I. THE STEREOCHEMISTRY OF THE [3,3] SIGMATROPIC REARRANGEMENT OF 1,5-DIENE-3-ALKOXIDES

II. STEREOSELECTIVE ALDOL CONDENSATIONS VIA DIALKYLBORON ENOLATES

Thesis by

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To My Parents

"... That is the only way I ever heard of research going. I asked a question, devised some method of getting an answer, and got — a fresh question."

H. G. Wells
"The Island of Dr. Moreau"

"The idea is like grass. It craves light, likes crowds, thrives on crossbreeding, grows better for being stepped on."

U. K. Le Guin
"The Dispossessed"

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ABSTRACT

A study was carried out on the [3,3] sigmatropic rearrangement of the potassium salts of the four diastereomers (both cis,trans and erythro,threo) of 1-(1-methoxy-2-butenyl)-2-cyclohexen-1-ol. It was found that these rearrangements proceed in a concerted fashion predominately via chair-like transition states to give diastereomers of 3-(3-methoxy-1-methyl-2-propenyl)-cyclohexanone. The application of these modified oxy-Cope rearrangements to the synthesis of (±)-erythro-juvabione is reported.

A detailed investigation of the enolization of a variety of ketones and carboxylic acid derivatives with dialkylboryl triflates in the presence of a tertiary amine and the subsequent aldol condensations of these boron enolates was conducted. The stereochemistry of the enolates formed from acyclic ketones was found to be dependent on the structure of the ketone, the dialkylboryl triflate, and the tertiary amine. A mechanism for the enolization involving initial coordination of the boryl triflate to the ketone carbonyl with subsequent deprotonation by the amine is proposed to explain the results. The boron enolates derived from these acyclic ketones undergo aldol condensation with a number of aldehydes in good yield. Consistently good correlation

was observed between the enolate geometry and the product aldol stereochemistry for these acyclic ketones regardless of the structure of the ketone or the boron ligands. However, for the boron enolate derived from cyclohexanone the aldol stereoselectivity was dependent on the boron ligands and the solvent. In this case, the use of a cyclopentylthexylboron enolate in tetrahydrofuran as solvent resulted in complete stereocontrol in the condensation. Although simple esters and amides cannot be enolized with the triflate reagents, tert-butyl thiopropionate was readily converted to the trans-enolate. The stereoselectivity of the aldol condensations of this enolate are also dependent on the boron ligands and the solvent; again, the proper choice of these parameters allowed total stereocontrol of the condensation. It was found that carboxylic acids could be converted to the dialkyl boron enediolates and the aldol condensations of these species were used to probe the relative reactivity of cis- and trans-enolates.

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CHAPTER I

Stereochemical Study of the [3,3] Sigmatropic Rearrangement of 1,5-Diene-3-alkoxides. Application to the Stereoselective Synthesis of (±)-Juvabione

Introduction

In 1975 we[1] reported the observation that the oxy-Cope rearrangement of diene alkoxide 1a proceeded at approximately 10^{12} times the rate of the corresponding alcohol 1b (eq 1).[2] In subsequent investigations, we[3] and others[4] have established that these initial alkoxide-promoted rate accelerations are generalizable to other systems (eqs 2 and 3).

(1)

1 a, M = K b, M = H 2

(2)

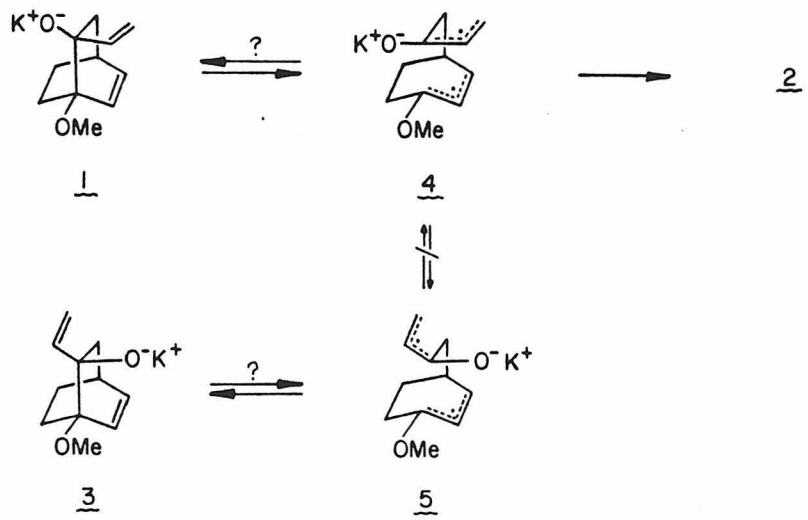
X = H, OMe, SPh

(3)

In spite of the apparently "concerted" nature of these rearrangements, only one published experiment bears on this important issue.[2] In this regard, we[1] found that, under conditions in which 1a underwent rearrangement with a half-life of 1.4 min (THF, 60°C), the diastereoisomeric

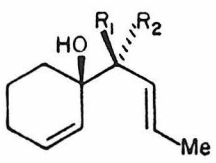
alkoxide 3 was stable for ca. 24 h. While these experiments contribute permissive evidence for the concerted nature of the transformation of 1a → 2a, it does not rule out a nonsynchronous mechanism. The observations could be equally well explained by assuming that single-bond cleavage occurs in both substrates via either a homolytic or heterolytic pathway[5] but that the rotational barrier for the interconversion of these intermediates (cf. 4 and 5) is large relative to the recombination barrier 5 → 3 (Scheme I, homolysis).

Scheme I



In the present study, two sets of diastereoisomeric dienols 6a,6b and 7a,7b were chosen as informative sub-

strates. In the rearrangement of dienols 6ab and 7ab, it should be possible to examine two structural featues associated with each reaction: transfer of chirality and creation of specific product olefin geometry.



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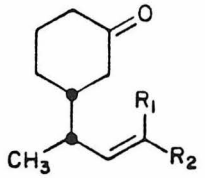

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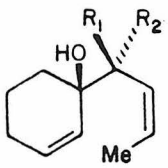

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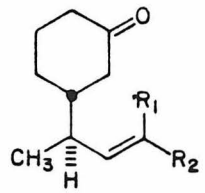
a; R_1 = H, R_2 = OMe

b; R_1 = OMe, R_2 = H



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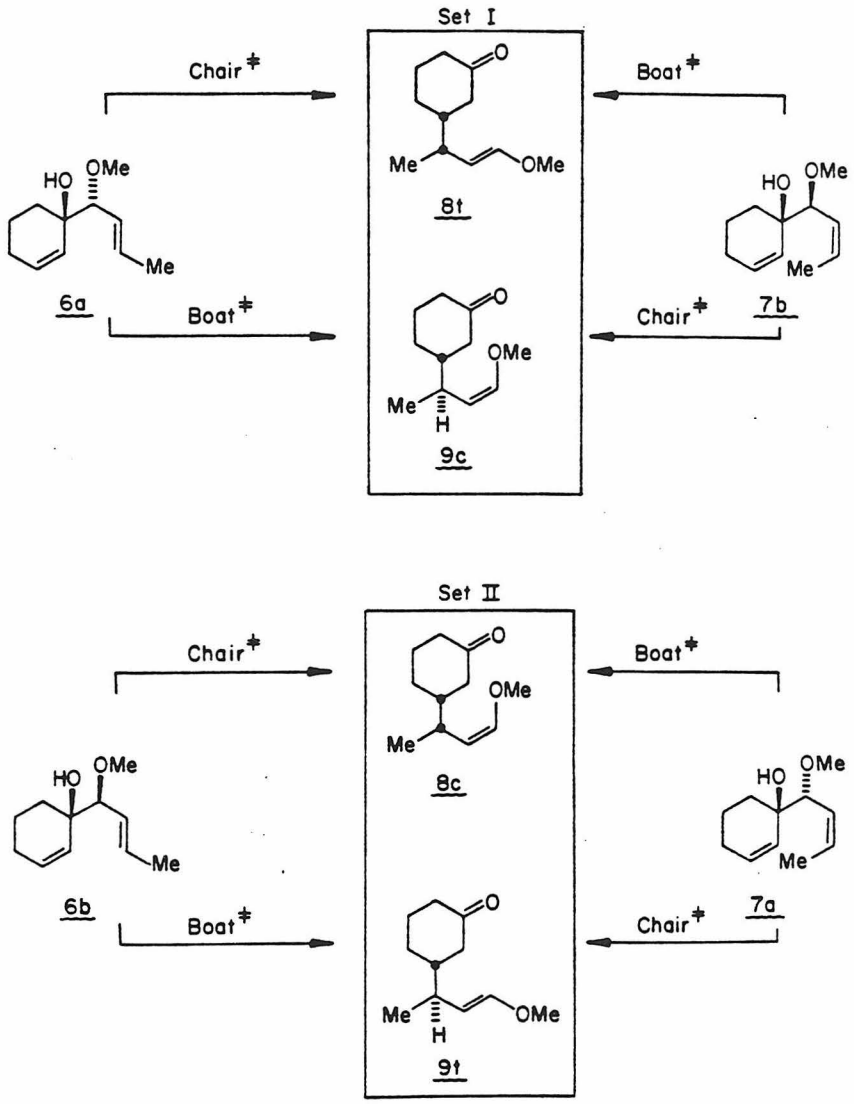
t; R_1 = H, R_2 = OMe

c; R_1 = OMe, R_2 = H

As illustrated in Scheme II, if any given dienol underwent concerted rearrangement, only two predictable ketonic products (product set I or II) would be produced via chair and boat transition states (e.g., 6a → 8t + 9c). In the event that all four dienols rearranged in a concerted fashion, the dienol pair 6a and 7b will afford only ketones 8t and 9c (set I), while dienols 6b and 7a will give only ketones 8c and 9t (set II). If the above situation were found to be the case, complete erythro-

Scheme II

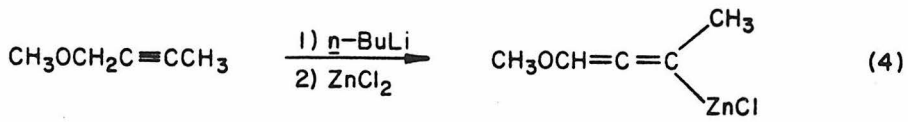


and threo-dienol stereochemical assignments can be unambiguously made for the diastereoisomeric trans-olefin pair 6a,6b and cis-olefin pair 7a,7b. On the other hand, from any given dienol, the co-occurrence of more than two ketone rearrangement products or a combination of any two

products derived from sets I and II constitutes unequivocal evidence for nonconcerted rearrangement from that substrate.

Results and Discussion

Substrate Synthesis. The four dienols 6a,b and 7a,b were prepared via stereoselective trans and cis reduction of the diastereoisomeric hydroxy acetylenes 11. Metallation of 1-methoxy-2-butyne[6] with n-butyllithium (-79°C, 30 min) followed by the addition of zinc chloride (1 equiv) resulted in the formation of the presumed organozinc reagent 10 (eq 4). The addition of cyclohexenone to 10



(4)

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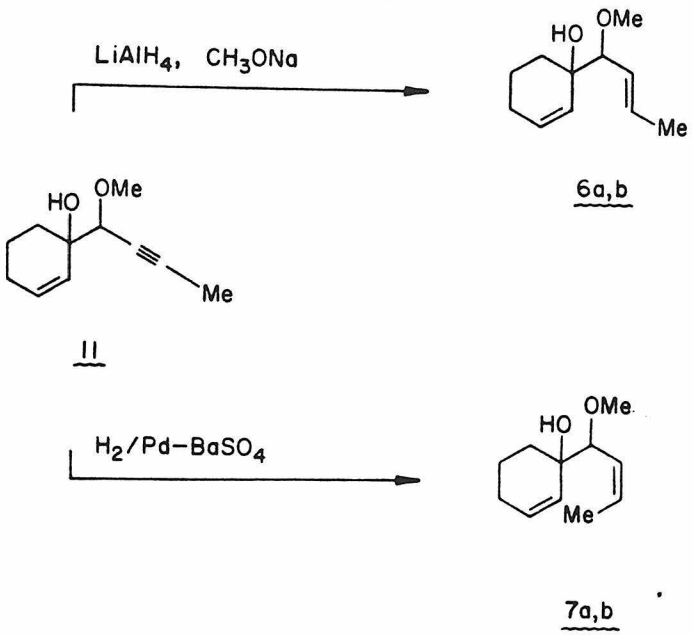
afforded the acetylenic alcohol 11 in 95% yield as a 65:35 mixture of diastereoisomers. A number of the advertised procedures for the reduction of acetylenes to trans-olefins were found to convert acetylene 11 to a mixture of trans-olefin 6 and a compound whose spectra were consistent with the allene, 1-(1,2-butadienyl)-2-cyclohexen-1-ol (12). For example, sodium/ammonia reduction[8] gave an 80:20 ratio of 6:12 in 90% yield, while lithium aluminum hydride[9] afforded a 94:6 ratio of 6:12 in only 60% yield



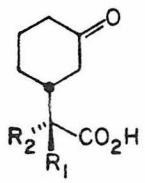
due to over-reduction. However, it was found that a 1:2 molar ratio of $LiAlH_4$:CH_3ONa[10] completely suppressed over-reduction and afforded an 85% yield of 6a,b containing only a trace (1%) of allene 12 and cis-alcohols 7a,b ($\leq$1%). Presumably, 12 is formed by elimination of methoxide from a vinyl anion intermediate; thus, the success of the mixed reagent may be due to delivery of the hydride predominantly to the acetylene carbon nearest the hydroxyl. Although these conditions are known to effect delivery of the hydride exclusively to the acetylene carbon proximal to the hydroxyl function in propargylic alcohols,[10] its success in a homopropargylic system was a

pleasant surprise and poses some interesting mechanistic questions. The diastereoisomeric mixture of cis-dienols 7a,b was obtained in 76% yield by catalytic hydrogenation of 11 over palladium on barium sulfate poisoned with quinoline[11] (6a,b:7a,b = 3:97). The two sets of diastereoisomeric alcohols 6a,b and 7a,b were cleanly separated by chromatography on silica gel impregnated with silver nitrate.[12] Although independent stereochemical assignments were not determined for the two sets of erythro-threo-alcohols, the following study (vide infra) leads to the unambiguous stereochemical assignments for 6a, 6b, 7a, and 7b as denoted in Scheme II.

Sigmatropic Rearrangements. Initial rearrangements were carried out on the unseparated diastereoisomeric trans-dienol mixture 6a,6b to determine optimal conditions and yields. In numerous preparative runs, it was found that the potassium alkoxides derived from 6a,6b (65:35) completely rearranged in diglyme at 110°C over a 38-h period to the mixture of ketonic products 8 and 9 in 75-80% isolated yields. Under identical conditions, the potassium alkoxides derived from the diastereoisomeric cis-dienols 7a,7b (65:35) afforded, in addition to the desired ketones 8 and 9, a 40% yield of an unstable trienol derived from the base-catalyzed elimination of methanol. Proton NMR analysis suggested its structure to

be 1-(1,3-butadienyl)-2-cyclohexen-1-ol. In contrast, the attempted thermal rearrangement of trans-dienol mixture 6a,b (250°C, 4 h) was totally unsuccessful, yielding products derived from β-hydroxy olefin cleavage, recovered starting material and intractable polymeric byproducts.

Structure determination of the ketonic rearrangement products 8t, 9c, 8c, and 9t was accomplished by combined degradation and spectroscopic techniques. Determination of the relative stereochemical relationships between the ring and methyl-bearing side chain stereocenters for sets of ketones 8 and 9 was accomplished by degradation (O_3, CrO_3) of the respective ketones to the erythro- and threo-keto acids 13a and 13b. The structures of these diastereoisomeric acids have been unequivocally established by X-ray



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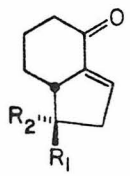

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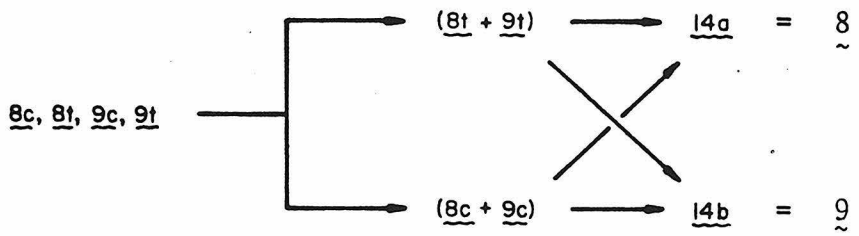
a, R_1 = H, R_2 = CH_3
b, R_1 = CH_3, R_2 = H

analysis.[13,14] It was found that product diastereoisomer analysis (8t + 8c:9t + 9c) was most conveniently carried out by gas chromatography on the bicyclic ketones 14a and 14b which were readily obtained from the respective ketones 8a,b and 9a,b in excellent yield by acid-catalyzed

aldol condensation.

No single analytical technique was found to be suitable for complete reaction product analysis. Nonetheless, the pairs of diastereoisomeric trans-olefinic ketones (8t + 9t) could be readily resolved from the cis-olefinic ketones (8c + 9c) analytically by gas chromatography to give product ratio, R_1 (8t + 9t):(8c + 9c), for each rearrangement experiment. This ratio was also cross-checked by ^{1}H NMR analysis of the unpurified product mixture. The vinyl protons (-CH=CHOMe) for the trans isomer pair appeared at 6.20 ppm (J = 13 Hz), while the cis isomer pair appeared at 5.88 ppm (J = 6 Hz). The successful determination of the diastereoisomer ratios, R_2-trans (8t:9t) and R_2-cis (8c:9c), was based on the observation that the trans-olefin pair (8t + 9t) could be separated from the cis-olefin pair (8c + 9c) by medium pressure column chromatography. Accordingly, for each experiment the diastereoisomer ratios R_2-trans (8t:9t) and R_2-cis (8c:9c) were determined by the following procedure: (a) preparative chromatographic separation of the trans and cis isomer pairs (8t + 9t) and (8c + 9c); (b) acid-catalyzed aldol condensation of each isomer pair to the diastereoisomeric ketones 14a and 14b which were readily resolved by GLC; (c) GLC analysis to determine the product ratios, R_2-trans and R_2-cis (14a:14b = 8:9) and consequently



$$R_1 = \frac{(8t\ 9t)}{(8c\ 9c)} \qquad R_2 = \frac{14a}{14b} = \frac{8}{9}$$

the ratios 8t:9t and 8c:9c. Thus, for each experiment, the determination of ratios R_1,R_2-cis, and R_1,R_2-trans enabled the complete product analysis, 8c:8t:9c:9t, to be determined.

The erythro and threo diastereoisomers of the trans-dienols 6a and 6b were separated by column chromatography. The first-eluted major isomer, called trans-dienol A, was treated with KH (diglyme, 110°C, 37.5 h). Product analysis by analytical GLC (Carbowax 20M) indicated a trans:cis ratio (8t + 9t):(8c + 9c) = 96:4. The trans isomers (8t + 9t) were separated from the cis isomers (8c + 9c) by medium-pressure chromatography. Treatment of the trans pair (8t + 9t) containing 1% of cis pair with acid (THF, H_2SO_4, 4 h) afforded a ratio of 14a:14b (8t:9t) = 98:2 by analytical GLC (Carbowax 20M). When corrected for the 1% cis pair contamination in (8t + 9t),

the ratio of 8t:9t was calculated to be 99:1. Similar treatment of the cis isomer pair (8c + 9c) afforded a ratio of 14a:14b (8c:9c) = 4:96. Therefore, the product ratio derived from trans-dienol A was found to be: 8t (96%), 9c (4%), 8c (≤1%), 9t (≤1%). Following the identical analytical procedure, the second-eluted trans dienol isomer, called trans-dienol B, was subjected to the identical rearrangement conditions. Product analysis was carried out as described above for the diastereoisomeric trans-alcohol A. The product ratio derived from trans-dienol B was found to be: 8t (≤1%), 9c (≤1%), 8c (77%), 9t (23%). These results confirm that trans-dienol A affords ≥99% product set I (8t + 9c), while trans-dienol B affords ≥99% product set II (8c + 9t). Because of the absence of crossover products (within experimental error), the product distribution obtained from the rearrangement of the diastereoisomeric trans alcohols A and B indicates that the stepwise rearrangement is not occurring (≤1%).

In a parallel series of experiments, the erythro and threo diastereoisomers of the cis-dienols 7a and 7b were separated by column chromatography. The first-eluted major isomer, called cis dienol A, obtained in 99% isomeric purity (1% trans-dienol A), was subjected to rearrangement and subsequent product analysis according to the identical format as described above. The ratio (8t

+ 9t:8c + 9c) was determined to be 98:2 by GLC analysis. Chromatographic separation of the trans (8t + 9t) and cis isomer (8c + 9c) pairs was carried out as previously described. Consecutive acid-catalyzed aldol condensation and GLC analysis of the trans pair (8t + 9t) afforded a ratio of 14a:14b (8t:9t) = 2:98. After correction for the 1% trans-dienol A contaminant (vide infra), the ratio 8t:9t was calculated to be 1:99. Unfortunately, due to the small quantities of the cis pair (8c + 9c) produced from cis-dienol A (2%), we were unable to determine the ratio 8c:9c. Nonetheless, the value of 8c + 9c = 2% indicated that the most conservative estimate for the extent of crossover is 2%. Therefore, the product ratio derived from cis-dienol A was found to be: 8t (≤1%), 9c (0-2%), 8c (2-0%), 9t (98%). Following the identical procedure, the second-eluted minor cis-dienol isomer, called cis-dienol B, was subjected to identical rearrangement conditions and product analysis. The observed product ratio derived from cis-dienol B was found to be: 8t (30%), 9c (70%), 8c (≤1%), 9t (≤1%). These results confirm that cis-dienol A affords ≥98% product set II (8c + 9t), while cis-dienol B affords ≥99% product set I (8t + 9c). Within the experimental error of our analytical scheme (±2%), no significant crossover was detected in the rearrangement of either cis-dienol A or B, again indicating

that the stepwise rearrangement is not occurring to an appreciable extent.

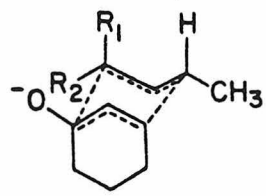
Alcohol Stereochemical Assignments. The foregoing data clearly indicate that all four isomeric dienol alkoxides rearrange via highly ordered transition states, and that no evidence for competing nonconcerted reaction pathways was observed. Based upon the conveyed stereochemical information in the reaction product (threo vs. erythro and cis vs. trans) and the unequivocally determined olefin geometry in each of the four dienols, it is possible to make unambiguous erythro and threo stereochemical assignments to all four dienols and to assign the transition state conformations (boat or chair) interrelating reactants and products. These stereochemical assignments in no way depend upon the a priori assumption of a preferred chair or boat transition state preference, but only upon the postulate that either chair or boat transition states are involved in these rearrangements. On this basis, trans-dienol A and cis-dienol A, both of which were derived from the major diastereoisomeric acetylene 11, are assigned as the threo isomers 6a and 7a, respectively. In a similar fashion, trans-dienol B and cis-dienol B are assigned as the erythro isomers 6b and 7b. The results obtained for the product ratios derived from the four dienols are summarized in Table I.

Table I. Rearrangement of Dienols 6a, 6b, 7a, 7b[a]

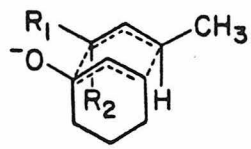
Alcohol	Product Composition, %			
	8t	9c	8c	9t
6a	96	4	≤1	≤1
7b	30	70	≤1	≤1
6b	≤1	≤1	77	23
7a	≤1	0-2[b]	0-2[b]	98

[a]Conditions: KH, 110°C, diglyme. [b]8c + 9c = 2%.

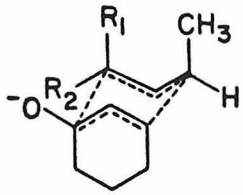
Transition State Conformations. In the rearrangements of all four dienols, chair transition states are preferred. As predicted from conformational analysis of chair and boat transition states, C_1 and B_1, the threo-trans-dienol 6a (R_1 = H, R_2 = OCH_3) should exhibit a larger $\Delta\Delta G^{\ddagger}$ between



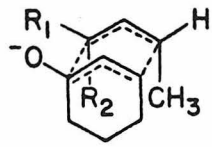
C_1



B_1



C_2



B_2

$\underset{\sim}{C}_1$ and $\underset{\sim}{B}_1$ than the erythro-trans-dienol $\underset{\sim\sim}{6b}$ ($R_1 = OCH_3$, $R_2 = H$).[15] The smaller $\Delta\Delta G^{\ddagger}$ observed in the rearrangement of $\underset{\sim\sim}{6b}$ is to be expected as a result of the destabilizing influence of the pseudo-axial methoxy substituent, R_1, in the transition state $\underset{\sim}{C}_1$. Likewise, in the rearrangements of diastereoisomeric cis-dienols $\underset{\sim\sim}{7a}$ and $\underset{\sim\sim}{7b}$, the chair transition state $\underset{\sim}{C}_2$ for $\underset{\sim\sim}{7b}$ ($R_1 = OCH_3$, $R_2 = H$) is again destabilized by the pseudo-axial methoxy substituent. These arguments correlate well with the observations that alcohols $\underset{\sim\sim}{6a}$ and possibly $\underset{\sim\sim}{7a}$ exhibit a greater preference for the chair transition state (96:4 and 98:2) in the Cope rearrangement than do $\underset{\sim\sim}{6b}$ and $\underset{\sim\sim}{7b}$ (77:23 and 70:30). Although the original studies by Doering and Roth[16] on the Cope rearrangement showed a large preference for the reaction to proceed via a chair transition state, later work,[17] mainly on Claisen rearrangements, has shown that hindered 3,3-rearrangements often proceed to some extent via boat transition states.

Conclusions

These results unequivocally demonstrate that the [3,3] sigmatropic rearrangements of 1,5-diene alkoxides possess the stereochemical characteristics of a concerted process. Consequently, these reactions can be employed in a

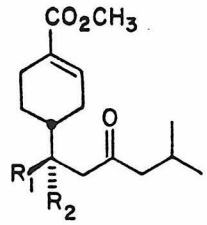
rational fashion in the stereoselective generation of asymmetry. In addition, we have found that dienols which are normally plagued with competing side reactions (β-hydroxy olefin cleavage) can be induced to rearrange in good yield as the conjugate bases. These innovations in the oxy-Cope rearrangement considerably extend the scope of these reactions. Just as important from a mechanistic standpoint, these studies demonstrate that the large rate accelerations associated with the substituent modification (R = OH → R = O^-M^+) do not change the reaction mechanism. It is quite obvious that the concepts

embodied in these studies can be applied to numerous other systems. Nonetheless, prior to the association of any mechanistic significance to related rate accelerations, a commonality of mechanism must be demonstrated between the neutral and charged substituents.

A Stereoselective Synthesis of (±)-Juvabione

Numerous terpenoid natural products possess methyl-bearing stereocenters on side chains proximal to a ring

fusion. Examples of molecules embodying this structural feature are the sesquiterpenes erythro-juvabione (15a) and threo-juvabione (15b), the sesterterpene ophiobolin C (16), as well as steroids (cf. 17) and numerous triterpenes. Recently, several methods have been developed to solve



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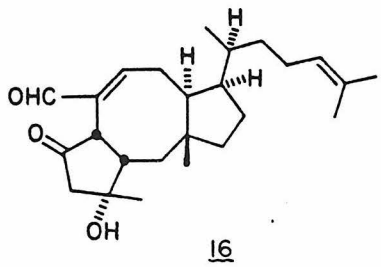
a, $R_1 = H$, $R_2 = CH_3$
b, $R_1 = CH_3$, $R_2 = H$



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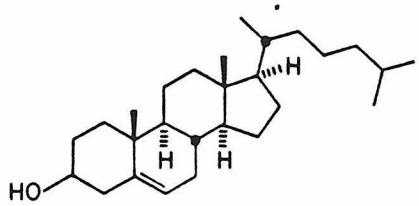

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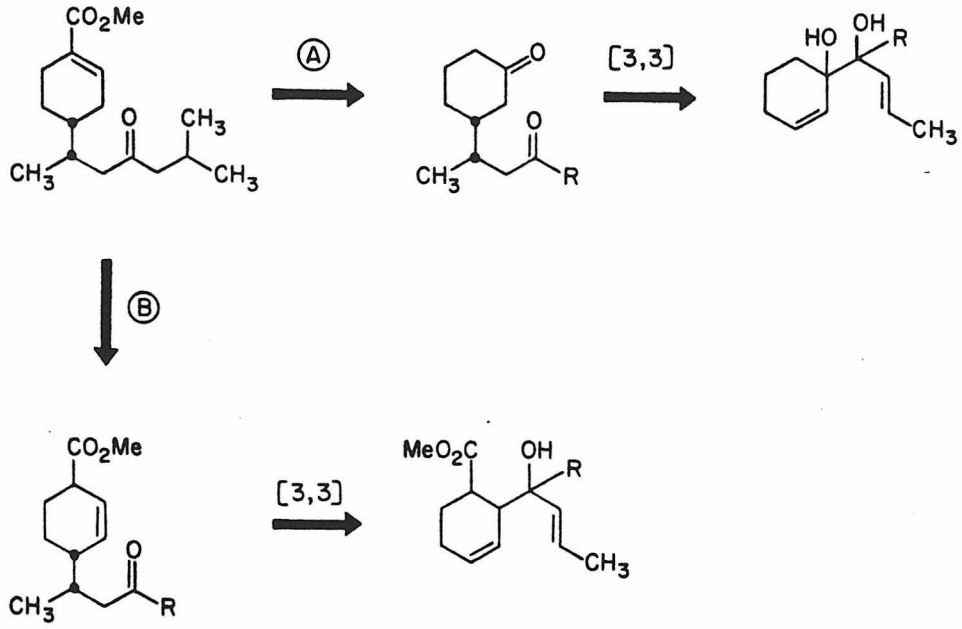
this ubiquitous stereochemical problem among which have been the creative contributions of Trost[18a,b] and Ficini.[18c] The present study reports an alternative protocol for the solution of this problem within the context of a synthesis of (±)-erythro-juvabione.

Juvabione, originally isolated by Bowers and co-workers[19] from Abies balsamea (L.) Miller, was assigned the structure 15b by analogy to the stereochemistry of todomatuic acid.[20] However, Saucy and co-workers synthesized both

enantiomers of 15a and 15b and found that comparison of their ORD spectra with that of the natural product,[21] provided by Cerny,[22] indicated 15a as the structure of juvabione. Although the source of Cerny's sample was originally believed to be a balsam fir, this identification has become uncertain.[23] More recently, Manville[23] reexamined juvabione and related compounds isolated from Abies balsamea and determined the structure of juvabione to be 15b by comparison of his ORD spectra with those of Saucy et al. Sakai and Hirose[24] found that juvabione from Douglas fir [Pseudotsuga menziesii (Mirb.) Franco] also possesses structure 15b. Although the identity of the natural source of 15a is in question, it appears that both 15a and 15b are natural products. Due to the fact that both 15a and 15b have been extensively referred to as juvabione and epi-juvabione, for clarity we shall refer to 15a and 15b as erythro- and threo-juvabione, respectively.

Although erythro-juvabione (15a) has been the target of numerous synthetic investigations,[18c,21,25] the only stereospecific synthesis has been that reported by Ficini and co-workers.[18c] A general alternative strategy for the synthesis of 15a is illustrated in Scheme III. In both routes the desired contiguous stereocenters can, in principle, be introduced via related [3,3] sigmatropic

Scheme III

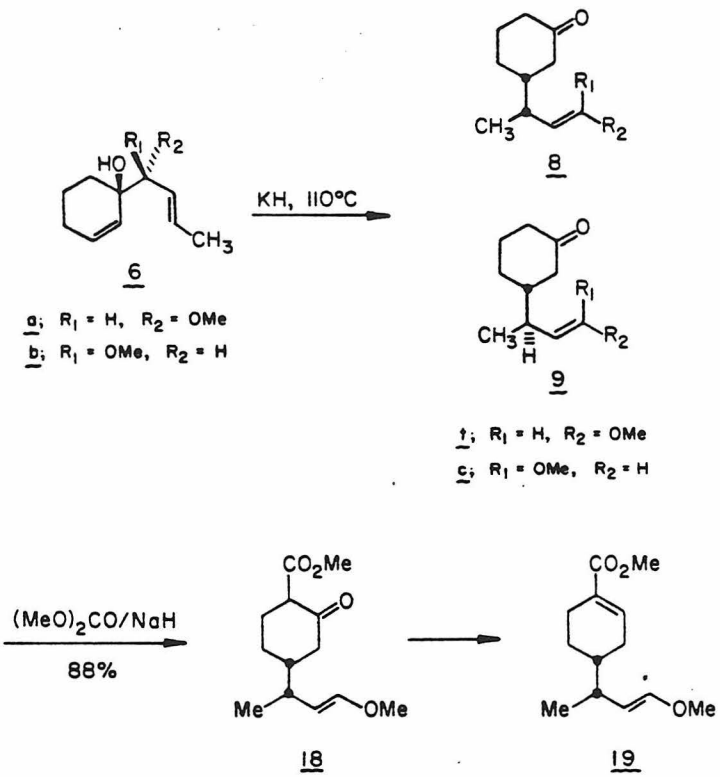


rearrangements. In the present study, path A was chosen in conjunction with the general stereochemical investigation of 1,5-diene alkoxide [3,3] sigmatropic rearrangements.

Based on the results presented in the preceding section, the 2:1 mixture of threo,erythro-dienols 6a, 6b, upon conversion to their respective potassium alkoxides with KH, underwent rearrangement in diglyme (110°C, 37 h) to ketones 8 and 9 in a ratio of 91:9 (77% yield) (Scheme IV). The ratio of 8:9 could be improved to 96:4 if pure threo-dienol 6a was employed in the reaction.

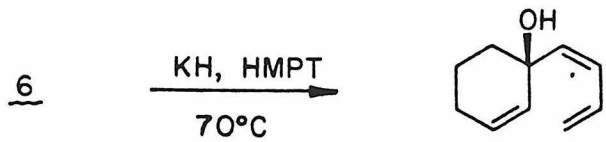
During the course of this investigation, we have found that the conditions employed for these rearrangements

Scheme IV



are critical. In an attempt to optimize the product ratio 8:9, it was reasoned that the stereoselectivity of the Cope process could be improved if the reaction could be carried out at lower temperatures. Unfortunately, this did not prove to be the case. Employing conditions which are known to provide maximal rate enhancements for these reactions, we have observed some side reactions which become important under these hyperbasic reaction conditions. For example, the rearrangement of 6 at 70°C with KH in HMPT results mainly in the formation of the unstable trienol 20 whose structure has been tentatively assigned by ^{1}H NMR. Apparently, the alkoxide is a strong

enough base under these conditions to effect elimination of methoxide from 6. Alternatively, the rearrangement of 6 with KH in diglyme at 70°C in the presence of 2 equiv of 18-crown-6 was successful. However, the ratio of 8:9 in this instance was 87:13 as compared with a 91:9 ratio in diglyme (110°C) in the absence of crown reagent. It thus appears that there is a ligand effect associated with 18-crown-6 which decreases the stereoselectivity of this rearrangement.



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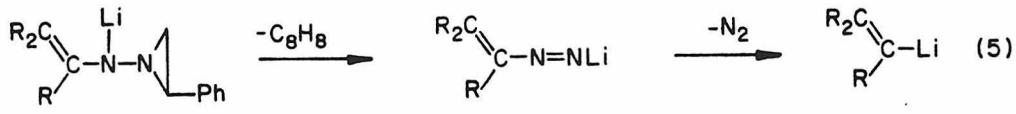
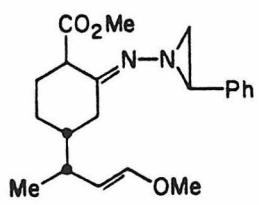
In the succeeding steps of the synthetic sequence, no effort was made to separate the undesired minor diastereoisomeric ketones (9t + 9c) (9%) formed during the oxy-Cope rearrangement. Carbomethoxylation of 8 followed by reduction ($NaBH_4$), esterification (CH_3SO_2Cl), and elimination afforded the α,β-unsaturated ester in an overall yield of 38%. In an effort to improve the overall yield in this latter transformation, we have investigated the use of a variant of the recently reported base-catalyzed β-keto ester tosylhydrazone elimination.[26] Based on the premise that N-aminoaziridines are tosyl-

hydrazine equivalents (eq 5),[27,28] the hydrazone 21 was prepared from the reaction of keto ester 18 with 1-amino-2-phenylaziridine.[29] The addition of 21 to 2.7 equiv of lithium diisopropylamide (THF, 0°C) resulted in the extrusion of styrene and nitrogen; subsequent protonation gave β,γ-unsaturated ester 22 which was equilibrated in situ with sodium methoxide to α,β-unsaturated ester 19 in an overall yield of 49%. It is noteworthy that these N-amino-aziridines, which are somewhat more nucleophilic than tosylhydrazine itself, appear to be generally applicable to the Shapiro elimination reaction.





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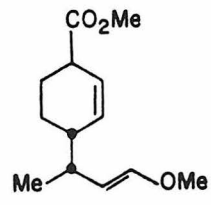

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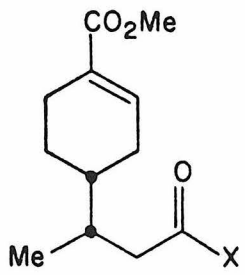
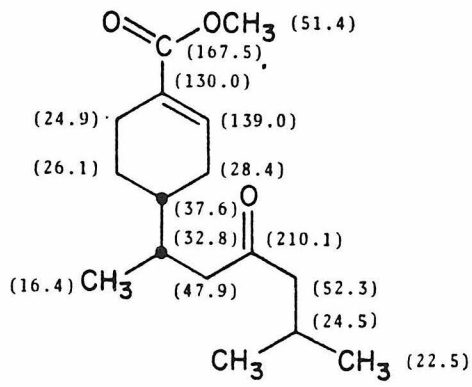
The latter stages of the synthetic plan were completed by acid hydrolysis of enol ether 19 followed by in situ oxidation of the resulting aldehyde to the carboxylic acid 23a with Jones reagent (77% overall). An attempt to effect both hydrolysis and oxidation simply by treat-

ment of 19 with Jones reagent was unsuccessful because the oxidative cleavage of the enol ether was found to be competitive with hydrolysis. The conversion of 23a to (±)-erythro-juvabione (15a) via acid chloride 23b and diisobutylcadmium[30] proceeded in 60% yield. Comparison of the spectra of (±)-15a above with spectra of an independently prepared sample of (±)-15a provided by Professor Ficini indicated that the samples were identical in all respects.



23 a; X = OH
b; X = Cl



15a (^{13}C-NMR)

The analysis of juvabione samples for stereochemical purity is complicated by the fact that both diastereoisomers have identical ^{1}H NMR, IR, mass spectra, and chromatographic properties; however, Manville and Bock[31] recently published carbon-13 NMR data which show differences between the diastereoisomers. Analysis of the (±)-erythro-juvabione (15a) prepared above indicates

the presence of 4-5% of (±)-threo-juvabione (15b). As discussed earlier, the source of this minor diastereoisomer has been identified with the oxy-Cope rearrangement step in the synthetic sequence.

Experimental Section

Infrared spectra were recorded on a Beckmann 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on Varian Associates A-60A (60 MHz) and EM-390 (90 MHz) spectrometers and are reported in ppm from internal tetramethylsilane on the δ-scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration, coupling constant (Hz), and interpretation. ^{13}C magnetic resonance spectra were recorded on a Varian Associates XL-100 (25.2 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ-scale. When multiplicities were determined on the ^{13}C spectra (by off-resonance decoupling) they are reported using the abbreviations given above. Mass spectra were recorded on a Dupont 21-492 B spectrometer. Mass spectral and combustion analyses were performed by the California Institute of Technology Microanalytical Laboratory.

Analytical gas-liquid chromatography was carried out on a Varian Aerograph model 1400 gas chromatograph equipped with a flame ionization detector using 6 ft by 0.125 in. stainless steel columns packed with 10% Carbowax 20M or 5% SE-30 on 60-80 mesh Chromosorb W or using a 20 ft by 0.125 in. Analabs Hi-Plate column with OV-17 packing. Preparative gas-liquid chromatography was performed on a Varian Aerograph model 90-P chromatograph using a 6ft by 0.25 in. copper column packed with 10% SE-30 on 40-60 mesh Chromosorb W. support. Medium pressure chromatography was performed using EM Laboratories LoBar Silica Gel 60 prepacked columns on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP Lab Pump. Silver nitrate impregnated silica

gel was made with Silica Gel 60 by the procedure of Djerassi, et. al.[12]

When necessary, solvents and reagents were dried prior to use: tetrahydrofuran, diglyme, diethyl ether, benzene (distilled from sodium metal/benzophenone ketyl); triethylamine (distilled from calcium hydride); methanesulfonyl chloride (distilled from phosphorus pentoxide); methanol (distilled from sodium methoxide); dichloromethane (passed through a column of Activity I Alumina); zinc chloride (fused four times under a vacuum of 0.1 mm). n-Butyllithium[32] was titrated by the procedure of Watson and Eastham.[33] Sodium and potassium hydrides[32] were purchased as dispersions in mineral oil, 50% and 22% respectively, and were not titrated before use. Reactions requiring an inert atmosphere were run under a blanket of nitrogen unless stated otherwise. All reaction temperatures refer to the reaction itself unless stated otherwise.

1-(1-Methoxy-2-butynyl)-2-cyclohexen-1-ol (11). To a -70°C solution of 100 mL tetrahydrofuran and 31 mL (71 mmol) of 2.28 M n-butyllithium in hexane was added 6.0 g (71 mmol) of 1-methoxy-2-butyne.[6] After 30 min. stirring at -70°C a solution of 9.7 g (71 mmol) of zinc chloride in 50 mL of tetrahydrofuran was added to the dark orange reaction to form a cloudy white solution. After 10 min. stirring 5.7 g (59 mmol) of 2-cyclohexen-1-one was added. The reaction was allowed to warm to room temperature where it was quenched with 10 mL of saturated aqueous ammonium chloride. After the addition of 150 mL ether the solution was filtered through Celite and concentrated in vacuo to approximately 50 mL of orange oil which was added to 100 mL ether. The ether solution was washed once with saturated aqueous sodium bicarbonate and twice with brine, dried (Na_2SO_4), and concentrated

in vacuo to yield 10.8 g of orange oil. Molecular distillation at 55°C (0.5 mm) yielded 10.2 g (95%) of pale yellow oil: IR (neat) 3500, 3030, 2940, 2300, 2230, 1650, 1450, 1375, 1085, 730 cm^{-1}; NMR ($CDCl_3$) 5.77 (m, 2, = CH-), 3.75 (q, 1, propargylic methine), 3.40 (s, 3, - OCH_3), 2.38 (b, 1, - OH), 2.14 to 1.47 (m, 9, aliphatic including ≡ C-CH_3 doublet at 1.85).

Anal. ($C_{11}H_{16}O_2$) C, H.

1-(1-Methoxy-(E)-2-butenyl)-2-cyclohexen-1-ol (6a, 6b). To a suspension of 1.3 g (33 mmol) of lithium aluminum hydride and 3.6 g (67 mmol) of sodium methoxide in 50 mL of tetrahydrofuran was slowly added 4.0 g (22 mmol) of acetylene 11. The mixture was heated at reflux for 45 min after which the reaction was quenched at 0°C by slow addition of 6.2 mL of water. The solution was filtered through Celite and concentrated in vacuo to yield 3.6 g of orange oil. The product was bulb-to-bulb distilled at 125°C (0.1 mm) to give 3.4 g (85%) of colorless oil: IR (neat) 3500, 3030, 2940, 1660, 1645, 1450, 1375, 1100, 970, 730 cm^{-1}. Analytical gas-liquid chromatography on the OV-17 column indicated the product contained no (<1%) cis-dienol 7.

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

The diastereoisomers, 6a and 6b, were separated by chromatography over silver nitrate impregnated silica gel (25% $AgNO_3$ by weight; 100 g of silica gel/g of 6; eluted with hexane:ethyl acetate, 70:30). 6a (trans-dienol A): ^1H NMR ($CDCl_3$) δ 5.50 (m, 4, =CH-), 3.25 (d, 1, allylic methine), 3.21 (s, 3, OCH_3), 2.61 (b, 1, -OH), 2.11 to 1.30

(m, 9, aliphatics including =CH-CH$_3$ doublet at 1.72); ^{13}C NMR ($CDCl_3$) δ 132.0 (d), 131.0 (d), 128.8 (d), 127.4 (d), 88.8 (d), 70.8 (s), 56.2 (q), 32.4 (t), 25.3 (t), 18.6 (t), 17.9 (q). 6b (trans-dienol B): ^{1}H NMR ($CDCl_3$) δ 5.50 (m, 4, =CH-), 3.31 (d, 1, allylic methine), 3.25 (s, 3, OCH$_3$), 2.30 (b, 1, OH), 2.11 to 1.30 (m, 9, aliphatics including =CH-CH$_3$ doublet at 1.71); ^{13}C NMR ($CDCl_3$) δ 131.2 (d), 130.9 (d), 129.6 (d), 126.8 (d), 88.8 (d), 70.8 (s), 56.5 (q), 31.6 (t), 25.4 (t), 18.3 (t), 17.9 (q).

1-(1-Methoxy-(Z)-2-butenyl)-2-cyclohexen-1-ol (7a, 7b). A rapidly stirred suspension of 3.3 g (18 mmol) of acetylene 11, 600 mg of 5% palladium on barium sulfate, and 36 drops of quinoline in 100 mL of methanol was hydrogenated at room temperature and atmospheric pressure until 400 mL (18 mmol) of hydrogen had been consumed (1 h). The solution was filtered through Celite and concentrated in vacuo to give a crude product which was chromatographed at medium pressure over silica gel (EM Laboratories size C LoBar column; eluted with hexane:ethyl acetate, 85:15) to yield 2.5 g (76%) of colorless oil: IR (neat) 3500, 3030, 2940, 1650, 1450, 1375, 1100, 730 cm^{-1}. Analytical gas-liquid chromatography on the OV-17 column revealed that 3% of the product was trans-dienol 6.

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

The diastereoisomers, 7a and 7b, were separated (and all but 1% of trans-dienol 6 removed) by chromatography over silver nitrate impregnated silica gel (25% $AgNO_3$ by weight; 100 g of silica gel/g of 7; eluted with hexane:ethyl acetate, 70:30). 7a (cis-dienol A):

^{1}H NMR ($CDCl_3$) δ 5.50 (m, 4, =C<u>H</u>-), 3.82 (d, 1, allylic methine), 3.25 (s, 3, OC<u>H</u>$_3$), 2.70 (b, 1, O<u>H</u>), 2.16 to 1.33 (m, 9, aliphatics); ^{13}C NMR ($CDCl_3$) δ 131.0 (d), 130.2 (d), 128.5 (d), 127.3 (d), 81.8 (d), 71.2 (s), 56.2 (q), 32.2 (t), 25.4 (t), 18.5 (t), 13.5 (q). <u>7b</u> (<u>cis</u>-dienol B): ^{1}H NMR ($CDCl_3$) δ 5.50 (m, 4, =C<u>H</u>-), 3.82 (d, 1, allylic methine), 3.25 (s, 3, OC<u>H</u>$_3$), 2.43 (b, 1, O<u>H</u>), 2.16 to 1.33 (m, 9, aliphatics); ^{13}C NMR ($CDCl_3$) δ 131.0 (d), 130.3 (d), 129.4 (d), 126.5 (d), 81.8 (d), 71.3 (s), 56.3 (q), 31.3 (t), 25.4 (t), 18.4 (t), 13.7 (q).

<u>Oxy-Cope Rearrangement of trans-Dienols 6a,b.</u> To a suspension of 2.0 g (50 mmol) of oil-free potassium hydride (from 8.9 g of 22% oil suspension) in 110 mL of diglyme under an argon atmosphere was added 3.0 g (17 mmol) of <u>trans</u>-olefin <u>6</u>. The solution was heated at 110°C for 37.5 h. The resulting dark brown solution was added to 50 mL saturated aqueous ammonium chloride and the aqueous phase extracted twice with pentane. The combined organic extracts were washed once with saturated aqueous ammonium chloride, twice with saturated aqueous sodium bicarbonate, and twice with brine. After drying (Na_2SO_4) the organic phase was concentrated in vacuo to leave an orange oil which was bulb-to-bulb distilled at 0.05 mm first at 35°C to remove residual diglyme then at 100°C to obtain 2.3 g (77%) of colorless oil: IR (neat) 3030, 2940, 1705, 1650, 1450, 1375, 1100, 940, 760 cm^{-1}; NMR ($CDCl_3$) 6.20 (d, 0.6, J = 13, <u>trans</u> - CH = <u>CH</u>-OCH$_3$), 5.88 (d, 0.4, J = 6, <u>cis</u> - CH = <u>CH</u>-OCH$_3$) 4.53 (m, 0.6, <u>trans</u> - <u>CH</u> = CH-OCH$_3$), 4.11 (m, 0.4, <u>cis</u> - <u>CH</u> = CH-OCH$_3$), 3.51 and 3.47 (two s, 3, <u>cis</u> and <u>trans</u> - CH = CH-OC<u>H</u>$_3$) 2.65 to 1.12 (m, 10, aliphatics), 0.99 and 0.94 (two d, 3, side chain methyl); ^{13}C NMR ($CDCl_3$) 212.6 (s, <u>C</u> = 0), 147.1 and 145.9 (two d,

cis and trans - CH = CH-OCH_3), 109.8 and 105.7 (two d, cis and trans - CH = CH-OCH_3), 59.4 and 55.9 (two q, cis and trans - CH = CH-OCH_3), 46.2 (t), 45.1 (t, weak, other diastereomer), 44.9 (d), 44.7 (d), 41.4 (t), 37.7 (d), 33.5 (d), 29.6 (t, weak, other diastereomer), 29.1 (t, weak, other diastereomer), 27.7 (t), 25.3 (t), 19.2 and 18.3 (two q, side chain methyl).

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

Oxy-Cope Rearrangement of cis-Dienols 7a,b. The rearrangement of 1.5 g (8.2 mmol) of cis-olefin 7 was carried out by the same procedure as for 6 using 0.75 (19 mmol) of oil-free potassium hydride (from 3.4 g of 22% oil suspension) and 100 mL of diglyme to yield 0.80 g (53%) of colorless oil which contained at least 40% of a side product identified (vide infra) as the triolefin 20. Pure oxy-Cope product was isolated by preparative gas-liquid chromatography and was found to have identical spectral properties to that prepared from the trans-olefin 6.

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

The side product could not be separated from the oxy-Cope product by any thin-layer or column chromatography methods examined. Comparison of the spectra of 7 isolated by prep GLC with the spectra of the mixture indicated the presence of a hydroxyl group and an approximate ratio of one olefinic proton for each aliphatic proton. These data implied that the side product was triolefin 20. The side product was separated from 7 by prep GLC; however, the highly unstable material (decomposed within 4 h at room temperature) thus obtained exhibited different spectral properties than those seen in the mixture: IR (neat) 3080, 3020, 2940, 1615, 1450,

1000, 940, 890, 690 cm^{-1}; NMR ($CDCl_3$) 6.80 to 4.80 (m, 8, olefins), 2.22 (m, 4, aliphatic). A mass spectrum was also obtained for this compound. These results indicate the formation of 2-(1,3-butadienyl)-1,3-cyclohexadiene from the trienol during separation.

Exact mass calcd for $C_{10}H_{12}$: 132.094. Found: 132.092.

2-(3-Oxocyclohexyl)propanoic Acid (13). Ozone was bubbled into a -70°C solution of 250 mg (1.4 mmol) of a 91:9 mixture of 8:9 in 10 mL of acetone until a blue-violet color developed. After flushing with nitrogen, the solution was warmed to 0°C, whereupon 2 mL (5 mmol) of 2.67 M Jones reagent and 2 mL of water were added. After stirring 2 h at room temperature, the reaction was quenched with isopropyl alcohol. The solution was extracted three times with ether; the ether extracts were washed twice with brine and concentrated in vacuo to give a crude oil. The crude oil was dissolved in 25 mL of ether and the ether solution extracted three times with saturated aqueous sodium bicarbonate. After neutralization (6 N HCl) and saturation with sodium chloride, the aqueous solution was extracted three times with ether. The ether extracts were dried (Na_2SO_4) and concentrated in vacuo to yield 137 mg (59%) of tan oil, 94 mg of this oil was bulb-to-bulb distilled at 100°C (0.01 mm) to yield 85 mg (53% overall) of colorless oil which crystallized on standing. One recrystallization from ethyl acetate-hexane afforded pure erythro acid 13a, mp 77-78°C (lit.[13] 76°C) which was identical in all respects with an authentic sample of 13a independently synthesized by Ficini:[14] IR (neat) 3200,

2940, 1700 cm^{-1}; NMR ($CDCl_3$) δ 9.78 (b, 1, CO_2H), 2.55-1.30 (m, 10, aliphatics), 1.17 (d, 3, methyl). The NMR spectrum of the unrecrystallized sample revealed a small doublet at δ 1.20 for the threo acid 13b (lit.[14] δ 1.21).

Exact mass calcd for $C_8H_{14}O_3$: 170.094. Found: 170.089.

7-Methylbicyclo[4.3.0]non-9-en-2-one (14). A solution of 150 mg (0.82 mmol) of a 91:9 mixture of 8:9 and 5 mL of 4 N sulfuric acid in 10 mL of tetrahydrofuran was heated at reflux for 4 h. The reaction was quenched by very slow addition of solid sodium bicarbonate until no additional gas evolution was seen. The solution was extracted three times with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to give a quantitative crude yield of yellow oil. Bulb-to-bulb distillation of the crude product at 125°C (4 mm) yielded 83 mg (67%) of colorless oil: IR (neat) 3030, 2960, 1670, 1605, 1450, 1375 cm^{-1}; NMR ($CDCl_3$) δ 6.59 (m, 1, =CH), 3.15 to 1.10 (m, 10, aliphatics including a small doublet at 1.16 for minor isomer), 0.85 (d, 3, methyl). Analytical gas-liquid chromatography on the Carbowax 20 M column indicated the minor bicyclic ketone 14b (9%) exhibited a lower retention time than the major product 14a (91%). Separation by preparative gas-liquid chromatography and analysis by IR, NMR, and mass spectra confirmed that the two products were diastereoisomers.

Exact mass calcd for $C_{10}H_{14}O$: 150.105. Found: 150.105 for both products.

Stereochemical Studies on the Oxy-Cope Rearrangement. trans-Dienol A (6a). The rearrangement of 770 mg of 6a (>99% pure by GLC) was carried out as described above for the mixture of trans-dienols 6a,b to yield 680 mg of crude oil. Analytical GLC using the Carbowax 20M column indicated the ratio (8t + 9t):(8c + 9c) was 96:4. The crude product was chromatographed at medium pressure over silica gel (EM Laboratories size B Lobar column). Elution with hexane:ethyl acetate (95:5) yielded 520 mg of (8t + 9t) (found to contain 1% cis-enol ether by GLC) and 16 mg of (8c + 9c) (>99% pure by GLC). Each enol ether was converted to the aldol products 14a,b by the procedure described above. Analytical GLC on the Carbowax 20M column of the products derived from (8t + 9t) indicated the ratio of 14a:14b was 98:2 and on the product derived from (8c + 9c) the ratio of 14a:14b was 4:96. When corrected for the presence of the cis-enol ether (1%), the ratio of 8t:9t is calculated to be 99:1. The results indicate a crossover to 9t and 8c of 0.9 and 0.2%, respectively (both less than 1% experimental error).

trans-Dienol B (6b). The stereochemistry of the rearrangement of 6b (containing 1% of 6a by GLC) was analyzed by the procedure described for trans-dienol 6a. The ratio of (8t + 9t):(8c + 9c) was 23:77. Aldol condensation on the separated trans-enol ether (found to contain 1% cis-enol ether) gave a ratio of 14a:14b equal to 10:90. Aldol condensation on the separated (8c + 9c) (>99% pure by GLC) gave a product greater than 99% 14a (14b not detected by GLC). After correction for the presence of 6a and cis-enol ether, the ratio

of 8t:9t is 2:98. These results indicate a crossover to 8t of 0.5% (less than experimental error). No crossover to 9c could be detected.

cis-Dienol A (7a). The rearrangement of 7a (containing 1% 6a by GLC) was carried out as described above. The ratio (8t + 9t): (8c + 9c) was found to be 98:2. Chromatographic separation followed by aldol condensation on the (8t + 9t) mixture (>99% pure by GLC) gave a ratio of 14a:14b equal to 2:98. The cis-enol ether could not be recovered after chromatography. After correction for the presence of 6a, the ratio of 8t:9t is 1:99. These results indicate a crossover to 8t of 0.9% (less than experimental error). The maximum crossover possible to 9c is 2%.

cis-Dienol B (7b). The stereochemistry of the rearrangement of 7b (containing 2% 6b by GLC) was analyzed by the procedure described for trans-dienol 6a. The ratio (8t + 9t):(8c + 9c) was found to be 30:70. Chromatographic separation of cis and trans vinyl ethers followed by aldol condensation of the (8t + 9t) mixture (>99% pure by GLC) afforded a ratio of 14a:14b equal to 96:4. Aldol condensation on the (8c + 9c) mixture (>99% pure by GLC) gave a ratio of 14a:14b equat to 3:97. After correction for the presence of 6b, the ratio of 8t:9t is 98:2 and 8c:9c is 1:99. These results indicate a crossover to 9t and 8c of 0.6 and 0.7%, respectively (both less than 1%).

Methyl 4-(3-Methoxy-1-methyl-(E,Z)-2-propenyl)-2-oxocyclohexane-1-carboxylate (18). To a suspension of 0.33 g (13 mmol) of oil-free

sodium hydride (from 0.66 g of 50% oil suspension) in 2.8 g (31 mmol) of dimethyl carbonate and 20 mL of tetrahydrofuran at reflux was added dropwise over 45 min a solution containing 1.2 g (6.3 mmol) of ketone 8 in 10 mL of tetrahydrofuran. The mixture was maintained at reflux for 2 h after the addition was complete. The deep red solution was added to 20 mL saturated aqueous ammonium chloride and the aqueous phase extracted twice with ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to yield 1.4 g of orange oil. The crude product was bulb-to-bulb distilled at 135°C (0.08 mm) to yield 1.3 g (88%) of colorless oil: IR (neat) 3030, 2960, 1740, 1705, 1650, 1615, 1450, 1375, 1275, 1200, 1100, 940, 830, 760 cm^{-1}; NMR ($CDCl_3$) 12.00 (b, 0.75, enol hydroxyl), 6.20 (d, 0.6, J = 13, trans - CH = CH-OCH_3), 5.88 (d, 0.4, J = 6, cis - CH = CH-OCH_3), 4.53 (m, 0.6, trans - CH = CH-OCH_3), 4.11 (m, 0.4, cis - CH = CH-OCH_3), 3.70 (s, 3, - CO_2CH_3), 3.51 and 3.47 (two s, 3, cis and trans - CH = CH-OCH_3), 3.31 (m, 0.25, keto tautomer methine), 2.77 to 1.11 (m, 8, aliphatic), 0.99 and 0.94 (two d, 3, side chain methyl).

Exact mass calcd for $C_{13}H_{20}O_4$: 240.136. Found: 240.133.

Methyl 4-(3-Methoxy-1-methyl-(E,Z)-2-propenyl)-1-cyclohexene-1-carboxylate (19). I. By Reduction, Esterification, and Elimination. A solution of 780 mg (3.2 mmol) of keto ester 18 and 61 mg (1.6 mmol) of sodium borohydride in 15 mL isopropanol at 0°C was stirred for 2 h. The solution was then added to 10 mL brine and extracted three times with ether. The ether extracts were washed with saturated aqueous sodium bicarbonate and brine, dried (K_2CO_3), and concentrated in

vacuo to yield 710 mg of crude product. The crude product was chromatographed at medium pressure over silica gel (EM Laboratories Size B LoBar column; eluted with hexane:ethyl acetate, 85:15) to yield 440 mg (56%) of colorless oil: IR (neat) 3500, 3030, 2960, 1730, 1650, 1450, 1375, 1250, 1200, 1100, 940, 760 cm^{-1}; NMR ($CDCl_3$) 6.20 (d, 0.6, J = 13, trans - CH = CH-OCH_3), 5.88 (d, 0.4, J = 6, cis - CH = CH-OCH_3), 4.53 (m, 0.6, trans - CH = CH-OCH_3), 4.11 (m, 0.4, cis - CH = CH-OCH_3), 3.68 (s, 3, - CO_2CH_3), 3.51 and 3.47 (two s, 3, cis and trans - CH = CH-OCH_3), 2.87 (b, 1, - OH), 2.55 to 0.90 (m, 12, aliphatics including side chain methyl doublets at 0.99 and 0.94).

Exact mass calcd for $C_{13}H_{22}O_4$: 242.152. Found: 242.153.

To a solution of 720 mg (3.0 mmol) of hydroxy-ester and 450 mg (4.4 mmol) of triethylamine in 20 mL of methylene chloride at 0°C was slowly added 370 mg (3.3 mmol) of methanesulfonyl chloride. The solution was stirred for 30 min at 0°C, added to 20 mL of 50% aqueous brine, and the organic phase washed twice with saturated aqueous sodium bicarbonate and once with water. After drying (Na_2SO_4) the organic phase was concentrated in vacuo to yield 910 mg (96%) of crude mesylate: IR (neat) 3030, 2960, 1735, 1650, 1450, 1350, 1250, 1210, 1175, 1100, 940, 760 cm^{-1}; NMR ($CDCl_3$) 6.20 (d, 0.6, J = 13, trans - CH = CH-OCH_3), 5.88 (d, 0.4, J = 6, cis - CH = CH-OCH_3), 4.53 (m, 1.6,- $CHOSO_2CH_3$ and trans - CH = CH-OCH_3), 4.11 (m, 0.4, cis - CH = CH-OCH_3), 3.67 (s, 3, - CO_2CH_3), 3.51 and 3.47 (two d, 3, cis and trans - CH = CH-OCH_3), 2.97 and 2.94 (two s, 3, CH_3SO_3-), 2.73 to 1.11 (m, 8, aliphatics), 0.99 and 0.94 (two d, 3, side chain methyl).

A solution of 910 mg (2.8 mmol) of crude mesylate and 3.10 mg (5.7 mmol) of sodium methoxide (from 130 mg of sodium metal) in 20 mL of methanol was heated at reflux for 8 h, a white precipitate appeared during the reaction. The solution was added to 20 mL of brine and extracted three times with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to yield a crude yellow oil which was bulb-to-bulb distilled at 115°C (0.1 mm) to obtain 490 mg (77%, overall 74% from 9) of colorless oil: ir (neat) 3030, 2960, 1710, 1650, 1450, 1375, 1250, 1210, 1100, 940, 760 cm^{-1}; nmr ($CDCl_3$) 6.94 (m, 1, = CH-), 6.20 (d, 0.6, J = 13, trans - CH = CH-OCH_3) 5.88 (d, 0.4, J = 6, cis - CH = CH-OCH_3), 4.53 (m, 0.6, trans - CH = CH-OCH_3), 4.11 (m, 0.4, cis - CH = CH-OCH_3), 3.70 (s, 3, -CO_2CH_3), 3.51 and 3.47 (two s, 3, cis and trans - CH = CH-OCH_3), 2.67 to 1.13 (m, 8, aliphatics), 0.99 and 0.94 (two d, 3, side chain methyl).

Exact mass calcd for $C_{13}H_{20}O_3$: 224.141. Found: 224.143.

II. By Formation of the Hydrazone 21 and Elimination. To a stirred 0°C solution of 250 mg (1.0 mmol) of β-keto ester 18 in 5 ml of dichloromethane was added 220 mg (1.1 mmol) of 1-amino-2-phenylaziridine acetate.[29] The resulting solution was stirred for 10 h at 0°C, after which it was added to 10 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic solution washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to yield 379 mg (102%) of crude hydrazone (21): IR (neat) 3060, 3030, 2960, 2880, 1730, 1650, 1630, 1500, 1450, 1210, 750, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (m, 5, aromatics), 5.40-6.52 (complex m, 1,

-CH=C<u>H</u>-OCH_3), 3.81-4.80 (complex m, 2, -<u>CH</u>=CH-OCH_3 and >C<u>H</u>-CO_2CH_3), 3.15-3.71 (m, 6, $CO_2C\underline{H}_3$ and -CH=CH-OCH_3), 0.62-3.15 (complex m, 14, aliphatics).

To a stirred 0°C solution of 280 mg (2.7 mmol) of lithium diisopropylamide in 10 mL of tetrahydrofuran (formed by the reaction of a solution of 320 mg (3.2 mmol) of diisopropylamine in tetrahydrofuran with 1.7 mL (2.7 mmol) of 1.6 M <u>n</u>-butyllithium in hexane at -78°C followed by warming to 0°C) under an argon atmosphere was dropwise added over 3 min 379 mg (1.1 mmol) of crude hydrazone. The resulting deep red solution was stirred at 0°C for 6 h. After the addition of a solution of 250 mg (4.6 mmol) of sodium methoxide in 5 mL of methanol, stirring was continued for 3 h at room temperature. The reaction solution was then added to 20 mL of saturated aqueous sodium bicarbonate and the aqueous phase extracted twice with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to yield 249 mg of brown oil which was chromatographed at medium pressure over silica gel (EM Laboratories size A LoBar column; eluted with hexane:ethyl acetate, 95:5) to yield 114 mg (49%) of product.

<u>3-(Methyl-4-carboxyl-3-cyclohexenyl)butanoic Acid (23a)</u>. A solution of 490 mg (2.2 mmol) of ester <u>19</u> and 10 mL of 8 N sulfuric acid in 15 mL of acetone was stirred at 0°C for 4 h. After addition of 3 mL (8 mmol) of 2.67 M Jones reagent stirring was continued for 30 min at 0°C. The reaction was quenched with isopropanol and the resulting solution extracted three times with ether. The ether solution was washed with

brine, dried (Na_2SO_4), and concentrated in vacuo to yield 440 mg of a pale yellow oil which crystallized on standing at room temperature overnight. Recrystallization from ethyl acetate/hexane gave 210 mg of analytically pure white crystals, melting point 89-91°C. The remaining material, which would not crystallize, was purified by preparative thin-layer chromatography on silica gel (eluted with ethyl acetate) and yielded 160 mg of product. Total yield of purified acid was 370 mg (76%): IR ($CHCl_3$) 3400, 3030, 2960, 1700, 1650, 1450, 1375, 1250, 1040 cm^{-1}; NMR ($CDCl_3$) δ 6.94 (m, 1, =C<u>H</u>-), 5.8 (b, 1, CO_2<u>H</u>), 3.70 (s, 3, CO_2C<u>H_3</u>), 2.70-1.11 (m, 10, aliphatic), 0.97 (d, 3, side chain methyl); ^{13}C NMR ($CDCl_3$) δ 179.3 (s), 167.9 (s), 139.1 (d), 130.3 (s), 51.6 (q), 39.0 (t), 37.4 (d), 34.2 (d), 28.3 (t), 26.1 (t), 24.9 (t), 16.2 (q).

Anal. ($C_{12}H_{18}O_4$): C, H.

(±)-erythro-Juvabione (15a). A solution of 175 mg (0.77 mmol) of crystalline acid 23a and 230 mg (1.8 mmol) oxalyl chloride in 15 mL of benzene was stirred at room temperature for 3 h. Concentration in vacuo yielded 180 mg (97%) of crude acid chloride: IR (neat) 3030, 2940, 1800, 1710, 1650, 1450, 1375, 1250, 1090 cm^{-1}.

To a 0°C solution of approximately 1.7 mmol of isobutyl Grignard in 10 mL ether, generated by the reaction of 42 mg (1.7 mmol) of magnesium turnings with 240 mg (1.7 mmol) of isobutyl bromide, was added 170 mg (0.95 mmol) of anhydrous cadmium chloride. After stirring 5 min at room temperature the ether was removed by distillation until the reaction was a thick brown slurry, 10 mL of benzene was added, and the solvent again removed by distillation. After the addition of 10 mL benzene the reaction

was cooled to 0°C and 180 mg (0.75 mmol) of crude acid chloride was added. The solution was heated at reflux for 1 h, added to 25 g ice and 25 mL of 10% sulfuric acid, and the aqueous phase extracted twice with benzene. The combined benzene extracts were washed successively with water, saturated aqueous sodium bicarbonate, water, and brine. After drying ($MgSO_4$), the solution was concentrated in vacuo to yield 200 mg of crude product. The crude product was chromatographed at medium pressure over silica gel (EM Laboratories Size B LoBar column; eluted with hexane:ethyl acetate, 95:5) to yield 120 mg (60% from 23a) of juvabione: IR (neat) 3030, 2960, 1705, 1650, 1450, 1375, 1250, 1090 cm^{-1}; NMR ($CDCl_3$) 6.90 (m, 1, = CH-), 3.70 (s, 3, - CO_2CH_3), 2.67 to 1.10 (m, 13, aliphatic), 0.90 and 0.86 (two d, 9, side chain methyls); ^{13}C NMR ($CDCl_3$) 210.1, 167.5, 139.0, 130.0, 52.3, 51.4, 47.9, 37.6, 32.8, 29.8 (about 4-5% of the height of the 28.4 signal), 28.4, 26.1, 24.9, 24.5, 22.5, 16.4. The assignments of Manville, et. al.,[31] were used in the analysis.

Exact mass calcd for $C_{16}H_{26}O_3$: 266.188. Found: 266.187.

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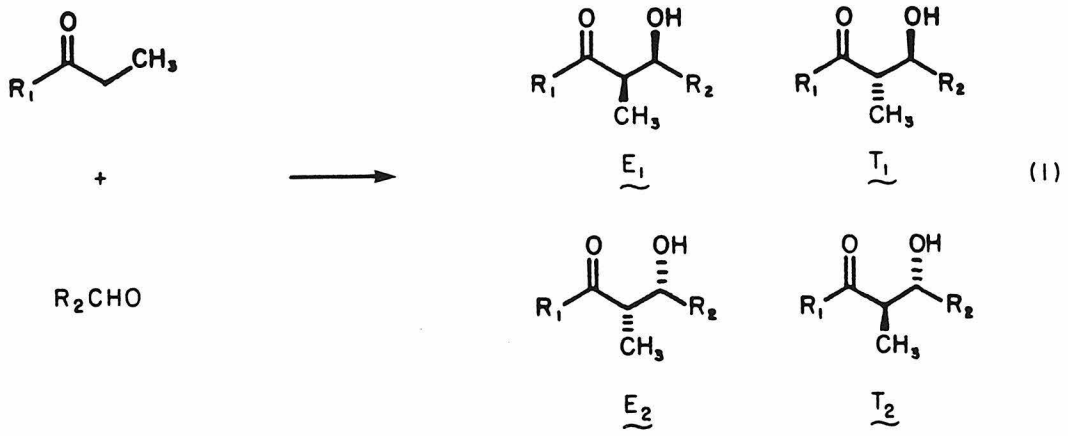
CHAPTER II

Stereoselective Aldol Condensations *Via* Dialkylboron Enolates

Introduction

The aldol condensation is a reaction of fundamental importance in the biosynthesis of a broad range of biologically significant natural products. The recognition of both the macrolide and ionophore antibiotics as attainable targets for synthesis has been instrumental in focusing renewed interest towards the development of stereoregulated variants of this process in the laboratory.[3] Ideally, it would be significant to reveal those stereochemical issues which deal with the control of <u>both</u> reaction diastereoselection ($\underset{\sim}{E}_1$ + $\underset{\sim}{E}_2$ <u>vs</u> $\underset{\sim}{T}_1$ + $\underset{\sim}{T}_2$) and enantioselection ($\underset{\sim}{E}_1$ <u>vs</u> $\underset{\sim}{E}_2$ or $\underset{\sim}{T}_1$ <u>vs</u> $\underset{\sim}{T}_2$) for a range of reaction substrates (eq. 1).

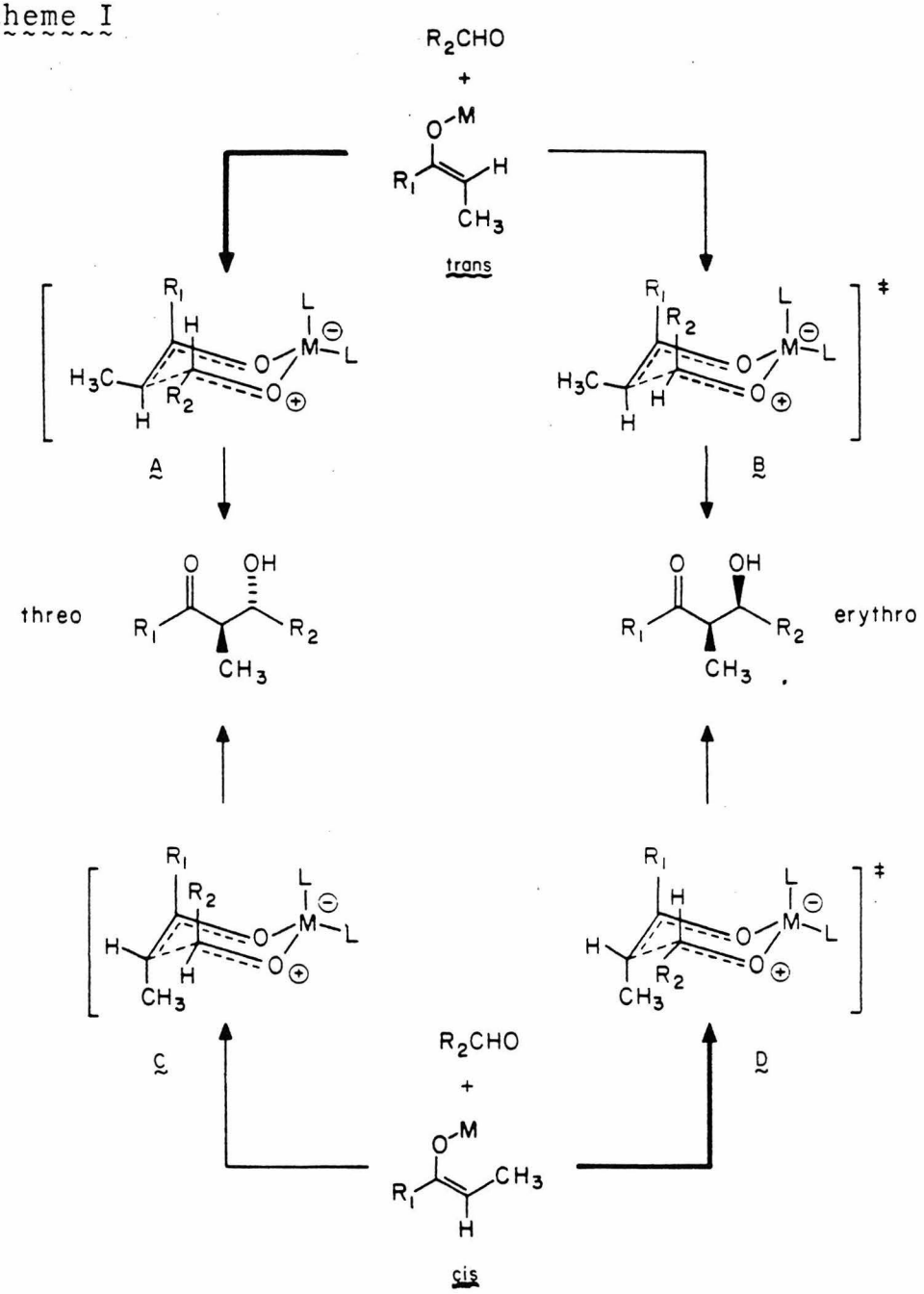


(1)

In 1957, in conjunction with a stereochemical study of the Ivanov and Reformatsky reactions, Zimmerman and Traxler accounted for the observed aldol diastereoselection by advancing the hypothesis that the reaction proceeded *via* a preferred chair-like transition state involving co-operative metal ion ligation of both the enolate and carbonyl substrates (*c.f.* Scheme I).[4] Subsequent investigations by Dubois[5] and more recently by Heathcock[6] on preformed lithium enolates have unambiguously shown that *kinetic* aldol diastereoselection is, in part, defined by enolate geometry. With regard to the pericyclic chair transition states illustrated in Scheme I, both "trans" and "cis" lithium enolates (M = Li) exhibit excellent kinetic threo and erythro product selection respectively when the enolate ligand, R_1, is sterically demanding such as *tert*-butyl. The observation that the steric bulk of R_1 ($\underline{t}$-C_4H_9 > $\underline{i}$-C_3H_7 > C_2H_5 > OCH_3 > H) and the attendant aldol diastereoselection[5,6] are directly coupled is consistent with the elaborated Zimmerman model (Scheme I).[4] For example, for *trans*-enolates transition state $\underset{\sim}{B}$ is destabilized relative to $\underset{\sim}{A}$ due to $R_1 \leftrightarrow R_2$ interactions. Related trends in aldol stereoselection have been noted for magnesium,[7] zinc,[8] and aluminum[9] enolates.

At the outset of the present study the decision was made to explore the role of "metal-centered steric effects"

Scheme I



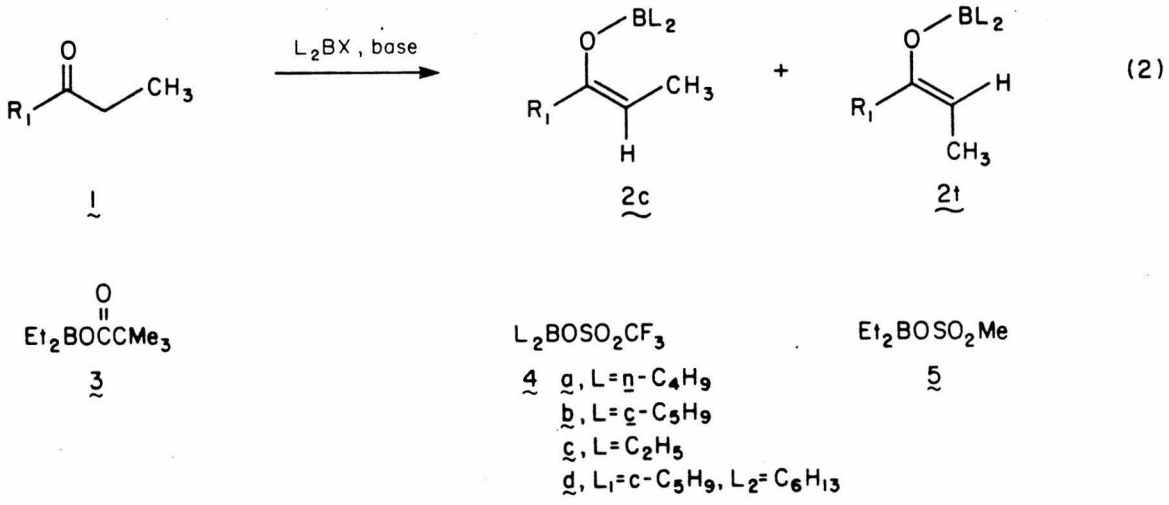
in the kinetic aldol process.[1] Accordingly, large pseudo-1,3-diaxial $R_2 \leftrightarrow L$ interactions in transition states B and C might render the aldol process, from either enolate

geometry, both highly stereoselective and independent of the steric requirements of the enolate ligand R_1. For the reasons outlined in our earlier communication,[1b] dialkylboron enolates appeared to be excellent candidates for study. A limited number of literature cases indicated that good levels of aldol diastereoselection might be anticipated.[10] This paper reports the full details of our initial investigations into the generation of stereochemically homogeneous boron enolates and their stereoselective aldol condensations with aldehydes. The parallel investigations of Masamune[11] and Mukaiyama[12] are in accord with those made in the present study.

Results and Discussion

Selective Generation of Boron Enolates. A variety of published methods exist for the generation of dialkylboron enolates;[13] Nonetheless, only two procedures have been developed which involve the direct enolization of carbonyl substrates.[10b,14] Köster has reported that ethyl ketones 1 (R_1 = C_2H_5, i-C_3H_7, C_6H_5, C-C_6H_{11}) react at elevated temperatures (85-110°C) with triethylborane under the catalytic influence of 3 to give enolates 2c,2t (L = Et) under presumed equilibrating conditions.[10b]

Mukaiyama has recently disclosed that the dibutylboryl trifluoromethane sulfonate (4a), in the presence of either 2,6-lutidine (Lut) or diisopropylethylamine (DPEA), rapidly enolizes ketones in ethereal solvents at low temperature ($\geq$ -78°C). Stereoselective enolate formation was not addressed in this study.[14] In conjunction with the present investigation, the issue of selective enolate generation via the boryl triflate reagents 4 was undertaken. Substrate and reaction variables which include the influence of carbonyl ligand (R_1), boron ligand (L), base, and solvent have been examined. The boryl triflate



reagents 4a-4c were prepared from the corresponding trialkylborane (L_3B) and trifluoromethane sulfonic acid in high yield as air and moisture sensitive distillable liquids in direct analogy with literature precedent.[14,15]

The general procedure for enolate formation involved reaction of equimolar quantities of ketone or thioester 1 and boryl triflate 4 in the presence of 1.1 equiv of tertiary amine base in anhydrous ether at temperatures ranging from -78 → 25°C depending upon the particular carbonyl substrate. The precipitation of insoluble ammonium triflate in etheral and hydrocarbon solvents accompanied enolate formation. Attempts to directly transform the resultant boron enolates, 2c,2t, to enol derivatives which could be more conveniently analyzed led to the unanticipated observation that these nucleophiles did not react cleanly with either chlorotrimethylsilane or acetic anhydride. This problem was circumvented by conversion of the 2c,2t-mixtures to the analogous lithium enolates with ≥2 equiv of butyl or methyllithium[16] followed by derivatization with chlorotrimethylsilane. The derived trimethylsilylenol ethers were compared with independently prepared samples which have been previously characterized.[6] The only ambiguity in enolate stereochemical assignment was that for the enol silane derived from tert-butyl thiopropionate (6)

(Table I, Entry N). The enolate stereochemistry in this system was assigned in analogy to that observed for the related propionate esters since the major enolsilane isomer derived from 6 had the same stereochemistry as that derived from enolization with lithium diisopropylamide (-78°C, THF; 10:90).[17] Table I summarizes the variable reaction and substrate parameters which were studied. Boron enolates 2c,2t were found to be configurationally stable at 25°C for as long as 2 h in the presence of the DPEA·HOTf and at 0°C (30 min) presence of Lut·HOTf. At elevated temperatures (77°C, CCl_4) complete enolate equilibration (2c $\rightleftharpoons$ 2t) could be achieved (Entries C, G). As anticipated, enolate equilibrium is reached more rapidly in the presence of the stronger acid, Lut·HOTf. With the exception of Entries C, G, and K, all reported enolate ratios are presumed to be kinetically controlled (Table I).

The data in Table I reveal a number of significant trends which bear on the enolization mechanism. Entries A and B illustrate the importance of increased amine steric hinderance in maximizing kinetic selection in the deprotonation process. Relative to the influence of the boron ligand (L), a comparison of the enolate ratios derived from the use of triflates 4a (L = n-C_4H_9) and 4b (c-C_5H_9) on 3-pentanone (Entries A, D) and isopropylethyl

Table I. Kinetic Enolate Formation With Triflates 4a and 4b (eq. 2).

Entry	1 (R_1)	4 (L)	Base[a]	Conditions[b]	Ratio, 2c:2t[c,d]
A	Et	L = n-C_4H_9	DPEA	-78°C, 30 min	>97:3
B	Et	L = n-C_4H_9	Lut	-78°C, 30 min	69:31
C	Et	L = n-C_4H_9	Lut	+77°C, 3 h[e]	(86:14)
D	Et	L = c-C_5H_9	DPEA	0°C, 30 min	82:18
E	Me_2CH	L = n-C_4H_9	DPEA	-78°C, 30 min	45:55
F	Me_2CH	L = n-C_4H_9	Lut	-78°C, 30 min	56:44
G	Me_2CH	L = n-C_4H_9	Lut	+77°C, 30 min[e]	(73:27)
H	Me_2CH	L = c-C_5H_9	Lut	0°C, 30 min	42:58
I	Me_2CH	L = c-C_5H_9	DPEA	0°C, 30 min	19:81
J	Me_3C	L = n-C_4H_9	DPEA	0°C, 30 min[f]	25:75
K	Me_3C	L = n-C_4H_9	DPEA	+35°C, 2 h	(>97:3)
L	Me_2CHCH_2	L = n-C_4H_9	DPEA	-78°C, 30 min	>97:3

Table I. Continued

Entry	1 (R_1)	4 (L)	Base[a]	Conditions[b]	Ratio, 2c:2t[c,d]
M	C_6H_5	L = n-C_4H_9	DPEA	25°C, 1 h	>97:3
N	Me_3CS	L = n-C_4H_9	DPEA	0°C, 30 min	≤ 5:95

a) DPEA = diisopropylethylamine, Lut = 2,6-lutidine. b) Except where noted, all reactions carried out in ether. c) Enolate ratios determined on trimethylsilylenol ethers (see text) by ^1H NMR and/or gas chromatography by comparison with independently prepared samples (c.f. ref. 6). d) Values reported are kinetic ratios; those in parentheses are equilibrium values. e) Reactions carried out in CCl_4; prolonged reaction times did not change enolate ratio. f) Incomplete enolization of substrate noted.

ketone (Entries E, I) is informative. With a given base (DPEA), the more hindered boryl triflate 4b exhibits enhanced kinetic selection for trans-enolate formation. These observations parallel those noted by Masamune and co-workers.[11b] As anticipated, the more hindered triflate (4b) is less reactive in the enolization process than either 4a or 4c, and reactions with this reagent must be carried out at 0°C (Entry D). No significant differences in reaction stereoselection were noted between the dibutyl and diethylboryl triflates 4a and 4c, and the pyrophoric nature of 4c renders it less attractive as a reagent. Finally, for a given amine base (DPEA) and triflate (4a), ketone substrates 1 (R_1 = Et, Me_2CH, Me_3C) exhibit a qualitative decrease in cis-enolate kinetic selection with increased steric requirements of R_1 (Entries A, E, J). In addition to the studies noted above which were carried out in ether, it was found that a range of other solvents could be employed with equal facility (CCl_4, $CHCl_3$, CH_2Cl_2, C_6H_6, C_5H_{12}) with only minor variations in kinetic enolate selection. However, those solvents which solubilize the ammonium triflate were generally employed to effect enolate equilibration at elevated temperatures (Entries, C, G, K). Solvent effects in the aldol condensation of these enolates, however, were found to be significant (cf. Table III) and

will be discussed in the following section.

In addition to the observations noted above, additional experiments which could have a bearing on the enolization mechanism were carried out. An examination of the ^1H NMR spectra ($CDCl_3$) of equimolar solutions of boryl triflate 4a and both 2,6-lutidine and diisopropylethylamine (DPEA) revealed 1:1-complexation between the two reagents (eq. 3).[2a] Complexation was complete within

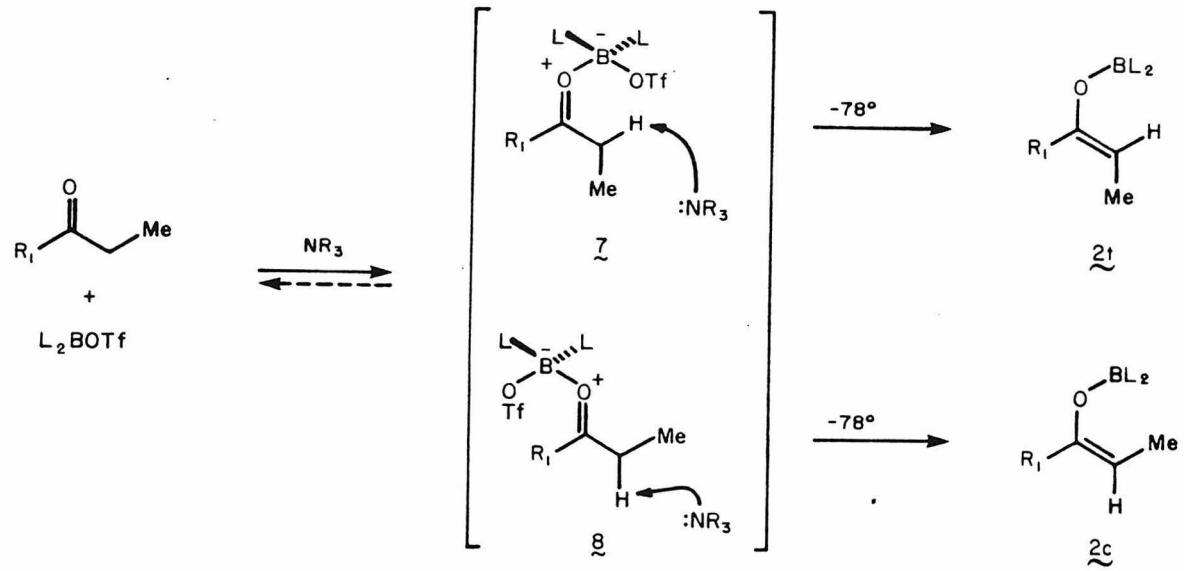
$$Bu_2B{-}OTf + R_3N \rightleftharpoons Bu_2B(OTf){-}NR_3 \qquad (3)$$

minutes with lutidine and in 30 minutes with the more hindered base at 25°C. The ^{11}B NMR spectrum of the complex was indicative of a tetracoordinate species.[18] Our observations that other less hindered nitrogen bases such as pyridine, DABCO, DBU, and tetramethylguanidine are totally ineffective in the enolization process could be attributed to the irreversible amine-borane complexation.[19]

To account for all observations pertaining to kinetic deprotonation, the following mechanistic model is proposed (Scheme II):

(A) Trans and cis-enolates 2t and 2c are derived from deprotonation of syn and anti-complexes

Scheme II



7 and 8 respectively.

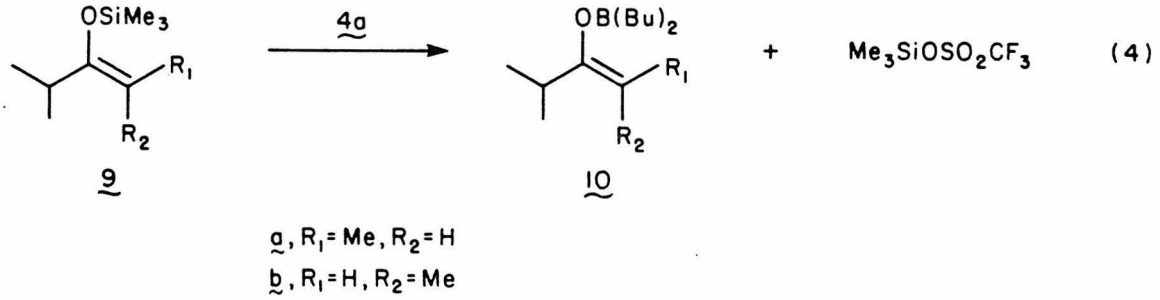
(B) Deprotonation is the rate-determining step rather than complexation.

(C) All factors being equal (R_1 = Et) e.g. 7 = 8 anti-deprotonation (8 → 2c) is preferred over syn-deprotonation (7 → 2t).

Assumption (A) is based upon allylic strain arguments and related observations in hydrazone deprotonation.[20] Assumption (B) is consistent with both the substrate

studies (Table I) and the product selection as a function of base structure. Finally, (C) must be proposed to explain the high cis-enolate stereoselection for 3-pentanone and related systems. The observation that tert-butyl thiopropionate (6) forms predominately the trans-enolate (2t:2c ≥ 95:5) is consistent with the expectation that 7 (R_1 = St-Bu) might be expected to be more stable than 8 (R_1 = St-Bu) based upon analogous geometrical preferences for related onium ions.[21] Nonetheless, these conclusions must be tempered by the observation by Masamune that for thioester 1 (R_1 = SC_6H_5) and 9-BBN triflate (Et_2O, 0°C, DPEA) selective cis enolate (2c) formation was noted.[11d]

One other potentially attractive method was briefly explored for the stereoselective synthesis of boron enolates (eq. 4). It was found that trimethylsilylenol ethers react rapidly with the boryl triflate reagents to give boron enolates in high yield. However, this exchange process is accompanied by a significant loss in enolate stereochemistry as judged by the resultant aldol condensation experiments (vide infra). The reaction of purified (Z)-silyl ether 9a[6] with 4a (Et_2O, -25°C, 30 min) either in the presence or absence of DPEA afforded a ratio 10a:10b ≅ 60:40. The analogous (E)-silyl ether 9b[6] afforded a ratio 10b:10a ≅ 80:20. Related observations with other silylenol ethers were also noted, and all attempts to



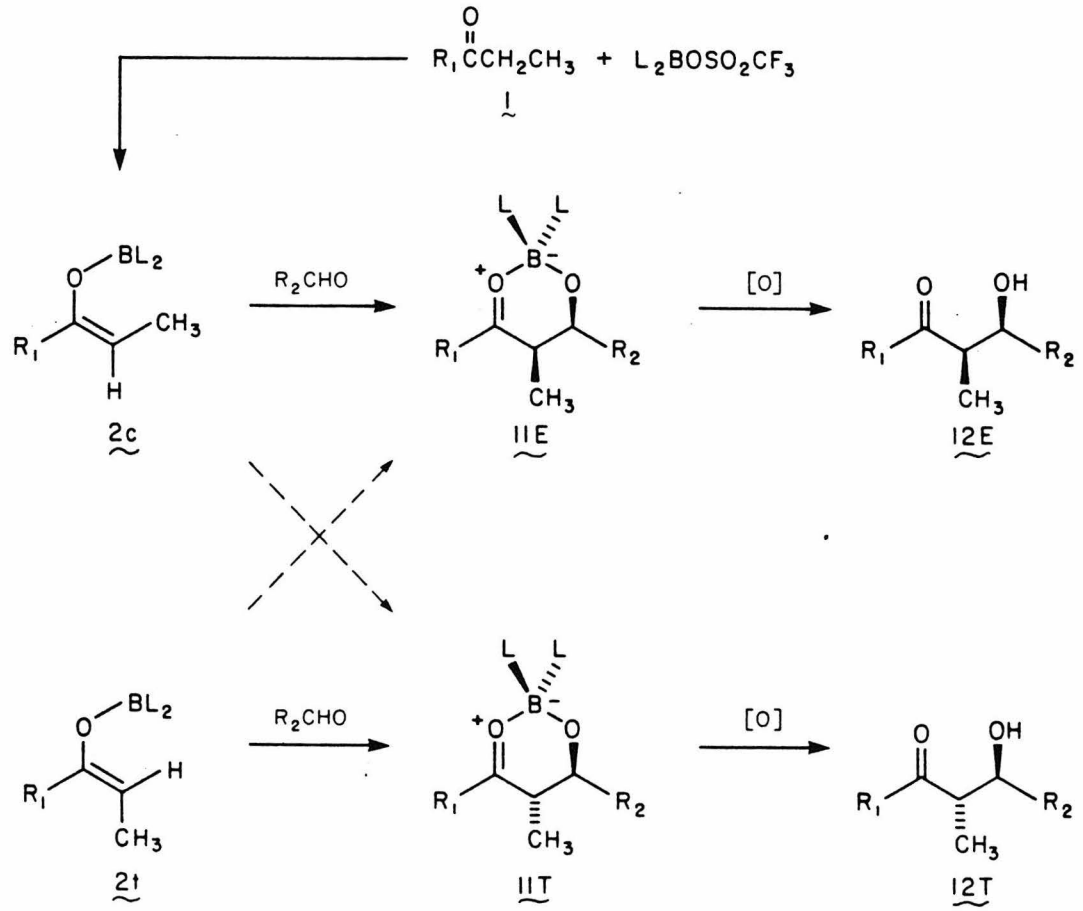
improve exchange stereoselection proved fruitless.[23] Nonetheless, this exchange method could prove useful in the synthesis of boron enolates which are inaccessible via the triflate reagents.[24]

Stereoselective Aldol Condensations. The initial set of aldol condensation conditions were similar to those reported by Mukaiyama (Et_2O, -78°C, DPEA)[14] with either dibutyl or dicyclopentyl boryl triflates 4a and 4b. The derived ketol borate complexes 11E,11T (Scheme III) were oxidized to the erythro and threo-ketols 12E,12T by one of two procedures. For some substrates the reported buffered hydrogen peroxide procedure[14] was found adequate; however, for more sensitive substrates such as thioesters

the oxidant, $MoO_5 \cdot py \cdot HMPT$ (MoOPH),[25] was found to be superior. In order to insure that the aldol diastereoisomer ratios, 12E,12T, reflected the kinetic product ratios, several aldol ate-complex stability studies were carried out.[2a] Treatment of 11E (R_1 = Et, R_2 = Ph; E:T $\geq$ 97:3), formed from 12E with triflate 4a, under the conditions of both aldol condensation and subsequent oxidative isolation resulted in recovery of the ketol 12E with no loss in stereochemistry. The ate-complex 11E (R_1 = Et, R_2 = Ph) exhibits no tendency to isomerize in refluxing ether (3 h) even in the presence of 0.3 equiv of DBU. Some isomerization was noted (11E:11T = 63:37), however, in refluxing toluene (1.0 h, 0.3 equiv DBU). We surmise that this equilibration is not proceeding via retro-aldolization, but by acid-base deprotonation of the ate-complex. It was found that the above equilibration procedure was not synthetically viable for the production of the thermodynamically more stable threo aldol chelates due to the intervention of other side reactions. Related stability studies on the cyclohexanone aldol adducts 14E and 14T also insured that kinetic product ratios were obtained.

From the data in Table II, in which reaction solvent and temperature (Et_2O, -78°C) variables were held constant, there is a consistently good correlation between enolate geometry and product aldol stereochemistry. For the

Scheme III



3-pentanone cis-enolate (2c, R_1 = Et), the aldol diastereoselection ratio, 12E:12T, corresponds to the enolate ratio 2c:2t within experimental error for not only benzaldehyde, but also the aliphatic aldehydes (Entries A, B, C, D, G). Both α-methacrolein and tigaldehyde (Entries E, F) were somewhat less stereoselective. Similar trends were also observed with the thioester 6 (Entries S-X). Another

Table II. Kinetic Aldol Condensations With Representative Aldehydes at -78°C (Scheme III).

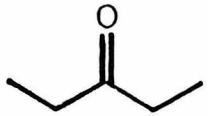
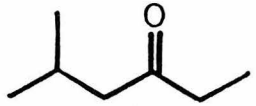
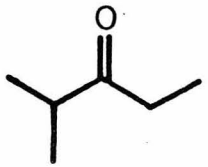
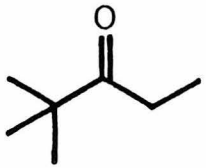
Entry	$R_1C(=O)-CH_2CH_3$	$R_2C(=O)-H$	L_2BOTf[a]	Enolization T°C	Ratio[b] 2c:2t	Ratio[c] 12E:12T	Yield, %[d]
A		C_6H_5-CHO	n-C_4H_9	-78	>97:3	>97:3	77[g]
B		C_6H_5-CHO	n-C_4H_9[e]	-78	69:31	72:28	76[g]
C		n-C_3H_7-CHO	n-C_4H_9	-78	>97:3	>97:3	65
D		i-C_3H_7-CHO	n-C_4H_9	-78	>97:3	>97:3	61
E		$CH_2=C(CH_3)$-CHO	n-C_4H_9	-78	>97:3	92:8	68
F		(E)$CH_3CH=C(CH_3)$-CHO	n-C_5H_9	-78	>97:3	93:7	65
G		C_6H_5-CHO	c-C_5H_9	0	82:18	84:16	(86)
H		C_6H_5-CHO	n-C_4H_9	-78	>99:1	>97:3	82[g]
I		C_6H_5-CHO	c-C_5H_9	0	--	84:16	(85)
J		C_6H_5-CHO	n-C_4H_9	-78	45:55	44:56	65[g]
K		C_6H_5-CHO	c-C_5H_9	0	19:81	18:82	(87)
L		C_6H_5-CHO	n-C_4H_9	+35	>99:1	>97:3	65[g]

Table II. Continued

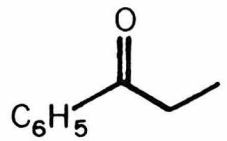
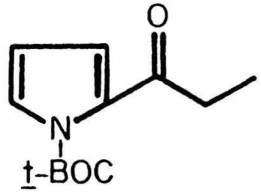
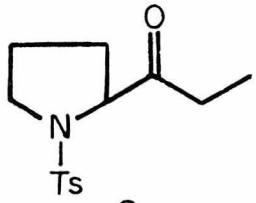
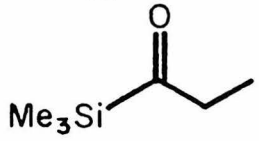
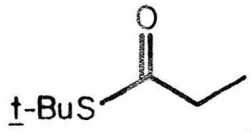
Entry	$R_1C(=O)-CH_2CH_3$	$R_2C(=O)-H$	L_2BoTf[a]	Enolization T°C	Ratio[b] 2c:2t	Ratio[c] 12E:12T	Yield, %[d]
M		C_6H_5-CHO	n-C_4H_9	+25	99:1	>97:3	82[g]
N		C_6H_5-CHO	n-C_4H_9	-78	--	>97:3	70[h]
O		i-C_3H_7-CHO	n-C_4H_9	+25	--	90:10	60[h]
P		i-C_3H_7-CHO	c-C_5H_9[f]	+25	--	87:13	57[h]
Q		C_6H_5-CHO	n-C_4H_9	-78	--	19:81	53
R		C_6H_5-CHO	c-C_5H_9	0	--	35:65	(68)

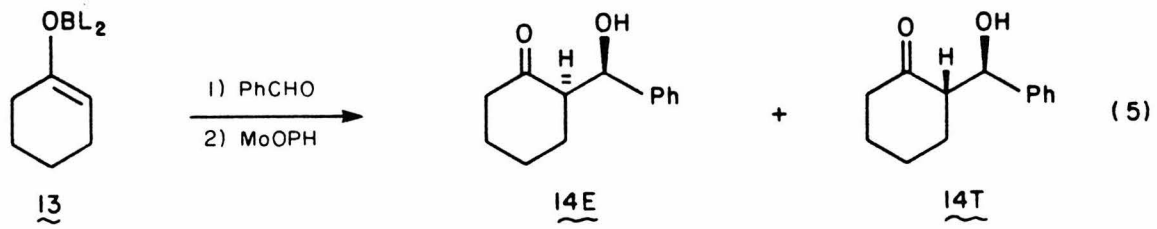
Table II. Continued

Entry	$R_1C(=O)-CH_2CH_3$	$R_2C(=O)-H$	L_2BOTf[a]	Enolization T°C	Ratio[b] 2c:2t	Ratio[c] 12E:12T	Yield, %[d]
S		C_6H_5-CHO	n-C_4H_9	0	≤5:95	10:90	75
T	 6	C_6H_5-CHO	c-C_5H_9	0	≤5:95	5:95	(90)
U		n-C_3H_7-CHO	n-C_4H_9	0	≤5:95	10:90	67
V		i-C_3H_7-CHO	n-C_4H_9	0	≤5:95	9:91	63
W		$CH_2=C(CH_3)$-CHO	n-C_4H_9	0	≤5:95	12:88	65
X		(E)$CH_3CH=C(CH_3)$-CHO	n-C_4H_9	0	≤5:95	18:82	61

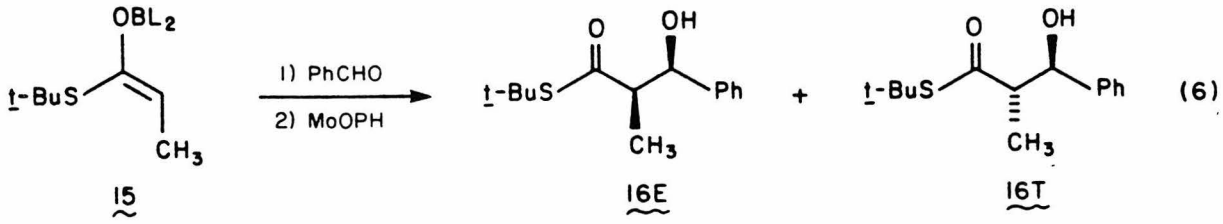
a) In all cases diisopropylethylamine (DPEA) was used as the base and enolization was carried out in ether for 30 min except for Entries M and N where a reaction time of 60 min was employed. b) Data derived from Table I. c) Aldol ratios determined by ^1H NMR or ^{13}C NMR. d) Values reported are for isolated yields. Those in parentheses determined by ^1H NMR. e) Lutidine was employed as the base. f) The reaction solvent was ether-CH_2Cl_2. g) Ref. 2a. h) Ref. 2b.

significant conclusion can be drawn from the data on the effects of the boron ligand, L, on aldol diastereoselection. For three enolates (R_1 = Et, i-C_3H_7, t-Bu-S), the change in boron ligand from n-butyl to cyclopentyl results in only a minor ($\leq$5%) enhancement reaction selectivity (Entries A, G; J, K; S, T). On the other hand, it is apparent that, in the majority of cases, boron ligand structure plays a significant role in the enolization process (Table I).

Based upon the excellent aldol diastereoselection observed with the acyclic carbonyl substrates, it was surprising to observe that the cyclohexanone enolate (L = n-C_4H_9) condensation (Et_2O, -78°C) with benzaldehyde (eq. 5) exhibited relatively low stereoselection (14E:14T =



13 14E 14T (5)



15 16E 16T (6)

33:67).[2a] Accordingly enolates 13 and 15 were chosen to study the interplay of both solvent effects and boron ligand structure on reaction stereoselection (Table III).

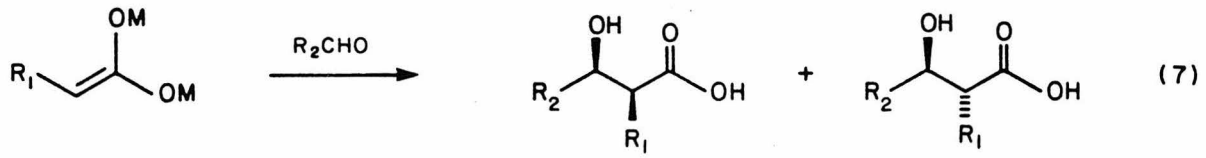
For a given boron ligand there is a small but consistent improvement in aldol diastereoselection when the less polar solvents are employed. This trend is observed for both enolates 13 and 15. In subsequent studies we have found that aldol diastereoselection in methylene chloride is comparable to that observed in pentane, and the former is frequently the solvent of choice.[2b] Assuming that these reactions proceed *via* the pericyclic aldol mechanism (Scheme I), the less polar solvents could well result in "transition state compression" thereby enhancing those steric parameters which appear to regulate diastereoselection. The solvent effects noted above have also been found to be significant in the enolate chirality transfer.[2b] In an effort to further enhance aldol selection for enolate 13, we prepared the sterically demanding thexylcyclopentylboryl triflate 4d from the corresponding boron hydride[26] and TfOH.[2a] In view of our earlier results, the high diastereoselection observed with this mixed ligand was gratifying.

A significant body of literature has been devoted to an examination of enediolate aldol stereoselection (eq. 7).[4,27] Although our earlier attempts to enolize alkyl esters (methyl propionate) had not been successful, it

Table III. Aldol Condensation of 13 and 15 With Benzaldehyde (eq. 5, 6). Solvent and Ligand Effects.

Entry	Enolate	L_1L_2BOTf[a]	Solvent	Ratio[b] E:T	Yield, %[c] E + T
A	13	L_1, L_2 = n-C_4H_9	ether	33:67	71[f]
B	13	L_1, L_2 = n-C_4H_9	pentane	17:83	100[f]
C	13	L_1, L_2 = c-C_5H_9	ether	32:68	(74)
D	13	L_1, L_2 = c-C_5H_9	pentane	15:85	80[f]
E	13	L_1 = c-C_5H_9 L_2 = C_6H_{13}[d]	CH_2Cl_2	6:94	68[f]
F	13	L_1 = c-C_5H_9 (4d) L_2 = C_6H_{13}[d]	THF	<4:96	94 (73)[f]
G	15	L_1, L_2 = n-C_4H_9 (4d)	pentane[e]	5:95	92
		L_1, L_2 = c-C_5H_9	pentane[e]	≤5:95	84

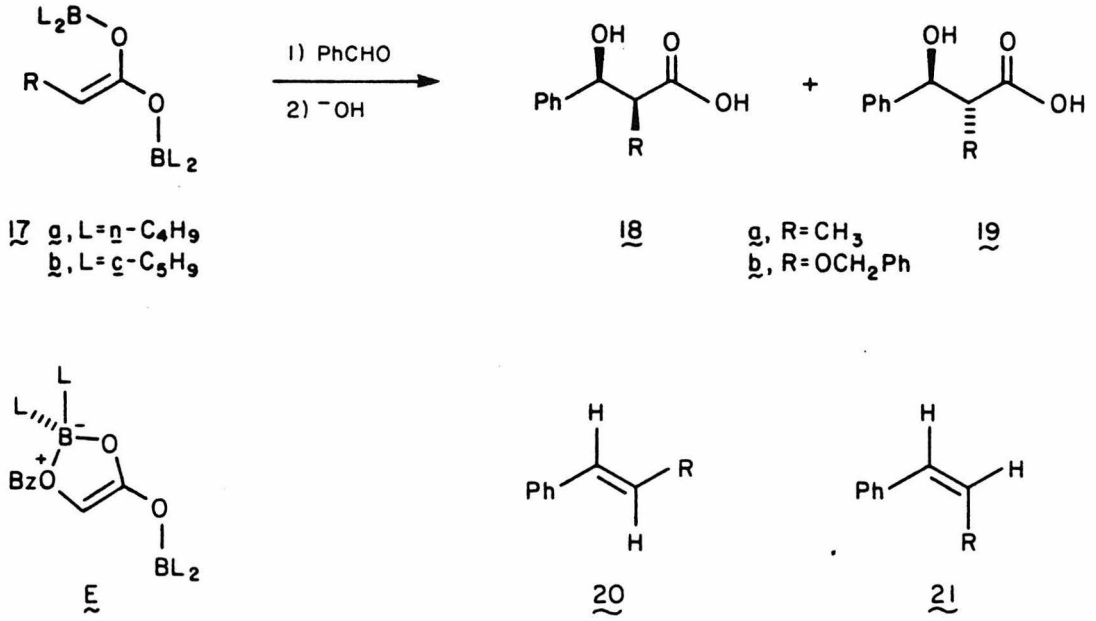
a) All reactions employed DPEA as base and were carried out at -78°C. b) Ratios determined by ^{1}H NMR. c) Values refer to yields determined by ^{1}H NMR; those in parentheses were isolated. d) 2,3-Dimethyl-2-butyl (thexyl). e) For the comparative experiments in ether see Table II, Entries S, T. f) Ref. 2a.



(7)

was found that dialkylboryl propionates ($L_2BOCOEt$) are readily enolized by DPEA and triflates 4a and 4b. The addition of propanoic acid to 2 equiv of triflate and DPEA (Et_2O, 0°C) resulted in the formation of enediolates 17a and 17b (R = CH_3) respectively. Both enolates were subject to aldol condensation under the usual conditions (Et_2O, -78°C). Enediolate 17a (R = CH_3) afforded a ratio 18a:19a = 35:65 while 17b (R = CH_3) exhibited moderately greater threo-diastereoselection (18a:19a = 20:80). Under similar conditions, the enediolate 17a (R = OCH_2Ph) derived from benzyloxyacetic acid afforded exclusively the aldol stereoisomer 19b in 85% yield. Confirmation of the aldol stereochemistry in both cases was achieved by stereospecific trans-fragmentation with dimethylformamide dimethylacetal to the trans and cis-olefins 20 and 21.[28,29] From the propionate aldol mixture (18a:19a = 20:80), this procedure afforded the ratio 20a:21a = 20:80 while the

Scheme IV

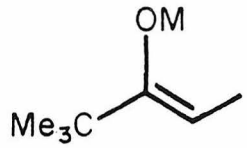
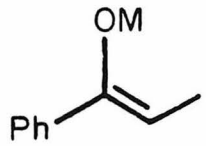
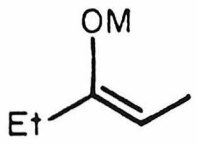
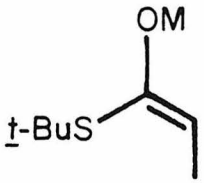
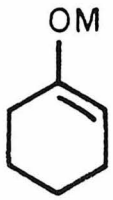


hydroxy acid 19b was observed to give exclusively the cis-vinyl ether 21b (20b:21b $\leq$ 3:97). Since our earlier studies have demonstrated that boron enolate geometry strongly correlates with product stereochemistry, enediolate 17 can be employed to directly compare cis vs trans-boron enolate reactivity ($k_{cis}:k_{trans} \cong$ 18:19) via internal competition. These experiments imply that trans-propionate enolates, and presumably trans-ethyl ketone enolates (c.f. 2t) exhibit somewhat greater reactivity (2-4X) than the corresponding cis-isomers.[30] These observations are

in marked contrast to those of Dubois[5c] who observed that the trans-lithium enolate derived from 3-pentanone reacted 7-8 times more slowly than the corresponding cis-isomer. These differential rate effects could be interpreted in terms of diastereoisomeric transition state steric effects;[6] alternatively, differing levels of aggregation of the two lithium enolates could also account for the observed rate differences. The markedly enhanced aldol stereoselection which was observed for the benzyloxyacetic acid enediolate 17a (R = OCH_2Ph) can be rationalized by invoking internal complexation (c.f. E, Scheme IV) between the (Z)-boron and benzyloxy substituents.[30]

Table IV summarizes the results of five kinetic metal enolate condensations with benzaldehyde. The influence of the metal center, M, and enolate ligand, R_1, on aldol stereoselection are readily accommodated by the general transition state model (Scheme I). For cis-enolates, when R_1 is large (Entry A) transition state C is strongly destabilized relative to D by $R_1 \leftrightarrow R_2$ interactions, and erythro-diastereoselection is uniformly high. As the enolate ligand, R_1, is decreased in size, the combination of steric effects of both R_1 and the metal center ($R_1 \leftrightarrow R_2$ and $R_2 \leftrightarrow L$) become important in maintaining erythro-selectivity (Entries B, C). Related arguments hold for trans-enolates relative to transition state B.

Table IV. Influence of Metal Center on Kinetic Aldol Reactions With Benzaldehyde.

Entry	Enolate	Metal (M)	Erythro:Threo
A		Li	>98:2[c]
		MgBr	>97:3[d]
		$B(C_4H_9)_2$	>97:3[f]
B		Li	88:12[c]
		$B(C_4H_9)_2$	>97:3[f]
C		Li[a]	80:20
		$B(C_4H_9)_2$	>97:3[f]
D		Li[b]	60:40
		$B(C_4H_9)_2$	5:95
E		Li	48:52[c]
		$Al(Et)_2$	50:50[e]
		$B(C_5H_9)C_6H_{13}$	4:96[f]

a) Prepared from the (Z)-silylenol ether and methyllithium (Ref. 5c). b) Prepared from 6 and LDA (THF); enolate ratio, 9:91; condensation carried out for 5 sec. c) Ref. 6. d) Ref. 5b. e) Ref. 9b. f) Ref. 2a.

Conclusions

The results discussed above illustrate the importance of the metal center in controlling aldol diastereoselection. By proper choice of the boron ligands and reaction solvent, we have shown that consistently good correlation between enolate geometry and aldol product stereochemistry can be obtained. These methods should find numerous applications in the total synthesis of natural products.

Experimental Section

Infrared spectra were recorded on a Beckmann 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz), integration, and interpretation. ^{13}C magnetic resonance spectra were recorded on a JEOL-FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Multiplicities are reported using the format given above. Mass spectra were recorded on a Dupont 21-492B spectrometer by the California Institute of Technology Microanalytical Laboratory. Combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Analytical gas-liquid chromatography was carried out on a Varian Aerograph Model 1400 gas chromatograph, equipped with a flame ionization detector, using a 6 ft x 0.125 in stainless steel column packed with 10% Carbowax 20M on 60-80 mesh Chromosorb W. Preparative gas-liquid chromatography was performed on a Varian Aerograph Model 90-P gas chromatograph using a 6 ft x 0.25 in copper

column packed with 10% SE-30 on 40-60 mesh Chromosorb W support. Medium pressure chromatography was performed using EM Laboratories LoBar silica gel 60 prepacked columns on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP Lab Pump. Analytical HPLC was performed on a Water's Associates Model ALC 202/401 high pressure liquid chromatograph equipped with a Model 6000 pump and ultraviolet and refractive index detectors.

Optical rotations were recorded on a Perkin Elmer 141 polarimeter at the sodium D line.

When necessary, solvents and reagents were dried prior to use. Diethyl ether and tetrahydrofuran were distilled from benzophenone ketyl. Pentane and chloroform were filtered through activity I alumina. Methylene chloride, diisopropylethylamine, 2,6-lutidine, and 2,4-lutidine were distilled from calcium hydride. Benzaldehyde, n-butyraldehyde, and isobutyraldehyde were distilled and stored at 0°C. Methacrolein and tiglic aldehyde were distilled immediately prior to use. Chlorotrimethylsilane was distilled from quinoline immediately prior to use. Propionyltrimethylsilane was prepared by the procedure of Heathcock[6] and co-workers. The method of Vedejs[31] and co-workers was used for the preparation of MoO_5·pyridine·HMPT (MoOPH). n-Butyllithium was titrated by the procedure of Watson and Eastham.[32] All other reagents were used as

received.

Preparation of Dialkylboryl trifluoromethanesulfonates.

General Considerations on Handling and Storage. The dialkylboryl triflates are extremely air and moisture sensitive reagents which must be transferred and stored under a scrupulously maintained argon atmosphere. With proper handling the reagents can be stored for several months without any significant decomposition. Although the dialkylboryl triflates often become yellow or orange upon storage, this discoloration had no significant effect on the yields of subsequent reactions. The trifluoromethanesulfonic acid[33] used in the procedures below was obtained from a freshly opened bottle and was not purified before use; partially used bottles which have been opened more than a few weeks should be avoided.

Diethylboryl trifluoromethanesulfonate (4c).[2a] To 13.1 g (0.133 mol) of triethylboron[34] under argon at 0°C was added 20.0 g (0.133 mol) of trifluoromethanesulfonic acid dropwise over 25 min. After the addition, the pale brown solution was stirred for 30 min at room temperature and was then distilled (54-55°C, 24 mm) to yield 26.0 g (90%) of diethylboryl triflate as a colorless, pyrophoric liquid. This reagent offered no advantages in reactivity or selectivity over di-n-butylboryl triflate which is more easily handled due to its greater stability.

Di-n-butylboryl trifluoromethanesulfonate (4a). The reagent was prepared by the procedure of Mukaiyama[12] and co-workers and was stored at room temperature.

Dicyclopentylboryl trifluoromethanesulfonate (4b). To 14.9 g (68 mmol) of tricyclopentylboron[35] at room temperature under argon was added 10.2 g (68 mmol) of trifluoromethanesulfonic acid dropwise with intermittent cooling to maintain the reaction temperature at approximately room temperature. The deep orange solution was stirred for 30 min at room temperature and was then distilled (70-72°C, 1 mm) to yield 18.3 g (90%) of the air-sensitive boryl triflate as a colorless liquid. Dicyclopentylboryl triflate was stored at 0°C.

Cyclopentylthexylboryl trifluoromethanesulfonate (4d)[2a]. A solution of 1.25 mL (12 mmol) of 9.6 M borane methyl-sulfide complex and 1.01 g (12 mmol) of 2,3-dimethyl-2-butene was stirred under argon for 2 h at 0°C. After the addition of 10 mL of tetrahydrofuran the solution was cooled to -30°C and 0.82 g (12 mmol) of cyclopentene were rapidly added. The solution was stirred 1 h at -30°C to 25°C, cooled to -78°C, and 1.65 g (11 mmol) of trifluoromethanesulfonic acid added dropwise (hydrogen evolved with foaming). After the addition the solution was stirred at -78°C for 1 h and at -60°C for 15 min. The reagent was then ready for use in subsequent reactions,

it was not isolated.

General Procedures for the Formation of Boron Enolates.

Kinetic Generation of Boron Enolates. To a stirred solution of amine (1.1-1.2 equiv) and dialkylboryl triflate (1.1 equiv) in the indicated solvents (2-3 mL/mmol substrate) at the indicated temperatures ($\leq$25°C) under an argon atmosphere was added the substrate (1.0 equiv) dropwise. For reactions in ether and pentane, the progress of the reaction could be monitored by the formation of a white precipitate of ammonium triflate. After the indicated time period the dialkylboron enolate was ready for subsequent reactions.

Equilibration of Boron Enolates. After kinetic enolization at 0°C for 5 min the mixture was heated at reflux for 2-3 h. The dialkylboron enolate solution was then ready for subsequent reactions. The choice of amine and solvent is dependent upon the structure of the ketone. While sterically hindered ketones, such as tert-butylethylketone, can be equilibrated by diisopropylethylammonium triflate in ether, simpler ketones, such as diethylketone, require use of the more acidic 2,6-lutidinium triflate in carbon tetrachloride for equilibration (see text for additional details). No precipitate was observed when chlorinated hydrocarbons were used as solvents due to the solubility of ammonium triflates in these solvents.

Silylation of Boron Enolates. To a 0.5 M solution of boron enolate in ether at -78°C under an argon atmosphere was added n-butyllithium (3.3 equiv). After 15 min, chlorotrimethylsilane (3.3 equiv) was added and the solution allowed to warm to room temperature where a white precipitate formed. The mixture was partitioned between brine and pentane and the brine extracted once with pentane; the combined pentane extracts were washed successively with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude trimethylsilylenol ethers. Yields in this reaction exceeded 100% due to the presence of boron-derived side products. The enol ethers were analyzed by comparison with authentic samples[6] using gas-liquid chromatography or ^1H NMR (although the spectrum was complicated by the side products the olefin region was clean).

General Procedures for the Aldol Condensation of Dialkylboron Enolates.

To a solution of the dialkylboron enolate at -78°C under an argon atmosphere was added the aldehyde (non-enolizable: 1.0 equiv, neat; enolizable: 1.2-1.5 equiv, solution in 2-3 mL solvent/mmol aldehyde). The mixture was then stirred for 30 min at -78°C and 1 h at 0°C.

Hydrogen Peroxide Workup. The reaction was quenched

by addition to pH 7 phosphate buffer. The mixture was extracted twice with ether and the combined ether extracts were washed with brine and concentrated in vacuo. The crude oil was then dissolved in methanol (3 mL/mmol) at 0°C and 30% hydrogen peroxide (1 mL/mmol) added. After stirring at room temperature for 2 h, water (5-10 mL/mmol) was added, and the milky mixture concentrated in vacuo to remove most of the methanol. The residue was extracted twice with ether and the combined ether solution was washed with 5% aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude aldol adducts.

MoOPH Workup. The dialkylboron alkoxides were oxidized by the addition of MoOPH (1.5 equiv) and the yellow slurry was stirred initially at 0°C (30 min) then at room temperature (45 min). The mixture was added to 1 N aqueous sodium hydroxide and extracted with ether. The ether solution was washed with dilute brine and brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude aldol adducts.

Silylation of the di-n-butylboron enolate of 3-pentanone (Table I, Entry B). Kinetic enolization of 0.17 g (2.0 mmol) of diethyl ketone with 0.26 g (2.4 mmol) of 2,6-lutidine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at -78°C for 30 min was

followed by silylation to afford 1.1 g (>100%) of unpurified trimethylsilylenol ether. Analytical gas-liquid chromatography indicated the ratio of 2c:2t was 69:31. Assignments were made by comparison to a known mixture[6] generated by trapping the enolates formed using lithium diisopropylamide.

Silylation of the dicyclopentylboron enolate of 2-methyl-3-pentanone (Table I, Entry I). Kinetic enolization of 0.20 g (2.0 mmol) of 2-methyl-3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.66 g (2.2 mmol) of dicyclopentylboryl triflate in 5 mL of ether at 0°C for 30 min was followed by silylation to afford 0.81 g (>100%) of unpurified trimethylsilylenol ether. Analytical gas-liquid chromatography indicated the ratio of 2c:2t was 19:81. Assignments were made by comparison to a known mixture[6] generated by trapping the enolates formed with lithium diisopropylamide.

Silylation of the di-n-butylboron enolate of 2,2-dimethyl-3-pentanone (Table I, Entry K). Enolization and equilibration of 0.23 g (2.0 mmol) of 2,2-dimethyl-3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of refluxing ether for 2 h was followed by silylation to afford 1.4 g (>100%)

of unpurified trimethylsilylenol ether. A sharp quartet for the vinyl proton appeared at δ 4.47 (lit.[6] 4.40) in the ^{1}H NMR spectrum for the cis-enolate, 2c. Assignment was made by comparison to a known sample generated by trapping the enolate formed using lithium diisopropylamide.

Silylation of the di-n-butylboron enolate of 4-methyl-3-hexanone (Table I, Entry L). Kinetic enolization of 0.23 g (2.0 mmol) of 5-methyl-3-hexanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at -78°C for 30 min was followed by silylation to afford 1.2 g (>100%) of unpurified trimethylsilylenol ether. A sharp quartet for the vinyl proton appeared at δ 4.43 in the ^{1}H NMR spectrum for the cis-enolate, 2c.

Silylation of the di-n-butylboron enolate of propiophenone (Table I, Entry M). Kinetic enolization of 0.27 g (2.0 mmol) of propiophenone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at room temperature for 1 h was followed by silylation to afford 1.3 g (>100%) of unpurified trimethylsilylenol ether. Analytical gas-liquid chromatography indicated only cis-enol ether, 2c

(<1% trans) was present. Assignment was made by comparison to an authentic sample[6] generated by trapping the enolate formed with lithium diisopropylamide. A sharp quartet for the vinyl proton appeared at δ 5.31 in the ^{1}H NMR spectrum

Silylation of the di-n-butylboron enolate of S-tert-butyl propanethioate (Table I, Entry N). Kinetic enolization of 0.15 g (1.0 mmol) of S-tert-butyl propanethioate with 0.14 g (1.1 mmol) of diisopropylethylamine and 0.30 g (1.1 mmol) of di-n-butylboryl triflate in 5 mL of ether at 0°C for 30 min was followed by silylation to afford (0.95 g (>100%) of unpurified trimethylsilylenol ether. A shart quartet for the vinyl proton appeared at δ 5.25 in the ^{1}H NMR spectrum for the trans-enolate, 2t. In samples containing cis-enolate, 2c, an additional signal appeared at δ 5.21 (q). Assignments were made by comparison to known mixtures generated by trapping the enolates formed using lithium diisopropylamide in analogy to the work of Ireland,[17] et al.

Erythro-1-hydroxy-2-methyl-1-phenyl-3-pentanone (Table II, Entry A).[2a] Kinetic enolization of 0.52 g (6.0 mmol) of 3-pentanone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol)

of di-n-butylboryl triflate in 15 mL ether at -78°C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.01 g (88%) of colorless oil. No threo-aldol adduct, 12T, was detected by ^{1}H NMR of the unpurified product, vide infra. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 8:1) to afford 0.89 g (77%) of erythro aldol adduct 12E as a colorless oil: IR (CCl_4, 5%) 3605, 3500, 2985, 2969, 1705, 1695, 696 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.17 (s, 5, aromatic), 4.80 (d, J = 3 Hz, 1, erythro-C<u>H</u>-OH), 3.19 (s, 1, -O<u>H</u>), 2.65 (m, 1, -CO-C<u>H</u>-), 2.21 (m, 2, -CO-C<u>H$_2$</u>-), 0.98 (d, 3, -CH-C<u>H$_3$</u>), 0.89 (t, 3, -CH$_2$-C<u>H$_3$</u>). Authentic[6] threo-adduct gave rise to an additional signal at δ 4.48 (d, J = 8 Hz, threo-C<u>H</u>-OH). These spectra are identical with those reported in the literature[6] for this compound.

Erythro-5-hydroxy-4-methyl-3-octanone (Table II, Entry C). Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at -78°C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of n-butyraldehyde to yield 0.22 g (69%) of a colorless oil. No threo-aldol adduct, 12T, was

detected by ^{1}H NMR of the unpurified product, vide infra. The product was bulb-to-bulb distilled (130°C, 1 mm) to afford 0.20 g (65%) of erythro-aldol adduct, 12E, as a colorless oil: IR (neat) 3480, 2960, 1700, 1455, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.89 (m, 1, erythro-C<u>H</u>-OH), 2.92-2.38 (m, 4, -CO-C<u>H</u>$_2$-, -CO-C<u>H</u>-, -O<u>H</u>), 1.65-0.82 (m, 13, aliphatic). Preparative gas-liquid chromatographic separation of a mixture of aldol products generated by lithium enolate condensation provided compounds for which assignments for the ^{1}H NMR spectra were made by a comparison of the carbinol protons: erythro δ 3.89 (m, J = 3 Hz) and threo δ 3.65 (m, J = 7 Hz). The coupling constants were determined by an analysis of the signal of the proton on carbon 4.

Exact mass calcd. for $C_9H_{18}O_2$: 158.131. Found: 158.132.

Erythro-5-hydroxy-4,6-dimethyl-3-heptanone (Table II, Entry D). Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at -78°C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of isobutyraldehyde to yield 0.21 g (65%) of a colorless oil. No threo-aldol adduct, 12T, was detected by ^{1}H NMR

of the unpurified product, vide infra. The product was bulb-to-bulb distilled (130°C, 1 mm) to afford 0.19 g (61%) of erythro-aldol adduct, 12E, as a colorless oil: IR (neat) 3490, 2970, 1700, 1455, 973 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (d of d, J = 3 Hz and 8 Hz, 1, erythro-CH-OH), 2.95 (s, 1, -OH), 2.71 (d of q, J = 3 Hz and 7 Hz, 1, -CO-CH-), 2.50 (q, 2, -CO-CH_2-), 1.61 [m, 1, -CH$(CH_3)_2$], 1.29-0.80 (m, 12, methyls). Threo-aldol adduct, prepared via the lithium enolate, gave rise to an additional signal at δ 3.41 (t, J = 7 Hz, threo-CH-OH).

Exact mass calcd. for $C_9H_{18}O_2$: 158.131. Found: 158.134.

Erythro- and threo-5-hydroxy-4,6-dimethyl-6-hepten-3-one (Table II, Entry E). Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at -78°C for 30 min was followed by aldol condensation and MoOPH workup with 0.21 g (3.0 mmol) of methacrolein to yield 0.23 g (72%) of a yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^1H NMR to be 92:8. The product was bulb-to-bulb distilled (150°C, 1 mm) to afford 0.21 g (68%) of a colorless oil: IR (neat) 3480, 3100, 2980, 1705, 1650, 1457, 977, 900

cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.98 (m, 2, olefin), 4.36 (d, J = 3 Hz, 0.92, erythro-CH-OH), 4.17 (d, J = 8 Hz, 0.08, threo-CHOH), 2.90 to 2.39 (m, 4, -CO-CH, -CO-CH_2-, and -OH), 1.69 (s, 3, =C-CH_3), 1.20 to 0.95 (m, 6, methyls).

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

Erythro- and threo-5-hydroxy-4,6-dimethyl-(E)-6-octen-3-one (Table II, Entry F). Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at -78°C for 30 min was followed by aldol condensation and MoOPH workup with 0.25 g (3.0 mmol) of tiglic aldehyde to yield 0.24 g (70%) of a yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^1H NMR to be 93:7. The product was bulb-to-bulb distilled (150°C, 1 mm) to afford 0.22 g (65%) of a colorless oil: IR (neat) 3490, 2970, 1700, 1667, 1450, 970, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.47 (m, 1, olefin), 4.58 (s, 1, -OH), 4.24 (d, J = 5 Hz, 0.93, erythro-CH-OH), 4.11 (d, J = 9 Hz, 0.07, threo-CH-OH), 2.92 to 2.32 (m, 3, -CO-CH- and -CO-CH_2-), 1.60 and 1.55 (d and s, 6, =CH-CH_3 and =C-CH_3), 1.22 (m, 6, methyls).

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

Erythro-1-hydroxy-5-methyl-1-phenyl-3-hexanone (Table II, Entry H).[2a] Kinetic enolization of 0.68 g (6.0 mmol) of 2-methyl-4-hexanone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-n-butylboryl triflate in 15 mL of ether at -78°C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.44 g (>100%) of a pale yellow oil. No threo-aldol adduct, 12T, was detected by ^{1}H NMR of the unpurified product, vide infra. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 8:1) to afford 1.09 g (82%) of erythro-aldol adduct, 12E, as a colorless oil: IR (CCl_4, 5%) 3605, 3510, 2958, 1707, 1694, 1098, 1078, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.23 (s, 5, aromatic), 4.88 (d, J = 4 Hz, 1, erythro-C<u>H</u>-OH), 3.0 (s, 1, -O<u>H</u>), 2.64 (m, 1, -CO-C<u>H</u>-), 2.3-1.75 (m, 3, -CO-C<u>H</u>$_2$-C<u>H</u>-), 0.98 (d, 3, -CH-C<u>H</u>$_3$), 0.83 [d, 6, -CH-(C<u>H</u>$_3$)$_2$]. Threo-aldol adduct, from reactions using dicyclopentylboryl triflate, gave rise to an additional signal at δ 4.64 (d, J = 9 Hz, threo-C<u>H</u>-OH).

Exact mass calcd. for $C_{14}H_{20}O_2$: 220.146. Found: 220.146.

Erythro- and threo-1-hydroxy-2,4-dimethyl-1-phenyl-3-pentanone (Table II, Entry J).[2a] Kinetic enolization

of 0.60 g (6.0 mmol) of 2-methyl-3-pentanone with 0.31 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-n-butylboryl triflate in 15 mL of ether at -78°C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.10 g (89%) of a pale yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^{1}H NMR to be 44:56. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 12:1) to afford 0.80 g (65%) of a colorless oil: IR (CCl_4, 5%) 3480, 3030, 2970, 1707, 1450, 1100, 1005, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.30 (s, 5, aromatic), 4.91 (d, J = 5 Hz, 0.44, erythro-CH-OH), 4.70 (d, J = 8 Hz, 0.56, threo-CH-OH), 3.40 (s, 1, -OH), 3.22 to 2.46 [m, 2, -CO-CH-CH and -CO-CH-$(CH_3)_2$], 1.19 to 0.89 (m, 9, methyls). These spectra are identical with those reported in the literature[6] for this compound.

Erythro-1-hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone (Table II, Entry L).[2a] Enolization and equilibration of 0.68 g (6.0 mmol) of 2,2-dimethyl-3-pentanone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.82 g (6.6 mmol) of di-n-butylboryl triflate in 15 mL of refluxing ether for 2 h was followed by aldol condensation and hydrogen peroxide workup woth 0.64 g (6.0

mmol) of benzaldehyde to yield 1.01 g (76%) of a yellow oil. No threo-aldol adduct, 12T, was detected by ^{1}H NMR of the unpurified product, vide infra. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 8:1) to afford 0.86 g (65%) of erythro-aldol adduct, 12E, as a colorless oil: IR (CCl_4, 5%) 3620, 3500, 2970, 1695, 1685, 982, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.25 (s, 5, aromatic), 4.76 (d, J = 4 Hz, 1, erythro-CH-OH), 3.32-2.97 (m, 1, -CO-CH-), 3.18 (s, 1, -OH), 1.02 [s, 9, -C-$(CH_3)_3$], 0.99 (s, 3, -CH-CH_3). Authentic[6] threo-adduct gave rise to an additional signal at δ 4.60 (d, J = 7 Hz, threo-CH-OH). These spectra are identical with those reported in the literature[6] for this compound.

Erythro-3-hydroxy-2-methyl-1,3-diphenyl-1-propanone (Table II, Entry M).[2a] Kinetic enolization of 0.80 g (6.0 mmol) of propiophenone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-n-butylboryl triflate in 15 mL of ether at room temperature for 1 h was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.60 g (>100%) of a yellow oil. No threo-aldol adduct, 12T. was detected by ^{1}H NMR of the unpurified product, vide infra. The product was

chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 9:1) to afford 1.12 g (78%) of erythro-aldol adduct, 12E, as a viscous oil: IR (CCl_4, 4%) 3605, 3520, 1670, 1662, 1211, 970, 698 cm^{-1}; ^1H NMR (CCl_4) δ 7.95-7.75 (m, 2, aromatic), 7.55-7.0 (m, 8, aromatic), 5.05 (d, J = 3 Hz, 1, erythro-CH-OH), 3.53 (m, 1, -CO-CH-), 3.4 (s, 1, -OH), 1.1 (d, 3, $-CH_3$). Authentic[6] threo-adduct gave rise to an additional signal at δ 4.92 (d, J = 9 Hz, threo-CH-OH). These spectra are identical with those reported in the literature[6] for this compound.

Erythro-1-(1-t-butyloxycarbonyl-1-azacyclopenta-2,4-dien-2-yl)-3-hydroxy-2-methyl-3-phenyl-1-propanone (Table II, Entry N).[26] Kinetic enolization of 0.446 g (2.0 mmol) of 1-(1-t-butyloxycarbonyl-1-aza-cyclopenta-2,4-dien-2-yl)-1-propanone[36] with 0.310 g (2.4 mmol) of diisopropylethylamine and 0.603 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL ether at -78°C for 45 min was followed by aldol condensation and MoOPH workup with 0.22 g (2.0 mmol) of benzaldehyde to yield 0.723 g (>100%) of a light yellow oil. No threo-aldol adduct 12T was detected by ^1H NMR of the unpurified product, vide infra. The product was chromatographed at medium pressure over silica gel (hexane, ethyl acetate) to give 0.47 g (70%) of erythro-aldol adduct 12E as a colorless oil: IR (CCl_4) 3500, 2980,

2940, 1750, 1700, 1650, 1440, 1410, 1370, 1310, 1150, 945, 845, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (broad s, 5, phenyl), 7.28-7.15 (m, 1, pyrrole), 6.78-6.70 (m, 1, pyrrole), 6.15-6.05 (m, 1, pyrrole), 5.19 (d, J = 4 Hz, 1, -CHCHOH), 3.64 (broad s, 1, -OH), 3.40 (d of q, J = 7 Hz, 4Hz, 1, CH_3CHCHOH), 1.57 (s, 9, t-butyl CH_3's), 1.13 (d, J = 7 Hz, 3, CH_3CH-). In the threo-aldol adduct[36] the signal for CH_3CHCHOH (carbinol center proton) appears at δ 4.90 (d, J = 8 Hz). These spectra are identical with those reported in the literature[36] for this compound.

Erythro- and threo-3-hydroxy-2-methyl-1-trimethylsilyl-1-propanone (Table II, Entry 0). Kinetic enolization of 0.13 g (1.0 mmol) of propionyltrimethylsilane with 0.16 g (1.2 mmol) of diisopropylethylamine and 0.30 g (1.1 mmol) of di-n-butylboryl triflate in 5 mL of ether at -78°C for 30 min was followed by aldol condensation and MoOPH workup with 0.11 g (1.0 mmol) of benzaldehyde to yield 0.16 g (66%) of a yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^1H NMR to be 19:81. The product was bulb-to-bulb distilled (150°C, 1 mm) to afford 0.12 g (53%) of a colorless oil: IR (neat) 3460, 3030, 2960, 1635, 1450, 1250, 843, 755, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (s, 5,

aromatic), 5.03 (d, J = 3 Hz, 0.23, erythro-CH-OH), 4.72 (d, J = 8 Hz, 0.77, threo-CH-OH), 3.31 (m, 1, -CO-CH-), 2.8 (b, 1, -OH), 0.83 (two d, 3, -CH-CH_3), 0.19 [s, 9, -Si-$(CH_3)_3$]. Distillation resulted in a slight enrichment in the erythro-adduct. These spectra are identical with those reported in the literature[6] for this compound.

Erythro- and threo-S-(1,1-dimethylethyl)-3-hydroxy-2-methyl-3-phenylpropanethioate (Table II, Entry S). Kinetic enolization of 0.29 g (2.0 mmol) of S-tert-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at 0°C for 30 min was followed by aldol condensation and MoOPH workup with 0.21 g (2.0 mmol) of benzaldehyde to yield 0.40 g (80%) of a yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^1H NMR be 10:90. The product was bulb-to-bulb distilled (150°C, 0.5 mm) to afford 0.31 g (75%) of a colorless oil: IR (neat) 3450, 3030, 2960, 1675, 1450, 1365, 960, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (s, 5, aromatic), 5.03 (d, J = 4 Hz, 0.10, erythro-CH-OH), 4.74 (d, J = 8 Hz, 0.90, threo-CH-OH), 2.85 (m, 1, -CO-CH-), 2.5 (b, 1, -OH-), 1.48 [s, 9, -S-$(CH_3)_3$], 1.03 (two d, 3, -CH_3).

Exact mass calcd. for $C_{14}H_{20}O_2S$: 252.118. Found: 252.119.

Erythro- and threo-S-(1,1-dimethylethyl-3-hydroxy-2-methylhexanethioate (Table II, Entry U). Kinetic enolization of 0.29 g (2.0 mmol) of S-tert-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at 0°C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of n-butyraldehyde to yield 0.31 g (70%) of a pale yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^{1}H NMR to be 10:90. The product was bulb-to-bulb distilled (150°C, 1 mm) to afford 0.29 g (67%) of a colorless oil: IR (neat) 3450, 2960, 1675, 1455, 1365, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.8 (b, 1, -OH), 3.89 (m, 0.10, erythro-CH-OH), 3.64 (m, 0.90, threo-CH-OH), 2.61 (m, 1, -CO-CH-), 1.49 (s, 9, -S-$(CH_3)_3$), 1.27 to 0.75 (m, 10, aliphatics). Preparative gas-liquid chromatographic separation of a mixture of aldol products generated by lithium enolate condensation provided compounds for which assignments for the ^{1}H NMR spectra were made by a comparison of the carbinol protons: erythro δ 3.89 (m, J = 3 Hz) and threo δ 3.64 (m, J = 6Hz). The coupling constants were determined by an analysis of the signal of the proton on carbon 2.

Exact mass calcd. for $C_{10}H_{22}O_2S$: 218.134. Found: 218.133.

Erythro- and threo-S-(1,1-dimethylethyl)-3-hydroxy-2,4-dimethylpentanethioate (Table II, Entry V). Kinetic enolization of 0.29 g (2.0 mmol) of S-tert-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at 0°C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of isobutyaldehyde to yield 0.29 g (66%) of a pale yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^{1}H NMR to be 9:91. The product was bulb-to-bulb distilled (150°C, 1 mm) to afford 0.26 g (63%) of a colorless oil: IR (neat) 3500, 2960, 1650, 1455, 1365, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.51 (d of d, J = 3 Hz and 8 Hz, 0.09, erythro-C<u>H</u>-OH), 3.30 (t, J = 7 Hz, 0.91, threo-C<u>H</u>-OH), 2.82 (s, 1, -O<u>H</u>), 2.69 (m, J = 7 Hz, -CO-C<u>H</u>-), 1.70 (m, J = 7 Hz, 1, -C<u>H</u>-$(CH_3)_2$), 1.48 (s, 9, -S-$(C\underline{H}_3)_3$), 1.18 (d, 3, -C<u>H</u>$_3$), 0.89 (two d, 6, -CH-$(C\underline{H}_3)_3$).

Exact mass calcd. for $C_{11}H_{22}O_2S$: 218.134. Found: 218.133.

Erythro- and threo-S-(1,1-dimethylethyl)-3-hydroxy-2,4-dimethyl-4-pentenethioate (Table II, Entry W). Kinetic enolization of 0.29 g (2.0 mmol) of S-tert-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL

of ether at 0°C for 30 min was followed by aldol condensation and MoOPH workup with 0.21 g (3.0 mmol) of methacrolein to yield 0.29 g (66%) of a yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^{1}H NMR to be 12:88. The product was bulb-to-bulb distilled (150°C, 1 mm) to afford 0.28 g (65%) of a pale yellow oil: IR (neat) 3460, 3080, 2960, 1675, 1455, 1365, 960, 900, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.92 (m, 2, olefins), 4.37 (d, J = 4 Hz, 0.12, erythro-CH-OH), 4.14 (d, J = 9 Hz, 0.88, threo-CH-OH), 2.76 (m, 1, -CO-CH-), 2.49 (s, 1, -OH), 1.73 (s, 3, =C-CH_3), 1.50 (s, 9, -S-$(CH_3)_3$), 1.13 (d, 3, -CH_3).

Exact mass calcd. for $C_{11}H_{20}O_2S$: 216.118. Found: 216.119.

Erythro- and threo-S-(1,1-dimethylethyl)-3-hydroxy-2,4-dimethyl-4-hexenethioate (Table II, Entry X). Kinetic enolization of 0.29 g (2.0 mmol) of S-tert-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL of ether at 0°C for 30 min was followed by aldol condensation and MoOPH workup with 0.25 g (3.0 mmol) of tiglic aldehyde to yield 0.31 g (71%) of a yellow oil. The ratio of erythro:threo-aldol adducts, 12E:12T, in the unpurified product was determined by ^{1}H NMR to be 18:82. The product was

bulb-to-bulb distilled (150°C, 1 mm) to afford 0.28 g (68%) of a colorless oil: IR (neat) 3480, 1680, 1455, 1370, 960, 830, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.47 (m, 1, olefin), 5.03 (b, 1, -OH), 4.19 (d, J = 5 Hz, 0.18, erythro-CH-OH), 4.10 (d, J = 9 Hz, 0.82, threo-CH-OH), 2.72 (m, 1, -CO-CH-), 1.59 and 1.53 (d and s, 6, =CH-CH_3, =C-CH_3), 1.48 (s, 9, -S-$(CH_3)_3$), 1.03 (two d, 3, -CH_3).

Exact mass calcd. for $C_{12}H_{22}O_2S$: 230.134. Found: 230.134.

Threo-2-phenylhydroxymethyl-1-cyclohexanone (Table III, Entry F).[2a] Kinetic enolization of 0.98 g (10 mmol) of cyclohexanone with 1.42 g (11 mmol) of diisopropylethylamine and 11 mmol of cyclopentylthexylboryl triflate (2c), generated in situ, in 20 mL of tetrahydrofuran at -78°C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 1.06 g (10.0 mmol) of benzaldehyde to yield 1.92 g (94%) of a pale yellow oil. No erythro-aldol adduct, 14E, was detected by ^1H NMR of the unpurified product, vide infra. The product was chromatographed on 40 g of silica gel (hexane:ethyl acetate, 1:1) to afford 1.49 g (73%) of threo-aldol adduct, 14T, as a white crystalline solid: mp 73.5-76°C; IR (CCl_4) 3540, 2943, 1697, 1450, 1129, 1043, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (s, 5, aromatic),

4.6 (d, J = 8 Hz, 1, threo-CH-OH), 3.6 (b, 1, -OH), 2.6-1.0 (m, 9, cyclohexyl). Authentic[6] erythro-adduct gave rise to an additional signal at δ 5.31 (d, J = 3 Hz, erythro-CH-OH). The melting point and spectra of this compound are identical with those reported in the literature.[8]

Erythro- and threo-3-hydroxy-2-methyl-3-phenylpropanoic acid (18,19a). To a stirred solution of 0.57 g (4.4 mmol) of diisopropylethylamine and 1.15 g (4.2 mmol) of di-n-butylboryl triflate in 15 mL of ether at 0°C under an argon atmosphere was added 0.15 g (2.0 mmol) of propanoic acid dropwise. A white precipitate appeared immediately. After 45 min the white slurry was cooled to -78°C and 0.21 g (2.0 mmol) of benzaldehyde was added. The mixture was stirred for 30 min at -78°C and 1 h at 0°C. The reaction mixture was then added to saturated aqueous sodium bicarbonate and ether. After separation of the layers the organic phase was extracted with additional saturated aqueous sodium bicarbonate. The combined aqueous solution was successively acidified to pH 2 with 6 N hydrochloric acid, saturated with sodium chloride, extracted twice with ether, and dried (Na_2SO_4). Concentration of the ether solution in vacuo gave 0.31 g (87%) of clear oil: IR (neat) 3420, 2980, 1710, 1450, 1200, 1010, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ

7.33 (s, 5, aromatic), 5.42 (s, 2, -O<u>H</u> and -CO_2<u>H</u>), 5.16 (d, J = 4 Hz, 0.35, <u>erythro</u>-C<u>H</u>-OH), 4.73 (d, J = 9 Hz, 0.65, <u>threo</u>-C<u>H</u>-OH), 2.79 (m, 1, -CO-C<u>H</u>-), 1.10 and 0.98 (two d, 3, -$C\underline{H}_3$). The spectra of this compound are identical with those reported in the literature.[6]

<u>Threo</u>-3-hydroxy-3-phenyl-2-phenylmethoxypropanoic acid (19b). To a stirred solution of 0.32 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-<u>n</u>-butylboryl triflate in 5 mL of ether at 0°C under an argon atmosphere was added 0.17 g (1 mmol) of phenylmethoxyethanoic acid dropwise. A white precipitate appeared immediately. After 1 h the white slurry was cooled to -78°C and 0.11 g (1.0 mmol) of benzaldehyde was added. The mixture was stirred for 30 min at -78°C and 1 h at 0°C. The reaction mixture was then added to saturated aqueous sodium bicarbonate and ether. After separation of the layers the organic phase was extracted with additional saturated aqueous sodium bicarbonate. The combined aqueous solution was successively acidified to pH 2 with 6 <u>N</u> hydrochloric acid, saturated with sodium chloride, extracted twice with ether, and dried (Na_2SO_4). Concentration of the ether solution in vacuo gave 0.23 g (85%) of a viscous colorless oil: IR (neat) 3400, 3020, 2860, 1730, 1495, 1455, 1100, 910, 735, 700 cm^{-1}; ^1H NMR

($CDCl_3$) δ 7.27 (s and m, 10, aromatic), 6.77 (s, 2, -O<u>H</u> and -CO_2<u>H</u>), 4.92 (d, J = 7 Hz, 1, <u>threo</u>-C<u>H</u>-OH), 4.41 (AB q, J = 12 and 28 Hz, 2, -O-C<u>H_2</u>-C_6H_5), 4.03 (d, J = 7 Hz, 1, -C<u>H</u>-CO_2H). The stereochemistry of this product was confirmed by dehydrative decarboxylation, <u>vide infra</u>. The product was characterized by conversion to a dicyclohexylammonium salt: mp 175-176°C after recrystallization from ethyl acetate.

Anal. ($C_{28}H_{39}NO_4$): C, H, N.

(Z)-2-Phenylmethoxy-1-phenylethene (21b). A solution of 0.25 g (0.92 mmol) of <u>threo</u>-3-hydroxy-3-phenyl-2-phenylmethoxypropanoic acid, <u>vide supra</u>, and 0.66 g (5.5 mmol) of dimethylformamide dimethylacetal in 10 mL of chloroform under a nitrogen atmosphere was stirred for 1 h at room temperature and was then heated at reflux for 7 h. The reaction mixture was concentrated in vacuo to afford an oil which was dissolved in hexane. The hexane solution was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo to yield 0.18 g of a yellow oil. The product was bulb-to-bulb distilled (150°C, 0.1 mm) to afford 0.16 g (81%) of a colorless oil: IR (neat) 3030, 2940, 1645, 1487, 1445, 1365, 1090, 775, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (s and m, 10, aromatic), 6.22 (d, J = 7 Hz, 1, (Z)-CH=C<u>H</u>-O-), 5.23 (d, J = 7 Hz, 1, (Z)-C<u>H</u>=CH-O-), 4.92 (s, 2, -O-C<u>H_2</u>-C_6H_5).

Exact mass calcd. for $C_{15}H_{14}O$: 210.104. Found: 210.105.

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APPENDIX I

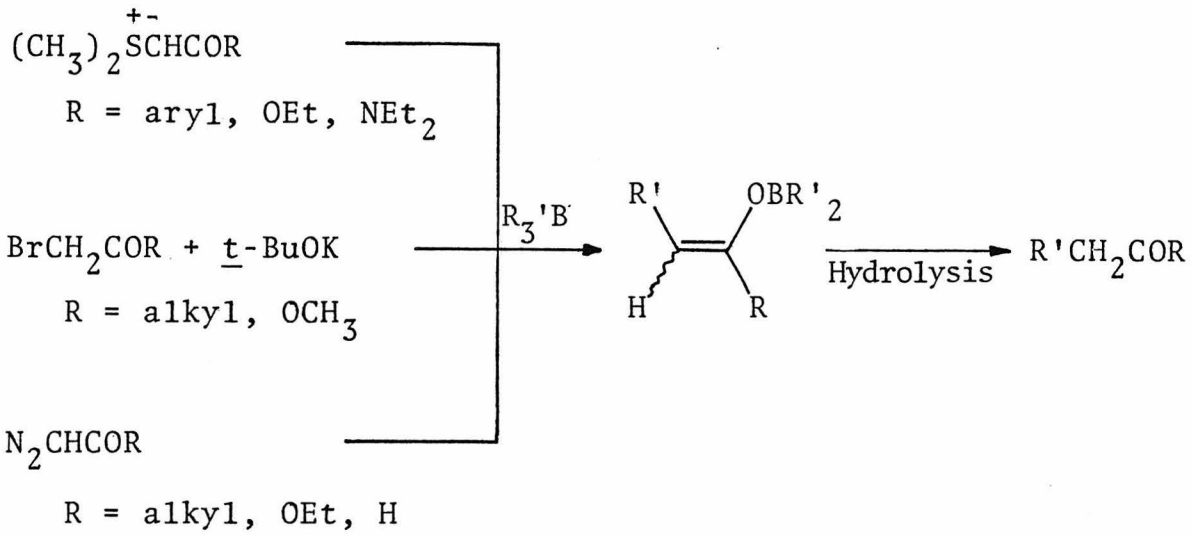
A Brief Review of the Methods for the Generation of Boron Enolates

In previous work,[1] we have demonstrated the utility of boron enolates for stereoselective aldol condensation. In that study we concluded that the geometry of the boron enolate could be completely translated into aldol stereochemistry. The ability to generate stereo-defined boron enolates is, therefore, extremely important. This appendix summarizes the literature methods for the generation of boron enolates with particular emphasis on the geometry of the enolates formed.

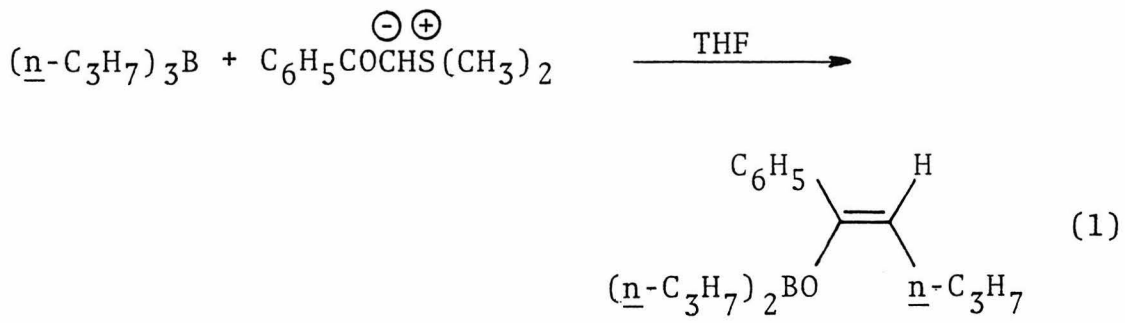
The methods of generating boron enolates can be divided into two classes: those involving the indirect formation of the enolate by the insertion of an enolate precursor into the carbon-boron or heteroatom-boron bond of the organoborane and those involving the direct enolization of the substrate with a dialkylboron enolization reagent. The general applicability of the indirect methods is limited due to the required incorporation of a group from the organoborane into the enolate; however, for some applications this may not be a problem.

Indirect Methods. In the late 1960's, methods were developed for the synthesis of alkylated ketones, esters, and amides by the reactions of trialkylboranes with sulfur ylids,[2] α-diazo-ketones, and esters;[4] Scheme I. The intermediacy of a boron enolate was not recognized until 1970.[5] The geometry of the boron enolate in the sulfur

Scheme I



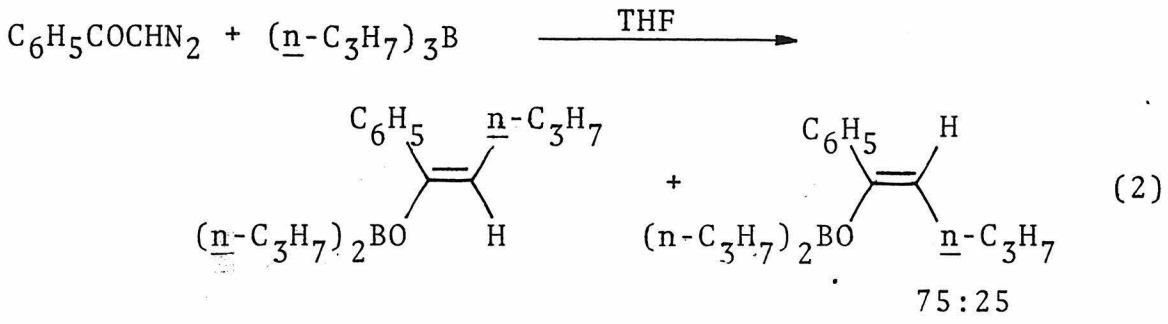
ylid reaction is known in only one case, eq 1, where it is "almost exclusively" (Z)-enolate. There have been no studies on the geometry of the enolates generated from α-bromoketones and esters. The generation of boron enolates

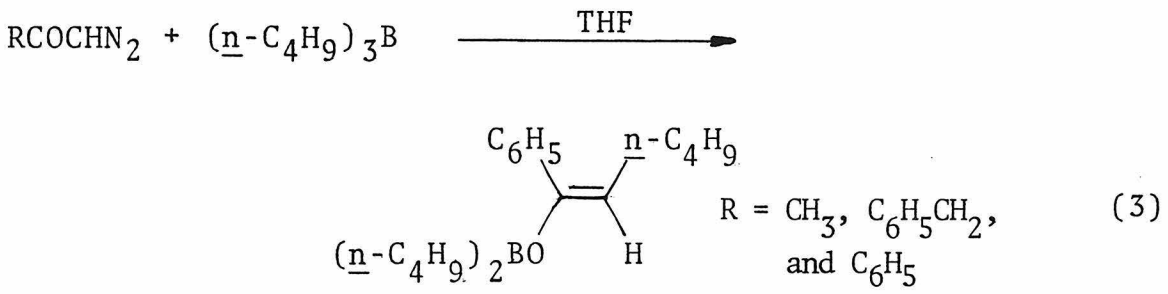


(1)

from α-diazoketones and esters has been more extensively investigated. Pasto and Wojtkowski[5] have reported one

case of the reaction generating a mixture of (E)- and (Z)-enolates in a 3:1 ratio, eq 2; while Masamune[6] and co-workers have reported that the reaction produced "nearly exclusively" the (E)-enolate for all three cases studied, eq 3. Masamune suggests that the lower selectivity observed by Pasto is due to trace contamination by moisture

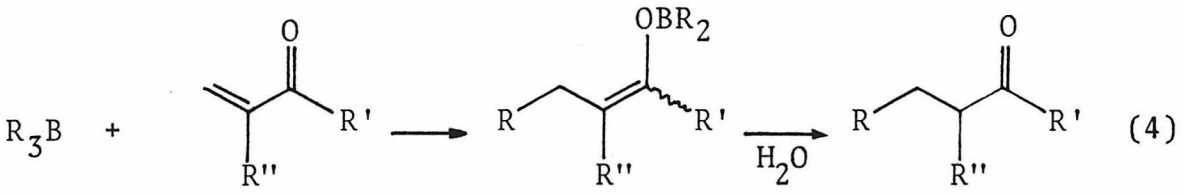




or to isomerization during distillation. The isomerization of (E)-enolates to (Z)-enolates and aldol condensations of both (E)- and (Z)-enolates were also discussed by Masamune. Mukaiyama[7a] and Daniewski[7b] have also used this reaction to generate boron enolates for aldol condensation; however, these investigators did not determine the enolate geometries.

In 1967, Brown[8] reported that trialkylboranes add to

α,β-unsaturated ketones to afford, after hydrolysis of the intermediate boron enolate, a β-alkylated ketone (eq 4). Köster[9] and co-workers have studied the stereo-



(4)

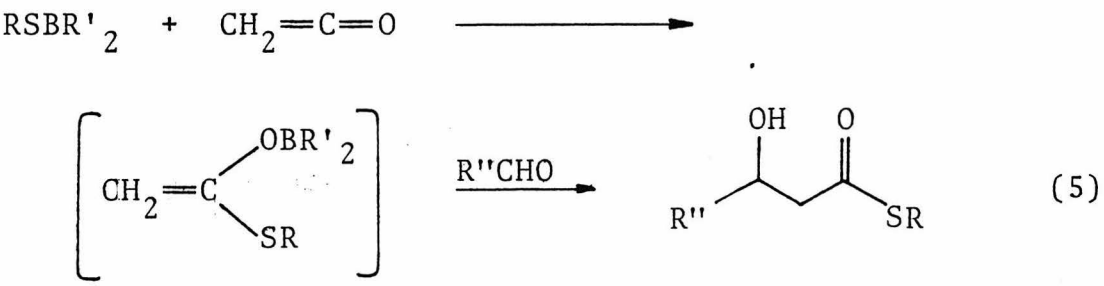
chemistry of the enolates generated from triethylborane and a variety of enones; their results are summarized in Table I. An analysis of these results does not reveal

Table I. Stereochemistry of the Boron Enolates Generated by the Addition of Triethylboron to Enones

R'	R''	Enolate Ratio Z:E
H	CH_3	0:100
CH_3	H	≈55:45
CH_3	CH_3	15:85
C_6H_5	H	100:0
C_6H_5	CH_3	50:50

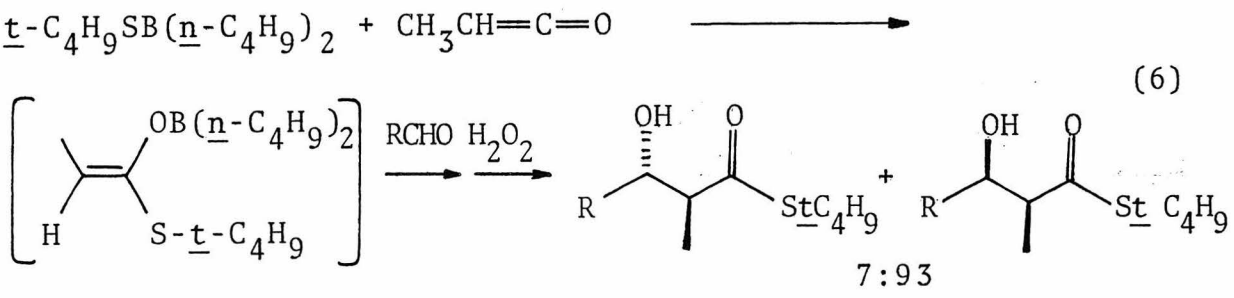
any clear trends. Köster also reported several stereoselective aldol condensations using these enolates. Mukaiyama[7a] has also used this reaction to generate boron enolates for aldol condensations; however, he did not determine the enolate ratio.

The addition of a thioborinate to ketene generates a boron enolate[10] which can be trapped *in situ* by an aldehyde to afford an aldol adduct in good yield, eq 5. However, the boron enolate must be generated in the



(5)

presence of the aldehyde to prevent condensation of the enolate with ketene. Masamune[11] has used methylketene in this reaction for a highly selective synthesis of *erythro*-aldol adducts, eq 6, presumably *via* an (*E*)-enolate.



(6)

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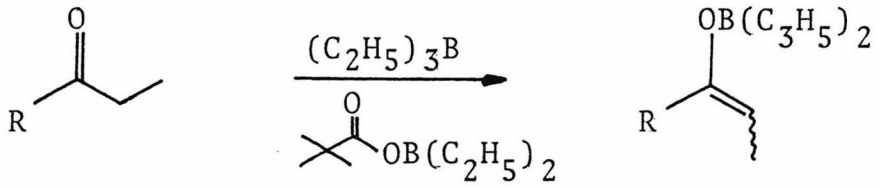
Direct Methods. Köster[12] has developed two reagents for direct enolization, one for ketones and one for aldehydes. Diethylboron pivalate[12a] has been used to enolize a number of ketones, eq 7 and Table II, and some of these reactions are quite stereoselective. In addition,



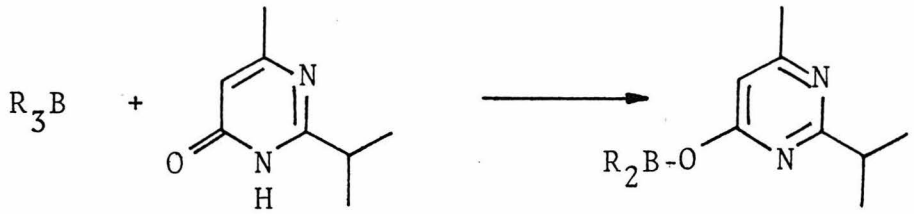
(7)

only a catalytic amount (1-10%) of the reagent is needed since the pivalic acid generated in the reaction reacts with triethylboron to regenerate the pivalate. However,

Table II. Stereochemistry of the Enolates Generated by the Reaction of Ketones and Diethylboron Pivalate

R	Enolate Ratio Z:E
C_2H_5	≈90:10
i-C_3H_7	≈90:10
C_6H_{11}	>95:5
$C_6H_5CH_2$	75:25
C_6H_5	100:0

the long reaction times and high temperatures required by this reaction limit its utility. Köster has also prepared the boron enolates of aldehydes using 4-dialkylboryloxy-2-isopropyl-6-methylpyrimidines, eq 8 and 9, which are readily prepared as shown below, eq 8.



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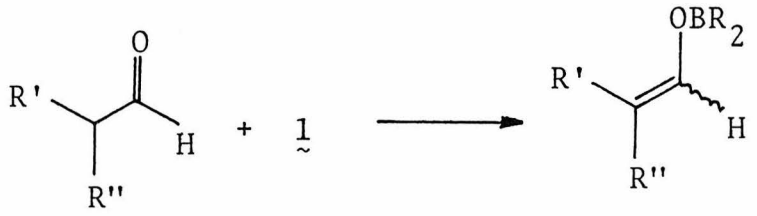
R = C_2H_5, i-C_3H_7, and 9-BBN



(9)

Unfortunately, the enolates generated were mixtures of (E)- and (Z)-isomers. Köster has used the boron enolates generated from both of these methods for aldol condensations.

The dialkylboryl triflate reagents, which have been used extensively in this laboratory[1] as well as by

Masamune[11,14] for aldol condensation, were developed by Mukaiyama[13] and co-workers. These reagents enolize ketones under extremely mild conditions and are highly stereoselective in many cases. Sugasawa[15] has reported stereoselective aldol condensations using boryl chlorides to generate the boron enolates but these reagents are less reactive than boryl triflates.

Although a considerable amount of work has been reported in this area, the problem of stereocontrolled boron enolate generation has not been completely solved. Further investigations will hopefully lead to a solution.

References and Notes

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APPENDIX II

IR and ^{1}H NMR Spectral Catalog for Chapter I

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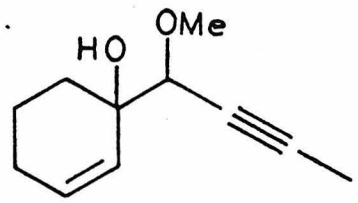

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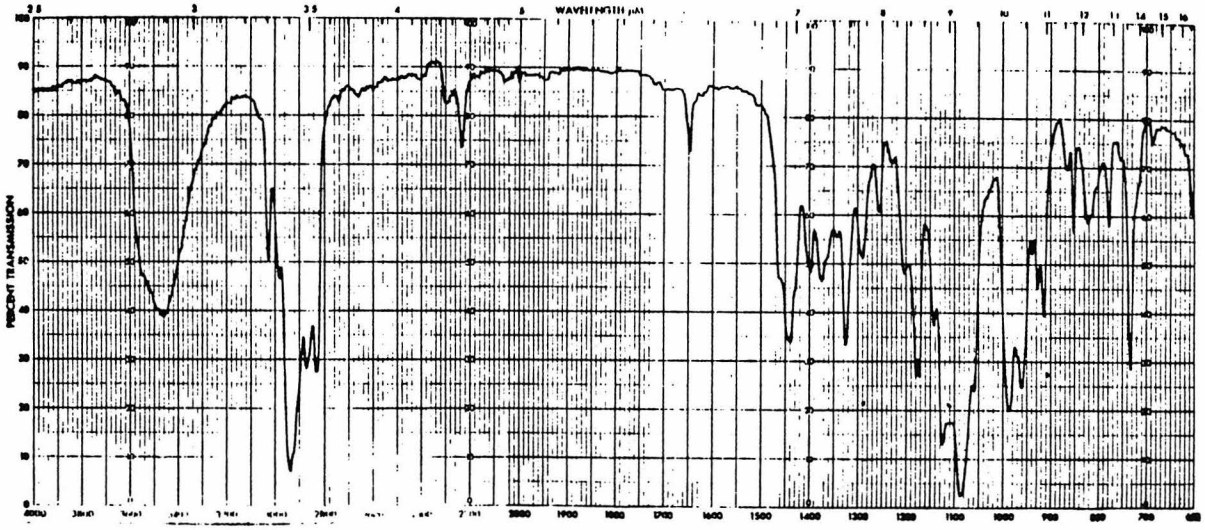

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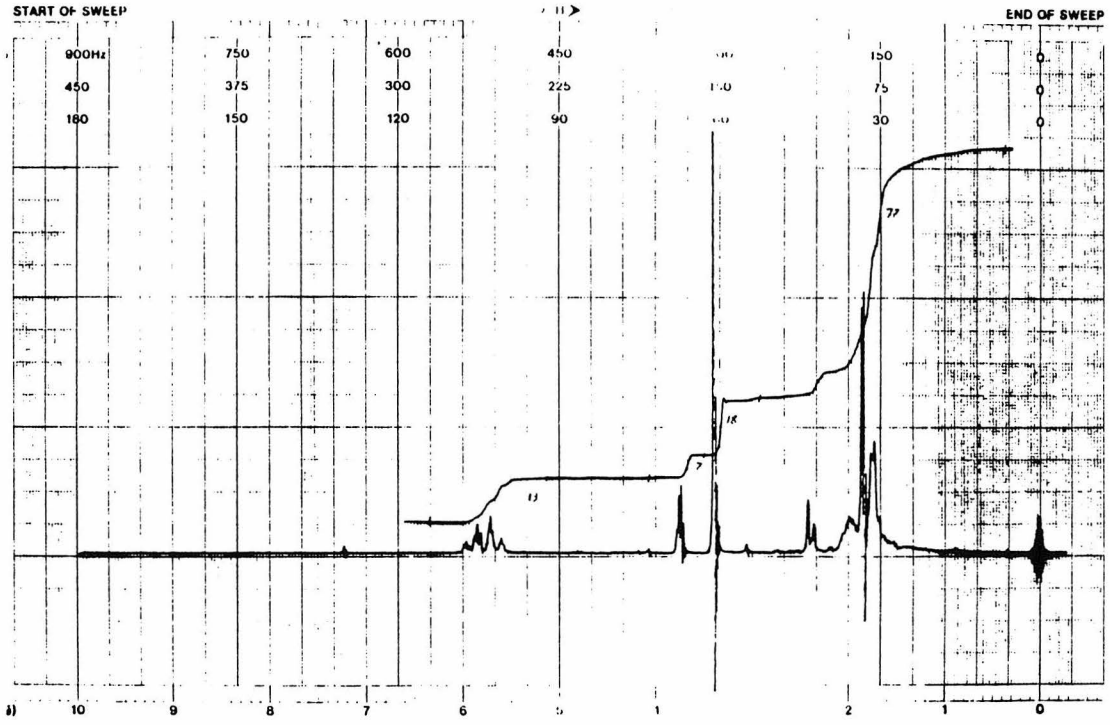

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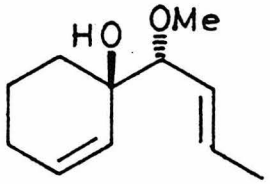

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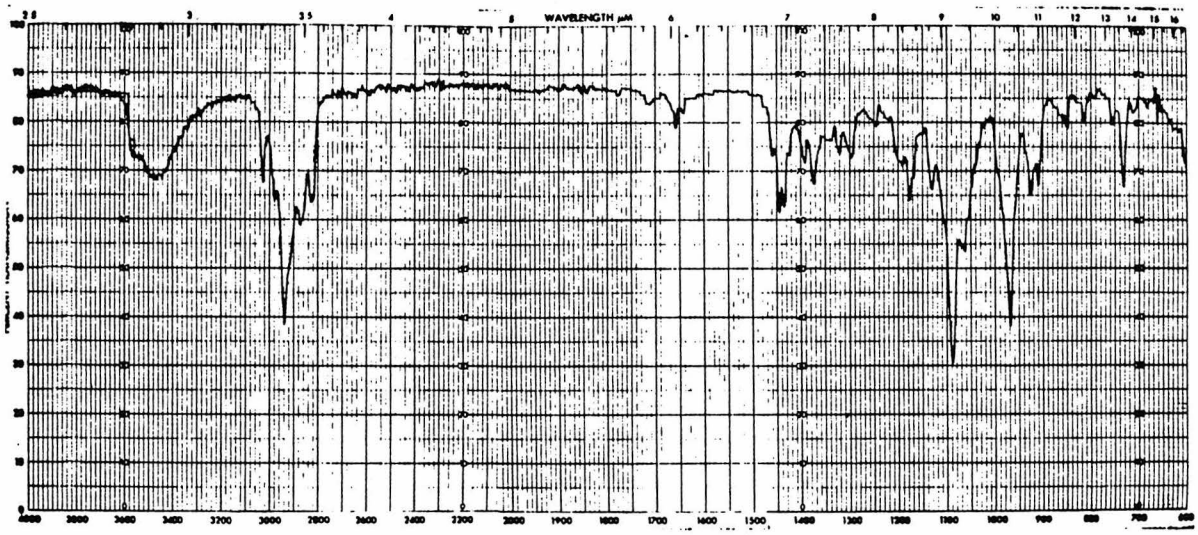

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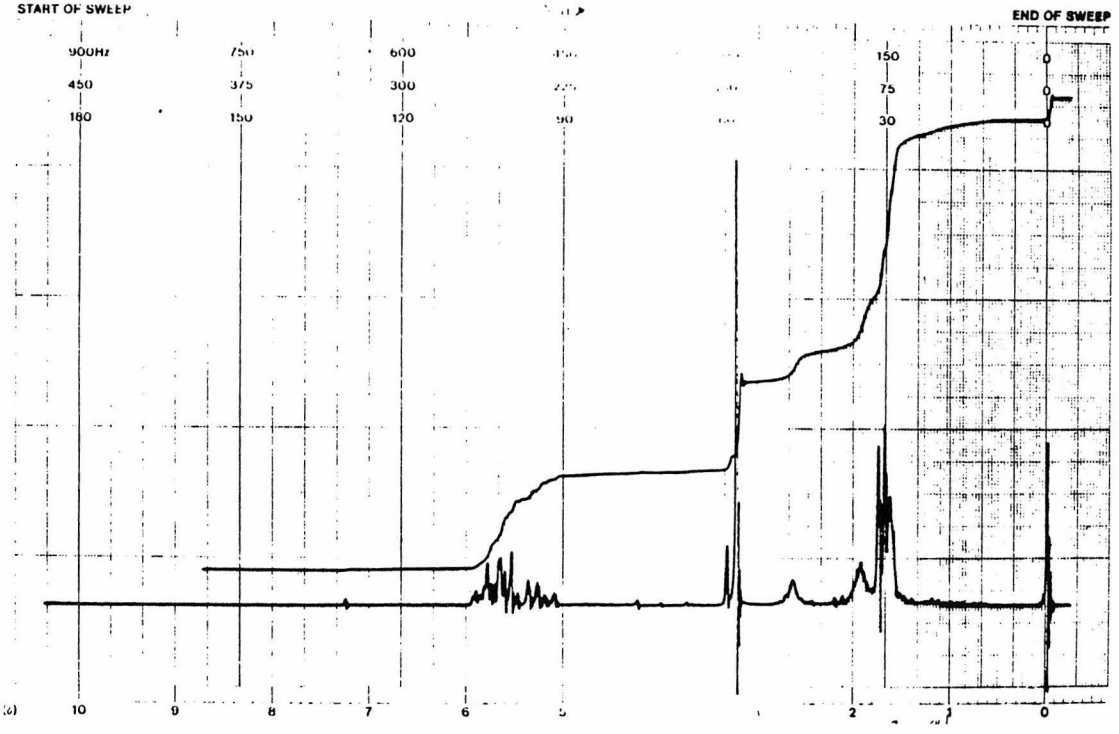

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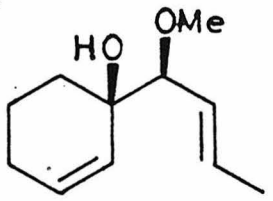

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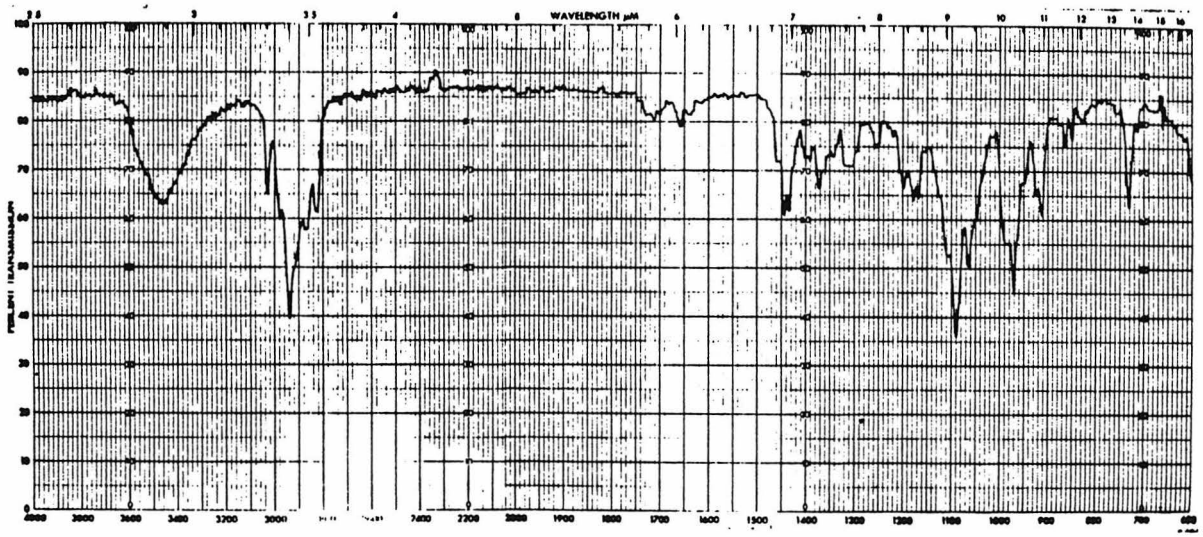

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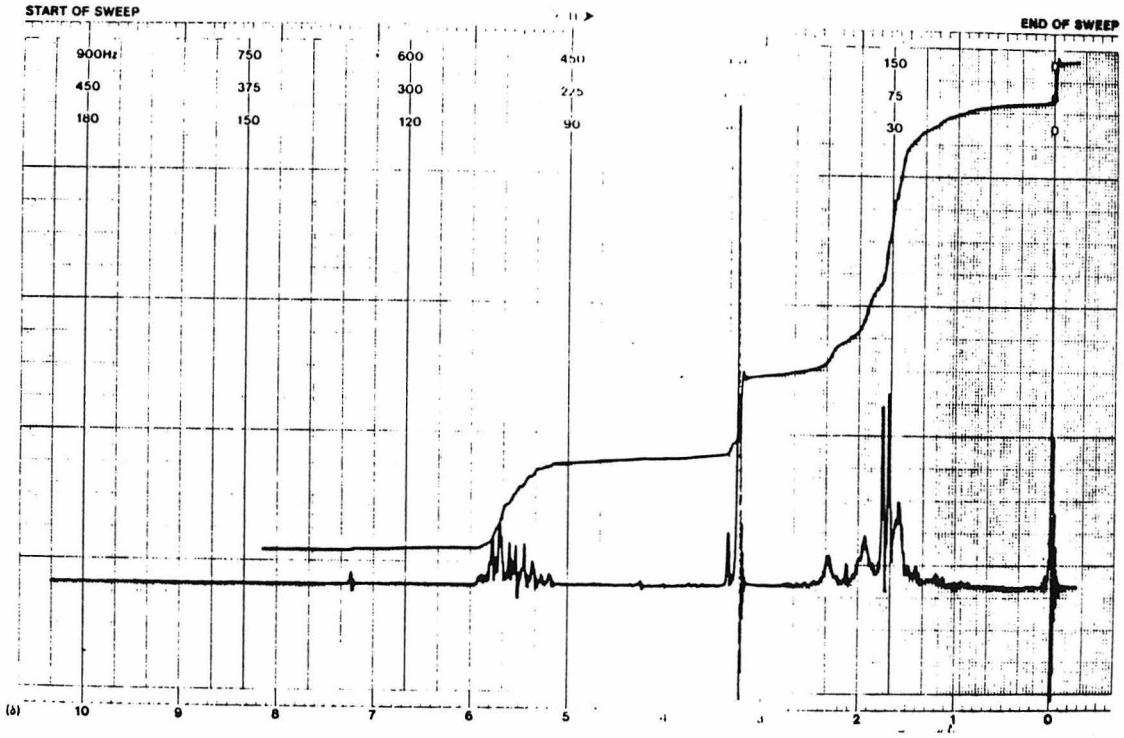

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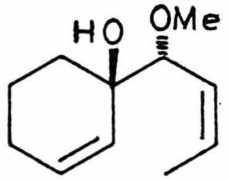

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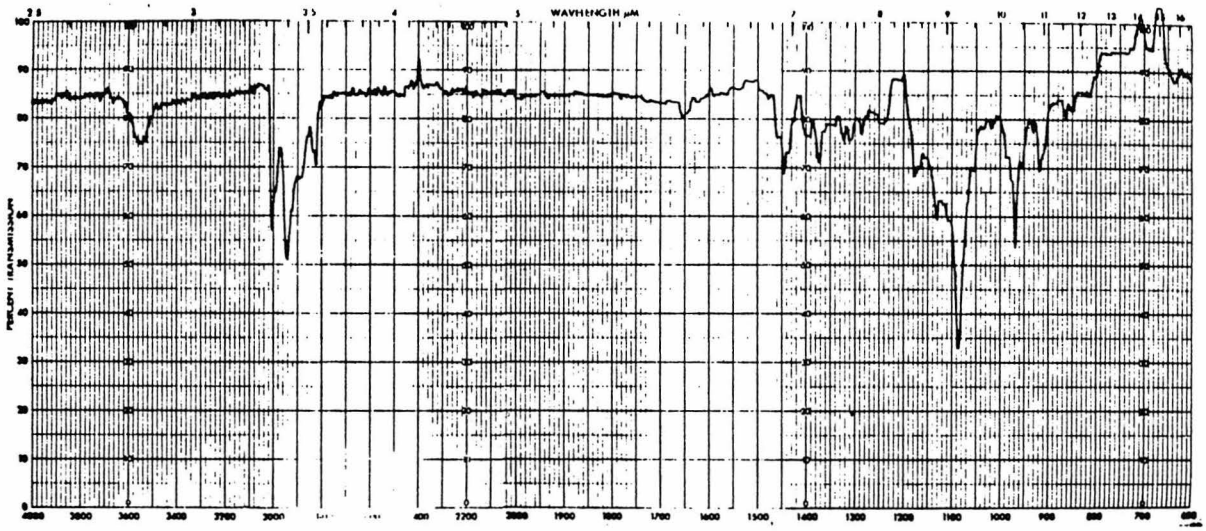

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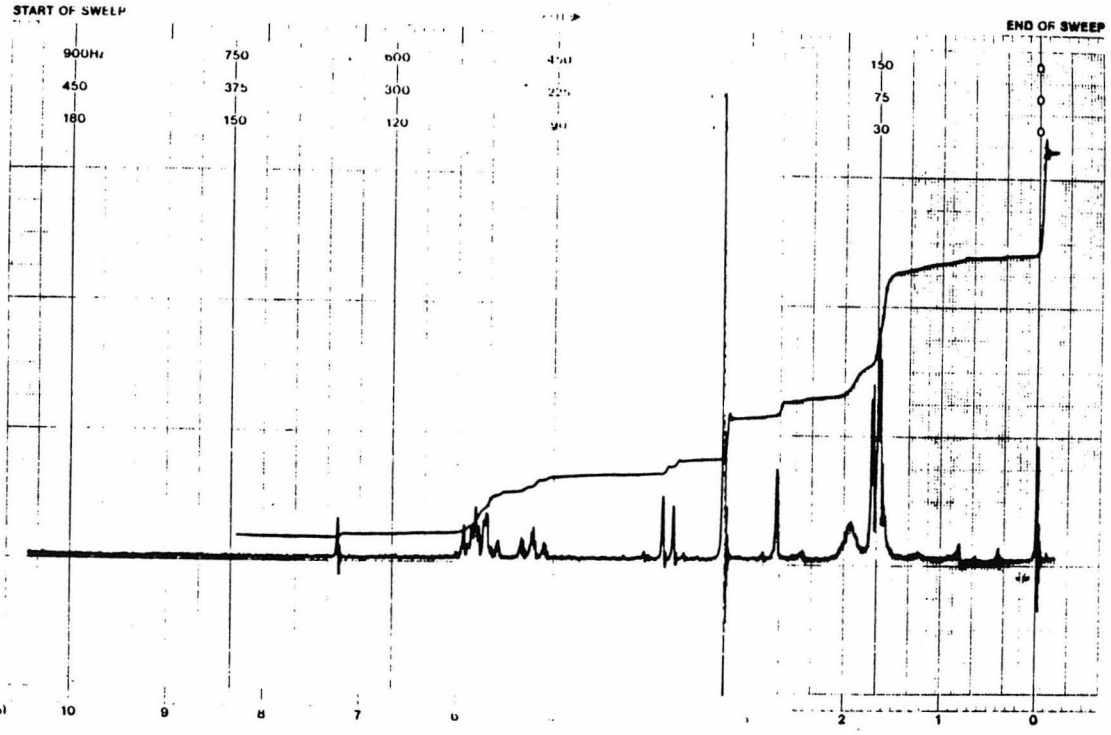

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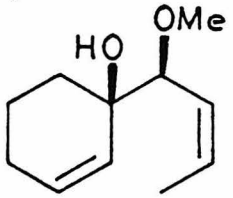

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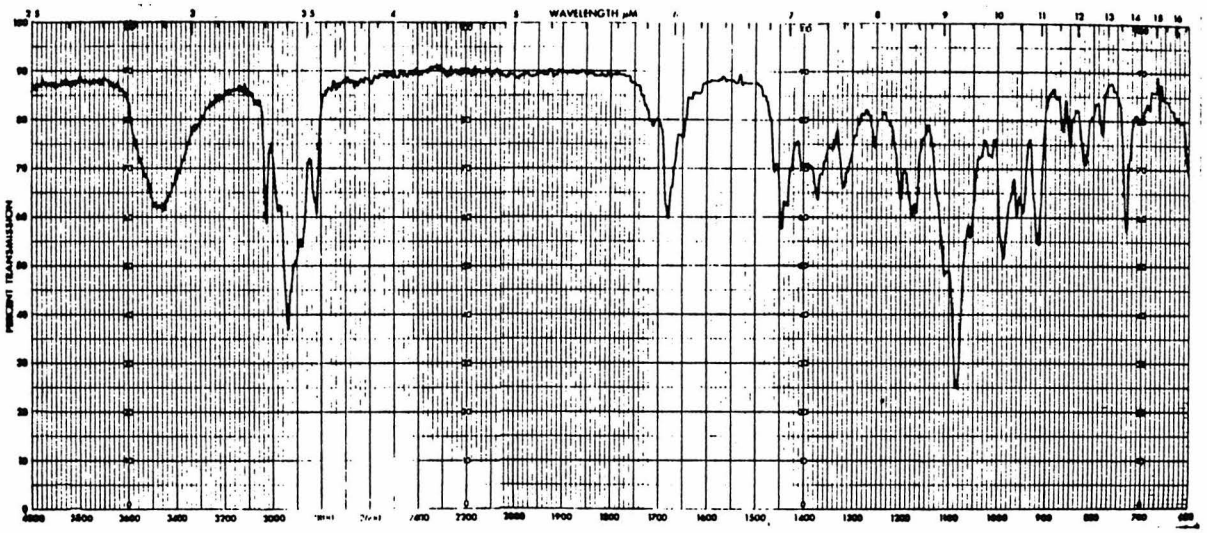

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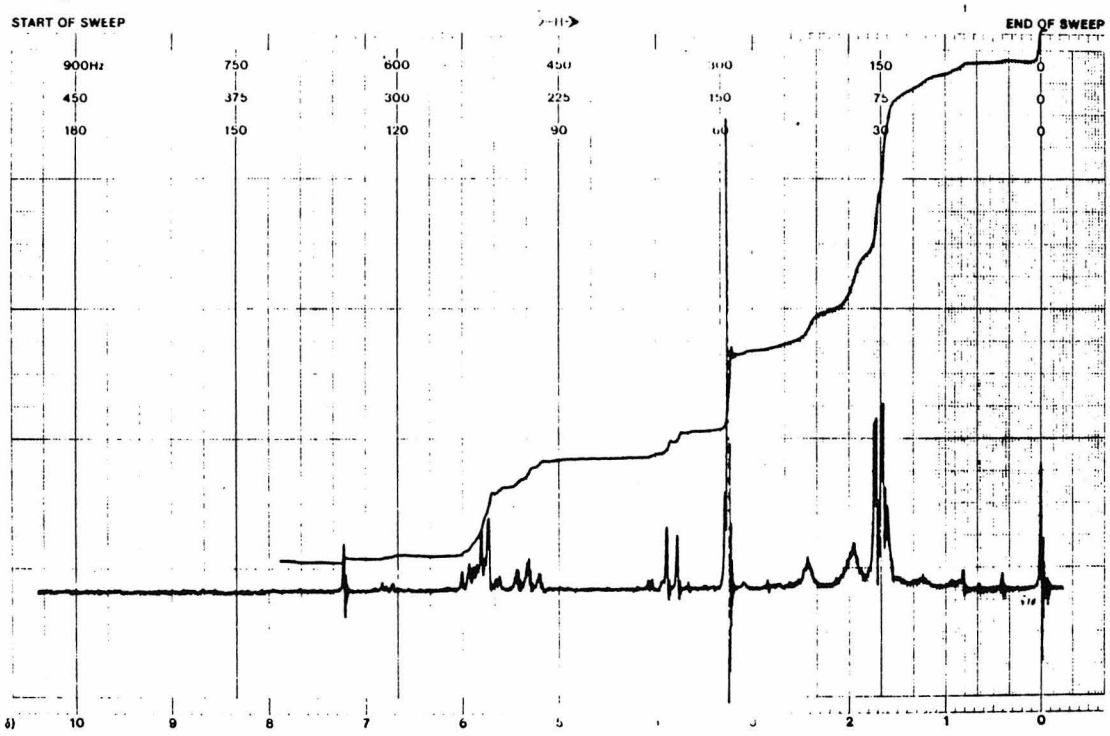

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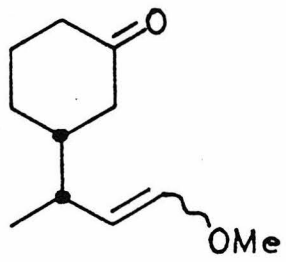

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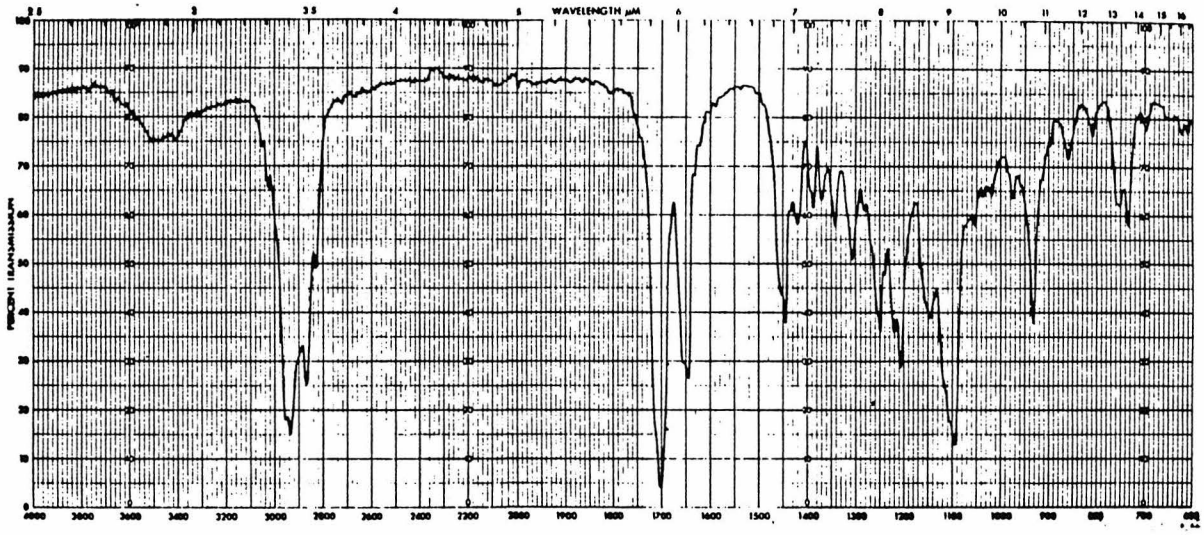

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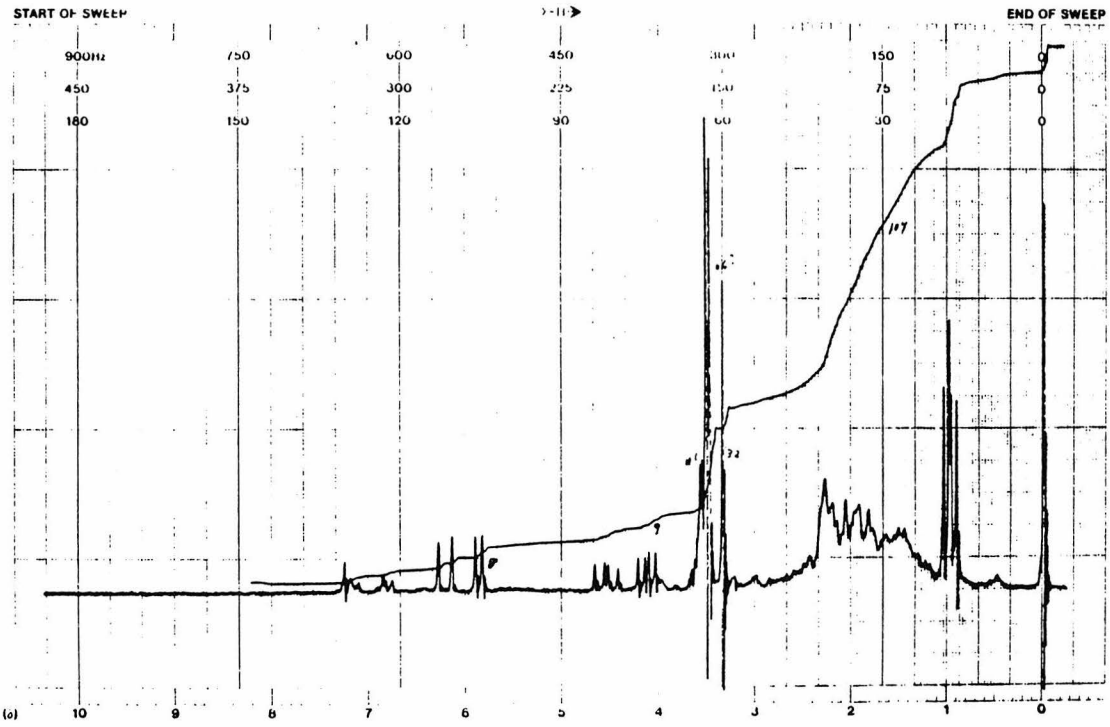

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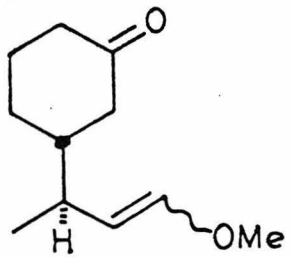

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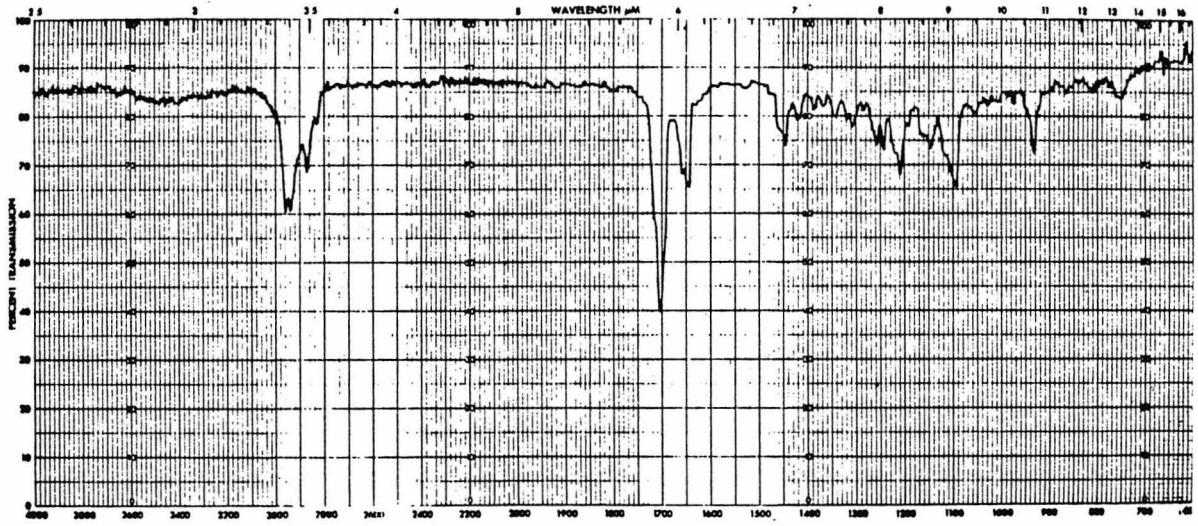

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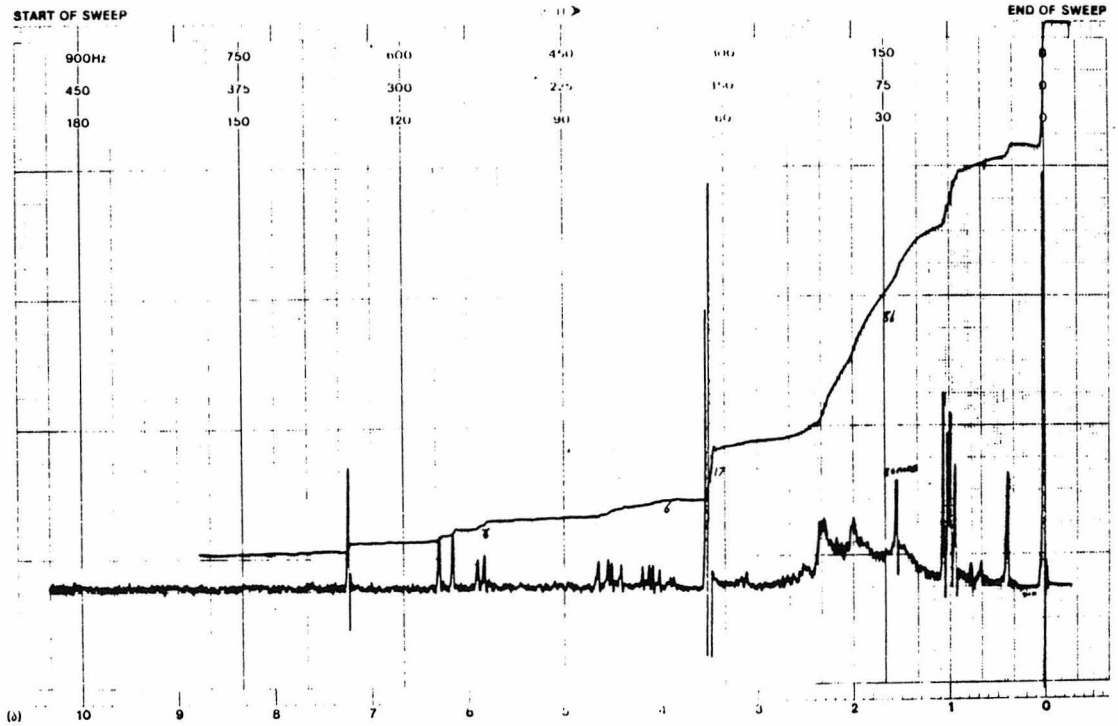

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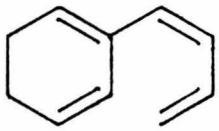

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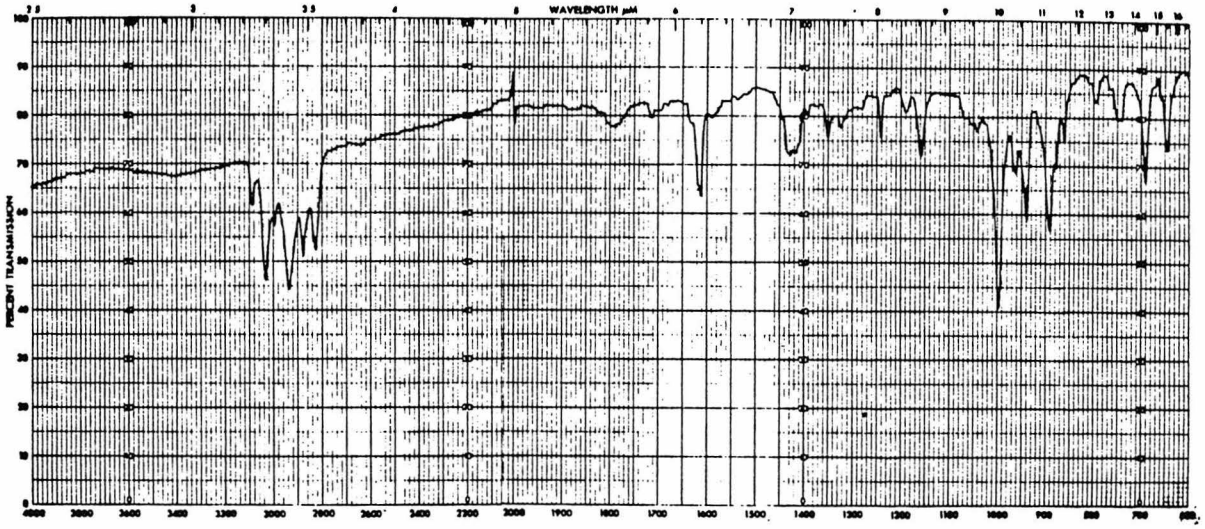

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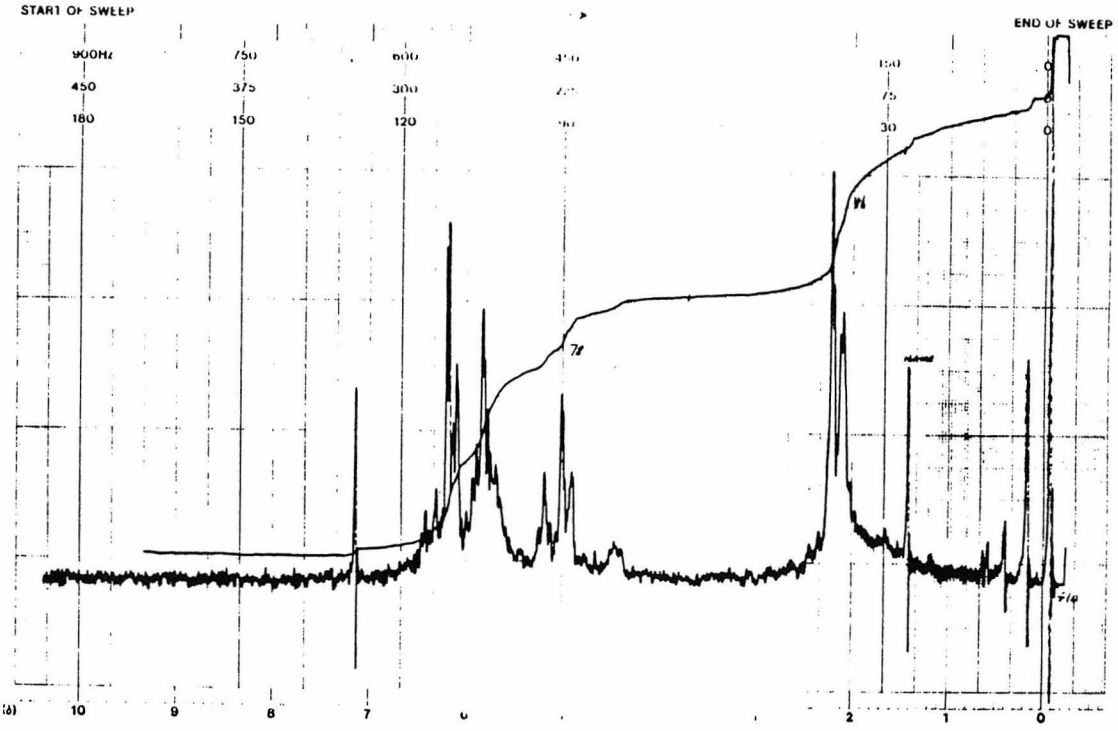

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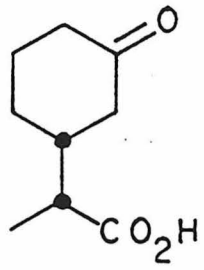

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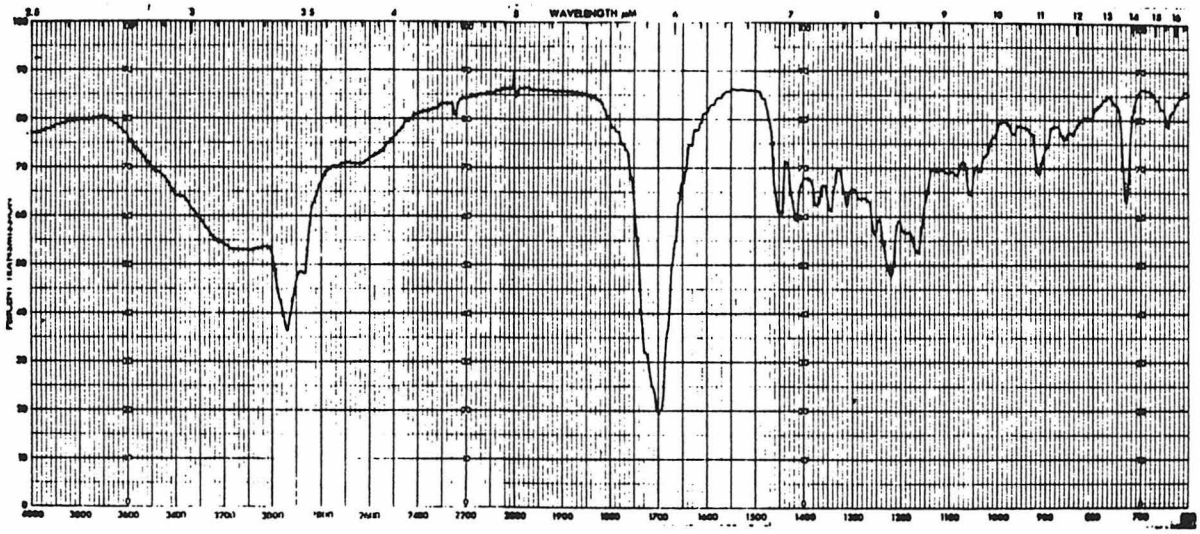

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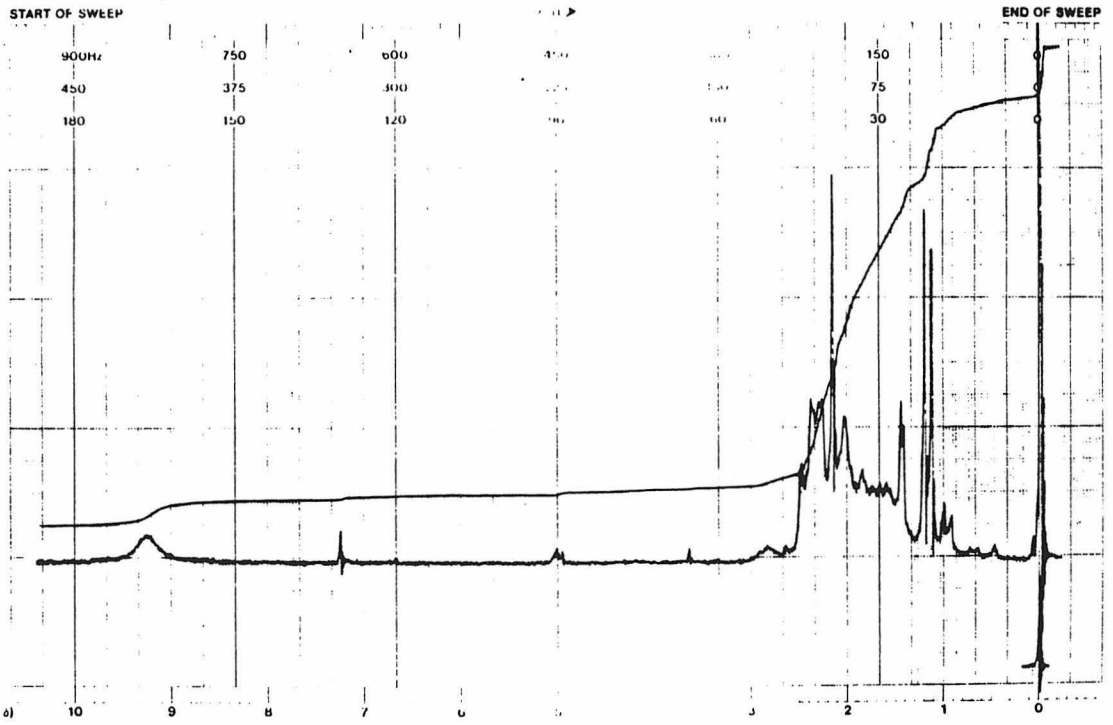

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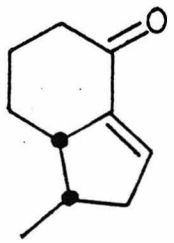

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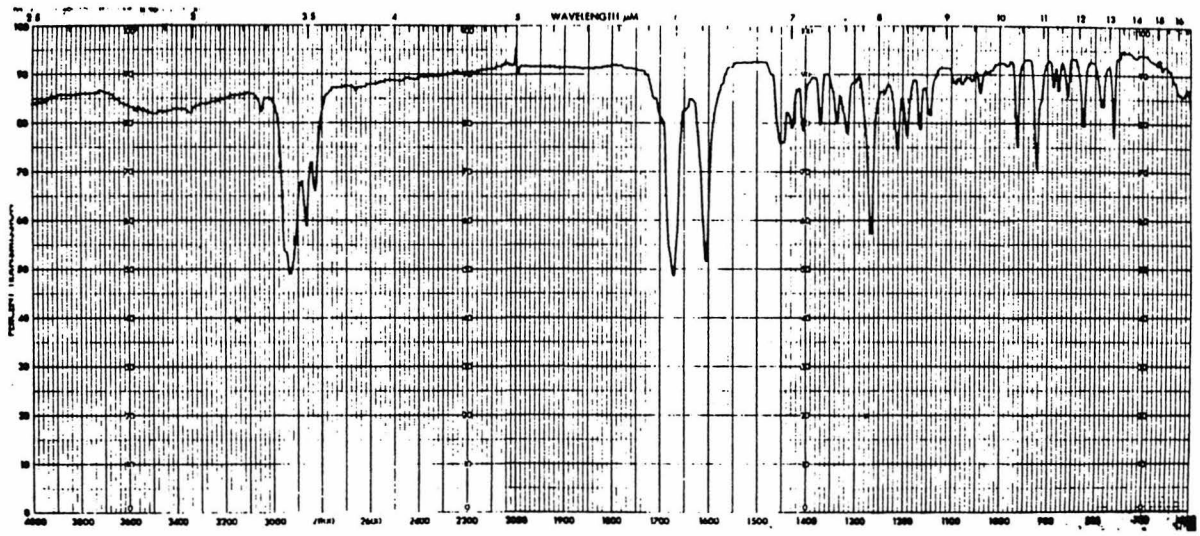

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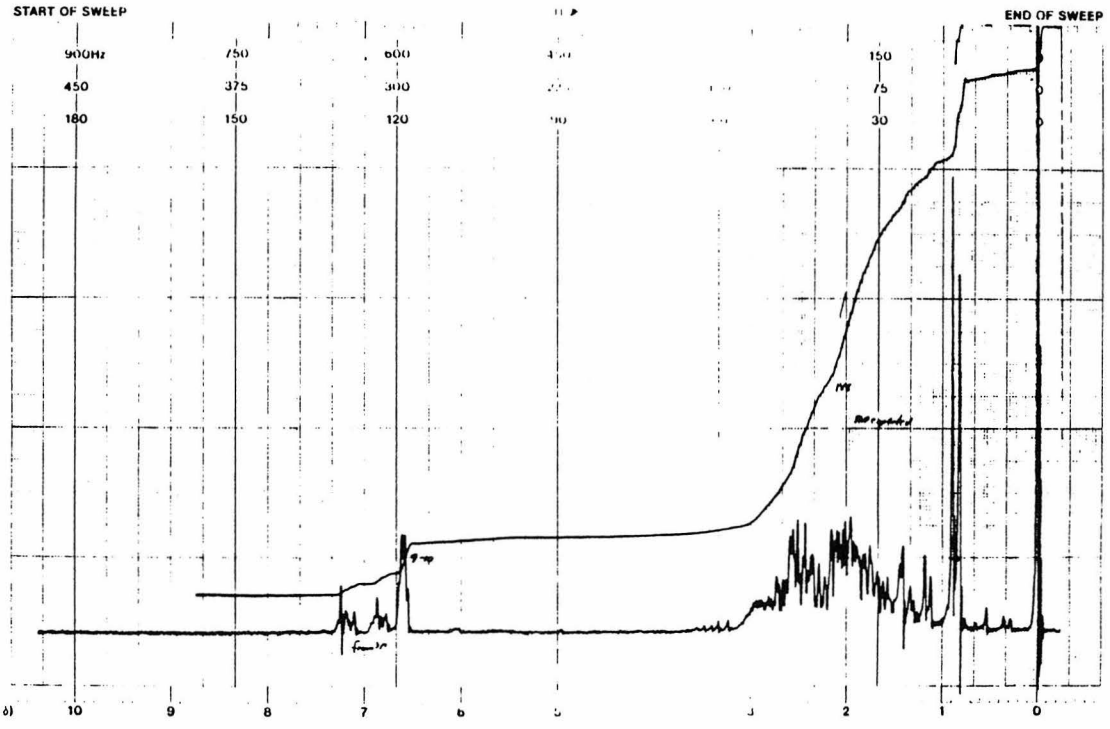

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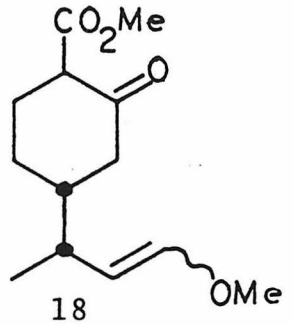

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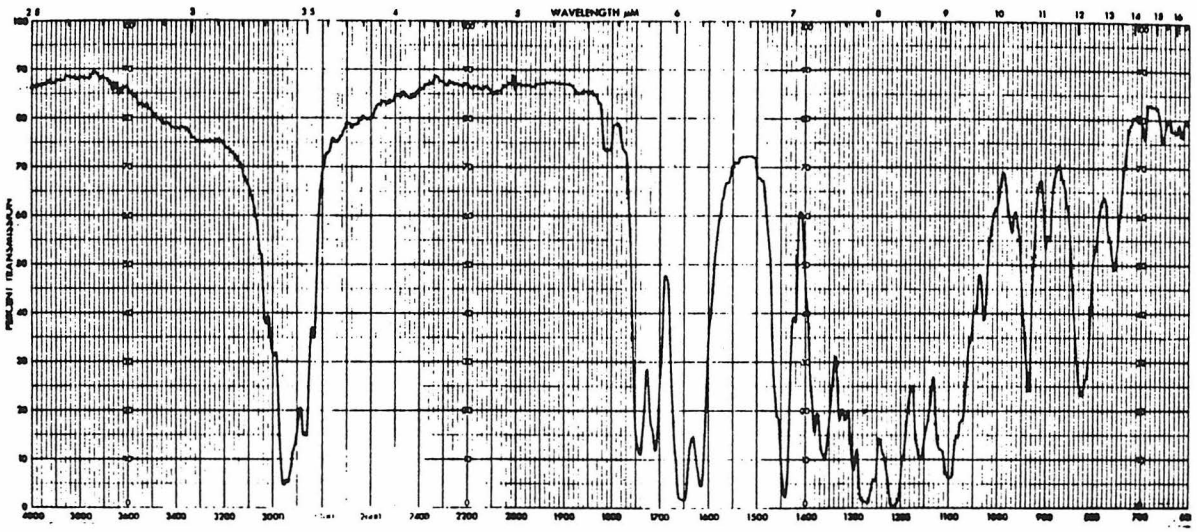

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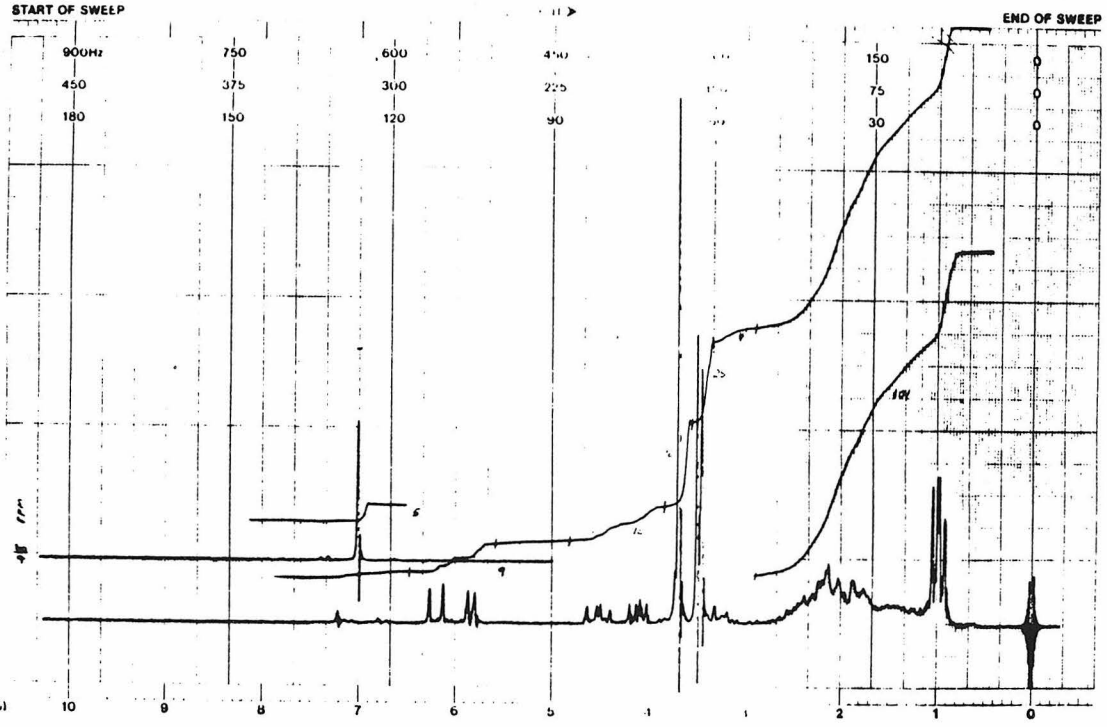

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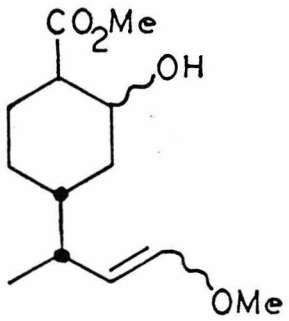

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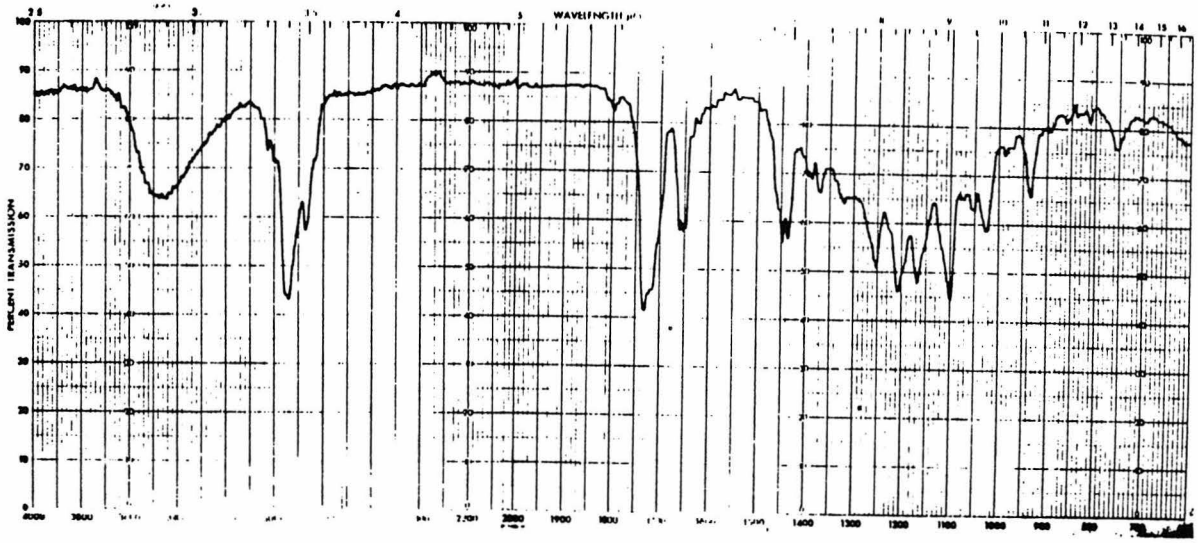

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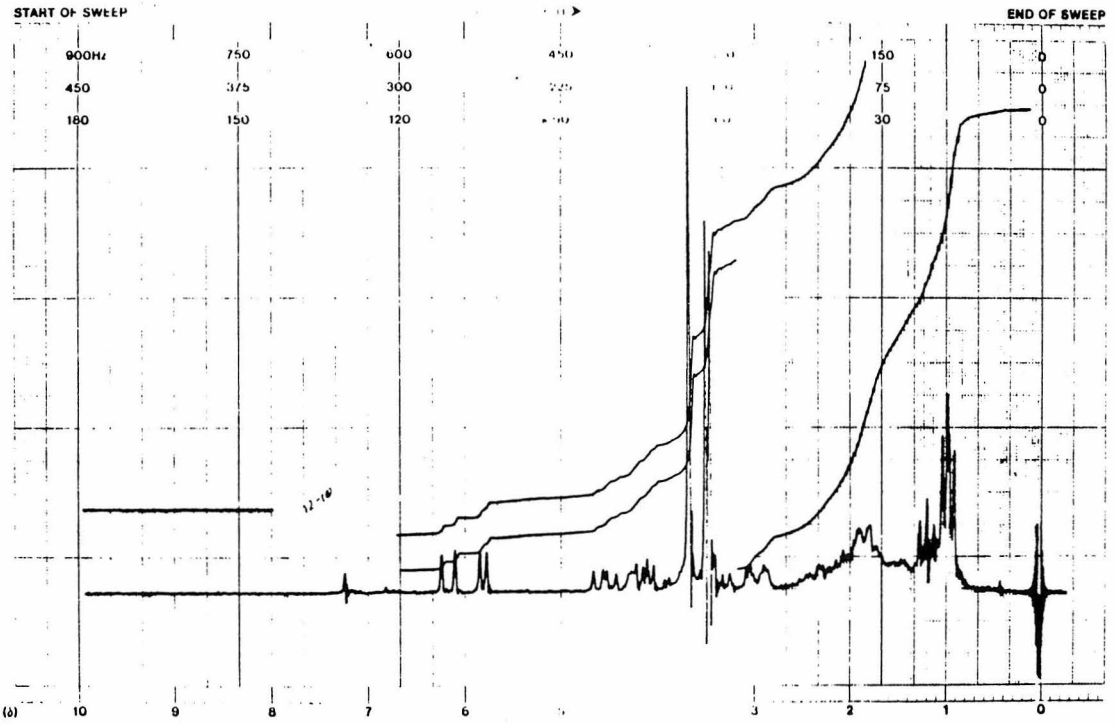

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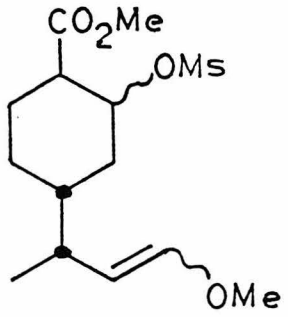

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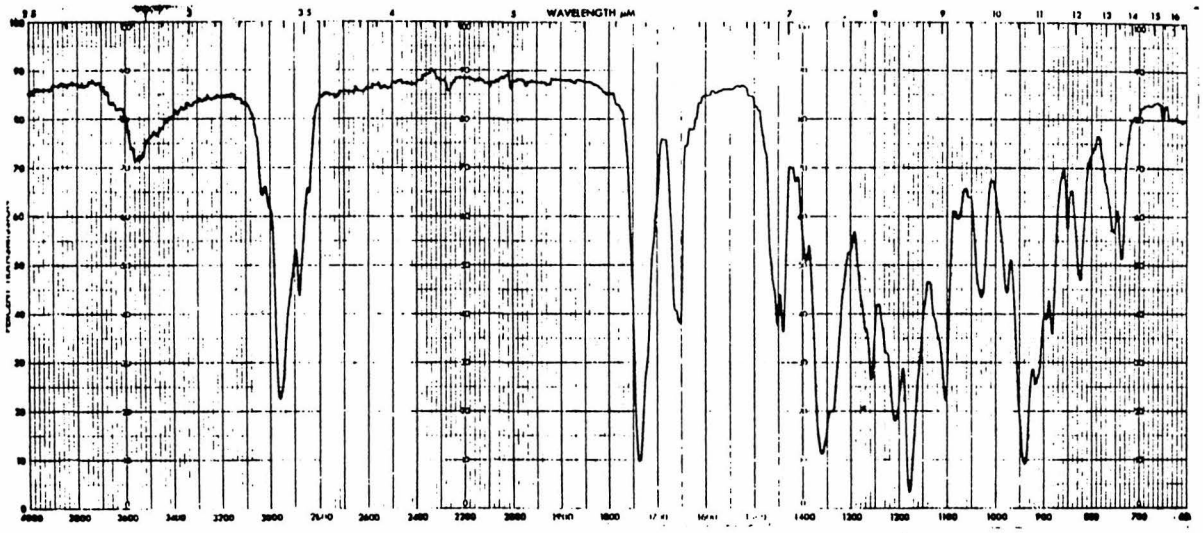

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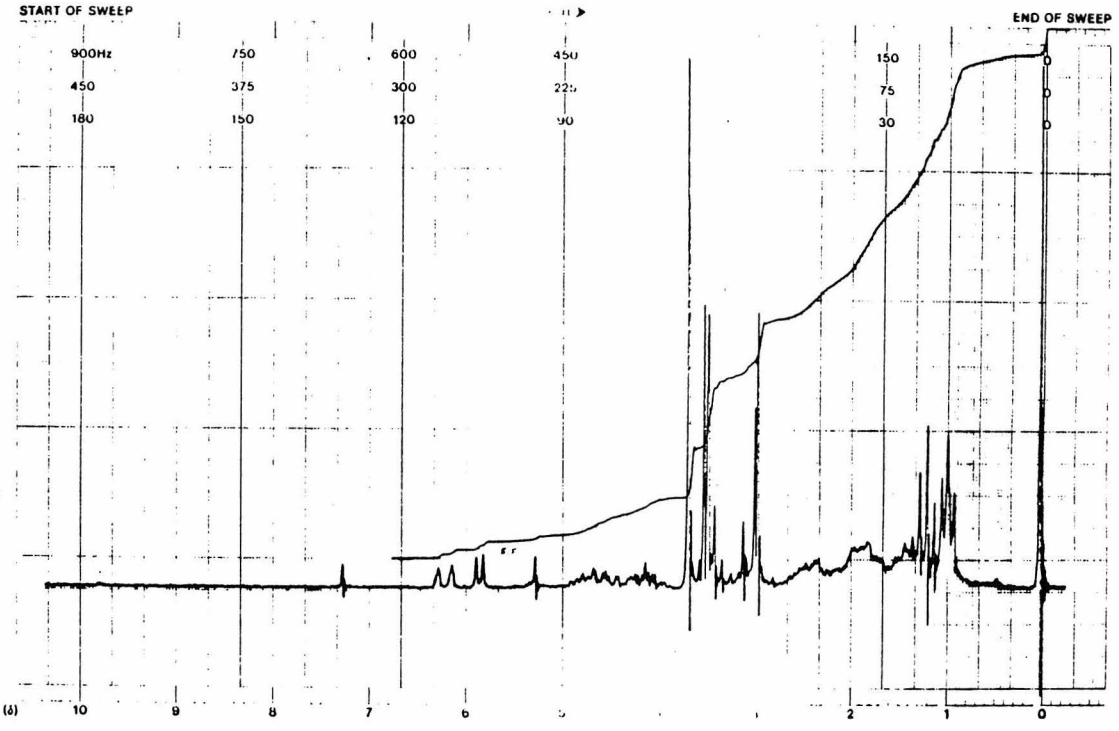

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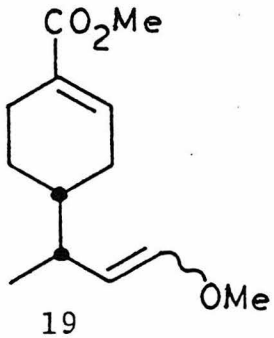

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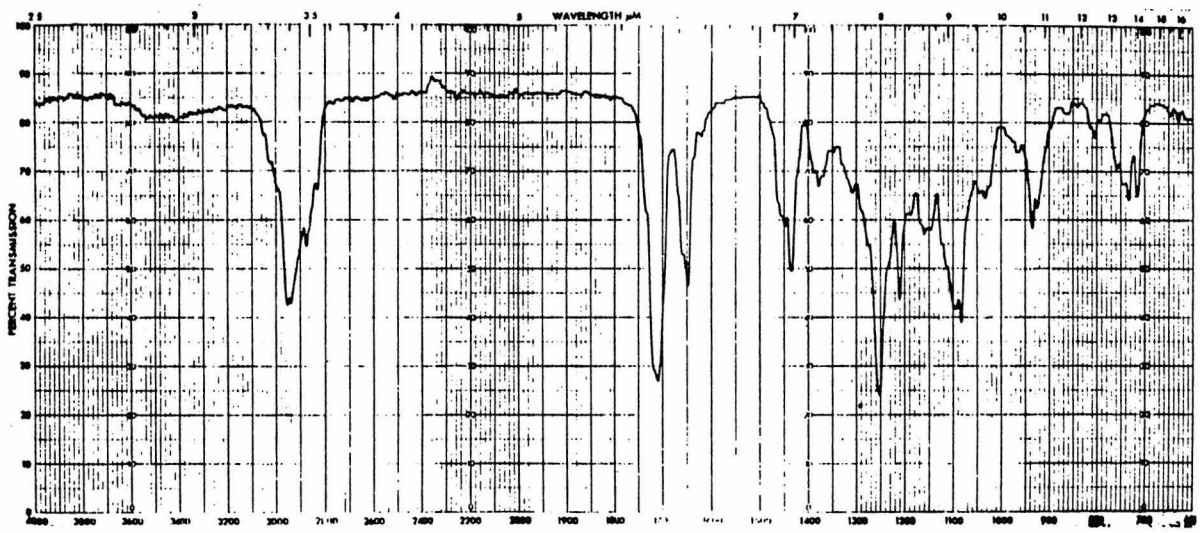

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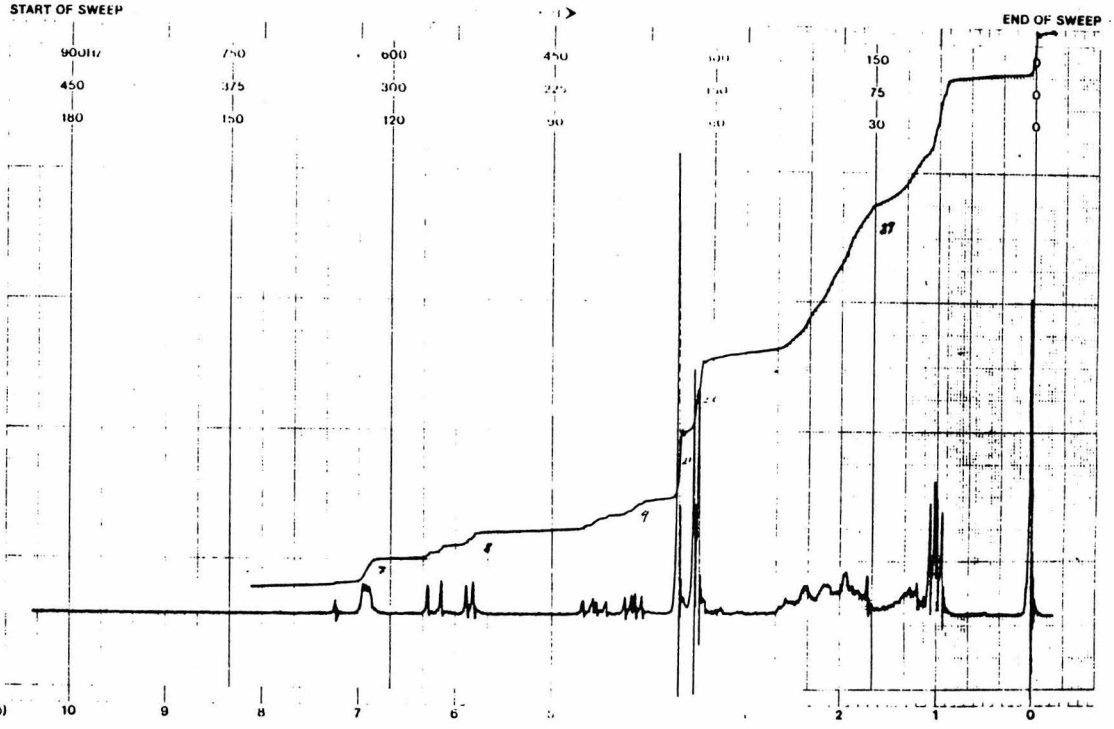

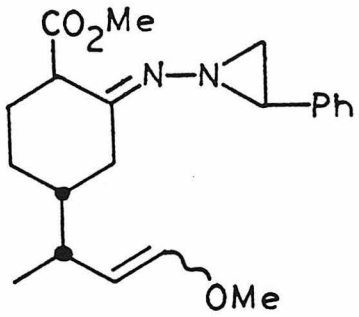

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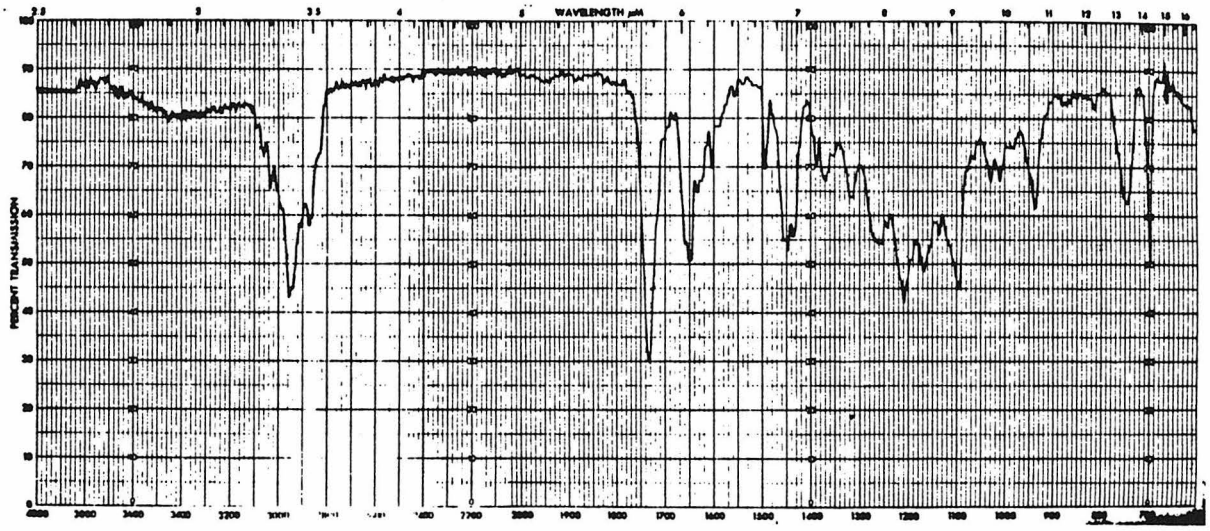

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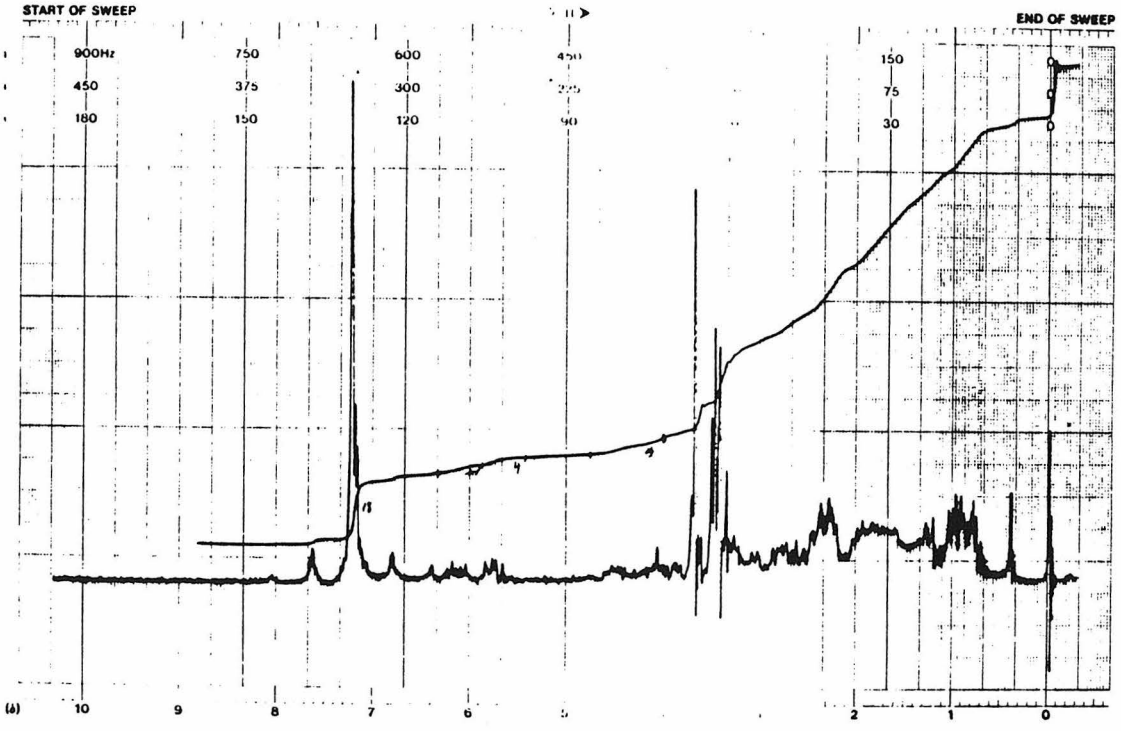

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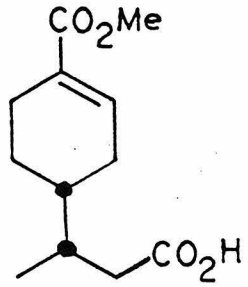

23a

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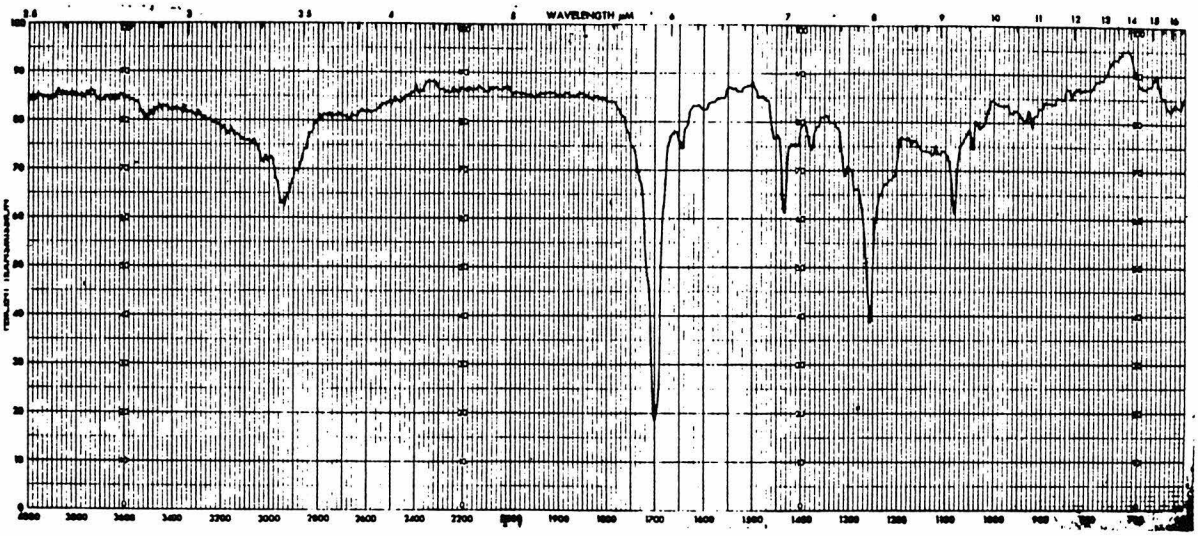

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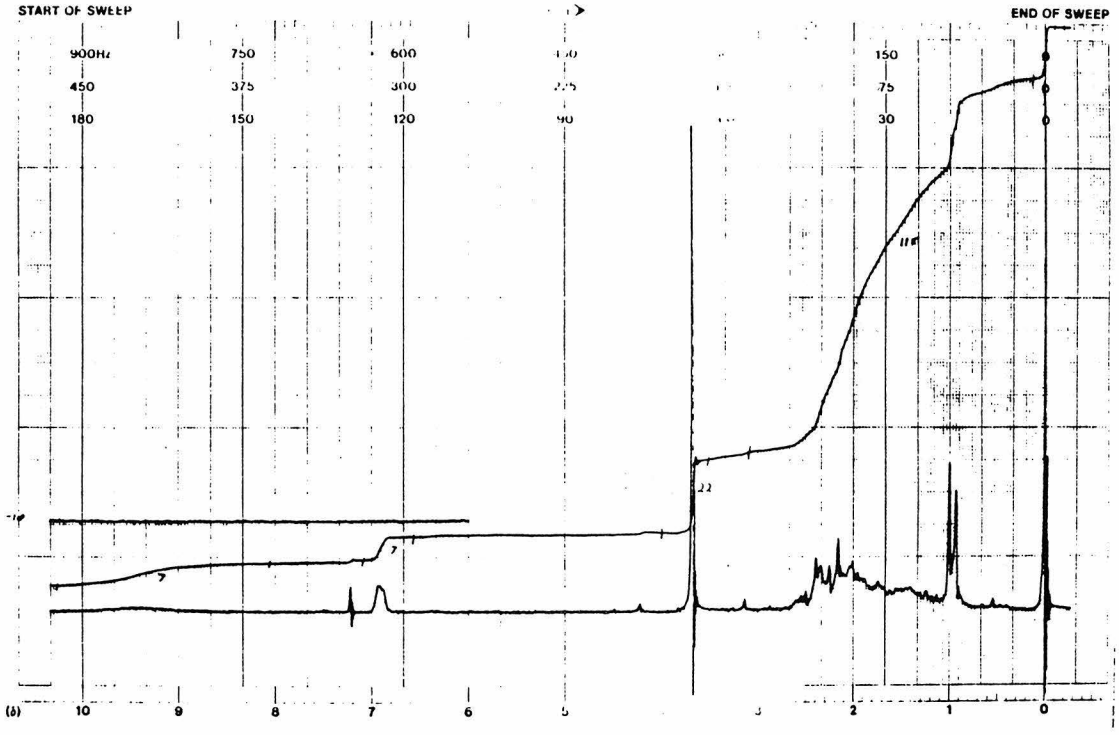

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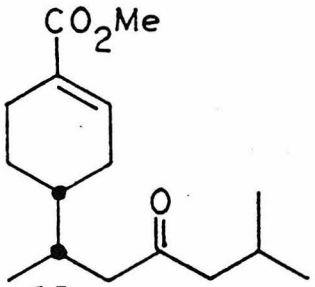
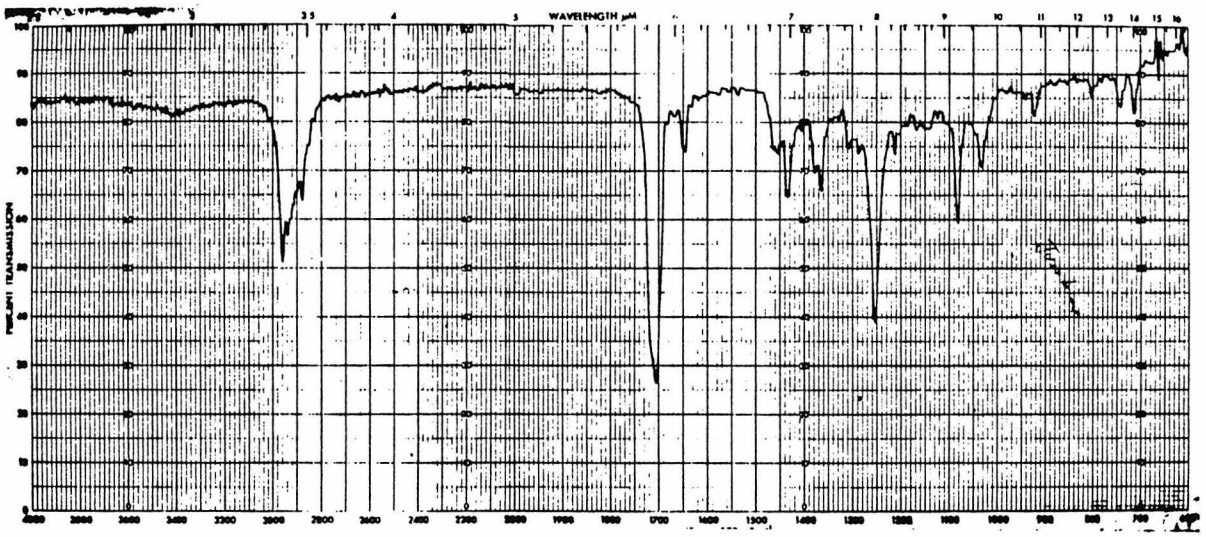


15a

neat



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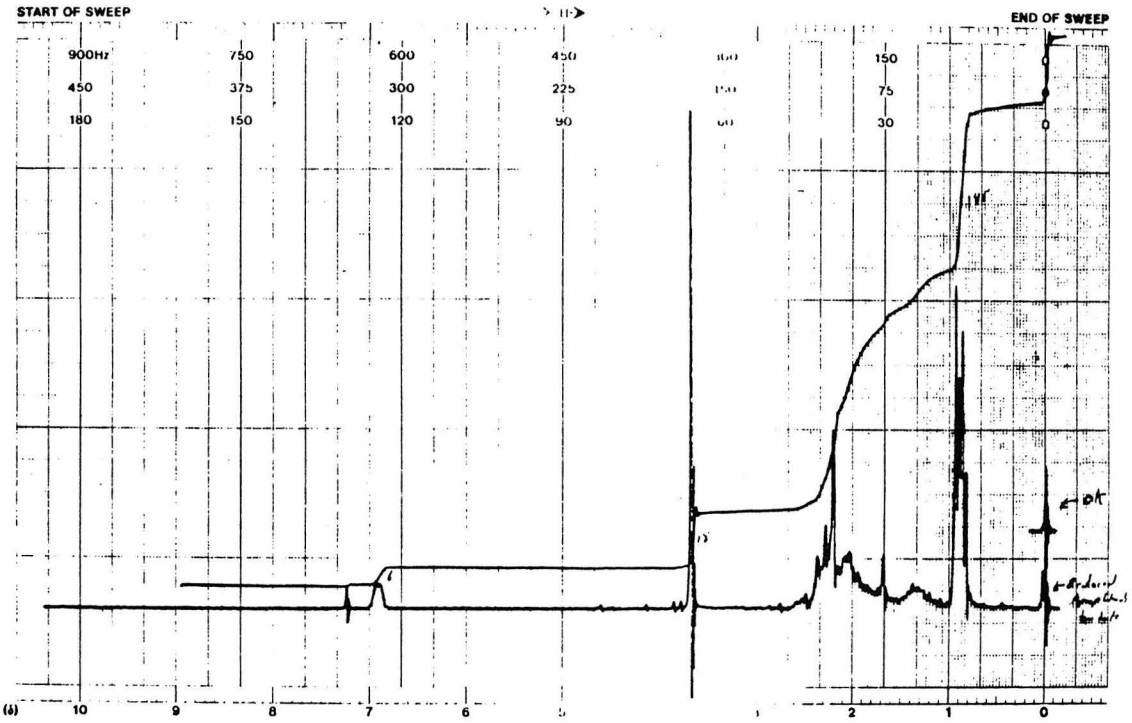

APPENDIX III

IR and ^{1}H NMR Spectral Catalog for Chapter II

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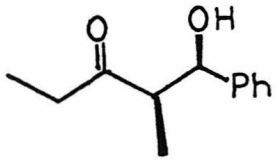
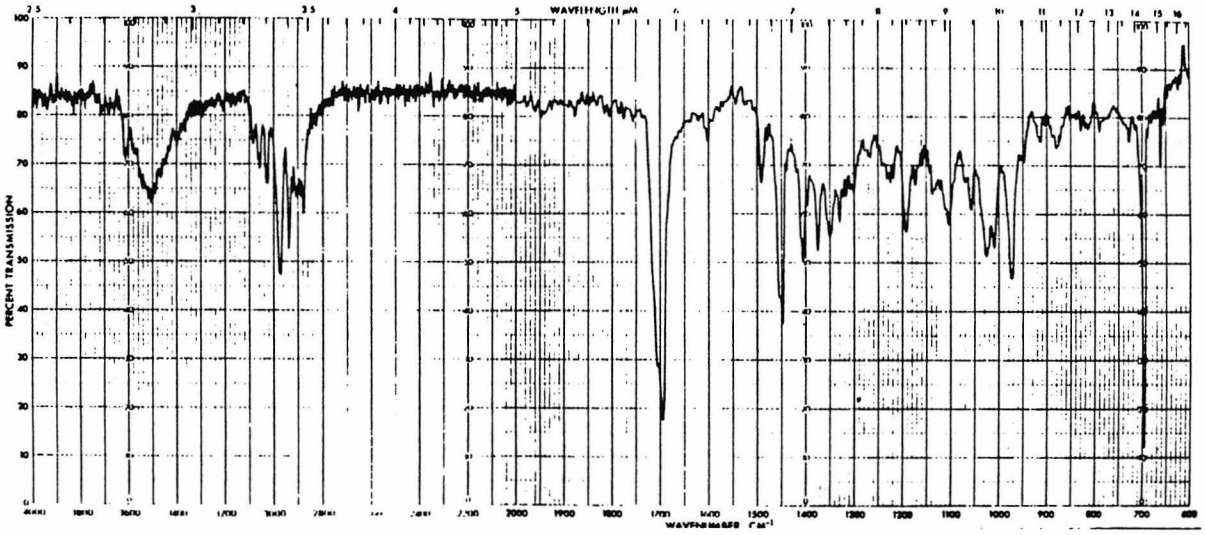


Table II, Entry A

CCl_4, 5%



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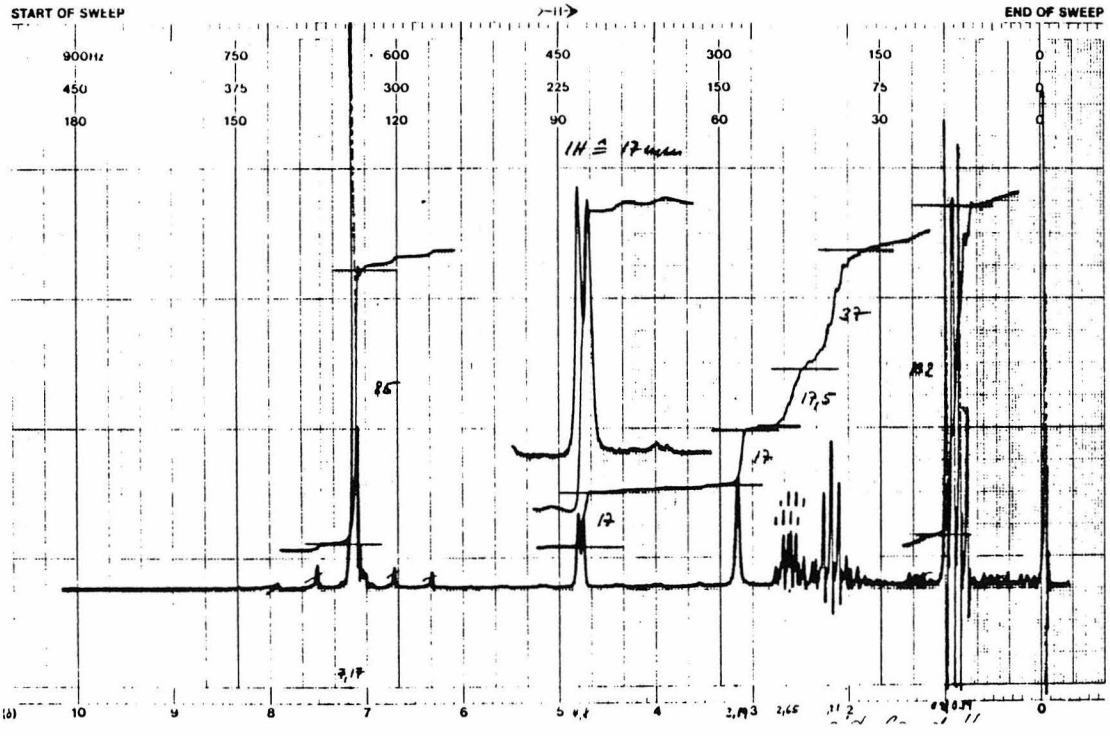

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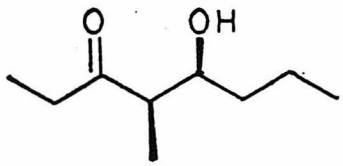

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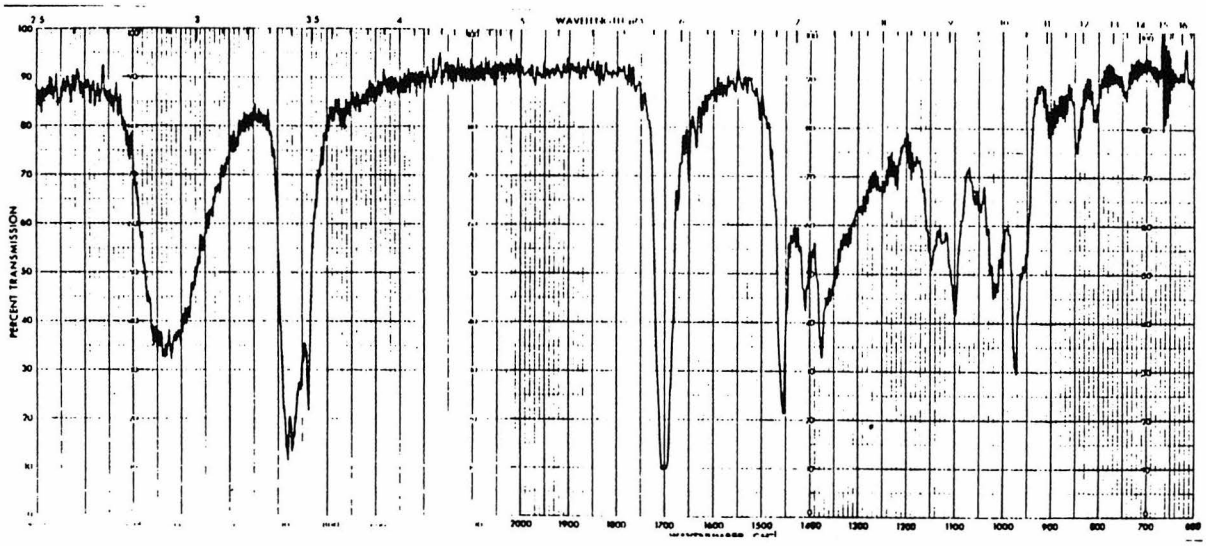

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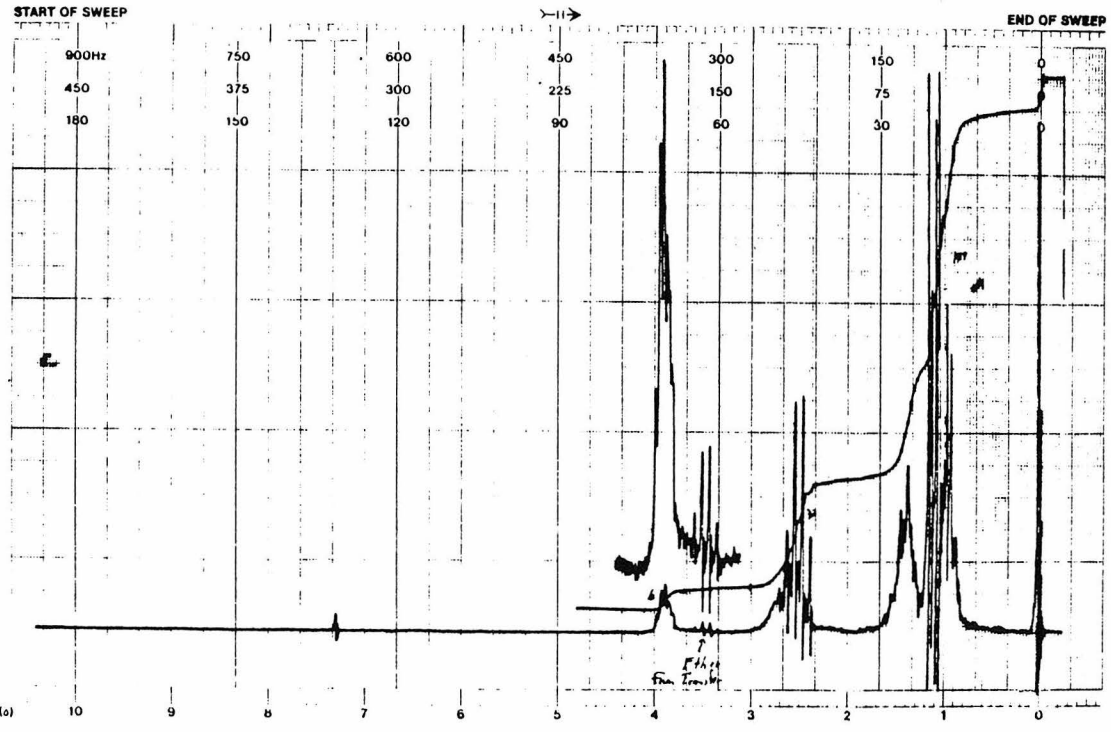

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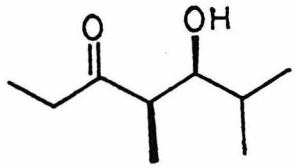

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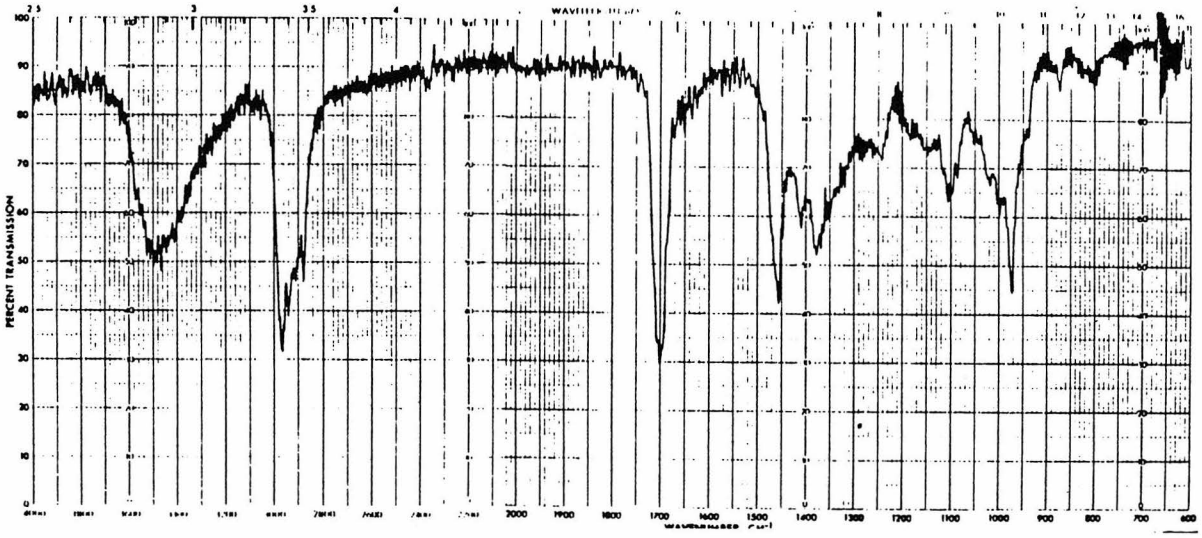

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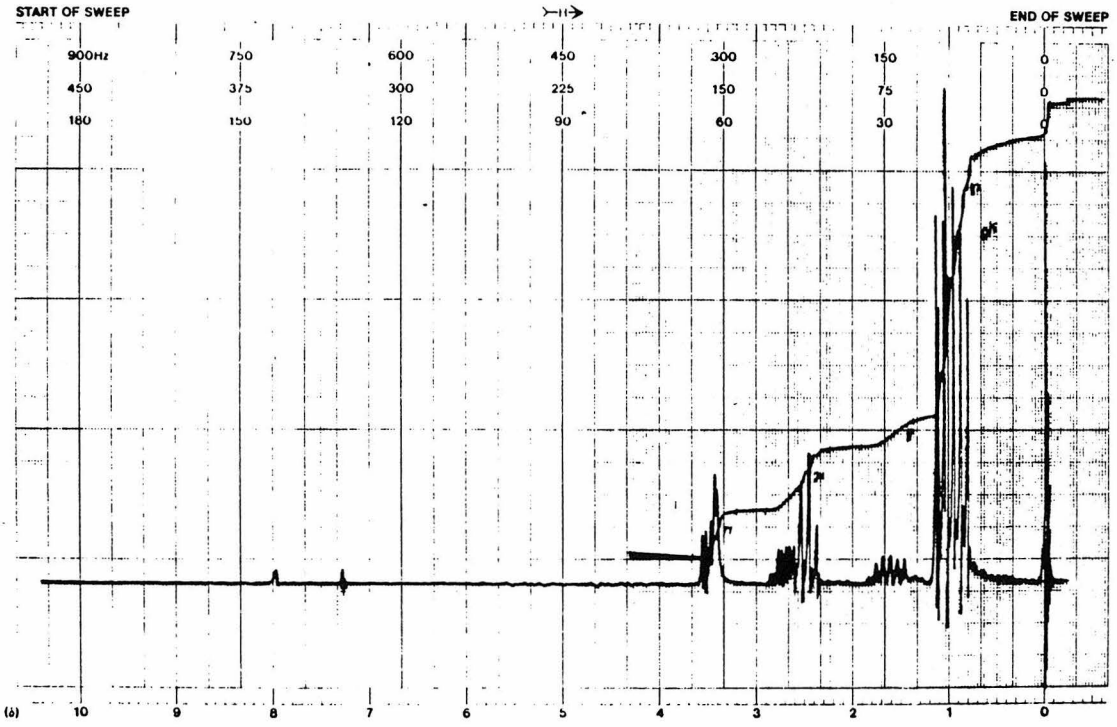

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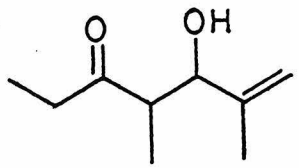

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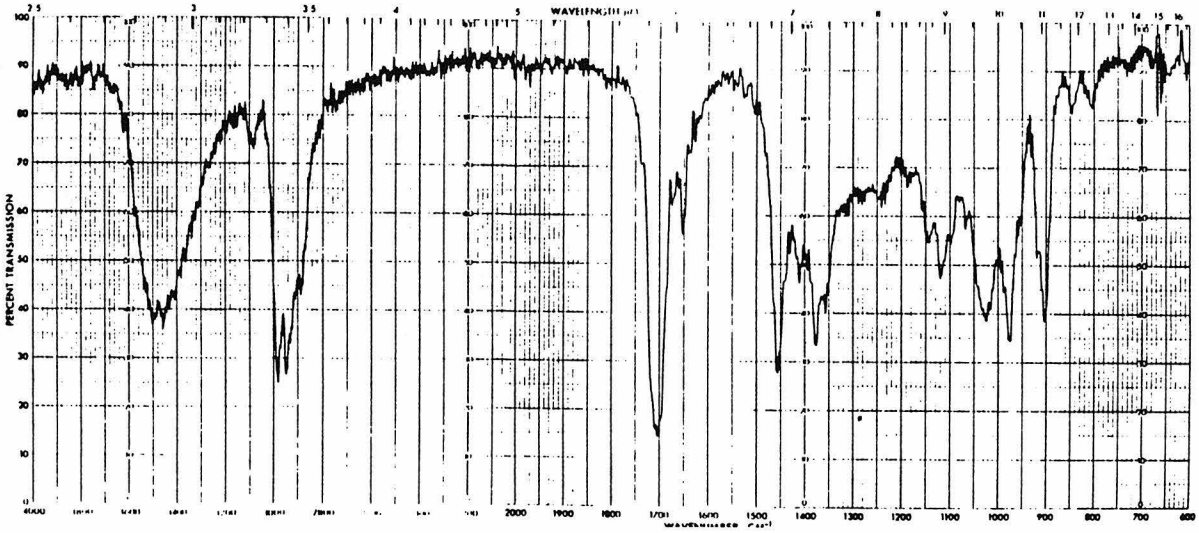

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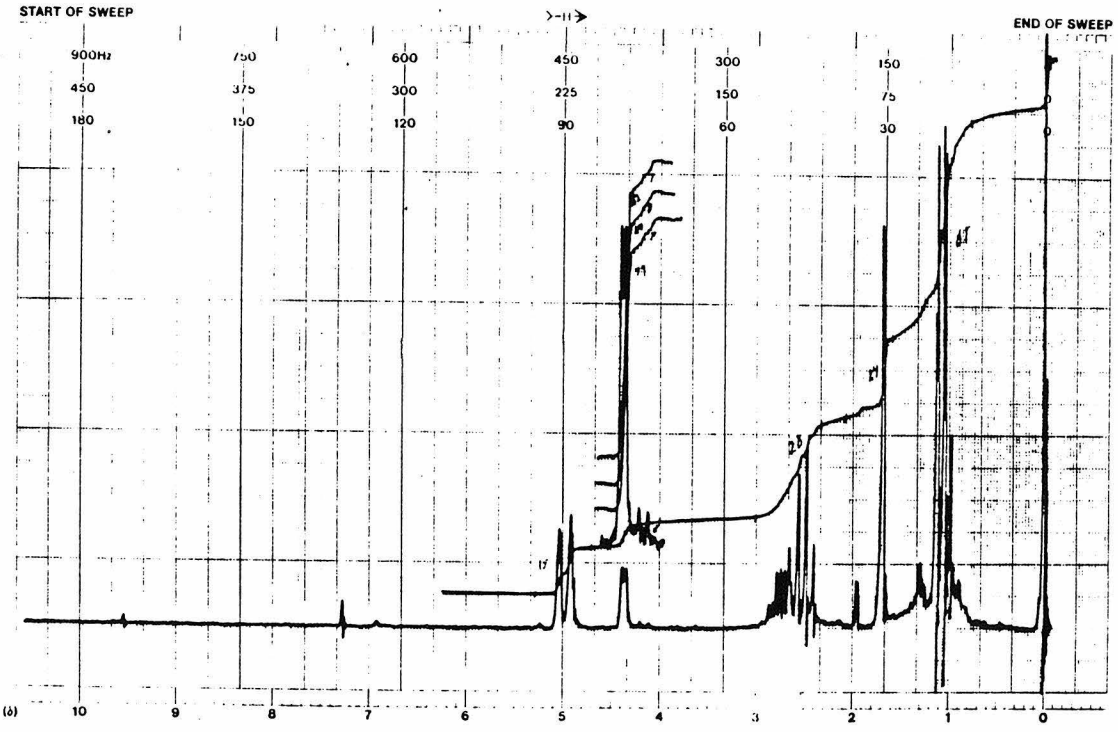

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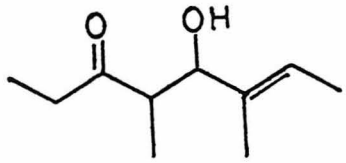

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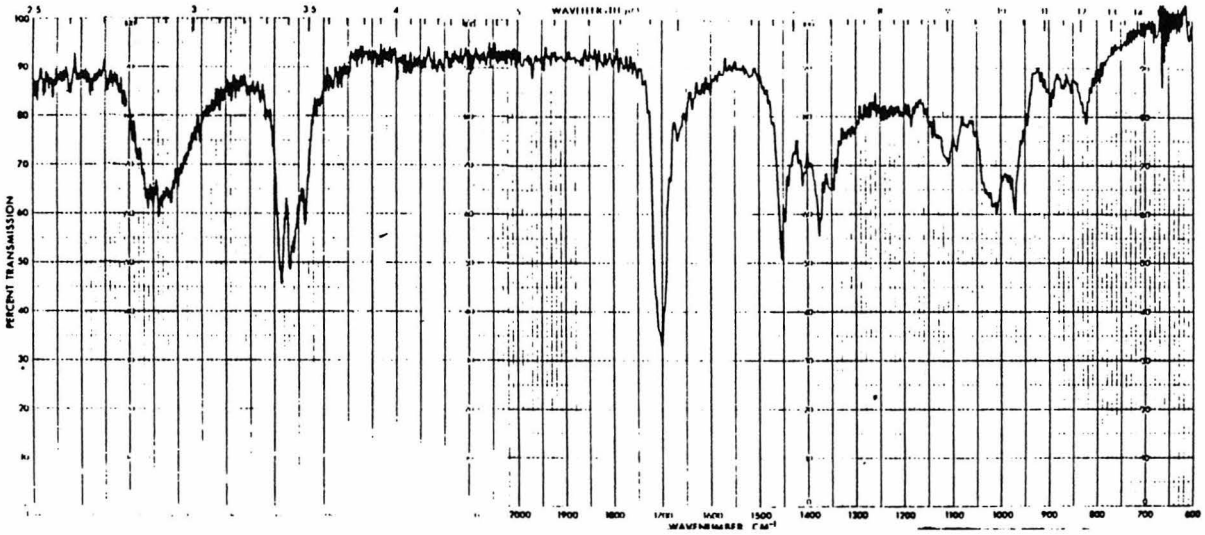

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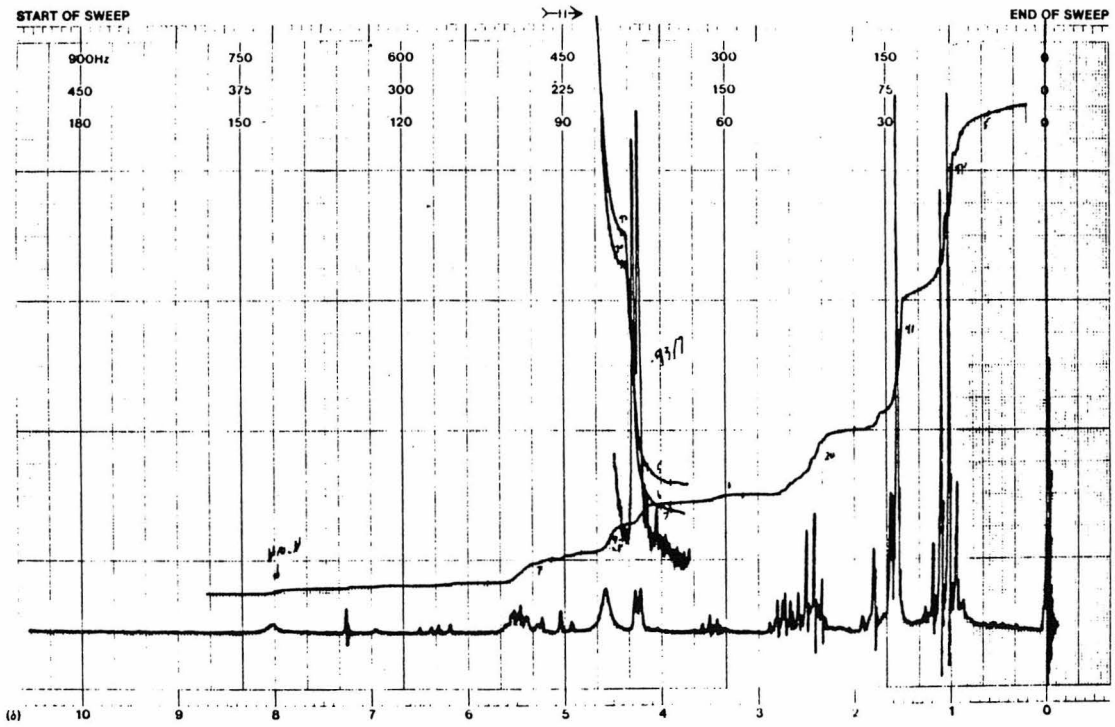

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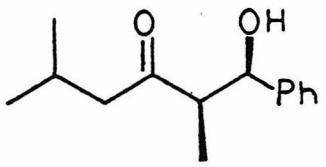

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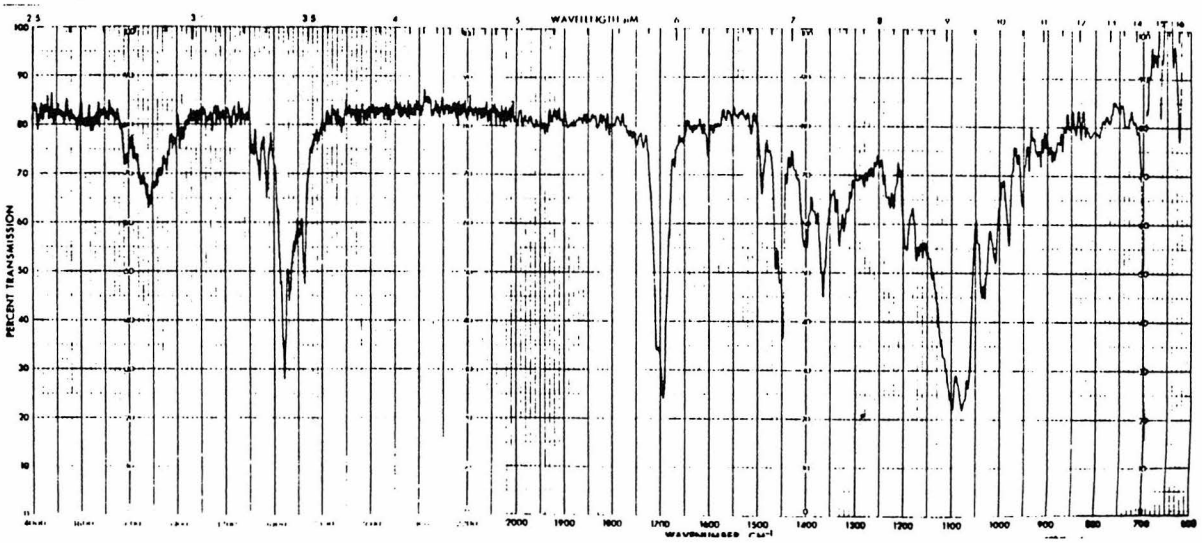

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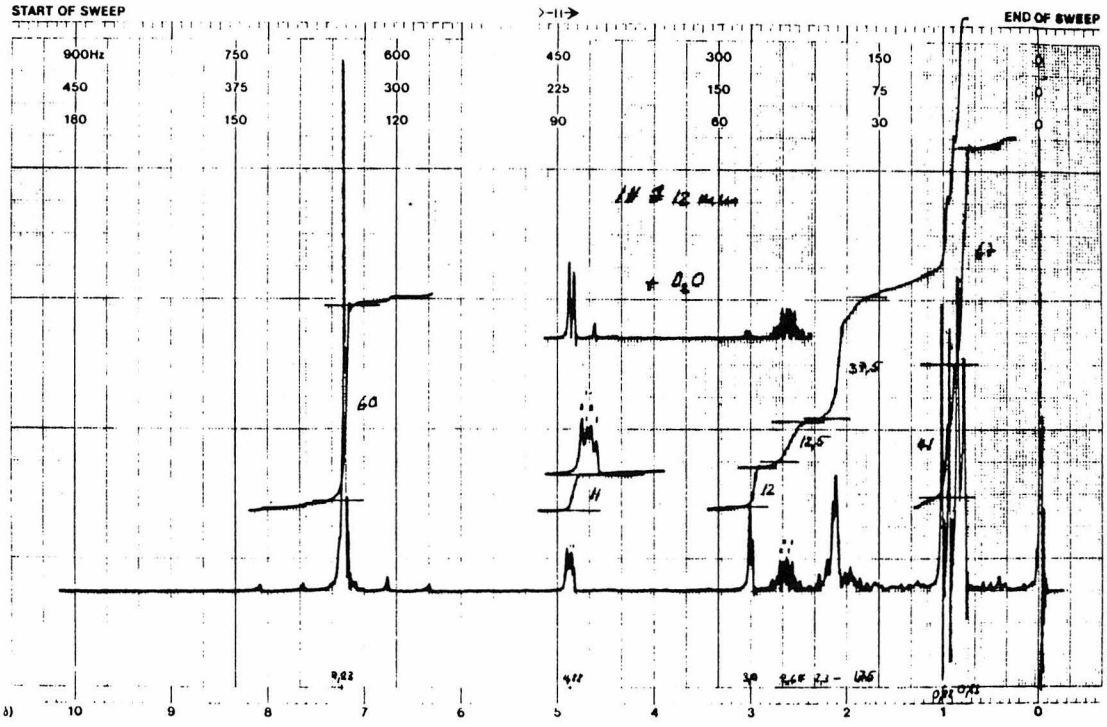

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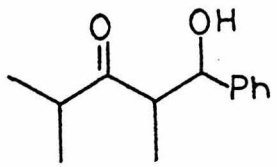

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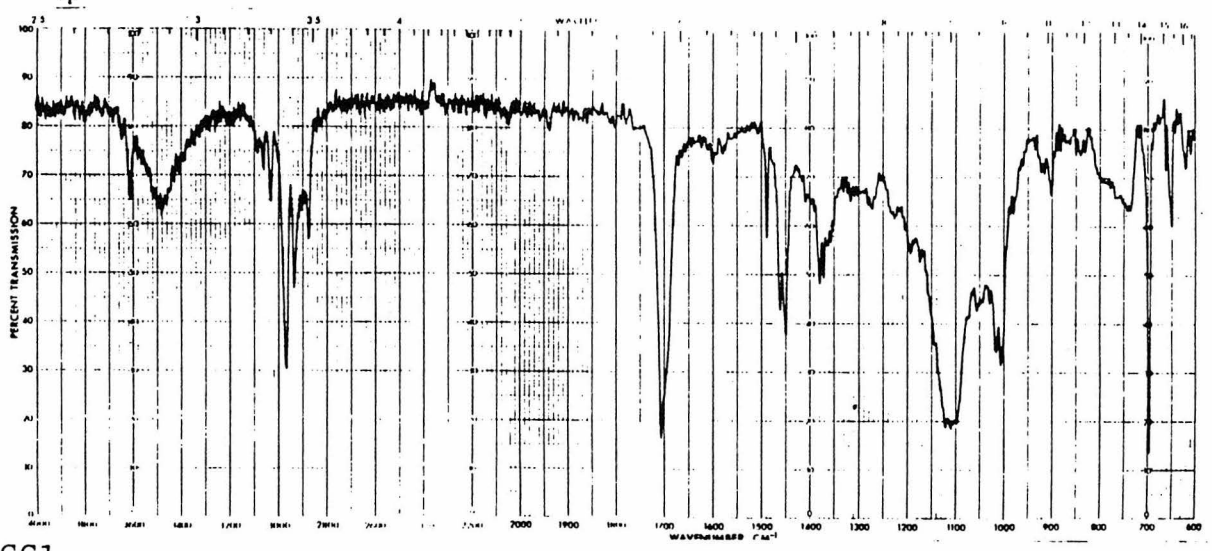

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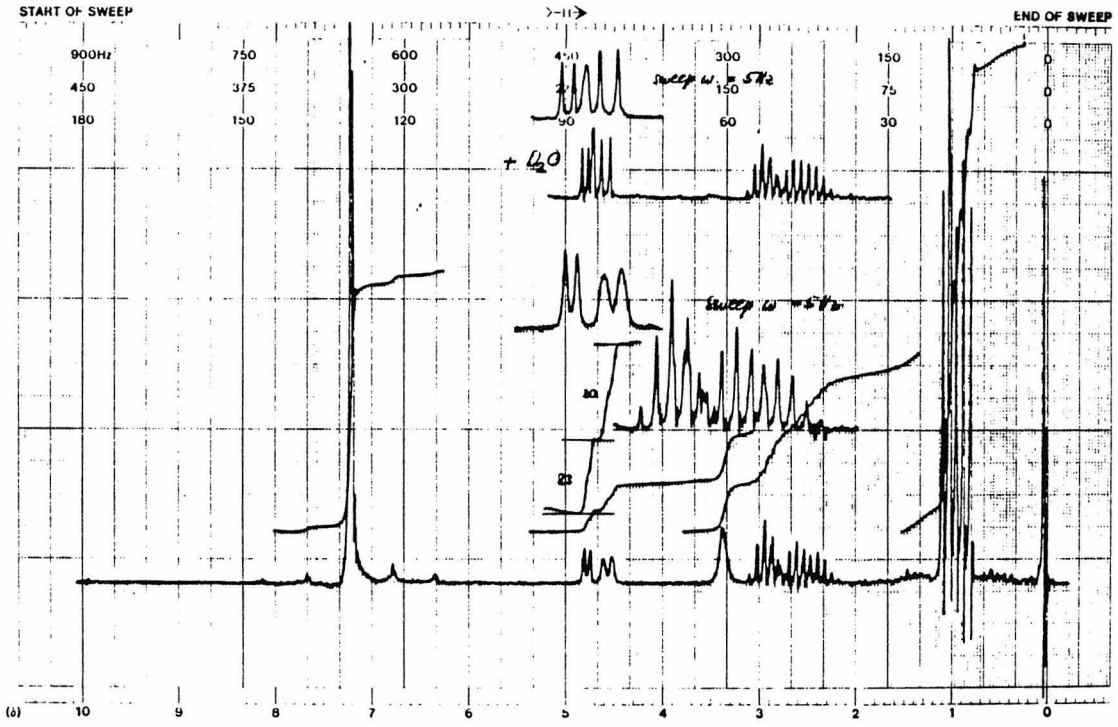

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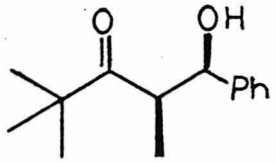

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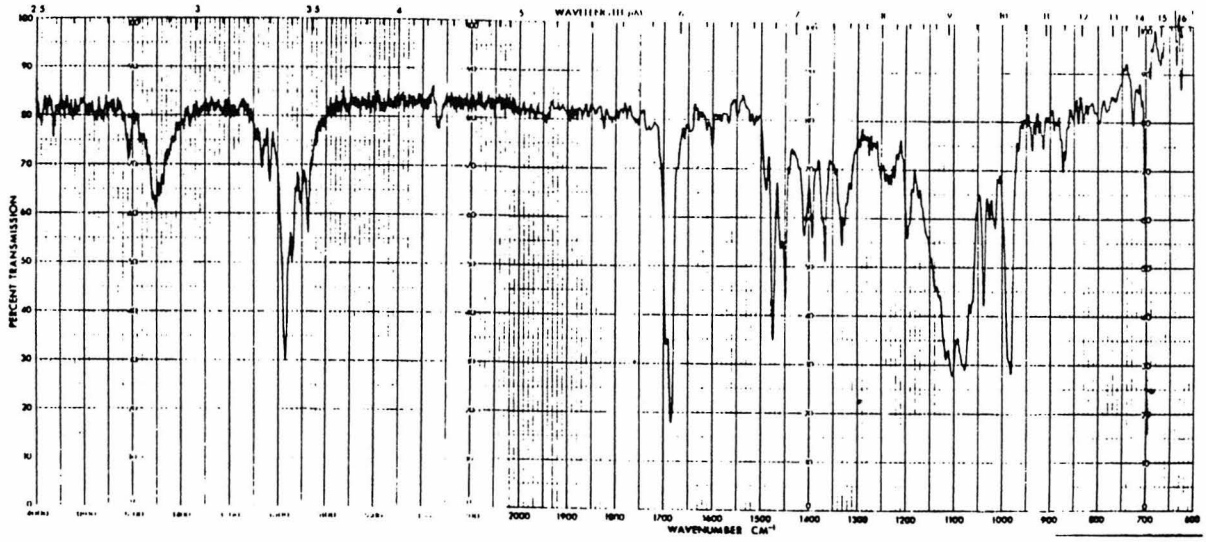

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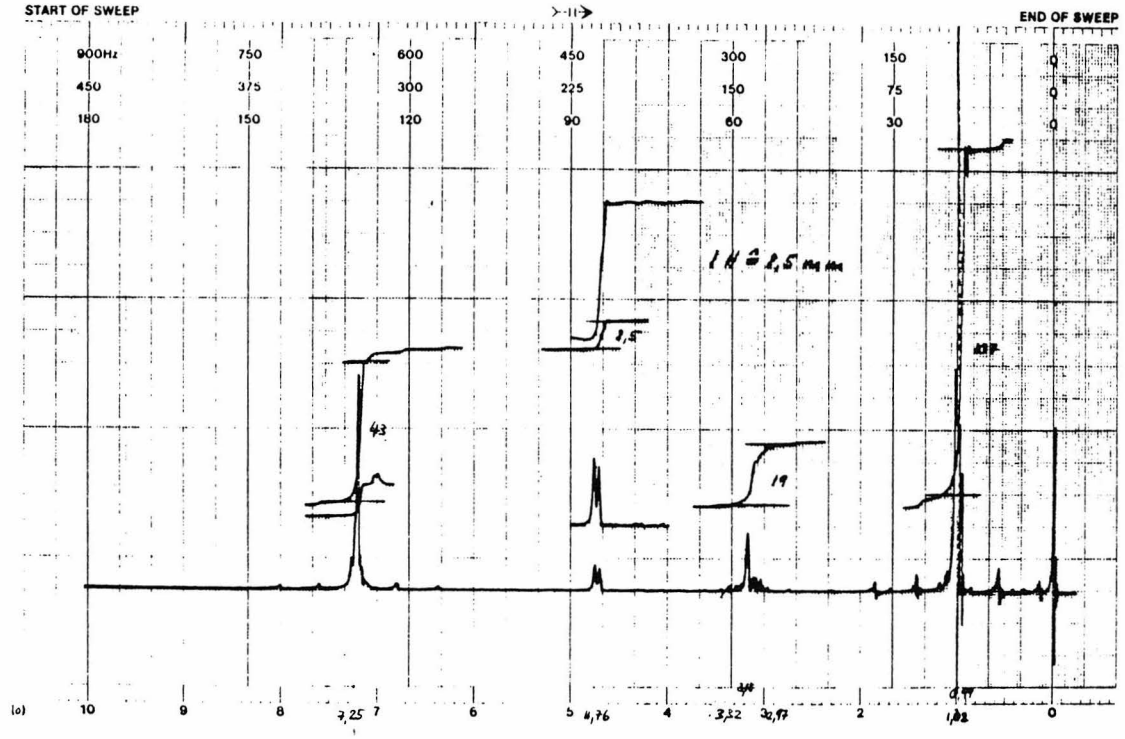

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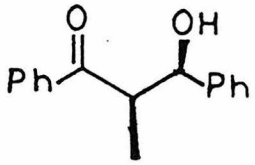

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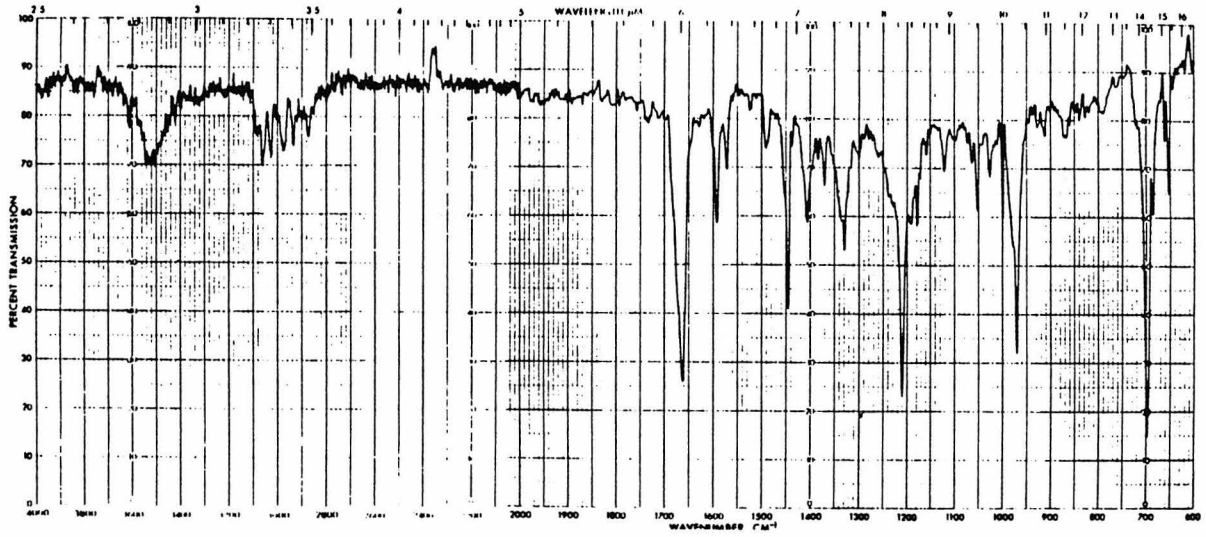
CCl_4, 4%



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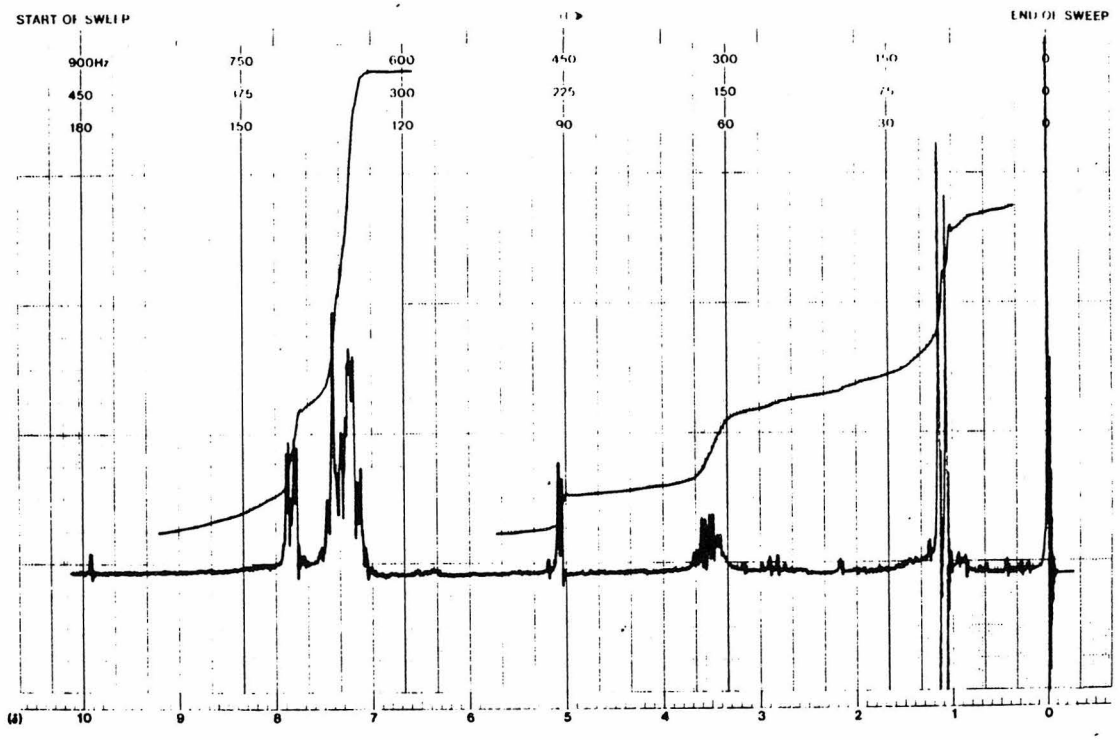

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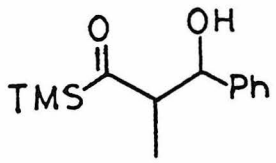

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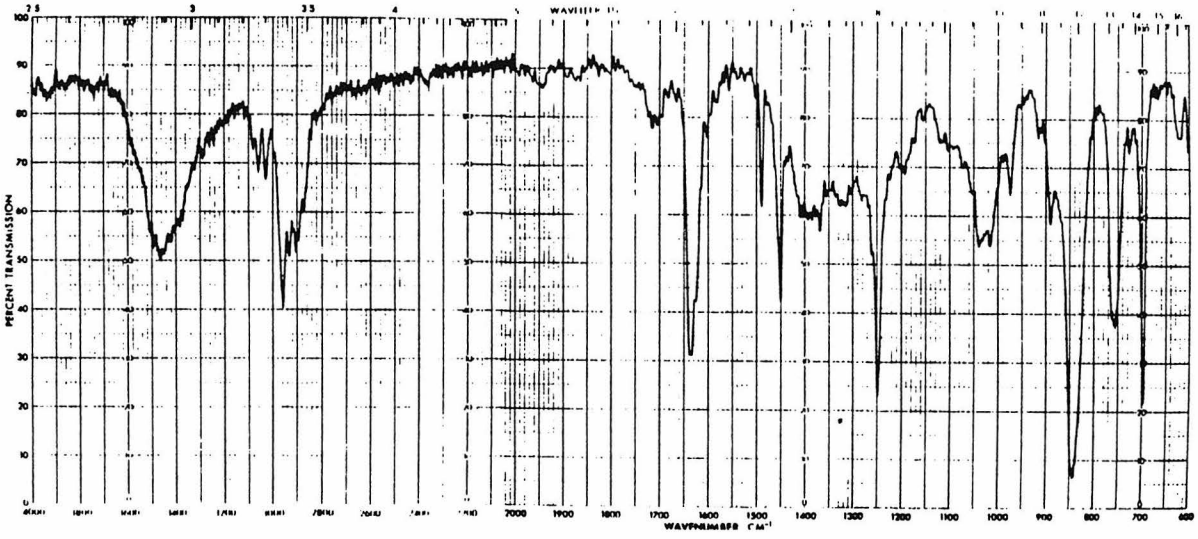

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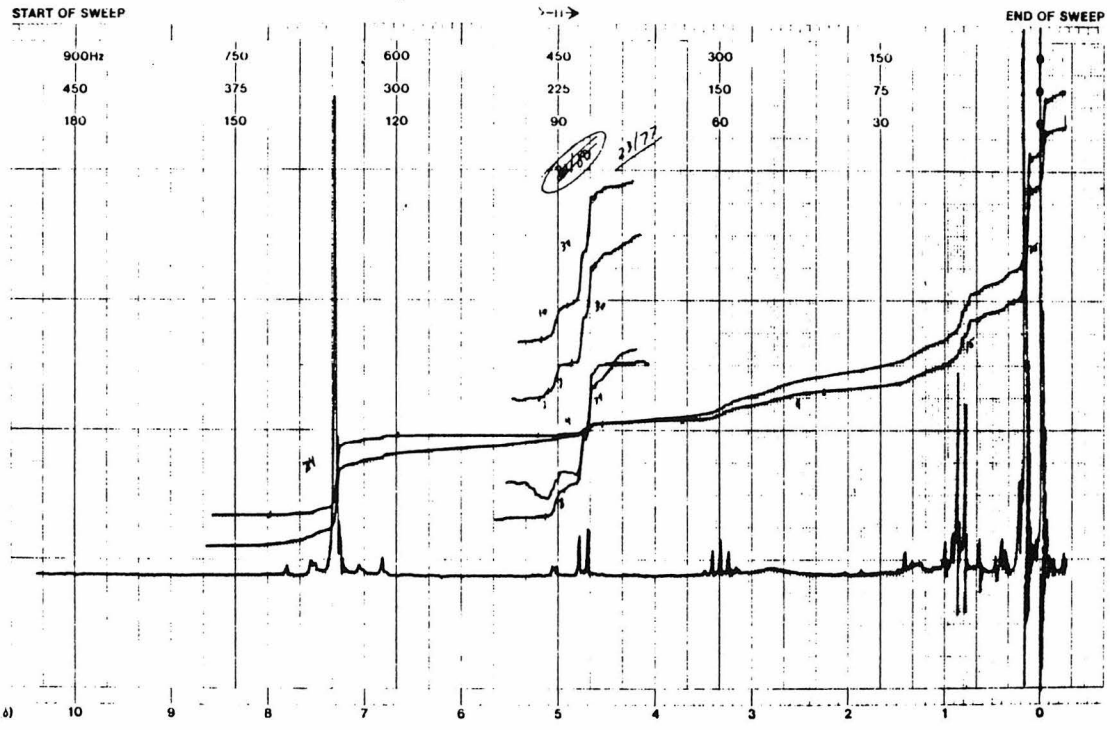

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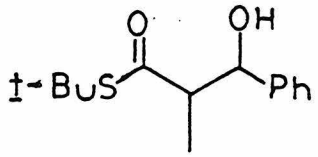

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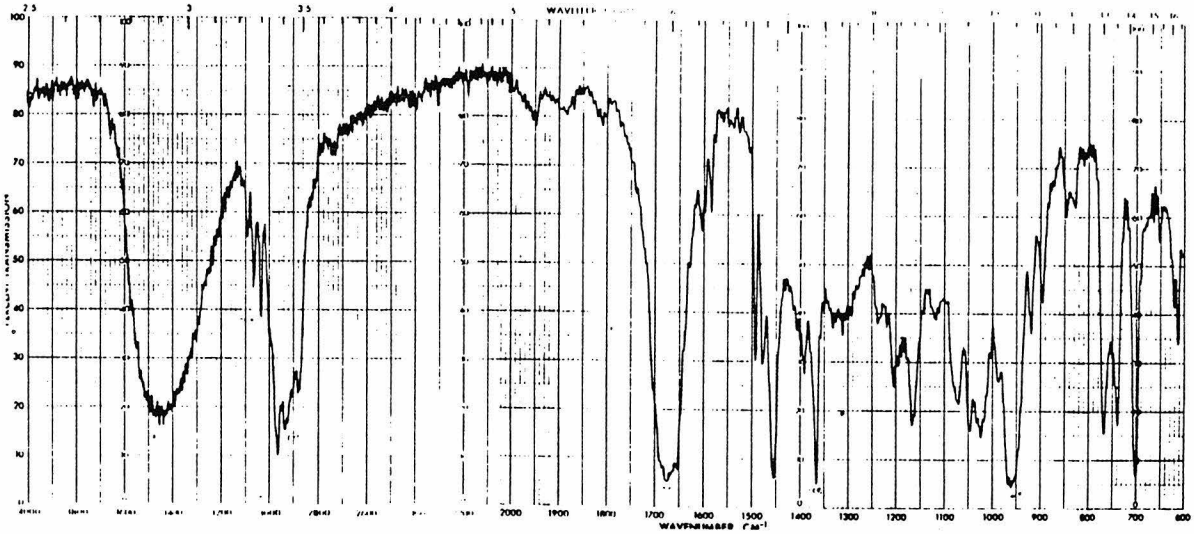

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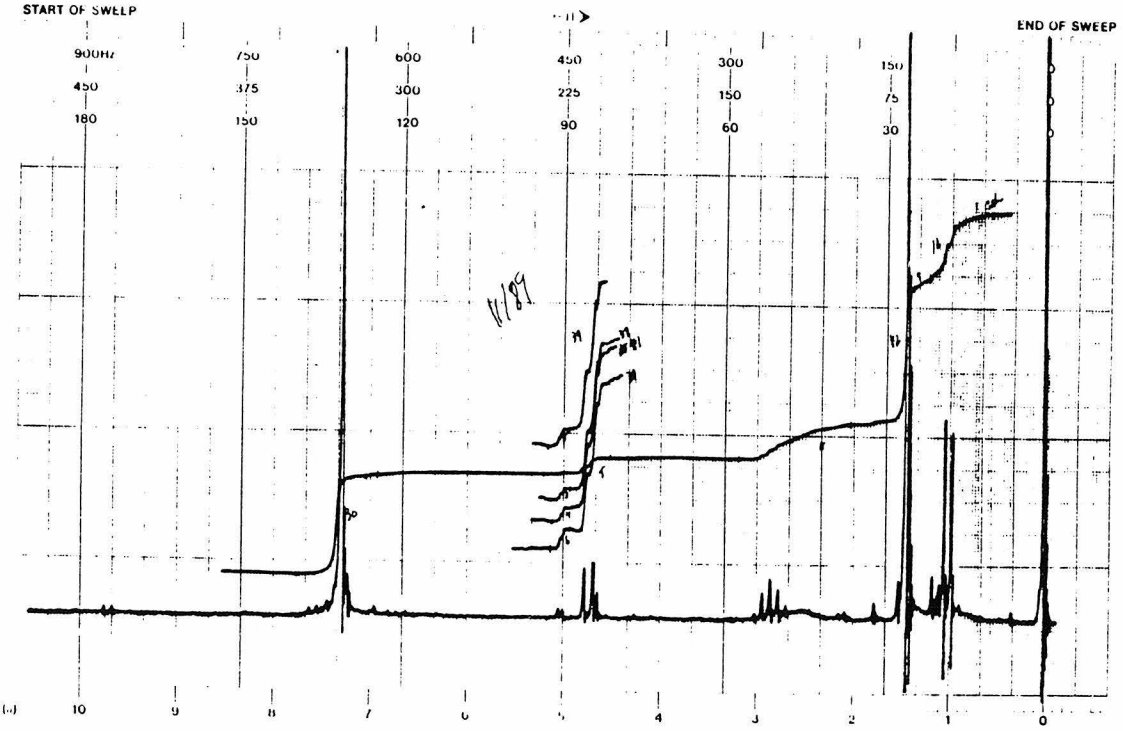

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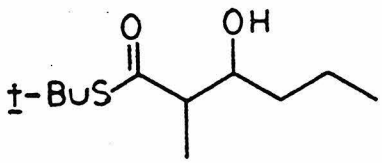

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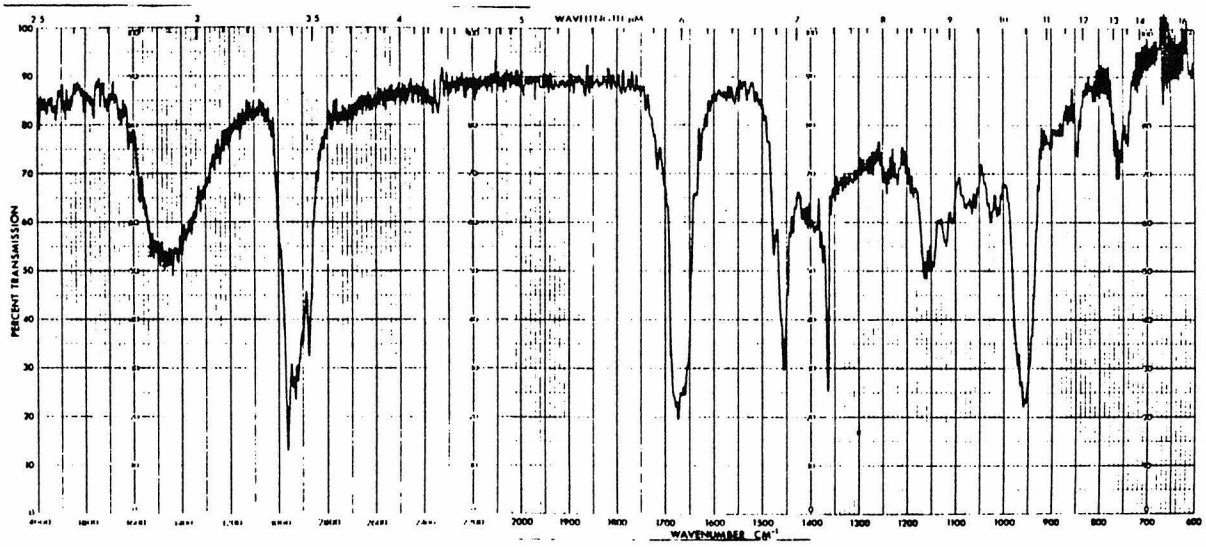

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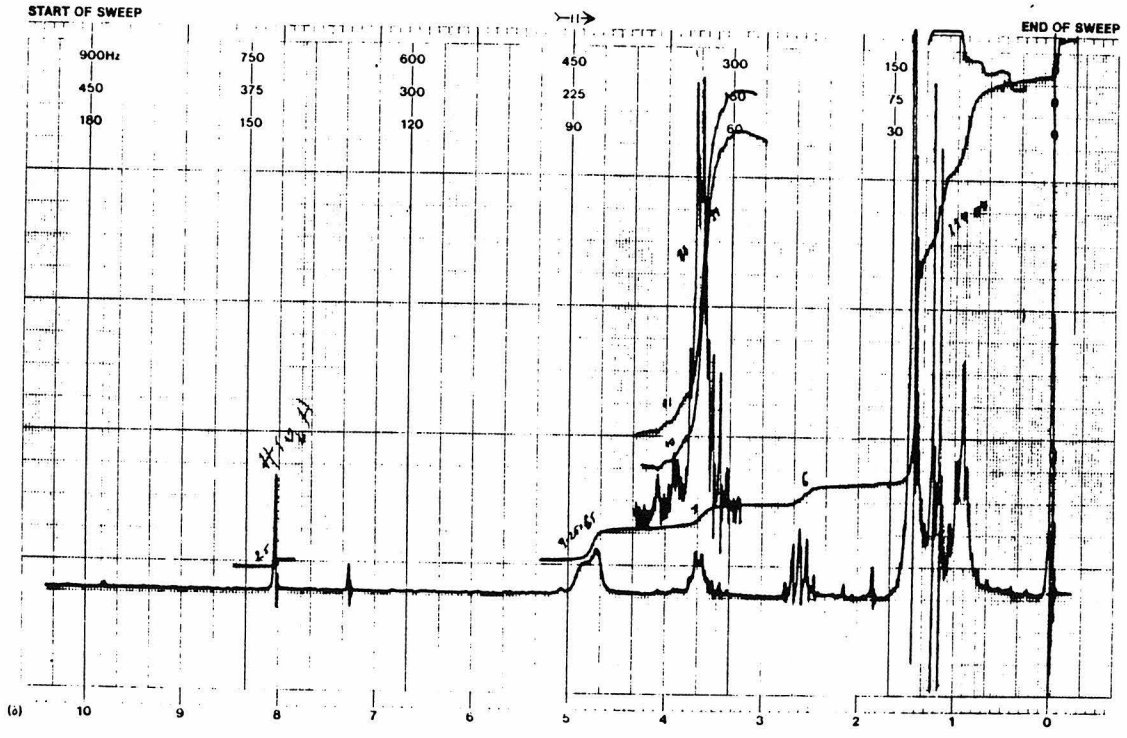

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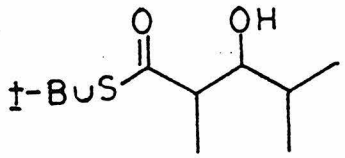

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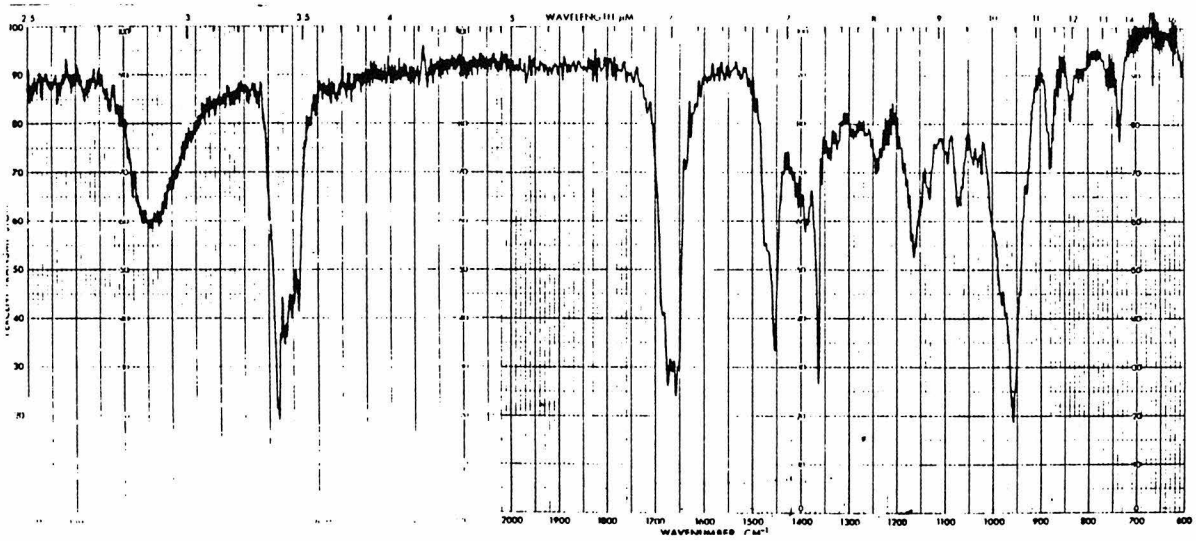

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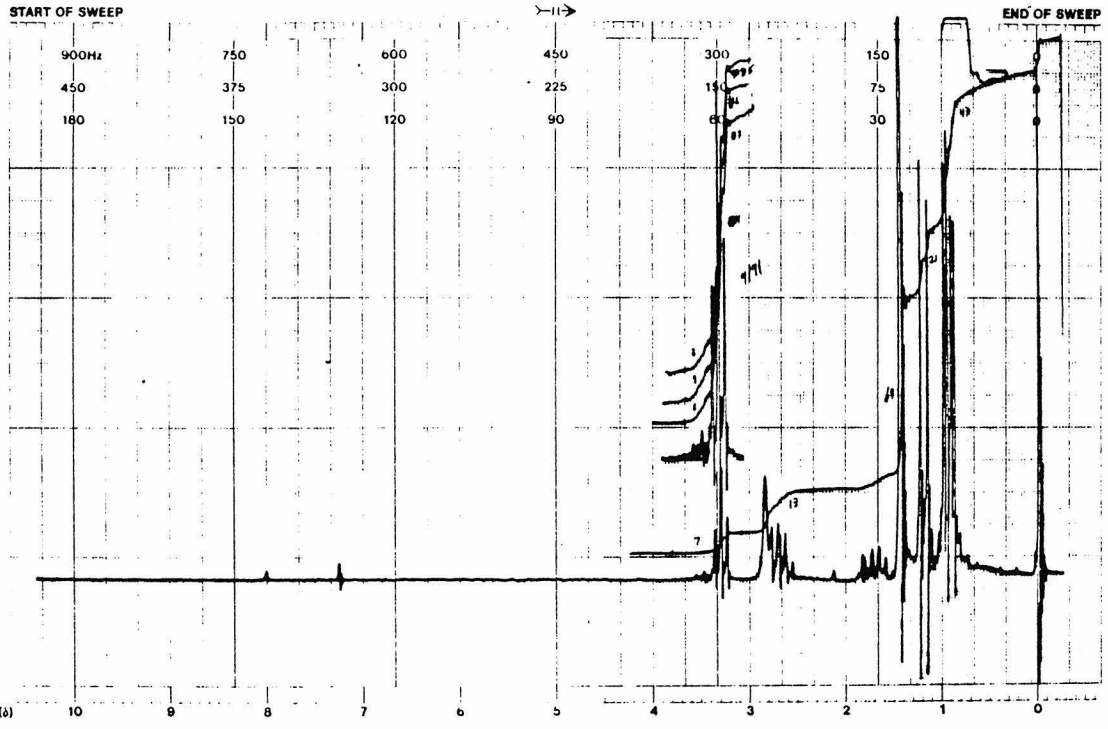

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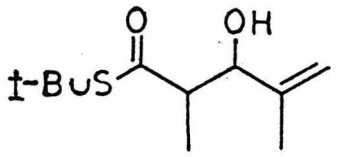

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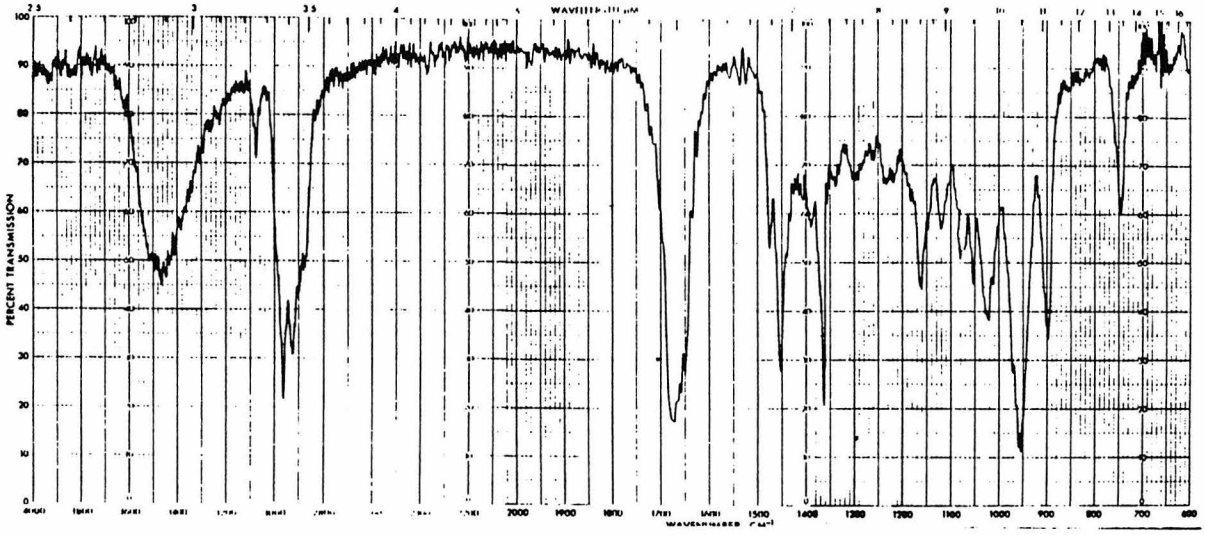

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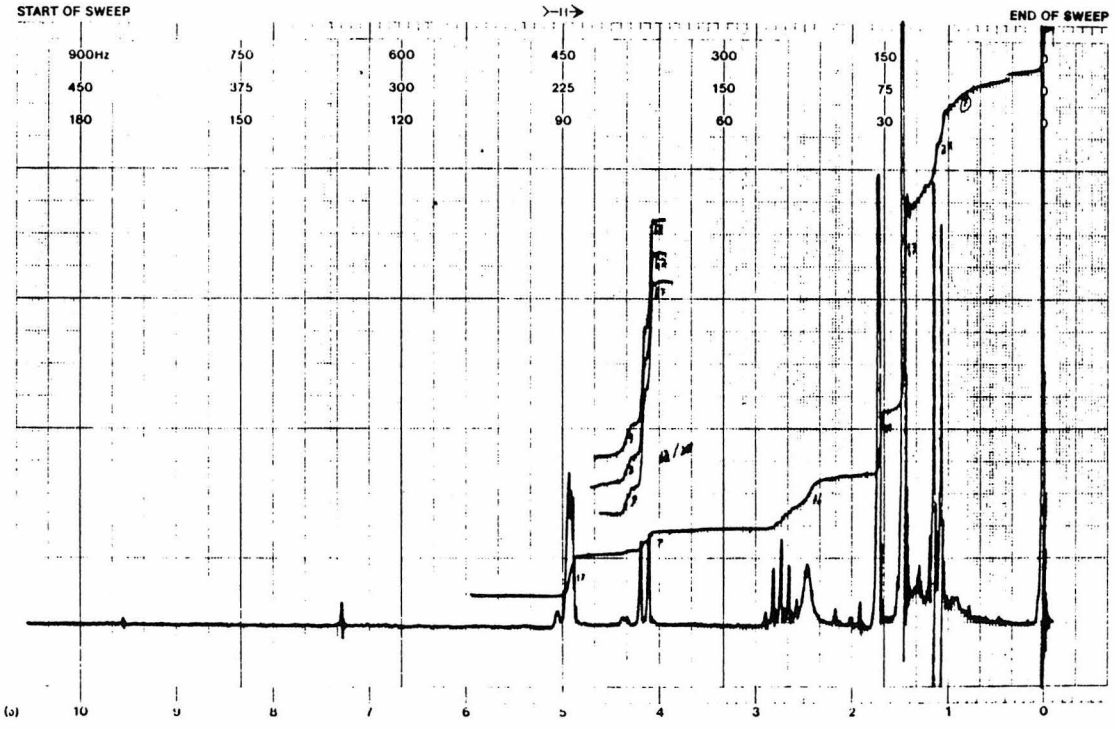

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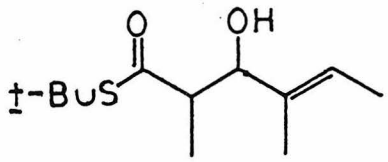
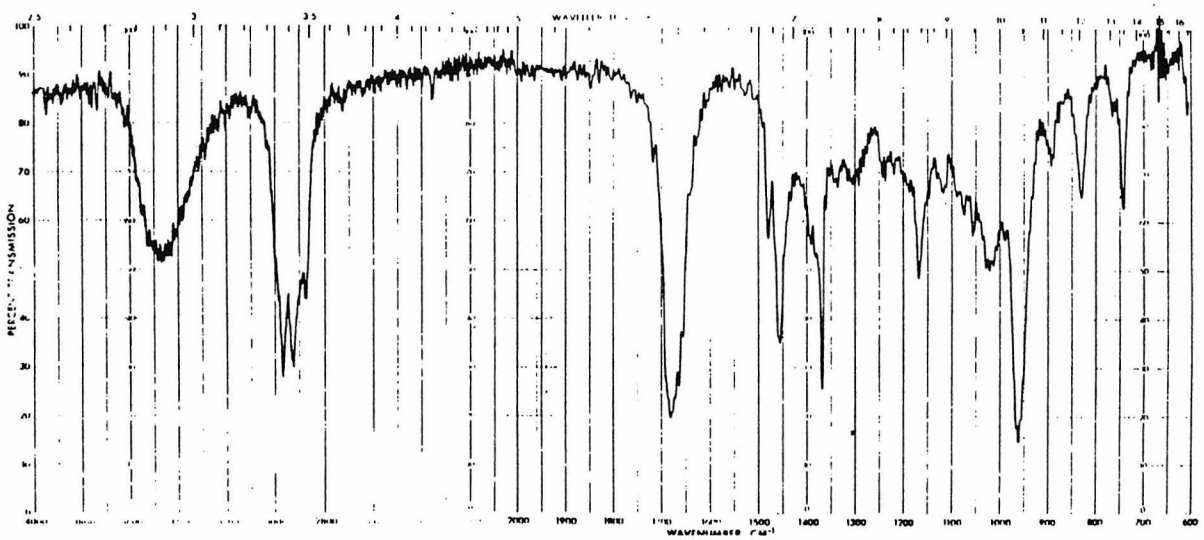


Table II, Entry X

neat



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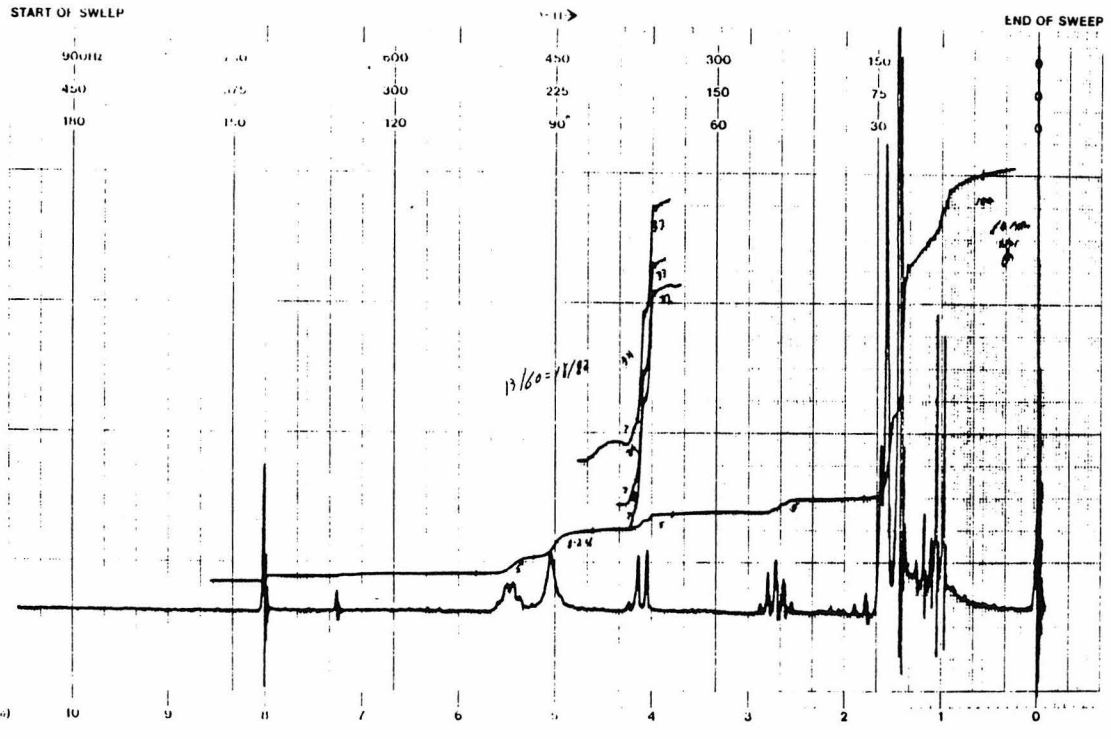

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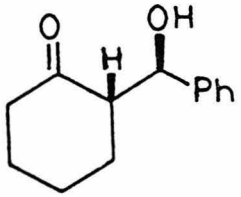

Table III, Entry F

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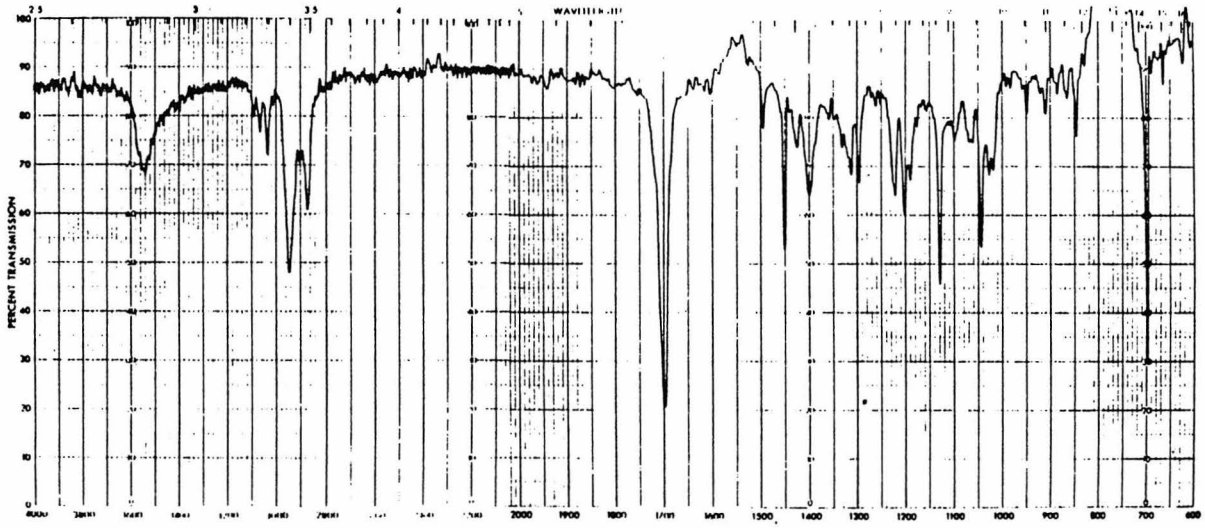

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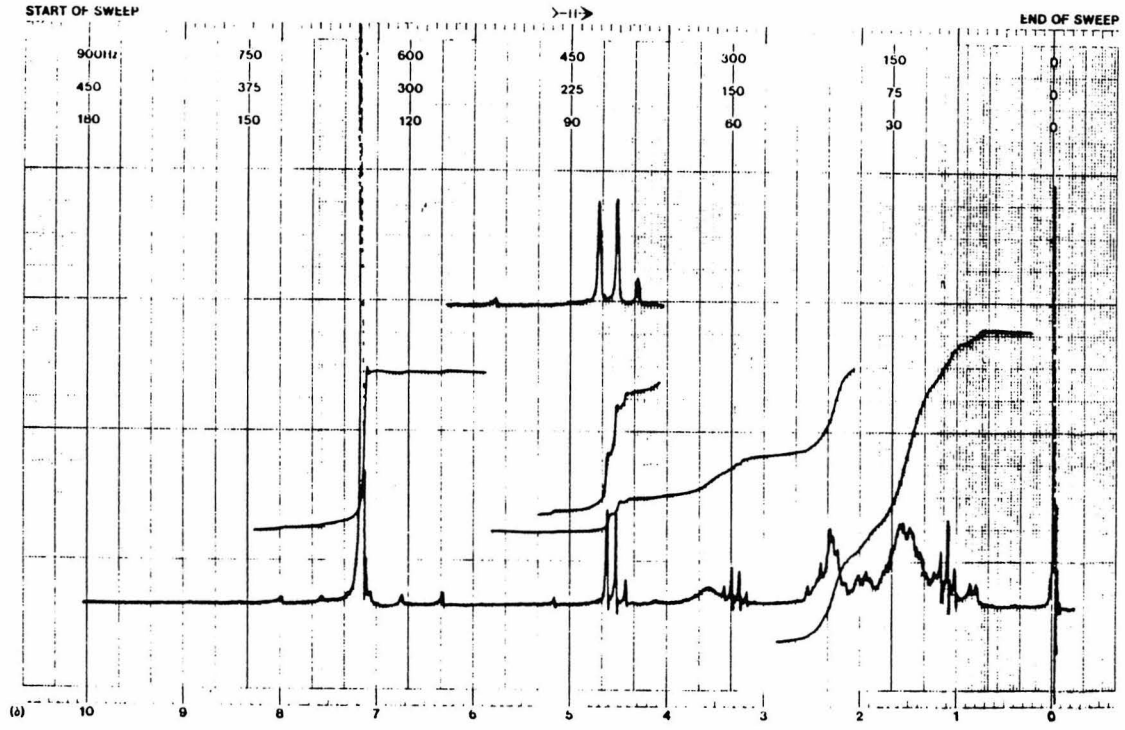

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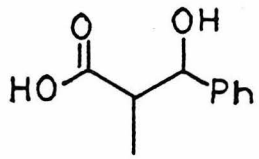
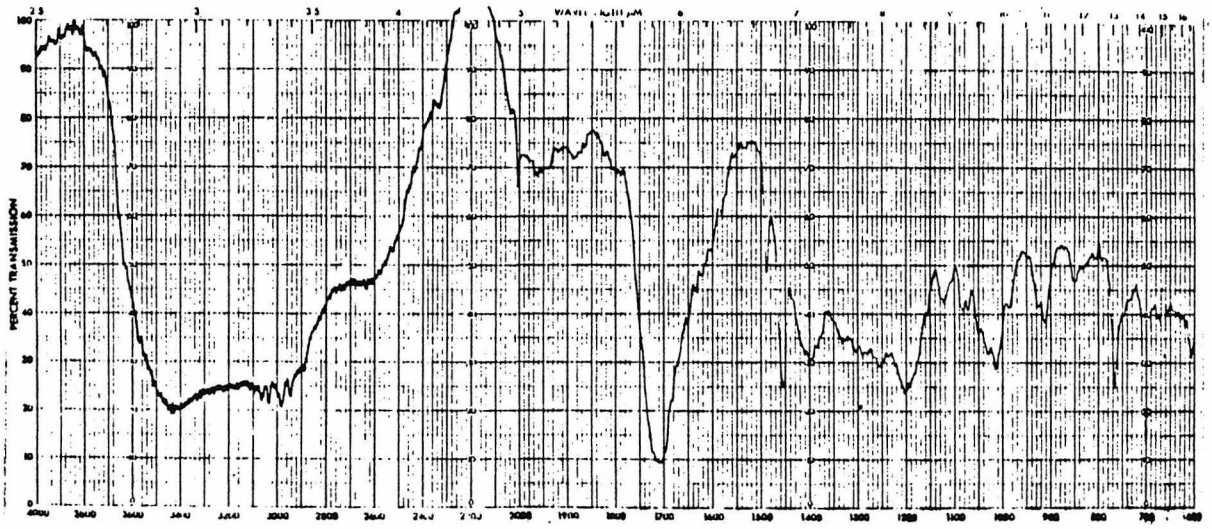


18a,19a

neat



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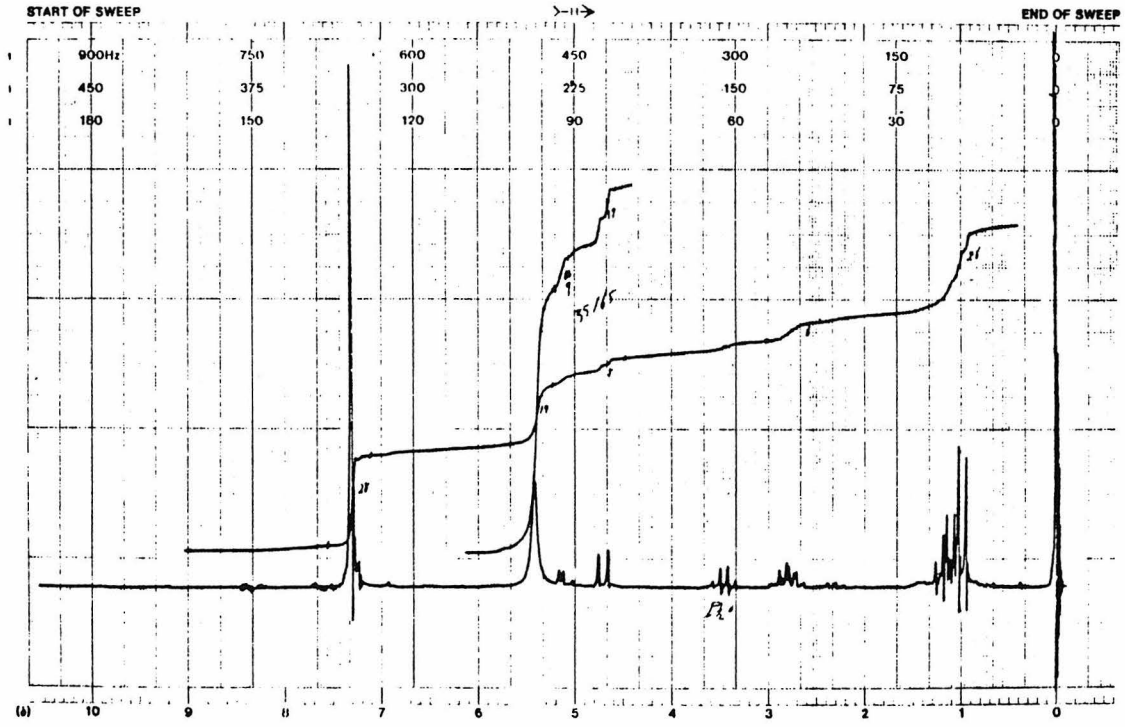

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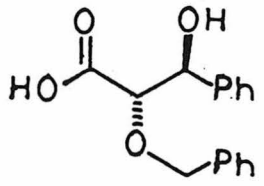
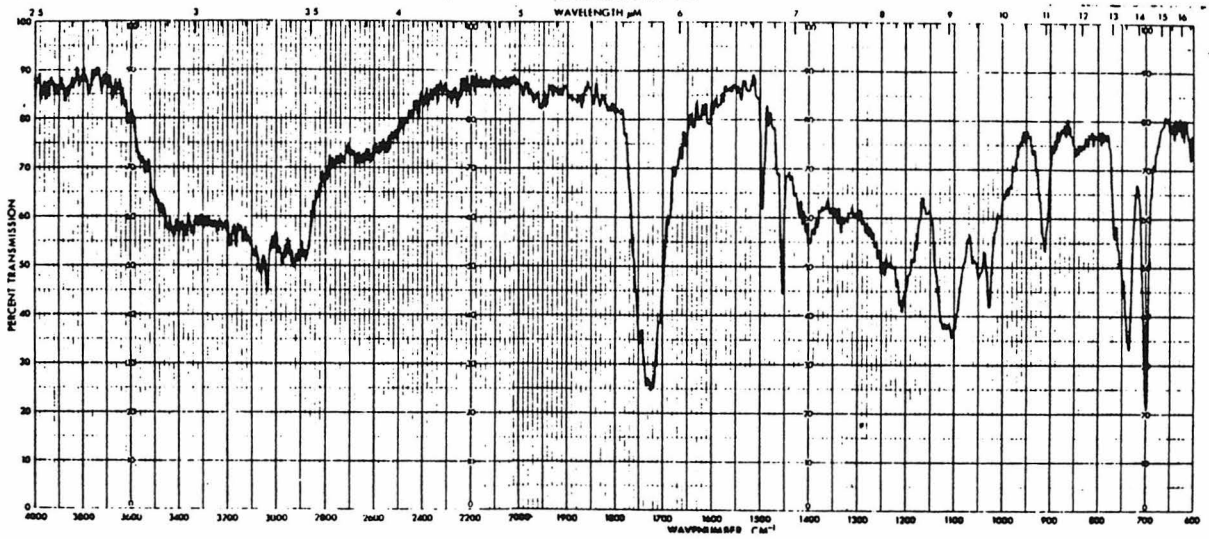


19b

neat



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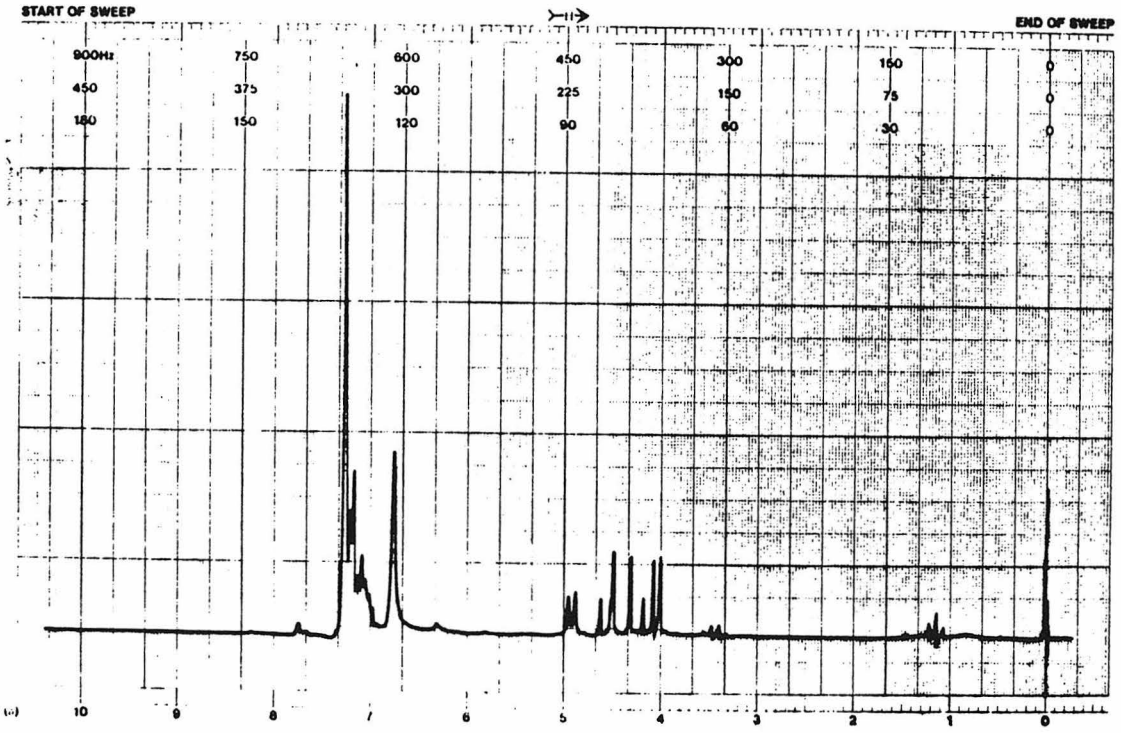

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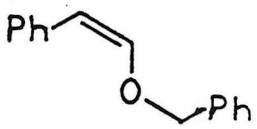
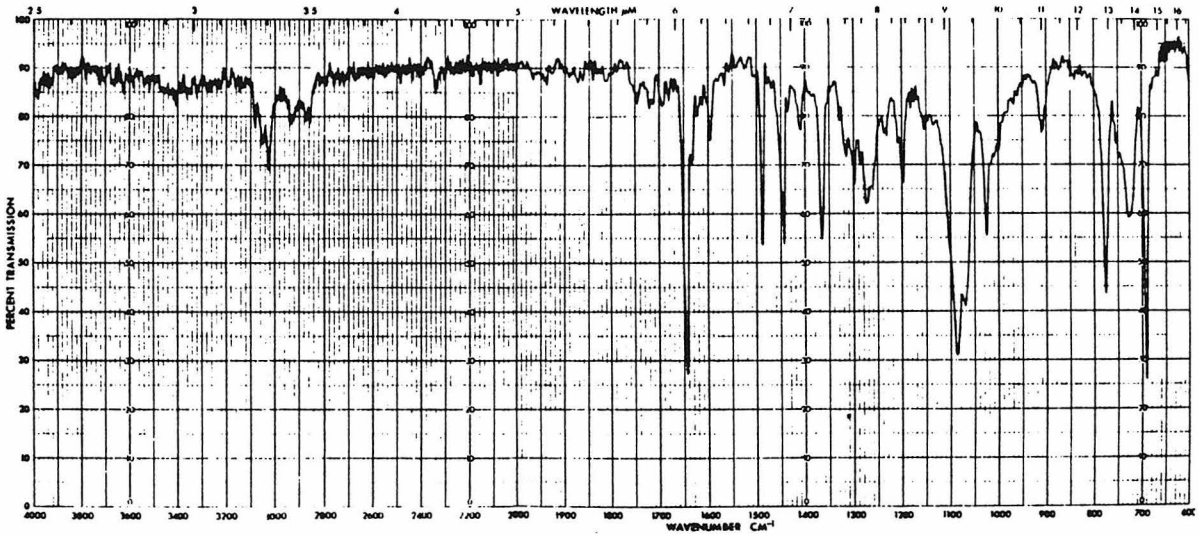


21b

neat



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