STEREOSELECTIVE ALDOL CONDENSATIONS *VIA* BORON ENOLATES. THE SYNTHESES OF (+)-PRELOG-DJERASSI LACTONE AND (+)-TYLONOLIDE

Thesis by

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Als Meus Pares

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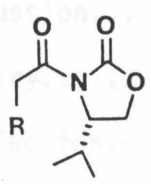
ABSTRACT

The use of boron enolates of chiral N-acyl oxazolidinones **i** and **ii** in highly stereoselective aldol condensations is described. Mild base hydrolysis of the products affords optically pure erythro β-hydroxy acids and the chiral auxiliary, which can be reconverted into **i** or **ii** in one step.

The utility and scope of these reactions is demonstrated by the total syntheses of (+)-Prelog-Djerassi lactone (**34**) and (+)-Tylonolide, cyclic 5,20-hemiacetal (**87**).



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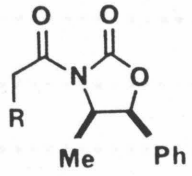

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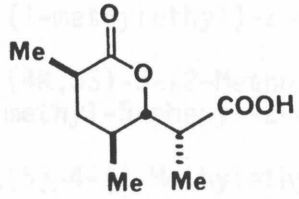

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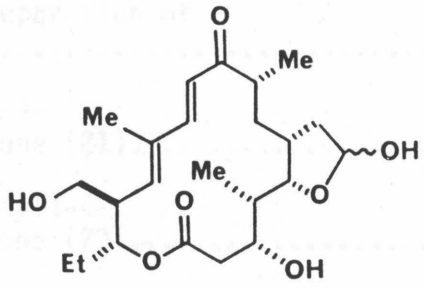

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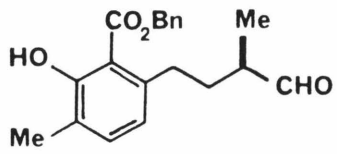
CHAPTER I

Stereoselective Aldol Condensations Via Boron Enolates[1]

I. Introduction

The aldol condensation is one of the oldest carbon-carbon bond forming reactions known in chemistry. It has not been until recent years, however, that organic chemists have learned how to control its intrinsic stereochemistry when performed in acyclic systems.[2] Today, this reaction constitutes a powerful tool in the synthesis of macrolide and polyether antibiotics.

Before the reaction achieved practicability, one problem needed to be addressed: the selective formation of the desired product stereochemistry. The issue can be approached in two different ways: a), Via induction by the molecule's intrinsic chirality, for example the final aldol condensation of the Ireland and Kishi syntheses[3] of lasalocid A (eq. 1); or b), via induction by a removable, chiral



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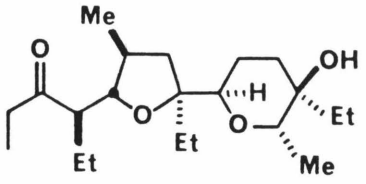
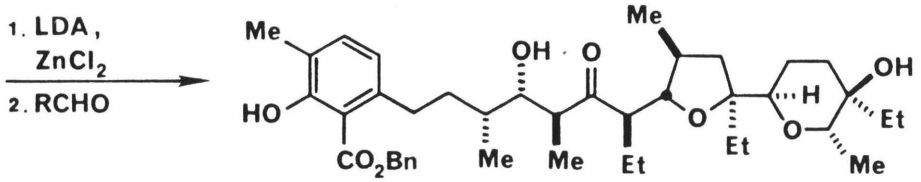


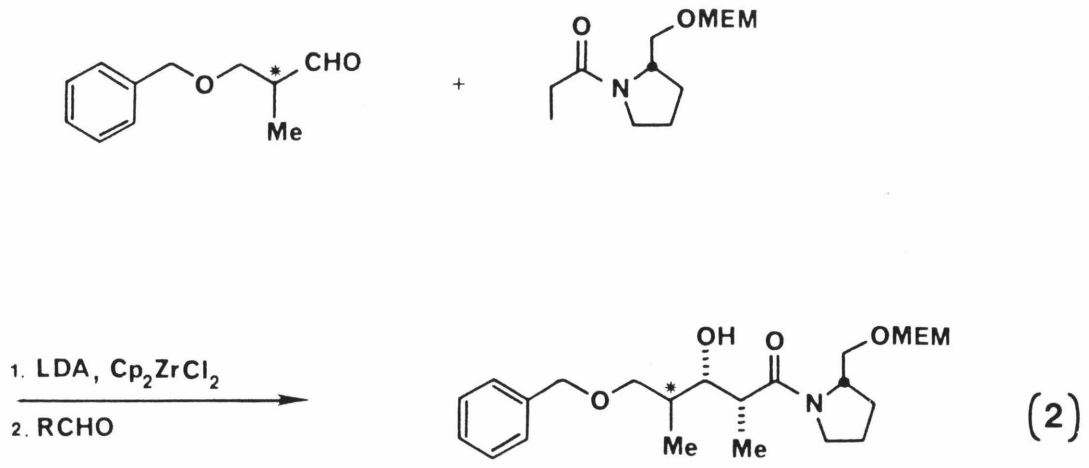


(1)

(major)

(ref. 3)

auxiliary (eq .2).[4] Due to its wider scope, the latter method interested us more.

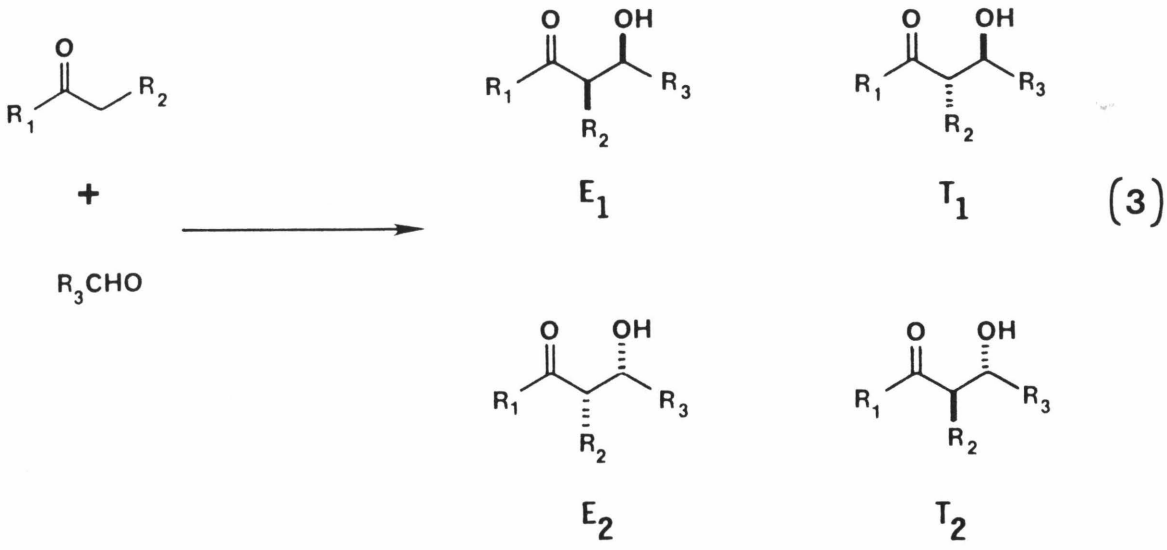


(2)

* denotes either the (R)-isomer or the (S)-isomer.

(ref. 4)

Because an aldol condensation involves the creation of two sp^3 carbons, four possible stereoisomers can in principle be formed (eq. 3). In planning the selective formation of only one of them, two separate issues need to be addressed: The control of the reaction erythro:threo[5] selection (E vs T), and the control of the reaction enantioselection (E_1 vs E_2 or T_1 vs T_2). We present here a practical way of preparing either E_1 or E_2-type products in a highly selective fashion.

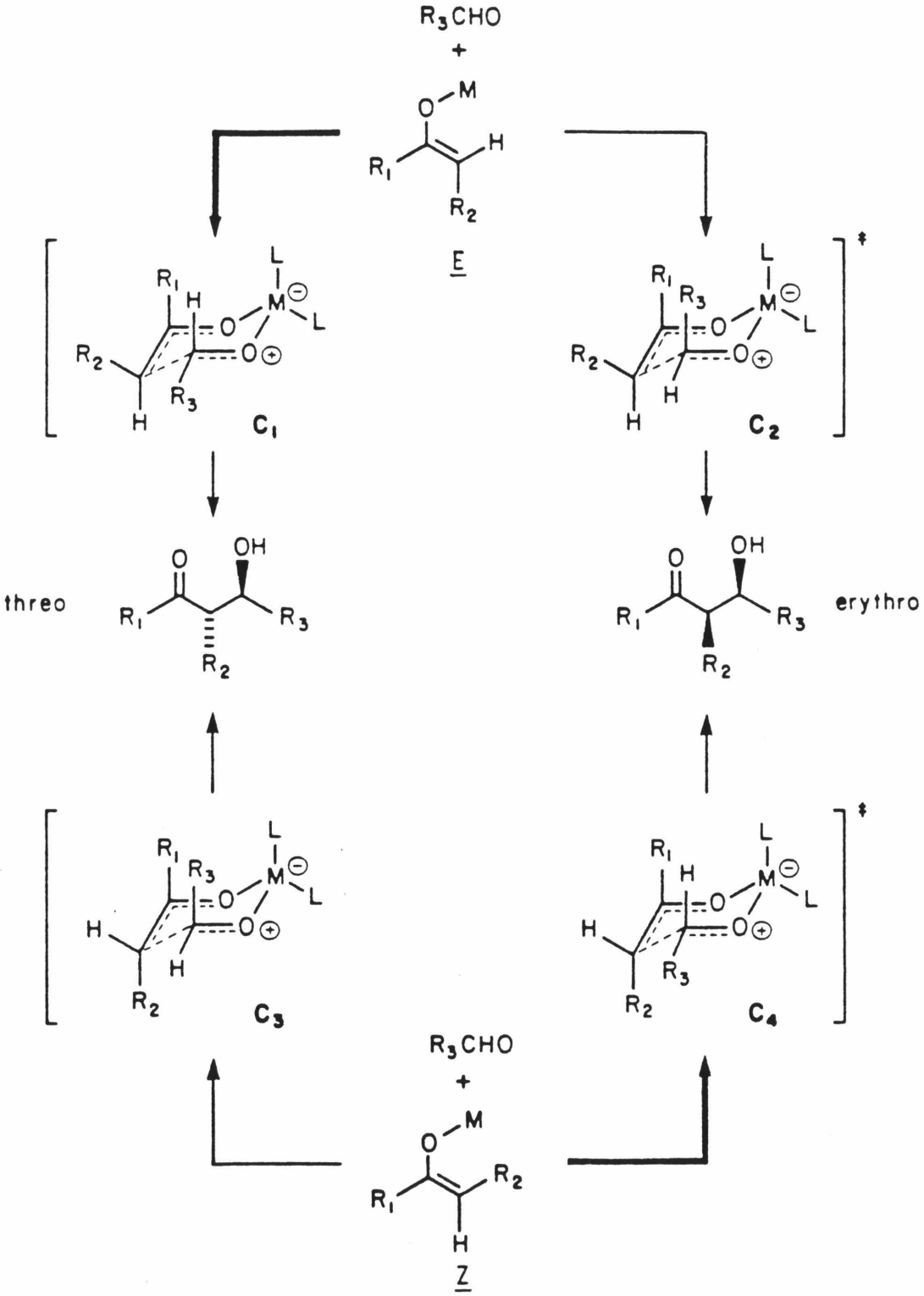


(3)

II. Background

In 1957 Zimmerman and Traxler proposed a six membered cyclic transition state to rationalize the diastereoselection of the Reformatsky and Ivanov reactions of phenylacetic acid with benzaldehyde.[6] In this model, the enolate and the aldehyde are held together by the metal, forming a chair-like structure. More recently, Dubois[7] and subsequently Heathcock[8] have demonstrated the role of enolate geometry on the kinetic product distribution in the aldol condensation. Thus, the magnesium and lithium (Z) enolates of a variety of ketones afford erythro adducts with very good selection, whereas the corresponding (E) enolates give mainly threo products. With this information in hand, a more elaborated cyclic aldol transition state was proposed by Evans in 1979 (Scheme I).[9a] This model strongly emphasizes the role of the enolate geometry and nonbonding interactions in determining the product stereochemistry.

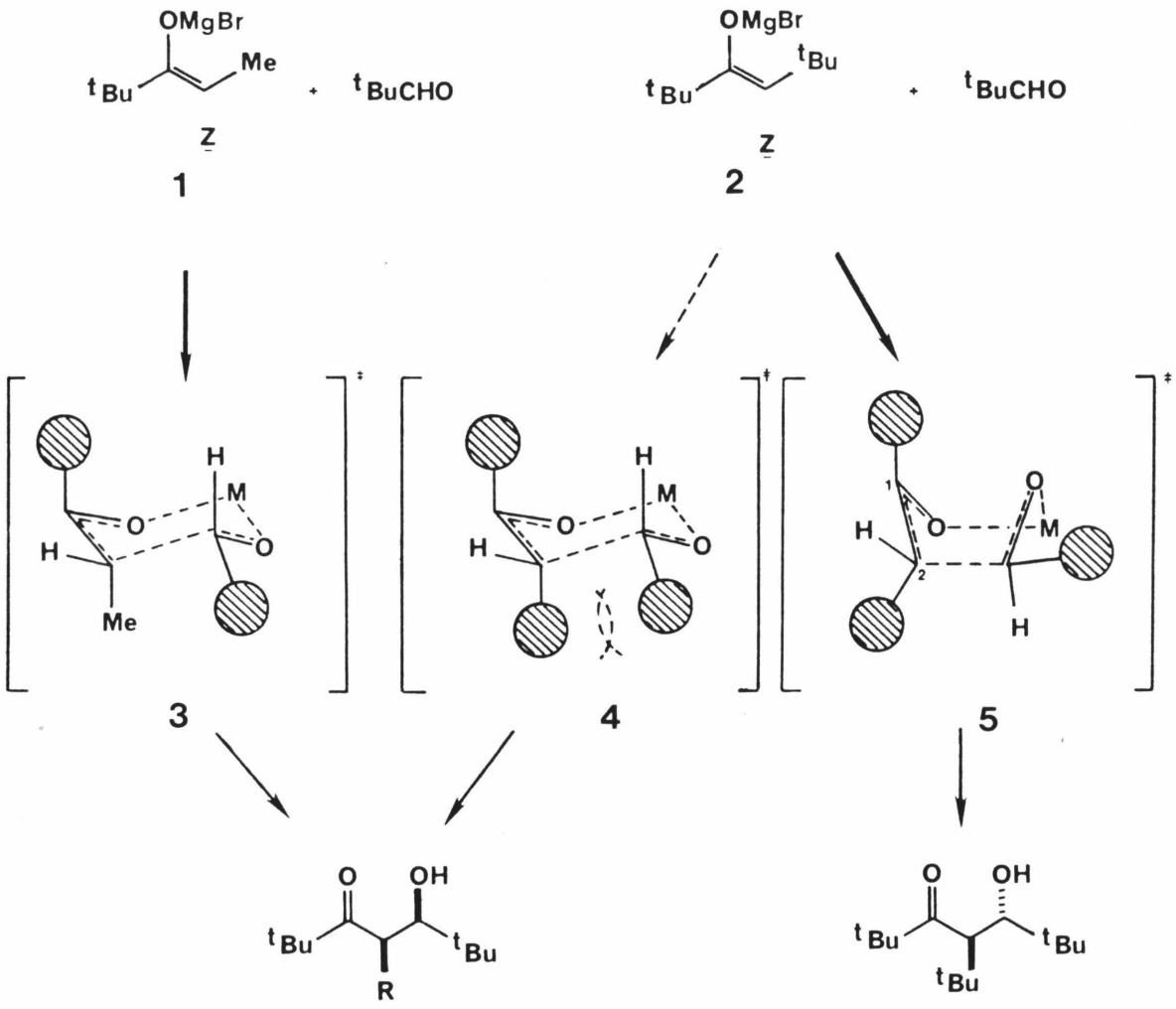
Scheme I



For example, the (Z) enolate is predicted to give the erythro product via transition state **C_4**, in which 1,3-diaxial interactions have been minimized. The (Z) enolate derived transition state **C_3** which leads to the threo product, has two additional diaxial interactions ($R_3 \leftrightarrow R_1$ and $R_3 \leftrightarrow L$) thus raising its heat of formation relative to transition state **C_4**. The observed enhancement of the reaction diastereoselection upon increasing the size of R_1 is in full agreement with this model.

A high level of aldol diastereoselection has been observed with boron enolates.[9,10] Whereas most metals (M= Li, Mg, Zn, Al) have a M-O bond length in the range of 2 Å, the B-O and the B-C bond lengths are 1.4 Å and 1.5 Å respectively. This shorter bond distance is presumably translated into a tighter, more compact transition state, thereby enhancing the nonbonding interactions. This creates larger differences in the energies of the corresponding transition state structures **C_1**, **C_2**, **C_3** and **C_4** (Scheme I).

Although chair transition states are more generally appealing, in some cases the related boat transition states are equal, or even favored energetically. Thus, the opposite erythro:threo ratios observed for the magnesium (Z) enolates **1** and **2** (Scheme II) upon condensation with pivaldehyde[7d] has been rationalized by the participation of boat transition state **5** for enolate **2**. In this transition state the C_2 enolate substituent and the aldehyde substituent have avoided the gauche interaction present in the



erythro

threo

R=Me $\underline{E}:\underline{T}=$ 100:0

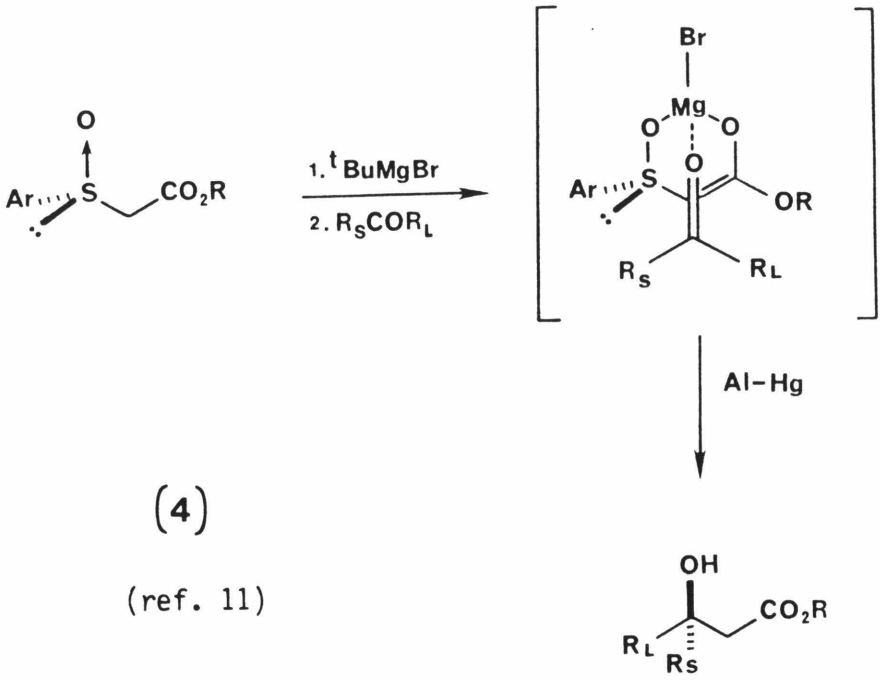
R=^{t}Bu $\underline{E}:\underline{T}=$ 0:100

diastereomeric chair **4**.[2a] Boat transition states are more likely to occur with lithium and magnesium enolates, where the M-O and M-L bond distances are long and, consequently, the bowsprit-flagpole interaction is relatively small. Nonetheless, this latter assertion is difficult if not impossible to prove.

Up to this point, we have discussed the elements that control the erythro:threo selection. We address now the architectural features necessary for control of the reaction enantioselection (i.e. E_1 vs E_2, T_1 vs T_2, see eq. 3). In principle, there are three approaches to the preparation of a chiral aldol adduct: a), Condensation of a chiral aldehyde with an achiral enolate; b), condensation of an achiral aldehyde with a chiral enolate; and c), condensation of a chiral aldehyde with a chiral enolate. In this chapter we will deal exclusively with the second class of reactions.

In designing a chiral enolate, one must pursue one principal goal. The enolate must induce an effective π-facial differentiation through an organized, conformationally rigid transition state. An example that satisfies these criteria is illustrated in eq. 4. In this case, a sterically differentiated enolate π-face is established via chelate formation, which provides a fixed topology between the chiral and prochiral centers.

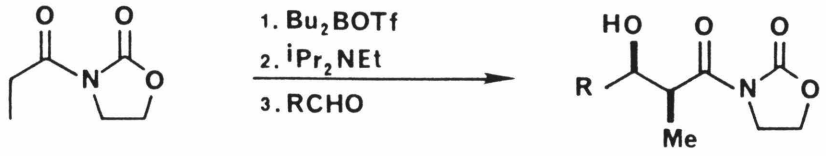
Encouraged by the high levels (>97.3) of erythro:threo selection obtained upon condensation of the boron enolate of oxazolidinone **6** with a variety of aldehydes (eq. 5),[12] we decided to



(4)

(ref. 11)

study the aldol condensation of its chiral counterpart **7**. Oxazolidinone **7** has been efficiently prepared from (S)-valine in three

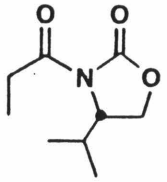


6

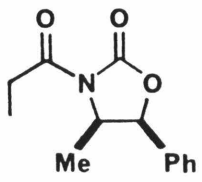
E:T >97:3

(5)

(ref. 12)

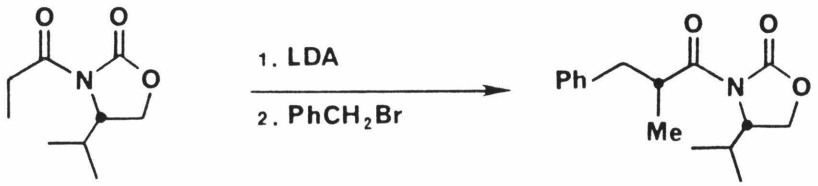


7



8

steps.[13] Although we expected the erythro:threo selection to be maintained, a priori we did not have a feeling for either the magnitude or sense of the chirality transfer (i.e. E_1 vs E_2). By the time this project was started, however, the lithium enolate of **7** had already shown very high levels (120:1) of diastereoselection upon alkylation with benzyl bromide (eq. 6).[13] Although not



7

120:1

(6)

(ref. 13)

intimately related to our aldol reaction, this constituted an encouraging result. Concomitantly with oxazolidininone **7**, we studied the reactions of its chiral antipode **8**, derived in three steps from commercially available (1R,2S)-norephedrine hydrochloride. Both, (S)-valine and norephedrine hydrochloride are inexpensive chiral starting materials.

III. Results and Discussion[14]

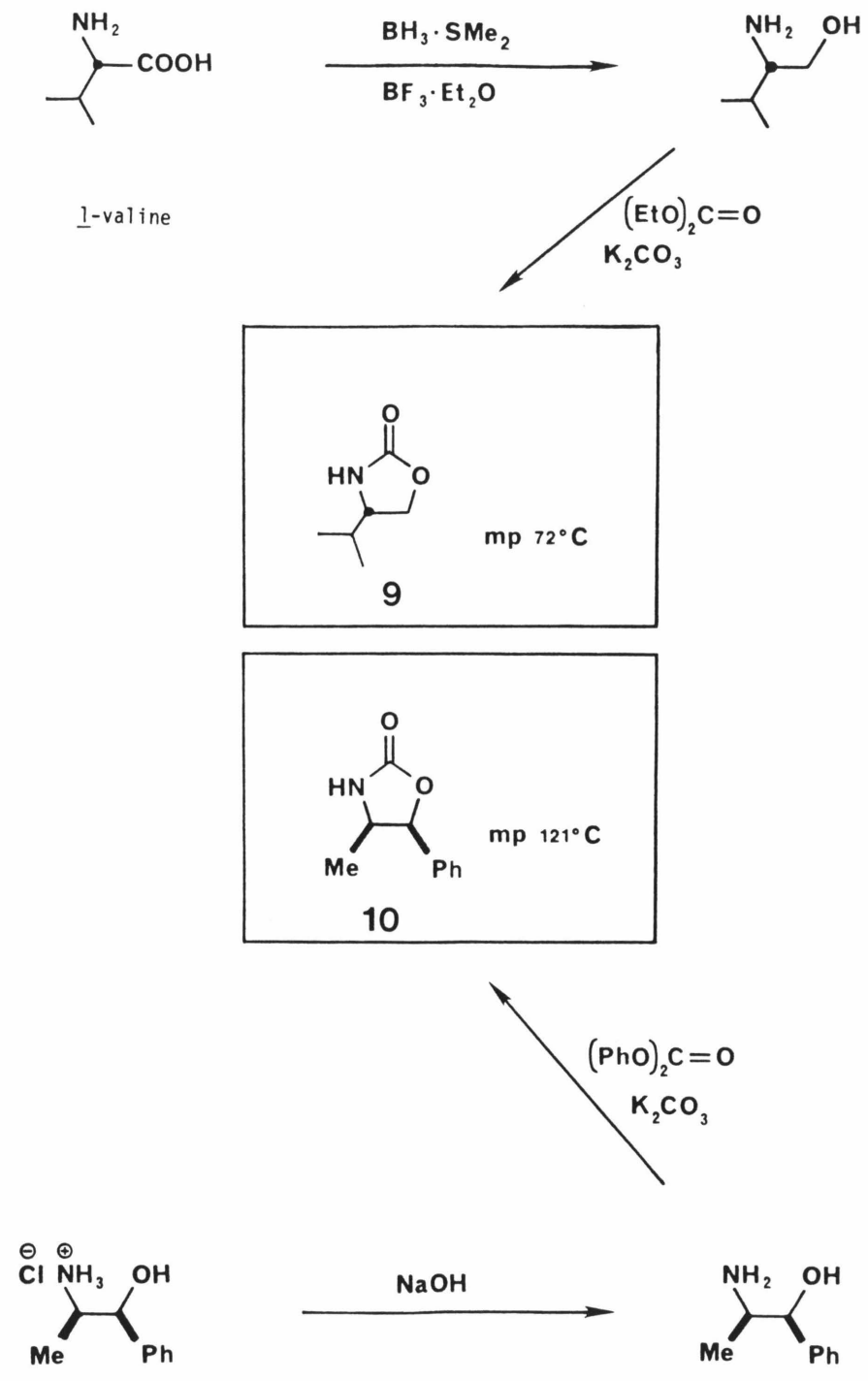
1. Synthesis of Starting Materials

(a) Preparation of 3-acyl-2-oxazolidinones. Our two starting materials **9** and **10** were prepared from commercially available (S)-valine and (1S,2R)-norephedrine hydrochloride respectively. As indicated in Scheme III, (S)-valine was reduced to (S)-valinol with 1.15 equivalent of borane in the presence of 1.15 equivalents of boron trifluoride etherate (THF, reflux, 18 h; then aq. NaOH, reflux, 2 h) in 81% yield.[16] Subsequent treatment with diethyl carbonate (1.1 equiv.) in the presence of a catalytic amount of potassium carbonate (neat, 120°C, 24 h) gave oxazolidinone **9** in 74% yield after recrystallization. In a similar way, **10** was obtained from norephedrine hydrochloride by neutralization (aq. NaOH, 100% yield) and reaction with diphenylcarbonate (1.2 equiv.) in the presence of 1 equivalent of potassium carbonate (neat, 130°C, 5 h) in 73% yield after recrystallization. Both materials could be prepared in molar quantities without changes in the reaction yields. Their enantiomeric excess was shown to be $\geq$99% by gas chromatography analysis of their corresponding Mosher imides.[17]

The desired acyl derivatives were prepared in high yields by lithiation (n-BuLi, THF, -78°C) and subsequent reaction with the corresponding acid chloride or anhydride.

(b) Preparation of the Boron Reagents. Di-n-butylboryl trifluoromethanesulfonate (di-n-butylboryl triflate) was

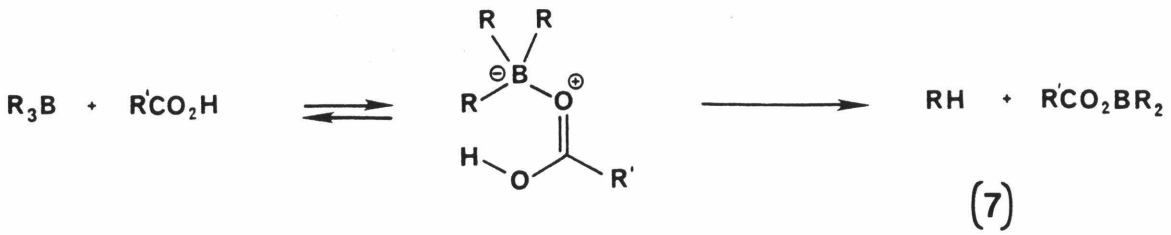
Scheme III



(1S,2R)-norephedrine hydrochloride

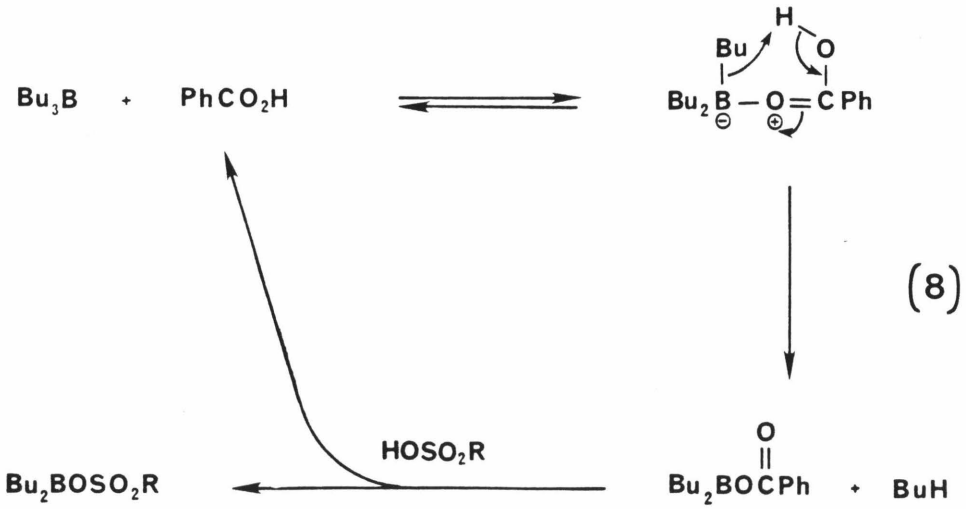
obtained by the reaction of tri-n-butylborane and trifluoromethanesulfonic acid, according to Mukaiyama's procedure.[18] Although di-n-butylboryl triflate was the common boron source used in this aldol study, we also investigated the effect that other di-n-butylboryl sulfonates have on the yields and product distribution of this reaction.

In an attempt to prepare di-n-butylboryl methanesulfonate by mixing tri-n-butylborane and methanesulfonic acid, decomposition (black tar) was observed and no product could be isolated. Our eventual solution to a successful synthesis of boryl sulfonate esters utilized the mechanistic observations of Dessy on the protonolysis of triethylborane by carboxylic acids.[19] He observed that the log of the reaction rate constant increased linearly with the pK_a of the carboxylic acid. This, together with an observed primary isotope effect of 3.3, suggested that the reaction proceeds by a preequilibrium step, consisting of nucleophilic carbonyl coordination of the acid to the borane, followed by a rate determining proton transfer (eq. 7).



(7)

We do not have an explanation to our observation that the stronger acid trifluoromethanesulfonic acid reacts with tri-n-butylborane whereas the milder methanesulfonic acid does not. Sulfonic acids and carboxylic acids might well react via different mechanisms. Based on Dessy's observations, we envisioned an alternative way to obtain the desired sulfonates. In presence of a catalytic amount of a mild carboxylic acid (like benzoic acid, for example), formation of the corresponding di-n-butylboryl carboxylate might take place (eq. 8). This compound, in turn, would be displaced by the sulfonic acid giving product and regeneration of the carboxylic acid. This approach proved to be successful using 0.05 equivalent of benzoic acid, tri-n-butylborane and methanesulfonic acid or chlorosulfonic acid. Although low yields (ca. ≤30%) were obtained in these first attempts, distillation afforded the desired boryl sulfonates.



(8)

2. The Aldol Condensation Using Chiral Propionyl Oxazolidinones

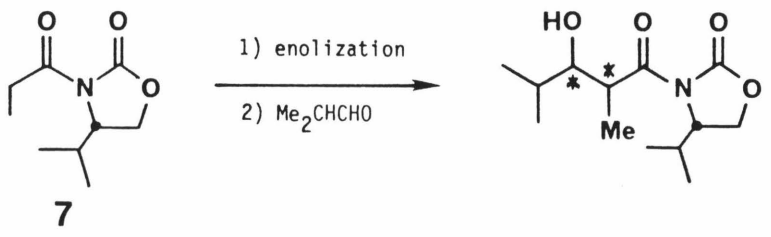
The reaction of the di-n-butylboron enolates of **7** and **8** with a variety of aldehydes was investigated.

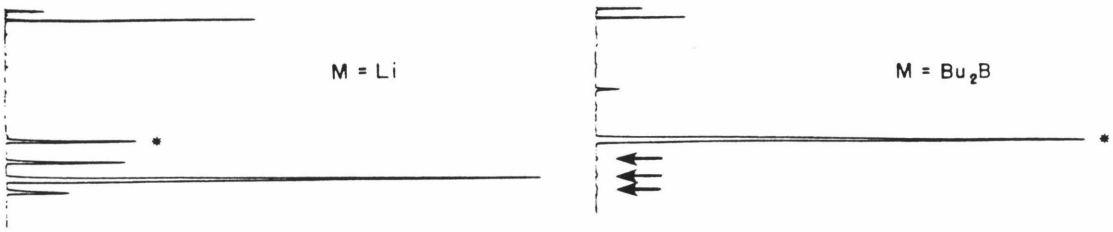
(a) Results. The di-n-butylboron enolates of imides **7** and **8** were prepared by the successive addition of 1.1 equivalents of di-n-butylboryl triflate and 1.2 equivalents of diisopropylethylamine to cooled (-78°C) solutions (1 to 0.25 M) of **7** or **8** in dichloromethane. The mixtures were stirred at -78°C for 0.5 h and at 0°C for 1 h. To these solutions, neat aldehyde (1 to 1.1 equiv.) was added at -78°C and the reactions were stirred for 0.5 h, then allowed to warm up to 0°C and stirred for 1 h. Oxidative workup (H_2O_2, MeOH, pH 7) and product isolation afforded the corresponding aldol adducts (eq. 9, 10). Although direct gas chromatography (GC) analysis of the reaction mixtures resulted in product decomposition, analysis of their corresponding trimethylsilyl ethers proved to be successful. For this purpose, a small sample of the isolated, unpurified reaction mixture was silylated (excess $TMSNEt_2$, DMAP, CH_2Cl_2). When TLC analysis showed complete reaction, the mixture, without purification, was analyzed by GC. The peaks were assigned by comparison with authentic diastereomeric mixtures obtained by the corresponding lithium aldol condensations.[20] As observed with chiral amides,[4] the lithium enolates of **7** and **8** reacted with aldehydes (-78°C, 5 sec) in high yields but with poor

overall selectivity, thus affording a valuable authentic isomeric mixture. When monitored, the erythro:threo ratios obtained by GC analysis were shown to be identical with those obtained by integration of the carbinol proton (-C<u>H</u>OH) in their NMR spectra proving the authenticity of the GC data.

The results are summarized in Table I. In all cases, the boron enolates showed remarkably high levels of both erythro:threo selection ($E_1 + E_2$ vs $T_1 + T_2$) and enantioselection in the erythro manifold (E_1 vs E_2). In some cases, especially in the norephedrine series, the ratio E_2':($E_1' + T_1' + T_2'$) was $\geq$1000:1. Recrystallization or flash chromatography afforded the adducts in high yield. As a representative example, the boron and lithium reaction GC traces of Entry C of Table I are shown in Scheme IV.

Scheme IV





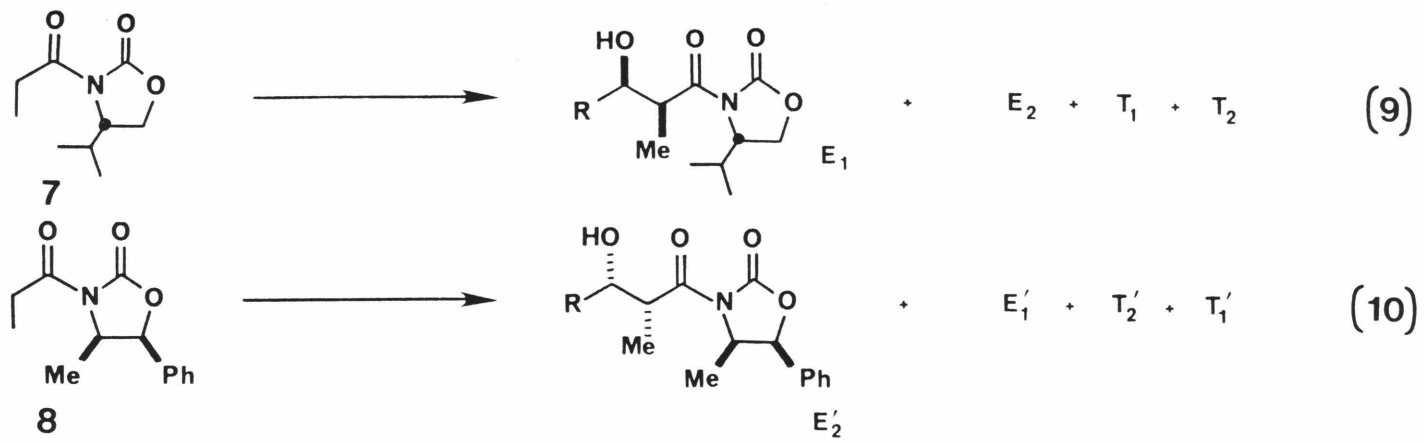


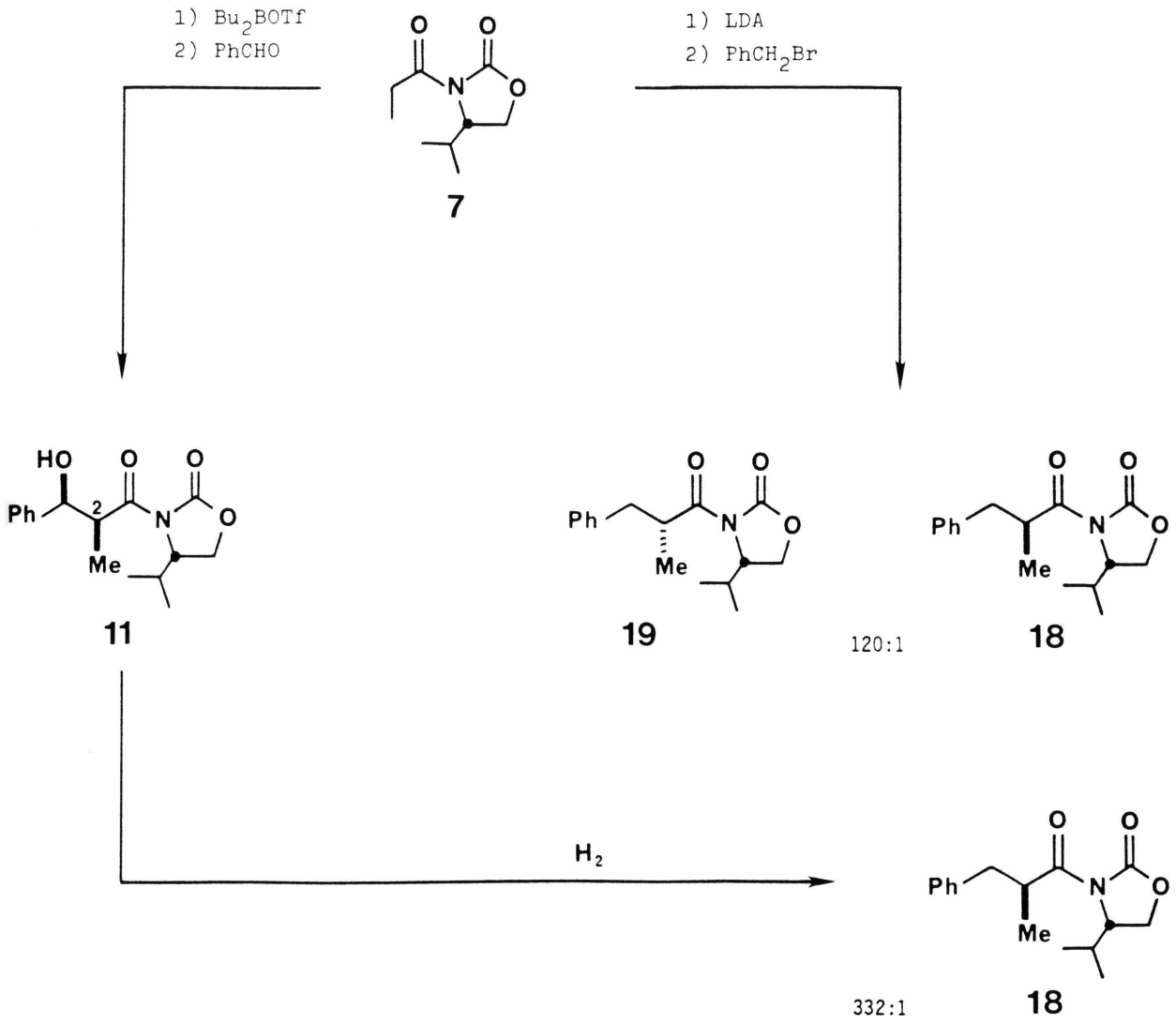
Table 1. Aldol Condensations of 7 and 8 with Representative Aldehydes.

				Boron-aldol kinetic ratios				Lithium-aldol kinetic ratios				
Entry	Imide	Product RCHO	$E_1(E_2)$	$E_1(E_2)$(% yield)[a]	$E_2(E_1)$	$T_1(T_2)$	$T_2(T_1)$	$E_1(E_2)$	$E_2(E_1)$	$T_1(T_2)$	$T_2(T_1)$	
A	**7**	C_6H_5CHO	**11**	99.8 (88%)	0.04	0.14	0.06	9.8	29.5	59.0[c]	1.7	
B	**8**	C_6H_5CHO	**12**	>99.9 (89%)	<0.1	<0.1[b]		8.5	28.6	62.7[b]		
C	7	Me_2CHCHO	**13**	99.4 (78%)	0.2	0.2	0.2	10.6	11.0	71.4	7.0	
D	**8**	Me_2CHCHO	**14**	99.8 (91%)	0.04	0.15[b]		13.2	8.1	78.7[b]		i
E	7	n-C_4H_9CHO	**15**	99.0 (75%)	0.7	0.1	0.1	14.3	3.7	24.4	57.6	
F	8	n-C_4H_9CHO	**16**	99.9 (95%)	0.1	<0.1[b]		16.7	18.0	65.3[b]		i
G	**8**	Furaldehyde	**17**	≥99.3 (91%)	-	-	-	-	-	-	-	

[a] Isolated yields, except for Entries B and F where the yield is referred to the unpurified crystalline product. [b] The second threo isomer either was not formed or did not resolve on the GC. [c] The absolute stereochemistry of T_1(R=Ph, **11T**) was determined to be (2R,3S) by hydrogenolysis, following the method used for compound **11** (Scheme V).

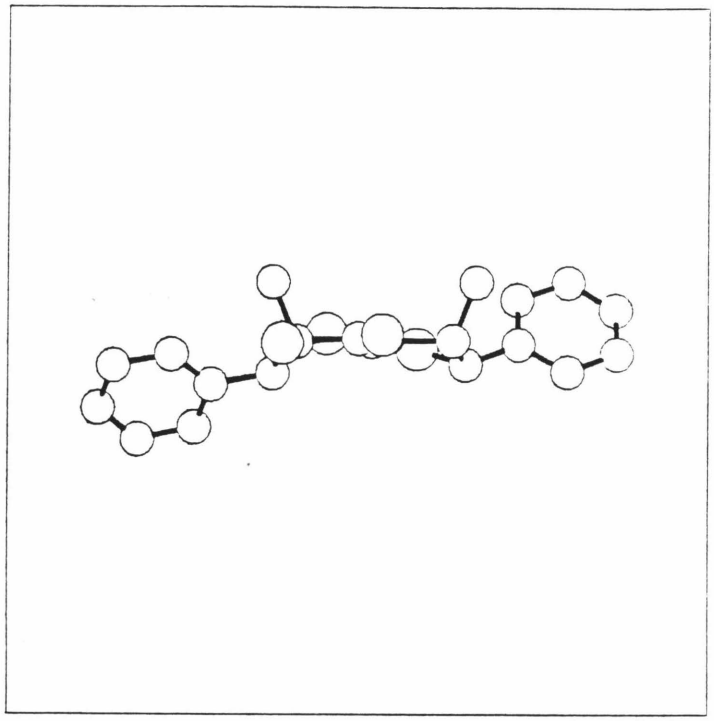
(b) Absolute Configuration. The *erythro* relative stereochemistry of the major isomers E_1 and E_2' obtained in the boron series was first suggested by the presence of small C_2-H, C_3-H coupling constants (*ca.* 3-5 Hz). This is typical for *erythro*-β-hydroxy-α-alkyl carbonylic compounds that have relatively small substituents at the C_2 and C_3 positions.[21] The absolute stereochemistry of the α-carbon of **11** was determined by its transformation into **18** (Scheme V) *via* hydrogenolysis (H_2, 10% Pd-C, EtOH, cat. $HClO_4$) and subsequent comparison with an epimeric mixture obtained *via* alkylation of the lithium enolate of **7** with benzyl bromide. Since the absolute configuration of products **18** and **19** was already known,[13] we were able to deduce that the C_2 stereocenter of **11** possessed the (S) configuration. This conclusion, together with the small *erythro* coupling constant recorded for **11** (4.5 Hz) defined its absolute stereochemistry as (2S,3S). More generally, the absolute configuration of compounds **11-17** was proven by the conversion of the imides into the corresponding methyl esters (*vide infra*), the absolute stereochemistry of which had already been determined.[4,25] In one case (**12**), an X-ray structure analysis was carried out, revealing the relative stereochemistry of all chiral centers. The ORTEP drawings in two different perspectives are shown in Fig. 1. Since the absolute stereochemistry of the chiral auxiliary was known, this constituted an unequivocal proof of the absolute stereochemistry of **12**. In addition, the X-ray analysis

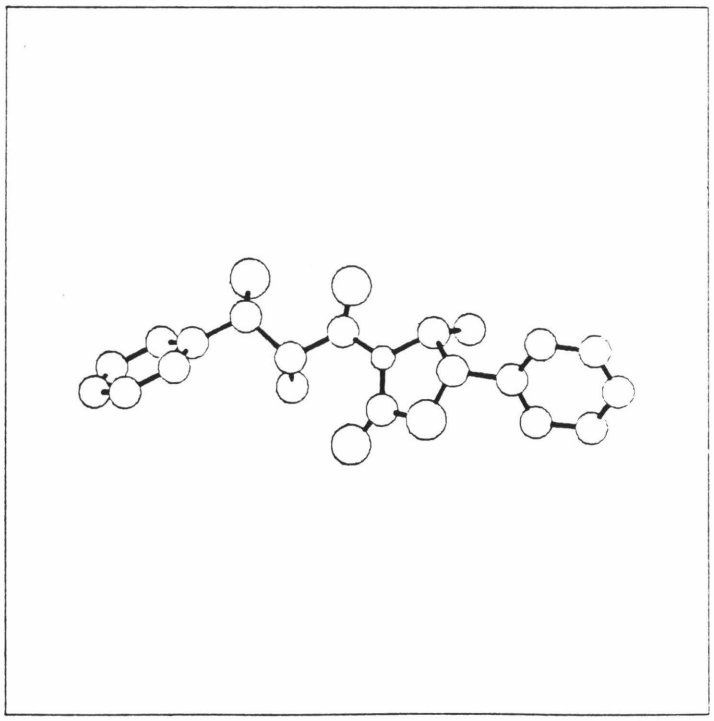
Scheme V

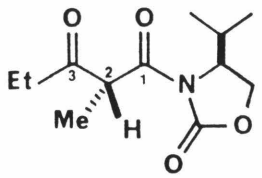


revealed the expected anti conformation of the imidic carbonyl moiety as the result of allylic strain (vide infra) and dipole minimization. Finally, the analysis indicated an approximately 120° angle between the C_2-H bond and the C_1-carbonyl. This geometry has also been observed in β-keto imide **20**, where the X-ray structure showed the C_2-H bond to be in a similar orientation.[22]

Fig. 1. ORTEP Drawings of **12**







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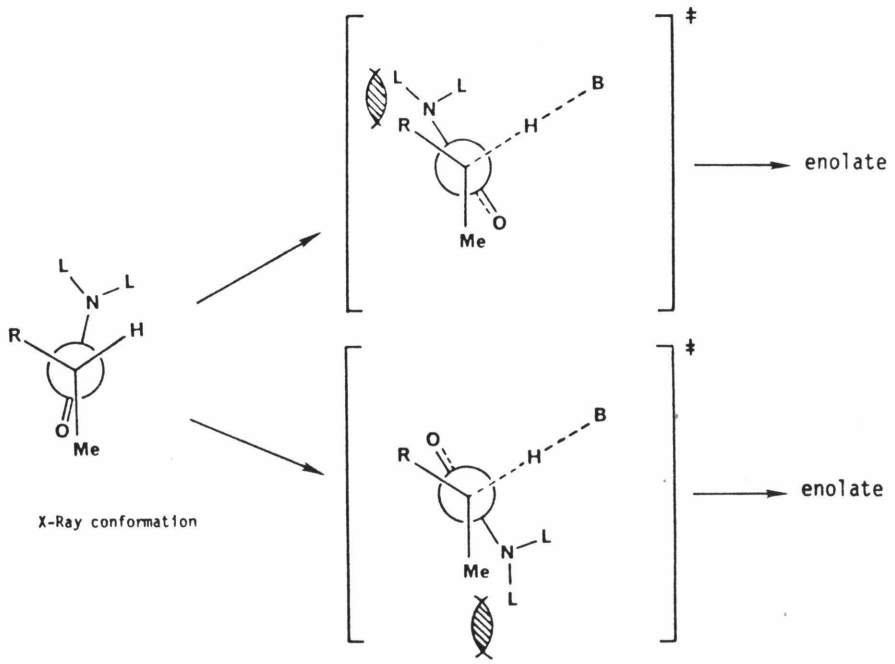
The surprisingly high resistence to epimerization observed for these β-keto imide systems has been rationalized in the following way.[22] $A^{1,3}$-strain arguments suggest that the C_1-C_2 bond rotation might be severely restricted (Fig. 2), making the enolization required perpendicular relationship between the σC-H bond and the C_1=O system difficult to reach (Fig. 2). The same kind of restrictions are believed to account for the aldol adducts, hence preventing epimerization under relatively strongly acidic or basic conditions.

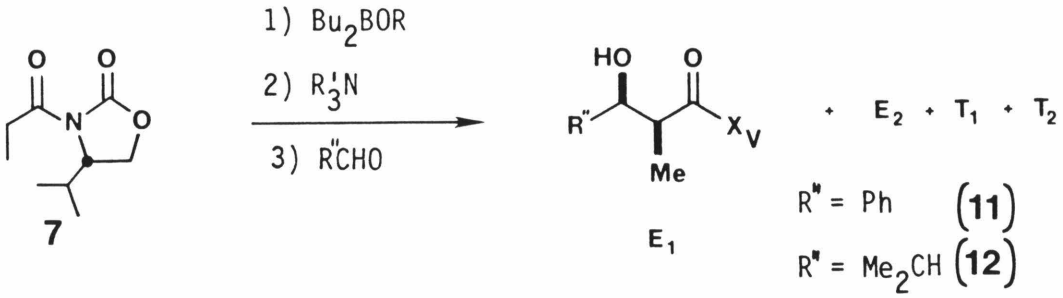
Fig. 2. Enolization Transition States of an Imide Aldol Adduct



(c) Reaction Variables. In conjunction with the present study, a systematic evaluation of the reaction parameters was undertaken in order to define optimal conditions for carrying out these transformations. The results of this study are summarized in Table 2.

i) **Temperature.** When the reaction shown in eq. 13 was performed at -78°C throughout the whole process (Table 2, Entry 3) no difference in the observed ratios was observed. The GC yield (i.e. % conversion) was similar to that of the parent case (Entry 2). On the other hand, when the reaction was carried at 0°C, (Entry 4) a slight decrease of specificity was observed.

ii) **Solvent.** The reactions carried out in ether or toluene proved



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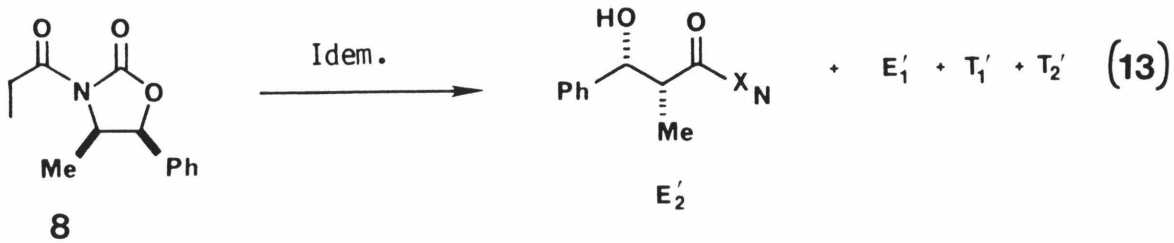

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Table 2. The Influence of Reaction Variables on the Aldol Process (Eq. 11-13).

Entry	equation	Solvent	Amine[a]	Bu_2BOR	Enol. Temp.	Condens. Temp.	E_1 :	E_2 :	T_1 :	T_2
1	11	CH_2Cl_2	HB	Bu_2BOTF	-78°C → 0°C	-78°C → 0°C	99.8 :	0.04 :	0.14 :	0.06
2	13	CH_2Cl_2	HB	Bu_2BOTF	-78°C → 0°C	-78°C → 0°C	>99.9 :	<0.1 :	<0.1	
3	13	CH_2Cl_2	HB	Bu_2BOTF	-78°C	-78°C	>99.9 :	<0.1 :	<0.1	
4	13	CH_2Cl_2	HB	Bu_2BOTF	0°C	0°C	97.6 :	0.75 :	0.75 :	0.9
5	13	Et_2O	HB	Bu_2BOTF	-78°C → 0°C	-78°C → 0°C	99.3 :	<0.1 :	0.20 :	0.5
6	13	Toluene	HB	Bu_2BOTF	-78°C → 0°C	-78°C → 0°C	99.3 :	<0.1 :	0.34 :	0.36
7	12	CH_2Cl_2	TEA	Bu_2BOTF	RT	RT	99.9 :	0.07 :	<0.1 :	<0.1
8	11	CH_2Cl_2	HB	Bu_2BOSO_2Me	0°C → RT	0°C → RT	NO REACTION			
9	11	CH_2Cl_2	TEA	Bu_2BOSO_2Cl	-78°C → 0°C	-78°C → 0°C	1.31 :	57.76 :	40.06[b] :	0.32
10	13	CH_2Cl_2	TEA	Bu_2BOSO_2Cl	-78°C → 0°C	-78°C → 0°C	ca. 2 :	76 :	22	

[a] HB= Hünig's base = diisopropylethylamine; TEA= triethylamine

[b] The absolute stereochemistry of T_1 was determined to be (2R,3S) by hydrogenolysis, following the method used for compound **11** (Scheme V).

to be equally clean, giving essentially the same product distribution with dichloromethane (Entries 5 and 6), the solvent of choice.

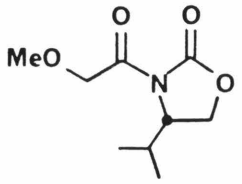
iii) **Amine Structure.** Replacement of diisopropylethylamine by the less hindered base triethylamine did not affect yields or product ratios (entry 7).

iv) **Boron Reagent.** The reaction response to the di-n-butylboryl sulfonate reagent was, on the other hand, very dramatic. Thus, the use of di-n-butylboryl methylsulfonate resulted in starting material recovery, even after warming up the reaction mixture to room temperature (Entry 8). On the other hand, when the corresponding chlorosulfonate reagent was used, a very surprising result was obtained. GC analysis indicated the predominance of the E_2 and the T_1 isomers (Entries 9, 10). We do not have an explanation for these results.

v) **Aldehyde Electronic Characteristics.** The reaction of the boron enolate of **7** with p-anisaldehyde and p-nitrobenzaldehyde was also investigated. Both reactions were equally selective ($\geq$99.5%) and proceeded in similar GC yield (i.e. % conversion). In a competition experiment, 1 equivalent of the boron enolate of **7** was condensed with a mixture containing 1 equivalent of each of the two mentioned aldehydes. ^{1}H NMR analysis of the unpurified reaction mixture revealed a 65:35 ratio of compounds, in favor of the p-nitro phenyl adduct. The low selectivity observed in this competition experiment suggests that the aldehyde coordination to the boron is a rapid equilibrium process (vide infra).

3. The Aldol Condensation of Chiral, Functionalized Acyl Oxazolidinones

Up to this point we have discussed the use of the propionyl imides **7** and **8** in the aldol condensation. We were pleased to find that the reaction works equally well with imides having other, more functionalized acyl substituents. One such family of compounds is the alkoxyacetyl oxazolidinones **21**, **22** and **23**.



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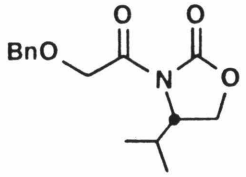

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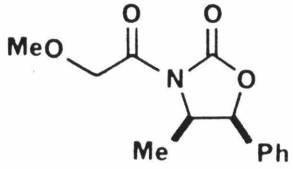

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The success obtained in these reactions constitutes an invitation to future applications in the construction of sugars and other compounds such as polyether and macrolide antibiotics. The results are shown in Table 3. Unlike **7** or **8**, the use of this family of oxazolidinones requires low temperatures or the diastereoselection drops noticeably (compare Entries A and B). This reaction has recently found application in efforts directed toward the synthesis of the macrolidic antibiotic Macbecin, where the boron enolate of **21**

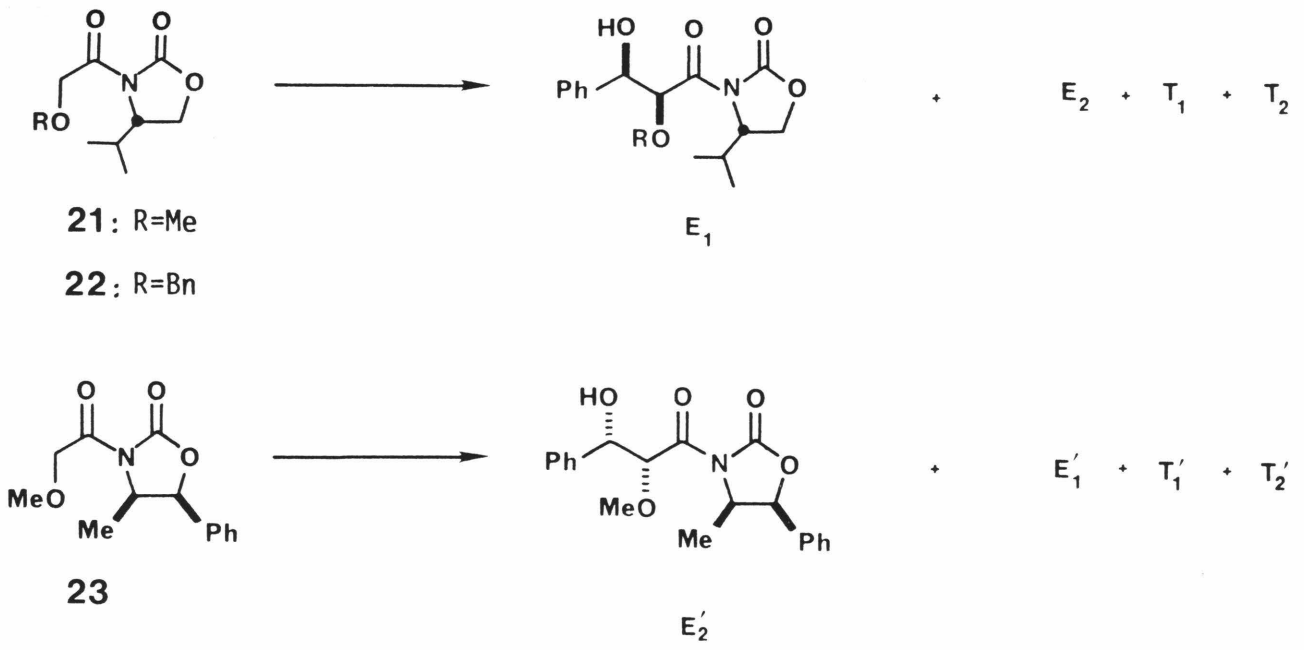
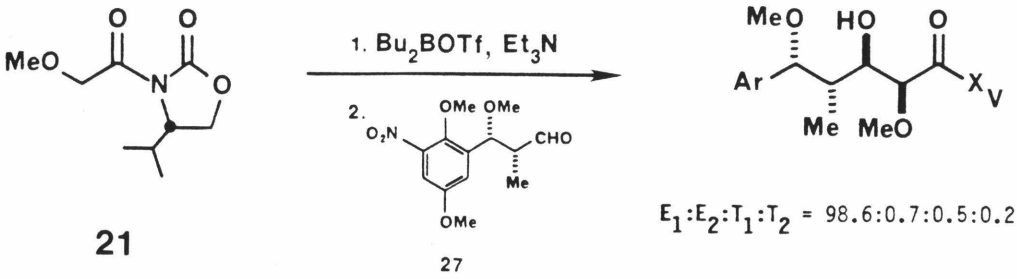


Table 3. Aldol Condensations of Imides **21-23** with Benzaldehyde.

Entry	Imide	Enoliz. Temp.	Cond. Temp	Product $E_1(E_2)$	Boron-aldol Kinetic ratios $E_1(E_2)$(% yield)[b]	$E_2(E_1)$	$T_1(T_2)$	$T_2(T_1)$
A	**22**	-78°C → 0°C	-78°C → 0°C	**24**	80.9 (62%)	3.6	4.2	11.3
B	**22**	-78°C	-78°C	**24**	98.0 (76%)	0.5	1.3	0.3
C	**21**	-78°C	-78°C	**25**	99.2 (80%)	0.4	0.1	0.3
D[a]	**23**	-78°C	-78°C → 0°C	**26**	98.6 (89%)	0.6	0.3	0.5

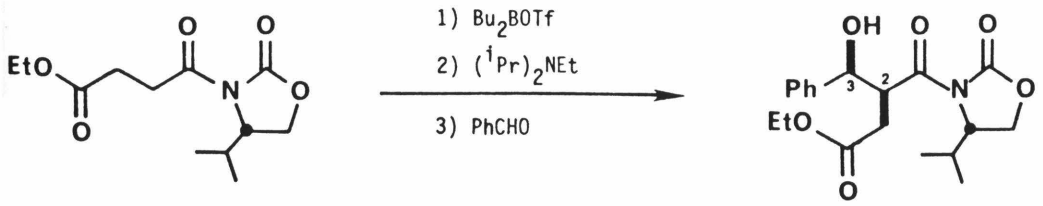
[a] Experiment performed by Dr. R. Conn. [b] Isolated yields.



21 27 (14) (ref. 22)

was condensed with chiral aldehyde **27** in 80-85% yield, with excellent diastereoselection (eq. 14).[22]

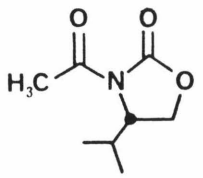
The aldol condensation of the functionalized oxazolidinone **28** was also investigated (eq. 15). Succinyloxazolidinone **28** has the interesting feature of possessing two enolizable carbonyls. Although we knew in advance that esters do not enolize with boryl triflates and diisopropylethylamine, the role of an additional chelation site on the product stereochemistry remained uncertain. However, as in the other cases, only one isomer was formed. Best results were obtained when low temperatures (-78°C) were maintained throughout the reaction. Product isolation and chromatography afforded **29** in 67% yield. The 90 MHz ^{1}H NMR spectrum revealed a 5.0 Hz C_2-H↔C_3-H coupling constant, indicative of an <u>erythro</u>



28 29 (15)

relationship between substituents. The absolute stereochemistry of C_2 was proven by hydrogenolysis and hydrolysis to (2R)-benzyl-succinic acid, the absolute configuration of which has already been established.[23]

In view of the high levels of asymmetric induction observed in the cases cited above, it was surprising that the di-n-butylboron enolates of imides **30** and **31** behaved in a nonselective fashion, giving nearly 1:1 mixtures of products.[24] These results turned out to be of great utility when we elaborated the transition state model (vide infra).



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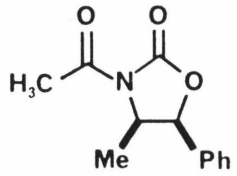

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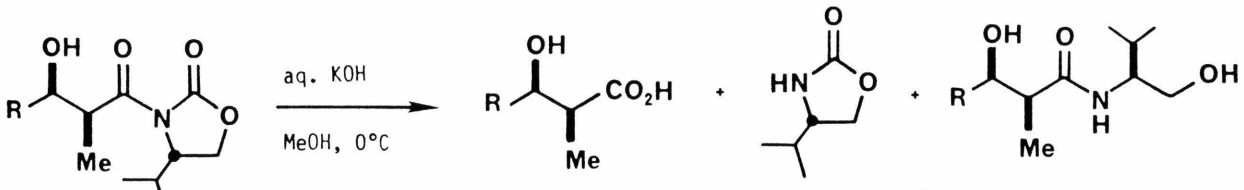
4. Chiral Auxiliary Removal

The role of the chiral oxazolidinones in the boron enolate aldol condensation has been to provide good reaction stereospecificity. Once the desired stereocenters have been formed, the chiral auxiliary must be removed. This removal needs to be

site-specific and, preferentially nondestructive of the auxiliary, thus allowing its recovery. We were very pleased to find that treatment of a methanolic solution of the aldol adducts with a 2N aqueous solution of potassium hydroxide and subsequent acidification gave the corresponding acids and the chiral oxazolidinone **9** or **10**, thus meeting our two initial requirements. Under these conditions direct TLC analysis indicated that the reaction proceeded by the very rapid displacement of the chiral auxiliary by the methoxide ion, to form the methyl ester which smoothly hydrolized to the acid. A minor byproduct was consistently formed in these reactions in ca. 5-15% yield. Spectral analysis suggested it to be the product resulting from attack at the oxazolidinone carbonyl (eq. 16).



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The acids were esterified with diazomethane and the corresponding methyl esters purified by bulb-to-bulb distillation.[25] Table 4 summarizes the results obtained in this process. The rotations recorded for each pair of enantiomers were consistently

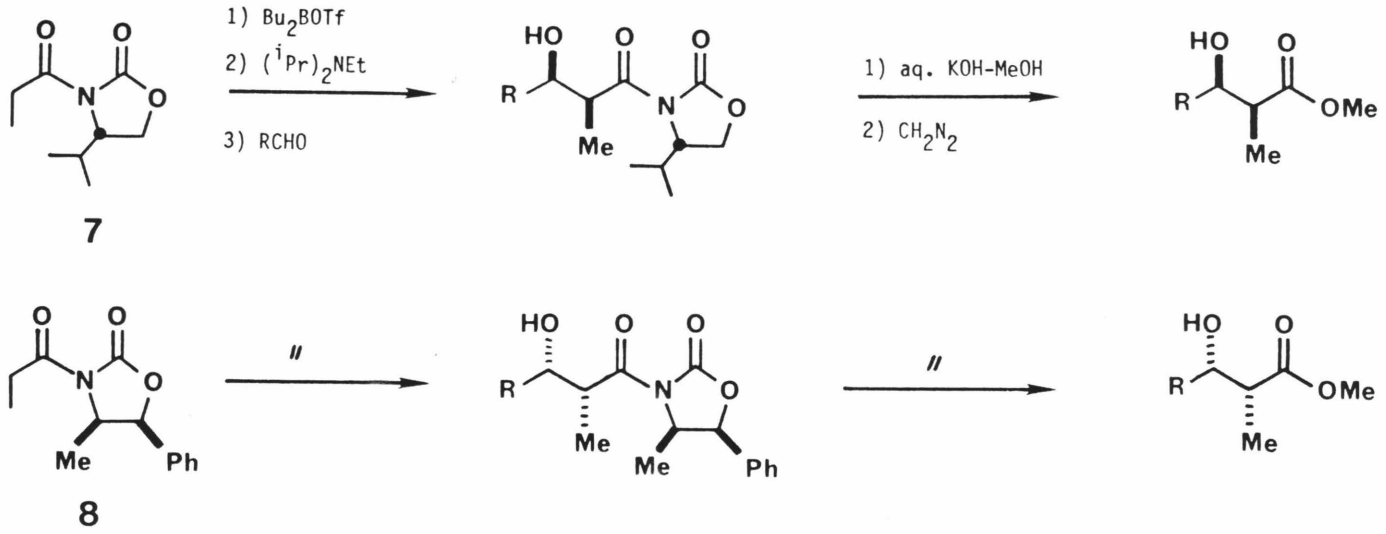


Table 4. Base Hydrolysis of Imide Aldol Adducts.

Entry	Imide	RCHO	ester % overall yield[a]	ester $[\alpha]^{25}$	ester erythro/threo ratio
A	**7**	C_6H_5CHO	82	-23.1° (c 3.2, $CHCl_3$)	99.5 : 0.5
B	**8**	C_6H_5CHO	60	+23.2° (c 3.2, $CHCl_3$)	99.4 : 0.6
C	**7**	Me_2CHCHO	69	-7.9° (c 5.7, $CHCl_3$)	99.4 : 0.6
D	**8**	Me_2CHCHO	78	+7.7° (c 5.4, $CHCl_3$)	99.1 : 0.9
E	**7**	n-C_4H_9CHO	68	+14.9° (c 6.6, CH_2Cl_2)[b]	98.9 : 1.1[b]
F	**8**	n-C_4H_9CHO	71	-15.0° (c 5.0, CH_2Cl_2)[b]	99.8 : 0.2[b]

[a] These yields are based on the imide **7(8)** and refer to distilled methyl ester. [b] Values obtained from methanolysis of the aldol adducts into the methyl esters.

equal in magnitude and opposite in sign.[26] Diastereomeric analysis (GC) of the methyl esters revealed that hydrolysis proceeded, in general, with $\leq$1% epimerization. A somewhat higher percentage of epimerization (1 to 2%) was consistently found for Entries E and F. Direct conversion of the aldol adducts into the methyl esters could be achieved by transesterification, that is, by adding 1 equivalent or a catalytic amount of K_2CO_3, NaOMe or CH_3MgBr to methanolic solutions of the substrates.

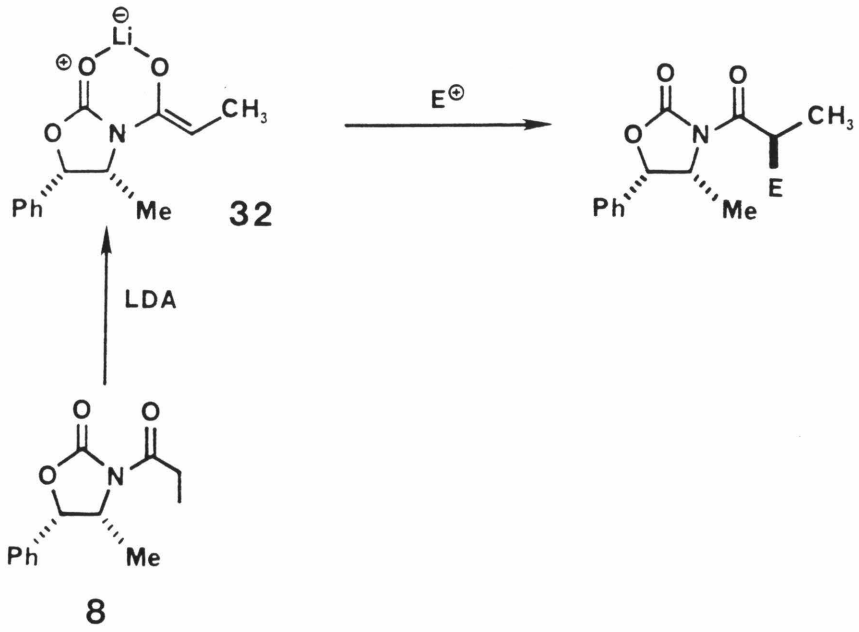
These and other examples have shown that the exocyclic carbonyl of these and other related compounds has a reactivity somewhat greater than that of an ester. Although hydrolysis or transesterification of the aldol adducts hereby presented proceeded in high yields, later examples have shown that these reactions, as well as other nucleophilic additions (i.e. reductions), are highly substrate dependent. Indeed, aldol adducts having a slightly bulkier α-substituent are much more resistant to displacement of the chiral auxiliary and proceed with a considerable degree of ring opening and/or retroaldol reaction. For some of these cases, we have found that the desired carbonyl regioselectivity can be recovered by formation of the boron aldolate prior to the addition of the nucleophile. Simultaneous hydroxyl protection and carbonyl complexation by the boron atom both, prevents retroaldol reaction and selectively activates the exocyclic carbonyl for nucleophilic attack. This alternative method will be discussed in more detail in Ch. 3 (section 3) of this thesis report.

5. Discussion

On the basis of the results obtained in the aldol condensation, we present and discuss in this section our proposed transition state models. As we mentioned earlier, the stereoselectivity of these reactions is believed to be caused by two factors: the enolate geometry and the enolate π-facial differentiation.

a) The Enolate Geometry. Although we do not have a definite proof of the geometry of our imide enolates, there is strong evidence supporting the (Z) configuration. For example, experimental data strongly suggest that enolization of N,N-dialkyl-propionamides with LDA in THF proceeds stereoselectively to afford the (Z) enolate.[27,28] It appears reasonable to assume that the closely related propionimides behave in a similar way. The large precedent for correlation between (Z) enolates and erythro products in the aldol condensation of propionyl derivatives,[2a] also supports the (Z) enolate geometry. Finally, the sense of induction observed in the alkylation reaction of lithium enolates of these propionyl oxazolidinones, is in complete agreement with the participation of the chelated (Z) enolate **32** (eq. 17).[13]

In an attempt to gain some further information concerning this issue, imide **8** was enolized with LDA (1.1 equiv, THF, -78°C, 30 m) and quenched with t-butyldimethylsilyl chloride (1 equiv, -78°C → 25°C) (eq. 18). The 500 MHz ^{1}H NMR spectrum of the unpurified mixture revealed the presence of only one quartet plus



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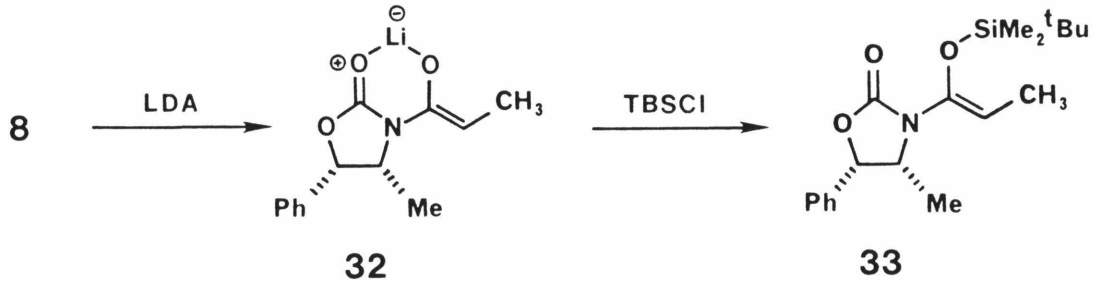
some minor resonance in the vinylic region (4.86 ppm), and clearly one single doublet in the vinylmethyl region (1.64 ppm), suggesting exclusive formation of one geometrical isomer. An ^{1}H NMR study of



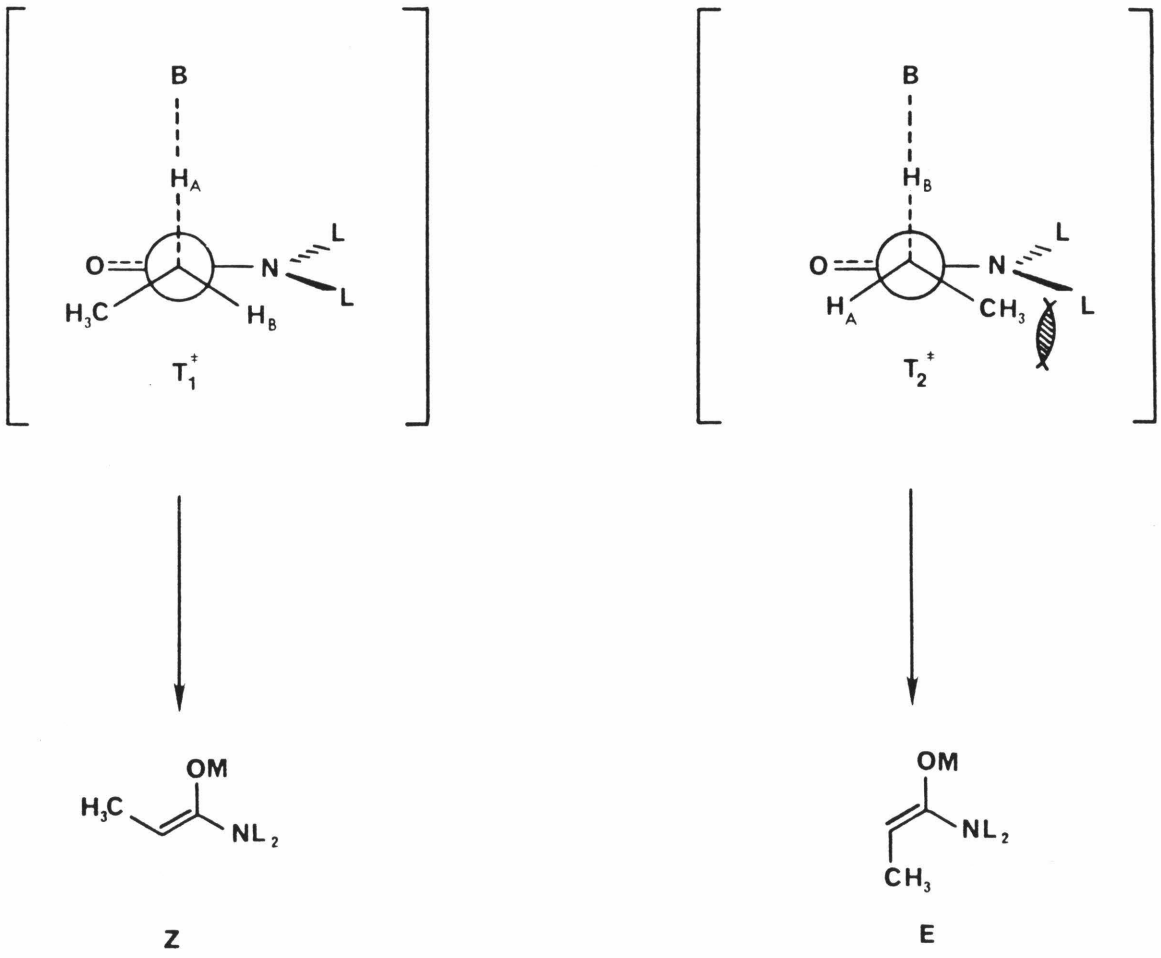
(18)

lithium enolate **32** (or the boron enolate) was not performed. Such an experiment would rule out the possibility of an equilibrium between enolates, where the (Z) enolate reacts faster towards

electrophiles than the (E) enolate. Chromatography and recrystallization afforded **33** as white needles. An X-ray structure analysis that could unambiguously determine the structure of **33** remains to be done.

The selective enolization of these systems can be rationalized as depicted in Scheme VI, by the same argument that we used to

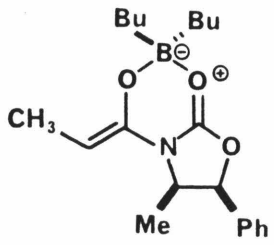
Scheme VI



explain the epimerization resistance of these imides. Thus, stereoelectronic constraints demand that the transition states for enolization must possess a colinear geometry between the $C\text{-}H_{A(B)}$ bond and the carbonyl π-system. In addition, we will make the assumption that the partial delocalization of the nitrogen lone pair into the forming enolate locks the N-substituents in the σ-plane. With these two reminders, the transition states corresponding to the enolization of each diastereotopic proton will look like the ones depicted in Scheme VI. The unfavorable developing 1,3-allylic interaction between the methyl group and the nitrogen substituent in the transition state leading to the (E) enolate, ($T_2^{\ddagger}$), could be then the reason for the selective formation of the (Z) enolate.

In summary, we believe that the structure of our enolate is the one dipicted in Fig. 3 where the olefin has a (Z) configuration and the boron is chelated to the ring carbonyl, in analogy to the lithium enolate.

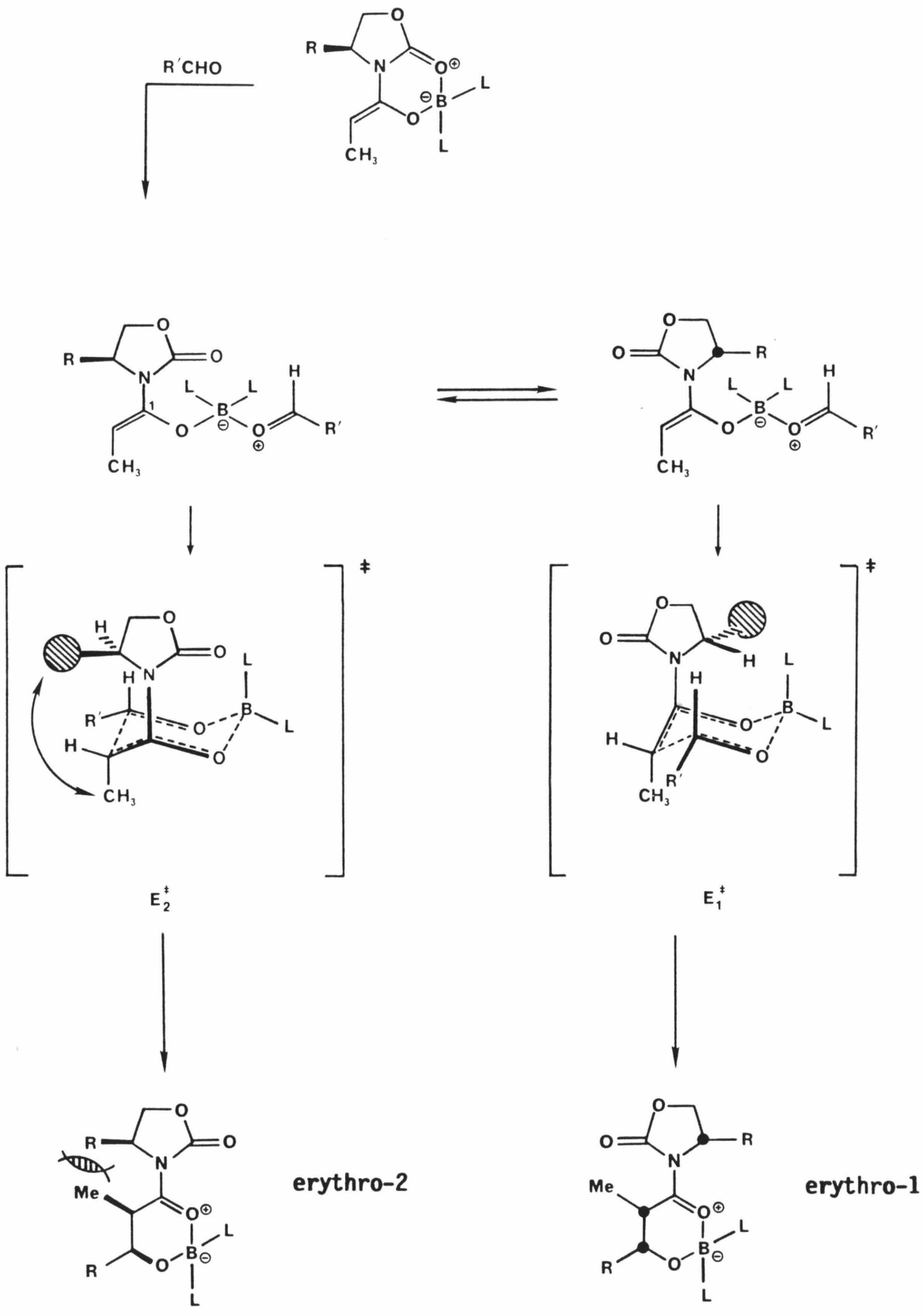
Fig. 3. Proposed Structure of the Di-n-butylboron Enolate of **8.**



(b) The Sense of Asymmetric Induction. In order to reach the required reactivity, the aldehydic carbonyl needs to be activated by coordination to boron. That precoordination might be a requirement is substantiated by the non-reactivity of these boron enolates towards acid chlorides. Although the intrinsic reactivity of acyl chlorides towards nucleophiles is higher than that of aldehydes, the electron-withdrawing character of the chlorine atom might prevent coordination, and consequently lower the reactivity. If this coordination was the rate determining step, p-anysaldehyde would have reacted much faster than p-nitrobenzaldehyde in the competition experiment (see p. 24), due to the higher Lewis basicity of the former over the latter. Instead, very poor aldehyde selection was observed (1.7:1), favoring, in fact, the p-nitro adduct.

Before reaction takes place, then, the boron must switch its coordination site from the ring carbonyl to the aldehydic carbonyl (Scheme VII), leaving the C_1-N bond free for rotation. Assuming the aldehyde approaches from the less hindered side (the face opposite to the ring substituent R) and that the aldehyde substituent bears an equatorial position (see Section 2) we can envision two chair-like transition states, $E_2^{\ddagger}$ and $E_1^{\ddagger}$ (Scheme VII) in which the ring has adopted either one of the two resonance-stabilized conformations. The selective formation of the <u>erythro-1</u> product might then be caused by the developing $CH_3 \leftrightarrow R$ allylic strain interaction present in the transition state $E_2^{\ddagger}$ leading into the <u>erythro-2</u>

Scheme VII



product. The related interaction in $E_1^{\ddagger}$ would be anticipated to be smaller, then offering a lower energy pathway to the reaction. If these transition states are the only ones that account for the reaction erythro enantioselection, their difference in energy would be 2.6 kcal/mol, as deduced from the observed E_1:E_2 product distribution obtained in Entry 4, Table 2.[29] To the best of our knowledge, this is one of the largest transition state energy differences ever recorded in an enantioselective process.

Support for this model is given by the loss of selectivity observed in the related reaction of acetyloxazolidinones **30** and **31**, where the lack of the α-substituent makes both transition state ring conformers similar in energy.

In summary, based on the chair models presented in Section 2 of this chapter, and assuming the aldehyde approaches from the enolate's least hindered side, we propose the structure $E_1^{\ddagger}$ depicted in Scheme VII for the transition state of the present aldol condensation. The main difference between structures $E_1^{\ddagger}$ and $E_2^{\ddagger}$ is the orientation of the oxazolidinone ring (transoid vs cisoid) which is translated into a difference in energy due to allylic interactions.

IV. Summary

The boron enolates of chiral oxazolidinones **7** and **8** have been demonstrated to react with aldehydes to afford erythro aldol adducts with excellent diastereoselection and high yields. The reaction can

also be performed with more functionalized oxazolidinones, such as **21** or **28**. Mild base hydrolysis of the adducts leads to optically pure ($\geq$99% ee) β-hydroxy acids, along with the chiral auxiliary, which can be reused. The reaction is believed to go through a pericyclic, chair transition state in which 1,3-diaxial and A-strain interactions have been minimized.

Experimental Section

General. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4210 spectrophotometer. 90 MHz ^{1}H NMR spectra were recorded on a Varian Associates EM-390 spectrometer and are reported in ppm on the δ scale, from the indicated reference. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), coupling constant (in Hz), integration and interpretation. 500 MHz ^{1}H NMR spectra were recorded on a Bruker WM-500 spectrometer at the Southern California Regional NMR facility. ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz) spectrometer and are reported in ppm on the δ scale from the indicated reference. Combustion analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, Michigan), Galbraith Laboratories, Inc. (Knoxville, Tennessee), or Mr. Lawrence Henling (California Institute of Technology). Optical rotations were recorded on a Jasco DIP-181 digital polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^{25}$, solvent, and concentration (c = g/100 ml).

Analytical gas-liquid chromatography (GC) was carried out on a Hewlett Packard 5880 A level 3 gas chromatograph equipped with a split mode capillary injection system and a flame ionization detector, using a 25 m x 0.2 mm flexible fused silica capillary

column wall-coated with Carbowax 20 M or Methyl Silicone (SP-2100), or a 30 m x 0.32 mm fused silica capillary wall-coated with SE-54. Unless otherwise noted, injector and detector temperatures were 250°C. Data are reported as follows: column type, oven temperature, and retention time (t_r).

Liquid chromatography was performed using a forced flow (flash-chromatography) of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). Data are reported as follows: column diameter, weight of silica and eluent composition. Medium pressure liquid chromatography (MPLC) was carried out using EM Reagents LoBar Silica Gel 60 prepacked columns (column size indicated) on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP-SY Lab Pump. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates.

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, benzene and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, diisopropylethylamine, diisopropylamine, triethylamine and boron trifluoride etherate were distilled from calcium hydride. Dimethyl sulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over activated 4 Å molecular sieves.

Unless otherwise specified, all non-aqueous reactions were conducted under a rigorously dried argon atmosphere, using oven-dried glassware.

Di-n-butylboryl trifluoromethanesulfonate[18] (Di-n-butyl boryltriflate). To rapidly stirred tri-n-butylborane (22.3 mL, 16.7 g, 91 mmol, Callery Chemical) in a dry, three-necked, 100-mL flask, connected to an argon bubbler was added ca. 2 mL of anhydrous trifluoromethanesulfonic acid (triflic acid). The reaction was initiated by the application of heat (heat gun) and monitored by the evolution of butane. The remaining triflic acid for a total of 8.05 mL (13.76 g, 91 mmol) was added dropwise at a rate that maintained a steady evolution of butane. Caution: Do not allow the accumulation of large amounts of unreacted triflic acid evidenced by formation of a two phase mixture, as the reaction may become violent. In order to prevent this from occurring, additional heating may be required. When the addition was complete, the resulting orange solution was then stirred at room temperature for 1 h and distilled at reduced pressure through a Vigreux column (15 cm) to afford the title compound as a colorless, highly air-sensitive liquid (bp 70°C at ca. 2 mm; d = 1.1). The product was stored at ambient temperature under an argon atmosphere. Although the product often developed an orange coloration upon storage, it seemed not to affect the yields of subsequent reactions.

Di-n-butylboryl methanesulfonate. Into a dry 50-mL, three-necked flask connected to an argon bubbler was introduced tri-n-butylborane (4.4 mL, 18.3 mmol) followed by a catalytic amount of benzoic acid (0.11 g, 0.9 mmol, 0.05 equiv). The solution was heated with a heat gun until butane was evolved. Methanesulfonic acid (1.18 mL, 18.3 mmol, 1 equiv) was then introduced in portions, with the careful control of heating. After the addition was completed, the orange solution was stirred at room temperature for 1 h, then distilled through a short-path distillation head to afford di-n-butylboryl methanesulfonate as a colorless oil which was stored under an argon atmosphere at 4°C: bp 84°C at 0.5 mm; ^{1}H NMR (90 MHz, $CDCl_3$) δ (TMS) 3.13 (s, 3H,-$SO_2\underline{CH}_3$), 1.5-1.0 (m, 12 H, ($CH_3\underline{CH}_2\underline{CH}_2\underline{CH}_2)_2$), 1.0-0.7 (m, 6H, ($\underline{CH}_3CH_2)_2$).

General Procedure for the Preparation of 3-acyl-2-oxazolidinones. In a dry, 1-L flask was placed 130 mmol of oxazolidinone **9** or **10**. The flask was flushed with argon and charged with tetrahydrofuran (300 mL). The solution was cooled to -78°C and a 1.65 M solution of n-butyllithium in hexane (79 mL, 130 mmol, 1 equiv) was added slowly. When **10** was used as the starting material, appearance of a red coloration, due to dianion formation, indicated that one equivalent of base had been added. The acid chloride (156 mmol, 1.2 equiv, neat) was then added in one portion, and the reaction mixture was allowed to warm slowly to room temperature (45 min). The

reaction was quenched by the addition of saturated aqueous ammonium chloride and the organic volatiles removed in vacuo. The remaining aqueous slurry was extracted with dichloromethane (2 x 150 mL), and the combined organic layers were washed subsequently with 5% aqueous sodium hydroxide, and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The product was purified by molecular distillation (Kügelrohr, vacuum) followed by flash chromatography (when necessary) or recrystallization.

(S)-3-(2-Methoxy-1-oxoethyl)-4-(1-methylethyl)-2-oxazolidinone (21). Freshly distilled methoxyacetyl chloride (1.51 mL, 16.5 mmol) was added dropwise into a cooled (-5°C) solution containing the lithium salt of **9** (15 mmol) in anhydrous tetrahydrofuran, following the previously described general acylation procedure. The resulting oil was purified by bulb-to-bulb distillation (Kügelrohr, 140°C, 0.005 mm), followed by flash chromatography (50 mm, 150 g silica, 40% ethyl acetate:hexane) to afford 2.31 g (76%) of compound **21** as a colorless oil: IR (CH_2Cl_2) 3060, 2985, 1783, 1722, 1390, 1203, 892 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 4.58 (s, 2H, $O{=}C\overset{|}{C}\underline{H}_2$), 4.55-4.25 (m, 3H, $-N\overset{|}{C}\underline{H}\overset{|}{C}\underline{H}_2$), 3.45 (s, 3H, $C\underline{H}_3\overset{|}{O}$), 2.42 (qn of d, J_d = 3, J_{qn} = 7, 1H, $(CH_3)_2\overset{|}{C}\underline{H}$), 0.92 (d, J = 7, 3H, $C\underline{H}_3\overset{|}{C}HCH_3$), 0.87 (d, J = 7, 3H, $CH_3\overset{|}{C}HC\underline{H}_3$); $[\alpha]_D^{25}$ = +92.6° (CH_2Cl_2, c 5.5).

Anal. calcd. for $C_9H_{15}O_4$ N: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.56; H, 7.45; N, 6.82.

(4R,5S)-3-(2-Methoxy-1-oxoethyl)-4-methyl-5-phenyl-2-oxazolidinone (23). To a stirred, cooled (-5°C) solution of the lithium salt of **10** (40 mmol) in anhydrous tetrahydrofuran was added methoxyacetyl chloride (4.02 mL, 42 mmol) following the previously described general procedure for acylation. The unpurified, solid product was recrystallized (ether: pet. ether) to afford 8.65 g (87%) of the title compound as colorless needles: mp 61-63°C; IR (CH_2Cl_2) 3050, 2990, 1782, 1720, 1350, 1200, 1125, 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.2 (m, 5H, aromatic H), 5.74 (d, J = 7.0, 1H, $Ph\underline{C}\underline{H}$-), 4.78 (qn, J = 7.0, 1H, $CH_3\underline{C}\underline{H}$-), 4.63 (s, 2H, $CH_3O\underline{C}\underline{H}_2$), 3.49 (s, 3H, $\underline{C}\underline{H}_3O\underline{C}\underline{H}_2$), 0.93 (d, J = 7.0, 3H, $\underline{C}\underline{H}_3\underline{C}\underline{H}$-); ^{13}C NMR ($CDCl_3$) δ 169.15, 152.38, 132.69, 128.08, 125.09, 79.34, 78.36, 71.54, 58.74, 53.73, 13.90; $[\alpha]_D^{25}$ = +30.8° (CH_2Cl_2, c 5.0).

Anal. calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.70; H, 6.01; N, 5.59.

(S)-4-(1-Methylethyl)-3-(1-oxo-2-(phenylmethoxy)-ethyl)-2-oxazolidinone (22). Phenylmethoxyacetyl chloride (3.32 g, 18 mmol, 1 equiv) was added to a cooled (-10°C) solution of the lithium salt of **9** (18 mmol), according to the previously described general procedure. The unpurified, crystalline product was recrystallized

from ether-pet. ether. ^{1}H NMR analysis indicated the presence of unreacted starting material **9**. The product was dissolved in dichloromethane, washed twice with water to remove **9**, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford 3.10 g (62%) of the title compound as a white solid: mp 86.5-87.0°C; IR (CH_2Cl_2) 2970, 1785, 1723, 1488, 1390, 1213, 1122 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.25 (m, 5 H, aromatic H), 4.65 (d, J = 3.5, 2H, $PhC\underline{H}_2$), 4.53-4.20 (m, 3H, $-N\underline{C}H\underline{C}H_2$), 2.42 (qn of d, J_d = 3, J_q = 7, 1H, $(CH_3)_2C\underline{H}$), 0.93 (d, J = 7, 3H, $C\underline{H}_3CHCH_3$), 0.89 (d, J = 7, 3H, $CH_3CHC\underline{H}_3$).

Anal. calcd. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91. Found: C, 65.12; H, 7.04.

(S)-4-(1-Methylethyl)-γ,2-dioxo-3-oxazolidinebutanoic acid, ethyl ester (28). Ethyl succinyl chloride (5.4 mL, 37.7 mmol, 1.2 equiv) was added into a solution containing the lithium salt of **9** (31.4 mmol) in anhydrous tetrahydrofuran, following the previously described general procedure. Flash chromatography (50 mm, 220 g silica, 30% ethyl acetate:hexane) afforded 6.75 g (83%) of the title compound as a colorless oil: Rf 0.28 (70% ethyl acetate:hexane); IR (film) 2975, 1785, 1735, 1705, 1390, 1210, 1170 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ (TMS) 4.55-4.00 (m, 5H, $-N\underline{C}H\underline{C}H_2O$; $CH_3C\underline{H}_2O$-), 3.34 (m, 2H, $-CH_2C\underline{H}_2CON$-), 2.65-2.55 (m, 2H, $-C\underline{H}_2CH_2CON$-), 2.38 (qn of d, J_d = 3, J_{qn} = 7, 1H, $CH_3C\underline{H}CH_3$), 1.25 (t, J = 8, 3H, $C\underline{H}_3CH_2O$-), 0.90

(d, J = 7.5, 3H, $CH_3\underline{C}HCH_3$), 0.88 (d, J = 7.5, 3H, $CH_3CHC\underline{H}_3$); $[\alpha]_D^{25}$ = +73.2° (CH_2Cl_2, c 3.7).

Anal. calcd. for $C_{12}H_{19}O_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.17; H, 7.39; N, 5.36.

General Procedure for the Formation of the Boron Enolates of Acyloxazolidinones and Subsequent Condensation with Aldehydes. The following reactions were done on a scale ranging from 0.5 mmol to 300 mmol, at concentrations of starting oxazolidinones of 0.25 M to 1 M. All reagent additions were made via hypodermic syringe.

Method A: In a dry, two-necked, 25-mL flask equipped with a magnetic spin bar was introduced 1.0 mmol of the indicated oxazolidinone. The flask was purged with argon, charged with freshly distilled dichloromethane (2-4 mL), and the solution cooled to -78°C. Di-n-butylboryl triflate (0.27 mL, 1.1 mmol) was added dropwise, often resulting in a yellow solution, and partial freezing of the reagent. The cooling bath was removed until the triflate dissolved. The solution was recooled (-78°C) and freshly distilled diisopropylethylamine (0.21 mL, 1.2 mmol) (or freshly distilled triethylamine (0.17 mL, 1.2 mmol)) was then added dropwise resulting in a colorless, clear solution. The mixture was stirred at -78°C for 0.5 h, then at 0°C for 1 h. The solution was recooled to -78°C, and anhydrous aldehyde (neat, 1.0 mmol of non-enolizable aldehyde, or 1.1 to 1.2 mmol of enolizable aldehyde) was added in one portion.

The solution was stirred at -78°C for 0.5 h and then at 0°C for 1 h. The reaction was quenched by the successive addition of aqueous phosphate buffer (pH 7) (1 mL), methanol (sufficient to afford a homogeneous solution) and a solution of 30% aqueous hydrogen peroxide (1 mL) in methanol (2 mL). The mixture was stirred at 0°C for 1 h. Volatiles were removed in vacuo and the remaining aqueous mixture was extracted with ether (2 x 30 mL). The combined ethereal phases were washed with 5% aqueous sodium bicarbonate, and with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The resulting aldol adduct was purified either by recrystallization or flash chromatography.

Method B: This method was used for α-alkoxyacetyloxazolidinones. It is identical to method A, except that the temperature was maintained at -78°C during both the enolization and condensation processes. The reactions were quenched at -78°C.

General Procedure for the Formation of the Lithium Enolates of Acyloxazolidinones and Subsequent Condensation with Aldehydes. In a dry, argon-filled, two-necked, 25-mL flask equipped with a magnetic spin bar, a rubber septum and an argon gas-inlet, was introduced 3 mL of anhydrous tetrahydrofuran and 0.15 mL (1.1 mmol) of diisopropylamine. The solution was cooled to -78°C and 0.68 mL (1.1 mmol) of a 1.6 M solution of n-butyllithium in hexane was added dropwise. After 20 min a solution of 1.0 mmol of the indicated

oxazolidinone in 1 mL of tetrahydrofuran was added dropwise (1 x 1 mL rinse). The solution was stirred 30 min and then treated with 1.0 mmol of non-enolizable aldehyde (or 1.1 to 1.2 mmol of enolizable aldehyde) in one portion. The reaction was quenched after 5-10 seconds by the addition of 2 mL of saturated aqueous ammonium chloride, and allowed to warm to room temperature. Volatiles were removed in vacuo and the remaining mixture was extracted with ether or dichloromethane (2 x 30 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to slightly yellow oils.

(3Z,4R,5S)-3-((((1,1-Dimethylethyl)dimethylsilyl)oxy)-1-propenyl)-4-methyl-5-phenyl-2-oxazolidinone (33). Enolization was performed according to the previously described procedure for the generation of lithium enolates. To a cooled (-78°C) solution of LDA (1.1 equiv, 1.1 mmol) in tetrahydrofuran (3 mL) was added dropwise a solution containing imide **8** (233 mg, 1 mmol) in tetrahydrofuran (1 mL). The mixture was stirred for 30 min, and then t-butyldimethylsilylchloride (151 mg, 1 mmol, 1 equiv) was added. The reaction mixture was slowly warmed up to room temperature, then stirred for 1 h and finally quenched by the addition of pH 7 phosphate buffer solution. The mixture was diluted with water and extracted with ether, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to 300 mg of a colorless oil. Flash

chromatography (30 mm, 45 g silica, 30% ethyl acetate:hexane) afforded 254 mg (73%) of the title compound as a white solid. Recrystallization (ether:pet. ether) afforded pure material as white needles: mp 88-89°C; IR ($CHCl_3$) 3022, 2965, 2941, 2870, 1756, 1687, 1390, 1055, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.42-7.24 (m, 5H, aromatic H), 5.57 (d, J = 7.0, 1H, -NCHCH-), 4.86 (q, J = 7.0, 1H, $H_3CCH=$), 4.290 (qn, J = 6.5, -NCHCH-), 4.284 (qn, J = 6.5, -NCHCH-), 1.64 (d, J = 7.0, 3H, $CH_3CH=$), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.771 (d, J = 6.5, 3H, CH_3CHN-), 0.23 (s, 6H, $(CH_3)_2Si$-); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 143.12, 138.19, 135.07, 128.6, 120.1, 103.81, 55.46, 25.76, 18.16, 14.52, 11.01, -4.2, -4.6; $[\alpha]_D^{25}$ = +106.9° ($CHCl_3$, c 1.1).

Anal. calcd. for $C_{19}H_{29}NO_3Si$: C, 65.67; H, 8.41. Found: C, 65.74; H, 8.37.

(3(2S,3S),4S)-3-(3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone (11). (Table I, Entry A). Enolization, aldol condensation, oxidation and product isolation were performed according to the previously described method A. To a cooled (-78°C) solution of the boron enolate of **7** in 8 mL of anhydrous dichloromethane (prepared from 370.4 mg (2.0 mmol) of oxazolidinone **7**, 0.54 mL (2.2 mmol) of di-n-butylboryl triflate, and 0.42 mL (2.4 mmol) of diisopropylethylamine) was added benzaldehyde (0.21 mL, 2 mmol, 1 equiv). The reaction was stirred at -78°C for 0.5 h and

at 0°C for 1 h. Product isolation afforded 534 mg of a white solid. Diastereomer analysis (Carbowax, T = 200°C, t_r **E_1** = 5.42 min, t_r **E_2** = 7.17 min, t_r **T_1** = 8.40 min, t_r **T_2** = 9.23 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) revealed a ratio of **E_1**:**E_2**:**T_1**:**T_2** = 99.8:0.04:0.14:0.04. Recrystallization (ether:pet. ether) gave 510.3 mg (88%) of the title product as white needles: mp 97-98°C; IR (CH_2Cl_2) 3540 (br), 2970, 2880, 1780, 1680, 1385, 1300, 1205, 660 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.2 (m, 5H, aromatic H), 4.98 (d, J = 4.5, 1H, HOC$\underline{H}$-), 4.4-3.9 (m, 4H, O=CC$\underline{H}$-, -NC$\underline{H}$C$\underline{H}_2$O), 3.5-3.2 (br s, 1H, $\underline{H}$O-), 2.17 (qn of d, J_d = 3.5, J_{qn} = 7 1H, $CH_3C\underline{H}CH_3$), 1.20 (d, J = 7.0, 3H, O=CCHC$\underline{H}_3$), 0.87 (d, J = 7, 3H, $C\underline{H}_3CHCH_3$), 0.83 (d, J = 7, 3H, $CH_3CHC\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ (TMS) 176.64, 153.44, 141.67, 128.15, 127.37, 126.21, 73.76, 63.43, 58.42, 44.58, 28.53, 17.81, 14.75, 11.50; $[\alpha]_D^{25}$ = +64.5° (CH_2Cl_2, c 8.4).

Anal. calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.04; H, 7.26; N, 4.71.

(3(2R,3S),4S)-3-(3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone (11T). Lithium enolate formation, aldol condensation and product isolation were performed according to the previously described procedure. To a cooled (-78°C) solution of the lithium enolate of **7** in 5 mL of anhydrous tetrahydrofuran (prepared from 185.2 mg (1 mmol) of **7**, 0.15 mL (1.1 mmol) of

diisopropylamine, and 0.8 mL (1.1 mmol) of a 1.37 M solution of n-butyllithium), was added benzaldehyde (1 mmol). Product isolation afforded a yellow oil. Diastereomer analysis (Carbowax, 200°C, t_r E_1 = 7.71 min, t_r E_2 = 10.17 min, t_r T_1 = 11.86 min, t_r T_2 = 13.16 min) afforded a ratio of E_1:E_2:T_1:T_2 of 9.8:29.5:59.0:1.7. Chromatography on silica gel (MPLC, Merck LoBar size B, 43% dichloromethane, 43% hexane, 14% ethyl acetate) afforded 50 mg of the title compound as a white solid. Diastereomer analysis of a chromatographed, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) afforded a ratio of E_1:E_2:T_1:T_2 = 0.1:$\leq$0.01:99.5:0.4: R_f 0.25 (43% dichloromethane, 43% hexane, 14% ethyl acetate); mp 103-104°C; IR (CH_2Cl_2) 3600, 3520, 2970, 1780, 1700, 1385, 1210 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.25 (m, 5H, aromatic H), 4.70 (t, J = 8, 1H, HOC<u>H</u>-), 4.55-4.05 (m, 4H, O=CC<u>H</u>-, -NC<u>H</u>C<u>H</u>$_2$), 3.40 (d, J = 7, 1H, <u>H</u>O), 2.23 (qn of d, J_d = 3, J_{qn} = 7, 1H, $(CH_3)_2$C<u>H</u>), 1.06 (d, J = 7, 3H, O=CCHC<u>H</u>$_3$), 0.85 (d, J = 7, 3H, C<u>H</u>$_3$CHCH$_3$), 0.72 (d, J = 7, 3H, CH$_3$CHC<u>H</u>$_3$); ^{13}C NMR (CCl_4) δ (TMS) 175.66, 153.04, 142.71, 128.09, 127.24, 126.33, 77.14, 62.32, 58.16, 43.41, 28.01, 17.80, 14.49, 14.23; $[\alpha]_D^{25}$ = -3.18° (CH_2Cl_2, c 8.3).

<u>Anal</u>. calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.22; H, 7.30; N, 4.76.

(3(2S,3R),4S)-3-(3-Hydroxy-2,4-dimethyl-1-oxopentyl)-4-(1-methylethyl)-2-oxazolidinone (13). (Table 1, Entry C).

Enolization, condensation, oxidation and product isolation were performed according to the previously described method A. To a cooled (-78°C) solution of the boron enolate of **7** in 12 mL of anhydrous dichloromethane (prepared from 555 mg (3 mmol) of oxazolidinone **7**, 0.81 mL (3.3 mmol) of di-n-butylboryl triflate, and 0.63 mL (3.6 mmol) of diisopropylethylamine) was added 0.33 mL (3.6 mmol) of isobutyraldehyde. The reaction was stirred at -78°C for 0.5 h and at 0°C for 1 h. Product isolation gave 670 mg of a white solid. Diastereomer analysis (Carbowax, T = 180°C, t_r E_1 = 10.18 min, t_r E_2 = 11.29 min, t_r T_1 = 12.27 min, t_r T_2 = 12.87 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) afforded a ratio of E_1:E_2:T_1:T_2 = 99.4:0.2:0.2:0.2. Recrystallization (ether:pet. ether) gave 604.1 mg (78%) of compound **13** as white needles: mp 88-89°C; IR (CH_2Cl_2) 3550 (br), 2970, 1783, 1683, 1386, 1208 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 4.55-4.1 (m, 3H, -NCHCH$_2$O), 3.93 (q of d, J_d = 3, J_q = 6.5, 1H, O=CCH-), 3.47 (d of t, J_t = 3, J_d = 8.5, 1H, HOCH-), 2.95 (d, J = 3, 1H, HO-), 2.32 (qn of d, J_d = 3.5, J_{qn} = 7, 1H, CH_3CHCH$_3$), 1.85-1.45 (m, 1H, HOCHCH(CH$_3$)$_2$), 1.21 (d, J = 7, 3H, O=CCHCH$_3$), 1.1-0.8 (m, 12H, two (CH$_3$)$_2$CH); $[\alpha]_D^{25}$ = +60.3° (CH_2Cl_2, c 2.3).

Anal. calcd. for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.52; H, 9.01; N, 5.38.

(3(2S,3R),4S)-3-(3-Hydroxy-2-methyl-1-oxoheptyl)-4-(1-methylethyl)-2-oxazolidinone (15). (Table 1, Entry E). Enolization, condensation, oxidation and product isolation were performed according to the previously described method A. To a cooled (-78°C) solution of the boron enolate of **7** in 16 mL of anhydrous dichloromethane (prepared from 741 mg (4 mmol) of oxazolidinone **7**, 1.08 mL (4.4 mmol) of di-n-butylboryl triflate and 0.84 mL (4.8 mmol) of diisopropylethylamine) was added 0.44 mL (4.4 mmol) of freshly distilled pentanal. The reaction was stirred at -78°C for 0.5 h and at 0°C for 1 h. Product isolation afforded 952 mg of an oil. Diastereomer analysis (Carbowax, 170°C, t_r E_1 = 5.96 min, t_r E_2 = 6.16 min, t_r T_1 = 7.18 min; t_r T_2 = 7.78 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) revealed at ratio of E_1:E_2:T_1:T_2 = 99.0:0.76:0.18:0.06. A portion (322 mg) was flash chromatographed (25 mm, 35 g silica, 30% ethyl acetate:hexane) to afford 30 mg of starting material (**7**) and 274.6 mg (75%) of compound **15** as a colorless oil: IR (CH_2Cl_2) 3560 (br), 2970, 1780, 1680, 1455, 1385, 1300, 1205 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 4.55-4.05 (m, 3H, -NC<u>H</u>C<u>H</u>$_2$), 4.0-3.55 (m, 2H, O=CC<u>H</u>C<u>H</u>-), 3.05 (br d, J = 3, 1H, <u>H</u>O-), 2.33 (qn of d, J_d = 3.5, J_{qn} = 7, 1H, $(CH_3)_2$C<u>H</u>), 1.7-1.0 (m, 6H, CH_3<u>$CH_2CH_2CH_2$</u>), 1.25 (d, J = 7, 3H, O=CCH<u>CH_3</u>), 1.0-0.7 (m, 9H, <u>CH_3</u>C<u>H_2</u>, $(C\underline{H_3})_2$CH); $[\alpha]_D^{25}$ = +75.2° (CH_2Cl_2, <u>c</u> 3.4).

<u>Anal</u>. calcd. for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.93; H, 9.35; N, 5.10.

(3(2R,3R),4R,5S)-3-(3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (12). (Table 1, Entry B). Enolization, condensation, oxidation and product isolation were performed according to the previously described method A. To a cooled (-78°C) solution of the boron enolate of **8** in 40 mL of anhydrous dichloromethane (prepared from 2.33 g (10 mmol) of oxazolidinone **8**, 2.7 mL (11 mmol) of di-n-butylboryl triflate, and 2.1 mL (12 mmol) of diisopropylethylamine) was added 1.01 mL (10 mmol) of benzaldehyde. The reaction was stirred at -78°C for 0.5 h and at 0°C for 1 h. Product isolation afforded 3.04 g (89%) of compound **12** as a white solid, pure by TLC and proton NMR. Diastereomer analysis (SE-54, T = 225°C, 10 PSI, t_r E_1 = 10.22 min, t_r E_2 = 12.61 min, t_r T = 13.62 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) afforded a ratio of E_1:E_2:T = ≥99.9:≤0.1:≤0.1. Recrystallization (ether:pet. ether) provided an analytical sample of **12**: mp 138-139°C; IR (CH_2Cl_2) 3500 (br), 1770, 1675, 1352, 1183 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.15 (m, 10H, aromatic H), 5.40 (d, J = 7, 1H, -NCHCHO-), 5.04 (d, J = 4.5, 1H, HOCH-), 4.62 (qn, J = 7, 1H, -NCH-), 4.11 (q of d, J_d = 4.5, J_q = 7, 1H, O=CCH-), 3.2-3.0 (br, 1H, HO-), 1.22 (d, J = 7, 3H, O=CCHCH$_3$), 0.88 (d, J = 7, 3H, -NCHCH$_3$); $[\alpha]_D^{25}$ = +5.5° (CH_2Cl_2, c 6).

Anal. calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.78; H, 6.21; N, 4.10.

(3(2R,3S),4R,5S)-3-(3-Hydroxy-2,4-dimethyl-1-oxopentyl)-4-methyl-5-phenyl-2-oxazolidinone (14). (Table 1, Entry D). Enolization, condensation, oxidation and product isolation were performed according to the previously described method A. To a cooled (-78°C) solution of the boron enolate of **8** in 40 mL of anhydrous dichloromethane (prepared from 2.33 g (10 mmol) of oxazolidinone **8**, 2.7 mL (11 mmol) of di-n-butylboryl triflate, and 2.1 mL (12 mmol) of diisopropylethylamine) was added 1.1 mL (11 mmol) of isobutyraldehyde. The reaction was stirred at -78°C for 0.5 h and at 0°C for 1 h. Product isolation gave 3.51 g of a thick oil. Diastereomer analysis (SE-54, 200°C, 10 PSI, t_r E_1 = 11.88 min, t_r E_2 = 13.09 min, t_r T = 13.50 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) afforded a ratio of E_1:E_2:T = 99.8:0.15:0.05. A portion (243 mg) was flash chromatographed (25 mm, 32 g silica, 40% ethyl acetate:hexane) to afford 226.1 mg (91%) of the title compound as a colorless, thick oil: IR (film) 3700-3100 (br), 2970, 1782, 1700, 1455, 1200, 1120 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.2 (m, 5H, aromatic H), 5.67 (d, J = 7, 1H, -NCHC<u>H</u>O), 4.76 (qn, J = 7, 1H, -NC<u>H</u>-), 3.95 (q of d, J_d = 3.5, J_q = 7, 1H, O=CC<u>H</u>-), 3.56 (d of d, J = 3.5, J = 8.5, 1H, HOC<u>H</u>-), 3.25-3.1 (br, 1H, <u>H</u>O)-, 1.9-1.45 (m, 1H, $(CH_3)_2$C<u>H</u>), 1.22 (d, J = 7, 3H, O=CCHC<u>H</u>$_3$), 1.02 (d, J = 7, 3H, C<u>H</u>$_3$CHCH$_3$), 0.93 (d, J = 7, 3H, CH$_3$CHC<u>H</u>$_3$), 0.88 (d, J = 7, 3H, -NCHC<u>H</u>$_3$); $[\alpha]_D^{25}$ = +30.2° (CH_2Cl_2, <u>c</u> 5.9).

Anal. calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.94; H, 7.73; N, 4.44.

(3(2R,3S),4R,5S)-3-(3-Hydroxy-2-methyl-1-oxoheptyl)-4-methyl-5-phenyl-2-oxazolidinone (16). (Table 1, Entry F). Enolization, condensation, oxidation and product isolation were performed according to the previously described method A. To a cooled (-78°C) solution of the boron enolate of **8** in 40 mL of anhydrous dichloromethane (prepared from 2.33 g (10 mmol) of oxazolidinone **8**, 2.7 mL (11 mmol) of di-n-butylboryl triflate, and 2.1 mL (12 mmol) of diisopropylethylamine) was added 1.17 mL (11 mmol) of freshly distilled pentanal. The reaction was stirred at -78°C for 0.5 h and at 0°C for 1 h. Product isolation afforded 3.02 g (95%) of compound **16** as a white solid, pure by TLC and proton NMR. Diastereomer analysis (SE-54, 200°C, t_r E_1 = 12.71 min, t_r E_2 = 14.04 min, t_r T = 14.87 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) gave a ratio of E_1:E_2:T = 99.9:≤0.01:0.1. Recrystallization from ether:pet. ether afforded an analytical sample of **16**: mp 98-100°C; IR (CH_2Cl_2) 3700-3400 (br), 2970, 2950, 1785, 1685, 1458, 1347, 1200, 1123 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.2 (m, 5H, aromatic H), 5.68 (d, J = 7, 1H, -NCHC<u>H</u>O), 4.79 (qn, J = 7, 1H, -NC<u>H</u>CHO), 4.1-3.8 (br, 1H, HOC<u>H</u>-), 3.89 (q of d, J_d = 3.5, J_q = 7, 1H, O=CC<u>H</u>-), 3.05-2.85 (br s, 1H, <u>H</u>O-), 1.7-1.1 (m, 6H, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.25 (d, J = 7, 3H, O=CCHC<u>H</u>$_3$), 1.1-0.85 (m, 3H,

$C\underline{H}_3CH_2$), 0.90 (d, J = 7, 3H, $-N\overset{|}{C}H\overset{|}{C}\underline{H}_3$); $[\alpha]_D^{25}$ = +12.2° (CH_2Cl_2, c 3.5).

Anal. calcd. for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.54; H, 7.88; N, 4.31.

(3(2R,3R),4R,5S)-3-(3-(2-Furanyl)-3-hydroxy-2-methyl-1-oxopropyl)-4-methyl-5-phenyl-2-oxazolidinone (17). (Table 1, Entry G). Enolization, condensation, oxidation, and product isolation were performed according to the previously described method A. To a cooled (-78°C) solution of the boron enolate of **8** in 3 mL of anhydrous dichloromethane (prepared from 700 mg (3 mmol) of oxazolidinone **8**, 0.81 mL (3.3 mmol) of di-n-butylboryl triflate, and 0.50 mL (3.6 mmol) of triethylamine) was added 0.27 mL (3.3 mmol) of freshly distilled furaldehyde. The mixture was stirred at -78°C for 0.5 h and at 0°C for 0.5 h. Product isolation afforded a colorless oil. Gas chromatography analysis (SE-54, 200°C, 15 PSI, t_r = 11.07 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) indicated ≥99.3 diastereomeric purity. Flash chromatography (40 mm, 130 g silica, 42% ethyl acetate:hexane) afforded 901.3 mg (91%) of the title compound as a white solid: mp 82-83°C; IR ($CHCl_3$) 3650-3300 (br), 3630, 1782, 1690, 1440, 1352, 1180, 945 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.6-7.2 (m, 6H, $C_6\underline{H}_5$-, furfuryl C_5-$\underline{H}$), 6.4 (s, 2H, furfuryl C_3-$\underline{H}$ and C_4-$\underline{H}$), 5.65 (d, J = 7, 1H, $-N\overset{|}{C}H\overset{|}{C}\underline{H}O$), 5.11 (t, J = 5.5, 1H, $HO\overset{|}{C}\underline{H}$-), 4.75 (qn, J = 7, 1H, $-N\overset{|}{C}\underline{H}$-),

4.25 (q of d, J_d = 5.5 J_q = 7, 1H, O=CC<u>H</u>-), 3.1 (d, J = 5.5, 1H, <u>H</u>O-), 1.35 (d, J = 7, 3H, O=CCHC<u>H</u>$_3$), 0.90 (d, J = 7, 3H, -NCHC<u>H</u>$_3$); $[\alpha]_D^{25}$ = +16.1° ($CHCl_3$, <u>c</u> 2.3).

<u>Anal</u>. calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81. Found: C, 65.49; H, 5.88.

(3(2S,3R),4S)-3-(3-Hydroxy-2-methoxy-1-oxo-3-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone (25). (Table 3, Entry C). Enolization, condensation, oxidation and product isolation were performed according to the previously described method B. To a cooled (-78°C) solution of the boron enolate of **21** in 4 mL of anhydrous dichloromethane (prepared from 201 mg (1 mmol) of compound **21**, 0.27 mL (1.1 mmol) of di-<u>n</u>-butylboryl triflate, and 0.21 mL (1.2 mmol)of diisopropylethylamine) was added 0.10 mL (1.0 mmol) of benzaldehyde. Product isolation afforded 245 mg (80%) of compound **25** as a white solid, pure by TLC analysis and proton NMR. Diastereomer analysis (SE-54, 200°C, 15 PSI, t_r E_1 = 4.58 min, t_r E_2 = 4.80 min; t_r T_1 = 5.53 min; t_r T_2 = 5.94 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) afforded a ratio of E_1:E_2:T_1:T_2 = 99.2:0.4:0.14:0.26. Recrystallization (ether:pet. ether) afforded an analytical sample of **25**: mp 105-106°C; IR (CH_2Cl_2) 3580, 3060, 2980, 1782, 1710, 1385, 1202, 1155, 891 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.25 (m, 5H, aromatic H), 5.35 (d, J = 5.5, 1H, $CH_3OC\underline{H}$-), 4.87 (d, J = 5.5, 1H,

-CHOH), 4.2-4.0 (m, 2H), 3.81 (q, J = 8.5, 1H), 3.38 (s, 3H, CH_3O), 3.0-2.5 (br, 1H, HO-), 2.6-2.2 (m, 1H, $(CH_3)_2CH$), 0.88 (d, J = 7, 3H, CH_3CHCH_3), 0.83 (d, J = 7, 3H, CH_3CHCH_3); $[\alpha]_D^{25}$ = +92.4° (CH_2Cl_2, c 1.6).

Anal. calcd. for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.54; H, 6.82; N, 4.48.

(3(R(R)),4R)-β-(Hydroxyphenylmethyl)-4-(1-methylethyl)-α,2-dioxo-3-oxazolidinebutanoic acid, ethyl ester (29). Enolization, condensation, oxidation and product isolation were performed according to the previously defined method B. To a cooled (-78°C) solution of the boron enolate of compound **28** in 4 mL of anhydrous dichloromethane (prepared from 257.3 mg (1.0 mmol) of oxazolidinone **28**, 0.27 mL (1.1 mmol) of di-n-butylboryl triflate, and 0.21 mL (1.2 mmol) of diisopropylethylamine), was added 1.0 mL (1.0 mmol) of benzaldehyde. After stirring at -78°C for 1.5 h, the reaction was quenched, oxidized, and the product isolated to give 311.4 mg of a thick oil. Flash chromatography (25 mm, 27 g silica, 30% ethyl acetate:hexane) afforded 242.3 mg (67%) of the title compound as a white solid. Recrystallization (ether:pet. ether) afforded an analytical sample: R_f 0.31 (30% ethyl acetate:hexane); mp 101-102°C; IR (CH_2Cl_2) 3600, 3060, 2990, 1781, 1730, 1695, 1387, 1205, 1055 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.2 (m, 5H, aromatic), 4.99 (t, J = 5.5, 1H, HOCH-), 4.58 (d of t, J_t = 4.5,

J_d = 10.5, 1H, -NC(=O)CH-), 4.45-3.85 (m, 5H, CH_3CH_2O, -NCHCH$_2$O), 2.97 (d of d, J = 10.5, J = 17.5, 1H, -OC(=O)CH(H)), 2.70 (d, J = 3.5, 1H, HO), 2.50 (d of d, J = 4, J = 17.5, 1H, -OC(=O)CH(H)), 2.5-2.2 (m, 1H, $(CH_3)_2CH$), 1.17 (t, J = 7, 3H, CH_3CH_2O), 0.89 (d, J = 7, 6H, $(CH_3)_2CH$); $[\alpha]_D^{25}$ = +96.0° (CH_2Cl_2, c 3.6).

Anal. calcd. for $C_{19}H_{25}NO_5$: C, 62.80; H, 6.93; N: 3.85. Found: C, 62.96; H, 6.90; N, 3.81.

General Procedure for the Hydrolysis of Chiral Imide Aldol Adducts to β-Hydroxy Acids. The unpurified aldol adduct was dissolved in methanol (ca. 6 mL per mmol). Water was added until the aldol adduct started to precipitate. The solution was cooled to 0°C and 2 N aqueous potassium hydroxide (2 mL per mmol) was added dropwise. The reaction mixture was stirred at 0°C for 45 min. Concentration in vacuo (30°C, ca. 15 min) hydrolyzed any remaining methyl ester formed during the reaction. The remaining aqueous phase was extracted with dichloromethane (3x), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to the corresponding, crystalline oxazolidinone **9** or **10.** The alkaline aqueous phase was acidified to pH 1 with 6 N aqueous hydrochloric acid, and saturated with sodium chloride. The aqueous solution was extracted with ether (2x), and the combined ethereal layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to the corresponding acids.

General Procedure for the Esterification of Acids. A solution of diazomethane in ether was prepared by the slow addition of N-nitrosomethyl urea to a cooled (0°C), well stirred mixture of 50% aqueous potassium hydroxide and ether.[30] After the urea dissolved, the reaction mixture was gently warmed and the ethereal solution distilled in glass apparatus with Clear Seal glass joints. An aliquot of the collected ethereal diazomethane solution was added to a stirred solution containing the acid in dichloromethane, until a yellow coloration remained. Argon was bubbled through the solution until the yellow color disappeared. The solvent was removed in vacuo to afford the methyl esters in quantitative yields. Molecular distillation (Kügelrohr) afforded analytical samples.

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CHAPTER II

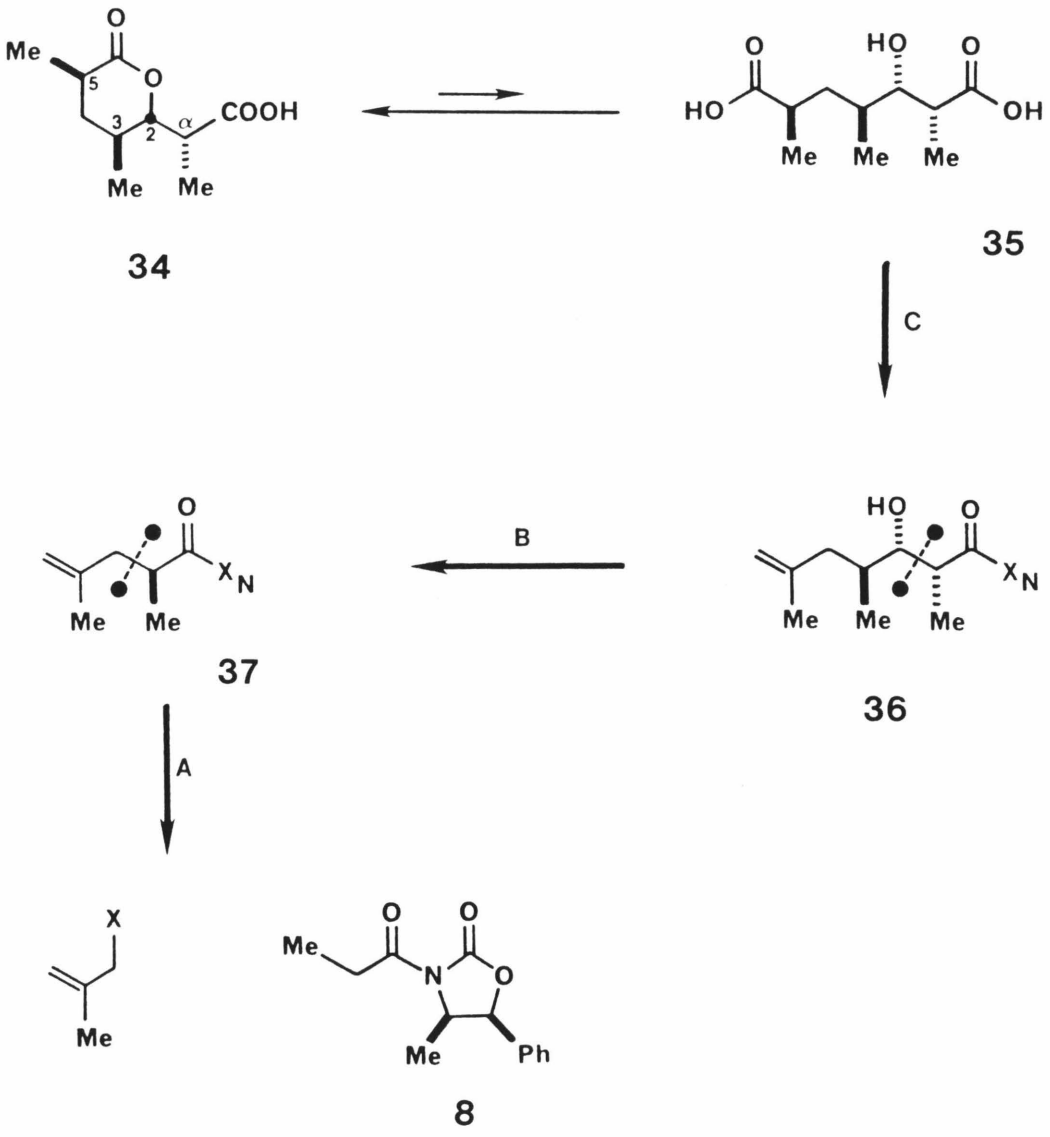
The Total Synthesis of (+)-Prelog-Djerassi Lactone[1a].
1,3-Acyclic Induction in Hydroboration Processes[1b].

I. Introduction and Strategy

In 1956, Prelog[2] and Djerassi[3] independently obtained compound **34** as a degradation product from the antibiotics narbomycin and methymycin respectively. One year later, **34** was also found to constitute part of the backbone of neomethymycin[4] and pycromycin.[5,6] Its structure was established by Djerassi in 1958,[7] and the stereochemistry assigned by Rickards[8] in 1970. Compound **34**, which soon became known as Prelog-Djerassi lactone, has since been a very popular target molecule among synthetic organic chemists, serving as a focal point for the development of a diversity of new stereoselective chemical operations. Indeed, by the end of 1982 there were 19 published total syntheses, including the one that is reported here.[1a,9-17] The following approaches have been undertaken: aldol condensation,[1a,9] ring opening of cyclic precursors,[10] carbohydrate derivatization,[11] ene reaction,[12] organomercuration,[13] hydroboration,[14] Diels-Alder[15] and carbonyl additions.[16] Seven of the syntheses are enantioselective[1a,9b,10c,11,16b] and two are nonstereoselective.[17]

Due to its stereochemical features, Prelog-Djerassi lactone was chosen as the target molecule for the first application of our imide chemistry, partially presented in Chapter I. A retrosynthetic analysis of **34** is shown in Scheme I. Three main disconnections are emphasized in this scheme: an alkylation reaction (**A**), an aldol condensation (**B**) and a hydroboration (**C**). The two former reactions

Scheme I

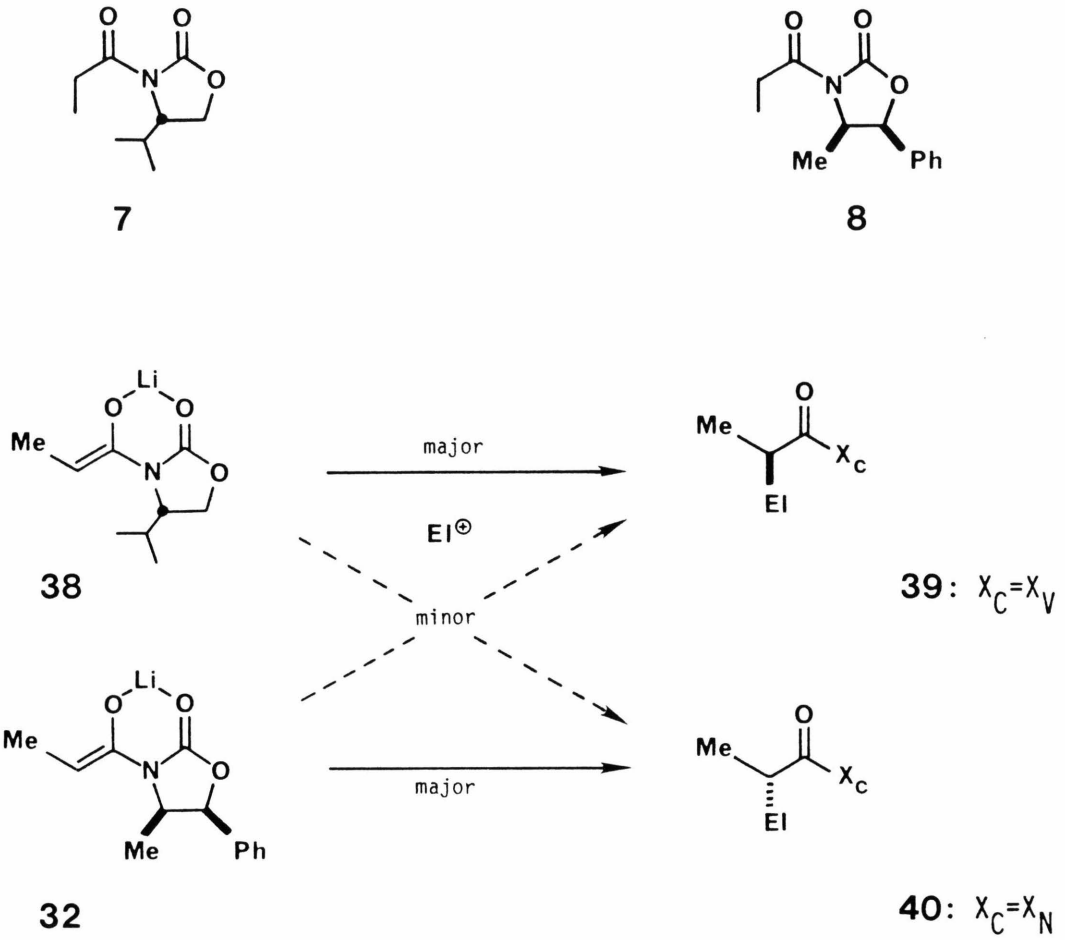

Me
O
5
O
3
2
α
COOH
Me
Me
34
HO
O
HO
O
OH
Me
Me
Me
35
C
HO
O
X
N
Me
Me
Me
36
B
O
X
N
Me
Me
37
A
X
Me
Me
O
O
N
O
Me
Me
Ph
8

would constitute the only carbon-carbon bond formations in the synthesis. By their execution, three of the four asymmetric centers present in **34** would be introduced. The fourth center would be established *via* hydroboration of an olefin like **36**. Before the fact, we did not expect this last reaction to be stereoselective and we first planned to equilibrate the mixture of the diastereomers at a later stage.

A. The C_2-C_3 Bond Construction

We envisioned the stereoselective formation of chiral center at C_3 by an alkylation reaction using chiral enolate **32** (Scheme II). The reaction of the lithium enolates derived from oxazolidinones **7** and **8** with a variety of electrophiles has been shown to give very good levels of diastereoselection.[18] The results are rationalized by an approach of the electrophile from the less hindered side of the highly organized (Z) enolates **38** and **32** to afford, respectively, adducts **39** and **40**. Allylic and benzylic bromides give kinetic ratios in the range of 97 to 120:1 in high yields. Less sterically demanding electrophiles (CH_3I) afford lower ratios (*ca.* 10:1) when reacted with the butyrate counterparts. However, when a >99:1 degree of diastereomer purity is desired, the small amounts of the minor diastereomer can generally be removed by chromatography. Like the aldol adducts, the alkylation products can be transformed into valuable synthons by the nucleophilic, nondestructive displacement of the chiral auxiliary.

Scheme II



B. The C_α-C_2 Bond Construction

We envisioned the establishment of the chiral centers C_α and C_2 by means of an aldol condensation using the chiral boron enolate derived from oxazolidinone **8**.[19] A detailed study on this general reaction is presented in Chapter I of this thesis. Although <u>a priori</u> we did not know what the effect of the resident chirality in the aldehyde on the overall stereochemical outcome would be, we

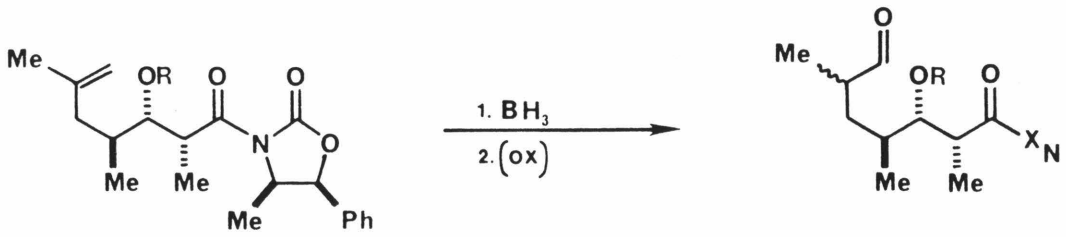
anticipated it to be small based on literature precedence.[31] This additional stereochemical point was planned to be elucidated in this work.

C. The Establishment of the C_5 Chiral Center

In our first plan, we envisioned the elaboration of center C_5 in a nonstereoselective way. The desired 5(R) stereochemistry would be accomplished by equilibration of a cyclic intermediate. Thus, hydroboration of olefin **36** (or **41**) (Scheme III), followed by oxidation, would presumably afford an epimeric mixture of aldehydes **42**. Upon deprotection of the hydroxylic functionality, the cyclic 2,6-hemiacetal would be spontaneously formed. Submitting this 6-membered ring lactol to equilibrating conditions would proceed through the enol form to give, ultimately, the most stable chair **43**, in which the C_5 methyl adopts an equatorial position (Scheme III). Using C-C and C-OH skew interaction values of 0.8 and 0.45 kcal/mol respectively[20] and assuming that, due to the anomeric effect, the C_6-hydroxyl adopts the axial configuration, compound **43** was calculated to be 0.8 kcal/mol more stable than **44**. At 25°C, this difference in energy represents an equilibrium ratio of roughly 4:1. The mixture would then be separated and the minor isomer resubmitted to equilibration.

We were happy to discover, however, that the hydroboration itself proceeded with good diastereoselection when hindered boranes were used. This unexpected result gave birth to a series of

Scheme III

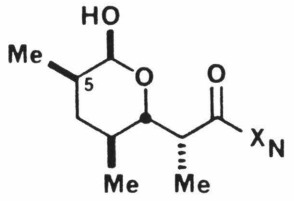


36: R=H

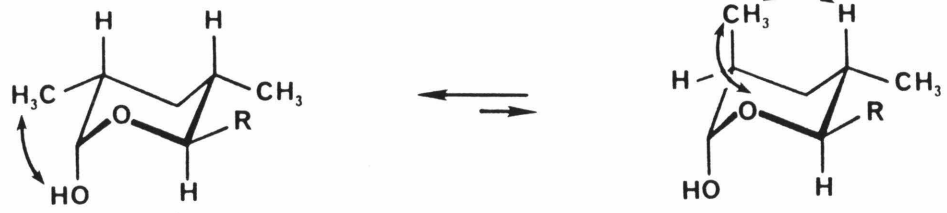
41: R=$SiMe_3$

42

1. −R
2. $H^{\oplus}$



43



(R=CHMeCOX_N)

43

1 C_1-O_2: 0.45 kcal/mol

44

1 Cα-H: 0.8 kcal/mol

1 Cα-O: 0.45 kcal/mol

calculated ΔG = 0.8 kcal/mol

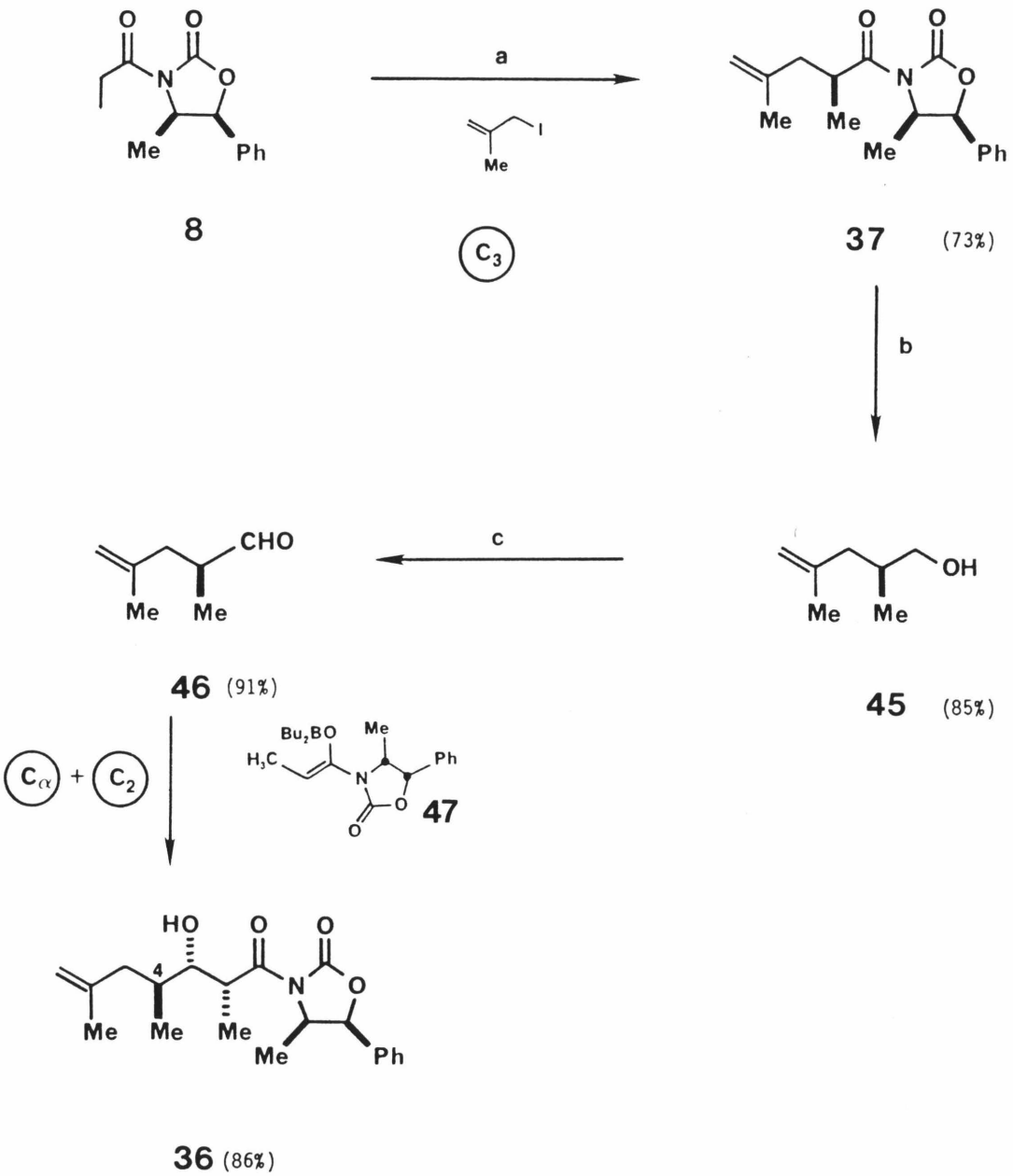
experiments aimed at a better understanding of the control elements in this reaction, and culminated in the proposal of a transition state model.

II. Results and Discussion

1. The Total Synthesis of (+)-Prelog-Djerassi Lactone

The first step of the synthesis (Scheme IV) involved the construction of the C_3 chiral center. We planned to establish the 3(S) stereochemistry by means of an alkylation using chiral imide **8**, easily prepared from (1S,2R)-norephedrine.[21] Thus, addition of propionyl oxazolidinone **8** to a LDA solution (1.1 equiv, THF, -78°C, 30 min) resulted in the formation of lithium enolate **32**. Reaction with methallyl iodide[23,24] (neat, 2 equiv, -50°C → -20°C, 3 h) afforded crystalline oxazolidinone **37**, as a 97:3 mixture of C_2-epimers (determined by GC analysis). Chromatography (MPLC) afforded **37** in 73% yield, with a diastereomeric purity of 500:1. For large scale operations, however, it was found most convenient to carry the mixture of diastereomers as obtained and to separate the minor diastereomeric contaminant by recrystallization of a more advanced intermediate. The reaction with methallyl bromide was found to give the same 97:3 ratio, but due to its lower reactivity, the reaction mixture needed to be warmed up resulting in some enolate decomposition.

Scheme IV



(a) LDA, THF; (b) LAH, Et_2O, o°C; (c) SO_3.py, Et_3N, DMSO.

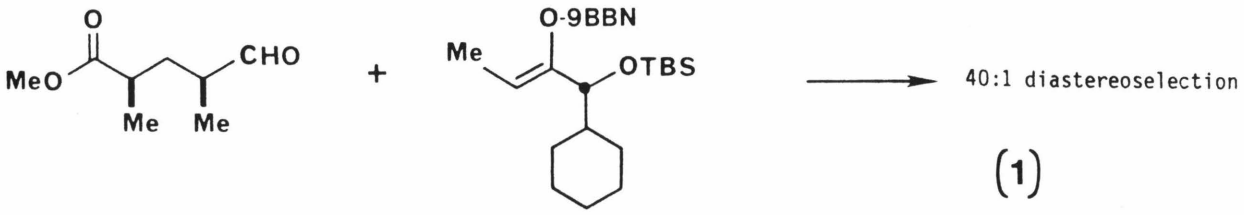
The preparation of aldehyde **46** was carried out by a two step sequence from oxazolidinone **37**. Thus, **37** was reduced (LAH, 1 mol equiv, Et_2O, 0°C, 5 min) to the corresponding alcohol **45** in 85% yield after distillation. The remaining crystalline oxazolidinone **10** (for structure see footnote 21) was purified by recrystallization and stored for further use. Aldehyde **46** was then obtained by oxidation of alcohol **45**. Two problems were anticipated regarding this transformation: first, the chiral center could potentially racemize under the reaction conditions, and second, the product would probably have a relatively low boiling point, making its isolation rather difficult. The second point was solved by limiting our oxidation choice to the methods that involved the use of a low-boiling solvent, preferably ether or dichloromethane. Epimerization, however, turned out to be a more tricky issue. This was monitored by GC analysis of the aldol adduct obtained upon condensation of the freshly prepared aldehyde and the boron enolate **47**. For this purpose, an authentic mixture of epimers at C_4 of aldol adduct **36** was prepared by condensation of **47** with the racemic aldehyde. With this test in hand, we found that celite supported Collin's oxidation (6 equiv of $CrO_3.2py$, celite, CH_2Cl_2, 25°C, 3 h)[25] proceeded with 2.5 to 1.5% epimerization, and in moderate yields (50-70%). Oxidation using chromic acid suspended on silica gel (Et_2O, RT, 15 m)[26] afforded <u>ca</u>. 30% yield of aldehyde **46**, with 11% epimerization. We were gratified to find, however, that the

Parikh modification of the Moffat oxidation[27] (3 equiv of SO_3.py, 7 equiv of Et_3N, DMSO, 25°C, 1 h) gave aldehyde **46** not only in high yields (85-91%) but with negligible epimerization (0.3 to 0.1%). This method has since been applied with similar success to the preparation of a variety of α-branched optically pure aldehydes. For very sensitive aldehydes, however, a considerable degree of epimerization under the mentioned reaction conditions has still been observed.[28] For these exceptional cases, best results were obtained by using the Swern procedure.[28,29]

With aldehyde **46** in hand, we were ready to form the second and last carbon-carbon bond. In doing so we simultaneously established the C_α and C_2 stereochemistries of Prelog-Djerassi lactone. As mentioned in the introduction, by the time we planned this synthesis, we already had a full body of information concerning the aldol condensation of chiral boron enolates with simple aldehydes.[19] We had demonstrated that these reactions proceeded with very high levels of diastereoselection to afford <u>erythro</u> adducts. However, the mutal influence of the chirality of these enolates and that of an asymmetric aldehyde on the product ratio distribution, was a matter that remained to be tested. The results obtained in this area are reported below.

Formation of the boron enolate of **8** (1.1 equiv of di-<u>n</u>-butylboryl triflate, 1.2 equiv of triethylamine, CH_2Cl_2, -78°C, 1 h) and subsequent condensation with freshly prepared aldehyde **46** (neat,

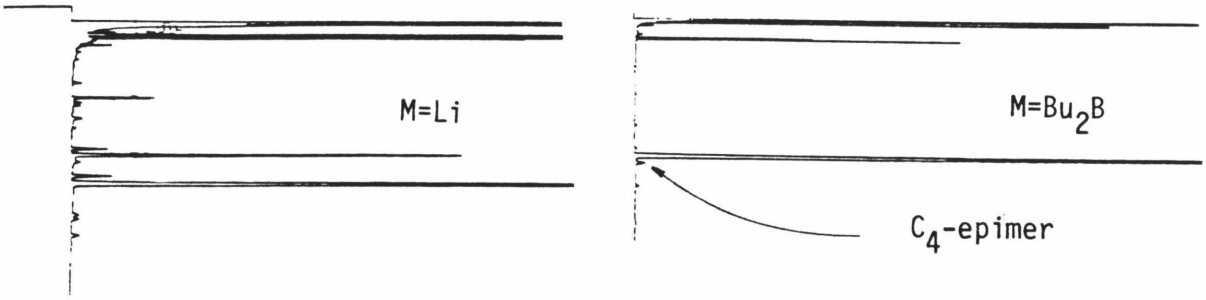
1 equiv, -78°C→0°C) afforded the crystalline aldol adduct **36** in 86% yield. An authentic isomeric mixture was obtained for analysis purposes by an analogous condensation of the corresponding lithium enolate **32**. The stereochemical control in this aldol process was truly remarkable. Diastereomeric analysis of the unpurified, silylated ($TMSNEt_2$, DMAP) reaction mixture revealed that the total erythro:threo diastereoselection was 400:1, while the asymmetric induction within the erythro manifold was 660:1 (Scheme V). High levels of diastereoselection have been also observed in a similar reaction using boron enolates derived from (+)-mandelic acid (eq. 1).[9b]

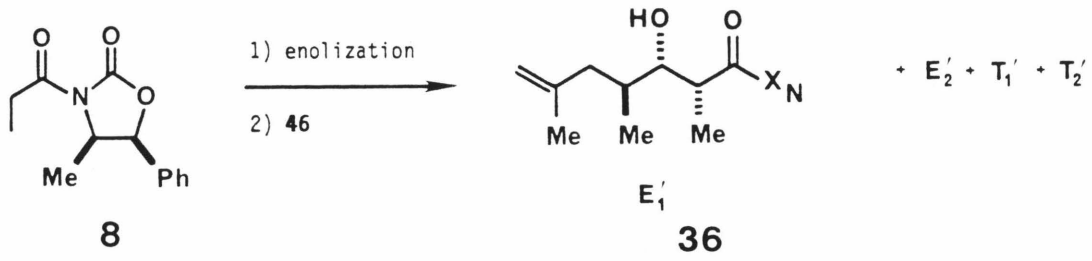


(1)

We also examined the aldol condensation of aldehyde **46** with the boron and lithium enolates of imide **7** (Scheme VI). Treatment of the boron enolate of **7** with 1.3 equiv of **46** gave a 73% yield of aldol adduct **48** after chromatography. Diastereomer analysis of an unpurified, silylated sample showed that the overall erythro:threo

Scheme V

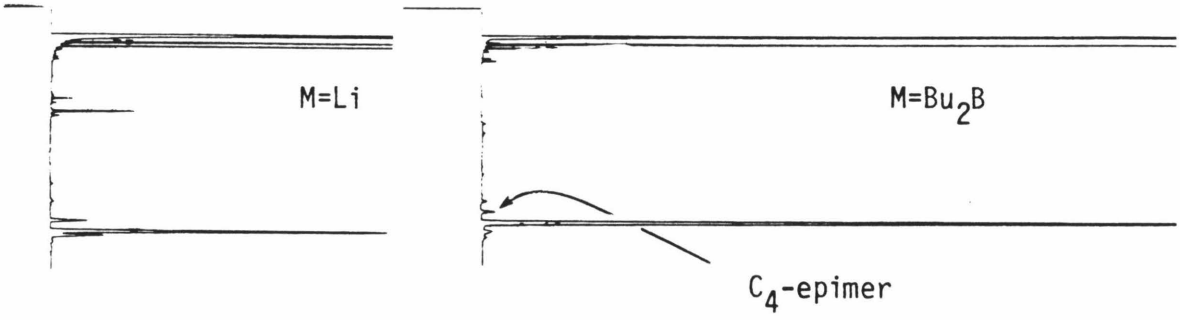


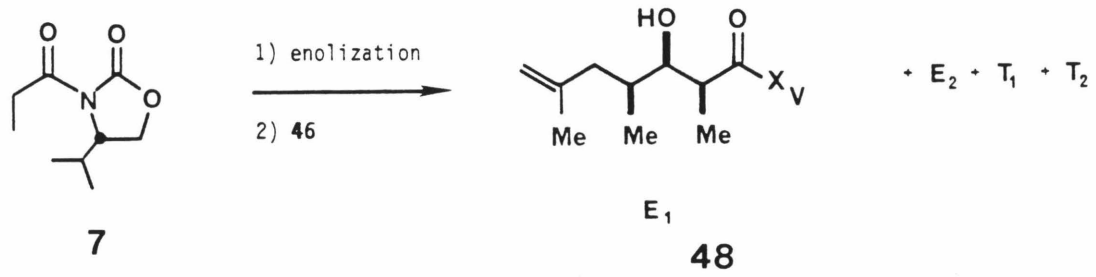


8 E1' 36

Metal	E_1' :	E_2' :	T_1' :	T_2'
BBu_2	99.6	0.15	-	0.25
Li	21.0	1.8	2.5	74.7

Scheme VI





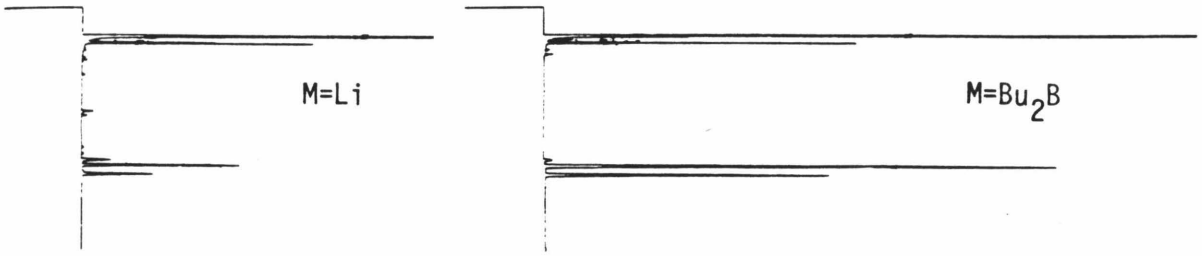
7

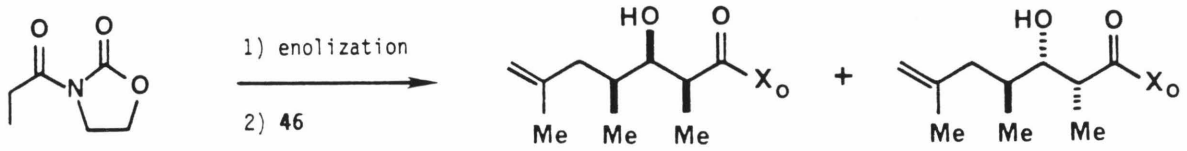
E1

48

Metal	E_1 :	E_2 :	T_1 :	T_2
BBu_2	98.76	0.25	0.67	0.32
Li	7.6	81.6		10.8

Scheme VII



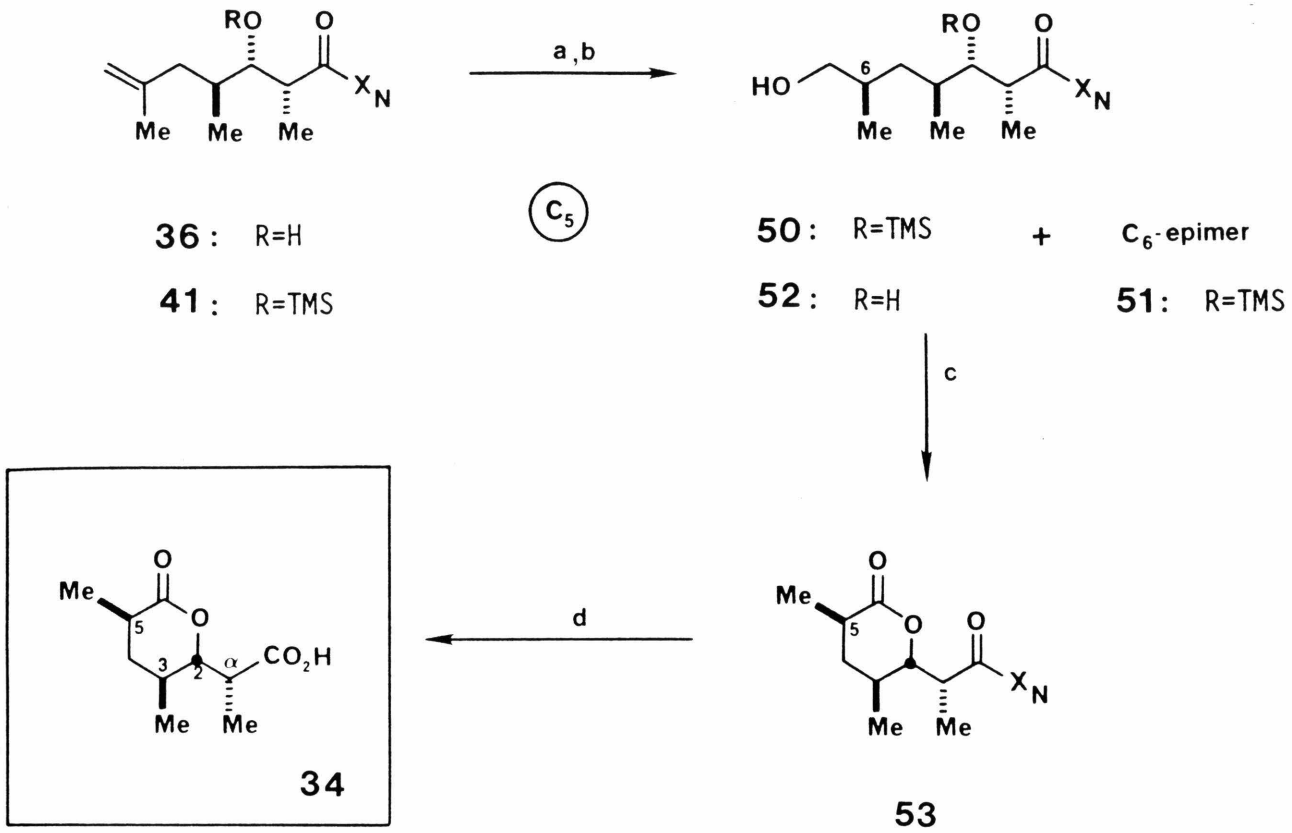


E_1 E_2 + T_1 + T_2

Metal	E_1 :	E_2 :	T_1 :	T_2
BBu_2	35.5	63.4	1.1	-
Li	27.4	57.0	12.6	1.2

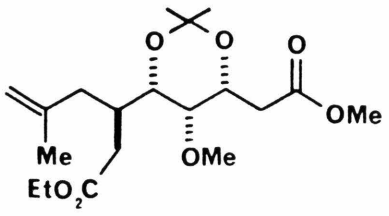
diastereoselection was 99:1, while the enantioselection within the erythro adducts was 395:1. Finally, a third aldol condensation was investigated, this time with the achiral oxazolidinone **6** (Scheme VII). It had previously been shown that the boron enolate of **6** reacts with aldehydes affording erythro adducts with excellent diastereoselection.[30] Therefore, its condensation with **46** was expected to give two erythro products (Cram and anti-Cram) in a ratio reflecting the aldehyde diastereoface selection. Indeed, upon condensation and diastereomer analysis of the silylated, unpurified reaction mixture, two products were obtained in a 64:36 ratio. The mixture was transesterificated ($PhCH_2OLi$, THF) to a 63:37 mixture of benzyl esters and compared with the benzyl ester derived from **36.** GC analysis indicated that the major isomer was the one corresponding to the anti-Cram addition. Although the Cram adducts usually predominate in the aldol condensation between achiral enolates and chiral aldehydes, reversed selectivity has also been noticed in some special cases.[31] In these systems, secondary effects must be taking place and the product ratio is somewhat unpredictable. In summary, these experiments suggest that in the aldol condensation of chiral boron imide enolates with chiral aldehyde **46**, the diastereoface selection is dictated only by the enolate chirality. Subsequent examples using other chiral aldehydes have extended the generality of this result. Similar conclusions had already been obtained for chiral zirconium amide enolates in our laboratories.[32]

Scheme VIII



(a) $ThxBH_2$; (b) H_2O_2; (c) $R_3N\rightarrow O$, $RuCl_2(PPh_3)_3$; (d) LiOH, MeOH.

The final asymmetric center was created <u>via</u> a hydroboration process (Scheme VIII). Based on an example showing moderate selectivity in the hydroboration of the josamycin synthon **49** with disiamylborane (eq 2),[33] we were not optimistic of obtaining good levels of selection in the hydroboration of olefin **41**.



49

Sia_2BH, 0°C → 2.5:1 mixture (ref. 33) (2)

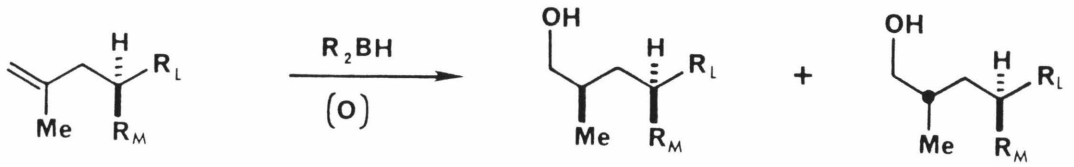
We were surprised to discover, however, that this was not the case. Protection of the aldol adduct **36** ($TMSNEt_2$, DMAP, CH_2Cl_2, 100% yield) followed by treatment with 2 molar equivalents of thexylborane (THF, 0°C, 5 h) and oxidative workup (H_2O_2, MeOH, H_2O, pH 8) afforded, after chromatography, a 79% yield of alcohol **50** and 11% yield of its C_6 epimer, **51**. Gas chromatography analysis of the unpurified, silylated mixture revealed a 85:15 ratio of epimers. The absolute configuration of alcohols **50** and **51** at C_6 was assigned by their individual conversion into Prelog-Djerassi lactone and its C_5-epimer, respectively.[34] A similar 1,3-induction was simultaneously found in the elaboration of the C_1-C_{10} tylosin fragment[1b] (vide infra). This observation led to a series of experiments which will be presented in the second part of this chapter.

The final steps of the synthesis proceeded as follows. Cleavage of the trimethylsilyl ether **50** with oxalic acid (1.1 equiv, MeOH, 25°C, 30 min) proceeded cleanly to afford a 94% yield of unpurified diol **52**. The next step required the selective oxidation of the primary alcohol to form the corresponding δ-lactone. This was best achieved by means of the Sharpless' ruthenium-catalyzed oxidation [35] (4.2 equiv of N-methylmorpholine N-oxide, 1.6% of $RuCl_2(PPh_3)_3$, acetone, 25°C, 4 h) which afforded crystalline lactone **53** in 78% yield after chromatography. Gas chromatography analysis of unpurified lactone **53** confirmed that it was 99% pure, contami-

nated with 1% of its C_5-epimer. Finally, base hydrolysis (aq. 1N LiOH, MeOH, 0°C, 1 h) afforded a 62% yield of oxazolidinone **10**[21] and 70% of (+)-Prelog-Djerassi lactone, **34**. Gas chromatography analysis of the methyl ester (CH_2N_2, CH_2Cl_2) of the unpurified reaction mixture revealed that ca. 2% epimerization at C_5 had occurred.[34] Recrystallization from hot n-pentane:ether afforded **34** as white, amorphous crystals melting at 122-123°C, with a specific rotation of $[\alpha]^{25} = +41.3°$ ($CHCl_3$, c 2.1). GC analysis of its unpurified methyl ester (**54**) (CH_2N_2, CH_2Cl_2) indicated ≥99.9% chemical and diastereomeric purity. A spectral (IR, 90 MHz ^1H NMR, ^{13}C NMR) comparison of (+)-Prelog-Djerassi lactone obtained via the present route and that derived from the Ireland carbohydrate-based total synthesis[11a] established the identity of the two samples.

2. Acyclic 1,3-Asymmetric Induction in the Hydroboration Process[1b]

Based on our preliminary observation concerning the 1,3-induction in the hydroboration process, we decided to initiate a detailed study of the general reaction depicted in equation 3.



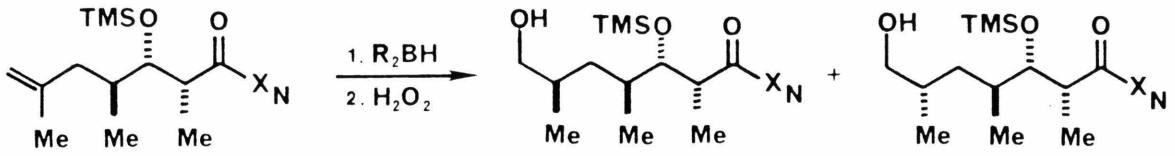
(3)

(R_L sterically larger than R_M)

Although by the time this project was started several cases of 1,2-induction had been reported for similar reactions,[36] very little information concerning the corresponding 1,3-induction was available.[33]

In the course of trying to improve the observed 1,3-induction levels, we initially focused our attention on the structure of the borane. For this purpose, several mono and dialkylboranes were prepared. In an attempt to enhance the observed hydroboration diastereoselection by a cooperative effect of both, the olefin resident chirality and the borane ligand chirality, we also prepared the corresponding (α)-pinene-derived chiral reagents.[37] The results obtained upon reaction of olefin **41** with the different boranes are summarized in Scheme IX. In a typical experiment, the borane (2-4

Scheme IX



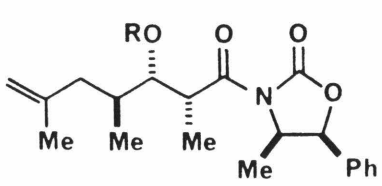
41 **50** **51**

Entry	Solvent	Borane	Ratio (**50**:**51**)
A	THF	BH_3	78:22
B	THF	$(Sia)_2BH$	85:15
C	CH_2Cl_2	$(Sia)_2BH$	85:15
D	THF	Thexyl-BH_2	85:15
E	CH_2Cl_2	$(cyclohexyl)_2BH$	81:19
F	THF	(+)-IPC-BH_2	79:21
G	THF	(-)-IPC-BH_2	83:17
H	Et_2O	(+)-IPC_2BH	79:21
I	Et_2O	(-)-IPC_2BH	82:18

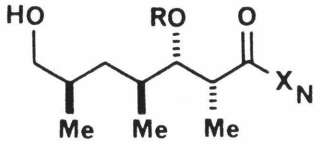
molar equivalents) was added to a solution of olefin **41** in the indicated solvent at 0°C. After 4-6 h, the reaction mixture was oxidized (H_2O_2, MeOH, pH 7-8, 0°C, 1 h) and the unpurified mixture silylated ($TMSNEt_2$, DMAP) and analyzed by GC. Very little influence of the borane structure on the product diastereomeric ratio was observed. Even the use of the chiral mono and dialkylboranes derived from (+) and (-)-α-pinene, effected minimal changes on the reaction diastereoselection.[38] We therefore concluded that the diastereoselection noted in this process is derived almost exclusively from the structure of the olefin.

Our next goal was then, to establish the influence of the structural features of the olefin. A general survey of a number of olefinic substrates (Schemes X and XI) with regard to diastereoselective hydroboration under the previously defined conditions (0°C) reveals several important points. A comparison of olefins **41** and **59** shows that preferential si-facial olefin hydroboration appears to be directed primarily by the proximal center of asymmetry. This result is corroborated by the hydroboration of olefin **61**, which bears only one chiral center. The absolute configurations of the alcohols obtained in these cases were determined by spectral analysis of a meso derivative prepared as shown in Scheme XII. Details for these transformations will be discussed later.

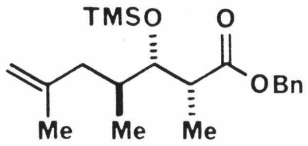
Scheme X



Sia_2BH

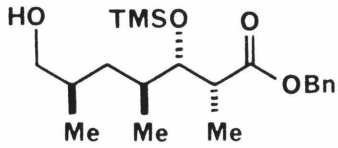


		R:S ratio
36:	R=H	
41:	R=TMS	
55:	R=TES	
52:	R=H	87:13
50:	R=TMS	85:15
56:	R=TES	85:15

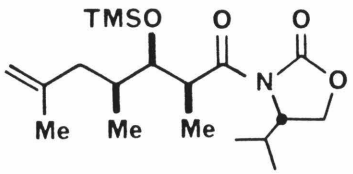


57

Sia_2BH

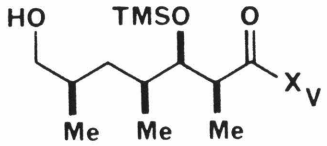


58 87:13

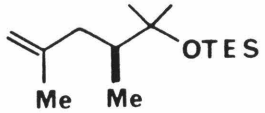


59

Sia_2BH

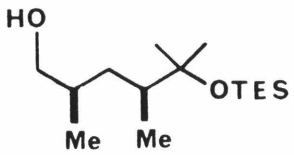


60 77:23



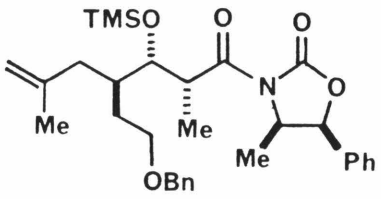
61

Sia_2BH

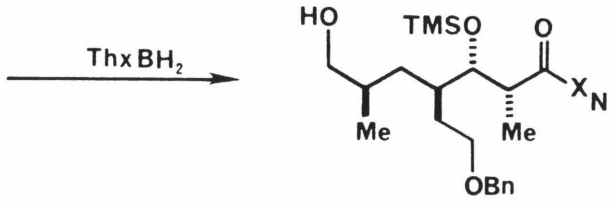


62 82:18

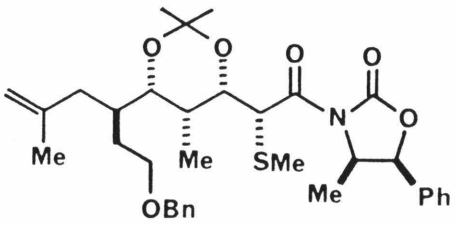
Scheme XI



63



64 75:15 (ref. 40)



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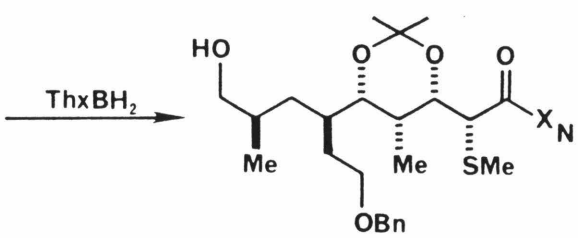
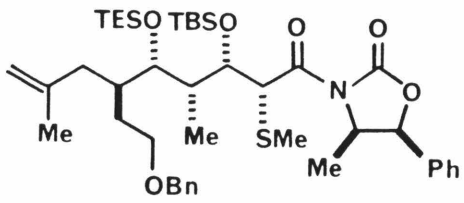


66 60:40 (ref. 40)



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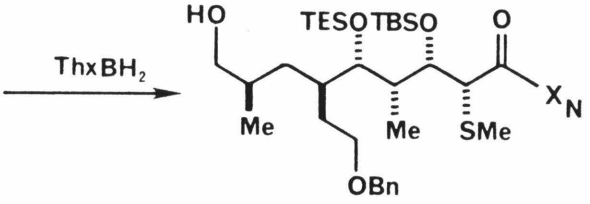
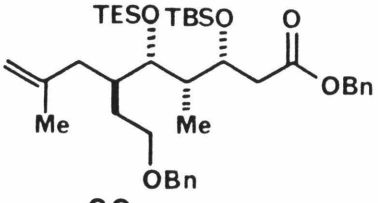
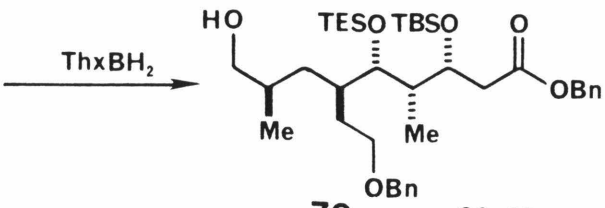


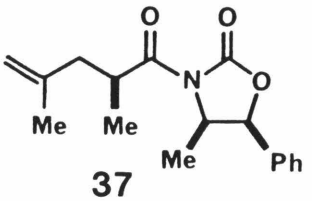
68 91:9



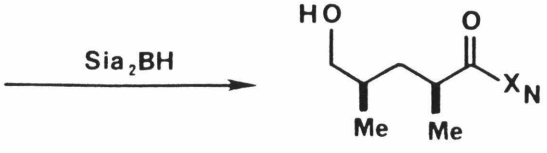
69



70 82:18

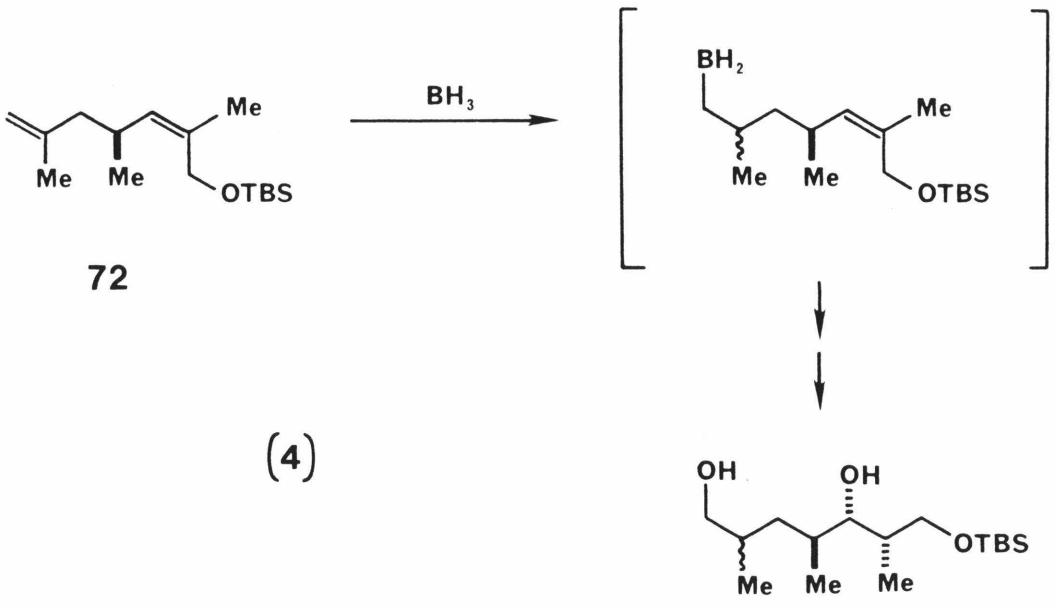


37



71 50:50

The sense of induction observed for the substrates illustrated in Scheme X was maintained in the related olefins **63, 65, 67** and **69** (Scheme XI), where the methyl substituent at C_4 had been substituted by a slightly larger ligand. Interestingly, conformational changes imposed by the presence of a ring seemed to play an important role in the degree of induction (cf **65** vs **67**). Finally, the lack of induction observed for olefin **37** suggested that there is a definite "size requirement" for the ligands on the asymmetric center. In **37**, the trigonal substituent is not large enough to create a diastereofacial bias during hydroboration. A similar non-stereoselective process has been reported for the first step of the hydroboration of diene **72** (eq. 4).[14b]



72

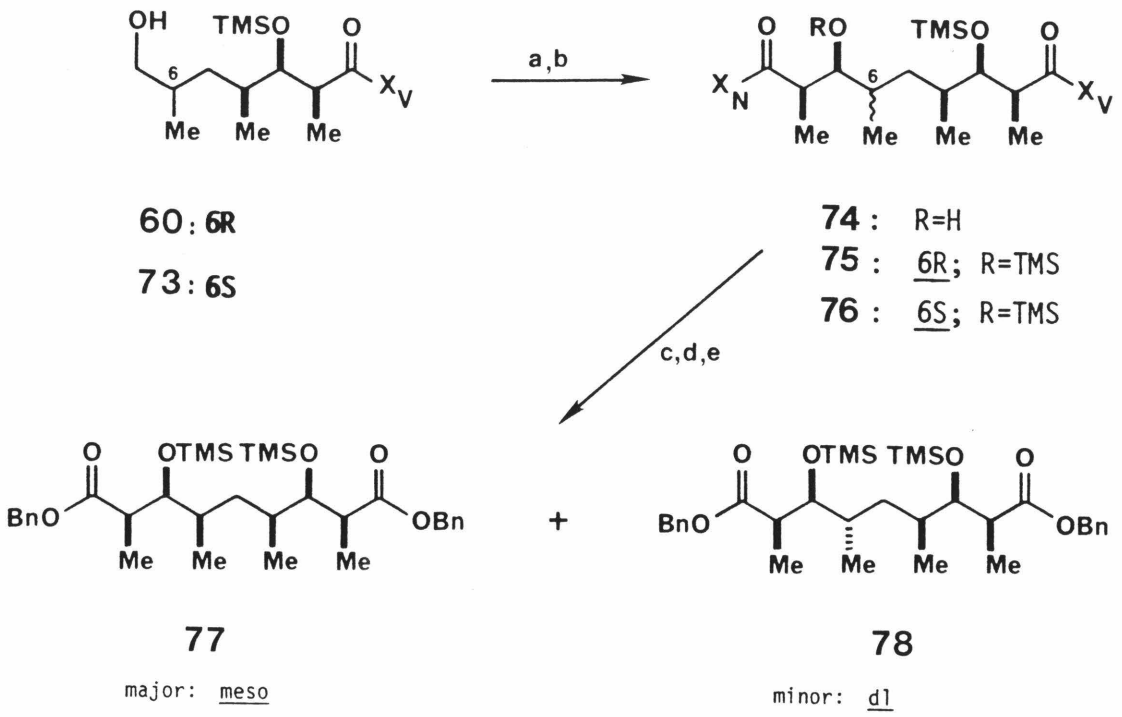
(4)

1:1 mixture

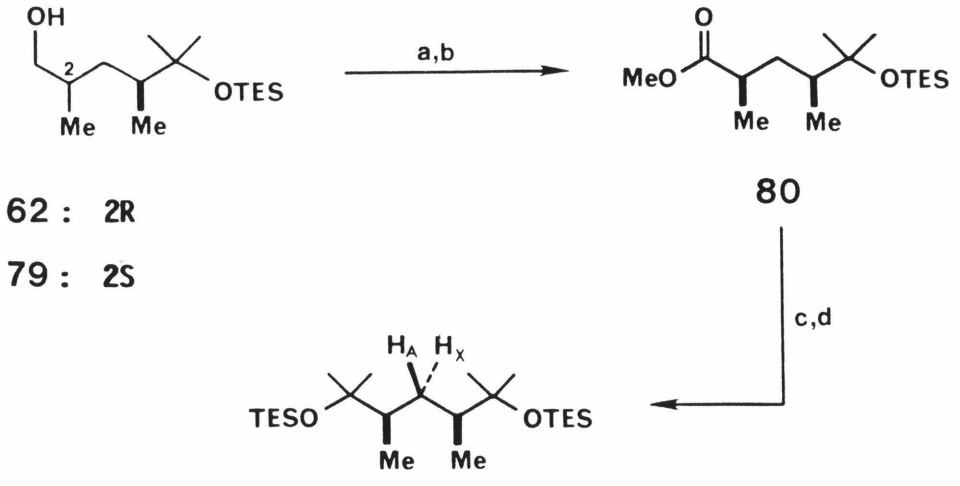
The absolute configuration of the major isomer obtained upon hydroboration of **59** was determined by the NMR spectrum of a derived product (Scheme XII). Thus, the unseparable alcoholic mixture **60** and **73** was converted into the corresponding aldehydic mixture and condensed with the boron enolate of imide **8** following the usual procedure to yield aldol adduct **74** as an unseparable 3:1 mixture (indicated by GC analysis of an unpurified, silylated sample). Silylation ($TMSNEt_2$, DMAP, CH_2Cl_2) afforded a separable mixture of isomers **75** and **76.** Finally, each isomer was transesterified (3 equiv of $PHCH_2OLi$, THF, 0°C) independently and purified by chromatography. Diester **77**, derived from **60**, showed proton and ^{13}C NMR spectra consistent with a meso structure. Diester **78**, derived from alcohol **73**, showed, as expected, more complicated spectra, consistent with the structure lacking a mirror plane.

Similarly, alcohol **62**, the major isomer from the hydroboration of olefin **61**, was converted into methyl ester **80** and treated with methyl magnesium bromide to afford the corresponding tertiary alcohol, which was treated with triethylsilyltriflate to afford **81.** The 500 MHz ^1H NMR spectrum of **81** revealed H_A and H_X to be diastereotopic ($\Delta\delta$ = 1.2 ppm), thus demonstrating the assigned stereochemistry. If the stereochemistry of this final adduct had been (S,S), protons H_A and H_X would have been magnetically equivalent.

Scheme XII



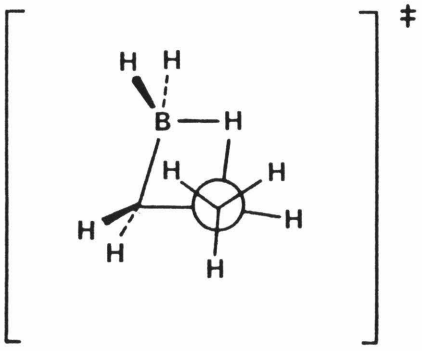
(a) SO_3.py, Et_3N, DMSO; (b) **47** ; (c) $TMSNEt_2$, DMAP; (d) Separate; (e) BnOLi, THF.



(a) MeI, KOH, DMSO; (b) $NaIO_4$, $RuCl_3.H_2O$; (c) MeMgBr; (d) TESOTf, Et_3N.

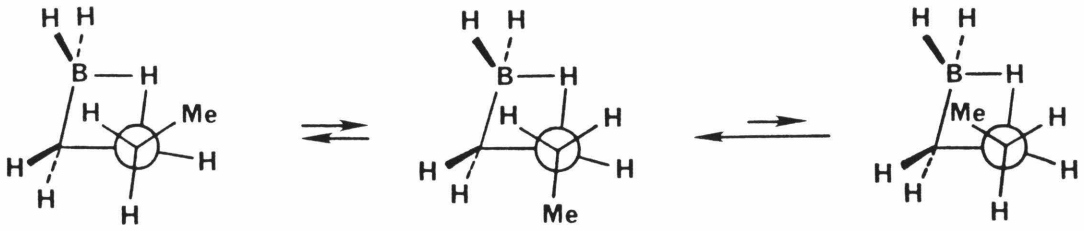
With these experimental data in hand, our next goal was to elaborate a working model capable of accommodating the observed results and, most importantly, able to predict the sense and degree of induction for other related hydroborations. According to Houk's recent ab initio calculations on olefin addition reactions[41] the transition state structure of minimal energy corresponding to the reaction BH_3 + $H_2C{=}CHCH_3$ has the conformation depicted in Fig. 1. This geometry has maximal staggering between the allylic bonds and the partially formed bonds. The rotational energy barrier for the methyl substituent was calculated to be 3 kcal/mol.[41b]

Fig. 1. Optimized (3-21G) Transition Structure[41b] for the Hydroboration of Propene with Borane



This perpendicular model proposed by Houk is comparable to that first suggested by Felkin[42] and then calculated by Anh[43] on the hydride addition to carbonyls. Houk also calculated the differences in energy of the corresponding propene transition states in which each allylic hydrogen, in turn, had been replaced by a standard methyl.[41b] The reported values are shown in Fig. 2.

Fig. 2. STO-3G Relative Energies of Model Transition Structures for Attack of Borane to 1-Butene.



outside anti inside

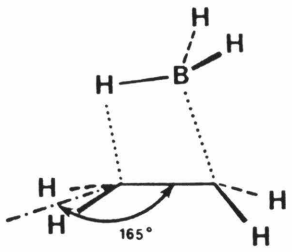
$G_{out.}-G_{anti}$ = 0.56 kcal/mol

$G_{ins.}-G_{anti}$ = 5.41 kcal/mol

Whereas there is only a relatively small energy difference between the "outside" and the "anti" transition states, the "inside" structure is clearly disfavored, due to the non-bonding interactions of the methyl with the approaching borane and the partial double bond.

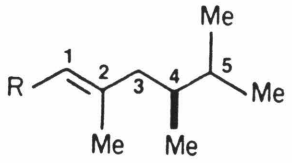
Careful ab initio calculations carried out by Morokuma[44] have shown that in the transition state corresponding to the C_2H_4 + BH_3 reaction, the carbon to which the borane hydrogen is delivered has suffered very little pyramidalization. The reported optimized geometry is depicted in Fig. 3.

Fig. 3. Optimized Geometry (4-31G SCF) for the Transition State Corresponding to the Reaction of Ethylene with Borane.[44]

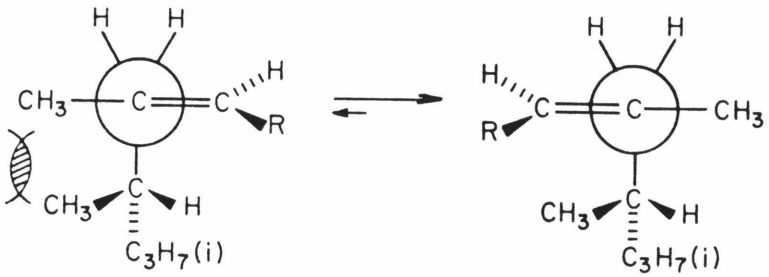


Finally, simple MM2 calculations performed on the ground state of compound **82** (Scheme XIII) indicated that conformer **B** (R=H) is 1.05 kcal/mol more stable than conformer **A** (R=H).[45] We believe that

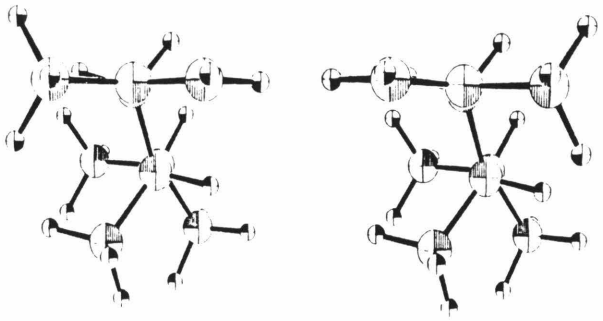
Scheme XIII



82: R=H
83: R=Me



A **B**



A **B**

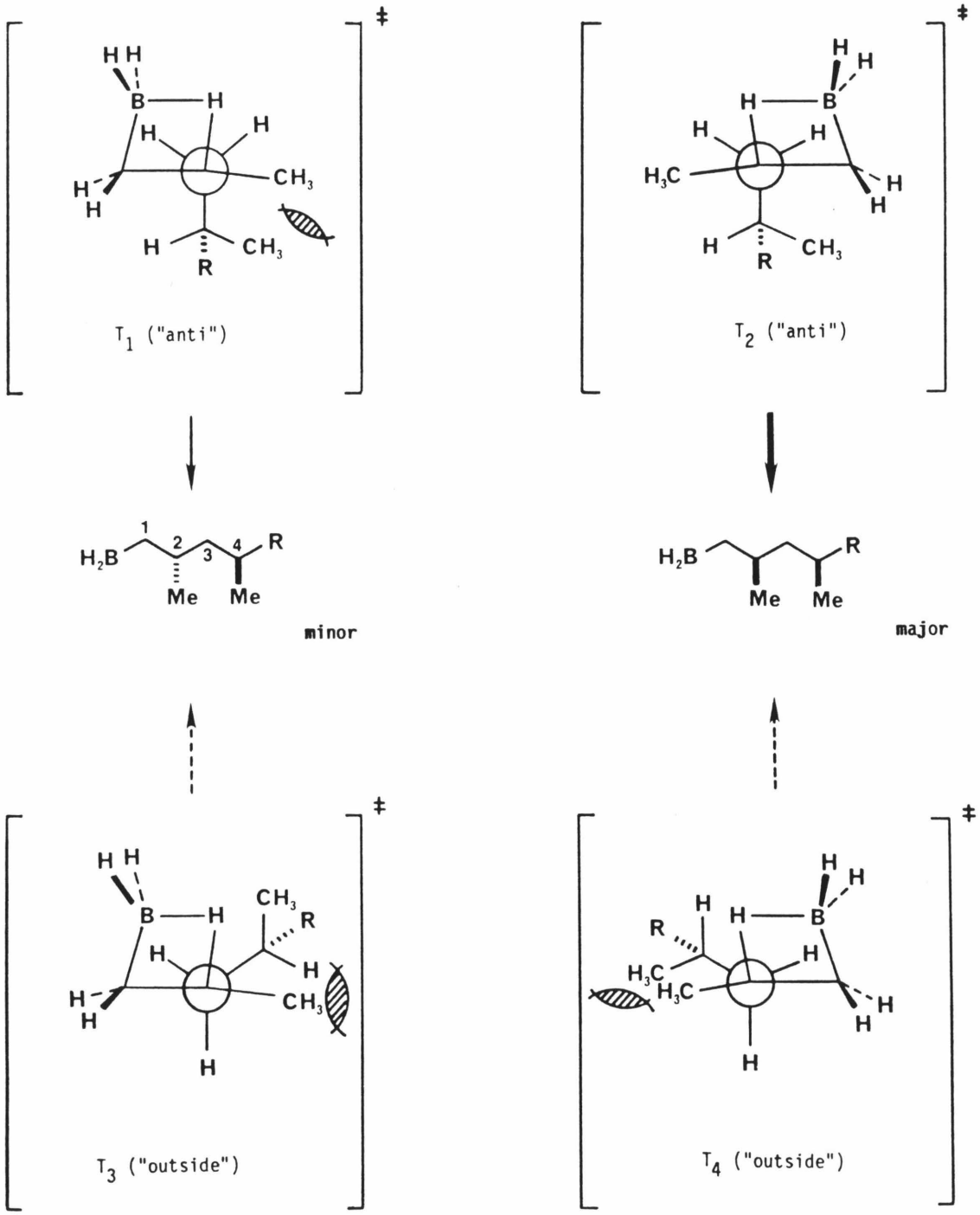
this energy difference arises from the nonbonding $CH_3 \leftrightarrow CH_3$ interaction present in conformer **A**, but absent in **B**. The geometries were optimized for all substituents with the exception of the C_4-C_5 bond (i.e., the isopropyl substituent).

Based on this result, and on the theoretical background presented above, we can consider four possible transition states that would account for the observed induction: two of them would

belong to the Houk's "anti" type ($T_1^{\ddagger}$ and $T_2^{\ddagger}$) and two other to the "outside" type ($T_3^{\ddagger}$ and $T_4^{\ddagger}$)(Scheme XIV). Because of their anticipated higher energy, we disregarded the two corresponding "inside" transition structures (not illustrated). If we make the assumption that the low degree of pyramidalization calculated by Morokuma for the hydroboration transition state of ethylene applies to our system, we can draw two conclusions: first, the isopropyl$\leftrightarrow$methyl interaction in the "outside" structures will be more important than in the "anti" structures, thereby increasing their relative energy. Second, this interaction will be of comparable magnitude in both the ground and the transition states. Thus, the obtained 1.05 kcal/mol energy difference for the two ground state conformers **A** and **B** (Scheme XIII) should be very similar to that of the transition states $T_1^{\ddagger}$ and $T_2^{\ddagger}$. Interestingly, a difference in energy of 1.05 kcal/mol corresponds, at 0°C, to an equilibrium mixture of 87:13, which is in very good agreement with the observed product distribution.

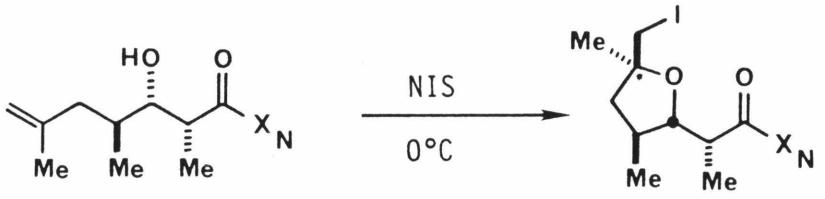
In summary, we propose a transition state for this reaction in which the borane reagent bears an <u>anti</u> relationship with the allylic substituent, in full accord with the theoretical studies of Houk. The diastereofacial bias would then be created when the largest C_4 substituent (R_L) adopts the <u>anti</u>-conformation. In this orientation, we propose that the destabilizing feature which disfavors

Scheme XIV



transition state $T_1^{\ddagger}$ is the C_2-methyl$\leftrightarrow$$C_4$-methyl nonbonding interaction. Based on Morokuma's calculations of the hydroboration transition geometries, we propose that this interaction is very close in magnitude to that of the ground state.

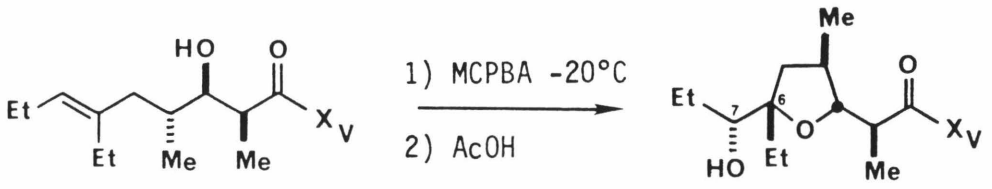
Similar arguments might also apply to other olefin electrophilic additions. For example, when olefin **36** was treated with 1.5 equiv of N-iodosuccinimide ($CHCl_3$, 0°C, 30 min) , an 83:17 mixture of tetrahydrofuranes was obtained (eq. 5) (the absolute configuration of the new center was not proved).



(5)

83:17

In more recent work, a related 1,3-induction has been observed upon epoxidation of a related olefin using MCPBA (eq. 6).[22] This result agrees with the related MM2 calculations performed on olefin **83** (Scheme XIII), which predicted a ΔG = 1.1 kcal/mol for the ground state conformers.



(6)

36

(6S,7R):(6R,7S) = 77:23 (ref. 22)

III. Summary

The total synthesis of (+)-Prelog-Djerassi lactone has been described. The stereocenters C_α, C_2 and C_3 are introduced in an absolute fashion by means of an alkylation and an aldol reaction using chiral oxazolidinone **8**. The remaining center, C_5, is created via a hydroboration reaction. The synthesis consists of 9 steps from **8**, and proceeds with an overall yield of 13%. A study on the factors that regulate the 1,3-induction observed in the mentioned hydroboration process has been also undertaken. The sense and degree of induction is dictated by the size requirements of the substituents at the homoallylic position.

Experimental Section

General. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4210 spectrophotometer. 90 MHz ^{1}H NMR spectra were recorded on a Varian Associates EM-390 spectrometer and are reported in ppm on the δ scale, from the indicated reference. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), coupling constant (in Hz), integration and interpretation. 500 MHz ^{1}H NMR spectra were recorded on a Bruker WM-500 spectrometer at the Southern California Regional NMR facility. ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz) spectrometer and are reported in ppm on the δ scale from the indicated reference. Combustion analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, Michigan), Galbraith Laboratories, Inc. (Knoxville, Tennessee), or Mr. Lawrence Henling (California Institute of Technology). Optical rotations were recorded on a Jasco DIP-181 digital polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^{25}$, solvent, and concentration (c = g/100 ml).

Analytical gas-liquid chromatography (GC) was carried out on a Hewlett Packard 5880 A level 3 gas chromatograph equipped with a split mode capillary injection system and a flame ionization detector, using a 25 m x 0.2 mm flexible fused silica capillary

column wall-coated with Carbowax 20 M or Methyl Silicone (SP-2100), or a 30 m x 0.32 mm fused silica capillary wall-coated with SE-54. Unless otherwise noted, injector and detector temperatures were 250°C. Data are reported as follows: column type, oven temperature, and retention time (t_r).

Liquid chromatography was performed using a forced flow (flash-chromatography) of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). Data are reported as follows: column diameter, weight of silica and eluent composition. Medium pressure liquid chromatography (MPLC) was carried out using EM Reagents LoBar Silica Gel 60 prepacked columns (column size indicated) on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP-SY Lab Pump. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates.

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, benzene and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, diisopropylethylamine, diisopropylamine, triethylamine and boron trifluoride etherate were distilled from calcium hydride. Dimethyl sulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over activated 4 Å molecular sieves.

Unless otherwise specified, all non-aqueous reactions were conducted under a rigorously dried argon atmosphere, using oven-dried glassware.

(3(S),4R,5S)-3-(2,4-Dimethyl-1-oxo-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (37). To a stirred, cooled (-78°C) solution of freshly distilled diisopropylamine (3.0 mL, 21.5 mmol, 1.075 equiv) in anhydrous tetrahydrofuran (45 mL) was added a 1.57 M solution of n-butyllithium in hexane (13.5 mL, 21.2 mmol, 1.06 equiv). After 30 min a solution containing imide **8** in 5 mL of anhydrous tetrahydrofuran was added dropwise, resulting in a pale yellow coloration. After stirring for 30 min, methallyl iodide[23,24] (4.5 mL, 40 mmol, 2 equiv, neat) was added dropwise and the mixture stirred subsequently 1 h at -78°C, 2 h at -40°C and 15 min at -20°C. The reaction was quenched by the quick addition of saturated aqueous ammonium chloride. The volatiles were removed in vacuo and the resulting aqueous solution was extracted with dichloromethane (3 x 75 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to 6.75 g of a yellowish oil. Gas chromatography analysis (SE-54, T = 175°C, 15 PSI, t_r **37** = 8.24 min, t_r 2-epi-**37** = 8.94 min) afforded a ratio of **37**:2-epi **37** = 96.3:3.7. Chromatography on silica gel (MPLC, Merck Lobar C column, 5% ethyl acetate:hexane) of 6.19 g of

the unpurified reaction mixture afforded 4.21 g (73%) of the title compound as a white solid. Diastereomer analysis showed **37** to be >99% pure: R_f 0.52 (50% ethyl acetate:hexane); mp 42-44°C; IR (CH_2Cl_2) 3062, 2998, 1780, 1700, 1342, 1195, 1120, 890 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.35 (m, 5H, aromatic H), 5.60 (d, J = 7.5, 1H, -NCHCHO), 4.90-4.55 (m, 3H, -NCHCHO, H_2C=), 4.00 (sextuplet, J = 7.0, 1H, O=CCH-), 2.52 (d of d, J = 7.0, J = 14.0, 1H, O=CCHCH(H)), 2.04 (d of d, J = 7.8, J = 14, 1H, O=CCHCH(H)), 1.75 (s, 3H, =CCH_3), 1.14 (d, J = 7.0, 3H, O=CCHCH_3), 0.84 (d, J = 7.5, 3H, -NCHCH_3); ^{13}C NMR ($CDCl_3$) δ (TMS) 176.70, 152.72, 142.91, 133.42, 128.67, 125.62, 112.30, 78.70, 54.85, 41.66, 35.61, 22.29, 16.77, 14.49; $[\alpha]_D^{25}$ = +33.7° (CH_2Cl_2, c 5.9).

Anal. calcd. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.94; H, 7.26; N, 4.76.

(S)-2,4-Dimethyl-4-penten-1-ol (45). To a cooled (0°C), well stirred suspension of lithium aluminum hydride (2.23 g, 58.8 mmol, 1 molar equiv) in 120 mL of anhydrous diethyl ether was added dropwise a solution of imide **37** (16.91 g, 58.8 mmol) in dry ether (25 mL). The ice bath was removed and the mixture let warm to ambient temperature. After 30 min, the reaction was quenched by the subsequent cautious addition of water (2.2 mL), 15% aqueous sodium hydroxide (2.2 mL) and water (6.6 mL). The mixture was filtered and the filtrate washed with brine, dried over anhydrous magnesium

sulfate, and filtered. Diethyl ether was removed by fractional distillation. Molecular distillation of the remaining oil (Kügelrohr, 73°C, 18 mm) afforded 5.10 g of product as a colorless liquid. The non-distilled residue was dissolved in warm ether and the oxazolidinone **10** was partially precipitated by addition of petroleum ether. Filtration followed by concentration and distillation as above gave an additional 568 mg of product (85% combined yield): R_f 0.44 (50% ethyl acetate:hexane); IR ($CHCl_3$) 3645, 3600-3200, 3090, 2940, 1649, 1453, 1375, 1123, 893 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 4.75 (s, 1H, $\underline{H}$(H)C=), 4.71 (s, 1H, H($\underline{H}$)C=), 3.50 (m, 1H, HOC$\underline{H}$(H)), 3.42 (m, 1H, HOCH($\underline{H}$)), 2.64 (br s, 1H, $\underline{HO}$), 2.20-2.07 (m, 1H, $HOCH_2\underline{CH}$-), 1.92-1.74 (m, 2H, $HOCH_2CH\underline{CH_2}$), 1.72 (s, 3H, $\underline{H_3}CC$=), 0.90 (d, J = 6.5, 3H, $\underline{H_3}CCH$-); ^{13}C NMR ($CDCl_3$) δ (TMS) 144.34, 111.71, 67.98, 42.24, 33.60, 22.22, 16.57; $[\alpha]_D^{25}$ = -3.9° (CH_2Cl_2, c 4.1).

Anal. calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.58; H, 12.10.

(S)-2,4-Dimethyl-4-pentenal (46). To a stirred solution containing alcohol **45** (2.66 g, 23.3 mmol), and freshly distilled triethylamine (22.7 mL, 163 mmol, 7 equiv) in 50 mL of dry dimethyl sulfoxide at 25°C, was slowly added (5 min) a solution of sulfur trioxide pyridine complex (11.11 g, 69.6 mmol, 3 equiv, Aldrich, 95% pure) in 50 mL of dry dimethyl sulfoxide. After 15 min, a mixture

of diethyl ether (250 mL) and water (150 mL) was carefully added. The mixture was transferred to a separation funnel, and the aqueous layer discarded. The remaining cloudy, ethereal layer was washed with saturated aqueous cupric sulfate (2 x 50 mL), and water (1 x 25 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated by the fractional distillation of ether. Molecular distillation of the remaining liquid (Kügelrohr, 90°C, 140 mm) afforded 2.21 g (87%) of aldehyde **46**: R_f 0.66 (50% ethyl acetate: hexane); IR ($CHCl_3$) 2985, 2955, 1715, 1460, 1383, 1235 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 9.64 (d, J = 2, 1H,-C<u>H</u>O), 4.80 (br s, 1H, (H)C<u>H</u>=), 4.71 (br s, 1H, (<u>H</u>)CH=), 2.65-1.80 (m, 3H, C<u>H</u>$_2$C<u>H</u>-), 1.72 (s, 3H, <u>H</u>$_3$CC=), 1.05 (d, J = 6.5, 3H, <u>H</u>$_3$CCH-).

(3(2R,3S,4S),4R,5S)-3-(3-Hydroxy-2,4,6-trimethyl-1-oxo-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (36). To a cooled (-78°C) solution of imide **8** (1.75 g, 7.5 mmol) in 20 mL of anhydrous dichloromethane was added di-<u>n</u>-butylboryl triflate (2.02 mL, 8.25 mmol, 1.1 equiv). The dry ice bath was removed temporarily until the frozen triflate melted. After recooling the solution to -78°C, freshly distilled triethylamine (1.25 mL, 9 mmol, 1.2 equiv) was added dropwise. After 1 h, aldehyde **46** (0.98 mL, 7.5 mmol, 1 equiv, neat) was added in one portion. The solution was stirred 30 min at -78°C, 1 h at 0°C, and then quenched by the addition of 7 mL of aqueous phosphate pH 7 buffer solution. Enough methanol was added

to make the solution homogeneous. Then, a solution containing 7 mL of 30% aqueous hydrogen peroxide in 7 mL of methanol was slowly added and the mixture stirred at 0°C for 1 h. Volatiles were removed in vacuo and the remaining aqueous slurry was extracted with diethyl ether (2 x 100 mL). The combined ethereal layers were washed with 5% aqueous sodium bicarbonate, and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to a white solid (2.55 g). Diastereomer analysis (SE-54, T = 225°C, 5 PSI, t_r **E**$_2$ = 7.02 min, t_r **E**$_1$ = 7.35 min, t_r 4-epi-**E**$_1$ = 7.60 min, t_r **T**$_2$ = 8.53 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 6 h) afforded a ratio **E**$_2$:**E**$_1$:4-epi-**E**$_1$:**T**$_1$:**T**$_2$ of 0.15:99.12:0.50:$\leq$0.1:0.22. The presence of 0.5% of 4-epi-**E**$_1$ was due to the fact that in this particular run, aldehyde **46** was obtained from a 99.5:0.5 epimeric mixture of oxazolidinone **37**. A portion of the product (2.383 g) was chromatographed on silica gel (MPLC, Merck Lobar C col., 20%$\rightarrow$30% ethyl acetate:hexane) to afford 2.093 g (86%) of pure imide **36** as white crystals: R_f 0.41 (50% ethyl acetate:hexane); mp 110-111°C; IR (CH_2Cl_2) 3695, 3550, 3060, 2980, 1785, 1685, 1346, 1198, 892 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.15 (m, 5H, aromatic H), 5.65 (d, J = 7, 1H, -NCHCHO), 4.95-4.60 (m, 3H, -NCHCHO, H_2C=C-), 3.98 (q of d, J_d = 2.5, J_q = 7.3, 1H, O=CCH-), 3.62 (d of d, J = 2.5, J = 8.0, 1H, HOCH-), 3.00 (br, 1H, HO-), 2.57 (br q, J = 9, 1H, H_2C=CCH(H)), 2.10-1.5 (m, 2H, H_2C=CCH(H)CH-), 1.73 (s, 3H, H_3CC=), 1.24 (d, J = 7.3, 3H, CH_3CH-),

0.90 (d, J = 7, 3H, $=\overset{|}{C}CH_2\overset{|}{C}H\underline{C}H_3$), 0.87 (d, J = 7, 3H, $-\overset{|}{N}\overset{|}{C}H\underline{C}H_3$); ^{13}C NMR (CCl_4) δ (CCl_4) 176.84, 151.56, 144.09, 133.56, 128.43, 125.44, 111.86, 78.39, 75.27 (carbinol), 54.34, 41.61, 39.72, 33.74, 22.24, 14.96, 14.18, 9.37; $[\alpha]_D^{25}$ = +17.0° (CH_2Cl_2, c 2.6).

Anal. calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.36; H, 7.75; N, 3.93.

(3(2R,3S,4S,6R),4R,5S)-3-(7-Hydroxy-2,4,6-trimethyl-1-oxo-3-((trimethylsilyl)oxy)heptyl)-4-methyl-5-phenyl-2-oxazolidinone (50), and the corresponding (3(2R,3S,4S,6S),4R,5S)-Isomer, (51). To a stirred solution of aldol adduct **36** (345.5 mg, 1 mmol) in 5 mL of anhydrous dichloromethane was added N,N-diethyltrimethylsilylamine (0.94 mL, 5 mmol, 5 equiv) and N,N-dimethyl-4-aminopyridine (45 mg, 0.36 equiv). The reaction mixture was stirred for 30 min at 25°C. The volatiles were removed in vacuo and the remaining yellow oil was chromatographed on silica gel (30 mm, 40 g silica, 10% ethyl acetate:hexane) to afford 417 mg (100%) of silylated product **41** as a pale slightly yellow oil: R_f 0.50 (30% ethyl acetate:hexane).

Anal. calcd. for $C_{23}H_{35}NO_4Si$: C, 66.15; H, 8.45. Found: C, 66.18; H, 8.46.

In another flask was placed a 1 M solution of borane tetrahydrofuran complex (2 mL, 2 mmol, Aldrich), and cooled to -15°C. A solution containing 2,3-dimethyl-2-butene (0.23 mL, 2 mmol) in 1 mL of anhydrous tetrahydrofuran was added dropwise (10 min) and the clear mixture stirred at 0°C for 2 h.

An aliquot (1.6 mL, ca. 2 molar equiv) was added to a cooled (0°C) solution containing the silylated aldol adduct **41** (210 mg, 0.503 mmol) in anhydrous tetrahydrofuran (2 mL). After stirring at 0°C for 5 h, 5% aqueous sodium bicarbonate (2 mL) was added, followed by methanol (10 mL) and 30% aqueous hydrogen peroxide (2 mL). The white slurry was stirred at 0°C for 1 h. Extraction with diethyl ether (3 x 50 mL) and concentration in vacuo afforded an aqueous solution which was extracted (2 x 50 mL) with diethyl ether. The combined ethereal layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. Diastereomer analysis (SE-54, T = 225°C, 13 PSI, t_r **50** = 4.82 min, t_r **51** = 5.17 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 15 min) afforded a **50**:**51** ratio of 84:16. Flash chromatography (20 mm, 25 g, 18% ethyl acetate:hexane) afforded 173.0 mg (79%) of the major isomer, **50**, (99.8% diastereomerically pure), and 24.8 mg (11%) of the minor isomer, **51**, (99% diastereomerically pure), both as colorless oils.

50: R_f 0.29 (30% ethyl acetate:hexane); IR (CH_2Cl_2) 3615, 3060, 2965, 2922, 1779, 1690, 1454, 1345, 1198, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.50-7.25 (m, 5H, aromatic H), 5.68 (d, J = 6.8, 1H, -NCHCHO), 4.71 (qn, J = 6.8, 1H, -NCHCHO), 4.05 (qn, J = 7.2, 1H, O=CCH-), 3.90 (d of d, J = 3.5, J = 7.2, 1H, O=CCHCH-), 3.52-3.42 (m, 2H, $HOCH_2$), 1.83-1.50 (m, 5H, HO-, -CHCH$_2$CH-), 1.21 (d, J = 6.8, 3H, O=CCHCH_3), 0.960 (d, J = 6.5, 3H, CH_3CH-), 0.947

(d, J = 6.3, 3H, $C\underline{H}_3CH$-), 0.87 (d, J = 6.8, 3H, -NCHC$\underline{H}_3$), 0.16 (s, 9H, $(C\underline{H}_3)_3Si$-); $[\alpha]_D^{25}$ = -20.6° (CH_2Cl_2, c 5.0).

Anal. calcd. for $C_{23}H_{37}NO_5Si$: C, 63.41; H, 8.56. Found: C, 63.35; H, 8.67.

51: R_f 0.24 (30% ethyl acetate:hexane); IR (CH_2Cl_2) 3670, 3600, 2945, 1768, 1685, 1331, 1183, 840 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.55-7.15 (m, 5H, aromatic H), 5.60 (d, J = 6.5, 1H, -NC$\underline{H}$CHO), 4.72 (qn, J = 6.5, 1H, -NCHC$\underline{H}$O), 4.20-4.75 (m, 2H, O=CC$\underline{H}$C$\underline{H}$-), 3.43 (d, J = 6.3, 2H, HOC$\underline{H}_2$), 1.9-1.4 (m, 4H, -C$\underline{H}$C$\underline{H}_2$C$\underline{H}$-), 1.22 (d, J = 6.0, 3H, O=CCHC$\underline{H}_3$), 1.07-0.7 (m, 9H, $C\underline{H}_3CH$-, $C\underline{H}_3CH$-, $C\underline{H}_3CH$-), 0.17 (s, 9H, $(C\underline{H}_3)_3Si$-); $[\alpha]_D^{25}$ = -21.3° (CH_2Cl_2, c 3.5).

Anal. calcd. for $C_{23}H_{37}NO_5Si$: C, 63.41; H, 8.56. Found: C, 63.60; H, 8.42.

(3(R(2S,3S,5R)),4R,5S)-4-Methyl-3-(1-oxo-2-(tetrahydro-3,5-dimethyl-6-oxo-2H-pyran-2-yl)propyl)-5-phenyl-2-oxazolidinone (53). To a well stirred solution of alcohol **50** (234.0 mg, 0.537 mmol) in dry methanol (5 mL) was added oxalic acid (53 mg, 0.59 mmol, 1.1 equiv). After 30 min, the reaction was quenched by the addition of aqueous phosphate buffer solution. The volatiles were removed in vacuo and the remaining aqueous solution was extracted with diethyl ether (4 x 25 mL). The combined ethereal layers were dried over anhydrous magnesium sulfate, filtered and concentrated to afford 182.8 mg (94%) of pure diol **52** as a very thick oil: R_f 0.20

(50% ethyl acetate:hexane); $[\alpha]^{25}$ = +15.3° (CH_2Cl_2, c 4.5).

Anal. calcd. for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04. Found: C, 65.94; H, 8.05.

To a solution of diol **52** (181.4 mg, 0.50 mmol) in dry acetone (8 mL, previously distilled and stored under drierite) was added anhydrous N-methylmorpholine-N-oxide (245 mg, 2.09 mmol, 4.2 equiv) followed by a catalytic amount of tris-triphenylphosphinedichloro-ruthenium complex (8 mg, 8.3 μmol, 1.6% equiv, Strem. Chem. Inc.),[35] resulting in a yellow solution that turned dark brown after 10 min. The reaction mixture was stirred for 4 h, concentrated in vacuo and purified by flash chromatography (30 mm, 40 g silica, 25% ethyl acetate:hexane) to afford 142.1 mg (78%) of compound **53** as a colorless foam, which crystallized on standing. Diastereomer analysis (SE-54, 225°C, 13 PSI, t_r = 5.29 min) indicated **53** to be ≥ 99.3% one diastereomer: R_f 0.29 (30% ethyl acetate:hexane); mp 123.5-124.5°C; IR (CH_2Cl_2) 3065, 2980, 2950, 1780, 1730 (br), 1457, 1348, 1200 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.6-7.2 (m, 5H, aromatic H), 5.68 (d, J = 6.5, 1H, -NCHCHO), 4.64 (qn, J = 7.0, 1H, -NCHCHO), 4.39 (d of d, J = 3.0, J = 10.0, 1H, O=CCHCHO-), 4.25-3.85 (m, 1H, O=CCHCHO-), 2.50 (sextuplet, J = 6.5, 1H, H_3CCHCO_2-), 2.2-1.4 (m, 3H, -OCHCHCH$_2$), 1.28 (d, J = 6.5, 3H, H_3CCH-), 1.21 (d, J = 6.5, 3H, H_3CCH-), 1.09 (d, J = 6.0, 3H, H_3CCH-), 0.93 (d, J = 6.5, 3H, -NCHCH$_3$). ^{13}C NMR (CCl_4) δ (CCl_4) 172.81, 172.50, 152.54, 134.60, 128.17, 127.65, 125.57, 85.08 (carbinol), 78.58, 54.86,

39.91, 37.31, 36.28, 31.21, 16.52, 16.25, 13.92, 8.01; $[\alpha]_D^{25}$ = +51.5° (CH_2Cl_2, c 6.2).

Anal. calcd. for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01. Found: C, 66.78; H, 6.99.

(2S(R),3S,5R)-Tetrahydro-α,3,5-trimethyl-6-oxo-2H-pyran-2-acetic acid (34). Imide **53** (78.7 mg, 0.219 mmol) in 5 mL of methanol, at -12°C, was treated with cold (0°C), 1 N aqueous lithium hydroxide (1 mL, 1 mmol). The mixture was stirred between -12°C and 0°C for 1 h, concentrated in vacuo and extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford 24 mg (62%) of norephedrine oxazolidinone **10.** The alkaline aqueous phase was acidified to pH 1 with aqueous 10% hydrochloric acid, saturated with sodium chloride and extracted with diethyl ether (4 x 30 mL). The combined ethereal extracts were dried over anhydrous sodium sulfate, filtered and concentrated to 44.0 mg of an oil. A portion (4 mg) was esterified with diazomethane in dichloromethane and analyzed by GC. Diastereomer analysis (SE-54, T = 120°C, 10 PSI, t_r 5-epi-**54** = 5.53 min, t_r **54** = 5.76 min) of the unpurified methyl ester afforded a 5-epi-**54**:**54** ratio of 4.3:95.7. The remaining acid (40 mg) was purified by chromatography on acidic silica gel (10 mm, 7 g of "Silicar CC-4 special" Mallinckrodt, 2:1 ether:pet. ether) to afford 30.4 mg (70%) of Prelog-Djerassi lactone

34 as white crystals. A portion (28.3 mg) was recrystallized from ether:pet. ether to yield 21 mg of white crystals, as a 0.7:99.3 mixture of epimers at C_5, as indicated by diastereomeric analysis of the methyl ester (same conditions): mp 122-123°C (a sample generously provided by Dr. Ireland had a mp 122-122.5°C) (lit. mp 123.5°C,[11c] mp 123.5-125°C,[10c] mp 123-125°C,[17b] 123.5-125°C,[11a] 124-125°C[16b]); IR (CH_2Cl_2) 3685, 3025, 1725, 1458, 1382, 1205, 907 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 9.0-8.5 (br, 1H,-$CO_2\underline{H}$), 4.62 (d of d, J = 2.0, J = 10.8, 1H, C_2-H), 2.78 (q of d, J_d = 2.0, J_q = 7.0, 1H, α-H), 2.53 (q of d of d, J_d = 6.3, J_q = 7.0, J_d = 12.5, 1H, C_5-H), 2.0-1.9 (m, 2H, C_3-H, C_4-Heq), 1.32 (q, J = 13, 1H, C_4-Hax), 1.30 (d, J = 7.0, 3H, α-CH_3), 1.22 (d, J = 6.9, 3H, C_5-CH_3), 1.01 (d, J = 6.7, 3H, C_3-CH_3); ^{13}C NMR ($CDCl_3$) δ (TMS) 177.62, 174.75, 86.43, 41.07, 37.17, 36.20, 30.87, 17.22, 16.90, 8.38; $[\alpha]_D^{25}$ = +41.3° ($CHCl_3$, c 2.1) (lit. $[\alpha]_D^{21}$ = +47.7° ($CHCl_3$, c 1.93),[11a] $[\alpha]_D$ = +38.6° (c 1.92),[11c] $[\alpha]_D^{25}$ = +47.5° ($CHCl_3$, c 1.10),[9b] $[\alpha]_D^{25}$ = +38.7° (c 1.90),[10c] $[\alpha]_D^{23}$ = +31.2° ($CDCl_3$, c 0.88).[16b] From resolution: $[\alpha]_D^{25}$ = +43.3° ($CHCl_3$, c 2.40).[17b] From degradation: $[\alpha]_D$ = +33° ($CHCl_3$, c 0.797),[2] $[\alpha]_D$ = +38° ($CHCl_3$),[3] $[\alpha]_D$ = +43° ($CHCl_3$)[5]).

Anal. calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.86; H, 7.91.

(2S(R),3S,5R)-Tetrahydro-α,3,5-trimethyl-6-oxo-2H-pyran-2-acetic acid, methyl ester (54). To a solution of acid **34** (27.4 mg, 0.137 mmol, recrystallized 2x from ether:pet. ether) in 3 mL of dichloromethane was added a solution of diazomethane in diethyl ether until the yellow color persisted. The solvents were removed in vacuo to afford 29.0 mg (100%) of methyl ester **54** as a white solid melting at 76-77°C. Recrystallization from pentane afforded 20.8 mg of white crystals: mp 91.5-92.5°C (lit. mp 78-78.5°C,[11a] 75.5-76.5°C,[2] 79-81°C,[3] 94-95°C[17b]). Diastereomer analysis (SE-54, 120°C, 4 PSI, t_r = 9.99 min, then 200°C, 4 PSI, t_r = 2.19 min) indicated both the chemical and diastereomer purity to be $\geq$ 99.9%: IR ($CHCl_3$) 3025, 1729, 1457, 1233, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 4.543 (d of d, J = 2.7, J = 10.6, C_2-H), 3.733 (s, 3H, CH_3O), 2.730 (q of d, J_d = 2.7, J_q = 7.1, 1H, α-H), 2.508 (q of d of d, J_d = 6.5, J_q = 7.0, J_d = 12.5, 1H, C_5-H), 1.98-1.85 (m, 2H, C_3-H, C_4-Heq), 1.422 (q, J = 12.5, 1H, C_4-Hax), 1.283 (d, J = 7.1, 3H, α-CH_3), 1.200 (d, J = 7.0, 3H, C_5-CH_3), 1.007 (d, J = 6.5, 3H, C_3-CH_3); ^{13}C NMR ($CDCl_3$) δ (TMS) 173.71, 173.39, 86.30, 52.18, 41.33, 37.37, 36.26, 31.00, 17.29, 17.03, 8.77; $[\alpha]_D^{25}$ = +37.0° ($CHCl_3$, c 0.9) (lit. $[\alpha]_D$ =+38° ($CHCl_3$, c 1.03)[11a]).

Anal. calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.42; H, 8.33.

(3(2S,3R,4S),4S)-3-(3-Hydroxy-2,4,6-trimethyl-1-oxo-6-heptenyl-4-(1-methylethyl)-2-oxazolidinone (48). Enolization, condensation, oxidation and product isolation were performed according to the preparation of compound **36.** To a cooled (-78°C) solution of the boron enolate of **7** in 24 mL of anhydrous dichloromethane (prepared from 2.22 g (12 mmol) of oxozolidinone **7**, 3.24 mL (13.2 mmol) of di-n-butylboryl triflate, and 2.0 mL (14.4 mmol) of triethylamine) was added 1.06 g (9.4 mmol, 0.78 equiv) of aldehyde **46.** Product isolation gave 3.86 g of a yellow oil. Diastereomer analysis (SE-54, T = 170°C, 7 PSI, t_r 4-epi-$\mathbf{E_2}$ = 8.23 min, t_r $\mathbf{E_2}$ = 8.82 min, t_r $\mathbf{E_1}$ = 9.01 min, t_r $\mathbf{T_1}$ = 9.10 min, t_r $\mathbf{T_2}$ = 9.26 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) afforded a ratio of 4-epi-$\mathbf{E_2}$:$\mathbf{E_2}$:$\mathbf{E_1}$:$\mathbf{T_1}$:$\mathbf{T_2}$ = 1.05:97.72:0.25:0.66:0.32. Flash chromatography (50 mm, 180 g silica, 20% ethyl acetate:hexane) afforded 2.06 g (73% based on aldehyde **46**) of compound **48** as a colorless oil: R_f 0.25 (20% ethyl acetate:hexane); IR ($CHCl_3$) 3500 (br), 3035, 2980, 2960, 1780, 1695, 1385, 1220 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 4.75 (br s, 1H, (H)HC=C-), 4.68 (br s, 1H, (H)HC=C-), 4.60-4.15 (m, 3H, -NCHCH$_2$O), 3.98 (d of d, J = 4, J = 7, 1H, O=CCH-), 3.66 (q, J = 4.5, 1H, HOCH-), 2.58 (d, J = 4.5, 1H, HO-), 2.55-1.55 (m, 4H, $(CH_3)_2$CH, HOCHCHCH$_2$), 1.68 (s, 3H, H_3CC=), 1.27 (d, J = 6.9, 3H, O=CCHCH_3), 1.0-0.8 (m, 9H, HOCHCHCH_3, $(CH_3)_2$CH); ^{13}C NMR (CCl_4) δ (CCl_4) 176.52, 152.80, 143.38, 112.05, 74.03,

62.86, 57.98, 42.06, 40.18, 33.22, 28.22, 21.91, 17.75, 14.57, 14.38, 12.49; $[\alpha]_D^{25}$ = +61.7° (CH_2Cl_2, c 3.3).

Anal. calcd. for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15. Found: C, 64.48; H, 9.04.

Mixture of (3(2S,3R,4S,6R),4S)-3-(7-hydroxy-2,4,6-trimethyl-1-oxo-3-((trimethylsilyl)oxy)heptyl)-4-(1-methylethyl)-2-oxazolidinone (60) and the Corresponding (3(2S,3R,4S,6S),4S)-Isomer (73). Aldol adduct **48** (911 mg, 3.06 mmol) was silylated (Et_2NSiMe_3, DMAP, CH_2Cl_2, 4.5 h) following the procedure used for the preparation of compound **41.** Flash chromatography (50 mm, 100 g silica, 10% ethyl acetate:hexane) afforded 1,000 mg (84%) of silylated alcohol as a colorless oil. Hydroboration using thexylborane in tetrahydrofuran (2 equiv, 3.5 h, 0°C) was performed in the same way as for the preparation of compound **50.** Diastereomer analysis (SE-54, 195°C, 5 PSI, t_r **6R** = 11.00 min, t_r **6S** = 11.36 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 15 min) afforded a ratio of **60**:**73** = 75:25. Flash chromatography (40 mm, 85 g silica, 40% ethyl acetate:hexane) gave 1.00 g (96%) of a colorless oil as an inseparable, 3:1 mixture of epimers **60** and **73** as indicated by GC analysis: R_f 0.10 (30% ethyl acetate:hexane); ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 4.5-4.1 (m, 3H, -NC<u>H</u>C<u>H</u>$_2$O), 4.1-3.75 (m , 2H, O=CC<u>H</u>C<u>H</u>-), 3.60-3.25 (m, 2H, HOC<u>H</u>$_2$), 2.55-2.10 (m, 1H, $(CH_3)_2$C<u>H</u>-), 1.9-1.1 (m, 5H, <u>H</u>OCH$_2$C<u>H</u>C<u>H</u>$_2$C<u>H</u>-), 1.22 (d, J = 6.0, 3H, O=CCHC<u>H</u>$_3$),

1.05-0.85 (m, 12H, $C\underline{H}_3\dot{C}HCH_2\dot{C}HC\underline{H}_3$, $(C\underline{H}_3)_2\dot{C}H$), 0.13 (s, 9H, $(C\underline{H}_3)_3Si$).

Anal. calcd. for $C_{17}H_{37}NO_5Si$: C, 58.80; H, 9.62. Found: C, 59.02; H, 9.52.

Determination of the absolute configuration of compounds 60 and 73. (Scheme XII). A solution containing a 3:1 mixture of alcohols **60** and **73** (1.005 g, 2.72 mmol) and freshly distilled triethylamine (3.9 mL, 27 mmol, 10 equiv) in 10 mL of dry dimethyl sulfoxide, was treated with a solution of sulfur trioxide pyridine complex (1.91 g, 13.6 mmol, 5 equiv, Aldrich, 95% pure) in 10 mL of dry dimethyl sulfoxide. After 30 min, ether (100 mL) was added, and the mixture partitioned with water (25 mL). The ethereal layer was decanted and the aqueous phase was extracted with ether (1 x 25 mL). The combined organic layers were washed with saturated aqueous cupric sulfate (1 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield the corresponding mixture of aldehydes as a slightly yellow oil, pure by TLC analysis: R_f 0.36 (30% ethyl acetate:hexane).

The oil was diluted in 1.5 mL of anhydrous dichloromethane and added dropwise into a cooled (-78°C) solution containing 3 mmol of boron enolate **47** in 12 mL of dichloromethane, prepared as described in p. 47. The mixture was stirred at -78°C for 0.5 h and then at 0°C for 1.8 h. General aldol workup (p. 47) and purification by flash chromatography (50 mm, 150 g silica, 35% ethyl acetate:hexane)

afforded 1.10 g (65% from alcohol **60**) of product **74** as a 3:1 mixture at C_6.

The mixture was then treated with an excess of N,N-diethyltrimethylsilylamine (2.6 mL, 13.6 mmol), in presence of DMAP (166 mg, 1.4 mmol) in anhydrous dichloromethane (10 mL), for 4.5 h. Concentration in vacuo afforded an oil. Diastereomer analysis (SE-54, T = 275°C, Tinj = 285°C, 15 PSI, t_r **75** = 7.67 min, t_r **76** = 8.21 min) afforded a ratio of **75**:**76** = 72:28. Purification by flash chromatography (50 mm, 150 g silica, 10% ethyl acetate:hexane) resulted in a non-baseline separation of the epimers, affording 643.3 mg of **75** (R_f 0.52 in 50% ethyl acetate:hexane) (contaminated with 0.2% of **76**) and 121 mg of **76** (R_f 0.46 in 50% ethyl acetate:hexane) (contaminated with 10% of **75**).

In another flask was placed benzyl alcohol (0.38 mL, 3.72 mmol, 4 equiv) and anhydrous tetrahydrofuran (4 mL). The solution was cooled to 0°C and a 1.7 M solution of n-butyllithium in hexane (1.65 mL, 2.8 mmol, 3 equiv) was added dropwise. The mixture was stirred at 0°C for 20 min. Then, a solution containing **75** in ca. 1 mL of tetrahydrofuran was slowly added (1 mL rinse), and the resulting mixture stirred at 0°C for 3 h, after which period the reaction was quenched by the addition of aqueous ammonium chloride. The volatiles were removed in vacuo and the remaining aqueous slurry was partitioned between water and dichloromethane. The organic layer was decanted, dried over anhydrous sodium sulfate, filtered and

concentrated to an oil. Flash chromatography (5% ethyl acetate: hexane) afforded an analytical sample of **77**, contaminated with only 0.2% of **78**: R_f 0.62 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3035, 2990, 1730, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ($CHCl_3$) 7.30-7.10 (m, 10H, aromatic H), 5.08 (d, J = 12.5, 2H, two PhC<u>H</u>(H)O), 4.99 (d, J = 12.5, 2H, two PhCH(<u>H</u>)O), 3.73 (d of d, J = 2.0, J = 8.3, 2H, two TMSOC<u>H</u>-), 2.61 (qn, J = 7.5, 2H, two O=CC<u>H</u>-), 1.50 (br q, J = 7, 2H, two TMSOCHC<u>H</u>CH_2), 1.34 (d of d of d, J = 7, J = 7, J = 13.5, 1H, -CHC<u>H</u>(H)CH-), 1.16 (d, J = 6.8, 6H, two O=CCHC<u>H_3</u>), 0.97 (d of d of d, J = 7.0, J = 7.0, J = 13.5, 1H, -CHCH(<u>H</u>)CH-), 0.14 (s, 18H, two (C<u>H_3</u>)$_3$Si); ^{13}C NMR (CCl_4) δ (CCl_4) 171.98, 134.10, 126.23, 125.91, 125.78, 75.02, 63.58, 41.88, 37.46, 32.33, 12.63, 11.92, -1.21.

Compound **78** was obtained following the same procedure. Flash chromatography (same cond.) afforded a sample of **78** contaminated with 10% of **77**: R_f 0.62 (30% ethyl acetate:hexane); ^1H NMR (500 MHz, $CDCl_3$) δ ($CHCl_3$) 7.3-7.16 (m, 10H, aromatic H), 5.10-4.96 (m, 4H, two PhC<u>H_2</u>O), 3.80-3.75 (m, 2H, two TMSOC<u>H</u>-), 2.65-2.57 (m, 2H, two O=CC<u>H</u>-), 1.53-1.38 (m, 2H, two TMSOCHC<u>H</u>CH_2), 1.28 (d of d of d, J = 2.5, J = 13, J = 13, 1H, -CHC<u>H</u>(H)CH-), 1.15 (d, J = 7.0, 6H, two O=CCHCH_3), 0.99 (d of d of d, J = 2.5, J = 13, J = 13, 1H, -CHC<u>H</u>(H)CH-), 0.75 (d, J = 6.8, 3H, <u>H_3</u>CCHCH_2CHCH_3), 0.73 (d, J = 6.8, 3H, H_3CCHCH_2CHC<u>H_3</u>), 0.10 (s, 18 H, two (C<u>H_3</u>)$_3$Si); ^{13}C NMR (CCl_4) δ (CCl_4) 171.72, 133.90, 126.10, 125.78, 124.67, 76.39,

76.26, 63.52, 40.97, 40.77, 33.24, 32.78, 32.46, 14.45, 11.72, 11.07, 10.75, -1.34.

(2R,4S)-5-((Triethylsilyl)oxy)-2,4,5-trimethylhexanol (62), and the corresponding (2S,4S)-Isomer (79). To a cooled (-15°C), 5:1 mixture of anhydrous tetrahydrofuran and 10 M borane dimethyl sulfide complex solution (Aldrich), was added neat 2-methyl-2-butene (2 equiv) dropwise. The solution was warmed to room temperature and stirred for 2 h.

Into another flask containing olefin **61** (124 mg, 0.48 mmol) in anhydrous tetrahydrofuran (1 mL) at -10°C, was added dropwise an aliquot of the disiamylborane solution (ca. 3 molar equiv). The solution was then warmed to 0°C and stirred at this temperature for 4 h. The excess borane was destroyed by the addition of aqueous phosphate buffer solution. Methanol was added, followed by a solution of 30% aqueous hydrogen peroxide (ca. 1 mL) in methanol. The slurry was stirred at 0°C for 1 h, concentrated in vacuo and the remaining aqueous solution extracted with ether (2 x 30 mL). The combined ethereal layers were dried over anhydrous sodium sulfate, filtered and concentrated to an oil. Neither the product, or its silylated (TMS) counterpart, proved to be suitable for GC analysis. Purification by flash chromatography (20 mm, 45 g silica, 10% ethyl acetate:hexane) afforded 61.9 mg (47%) of **62** and 13.4 mg (10%) of **79**, both as colorless oils.

62: R_f 0.52 (30% ethyl acetate:hexane); ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 3.65-3.25 (m, 2H, $HOC\underline{H}_2$), 1.85-0.45 (m, 26H), 1.15 (s, 3H, $C\underline{H}_3CCH_3$), 1.10 (s, 3H, $CH_3CC\underline{H}_3$).

Anal. calcd. for $C_{15}H_{34}O_2Si$: C, 65.63; H, 12.48. Found: C, 65.53; H, 12.35.

79: R_f 0.43 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3645, 3480 (br), 2970, 2885, 1458, 1236, 1040, 710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 3.65-3.25 (m, 2H, $HOC\underline{H}_2$), 1.7-0.45 (m, 26H), 1.13 (s, 3H, $C\underline{H}_3CCH_3$), 1.11 (s, 3H, $CH_3CC\underline{H}_3$).

Anal. calcd. for $C_{15}H_{34}O_2Si$: C, 65.63; H, 12.48. Found: C, 65.75; H, 12.42.

Determination of the Absolute Configuration of Compound 62. (Scheme XII) Compound **62** (50 mg, 180 μmol) was methylated (KOH, CH_3I, DMSO, 48 h) according to the procedure of Johnstone.[46] The unpurified product was oxidized ($NaIO_4$, $RuCl_3.H_2O$, CCl_4, CH_3CN, H_2O) according to the procedure of Sharpless.[47] The resulting unpurified methyl ester **80** was then treated with methyl Grignard (3 M sol. in ether) in ether, at 0°C, for 4 h. The resulting alcohol treated with triethylsilyl trifluoromethanesulfonate (3.5 equiv) in presence of triethylamine (4.5 equiv) in dichloromethane. Flash chromatography (10 mm, 7 g silica, hexane) afforded 9 mg (12%) of compound **81**. (The low overall yield is attributed to the loss of part of one of the intermediates upon concentration under low pressure.) Gas

chromatographic analysis (SE-54, 200°C, t_r = 3.18 min) indicated **81** to be $\geq$ 99.8% pure: ^{1}H NMR (500 MHz, $CDCl_3$) δ (TMS) 1.91 (d of d of d, J = 4.0, J = 4.0, J = 14.0, 1H, -C<u>H</u>(H)-), 1.41 (q of d of d, J_d = 3.5, J_d = 7.0, J_q = 7.0, 2H, two -C<u>H</u>CH_3), 1.15 (s, 6H, two <u>H</u>$_3$C$\overset{|}{C}$C<u>H</u>$_3$), 1.14 (s, 6H, two $H_3C\overset{|}{C}C\underline{H}_3$), 0.95 (t, J = 8.0, 18H, two (C<u>H</u>$_3$C<u>H</u>$_2$)$_3$$\overset{|}{S}$i), 0.90 (d, J = 7.0, 6H, two -C<u>H</u>C<u>H</u>$_3$), 0.58 (q, J = 8.0, 12H, two ($CH_3C\underline{H}_2)_3\overset{|}{S}i$), 0.54 (d of t, J = 7.5, J = 7.5, J = 14.0, 1H, -C<u>H</u>(<u>H</u>)).

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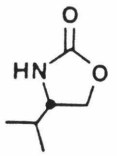

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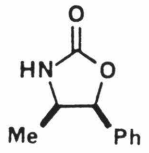

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(23) Prepared in two steps from methallyl alcohol (a: MsCl, Et_3N, CH_2Cl_2, 0°C; b LiI, Et_2O, 0°C → 25°C) in 85% yield after distillation.

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CHAPTER III

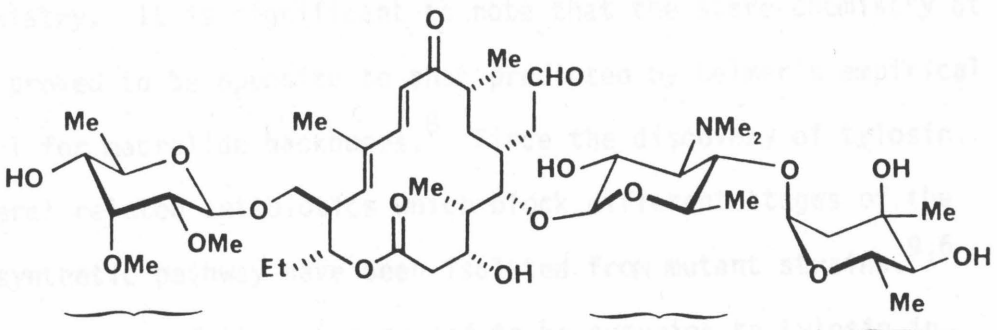
The Total Synthesis of (+)-Tylonolide, Cyclic 5,20-Hemiacetal

I. Introduction

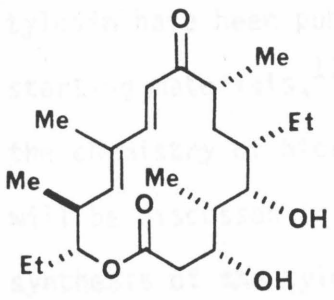
In 1961, McGuire and coworkers reported the discovery of a new antibiotic from strains of Streptomyces fradiae.[1] The compound was given the name of tylosin after its isolation from soils collected in Thailand. It was shown to be relatively nontoxic and highly active in vitro against gram-positive bacteria, certain gram-negative bacteria, and mycobacteria.[1a] Today it is extensively used both as a nutrient and as a treatment for respiratory diseases in poultry.

Early studies[1b] showed that tylosin (**84**) belongs to the growing class of macrolide antibiotics.[2] Hydrolysis experiments indicated that two neutral sugars (mycarose and mycinose) and one aminosugar (mycaminose) form part of the molecule.[1b,3] In 1970 Morin and coworkers[4] elucidated the structure indicating that the antibiotic belongs to the 16-membered ring family of macrolides. There is no X-ray crystal structure analysis reported directly on tylosin; however, X-ray structures of two metabolites obtained from mutants of S. fradiae have recently appeared in the literature. Thus, the X-ray structures of protylonolide (**85**) and 5-O-mycarosyltylactone (**86**) were reported in 1980 and 1982 respectively.[5a,6] Because the absolute configuration of mycarose was already known, the absolute stereochemistry of **86** was unequivocally assigned as drawn in Scheme I. Furthermore, conversion of **86** into **85** by hydrolysis established the absolute configuration of **85**. Since it was previously shown

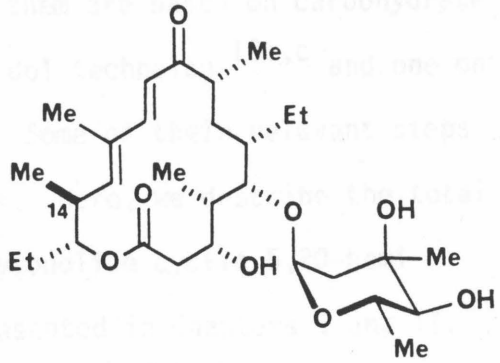
Scheme I



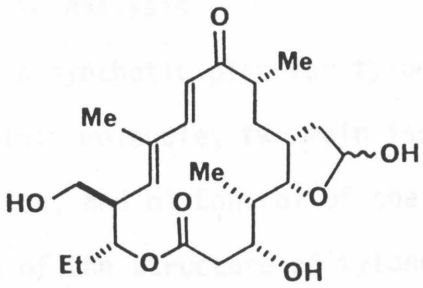
Tylosin (84)



85



86



87

that protylonolide, **85**, is converted into tylosin by mutants of S. fradiae,[7] this constituted a proof of the absolute stereochemistry. It is significant to note that the stereochemistry at C_{14} proved to be opposite to that predicted by Celmer's empirical model for macrolide backbones.[8] Since the discovery of tylosin, several related antibiotics which block different stages of the biosynthetic pathway have been isolated from mutant strains.[9,6] However, none of these has proved to be superior to tylosin in treating bacterial or mycoplasmal infections caused by sensitive organisms.[10]

To date, four syntheses of compounds directly related to tylosin have been published. Two of them are based on carbohydrate starting materials,[11,12,15] one on aldol technology[13b,c] and one on the chemistry of bicyclic systems.[14] Some of their relevant steps will be discussed in the next section. Here, we describe the total synthesis of the tylosin aglycone, tylonolide cyclic 5,20-hemiacetal, **87**, using the methodology presented in Chapters I and II.

II. Retrosynthetic Analysis

In deriving a synthetic plan for tylonolide hemiacetal (**87**), or any other macrolidic molecule, two main issues need to be addressed: a) Macrocyclization, and b) Control of the stereochemistry.

Examination of the structure of tylonolide quickly suggests two possible bond disconnections that would lead to a linear precursor:

the C_1-O bond and the C_{10}-C_{11} bond (Scheme II). Due to the fact that both disconnections were envisioned in our overall plan, either route would ultimately lead to the same two fragments **A** and **B**.

An inspection of the large amount of literature concerning the C-O closure (i.e. macrolactonization)[16] reveals that these reactions often proceed in rather low yields when carried on stereochemically complex substrates. Indeed, when some of these macrolactonization methods were applied to the syntheses of 16-membered-ring macrolides, yields in the range of 40 to 15% were obtained. Table 1 summarizes some of these results.

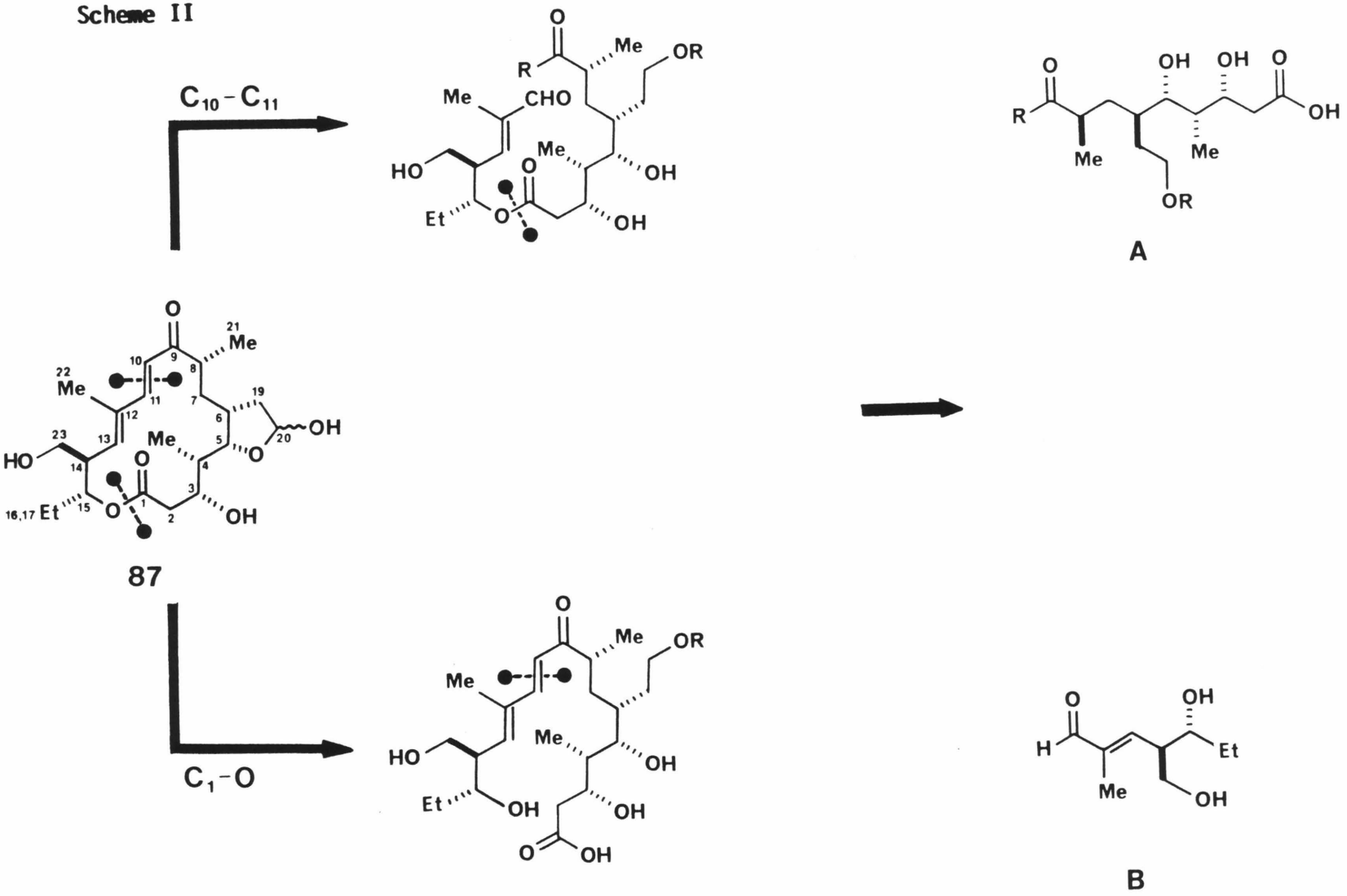
Table 1. Macrolactonization yields.

Target	Activated carbonyl	Conditions	Yield[a]	Ref
Tylonolide	R-C(O)SPh	$Hg(OSO_2Me)_2$,$NaHPO_4$	17%	13a
Tylonolide	R-C(O)OP(O)$(OPh)_2$	DMAP, C_6H_6	32%	13b
Tylonolide	R-C(O)S-2-pyr	Toluene	41%	11
Tylonolide	R-C(O)S-2-pyr	Toluene	19%[b]	14
Josamycin	R-C(O)SPh	Na_2HPO_4,AgOTF	17%	17

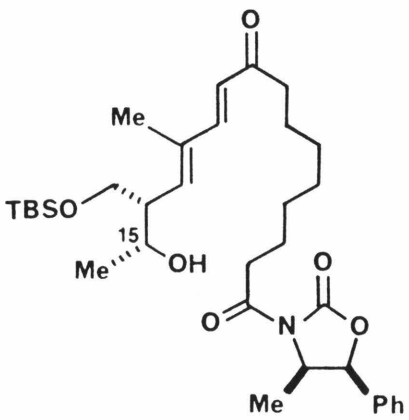
[a] The yields are based on the acid precursor. [b] Yield based on the corresponding methyl ester, and included is its basic hydrolysis to the acid.

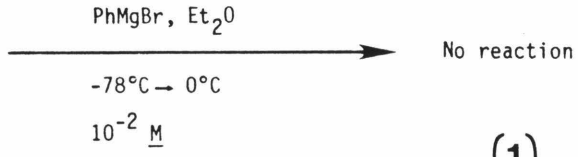
Based on our observations regarding the carbonyl reactivity of the acyl oxazolidinones towards nucleophiles, we did some preliminary

Scheme II



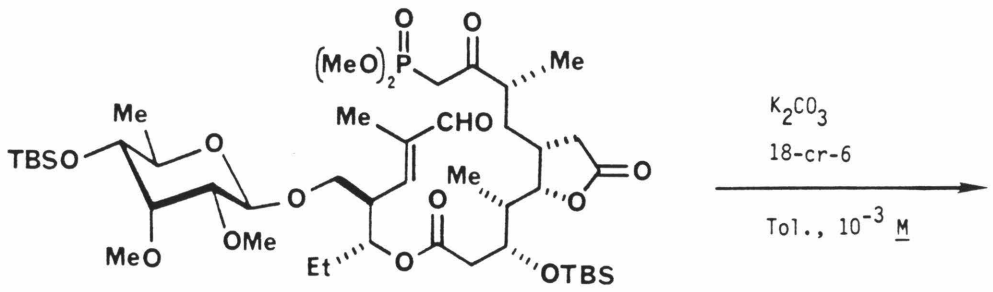
macrolactonization studies on a model compound (eq. 1). We were hoping that the oxazolidinone moiety would be internally displaced by the C_{15}-oxygen upon addition of a catalytic amount of a Grignard reagent. Unfortunately, no reaction was observed in the range of temperature indicated. This result, together with the low yields mentioned above led us to abandon this approach.

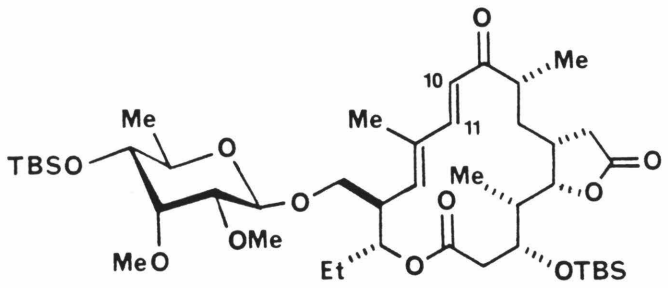




(1)

By the time we were in the planning stages of our synthesis, Stork and Nicolaou[18] had independently reported model studies on macrocyclization wherein the Wittig-Horner reaction was employed in the intramolecular reaction leading to the macrocycle. Later, in an advanced stage of our work, Nicolaou published the synthesis of 23-O-mycinosyltylonolide and reported an outstanding 80% yield for the ring closure using this reaction (eq. 2).[12]





(80%) (2)

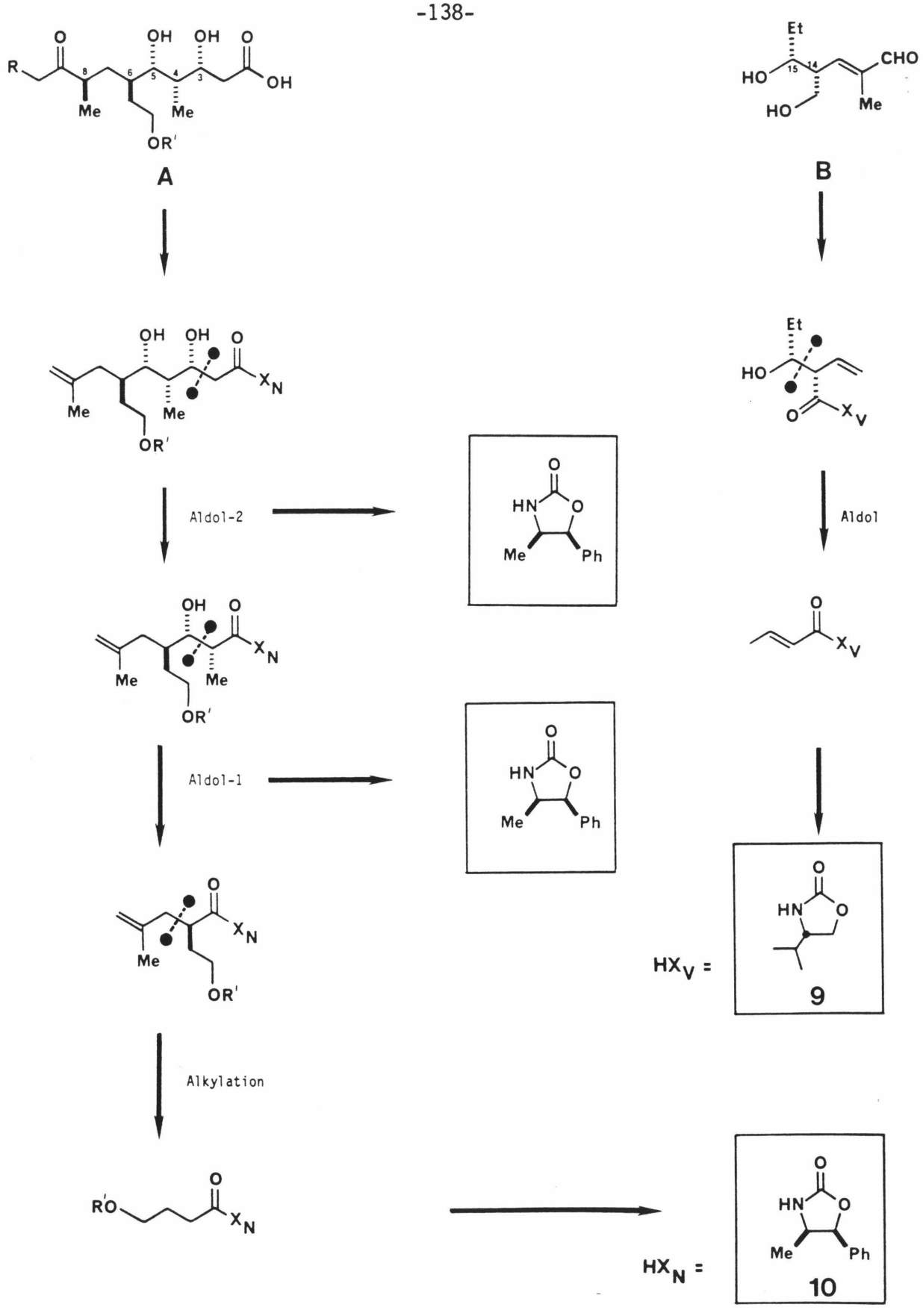
The relative facility observed in the formation of the C_{10}-C_{11} bond in this study, encouraged us to direct our efforts towards an intramolecular macroaldol condensation connecting these two carbons. In the event this reaction failed, the corresponding phosphonate could be easily prepared from a common advanced intermediate and the ring would be formed <u>via</u> a Wittig-Horner reaction.

With the total synthesis of (+)-Prelog-Djerassi lactone presented in Chapter II, we demonstrated the utility of chiral acyl oxazolidinones in the creation of asymmetric centers by means of alkylation [19] and aldol[20] reactions. In a similar way, we planned to use this powerful tool in the elaboration of (+)-tylonolide. As already mentioned, the two first main disconnections would lead us to two subunits **A** and **B** (Scheme II), possessing all the chiral centers present in tylonolide. A retrosynthetic analysis of fragments **A** and **B** is presented in Scheme III.

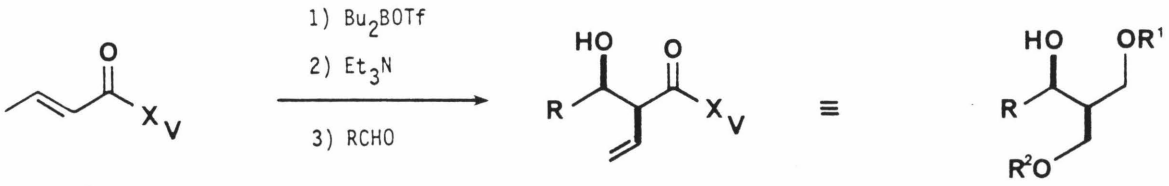
Subunit A: The synthesis of this segment was envisioned to follow the basic steps used in the elaboration of the Prelog-Djerassi lactone. Indeed, carbons 4, 5, 6 and 8 bear the same stereochemical relationships in both compounds. Therefore, the C_6-C_7 bond would be created by means of an alkylation; an aldol reaction would set the C_4 and C_5 stereochemistry, and a hydroboration would create the C_8 chirality. The remaining asymmetric center, C_3, would be introduced by an additional aldol condensation. Analysis of the absolute configuration of the centers indicates that our norephedrine-derived chiral auxiliary could be employed as the sole source of chirality.

Subunit B: Analysis of this segment revealed a pattern that we had not encountered before, namely, a <u>threo</u> hydroxy-hydroxymethyl relationship. We envisioned its elaboration through the use of imide **92.** The boron enolates of chiral crotonate imides have been

Scheme III



shown to react with aldehydes in high yields and with excellent diastereoselection (eq. 3).[21] Since olefin and carbonyl functionalities are easily interconvertible, these aldol adducts have the



92 (3)

interesting property of leading eventually into threo or erythro relationships. The application of this reaction to our case would set the absolute stereochemistry of this subunit. Transformation into **B** would then be accomplished in a straightforward fashion. The chirality of this fragment requires the valine-derived oxazolidinone.

Finally, a comment on protecting groups is worthwhile here. Since tylonolide has seven oxygens, their selection order of introduction is a critical aspect of the projected synthesis. We planned to generate the aldehyde oxidation state of C_{20} towards the end of the synthesis via an oxidation of the C_{20} primary alcohol. Throughout the synthesis, this alcohol functionality would be masked with a reasonable stable, mildly removable protecting group. We avoided the common protection of the C_{20} aldehyde and the C_5 alcohol

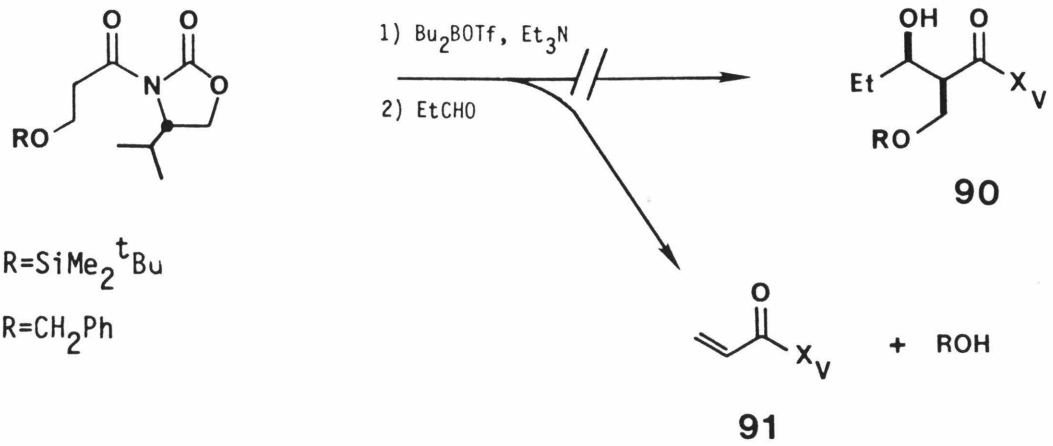
as the methyl acetal because this would, presumably, generate undesirable anomeric mixtures.

III. Discussion and Results

1. The Synthesis of the C_{11}-C_{15} Fragment

The β,β' dihydroxy carbonyl functionality present in this segment was stereospecifically introduced in the first step. Our first attempt at this problem was to carry out a direct aldol condensation between β-alcoxypropionate **88** and propionaldehyde which would lead to the desired adduct **90** (Scheme IV). However, enolization of **88** with di-n-butylboryl triflate and triethylamine (CH_2Cl_2, -78°C) resulted in the clean formation of a very UV active spot in the TLC plate, presumably the acrylate imide **91**. Such β-elimination had been observed before when the corresponding benzyl ether, **89**, was submitted to the same conditions.[22]

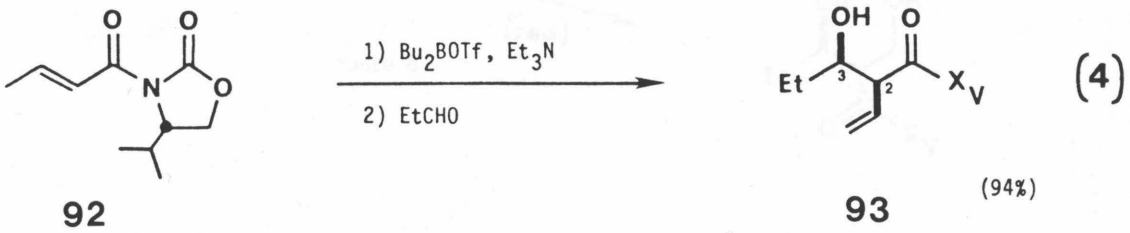
Scheme IV



88: R=$SiMe_2{}^tBu$

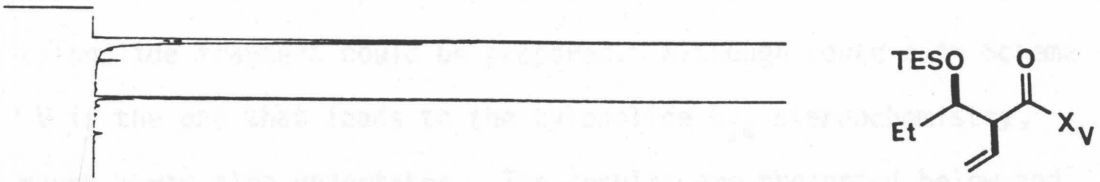
89: R=CH_2Ph

This problem was solved by using crotonate imide **92** (eq. 4), obtained in 78% yield from oxazolidinone **9**.[23] Thus, addition of di-n-butylboryl triflate (1.1 equiv) and triethylamine (1.2 equiv) to a cooled (-78°C) solution of **92** in CH_2Cl_2 resulted in formation of its boron enolate, which was condensed with propionaldehyde (1.3 equiv, -78°C, 1 h, then 0°C, 45 min). Oxidative workup (H_2O_2, MeOH, 0°C, 1 h) and product isolation afforded imide **93** in 94% yield after chromatography. The 500 MHz proton NMR spectrum of this compound indicated a C_2-**H**:C_3-**H** coupling constant of 3.5 Hz, supportive of the expected erythro relationship between the substituents.[24] A sample of the unpurified mixture was converted into its triethylsilylether and was analyzed by GC. The product proved to be 98.6% of one diastereomer. The GC trace is shown in Fig. 1.



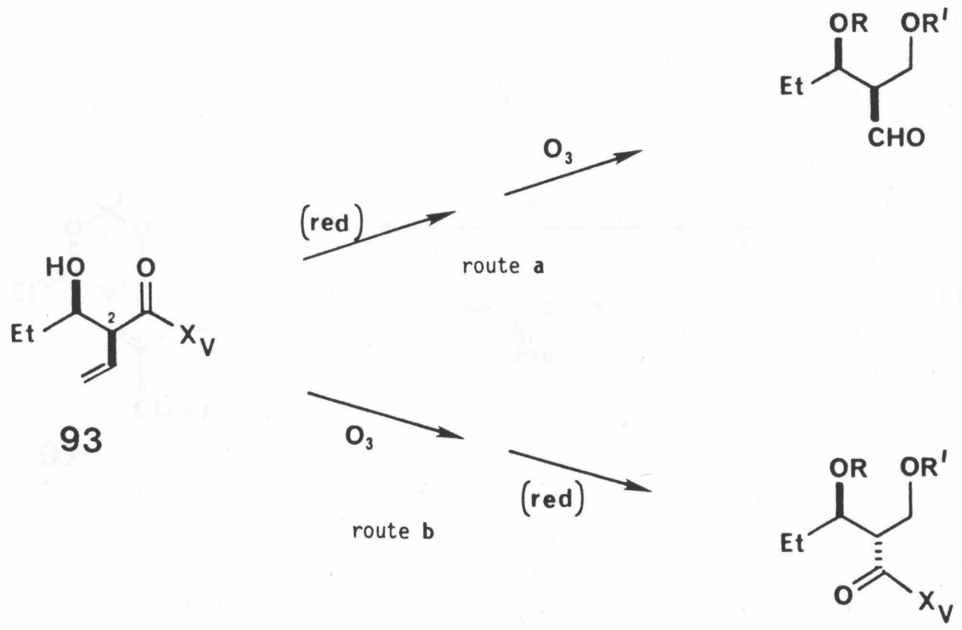
92 **93** (94%) (4)

Fig. 1. GC Trace of the Triethylsilyl Derivative of the Unpurified Aldol Adduct **93**.



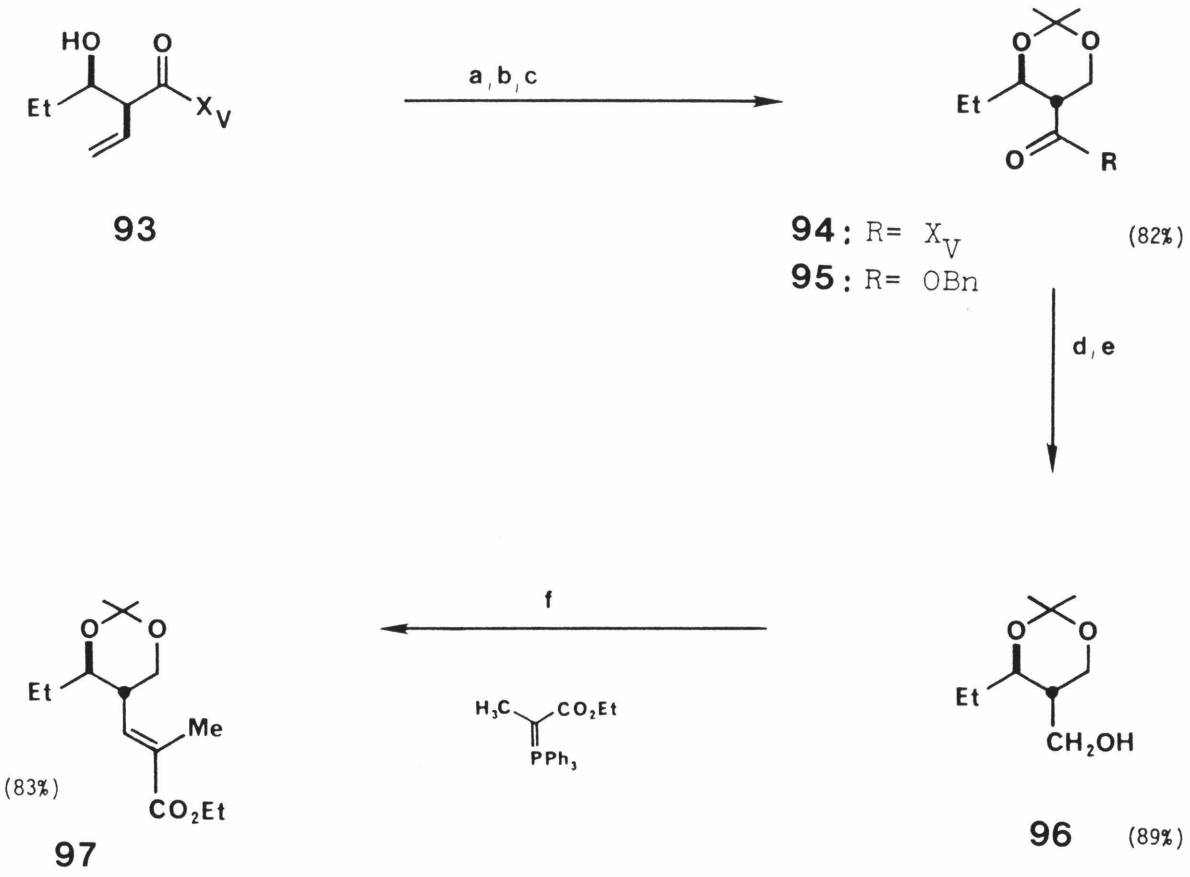
As we already mentioned, an interesting feature of this aldol adduct is that it contains a latent element of symmetry at C_2, due to the facile chemical interconversion of olefins and carbonyls. This is illustrated in Scheme V.

Scheme V



Since the same sequence of reactions could, in principle, be performed in the norephedrine series, all four diastereomers of this tylonolide fragment could be prepared. Although route **a** in Scheme V is the one that leads to the tylonolide C_{14} stereochemistry, route **b** was also undertaken. The results are presented below and summarized in Scheme VI.

Scheme VI



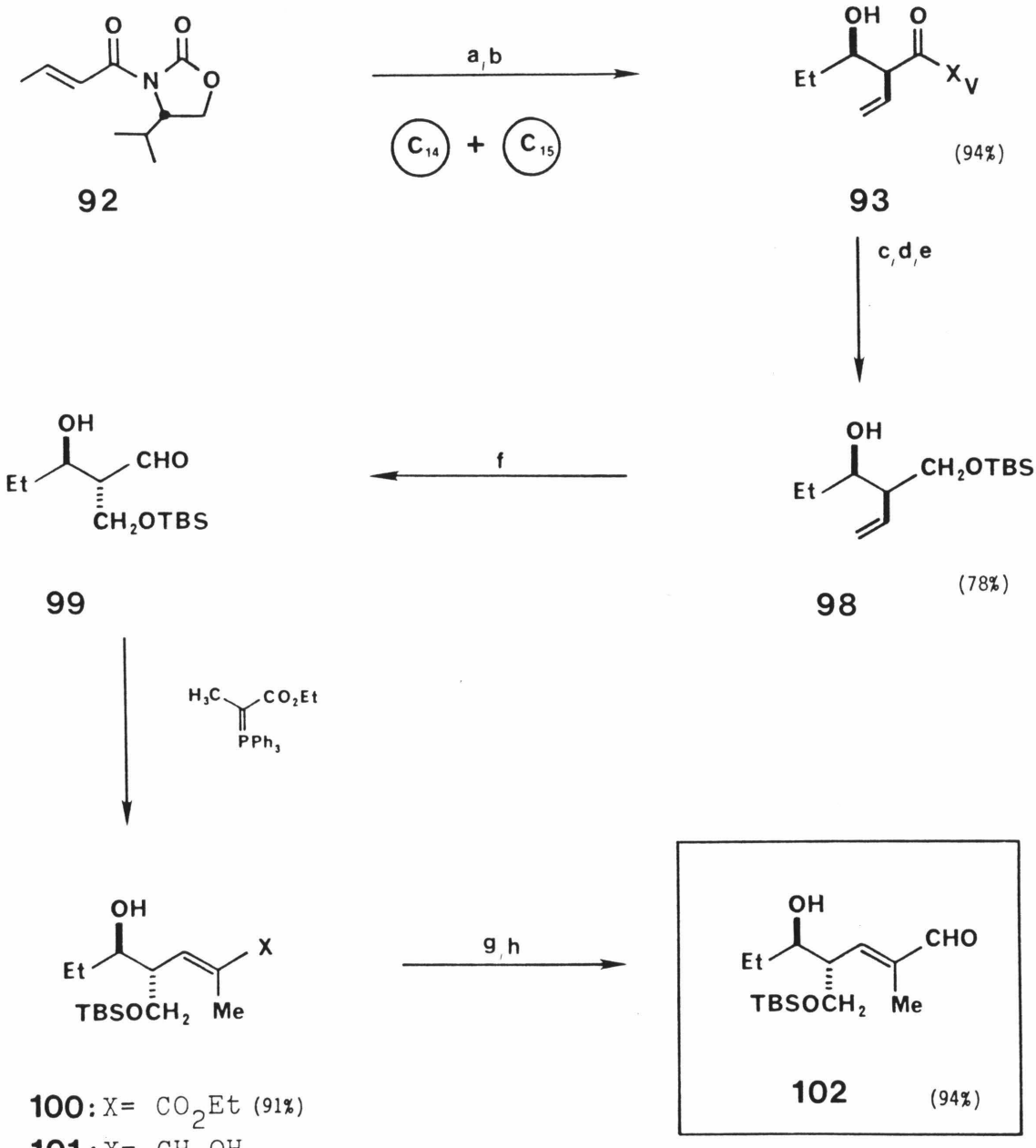
(a) O_3, MeOH; (b) $ZnBH_4$; (c) $Me_2C(OMe)_2$, H^+; (d) $PhCH_2OLi$, (**94**→**95**); (e) LAH (**95**→**96**); (f) SO_3.py, Et_3N, DMSO.

Ozonolysis of olefin **93** in methanol (-78°C), followed by reductive workup ($Zn(BH_4)_2$ sol. in ether, -78°C, 20 h)[25] and protection of the diol (dimethoxypropane, CSA, acetone) afforded crystalline acetonide **94** in 82% overall yield after chromatography.

Reduction of **94** by treatment with a solution of lithium borohydride in tetrahydrofuran, at 0°C or 25°C resulted in very slow conversion. On the other hand, lithium aluminum hydride in tetrahydrofuran at -78°C gave mainly attack to the undesired oxazolidinone carbonyl. This problem was overcome by a two step sequence. Thus, imide **94** was converted into benzyl ester **95** (BnOLi, 1.7 equiv, THF, -15°C, 1.5 h) in 91% yield, along with a 92% yield of recovered oxazolidinone **9**. Reduction of **95** (1M LAH in Et_2O, -15°C, 15 min) proceeded cleanly to give alcohol **96** in 98% yield. GC analysis of the unpurified compounds **94**, **95** and **96** showed that no detectable epimerization had occurred at any point. Finally, alcohol **96** was oxidized to the corresponding aldehyde (DMSO, SO_3.pyr, Et_3N, 0.5 h,)[26] and the latter, without purification, reacted with (carbethoxyethylidene) triphenylphosphorane (1.5 equiv, toluene, 60°C, 4 h) to afford unsaturated ethyl ester **97** in 83% yield. The configuration of the double bond was assumed to be **E** by analogy to a similar reaction reported in the literature.[12a] Although this product was not to be used in the synthesis of tylonolide, its elaboration demonstrated the versatility of aldol adduct **93**, especially its threo:erythro duality.

At this point, our efforts were directed to Route **a** (Scheme V) which would ultimately lead to the tylonolide fragment **B** (Scheme VII). Direct reduction of aldol adduct **93** with a variety of reducing agents proved to be difficult. Indeed, treatment of **93** with lithium borohydride (THF sol., 0°C → 25°C) resulted in partial

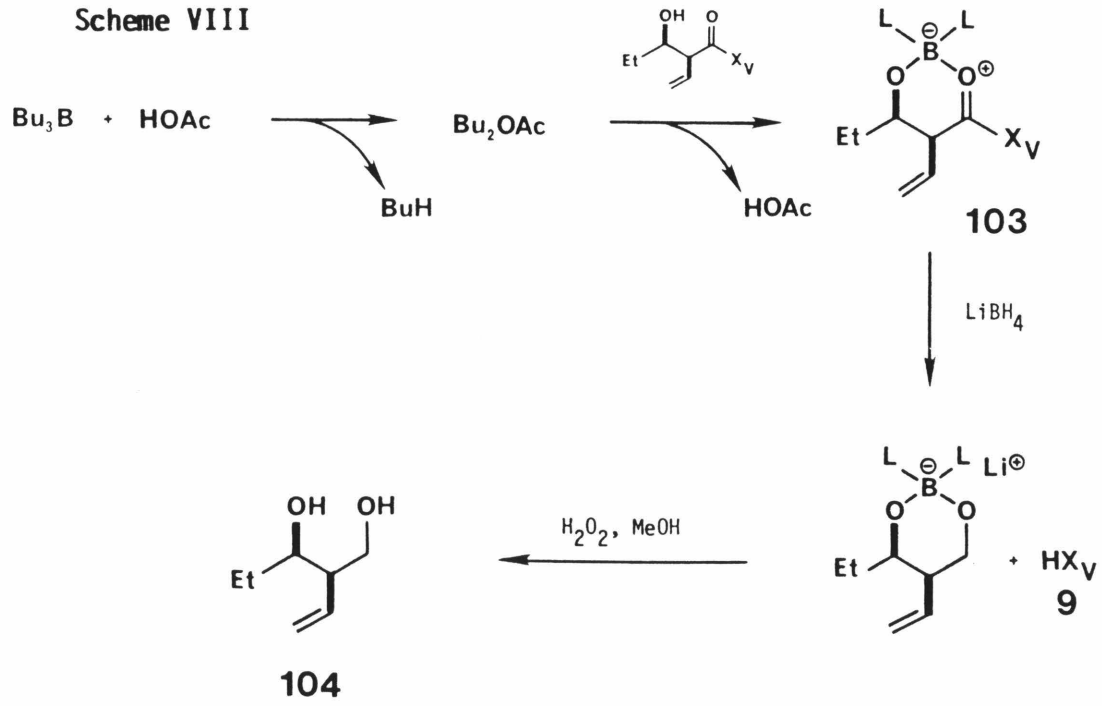
Scheme VII



(a) Bu_2BOTf, Et_3N; (b) EtCHO; (c) Bu_2BOAc; (d) $LiBH_4$; (e) TBSCl, Et_3N; (f) O_3, MeOH; SMe_2; (g) DIBAL (**100**→**101**); (h) MnO_2 (**101**→**102**).

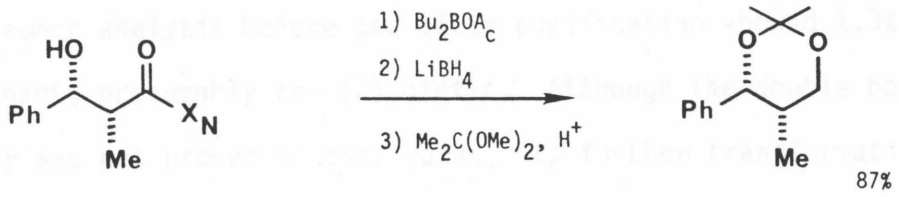
retroaldol reaction. Conversion of the unpurified diol into the acetonide (dimethoxypropane, CSA) gave only a 52% overall yield of product. The use of lithium aluminum hydride (THF sol., 5 molar equiv, -78°C, 45 m) as the reducing agent followed by protection, gave a 32% yield of acetonide. Attempts to improve these yields using solutions of zinc borohydride in ether, lithium aluminum hydride in ether and aluminum hydride (AlH_3) in THF met with only partial success. Similarly, when reduction was performed after protection of the aldol adduct (TES and THP ether), reaction at the oxazolidinone ring carbonyl was the predominant mode of attack. After all these failures, we were gratified to discover that both, retroaldol and reaction at the undesired carbonyl were absent when the reduction was performed on the boron aldolate **103**[27] (Scheme VIII).

Scheme VIII

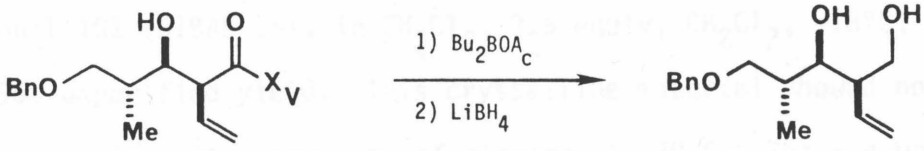


Thus, treatment of a solution of **93** in THF with tri-n-butylborane (1.1 equiv) and glacial acetic acid (1.5 equiv) at room temperature for 1.5 h, followed by reaction with lithium borohydride (2 molar equiv, 1.3M sol. in THF, 0°C, 1 h) afforded, after oxidative workup, (30% H_2O_2, RT, 1.5 h) an 86% yield of diol **104**, with a 99% recovery of the valine-derived oxazolidinone **9.** This method for reducing aldol adducts has since found application in other examples encountered in these laboratories (Scheme IX).

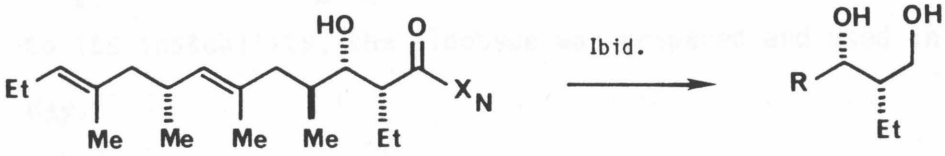
Scheme IX



87%



92% (ref. 28)



83% (ref. 29)

Selective protection of the primary hydroxyl of diol **104** as the t-butyldimethylsilylether (1.3 equiv of TBSCl, 1.3 equiv of Et_3N, 6% equiv of DMAP, CH_2Cl_2, 25°C, 3.5 h)[30] proceeded in 91% yield to give **98.** GC analysis of both, the unpurified diol **104** and its corresponding silyl ether **98,** showed no observable epimerization.

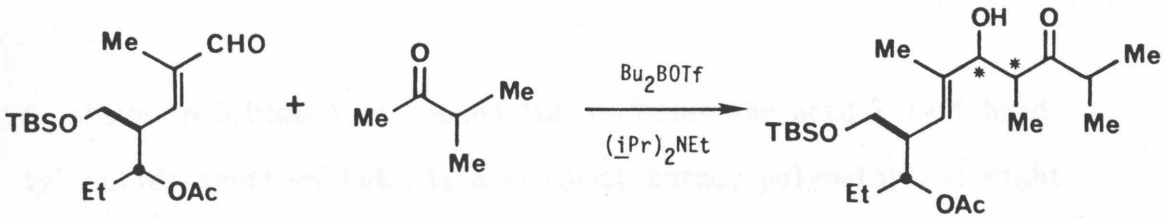
Ozonolysis of olefin **98** (MeOH, -78°C) followed by reductive workup (SMe_2), resulted in formation of β-hydroxyaldehyde **99,** which without purification, was treated with 1.8 equiv of (carbethoxyethylidene)triphenylphosphorane (toluene, 70°C, 9 h). Chromatography afforded ethyl ester **100** in 91% yield from olefin **98.** GC diastereomer analysis before and after purification showed 1.3% of a contaminant, presumably the (Z) olefin. Although the double bond geometry was not proved at this point, its further transformation into tylonolide hemiacetal corroborated our (E) geometry assignment.

Because this material was unstable upon standing at room temperature for several days, it was immediately reduced to allylic alcohol **101** (DIBAL sol. in CH_2Cl_2, 3.5 equiv, CH_2Cl_2, -78°C, 15 min) in 96% unpurified yield. This crystalline material showed no decomposition after one year of storage at -20°C. The α,β-unsaturated aldehyde **102** was obtained by oxidation of **101** using activated MnO_2 (10 equiv, CH_2Cl_2, RT, 1 h) in 94-100% unpurified yield. Due to its instability, the aldehyde was prepared and used in the same day.

This completes the synthesis of the left hand side part of tylonolide which proceeded in seven steps from crotonate imide **92** with an overall yield of 63%, and, at least, 98.6% stereoselection. Compared to the other published routes, this is the shortest and the most efficient approach to the synthesis of this tylosin synthon.

2. Macrocyclization Studies

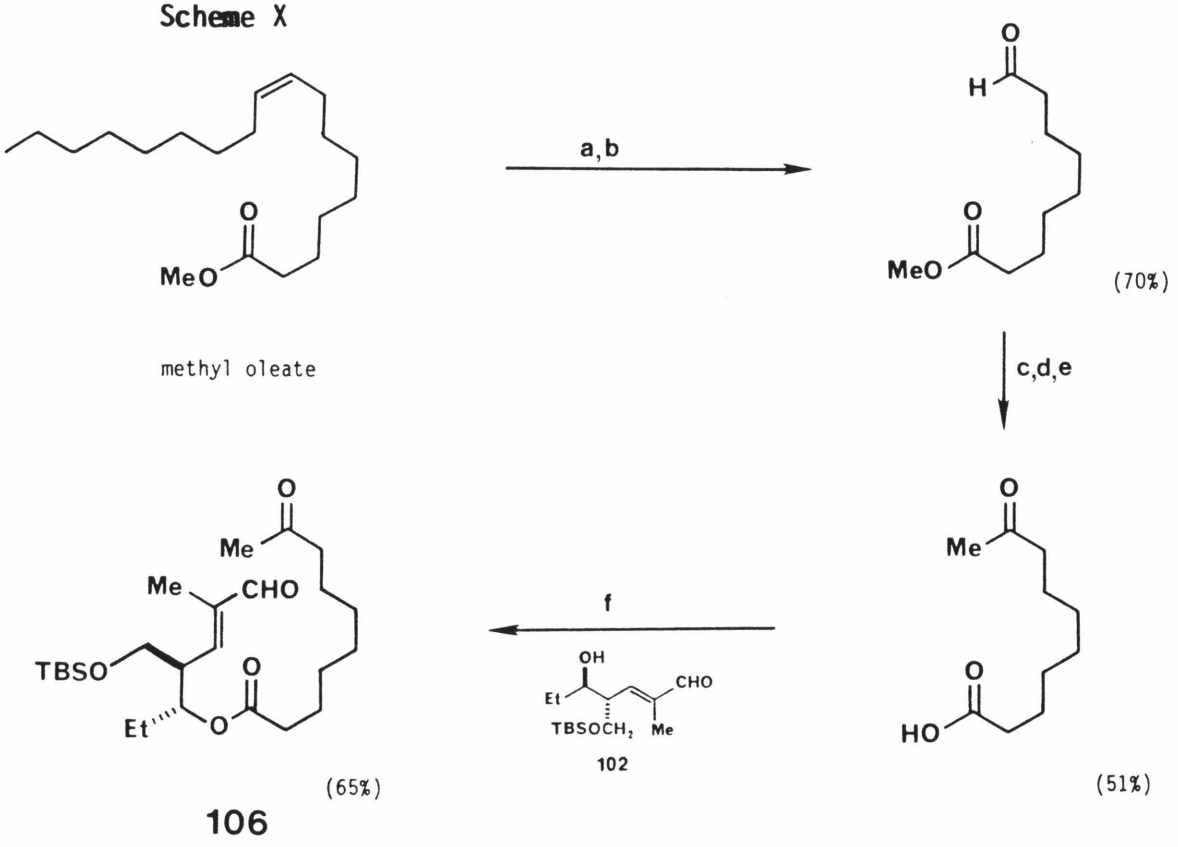
Prior to committing ourselves to a macroaldol condensation strategy, the selective enolization of a methyl ketone in presence of a γ-branched-α,β-unsaturated aldehyde had to be tested. For this purpose, alcohol **102** was acetylated (Ac_2O, pyridine, DMAP) to give **105**, and an equimolecular mixture of **105** and methyl isopropyl ketone in ether was added into a solution containing di-n-butylboryl triflate (1.1 equiv) and diisopropylethylamine (1.1 equiv) in ether (-78°C, 2 h, then 0°C) (eq. 5). TLC analysis showed very clean, but incomplete, conversion. Upon warming to 0°C no major change was observed, indicating that very probably, the reaction mixture had been quenched by traces of moisture.[31] The aldol adduct was isolated



105 (5)

in 40% yield after chromatography. Encouraged by this result, we decided to try the macroaldol on a model compound, prepared from methyl oleate in a straightforward fashion (Scheme X).

Scheme X

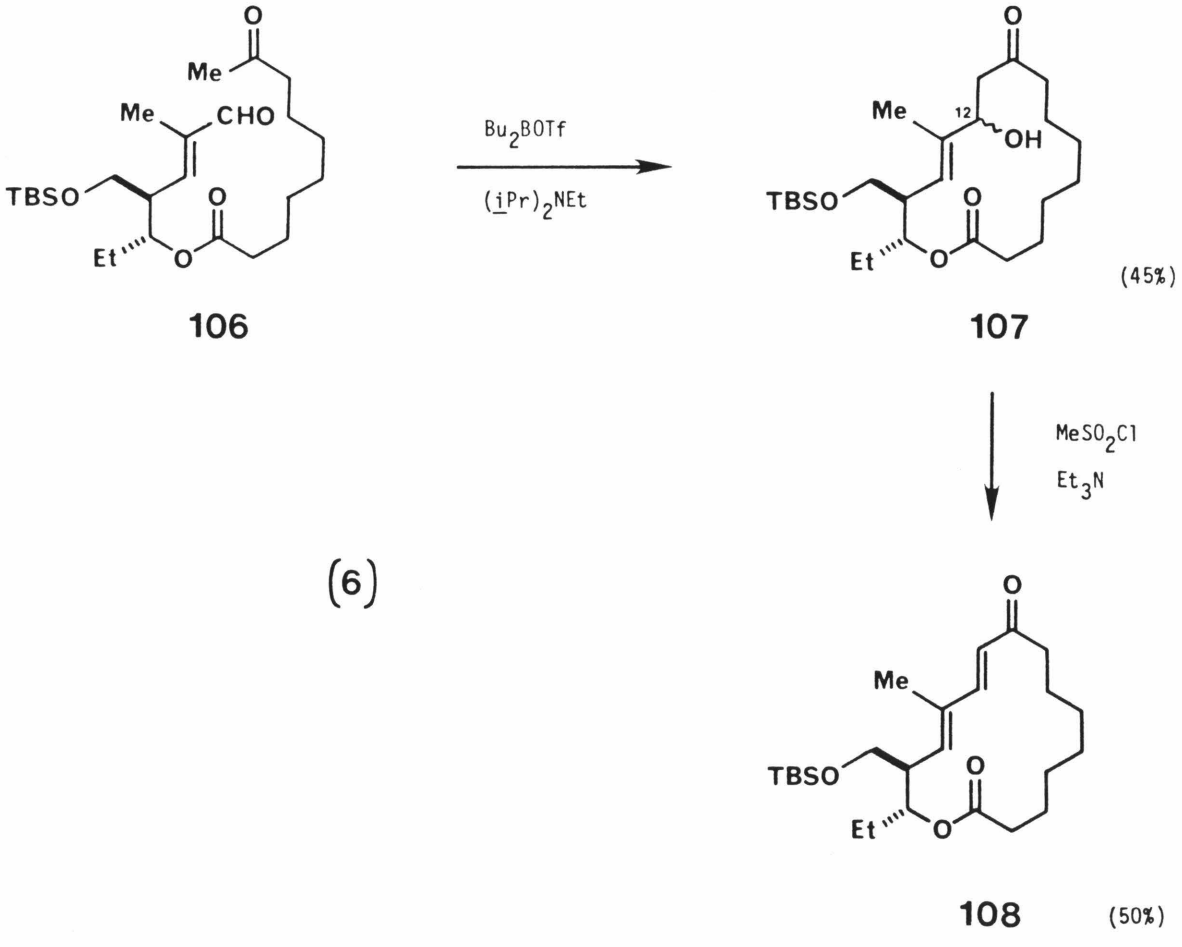


106

(a) O_3, MeOH; SMe_2; (b) HCl, H_2O, acetone, 25°C, 30 m; (c) Me_2CuLi, Et_2O, -78°C, 1.5 h; (d) Jones' oxid., acetone, 25°C; (e) 2N LiOH, MeOH, 25°C, 4 h; (f) **102**, DCC, DMAP.

As shown in Scheme X, compound **106** includes the actual left hand tylonolide synthon, but has a nonsubstituted, polymethylene right fragment. Unfortunately, this material proved to be very unstable,

showing considerable decomposition one hour after its purification. However, when freshly purified **106** was diluted in ether and added into a cooled (-78°C) solution containing di-n-butylboryl triflate (1.2 equiv) and diisopropylethylamine (1.4 equiv) in ether under high dilution conditions (8×10^{-3} M) (eq. 6), clean but partial conversion was observed. Oxidative workup and chromatography afforded an inseparable 1:1 mixture (GC) of epimers at C_{12} (**107**) in



106 → **107** (45%)

(6)

107 → **108** (50%)

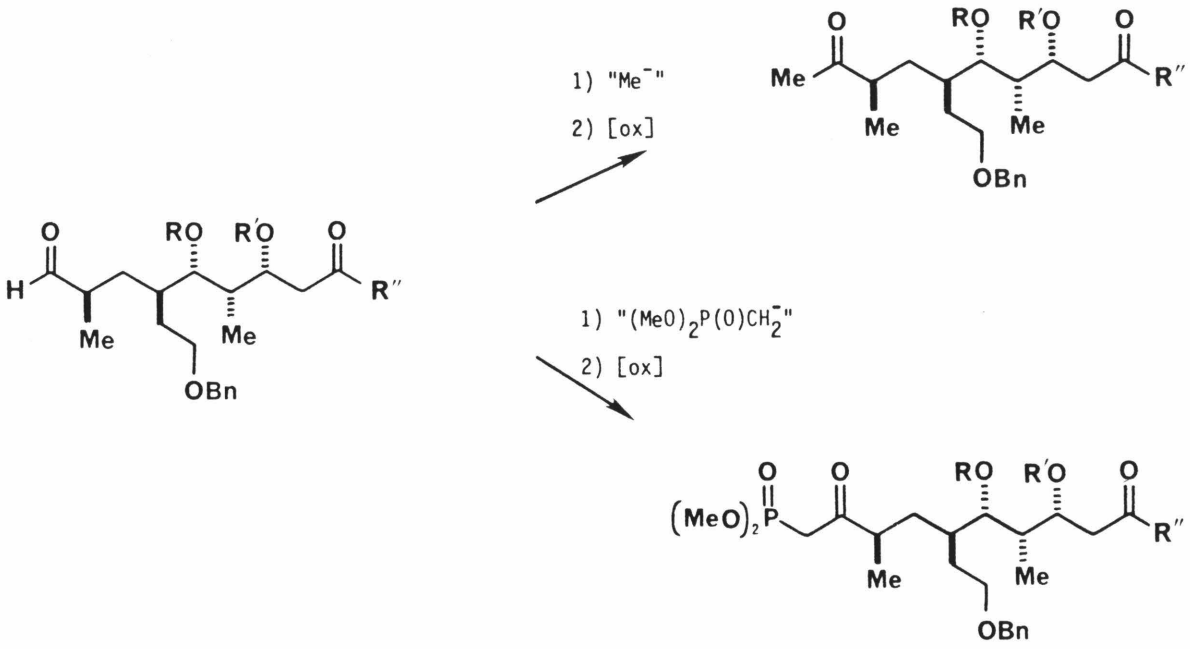
45% yield. This material was converted into the unsaturated ketone **108** by treatment with methyl sulfonyl chloride and triethylamine (excess, CH_2Cl_2, 25°C, 12 h) in 50% yield after chromatography (eq. 6). The olefinic portion of the ^1H NMR of **108** greatly resembled the spectrum reported[32] for tylonolide. Like tylonolide, **108** showed an IR band at ca. 1680 cm^{-1}, characteristic of an unsaturated ketone.

3. The Construction of the C_1-C_{10} Fragment and the Final Steps of the Synthesis of Tylonolide

The relatively high yield obtained in the model macroaldol reaction, together with its novelty, encouraged us to build methyl ketone **130** (Scheme XV). As was pointed out in the strategic plan, if the macroaldol reaction did not work on this substrate, the corresponding phosphonate would be easily prepared from a common intermediate, (see Scheme XI) and the ring would be formed via a Wittig-Horner reaction, as in the Nicolaou's synthesis.[12b]

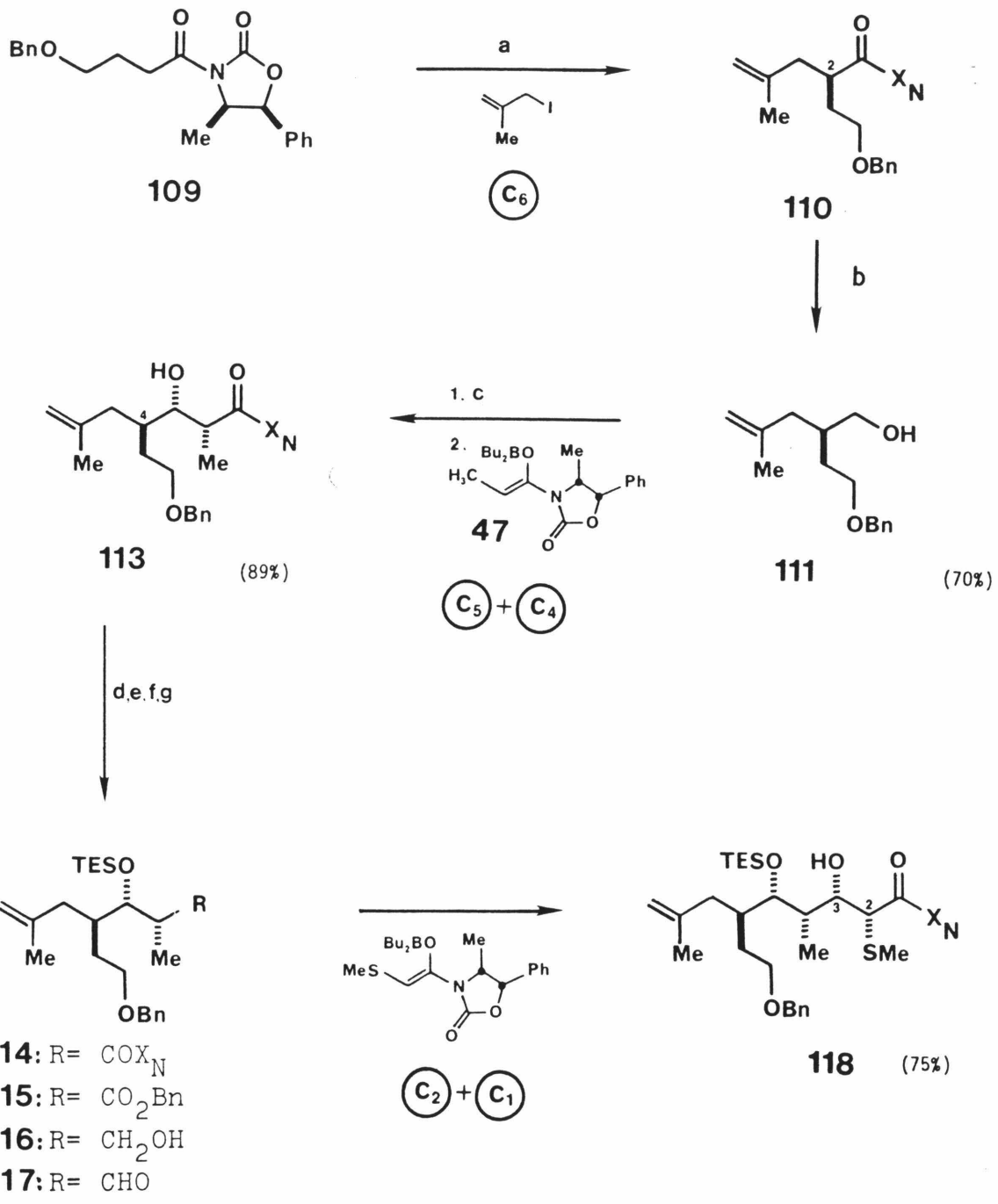
Following the basic strategy employed in the construction of the Prelog-Djerassi lactone,[35] compound **118** was synthesized in 9 steps from imide **109** in 33% overall yield[33,34] (Scheme XII). Thus, the starting imide **109** was prepared by the reaction of the preformed mixed anhydride of 4-benzyloxybutyric acid and pivaloyl chloride, with the lithium salt of oxazolidinone **10**, in 72% yield after recrystallization. Treatment of imide **109** with 1.05 equiv of LDA (-78°C, THF, 0.5 h) followed by the reaction with methallyl iodide

Scheme XI



(5 equiv, -40°C, 12 h) afforded oxazolidinone **110** as a 95:5 mixture of epimers at C_2. The unpurified mixture was then treated with LAH (2 mol equiv, THF, -78°C→0°C) to afford alcohol **111** in 70% yield after chromatography and distillation. Oxazolidinone **10** was recovered in 73% yield. Oxidation with sulfur trioxide pyridine complex in dimethyl sulfoxide (3 equiv of SO_3.py, 6.5 equiv of Et_3N, DMSO, 25°C, 30 min) afforded aldehyde **112**. Aldol condensation of the unpurified aldehyde **112** with 1.1 equiv of boron enolate **47** (CH_2Cl_2, -78°C→0°C) gave aldol adduct **113**. GC analysis indicated 4.5% of an isomer (presumably the C_4-epimer) and less than 0.7% of any other observable epimer. Recrystallization afforded pure **113** in 89% yield based on alcohol **111**.

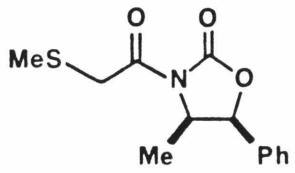
Scheme XII[33]



(a) LDA, THF, -78°C; (b) LAH, THF, -78°C; (c) SO_3.py, Et_3N, DMSO (**111**→**112**); (d) TESOTf, Et_3N, CH_2Cl_2 (**113**→**114**); (e) $PhCH_2OLi$, THF, 0°C (**114**→**115**); (f) RED-AL, THF, -10°C (**115**→**116**); (g) SO_3.py, Et_3N, DMSO (**116**→**117**).

The results on this scheme are due to Dr. T. Godel.

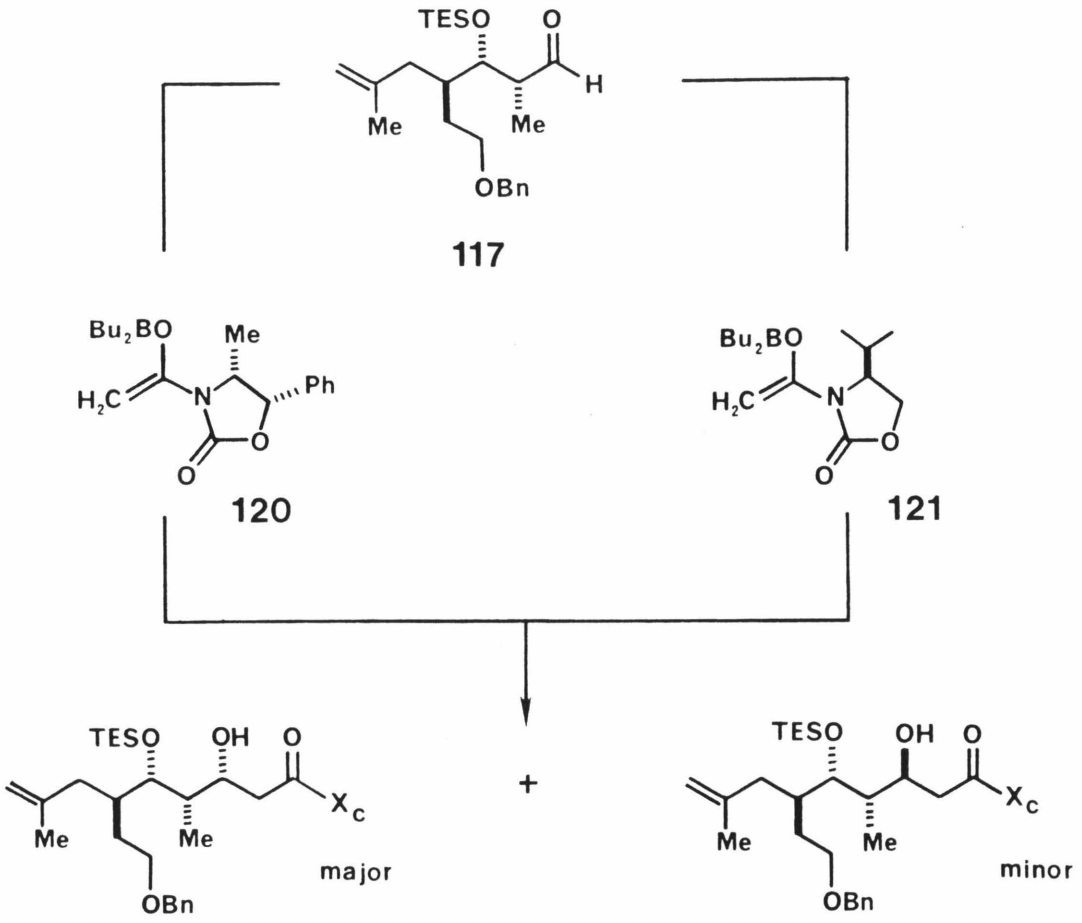
Conversion of **113** into the desired aldehyde **117** involved the following series of reactions: (1) protection of the alcohol as the triethylsilyl ether (TESOTF, NEt_3, CH_2Cl_2, 25°C) to afford **114**; (2) transesterification into benzyl ester **115** ($PhCH_2OLi$, THF, 0°C, 4 h, 88% yield from **112**); (3) reduction to alcohol **116** (RED-AL, THF, -10°C, 20 min, 84% yield) and; (4) oxidation to aldehyde **117** (SO_3.py, Et_3N, DMSO, 25°C, 97% yield). Reaction of aldehyde **117** with 1.05 equiv of the preformed boron enolate of the thiomethyl-acetyl imide **119** (CH_2Cl_2, -78°C → 0°C) afforded aldol adduct **118** in 75% yield after chromatography.



119

Before further elaboration of compound **118**, we felt that the aldol condensation leading into the C_2-C_3 bond formation needed to be studied in some more detail. We knew from early studies[20] that boron enolates **120** and **121** (Scheme XIII) react with poor selectivity when condensed with aldehydes not bearing a chiral center. However, their condensation with chiral aldehydes had never been tested.

Scheme XIII



122: $X_c = X_N$

123: $X_c = X_V$

124: $X_c = X_N$

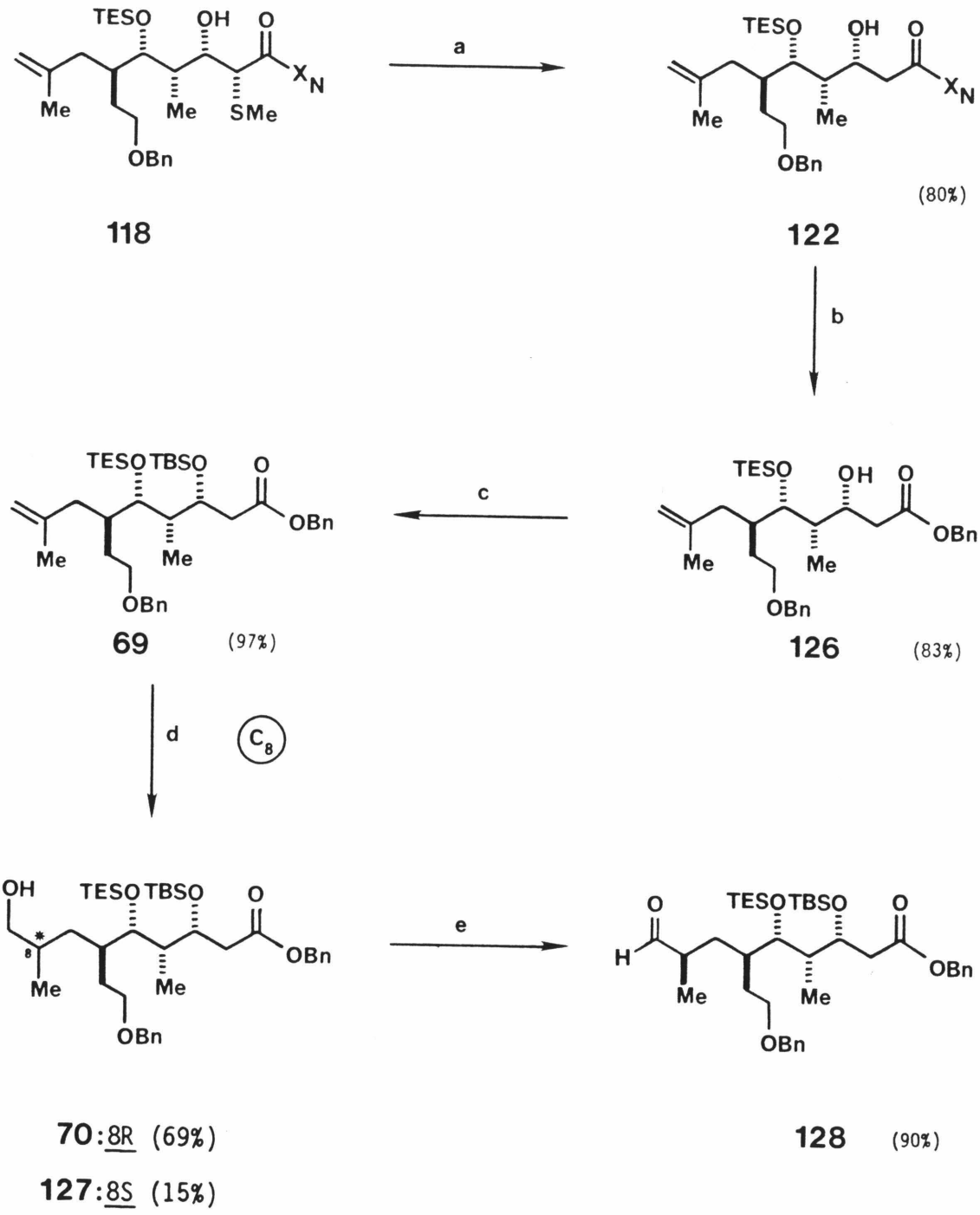
125: $X_c = X_V$

Normally, the aldol condensation of chiral aldehydes with achiral enolates affords ratios of products that fall in the 1 to 4:1 range, the so called Cram-adduct being generally predominant.[36]

However, these ratios can be improved to high levels of diastereoselection if both the aldehyde and the enolate have consonant chirality, that is, when both favor one particular relative stereochemistry of the new asymmetric centers (double stereodifferentiation). In a similar way, we felt that the resident chiralities of aldehyde **117** and enolate **120** could cooperate in a consonant fashion to afford good diastereofacial selection. However, when aldehyde **117** was condensed with boron enolate **120** (CH_2Cl_2, -78°C →0°C) (Scheme XIII) compound **122** was formed only with moderate preference over **124** (**122**:**124** = 75:25, as indicated by GC). Aldehyde **117** was also condensed under the same conditions with enolate **121**, yielding a **123**:**125** ratio of 70:30. Thus, independently of the imide used in the reaction, we obtained the 3(R) adduct with a selection of ca. 3:1 in both cases. In this reaction the chirality transfer from the enolate was negligible, as we had previously observed with simpler, achiral aldehydes.[20b] The moderate selection was due almost entirely to the aldehyde's chirality. The absolute configuration of C_3 in **122** was assigned (R) by an alternative preparation (see Scheme XIV). Transesterification ($PhCH_2OLi$, THF) of **122** and **123** lead to the same benzyl ester **126**. Transesterification of **124** and **125** gave also one ester, different from **126**. These results proved the 3(R) and 3(S) stereochemistries of compounds **123** and **124** respectively.

The disappointing results described above, which were aimed at establishing the C_3 hydroxyl stereochemistry, led us back to the utilization of our operationally effective chiral acetate enolate synthon **119**. Thus, with compound **118** in hand, two main transformations needed to be accomplished: desulfurization and hydroboration of the olefin. We found out that best yields on subsequent reactions were obtained when desulfurization was performed immediately after the aldol condensation. Indeed, the release of congestion at the C_2 position facilitated in a great deal both, the C_3 hydroxyl protection and the chiral auxiliary removal necessary for our synthesis. Thus, treatment of thioether **118** with a suspension of Raney-Nickel[47] (acetone, EtOH, 25°C) afforded **122** in 80% yield (Scheme XIV). A byproduct, tentatively assigned as the 3-dehydroxy-**122**, was isolated in 10% yield. This material was probably formed *via* elimination of water followed by the *in situ* reduction of the α,β-unsaturated imide. Transesterification of **122** with 1.8 equiv of lithium benzyloxide (THF, -50°C, 4 h) afforded benzyl ester **126** in 83% yield. As we already mentioned, the absence of an α substituent in **122** allowed this reaction to proceed at low temperatures, affording better yields. Benzyl ester **126** was protected as the *t*-butyldimethylsilylether **69** (TBSOTF, 1.5 equiv, Et_3N, CH_2Cl_2) in 97% yield. The final asymmetric center, C_8, was constructed *via* a hydroboration process of **69** (2 equiv of thexylborane, THF, 0°C, 5 h; then H_2O_2, pH 9.2, MeOH, 0°C) which gave a

Scheme XIV



(a) Ni-Ra, acetone, 25°C; (b) $PhCH_2OLi$, THF, -50°C; (c) TBSOTf, Et_3N, CH_2Cl_2; (d) $ThxBH_2$, THF, 0°C; H_2O_2; (e) SO_3-py, Et_3N, DMSO.

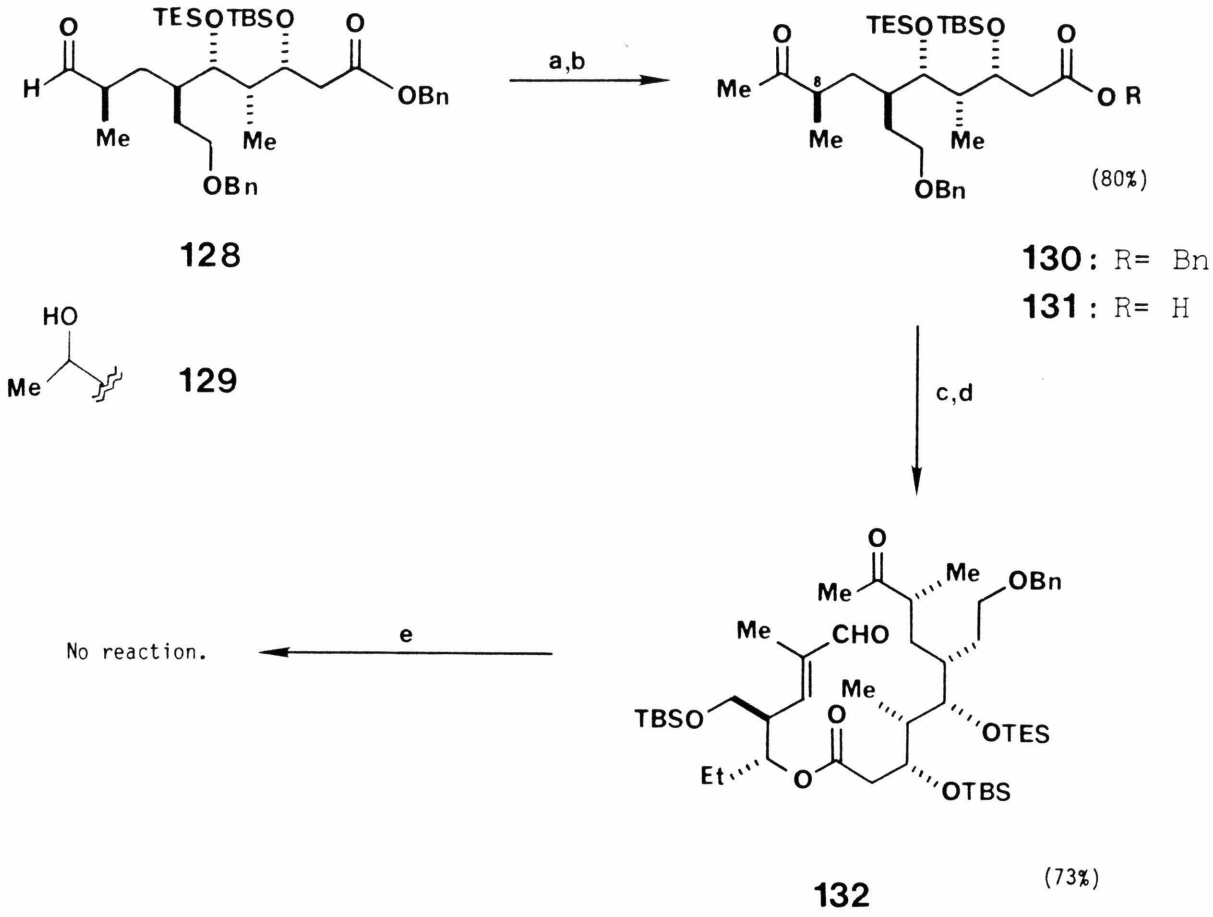
69% yield of alcohol **70** along with a 15% yield of its C_8-epimer, **127**. This 4.5:1 ratio was also supported by the careful integration of the C_5-**H** in the 500 MHz ^1H NMR spectrum of an unpurified reaction mixture.

The conversion of alcohol **70** to methyl ketone **130** was accomplished in three steps. Thus, oxidation of **70** (SO_3.py, NEt_3, DMSO) gave aldehyde **128** in 93% yield, which upon treatment with lithium dimethyl cuprate (Et_2O, -78°C, 1.5 h) afforded an 87% yield (based on alcohol **70**) of the corresponding secondary alcohol **129** (Scheme XV). Two-phase Jones' oxidation[37] ($Na_2Cr_2O_7$, H_2SO_4, H_2O-Et_2O, 25°C, 2 h) afforded **130** in 86% yield. This process occurred without any detectable epimerization by TLC analysis, as determined by monitoring the reaction with an authentic sample of the C_8-epimer of **130**, derived from alcohol **127**.

Selective hydrogenolysis of **130** (H_2, 5% Pd-C, EtOAc, 25°C 45 min) afforded a quantitative yield of unpurified keto acid **131**, which was coupled with alcohol **102** (1:1 mixt. of substrates, DCC (1.1 equiv), DMAP (catalytic), CH_2Cl_2, 25°C, 7 h) to give **132** in 73% yield, based on **130**. This material showed a much lower rate of decomposition than the corresponding unsubstituted counterpart **106** (Scheme X).

The setting for the projected macroaldol reaction was now completed. Thus, compound **132** was diluted in ether and added to a cooled (-78°C) solution containing 2.2 equiv of di-n-butylboryl

Scheme XV



(a) Me_2CuLi, Et_2O, -78°C (**128**→**129**); Jones' oxid., H_2O-Et_2O, 25°C (**129**→**130**); (c) H_2 (Pd-C), EtOAc, 25°C (**130**→**131**); (d) **102**, DCC, DMAP (**131**→**132**); (e) Bu_2BOTf, $(\underline{i}Pr)_2NEt$, Et_2O, 10^{-3} $\underline{M}$.

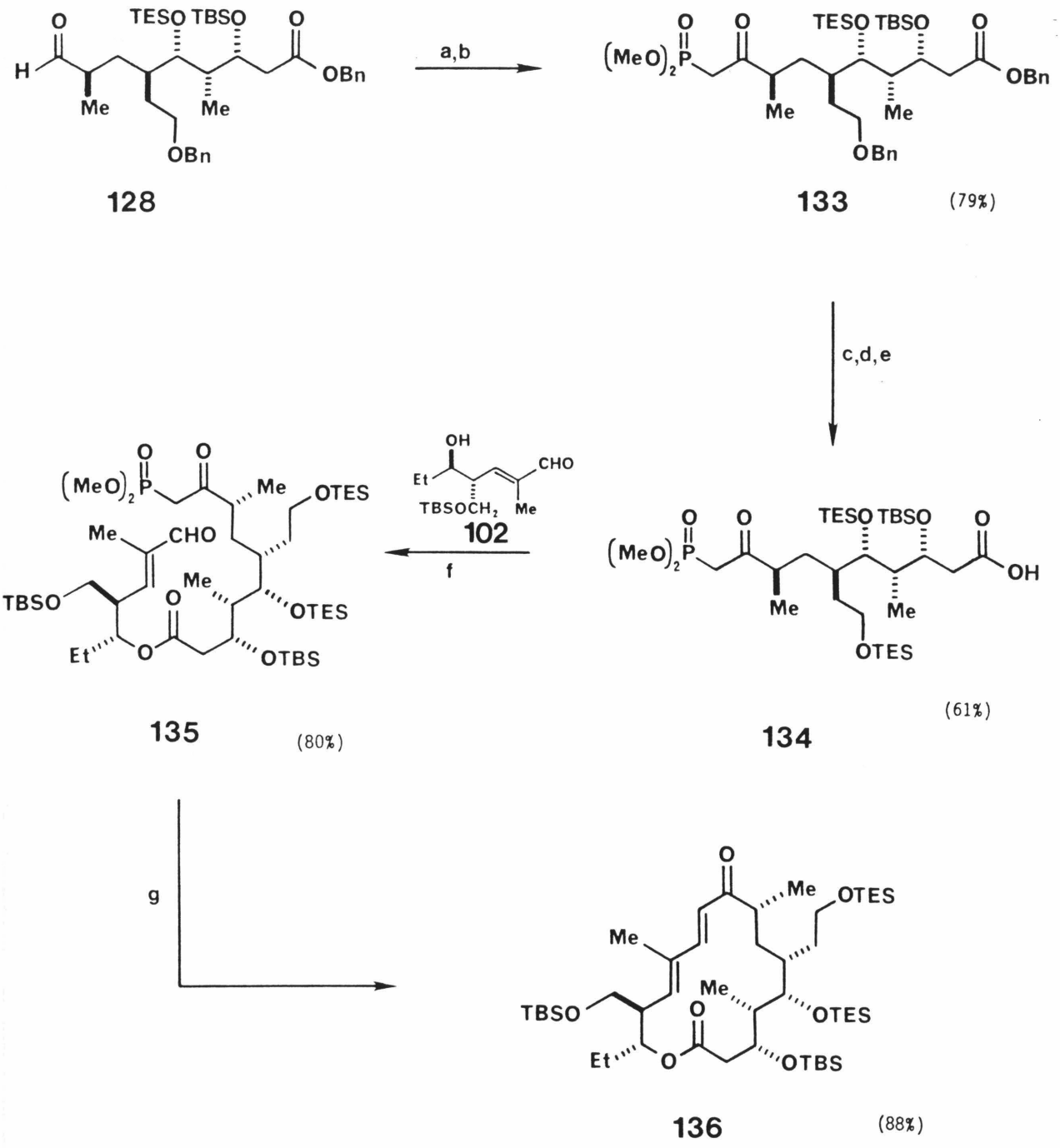
triflate and 2.4 equiv of diisopropylethylamine in ether (concentration of **132** = 10^{-3} $\underline{M}$). After 1.5 h, no reaction was observed by TLC. Subsequent additions of solutions containing 1:1.1 mixtures of

triflate and amine did not make any change. No transformation was observed after stirring the mixture at -20°C overnight. Oxidative workup and product isolation resulted in recovery of **132**. A similar reaction carried out in CH_2Cl_2 again failed to proceed at -78°C, and, upon warming to 0°C, afforded a complex mixture of unidentified products.

In an attempt to understand the cause of this failure, we tested the reaction on its bimolecular counterpart. For this purpose, alcohol **102** was protected as the acetate, and acid **131** was transformed into the methyl ester. Then, when a 1:1 mixture of these compounds in CH_2Cl_2 (0.06 M) was successively treated with diisopropylethylamine (1.8 equiv) and di-n-butylboryl triflate (1.2 equiv), again TLC showed no reaction at -78°C, 0°C or 25°C for 0.5 h. Product isolation afforded starting materials. The mixture did not react even upon treatment with 2 equiv of LDA (THF, -78°C, 0°C, 25°C). These experiments indicated that, for some unknown reason, the substrate was very reluctant to enolize, or, in the case that it did, the enolate was very unreactive. The possibility existed that the reaction might have been quenched by adventious traces of moisture that might have been present in the large amount of solvent (ether) required for the intramolecular reaction. However, if this were the case, at least some reaction should have been observed in the bimolecular case, where the amount of solvent was much smaller.

Disappointed by these results, we decided to direct our efforts towards the synthesis of the macro-Wittig precursor, as depicted in Scheme XVI. Addition of a THF solution of aldehyde **128** into a cooled (-100°C) solution containing the lithium salt of dimethylmethylphosphonate[38] resulted in attack at both the aldehyde and the ester carbonyls, affording only 54% yield of the desired secondary alcohol (based on alcohol **70**). Attempts to improve the regioselectivity using milder nucleophiles (organocuprate[38] and organozinc[39] derivatives) (-78°C → 25°C) resulted in recovery of starting material. Fortunately, however, the organomagnesium derivative proved to have the desired reactivity, in that it reacted very selectively with the aldehydic functionality at -50°C. Thus, the lithium salt of dimethylmethylphosphonate in THF was treated with a solution of magnesium bromide (-78°C → 0°C), and an aliquot (1.6 equiv) was added to a solution of aldehyde **128** in THF (-78°C → -50°C). Collins' oxidation (7 equiv of CrO_3.2py, CH_2Cl_2)[40] of the unpurified resulting β-hydroxyphosphonate afforded β-ketophosphonate **133** in 79% overall yield from aldehyde **128** after chromatography. Both benzyl ester and benzyl ether groups of **133** were cleaved by hydrogenolysis (H_2, 10% Pd-C, CH_2Cl_2, 25°C, 1 h). The unpurified resulting hydroxyacid was diluted in CH_2Cl_2 and treated successively with triethylamine (4 equiv) and t-butyldimethylsilyltriflate (2.5 equiv). The silyl ester functionality was selectively hydrolyzed (H_2O, 3 h) to afford acid **134** in 61%

Scheme XVI



(a) $(MeO)_2P(O)CH_2MgBr$, THF, -50°C; (b) $CrO_3.2py$, CH_2Cl_2; (c) H_2, 10% Pd-C, CH_2Cl_2; (d) TESOTf, Et_3N, CH_2Cl_2; (e) H_2O; (f) **102**, DCC, DMAP; (g) K_2CO_3; 18-cr-6, 10^{-3} M, tol.

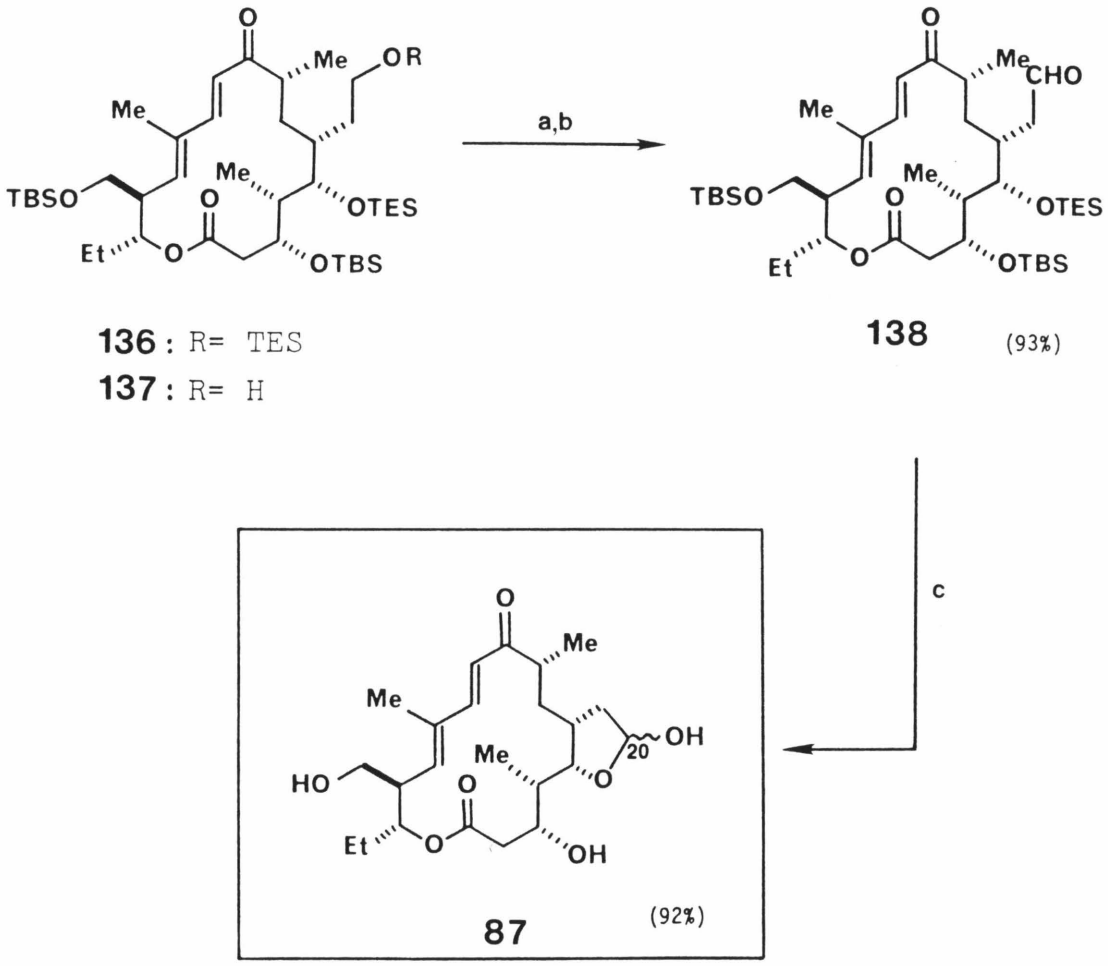
yield from **133**. Acid **134** was esterified with freshly prepared alcohol **102** (1.15 equiv) (DCC, DMAP, CH_2Cl_2, 1M, 25°C, 6 h) affording ester **135** in 80% yield.

When a 10^{-3} M solution of **135** in anhydrous toluene was treated with anhydrous K_2CO_3 (12 equiv) in presence of 18-crown-6 ether at 60°C,[12b] formation of macrocycle **136** occurred very smoothly and cleanly (16 h). Aqueous workup and flash chromatography afforded a 88% yield of cyclized product, **136**. Clearly, this method developed by Nicolaou stands unique in its high efficiency.

The last sequence of steps leading to our target molecule are shown in Scheme XVII. The primary triethylsilyl ether functionality in **136** was selectively hydrolyzed by treatment with mild acid (1:4 of 0.1% HCl:THF, 25°C, 1 h) and oxidized (10 equiv of CrO_3.2py)[40] to the crystalline aldehyde **138** in 93% yield. Finally, the three remaining silyl ethers were removed by treatment of **138** with hydrofluoric acid (1:5 of 48% aq. HF:CH_3CN, 25°C, 12 h). Crystalline, (+)-tylonolide hemiacetal **87** was isolated in 92% yield after chromatography, as a mixture of anomers at C_{20}.

A sample of **87** derived from natural tylosin[41] was prepared for comparison purposes, following the literature procedure.[2,32] Thus, mild acidic hydrolysis (2:1 THF:10% aq HCl, 25°C, 1 h) of tylosin detached the sugar mycarose affording desmycosin in 95% yield. Stronger acidic conditions (5% HCl, 90°C, 24 h) hydrolyzed the remaining neutral sugar linkage, delivering mycinose, and affording

Scheme XVII



136 : R= TES

137 : R= H

138 (93%)

87 (92%)

(a) 0.1% HCl:THF, 25°C; (b) CrO_3.2py, CH_2Cl_2; (c) HF, H_2O-CH_3CN, 25°C.

5-O-mycaminosyltylonolide (OMT) in low yield (7%). Finally, the mycaminosyl moiety was removed *via* a Polonovsky reaction of the corresponding N-oxide (MCPBA, CH_2Cl_2; then TFAA, CH_2Cl_2; then NaOAc in THF:H_2O). Chromatography afforded a sample of naturally derived **87**, in 28% yield. The synthetic and the naturally derived materials showed identical physical properties (TLC, mp, IR, 500 MHz ^1H NMR, ^{13}C NMR and specific rotation).

Tylonolide hemiacetal presents some unexpected features. When a solution of **87** in chloroform was concentrated *in vacuo*, the material was semicrystalline and had no sharp melting point. On the other hand, crystallization from dichloromethane:hexane afforded a crystalline compound (mp synth: 154.5-156.5°C; nat: 155-157°C). The proton NMR spectrum of this material indicated that hexane had been occluded during crystallization in a proportion of *ca*. 2:1 of **87**:hexane. The 500 MHz ^1H NMR spectra of the synthetic and naturally derived tylonolide hexane complexes are showed in pages 351-356. Due to the presence of two isomers (*ca*. 3:1 anomeric mixture at C 20) most of the signals are doubled. The peaks are assigned based on the reported spectrum of tylonolide[5b] or by comparison with the reported spectra of tylosin derivatives.[6,9] In p. 356, the peaks labeled "hex" are due to the hexane occluded during recrystallization. In p. 350 is shown the spectrum of free tylonolide (*i.e.* without hexane) in presence of D_2O. The changeable protons resonate at δ 3.8, 3.2 (1/3 H) and 2.9 (2/3 H). The third

hydroxylic proton might be forming part of one of the multiplets, and therefore, difficult to visualize.

IV. Summary

The enantioselective total synthesis of (+)-tylonolide, cyclic 5,20-hemiacetal is reported. The utility of highly selective alkylation and aldol reactions, using norephedrine and valine-derived oxazolidinones, is demonstrated by the construction of 6 of the 7 chiral centers present in the molecule. The remaining asymmetric center is created *via* hydroboration. The linear precursor is closed to a 16-membered ring by means of a Wittig-Horner reaction. The longest sequence in the synthesis involves 24 steps (from oxazolidinone **109**) and proceeds with an overall yield of 3%.

Experimental Section

General. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4210 spectrophotometer. 90 MHz ^{1}H NMR spectra were recorded on a Varian Associates EM-390 spectrometer and are reported in ppm on the δ scale, from the indicated reference. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), coupling constant (in Hz), integration and interpretation. 500 MHz ^{1}H NMR spectra were recorded on a Bruker WM-500 spectrometer at the Southern California Regional NMR facility. ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz) spectrometer and are reported in ppm on the δ scale from the indicated reference. Combustion analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, Michigan), Galbraith Laboratories, Inc. (Knoxville, Tennessee), or Mr. Lawrence Henling (California Institute of Technology). Optical rotations were recorded on a Jasco DIP-181 digital polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^{25}$, solvent, and concentration (c = g/100 ml).

Analytical gas-liquid chromatography (GC) was carried out on a Hewlett Packard 5880 A level 3 gas chromatograph equipped with a split mode capillary injection system and a flame ionization detector, using a 25 m x 0.2 mm flexible fused silica capillary

column wall-coated with Carbowax 20 M or Methyl Silicone (SP-2100), or a 30 m x 0.32 mm fused silica capillary wall-coated with SE-54. Unless otherwise noted, injector and detector temperatures were 250°C. Data are reported as follows: column type, oven temperature, and retention time (t_r).

Liquid chromatography was performed using a forced flow (flash-chromatography) of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). Data are reported as follows: column diameter, weight of silica and eluent composition. Medium pressure liquid chromatography (MPLC) was carried out using EM Reagents LoBar Silica Gel 60 prepacked columns (column size indicated) on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP-SY Lab Pump. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates.

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, benzene and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, diisopropylethylamine, diisopropylamine, triethylamine and boron trifluoride etherate were distilled from calcium hydride. Dimethyl sulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over activated 4 Å molecular sieves.

Unless otherwise specified, all non-aqueous reactions were conducted under a rigorously dried argon atmosphere, using oven-dried glassware.

(S,E)-4-(1-Methylethyl)-3-(1-oxo-2-butenyl)-2-oxazolidinone (92). To a mechanically stirred, cooled (-78°C) solution of **9** (11.62 g, 90 mmol) and a trace amount of diphenylacetic acid (used as an indicator) in anhydrous tetrahydrofuran (250 mL), was added a 1.7 M solution of n-butyllithium in hexane (52.5 mL, 90 mmol, 1 equiv) until appearance of a pink coloration (i.e. formation of the diphenylacetate dianion). The slurry was stirred at -78°C for 15 min, and then quenched by the quick addition of purified crotonyl chloride[42] (9.0 mL, 94.5 mmol, 1.05 equiv). The cooling bath was removed and the mixture was allowed to warm slowly (45 min) to room temperature, stirred an additional 1.5 h and quenched with 100 mL of saturated aqueous ammonium chloride. The volatiles were removed in vacuo, and the remaining mixture extracted with dichloromethane (2 x 200 mL). The organic phase was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), and with brine (1 x 100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to 18 g of a yellowish solid. Recrystallization (ether-hexane) afforded 13.7 g (78%) of the title compound as white needles: mp 56.5-57.5°C; IR (CH_2Cl_2) 3060, 2975, 1780, 1685, 1640, 1340, 1210, 1038 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.27-6.97 (m, 2H, olefinic

H), 4.56-4.13 (m, 3H, -NC$\underline{H}$C$\underline{H}_2$O), 2.60-2.23 (m, sym, 1H, $(CH_3)_2C\underline{H}$), 1.95 (d, J = 5.5, 3H, $C\underline{H}_3CH$=), 0.92 (d, J = 7, 3H, $C\underline{H}_3CHCH_3$), 0.89 (d, J = 7, 3H, $CH_3CHC\underline{H}_3$); $[\alpha]_D^{25}$ = +109.9° (CH_2Cl_2, c = 2.5).

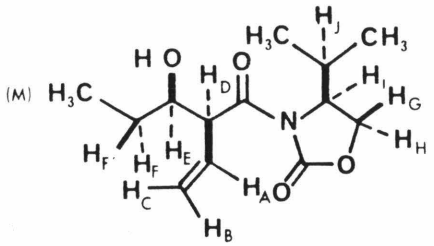
Anal. calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67. Found: C, 60.99; H, 7.56.

(3(2S,3R),4S)-3-(2-Ethenyl-3-hydroxy-1-oxopentyl)-4-(1-methylethyl)-2-oxazolidinone (93). To a cooled (-78°C) solution of imide **92** (5.85 g, 29.6 mmol) in anhydrous dichloromethane (50 mL) was added di-n-butylboryl triflate (8.00 mL, 32.6 mmol, 1.1 equiv) over 30 seconds, resulting in a yellow solution. After 5 min, anhydrous triethylamine (4.97 mL, 35.5 mmol, 1.2 equiv) was added over 2 min, resulting in the disappearance of most of the yellow color. The solution was stirred at -78°C for 30 min, then allowed to warm to 0°C slowly, and stirred at this temperature for 1 h. The solution was recooled (-78°C) and freshly distilled propionaldehyde (2.77 mL, 38.5 mmol, 1.3 equiv) was added in one portion. The clear solution was stirred at -78°C for 1.5 h, slowly warmed to 0°C and stirred for 45 min. The reaction was quenched by the addition of 30 mL of phosphate buffer (pH 7), poured into a 500-mL flask containing 70 mL of methanol, cooled to 0°C, and treated with a solution of 25 mL of 30% aqueous hydrogen peroxide in 25 mL of methanol for 1 h. The organic solvents were removed in vacuo, and the aqueous residue extracted with ether (3 x 100 mL). The combined ethereal layers

were carefully washed with saturated aqueous sodium sulfite. The sulfite aqueous solution was back extracted with ether (1 x 50 mL), and the combined ethereal layers were washed with 5% aqueous sodium bicarbonate. The aqueous bicarbonate solution was back extracted with ether (3 x 20 mL). Pentane was added to the combined organic layers, and the cloudy solution was dried over anhydrous sodium sulfate, filtered and concentrated to a colorless oil. Gas chromatography analysis (SE-54, 220°C, 5 PSI, t_r = 3.63 min) of the silylated (triethylsilyltriflate, triethylamine, CH_2Cl_2, 5 min) unpurified aldol adduct indicated **93** to be $\geq$ 98.6% diastereomerically pure. Flash chromatography (50 mm, 210 g silica, 50% ethyl acetate:hexane) afforded 7.09 g (94% yield) of pure **93** as a colorless oil: R_f 0.23 (30% ethyl acetate:hexane); IR (CH_2Cl_2) 3800-3400 (br), 3060, 2970, 1783, 1685, 1385, 1372, 1225, 1210, 750 cm^{-1}; ^1H NMR (500 MHz, CCl_4) δ (TMS) 6.000 (d of d of d, J_{AC} = 18.0, J_{AB} = 10.0, J_{AD} = 9.1, 1H, H_A), 5.376 (d of d, J_{CA} = 18.0, J_{CB} = 2.0, 1H, H_C), 5.216 (d of d, J_{BA} = 10.0, J_{BC} = 2.0, 1H, H_B), 4.654 (d of d, J_{DE} = 3.5, J_{DA} = 9.1, 1H, H_D), 4.122-4.082 (m, 1H, H_E), 3.853 (d of d of d, J_{IG} = 8.5, J_{IH} = 4.7, J_{IJ} = 3.5, 1H, H_I), 3.697-3.608 (m, 2H, H_G, H_H), 3.086 (br s, 1H, -O$\underline{H}$), 2.125 (q of q of d, J_{JK} = J_{JL} = 7.0, J_{JI} = 3.5, 1H, H_J), 1.610-1.514 (m, 1H, $CH_3\dot{C}\underline{H}(H)$), 1.480-1.393 (m, 1H, $CH_3\dot{C}H(\underline{H})$), 0.993 (t, J_{MF} = 7.5, 3H, $CH_{3(M)}$), 0.618 (d, J = 7.0, 3H, $C\underline{H}_3\dot{C}HCH_3$), 0.600 (d, J = 7.0, 3H, $CH_3\dot{C}HC\underline{H}_3$); ^{13}C NMR (CCl_4) δ (TMS) 173.65, 152.66, 131.99, 120.23,

72.53 (carbinol), 62.58, 57.77, 51.47, 28.07, 26.84, 17.74, 14.49, 10.07; $[\alpha]_D^{25}$ = -12.4° ($CHCl_3$, c 3.2).

Anal. calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29. Found: C, 60.97; H, 8.38.



93

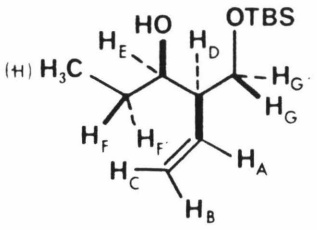
(3R,4R)-4-Hydroxy-3-((((1,1-dimethylethyl)dimethylsilyl)oxy)-methyl)-1-hexene (98). A solution containing imide **93** (1.49 g, 5.83 mmol) in 20 mL of anhydrous tetrahydrofuran was treated successively with glacial acetic acid (0.5 mL, 8.7 mmol, 1.5 equiv) and tri-n-butylborane (1.75 mL, 6.4 mmol, 1.1 equiv). After stirring the colorless solution for 1.5 h at room temperature, the resultant boron aldolate **103** was cooled to 0°C and a 1.3 M solution of lithiumborohydride in dry tetrahydrofuran (8 mL, 2 molar equiv) was added over 30 sec, occasioning evolution of hydrogen. The reaction mixture was stirred at 0°C for 1 h, and quenched by the careful addition of a solution containing 20 mL of methanol, 20 mL of phosphate buffer (pH 7), and 10 mL of 30% aqueous hydrogen peroxide. The mixture was stirred for 10 min at 0°C followed by 1.5 h at room

temperature. The volatiles were removed in vacuo and the remaining aqueous solution extracted with dichloromethane 20x (i.e. until TLC analysis indicated the absence of diol **104** in the aqueous phase). The combined organic layers were washed with 40 mL of 5% aqueous sodium bicarbonate, and the aqueous layer back extracted with dichloromethane until TLC analysis indicated absence of diol **104** in the aqueous phase. The combined layers were dried over anhydrous sodium sulfate, filtered and concentrated to a colorless, clear liquid. Flash chromatography (50 mm, 140 g silica, diethyl ether) afforded 653 mg (86%) of diol **104** (R_f 0.26, ether) as a clear liquid, and 747.4 mg (99%) of valine oxazolidinone **9** (R_f 0.17, ether).

A portion of diol **104** (338 mg, 2.6 mmol) was diluted in anhydrous dichloromethane (3.5 mL), and treated successively with dry triethylamine (0.47 mL, 3.35 mmol, 1.3 equiv), N,N-dimethyl-4-amino pyridine (20 mg, 6% molar equiv) and t-butyldimethylsilyl-chloride (509 mg, 3.35 mmol, 1.3 equiv) according to the procedure described by Hernandez.[30] After stirring the solution for 3.5 h at room temperature, saturated aqueous ammonium chloride was added. The layers were separated and the aqueous layer was extracted once with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to a colorless oil. Gas chromatography analysis (SE-54, 100°C, 15 PSI, t_r = 2.76 min) showed **98** to be $\geq$ 97% pure. Flash chromatography (40 mm, 70 g

silica, 20% ethyl acetate:hexane) afforded 578.0 mg (78% from **93**) of alcohol **98** as a colorless oil: R_f 0.50 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3500 (br), 3090, 3020, 1638, 1462, 1255, 1110, 1085, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ($CHCl_3$) 5.907 (d of d of d, J_{AC} = 17.5, J_{AB} = 10.3, J_{AD} = 9.2, 1H, H_A), 5.165 (d of d, J_{BA} = 10.3, J_{BC} = 2.2, 1H, H_B), 5.095 (d of d, J_{CB} = 2.2, J_{CA} = 17.5, 1H, H_C), 3.815 (m, 2H, H_G, $H_{G'}$), 3.743 (octuplet, J = 3, 1H, H_E), 3.027 (d, J = 3.5, 1H, O<u>H</u>), 2.252-2.204 (m, 1H, H_D), 1.53-1.38 (m, 2H, H_F,$H_{F'}$), 0.926 (t, J = 7.5, 3H, $CH_{3(H)}$), 0.880 (s, 9H, $(\underline{CH}_3)_3\overset{|}{C}$), 0.058 (s, 3H, $\underline{CH}_3\overset{|}{Si}CH_3$), 0.054 (s, 3H, $CH_3\overset{|}{Si}\underline{CH}_3$); $[\alpha]_D^{25}$ = -20.1° ($CHCl_3$, <u>c</u> 4.4).

<u>Anal</u>. calcd. for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.54. Found: C, 63.72; H, 11.27.



98

(2E,4R,5R)-5-Hydroxy-4-((((1,1-dimethylethyl)dimethylsilyl)-oxy)methyl)-2-methyl-2-heptenoic acid, ethyl ester (100). Into a cooled (-78°C) solution of olefin **98** (2.91 g, 11.9 mmol) in 50 mL of methanol, containing 10 drops of Sudan III ozonolysis indicator

solution (pink color), was bubbled ozone until the pink color disappeared. Argon was bubbled and then dimethylsulfide (15 mL, 240 mmol, 20 equiv) was added. The solution was slowly warmed to room temperature and stirred for 4 h. The volatiles were removed in vacuo, and the slightly yellow remaining oil diluted in 40 mL of freshly distilled toluene, under argon. The solution was then treated with (carbethoxyethylidene)triphenylphosphorane (7.76 g, 21 mmol, 1.8 equiv) which was added in portions into the reaction flask. The solution was stirred at 70°C for 9 h, then concentrated in vacuo. Most of the triphenylphosphine oxide formed during the reaction was removed by precipitation with ether first, then with 20% ethyl acetate:hexane. Filtration, concentration and flash chromatography (50 mm, 200 g silica, 20% ethyl acetate:hexane) afforded 3.57 g (91% from **98**) of ethyl ester **100** as a slightly yellow oil. Diastereomer analysis before and/or after chromatography (SE-54, 150°C, 10 PSI, t_r **isomer** = 6.24 min, t_r **100** = 6.48 min) revealed a ratio of **isomer**:**100** of 1.3:98.7: R_f 0.44 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3500 (br), 3015, 2862, 2840, 1700, 1460, 1355, 1090, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ($CHCl_3$) 6.886 (d of q, J_q = 1.2, J_d = 10.5, 1H, olefinic H), 4.238-4.104 (m, 2H, $CH_3C\underline{H}_2OC(=O)$), 3.846 (octuplet, J = 2.5, J = 3.2, 1H, $HOC\underline{H}$-), 3.808 (q, J = 10.0, 1H, $TBSOC\underline{H}(H)$), 3.799 (q, J = 10.5, 1H, $TBSOCH(\underline{H})$), 3.015 (d, J = 3.2, 1H, -O$\underline{H}$), 2.634-2.586 (m, 1H, $TBSOCH_2C\underline{H}$-), 1.854 (d, J = 1.2, 3H, $C\underline{H}_3C$=), 1.500-1.330 (m, 2H, $CH_3C\underline{H}_2CH$-), 1.271 (t,

J = 7.3, 3H, $C\underline{H}_3CH_2OC{=}O$), 0.932 (t, J = 7.5, 3H, $C\underline{H}_3CH_2CH$-), 0.881 (s, 9H, $(C\underline{H}_3)_3C$), 0.046 (s, 6H, $(C\underline{H}_3)_2Si$-); $[\alpha]_D^{25}$ = -11.6° ($CHCl_3$, c 2.2).

Anal. calcd. for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found: C, 61.83; H, 10.25.

Note: This compound decomposed almost completely after two weeks of standing at room temperature.

(2E,4R,5R)-4-((((1,1-Dimethylethyl)dimethylsilyl)oxy)methyl)-2-methyl-2-heptene-1,5-diol (101). To a well stirred, cooled (-78°C) solution of ethyl ester **100** (44 mg, 0.133 mmol) in 3 mL of anhydrous dichloromethane was added a 1 M solution of diisobutylaluminum hydride in dichloromethane (0.46 mL, 0.46 mmol, 3.5 equiv). The solution was stirred for 15 min and quenched by the addition of saturated aqueous ammonium chloride. The white slurry was carefully acidified with 1 N aqueous hydrochloric acid, and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 36.0 mg (96%) of diol **101** as a white crystalline compound, pure by ^1H NMR and TLC analysis. An analytical sample was obtained by recrystallization from ether:pet. ether: R_f 0.33 (50% ethyl acetate:hexane); mp 68-70°C; IR ($CHCl_3$) 3620, 3490 (br), 3020, 1465 (d), 1255, 835; ^1H NMR (500 MHz, $CDCl_3$) δ

($CHCl_3$) 5.464 (br d of q, J_q = 1.5, J_d = 10.0, 1H, olefinic H), 3.986 (br s, 2H, HOC$\underline{H}_2$), 3.760-3.710 (br m, 1H, HOC$\underline{H}$-), 3.700 (d, J = 5.5, 2H, TBSOC$\underline{H}_2$CH-), 3.073 (br s, 1H, -O$\underline{H}$), 2.504 (decaplet, J = 2.5, 1H, TBSOCH$_2$C$\underline{H}$-), 2.154 (br, 1H, -O$\underline{H}$), 1.650 (br d, J = 1.2, 3H, $\underline{H}_3$CC=), 1.47-1.34 (m, 2H, $CH_3C\underline{H}_2$), 0.906 (t, 3H, $C\underline{H}_3CH_2$), 0.860 (s, 9H, $(C\underline{H}_3)_3C$), 0.030 (s, 3H, $C\underline{H}_3SiCH_3$), 0.025 (s, 3H, $CH_3SiC\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 137.89, 121.52, 75.11, 68.49, 65.89, 43.86, 27.54, 25.79, 18.12, 14.22, 10.39, -5.60; $[\alpha]_D^{25}$ = -19.3° ($CHCl_3$, c 1.5).

Anal. calcd. for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.34; H, 11.02.

(2E,4R,5R)-5-Hydroxy-4-((((1,1-dimethylethyl)dimethylsilyl)-oxy)methyl)-2-methyl-2-heptenal (102). A solution containing diol **101** (40.7 mg, 0.14 mmol) in 1 mL of anhydrous dichloromethane was treated with activated manganese dioxide (126 mg, 10 equiv). The black slurry was stirred at ambient temperature for 1 h, and filtered through celite. The celite was washed several times with dichloromethane and the combined filtrates were concentrated to yield 40.0 mg (100%) of aldehyde **102** as a colorless oil, pure by ^1H NMR and TLC analysis: R_f 0.31 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3500 (br), 3020, 1685, 1465 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 9.39 (s, 1H,-C$\underline{H}$O), 6.66 (br d, J = 10, 1H, olefinic H), 3.99-3.58 (m, 1H, HOC$\underline{H}$-), 3.78 (d, J = 5, 2H, TBSOC$\underline{H}_2$), 2.93 (d,

J = 3, 1H,-OH), 2.85-2.58 (decaplet, J = 3, 1H, $TBSOCH_2\underline{C}\underline{H}$-), 1.73 (d, J = 1, 3H, $\underline{C}\underline{H}_3\underline{C}$=), 1.55-1.15 (m, 2H, $CH_3\underline{C}\underline{H}_2$), 0.85 (t, J = 7, 3H, $\underline{C}\underline{H}_3\underline{C}\underline{H}_2$), 0.82 (s, 9H, $(\underline{C}\underline{H}_3)_3\underline{C}$), 0.03 (s, 6H, $(\underline{C}\underline{H}_3)_2\underline{Si}$-). A portion was chromatographed to afford an analytical sample: $[\alpha]_D^{25}$ = -29.2° ($CHCl_3$, c 1).

Note: This substance partially decomposed upon 1 day of storage at -20°C.

(4R,5S(S))-3-((4-Ethyl-2,2-dimethyl-1,3-dioxan-5-yl)carbonyl)-4-(1-methylethyl)-2-oxazolidinone (94). A cooled (-78°C) solution containing aldol adduct **93** (6.44 g, 25.2 mmol) and several drops of Sudan III ozonolysis indicator solution (pink color) in 300 mL of methanol was treated with ozone until the pinkish color disappeared. The solution was bubbled with argon to remove excess ozone and then treated dropwise with a 0.145 M solution of zinc borohydride in diethyl ether (170 mL, 1 molar equiv).[25] The solution was stirred at -78°C for 20 h, then slowly warmed to -20°C, and finally quenched by the slow addition of 5 M aqueous phosphate buffer (pH 7). The volatiles were removed in vacuo, and the remaining white slurry acidified with 3 N aqueous hydrochloric acid to pH 1 resulting in a clear solution, which was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 7.58 g of an oil.

The unpurified product was dissolved in 60 mL of acetone and treated successively with 2,2-dimethoxypropane (35 mL, 283 mmol, 11 equiv) and a catalytic amount of camphorsulfonic acid. The reaction mixture was stirred at room temperature for 2 h, quenched by the addition of saturated aqueous sodium bicarbonate and concentrated *in vacuo*. The aqueous residue was extracted with dichloromethane (3 x 100 mL), and the combined extracts filtered and concentrated to give acetonide **94** as an oil. Gas chromatography analysis (SE-54, 160°C, 10 PSI, t_r = 5.22 min) indicated **94** to be $\geq$99.7% diastereomeric pure. Flash chromatography (50 mm, 300 g silica, 26% ethyl acetate:hexane) afforded 6.19 g (82% from **93**) of the title compound as white crystals: R_f 0.42 (30% ethyl acetate:hexane); mp 48.5°-49.5°C; IR ($CHCl_3$) 3055, 2970, 1782, 1690, 1385, 1367, 1205 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 4.53-3.65 (m, 7H, -CHOC(Me)$_2$OCH$_2$CH; -NCHCH$_2$-), 2.50-2.05 (m, 1H, CH_3CHCH_3), 1.6-1.2 (m, 2H, CH_3CH_2), 1.45 (s, 3H, H_3CCCH_3), 1.37 (s, 3H, H_3CCCH_3), 1.05-0.70 (m, 9H, CH_3CHCH_3, CH_3CH_2); $[\alpha]_D^{25}$ = +142.0° ($CHCl_3$, *c* 1.85).

Anal. calcd. for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42. Found: C, 60.44; H, 8.57.

(4R,5S)-4-Ethyl-2,2-dimethyl-1,3-dioxan-5-methanoic acid, phenylmethyl ester (95). To a cooled (-15°C) solution of benzyl

alcohol (3.19 mL, 30.84 mmol, 1.9 equiv) in anhydrous tetrahydrofuran (20 mL), was added a 1.7 M solution of n-butyllithium in hexane (16.2 mL, 27.6 mmol, 1.7 equiv). After stirring for 15 min, a solution containing acetonide **94** (4.86 g, 16.23 mmol) in 16 mL of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred between -15°C and -5°C for 1.5 h, quenched with pH 7 phosphate buffer solution and concentrated in vacuo. The aqueous layer was extracted with dichloromethane (2 x 150 mL), and the combined organic layers dried over anhydrous sodium sulfate, filtered and concentrated to a yellow liquid. Gas chromatography analysis of the unpurified reaction mixture (SE-54, 150°C, 10 PSI, t_r = 4.59 min) showed **95** to be $\geq$ 98.6 diastereomerically pure. Flash chromatography (50 mm, 250 g silica, 10% ethyl acetate:hexane) afforded 4.10 g (91%) of the title compound as a colorless oil (the column was then flushed with 1:1 ethyl acetate:methanol and 1.92 g (92%) of valine oxazolidone **9** was obtained): R_f 0.53 (30% ethyl acetate:hexane); IR (CH_2Cl_2) 3050, 2990, 1730, 1453, 1384, 1202, 1168, 1102, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.58-7.25 (m, 5H, aromatic H), 5.125 (s, 2H, $PhC\underline{H}_2O$), 4.018 (t, J = 11.5, 1H, $-OCH(\underline{H})$), 3.963 (d of d of d, J = 3.1, J = 8.1, J = 11, 1H; $-OC\underline{H}-$), 3.946 (d of d, J = 5.5, J = 11.2, 1H, $-OC\underline{H}(H)$), 2.650 (d of t, J_d = 5.2, J_t = 10.2, 1H, $-C\underline{H}C=O$), 1.590-1.49 (m, 1H, $C\underline{H}(H)CH_3$), 1.472 (s, 3H, $C\underline{H}_3CHCH_3$), 1.480-1.380 (m, 1H, $CH(\underline{H})CH_3$), 1.390 (s, 3H, $CH_3C\underline{H}_3$), 0.911 (t, J = 7.2, 3H, $C\underline{H}_3CH_2$); ^{13}C NMR ($CDCl_3$) δ

(TMS) 171.37, 135.56, 128.61, 128.35, 128.09, 98.52, 71.16, 66.42, 61.35, 46.53, 29.18, 27.36, 19.30, 9.16; $[\alpha]_D^{25}$ = +30.8° ($CHCl_3$, c 2.1).

Anal. calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.33; H, 7.94.

(4R,5S)-4-Ethyl-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane (96). To a well stirred, cooled (-15°C) solution of benzyl ester **95** (3.99 g, 14.33 mmol) in 50 mL of anhydrous diethyl ether was added a 1 M solution of lithium aluminum hydride in ether (14.3 mL, 14.3 mmol, 1 molar equiv, Aldrich) dropwise. After 15 min, the reaction was quenched by the careful, successive addition of 0.5 mL of water, 0.5 mL of 15% aqueous sodium hydroxide and 1.5 mL of water. The mixture was filtered and the precipitate washed with ether. The combined filtrates were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield a clear liquid. Gas chromatography analysis (SE-54, 80°C, 10 PSI, t_r = 4.39 min) indicated **96** to be ≥99% diastereomeric pure. Flash chromatography (50 mm, 200 g, 48% ethyl acetate:hexane) afforded 2.43 g (98%) of alcohol **96** as a colorless liquid: R_f 0.21 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3630 (sharp), 3460 (br), 3010, 2940, 1460, 1380, 1368, 1195, 1000, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 3.887 (d of d, J = 5.0, J = 11.5, 1H, $-OCH_{ax}$(Heq)), 3.775 (d of d, J = 9.5, J = 11.5, $-OCH_{ax}$(Heq)), 3.654-3.586 (m, 2H, $HOCH$(H),$-OCH-$), 3.560-3.495 (m, 1H,

HOCH(H)), 2.16 (br, 1H, HO) 1.824-1.745 (m, 1H, $CH_3CH(H)$), 1.728-1.638 (m, 1H, $CH_3CH(H)$), 1.495-1.40 (m, 1H, $HOCH_2CH$-), 1.426 (s, 3H, H_3CCCH_3), 1.388 (s, 3H, H_3CCCH_3), 0.952 (t, J = 7.5, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$) δ (TMS) 98.39, 77.01, 71.36, 61.87, 61.15, 41.52, 28.72, 26.45, 19.95, 9.29; $[\alpha]_D^{25}$ = +22.3° ($CHCl_3$, c 2.1).

Anal. calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.78; H, 10.50.

(11E,13E,15R,16R)-14-((((-1,1-Dimethylethyl)dimethylsilyl)oxy)-methyl)-16-ethyl-12-methyl-oxacyclohexadeca-11,13-diene-2,10-dione (108). A solution containing di-n-butylboryltriflate (0.12 mL, 0.47 mmol, 1.2 equiv) and anhydrous diisopropylethylamine (0.095 mL, 0.55 mmol, 1.4 equiv) in anhydrous diethyl ether (30 mL) was stirred at room temperature for 10 min and then cooled to -78°C. A solution containing chromatographed, but partially decomposed,[43] ester **106** (178 mg, 0.39 mmol) in 20 mL of anhydrous diethyl ether, was added over a 10-minute period. After stirring at -78°C for 3 h, TLC analysis indicated that no further conversion was occurring. A solution containing an additional 0.12 mL (1.2 equiv) of triflate and 0.095 mL (1.4 equiv) of amine in 4 mL of ether was added slowly. The solution was stirred at -78°C for an additional 2 h, then slowly warmed to -20°C. TLC analysis now indicated that other products were being formed, probably coming from decomposition of the starting material. The reaction was quenched by the addition of

aqueous phosphate buffer, diluted with methanol and then treated with 30% aqueous hydrogen peroxide (0.5 mL) at 0°C for 1 h. Volatiles were removed in vacuo, and the remaining aqueous slurry was extracted with ether (2 x 50 mL). The combined ethereal phases were washed with 5% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. Diastereomer analysis (SE-54, 215°C, 10 PSI, t_r = 8.48 min, t_r' = 9.07 min) of the unpurified product **107** indicated a 45:55 mixture of epimers at the new created asymmetric center. Flash chromatography (20 mm, 30 g silica, 25% ethyl acetate:hexane) afforded 80 mg (45%) of compound **107** as a very thick oil, as a 44:56 (GC ratio, same conditions) mixture of TLC non-resolvable isomers. (The material was unstable to storage. Even at -20°C for 24 h considerable decomposition occurred): R_f 0.19 (30% ethyl acetate:hexane); ^{1}H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 5.6-4.8 (m, 2H, =C$\underline{H}$, O=COC$\underline{H}$-), 4.6-4.3 (m, 1H, HOC$\underline{H}$-), 3.42 (br t, J = 8, 2H, TBSOC$\underline{H}_2$), 2.9-2.1 (m, 7H, $\underline{H}$O, $\underline{H}_2$CC(=O)C$\underline{H}_2$, O=CC$\underline{H}_2$), 1.8-1.2 (m, 13H), 1.70 (s, 3H, $\underline{H}_3$CC=), 1.0-0.7 (m, 12H, C$\underline{H}_3$CH$_2$, (C$\underline{H}_3$)$_3$C), 0.0 (s, 6H, (C$\underline{H}_3$)$_2$Si-).

The mixture of isomers, **107**, (75 mg, 0.16 mmol) was then dissolved in anhydrous dichloromethane (4 mL). Freshly distilled triethylamine (0.22 mL, 1.6 mmol, 10 equiv) and dry methanesulfonyl chloride (24 μL, 0.32 mmol, 2 equiv) were added subsequently. The reaction was stirred overnight at room temperature, and at 40°C for 1.5 h. Saturated aqueous ammonium chloride was

added and the organic layer separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to an oil. Flash chromatography (20 mm, 28 g silica, 15% ethyl acetate:hexane) afforded 35.1 mg (50%) of the title compound as a colorless, thick oil: IR (CH_2Cl_2) 3030, 2745, 1728, 1680, 1598, 1460, 1210, 837 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 7.05 (d, J = 16.5, 1H, O=CCH=CH), 6.15 (d, J = 16.5, 1H, O=CCH=), 5.77 (br d, J = 12, 1H, O=CCH=CHC=CH), 4.95 (t of d, J = 3.5, J = 7.5, 1H, O=COCH-), 3.64 (d, J = 5.0, 2H, TBSOCH$_2$), 2.8-2.0 (m, 4H, -OC(=O)CH$_2$, O=CCH$_2$), 1.80 (d, J = 2, 3H, H$_3$CC=), 1.8-1.1 (m, 13H), 1.05-0.75 (m, 12H, CH$_3$CH$_2$, (CH$_3$)$_3$C), 0.05 (s, 6H, (CH$_3$)$_2$Si-); $[\alpha]_D^{25}$ = +45.8° ($CHCl_3$, c 1.7).

(4R,5S)-4-Methyl-3-(1-oxo-4-phenylmethoxybutyl)-5-phenyl-2-oxazolidinone (109). Into a dry, 3-necked, 5-L flask equipped with a constant pressure addition funnel, a septum and a mechanical stirrer was placed 4-phenylmethoxybutyric acid[44] (83.5 g, 0.43 mol), diethyl ether (2 L, freshly opened can), and triethylamine (62.2 mL, 0.44 mol, 1.03 equiv, freshly opened bottle). The solution was cooled to -78°C and pivaloyl chloride (54.6 mL, 0.44 mol, 1.03 equiv) was added over a 0.5-h period, resulting in the appearance of a white precipitate. The slurry was warmed to 0°C and stirred for 2.5 h.

In another dry, 2-L flask was weighed oxazolidone **10** (72.6 g, 0.41 mol, 0.95 equiv). The flask was purged with argon and 1 L of tetrahydrofuran (freshly opened bottle) was introduced. The solution was cooled to -78°C and a 1.65 M solution of n-butyllithium in hexane (248 mL, 0.95 equiv) was added slowly, until a pink color appeared, indicating formation of the dianion, and thus that exactly 0.95 equivalents of base had been added. The mixture was stirred for 0.5 h, and then transferred via cannula into the cooled (-78°C), mixed anhydride mixture, over a 1-h period. The reaction mixture was slowly warmed up to room temperature (1 h), then quenched by the addition of saturated aqueous ammonium chloride. Volatiles were removed in vacuo, and the remaining aqueous slurry was extracted with dichloromethane. The combined organic phases were successively washed with 1 N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 144 g of a yellow oil. Recrystallization from hot ethanol afforded 104.4 g (72%) of compound **109** as white crystals: R_f 0.32 (30% ethyl acetate:hexane); mp 69-70°C; IR (CCl_4) 3080, 3045, 2950, 2870, 1795, 1705, 1455, 1345, 1195, 1120, 1028 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.15 (m, 10H, aromatic H), 5.50 (d, J = 7, 1H, -NCHCHO-), 4.66 (qn, J = 7, 1H, -NCHCHO-), 4.48 (s, 2H, $PhCH_2$), 3.55 (t, J = 6, 2H, $PhCH_2OCH_2$), 3.06 (t, J = 8, 2H, O=CCH$_2$), 2.01 (qn, J = 7, 2H, O=CCH_2CH_2), 0.83 (d, J = 7, 3H, -NCHCH_3); ^{13}C NMR ($CDCl_3$) δ (TMS)

172.74, 152.98, 138.55, 133.42, 128.61, 128.35, 127.63, 127.50, 125.62, 78.83, 72.85, 69.28, 54.72, 32.62, 24.56, 14.56; $[\alpha]_D^{25}$ = +33.7° ($CHCl_3$, c 2.4).

Anal. calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56. Found: C, 71.43; H, 6.58.

(3(R),4R,5S)-4-Methyl-5-phenyl-3-(2-(2-(phenylmethoxy)ethyl)-1-oxo-4-pentenyl)-2-oxazolidinone (110).[33a] A dry, 3-necked, 1-L flask was fitted with a stirring bar, an additional funnel, a thermometer and a nitrogen inlet. The system was purged with nitrogen and charged with freshly distilled diisopropylamine (19.3 mL, 138 mmol, 1.1 equiv) and anhydrous tetrahydrofuran (125 mL). The solution was cooled to -78°C, and treated with a 1.63 M solution of n-butyllithium in hexane (80.3 mL, 131.2 mmol, 1.05 equiv) over a 1-h period. The mixture was stirred for 1 h and then a solution containing oxazolidone **109** (44.18 g, 125 mmol) in 125 mL of dry tetrahydrofuran was added at a rate which maintained the reaction temperature ≤-65°C. The mixture was stirred at -78°C for 0.5 h and then methallyl iodide[45] (68.8 mL, 0.625 mol, 5 equiv) was slowly added. The mixture was allowed to warm up to -40°C over a 2-h period, and stirred overnight at that temperature. The reaction was quenched by the addition of 125 mL of saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the residue partitioned between dichloromethane and water. The organic phase

was washed with saturated aqueous sodium bicarbonate (100 mL), 1 M aqueous sodium thiosulfate (100 mL), and brine (100 mL), dried over anhydrous magnesium sulfate, filtered through celite and concentrated in vacuo to afford compound **110**. The unpurified product was used in the next step without further purification. Gas chromatography analysis (SE-54, 225°C, r_t 2-epi-**110** = 9.02 min, r_t **110** = 9.87 min) afforded a ratio of 2-epi-**110**:**110** = 5:95. An analytical sample of **110** was obtained by chromatography on silica gel (MPLC, Merck-LoBar, 10% ethyl acetate:cyclohexane) as a colorless, viscous oil: R_f 0.45 (30% ethyl acetate:hexane); IR (CCl_4) 3030, 2930, 2862, 1775, 1690, 1340, 1194, 1120, 891, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.5-7.2 (m, 10H, aromatic H), 4.745-4.732 (m, 1H, H(H)C=), 4.712 (q, J = 1, 1H, H(H)C=), 4.672 (d, J = 7.5, 1H, -NCHCHO-), 4.433 (AB q, $\Delta\delta$ = 0.051 ppm, J = 11.5, 2H, $PhCH_2O$-), 4.387 (qn, 1H, J = 7.5, -NCH-), 4.32-4.26 (m, 1H, O=CCH-), 3.70-3.59 (m, 2H, $PhCH_2OCH_2$), 2.482 (d of d, J = 8, J = 13.5, 1H, =CCH(H)), 2.235-2.125 (m, 2H, =CCH(H), $PhCH_2OCH(H)$), 1.80-1.75 (m, 1H, $PhCH_2OCH(H)$), 1.775 (br s, 3H, H_3CC=), 0.705 (d, J = 6.5, 3H, -NCHCH_3); ^{13}C NMR ($CDCl_3$) δ (TMS) 176.05, 153.05, 142.65, 138.75, 133.68, 128.48, 128.28, 127.57, 125.56, 112.69, 78.18, 72.79, 69.41, 54.59, 41.53, 38.86, 32.49, 22.35, 14.62; $[\alpha]_D^{25}$ = +19.2° ($CHCl_3$, c 1.3).

Anal. calcd. for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17. Found: C, 73.75; H, 7.18.

(R)-4-Methyl-2-(2-(phenylmethoxy)ethyl)-4-pentenol (111).[33a] In a dry, 3-necked, 1-L flask fitted with a magnetic bar, addition funnel, thermometer and an argon gas-inlet was placed lithium aluminum hydride (9.40 g, 248 mmol, 2 molar equiv). The flask was purged with argon and charged with 400 mL of freshly distilled tetrahydrofuran. The slurry was cooled to -78°C and a solution containing 51.3 g (<125 mmol) of unpurified oxazolidone **110** in 200 mL of dry tetrahydrofuran was added at a rate which maintained the reaction temperature at $\leq$-65°C. The mixture was then allowed to warm to 0°C over a period of 2 h, and stirred at this temperature an additional 2 h. The mixture was cooled to -10°C and treated dropwise with 50 mL (0.5 mol, 4 equiv) of ethyl acetate. The mixture was stirred at 0°C for 15 min and then water (50 mL) was added. Concentrated hydrochloric acid was carefully added until the solution reached pH 1 and complete dissolution of the aluminum salts had occurred. The organic solvents were removed *in vacuo* and the aqueous residue extracted with ether. The combined ethereal phases were washed successively with 1 *N* aqueous hydrochloric acid (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), dried over anhydrous magnesium sulfate, filtered through celite and concentrated *in vacuo* to an oil. Flash chromatography (50 mm, 200 g silica, 10% ethyl acetate:cyclohexane) followed by molecular distillation (Kügelrohr, 180°C, mechanical pump), afforded 20.45 g (70% overall) of pure alcohol **111** as a colorless liquid. (16.28 g

(73%) of oxazolidone **10** was obtained after further elution of the column): R_f 0.19 (30% ethyl acetate:hexane); IR (CCl_4) 3600-3200 (br), 2920, 2865, 1430, 1360, 1090, 887, 691 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.31 (s, 5H, aromatic H), 4.8-4.6 (m, 2H, $\underline{H}_2C=$), 4.49 (s, 2H, $PhC\underline{H}_2O-$), 3.7-3.3 (m, 4H, $HOC\underline{H}_2\dot{C}HCH_2\dot{C}\underline{H}_2$), 3.05-2.70 (br, 1H, $\underline{H}O-$), 2.2-1.5 (m, 5H, $-OCH_2C\underline{H}_2\dot{C}\underline{H}C\underline{H}_2\dot{C}=$), 1.70 (s, 3H, $\underline{H}_3C\dot{C}=$); ^{13}C NMR ($CDCl_3$) δ (TMS) 143.95, 137.90, 128.41, 127.76, 112.10, 73.18, 68.82, 65.83, 40.62, 36.85, 31.84, 22.16; $[\alpha]_D^{25}$ = 6.5° ($CHCl_3$, c 2.5).

Anal. calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.67; H, 9.46.

(R)-4-Methyl-2-(2-(phenylmethoxy)ethyl)-4-pentenal (112).[33a] A dry, 3-necked, 250-mL flask was fitted with a stirring bar, addition funnel, thermometer and a nitrogen gas-inlet. Alcohol **111** (5.86 g, 25 mmol) was introduced, followed by dry dimethyl sulfoxide (62 mL) and freshly distilled triethylamine (22.6 mL, 162.5 mmol, 6.5 equiv). The solution was cooled to 15°C and then a solution of sulfur trioxide pyridine complex (11.94 g, 75 mmol, 3 equiv, Aldrich, 95%) in dry dimethyl sulfoxide (62 mL) was added at a rate which maintained the reaction mixture at $\leq$20°C. After the addition was complete the mixture was stirred at room temperature for 0.5 h. The reaction was quenched by the addition of 100 mL of cold (0°C) water. The mixture was extracted with ether. The organic phase was

washed successively with diluted aqueous cupric sulfate (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered through celite and concentrated *in vacuo* to afford aldehyde **112** as an oil. The unpurified product was used in the next step without further purification. An analytical sample of **112** was obtained by flash chromatography (silica, 10% ethyl acetate:cyclohexane) as a colorless liquid: R_f 0.41 (30% ethyl acetate:hexane); IR (CCl_4) 2920, 2860, 1720, 1435, 1355, 1095, 890, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 9.63 (d, J = 2, 1H, -CHO), 7.30 (s, 5H, aromatic H), 4.80 (br s, 1H, H(H)C=), 4.72 (br s, 1H, H(H)C=), 4.44 (s, 2H, $PhCH_2$), 3.50 (t, J = 6, 2H, $PhCH_2OCH_2$), 2.9-1.65 (m, 5H, $=CCH_2CHCH_2$), 1.68 (s, 3H, $H_3CC=$); ^{13}C NMR ($CDCl_3$) δ (TMS) 204.13, 142.13, 138.23, 128.35, 127.63, 112.88, 72.98, 67.59, 47.01, 37.17, 29.18, 22.29; $[\alpha]_D^{25}$ = -14.1° ($CHCl_3$, *c* 2.6).

Anal. calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.38; H, 8.47.

(3(2R,3S,4R),4R,5S)-3-(3-Hydroxy-2,6-dimethyl-1-oxo-4-(2-(phenylmethoxy)ethyl-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (113).[33a] Into a dry, 3-necked, 250-mL flask fitted with a stirring bar, thermometer and a nitrogen gas-inlet was introduced oxazolidone **8** (6.41 g, 27.5 mmol, 1.1 equiv). The system was purged with argon

and the flask charged with freshly distilled dichloromethane (60 mL). The solution was cooled to -78°C and di-n-butylboryl triflate (7.4 mL, 30.0 mmol, 1.2 equiv) was added dropwise, followed by freshly distilled triethylamine (4.5 mL, 32.5 mmol, 1.3 equiv) at a rate that maintained the reaction temperature at $\leq$-65°C. The mixture was slowly warmed to 0°C and stirred at this temperature for 0.5 h, recooled to -78°C and treated by the slow addition of unpurified aldehyde **112** (5.85 g, $\leq$25 mmol) in 10 mL of anhydrous dichloromethane. The mixture was stirred at -78°C for 30 min, then allowed to warm to 0°C over a 45-min period, and stirred at this temperature overnight. The reaction was quenched by the addition of 12 mL of aqueous phosphate buffer (pH 7) and 75 mL of methanol. The solution was oxidized by the slow addition of a cold (0°C) solution of 12 mL of 30% aqueous hydrogen peroxide in 50 mL of methanol. After 1 h of stirring at 0°C, the volatiles were removed *in vacuo* and the aqueous residue extracted with ether. The organic phase was decanted and washed with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered through celite and concentrated *in vacuo* to a solid. Diastereomer analysis (SE-54, 250°C, Tinj = 275°C, t_r 4-epi-E_1 = 9.80 min, t_r E_1 = 10.25 min, t_r E_2 = 11.7 min, t_r T_1 = 12.6 min, t_r T_2 = 14.3 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2, 12 h) afforded a 4-epi-E_1:E_1:E_2:T_1:T_2 ratio of 4.5:94.5:$\leq$0.7:$\leq$0.7:0.7 Chromatography on silica gel (MPLC,

Merck-LoBar C column, 20% ethyl acetate:cyclohexane) afforded 547.5 mg (4.7%) of an isomer, presumably the C_4-epimer of **113**,[46] and compound **113**. Recrystallization of the latter (ether:cyclohexane) afforded 10.33 g (89% based on alcohol **111**) of the title compound as a white solid. Diastereomer analysis (same conditions as above) indicated **113** to be 99.4% pure, contaminated with only 0.6% of 4-epi-**113**: R_f 0.21 (30% ethyl acetate:hexane); mp 98-99.5°C; IR (CCl_4) 3600-3400, 2943, 1795, 1690, 1341, 1196, 1122, 800, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.50-7.23 (m, 10H, aromatic H), 5.475 (d, J = 7.3, 1H, -NCHCHO-), 4.775 (br s, 1H, H(H)C=), 4.725 (br s, 1H, H(H)C=), 4.650 (qn, J = 6.5, 1H, -NCH-), 4.50 (AB q, $\Delta\delta$ = 0.018 ppm, J = 12, 2H, $PhCH_2$), 4.070 (q, J = 6.5, 1H, O=CCH-), 3.99-3.95 (m, 1H, HOCH-), 3.63-3.50 (symmetric m, 2H, $PhCH_2OCH_2$), 3.220 (d, J = 4.1, 1H, HO-), 2.350 (d of d, J = 3.0, J = 14.5, 1H, =CCH(H)), 2.030 (d of d, J = 10.0, J = 14.5, 1H, =CCH(H)), 1.97-1.87 (m, 1H, $=CCH_2CH$-), 1.78-1.68 (m, J = 6.0, 2H, $PhCH_2OCH_2CH_2$), 1.725 (s, 3H, H_3CC=), 1.320 (d, J = 7.1, 3H, O=CCHCH_3), 0.855 (d, J = 6.9, 3H, -NCHCH_3); ^{13}C NMR ($CDCl_3$) δ (TMS) 176.71, 152.34, 144.54, 138.43, 133.23, 128.68. 128.35, 127.64, 127.51, 125.63, 111.98, 78.77, 74.22, 72.99, 67.92, 54.79, 40.56, 37.37, 36.36, 30.42, 22.35, 14.29, 13.12; $[\alpha]_D^{25}$ = +4.9° ($CHCl_3$, c 2.4).

Anal. calcd. for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58. Found: C, 72.24; H, 7.47.

(3(2R,3S,4R),4R,5S)-3-(2,6-Dimethyl-1-oxo-4-(2-(phenylmethoxy)ethyl)-3-((triethylsilyl)oxy)-6-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (114).[33a] To a stirred, cooled (15°C) solution containing aldol adduct **113** (5.82 g, 12.5 mmol) and freshly distilled triethylamine (5.2 mL, 37.5 mmol, 3 equiv) in anhydrous dichloromethane (62 mL), was added triethylsilyltrifluoromethanesulfonate (4.4 mL, 18.7 mmol, 1.5 equiv) dropwise. The mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (15 mL). The organic phase was decanted and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered through celite and concentrated <u>in vacuo</u> to an oil. Flash chromatography (50 mm, 100 g silica, 5% ethyl acetate:hexane) afforded 7.46 g of a mixture of the title compound and 14% of triethylsilyl alcohol. An analytical sample of **114** was obtained by heating at 150°C under vacuum for 5 h: R_f 0.50 (30% ethyl acetate:hexane); IR (CCl_4) 2950, 2880, 1782, 1688, 1338, 1225, 1192, 1120, 885, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.39-7.17 (m, 10H, aromatic H), 5.402 (d, J = 7.5, 1H, -NCHC<u>H</u>O-), 4.761 (br s, 1H, <u>H</u>(H)C=), 4.723 (br s, 1H, H(<u>H</u>)C=), 4.509 (s, 2H, PhC<u>H_2</u>), 4.493 (qn, J = 7.0, 1H, -NC<u>H</u>-), 4.122 (d of d, J = 1.6, J = 8.5, 1H, TESOC<u>H</u>-), 4.042 (d of q, J_q = 6.8, J_d = 8.5, 1H, O=CC<u>H</u>-), 3.602-3.488 (m, 2H, $PhCH_2OC\underline{H}_2$), 2.244 (br d, J = 15.2, 1H, =CC<u>H</u>(H)), 1.886 (d of d, J = 9.8, J =

15.2, 1H, =CCH(H)), 1.80-1.6 (m, 3H, =CCH$_2$CH-, PhCH$_2$OCH$_2$CH$_2$), 1.698 (s, 3H, H$_3$CC=), 1.248 (d, J = 7.0, 3H, O=CCHCH$_3$), 0.995 (t, J = 8.0, 9H, (CH$_3$CH$_2$)$_3$Si), 0.816 (d, J = 6.8, 3H, -NCHCH$_3$), 0.655 (q, upper field peak is doubled, J = 8.0, 6H, (CH$_3$CH$_2$)$_3$Si); ^{13}C NMR (CDCl$_3$) δ (TMS) 176.11, 152.53, 144.79, 139.20, 133.42, 128.74, 128.41, 127,44, 125.75, 111.71, 78.90, 75.64, 72.85,68.69, 55.11, 42.05, 37.95, 37.56, 31.45, 22.55, 15.40, 14.66, 7.21, 5.72; $[\alpha]_D^{25}$ = +10.4° (CHCl$_3$, c 2.6).

Anal. calcd. for $C_{34}H_{49}NO_5Si$: C, 70.43; H, 8.52. Found: C, 70.39; H, 8.50.

(2R,3S,4R)-2,6-Dimethyl-4-(2-(phenylmethoxy)ethyl)-3-((triethylsilyl)oxy)-6-heptenoic acid, phenylmethyl ester (115).[33a] To a well stirred, cooled (-10°C) solution of benzyl alcohol (3.2 mL, 31 mmol) in anhydrous tetrahydrofuran (25 mL) was added a 1.61 M solution of n-butyllithium in hexane (15.3 mL, 24.7 mmol). The mixture was stirred at 0°C for 10 min. Then, a solution containing imide **114** (7.16 g of a mixture of **114** and triethylsilyl alcohol) in anhydrous tetrahydrofuran (25 mL) was added slowly. After the addition was complete, the mixture was stirred at 0°C for 4 h. The reaction was quenched by the addition of 15 mL of saturated aqueous sodium bicarbonate. The mixture was concentrated in vacuo and the residue partitioned between ether and water. The organic solution was washed with brine (15 mL), dried over anhydrous

sodium sulfate, filtered through celite, and concentrated in vacuo. Flash chromatography (50 mm, 100 g silica, 5% ethyl acetate: cyclohexane) afforded 5.56 g (88%, from **113**) of ester **115** as a colorless oil: R_f 0.55 (20% ethyl acetate:hexane); IR (CCl_4) 3070, 3035, 2960, 2915, 2880, 1730, 1450 1088, 1055, 888 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.8-7.4 (m, 10H, aromatic H), 5.050 (AB q, $\Delta\delta$ = 0.0125 ppm, J = 12.5, 2H, $PhC\underline{H}_2O\dot{C}$=O), 4.71 (br s, 1H, $\underline{H}$(H)C=), 4.64 (br s, 1H, H($\underline{H}$)C=), 4.439 (AB q, $\Delta\delta$ = 0.016 ppm, J = 12, 2H, $PhC\underline{H}_2O\dot{C}H_2$), 4.002 (d of d, J = 2.4, J = 7.0, 1H, $TESO\dot{C}\underline{H}$-), 3.48-3.35 (m, 2H, $PhCH_2O\dot{C}\underline{H}_2$), 2.710 (qn, J = 7.0, 1H, O=$\dot{C}\dot{C}\underline{H}$-), 2.138 (d of d, J = 2.5, J = 14.2, 1H, =$\dot{C}\dot{C}$(H)$\underline{H}$), 1.967 (d of d, J = 9.3, J = 14.2, 1H, =$\dot{C}\dot{C}$($\underline{H}$)H), 1.70-1.55 (m, 3H, $PhCH_2OCH_2C\underline{H}_2\dot{C}\underline{H}$), 1.593 (s, 3H, $\underline{H}_3C\dot{C}$=), 1.193 (d, J = 7.0, 3H, O=$\dot{C}\dot{C}$HC$\underline{H}_3$), 0.939 (t, J = 8.0, 9H, ($C\underline{H}_3CH_2)_3\dot{S}i$), 0.585 (q, J = 8.0, 6H, ($CH_3C\underline{H}_2)_3\dot{S}i$); ^{13}C NMR ($CDCl_3$) δ (TMS) 175.21, 144.21, 138.68, 135.95, 128.48, 128.28, 127.57, 127.37, 112.10, 75.25, 72.85, 68.76, 66.16, 43.61, 38.41, 37.95, 30.41, 22.03, 14.04, 7.02, 5.46; $[\alpha]_D^{25}$ = +12.7° ($CHCl_3$, c 2.4).

Anal. calcd. for $C_{31}H_{46}O_4Si$: C, 72.90; H, 9.08. Found: C, 72.90; H, 9.02.

(2S,3S,4R)-2,6-Dimethyl-4-(2-(phenylmethoxy)ethyl)-3-((triethylsilyl)oxy)-6-heptenol (116).[33a] Into a three-necked, 100-mL flask equipped with a thermometer, septum and an argon gas-inlet was placed ester **115** (5.45 g, 10.7 mmol). The system was

purged with argon and the flask charged with 40 mL of anhydrous tetrahydrofuran. The solution was cooled to -10° and a 70% solution of sodium bis(2-methoxyethoxy) aluminum hydride in toluene (Red-Al, 7.46 mL, 26.6 mmol, 2.5 molar equiv) was added dropwise, at a rate that maintained the reaction temperature below -5°C. The mixture was found to be rather difficult to stir. A mechanical stirrer would have been a better choice. The mixture was stirred at -10°C for 20 min, and then quenched very carefully by the addition of saturated aqueous ammonium chloride. The volatiles were removed in vacuo and the residue partitioned between ether and water. The aqueous, white slurry was decanted and the organic phase was washed with saturated aqueous sodium bicarbonate (10 mL), and brine (10 mL), dried over anhydrous sodium sulfate, filtered through celite and concentrated in vacuo. Flash chromatography (50 mm, 100 g silica, 10% ethyl acetate:cyclohexane) afforded 3.63 g (84%) of alcohol **116** as a colorless liquid: R_f 0.24 (30% ethyl acetate: hexane); IR (CCl_4) 3640, 3550-3400, 3070, 2960, 2940, 2875, 1450, 1235, 1085, 887, 722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.32-7.23 (m, 5H, aromatic H), 4.754 (br s, 1H, H(H)C=), 4.699 (br s, 1H, H(H)C=), 4.461 (AB q, $\Delta\delta$ = 0.0145 ppm, J = 12, 2H, $PhCH_2O$-), 3.775 (t, J = 3.8, 1H, TESOCH-), 3.53-3.40 (m, 4H, $PhCH_2OCH_2$, $HOCH_2$), 2.27-2.17 (br, 1H, HO-), 2.181 (d of d, J = 4.5, J = 14.3, 1H, =CCH(H)), 1.942 (d of d, J = 9.3, J = 14.3, 1H, =CCH(H)), 1.90-1.81 (m, 2H), 1.75-1.69 (m, 1H), 1.700 (s, 3H, H_3CC=), 1.604 (sextuplet,

J = 6.5, 1H), 0.956 (t, J = 8.0, 9H, $(C\underline{H}_3CH_2)_3Si$), 0.874 (d, J = 7.0, 3H, $HOCH_2\underline{C}HC\underline{H}_3$), 0.602 (q, J = 8.0, 6H, $(CH_3C\underline{H}_2)_3Si$); ^{13}C NMR ($CDCl_3$) δ (TMS) 144.53, 138.55, 128.28, 127.70, 111.97, 74.86, 72.92, 68.89, 66.35, 39.38, 38.80, 36.85, 30.61, 22.22, 12.54, 7.08, 5.46; $[\alpha]_D^{25}$ = +3.0° ($CHCl_3$, c 3.0).

Anal. calcd. for $C_{24}H_{42}O_3Si$: C, 70.88; H, 10.41. Found: C, 70.90; H, 10.25.

(2R,3S,4R)-2,6-Dimethyl-4-(2-(phenylmethoxy)ethyl)-3-((triethylsilyl)oxy)-6-heptenal (117).[33a] To a cooled (15°C) solution containing alcohol **116** (2.03 g, 5.0 mmol) and anhydrous triethylamine (4.52 mL, 32.5 mmol, 6.5 equiv) in anhydrous dimethyl sulfoxide (12.5 mL) under argon, was added a solution of sulfur trioxide pyridine complex (2.39 g, 15 mmol, 3 equiv, Aldrich, 95%) in dry dimethyl sulfoxide (12.5 mL) at a rate that maintained the reaction temperature below 20°C. The mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of 10 mL of cold (0°C) water and the mixture extracted with diethyl ether. The organic phase was washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered through celite and concentrated in vacuo. Flash chromatography (50 mm, 100 g silica, 10% ethyl acetate:cyclohexane) afforded 1.96 g (97%) of aldehyde **117** as a colorless liquid: R_f 0.60 (30% ethyl acetate:hexane); IR (CCl_4) 3070, 2950, 2915,

2878, 1722, 1095, 720, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 9.647 (d, J = 1.2, 1H,-C<u>H</u>O), 7.34-7.23 (m, 5H, aromatic H), 4.77-4.75 (m, 1H, <u>H</u>(H)C=), 4.69-4.67 (m, 1H, H(<u>H</u>)C=), 4.464 (s, 2H, PhC<u>H</u>$_2$O-), 4.182 (t, J = 4.4, 1H, TESOC<u>H</u>-), 3.52-3.45 (m, symm., 2H, PhCH$_2$OC<u>H</u>$_2$), 2.564 (q of d of d, J_d = 1.5, J_d = 4.4, J_q = 7.0, 1H, O=CC<u>H</u>-), 2.073 (d of d, J = 5.7, J = 14.0, 1H, =CCH(<u>H</u>)), 1.980 (d of d, J = 9.0, J = 14.0, 1H, =CC<u>H</u>(H)), 1.90-1.84 (m, 1H, =CCH$_2$C<u>H</u>-), 1.783 (d of q, J_q = 6.6, J_d = 14.3, 1H, PhCH$_2$OCH$_2$C<u>H</u>(H)), 1.683 (s, 3H, <u>H</u>$_3$CC=), 1.560 (d of d of d, J = 6.6, J = 13.0, J = 14.3, 1H, PhCH$_2$OCH$_2$CH(<u>H</u>)), 1.086 (d, J = 7.0, 3H, O=CCHC<u>H</u>$_3$), 0.934 (t, J = 8.0, 9H, (C<u>H</u>$_3$CH$_2$)$_3$Si), 0.573 (q, J = 8.0, 6H, (CH$_3$C<u>H</u>$_2$)$_3$Si); ^{13}C NMR ($CDCl_3$) δ (TMS) 204.45, 143.88, 138.55, 128.35, 127.70, 112.43, 73.05, 72.79, 68.63, 50.04, 39.19, 37.89, 30.22, 22.03, 9.23, 6.95, 5.33; $[\alpha]_D^{25}$ = -22.6° ($CHCl_3$, <u>c</u> 3.4).

(3(2R,3S,4S,5S,6R),4R,5S)-3-(3-Hydroxy-4,8-dimethyl-2-methylthio-1-oxo-6-(2-(phenylmethoxy)ethyl)-5-((triethylsilyl)oxy)-8-noneyl)-4-methyl-5-phenyl-2-oxazolidinone (118).[33a] Into a 3-necked, 50-mL flask fitted with a thermometer, septum and argon gas-inlet was introduced imide **119** (1.22 g, 4.6 mmol, 1.05 equiv). The system was purged with argon, and freshly distilled dichloromethane (11 mL) was introduced. The solution was cooled to -78°C, and di-<u>n</u>-butylboryl triflate (1.19 mL, 4.82 mmol, 1.1 equiv) and freshly distilled triethylamine (0.73 mL, 5.26, 1.2 equiv) were

successively added at a rate that maintained the reaction temperature below -60°C. After the addition was completed, the mixture was warmed up to 0°C and stirred for 0.5 h. The solution was recooled to -78°C and aldehyde **117** (1.77 g, 4.38 mmol, 1 equiv, neat) was added slowly. The mixture was stirred at -78°C for 0.5 h, allowed to warm slowly (45 min) to 0°C and stirred at this temperature overnight. The reaction was quenched by the addition of aqueous phosphate buffer (2.2 mL) and cold methanol (13 mL). The mixture was oxidized by the slow addition of a solution of 30% aqueous hydrogen peroxide (2.2 mL) in methanol (9 mL). The reaction was stirred at 0°C for 1 h, then concentrated in vacuo, and the residue partitioned between ether and water. The organic phase was separated and washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered through celite and concentrated in vacuo. Flash chromatography (50 mm, 100 g silica, 10% ethyl acetate:cyclohexane) afforded 1.61 g of compound **118** as a colorless oil. The impure fractions were rechromatographed (MPLC, Merck-LoBar, B column, 10% ethyl acetate: cyclohexane) to afford an additional 578 mg (78% combined yield) of product: R_f 0.51 (30% ethyl acetate:hexane); IR (CCl_4) 3600-3400, 2875, 2885, 1782, 1682, 1342, 1215, 1191, 1000, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.43-7.24 (m, 10H, aromatic H), 5.664 (d, J = 7.5, 1H, -NCHC<u>H</u>O-), 4.873 (d, J = 10.3, 1H, $CH_3SC\underline{H}$-), 4.780 (qn, J = 7.0, 1H, -NC<u>H</u>CHO-), 4.772 (br s, 1H, <u>H</u>(H)C=), 4.749 (br s, 1H,

H(H)C=), 4.499 (AB q, $\Delta\delta$ = 0.018 ppm, J = 12.0, 2H, $PhCH_2O$-), 4.072 (d of t, J_t = 2.0, J_d = 10.3, 1H, HOCH-), 3.876 (d of d, J = 1.3, J = 7.3, 1H, TESOCH-), 3.565-3.500 (m, symmetric, 2H, $PhCH_2OCH_2$), 2.510 (d of d, J = 1.2, J = 2.1, 1H, HO-), 2.151 (br q, J = 10, 1H), 2.017 (s, 3H, CH_3S-), 2.02-1.95 (m, 2H), 1.756 (s, 3H, CH_3C=), 1.76-1.65 (m, 3H), 0.977 (d, J = 7, 3H), 0.970 (t, J = 8.0, 9H, $(CH_3CH_2)_3Si$), 0.874 (d, J = 6.8, 3H), 0.633 (q, J = 8.0, 3H), 0.631 (q, J = 7.7, J = 8.1, 3H); ^{13}C NMR ($CDCl_3$) δ (TMS) 168.1, 152.3, 144.7, 138.7, 133.2, 128.7, 128.3, 127.6, 127.4, 125.7, 112.0, 78.8, 76.5, 72.9, 69.1, 67.8, 54.6, 48.2, 38.3, 37.9, 36.1, 30.3, 22.2, 14.0, 11.2, 9.7, 7.1, 5.7; $[\alpha]_D^{25}$ = +4.4° ($CHCl_3$, c 2.4).

Anal. calcd. for $C_{37}H_{55}NO_6SSi$: C, 66.33; H, 8.27. Found: C, 66.42; H, 8.32.

The Aldol Condensation of the Di-n-butylboron Enolates 121 and 120 with Aldehyde 117. A Cram- antiCram selection Study (Scheme XIII).Enolate formation, aldol condensation, oxidation and workup were performed according to the general method A described in Chapter I. To a cooled (-78°C) solution containing the boron enolate **121** in 1 mL of anhydrous dichloromethane (prepared from 42.8 mg (0.25 mmol) of the corresponding acetyloxazolidinone, 6.7 µl of di-n-butylboryl trifluoromethanesulfonate, and 42 µl of triethylamine) was added a solution containing ca. 0.25 mmol of unpurified

aldehyde **117** in 0.25 mL of anhydrous dichloromethane in one portion. The mixture was stirred at -78°C for 0.5 h and at 0°C for 1 h, oxidized and worked up to give an oil. Diastereomer analysis (SE-54, 280°C, Tinj = 320°C, 15 PSI, t_r **125** = 5.29 min, t_r **123** = 5.60 min) of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2), afforded a ratio of **125:123** = 30:70. Flash chromatography (20 mm, 25 g silica, 20% ethyl acetate:hexane) afforded an analytical sample of each isomer.

125: R_f 0.30 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3020, 2960, 1778, 1685, 1381, 1220 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.29 (s, 5H, aromatic H), 4.8-4.65 (br s, 2H, $\underline{H}_2C=$), 4.44 (s, 2H, $Ph\underline{CH}_2$), 4.5-3.7 (m, 5H, $TESO\underline{CH}$-, $HO\underline{CH}$-, $-N\underline{CH}\underline{CH}_2$), 3.47 (t, J = 7, 2H, $PhCH_2O\underline{CH}_2$), 3.21 (d, J = 5.5, 1H), 3.1-3.0 (m, 2H), 2.5-1.5 (m, 7H, $=C\underline{CH}_2\underline{CH}\underline{CH}_2$, $(CH_3)_2\underline{CH}$, $HO\underline{CH}\underline{CH}$-), 1.70 (s, 3H, $\underline{H}_3C\underline{C}=$), 1.1-0.8 (m, 18H, $(\underline{CH}_3CH_2)_3Si$, $HO\underline{CH}\underline{CH}\underline{CH}\underline{CH}_3$, $(\underline{CH}_3)_2\underline{CH}$), 0.8-0.4 (m, 6H, $(CH_3\underline{CH}_2)_3Si$); $[\alpha]_D^{25}$ = +20.1° ($CHCl_3$, c 1.27).

Anal. calcd. for $C_{32}H_{53}NO_6Si$: C, 66.74; H, 9.28. Found: C, 66.90; H, 9.37.

123: R_f 0.17 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3020, 2960, 1780, 1685, 1385, 1220 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.30 (s, 5H, aromatic H), 4.8-4.6 (br s, 2H, $\underline{H}_2C=$), 4.47 (s, 2H, $Ph\underline{CH}_2$), 4.5-4.1 (m, 4H, $HO\underline{CH}$-, $-N\underline{CH}\underline{CH}_2$), 3.82 (d of d, J = 1.5, J = 5.5, 1H, $TESO\underline{CH}$-), 3.47 (t, J = 7, 2H, $PhCH_2O\underline{CH}_2$), 3.05 (d, J = 7, 2H, $O=C\underline{CH}_2$), 2.63 (d, J = 4, 1H, $\underline{HO}$-), 2.5-1.55 (m, 7H, $=C\underline{CH}_2\underline{CH}\underline{CH}_2$,

HOCHCH-, $(CH_3)_2CH$), 1.70 (s, 3H, H_3CC=), 1.1-0.8 (m, 18H, $(CH_3CH_2)_3Si$, HOCHCHCH$_3$, $(CH_3)_2CH$), 0.8-0.4 (m, 6H, $(CH_3CH_2)_3Si$); $[\alpha]_D^{25}$ = +48.4° ($CHCl_3$, c 2.68).

Anal. calcd. for $C_{32}H_{53}NO_6Si$: C, 66.74; H, 9.28. Found: C, 66.68; H, 9.02.

In another flask containing the boron enolate **120** was added aldehyde **117** following the same procedure as described above. Diastereomer analysis (SE-54, 280°C, Tinj = 320°C, 15 PSI, t_r **124** = 14.93 min, t_r **122** = 15.73 min) of an unpurified, silylated sample (TMSNEt$_2$, DMAP, CH_2Cl_2) afforded a ratio of **124**:**122** = 25:75. Flash chromatography (20 mm, 25 g silica, 20% ethyl acetate:hexane) afforded an analytical sample of each isomer:

122: R_f 0.37 (30% ethyl acetate:hexane); for the physical data of this compound see next experimental.

124: R_f 0.30 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3030, 1783, 1696, 1375, 1225, 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.5-7.2 (m, 10H, aromatic H), 5.67 (d, J = 6.5, 1H, -NCHCHO), 4.9-4.7 (m, 3H, H_2C=, -NCHCHO-), 4.48 (s, 2H, $PhCH_2O$-), 4.2-3.8 (m, 2H, HOCH-, TESOCH-), 3.49 (t, J = 7, 2H, $PhCH_2OCH_2$), 3.27 (d, J = 4.5, 1H), 3.2-3.05 (m, 2H), 2.4-1.5 (m, 6H, =CCH$_2$CHCH$_2$, HOCHCH-), 1.70 (s, 3H, H_3CC=), 1.1-0.8 (m, 15H, $(CH_3CH_2)_3Si$, HOCHCHCH$_3$, -NCHCH$_3$), 0.8-0.45 (m, 6H, $(CH_3CH_2)_3Si$); $[\alpha]_D^{25}$ = +7.8° ($CHCl_3$, c 0.32).

Anal. calcd. for $C_{36}H_{53}NO_6Si$: C, 69.30; H, 8.56. Found: C, 69.80; H, 8.75.

(3(3R,4S,5S,6R),4R,5S)-3-(3-Hydroxy-4,8-dimethyl-1-oxo-6-(2-(phenylmethoxy)ethyl)-5-((triethylsilyl)oxy)-8-noneyl)-4-methyl-5-phenyl-2-oxazolidinone (122). Raney-Nickel was prepared according to the published procedure.[47] To a cold (0°C) solution containing 16 g of sodium hydroxide in 60 mL of water was slowly added nickel alloy (12.5 g, No. 2813 Raney Catalyst Powder Alloy, Davison Speciality Chemical Co.) at a rate that maintained the reaction temperature at ca. 50°C. When the addition was complete, the resulting heterogeneous black slurry was stirred at 50-60°C for 1 h, and washed with water (10 x 100 mL) until the slurry showed a pH = 7. Absolute ethanol was added, the mixture centrifugated and the supernatant decanted (10 x 50 mL). The material was used immediately after preparation. Batches that were stored as the ethanolic mixture at -20°C proved to be inactive after 48 h.

A well stirred solution of compound **118** (6.65 g, 9.93 mmol) in 50 mL of acetone (freshly opened bottle) was treated with an emulsion of the freshly prepared Raney-Nickel in ethanol. Batches were added until TLC analysis indicated complete disappearance of the starting material. Filtration through celite and concentration of the filtrate gave an oil which was flash chromatographed (60 mm, 350 g silica, 15% ethyl acetate:hexane) to afford 695 mg (11%) of

3-dehydroxy-**122** (R_f 0.66, 2% acetone:dichloromethane) and 4.93 g (80%) of the title compound: R_f 0.41 (2% acetone:dichloromethane); IR ($CHCl_3$) 3680 (sharp), 3550 (br), 3020, 1780, 1690, 1365, 1220, 1190, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 7.50-7.20 (m, 10H, aromatic H), 5.63 (d, J = 7, 1H, -NC$\underline{H}$-), 4.8-4.6 (m, 3H, $\underline{H}_2C$=, -NCHC$\underline{H}$O-), 4.47 (s, 2H, PhC$\underline{H}_2$O), 4.3-4.0 (m, 1H, -C$\underline{H}$OH), 3.85 (d, J = 6, 1H, -C$\underline{H}$OTES), 3.50 (t, J = 7, 2H, $PhCH_2OC\underline{H}_2$), 3.3-3.0 (m, 2H, O=CC$\underline{H}_2$), 2.75 (d, J = 4, 1H, -O$\underline{H}$), 2.2-1.20 (m, 6H, $PhCH_2OCH_2C\underline{H}_2C\underline{H}C\underline{H}_2$, O=CC$\underline{H}_2CHC\underline{H}$-), 1.72 (s, 3H, H_2C=CC$\underline{H}_3$), 1.2-0.8 (m, 15H, $(C\underline{H}_3CH_2)_3Si$, -NCHC$\underline{H}_3$, HOCHCHC$\underline{H}_3$), 0.80-0.45 (m, 6H, $(CH_3C\underline{H}_2)_3Si$); $[\alpha]_D^{25}$ = +30.0° ($CHCl_3$, c 2.15).

Anal. calcd. for $C_{36}H_{53}NO_6Si$: C, 69.30; H, 8.56. Found: C, 69.43; H, 8.77.

(3R,4S,5S,6R)-3-Hydroxy-4,8-dimethyl-6-(2-(phenylmethoxy)-ethyl)-5-((triethylsilyl)oxy)-8-nonenoic acid, phenylmethyl ester (126). To a cooled (-10°C) solution of benzyl alcohol (0.11 mL, 1.06 mmol, 2.3 equiv) in anhydrous tetrahydrofuran (2 mL) was added a 1.65 M solution of n-butyllithium in hexane (0.51 mL, 0.84 mmol, 1.83 equiv). After stirring for ca. 10 min, the solution was cooled to -78°C. A solution containing imide **122** (288 mg, 0.46 mmol) in 1.5 mL of dry tetrahydrofuran was added dropwise (2 x 1 mL rinses). The colorless, clear solution was stirred between -60° and -50°C for 4 h, then quenched with saturated aqueous ammonium chloride,

concentrated in vacuo, extracted with dichloromethane (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to an oil. Flash chromatography (30 mm, 68 g silica, 15% ethyl acetate:hexane) afforded 213.7 mg (83%) of the title compound as a colorless oil: R_f 0.45 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3640, 3500 (br), 3025, 2965, 1726, 1452, 1025, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (TMS) 7.38-7.30 (m, 10H, aromatic H), 5.159 (d, J = 12.5, 1H, PhC<u>H</u>(H)OC=O), 5.113 (d, J = 12.5, 1H, PhCH(<u>H</u>)OC=O), 4.740 (br s, 1H, <u>H</u>(H)C=), 4.678 (br s, 1H, H(<u>H</u>)C=), 4.473 (s, 2H, PhC<u>H</u>$_2$O-), 4.135 (d of d of d of d, J = 3.0, J = 3.3, J = 4.0, J = 9.3, 1H, HOC<u>H</u>-), 3.820 (d of d, J = 3.0, J = 5.4, 1H, TESOC<u>H</u>-), 3.52-3.43 (m, 2H, PhCH$_2$OC<u>H</u>$_2$), 2.748 (d, J = 3.3, 1H, <u>H</u>O-), 2.565 (d of d, J = 9.3, J = 16.0, 1H, O=CC<u>H</u>(H)), 2.435 (d of d, J = 4.0, J = 16.0, 1H, O=CC<u>H</u>(H)), 2.055 (d of d, J = 5, J = 13.5, 1H, =CC<u>H</u>(H)), 1.98-1.87 (m, 2H, =CCH$_2$C<u>H</u>CHC<u>H</u>-), 1.754 (d of d, J = 7, J = 13.5, 1H, =CC<u>H</u>(H)), 1.70-1.54 (m, 2H, PhCH$_2$OCH$_2$C<u>H</u>$_2$), 1.578 (s, 3H, <u>H</u>$_3$CC=), 0.946 (t, J = 8.0, 9H, (C<u>H</u>$_3$CH$_2$)$_3$Si), 0.93 (d, J = 7.1, 3H, C<u>H</u>$_3$CH-), 0.604 (q, J = 8.0, 6H, (CH$_3$C<u>H</u>$_2$)$_3$Si); $[\alpha]_D^{25}$ = +16.6° ($CHCl_3$, <u>c</u> 2.8).

<u>Anal</u>. calcd. for $C_{33}H_{50}O_5Si$: C, 71.44; H, 9.08. Found: C, 71.54; H, 9.23.

(3R,4R,5S,6R,8R)-3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-9-hydroxy-4,8-dimethyl-6-(2-(phenylmethoxy)ethyl)-5-((triethylsilyl)-oxy)-nonanoic acid, phenylmethyl ester, (70), and the Corresponding (3R,4R,5S,6R,8S)-Isomer (127). Benzyl ester **126** (2.62 g, 4.72 mmol)

was diluted in 10 mL of anhydrous dichloromethane. Freshly distilled triethylamine (1.65 mL, 11.8 mmol, 2.5 equiv) was added, followed by tert-butyldimethylsilyltrifluoromethanesulfonate (1.62 mL, 7.08 mmol, 1.5 equiv), resulting in a yellowish solution. The reaction mixture was stirred at room temperature for 20 min, and then quenched with saturated aqueous ammonium chloride. The organic layer was decanted and the aqueous solution was extracted with dichloromethane (2 x 50 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and flash chromatographed (60 mm, 220 g silica, 5% ethyl acetate:hexane) to afford 3.04 g (96%) of the corresponding tert-butyldimethylsilyl ether, **69**.

In another flask was introduced a 1 M solution of borane tetrahydrofuran complex in tetrahydrofuran (14 mL, 14 mmol), cooled to -15°C, and treated dropwise with a solution of 2,3-dimethyl-2-butene (1.64 mL, 4mmol) in anhydrous tetrahydrofuran (7 mL). The mixture was then warmed to 0°C and stirred for 2 h.

In another flask was weighed compound **69** (2.27 g, 3.39 mmol), and was diluted with 12 mL of dry tetrahydrofuran. The solution was cooled to -5°C, treated dropwise with an aliquot of the previously prepared thexylborane solution (10.8 mL, 2 equiv), warmed to 0°C, and stirred for 5 h at this temperature. The reaction was quenched by the addition of 30 mL of an aqueous sodium carbonate-sodium bicarbonate solution (pH 9.2). Then, 80 mL of methanol was added

and the mixture treated with 10 mL of 30% aqueous hydrogen peroxide. The white slurry was stirred at 0°C for 4 h, after which period TLC analysis still indicated presence of unoxidized material. The mixture was neutralized with aqueous phosphate buffer, concentrated in vacuo and the remaining white slurry extracted with ether (2 x 30 mL). The combined ethereal layers were washed with aqueous 10% sodium hydroxide (1 x 30 mL), then with saturated aqueous sodium sulfite solution, dried over anhydrous sodium sulfate, filtered and concentrated to a colorless oil. This was dissolved in a mixture containing 20 mL of methanol, 12 mL of aqueous sodium carbonate-sodium bicarbonate and 12 mL of tetrahydrofuran, cooled to 0°C and treated with 10 mL of 30% aqueous hydrogen peroxide for 0.5 h, after which time TLC analysis indicated no remaining organoborane. Workup as before gave an oil which was chromatographed (MPLC, Lo-bar, size C, 17% ethyl acetate:hexane) to afford 1.60 g (69%) of compound **70**, and 338 mg (15%) of **127**.

70: R_f 0.46 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3700, 3560 (br), 3030, 2965, 1725, 1455, 1220, 1130, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ($CHCl_3$) 7.38-7.24 (m, 10H, aromatic H), 5.078 (s, 2H, $PhC\underline{H}_2OC(=O)$), 4.502 (d, J = 11.7, 1H, $PhC\underline{H}(H)O$), 4.446 (d, J = 11.7, 1H, $PhCH(\underline{H})O$), 4.133 (m, 1H, $TBSOC\underline{H}$-), 3.681 (d of d, J = 2.5, J = 6.5, 1H, $TESOC\underline{H}$-), 3.52-3.36 (m, 4H, $HOC\underline{H}_2$, $PhCH_2OC\underline{H}_2$), 2.612 (d of d, J = 6.5, J = 15.5, 1H, $O{=}C\underline{C}H(H)$), 2.503 (d of d, J = 5.7, J = 15.5, 1H, $O{=}C\underline{C}H(\underline{H})$), 2.038 (t, J = 6.0, 1H,-O$\underline{H}$), 1.84-1.43 (five

multiplets, 7H, O=CCH$_2$CHCH-, HOCH$_2$CHCH$_2$CHCH$_2$), 0.934 (t, J = 8.0, 9H, (CH$_3$CH$_2$)$_3$Si), 0.925 (d, J = 7.0, 3H, H$_3$CCH-), 0.885 (d, J = 7.0, 3H, H$_3$CCH-), 0.830 (s, 9H, (CH$_3$)$_3$C), 0.591 (q, J = 8.0, 6H, (CH$_3$CH$_2$)$_3$Si), 0.003 (s, 3H, CH$_3$SiCH$_3$), -0.010 (s, 3H, CH$_3$SiCH$_3$); $[\alpha]_D^{25}$ = +6.9° ($CHCl_3$, c 1.8).

Anal. calcd. for $C_{39}H_{66}O_6Si_2$: C, 68.17; H, 9.68. Found: C, 68.32; H, 9.50.

127: R_f 0.39 (30% ethyl acetate:hexane); IR ($CHCl_3$) 3690, 3500 (br), 3025, 2965, 1728, 1455, 1250, 1220, 833, 690. ^{1}H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 7.35 (s, 5H, aromatic H), 7.32 (s, 5H, aromatic H), 5.10 (s, 2H, PhCH$_2$OC=O), 4.50 (s, 2H, PhCH$_2$O), 4.27-4.05 (m, 1H, TBSOCH-), 3.75 (d of d, J = 2.5, J = 5.5, 1H, TESOCH-), 3.65-3.30 (m, 4H, HOCH$_2$, PhCH$_2$OCH$_2$), 2.80-2.32 (m, 2H, O=CCH$_2$), 1.95-1.00 (m, 7H, O=CCH$_2$CHCH-, HOCH$_2$CHCH$_2$CHCH$_2$), 1.0-0.75 (m, 24H, H$_3$CCH-, HOCH$_2$CHCH$_3$, (CH$_3$)$_3$C, (CH$_3$CH$_2$)$_3$Si), 0.75-0.45 (m, 6H, (CH$_3$CH$_2$)Si), 0.05 (s, 3H, CH$_3$SiCH$_3$), 0.03 (s, 3H, CH$_3$SiCH$_3$); $[\alpha]_D^{25}$ = +11.2° ($CHCl_3$, c 1.4).

Anal. calcd. for $C_{39}H_{66}O_2Si$: C, 68.17; H, 9.68. Found: C, 68.08; H, 9.52.

(3R,4R,5S,6R,8R)-3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-4,8-dimethyl-9-oxo-6-(2-(phenylmethoxy)ethyl)-5-((triethylsilyl)oxy)-nonanoic acid, phenylmethyl ester (128). To a solution of alcohol **70** (1.600 g, 2.33 mmol)in anhydrous dimethyl sulfoxide (30 mL) was

subsequently added freshly distilled triethylamine (2.93 mL, 21 mmol, 9 equiv) and a solution of sulfur trioxide pyridine complex (1.298 g, 8.15 mmol, 3.5 equiv, Aldrich, 95% pure) in dry dimethyl sulfoxide (10 mL). The orange solution was stirred at room temperature for 1 h, then poured into a separation funnel containing 100 mL of saturated aqueous solution of cupric sulfate and 200 mL of diethyl ether. The ethereal layer was decanted and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine (3 x 25 mL). Pentane (100 mL) was added and the solution dried over anhydrous sodium sulfate, filtered and concentrated <u>in vacuo</u> to a colorless oil. Flash chromatography (45 mm, 160 g silica, 8% ethyl acetate:hexane) afforded 1.436 g (90%) of aldehyde **128** as a colorless oil: R_f 0.29 (10% ethyl acetate:hexane); ^{1}H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 9.58 (d, J = 1.5, 1H, $\underline{H}C{=}O$), 7.35 (s, 5H, aromatic H), 7.30 (s, 5H, aromatic H), 5.10 (s, 2H, $PhC\underline{H}_2OC{=}O$), 4.46 (s, 2H, $PhC\underline{H}_2O$), 4.13 (m, 1H, TBSOC<u>H</u>-), 3.75 (d of d, J = 1.5, J = 6.5, 1H, TESOC<u>H</u>-), 3.48 (br t, J = 6, 2H, $PhCH_2OC\underline{H}_2$), 2.80-2.32 (m, 2H, $O{=}CC\underline{H}_2$), 2.55-2.25 (m, 1H, $O{=}CHC\underline{H}$-), 2.0-1.5 (m, 6H, $O{=}CHCHC\underline{H}_2C\underline{H}C\underline{H}_2$, $O{=}CCH_2CHC\underline{H}$-), 1.1-0.8 (m, 15H, $O{=}CHCHC\underline{H}_3$), $O{=}CCH_2CHCHC\underline{H}_3$, $(C\underline{H}_3CH_2)_3Si$), 0.88 (s, 9H, $(C\underline{H}_3)_3C$), 0.8-0.4 (m, 6H, $(CH_3C\underline{H}_2)_3Si$), 0.03 (s, 6H, $(C\underline{H}_3)_2Si$-).

(3R,4R,5S,6R,8R)-10-(Dimethoxyphosphinyl)-3-(((1,1-dimethylethyl)dimethylsilyl)oxy)-4,8-dimethyl-9-oxo-6-(2-(phenylmethoxy)ethyl)-5-((triethylsilyl)oxy)-decanoic acid, phenylmethyl ester (133). A cooled (-60°C), 1.7 M solution of n-butyllithium in hexane (5.88 mL, 10 mmol) was diluted with 6 mL of anhydrous tetrahydrofuran, and treated dropwise with a solution containing methyldimethylphosphonate (1.2 mL, 11 mmol) in dry tetrahydrofuran (4 mL), resulting in a white slurry.[38] After stirring for 15 min between -60°C and -50°C, a 1.4 M solution of magnesium bromide in 5:4 ether: benzene (8.6 mL, 12 mmol) was added dropwise. The mixture was warmed up to 0°C and then anhydrous dichloromethane (2 mL) was added, resulting in a clear, homogeneous solution. An aliquot (9 mL, 3.36 mmol, 1.6 equiv) was then added very slowly into a well stirred, cooled (-78°C) solution containing aldehyde **128** (1.436 g, 2.1 mmol) in anhydrous tetrahydrofuran (50 mL). The temperature was kept between -60°C and -55°C. (Considerable attack at the ester carbonyl was observed in experiments where the temperature was raised to -45°C.) After 1.5 h, TLC analysis indicated almost complete disappearance of aldehyde. The reaction was quenched by the addition of saturated aqueous ammonium chloride, concentrated and the remaining aqueous slurry extracted with dichloromethane (5 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to afford the corresponding β-hydroxyphosphonate as an oil.

To another flask containing dichloromethane (35 mL) and pyridine (2.58 mL, 32 mmol, 15.2 equiv) was added dry chromium trioxide (1.6 g, 16 mmol, 7.1 equiv). The resultant red burgundy solution was stirred for 15 min. The unpurified β-hydroxyphosphonate in dry dichloromethane (2 mL) was then added in one portion resulting in the formation of a black tar. The mixture was stirred at ambient temperature for 3 h, after which period it was chromatographed directly through a florisil column containing ethyl acetate. The column was flushed thoroughly with ethyl acetate. Concentration and flash chromatography (50 mm, 180 g silica, 50% ethyl acetate:hexane) afforded 1.340 g (79% from **128**) of the title compound as a colorless oil: R_f 0.27 (50% ethyl acetate:hexane); IR (CH_2Cl_2) 3020, 2960, 1730-1712, 1455, 1254, 1035, 835 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 7.35 (s, 5H, aromatic H), 7.32 (s, 5H, aromatic H), 5.09 (s, 2H, $PhC\underline{H}_2OC(=O)$), 4.46 (s, 2H, $PhC\underline{H}_2O$), 4.24-4.00 (m, 1H, $TBSOC\underline{H}$-), 3.72 (d, J = 11.5, 3H, $C\underline{H}_3OP(=O)OCH_3$), 3.69 (d, J = 11.5, 3H, $CH_3OP(=O)OC\underline{H}_3$), 3.7-3.3 (m, 3H, $TESOC\underline{H}$-, $PhCH_2OC\underline{H}_2$), 3.10 (d, J = 22.5, 2H, $O=PC\underline{H}_2$), 2.78 (br t, J = 2.5, 1H, $O=CHC\underline{H}$-), 2.65-2.48 (m, 2H, $O=CC\underline{H}_2$), 2.0-1.3 (m, 6H, $O=CHCHCH_2C\underline{H}C\underline{H}_2$, $O=CCH_2CHC\underline{H}$-), 1.3-0.75 (m, 15H, $O=CHCHC\underline{H}_3$, $O=CCH_2CHCHC\underline{H}_3$, $(C\underline{H}_3CH_2)_3Si$), 0.84 (s, 9H, $(C\underline{H}_3)_3C$), 0.8-0.4 (m, 6H, $(CH_3C\underline{H}_2)_3Si$), 0.02 (s, 3H, $C\underline{H}_3SiCH_3$), 0.00 (s, 3H, $CH_3SiC\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 205.88, 205.62, 171.50, 138.36, 135.89, 128.41, 128.22, 127.63, 127.44, 75.19, 72.92, 70.38, 68.82, 66.15, 52.96, 52.70,

52.44, 45.43, 42.89, 41.59, 40.88, 37.37, 37.11, 33.01, 32.36, 25.86, 18.00, 17.35, 10.92, 7.08, 5.59, -4.42; $[\alpha]_D^{25}$ = +8.85° ($CHCl_3$, c 2.26).

Anal. calcd. for $C_{42}H_{71}O_9PSi_2$: C, 62.50; H, 8.87. Found: C, 62.30; H, 8.73.

(3R,4R,5S,6R,8R)-10-(Dimethoxyphosphinyl)-3-(((1,1-dimethylethyl)dimethylsilyl)oxy)-4,8-dimethyl-9-oxo-5-((triethylsilyl)oxy)-6-(2-((triethylsilyl)oxy)ethyl)-decanoic acid (134). To a solution of compound **133** (586.8 mg, 0.72 mmol) in anhydrous dichloromethane (60 mL) was added 10% palladium on carbon (290 mg). The mixture was hydrogenated (1 atm) for 1 h, filtered through celite and concentrated in vacuo.

The unpurified acid was dissolved in anhydrous dichloromethane (7 mL), and treated subsequently with anhydrous triethylamine (0.41 mL, 2.88 mmol, 4 equiv) and triethylsilyltrifluoromethanesulfonate (0.41 mL, 1.8 mmol, 2.5 equiv). After 15 min, water (15 mL) was added and the two layer mixture stirred vigorously for 2.5 h. The aqueous layer was carefully acidified to pH 3 with 5% aqueous hydrochloric acid and extracted with dichloromethane (2 x 30 mL). The combined organic layers were washed with saturated aqueous ammonium chloride (1 x 20 mL), dried over anhydrous sodium sulfate, filtered, concentrated and chromatographed (40 mm, 80 g silica, 80% ethyl acetate:hexane) to afford 325.4 mg (61% from **133**) of compound

134 as a colorless, very thick oil: R_f 0.40 (ethyl acetate); IR ($CHCl_3$) 3025, 2960, 1720 (br), 1457, 1225 (br), 1035 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 4.12-3.8 (m, 1H, TBSOC<u>H</u>-), 3.81 (d, J = 11.5, 3H, <u>H</u>$_3$COP(=O)OCH$_3$), 3.71 (d, J = 11.5, 3H, H$_3$COP(=O)OC<u>H</u>$_3$), 3.8-3.4 (m, 3H, TESOC<u>H</u>-, TESOC<u>H</u>$_2$), 3.19 (d, J = 21.3, 2H, O=CC<u>H</u>$_2$P=O), 2.8-2.35 (m, 3H, O=CC<u>H</u>-, O=CC<u>H</u>$_2$CH-), 2.2-1.3 (m, 6H, O=CCHC<u>H</u>$_2$C<u>H</u>C<u>H</u>$_2$, O=CCH$_2$CHC<u>H</u>-), 1.2-0.75 (m, 24H, O=CCHC<u>H</u>$_3$, O=CCH$_2$CHCHC<u>H</u>$_3$, (C<u>H</u>$_3$CH$_2$)$_3$Si, (C<u>H</u>$_3$CH$_2$)$_3$Si), 0.87 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.75-0.3 (m, 12H, (CH$_3$C<u>H</u>$_2$)$_3$Si, (CH$_3$C<u>H</u>$_2$)$_3$Si), 0.07 (s, 3H, C<u>H</u>$_3$SiCH$_3$), 0.05 (s, 3H, CH$_3$SiC<u>H</u>$_3$); $[\alpha]_D^{25}$ = -16.7° ($CHCl_3$, <u>c</u> 1.47).

<u>Anal</u>. calcd. for $C_{34}H_{73}O_9PSi_3$: C, 55.10; H, 9.93. Found: C, 55.10; H, 9.68.

(3R,4R,5S,6R,8R)-10-(Dimethoxyphosphinyl)-3-(((1,1-dimethylethyl)dimethylsilyl)oxy)-4,8-dimethyl-9-oxo-5-((triethylsilyl)oxy)-6-(2-((triethylsilyl)oxy)ethyl)-decanoic acid, (1R,2R,3E)-2-((((1,1-dimethylethyl)dimethylsilyl)oxy)methyl)-1-ethyl-4-methyl-5-oxo-3-pentenyl ester (135). To a well stirred solution of acid **134** (310 mg, 0.42 mmol) and alcohol **102** (137.7 mg, 0.48 mmol, 1.15 equiv) in anhydrous dichloromethane (0.2 mL) was added 0.27 mL of a solution 2.0 <u>M</u> in dicyclohexylcarbodiimide, and 0.18 <u>M</u> in N,N-dimethyl-4-aminopyridine (1.3 equiv of DCC, 12% molar equiv of DMAP), in dichloromethane. After approximately 2 min, dicyclohexylurea started to precipitate as a white cloud. The slurry was

stirred at room temperature for 5 h. TLC analysis indicated that the reaction had reached a point where no further conversion was occurring. An additional 50 µl (0.24 equiv) of the DCC solution was added and the mixture stirred another 1 h. Ethyl acetate (1 mL) was added and the mixture was concentrated under a flow of argon. Flash chromatography (40 mm, 110 g silica, 30% ethyl acetate:hexane) afforded 336.1 mg (80%) of compound **135** as a colorless, very thick oil: R_f 0.39 (50% ethyl acetate:hexane); IR ($CHCl_3$) 3010, 2965, 1730, 1715, 1685, 1639, 1460, 1255, 1175, 1038, 837 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 9.43 (s, 1H, O=C<u>H</u>), 6.45 (br d, J = 10.5, 1H, olefinic H), 5.25-4.95 (m, 1H, -C<u>H</u>OC=O), 4.25-4.00 (m, 1H, TBSOC<u>H</u>-), 3.77 (d, J = 11.5, 6H, $(C\underline{H}_3O)_2P$=O), 3.9-3.4 (m, 5H, TBSOC<u>H</u>$_2$, TESOC<u>H</u>-, TESOC<u>H</u>$_2$), 3.13 (d, J = 22.5, 2H, O=CC<u>H</u>$_2$P=O), 3.25-2.7 (m, 1H, O=CC<u>H</u>-), 2.61-2.46 (m, 2H, O=CC<u>H</u>$_2$CH-), 2.05-1.3 (m, 9H, O=CCHC<u>H</u>$_2$C<u>H</u>C<u>H</u>$_2$, O=CCH$_2$CHC<u>H</u>-, TBSOCH$_2$C<u>H</u>CHC<u>H</u>$_2$CH$_3$), 1.78 (d, J <u>ca</u>. 2, 3H, =CC<u>H</u>$_3$), 1.3-0.8 (m, 45H, O=CCHC<u>H</u>$_3$, O=CCH$_2$CHCHC<u>H</u>$_3$, $(C\underline{H}_3)_3C$, $(C\underline{H}_3)_3C$, $(C\underline{H}_3CH_2)_3Si$, $(C\underline{H}_3CH_2)_3Si$, C<u>H</u>$_3CH_2$CHO), 0.8-0.4 (m, 12H, $(CH_3C\underline{H}_2)_3Si$, $(CH_3C\underline{H}_2)_3Si$), 0.05 (s, 6H, $CH_3SiC\underline{H}_3$, $CH_3SiC\underline{H}_3$), 0.00 (s, 6H, $C\underline{H}_3SiCH_3$, $C\underline{H}_3SiCH_3$); $[\alpha]_D^{25}$ = +22.7° ($CHCl_3$, <u>c</u> 1.07).

20-Deoxy-3,23-di-<u>O</u>-((1,1-dimethylethyl)dimethylsilyl)-5,20-di-<u>O</u>-(triethylsilyl)-tylonolide (136). To a solution of phosphonate **135** (308.1 mg, 305 µmol) in 300 mL of freshly distilled toluene, was added 18-crown-6 (967 mg, 3.66 mmol, 12 equiv) and

finely powdered anhydrous potassium carbonate (253 mg, 1.86 mmol, 6 equiv). The mixture was stirred at 60°C for 16 h, after which period it was washed with water (1 x 50 mL), brine (1 x 50 mL), and aqueous phosphate buffer solution (1 x 50 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and flash chromatographed (40 mm, 50 g silica, 4% ethyl acetate:hexane) to give 238.1 mg (88%) of the title compound as a colorless, very thick oil: R_f 0.21 (5% ethyl acetate:hexane); IR ($CHCl_3$) 3020, 2065, 1741, 1678, 1593, 1460, 1253, 1095, 833 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 7.25 (d, J = 15.5, 1H, O=CCH=C<u>H</u>), 6.17 (d, J = 15.5, 1H, O=CC<u>H</u>=CH), 5.80 (d, J = 11.0, 1H, O=CCH=CHC=C<u>H</u>), 4.86 (t of d, J_d = 3, J_t = 9.5, 1H, O=COC<u>H</u>-), 3.90 (d, J = 7.5, 1H, TBSOC<u>H</u>-), 3.85-3.3 (m, 5H, TBSOC<u>H</u>$_2$, TESOC<u>H</u>-, TESOC<u>H</u>$_2$), 2.85-2.2 (m, 3H, O=CC<u>H</u>$_2$, O=CC<u>H</u>-), 2.1-0.3 (m, 66H), 1.74 (s, 3H, <u>H</u>$_3$CC=), 0.07 (s, 3H, C<u>H</u>$_3$SiCH$_3$), 0.02 (s, 6H, C<u>H</u>$_3$Si-CH$_3$, CH$_3$SiC<u>H</u>$_3$), -0.07 (s, 3H, CH$_3$SiC<u>H</u>$_3$); $[\alpha]_D^{25}$ = -32.5° ($CHCl_3$, <u>c</u> 0.8).

<u>Anal</u>. calcd. for $C_{47}H_{94}O_7Si_4$: C, 63.88; H, 10.72. Found: C, 63.88; H, 10.61.

3,23-Di-<u>O</u>-((1,1-dimethylethyl)dimethylsilyl)-5-<u>O</u>-(triethylsilyl)-tylonolide (138). To a solution of **136** (219.3 mg, 248 µmol) in 5 mL of tetrahydrofuran, was added dropwise a solution containing 15 mL of tetrahydrofuran and 5 mL of 0.1% aqueous hydrochloric acid. The mixture was stirred for 1 h, then neutralized with 6 mL of 2.5 <u>M</u>

aqueous phosphate buffer solution. The volatiles were removed *in vacuo*, and the remaining solution extracted with ethyl acetate (2 x 30 mL). Pentane was added and the combined organic layers, dried over anhydrous sodium sulfate. Filtration and concentration afforded 206 mg of alcohol **137** as a colorless, very thick oil (R_f 0.41 in 30% ethyl acetate:hexane).

To another flask containing a solution of pyridine (0.4 mL, 4.96 mmol, 20 equiv) in anhydrous dichloromethane (25 mL) was added dry chromium trioxide (250 mg, 2.48 mmol, 10 equiv). After stirring the burgundy mixture for 15 min, a solution containing 206 mg of unpurified alcohol **137** in 0.5 mL of dry dichloromethane was added *via* cannula, in one portion. The black slurry was vigorously stirred for 7 min, then filtered through celite, washed thoroughly with 250 mL of dichloromethane, concentrated *in vacuo*, diluted in diethyl ether and passed through a florisil column. The column was flushed with *ca*. 0.5 L of diethylether, and the solution concentrated *in vacuo* to an oil which was flash chromatographed (30 mm, 50 g silica, 15% ethyl acetate:hexane) to afford 177.1 mg (93% from **136**) of aldehyde **138** as a white solid. An analytical sample was obtained by recrystallization from hot methanol: R_f 0.75 (30% ethyl acetate:hexane); mp 139-142°C; IR ($CHCl_3$) 3025, 2960, 1740, 1725, 1678, 1591, 1456, 1252, 1100, 835 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ ($CHCl_3$) 9.68 (m, 1H, O=C$\underline{H}$), 7.35 (d, J = 16.2, 1H, O=CCH=C$\underline{H}$), 6.23 (d, J = 16.2, 1H, O=CC$\underline{H}$=), 5.87 (d, J = 10.5, 1H, O=CCH=CHC=C$\underline{H}$),

4.88 (t of d, J_d = 3.5, J_t = 9.5, 1H, O=COCH-), 4.02 (d, J = 7.5, 1H, TBSOCH-), 3.69 (d, J = 5.0, 2H, TBSOCH$_2$), 3.49 (d, J = 9.0, 1H, TESOCH), 2.9-2.3 (m, 5H, O=CHCH$_2$, O=CCH-, O=CCH$_2$), 2.15-0.4 (m, 62H), 1.78 (s, 3H, H$_3$CC=), 1.20 (d, J = 6.5, 3H, O=CCHCH$_3$), 0.13 (s, 3H, CH$_3$SiCH$_3$), 0.05 (s, 6H, CH$_3$SiCH$_3$, CH$_3$SiCH$_3$), -0.04 (s, 3H, CH$_3$SiCH$_3$); $[\alpha]_D^{25}$ = 11.8° ($CHCl_3$, c 1.54).

Anal. calcd. for $C_{47}H_{94}O_7Si_4$: C, 64.18; H, 10.25. Found: C, 63.90; H, 9.90.

Tylonolide, cyclic 5,20-hemiacetal (87). Aldehyde **138** (127.3 mg, 166 μmol) was dissolved in 10 mL of a 1:5 mixture of 48% aqueous hydrofluoric acid:acetonitrile, in a polyethylene bottle. The mixture was stirred for 12 h, then quenched by the careful addition of 25 mL of saturated aqueous sodium bicarbonate. The mixture was partitioned between chloroform and water. The phases were separated and the aqueous layer extracted (3 x 30 mL) with chloroform. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a white solid. Flash chromatography (30 mm, 40 g silica, 10% hexane:ethyl acetate) afforded a semicrystalline solid. This was dissolved in chloroform and concentrated in vacuo 3 times in order to remove all the hexane, to afford 65.2 mg (92%) of tylonolide hemiacetal **87** as a white, semicrystalline solid, identical in all aspects (TLC, mp behavior, IR, 500 MHz ^{1}H NMR, ^{13}C NMR, and optical rotation) to a sample

obtained by degradation of tylosin [2,32]: R_f 0.48 (ethyl acetate); the substance started to melt at 107°C and finished at 155°C; IR ($CHCl_3$, c = 10 mg/mL) 3700, 3610, 3650-3150 (br), 3025, 2975, 2935, 2890, 1711, 1681, 1600, 1457, 1321, 1185, 1068, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, c = 16 mg/mL) δ (TMS) 7.22 (d, J = 15.5, 1H, C_{11}-**H**), 6.318 (d, J = 16.0, 1/3 H, C_{10}-**H**), 6.268 (d, J = 15.5, 2/3 H, C_{10}-**H**), 5.735 (d, J = 10.5, 2/3 H, C_{13}-**H**), 5.728 (d, J = 10.5, 1/3 H, C_{13}-**H**), 5.452 (q, J = 4.5, 2/3 H, C_{20}-**H**), 5.385 (d of d, J = 3.5, J = 6.2, 1/3 H, C_{20}-**H**), 4.879 (t of d, J_d = 3.0, J_t = 9.7, 2/3 H, C_{15}-**H**), 4.872 (t of d, J_d = 3, J_t = 9.5, 1/3 H, C_{15}-**H**), 4.067 (d of d, J = 4.0, J = 10.5, 1H, C_5-**H**), 3.80-3.63 (m, 3H, C_{23}-$\mathbf{H}_2$, -OH), 3.588 (br d of d, J = 1.0, J = 10.5, 2/3 H, C_3-**H**), 3.479 (br d, partially buried, 1/3 H, C_3-**H**), 3.140 (d, J = 4.0, 1/3 H, **H**O-), 2.860 (d, J = 4.5, 2/3 H, **H**O-), 2.846 (t of d of d, J_t = 10.0, J_d = 6.3, J_d = 4.5, 1H, C_{14}-**H**), 2.56-2.47 (m, 1H, C_8-**H**), 2.440 (d of d, J = 11.0, J = 16.5, 1H), 2.138 (q, J = 7.0), 2.080 (d of d, J = 6.0, J = 14.0), 2.01-1.93 (m), 1.90-1.72 (m), 1.800 (d, J = 1.0, 3/3 H, C_{22}-$\mathbf{H}_3$), 1.792 (d, J = 1, 6/3 H, C_{22}-$\mathbf{H}_3$), 1.65-1.40 (m), 1.206 (d, J = 7.0, 3/3 H, C_{21}-$\mathbf{H}_3$), 1.183 (d, J = 7.0, 6/3 H, C_{21}-$\mathbf{H}_3$), 0.965 (d, J = 6.7, 3/3 H, C_{18}-$\mathbf{H}_3$), 0.957 (d, J = 6.7, 6/3 H, C_{18}-$\mathbf{H}_3$), 0.898 (t, J = 6.8, 3H, C_{17}-$\mathbf{H}_3$); ^{13}C NMR ($CDCl_3$) δ (TMS) 204.58 (m),[48] 204.26, 174.43, 147.00, 140.24, 136.15, 120.68, 97.48 (m), 97.09, 83.90 (m), 81.69, 75.39, 67.13, 62.65, 47.18, 45.82 (m), 45.49, 40.75, 39.31 (m), 38.34, 38.02, 37.62 (m), 37.17, 35.80 (m),

33.34, 32.81 (m), 25.80, 17.35, 13.19, 9.88, 9.62; $[\alpha]_D^{25}$ = +21.9° ($CHCl_3$, c 0.726, 36.3 mg in 5.00 mL). (Natural: $[\alpha]_D^{25}$ = +21.4° ($CHCl_3$, c 0.735, 14.7 mg in 2.00 mL)).

A portion of the material was dissolved in dichloromethane (ca. 0.1 mL/mg). Then, hexane was added slowly until a slight cloud remained. A stopper was placed into the flask and the mixture let stand for 2 h. Tylonolide hemiacetal crystallized as very small, amorphous white crystals. The mother liquors were removed and the crystals dried under high vacuum (25°C) to afford tylonolide hemiacetal, which had incorporated about 0.5 molecule of hexane per molecule of compound: mp 154.5-156.5°C (natural: mp 155.0-157.0°C; mixed mp 155.0-156.5°C); $[\alpha]_D^{25}$ = +26.5° ($CHCl_3$, c 0.550, 11.0 mg in 2.00 mL) (natural: $[\alpha]_D^{25}$ = +26.3° ($CHCl_3$, c 0.545, 10.9 mg in 2.00 mL).

Anal. calcd. for $C_{23}H_{36}O_7 \cdot 1/2\ C_6H_{12}$: C, 66.92; H, 9.07. Found: C, 66.85; H, 9.33.

(Natural: Found: C, 67.08; H, 9.02)

Recrystallization from acetone:diethyl ether:hexane afforded a semicrystalline substance: $[\alpha]_D^{25}$ = +25.2° ($CHCl_3$, c 0.524, 26.2 mg in 5.00 mL) (natural: $[\alpha]_D^{25}$ = +25.4° ($CHCl_3$, c 0.530, 10.6 mg in 2.00 mL).

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(31) During the course of our aldol studies we have invariably found that these reactions do not go to full conversion when they are performed on $\leq$0.1 mmol scale due, very probably, to the virtual impossibility of eliminating all traces of moisture.

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(33) (a) This section of the work was performed by my coworker Dr. Thierry Godel, to whom I am indebted. (b) The details concerning the preparation and physical properties of compounds **109 – 118** are included in the experimental section of this chapter.

(34) For a discussion and results of this section, see Godel, T. Research Report, California Institute of Technology, Pasadena, California.

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(41) A sample of 50 g of tylosin was generously provided by the Eli Lilly Company.

(42) Prepared from crotonic acid (Aldrich, 98% pure) and thionyl chloride, and distilled under reduced pressure (55-57°C, 60 mm). It contained approximately 2.3% of the cis isomer.[21a]

(43) Compound **106** was an unstable substance. TLC analysis showed partial decomposition 1 h after its purification.

(44) Prepared in two steps from 1,4-butanediol: (1) NaH, $PhCH_2Br$, cyclohexane, 80°C, 3 h, 79%; (2) Jones' oxidation, 25°C, 15 min, 80%.

(45) Although methallyl iodide showed no detectable decomposition when stored over cuper wire at 4°C for several months, a bottle that was stored at room temperature for ca. one year exploded violently.

(46) The presence of this isomer is due to the fact that the alkylation adduct **110** was carried on without separation of the diastereomers.

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(48) "m" stands for the resolved peaks of the minor anomer.

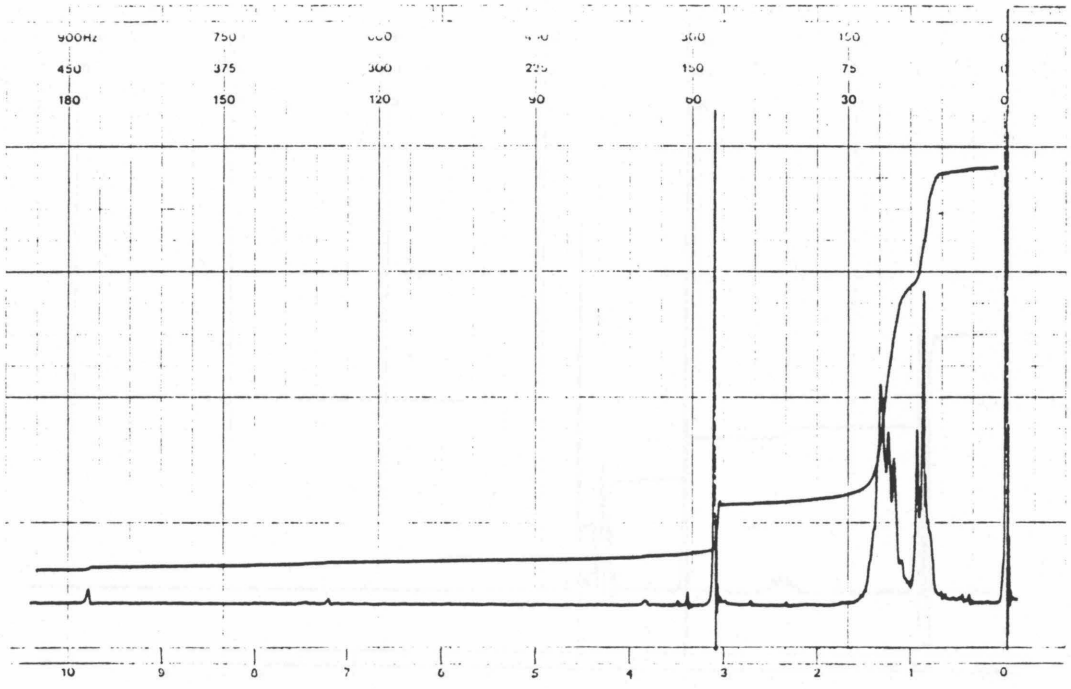
APPENDIX I

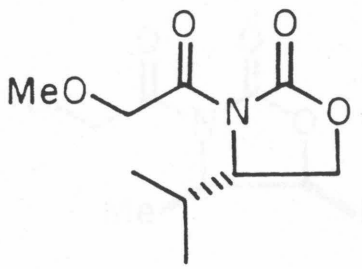
IR and ^{1}H NMR Spectral Catalog

for Chapter I

$\underline{n}Bu_2BOSO_2CH_3$

$CDCl_3$





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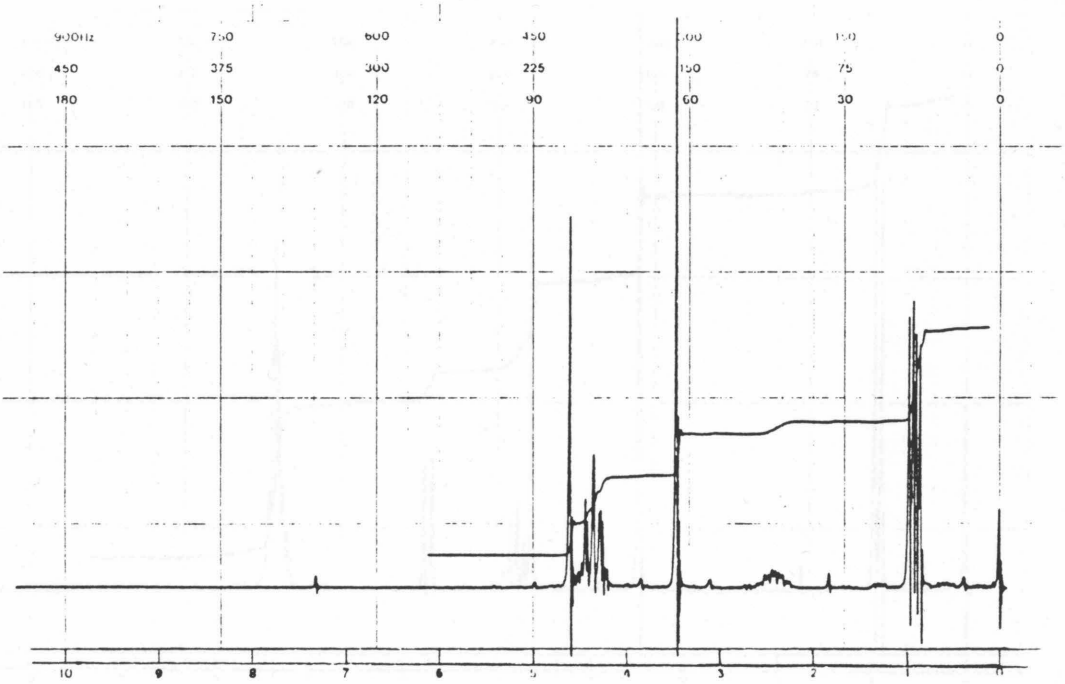

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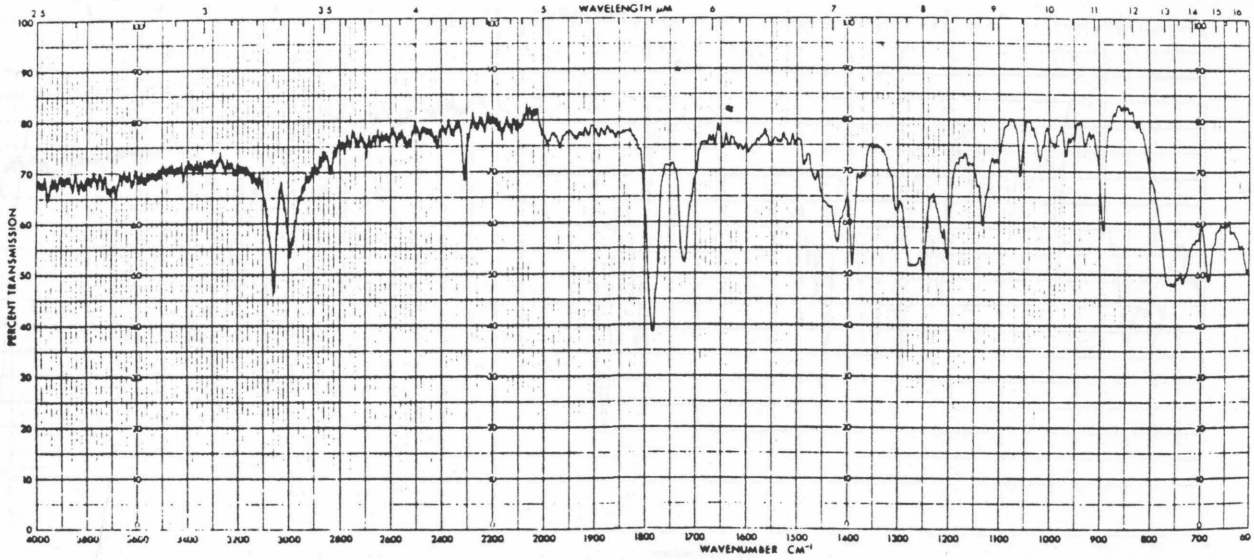

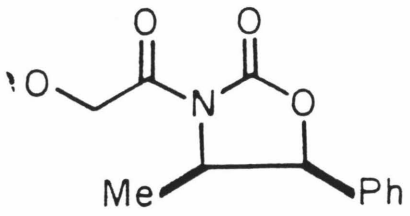

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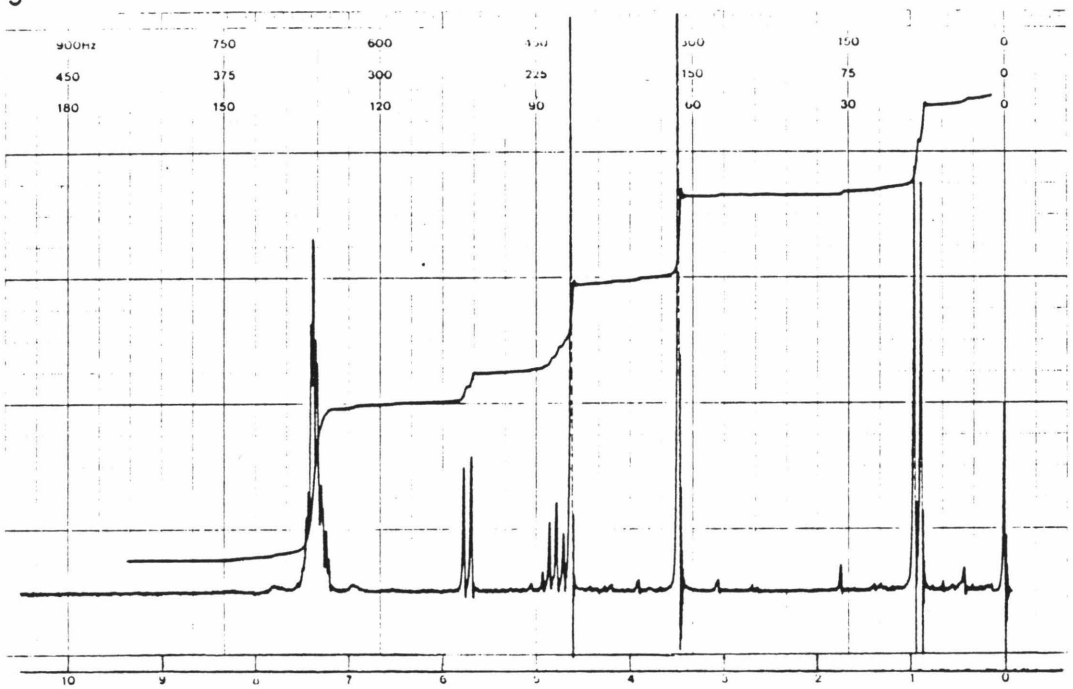

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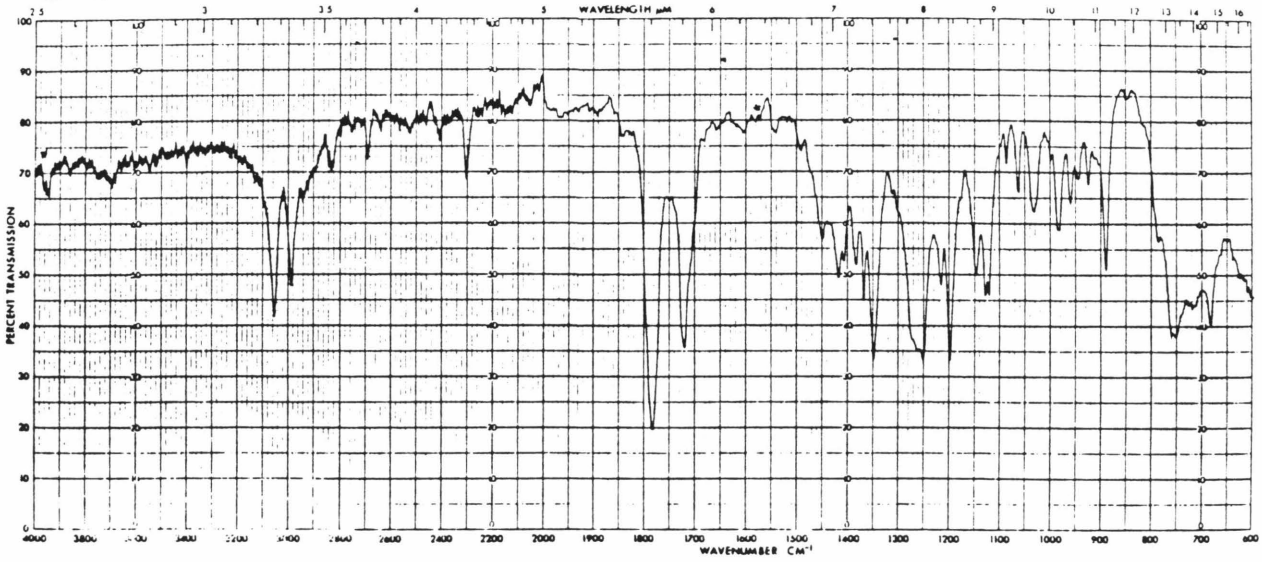

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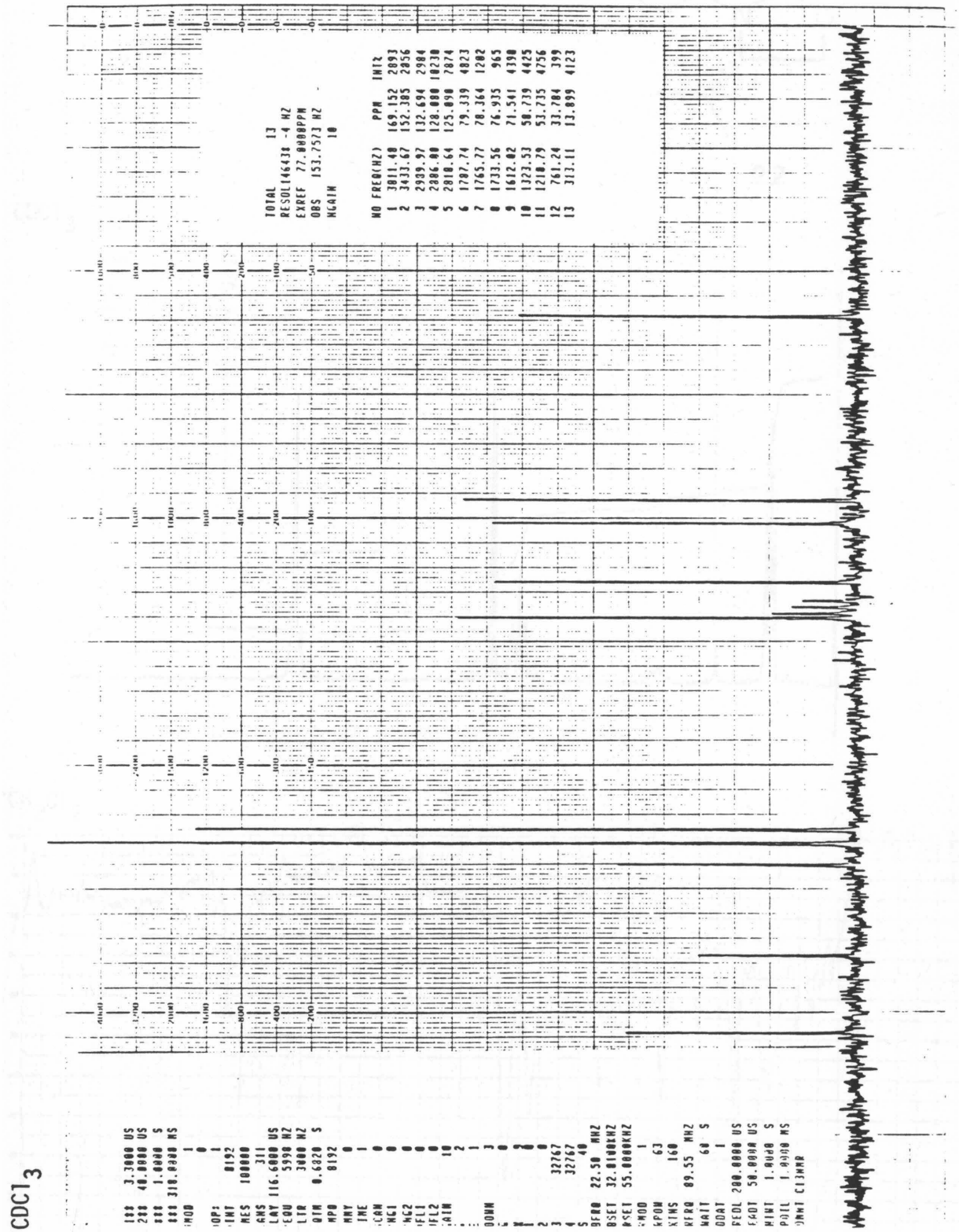
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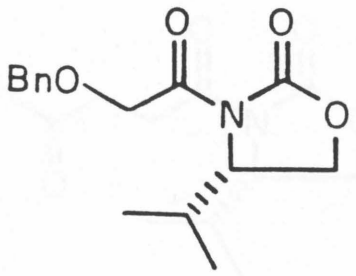

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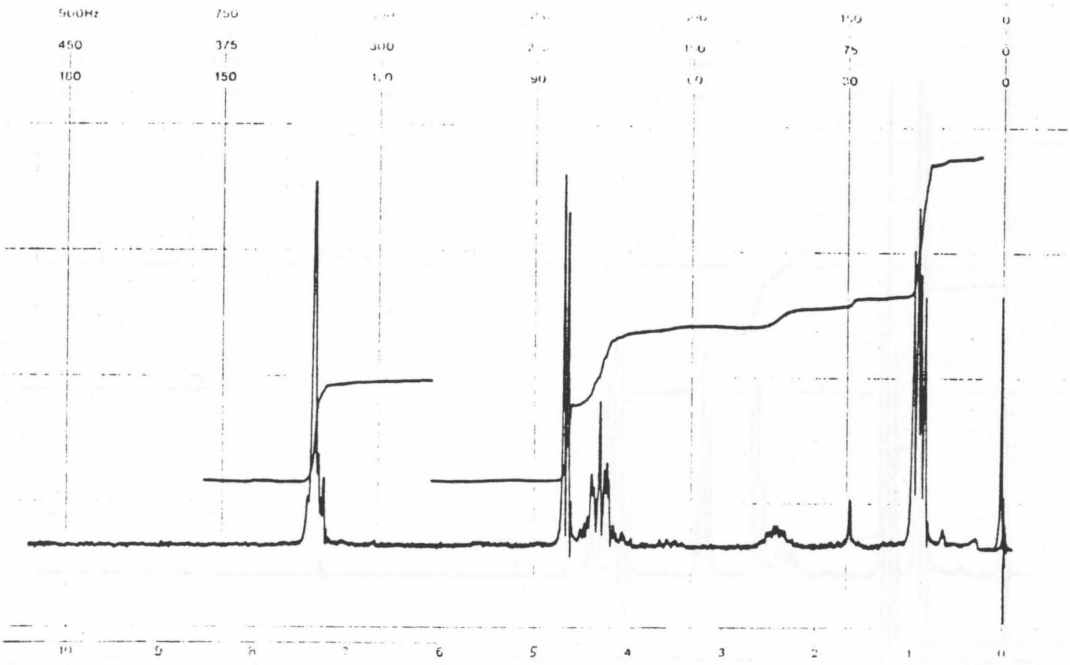

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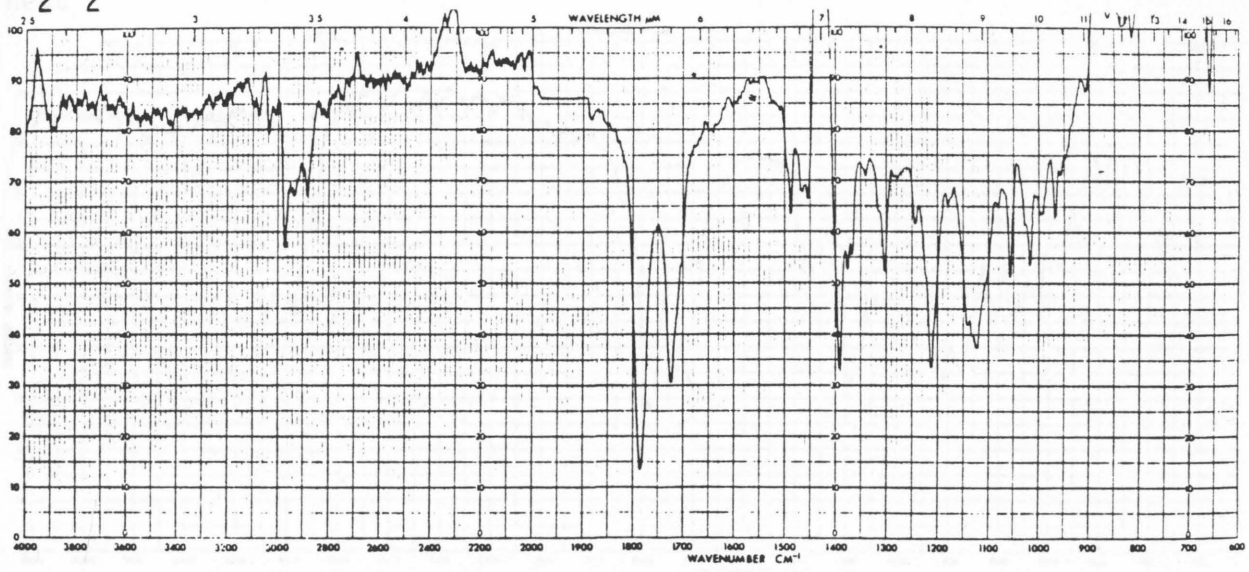

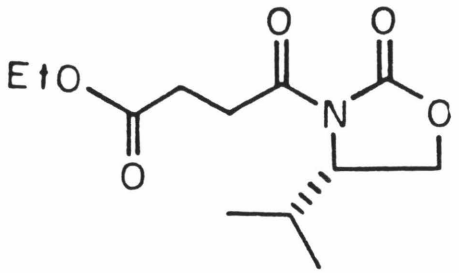

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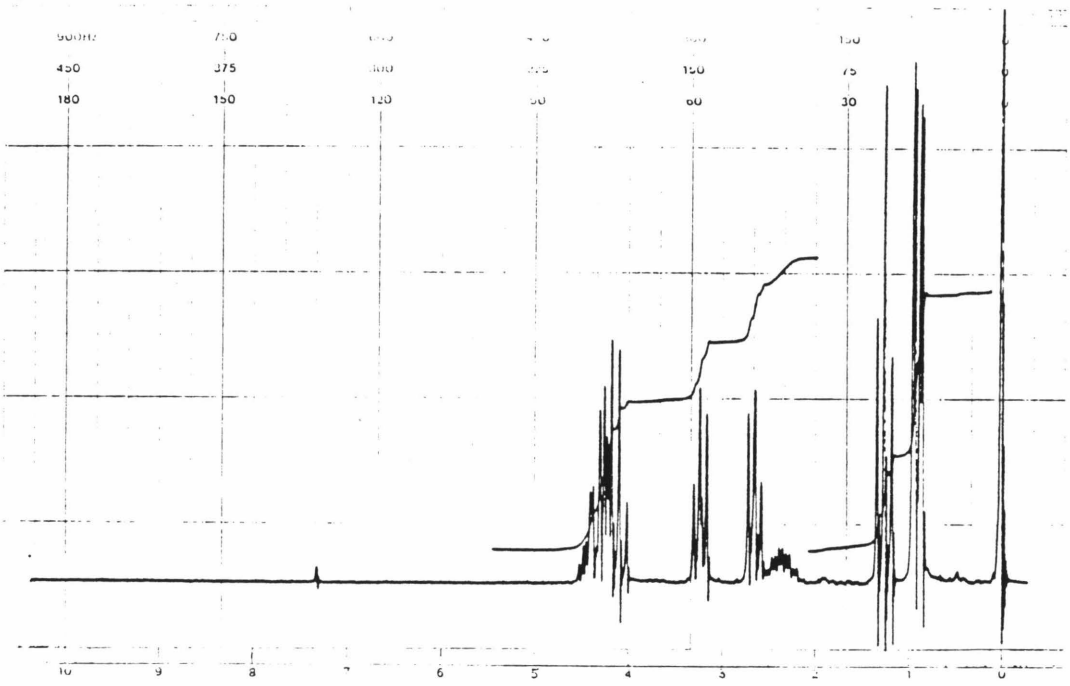

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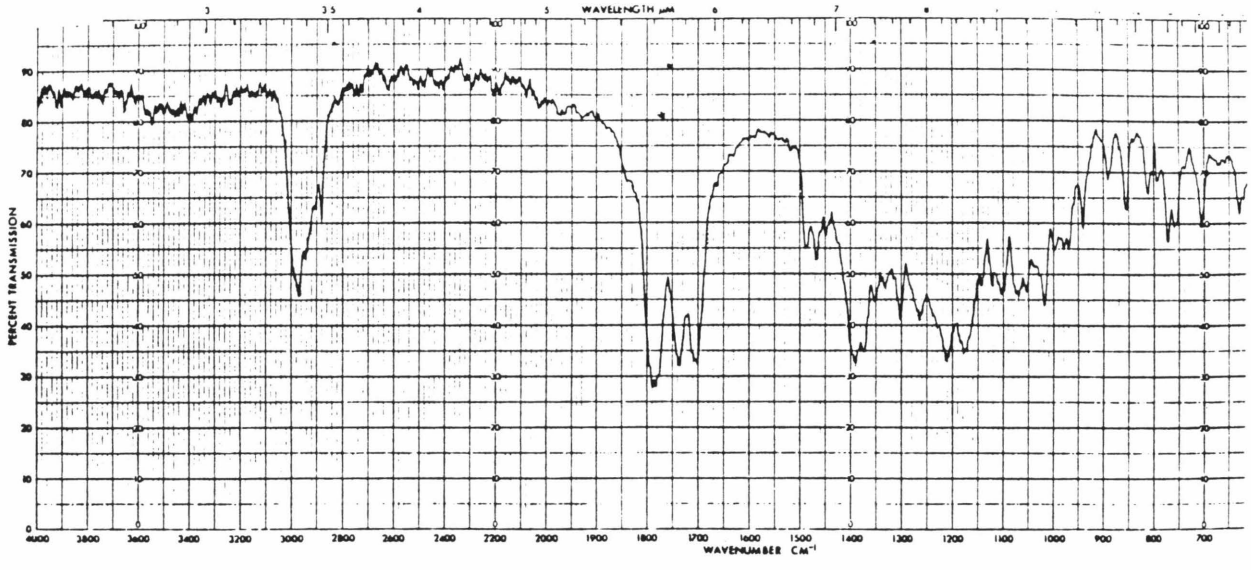

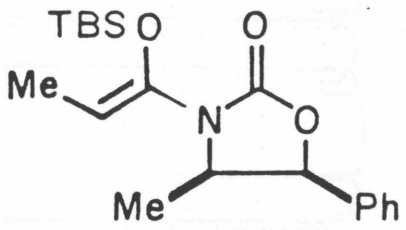

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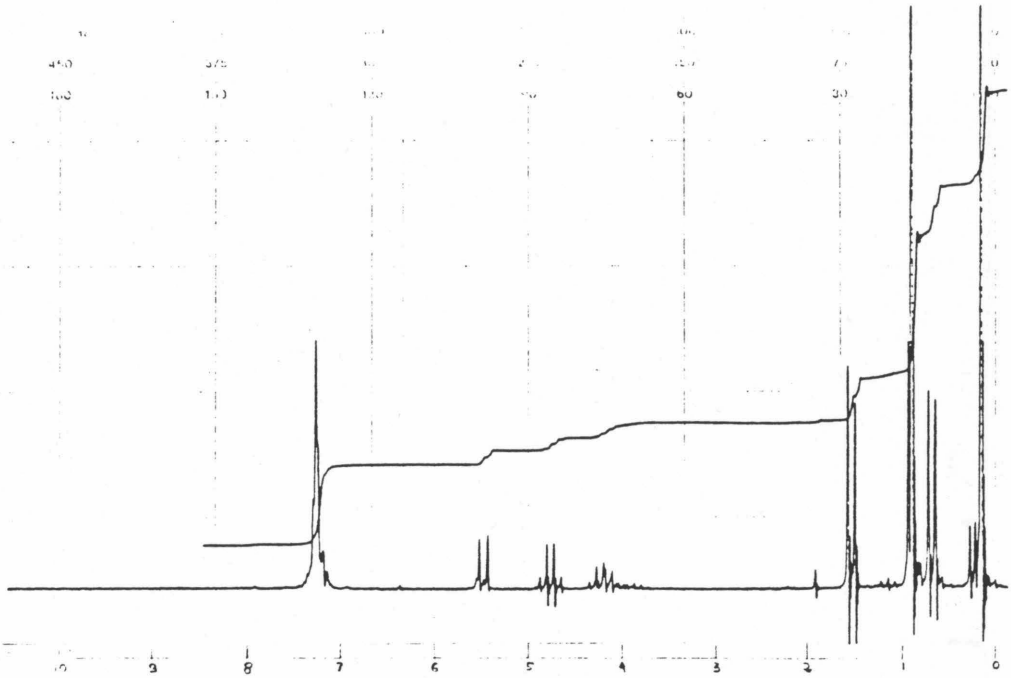

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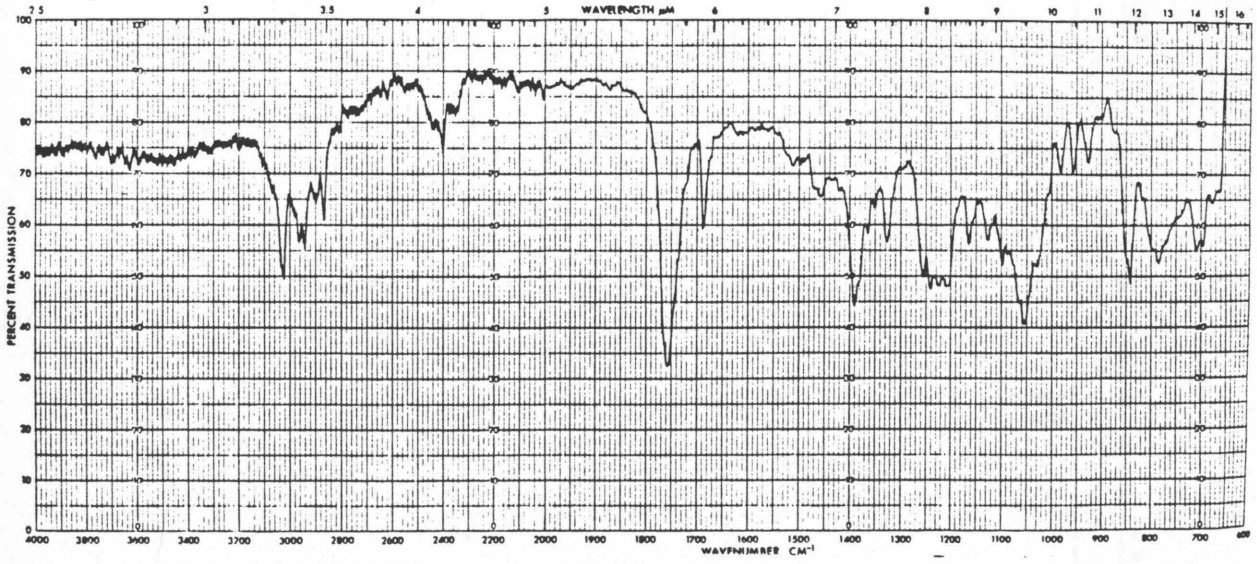
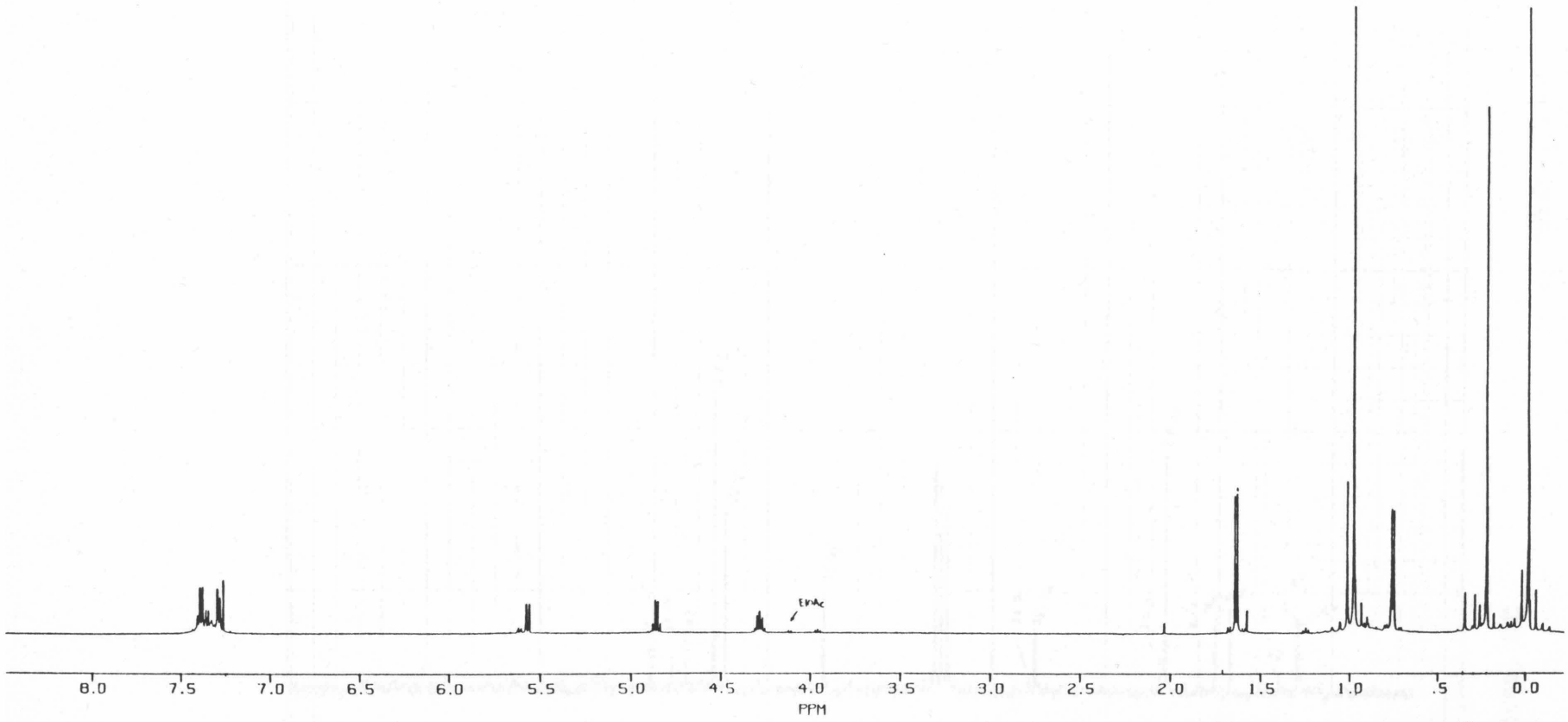
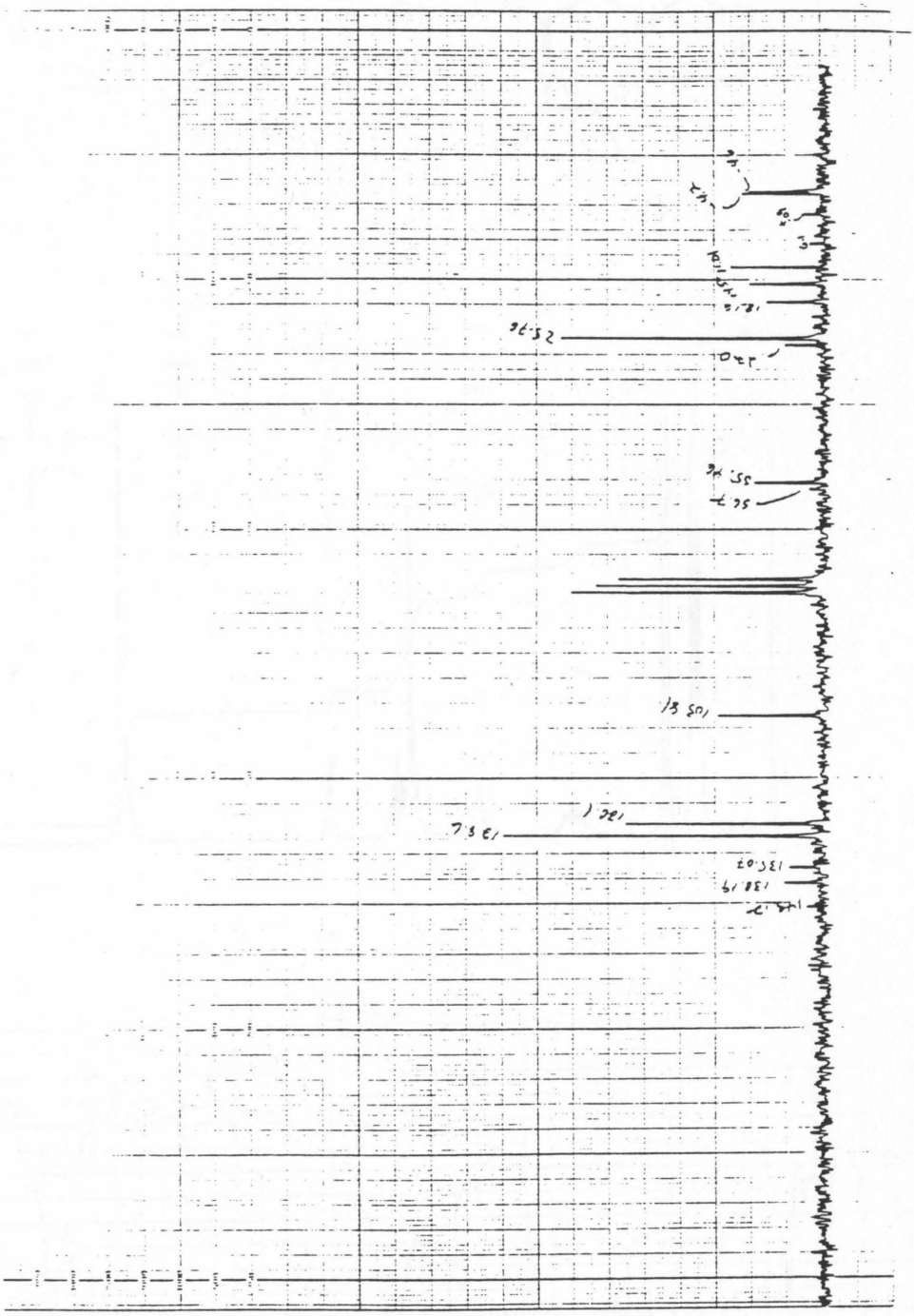


$CDCl_3$



33 (cont.)

33 (cont.)



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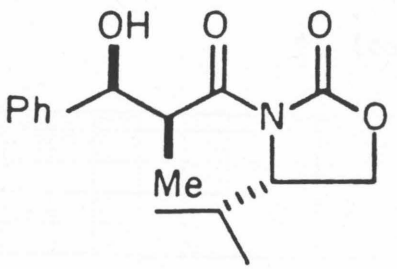
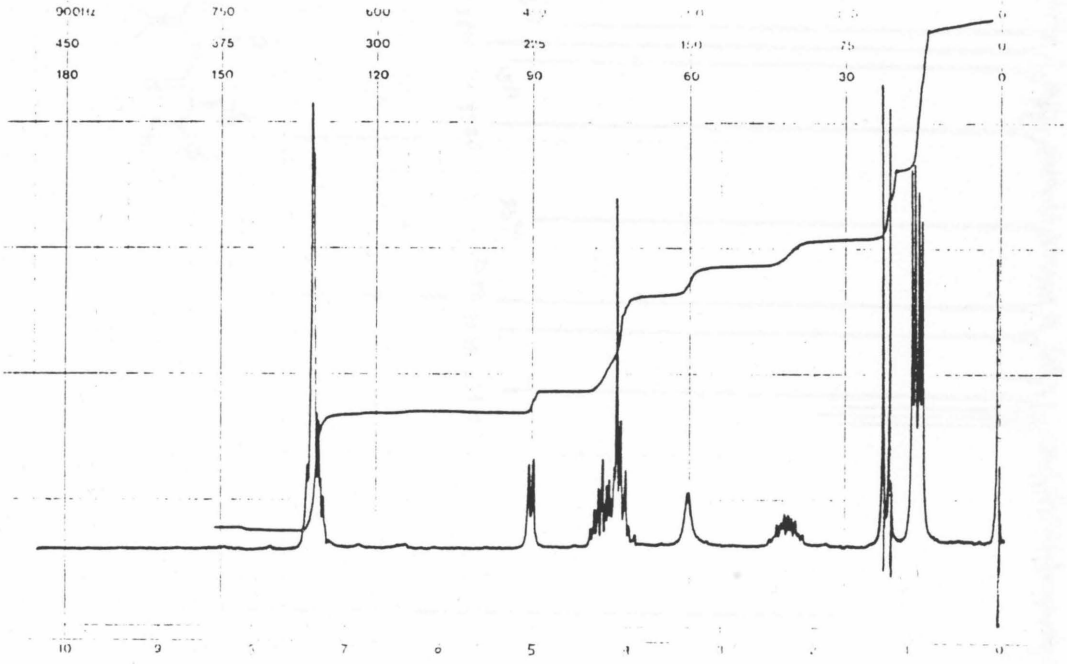
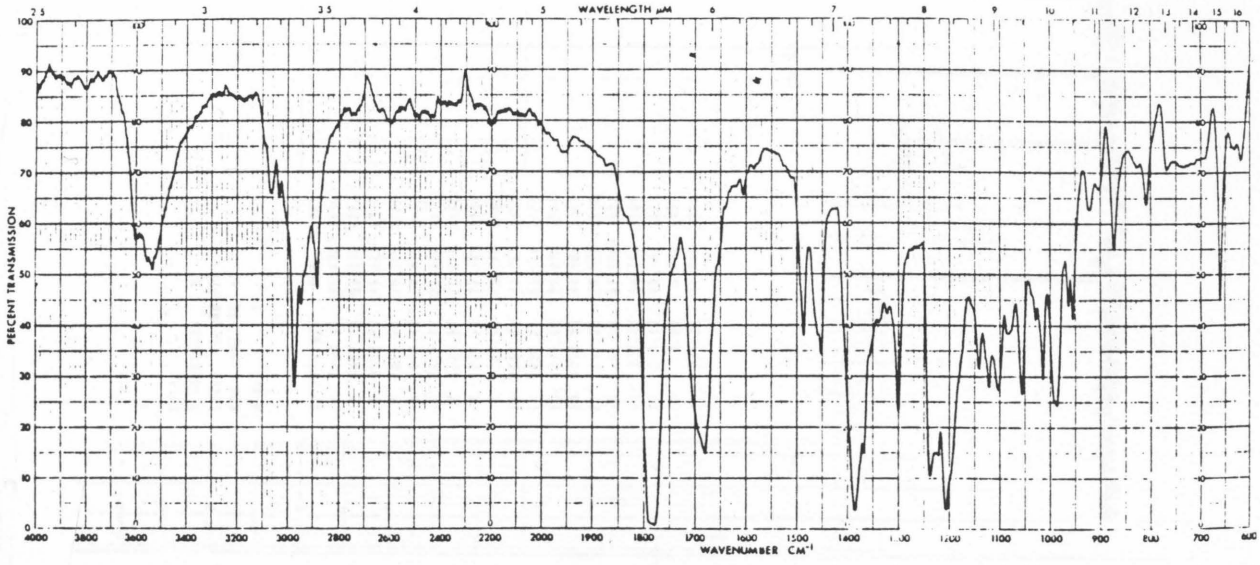

OH
O
O
Ph
N
O
Me

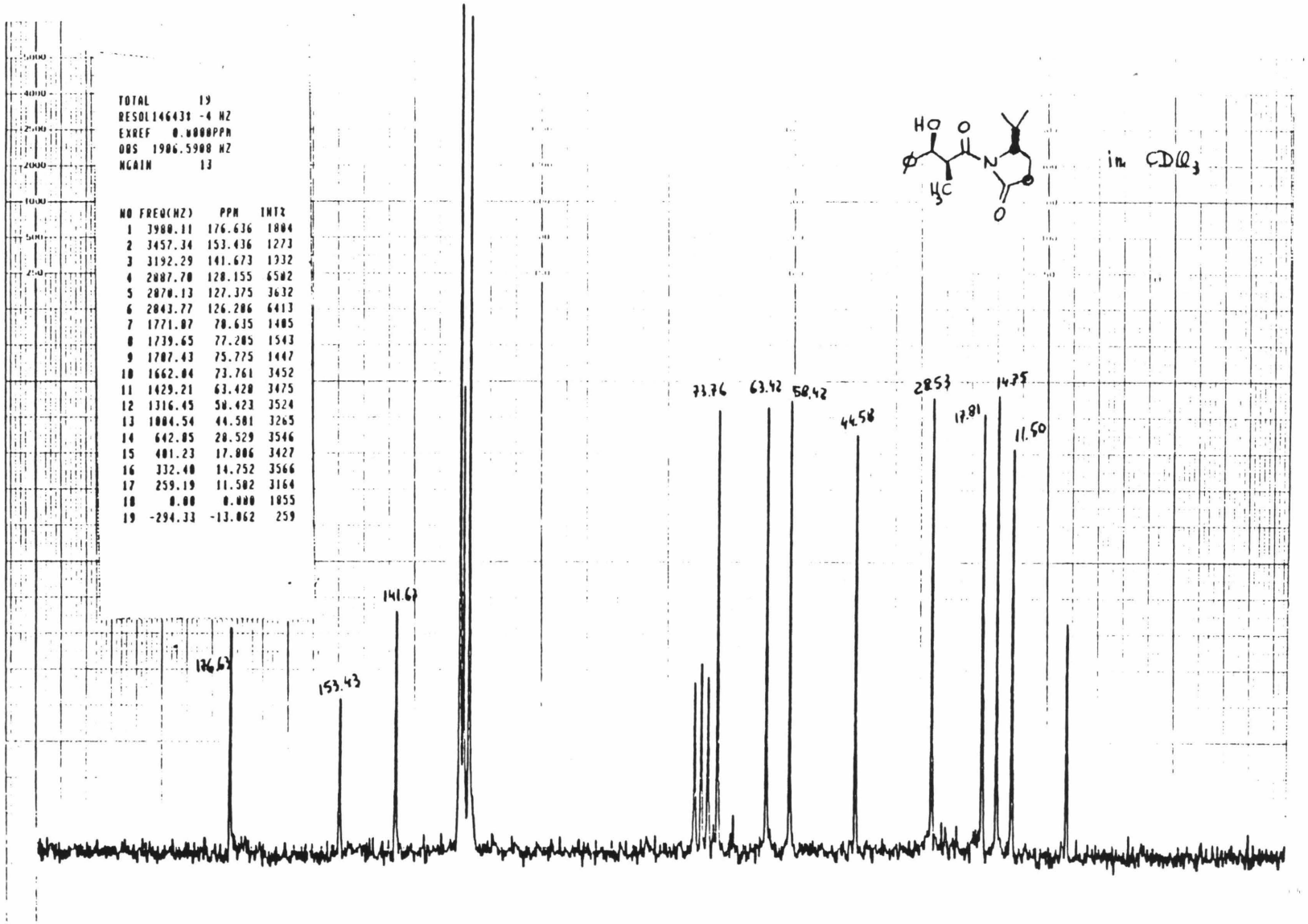
11

$CDCl_3$




WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

$CDCl_3$



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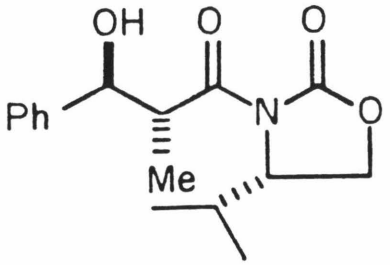

11 T

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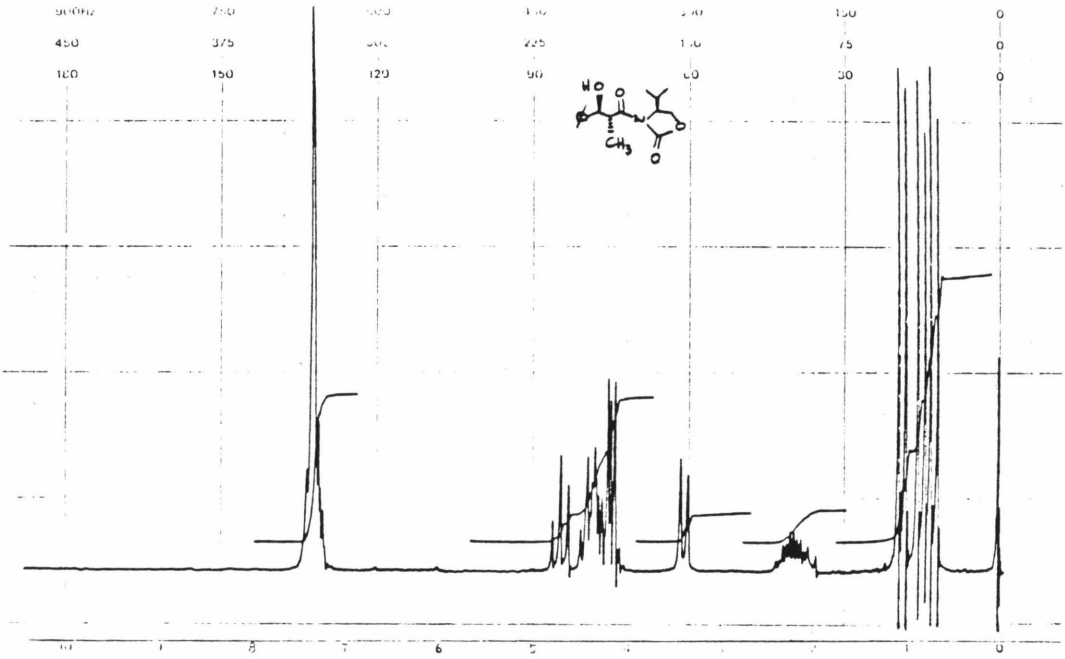
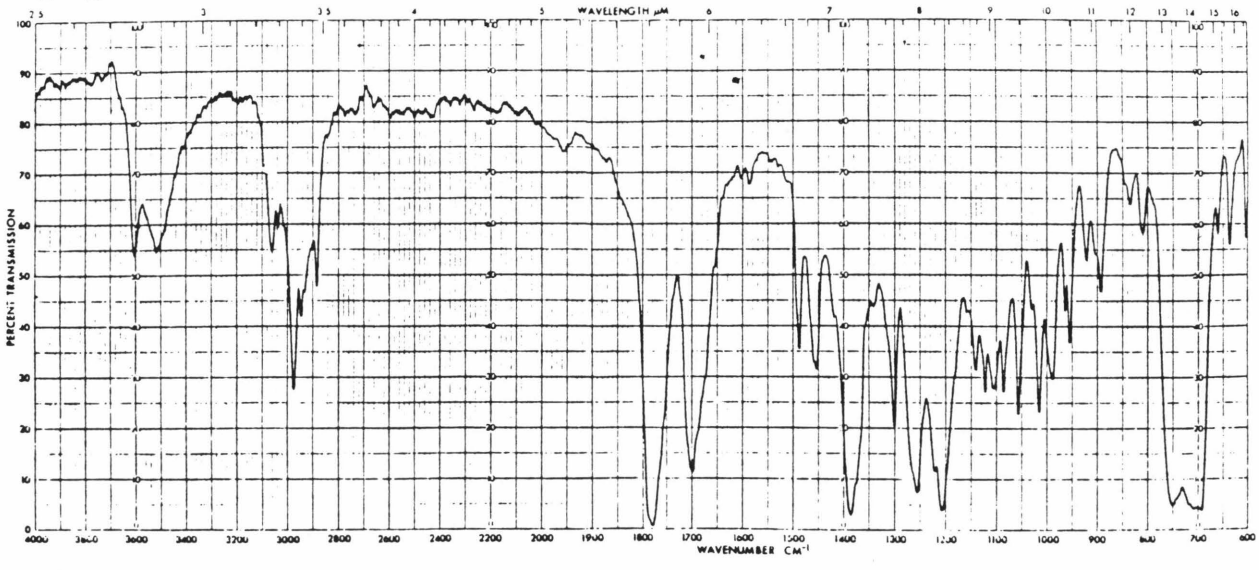
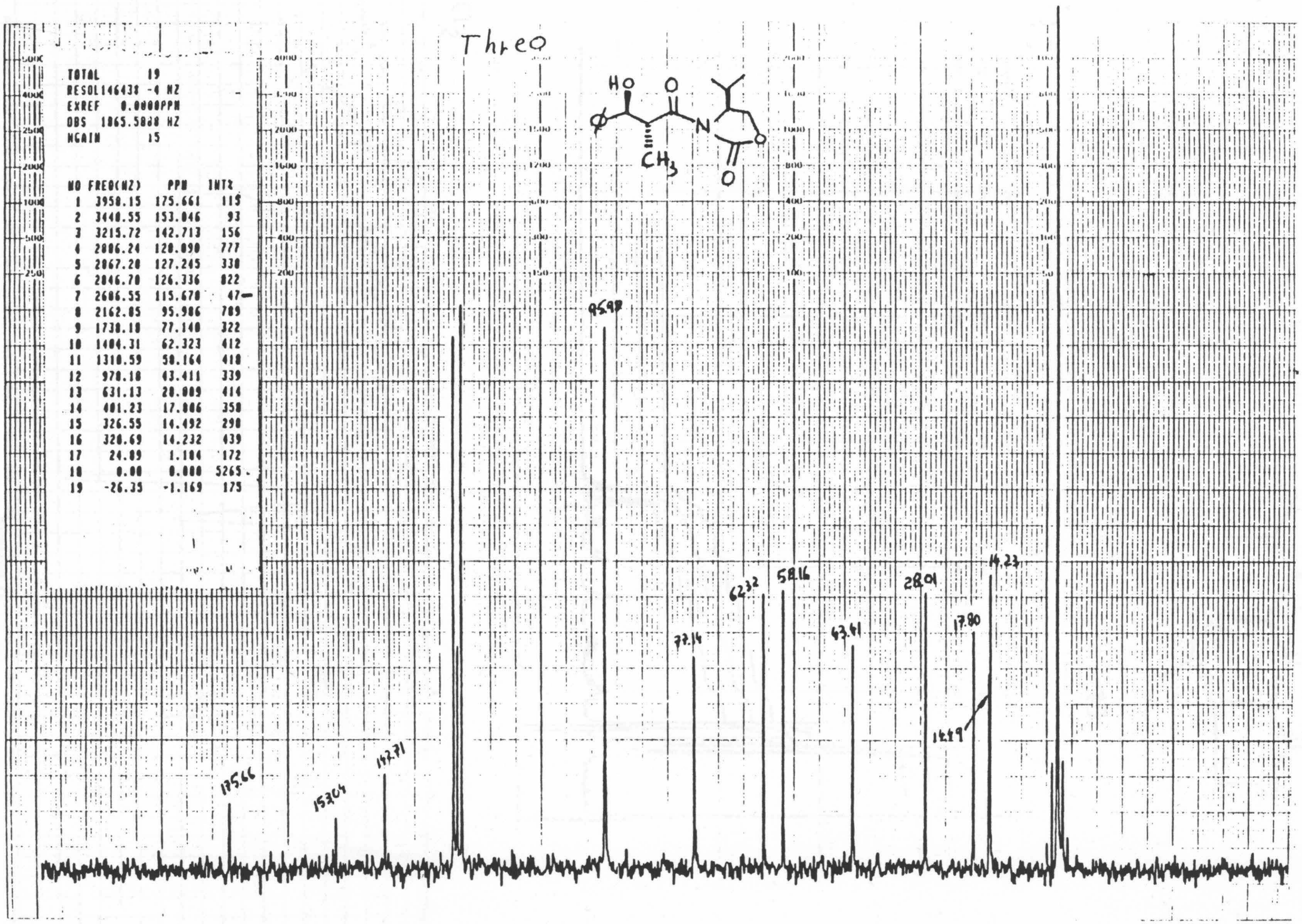


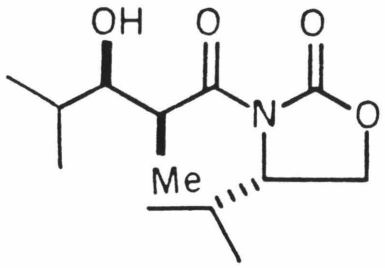
CH_2Cl_2



11 T (cont.)

CCl_4





13

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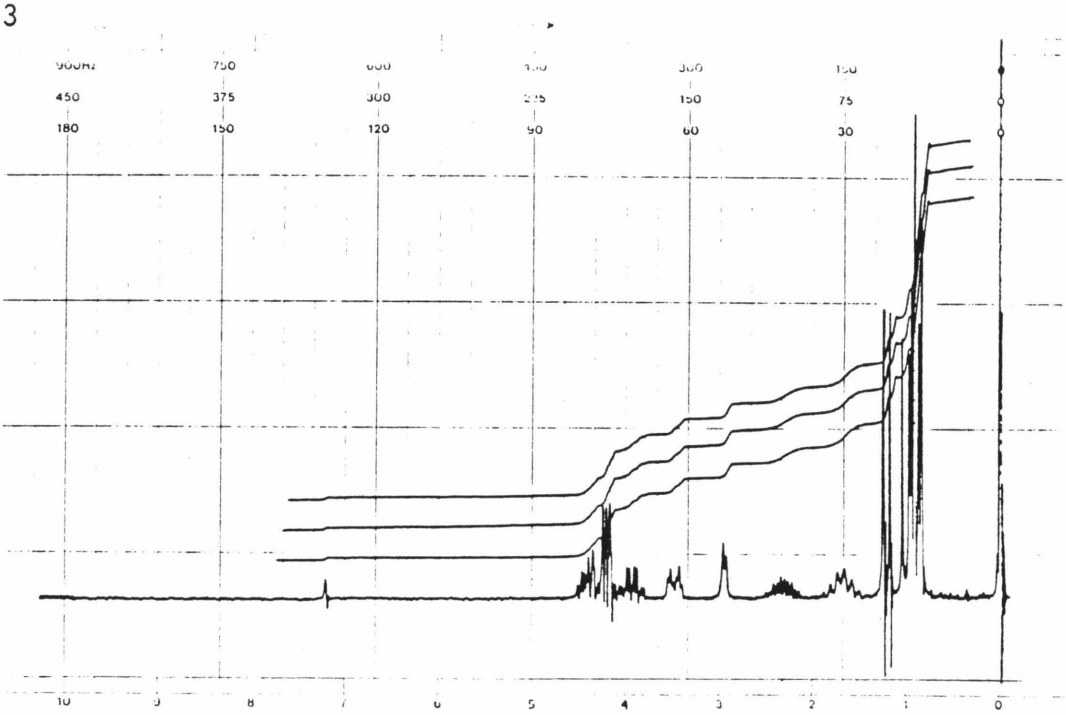

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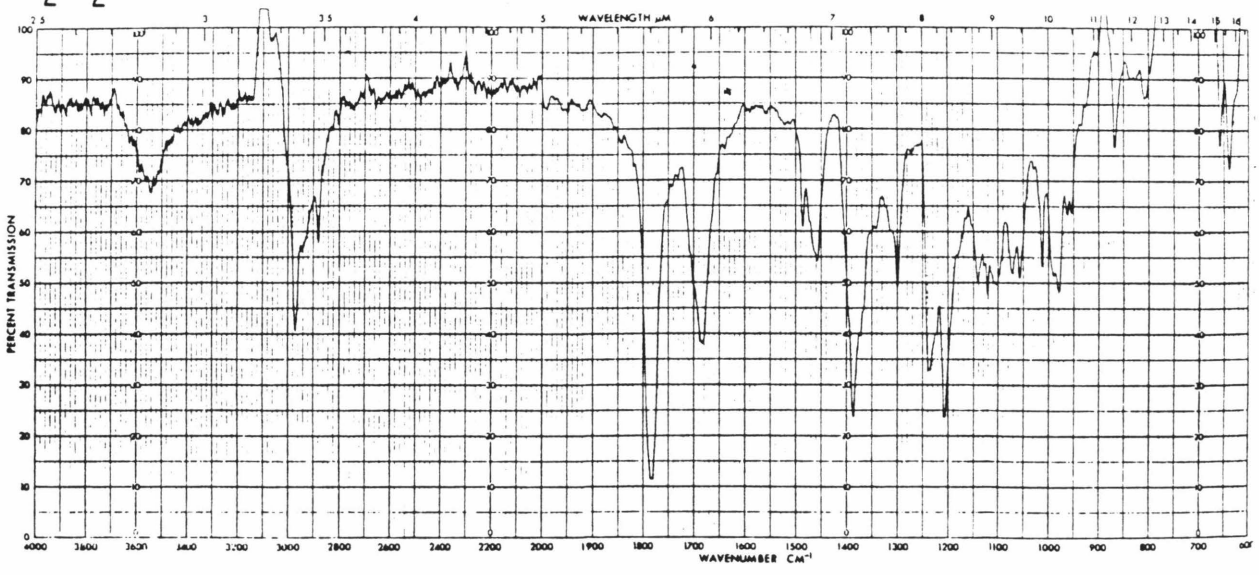

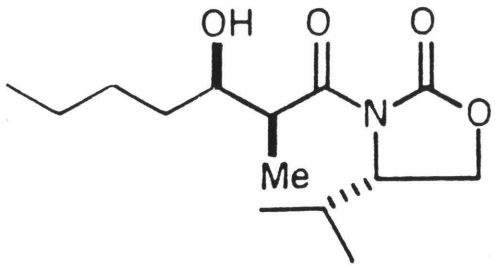

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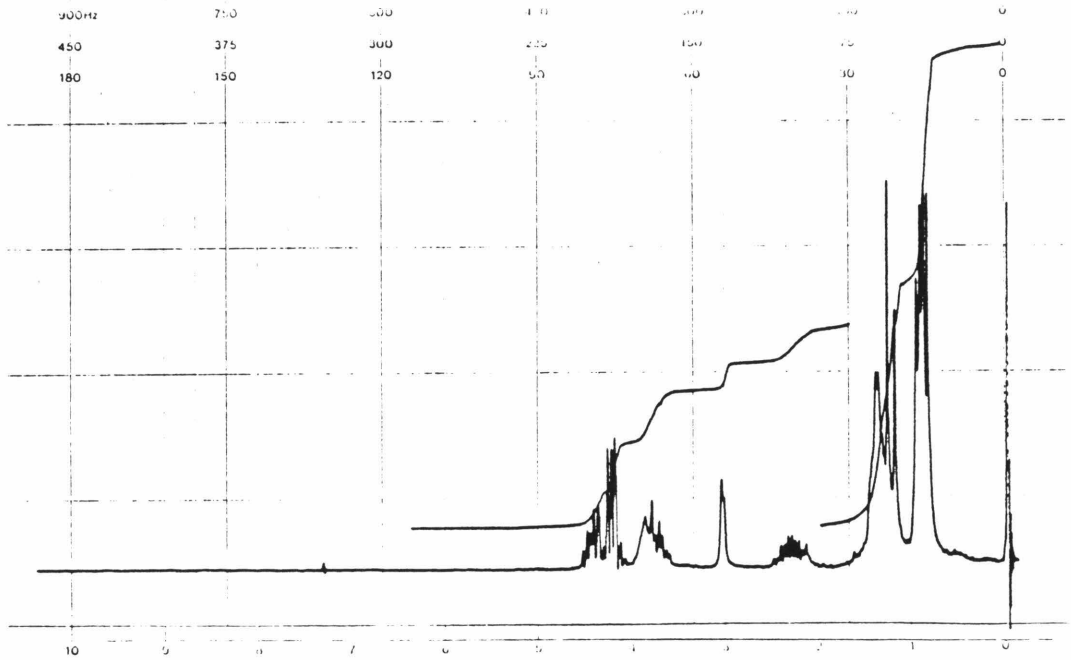

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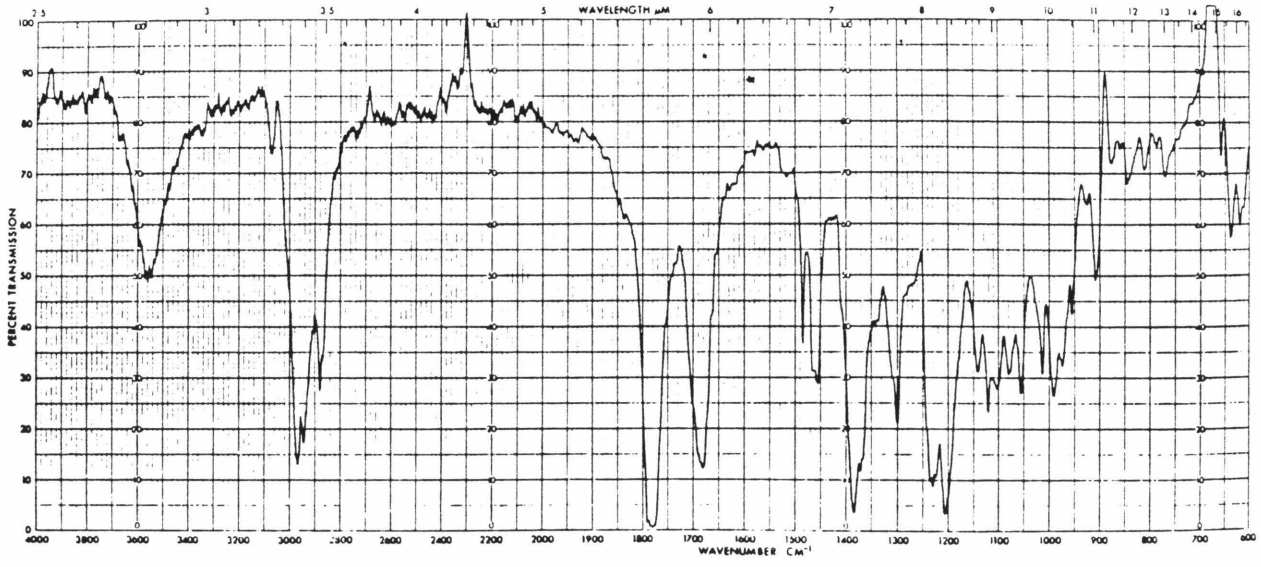

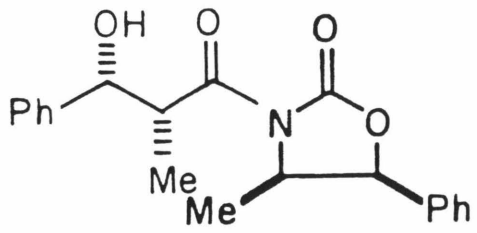

12

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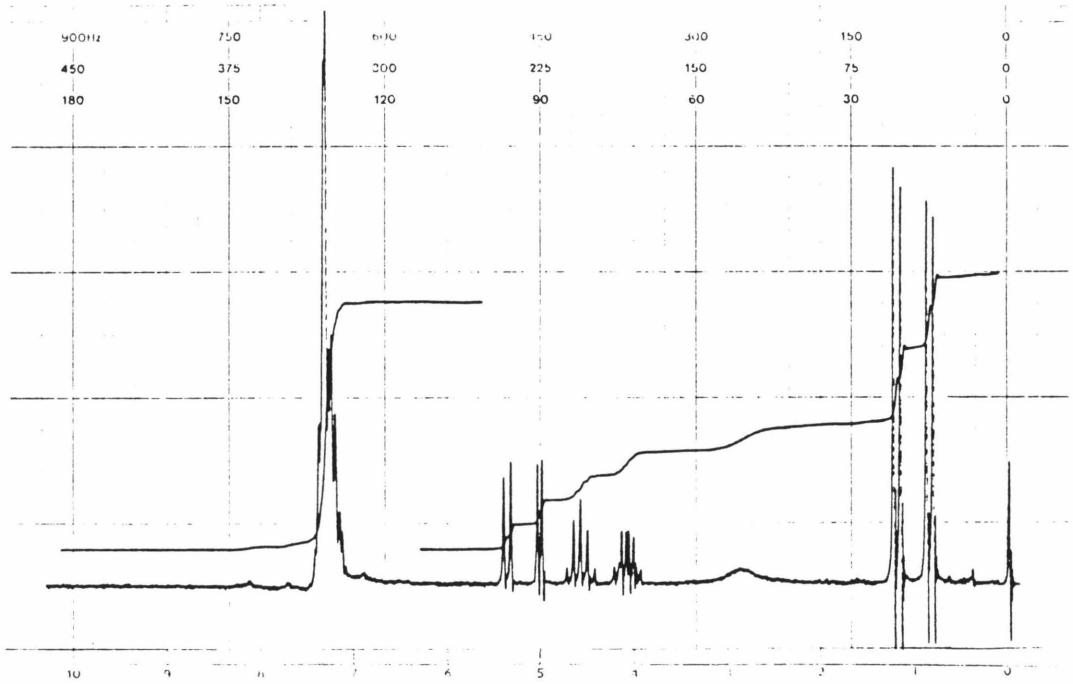

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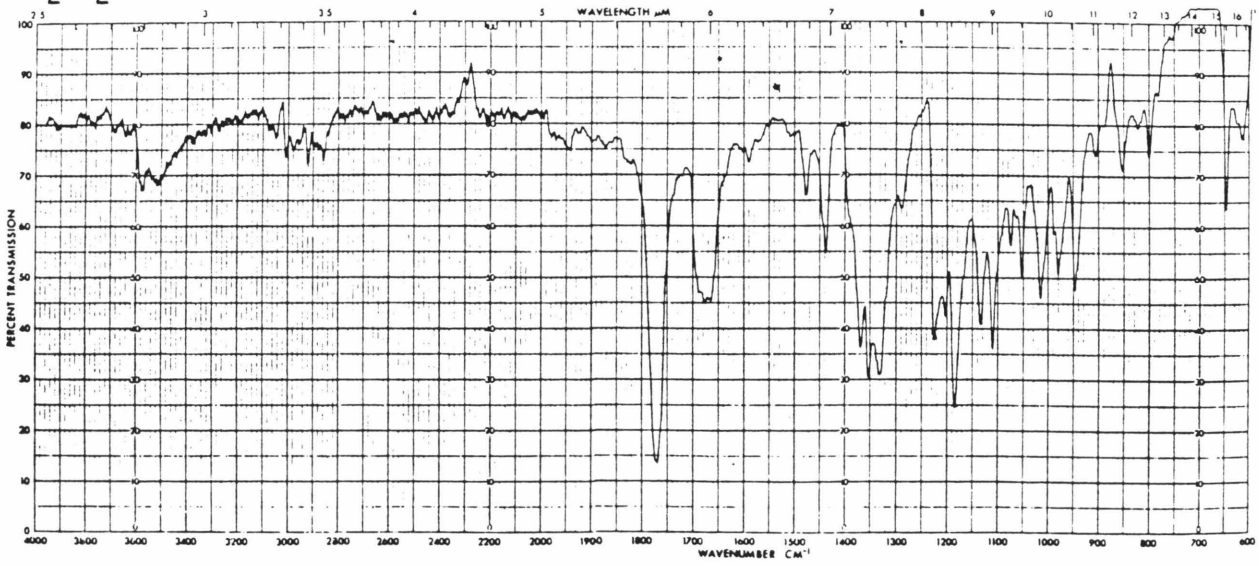
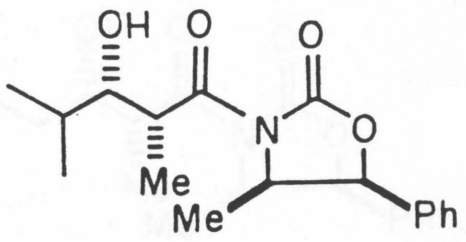
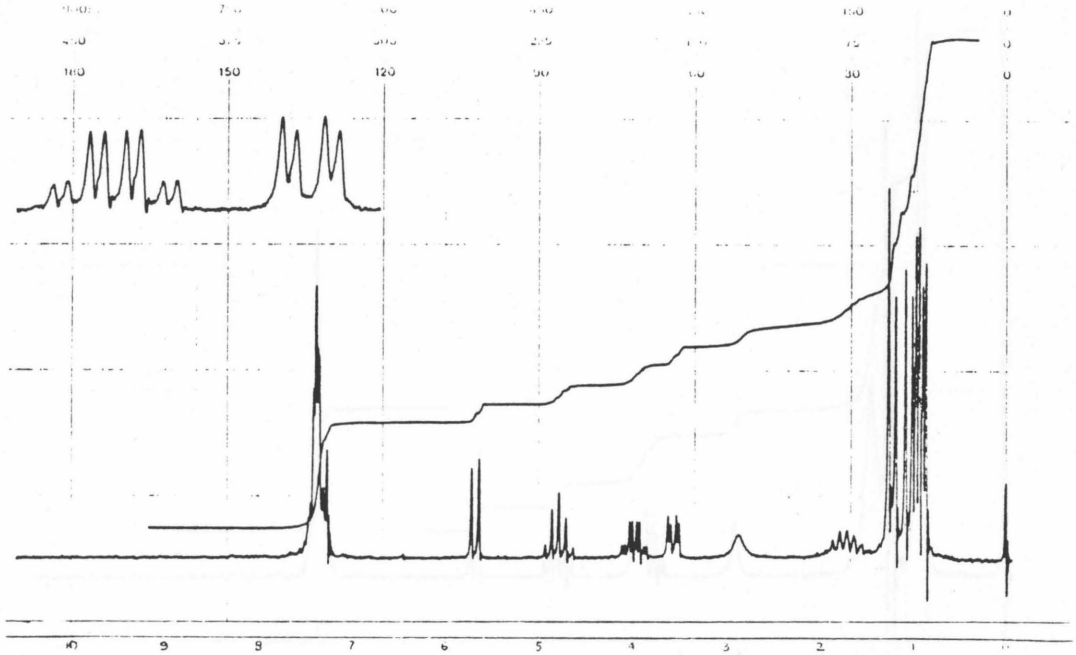




14

$CDCl_3$



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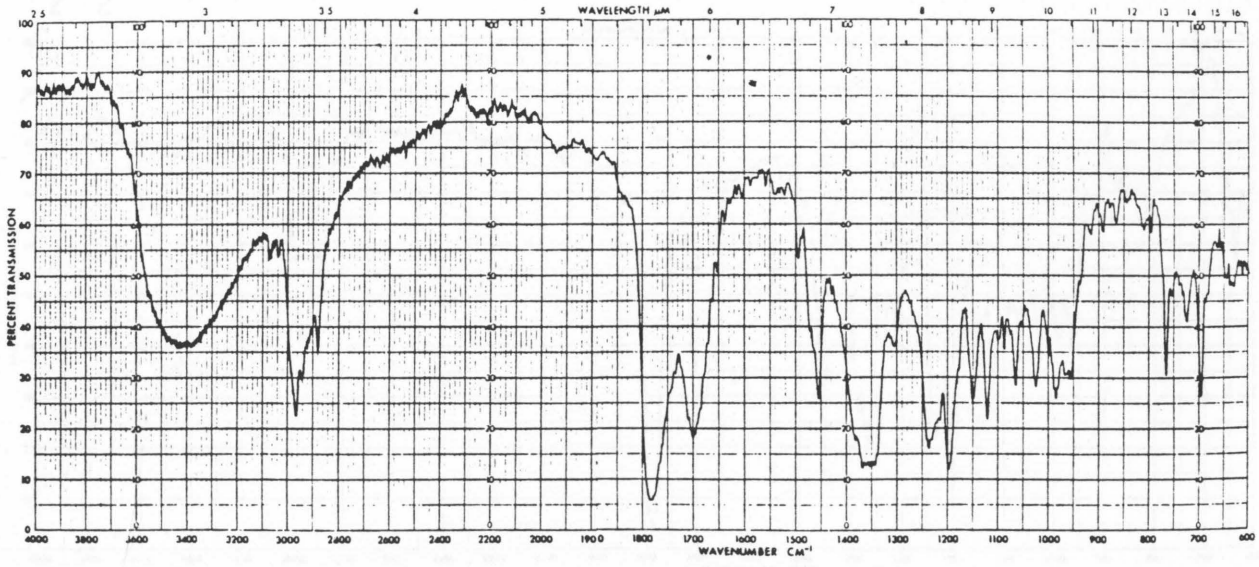

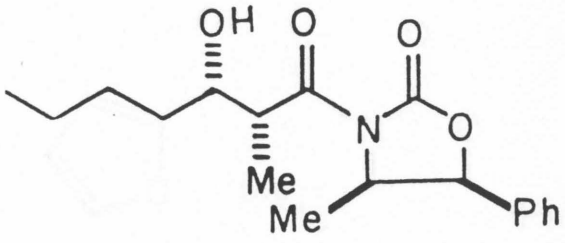

16

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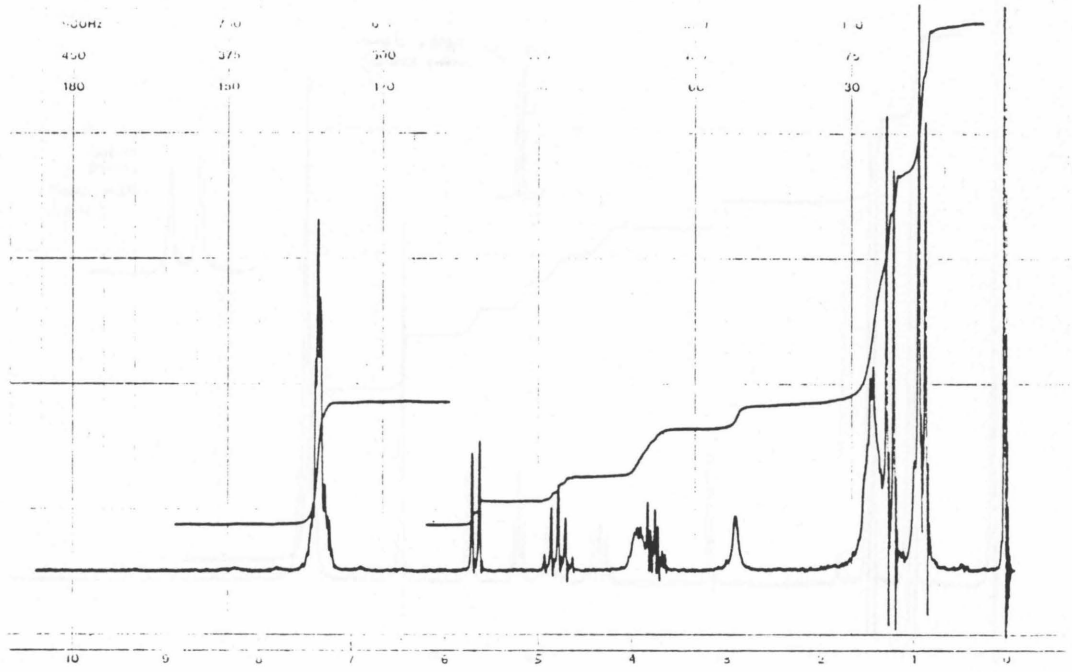
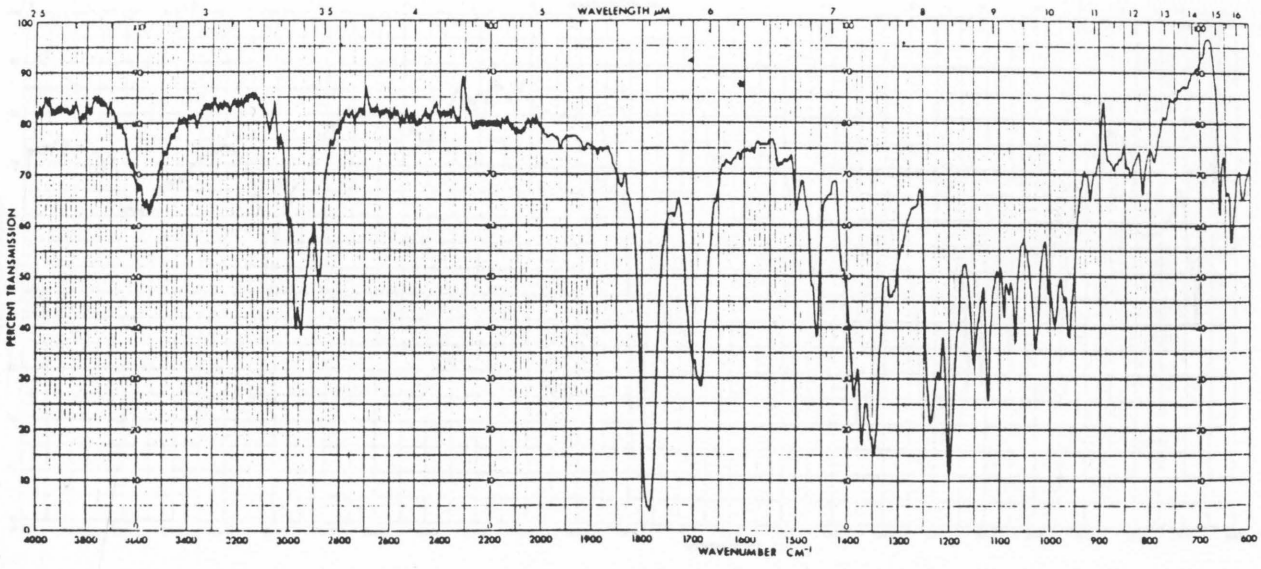
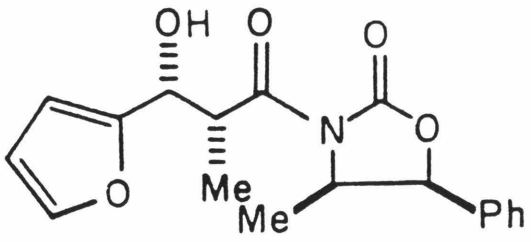


CH_2Cl_2





17

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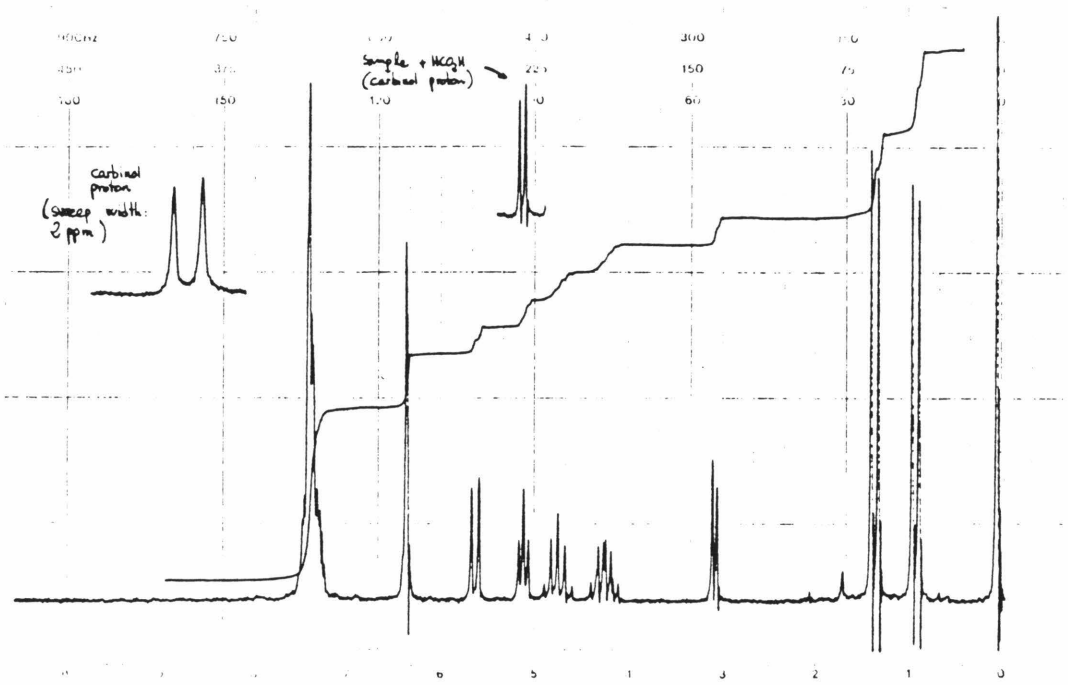

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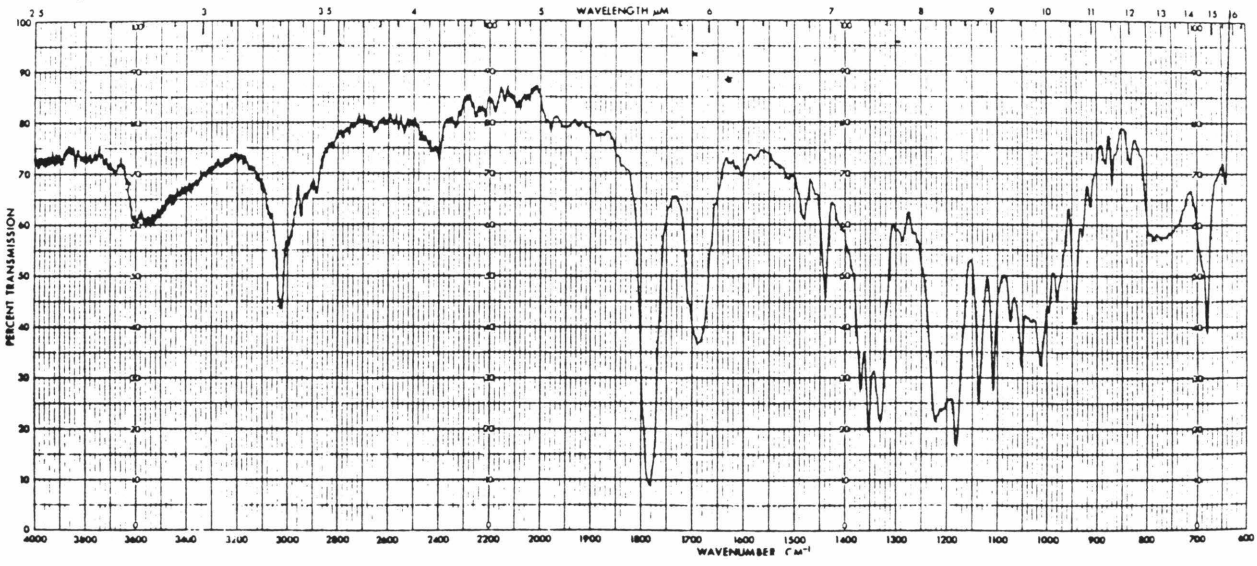

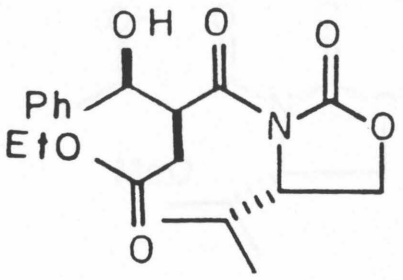

29

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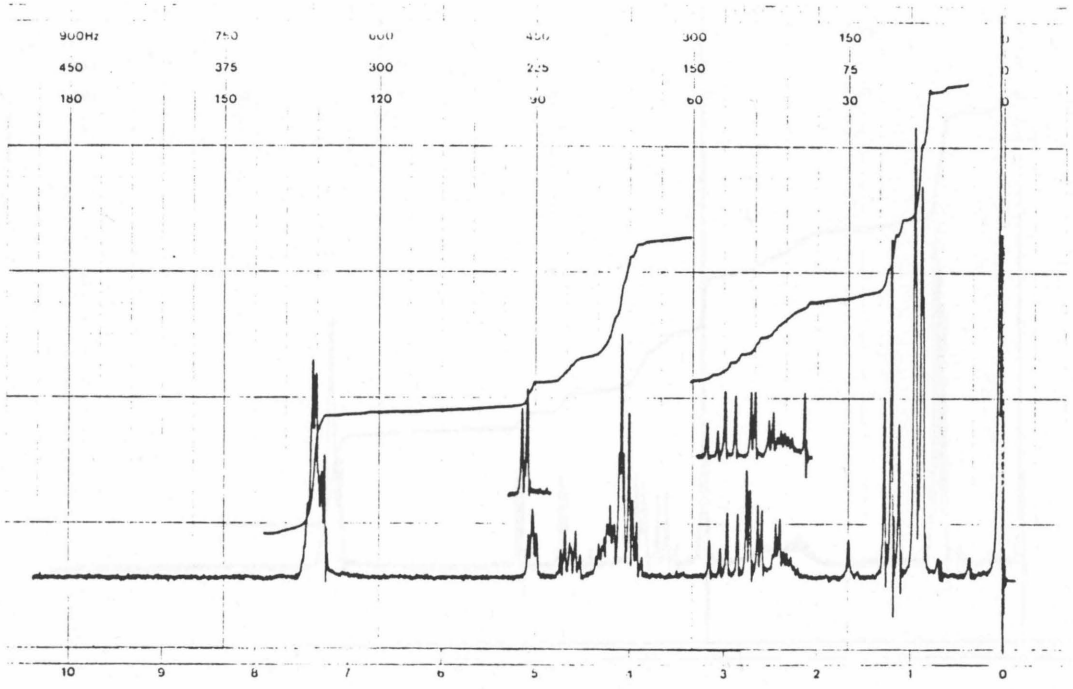
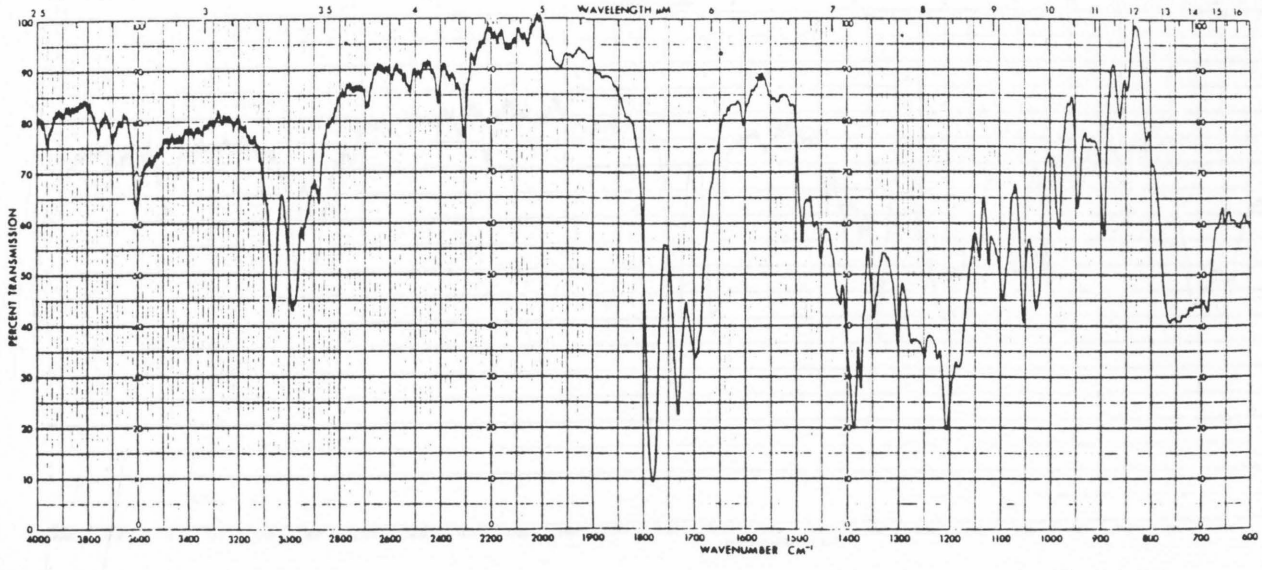
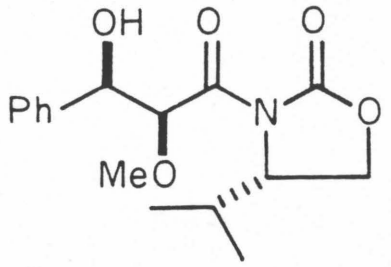


CH_2Cl_2





25

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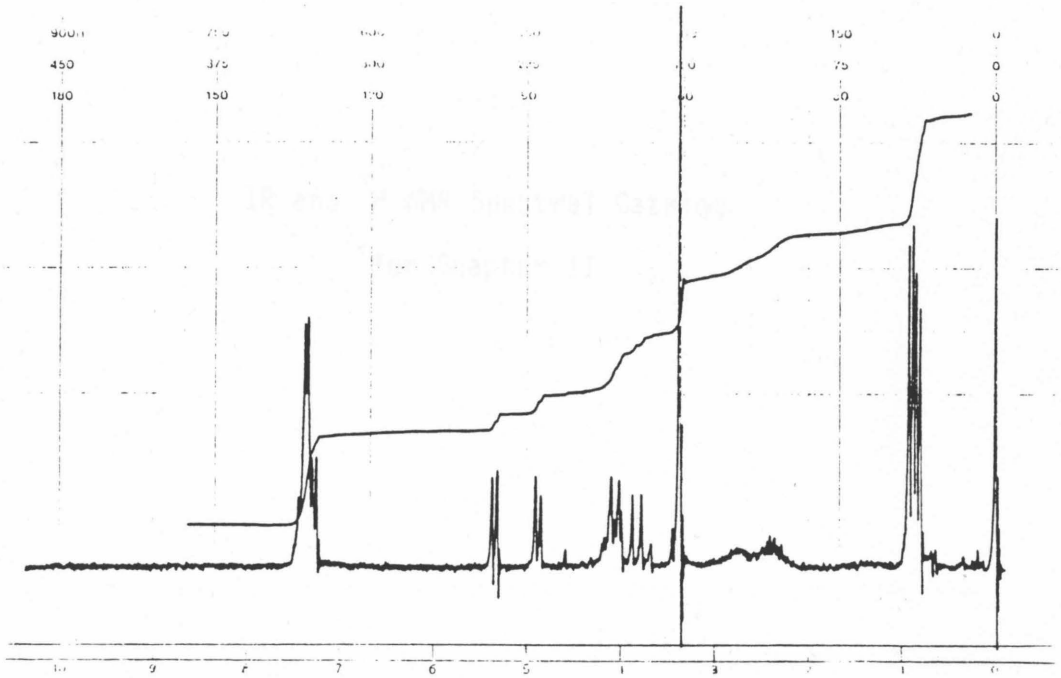
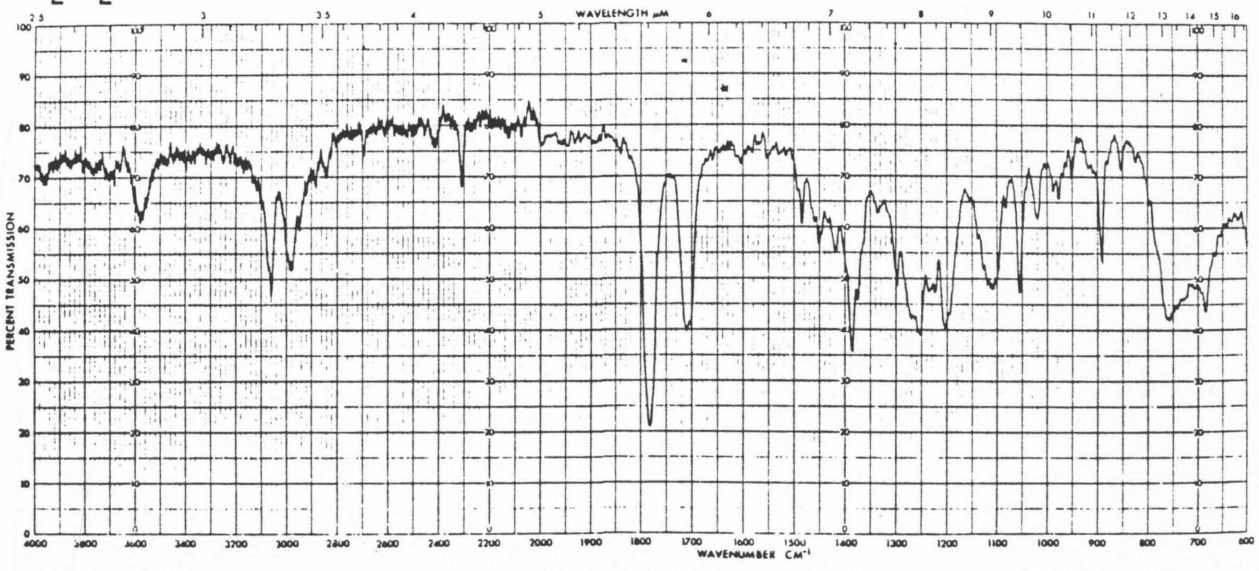


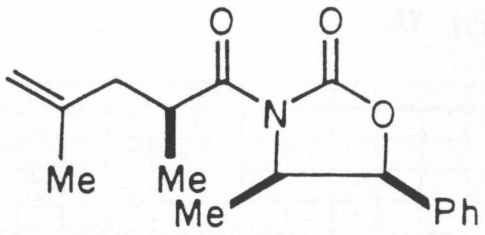
CH_2Cl_2



APPENDIX II

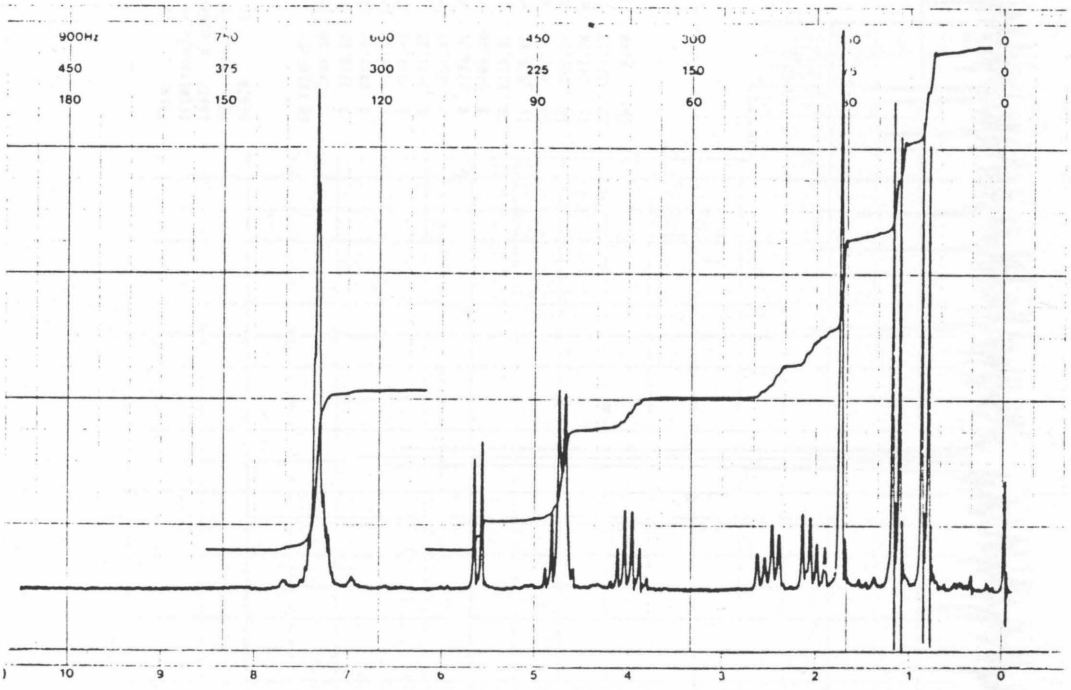
IR and ^{1}H NMR Spectral Catalog

for Chapter II

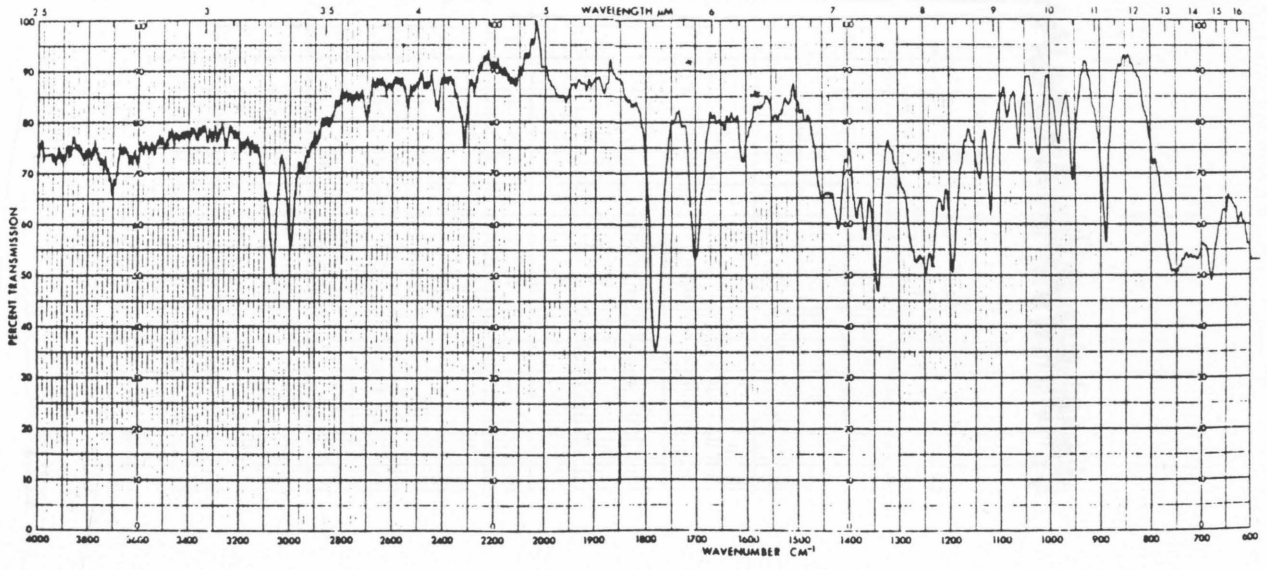


37

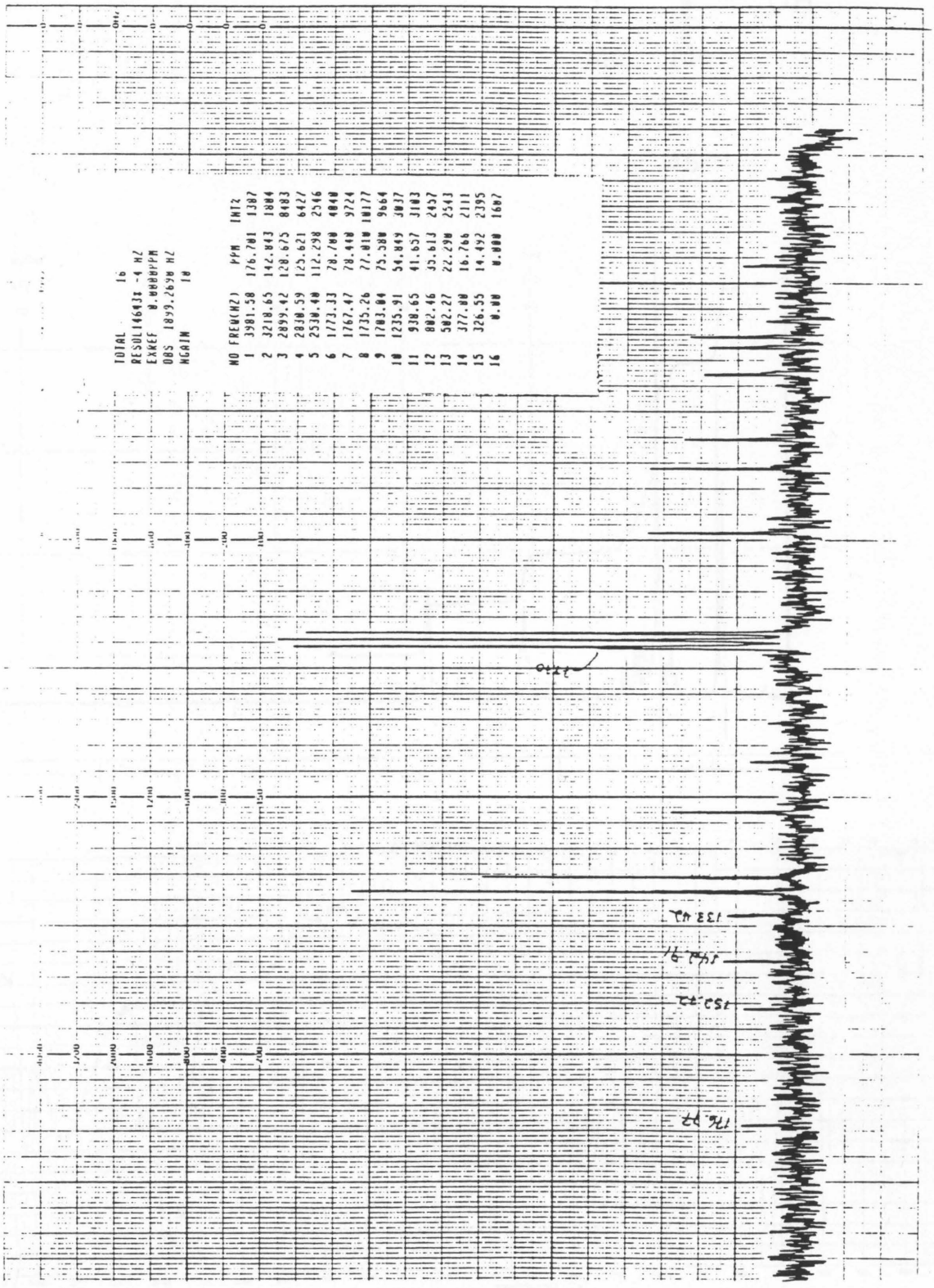
$CDCl_3$

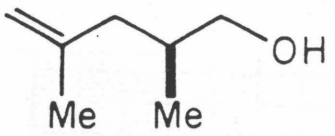


CH_2Cl_2



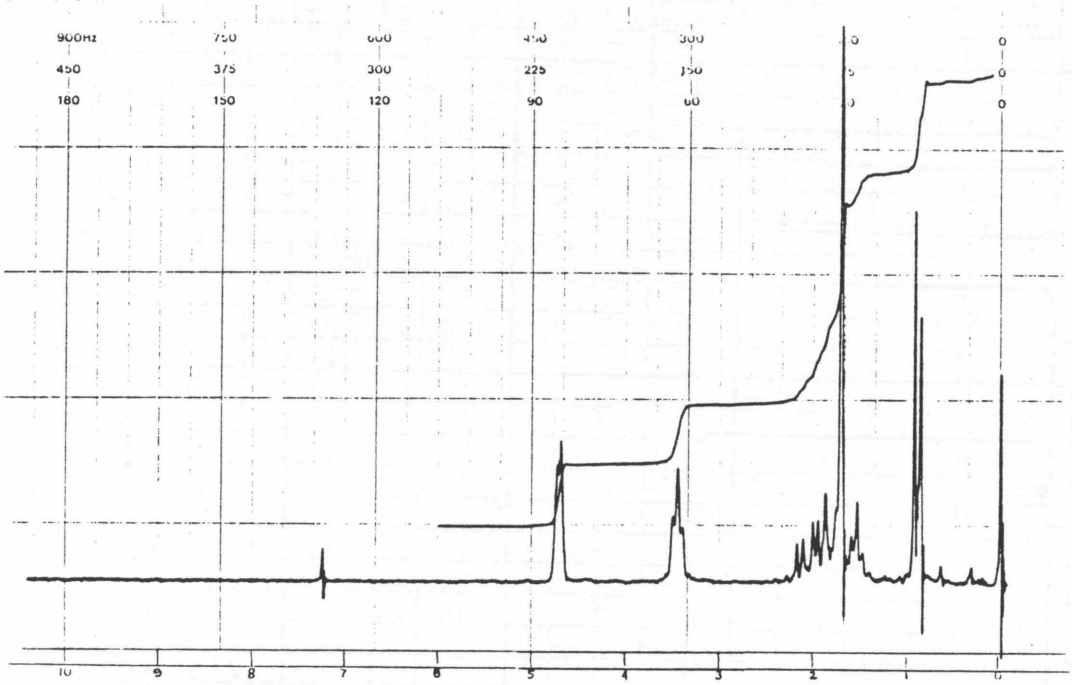
37 (cont.)


TOTAL 16
RESOLU46HZ -4 HZ
EXREF 0.0000PPM
OBS 1899.2698 HZ
NGAIN 10
NO FREQ(HZ) PPM INTZ
1 3981.58 176.701 1307
2 3218.65 142.843 1004
3 2899.42 128.675 0403
4 2810.59 125.621 6422
5 2530.40 112.298 2546
6 1773.33 78.700 4040
7 1767.47 78.440 9724
8 1735.26 77.010 10177
9 1703.04 75.580 9664
10 1235.91 54.849 3037
11 930.65 41.657 3103
12 802.46 35.613 2457
13 502.27 22.290 2543
14 377.00 16.766 2111
15 326.55 14.492 2395
16 0.00 0.000 1607
1210
133 Hz
152.32
CDCl3

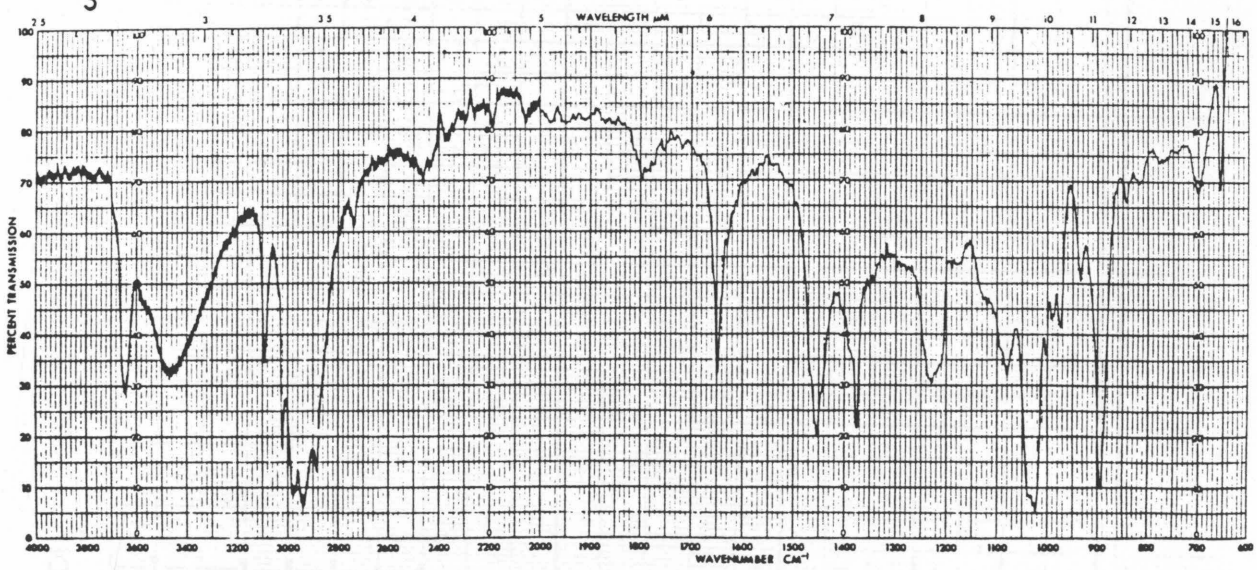


45

$CDCl_3$



$CHCl_3$



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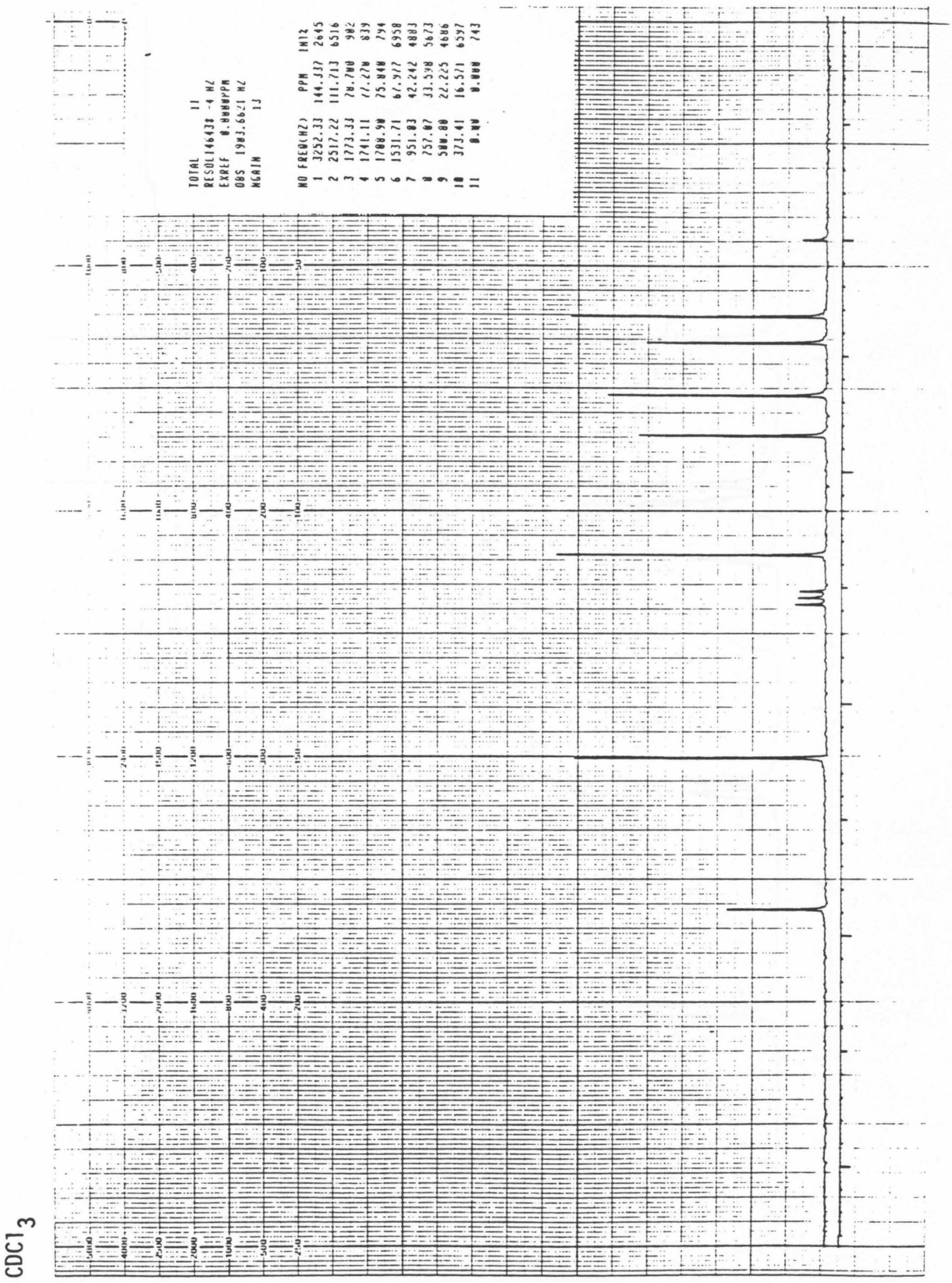
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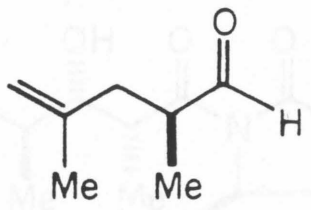
RESOL 146438 -4 HZ
EXREF 0.000PPM
OBS 1983.6621 HZ
MGAIN 13
NO FREQ(HZ) PPM INTG
1 3252.33 144.317 2645
2 2517.22 111.713 6516
3 1773.33 78.700 982
4 1741.11 77.270 839
5 1708.90 75.840 794
6 1531.71 67.977 6958
7 951.83 42.242 4883
8 757.07 33.598 5673
9 500.00 22.225 4686
10 373.41 16.571 6397
11 0.00 0.000 743
CDCl3

45 (cont.)



46

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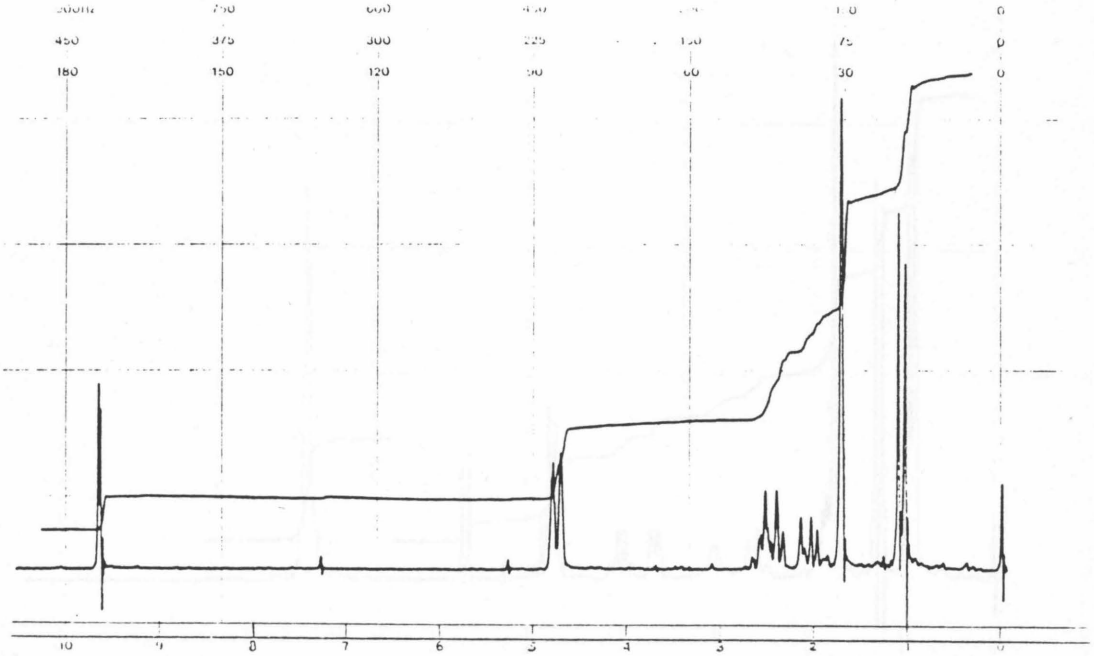

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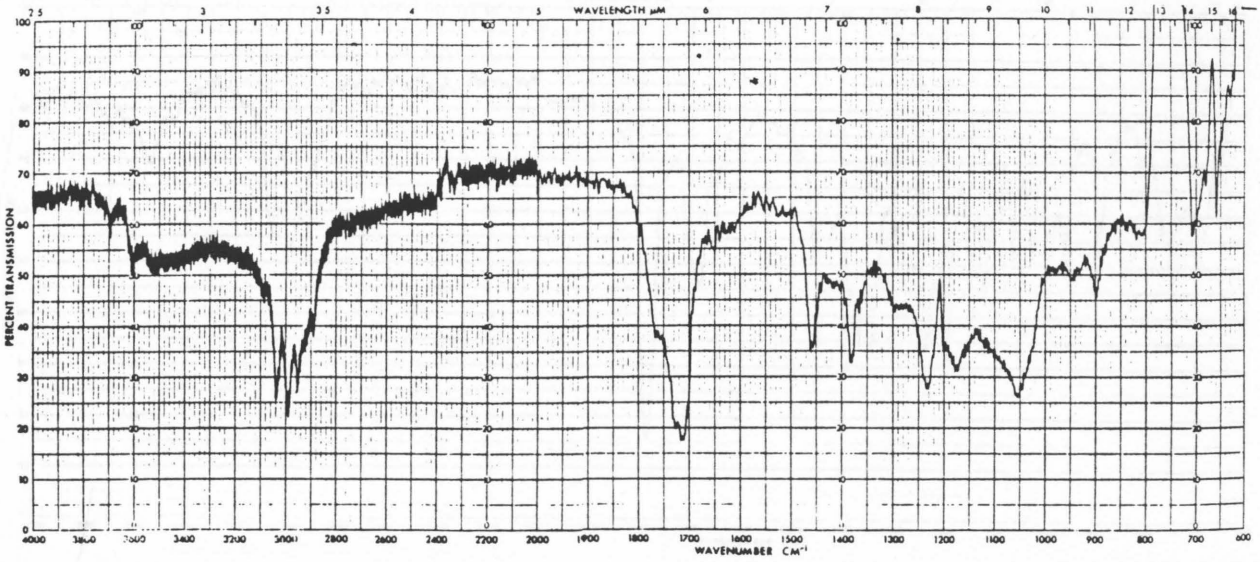
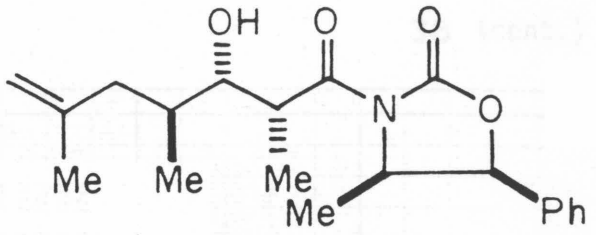
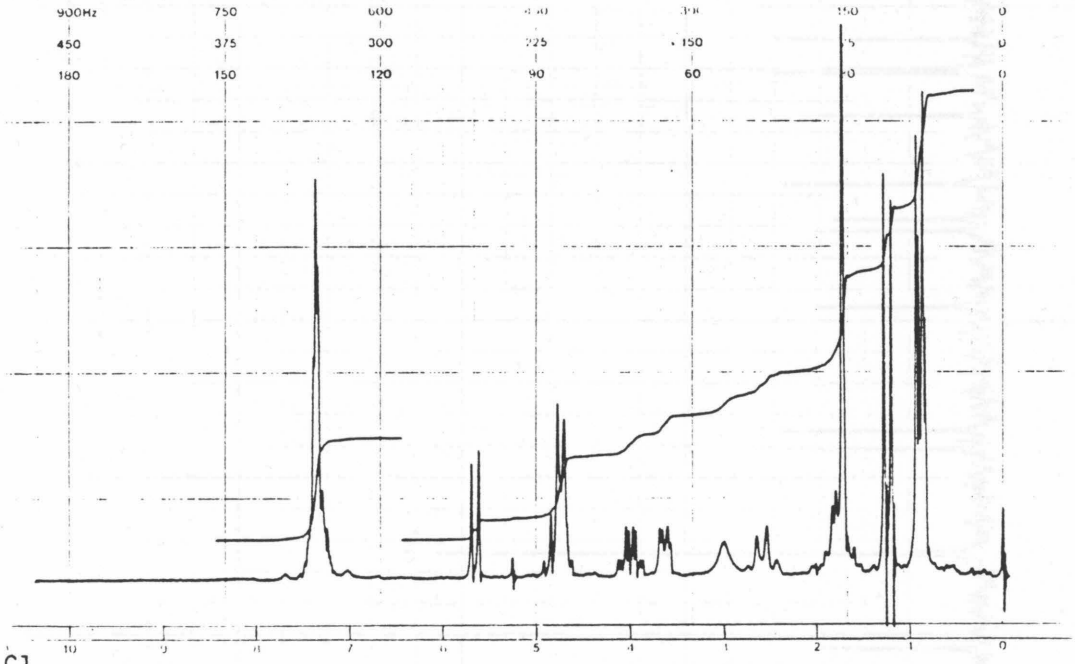


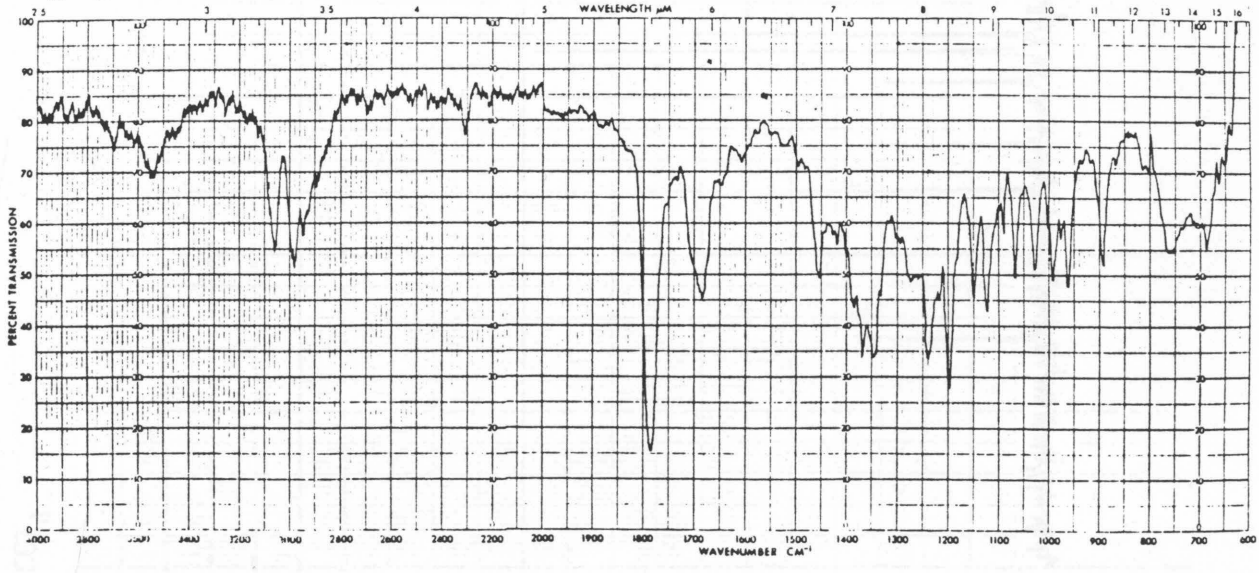


36

$CDCl_3$

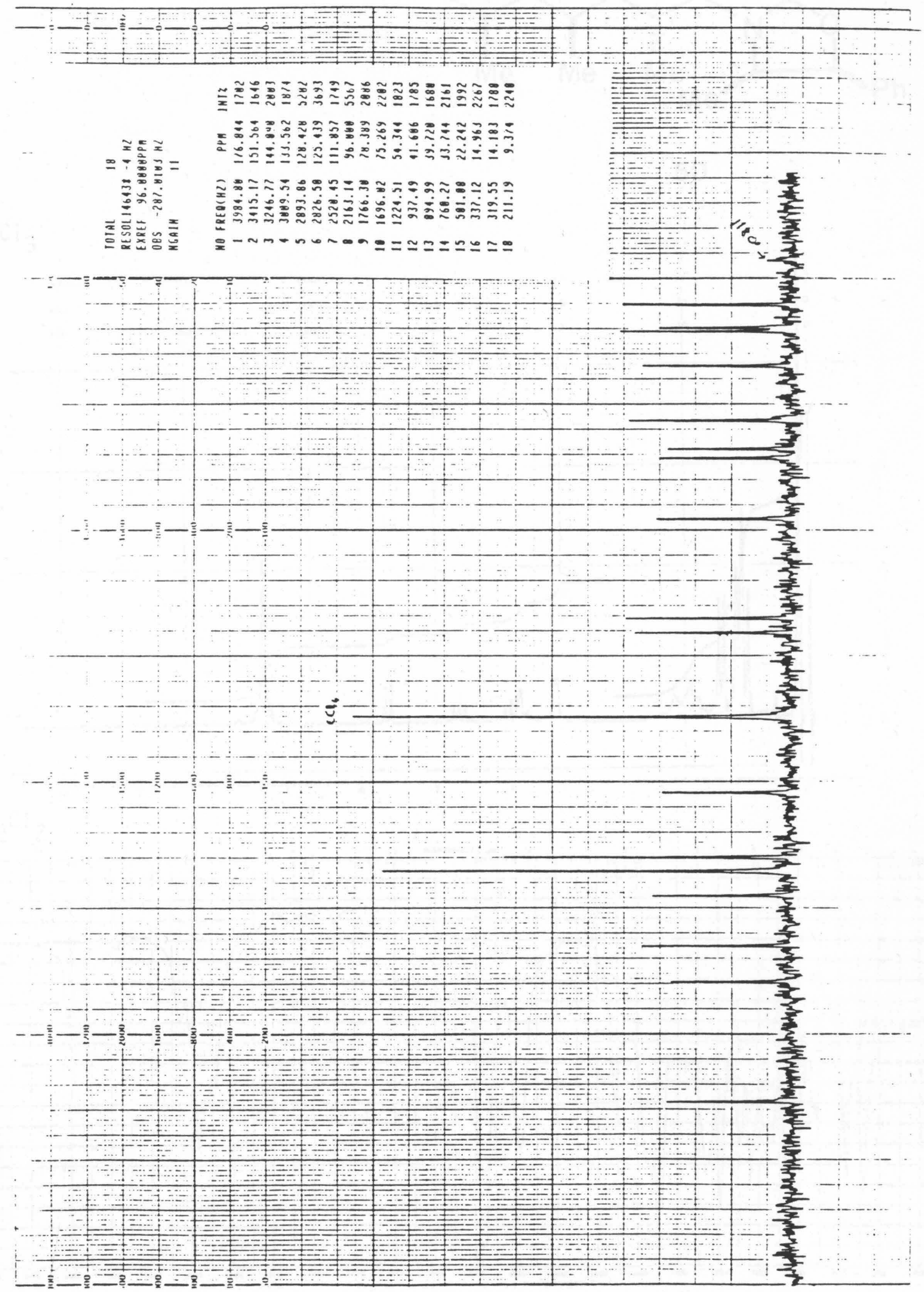


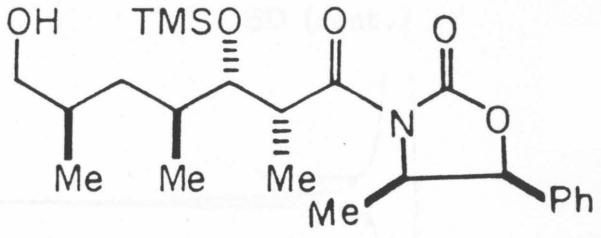
CH_2Cl_2



36 (cont.)

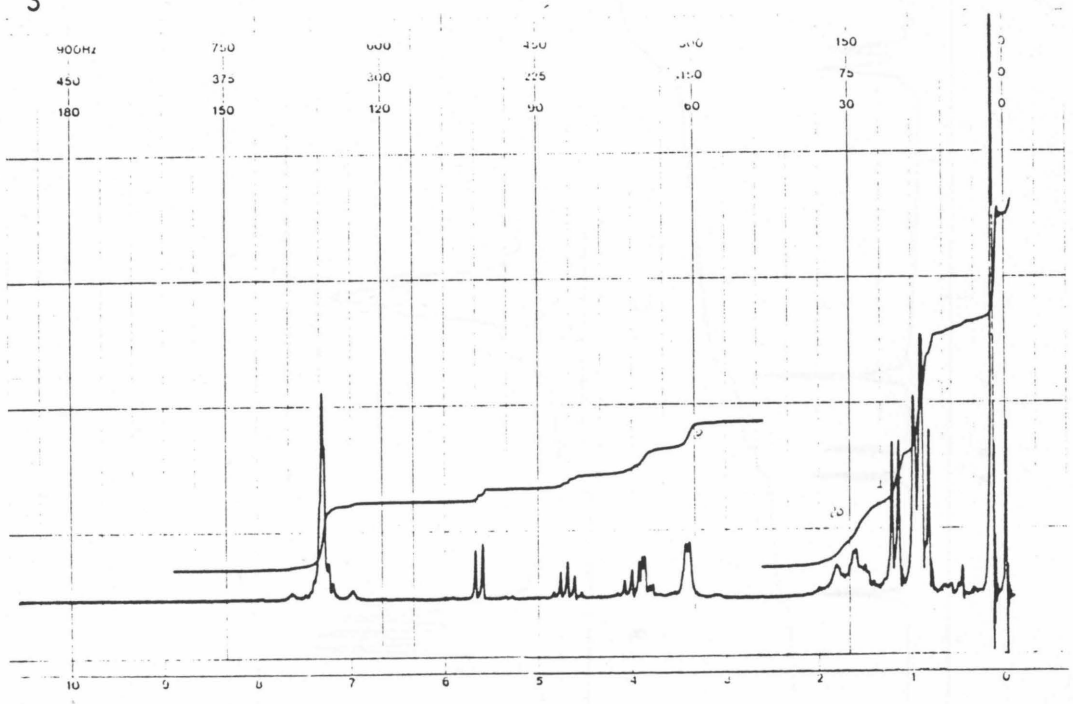
CCl$_4$


TOTAL 18
RESOL146430 -4 HZ
EXREF 96.0000PPM
OBS -287.0103 HZ
NGAIN 11
NO FREQ(HZ) PPM INT%
1 3984.80 176.844 1702
2 3415.17 151.564 1646
3 3246.77 144.098 2003
4 3009.54 133.562 1874
5 2893.86 128.428 5202
6 2826.50 125.439 3693
7 2520.45 111.857 1749
8 2163.14 96.000 5567
9 1766.30 78.389 2006
10 1696.02 75.269 2202
11 1224.51 54.344 1823
12 937.49 41.606 1785
13 894.99 39.720 1680
14 760.27 33.744 2161
15 501.00 22.242 1992
16 337.12 14.963 2267
17 319.55 14.183 1700
18 211.19 9.374 2240
CCl$_4$

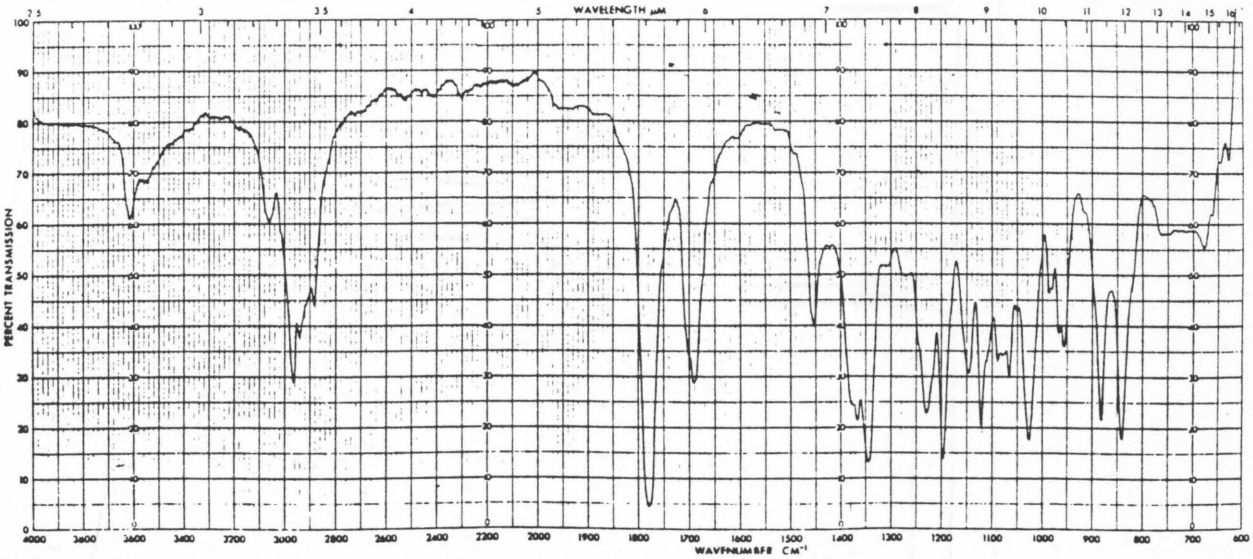


50

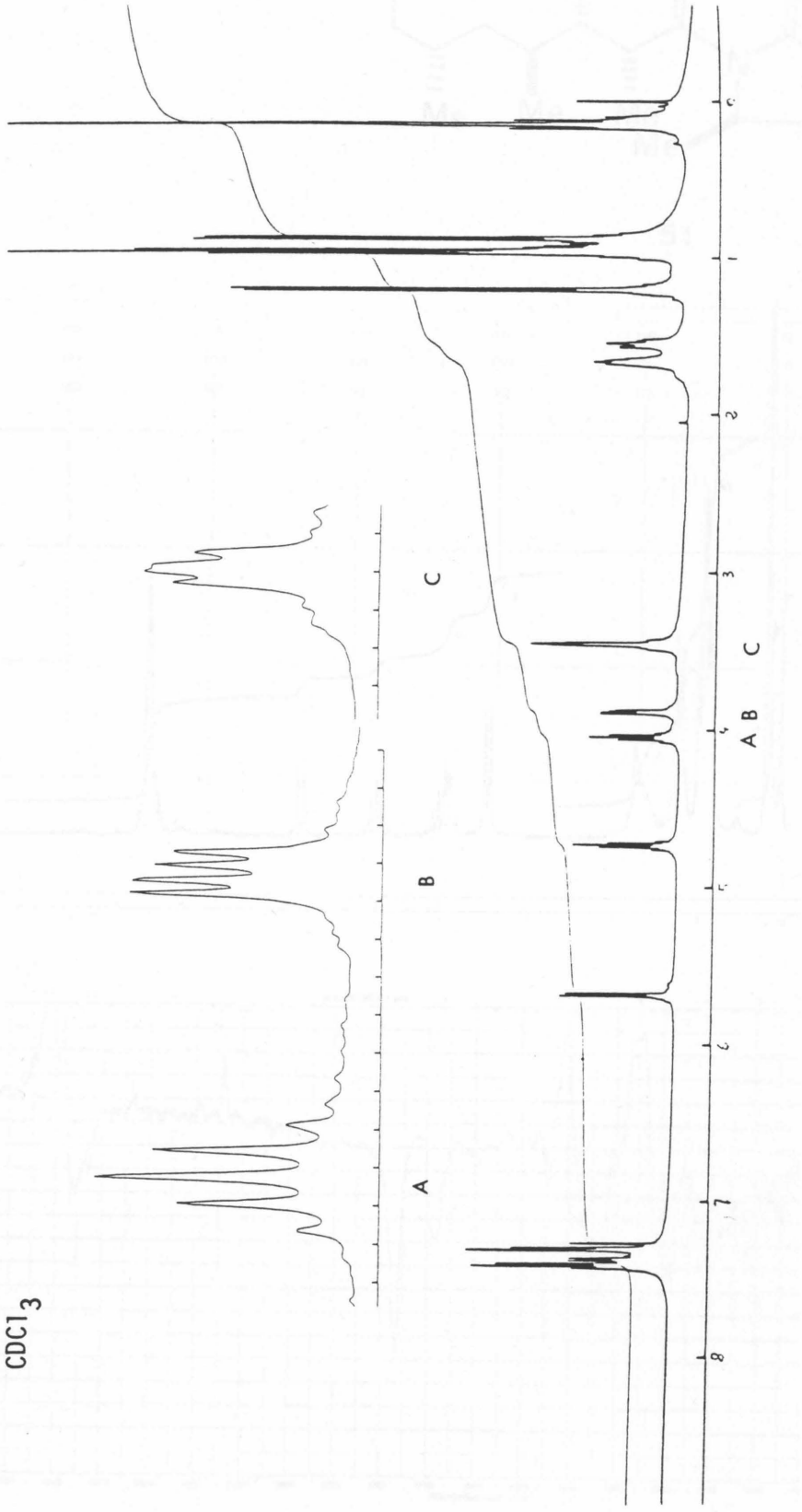
$CDCl_3$

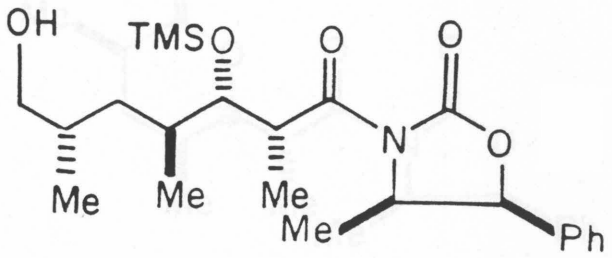


CH_2Cl_2



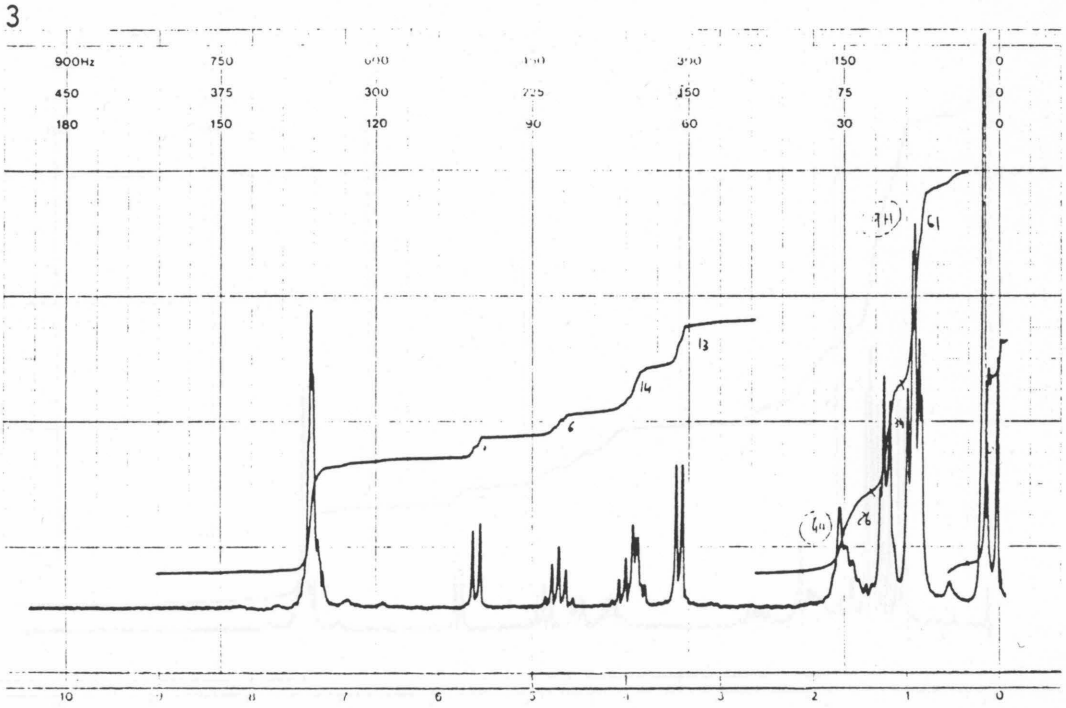
50 (cont.)



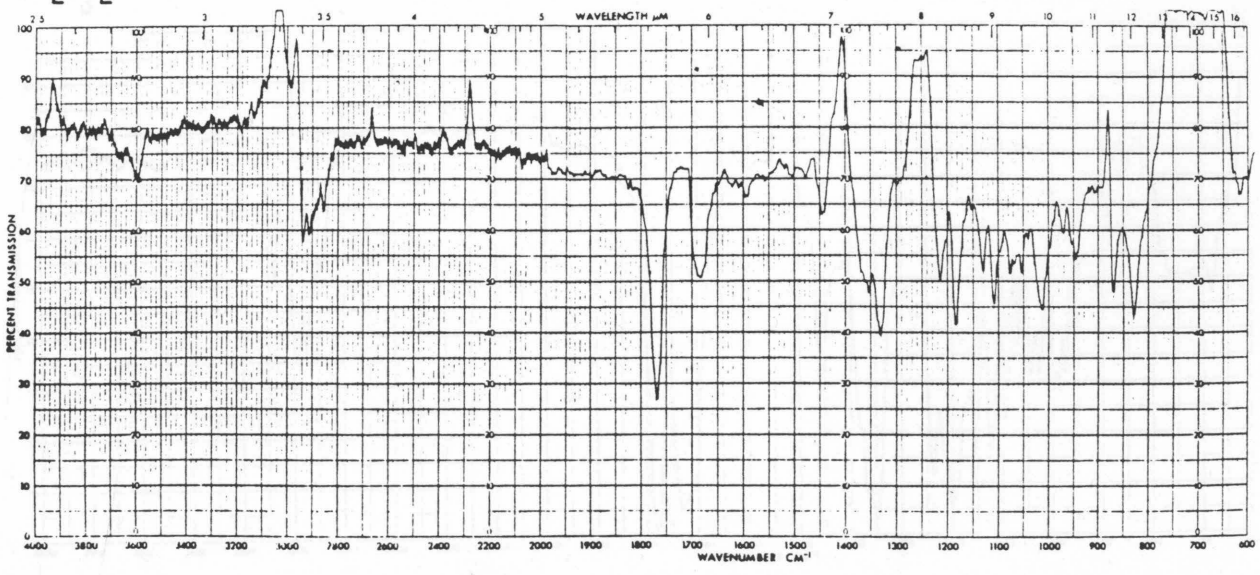


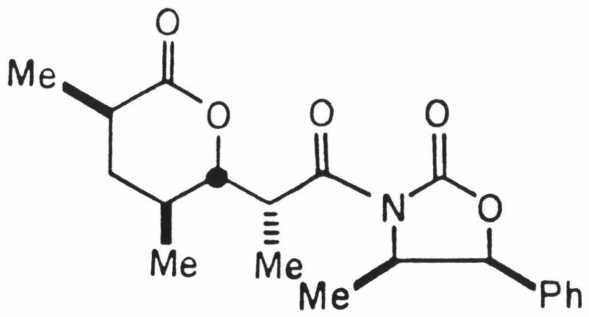
51

$CDCl_3$



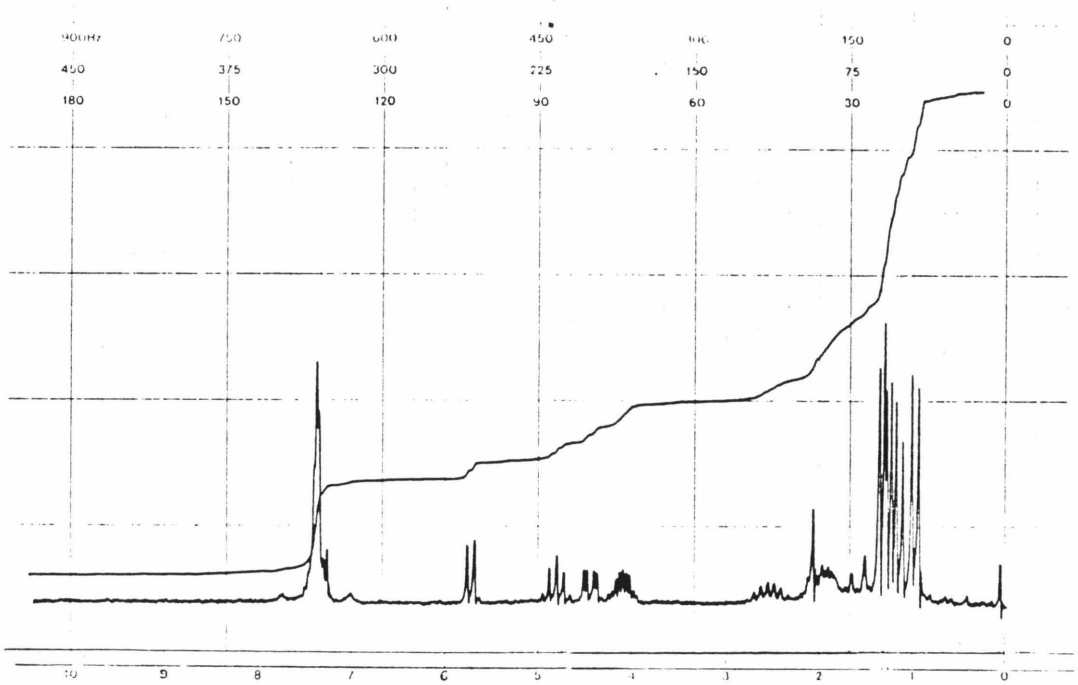
CH_2Cl_2



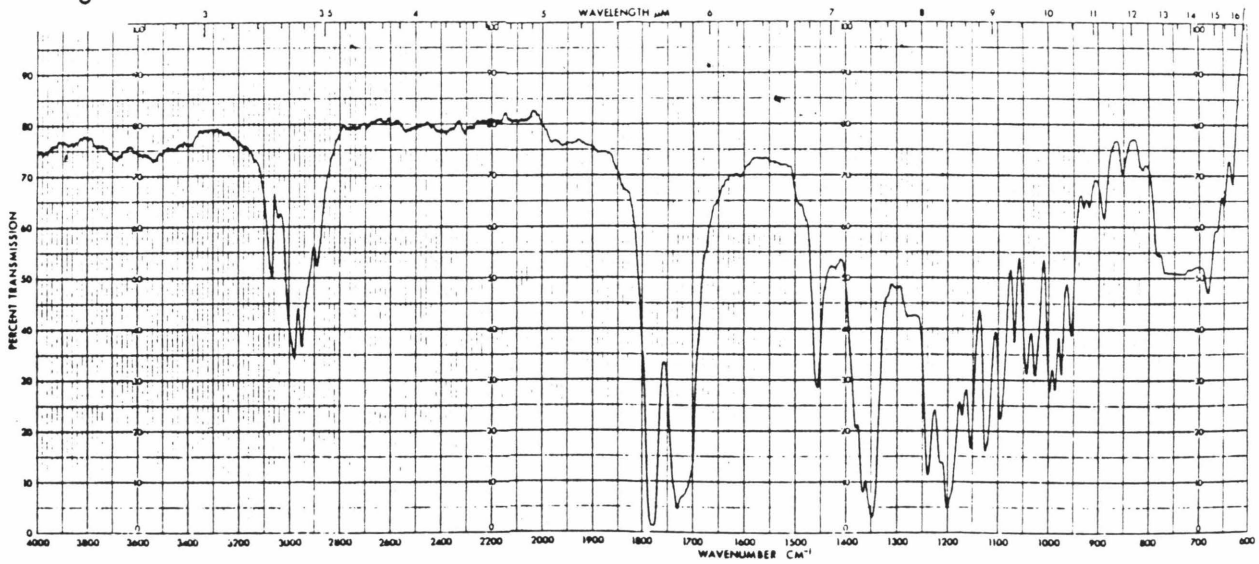


53

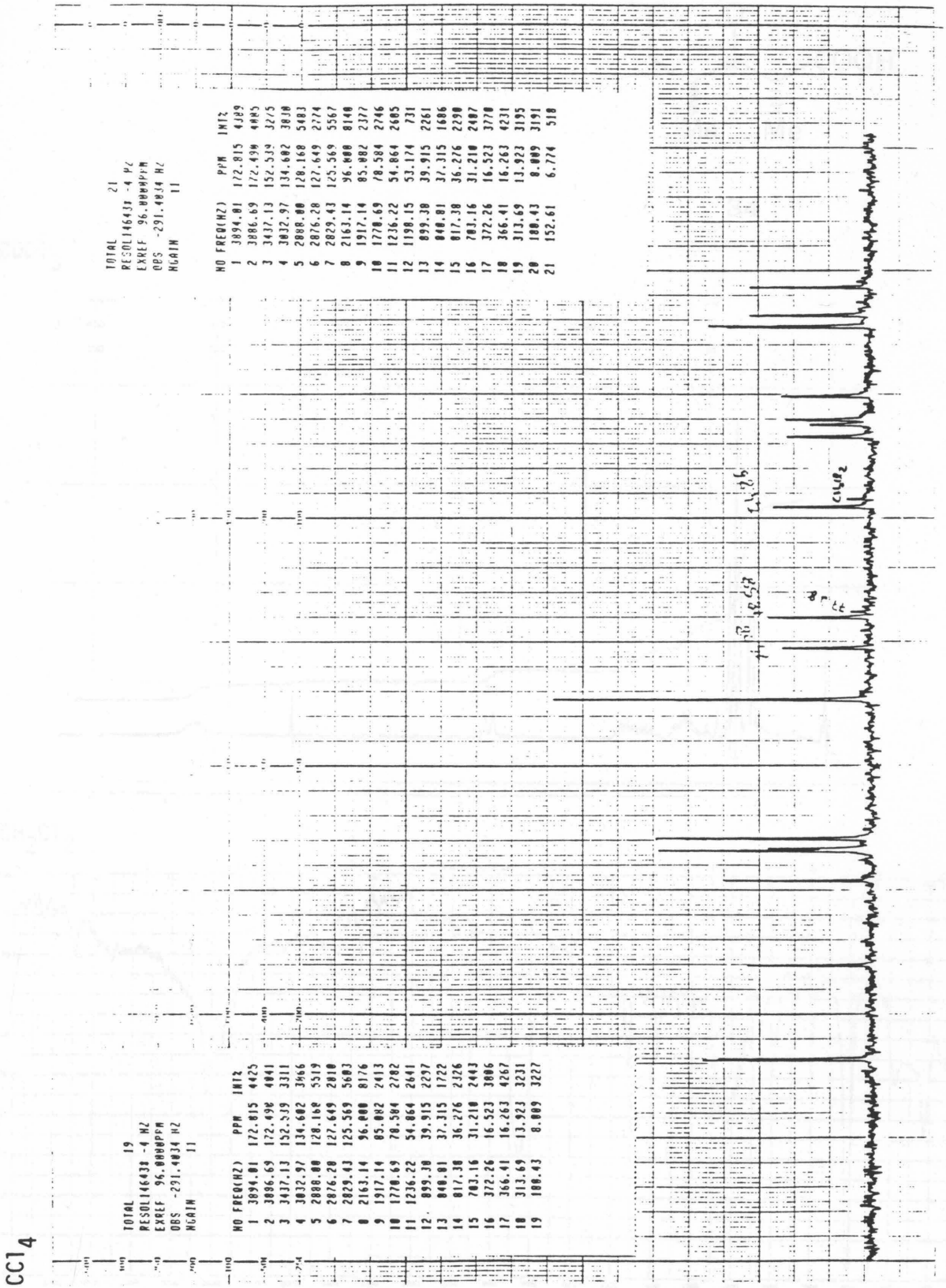
$CDCl_3$

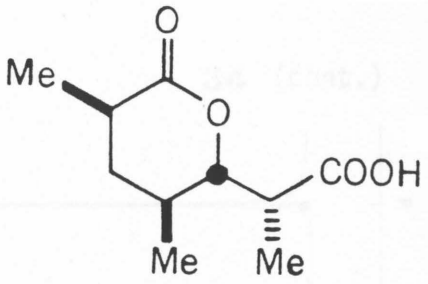


$CHCl_3$



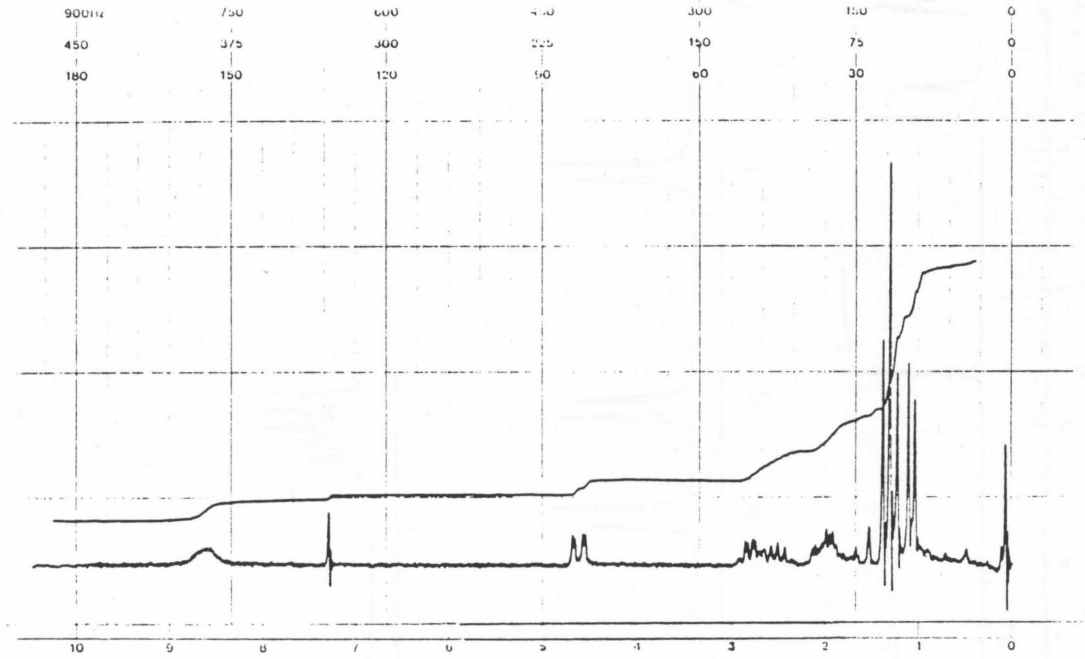
53 (cont.)


CCl4
TOTAL 19
RESOLI46438 -4 HZ
EXREF 96.0000PPM
OBS -291.4834 HZ
HGAIN 11
NO FREQ(HZ) PPM IMIZ
1 3894.81 172.815 4425
2 3886.69 172.498 4041
3 3437.13 152.539 3311
4 3032.97 134.602 3966
5 2888.88 128.168 5519
6 2876.28 127.649 2810
7 2829.43 125.569 5603
8 2163.14 96.000 8176
9 1917.14 85.082 2413
10 1770.69 78.584 2702
11 1236.22 54.864 2641
12 899.30 39.915 2297
13 840.81 37.315 1722
14 817.38 36.276 2326
15 783.16 31.210 2443
16 372.26 16.523 3006
17 366.41 16.263 4267
18 313.69 13.923 3231
19 180.43 8.009 3227
TOTAL 21
RESOLI46438 -4 HZ
EXREF 96.0000PPM
OBS -291.4834 HZ
HGAIN 11
NO FREQ(HZ) PPM IMIZ
1 3894.81 172.815 4089
2 3886.69 172.498 4005
3 3437.13 152.539 3215
4 3032.97 134.602 3810
5 2888.88 128.168 5403
6 2876.28 127.649 2774
7 2829.43 125.569 5567
8 2163.14 96.000 8140
9 1917.14 85.082 2377
10 1770.69 78.584 2746
11 1236.22 54.864 2605
12 1190.15 53.174 731
13 899.30 39.915 2261
14 840.81 37.315 1606
15 817.38 36.276 2290
16 783.16 31.210 2407
17 372.26 16.523 3770
18 366.41 16.263 4231
19 313.69 13.923 3195
20 180.43 8.009 3191
21 152.61 6.774 518

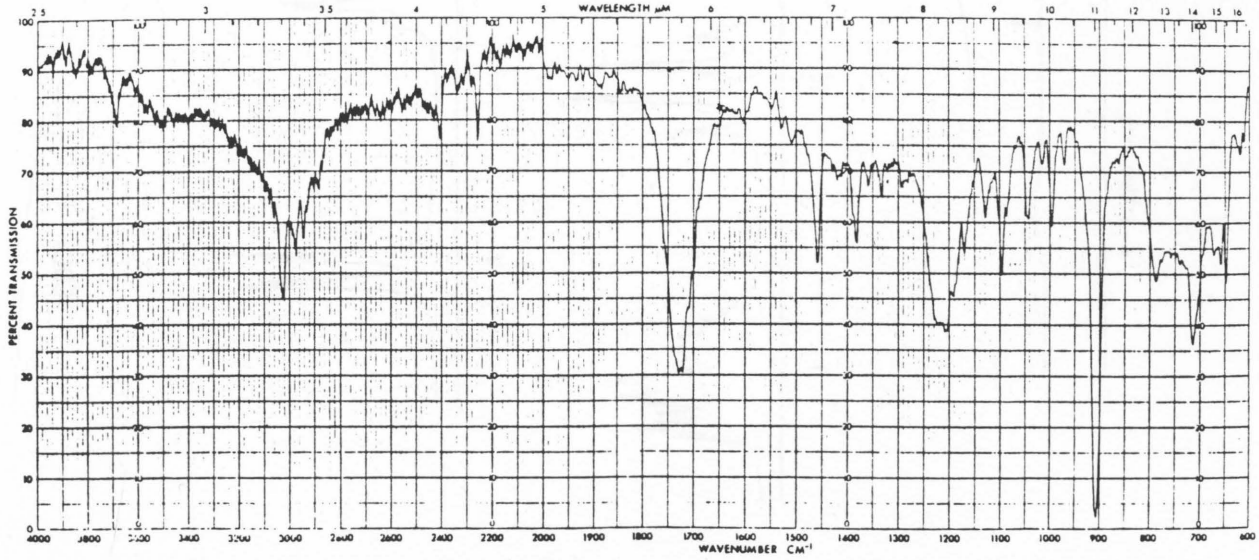


34

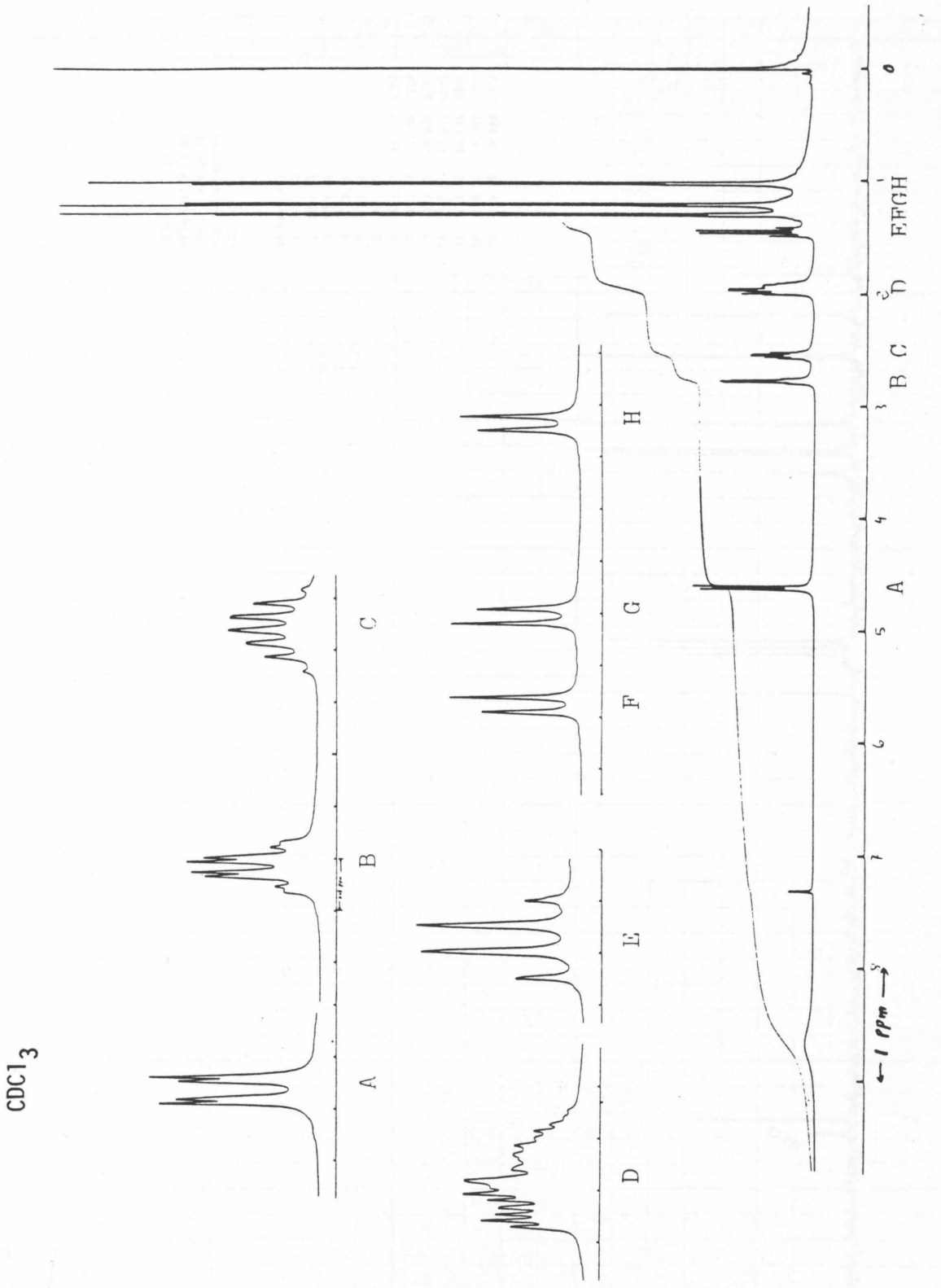
$CDCl_3$



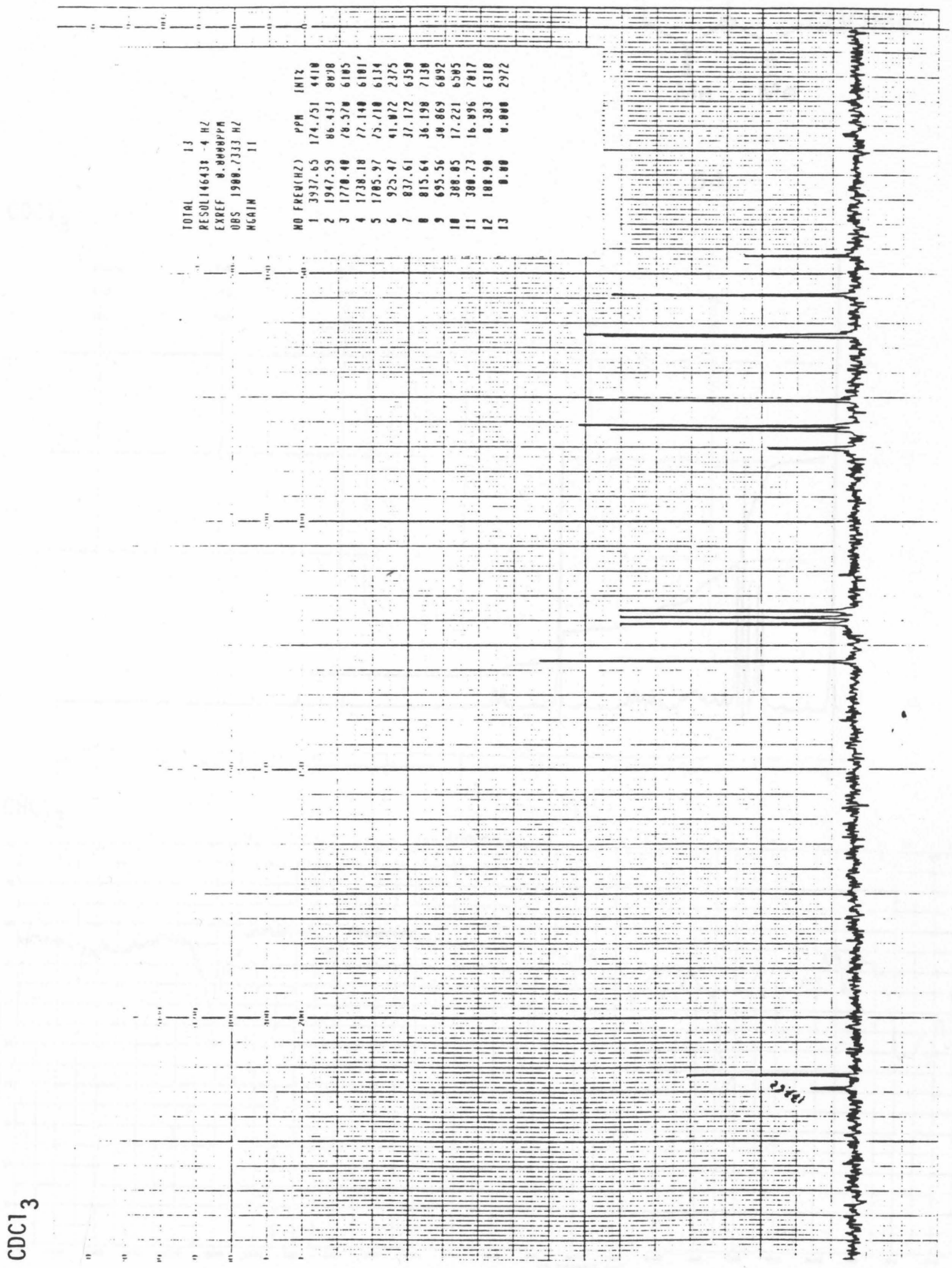
CH_2Cl_2



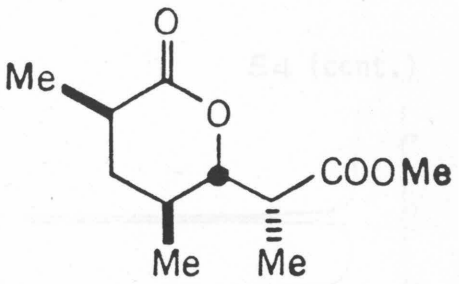
34 (cont.)



34 (cont.)

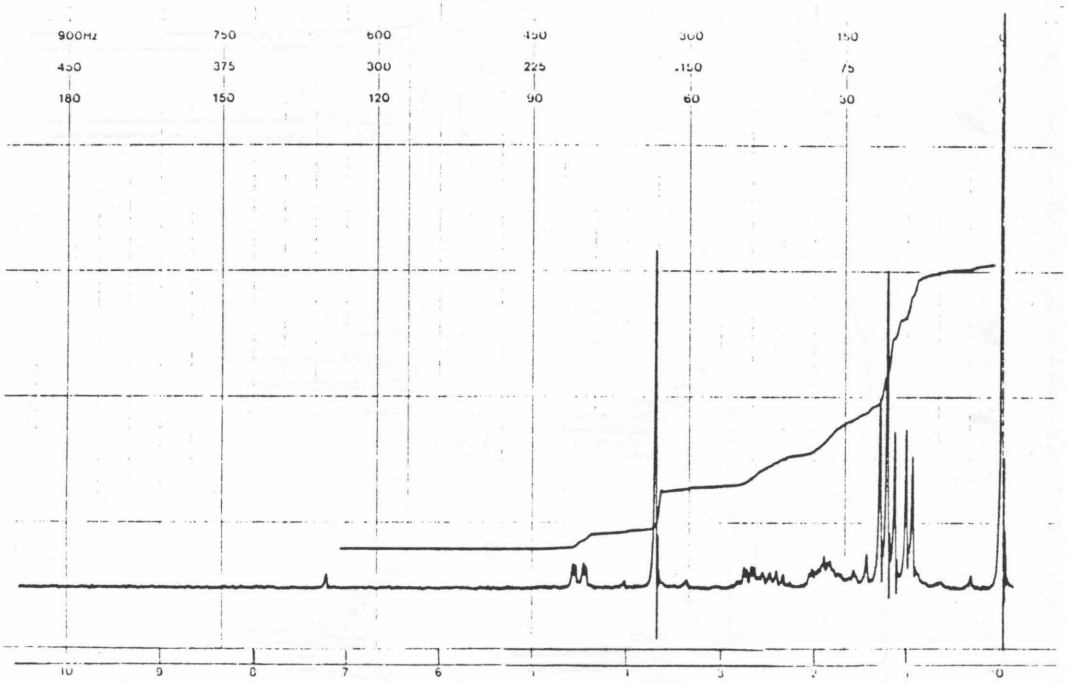


$CDCl_3$

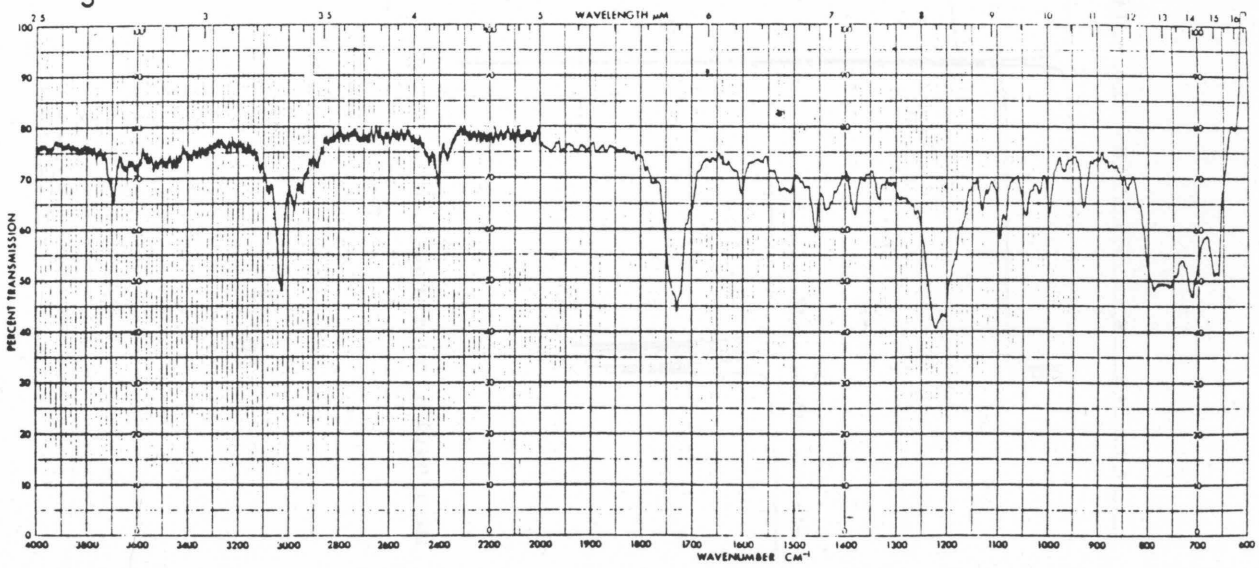


54

$CDCl_3$

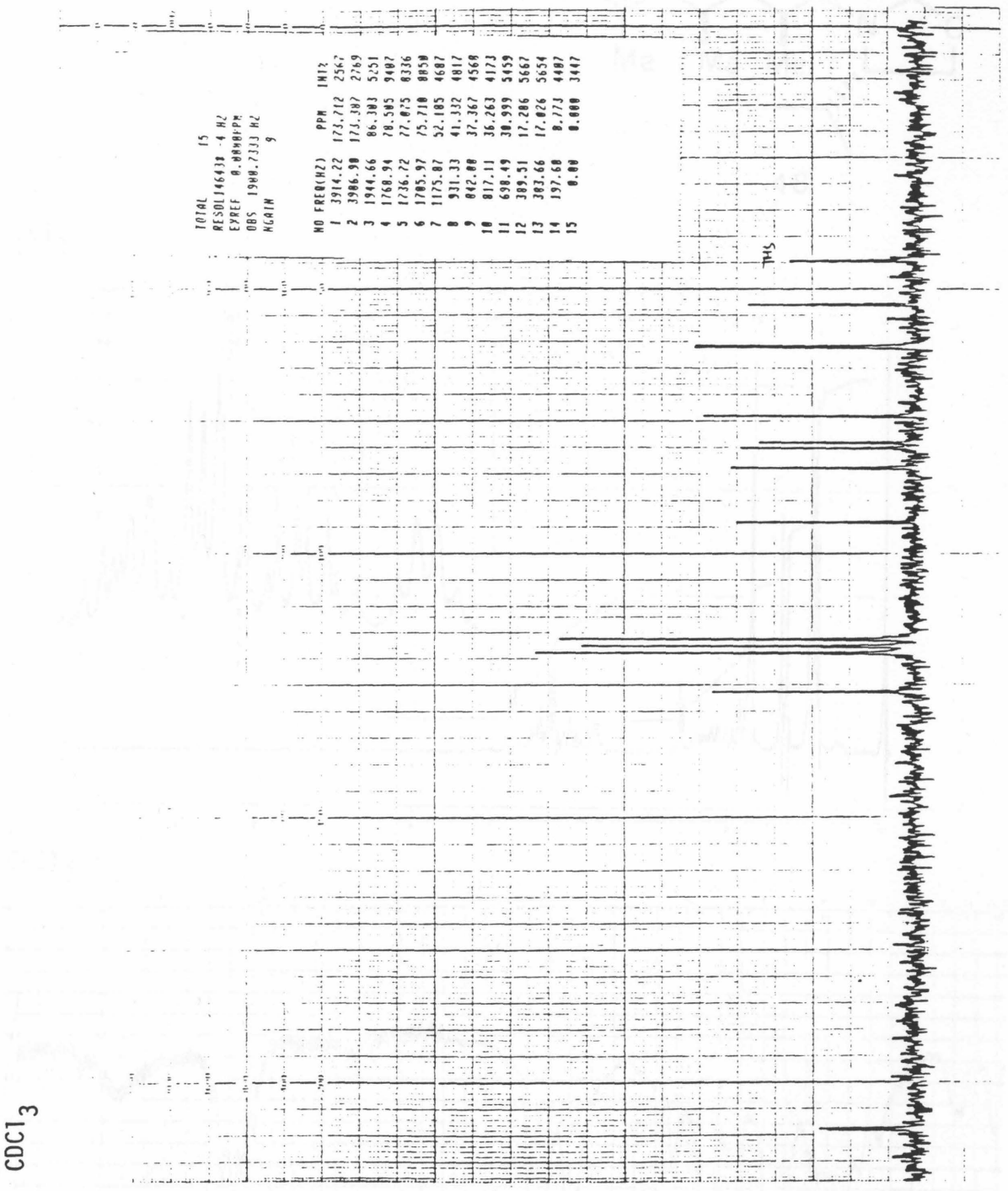


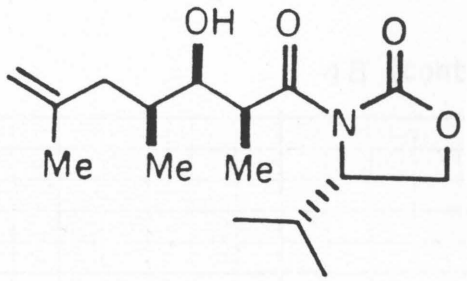
$CHCl_3$



54 (cont.)

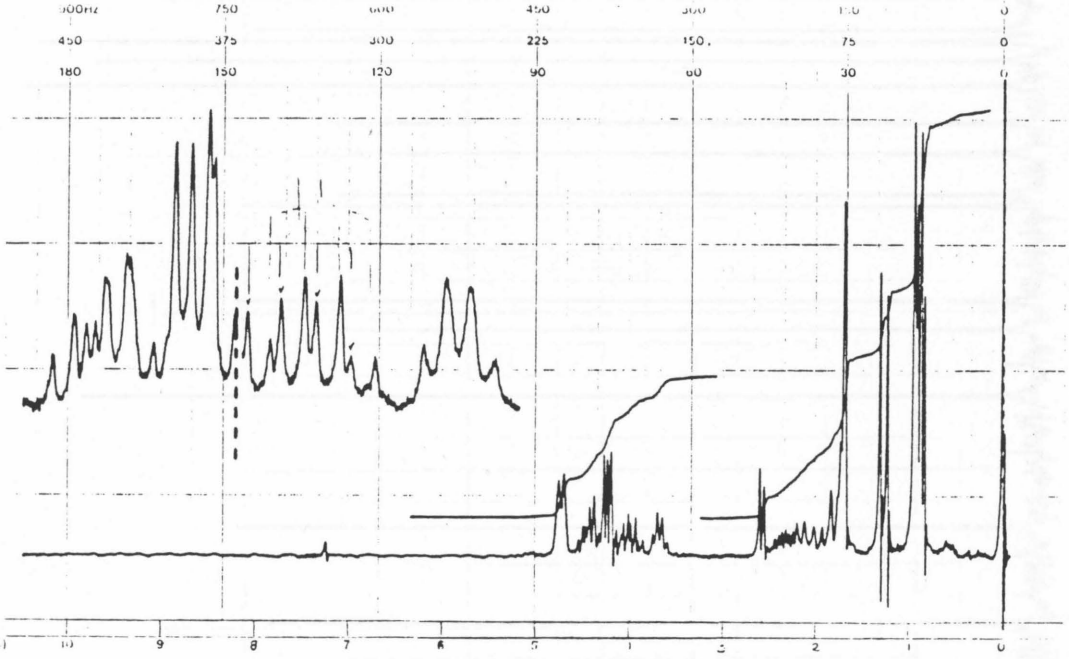
54 (cont.)


TOTAL 15
RESOL 14643 -4 HZ
EXREF 0.000 PPM
OBS 1900.7333 HZ
AGAIN 9
NO FREQ(HZ) PPM INTS
1 3914.22 173.712 2567
2 3906.98 173.397 2769
3 1944.66 86.303 5251
4 1768.94 78.505 9407
5 1736.72 77.075 8336
6 1705.97 75.710 8050
7 1175.87 52.185 4687
8 931.33 41.332 4017
9 842.88 37.367 4560
10 817.11 36.263 4173
11 698.49 30.999 5459
12 389.51 17.286 5667
13 383.66 17.026 5654
14 197.60 8.773 4407
15 0.00 0.000 3447
TMS
CDCl3

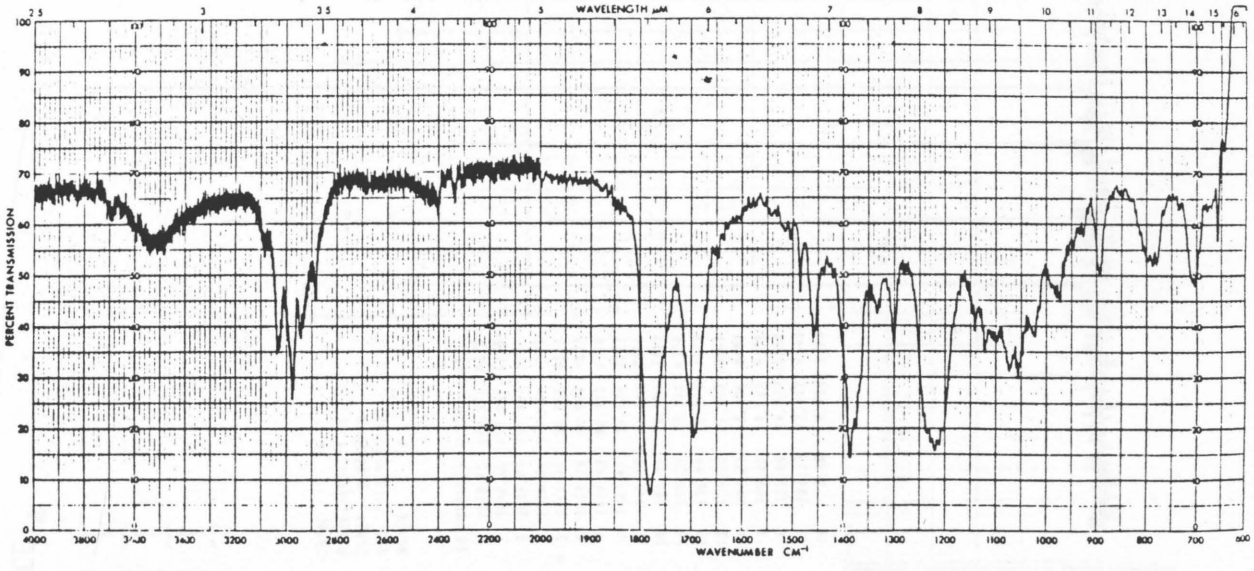


48

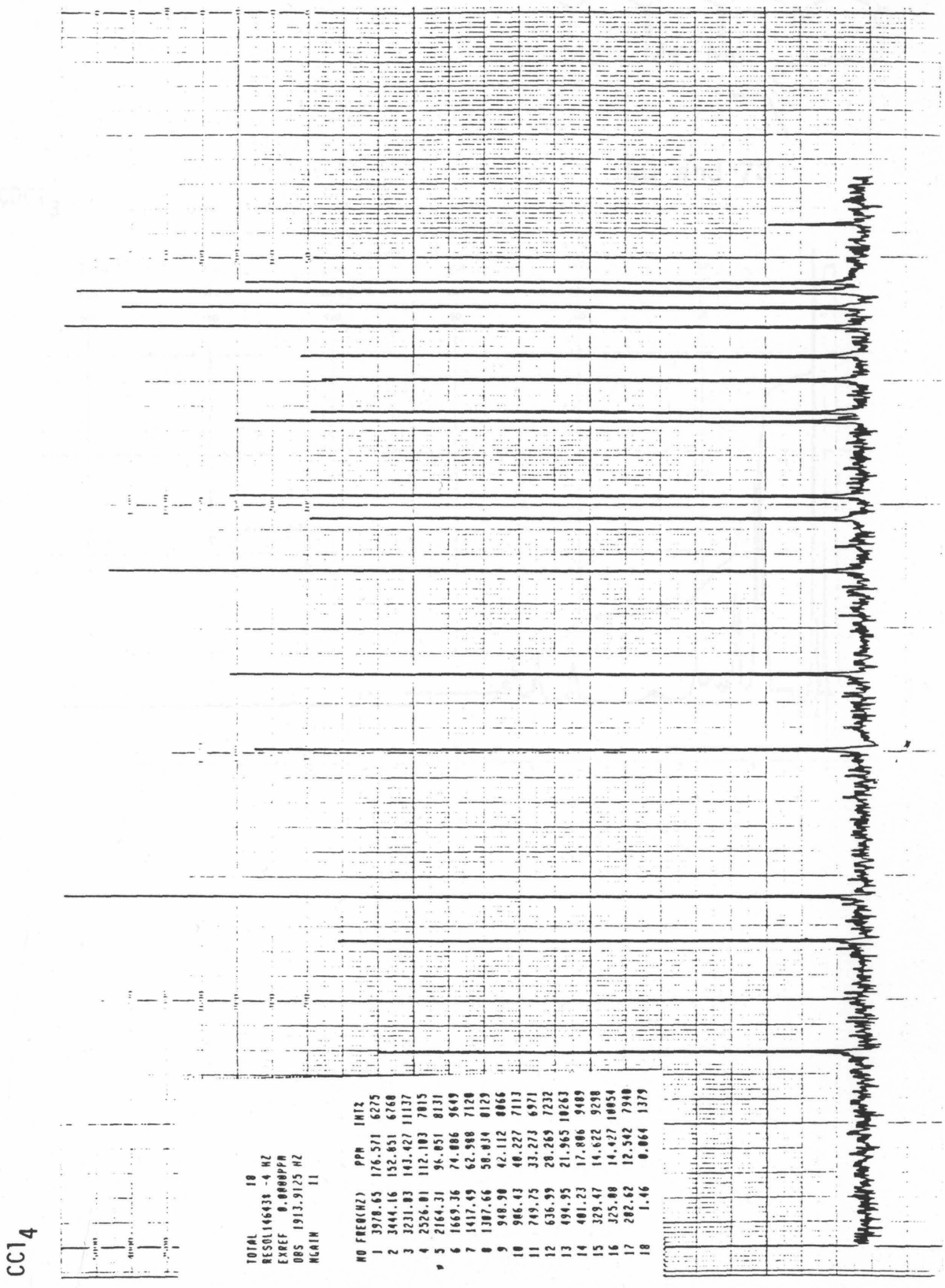
$CDCl_3$

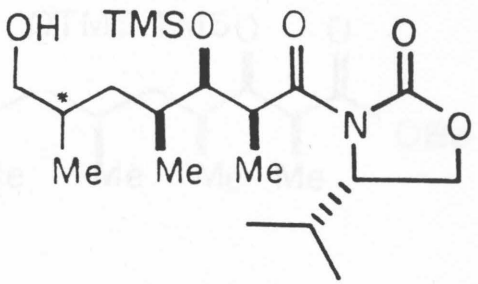


$CHCl_3$



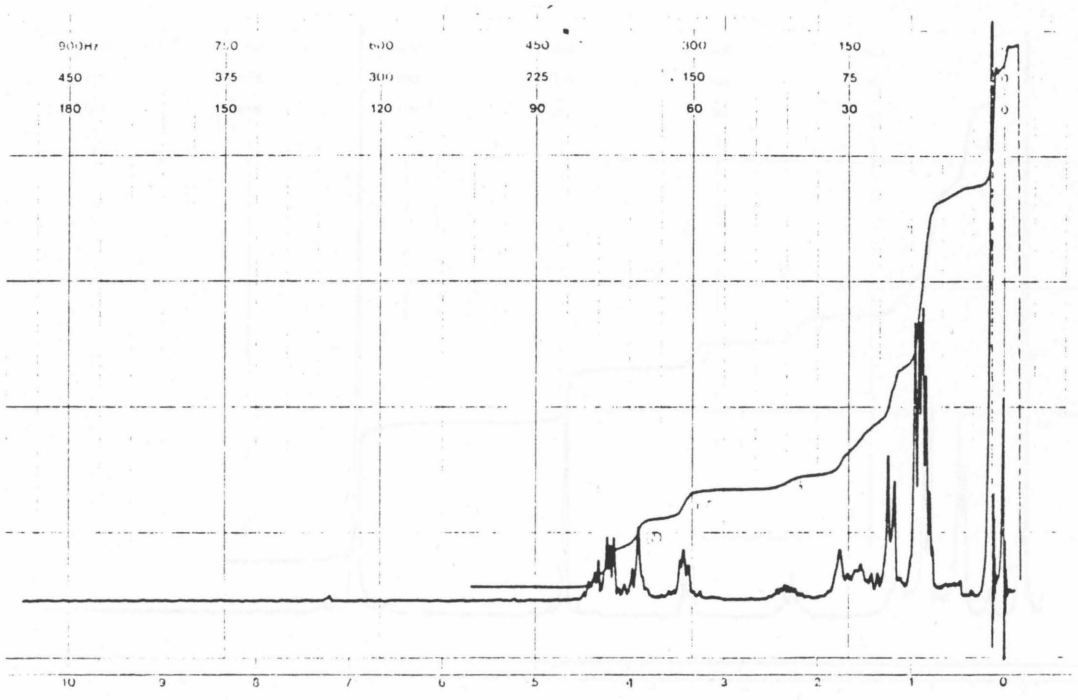
48 (cont.)

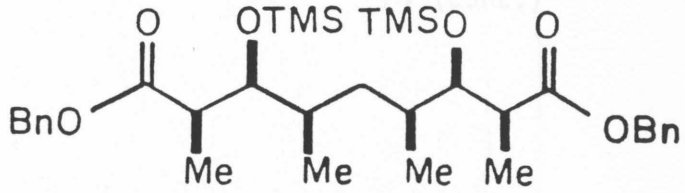

CCl_4
TOTAL 10
RESOL146438 -4 HZ
EXREF 0.000PPM
OBS 1913.9125 HZ
MGAIN 11
NO FREQ(HZ) PPM INT2
1 3978.65 176.571 6225
2 3444.16 152.851 6760
3 3231.83 143.427 11137
4 2526.81 112.103 7015
5 2164.31 96.051 8131
6 1669.36 74.086 9649
7 1417.49 62.908 7120
8 1307.66 58.034 8123
9 948.90 42.112 8066
10 906.43 40.227 7113
11 749.75 33.273 6971
12 636.99 28.269 7232
13 494.95 21.965 10263
14 401.23 17.806 9489
15 329.47 14.622 9298
16 325.00 14.427 10054
17 282.62 12.542 7940
18 1.46 0.064 1379



60 and 73

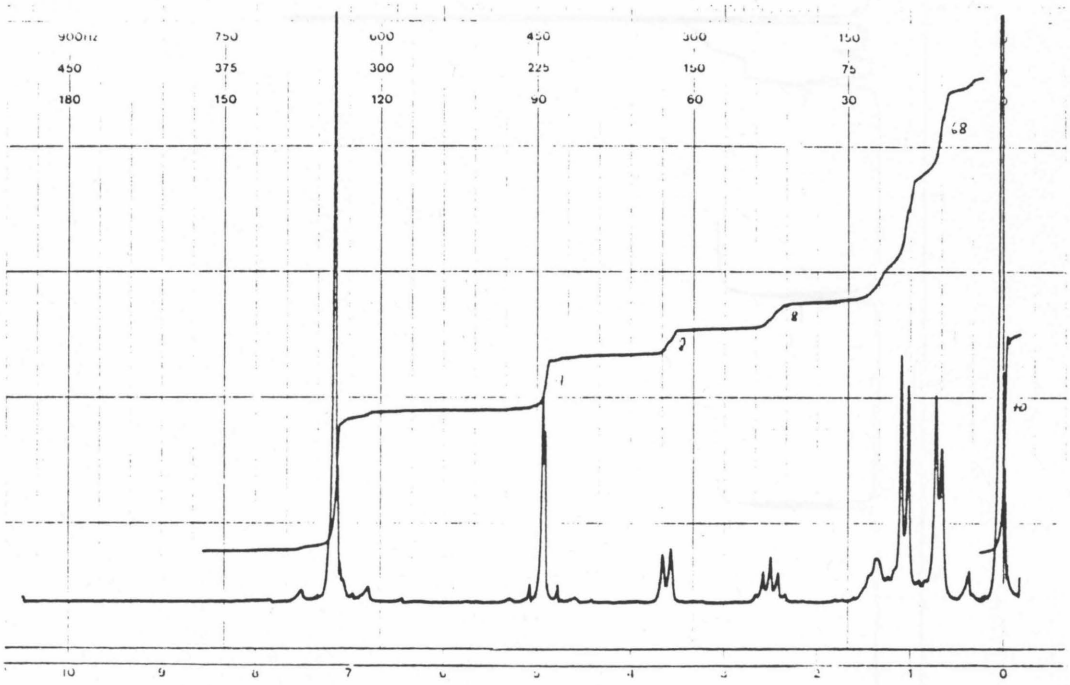
$CDCl_3$



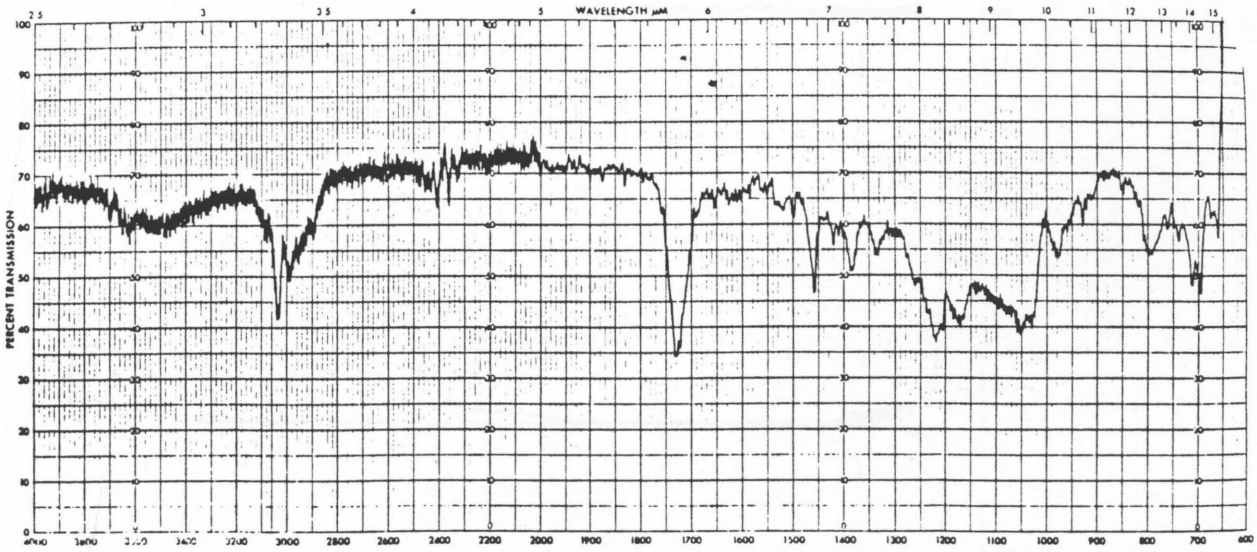


77

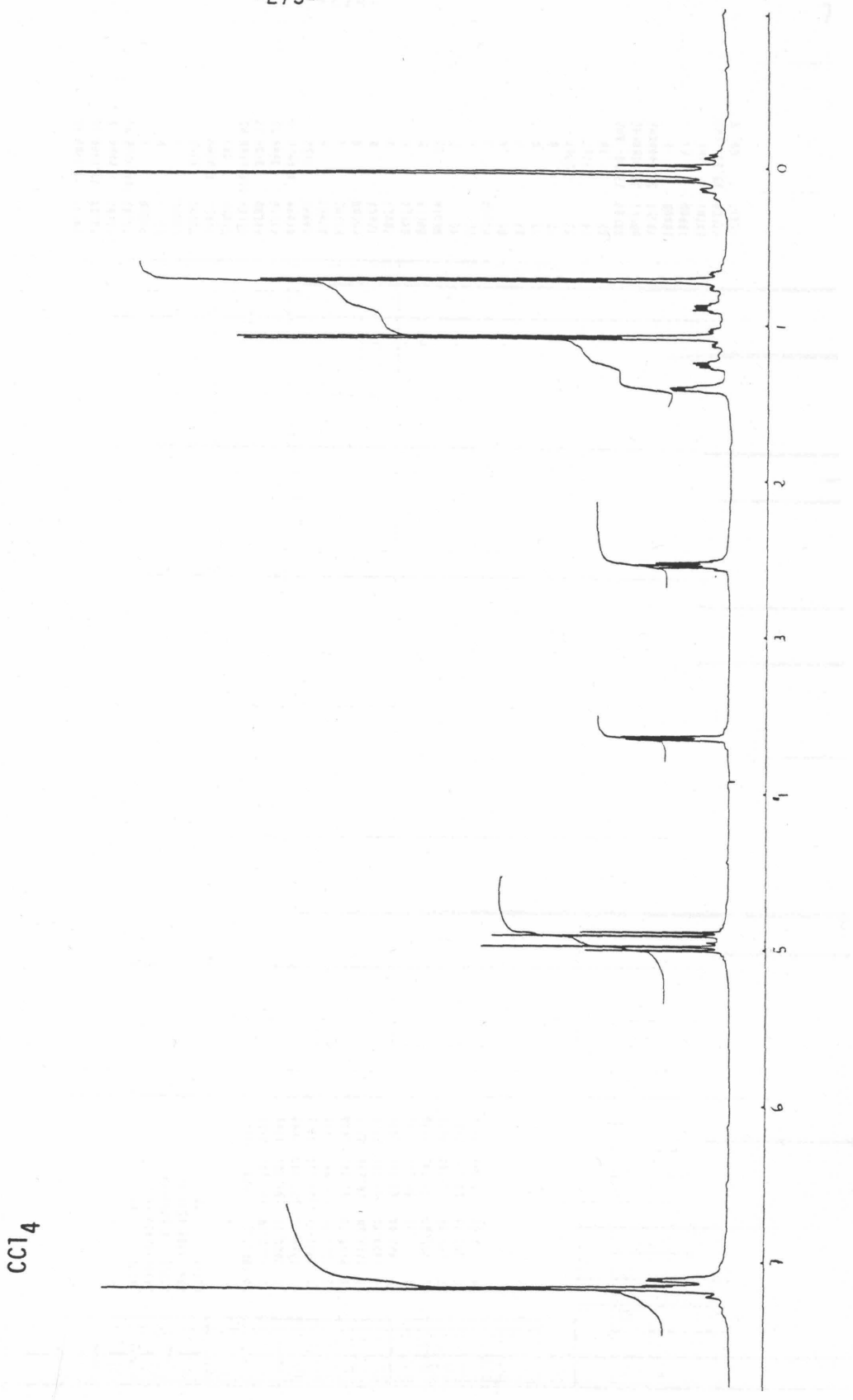
CCl_4



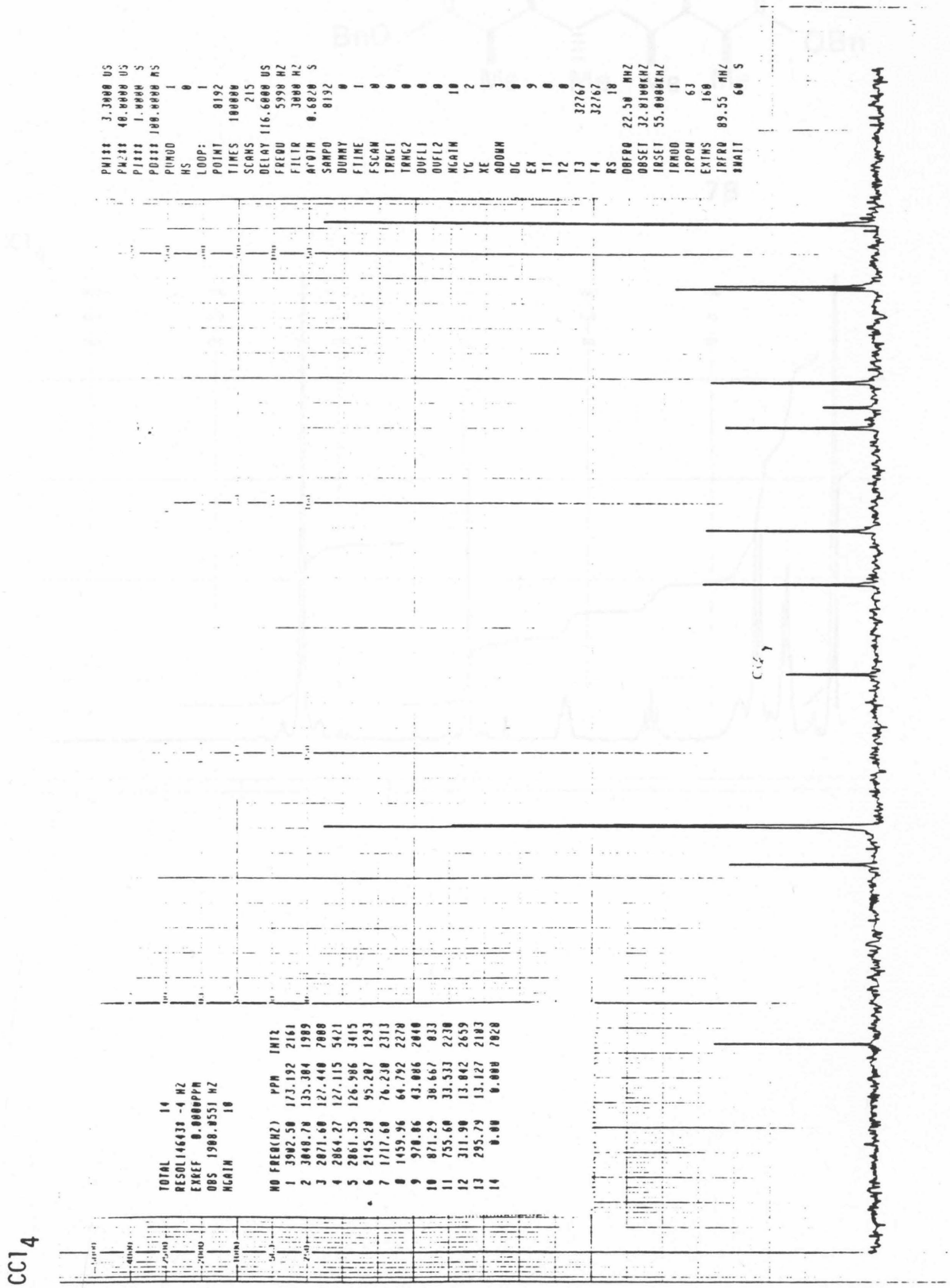
$CHCl_3$

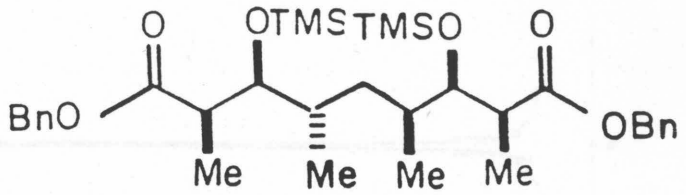


77 (cont.)



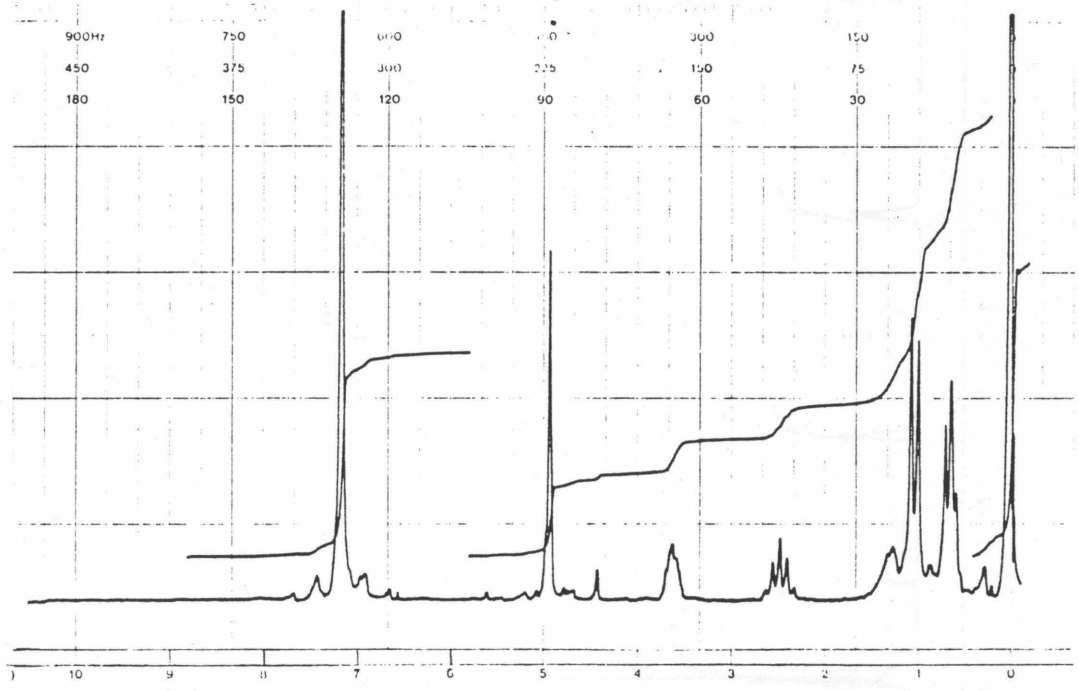
77 (cont.)


CCl4
TOTAL 14
RESOL146638 -4 HZ
EXREF 0.000PPM
OBS 1980.8551 HZ
HGAIN 10
NO FREQ(HZ) PPM IHTZ
1 3902.50 173.192 2161
2 3048.78 135.304 1989
3 2871.60 127.448 7000
4 2864.27 127.115 5421
5 2861.35 126.986 3415
6 2145.20 95.207 1293
7 1717.60 76.230 2311
8 1459.96 64.792 2270
9 970.86 43.086 2040
10 871.29 38.667 833
11 755.60 33.533 2230
12 311.90 13.842 2659
13 295.79 13.127 2103
14 0.00 0.000 7020
PW111 3.3000 US
PW211 40.0000 US
P1111 1.0000 S
PD111 100.0000 MS
PUMOD 1
NS 0
LOOP: 1
POINT 8192
TIMES 100000
SCANS 215
DELAT 116.6000 US
FREQU 5999 HZ
FILTR 3000 HZ
AFQTM 0.6820 S
SAMPO 8192
DUMMY 0
FTIME 1
FSCAN 0
TRHG1 0
TRHG2 0
OVFL1 0
OVFL2 0
HGAIN 10
YG 2
XE 1
ADOWN 3
DG 0
EX 5
T1 0
T2 0
T3 32767
T4 32767
RS 10
OBFRQ 22.50 MHZ
OBSET 32.0100KHZ
IRSET 55.0000KHZ
IRMOD 1
IRPOW 63
EXTNS 160
IRFRQ 89.55 MHZ
#WAIT 60 S

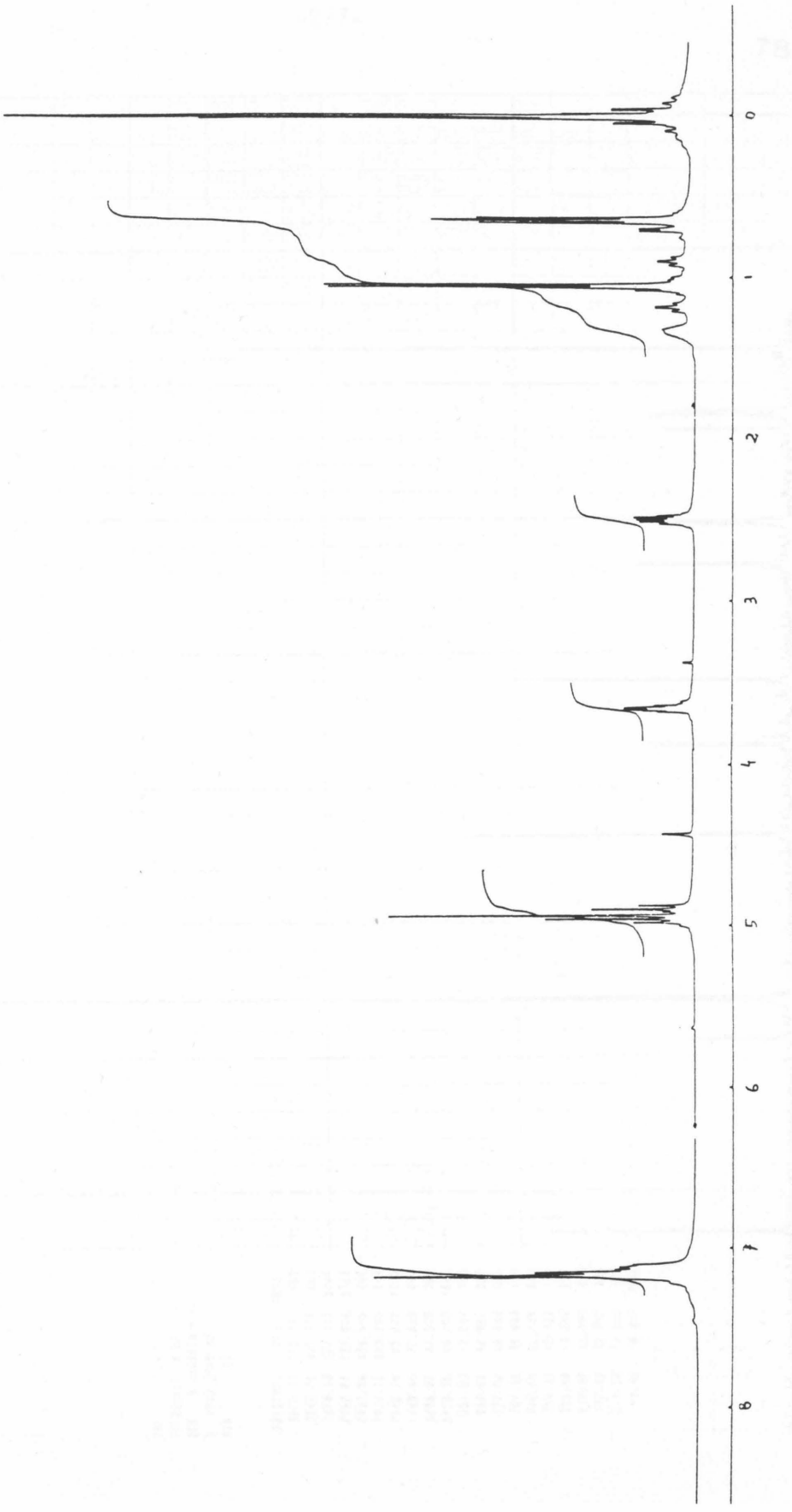

O
OTMS
TMSO
O
BnO
OBn
Me
Me
Me
Me

78

CCl_4.

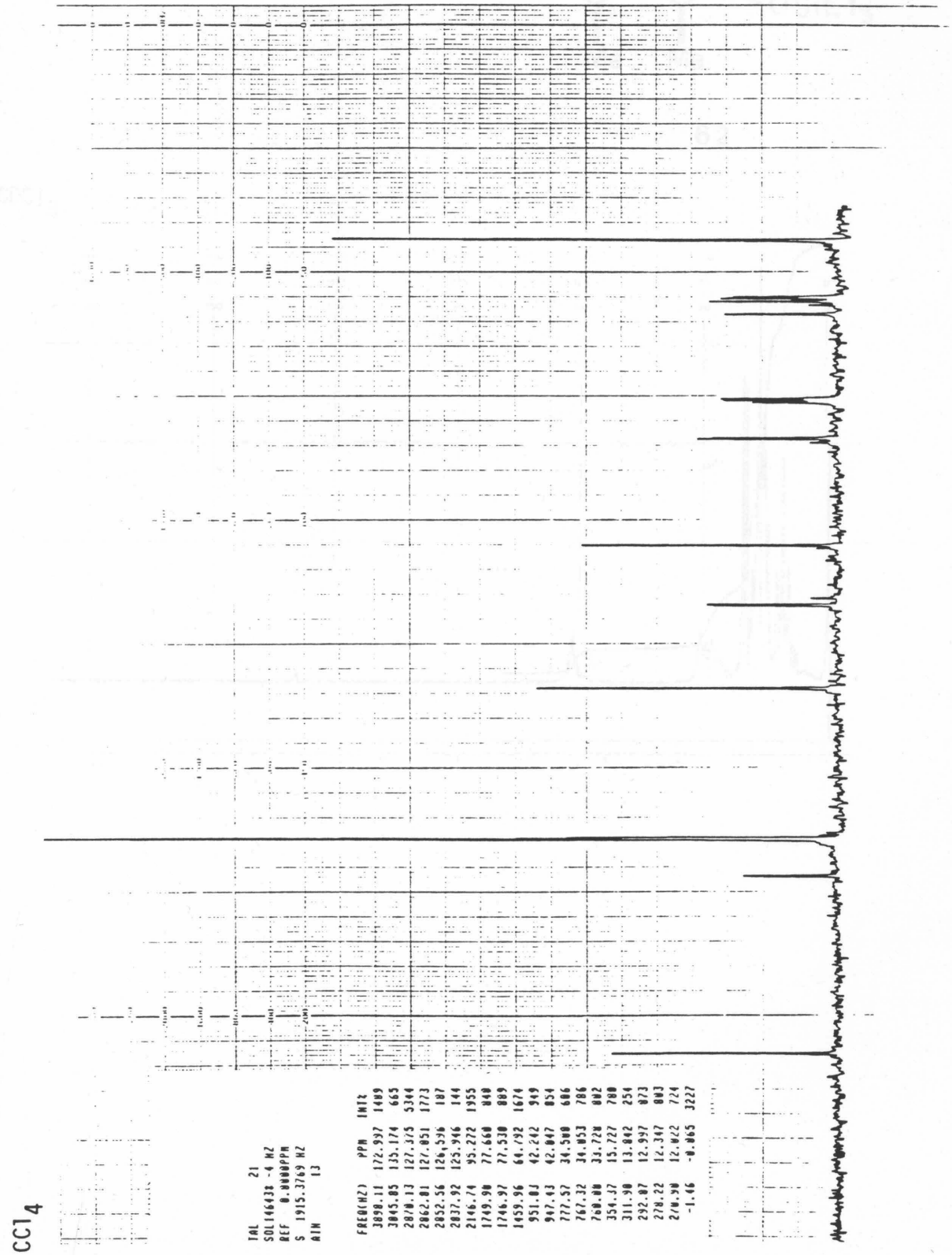

900Hz
750
450
375
180
150
120
90
60
30
10
9
8
7
6
5
4
3
2
1
0

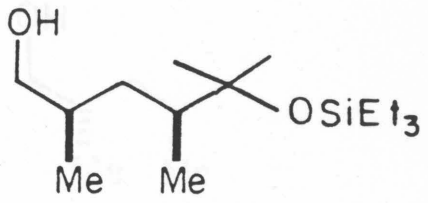
78 (cont.)



CCl_4

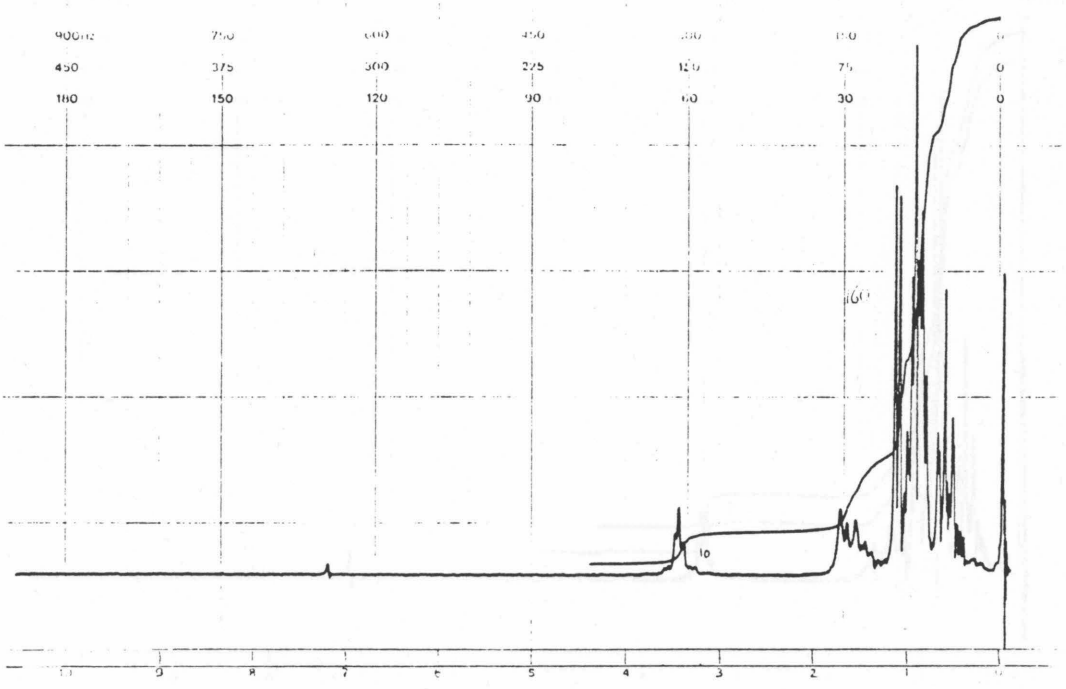
78 (cont.)

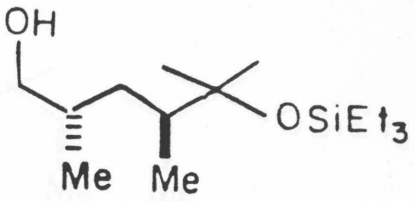

CCl_4
IAL 21
SOLI46432 -4 HZ
REF 0.0000PPM
S 1915.3769 HZ
AIM 13
FREQ(HZ) PPM INTI
3898.11 172.997 1409
3845.85 135.174 665
2870.13 127.375 5344
2862.81 127.051 1723
2852.56 126.596 187
2837.92 125.946 144
2146.74 95.272 1955
1749.98 77.660 840
1746.97 77.530 809
1459.96 64.792 1674
951.81 42.242 949
947.43 42.047 854
777.57 34.500 686
767.32 34.053 786
760.80 33.728 802
354.37 15.727 780
311.98 13.842 254
292.87 12.997 873
278.22 12.347 803
274.90 12.022 724
-1.46 -0.065 3227


OH
OSiEt3
Me
Me

62

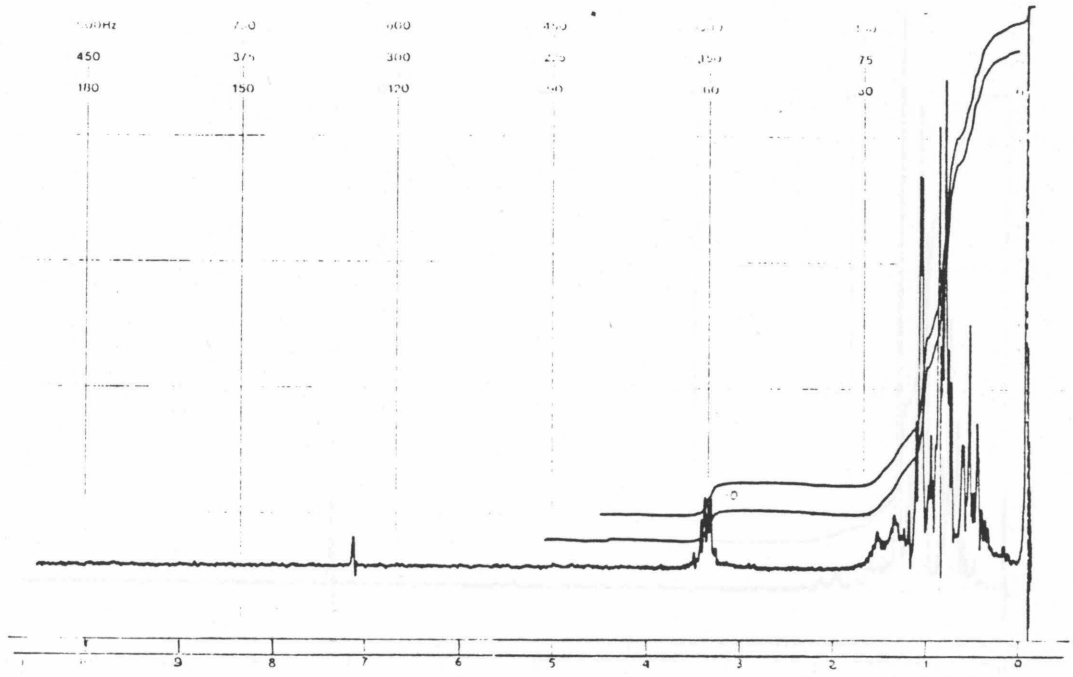
$CDCl_3$


900Hz
750
600
450
300
150
0
450
375
300
225
120
75
30
0
180
150
120
90
60
60
10
10
9
8
7
6
5
4
3
2
1
0

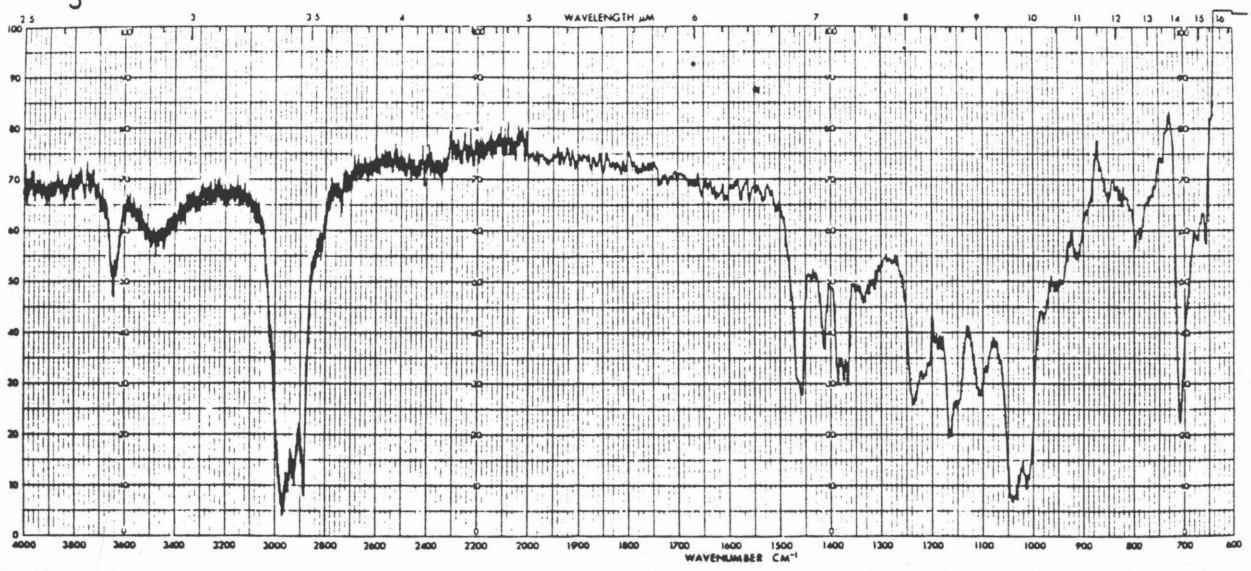


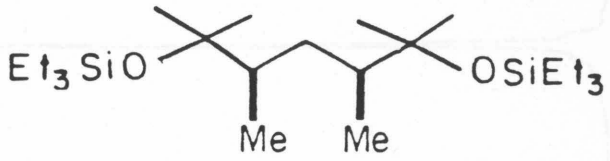
79

$CDCl_3$



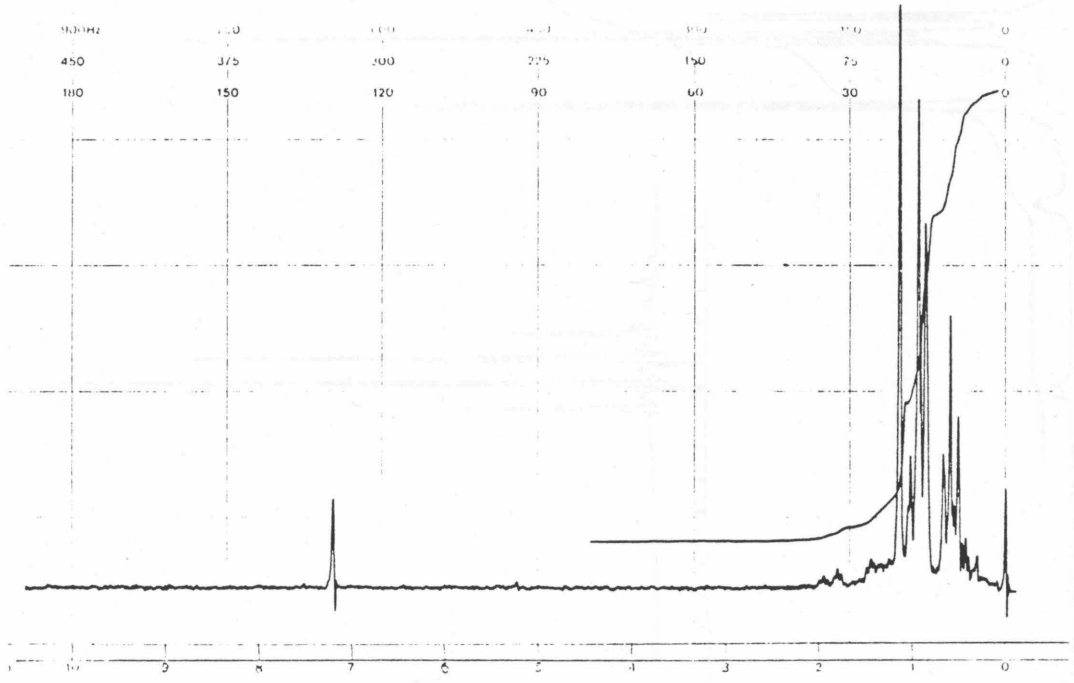
$CHCl_3$




Et3SiO
OSiEt3
Me
Me

81

CCl_4

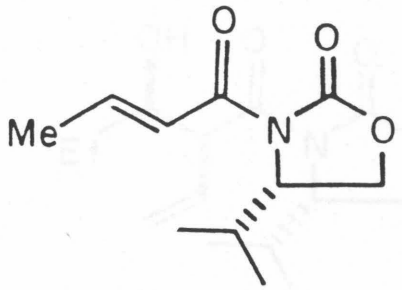

450
375
300
225
150
75
0
180
150
120
90
60
30
0
10
9
8
7
6
5
4
3
2
1
0

81 (cont.)

APPENDIX III

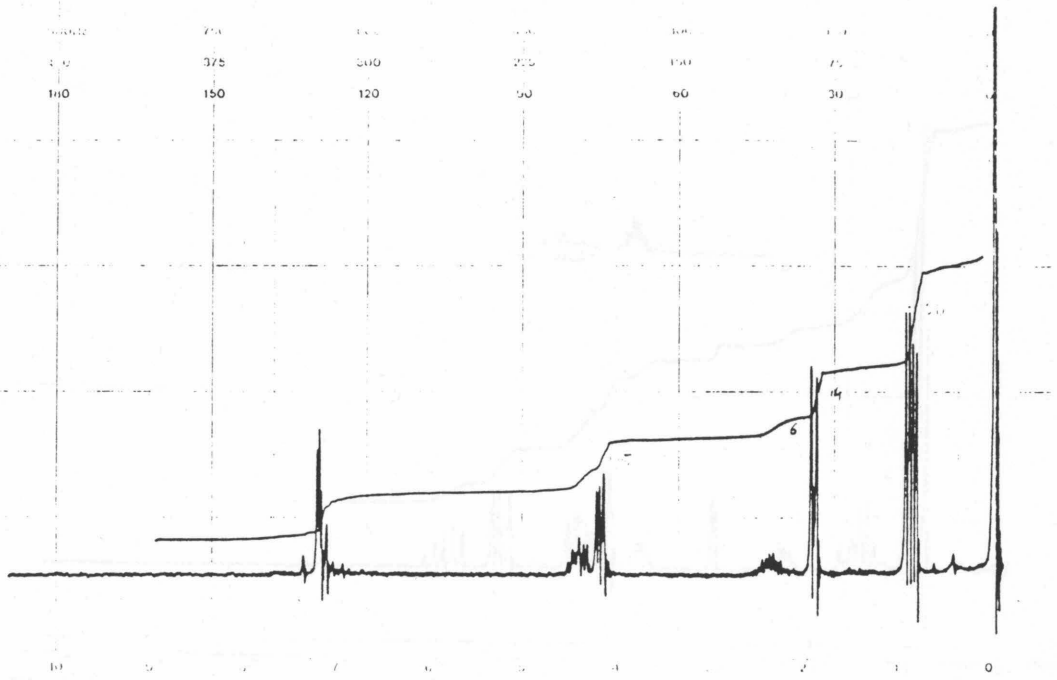
IR and ^{1}H NMR Spectral Catalog

for Chapter III

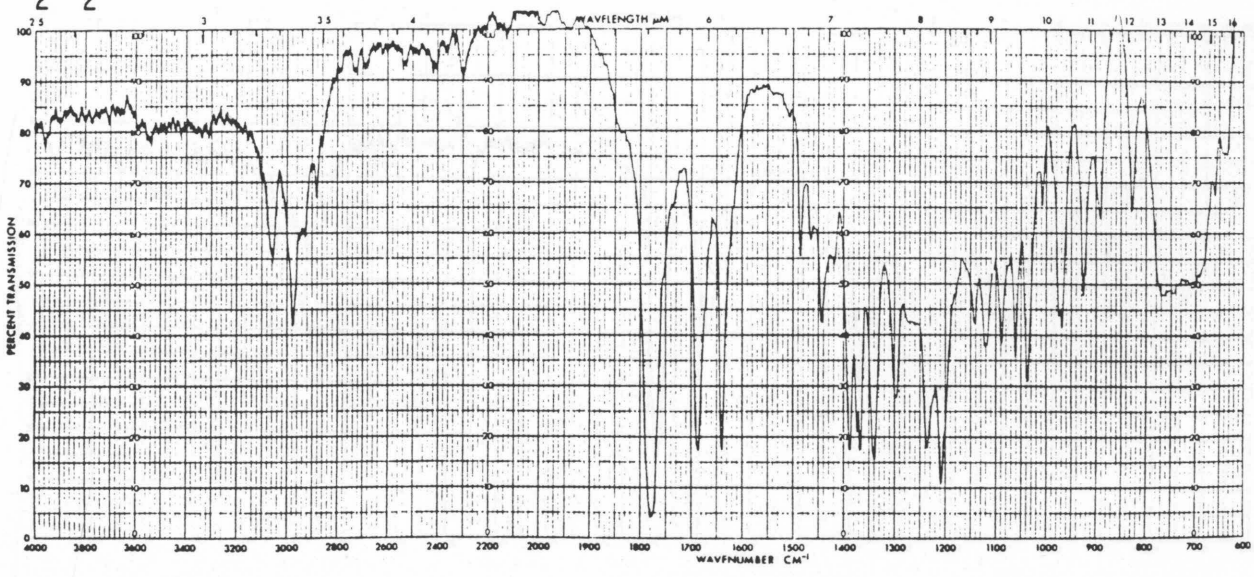


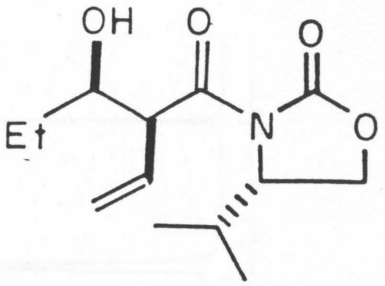
92

$CDCl_3$



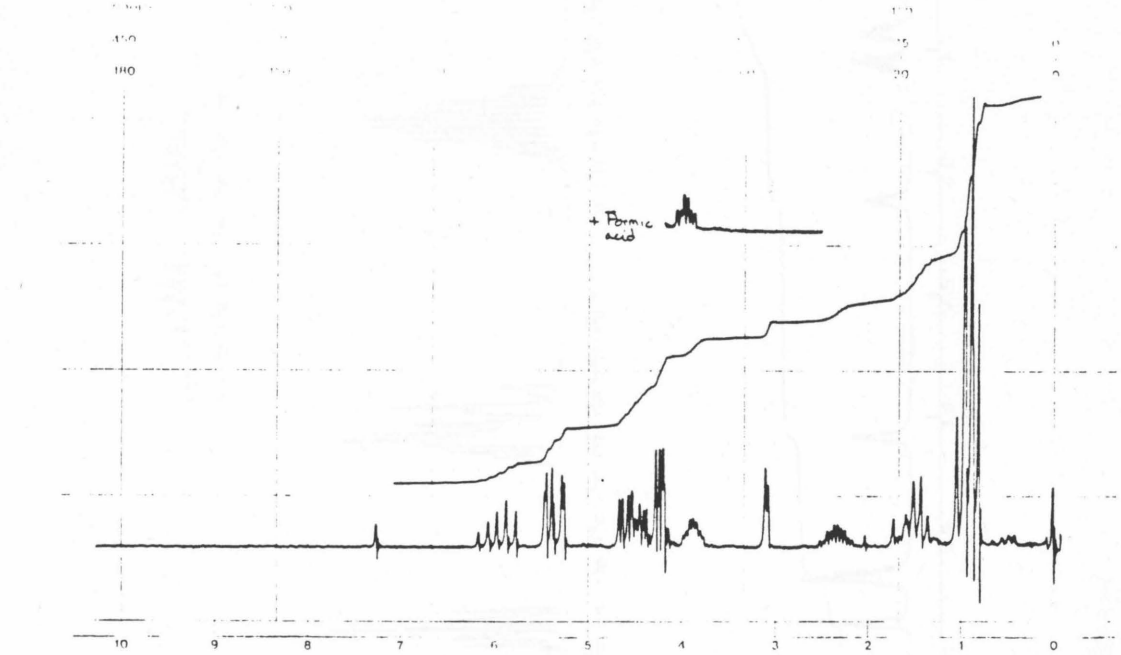
CH_2Cl_2



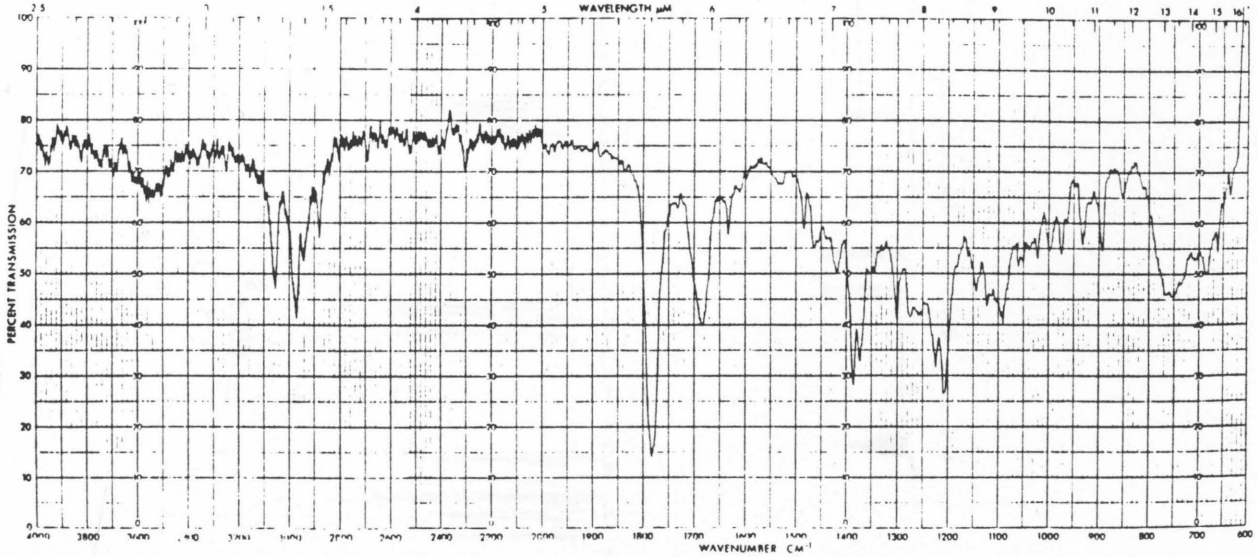


93

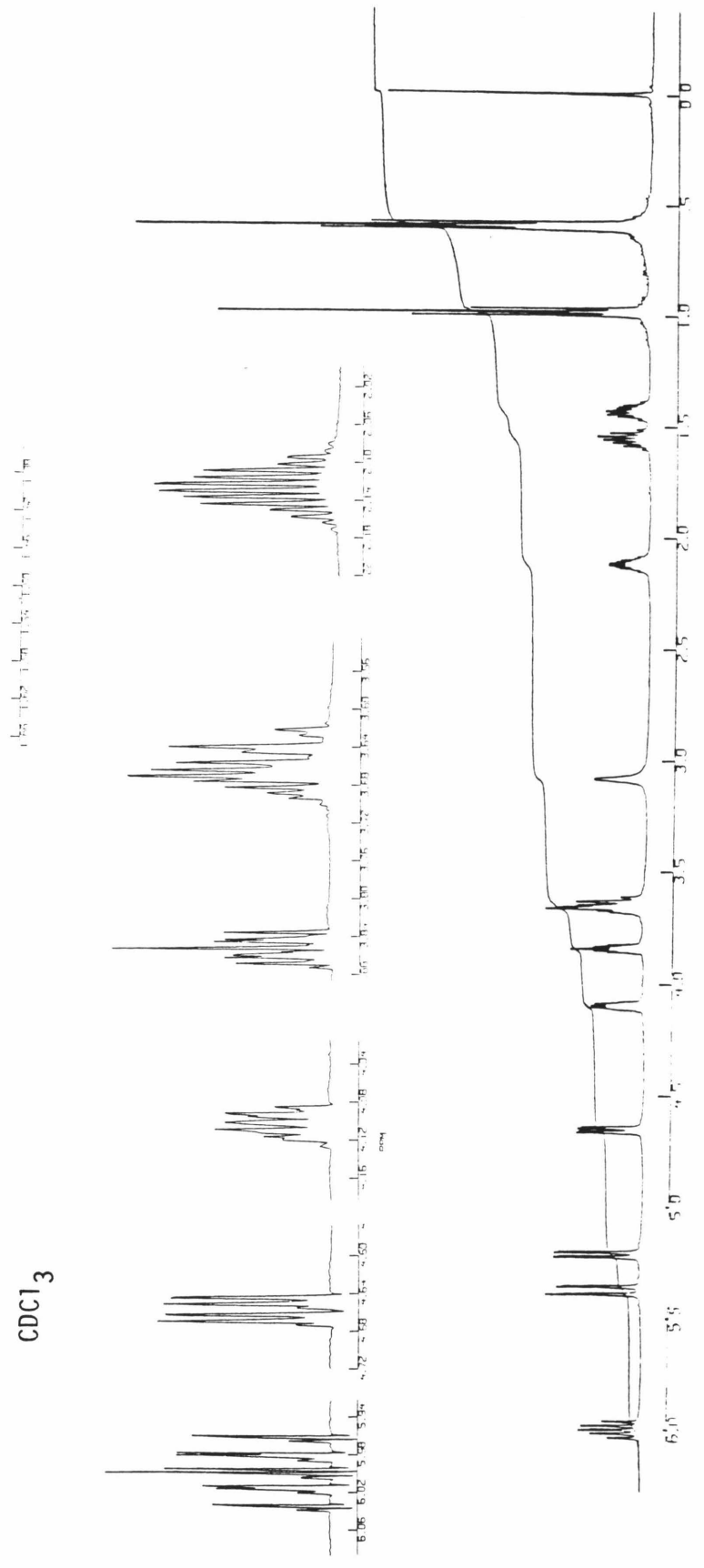
$CDCl_3$



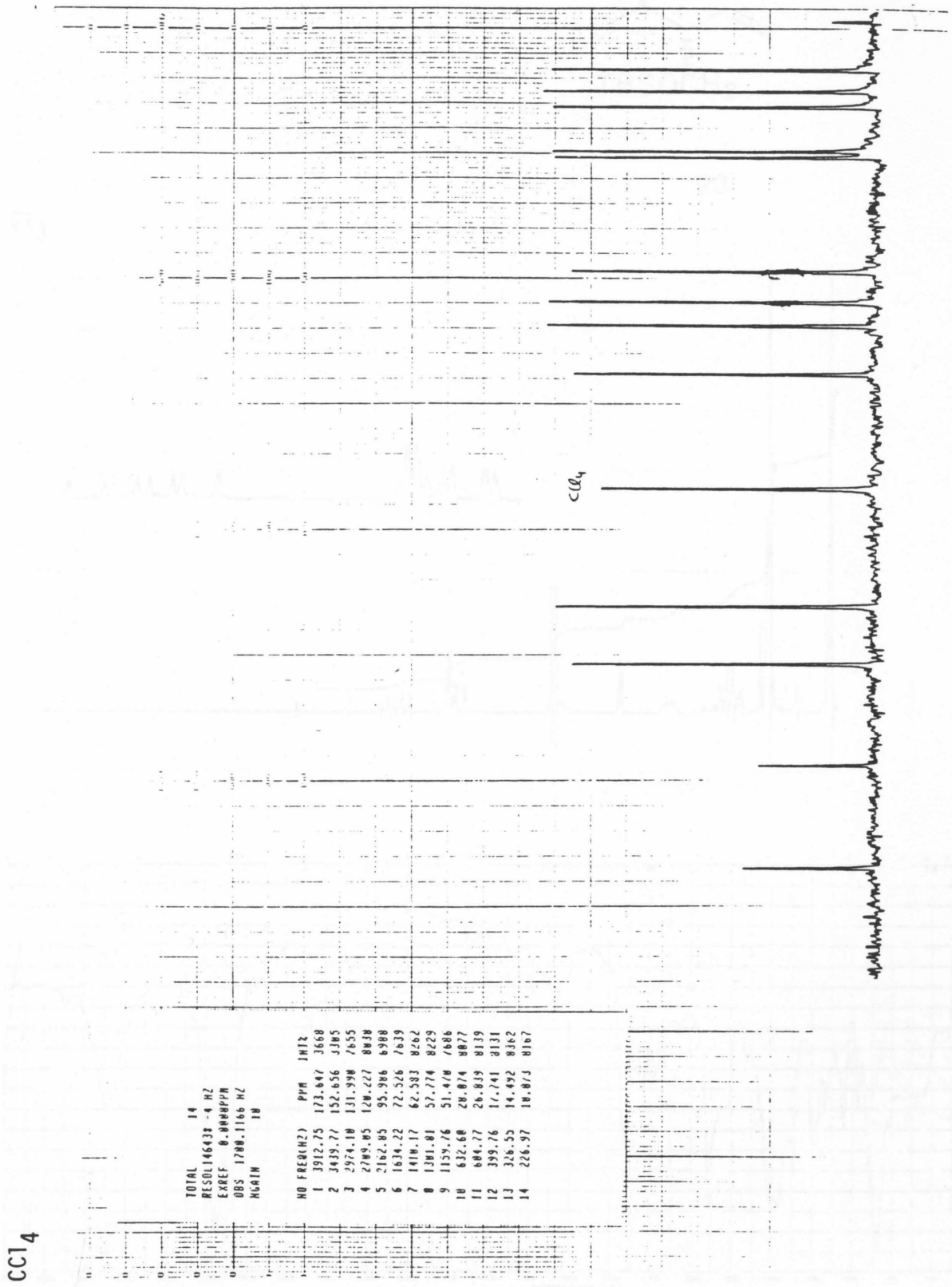
CH_2Cl_2

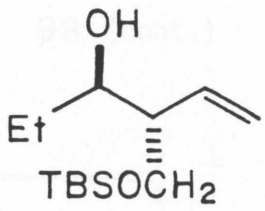


93 (cont.)



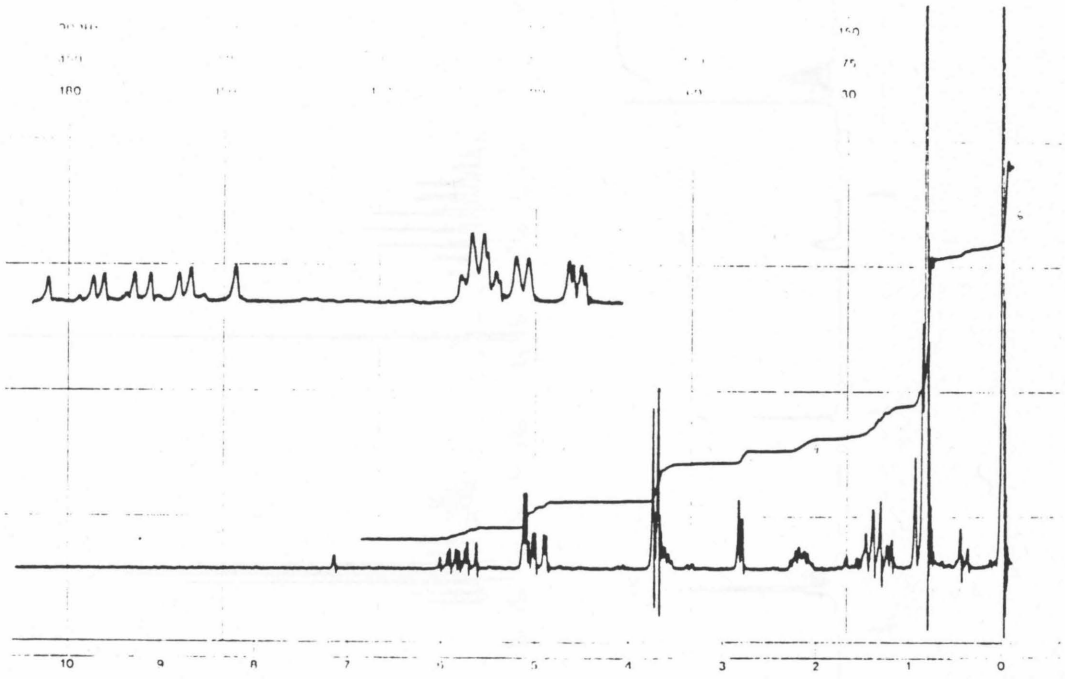
93 (cont.)

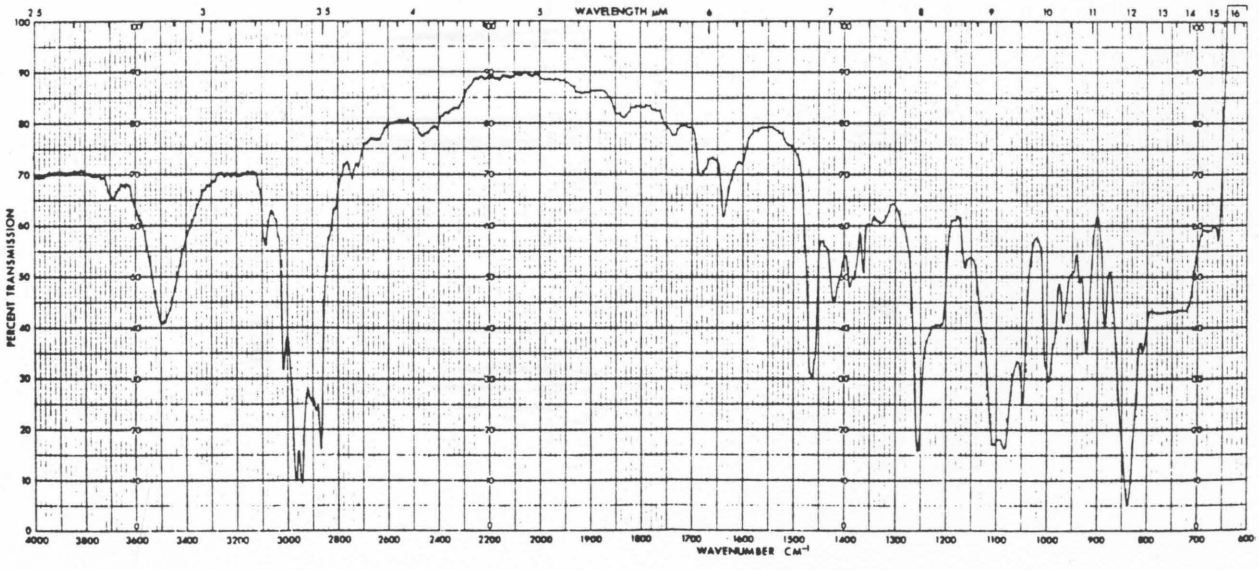

CCl4
TOTAL 14
RESOL146438 -4 HZ
EXREF 0.000PPM
OBS 1700.1166 HZ
MGAIN 10
NO FRE(HZ) PPM INTI
1 3912.75 173.647 3660
2 3439.77 152.636 3305
3 2974.10 131.998 2655
4 2709.05 120.227 8030
5 2162.85 95.986 6900
6 1634.22 72.526 7639
7 1410.17 62.583 8262
8 1301.81 57.774 8229
9 1159.76 51.470 7686
10 632.68 28.074 9877
11 604.77 26.839 8139
12 399.76 17.741 8131
13 326.55 14.492 8362
14 226.97 10.073 8167
CCl4


OH
Et
TBSOCH2

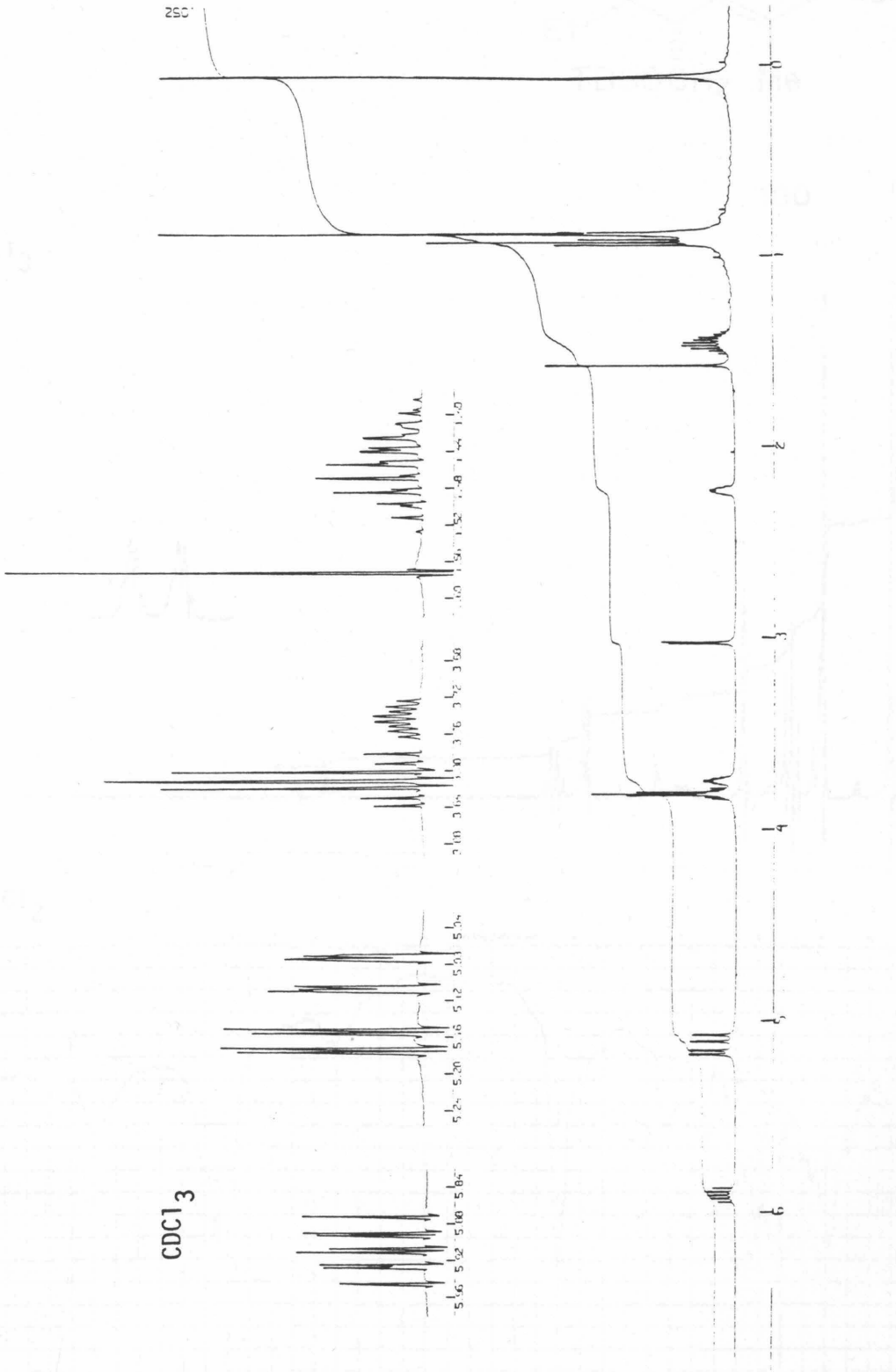
98

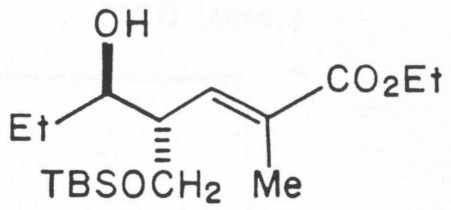
$CDCl_3$


10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM-1

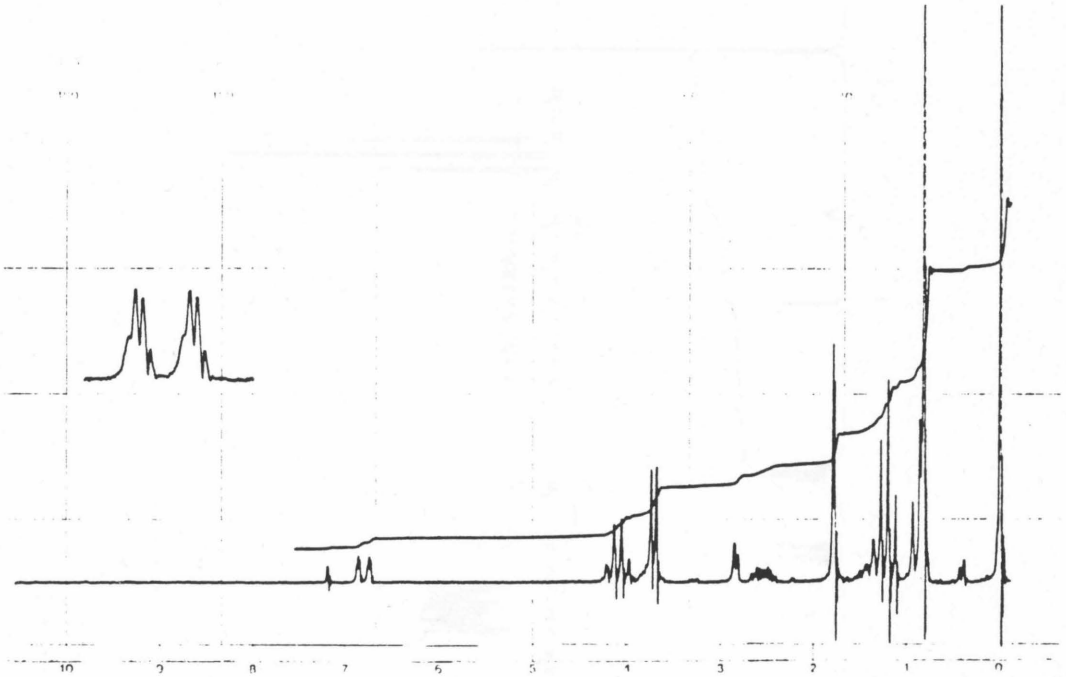
98 (cont.)



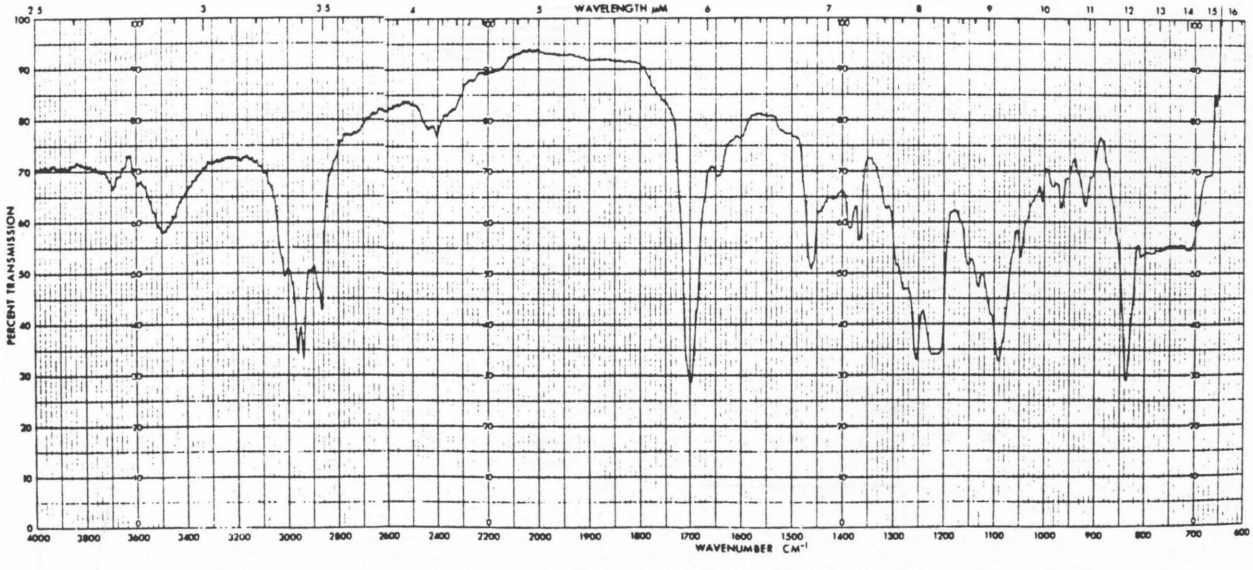


100

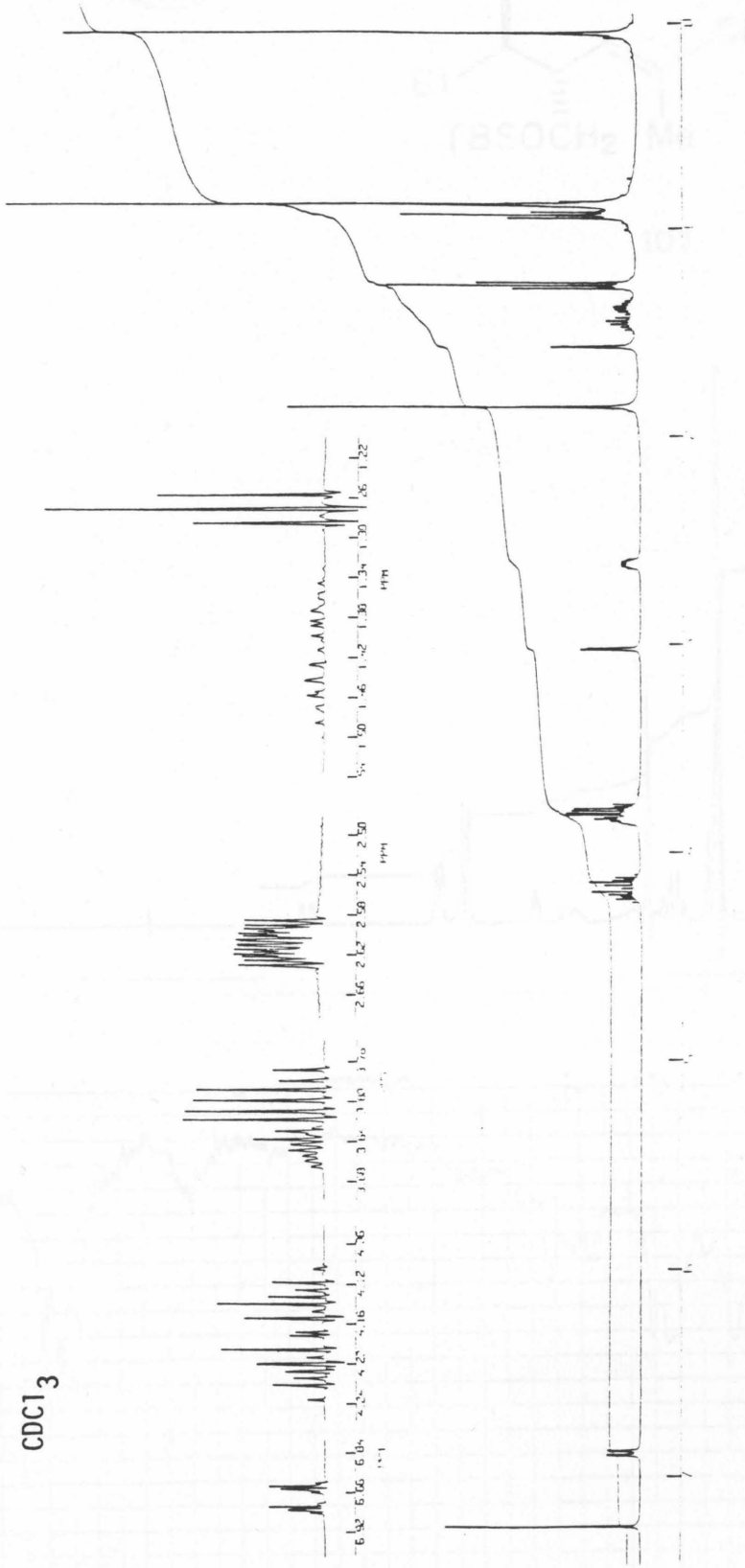
$CDCl_3$

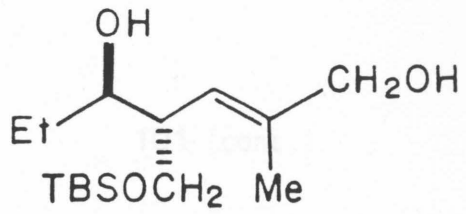


CH_2Cl_2



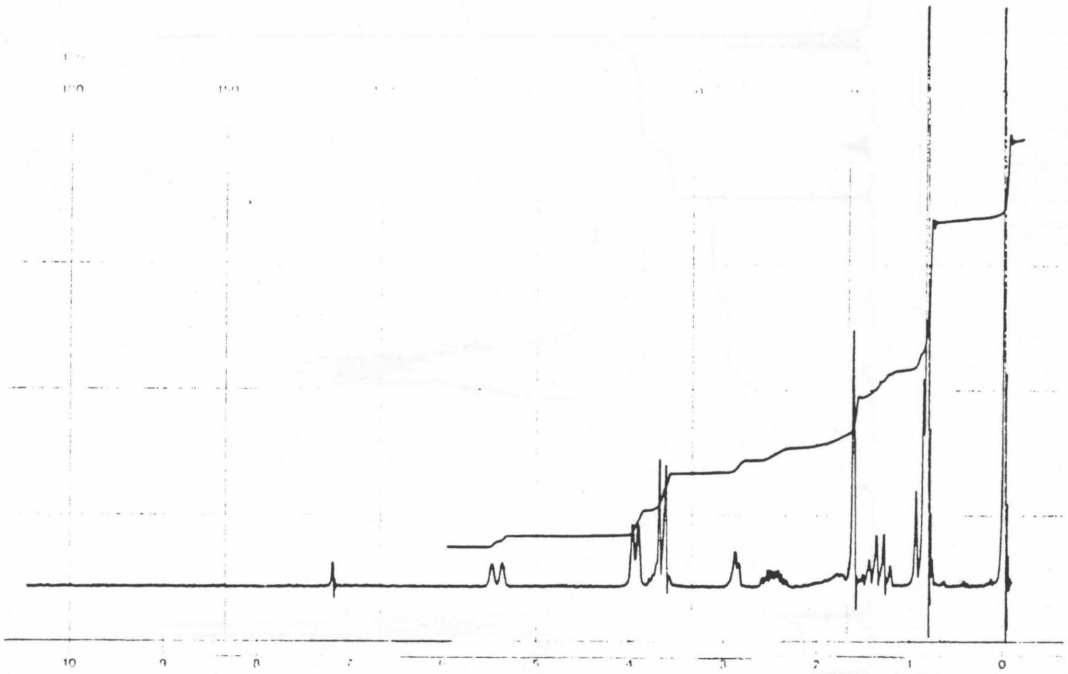
100 (cont.)



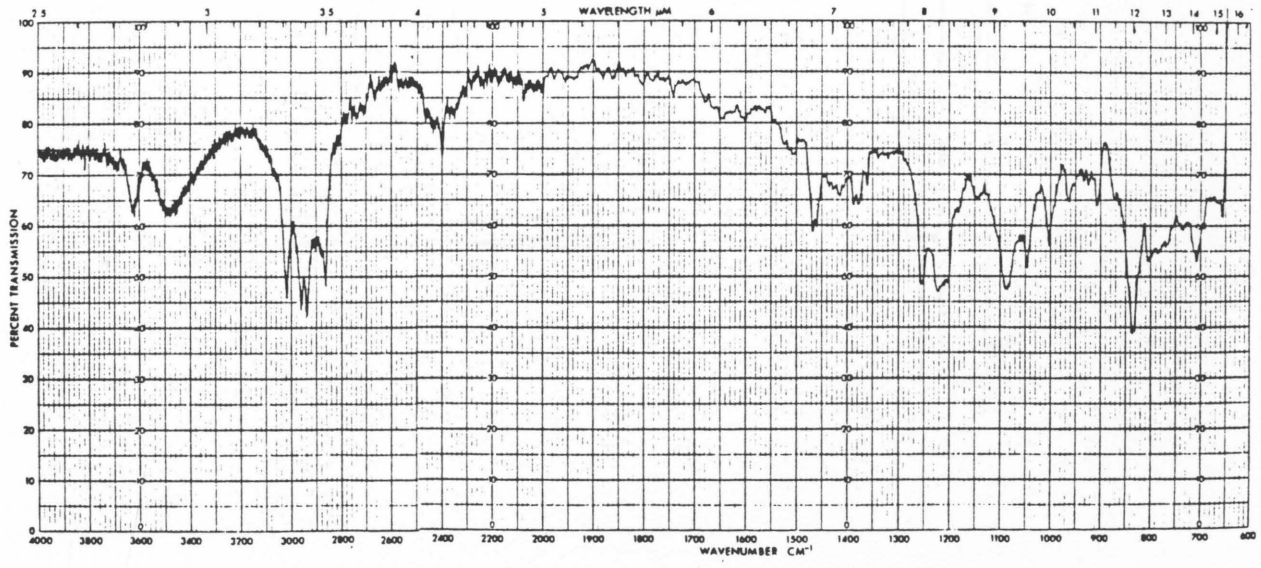


101

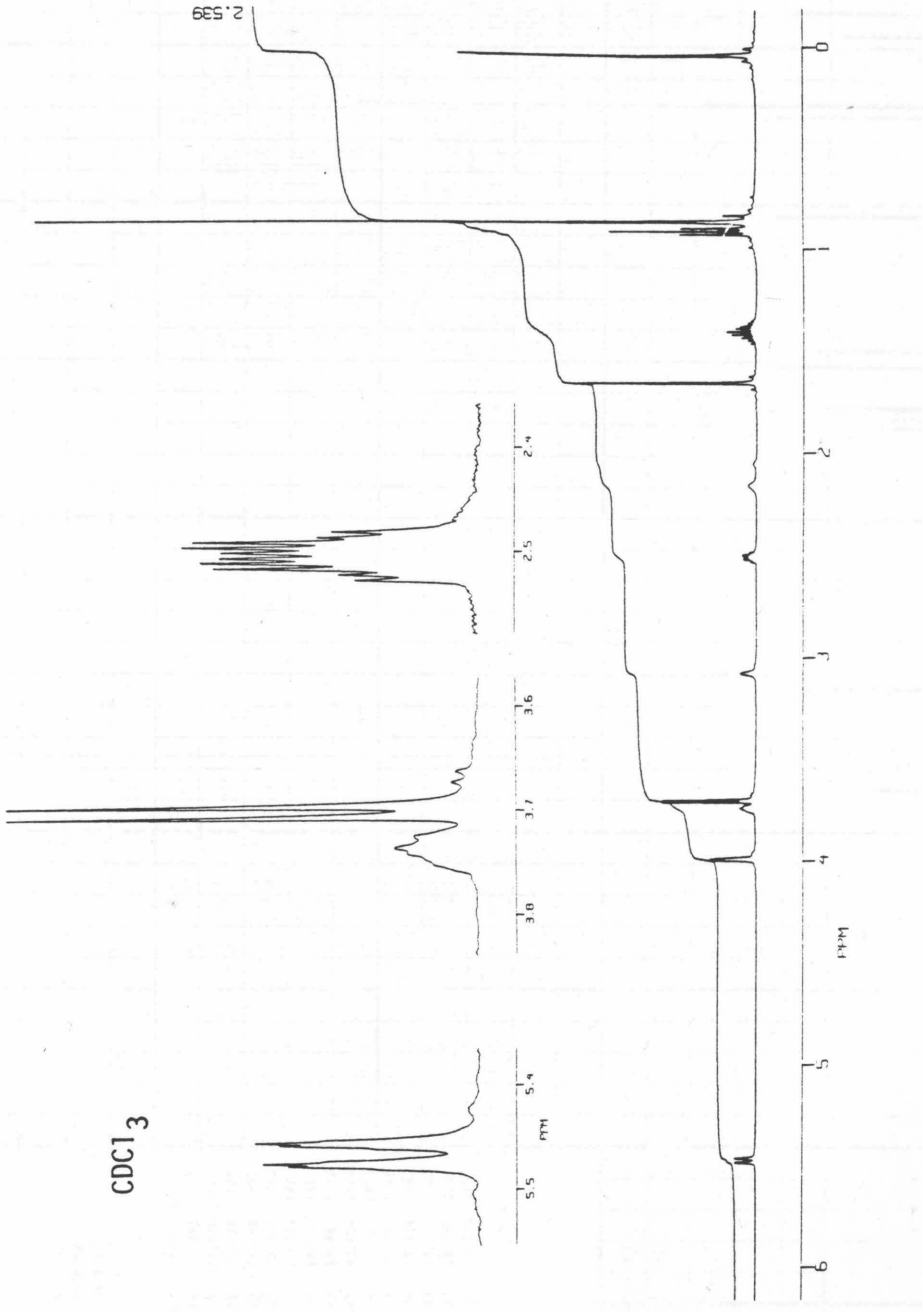
$CDCl_3$



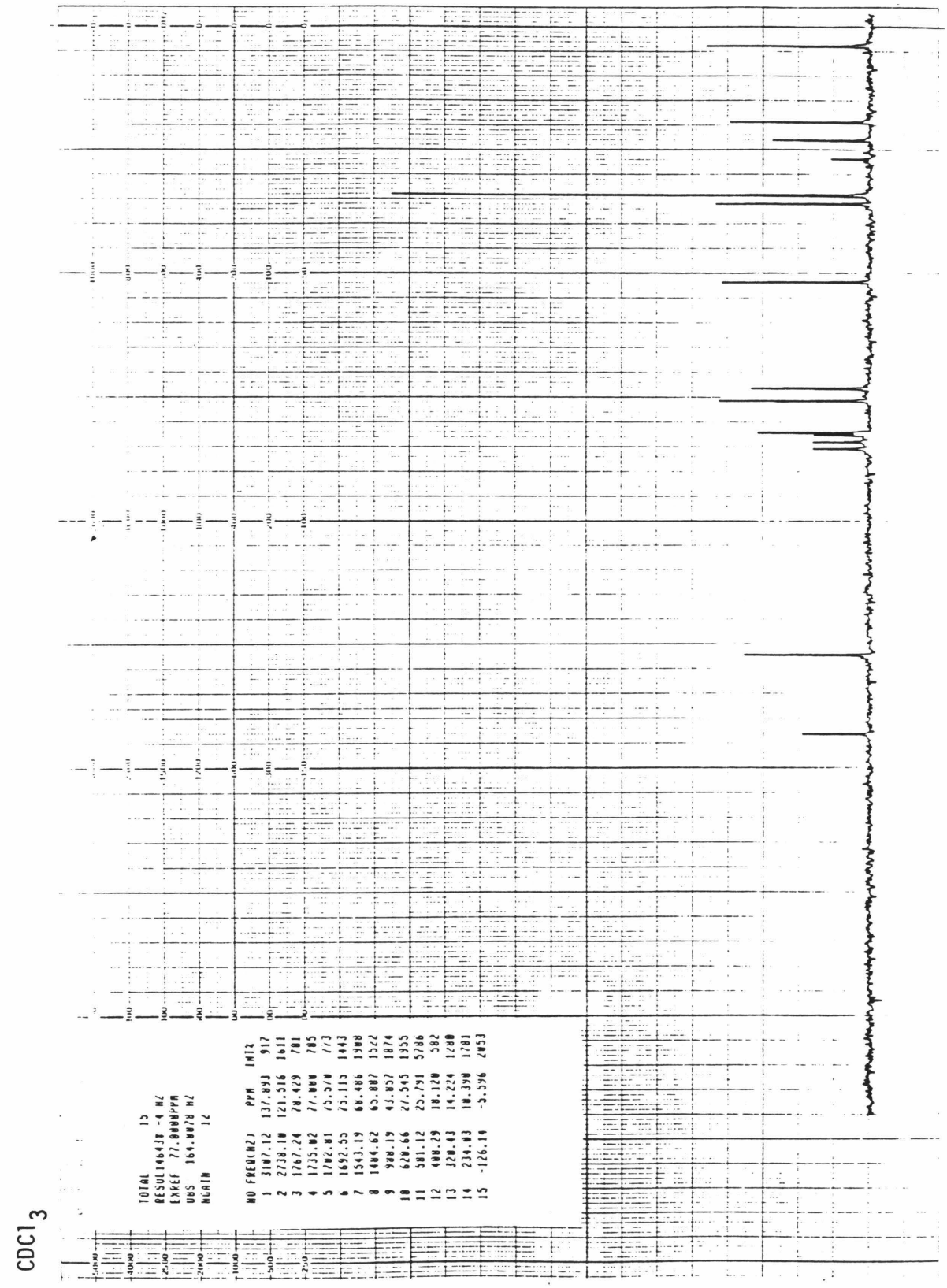
$CHCl_3$



101 (cont.)



101 (cont.)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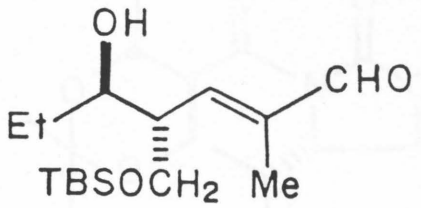
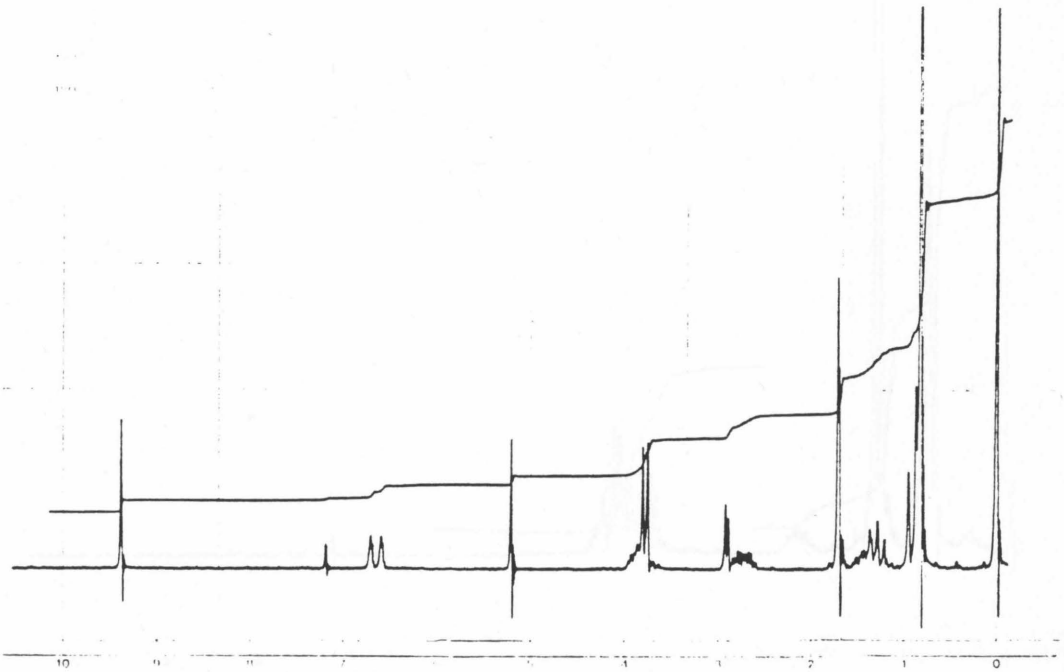
RESOL1464JI -4 HZ
EXREF 77.0000PPM
OBS 164.0078 MZ
NGAIN 12
NO FREQ(HZ) PPM HWIZ
1 3187.12 137.893 917
2 2738.10 121.516 1411
3 1767.24 78.429 781
4 1735.82 77.000 785
5 1702.81 75.570 773
6 1692.55 75.113 1443
7 1543.19 68.486 1988
8 1484.62 65.887 1522
9 988.19 43.852 1874
10 620.66 27.545 1955
11 581.12 25.791 5786
12 408.29 18.120 582
13 328.43 14.224 1280
14 234.83 10.390 1781
15 -126.14 -5.596 2853

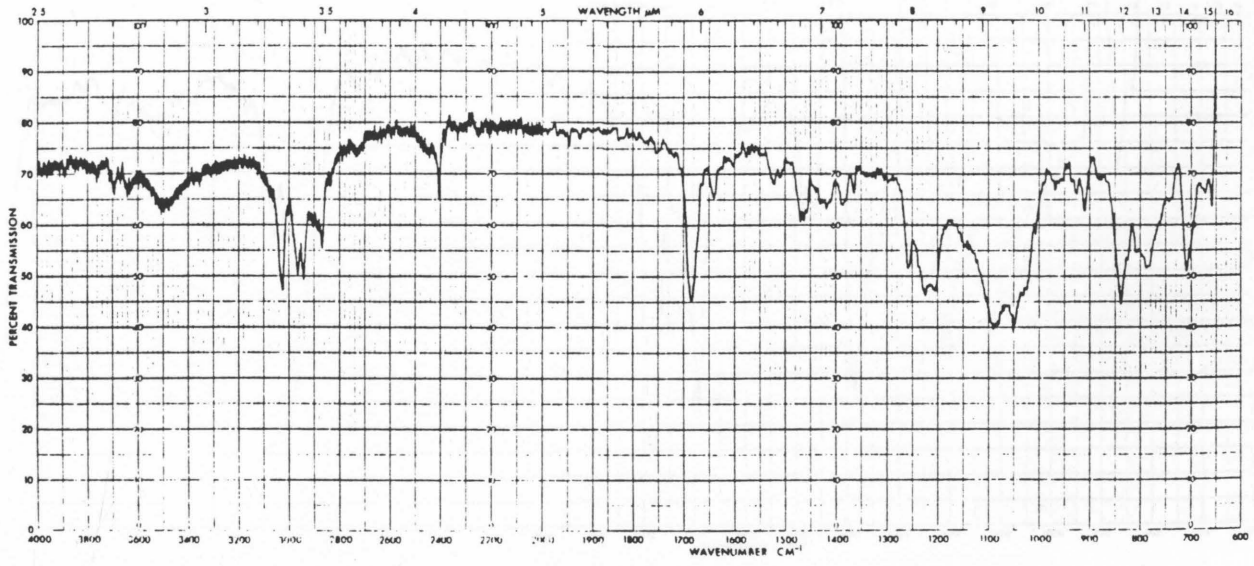


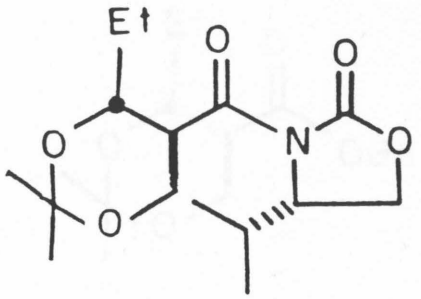
102

$CDCl_3$



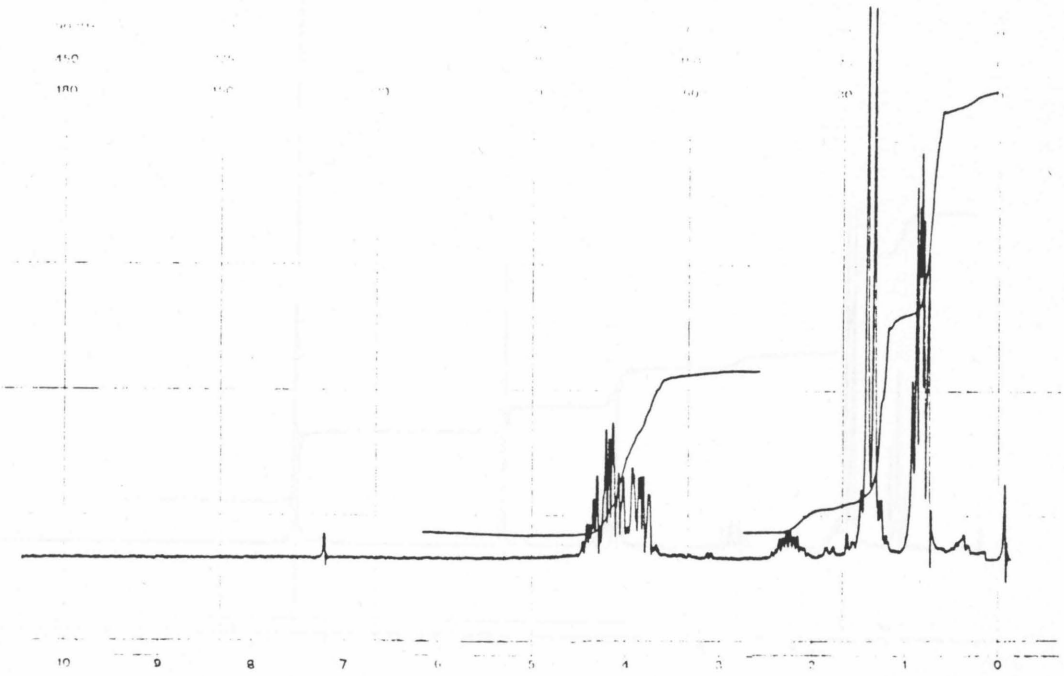
$CHCl_3$

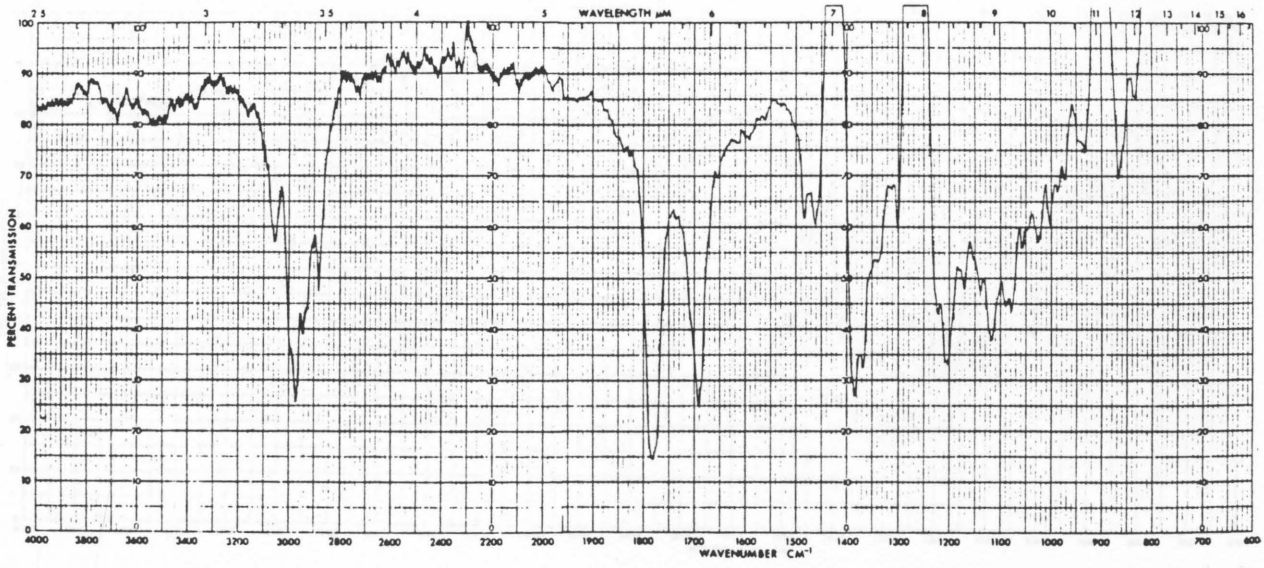


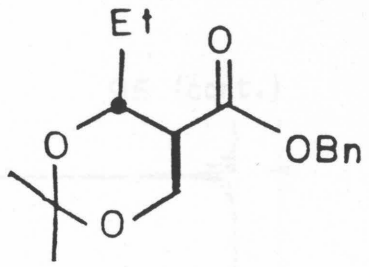

Et
O
O
O
N
O
O

94

$CDCl_3$

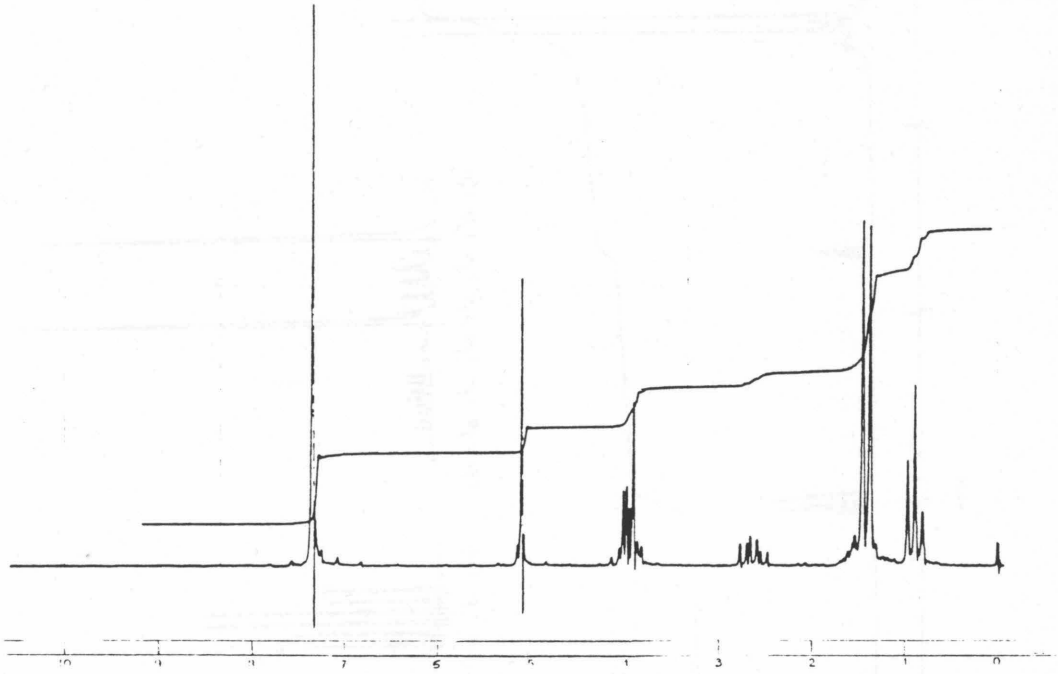

10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

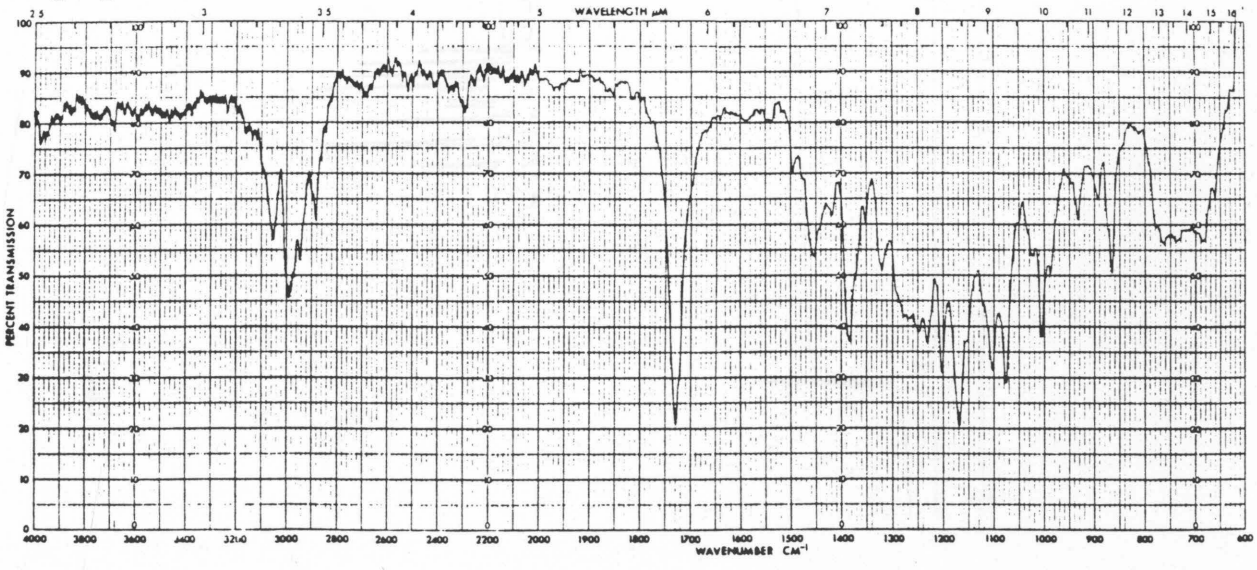


95

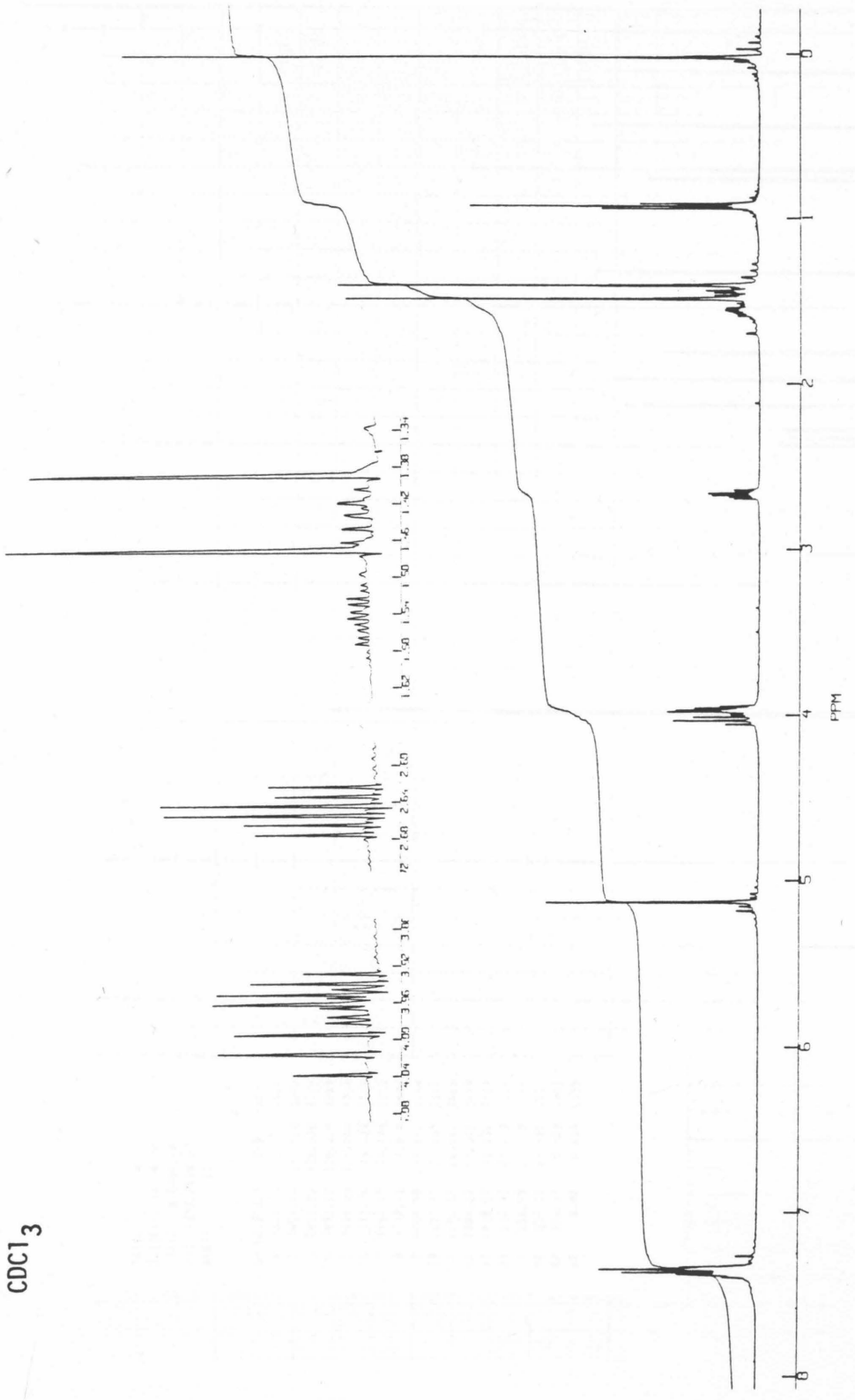
$CDCl_3$



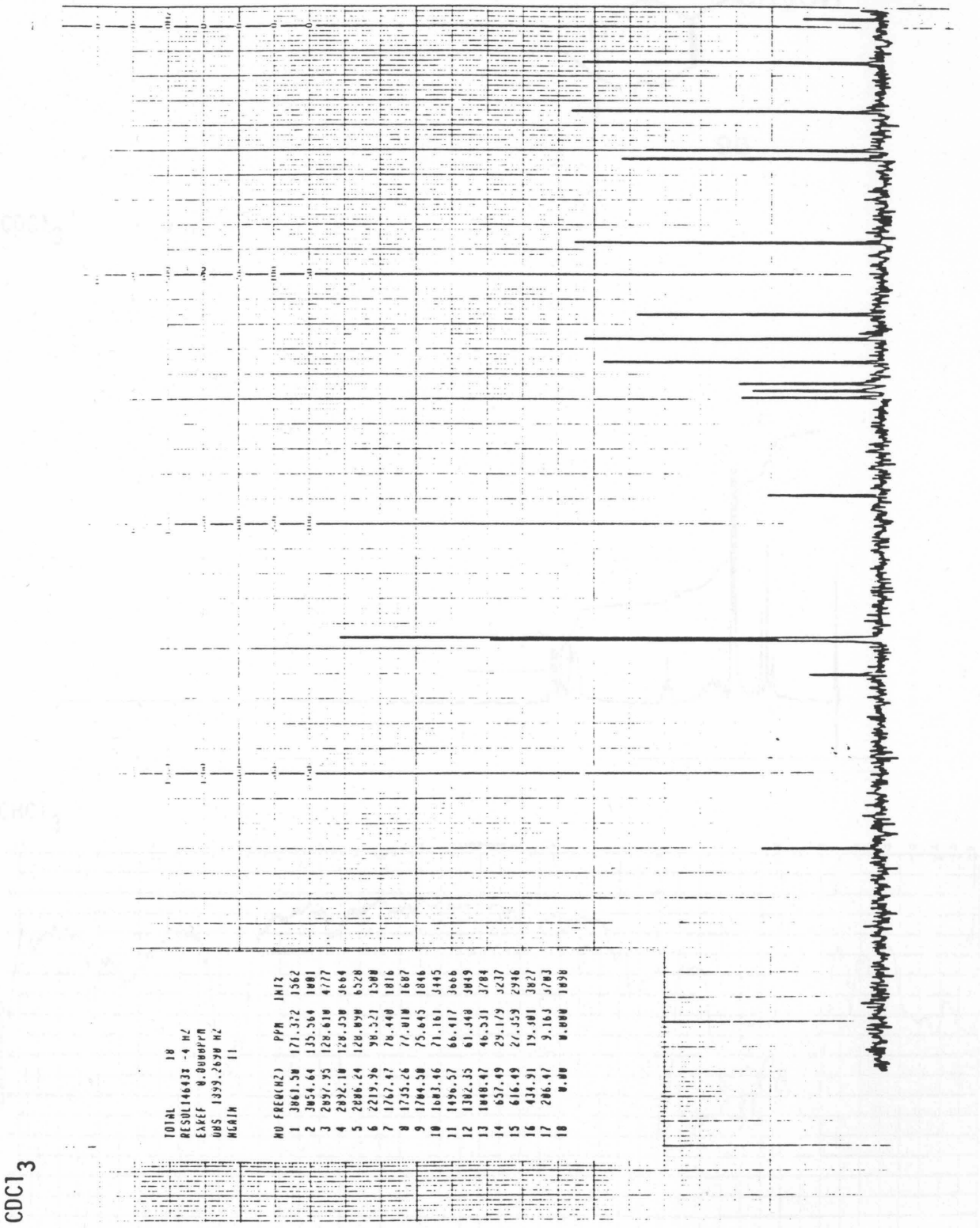
CH_2Cl_2

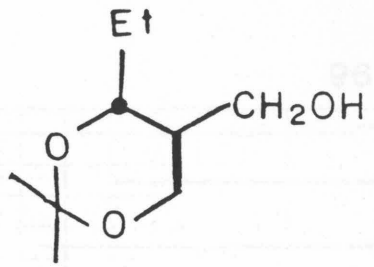


95 (cont.)



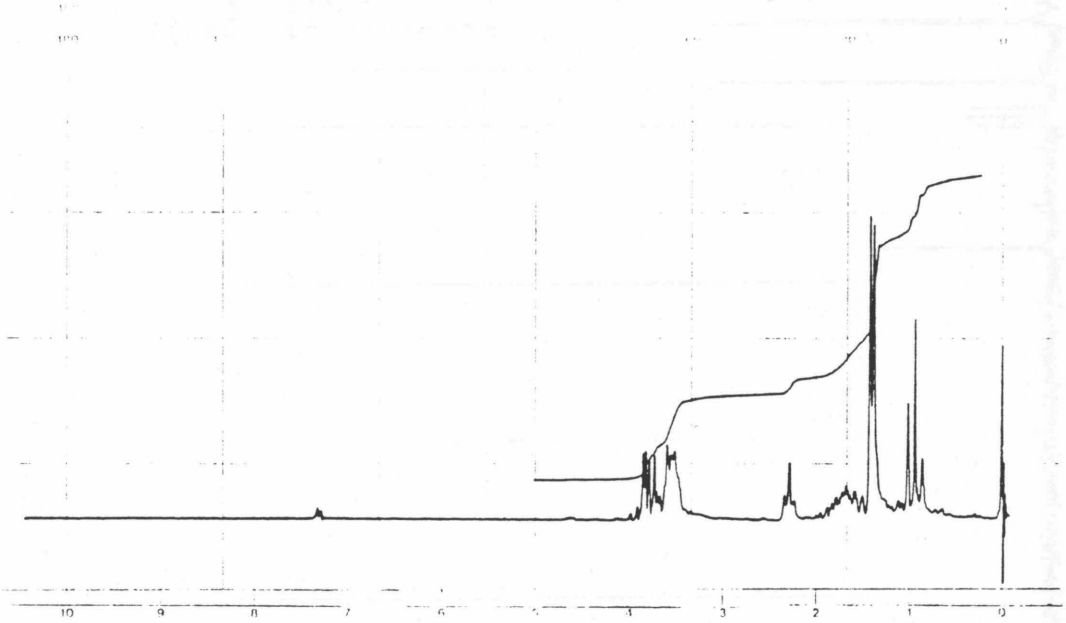
95 (cont.)


CDCl3
TOTAL 18
RESOL 14643 -4 HZ
EXREF 0.000PPM
OBS 1359.2630 HZ
MGAIN 11
NO FREQ(HZ) PPM INT2
1 3861.38 171.372 1562
2 3054.64 135.564 1081
3 2897.95 128.619 4777
4 2892.10 128.359 5664
5 2886.24 128.099 6528
6 2219.36 98.521 1588
7 1767.47 78.440 1816
8 1735.26 77.010 1687
9 1704.58 75.645 1846
10 1683.46 71.161 3445
11 1496.57 66.417 3666
12 1382.35 61.340 3849
13 1048.47 46.531 3784
14 657.49 29.179 3237
15 616.49 27.359 2946
16 434.91 19.301 3827
17 206.47 9.163 3783
18 0.00 0.000 1838

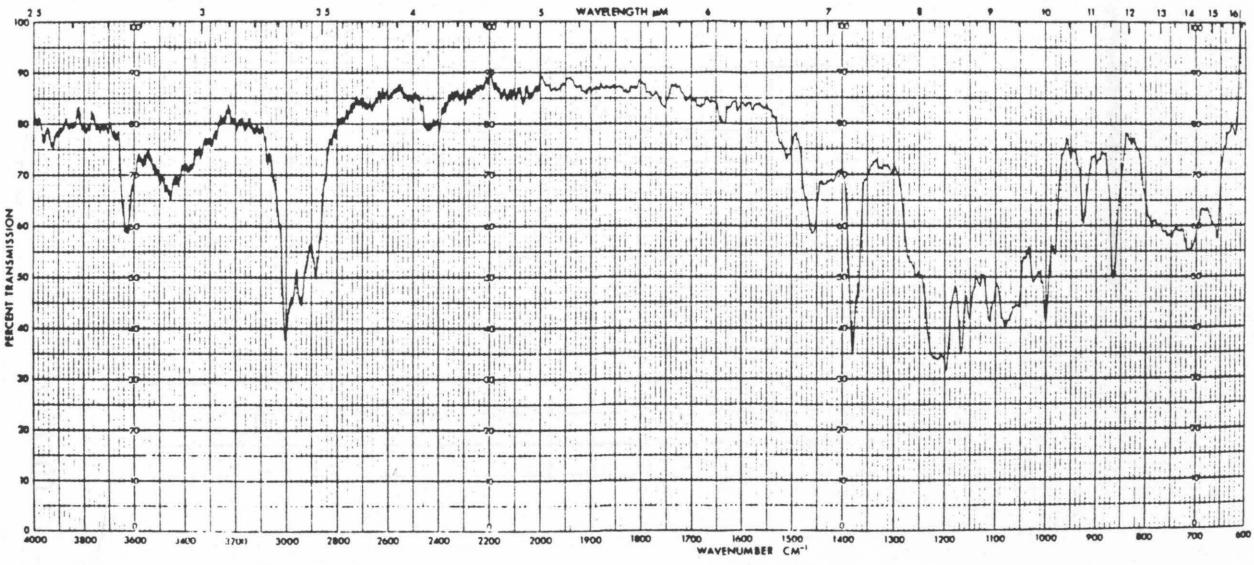


96

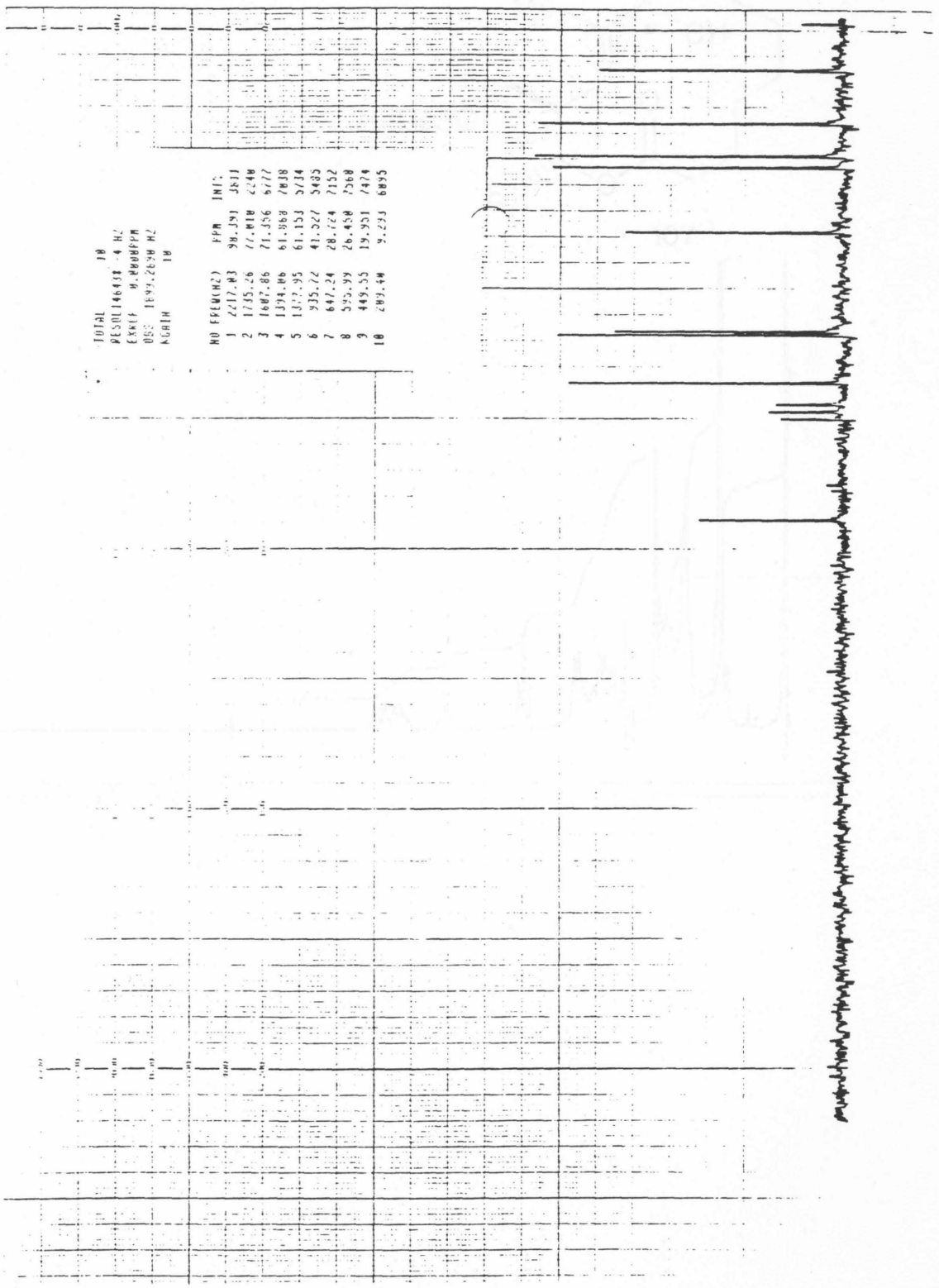
$CDCl_3$

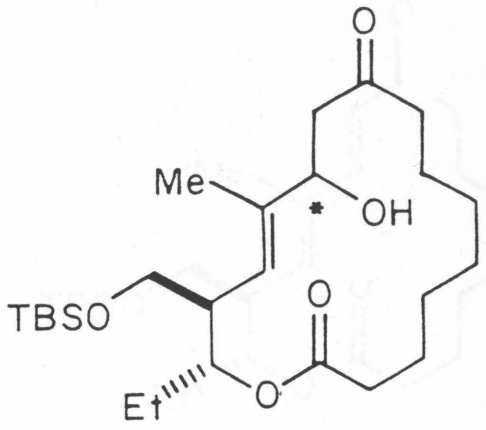


$CHCl_3$



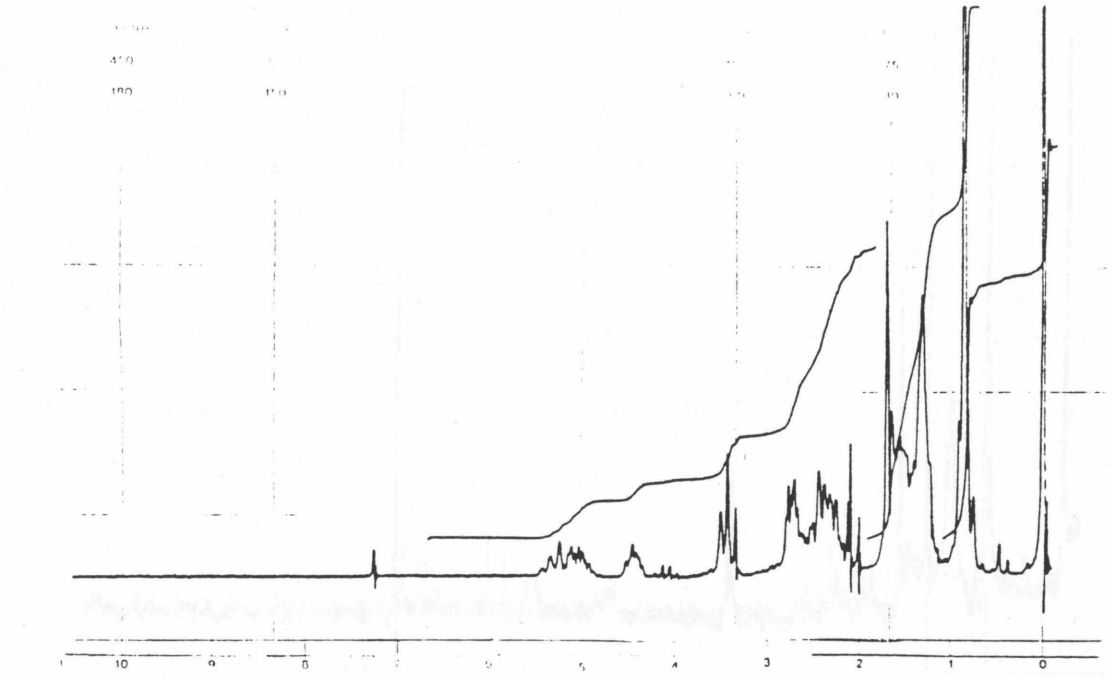
96 (cont.)

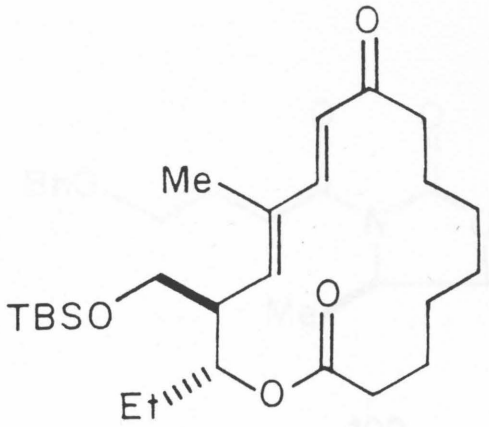

TOTAL 10
RESOLUTION 4 HZ
EXACT 0.000PPM
OBS 1599.2690 HZ
NORM 10
NO FREQ(HZ) PPM INT.
1 2217.83 98.391 3611
2 1735.26 77.018 2240
3 1607.86 71.356 6777
4 1394.06 61.868 7038
5 1382.95 61.153 5734
6 935.72 41.527 3485
7 647.24 28.724 2152
8 595.99 26.450 7560
9 449.55 19.951 7424
10 289.40 9.293 6895
CDCl3



107

$CDCl_3$





108

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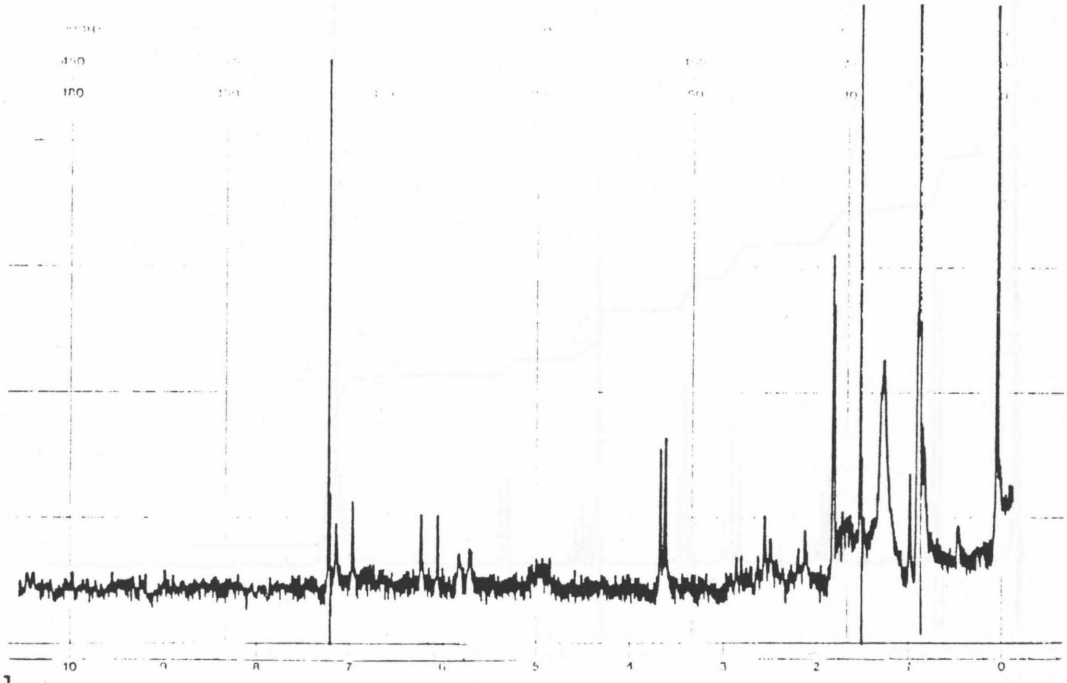
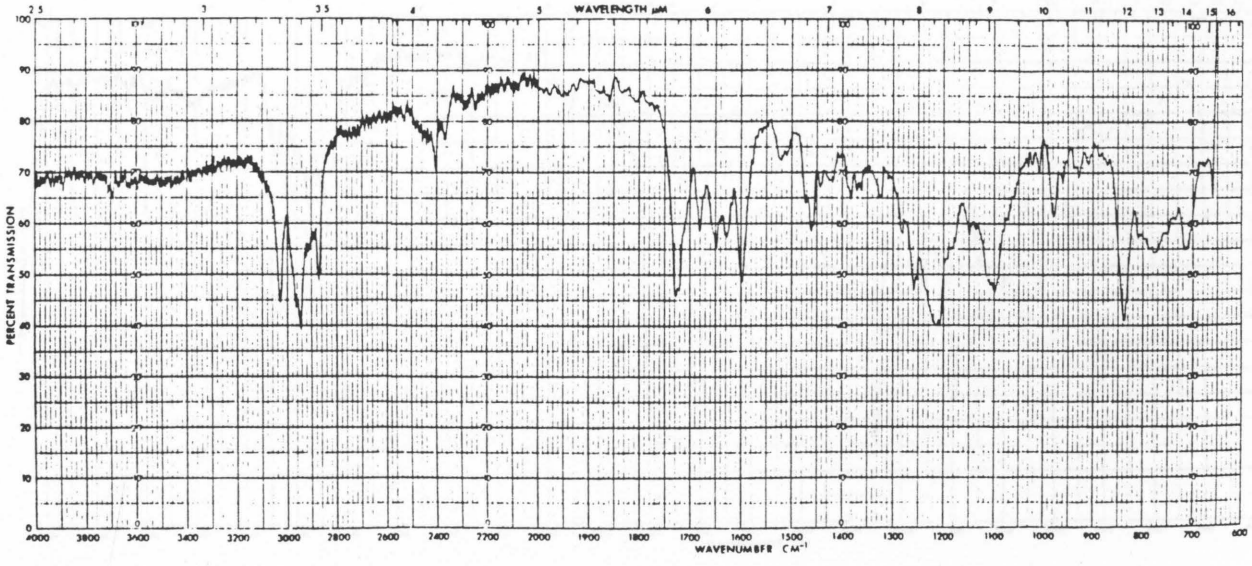
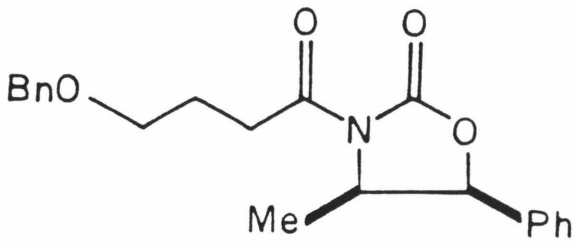


$CHCl_3$





109

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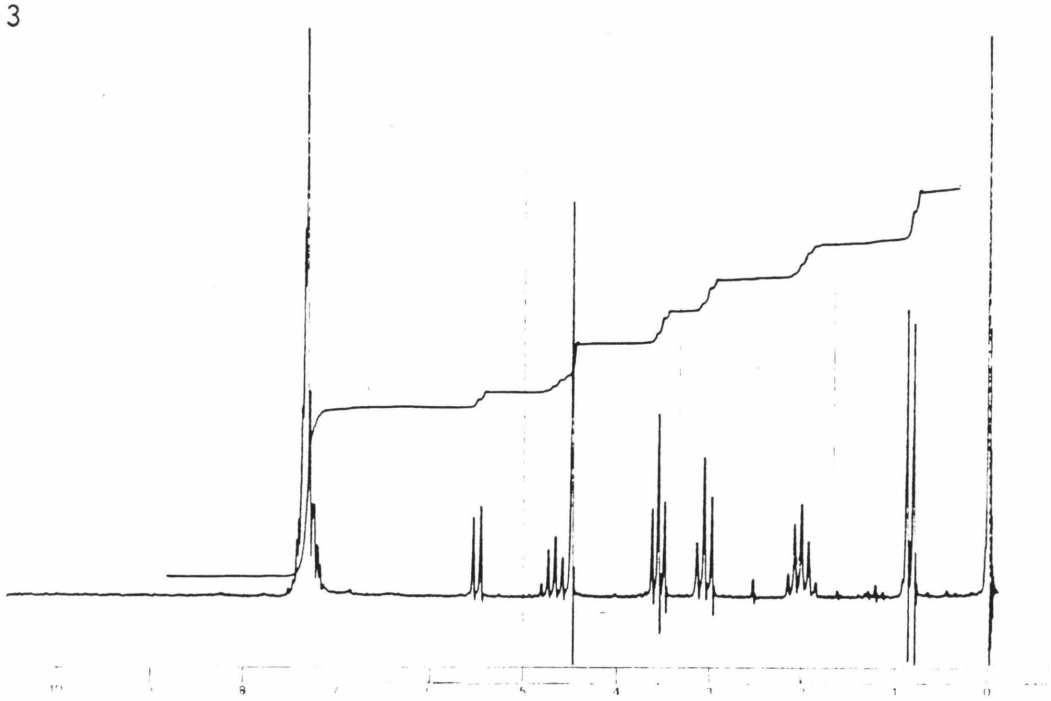
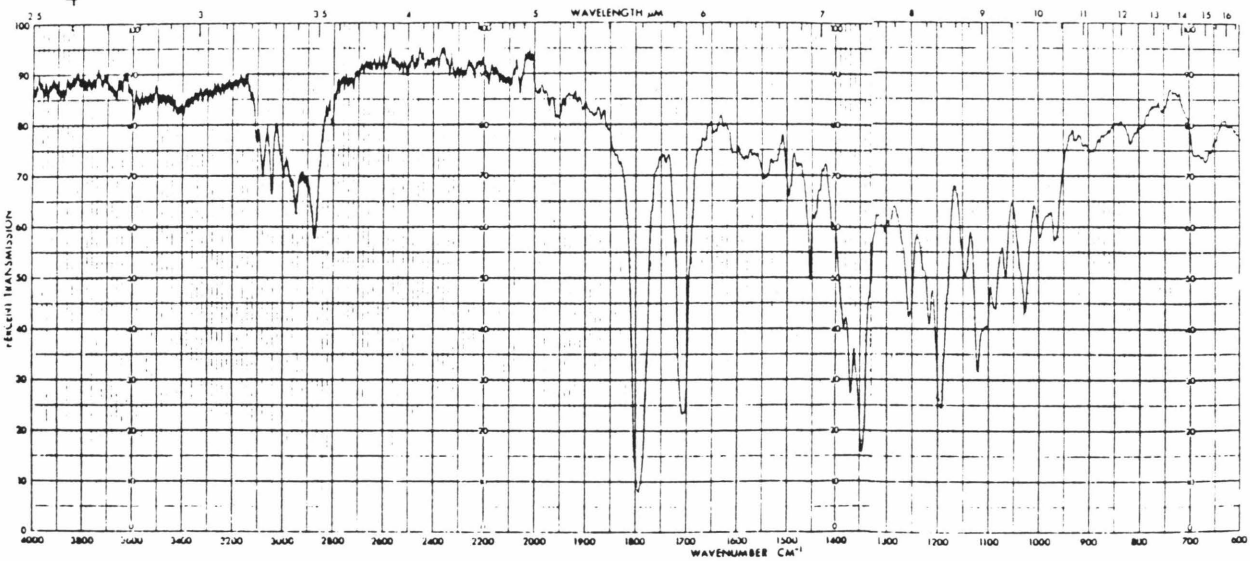
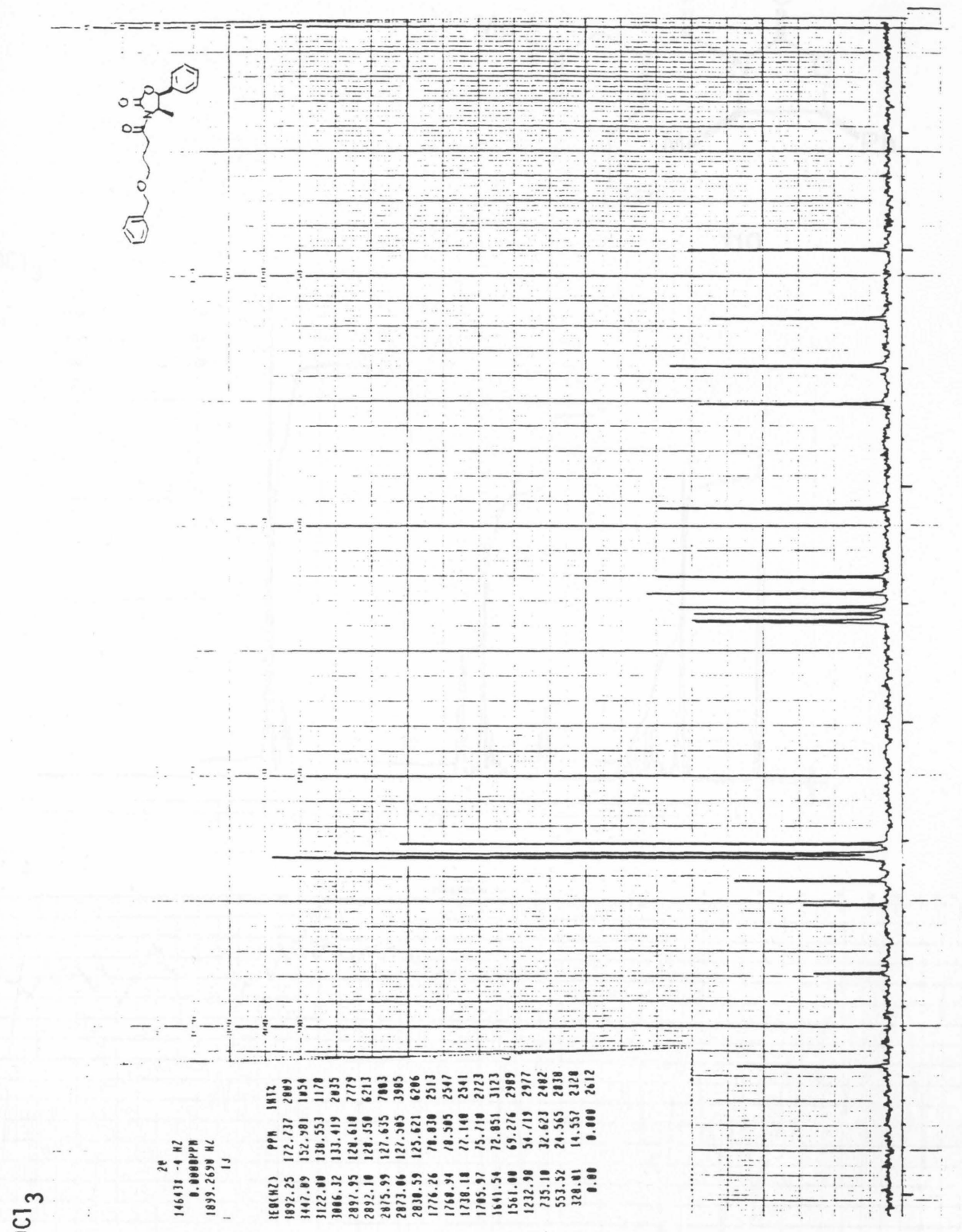
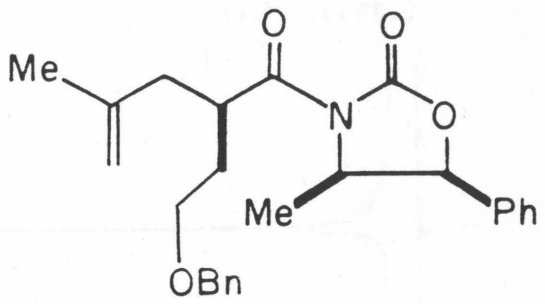


CCl_4



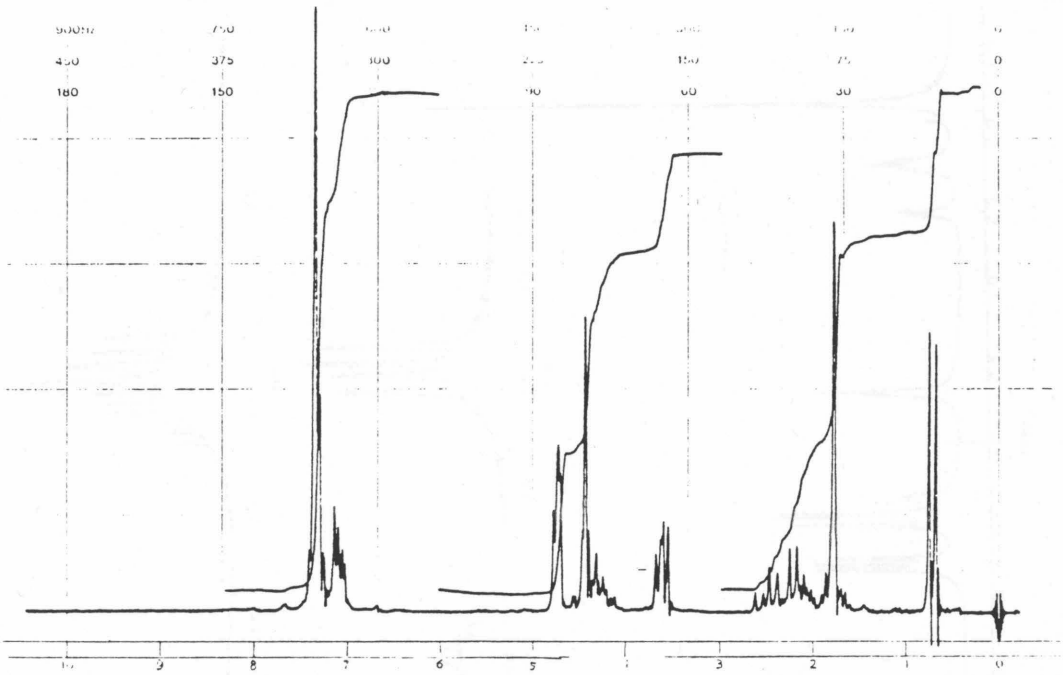
109 (cont.)


CDCl3
2#
14643H -4 HZ
0.0000PPM
1939.2690 HZ
13
FREQ(HZ) PPM INTG
1892.25 172.237 2009
1447.09 132.981 1454
1122.00 130.553 1170
1086.32 133.419 2035
2097.95 120.618 7779
2092.10 120.350 6213
2075.99 127.635 7003
2073.06 127.305 3905
2030.59 125.621 6206
1776.26 70.830 2513
1760.94 70.505 2547
1738.10 77.140 2541
1705.97 75.710 2723
1641.54 72.851 3123
1561.00 69.276 2909
1232.90 54.719 2977
735.10 32.621 2402
553.52 24.565 2030
328.01 14.557 2328
0.00 0.000 2612

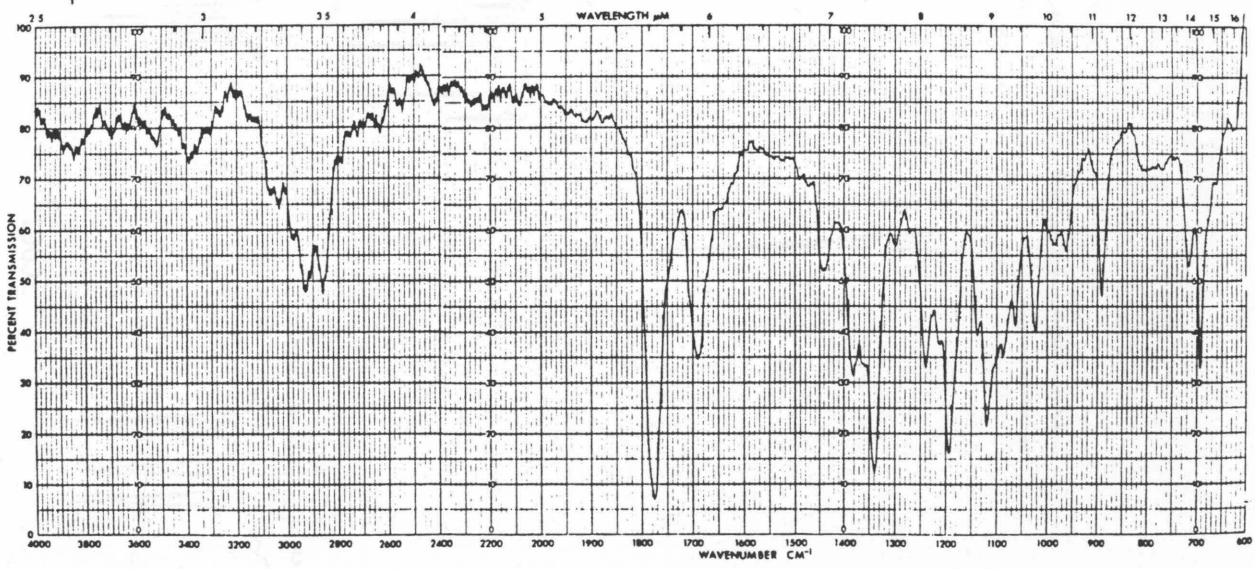


110

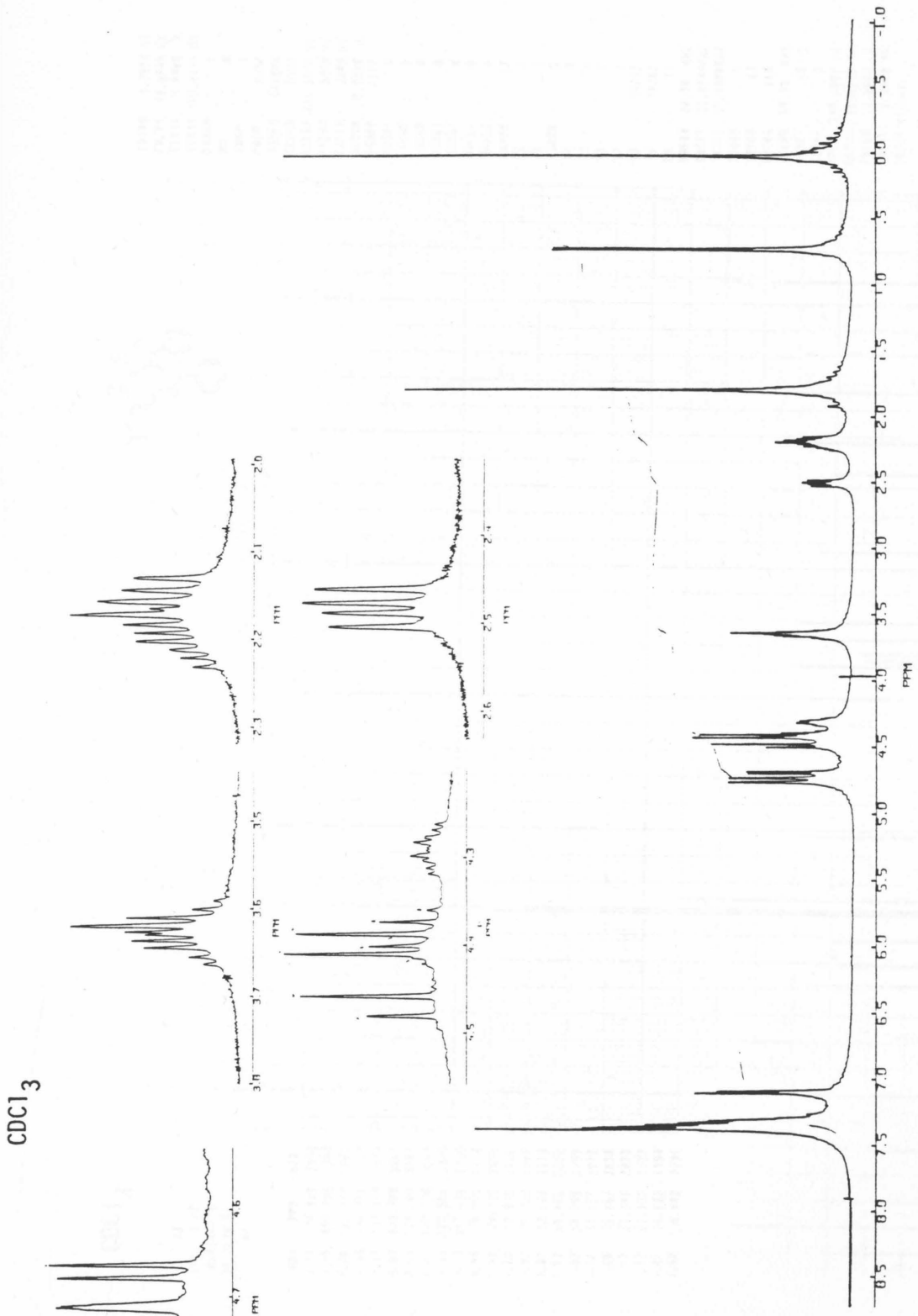
$CDCl_3$



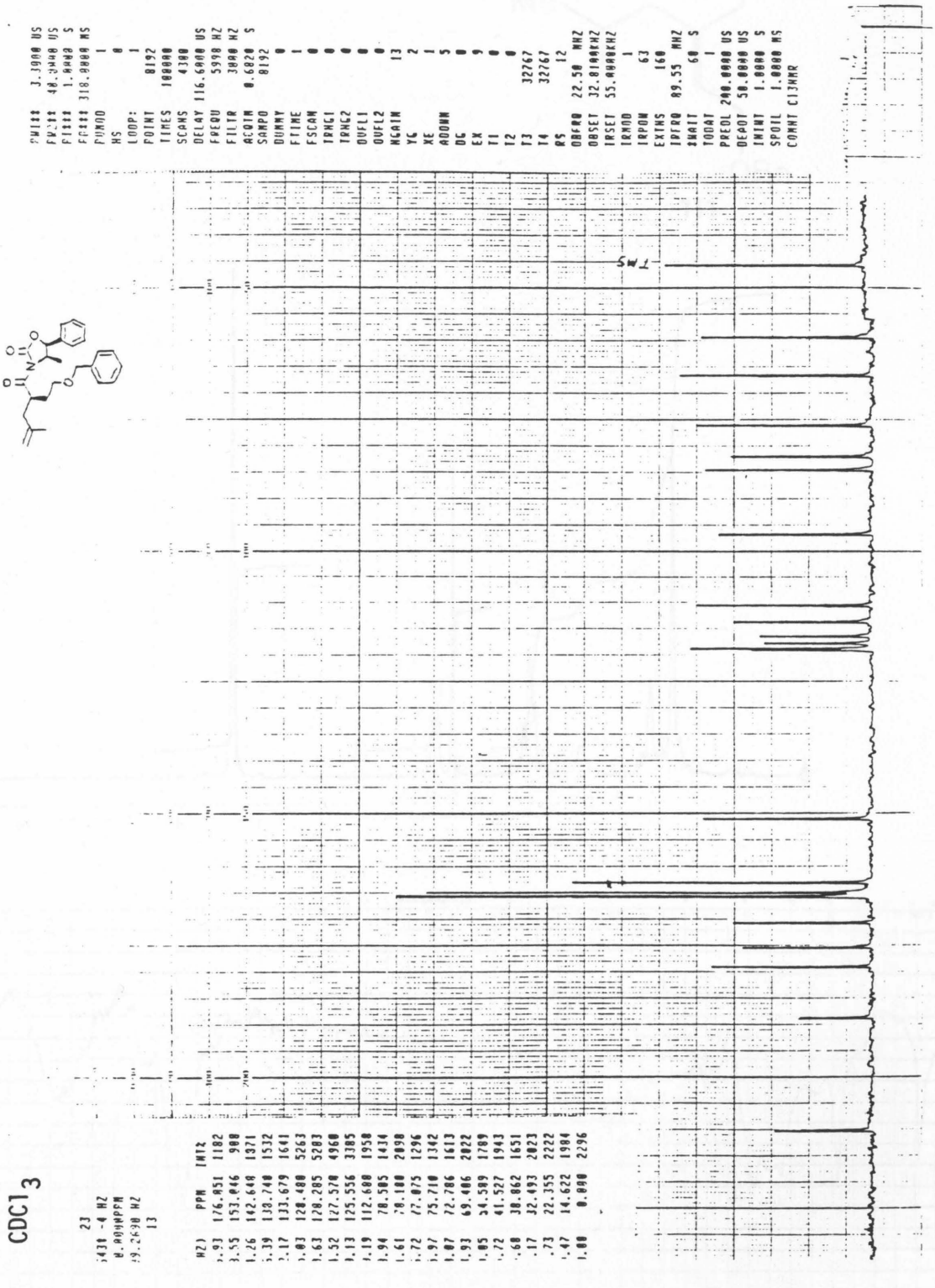
CCl_4

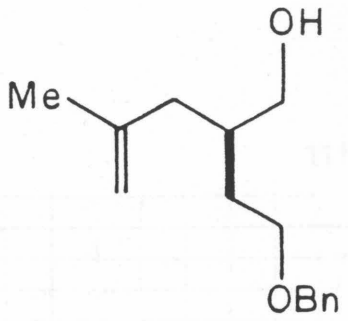


110 (cont.)



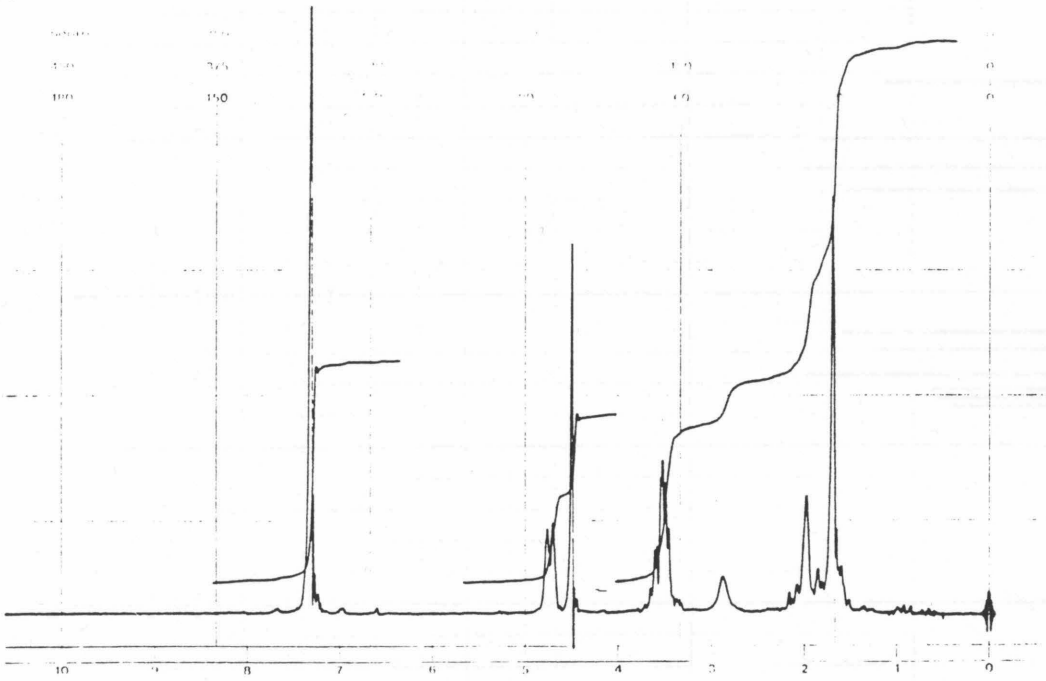
110 (cont.)



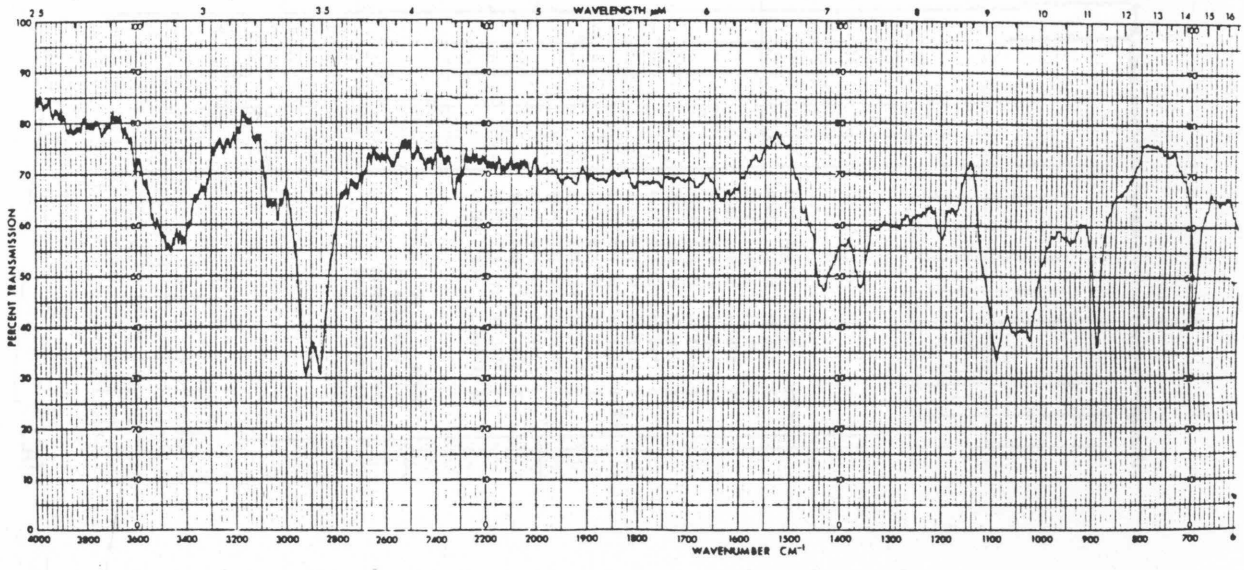


111

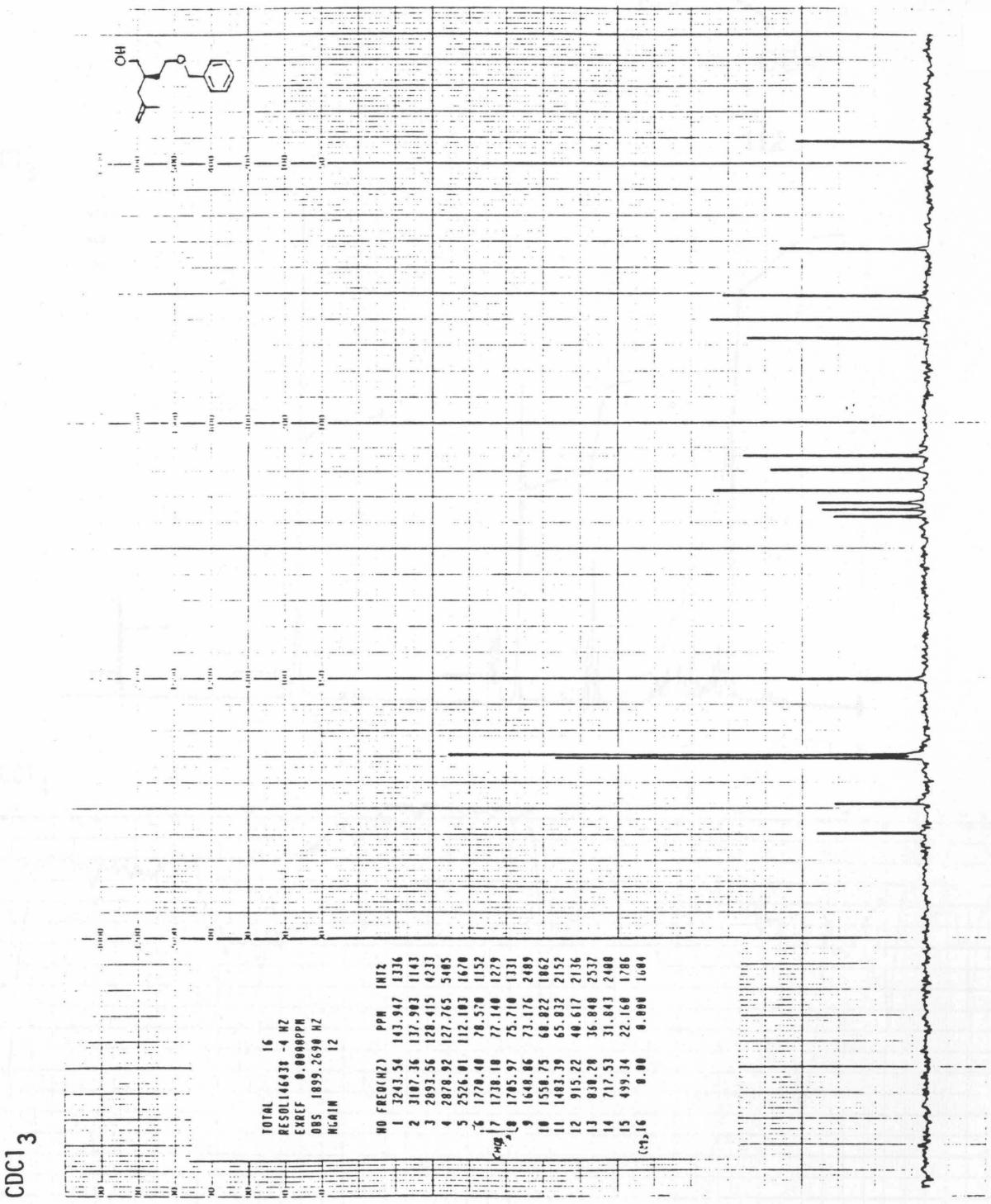
$CDCl_3$

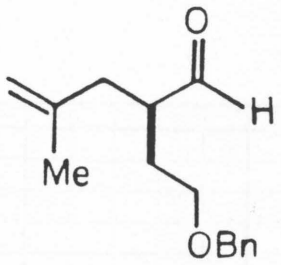


CCl_4



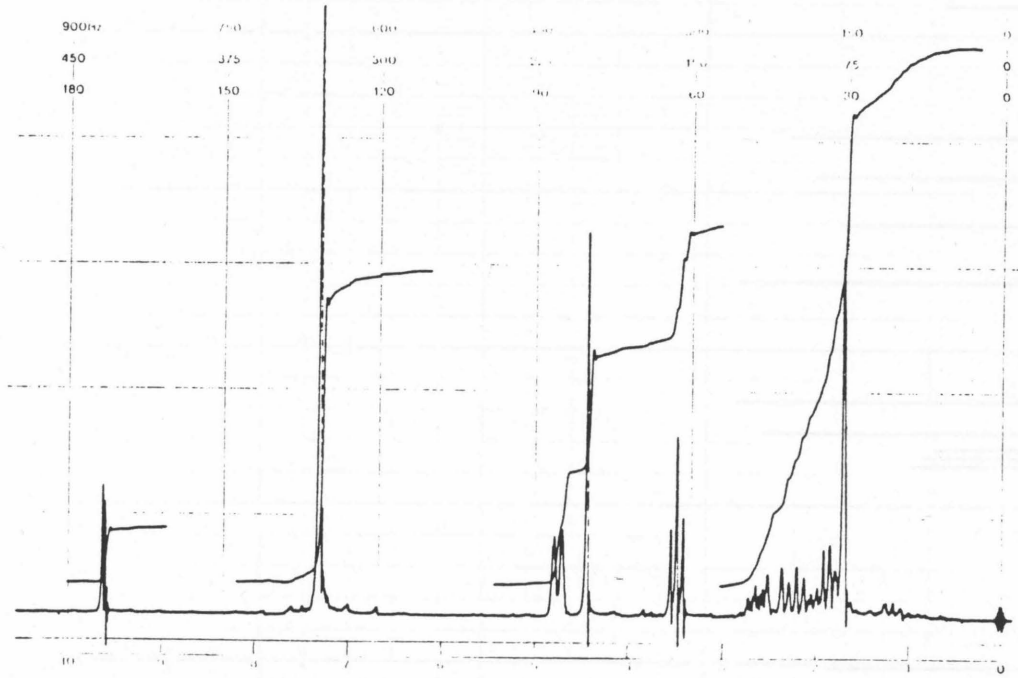
111 (cont.)


CDCl3
TOTAL 16
RESOL146431 -4 HZ
EXREF 0.0000PPM
OBS 1899.2690 HZ
NGAIN 12
NO FREQ(HZ) PPM INTZ
1 3243.54 143.947 1336
2 3107.36 137.903 1143
3 2893.56 128.415 4233
4 2870.92 127.765 5405
5 2526.81 112.103 1670
6 1770.40 78.570 1152
7 1738.18 77.140 1279
8 1705.97 75.710 1331
9 1640.86 73.176 2409
10 1558.75 68.822 1862
11 1483.39 65.832 2152
12 915.22 40.617 2136
13 838.28 36.840 2537
14 717.53 31.843 2400
15 499.34 22.160 1786
(1),16 0.00 0.000 1604

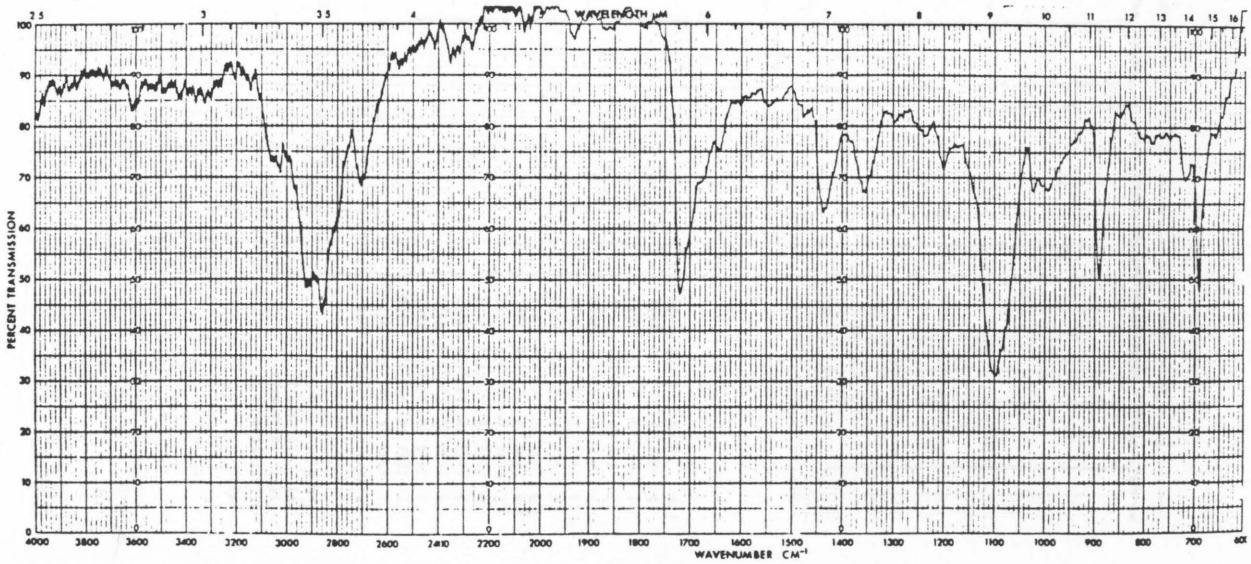


112

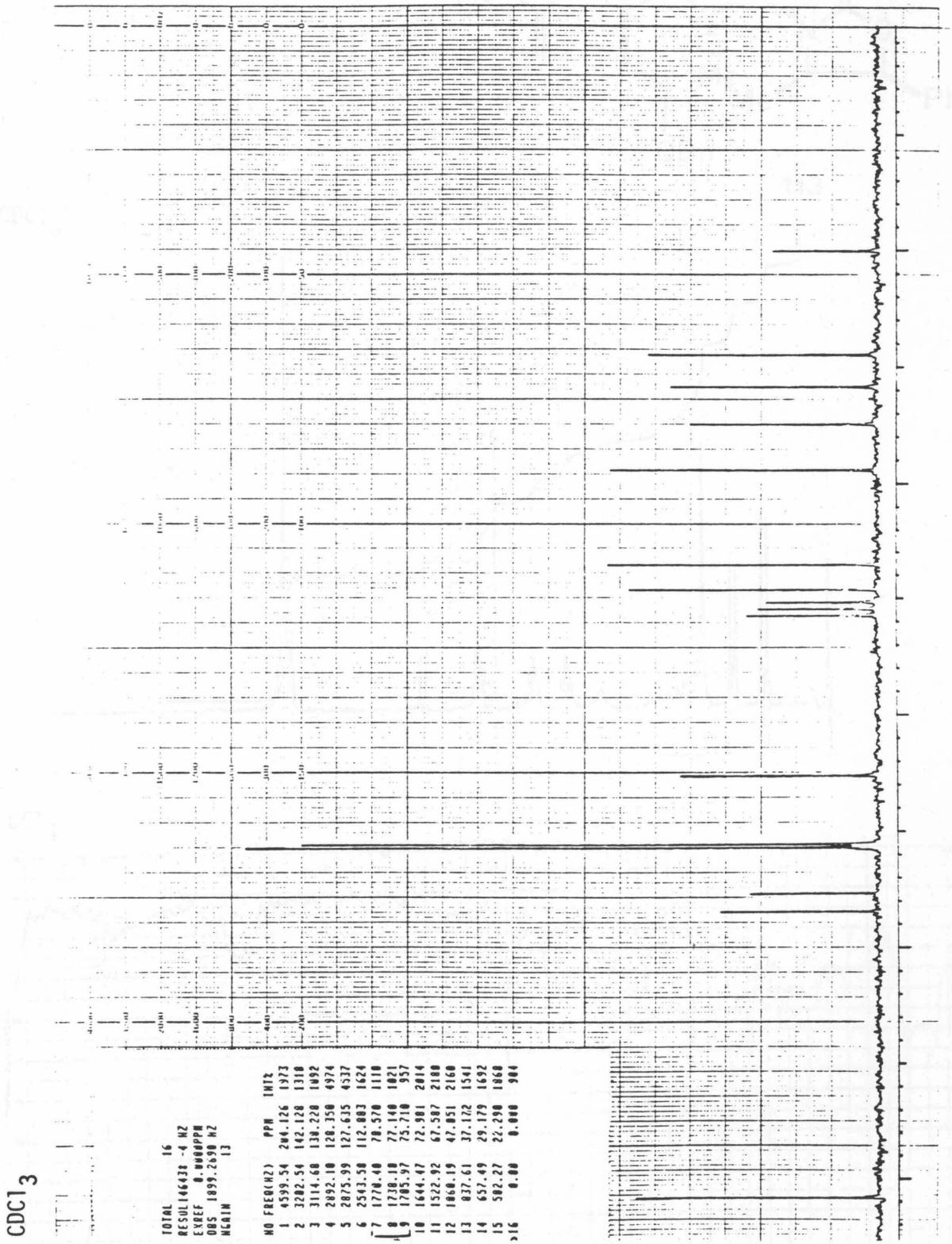
$CDCl_3$

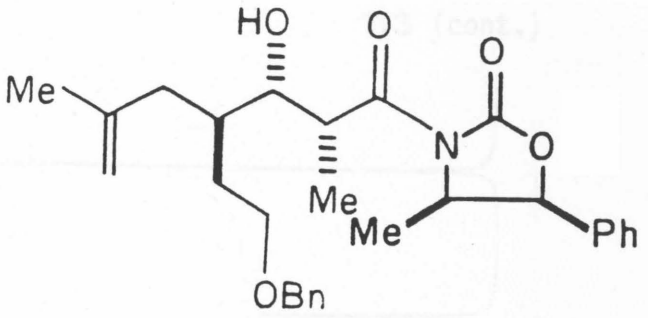


CCl_4



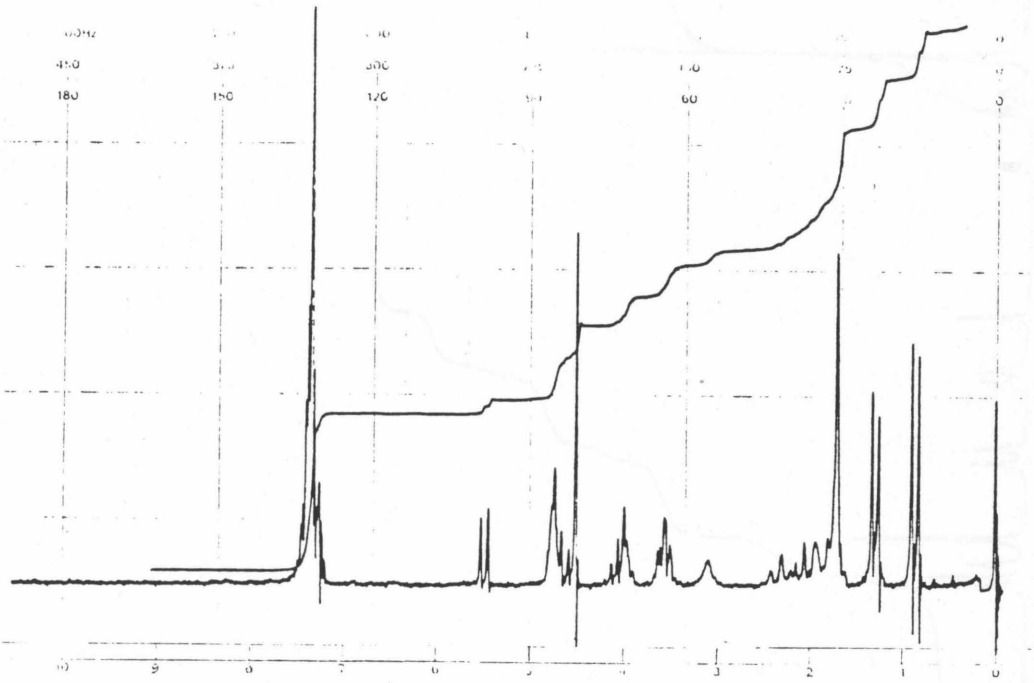
112 (cont.)


CDCl3
TOTAL 16
RESOL 146431 -4 HZ
EXREF 0.000PPM
OBS 1899.2690 HZ
NGAIN 13
NO FREQ(HZ) PPM INTI
1 4599.54 204.126 1973
2 3282.54 142.128 1310
3 3114.68 138.228 1092
4 2892.10 128.350 4974
5 2875.99 127.635 4537
6 2543.58 112.883 1624
7 1770.40 78.570 1110
8 1738.18 77.140 1021
9 1705.97 75.710 957
10 1644.47 72.981 2014
11 1522.92 67.587 2180
12 1060.19 47.051 2160
13 837.61 37.172 1541
14 657.49 29.179 1692
15 502.27 22.290 1868
>16 0.00 0.000 984

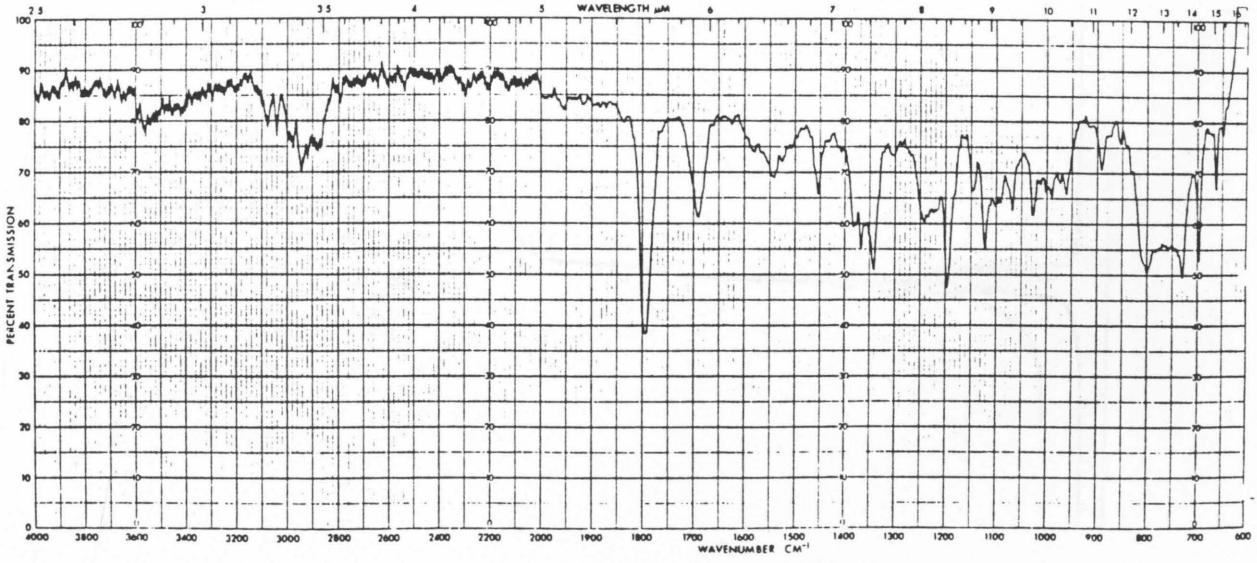


113

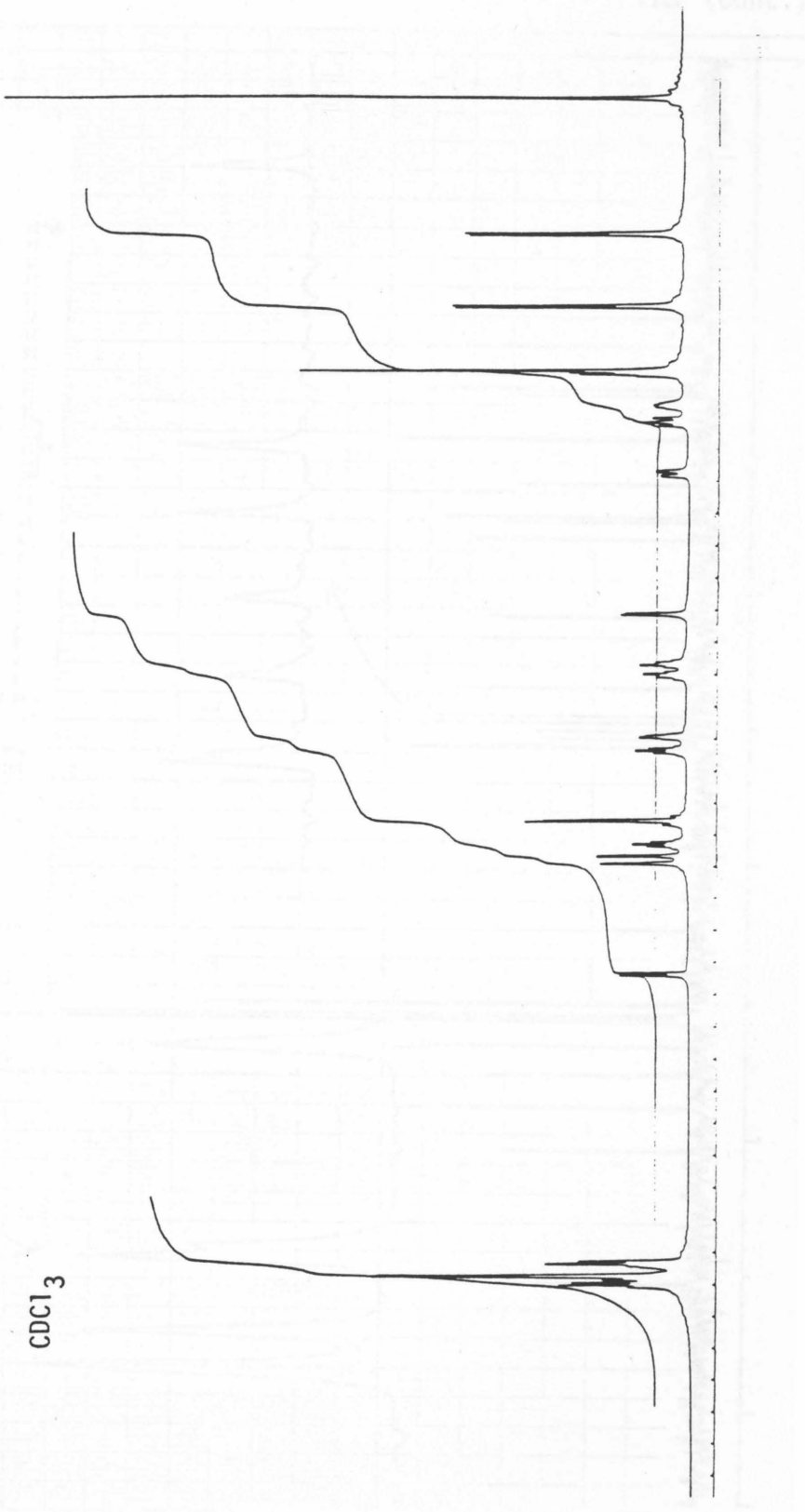
$CDCl_3$



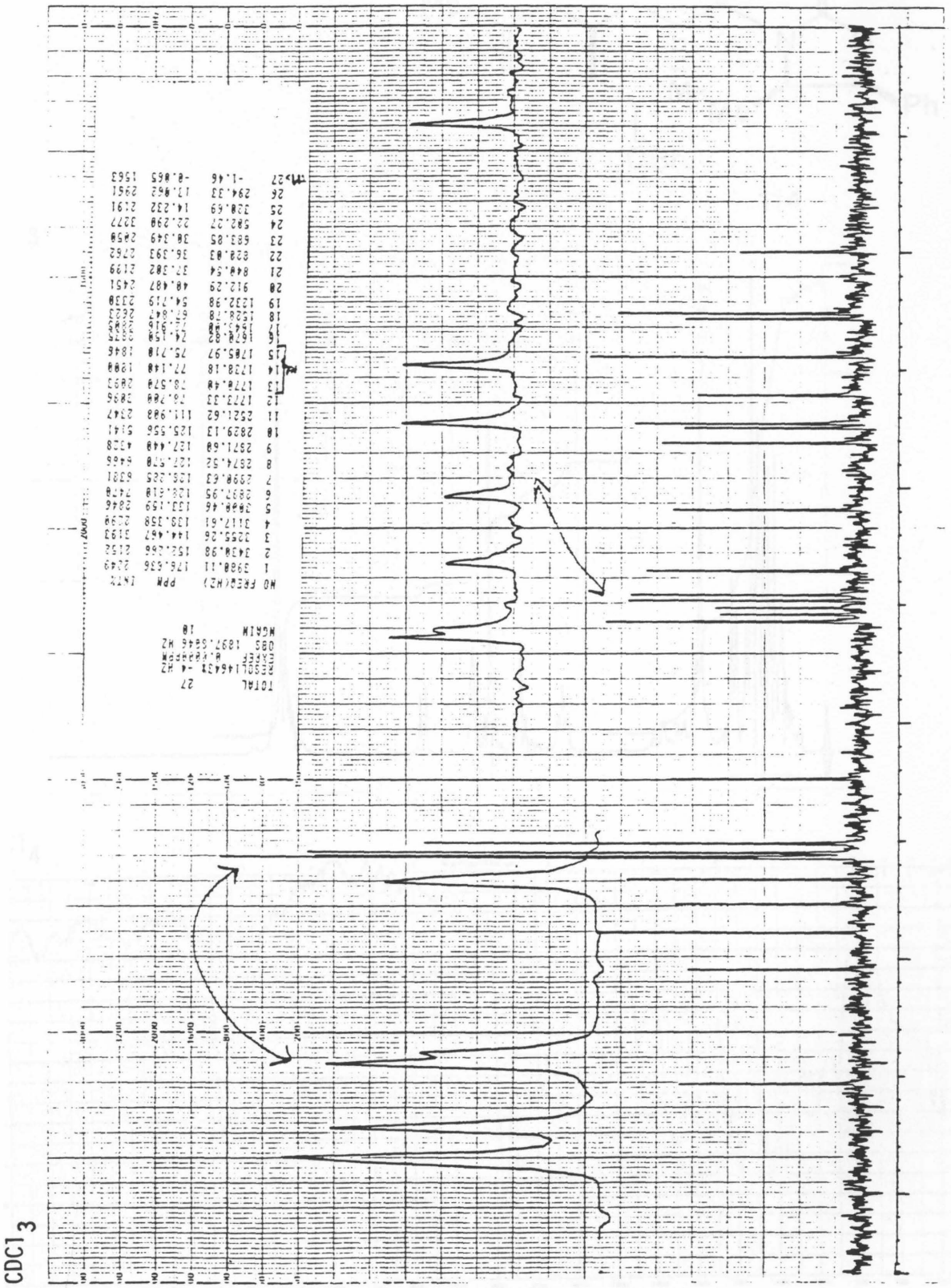
CCl_4

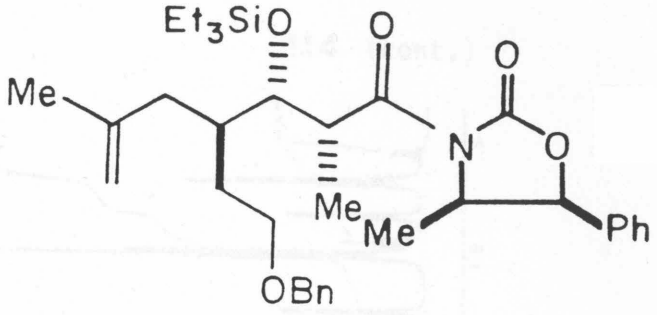


113 (cont.)



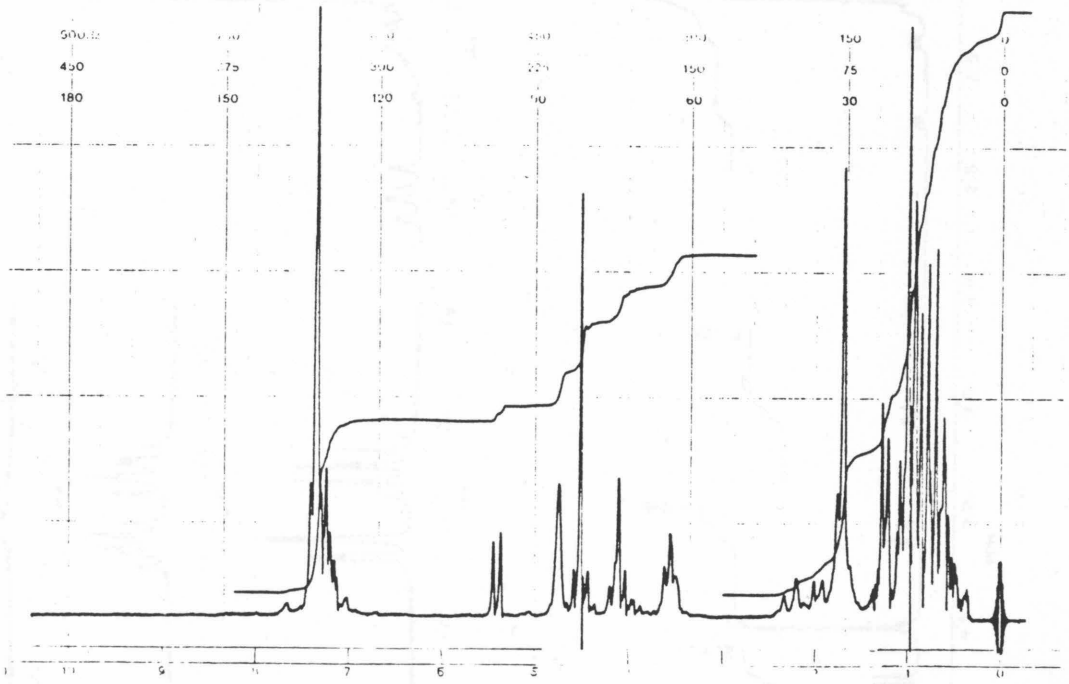
113 (cont.)



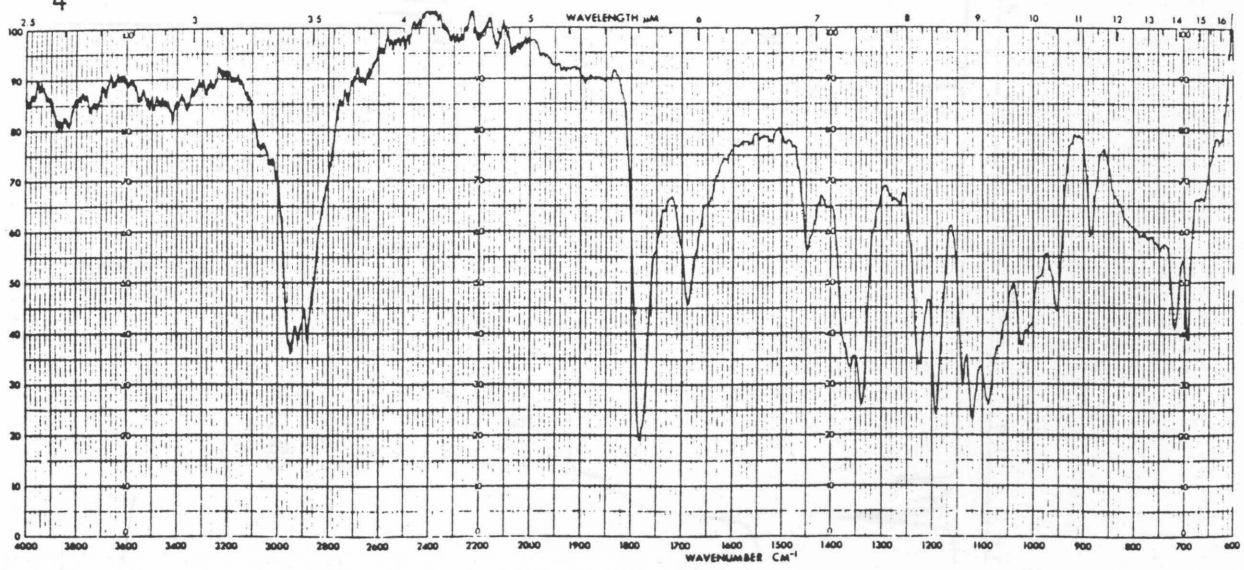


114

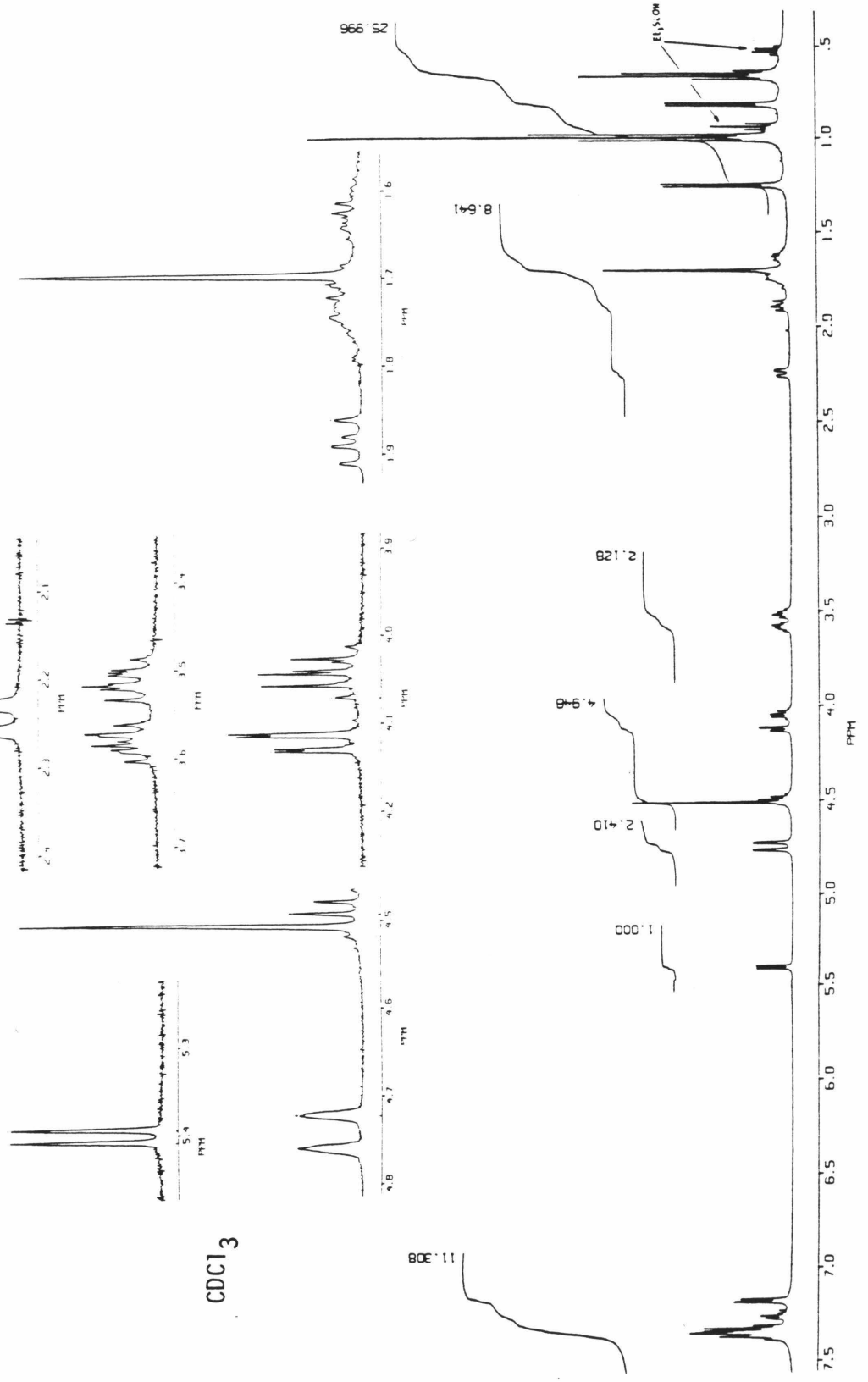
$CDCl_3$



CCl_4

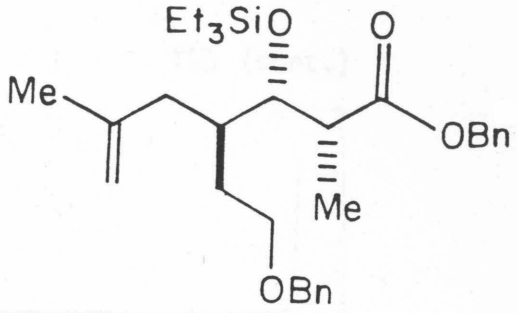


114 (cont.)



114 (cont.)

CDCl3
TOTAL 31
RESOL1464JS -4 HZ
ESREF 0.000PPM
OBS 1618.1127 HZ
NGAIN 12
NO FREQ(HZ) PPM IMTG
1 3966.93 176.851 2416
2 3435.37 152.461 2176
3 3261.11 144.727 2984
4 3135.18 139.130 1923
5 3004.65 133.354 3180
6 2893.42 128.675 8549
7 2892.10 128.350 5145
8 2870.13 127.375 9888
9 2832.06 125.686 5618
10 2515.76 111.648 2617
11 1776.26 78.838 3758
12 1771.87 78.635 2416
13 1739.65 77.205 2324
14 1707.43 75.775 2473
15 1701.84 75.500 3210
16 1648.87 72.786 3335
17 1546.35 68.627 2832
18 1240.30 55.044 2872
19 945.97 41.982 2963
20 853.71 37.887 2696
21 844.93 37.497 2684
22 787.28 34.389 2344
23 506.66 22.485 3001
24 345.58 15.337 3635
25 322.15 14.297 3446
26 161.07 7.148 6643
27 155.22 6.888 1615
28 147.89 6.563 1119
29 127.39 5.653 8413
30 98.11 4.354 542
31 1.46 0.064 6284



115

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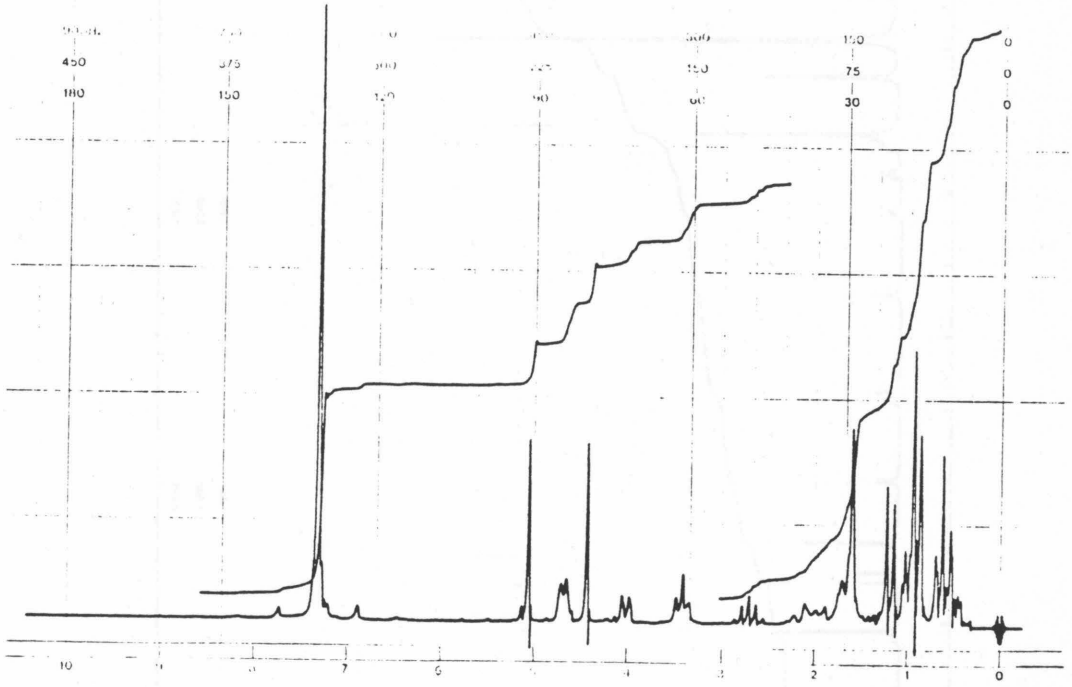
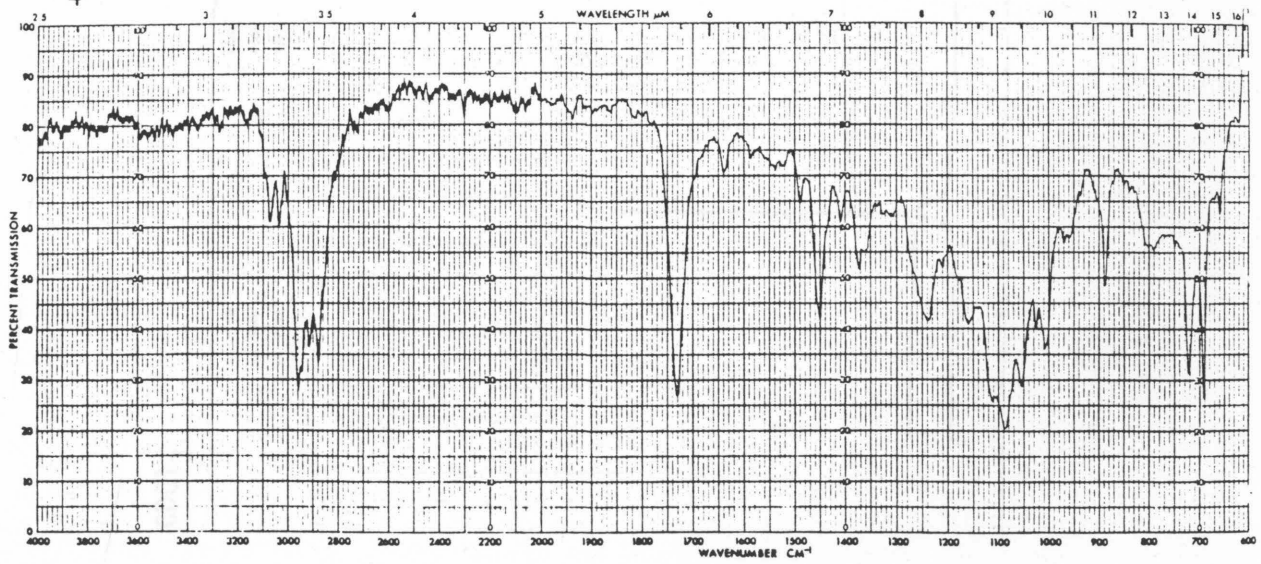
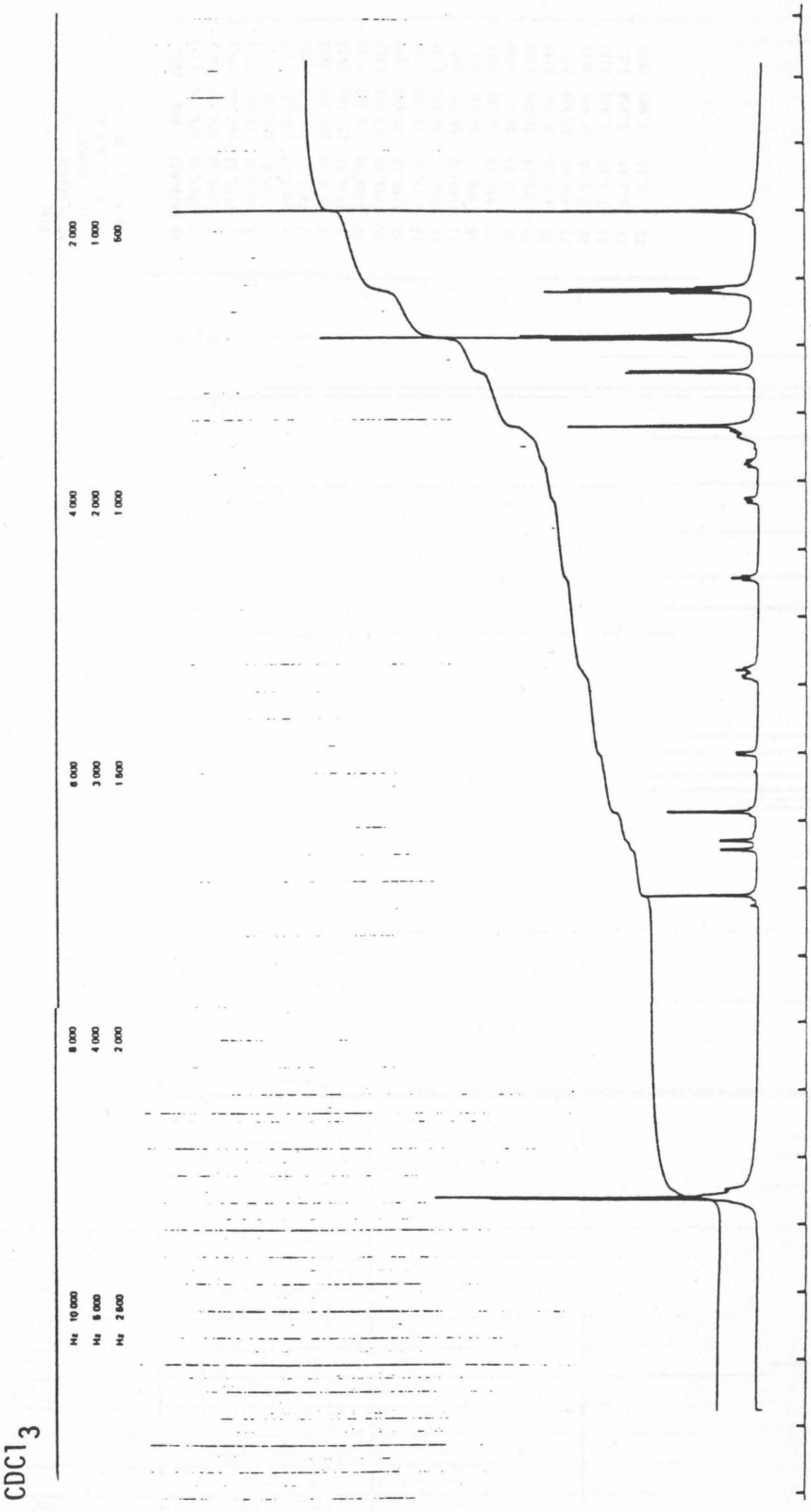


CCl_4

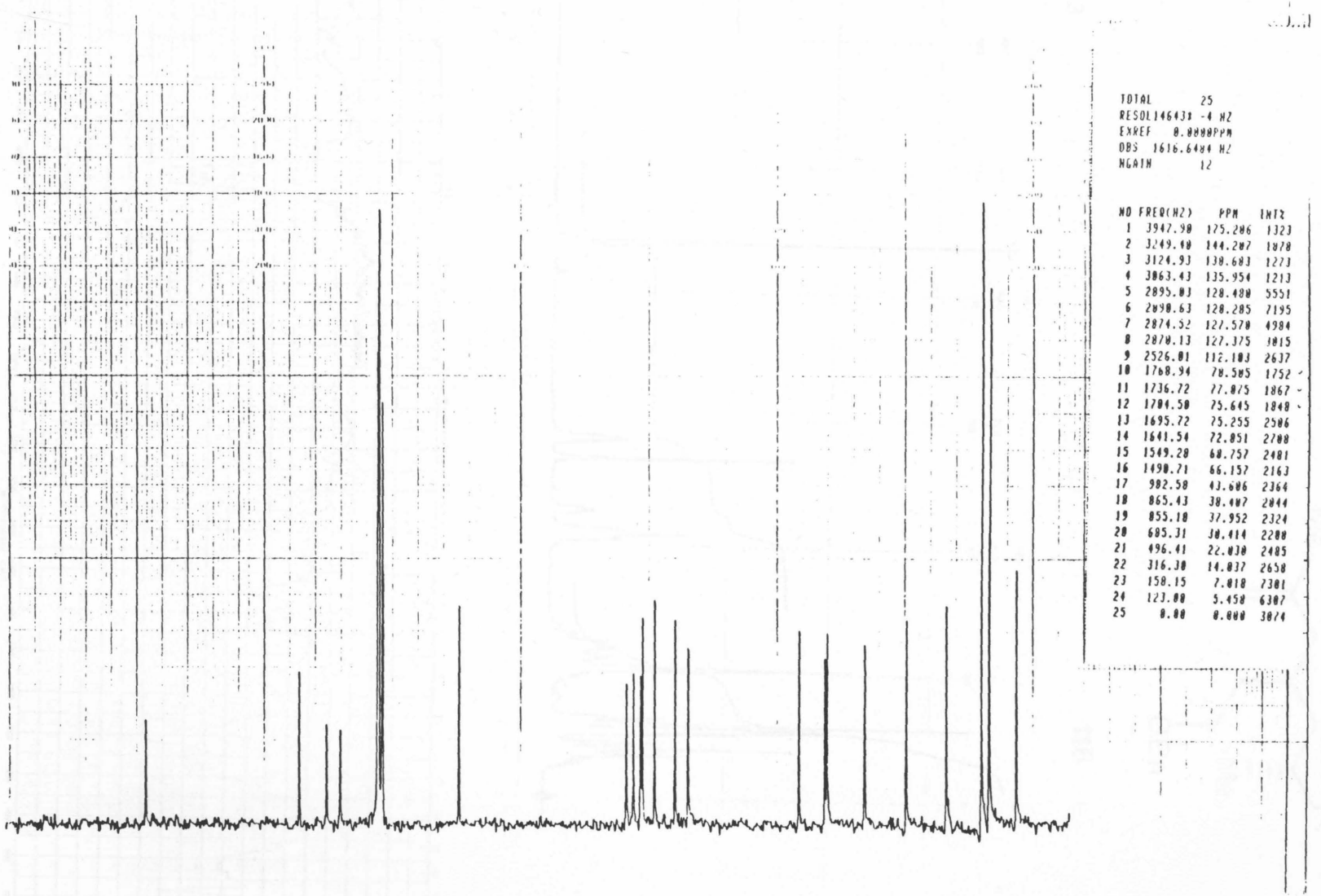


115 (cont.)


CDCl3
Hz 10 000
Hz 8 000
Hz 2 500
8 000
4 000
2 000
8 000
4 000
2 000
6 000
3 000
1 500
4 000
2 000
1 000
2 000
1 000
500

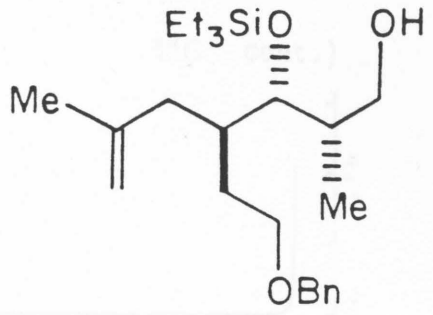
115 (cont.)

$CDCl_3$



TOTAL 25
RESOL 1464 31 -4 HZ
EXREF 0.0000PPM
OBS 1616.6484 HZ
NGAIN 12

NO	FREQ(HZ)	PPM	INTZ
1	3947.90	125.286	1323
2	3249.40	144.207	1078
3	3124.93	138.683	1273
4	3063.43	135.954	1213
5	2895.03	128.480	5551
6	2890.63	128.285	7195
7	2874.52	127.570	4984
8	2870.13	127.375	3015
9	2526.01	112.103	2637
10	1768.94	78.505	1752
11	1736.72	77.075	1867
12	1704.50	75.645	1848
13	1695.72	75.255	2586
14	1641.54	72.851	2788
15	1549.20	68.757	2481
16	1490.71	66.157	2163
17	982.58	43.606	2364
18	865.43	38.407	2844
19	855.18	37.952	2324
20	685.31	30.414	2288
21	496.41	22.030	2485
22	316.30	14.037	2658
23	158.15	7.018	7301
24	123.00	5.458	6307
25	0.00	0.000	3874



116

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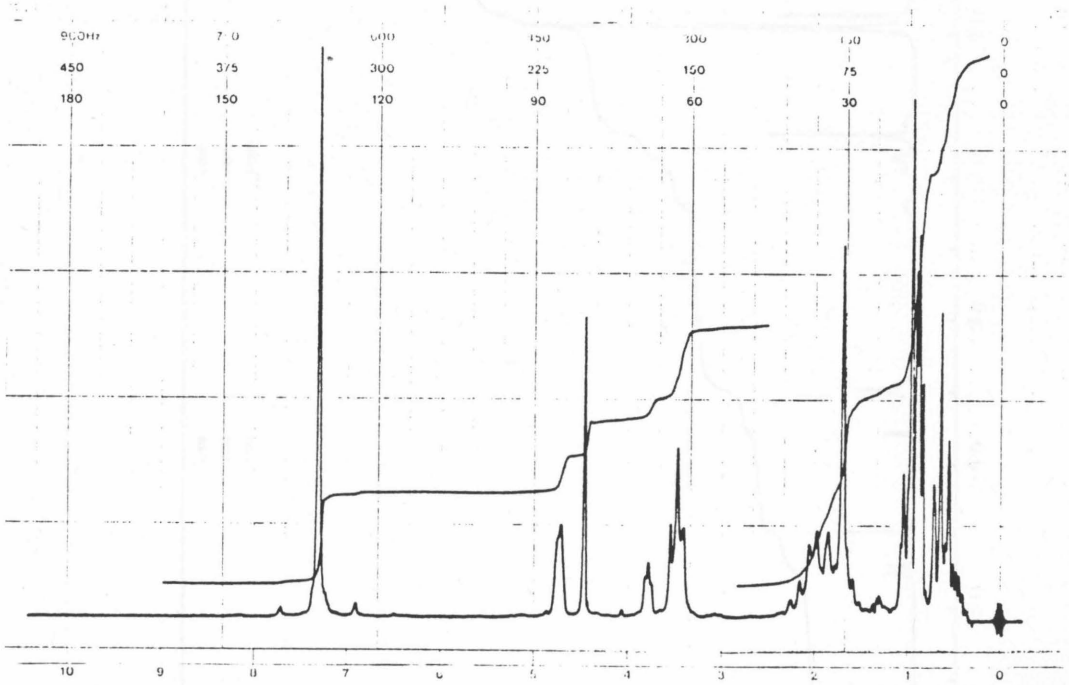
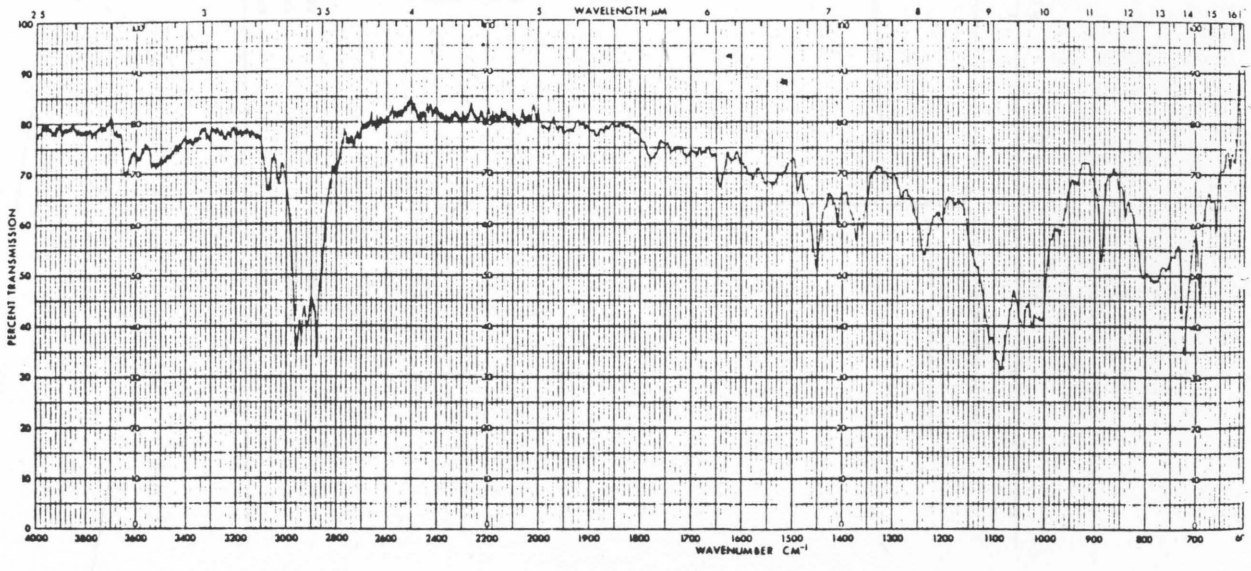
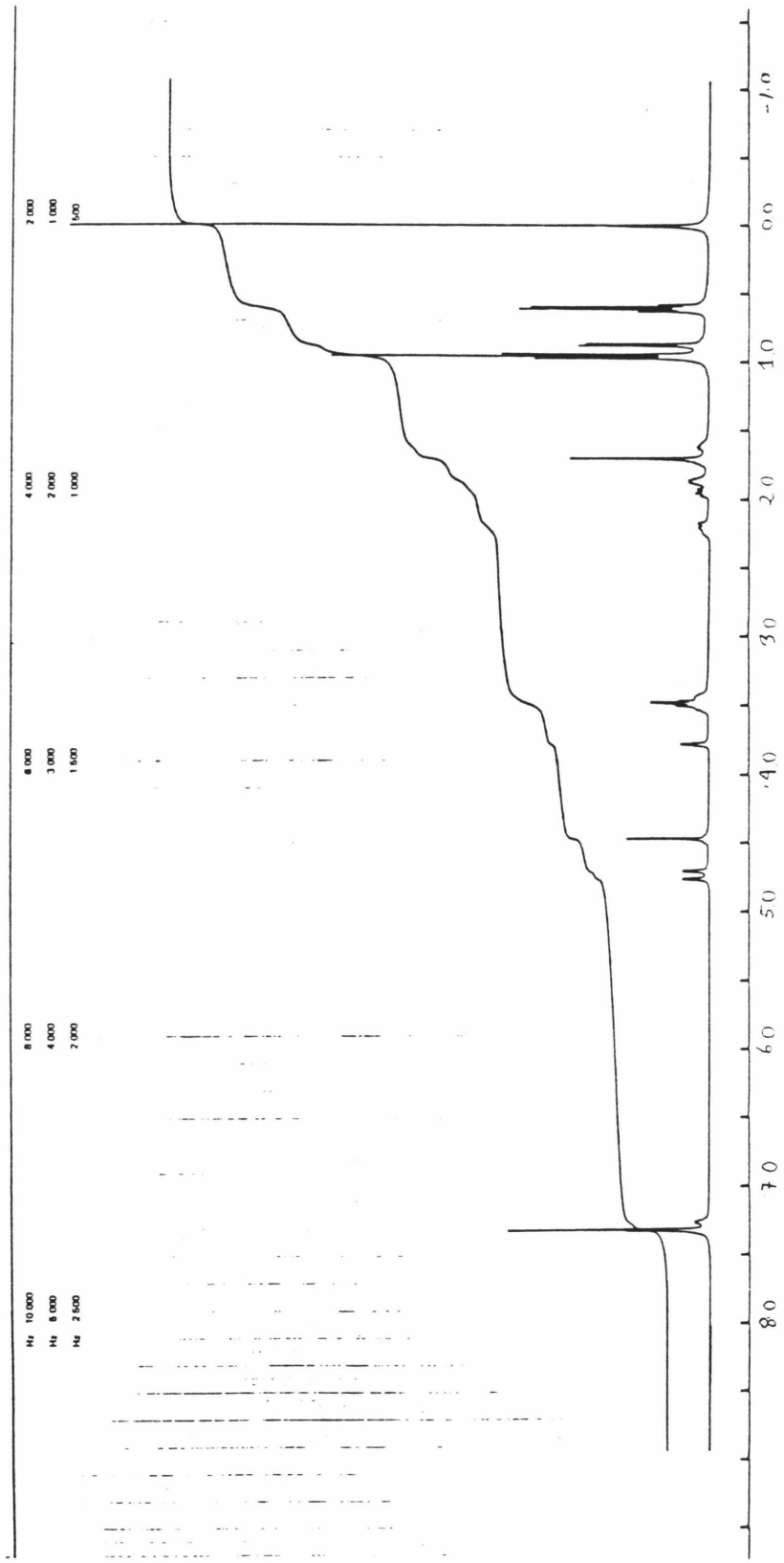


CCl_4



116 cont.)


CDCl3
10.000
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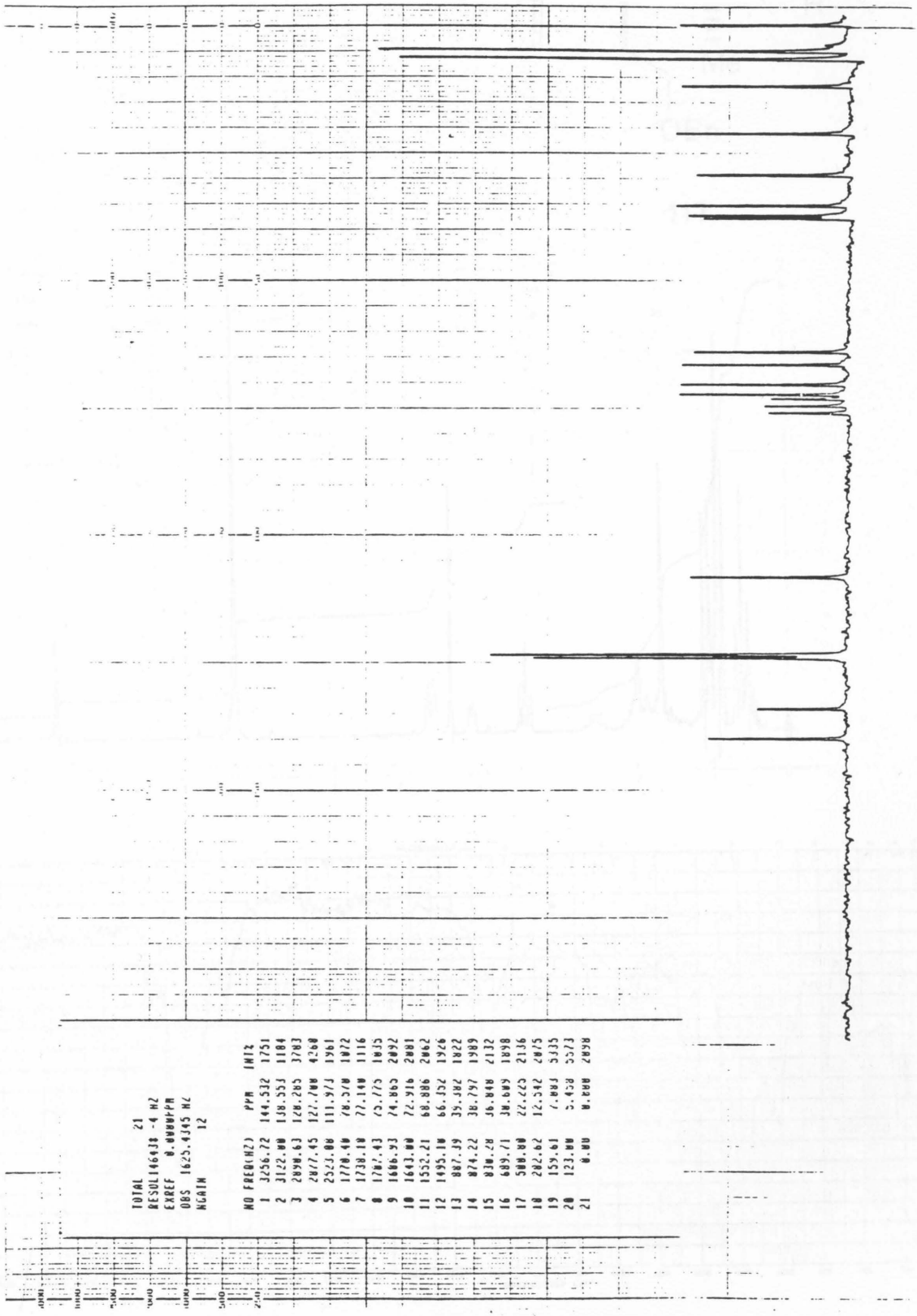
2.500
8.000
4.000
2.000
4.000
2.000
1.000
2.000
1.000
500
8.000
3.000
1.500
80
70
60
50
40
30
20
10
00
-10

116 (cont.)


CDCl3
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RESOL1464J$ -4 HZ
EXREF 0.0000PPM
OBS 1625.4345 MZ
NGAIN 12
NO FREQ(HZ) PPM INTG
1 3256.72 144.532 1751
2 3122.00 138.555 1184
3 2898.63 128.685 3783
4 2877.45 127.700 4260
5 2523.00 111.971 1961
6 1770.40 78.570 1072
7 1738.10 77.140 1116
8 1707.43 75.775 1035
9 1666.93 73.965 2092
10 1643.00 72.916 2001
11 1552.21 68.886 2062
12 1495.10 66.352 1926
13 887.39 39.382 1822
14 874.22 38.797 1989
15 838.28 36.848 2132
16 689.71 30.609 1898
17 500.00 22.225 2136
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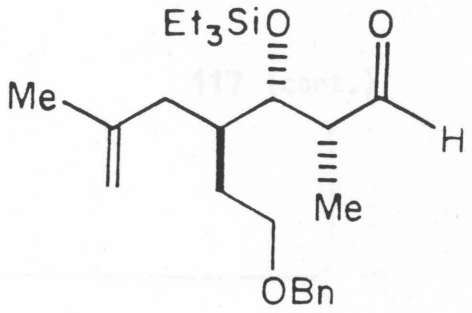
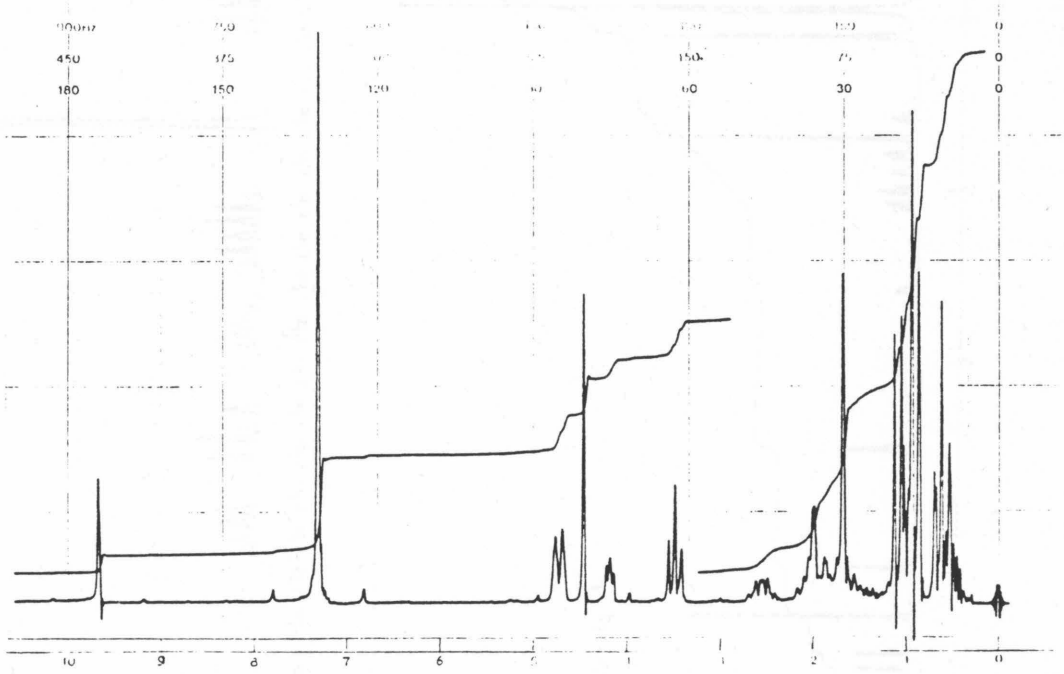


$CDCl_3$ **117**



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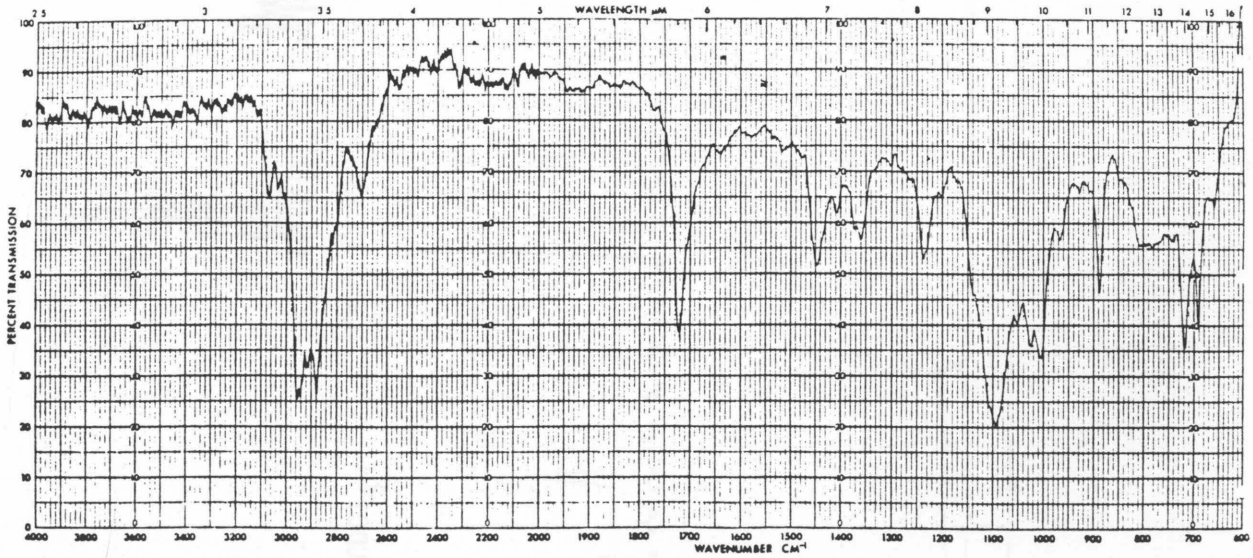
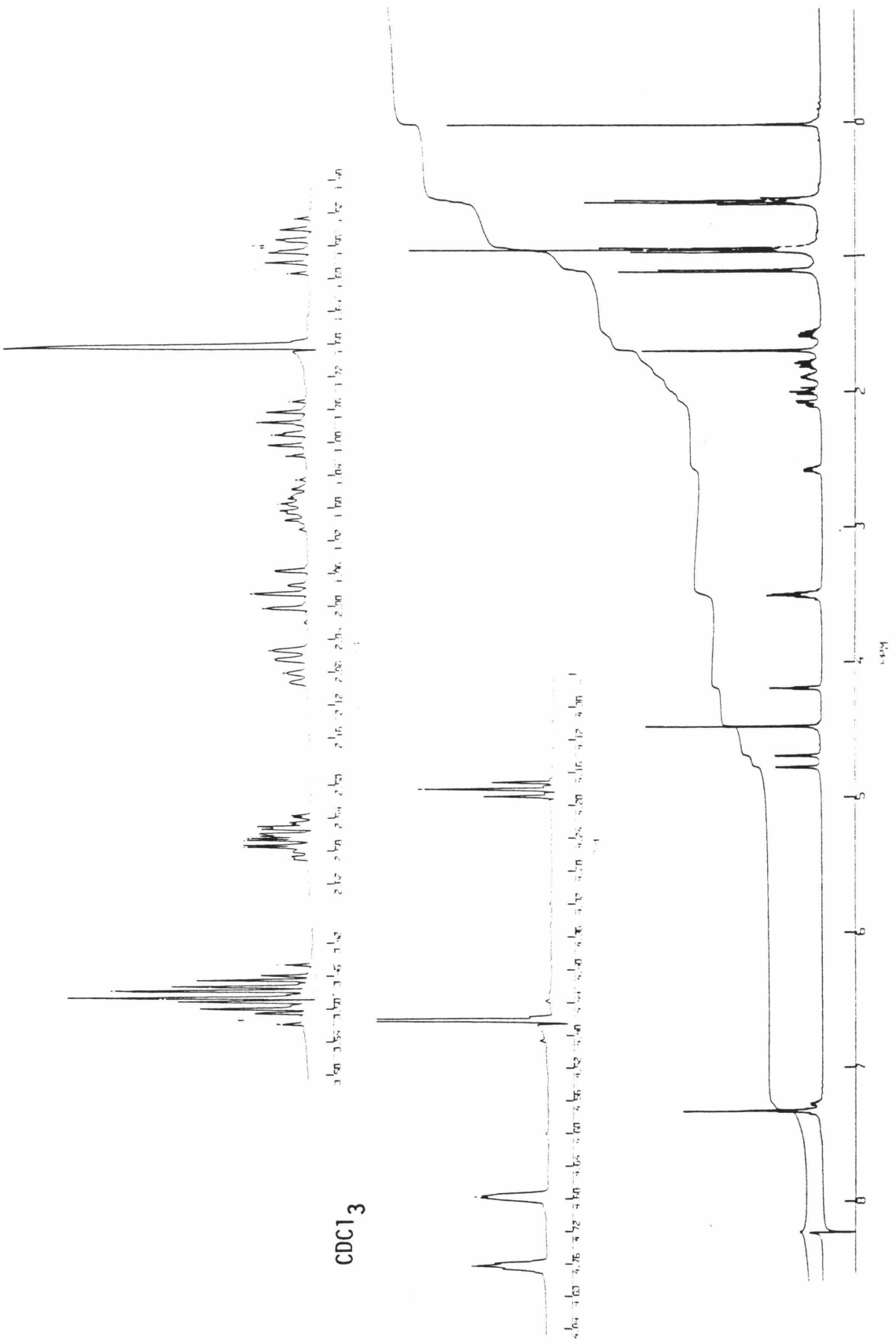
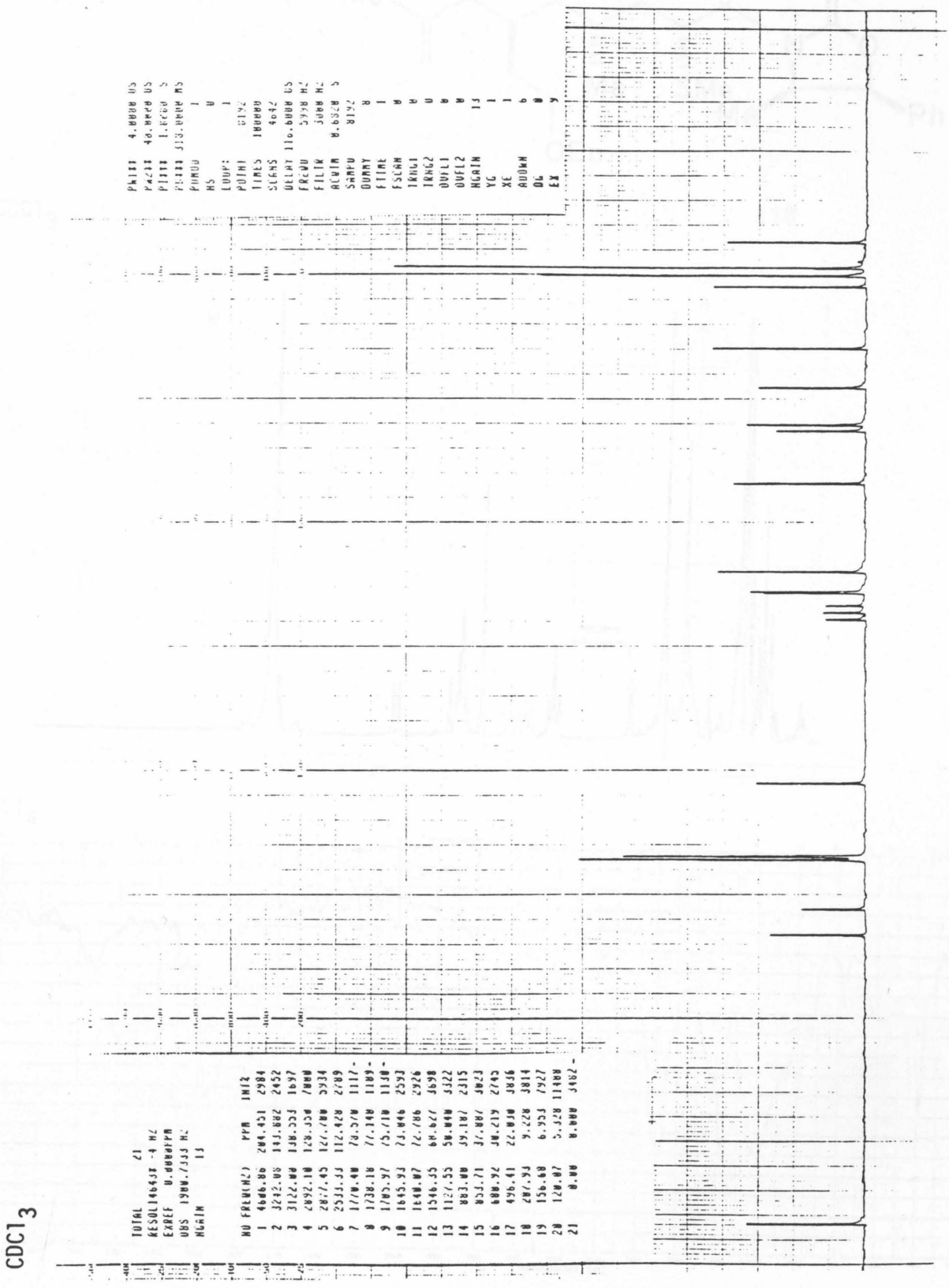
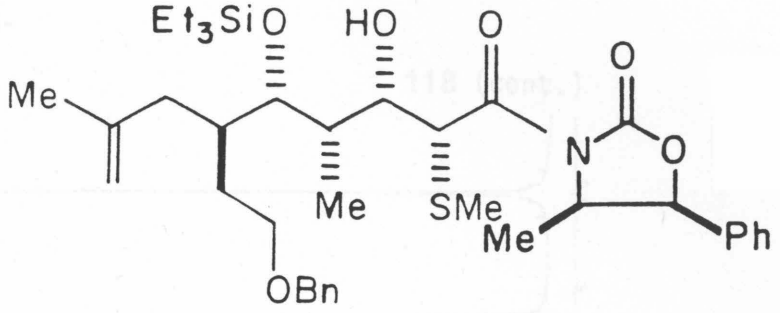


117 (cont.)



117 (cont.)





118

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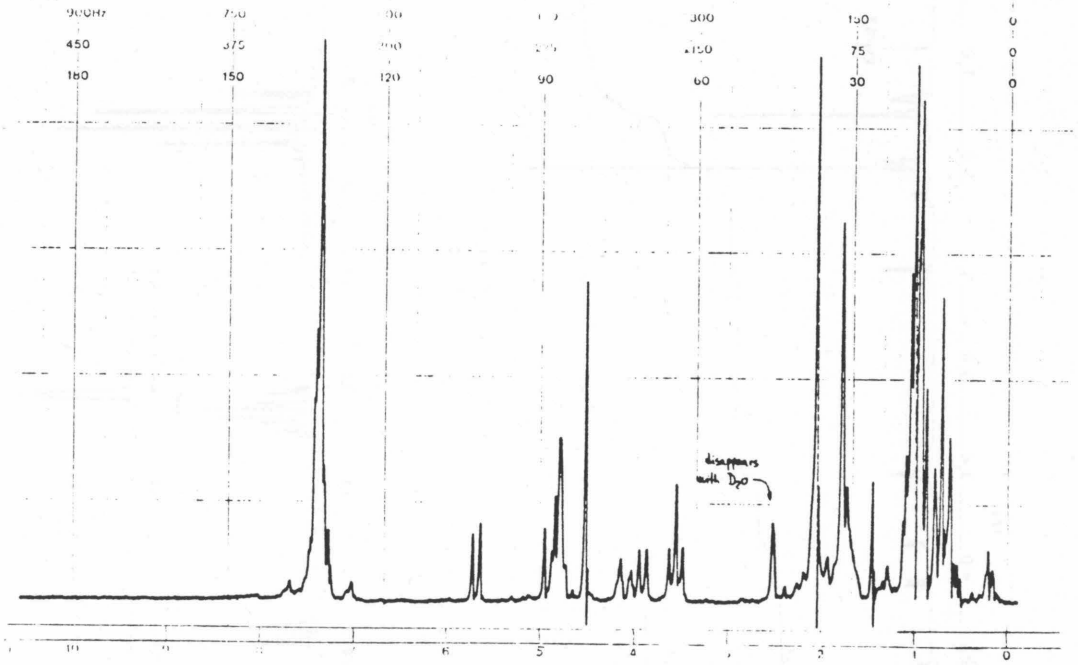

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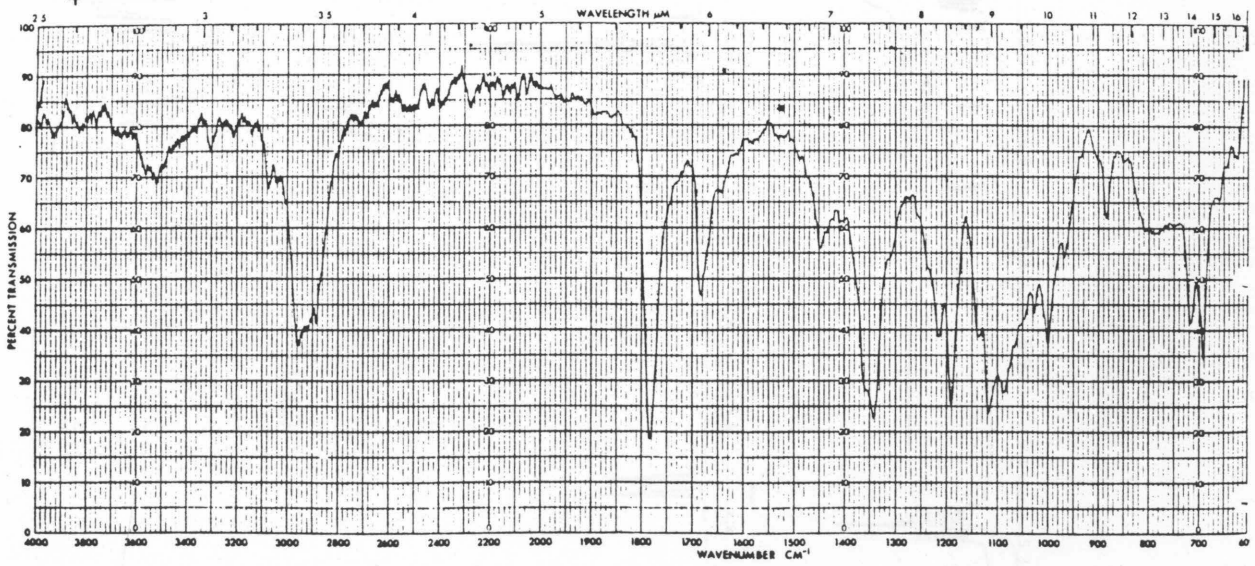

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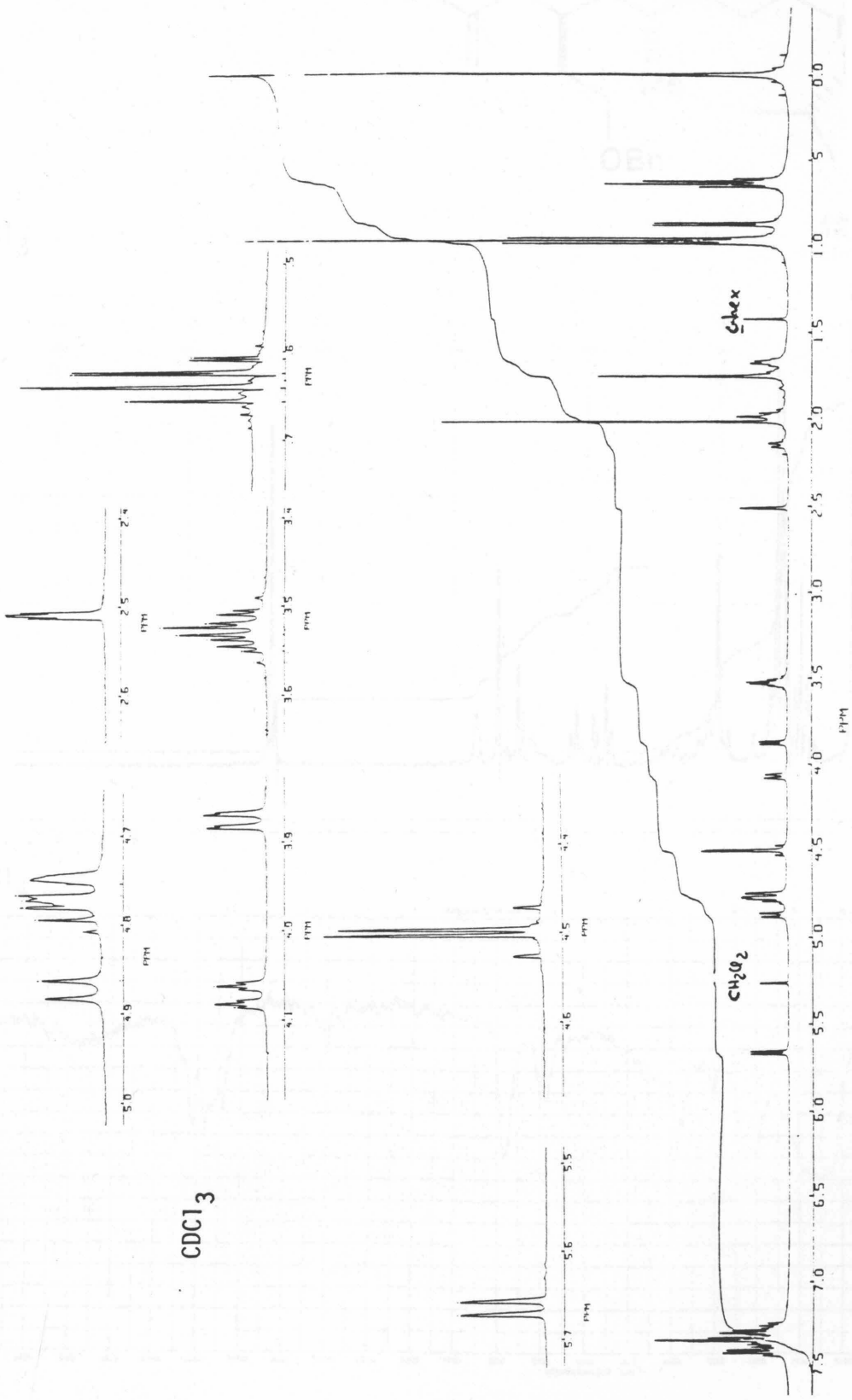

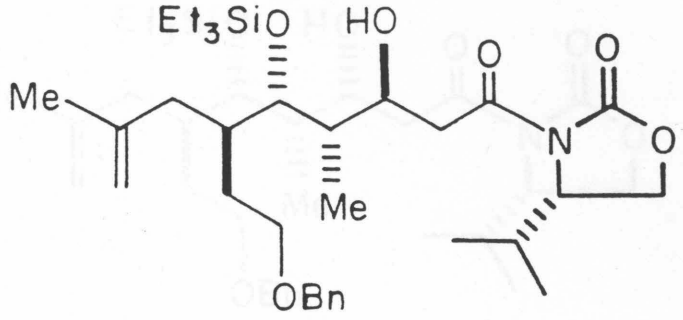

125

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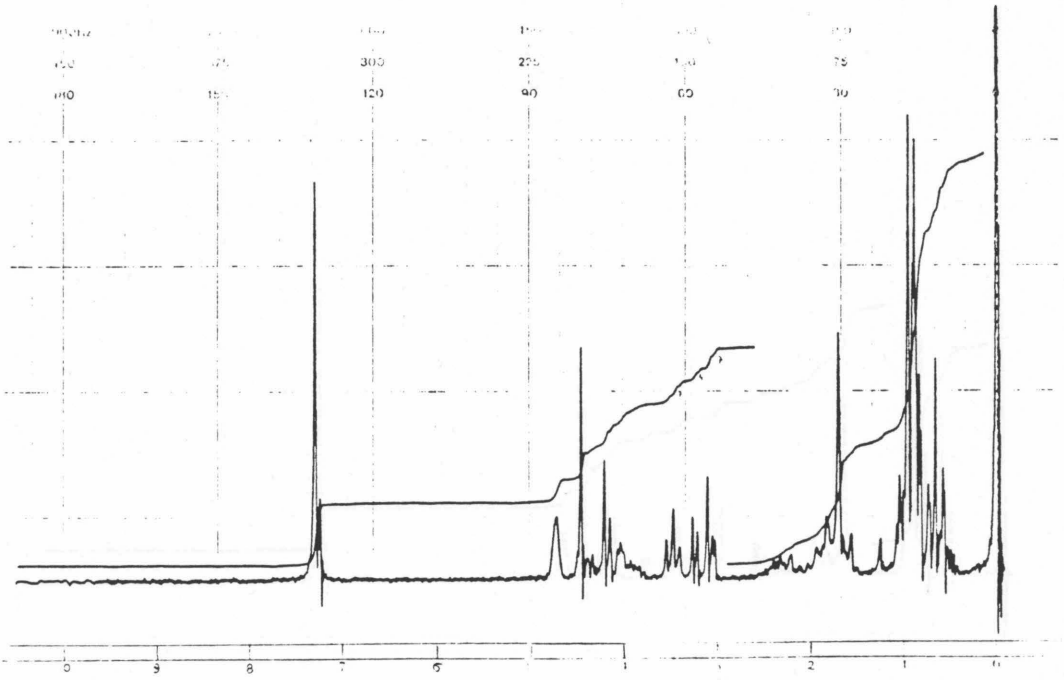

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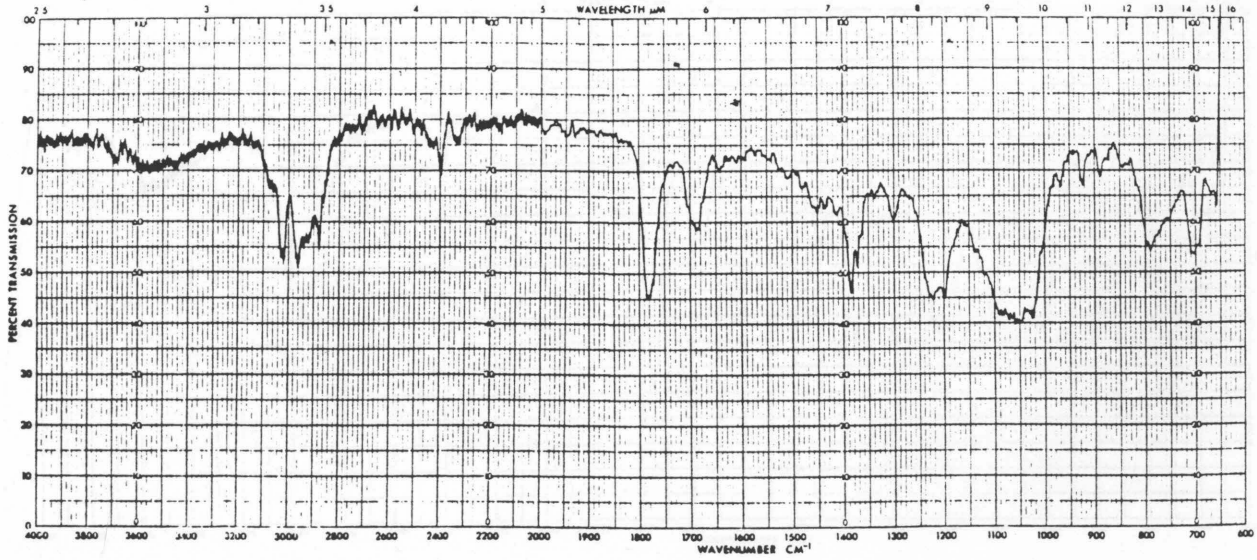

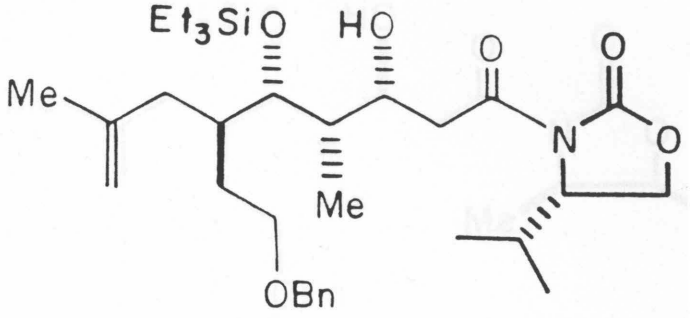

123

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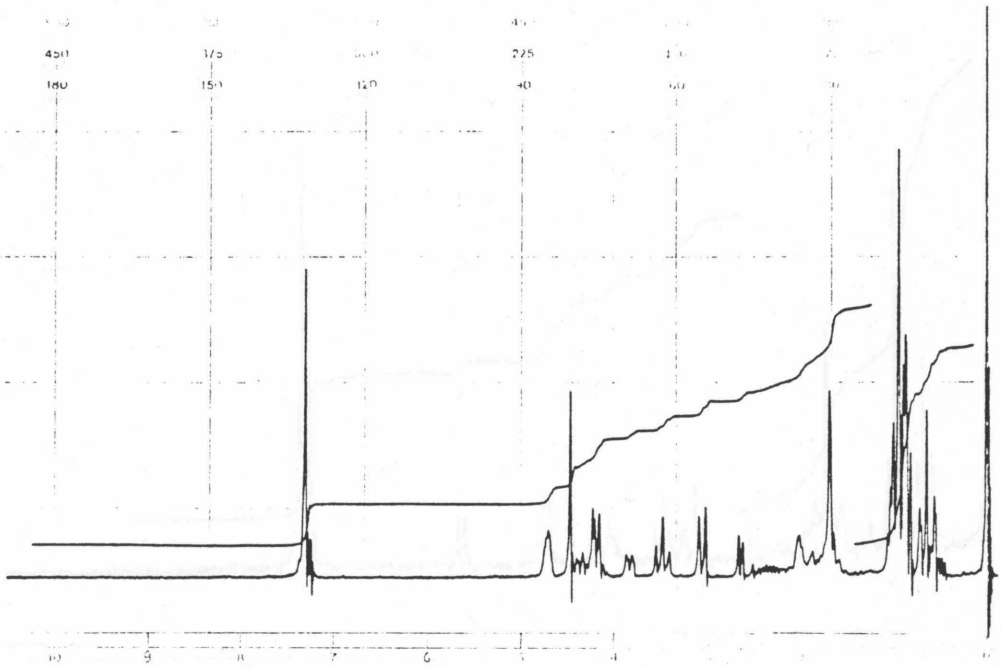

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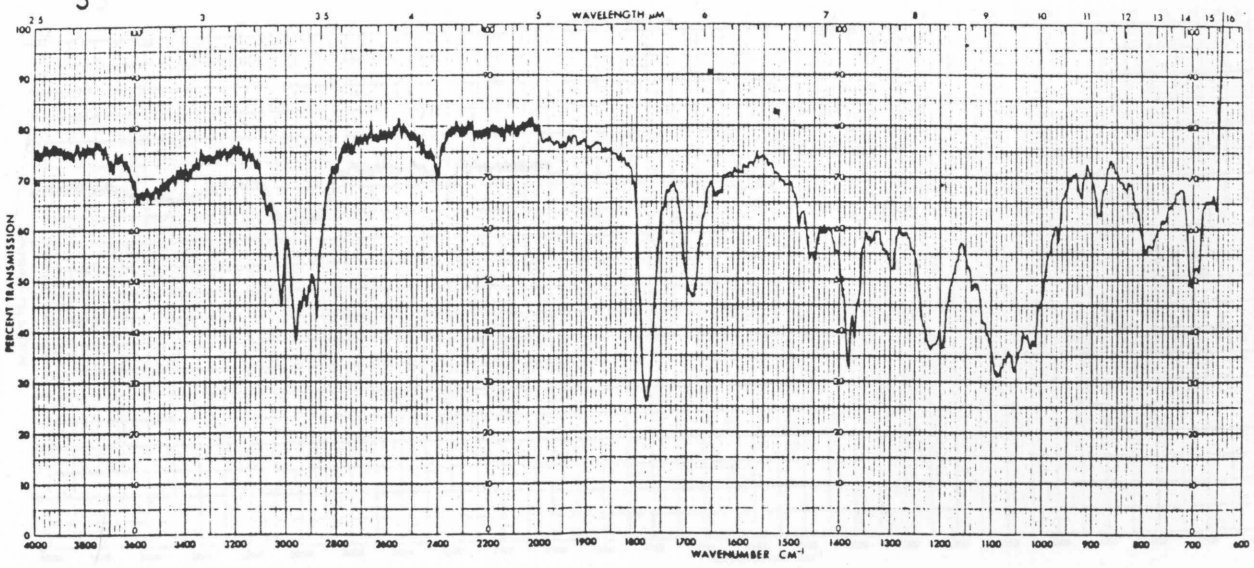

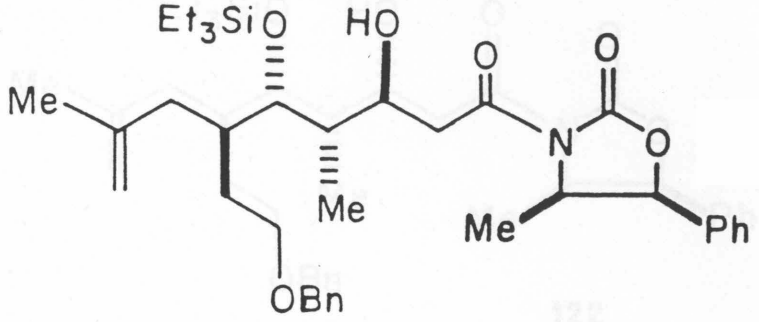

124

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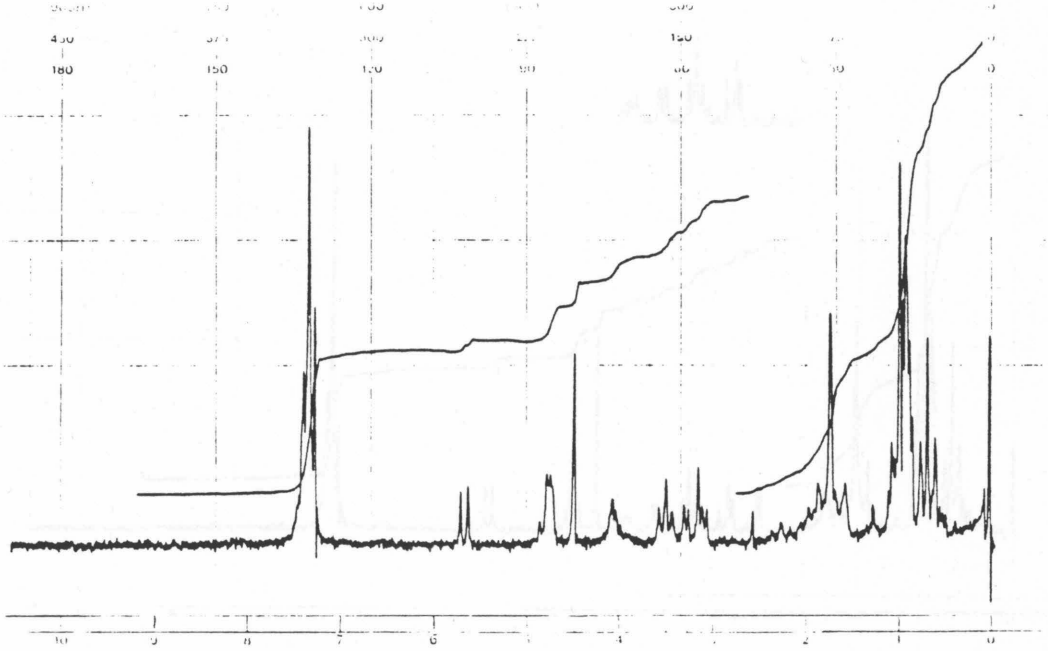

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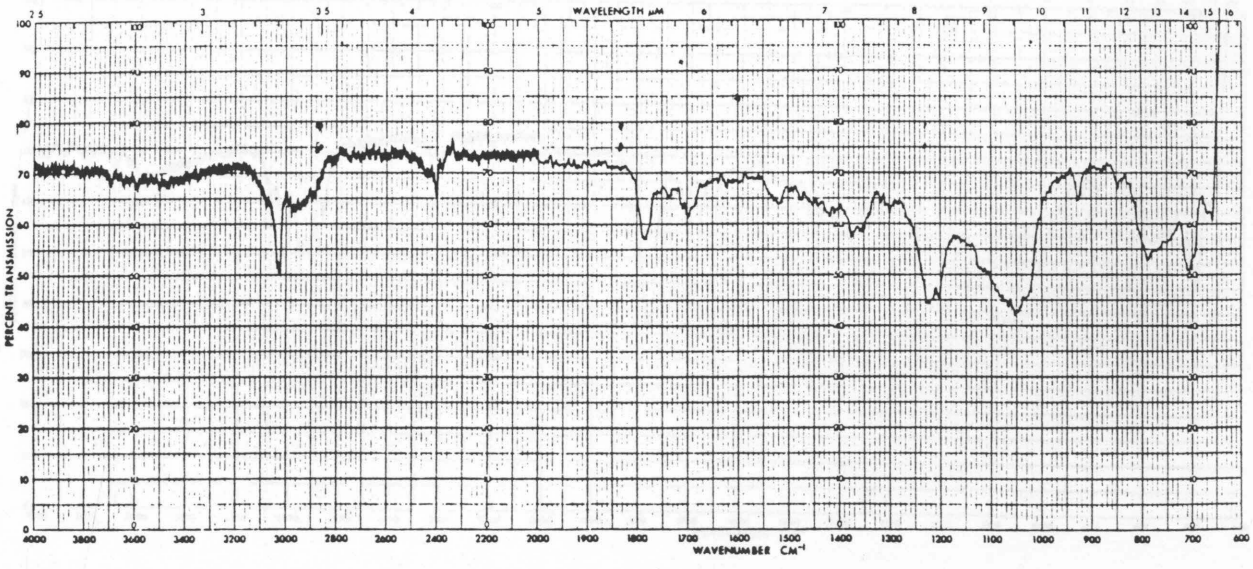

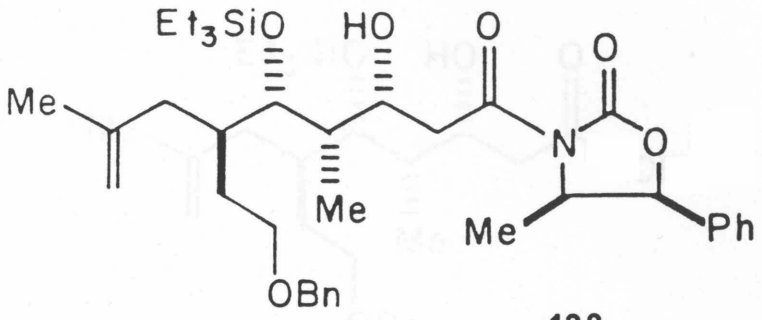

122

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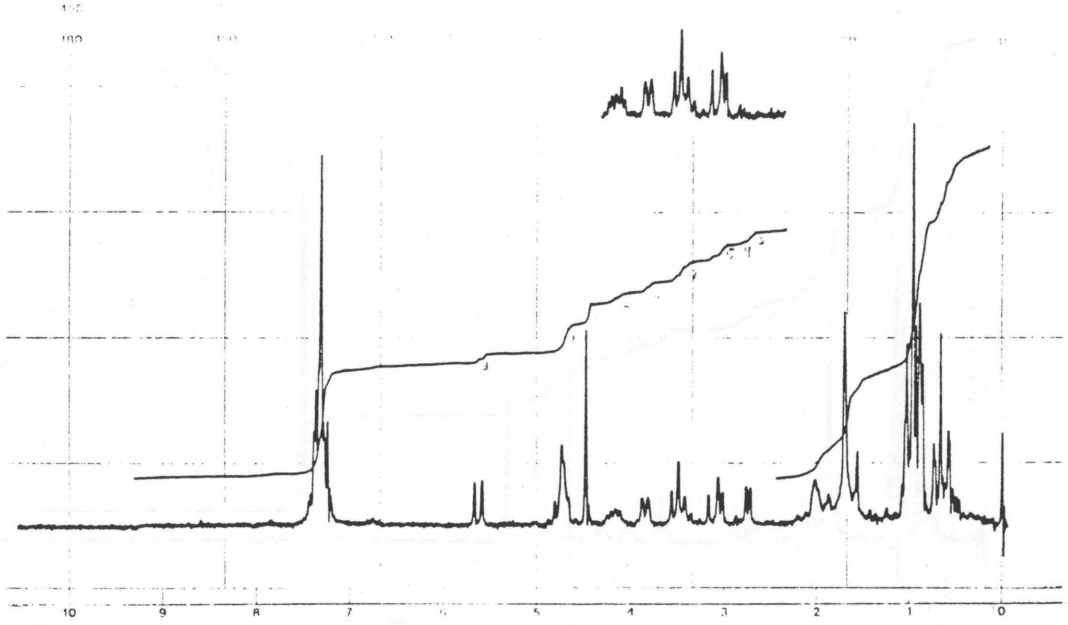

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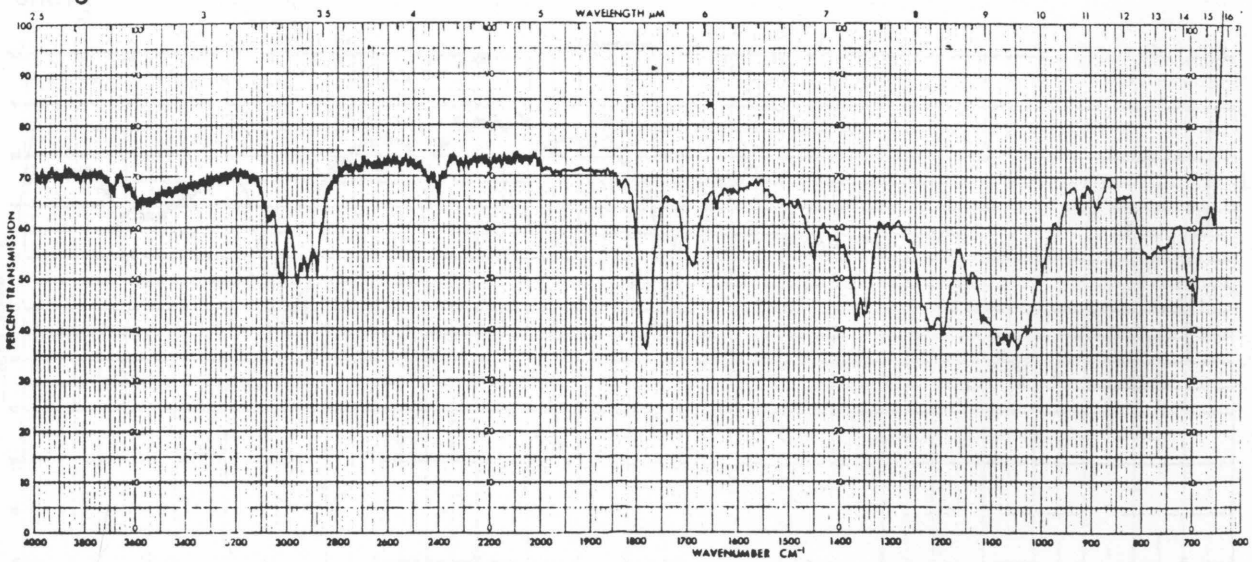

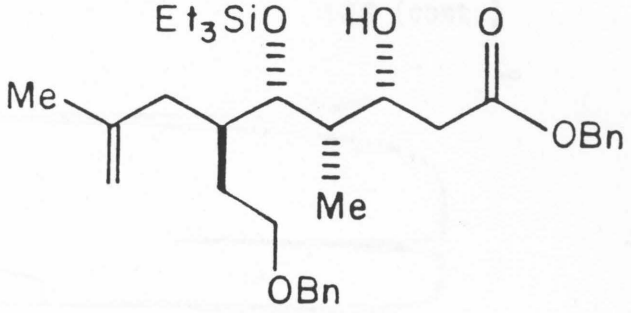

126

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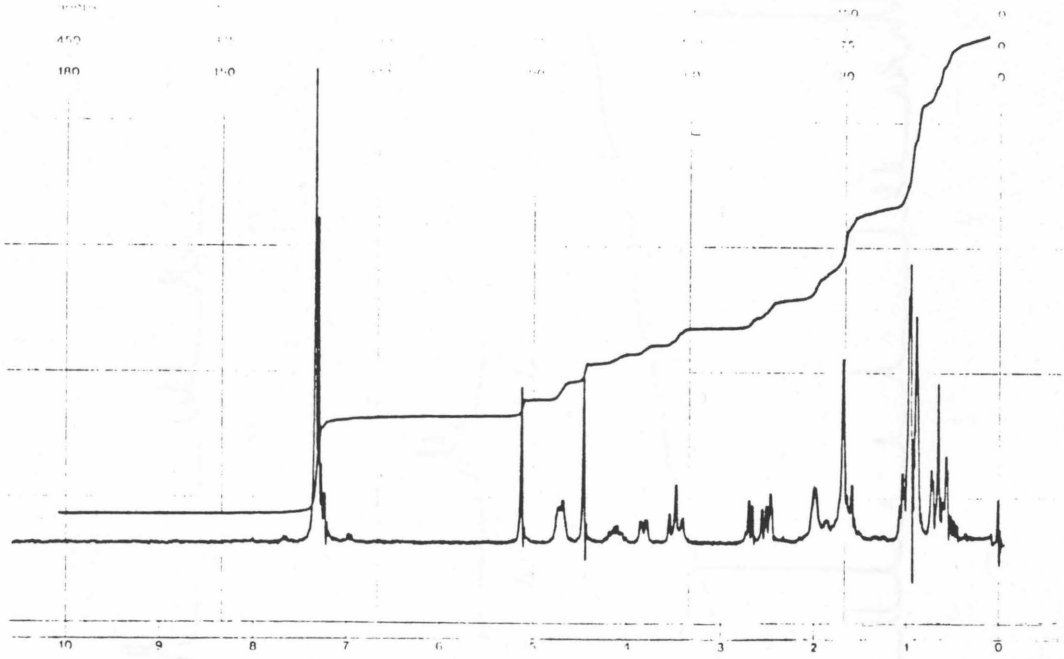

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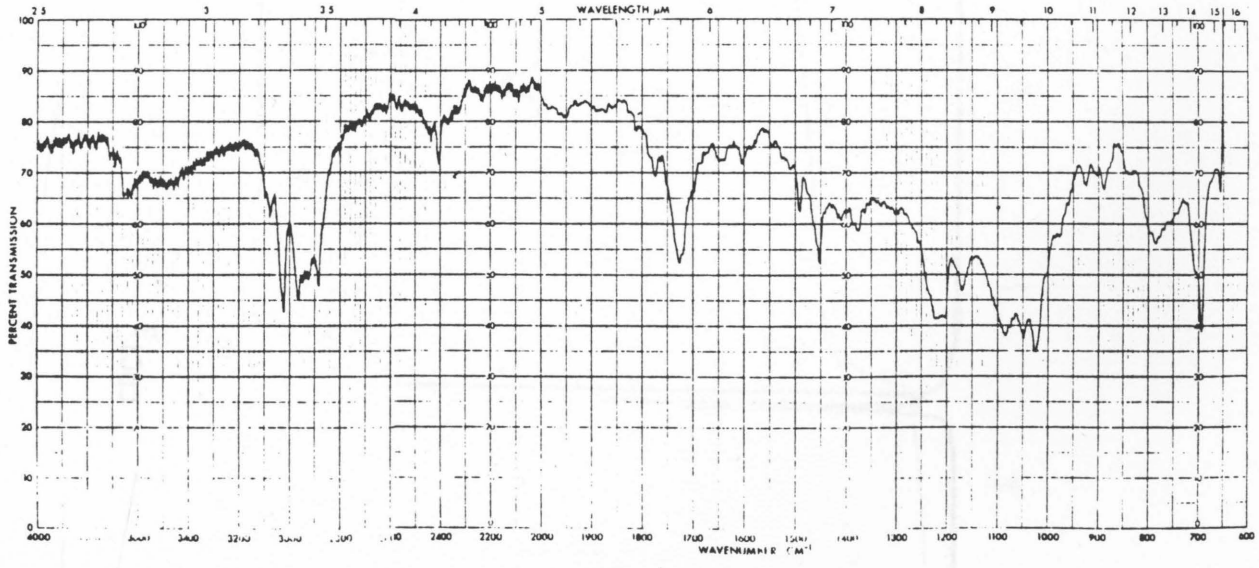
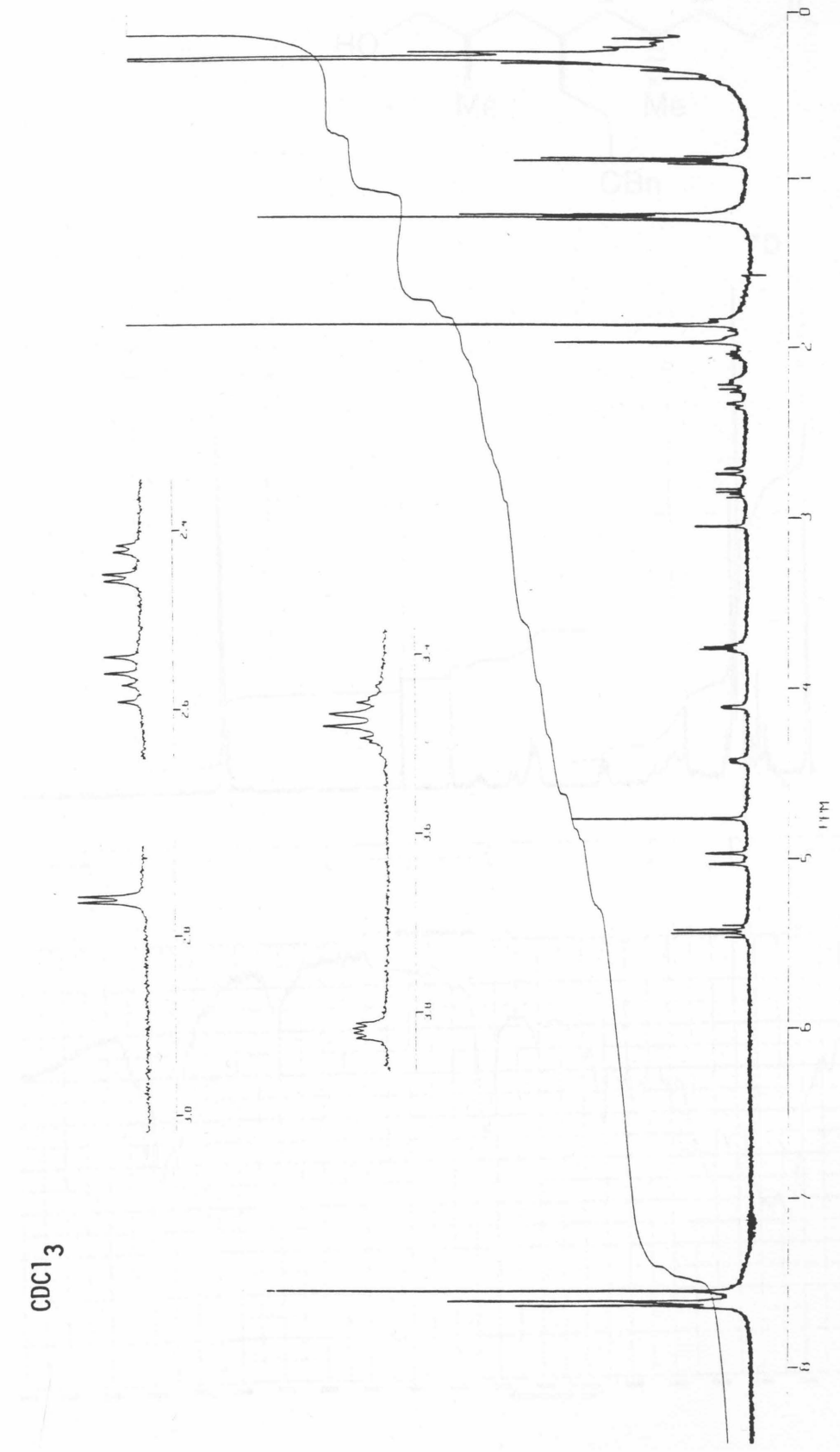
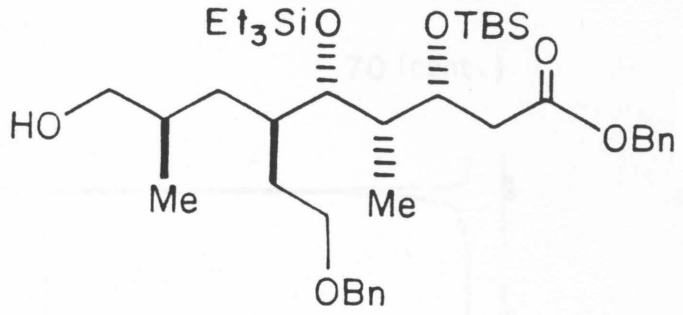


126 (cont.)





70

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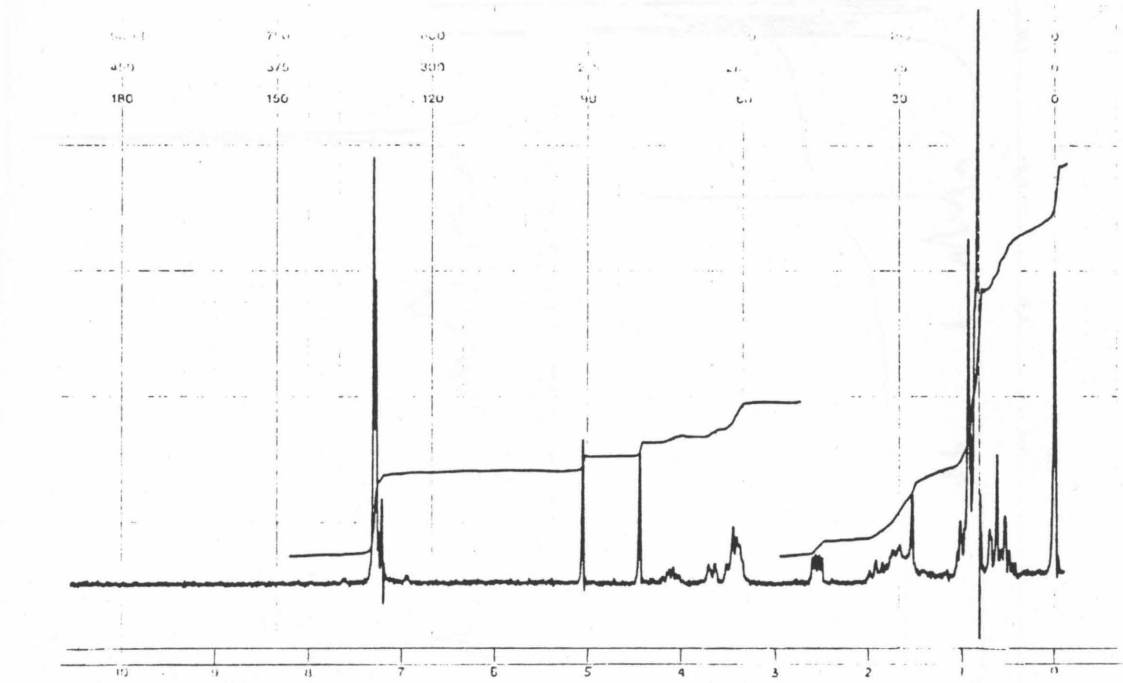

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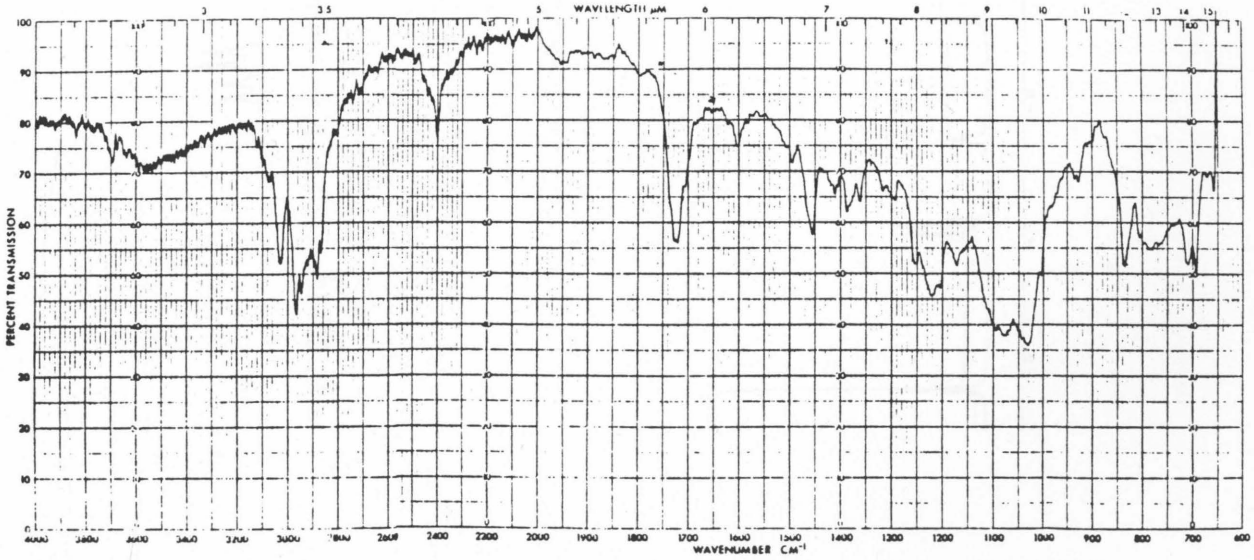

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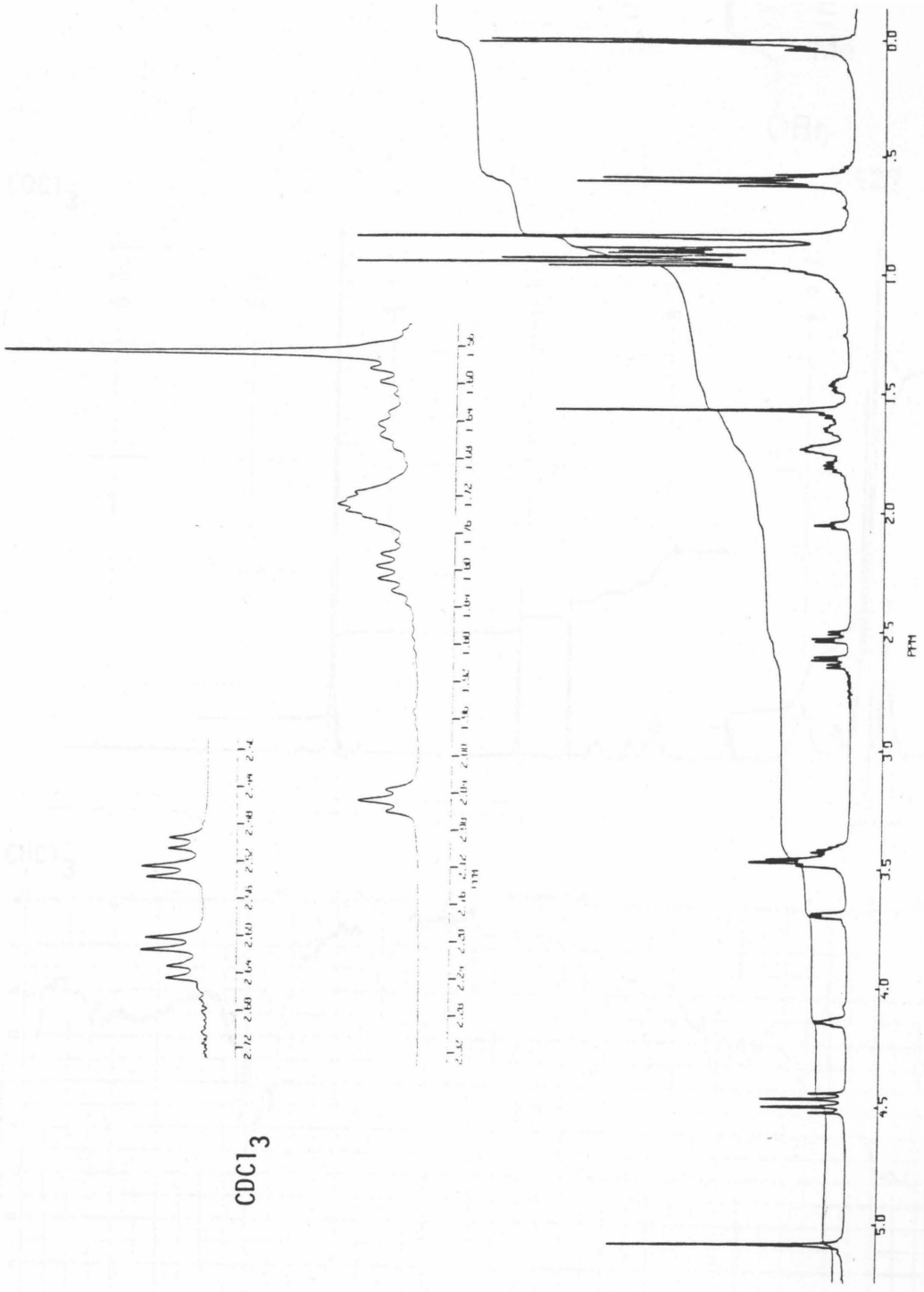

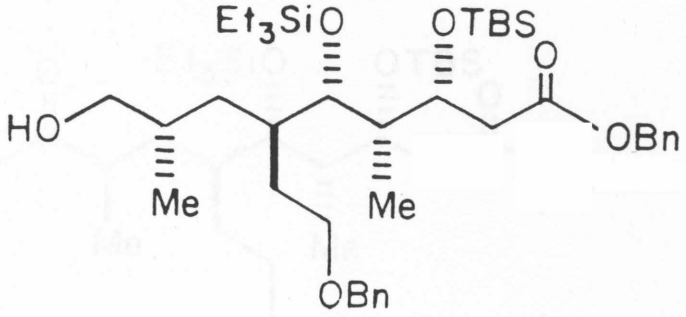

127

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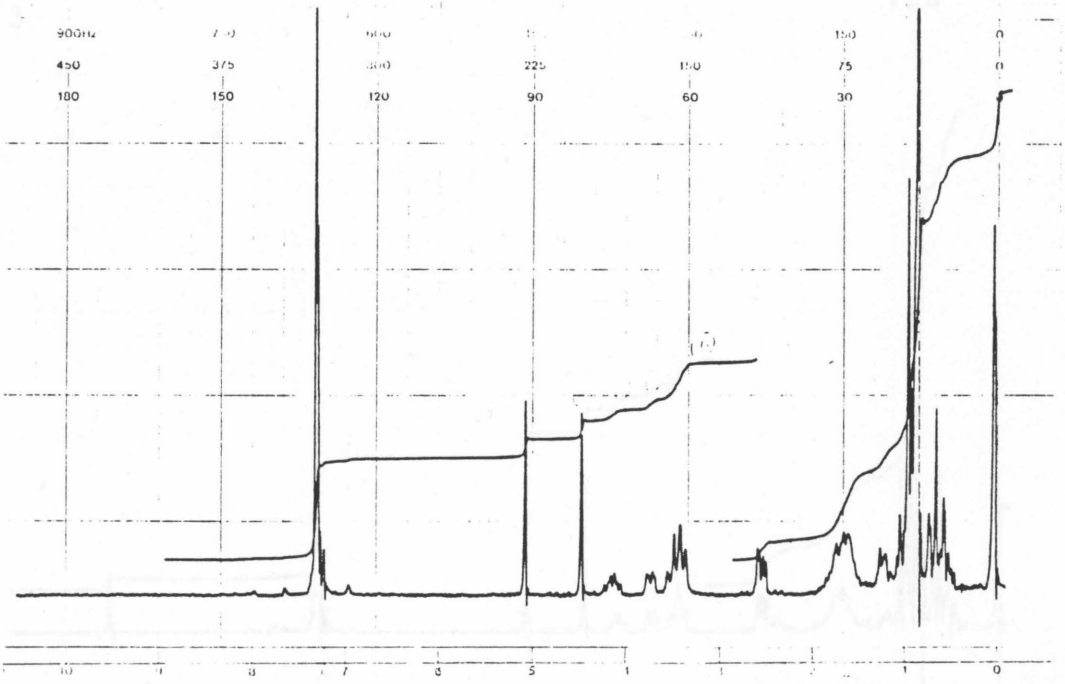

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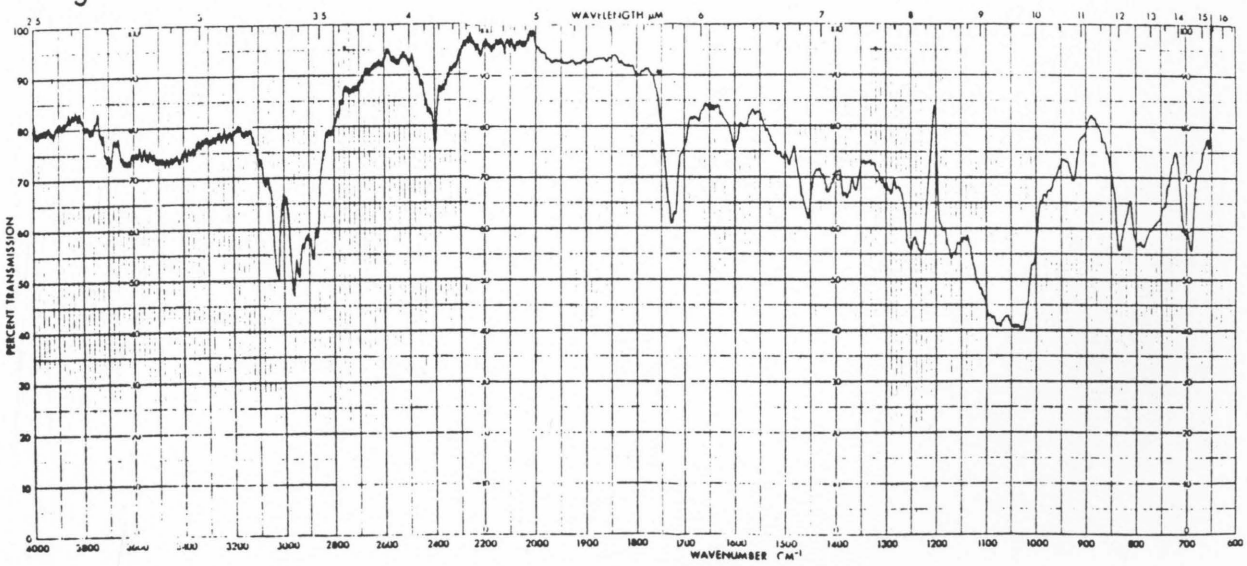

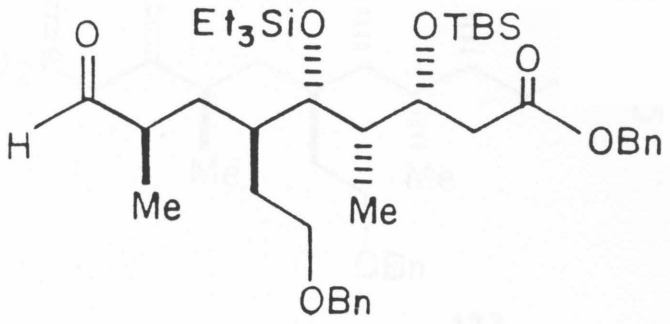

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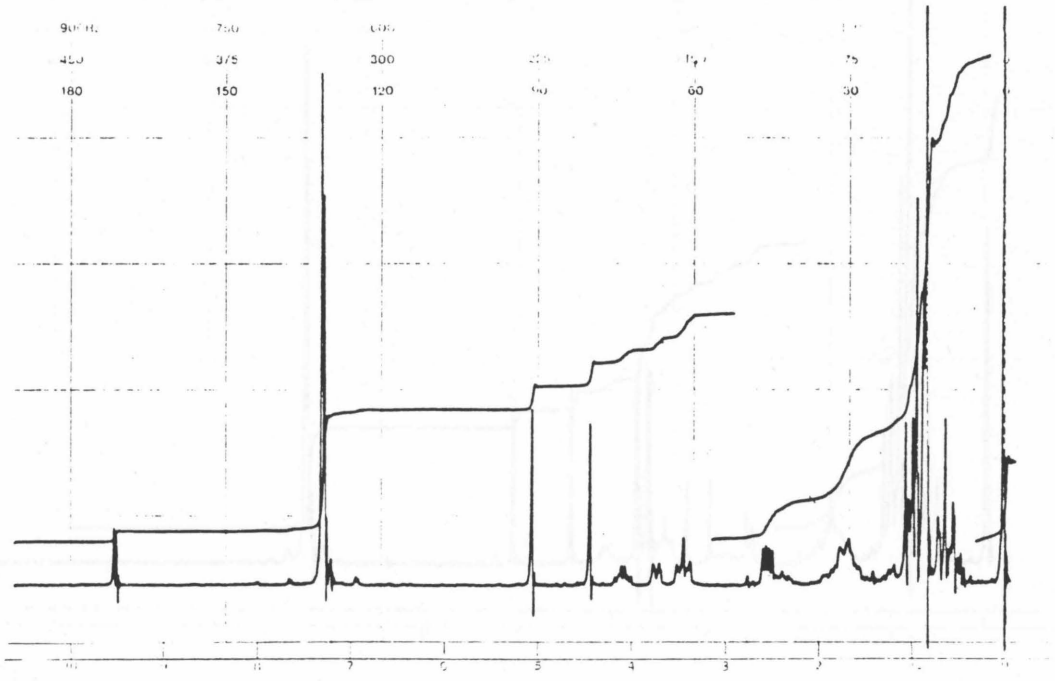
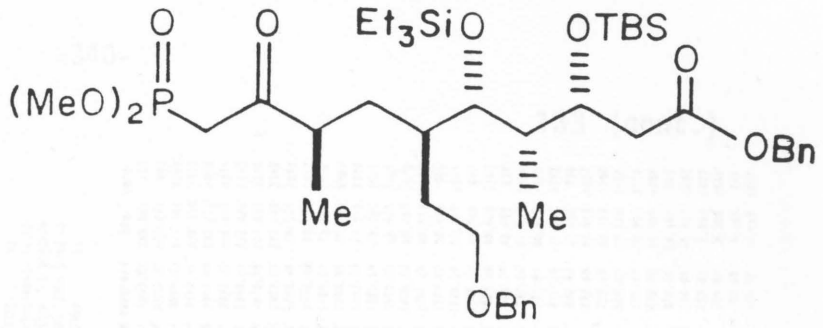
128





133

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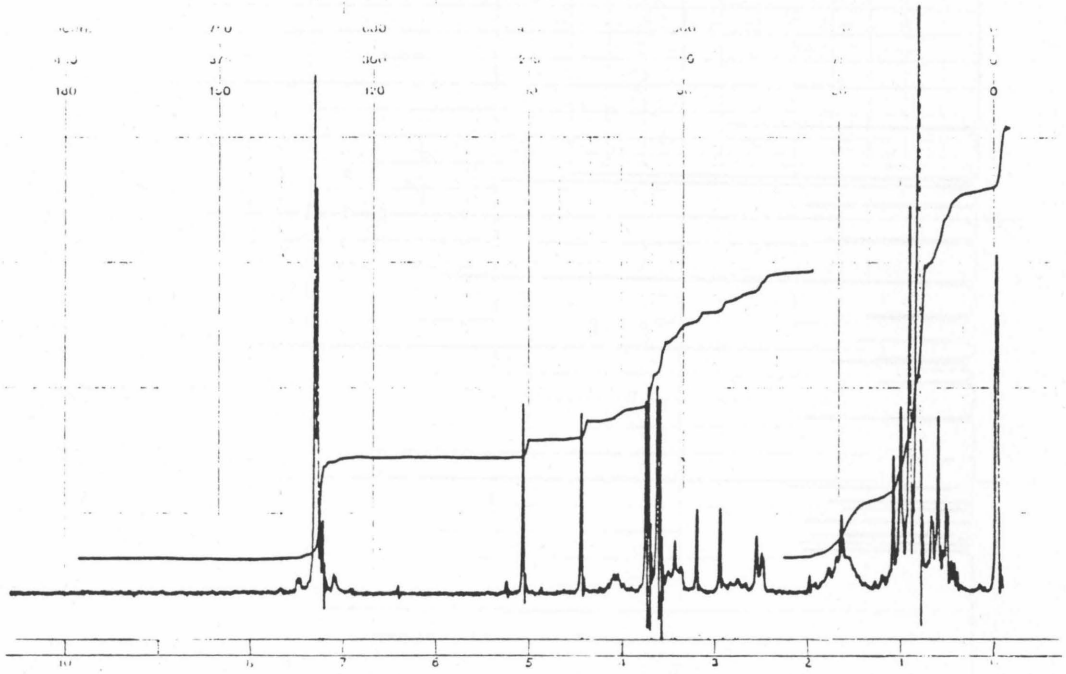

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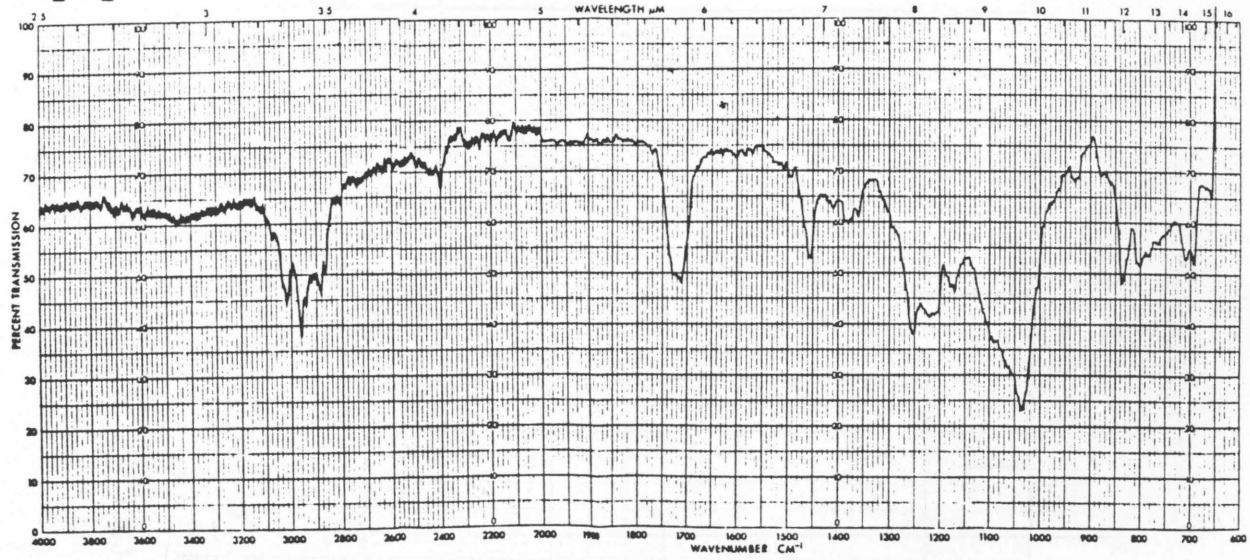

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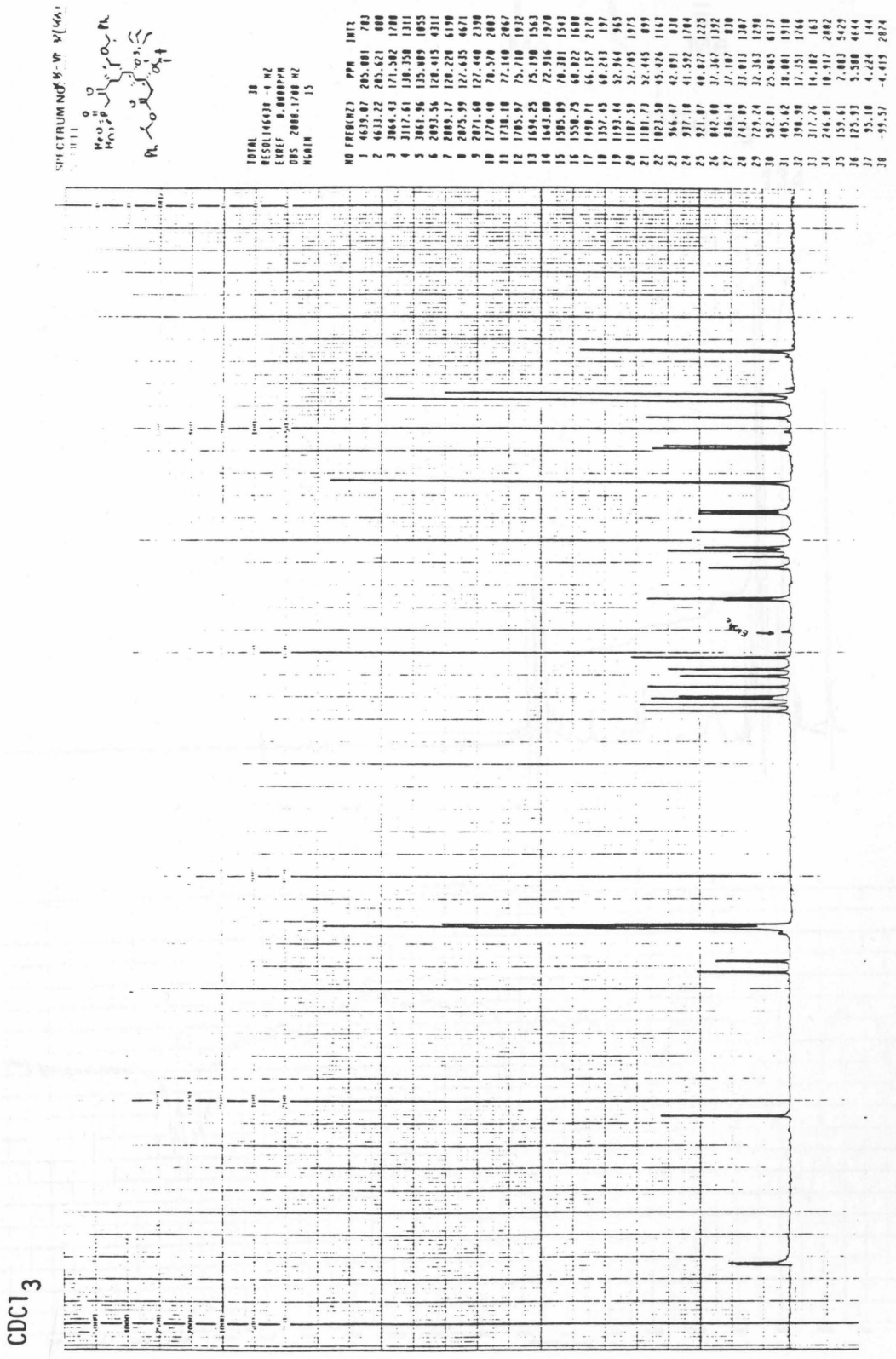

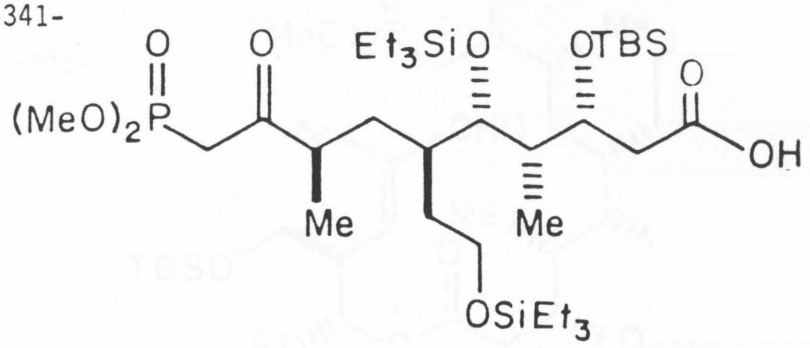

134

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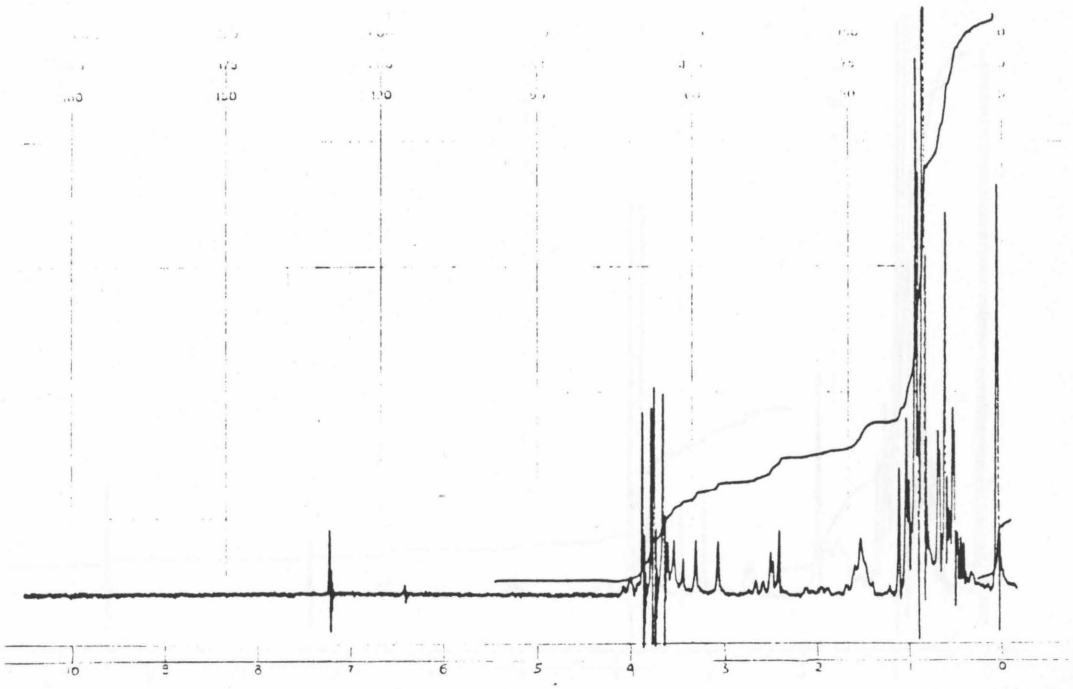

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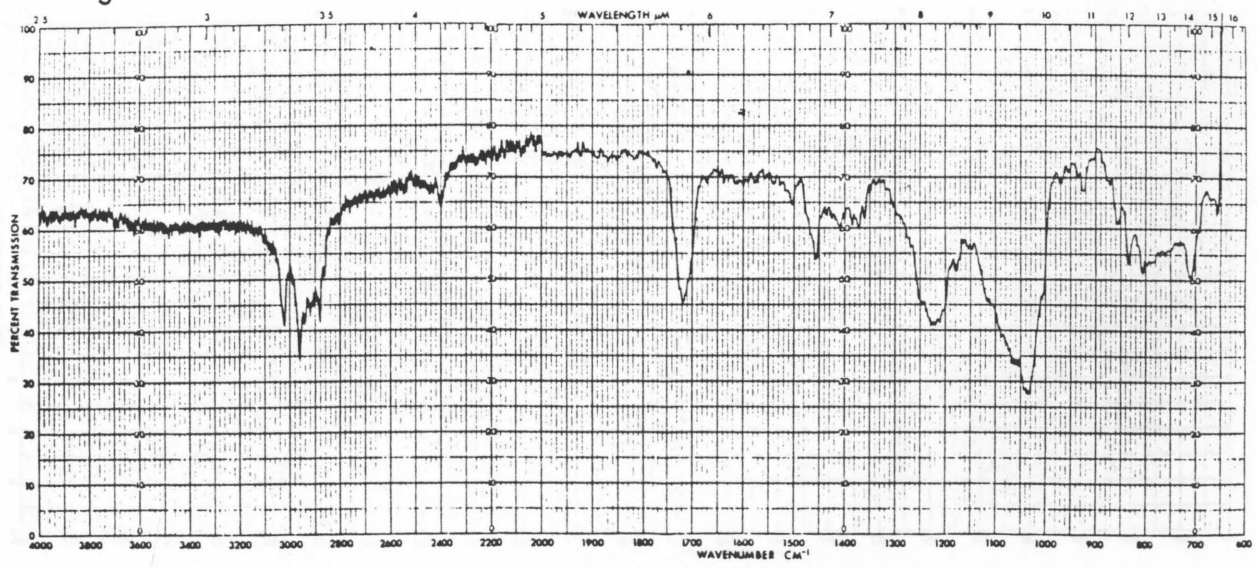

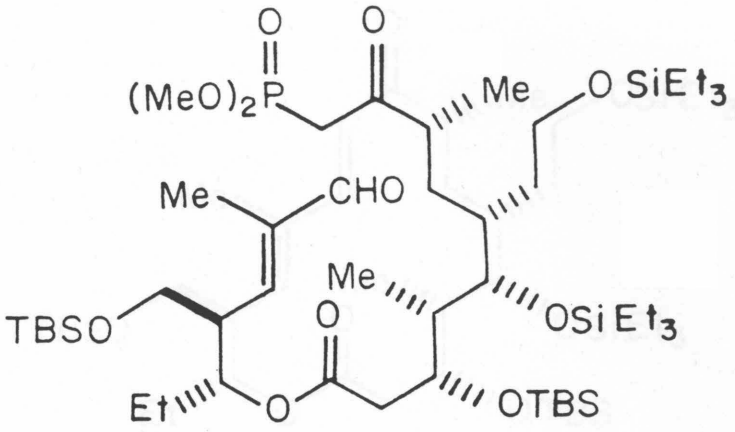

135

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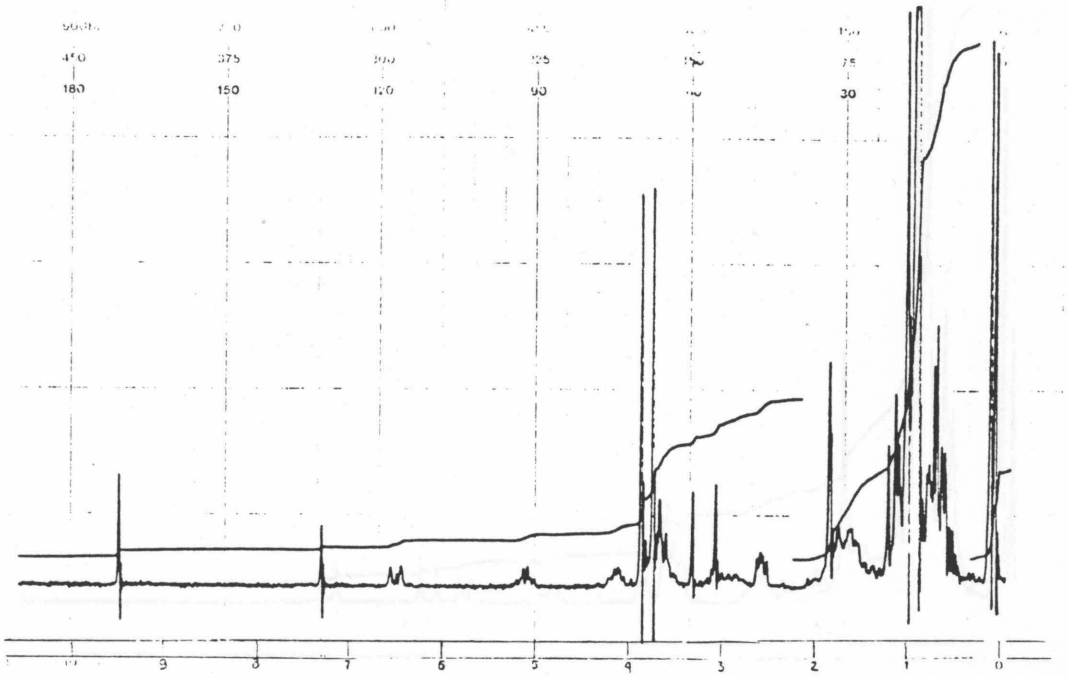

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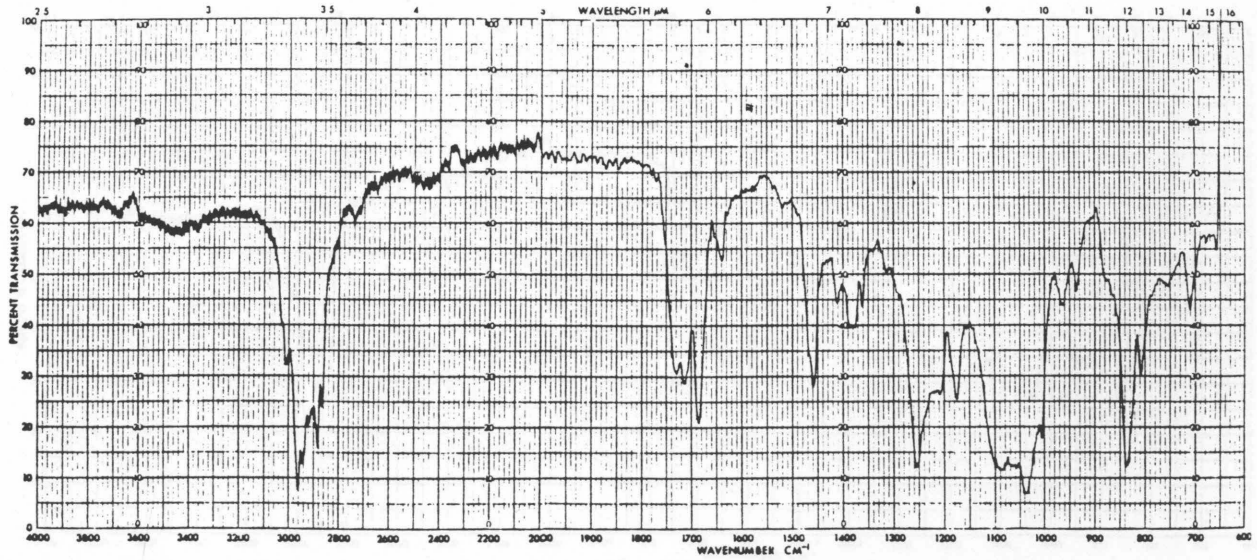

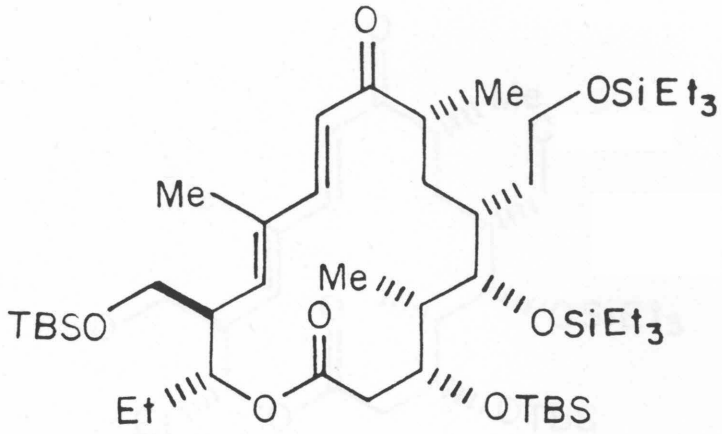

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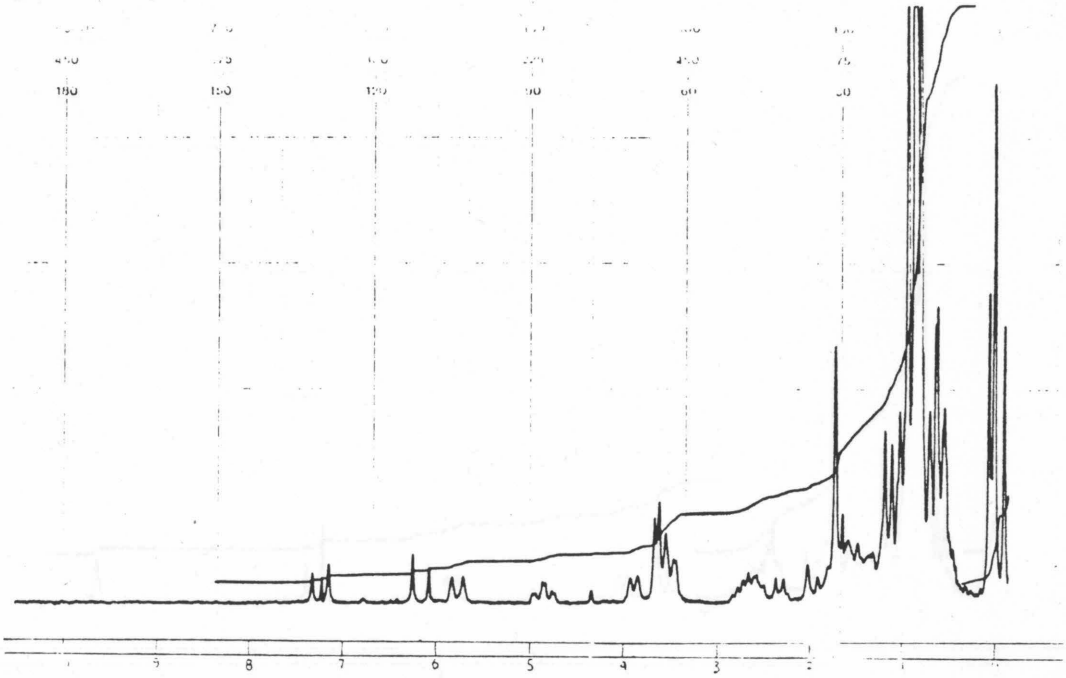

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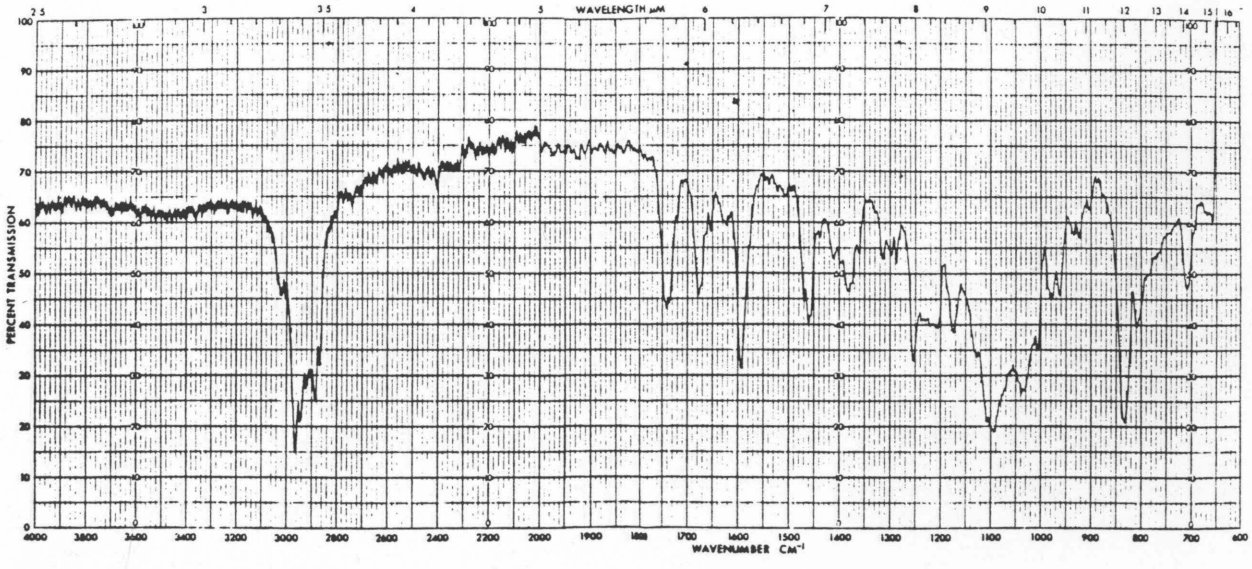

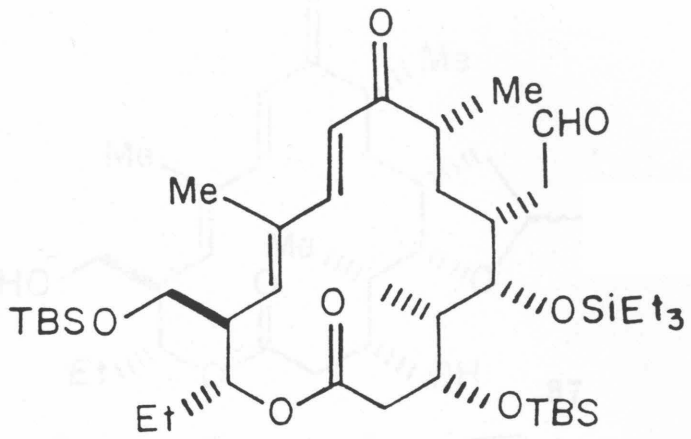

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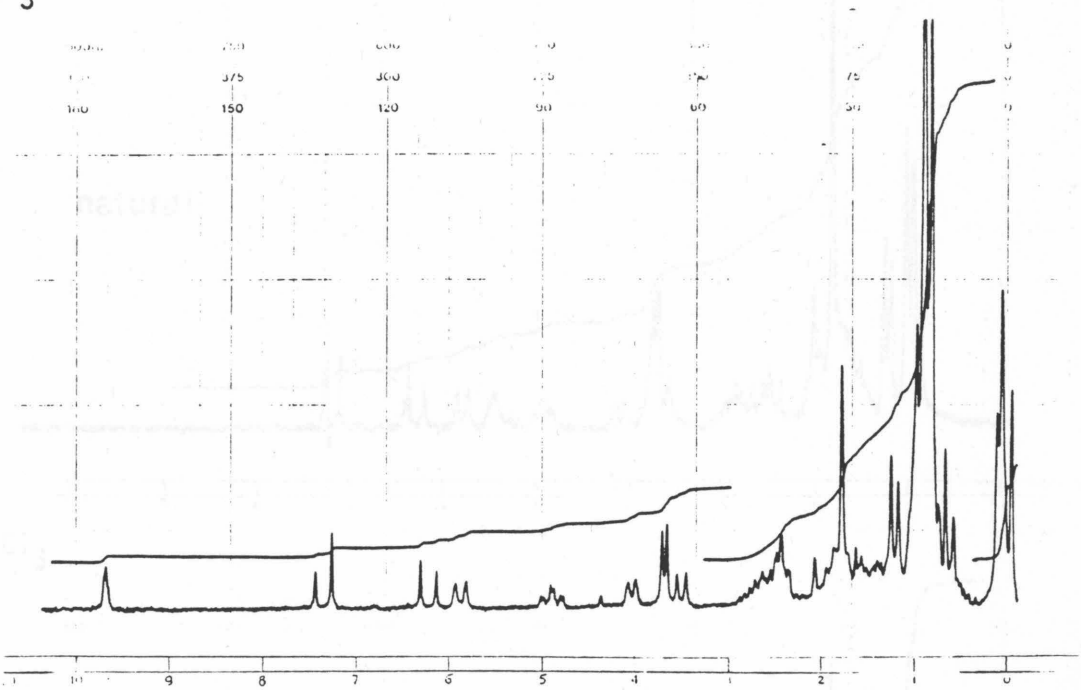

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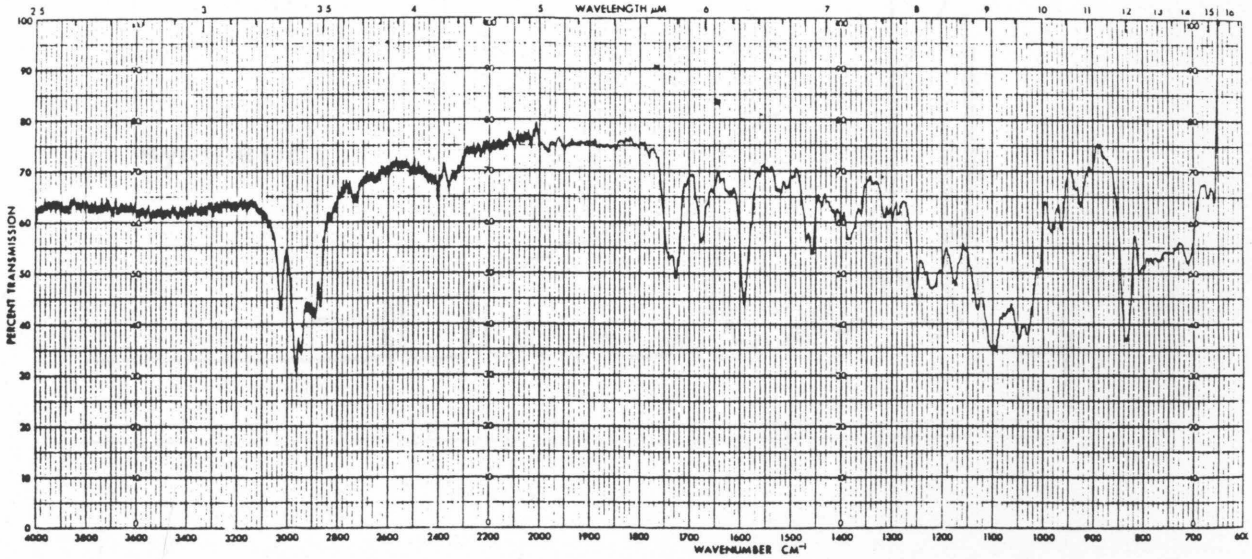

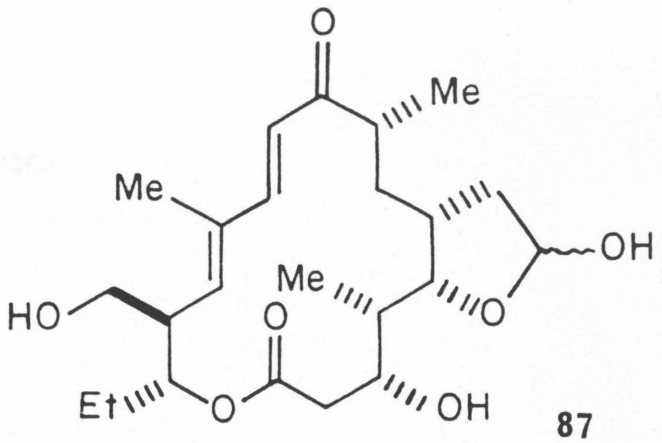

87

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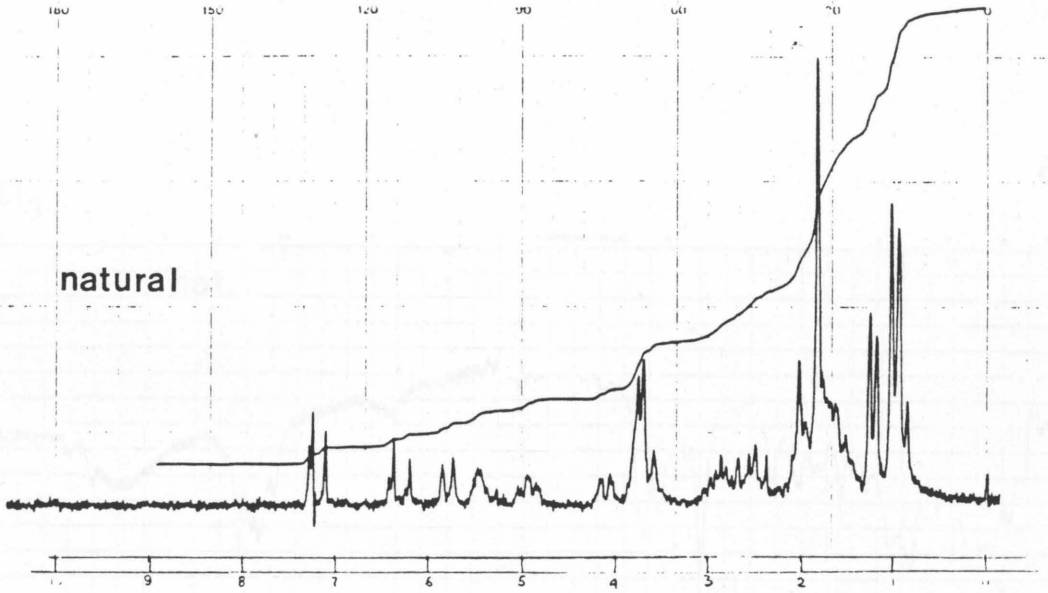

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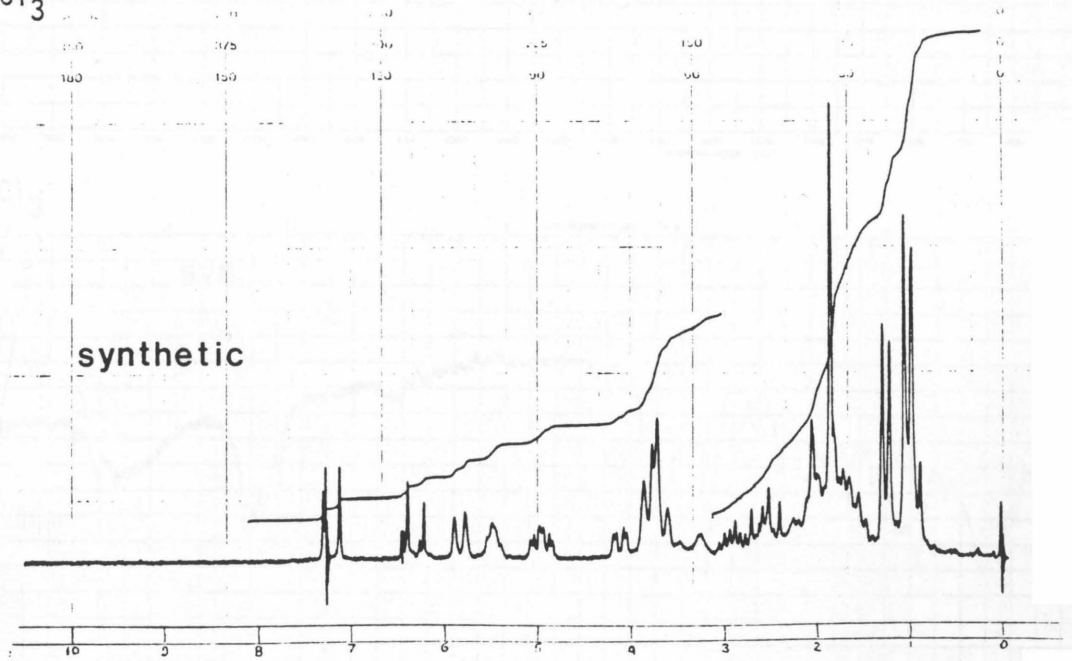

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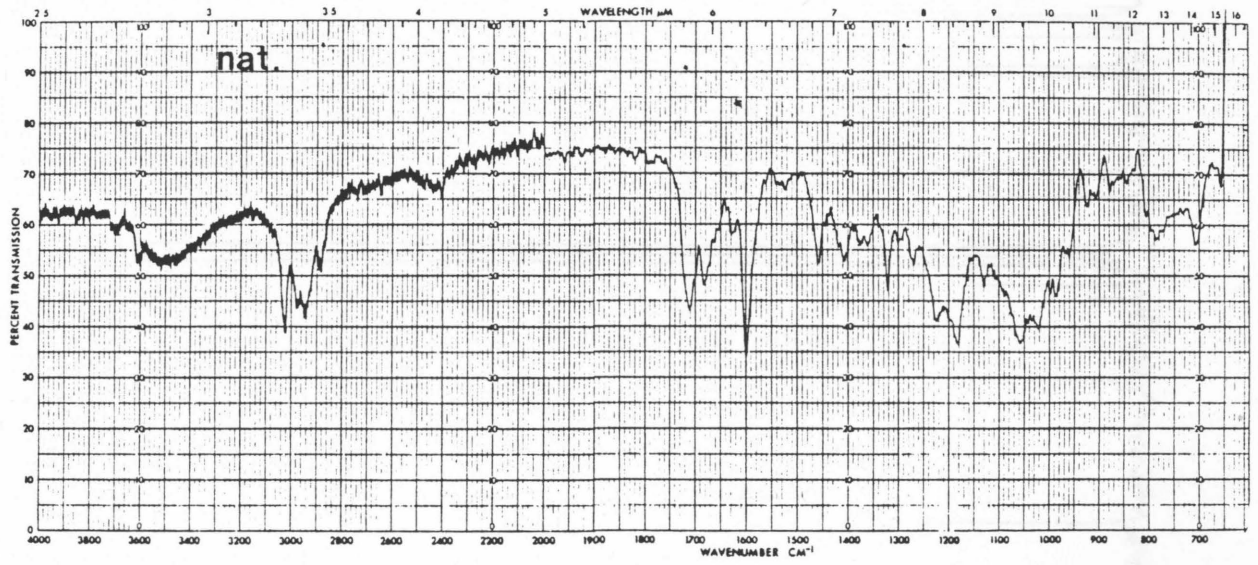

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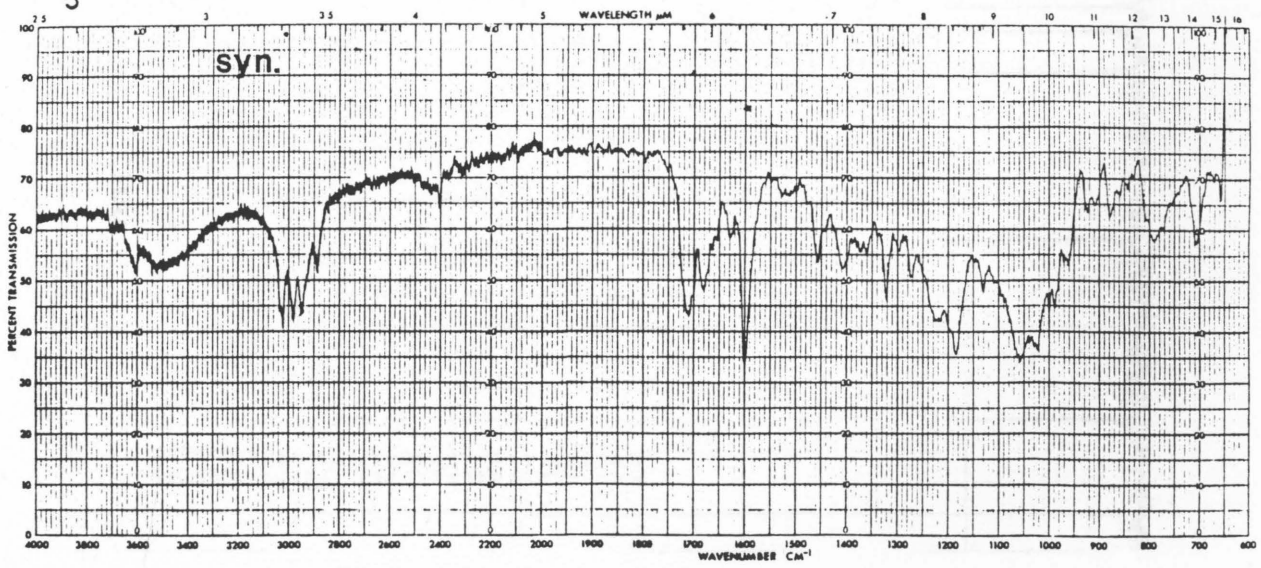

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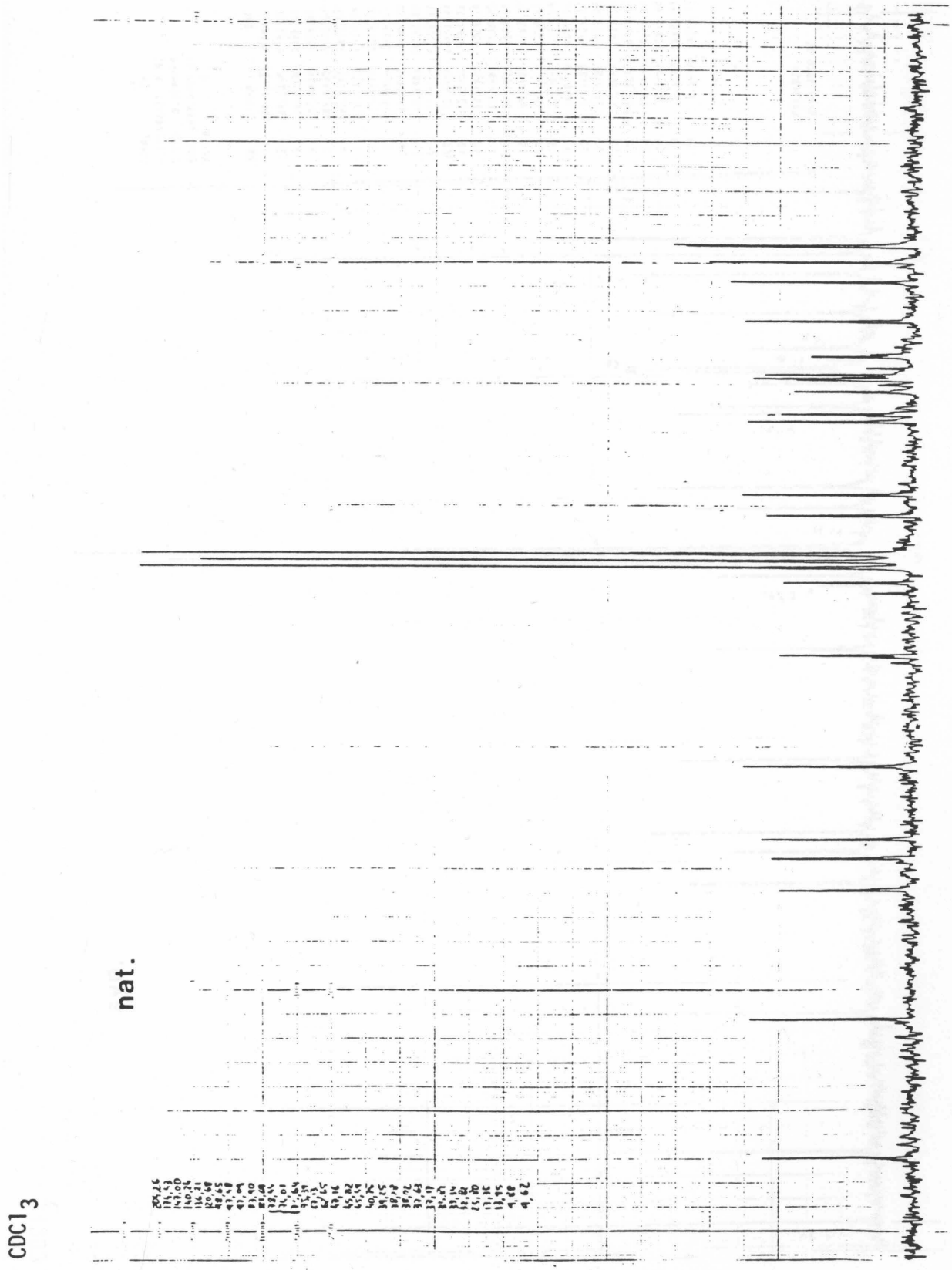

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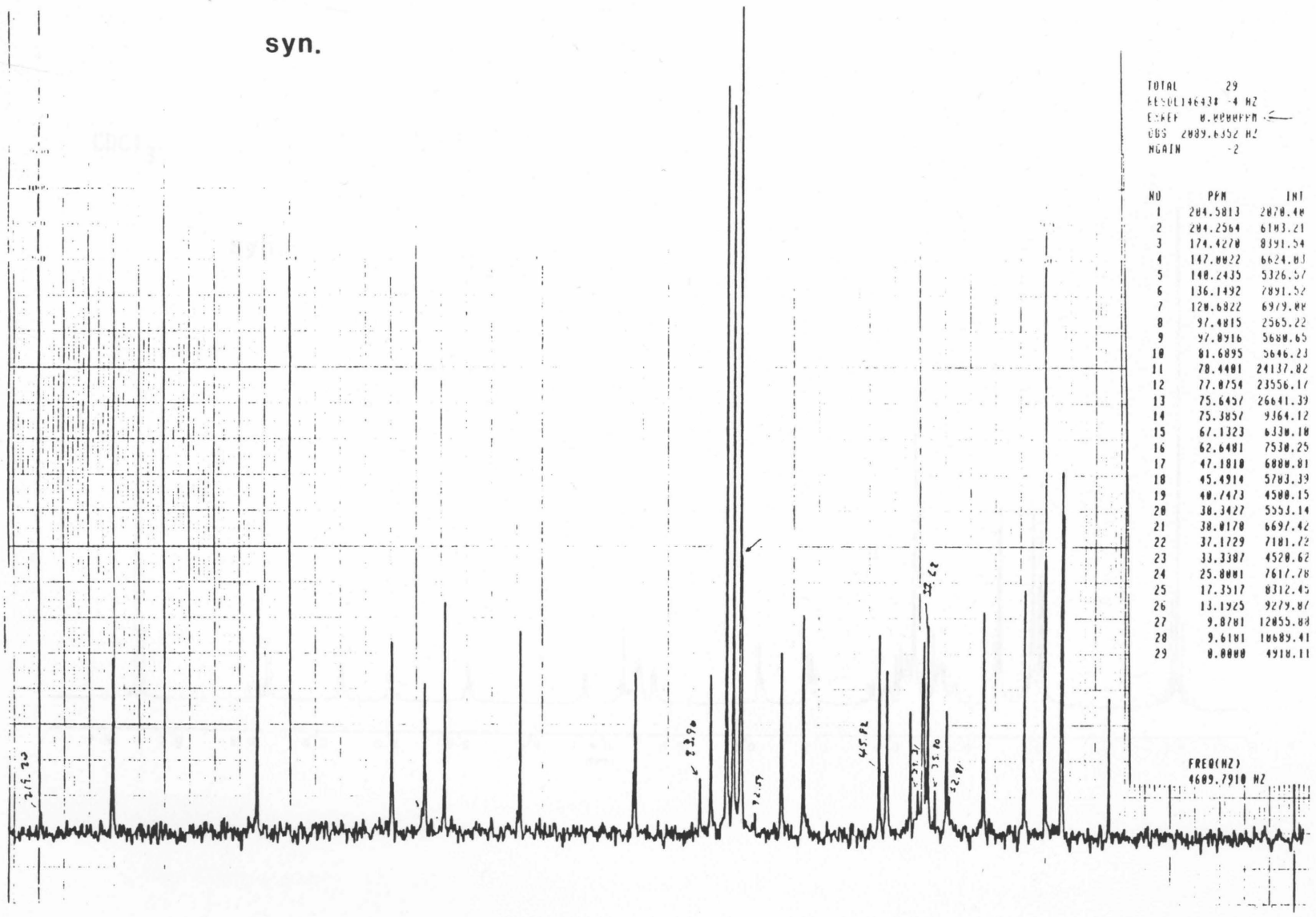
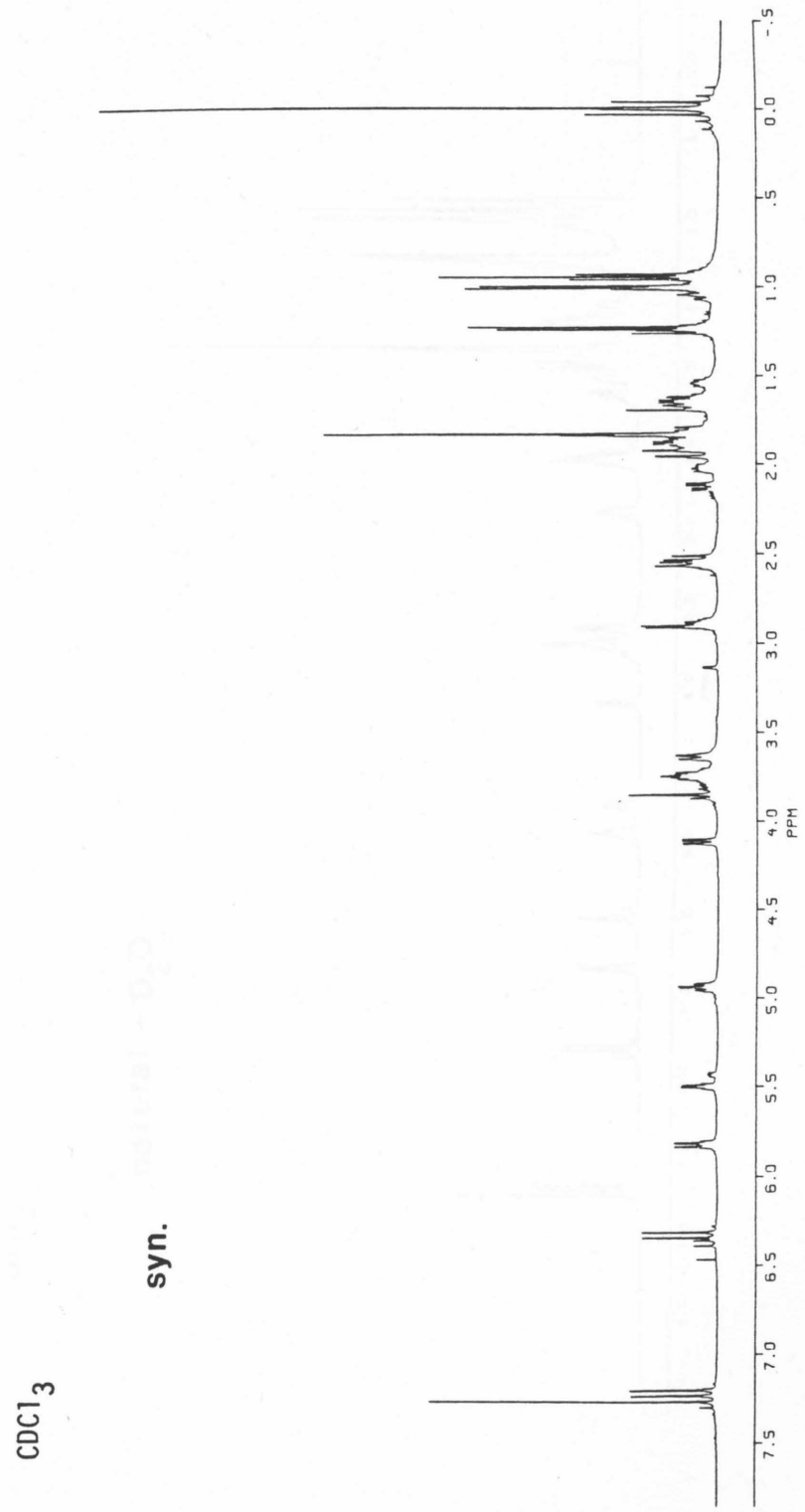


87 (cont.)

87 (cont.)



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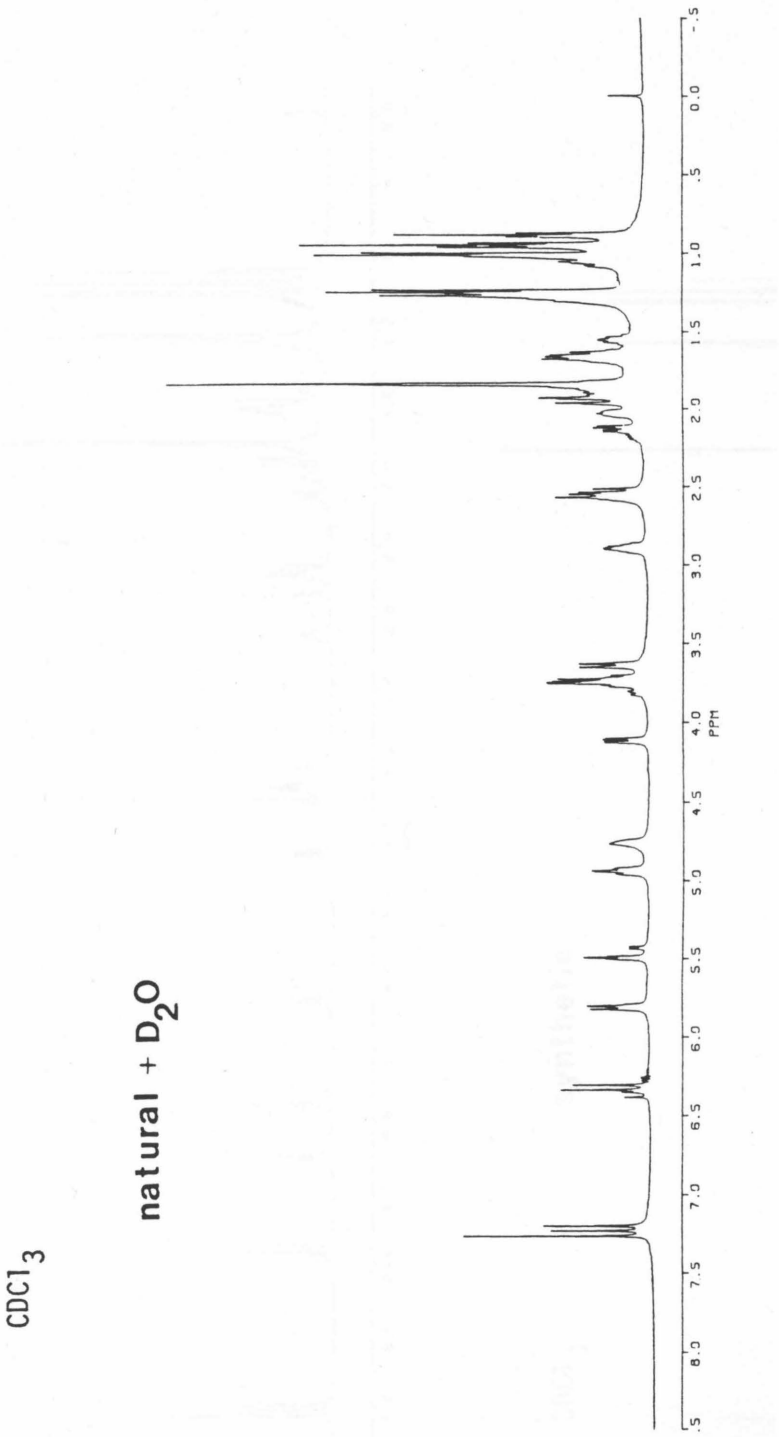

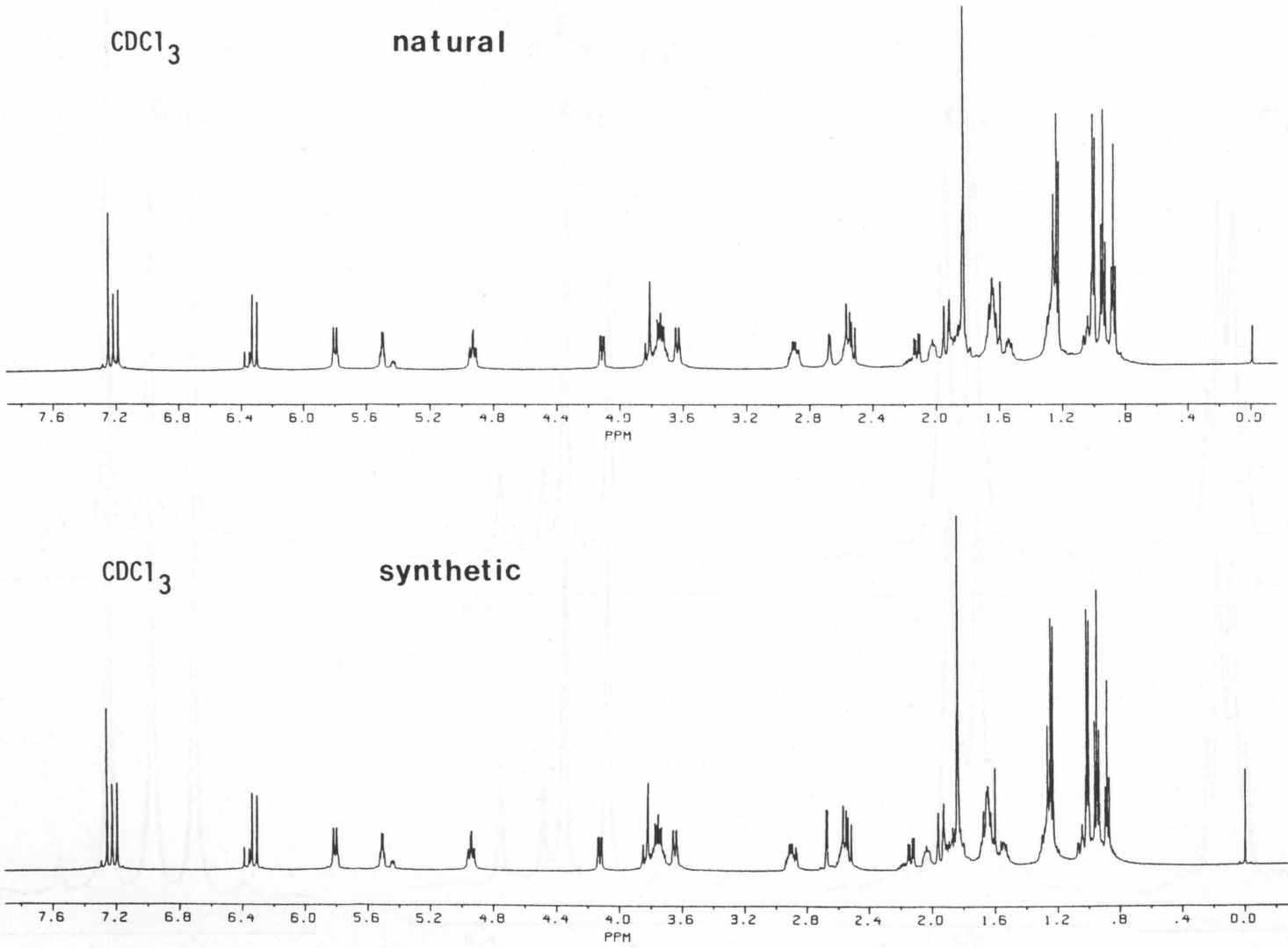

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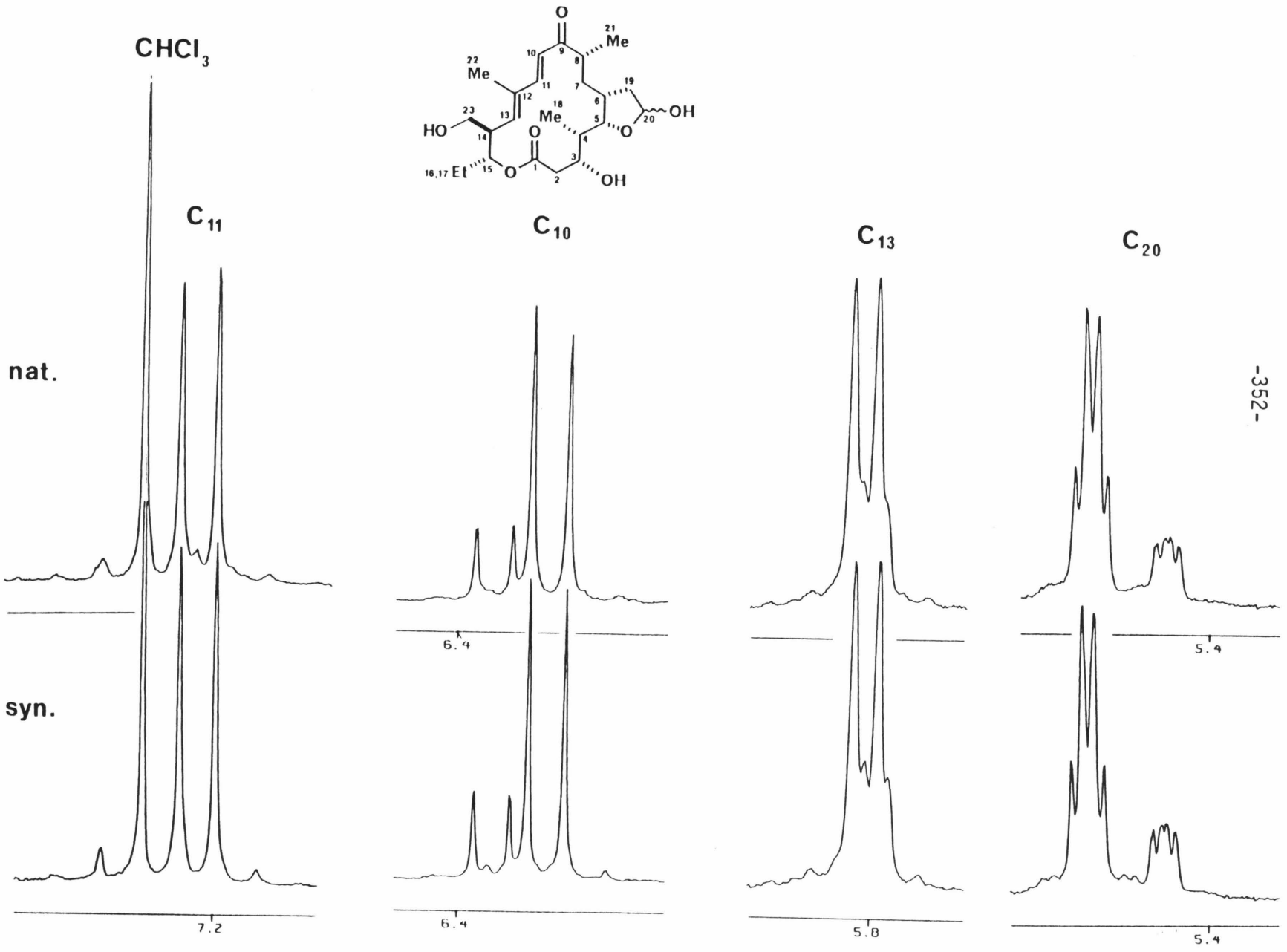
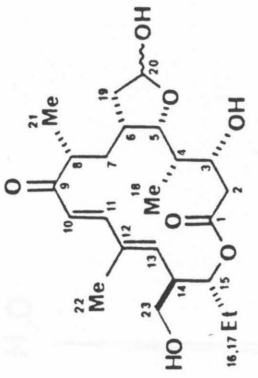
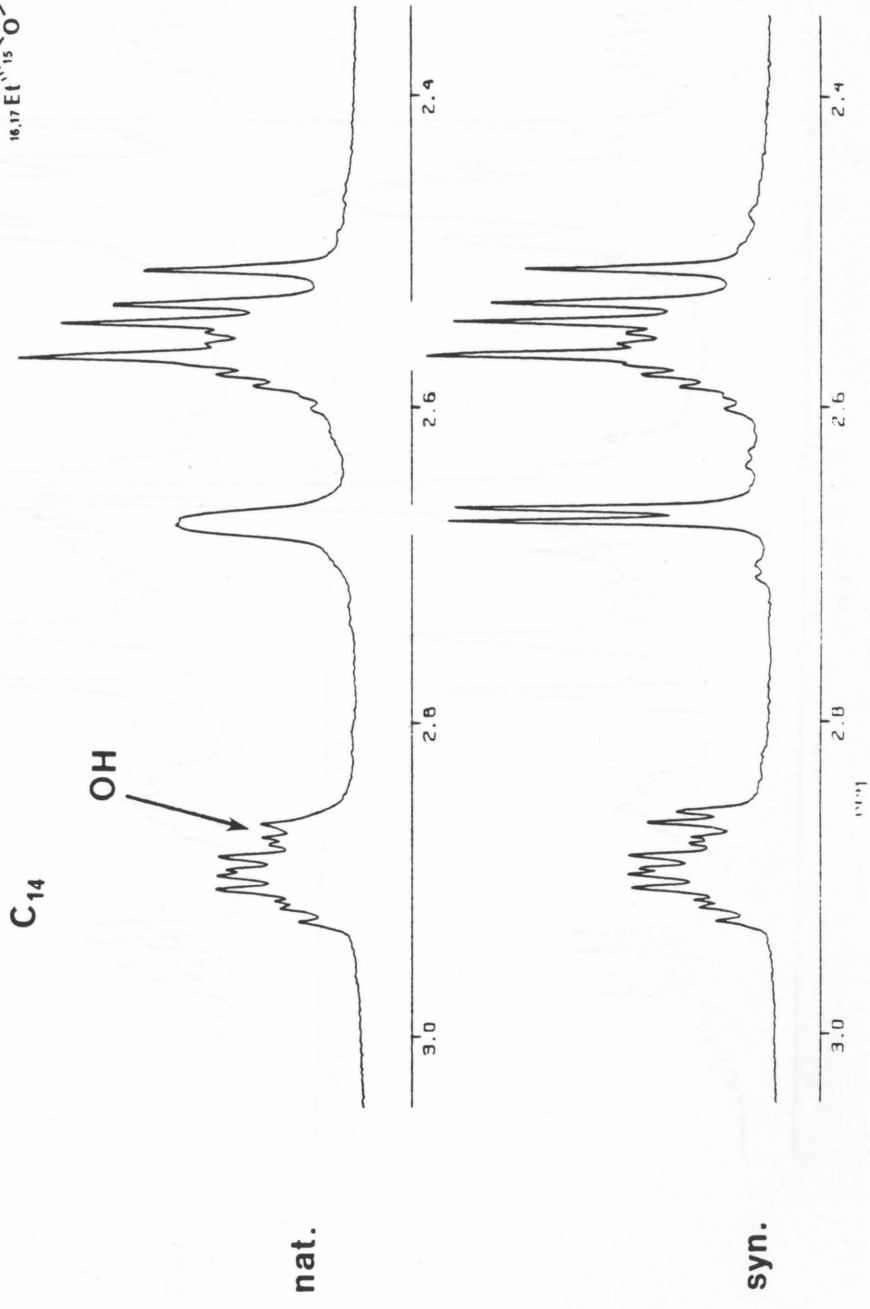


87, hexane complex (cont.)

87, hexane complex (cont.)





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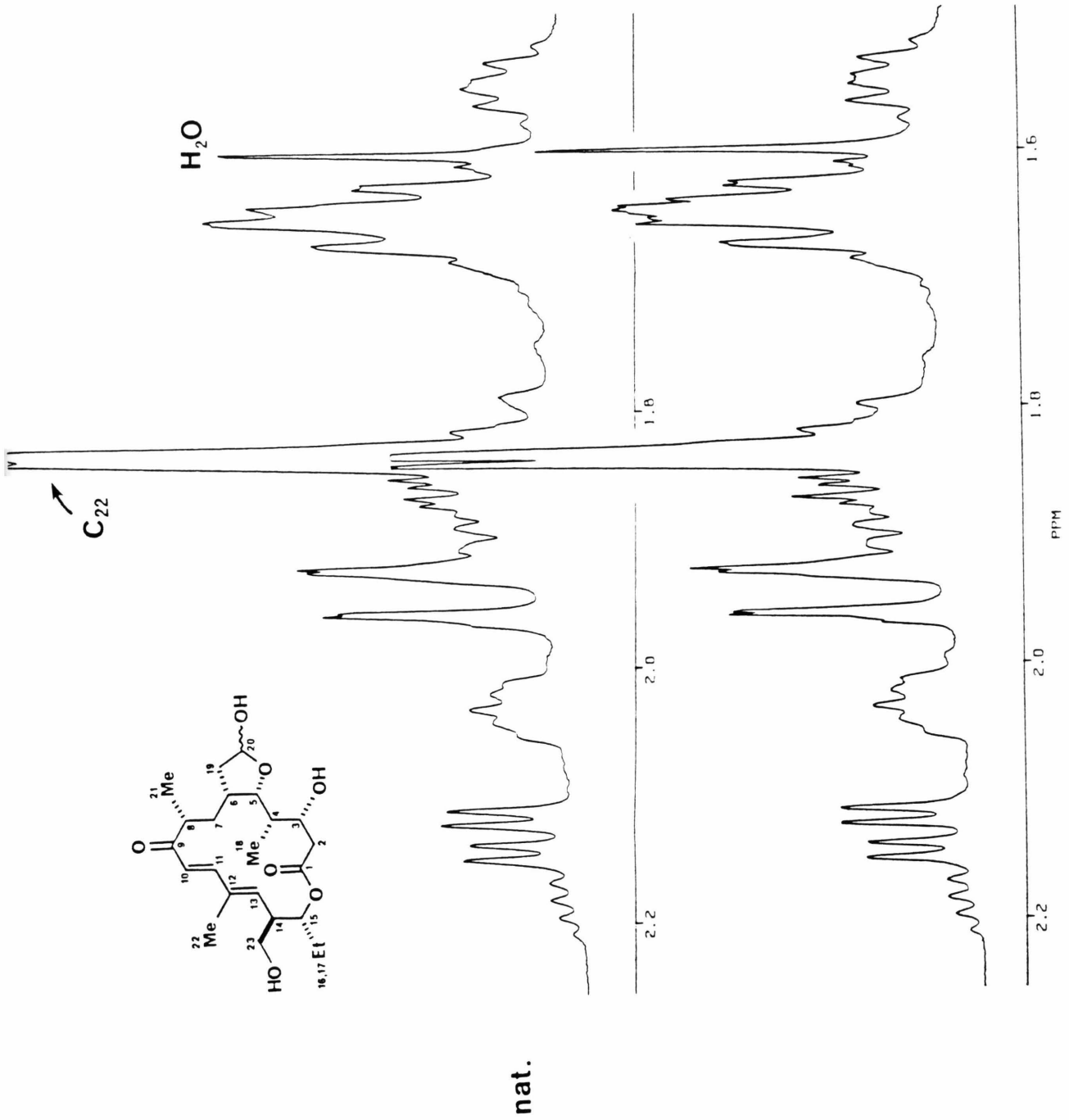

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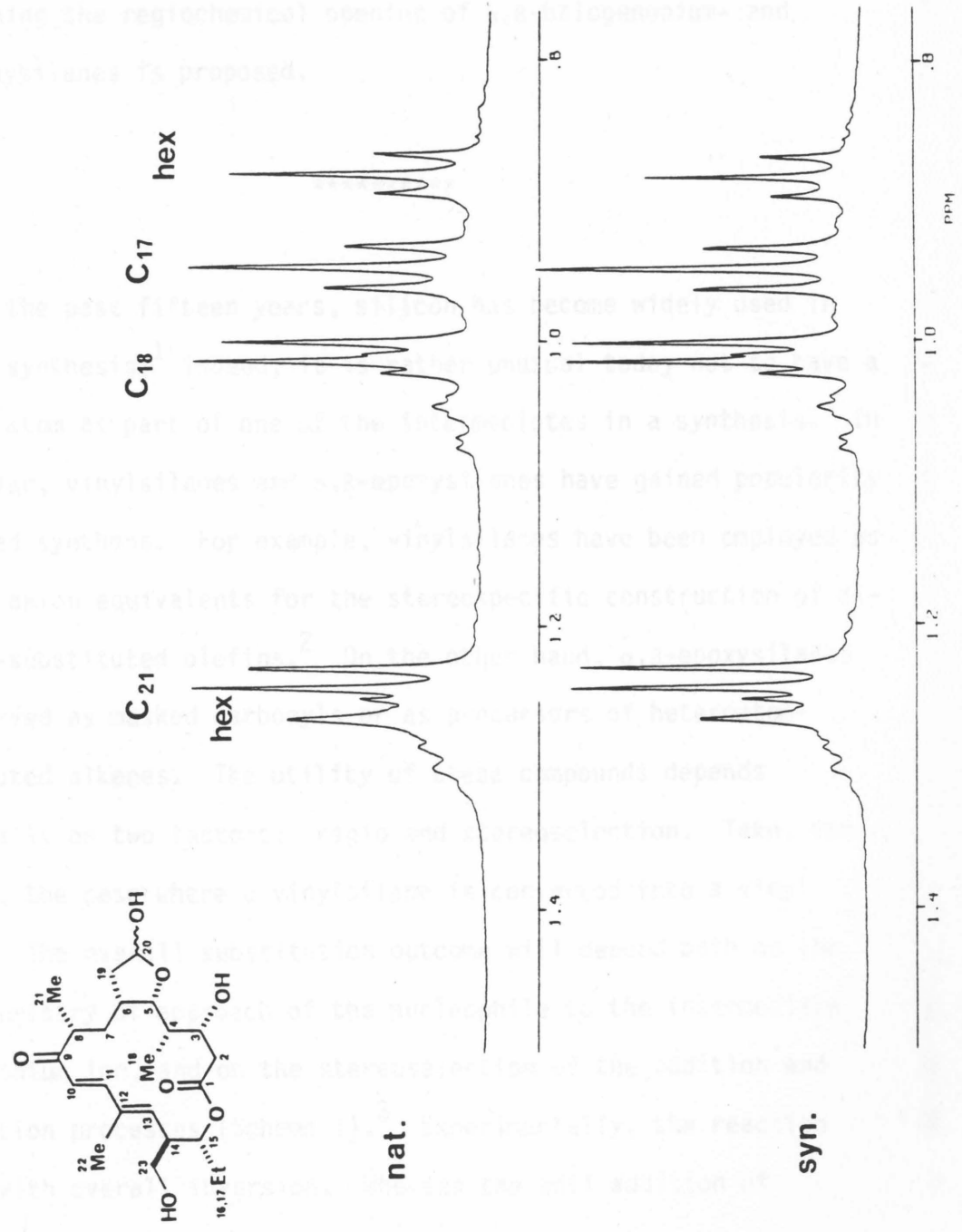


PROPOSITION I

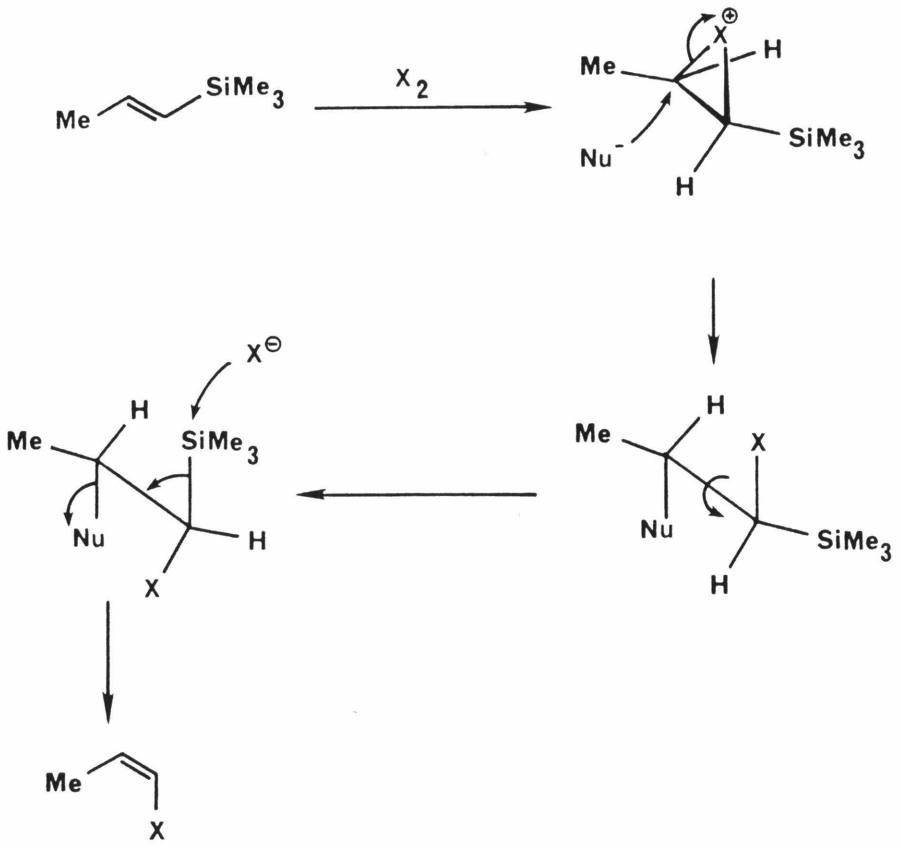
Abstract: A test of the strength of the β-effect in determining the regiochemical opening of α,β-halogenonium- and α,β-epoxysilanes is proposed.

****

In the past fifteen years, silicon has become widely used in organic synthesis;[1] indeed, it is rather unusual today not to have a silicon atom as part of one of the intermediates in a synthesis. In particular, vinylsilanes and α,β-epoxysilanes have gained popularity as masked synthons. For example, vinylsilanes have been employed as α-vinyl anion equivalents for the stereospecific construction of di- and tri-substituted olefins.[2] On the other hand, α,β-epoxysilanes have served as masked carbonyls or as precursors of heteroatom-substituted alkenes. The utility of these compounds depends principally on two factors: regio and stereoselection. Take, for example, the case where a vinylsilane is converted into a vinyl halide. The overall substitution outcome will depend both on the regiochemistry of approach of the nucleophile to the intermediate halogenonium ion, and on the stereoselection of the addition and elimination processes (Scheme I).[3] Experimentally, the reaction occurs with overall inversion. Whereas the anti addition of

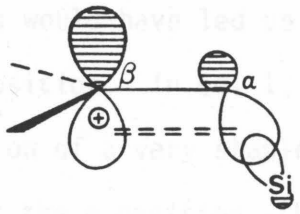
halogens to regular olefins and the anti elimination of 1,2-diheterosubstituted alkanes are well documented, the preferred attack to the carbon β to silicon needs to be rationalized. It is well accepted that the trialkylsilylmethyl unit offers a strong

Scheme I



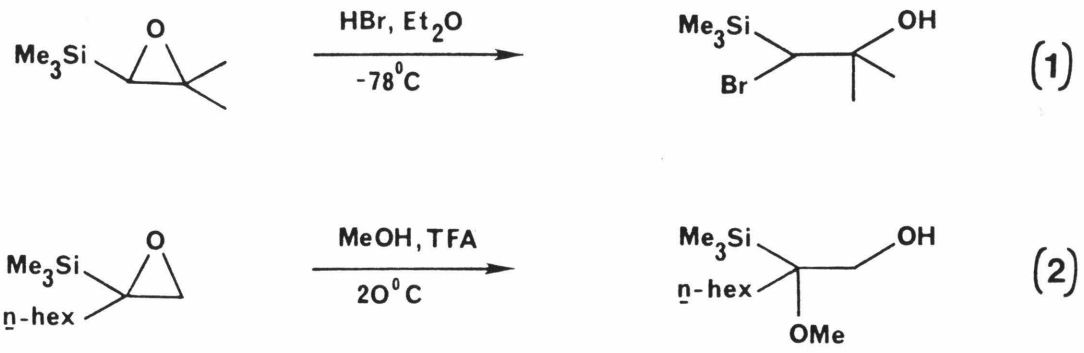
stabilizing electron-donating effect to a β electron defficient center (β-effect).[4] Due to the polarization of the C-Si σ-bond, the carbon atom bears a larger atomic coefficient. This enables good overlap in the hyperconjugation with the empty p-orbital of an adjacent carbocation (fig. 1). Furthermore, this polarization

Fig. 1



puts the σ-bond in a higher energy level, close to that of a p-orbital. Studies have shown that the Me_3SiCH_2- group has a σp* intermediate between that of a methyl and a methoxy group.[5]

Therefore, the β-effect will <u>generally</u> direct the approach of nucleophiles to the carbon β to silicon. Exceptions to this rule are observed when the α carbon itself has an electron donating group that can stabilize a positive charge, or in the chemistry of α,β-epoxysilanes. This latter family of compounds shows opening by nucleophiles at the α position, almost without exception. The two following examples[6] show the strength of silicon in directing α-opening, independently of other features. In eq. 2, steric



effects arguments would have led us to predict attack at the less substituted, β position. In eq. 1, a cationic pathway would have suggested formation of a very stable, tertiary cation stabilized by a silicon atom at the β position. However, only attack at the α position was observed in both cases. Why is the β-effect of silicon which dictated opening at the β position in halogenonium silanes, not operating with α,β-epoxysilanes? Is the β-effect the only cause of the observed regioselection in the former compounds?

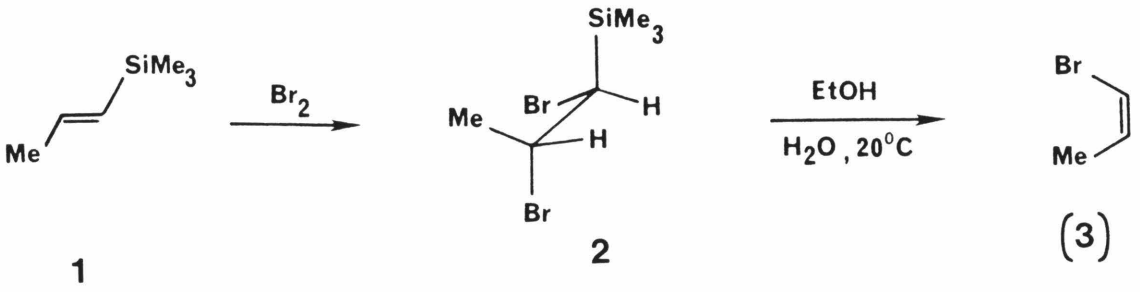
An explanation to this problem has been proposed by Thomas and Whitham.[7] According to them, the transition state leading to the opening of halogenonium silanes must be a fairly late one, in which the β-halogen bond is highly broken and the β-effect is stabilizing the partial positive charge. In contrast, the α,β-epoxysilane ring opening must have an early, reactant-like transition state in where the β-effect cannot be operating due to geometrical reasons.

However, the question why in this latter case the α-position is preferred remains still unaddressed.

Earlier work done by Eisch[8] on the opening of α,β-epoxysilanes with lithium aluminum deuteride proved that the reaction occurs via direct attack to the α-position, and that no rearrangement takes place. He also studied the regiochemistry of the reaction using different p-substituted phenyl groups attached to the silicon and found that the mode of opening was insensitive to electronic effects. However, it should be noted at this point that if silicon stabilizes charges by hyperconjugation of the C-Si sigma bond, only inductive effects of the substituents will be relevant. These substituents will make the C-Si sigma bond to be more or less polarized, thus changing the orbital coefficients and therefore making the β-effect more or less effective. Eisch used, among others a highly negative inductive group (CF_3), which should have had enhanced the C-Si bond polarization and consequently favor the β-effect. However, α opening was still the only product observed. These results suggest that the reaction regioselection is insensitive to the extent of the β-effect. However, they do not indicate if a charge around the α carbon is ever formed. This could be tested by doing the substitution studies directly on this carbon. For this purpose, several p-substituted, 2'-trimethylsilylstyrenes should be prepared. Here, if a partial positive charge is formed at the α carbon in the transition state, electron withdrawing groups

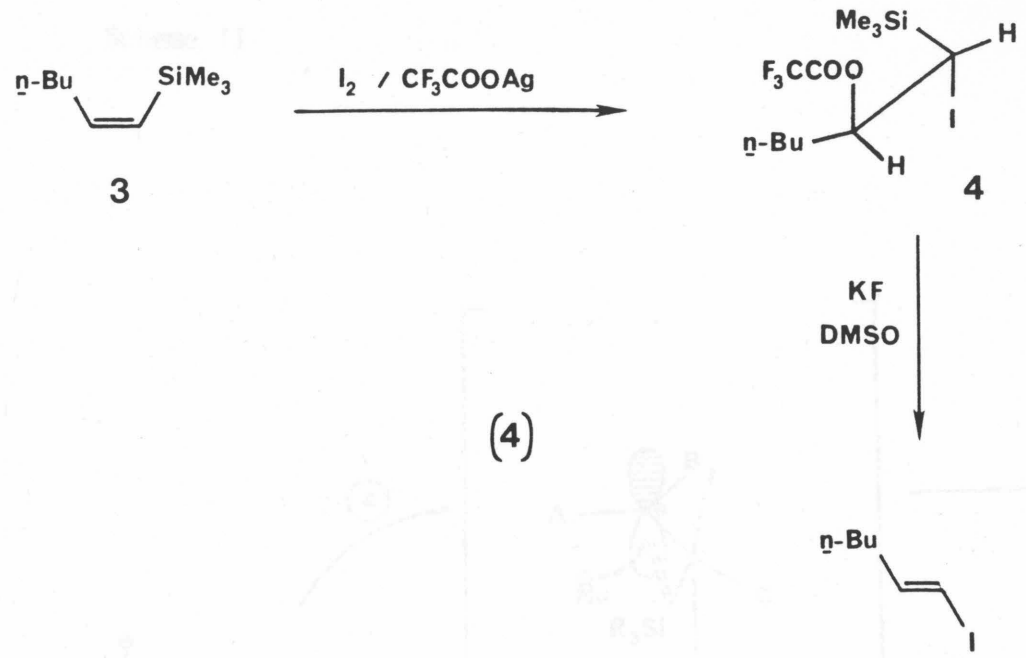
would disfavor the α opening and some β opening product would start to appear.

Lets focus now our attention in the α,β-halogenoniumsilanes. As mentioned earlier, anti opening at the α position is generally observed. Thus, when trans-1-trimethylsilyl-1-propene, **1**, was treated with bromine, erythro dibromide **2** could be isolated from the reaction[9] (eq. 3). Product **2** is the result of an anti attack of the



1 2 (3)

nucleophile to a bromonium ion. In another case, vinyl silane **3** was treated with I_2 and silver trifluoroacetate and adduct **4** was isolated[10] (eq. 4). The general explanation for this observed regio and stereochemistry is the following. The olefin reacts with the halide to form a halogenonium ion which is attacked at the β position by the nucleophile. This last step has an advanced transition state in which there is a net defficiency of charge at the β position, stabilized by hyperconjugation of the C-Si sigma bond (β effect). The maximum stabilization would be reached when

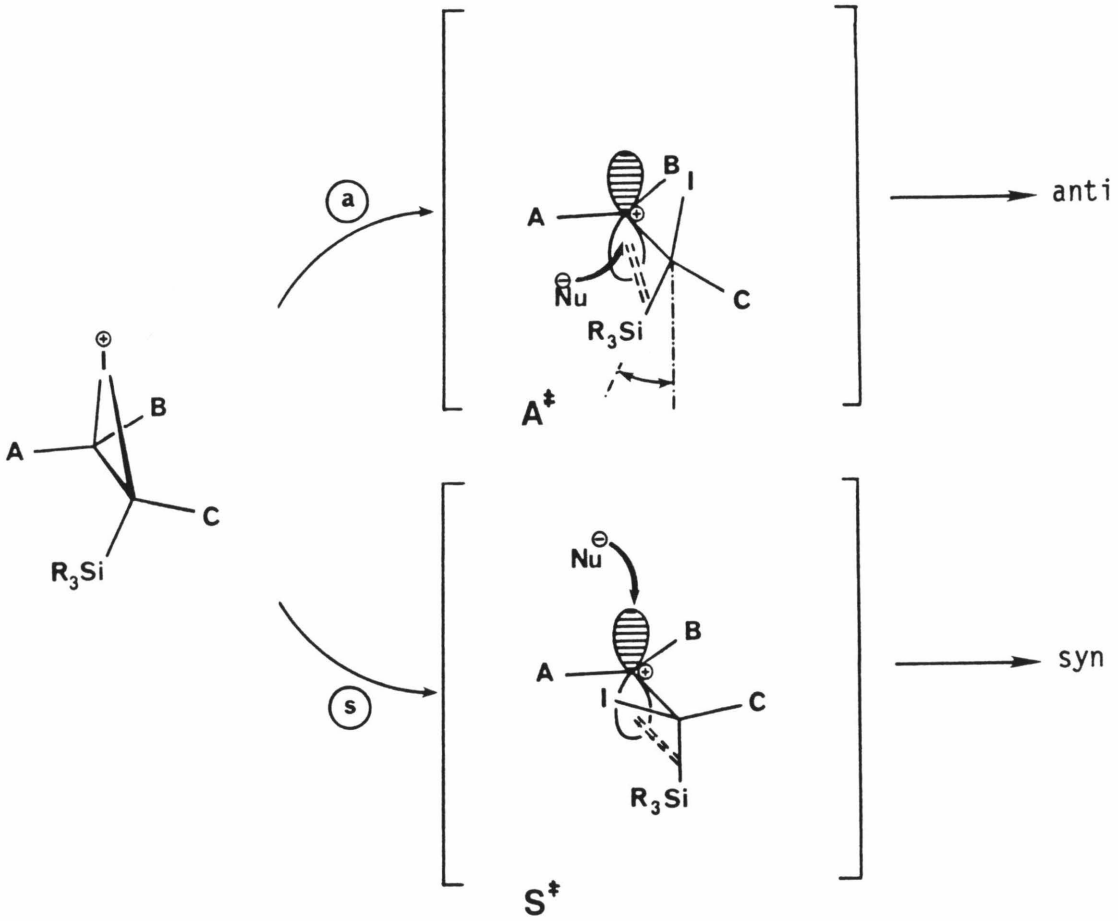


(4)

E, i.e.: inversion

the empty p orbital and the C_α-Si bond are in the same plane. In this orientation ($S^\ddagger$ in Scheme II), the bottom face would be blocked by the trialkylsilicon group and the nucleophile would approach from the top face giving syn addition. This is observed in the cases where A or B are groups that can stabilize an adjacent positive charge.[11] However, when they are usual alkyl groups, only anti addition is experimentally observed. This suggests that in this

Scheme II



latter case the transition state might be more reactant like than it was originally thought. That is, the C_α-C_β bond has not rotated from its original conformation ($A^\ddagger$ in Scheme II), having the trialkylsilyl unit not aligned with the adjacent p orbital. In this orientation, the β-effect is not operating fully.

At this point the question of how much of the overall regiochemistry is due to the β-effect comes into one's mind. Is this the only fact that determines β-attack to be more favorable?

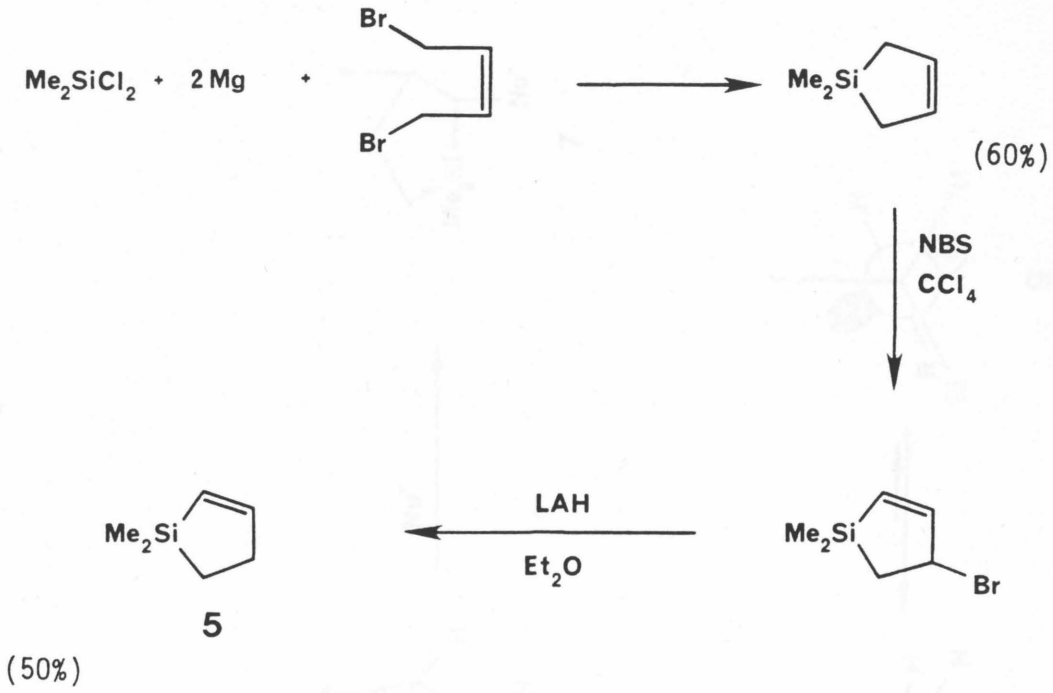
One way to evaluate it could be by means of an adduct in where the β-effect could not operate due to geometrical restrictions. One of these systems would be compound **5**.

5

Compound **5** has been synthesized by Manuel and coworkers.[12] The synthesis is straightforward and it is summarized in Scheme III.

Treatment of **5** with ICl, or $I_2/F_3CCO_2^-$ should give an addition adduct which regiochemistry would afford very valuable information.

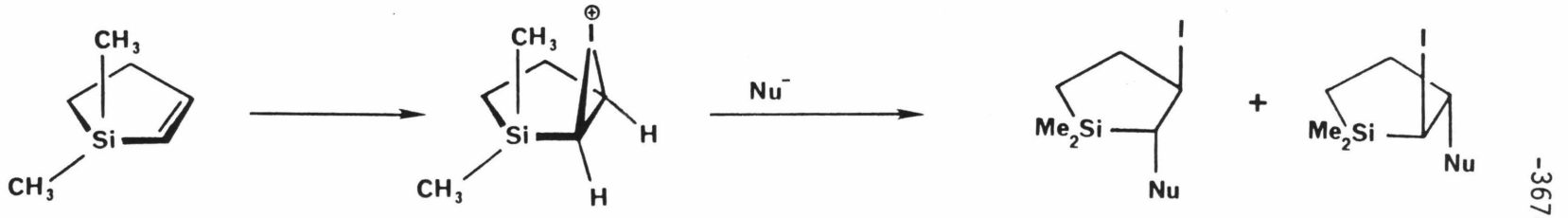
Scheme III



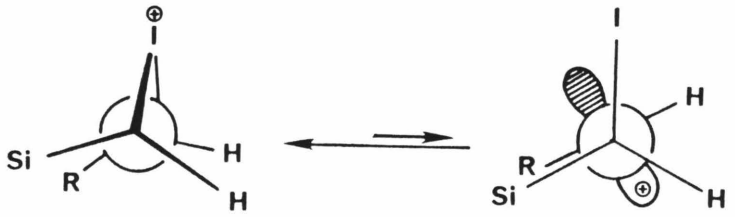
If we look at the structure of a possible β-cation intermediate **9**, we realize that the empty p ortibal is almost orthogonal to the C_α-Si bond, that is, no β-effect will be operating (Scheme IV).

The ratio of regioisomers will be mainly caused by the direct effect of silicon to its vicinal carbon. The difference in hinderance between the α and the β position in **6** should be similar to the one existing in the corresponding iodonium ion of **3**.

Scheme IV



III



9

Therefore, if the β-effect is the factor that is causing the observed regioselection in vinylsilanes, complete reversal should be observed and the system should behave like an α,β-epoxysilane, giving α-opening product **7**. Furthermore, compound **5** could be easily epoxidized (MCPBA) and treated with a nucleophilic agent. In principle, the reaction should proceed like with other epoxysilanes, where we concluded that no β-effect is operating, and afford α-opening product. This would serve as control experiment providing us with information concerning potential variations due to steric effects not present in the acyclic cases.

References and Notes

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(2) For a review see Chan, T. H.; Fleming, I. Synthesis **1979**, 761.

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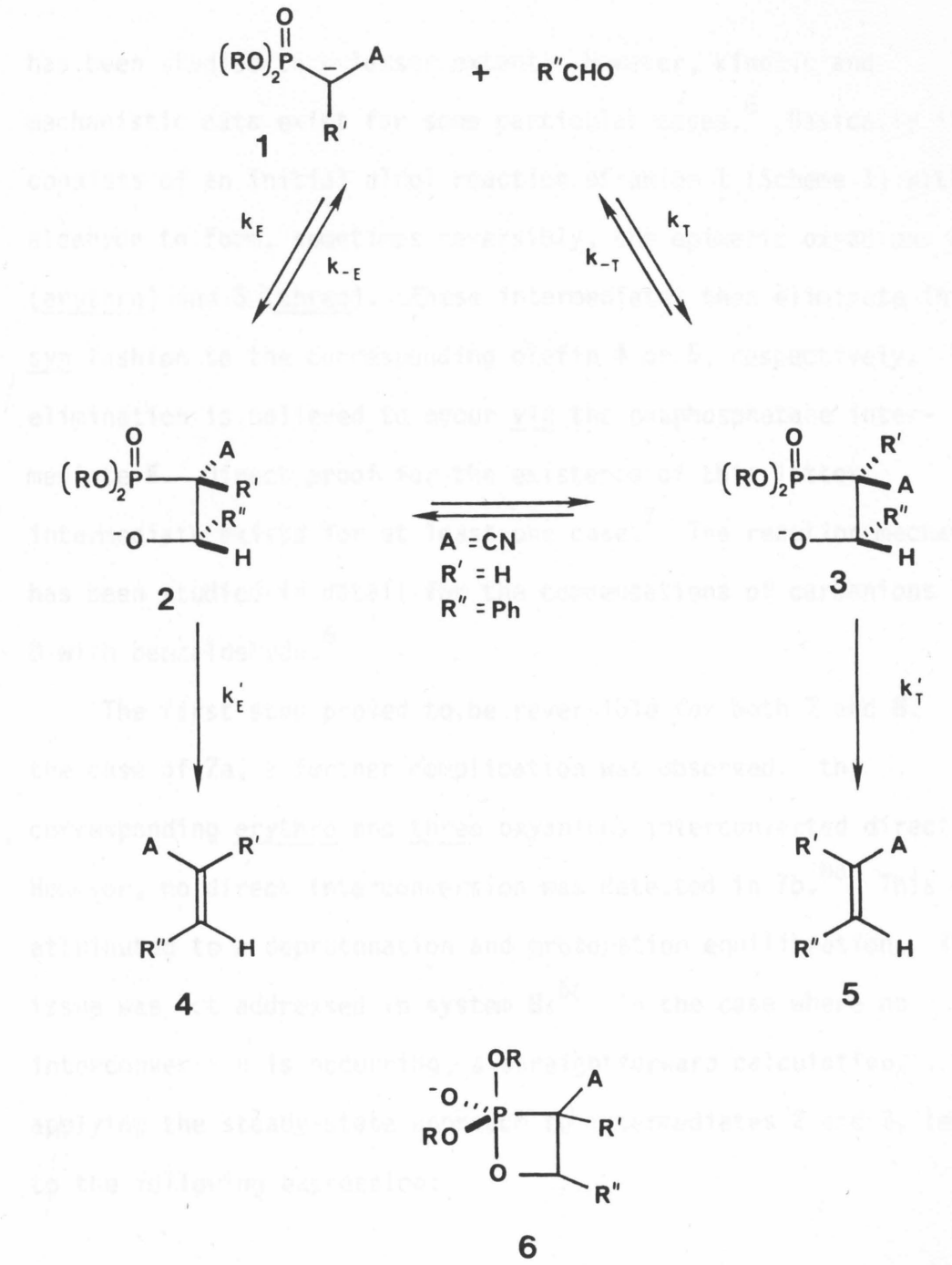
PROPOSITION II

Abstract: An explanation for the observed steric effects in the selectivity of the Horner-Emmons reaction is presentd. Experiments for its corroboration are proposed. Transition state structures are discussed.

****

The Wittig reaction constitutes one of the most common means of constructing olefins.[1] Since the original discovery by Wittig and Geissler in 1953,[2] a great deal of effort has been directed towards the control of the reaction diastereoselection by modification of the organosphosphorus reagent and/or the reaction conditions. One of the most significant improvements in this aspect was the introduction of the phosphoryl-stabilized carbanions by Horner and Wippel in 1958.[3] The phosphonate carbanions have been the most commonly used due to their readily availability and easy workup.[4,5] The method is now referred to as the Wadsworth-Emmons or the Horner-Emmons modification of the Wittig reaction. The general mechanism for the reaction of phosphonate carbanions with aldehydes to produce olefins is believed to be essentially identical to that of the Wittig reaction and it is summarized in Scheme I. Unlike the Wittig reaction itself, the mechanism of the Horner-Emmons reaction

Scheme I


(RO)2P
A
R'
1
+ R''CHO
kE
k-E
kT
k-T
2
3
A = CN
R' = H
R'' = Ph
k'E
k'T
4
5
OR
RO
6
Na+
(EtO)2P
CN
COOCH3
R
7a: R = H
7b: R = CH3
8a: R = H
8b: R = CH3

has been studied to a lesser extent. However, kinetic and mechanistic data exist for some particular cases.[6] Basically it consists of an initial aldol reaction of anion **1** (Scheme I) with the aldehyde to form, sometimes reversibly, the epimeric oxyanions **2** (erythro) and **3** (threo). These intermediates then eliminate in a syn fashion to the corresponding olefin **4** or **5**, respectively. This elimination is believed to occur via the oxaphosphetane intermediate **6**. Direct proof for the existence of this latter intermediate exists for at least one case.[7] The reaction mechanism has been studied in detail for the condensations of carbanions **7** and **8** with benzaldehyde.[6]

The first step proved to be reversible for both **7** and **8**. In the case of **7a**, a further complication was observed: the corresponding erythro and threo oxyanions interconverted directly. However, no direct interconversion was detected in **7b**.[6a] This was attributed to a deprotonation and protonation equilibration. This issue was not addressed in system **8**.[6c] In the case where no interconversion is occurring, a straightforward calculation, applying the steady-state approach to intermediates **2** and **3**, leads to the following expression:

$$\frac{4}{5} = \frac{k_E}{k_T} \frac{1 + k_{-T}/k'_T}{1 + k_{-E}/k'_E}$$

Two limiting cases can be envisioned:

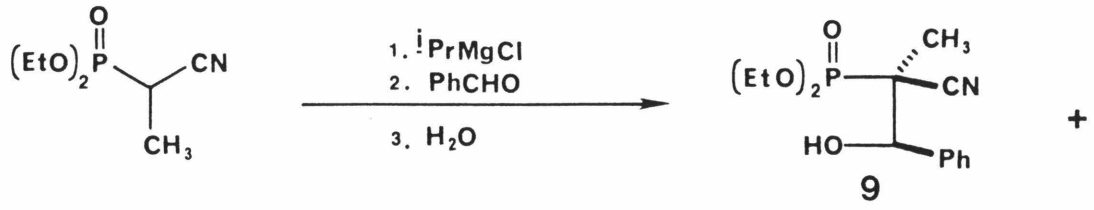
(a) k_{-T}/k'_T and k_{-E}/k'_E <<1, that is, the aldol condensation is highly irreversible. The olefin ratio is then equal to the aldol rate constant ratio k_E/k_T.

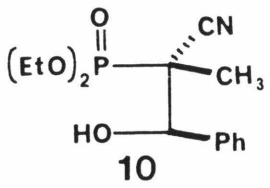
(b) k_{-T}/k'_T and k_{-E}/k'_E >>1, that is the aldol reaction is highly reversible, and the olefin ratio is given by the expression:

$$\frac{4}{5} = \frac{K_E}{K_T} \frac{k'_E}{k'_T}$$

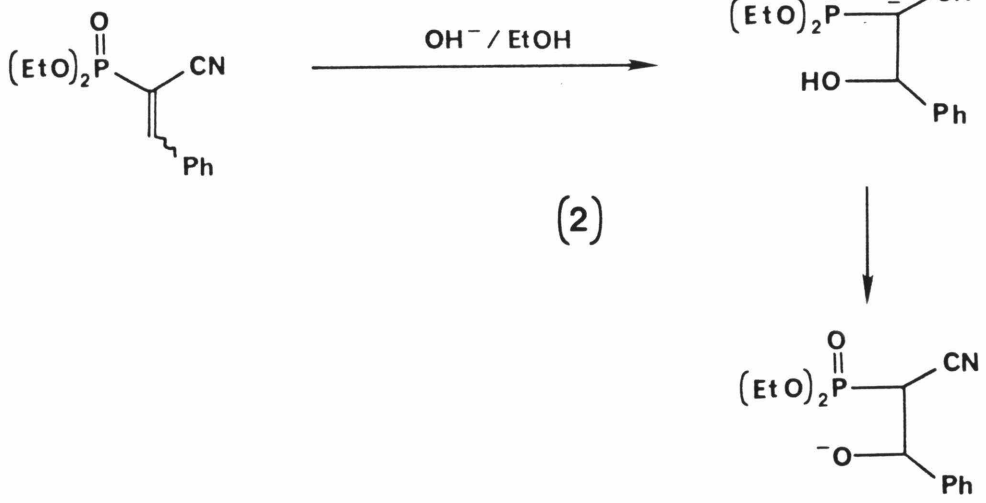
The overall reaction diastereoselection will then depend on the response of these rate constants to each particular substrate or conditions employed. For example, in the reaction of phosphonoester **8b** with benzaldehyde, the ratio k_{-E}/k'_E was found to be substantially higher than that of phosphononitrile **7b**, whereas the k_{-T}/k'_T coefficient proved to be similar.[6c] As a result, more E olefin was formed in the former case (Z:E = 3:97 for **8b** vs Z:E = 15:85 for **7b**).

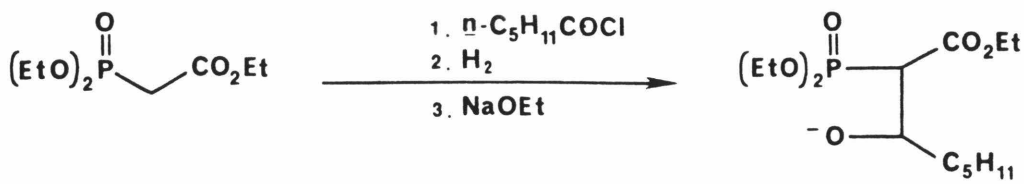
A very powerful method used in the elucidation of the mechanism of this reaction has been to study the product distributions derived from oxyanions **2** and **3** obtained by an independent way. These oxyanions have been obtained pure by base treatment of their corresponding conjugated acids **9** and **10** (eq. 1),[6] or as a mixture by the conjugated addition of hydroxide ion to α-cyanovinylphoshonoesters (eq. 2),[8] or by reduction of a α-ketophosphonate (eq. 3).[9]


(EtO)2P
CN
CH3
1. iPrMgCl
2. PhCHO
3. H2O
CH3
CN
HO
Ph
9
+


CN
CH3
HO
Ph
10

(1)


(EtO)2P
CN
Ph
OH⁻ / EtOH
HO
(2)
⁻O


(EtO)2P
CO2Et
1. n-C5H11COCl
2. H2
3. NaOEt
⁻O
C5H11

(3)

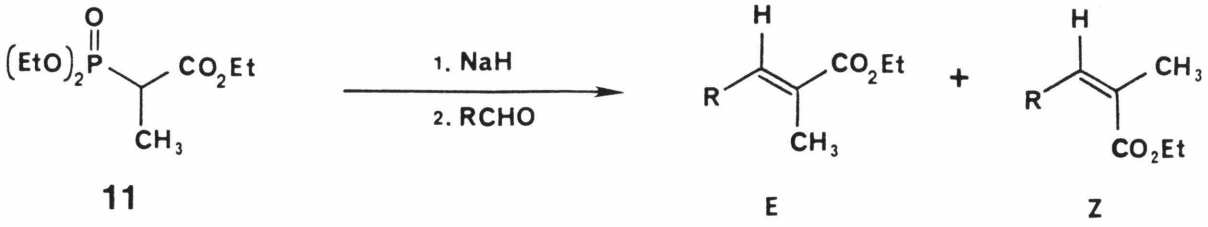
Their isolation (eq. 1) and conversion of their sodium conjugated bases into olefins constitutes a powerful proof of their existence as intermediates in the reaction. An analysis of the olefin distribution obtained upon treatment of each β-hydroxy-phosphonate (erythro and threo) with base, in presence of an excess of a competing aldehyde led, in the case of **7** and **8**, to the mechanism mentioned above, and provided some rate constant coefficients.[6a,c]

The stereoselection of the Horner-Emmons reaction, like the Wittig reaction, has shown to be highly dependent on the reaction conditions (temperature, solvent, counterion) and on the nature of the phosphonate, especially on its steric requirements. There is a large number of examples in the literature concerning the variability of the olefin distribution upon changes in the size of the groups of the reactants. However, no studies have been done to determine how these effects really modify the ratios. Some of these examples are presented below.

In general, for phosphonates not bearing a substituent α to phosphorus (**1**, R'=H), the E isomer is formed predominantly, independent of the steric requirements (nonetheless, some exceptions occur as will be noted later). For phosphonates bearing an alkyl group α to phosphorus, the size of this substituent and that of the aldehyde have shown to influence the product distribution. Thus, when phosphonate **11** was treated with sodium hydride and condensed

with different aliphatic aldehydes, an increase of the Z olefin percentage was observed concomitantly with the increasing size of the aldehyde (Scheme II).[10] Similar trends were observed when a given aldehyde was condensed with a variety of phosphonoesters having increasing sterically demanding α substituents.[11]

Scheme II



11 **E** **Z**

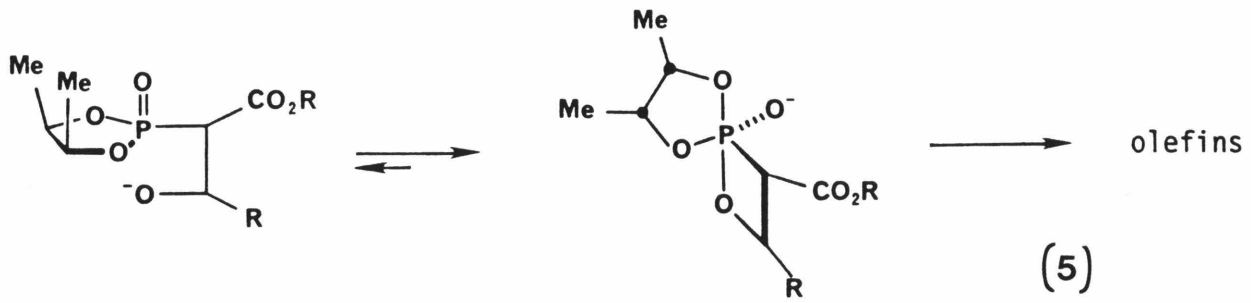
R	E : Z
Me	100:0
Et	84:16
i-C_3H_7	38:62
sec-C_4H_9	33:67

One interesting set of results is the influence of the size of the alkoxide groups attached at the phosphorus atom on the olefin distribution. When cyclic phosphonate **12** was treated with sodium hydride and condensed with different aldehydes, the Z olefin was obtained with a selection of ca. 3:2 (eq. 4).[12] This has been

12

minor (4) major

attributed to an enhancement of the rate of oxaphosphetane formation, due to ring strain release upon going from a tetrahedral to a pentacoordinate phosphorus, in which the five-membered ring occupies an apical-equatorial position (eq. 5). This rate

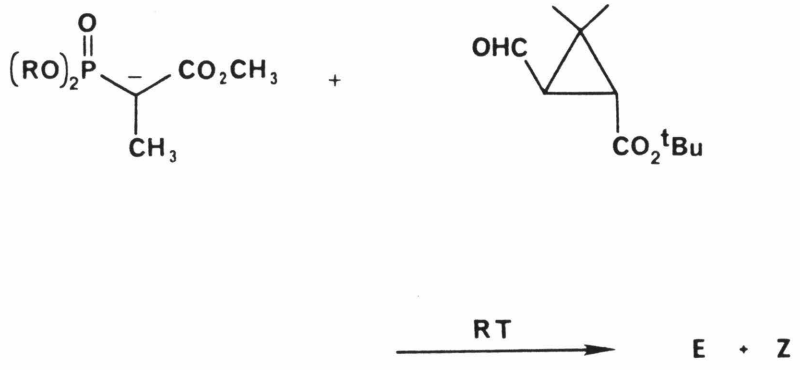


(5)

enhancement would represent a decrease of the k-/k' factor, leading towards a more kinetically controlled reaction (see Scheme I).

An interesting and synthetically useful control of the olefin distribution has been accomplished through the use of different sterically demanding alkoxide groups at the phosphorus. One of the earliest reports in this aspect is shown in Scheme III.[13]

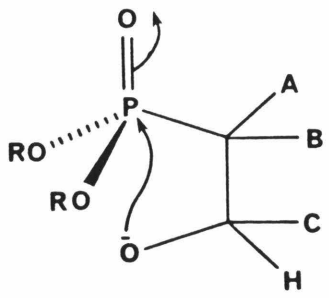
Scheme III



R	E : Z
Me	65:35
Et	83:17
i-C_3H_7	99:11

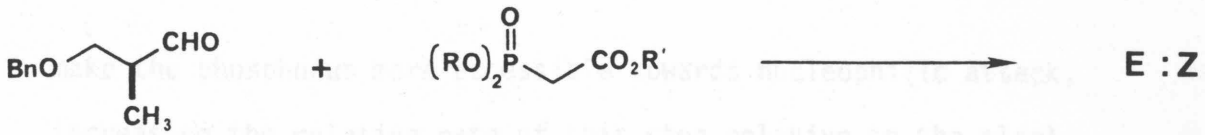
These results show that an increase in the E olefin selection correlates with an increase in the size of the alcoxide substituent of the phosphonate. Similar trends have been recently reported in other systems and are summarized in Scheme IV.[14] Interestingly enough, even the stereochemistry of the disubstituted olefins could be modified by this approach. The data however, were presented in a rather empirical way and were not accompanied by any kind of explanation.

One possible rationalization of these steric effects could be that the rate of oxaphosphetane formation might be highly modified by the steric hinderance at the phosphorus atom. Thus, when R (eq. 6) is sterically demanding, the intramolecular alkoxide attack at the phosphorus would be slowed down and the k-/k' coefficient increased. Under these conditions, the olefin geometry will be dictated by the relative transition state energies of the oxaphosphetane formation. On the other hand, a small R group would

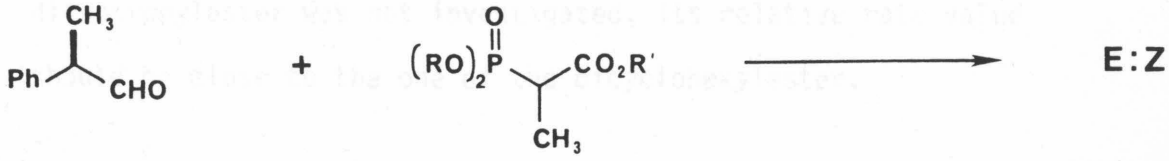


$\xrightarrow{k'}$ olefins (6)

Scheme IV



Entry	Phosphonate	Conditions	E:Z ratio
A	$(MeO)_2P(O)CH_2CO_2Me$	K*t*BuO/THF/-78°C	1:3
B	$(iPr)_2P(O)CH_2CO_2Et$	K*t*BuO/THF/-78°C	95:5



Entry	Phosphonate	Conditions	E:Z ratio
C	$(iPr)_2P(O)CH(MeCO_2iPr$	K*t*BO/THF/-78°C	95:5
D	$(iPr)_2P(O)CH(Me(CO_2Et$	K*t*BO/THF/-78°C	90:10
E	$(EtO)_2P(O)CH(Me)CO_2Et$	K*t*BO/THF/-78°C	40:60
F	$(MeO)_2P(O)CH(Me)CO_2Et$	K*t*BO/THF/-78°C	10:90
G	$(MeO)_2P(O)CH(Me)CO_2Me$	K*t*BO/THF/-78°C	5.95

make the phosphorus more accessible towards nucleophilic attack, increasing the relative rate of this step relative to the aldol step. Consequently, the olefin ratio would, in this case, reflect the aldol stereoselection.

Relevant data supporting the proposed explanation are given by studies on phosphonate hydrolysis. The kinetics of the hydrolysis of different methyl phosphonates in water:dioxane with sodium hydroxide have been described.[15] The results are reported in Table 1. It is clear from these data that there exists a strong dependence of the rate of hydrolysis on the steric effects of the substrate. The dicyclohexyl ester for example, hydrolyzes as much as 1000 x slower than the corresponding dimethyl ester. Although the diisopropylester was not investigated, its relative rate value should be close to the one of the dicyclohexylester.

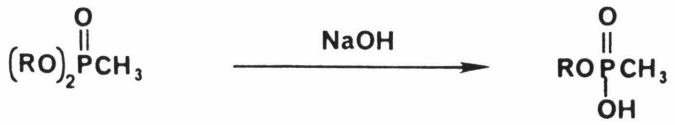
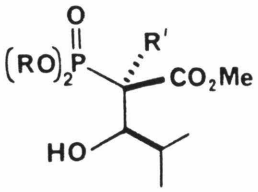


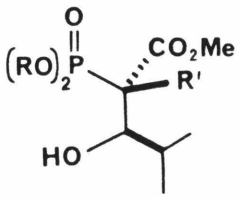
Table 1

R	rel. rate
CH_3	1000
Et^3	95
n-prop	49.7
n-but	29.5
cyclohexyl	1
$CH(Me)CMe_3$	0.2

Even if in our case the reaction proceeds intramolecularly, a similar trend should be expected for the formation of the oxaphosphetane intermediate. A factor of 1000 would be, indeed, more than enough to reverse the control of the reaction.

One way of gaining further information about the proposed explanation would be through the study of the evolution of the independently generated oxyanion intermediates. For this purpose, β-hydroxyphosphonates **13-18** can be prepared following the





13: R=R'=Me

14: R=R'=Me

15: R=iPr, R'=Me

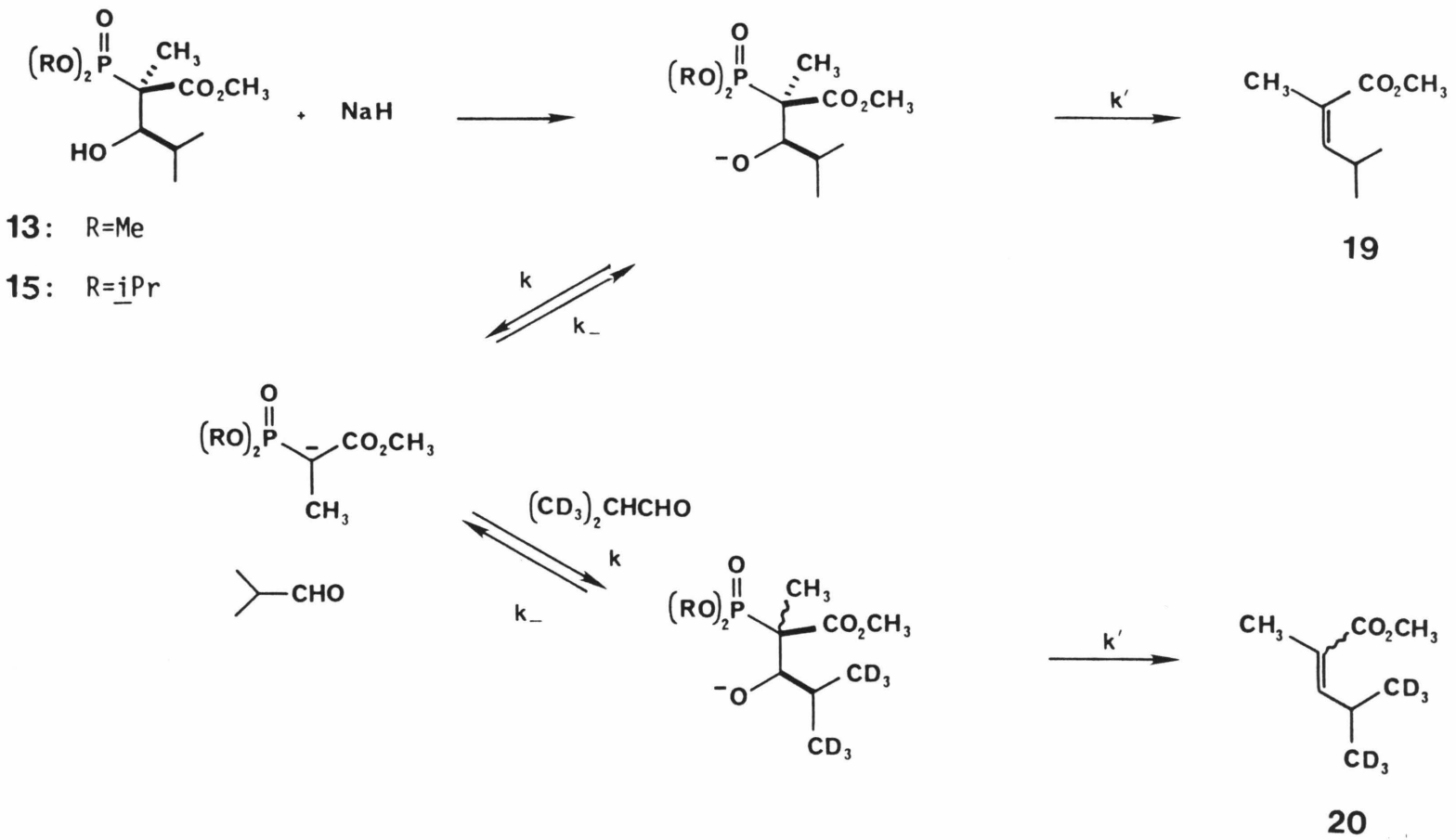
16: R=iPr, R'=Me

17: R=Me, R'=H

18: R=Me, R'=H

procedure described in the literature.[6a] If the olefin ratio is indeed dictated by the alteration of the k-/k' ratio, treatment of each of these compounds with sodium hydride in presence of an excess of a competing aldehyde, for example $(CD_3)_2CHCHO$ (readily available from acetone-d_6), should give different results (see Scheme V). Thus, the oxyanion derived from **13**, which should have a small k-/k' coefficient according to our model, should show mainly formation of

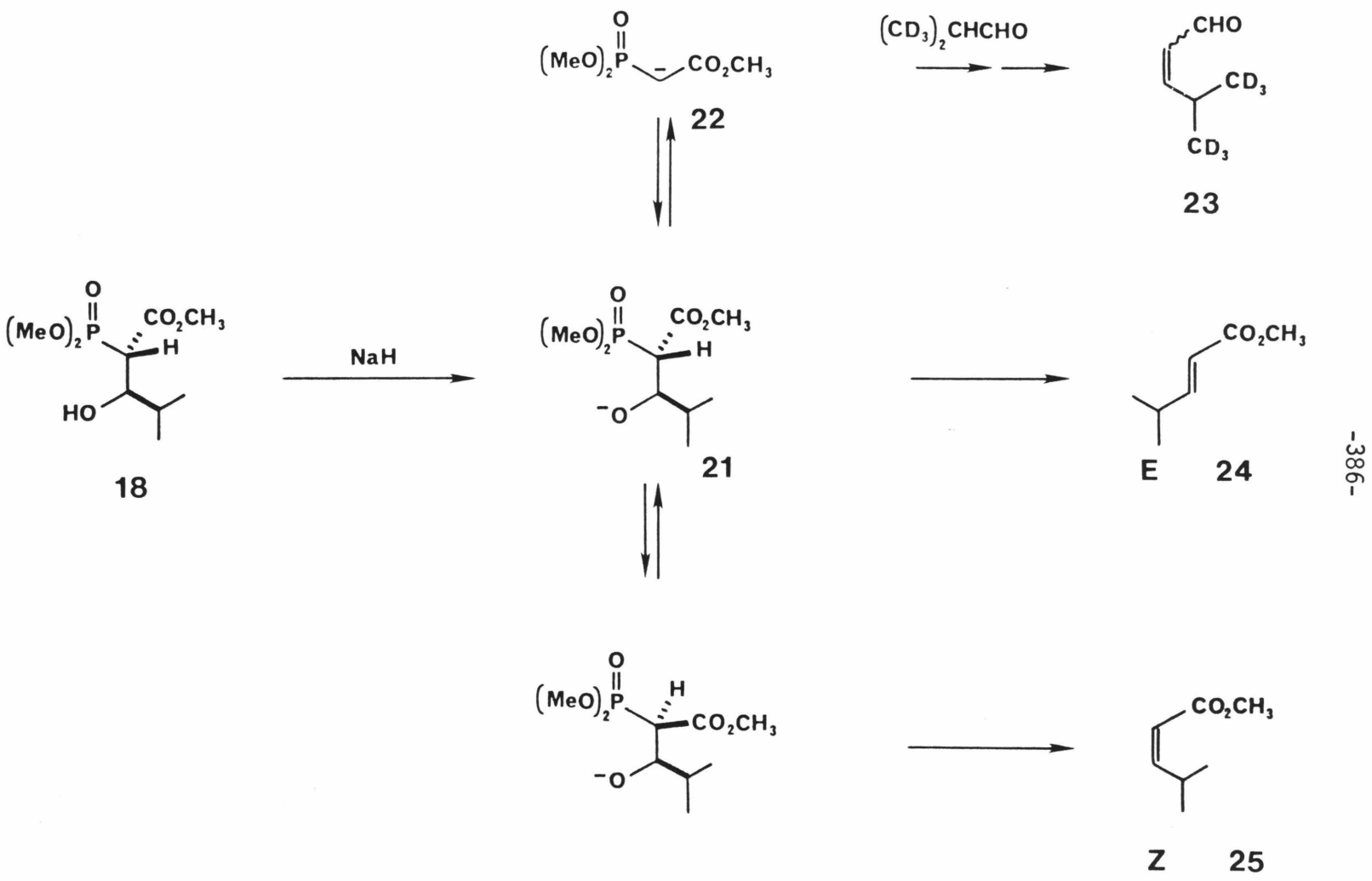
Scheme V


(RO)2P(O)(CH3)CO2CH3
HO
+ NaH
-O
k'
CH3CO2CH3
19
13: R=Me
15: R=iPr
k
k_
(CD3)2CHCHO
CHO
CD3
CD3
20

the Z olefin **19**, and little of the cross-over product **20**. On the other hand, the oxyanion derived from β-hydroxyphosphonate **15** would have a large k-/k' coefficient, that is, it would revert into starting materials much faster than it would form product. In this case, then, deuterated olefin **20** should be formed in large amounts. Same trends should be observed in the threo series, **14** and **16**.

An interesting case is the one where R'=H, leading to the formation of disubstituted olefins. As shown in Scheme IV, the Z olefin selection using trimethylphosphonoesters is not as good in the synthesis of disubstituted olefins as it is in the trisubstituted counterparts. Is this due to a poorly diastereoselective aldol condensation (1st step) or is it due to a direct equilibration of oxyanions of the type observed for **7a**? Again, this could be tested by the study of the evolution of oxyanion **21**, derived from β-hydroxyphosphonate **18**, in presence of an excess of deuterated aldehyde (Scheme VI). Formation of the cross-over olefin **23** should be checked first. According to our model, oxyanion **21** should eliminate faster than revert to the starting trimethylphosphonoacetate anion **22**, because of the little hinderance around the phosphoryl group. We should not observe, therefore, formation of the cross-over olefin **23**. Assume the experiment has been done and that this has been found to be the case. Then, if there is direct epimerization between oxyanions, **21** should lead into a mixture of olefins **24** and **25**. Comparison of the olefinic ratio obtained this way and the olefinic ratio obtained in the direct reaction (that is,

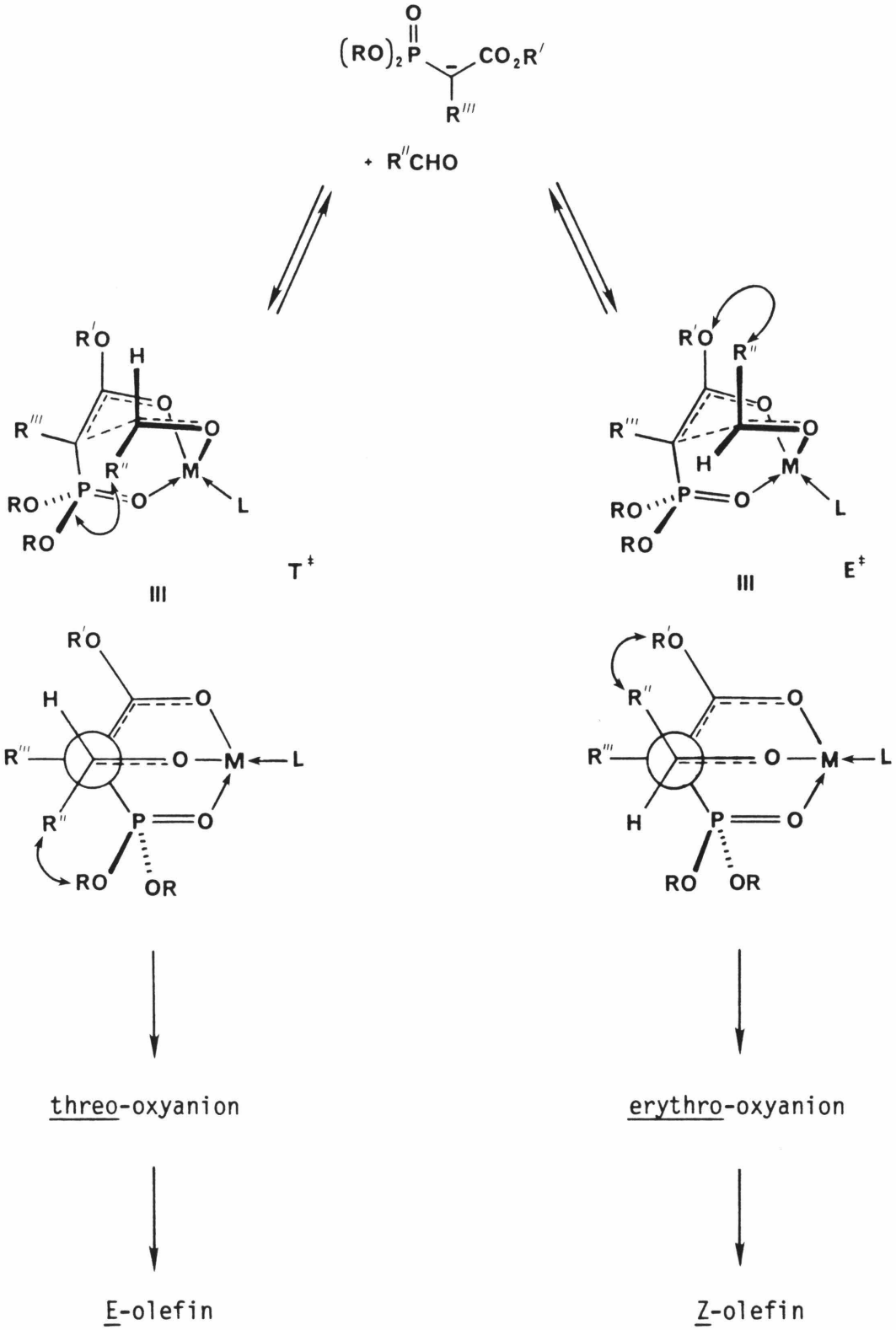
Scheme VI


(MeO)2P(O)CH(CO2CH3)
22
(CD3)2CHCHO
CHO
CD3
CD3
23
(MeO)2P(O)CH(CO2CH3)CH(OH)CH(CH3)2
18
NaH
(MeO)2P(O)CH(CO2CH3)CH(O-)CH(CH3)2
21
CO2CH3
E
24
(MeO)2P(O)CH(CO2CH3)CH(O-)CH(CH3)2
CO2CH3
Z
25

using **22** and isobutyraldehyde as the starting materials) would indicate how fast equilibration is relative to olefin formation (Curtin-Hammett principle[16]). If, on the contrary, **21** does not epimerize directly, it should afford only E olefin **24**, since the elimination is known to proceed stereospecifically syn.[6a] In this case, then, the olefinic ratio obtained in the direct reaction of phosphonate **22** and isobutyraldehyde (which by comparison to the data presented in Scheme IV should be around 3:1 Z:E) would be reflecting the aldol stereoselectivly. Then, we would conclude that, according to the data on Scheme IV, an α-alkyl group is necessary to reach high (>>3:1 erythro:threo) diastereoselection in the aldol step. As we will see in a moment, this would be unlikely.

So far we have talked about the influence of the size of the R group attached to the phosphorus. Examination of the data in Scheme IV shows that, in addition, there is a small effect on the olefinic ratio caused by the size of the ester attached to the carbonyl of the phosphonoester molecule. Lets assume that the experiments mentioned above proved that when the alcoxide group of the phosphorus is small the reaction is kinetically controlled, that is, the aldol step is the rate determining step. Seyden-Penne has demonstrated that the potassium enolate of triethylphosphonoacetate is 100% in the Z form in THF.[17] Then, assuming that the aldol reaction goes through a pericyclic transition state[18] with the metal chelating the three sp^2 oxygens, we can think of two possible structures

Scheme VII


(RO)2P
CO2R'
R'''
+ R''CHO
R'O
H
R'''
R''
M
L
RO
P
O
RO
T‡
III
R''
E‡
III
threo-oxyanion
erythro-oxyanion
E-olefin
Z-olefin

for the Z enolate: $T^{\ddagger}$, leading to the threo oxyanion and $E^{\ddagger}$, leading to the erythro oxyanion (Scheme VII). Transition state $T^{\ddagger}$ has a disfavored 1,3-diaxial interaction between the aldehyde substituent R" and the phosphorus substituent OR. Transition state $E^{\ddagger}$, on the other hand, lacks this particular interaction but has a 1,3-diaxial interaction between the aldehyde substituent R" and the carbon ester group OR'. One can anticipate that the 1,3-diaxial interaction should be more severe in $T^{\ddagger}$ than in $E^{\ddagger}$ as the phosphorus is tetrahedral whereas the ester carbon is planar. However, if R'O is considerably large (i.e. R'=iPr), then the interaction R"$\leftrightarrow$OR' in $E^{\ddagger}$ might become more important putting this transition state somewhat closer in energy to $T^{\ddagger}$, therefore decreasing the reaction selection. This could account, then, for the selection improvement observed in entry G (Scheme IV).

According to this model, the size of the α-substituent R'" should not influence the stereoselection in the aldol condensation since it would be affecting the energies of $E^{\ddagger}$ and $T^{\ddagger}$ in a comparable way. The observed dependence of the olefin ratios on the size of R'" (vide supra) must then be caused by a different rate of oxaphosphetane formation. The reason for the differences in olefinic ratios observed in entries C and D of Scheme IV remains, at this point, unknown.

The proposed transition states predict a higher percentage of erythro oxoanion formation as the phosphorus substituents increase in size. If this was the only effect on the diastereoselection of

the reaction, higher percentages of Z olefin should be observed. However, concomitantly with this increasing erythro selection, the rate of the oxaphosphetane formation should be decreased by large size substituents (vide supra) and this last step would then eventually become the rate determining step, favoring E olefin formation. The experimental results indicate that sterics must be felt in a more dramatic way in the oxaphosphetane formation than in the aldol reaction. This is supported by the strong steric dependance showed in the rate of the basic hydrolysis of phosphonates.

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PROPOSITION III

Abstract: A mechanism for the disassembly of microtubules is proposed. The use of [β-^{32}P]-GTP to provide experimental evidence for the proposed mechanism is discussed.

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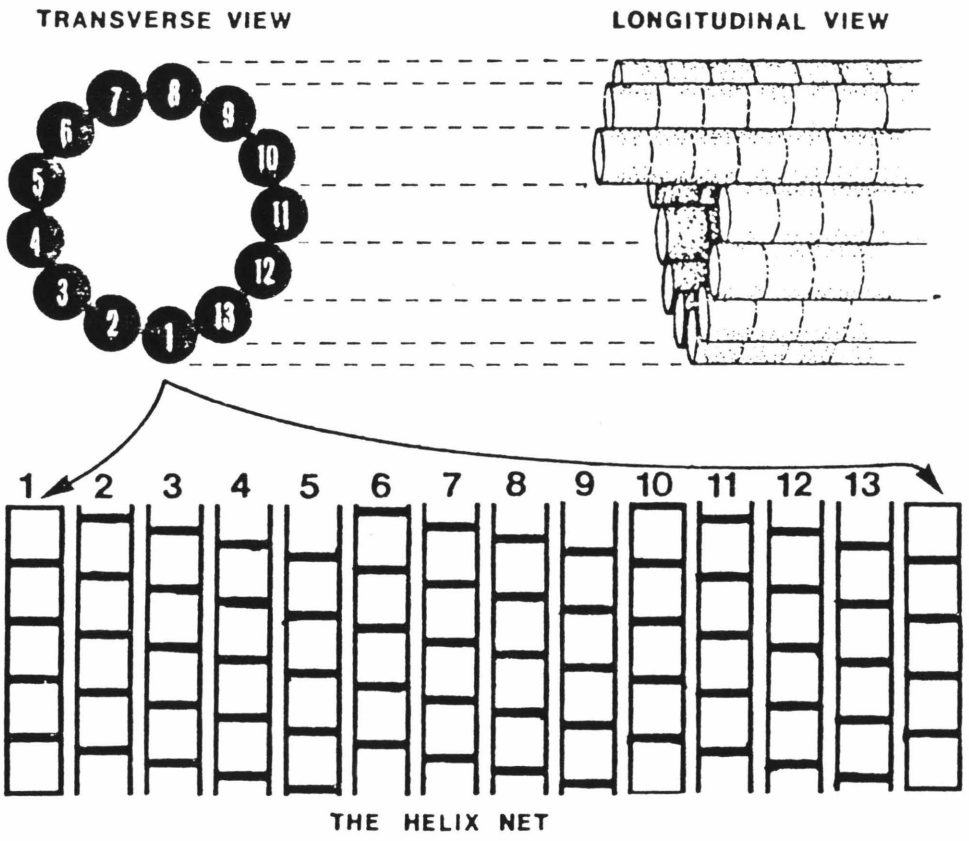
Microtubules[1] are proteinaceous organelles, present in nearly all eucaryotic cells, made of subunits assembled into elongated tubular structures. Together with other proteins, they are the building blocks of complex assemblies like mitotic spindles, centrioles, cilia and flagella, oxonemes and neurotubules. Microtubules may be described as regular helical assemblies of two protein subunits,[2] tubulins α and β, each of about 55,000 daltons molecular weight.[3] It has been shown that one mole of purified tubulin binds two moles of GTP.[4] There are two sites: at one, GTP is tightly bound to the protein and does not exchange with exogenous GTP; at the other, GTP is weakly bound to the protein and exchanges with the GTP in the medium. These sites are called E (exchangeable) and N (non-exchangeable).

Microtubules consist of chains (protofilaments) of the subunit protein, tubulin, aligned longitudinally along the axis of the cylinder with 13 protofilaments arranged around the circumference (see fig. 1). In 1972, Weisenberg[5] described the conditions for

Figure 1


TRANSVERSE VIEW
LONGITUDINAL VIEW
1 2 3 4 5 6 7 8 9 10 11 12 13
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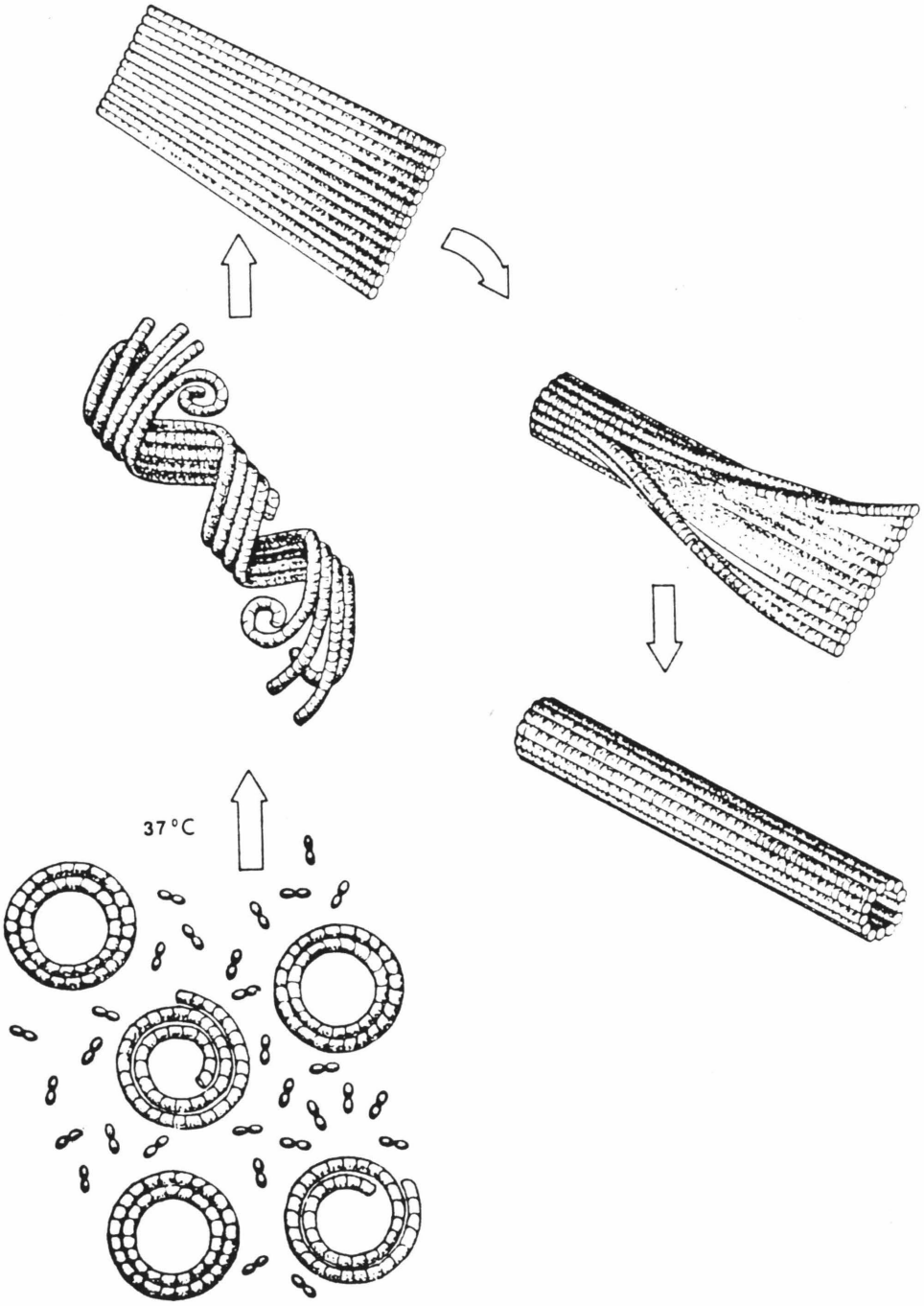
microtubule polymerization in vitro using brain tubulin. He found that the following conditions were required: (1) a minimum tubulin concentration, (2) presence of GTP, (3) presence of Mg^{2+} and absence of Ca^{2+}, and (4) a temperature of 37°C. The evolution of microtubule polymerization can be followed by turbidimetry and visualized by electron microscopy.

Tubulin isolated by cycles of temperature dependent polymerization-depolymerization copurified with some other proteins called MAP's (Microtubule Associated Proteins). The MAP's belong to two classes: one, with high molecular weight (ca. 300,000 daltons) called MAP_2; the other, with lower molecular weight (55,000 to 70,000 daltons) called the τ factor. Under physiological concentrations of Mg^{2+} (1 mM) and GTP (1 mM), polymerization of tubulin into microtubules requires the presence of these MAP's. However, the role that these proteins play in the process remains unclear.

Thermodynamically, the tubulin-microtubule system is in dynamic equilibrium. The free tubulin is always equal to the minimal concentration required for polymerization (called the critical concentration). Tubulin assembly occurs by a polymerization-condensation mechanism consisting of two different phases: nucleation and elongation (see fig. 2). Some of these nuclei have been isolated and purified,[6] and show the presence of ribbon precursors. This tendency of tubulin to self-associate and to form intermediate polymers complicates the study of the assembly

Figure 2



mechanism. Once the assembly process has started, it proceeds until the tubulin-dimer concentration reaches the critical concentration. At this point the steady-state has been achieved and the weight of total microtubule stays constant. The system is then continually undergoing assembly and disassembly. These two different processes are occurring preferently at opposite ends of the microtubules at equal rates. Addition of Ca^{2+}, antimicrotubular drugs such as colchicine or Vinca alkaloids, or low temperatures (0 - 4°C) results in complete depolymerization.

An essential point in the process of microtubule assembly is the role played by GTP. It has been shown that the E-GTP was hydrolyzed to GDP during polymerization, while the N-GTP was not.[7] However, hydrolysis of the E-GTP into GDP was shown not to be required for polymerization, since non-hydrolyzable analogs of GTP (such as $GMPP(CH_2)P$ and GMPP(NH)P) have the capacity to promote assembly.[7c,8] The use of the α-β hydrolysis resistant GTP analogs (like $GMP(CH_2)PP$ and $GMP(CH_2)P$) has also been investigated,[9,10] showing interesting properties. Microtubules polymerized with $GMP(CH_2)PP$ are assembled at lower tubulin concentrations than those with GTP, resulting in faster rates of microtubule nucleation. In addition, these microtubules do not depolymerize when exposed to cold or Ca^{2+} ions. Experiments with $GMP(CH_2)P$, the α-β non-hydrolyzable analog of GDP, once again showed assembly, but to a lesser extent.[10] Its equivalent, GDP, however, did not induce tubulin polymerization.[11]

It seems, then, that α-β hydrolysis might play a critical role in the process of disassembly. Then, conversion of GDP into GMP could be a requirement for microtubule disassembly. In fact, incubation of GTP with tubulin under polymerization conditions results in production of GDP and GMP.[10] However, this GMP could be the product of the hydrolysis of GDP in the medium, due to the action of minor impurities of phosphatases that copurified with the tubulin. On the other hand, E-GMP bound to the tubulin at the microtubule stage has never been detected.

One possible explanation for this apparent controversy could be the participation of the N-GTP. If one makes the assumption that a conformational change in the tubulin molecule is required in order to cleave the dimer from the microtubule (i.e. disassembly), then, this change could be the result of a rapid interchange of the N-GTP γ-phosphate and the E-GDP β-phosphate. Such an interchange, with the transferred phosphate stabilized by some amino acid, would provide the tubulin molecule with a conformation suitable for depolymerization. This would explain why no GMP is detected in the microtubule and why microtubules containing α-β non-hydrolyzable GTP analogs at the E-site are resistant to depolymerization.

The hypothesis described above could be tested experimentally in the following manner. Tubulin would be polymerized in presence of [β-^{32}P]-GTP in order to load the E-site with this nucleotide. It is important to point out that interchange of nucleotides between

the E and the N-sites has never been observed. The microtubules would then be broken by the exposure to cold temperatures (vide supra). Then, the labeled nucleotide at the E-site would be displaced by use of an excess of non-labeled GTP, and subsequently removed by chromatography. Thus, after this treatment, any radioactivity found in the tubulin molecule would be due to labeled phosphorus at the N-GTP, therefore showing that ^{32}P interchange has occurred. This would not only account for a mechanistic function of the N-GTP, but would also help explain some of the experimental facts mentioned above.

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PROPOSITION IV

Abstract: The use of a Claisen rearrangement in the construction of vicinal quaternary centers is discussed. Its application to the total synthesis of (±)-Verrucarol is proposed.

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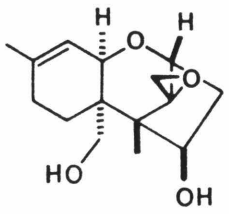
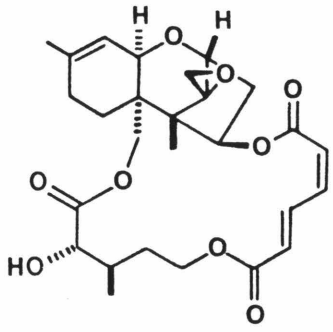
The trichothecene antibiotics are a clinically promising family of compounds.[1] These sesquiterpene metabolites show antibiotic, antifungal, antiviral and cytotoxic properties as well as anti-leukemic activity.[2] Indeed, laboratory-derived oxygenated trichothecenes have proved to be the most potent antileukemic agents known to date against mouse P388 leukemia.[2] As a consequence, it is not surprising that a lot of effort has been directed towards the laboratory syntheses of these compounds.

Structurally, they have interesting and challenging chemical features (Scheme I). The family can be divided in two groups. Both classes share a common, tetracyclic sesquiterpene, containing a spiro epoxide. However, one group contains an additional carbon chain forming a macrocyclic structure (Verrucarins and Roridins), whereas the other lacks this unit (Trichodermol and Verrucarol, among others).

Scheme I



Verrucarol (1)



Verrucarin A

Verrucarol, 1, contains the basic structure of nearly all the trichothecene members. It includes three cycles (named A, B and C going from left to right as represented in Scheme I), and an epoxide. The molecule has six oxygen functionalized carbons and one unsaturation. Finally, the carbon-carbon connection between rings A and C involves two vicinal quaternary centers. To date, three syntheses of Verrucarol have been published.[3,4,5] One key point in these syntheses and in those of related compounds is the stereo-selective introduction of the aforementioned quaternary centers.

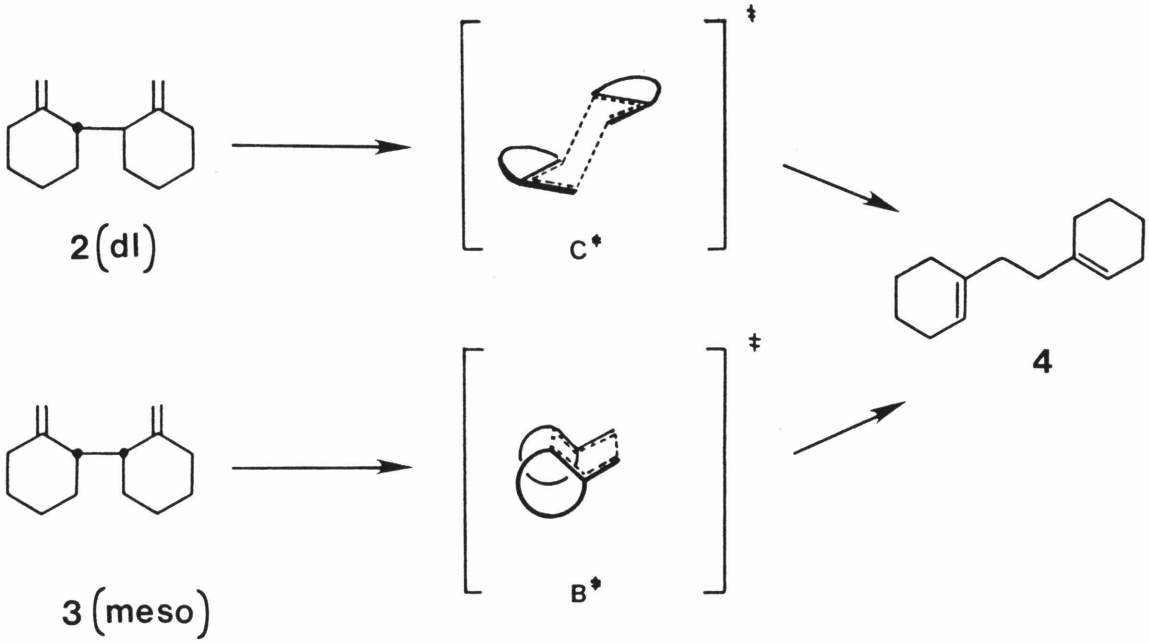
Useful methods that have been used for the construction of quaternary carbons[6] involve electrocyclic reactions. Indeed, in the mentioned syntheses of verrucarol these centers are created via Diels-Alder reactions or Claisen rearrangements, in a stepwise

fashion. It is conceivable, however, to envision the construction of the two quaternary carbons in one step by means of one of these processes. Because the non-bonding interactions in the transition state of such a reaction must be very severe, the presence of some "equilibrium-pulling" factor is required. Two examples of this are the Claisen and oxy-Cope rearrangements. In these cases, the formation of a carbon-heteroatom bond is the driving force of the reaction. Indeed, a quick calculation on the energy of the Claisen rearrangement of vinyl allylether (based on bond energies) favors the formation of the rearranged product by ca. 30 kcal/mol.

It is well accepted that, when possible, Claisen and Cope type rearrangements proceed via a cyclic, chair-like transition state, in which non-bonding interactions have been minimized.[7] This has been used for the stereospecific construction of substituted olefins or for chirality transfer along two points of a molecule. The energy difference between the corresponding chair and boat transition states for the Cope rearrangement of 1,5-hexadiene has been found to be 5.8 kcal/mol. This value is very close to the difference in energy of boat and chair cyclohexanes (5.5 kcal/mol). Furthermore, there has been found a correlation between the relative free energies of formation of the substituted Claisen chair transition states and those of the corresponding cyclohexanes.[8] This provides, then, a powerful tool to predict product distributions.

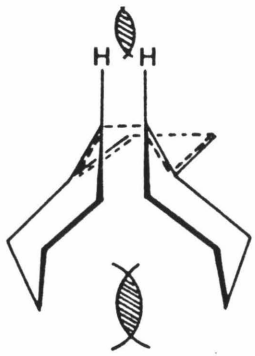
The kinetics of the Cope rearrangement of compounds **2** and **3** have been recently studied by Shea.[9] Both compounds lead to the same product **4** upon heating (Scheme II). However, the conformation

Scheme II



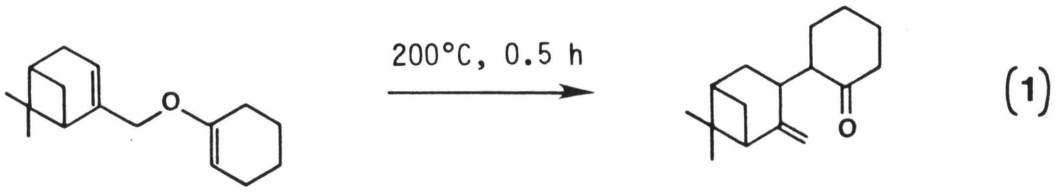
of their transition states must be different due to geometrical constraints. Thus, the dl compound can undergo rearrangement only through a chair transition state, whereas the meso counterpart can only rearrange via a boat. Analysis of the molecular models of the two transition states predicts serious non-bonding interactions between the two rings and the two vicinal hydrogens (see fig. 1) in

Fig. 1



transition state B. The difference in energy for these transition states was calculated to be 9.1 kcal/mol.

The equilibrium in this reaction lies completely towards product **4**. However, the introduction of an heteroatom in a suitable place could shift completely the equilibrium position to the opposite direction. Indeed, compound **5** undergoes rearrangement to the ketone in 75% yield (eq. 1).[10] By the principle of

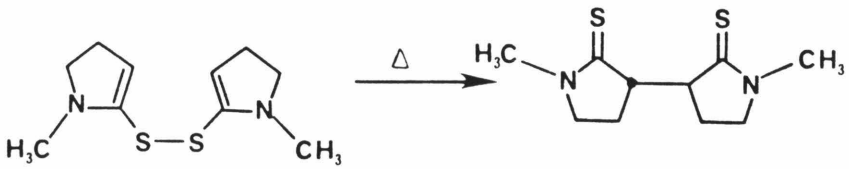


5 (75%) (1)

microrreversibility one can think that the arguments presented above will hold for this process. Therefore, only one compound (the

dl-type) should arise for this reaction. Unfortunately, the authors made no comment on the stereospecificity of the reaction.

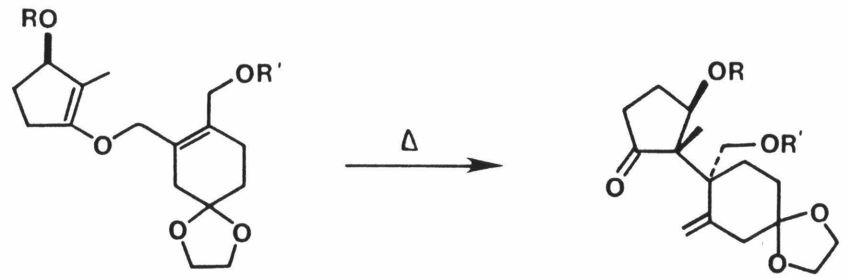
Data exist, however, on the stereospecificity of the rearrangement of compound **6** (eq. 2).[11] In this reaction, only the dl compound was formed.



(2)

6

Taking into consideration the data above, we can envision then the rearrangement of a compound like **7** into keto-olefin **8** (eq. 3). In this process, the overall stereochemical outcome would be dictated by two independent factors: a) according to the arguments presented above, the rearrangement would proceed through a chair transition state to afford exclusively the dl-type product; b) the chiral center in the molecule would ensure approach of the cyclohexene moiety from the less hindered side, that is, the α side.

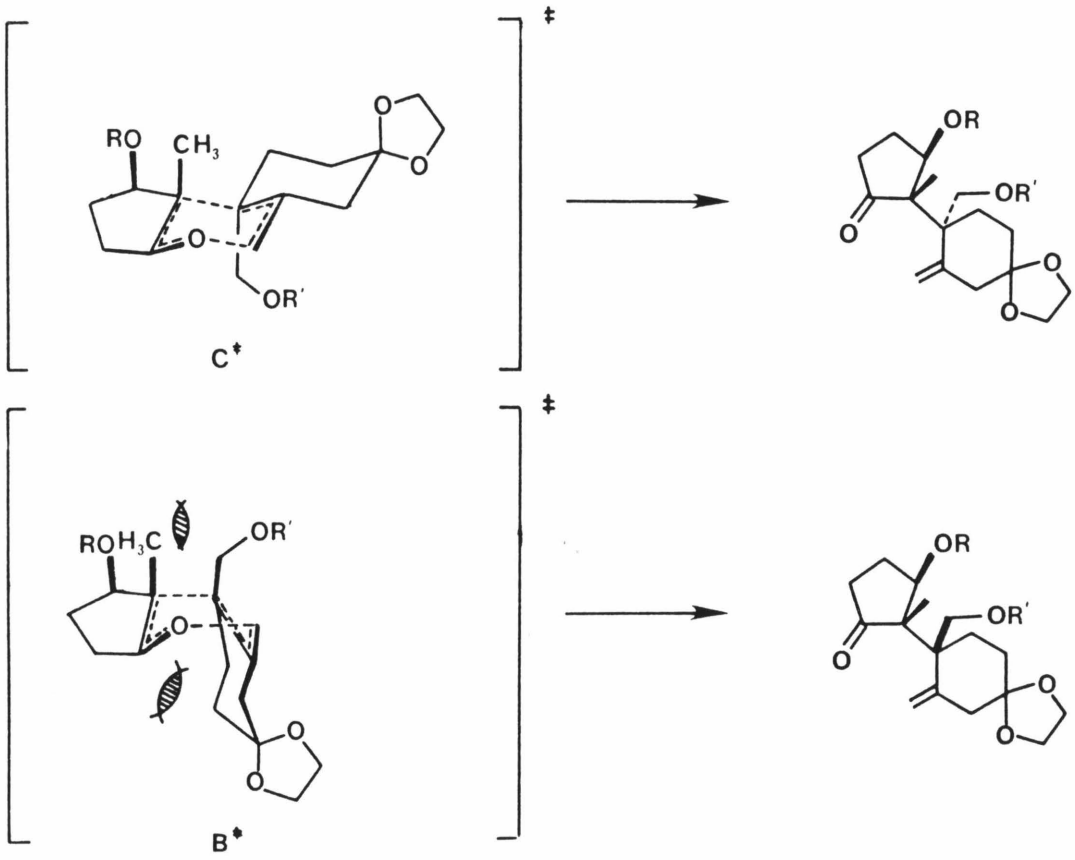


(3)

7 **8**

The two transition states (chair $C^{\ddagger}$, and boat $B^{\ddagger}$) of this mode of approach are represented in fig. 2.

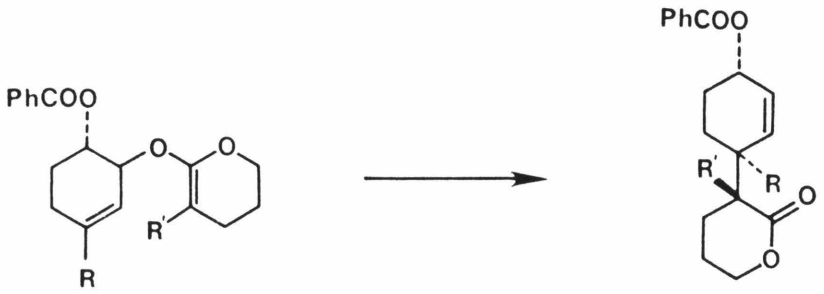
Fig. 2



It is clear from molecular models that transition state $B^{\ddagger}$ should be highly disfavored by a) the developing 1,2 $CH_3 \leftrightarrow CH_2OR$ interaction, and b) the interaction between rings. Both of these are absent in transition state $C^{\ddagger}$.

One aspect that has not been addressed up to this point is the potentially serious steric constraints of approaching two tetrasubstituted olefins. Although such a reaction has never been reported in the literature, a comparison with closely related systems indicates that yields are not substantially lowered when the degree of substitution is increased in sterically constrained systems. Scheme III summarizes one of these examples.[12]

Scheme III



	Yield
R= R'= H	80%
R= Me, R'= H	84%
R= H, R'= Me	75%
R= Me, R'= Me	77%

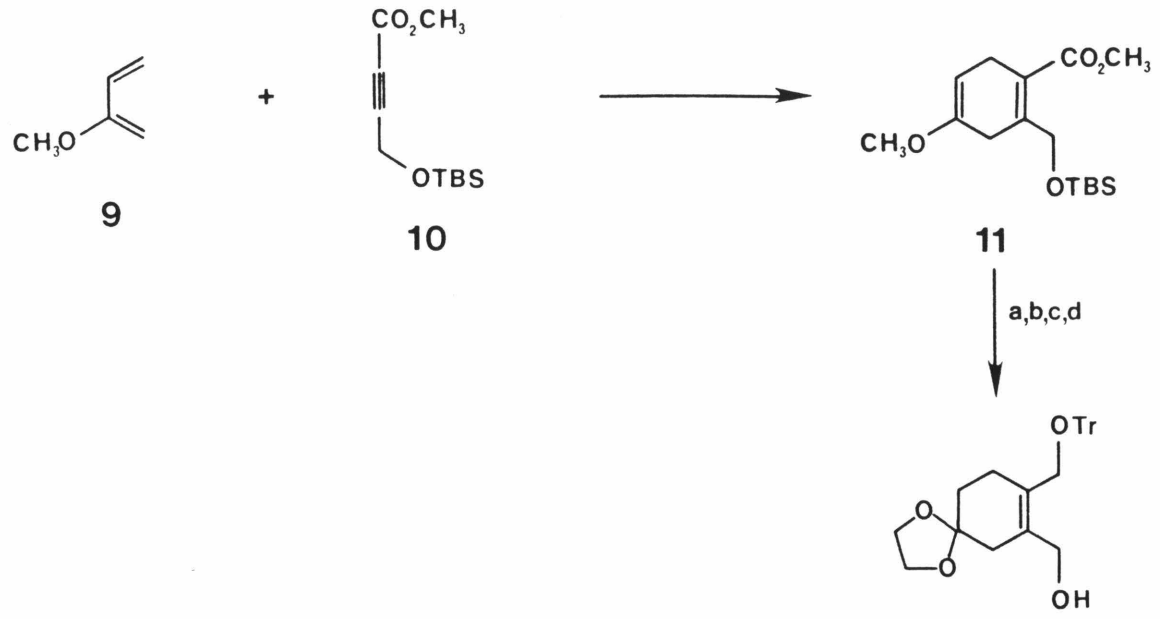
It should be mentioned that in this particular example, all three carbons of the allylic moiety are part of a ring and therefore

the corresponding transition states for the rearrangement are even more crowded that the ones of the reaction it is being proposed here.

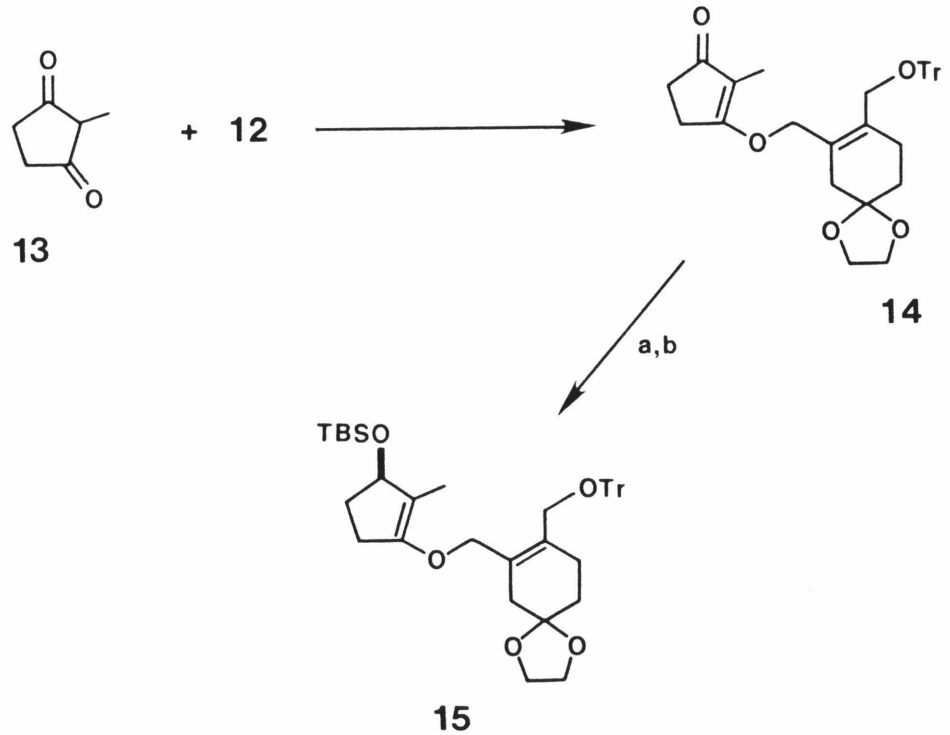
A possible preparation of the Claisen precursor is outlined in Scheme IV. The ring that would ultimately become the A ring of Verrucarol would be synthesized via a Diels-Alder reaction of 2-methoxy-1,3-butadiene (**9**) and acetylene **10.** Compound **10** could be easily prepared from commercially available dimethyl acetylene-dicarboxylate by reduction and protection as the t-butyldimethyl-silylether. The Diels-Alder adduct **11**, which should have the carboxylate and the methoxy substituents in a para relationship, would then be reduced to the alcohol (DIBAL, CH_2Cl_2), and this protected as the triphenylmethylether. Deprotection of the silyl ether (Bu_4NF, THF) and transformation of the methylenolether functionality into a cyclic acetal (ethyleneglycol, TsOH) would afford compound **12.**

The vinylic portion of the Claisen precursor, which would ultimately become the C ring of our target molecule, could be derived from 2-methyl-1,3-cyclopentadione, **13.** The coupling of the two pieces, **13** and **12**, in presence of a catalytic amount of acid (CSA) should give compound **14.** Reduction with sodium borohydride in presence of cerium cation,[13] and careful quenching (pH 7) to avoid elimination, followed by protection as the TBS ether (TBSOTf, Et_3N) would finally afford our desired product **15.**

Scheme IV



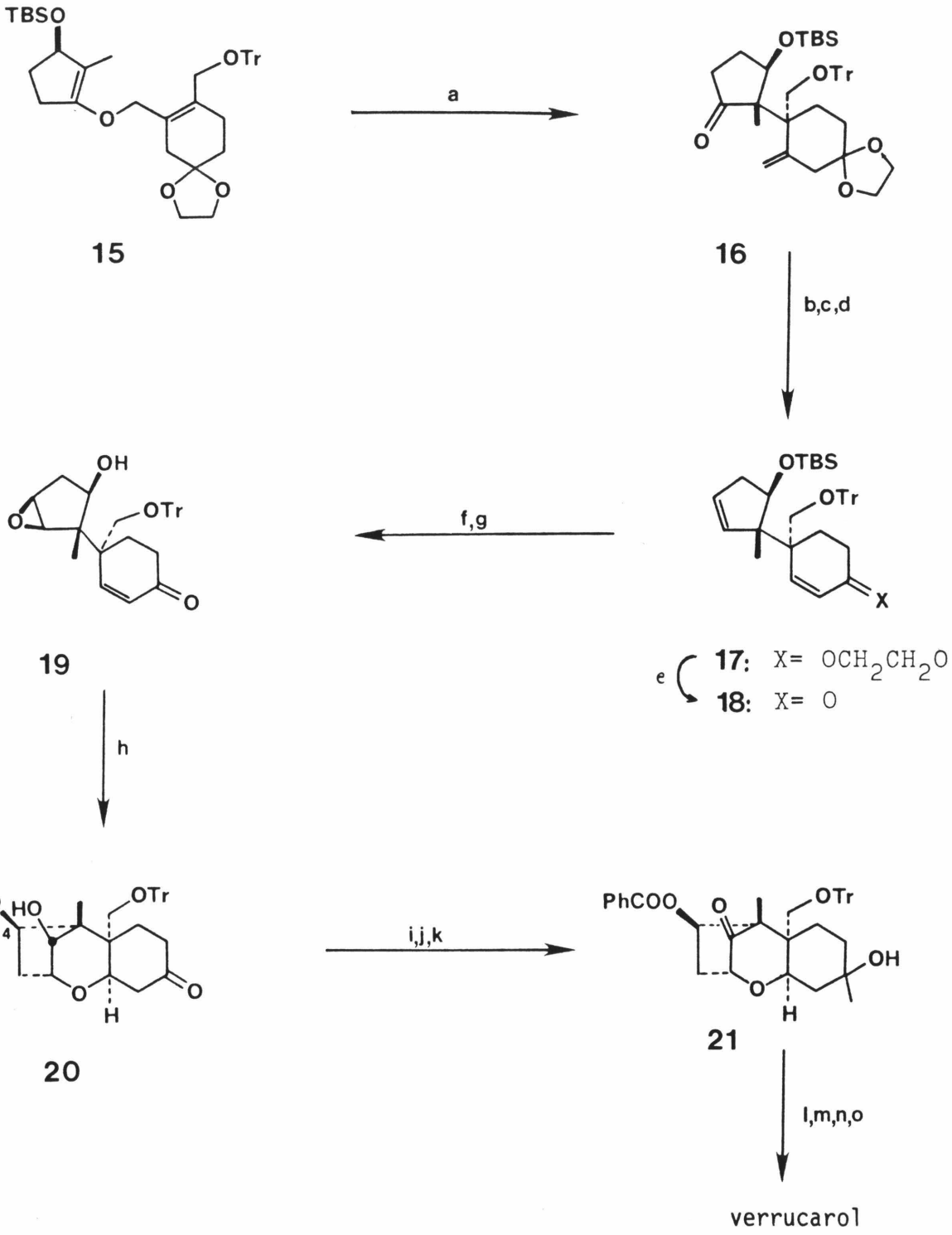
(a) DIBAL, CH_2Cl_2; (b) TrCl, Et_3N, CH_2Cl_2; (c) Bu_4NF, THF;
(d) $HOCH_2CH_2OH$, TsOH.



(a) $NaBH_4$, $CeCl_3 \times H_2O$; (b) TBSOTf, Et_3N.

Based on the arguments presented above, compound **15** should rearrange to ketone **16** upon heating. The final steps of the synthesis are outlined in Scheme V. Ozonolysis, followed by reduction ($LiBH_4$, THF) would presumably afford a complex mixture of diols. Without purification, the mixture would be treated with $POCl_3$ in pyridine to afford bis olefin **17.** Under mild acid conditions, selective deprotection of the acetal in presence of the other protecting groups should be feasible. The remaining steps leading into our final target would then proceed in analogy to Still's synthesis of Trichodermol.[14] Thus, deprotection of the silyl ether (HF, pyridine) would regenerate the alcohol functionality needed for the stereoselective epoxidation of the five membered ring olefin. Treatment of this alcohol with t-BuOOH in presence of $VO(acac)_2$ would afford epoxide **19.** Subjecting the epoxide to acid conditions (H_2SO_4, acetone) should proceed with the regioselective opening of the epoxide at the least hindered site, and consequent internal Michael addition to afford **20.** Under these mild conditions the primary, but somewhat hindered trityl ether should not be affected. Reaction of **19** with methyllithium would form the corresponding tertiary alcohol. Selective protection of the C_4 hydroxyl as the benzyl ester (PhCOCl, pyridine) and Collin's oxidation would then afford ketone **21.** The four final steps of the synthesis would proceed as follows: the tertiary alcohol would be dehydrated to the desired olefin with $POCl_3$ in pyridine (7:1 ratio

Scheme V



(a) heat; (b) O_3; (c) $LiBH_4$, THF; (d) $POCl_3$, pyridine; (e) aq. HCl: THF, 0°C; (f) HF, pyridine; (g) t-BuOOH, $VO(acac)_2$; (h) H_2SO_4, acetone; (i) MeLi, THF; (j) PhCOCl, pyridine; (k) CrO_3.2py, CH_2Cl_2; (l) $POCl_3$, pyridine; (m) aq. HCl:THF; (n) $Ph_3P{=}CH_2$, THF; (o) MCPBA.

of olefins in Still's synthesis). Deprotection of both alcohol protecting groups (aq. HCl, THF) and methylenation ($Ph_3P = CH_2$), followed by C_4 hydroxyl directed epoxidation (MCPBA) would then give (±)-Verrucarol.

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PROPOSITION V

Abstract: The classification of the Great Grebe (Podiceps major) as a non-Podiceps species is proposed on the basis of behavioral differences in the water courtship.

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Ethology, or the study of animal behavior, is a relatively young science that has become very popular in the last two decades, especially since 1973 when the Nobel Prize in medicine was given to three scientists working in this field.[1] The science relies very heavily on one basic aspect: observation.[2] For many years ethologists have been compiling data on animal behavior. Since long ago, a class of behavior that has intrigued most biologists has been the innate or instinctive behavior. Instincts, just like physiological characteristics, are intrinsic to the species and are transmitted from generation to generation by genetic mechanisms. They are, therefore, subject to the laws of natural selection, as Darwin already pointed out in 1886 in his "Origin of Species."

In trying to classify the animal kingdom, taxonomists put all their emphasis on the comparison of the physiological characteristics. Based on these features, they speculated about the origin and evolution (phylogeny) of the different families and orders of

animals. Recently, though, and coinciding with the development of ethology as an "accepted" science, behavior has been incorporated to these evolutionary and taxonomic studies. Indeed, by the comparative study of the innate behaviors of the species of a family, ethologists have been able to trace their evolutionary history.

Grebes (Podicipediformes) constitute an order of birds particularly interesting for their primitive stage in the evolutionary scale. They are small to medium-large in size, foot-propelled diving birds, widely spread throughout the world. The order has a single family (Podicipedidae), formed by 20 species grouped in 5 genera, Tachybaptus, Podilymbus, Rollandia, Podiceps and Aechmophorus.[3,4] The family has generally been divided into two tribes. The Podilymbini, which includes Podilymbus and Tachybaptus, are characterized by having a well developed Musculus flexor perforatus digiti II, and extra bony channels for its tendon in the hypotarsus[3] (see fig. 1), and by presenting a particular copulatory behavior. The other tribe, the Podicipedini, includes the remaining three genera. Its members are characterized by the lack of the mentioned canal in the hypotarsus (fig. 1), and by their copulatory behavior. The members of the genus Podiceps have one of the most interesting and sophisticated courtship displays observed in birds. The genus is formed by eleven species, one of them (gallardoi)

Figure 1[5]: Tarsometatarsus of the Red-necked Grebe (Podiceps grisegena) (left) and the Pie-billed Grebe (Podilymbus podiceps) (right). The arrow demarks the canal for the tendon of insertion of Musculus flexor perforatus digiti II, present in the Podilymbini tribe, but lacking in the Podicipedini.

discovered as late as 1974[4]. Some of them are represented in fig. 2.[5] The six top birds are generally accepted as the six species of Podiceps, sensu stricto. The bird at the bottom (the Great Grebe) is the subject of this proposal. The remaining four species of the genus Podiceps (not represented) will not be considered here because of the lack of data concerning details of their behavior.

The Great Grebe (Podiceps major) is a species that has been difficult to classify. This South American bird was originally thought to be closely related to the palearctic, Red-necked Grebe

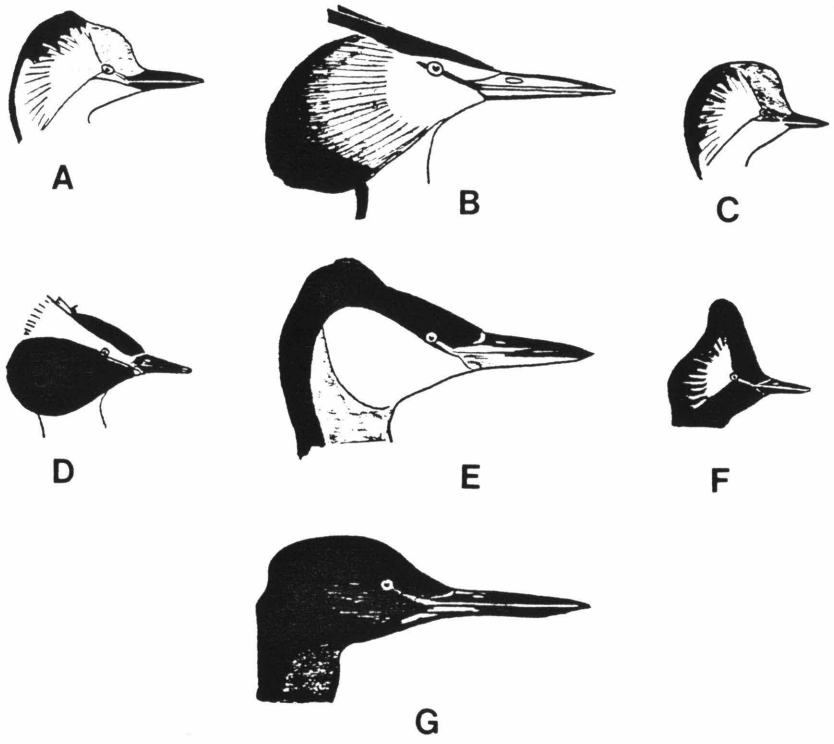


Figure2[6]: Head patterns of some Podiceps species in nuptial plumages: **A**, Taczanowski (P. taczanowski); **B**, Great-necked (P. cristatus); **C**, Silver (P. occipitalis); **D**, Eared (P. auritus); **E**, Red-necked (P. grisegena); **F**, Black-necked (P. nigricollis); **G**, Great (P. major).

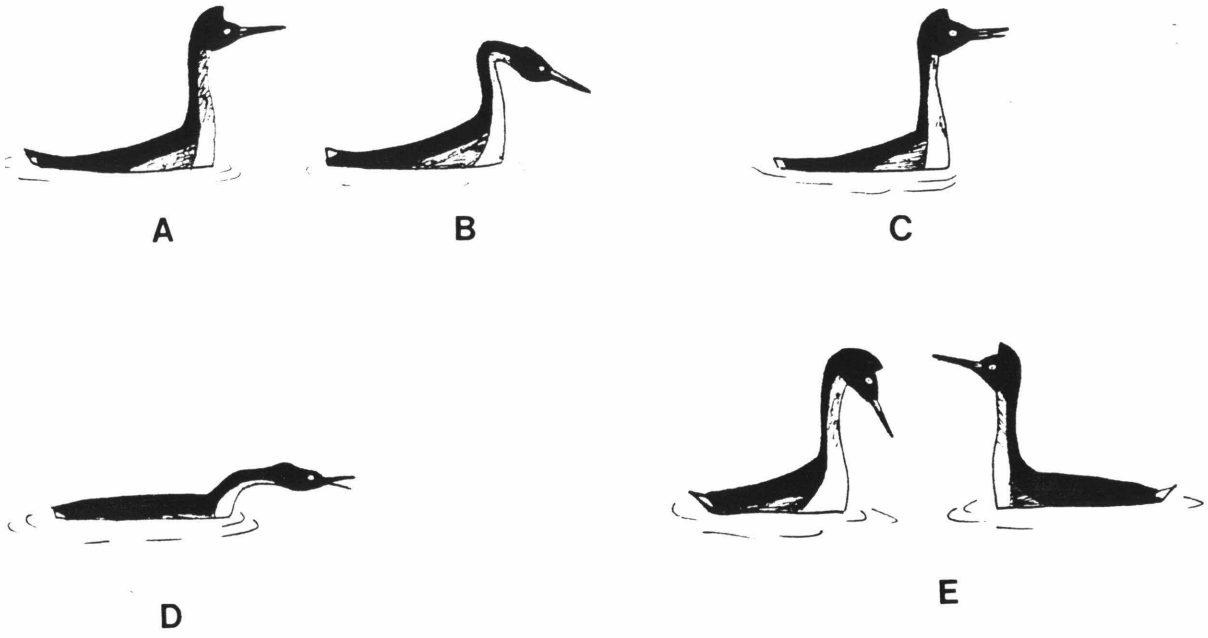
(P. grisegena) based on analogies in the head pattern.[9] These resemblances, however, might well be due to convergent evolution. Indeed, while based on morphological features one would quickly classify the Great Grebe as a Podiceps member, a close comparison of their courtship behavior will demonstrate that, in fact, it might not be as closely related as it is commonly accepted. The following is a series of water displays and ceremonies reported for the Great Grebe by Storer[10] and Greenquist.[11] In the present description of the displays, details have been ommitted to keep the text compact. The descriptions will rely heavily on the corresponding accompanying figures, which are based on the ones reported by the authors.

(a) The Upright Mohawk Position (fig. 3A). In this position, the neck is stretched upward, and the crest (mohawk type) is fully erected. It is used as part of the ceremonies (vide infra).

(b) The S-neck Position (fig. 3B). The mohawk crest is partially erected and the neck forms an S-type curve. It is used in mildly aggressive situations.

(c) Advertising (fig. 3C). The head is held high, the neck is nearly stretched vertically, the mohawk crest may or may not be spread, and a specific call is given while in this posture. This display is common throughout all the members of the family, with minor differences.

(d) The Gunner's Display (fig. 3D). The neck is extended to the front and the head is held low over the water, while a call is



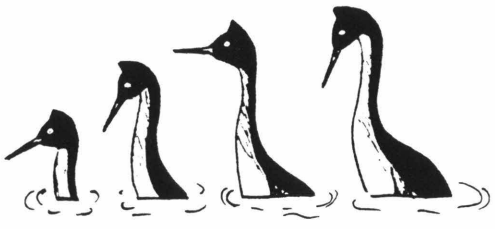


Figure 3: Courtship displays of the Great Grebe: **A.** Upright Mohawk position; **B.** S-neck position; **C.** Advertising; **D.** The Gunner's Display; **E.** The Nodding Display; **F.** The Ceremonial Flying Display; **G.** Progressive stages of the Ghostly-penguin Display, with Nodding.

given. The meaning of this display is not well understood, since no reaction to it is observed by other individuals.

(e) The Nodding Display (fig. 3E). In this display, two birds approach each other in the Upright Mohawk posture and start nodding their heads slowly. Their movements may or may not be synchronized.

(f) The Turning Display. It always follows the Nodding Display. The birds, usually in the Upright Mohawk posture, perform rigid, synchronized, 90° turns to the same side swimming side by side for 1 to 2 feet, back and forth between 5 to 10 times.

(g) The Turning-away Display. It is the usual conclusion of the Turning Display. The birds turn tail to tail and slowly separate, periodically "glancing" at each other.

(h) The Ceremonial Flying-away Display (fig. 3F). A bird suddenly turns and flies away from its mate, with the mohawk crest partially raised, the head held down and wings flapping.

(i) The Ghostly-penguin Display (fig. 3G). The bird dives, swims underwater past the other bird, and slowly emerges, adopting a risen posture, facing away from the second bird; the neck is extended upward, the bill is dipped about 45° below the horizontal and the mohawk crest is raised. In 10% of the displays, bill raising is quickly followed by a single, pronounced nod.

The most common displays in a complete ceremony are Nodding, Turning and Turning-away, which are performed always in the stated order. The Ghostly-penguin and the Flying-away Displays appear less frequently.

When compared with the displays observed in the true Podiceps members (P. cristatus, grisegena, auritus, nigricollis, taczanowskii and occipitalis), the activities of the Great Grebe seem to be much more simple.[10] The true Podiceps have a large number of complicated ceremonies which are common, except for minor variants, to all members of the group. Some of the displays of the Great Grebe have been proposed to be homologous[12] to some displays used by the true Podiceps species in the so called Discovery Ceremony. This ceremony is performed by all members of the Podiceps genus in a strikingly similar way; only the New Zealand species P. poliocephalus and P. rufopectus have lost it to a certain degree.[13] It can be summarized as follows:[14] (1) one grebe dives while the other automatically changes its appearance from relaxed to the so-called Cat Display (see fig. 4); (2) at a distance of about 1 m away from the second bird, the first bird emerges vertically, in an erected position, known as the Ghostly-penguin Display; (3) a penguin dance follows, in which both partners dance, breast to breast, in an erected position of the body; in the Great-crested Grebe (P. cristatus), this display is replaced by the Head-shaking Display, in which the birds perform a rapid side to side head movement; (4) the end of the ceremony is different between species and might include habit preening, where the head is turned away and the bird starts touching its back or wing feathers with its bill, or

it might finish with the turning away, where the two birds slowly separate from each other in a stereotype fashion.

This ceremony, which is common for the six top species shown in fig. 2, appears to be acting as a bond strengthner of the members of a pair.[3] As an example, figure 4 intends to show the similarities of the already mentioned ghostly-penguin display of four different species of the genus Podiceps (drawings based on ref. 14).

In most of the Podiceps species, the Discovery Ceremony is either followed by repeating the same performance or by the completely different, Weeding Ceremony. This consists of either a penguin dance (or a side by side rush) performed with weeds in the bills of both partners (fig. 5) (P. cristatus, P. grisegena, P. auritus and Aechmophorus occidentalis), or in some kind of other weed-presentation display (P. occipitalis, P. gallardoi, P. nigricollis and presumably P. taczanowskii).[15] It is somewhat surprising that the Western grebe (Aechmophorus occidentalis) has a Weeding Ceremony, since the genus Aechmophorus is believed to have separated from the Pociceps branch a long time ago. However, no kind of weeding display has ever been recorded for the Great Grebe.[10,11]

Once we have presented some of the more characteristic displays of both sides, the Great Grebe and the rest of the Podiceps grebes, we are ready to discuss their similarities and discrepancies, and to speculate about their common or independent origin.

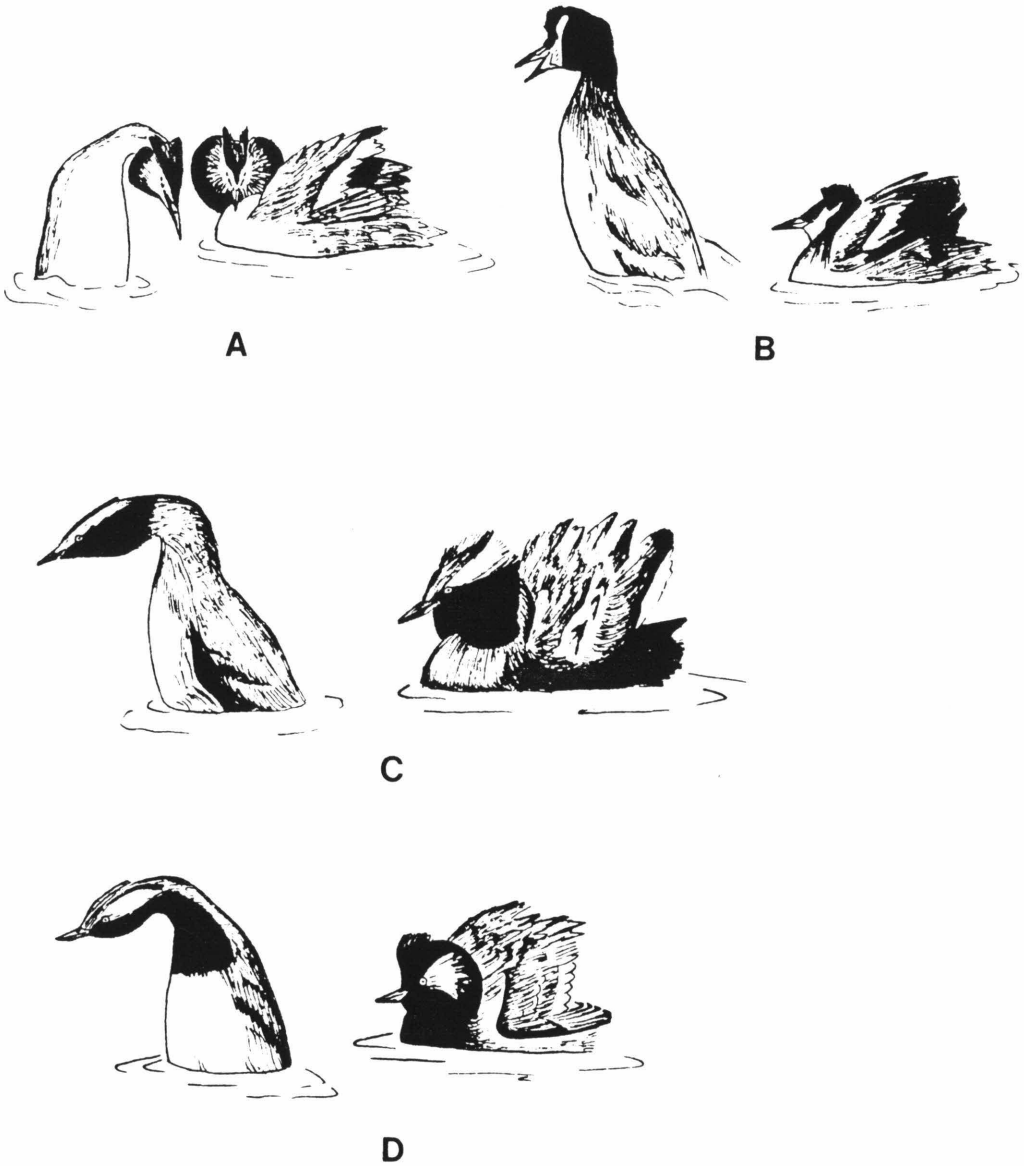


Figure 4: The Ghostly-penguin and Cat Displays of four Podiceps species: **A.** Great-crested (cristatus); **B.** Red-necked (grisegena); **C.** Eared (auritus); **D.** Black-necked (nigricollis). (Drawings based on ref. 14).

Figure 5: The Weed-Ceremony. **A.** Great-crested Grebe (Podiceps cristatus); **B.** Black-necked Grebe (Podiceps nigricollis); C. Western Grebe (Aechmophorus occidentalis)

Contrary to the other Podiceps, the Great Grebe lacks a Discovery Ceremony. However, one of the displays of this ceremony, the Ghostly-penguin Display (fig. 4) has been proposed to have its counterpart in the Great Grebe (fig. 3H). Storer[10] compared these two displays and concludedthat they were phylogenetically related. Nonetheless, he pointed out the following discrepancies: (1) the

long dive is not interrupted by emergences like in P. nigricollis, auritus and grisegena, nor is the bird close enough to the surface to make a ripple, as in P. cristatus; (2) in some cases, the emergent bird makes a nod; (3) during emergence, the bird does not bend its neck, contrary to P. nigricollis, auritus and grisegena; (4) the body of the emerging bird remains in a horizontal position. Although not mentioned by Storer, two other discrepancies should be added: (5) while in the other Podiceps species the display involves two partners (the diving bird and the Cat-displaying bird, see fig. 4), the Great Grebe performs it generally alone and unpredictably, during the ceremonies;[11] (6) finally, courting Great Grebe pair members might perform Ghostly-penguin Displays at the same time,[11] which is unprecedented for other Podiceps grebes.

The above-mentioned differences in the execution of the Ghostly-penguin Display by the Great Grebe makes this display of questionable homology with the one observed in the other Podiceps members. The fact that the display is more or less similar in both counterparts might well be the consequence of a convergent evolution. Moynihan[16] defines a display as "any behavior especially adapted in physical form or frequency to function as a social signal." In other words, a display is, in one way or another, the consequence of a modified, "every day" behavior via natural selection. It would be logical, then, to believe that the Ghostly-

penguin Display of the grebes was originated through the ritualization of the normal fishing dive. Because all grebes dive for fish, it is perfectly possible that the Ghostly-penguin Display appeared independently in the Great Grebe and in the other Podiceps members after they separated in the evolutionary tree, and that their similarities are the result of convergent evolution. As the behavior transformed into a display, in one branch (true Podiceps) it became a uniformly consistent part of a ceremony, whereas in the other branch (Great Grebe) it became a single display, unpredictably performed.

It has been proposed that the Nodding and Turning ceremonies are related to the Discovery Ceremony of the Podiceps grebes, but details were not given.[10] For example, it was pointed out that the Turning Display of the Great Grebe might be derived from the Head-shaking of the Great Crested grebe (P. cristatus).[10] A close analysis of these two displays, however, shows important differences. Indeed, in the Great Grebe, it involves displacement of the whole body,[10,11] whereas in the Great Crested grebe it represents only a rapid side to side movement of the head.[14]

The fact that the Great Grebe lacks any form of Weed Ceremony might be used as an indication of the age of this species. As we mentioned earlier, even the separate Western grebe (genus Aechmophorus) shows a Weed Ceremony, which suggests that the Great Grebe might have detached from the main Podiceps branch even earlier

than the Western grebe. One could argue, though, that in the same way that the Ghostly-penguin Display of the Great Grebe might be the result of convergent evolution (vide supra), the Weeding Ceremony of the Western grebe could also have appeared independently of the Weeding Ceremony of the other Podiceps members. However, contrary to the Ghostly-penguin Display, the Weeding Ceremony of both counterparts involves a sequence of different actions (Weed-trick, Weed-approach and Weed-dance).[14] It is highly improbable that the identical sequence had evolved independently in the two genera.

In summary, the above mentioned differences in the courtship behavior of the Great Grebe (Podiceps major) seem to indicate that this species separated from the old Podiceps stock at an early stage in the evolutionary history of the family, before the Aechmophorus branch differentiated, and when the display behaviors of the members of the family were still very simple. The comparative analysis presented above suggests that the species should not be classified as a Podiceps member.

References and Notes

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