scheme V; a few of these systems

Scheme VI



and their corresponding oxy-Cope rearrangements are shown below (eq 24-27).

(24)

(25)

(26)

(27)

Conclusions

The base-catalyzed oxy-Cope rearrangement is indeed a general phenomenon. Our initial investigations in simple bicyclic systems have now been extended to a variety of acyclic, alicyclic, and bicyclic substrates. The consequences of modifying the basic system by altering substituents and by changing molecular structures and geometries were studied. The potential utility of the rearrangement in a number of synthetic applications was also demonstrated.

Our work in this area is continuing, with particular attention being focused on the very fundamental aspects of the concept of anion-promoted bond reorganizations.

Experimental Section

General. Diethyl ether, 1,2-dimethoxyethane (DME), tetrahydrofuran (THF), diglyme, and triglyme were dried by distillation under nitrogen from benzophenone ketyl or lithium aluminum hydride. Triethylamine and hexamethylphosphoric triamide (HMPA) were distilled under nitrogen from calcium hydride. Pentane, hexane, petroleum ether (30-60°C), ethyl acetate, methanol, and the various α,β-unsaturated aldehydes and ketones were dried and purified according to standard procedures.[54] 18-Crown-6 was dried by elution through activity I alumina with ether, followed by solvent removal and drying in vacuo. Reagent grade hydrocarbons were used without further purification as glpc standards.

Oil dispersions of potassium hydride (24%) and sodium hydride (50%) were washed free of oil with ether or pentane and dried under vacuum before use. All Grignard and alkyllithium reagents were standardized by the procedure of Watson and Eastham.[55]

Unless otherwise specified, reactions were run under an inert atmosphere of nitrogen or argon.

Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected, as are boiling points. Infrared spectra were recorded on a Beckman IR 4210 spectrophotometer and are reported in cm^{-1}. Proton

nuclear magnetic resonance spectra were recorded on a Varian Associates Model T-60, A-60, or EM-390 spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (Hz), and interpretation. Carbon-13 nuclear magnetic resonance spectra were recorded on a Varian Associates XL-100 (25.2 MHz) or T-60 (15.1 MHz) spectrometer and are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Mass spectra were recorded on a DuPont MS 21-492B mass spectrometer at 70 eV. Mass spectral analyses as well as combustion analyses were performed by Dr. Susan Rottschaeffer and Mrs. Jan Mitchell of the California Institute of Technology Microanalytical Laboratory.

Analytical gas chromatographic analyses were performed on a Varian-Aerograph Model 1440 gas chromatograph equipped with a flame ionization detector using 2 m by 3.18 mm stainless steel columns of 10% Carbowax 20 M, 6% FFAP, or 10% SE-30 on 80-100 mesh DMCS Chromosorb W support. Preparative glpc separations were performed on a Varian Aerograph Model 90-P instrument using a 2 m by 6.35 mm column of 15% SE-30 on 40-60 mesh Chromosorb W support.

Detector response calibrations were determined by comparison of the peak areas (measured by triangulation) of a compound and a standard at a variety of weight ratios.

(E)-1-Methoxy-2-butene (4). The title compound was prepared from crotyl alcohol, dimethyl sulfate, and 50% aqueous NaOH according to the procedure of Couffignal, et al.,[56] in 49% yield: bp 75-77°C [lit.[57] bp 76-77°C]; IR ($CHCl_3$) 3000, 2815, 1665, 1444, 1373, 1097, 965 900 cm^{-1}; NMR ($CDCl_3$) δ 6.08-5.27 (m, 2, vinyl), 4.00-3.75 (m, 2, $-CH_2-$), 3.28 (s, 3, $-OCH_3$), 1.70 (broad d, 3, J = 4.5 Hz, allylic $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 128.4 and 126.6 (=C<), 72.7 ($-CH_2-$), 57.1 ($-OCH_3$), 17.6 (allylic $-CH_3$).

1-Phenylthio-2-propene (5). The title compound was prepared from thiophenol, sodium methoxide, and allyl bromide in methanol as described by Hurd and Greengard[58] in 81% yield: bp 32-34°C (0.06 mm) [lit. bp 104-106°C (25 mm),[58] bp 48-49°C (0.43 mm)[59]].

1-Chloro-3,4-dihydro-6-methoxynaphthalene (10). To 9.52 g (75.0 mmol) of oxalyl chloride in 40 mL of benzene was added 10.57 g (60.0 mmol) of 6-methoxy-1-tetralone in 20 mL of benzene with stirring at 0°C. After 5 h at 25°C, an excess of cold saturated aqueous $NaHCO_3$ and 250 mL of ether were added to the reaction mixture. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and brine,

and dried (Na_2SO_4). Solvent removal *in vacuo* gave 11.13 g of an air-sensitive dark green liquid. Short-path distillation afforded 8.876 g (76%) of **10** as a clear, colorless liquid: bp 86-87°C (0.001 mm); IR (neat) 2938, 2828, 1600, 1488, 1298, 1274, 1248, 1121, 1038, 963, 810 cm^{-1}; NMR ($CDCl_3$) δ 7.47 (broad d, 1, J = 8 Hz, aromatic *meta* to methoxy), 6.80-6.60 (m, 2, aromatic *ortho* to methoxy), 5.96 (t, 1, J = 5 Hz, vinyl), 3.78 (s, 3, $-OCH_3$), 2.77 (broad t, 2, J = 8 Hz, benzylic $-CH_2-$), 2.46-2.17 (m, 2, allylic $-CH_2-$).

Anal. ($C_{11}H_{11}ClO$): C, H.

1,5-Heptadien-4-ol (11). The title compound was prepared from crotonaldehyde and allylmagnesium bromide in ether as described by Viola,[4] and was isolated in 77% yield by chromatography on activity III neutral alumina (ether/pentane, 10:90, followed by ether gradient) and molecular distillation at 45°C (65 mm) [lit.[4] 151-152°C].

3-Methyl-1,5-hexadien-3-ol (13). The title compound was prepared from methyl vinyl ketone and allylmagnesium bromide in ether as described by Fleischacker and Woods[60] in 64% yield, bp 80-85°C (200 mm) [lit.[60] bp 137°C].

4-Methyl-1,5-heptadien-4-ol (15). The title compound was prepared from 3-penten-2-one and allylmagnesium bromide in ether as described by Sorensen[61] in 11% yield, bp 40-42°C (3-4 mm) [lit.[61] bp 44-46°C (5-6 mm)].

3,5-Dimethyl-1,5-hexadien-3-ol (17). The title

compound was prepared from methyl vinyl ketone and 2-methyl-2-propenylmagnesium chloride in ether as described by Woods and Viola[62] in 45% yield, bp 47-50°C (8 mm) [lit.[62] 46-47°C (10 mm)].

1-Allyl-2-cyclohexen-1-ol (19). To 200 mL of 0.74 M (0.148 mol) allylmagnesium bromide in ether was added 9.73 g (0.101 mol) of cyclohexenone in 30 mL ether over a period of 2.5 h at -72°C; the reaction was continued 2 h longer at -72°C. The cold reaction was quenched with saturated aqueous NH_4Cl, and the precipitated salts were removed by filtration through Celite and activity III basic alumina.[63] Removal of solvent in vacuo gave 13.38 g of a pale yellow liquid. Short-path vacuum distillation afforded 10.75 g of ~90% pure 19 as a clear colorless liquid: bp 47-51°C (0.02 mm), 69% yield. Pure 19 was obtained by chromatography on activity III neutral alumina (ether/hexane, 10:90): IR (neat) 3380, 3070, 3015, 2930, 1634, 1434, 1167, 1083, 980, 910, 731 cm^{-1}; NMR ($CDCl_3$) δ 6.23-4.87 (m, 5, vinyl), 2.31 (d with fine structure, 2, J = 7 Hz, $=C-CH_2-C-O$), 2.18-1.87 (m, 2, $=C-CH_2-C-C$), 1.87-1.47 (m, 5H, $-CH_2-$ and OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 139 ($M^+ + 1$, 0.6), 97 (base), 79 (20), 55 (23), 41 (24).

Anal. ($C_9H_{14}O$): C, H.

3-Methyl-1-vinyl-3-cyclohexen-1-ol (7). To a 50-mL

solution of 0.67 M (33.5 mmol) vinylmagnesium bromide in THF was added 1.80 g (16.3 mmol) of 3-methyl-3-cyclohexen-1-one[21] at 0°C over 30 min. After one hour at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution, and precipitated salts were removed by filtration. The THF solution was diluted with ether, washed with brine, and dried (Na_2SO_4). Removal of solvent in vacuo gave 2.07 g of a yellow liquid which was purified by chromatography on activity III neutral alumina (ether/hexane, 10:90, followed by ether gradient) to give 1.43 g (64%) of 7 as a clear colorless liquid: IR (CCl_4) 3600, 3460, 2920, 1662, 1632, 1433, 1370, 1072, 987, 920, 871 cm^{-1}; NMR ($CDCl_3$) δ 6.30-4.93 (m, 4, vinyl), 2.10 (m, 4, allylic $-CH_2-$), 1.70 (m, 6, allylic $-CH_3$, $-CH_2-$, -OH, D_2O exchangeable).

Anal. ($C_9H_{14}O$): C, H.

Addition of Allylic Ether Anions and Allylic Thioether Anions to Keto Electrophiles. General Procedure.

A) Allylic Ether Anions.[19] To a stirred -65°C solution of THF and 1.0 equiv of s-butyllithium in cyclohexane (at least 2:1 by volume) was added 1.0 equiv of the allylic ether. After 30 min, 1.2 equiv of anhydrous $ZnCl_2$ in THF was added; 30 min later, 0.5-1.0 equiv of ketone or aldehyde was added. The reaction was kept at -65°C for 1 h, was allowed to warm slowly to room temperature, and was then quenched with saturated aqueous NH_4Cl. Precipitated salts were

removed by filtration through Celite, excess THF was removed *in vacuo*, and the residue was dissolved in ether. The ethereal solution was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, and was dried (Na_2SO_4). Removal of solvent *in vacuo* gave the desired alcohol which was typically purified by distillation.

B) Allylic Thioether Anions.[64] To a stirred -65°C solution of THF and 1.0 equiv of *s*-butyllithium in cyclohexane (at least 2:1 by volume) was added 1.0 equiv of allylic thioether. After 30 min, 1.2 equiv of anhydrous $CdCl_2$ was added, and the reaction mixture was warmed to -25°C for 5-10 min until the yellow color of the lithium allyl anion had disappeared. The mixture was cooled to -65°C and 1.0 equiv of ketone or aldehyde was added. Subsequent reaction conditions and isolation procedure were identical to that described in Part A above. The desired alcohols were typically purified by distillation.

4-Methoxy-3-methyl-1,5-hexadien-3-ol (21). As described in the standard procedure, 14.0 mL of 0.72 *M* (10 mmol) *s*-butyllithium in cyclohexane dissolved in 50 mL of THF was treated successively with 0.72 g (10 mmol) of 1-methoxy-2-propene, 12 mL of 1.0 *M* (12 mmol) $ZnCl_2$ in THF, and 0.70 g (10 mmol) of methyl vinyl ketone. Molecular distillation of the reaction product at 40°C (20 mm) afforded 1.25 g (88%) of **21** as a clear colorless liquid, and as a mixture of

diastereomers: IR (neat) 3440, 3040, 2974, 2930, 2816, 1634, 1087, 989, 920 cm^{-1}; NMR ($CDCl_3$) δ 6.22-4.97 (m, 6, vinyl), 3.55-3.25 and 3.32 (overlapping m and s, respectively, 4, -CH- and $-OCH_3$), 2.82 and 2.64 (broad s, 1, -OH, D_2O exchangeable), 1.23 and 1.20 (s each, 3, $-CH_3$).

Anal. ($C_8H_{14}O_2$): C, H.

3-Methoxy-4-methyl-1,5-heptadien-4-ol (23). As described in the standard procedure, 52 mL of 1.55 M (80 mmol) s-butyllithium in cyclohexane dissolved in 75 mL of THF was treated successively with 5.77 g (80 mmol) of 1-methoxy-2-propene, 57 mL of 1.69 M (96 mmol) of $ZnCl_2$ in THF, and 5.05 g (60 mmol) of 3-penten-2-one. Molecular distillation of the reaction product at 70°C (50 mm) afforded 9.12 g (97%) of 23 as a clear colorless liquid, and as a mixture of diastereomers: IR (neat) 3470, 3070, 2968, 2926, 2815, 1664, 1633, 1442, 1368, 1171, 1074, 987, 963, 920 cm^{-1}; NMR ($CDCl_3$) δ 6.17-5.05 (m, 5, vinyl), 3.48-3.25 and 3.32 (overlapping m and s, respectively, 4, -CH- and $-OCH_3$), 2.80-2.42 (m, 1, -OH, D_2O exchangeable), 1.71 (d, 3, J = 5 Hz, allylic $-CH_3$), 1.21 and 1.18 (s each, 3, $-CH_3$); mass spectrum m/e (rel intensity) 85 (base), 72 (base), 71 (47), 67 (46), 43 (43).

Anal. ($C_9H_{16}O_2$): C, H.

(Z)- and (E)-4-Methoxy-3-methyl-1,5-heptadien-3-ol (25). As described in the standard procedure, 52 mL of

1.55 M (80 mmol) s-butyllithium in cyclohexane dissolved in 75 mL THF was treated successively with 6.89 g (80 mmol) of 1-methoxy-2-butene, 77 mL of 1.25 M (96 mmol) $ZnCl_2$ in THF, and 4.56 g (65 mmol) of methyl vinyl ketone. Distillation of the reaction product afforded 5.91 g (58%) of 25 as a clear, colorless liquid, and as a mixture of diastereomers and olefin isomers: bp 54-57°C; IR (neat) 3475, 3080, 2970, 2925, 2812, 1652, 1634, 1442, 1086, 987, 961, 914, 708 cm^{-1}; NMR ($CDCl_3$) δ 6.30-4.93 (m, 5, vinyl), 3.91 and 3.86 (d each, 0.6, J = 10 Hz, -CH- from one olefin isomer), 3.50-3.22 and 3.30 (overlapping m and s, respectively, 3.4, -CH- from other olefin isomers $-OCH_3$), 2.92-2.43 (broad m, 1, -OH, D_2O exchangeable), 1.88-1.62 (m, 3, allylic CH_3), 1.22 and 1.19 (s each, 3, $-CH_3$).

Anal. ($C_9H_{16}O_2$): C, H.

(6Z)- and (6E)-5-Methoxy-4-methyl-2,6-octadien-4-ol (27). As described in the standard procedure, 52 mL of 1.55 M (80 mmol) s-butyllithium in cyclohexane dissolved in 75 mL of THF was treated successively with 6.89 g (80 mmol) of 1-methoxy-2-butene, 77 mL of 1.25 M (96 mmol) $ZnCl_2$ in THF, and 5.47 g (65 mmol) of 3-penten-2-one. Distillation of the reaction product afforded 6.43 g (58%) of 27 as a clear colorless liquid, and as a mixture of diastereomers and olefin isomers: bp 35-39°C (0.5-1.0 mm); IR (neat) 3480, 3020, 2970, 2930, 2815, 1663, 1445, 1090, 966, 918,

730 cm^{-1}; NMR ($CDCl_3$) δ 6.22-5.05 (m, 4, vinyl), 3.87 and 3.82 (d each, 0.5, J = 10 Hz, -CH- from one olefin isomer), 3.48-3.23 and 3.30 (overlapping m and s, respectively, 3.5, -CH- from other olefin isomer, and $-OCH_3$), 2.57 (m, 1, -OH, D_2O exchangeable), 1.95-1.61 (m, 6, allylic $-CH_3$), 1.20 and 1.18 (s each, 3, $-CH_3$).

Anal. ($C_{10}H_{18}O_2$): C, H.

3-Methoxy-4,6-dimethyl-1,5-heptadien-4-ol (29). As described in the standard procedure, 14 mL of 0.72 M (10 mmol) s-butyllithium in cyclohexane dissolved in 50 mL of THF was successively treated with 0.72 g (10 mmol) of 1-methoxy-2-propene, 12 mL of 1.0 M (12 mmol) $ZnCl_2$ in THF, and 0.98 g (10 mmol) of mesityl oxide. Molecular distillation of the reaction product at 45°C (15 mm) afforded 1.55 g (91%) of 29 as a clear colorless liquid, and as a mixture of diastereomers: IR (neat) 3480, 3071, 2975, 2932, 2815, 1660, 1635, 1445, 1370, 1090, 993, 975, 926 cm^{-1}; NMR ($CDCl_3$) δ 6.08-5.00 (m, 4, vinyl), 3.55-3.30 and 3.33 (overlapping m and s, respectively, 4, -CH- and $-OCH_3$), 2.57 (broad s, 1, -OH, D_2O exchangeable), 1.87 (d, 3, J = 1 Hz, allylic $-CH_3$), 1.71 (d, 3, J = 1 Hz, allylic $-CH_3$), 1.28 and 1.23 (s each, 3, $-CH_3$).

Anal. ($C_{10}H_{18}O_2$): C, H.

1-(1-Methoxy-2-propenyl)-2-cyclohexen-1-ol (31). As described in the standard procedure, 71 mL of 1.41 M (0.10

mol) s-butyllithium in cyclohexane dissolved in 100 mL of THF was successively treated with 7.21 g (0.10 mol) of 1-methoxy-2-propene, 80 mL of 1.50 M (0.12 mol) $ZnCl_2$ in THF and 8.17 g (0.085 mol) of 2-cyclohexen-1-one. Distillation of the reaction product afforded 11.34 g (79%) of 31 as a clear colorless liquid, and as a mixture of diastereomers: bp 54-55°C (0.03 mm); IR (neat) 3470, 3070, 3013, 2935, 2825, 1634, 1083, 974, 925, 729 cm^{-1}; NMR ($CDCl_3$) δ 6.13-5.03 (m, 5, vinyl), 3.55-3.23 (m with sharp s at 3.32 and 3.29, 4, -CH- and $-OCH_3$), 2.37 (broad s, 1, -OH, D_2O exchangeable), 1.97 (m, 2, allylic $-CH_2-$), 1.67 (m, 4, $-CH_2-$); mass spectrum m/e (rel intensity) 168 (M^+, 0.2), 97 (base), 72 (50), 55 (25), 41 (28).

Anal. ($C_{10}H_{16}O_2$): C, H.

1-(1-Methoxy-2-propenyl)-3-methyl-2-cyclohexen-1-ol (33). As described in the standard procedure, 43 mL of 1.41 M (60 mmol) s-butyllithium in cyclohexane dissolved in 50 mL of THF was successively treated with 4.33 g (60 mmol) of 1-methoxy-2-propene, 60 mL of 1.20 M (72 mmol) $ZnCl_2$ in THF, and 4.61 g (40 mmol) of 3-methyl-2-cyclohexen-1-one. Molecular distillation of the reaction product at 46°C (0.007 mm) afforded 6.50 g (89%) of 33 as a clear colorless liquid, and as a mixture of diastereomers: IR (neat) 3465, 3070, 2930, 2820, 1657, 1631, 1441, 1184, 990, 975, 958, 920 cm^{-1}; NMR ($CDCl_3$) δ 6.18-5.02 (m, 4, vinyl),

3.52-3.27 (m with sharp s at 3.34 and 3.32, 4, -CH- and $-OCH_3$), 2.52 (m, 1, -OH, D_2O exchangeable), 2.12-1.43 (m, 9, $-CH_2-$ and $-CH_3$).

Anal. ($C_{11}H_{18}O_2$): C, H.

1-(1-Methoxy-2-propenyl)-2-cyclopenten-1-ol (35). As described in the standard procedure, 35.5 mL of 1.41 M (50 mmol) s-butyllithium in cyclohexane dissolved in 50 mL of THF was successively treated with 3.61 g (50 mmol) of 1-methoxy-2-propene, 40 mL of 1.50 M (60 mmol) $ZnCl_2$ in THF, and 3.28 g (40 mmol) of 2-cyclopenten-1-one. Molecular distillation of the reaction product at 45°C (0.005 mm) afforded 3.81 g (62%) of 35 as a clear colorless liquid, and as a mixture of diastereomers: IR (neat) 3460, 3045, 2935, 2820, 1633, 1611, 1445, 1084, 991, 964, 925, 770 cm^{-1}; NMR ($CDCl_3$) δ 6.07-5.05 (m, 5, vinyl), 3.53 (d, 1, J = 8 Hz, -CH-), 3.33 (broad s, 3, $-OCH_3$), 2.88 (s, 1, -OH, D_2O exchangeable), 2.62-2.13 (m, 2, allylic $-CH_2-$), 2.08-1.62 (m, 2, $-CH_2-$); mass spectrum m/e (rel intensity) 83 (base), 72 (51), 71 (15), 55 (25), 41 (14).

Anal. ($C_9H_{14}O_2$): C, H.

4-Phenylthio-1,5-hexadien-3-ol (37). As described in the standard procedure, 37 mL of 1.36 M (50 mmol) s-butyllithium in cyclohexane dissolved in 120 mL of THF was successively treated with 7.51 g (50 mmol) of 1-phenylthio-2-propene, 11.00 g (60 mmol) of $CdCl_2$, and 2.80 g (50 mmol)

of acrolein. Molecular distillation of the reaction product at 55°C (0.005 mm) afforded 4.93 g (48%) of 37 as a pale yellow oil and as a mixture of diastereomers: IR (neat) 3430, 3075, 3050, 3015, 1631, 1577, 1477, 1435, 984, 923, 791, 736, 689 cm^{-1}; NMR ($CDCl_3$) δ 7.65-7.17 (m, 5, aromatic), 6.38-4.88 (m, 6, vinyl), 4.48-4.07 (m, 1, -O-CH-), 3.97-3.47 (m, 1, -S-CH-), 2.45 (broad s, 1, -OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 206 (M^+, 12), 150 (base), 149 (52), 110 (72).

Exact mass calcd. for $C_{12}H_{14}OS$: 206.077. Found: 206.077.

4-Methyl-3-phenylthio-1,5-heptadien-4-ol (39). As described in the standard procedure, 37 mL of 1.36 M (50 mmol) s-butyllithium in cyclohexane dissolved in 120 mL of THF was successively treated with 7.51 g (50 mmol) of 1-phenylthio-2-propene, 11.02 g (60 mmol) of $CdCl_2$, and 4.21 g (50 mmol) of 3-penten-2-one. Molecular distillation of the reaction product at 75°C (0.005 mm) afforded 8.32 g (71%) of 39 as a clear, nearly colorless oil, and as a mixture of diastereomers: IR (neat) 3460, 3075, 3050, 2970, 1663, 1626, 1578, 1478, 1435, 965, 917, 737, 689 cm^{-1}; NMR ($CDCl_3$) δ 7.62-7.12 (m, 5, aromatic), 6.25-4.75 (m, 5, vinyl), 3.59 (d, 1, J = 9 Hz, -CH-), 2.85 and 2.47 (s each, 1, -OH, D_2O exchangeable), 1.73 (d of d, 3, J = 1.5, 5 Hz, allylic $-CH_3$), 1.38 and 1.35 (s each, 3, $-CH_3$); mass

spectrum m/e (rel intensity) 234 (M^+, 9), 150 (89), 149 (26), 85 (base).

Exact mass calcd. for $C_{14}H_{18}OS$: 234.108. Found: 234.106.

3,4-Dimethyl-1,5-hexadien-3,4-diol (41). The title compound was prepared from 2,3-butanedione and vinylmagnesium bromide in THF according to the procedure of Leriverend and Conia[9] in 51% yield, bp 86.5-89°C (11-12 mm) [lit.[9] bp 85-88°C (20 mm)].

2-(3,4-Dihydro-6-methoxynaphthyl)-1-methoxy-4-methyl-exo-bicyclo[2.2.2]oct-5-en-2-ol (43). A solution of 3,4-dihydro-6-methoxy-1-naphthylmagnesium chloride in THF was prepared by treating 3.44 g (17.7 mmol) of the vinyl chloride 10 with 1.27 g (52.3 mmol) of magnesium (Rieke modification[23]) in 150 mL of THF for 2 h at 66°C. To the Grignard reagent was added 1.33 g (8.00 mmol) of 1-methoxy-4-methylbicyclo[2.2.2]-oct-5-en-2-one[22] in 25 mL of THF at -72°C over 1 h, followed by warming to 25°C for 10 h. The reaction was quenched with saturated aqueous NH_4Cl, and filtered through Celite. Excess THF was removed in vacuo, and the residue was taken up in ether, washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Removal of solvent in vacuo gave a mixture of the crude exo and endo alcohols as a viscous oil. Chromatography on activity III neutral alumina (ether/hexane, 10:90, followed by ether gradient) afforded 1.408 g (54%) of the

43. Recrystallization from hexane gave an analytical sample as white crystals: mp 119.5-120.5°C; IR (CCl_4) 3565, 2943, 2821, 1600, 1484, 1294, 1245, 1125, 1039, 833, 684 cm^{-1}; NMR ($CDCl_3$) δ 7.85 (broad d, 1, J = 10 Hz, aromatic meta to methoxy), 6.77-6.61 (m, 2, aromatic ortho to methoxy), 6.22 (t, 1, J = 5 Hz, vinyl of dihydronaphthyl), 6.06 (AB quartet, 2, J = 8.5 Hz, $\Delta\nu_{AB}$ = 66 Hz, vinyl of bicyclic), 3.77 (s, 3, aromatic $-OCH_3$), 3.41 (s, 3, bridgehead $-OCH_3$), 2.73-0.87 (m, 11, $-CH_2-$ and -OH, D_2O exchangeable), 0.74 (s, 3, $-CH_3$).

Anal. ($C_{21}H_{26}O_3$): C, H.

Sigmatropic Rearrangements. General Procedure.

A) 1,5-Diene Alkoxide Rearrangements. A dry flask, equipped with a magnetic stirring bar, an inert gas inlet, a reflux condenser (if necessary), and a syringe inlet, was charged with an excess of oil-free metal hydride or alkyllithium reagent as the strong base, and with the reaction solvent. The alcohol and the crown reagent (if required) were dissolved in the same solvent and were added at 0°C to the stirred base solution. The resulting mixture was heated to the appropriate reaction temperature, and the progress of the rearrangement was monitored by glpc.

The reaction was terminated by cooling the mixture to 0°C and by slowly adding it to an excess of ice-cold saturated aqueous NH_4Cl solution. The aqueous solution was extracted with ether, and the combined ethereal extracts were successively washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The ethereal solution was dried (Na_2SO_4), and filtered. Solvent was removed *in vacuo* to give the crude rearrangement product. Purification was usually effected by column chromatography or distillation.

B) 1,5-Dienol Rearrangements. A dry, base-washed, heavy-wall, Pyrex capillary tube (2.5 mm i.d., 8.5 mm o.d.) was charged with freshly distilled alcohol, was degassed under vacuum *via* at least three freeze-thaw cycles, and was sealed under vacuum. The sealed tube was heated in a Wood's

metal bath under specified conditions of time and temperature, after which it was cooled to 0°C and was opened under a blanket of argon. The crude residue was analyzed for rearrangement product and a glpc yield was obtained from a weighed amount of crude material and a weighed amount of a hydrocarbon standard on a gas chromatograph whose detector had been calibrated with mixtures of known composition.

3-Methyl-5-hexenal (12). As described in the standard procedure, 1.01 g (8.98 mmol) of alcohol 11 was treated with 1.6 g (40.0 mmol) of potassium hydride in 60 mL of DME, and the solution was heated at reflux for 12 h. A mixture of the crude product (56.9 mg) and dodecane (40.9 mg) as internal standard were analyzed by glpc and the desired aldehyde 12 was obtained in 92% yield. A pure sample of 12 was obtained as a clear colorless liquid via preparative glpc: IR (neat) 3075, 2955, 2720, 1721, 1636, 1453, 995, 914 cm^{-1}; NMR ($CDCl_3$) δ 9.68 (t, 1, J = 2 Hz, -CHO), 6.07-4.80 (m, 3, vinyl), 2.53-1.92 (m, 5, -CH- and $-CH_2-$), 1.08-0.91 (m, 3, $-CH_3$); mass spectrum m/e (rel intensity) 112 (M^+, 1), 69 (47), 68 (base), 41 (49).

Exact mass calcd. for $C_7H_{12}O$: 112.089. Found: 112.089.

6-Hepten-2-one (14). As described in the standard procedure, 0.569 g (5.07 mmol) of alcohol 13 was treated with 0.24 g (6.0 mmol) of potassium hydride in 50 mL of THF, and

the solution was heated at reflux for 5 h. A mixture of the crude product (24.0 mg) and tetradecane (21.1 mg) as internal standard were analyzed by glpc, and the desired ketone 14 was obtained in 97% yield. A 2,4-dinitrophenylhydrazone derivative was prepared and was recrystallized from ethanol/water: mp 74-75°C [lit.[4] mp 72.5-73.5°C].

4-Methyl-6-hepten-2-one (16). As described in the standard procedure, 0.393 g (3.12 mmol) of alcohol 15 was treated with 0.42 g (10.5 mmol) of potassium hydride in 10 mL of HMPA, and the solution was heated to 35°C for 9 h. Chromatography of the reaction product on activity III neutral alumina (ether/pentane, 0:100, followed by ether gradient) afforded 0.316 g (80%) of 16 as a clear colorless liquid: IR (neat) 3075, 2955, 1708, 1636, 1362, 1167, 993, 911 cm^{-1}; NMR ($CDCl_3$) δ 6.17-4.77 (m, 3, vinyl), 2.47-1.88 (m with s at 2.12, 8, -CH-, $-CH_2-$, and $CO-CH_3$), 1.05-0.83 (m, 3, $-CH_3$); mass spectrum m/e (rel intensity) 126 (M^+, 1), 68 (39), 43 (base), 41 (23).

Exact mass calcd. for $C_8H_{14}O$: 126.104. Found: 126.104.

6-Methyl-6-hepten-2-one (18). As described in the standard procedure, 1.186 g (9.40 mmol) of alcohol 17 was treated with 0.58 g (14.6 mmol) of potassium hydride in 20 mL of THF, and the solution was heated to reflux for 12 h. Chromatography of the crude product on silica gel (CH_2Cl_2/pentane, 40:60, fol-

lowed by CH_2Cl_2 gradient) afforded 1.042 g (88%) of 18 as a clear colorless liquid: IR (neat) 3072, 2937, 1713, 1642, 1443, 1360, 1156, 884 cm^{-1}; NMR ($CDCl_3$) δ 4.73 (m, 2, vinyl) 2.43 (t, 2, J = 7 Hz, -CO-CH_2-), 2.14 (s, 3, -CO-CH_3), 2.10-1.53 (m with broad s at 1.72, 7, -CH_2-, =C-CH_2-, and =C-CH_3); mass spectrum m/e (rel intensity) 126 (M^+, 5), 68 (32), 58 (45), 43 (base), 41 (32).

Exact mass calcd. for $C_8H_{14}O$: 126.104. Found: 126.104.

3-Allylcyclohexanone (20). As described in the standard procedure, 1.024 g (7.41 mmol) of alcohol 19 was treated with 0.58 g (14.5 mmol) of potassium hydride in 30 mL of DME, and the solution was heated at reflux for 12 h. Molecular distillation of the crude product at 60°C (0.05 mm) afforded 0.777 g (76%) of 20 as a clear colorless liquid: IR (neat) 3070, 2930, 1703, 1635, 1443, 1219, 990, 911 cm^{-1}; NMR (CCl_4) δ 5.93-4.78 (m, 3, vinyl), 2.49-1.04 (m, 11, -CH- and -CH_2-).

Anal. ($C_9H_{14}O$): C, H.

7-Methoxy-6-hepten-2-one (22). As described in the standard procedure, 0.694 g (4.88 mmol) of alcohol 21 was treated with 0.29 g (7.13 mmol) of KH in 30 mL of THF, and the solution was heated to reflux for 9.5 h. Molecular distillation of the reaction product at 55°C (0.15 mm) afforded 0.590 g (85%) of 22 as a clear colorless liquid,

and as a mixture of E and Z (3.75:1) isomers: IR (neat) 2935, 1706, 1665, 1648, 1445, 1360, 1205, 1128, 1103, 930, 730 cm^{-1}; NMR ($CDCl_3$) δ 6.32 (broad d, 0.79, J = 13 Hz, trans =CH-O), 5.92 (broad d, 0.21, J = 6 Hz, cis =CH-O), 4.90-4.04 (m, 1, =CH-C), 3.58 and 3.52 (s each, 3, $-OCH_3$ of Z and E, respectively), 2.44 (t, 2, J = 7 Hz, $CO-CH_2-$), 2.24-1.38 (m with s at 2.14, 7, allylic $-CH_2-$, $-CH_2-$, and $CO-CH_3$); mass spectrum m/e (rel intensity) 142 (M^+, 12), 84 (base), 71 (31), 69 (22), 43 (33), 41 (31).

Exact mass calcd. for $C_8H_{14}O_2$: 142.099. Found: 142.101.

7-Methoxy-4-methyl-6-hepten-2-one (24). A) As described in the standard procedure 1.865 g (11.9 mmol) of alcohol 23 was treated with 0.67 g (16.7 mmol) of potassium hydride in 30 mL of DME, and the solution was heated at reflux for 6 h. Molecular distillation of the reaction product at 60°C (0.2-0.3 mm) afforded 1.469 g (79%) of 24 as a clear colorless liquid, and as a mixture of E and Z (5.40:1) isomers: IR (neat) 2950, 2825, 1705, 1648, 1453, 1361, 1203, 1099, 929 cm^{-1}; NMR ($CDCl_3$) δ 6.30 (broad d, 0.84, J = 12.5 Hz, trans =CH-O), 5.97 (broad d, 0.16, J = 5 Hz, cis =CH-O), 4.95-4.17 (m, 1, =CH-C), 3.58 and 3.52 (s each, 3, $-OCH_3$ from Z and E, respectively), 2.70-1.65 (m with s at 2.12, 8, $-CH_2-CO-CH_3$, -CH- and $-CH_2-$), 0.91 (broad d, 3, J = 5 Hz, $-CH_3$); mass spectrum m/e (rel

intensity) 156 (M^+, 0.4), 98 (base), 71 (70), 43 (46), 41 (38).

Exact mass calcd. for $C_9H_{16}O_2$: 156.115. Found: 156.116.

B) As described in the standard procedure, 50.8 mg of alcohol 23 was heated in a sealed tube at 230°C for 8 h. Under these conditions, the starting material was entirely consumed. A mixture of the crude product (14.7 mg) and heptadecane (12.0 mg) as internal standard was analyzed by glpc, and the desired ketone 24 was obtained in 93% yield as a mixture of E and Z (1.4:1) isomers.

The ketone products of the alkoxide and the alcohol rearrangement were chromatographically and spectroscopically identical.

7-Methoxy-5-methyl-6-hepten-2-one (26). As described in the standard procedure 1.654 g (10.6 mmol) of alcohol 25 was treated with 0.61 g (15.1 mmol) of potassium hydride in 30 mL of DME, and the solution was heated at reflux for 10.5 h. Molecular distillation of the reaction product at 50°C (0.20 mm) afforded 1.334 g (81%) of 26 as a clear colorless oil, and as a mixture of E and Z (5:1) isomers: IR (neat) 2950, 1711, 1646, 1447, 1359, 1208, 1168, 936 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (broad d, 0.83, J = 12.5 Hz, trans =CH-O), 5.88 (broad d, 0.17, J = 6.5 Hz, cis =CH-O), 4.54 (d of d, 1, J = 8.5, 12.5 Hz, =CH-C), 3.57 and 3.50 (s each, 3, $-OCH_3$ from Z and E, respec-

tively), 2.59 (t, 2, J = 7.5 Hz, $-CH_2-CO-$), 2.13 (s, 3, $-CO-CH_3$), 1.98-1.18 (m, 3, -CH- and $-CH_2-$), 1.01 and 0.97 (d each, 3, J = 6.5 Hz, $-CH_3$); mass spectrum m/e (rel intensity) 156 (M^+, 10), 98 (base), 85 (69), 83 (23), 55 (27), 43 (56).

Exact mass calcd. for $C_9H_{16}O_2$: 156.115. Found: 156.115.

7-Methoxy-4,5-dimethyl-6-hepten-2-one (28). As described in the standard procedure, 1.020 g (5.99 mmol) of alcohol 27 was treated with 0.41 g (10.2 mmol) of potassium hydride in 30 mL of DME, and the solution was heated at reflux for 24 h. Molecular distillation of the reaction product at 60°C (0.1-0.2 mm) afforded 0.827 g (81%) of 28 as a clear colorless liquid, and as a mixture of E and Z (8:1) isomers: IR (neat) 2955, 2820, 1705, 1644, 1450, 1365, 1205, 1170, 932, 813 cm^{-1}; NMR ($CDCl_3$) δ 6.27 (broad d, 0.89, J = 12 Hz, trans =CH-O), 5.90 (broad d, 0.11, J = 6 Hz, cis =CH-O), 4.84-4.34 (m, 1, =CH-C), 3.50 (broad s, 3, $-OCH_3$), 2.75-1.68 (m with s at 2.11, 7, $CH_3-CO-CH_2-$ and -CH-), 1.13-0.70 (m, 6, $-CH_3$); mass spectrum m/e (rel intensity) 112 (41), 85 (base), 43 (33).

Anal. ($C_{10}H_{18}O_2$): C, H.

7-Methoxy-4,4-dimethyl-6-hepten-2-one (30). As

described in the standard procedure, 1.224 g (7.19 mmol) of alcohol 29 was treated with 0.61 g (15.2 mmol) of potassium hydride in 20 mL of DME, and the solution was heated at reflux for 24 h. Chromatography of the reaction product on silica gel (ether/pentane, 10:90) afforded 0.130 g (11%) of 30 as a clear colorless liquid, and as a mixture of E and Z (6:1) isomers: IR ($CHCl_3$) 2955, 1700, 1644, 1458, 1358, 1206, 1125, 930 cm^{-1}; NMR ($CDCl_3$) δ 6.24 (broad d, 0.86, J = 13 Hz, trans =CH-O), 5.98 (broad d, 0.14, J = 6 Hz, cis =CH-O), 5.00-4.25 (m, 1, =CH-C), 3.56 and 3.52 (s each, 2, $-OCH_3$ from Z and E, respectively), 2.30 (s, 2, $-CO-CH_2-$), 2.11 (s, 3, CH_3-CO-), 1.94 (d of d, 2, J = 1, 8 Hz, allylic $-CH_2-$), 0.97 (s, 6, $-CH_3$); mass spectrum m/e (rel intensity) 170 (M^+, 0.7), 112 (base), 95 (68), 71 (98), 43 (83).

Exact mass calcd. for $C_{10}H_{18}O_2$: 170.131. Found: 170.134.

3-(3-Methoxy-2-propenyl)cyclohexanone (32). A) As described in the standard procedure 7.478 g (44.5 mmol) of alcohol 31 was treated with 2.86 g (71.2 mmol) of potassium hydride in 60 mL of DME, and the solution was heated at reflux for 30 h. Chromatography of the reaction product on activity III neutral alumina (ether/hexane, 10:90) to give 4.978 g (70%) of 32 as a clear colorless liquid, and as a mixture of E and Z (2.10:1) isomers: IR (neat) 2935, 1700, 1646, 1443, 1204, 1105, 933, 746 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (broad d, 0.68, J = 12.5 Hz, trans =CH-O), 5.95

(broad d, 0.32, J = 6 Hz, cis =CH-O), 4.95-4.13 (m, 1, =CH-C), 3.58 and 3.53 (s each, 3, $-OCH_3$ of Z and E, respectively), 2.64-1.18 (m, 11, -CH- and $-CH_2-$); mass spectrum m/e (rel intensity) 168 (M^+, 9), 71 (base), 41 (39).

Anal. ($C_{10}H_{16}O_2$): C, H.

B) As described in the standard procedure, 33 mg of alcohol 31 was heated in a sealed tube at 270°C for 8 h. Under these conditions, the starting material was entirely consumed. A mixture of the crude product (13.3 mg) and nonadecane (6.8 mg) as internal standard were analyzed by glpc, and the desired ketone 32 was obtained in 24% yield as a mixture of E and Z (1:1) isomers.

The ketone products of the alkoxide and the alcohol rearrangement were chromatographically and spectroscopically identical.

3-(3-Methoxy-2-propenyl)-3-methylcyclohexanone (34). As described in the standard procedure, 4.00 g (21.9 mmol) of alcohol 33 was treated with 1.19 g (29.7 mmol) of potassium hydride in 30 mL of DME, and the solution was heated at reflux for 30 h. The crude reaction product was a mixture of the desired rearrangement product, 34, and the cleavage product, 3-methyl-2-cyclohexen-1-one, in a ratio of 1:3.2 by glpc. Purification by chromatography on activity III neutral alumina (ethyl acetate/hexane, 3:97) afforded 0.391 g

(10%) of 34 as a clear colorless liquid, and as a mixture of E and Z (1:1) isomers: IR (neat) 2935, 1703, 1650, 1450, 1222, 1208, 1104, 938, 753 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (broad d, 0.5, J = 13 Hz, trans =CH-O), 6.02 (broad d, 0.5, J = 6 Hz, cis =CH-O), 4.98-4.13 (m, 1, =CH-C), 3.57 and 3.53 (s each, 3, $-OCH_3$ from Z and E, respectively), 2.47-1.38 (m, 10, $-CH_2-$), 0.90 (s, 3, $-CH_3$); mass spectrum m/e (rel intensity) 182 (M^+, 20), 111 (18), 72 (21), 71 (base), 55 (44), 41 (18).

Exact mass calcd. for $C_{11}H_{18}O_2$: 182.131. Found: 182.131.

3-(3-Methoxy-2-propenyl)cyclopentanone (36). As described in the standard procedure, 0.638 g (4.14 mmol) of alcohol 35 was treated with 0.30 g (7.40 mmol) of potassium hydride in 30 mL of DME, and the solution was heated at reflux for 9 h. Molecular distillation of the reaction product at 60°C (0.20 mm) afforded 0.407 g (64%) of 36 as a clear colorless liquid, and as a mixture of E and Z (1:2.56) isomers: IR (neat) 2930, 1730, 1655, 1254, 1154, 1100, 926, 739 cm^{-1}; NMR ($CDCl_3$) δ 6.35 (broad d, 0.28, J = 13 Hz, trans =CH-O), 5.98 (broad d, 0.72, J = 6.5 Hz, cis =CH-O), 5.00-4.15 (m, 1, =CH-C), 3.58 and 3.53 (s each, 3, $-OCH_3$ from Z and E, respectively), 2.70-1.40 (m, 9, -CH- and $-CH_2-$); mass spectrum m/e (rel intensity) 154 (M^+, 0.4), 71 (base), 41 (16).

Exact mass calcd. for $C_9H_{14}O_2$: 154.099. Found:

154.097.

6-Phenylthio-5-hexenal (38). As described in the standard procedure, 0.776 g (3.76 mmol) of alcohol 37 was treated with 0.31 g (7.85 mmol) of potassium hydride in 30 mL of THF, and the solution was kept at 25°C for 1 h. Molecular distillation of the reaction product at 120°C (0.005 mm) afforded 0.324 g (42%) of 38 as a pale yellow oil: IR (neat) 3050, 3015, 2932, 2720, 1718, 1576, 1473, 1433, 1084, 1019, 947, 735, 686 cm^{-1}; NMR ($CDCl_3$) δ 9.74 (t, 1, J = 1.5 Hz, -CHO), 7.24 (broad s, 5, aromatic), 6.43-5.45 (m, 2, vinyl), 2.68-1.50 (m, 6, $-CH_2-$); mass spectrum m/e (rel intensity) 206 (M^+, 50), 162 (45), 149 (30), 116 (38), 110 (base), 85 (45), 41 (25).

Exact mass calcd. for $C_{12}H_{14}OS$: 206.077. Found: 206.077.

4-Methyl-7-phenylthio-6-hepten-2-one (40). As described in the standard procedure, 1.510 g (6.44 mmol) of alcohol 39 was treated with 0.28 g (11.5 mmol) of sodium hydride in 30 mL of ether, and the solution was kept at 25°C for 6 h. Molecular distillation of the reaction product at 120°C (0.002 mm) afforded 1.074 g (71%) of 40 as a pale yellow oil: IR (neat) 3055, 2955, 1705, 1578, 1477, 1437, 1363, 1156, 1087, 1021, 950, 738, 689 cm^{-1}; NMR ($CDCl_3$) δ 7.29 (broad s, 5, aromatic), 6.27-5.53 (m, 2, vinyl), 2.48-1.97 (m with s at 2.09, 8, CH_3-CO, $-CH_2-$ and -CH-), 1.05-0.85 (m, 3, $-CH_3$); mass spectrum m/e (rel intensity) 234 (M^+,

24), 176 (base), 149 (35), 116 (35), 43 (71).

Exact mass calcd. for $C_{14}H_{18}OS$: 234.108. Found: 234.106.

2,7-Octanedione (42). As described in the standard procedure, 0.304 g (2.14 mmol) of diol 41 was treated with 7.0 mL of 1.64 M (11.4 mmol) methyllithium/ether in a reaction solvent of 1.0 mL of HMPA and 2.0 mL of ether, and the solution was maintained at 25°C for 2.5 h. A mixture of the crude product (13.3 mg) and heptadecane (7.5 mg) as internal standard were analyzed by glpc, and the desired dione 42 was obtained in 62% yield. Chromatography of the reaction product on activity III neutral alumina (ether/pentane, 10:90, followed by ether gradient) afforded 0.132 g (43%) of pure 42 as a white flaky solid: mp 39-40°C [lit.[9] mp 38-40 C].

3,16-Dimethoxy-D-homo-9ξ,14β-1,3,5(10),15-estratetraen-11-one (44). As described in the standard procedure, 2.233 g (7.12 mmol) of alcohol 43 was treated with 0.60 g (15.0 mmol) of potassium hydride in 70 mL of THF, and the solution was kept at 25°C for 1 h. Chromatography of the crude reaction product on silica gel (ether/hexane, 10:90, followed by ether gradient) afforded 1.588 g (68%) of 44 as a clear colorless oil, and as a mixture of 9α and 9β isomers: IR (CCl_4) 2990, 2935, 2833, 1712, 1657, 1605, 1494, 1458, 1251, 1242, 1217, 1209, 1203, 1168, 1159, 1153, 1040 cm^{-1}; NMR ($CDCl_3$) δ 6.97-6.37 (m, 3, aromatic), 4.57 and 4.32 (broad s and d,

respectively, 1, vinyl), 3.74-3.37 [m, 7, benzylic -CH-, aromatic $-OCH_3$ (s at 3.68), vinylic $-OCH_3$ (s at 3.45 and 3.42)], 2.93-0.91 [m, 15, -CH-, $-CH_2-$, $-CH_3$ (s at 1.05 and 1.03)].

On standing, the oil partially crystallized, and 0.83 g of white solid was separated from the remaining oil. Spectral data indicated that the solid was a single diastereomer: NMR ($CDCl_3$) δ 6.91-6.43 (m, 3, aromatic), 4.32 (d, 1, J = 4.5 Hz, vinyl), 3.75-3.53 (m with s at 3.69, 4, benzylic -CH- and aromatic $-OCH_3$), 3.42 (s, 3, vinylic $-OCH_3$), 2.92-1.00 [m, 15, -CH-, $-CH_2-$, $-CO-CH_2-$ (s at 2.31), $-CH_3$ (s at 1.05)]. With the solid dissolved in benzene, the nmr spectrum showed both methoxy singlets shifted far enough upfield to reveal the benzylic -CH- as a doublet, J = 6 Hz, at 3.46 δ. The coupling constant thus proved that the solid was the 9β isomer with the cis B-C ring fusion. Further verification of this structural assignment was obtained by converting the 9β isomer to the more stable 9α isomer by treatment with a catalytic amount of sodium methoxide in methanol at 25°C for 12 h. The resulting product was dissolved in benzene, and the benzylic -CH- was plainly visible by nmr as a doublet, J = 12.5 Hz, at 3.62 δ. This large coupling constant is characteristic of a trans ring fusion. Features of the spectrum of the 9α isomer corresponded exactly to those

observed for the mixture above: NMR ($CDCl_3$) δ 4.57 (broad s, vinyl), 3.45 (s, vinylic $-OCH_3$), and 1.03 (s, $-CH_3$). From the integration of the easily distinguished isomeric vinyl protons, the ratio of 9α:9β in the original product mixture was measured to be 1:2.2.

Recrystallization of the solid 9α isomer from ether/hexane afforded analytically pure material: mp 152-153.5°C.

Anal. ($C_{21}H_{26}O_3$): C, H.

Frontalin (52). Analogous to the procedures used by Kocienski and Ostrow[41] in the synthesis of brevicomin, a solution of 0.521 g (4.13 mmol) of ketone 18 in 20 mL of CH_2Cl_2 and 0.763 g (4.42 mmol) of 85% m-chloroperbenzoic acid was stirred at 0°C. After 2 h at 0°C, the solution was treated with 15 mL of 0.1 N $HClO_4$, and stirring was continued at 25°C for 4 h. The reaction mixture was poured into ice-cold saturated aqueous $NaHCO_3$, which was then extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered; solvent removal in vacuo gave a nearly colorless liquid. Chromatography of the crude product on silica gel (ether/pentane, 10:90) afforded 0.482 g (82%) of frontalin (52) as a clear colorless liquid. Spectral properties of frontalin prepared above match those reported for the naturally occurring substance.[38] The product is also identical to a sample of frontalin prepared independently by the route of Mundy and coworkers.[39]

2,3,4,5-Tetrahydro-3aH-inden-7-one (60). A solution consisting of 1.701 g (10.1 mmol) of keto-enol ether 32, 2.5 mL of 4 N H_2SO_4, and 25 mL of THF was heated at reflux for 2.5 h. The reaction solution was cooled to 0°C, and solid $NaHCO_3$ was carefully added to neutralize the acid. The solution was diluted with ether, filtered, washed with water and brine, and dried (Na_2SO_4). Removal of solvent in vacuo gave a yellow liquid as residue. Chromatography of the crude product on silica gel (ether/hexane, 10:90, followed by ether gradient) afforded 1.098 g (80%) of 60 as a clear, colorless liquid: IR (neat) 2930, 2858, 1673, 1607, 1445, 1256, 935, 759 cm^{-1}; NMR ($CDCl_3$) δ 6.75-6.52 (m, 1, vinyl), 2.82 (broad m, 1, -CH-), 2.63-0.97 (m, 10, $-CH_2-$); mass spectrum m/e (rel intensity) 136 (M^+, 49), 80 (base), 79 (49).

Exact mass calcd. for $C_9H_{12}O$: 136.089. Found: 136.089.

2,3,4,5-Tetrahydro-3a-methylinden-7-one (61). A solution consisting of 0.154 g (0.846 mmol) of keto-enol ether 34, 0.5 mL of 4 N H_2SO_4, and 10 mL of THF was heated at reflux for 5 h. The reaction solution was cooled to 0°C, and solid $NaHCO_3$ was carefully added to neutralize the acid. The solution was diluted with ether, filtered, washed with brine, and dried (Na_2SO_4). Removal of solvent in vacuo gave a yellow liquid as residue.

Chromatography of the crude product on silica gel (ether/hexane, 5:95, followed by ether gradient) afforded 0.0600 g (47%) of 61 as a clear colorless liquid: IR (neat) 2940, 1680, 1612, 1448, 1240, 1158, 924, 702 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (t, 1, J = 3 Hz, vinyl), 2.73-1.38 (m, 10, $-CH_2-$), 1.08 (s, 3, $-CH_3$); mass spectrum m/e (rel intensity) 150 (M^+, base), 135 (74), 107 (97), 94 (58), 93 (35), 79 (94), 55 (32).

Exact mass calcd. for $C_{10}H_{14}O$: 150.104. Found: 150.104.

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26. Additional support for this view is provided in Ref. 12c; the rearrangement below proceeds in 78% yield as the alkoxide (M = K, diglyme, 110°C, 24 h), but

proceeds in 0% yield (mostly degradation with some starting material left) as the alcohol (M = H, sealed tube, 250°C, 4 h).

27. The ordering $MgX^+ < Li^+$ can be deduced from the following observations: (1) Diol 41 undergoes a [3,3]-rearrangement as a dilithium salt but not as a dimagnesium salt (see text). (2) The reversibility of addition of allylic organometallic reagents to ketones is ten times faster for Li^+ alkoxide than for MgX^+ alkoxide (see ref. 25a).

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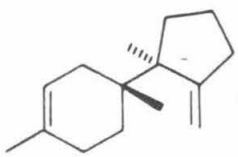

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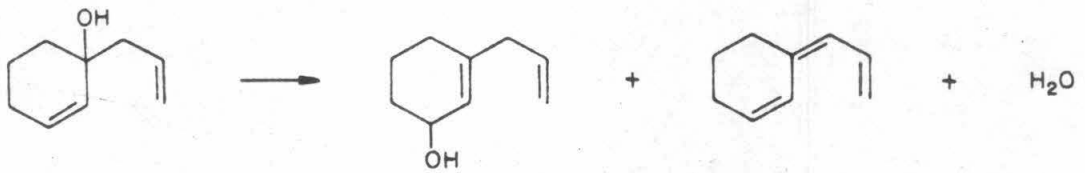

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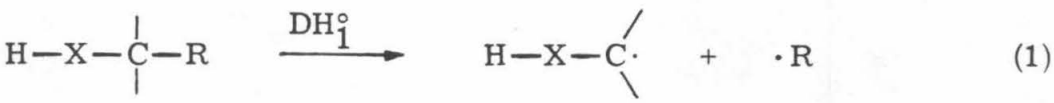
CHAPTER II

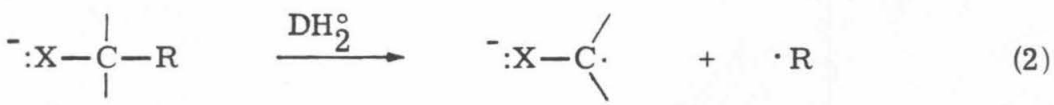
Oxy Anion Substituent Effects and the Thermochemistry of the Oxy-Cope Rearrangement

Introduction

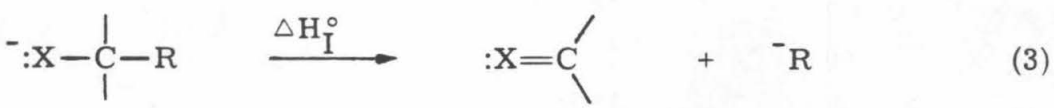
Our investigation into the scope and utility of the base-accelerated oxy-Cope rearrangement has illustrated the tremendous substituent effect of an oxy anion in promoting bond reorganizations involving an adjacent breaking bond.[1] Numerous recent examples of [3,3]- and [1,3]-sigmatropic rearrangements which are strongly promoted by charged heteroatom substituents have been reported.[1] Similar to sigmatropic rearrangements in neutral molecules, rearrangements in charged systems may proceed via concerted, stepwise radical, or stepwise ionic pathways. Unfortunately, no information is available on the perturbation of charged heteroatoms on adjacent bond strengths and consequent bond homolysis (eq 2), or on the alternate ionic fragmentation (eq 3). We have thus attempted to



(1)



(2)



(3)

evaluate the substituent effect of an oxy anion (X = O)

on bond reorganizations by estimating the gas phase bond dissociation energy DH°_2 and the heterolytic fragmentation energy ΔH°_I. In principle, the approach used to make these estimates can be generalized to include a variety of more complex anionic systems. From a practical standpoint, however, the calculations are limited by the availability of reliable gas phase thermochemical data, and therefore, only simple alkoxides could be examined. Despite these drawbacks, the results are significant, and they are relevant to a number of chemical systems involving bond reorganizations.

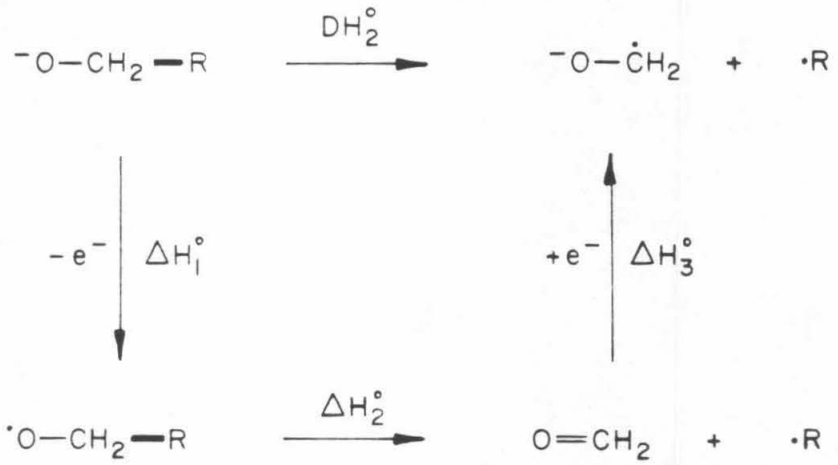
In addition, some general features of the thermochemistry of the anionic oxy-Cope rearrangement will be examined. An alternate approach using pK_a's to estimate the alkoxide substituent effect in the oxy-Cope system will be presented. Finally, the implications of the substituent effect data with respect to the mechanism of the rearrangement will be discussed.

Oxy Anion Substituent Effects in Simple Alkoxides

Homolytic Bond Fragmentations. The bond dissociation energies DH°_2 (eq 2) of several alkoxides were estimated and were compared with the corresponding bond energy data DH°_1 (eq 1) for alcohols. The resulting difference in bond energies is a measure of the substituent effect of

O^-. Accordingly, a simple Born-Haber cycle (Scheme I) was established and the gas phase bond dissociation energies DH°_2 were calculated for primary alkoxide ions, R = H, CH_3, $CH_2CH{=}CH_2$.

Scheme I



$$DH^\circ(\bar{O}CH_2{-}R) = EA(\dot{O}CH_2R) - EA(CH_2O) + DH^\circ(\dot{O}CH_2{-}R)$$

The thermochemical data used in the cycle is given in Table I. From the recent work of McIver and of Hamill, the gas phase electron affinities (EA) of simple alkoxy radicals are available, $\Delta H^\circ_1 = EA(RO\cdot)$.[5,6] The necessary bond dissociation energies $DH^\circ(\cdot OCH_2\text{-}R)$ have either been determined or can be estimated.[2,3,8,9] Experimentally determined EA's for aliphatic carbonyl compounds, $\Delta H^\circ_3 = EA(RR'C{=}O)$, are generally unavailable. However, recent electron transmission spectroscopic studies on formaldehyde

Table I. Electron Affinities (EA) and Bond Dissociation Energies (DH°) of Simple Radicals and Molecules.[a]

	EA	DH° ($\cdot O-\overset{|}{\underset{|}{C}}-R$)
$\cdot OCH_2-H$	39[b]	22[h]
$\cdot O\underset{\underset{H}{|}}{C}HCH_3$	40[b]	19[i]
$\cdot OCH_2-CH_3$	40	13[h]
$\cdot OCH_2-CH_2CH=CH_2$	44[c]	-1[j]
$O=CH_2$	-15.2[d]	
$O=CHCH_3$	-22.4[d]	
$\cdot H$	18.9[e]	
$\cdot CH_3$	1.8[f]	
$\cdot CH_2CH=CH_2$	12.7[g]	

[a]All values reported in kcal/mol. [b]Ref. 5. [c]Assumed to be approximately equal to EA (n-BuO·); ref. 6. [d]Ref. 7. [e]Ref. 13. [f]Ref. 27. [g]Ref. 28. [h]Ref. 2 and 3. [i]Calculated from heats of formation; ref. 8. [j]Calculated from heats of formation; ref. 9.

provide the most reliable measurement for its EA (-15.2 kcal/mol).[7] An important feature to note is that the calculation applies only to idealized "free" alkoxides (no counterion) in the gas phase at 298°K. The calculated values for $DH°(\bar{O}CH_2\text{-}R)$, literature values for $DH°(HOCH_2\text{-}R)$,[2-4] and the substituent effects (ΔD) are shown in Table II.[25]

The data in Table II indicate that the effect of O^- in promoting bond homolysis in primary alkoxides is quite significant, ΔD = 13-17 kcal/mol. These results have been corroborated by Goddard and coworkers[15] in a series of calculations employing ab initio generalized valence bond and configuration interaction theoretical methods. The substituent effect of the oxy anion in CH_3O^- at 298°K was calculated to be 16.5 kcal/mol. The origin of this observed bond weakening is differential stabilization of the developing radical by overlap with orbitals of each of the oxygen species. In effect, delocalization via a two-center three-electron bond is better in $\cdot CH_2\text{-}O^-$ ($\cdot CH_2\text{-}O^- \longleftrightarrow CH_2\dot{=}O$) than in $\cdot CH_2OH$.[15] Similarly, the effect of negatively charged heteroatoms on adjacent bond strengths has been investigated by McIver, Hehre, and coworkers,[16] and the observed bond weakening was explained in terms of anionic hyperconjugation and perturbation molecular orbital theory. Our estimated oxy anion substituent effects are also in agreement with the few experimental cases in which these values were determined: (1) base-accelerated oxy-Cope

Table II. Calculated Bond Dissociation Energies of $^{-}OCH_2-R$ and Substituent Effects for:[a]

$$XCH_2-R \longrightarrow XCH_2\cdot + \cdot R$$

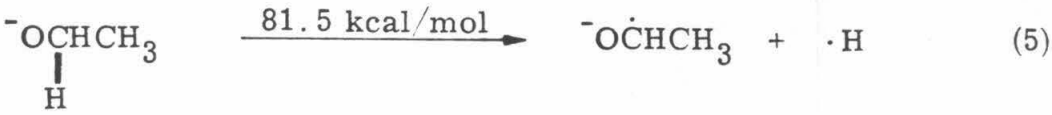
R	$DH^\circ(HOCH_2-R)$	$DH^\circ(\bar{O}CH_2-R)$[b]	ΔD[e]
H	93[c]	76	17
CH_3	83[c]	68	15
$CH_2CH=CH_2$	71[d]	58	13

[a]All values reported in kcal/mol. [b]Gas phase, 298°K. [c]Ref. 2, 3. [d]Ref. 4. [e]$\Delta D = DH^\circ(HOCH_2-R) - DH^\circ(\bar{O}CH_2-R)$.

rearrangement, $\Delta\Delta H^{\ddagger}$ = 17.8 kcal/mol,[17,18] and (2) base-accelerated [1,3]-rearrangement of 7-hydroxybicyclo[2.2.1]-hepta-2,5-diene, $\Delta\Delta H^{\ddagger}$ = 15.7 kcal/mol.[17,19]

In a completely analogous fashion, the oxy anion substituent effect in stabilizing a secondary radical can be calculated in a simple case such as ethoxide, $^{-}OCH_2CH_3$. The bond dissociation energy $DH^\circ[^{-}OCH(-H)CH_3]$ can be calculated from the appropriate data in Table I *via* a thermodynamic cycle similar to that in Scheme I; the result is $DH^\circ[^{-}OCH(-H)CH_3]$ = 81.5 kcal/mol. A comparison

$$\mathrm{HOCHCH_3} \xrightarrow{90\ \text{kcal/mol}} \mathrm{HO\dot{C}HCH_3} + \cdot\mathrm{H} \qquad (4)$$



$$\mathrm{^-OCHCH_3} \xrightarrow{81.5\ \text{kcal/mol}} \mathrm{^-O\dot{C}HCH_3} + \cdot\mathrm{H} \qquad (5)$$

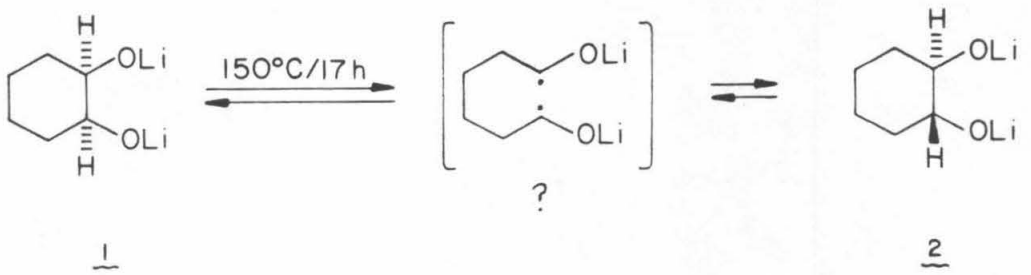
of the bond dissociation energies from equation 4[3] and equation 5 shows that the oxy anion substituent effect, ΔD = 8.5 kcal/mol, is considerably reduced at a secondary carbon in comparison to that calculated at a primary carbon, ΔD = 17 kcal/mol (vide supra).

At this point, the effects of counterions, M^+ (Li^+, Na^+, K^+), on DH° ($MOCH_2$–R) are only speculative. However, the electrostatic effect of M^+ is predicted to cause a greater net stabilization of the charge-localized alkoxide than of the charge-delocalized ketyl. These projections are consistent with the observations of Hirota on the counter-ion effects on pinacolate $\rightleftharpoons$ ketyl dissociation constants (eq. 6, R = fluorenyl).[20] Qualitatively, K_d increases

$$\mathrm{MO{-}C(R)(R){-}C(R)(R){-}OM} \xrightleftharpoons{K_d} 2\ \mathrm{R_2\dot{C}{-}OM} \qquad (6)$$

with decreasing alkali metal electronegativity (Li > Na > K). At the present time, no quantitative estimates can be made

for the counterion effects on $DH°(MO\dot{C}-R)$. Such estimates would be important in evaluating the feasibility of ketyl intermediates in systems such as the proposed equilibration of the cis dialkoxide 1 to the more stable trans form 2 (eq 7).[21] Assuming the reaction time represents 10 half-



1 2 (7)

lives, the reaction is clean and first order in dialkoxide, and $\Delta S^{\ddagger} \cong +22$ eu (from Benson's group additivity data[14]), then E_a is estimated to be 42 kcal/mol. By comparison, the strength of the fragmenting carbon-carbon bond, considering the cumulative substituent effects of the hydroxyl group (7 kcal/mol weakening[19]) and the oxy anion at a secondary center (8.5 kcal/mol weakening, vide supra), is estimated to be 51 kcal/mol. Thus, the energetics of the fragmentation process argue against the proposed intermediacy of the ketyl under the given reaction conditions. Indeed, a careful examination of the equilibration 1 ⇌ 2 by McMurry and Choy[22] revealed that the transformation occurred via a redox process, and that ketyl intermediates could be ruled out unequivocally.

Over the years, a substantial body of data has accumulated which indicates that methoxide ion is an effective hydrogen atom donor (eq 8).[23] The data in Table II suggest that methoxide ion [$DH°(^{-}OCH_2-H)$ = 76 kcal/mol] could be a better

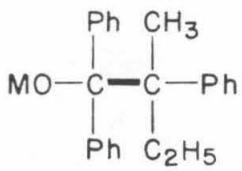
$$R\cdot + CH_3O^- \longrightarrow R-H + \cdot CH_2O^- \qquad (8)$$

hydrogen atom donor than thiols [$DH°(CH_3S-H)$ = 88 kcal/mol[4]] which are commonly employed hydrogen atom transfer agents. Not surprisingly, the sodium salt of methyl mercaptan has similarly been utilized as a hydrogen atom source.[24]

The large magnitude of oxy anion substituent effects is in striking contrast to the initial intuitive prediction of many chemists that the effect would be small; however, the thermochemical values calculated above are consistent with recent experimental evidence.[1,23,24]

Heterolytic Bond Fragmentation. In the previous section, the perturbation of negatively charged oxygen on bond homolysis was examined (eq 2, X = O). In this section, the energetics of gas phase heterolysis (eq 3, X = O) will be estimated and will be compared to that of the corresponding homolysis. The results will be correlated with analogous processes in solution where metal counterions are known to play an important role in the mode of alkoxide fragmentation.

Alkoxide fragmentation processes, both in solution[20,29-33] and in the gas phase,[32] have been reported. From these studies the fragmentation mode (homolysis vs heterolysis) appears to be defined not only by substrate alkoxide but also by counterion and solvent. In a detailed study of optically active alkoxides, Cram demonstrated the importance of alkali metal counterions in directing the course of fragmentation.[30] In the case of substrate 3 (M = K, Na, Li), heterolysis predominated for M = K while homolysis was preferred for M = Li.[30]



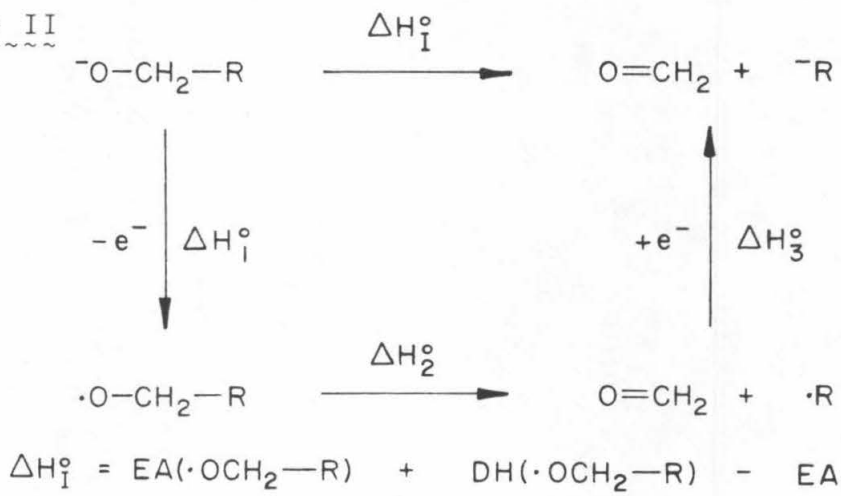
3

M	k_{het}/k_{hom}
K	2.2
Na	1.6
Li	0.05

The intrinsic reactivities of alkoxides in the absence of metal counterions and solvent effects can be determined, however, by comparing the enthalpies of reaction for the two fragmentation modes, radical (DH_2°) vs ionic (ΔH_I°). The estimates for DH_2° have previously been made (vide supra); because of the unavailability of suitable thermochemical data, ΔH_I° must be estimated also. Analogous to the procedure for estimating bond dissociation energies, the enthalpy for the ionic fragmentation process can be calculated from

the thermochemical cycle illustrated in Scheme II. The values for the required EA's and bond strengths are listed

Scheme II



$$\Delta H_I^\circ = EA(\cdot OCH_2-R) + DH(\cdot OCH_2-R) - EA(\cdot R)$$

in Table I. The results are summarized in Table III.

Table III. Calculated Fragmentation Energies for Primary Alkoxides, $^{-}OCH_2-R$.[a, b]

R	$DH^\circ(\bar{O}CH_2-R)$	ΔH_I°
H	76	42
CH_3	68	51
$CH_2CH=CH_2$	58	30

[a]All values reported in kcal/mol. [b]Gas phase, 298°K.

In the case of fragmentation at a secondary carbon center such as in $^{-}OCH_2CH_3$ (eq 9), the enthalpy of the heterolytic mode can also be estimated *via* a thermochemical cycle. Such a process was found to require only 40 kcal/mol (eq 9). By comparison, the homolytic

$$^{-}OCHCH_3 \xrightarrow{40\ \text{kcal/mol}} O{=}CHCH_3 + {}^{-}H \qquad (9)$$
$$\quad\ H$$

cleavage of the same C-H bond (eq 5) is higher in energy by 41.5 kcal/mol. The $^{-}OCH_2CH_3$ case also provides an opportunity to compare the relative leaving capabilities of hydrogen *vs* methyl. In a radical process, $\cdot CH_3$ is ejected preferentially (DH°_2 = 68 kcal/mol) rather than $\cdot H$ (DH°_2 = 81.5 kcal/mol). However, in an ionic process, H^- is ejected (ΔH°_I = 40 kcal/mol) instead of CH_3^- (ΔH°_I = 51 kcal/mol).

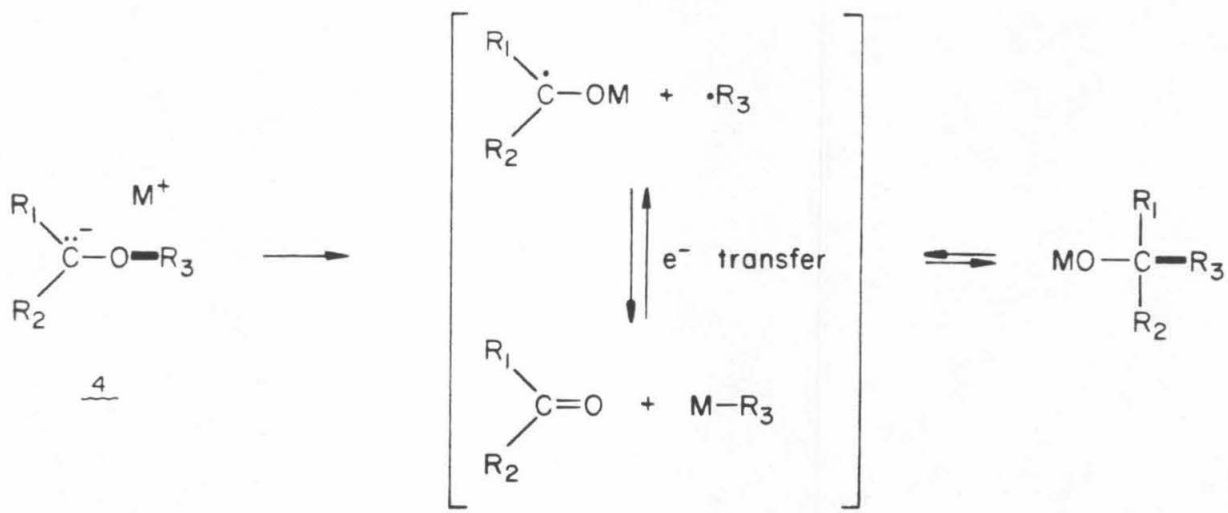
Clearly, heterolysis is preferred over homolysis to a significant degree in free alkoxides, and is favored by 17-41.5 kcal/mol. In contrast to DH°_2, no regular trends are discernible for ΔH°_I because of its dependence on widely varying EA($\cdot$R) values. The preference for heterolysis by free alkoxides agrees with Cram's observations on the counterion trend in the cleavage of $\underset{\sim}{3}$ in solution, *ie*,

an increase in the ionic character of the oxygen-alkali metal bond promotes a corresponding increase in the ratio of heterolysis/homolysis.[30] Recently, Arnett and McIver[32] have reported the fragmentation of the potassium salt of tri-tert-butylcarbinol in solution (25°C, DMSO). Due to the absence of radical coupling products, they concluded that alkoxide decomposition was probably proceeding via heterolytic rather than homolytic cleavage, although the latter process couldn't be ruled out. Our thermochemical estimates for DH° and ΔH_I° lend support to the above conclusions. At the present time thermochemical data is not available on the effect of metal cations, M^+, on DH°($MOCH_2$–R) and ΔH_I°($MOCH_2$–R). However, both DH° and ΔH_I° values should increase, but by differing increments, as the electron donor properties of oxygen are diminished by ion pairing to increasingly electronegative metal counterions. As suggested by Cram's study,[30] bond homolysis may well be preferred in many lithium and magnesium alkoxides.

Mechanistically, alkoxide fragmentation such as those discussed above bears a striking resemblance to the well-known Wittig rearrangement of metallated ethers $\underset{\sim}{4}$ (Scheme III).[34] Homolytic as well as heterolytic dissociation modes of $\underset{\sim}{4}$ have been intensively examined mechanistic issues. Recent studies have provided evidence for radical pair intermediates in this [1,2] sigmatropic process.[34] In

the Wittig rearrangement the charged carbon donor substituent which facilitates carbon-oxygen bond cleavage is subject to counterion effects similar to that found in alkoxide fragmentation.[34,35] Thus, dissociated metal alkyls undergo rearrangement while covalent metal alkyls do not. Finally, the radical and/or charged intermediates accessible from metallated ethers or alkoxides are simply

Scheme III



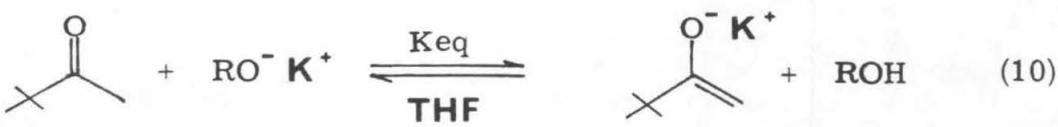
4

related by an electron transfer process. This corresponds to the single electron transfer (SET) mechanism proposed by Ashby for the addition of organometallics to carbonyl compounds.[36] Accordingly, those factors identified by Ashby which favor the SET mechanism in organometallic-carbonyl

addition should be relevant to defining the course of alkoxide fragmentation.

Oxy Anion Substituent Effects in the Oxy-Cope Rearrangement

Thermochemistry. The presence of an oxy anion at C-3 or C-4 of a Cope system not only causes a decrease in the activation parameters of the rearrangement but also causes the anionic rearrangement to be more exothermic than the neutral rearrangement. The difference in reaction profiles of the two rearrangements is shown in Figure I. The magnitude of the difference between ΔG_1 and ΔG_2 can be estimated from equilibrium data obtained by Brown[37] concerning the deprotonation of a carbonyl compound by alkoxide bases (eq 10). The experimental conditions in this study were nearly identical to those utilized in the anionic oxy-Cope rearrangements. The equilibrium constant Keq can



(10)

be expressed as follows:

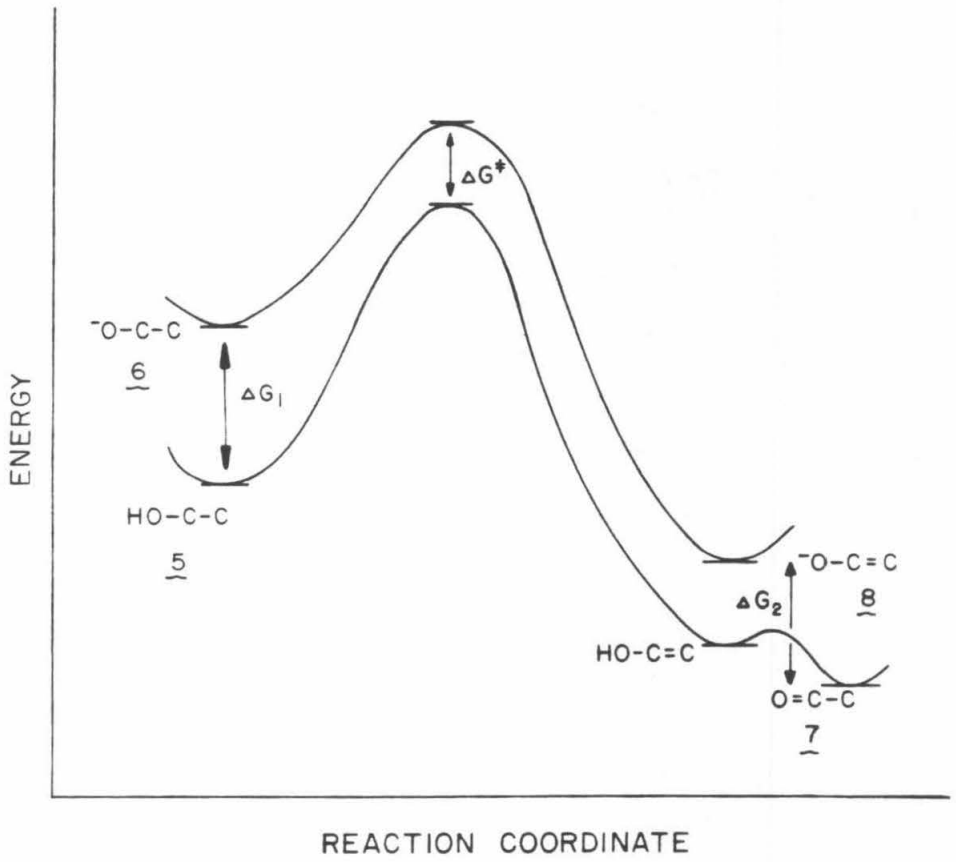
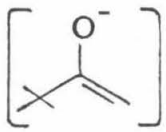
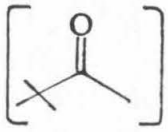


Figure 1. Reaction Profile of the Neutral vs Anionic Oxy-Cope Rearrangement.

$$Keq = K_2/K_1 \qquad (11)$$

where

$$K_1 = [RO^-][H^+]/[ROH]$$

$$K_2 = \left[\text{  }\right]\left[H^+\right] \Big/ \left[\text{  }\right]$$

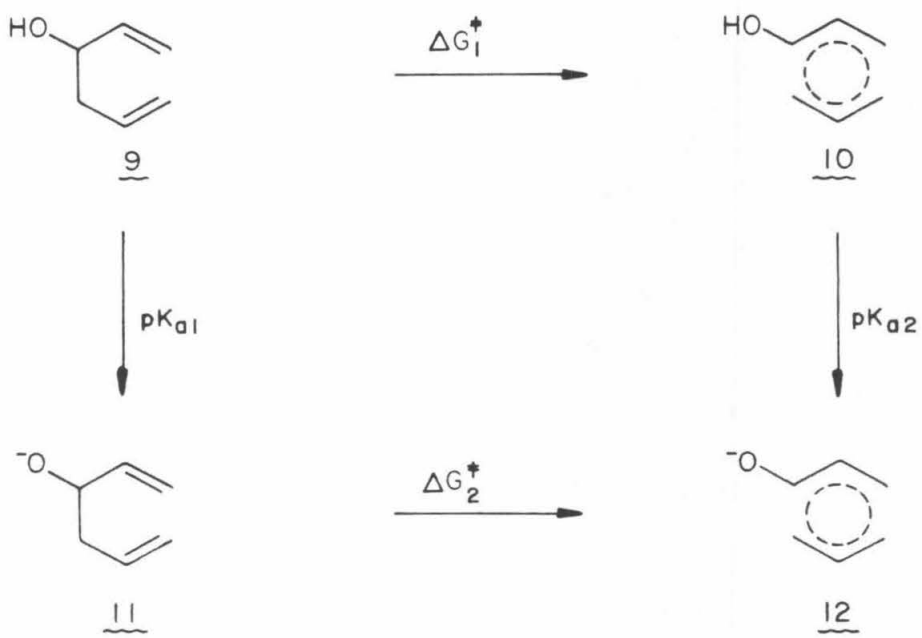
Using the relationship between free energy and an equilibrium constant, an expression for the difference in free energies (eq 12) can be derived from equation 11. Because Keq is

$$\Delta G_1 - \Delta G_2 = RT \ln Keq \qquad (12)$$

greater than unity in all cases,[37] ΔG_1 is greater than ΔG_2. Applying these findings to the Cope system (Figure I) demonstrates that the alkoxide rearrangement (6 → 8) is more exothermic than the neutral alcohol rearrangement (5 → 7).

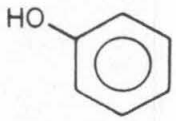
Oxy Anion Substituent Effect. An alternate method of estimating the substituent effect of an oxy anion can be devised specifically for the case of the oxy-Cope rearrangement. Again a thermodynamic cycle can be established (Scheme IV) which relates the different species of the neutral and

Scheme IV



the anionic rearrangement. A concerted cyclic transition state is assumed in each case, and these states are most conveniently represented by species 10 and 12. Recent experimental evidence consistent with a concerted mechanism[38] tends to support this assumption. The alcohols 9 and 10 are related to the alkoxides by their pK_a's. Allyl alcohol and phenol will serve as model compounds for 9 and 10, respectively, and their pK_a's have been determined in an aprotic medium, dimethylsulfoxide (DMSO): pK_a (allyl alcohol) = 27.0,[39] and pK_a (phenol) = 18.4.[40] Assuming that the entropy changes for 9 → 11 and 10 → 12 are approximately the same and thus will cancel, the enthalpies $\Delta H^{\ddagger}$

pK_a = 27.0



pK_a = 18.4

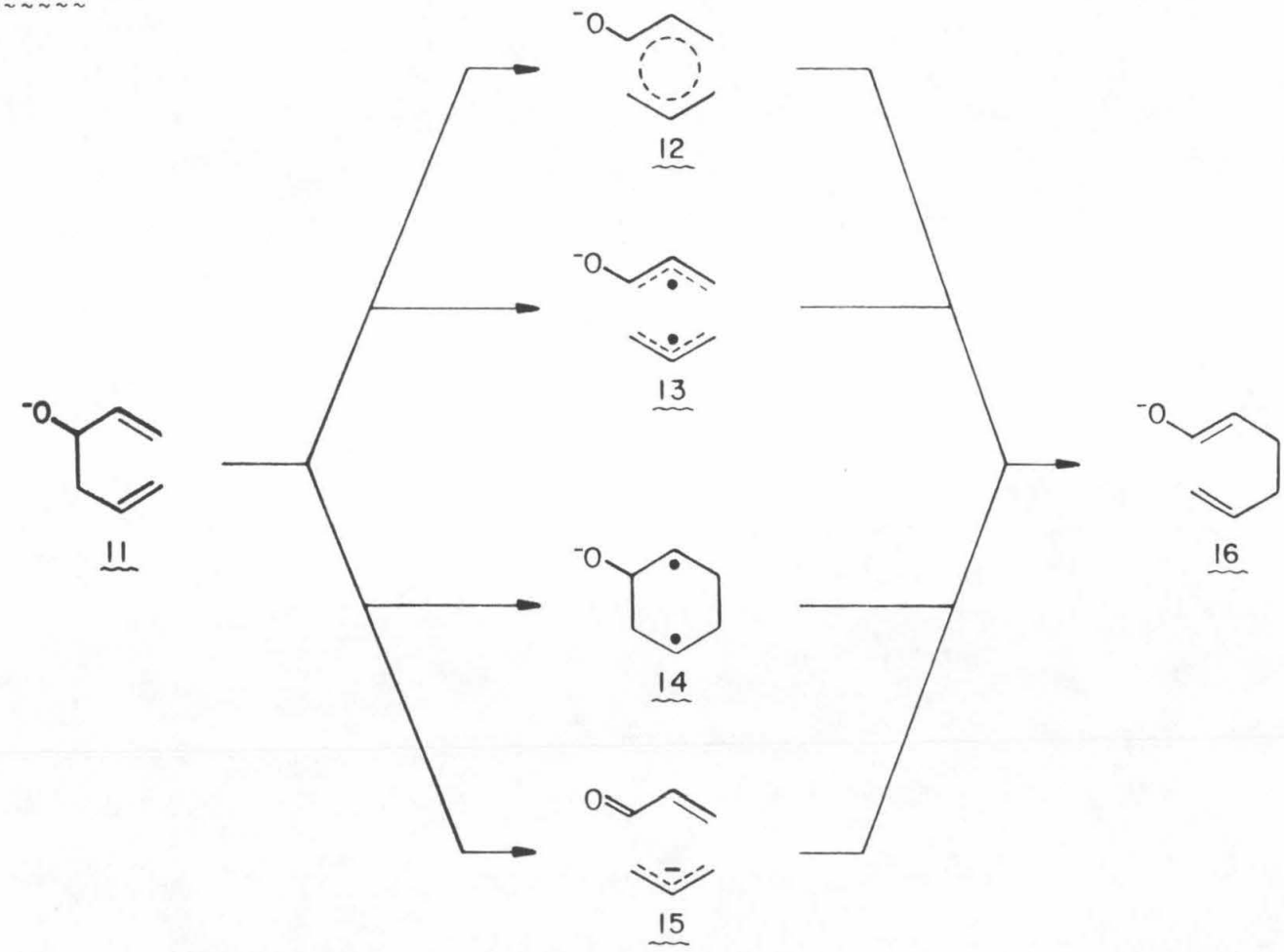
and pK_a's can be related (eq 13). Therefore, at 298°K the net difference in enthalpies is $\Delta H^{\ddagger}$ = 11.8 kcal/mol. Given the different assumptions and approximations made

$$\Delta H_1^{\ddagger} - \Delta H_2^{\ddagger} = 2.3\,RT\,(pK_{a_1} - pK_{a_2}) \qquad (13)$$

in each approach, the oxy anion substituent effects calculated using pK_a data in a concerted process ($\Delta H^{\ddagger}$ = 11.8 kcal/mol), and using EA's and bond strengths in a radical process (ΔD = 13 kcal/mol, Table II, R = allyl) are remarkably similar.

Mechanistic Implications. The [3,3]-rearrangement of diene alkoxides could proceed by a number of different mechanistic pathways (Scheme V).[41,42] Each of these transition states or intermediates can now be examined in light of the oxy anion substituent effects discussed above to determine whether they are thermodynamically feasible with respect to known experimental data.[1,18] To make such estimates, the substituent effects of the

Scheme V



hydroxyl group and the oxy anion are simply added to the enthalpy of reaction for the rate determining step of the parent rearrangement, the classical Cope rearrangement.

In the case of the concerted pathway, 11 → 12, hydroxyl on an allylic carbon lowers ΔH by ~3 kcal/mol,[43] $\Delta H^{\ddagger}$ ($-O^{-}$, concerted) = 11.8 kcal/mol, and $\Delta H^{\ddagger}$ (Cope) = 33.5 kcal/mol.[44] Thus, ΔH (11 → 12) = 18.7 kcal/mol. This is a sufficiently small value to make the concerted pathway a permissible mechanism.

In the case of the homolytic fragmentation process, 11 → 13, hydroxyl on an allylic carbon lowers ΔH by ~3 kcal/mol,[43] ΔD ($-O^{-}$, R = allyl) = 13 kcal/mol, and $\Delta H^{\ddagger}$ = 62 kcal/mol[11] which is the difference in enthalpy between 1,5-hexadiene and two allyl radicals. Thus, ΔH (11 → 13) = 46 kcal/mol. Such a high value for ΔH is not consistent with the low activation parameters of the anion rearrangement, 11 → 16.

The intermediacy of biradicaloids such as 14 has been the topic of much debate in studies of the mechanism of the Cope rearrangement.[42] Because the rate determining step is 14 → 16, the hydroxyl at a saturated carbon lowers ΔH by ~7 kcal/mol,[19] ΔD ($-O^{-}$, at secondary carbon) = 8.5 kcal/mol, and $\Delta H^{\ddagger}$ (diyl cleavage) = 53 kcal/mol.[42] Thus, ΔH (14 → 16) = 37.5 kcal/mol. This large value is inconsistent with the energetics of the anionic oxy-Cope, and

thus the occurrence of 14 seems unlikely.

Ionic pathway 11 → 15 is interesting in that the intermediate pair 15 results simply from an electron transfer between the two radicals of 13 (eq 14). The magnitude of the electron transfer reaction is determined by the EA's

13 15 (14)

of the two species (eq 15). Although the exact gas phase value of EA ($O{=}CHCH{=}CH_2$) is unknown, the recent work of Jordan and Burrow[45] permitted a value of EA > 0 kcal/mol to

$$\Delta H\ (e^- \text{ transfer}) = EA\ (O{=}CHCH{=}CH_2) - EA\ (\cdot CH_2CH{=}CH_2) \qquad (15)$$

be estimated. From this EA value, the data from Table I, and according to equation 15, ΔH (e^- transfer) > -12.7 kcal/mol is calculated. The net enthalpy of 11 → 15 is ΔH (11 → 15) = ΔH (11 → 13) + ΔH (e^- transfer) > 33.3 kcal/mol. Although the ionic fragmentation pathway is more favorable than either of the radical processes, it still appears to be too high in energy for the overall transformation of 11 → 16.

To summarize, only the concerted mechanism (via 12) appears to be feasible, and both the radical mechanisms and the ionic mechanism (via 13, 14, and 15 respectively) appear to be unfeasible based strictly on thermochemical estimates of activation energies and substituent effects. One should note carefully, however, that only the fully dissociated radical and polar species were treated above. Application of the calculated substituent effects is somewhat more tentative in systems where bond making and bond breaking occur simultaneously, but in an unsymmetrical fashion. The case for the concerted mechanism, however, has received experimental support from a careful investigation into the stereochemistry of the anionic oxy-Cope rearrangement.[38] All the observed stereochemical results were consistent with predicted steric interactions in both chair-like and boat-like concerted transition states.

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9. Estimate based upon ΔH_f° ($CH_2{=}O$) = -26.0 kcal/mol (ref. 10), ΔH_f° ($\cdot CH_2CH{=}CH_2$) = 41.2 kcal/mol (ref. 11), and ΔH_f° ($\cdot OCH_2CH_2CH{=}CH_2$) $\cong$ 16 kcal/mol (references 5 and 12-14).
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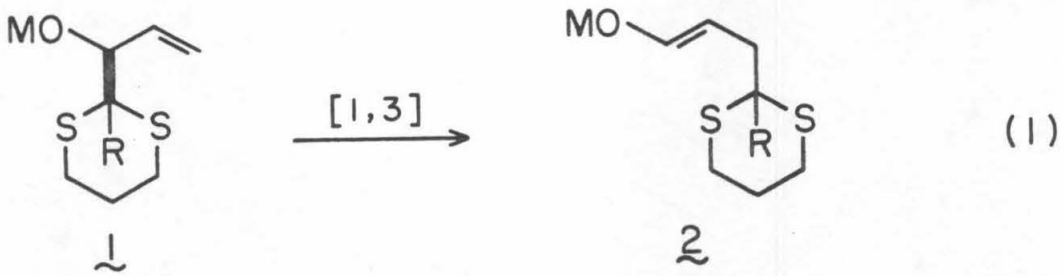
CHAPTER III

Oxy Anion-Accelerated Rearrangements: [1,3]-Dithiane Shifts and the Ene Reaction

Accelerated [1,3]-Rearrangement of Dithianes

Introduction. The powerful substituent effect of an oxy anion in promoting bond reorganizations, such as the oxy-Cope rearrangement[1] and bond homolysis/heterolysis of simple alkoxides,[2] has previously been examined. Extension of the concepts developed in this work led us to investigate other, more diverse chemical systems undergoing bond reorganizations which could be facilitated by an anionic substituent.

In particular, the formal [1,3]-shift of a 1,3-dithiane appeared to be an appropriate system (eq 1). The alkoxide species 1 and 2 simply correspond to the 1,2- and 1,4-

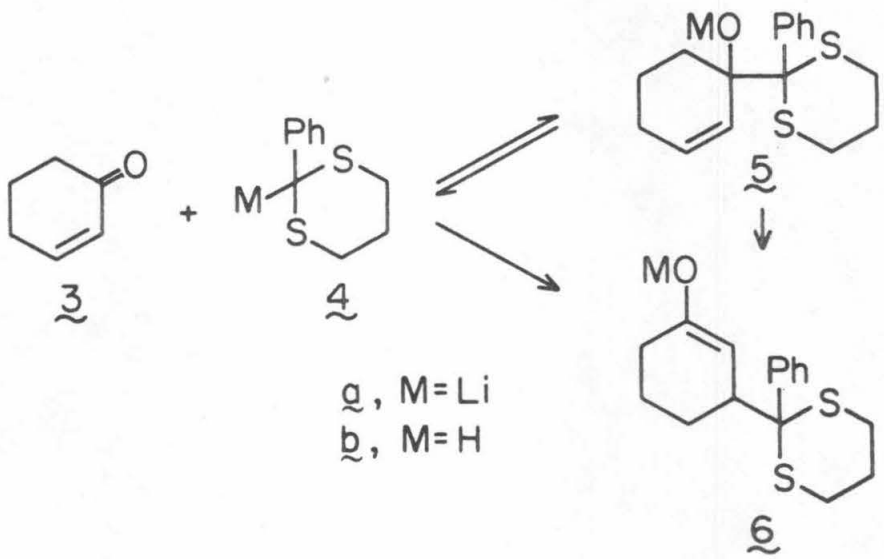


1 2 (1)

addition products of a dithiane anion and an α,β-unsaturated carbonyl compound.[3] Most dithiane anions which undergo 1,4-addition to enones have R as an anion-stabilizing group.[3] In certain instances, rearrangement of the kinetic adduct to the thermodynamically more stable 1,4-adduct was observed. For example, Ostrowski and Kane[4] studied the reaction of 2-lithio-2-phenyl-1,3-dithiane (4a) with

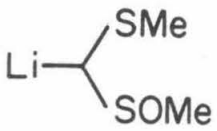
cyclohexenone (3) under a variety of conditions (Scheme I). The 1,2-adduct (5) was obtained under kinetic conditions (low temperature, poor ionizing solvent) and the 1,4-adduct (6) was obtained under thermodynamic conditions (higher temperature, better ionizing solvent). The interconversion of the products, 5b → 6b, was also demonstrated under the reaction conditions.

Scheme I



In a number of analogous cases, other stabilized anions exhibited both 1,2- and 1,4-addition modes to enones.

Ogura and coworkers[5] reported an unusual system where kinetic control was apparently operating. The 1,4-adduct of 7 with an enone such as cyclopentenone was favored at low temperature (-78°C) rather than at higher temperature



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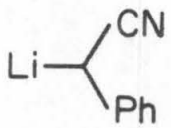

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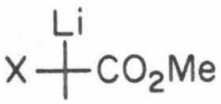
(0°C), and attempted conversion of the 1,2-adduct to the 1,4-adduct was unsuccessful. However, the benzyl anion 8,[6] the ester enolate 9 (X = OR, SR, R),[7]



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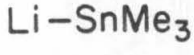


10

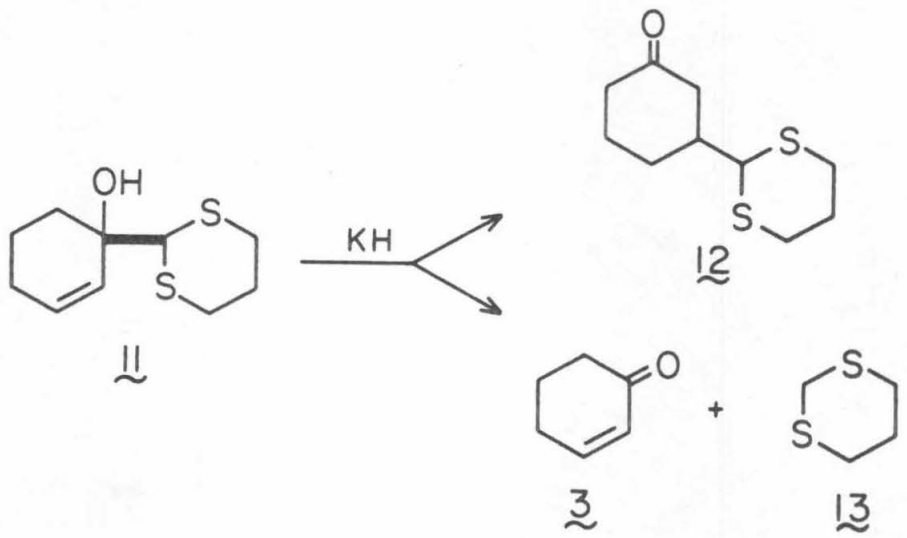
and the stannyl anion 10[8] react with enones kinetically in a 1,2-sense and thermodynamically in a 1,4-sense. The conversion of 1,2-products to 1,4-products under basic conditions was successfully demonstrated in each case.

In the case of unstabilized anions which give 1,2-adducts with enones, such as 1 (R = H), the possibility of obtaining a formal 1,4-adduct *via* an oxy anion-promoted conversion of 1 to 2 seemed promising. The question of the

mechanism of such a [1,3]-shift was also of interest. Therefore, these aspects of accelerated [1,3]-shifts were briefly examined.

Results and Discussion. The activating capability of an oxy anion in promoting a dithiane [1,3]-rearrangement was probed in the simple case shown in Scheme II.[9] Treatment of allylic alcohol 11 with potassium hydride

Scheme II



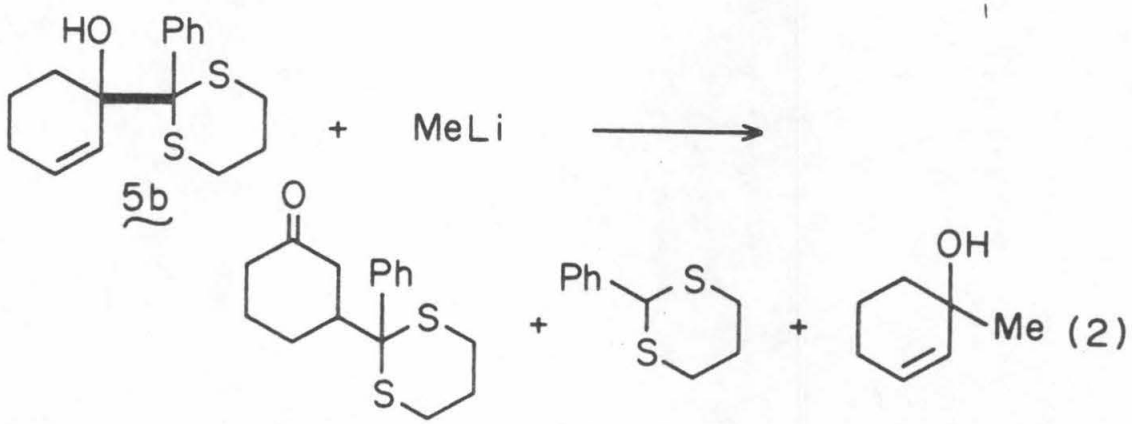
11 12 3 13

(KH) in 1,2-dimethoxyethane (DME) at 85°C quickly led to disappearance of the starting material. Under these conditions rearrangement and fragmentation were competing processes because both ketone 12 (15% yield) and dithiane 13 (66% yield) were isolated. In an attempt to optimize the [1,3]-rearrangement product, milder reaction conditions were employed.[1c] Surprisingly, the attempted rearrange-

of the potassium salt of 11 in DME at 25°C led only to the fragmentation products 3 and 13 and not to the desired 12. Thus, the rearrangement 11 → 12 appears to follow a higher energy pathway than the fragmentation, perhaps indicating the existence of a concerted process with a much greater negative entropy of activation. Despite the low yield, the successful isolation of the product 12 illustrates the feasibility of an oxy anion-promoted [1,3]-rearrangement of an unactivated dithiane group, 1 → 2 (eq. 1). It also raises the possibility that the 1,2- and 1,4-adducts of metallated dithianes and enones are interconvertible *via* a concerted pathway as well as a dissociation-recombination pathway.

The question of mechanism was examined more closely in the conversion of 5 to 6 (Scheme I) by Ostrowski and Kane.[4] The mechanistic possibilities are the same as in other oxy anion-promoted rearrangements, *ie* a concerted shift, or a dissociation-recombination *via* radical or ionic pathways. Of the three alternatives, the ionic pathway seemed to be the most favorable because: (1) the phenyldithiane anion was considerably stabilized; (2) the concerted shift appeared to experience unfavorable steric interactions between the migrating group and the cyclohexyl ring, and (3) the radical pathway appeared to suffer from the

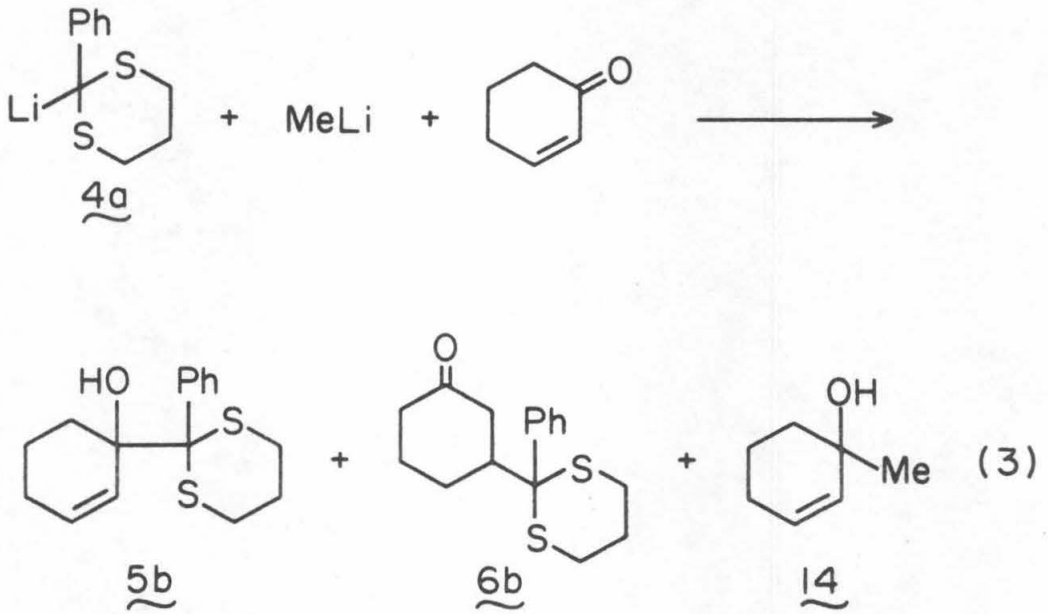
instability of the cyclohexenone ketyl toward electron ejection. Thus, an attempt was made to trap cyclohexenone, one of the ionic fragmentation products, with a large excess (10 equiv) of methyllithium (eq 2).



(2)

Nmr analysis of the reaction product from the trapping experiment revealed the ratio 6b:4b:14 to be 9.6:0.89:1.0. A control experiment with only 0.1 equiv excess MeLi and run identically to the trapping experiment showed that no fragmentation of 5a occurred alone under the reaction conditions. The trapping product 14 therefore accounted for only 9.4% of the entire reaction.

A competition experiment was run to determine the relative rates of capturing cyclohexenone by MeLi and phenyldithiane anion, 4a (eq 3). The ratio of MeLi:4a was kept at 10:1, the minimum ratio possible in the actual trapping experiment. Under these conditions, MeLi was effective in capturing 63% of the available cyclohexenone;



4a 5b 6b 14 (3)

this value represented a lower limit to the amount of free cyclohexenone that was captured by MeLi in the original trapping experiment, eq 2. Thus, heterolytic cleavage of the lithium alkoxide 5a and diffusion of the resulting cyclohexenone out of the solvent cage could only have occurred a maximum of 15% of the time. The other 85% of the reaction apparently occurred within a solvent cage and/or proceeded via intermediates which could not be intercepted by MeLi.

Even the confirmed presence of free cyclohexenone was insufficient to prove that heterolytic dissociation-recombination led to the rearranged product because of Eliel's work demonstrating the reversibility of 1,2-additions of dithiane anions to ketones[10] (for example, 3 + 4a $\rightleftharpoons$ 5a, Scheme I). Therefore, distinguishing

among the various mechanistic alternatives of the dithiane [1,3]-shift was not possible due to the limited information available from this series of experiments.

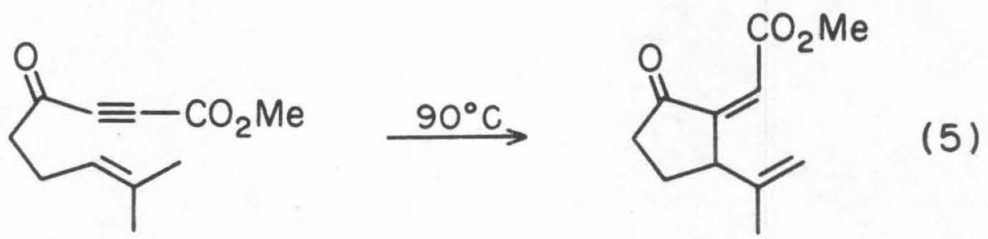
Accelerated Ene Reactions

Introduction. Another system in which an anion substituent (X) might be advantageously employed is the ene reaction (eq. 4).[11,12] According to previously developed concepts, the anion should weaken the adjacent C-H bond

(4)

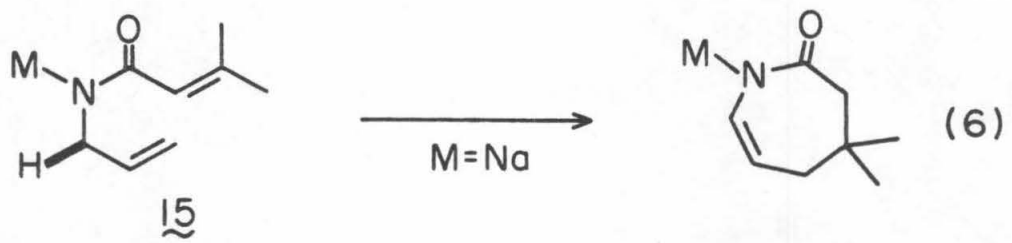
and thus lower the energy barrier of the overall process. The magnitude of the projected substituent effect is uncertain because recent work[11,12] suggests that the transition state is unsymmetrical with the degree of C-C bond formation being greater than the degree of H-transfer.

Activation of the ene reaction is a common problem, and usually involves making the enophile electron poor and the ene fragment electron rich. Activating the enophile with electron withdrawing groups is the most frequently used strategy, and the effectiveness of this approach was recently demonstrated in the efficient cyclization of 1,6-



(5)

enynes (eq 5) and 1,7-enynes under mild conditions.[13] Activation of the ene fragment is a much less common approach. A recent report,[14] however, describes an ene cyclization (eq 6) which appears to fall in this latter category and may represent an example of an anion-accelerated ene reaction (eq 4). Superficially, the anion-promoted



15

(6)

cyclization of 15 appears to be an adequate explanation, yet it does not account for other experimental observations such as the requirement of more than one equivalent of base to catalyze the reaction and the failure of other salts of 15 (M = Li, K) to cyclize. The authors favor a

dianion as the reactive species.

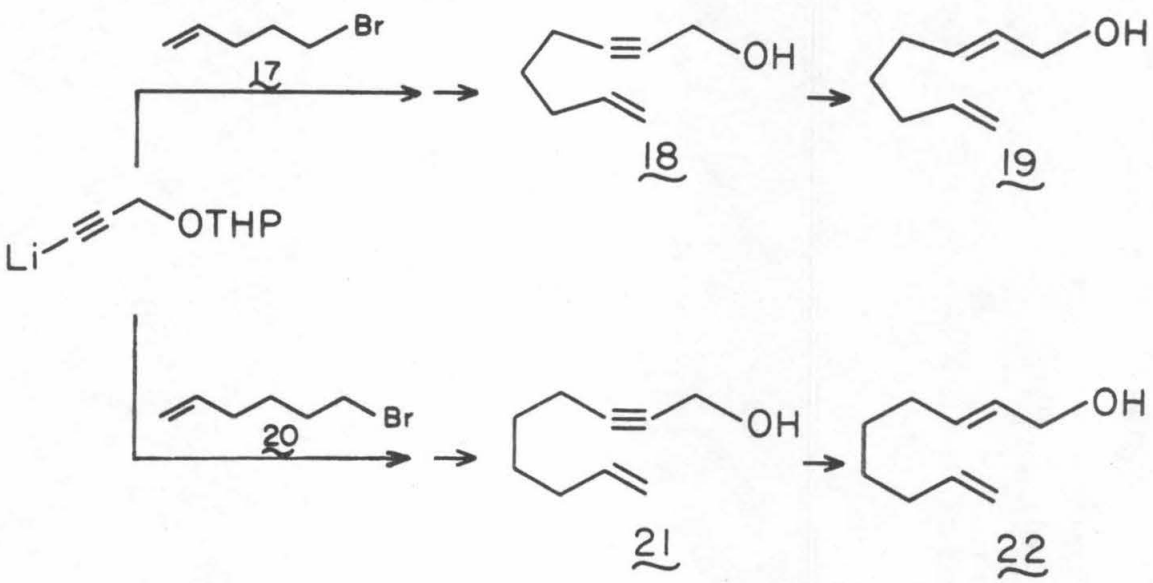
The specific case of the ene reaction designed to test the concepts of anion-induced bond weakening and subsequent rate accelerations of bond reorganizations is shown in eq 7. This intramolecular cyclization is

(7)

especially significant in that a facile reaction of this type would prove to be a valuable tool in synthesis.

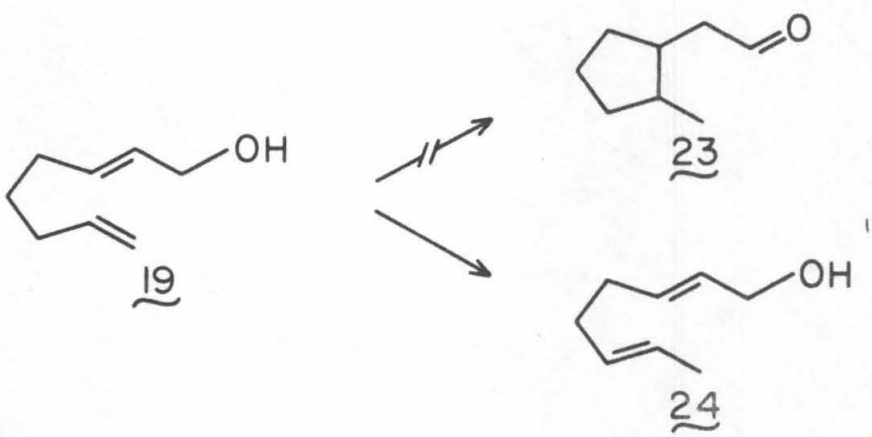
Results and Discussion. Two particular substrates, 19 and 22 (Scheme III), were used to explore the feasibility of an anion-promoted ene reaction. Each of these substrates was prepared according to the sequence shown in Scheme III. The tetrahydropyranyl (THP) derivative 16 of propargyl alcohol was lithiated, alkylated with either 5-bromopentene (17) or 6-bromohexene (20), and subsequently deprotected (THP removed) under mild acidic conditions (methanol, acid resin) to give the intermediate propargyl alcohols, 18 and 21.[28] The reduction of the alkyne to the trans olefin was easily accomplished using lithium aluminum hydride/sodium methoxide reagent.[29]

Scheme III



The ene reaction was first attempted with the potassium salt of dienol 19 in the presence of two equivalents of 18-crown-6 in dimethoxyethane at 85°C. The expected cyclization product was a cyclopentyl-substituted aldehyde, 23; however, not a trace of this product was detected (Scheme IV). Under the strongly basic conditions of the reaction, the terminal olefin slowly isomerized to the internal olefin of alcohol 24. Over the course of 30 h, approximately 55% of the starting material 19 was consumed in this manner. In the absence of 18-crown-6, the course of the reaction was unchanged; the rate was just drastically slower.

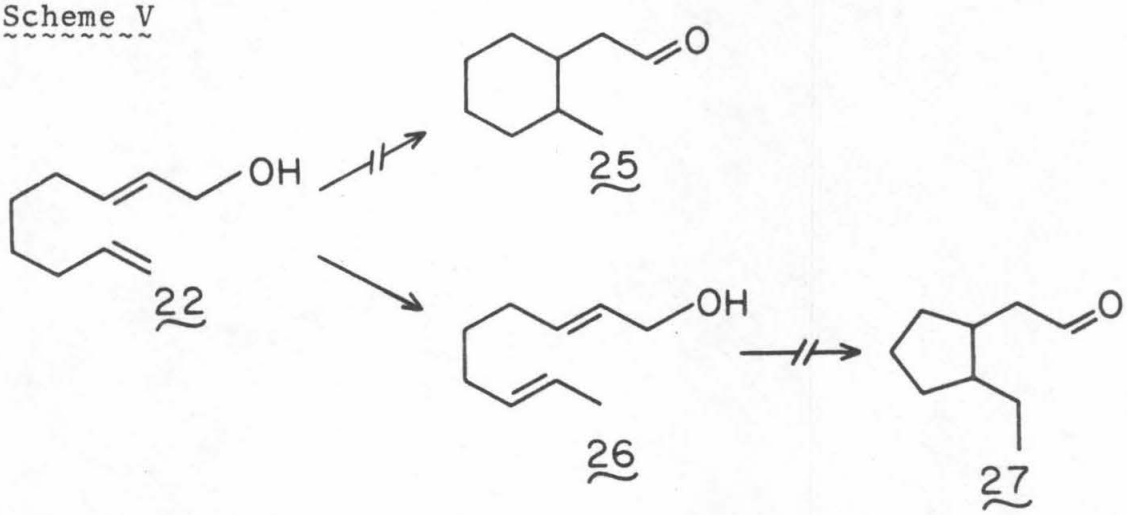
Scheme IV



Dienol 22 was tested under exactly the same conditions as 19. The outcome of this reaction (Scheme V) was analogous to that of the previous attempt. No cyclization product 25 was found, and the only major product was identified as the isomerized material 26. The possibility of 26 cyclizing to 27 appeared to have failed also because no aldehyde group was detected, even in the crude product mixture. The rate of olefin isomerization in 22 was slower than in 19; approximately 53% of the starting material was consumed in 48 h.

Thus, the intramolecular ene cyclization of the potassium salts of dienols 19 and 22 did not occur even under highly ionizing conditions. The expected oxy anion substituent effect on the adjacent C-H bond seemed to be insufficient in lowering the activation parameters enough so that the reaction could occur at low temperatures

Scheme V



(85°C). A more worrisome problem is that of the comparatively faster olefin migration induced under the strongly basic conditions of the reaction. Unless the enophile were somehow blocked to prevent olefin migration, many of the advantages of a possible anion-promoted ene reaction would be severely limited by this problem.

Experimental Section

General. Diethyl ether, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were dried by distillation from benzophenone ketyl under nitrogen. Pentane, hexane, ethyl acetate, methanol, triethylamine, and methanesulfonyl chloride were dried and purified according to standard procedures.[15] Cyclohexenone, dihydropyran, tetrahydrofurfuryl alcohol, and (2-tetrahydropyranyl)methanol were dried and distilled before use. 2-Phenyl-1,3-dithiane was recrystallized and 1,3-dithiane was sublimed. 18-Crown-6 was dried by elution through activity I alumina with ether, followed by solvent removal and drying *in vacuo*.

Oil dispersions of potassium hydride (24%) and sodium hydride (50%) were washed free of oil and dried under vacuum before use. All Grignard and alkyllithium reagents were standardized by the procedure of Watson and Eastham.[16]

Unless otherwise specified, reactions were run under an inert atmosphere of nitrogen or argon.

Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected, as are boiling points. Infrared spectra were recorded on a Beckman IR 4210 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra were recorded on a Varian Associates Model EM-390 or T-60 spectrometer.

Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (Hz), and interpretation. Mass spectra were recorded on a DuPont MS 21-492B mass spectrometer at 70 eV. Mass spectral analyses as well as combustion analyses were performed by the California Institute of Technology Microanalytical Laboratory.

Analytical gas chromatographic analyses were performed on a Varian-Aerograph Model 1440 gas chromatograph equipped with a flame ionization detector using 2 m by 3.18 mm stainless steel columns of 10% Carbowax 20 M, 6% FFAP, or 10% SE-30 on 80-100 mesh DMCS Chromosorb W support. Preparative glpc separations were performed on a Varian Aerograph Model 90-P instrument using a 2 m by 6.35 mm column of 15% SE-30 or 20% FFAP on 40-60 mesh Chromosorb W support.

1-(1,3-Dithiacyclohex-2-yl)-2-cyclohexen-1-ol (11). The title compound was prepared from 2-cyclohexen-1-one and 2-lithio-1,3-dithiane at 0°C in THF as described by Seebach and Corey.[17] Chromatography of the reaction product on silica gel (ethyl acetate/hexane, 10:90, followed by ethyl acetate gradient) afforded pure 11 as a clear colorless viscous oil in 80% yield: IR (neat) 3440, 3020, 2930, 2820, 1639, 1413, 1315,

1272, 1176, 1077, 974, 905, 874, 848, 830 cm^{-1}; NMR (CCl_4) δ 5.93-5.51 (m, 2, vinyl), 4.01 (s, 1, S-CH-S), 3.03-2.50 (m, 4, S-CH_2-), 2.20-1.37 (m, 9, -CH_2- and -OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 216 (M^+, 1), 120 (69), 119 (base), 97 (49).

Exact mass calcd for $C_{10}H_{16}OS_2$: 216.063. Found: 216.064.

3-(1,3-Dithiacyclohex-2-yl)-cyclohexanone (12). To a stirred 0°C suspension of 1.21 g (30.2 mmol) of oil-free potassium hydride and 60 mL of DME was added 5.00 g (23.1 mmol) of 11 dissolved in 15 mL of DME. The reaction solution was heated at reflux for 4 h and after cooling to 0°C was slowly added to an ice-cold solution of saturated aqueous NH_4Cl. The aqueous solution was extracted with ether, and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Solvent removal in vacuo gave a crude yellow oil which was chromatographed on silica gel (ethyl acetate/hexane, 5:95, followed by ethyl acetate gradient) to afford 0.732 g (15%) of 12 as a clear colorless oil: IR (CCl_4) 2940, 2895, 1710, 1444, 1418, 1274 1219, 1176, 908 cm^{-1}; NMR (CCl_4) δ 3.97 (d, 1, J = 4 Hz, S-CH-S), 2.96-2.64 (m, 4, S-CH_2-), 2.49-1.33 (m, 11, -CH- and -CH_2-); mass spectrum m/e (rel intensity) 216 (M^+, 20), 119 (base).

Exact mass calcd. for $C_{10}H_{16}OS_2$: 216.063. Found: 216.063.

1-(2-Phenyl-1,3-dithiacyclohex-2-yl)-2-cyclohexen-1-ol (5b). The title compound was prepared from 2-cyclohexen-1-one and 2-lithio-2-phenyl-1,3-dithiane at -78°C in hexane/THF (1.8:1) as described by Ostrowski and Kane.[4] Chromatography of the crude reaction product on silica gel (ethyl acetate/hexane, 4:96, followed by ethyl acetate gradient) afforded pure 5b as a clear colorless viscous oil in 68% yield: IR (CCl_4) 3590, 3055, 3025, 2935, 2905, 2830, 1635, 1473, 1435, 1339, 1307, 1168, 1080, 971, 948, 902, 878, 862, 710, 692 cm^{-1}; NMR (CCl_4) δ 8.13-7.88 (m, 2, aromatic), 7.47-7.04 (m, 3, aromatic), 6.11-5.67 (m, 2, vinyl), 2.73-2.40 (m, 4, -S-CH_2-), 2.07-1.13 (m, 9, -CH_2- and -OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 292 (M^+, 10), 195 (37), 105 (44), 97 (base), 77 (35).

Exact mass calcd. for $C_{16}H_{20}OS_2$: 292.095. Found: 292.094.

3-(2-Phenyl-1,3-dithiacyclohex-2-yl)-cyclohexanone (6b). The title compound was prepared from 2-cyclohexen-1-one and 2-lithio-2-phenyl-1,3-dithiane in THF as described by Ostrowski and Kane[4] in 55% yield, mp 120-122 [lit.[4] mp 124-125°C]: IR (CCl_4) 3050, 2943, 2900, 1708, 1473, 1436, 1415, 1274, 1220, 908, 697 cm^{-1}; NMR (CCl_4) δ 7.99-7.77 (m, 2, aromatic), 7.48-7.03 (m, 3, aromatic), 2.74-1.10 (m, 15, -CH- and -CH_2-).

1-Methyl-2-cyclohexen-1-ol (14). The title compound

was prepared according to standard procedures by treating 2-cyclohexen-1-one with methyllithium in ether solution at 0°C. Molecular distillation of the reaction product at 90°C (30 mm) afforded pure 14 in 47% yield [bp[18] 60-61°C (15 mm)]; spectral data of 14 also matched that previously reported:[18,19] IR (neat) 3370, 3020, 2935, 2835, 1645, 1365, 1176, 1120, 1094, 1013, 995, 960, 908, 900, 731 cm^{-1}; NMR (CCl_4) δ 5.73-5.41 (m, 2, vinyl), 2.10-1.33 (overlapping m, 7, $-CH_2-$ and -OH, D_2O exchangeable), 1.21 (s, 3, $-CH_3$).

Trapping of Intermediates in an Accelerated [1,3]-Dithiane Shift. Rearrangement of 1-(2-Phenyl-1,3-dithiacyclohex-2-yl)-2-cyclohexen-1-ol (5b). A. General. The concentration of the rearranging species was maintained at 0.035-0.037 M throughout the experiments below. Quantitative analysis of the reaction mixtures was carried out by proton nmr, and each of the following species was easily distinguishable: the 1,2-dithiane addition product 5b (8.13-7.88 δ), the 1,4-dithiane addition product 6b (7.99-7.77 δ), the MeLi addition product 14 (5.73-5.41 δ), and the phenyldithiane fragment 4b (5.13 δ).

B. Trapping Experiment. To a dry flask equipped with a magnetic stirring bar, a nitrogen gas inlet, and a rubber serum cap was added 0.105 g (0.36 mmol) of the 1,2-dithiane adduct 5b, 8.44 mL of THF, and, after cooling to -72°C, 1.56 mL of 2.53 M (3.95 mmol) methyllithium/

ether solution. The stirred reaction solution was warmed to 0°C and maintained at this temperature for 18 h. The reaction was quenched by slow addition of the THF solution to ice-cold saturated aqueous NH_4Cl. The aqueous solution was extracted with ether, and the combined ether extracts were washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Solvent removal in vacuo gave 0.117 g of a pale yellow oil which slowly solidified upon standing. Nmr analysis revealed the ratio of products 6b:4b:14 to be 9.6:0.89:1.0. Therefore, the trapping material 14 only accounted for 9.4% of the total reaction.

C. Control Experiment. The control experiment was run simultaneously with the trapping experiment, and the reaction conditions and workup procedure were identical in both cases. As described above, 0.108 g (0.37 mmol) of the 1,2-dithiane adduct 5b dissolved in 9.84 mL of THF was treated with 0.16 mL of 2.53 M (0.41 mmol) methyllithium/ether solution. Isolation afforded 0.106 g of a pale yellow oil which solidified on standing. Nmr analysis revealed the ratio of products 6b:4b:14 to be >98:<1:<1. The absence of any detectable amounts of 14 and 4b was confirmed by the analysis of the product mixture by thin layer chromatography on silica gel (50% ether/hexane).

D. Competitive Rates of Trapping. 2-Lithio-2-phenyl-1,3-dithiane (0.70 mmol) was prepared from 0.136 g (0.70

mmol) of 2-phenyl-1,3-dithiane and 0.46 mL of 1.51 M (0.70 mmol) of n-butyllithium in 16.8 mL of THF according to the procedure of Seebach and Corey.[17] At 0°C, 2.70 mL of 2.53 M (6.83 mmol) of methyllithium/ether solution was added, followed by 0.034 g (0.35 mmol) of cyclohexenone added quickly in one portion. After 1.5 h at 0°C, the reaction was worked up exactly as described for the trapping experiment above. According to the nmr spectrum of the isolated product, the ratio (5b + 6b)/14 was equal to 0.58. Thus, 63% of all available cyclohexenone was trapped by methyllithium in this competition experiment. Subsequent work showed that the relative amount of trapping of cyclohexenone by each anion was not very sensitive to changes in reaction conditions, such as time (10 min vs 1.5 h), temperature (25°C vs 0°C), or the final composition of the dithiane adducts (only 6b vs 5b + 6b).

1-(Tetrahydropyran-2-yl)oxy-2-propyne (16). The title compound was prepared from 2-propyn-1-ol and dihydropyran according to the procedure of Robertson[20] in 86% yield, by 67-68°C (8 mm) [lit.[21] bp 78°C (25 mm)].

5-Bromopentene (17). The title compound was prepared according to a simple four-step sequence: (1) tetrahydrofurfuryl alcohol was treated with triphenylphosphine in CCl_4[22] to give 2-(chloromethyl)tetrahydrofuran in 57% yield; (2) 2-(chloromethyl)tetrahydrofuran was treated

with powdered sodium in ether to give 4-penten-1-ol in 60% yield;[23] (3) 4-penten-1-ol was converted to the mesylate[24] with methanesulfonyl chloride and triethylamine in CH_2Cl_2; and (4) the mesylate was treated with anhydrous lithium bromide in acetone at reflux[25] to give 5-bromopentene (17) in 40% yield, bp 119-121°C [lit.[26] bp 125-126°C].

6-Bromohexene (20). The title compound was prepared according to a simple four-step sequence: (1) 2-tetrahydropyranyl methanol was treated with triphenylphosphine in CCl_4[22] to give 2-(chloromethyl)tetrahydropyran in 70% yield; (2) 2-(chloromethyl)tetrahydropyran was treated with powdered sodium in ether at reflux to give 5-hexen-1-ol in 67% yield;[27] (3) 5-hexen-1-ol was converted to the mesylate[24] with methanesulfonyl chloride and triethylamine in CH_2Cl_2; and (4) the mesylate was treated with anhydrous lithium bromide in acetone at reflux[25] to give 6-bromohexene (20) in 78% yield after molecular distillation at 55°C (15 mm) [lit.[27] bp 76-78°C (4-5 mm)].

7-Octen-2-yn-1-ol (18). According to the procedure of Corey and Sachdev,[28] the 3-lithio derivative of 1.96 g (14.0 mmol) of 1-(tetrahydropyran-2-yl)oxy-2-propyne (16) was treated with 2.09 g (14.0 mmol) of 5-bromopentene (17) in THF at reflux, followed by removal of the tetrahydropyranyl group in methanol with Amberlite IR 120 acid resin. Chromatography of the crude product on silica gel (ethyl acetate/hexane, 5:95, followed by ethyl acetate gradient) afforded 1.061 g (61%) of pure 18

as a clear colorless liquid: IR (neat) 3340, 3075, 2935, 2285, 2223, 1637, 1134, 1008, 912 cm^{-1}; NMR (CCl_4) δ 5.98-5.48 (m, 1, vinyl), 5.11-4.82 (m, 2, vinyl), 4.09 (t, 2, J = 2 Hz, ≡C-CH_2-O), 2.31-1.93 (m, 4, ≡C-CH_2- and =C-CH_2-), 1.57 (quintet, 2, J = 7 Hz, -CH_2-), 1.29 (s, 1, -OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 124 (M^+, 1), 91 (81), 55(57), 54 (57), 41 (57), 39 (base).

Exact mass calcd. for $C_8H_{12}O$: 124.089. Found: 124.089.

8-Nonen-2-yn-1-ol (21). According to the procedure of Corey and Sachdev,[28] the 3-lithio derivative of 2.80 g (20.0 mmol) of 1-(tetrahydropyran-2-yl)oxy-2-propyne (16) was treated with 3.26 g (20.0 mmol) of 6-bromohexene (20) in THF at reflux, followed by removal of the tetrahydropyranyl group in methanol with Amberlite IR 120 acid resin. Chromatography of the crude product on silica gel (ethyl acetate/hexane, 5:95, followed by ethyl acetate gradient) afforded 1.616 g (59%) of pure 21 as a clear colorless liquid: IR (neat) 3340, 3070, 2927, 2855, 2282, 2221, 1634, 1130, 1008, 907 cm^{-1}; NMR (CCl_4) δ 6.00-5.50 (m, 1, vinyl), 5.11-4.80 (m, 2, vinyl), 4.09 (broad s, 2, ≡C-CH_2-O), 2.33-1.87 (m, 4, ≡C-CH_2- and =C-CH_2-), 1.73-1.30 (m, 4, -CH_2-), 1.17 (broad s, 1, -OH, D_2O exchangeable).

Anal. ($C_9H_{14}O$): C, H.

(2E)-2,7-Octadien-1-ol (19). Reduction of propargyl alcohol 18 to trans allyl alcohol 19 was accomplished using $LiAlH_4$/NaOMe.[29] To a suspension of 0.525 g (15.8 mmol)

of lithium aluminum hydride and 1.50 g (27.7 mmol) of sodium methoxide in 30 mL of THF was added 1.146 g (9.23 mmol) of propargyl alcohol 18 at 0°C. The suspension was heated at reflux for 5 h, and was then quenched at 0°C with enough water to precipitate the aluminum salts. The solution was filtered through Celite and dried (Na_2SO_4), and solvent was removed *in vacuo*. Molecular distillation of the crude product at 90°C (1-2 mm) afforded 0.993 g (85%) of pure 19 as a clear colorless liquid: IR (neat) 3330, 3075, 2925, 2855, 1662, 1634, 1083, 994, 964, 906 cm^{-1}; NMR (CCl_4) δ 5.99-5.48 (m, 3, vinyl), 5.11-4.78 (m, 2, vinyl), 4.09 (d, 2, J = 3 Hz, $=C-CH_2-O$), 2.18-1.82 (m, 4, $=C-CH_2-$), 1.67-1.28 (m, 2, $-CH_2$), 0.92 (broad s, 1, -OH, D_2O exchangeable); mass spectrum *m/e* (rel intensity) 126 (M^+, 1), 67 (70), 57 (64), 55 (79), 54 (64), 41 (base), 39 (55).

Exact mass calcd. for $C_8H_{14}O$: 126.105. Found: 126.105.

(2*E*)-2,8-Nonadien-1-ol (22). Preparation of 22 was analogous to that of allyl alcohol 19. To a suspension of 0.670 g (17.7 mmol) of lithium aluminum hydride and 1.90 g (35.2 mmol) of sodium methoxide in 50 mL of THF was added 1.616 g (11.7 mmol) of propargyl alcohol 21 at 0°C. The suspension was heated at reflux for 5 h, was quenched, and was worked up as before. Molecular distillation of the crude product at 90°C (0.04 mm) afforded 1.309 g (80%) of

pure 22 as a clear colorless liquid: IR (neat) 3330, 3070, 2930, 2855, 1663, 1635, 1452, 1432, 1086, 990 967, 906 cm^{-1}; NMR (CCl_4) δ 6.06-5.31 (m, 3, vinyl), 5.07-4.74 (m, 2, vinyl), 3.94 (d, 2, J = 3 Hz, $=C-CH_2-O$), 2.19-1.76 (m, 4, $=C-CH_2-$), 1.59-1.10 (m, 4, $-CH_2-$), 0.96 (s, 1, -OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 140 (M^+, 1), 67 (61), 57 (72), 55 (67), 54 (50), 41 (base).

Exact mass calcd. for $C_9H_{16}O$: 140.120. Found: 140.122.

Attempted Intramolecular Ene Reaction of the Potassium Salt of (2E)-2,7-Octadien-1-ol (19). To a suspension of 0.660 g (16.5 mmol) of oil-free potassium hydride in 75 mL of DME was added 1.007 g (7.98 mmol) of dienol 19 and 4.30 g (16.3 mmol) of 18-crown-6. The mixture was heated at reflux for 30 h, over which time ~55% of the starting material was converted to one major product. The reaction was terminated by adding the cold reaction mixture to an excess of ice-cold saturated aqueous NH_4Cl solution. The aqueous solution was extracted with ether, and the combined ethereal extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The ethereal solution was dried (Na_2SO_4), filtered, and solvent was removed in vacuo to give 1.26 g of a yellow liquid as a residue.

Examination of the crude product by ir and nmr revealed no trace of the expected cyclic aldehyde product. The major product of the reaction was isolated by preparative

glpc using 20% FFAP on Chromosorb W support and was identified as the isomeric dienol (2E)-2,6-octadien-1-ol (24): IR (CCl_4) 3610, 3360, 3010, 2915, 2860, 1660, 1647, 1434, 1372, 1082, 991, 964, 698 cm^{-1}; NMR (CCl_4) δ 5.70-5.49 (m, 2, vinyl), 5.49-5.23 (m, 2, vinyl), 3.96 (d, 2, J = 3 Hz, =C-CH_2-O), 2.09 (broad s, 4, =C-CH_2-), 1.60 (d, 3, J = 5 Hz, -CH_3), 1.07 (s, 1, -OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 126 (M^+, 1), 55 (base), 54 (55), 43 (70), 41 (65).

Exact mass calcd. for $C_8H_{14}O$: 126.105. Found: 126.106.

Attempted Intramolecular Ene Reaction of the Potassium Salt of (2E)-2,8-Nonadien-1-ol (22). To a suspension of 0.660 g (16.5 mmol) of oil-free potassium hydride in 60 mL of DME was added 0.504 g (3.60 mmol) of dienol 22 and 1.94 g (7.34 mmol) of 18-crown-6. The mixture was heated at reflux for 48 h, over which time ~53% of the starting material was converted to one major product. The reaction was terminated by adding the cold reaction mixture to an excess of ice-cold saturated aqueous NH_4Cl solution. The aqueous solution was extracted with ether, and the combined ethereal extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The ethereal solution was dried (Na_2SO_4), filtered, and solvent removed in vacuo to give 0.564 g of a yellow liquid as a residue.

Examination of the crude product by ir and nmr revealed no trace of the expected cyclic aldehyde product. The major product of the reaction was isolated by preparative glpc using 20% FFAP on Chromosorb W support and was identified as the isomeric dienol (2E)-2,7-nonadien-1-ol (26): IR (CCl_4) 3610, 3380, 3010, 2930, 2855, 1658, 1650, 1432, 1376, 1083, 997, 965, 696 cm^{-1}; NMR (CCl_4) δ 5.77-5.47 (m, 2, vinyl), 5.47-5.17 (m, 2, vinyl), 3.98 (d, 2, J = 2.5 Hz, $=C-CH_2-O$), 2.27-1.73 (m, 4, $=C-CH_2-$), 1.59 (d, 3, J = 5 Hz, $-CH_3$), 1.47-1.20 (m, 2, $-CH_2-$), 0.85 (s, 1, -OH, D_2O exchangeable); mass spectrum m/e (rel intensity) 140 (M^+, 1), 68 (92), 67 (67), 55 (79), 41 (base).

Exact mass calcd. for $C_9H_{16}O$: 140.120. Found: 140.120.

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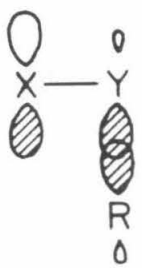
CHAPTER IV

Charged Substituent Effects on Molecular Bond Reorganizations

Introduction

Molecular bond reorganizations[1] have fired the enthusiasm and imagination of chemists since the earliest history of chemistry. Promoting bond reorganizations by utilizing and manipulating substituents has been an integral part of investigations in this area. Substituents may be classified in two general categories: electron rich substituents (anions, X^-), and electron deficient substituents (cations, X^+; radicals, $X\cdot$). Each of these substituents strongly influences the reactivity of adjacent bonds in unimolecular reactions, which may include either fragmentations or rearrangements. The spatial relationship of orbitals which are most important in these substituent effects is defined for the saturated case by 1 and for the vinylogous case by 2.



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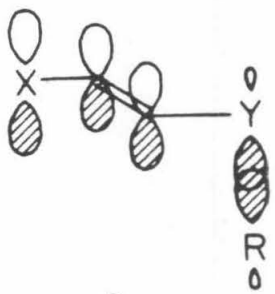

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The X orbital (filled, half-filled, or empty) directly affects the reactivity of the Y-R bond through orbital overlap in any bond reorganization involving a breaking of the

Y-R bond. As illustrated in following sections, these orbital interactions are operational in both concerted and nonconcerted, stepwise reactions and rearrangements.

Anions are of particular interest in organic chemistry because of the ease with which they are generated. Anion substituent effects have long been recognized in various specific classes of chemical reactions such as β-eliminations. However, the concept of anion-promoted bond reorganizations has not been fully recognized in a general sense. Typical reactions in which anions may affect adjacent bonds are homolytic fragmentation (eq 1) heterolytic fragmentation (eq 2) and rearrangements (eq 3). The broad range of

$$^{-}X-Y-R \longrightarrow {}^{-}X-Y\bullet + \bullet R \qquad (1)$$

$$^{-}X-Y-R \longrightarrow X=Y + {}^{-}R \qquad (2)$$

$$^{-}X-Y-R \xrightarrow{e} {}^{-}X'-Y'-R' \qquad (3)$$

chemistry encompassed by these catagories is further illustrated by considering the number of different atoms which could be represented by X and Y. A variety of molecular structures, $^{-}$X-Y-R, which are simple permutations of the first-row elements C, N, and O can be devised (Table I). Many of these structures are easily recognizable. For example, the second entry in the first column of Table I represents the substrate for a Wittig rearrangement, and

the first entry of the second column is the substrate for a Stevens rearrangement (vide infra).

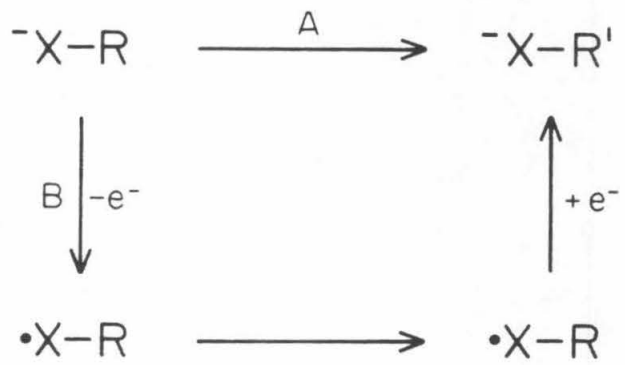
Table I. Possible Structures $^{-}$X-Y-R With X,Y = C,N,O.

$^{-}O-\underset{\vert}{\overset{\vert}{C}}-R$	$>\bar{C}-\overset{+}{N}-R$
$>\bar{C}-O-R$	$^{-}O-N<^{R}$
$-\bar{N}-\underset{\vert}{\overset{\vert}{C}}-R$	$^{-}O-\overset{+}{N}-R$
$>\bar{C}-N<^{R}$	

Comparison of substituent effects in any of these chemical systems must be done with due caution, however, because of the close interrelationship between the substituent effect and the mechanism of the bond reorganization. In a strict sense, a valid determination of a substituent effect between a protic case (H—X—Y—R) and the corresponding anionic case ($^{-}$X—Y—R) can only be made when the reaction mechanism remains unchanged. Unfortunately, the mechanisms of many reactions of interest are not sufficiently well documented to easily maintain such a rigorous approach.

To further complicate matters, the reactivity of an anion may be intimately related to its capacity to undergo electron transfer reactions. This concept is illustrated in Scheme I. The reaction of anion $^{-}$X-R may occur in a

Scheme I



straightforward ionic manner along path A, or the transformation may involve radical intermediates along alternate path B. Superficially, the two pathways would be indistinguishable because the resulting product(s) $^{-}$X-R' would be identical. Thus, anion-promoted bond reorganizations could be mechanistically complicated, and comparison of anion substituent effects could be difficult.

With these reservations in mind, comparison of

the effects of anions on molecular bond reorganizations can still be fruitful and yield useful generalizations.

In this review some of the widely dispersed data concerning anion substituent effects on bond reorganizations will be assembled and correlated. The theoretical basis for expecting such anion effects will be considered according to several different approaches. Experimental factors which serve to modify the reactivity of anionic systems and the resultant substituent effect will be delineated. Finally, the generality and utility of these effects will be illustrated in a wide variety of chemical systems.

Theoretical Considerations

Anion substituent effects can be examined in terms of the weakening of the bond strength of an adjacent bond. Thermochemical estimates of bond weakening in simple alkoxides were made by Evans and Baillargeon.[2] A Born-Haber cycle utilizing bond strengths and electron affinities was employed to calculate the gas-phase bond dissociation energy, $DH°(\bar{O}CH_2—R)$, for primary alkoxide ions (R = H, CH_3, and $CH_2CH{=}CH_2$). The resulting substituent effects, $\Delta D = DH°(HOCH_2—R) - DH°(\bar{O}CH_2—R)$, were estimated to be 17, 15, and 13 kcal/mol, respectively. Thus, the oxy anion apparently causes a significant decrease in the strength of an adjacent C-R bond.

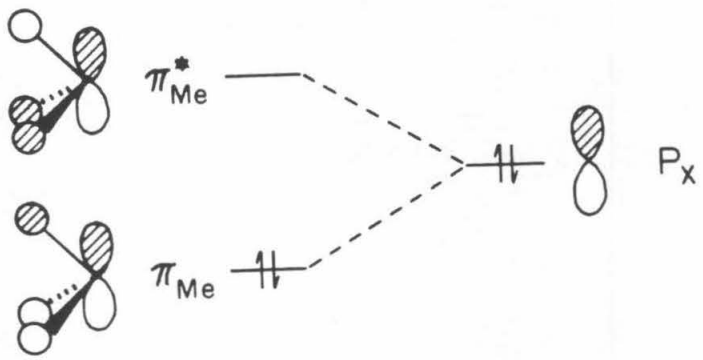
These estimates were corroborated by the theoretical work of Goddard and coworkers.[3] Ab initio generalized valence bond and configuration interaction methods were used to calculate the C-H bond energy of methoxide bound to a cation (Na^+ or K^+) under different conditions. In the free anion, the calculated substituent effect was ΔD = 16.5 kcal/mol which agrees with the thermochemical estimate. The decrease in C-H bond strength was explained in terms of a two-center three-electron bond and the greater tendency of the oxygen p_π electrons to delocalize onto the carbon in the radical anion ($\cdot CH_2\text{-}O^- \leftrightarrow CH_2{=}\dot{O}$) than in the hydroxy radical ($\cdot CH_2\text{-}OH$).

The methyl stabilization of anions ($H_3C\text{-}X^-$) and the simultaneous weakening of methyl C-H bonds were explained by Hehre and coworkers[4] in terms of anionic hyperconjugation.

$$H_3C-X^- \longleftrightarrow H^- \; H_2C=X$$

Perturbation molecular orbital theory illustrates (Scheme II) the stabilization of the filled orbital (p_X) at the anionic center (X = O, S, N) by interaction with the antibonding orbital on methyl (π^*_{Me}). This results in a weakening of the C-H bonds. Very similar conclusions were reached by Pross and Radom[5] in an analogous study.

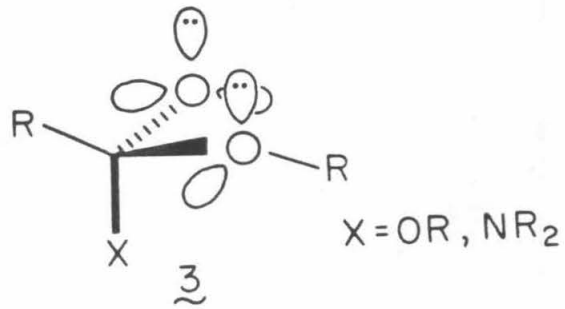
Scheme II



Anion substituent effects can be viewed from a different perspective, that of stabilizing the transition state of a molecular reorganization. Bingham and Dewar[6] examined the energetics of some sigmatropic rearrangements using configuration interaction and MINDO/2 calculations. In the case of a [1,5] hydrogen shift, the predicted effect of an anion substituent (such as O^-) was the lowering of the transition state energy due to a favorable interaction between the anion and the pentadienide fragment. In a more general treatment, Epiotis described anion effects on potential energy surfaces for sigmatropic shifts[7] in terms of electronic states arising from the mixing of configurations (wavefunctions).[8] Any anion substituent which increases the polarity of a transition state lowers the energy of the polar configuration and of the resulting electronic states. The lower transition state energy thus predicts a rate acceleration. A conceptually simple model based on

Hückel MO theory was developed by Carpenter.[9] A fundamental assumption is that, in a concerted thermal pericyclic reaction, the effect of a substituent on reaction rate is due solely to a change in the degree of orbital delocalization developed between the ground state and the transition state. Based on a determination of these energy changes in all-carbon analogues, several predictions are consistent with examples of anion-promoted rearrangements.

Certain qualitative aspects of anion substituent effects can be examined according to Deslongchamps' principle of stereoelectronic control in hydrolytic reactions.[10] The breakdown of tetrahedral intermediates such as 3 depends on the specific orientation (antiperiplanar) of two sets



3

of non-bonded electron pairs. Such a spatial requirement of orbitals could be present in anion-promoted bond reorganizations.

All the theoretical considerations discussed above seem to lead to the same fundamental conclusion: an

appropriately placed anion substituent will facilitate a bond reorganization. The details of such a process are not clearly defined, however, and the relative importance of ground state destabilization (via adjacent bond weakening) vs transition state stabilization (via orbital overlap) is difficult to evaluate.

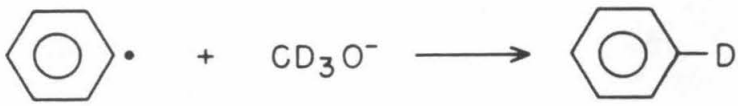
Anion-Promoted Bond Fragmentations

Homolysis. According to the theoretical predictions above, bond strengths are significantly lowered in bonds adjacent to an anion. Several examples of this phenomenon,

$$R\cdot + CH_3X^- \longrightarrow RH + \cdot CH_2X^- \qquad (4)$$

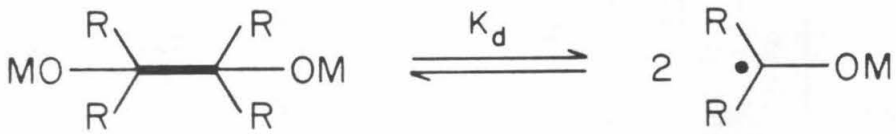
particularly in radical reactions such as eq 4, have been observed.

In the radical chain reduction of aryl halides and aryl nitro compounds in the presence of sodium methoxide, the aryl radical removes a hydrogen atom from methoxide to form a formaldehyde radical anion as a postulated reactive intermediate (eq 4, X = O).[11,12] Evidence such as deuterium labeling studies[11a,12] (eq 5) confirmed that the hydrogen atom source was methoxide and not solvent. Similarly, sodium thiolate[13a] and more complex alkoxides[13b] may serve as efficient hydrogen atom sources.



(5)

Pinacols are subject to anion-promoted cleavage to give ketyl intermediates (eq 6).[14,15] Dissociation of pinacol



(6)

4 a, M = H
b, M = Na

5

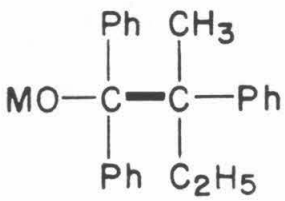
4 (R = Ph) to radical 5 (R = Ph) readily occur under basic conditions, and activation parameters were determined[14] for both the neutral case, 4a (R = Ph), and the anionic case, 4b (R = Ph): E_a (4a) = 36.9 kcal/mol, and E_a (4b) = 19 kcal/mol. Thus, the anion substituent effect was approximately 18 kcal/mol of stabilization or 9 kcal/mol per oxy anion. The dependence of K_d on experimental parameters was clearly demonstrated in a study of pinacolate 4 (R,R = fluorenyl, eq 6).[16] From spectroscopic data, K_d was found to increase according to the following counterion and solvent trends: Li < Na < K < Cs and THF < DME. Thus, the greater the degree of separation of the metal-alkoxide ion pair, the greater the anion effect in promoting homolytic cleavage.

Corresponding substituent effects are also evident in reactions where the initial homolytic cleavage leads to rearrangements *via* dissociation-recombination type mechanisms. Two prominent classes of such reactions are the Wittig and the Meisenheimer rearrangements (*vide infra*). The comparison to the Wittig rearrangement is particularly noteworthy because the Wittig structure is simply a permutation of C and O atoms of the alkoxide structure (Table I).

Heterolysis. Heterolysis of a bond adjacent to an anionic center (eq 2) is a feasible alternative to homolysis and is often the preferred mechanistic pathway. The intrinsic fragmentation modes of several primary alkoxides in the absence of any counterion and solvent effects were evaluated by Evans and Baillargeon.[17] Thermochemical estimates of the homolytic fragmentation energy and the heterolytic fragmentation energy were made by employing simple Born-Haber cycles.[2,17] Comparison of the energies of the two competing processes showed that heterolysis was favored over homolysis by 17-34 kcal/mol. This preference reflects the instability of the formaldehyde ketyl toward an electron transfer reaction.

When the radical anion fragment is sufficiently well stabilized, however, both fragmentation processes can be observed. In a detailed study of optically active alkoxides, Cram demonstrated the importance of alkali metal counterions in directing the course of fragmentation *via* heterolytic

or homolytic modes.[18] In the case of substrate 6 (M = K, Na, Li), heterolysis predominated for M = K while homolysis was preferred for M = Li.

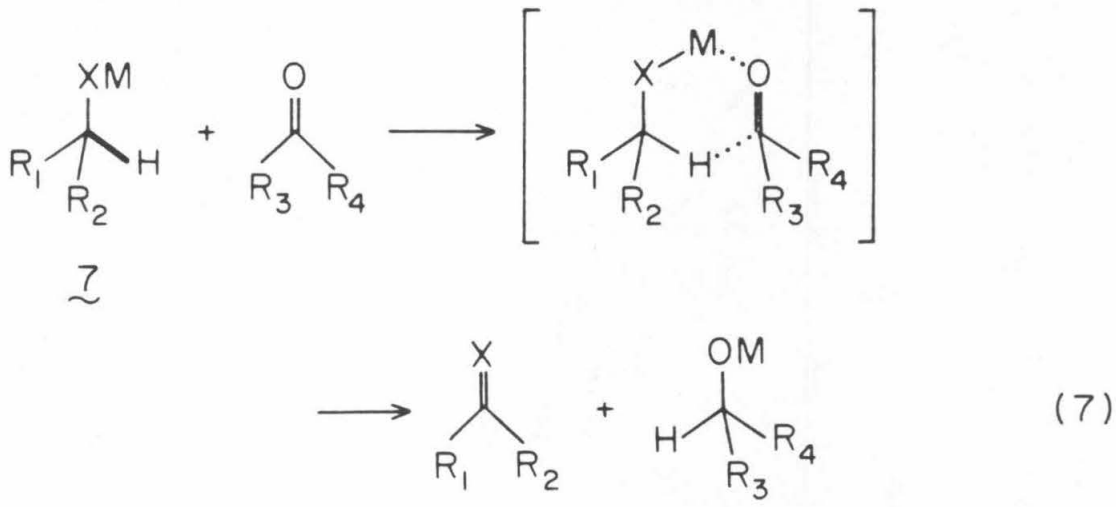


6

M	k_{het} / k_{hom}
K	2.2
Na	1.6
Li	0.05

In a broad sense, all anion-assisted β-eliminations can be viewed as resulting from a bond weakening due to an anion substituent effect. Such a topic is beyond the scope of this review, but a few selected examples will be presented to illustrate the concept.

Reagents which react with carbonyl compounds via Meerwein-Ponndorf-Verley type reductions formally eject a hydride ion during the reaction (eq 7). A wide variety of organometallic reagents can undergo this fragmentation reaction. Alkoxides (7, X = O) with different counterions, M = AlR_2,[19] MgBr,[20] Li,[21] and K[22] have been used as reducing agents. Lithium diisopropylamide (LDA), an azo analogue of 7 (X = N), was reported[23,24] capable of reducing even enolizable ketones in varying yields to give alcohols and an acetone imine. The Cannizzaro reaction[25] can be



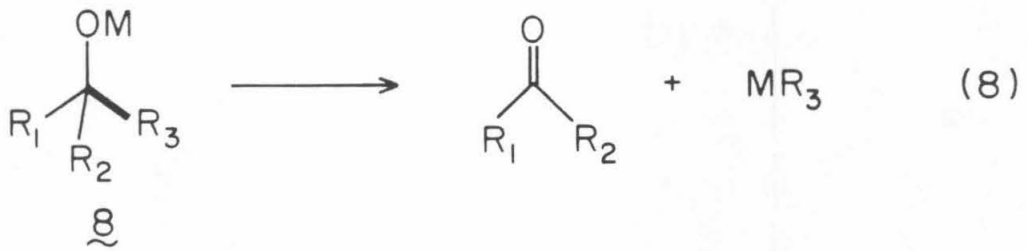
(7)

included in this class of reactions. Under the basic conditions of such a reaction, the dianion (7, X = O, R_1 = OM) would be an especially effective hydride transfer agent. Organometallic species such as Grignard reagents possessing β hydrogens (7, X = C) can also function as reducing agents.[26,27] For example, chiral Grignard reagents have proven useful in the asymmetric reduction of ketones.[27]

Mechanistically, these Meerwein-Ponndorf-Verley type reductions appear to involve more than just a simple β-hydride transfer. Two independent studies[21,24] have demonstrated the possibility of an electron transfer process as an alternate mechanism in these reactions (cf Scheme I). Screttas and Cazianis[21] demonstrated that lithium sec-butoxide readily reduced fluorenone to the ketyl species, and Scott

and coworkers[24] showed that LDA as well as lithium-2,2,6,6-tetramethylpiperidide (no β hydrogens) reduced benzophenone. Under the appropriate conditions, therefore, an anion could undergo successive electron transfer and hydrogen-atom transfer as an alternative to a direct β-hydride transfer in these reductions.

In addition to expulsion of hydride ion, anions may similarly eject β alkyl groups. In the fragmentaion of sterically crowded alkoxides (eq 8), Zook and coworkers[28] found that the bulkiest alkyl groups were ejected preferentially and that a counterion dependence existed. The ease of



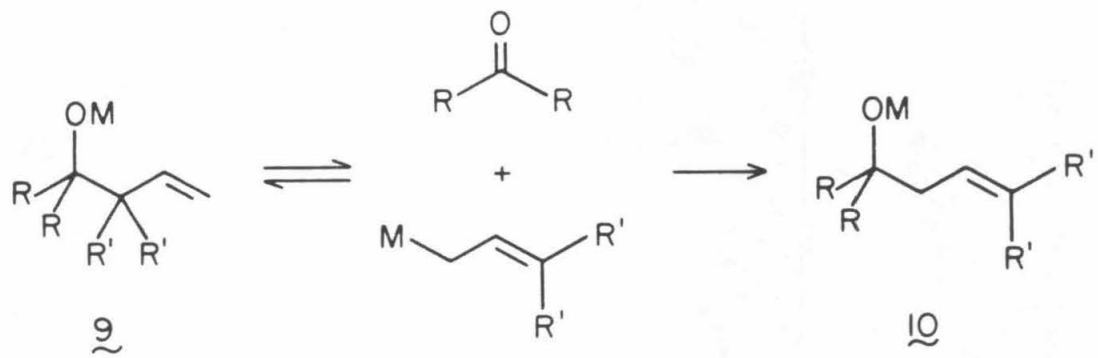
8 (8)

elimination increased with the increasing electropositive character of the cation: $Li^+ < Na^+ < K^+$. In the deprotonation of tri-t-butylcarbinol, Arnett and coworkers[29] observed instantaneous cleavage at room temperature, both in DMSO solution (M = K) and in the gas phase. A heterolytic cleavage mechanism was postulated in both investigations due to the absence of radical recombination products,

but the homolytic pathway could never be ruled out with certainty.

An allyl species is a suitable leaving group in an alkoxide heterolysis (eq 8), and such a fragmentation has been observed in studies on the reversibility of allyl Grignard additions to ketones (Scheme III).[30,31] Fragmentation of the kinetic product 9 via a postulated

Scheme III

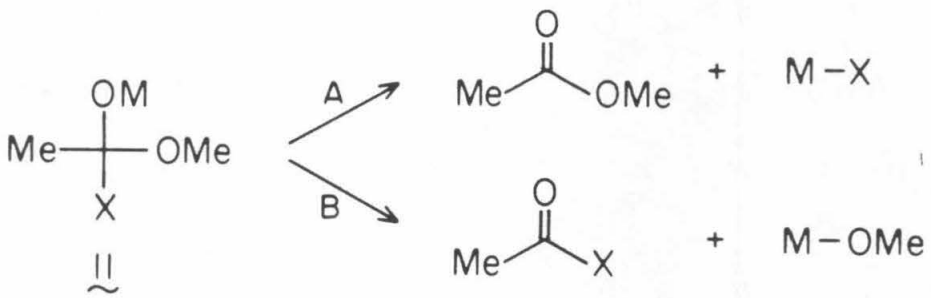


9 10

heterolytic process[30c] was promoted by steric crowding of bulky substituents (R: Et < i-Pr < t-Bu; R': H < Me), by more loosely bound cations ($MgBr^+$ < Li^+ < $ZnBr^+$),[31] and by good cation-solvating solvents (Et_2O < THF).[31]

Finally, an anion substituent effect may be discerned for the breakdown of tetrahedral intermediates in the hydrolysis of esters and amides (Scheme IV).[32] For

Scheme IV



a, X = OH
b, X = NMe_2

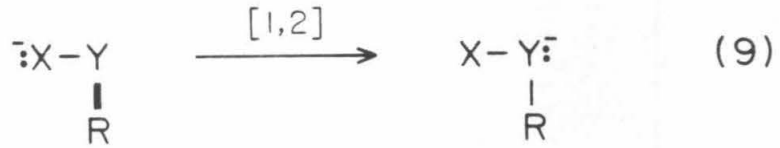
example, in the hydrolysis of methyl acetate, the fragmentation energy of anion 11a (M = Na) was lower than that of neutral 11a (M = H), and the substituent effect was 9.7 kcal/mol for both A and B. Similarly, in the hydrolysis of N,N-dimethylacetamide, 11b exhibited a substituent effect of 6.8 kcal/mol for path A and 5.7 kcal/mol for path B. Thus, the ionic state of the tetrahedral intermediate 11 greatly affects the ease of subsequent cleavage reactions.

Anion-Promoted Sigmatropic Rearrangements

Many of the general features concerning the previously discussed fragmentation reactions (vide supra) are applicable in the case of anion-promoted sigmatropic rearrangements.[33] Rearrangement mechanisms are often subtle and complex problems involving possible dissociation-recombination

processes, both homolytic and heterolytic modes, as well as concerted processes. In many cases, rearrangements proceed through more than a single mechanistic pathway, and related reactions such as fragmentation often compete effectively with the rearrangement itself. Solvent effects and counterion effects are equally important in this reaction class, and can significantly influence the mechanism and overall course of the reaction. Several catagories of sigmatropic rearrangements are examined below and the effect of an anion on bond reorganization is discussed.

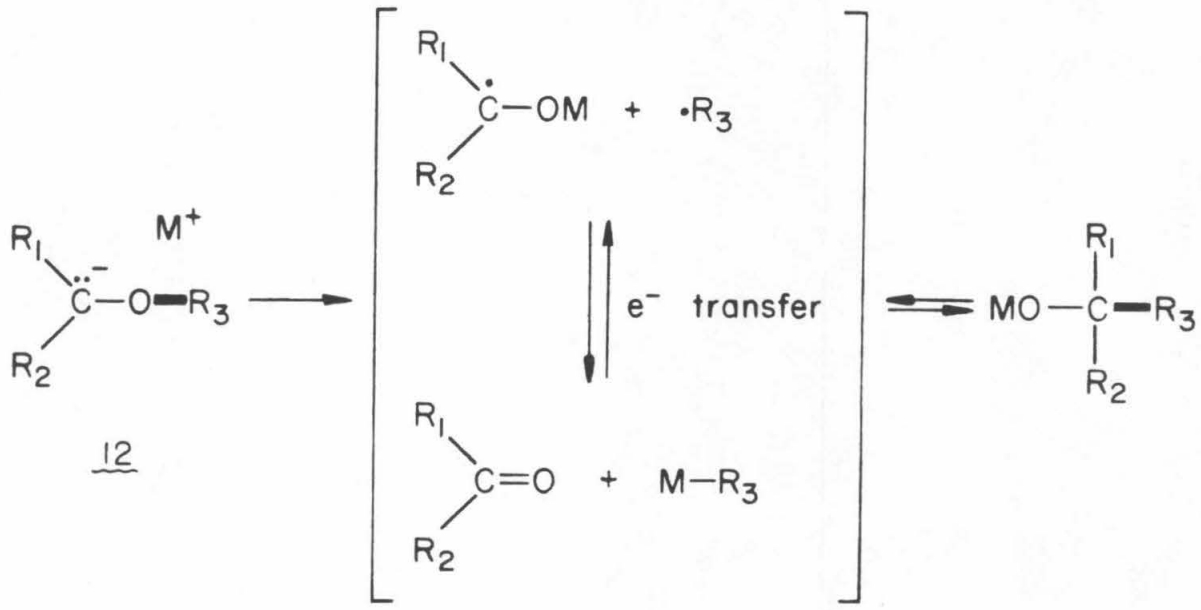
[1,2]-Rearrangements. Bond weakening effects predicted for anions are evident in a variety of [1,2]-sigmatropic rearrangements (eq 9; Table II). The Wittig rearrange-



(9)

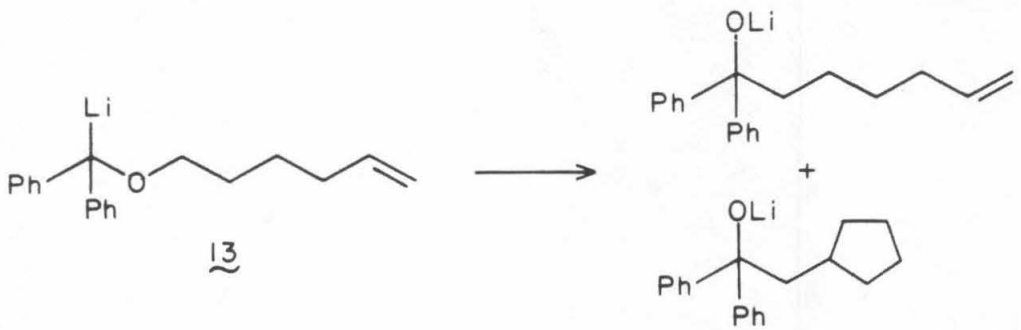
ment[34] of metallated ethers 12 involves the breaking of a weakened C-O bond and a [1,2]-shift of the alkyl substituent to the negatively charged center (Scheme V). Mechanistically, the Wittig rearrangement bears a striking resemblance to alkoxide fragmentations (vide supra). Both homolytic and heterolytic modes are possible, but recent studies[35,36] demonstrated that alkyllithium species such as 13[36] rearrange

Scheme V



via radical pair intermediates or what has been labeled a "radical-concerted" process.[36] As with alkoxides, metallated ethers are also subject to counterion effects. The more ionic dissociated metal alkyls (12, M = alkali metals) undergo rearrangement while the more covalent undissociated metal alkyls (12, M = MgX, ZnX) do not.[36,37] An estimate of the anion substituent effect can be made using activation parameters[38] and bond strengths.[39] The E_a for the isopropyl ether 14 is 16 kcal/mol[51] and a typical C-O bond strength is DH (C-O) ≅ 80 kcal/mol.[52] Thus, the estimated anion substituent effect is an amazing 64 kcal/mol.

Table II. Anion-Promoted [1,2]-Rearrangements.



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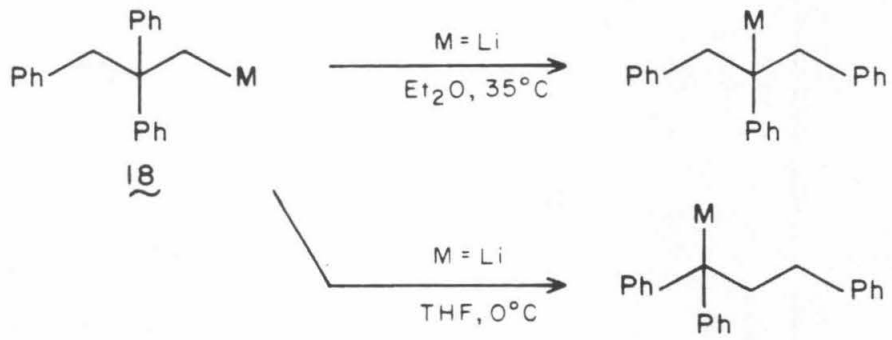
16

17

Table II. (continued)



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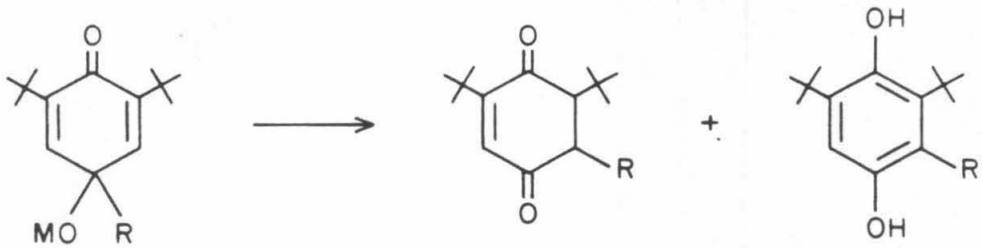
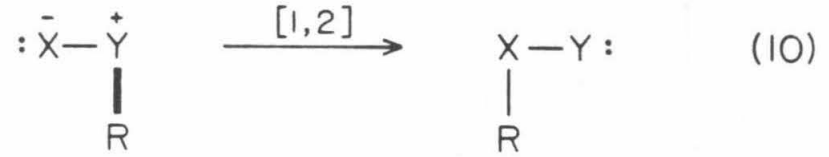


19

Sigmatropic rearrangements of ylids (eq 10) may also be classified as anion-promoted rearrangements. Examples



(10)

of this type are the Stevens rearrangement[40] of nitrogen and sulfur ylids such as 15[42] and 16,[43] respectively, and the Meisenheimer rearrangement[41] of tertiary amine oxides such as 17.

The mechanism of the Stevens and Meisenheimer shifts is generally thought to involve a dissociation-recombination process.[39,40] Because of a long-running controversy over the mechanism of the Stevens rearrangement, both 15 and 16 have been intensively studied. Recent investigations[40a,43] suggest that the 1,2-migration occurs *via* radical-pair rather than ion-pair intermediates. However, Baldwin[43] pointed out that a component of concertedness could not be ruled out in these reactions; in the case of 16, only 18% of the reaction could be definitely ascribed to a radical process.

Anion-promoted [1,2] shifts in all carbon systems have also been investigated.[44] Competitive benzyl *vs* phenyl migration in carbanion 18[45] reflects the occurrence of a loose *vs* a tight transition state (respectively) and can

be controlled by temperature, solvent polarity, counterion, and cation ligands (such as crown ethers). Acyloin rearrangements[46] of substrates such as 19 are promoted by oxy anions. The ease of alkyl migration in 19 was dependent on the nature of the counterion, M;[47] the rate increased in the sequence Li << Na < K.

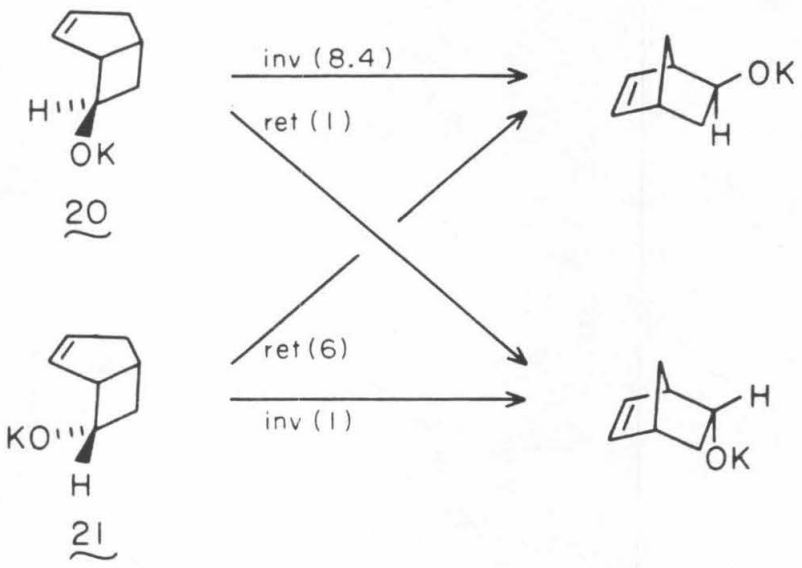
[1,3]-Rearrangements. Examples of anion-accelerated [1,3]-shifts (eq 11, 12) are fairly numerous, especially

(11)

(12)

alkoxides (X = O). One of the most important recent studies was a careful examination of the mechanism of an alkoxide [1,3]-rearrangement conducted by Wilson and Mao[48] using the stereochemistry of substrates 20 and 21 as a mechanistic probe (Scheme VI). Alkoxide 20 rapidly rearranged at 25°C to the bicyclic exo (inversion) and endo (retention) products in a ratio of 8.4:1, respectively. Alkoxide 21 rearranged with much greater difficulty because of steric crowding in the transition state to give the exo and endo

Scheme VI



products in a ratio of 6:1, respectively. Each of these reactions is consistent with a concerted mechanism.

A number of other alkoxide [1,3]-rearrangements are known. Acyclic molecules 22 (M = Li)[49] and 23 (M = K)[50] rearranged under mild conditions and both exhibited a "solvent" dependence. Alkoxide 22 rearranged in THF but not in ether, and 23 reacted much faster in the presence of 18-Crown-6. Such conditions are designed to favor a greater degree of separated ion pairs. Competing [1,3] and [3,3] pathways existed in the rearrangement of alkoxide 24 (M = K).[51] Because of the steric constraints of the medium ring, however, ring expansion via a [1,3]-shift predominated (60%) and very little [3,3] product (7%)

was evident. Oxy anion effects were clearly demonstrated in this case[51] because alkoxide 24 (M = K) rearranged at 25°C in <3 h in HMPA while the silyl ether 24 (M = $SiMe_3$) rearranged with comparable results upon pyrolysis at ~300°C for 12 h.

Bicyclic and polycyclic molecules undergo particularly facile anion-promoted [1,3]-rearrangements. In the reaction of 25 (M = Na), a rapid [1,3]-shift is followed by an electrocyclic cyclopropane ring opening. The activation energy for the first step was 18.9 kcal/mol,[52] which reflects an anion-induced stabilization of 16.6 kcal/mol over that of the corresponding ether (M = t-Bu) rearrangement.[53] Semidione 26 (M = K) underwent both possible [1,3]-migrations and the products were observed by esr.[54] Polycyclic 27 (M = Na) suffered a deep-seated rearrangement with both [1,3]- and [3,3]-shifts invoked in the proposed mechanims.[55]

Amide anions (X = N, eq 12) also facilitated bond reorganizations. Amine 28 (M = H) rearranged quickly and efficiently (90% recovery) in a glpc injector port at 250°C, but anion 28 (M = Li) rearranged completely in 1 min at 30°C.[56] Selectively labeled 28 (deuterium α to nitrogen) was used in determining the stereochemistry of the [1,3]-migration; in both the neutral and anionic case, the rearrangement was suprafacial with retention of stereochemistry at the migrating center. Although con-

Table III. Anion-Promoted [1,3]-Rearrangements.

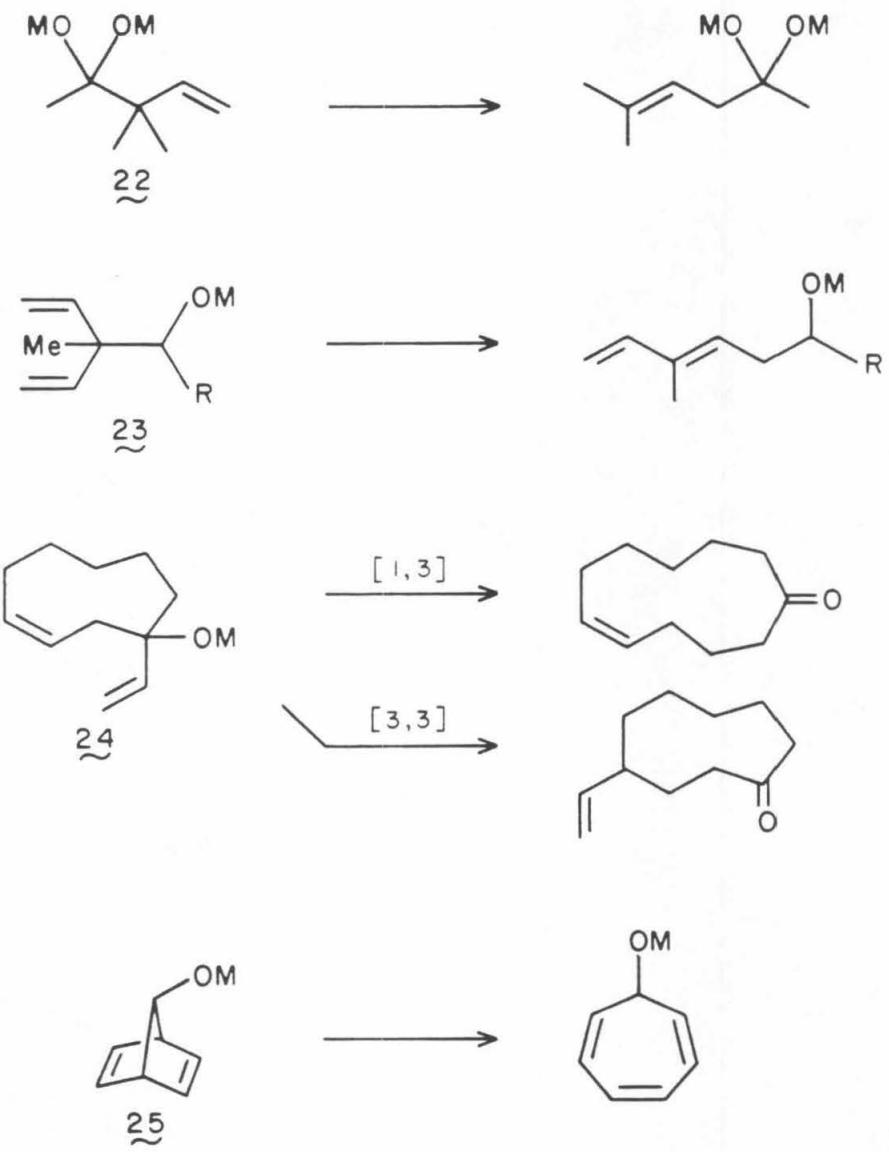
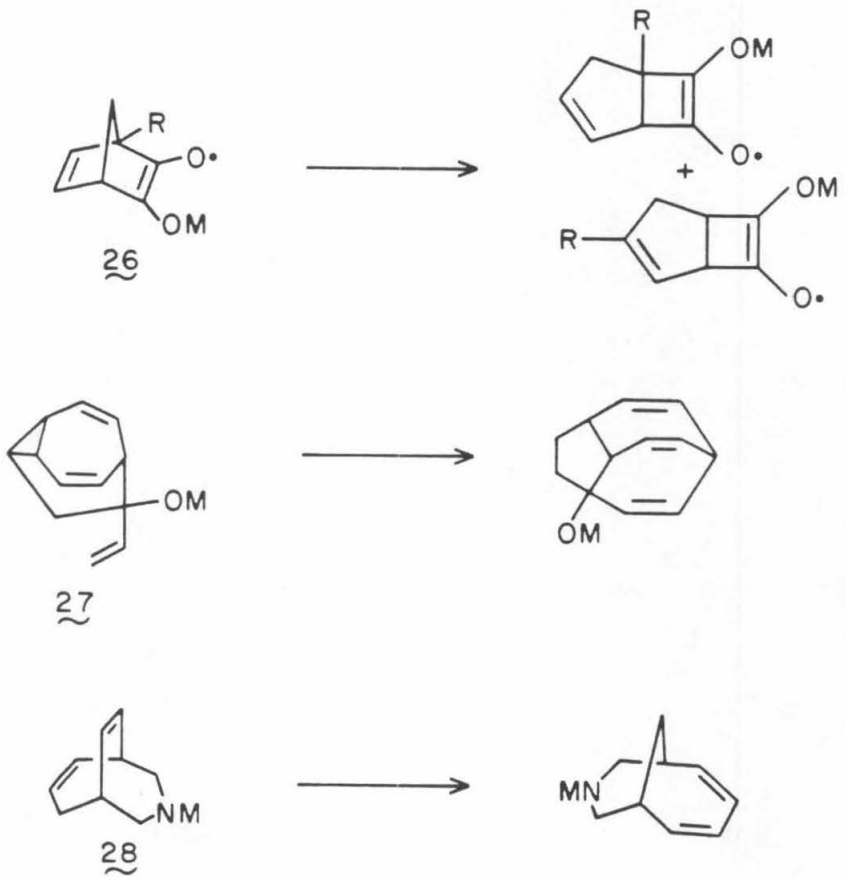
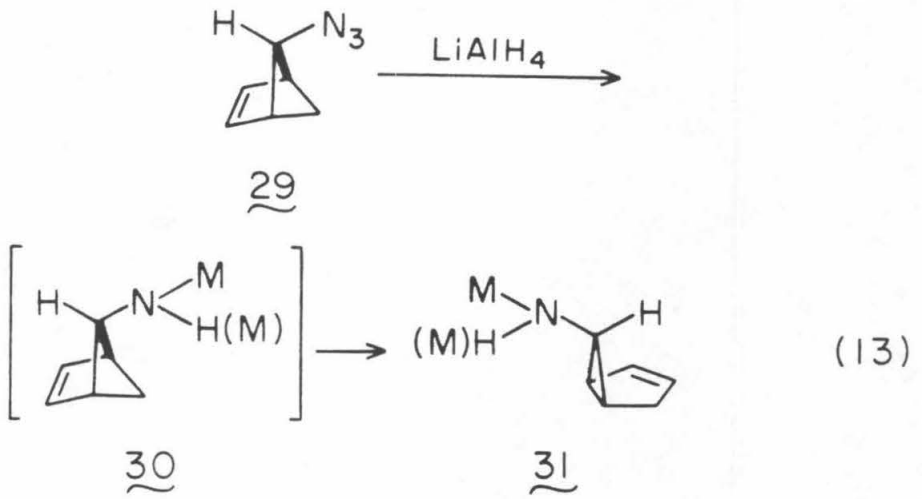


Table III. (continued)



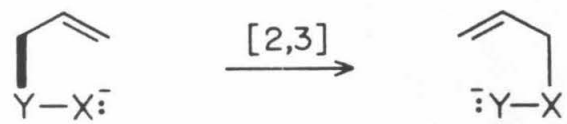
sistent with a concerted process, these results don't rule out radical or ionic mechanisms. Another fast rearrangement occurred in the reduction of azide 29 (eq 13) to give



(13)

the unexpected amine product 31 (M = H).[57] No clear explanation for such a [1,3]-shift was offered. We propose that the intermediacy of metallated amine 30 is consistent with our concepts of anion-induced bond weakening and subsequent accelerated bond reorganization which, in this case, is a [1,3]-shift.

[2,3]-Rearrangements. A general representation of anion-promoted [2,3]-rearrangements is shown in eq 14.

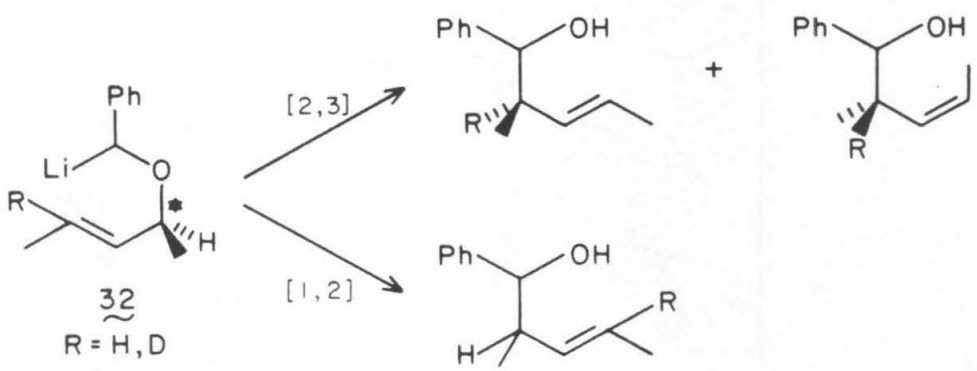


(14)

A common problem in these reactions is the existence of a competitive [1,2]-sigmatropic shift. Baldwin and

Patrick[58] carefully examined this problem as well as the question of the stereochemistry of the [2,3]-migration (Scheme VII) in the reaction of chiral ether 32. A

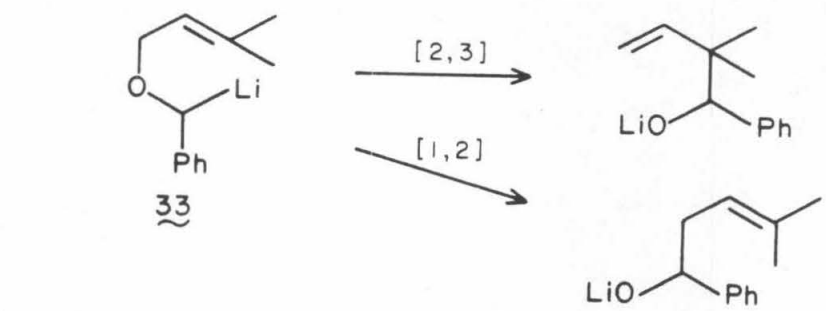
Scheme VII



deuterium label revealed the temperature dependence of the [1,2]-shift; at 0°C there was 14% [1,2]-shift, but at -80°C there was essentially 0%. Analysis of the fate of the chiral center showed that the [2,3]-sigmatropic pathway to the trans product was essentially 100% stereospecific via a suprafacial transition state.

Many examples of Wittig rearrangements of alkyl ethers have been reported. Rautenstrauch[59] estimated that the [2,3]-shift of 33 had a very low free energy of activation, $\Delta F^{\ddagger} \cong 13$ kcal/mol, which could be an indication of a concerted process.[60] Despite this low energy barrier, 33

Table IV. Anion-Promoted [2,3]-Rearrangements.



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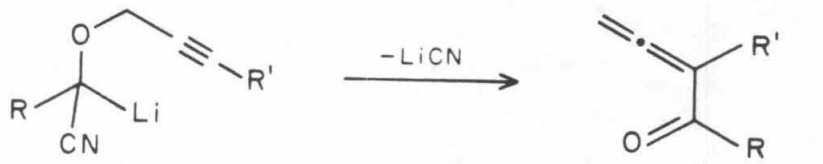

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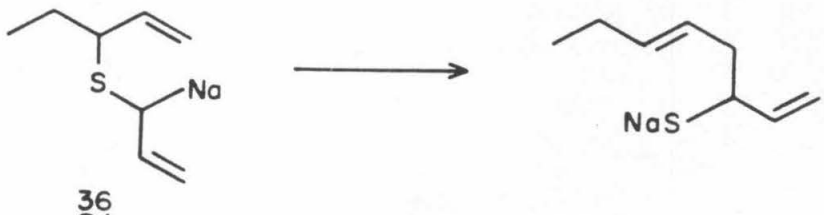

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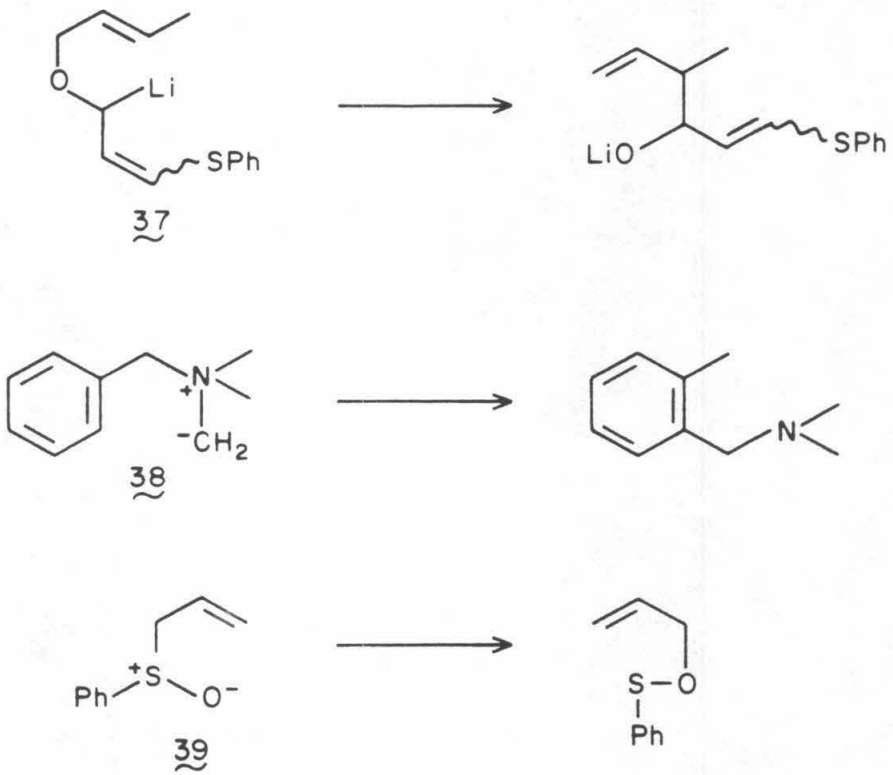
Table IV. (continued)



37

38

39

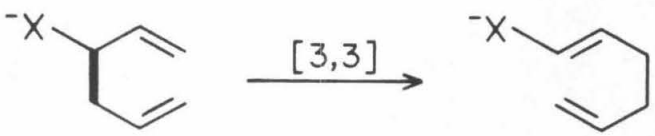
usually produced varying amounts of the [1,2]-shift product. Propargyl ether 34[61] rearranged followed by elimination of LiCN salt, and aromatic ether 35[62] underwent a succession of possible [2,3]-, [1,2]-, and [3,3]-shifts. Substrates 36[63] and 37[64] are interesting in that the alternate allyl resonance form could undergo a [3,3]-shift in a Claisen rearrangement. However, the products were due exclusively to the [2,3]-pathway.

All-carbon systems were investigated by both Baldwin[65] and Grovenstein.[44,66] Low reaction temperatures typically favored the more facile [2,3]-shift over the [1,2]-shift.[65] In a case where either an allyl or a phenyl group could migrate,[66] control of the reaction conditions was used to promote a [2,3] allyl shift in a "loose" ion pair transition state and a [1,2] phenyl shift in a "tight" ion pair transition state.

Ylid structures are also prone to undergo [2,3]-rearrangements. The Sommelet-Hauser rearrangement[40a] of metallated ammonium ions such as 38 is competitive with the [1,2]-shift of the Stevens rearrangement. The allylic sulfoxide-sulfenic ester rearrangement[67] of substrates such as 39 is actually an equilibrium favoring the sulfoxide; however, the sulfenic ester may be trapped with an appropriate thiophile to give the allyl alcohol.

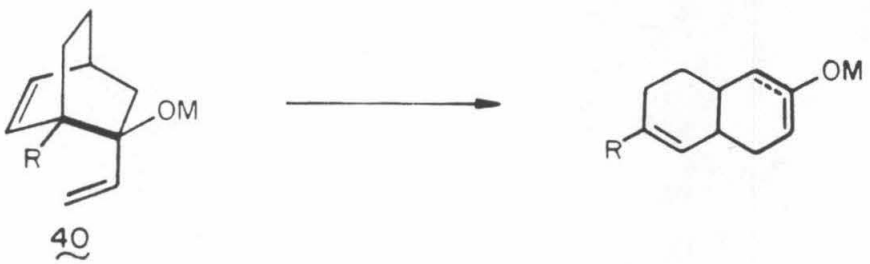
[3,3]-Rearrangements. Much of the recent interest in

anion-accelerated [3,3]-sigmatropic rearrangements (eq 15) has been sparked by the observation of Evans and Golob[68]



(15)

that base catalysis of the oxy-Cope rearrangement increased reaction rates by a factor of 10^{10}-10^{17} (eq 16). Further



40

(16)

R = H, OMe
M = H, K

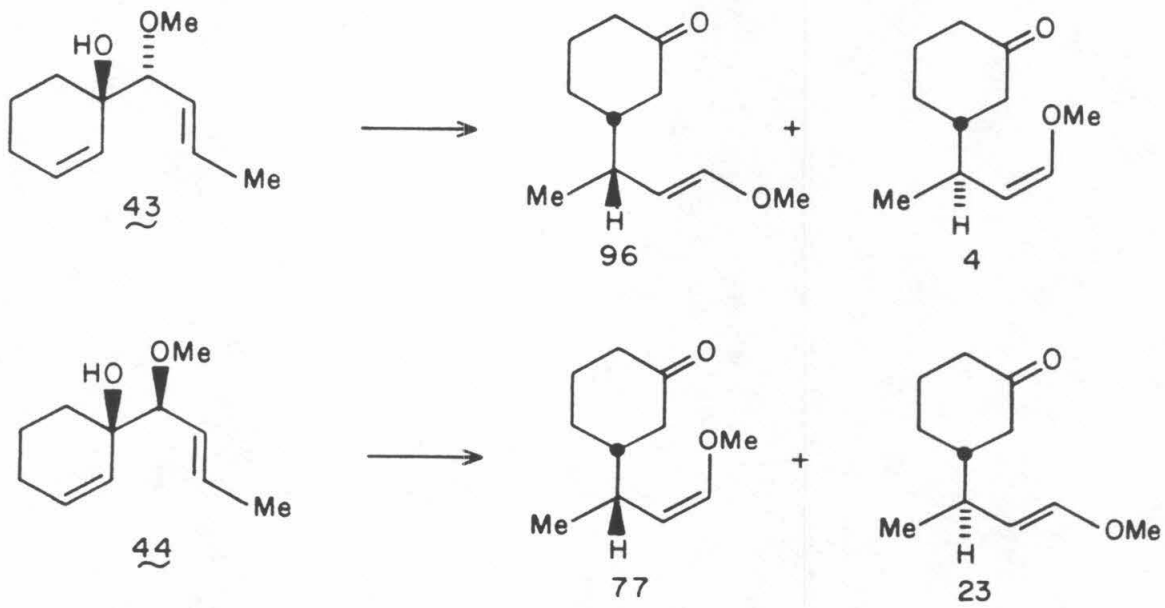
$$\frac{k_M}{k_H} = 10^{12}-10^{17}$$

investigation revealed that the rate increased with the increasing electropositive character of the counterions (Li < Na < K ≈ Cs) and the increasing cation-solvating power of solvents (Et_2O < THF < HMPA). In general terms, the greater the ionic character of the O-M bond, then the greater the observed rate acceleration.[68] These concepts have since been extended to other acyclic and alicyclic

[3,3]-rearrangements (Table V): the preparation of of δ,ε-unsaturated carbonyl compounds from 41 (X = H, R),[69] the preparation of selectivley masked 1,6-dicarbonyl products from 41 (X = OR, SR),[70] and the isoprenylation of quinones via 42.[71]

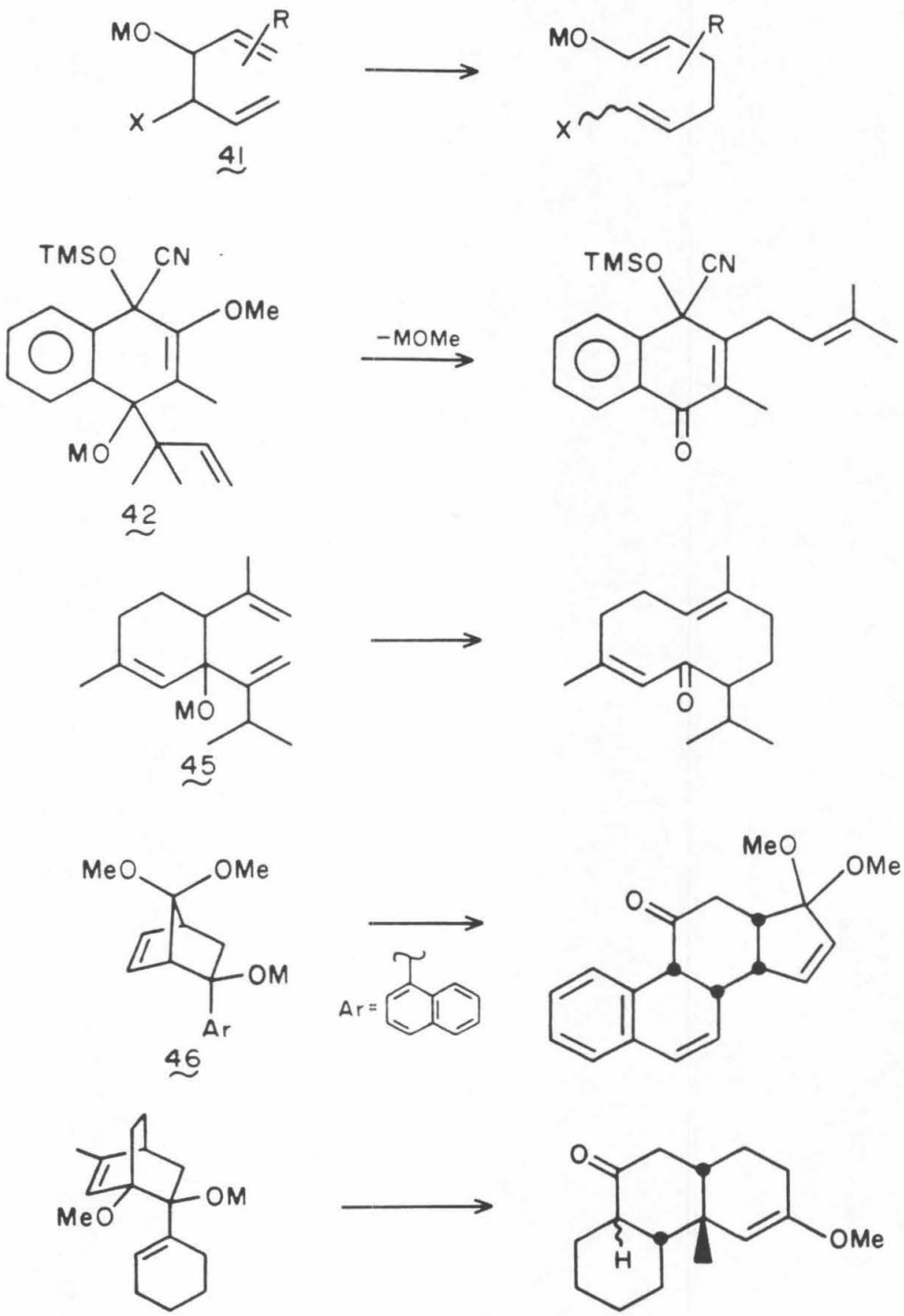
Rearrangement of diastereomers 43 and 44 is particularly noteworthy in that a careful stereochemical study was conducted[70a,72] to probe the mechanism of the base-accelerated oxy-Cope (Scheme VIII). The stereoselectivity of each of the rearrangements was in qualitative agreement with pre-

Scheme VIII



dictions based upon transition state conformational analysis. The major product isomers arose from a chair-like transition

Table V. Anion-Promoted [3,3]-Rearrangements.

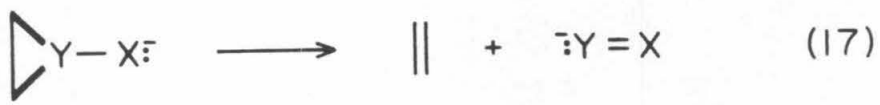


state and the minor isomers from a boat-like transition state. As in Wilson's study[48] of oxy anion accelerated [1,3]-shifts, these results were consistent with a fully concerted sigmatropic rearrangement.

Several examples of complex ring construction are based on the accelerated oxy-Cope rearrangement. A structure proof of the alkaloid cannivonine utilized the oxy-Cope substrate 40.[73] Alkoxide 45 was used in a short, efficient synthesis of (±)-acoragermacrone, a member of the germacrene class of compounds.[74] Aromatically substituted norbornenyl substrates, 46, were rearranged to cis-hydrindanones.[75] The rearrangement of 47 was used in studies directed toward the total synthesis of the macrolide antibiotic chlorothricolide.[76]

Cheletropic Reactions

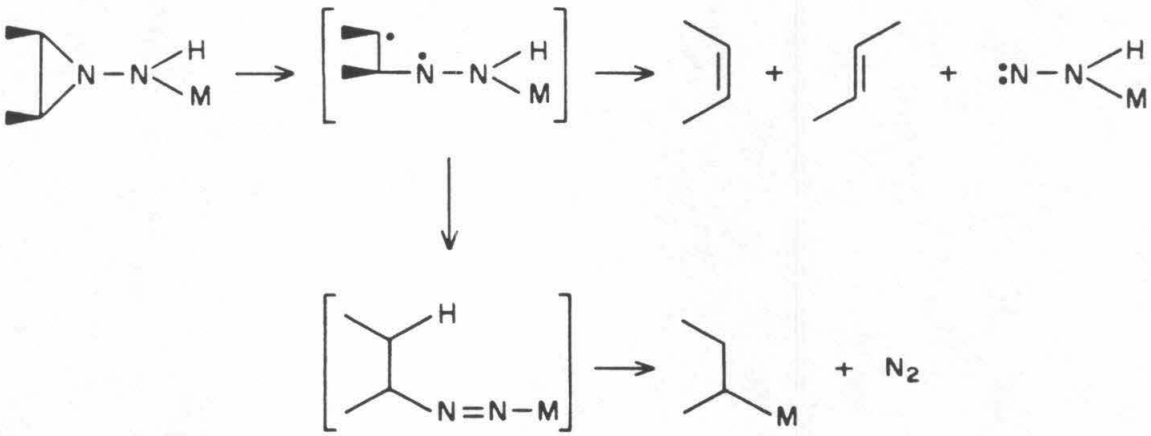
A number of classes of cheletropic reactions exhibit large anion substituent effects in the fragmentation process. One such class is the extrusion of a small molecule from a three-membered heterocycle to give an olefin (eq 17).



(17)

Dramatic anion substituent effects were recently observed in studies of the decomposition of 1-aminoaziridines[77,78] (Table VI). Dervan and Ingle[77] investigated the decomposition of aziridines 48 and 49, and found that gas-phase thermolysis of neutral 48 at >200°C produced mostly cis and trans butene. However, anion 49 decomposed rapidly at <0°C in DME to give mostly butane as well as cis and trans butene. Results of both reactions are consistent with a stepwise radical cleavage mechanism (Scheme IX) with a predominant hydrogen atom transfer step in the anionic case. Simultaneously, Evans and Biller[78] explored the synthetic utility of aminoaziridine

Scheme IX



decompositions in generating vinyl anions. Ketones and 1-aminoaziridines readily formed hydrazones which could

be metallated to the reactive intermediate 50, and subsquent decomposition occurred under mild conditions. The magnitude of the anion effect was demonstrated with the hydrazone of 1-amino-2-phenylaziridine and 3-cholestanone; the neutral hydrazone decomposed in 3.5 h at 126°C while the lithium salt decomposed in < 15 min at 0°C.

Several other types of 1-substituted aziridines undergo anion-accelerated extrusion reactions (Table VI). Aziridine N-oxides fragment to olefins and nitroso compounds at or below 25°C.[79] Most cases exhibit some degree of olefin scrambling, but 51 was found to decompose stereospecifically.[79b] The mechanism of the fragmentation of 52 is obscured by a major side reaction, competitive Meisenheimer rearrangement to a 1,2-oxazetidine followed by cleavage of the four-membered ring.[79c] This alternate pathway accounts for all the observed products, but does not rule out the direct extrusion process as a component of the overall reaction. Aziridinium ylids such as 53 are readily cleaved to olefin and imines,[80] often with high stereoselectivity.[80a] Cleavage of 1,1-diazenes is a particularly good illustration of the concept of an anion substituent effect because protonation of the terminal amine greatly stabilizes the molecule.[81] Decomposition of diazenes 54 and 55 exhibit moderate to high stereoselectivity.[82]

Analogous to the aziridine N-oxides, episulfoxides undergo cheletropic reactions to give an olefin and sulfur

monoxide (Table VI).[83,84] Because of conflicting reports on the mechanism of this type of extrusion reaction, Aalbersberg and Vollhardt[84] investigated the thermolysis of the specifically labeled parent episulfoxide 56. In either the gas or solution phase, 95% of the initial stereochemistry was retained in the product. The conclusion was that a significant contribution from the concerted process to the mechanism could not be ruled out.

Closely related to the episulfoxides are the episulfones. Episulfones are more susceptible to fragmentation than the sulfoxides and are key intermediates in the preparation of olefins *via* the Ramberg-Bäcklung rearrangement.[85]

A second class of anion-assisted cheletropic reactions involves the breakdown of five-membered heterocycles (eq 18). For example, the 1,1-diazene 57 rapidly extruded N_2 in a stereospecific and orbital symmetry-allowed

(18)

disrotatory manner.[81a,86] Similarly, the amine oxide 58 decomposed rapidly at room temperature to give 1,2,3,4-tetrafluoronaphthalene and nitrosomethane.[87]

A third general class of cheletropic reactions formally involves the extrusion of an olefin to generate an allyl

Table VI. Anion-Promoted Cheletropic Reactions

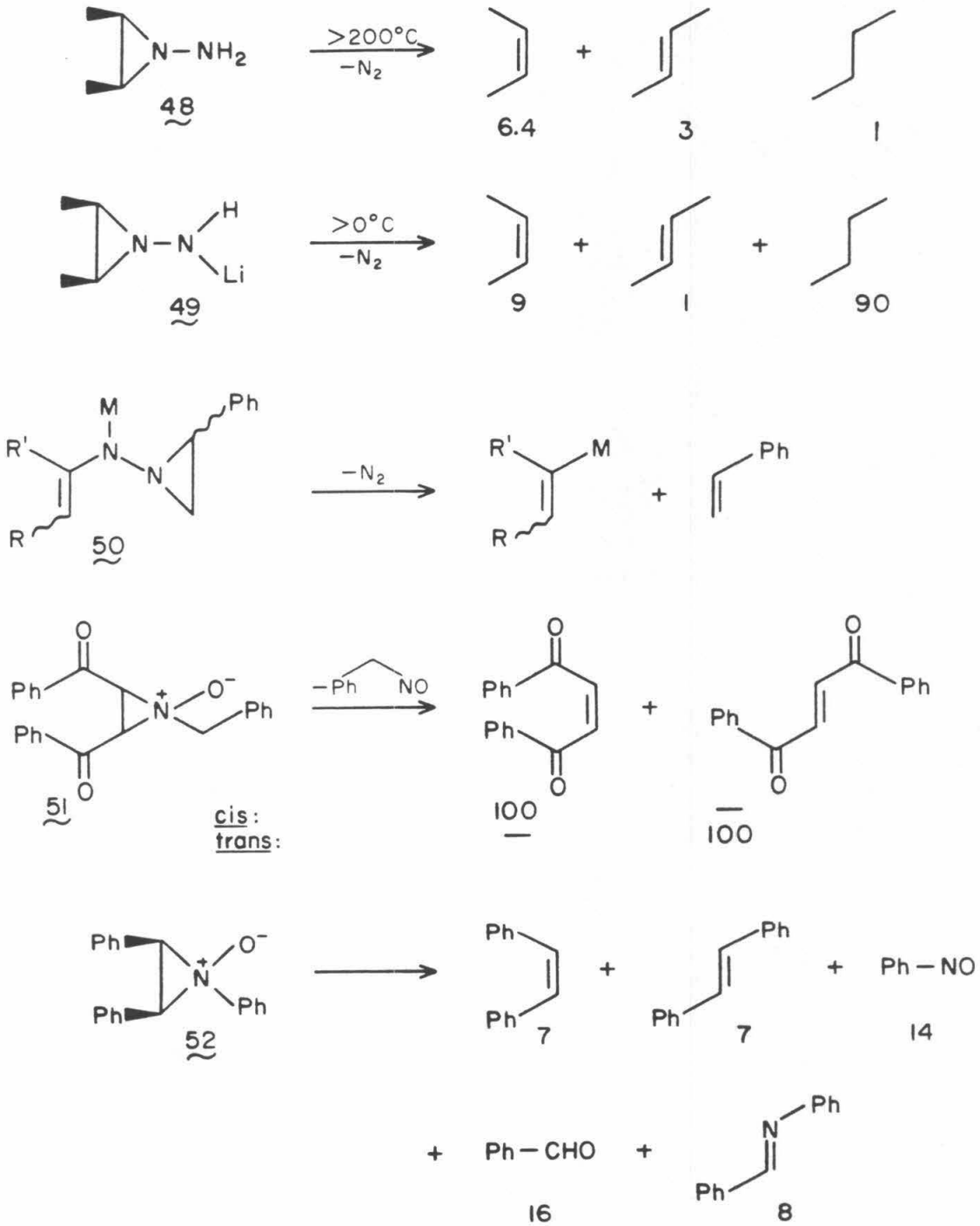


Table VI. (continued)

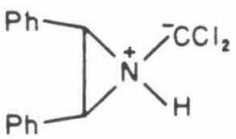
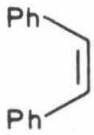
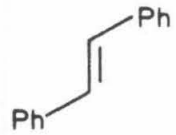
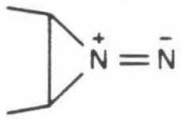
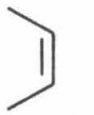
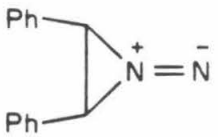
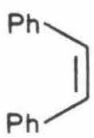
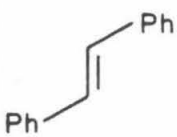
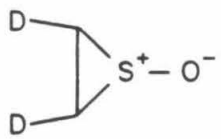
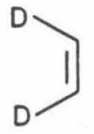
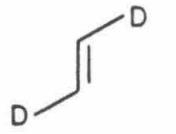
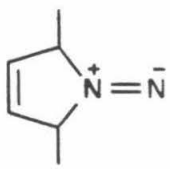
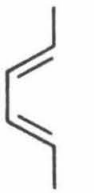
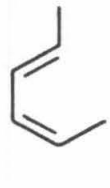
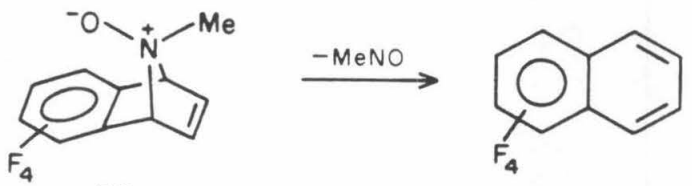
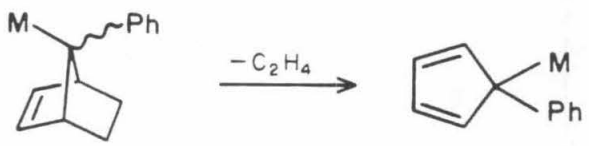
		 + 	
53	cis:	95.5	4.5
	trans:	<1	>99
		 + 	
54	cis:	⩾96	⩽ 4
	trans:	⩽ 4	⩾96
		 + 	
55	cis:	15	85
	trans:	—	100
		 + 	
56	cis:	95	5
	trans:	5	95
		 + 	
57	cis:	100	—
	trans:	—	100

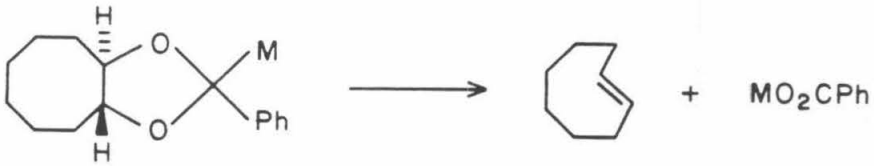
Table VI. (continued)



58



59



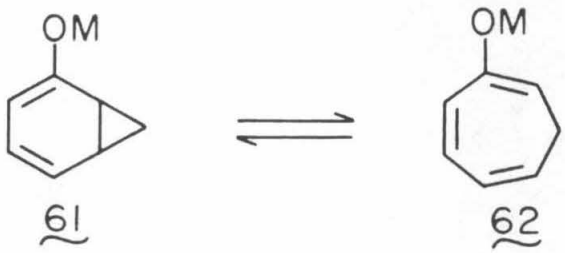
60

(19)

anion (eq 19). For example, 59 (M = Na, K)[88] undergoes a facile retro-Diels-Alder reaction to yield ethylene and phenylcyclopentadienyl anion. The activation energy for the cleavage was estimated to be $\leq$ 23 kcal/mol which reflects an anion substituent effect of $\geq$ 15 kcal/mol. Another reaction in this class is the decomposition of metallated 2-phenyl-1,3-dioxolans[89] such as 60 (M = Li).[90] Evidence clearly indicates that these extrusion reactions are stereospecific.[89] A solvent dependence has also been observed and the rate of decomposition increases with the increasing polarity of the solvent.[89]

Electrocyclic Rearrangements

The concept of anion-promoted rearrangements can also be extended to electrocyclic rearrangements. An example of this can be found in the transformation of the extended enolate 61 (M = Na, K) to enolate 62 via a formal cyclohexadiene-hexatriene electrocyclic ring opening (eq 20).[91] The oxy anion is suitably conjugated in order to promote bond weakening of the cyclopropyl bond.



61 62 (20)

Conclusion

Anion substituent effects on adjacent bonds generally facilitate both fragmentations and rearrangements in a wide variety of molecules. Only a few examples in a limited number of categories were cited above, but they serve to illustrate the concepts associated with these substituent effects. The change in the activation parameters and the course of the resulting bond reorganization ultimately depends on the degree of ionic character developed in the anion-metal counterion bond. Consequently, the nature of the anion, the nature of the counterion, the solvent, and the temperature all influence the course of anion-promoted bond reorganizations.

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APPENDIX I

Additional Thermochemical Estimates on the Fragmentations of Alkoxides

In previous work,[1] thermochemical estimates of the fragmentation energies of simple gas phase alkoxides were made. Both homolytic (radical) and heterolytic (ionic) fragmentation modes were examined and compared. Since only primary and secondary alkoxides were treated, additional thermochemical estimates have been made and tertiary alkoxides can now be included in this general study.[2] As with the previous work, the estimates are limited by the availability of reliable gas phase thermochemical data.

The two fragmentation modes which will be examined are shown below (eq 1 and 2). Born-Haber cycles can be

$$^{-}O{-}C(CH_3)_2{-}R \xrightarrow{DH^\circ} {}^{-}O{-}\dot{C}(CH_3)_2 + \cdot R \qquad (1)$$

$$^{-}O{-}C(CH_3)_2{-}R \xrightarrow{\Delta H_I^\circ} O{=}C(CH_3)_2 + {}^{-}R \qquad (2)$$

constructed for each of these processes. From electron affinity (EA) and bond strength (DH°) data, the fragmentation energies for the two processes can be calculated according to the following expressions:

$$DH^\circ(^{-}O\overset{|}{\underset{|}{C}}{-}R) = EA\,(\cdot O\overset{|}{\underset{|}{C}}{-}R) + DH^\circ(\cdot O\overset{|}{\underset{|}{C}}{-}R) - EA\,(O{=}C\langle) \qquad (3)$$

$$\Delta H_I^\circ = EA\,(\cdot O\overset{|}{\underset{|}{C}}{-}R) + DH^\circ(\cdot O\overset{|}{\underset{|}{C}}{-}R) - EA\,(\cdot R) \qquad (4)$$

In addition to the thermochemical data previously used,[1] new data are listed in Table I. The results of the calculations are listed in Table II.

In general, the tertiary alkoxides[2] follow the same trends as primary alkoxides. The heterolytic dissociation energy ΔH_I° is much lower than the homolytic dissociation energy DH°, and DH° decreases as the leaving group grows large and/or becomes a more stable radical. Certain values in Table II also have added significance. The dissociation energy of isopropoxide (ΔH_I° = 39 kcal/mol) is lower than but close to the value of the electron affinity of isopropoxy radical. The difference between these two values is directly related to the competition between electron and hydride transfer in Merwein-Ponndorf-Verley-type reductions. In the gas phase hydride transfer would be favored.

The heterolytic cleavage of $^-OC(CH_3)_2-CH_2CH=CH_2$ can be related to studies on reversible allylic Grignard additions to ketones. The dissociation value in this case, ΔH_I° = 29 kcal/mol, could serve as an upper limit to the dissociation energy for more sterically crowded tertiary allylic alkoxides.

Table I. Electron Affinities (EA) and Bond Dissociation Energies (DH°) of Simple Radicals and Molecules.[a]

	EA	DH° ($^{-}$OC(R)—R)
$\cdot OC(CH_3)_2—H$	43[b]	15.2[f]
$\cdot OC(CH_3)_2—CH_3$	43.1[c]	6[g]
$\cdot OC(CH_3)_2—CH_2CH=CH_2$	43.1[d]	-2.7[h]
$O=C(CH_3)_2$	-34.8[e]	

[a]All values reported in kcal/mol. [b]Ref. 3. [c]Ref. 4. [d]Assumed to be equal to EA [$\cdot OC(CH_3)_2—CH_3$]. [e]Ref. 5. [f]Calculated from heats of formation; ref. 6. [g]Ref. 9. [h]Calculated from heats of formation; ref. 10.

Table II. Calculated Fragmentation Energies for Alkoxides $^{-}OC(CH_3)_2-R$.[a,b]

R	DH° [$\bar{O}C(CH_3)_2-R$]	ΔH_I°
H	92	39
CH_3	83	47
$CH_2CH=CH_2$	74	29

[a]All values reported in kcal/mol. [b]Gas phase, 298°K.

References and Notes

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6. Estimate based upon ΔH_f° [$O=C(CH_3)_2$] = -51.9 kcal/mol (ref. 7), ΔH_f° ($H\cdot$) = 52.1 kcal/mol (ref. 8), and ΔH_f° [$\cdot OC(CH_3)_2H$] = -15 kcal/mol (ref. 9).
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10. Estimate based upon ΔH_f° [$O=C(CH_3)_2$] = 51.9 kcal/mol (ref. 7), ΔH_f° ($\cdot CH_2CH=CH_2$) = 41.2 kcal/mol (ref. 11),

and ΔH_f° [$\cdot OC(CH_3)_2CH_2CH=CH_2$] = -2.7 kcal/mol (references 8, 9, and 12).

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APPENDIX II

Spectral Catalogue for Chapter I


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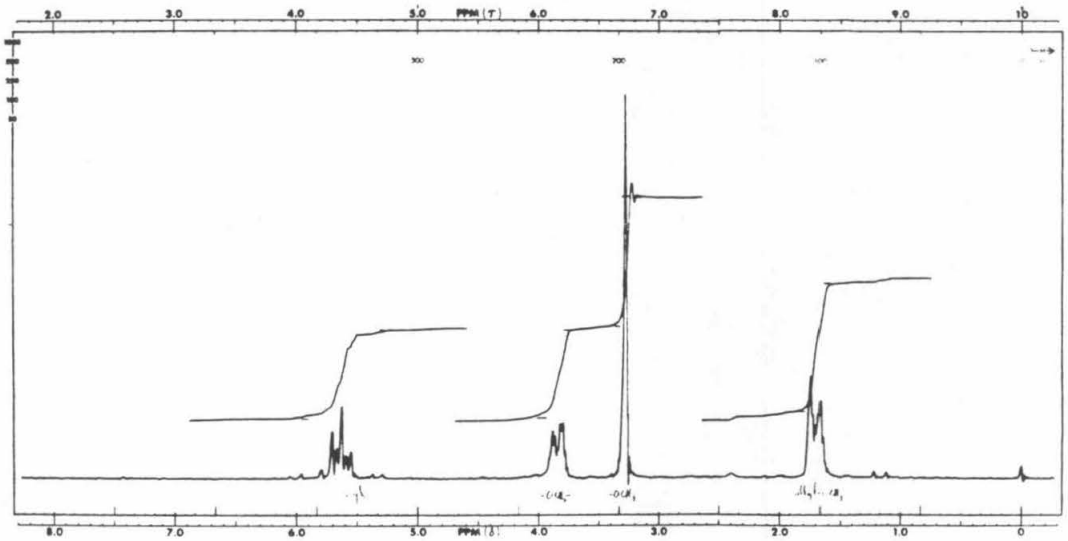
Page 42

4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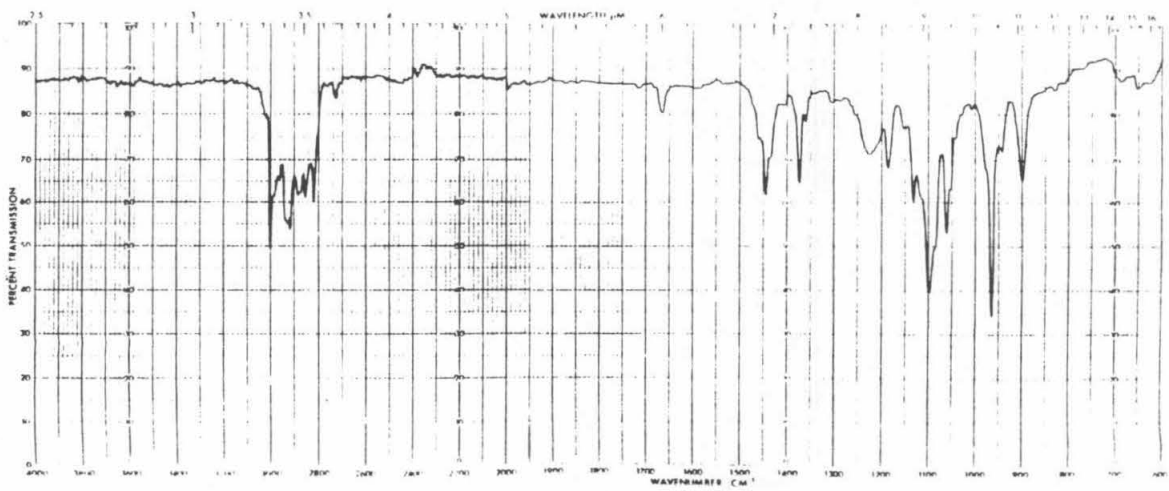
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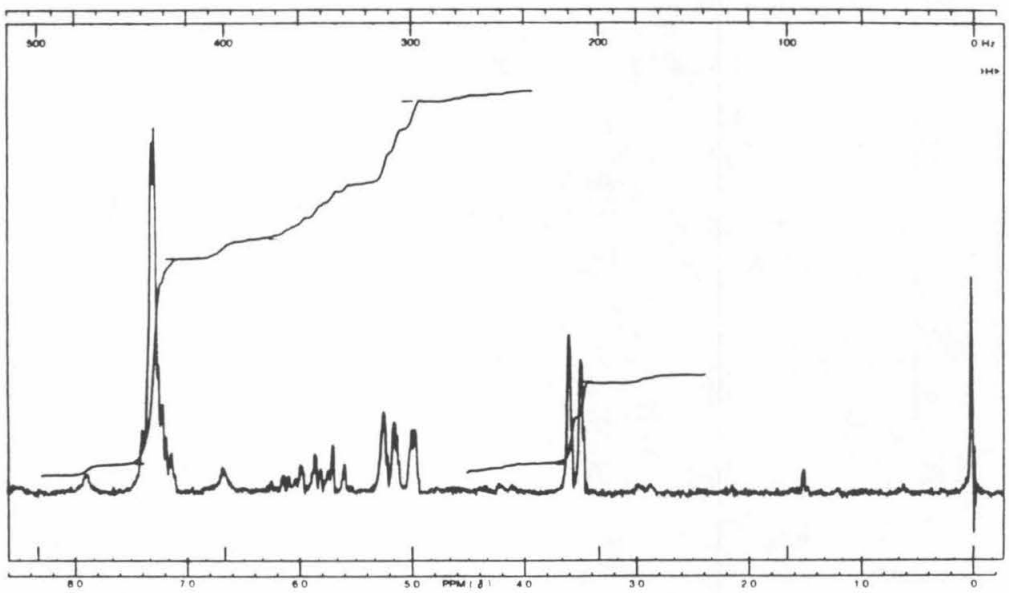
WAVELENGTH, μM
WAVENUMBER, CM⁻¹

Page 42


PhS

5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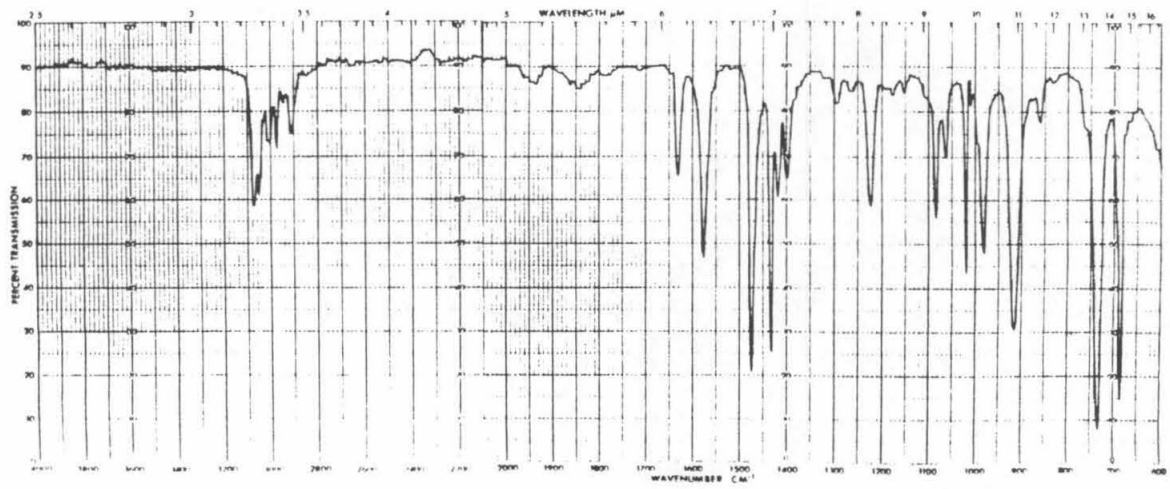
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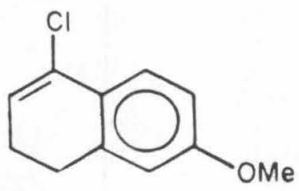
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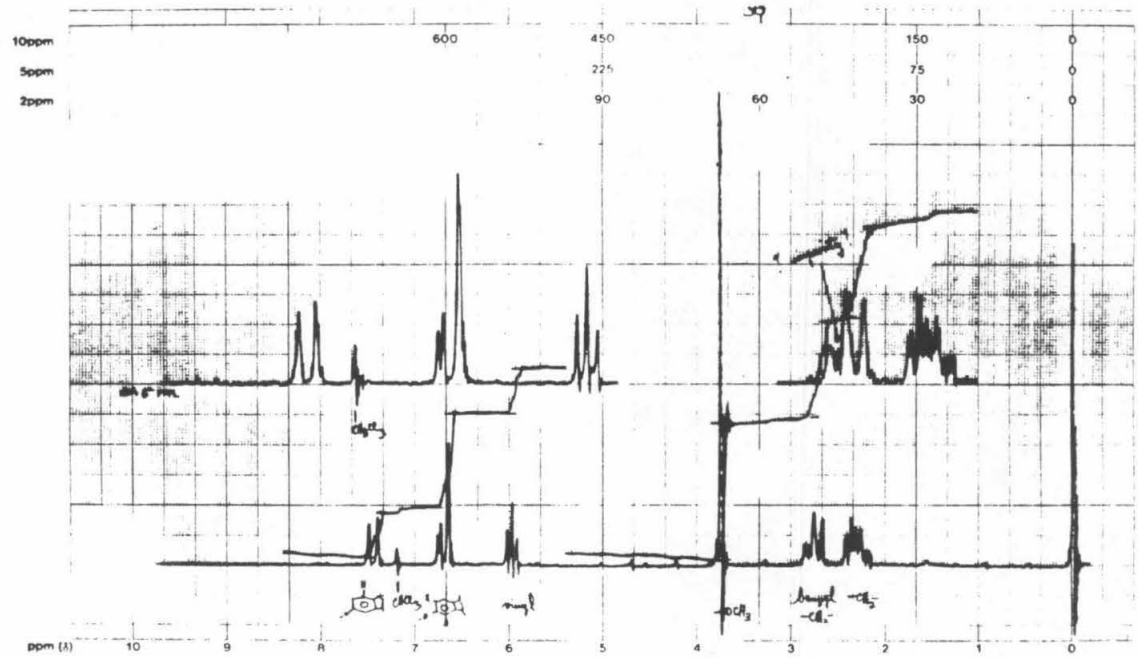
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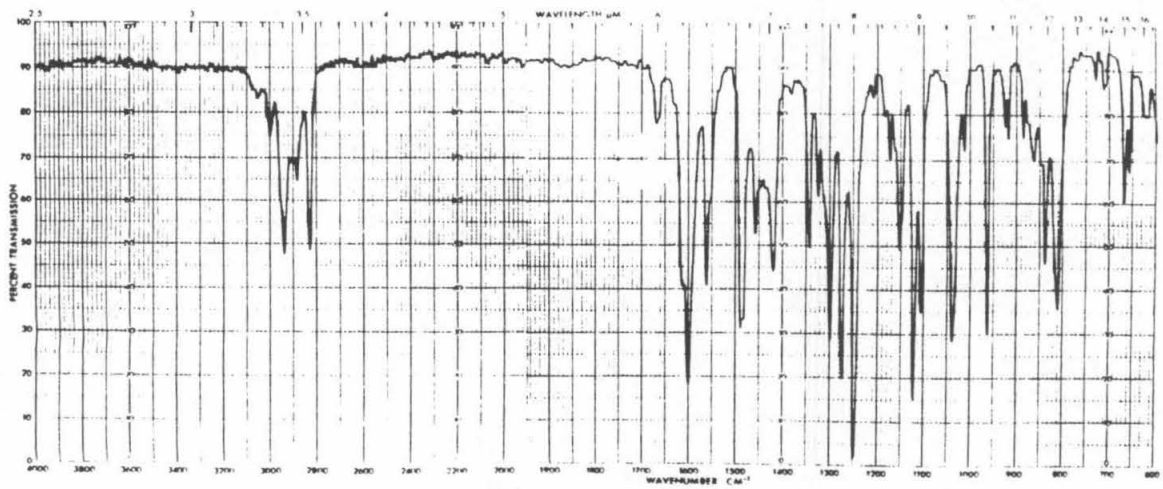
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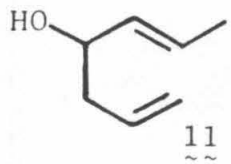

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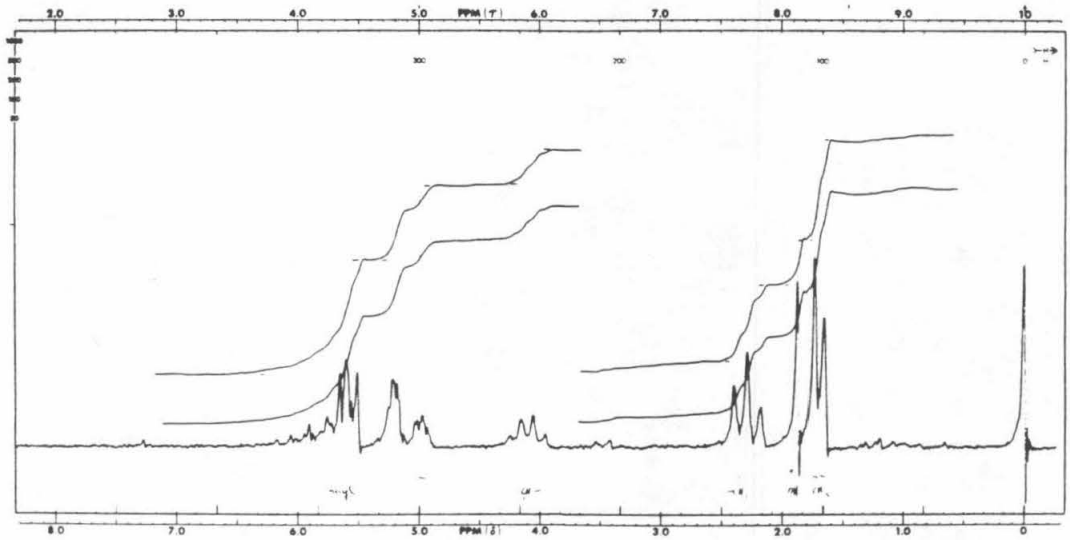
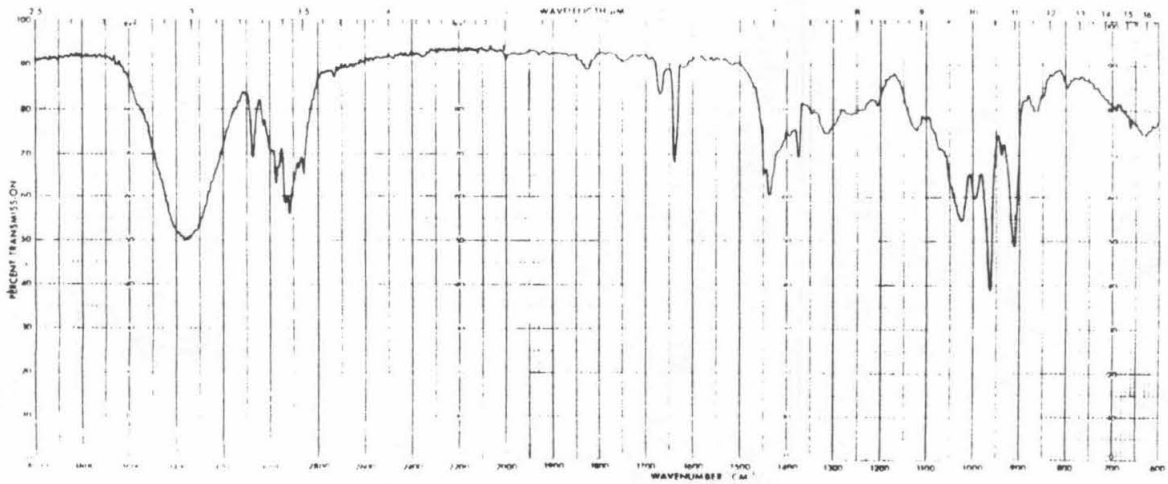
Page 43





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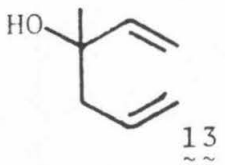
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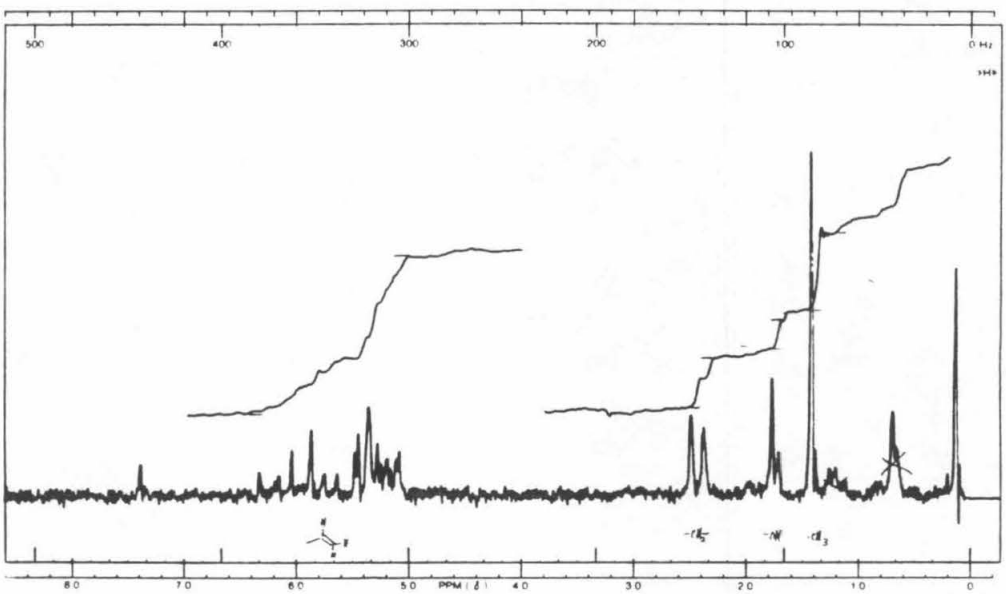
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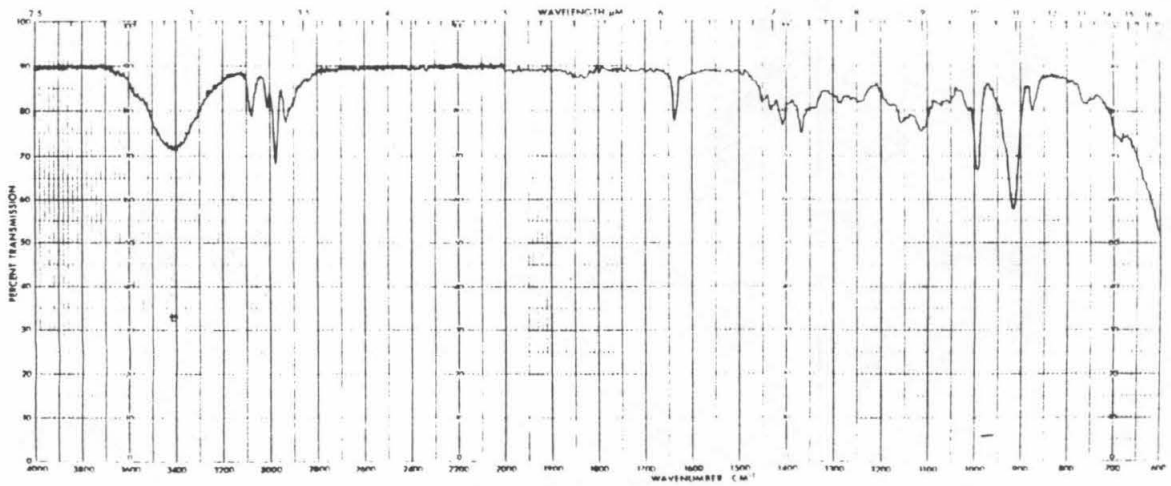
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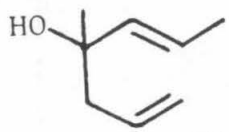
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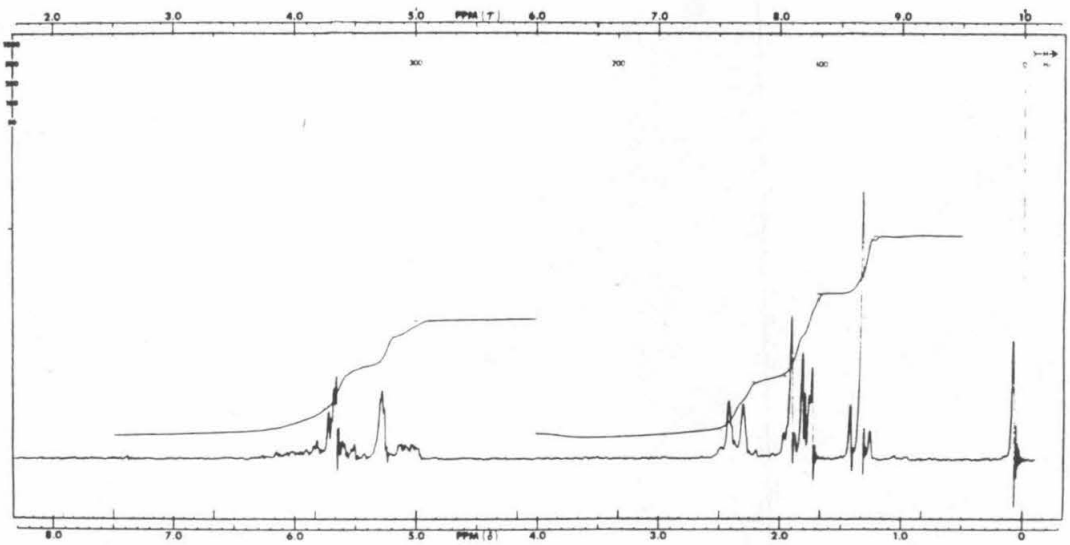
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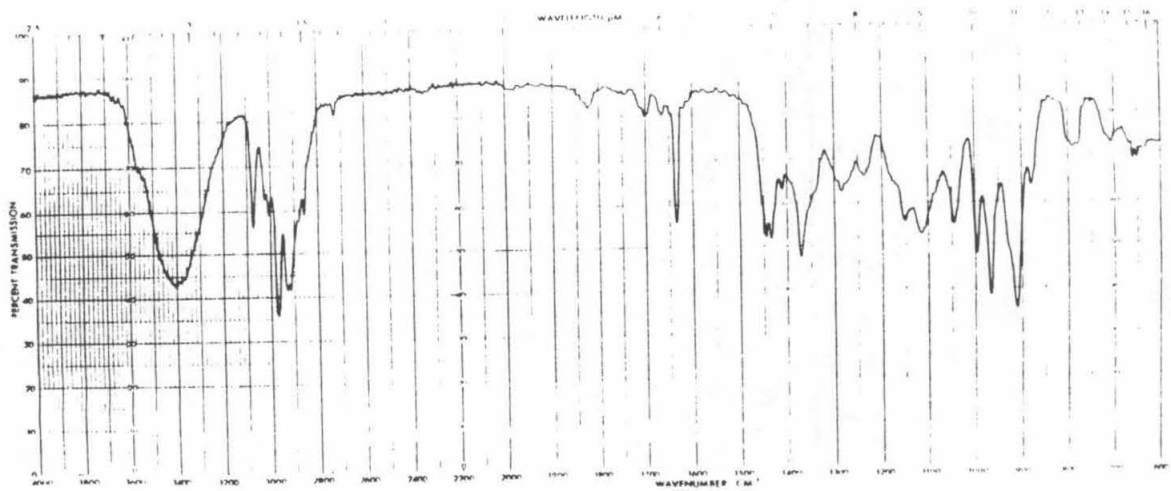
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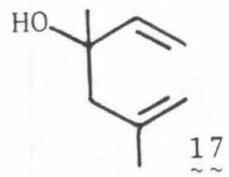
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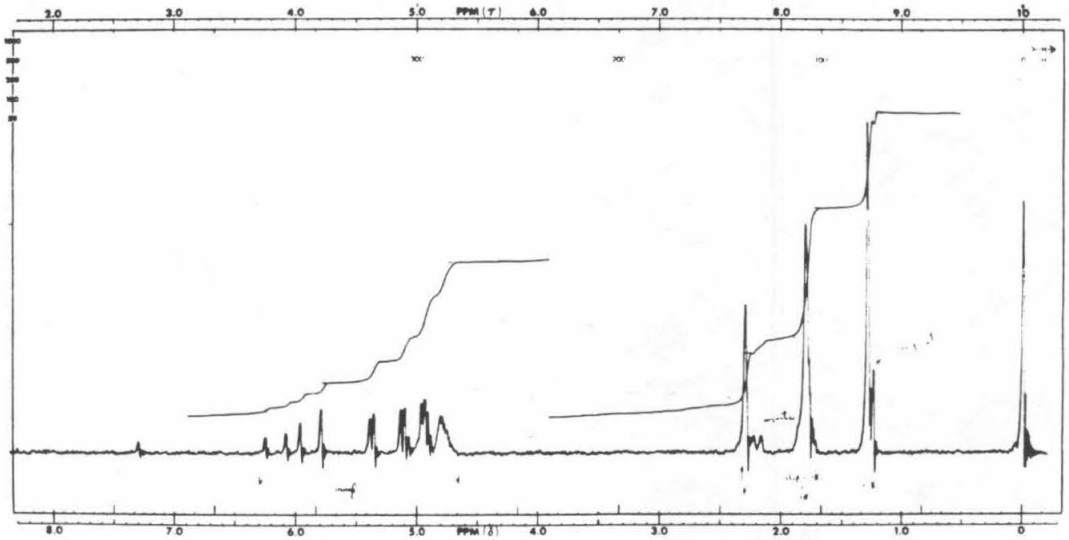
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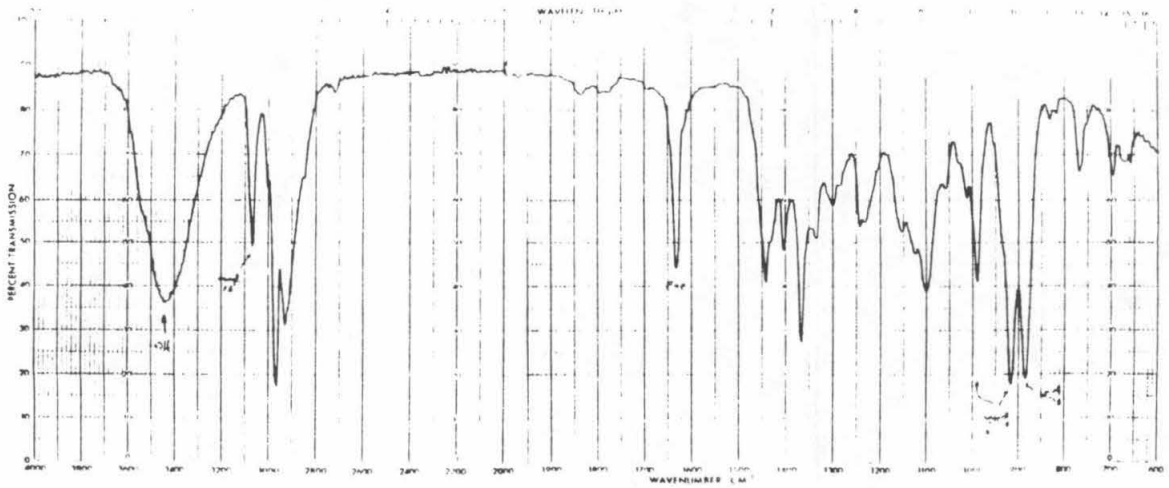
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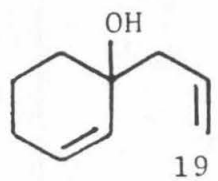
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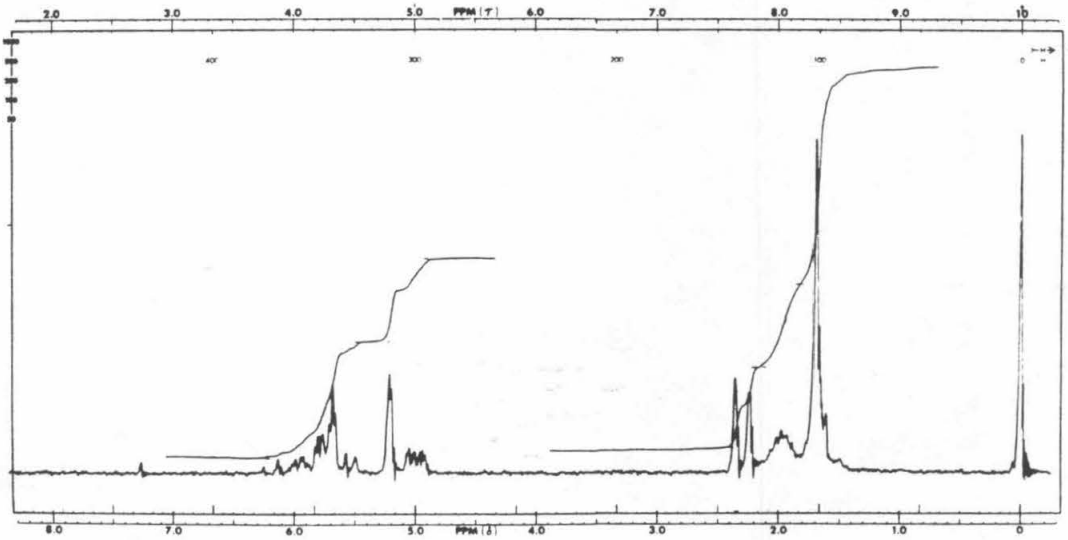
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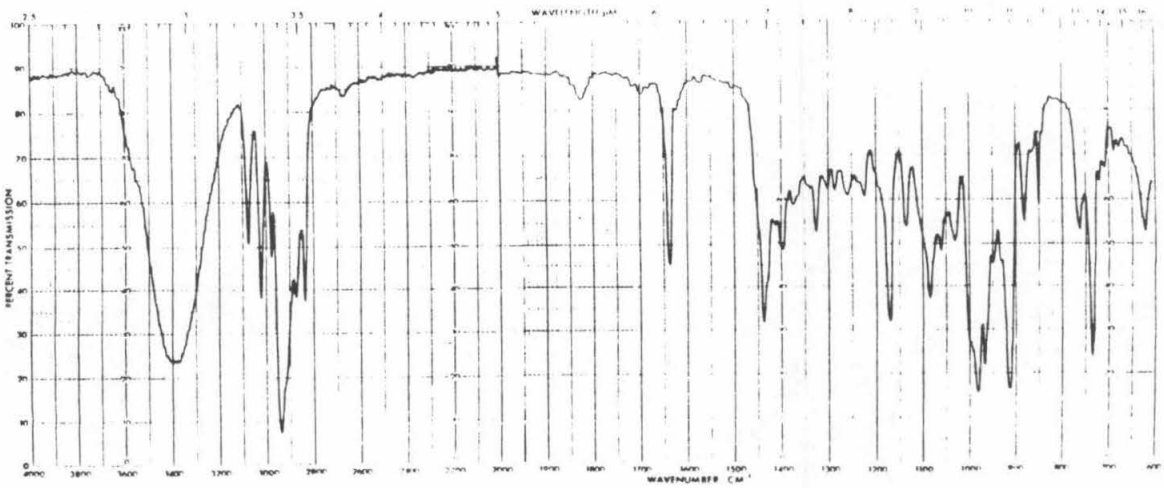
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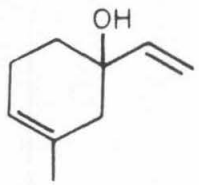
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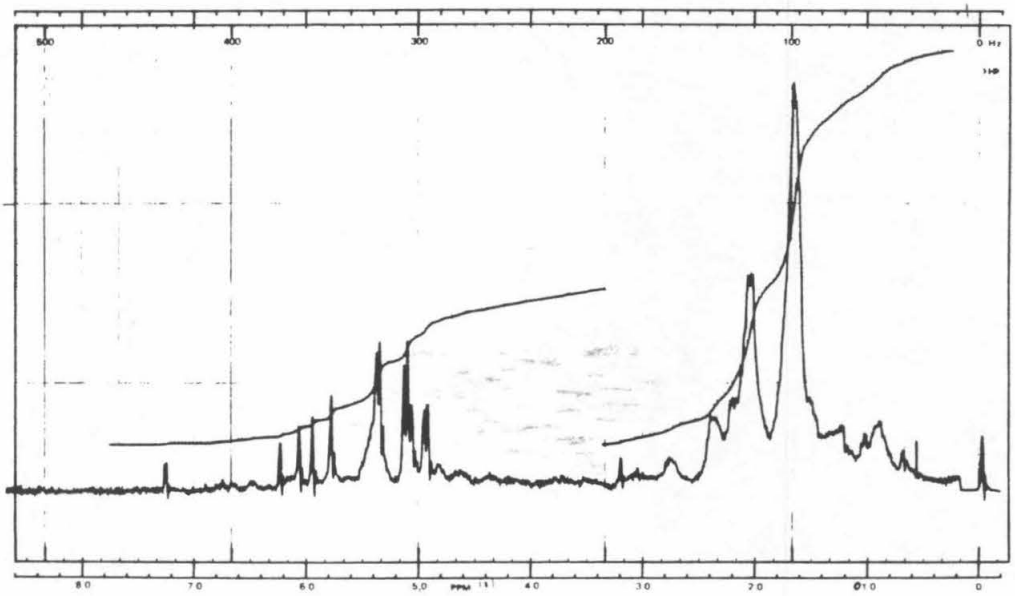
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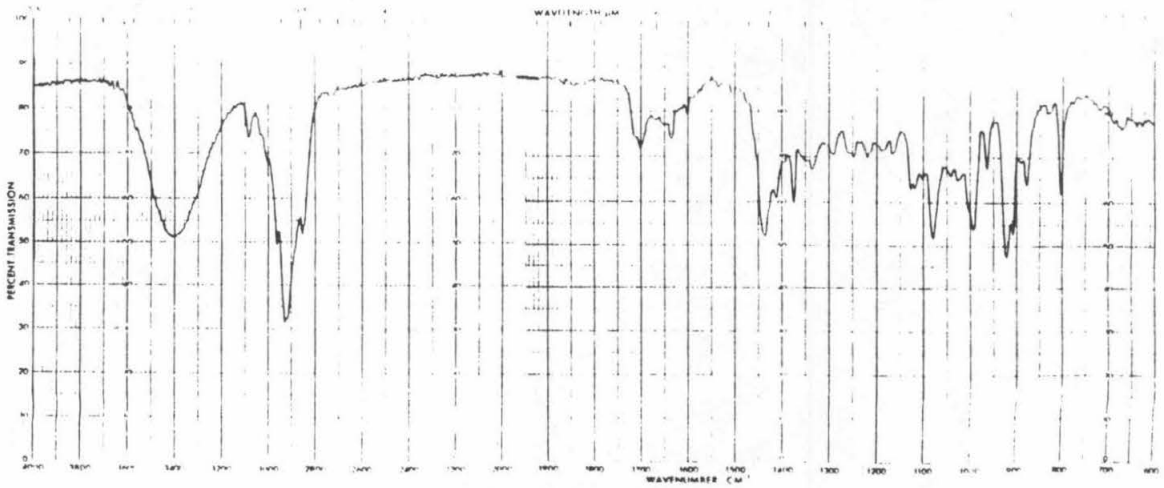
PERCENT TRANSMISSION
WAVENUMBER CM

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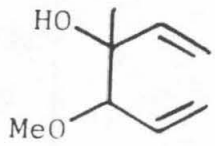

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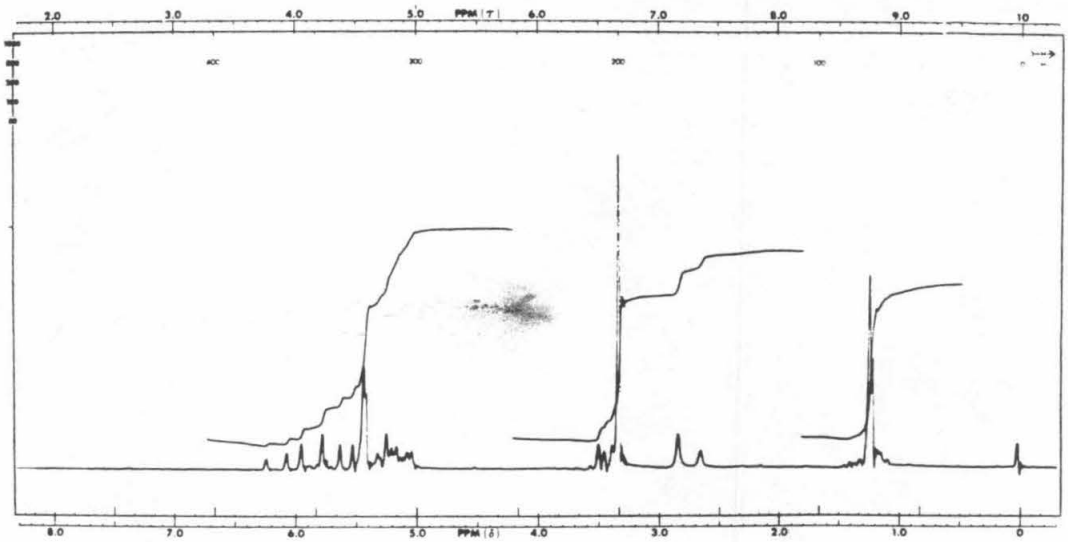

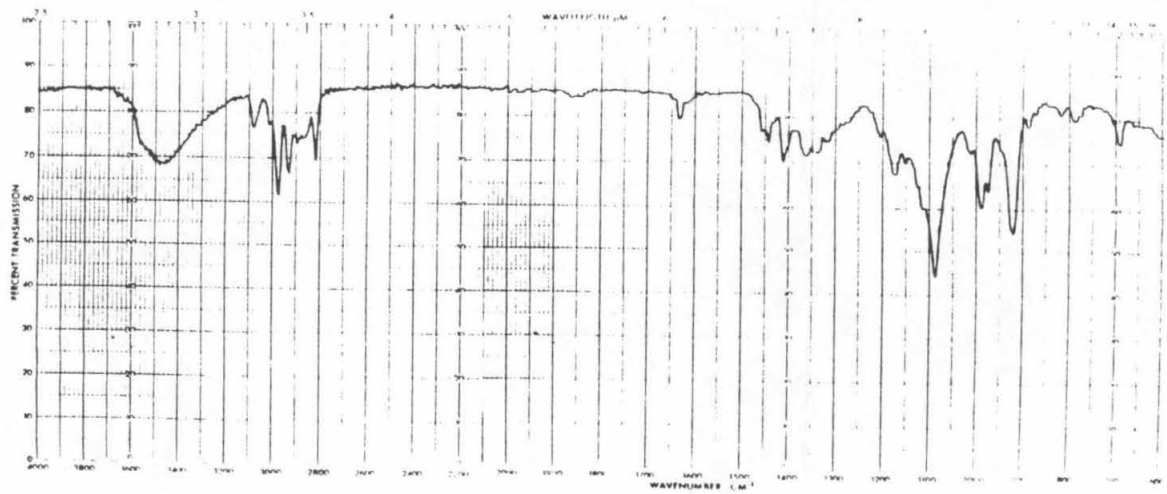

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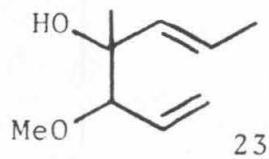

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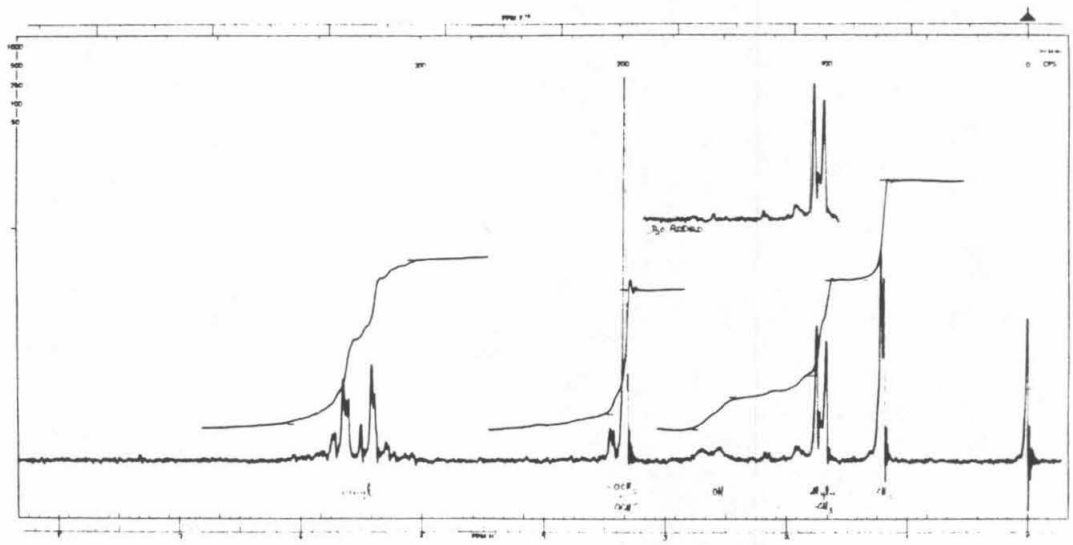
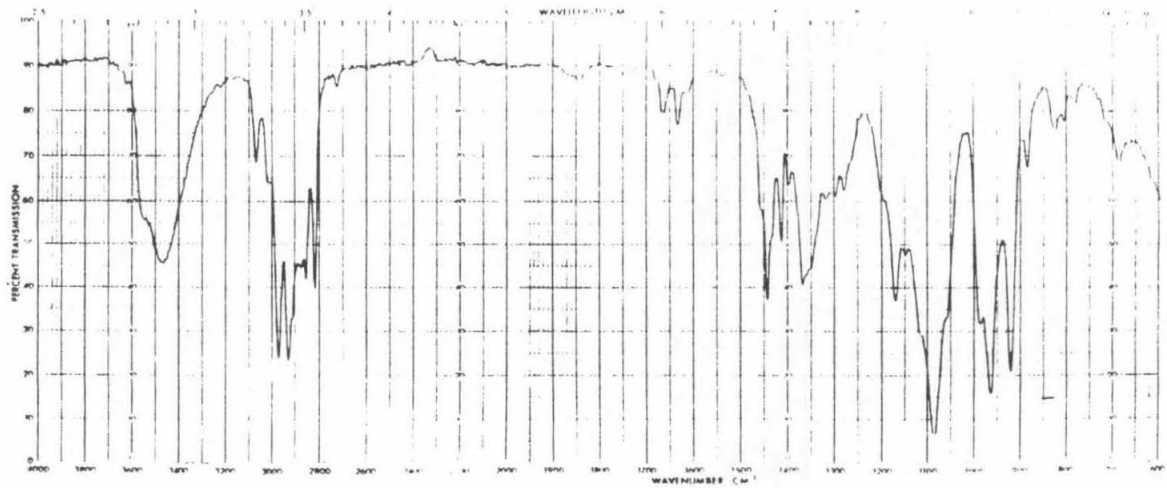
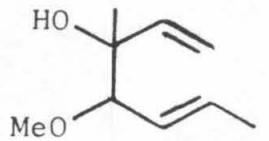
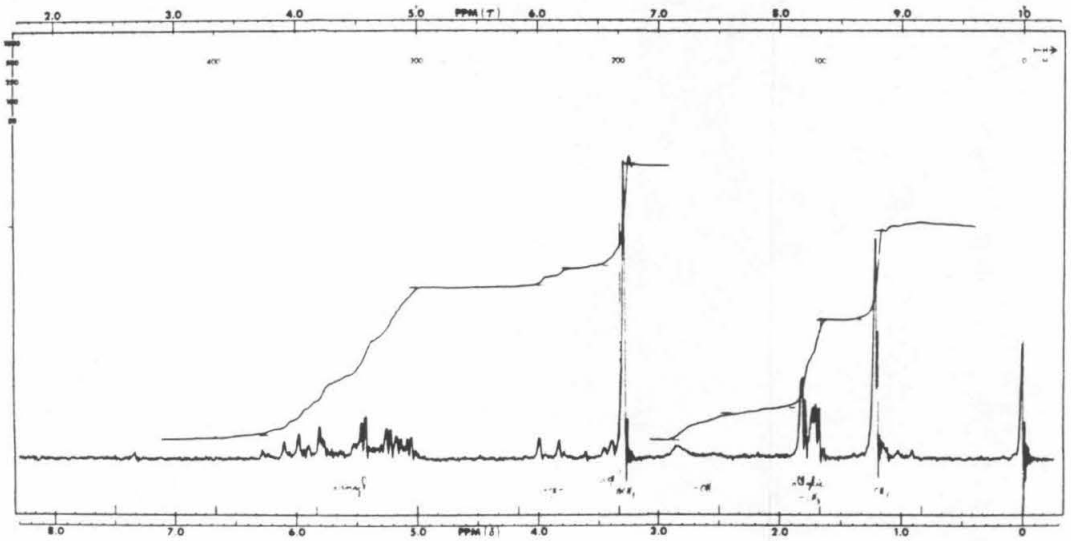


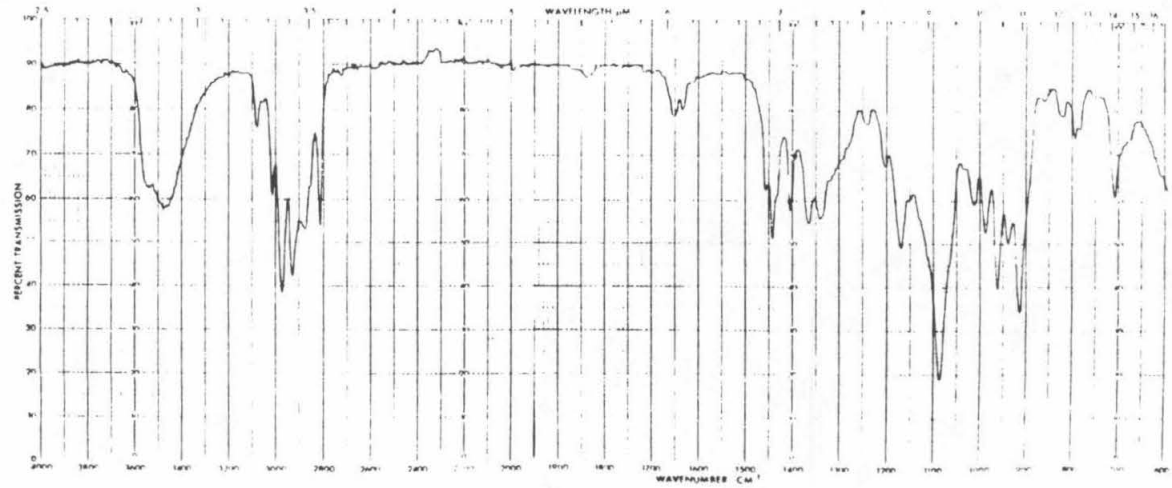


Page 47


HO
MeO

25


PPM (τ)
PPM (δ)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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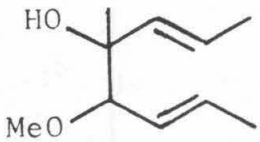
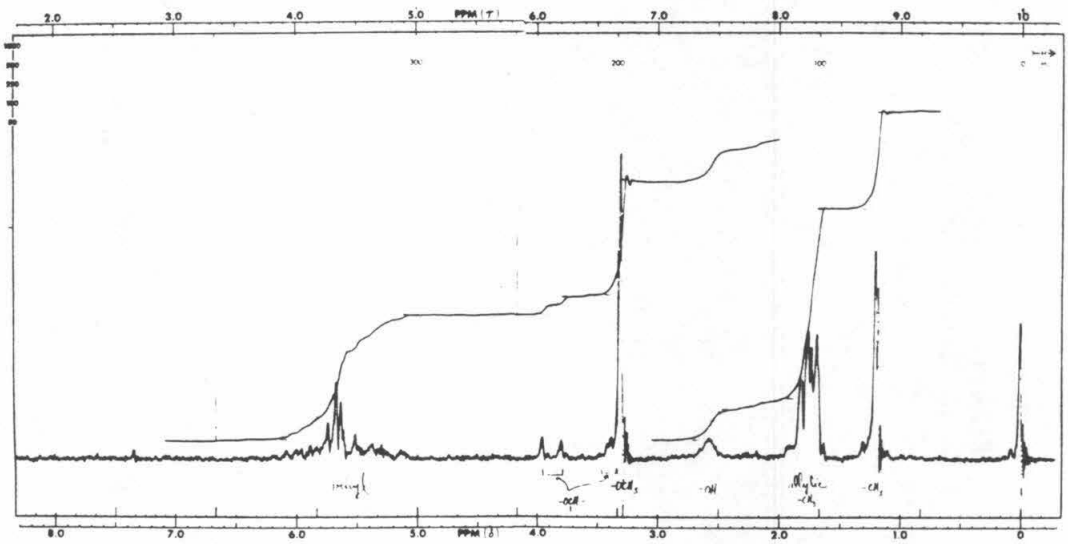
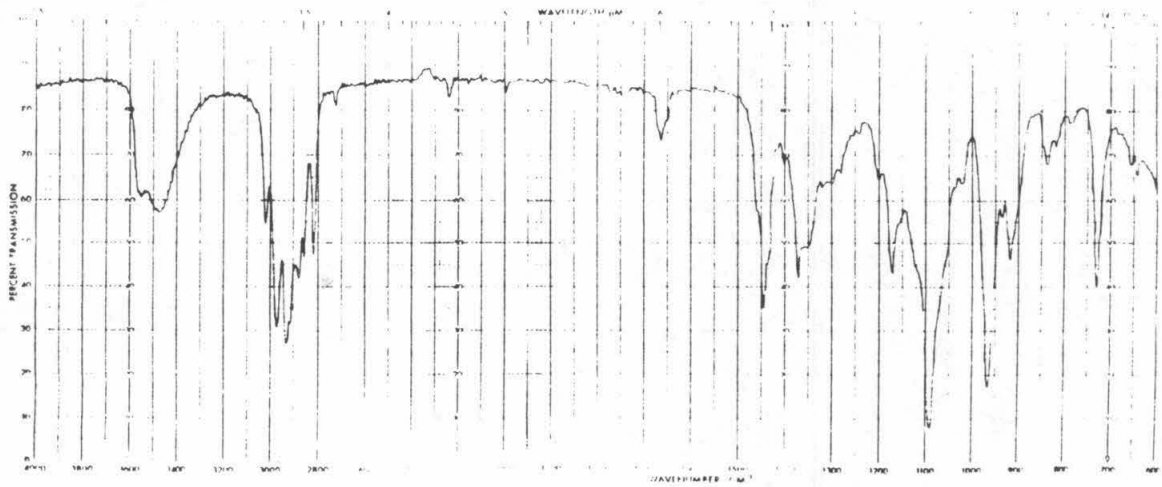
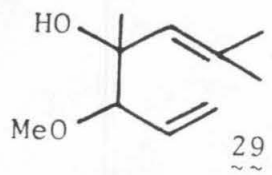

HO
MeO

27


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
PPM (δ)


PERCENT TRANSMISSION

Page 49



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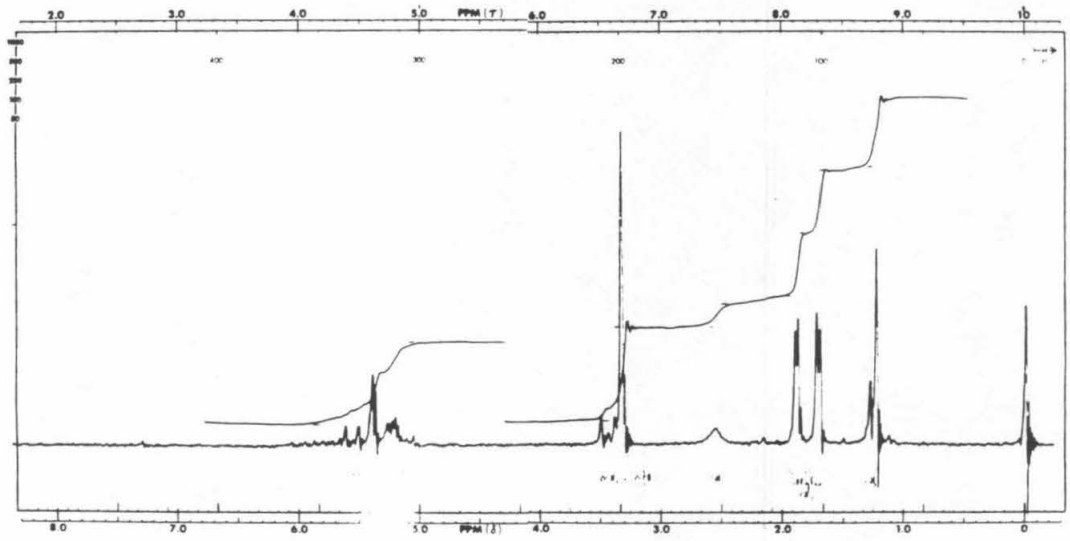
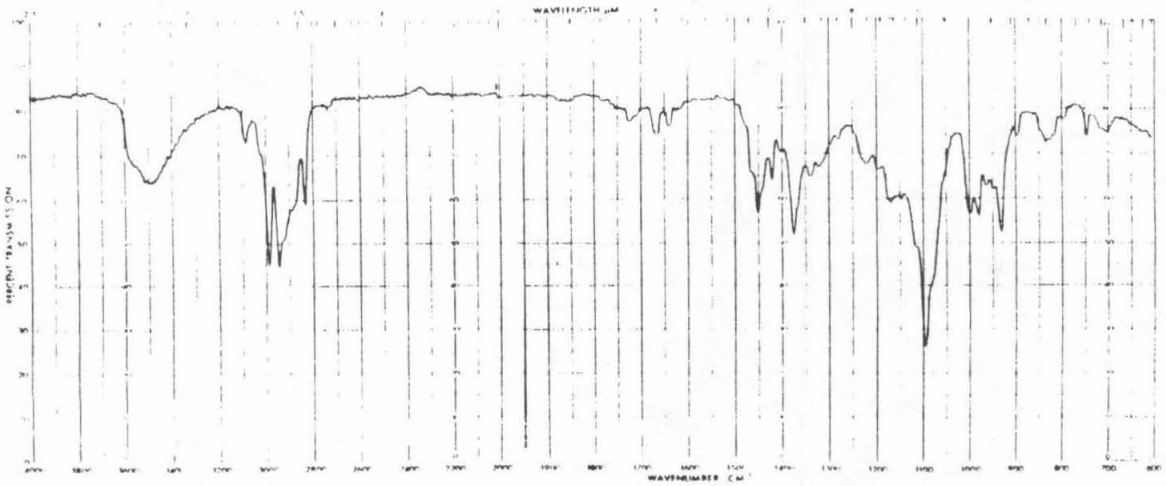
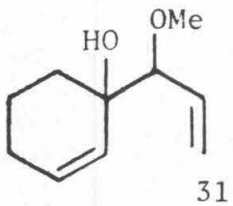




Page 49



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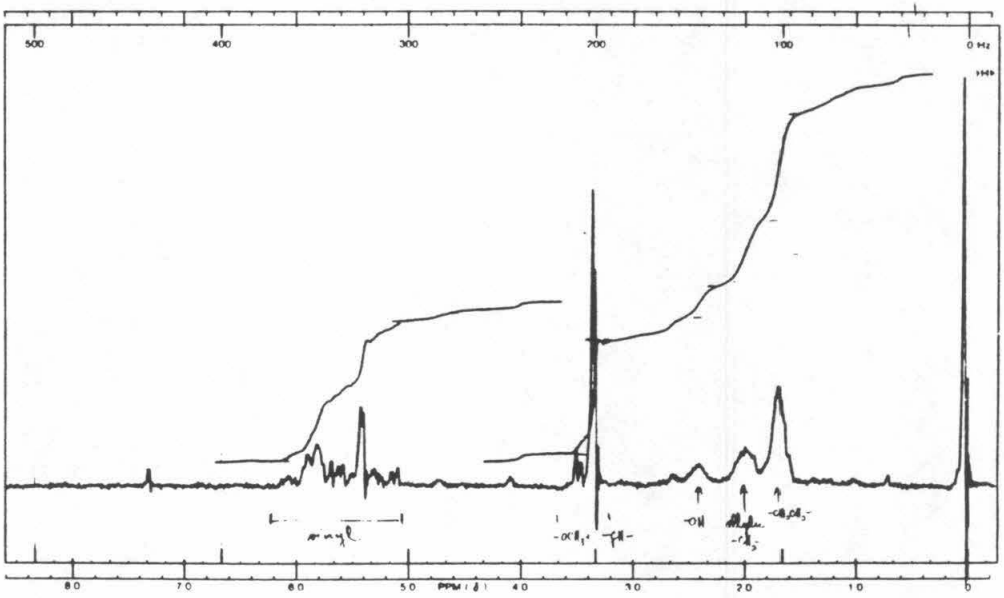
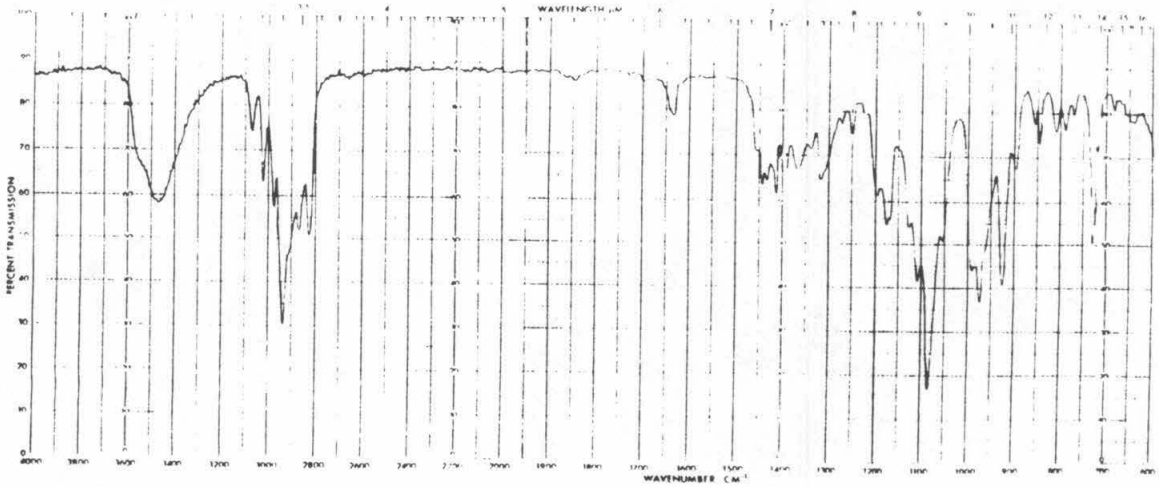
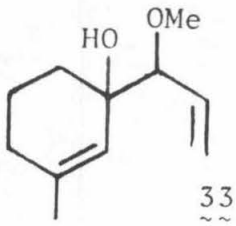




Page 50



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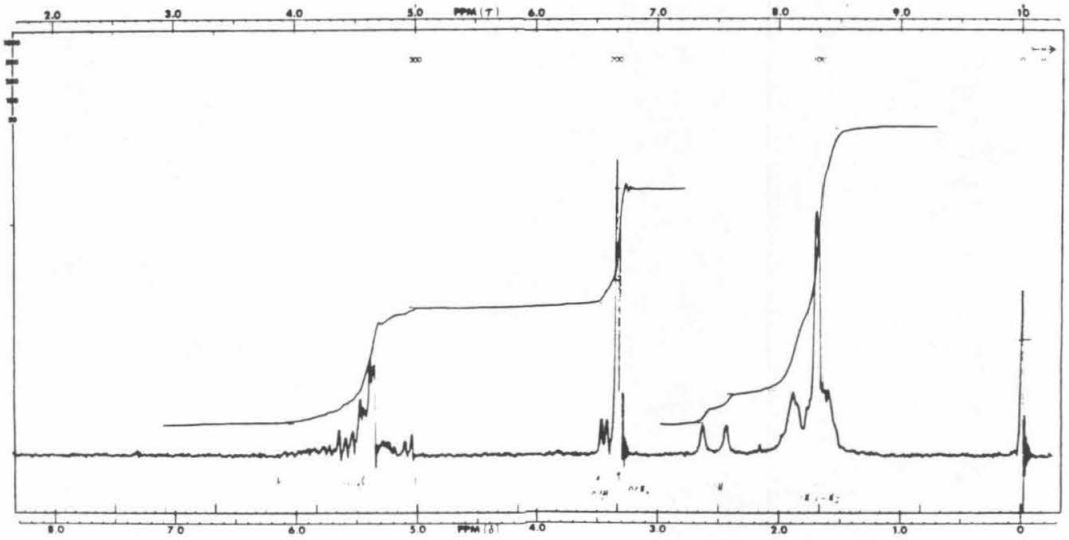

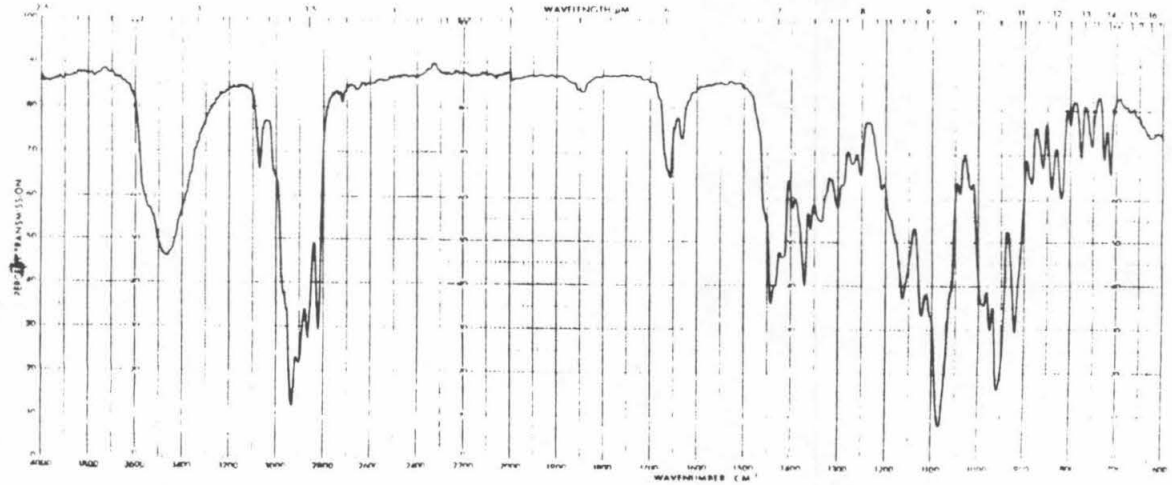

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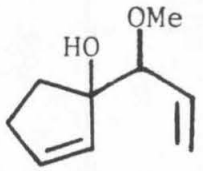

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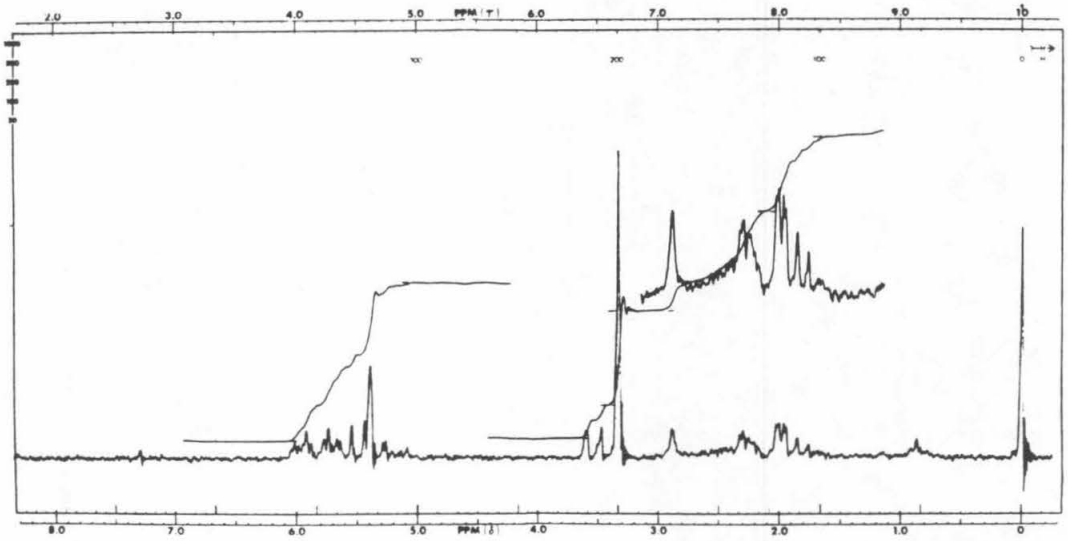
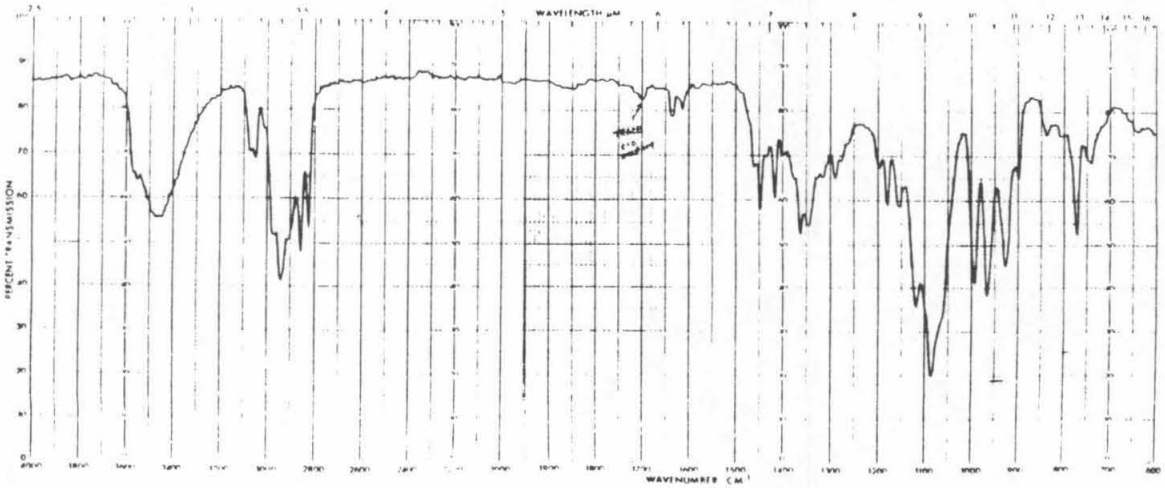
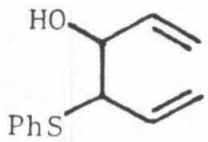
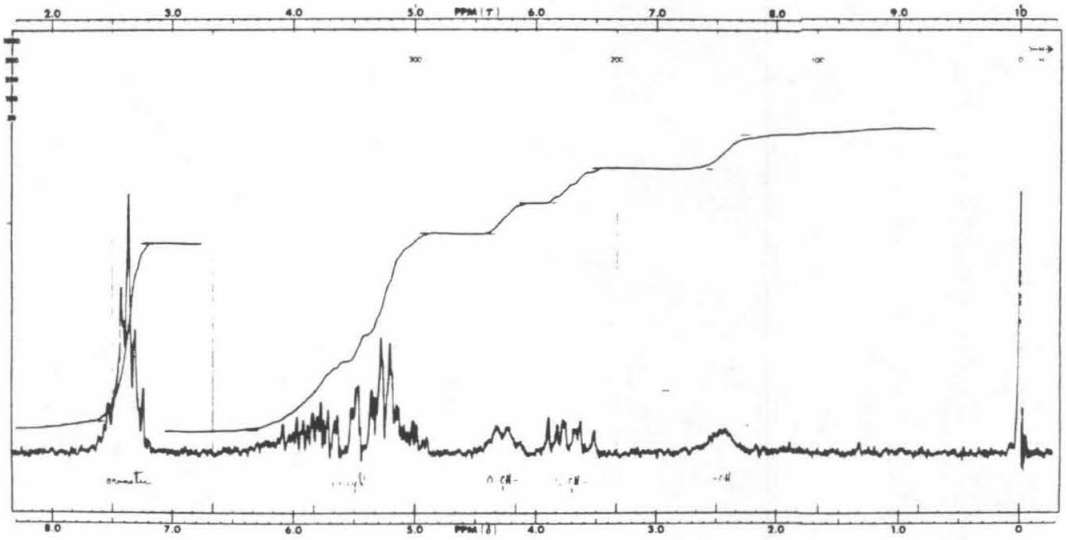


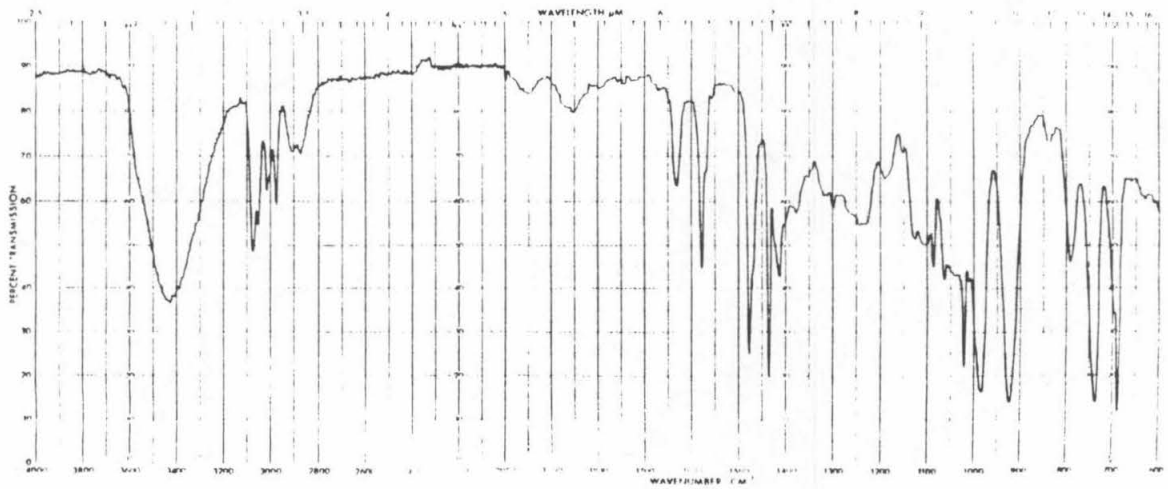


Page 51

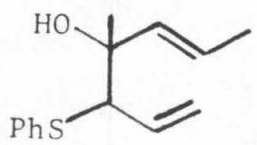

HO
PhS

37

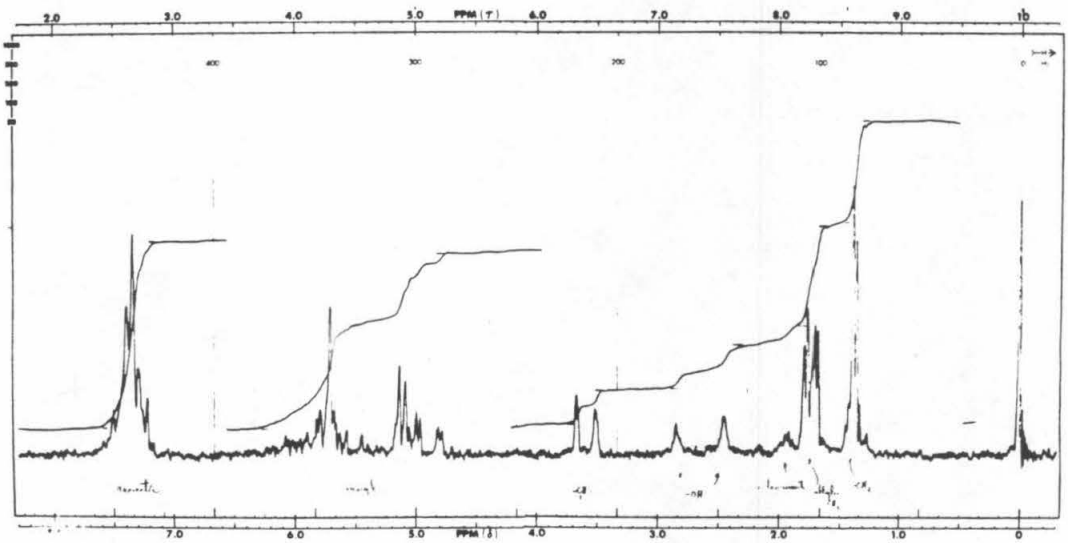

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

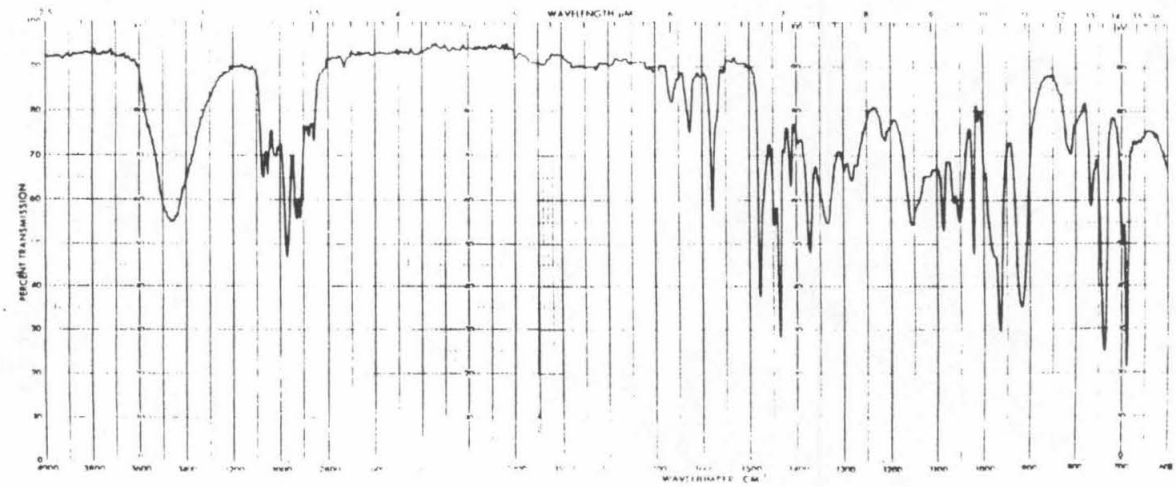

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (CM⁻¹)

Page 52


HO
PhS

39


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
PERCENT TRANSMISSION

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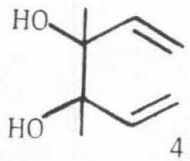
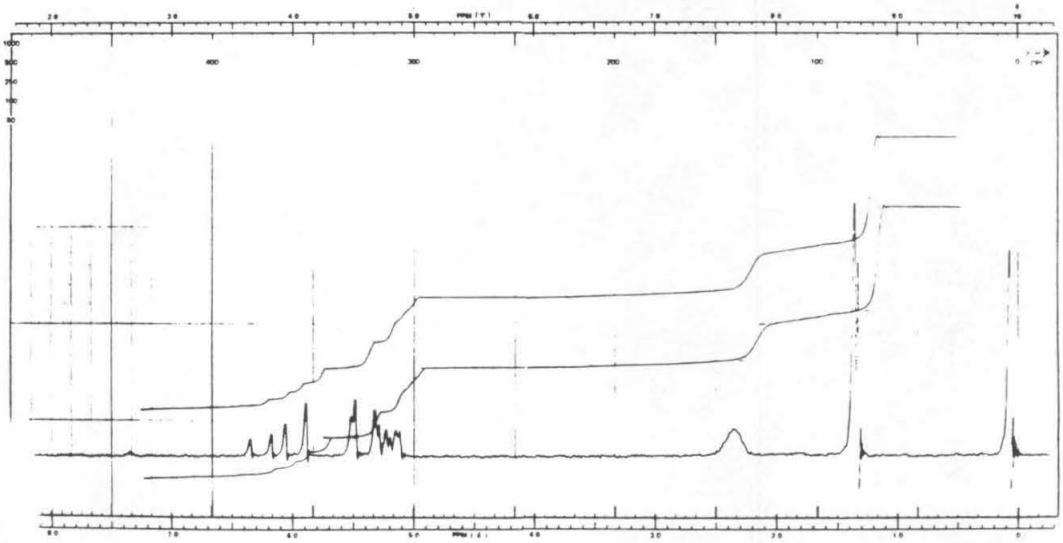
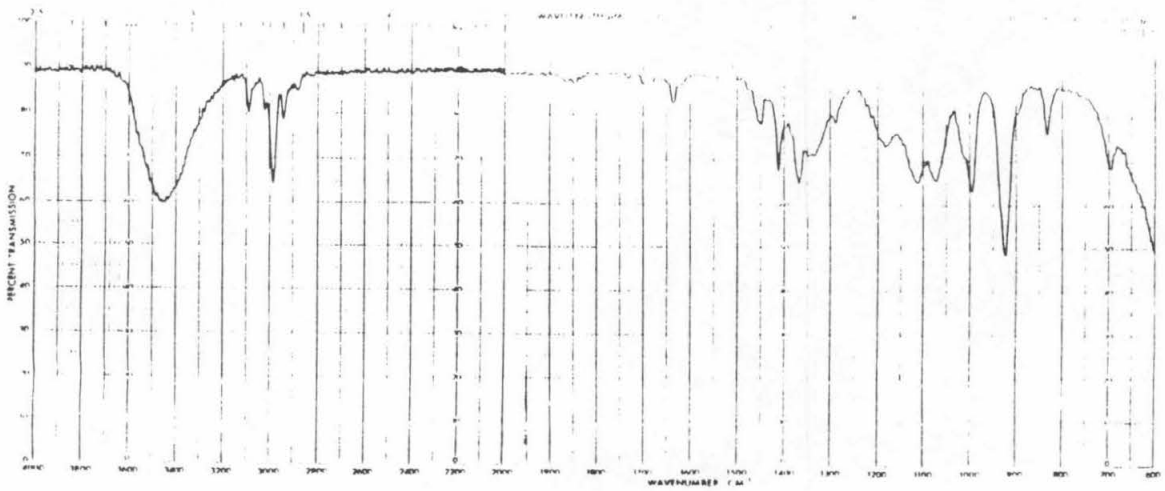


41





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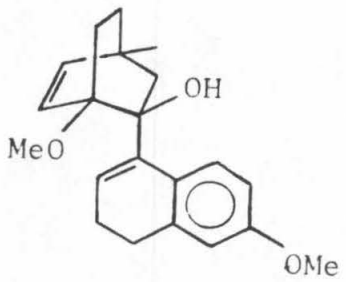
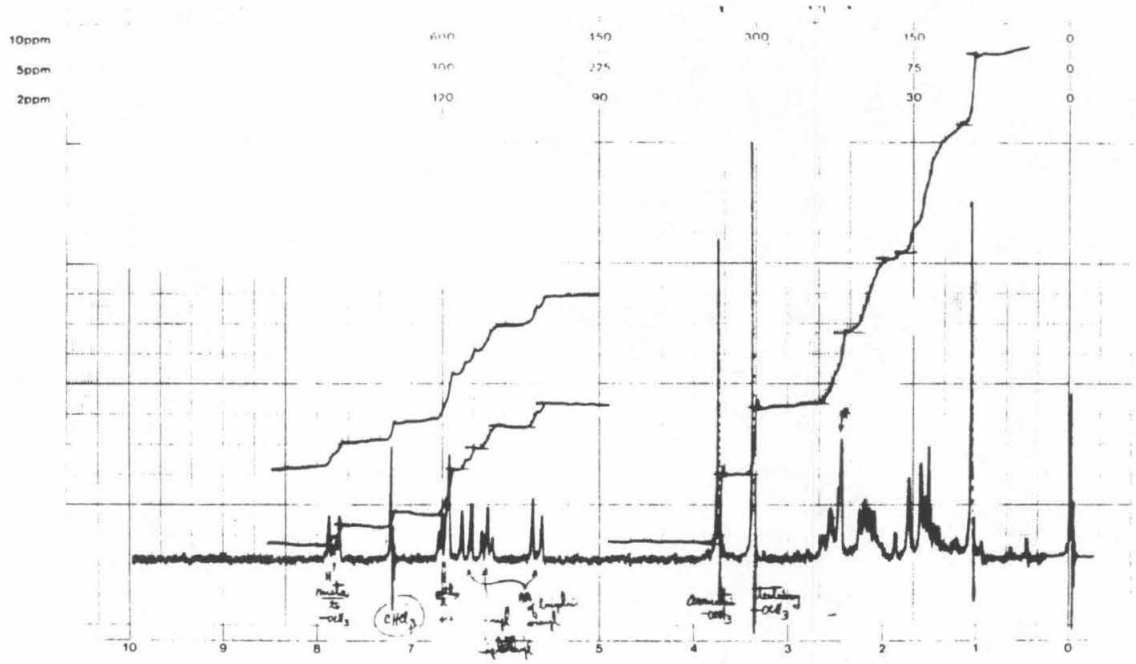
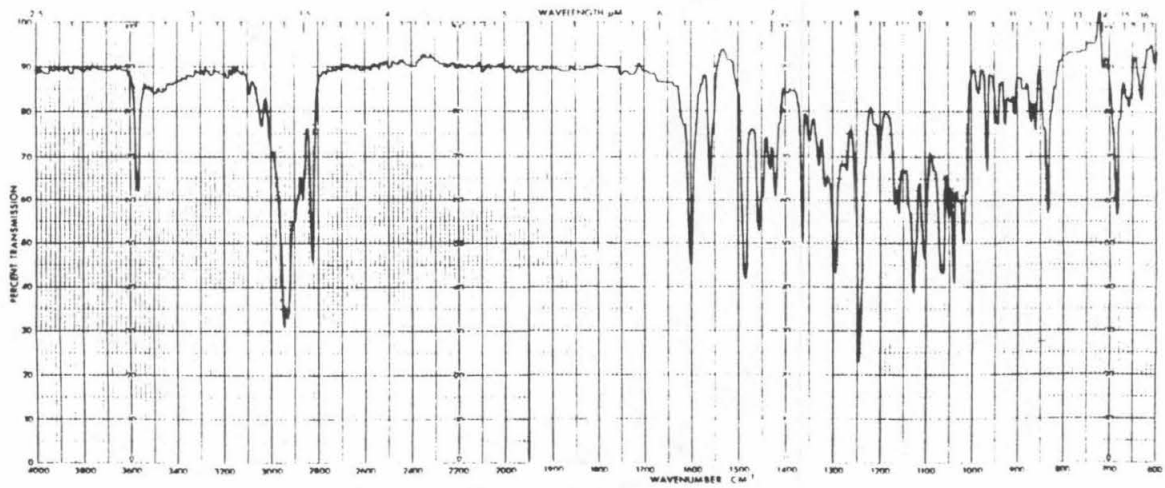

OH
MeO
OMe

43


10ppm
5ppm
2ppm
600
300
120
150
225
90
300
75
30
150
0
0
0
10
9
8
7
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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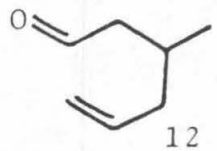
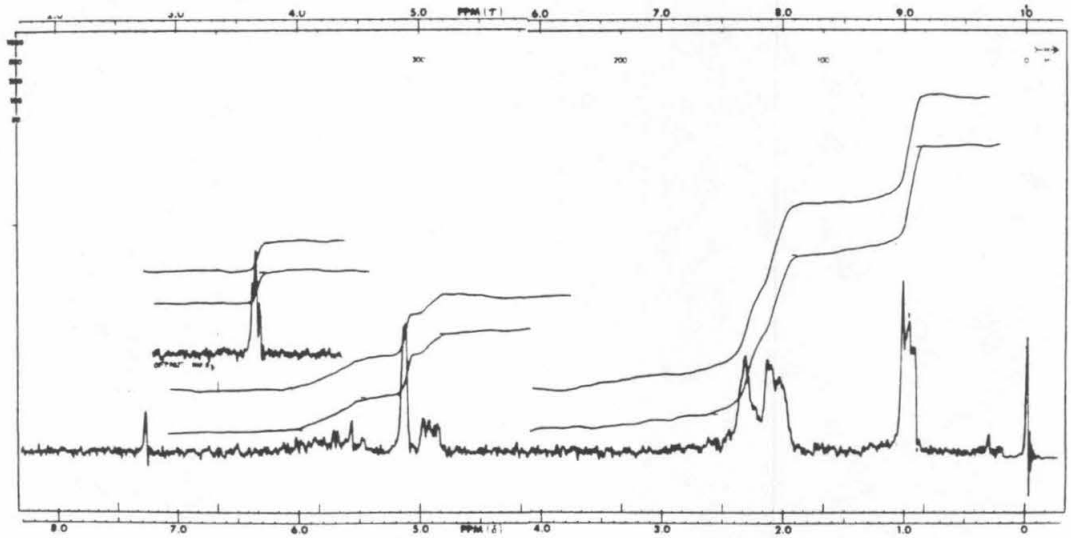
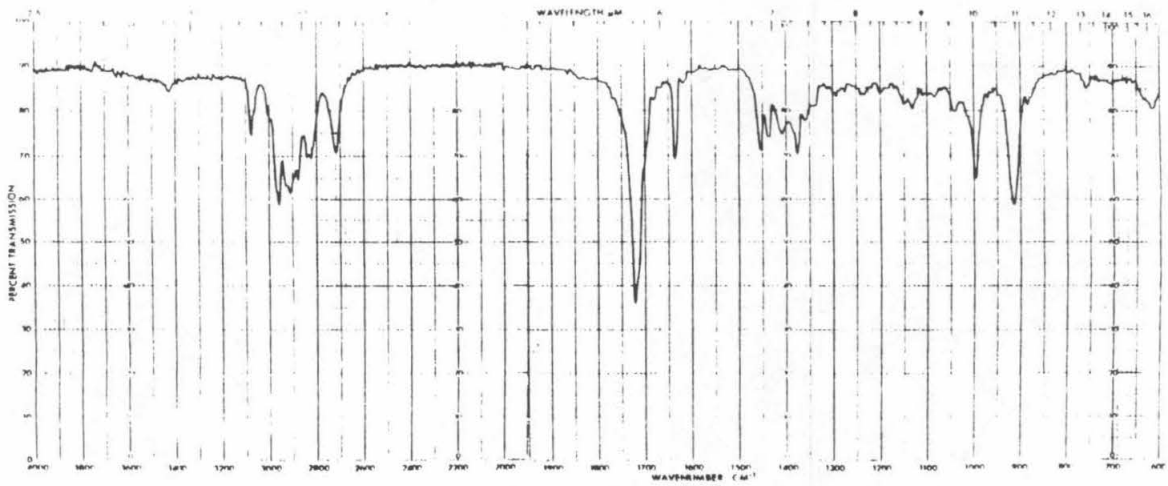
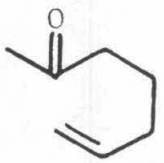


12

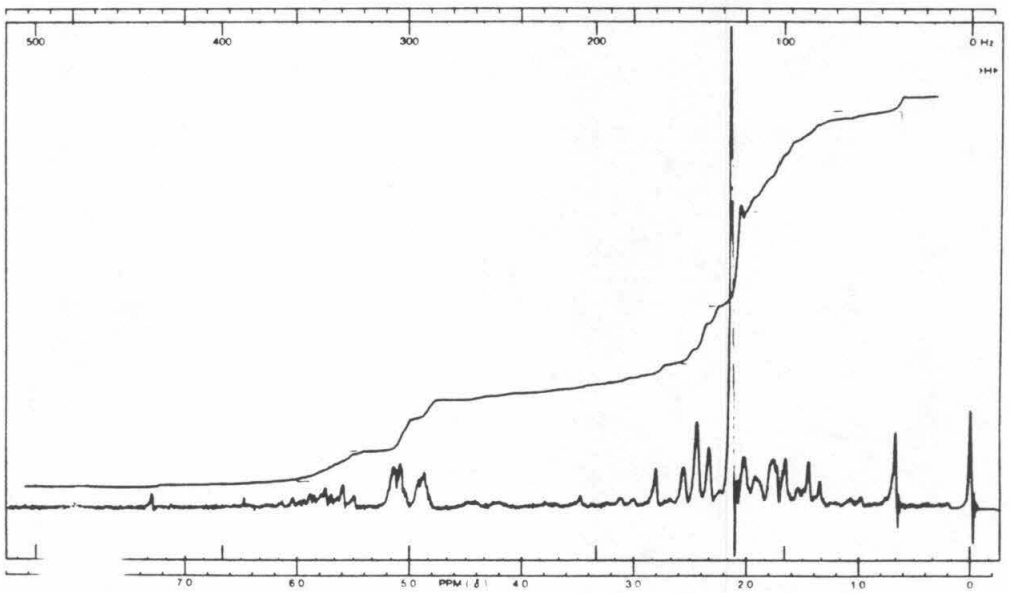

PPM (T)
PPM (2)

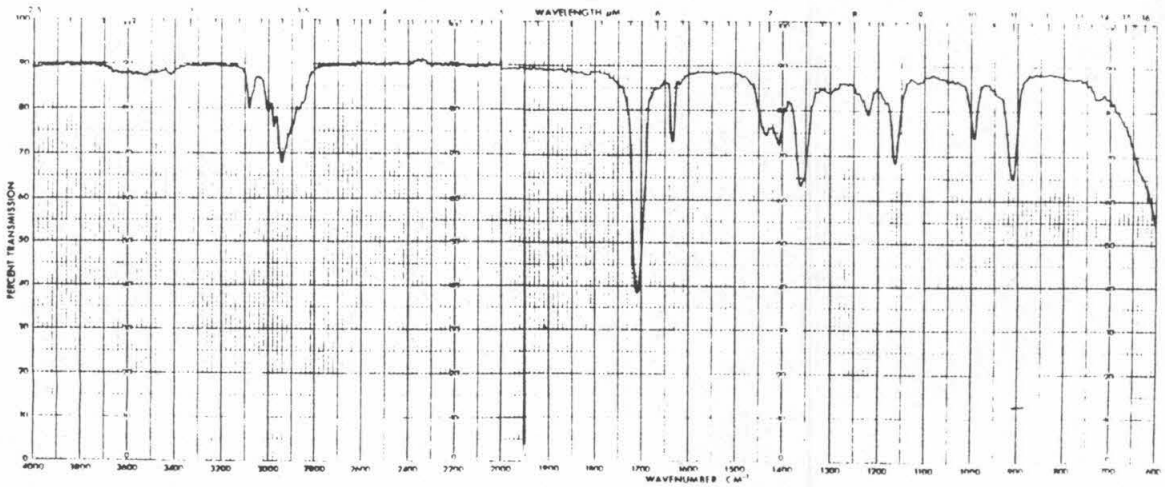

WAVELENGTH, μM
PERCENT TRANSMISSION
WAVENUMBER (CM⁻¹)

Page 56



14


500
400
300
200
100
0 Hz
PPM (δ)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (CM⁻¹)

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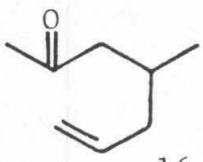
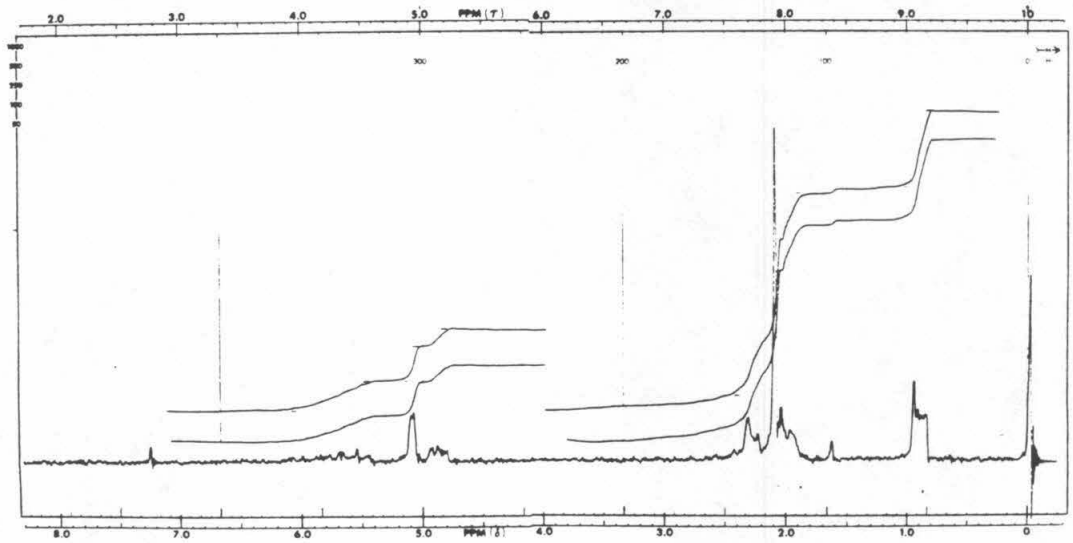
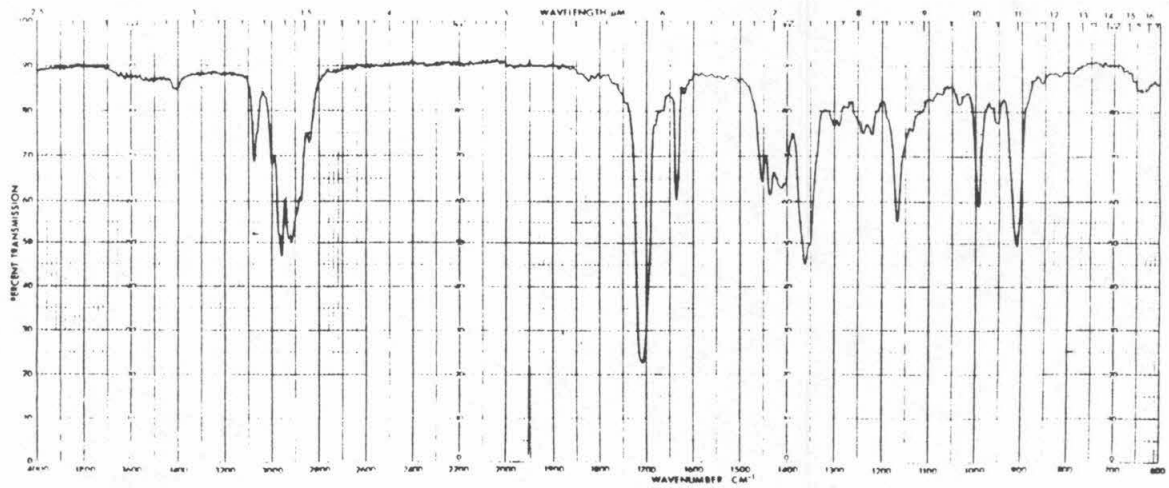


16


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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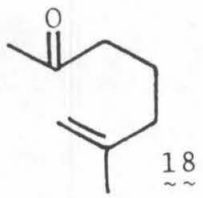
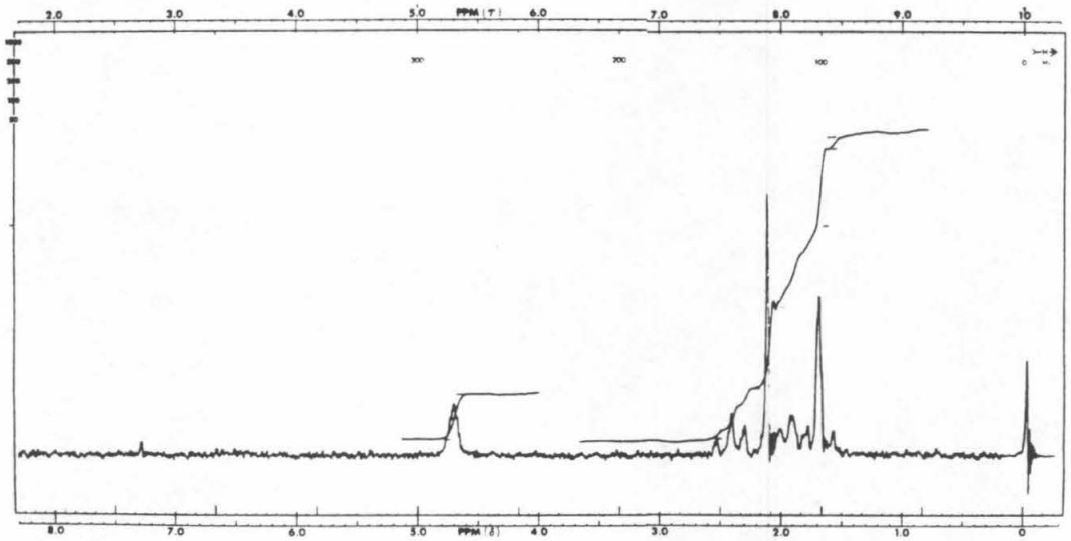
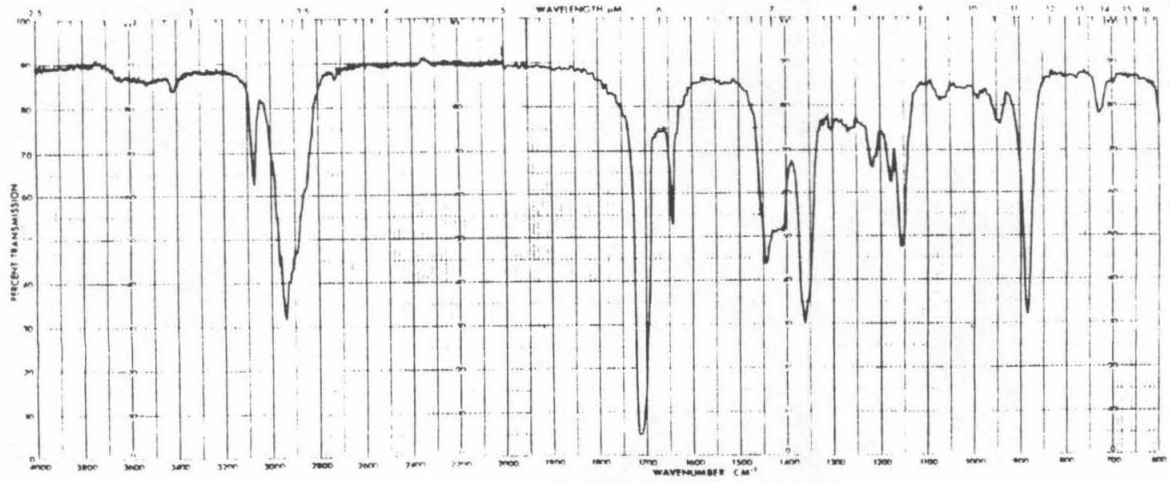


18


PPM (τ)
PPM (δ)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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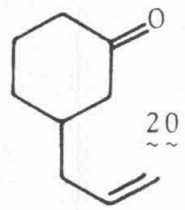
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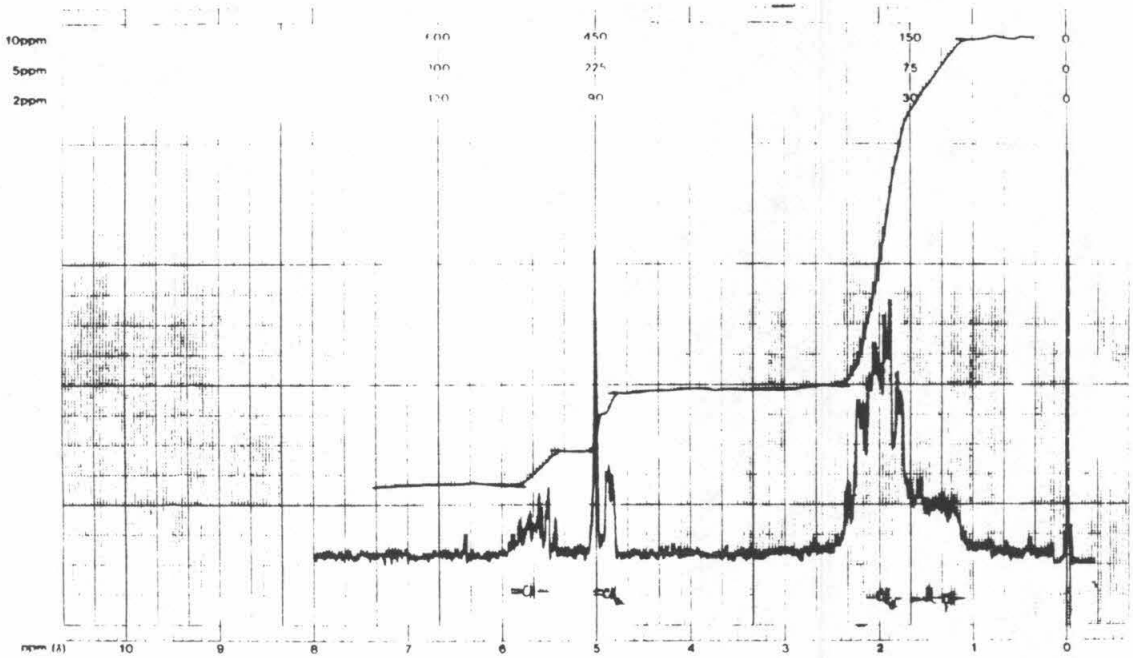
20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5ppm
2ppm
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300
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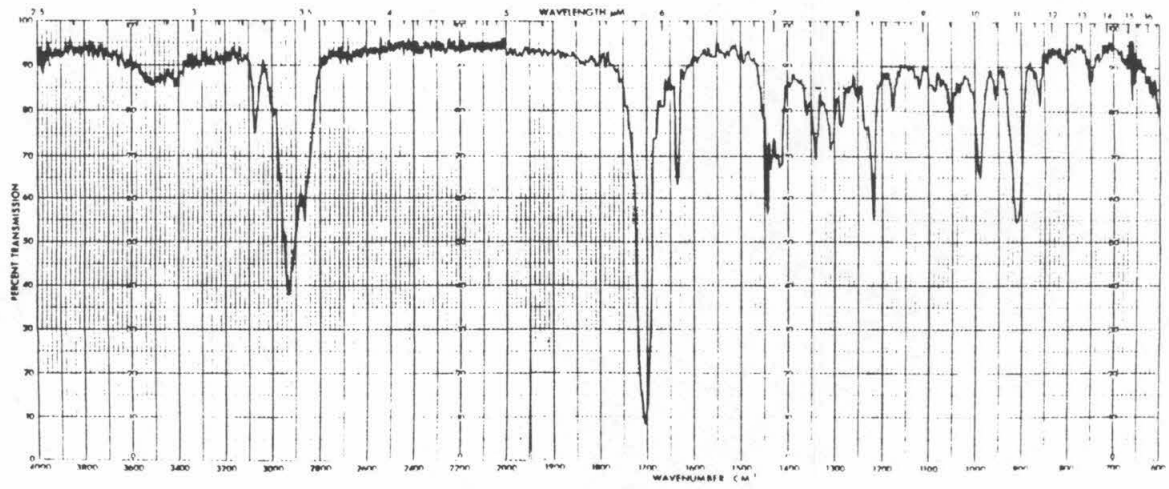
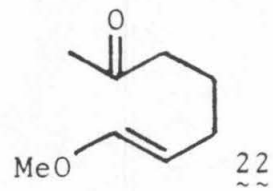
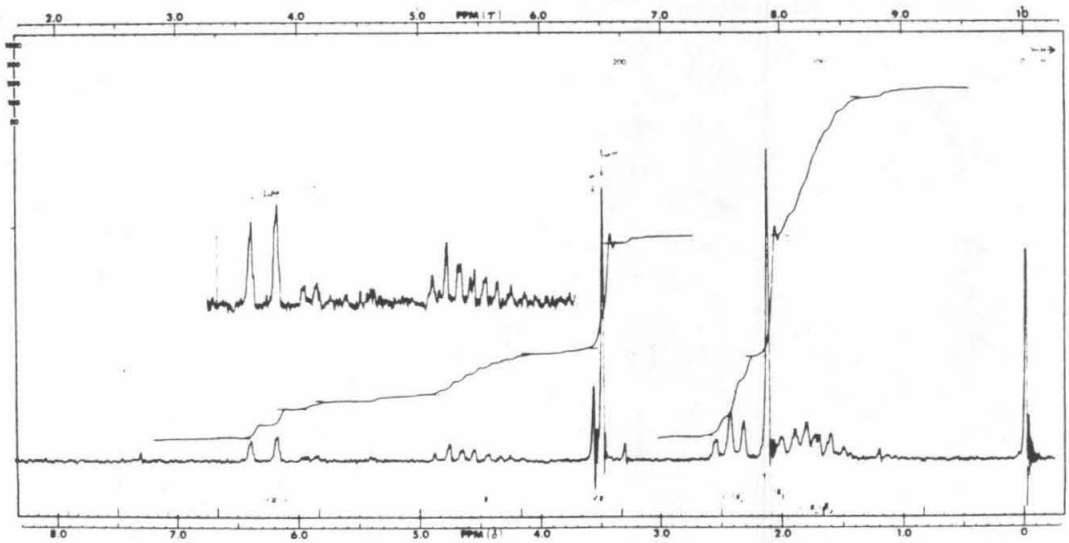
2
1
0

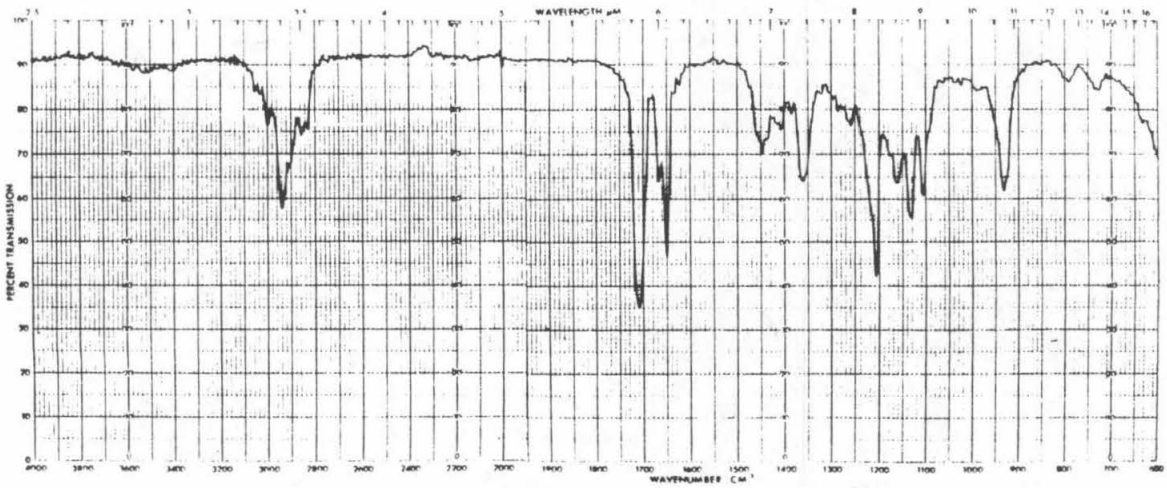

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (cm⁻¹)

Page 58

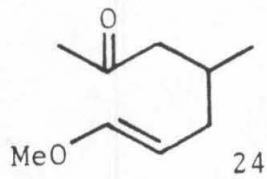

O
MeO

22

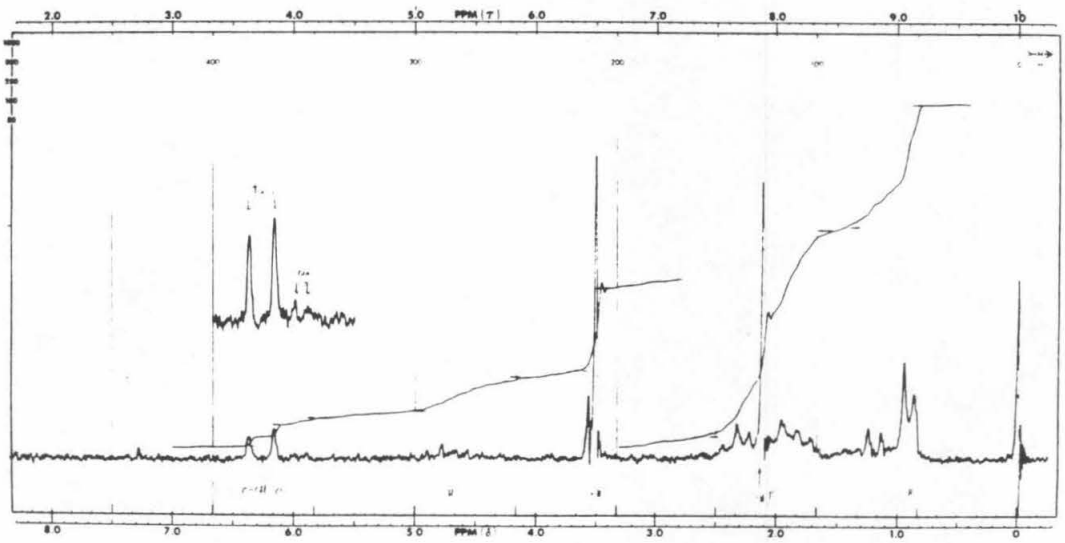

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

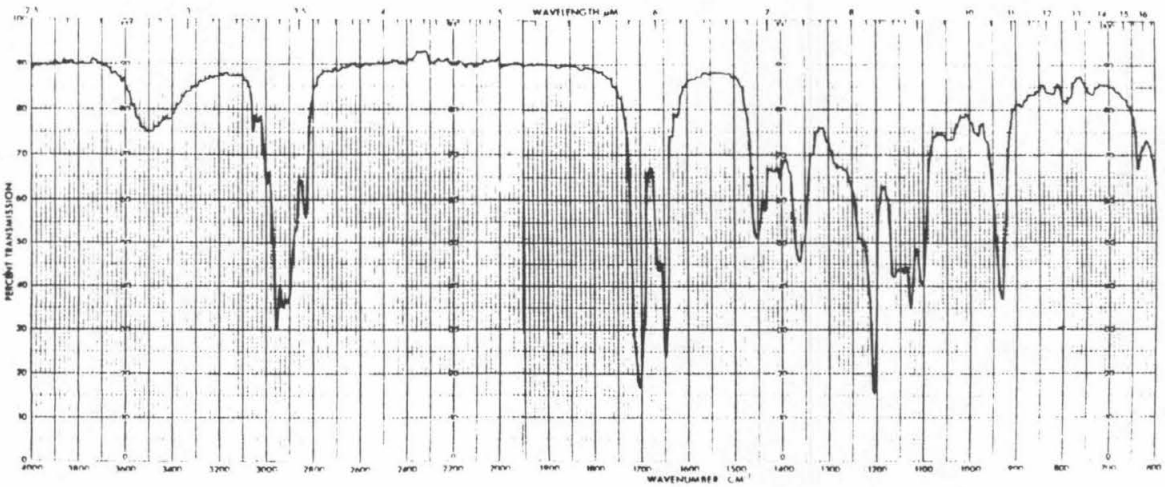

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 59

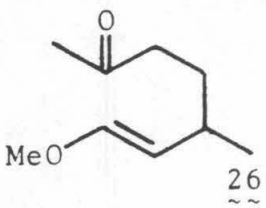

O
MeO

24

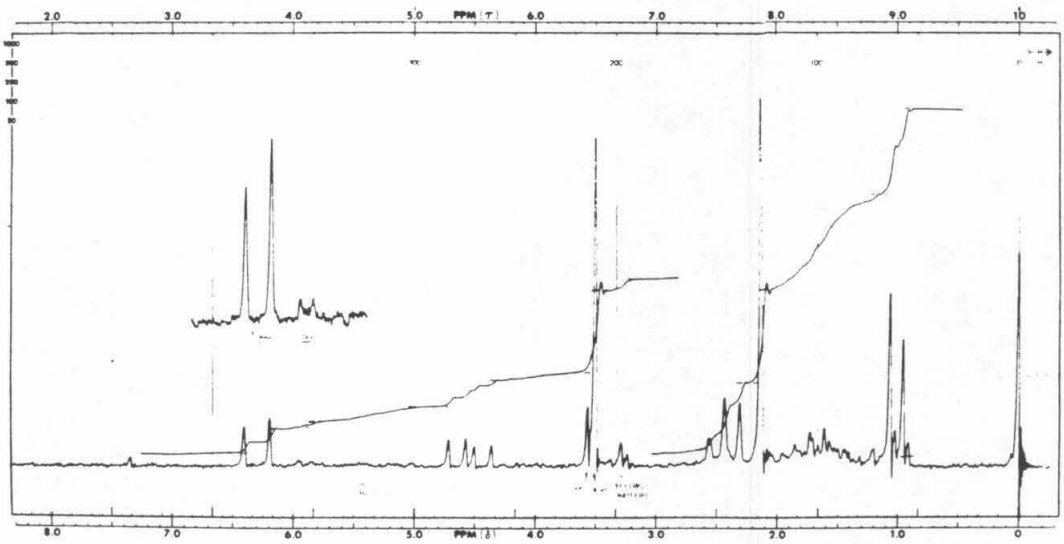

PPM (τ)
PPM (δ)

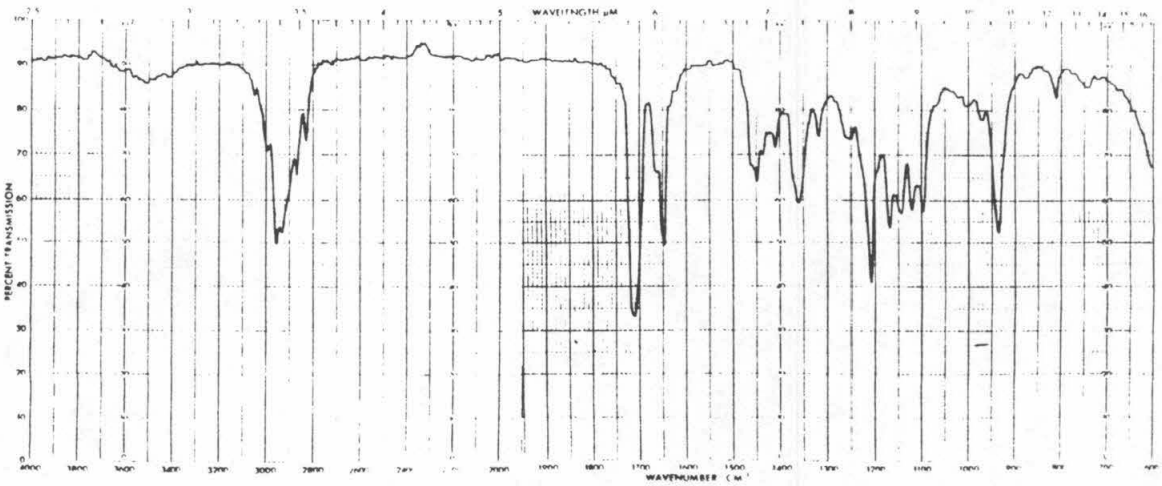

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 60

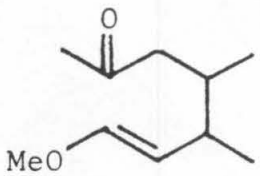

O
MeO

26

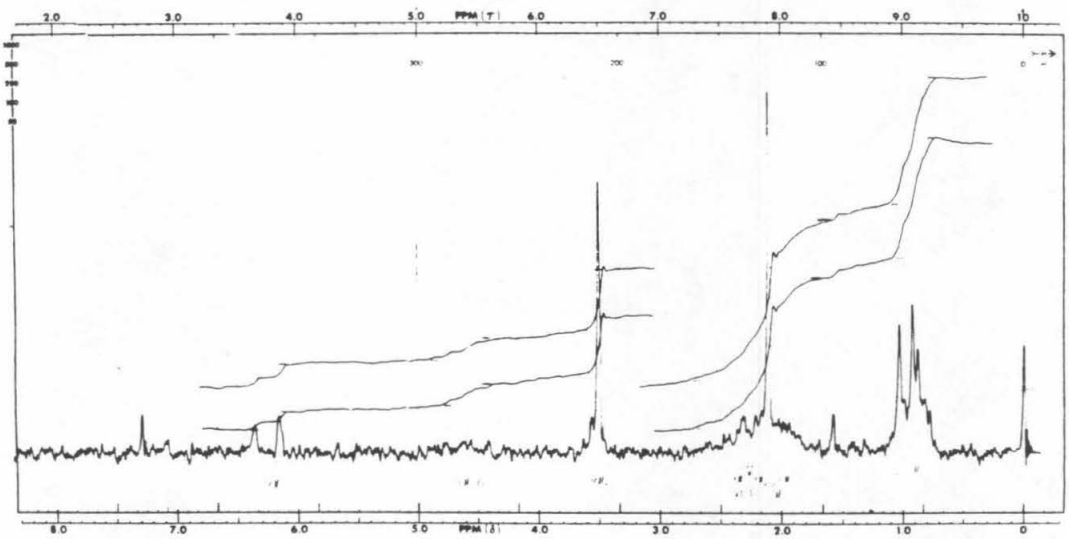

PPM (τ)
PPM (δ)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (K

Page 61


O
MeO

28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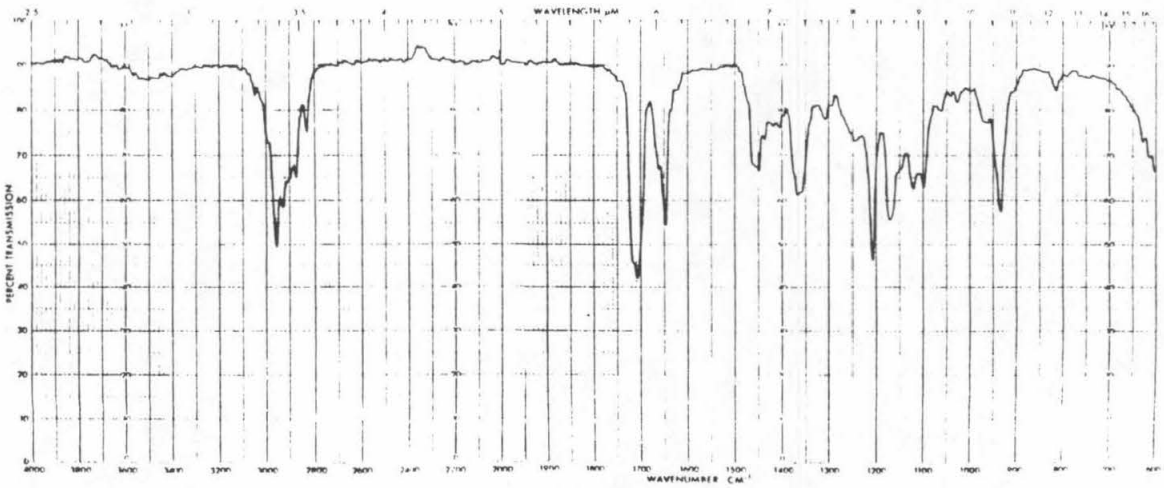
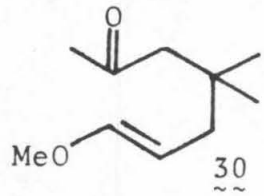
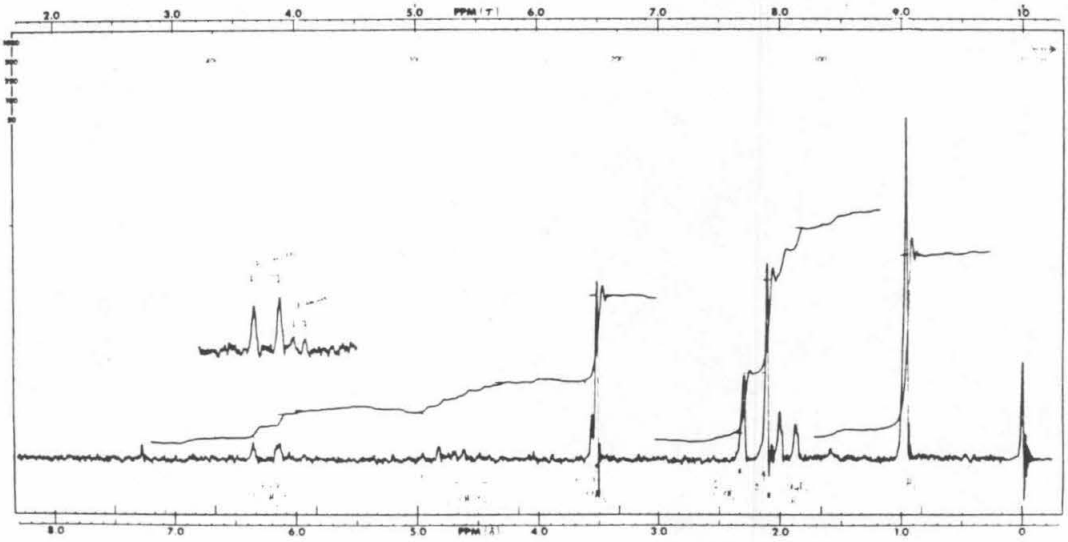
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 61


O
MeO

30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PPM (τ)
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6.0
5.0
PPM (δ)
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2.0
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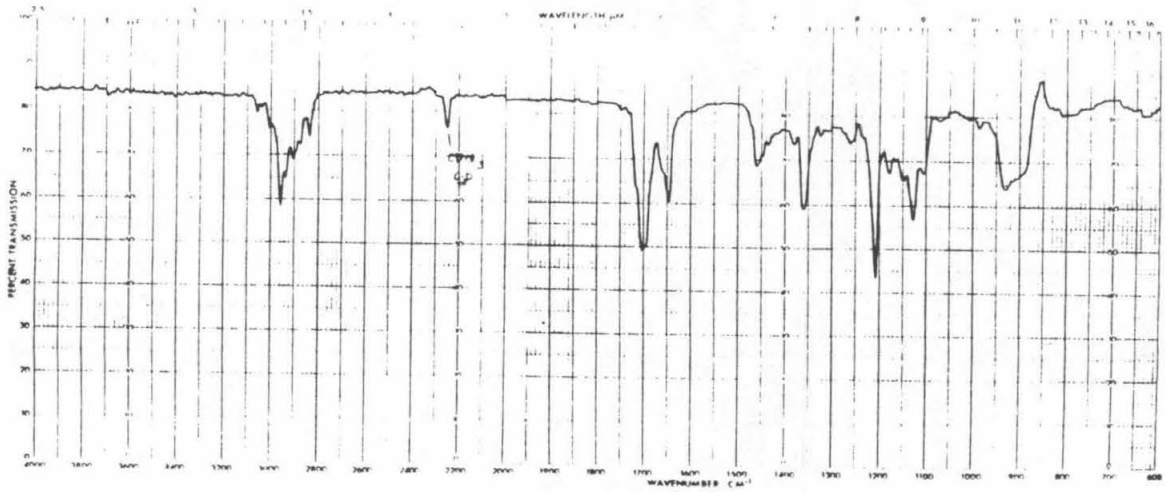
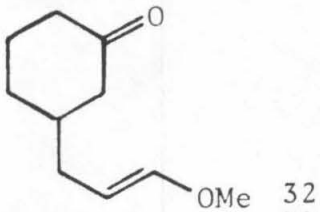
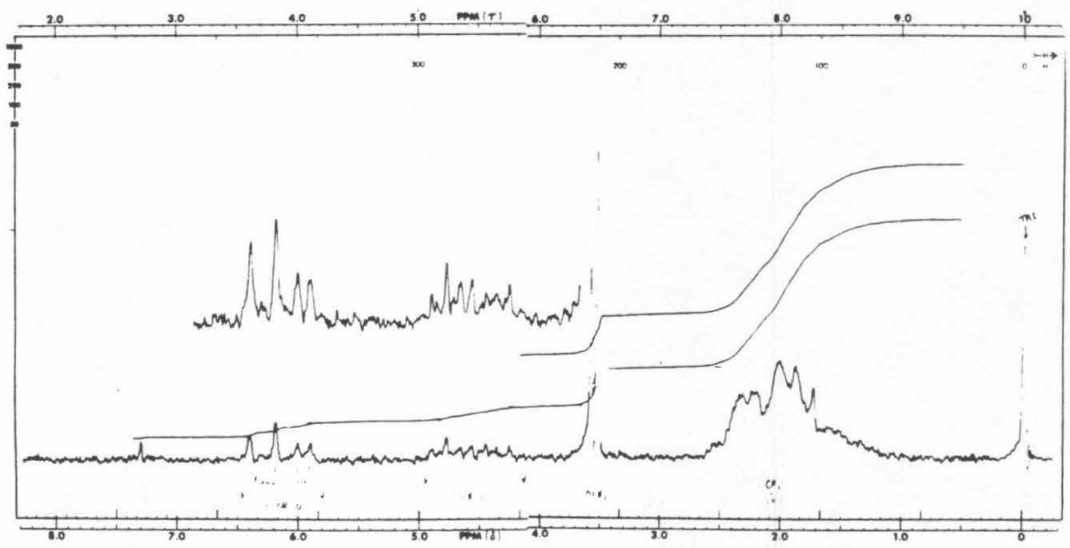

PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 62


O
OMe

32


2.0
3.0
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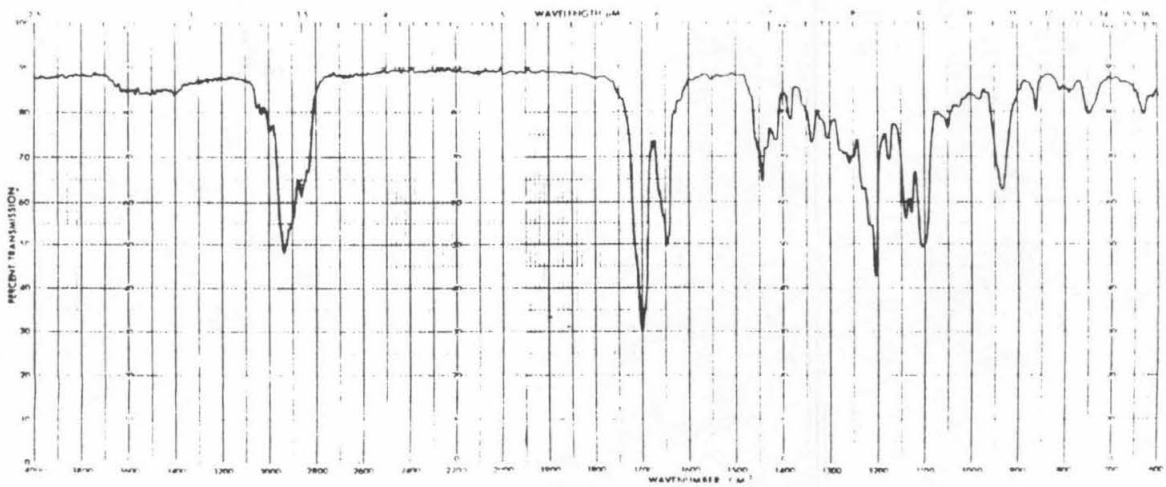
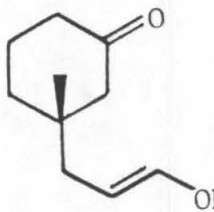
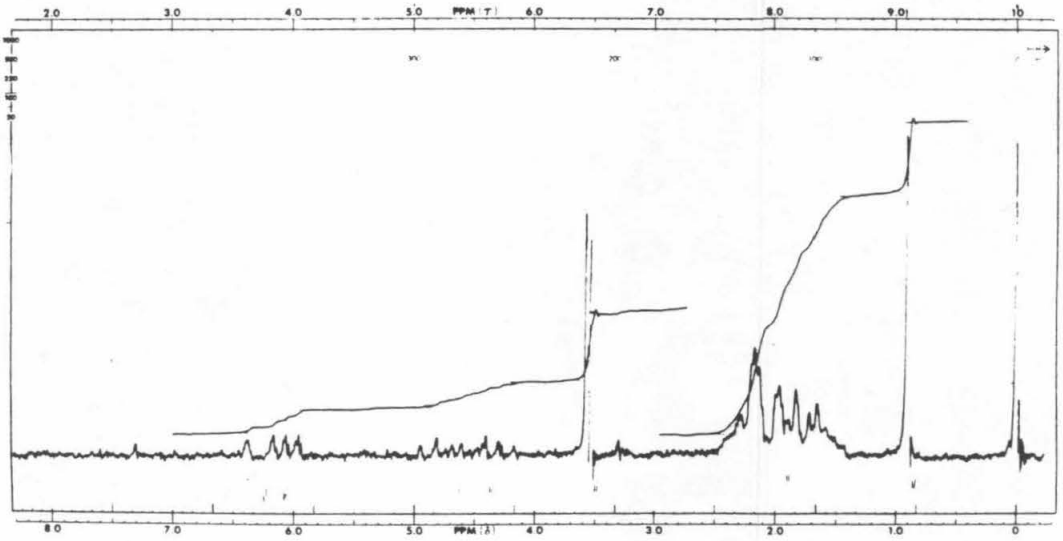
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (CM⁻¹)

Page 63


O
OMe

34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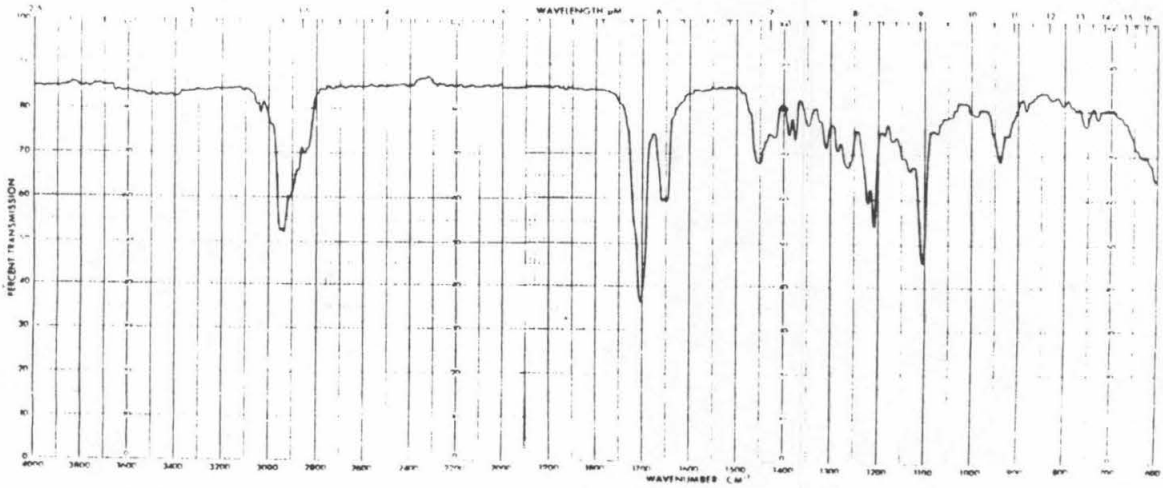
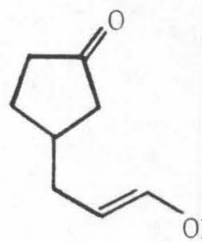
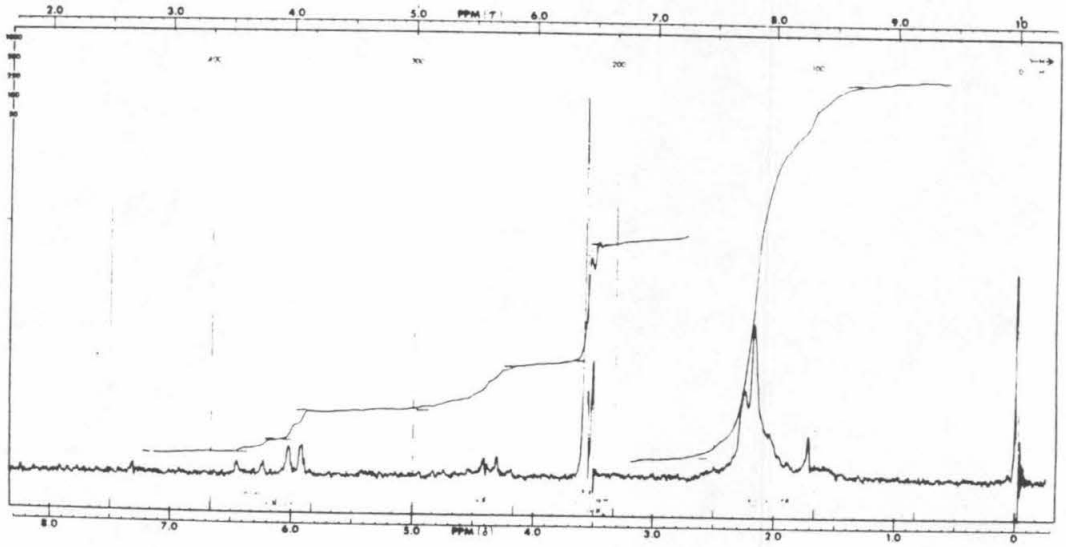
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (cm⁻¹)

Page 64


O
OMe

36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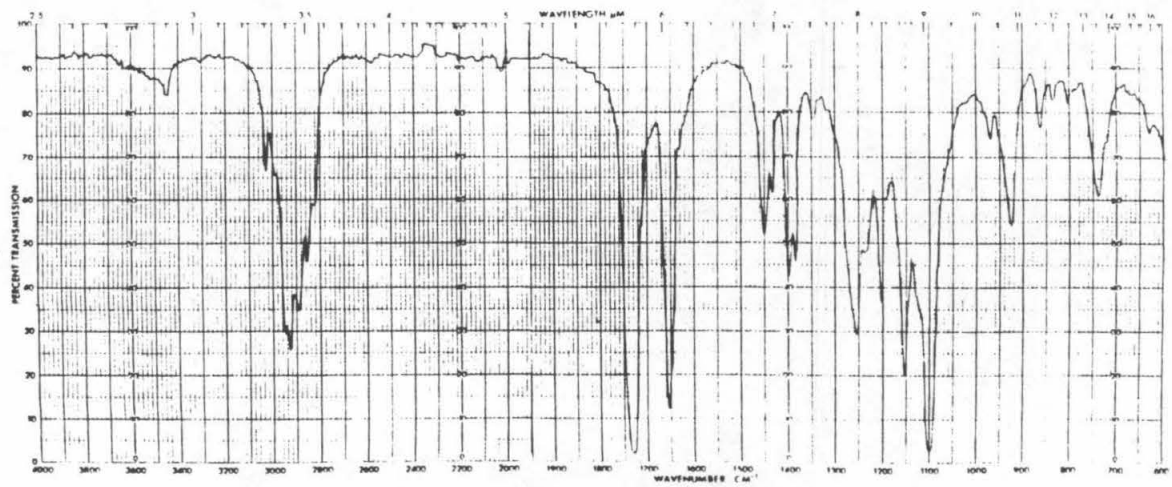
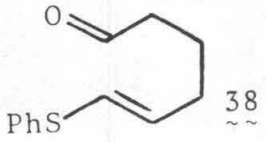
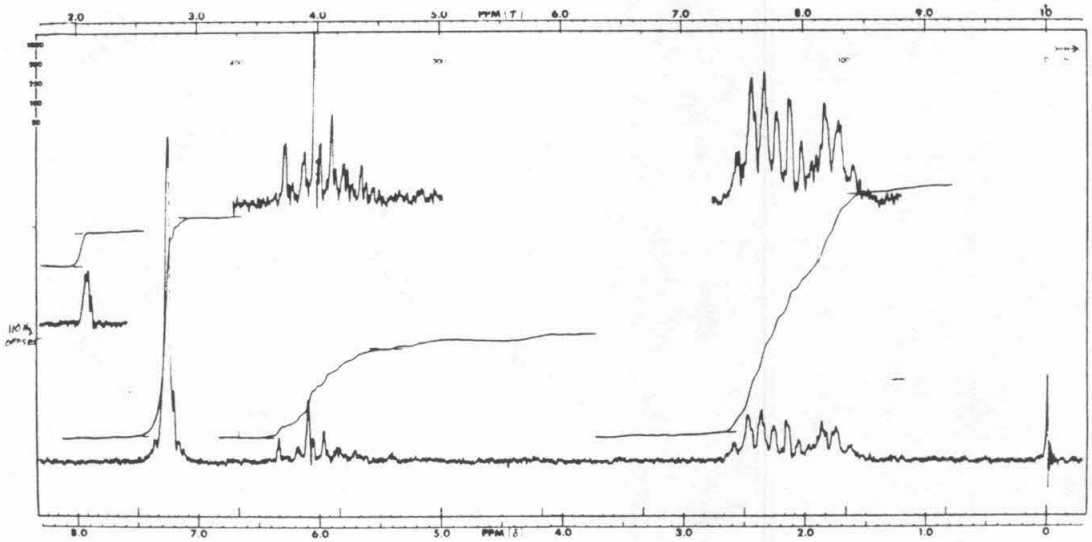
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

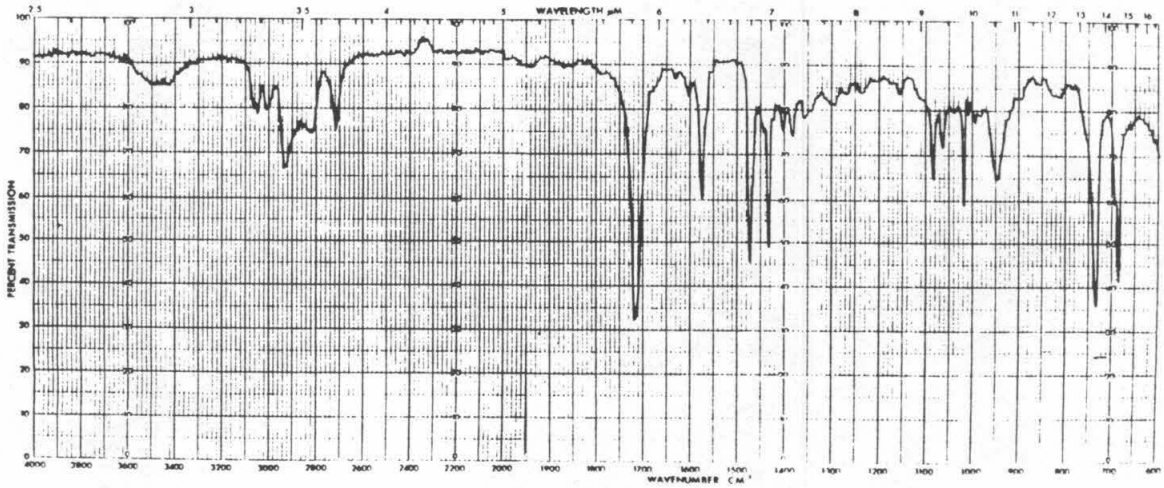

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (cm⁻¹)

Page 65

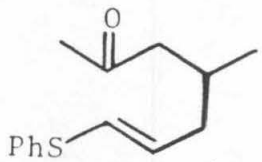

O
PhS

38

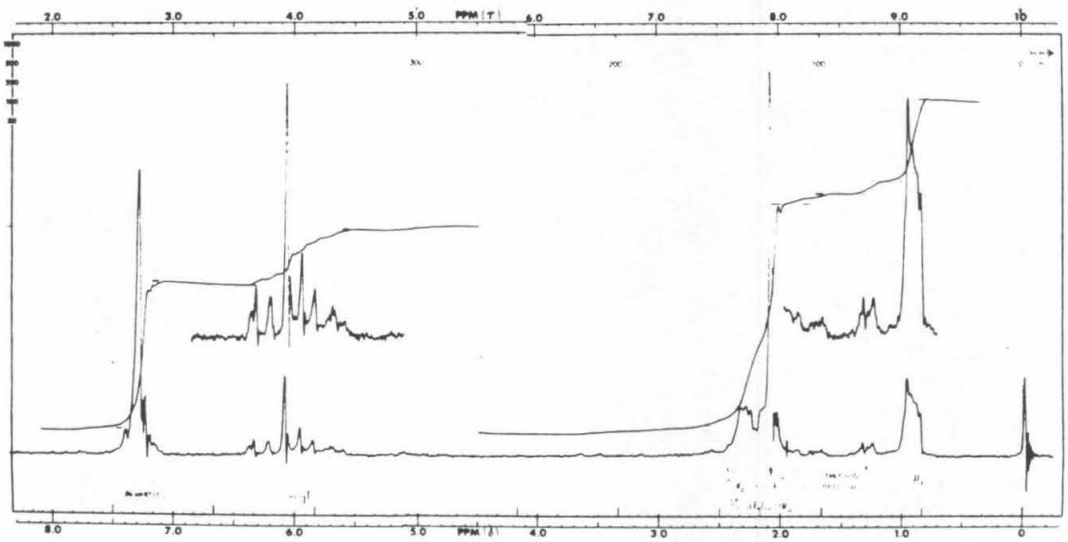

PPM (τ)
PPM (δ)

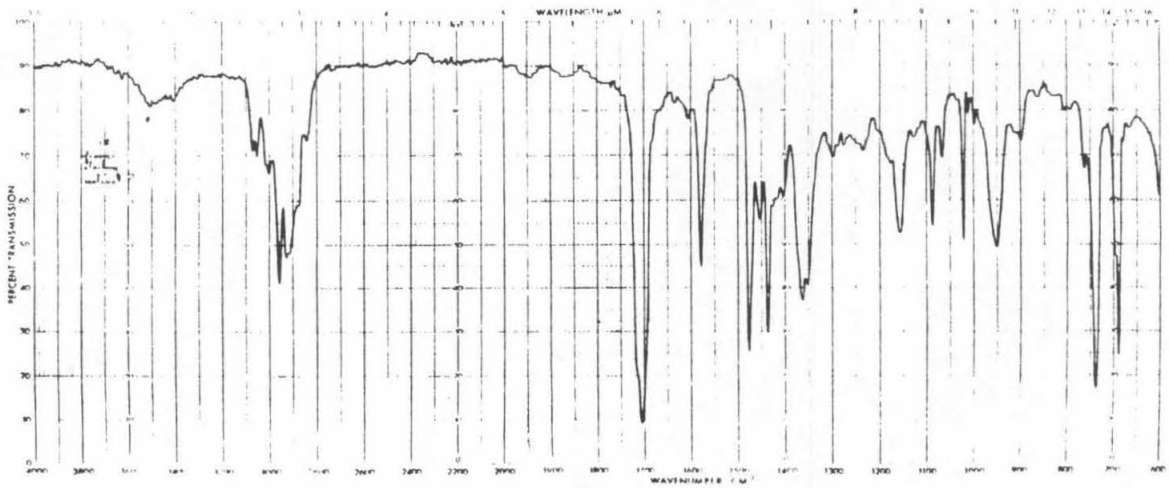

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 65

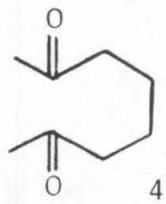

O
PhS

40

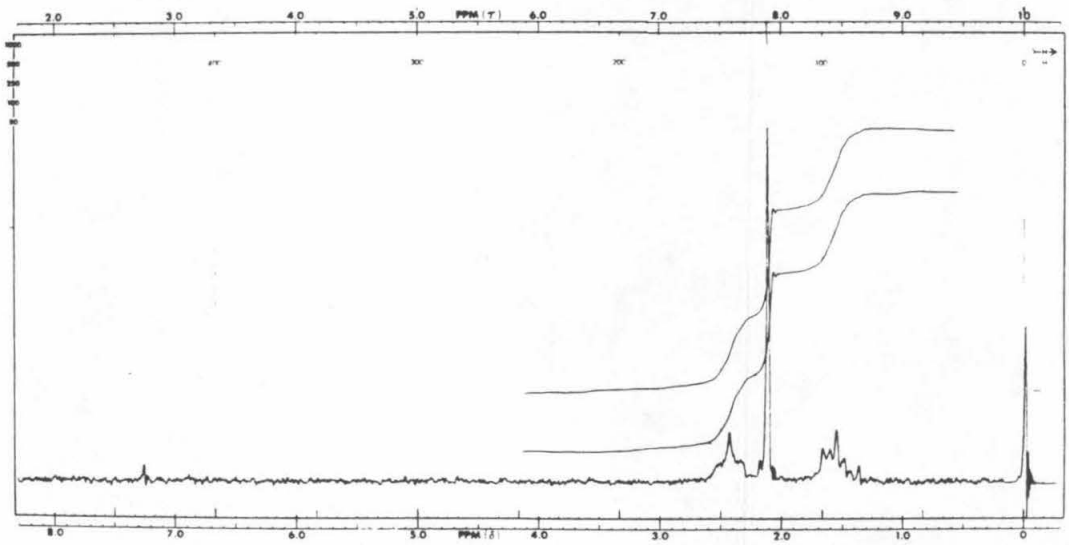

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

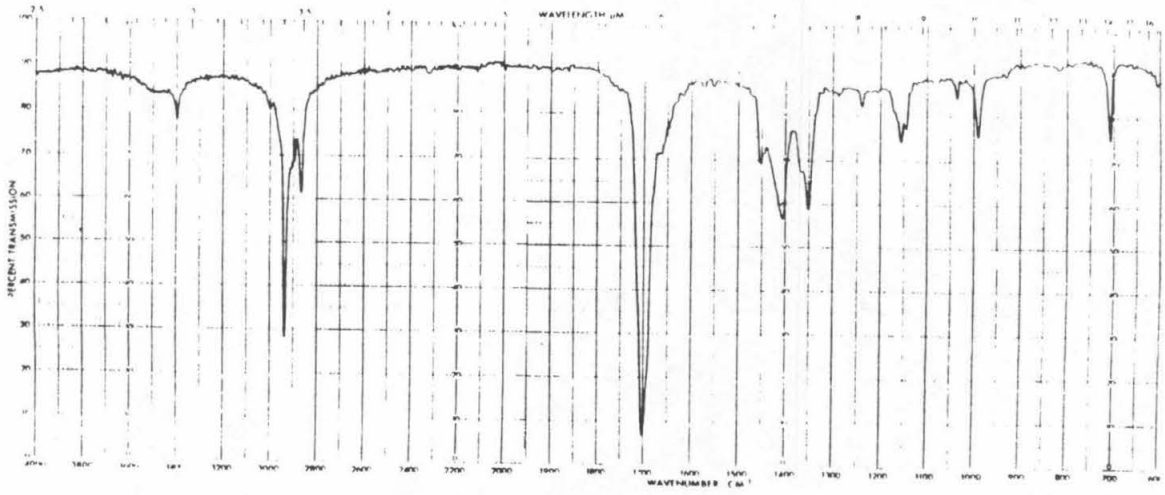

WAVELENGTH μM
PERCENT TRANSMISSION

Page 66

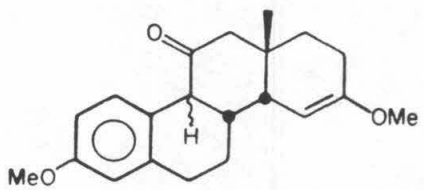


42

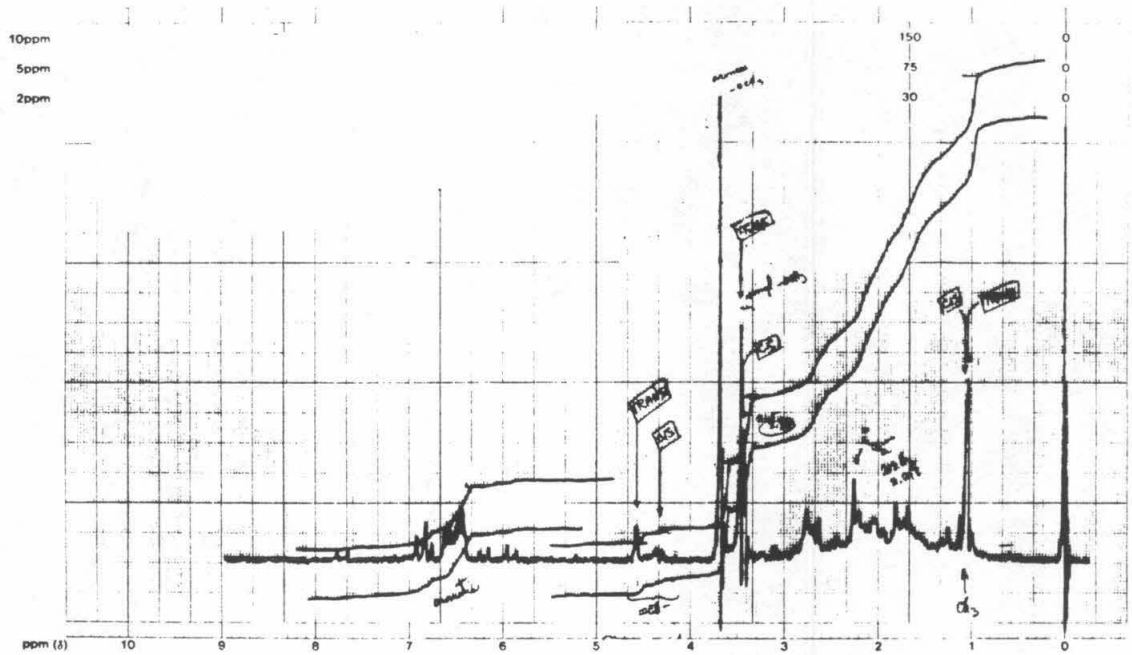


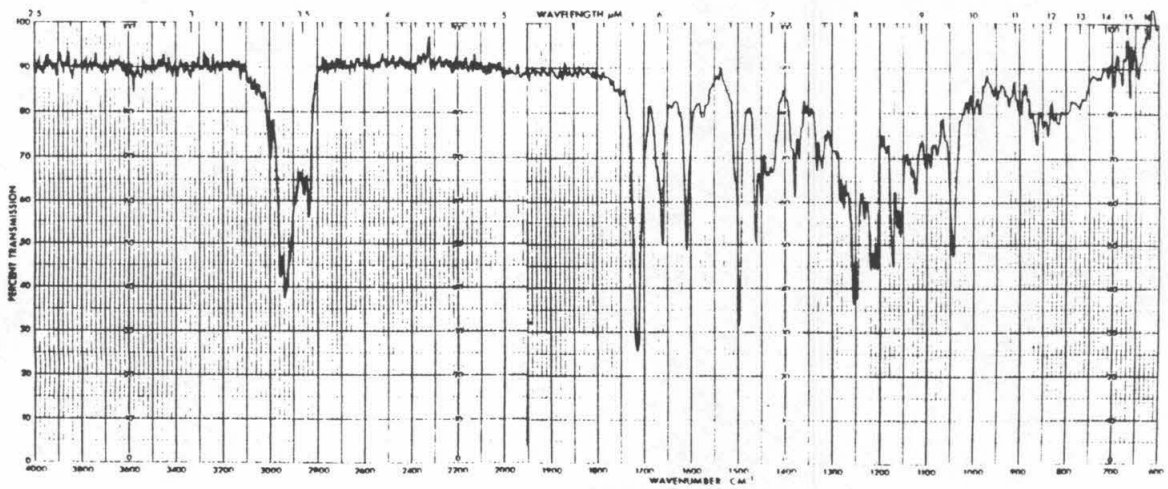


Page 66

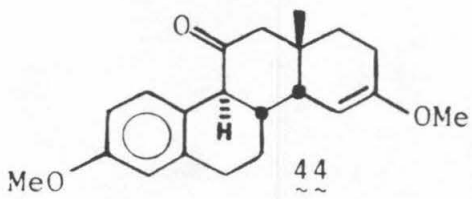

O
H
OMe
MeO

44

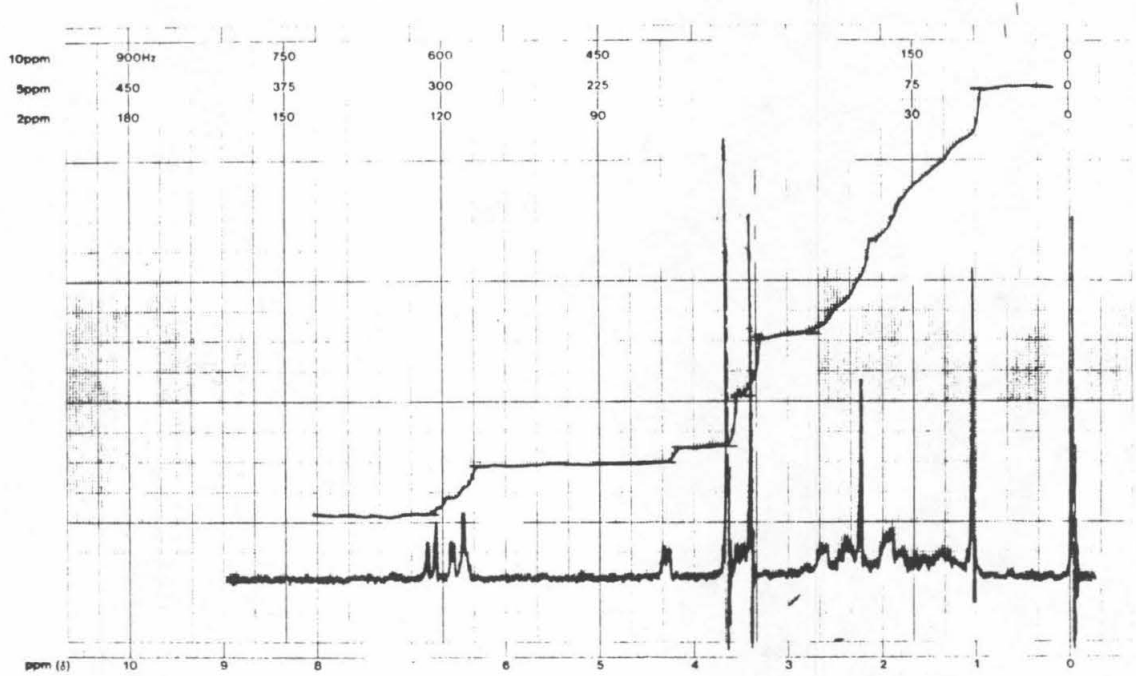

10ppm
5ppm
2ppm
150
75
30
0
0
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 66


O
H
OMe
MeO

44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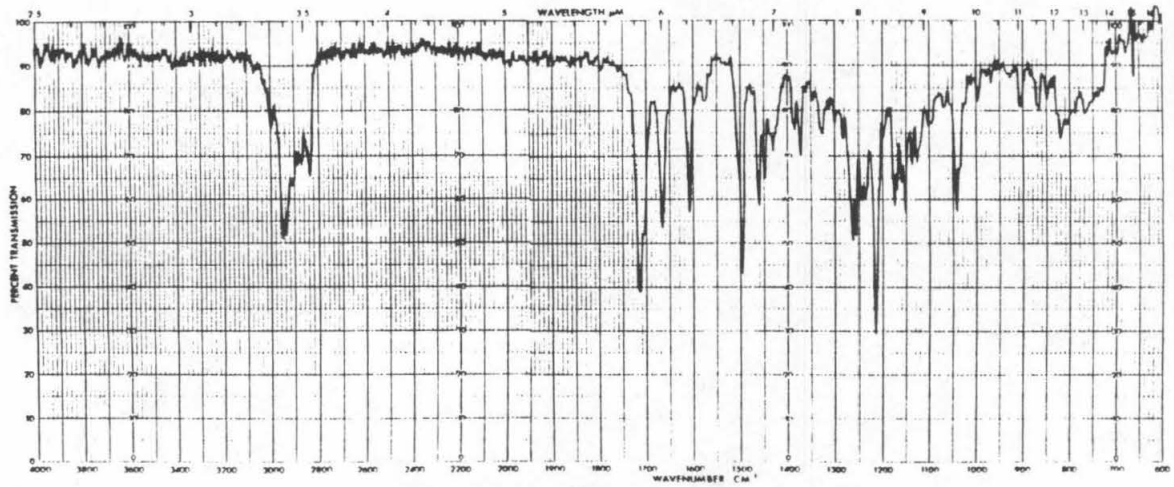
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
150
75
30
0
0
0
ppm (δ)
10
9
8
6
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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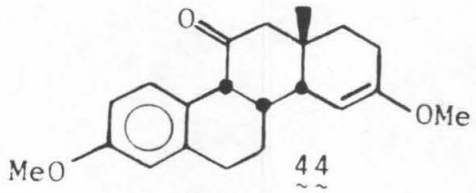

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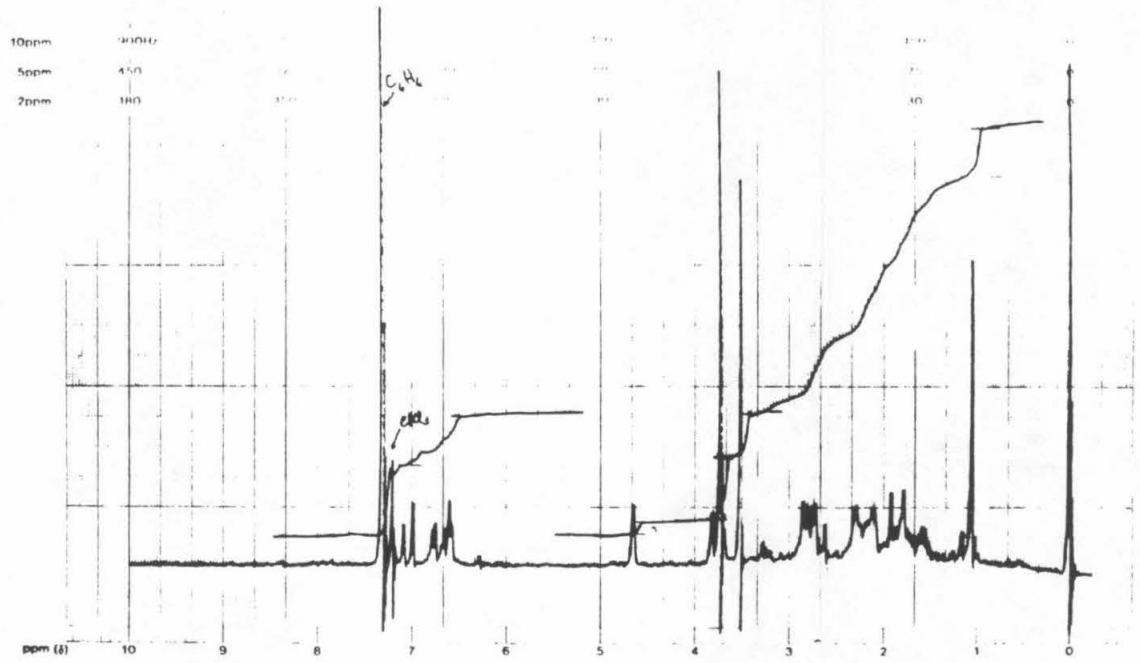
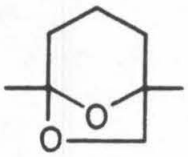


Page 68



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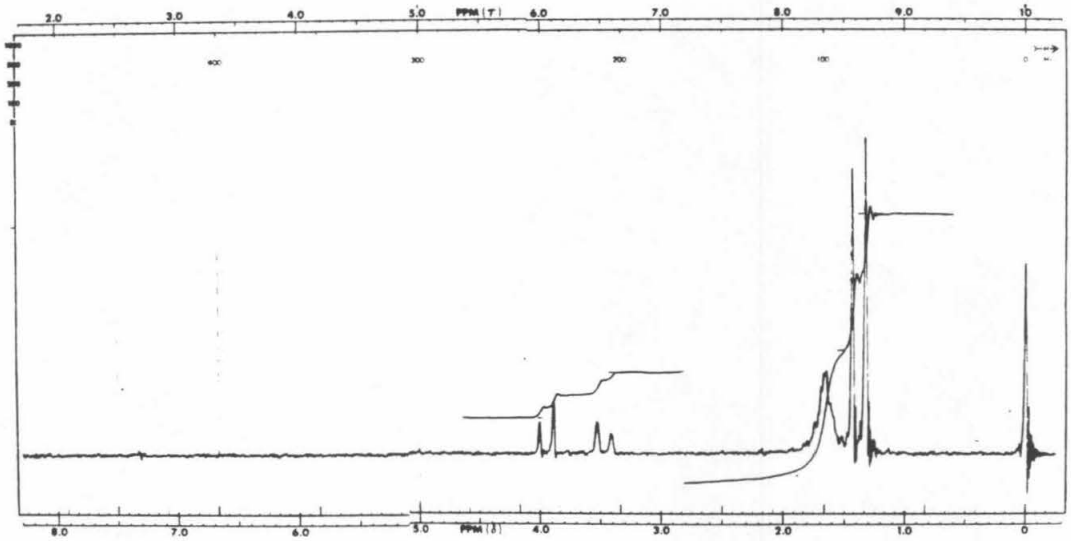
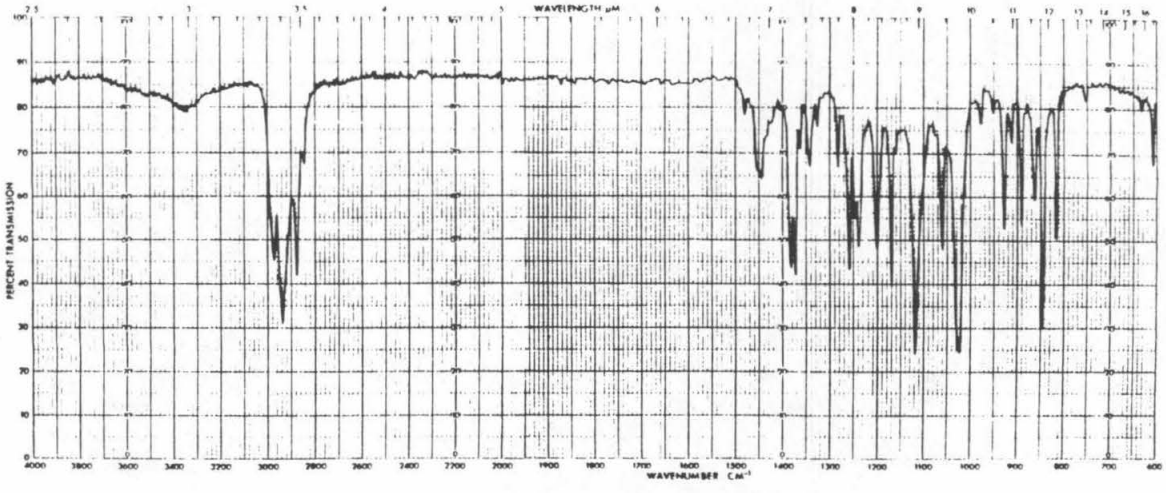
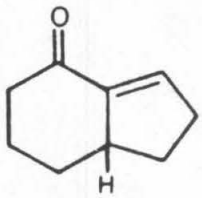

PPM (τ)
PPM (δ)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 69



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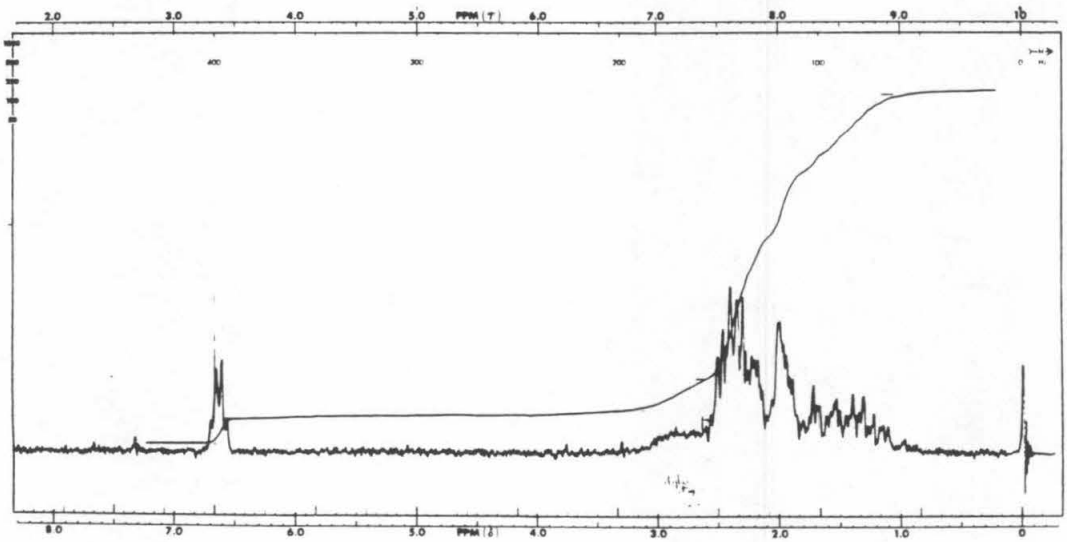
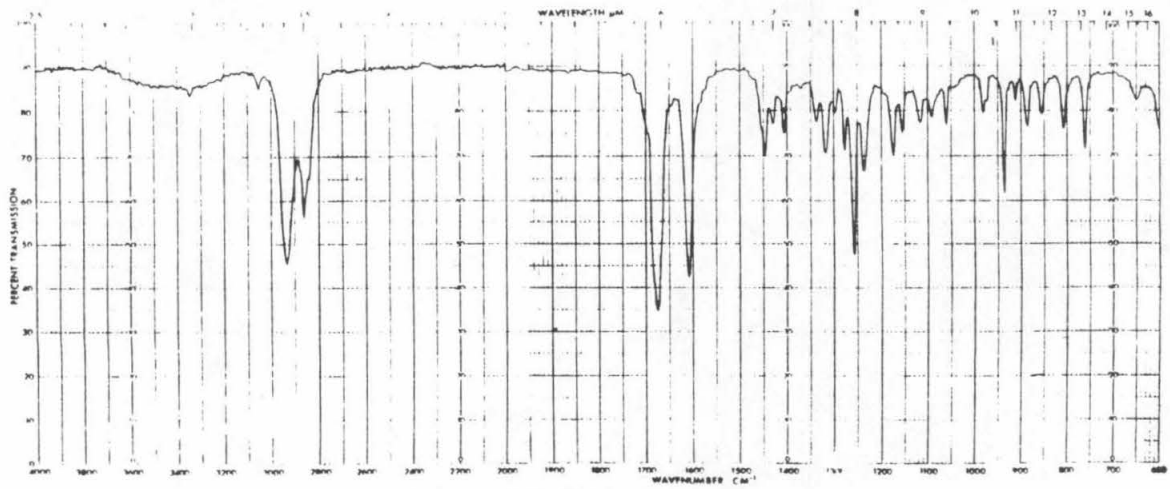
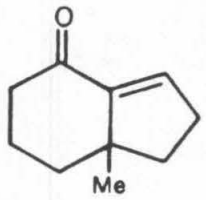
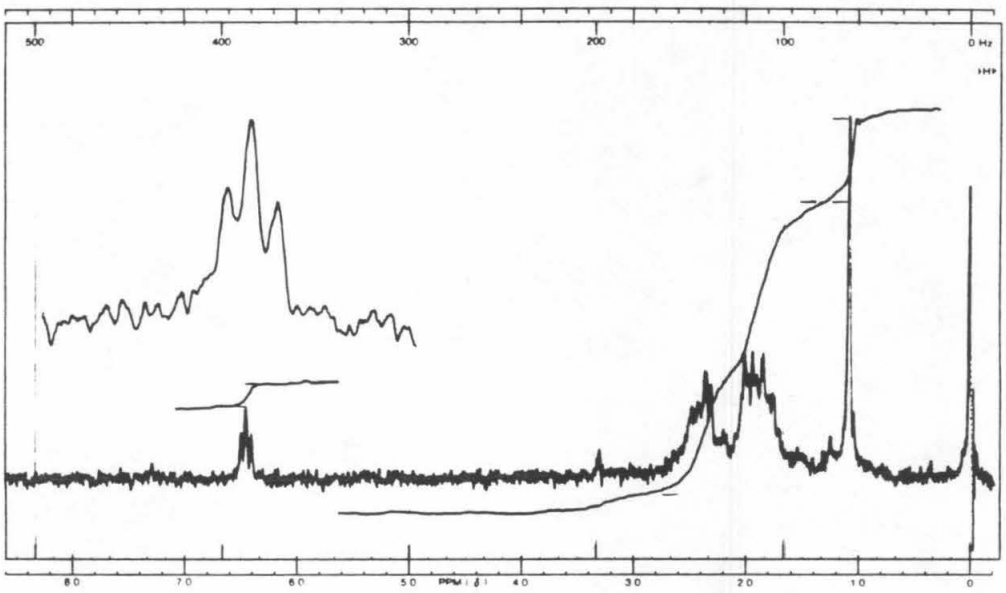

PPM (τ)
PPM (δ)

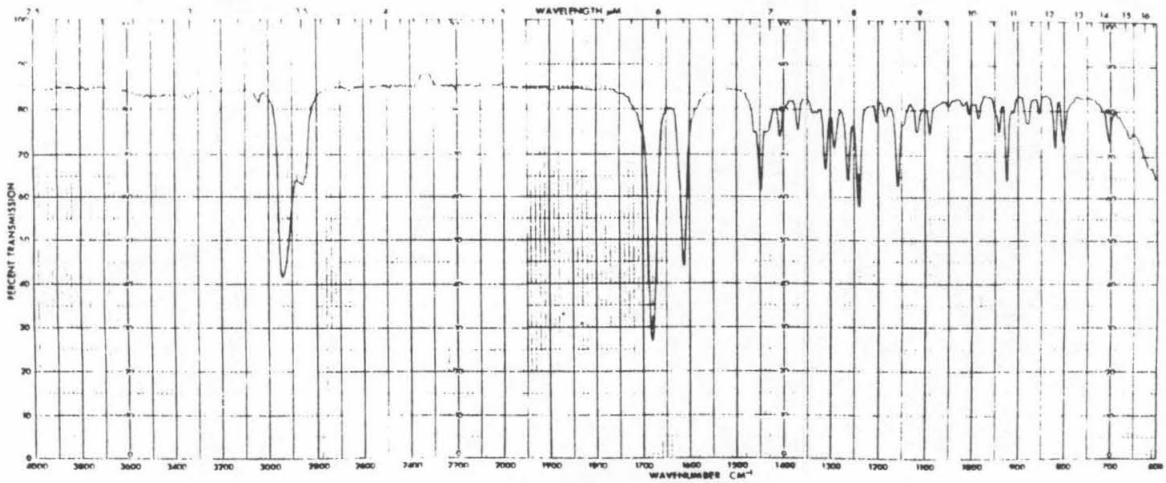

PERCENT TRANSMISSION
WAVELENGTH μM
WAVENUMBER cm⁻¹

Page 69


O
Me

61


500
400
300
200
100
0 Hz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0


PERCENT TRANSMISSION
WAVELENGTH μM
WAVENUMBER cm⁻¹

APPENDIX III

Spectral Catalogue for Chapter III

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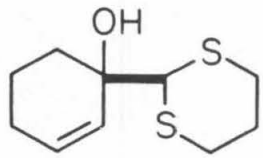
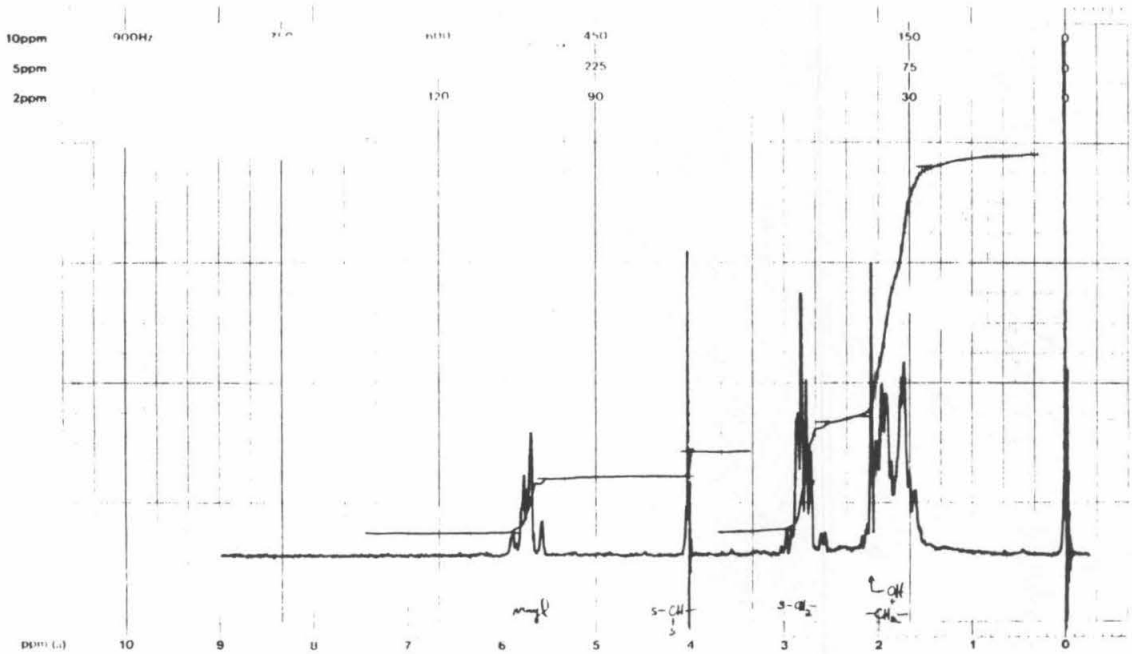
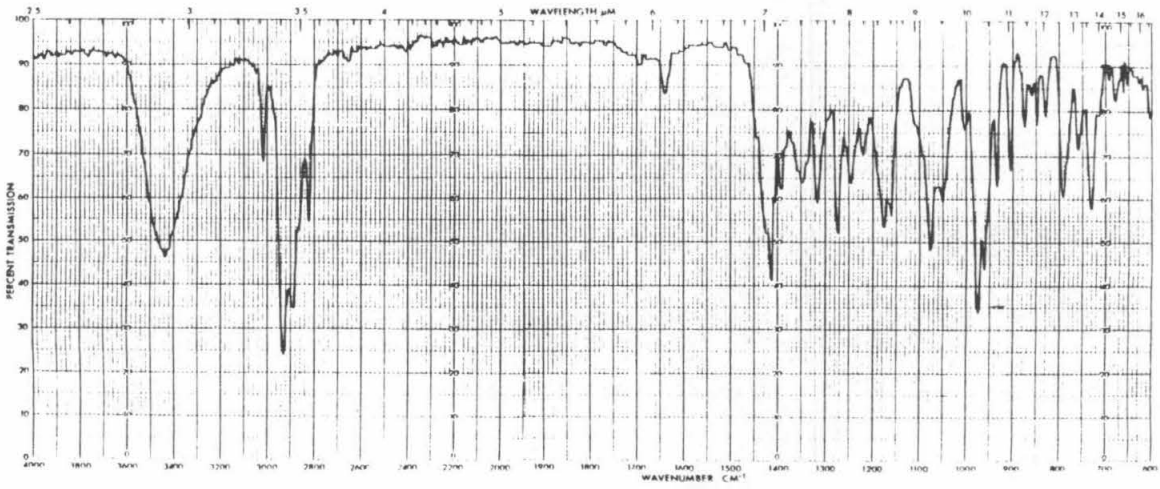

OH
S
S

II


10ppm
5ppm
2ppm
900Hz
450
225
120
90
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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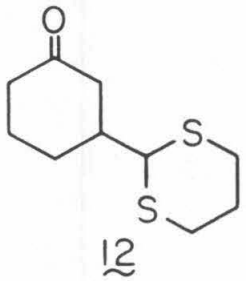

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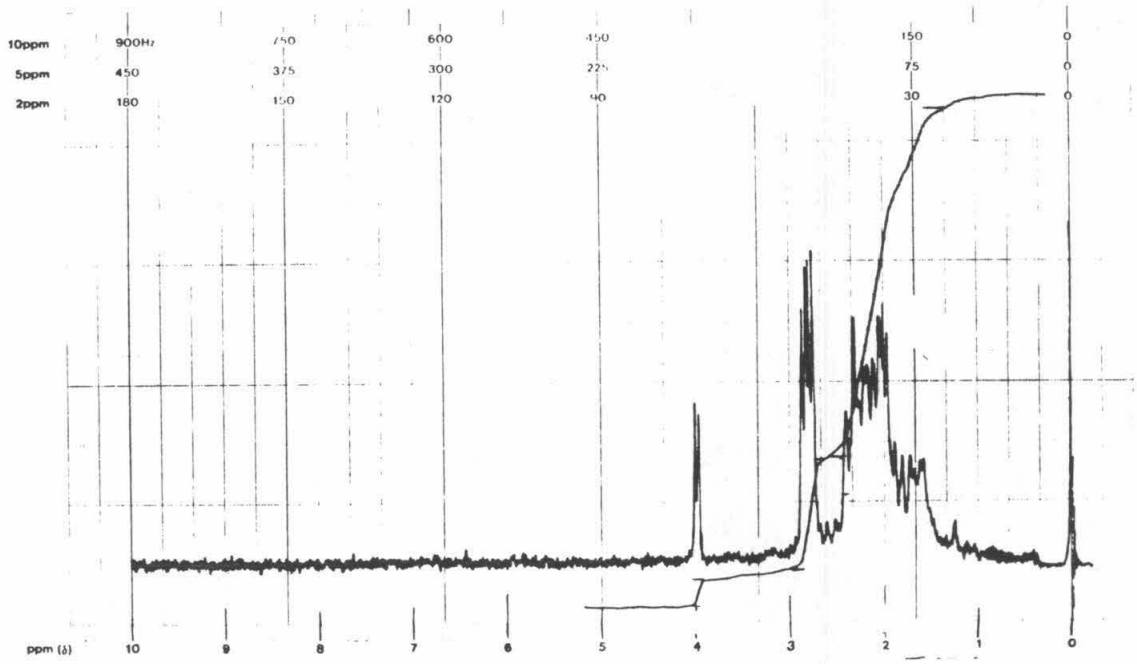
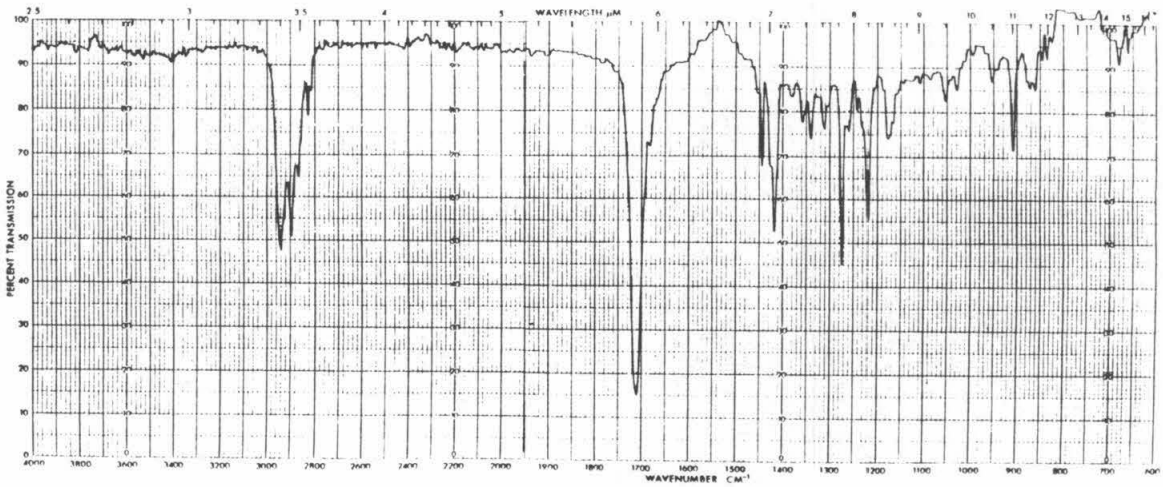
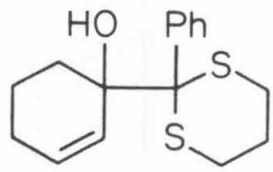
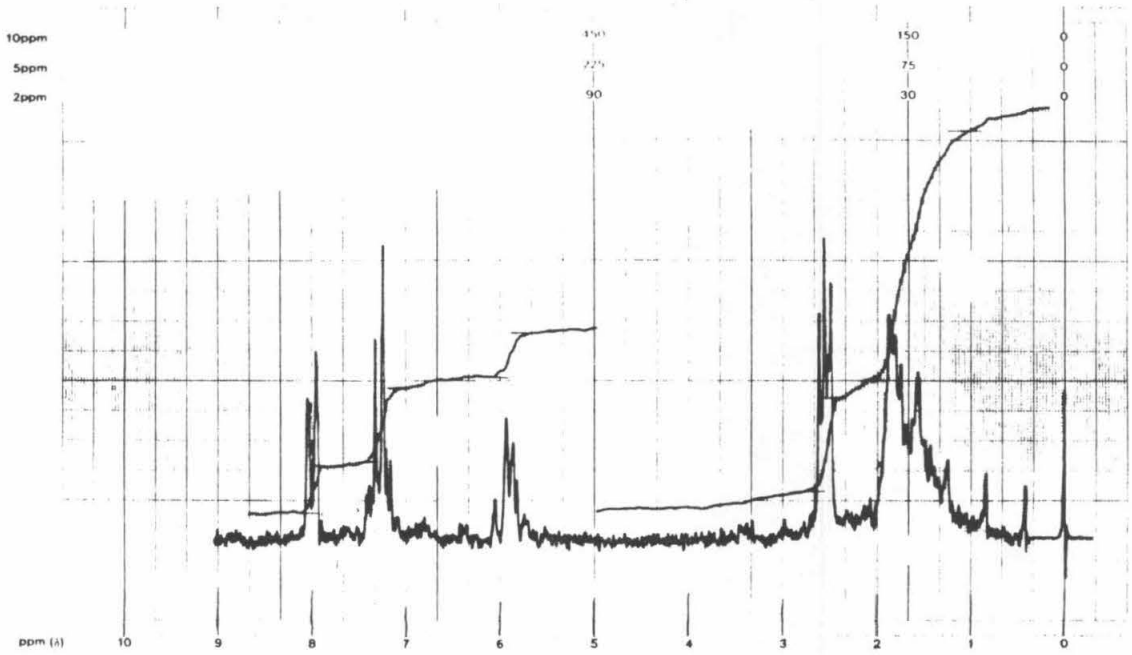

10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
150
75
30
0
0
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0

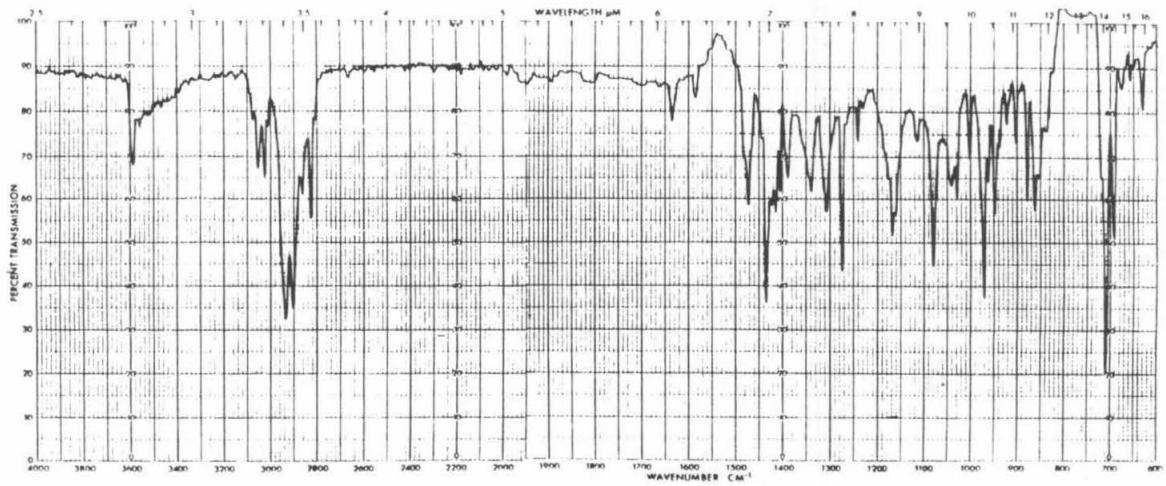

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 127

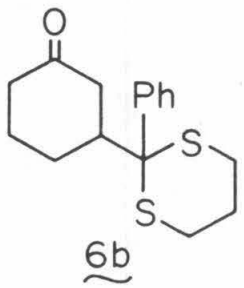

HO
Ph
S
S

5b

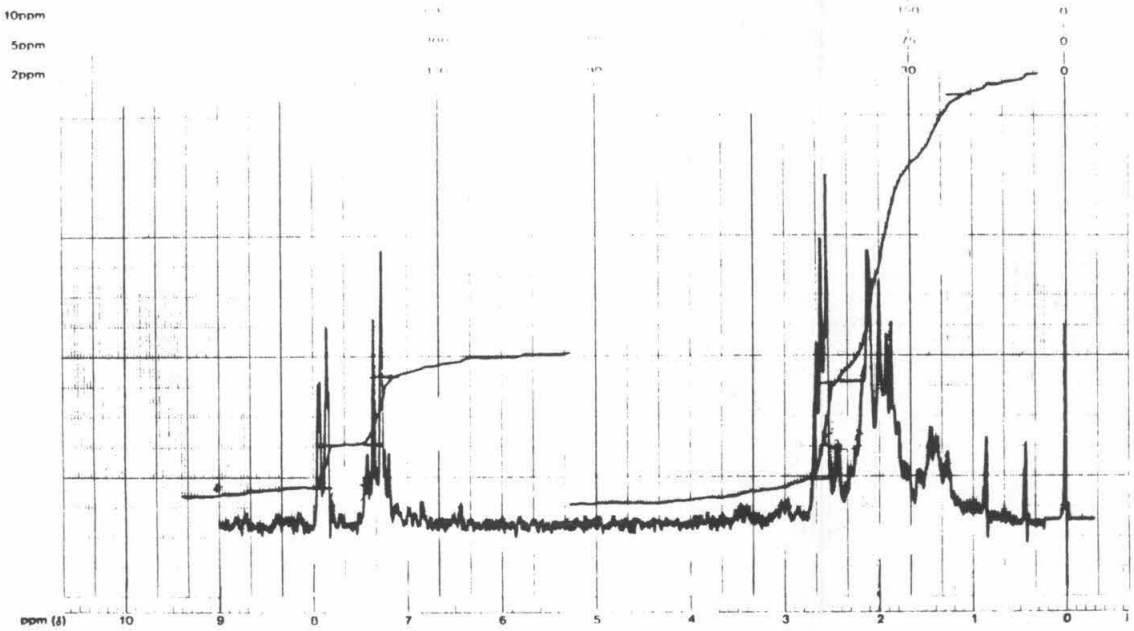

10ppm
5ppm
2ppm
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0

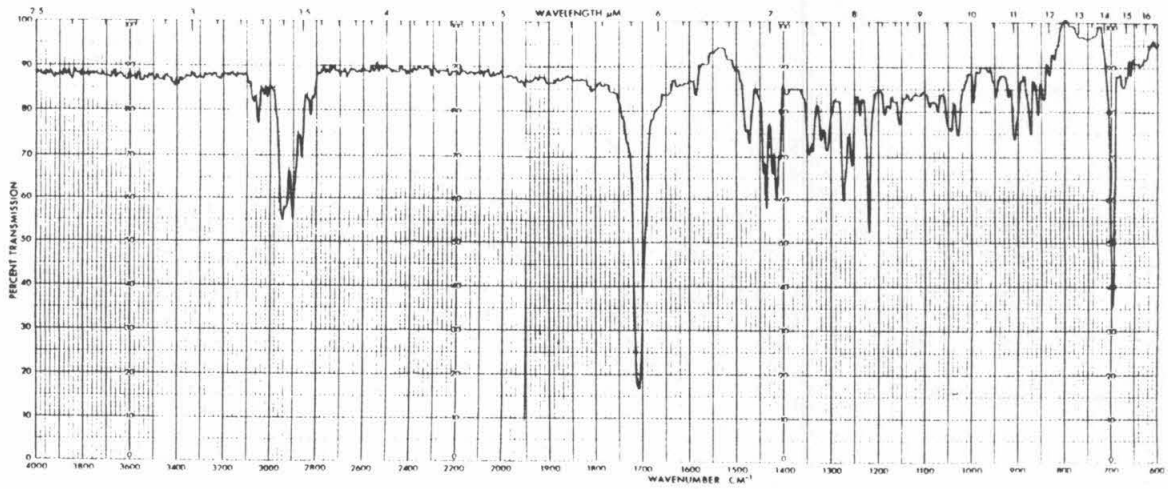

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 127

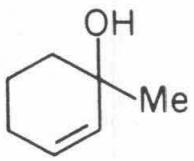

O
Ph
S
S

6b

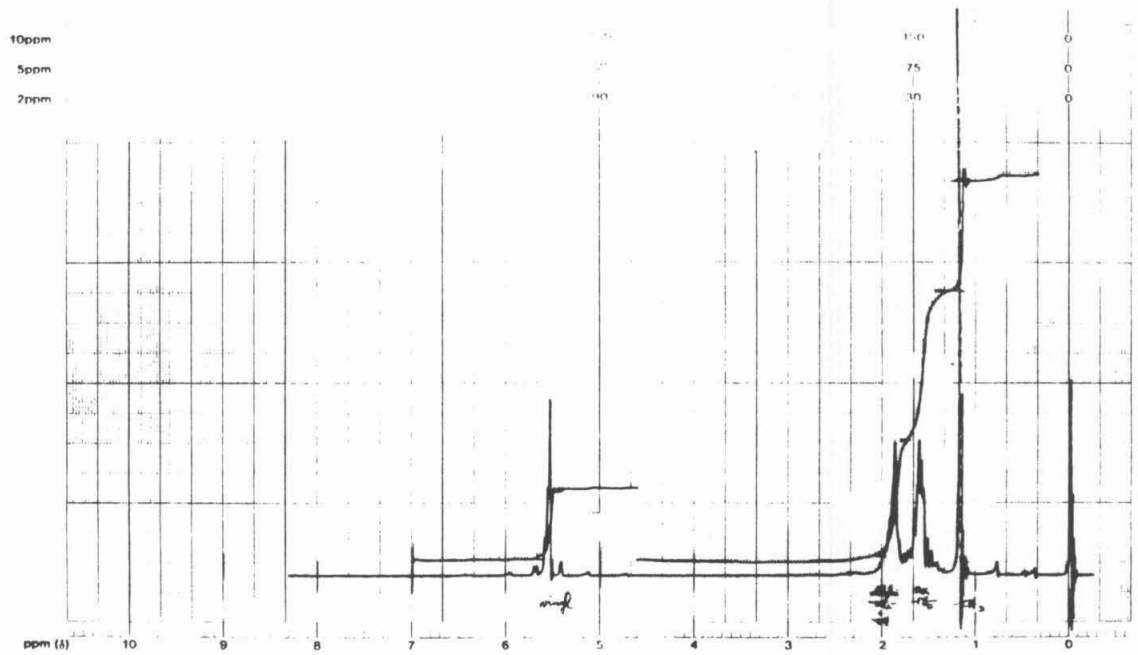

10ppm
5ppm
2ppm
ppm (δ)

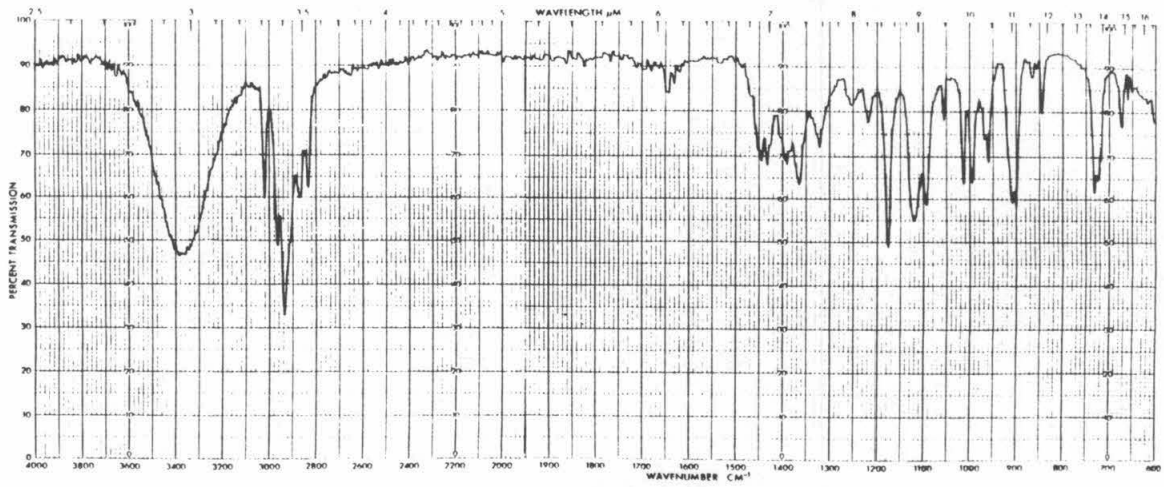

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 127

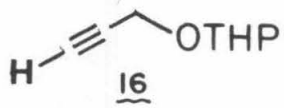

OH
Me

14

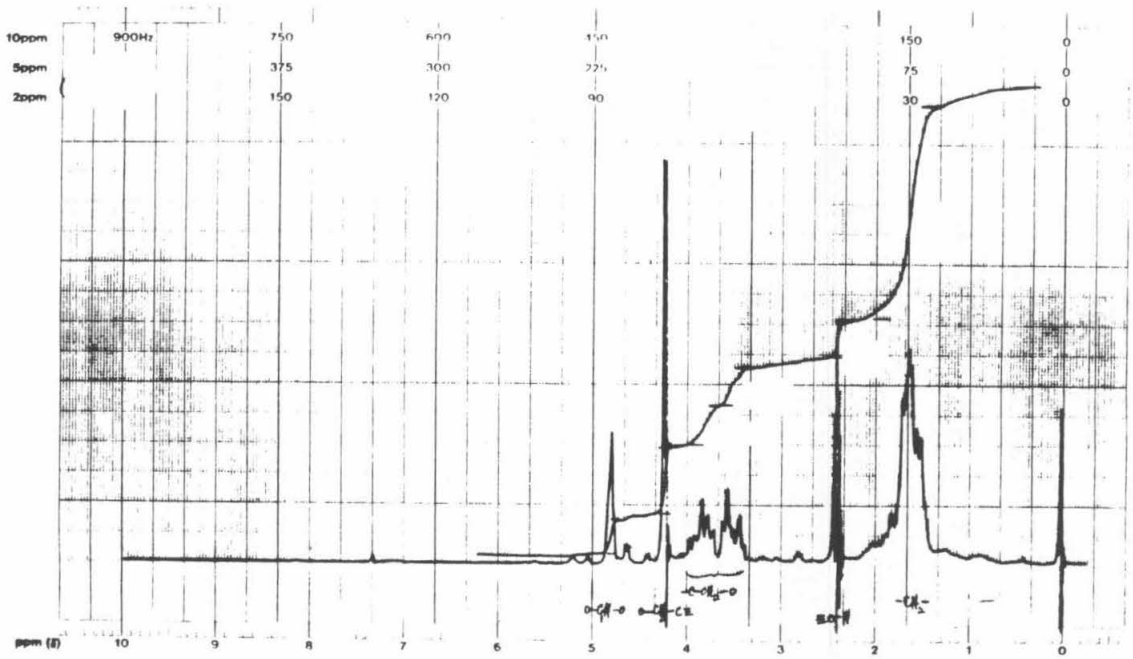

10ppm
5ppm
2ppm
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0

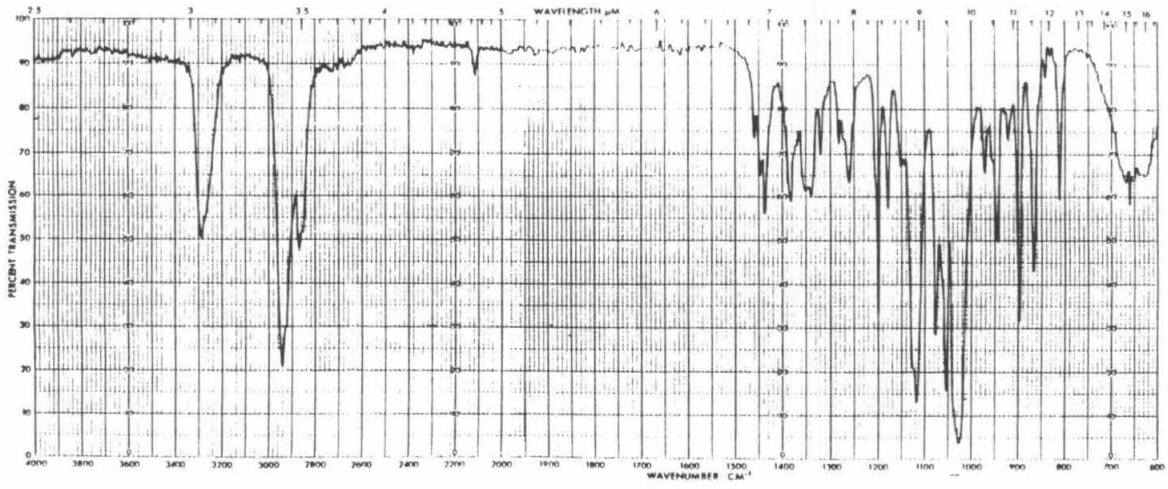

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 130

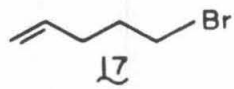

H
OTHP

16

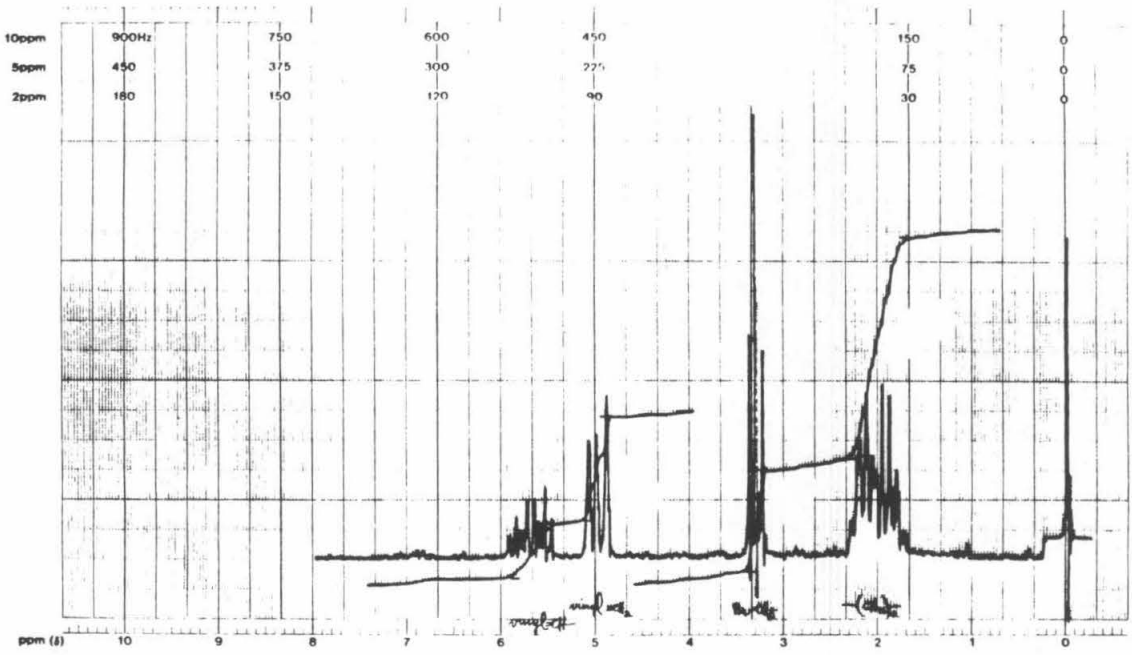

10ppm
5ppm
2ppm
900Hz
ppm (δ)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 130


Br

17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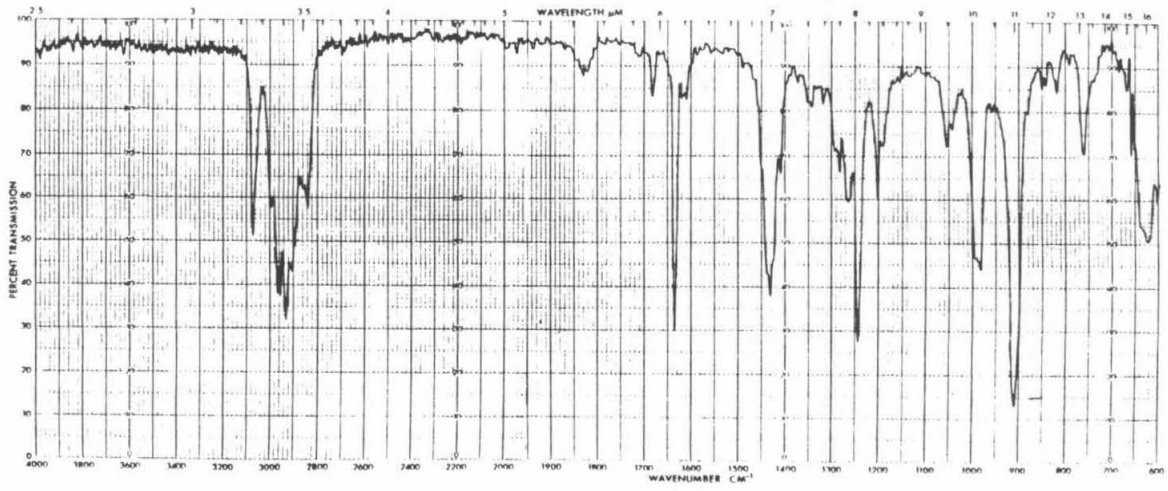
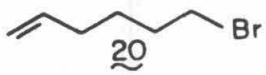
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
150
75
30
0
0
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 131


Br

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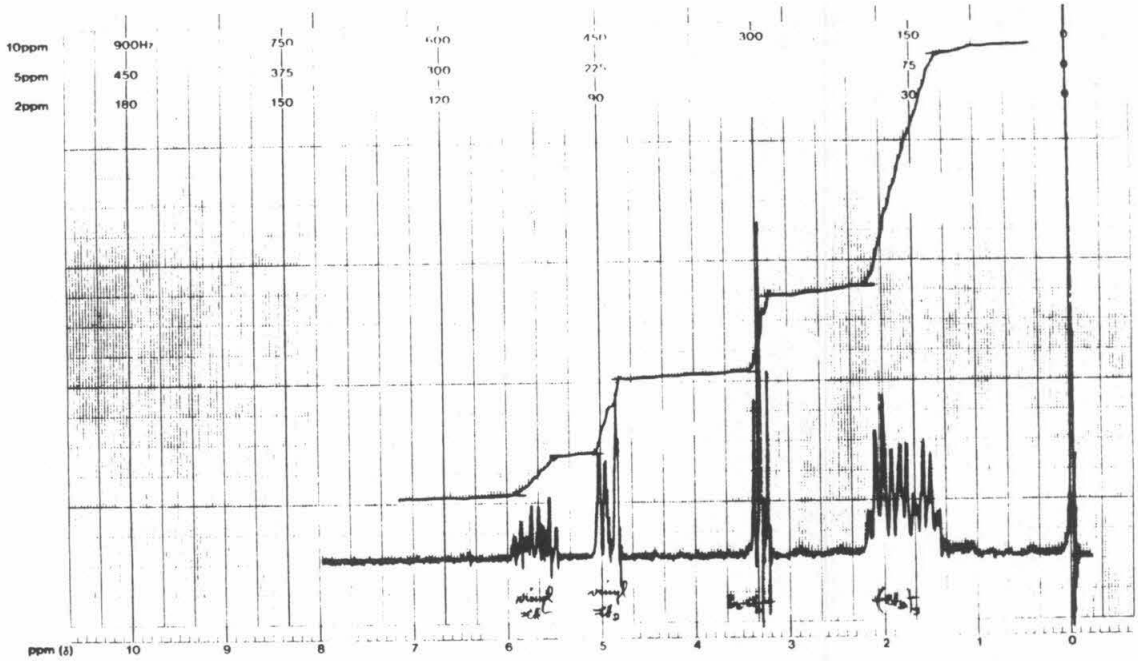
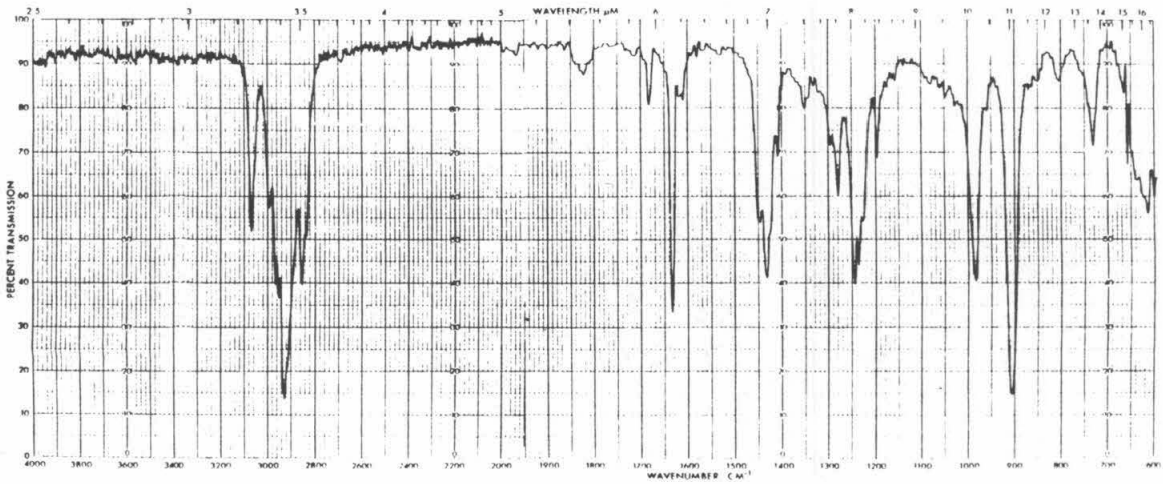
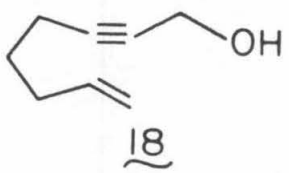
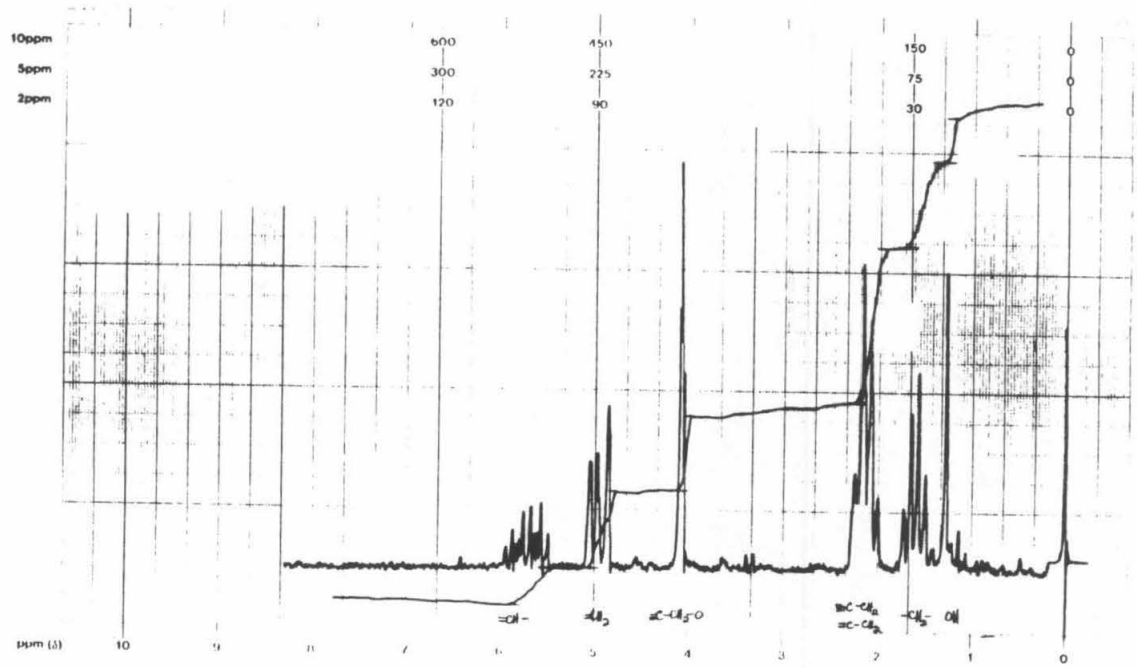

10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0

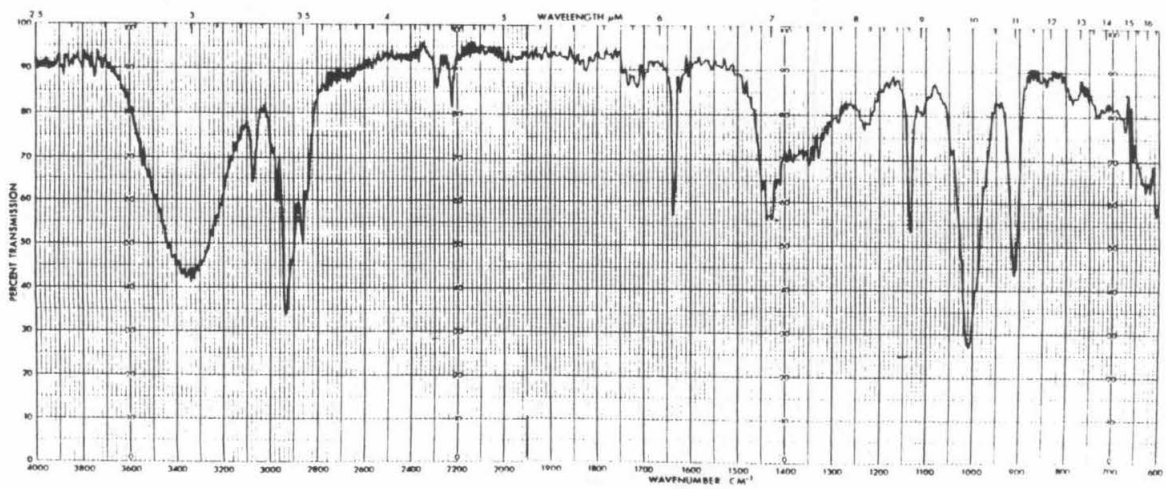

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER (CM⁻¹)

Page 131

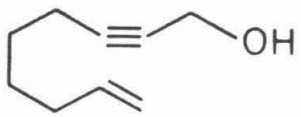

OH

18

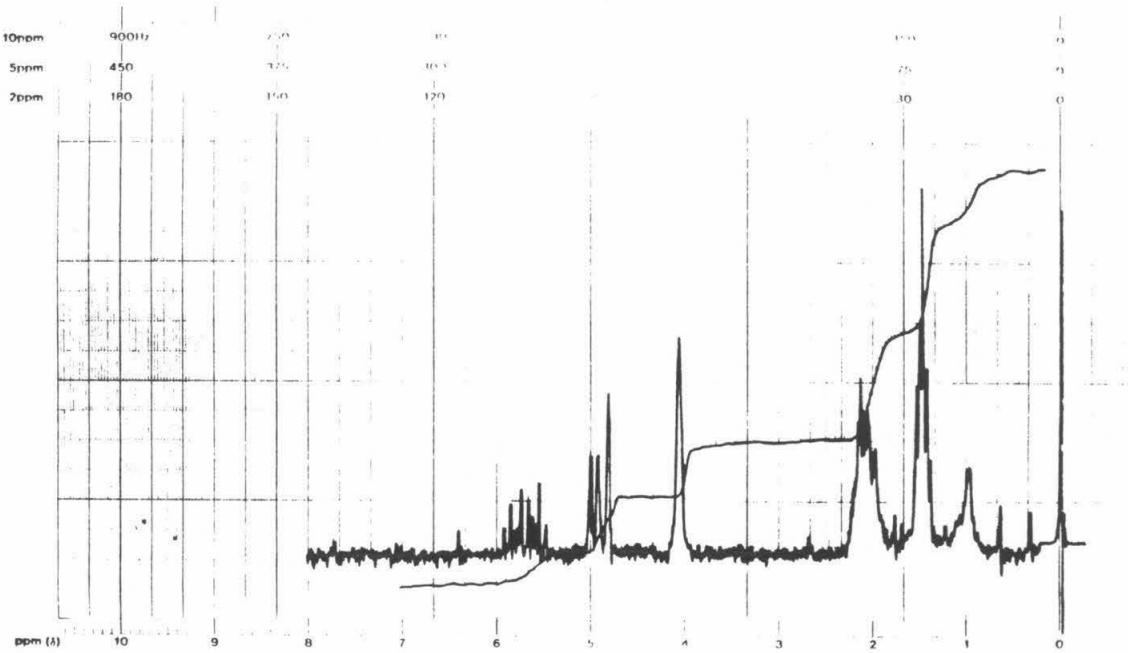

10ppm
5ppm
2ppm
600
300
120
450
225
90
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0

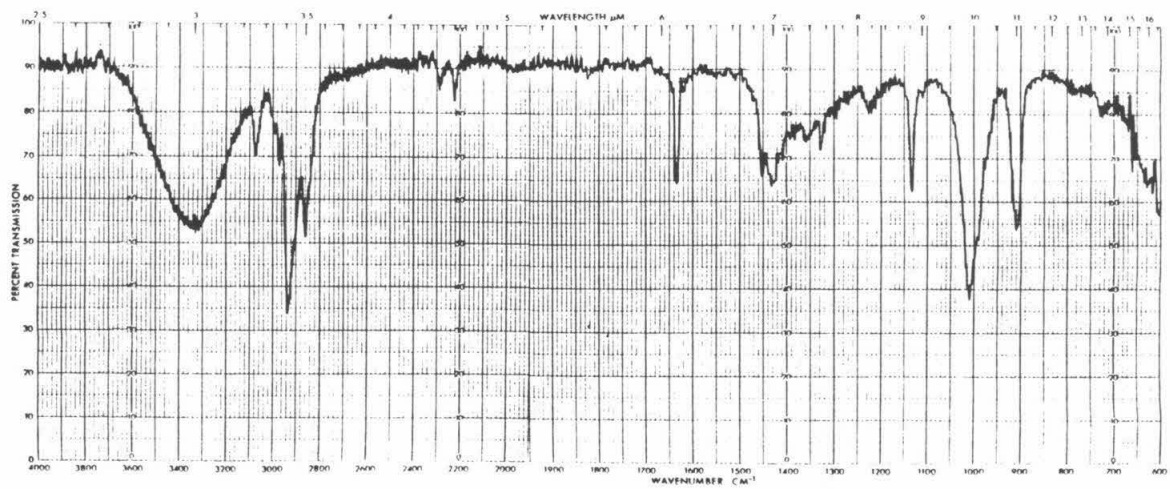

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600

Page 132

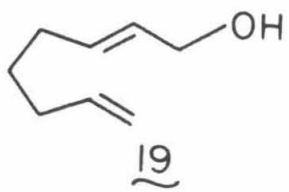

OH

21

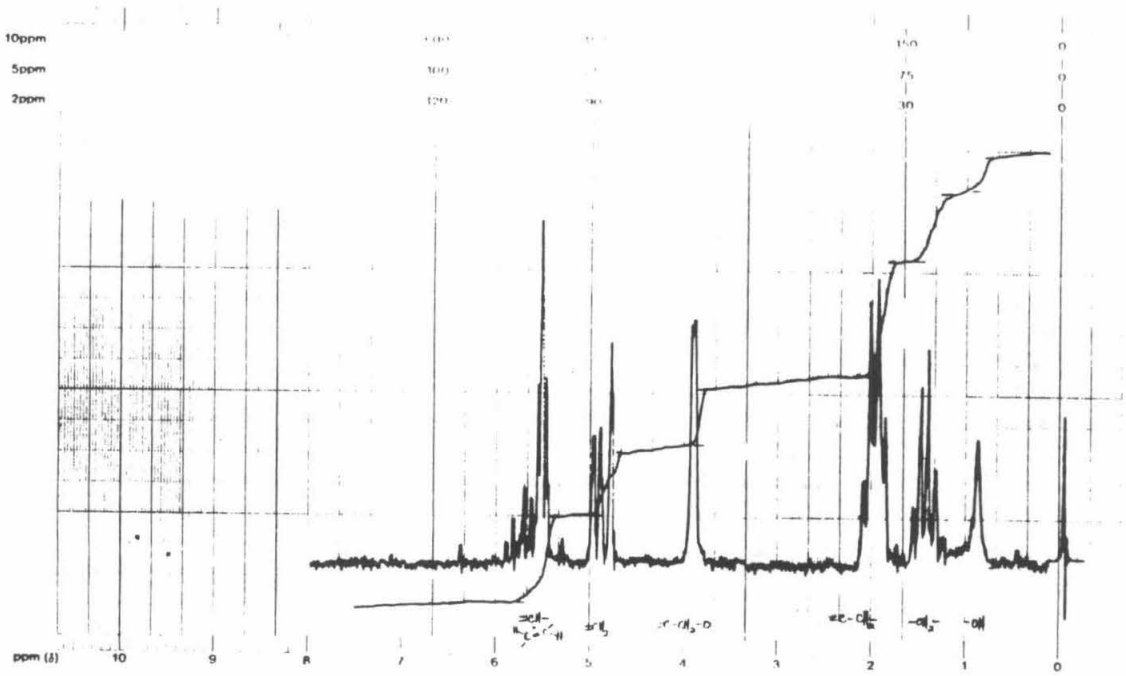

10ppm
900Hz
5ppm
450
2ppm
180
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 132


OH

19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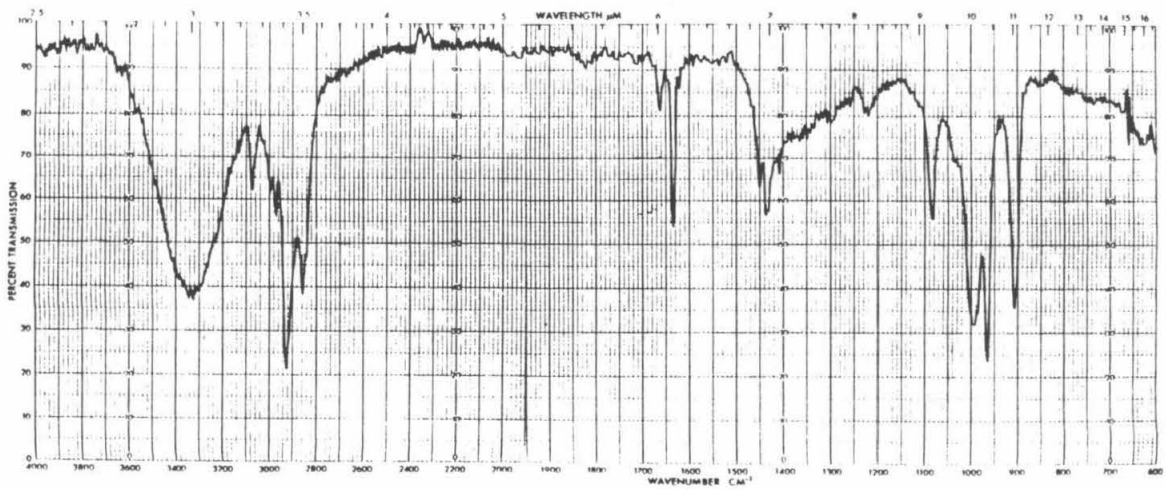
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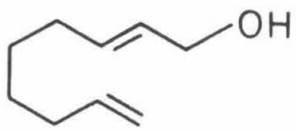
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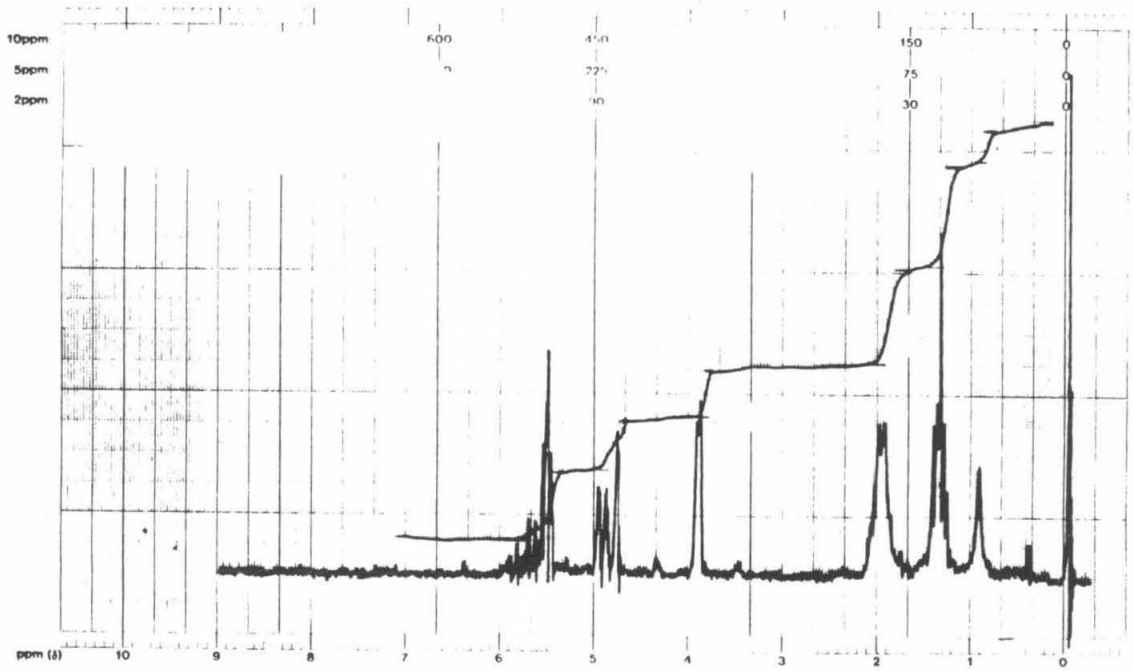
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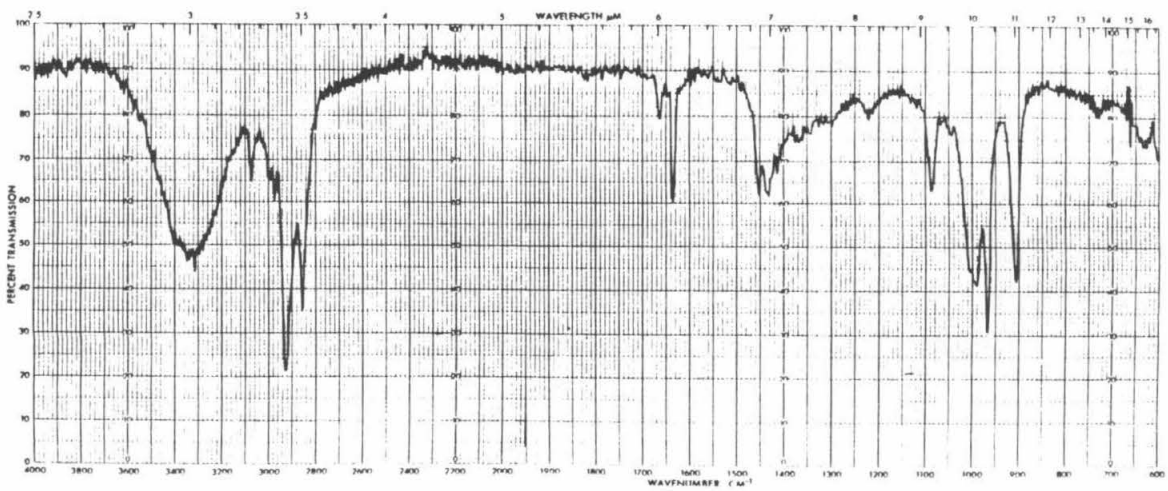
WAVELENGTH μM
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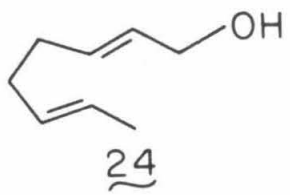
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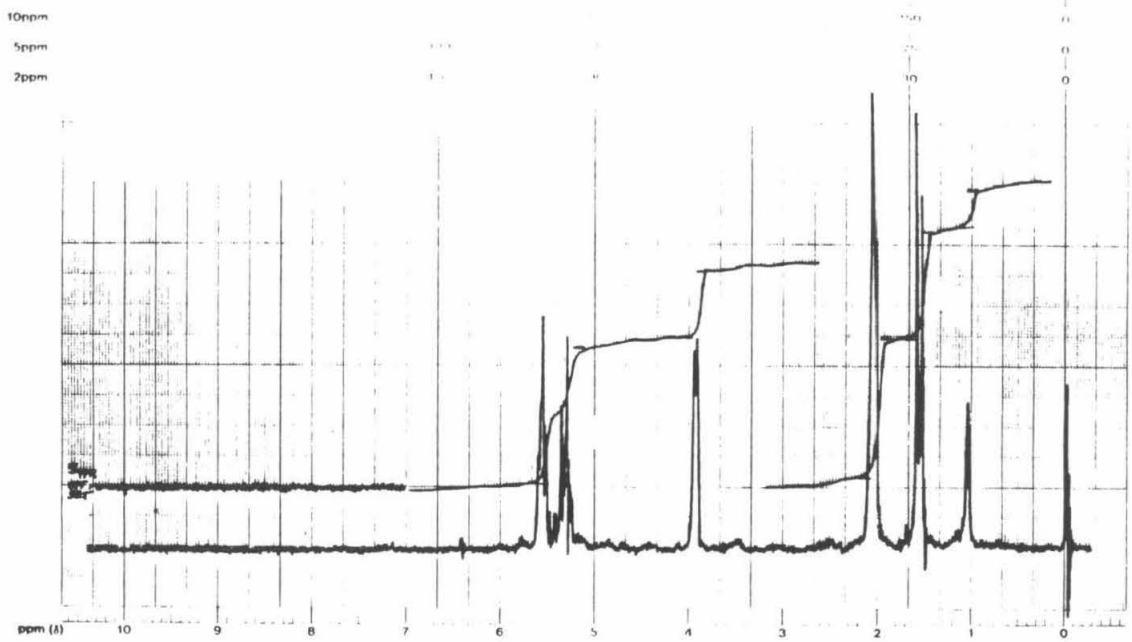
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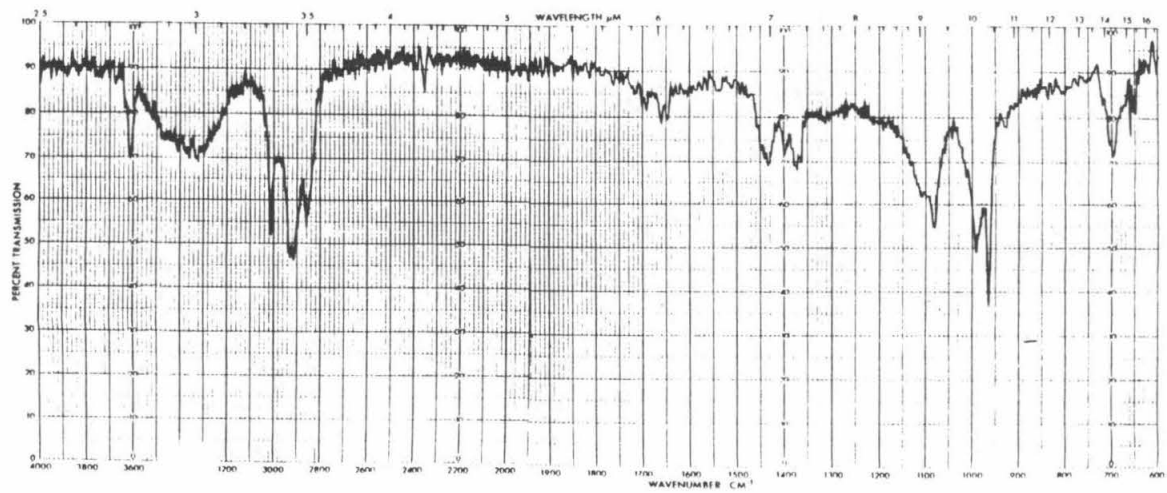
WAVELENGTH μM
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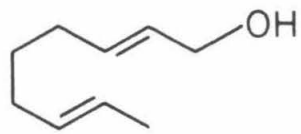

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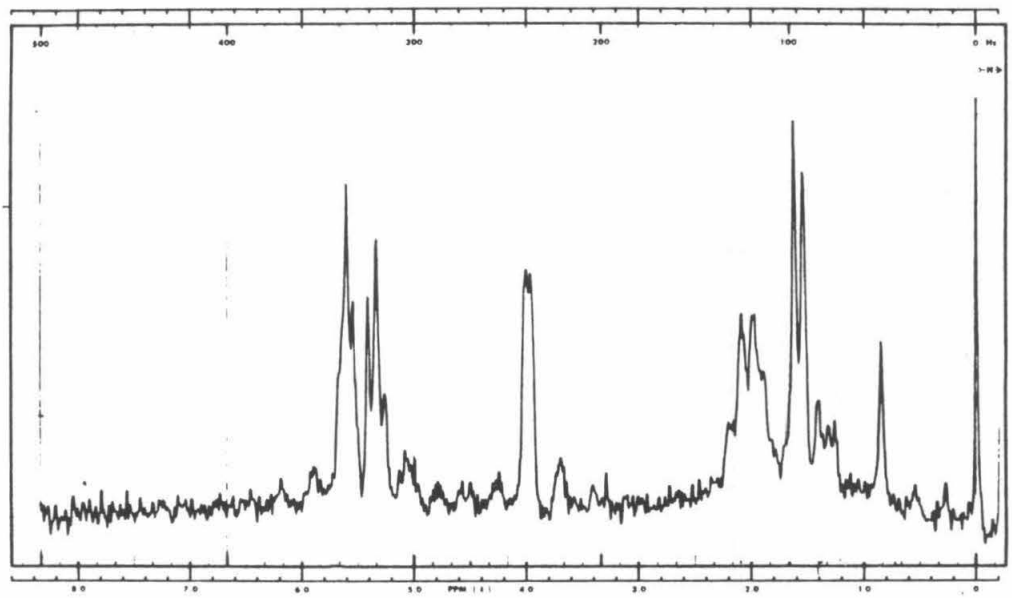
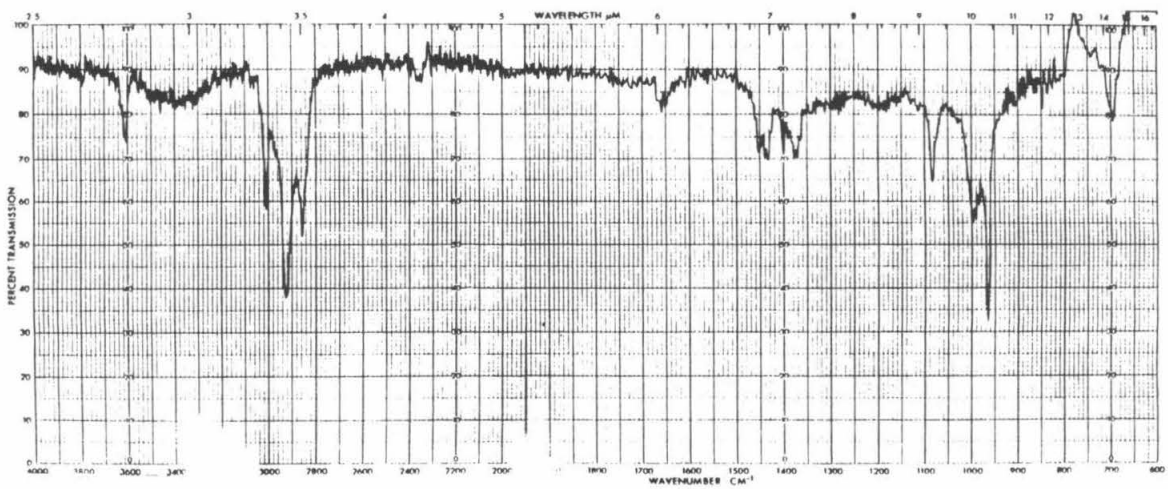




PROPOSITIONS

ABSTRACTS

Proposition I: A study of the orientation dependence of the orbital interaction between an oxy anion and an allylic olefin by photoelectron spectroscopy and by solution kinetics is proposed.

Proposition II: Two alternative syntheses are proposed for the monoterpene (±)-sarracenin.

Proposition III: Modification of nitrene precursors with new, more easily eliminated substituents is proposed.

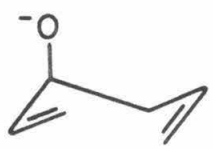
Proposition IV: Ion cyclotron resonance spectroscopy will be used to study the internal solvation of a cation by a suitable substituent possessing nonbonded electron pairs.

Proposition V: The preparation and use of chiral acyloxyborohydride reagents are proposed.

PROPOSITION I

Abstract: A study of the orientation dependence of the orbital interaction between an oxy anion and an allylic olefin by photoelectron spectroscopy and by solution kinetics is proposed.

A mechanistically important question in recent investigations[1] of the anionic oxy-Cope rearrangement concerns the spatial orientation of the oxy anion during the transition state of the rearrangement. In a conformationally unconstrained system, does the oxy anion prefer to reside in an axial position, 1, or equatorial position, 2? The problem



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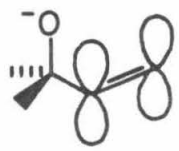
is determining the preferred rearrangement conformation. An investigation into this stereochemical problem using photoelectron spectroscopy and kinetic studies of conformationally defined substrates is proposed.

Interaction of the O–C σ bond and the C–C π bond is of fundamental importance in controlling the conformation of 1 or 2. In one case, 3, the orbitals are all parallel; in the alternative case, 4, the sets of orbitals are mutually perpendicular. Bach[2] performed CNDO/2 calculations on simple allylic alkoxides such as



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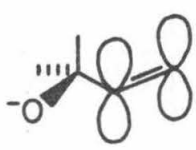

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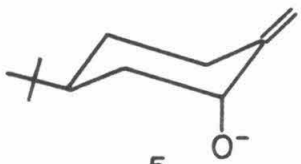
3 and 4 and found that the parallel orientation of 3 was preferred. Based on further calculations, Bach[2] predicted that the favored conformation of the parent oxy-Cope system would be 1 where the oxy anion is axial and the O–C σ and C–C π orbitals are also parallel. A recent study[3] of the orientation of an allylic oxygen species (alcohol or ether) with respect to the olefin in conformationally frozen systems seems to support Bach's prediction. Photoelectron spectroscopic determinations of the ionization potential of the olefin in these systems indicated a significant stabilization of the π bond due to σ^*-π interaction in the cases where the σ bond and π orbitals were parallel rather than perpendicular to one another.

Photoelectron spectroscopy (PES)[4] is equally useful in examining the effect of substituents on oxy anions. Engelking and coworkers[5] have demonstrated the feasibility of measuring alkoxide photodetachment energies using PES and estimating the closely related electron affinities (EA) of the oxy radicals. Because the photodetachment energies and electron affinities reflect the stability of the negative ion,[6] these values should also show a dependence on the orientation with respect to an allylic olefin.

Interaction of an oxy anion and an allylic olefin can be tested by determining the changes in electron photodetachment energies of the

oxy anion in a number of molecules, such as 5-8,[3] possessing rigidly fixed geometries. The saturated analogues of alkoxides 5-8 would be the reference compounds for the PES measurements. In 5 and 7, the



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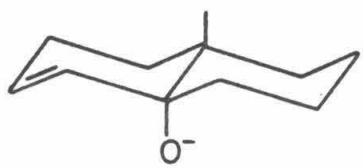

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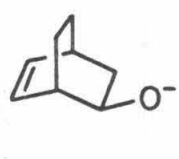
σ and π orbitals are parallel to one another and in 6 and 8, the σ and π orbitals are mutually perpendicular. If the σ^*-π interaction is a significant factor in stabilizing these alkoxide systems, then the photodetachment energies of 5 and 7 should be greater than 6 and 8. A comparison of the photodetachment energies of the above olefinic molecules (especially 6 and 8) to their saturated analogues would help define the intrinsic inductive effect of the olefin on the oxy anion.

An interesting extension of this concept can be tested in the bridged homoallylic alkoxide, 9,[7] where orbital interaction between

9



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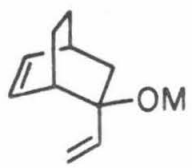
the σ and π orbitals can occur. Such homoconjugation is not possible in the corresponding isomer 10.[7]

What then is the significance of the probable σ^*-π interaction with respect to the anionic oxy-Cope rearrangement? In an acyclic system, there are two possibilities. The σ^*-π interaction may simply serve to fix the conformation of the molecule as it enters into the transition state but does not contribute at all to the observed rate acceleration. The other extreme is that the σ^*-π interaction fixes the conformation and simultaneously contributes significantly to the rate acceleration of the rearrangement. The extent to which this orbital mixing contributes to the rate acceleration may be determined by a kinetic study of substrates 11[8] and 12.[9] In both cases, the direct



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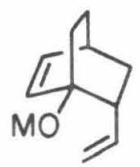

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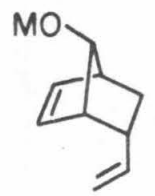
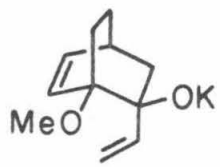


13

effect of the oxy anion on the breaking σ bond is unchanged. However, the conjugative effect of the O–C bond on the adjacent olefin is maintained to a reasonable extent in 11 but is geometrically precluded in 12. Another more unusual test of the possible contribution of the σ^*-π interaction to the Cope rearrangement depends on the existence of the homoconjugation interaction previously described. A comparison of the rearrangement of 13[10] *vs* the parent bicyclic diene could shed light on the homoconjugation problem as well as its possible effect on

the [3,3]-shift.

The homoconjugative σ^*-π interaction may also be an important concept in explaining some of the observations made in the early phases of the oxy-Cope investigation. Although the rearrangement of bicyclic diene alkoxide 14 occurred within minutes ($t_{\frac{1}{2}} \cong 1.4$ min) at 66° C, no rearrangement of the other isomer 15 occurred over 24 h



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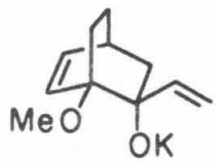

15

under the same conditions.[11] In addition to the energy barrier of bond dissociation and bond rotation in case 15, possible homoconjugative σ^*-π interaction between the alkoxide and the bicyclic olefin could have also contributed to the overall barrier to dissociation-recombination. If the homoconjugative effect is even a fraction of the stabilization energy observed for allylic alcohols and ethers (0.2-0.35 eV),[3] then the energy contribution by such an effect could be significantly large. The stability of 15 could thus be due to geometrical constraints as well as an additional electronic effect due to homoconjugation.

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2. R. D. Bach, Wayne State University, personal communication, 1978.
3. R. S. Brown and R. W. Marcinko, J. Am. Chem. Soc., 100, 5721 (1978).
4. For some general reviews, see: (a) J. P. Maier, Ann. Rep. Prog. Chem., Sect. B, 71, 75 (1974); (b) S. D. Worley, Chem. Rev., 71, 295 (1971); (c) A. D. Baker, Acc. Chem. Res., 3, 17 (1970).
5. P. C. Engelking, G. B. Ellison, and W. C. Lineberger, J. Chem. Phys., 69, 1826 (1978).
6. A. H. Zimmerman, R. L. Jackson, B. K. Janousek, and J. I. Brauman, J. Am. Chem. Soc., 100, 4674 (1978) and references cited therein.
7. Compounds 9 and 10 can be prepared as follows: (1) Diels-Alder reaction of 1,3-cyclohexadiene and α-chloroacrylonitrile, followed by base hydrolysis to ketone; (2) reduction of ketone to alcohols 9 and 10, and separation of isomers.
8. J. A. Berson and M. Jones, Jr., J. Am. Chem. Soc., 86, 5019 (1964).
9. Compound 12 may be prepared as follows: (a) Protection of phenol as a ketal with ethyl vinyl ether; (b) Birch reduction of the phenyl ring to the 1,4-cyclohexadiene; (c) Diels-Alder

REFERENCES (continued)

reaction of Birch product with acrolein to give the bicyclic aldehyde; (d) transformation of aldehyde to vinyl group via Wittig reaction; (e) deprotection of alcohol followed by separation of isomers to give 12.

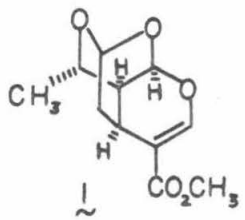
10. Compound 13 may be prepared as follows: (a) Diels-Alder reaction between butadiene and 1,2,3,4-tetrachloro-5,5-dimethoxy-1,3-cyclopentadiene; (b) removal of chloride groups in a Birch reduction; (c) hydrolysis of ketal to ketone; (d) reduction of ketone to alcohol, and separation of isomers to give 13.

11. D. A. Evans and A. M. Golob, J. Am. Chem. Soc., 97, 4765 (1975).

PROPOSITION II

Abstract: Two alternative syntheses are proposed for the monoterpene (±)-sarracenin.

The unusual enol diacetal monoterpene, sarracenin (1), is isolated from the roots of the insectivorous plant Sarracenia flava.[1]



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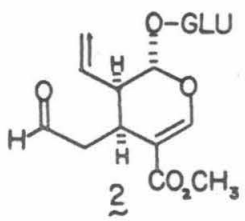
Sarracenin is of current interest because a plant extract containing sarracenin displayed activity against p-388 lymphocytic leukemia; the pure material is being tested for such activity.[1] Sarracenin is also important in that it is a possible intermediate in the biogenesis of certain monoterpenes and indole alkaloids. The postulated precursors to sarracenin are secologanin (2) and/or morroniside (3).[1]



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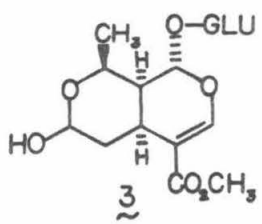

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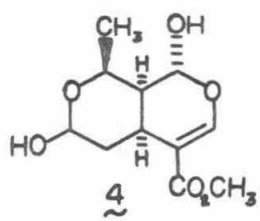

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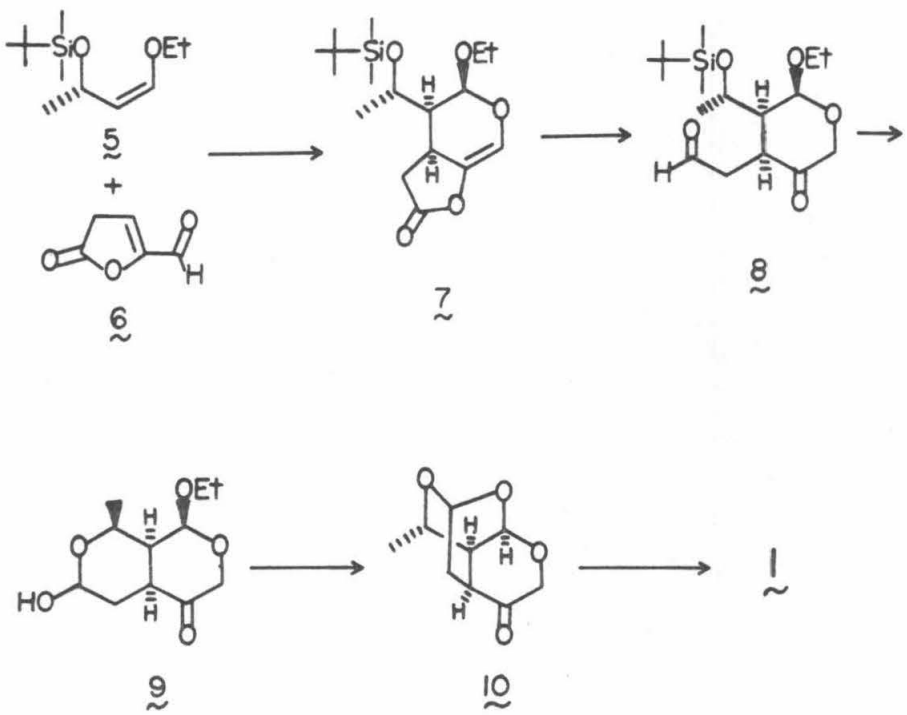
Independent work[2] has indeed demonstrated that morroniside (3) can be easily converted to sarracenin via the unstable aglycone 4.

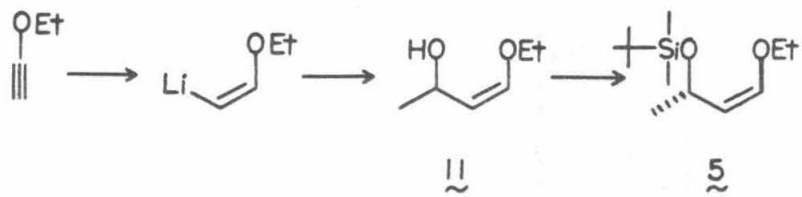
Recently, Whitesell and coworkers[3] reported the total synthesis of (±)-sarracenin starting from cis-7-bicyclo[3.3.0]octen-2-one. Two different approaches to (±)-sarracenin are proposed below.

The first synthetic plan is shown in Scheme I. Preparation of the required starting materials is illustrated in Schemes II and III. Consider first the starting materials 5 and 6.

Scheme I



Scheme II

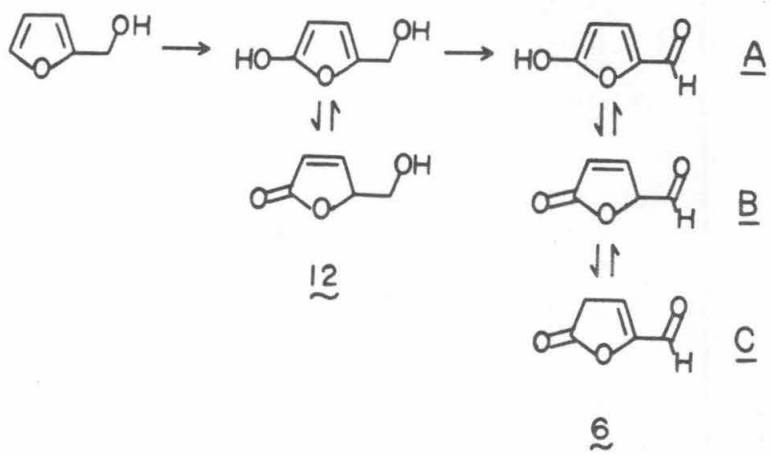


11 5

In the preparation of the cis enol ether 5 (Scheme II), ethoxyacetylene is first converted to cis-2-ethoxyvinyllithium via hydrostannation with tri-n-butyltin hydride and subsequent treatment with n-butyllithium.[4] Condensation of acetaldehyde with the vinyllithium reagent gives racemic alcohol 11. In order to control the stereochemistry about this asymmetric center in the target molecule 1, alcohol 11 must be resolved. Several methods are available,[5] one of which involves the use of R-(+)-α-methylbenzylisocyanate[6] as the resolving agent. The resolved alcohol is then protected with a t-butyldimethylsilyl group[7] to give 5.

The preparation of the butenolide 6 (Scheme III) involves some interesting chemistry. Furfuryl alcohol is treated with n-butyllithium to give the dianion, and metallation of the furan ring occurs α to the oxygen.[8] The dianion is treated with molecular oxygen, and the carbanion reacts to form the hydroperoxy anion.[9] Disproportionation of this anion could occur[8] to give directly the 2-alkoxy furan, and workup would afford the butenolide 12. Even if disproportionation

Scheme III



does not occur, the resulting hydroperoxides can be reduced to 12 with triphenylphosphine.[10] The alcohol in 12 is then converted to an aldehyde using activated MnO_2,[11] and 6 is obtained. Compound 6 is interesting in that several tautomeric forms exist. Evidence[12] seems to indicate that form C may be predominant. However, this probably should not matter since only form C will be reactive in the first step of the synthesis (vide infra), and forms A and B will eventually drain over to C.

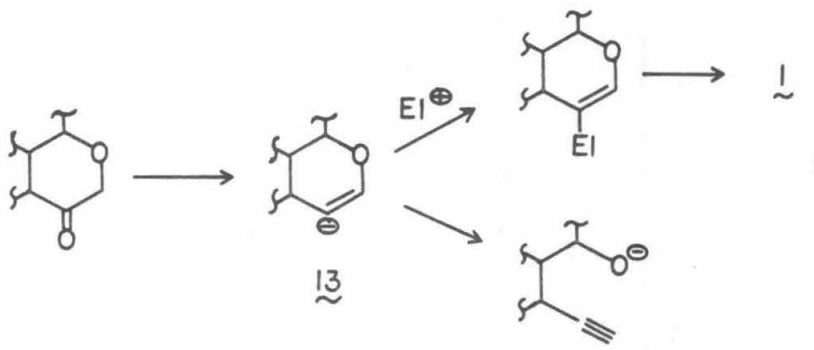
Consider now the total synthesis outlined in Scheme I. The first step in the sequence is a cycloaddition reaction of enol ether 5 to the α,β-unsaturated aldehyde 6. Such cycloadditions are well precedented,[12] especially with heteroatom substituents α to the aldehyde carbonyl. The cis geometry of the enol ether 5 and the endo orientation of the two fragments during the addition establishes the required

all cis stereochemistry in the dihydropyran ring of 7. At this point in the synthesis, two diastereomers will form and will have to be separated at some point in order to ultimately obtain the correct stereoisomer of 1. However, one of the diastereomers may be formed preferentially by asymmetric induction in the cyclization due to the optical activity of 5.[14]

The initial ring construction is followed by several functional group manipulations. Reduction of the lactone in 7 with diisobutylaluminum hydride liberates the desired aldehyde in 8. The silicon blocking group is removed[7] with anhydrous fluoride ion (n-$Bu_4N^+F^-$), and after neutralization, the lactol 9 is formed.[15] By analogy to the cyclization of morroniside (3),[2] mildly acidic conditions are used to cyclize 9 to 10.

The final construction (Scheme IV) utilizes the ketone formed during the metal hydride reduction of 7. The desired vinyl anion 13 can be generated under mild conditions using a 2,4,6-triisopropylbenzenesulfonylhydrazone adduct in a modified Shapiro olefin synthesis.[16] Capture of the vinyl anion with an electrophile (El^+) such as dimethylcarbonate would lead directly to sarracenin (1). As an alternative, dimethylformamide will capture the vinyl anion to give an aldehyde,[16] and subsequent oxidation and esterification will again lead to 1. Fragmentation of the ring in this final step to give an alkoxide and a terminal acetylene is a possibility, but careful control of the reaction at a low temperature should prevent it.[17]

Scheme IV

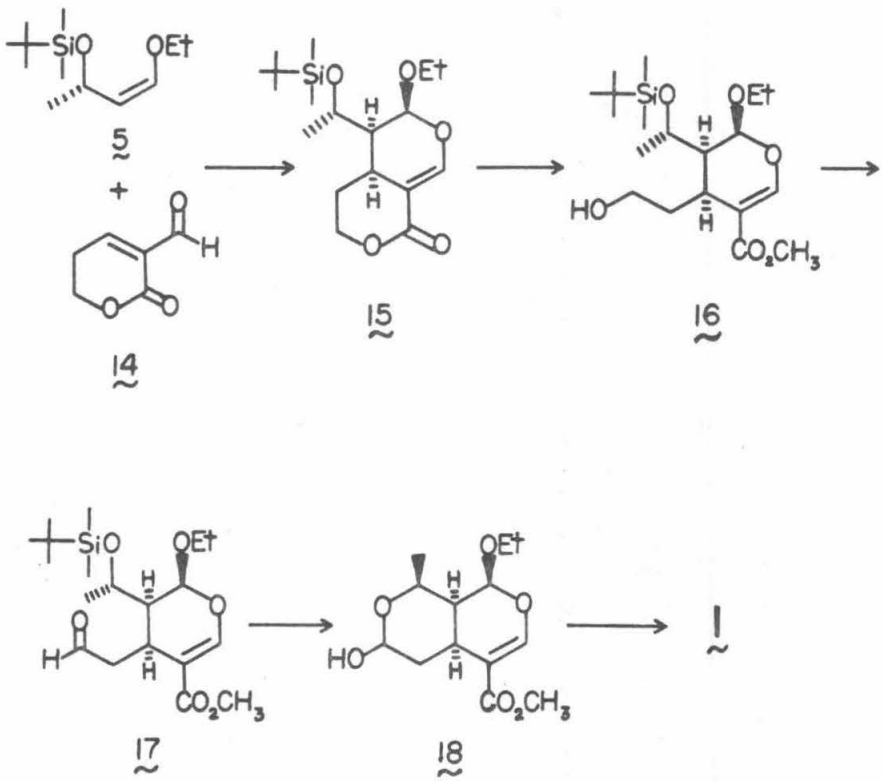


A second approach to the synthesis of sarracenin is proposed (Scheme V) in which the possibly dangerous vinyl anion intermediate 13 is avoided. Conceptually, this proposed route is almost identical to the first one above. The only major difference is the use of a different dienophile, 14.

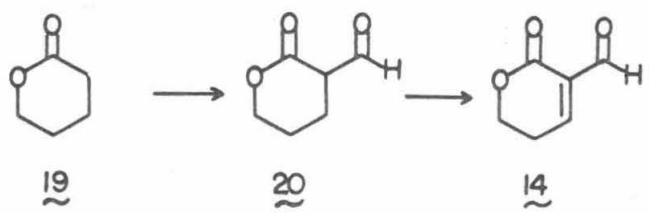
Dienophile 14 can be easily prepared from δ-valerolactone, 19, (Scheme VI). Treatment of 19 with reagents such as triethylorthoformate or t-butoxybis(dimethylamino)methane[11] affords the dione 20. To obtain 14, the olefin is then introduced by alkylating the enolate of 20 with phenylselenenyl chloride, oxidizing to the selenoxide, and eliminating selenenic acid.[18]

This synthesis of sarracenin (Scheme V) again depends on a cycloaddition; 5 and 14 react to give 15 with all the appropriate functionality and stereochemistry.[12] Transesterification of the

Scheme V



Scheme VI



lactone in 15 with methanol gives the desired carbomethoxy group and a free terminal alcohol in 16. The alcohol can be oxidized under mild

conditions such as pyruvate ester formation and photolysis[19] to the aldehyde 17, followed by silyl group removal and formation of the lactol 18. Note that morroniside (3) and 18 are virtually identical. Acid catalyzed cyclization[2] of 18, presumably through intermediate 4, leads directly to sarracenin (1).

In summary, the second proposed synthesis of sarracenin (Scheme V) probably offers the easier route to the target molecule, but the first proposed synthesis (Scheme I) deals with potentially much more interesting chemistry.

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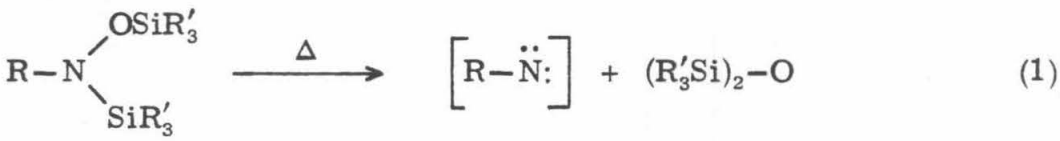
PROPOSITION III

Abstract: Modification of nitrene precursors with new, more easily eliminated substituents is proposed.

Recent work in the development of new methodology in generating nitrenes has centered on the thermolysis (Eq. 1) of silylated hydroxylamines (1a)[1] and silylated hydroxamic acids (1b).[2] This approach has



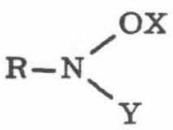
(1)

1

2

a, R = aryl
b, R = acyl

provided a basis for mechanistic studies of nitrenes,[1] as well as synthetic applications in a modified Lossen rearrangement[2] (1b → 2b) to generate isocyanates, R–N=C=O. Despite the relative ease and efficiency of these fragmentation reactions, moderate (90-110°C)[1] to high (140-160°C)[2] temperatures are still required to promote α-alimination of the siloxane fragment.



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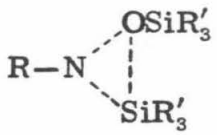

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Mechanistic evidence[1] indicates that the electronic characteristics of the oxygen and nitrogen substituents (3, X and Y, respectively)

dominate the course of the reaction. The nucleophilic character of oxygen and the electrophilic character of silicon in a proposed transition state, 4, are clearly important. The use of different substituents, X and Y, in nitrene precursor 3 to alter the electronics of the system, and thus facilitate the fragmentation at lower temperatures is proposed.

The ease of the α-elimination of fragment X–O–Y from 3 should be enhanced by increasing the effective electropositive character of both X and Y. This would result in a more nucleophilic oxygen species and a more reactive electrophilic center on nitrogen. Two types of substituents which fit these criteria are X = SnR_3 and Y = $Si(C_6F_5)_nR_{3-n}$.

The use of a trialkyltin substituent on oxygen is particularly attractive because of the pronounced nucleophilic character imparted to the oxygen atom.[3] Numerous organotin alkoxide reactions are based on this unique reactivity.[3] A variety of different organotin reagents react readily with nucleophiles such as hydroxides or alkoxides to give organotin alkoxide species. These reagents (stannyl halides, amines, and alkoxides) are available from commercial sources directly or via simple chemical preparations.

Electron deficient substituents such as fluorinated aralkyl silanes, $Si(C_6F_5)_nR_{3-n}$, are particularly well-suited as the electrophilic partner in these α-elimination reactions. The degree of electrophilic character of the Si atom can be controlled by the number of pentafluorophenyl groups which are attached. All three of the pentafluorophenylmethylsilyl chlorides are available,[4,5] and the efficient silylating capabilities of X–$Si(C_6F_5)Me_2$ (X = Cl, NH_2, NEt_2) are well

known.[5] Numerous other fluoroalkyl silanes are available,[4] and thus a high degree of control over the electronic character of Y in 3 is afforded.

Although SnR_3 and $Si(C_6F_5)_nR_{3-n}$ may well be used individually to activate the α-elimination in the formation of nitrenes, their use together will be illustrated below. The case of N-phenylhydroxylamine is shown in Scheme I. The hydrochloride salt of the hydroxylamine

Scheme I

$$Ph-NH-OH\cdot HCl \xrightarrow[[Me_2(C_6F_5)Si]_2-NH]{Et_3N} Ph-NH-OSi(C_6F_5)Me_2$$

5 6

$$\xrightarrow[2.\ ClSnBu_3]{1.\ base} Ph-N(Si(C_6F_5)Me_2)-OSnBu_3 \xrightarrow{\Delta}$$

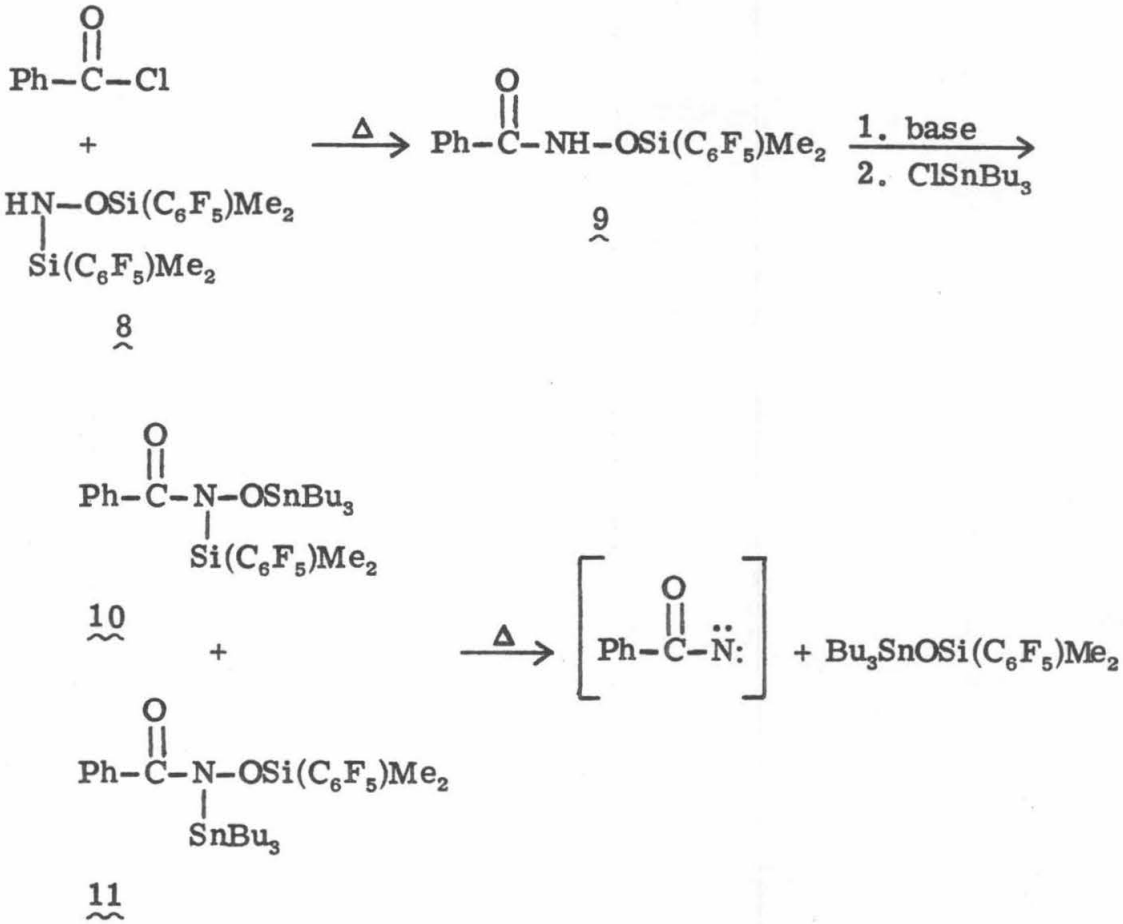
7

$$[Ph-\ddot{N}:] + Bu_3SnOSi(C_6F_5)Me_2$$

can be specifically O-silylated[6] with the fluorinated disilazane derivative 5.[5] The monosilylated compound 6 is metallated with a strong hindered base such as lithium 2,2,6,6-tetramethylpiperidide under conditions which allow the silicon to migrate to nitrogen;[6] the resulting alkoxide is trapped with tri-n-butyltin chloride to give the nitrene precursor 7. Subsequent α-elimination should occur under milder thermolysis conditions than that of the disilylated hydroxylamine.

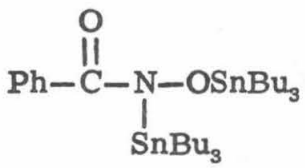
In an analogous approach, benzoyl chloride can be converted to phenylisocyanate according to Scheme II. The acid chloride and the

Scheme II



silylated hydroxylamine 8 react to form the hydroxamic acid derivative 9. Treatment of 9 with base and $ClSnBu_3$ could give a mixture of both 10 and 11 depending on the extent of migration of the silicon group to the now stabilized nitrogen anion. The desired nitrene precursor 10 should easily fragment as discussed above. Isomer 11 could also prove to be a suitable nitrene precursor because of a few cases in which a tin derivative participated in the generation of carbenes.[7] This problem might be avoided by preparing the bisstannyl derivative,

12, and testing its suitability as a nitrene precursor.



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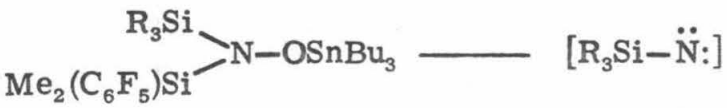
Depending on the degree of activation provided by these different substituents, it may be possible to use a substrate such as hydroxylamine 13 in generating the elusive[8] silyl nitrene 14.



13 14

Thus, the use of different oxygen and nitrogen substituents in hydroxylamines and hydroxamic acids to control the electronic characteristics of the expected α-elimination could be very valuable. Mechanistically, the range of investigations into nitrene chemistry could be extended, and synthetically, the utility of nitrenes would be enhanced by the much milder reaction conditions.

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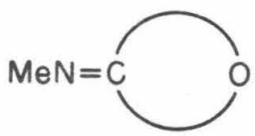
PROPOSITION IV

Abstract: Ion cyclotron resonance spectroscopy will be used to study the internal solvation of a cation by a suitable substituent possessing nonbonded electron pairs.

Ion cyclotron resonance (ICR) spectroscopy is a powerful new spectroscopic technique for studying the gas phase chemistry of ions, both cations and anions.[1] One of the big advantages of ICR is that ion-molecule reactions can be examined at moderately high gas pressures, 10^{-4} mm or higher. Under such conditions, the frequency of ion-molecule collisions is high enough that equilibrium between reactants and products can easily be reached. Because these reactions are in the gas phase, the intervention of solvent effects can be eliminated and and the intrinsic reactivities of molecules can be studied. By the same token, these same features of ICR make it a useful tool in investigating solvent effects on ion reactivity. Internal solvation of ions is one aspect of this area which has not received much attention. Thus, a study of internal solvation of ions in the gas phase by ICR is proposed.

The specific system chosen for this study is the cyclic imine 1.



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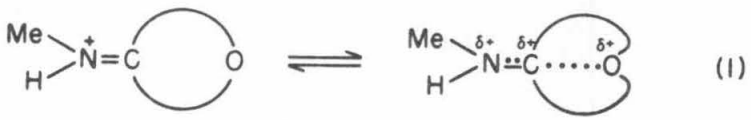
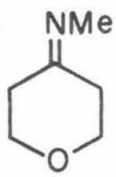
The ion of interest will be the cation generated by protonation of the imine (see below) which places a high degree of electrophilic character on carbon. The internal "solvent" or nucleophile will be the ether oxygen. The interaction of these two functional groups is shown in equation 1. This system is designed so that two aspects of internal



(1)

solvation may be investigated. The degree of interaction between the electrophilic and nucleophilic sites can be correlated with respect to the distance between the two centers. This distance can be controlled by altering the size and stiffness of the ring.[2] For example, a series of molecules such as 2-4 could serve to vary the carbon-oxygen distance. The second aspect to be considered is the dependence of the



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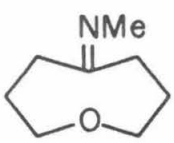

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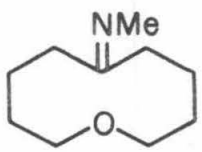

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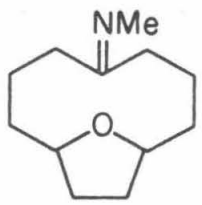
interaction on the electronic character of the nucleophile in structurally

equivalent systems. Molecules such as 5-7 could be used to test this



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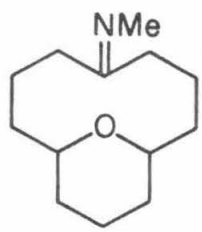

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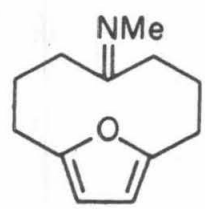

7

feature of the system. Each of these structures incorporates an ether fragment which formally corresponds to a common solution phase solvent: tetrahydrofuran, tetrahydropyran, and furan.

Determination of the extent of interaction is based on changes in the gas phase basicity (GB)[1] or proton affinity (PA)[1] of the imine. ICR spectroscopy is particularly well suited for evaluation of these physical properties. The proton affinity of common functional groups such as amines[3] are very sensitive to structural and electronic changes in surrounding substitutents. The imine should be just as sensitive to changes as amines. Although virtually no information is available on the gas phase reactivity of imines, the proton affinity probably would not differ too much from that of pyridine (PA = 225 kcal/mol)[4] and should be much higher than that of ammonia (PA = 207 kcal/mol).[3] Because the proton affinities of ethers are so much lower [PA (diethyl ether) = 199 kcal/mol][1b] than that of amines, the site of protonation of the substrate molecule at equilibrium will be the imine nitrogen exclusively.

As the substrate 1 increases in size and flexibility to permit a greater degree of internal solvation (eq 1), a number of factors will cause a change in the proton affinity of the imine. As the size of the molecule increases, the PA will increase.[1] As the number of bonds between the ether and the imine increases, the electron-withdrawing inductive effect will rapidly diminish to a negligible level.[5] Consequently, this component of the PA will increase to a certain point and then remain constant. Finally, the increased ring size will allow the ether oxygen to approach the protonated imine in a manner analogous to the nucleophilic approach to a carbonyl invoked by Baldwin[6] and and correlated by Bürgi.[2] These three factors can be sorted out by measuring the trend in PA of the imine hydrocarbon analogues (ether removed). These data would account for the change in PA due to changes in molecular size. In the larger molecules where the inductive effect of oxygen is negligible, the change in PA due solely to the field effect of oxygen can be estimated.

An estimate of the distance between the electrophilic and nucleophilic sites is a much more difficult problem. If the attraction between the two centers were strong enough, perhaps an X-ray crystallographic analysis would provide the data.[2] Otherwise, a very crude analysis might be possible using space-filling molecular models and by making a number of assumptions about preferred molecular conformations.

Thus, measuring and evaluating the dependence of the proton affinity on the proximity of the ether oxygen in 1 would appear to be

quite feasible. In principle, the effect of other "nucleophilic" functional groups such as thioethers, ketones, and olefins could also be investigated. Such studies could yield data applicable to internal solvation of cations in other more diverse chemical systems.

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PROPOSITION V

Abstract: The preparation and use of chiral acyloxyborohydride reagents are proposed.

Acyloxyborohydrides $\underset{\frown}{1}$ are relatively new and little used reducing agents. Until recently, only a few examples of these

$$M^+ \ ^-BH_n(O_2CR)_{4-n}, \qquad n = 1,2,3$$

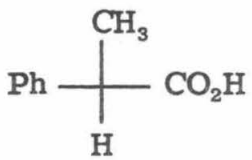
$\underset{\frown}{1}$

reagents had been reported[1] and their reactivity was essentially unknown. Investigations into the reduction of indoles with sodium borohydride/acetic acid ($NaBH_4$/HOAc), however, led Gribble and coworkers[2] to postulate the probable intermediacy of acyloxyborohydride species as reactive intermediates. Subsequently, the preformed reducing agents, $NaBH(OAc)_3$ and $NaBH_3(OAc)$, were used in the selective reduction of aldehydes[3] and the reduction of amides,[4] respectively. The flexibility of these reagents was demonstrated by the use of different carboxylic acid media and thereby modifying the nature of the acyloxy substituent. This versatility promised a potentially valuable application in another area, that of asymmetric induction in chemical reactions. Therefore, the use of chiral acyloxy ligands in the preparation of chiral acyloxyborohydride reagents is proposed.

These new chiral reducing agents have a number of advantages. The acyloxyborohydrides are easy to prepare; to form the reagent, $NaBH_4$ and the carboxylic acid are heated to reflux in a solvent such

as benzene for one hour.[3] The nature of the reagent may be altered in a variety of ways. The number of acyloxy groups may vary from one to three (see 1), and the nature of the chiral group may change over a wide range. The ready availability of chiral carboxylic acids,[5] many of which are commercial products, is an enormous advantage.

The capability of tailoring the chiral environment around the boron atom is particularly important in increasing any potential asymmetric interaction between the substrate and the reducing agent. For example, the optically active acids hydratropic acid 2 and mandelic acid 3 would make suitable acyloxy substituents. The hydratropic acid



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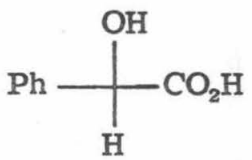

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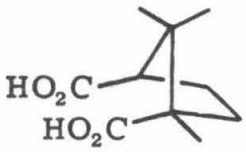
2 would be most suitable for nonpolar hydrocarbon substrates, while the mandelic acid 3 would interact more strongly with a polar substrate. Conformationally mobile acyloxy fragments such as those from 2 and 3 could probably be considered as functioning as tightly bound chiral solvent during the reduction.

Because more rigid acyloxyborohydride reagents may induce higher levels of asymmetric induction, a number of structures may be imagined which utilize dicarboxylic acids. Chiral diacids[5] such as (+)-camphoric acid 4, L-(-)-malic acid 5, and (+)-tartaric acid 6 could be used. These would be most useful in preparing diacyloxy



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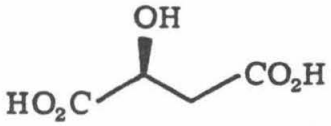

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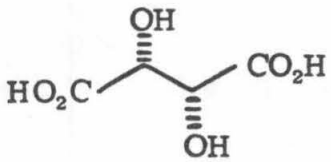


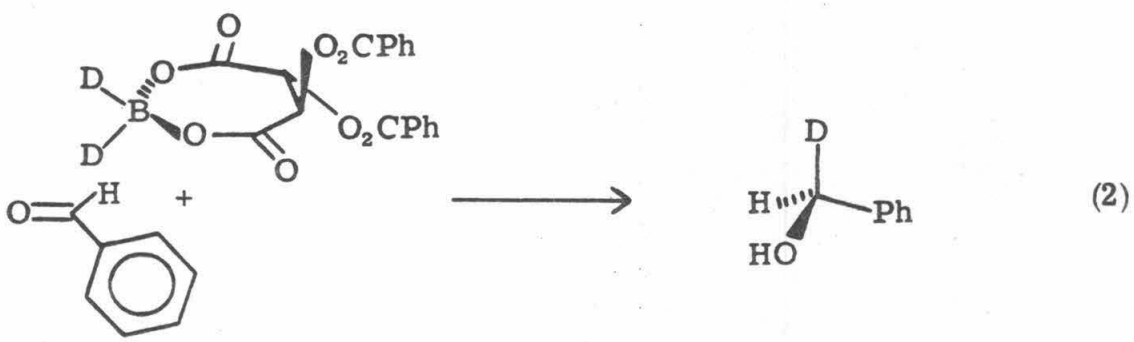
6

compounds such as 7. The hydroxy acids 5 and 6 are particularly interesting in that intramolecular deprotonation of the hydroxyl group by the borohydride would lead to a more rigid bicyclic system. Such a reaction with a malic acid fragment is shown below (eq 1). Whether the new reagent 8 would function any better than 7 in promoting asymmetric reductions is not certain.

7 8 (1)

A test can be devised to probe the suitability of these new borohydrides as asymmetric reducing agents. Recently, Midland and coworkers[6] used B-3α-pinanyl-9-borabicyclo[3.3.1]nonane to reduce benzaldehyde-α-d to the optically active (S)-(+)-benzyl-α-d alcohol with nearly quantiative asymmetric induction. A similar reaction could be attempted using benzaldehyde and the adduct from $NaBD_4$ and

(-)-dibenzoyl-L-tartaric acid (eq 2). If the steric interference between



(2)

the phenyl group of the aldehyde and the benzoyl group of the borohydride reagent is great enough, then an asymmetric reduction should occur to give the same (S)-(+)-benzyl-α-d alcohol that Midland obtained.

In summary, there is great potential for use of chiral acyloxyborohydride reagents in asymmetric reductions. An investigation of the chemistry of these new reagents would surely prove fruitful.

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