Diastereoselective and Enantioselective Aldol Condensations with Bis-Cyclopentadienyl Zirconium Enolates

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1982

(Submitted June 17, 1981)

To Paula

ACKNOWLEDGMENTS

I would like to thank the past and present members of the Evans group for providing an enjoyable atmosphere in which to learn and do chemistry.

A special thanks to Dave Evans for the opportunity to work with the best equipment and abundant supplies but more importantly for giving me the freedom to get sidetracked on my own ideas and for having the patience to allow me to stay until something worked.

Most important I want to thank Paula, Danny and Laura McGee for helping me keep my priorities straight.

ABSTRACT

Bis-cyclopentadienyl zirconium enolates undergo aldol condensation to afford erythro aldol adducts regardless of enolate configuration. Enolates of chiral amides afford high levels of asymmetric induction at the erythro stereocenters. Mild hydrolysis of the chiral auxiliaries occurs via intramolecular assistance by hydroxyl neighboring groups in the chiral auxiliary. The absolute configurations of the erythro-aldol products have been determined by independent correlations to compounds of known absolute configuration. A cyclic metal-centered transition state model has been developed which accounts for the stereoselectivity observed with zirconium enolates.

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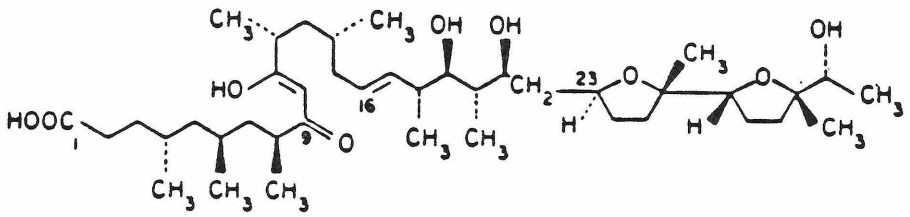
Diastereoselective and Enantioselective Aldol Condensations with Bis-Cyclopentadienyl Zirconium Enolates

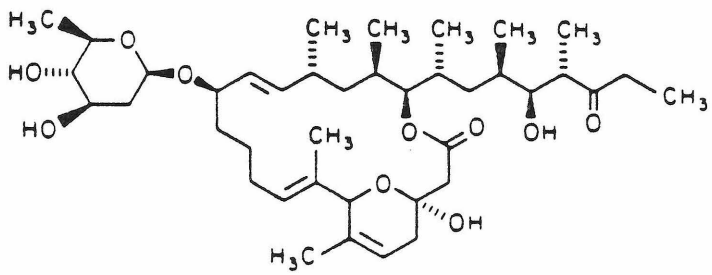
I. Introduction

The aldol condensation is one of the oldest classes of organic reactions and is the most obvious bond construction for the creation of 1,3-oxygen-oxygen heteroatom relationships. The recent interest in stereoregulated variants of the aldol condensation has been spurred by the recognition of macrolide and ionophoric antibiotics as viable targets for total synthesis.[1] The three examples shown in Figure 1 are representative of these classes of molecules. They or their seco-acids can be characterized as linear arrays of stereocenters along an acyclic carbon backbone. The regular occurrence of 1,3-oxygen functionality as well as 1,3-methyl-bearing stereocenters reflects the biosynthetic origin[2] of these compounds and suggests the use of the aldol condensation in their synthesis.

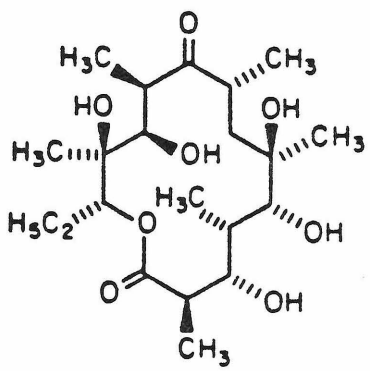
Scheme I presents a retrosynthetic analysis of 6-deoxyerythroholide B (4).[4] Six carbon-carbon bonds and the ten stereocenters of 4 derive from potential aldol reactions. The major impediment to the polymerization of propionaldehyde leading to acid 5 has been associated with the stereochemical aspects of the aldol process. In a nonstereocontrolled process, 5 would be expected as only a small percentage of the final product mix of 2^{12} stereoisomers.



1 Ionomycin[3a]



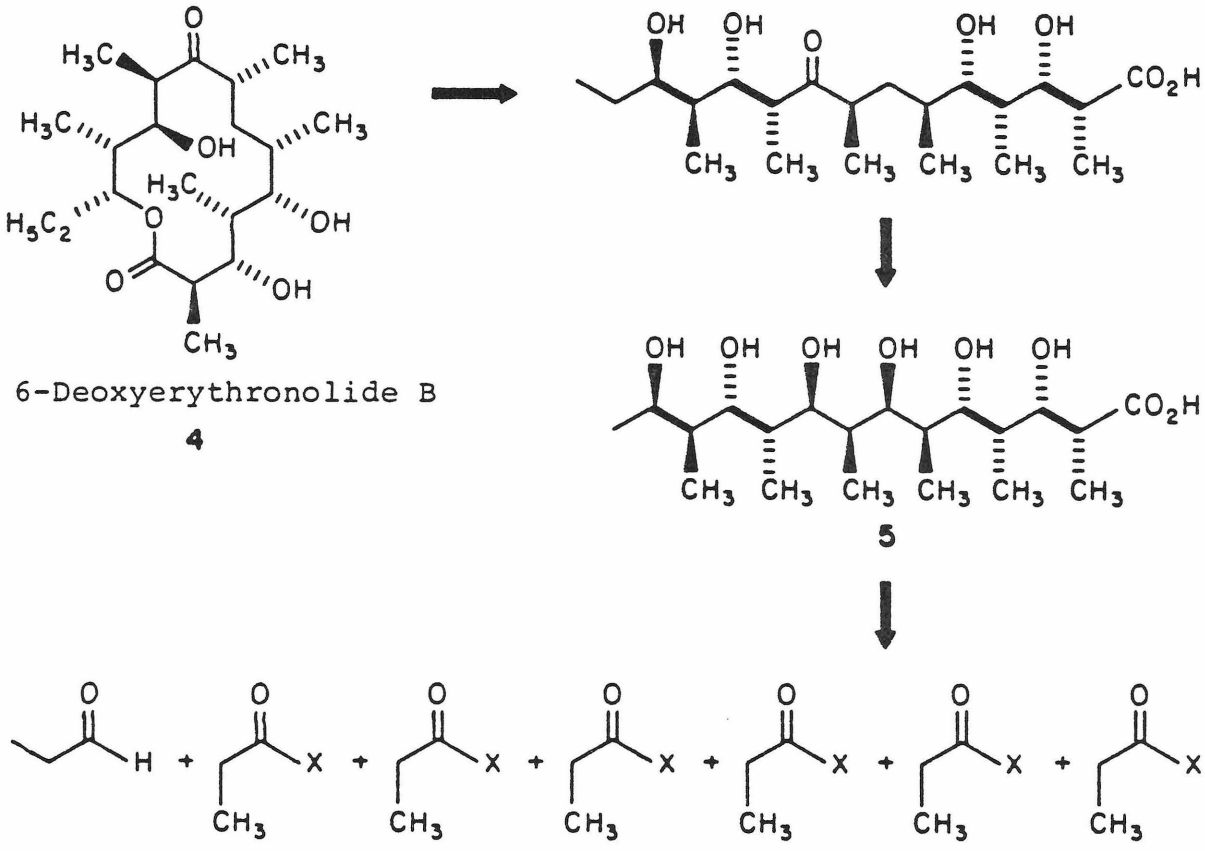
2 Venturicidin B[3b]



3 Erythronolide A[3c]

Figure 1.

Scheme I



6-Deoxyerythronolide B

4

5

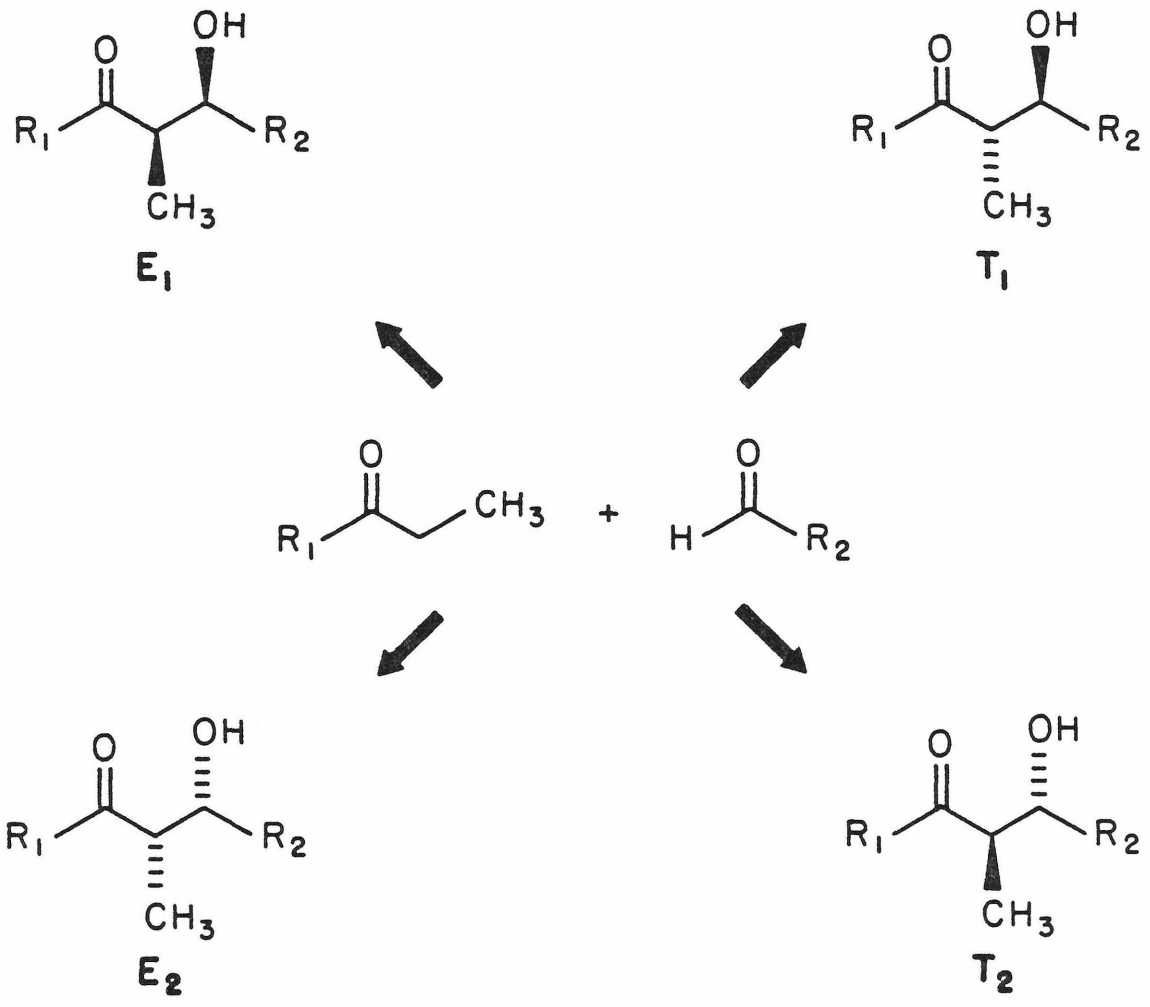
Over the last few years considerable progress has been made in the control of stereochemistry of the aldol process. This has been the subject of two recent reviews.[5,6] The important role that sterically demanding metal centers play in the enhancement of aldol stereoregulation has become apparent. In this report we discuss our observations during the development of zirconocenyl enolates for stereoselective aldol condensations.

Stereoregulation in the Aldol Condensation. The crossed aldol condensation of a preformed enolate with an aldehyde presents two stereochemical issues (Scheme II). The first deals with internal stereochemical control or 1,2-diastereoselection ($\underset{\sim}{E}_1$ and $\underset{\sim}{E}_2$ vs $\underset{\sim}{T}_1$ and $\underset{\sim}{T}_2$) and the second deals with absolute stereochemical control, asymmetric induction from another stereocenter, or enantioselection ($\underset{\sim}{E}_1$ vs $\underset{\sim}{E}_2$ or $\underset{\sim}{T}_1$ vs $\underset{\sim}{T}_2$).[7] The ability to control both the relative and absolute stereochemistry of two adjacent stereocenters formed during the construction of the carbon framework would be a valuable addition to the synthetic chemist's repertoire.

Our approach has been to deal with the issue of diastereoselection first and then, given good levels of diastereoselectivity, to extend the methodology to the issue of absolute stereoselection. The ultimate goal is to possess methodology which can selectively generate each of the four stereochemical relationships as required by target molecules.

Transition State Considerations.[9] In 1957 Zimmerman and Traxler[10] invoked a six-membered cyclic transition state for the aldol condensation involving coordination of the enolate and carbonyl partners via the enolate metal center, to account for the observed aldol diastereoselection. With subsequent observations by Dubois[11] and Heathcock[12] that

Scheme II Stereoregulated Aldol Condensation

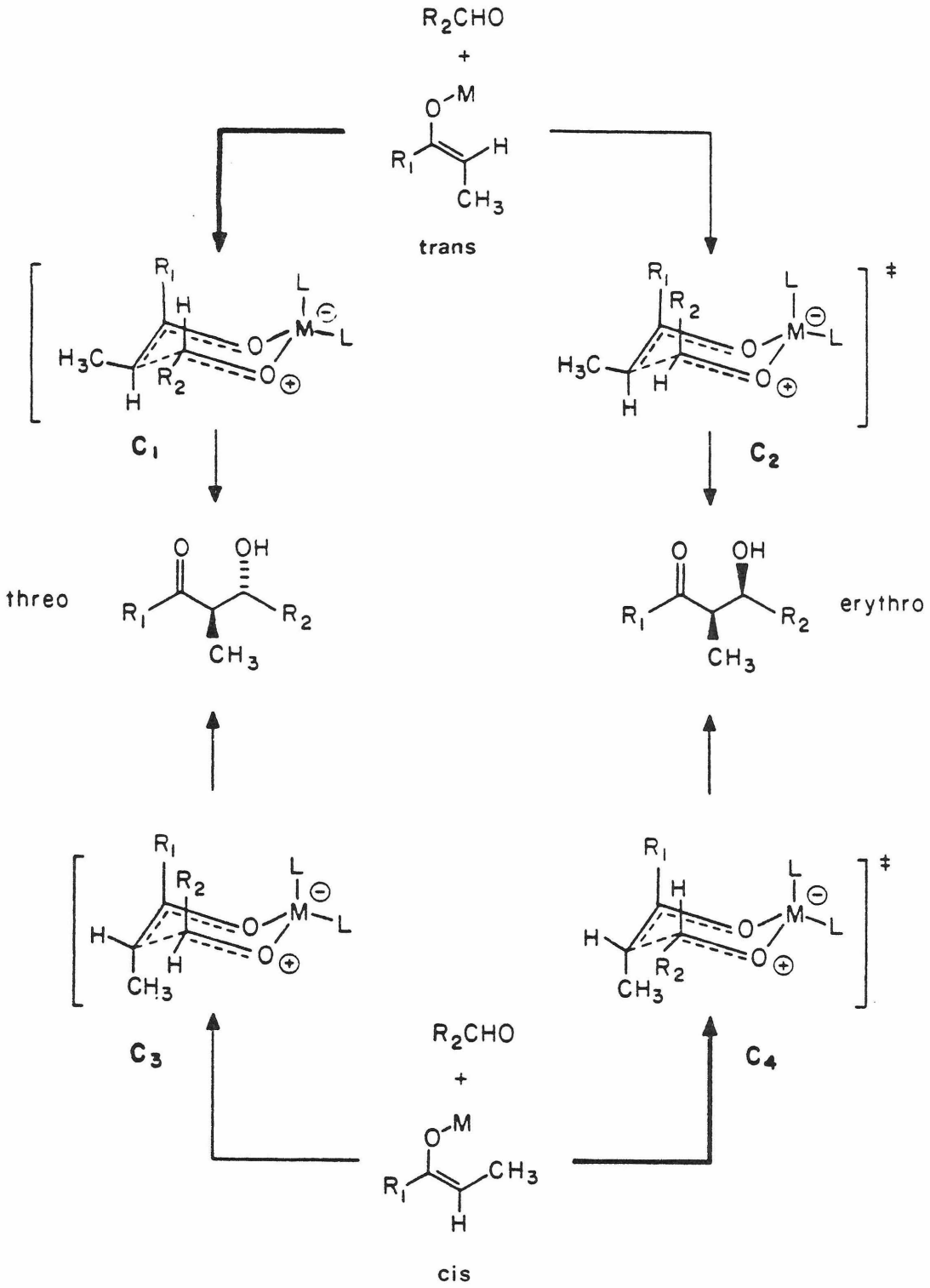


kinetic aldol diastereoselection is, in part, defined by enolate configuration, an elaborated version of the Zimmerman transition state has emerged.[13] In this model, illustrated in Scheme III, steric interactions around a chair-like six-membered ring transition state are responsible for the energy differences between diastereomeric transition states. By analogy to chair cyclohexane, 1,3-diaxial interactions are disfavored with respect to 1,3-diequatorial or 1,3-equatorial-axial orientations. The preferred chair-like transition state gives for trans enolates threo isomers and for cis enolates erythro isomers.[14]

The ratio of isomers obtained from a reaction involving competing diastereomeric transition states is related to the difference in activation energy between the pathways.[15] As illustrated in Figure 2 a synthetically useful isomer ratio of 19:1 requires less than 1.2 kcal/mole energy difference at -78°C. That this energy difference is rarely achieved in the aldol condensation is an indication of the limitations of the transition state analogy to chair cyclohexane.

One limitation is that the steric interactions of the substituents around the six-membered ring are diminished by the long metal-oxygen and metal-ligand bond lengths associated with the traditional metals of the aldol condensation (Table 1).

Scheme III



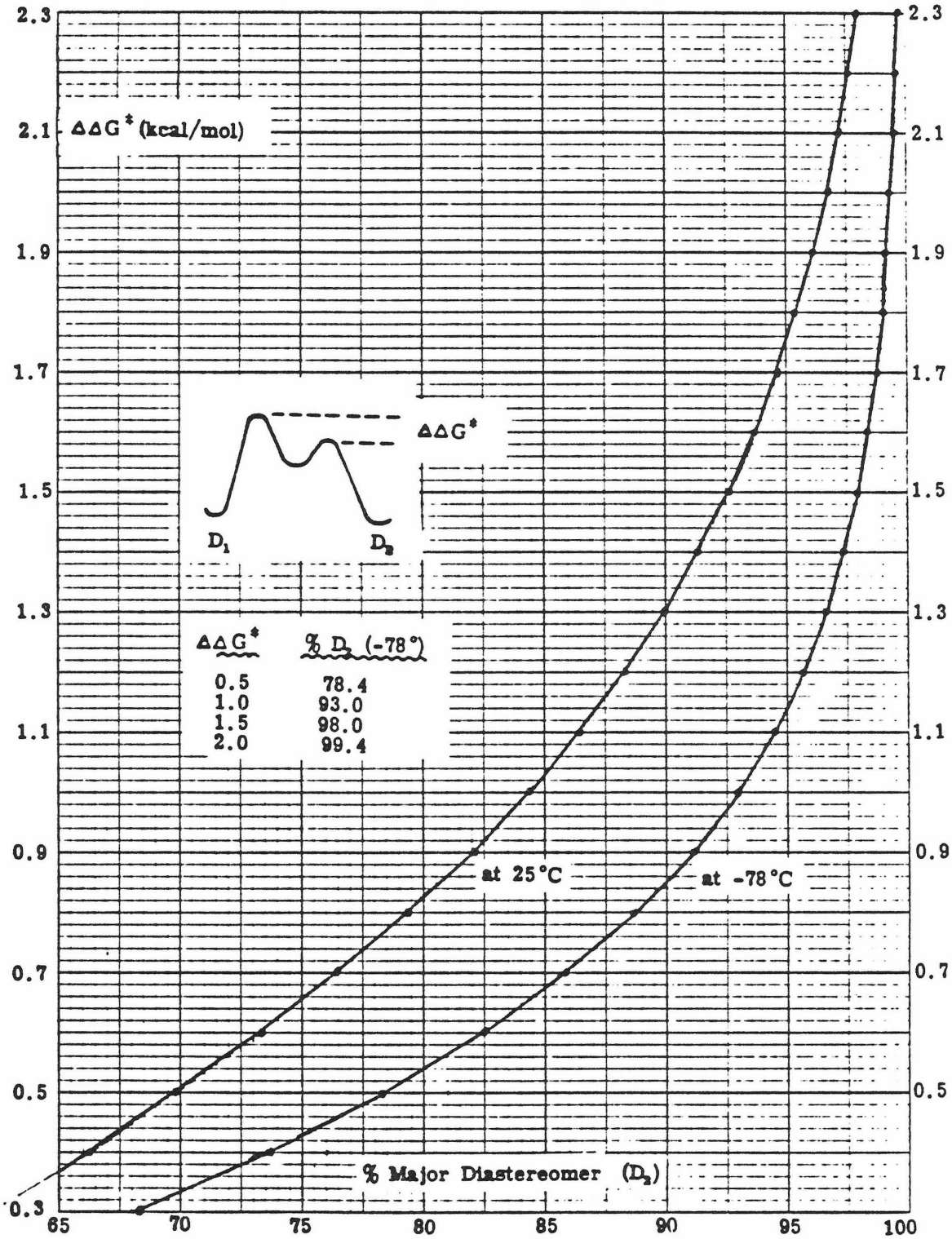

ΔΔG‡ (kcal/mol)
ΔΔG‡
D1
D2
ΔΔG‡ % D2 (-78°)
0.5 78.4
1.0 93.0
1.5 98.0
2.0 99.4
at 25°C
at -78°C
% Major Diastereomer (D2)
2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
0.3
65
70
75
80
85
90
95
100

Figure 2.

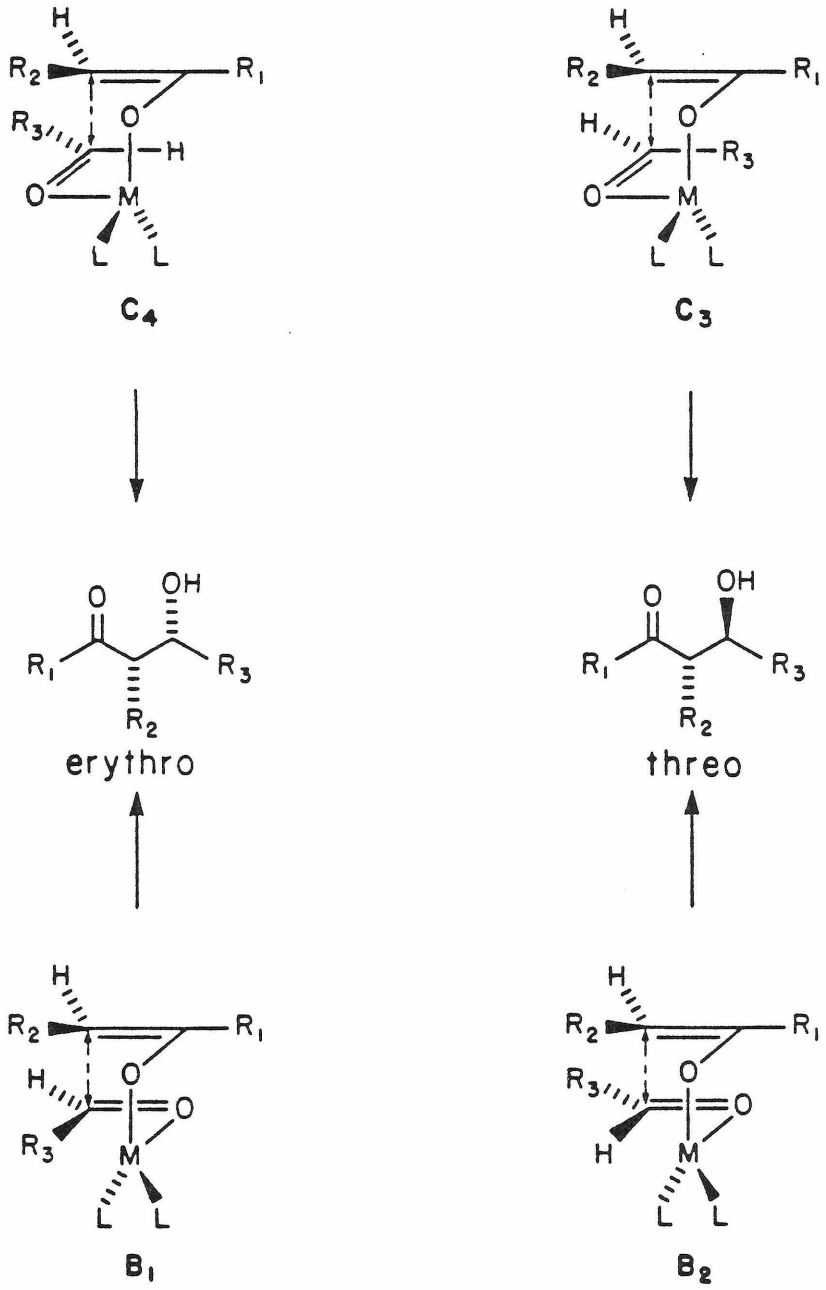
Table 1. Metal-Oxygen and Metal-Ligand Bond Lengths for Metals Commonly Used in the Aldol Condensation[a]

Metal	M-O Bond Length (Å)	L	M-L Bond Length (Å)
Li	1.92-2.00	OR_2	1.92-2.00[b]
Mg	2.01-2.13	Br	2.43
		Cl	2.18
		OR_2	2.01-2.13[b]
Zn	1.92-2.16	Cl	2.18-2.25
		I	2.42
		OR_2	1.92-2.16[b]
Al	1.92	CR_3	2.00-2.24
B	1.36-1.47	CR_3	1.51-1.58
Ti	1.62-1.73	Cl	2.18-2.21
Zr	2.15	Cp	2.21

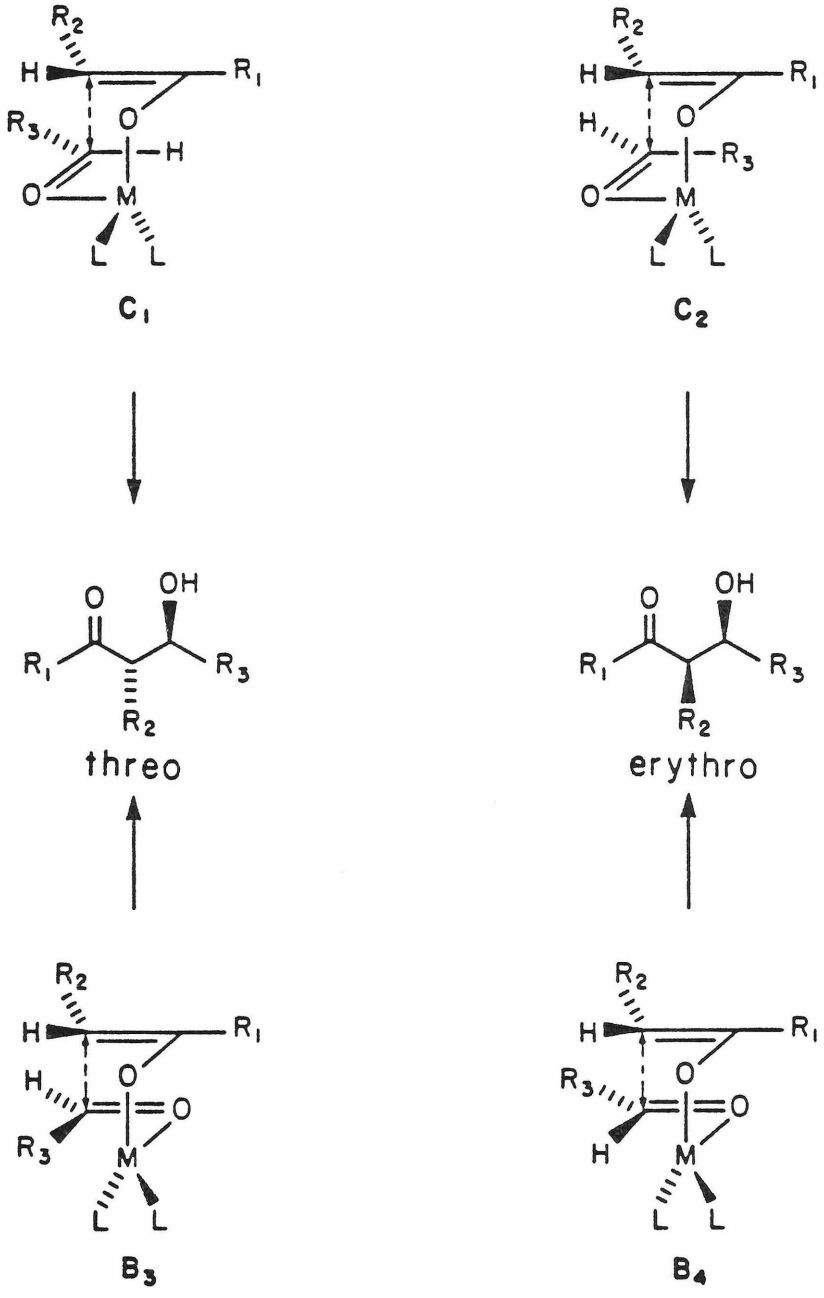
[a]Data taken from Ref. 16. [b]Value cited is for covalently bound alkoxide or acid and should be interpreted as a minimum bond length.

A second limitation of the analogy is that, in addition to the two chair-like conformations, there also exist two boat-like conformations of the cyclic transition states for each enolate configuration. The four competing transition states are illustrated in Scheme IV for cis enolates and in Scheme V for trans enolates.[6] In many cases for which chair-like transition states have been

Scheme IV



Scheme V

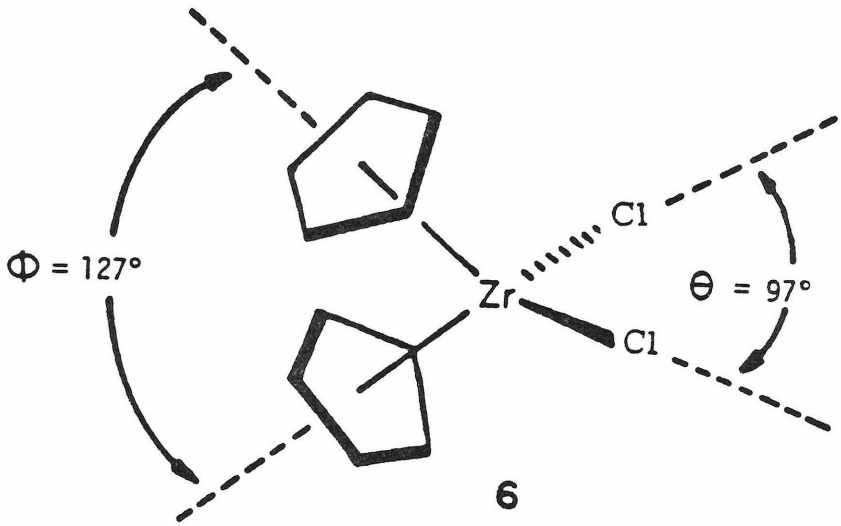


invoked, the minor aldol diastereomer may arise from a boat-like conformation rather than the less-favored chair-like conformation.

The success of dialkyl boron enolates in translating enolate configuration stereospecifically into aldol product stereochemistry[13,17] has been attributed to the relatively short boron-oxygen and boron-carbon bond lengths which enhance the difference between steric interactions in the competing transition states.

Other metals might also have interesting effects on the stereochemical outcome of the aldol condensation. Metals with bulky covalently bound ligands which project forward from the metal center might exhibit steric interactions otherwise lost due to the long bond lengths. And metals with bond angles narrower than the tetrahedral angle of traditional aldol metals might perturb the diastereometric transition state orientations of the aldol partners with a corresponding effect on the reaction stereoselection. The bent sandwich complexes of zirconium and titanium[18] provided an opportunity to investigate both of these features.

Bent Sandwich Complexes. The commercially available zirconocene dichloride (Cp_2ZrCl_2, 6) (Figure 3) and its titanium analog (Cp_2TiCl_2) have pseudo-tetrahedral geometries



6

Figure 3.

in which the steric demand of the cyclopentadienyl ($\eta^5C_5H_5$ = Cp) ligands can be viewed as opening the Cp-Zr-Cp bond angle ϕ with a corresponding narrowing of the Cl-Zr-Cl bond angle Θ from the tetrahedral angle (Table 2).

These complexes are 16-electron species which possess a vacant orbital. This orbital lies in the plane of the metal and the chloride ligands and perpendicular to the plane defined by the metal and the ring centers.[21] It serves as a coordination site to allow the exchange of monovalent ligands via associative substitution processes at low temperatures.

A large number of titanocenyl and zirconocenyl complexes have been described in which one or both chlorides have been replaced. Typical structural features of these complexes

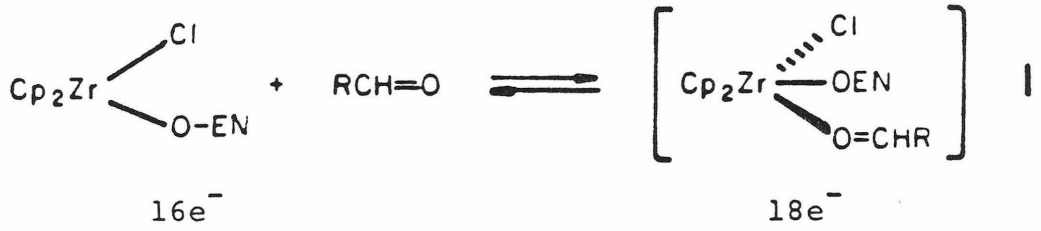
Table 2. Bond Lengths and Angles of $16e^-$ Titanocene and Zirconocene Derivatives

	Bond Lengths (Å)				Bond Angles[a]	
Metal	Cp-M	Cl-M	O-M	C-M	θ	φ
Ti[b]	2.0-2.1	2.37	1.9-2.1	2.0-2.2	70-99°	129-135°
Zr[c]	2.19-2.21	2.4-2.5	1.97[d]	2.2-2.4	94-97°	126-131°

[a]Labels refer to Figure 2. [b]Data taken from Ref. 19. [c]Data taken from Ref. 20. [d]Permethylzirconocene derivative, Ref. 20e.

are summarized in Table 2. Of particular importance is the bond angle Θ between the two nonring substituents on the metal of approximately 95°.

In the aldol condensation, with an enolate anion as one of the ligands, coordination of an aldehyde at the metal coordination site would result in an 18-electron complex (Equation 1). A few such complexes are known



(Table 3), in which the outer angle Θ opens (Figure 4) but the crucial inner angle Θ' is even narrower.

The effective steric demand of the Cp ligand is related to the metal-ring bond length. This bond is approximately 0.15 Å greater in zirconocenyl complexes than in titanocenyl complexes. The result is that the pocket of zirconocene dichloride (6) is less crowded. This may also relate to the important practical consideration that 6 is approximately ten times more soluble in tetrahydrofuran (THF) than its titanium analog.[23]

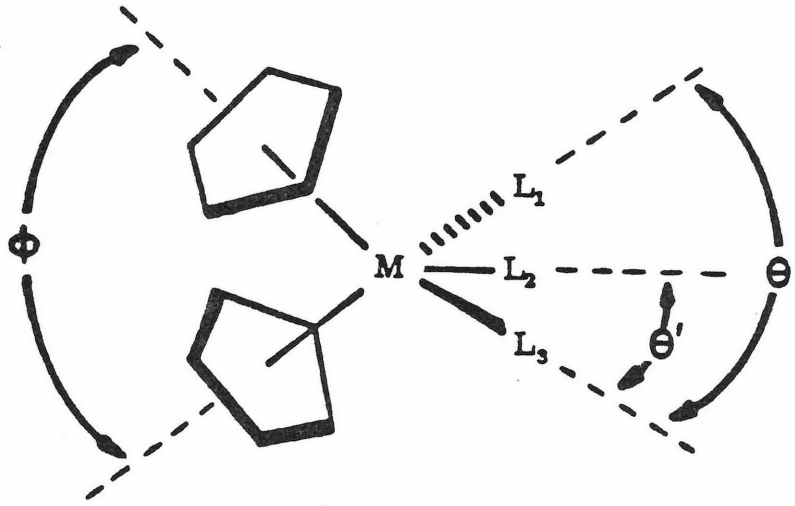


Figure 4.

Table 3. Bond Angles in "18e⁻" Titanocene and Zirconocene Derivatives

Complex	Bond Angles[a]		
	θ	θ'	φ
$Cp_2Ti(COMe)Cl$[b]	112.1°	80.2°	131.6°
$Cp_2Zr(COMe)Cl$[c]	110.8°	79.8°	--
$Cp_2Ti(NO_3)_2$[d]	--	69.5°	131.3°

[a]Labels refer to Figure 3. [b]Ref. 22a. [c]Ref. 22b. [d]Ref. 19c.

At the time we began this study, zirconocenyl enolates had been prepared by two groups: Schwartz and co-workers formed zirconocenyl enolates by nickel-catalyzed Michael addition of alkenyl zirconocenes to α,β-unsaturated ketones.[24] Aldol condensation with formaldehyde and acetaldehyde were reported. Bercaw and co-workers reported the formation of permethylzirconocenyl enolates during the reduction of carbon

monoxide by $Cp^*_2ZrH_2$ ($Cp^* = \eta^5C_5Me_5$) and during the absorption of carbon monoxide by $Cp^*_2Zr(R)H$ derivatives.[25] No aldol condensations were reported with these enolates. No titanocenyl enolates had been reported.[26]

We envisioned the formation of metallocenyl enolates from the exchange of preformed lithium enolates with Cp_2ZrCl_2 and Cp_2TiCl_2 (Equation 2). This is analogous to the formation of metallocenyl alkoxides.[18]

II. Achiral Aldol Condensations of Zirconocenyl Enolates

Results and Discussion. Treatment of several lithium enolates with solutions of Cp_2ZrCl_2 (6) in THF, followed by aldol condensation with benzaldehyde (Table 4), gave pairs of aldol diastereomers whose product ratios were compared with those obtained from the corresponding lithium-mediated aldol condensations.[8] That these ratios were different provided the first evidence for metal exchange and encouragement to pursue the effects of Cp_2ZrCl_2 in these reactions.

In a similar manner it was shown that Cp_2TiCl_2 had little influence when compared to lithium on the aldol product distribution.[27] This observation along with the inconvenient solubility of titanocene dichloride led us to concentrate

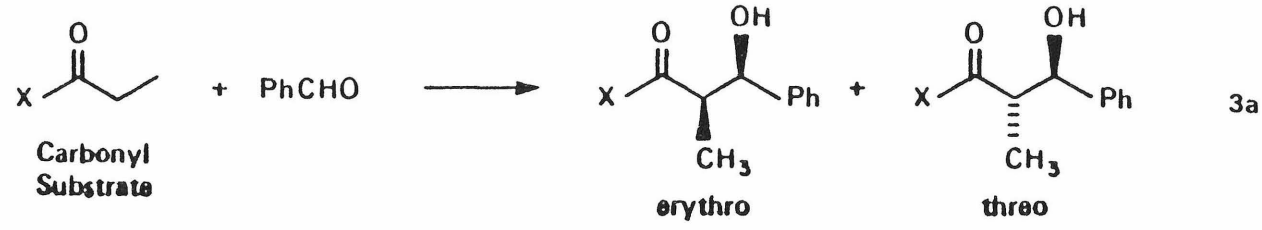


Table 4. Aldol Diastereoselection as a Function of Metal Enolate. Reactions with Benzaldehyde (16a). (Equation 3a)

Entry	Carbonyl Substrate	Enolate [a] Configuration (Cis/Trans)	Product	Product Distribution [b] Li (E/T)	Zr (E/T)	B [c] (E/T)
1	8 X=C_6H_5-	>98/2 [d]	17	88/12	90/10	>97/3
2	9 X=(t)BuS-	9/91	18	63/37	92/8	5/95
3	10 X=C_2H_5-	70/30 [d]	19	64/36	85/15	>97/3
4	11 X=(i)C_3H_7	40/60 [d]	20	74/26	85/15	18/82

[a] Configuration designated for Li and Zr data. [b] Diastereomer ratios determined by ^{1}H NMR. [c] ref. 13. [d] ref. 8.

on reactions involving the zirconium complex 6.

We chose first to investigate the influence of 6 on aldol condensations involving lithium enolates of predominantly a single configuration. The data reported in Table 4. compare the effect of enolate configuration on aldol diastereoselection for zirconocenyl, lithium and boron enolates.

In view of the previously discussed (Scheme III) chair-like transition states, the obtention of erythro diastereomers in the zirconium-mediated condensations of both the cis enolate of propiophenone (8) and the trans enolate of (t)butylthiopropionate (9) (Table 4, entries 1 and 2) was surprising. This indicated that the zirconium-mediated aldol stereoselection is independent of the enolate configuration. This hypothesis was further supported by the preponderance of erythro diastereomer obtained from mixtures of cis and trans enolates (Table 4, entries 3 and 4). Yamamoto and co-workers have independently noted the erythro selective nature of zirconocenyl enolates in the aldol condensation.[28]

The aldol condensations of lithium and zirconocenyl enolates of ester and amides are compared in Table 5. The erythro preference of the zirconocenyl enolates is maintained in this series. An interesting trend is evident with these enolates. Increasing steric bulk in the X portion of the

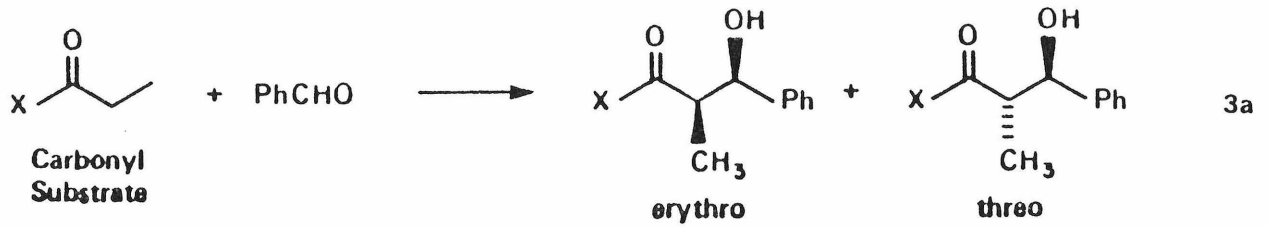


Table 5. Aldol Diastereoselection With Ester and Amide Substrates[a]

Entry	Substrate	Enolate Configuration (Cis/Trans)	Product	Product Distribution[b] Li (E/T)	Product Distribution[b] Zr (E/T)	% Yield
1	12 X=MeO-	5/95[c]	21[a]	62/38	87/13	79
2	12	84/16[e]		--	84/16	[f,g]
3	13 X=(t)BuO-	5/95[c]	22[a]	37/63	72/28	[g]
4	13	77/23[e]		--	77/23	[f,g]
5	14 X= 	>97/3[d]	23[a]	60/40	95/5	80
6	15 X=(i)Pr_2N-	81/19[c]	24[a]	63/37	>98/12	77

[a]Equation 3a. [b]Condensation with benzaldehyde (16a). NMR ratio ±3%. [c]Ref. 8. [d]Ref. 29. [e]Enolization in the presence of HMPA. Ref. 30. [f]Low. [g]Qualitative experiment.

enolate leads to lower erythro diastereoselection with trans enolates (Table 5, entries 1 and 3) and higher erythro diastereoselection with cis enolates (entries 5 and 6). The small but significant differences noted here bear on the question of cyclic vs acyclic transition states discussed later (page 36).

There was one other unexpected experimental observation that may bear on the mechanism of the zirconium-mediated aldol condensation. Under the initial conditions used for the aldol condensations, ester enolates afforded much lower stereoselectivity than is reported in Table 5. At that time, metal exchange was conducted at -78°C followed by addition of the aldehyde, also at low temperature. As reported in Table 6, the temperature of metal exchange has a dramatic effect on the stereochemical outcome of the subsequent aldol condensation for ester enolates but little or no effect on the results for thioester or amide enolates.

There are two questions which must be answered before these observations can be interpreted. First, are the observed diastereomer ratios the result of kinetic reaction or do they represent thermodynamic equilibration? And second, are the configurations of the lithium enolates preserved during the metal exchange?

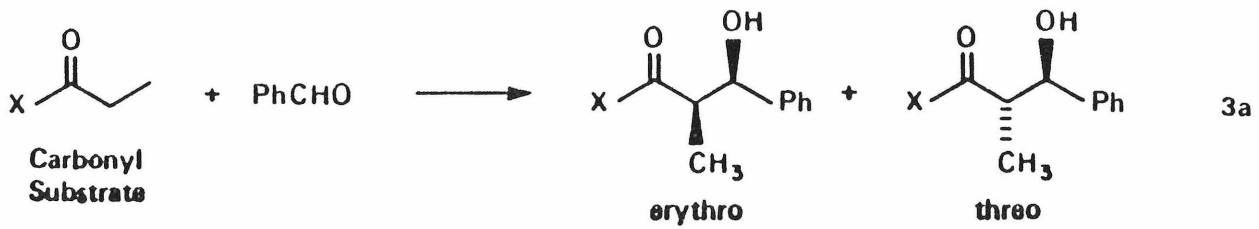


Table 6. Metal Exchange Temperature Effect[a] on Aldol Diastereomer Ratio[b]

Exchange Temperature	Product Distribution (E/T) for Carbonyl Substrate[c]				
	13 X=(t)BuO-	12 X=MeO-	8 X=C_6H_5-	9 X=(t)BuS-	14 X= 
-78°	58/42	70/30	87/13	92/8	95/5
-40°	60/40	--	--	--	--
+0°	73/27	--	--	--	--
+30°	75/25	87/13	89/11	93/7	93/7

[a]Exchange for 30-60 min at indicated temperature followed by aldol condensation at -78°C with benzaldehyde. [b]NMR ratio ±2%. [c]Equation 3a.

Kinetic vs Thermodynamic Aldol Condensation. Thermodyanmic equilibration of metal aldolates usually results in increased amounts of threo products without regard to initial enolate geometry.[6] It is conceivable that the special steric environment of the Cp_2ZrCl moiety could favor the observed erythro product as a thermodynamic sink. That the results are in fact kinetic was shown by the following experiments.

The zirconocenyl enolate of propiophenone (8) was allowed to react with benzaldehyde (16a) (Equation 4). The aldol diastereomer ratio was measured as a function of reaction time and temperature. The results in Table 7 indicate that equilibration in this sytem occurs towards the threo diastereomer. The equilibration is, however, slow even on warming to room temperature. The corresponding lithium aldolate equilibrates rapidly at -78°C.[8]

A more sensitive test for equilibration via a retro-aldol process involves a crossover experiment (Scheme VI) in which p-chlorobenzaldehyde (16g) is added to a solution of the metal aldolate preformed from a zirconocenyl enolate and benzaldehyde (16a). Incorporation of the added aldehyde is indicative of the retro-aldol process.[31] The zirconocenyl enolates of (t)butylthiopropionate (9), methyl proprionate (12), pyrrolidine propionamide (14) and N,N diisopropylpropionamide (15) were condensed with 16a under the usual

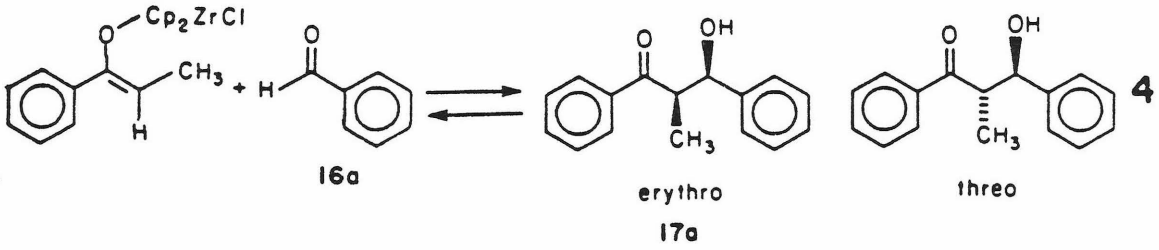
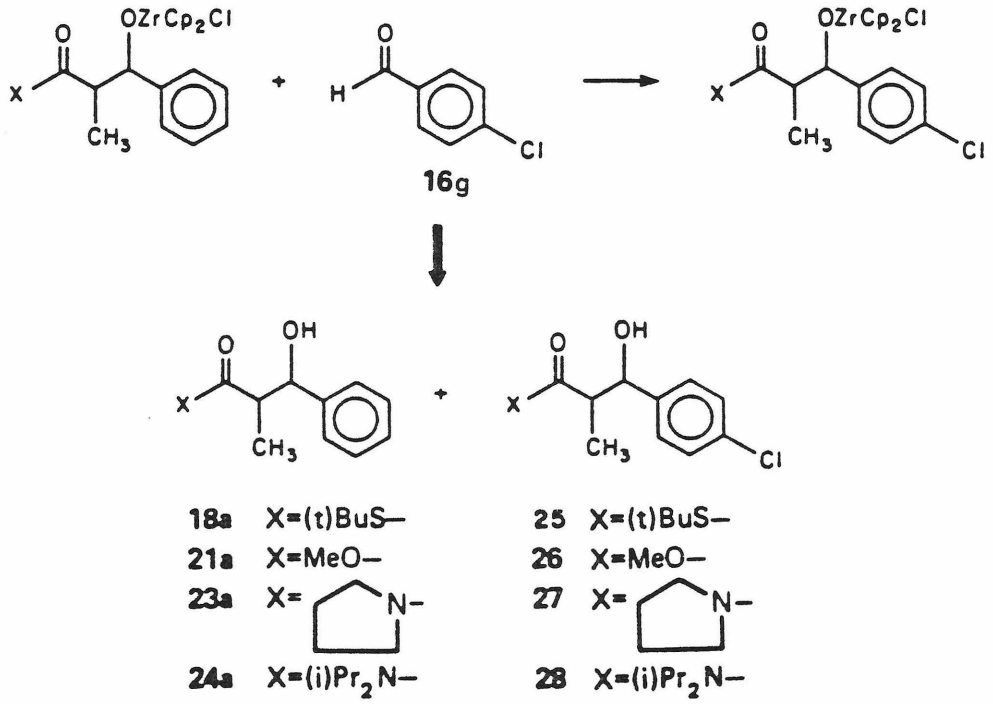


Table 7. Zirconocenyl Aldolate Equilibration[a]

Elapsed Time	Temperature	Aldol Diastereomer Ratio[b] (E/T)
10 min	-78°C	84:16
30 min	-78°C	87:13
1 h	-78°C	87:13
2 h	-78°C	87:13
4 h	0°[c]	80:20
8 h	25°[d]	75:25
29 h	25°C	54:44[e]

[a]Equation 4. [b]NMR ratio 3%. [c]Warmed to 0° after 2 h of -78°. [d]Warmed to 25° after 2 h at 0°. [e]Accompanied by extensive decomposition.

Scheme VI Crossover Experiments: Aldol Equilibration



conditions. The aldolates were warmed to 0°C to ensure complete reaction. After recooling to -78°C, a solution of p-chlorobenzaldehyde (16g) in THF was added and the reaction returned to 25°C for 30 min. After quenching, the products were examined by ^{1}H NMR. There was no indication of the crossover products 26, 27 and 28 from the ester and amide aldolates. Approximately 20% of the (t)butylthiopropionate adduct was the chlorine-containing product 25. This small amount of crossover product was essentially only the erythro diastereomer. When this experiment was repeated

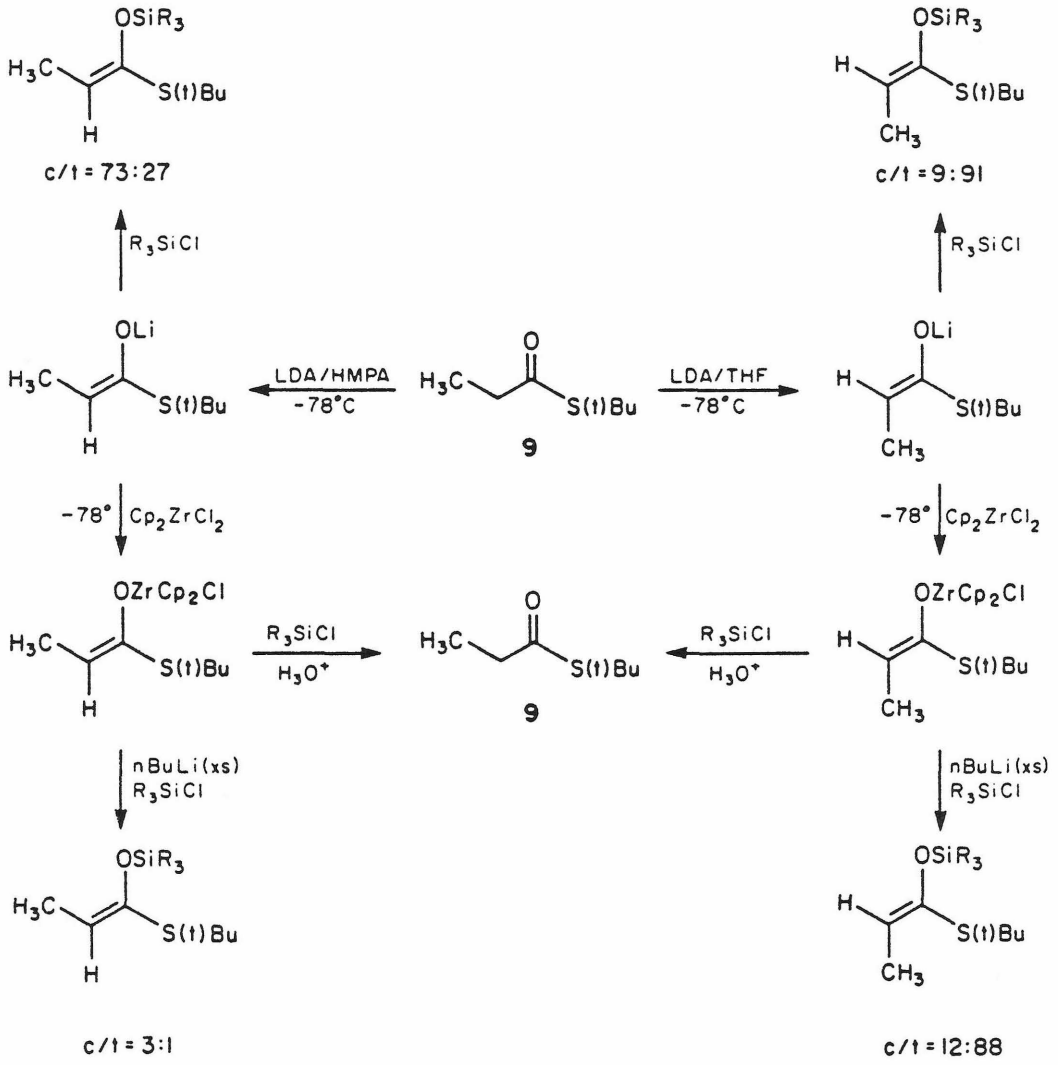
with the lithium enolate of methyl propionate (12) there was again no trace of the crossover product 26.

We conclude that equilibration is not a problem with ester and amide aldolates and that it can be controlled with low reaction temperatures for zirconocenyl aldolates of ketones and thioesters.

Enolate Configurational Stability. Equilibration of the enolate configuration to a common geometry under the conditions of the metal exchange reaction could account for the configurational independence of the zirconium-mediated stereoselection. The temperature effect reported in Table 7 may reflect such an equilibration.

The stability of the enolate configuration under the conditions of metal exchange was investigated with the following experiments illustrated in Scheme VII. Trapping of the lithium enolate of (t)butylthiopropionate (9) with trimethylsilyl chloride (TMSCl) gave a 91:9 mixture of silylenol ethers as measured by capillary gas chromatography. The configuration of the major isomer had previously been assigned trans (Z).[13] Treatment of a solution of the zirconocenyl enolate of 9 with excess n-butyllithium followed by TMSCl afforded an 88:12 mixture in which the trans isomer remained predominant. Direct treatment of the zirconocenyl enolates of 9 with TMSCl failed to produce any

Scheme VII


OSiR3
H3C
S(t)Bu
H
c/t = 73:27
R3SiCl
OLi
LDA/HMPA
-78°C
O
9
LDA/THF
-78°C
CH3
-78°
Cp2ZrCl2
OZrCp2Cl
R3SiCl
H3O+
nBuLi(xs)
R3SiCl
c/t = 3:1
c/t = 9:91
c/t = 12:88

silylenol ether. When the enolization of thioester 9 was conducted with lithium diisopropylamide (LDA) in the presence of HMPA (hexamethylphosphorictriamide), the cis silylenol ether was obtained as the major isomer from both the lithium and zirconocenyl enolates. We conclude that for thioester 9 the enolate configuration is maintained during the metal exchange.

In order to understand the temperature-dependent process which occurs during metal exchange with ester enolates, the exchange reaction was investigated by ^{1}H and ^{13}C NMR for a number of enolate systems. The Cp ligand signals are clearly visible in both the ^{1}H and ^{13}C NMR spectra measured in protio-THF. By control of the reaction stoichiometry both mono and bis substitution of the metal center could be affected. The chemical shifts for the various enolate species are listed in Table 8.[32]

The metal exchange involving ester enolates was noticeably slower than for the other enolate systems. While exchange with lithium enolates derived from ketones, thioesters and amides appeared to proceed smoothly at -50°C, complete exchange with lithium ester enolates required warming the solution to +25°C. We conclude that the low levels of aldol diastereoselection observed with low exchange temperatures are due to large proportions of lithium ester enolates remaining when the

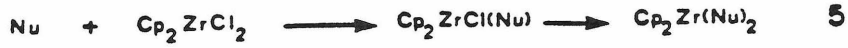


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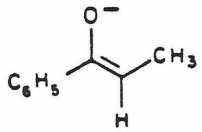
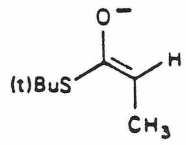
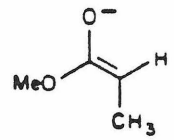
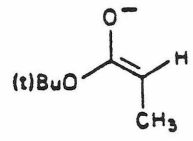
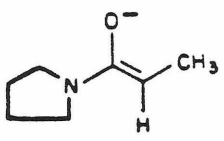
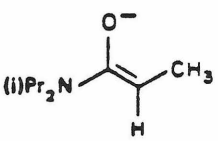
Table 8. ^{1}H and ^{13}C NMR Chemical Shift Data for the Cyclopentadienyl (Cp) Ligands in Zirconocenyl Enolates

Nu		mono δ (ppm)	bis δ (ppm)
Cl^-	^{1}H	6.52 ($CDCl_3$)[b]	6.53 (THF)
	^{13}C	115.7 ($CDCl_3$)[b]	116.1 (THF)
^-OMe	^{1}H	6.35 ($CDCl_3$)[b]	6.02 ($CDCl_3$)[b]
	^{1}H	6.39	-- [c]
	^{13}C	114.6	-- [c]
	^{1}H	6.41	6.35
	^{13}C	114.1	112.7
	^{1}H	6.37	6.31
	^{13}C	115.9 & 114.6	113.2 & 112.0
	^{1}H	6.43	6.34
	^{13}C	114.7 & 114.4	-- [c]
	^{1}H	6.40	6.33
	^{13}C	114.7	114.1
	^{1}H	6.41	6.36
	^{13}C	114.1	-- [d]

[a]Spectra recorded in THF with hexane (δ_{CH_3} = 13.7 ppm) as chemical shift reference. [b]Ref. 18. [c]Not determined. [d]Addition of the second equivalent of enolate did not affect the shift of the Cp ligands.

aldehyde was added.

In conjunction with the NMR studies on the metal exchange process the ^{1}H and ^{13}C NMR spectra of the lithium and zirconocenyl enolates of pyrrolidylpropionamide (14) were investigated in more detail. The lithium enolate of 14, labeled with ^{13}C at the methyl carbon, in THF afforded single methyl resonance at 11.7 ppm. Addition of 1 equivalent of Cp_2ZrCl_2 gave a new signal at 11.3 ppm with a small residual signal at 11.7 ppm and a trace of the propionamide 14 at 9.3 ppm. The important features of the 500 MHz ^{1}H NMR spectra of the lithium and zirconocenyl enolates of 14 in d^{8}-THF are reproduced in Figures 5 and 6. The extremely broad signal at 3 ppm for the vinyl proton of the lithium enolate coalesces to a major quartet at 3.052 ppm and a minor quartet at 3.099 upon the addition of 1 equivalent of Cp_2ZrCl_2. The methyl doublet of the lithium enolate at 1.544 ppm separates into a major doublet at 1.589 ppm and a minor doublet at 1.531 ppm. The major signals are associated with the Cp ring signal at 6.375 ppm indicative of a mono enolate while the minor signals are associated with the ring signal at 6.315 ppm for the bis-substituted metal complex. The lithium enolate prepared from propionamide 14 and LDA has been assigned the cis (Z) configuration with less than 3% of the opposite configuration.[29b] These

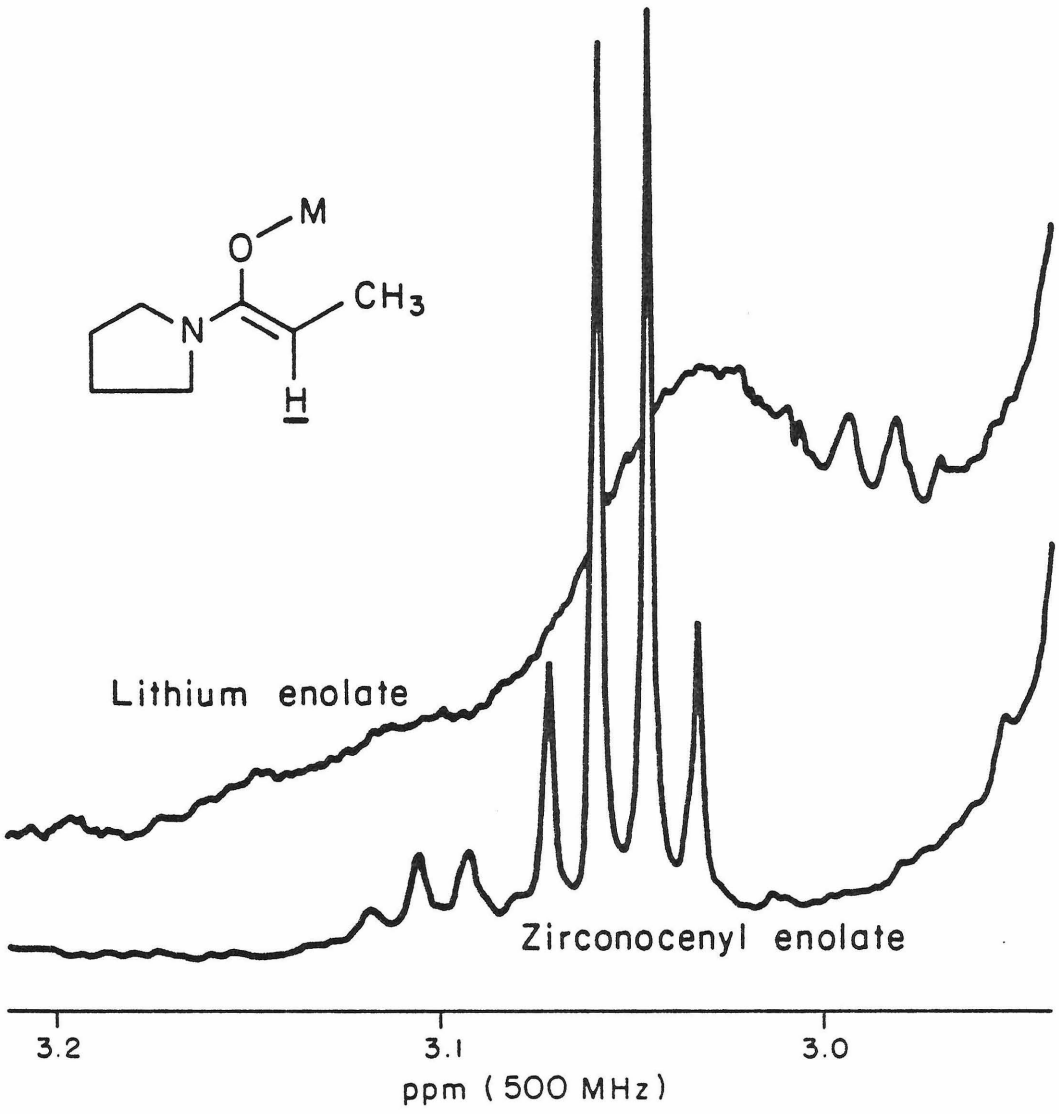


Figure 5. ^{1}H NMR vinyl region.

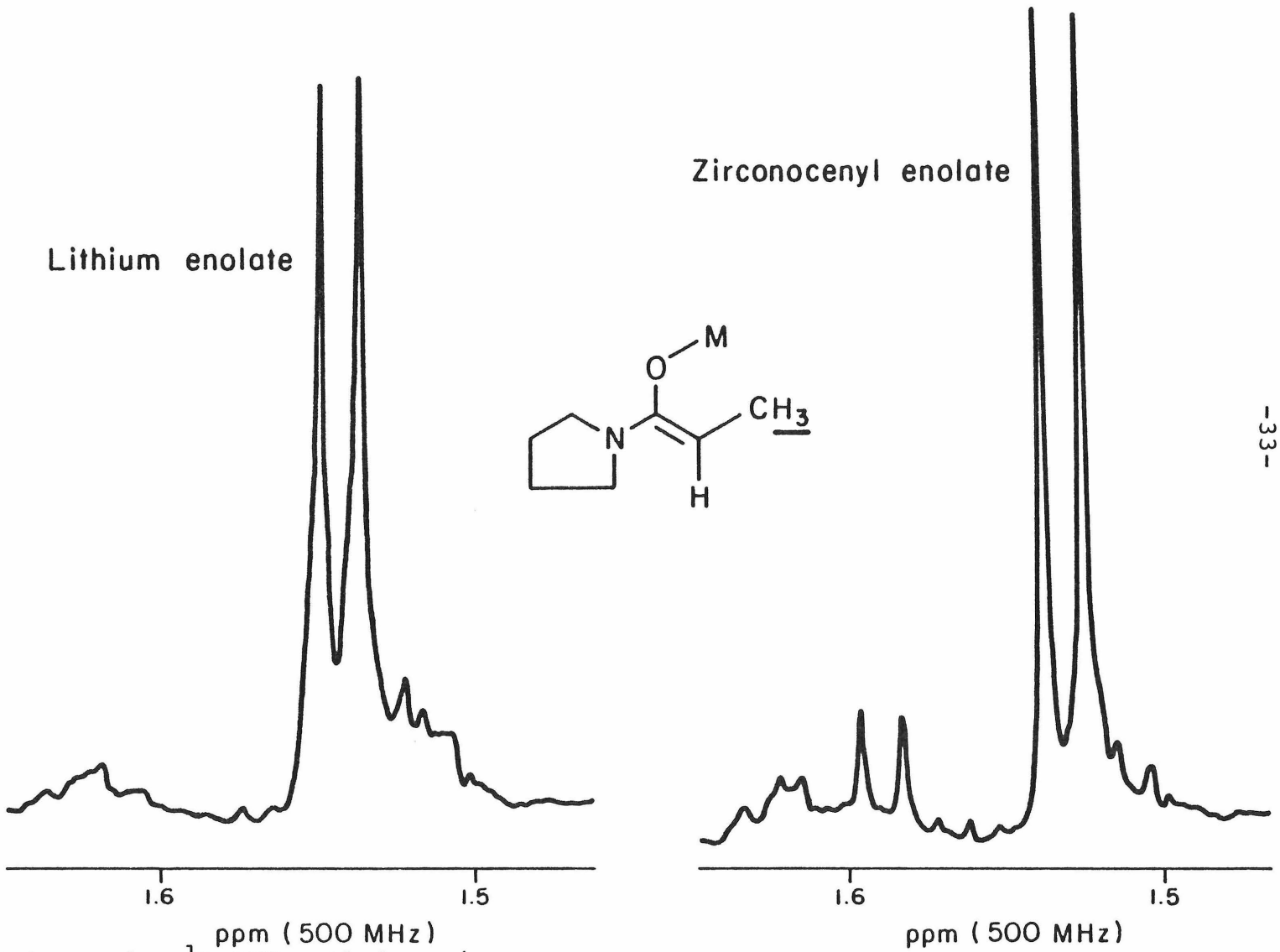
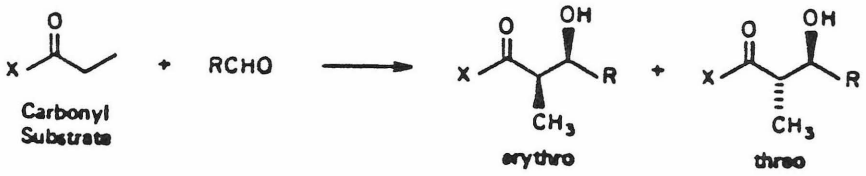


Figure 6. ^{1}H NMR methyl region.

NMR spectra are consistent with this assignment and suggest that the lithium enolate exists as enolate aggregates which exchange among themselves on the NMR time scale. Substitution with Cp_2ZrCl_2 forms monomeric species stable on the NMR time scale.

Aldehyde Influence on Aldol Diastereoselection. To further probe the steric requirements of the zirconium-mediated aldol condensation, aldehydes of varying steric demand were condensed with six representative enolate systems. The diastereomer ratios obtained from the zirconium-mediated condensations and the corresponding lithium-mediated condensations are compared in Table 9. While the erythro preference is maintained throughout the series and, in general, cis enolates afford higher stereoselectivity than trans enolates,[33] there is no systematic effect of aldehyde branching or unsaturation on the reaction diastereoselectivity. The consistently high levels of diastereoselection produced with amide enolates are encouraging for the potential synthetic application of these substrates.

Transition State Models. It is apparent from the preceding results that the chair-like Zimmerman transition state is inadequate to describe the stereoselection of zirconium-mediated aldol condensations using Cp_2ZrCl_2.



3b

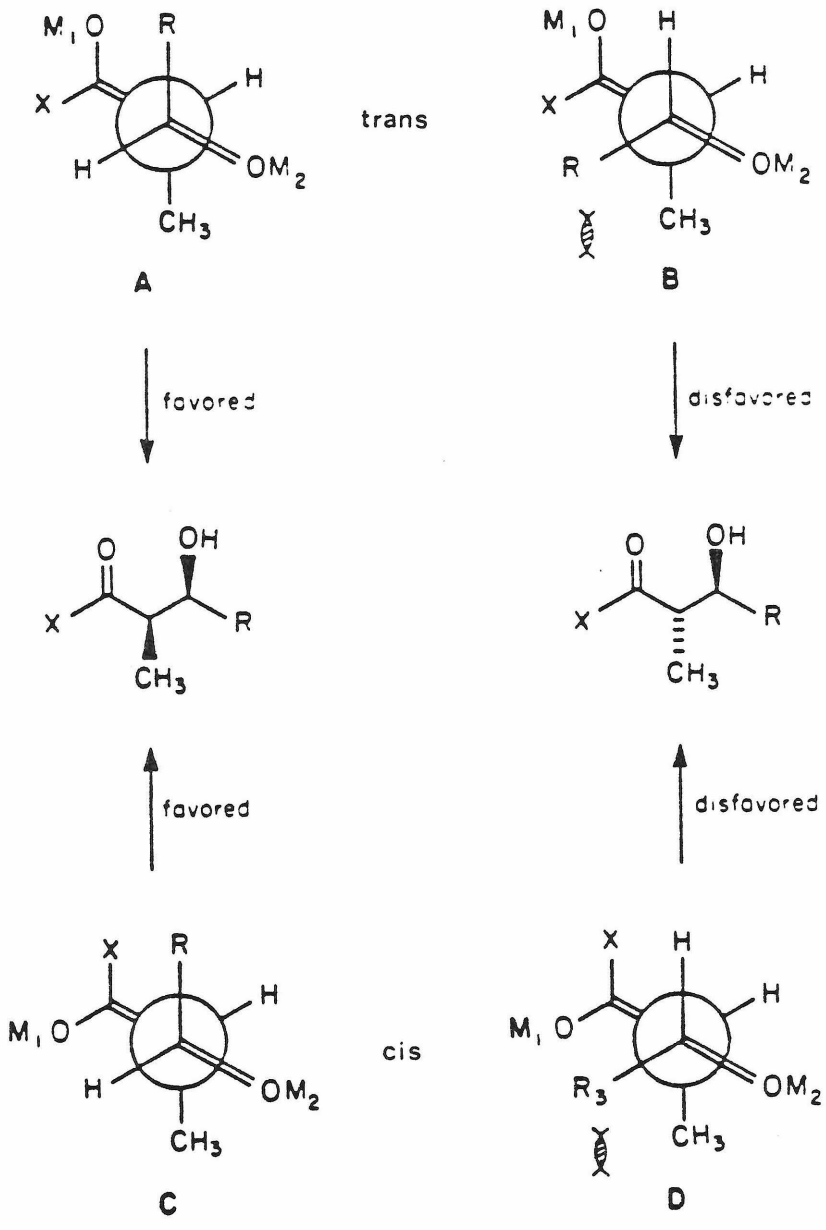
Table 9. Lithium and Zirconium-Mediated Aldol Condensations With Aldehydes 16b,c,d.[a]

Entry	Carbonyl Substrate	Aldehyde	Product Distribution[b] Li (E/T)	Zr (E/T)	Yield (Zr)
1	8 X=C_6H_5-	16c R=(i)C_3H_7-	65:35	80:20	(37%)[c]
2	8	16d R=(i)C_3H_5-	78:22	>98:2	(46%)[c]
3	9 X=(t)BuS-	16b R=(n)C_3H_7-	61:39	78:22	--[c]
4	9	16c	24:76	62:38	(47%)[c]
5	9	16d	31:69	88:12	(47%)[c]
6	12 X=MeO-	16b	74:26	87:13	--[c]
7	12	16c	51:49	86:14	98%
8	12	16d	51:49	86:14	89%
9	13 X=(t)BuO-	16b	52:48	71:29	--[c]
10	13	16c	40:60	75:25	--[c]
11	13	16d	32:68	82:18	(72%)[c]
12	14 X= 	16b	64:36	94:6	71%
13	14	16c	79:21	95:5	89%
14	14	16d	70:30	90:10	87%
15	15 X=(i)Pr_2N-	16b	79:21	98:2	(55%)[c]
16	15	16c	80:20	>97:3	87%
17	15	16d	85:15	95:5	81%

[a]Equation 3b. [b]^{13}C NMR Ratio ±2%. [c]Qualitative.

Yamamoto has suggested an acyclic or extended transition state for these aldol condensations in analogy to that proposed by Noyori to account for the configuration-independent erythro diastereoselection observed in electrophilic aldol condensations.[34] Noyori suggests "that the observed unique stereochemical outcome, a moderate to very high level of erythro selection which is independent of enolate geometry, indicates the operation of the mechanism involving the extended transition state."[35]

Acyclic Transition States. In Scheme VIII the Noyori extended transition states are considered.[35] After assuming the enolate and aldehyde oxygens will become aligned at opposite ends of the transition state, the major factor affecting product stereochemistry is the steric interaction between the aldehyde alkyl group and the enolate methyl group. Those orientations (A and C) in which these groups are anti-periplanar lead to erythro product and are preferred over those orientations (B and D) in which these groups are syn-clinal to each other. Increasing steric demand in the enolate X group should unfavorably affect B more than A and C more than D. Thus, this transition state model predicts that increasing the steric bulk of the enolate X group should



Scheme VIII Extended Acyclic Transition States

enhance the erythro selectivity for trans enolates and diminish the diastereoselectivity for cis enolates. This is exactly opposite to the experimental trend noted earlier, page 20 and Table 5.

In addition to these conformations considered by Noyori, there are conformations for each enolate configuration in which the aldehyde oxygen is syn-clinal to the enolate double bond. These conformations are stereochemically equivalent to cyclic chair and boat transition states. There is however no reason to expect the oxygen atoms of the aldol transition state to remain in proximity to each other unless they coordinate to the same metal complex.[35]

Cyclic Transition States. In order to visualize potential cyclic transition states, Dreiding molecular models were modified to represent the expected narrow metal-centered bond angle between the aldol partners and the steric demand of the bulky Cp ligands.[36]

The assumption that the aldehyde will coordinate to the metal center's vacant orbital was mentioned earlier. An additional assumption that the orientation of the coordinated aldehyde will be fixed with the R group out of the pocket formed by the Cp ligands, as shown in Figure 7, seems justified by steric interactions obvious in the molecular models. This 18-electron transition state complex is

Figure 7. Aldehyde orientation.

depicted in Figure 8 with the trans-enolate configuration in the most accessible conformation. Formation of the aldol carbon-carbon bond from this orientation leads to the observed erythro product. Figure 9 presents a Newman

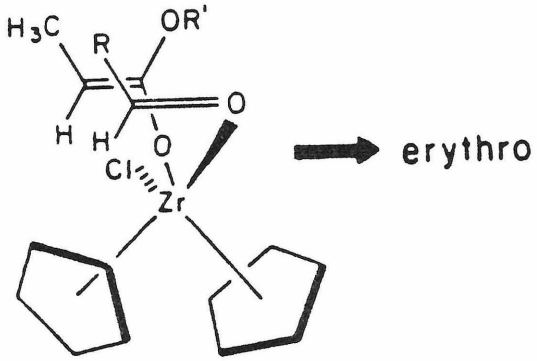


Figure 8.

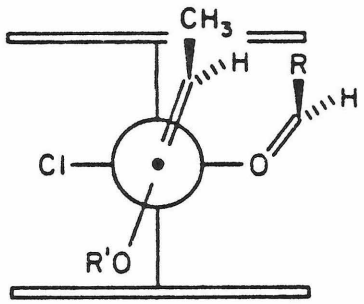


Figure 9. Newman projection.

projection of this transition state in which the Cp ligands are represented by bars, the metal is represented as an open circle and the enolate oxygen as a filled circle. The projection is along the carbon-oxygen-zirconium bonds.[37]

Upon interchanging the enolate configuration, the diastereomeric product should result from this transition state. In the molecular model, however, the cis methyl

group of the enolate displays a significant interaction with the Cp ligands. This interaction is reinforced by the bulk of the enolate X group as illustrated in Figure 10. Canting the enolate in a skew orientation across the face of the metal center, Figure 11, relieves both of these interactions.[38]

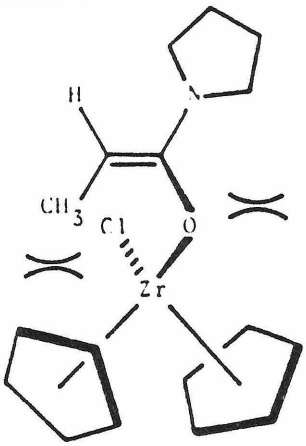


Figure 10.

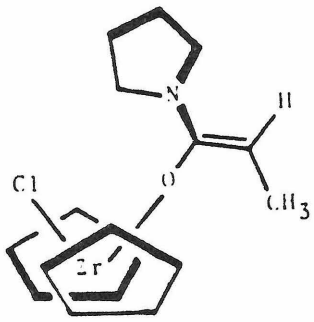


Figure 11.

Coordination of the aldehyde to the metal with this enolate orientation, Figure 12,leaves the reactive carbon centers at nonbonding distances from each other. Eventual orientation of the aldehyde partner in the less accessible orientation shown in Figure 13, brings the reactive carbon

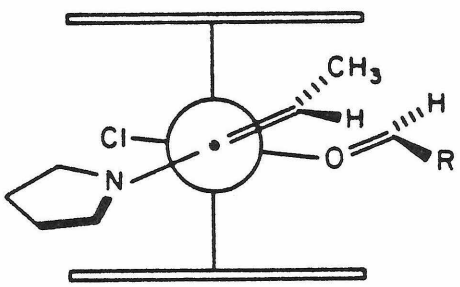


Figure 12.

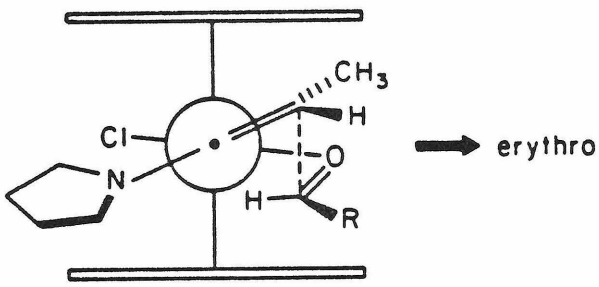


Figure 13.

centers into bonding distance. This configuration results in the erythro product.

In terms of the Zimmerman transition states represented in Schemes IV (page 11) and V (page 12), the requirement for the aldehyde partner to maintain its bulky substituent out of the pocket excludes $\underset{\sim}{C}_3$ and $\underset{\sim}{B}_1$, $\underset{\sim}{C}_2$ and $\underset{\sim}{B}_3$. The remaining competing aldol transition states are $\underset{\sim}{C}_4$ and $\underset{\sim}{B}_2$, $\underset{\sim}{C}_1$ and $\underset{\sim}{B}_4$. The preferred transition state for trans enolates, shown in Figure 9, bears closest resemblance to $\underset{\sim}{B}_4$. The preferred transition state for cis enolates, Figure 13, resembles $\underset{\sim}{C}_4$.

These pairs of competing diastereomeric transition states are consistent with the effect of the steric demand of the enolate X group on aldol diastereoselection. The skew arrangement of enolate to metal pocket (Figure 11) will be reinforced by increasing steric demand in the X group. This will diminish erythro selectivity for trans enolates (Figure 9) and enhance erythro selectivity for cis enolates (Figure 13).

Monocyclopentadienyl Transition State. Replacing one bulky ligand on the metal center with a sterically nondemanding ligand should have a predictable effect on the reaction diastereoselection if the narrow aldol bond angle can be maintained and if the aldehyde orientation will be fixed by the remaining bulky ligand. Trans enolates should still give erythro product but increased steric demand in X should

reinforce the erythro selectivity. More interestingly, cis enolates should give threo products. These transition states are illustrated in Figures 14 and 15 respectively.

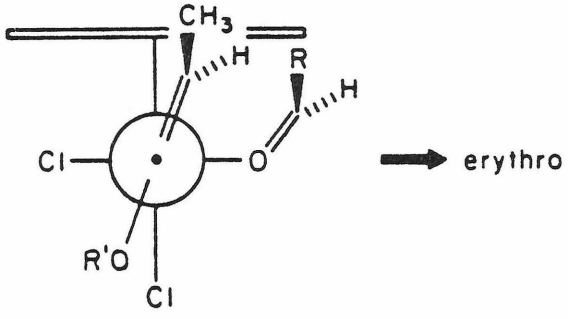


Figure 14. Trans enolate.

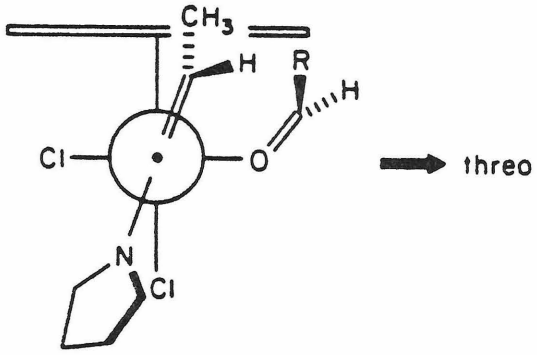


Figure 15. Cis enolate.

Based on these considerations $CpTiCl_3$[41] was used in the aldol condensations in a procedure identical to that used for Cp_2ZrCl_2. The results in Table 10 are generally consistent with our expectations. The yields were not determined because the mass recovery was not encouraging. This was not surprising in view of reported side products from reactions which may have involved titanium enolates.[26] In addition to these experiments, several zirconium and titanium complexes lacking both Cp ligands were investigated.[42] The levels of diastereoselection with these complexes confirm the requirement for the bulky Cp ligands.

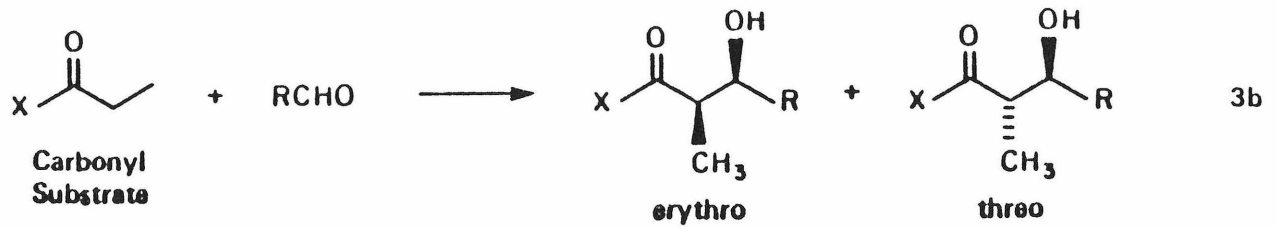


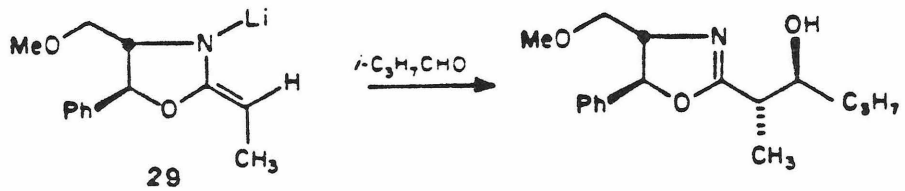
Table 10. Aldol Diastereoselection: $CpTiCl_3$ Mediated Condensations[a]

Entry	Carbonyl Substrate	Aldehyde	Product Distribution Li[b] (E/T)	Zr[b] (E/T)	$CpTiCl_3$[c] (E/T)
1	12 X=MeO-	16a R=C_6H_5-	56/44	85/15	39/61
2	12	16c R=(i)C_3H_7-	62/38	87/13	57/43
3	13 X=(t)BuO-	16a	34/66	75/25	84/16
4	13	16c	40/60	73/27	87/13
5	14 X= 	16a	60/40	95/5	27/73
6	14	16c	78/22	96/4	9/91
7	15 X=(i)Pr_2N-	16a	65/35	>98/2	32/68

[a]Equation 3b. [b]Tables 4, 5, and 9. [c]GC ratio rounded to nearest %.

III. Asymmetric Aldol Condensations

Introduction. The field of asymmetric synthesis has been an area of great progress and excitement during the course of this work. Several excellent reviews have appeared touching upon various aspects of the topic.[43,44] Scott and Valentine, in discussing the basic requirements for designing an asymmetric synthesis, suggest the choice of "a reaction whose mechanism is known, which has an ordered transition state without accessible symmetry elements, and which is already known to proceed generally in a stereoselective manner."[45] With the recent advances in the control of achiral aldol stereoselectivity the aldol reaction would appear to be a prime candidate for asymmetric induction. At the time we began our study only a few examples of asymmetric aldol reactions which produced significant levels of induction were known. Meyer's lithio oxazoline enolate 29 with isobutyraldehyde afforded a mixture of diastereomers in which the threo (2S, 3S) isomer represented 75% of the total.[46]



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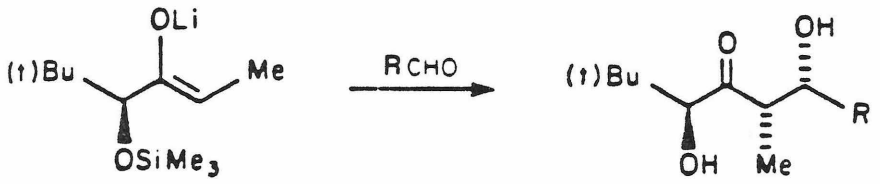
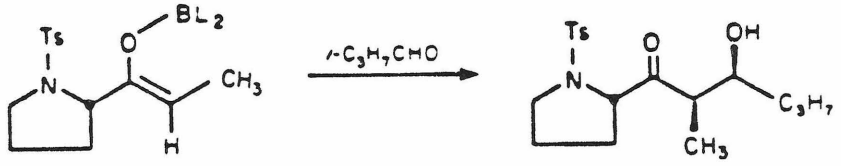
Heathcock's asymmetric but racemic ketone enolate 30 showed excellent asymmetric induction for erythro diastereomers[47] especially when the aldehyde was also asymmetric and racemic. Finally, Taber found excellent levels of asymmetric



30

induction with the sulfonamide ketone boron enolate 31.[48]



31

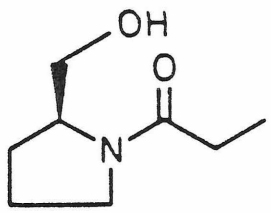
These systems suffer from either a lack of generality in the levels of diastereoselection observed with aldehydes of differing steric requirements or the difficulty of obtaining the chiral, enantiomerically pure propionyl substrate or both.

Recently Takacs has described the use of chiral amides 32-34, derived from ℓ-prolinol, in asymmetric alkylations.[29] During the design of this enolate system, he identified the following key features sufficient for synthetically useful asymmetric alkylation. The amide enolates are strong nucleophiles and react with a wide variety of electrophilic reagents. The pyrrolidine ring system directs the stereospecific formation of the cis enolate configuration. The hydroxymethyl side chain provides a chiral bias to one diastereotopic face of the enolate. The magnitude of the chiral bias can be manipulated by adjusting reaction parameters which affect the coordination of the side chain to the enolate metal center. Finally, the chiral auxiliary may be removed under mild conditions with the participation of the hydroxymethyl function.

In view of the high levels of asymmetric induction obtained in the alkylation reaction it was somewhat surprising that the corresponding lithium-mediated aldol condensations afforded low levels of both relative 1,2 diastereoselection and 1,4 asymmetric induction.

Having achieved useful erythro diastereoselectivity with amide enolates, we also addressed the question of asymmetric induction within the erythro product manifold.[49]

Results and Discussion. We felt that the use of Cp_2ZrCl_2 (6) in the chiral aldol condensation would at least render the reaction erythro diastereoselective in analogy to the results observed with the achiral parent amide 14. In fact, however, addition of one or two equivalents of the zirconium complex 6 to the lithium dianion of prolinol amide 32 failed to improve the aldol stereoselection. That the side chain alkoxide was interfering in the stereoselectivity of the reaction was shown by blocking it as the methyl ether 33. While the lithium-mediated aldol condensation remained



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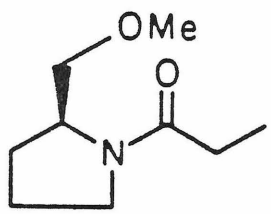
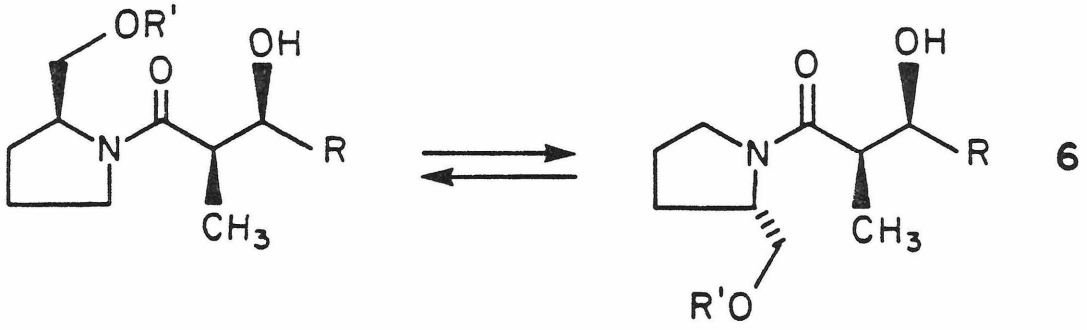


33

stereorandom, the zirconium-mediated condensation displayed excellent selection for erythro diastereomers as evidenced by ^{1}H and ^{13}C NMR. However, analysis by NMR of the aldol product containing a chiral amide moiety is complicated by hindered rotation about the amide bond, Equation 6.

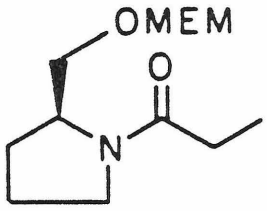
Capillary gas chromatography (GC) of the amide aldol diastereomers simplified the product analysis and verified that the erythro isomers observed by NMR were indeed a



6

single diastereomer.[50] That the aldol adducts were stable to the GC analysis conditions was inferred from a comparison of the integration ratios obtained by GC with the ratios obtained by ^{1}H and ^{13}C NMR for a number of achiral aldol adducts.[51] The consistency of amide aldol diastereomer ratios between ^{1}H NMR, ^{13}C NMR and GC as well as the lack of signs of decomposition during GC analysis of the chiral amide aldol adducts gave us confidence that the observed ratios were real. Figure 16 illustrates a typical GC analysis of the crude product of the lithium and corresponding zirconium-mediated aldol condensations.

The success of the methyl ether 33 prompted the use of a removable hydroxyl blocking group which would allow the hydroxymethyl side chain to participate in the subsequent amide hydrolysis. The methoxyethoxymethoxy (MEM) group proved suitable.[53] The MEM ether 34 had a small but significant increase relative to



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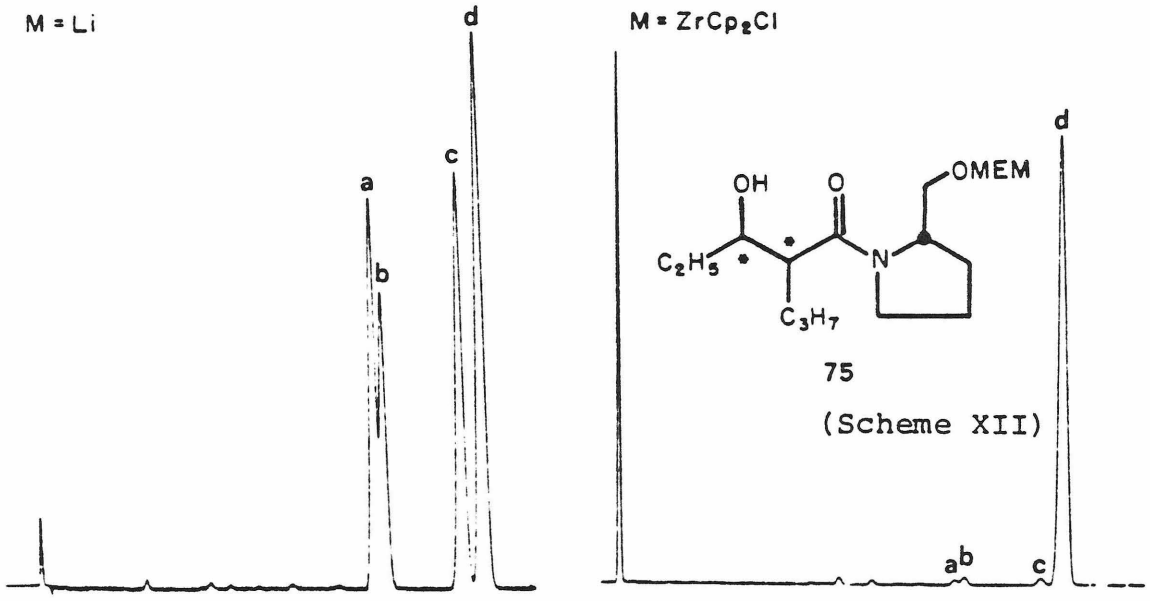
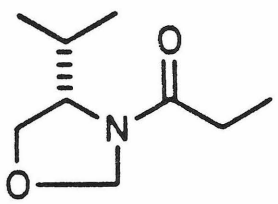


Figure 16. Typical GC trace of unpurified aldol adducts.

methyl ether 33 in aldol diastereoselectivity. The increased stereoselectivity afforded by MEM ester enolates in the aldol condensation has been attributed to coordination of the metal cation by the polyether chain.[46] That the influence of ether side chains in the chiral amide enolates was a steric effect rather than a metal coordination effect was shown by the aldol condensation with the enolate derived from the valinol-derived acyl oxazolidine 35. The major diastereomer of the aldol condensations of 33, 34



35

and 35 with isobutyraldehyde (16c) increases from 92% to 96% to 98% of the total aldol diastereomers in line with the increasing steric demand of the chiral auxiliary side chain.

Oxazolidine 35 is readily prepared from commercially available ℓ-valinol. The oxazolidine ring system should direct the stereospecific enolization of the propionamide in analogy to results observed with the pyrrolidylpropionamide (14). Although 35 is derived from the natural configuration of valine it has its chiral side chain on the opposite face of the ring system when compared to the prolinol-derived propionamides, thus the enantiomeric aldol stereocenters should be produced from this chiral auxiliary. We envisioned the latent hydroxyl hidden in the ring system as a potential participant in the amide hydrolysis under acidic conditions.

The valinol- and prolinol-derived chiral auxiliaries might also serve as resolving agents[54] so that initial aldol diastereoselection could be further enhanced by simple flash chromatographic[55] removal of the unwanted isomers.

In Table 11 the ratios of aldol diastereomers obtained from the zirconocenyl enolate of the prolinol-derived propionamide 34 are compared with those obtained from the corresponding lithium enolate. Table 12 contains the same data for condensations of the valinol-derived propionamide 35. In all cases the lithium-mediated condensations afforded

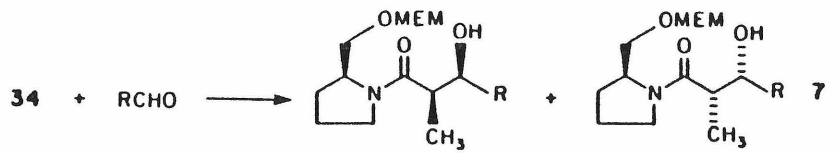
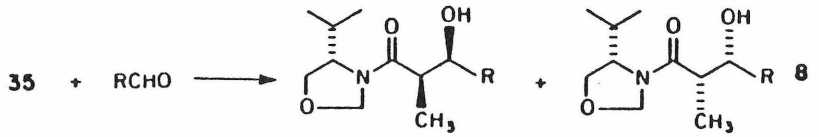


Table 11. Aldol Diastereoselection for Chiral Amide 34[a]

Entry	Metal[b]	Aldehyde	Product Distribution[c] 36:37	:	T_1:T_2	% Yield
1	Zr	16a R=C_6H_5-	96.0 : 1.2	:	1.8: 1.0	71[d]
2	Li		31.3 :32.7	:	22.7:13.4	
3	Zr	16c R=(i)-C_3H_7-	96.1 : 1.4	:	1.8: 0.7	77[d]
4	Li		42.6 :36.1	:	8.8:12.5	
5	Zr	16e R=(n)-C_4H_9-	95.7 : 1.9	:	1.2: 1.0	69[d]
6	Li		38.6 :29.0	:	17.1:15.3	
7	Zr	40	94.4[e]: 1.5	:	2.8: 1.4	39[f]
8	Li		42.8 :13.0	:	15.6:28.7	
9	Zr	41	94.3[g]: 2.6	:	0.8: 2.4	43[h]
10	Li		37.0 :12.5	:	36.8:13.8	

[a]Equation 7. [b]Zr refers to Cp_2ZrCl_2. [c]GC ratio ±0.2%, standardized to base 100. T_1 and T_2 are the threo diastereomers. [d]Chromatographed to 99% 36. [e]Compound 42. [f]Unpurified yield 97%. The yield reported is for the overall transformation to methyl ester 61. [g]Compound 43. [h]Chromatographed material contains 3% of aldol 42.



38 39

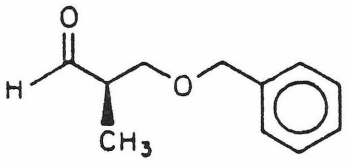
Table 12. Aldol Diastereoselection for Chiral Amide 35[a]

Entry	Metal[b]	Aldehyde	Product Distribution[c] 38:39	:	T_1:T_2	% Yield
1	Zr	16a R=C_6H_5-	1.3:95.3	:	1.2: 2.2	71[d]
2	Li		41.4:29.2	:	23.4: 6.0	
3	Zr	16c R=(i)-C_3H_7-	0.5:98.3	:	0.8: 0.4	77[d]
4	Li		42.6:40.5	:	12.5: 4.4	
5	Zr	16e R=(n)-C_5H_9-	1.1:96.9	:	1.3: 0.7	96[e]
6	Li		35.2:42.0	:	6.1:16.8	
7	Zr	40	1.7:94.4[f]	:	0.3: 3.6	(96)[g]
8	Li		5.4:31.4	:	44.7:18.6	
9	Zr	41	0.9:98.7[h]	:	0.1: 0.3	77[i]
10	Li		7.1:34.5	:	18.5:39.8	

[a]Equation 8. [b]Zr refers to Cp_2ZrCl_2. [c]GC ratio ±0.2%, standardized to base 100. T_1 and T_2 are the threo diastereomers. [d]Chromatographed to 99% 39. [e]Kugelrohr distillation. [f]Diastereomer ratio unchanged. [g]Compound 44. [h]Solid, unpurified aldol yield. [i]Compound 45. [j]Chromatographed.

low levels of 1,4 asymmetric induction and little or no 1,2 diastereoselection. The zirconium-mediated aldol condensations gave predominantly a single erythro diastereomer with small amounts of the other three isomers.

Chiral Branched Aldehydes. The aldol condensations of the zirconcenyl enolates of 34 and 35 with the enantiomeric α-substituted aldehydes 40 and 41 to afford aldol adducts 42-45



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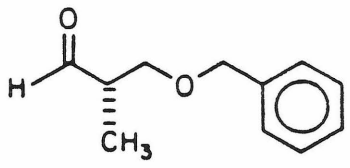

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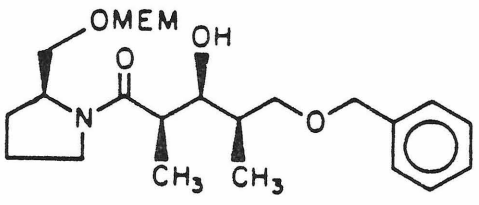

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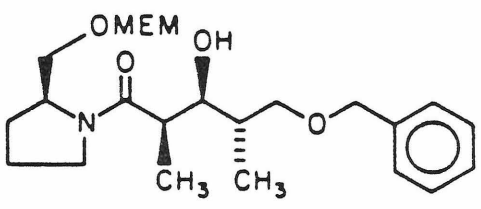

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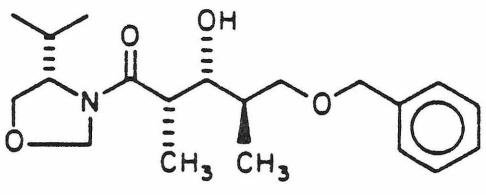

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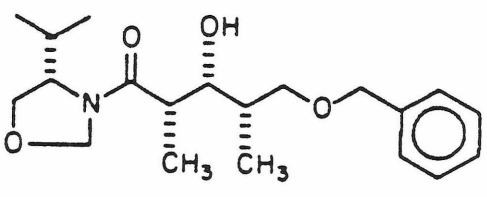
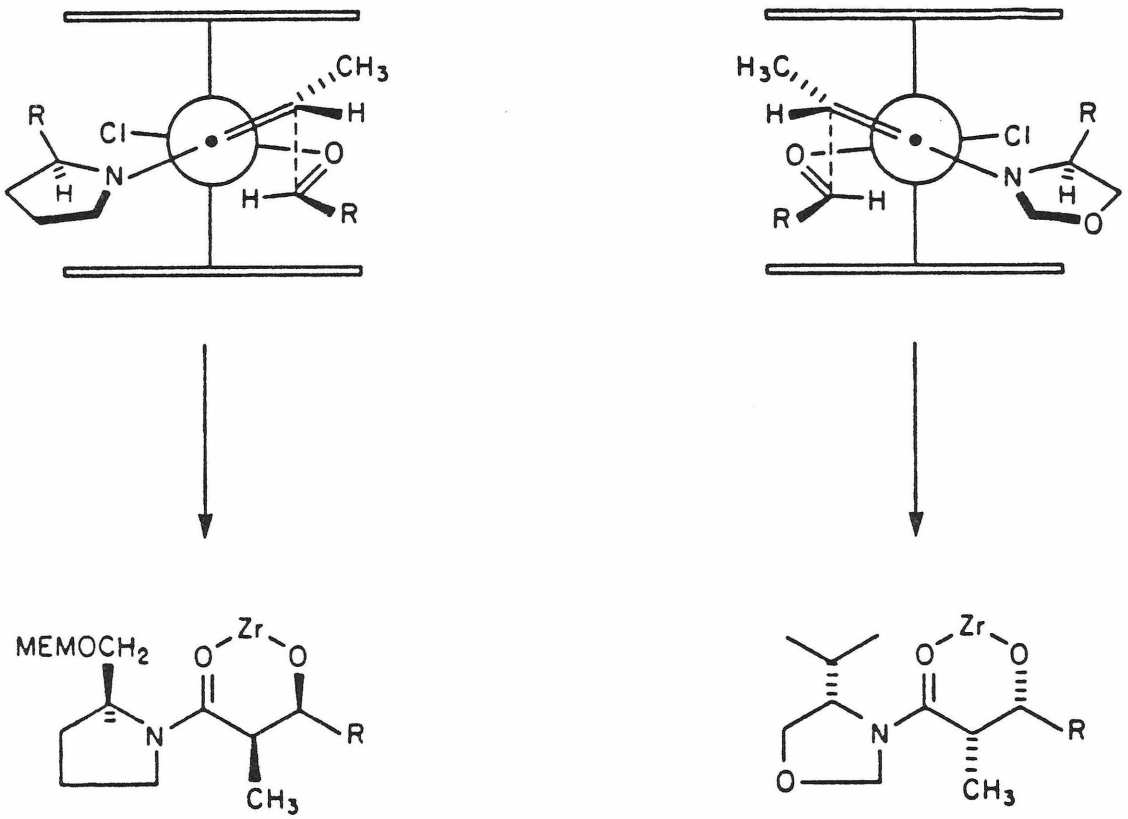


45

are also included in Tables 11 and 12. In these cases diastereoface selection on the enolate overrides any diastereoface selectivity imposed by resident chirality in the aldehyde condensation partner.[56] This is a feature essential for the design and implementation of syntheses involving chirality in the aldehyde partner, the importance of which has been demonstrated recently in Masamune's synthesis of 6-deoxyerythronolide B.[4]

Transition State Model. The aldol transition state model developed for achiral cis enolates, Figure 13, can be readily applied to the chiral amide enolates. Projection of the steric demand of the amide sidechain onto this model generates the transition states depicted in Scheme IX.[57] As illustrated, the prolinol- and valinol-derived amides yield a complementary sense of asymmetric induction. After hydrolysis, either enantiomer of the erythro β-hydroxy acid is available. The absolute and relative configurations of most of the chiral aldol adducts discussed in this report were proven by independent correlations to compounds of known configuration. These correlations will be discussed below. In all cases the configurations were those expected on the basis of Scheme IX.

Scheme IX

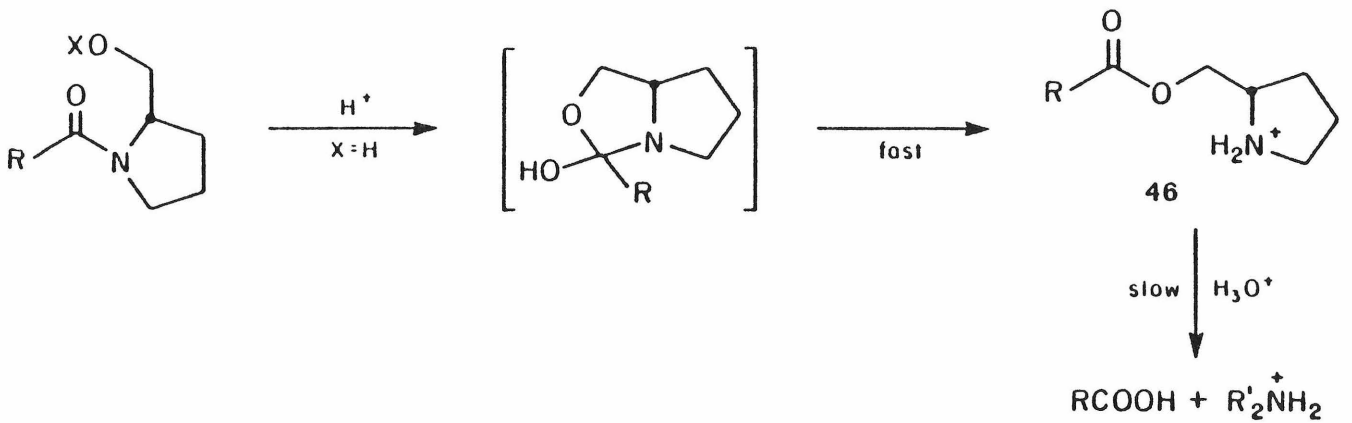


Chiral Threo Aldol Attempt. In spite of the success of asymmetric induction with erythro-selective aldol condensations, little progress has been made within the threo product manifold. The best levels of asymmetric induction in threo diastereomers occur with the lithium enolate of Meyer's chiral oxazoline[46a] and more recently with achiral oxazoline enolates of chiral boron species.[46b]

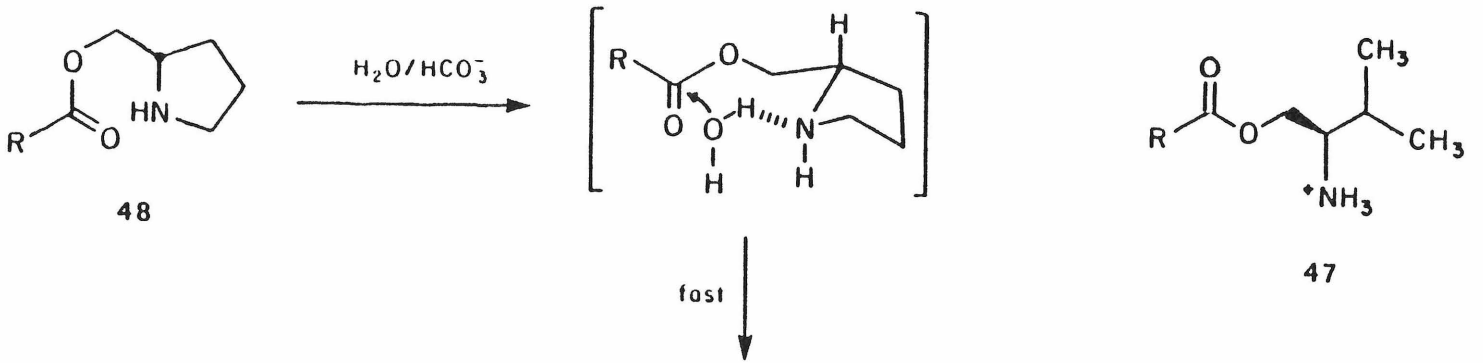
Our results with $CpTiCl_3$ as a threo selective metal gave a lead which we hoped might develop into a solution for asymmetric induction of threo stereocenters. Thus $CpTiCl_3$-mediated condensation of the valinol-derived propionamide 35 with isobutyraldehyde afforded as expected threo products as 90% of the aldol diastereomers. Unfortunately both threo diastereomers were produced in approximately equal amounts.

Hydrolysis of Chiral Aldol Adducts. The ability to remove the chiral auxiliary under conditions which do not destroy the newly created stereocenters and allow for the recovery of the chiral auxiliary was an important feature in the design of the chiral propionamides 34 and 35. The details of the acid-catalyzed hydrolysis of the aldol adducts are illustrated in Scheme X. The intermediates depicted in this scheme are well-precedented in the literature. Initial treatment of the aldol adducts 36 and 39 with dilute hydrochloric acid unmasks[53] the latent hydroxyl functionality and affects subsequent N → O acyl transfer[54a] to give the ammonium esters 46 and 47. These are essentially inert to further acidic hydrolysis.[58] Neutralization with aqueous sodium bicarbonate, however, results in the rapid liberation of the desired carboxylates.[59] The general base-catalyzed hydrolysis of ester 48 is well-precedented for related tertiary β-amino esters[60] but was somewhat surprising in view of the potential

Scheme X AMIDE HYDROLYSIS



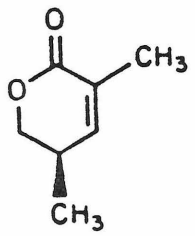
General Base Catalysis



competing O → N acyl transfer which has been documented for primary[61] and secondary β-amino esters.[29b] An excellent review is available which considers examples of acyl transfer in both directions.[62] Observations by Kemp and co-workers on the effect of solvent polarity and ring size on the rate of intramolecular O → N acyl transfer may relate to this concern.[63]

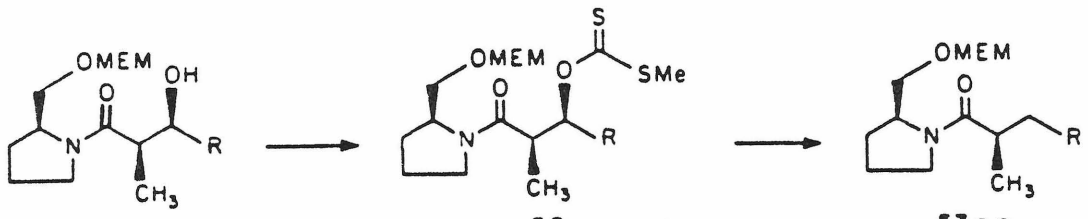
The results of the hydrolysis of amides 36, 39 and 42-45 are in Table 13. The standard hydrolysis conditions involve treating the amide with ten equivalents of 5% hydrochloric acid at reflux for 2 h to affect acyl transfer followed by neutralization with saturated sodium bicarbonate solution. For aliphatic aldol adducts the enantiomeric erythro-β-hydroxy acids 49 and 50 are obtained in good yield without loss of stereochemistry at either stereocenter. Adducts containing acid sensitive functionality required less vigorous conditions. Hydrolysis of the amide 39a possessing the benzylic alcohol function under the standard procedure gave complete epimerization of the benzylic stereocenter. This side reaction was minimized by adding p-dioxane to change the polarity of the solvent system and by reducing the amount of acid to four equivalents. Acyl transfer required 4 h at reflux but epimerization was reduced to ~ 3%.

Under the standard conditions, benzylic ethers 42-44 underwent partial debenzylation resulting ultimately in the formation of a volatile product believed to be lactone 51 as a major side product. With the addition of p-dioxane to the hydrolysis of amide 45 the debenzylation was essentially eliminated and the yield of acid 60 increased substantially (Table 13, entry 10).



51

Absolute Configuration Correlations. The absolute configurations of the aldol adducts were proven by a variety of independent procedures. Aldol adducts 36c and 36e were converted to their methyl dithiocarbonate derivates 52c and 52e which were reduced[64] with tri-butyltin hydride to the

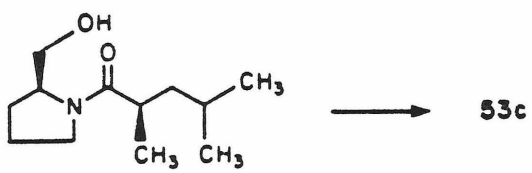


36 c R=(i)C_3H_7–
e R=(n)C_4H_9–

52c,e

53c,e

α-methylamides 53c and 53e. Amide 53c was identical to material prepared by the MEMCl protection of hydroxyamide 54.



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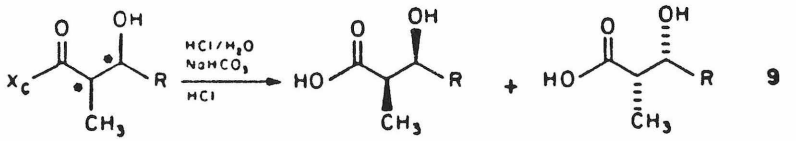
53c



49 a R=C_6H_5- c R=(i)C_3H_7- e R=(n)C_4H_9-

50 a,c,e

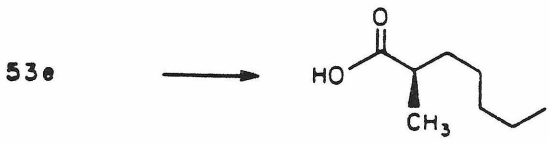
9

Table 13. Hydrolysis Products,[a] Yields, Rotations

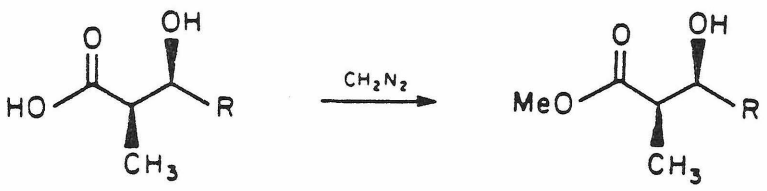
Entry	Amide	Acid	% Threo[b]	% Yield	Rotation
1	36a R=C_6H_5	49a	3.1[c]	78[d]	+29.5 (c 3.7, $CHCl_3$)[e]
2	39a	50a	3.2[c]	79[d]	-30.0 (c 3.7, $CHCl_3$)[f]
3	36c R=(i)-C_3H_7	49c	0.9[g]	90	+ 9.3 (c 2.6, CH_2Cl_2)[h]
4	39c	50a	0.2[g]	91	- 9.7 (c 1.5, CH_2Cl_2)
5	36e R=(n)-C_4H_9	49e	3.4[g]	89	-13.8 (c 6.9, CH_2Cl_2)
6	36e	50e	2.6[g]	91	+14.9 (c 6.8, CH_2Cl_2)
7	42	57	[i]	56	- 5.3 (c 6.9, CH_2Cl_2)
8	43	58	[j]	34	--
9	44	59	[k]	33	-20.9 (c 3.8, CH_2Cl_2)
10	45	60	[l]	82[d]	+13.7 (c 2.7, CH_2Cl_3)

[a]Equation 9. [b]Based on GC analysis of the corresponding methyl ester. [c]From benzylic epimerization. [d]Modified hydrolysis conditions. [e]Lit. +31.03 (c 1.07, $CHCl_3$), Ref. 70. [f]Lit. -29.5 (c 2.03, $CHCl_3$), Ref. 56. [g]From residual threo isomers in the amide. [h]Lit. +10.54 (c 1.40, $CHCl_3$), Ref. 70. [i]Contains 6.4% of acid 58.[b] [j]Contains 21% of acid 57.[b] [k]Contains 11% of acid 60.[b] [l]Contains 2% of acid 59.[b]

The preparation of 54 and its hydrolysis to known (-)2(R),4-dimethylpentanoic acid[65,66] have been described.[29]



Hydrolysis of amide 53e afforded the known (-)2(R)-methylheptanoic acid.[65,67] Hydrolysis of the aldol adducts 36c and 36e afforded the acids 49c and 49e (Table 13, entries 3 and 5) which were esterified to the methyl esters 55c and 55e.

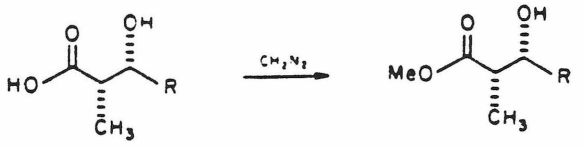


49 a R=C6H5–
c R=(i)C3H7–
e R=(n)C4H9–

55 a,c,e

The erythro relative configuration of 55c was established by comparison to authentic racemic erythro ester 21c prepared earlier (Table 9, entry 7). The erythro relative configuration of ester 55e was assigned on the basis of ^{1}H and ^{13}C NMR.[68] This sequence confirms the configurations of 36c and 36e as 2R, 3S at the aldol stereocenters.[69] Reference has been made to this correlation of acid 49c.[48,52]

Hydrolysis of the valinol-derived amides 39c and 39e afforded the erythro acids 50c and 50e (Table 13, entries 4 and 6) which were esterified to the methyl esters 56c and 56e.



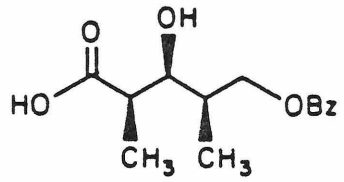
50 a R=C6H5-
c R=(i)C3H7-
e R=(n)C4H9-

56 a,c,e

These were identical to esters 55c and 55e except for rotations which were of opposite sign and slightly larger magnitude.

Careful hydrolysis of the benzylic alcohol 39a gave the crystalline acid 50a (Table 13, entry 2), the absolute configuration of which has been correlated to (-) ephedrine.[56,69] Similar hydrolysis of amide 36a gave the enantiomeric acid 49a (Table 13, entry 1).

The aldol adducts 42-45 were correlated to each other by hydrolysis to the acids 57-60 and esterification to the methyl esters 61-64. Esters 61 and 64 form an enantiomeric pair as do esters 62 and 63. These enantiomeric pairs are diastereomeric to each other. The absolute stereochemistry was established by reduction of methyl ester 61 to the dihydroxyether 65 which was converted to the tribenzylether 66. The stereocenter at the 4 position has the R



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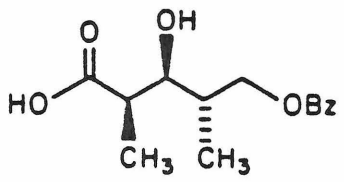

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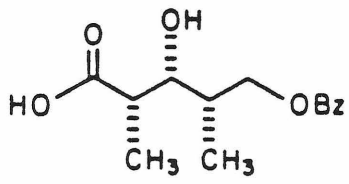

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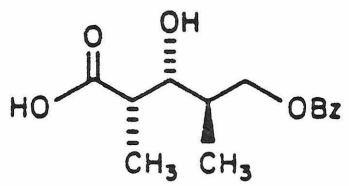

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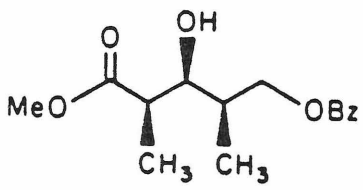

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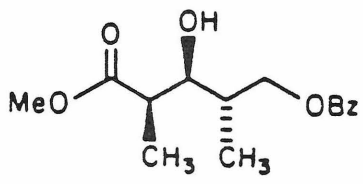

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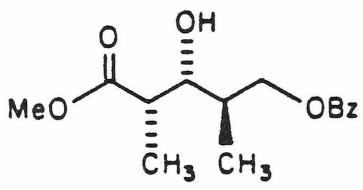

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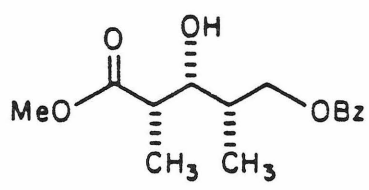

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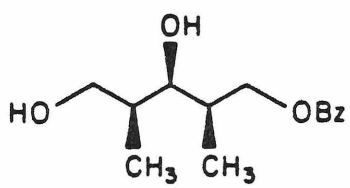

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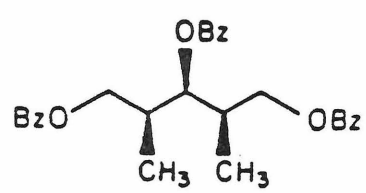


66

configuration since it derives from aldehyde 40 of known absolute configuration. The symmetrical nature of the tri-ether 66, readily apparent from ^{1}H and ^{13}C NMR, establishes the other stereocenters of 61 as 2R, 3S.

Nonpropionyl Aldol Condensations.

Acetate Equivalents. While chiral propionyl enolates have broad applications in organic synthesis, other acyl enolates were also of interest. Trends observed in the aldol condensations with propionyl enolates do not always hold when altering the substitution in the acyl portion of the enolate.[6]

The application of our observations on propionyl enolates to acetyl enolate equivalents is an important and nontrivial extension. The acetamide enolate presents the steric demand of a trans enolate towards the metal center and lacks the steric interaction of a cis substituent with the bulky Cp ligands of the metal. This missing interaction was postulated as an important factor regulating the stereoselectivity of the reaction. In terms of the transition state model presented earlier, the nonskew orientation of the enolate, Figure 17, may compete with or even predominate over the skew orientation, Figure 18. These orientations afford opposite configurations at the newly created carbinol center.

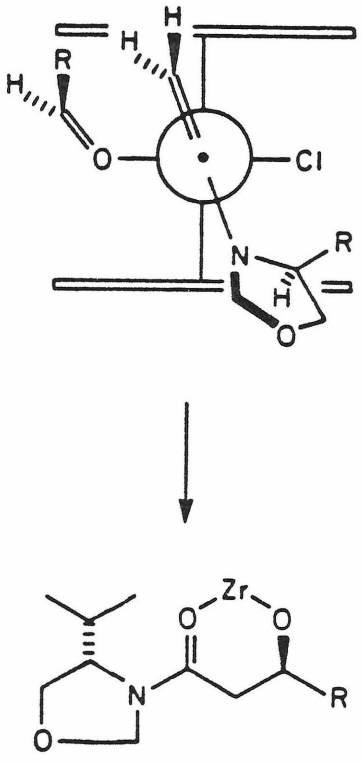


Figure 17.

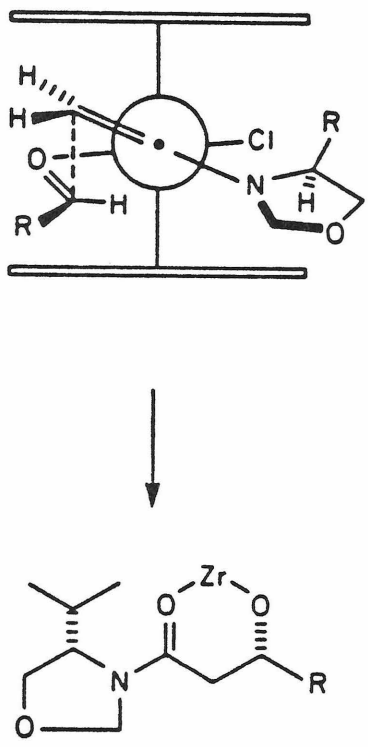
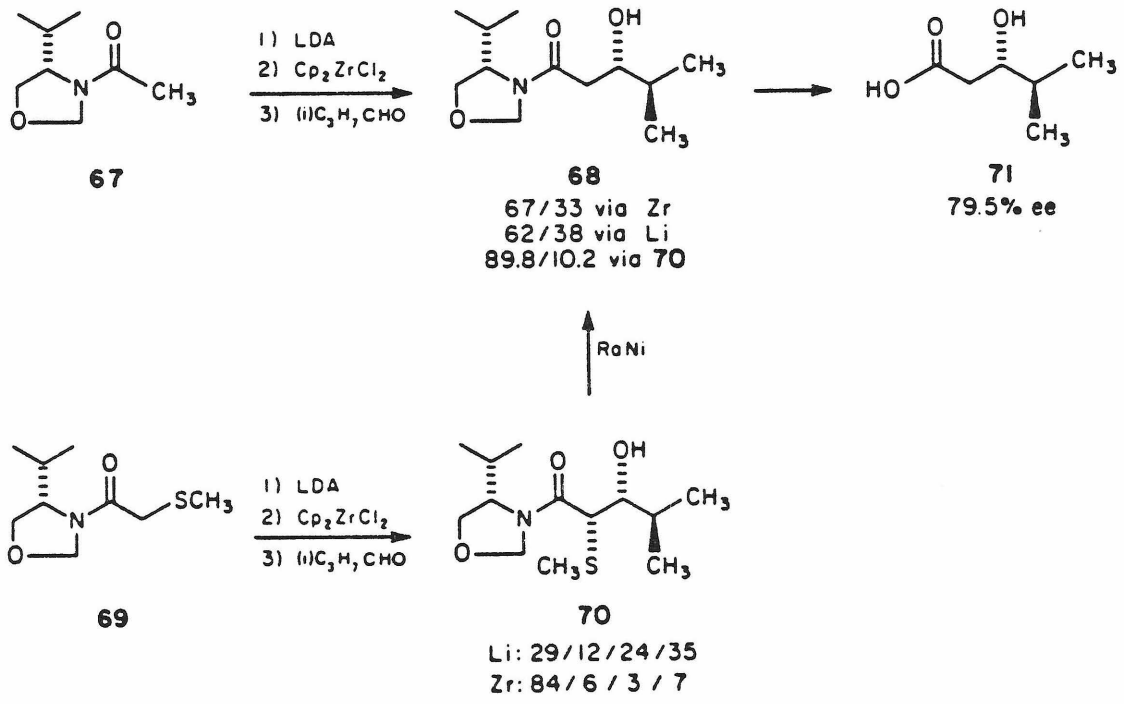


Figure 18.

It was therefore not surprising that condensation of the zirconocenyl enolate of the valinol-derived acetamide 67 gave a 67:33 ratio of alcohol 68 and its diastereomer, only slightly better than the 62:38 ratio obtained from the corresponding lithium enolate (Scheme XI). Similar results have been observed with other chiral acetate enolate equivalents.[48,52,73]

The absolute requirement of a cis substituent on the enolate for good levels of enantioselection was further demonstrated with the valinol-derived methylthioacetamide 69.

Scheme XI



Aldol condensation via the zirconocenyl enolate with isobutyraldehyde (16c) gave the four possible aldol diastereomers of 70 in a ratio of 84:6:3:7. Desulfurization of this mixture gave an 89.8:10.2 ratio of alcohol 68 and its diastereomer. Hydrolysis of this mixture gave the known 3(S)-hydroxy acid 71.[48,52] Based on the 89.8:10.2 ratio of the amide precursor, this sample of 71 should have an enantiomeric excess of 79.5%. The optical rotation of -32.4° translates to -40.8° for optically pure material. This value compares well with the value of +40.5° reported for the enantiomer.[48]

The relatively large percentages of diastereomeric impurities in the aldol condensation of 69 could be the result of as little as 6 to 12% of the trans enolate configuration. Arguments involving A-strain between the amide substituents and the enolate substituent on the developing enolate double bond have been presented to account for the high specificity of propionamide enolization.[29b] The long carbon-sulfur bond length should relieve such A-strain in the enolization of the methylthioacetamide 69 allowing the higher percentage of trans enolate.

Valerate Equivalent. Enolization of the prolinol-derived valeramide 72 should be as stereospecific as that of the propionamide 34. Indeed,aldol condensation of the zirconocenyl enolate of amide 72 with propionaldehyde (16f) afforded aldol adduct 73 and its diastereomers in a ratio of 97.8%:0.4%:1.3%:0.5%. The slightly higher levels of stereoselection observed here compared to those obtained from amide 34 (Table 11) possibly reflect the increased steric demand of the cis alkyl group of the enolate which favors the skew transition state, Figure 13.

Hydrolysis and methylation gave a 98.2%:1.8% mixture of ester 75 and its threo diastereomer. Racemic 75 was prepared as an 86.3%:13.7% erythro:threo mixture by the aldol condensation of the zirconocenyl enolate of methyl valerate

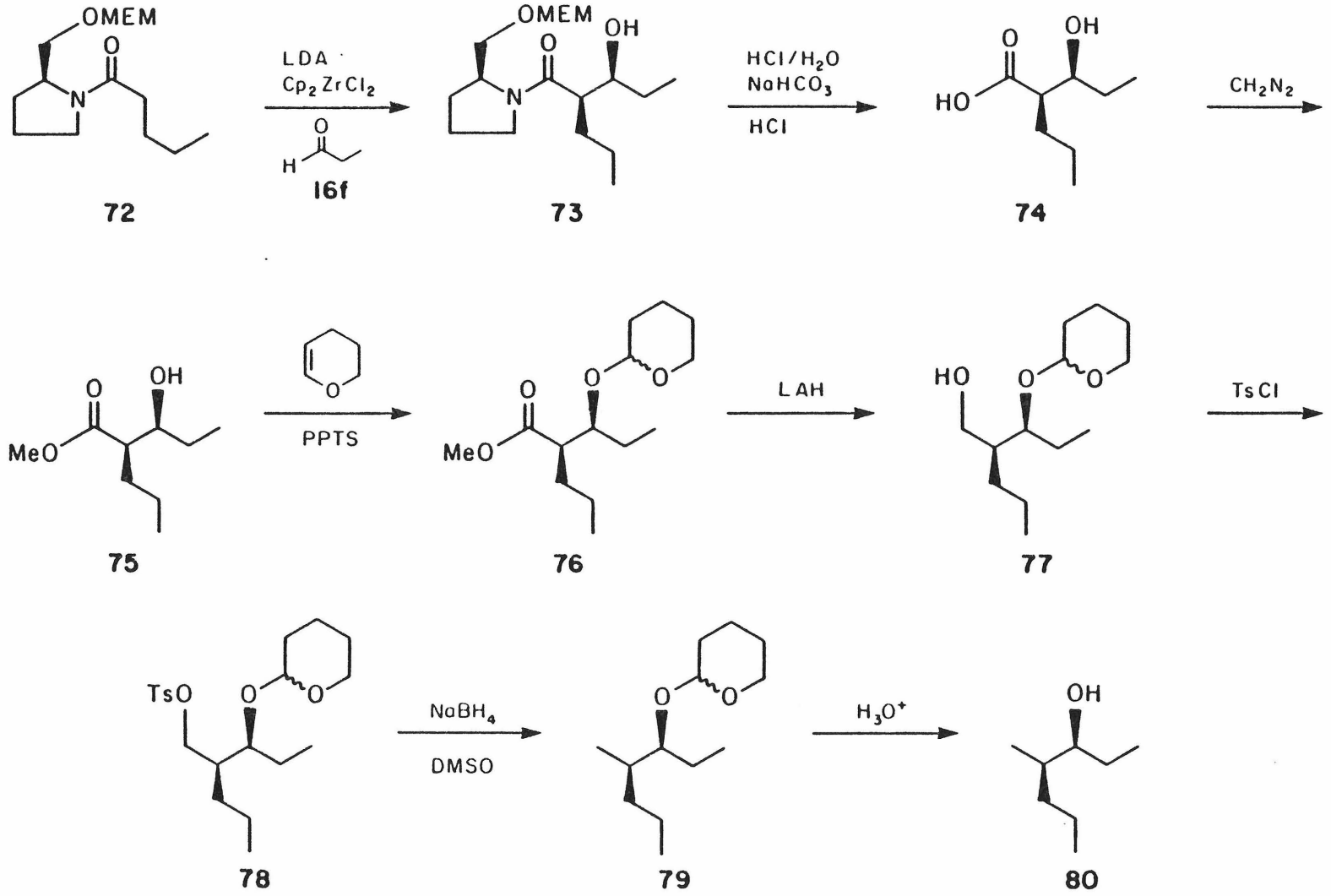
with propionaldehyde.

The relative and absolute configuration of amide 73 and ester 75 were proven by the conversion of 75 to known (+)3(S)-hydroxy-4(R)-methylheptane (80)[74,75] as outlined in Scheme XII.[76]

Although the IR, ^{1}H NMR and ^{13}C NMR spectra of our sample of 80 were consistent with the proposed structure, the correlation was marred by the nonequivalence of the ^{1}H NMR spectrum of alcohol 80 with that reported by Mori[74] and sustained by Vigneron and co-workers.[75] Figure 19 reproduces the carbinol region of the 500 MHz ^{1}H NMR spectrum of 80 in $CDCl_3$ in which 3 coupling constants are clearly visible, J = 3.65 Hz, J = 5.20 Hz and J = 8.85 Hz. At 90 MHz in CCl_4/D_2O this multiplet appears as a double triplet, J_d = 7.9 Hz, J_t = 4.5 Hz. The reported couplings in CCl_4 are J_d = 4.0 Hz and J_t = 2.0 Hz. This discrepancy may be solvent dependent since it was necessary to add deuterated water in order to observe the couplings in the 90 MHz spectrum and to use deuteriochloroform as a lock signal for the 500 MHz spectrometer.

To further correlate our alcohol 80, an authentic mixture of 80 and its diastereomer was prepared by the condensation of the Grignard reagent derived from 2-bromopentane with propionaldehyde. The capillary GC behavior of

Scheme XII Valeramide Aldol Condensation and Absolute Configuration Proof



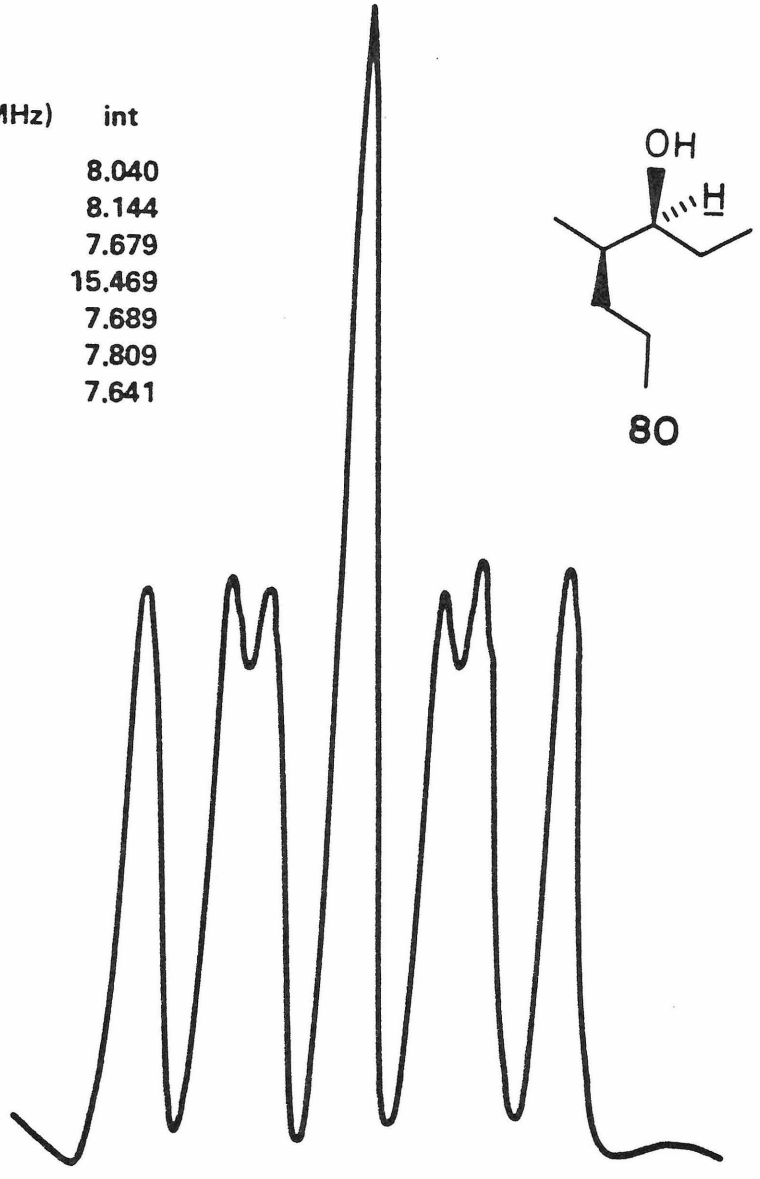


Figure 19. 500 MHz ^{1}H NMR of carbinol region from 80.

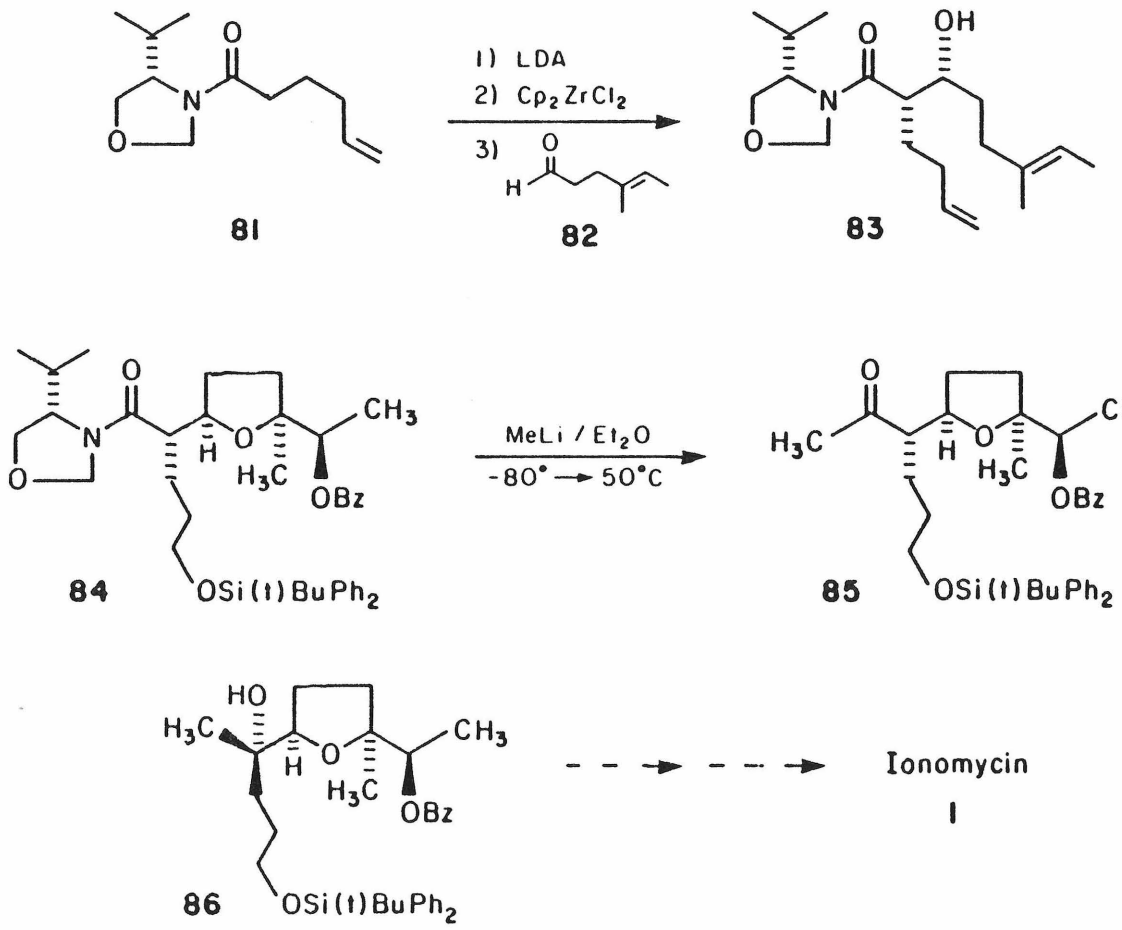
this pair of diastereomers as described by Mori was consistent with our observations. Our 80 coeluted with the more retained component of this mixture. Another sample of 80 prepared from racemic ester 75 contained some of the diastereomer derived from the threo diastereomer present in 75. This component coeluted with the less retained component of the Grignard product mixture.[77]

Finally the optical rotation of our 80 [$[\alpha]_D$ + 9.67 (c 8.1, hexane)] was in perfect agreement[78] with the value of $[\alpha]_D$ -9.75° reported for the optically pure enantiomer of 80.[75]

Application to the Synthesis of Ionomycin 1. The methodology developed here has been applied by Zahler to the synthesis of the righthand portion of ionomycin (1)[79] (Scheme XIII). The zirconocenyl enolate of the valinol-derived amide 81 was condensed with aldehyde 82 to afford the diene 83 and its aldol diastereomers in a ratio of 95.5%:0.5%:2%:2%.

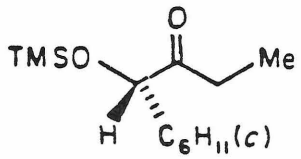
Acidic hydration of the olefins precludes the removal of the chiral auxiliary under the usual conditions. After a few functional group manipulations the chiral auxiliary was cleaved from the protected amide 84 with methyllithium under carefully controlled conditions to afford the methyl ketone 85.[80]

Scheme XIII


1) LDA
2) Cp_2ZrCl_2
3)
81
82
83
84
85
86
MeLi / Et_2O
-80° → 50°C
OBz
OSi(t)BuPh$_2$
Ionomycin
I

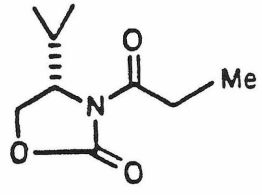
Zahler has further transformed ketone 85 into the alcohol 86 which represents the C_{23}-C_{32} portion of the target. The absolute configuration of the aldol adduct 83 was assigned by analogy to the other asymmetric aldol condensations and will be confirmed with the completion of the total synthesis of ionomycin (1).

Complementary Work. During the course of our study two additional enolate systems have been developed which deliver high levels of erythro asymmetric induction. Masamune's asymmetric ketone 87[70] derived from mandelic acid is analogous to Heathcock's racemic ketone 30. The boron enolate of of this ketone affords erythro aldol products with 99% ee after oxidative removal of the chiral auxiliary. The destruction of the chiral auxiliary is a major disadvantage made tolerable by the ready availability of the starting chirality.

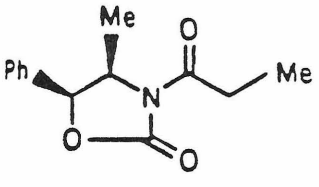


87

The imides (88 and 89) derived from the amino alcohols



88



89

valinol and norephedrine have been developed in this laboratory. Aldol condensations of the boron enolates of these imides display diastereoselectivities typically greater than 99.5% of a single erythro isomer. Hydrolysis of the chiral auxiliary occurs usually under mildly basic conditions which allows the recovery of the amino alcohol oxazolidones.

These two systems along with the zirconium-mediated aldol system described in this report provide a battery of synthetically appealing methods for the highly enantioselective preparation of erythro β-hydroxy carbonyl compounds.

IV. Summary

The concept of metal-centered steric effects applied here should have applications to many other reactions. A cyclic transition state model has been developed which adequately accounts for the following observations.

1. Zirconocenyl enolates are erythro selective without regard to enolate configuration.

2. Mono-cyclopentadienyl titanium enolates are erythro selective for trans enolates and threo selective for cis enolates.

3. Asymmetric induction with chiral amide enolates is consistent in both magnitude and direction with the metal-centered steric effects illustrated in the transition state model.

4. Good levels of asymmetric induction require a cis enolate substituent.

The high levels of asymmetric induction obtained with the asymmetric zirconocenyl enolates as well as with Evans' boron imide enolates set new standards by which asymmetric synthesis may be judged.

The application of these techniques to the synthesis of complex natural products should prove exciting and fruitful for some time to come.

V. Experimental Section

Infrared spectra were recorded on a Beckman 4210 spectrophotometer. 90 MHz ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates EM-390 spectrometer. 500 MHz ^{1}H NMR spectra were recorded on the Bruker WM-500 spectrometer at the Southern California Regional NMR Facility under National Science Foundation Grant Number CHE-7916324. 22.5 MHz ^{13}C nuclear magnetic resonance spectra were recorded on a Jeol FX-90Q spectrometer. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale. Multiplicities are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad with coupling constants in Hz.

Combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan, or by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Analytical gas-liquid chromatography (GC) was carried out on a Hewlett Packard 5880A Level 3 gas chromatograph with split mode capillary injection system, split ratio 100:1, flame ionization detector using one of four capillary GC columns. The four capillary GC columns which were utilized were a 9.5 M methyl silicone (Hewlett-Packard fused silica WCOT 0.21 mM i.d.), 25 M

Carbowax 20M (Hewlett-Packard fused silica WCOT 0.21 mM i.d.), a 50 M Carbowax 20M (Hewlett-Packard fused silica WCOT 0.21 mM i.d.) or a 30 M SE-54 (J and W fused silica WCOT 0.32 mM i.d.). Unless otherwise specified, injector and detector temperatures were 250°C. Helium or hydrogen gas was used as carrier. Specific conditions are included in the experimental details in the following format: GC column, oven temperature, carrier gas, carrier gas pressure, with injector and detector temperatures when other than 250°C.

Chromatography on silica was performed using a forced flow of the indicated solvent on Merck Silica Gel 60 (230-400 mesh).[55] Analytical HPLC was performed on a Water's Associates Model ALC 202/401 high pressure liquid chromatograph equipped with a Model 6000 pump and ultraviolet and refractive index detectors.

Optical rotations were recorded on a Perkin Elmer 141 polarimeter or a Jasco DIP-181 digital polarimeter and are reported as follows: $[\alpha]_D$, concentration, $\underline{c}$ (g/100 mL), solvent.

Tetrahydrofuran (THF) was dried by distillation from benzophenone ketyl. Aldehydes were prepared or distilled fresh prior to use except benzaldehyde which was distilled and stored under argon. Diisopropylamine

was distilled fresh from calcium hydride. n-BuLi (Aldrich Chemical Co.) was standardized by double titration.

Lithium diisopropylamide (LDA) was generated at -78°C under an argon atmosphere by the addition of 1.0 equivalents of n-BuLi in hexane to 1.1 equivalent of diisopropylamine in THF (0.1 M to 0.5 M).

Bis (cyclopentadienyl) zirconium dichloride (Cp_2ZrCl_2, 6) was dried under vacuum at 100°C for 12 h and stored under an inert atmosphere. Individual portions were weighed in air and dissolved in fresh THF under a blanket of nitrogen.

General Procedures for Zirconium-Mediated Aldol Condensations.

A. Carbonyl Substrate as Limiting Reagent. To a solution of 1.2 equiv of LDA (0.2M-1.0M in THF) at -78°C was added the carbonyl substrate. After 30 min, 1.1 equiv of Cp_2ZrCl_2 (6) (0.16 M in THF) was added. The enolate solution was allowed to warm to 0°C for 30 min. Ketone and thioester enolates develop a faint yellow tint, ester enolates develop a yellow color, amide enolates develop a deep yellow to deep orange color upon exchange with the zirconium salt. After recooling to -78°C the aldehyde (1.0 to 1.3 equiv) was added rapidly without solvent via syringe. The color quenched rapidly. The solution was

warmed to 0°C, quenched with saturated ammonium chloride solution and stirred vigorously for 3 h at ambient temperature to hydrolyze the zirconocenyl aldolate. During this time a white precipitate formed which was removed by filtration through celite.[81] The filtrate was extracted between methylene chloride and water. The organic phase was dried over magnesium sulfate. GC analysis was performed at this stage. The organic layer was filtered and concentrated to give the crude aldol adduct. NMR analysis for the aldol diasteroemer ratio was performed at this stage.

B. Aldehyde as Limiting Reagent. Some of the condensations were conducted with 0.9 → 1.0 equiv of aldehyde in procedure A. Product yields were based on aldehyde.

C. Qualitative Experiments. So-called "qualitative" experiments were done on a 0.3 mmol scale with volumetric rather than gravimetric addition of carbonyl substrate and aldehyde. Several of these were adequate as probes of transition state steric demands, but were not of sufficient interest or importance to warrant repetition as a quantitative experiment under optimal conditions.

Aldol adducts were purified by evaporative distillation at low pressure in most cases. Diastereomer ratios

are usually unchanged as a result of this process. Chiral amide aldol adducts could also be purified by flash chromatography. Using GC to monitor fractions it was possible to obtain the major diastereomer >99% pure of its other isomers in general cases. Several chiral amide aldol adducts could also be purified by recrystallization to >99% of a pure single diastereomer. Unless otherwise noted, yields are based on purified isolated material.

Lithium Mediated Aldol Condensations.[8] To a solution of 1.2 equiv of LDA at -78°C in THF was added the carbonyl substrate. After 30 min, 1.3 equiv of aldehyde was added rapidly without solvent via syringe. After 3-5 sec the condensation was quenched with saturated ammonium chloride solution. After extraction between methulene chloride and water, the organic phase was dried over magnesium sulfate. GC analysis was performed at this stage. The organic layer was filtered and concentrated to give the crude aldol adduct. NMR analysis for the diastereomer ratio was performed at this stage.

The mixture obtained from the lithium-mediated condensations served as NMR and GC standards to fix the position of the signals of the minor diastereomers during the analysis of the zirconium mediated condensation products.

Analysis of Aldol Diastereomer Ratios. Initially diastereomer ratios were determined by integration of the NMR signals associated with diastereotopic protons or carbons.[8,12,68] Differential relaxation phenomena and NOE effects were minimized in ^{13}C NMR spectra intended for integration by utilizing small flip angles with long pulse delays and gated decoupling of the ^{1}H-^{13}C coupling.[82] Where possible integration results from ^{13}C spectra were correlated with the ^{1}H integration values. Several of these ratios were also correlated to capillary GC analyses when that technique became available. In terms of reproducibility, precision and speed of analysis, capillary GC was the method of choice. For chiral amide aldols which exhibit isomers in the NMR spectrum due to hindered rotation about the amide bond, the product distribution could only be obtained by GC.

Erythro-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (17a, Table 4, Entry 1). The title compound, 17a, was prepared according to the general recipe described in procedure A from 0.545g (4.06 mmol) of propiophenone (8) and 1.3 equiv of benzaldehyde (16a). GC analysis of the aldol adduct was not useful due to decomposition in the injection port. Evaporative distillation (180°C/0.005 mm)

afforded 0.552 g of 17a contaminated with 14% (NMR) of 8, yield calculated as 62%. The IR, ^{1}H NMR and ^{13}C NMR spectra were consistent with those data previously reported for 17a.[8] The diastereomer ratio (NMR) of the distilled sample was erythro 82.6% : threo 17.4%. In an independent experiment the unpurified aldol adduct had a diastereomer ratio of erythro 90% : threo 10%. The occurrence of 8 in the distilled product and this change in diastereomer ratio were taken as evidence for retro-aldol decomposition during distillation.

Erythro-S-(1,1-Dimethylethyl)-3-hydroxy-2-methyl-3-phenylpropanthioate (18a, Table 4, Entry 2). The title compound, 18a, was prepared according to the general recipe described in Procedure A. From 0.225 g (1.54 mmol) of (t)-butyl thiopropioante (9) and 1.1 equiv of benzaldehyde (16a) was obtained 0.294 g of unpurified 18a as a 91:9 mixture (^{1}H NMR) of erythro and threo diastereomers. Distillation (150°C/0.05 mm) gave 0.271 g (1.97 mmol, 70%) of 18a and its diastereomer. The IR and ^{1}H NMR spectra were in agreement with the reported values.[13]

Erythro-3-hydroxy-2-methyl-3-phenylpropanoic Acid, Methyl Ester (21a, Table 5, Entry 1). The title compound, 21a, was prepared from 0.138 g (1.57 mmol) of methyl

propionate (12) and 0.149 g (1.40 mmol) of benzaldehyde (16a) according to the general recipe described in Procedure B. Distillation (120°C/0.005 mm) afforded 0.217 g (1.12 mmol, 80%) of the ester 21a and its diastereomer as a colorless oil. IR (neat) 3600-3200 (br), 3040, 2990, 2950, 2910, 2880, 1735, 1492, 1452, 1436, 1355, 1345, 1255, 1200, 1173, 1055, 1035, 1025, 995, 900, 770, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.23 (s, 5H, $C_6\underline{H}_5$), 4.92 (d, J = 4.5 Hz, 1H, C$\underline{H}$OH), 3.50 (s, 3H, OC$\underline{H}_3$), 3.33 (br s, 1H, O$\underline{H}$), 2.62 (dq, J_d = 4.5 Hz, J_q = 7 Hz, 1H, COC$\underline{H}$CH$_3$), 1.05 (d, J = 7 Hz, 3H, COCHC$\underline{H}_3$) with threo signals at 4.57 (d, J = 9 Hz, C$\underline{H}$OH), 3.57 (s, OC$\underline{H}_3$) and 0.89 (d, J = 7 Hz COCHC$\underline{H}_3$); ^{13}C NMR (CCl_4) δ 175.0 ($\underline{C}$=O), 141.9, 127.7, 126.9, 125.8 ($\underline{C}_6H_5$), 73.2 ($\underline{C}$HOH), 51.1 (O$\underline{C}H_3$), 46.5 (CO$\underline{C}$HCH$_3$), 10.6 (COCH$\underline{C}H_3$) with threo signals at 75.8 ($\underline{C}$HOH), 47.0 (CO$\underline{C}$HCH$_3$) and 14.0 (COCH$\underline{C}H_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was erythro 85.3% : threo 14.6%. The corresponding lithium mediated aldol condensation had a diastereomer ratio of erythro 56.7% : threo 43.3%. GC conditions were 25 M carbowax 20M, 160°C, helium at 21 psi, erythro 10.87 min, threo 11.58 min and 30 M SE-54, 130°C, hydrogen at 10 psi, erythro 5.41 min, threo 5.51 min.

Anal. calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.30.

Erythro-1-[pyrrolid-1-yl]-3-hydroxy-2-methyl-3-phenylpropanoic Acid (23a, Table 5, Entry 5). According to the general Procedure B, the title amide (23a) was prepared from 0.043 g (0.34 mmol) of pyrrolidylpropionamide (14) and 0.025 g (0.23 mmol) of benzaldehyde (16a). Distillation (150°C/0.01 mm) afforded 0.044 g (0.19 mmol, 80%) of amide 23a as a solid, mp 116-116.5°C. IR (CH_2Cl_2) 3500-3200 (br), 3060, 2990, 2880, 1615, 1445, 1270, 985, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (br s, 5H, phenyl), 5.03 (d, J = 3 Hz, 1H, C<u>H</u>-OH), 4.90 (m, 1H, O<u>H</u>), 3.6-3.3 (m, 4H, N-C<u>H</u>$_2$-), 2.7 (dq, J_d = 3 Hz, J_q = 7 Hz, 1H, CO-C<u>H</u>-CH_3), 2.0-1.6 (m, 4H, -C<u>H</u>$_2$-CH_2-N), 1.04 (d, J = 7 Hz, 3H, CO-CH-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3/CCl_4$) δ 175.3 (<u>C</u>O), 141.8, 127.8, 126.8, 125.8 (phenyl), 72.9 (<u>C</u>H-OH), 46.4, 45.4 (N-<u>C</u>H_2-), 43.8 (CO-<u>C</u>H-CH_3), 26.0, 24.7 (N-CH_2-<u>C</u>H_2-), 9.6 (CO-CH-<u>C</u>H_3). The diastereomer ratio (NMR) of the unpurified aldol adduct was erythro 95%:threo 5%. The corresponding lithium-mediated aldol condensation had a diastereomer ratio of erythro 60%:threo 40%. The characteristic threo ^1H NMR signal was at δ 4.66 (d, J = 8 Hz, C<u>H</u>OH) and the characteristic threo ^{13}C NMR signals were at δ 76.0 (<u>C</u>HOH), 44.3 (CO<u>C</u>HCH$_3$) and 14.9

($COCH\underline{C}H_3$).

Anal. calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.91; H, 8.30; N, 6.00.

Erythro-1-[N,N-bis-(2-propyl)-amino]-3-hydroxy-2-methyl-3-phenylpropanoic Acid (24a, Table 5, Entry 6). The title amide, 24a, was prepared according to the recipe described in Procedure B. Condensation of 0.053 g (0.34 mmol) of propionamide 15 with 0.025 g (0.24 mmol) of benzaldehyde (16a) afforded after distillation (120°C/0.006 mm) 0.048 g (0.18 mmol, 77%) of amide 24a as a crystalline solid, mp 109.5-111°C: IR (CH_2Cl_2) 3500-3200 (br), 3060, 2990, 1612, 1450, 1420, 1375, 1345, 1270, 1260, 1140, 1035, 985, 760, 685 cm^{-1}; ^1H NMR ($CDCl_3/CCl_4$) δ 7.28 (br s, 5H, phenyl), 4.93 (d, J = 3 Hz, 1H, $C\underline{H}$-OH), 4.90 (s, 1H, $O\underline{H}$), 3.84, 3.51 each [heptuplet, J = 7 Hz, 1H, N-$C\underline{H}(CH_3)_2$], 2.68 (dq, J_d = 3 Hz, J_q = 7 Hz, 1H, $COC\underline{H}CH_3$), 1.35, 1.35, 1.20, 1.13 each [d, J = 7 Hz, 3H, $NCH(C\underline{H}_3)_2$], 1.00 (d, J = 7 Hz, 3H, $COCHC\underline{H}_3$); ^{13}C NMR (CCl_4) δ 175.7 ($\underline{C}$=O), 142.4, 127.7, 126.7, 126.2 ($\underline{C}_6H_5$), 73.7 ($\underline{C}$HOH), 48.1, 45.9 each [N-$\underline{C}$H-$(CH_3)_2$], 43.5 ($CO\underline{C}HCH_3$), 21.1, 20.8, 20.5 [N-CH-$(\underline{C}H_3)_2$], 11.6 ($COCH\underline{C}H_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was erythro 98.6%:threo 1.4%. The corresponding lithium-mediated aldol condensation had a diastereomer ratio of

erythro 64.9%:threo 35.1%. The GC conditions were 9.5 M methyl silicone, 210°C, helium at 10 psi, threo 3.82 min, erythro 4.06 min.

Anal. calcd. for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.94; H, 9.75; N, 5.49.

Erythro-2,4-dimethyl-3-hydroxypentanoic Acid, Methyl Ester (21c, Table 9, Entry 7). The title ester, 21c, was prepared according to Procedure B from 0.129 g (1.47 mmol) of methyl propionate (12) and 0.0910 g (1.37 mmol) of isobutyraldehyde (16c). Distillation (110°C/10 mm) afforded 0.200 g (1.25 mmol, 98%) of ester 21c and its diastereomer as a colorless oil. The diastereomer ratio (GC) of the unpurified aldol adduct was erythro 86.3%:threo 13.7%. The corresponding lithium-mediated aldol condensation had a diastereomer ratio of erythro 54.2%:threo 45.8%. The GC conditions were 25 M Carbowax 20M 100°C, helium at 21 psi, threo 5.23 min, erythro 7.06 min. The erythro diastereomer was identical with the optically active ester, 57c and 58c, by IR, ^{1}H NMR, ^{13}C NMR and GC. The spectral values are tabulated with the experimental details for ester 57c.

Erythro-3-hydroxy-2,4-dimethylpent-4-enoic Acid, Methyl Ester (21d, Table 9, Entry 8). The title ester, 21d, was prepared according to Procedure B from 0.139 g

(1.58 mmol) of methyl propionate (12) and 0.0942 g (1.34 mmol) of 2-methylacrolein (16d). Distillation (110°C/ 10 mm) afforded 0.190 g (1.20 mmol, 89%) of ester 21d as an oil. IR (neat) 3600-3200 (br), 2990, 2960, 1735, 1455, 1440, 1205, 1175, 1035, 905 cm^{-1}; ^1H NMR (CCl_4) δ 4.97 (s, 1H, C=C$\underline{H}_2$), 4.81 (s, 1H, C=C$\underline{H}_2$), 4.25 (d, J = 5 Hz, 1H, C$\underline{H}$OH), 3.65 (s, 3H, OC$\underline{H}_3$), 2.92 (br s, 1H, O$\underline{H}$), 2.56 (dq, J_d = 5 Hz, J_q = 7 Hz, 1H, COC$\underline{H}$CH$_3$), 1.69 (s, 3H, CH_2=C-C$\underline{H}_3$), 1.07 (d, J = 7 Hz, CO-CH-C$\underline{H}_3$); ^{13}C NMR (CCl_4) δ 175.0 (C=O), 144.1 (C=CH_2), 117.8 (C=C$\underline{H}_2$), 74.5 (C$\underline{H}$OH), 51.2 (OC$\underline{H}_3$), 42.4 (CO-C$\underline{H}$-CH$_3$), 18.5 (CH_2=C-C$\underline{H}_3$), 10.5 (CO-CH-C$\underline{H}_3$). The diastereomer ratio (NMR) of the unpurified aldol adduct was erythro 83%:threo 17%. The corresponding lithium mediated aldol condensation had a diastereomer ratio of erythro 54%:threo 46%. The characteristic ^1H NMR signal for the threo diastereomer was at δ 4.06 (d, J = 9 Hz, C$\underline{H}$OH). The characteristic ^{13}C NMR signals for the threo diastereomer were at δ 77.5 (C$\underline{H}$OH), 42.8 (CO$\underline{C}$HCH$_3$) and 14.2 (COCH$\underline{C}$H$_3$).

Anal. calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.57; H, 8.92.

Erythro-1-[pyrrolid-1-yl]-3-hydroxy-2-methylhexanoic Acid (23b, Table 9, Entry 12). The title amide, 23b, was prepared according to Procedure B from 0.043 g (0.37

mmol) of pyrrolidylpropionamide (14) and 0.024 g (0.34 mmol) of n-butyraldehyde (16b). Distillation (120°C/ 0.005 mm) afforded 0.048 g (0.24 mmol, 71%) of amide 23b as a colorless liquid. IR (neat) 3600-3200 (br), 2970, 2940, 2880, 1615, 1455, 1440 cm^{-1}; ^1H NMR (CCl_4) δ 3.86 (s, 1H, OH), 3.70 (m, 1H, CH-OH), 3.5-3.2 (m, 4H, N-CH_2-CH_2), 2.30 (dq, J_d = 3 Hz, J_q = 7 Hz, 1H, COCH-CH_3), 2.1-1.7 (m, 4H, N-CH_2-CH_2-), 1.6-1.1 (m, 4H, CH_3-CH_2CH_2-CHOH-), 1.05 (d, J = 7 Hz, 3H, CO-CH-CH_3), 0.8-1.0 (m, 3H, CH_2-CH_3); ^{13}C NMR (CCl_4) δ 175.1 (CO), 70.3 (CHOH), 46.1, 45.2 (2 N-CH_2), 41.2 ($COCHCH_3$), 36.1 (-COH-CH_2-CH_2), 26.1, 24.2 (2 NCH_2CH_2), 19.1 (CH_2-CH_2-CH_3), 14.1 (CH_2-CH_3), 9.7 (COCH-CH_3). The diastereomer ratio (GC) of the unpurified aldol adduct was erythro 94.4%:threo 5.6%. The corresponding lithium-mediated aldol condensation had a diastereomer ratio of erythro 64.6%:threo 35.4%. The GC conditions were 25 M Carbowax 20M, 180°C, helium at 21 psi, threo 7.08 min, erythro 8.36 min.

Anal. calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62. Found: C, 65.82; H, 10.68.

Erythro-1-[pyrrolid-1-yl]-3-hydroxy-2,4-dimethylpentanoic Acid (23c, Table 9, Entry 13). The title amide, 23c, was prepared according to the general recipe described in Procedure B. Condensation of 0.202 g (1.59

mmol) of pyrrolidylpropionamide (14) with 0.0925 g (1.28 mmol) of isobutyraldehyde (16c) gave after distillation (120°C/0.01 mm) the amide 23c contaminated with 14. Redistillation removed 14 as a forerun (80°C/0.01 mm) and afforded 0.228 g (1.14 mmol, 89%) of 23c as a solid, mp 82-84°C: IR (CH_2Cl_2) 3560-3250 (br), 3060, 2980, 2880, 1615, 1470, 1460, 1445, 1385, 1375, 1340, 1330, 1275, 1230, 1190, 1170, 1110, 1075, 1035, 980, 965, 915, 895, 850, 770, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.67 (s, 1H, OH), 3.6-3.3 (br m, 5H, 2-N-CH_2 and CHOH), 2.67 (dq, J_d = 2Hz, J_q = 7 Hz, 1H), 2.1-1.7 (br m, 4H, 2-N-CH_2-CH_2), 1.7-1.4 (m, 1H, CHOH-CH-Me_2), 1.12, 1.02, 0.86 each (d, J = 7 Hz, 3H, CH-CH_3); ^{13}C NMR (CCl_4) δ 175.1 (CO), 75.9 (CHOH), 46.0, 45.3 each (N-CH_2), 37.9 (CO-CH-CH_3), 30.0 (CHOH-CH-Me_2), 26.1, 24.2 (N-CH_2-CH_2), 19.5, 18.8 [CH-(CH_3)$_2$], 9.2 (CO-CH-CH_3). The diastereomer ratio (GC) of the unpurified aldol adduct was erythro 97.3%:threo 2.7%. The corresponding lithium mediated condensation had a diastereomer ratio of erythro 77.4%:threo 22.6%. The GC conditions were 25 M Carbowax 20M, 185°C, helium at 21 psi, threo 8.07 min, erythro 9.25 min.

Anal. calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.20; H, 10.29; N, 6.95.

Erythro-1-[pyrrolid-1-yl]-3-hydroxy-2,4-dimethyl-

pent-4-enoic Acid (23d, Table 9, Entry 14). The title amide 23d was prepared according to the general recipe described in Procedure B. Condensation of 0.950 g (1.36 mmol) of 2-methylacrolein (16d) with 0.202 g (1.58 mmol) of pyrrolidylpropionamide (14) afforded after distillation (150°C/0.001 mm) 0.263 g of aldol adduct containing 23d and ~17% (NMR) of the starting amide 14, for a calculated yield of 87%. Redistillation gave an analytical sample of 23d. IR (neat) 3500-3200 (br), 2960, 2870, 1610, 1440, 1335, 1220, 1030, 980, 890 cm^{-1}; ^1H NMR (CCl_4) δ 5.0 (br s) and 4.78 (br m) (3H, C=C$\underline{H}_2$ and O$\underline{H}$), 4.13 (d, J = 3 Hz, 1H, C$\underline{H}$OH), 3.6-3.2 (m, 4H, 2-N-C$\underline{H}_2$), 2.57 (dq, J_d = 3 Hz, J_q = 7 Hz, 1H, COC$\underline{H}$-CH_3), 2.1-1.7 (m, 4H, 2-N-CH_2-C$\underline{H}_2$), 1.65 (s, 3H, CH_2=C-C$\underline{H}_3$), 1.01 (d, J = 7 Hz, 3H, CO-CH-C$\underline{H}_3$); ^{13}C NMR (CCl_4) δ 174.8 (C$\underline{O}$), 143.5 (CH_3-C$\underline{=}$$CH_2$), 111.2 ($CH_3$-C=C$\underline{H}_2$), 73.5 (C$\underline{H}$-OH), 46.3, 45.4 (N-C$\underline{H}_2$), 39.1 (CO-C$\underline{H}$-$CH_3$), 26.0, 24.1 (N-$CH_2$-C$\underline{H}_2$-), 19.4 (C$\underline{H}_3$-C=$CH_2$), 9.8 (CO-CH-C$\underline{H}_3$). The diastereomer ratio (NMR) of the unpurified aldol adduct was erythro 90%:threo 10%. The corresponding lithium mediated condensation had a diastereomer ratio of erythro 70%:threo 30%. The characteristic ^1H NMR signal for the threo diastereomer was at δ 3.95 (d, J = 7 Hz, C$\underline{H}$OH). The characteristic ^{13}C NMR signals for the threo diastereomer were at δ 77.8 (C$\underline{H}$OH), 40.6 (CO$\underline{C}$HCH$_3$) and 14.7 (COCH$\underline{C}$H$_3$).

Anal. calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 66.81; H, 9.70.

Erythro-1-[N,N-bis(2-propyl)-amino]-3-hydroxy-2-methylhexanoic Acid (24b, Table 9, Entry 15). The title amide 24b was prepared according to Procedure B from 0.054 g (0.34 mmol) of amide 15 and 0.024 g (0.34 mmol) fo n-butyraldehyde (16b). Distillation (90°C/0.005 mm) afforded 0.043 g (0.19 mmol, 55%) of amide 24b as an oil. IR (neat) 3600-3200 (br), 2970, 2940-2880, 1615, 1445, 1370, 1340, 1210, 1135, 1040, 1015, 970, 610 cm^{-1}; NMR (CCl_4) δ 4.23 (s, 1H, OH), 3.92, 3.46 each (heptuplet, J = 7 Hz, 1H, N-CH-Me_2), 3.70 (m, 1H, CHOH), 2.37 (dq, J_d = 2 Hz, J_q = 7 Hz, 1H, COCH-CH_3), 1.7-1.1 (m, 16H), 1.04 (d, J = 7 Hz, 3H, CO-CH-CH_3), 1.1-0.8 (m, 3H, $-CH_2-CH_3$); ^{13}C NMR (CCl_4) δ 176.3 (C=O), 70.5 (CH-OH), 47.4, 45.4 (N-CH-Me_2), 40.2 (COCH-CH_3), 36.2 (CHOH-CH_2-CH_2), 21.3, 20.8, 20.7, 20.4 (N-CH-CH_3's), 19.2 ($CH_2-CH_2-CH_3$), 14.2 (CH_2-CH_3), 10.2 (CO-CH-CH_3). The diastereomer ratio (GC) of the unpurified aldol product was erythro 98.1%:threo 1.9%. The diastereomer ratio of the corresponding lithium mediated aldol condensation was erythro 79.1%:threo 20.9%. The GC conditions were 25 M Carbowax 20M, 185°C, helium at 13 psi, threo 4.69 min, erythro 5.02 min.

Anal. calcd. for $C_{13}H_{27}NO_2$: C, 68.08; H, 11.87.

Found: C, 68.04; H, 11.87.

Erythro-1-[N,N-bis(2-propyl)-amino]-3-hydroxy-2,4-dimethylpentanoic Acid (24c, Table 9, Entry 16). The title amide 24c was prepared according to Procedure B from 0.250 g (1.59 mmol) of propionamide 15 with 0.0902 g (1.25 mmol) of isobutyraldehyde (16c) to afford after distillation (110°C/0.01 mm) 0.292 g of aldol product contaminated with ~14% starting amide 15 for a calculated yield of 87%. Redistillation gave an analytical sample. IR (neat) 3600-3100 (br) 2970, 2940, 2880, 1720 (weak), 1613, 1460, 1445, 1370, 1335, 1270, 1210, 1135, 1030, 985 cm^{-1}; ^{1}H NMR (CCl_4) δ 4.43 (s, 1H, OH), 3.90 (heptuplet, J = 7 Hz, 1H, N-CH-Me_2), 3.50 (heptuplet, J = 7 Hz, 1H, N-CH-Me_2), 3.20 (dd, J = 2 Hz, J = 9 Hz, 1H, CH-OH), 2.60 (dq, J_d = 2 Hz, J_q = 7 Hz, 1H, COCHCH$_3$), 1.8-1.4 (m, 1H, CHOH-CH-Me_2), 1.4-1.1 (m, 12H, NCH-CH_3's), 1.01 (d, J = 7 Hz, 3H, CO-CH-CH_3), 0.95 and 0.79 (d, J = 7 Hz, 3H, CHOH-CH-CH_3's); ^{13}C NMR (CCl_4) δ 176.4 (CO), 76.4 (CHOH), 47.5, 45.4 (N-CH-Me_2's), 36.7 (CO-CH-CH_3), 30.2 (CHOH-CH-Me_2), 21.3, 20.8, 20.6, 20.4 (NCH-CH_3's), 19.6, 18.9 (CHOH-CH-CH_3's), 10.0 (CO-CH-CH_3). The diastereomer ratio (NMR) of the unpurified aldol adduct was erythro >97%:threo <3%. The corresponding lithium mediated aldol condensation had a diastereomer ratio of erythro 80%:

threo 20%. The characteristic ^{13}C NMR signals for the threo diastereomer were at δ 79.5 (CHOH), 37.2 ($COCHCH_3$) and 16.0 ($COCHCH_3$).

Anal. calcd. for $C_{13}H_{27}NO_2$: C, 68.08; H, 11.87. Found: C, 68.17; H, 11.73.

Erythro-1-[N,N-bis-(2-propyl)-amino]-3-hydroxy-2,4-dimethylpent-4-enoic Acid (24d, Table 9, Entry 17). Condensation of 0.249 g (1.58 mmol) of propionamide 15 with 0.0935 g (1.33 mmol) of 2-methylacrolein (16d) according to Procedure B afforded the title amide 24d as an oil. After distillation (170°C/0.005 mm) 24d remained contaminated with the starting amide 15. Redistillation afforded 0.245 g (1.08 mmol, 81%) of 24d as a solid, mp 79-80°C. IR (film) 3500-3200 (br), 2960, 2880, 1610, 1445, 1370, 1335, 1205, 1130, 1030, 890 cm^{-1}; ^1H NMR (CCl_4) δ 5.07 (br s) and 4.83 (m) (together 3H, OH and $C=CH_2$), 4.14 (br s, 1H, CH-OH), 3.97 (heptuplet, J = 7 Hz, 1H, $N-CHMe_2$), 3.52 (heptuplet, J = 7 Hz, 1H, $N-CHMe_2$), 2.60 (dq, J_d = 2 Hz, J_q = 7 Hz, 1H, CO-CH-), 1.63 (s, 3H, $CH_2=C-CH_3$), 1.5-1.1 (m, 12H, $-CH_3$), 0.97 (d, J = 7 Hz, 3H, $CO-CH-CH_3$); ^{13}C NMR (CCl_4) δ 176.1 (CO), 143.3 ($C=CH_2$), 111.4 ($C=CH_2$), 73.6 (CH-OH), 47.8, 45.5, 37.8 ($CO-CH-CH_3$), 21.1, 20.7, 20.6, 20.2 ($NCH-CH_3$'s), 19.1 ($CH_2=C-CH_3$), 10.2 ($CO-CH-CH_3$). The diastereomer ratio

(NMR) of the unpurified aldol adduct was erythro 95%: threo 5%. The diastereomer ratio of the product of the corresponding lithium-mediated aldol condensation was erythro 85%:threo 15%. The characteristic ^{13}C NMR signals for the threo diastereomer were δ 77.8 (CHOH), 38.9 ($COCHCH_3$) and 15.8 ($COCHCH_3$).

Anal. calcd. for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.55; H, 11.15; N, 6.19.

1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-propanoic Acid (34). The preparation of the prolinol-derived propionamide 34 has been described.[29] In addition to the published data, the ^{13}C NMR spectrum is included here. ^{13}C NMR (CCl_4) δ 170.7 (C=O), 95.2 (OCH_2O), 71.6 ($CH-CH_2-O$), 67.5, 66.6 (OCH_2CH_2O), 58.2 (OCH_3), 56.2 (CH-N), 46.7 (CH_2-N), 27.4 ($COCH_2$), 27.4, 24.0 ($N-CH_2-CH_2-CH_2$), 8.6 (CH_2CH_3).

1-[4(S)-(2-Propyl)-oxazolidin-3-yl]propanoic Acid (35). From a mixture of 15.16 g (147 mmol) of L-2-amino-3-methyl-1-butanol (ℓ-valinol)[84] and 4.42 g (147 mmol of paraformaldehyde in 75 mL of benzene was removed 2.6 mL of water by azeotropic distillation. 19.15 g (147 mmol) of propionic anhydride was added slowly to the reaction mixture held at 25°C. This was followed by 18 mL of triethylamine. The mixture was then heated to

reflux for 1 h, cooled to 25°C and concentrated under vacuum. The crude product was vigorously stirred with 30 mL of 10% NaOH solution for 2 h. Propionamide 35 was extracted into ether. The organic layer was dried over $MgSO_4$, filtered and concentrated to give after distillation (90°C/0.005 mm) 20.17 g (117 mmol, 80%) of the valinol-derived propionamide 35 as a colorless oil. IR (neat) 2960, 2870, 1650, 1460, 1418, 1385, 1375, 1305, 1208, 1170, 1085, 940 cm^{-1}; ^1H NMR (CCl_4) δ 4.87 (d, J = 5 Hz, 1H, N-C<u>H</u>$_2$-O), 4.70 (d, J = 5 Hz, 1H, N-C<u>H</u>$_2$-O), 3.80 (m, 3H, N-C<u>H</u>-C<u>H</u>$_2$-O), 2.10 (q, J = 7.5 Hz, 2H, CO-C<u>H</u>$_2$), 2.0 (m, 1H, Me$_2$C<u>H</u>-CHN), 1.10 (t, J = 7.5 Hz, 3H, CH_2-C<u>H</u>$_3$), 0.89 (d, J = 7.5 Hz, 3H) and 0.84 (d, J = 7.5 Hz, 3H) [CH-(C<u>H</u>$_3$)$_2$]; ^{13}C NMR (CCl_4) δ 168.8 (<u>C</u>=O), 78.6 (N<u>C</u>H$_2$O), 67.6 (CH-<u>C</u>H$_2$O), 59.7 (<u>C</u>H-N), 29.4 [<u>C</u>H(CH$_3$)$_2$], 27.8 (CO<u>C</u>H$_2$), 19.1, 16.9 [CH-(<u>C</u>H$_3$)$_2$], 8.7 (CH_2<u>C</u>H$_3$); $[\alpha]_D$ + 20.7° (<u>c</u> 2.34, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_9H_{17}NO_2$: C, 63.14; H, 10.01; N, 8.18. Found: C, 63.16; H, 9.89; N, 8.24.

<u>(2R,3R)-1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-3-hydroxy-2-methyl-3-phenylpropanoic Acid (36a, Table 11, Entry 1)</u>. The title compound 36a was prepared according to the general recipe described in Procedure A by the condensation of 1.03 g (4.21 mmol) of the prolinol-

derived propionamide 34 with 0.562 g (5.30 mmol) of benzaldehyde (16a). The reaction afforded 1.49 g of 36a and its aldol diastereomers as an orange oil. Flash chromatography (60% ethylacetate in hexane on silica gel) afforded 1.05 g (2.98 mmol, 71%) of amide 36a greater than 99% diastereomerically pure as a colorless oil. IR (neat) 3600-3200 (br), 2980, 2945, 2890, 1640, 1455, 1440, 1200, 1120, 1050, 985, 850, 765, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.20 (br s, 5H, $C_6\underline{H}_5$-), 5.1-4.7 (m, 2H, C$\underline{H}$-OH and O$\underline{H}$), 4.7-4.5 (s, 2H, O-C$\underline{H}_2$-O), 4.05 (m, 2H, N-CH-C$\underline{H}_2$-O), 3.7-3.3 (m, 7H, OC$\underline{H}_2$-C$\underline{H}_2$O, C$\underline{H}_2$-N-C$\underline{H}$), 3.26 (s, 3H, OC$\underline{H}_3$), 3.1-2.4 (m, 1H, CO-C$\underline{H}$-CH_3), 1.9 (br s, 4H, N-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH), 1.03 and 0.9 (d, J = 7 Hz, 3H, CO-CH-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 176.1 and 174.7 (C=O), 142.9 and 142.7, 127.6, 126.5, 126.0 ($\underline{C}_6H_5$), 95.2 (O$\underline{C}H_2$), 73.1 and 72.5 (C$\underline{H}$-OH), 71.6 and 68.8 (NCH-C$\underline{H}_2$-O), 67.0 and 66.8, 66.5 (O$\underline{C}H_2$-C$\underline{H}_2$-O, 58.3 (O$\underline{C}H_3$), 56.4 and 56.0 (N$\underline{C}$H-CH_2-O), 44.6 and 42.8 (CO-$\underline{C}$H-CH_3), 28.3 and 27.2 (NCH-$\underline{C}H_2$-CH_2), 23.9 and 21.6 (N-CH_2-$\underline{C}H_2$), 11.3 and 10.2 (CO-CH-$\underline{C}H_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was T_1 1.8%:T_2 1.0%:36a 96%:37a 1.2%. The corresponding lithium mediated aldol condensation product had a diastereomer ratio of T_1 22.7%:T_2 13.4%:36a 31.3%:37a 32.7%. The GC conditions were 30 M SE-54, 200°C, hydrogen at 15 psi,

T_1 18.20 min, T_2 17.24 min, 36a 21.28 min, 37a 19.49 min. The rotation of the purified diastereomer 36a was $[\alpha]_D$ -46.8 (c 3.35, CH_2Cl_2).

Anal. calcd. for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found: C, 65.01; H, 8.23; N, 3.93.

(2R,3S)-1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-3-hydroxy-2,4-dimethylpentanoic Acid (36c, Table 11, Entry 3). Condensation of 1.01 g (4.11 mmol) of the prolinol-derived amide 34 with 0.381 g (5.27 mmol) of isobutyraldehyde (16c) according to the general Procedure A afforded 1.240 g of 36c and its aldol diastereomers as a colorless oil. Flash chromatography (50% ethyl acetate in hexane on silica gel) gave 0.995 g (3.13 mmol, 76%) of amide 36c greater than 99% diastereomerically pure. IR (neat) 3600-3250 (br), 2970, 2880, 1615, 1455, 1430, 1115, 1045, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (s, 2H, $OC\underline{H}_2O$), 4.55-4.00 (br, 3H), 3.80-3.40 (m, 8H), 3.35 (s, 3H, $OC\underline{H}_3$), 3.20-2.60 (m, 1H, CO-C$\underline{H}$-CH_3), 1.95 (br s, 4H, C-CH_2-C), 2.2-1.5 (br m, 1H, C$\underline{H}$-Me_2), 1.2-0.9 (m, 6H, CH_2-$C\underline{H}_3$), 0.82 (d, J = 7 Hz, 3H, CO-CH-$C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 176.6 (177.6) ($\underline{C}$=O), 95.5 ($O\underline{C}H_2O$), 76.3 (76.7) ($\underline{C}$HOH), 71.5 (69.1) ($CH\underline{C}H_2O$), 67.2 (66.9), 66.6, ($O\underline{C}H_2\underline{C}H_2O$), 58.8 ($O\underline{C}H_3$), 56.1 (56.7) (N-$\underline{C}$H), 47.2 (45.0) (N-$\underline{C}H_2$), 38.0 (36.9) ($CO\underline{C}HCH_3$), 30.0 [$\underline{C}$H-$(CH_3)_2$], 27.3

(28.4), 23.9 (21.6) (N-CH_2-$\underline{C}H_2\underline{C}H_2$), 19.3 (19.7), 18.6 [$CH(\underline{C}H_3)_2$], 9.5 ($COCH\underline{C}H_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was $\underset{\sim}{T}_1$ 1.8%, $\underset{\sim}{T}_2$ 0.7%, 36c 96.1%, 37c 1.4%. The corresponding lithium mediated aldol condensation had a product distribution of $\underset{\sim}{T}_1$ 8.8%, $\underset{\sim}{T}_2$ 12.5%, 36c 42.6%, 37c 36.1%. The GC conditions were 25 M Carbowax 20M, 200°C, hydrogen at 15 psi, $\underset{\sim}{T}_1$ 14.30 min, $\underset{\sim}{T}_2$ 13.67 min, 36c 16.38 min, 37c 15.41 min, and 30 M SE-54, 180°C, hydrogen at 15 psi, $\underset{\sim}{T}_1$ 11.08 min, $\underset{\sim}{T}_2$ 10.51 min, 36c 12.50 min, 37c 11.08 min. The optical rotation of the purified adduct 36c was $[\alpha]_D$ -44.5 ($\underline{c}$ 4.62, CH_2Cl_2).

Anal. calcd. for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41. Found: C, 60.38; H, 10.29; N, 4.31.

(2R,3S)-1[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-3-hydroxy-2-methylheptanoic Acid (36e, Table 11, Entry 5). The chiral amide aldol 36e was prepared according to Procedure A. Condensation of 0.995 g (4.05 mmol) of the prolinol-derived amide 34 with 0.456 g (5.29 mmol) of n-pentanal (16e) gave after workup 1.29 g of 36e and its aldol diastereomers as an orange oil. Flash chromatography (75% ethyl acetate in hexane, silica gel) afforded 0.930 g (2.81 mmol, 69%) of amide 36e greater than 97% diastereomeric purity along with a

second fraction (0.238 g) made up of ~20% starting amide 34 and 80% of 36e further contaminated by the other aldol diastereomers. Distillation (170°C/0.001 mm) of the diastereomerically pure 36e afforded an analytical sample. IR (neat) 3430, 2960, 2940, 2880, 1620, 1460, 1435, 1120, 1050, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.68 (s, 2H, $OC\underline{H}_2O$), 4.5-3.7 (m, 2H), 3.7-3.4 (m, 9H), 3.35 (s, 3H, $OC\underline{H}_3$), 2.75 and 2.50 (dq, J_d = 3 Hz, J_q = 7 Hz, $CO-C\underline{H}-CH_3$), 1.95 (br s, 4H, $N-CH_2-C\underline{H}_2-C\underline{H}_2-CH$, 1.40 (m, 6H, 3 $C\underline{H}_2$'s), 1.10 (d, J = 7 Hz, 3H, $CO-CH-C\underline{H}_3$), 0.89 (t, 3H, $C\underline{H}_3CH_2$-); ^{13}C NMR ($CDCl_3$) δ 177.1 (176.3) ($\underline{C}$=O), 95.3 (95.2) ($O\underline{C}H_2O$), 71.3 (68.9) ($NCH-\underline{C}H_2O$), 70.6 (71.0) ($\underline{C}HOH$), 67.0, 66.7 (66.4) ($O\underline{C}H_2\underline{C}H_2O$), 58.6 ($O\underline{C}H_3$), 56.5 (55.9) ($N\underline{C}H-CH_2O$), 47.0 (44.8) ($N-\underline{C}H_2$), 40.8 (39.7) ($CO\underline{C}HCH_3$), 33.2 ($CHOH-\underline{C}H_2$), 27.8 (28.2), 27.2, 23.8 (21.5), 22.3 ($\underline{C}H_2$'s), 13.7 ($CH_2-\underline{C}H_3$), 9.6 ($CO-CH\underline{C}H_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was T1 1.2%:T2 1.0%:36e 95.7%:37e 1.9%. The diastereomer ratio of the unpurified aldol product from the corresponding lithium-mediated aldol condensation was T1 17.1%:T2 15.3%: 36e 38.6%:37e 29.0%. The GC conditions were 25 M Carbowax 20M, 200°C, hydrogen at 15 psi, T1 20.28 min, T2 21.04 min, 37e 23.54 min, 36e 25.94 min and 30 M SE-54, 200°C, hydrogen at 15 psi, T1 8.04 min, T2 7.67 min, 37e 8.04 min,

36e 8.71 min. The optical rotation of the purified amide 36e was $[\alpha]_D$ -51.1° (c 4.57, CH_2Cl_2).

Anal. calcd. for $C_{17}H_{33}NO_5$: C, 61.60; H, 10.04; N, 4.23. Found: C, 61.55; H, 9.91; N, 4.26.

(-)(2R)-3-Benzyloxy-2-methylpropanaldehyde (40)

Chromium trioxide (4.75 g, 47.5 mmol) was added in one portion to a stirred suspension of Celite (25 g) in 7.7 mL of pyridine and 120 mL of methylene choride at 0°C.[84] After warming to room temperature for 30 min, (2S)-1-benzyloxy-3-hydroxy-2-methylpropane[85] (1.426 g, 7.912 mmol) was added in one portion. After 30 min the slurry was filtered. The filtrate was concentrated and the residue washed through a 10" column of florisil eluting with ether. After concentration the residual pyridine was removed under high vacuum to yield 1.162 g (6.52 mmol, 82%) of aldehyde 40 as a colorless oil which was used directly in the aldol condensations. IR (neat) 3030, 2970, 2940, 2860, 2730, 1720, 1450, 1360, 1100, 735, 695 cm^{-1}; ^1H NMR (CCl_4) δ 9.62 (br s, 1H, C<u>H</u>O), 7.20 (s, 5H, $C_6\underline{H}_5$), 4.40 (s, 2H, $OC\underline{H}_2Ph$), 3.53 (d, J = 6 Hz, 2H, $CHC\underline{H}_2O$), 2.48 (hexane, J = 7 Hz, 1H, $C\underline{H}CH_2O$), 1.04 (d, J = 7 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (CCl_4) δ 201.1 (<u>C</u>HO), 137.8, 128.1, 128.0, 127.2 (C_6H_5), 72.9 ($CH\underline{C}H_2O$), 69.9 ($O\underline{C}H_2Ph$), 46.4 ($\underline{C}HCH_2O$), 10.6 ($\underline{C}H_3$). The optical rotation

of the aldehyde 40 as used was $[\alpha]_D$ -33.3° (c 10.07, CH_2Cl_2).

(+)(2S)-3-Benzyloxy-2-methylpropanal 41. In an identical manner, 1.426 g (7.912 mmol) of (2R)-1-benzyloxy-3-hydroxy-2-methyl propane[86] was converted to 1.054 g (5.913 mmol, 74.7%) of 41 as a colorless oil. Identical with 40 except for rotation which was $[\alpha]_D$ +33.76° (c 1.65, CH_2Cl_2).

(2R,3S,4R)-1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid (42, Table 11, Entry 7). The title amide 42 was prepared by the condensation of 0.470 g (1.91 mmol) of the prolinol-derived amide 34 with 0.374 g (2.10 mmol) of the chiral aldehyde 40 according to the general Procedure A which afforded 0.790 g of unpurified aldol adduct contaminated by the excess aldehyde 40. This product was not purified but hydrolyzed directly to 57. The spectral data of the unpurified aldol are as follows. IR (neat) 3600-3200 (br), 2970, 2940, 2880, 1720 (residual 40), 1620, 1455, 1435, 1115, 1110, 1050, 980, 740, 695 cm^{-1}; ^1H NMR (CCl_4) δ 7.24 (s, 5H, C_6H_5), 4.6-4.3 (m, 4H, OCH_2O, OCH_2Ph), 4.3-3.8 (m, 2H), 3.7-3.2 (m, 9H), 3.23 (s, 3H, OCH_3), 3.0-2.2 (m, 2H, $COCHCH_3$, $CHOH-CH-CH_2O$), 1.83 (br s, 4H, $N-CH_2CH_2CH_2-CH$), 1.2-0.8 (m, 6H, 2 CH_3's); ^{13}C NMR (CCl_4) δ 175.5 (176.3) (C=O), 138.6, 128.0, 127.1,

127.0 (C_6H_5), 95.3 ($O\underline{C}H_2O$), 73.9, 73.2, 72.9 ($\underline{C}HOH$, $\underline{C}H_2O\underline{C}H_2Ph$), 71.7 ($NCH\underline{C}H_2O$), 67.2, 66.8 ($O\underline{C}H_2\underline{C}H_2O$), 58.4 ($O\underline{C}H_3$), 56.1 (56.5) ($N\underline{C}HCH_2O$), 46.9 (45.1) ($N\underline{C}H_2$), 39.7 (38.6) ($CO\underline{C}HCH_3$), 35.8 (36.1) ($CHOH\underline{C}HCH_2O$), 27.4 (28.4) (N-CH-$\underline{C}H_2CH_2$), 24.1 (21.7) ($NCH_2\underline{C}H_2$), 13.2 (13.8) ($\underline{C}H_3CHCH_2O$), 11.2 (11.6) ($COCH\underline{C}H_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was $\underset{\sim}{T}_1$ 2.8%: $\underset{\sim}{T}_2$ 1.4%:$\underset{\sim}{\underset{\sim}{42}}$ 94.4%:$\underset{\sim}{E}_2$ 1.5% contaminated with additional peaks totalling ~3.6% derived from aldehyde $\underset{\sim}{\underset{\sim}{41}}$. The product distribution of the corresponding lithium-mediated aldol adduct was $\underset{\sim}{T}_1$ 15.6%:$\underset{\sim}{T}_2$ 28.7%: $\underset{\sim}{\underset{\sim}{42}}$ 42.8%: $\underset{\sim}{E}_2$ 13.0%. The GC conditions were 30 M SE-54, 220°C, helium at 27 psi, injector 275°C, detector 275°C, $\underset{\sim}{T}_1$ 34.05 min, $\underset{\sim}{T}_2$ 35.57 min, $\underset{\sim}{\underset{\sim}{42}}$ 37.35 min, $\underset{\sim}{E}_2$ 36.38 min.

(2R,3S,4S)-1-[(2S)-Methoxyethoxymethoxypyrrolid-1-yl]-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid ($\underset{\sim}{\underset{\sim}{43}}$, Table II, Entry 9). The title amide $\underset{\sim}{\underset{\sim}{43}}$ was prepared according to the general Procedure A. Condensation of 0.505 g (2.06 mmol) of the prolinol-derived amide $\underset{\sim}{\underset{\sim}{34}}$ with 0.442 g (2.47 mmol) of the chiral aldehyde $\underset{\sim}{\underset{\sim}{41}}$ afforded after workup 0.848 g of $\underset{\sim}{\underset{\sim}{43}}$ and its aldol diastereomers as a yellow oil contaminated with $\underset{\sim}{\underset{\sim}{34}}$ and $\underset{\sim}{\underset{\sim}{41}}$. Flash chromatography (40% ethyl acetate in hexane on silica gel) afforded 0.378 g (0.891 mmol, 43%) of $\underset{\sim}{\underset{\sim}{43}}$ as an oil con-

contaminated with ~8% of 42 derived from 40, an impurity in the aldehyde 41. IR (neat) 3600-3200 (br), 3040, 2970, 2940, 2880, 1615, 1455, 1430, 1120, 1100, 1050, 985, 855, 742, 703 cm^{-1}; ^1H NMR (CCl_4) δ 7.26 (s, 5H, C_6H_5), 4.54 (s, 2H, OCH_2O), 4.42 (s, 2H, OCH_2Ph), 4.8-3.8 (m, 3H), 3.7-3.2 (m, 10H), 3.28 (s, 3H, OCH_3), 2.9-2.4 (m, 1H, $COCHCHOH$), 2.0-1.6 (m, 5H), 1.07, 0.89 each (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR (CCl_4) δ 175.5 (176.5 (C=O), 138.9, 127.8, 127.1, 126.8 (C_6H_5), 95.2 (OCH_2O), 72.8, 72.3, 72.0 ($CHOH$, CH_2OCH_2Ph), 71.6 ($NCHCH_2O$), 67.1, 66.6 (OCH_2CH_2O), 58.4 (OCH_3), 56.0 (56.4) ($NCHCH_2O$), 46.9 (44.8) (NCH_2), 38.2 (36.6), ($COCHCH_3$), 35.9 (36.1) ($CHOHCHCH_2O$), 27.3 (28.5) ($NCHCH_2CH_2$), 24.1 (21.6) (NCH_2CH_2), 14.0 (13.6) (CH_3CHCH_2O), 9.9 (9.4) (CH_3CHCO). The diastereomer ratio (GC) of the unpurified aldol adduct was T_1 0.8%:T_2 2.4%:43 94.3%:E_2 2.6% contaminated with additional peaks totalling ~8% derived from aldehyde 40. The corresponding lithium-mediated condensation had a diastereomer ratio of T_1 43.8%:T_2 36.8%:43 37.0%:E_2 12.4%. The GC conditions were 30 M SE-54, 220°C, helium at 27 psi, injector 275°C, detector 275°C, T_1 34.24 min, T_2 33.37 min, 43 43.12 min, E_2 38.75 min. HPLC (40% ethyl acetate on silica gel) on a portion of the unpurified aldol gave a sample contaminated with 10% of 42 but less than 1% of

the other diastereomers. The optical rotation of this sample was $[\alpha]_D$ -41.7° (c 10.65, CH_2Cl_2).

(2S,3S)-1-[(4S)-(2-Propyl)-oxazolidin-3-yl]-3-hydroxy-2-methyl-3-phenylpropanoic Acid (39a, Table 12, Entry 1). The title oxazolidine 39a was prepared according to the general recipe described in Procedure A. Condensation of 1.00 g (5.84 mmol) of the valinol-derived propionamide 35 with 0.861 g (8.09 mmol) of benzaldehyde (16a) afforded after workup 1.42 g of 39a and its aldol diastereomers as a brown solid. Flash chromatography (30% ethyl acetate in hexane on silica gel) and recrystallization from ether gave 1.15 g (4.15 mmol, 71%) of 39a as white crystals, mp 134-136°C greater than 99% diastereomerically pure. A second recrystallization gave an analytical sample mp 139.5-140°C. IR ($CHCl_3$) 3600-3250 (br), 3020, 2980, 2950, 2885, 1630, 1460, 1435, 985, 940, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, 5H, $C_6\underline{H}_5$-), 5.10 (d, J = 3 Hz, 1H, C<u>H</u>-OH), 4.9-4.5 (m, 2H, O-C<u>H</u>$_2$-N), 4.3-3.5 (m, 4H, OC<u>H</u>$_2$-C<u>H</u>-N and O<u>H</u>), 2.8-1.5 (m, 2H, CO-C<u>H</u>-CH_3 and C<u>H</u>-Me_2), 1.9-0.7 (m, 9H, C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 174.4 (<u>C</u>=O), 141.6, 128.2, 127.3, 126.0 (C_6H_5), 78.9 (79.4) (O<u>C</u>H$_2$N), 73.1 (<u>C</u>HOH), 68.9 (68.5) (O<u>C</u>H$_2$CHN), 59.6 (60.7) (OCH$_2$<u>C</u>HN), 45.6 (43.9) (CO<u>C</u>HCH$_3$), 29.2 (31.7) [<u>C</u>H-$(CH_3)_2$], 19.0 (19.4), 17.0 [CH-(<u>C</u>H$_3$)$_2$], 11.0 (10.2) (COCH<u>C</u>H$_3$). The

diastereomer ratio (GC) of the unpurified aldol adduct was $\underset{\sim}{T}_1$ 1.2%:$\underset{\sim}{T}_2$ 2.2%:$\underset{\sim\sim\sim}{38a}$ 1.3%:$\underset{\sim\sim\sim}{39a}$ 95.3%. The diastereomer ratio of the corresponding lithium-mediated aldol condensation was $\underset{\sim}{T}_1$ 23.4%:$\underset{\sim}{T}_2$ 6.1%:$\underset{\sim\sim\sim}{38a}$ 41.4%:$\underset{\sim\sim\sim}{39a}$ 29.2%. The GC conditions were 25 M Carbowax 20M, 200°C, hydrogen at 15 psi, $\underset{\sim}{T}_1$ 13.01 min, $\underset{\sim}{T}_2$ 13.59 min, $\underset{\sim\sim\sim}{38a}$ 15.51 min, $\underset{\sim\sim\sim}{39a}$ 14.33 min and 30 M SE-54, 180°C, hydrogen at 15 psi, $\underset{\sim}{T}_1$ 7.30 min, $\underset{\sim}{T}_2$ 7.51 min, $\underset{\sim\sim\sim}{38a}$ 7.89 min, $\underset{\sim\sim\sim}{39a}$ 8.32 min. The optical rotation of purified $\underset{\sim\sim\sim}{39a}$ was $[\alpha]_D$ +14.71 ($\underline{c}$ 1.4, CH_2Cl_2).

Anal. calcd. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.35; N, 5.05. Found: C, 69.38; H, 8.50; N, 4.98.

(2S,3R)-1-[(4S)-(2-Propyl)-oxazolidin-3-yl]-3-hydroxy-2,4-dimethylpentanoic Acid ($\underset{\sim\sim\sim}{39c}$, Table 12, Entry 3). The title amide $\underset{\sim\sim\sim}{39c}$ was prepared according to Procedure A from 0.995 g (5.81 mmol) of the valinol-derived propionamide $\underset{\sim\sim}{35}$ and 0.547 g (7.59 mmol) of isobutyraldehyde ($\underset{\sim\sim\sim}{16c}$) to afford 1.16 g of $\underset{\sim\sim\sim}{39c}$ and its aldol diastereomers as a colorless oil. Flash chromatography (25% ethyl acetate in hexane) gave 1.09 g (4.46 mmol, 77%) of amide $\underset{\sim\sim\sim}{39c}$ as a crystalline solid, mp 58-59°C, greater than 99% diastereomerically pure. IR (film) 3600-3200 (br), 2960, 2940, 2870, 1610, 1465, 1440, 1390, 1370, 1330, 1300, 1170, 1125, 1110, 1090, 980, 945, 845, 760, 735,

655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.92 (m, 2H, N-C<u>H</u>$_2$-O), 4.7-3.6 (m, 4H, O-C<u>H</u>$_2$-C<u>H</u>-N, O<u>H</u>), 3.45 (dd, J = 3 Hz, J = 8 Hz, 1H, C<u>H</u>-OH), 2.9-1.5 (m, 3H), 1.18 (d, J = 7 Hz, 3H, CH_3), 1.05 (d, J = 6 Hz, 3H, C<u>H</u>$_3$), 1.0-0.73 (m, 9H, 3 C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 175.1 (<u>C</u>=O), 78.9 (O<u>C</u>H$_2$N), 76.2 (<u>C</u>HOH), 68.0 (O<u>C</u>H$_2$CHN), 59.4 (60.7) (OCH$_2$<u>C</u>HN), 39.6 (37.9) (O<u>C</u>HCH$_3$), 30.1 (31.6), 29.0 [2 <u>C</u>H(CH$_3$)$_2$], 19.4, 19.0, 18.8, 16.9 (4 CH_3's), 10.3 (COCH<u>C</u>H$_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was <u>T</u>$_1$ 0.8%:<u>T</u>$_2$ 0.4%:<u>38c</u> 0.5%:<u>39c</u> 98.3%. The corresponding lithium-mediated aldol condensation product had a diastereomer distribution of <u>T</u>$_1$ 12.5%:<u>T</u>$_2$ 4.4%:<u>38c</u> 42.6%:<u>39c</u> 40.5%. The GC conditions were 25 M Carbowax 20M, 150°C, hydrogen at 15 psi, <u>T</u>$_1$ 9.49 min, <u>T</u>$_2$ 9.49 min, <u>38c</u> 9.67 min, <u>39c</u> 10.05 min and 30 M SE-54, 130°C, hydrogen at 15 psi, <u>T</u>$_1$ 9.65 min, <u>T</u>$_2$ 9.89 min, <u>38c</u> 9.89 min, <u>39c</u> 10.64 min. The optical rotation of the purified aldol adduct <u>39c</u> was $[\alpha]_D$ +8.94° (<u>c</u> 1.23, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.30; H, 10.48; N, 5.79.

<u>(2S,3R)-1-[(2S)-(2-Propyl)-oxazolidin-3-yl]-3-hydroxy-2-methylheptanoic Acid (39e, Table 12, Entry 5)</u>. The title amide <u>39e</u> was prepared according to Procedure A. Condensation of 0.899 g (5.25 mmol) of the valinol-derived

propionamide 35 with 0.584 g (6.78 mmol) of n-pentanal (16e) afforded after workup and distillation (150°C/0.001 mm) 1.30 g (5.05 mmol, 96%) of analytically pure 39e and its aldol diastereomers. IR (neat) 3430, 2970, 2940, 2880, 1630, 1455, 1430, 1425, 1210, 1180, 1120 cm^{-1}; ^1H NMR (CCl_4) δ 4.90 (br d, J = 4 Hz, 1H, OCH_2O), 4.78 (br d, J = 4 Hz, 1H, OCH_2O), 4.2-3.4 (br m, 5H, OCH_2CHN, CHOH), 2.4-1.9 [br m, 2H, $COCHCH_3$, $CH(CH_3)_2$], 1.6-1.1 (br s, 6H, 3 CH_2's), 1.13 (d, J = 7 Hz, 3H, CH_3), 1.05-0.75 (br m, 9H, 3 CH_3's); ^{13}C NMR (CCl_4) δ 174.1 (C=O), 78.6 (OCH_2N), 70.0 (CHOH), 67.6 (OCH_2CHN), 59.0 (OCH_2CHN), 42.6 ($COCHCH_3$), 33.4, 29.0, 28.0, 22.5 [$CH(CH_3)_2$ and 3 CH_2's], 19.0, 17.0 [$CH(CH_3)_2$], 13.9 (CH_3-CH_2), 10.5 ($COCHCH_3$). The diastereomer ratio (GC) of the unpurified aldol product mixture was T_1 1.3%:T_2 0.7%:38e 1.1%:39e 96.9%. The product distribution of the corresponding lithium mediated aldol condensation was T_1 6.1%:T_2 16.8%: 38e 35.2%:39e 42.0%. The GC conditions were 25 M Carbowax 20M, 170°C, helium at 27 psi, T_1 13.16 min, T_2 13.77 min, 39e 15.33 min, 38e 15.70 min. The optical rotation of the distilled 39e was $[\alpha]_D$ +23.9° (c 6.12, CH_2Cl_2).

Anal. calcd. for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.36; H, 10.59; N, 5.45.

(2S,3R,4R)-1-[(4S)-(2-Propyl)-oxazolidin-3-yl]-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid (44, Table 12, Entry 7). The title amide 44 was prepared according to the recipe outlined in Procedure A. The condensation of 0.356 g (2.08 mmol) of the valinol-derived propionamide 35 with 0.389 g (2.18 mmol) of chiral aldehyde 40 afforded after workup 0.702 g (2.01 mmol, 96%) of 44 and its diastereomers as a solid. Recrystallization from methylene chloride/pentane gave an analytical sample mp 98-98.5°C. IR (film) 3600-3200 (br), 3100, 3070, 3040, 2970, 2940, 2910, 2880, 2850, 2795, 1615, 1455, 1438, 1295, 1170, 1122, 1070, 980, 945, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (s, 5H, $C_6\underline{H}_5$), 4.87 (m, 2H, $OC\underline{H}_2N$), 4.49 (s, 2H, $OC\underline{H}_2Ph$), 4.3-3.4 (m, 7H), 2.7-1.5 (m, 3H), 1.18 (d, J = 7 Hz, 3H, $C\underline{H}_3$), 1.1-0.75 (m, 9H, 3 CH_3's); ^{13}C NMR ($CDCl_3$) δ 174.0 ($\underline{C}$=O), 138.8, 127.9, 127.2, 126.9 ($\underline{C}_6H_5$), 78.6 ($OC\underline{H}_2N$), 72.9 ($CHOHC\underline{H}_2O$), 72.2 ($\underline{C}HOH$ and $OC\underline{H}_2Ph$), 67.7 ($OC\underline{H}_2CHN$), 59.2 ($OCH_2\underline{C}HN$), 40.0 ($CO\underline{C}H$), 35.9 ($CH_3\underline{C}HCH_2O$), 29.0 [$\underline{C}H(CH_3)_2$], 19.0, 17.0 [$CH(\underline{C}H_3)_2$], 14.1 ($\underline{C}H_3CHCH_2O$), 11.0 (10.6) ($COCH\underline{C}H_3$). The diastereomer ratio (GC) of the unpurified aldol adduct was T_1 0.3%:T_2 3.6%:E_1 1.7%:44 94.4% plus peaks totalling ~8% derived from aldehyde 41. The corresponding lithium mediated aldol condensation had a product distribution

of $\underset{\sim}{T}_1$ 44.7%:$\underset{\sim}{T}_2$ 18.6%:$\underset{\sim}{E}_1$ 5.4%:$\underset{\sim}{\underset{\sim}{44}}$ 31.4%. The GC conditions were 25 M Carbowax 20M, 210°C, helium at 27 psi, $\underset{\sim}{T}_1$ 35.13 min, $\underset{\sim}{T}_2$ 36.18 min, $\underset{\sim}{E}_1$ 38.01 min, $\underset{\sim}{\underset{\sim}{44}}$ 40.24 min. The optical rotation of the recrystallized $\underset{\sim}{\underset{\sim}{44}}$ was $[\alpha]_D$ +20.6° (c 4.73, CH_2Cl_2).

Anal. calcd. for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.69; H, 8.72; N, 3.98.

(2S,3R,4S)-1-[(4S)-(2-Propyl)-oxazolidin-3-yl]-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid (45, Table 12, Entry 9). The title oxazolidine $\underset{\sim}{\underset{\sim}{45}}$ was prepared according to Procedure A. The condensation of 0.698 g (4.08 mmol) of the valinol-derived propionamide $\underset{\sim}{\underset{\sim}{35}}$ with 0.750 g (4.207 mmol) of chiral aldehyde $\underset{\sim}{\underset{\sim}{41}}$ afforded 1.38 g (3.95 mmol, 97%) of $\underset{\sim}{\underset{\sim}{45}}$ and its aldol diastereomers as white crystals. Flash chromatography with 10% ethyl acetate in hexane until $\underset{\sim}{\underset{\sim}{45}}$ began to elute followed by 30% ethyl acetate in hexane gave 1.09 g (3.12 mmol, 77%) of amide $\underset{\sim}{\underset{\sim}{45}}$. Recrystallization from ether/pentane afforded an analytical sample, mp 96.5-98.5°C. IR (film) 3060, 2990, 2880, 1625, 1420, 1260, 890, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5H, $C_6\underline{H}_5$), 4.76 (m, 2H, $OC\underline{H}_2N$), 4.42 (s, 2H, $OC\underline{H}_2Ph$), 4.2-3.2 (m, 7H), 2.8-1.6 (m, 3H), 1.18, 1.05, 0.88, 0.82 each (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.1 ($\underline{C}$=O),

138.0, 128.9, 128.1, 127.3 (C_6H_5), 78.6 (OCH_2N), 74.2, 73.4, 73.1 ($CHOHCH_2OCH_2Ph$), 67.7 (OCH_2CHN), 59.1 (OCH_2CNH), 40.9 (39.1) ($COCHCH_3$), 35.5 (33.3) ($CHOHCHCH_2O$), 29.0 [$CH(CH_3)_2$], 19.0, 16.9 [$CH(CH_3)_2$], 13.3 (14.0) (CH_3CHCH_2O), 11.8 (10.9) ($COCHCH_3$). The diastereomer ratio (GC) of the unpurified aldol product was $\underset{\sim}{T}_1$ 0.1%: $\underset{\sim}{T}_2$ 0.3%:$\underset{\sim}{E}_1$ 0.9%:$\underset{\sim\sim}{45}$ 98.7%, with additional peaks totalling ~5% derived from aldehyde $\underset{\sim\sim}{40}$. The corresponding lithium-mediated aldol condensation had a product distribution of $\underset{\sim}{T}_1$ 18.5%:$\underset{\sim}{T}_2$ 39.8%:$\underset{\sim}{E}_1$ 7.1%:$\underset{\sim\sim}{45}$ 34.5%. The GC conditions were 25 M Carbowax 20M, 210°C, helium at 27 psi, $\underset{\sim}{T}_1$ 36.89 min, $\underset{\sim}{T}_2$ 37.70 min, $\underset{\sim}{E}_1$ 34.27 min, $\underset{\sim\sim}{45}$ 35.34 min. The optical rotation of recrystallized $\underset{\sim\sim}{45}$ was $[\alpha]_D$ +26.2° ($\underline{c}$ 4.31, CH_2Cl_2).

Anal. calcd. for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.46; H, 8.75; N, 4.07.

General Procedure for the Hydrolysis of Chiral Amide Aldol Adducts to β-Hydroxy Acids. The aldol adduct was suspended in 10-20 equiv of 5% hydrochloric acid and heated to reflux for 1.5-2.0 h. The reaction was cautiously neutralized with saturated sodium bicarbonate solution until gas evolution ceased. This solution was washed with ether. The basic water layer was then carefully acidified to pH 1 with concentrated hydrochloric

acid. The acid layer was extracted several times with ether. This organic layer was concentrated under reduced pressure. The residue was dissolved in methylene chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give the specific β-hydroxy acid.

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 stirred solution of 50% potassium hydroxide in water at 0°C which was covered with a layer of ether.[87] After the solid urea dissolved, the yellow ether solution was decanted or distilled in glass apparatus with non-ground glass joints. This ether solution of diazomethane was then added via pipet to a solution of the acid in ether or methylene chloride until the solution remained yellow. The solution was then allowed to stand until the color dissipated. Concentration of this solution afforded the methyl ester.

(+) (2R,3R)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (49a, Table 13, Entry 1). The general hydrolysis conditions were too vigorous for the formation of acid 49a from amide 36a. Thus this modified procedure was used to minimize benzylic epimerization. The hydroxyamide 36a (0.248 g, 0.706 mmol) was dissolved in 2.5 mL of p-dioxane. To this solution was added 2.0 mL of 5% HCl (3.2 mmol, 4.5

equiv). This mixture was heated to reflux for 4 h. After cooling to 25°C the solution was cautiously neutralized with saturated sodium bicarbonate solution until gas evolution ceased. After washing with ether, the aqueous layer was carefully acidified to pH 1. The acid 45a was extracted into ether. After drying over magnesium sulfate, this organic phase was concentrated to give 0.103 g (0.572 mmol, 80%) of acid 49a as a crystalline solid, mp 79-81°C, identical except for rotation with acid 50a. A small sample of this acid was esterified to the methyl ester which was identical by GC with racemic ester 21a. The GC analysis revealed 3.2% of the threo diastereomer derived from benzylic epimerization. The optical rotation of the crystalline acid 49a is $[\alpha]_D$ +29.5° (c 3.74, $CHCl_3$) [Lit.[70] $[\alpha]_D$ +31.03° (c 1.07, $CHCl_3$)].

(-)(2S,3S)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (50a, Table 13, Entry 2). Acid 50a was prepared from amide 39a in a manner analogous to the preparation of acid 49a and for the same reasons. The hydroxyamide 39a (0.101 g, 0.369 mmol) was dissolved in 1 mL of p-dioxane with 1 mL of 5% (1.6 mmol, ~4 equiv) hydrochloric acid. This mixture was heated to reflux for 4 h. This solution was carefully neutralized with saturated sodium bicarbonate solution.

After washing with ether, the aqueous layer was carefully acidified. The product 50a was extracted into ether. This solution was dried over magnesium sulfate, filtered and concentrated to afford 0.0517 g (0.287 mmol, 79%) of 50a as a crystalline solid, mp 83-85°C. IR (film) 3600-2500 (br), 1715, 1490, 1460, 1200, 1125, 1025, 980, 910, 735, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 5H, $C_6\underline{H}_5$), 7.10 (br s, 2H, O$\underline{H}$'s), 5.10 (d, J = 4 Hz, 1H, C$\underline{H}$OH), 2.77 (dq, J_d = 4.5 Hz, J_q = 7 Hz, 1H, COC$\underline{H}$$CH_3$), 1.12 (d, J = 7 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 180.4 ($\underline{C}$=O), 141.0, 128.3, 127.6, 125.9 (C_6H_5), 73.4 ($\underline{C}$HOH), 46.1 (CO$\underline{C}$HCH$_3$), 10.2 ($\underline{C}H_3$). The optical rotation of this acid was $[\alpha]_D$ -30.0° ($\underline{c}$ 3.68, $CHCl_3$) [Lit.[56] $[\alpha]_D$ - 29.5 ($\underline{c}$ 2.03, $CHCl_3$)]. A portion of this acid was converted to the methyl ester which was identical by GC to the ester derived from 49a and to the racemic erythro diastereomer 21a. GC analysis revealed the presence of 3.1% of the threo diastereomer due to benzylic epimerization.

(+)(2R,3S)-3-Hydroxy-2,4-dimethylpentanoic Acid (49c, Table 13, Entry 3). Hydrolysis of 0.995 g (3.13 mmol) of amide 36c according to the general procedure afforded 0.413 g (2.83 mmol, 90%) of acid 49c as a colorless oil. IR (neat) 3600-2500 (br), 2980, 2900, 1715, 1470, 1465, 1385, 1215, 1115, 1055, 1005, 985, 955 cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 7.50 (br s, 2H, OH's), 3.61 (dd, J = 4 Hz, J = 7 Hz, 1H, CHOH), 2.66 (dq, J_d = 4 Hz, J_q = 7 Hz, 1H, $COCHCH_3$), 1.75 [octuplet, J = 7 Hz, 1H, $CHOHCH(CH_3)_2$], 1.18, 0.99, 0.89 each (d, J = 7 Hz, 3H, CH_3). In this experiment purified amide 36c was used. GC of the methyl ester 55c prepared from this sample of 49c demonstrated 0.9% threo diastereomer which is consistent with the diastereomeric composition of the amide 36c used in this hydrolysis. The optical rotation of this sample of 49c was $[\alpha]_D$ +9.30° (c 2.56, CH_2Cl_2) [Lit.[70] $[\alpha]_D$ +10.54° (c 1.40, $CHCl_3$).

(+) (2R,3S)-3-Hydroxy-2,4-dimethylpentanoic Acid, Methyl Ester (55c). Esterification of 0.420 g (2.87 mmol) of acid 49c according to the general procedure afforded after distillation (130°C/20 mm) 0.460 g (2.87 mmol, 100%) of the ester 55c as a colorless oil identical by GC and spectra with the racemic ester 21c and with the enantiomeric 56c. IR (neat) 3620-3250 (br), 2970, 2890, 1735, 1465, 1442, 1260, 1205, 1140, 1110, 1055, 1010, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H, OCH_3), 3.52 (m, 1H, CHOH), 3.05 (d, J = 5 Hz, 1H, OH), 2.64 (dq, J_d = 5 Hz, J_q = 7 Hz, 1H, $COCHCH_3$), 1.65 [octuplet, J = 7 Hz, 1H, $CH(CH_3)_2$], 1.18, 0.97, 0.89 each (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR (CCl_4) δ 175.8 (C=O), 76.3 (CHOH), 51.2

(OCH_3), 41.9 ($COCHCH_3$), 30.6 [$CH(CH_3)_2$], 19.2, 18.1 [$CH(CH_3)_2$], 10.5 ($COCHCH_3$). The diastereomer ratio (GC) of the distilled ester was erythro 99.1%:threo 0.9% which was consistent with the product distribution in the amide 49c used in this experiment. The GC conditions were 30 M SE-54, 75°C hydrogen at 10 psi, threo 4.54 min, erythro 5.12 min. The optical rotation of the distilled ester 55c was $[\alpha]_D$ +5.12° (c 9.53, CH_2Cl_2).

Anal. calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.99; H, 10.07.

(2R)-1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-2,4-dimethylpentanoic Acid (53c). A THF solution of 0.100 g (0.315 mmol) of hydroxy amide 36c was added to a suspension of excess sodium hydride in THF at 0°C. After 1 h carbon disulfide (95 μL, 1.5 mmol) was added. The solution was warmed to room temperature for 1 h then methyl iodide (41 μL , 0.66 mmol) was added. After stirring an additional 3 h the reaction was diluted with 70 mL of ether, washed twice with 20 mL of saturated sodium bicarbonate solution followed by 20 mL of water. The organic phase was concentrated. The residue in methylene chloride was dried over magnesium sulfate. After filtration, concentration left 0.139 g containing the methyl dithiocarbonate 52c.[64] This was dissolved

in 10 mL of dry toluene with 0.5 mL of tri-(n)butyl tin hydride and heated to reflux for 24 h. After cooling, the solvent was removed under reduced pressure. The product was isolated by silica gel filtration with hexane to elute the non-polar components followed by 50% ethyl acetate in hexane to elute the amide 53c. Concentration of the fractions containing 53c followed by distillation (150°C/0.001 mm) afforded 0.785 g (0.258 mmol, 82%) of the desired 53c as a colorless oil. IR (CH_2Cl_2) 3060, 2970, 2890, 1635, 1465, 1425, 1270, 1205, 1170, 1120, 1050, 895, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (s, 2H, $OC\underline{H}_2O$), 4.4-3.9 (br m, 2H), 3.8-3.4 (m, 7H), 3.28 (s, 3H, $OC\underline{H}_3$), 2.8-2.2 (m, 1H, CO-C<u>H</u>-CH_3), 1.90 (br s, 4H, -$C\underline{H}_2$-$C\underline{H}_2$-CH_2N), 1.8-1.1 (m, 3H, CO-CH-$C\underline{H}_2$-C<u>H</u>), 1.0 (d, J = 7 Hz, 3H, CO-CH-$C\underline{H}_3$), 0.78 [br d, J = 5 Hz, 6H, $CH(C\underline{H}_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 175.9 and 175.5 (<u>C</u>=O), 95.5 (O-$\underline{C}H_2$-O), 71.5 (N-CH-$\underline{C}H_2$-O), 67.4, 66.8 (O-$\underline{C}H_2$-$\underline{C}H_2$-O), 58.7 (O-$\underline{C}H_3$), 56.1 (CH_2-<u>C</u>H-N), 46.8 (N-$\underline{C}H_2$), 42.6 and 42.4 (CO-<u>C</u>H-CH_3), 35.7 and 35.3 (CH_2-<u>C</u>H-Me_2), 27.4, 24.0 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2N), 28.5 and 25.6 (CO-CH-$\underline{C}H_2$), 23.1 and 22.7, 22.4 and 21.5 [$(CH(\underline{C}H_3)_2$], 17.6 and 13.4 (CO-CH-$\underline{C}H_3$). This product showed 2.7% (GC) of the 2S epimer of 53c consistent with the diastereomeric composition of the aldol 36c used in the preparation of this sample. The GC conditions

were 30 M SE-54, 170°C, hydrogen at 15 psi, 2S epimer of 53c 8.52 min, 53c 8.90 min. The optical rotation of this sample was $[\alpha]_D$ -58.2° (c 4.01, CH_2Cl_2).

Anal. calcd. for $C_{16}H_{31}NO_4$: C, 63.76; H, 10.37; N, 4.65. Found: C, 63.58; H, 10.37; N, 4.70.

(-)(2S,3R)-3-Hydroxy-2,4-dimethylpentanoic Acid (50c, Table 13, Entry 4). Hydrolysis of 1.03 g (4.25 mmol) of amide 39c according to the general procedure afforded 0.567 g (3.88 mmol, 91%) of acid 50c whose IR and NMR spectra were identical with those of 49c. Recrystallized amide 39c was used in this experiment. GC analysis of the methyl ester 56c prepared from this sample of 50c revealed 0.2% threo diastereomer which is consistent with the diastereomeric composition of the amide 39c used in this reaction. The optical rotation of this sample of 50c was $[\alpha]_D$ -9.74° (c 1.53, CH_2Cl_2).

(-) (2S,3R)-3-Hydroxy-2,4-dimethylpentanoic Acid, Methyl Ester (56c). Esterification of 0.567 g (3.88 mmol) of acid 50c according to the general procedure afforded after distillation (130°C/20 mm) 0.617 g (3.85 mmol, 99%) of ester 56c as a colorless oil identical by spectra and GC with the enantiomeric acid 55c. The diastereomer ratio (GC) of this distilled ester was erythro 99.8%: threo 0.2% consistent with the diastereomeric composition

of the amide precursor 39c. The optical rotations of this sample were $[\alpha]_D$ -4.53° (c 14.6, CH_2Cl_2); $[\alpha]_D$ -7.20° (c 9.30, $CHCl_3$).

(-)(2R,3S)-3-Hydroxy-2-methylheptanoic Acid (49e, Table 13, Entry 5). Hydrolysis of 1.95 g (6.16 mmol) of unpurified amide 36e and its aldol diastereomers under the standard procedure afforded 0.875 g (5.46 mmol, 89%) of acid 49e as an oil whose spectra were identical with those reported below for acid 50e. GC analysis of the methyl ester 55e prepared from this sample of 49e revealed 3.4% of the threo diastereomer which is consistent with the diastereomeric composition of the amide 36e used in this experiment. The optical rotation of this sample of 49e was $[\alpha]_D$ -13.8° (c 6.89, CH_2Cl_2).

(2R,3S)-3-Hydroxy-2-methylheptanoic Acid,Methyl Ester (55e). Esterification of 0.875 g (5.46 mmol) of acid 49e under the standard conditions afforded after distillation (80°C/0.01 mm) 0.858 g (4.92 mmol, 90%) of ester 55e as a colorless oil, identical by GC and spectra with the enantiomeric ester 56e. The diastereomer ratio (GC) of the distilled ester was erythro 96.6%:threo 3.4% consistent with the diastereomeric composition of the amide precursor 36e used to prepare this sample. The optical rotation of this sample of ester 55e was $[\alpha]_D$ -14.2

(c 11.3, CH_2Cl_2).

(2R)-1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-2-methylheptanoic Acid (53e). In a procedure identical to that described for the preparation of amide 53c from hydroxy amide 36c, 0.101 g (0.305 mmol) of hydroxy amide 36e was deoxygenated to afford after distillation (170°C/0.001 mm) 0.0835 g (0.265 mmol, 87%) of the title amide 53e as a colorless oil. IR (CH_2Cl_2) 3060, 2990, 2970, 2945, 2890, 1635, 1465, 1422, 1270, 1050, 895, 765, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.60 (s, 2H, OCH_2O), 4.4-3.8 (m, 2H), 3.7-3.4 (m, 7H), 3.30 (s, 3H, OCH_3), 2.40 (m, 1H, CO-CH-CH_3), 1.90 (br s, 4H, N-CH_2-CH_2CH_2), 1.20 (br s, 8H, 4 CH_2's), 1.02 (d, J = 7 Hz, 3 H, COCH-CH_3), 0.80 (br t, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 175.2 (175.6) (C=O), 95.3 ($O-CH_2O$), 71.3 (68.9) (N-CH-CH_2O), 67.3, 66.6 and 66.3 (OCH_2CH_2O), 38.5 (OCH_3), 55.9 (56.1) (N-CH), 46.7 (45.1) (N-CH_2), 37.7 (37.4) ($COCHCH_3$), 33.4 (31.6) ($COCHCH_2$), 27.2 (28.4), 26.9, 23.8 (21.4), 22.2 (4 CH_2's), 17.3 (17.7) ($COCHCH_3$), 13.6 (13.2) (CH_2CH_3). GC analysis of this sample of 53e revealed 2.06% of the 2S epimer of 53e. The GC conditions were 30 M SE-54, 200°C, hydrogen at 15 psi, 53e 4.90 min, 2S epimer of 53e 4.66 min. The rotation was $[\alpha]_D$ -54.8° (c 1.07, CH_2Cl_2). This sample was hydrolyzed to known (2R)-methylheptanoic acid[65] in 49% yield.

Distillation (130°C/15 mm) gave a sample for optical rotation. IR (neat) 3600-2460 (br), 2940, 2860, 1710, 1465, 1455, 1240, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.0-7.0 (buried in baseline) (1H, O$\underline{H}$), 2.42 (m, J = 6 Hz, CO$\underline{CH}$), 1.25 (br s, 8H, 4 $C\underline{H}_2$), 1.15 (d, J = 7 Hz, 3H, COCH$\underline{CH}_3$), 0.88 (br t, $CH_2\underline{CH}_3$); ^{13}C NMR (CCl_4) δ 183.0 ($\underline{C}$=O), 39.2 (CO$\underline{CH}$), 33.4, 31.6, 26.7, 22.3 ($\underline{CH}_2$'s), 16.6 (COCH$\underline{CH}_3$), 13.8 ($CH_2\underline{CH}_3$). The rotation of the distilled acid was $[\alpha]_D$ -18.2° ($\underline{c}$ 0.45, CH_2Cl_2) $[\alpha]_D$ -16.6° (c 0.32, $CHCl_3$)[89] [Lit.[67] $[\alpha]_D^{25}$ -15.6° (neat) for estimated 86% ee].

(+) (2S,3R)-3-Hydroxy-2-methylheptanoic Acid (50e, Table 13, Entry 6). Hydrolysis of 1.07 g (4.17 mmol) of unpurified amide 39e under the standard procedure afforded 0.610 g (3.81 mmol, 91%) of acid 50e as an oil. IR (neat) 3500-2500 (br), 2960, 2930, 2870, 1705, 1460, 1455, 1190 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.77 (br s, 2H, O$\underline{H}$), 3.90 (m, 1H, C$\underline{H}$-OH), 2.47 (dq, J_d = 4 Hz, J_q = 7 Hz, 1H, CO-C$\underline{H}$-CH_3), 1.40 (br s, 6H, 3 $C\underline{H}_2$'s), 1.16 (d, J = 7 Hz, 3H, CO-CH-$C\underline{H}_3$), 0.90 (br t, 3H, CH_2-$C\underline{H}_3$); ^{13}C NMR (CCl_4) δ 180.0 ($\underline{C}$=O), 71.6 (C$\underline{H}$-OH), 44.2 (CO-C$\underline{H}$-CH_3), 33.4 (CHOH-$\underline{CH}_2$), 28.0 (CH_3-CH_2-$\underline{CH}_2$), 22.4 (CH_3-$\underline{CH}_2$), 13.9 ($\underline{CH}_3$-CH_2), 10.3 (CO-CH-$\underline{CH}_3$). GC Analysis of the methyl ester 56e prepared from this sample of 50e revealed 2.6% of the threo diastereomer which is consistent with the

diastereomeric composition of the starting amide 39e used in this experiment. The optical rotation of this sample of acid 50e is $[\alpha]_D$ +14.9° (c 6.79, CH_2Cl_2).

(+) (2S,3R)-3-Hydroxy-2-methylheptanoic Acid, Methyl Ester (56e). Esterification of 0.608 g (3.80 mmol) of acid 50e according to the standard procedure afforded after distillation (120°C/1 mm) 0.621 g (3.56 mmol, 94%) of ester 56e analytically pure. IR (neat) 3580-3250 (br), 2950, 2935, 2865, 1730, 1455, 1435, 1260, 1200, 1170, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 3.75 (m, 1H, C<u>H</u>-OH), 3.64 (s, 3H, OC<u>H</u>$_3$), 3.0-2.65 (br, 1H, O<u>H</u>), 2.38 (dq, J_d = 4 Hz, J_q = 7 Hz, 1H, CO-C<u>H</u>-CH_3), 1.35 (br s, 6H, 3 C<u>H</u>$_2$'s), 1.12 (d, J = 7 Hz, 3H, CO-CH-C<u>H</u>$_3$), 0.90 (br t, 3H, CH_2-C<u>H</u>$_3$); ^{13}C NMR (CCl_4) δ 175.4 (<u>C</u>=O), 71.2 (<u>C</u>H-OH), 51.0 (O<u>C</u>H$_3$), 44.5 (CO-<u>C</u>H-CH_3), 33.7 (CHOH-<u>C</u>H$_2$), 28.0 (CH_3-CH_2-<u>C</u>H$_2$), 22.4 (CH_3-<u>C</u>H$_2$-), 13.8 (<u>C</u>H$_3$-CH_2), 10.7 (CO-CH-<u>C</u>H$_3$). The diastereomer ratio of the distilled ester 56e was erythro 97.4% : threo 2.6% consistent with the diastereomeric composition of the amide precursor 39e used to prepare this sample. The GC conditions were 25 M Carbowax 20M, 100°C, helium at 25 psi, threo 9.40 min, erythro 11.20 min. $[\alpha]_D$ +14.8° (c 7.21, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.88; H, 10.18.

(-) (2R,3S,4R)-5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid (57, Table 13, Entry 7). Hydrolysis of 0.769 g (1.82 mmol) of unpurified 42 and its aldol diastereomer under the standard conditions gave after concentration to constant weight under high vacuum 0.258 g (1.02 mmol, 56.3%) of acid 57 as an oil. IR (neat) 3640-2450 (br), 2980, 1710, 1455, 1370, 1210, 1100, 980, 740, 695 cm^{-1}; ^1H NMR (CCl_4) δ 7.22 (s, 5H, $C_6\underline{H}_5$), 7.15 (br s, 2H, O$\underline{H}$'s), 4.38 (s, 2H, OC$\underline{H}_2$Ph), 3.83 (m, 1H, C$\underline{H}$OH), 3.37 (d, J = 5 Hz, 2H, CHC$\underline{H}_2$O), 2.8-2.3 (m, 1H, COC$\underline{H}$), 2.0-1.7 (m, 1H, C$\underline{H}$CH$_2$O), 1.20 and 0.95 each (d, J = 7 Hz, 3H, C$\underline{H}_3$); ^{13}C NMR (CCl_4) δ 180.2 ($\underline{C}$=O), 137.8, 128.0, 127.3 ($\underline{C}_6H_5$), 73.8, 73.5, 72.9 ($\underline{C}$HOHC$\underline{H}_2$-O$\underline{C}H_2$Ph), 42.8 (CO$\underline{C}$H), 35.3 (CH$_3\underline{C}$HCH$_2$O), 12.7 ($\underline{C}H_3$CHCH$_2$O), 11.2 (COCH$\underline{C}H_3$). The optical rotation of this sample of 57 was $[\alpha]_D$ -5.32° ($\underline{c}$ 6.93, CH_2Cl_2).

(-) (2R,3S,4R)-5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid, Methyl Ester (61). Esterification of 0.258 g (1.02 mmol) of unpurified acid 57 afforded after distillation (130°C/0.005 mm) 0.204 g (0.765 mmol, 74.8%) of ester 61 as an oil contaminated with 6.5% (GC) of ester 62 derived in the aldol from aldehyde 41. The yield of 61 overall from the condensation of 34 with 40 was 41% from pure amide 34 to pure ester 61. IR (neat) 3600-3200 (br),

3040, 2980, 2960, 2880, 1735, 1450, 1435, 1365, 1260, 1205, 1170, 1100, 1070, 1055, 1025, 990, 738, 695 cm^{-1}; ^1H NMR (CCl_4) δ 7.28 (s, 5H, $C_6\underline{H}_5$), 4.40 (s, 2H, $OC\underline{H}_2Ph$), 3.75 (m, 1H, $C\underline{H}OH$), 3.60 (s, 3H, $OC\underline{H}_3$), 3.36 (d, J = 5 Hz, 2H, $CHC\underline{H}_2O$), 2.85 (br s, 1H, $O\underline{H}$), 2.53 (pentuplet, J = 7 Hz, 1H, $COC\underline{H}CH_3$), 1.9-1.6 (m, 1H, $C\underline{H}CH_2O$), 1.17, 0.93 each (d, J = 7 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (CCl_4) δ 175.1 ($\underline{C}$=O), 138.0, 128.1, 127.3 ($\underline{C}_6H_5$), 74.1, 73.5, 72.9 ($\underline{C}HOH$, $\underline{C}H_2O\underline{C}H_2Ph$), 51.0 ($O\underline{C}H_3$), 42.8 ($CO\underline{C}H$), 36.0 ($\underline{C}HCH_2O$), 13.1, 11.2 (2 $\underline{C}H_3$'s). The GC analysis of the distilled ester 61 demonstrated 6.4% of the 4-epi isomer 62. The GC conditions were 30 M SE-54, 180°C, hydrogen at 10 psi, 61 4.78 min, 62 5.00 min. The optical rotation of this distilled sample of 61 was $[\alpha]_D$ -3.03° (c 19.07, CH_2Cl_2).

Anal. calcd. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.40; H, 8.37.

(2R,3S,4S)-5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid (58, Table 13, Entry 8). Hydrolysis of 0.334 g (0.789 mmol) of amide 43 according to the standard hydrolysis procedure afforded, after concentration but not to constant weight, 0.1084 g of an oil containing acid 58. The ^1H NMR and ^{13}C NMR spectra of this oil exhibited additional signals [^1H NMR δ 6.40 (br s), 1.79 (s), 1.05 (d, J = 7 Hz) ratio 1:3:3; ^{13}C NMR δ 163.7,

144.4, 71.6, 29.1, 17.0, 15.7] consistent with the presence of the unsaturated lactone 51. Continued concentration under high vacuum to constant weight left 0.0641 g (0.258 mmol, 33%) of acid 58 as an oil. The ^{1}H NMR and ^{13}C NMR spectra recorded on this material lacked the signals earlier associated with lactone 51. The spectra of 58 were identical with those reported below for acid 59, the enantiomer of 58.

(+) (2R,3S,4S)-5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid,Methyl Ester (62). Esterification of 0.0651 g (0.258 mmol) of acid 58 afforded after distillation 0.0376 g (0.141 mmol, 55%) of ester 62 identical by IR, ^{1}H NMR, ^{13}C NMR and GC with 63, its enantiomer. This sample of 62 was contaminated by 21% (GC) of ester 61 derived in the aldol from aldehyde 40 and concentrated during the purification of the amide 43 used in the preparation of acid 58. The GC conditions were 30 M SE-54, 180°C, hydrogen at 10 psi, 62 4.99 min, 61 4.78 min. The rotation of this sample was $[\alpha]_D$ +5.80° (c 3.76, CH_2Cl_2).

Anal. calcd. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.29; H, 8.38.

(-) (2S,3R,4R)-5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid (59, Table 13, Entry 9). Hydrolysis of 0.651 (1.86 mmol) of unpurified amide 44 and its aldol diastereomers

under the standard conditions gave after concentration to constant weight under high vacuum 0.159 g (0.628 mmol, 33%) of acid 59 as an oil. IR (neat) 3640-2500 (br), 2970, 2880, 1700, 1450, 1200, 1100, 1070, 975, 780, 750, 690 cm^{-1}; ^1H NMR (CCl_4) δ 7.25 (s, 5H, C_6H_5), 7.08 (br s, 2H, OH's), 4.44 (s, 2H, OCH_2Ph), 3.83 (dd, J = 4 Hz, J = 8 Hz, 1H, CHOH), 3.50 (d, J = 5 Hz, 2H, $CHCH_2O$), 2.54 (dq, J_d = 4 Hz, J_q = 7 Hz, 1H, $COCHCH_3$), 2.0-1.5 (m, 1H, $CHCH_2O$), 1.14, 0.90 both (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR (CCl_4) δ 179.8 (C=O), 137.8, 128.0, 127.3 (C_6H_5), 74.4, 73.1, 73.0 ($CHOHCHCH_2OCH_2Ph$), 42.1 (COCH), 35.8 ($CHCH_2O$), 14.0 (CH_3CHCH_2O), 9.6 (CH_3CHCO). The optical rotation of this sample of acid 59 was $[\alpha]_D$ -20.9° (c 3.81, CH_2Cl_2).

(-) (2S,3R,4R)-5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid, Methyl Ester (63). Esterification of 0.158 g (0.627 mmol) of unpurified acid 59 afforded after distillation (90°C/0.005 mm) 0.107 g (0.403 mmol, 64%) of 63 as an oil contaminated with 10.7% (GC) of ester 64 derived in the aldol from aldehyde 41. The yield of 63 overall from the condensation of amide 35 with aldehyde 40 was 19%. IR (neat) 3600-3200 (br), 2980, 2960, 2890, 1730, 1450, 1435, 1270, 1205, 1095, 1070, 995, 735, 695 cm^{-1}; ^1H NMR (CCl_4) δ 7.26 (s, 5H,

$C_6\underline{H}_5$), 4.40 (s, 2H, $OC\underline{H}_2Ph$), 3.8-3.5 (m, 1H, $C\underline{H}OH$), 3.60 (s, 3H, $OC\underline{H}_3$), 3.49 (d, J = 5 Hz, 2H, $C\underline{H}_2OBZ$), 3.15 (br s, 1H, $O\underline{H}$), 2.50 (dq, J_d = 5 Hz, J_q = 7 Hz, 1H, $COC\underline{H}CH_3$), 1.80 (m, 1H, $C\underline{H}CH_2OBZ$), 1.12, 0.90 each (d, J = 7 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (CCl_4) δ 175.1 ($\underline{C}$=O), 138.1, 128.0, 127.2 ($\underline{C}_6H_5$), 74.2, 73.2, 73.0 ($\underline{C}HOH$, $\underline{C}H_2O\underline{C}H_2Ph$), 51.0 ($OC\underline{H}_3$), 42.1 ($CO\underline{C}H$), 35.9 ($\underline{C}HCH_2O$), 14.1 ($\underline{C}H_3CHCH_2O$), 10.1 ($COCH\underline{C}H_3$). The GC conditions were 30 M SE-54, 180°C, hydrogen at 10 psi, 63 5.00 min, 64 4.78 min. The optical rotation of this sample containing 10.7% 64 was $[\alpha]_D$ -5.73° (c 10.7, CH_2Cl_2).

(+) (2S,3R,4S)-5-Benzyloxy-3-hydroxy-2,4-dimethyl pentanoic Acid (60, Table 13, Entry 10). In a modification of the general hydrolysis procedure, necessitated because of presumed cleavage of the benzyl ether, 0.102 g (0.292 mmol) of pure amide 45 was dissolved in 2.5 mL of p-dioxane. To this solution was added 3 mL of 2.4 M HCl (7.20 mmol). This mixture was heated to reflux for 3 h. The reaction was then quenched with saturated sodium bicarbonate solution until CO_2 evolution ceased. The basic layer was washed with ether then carefully acidified with concentrated hydrochloric acid. The product was extracted into ether, concentrated, dissolved in methylene chloride, dried over magnesium sulfate and

filtered. Concentration under vacuum afforded 0.0601 g (0.238 mmol, 82%) of acid 60. IR (neat) 3640-2450 (br), 2980, 1710, 1455, 1370, 1210, 1100, 980, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (s, 5H, C_6H_5), 6.90 (br s, 2H, OH's), 4.44 (s, 2H, OCH_2Ph), 3.93 (dd, J = 4 Hz, J = 7 Hz, 1H, CHOH), 3.47 (d, J = 5 Hz, 2H, CH_2OBZ), 2.65 (pentuplet, J = 7 Hz, 1H, COCH), 2.1-1.7 (m, 1H, CH_3CHCH_2O), 1.25, 1.01 each (d, J = 7 Hz, 3H, CH_3). The optical rotation of this sample was $[\alpha]_D$ +13.7° (c 2.68, CH_2Cl_2).

(+) (2S,3R,4S)-5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid,Methyl Ester (64). Esterification of 0.0601 g (0.238 mmol) of acid 60 under the usual conditions afforded after distillation (130°C/0.005 mm) 0.0565 g (0.212 mmol, 89%) of 64 as an oil containing 2% (GC) of 63 derived in the aldol from aldehyde 40. The yield of ester 64 overall from the aldol condensation of amide 35 with 41 was 56%. IR (neat) 3600-3250 (br), 2960, 2890, 1730, 1455, 1435, 1275, 1200, 1100, 990, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (s, 5H, C_6H_5), 4.47 (s, 2H, OCH_2Ph), 3.87 (dd, J = 4 Hz, J = 7 Hz, 1H, CHOH), 3.63 (s, 3H, OCH_3), 3.43 (d, J = 5 Hz, 2H, CH_2OBZ), 1.9-1.5 (m, 1H, $CHCH_2OBZ$), 1.21, 0.97 each (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 176.1 (C=O), 138.0, 128.4,

127.6, 127.5 ($\underline{C}_6H_5$), 74.5 ($\underline{C}HOH$), 74.5, 73.3 ($\underline{C}H_2O\underline{C}H_2Ph$), 51.6 ($O\underline{C}H_3$), 43.1 ($CO\underline{C}H$), 36.1 ($\underline{C}HCH_2OBZ$), 13.3, 11.2 ($\underline{C}H_3$). The GC conditions were 30 M SE-54, 180°C, hydrogen at 10 psi, 64 4.78 min, 63 5.00 min. The optical rotation of this sample of 64 was $[\alpha]_D$ +7.14° (c 2.20, CH_2Cl_2).

(2R,3R,4S)-1-Benzyloxy-3,5-dihydroxy-2,4-dimethylpentane (65). A solution of 0.0411 g (1.08 mmol) of lithium aluminium hydride (LAH) in ether was added to a cold ether solution of 0.144 g (0.542 mmol) of ester 61. After 3 h at room temperature the excess LAH was destroyed with Glauber's salt (sodium sulfate decahydrate). The white suspension was filtered and the filtrate concentrated to afford 0.111 g (0.464 mmol, 86%) of diol 65 as an oil. IR (neat) 3600-3200 (br), 3035, 2970, 2940, 2880, 1450, 1365, 1090, 1070, 1030, 975, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (s, 5H, $C_6\underline{H}_5$), 4.4 (s, 2H, $O\underline{C}H_2Ph$), 3.64 (t, J = 5 Hz, 1H, $C\underline{H}OH$), 3.50 (d, J = 5 Hz, 2H, $C\underline{H}_2OBZ$), 3.37 (d, J = 5 Hz, 2H, $HOC\underline{H}_2$), 2.84 (br s, 2H, $O\underline{H}$'s), 2.2-1.6 (m, 2H, $C\underline{H}$'s), 1.03, 0.95 each (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.0, 128.2, 127.4 ($\underline{C}_6H_5$), 75.5, 74.1, 73.1 ($\underline{C}HOH$, $\underline{C}H_2O\underline{C}H_2Ph$), 66.5 ($HO\underline{C}H_2$), 37.4, 36.1 (2 $\underline{C}H$'s), 12.4, 11.2 (2 $\underline{C}H_3$'s).

(2R,3R,4S)-1,3,5-Tribenzyloxy-2,4-dimethylpentane

(66). A solution of 0.0561 g (0.235 mmol) of diol 65 in THF was added to a suspension of potassium hydride (0.05 g, 1 mmol) in 5 mL of THF at 0°C. After 30 min, 84 μL (0.71 mmol) of benzyl bromide was added to this mixture. After warming to room temperature the reaction was heated at reflux for 30 min. After cooling, the excess potassium hydride was quenched with Glauber's salt. After dilution with ether, the organic layer was washed with water, dried over magnesium sulfate, filtered and concentrated to afford 0.111 g of 66 as an oil contaminated with benzyl bromide. Flash chromatography of 0.0551 g of this oil eluting with 10% ethyl acetate in hexane gave 0.0519 g (0.12 mmol, 100%) of triether 66. IR (neat) 3100, 3080, 3040, 2970, 2940, 2870, 1495, 1453, 1365, 1095, 1070, 1030, 735, 695 cm^{-1}; ^1H NMR (CCl_4) δ 7.22 (s, 5H, $C_6\underline{H}_5$), 4.47 (s, 2H, $CHOC\underline{H}_2Ph$), 4.38 (s, 4H, 2 $CH_2OC\underline{H}_2Ph$), 3.58 (t, J = 5 Hz, 1H, $C\underline{H}OBZ$), 3.28 (m, 4H, 2 $C\underline{H}_2OBZ$), 2.01 (heptuplet, J = 6 Hz, 2H, 2 $C\underline{H}CH_3$), 0.97 (d, J = 7 Hz, 6H, 2 $C\underline{H}_3$); ^{13}C NMR (CCl_4) δ 139.3 and 138.3 [ratio 1:2, (i)-$\underline{C}_6H_5$], 127.8, 217.6, 127.0 ($\underline{C}_6H_5$), 80.0 ($\underline{C}HOBZ$), 74.2 ($CHO\underline{C}H_2Ph$), 72.8, 72.5 (2 $\underline{C}H_2O\underline{C}H_2Ph$), 36.3 (2 $\underline{C}HCH_3$), 12.7 (2 $\underline{C}H_3$).

1-[(4S)-(2-Propyl)-oxazolidin-3-yl]acetic Acid (67). ℓ-Valinol (1.03 g, 9.98 mmol) was condensed with 0.3 g

(10 mmol) of paraformaldehyde in benzene with azeotropic removal of water. After cooling the solvent was replaced with methylene chloride. After cooling to 0°C, 0.785 g (10.0 mmol) of acetyl chloride in methylene chloride was added slowly. After 20 min, the reaction was neutralized carefully with saturated sodium bicarbonate solution. The acetamide 67 was isolated by extraction into methylene chloride. The organic phase was dried over magnesium sulfate, filtered and concentrated to afford after distillation (80°C, 0.005 mm) 1.01 g (6.46 mmol, 65%) of the valinol-derived acetamide 67 as a colorless oil. IR (neat) 3500 (br weak), 2970, 2880, 1645, 1415, 1210, 1180, 1090, 940 cm^{-1}; ^{1}H NMR (CCl_4) δ 4.86 (br s, 1H, OCH_2-N), 4.77 (br s, 1H, OCH_2-N), 3.85 (br s, 3H, OCH_2-CH-N), 2.05 [m, 1H, NCH-$CH(CH_3)_2$], 1.95 (s, 3H, CO-CH_3), 1.1-0.7 [m, 6H, $CH(CH_3)_2$]; ^{13}C NMR (CCl_4) δ 166.8 (167.9) (C=O), 78.9 (OCH_2-N), 67.6 (67.8) (OCH_2-CH-N), 59.1 (60.8) (OCH_2-CH-N), 28.8 (30.5) [N-CH-$CH(CH_3)_2$], 22.2 (21.6) (CO-CH_3), 18.6, 16.4, 16.2 [$CH(CH_3)_2$]. The rotation of the distilled acetamide 67 was $[\alpha]_D$ +16.4° (c 1.31, $CHCl_3$).

Anal. calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.18; H, 9.51; N, 8.98.

1-[(4S)-(2-Propyl)-oxazolidin-3-yl]-2-methylthio-

acetic Acid (69). Water was azeotropically removed from the condensation of 0.62 g (6.0 mmol) of ℓ-valinol and 0.18 g (6.0 mmol) of paraformaldehyde in benzene. After cooling the solvent was replaced with methylene chloride. To this solution at 0°C was added a solution of 0.73 g (5.9 mmol) of 2-methylthioacetyl chloride[89] in methylene chloride. In a manner identical to that described for acetamide 67, the methylthioacetamide 69 was isolated. Distillation (100°C/0.005 mm) afforded 0.92 g (4.5 mmol, 77%) of the valinol-derived methylthioacetamide 69 as a colorless oil. IR (neat) 2960, 2930, 2880, 1720 (weak), 1645, 1425, 1210, 1180, 1150, 1120, 1090, 1070, 980, 935, 845, 795, 790, 735, 710, 675 cm^{-1}; ^{1}H NMR (CCl_4) δ 4.92 (m, 2H, O-C$\underline{H}_2$-N), 4.1-3.7 (m, 3H, O-C$\underline{H}_2$-C$\underline{H}$-N), 3.04 (s, 2H, CO-C$\underline{H}_2$-S-), 2.16 (s, 3H, S-C$\underline{H}_3$), 1.1-0.7 [m, 6H, CH(-C$\underline{H}_3$)$_2$]; ^{13}C NMR (CCl_4) δ 165.2 (C$\underline{O}$), 78.8 (O-C$\underline{H}_2$-C$\underline{H}$-N), 3.04 67.5 (O-C$\underline{H}_2$-CH-N), 59.6 (O-CH$_2$-C$\underline{H}$-N), 36.1 (CO-C$\underline{H}_2$-S), 29.1 (C$\underline{H}$-Me$_2$), 19.0, 16.9 [CH(-C$\underline{H}_3$)$_2$], 15.0 (S-C$\underline{H}_3$). The optical rotation of distilled amide 69 was $[\alpha]_D$ +53.0° (c 7.11, $CHCl_3$).

(2S,3R)-1-[(4S)-(2-Propyl)-oxazolidin-3-yl]-2-methylthio-3-hydroxy-4-methylpentanoic Acid (70). Aldol condensation of the zirconocenyl enolate generated from 0.101 g (0.496 mmol) of the methylthioacetamide 69 with 0.461 g

(0.638 mmol) of isobutyraldehyde (16c) according to the general recipe described in Procedure A afforded after workup 0.0979 g of an oil containing hydroxy amide 70 contaminated with some starting amide 69. The diastereomer ratio (GC) of the unpurified aldol adduct was 70 83.8% : E_2 6.0% : T_1 3.4% : T_2 6.8%. The corresponding lithium-mediated aldol condensation had a product distribution of 70 29.1% : E_2 12.1% : T_1 24.1% : T_2 34.7%. The GC conditions were 25 M Carbowax 20M, 120°C for 5 min then 200°C for 2 min, hydrogen at 13 psi, 70 31.94 min, E_2 32.06 min, T_1 32.24 min, T_2 32.74 min. This material was desulfurized directly to amide 68 without further characterization or purification.

(3S)-1-[(4S)-(2-Propyl)-ozazolidin-3-yl]-3-hydroxy-4-methylpentanoic Acid (68). Unpurified methylthioamide 70 (0.0979 g) contaminated with 69 in 5 mL of dry acetone was treated with 1 g of Raney nickel, added as a slurry, and heated to reflux for 20 min.[90] After cooling to room temperature, the suspension was filtered through Celite. Concentration of the filtrate afforded 0.0721 g of an oil containing hydroxy amide 68 contaminated with acetamide 67. The desired 68 was not purified at this stage. The unpurified product yielded the following spectral data. IR (neat) 3600-3200 (br), 2970, 2880,

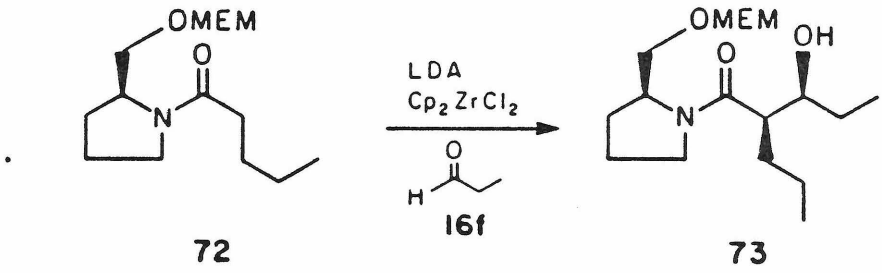
1650, 1420, 1210, 1185, 1125, 1095, 1075, 940 cm^{-1}; ^1H NMR (CCl_4) δ 5.05-4.6 (m, 2H, OCH_2N), 4.83 (br s, 4H), 2.5-1.9 (m, 4H), 1.9-1.3 (m, 1H), 1.3-0.7 (m, 12H, 4 CH_3's). The unpurified product of the desulfurization of hydroxy amide 70 had a diastereomer ratio (GC) of 68 89.8% : 3-epi-68 10.2%. The material prepared from the condensation of the zirconocenyl enolate of acetamide 67 with isobutyraldehyde had a ratio of 68 67.1% : 3-epi-68 32.9% while the material prepared from the lithium enolate of 67 had a ratio of 68 62% : 3-epi-68 38%. The GC conditions were 30 M SE-54, 150°C, hydrogen at 15 psi, 68 5.07 min, 3-epi-68 4.96 min.

(-) (3S)-3-Hydroxy-4-methylpentanoic Acid (71). Hydrolysis of the unpurified hydroxy amide 68 derived from the sulfur-containing 70 afforded 0.0151 g (0.114 mmol) of acid 71, an overall yield of 23% from the methylthioacetamide 71. This sample of 71 was identical except for rotation with material prepared by Taber.[48] IR (neat) 3600-2500 (br), 2970, 2880, 1720, 1465, 1410, 1280, 1180, 1045, 1010, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (br s, 2H, OH's), 3.80 (dt, J_d = 7 Hz, J_t = 5 Hz, 1H, CHOH), 2.50 (m, 2H, $COCH_2$), 1.75 [octuplet, J = 7 Hz, 1H, $CH(CH_3)_2$], 0.95 and 0.91 each (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.0 (C=O), 72.9 (CHOH), 38.4 ($COCH_2$),

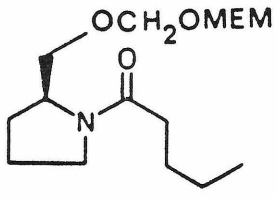
38.4 ($CO\underline{C}H_2$), 33.2 [$(CH_3)_2\underline{C}H$], 18.3 and 17.7 (2 CH_3's). Based on the diastereomeric composition of amide 68 this sample of hydroxy acid 71 should be 79.5% optically pure. This sample had an optical rotation of $[\alpha]_D$ -32.4° (c 1.50, $CHCl_3$). Completely optically pure 71 should therefore exhibit an optical rotation of -40.8°C. This compares well with the value of $[\alpha]_D$ +40.5° (c 0.63, $CHCl_3$) reported for the R enantiomer of 71.[48]

1-[(2S)-Methoxyethoxymethoxypyrrolid-1-yl]pentanoic Acid (72). 8.45 g (70.0 mmol) of valeryl chloride in methylene chloride was added slowly to a solution of ℓ-prolinol (10.23 g, 100 mmol) in methylene chloride at 0°C. After the addition was complete the reaction was warmed and the solvent removed by distillation. After cooling the mixture was dispersed in water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate, filtered and concentrated to afford 9.93 g of an oil containing substantial amounts of ester (IR). This mixture was stirred vigorously for 6 h with 20% sodium hydroxide solution. Isolation of the product left 8.23 g (44.4 mmol, 63%) of the intermediate hydroxyamide free of ester. An optimized procedure would use ℓ-prolinol as the limiting reagent. The hydroxyamide in THF was slowly added to

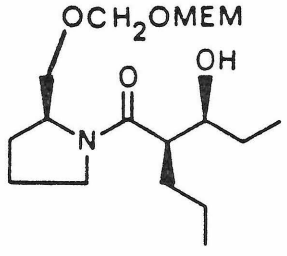
a slight excess of sodium hydride in THF at 0°C. After gas evolution had ceased, methoxyethoxymethyl chloride (MEMCl) (7.2 g, 58 mmol) was added.[53] The reaction was allowed to stir overnight at room temperature. The suspension was filtered and the solid cautiously quenched with Glauber's salt under ether. After filtration, the combined filtrate was concentrated and distilled (175°C/ 0.005 mm) to afford 11.6 g (41.6 mmol, 94%) of the prolinol-derived valeramide 72 as a faintly colored oil, 59% yield from valeryl chloride. Redistillation gave an analytical sample. GC analysis revealed approximately 16% of a second component which on the basis of the NMR was assigned the structure 72a. This side product results from $MEMOCH_2Cl$, a contaminant in the MEMCl. The yield is based on 84 mole % of 72 and 16 mole % of 72a. The GC conditions were 30 M SE-54, 200°C, hydrogen at 15 psi, 72 4.07 min, 72a, 7.28 min. IR (neat) 2960, 2940, 2880, 1640, 1420, 1200, 1155, 1048, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.68 (s, 2H, $OC\underline{H}_2O$) (4.80, singlets for 16% 72a), 4.4-3.9 (m, 1H), 3.7-3.3 (m, 8H), 3.35 (s, 3H, $OC\underline{H}_3$), 2.5-2.1 (m, 2H), 1.95 (br s, 4H), 1.8-1.1 (m, 4H), 1.1-0.8 (m, 3H, $C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 171.6 (171.9) ($\underline{C}$=O), 95.3 ($O\underline{C}H_2O$), 71.8 (68.6) ($NCH\underline{C}H_2O$), 66.4, 67.4 ($O\underline{C}H_2\underline{C}H_2O$), 58.5 ($O\underline{C}H_3$), 56.2 (56.6) ($N\underline{C}H$), 47.0 (45.2)



72 16f 73



72a



73a

(NCH_2), 34.3 (33.6) ($COCH_2$), 27.3 ($NCHCH_2CH_2$), 26.6 ($COCH_2CH_2$), 23.8 (NCH_2CH_2), 22.2 (21.5) (CH_3CH_2), 14.0 (CH_3CH_2). The optical rotation of this sample of distilled amide 72 was $[\alpha]_D$ -56.0° (c 8.59, $CHCl_3$). The rotation of another sample containing about 5% of 72a was $[\alpha]_D$ -56.4° (c 12.6, $CHCl_3$).

Anal. calcd. for 84% $C_{14}H_{27}O_4N$ and 16% $C_{15}H_{29}O_5N$: C, 61.14; H, 9.90. Found: C, 60.98; H, 10.13.

(2R,3S)-1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-3-hydroxy-3-propylpentanoic Acid (73). The title hydroxyamide 73 was prepared according to the general recipe for zirconium-mediated aldol condensation described in Procedure A from 10.0 g (35.9 mmol) of the prolinol-derived valeramide 72 (containing 16% 72a) and 2.71 g (46.7 mmol) of n-propionaldehyde (16f). Workup of the reaction afforded 11.2 g (33.4 mmol, 93%) of an orange oil containing about 6% (GC) of unconverted amide 72. This oil was hydrolyzed directly to the hydroxyacid 74 without purification. The unpurified aldol adduct 73 afforded the following spectra data. IR (neat) 3600-3200 (br), 2960, 2940, 2880, 1620, 1440, 1120, 1050, 985, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.67 (s, 2H, OCH_2O), 4.6-3.8 (m, 2H), 3.8-3.3 (m, 9H), 3.35 (s, 3H, OCH_3), 2.9-2.4 (m, 1H), 1.93 (br s, 4H), 1.8-1.1 (m, 6H), 1.1-0.67 (m,

6H, 2 CH_3's). The signals for the extra OCH_2O of 73a appear at 4.76. ^{13}C NMR ($CDCl_3$) δ 175.2 (176.5) (C=O), 95.6 (95.4) (OCH_2O), 73.1 (73.4) (CHOH), 71.5 ($NCHCH_2O$), 67.3 and 66.7 (68.9 and 66.9) (OCH_2CH_2O), 58.7 (OCH_3), 56.3 (56.8) (NCH), 47.6 and 47.0 (45.7 and 45.0) (NCH_2 and COCH), 28.5, 28.0, 27.4, 27.0 (CH_3CH_2CHOH, $CH_3CH_2CH_2$, $NCHCH_2$), 23.8 (NCH_2CH_2), 20.5 (21.7) ($CH_3CH_2CH_2$), 14.2 ($CH_3CH_2CH_2$), 10.3 (CH_3CH_2CHOH). The diastereomer ratio (GC, Fig. 15) of the unpurified aldol adduct was T_1 0.5% : T_2 1.38% : E_1 0.4% : 73 97.8%. The product distribution of the corresponding lithium mediated aldol condensation was T_1 27.5% : T_2 15.5% : E_1 26.5% : 73 36.5%. The diastereomer ratio obtained in 73a mirrors that obtained in 75. The GC conditions were 25 M Carbowax 20M, 210°C, hydrogen at 10 psi, T_1 16.26 min, T_2 16.50 min, E_1 18.49 min, 73 20.36 min, 73a 42.13 min.

(2R,3S)-3-Hydroxy-2-propylpentanoic Acid (74). Hydrolysis of 10.9 g (32.6 mmol) of hydroxyamide 73 according to the general procedure afforded 3.68 g (23.0 mmol, 70.5%) of acid 74 as a colorless oil. Distillation (120°C/0.001 mm) provided an analytical sample. IR (neat) 3600-2500 (br), 2970, 2950, 2885, 1710, 1465, 1455, 1250, 1195, 1105, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10 (br s, 2H, OH's), 3.75 (dt, J_d = 6.3 Hz,

J_t = 5.4 Hz, 1H, C<u>H</u>OH), 2.49 (dt, J_d = 7.5 Hz, J_t = 5.4 Hz, 1H, COC<u>H</u>CHOH), 1.9-1.1 (m, 6H, 3 CH_2's), 0.97 (br t, 6H, 2 CH_3's); ^{13}C NMR ($CDCl_3$) δ 179.7 (<u>C</u>=O), 73.6 (<u>C</u>HOH), 50.6 (CO<u>C</u>HCHOH), 29.1 (CHOH-<u>C</u>H_2CH_3), 26.9 (COCH<u>C</u>H_2), 20.7 (CH_3<u>C</u>H_2CH_2), 13.8 (<u>C</u>$H_3CH_2CH_2$), 10.1 (<u>C</u>H_3CH_2CHOH). GC analysis of the methylester 75 prepared from this sample of acid 74 revealed 1.8% of the threo diastereomer. The optical rotation of this sample of acid 74 was $[\alpha]_D$ +4.18° (<u>c</u> 2.39, $CHCl_3$).

<u>Anal.</u> calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.93; H, 10.33.

<u>Erythro-3-hydroxy-2-propylpentanoic Acid,Methyl Ester (75)</u>. The racemic ester was prepared according to the general Procedure A from 1.08 g (9.33 mmol) of methyl valerate and 0.704 g (12.1 mmol) of <u>n</u>-propionaldehyde (16f) to afford after distillation (70°C/0.001 mm) 1.06 g (6.10 mmol, 65%) of the racemic hydroxy ester 75 as an oil containing 13.7% of the threo diastereomer, identical by GC and spectra with the optically active 75 described below.

<u>(2R,3S)-3-Hydroxy-2-propylpentanoic Acid,Methyl Ester (75)</u>. Esterification of 3.15 g (19.7 mmol) of hydroxy acid 74 according to the general procedure afforded after distillation (70°C/0.001 mm) 2.84 g

(16.3 mmol, 83%) of optically active 75 as an oil, 55% overall yield from the prolinol-derived valeramide 72. IR (neat) 3600-3200 (br), 2970, 2950, 2885, 1738, 1467, 1440, 1365, 1245, 1200, 1170, 1105, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 3H, OCH_3) 3.8-3.6 (m, 1H, CHOH), 2.7 (br s, 1H, OH), 2.47 (dt, J_d = 8 Hz, J_t = 5 Hz, 1H, COCHCHOH), 1.8-1.1 (m, 6H, 3 CH_2's), 1.1-0.7 (br t, 6H, 2 CH_3's); ^{13}C NMR ($CDCl_3$) δ 174.8 (C=O), 73.0 (CHOH), 50.8 (OCH_3), 50.6 (COCHCHOH), 29.3 ($CHOHCH_2CH_3$), 27.3 ($COCHCH_2$), 20.8 ($CH_3CH_2CH_2$, 13.9 ($CH_3CH_2CH_2$), 10.1 (CH_3CH_2CHOH). The diastereomer ratio (GC) of this ester was erythro 98.2% : threo 2.8%. The GC conditions were 30 M SE-54, 70°C/5 min then 5°/min to 200°C, hydrogen at 10 psi, threo 6.63 min, erythro 7.43 min. The optical rotation of this sample of ester 75 was $[\alpha]_D$ +6.99° (c 7.12, $CHCl_3$).

Anal. calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.90; H, 10.33.

(2R,3S)-3-[Tetrahydropyran-2-yloxy]-2-propylpentanoic Acid,Methyl Ester (76). A solution of 2.49 g (14.3 mmol) of (+)-75 in 20 mL of methylene chloride with 1.81 g (21.5 mmol) of dihydropyran and 0.358 g (1.43 mmol) of pyridinium tosylate (PPTS)[91] was stirred for 12 h.[76] The reaction was washed twice with 20 mL of water, dried

over magnesium sulfate, filtered and concentrated to give 3.68 g (14.3 mmol, 99.6%) of ester 76 as a mixture of tetrahydropyranyl (THP)-diastereomers contaminated with 3% (GC) of residual hydroxy ester 75. IR (neat) 2960, 2880, 1738, 1468, 1456, 1440, 1380, 1355, 1200, 1168, 1133, 1068, 1035, 1022, 1000, 900, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.63 (br d, 1H, OCHO), 4.0-3.2 (m, 3H), 3.63 (s, 3H, OCH_3), 2.8-2.4 (m, 1H, $COCHCH_2$), 1.9-1.1 (m, 12H, 6 CH_2's), 1.05-1.07 (m, 6H, 2 CH_3's); ^{13}C NMR ($CDCl_3$) δ 174.5 (C=O), 98.3 and 97.3 (OCHO), 79.0 and 77.7 (CHOTHP), 62.4 (CH_2O), 50.9 (OCH_3), 49.4 and 48.3 ($COCHCH_2$), 30.7, 30.4 and 30.0, 25.3, 23.8, 20.9, 19.6 (6 CH_2's), 13.7 ($CH_2CH_2CH_3$), 9.6 and 8.6 ($CH_3CH_2CHOTHP$). This sample was reduced directly to alcohol 77 without purification. The THP diastereomers did not resolve upon GC analysis. The GC conditions were 30 M SE-54, 70°C for 2 min then 5°C/min to 200°C, 76 16.33 min.

(2S,3S)-3-[Tetrahydropyran-2-yloxy]-2-propylpentan-1-ol (77). An ether solution of 3.16 g (12.2 mmol) of ester 76 was added slowly to a stirred solution of LAH (0.67 g, 6.7 mmol) in ether at 0°C.[76] After the addition was complete, the reaction was warmed to room temperature and stirred for 1 h. The excess LAH was destroyed cautiously with Glauber's salt until a white solid

remained. The product was isolated by filtration. Concentration of the ether filtrate afforded 2.68 g (11.6 mmol, 95%) of alcohol 77 as a mixture of THP-diastereomers. IR (neat) 3600-3200 (br), 2960, 2880, 1465, 1455, 1440, 1380, 1355, 1203, 1165, 1135, 1115, 1080, 1020, 1000, 900, 870, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.66 (br s, 0.5H) and 4.42 (br d, J = 6 Hz, 0.5H) (OC$\underline{H}$O), 4.1-2.8 (m, 6H), 2.1-1.2 (m, 13H), 1.1-0.8 (m, 6H, 2 CH_3's); ^{13}C NMR ($CDCl_3$) δ 100.9 and 97.3 (O$\underline{C}$HO), 81.3 and 80.4 ($\underline{C}$HOTHP), 64.8 and 63.7, 63.2 and 62.7 (HO$\underline{C}H_2$ and $CH_2\underline{C}H_2O$), 42.5 and 41.0 ($HOCH_2\underline{C}H$), 31.3 and 31.0 (THPOCH$\underline{C}H_2$), 29.4 and 27.6, 24.2 and 22.9, 19.7 [3 CH_2's (THP)], 25.3 and 25.1 ($CH_3CH_2\underline{C}H_2$), 21.2 and 20.7 ($\underline{C}H_3CH_2CH_2$), 14.2 ($\underline{C}H_3CH_2CH_2$), 11.0 and 10.5 ($THPOCHCH_2\underline{C}H_3$). The diastereomer ratio (GC) of the THP-diastereomer was 54:46. The GC conditions were 30 M SE-54, 70°C for 2 min then 5°C/min to 200°C, 77 16.43 min and 16.61 min.

(2S,3S)-3-[Tetrahydropyran-2-yloxy]-2-propylpentan-1-ol, p-Toluenesulfonic Acid Ester (78). Tosyl chloride (1.86 g, 9.80 mmol) was added as a solid to a solution of 2.05 g (8.91 mmol) of alcohol 77 in 20 mL of dry pyridine at 0°C.[76] After 24 h the reaction mixture was diluted with 50 mL of cold methylene chloride and washed with 25 mL of cold saturated sodium bicarbonate solution. The

organic phase was dried over magnesium sulfate, filtered, and concentrated to give 3.32 g of 78 as an orange oil which was not purified further. IR (neat) 2960, 2880, 1600, 1465, 1455, 1440, 1365, 1190, 1180, 1132, 1120, 1098, 1075, 1033, 1000, 960, 835, 812, 703, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H) (Ar-H), 4.46 (m, 1H, OCHO), 4.3-3.3 (m, 5H), 2.43 (s, 3H, CH_3-Ar), 2.1-1.1 (m, 13H), 1.1-0.7 (m, 6H, 2 CH_3's); ^{13}C NMR ($CDCl_3$) δ 144.6, 144.4, 133.1, 133.0, 129.7, 129.6, 127.8 ($-C_6H_4-$), 99.2 and 98.7 (OCHO), 78.9 and 78.6 (CHOTHP), 71.2 and 70.6 (CH_2OTs), 62.9 and 62.8 (CH_2CH_2O), 41.5 and 39.6 ($TsOCH_2CH$), 31.0 ($CH_3CH_2CHOTHP$), 28.8 and 28.4, 24.1 and 23.6, 19.9 (THP-CH_2's), 25.3 ($CH_3CH_2CH_2$), 21.5 and 20.0 ($CH_3CH_2CH_2$), 20.5 (CH_3-Ar), 14.1 ($CH_3CH_2CH_2$), 10.5 and 10.3 ($CH_3CH_2CHOTHP$).

(3S,4R)-3-[Tetrahydropyran-2-yloxy]-4-methylheptane (79). Sodium borohydride (0.60 g, 16 mmol) was added as a solid to a solution of 2.04 g (5.30 mmol) of tosylate 78 in 20 mL of dry dimethyl sulfoxide (DMSO).[92] This mixture was heated to 100°C for 3 h. After cooling to room temperature, water was carefully added until gas evolution ceased. The mixture was further diluted with 100 mL of water and extracted three times with 75 mL of ether. The organic phase was dried over magnesium

sulfate, filtered and concentrated to give 1.12 g of a colorless liquid displaying two phases. This mixture was filtered through 20 g of silica gel eluting with 10% ethyl acetate in hexane. The second 25 ml fraction was concentrated to afford after distillation (40°C/0.005 mm) 0.944 g (4.40 mmol, 83%) of THP-ether 79, in an overall yield of 76% from methyl ester 75. IR (neat) 2970,2950,2880, 1465, 1455, 1440, 1380, 1350, 1205, 1170, 1135, 1120, 1080, 1035, 1025, 1000, 960, 905, 870, 820, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.70 (br s, 1H, OC<u>H</u>O), 4.05-3.7 (m, 1H, C<u>H</u>OTHP), 3.7-3.2 (m, 2H, C<u>H</u>$_2$O), 2.1-1.1 (m, 13H), 1.1-0.7 (m, 9H, 3 CH_3's); ^{13}C NMR ($CDCl_3$) δ 98.6 and 97.2 (O<u>C</u>HO), 82.6 and 81.7 (<u>C</u>HOTHP), 62.4 (<u>C</u>H$_2$O), 36.1 and 35.0 (CH_3<u>C</u>H), 34.8 and 34.1 (CH_3<u>C</u>H$_2$CHOTHP), 31.0, 22.9 and 21.8, 19.8 (THP CH_2's), 25.5 (CH_3CH_2<u>C</u>H$_2$), 20.5 and 20.4 (CH_3<u>C</u>H$_2CH_2$), 14.2 (<u>C</u>H$_3CH_2CH_2$), 10.4 and 9.7 (<u>C</u>H$_3CH_2$CHOTHP). The ratio of the THP-diastereomers was 57:43. The GC conditions were 30 M SE-54, 70°C for 2 min then 5°C/min to 200°C, hydrogen at 15 psi, 79 10.53 min and 10.75 min. Redistillation afforded an analytical sample.

<u>Anal.</u> calcd. for $C_{13}H_{26}O_2$: C, 72.85;, H, 12.23. Found: C, 72.79; H, 12.17.

<u>(+)(3S,4R)-3-Hydroxy-4-methylheptane (80)</u>. The THP-blocking group was removed from 0.656 g (3.06 mmol) of ether 79 with 5 ml of concentrated hydrochloric acid at

room temperature for 5 min.[76] The reaction was diluted with 70 mL of water. The alcohol 80 was extracted into ether. The organic phase was dried over magnesium sulfate, filtered and concentrated to afford after distillation (130°C/ 90 mm) 0.2484 g of a colorless oil. This oil was chromatographed on 15 g of silica gel eluting with 600 mL of hexane followed by 10% ether in hexane. Concentration of the fractions containing pure 80 and distillation (85°C/ 15 mm) afforded 0.160 g (1.23 mmol, 40%) of the alcohol 80. IR (neat) 3600-3200 (br), 2960, 2940, 2880, 1465, 1455, 1375, 1175, 1105, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) (90 MHz) δ 3.32 (dt, $J_d = 7.5$ Hz, $J_t = 4.2$ Hz, 1H, C<u>H</u>OH), 1.7-1.1 (m, 8H), 1.1-0.7 (m, 9H, 3 CH_3's); (500 MHz, Fig.19) δ 3.343 (ddd, J = 8.85 Hz, J = 5.20 Hz, J = 3.65 Hz, C<u>H</u>OH); ^{13}C NMR ($CDCl_3$) δ 77.5 (<u>C</u>HOH), 38.2 (CH_3<u>C</u>H), 34.1 (CH_3<u>C</u>H_2CHOH), 26.1 (CH_3CH<u>C</u>H_2), 20.3 (CH_3<u>C</u>$H_2$$CH_2$), 15.3 (<u>C</u>$H_3$CH), 14.3 (<u>C</u>$H_3$$CH_2$$CH_2$), 10.3 (<u>C</u>$H_3$$CH_2$CHOH). The optical rotation of the distilled alcohol 80 was $[\alpha]_D$ +9.67° (<u>c</u> 8.1, hexane) [Lit.[75] $[\alpha]_D$ +9.75 (<u>c</u> 0.4, hexane)].

<u>Anal.</u> calcd. for $C_8H_{10}O$: C, 73.78; H, 13.93. Found: C, 73.63, H, 13.86

This sample of alcohol 80 was free of its (3<u>S</u>,4<u>S</u>)-diastereomer to the limits of detection (0.04%). The GC conditions were 30 M SE-54, 70°C, hydrogen at 15 psi,

(3S,4S) diastereomer 1.73 min, 80 1.95 min. An authentic mixture of 80 and its diastereomer was prepared by the Grignard reaction of 2-bromopentane with n-propionaldehyde. The diastereomer ratio of this condensation was (3SR,4SR) 50.4% : (3RS,4SR) 49.6%.

VI. References and Notes

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(7) The widely held practice of referring to E and T as the erythro and threo diastereomers respectively is not rigorously correct for all possible permutations of R_2 and R_3. The issue has been discussed by Heathcock.[8] We use the terms erythro for E and threo for T as illustrated in Scheme II.

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(77) Alcohol 82 prepared from the prolinol-derived amide 75 contained no trace of the minor diastereomer to the limits of GC detection (0.04%).

(78) Based on the 97.8:0.4 ratio of erythro diastereomers of 75, the alcohol 82 should be 99.2% enantiomerically pure. This affords a corrected value of +9.75° for optically pure material.

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(80) MeLi (5 equivalents) was added to the protected amide 84 at -78°C and maintained at -50°C for 14 h. Quenching was performed by adding the cold reaction mixture to vigorously stirred dilute HCl at 0°C. For a similar transformation see: Larchevaeque, M.; Ignatova, E.; Cuvigny, T. J. Organomet. Chem. 1979, 177, 5-15.

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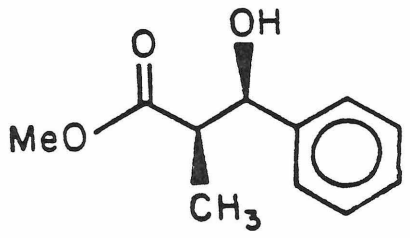
VII. APPENDIX I

IR, ^{1}H NMR and ^{13}C NMR

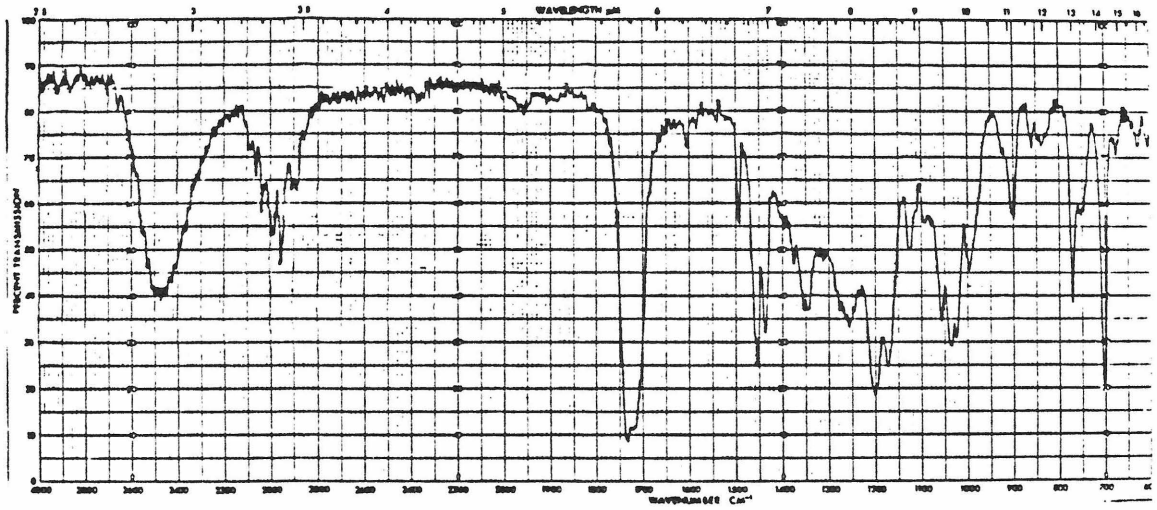
Spectral Catalog

Page 82



21a

Neat



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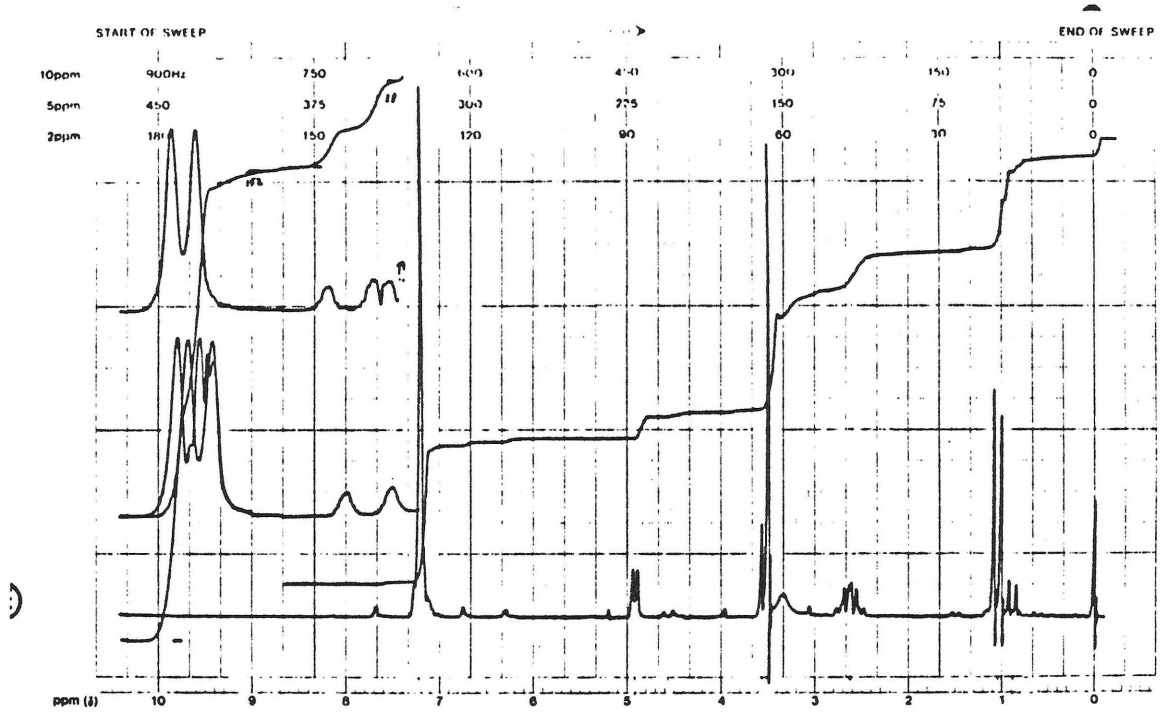

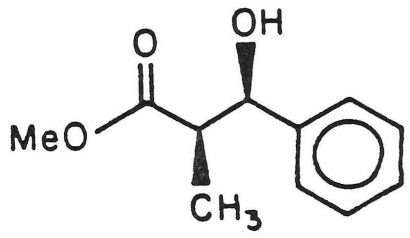

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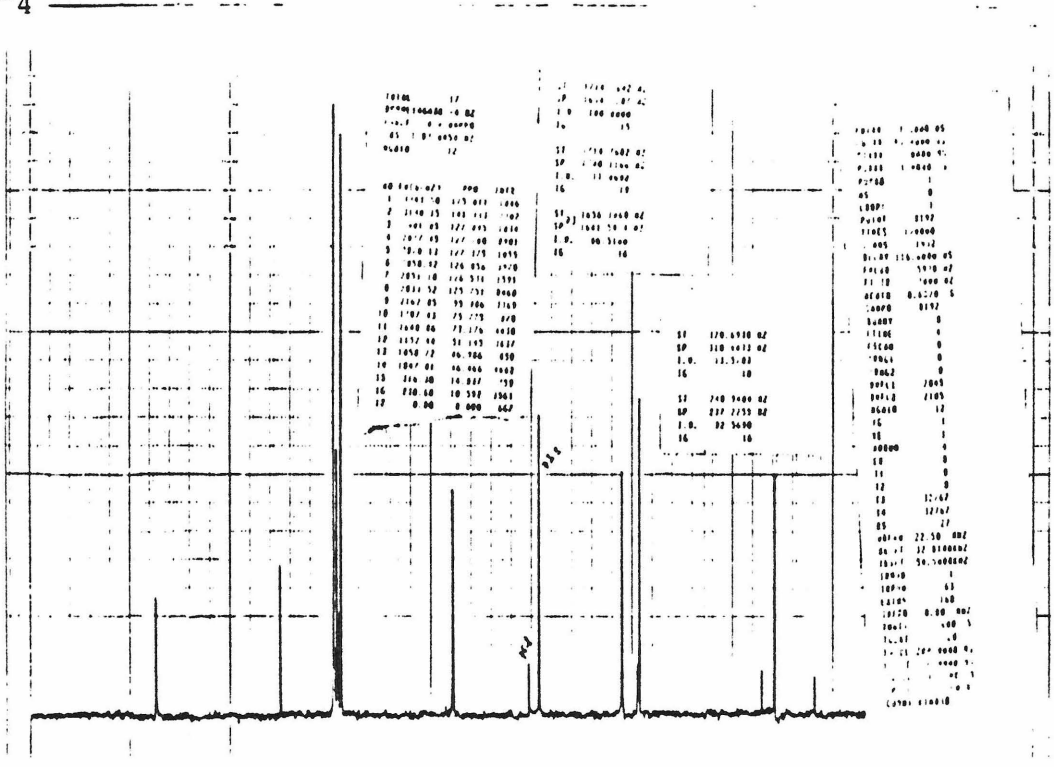

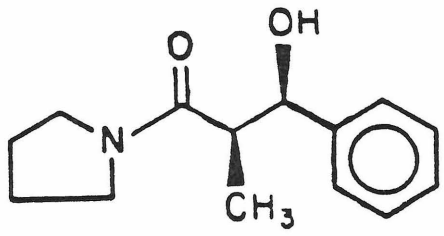

23a

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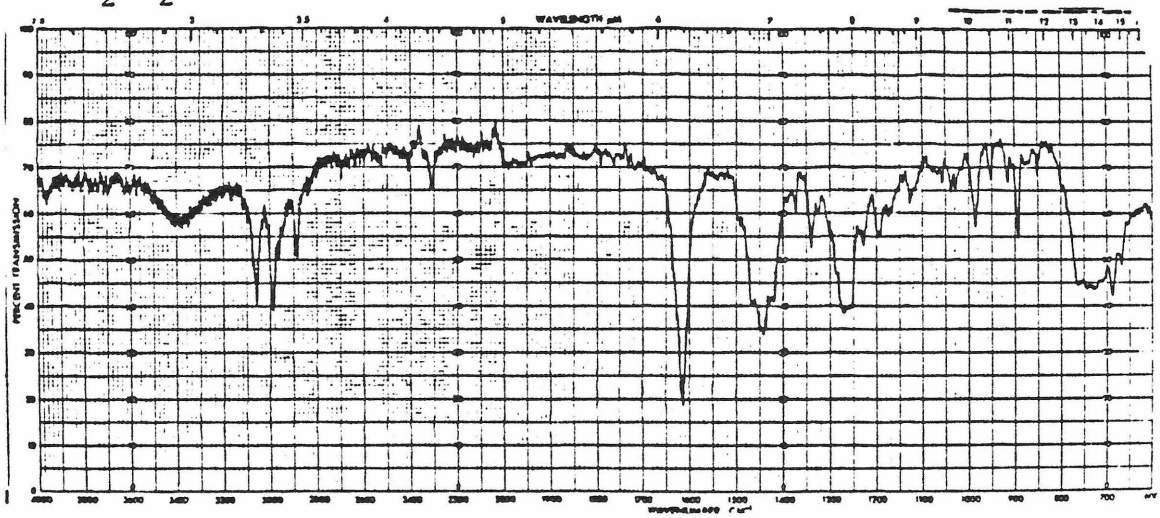

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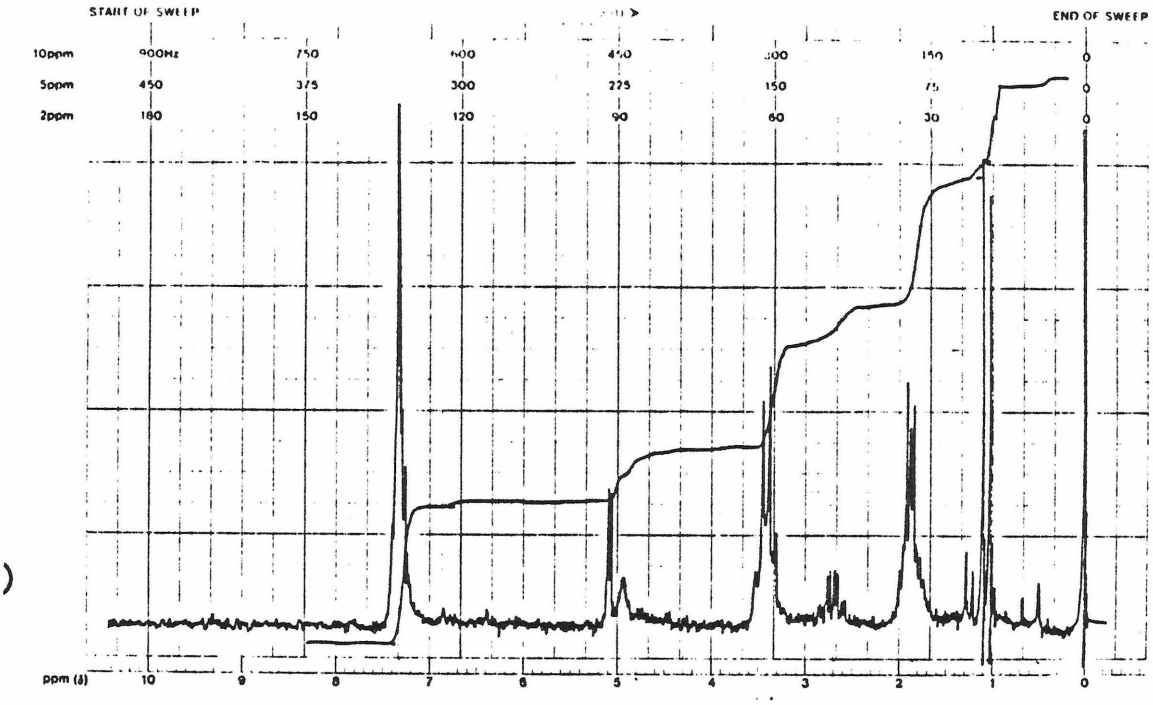
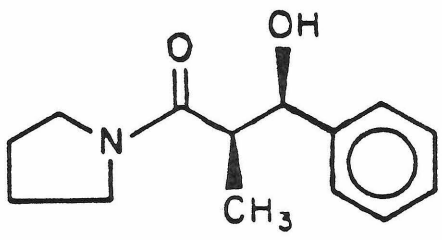
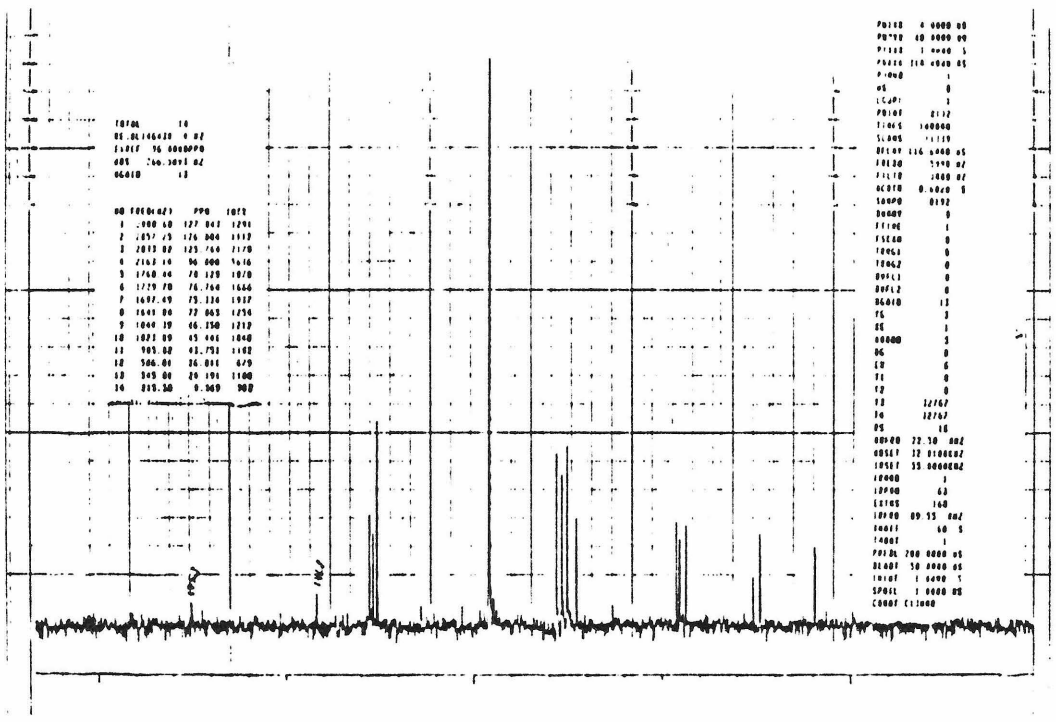




23a

CCl_4 $CDCl_3$



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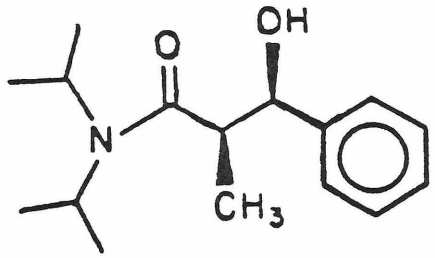
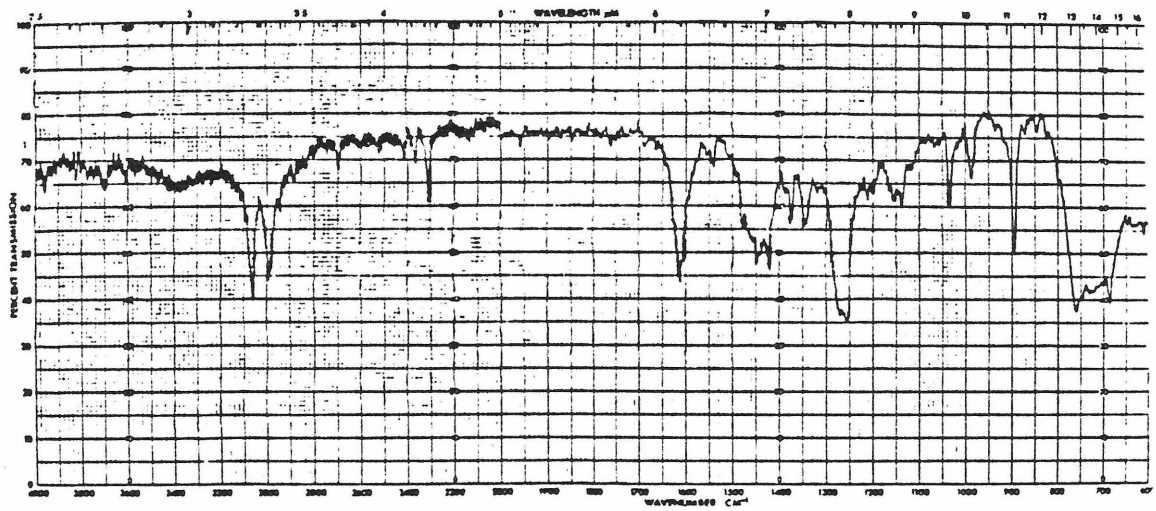


24a

CH_2Cl_2



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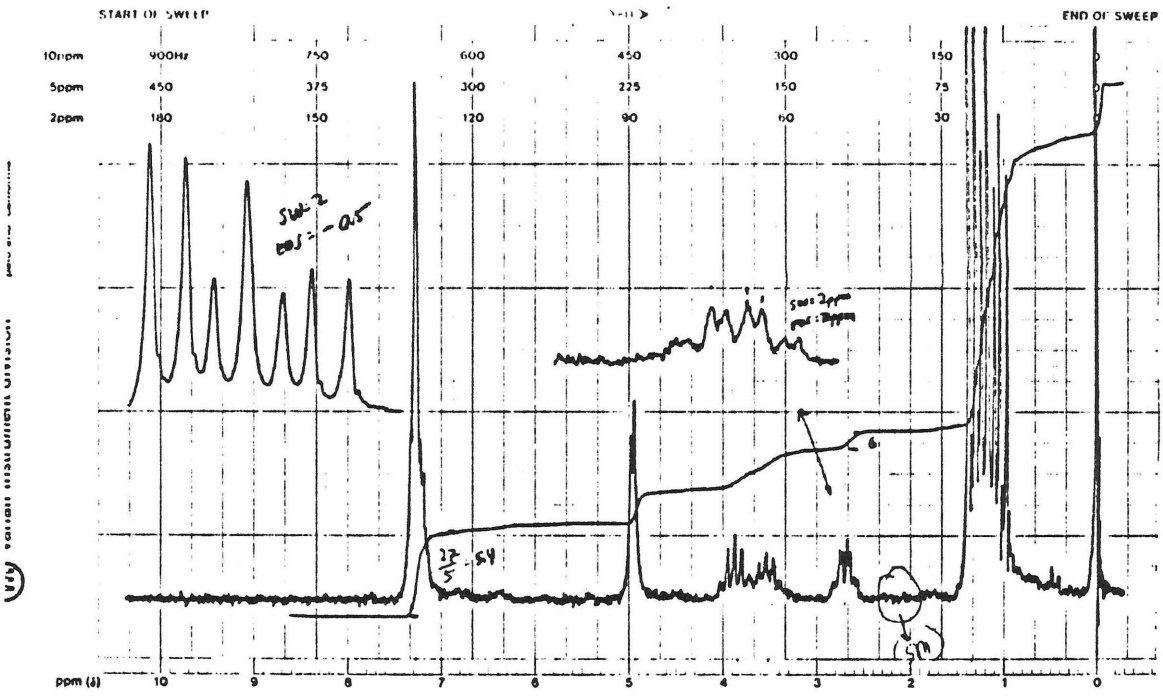

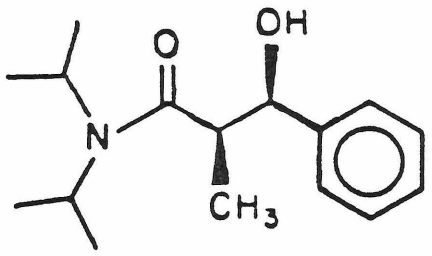

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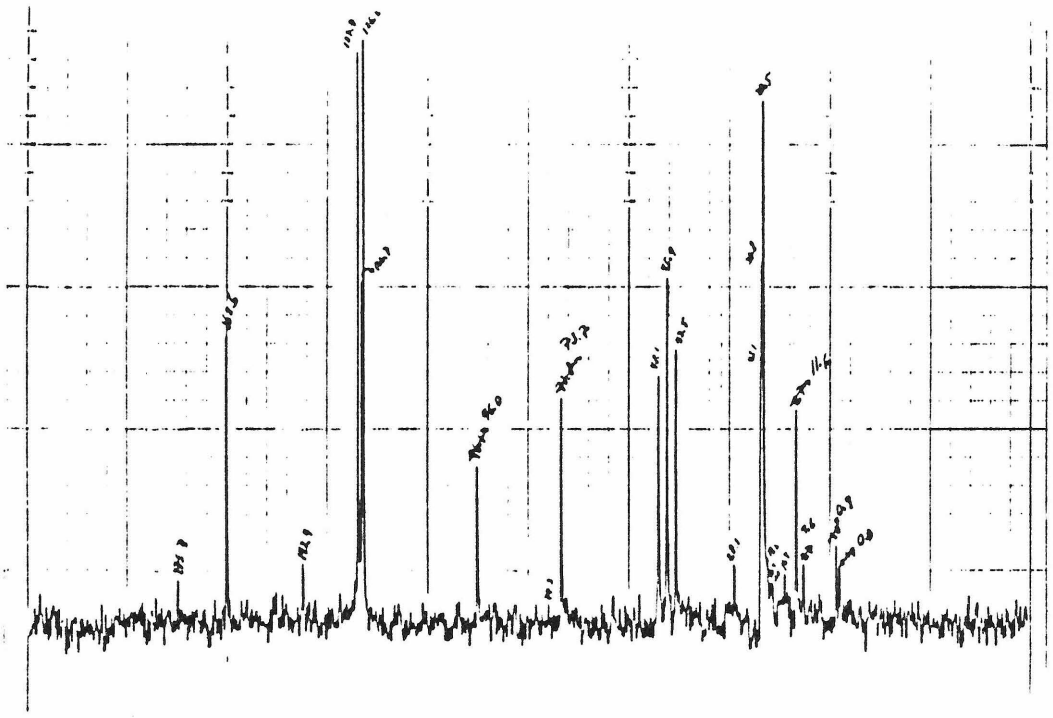

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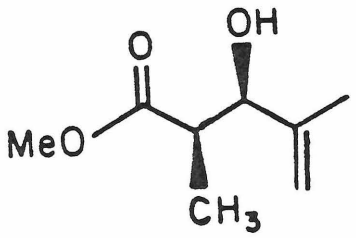

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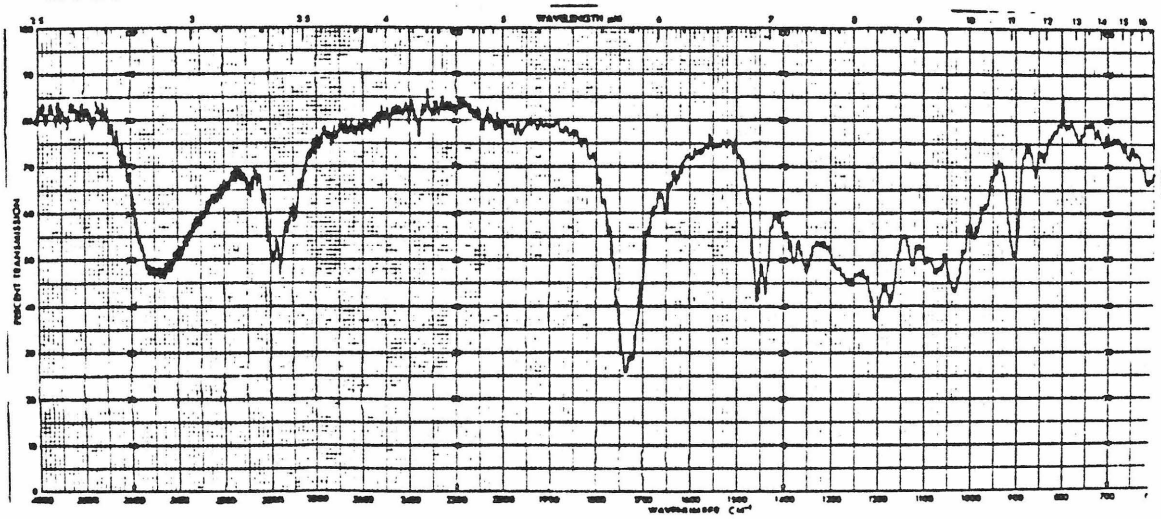

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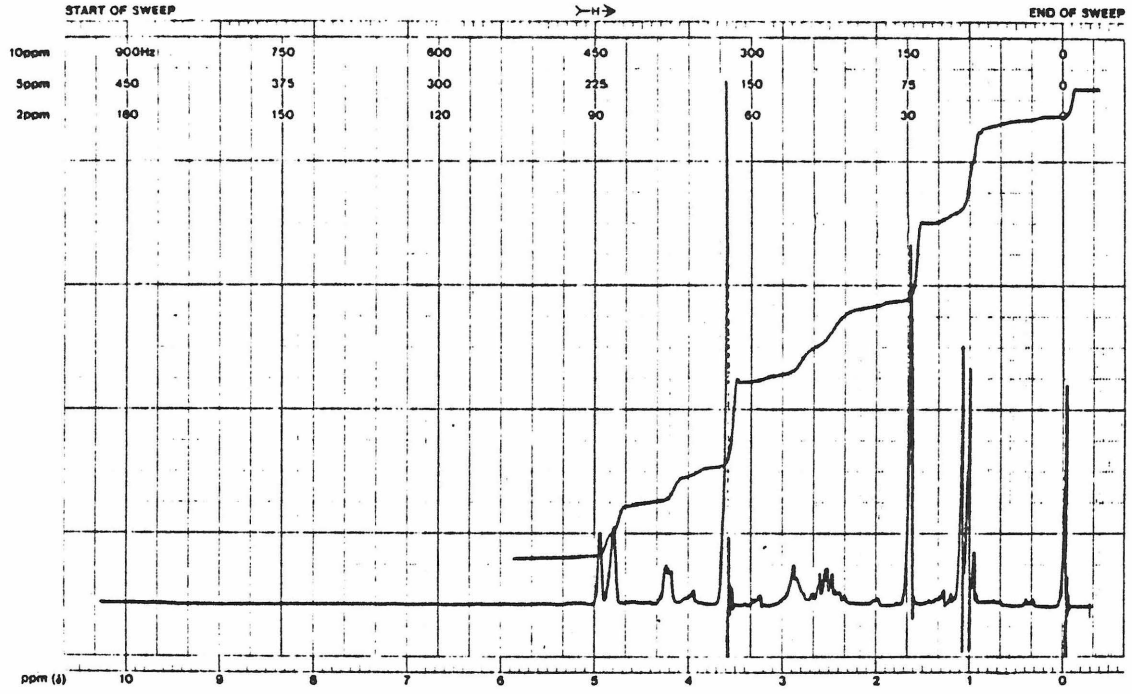

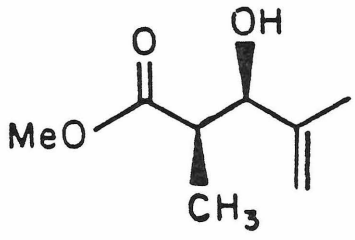

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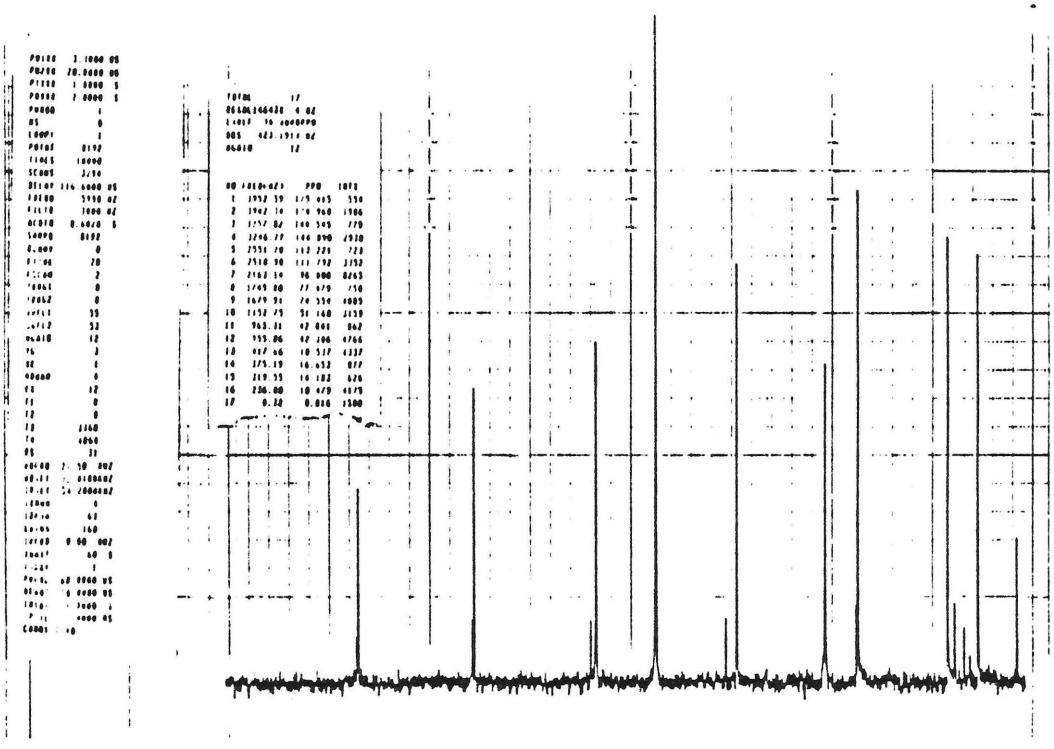

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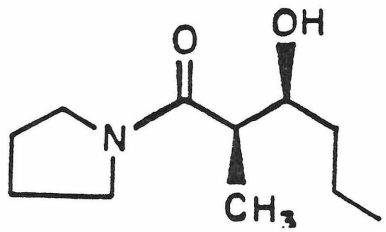

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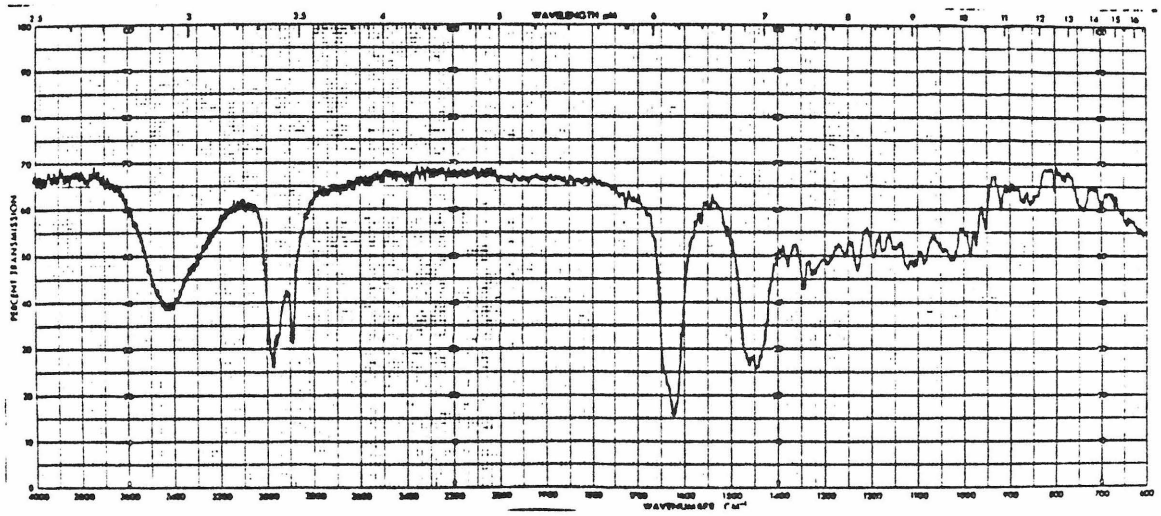

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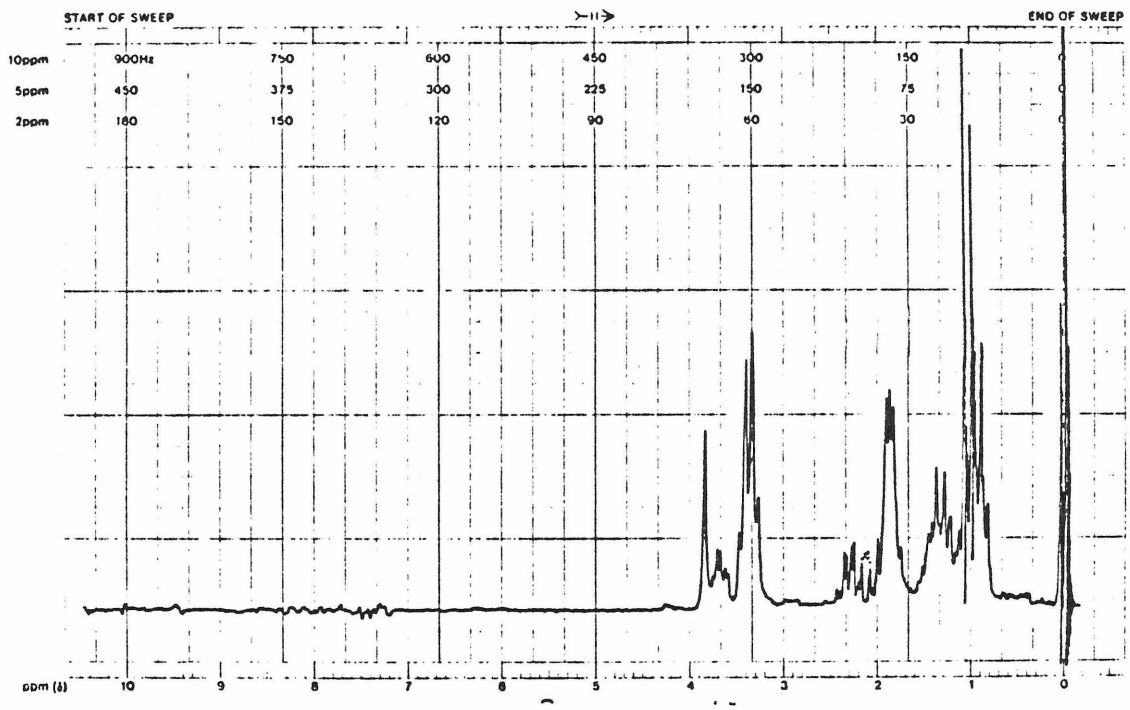

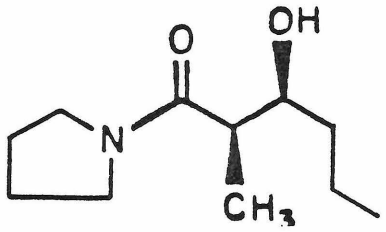

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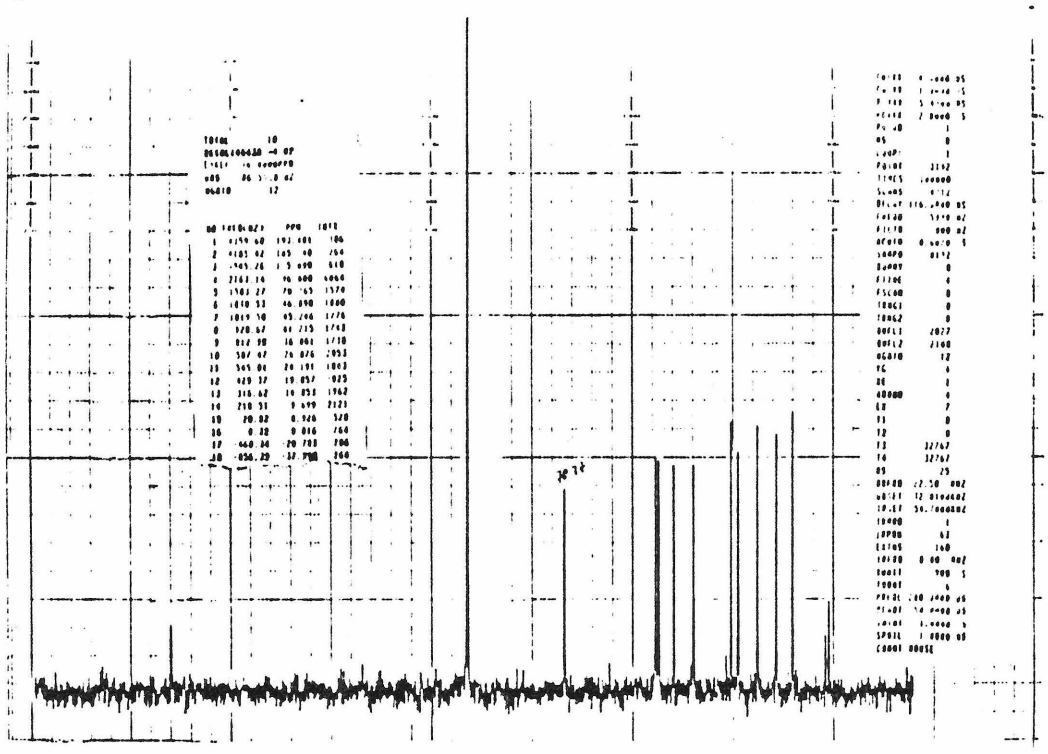

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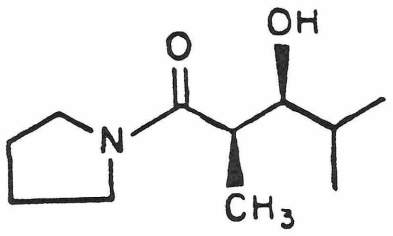

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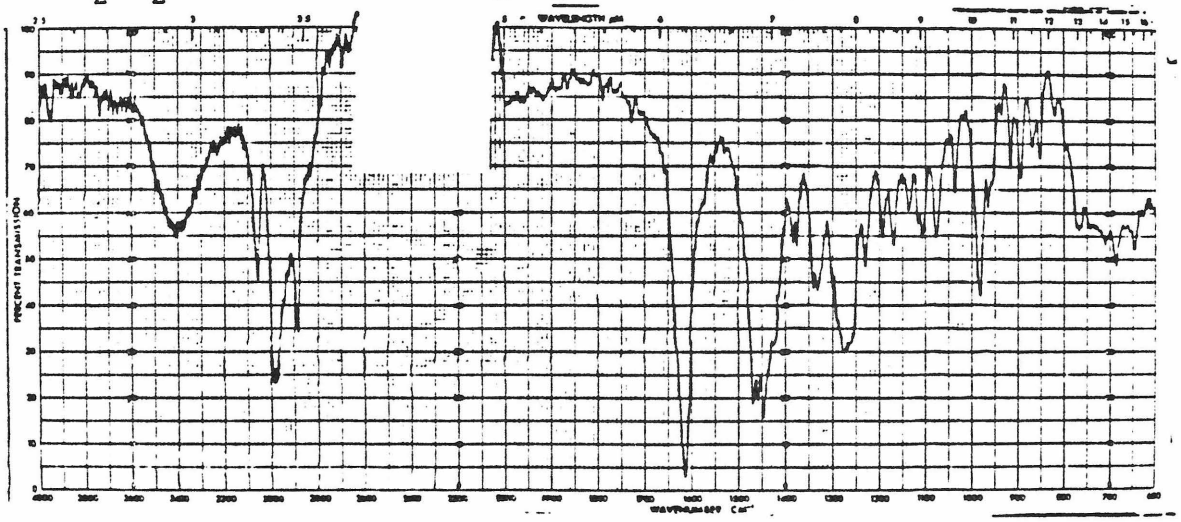

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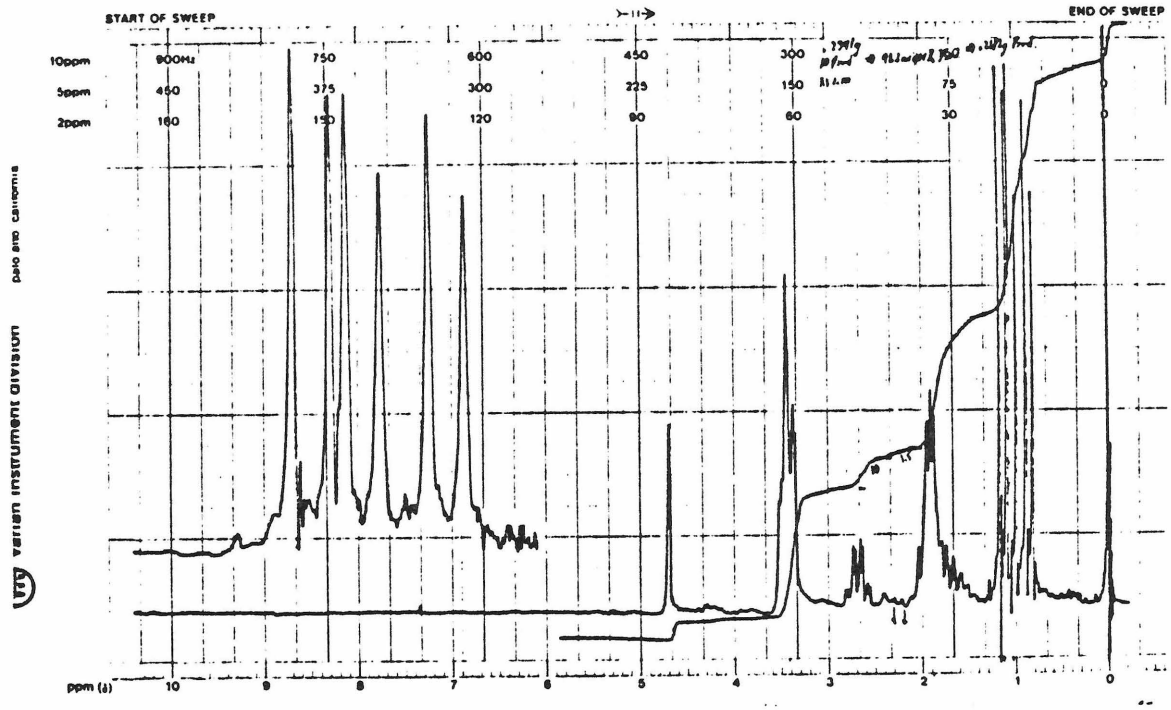

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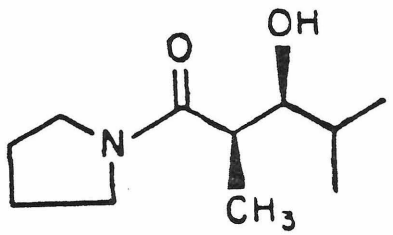

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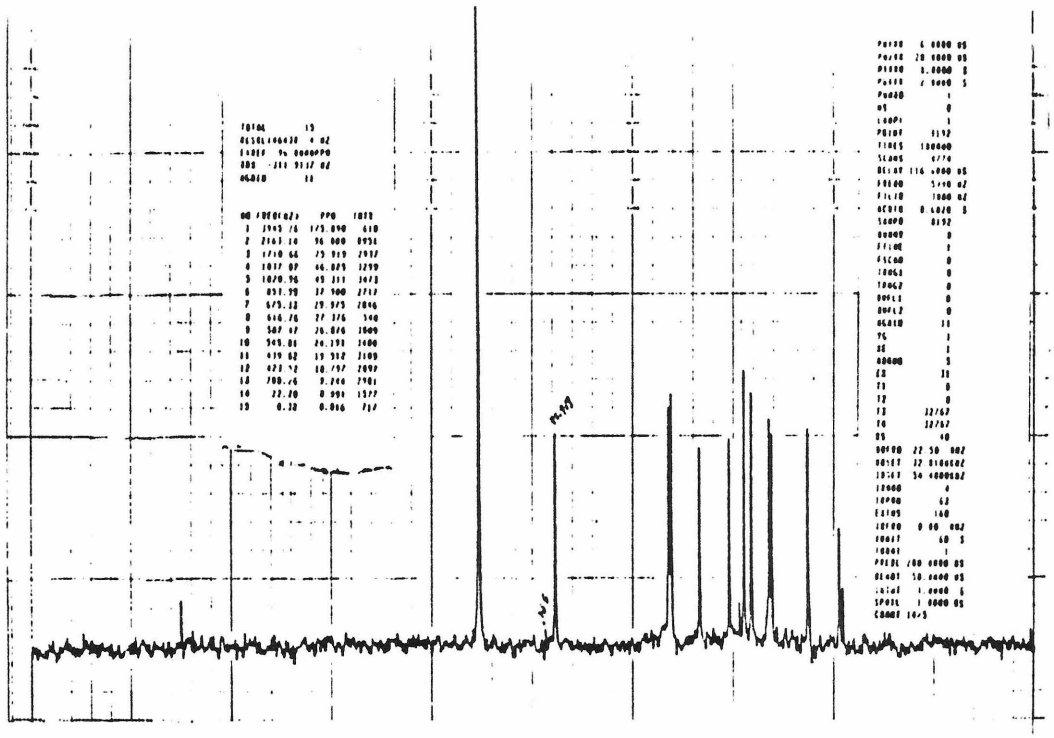

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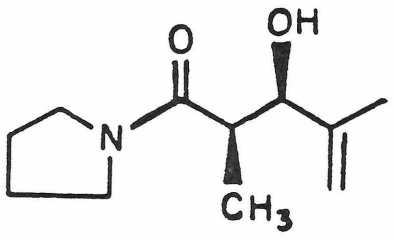

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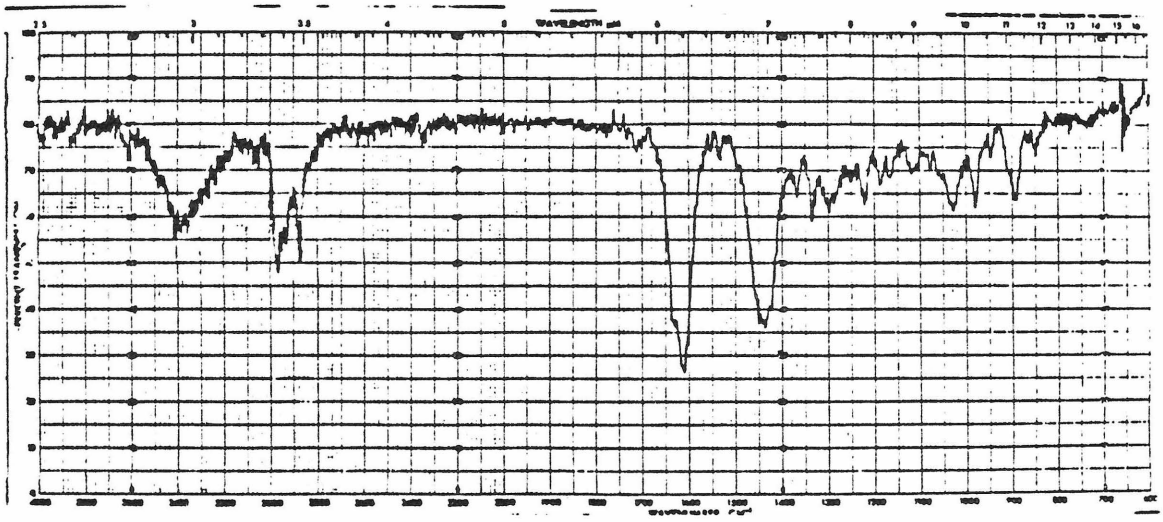

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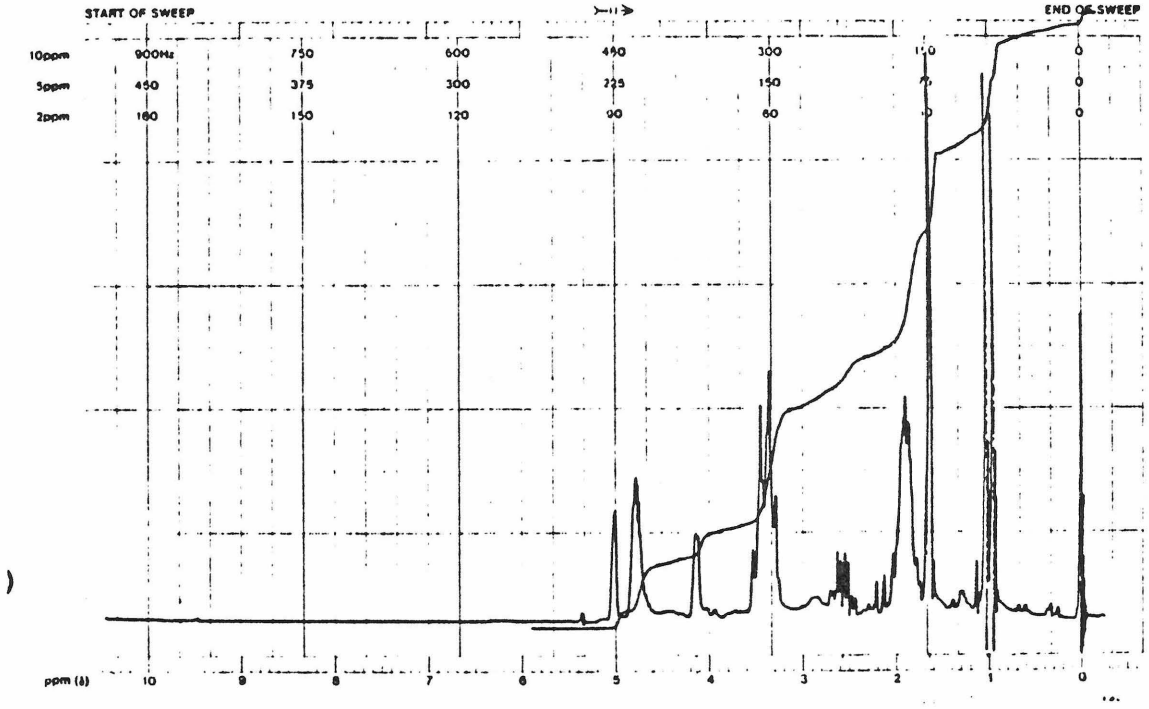

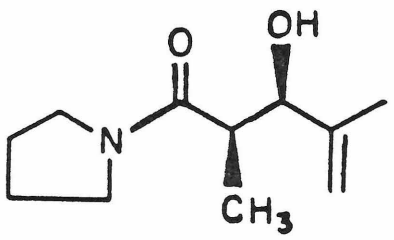

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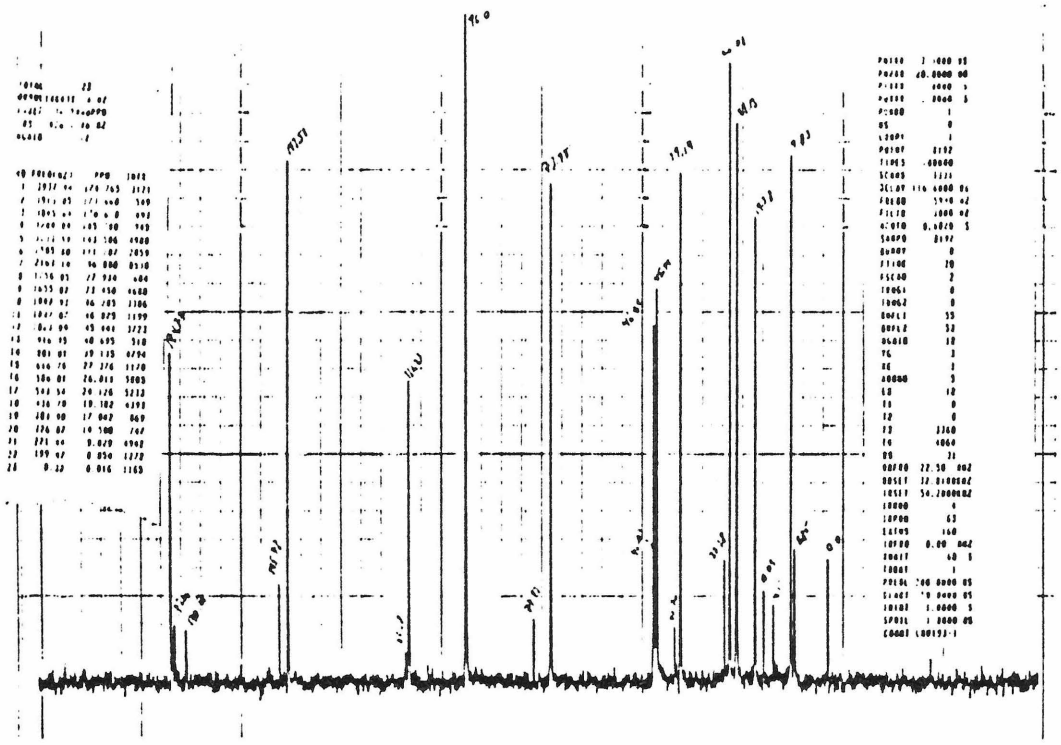

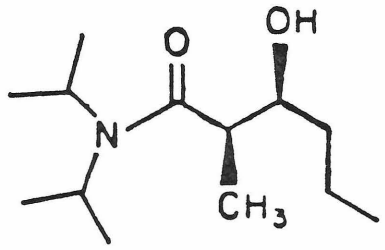

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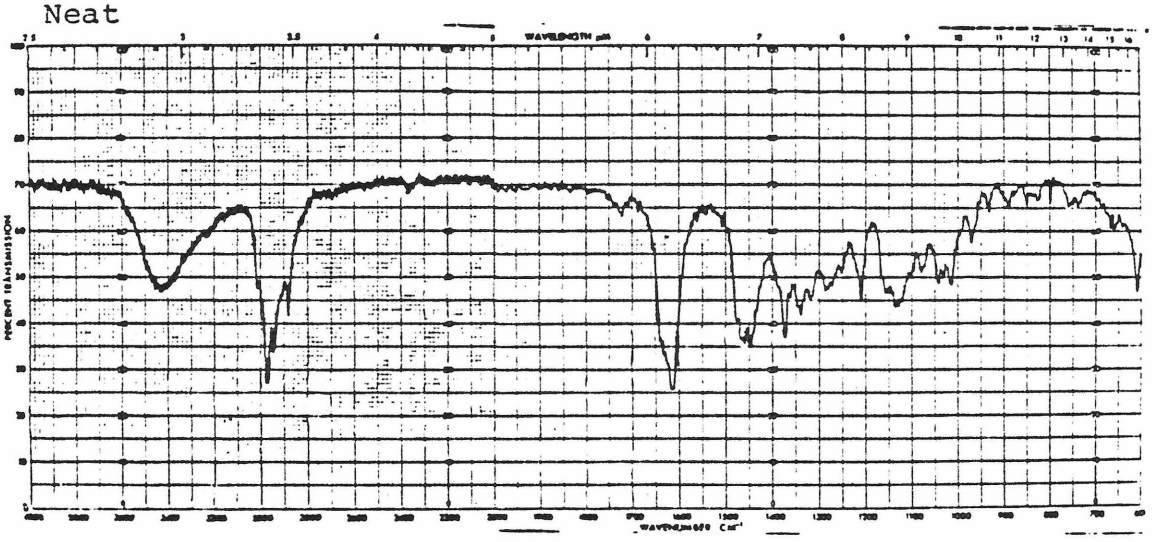

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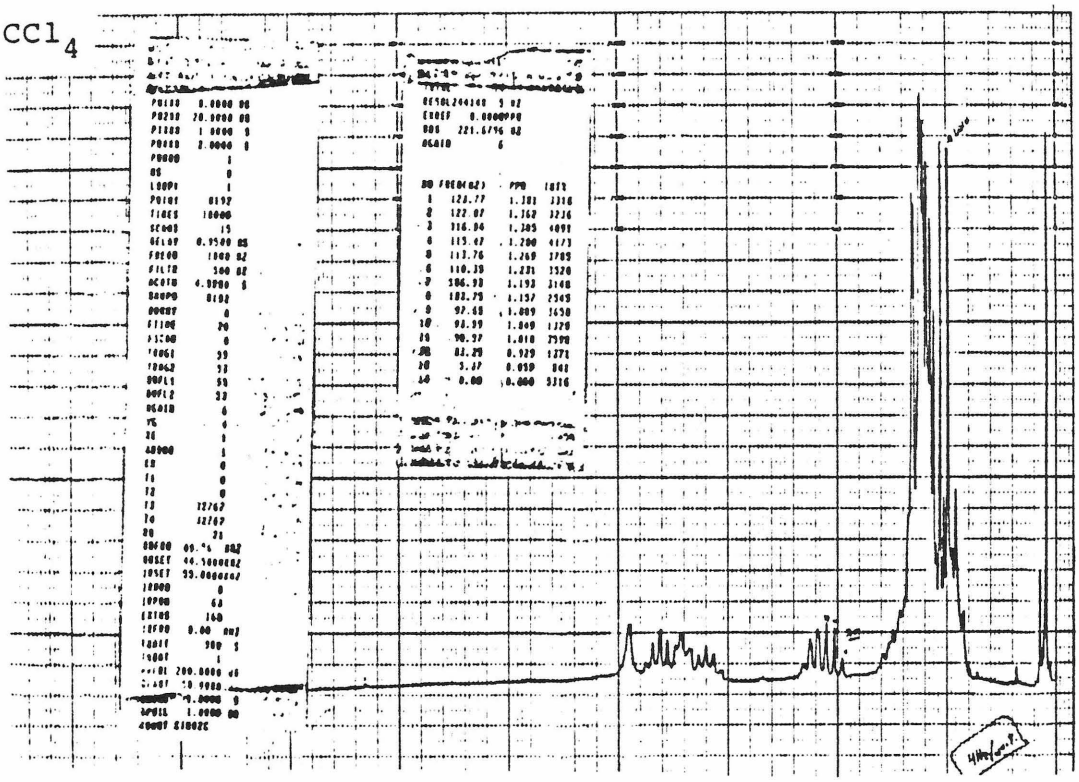

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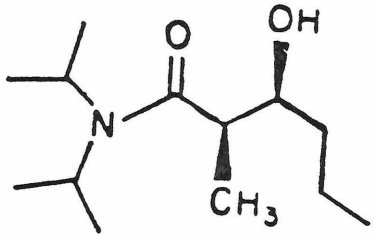

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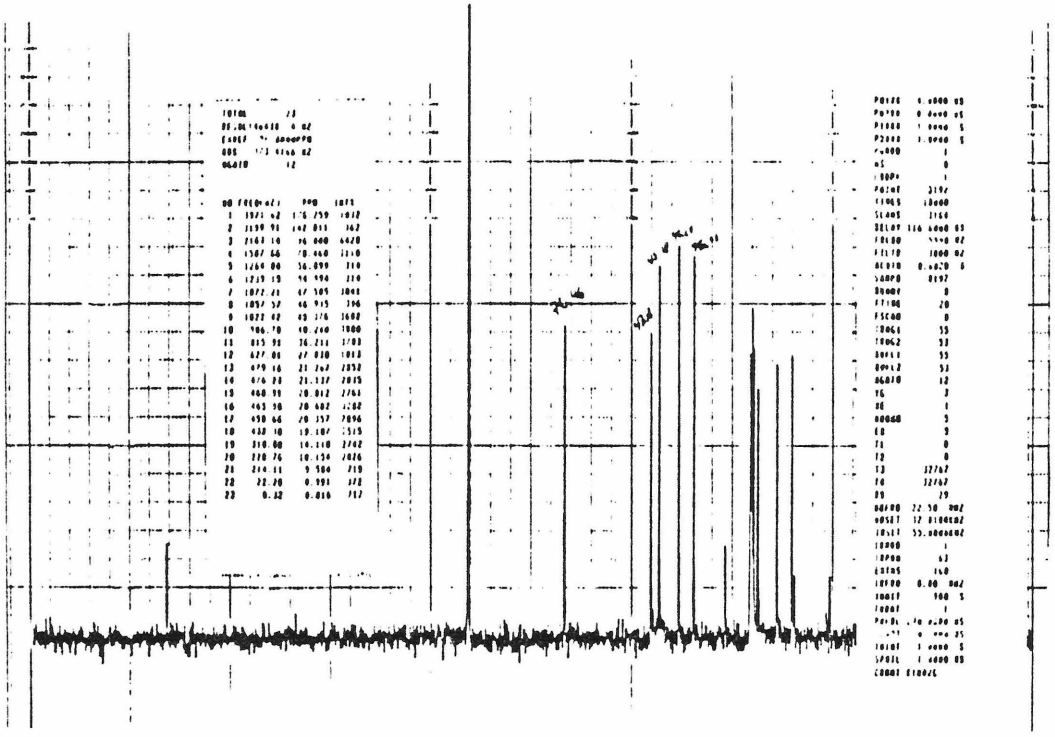

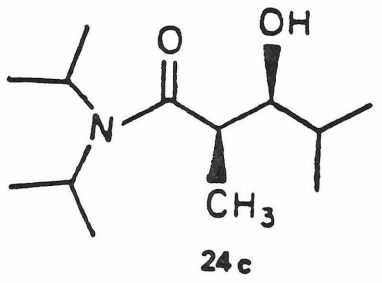

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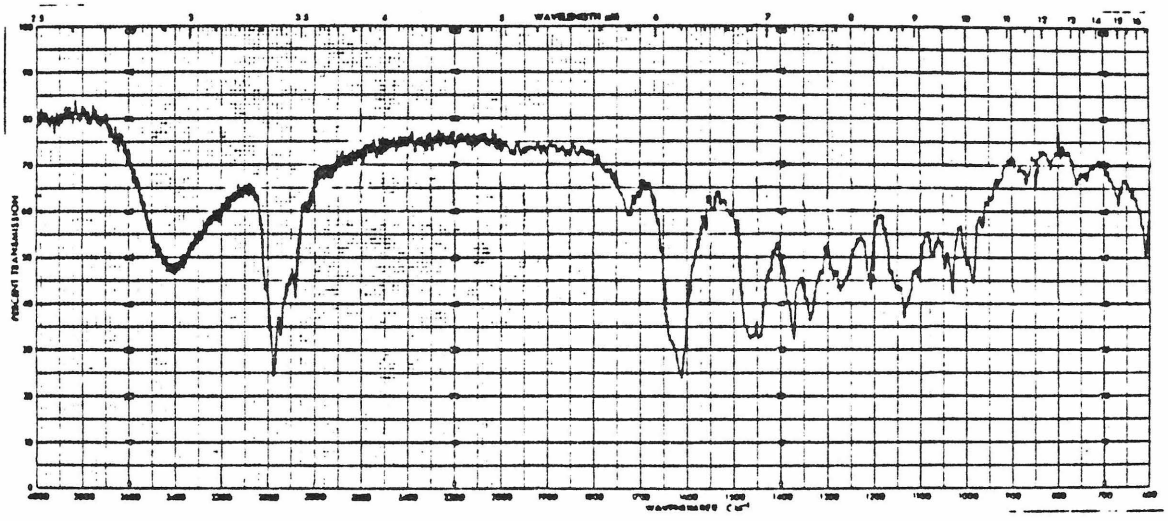

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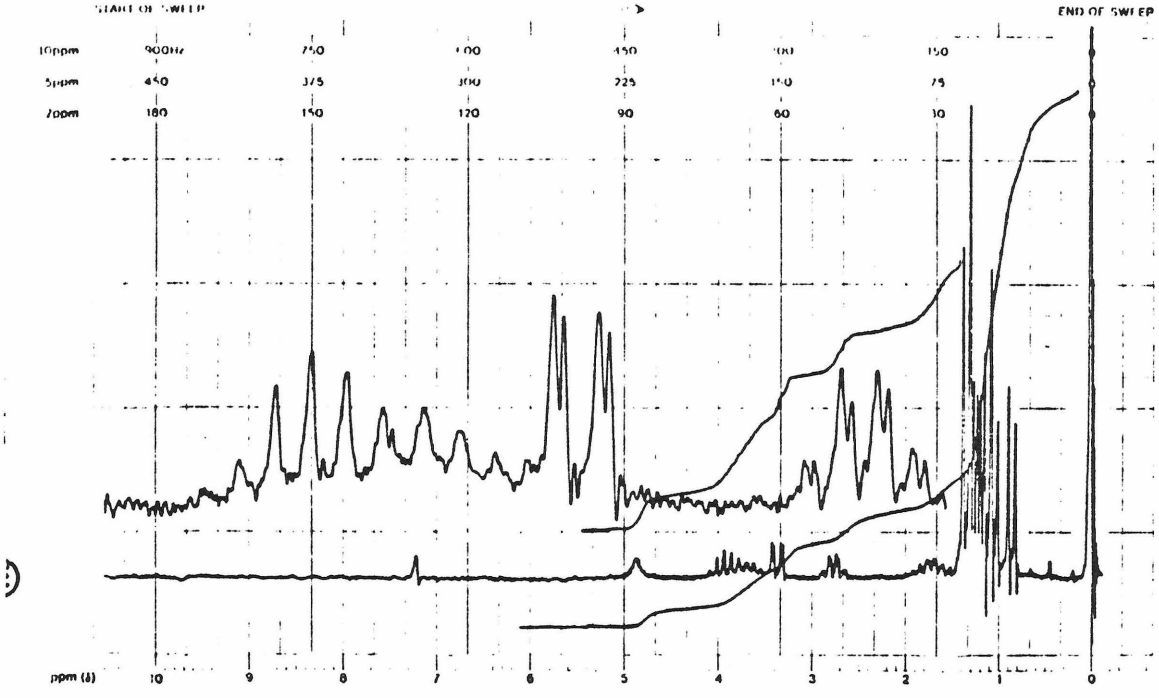

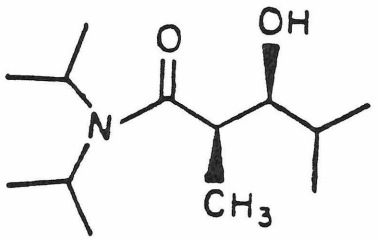

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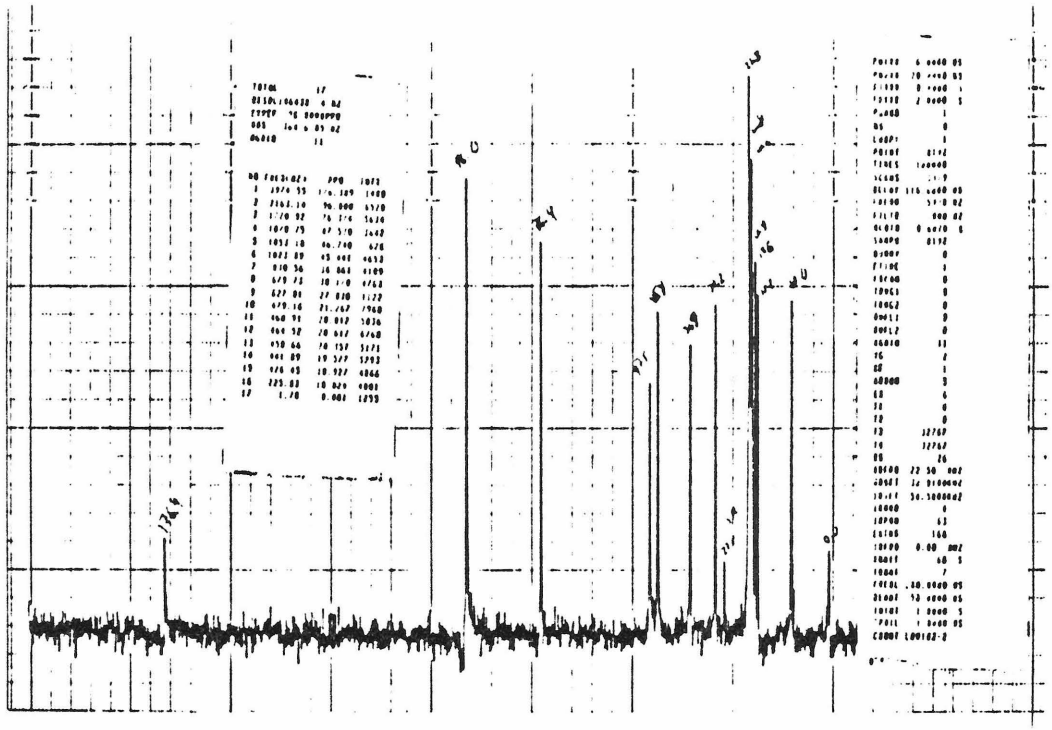

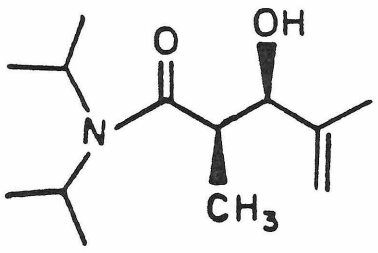

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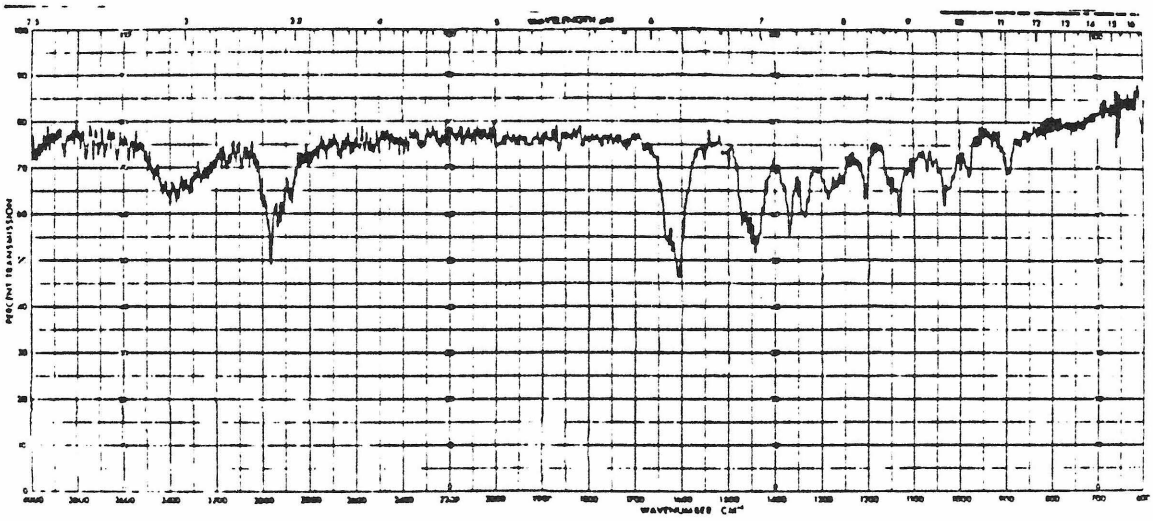

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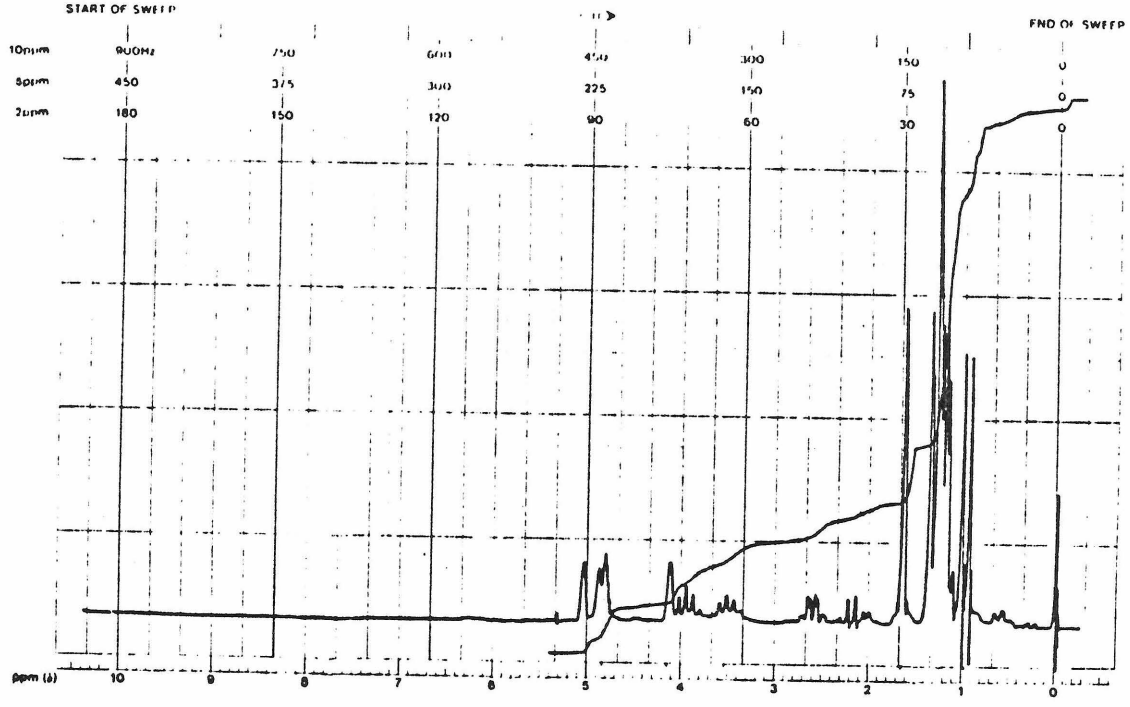

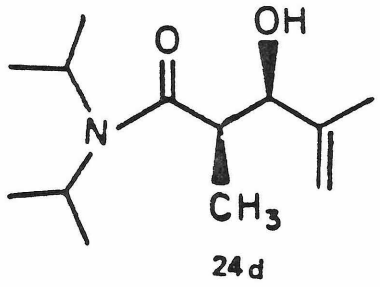

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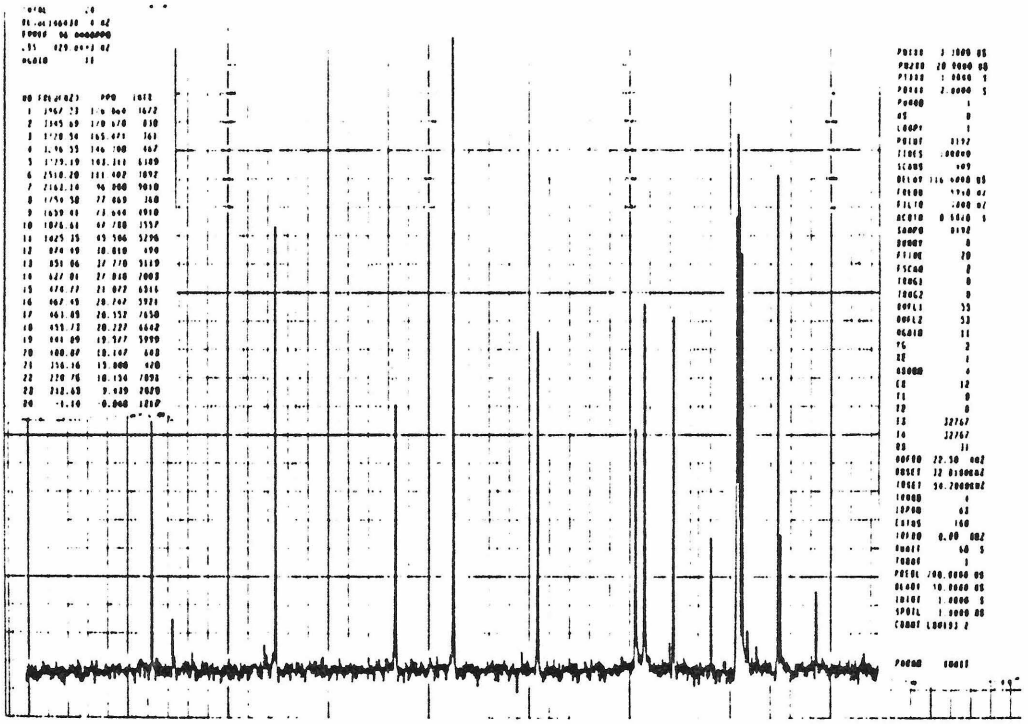

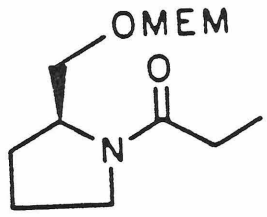

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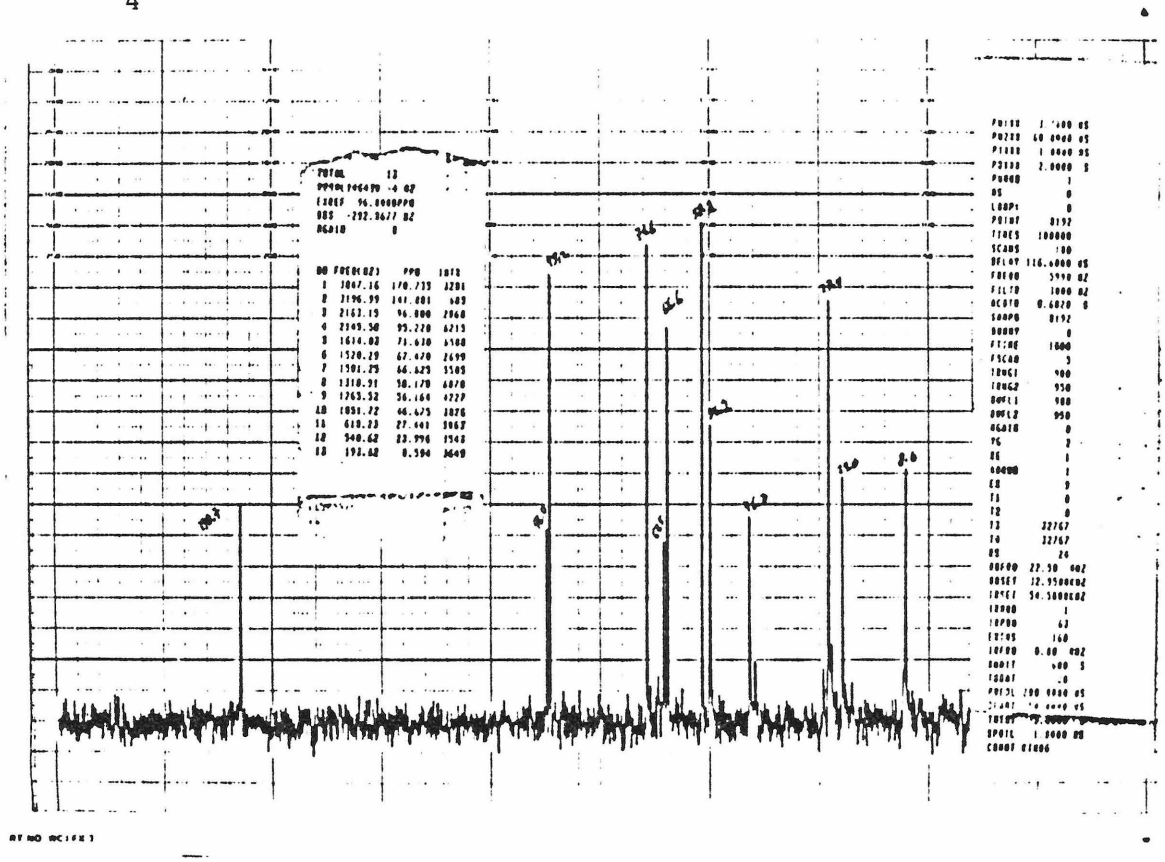

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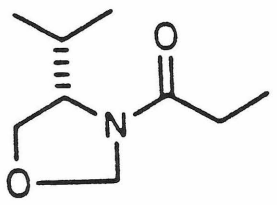

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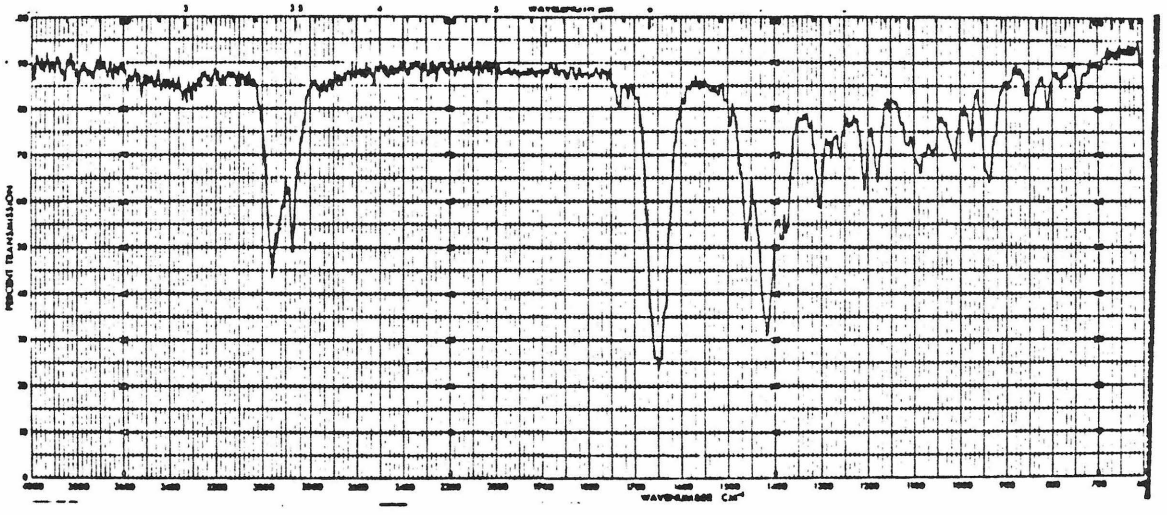

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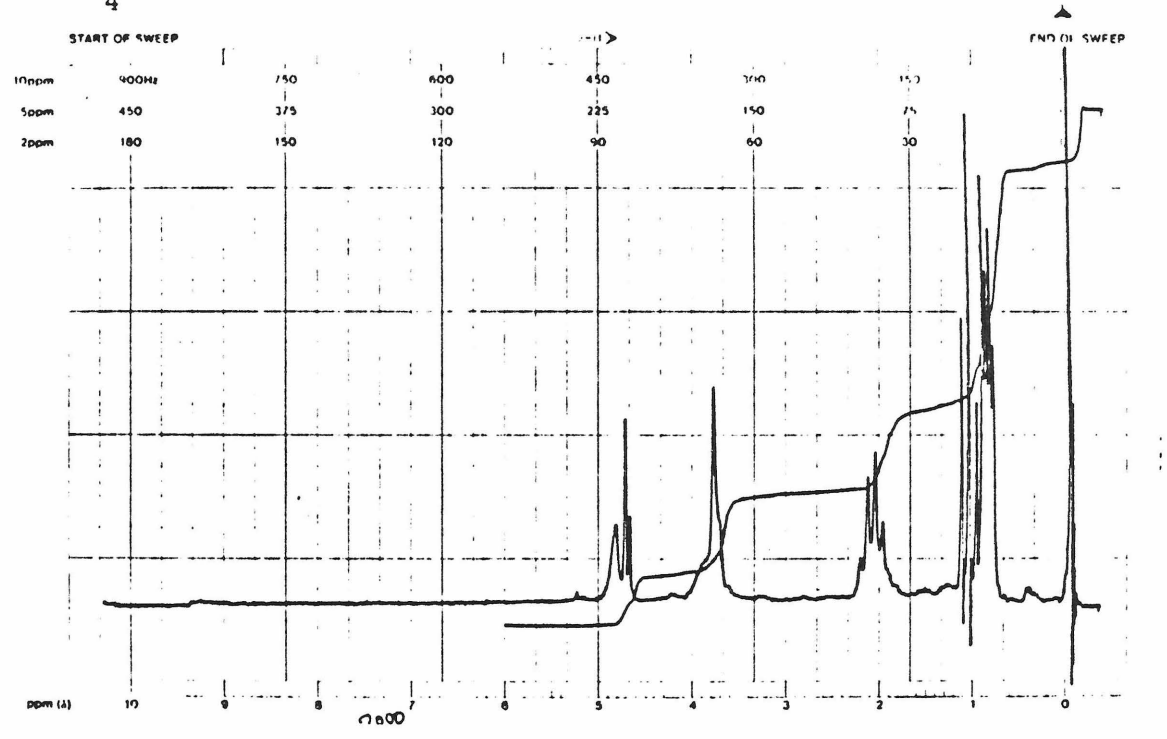

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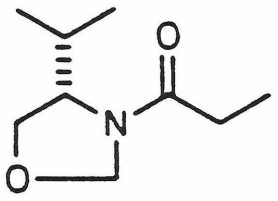

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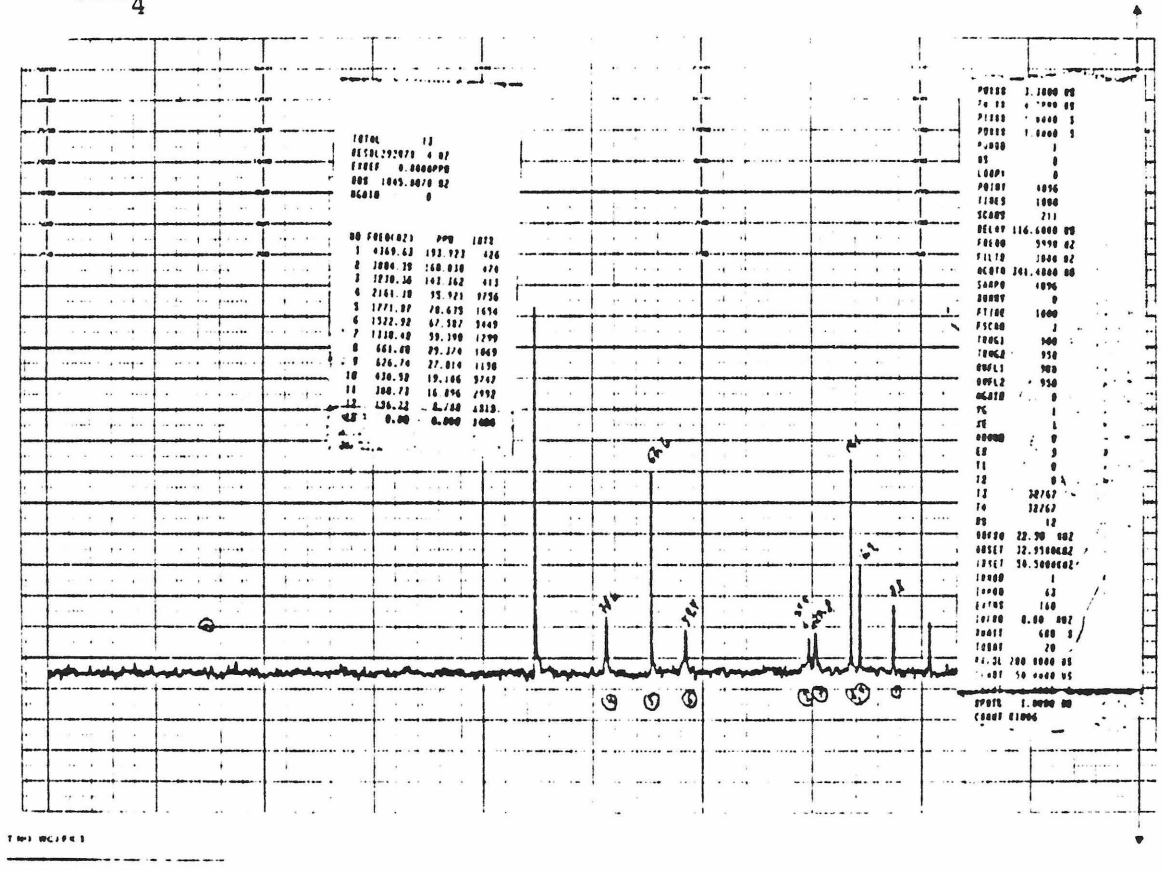

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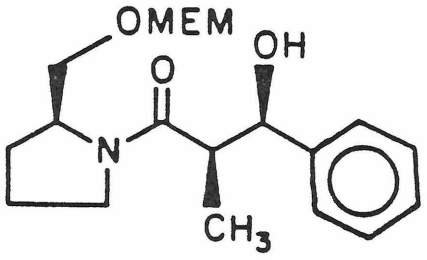

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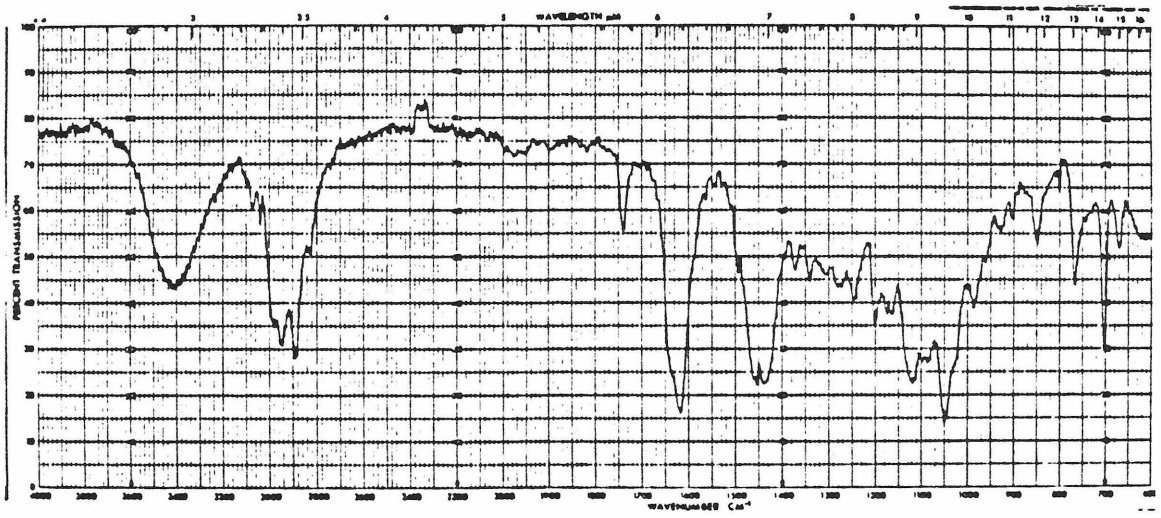

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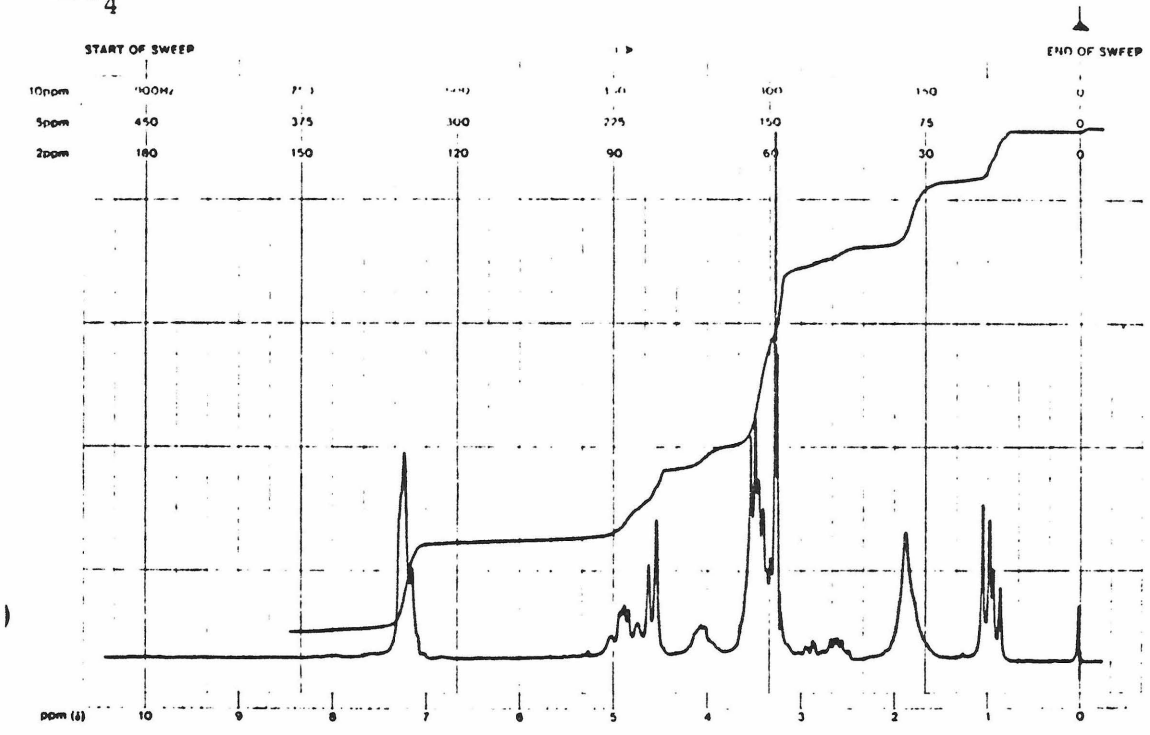

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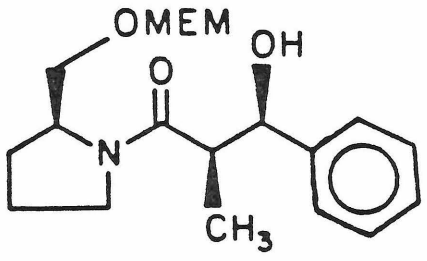

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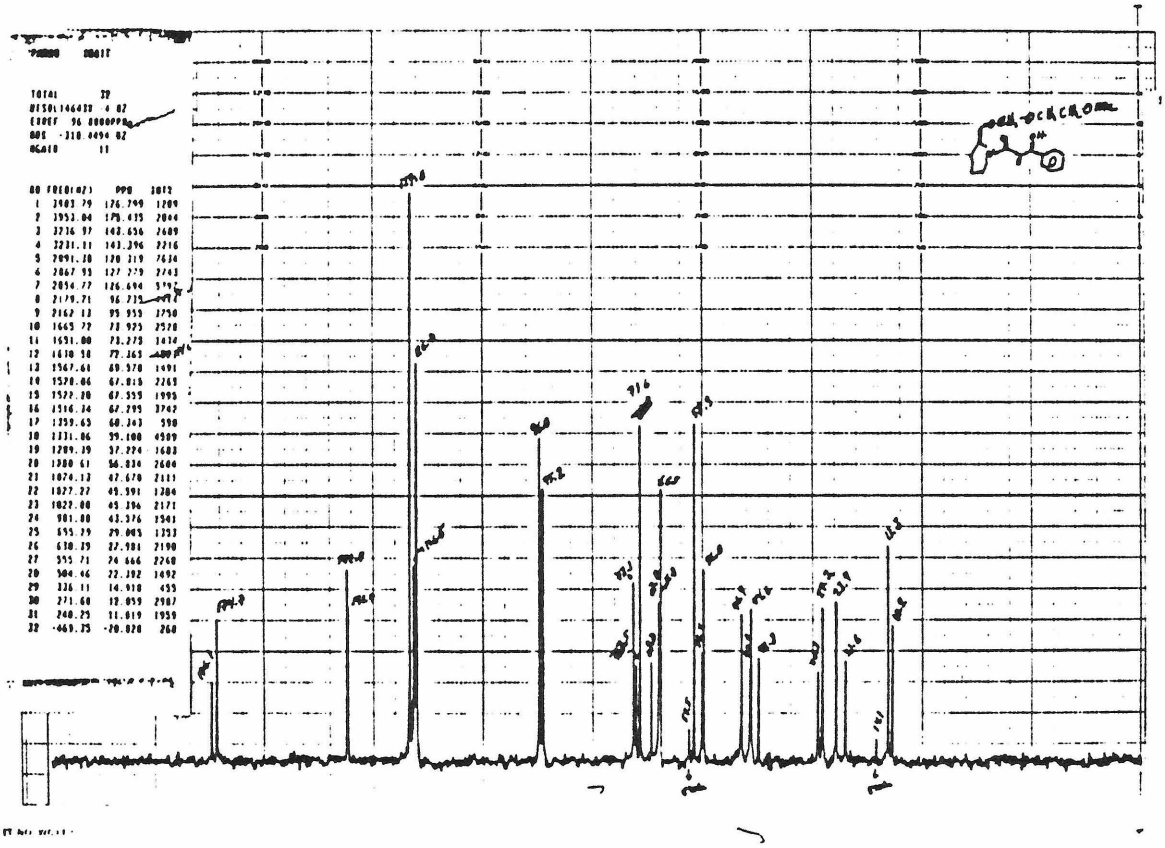

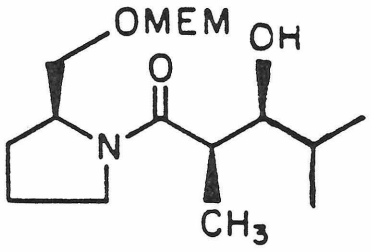

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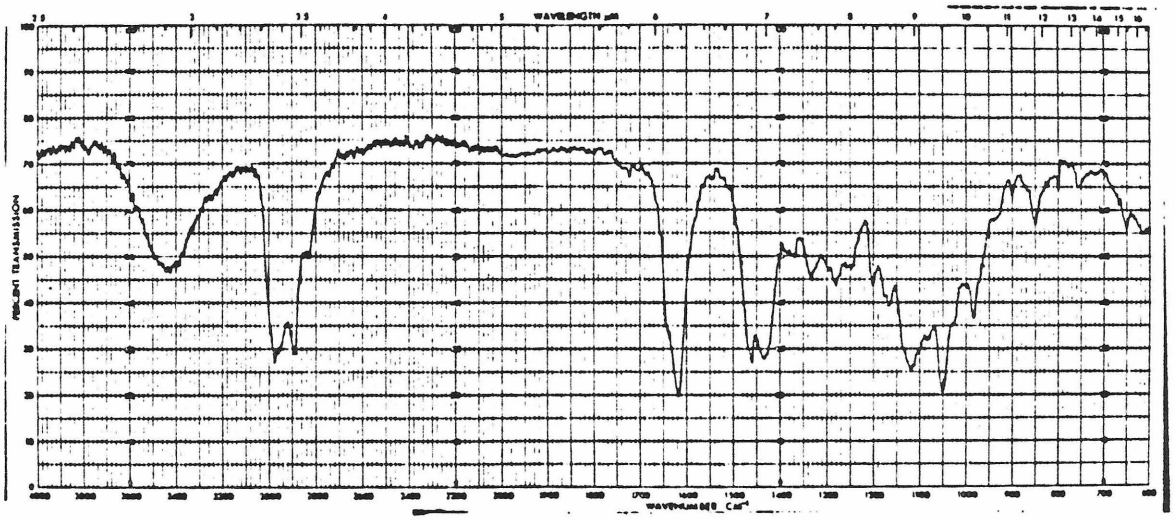

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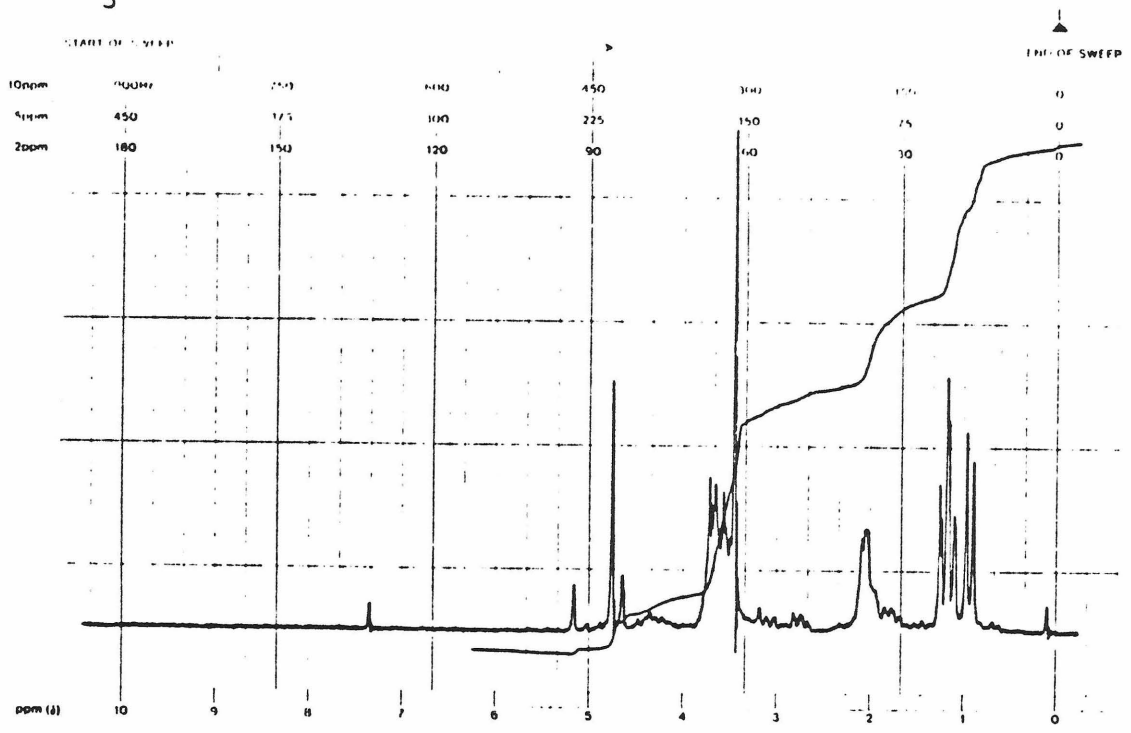

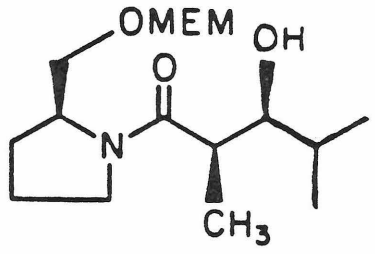

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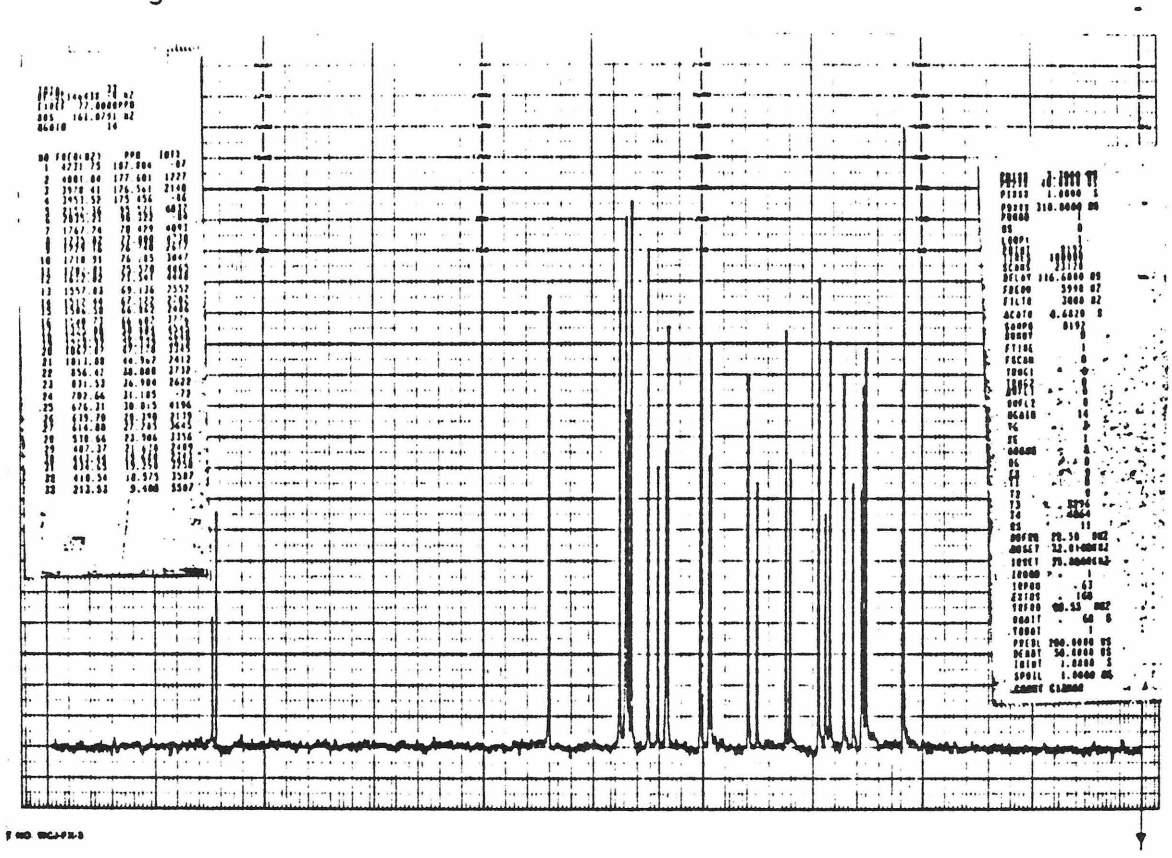

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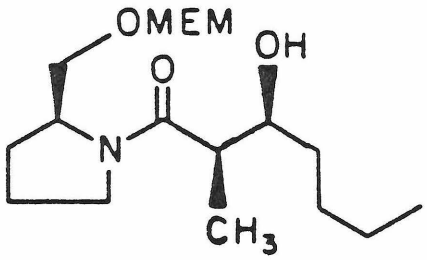

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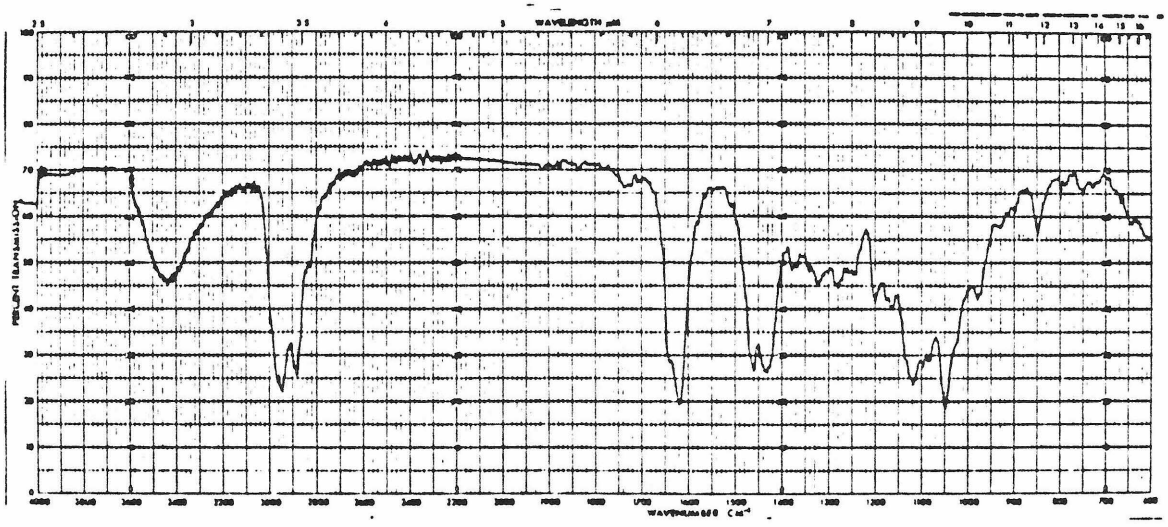

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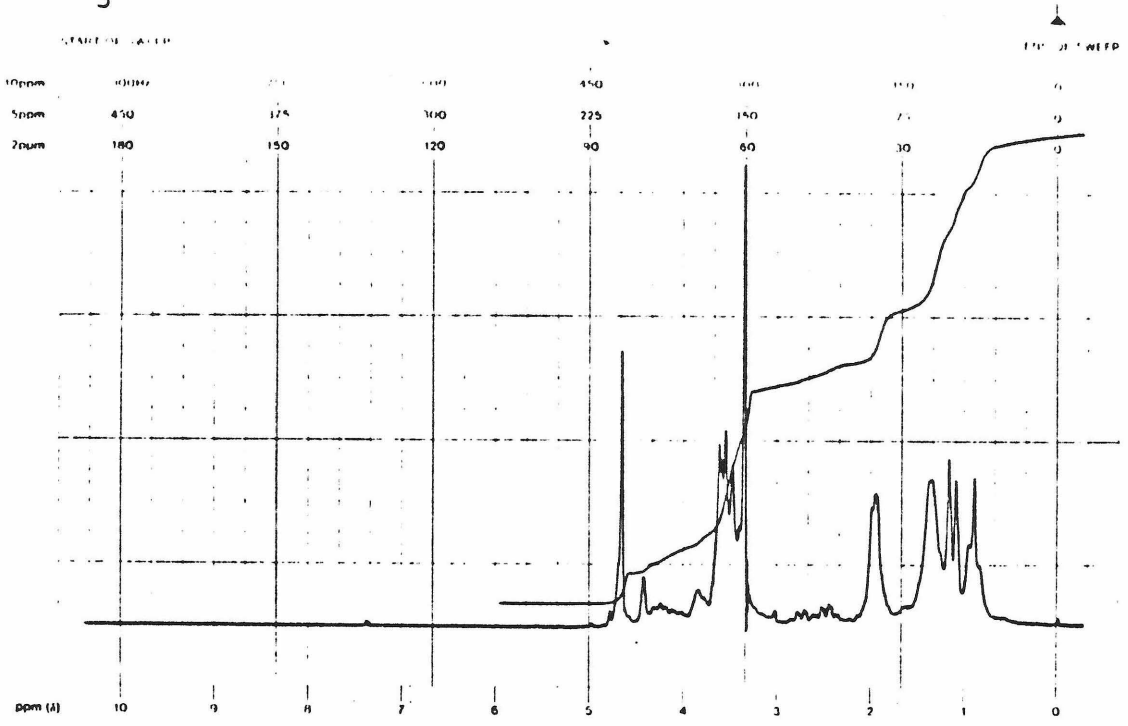

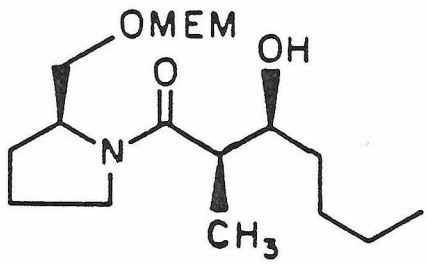

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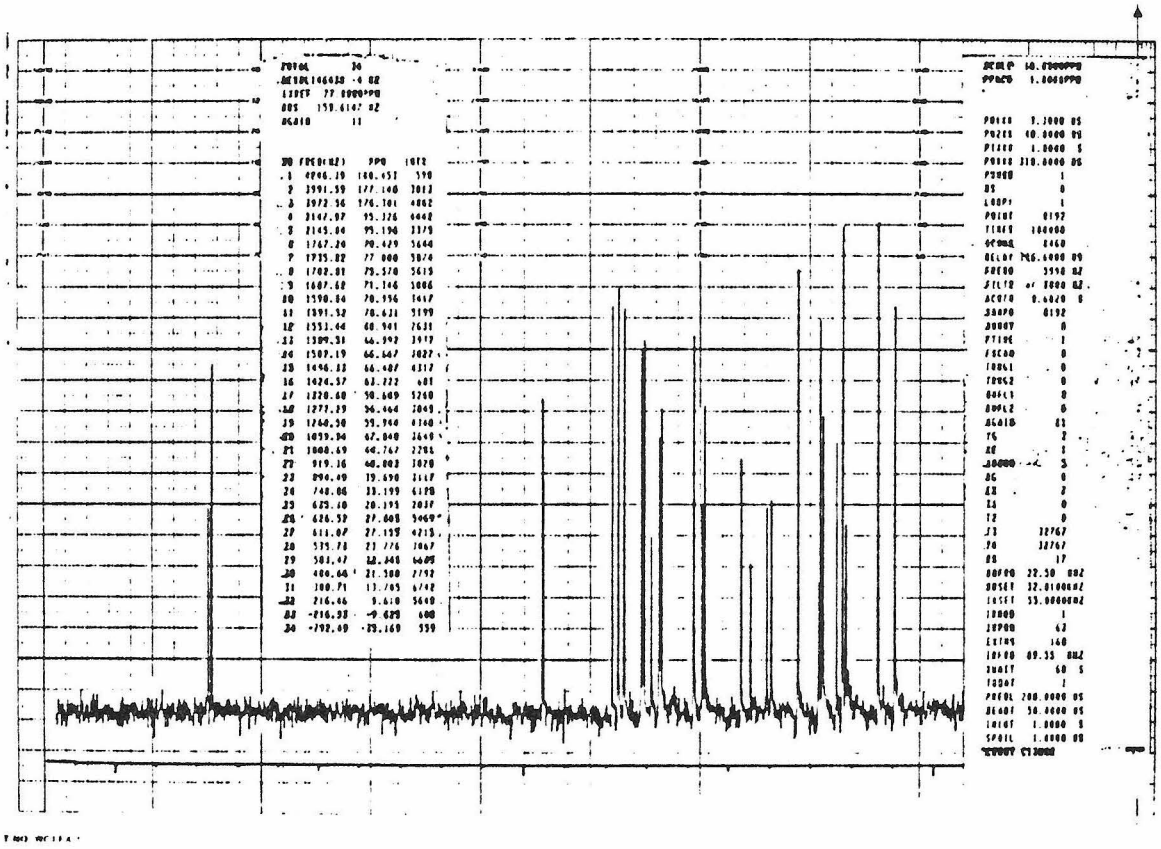

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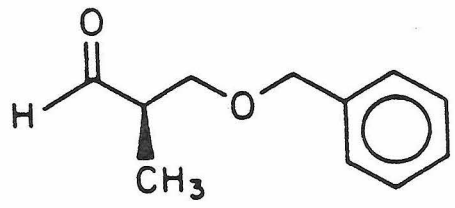

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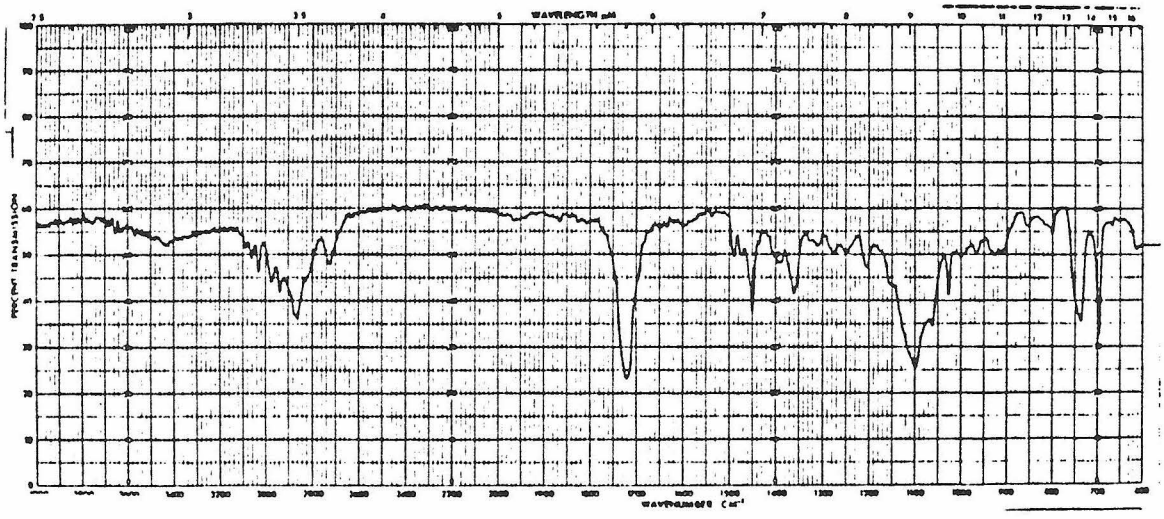

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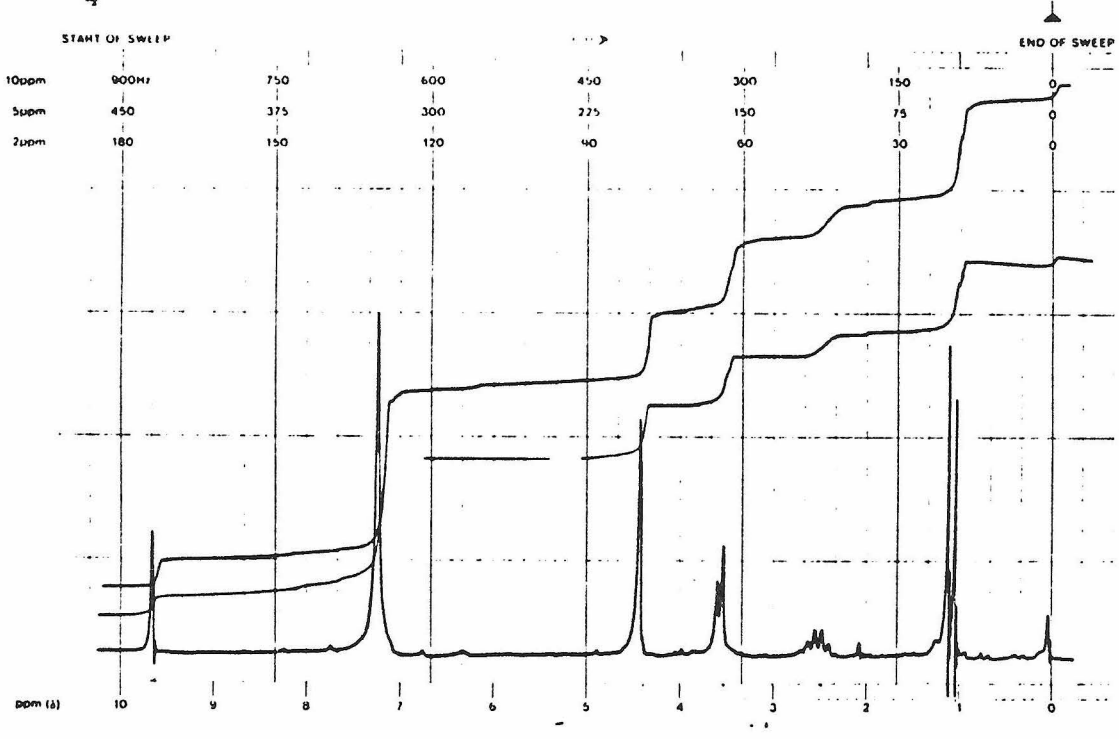

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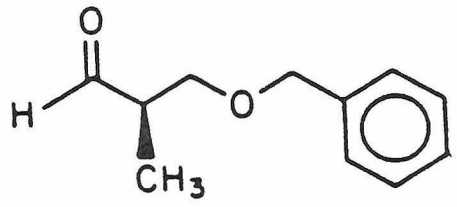

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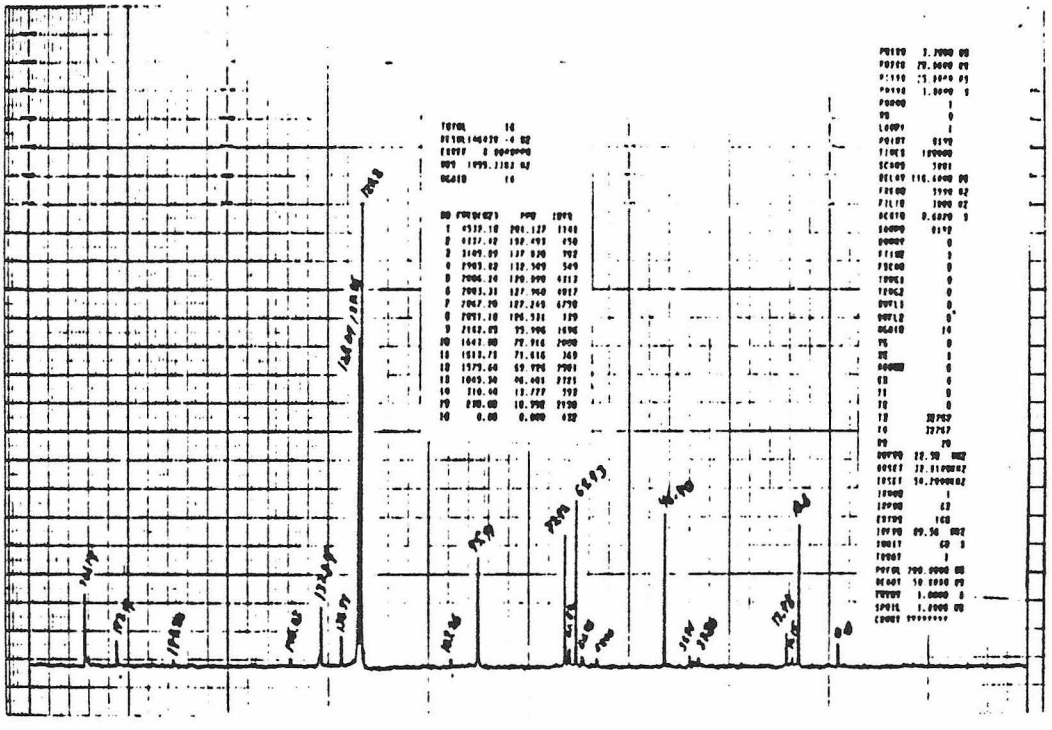

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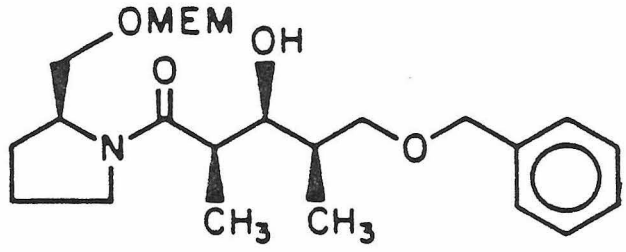

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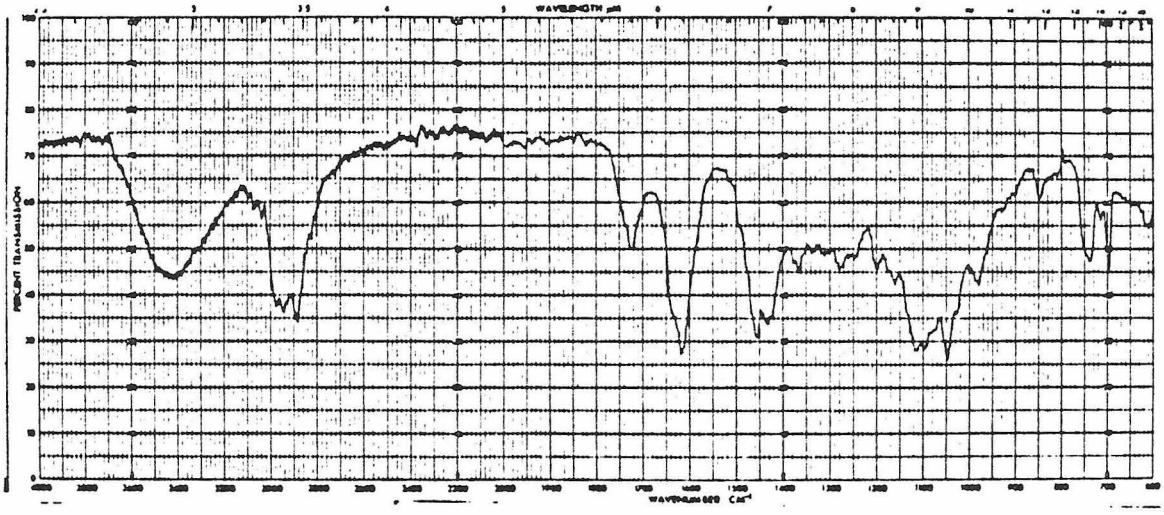

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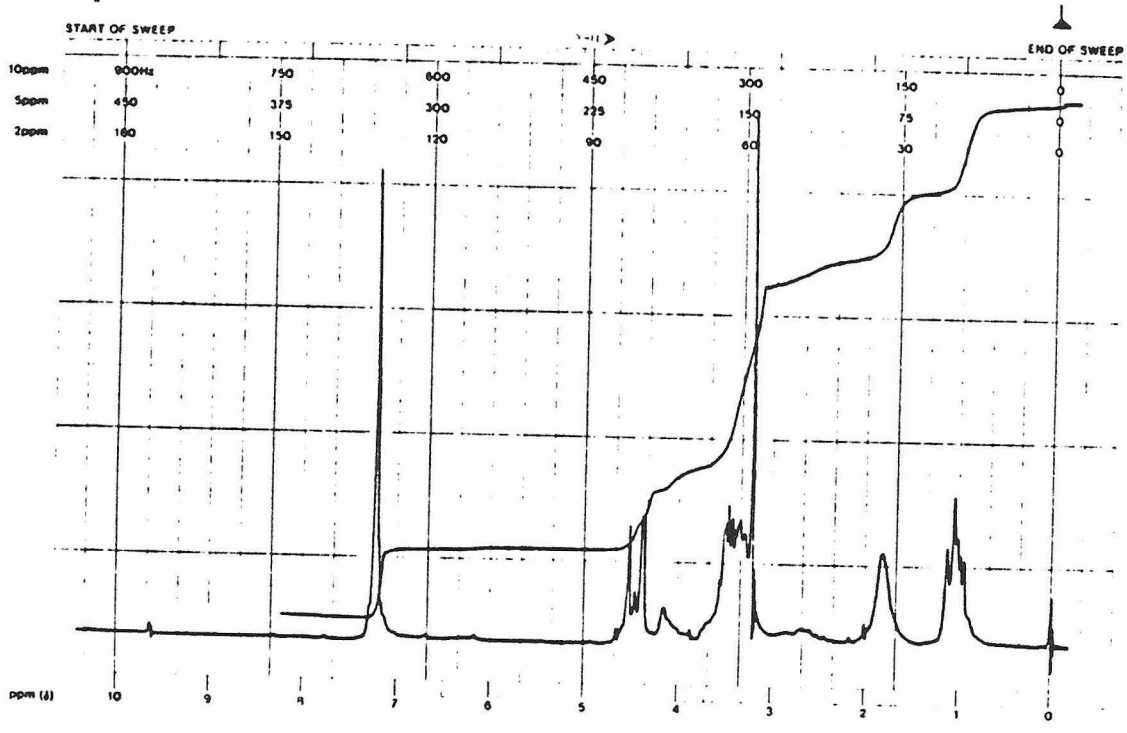

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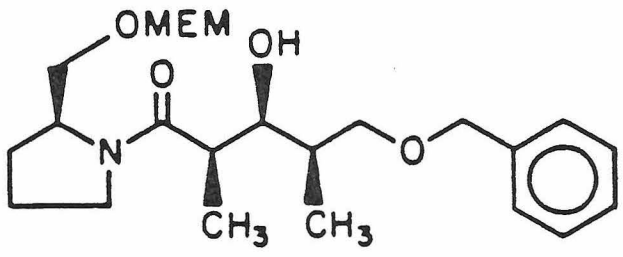

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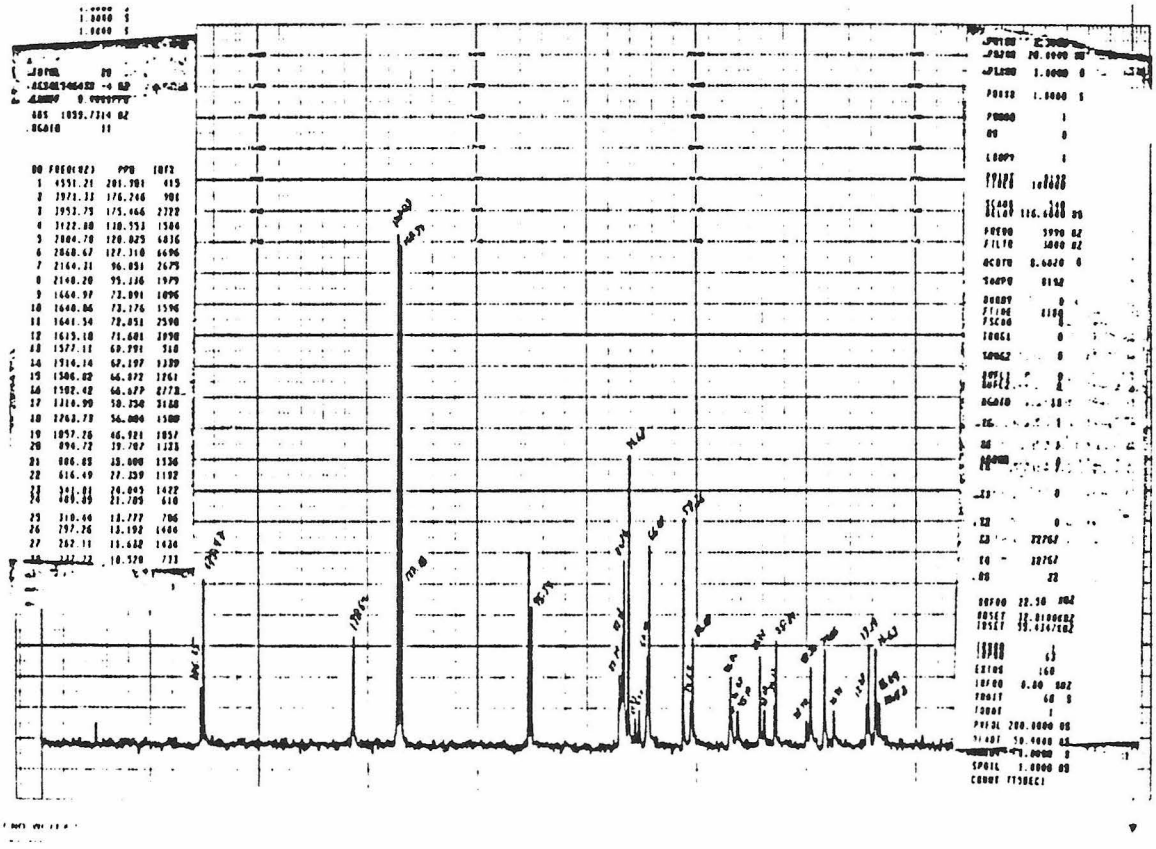

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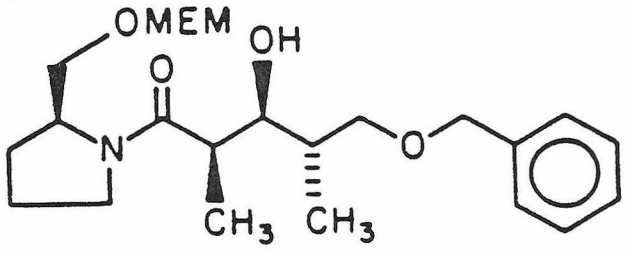

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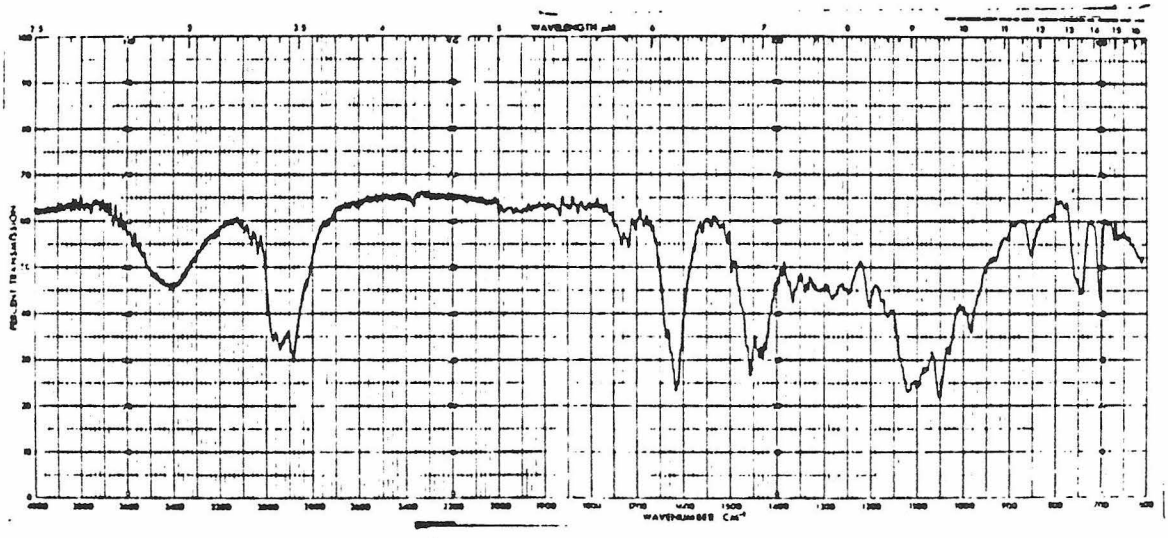

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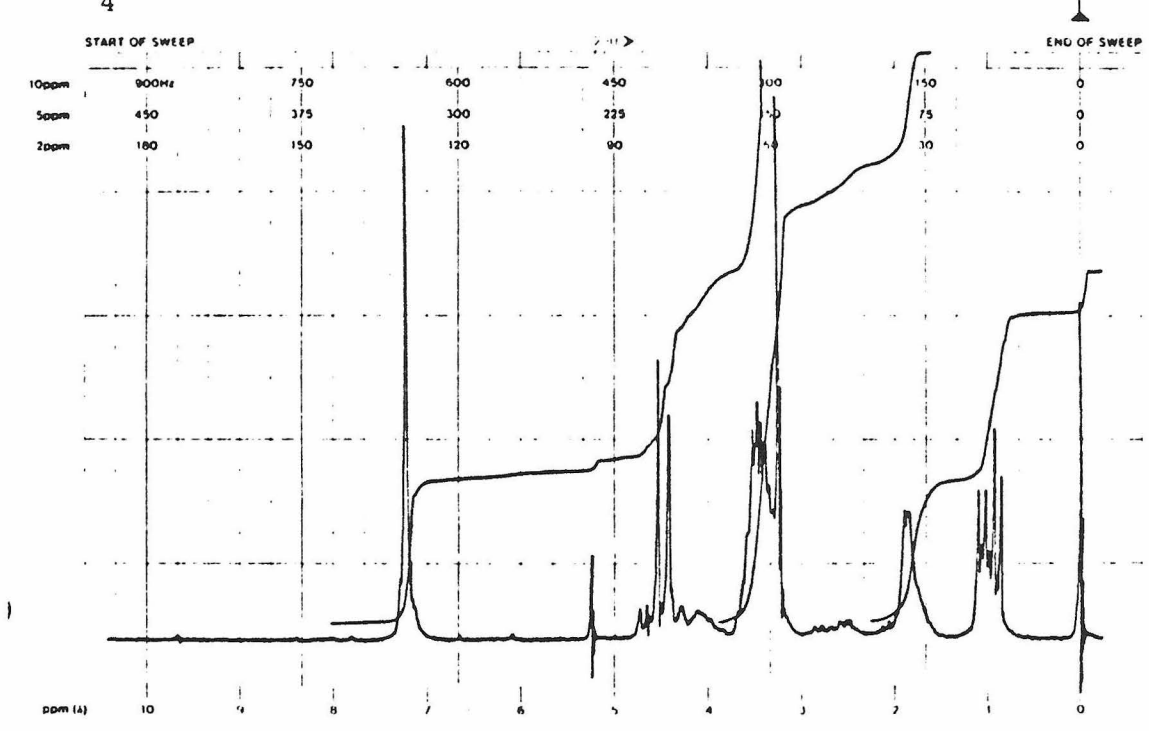

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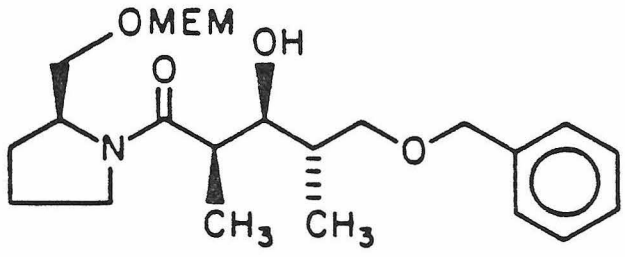

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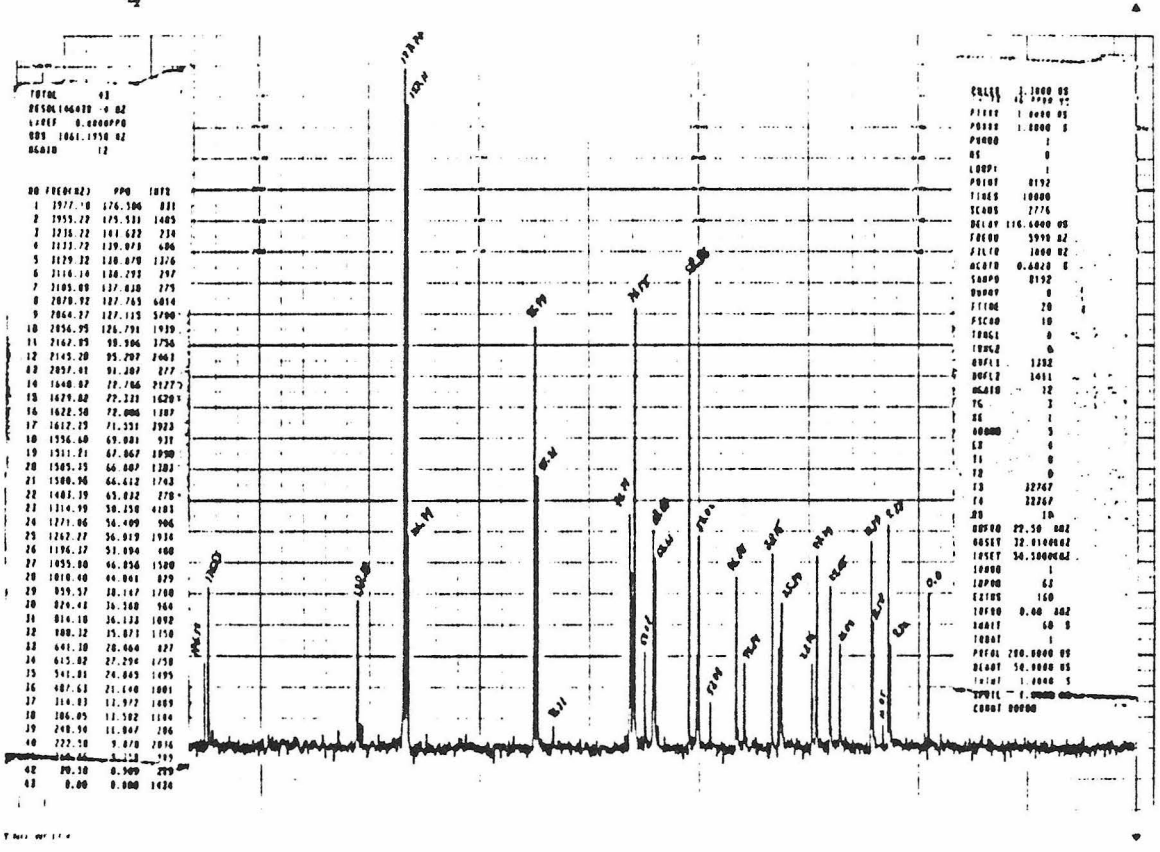

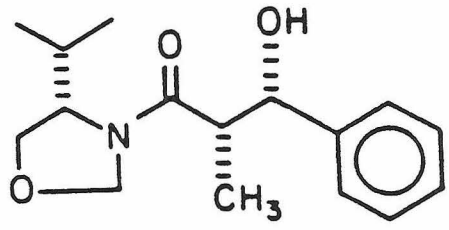

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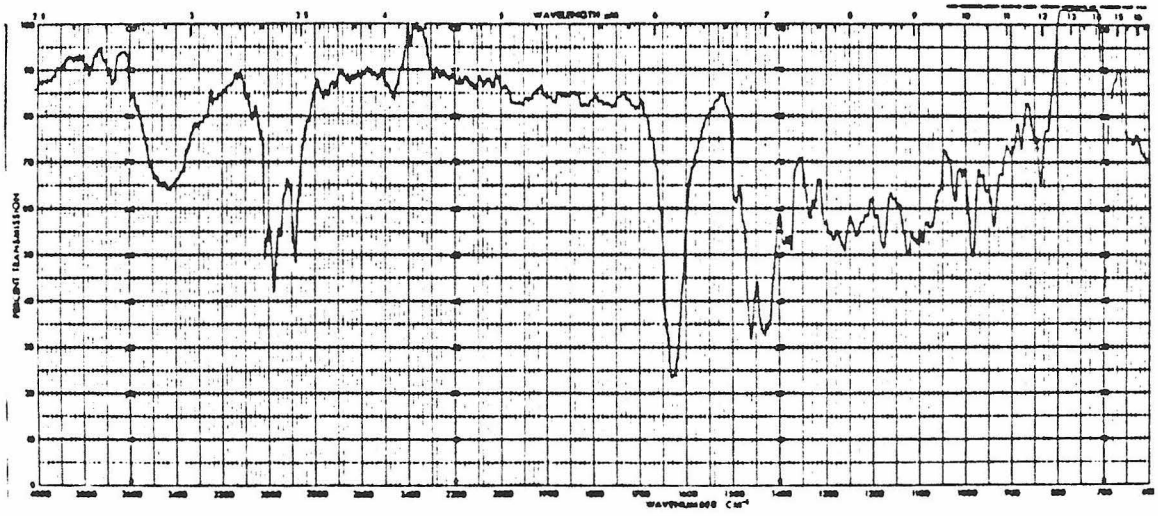

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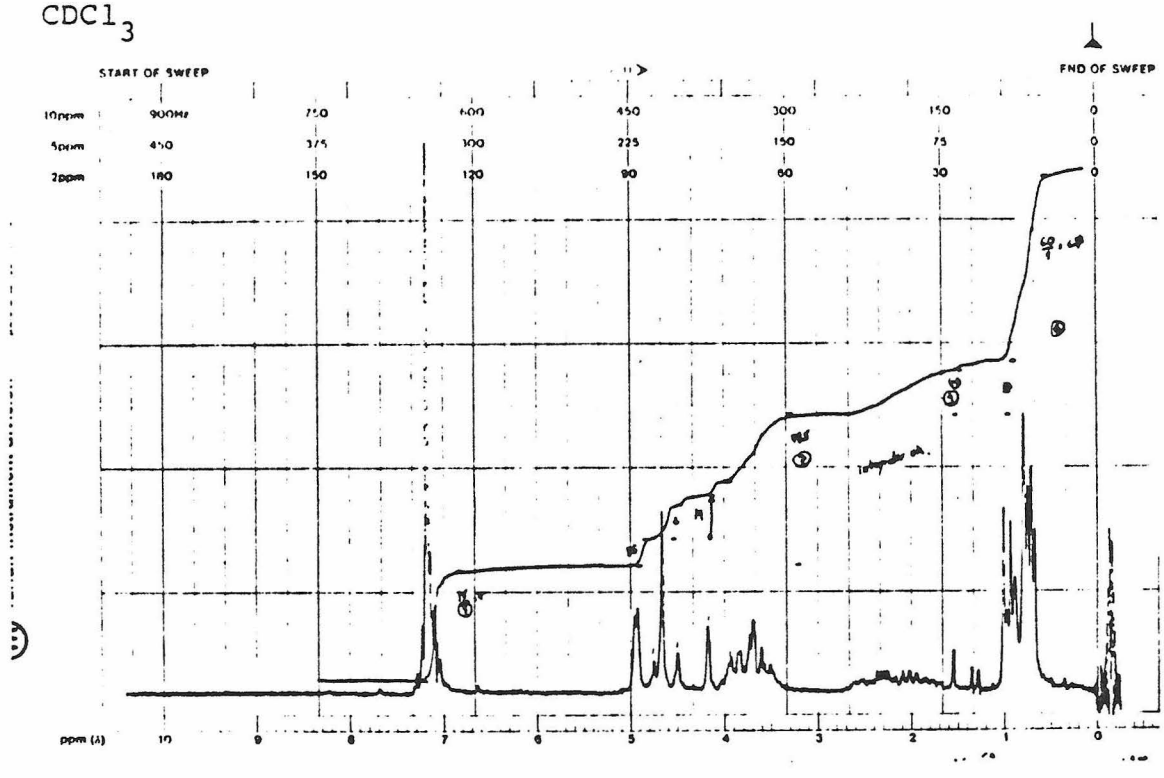

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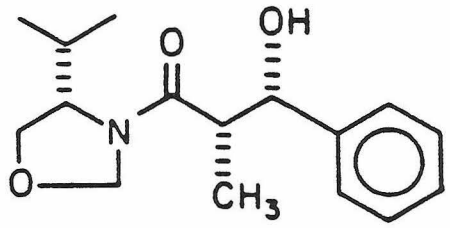

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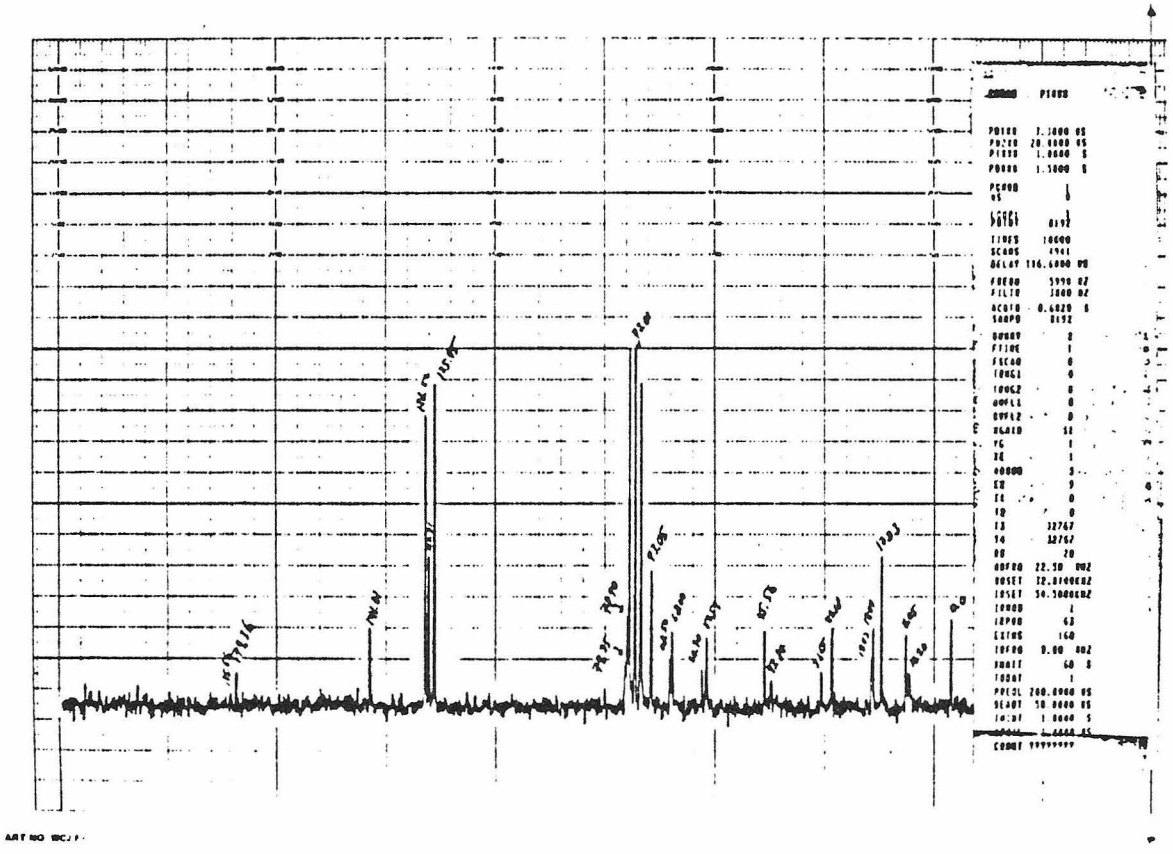

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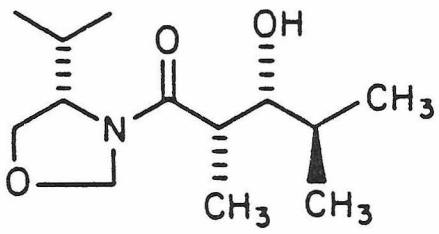

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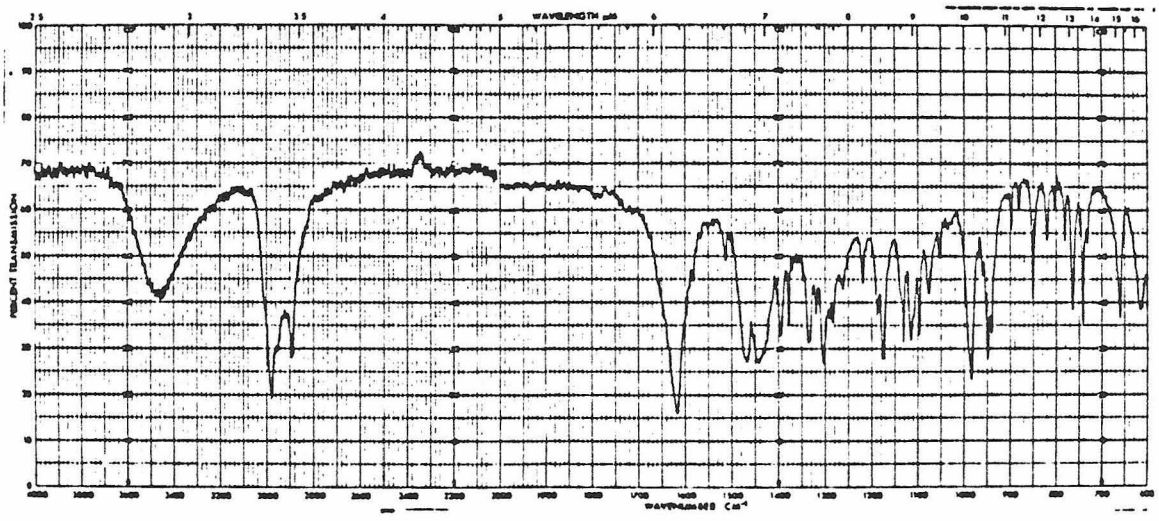

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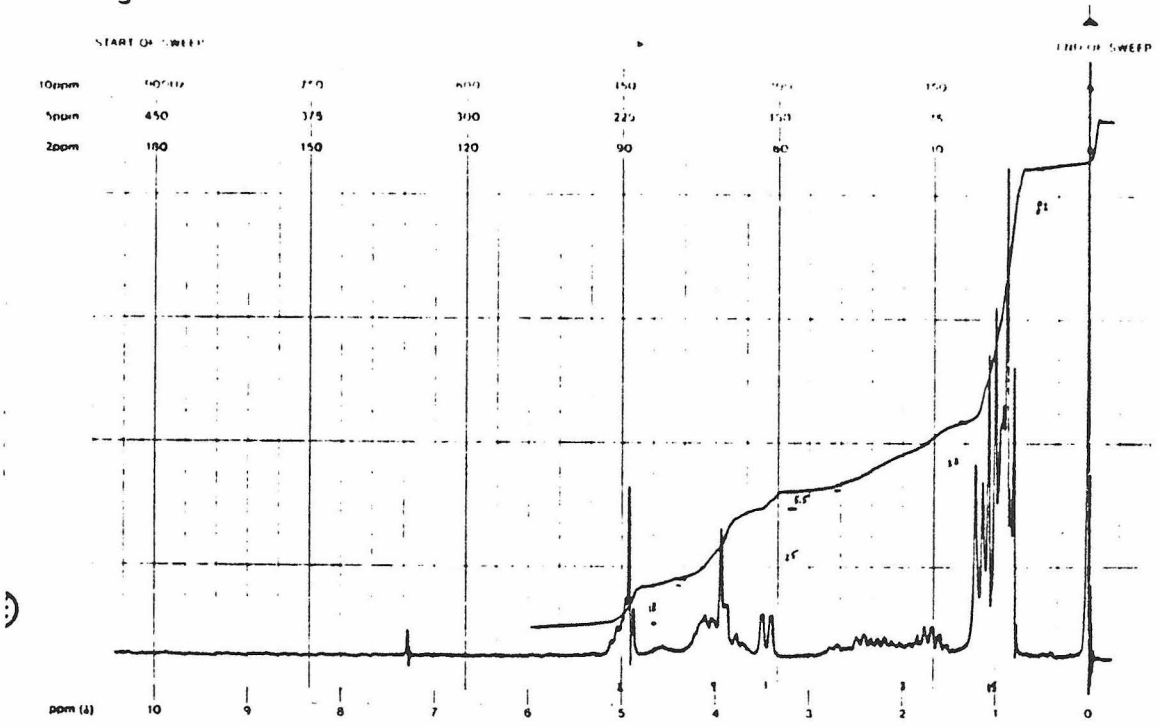

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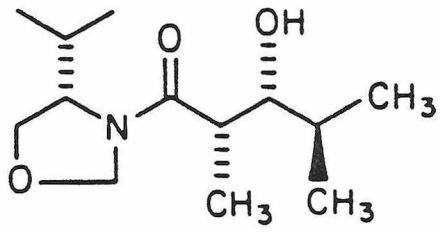

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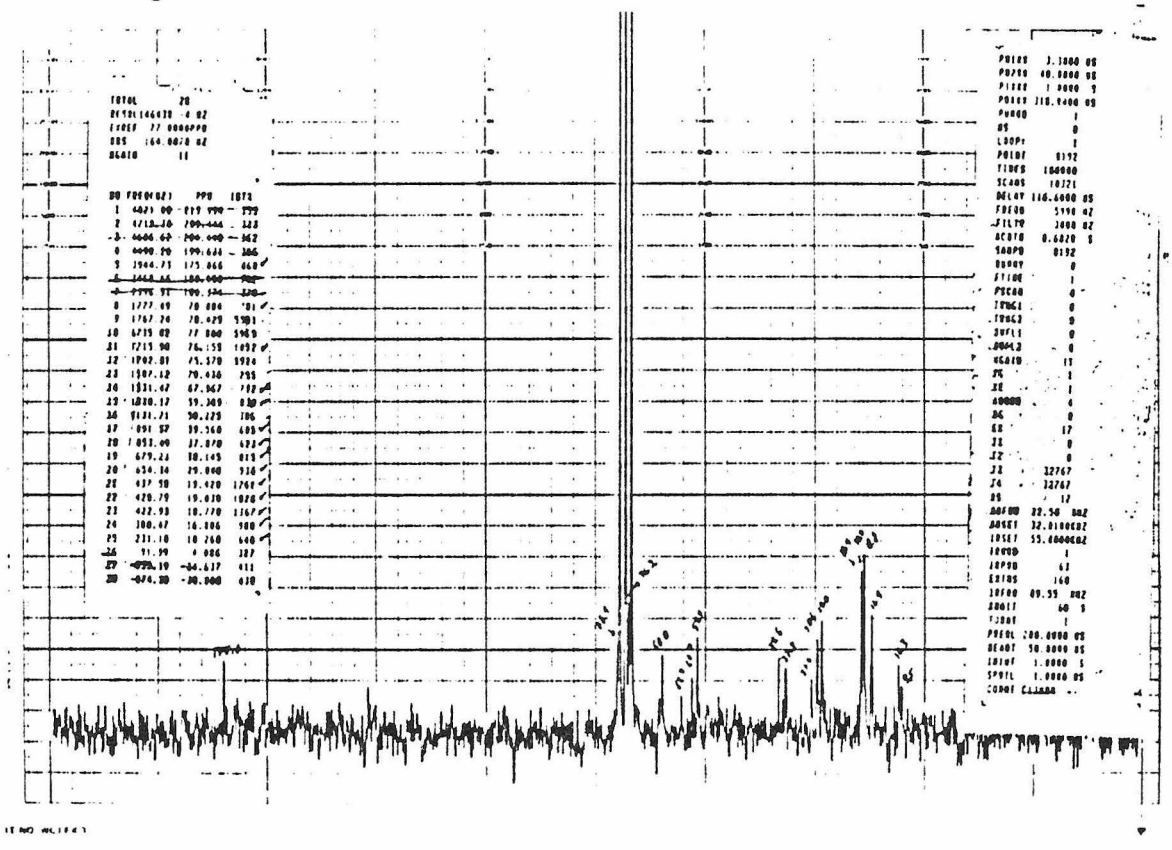

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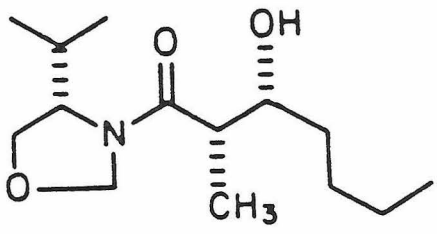

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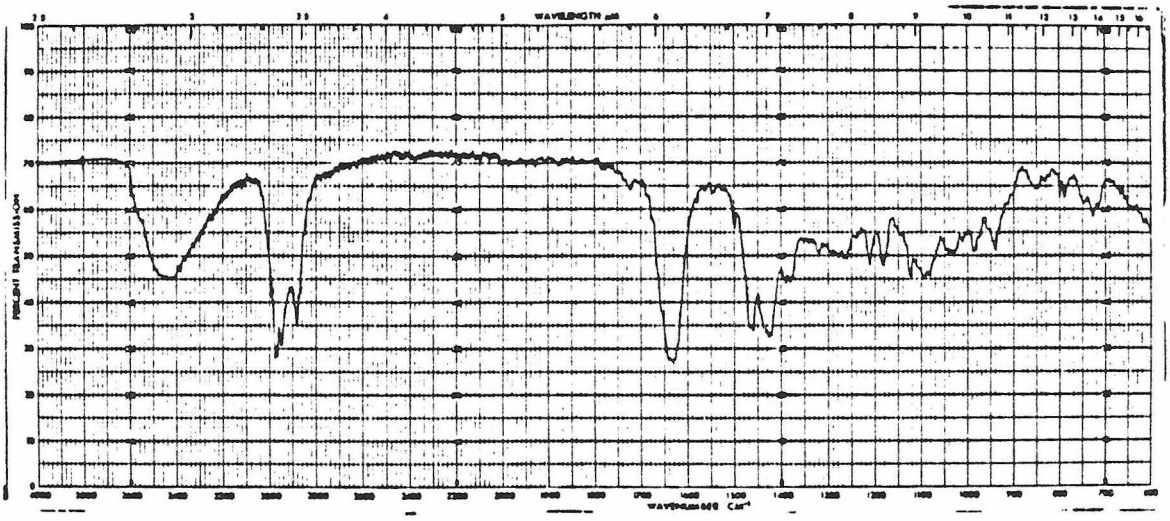

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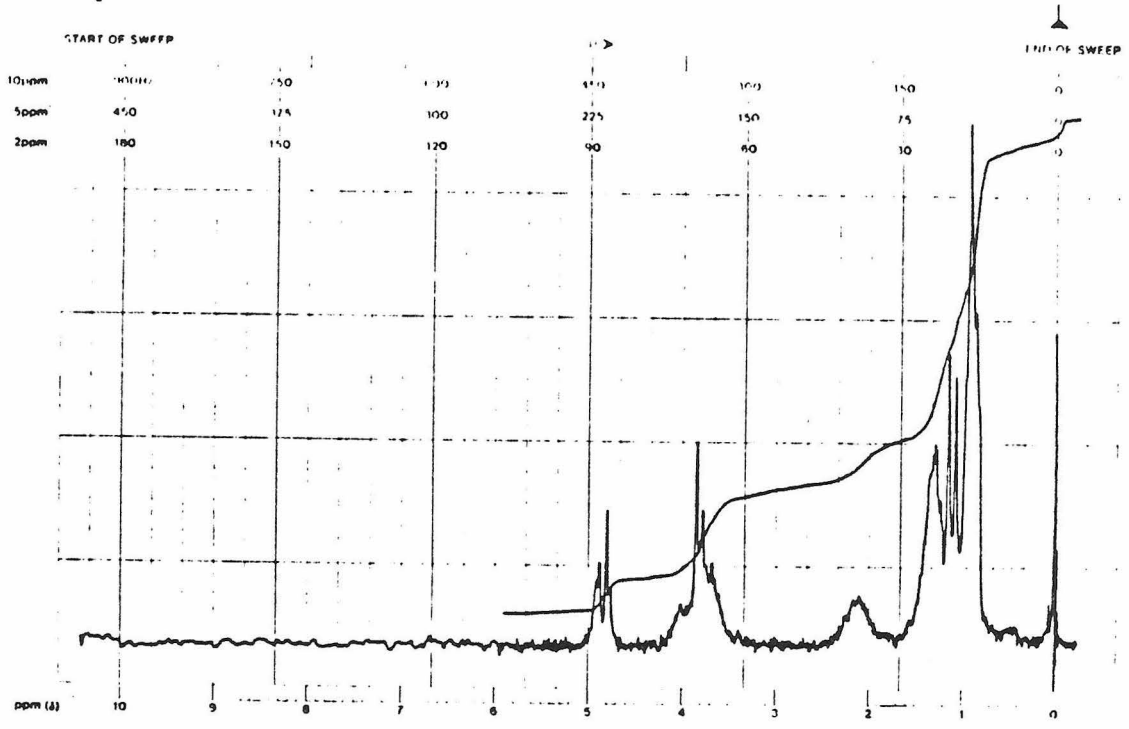

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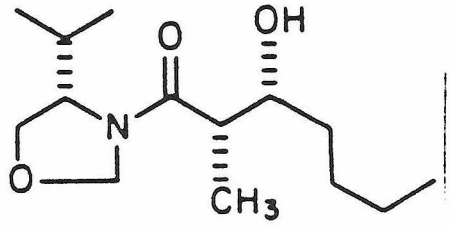

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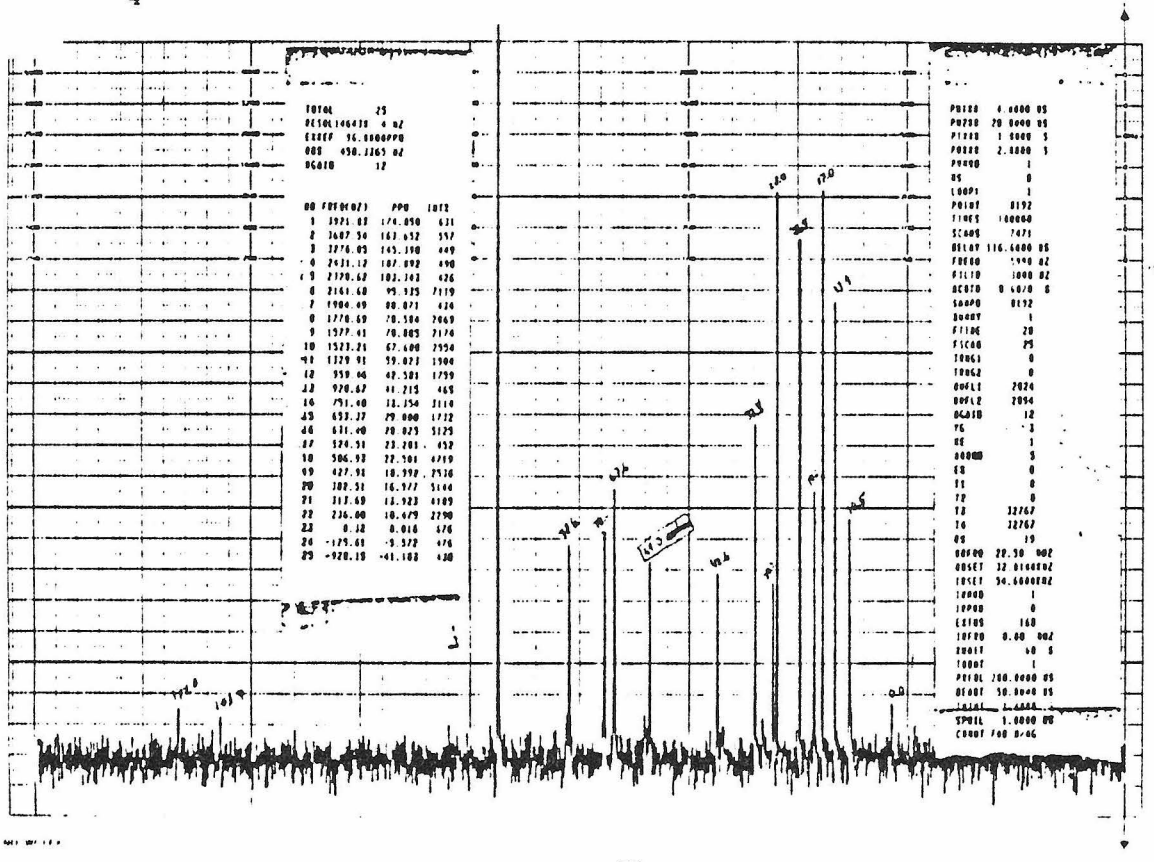

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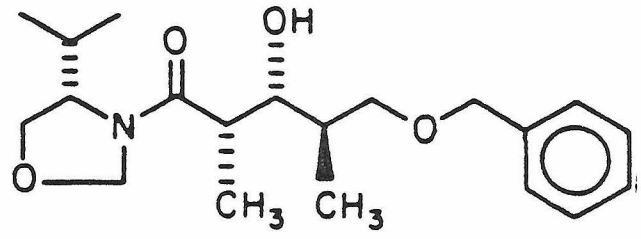

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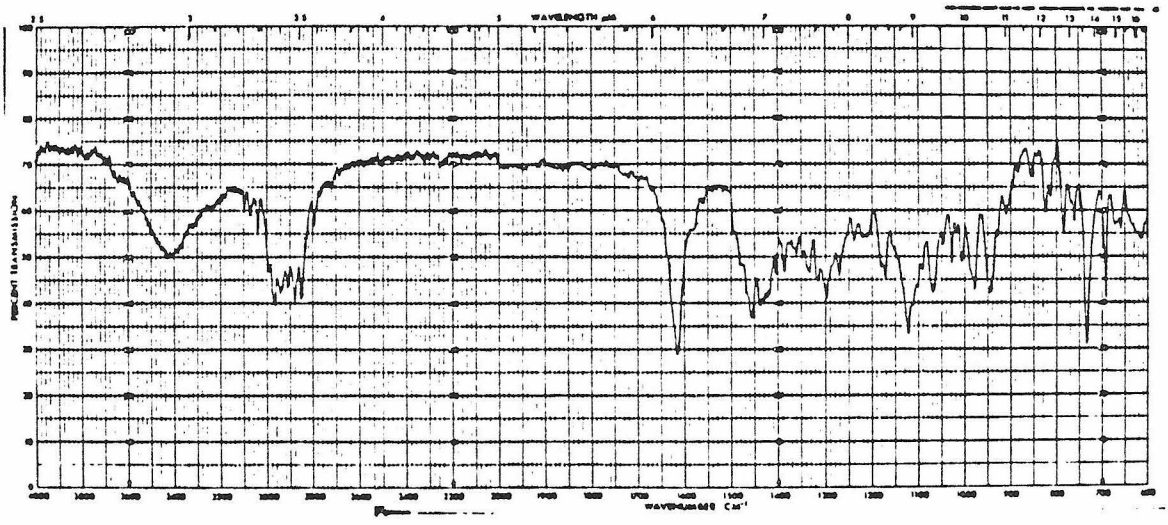

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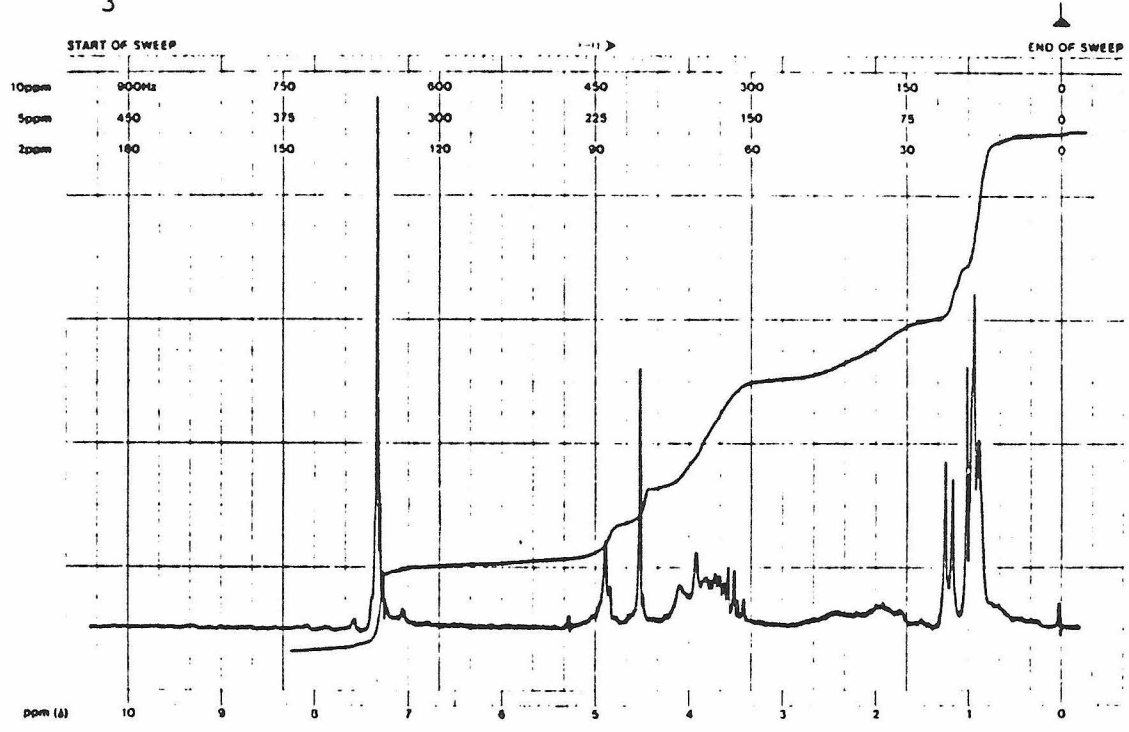

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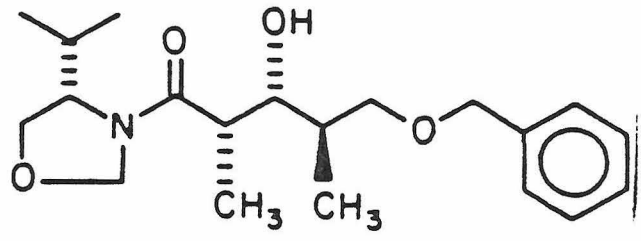

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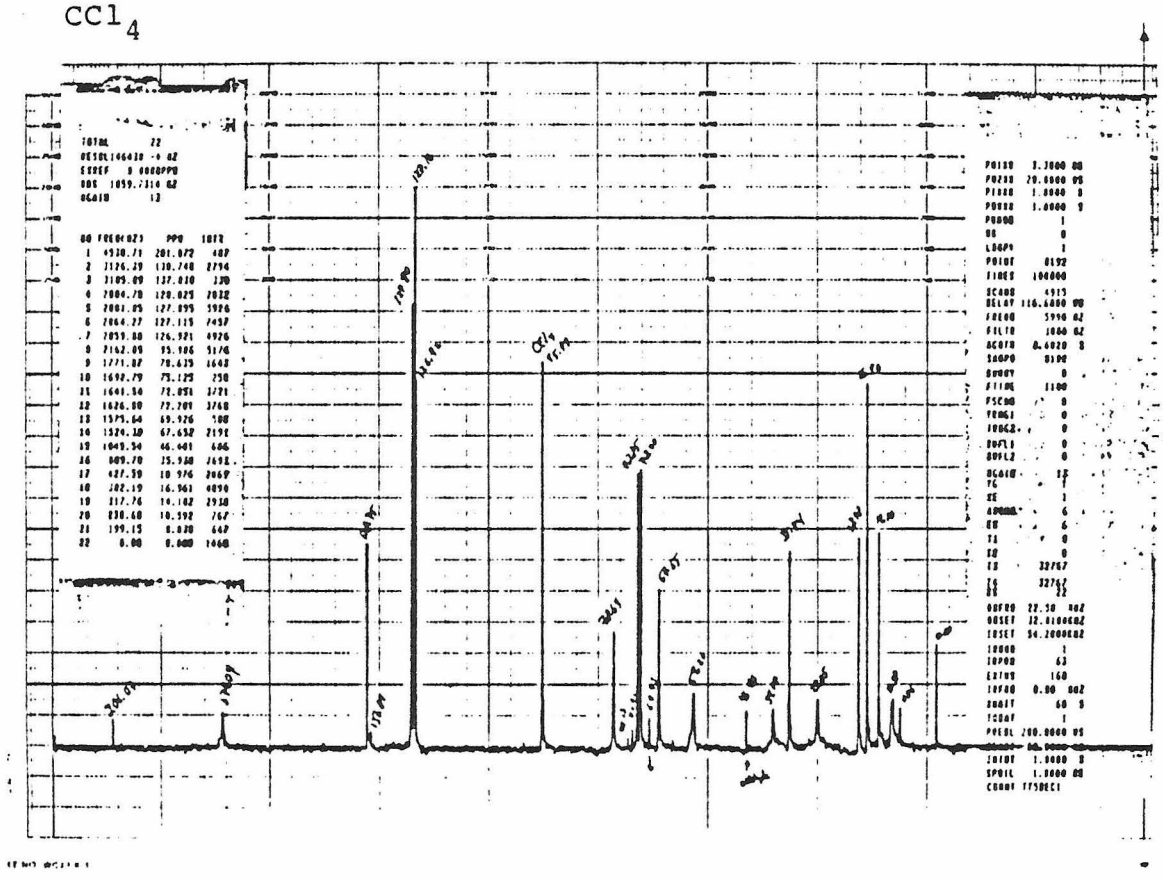

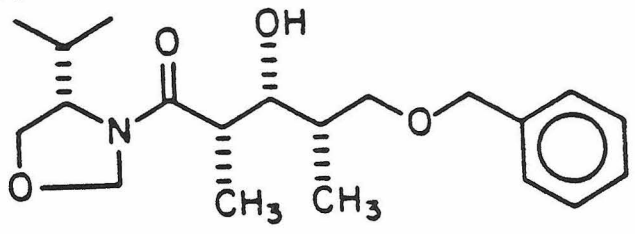

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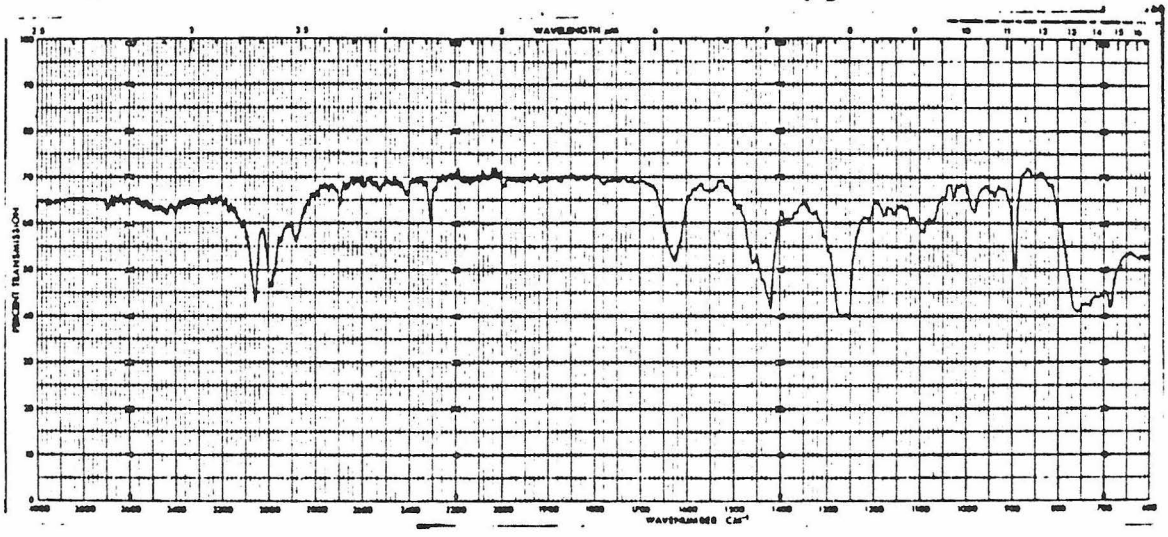

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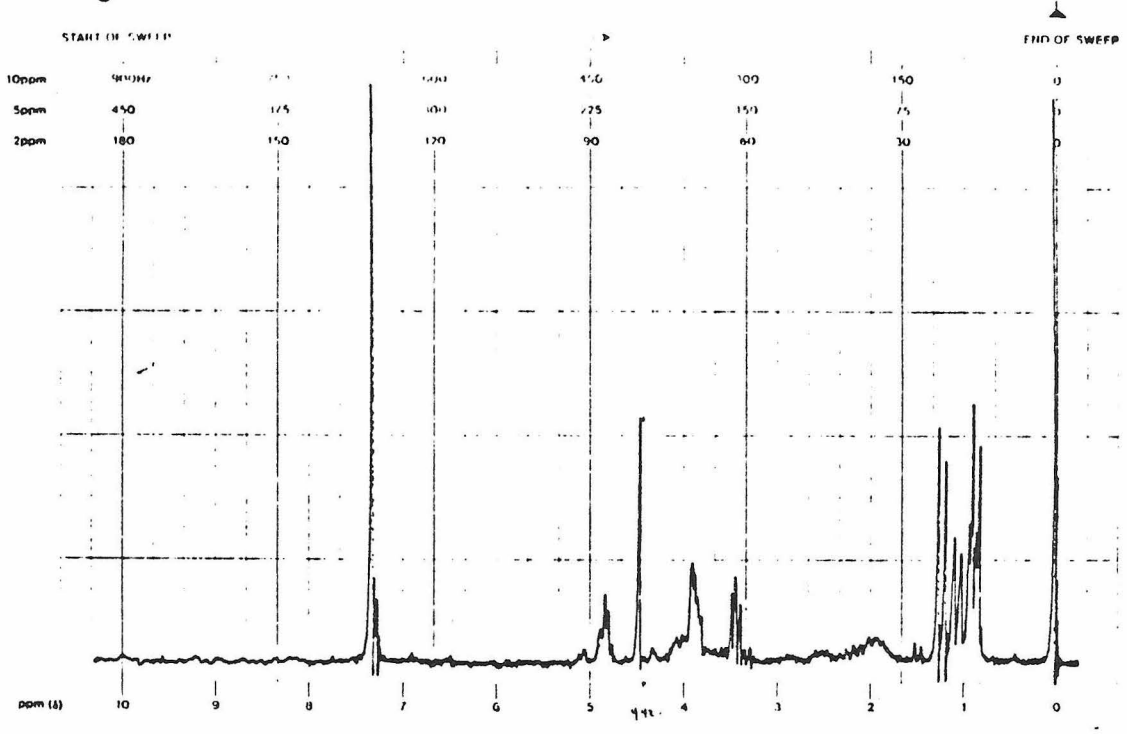

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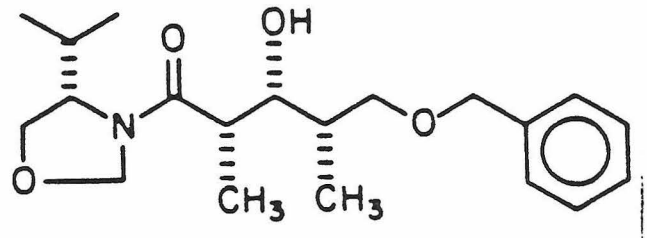

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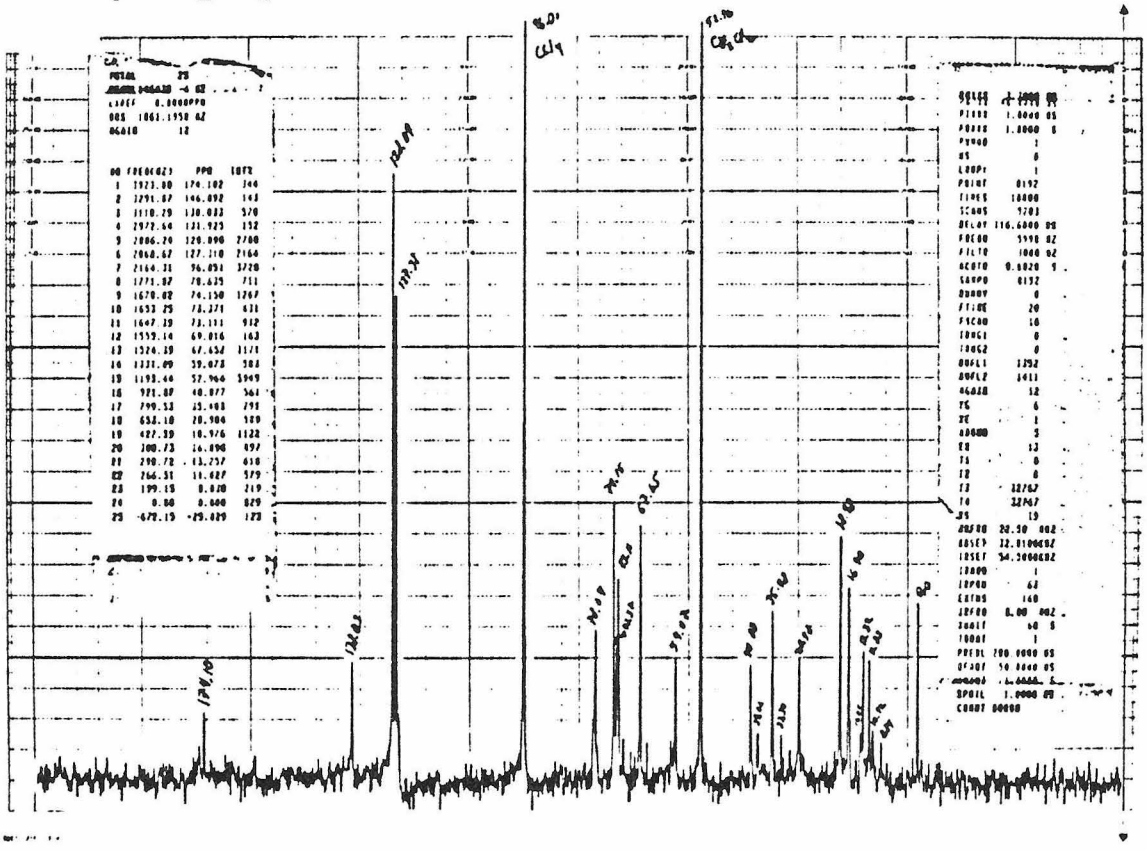

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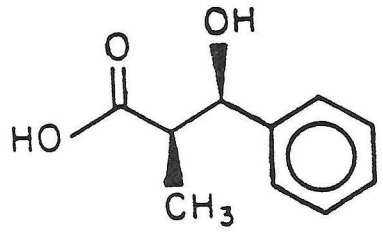
Page 112



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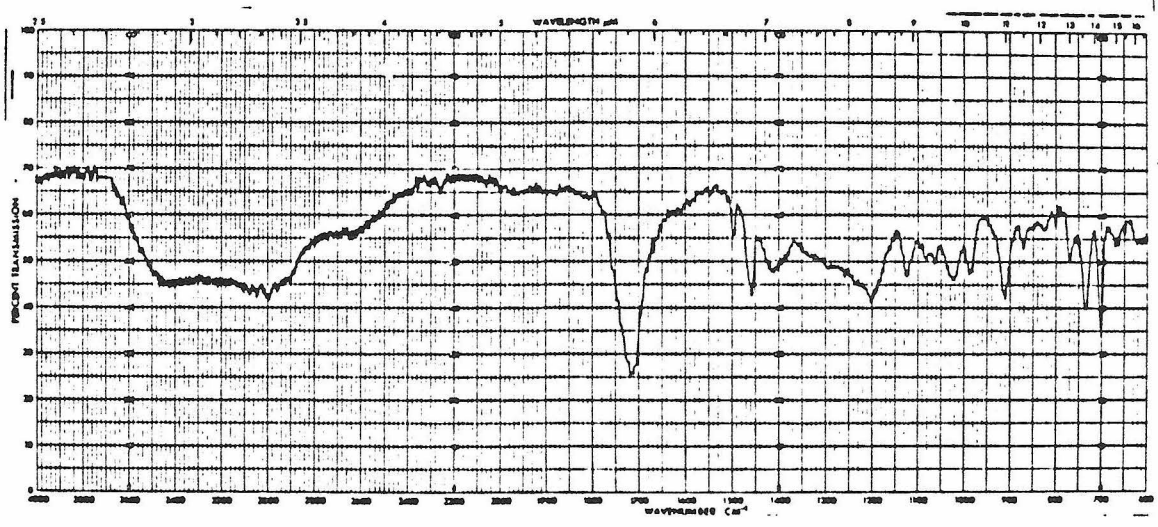

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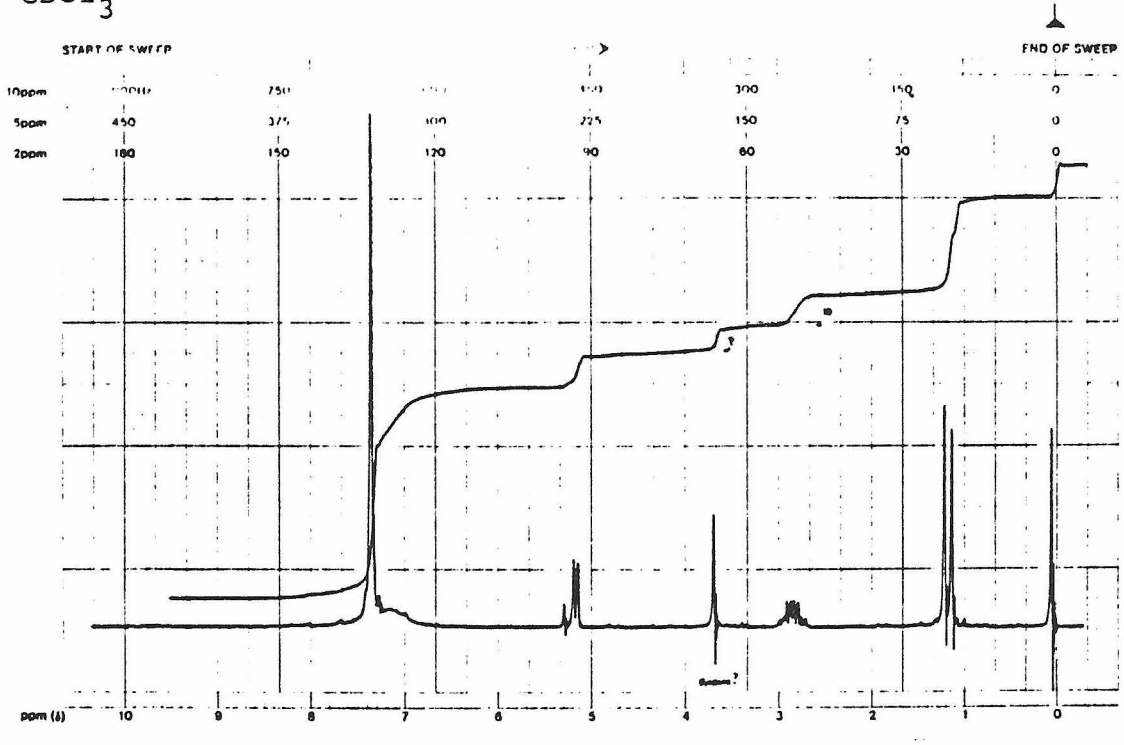

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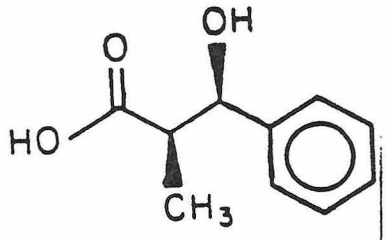

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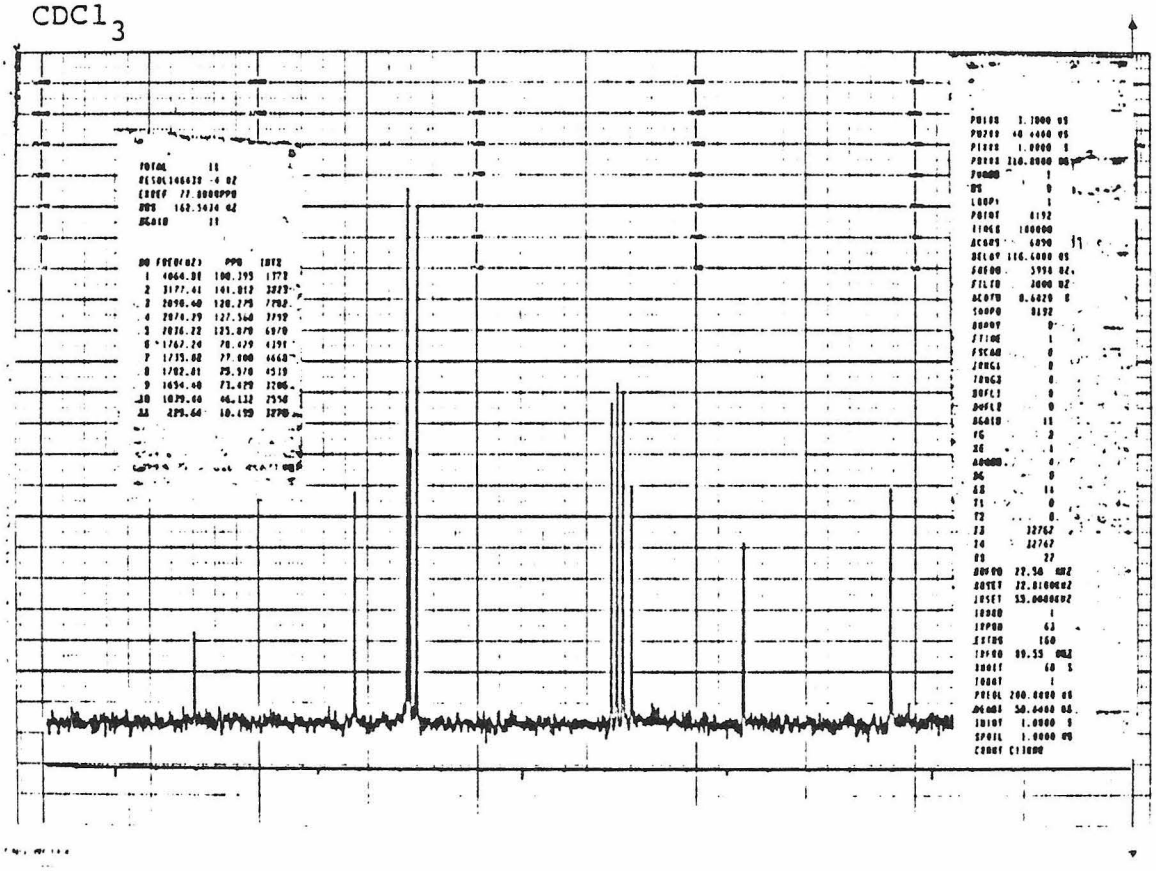

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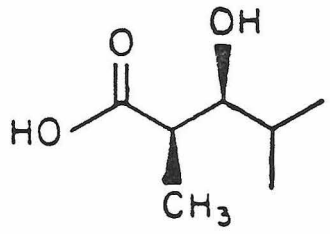

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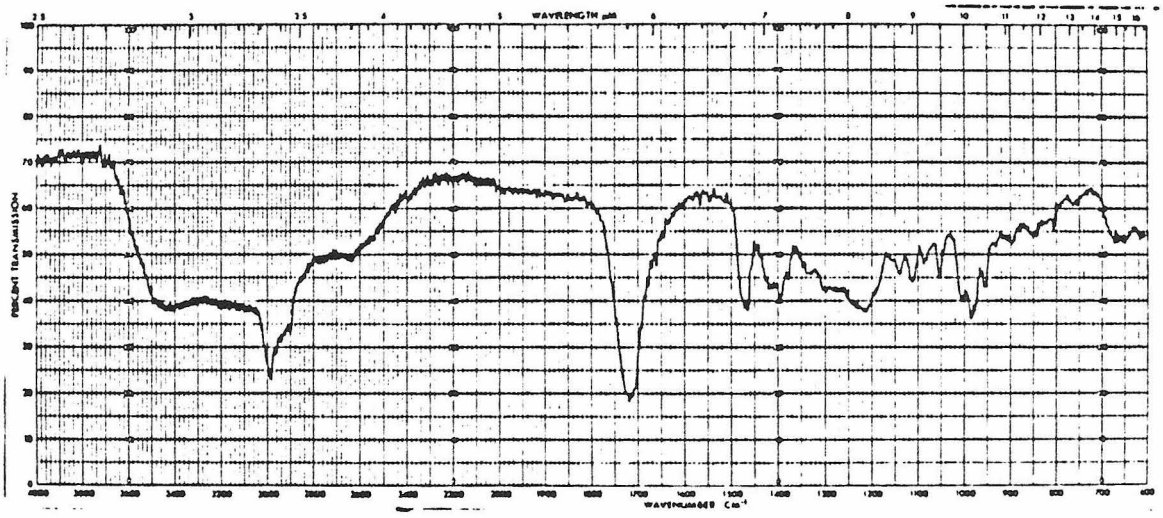

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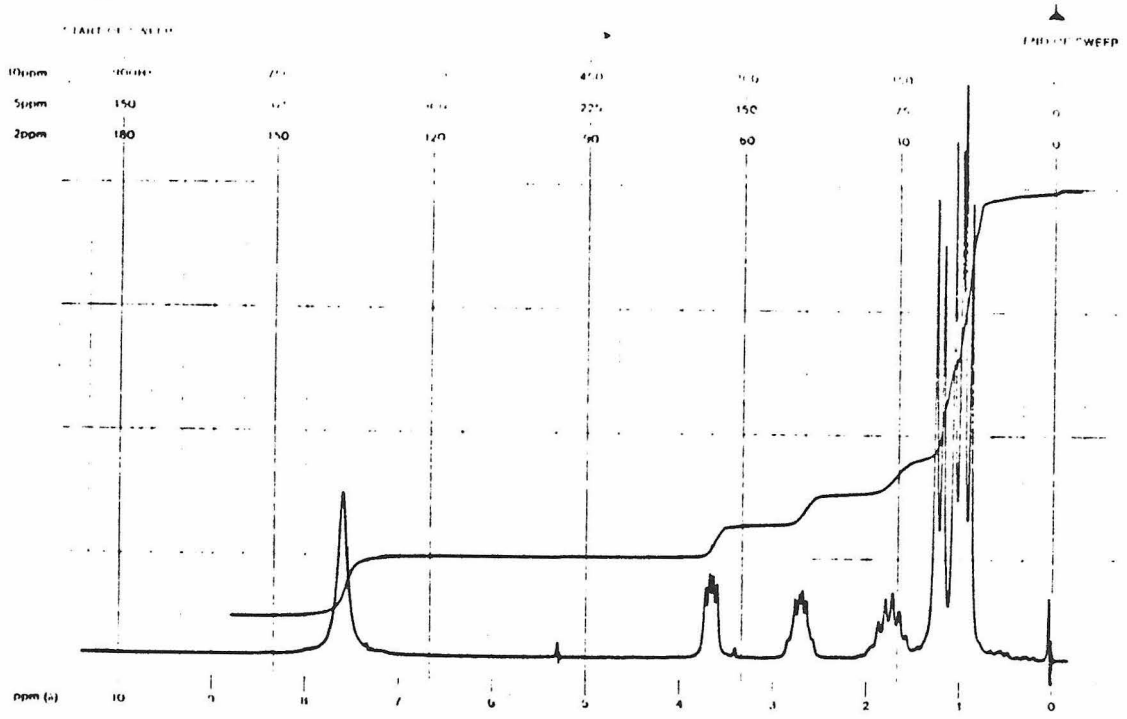

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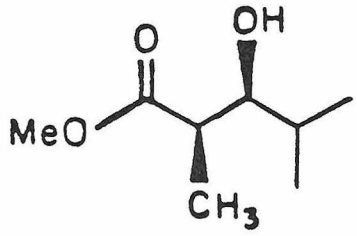

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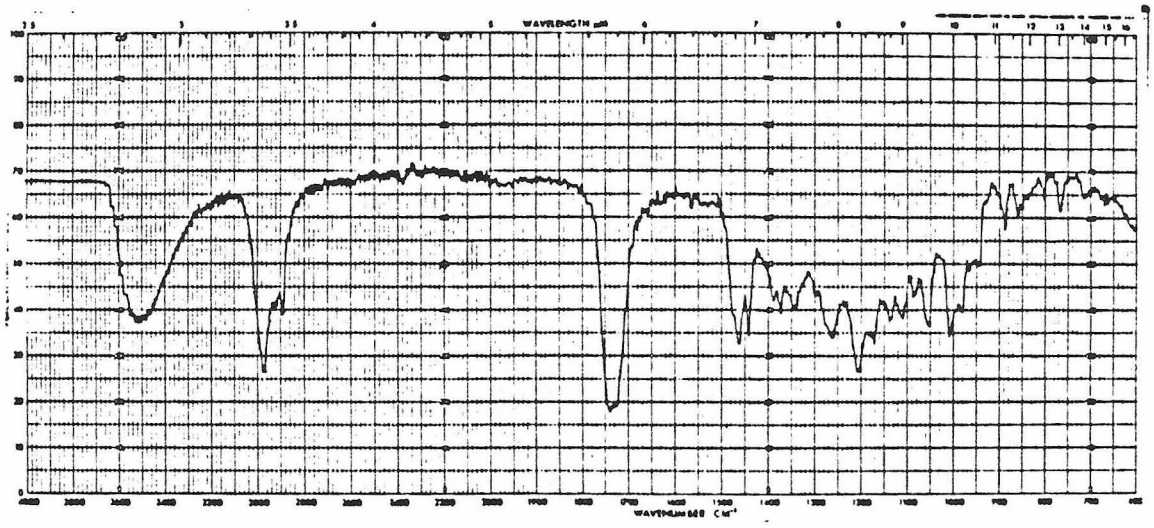

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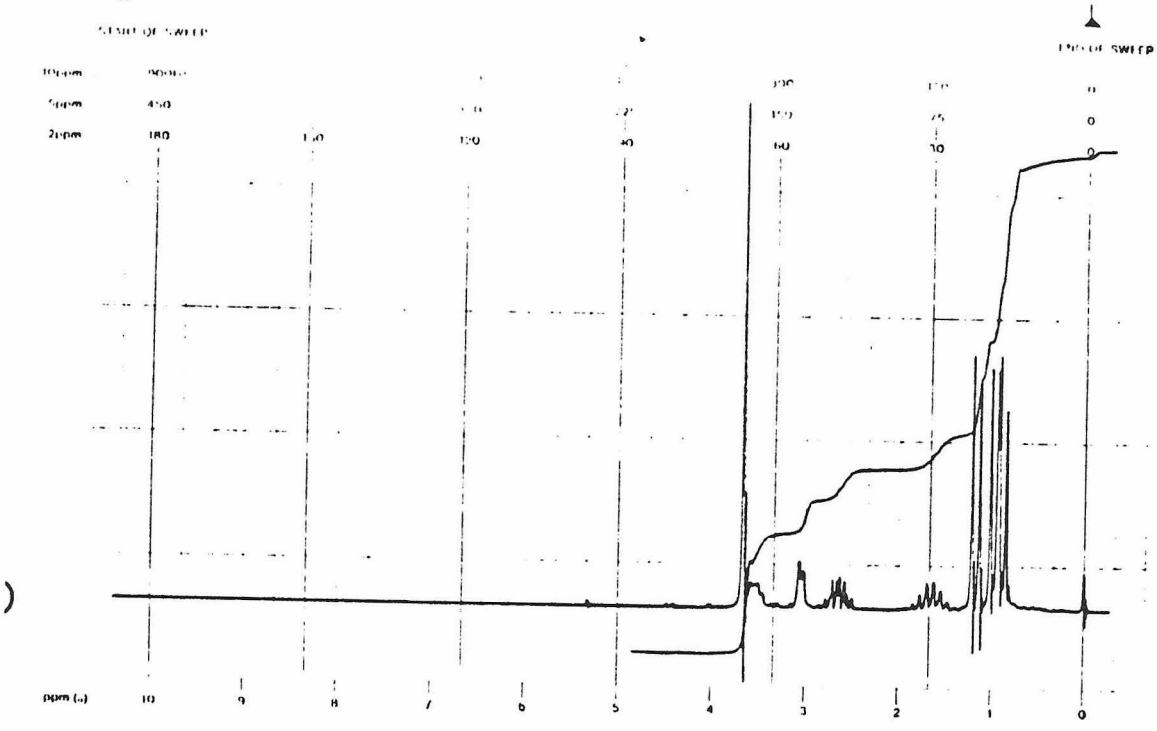

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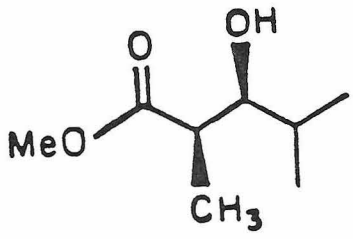

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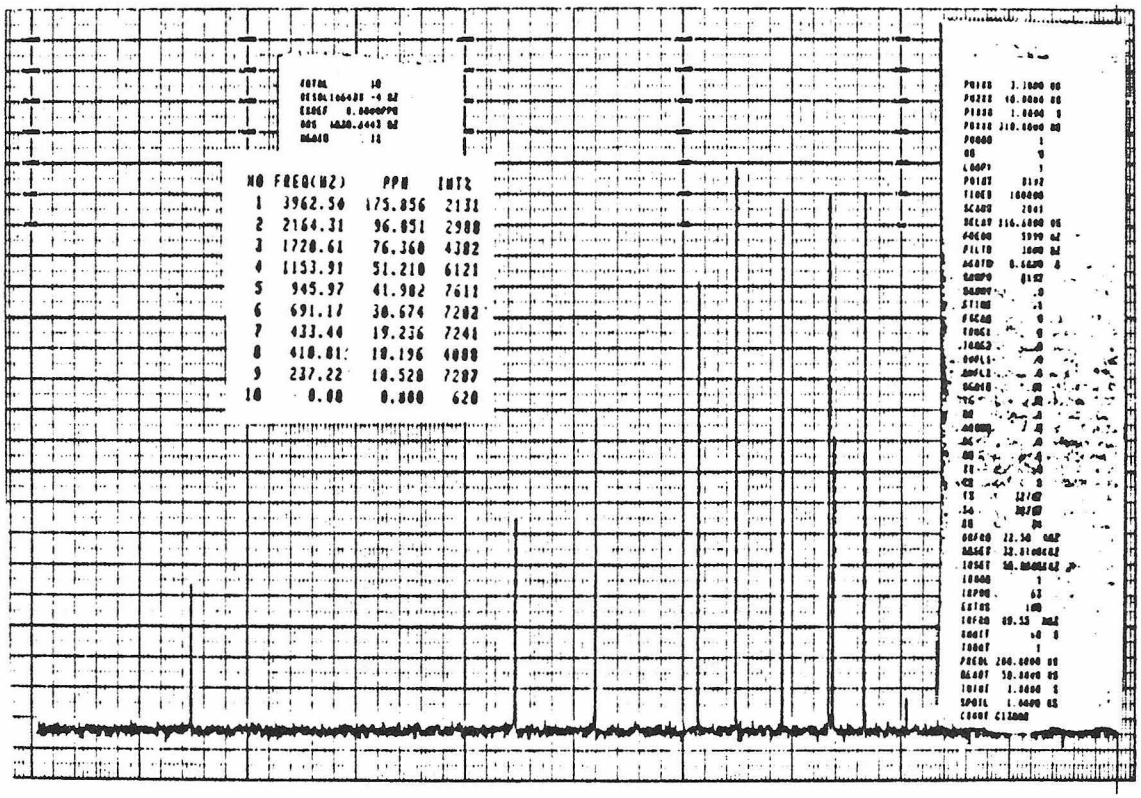

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2	2164.31	96.051	2988
3	1720.61	76.360	4382
4	1153.91	51.210	6121
5	945.97	41.982	7611
6	691.17	30.674	7282
7	433.44	19.236	7241
8	418.81	18.196	4088
9	237.22	10.528	7287
10	0.00	0.000	620

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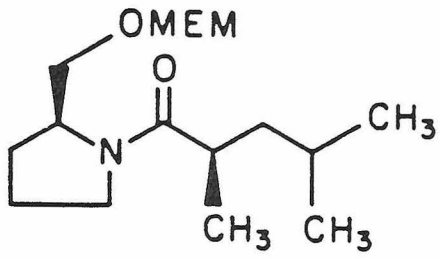

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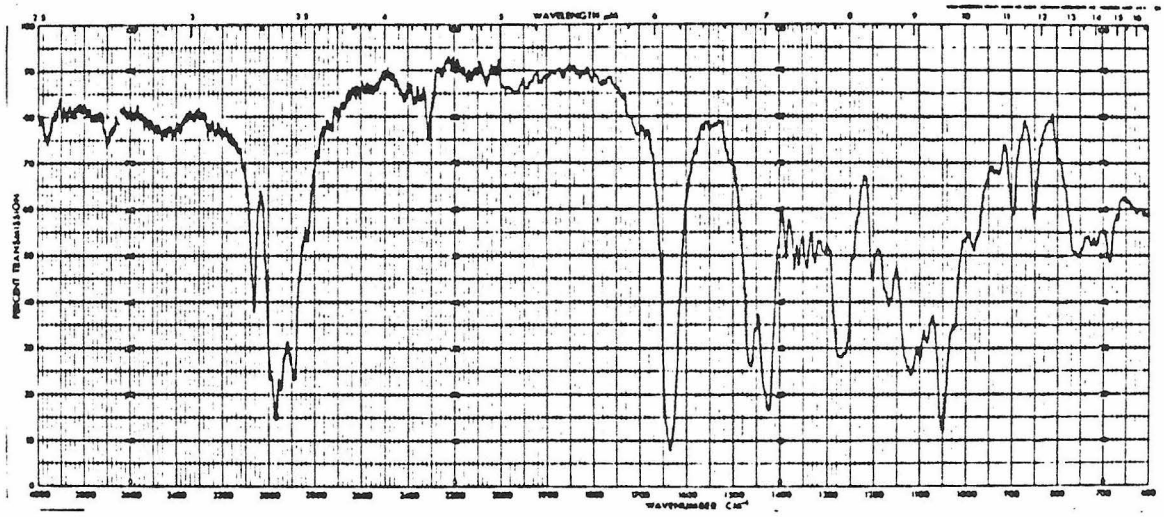

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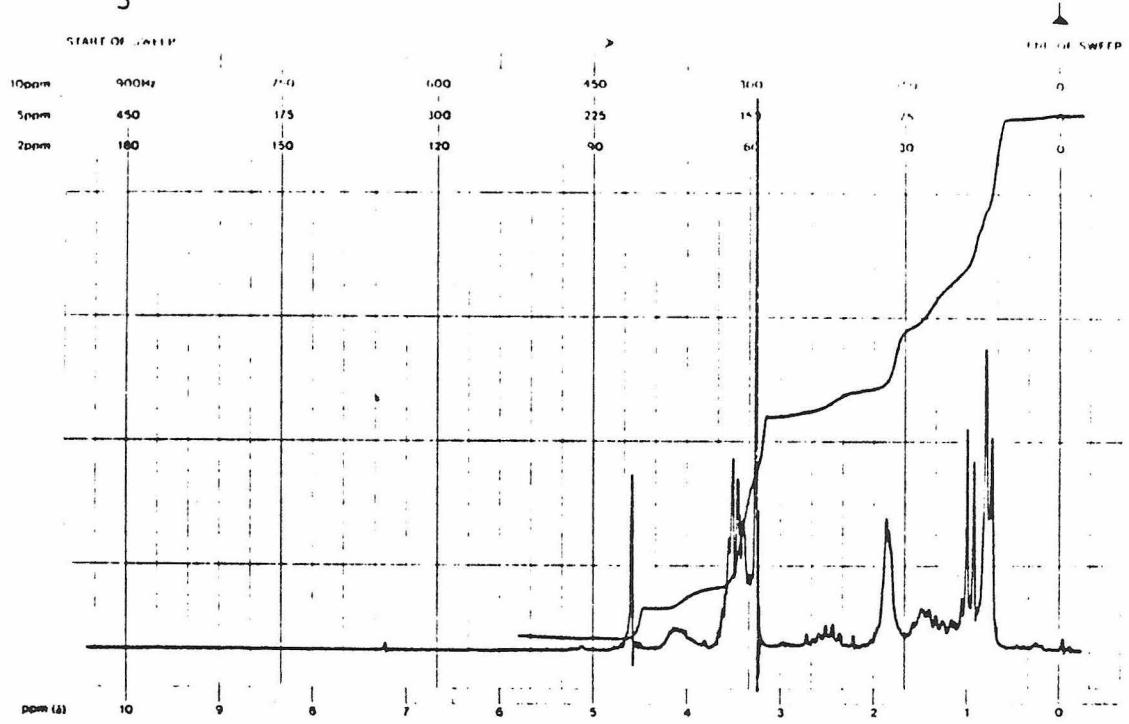

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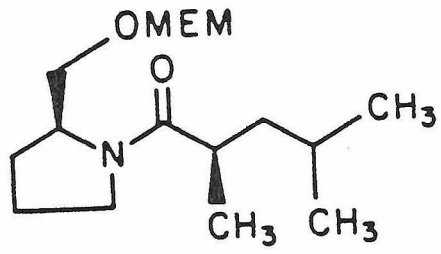

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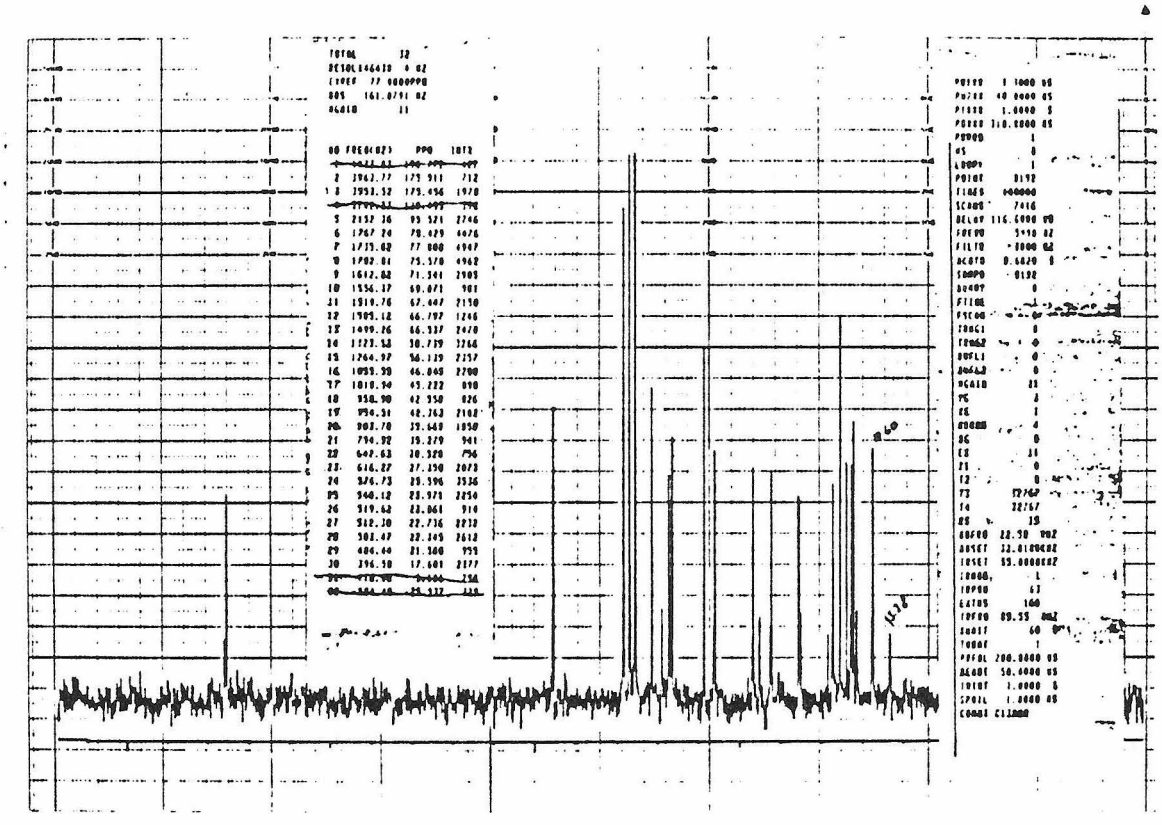

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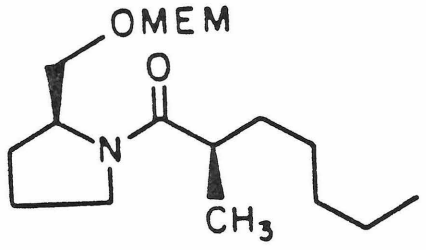

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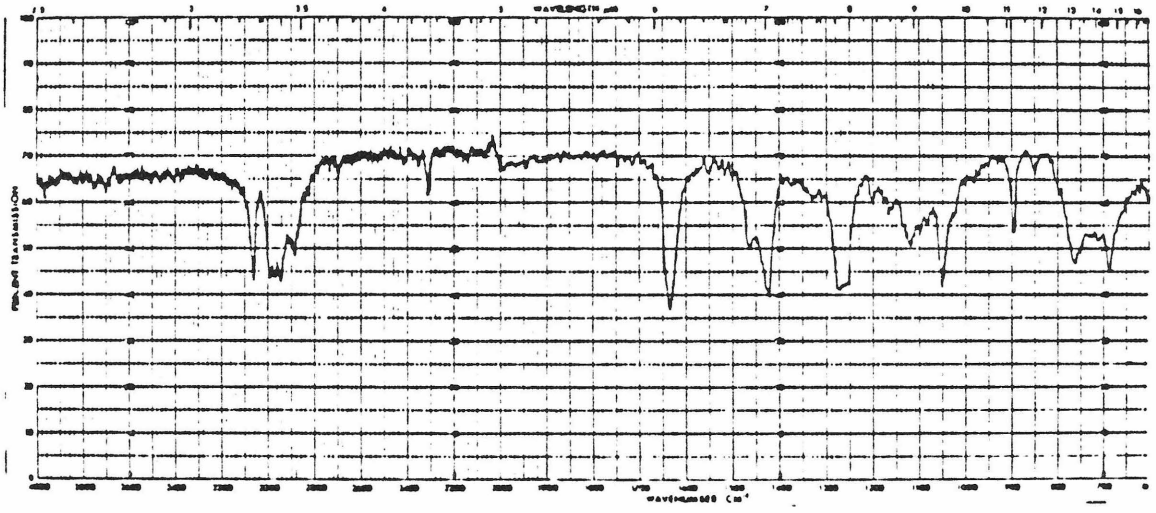

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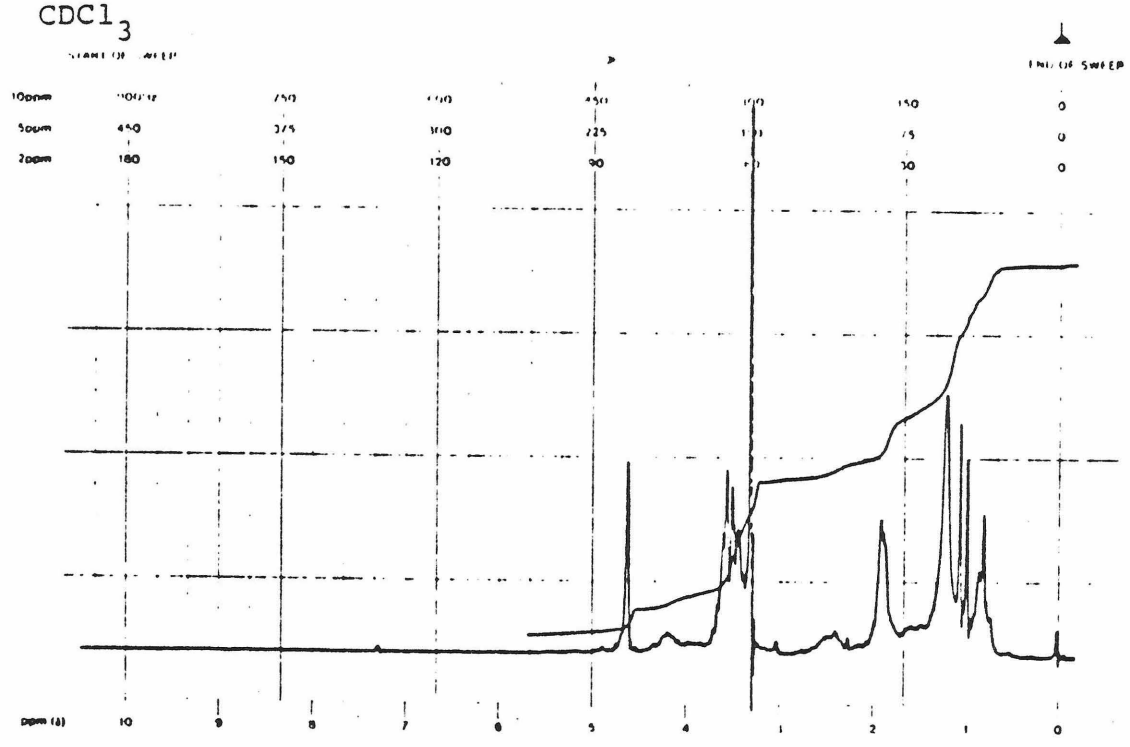

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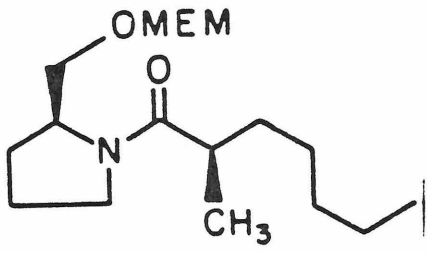

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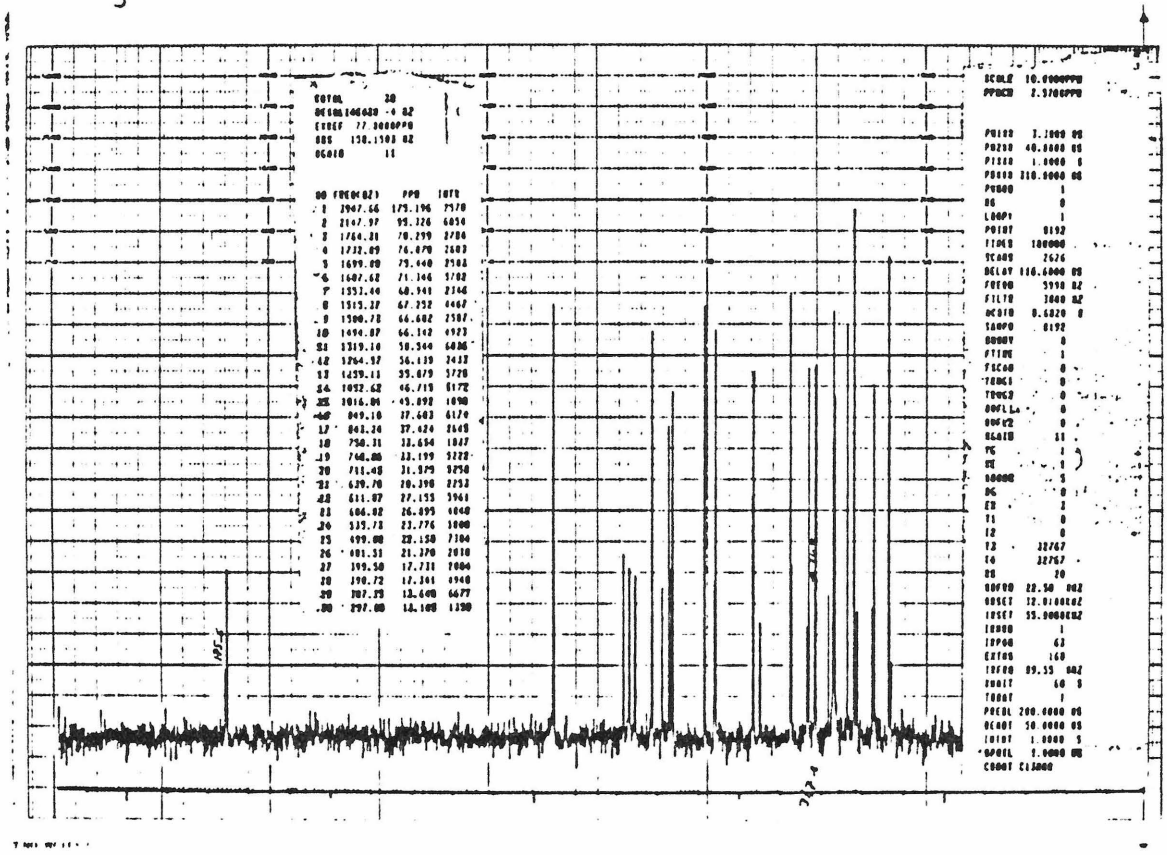

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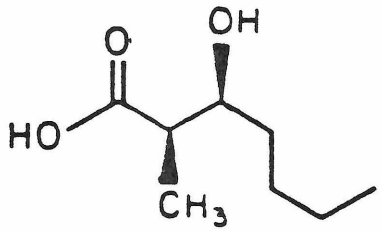

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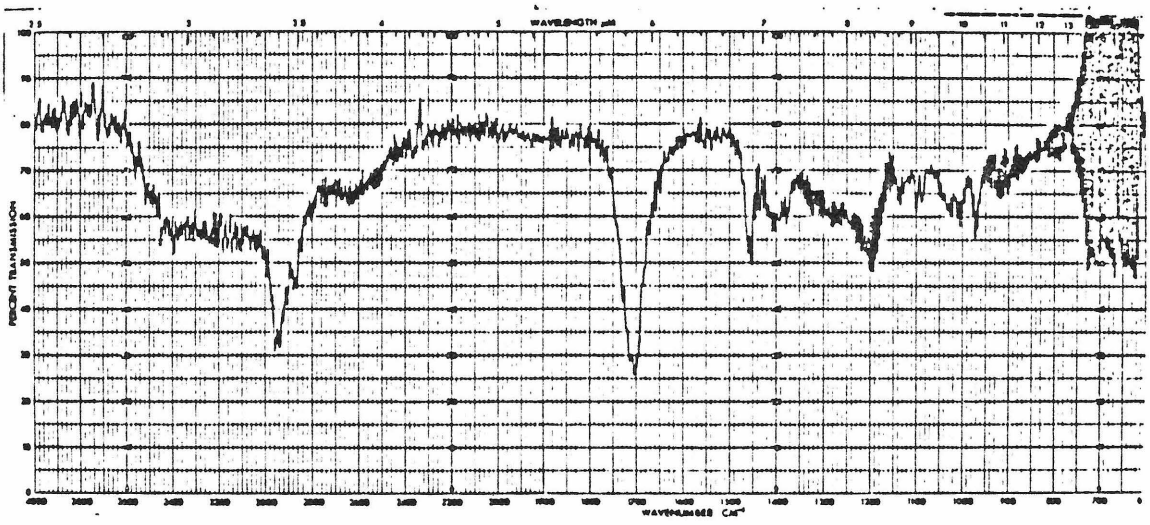

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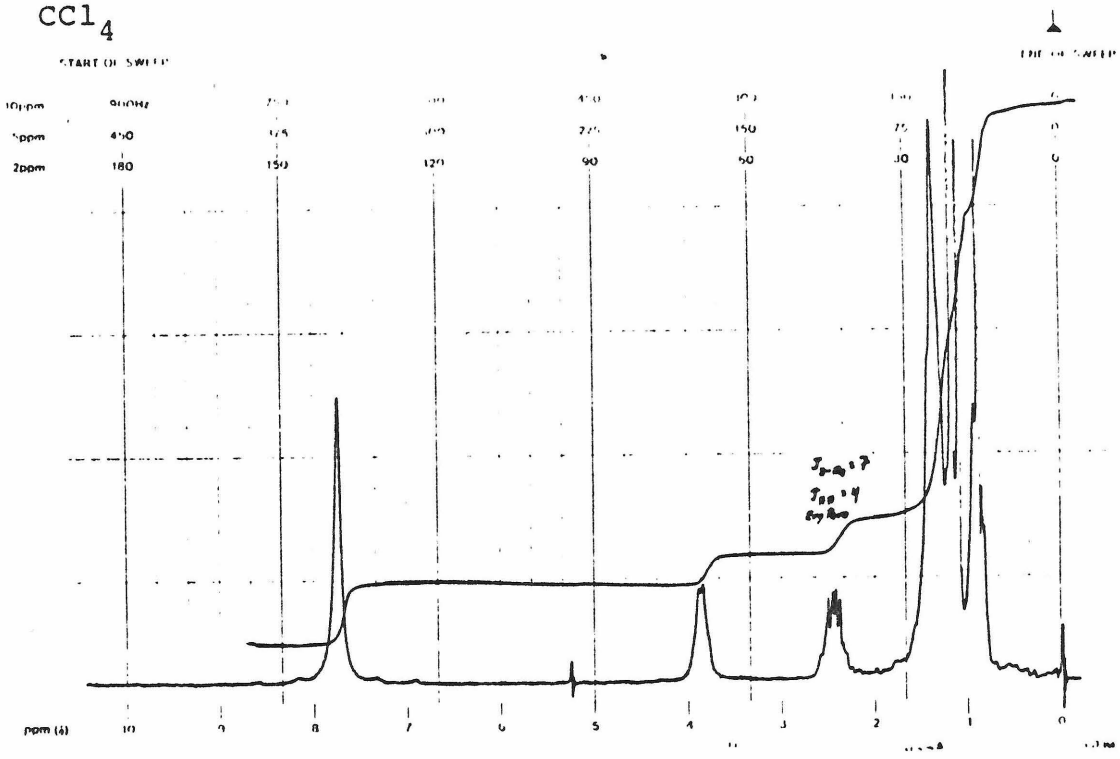

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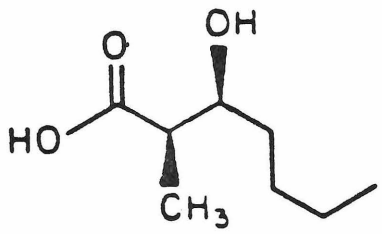

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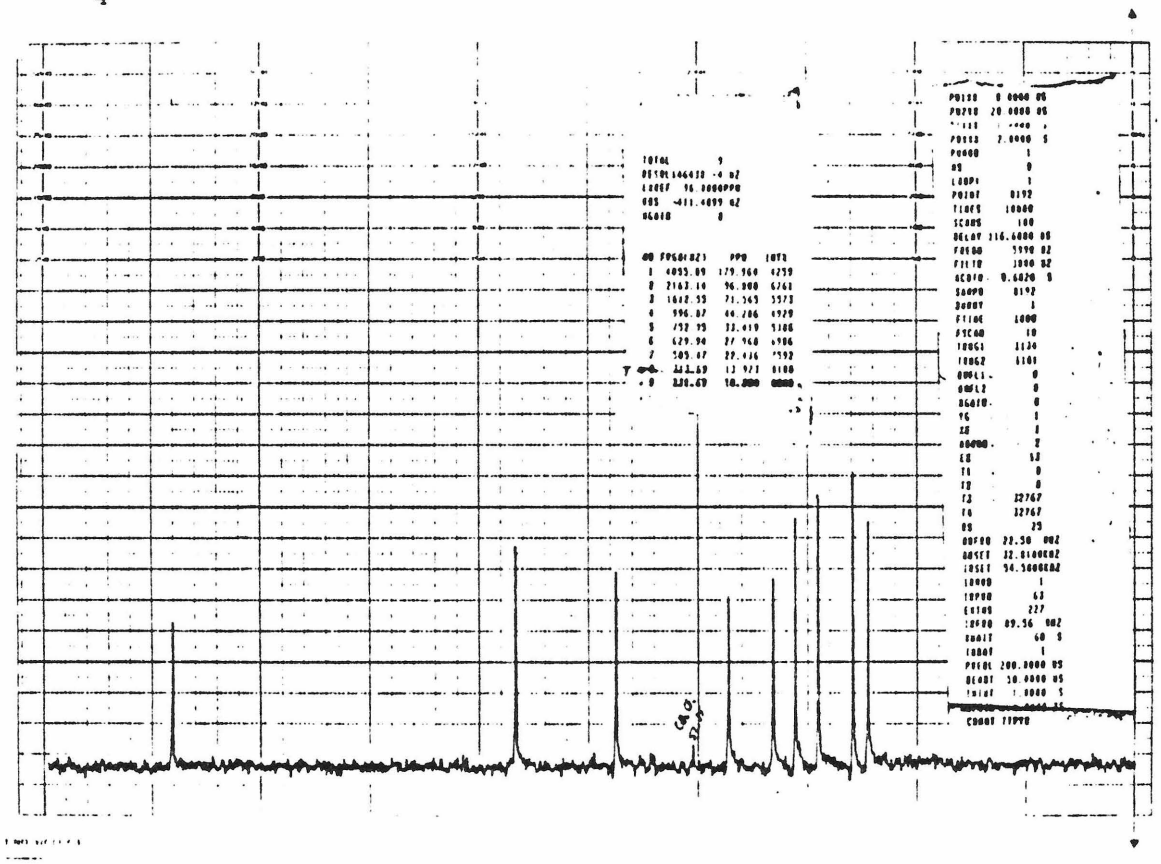

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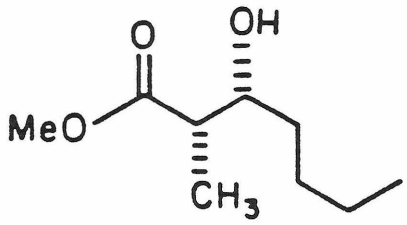

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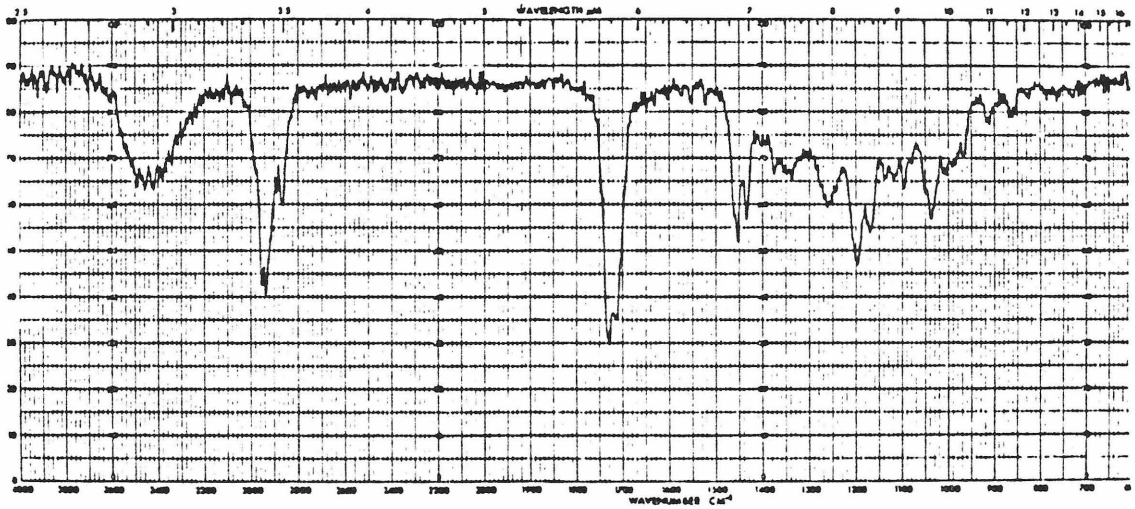

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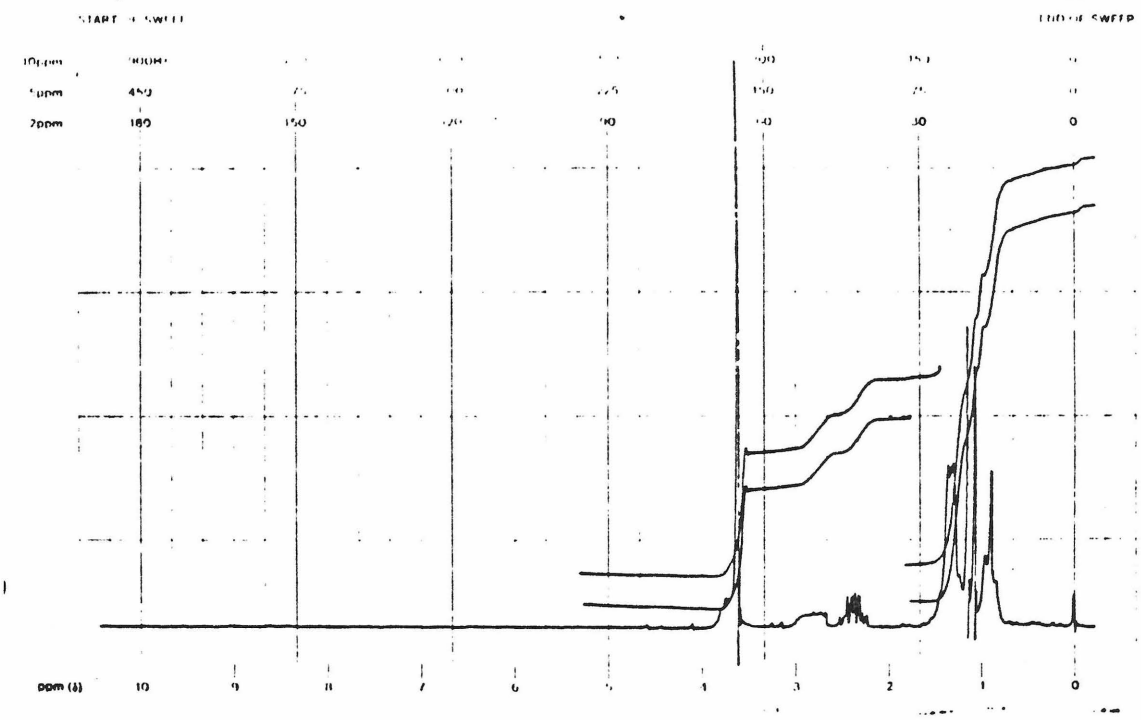

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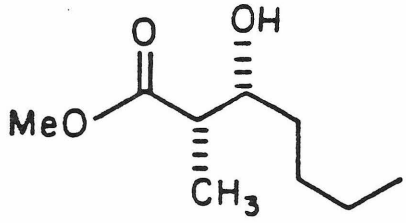

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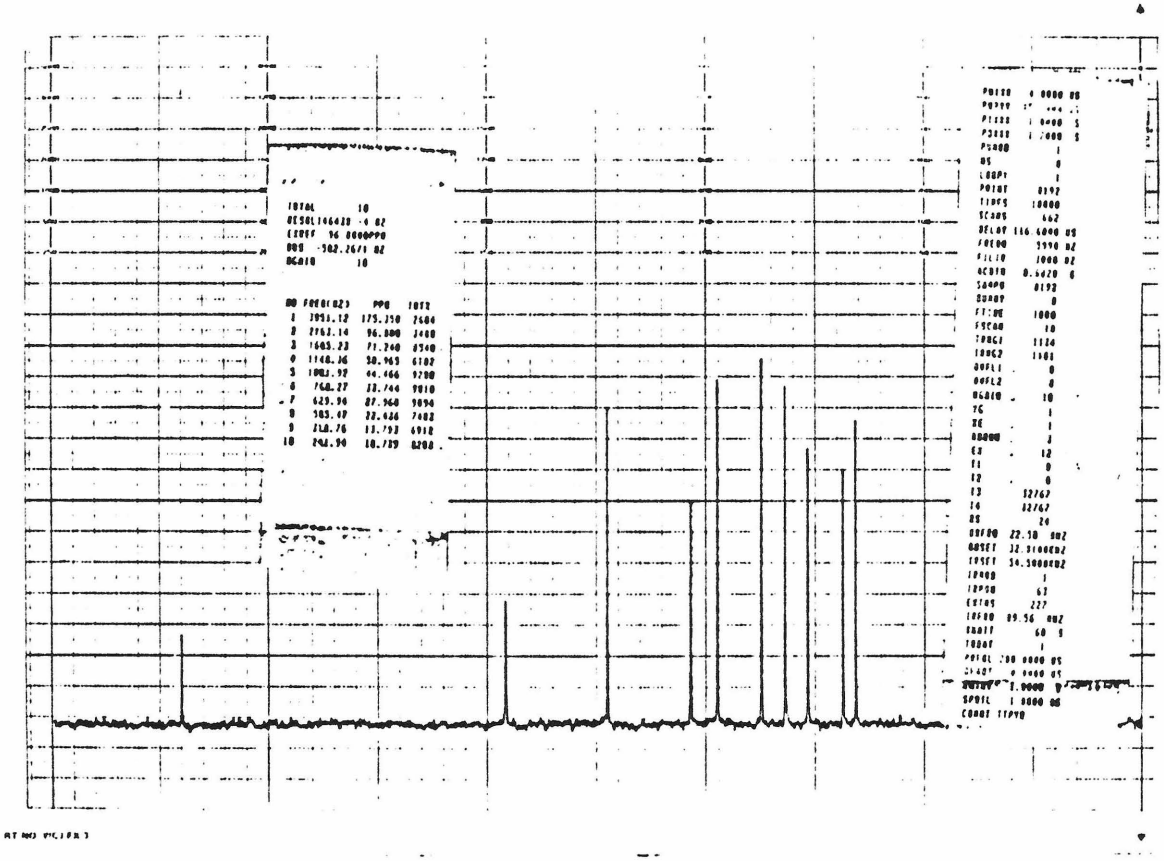

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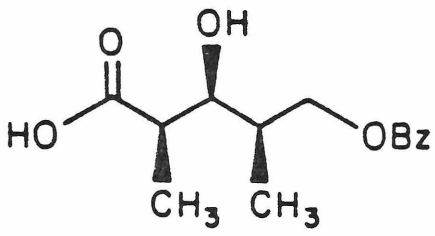

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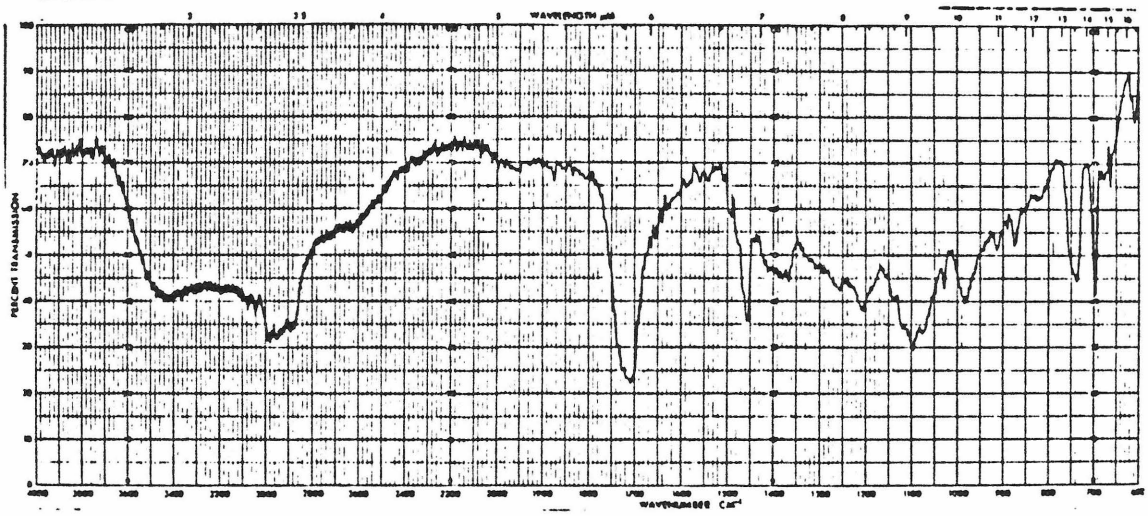

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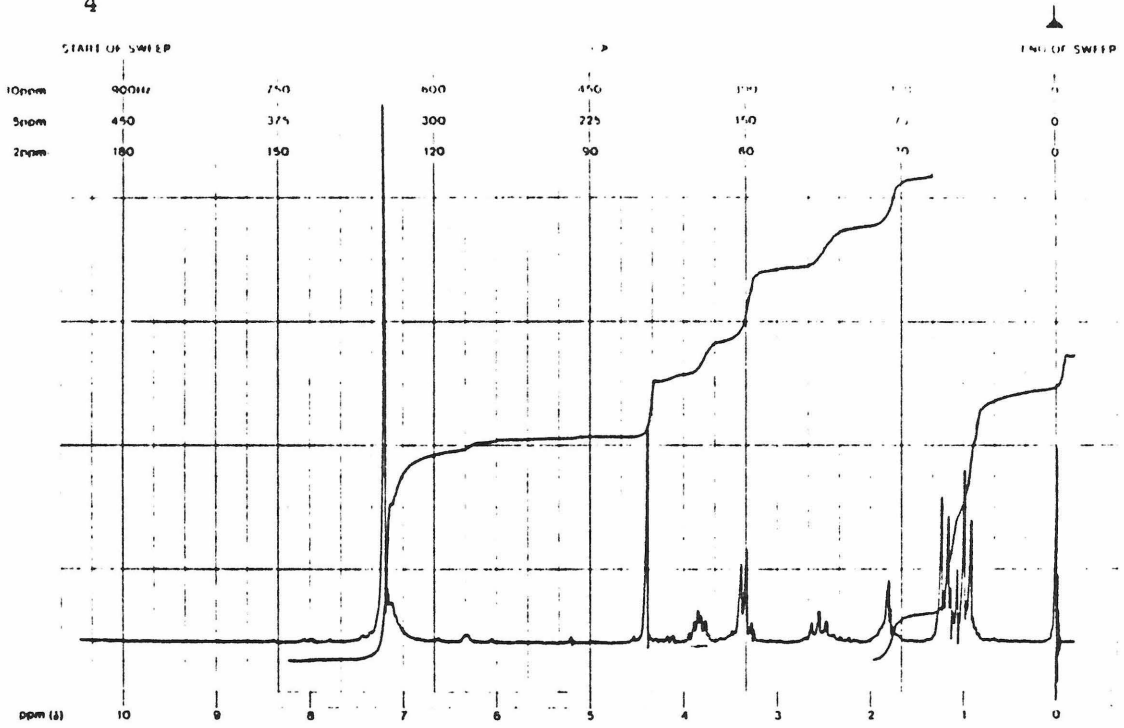

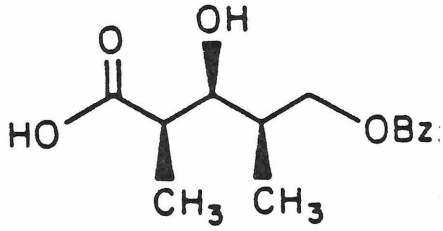

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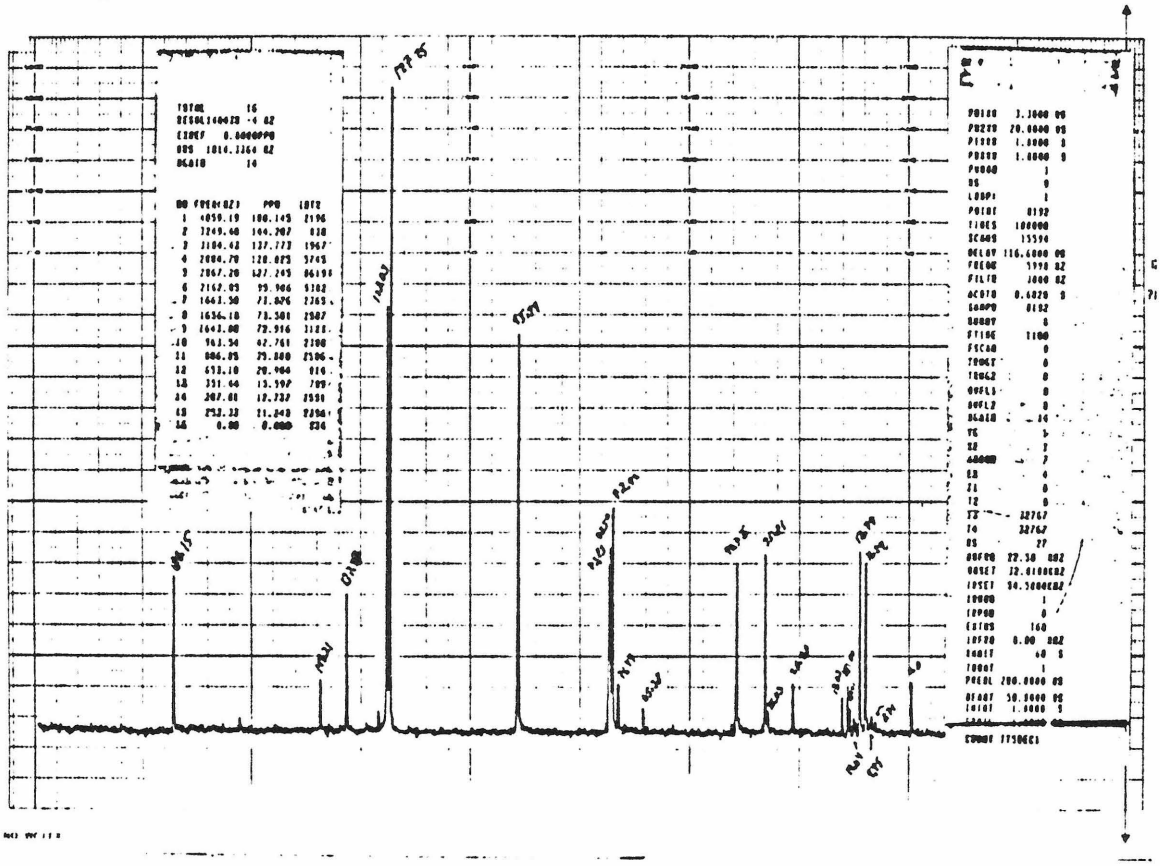

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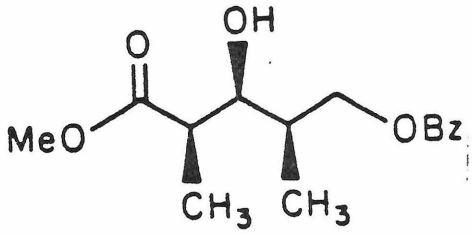

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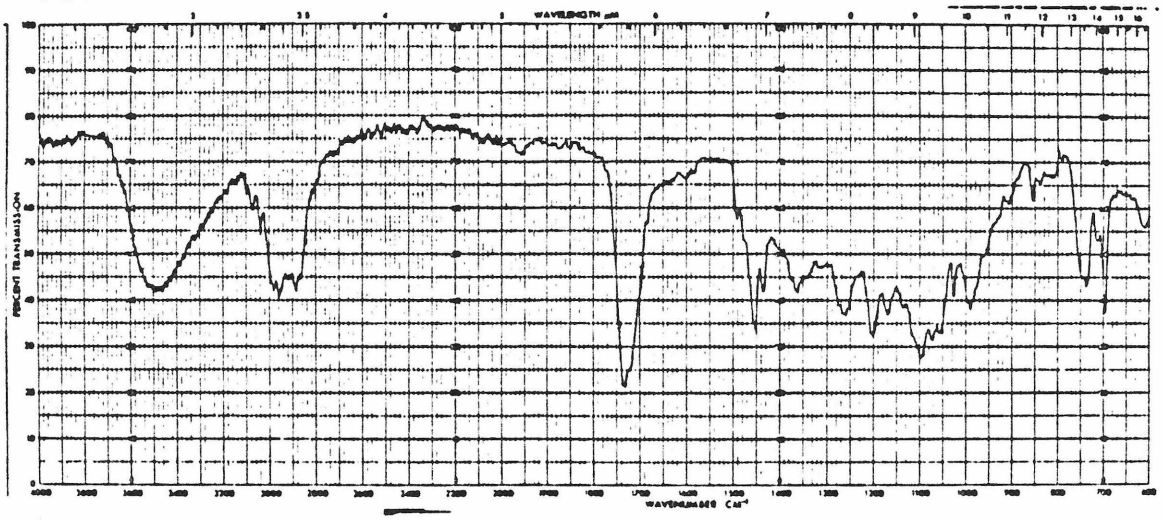

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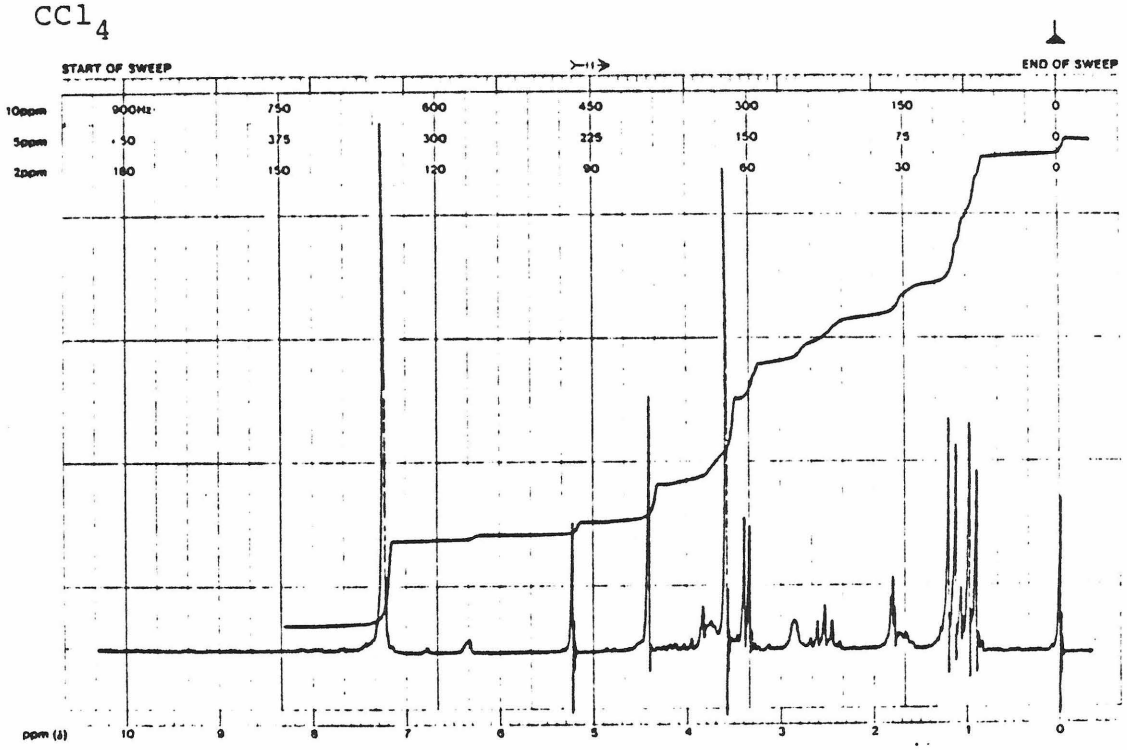

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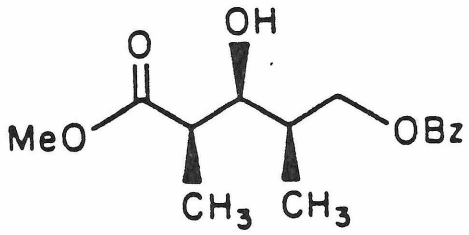

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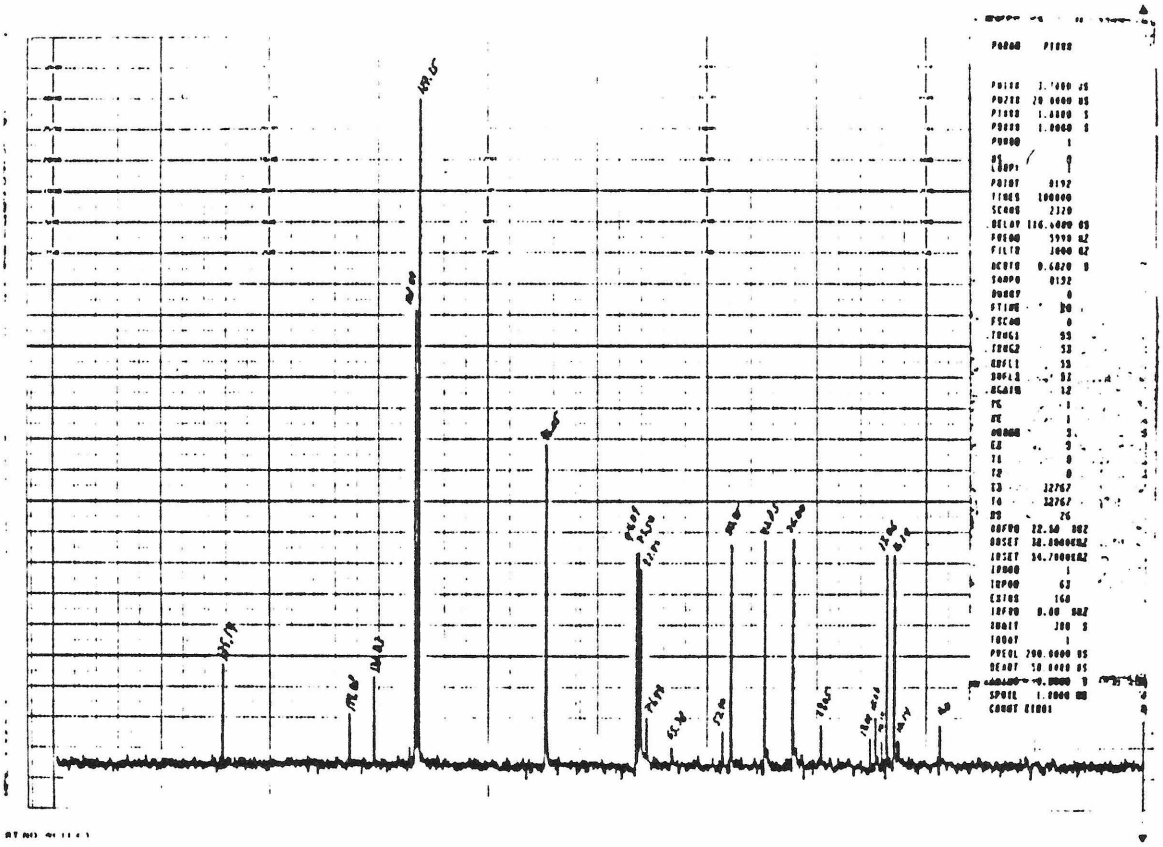

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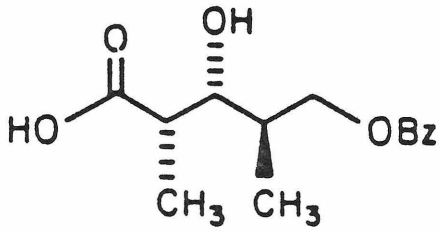

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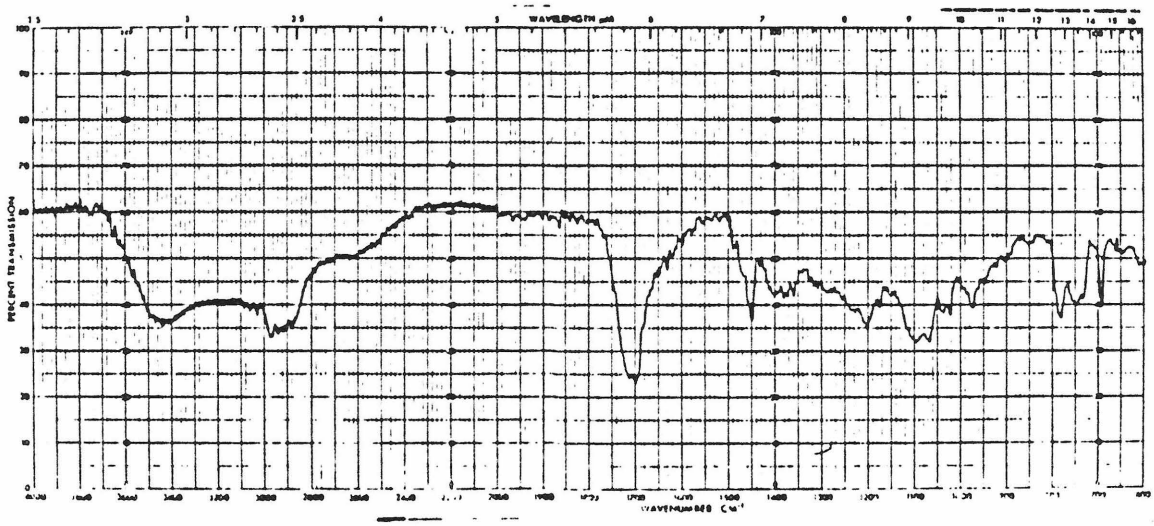

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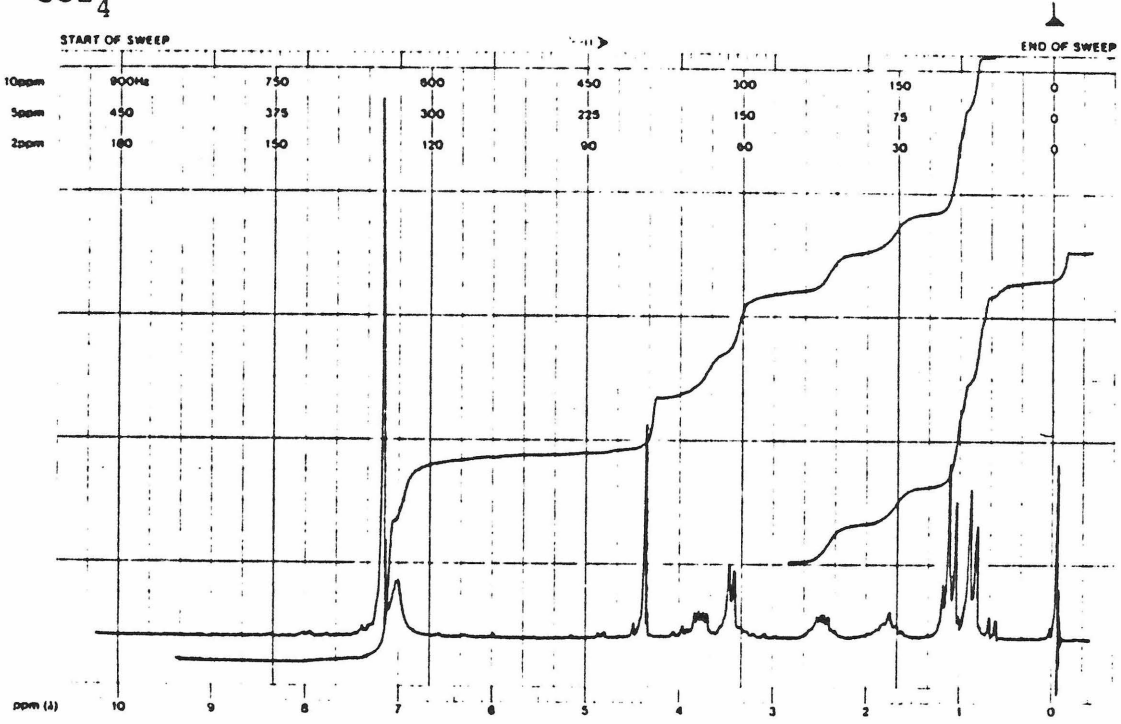

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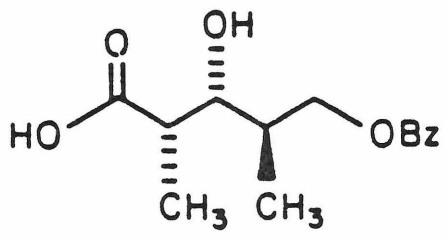

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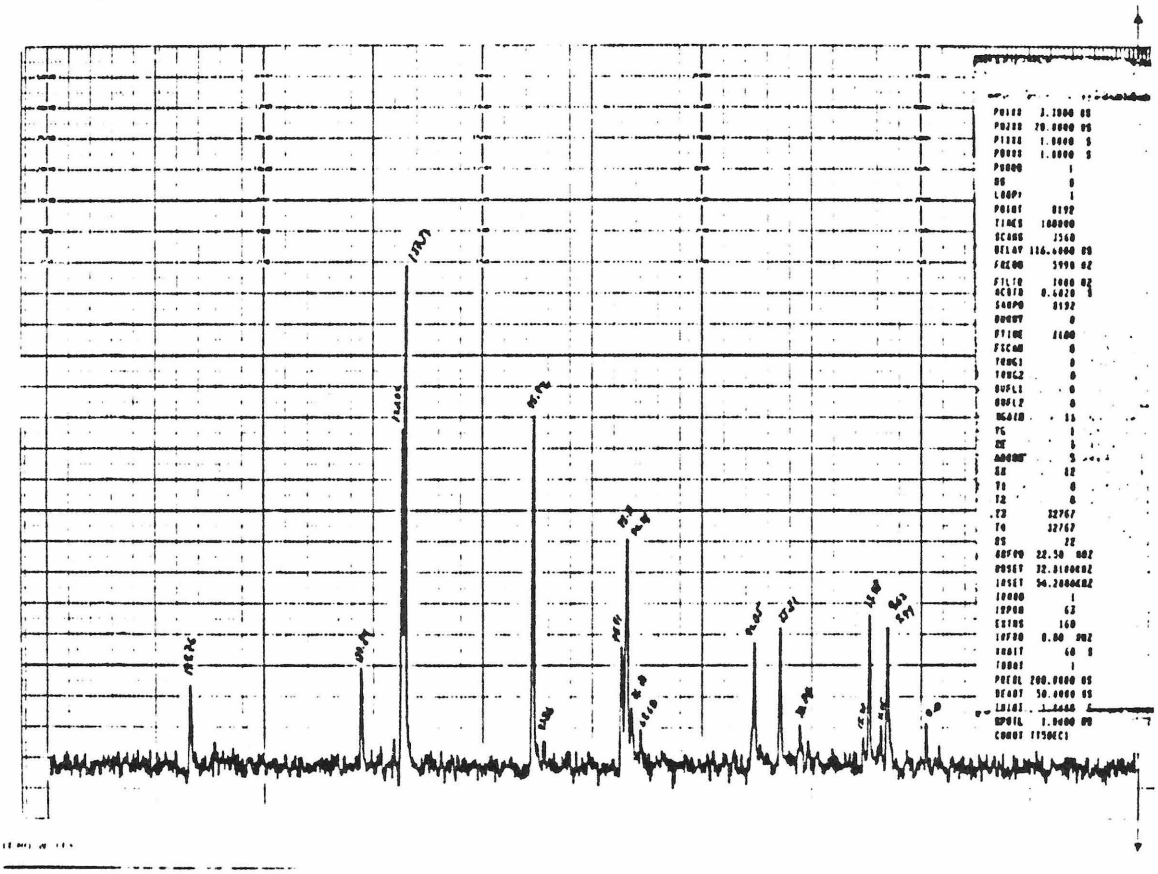

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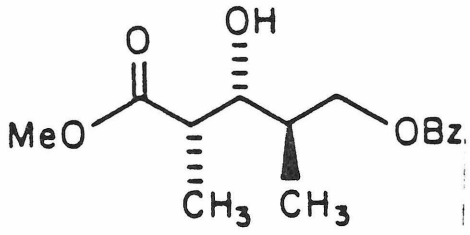
Page 124



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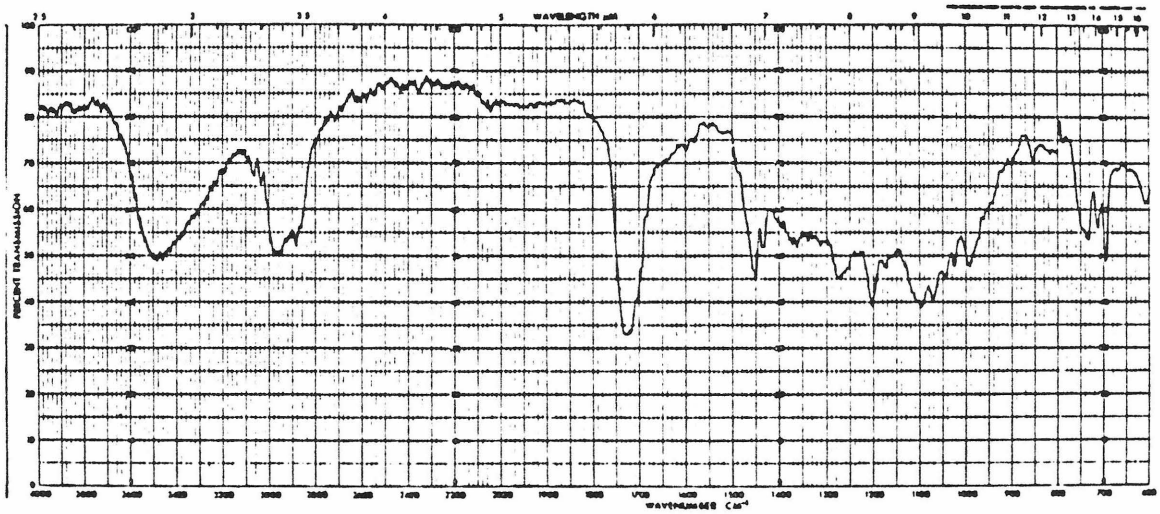

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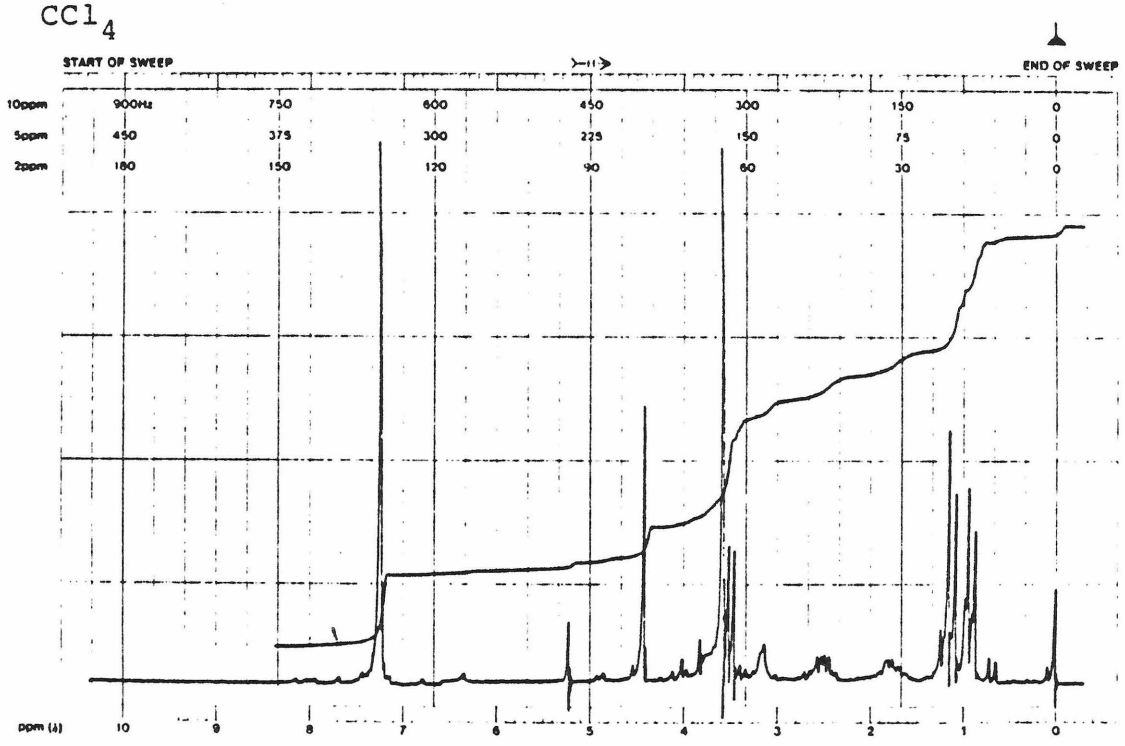

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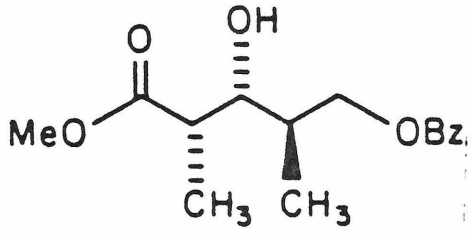

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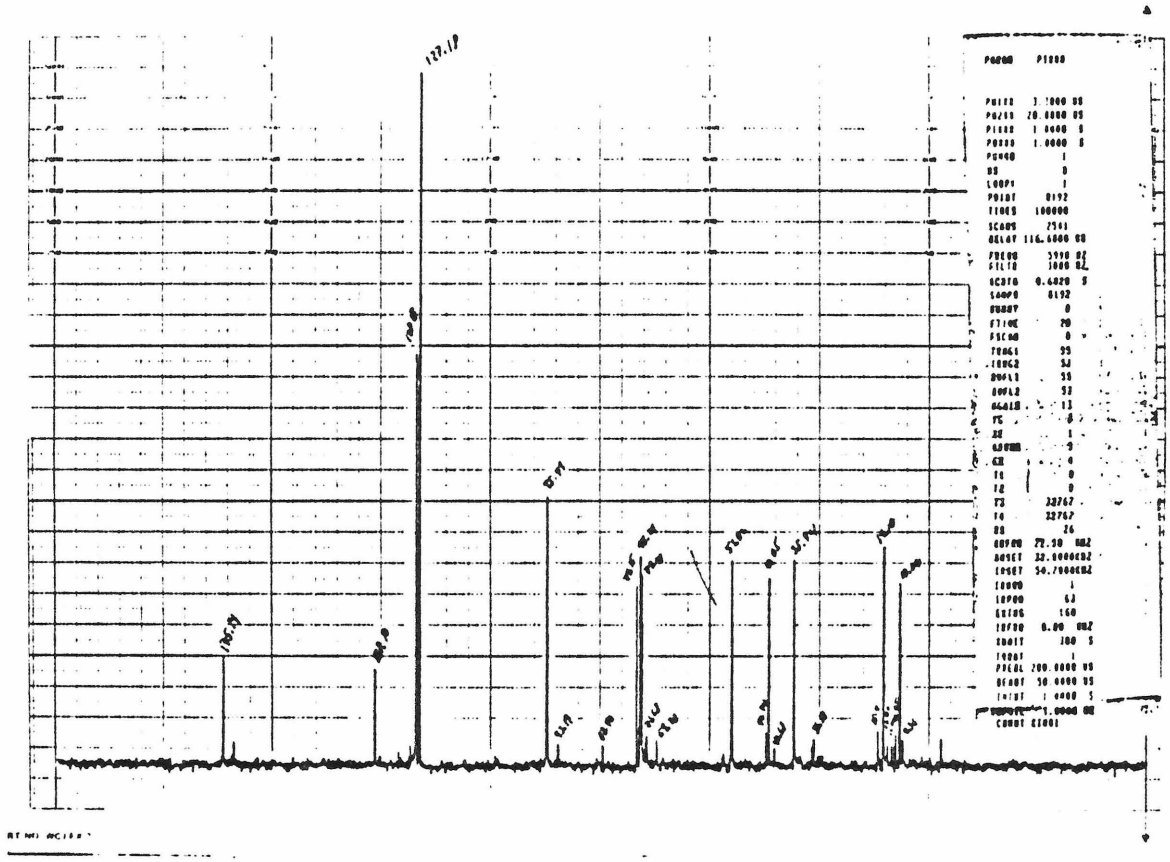

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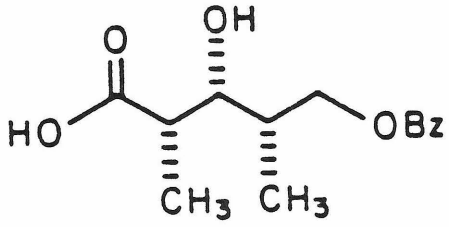

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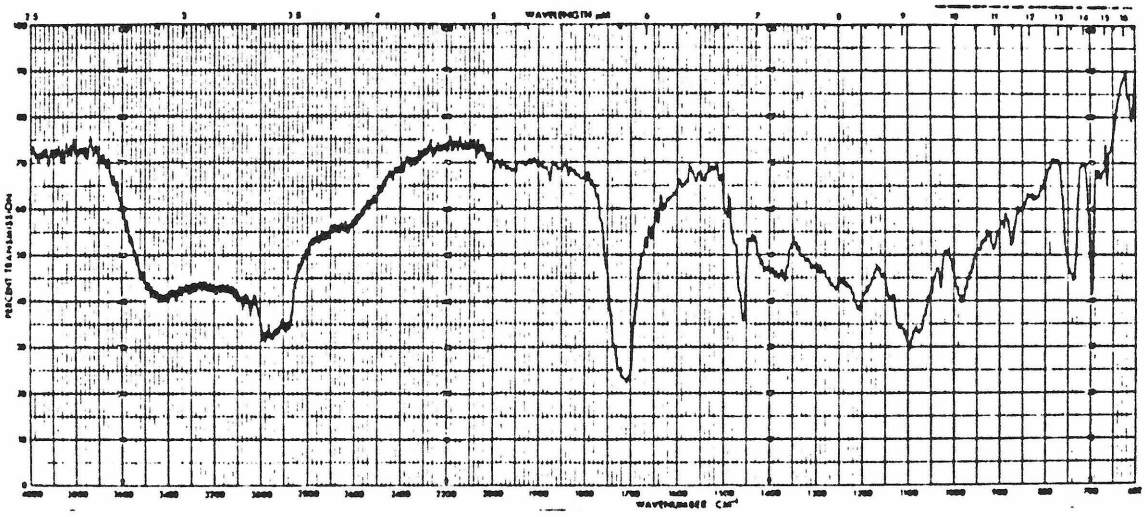

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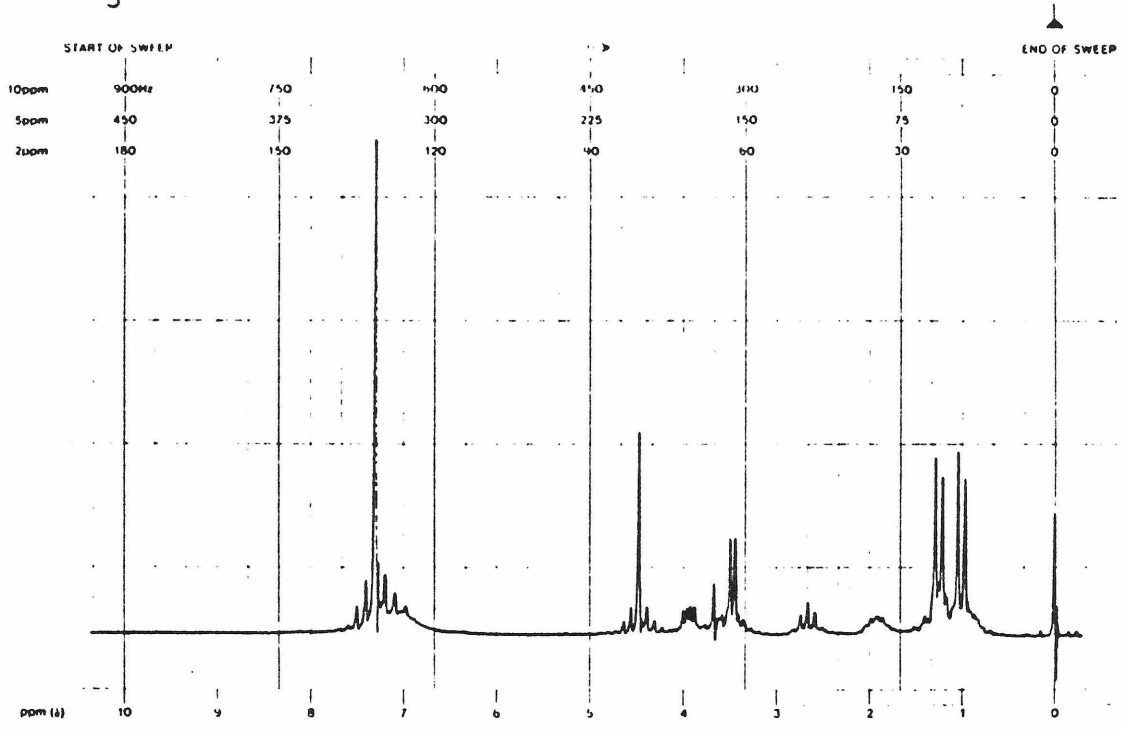

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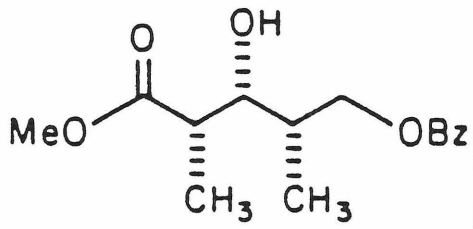

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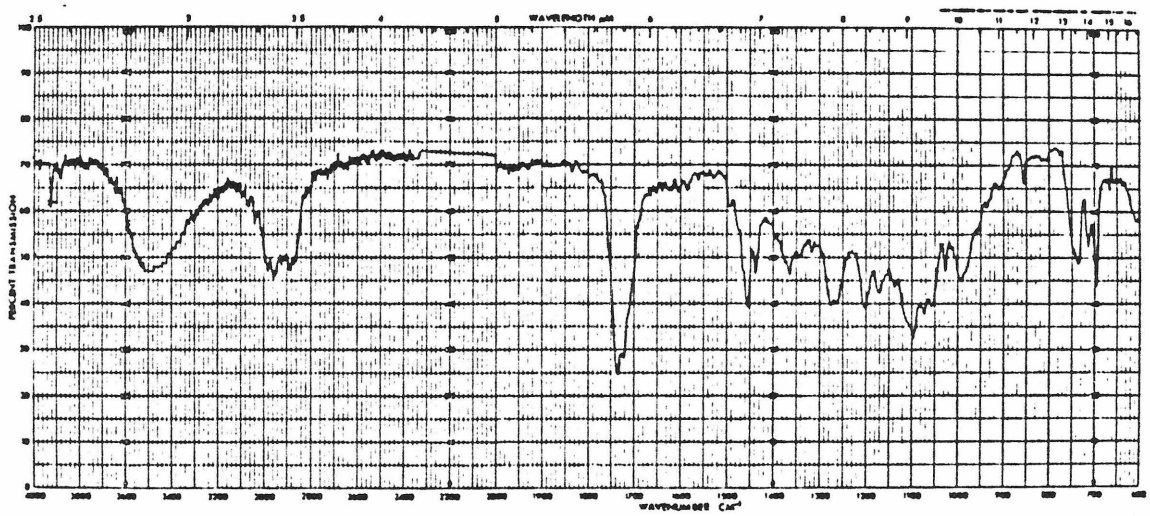

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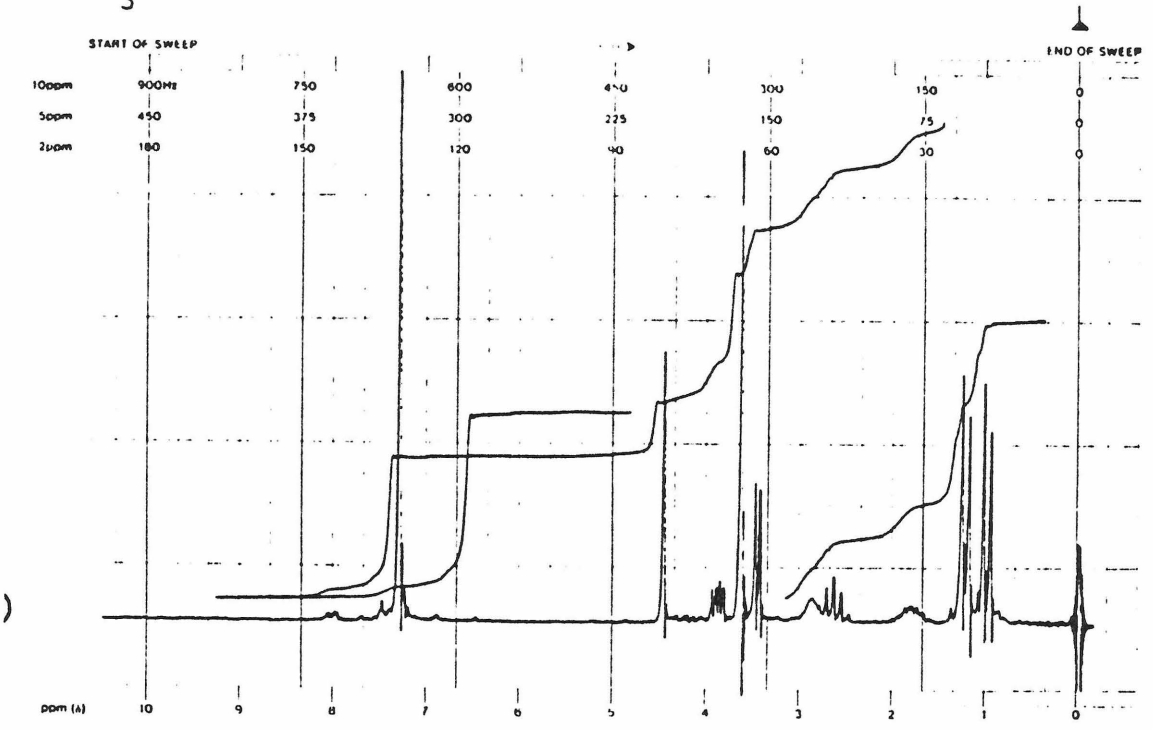

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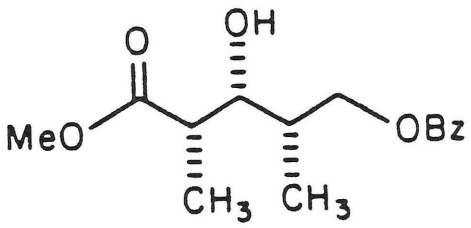

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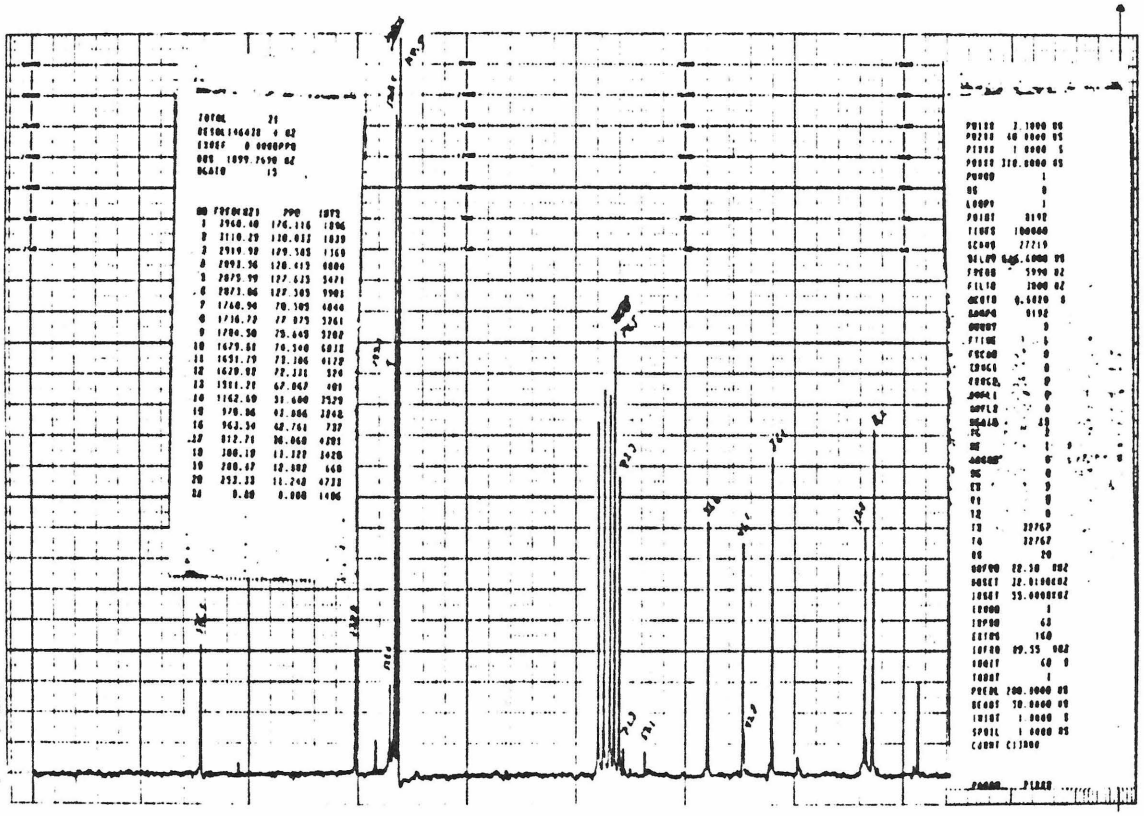

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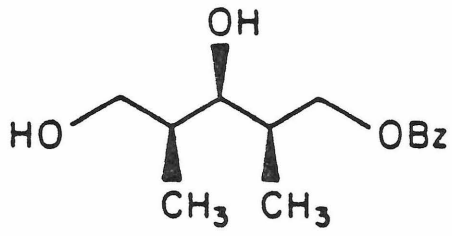

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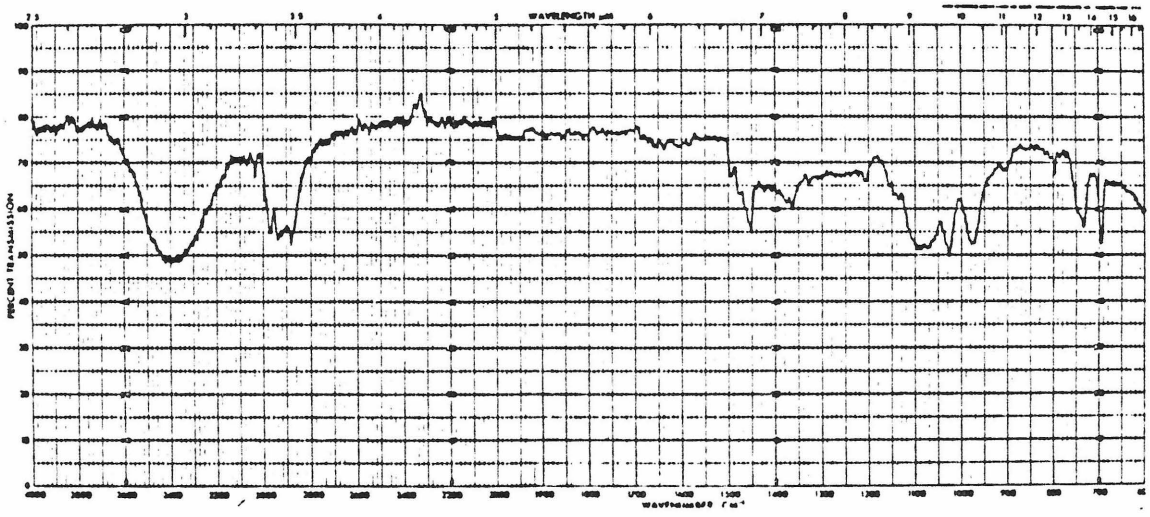

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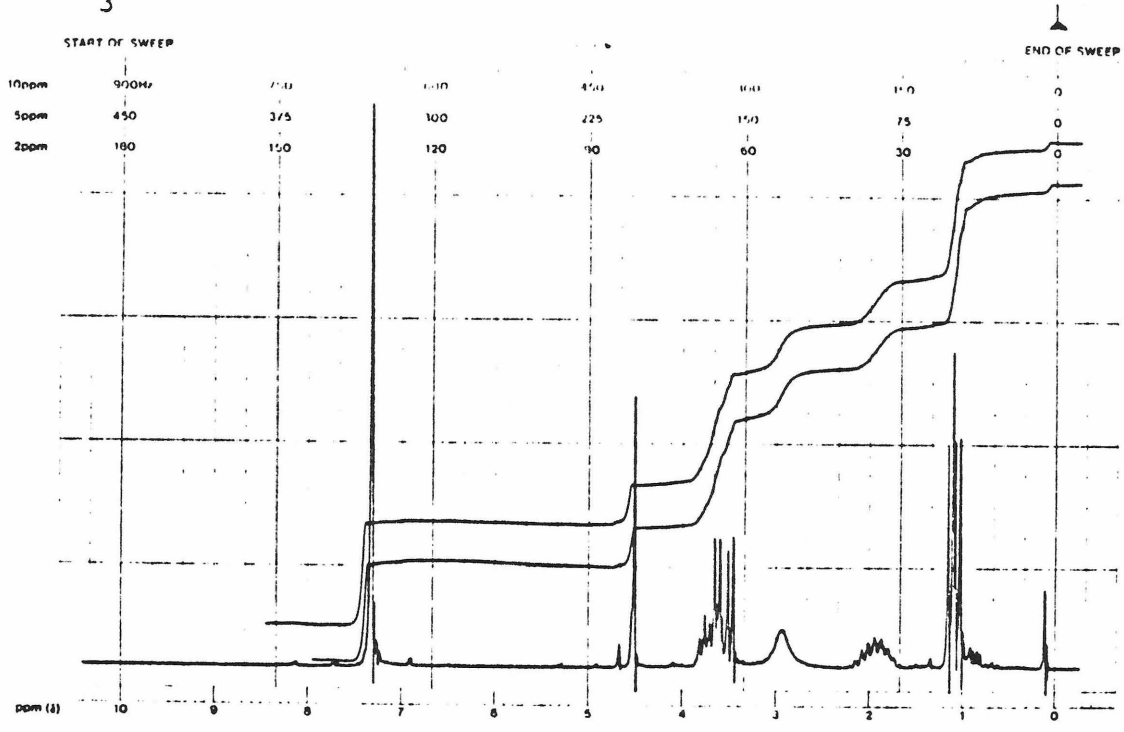

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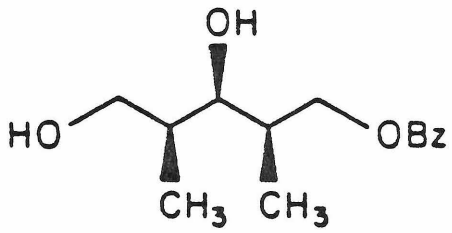

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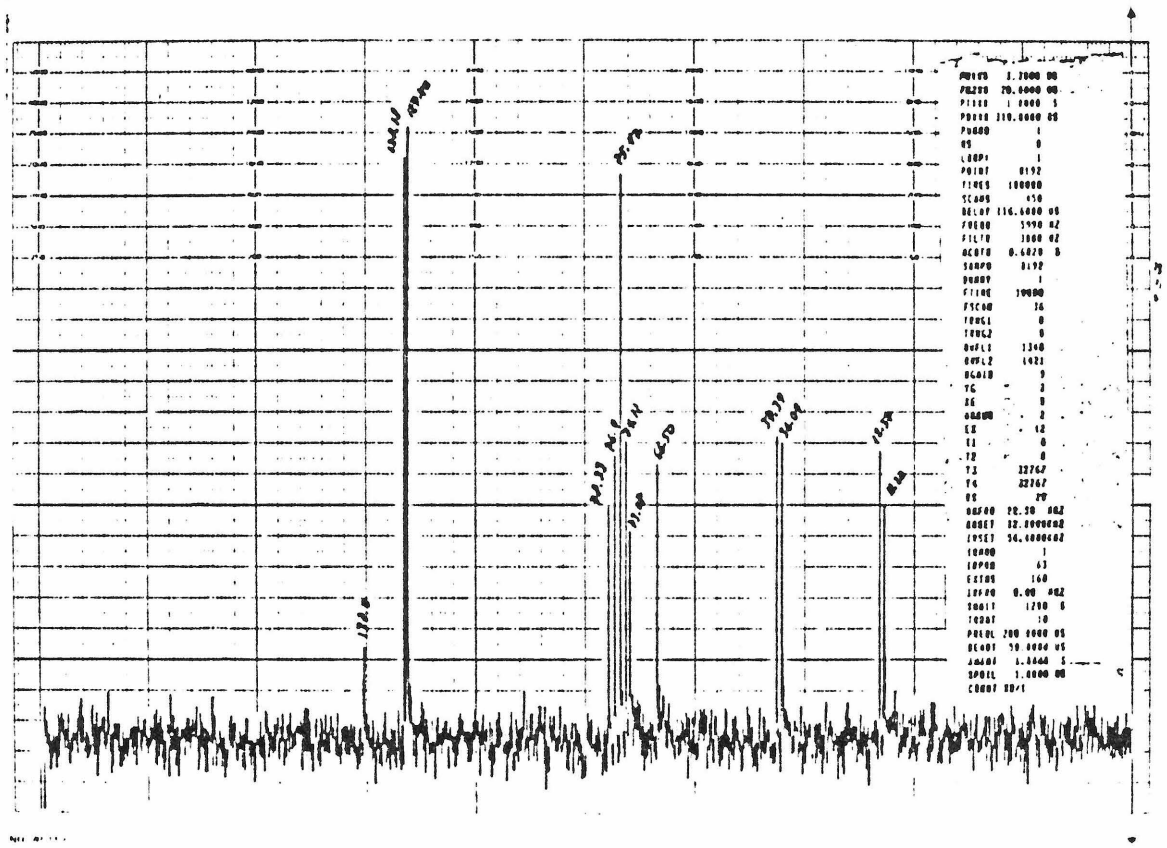

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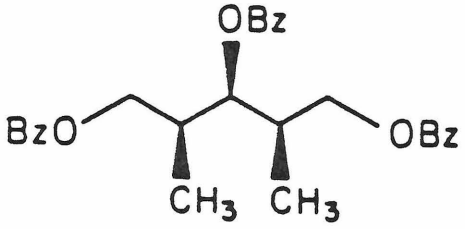

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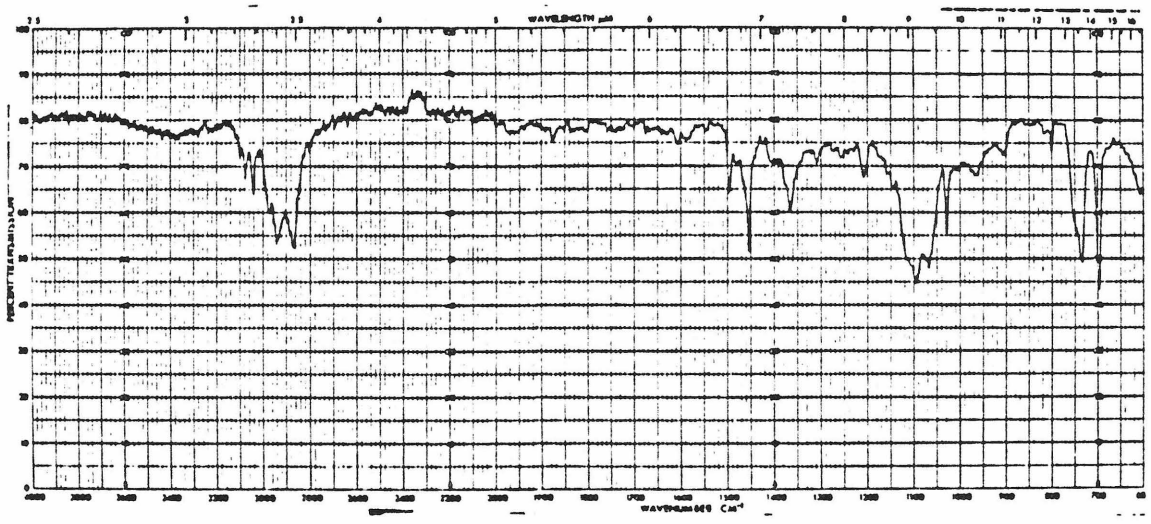

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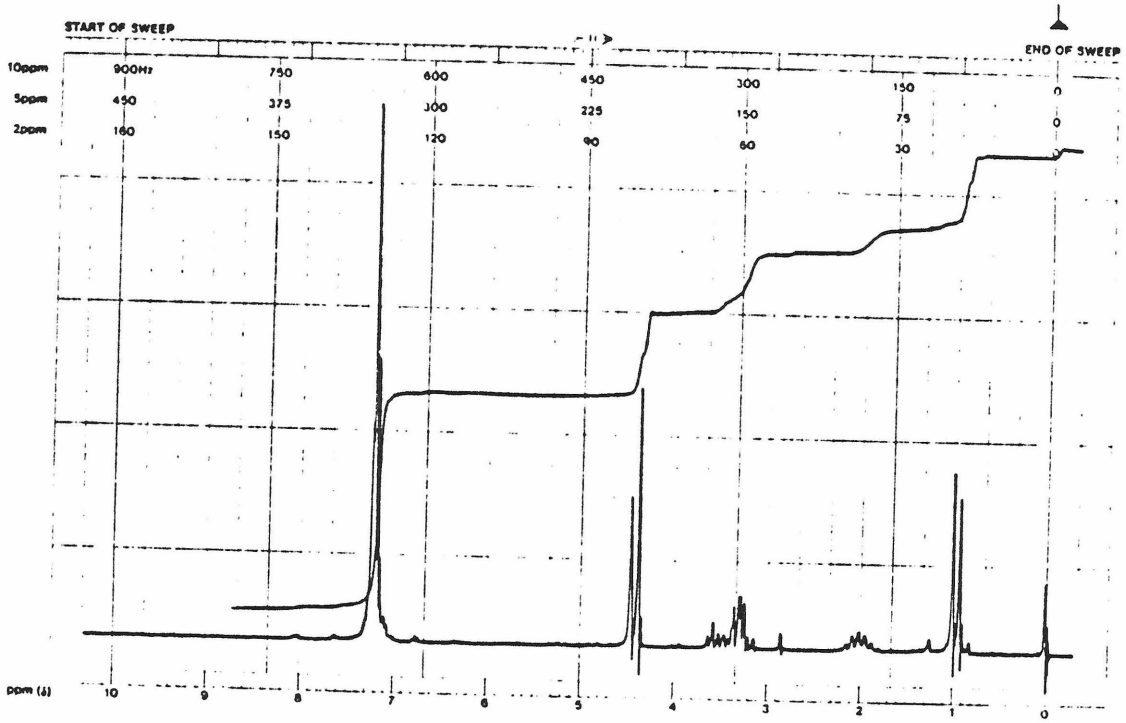

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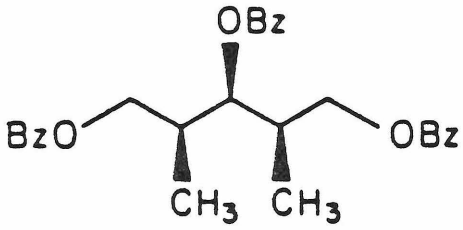

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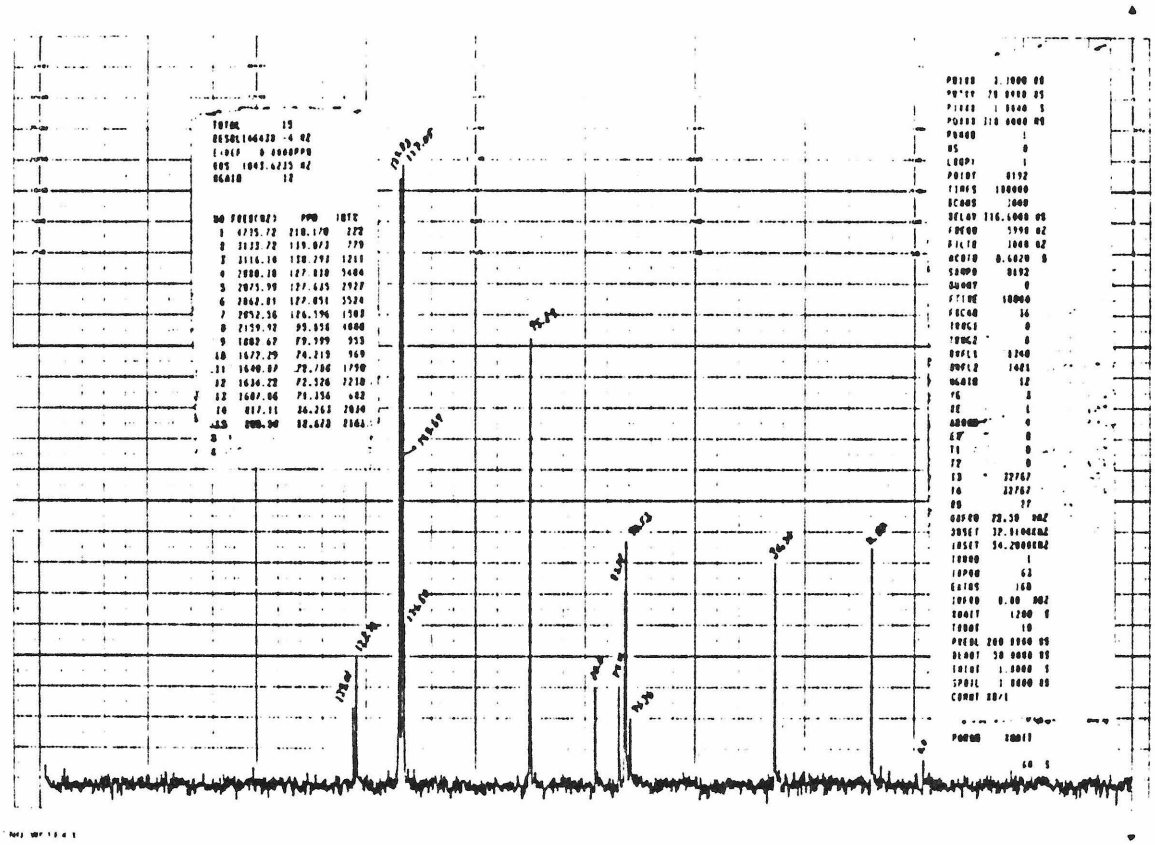

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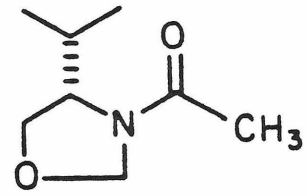

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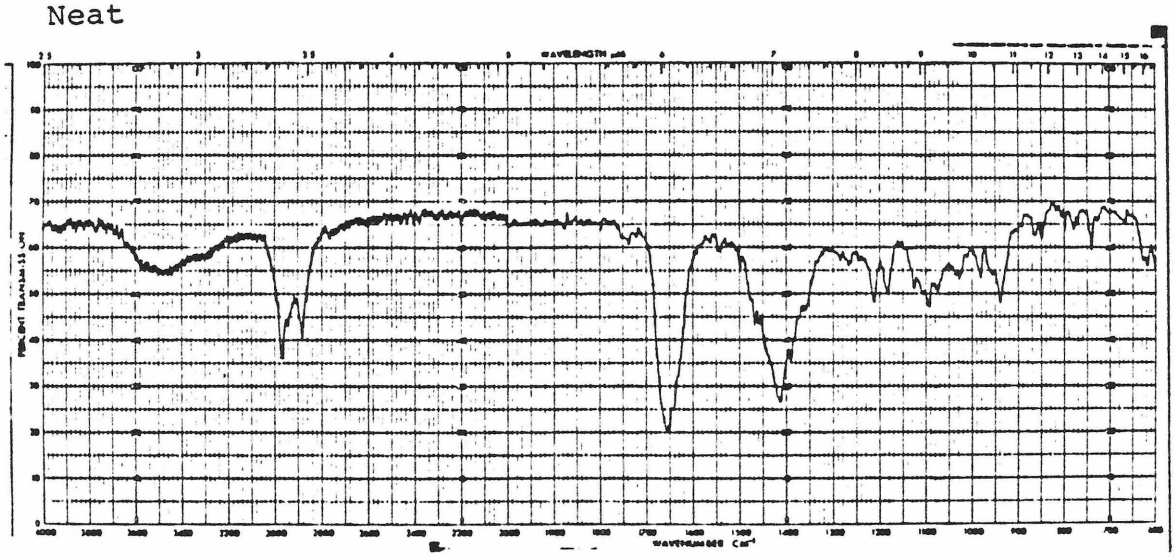

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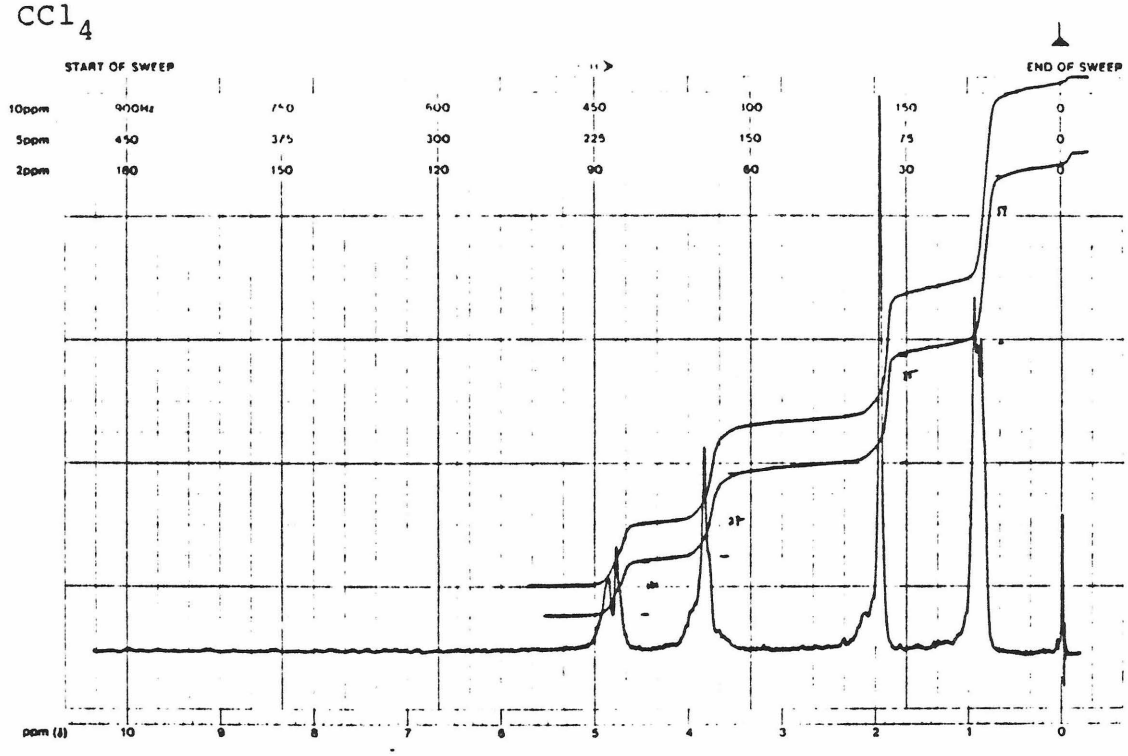

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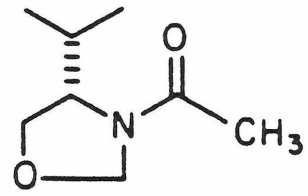

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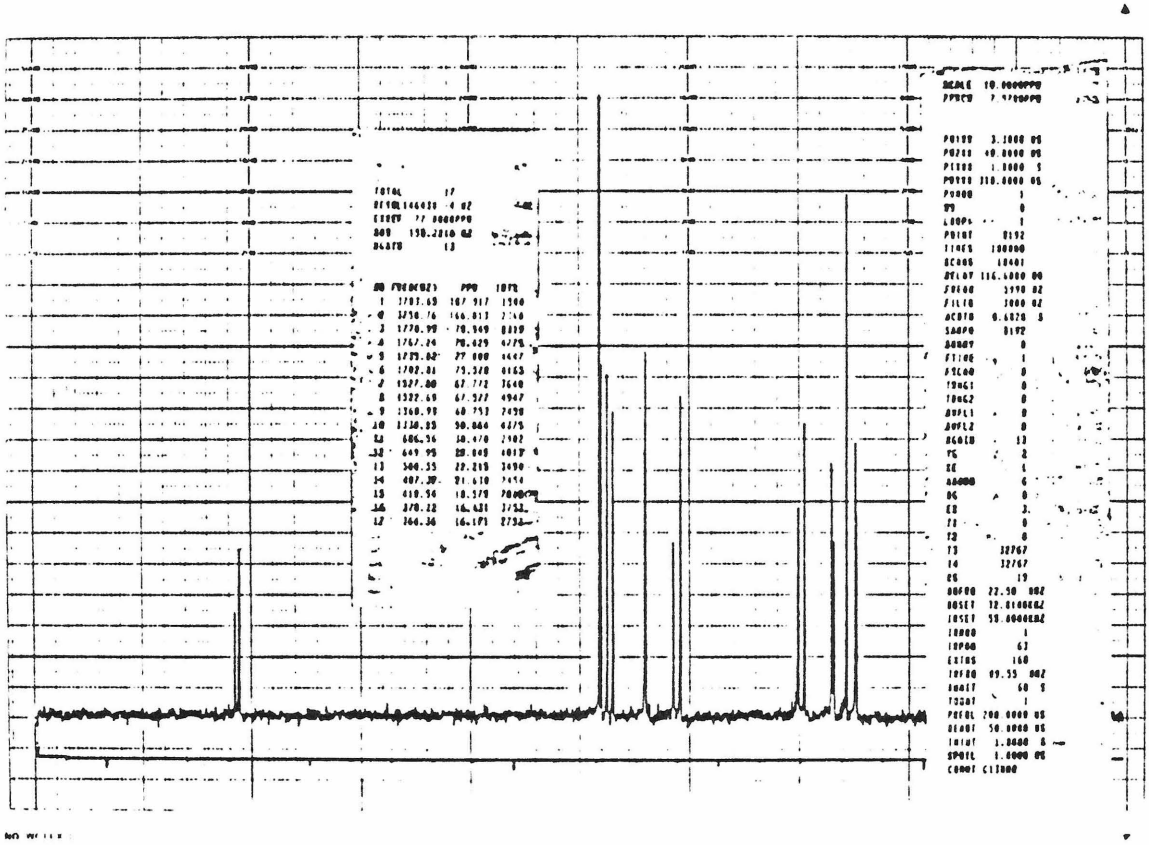

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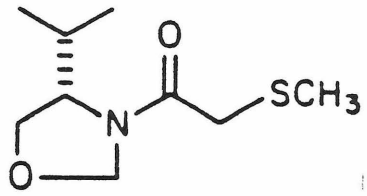

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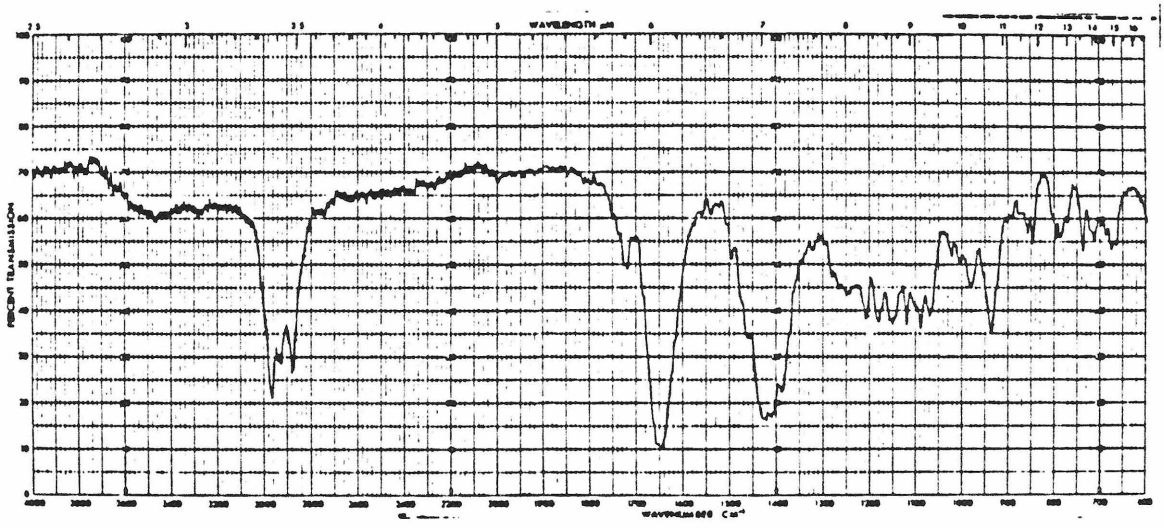

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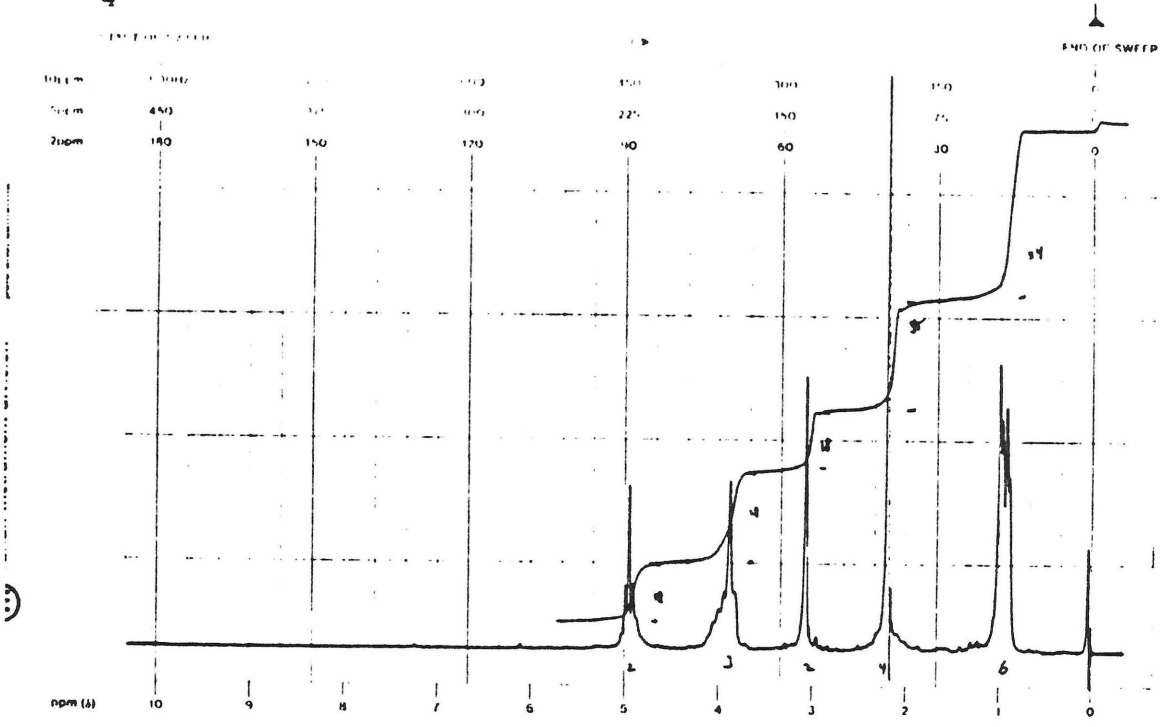

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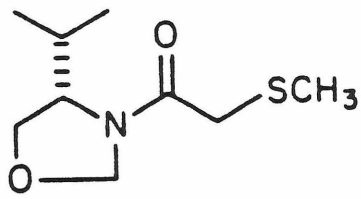

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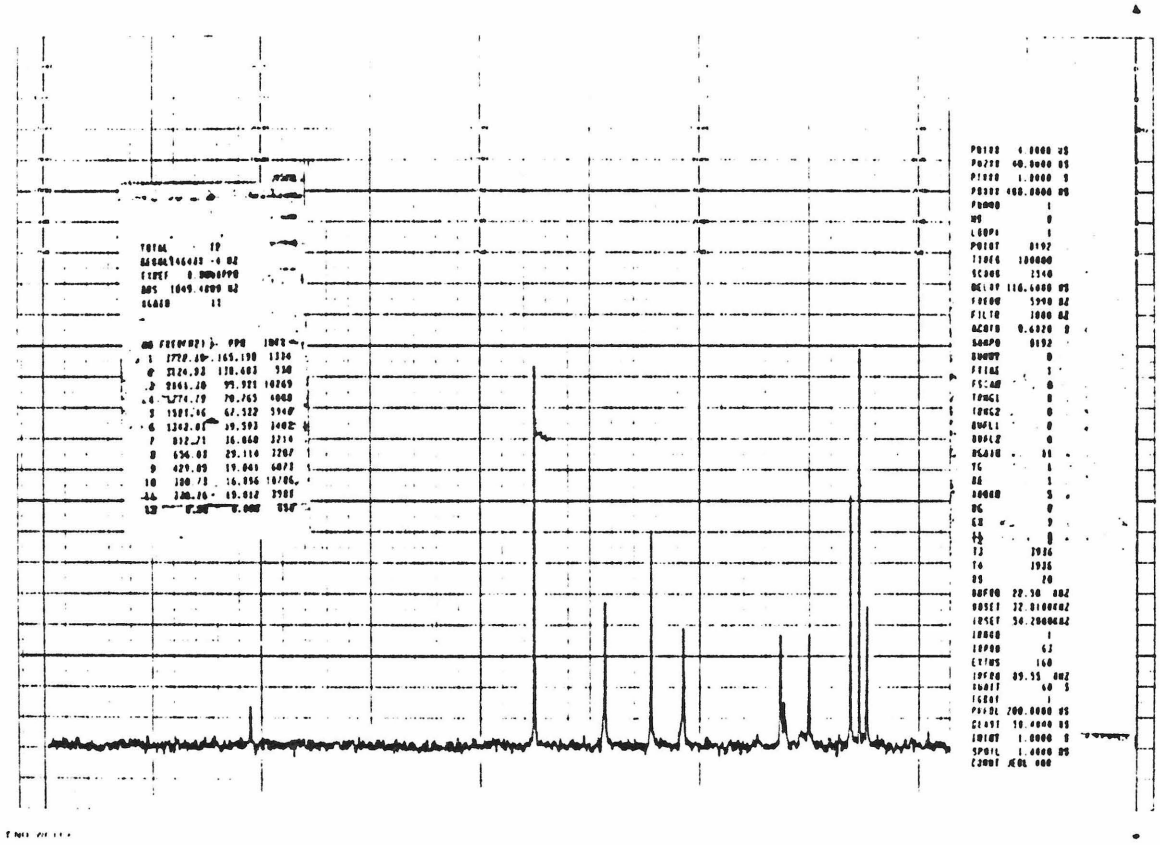

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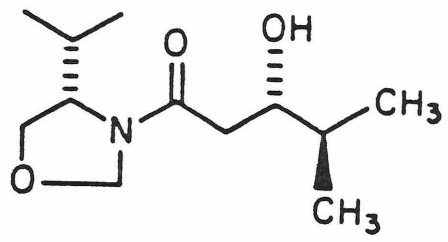

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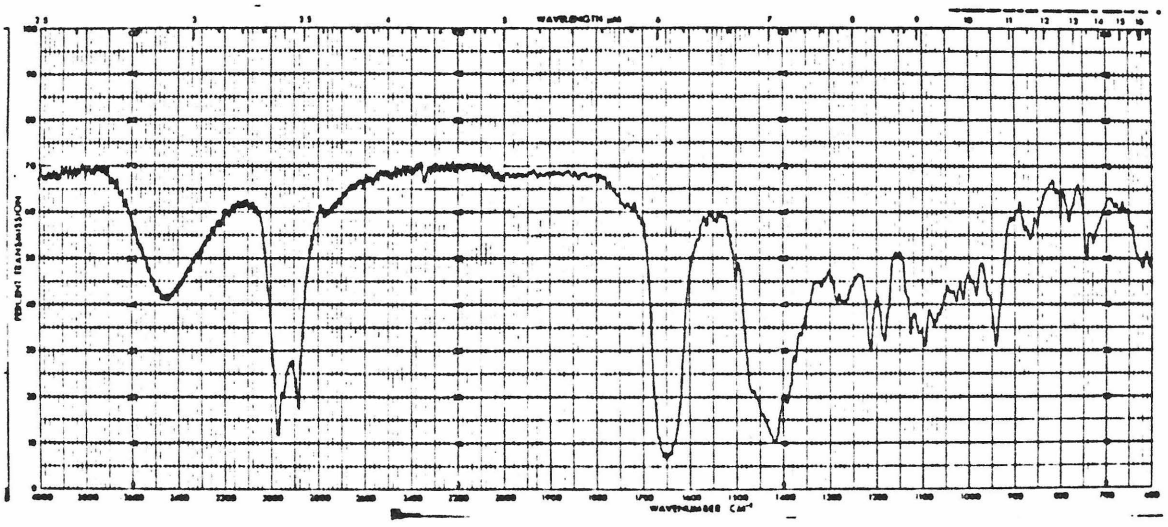

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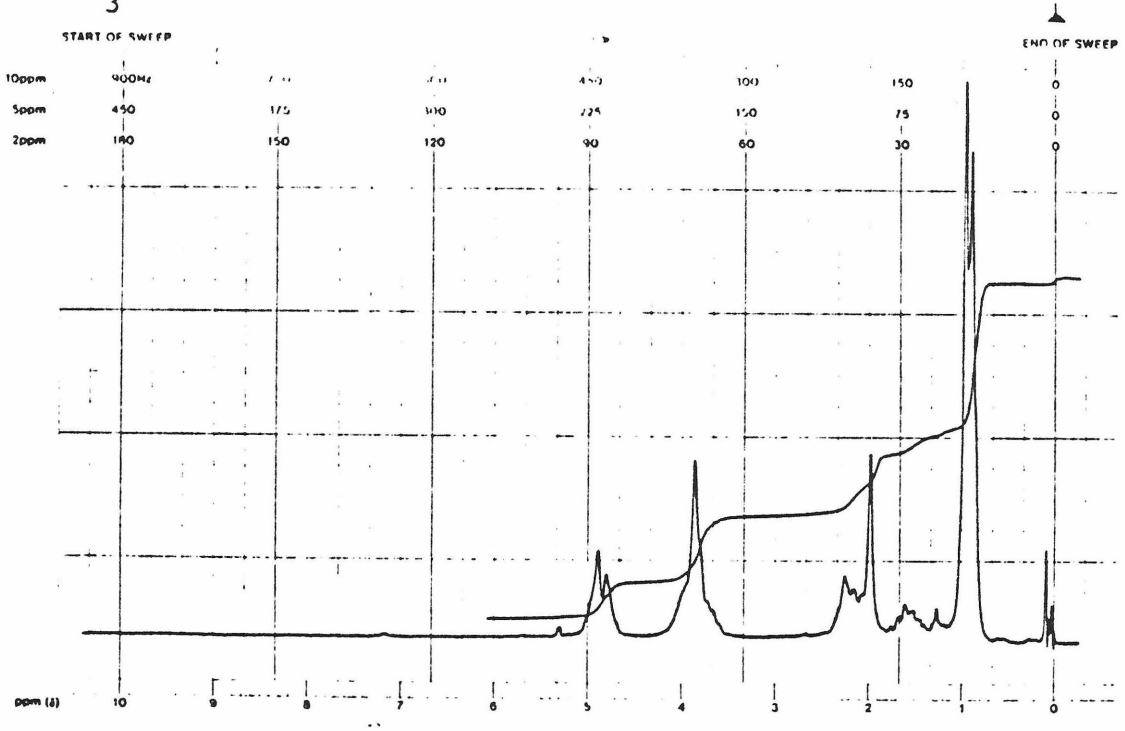

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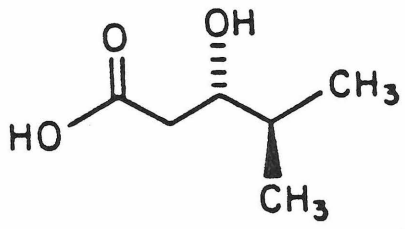

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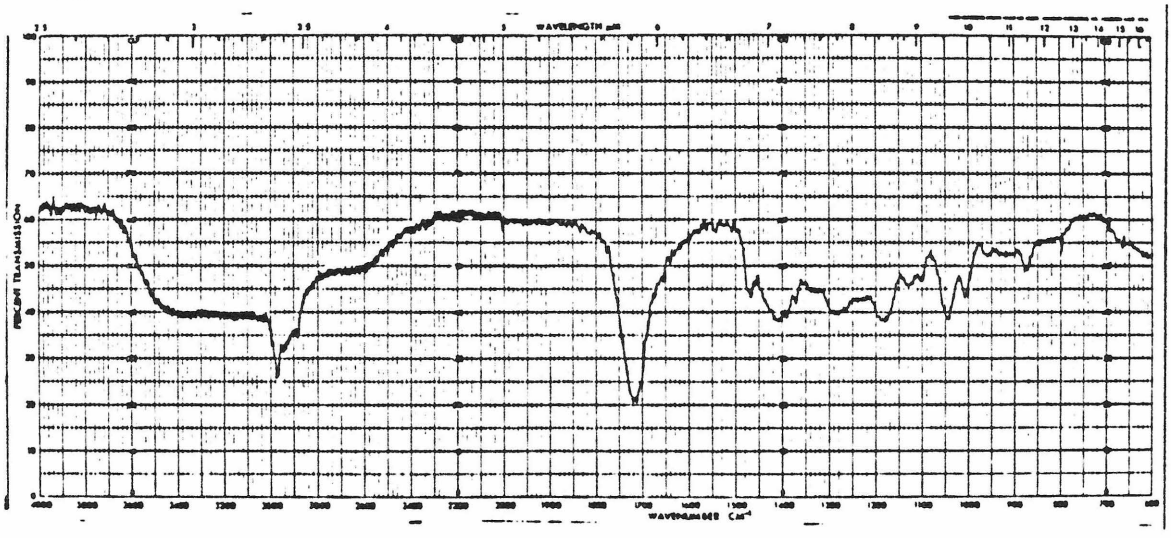

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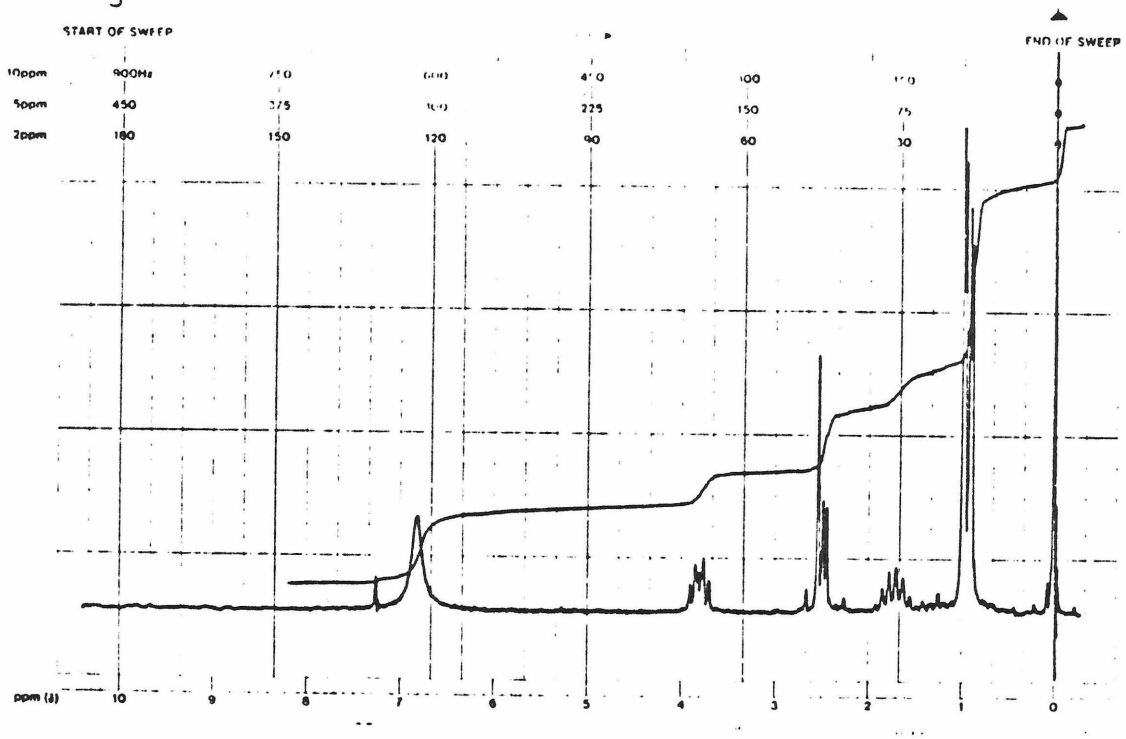

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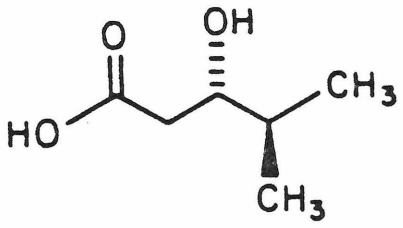

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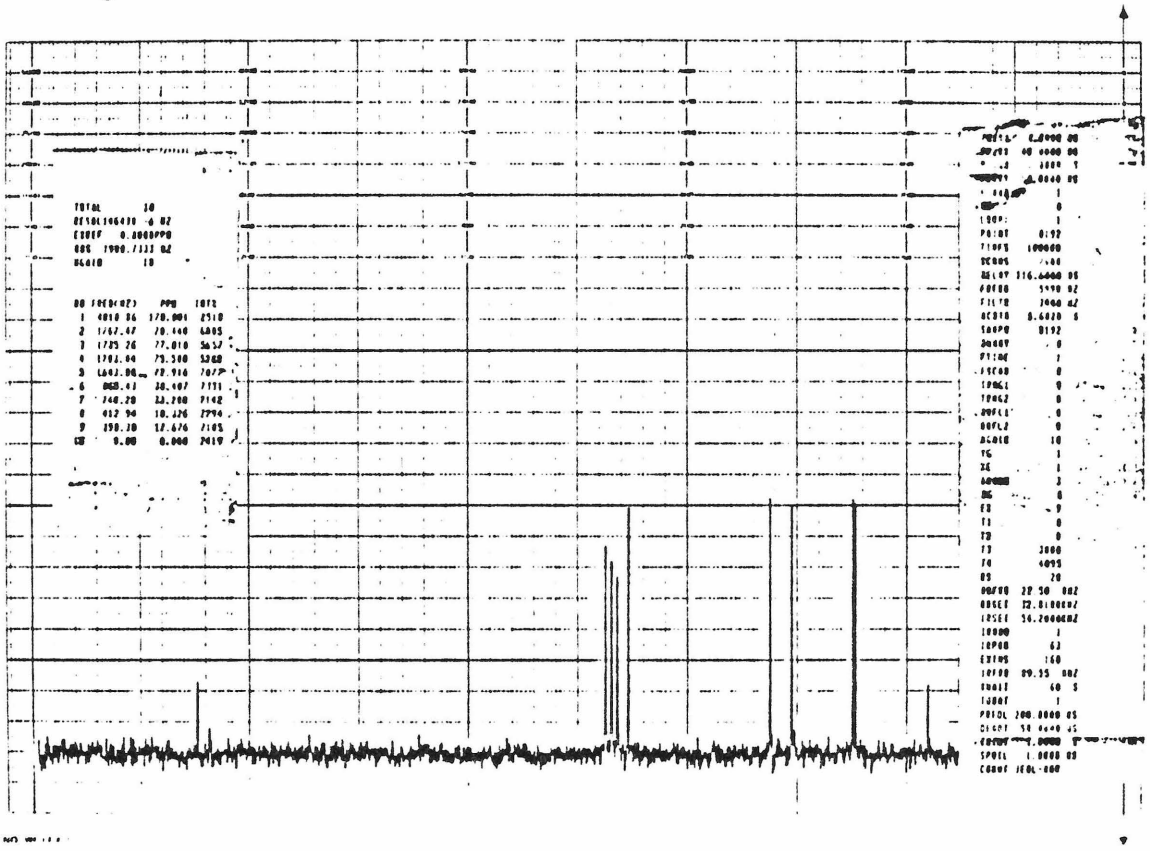

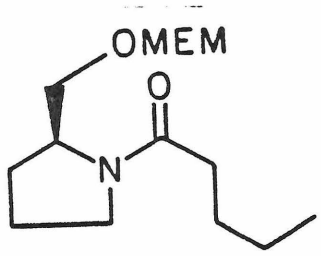

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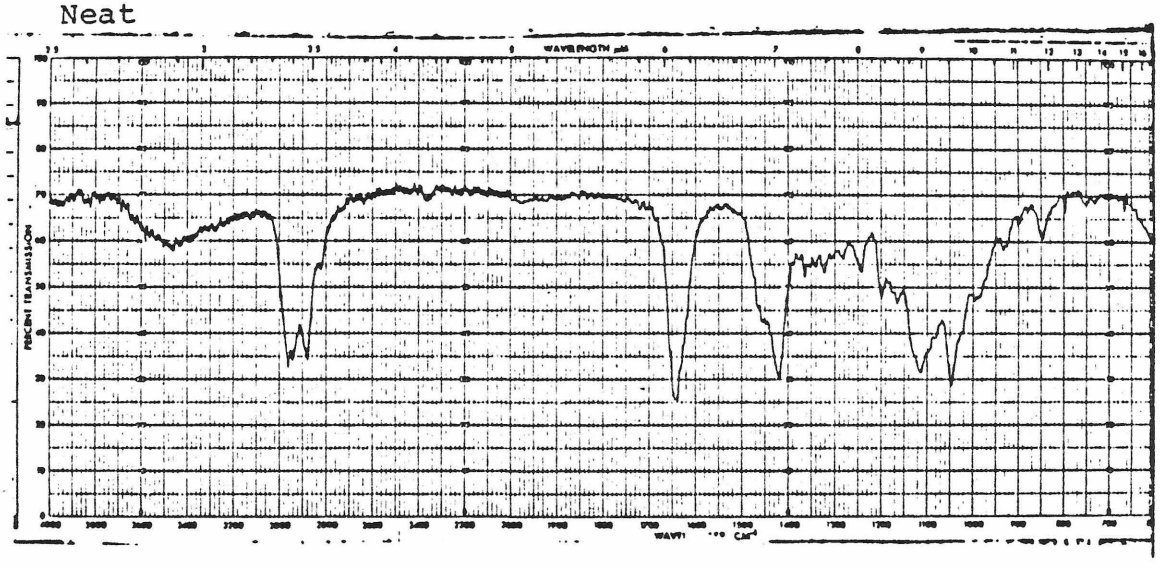

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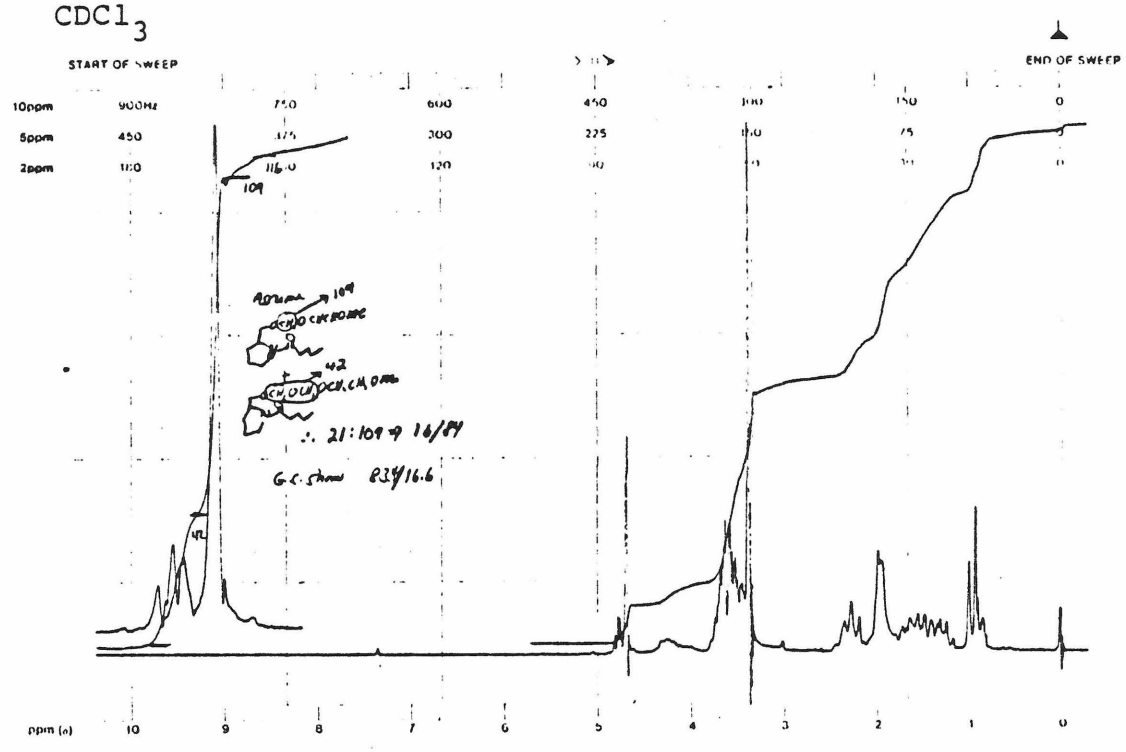

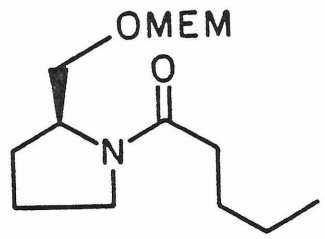

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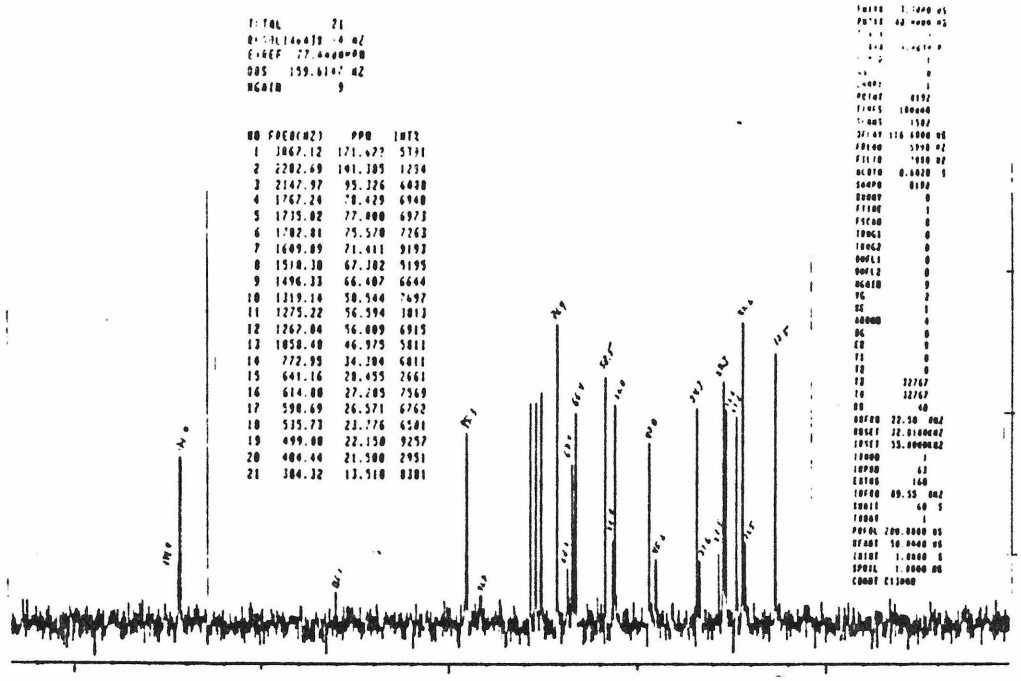

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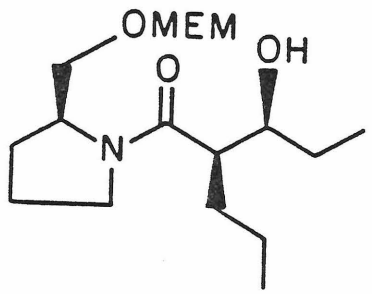

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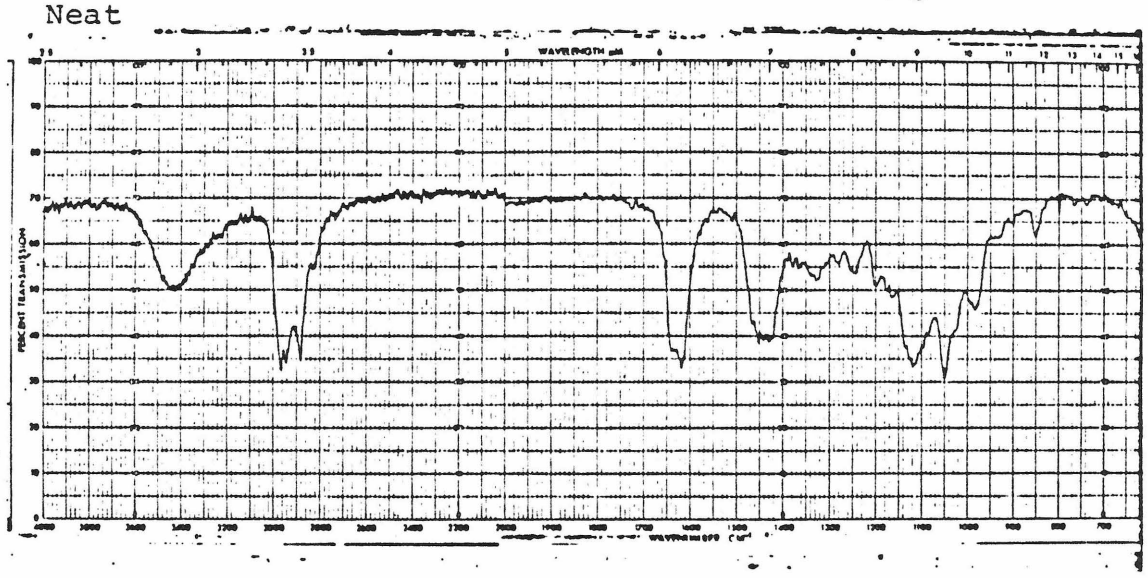

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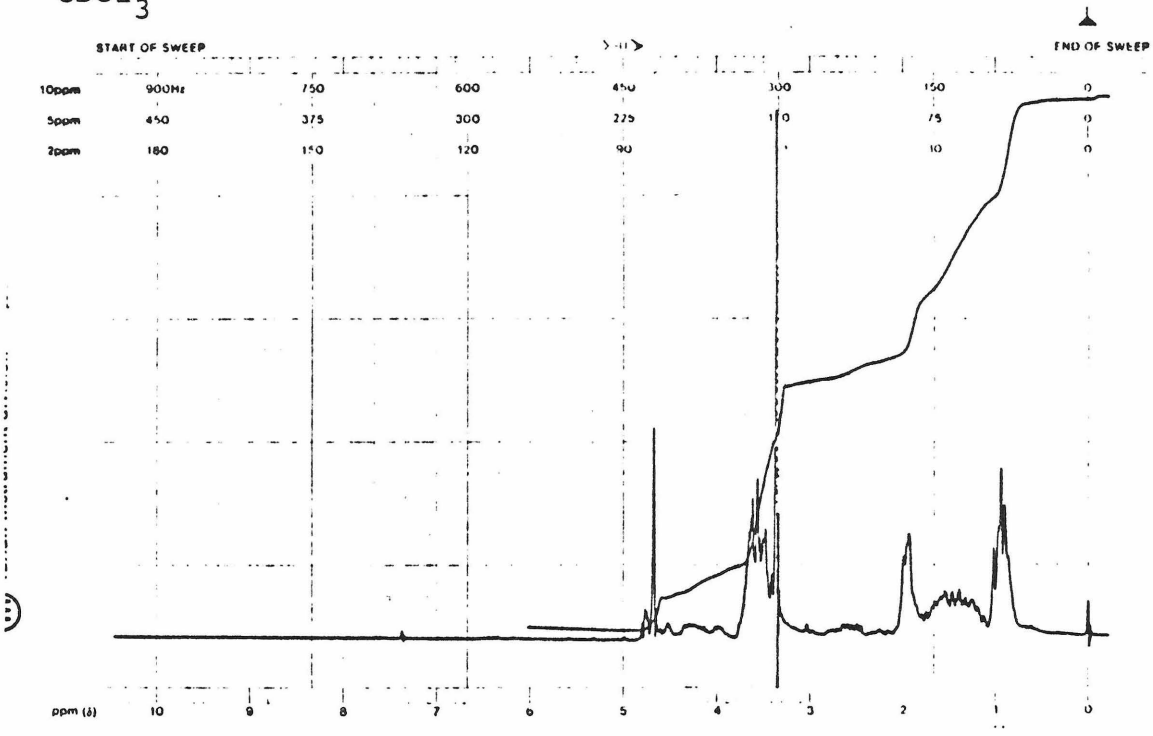

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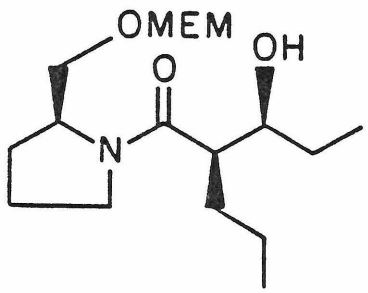

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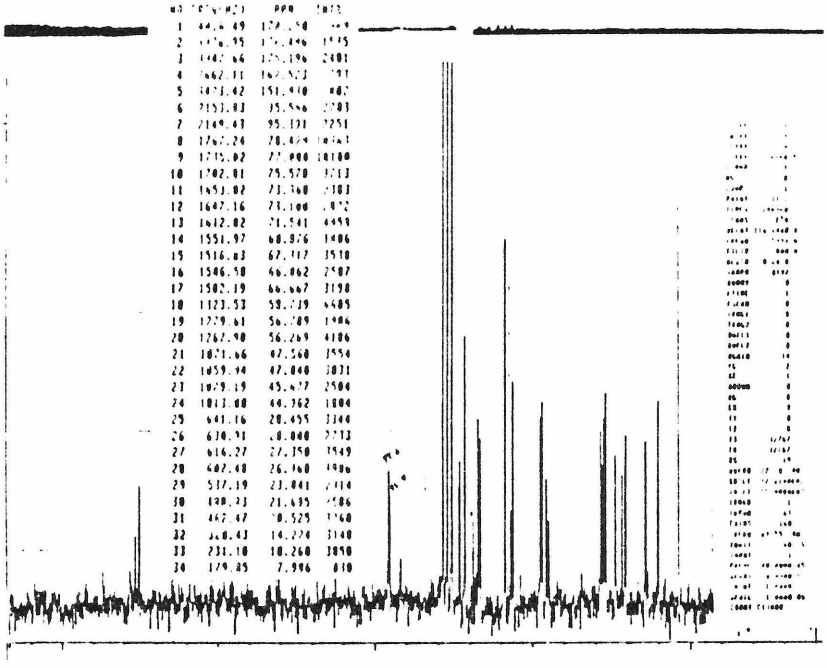

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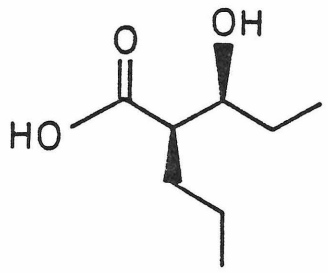

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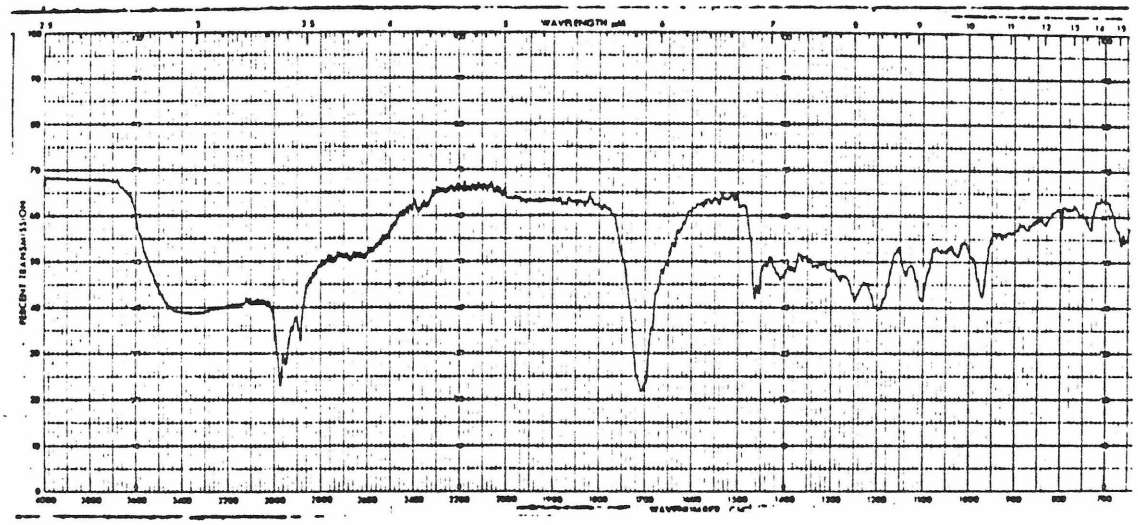

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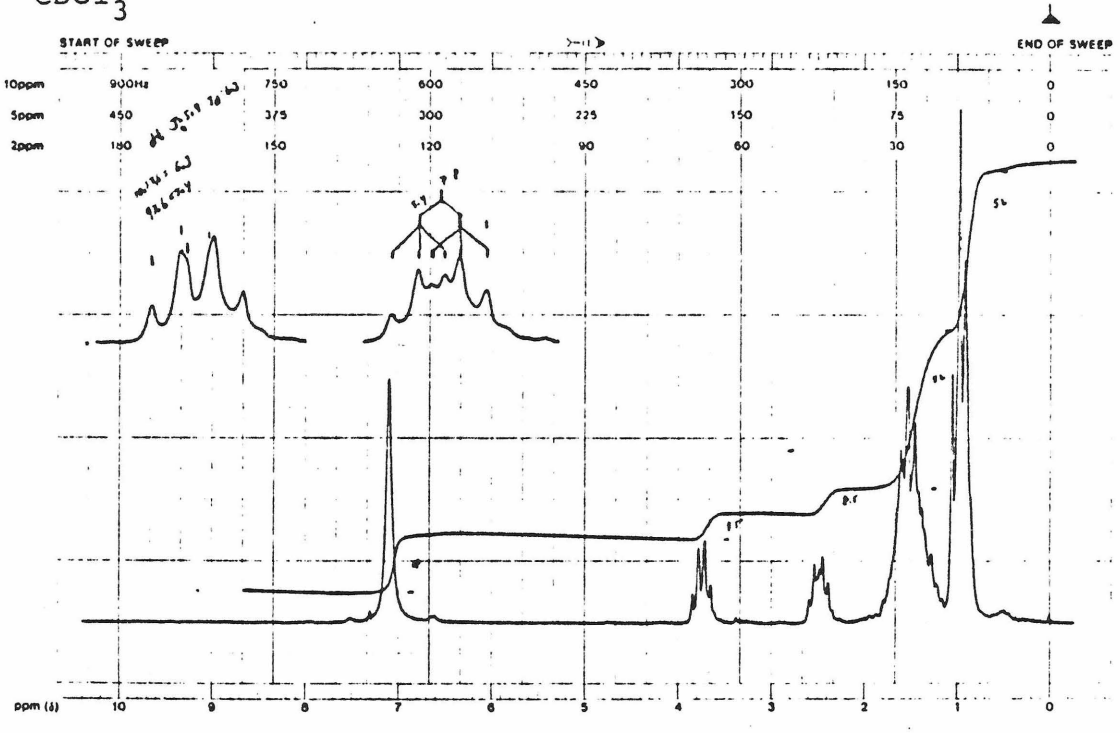

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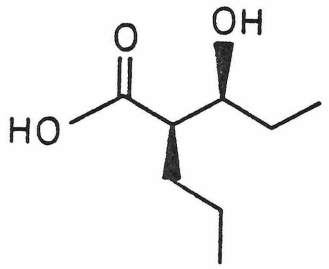

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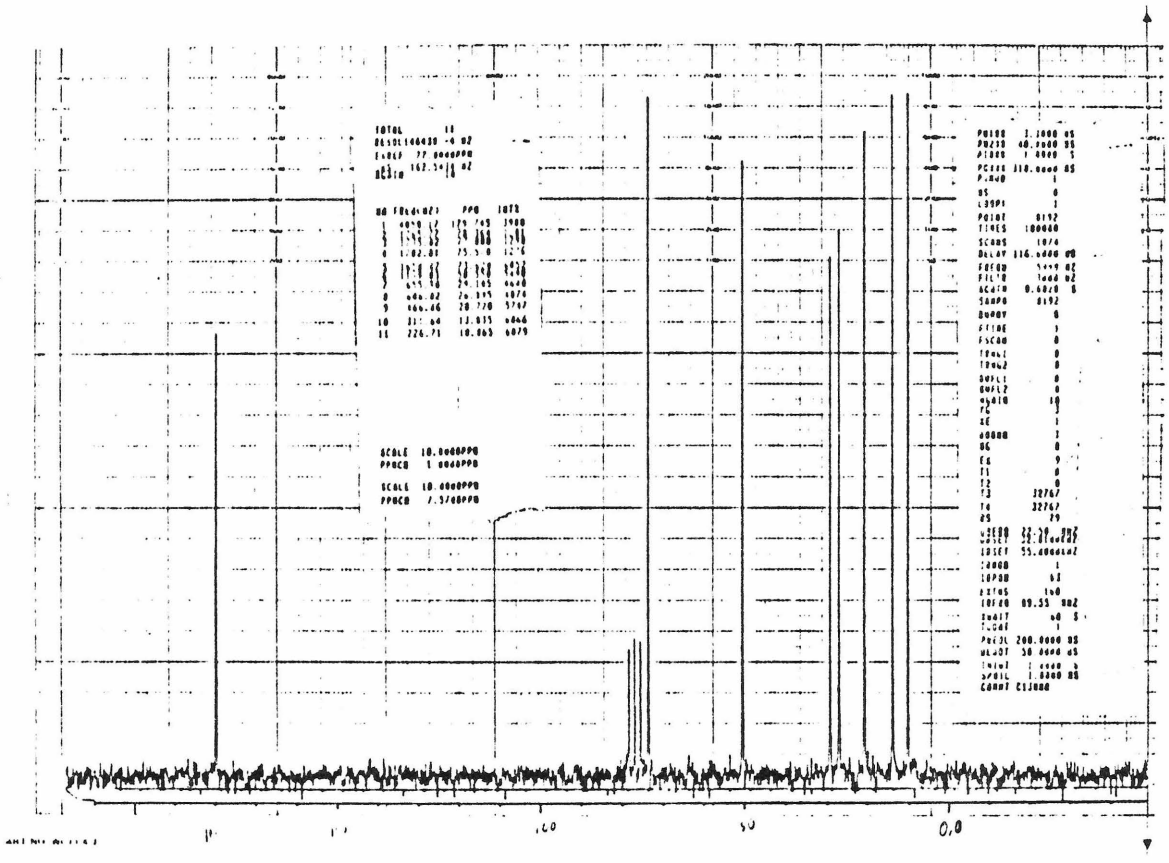

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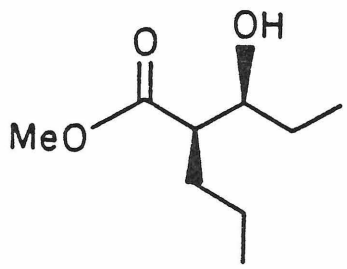

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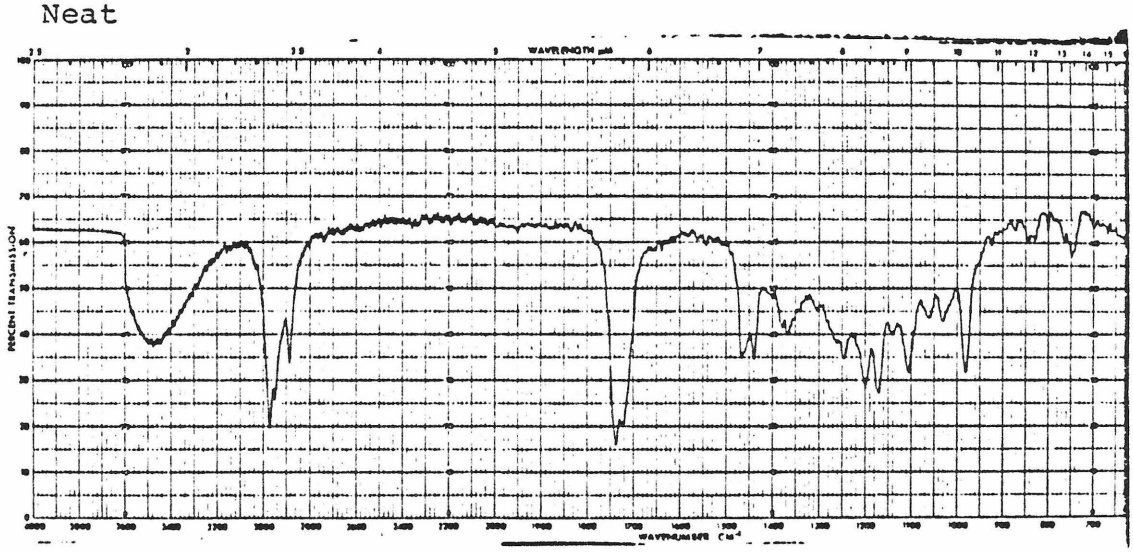

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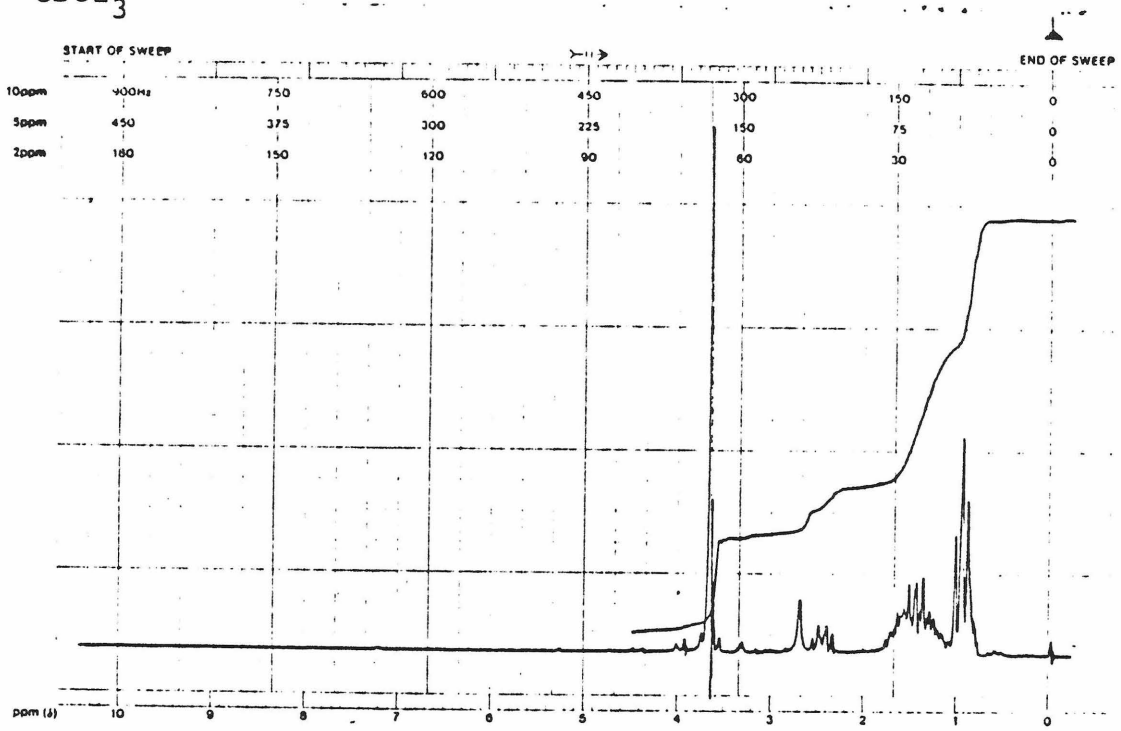

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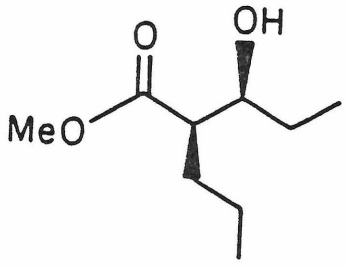

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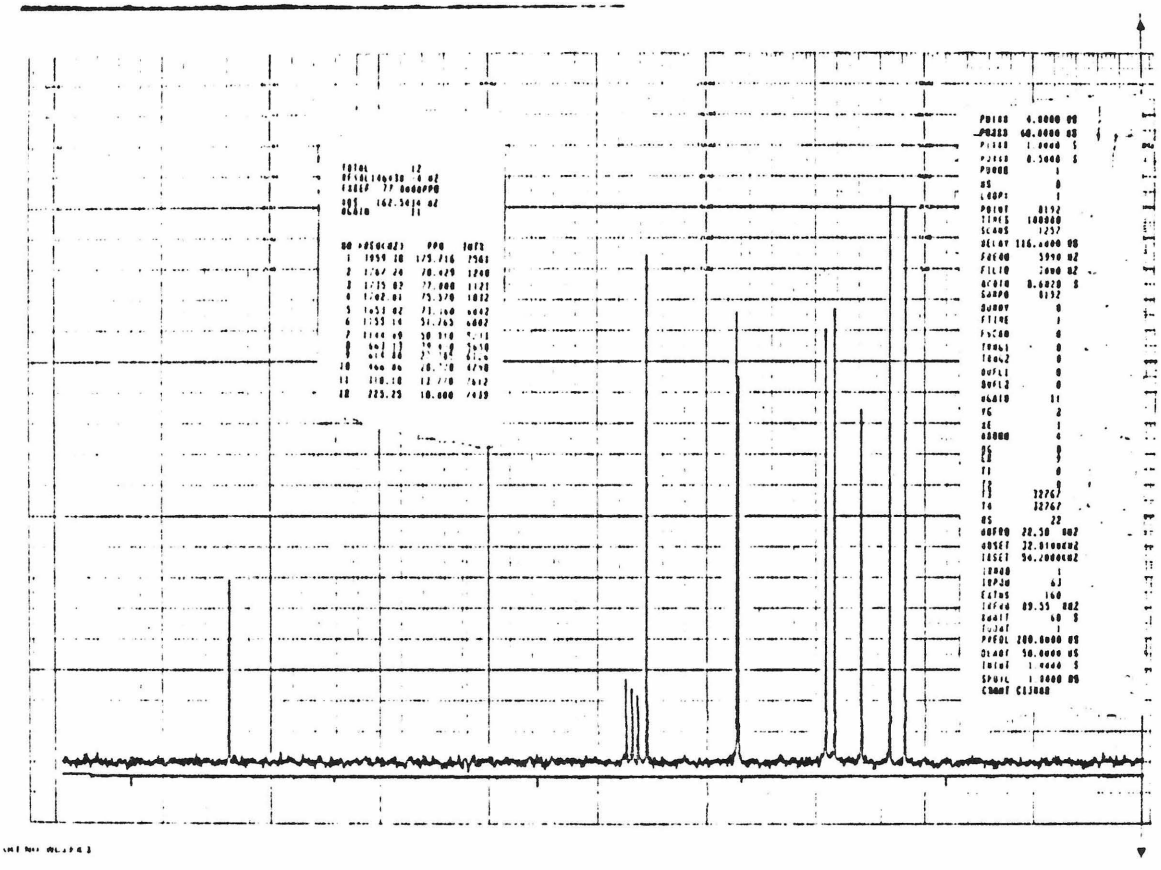

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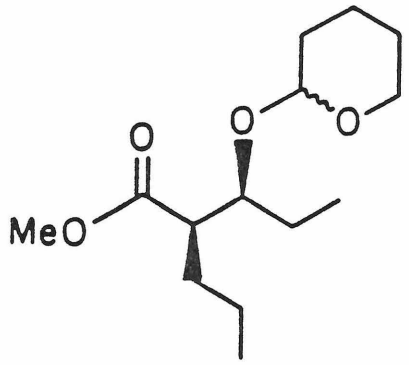

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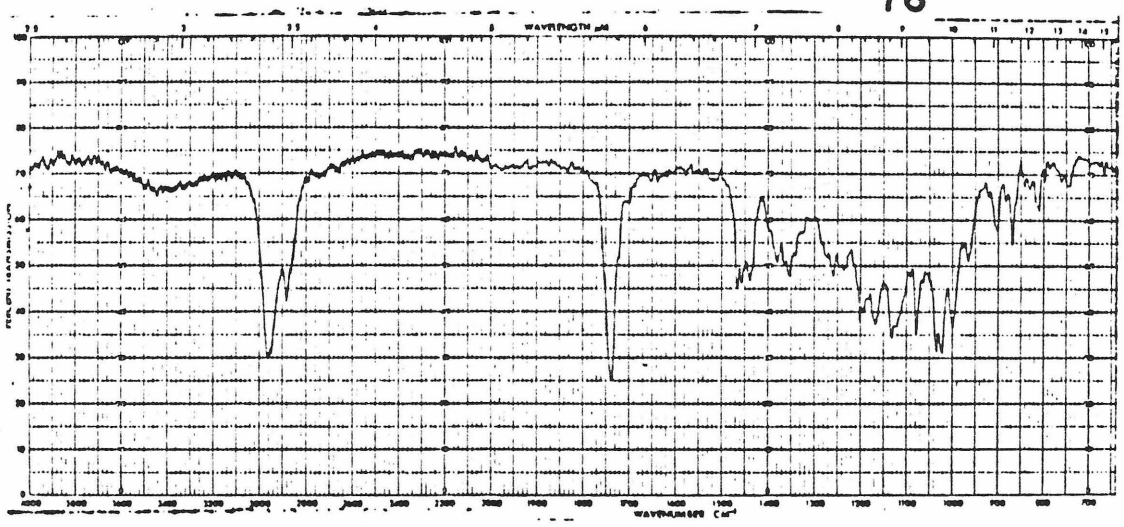

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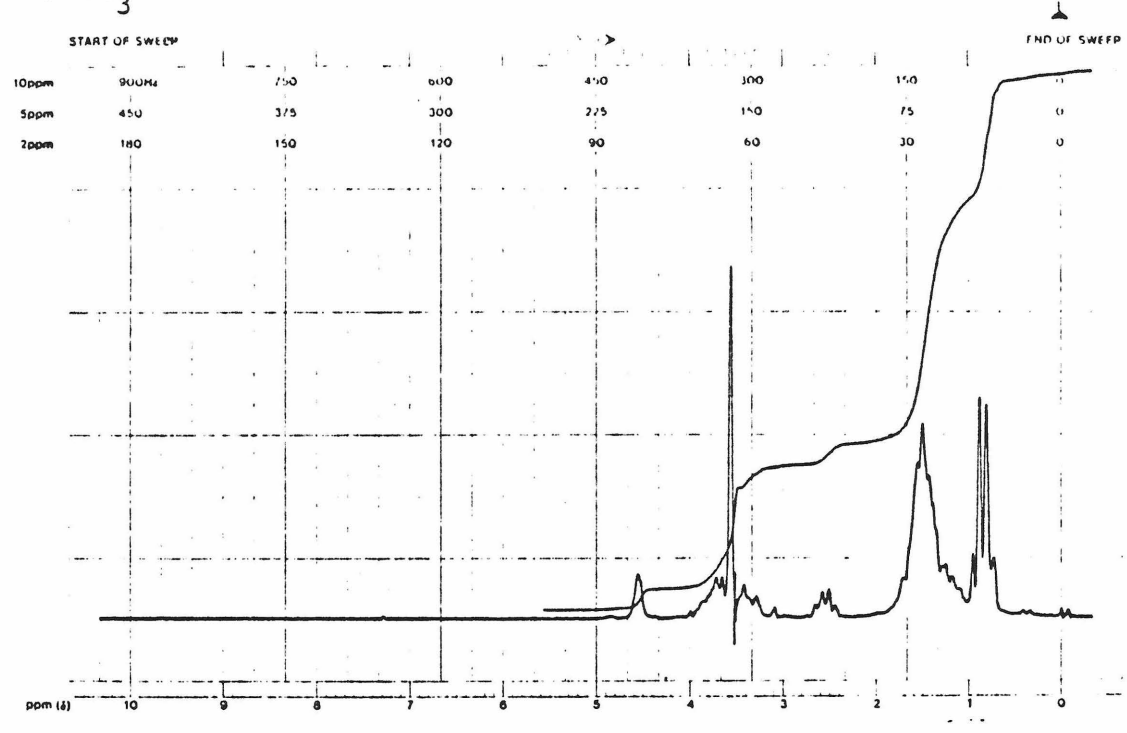

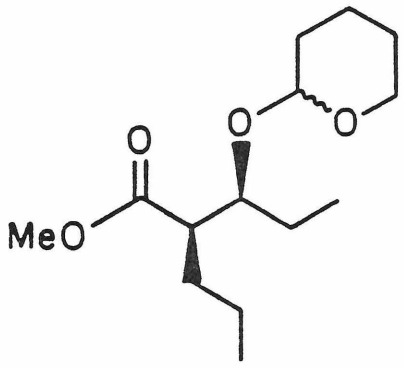

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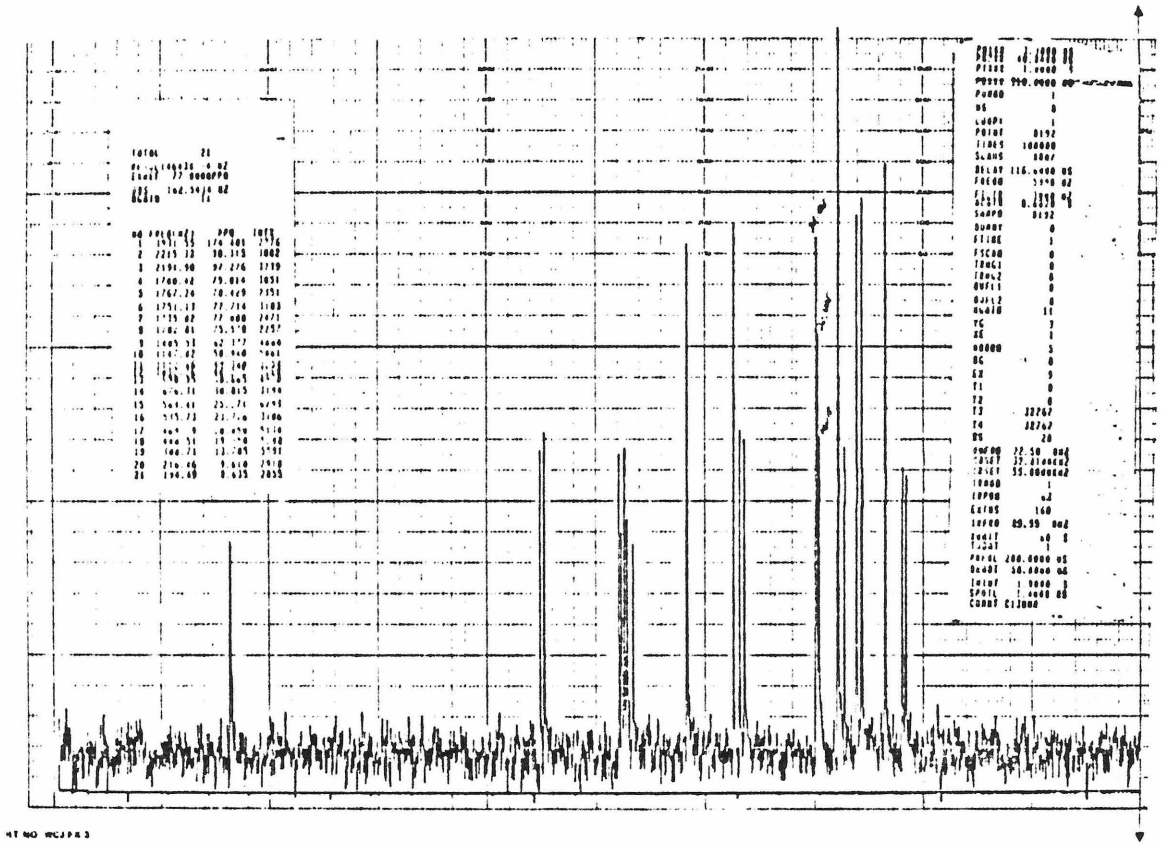

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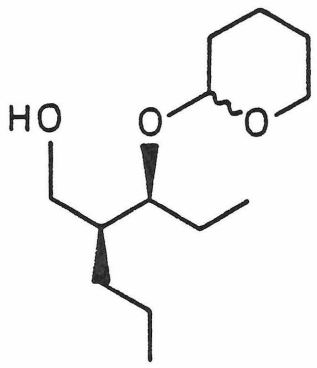

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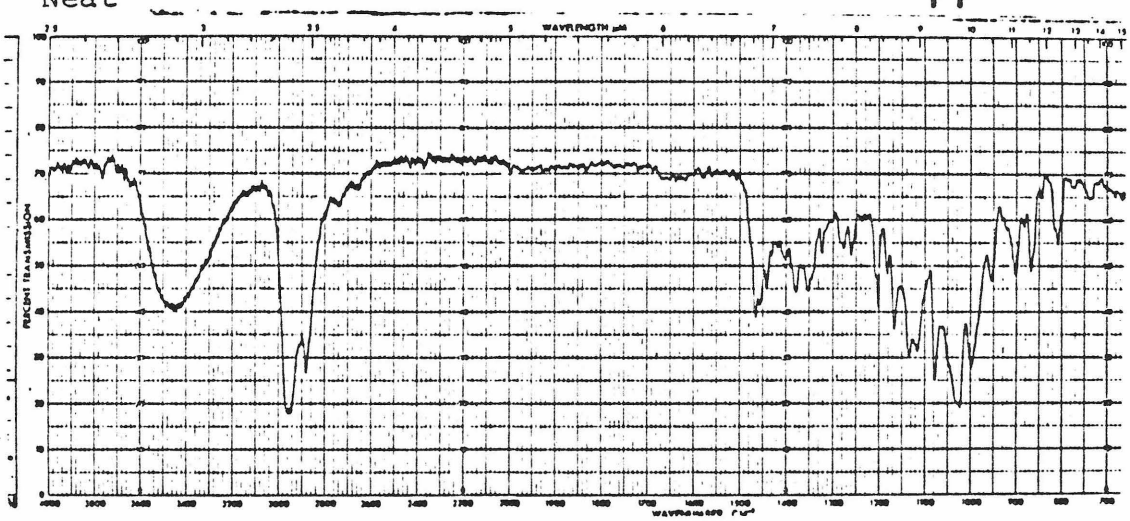

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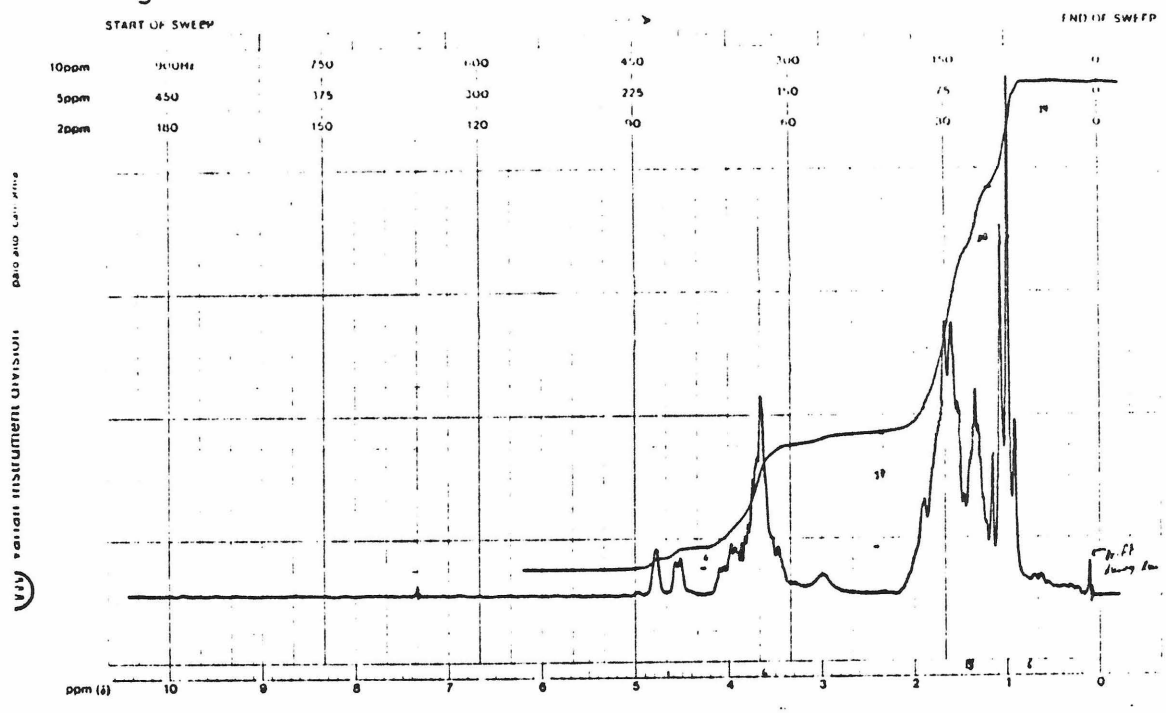

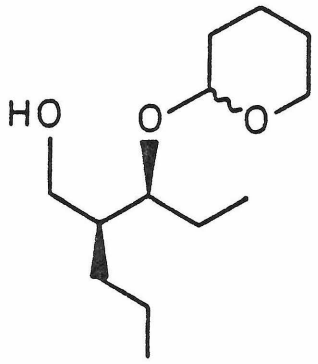

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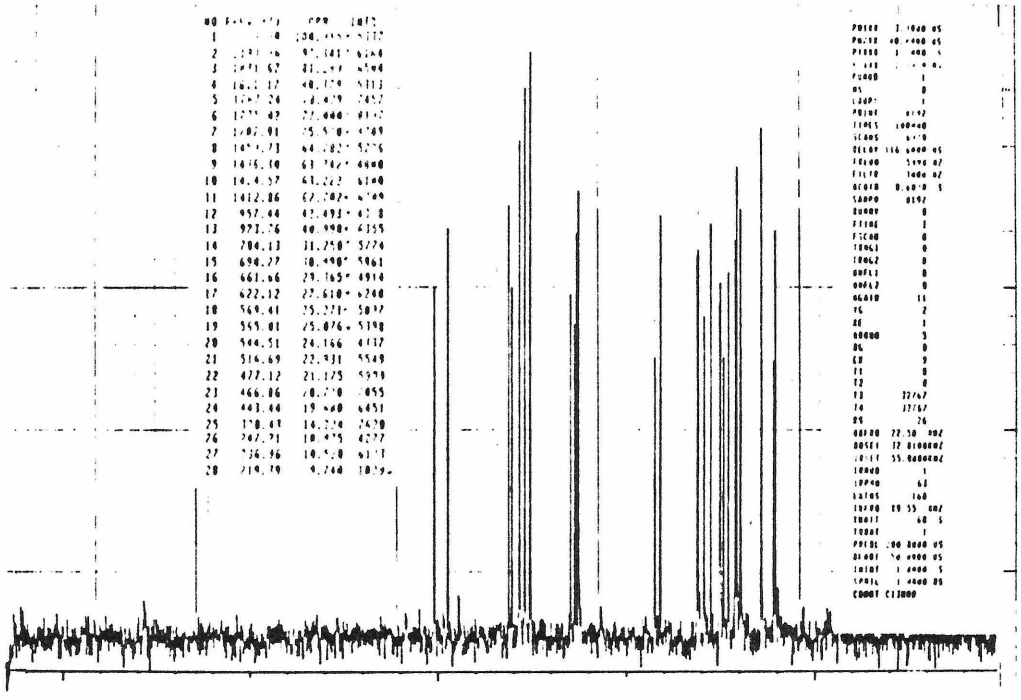

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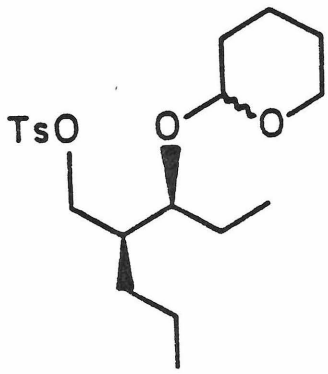

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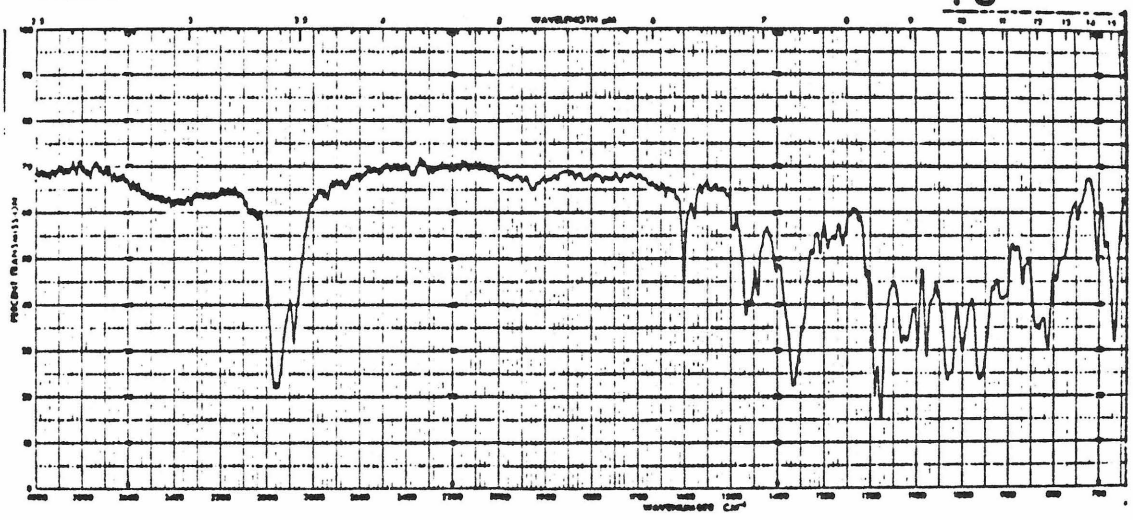

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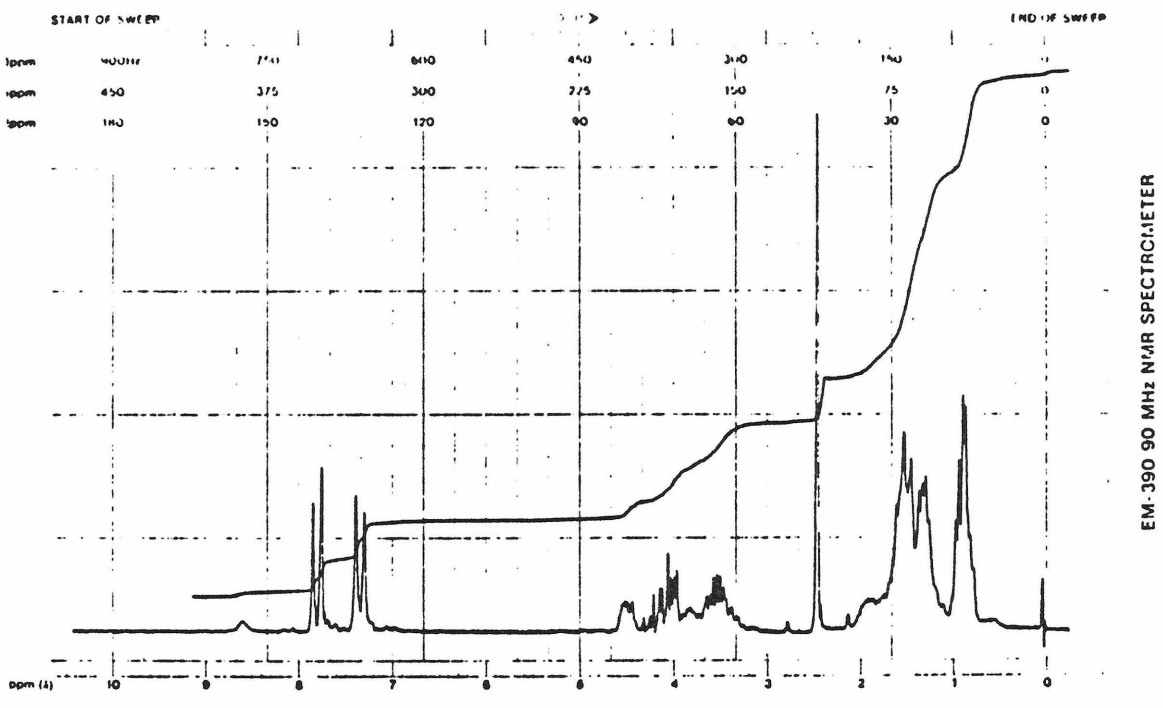

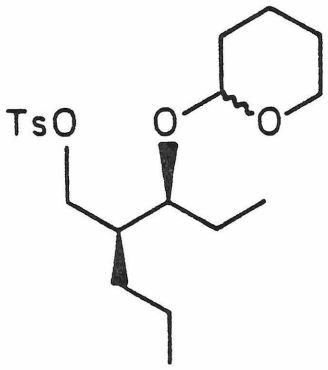

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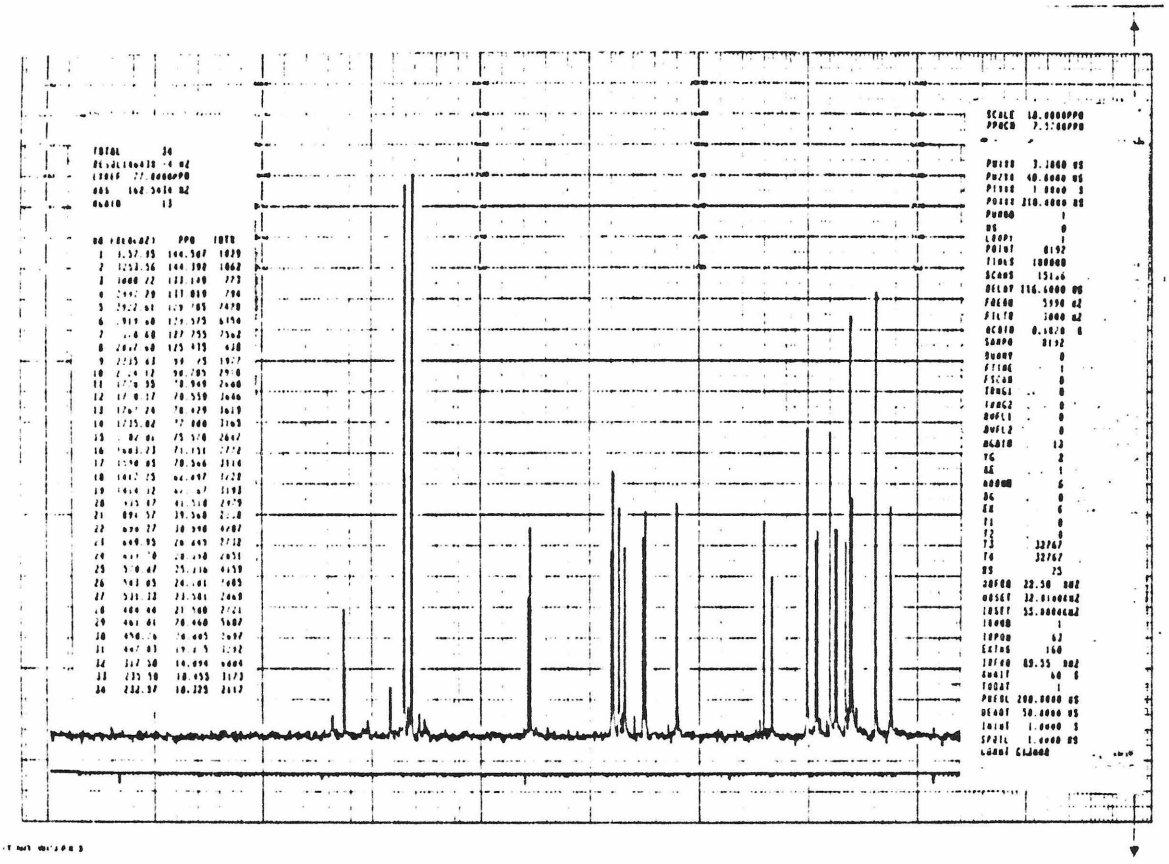

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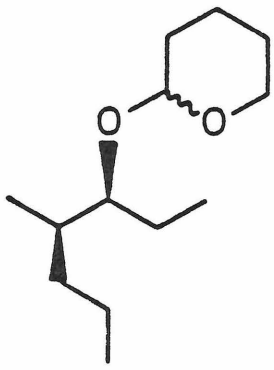

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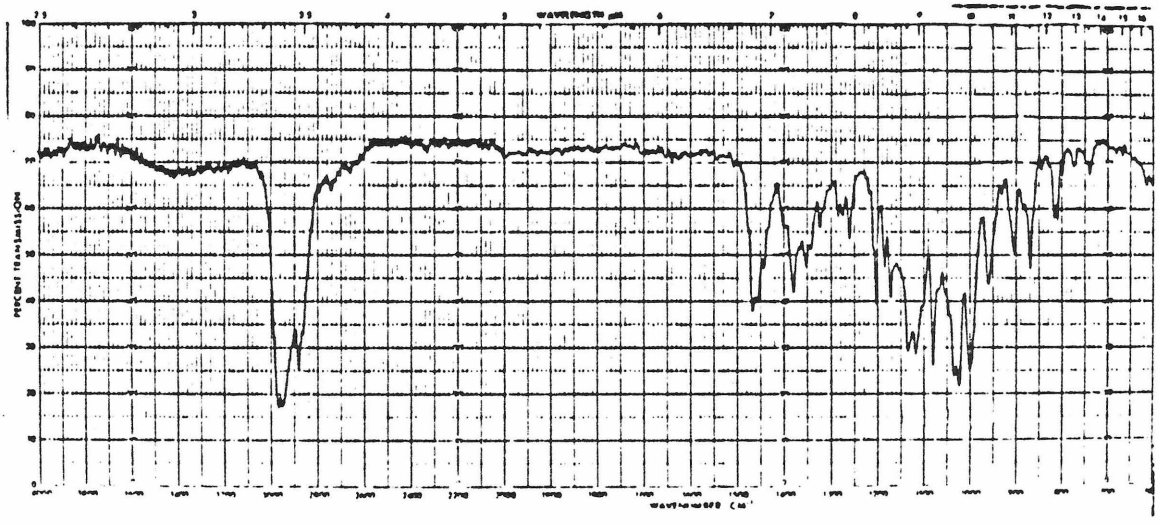

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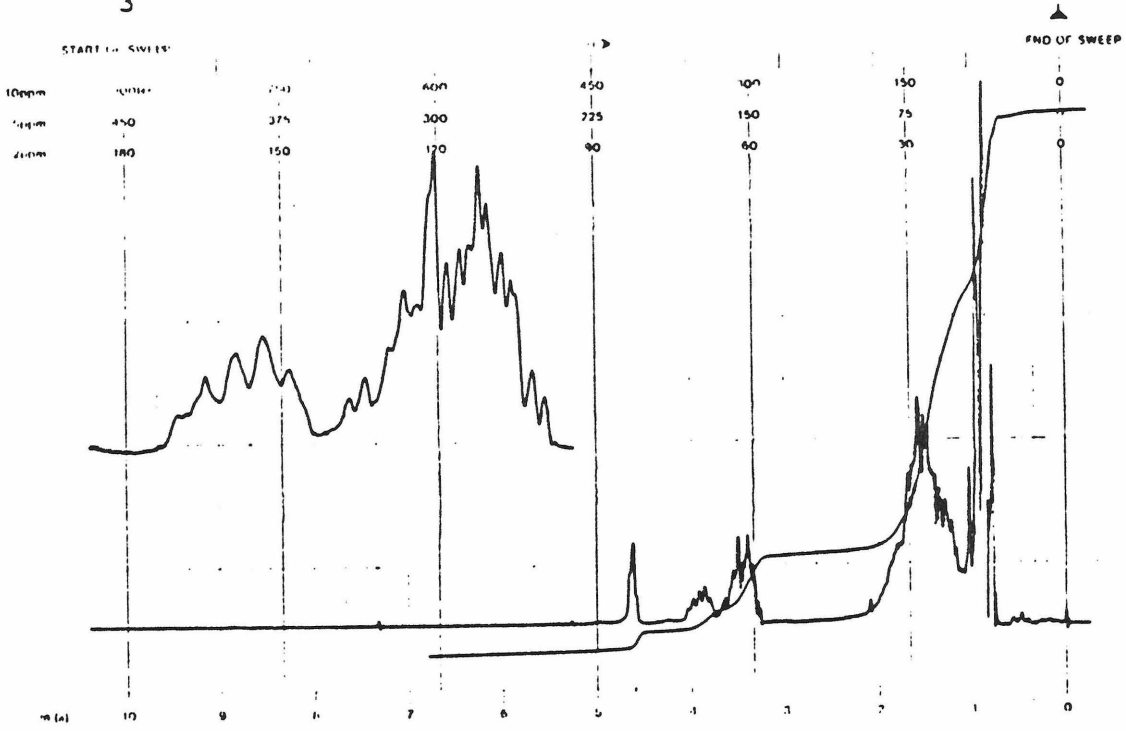

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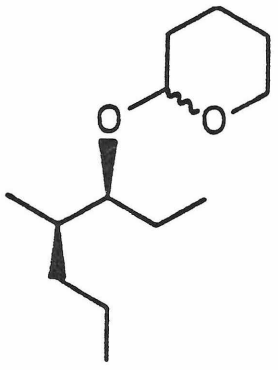

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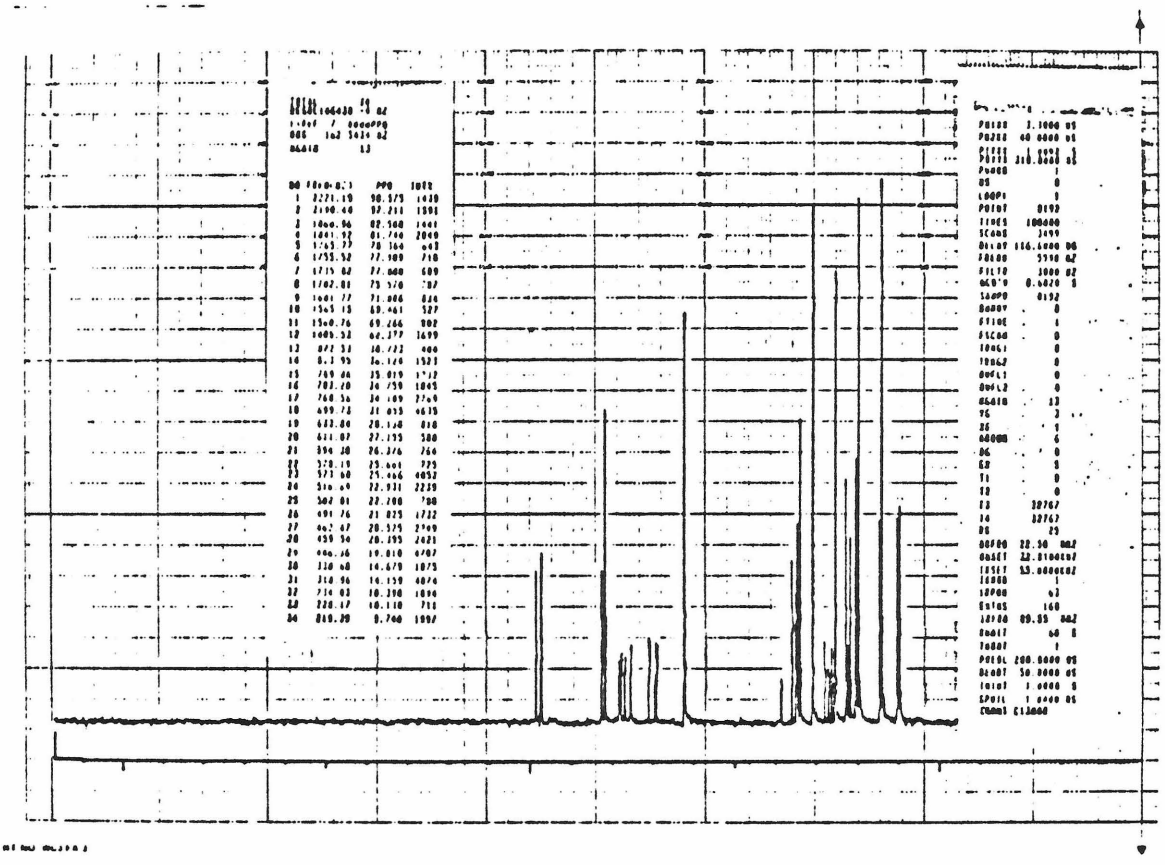

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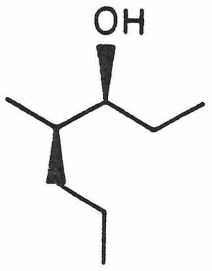

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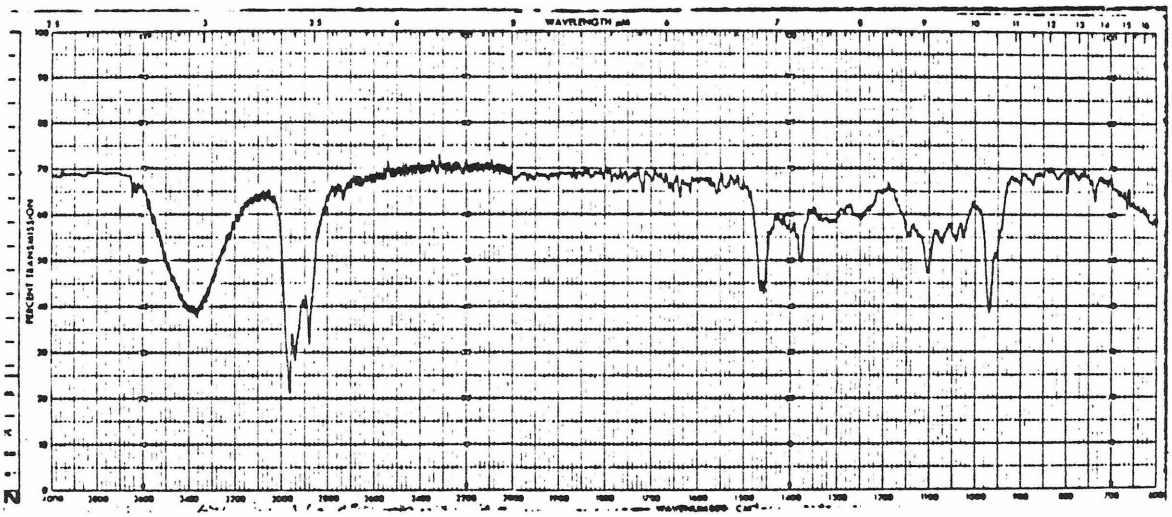

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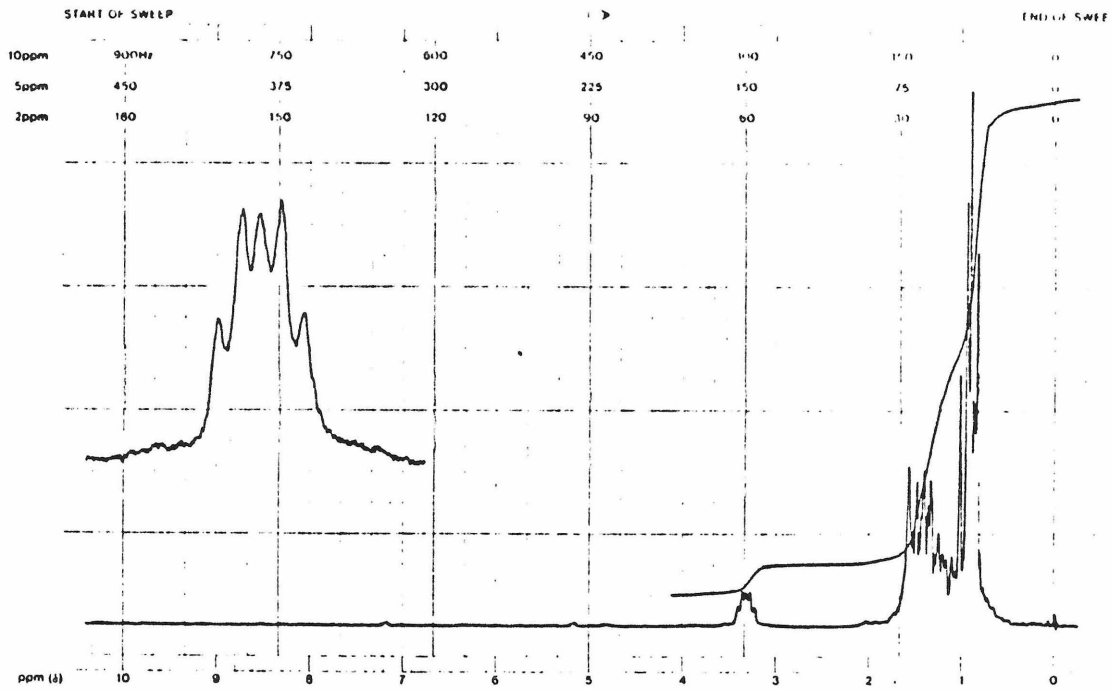

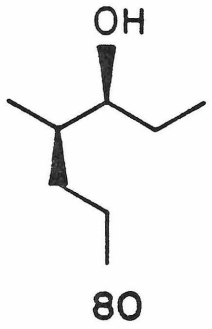

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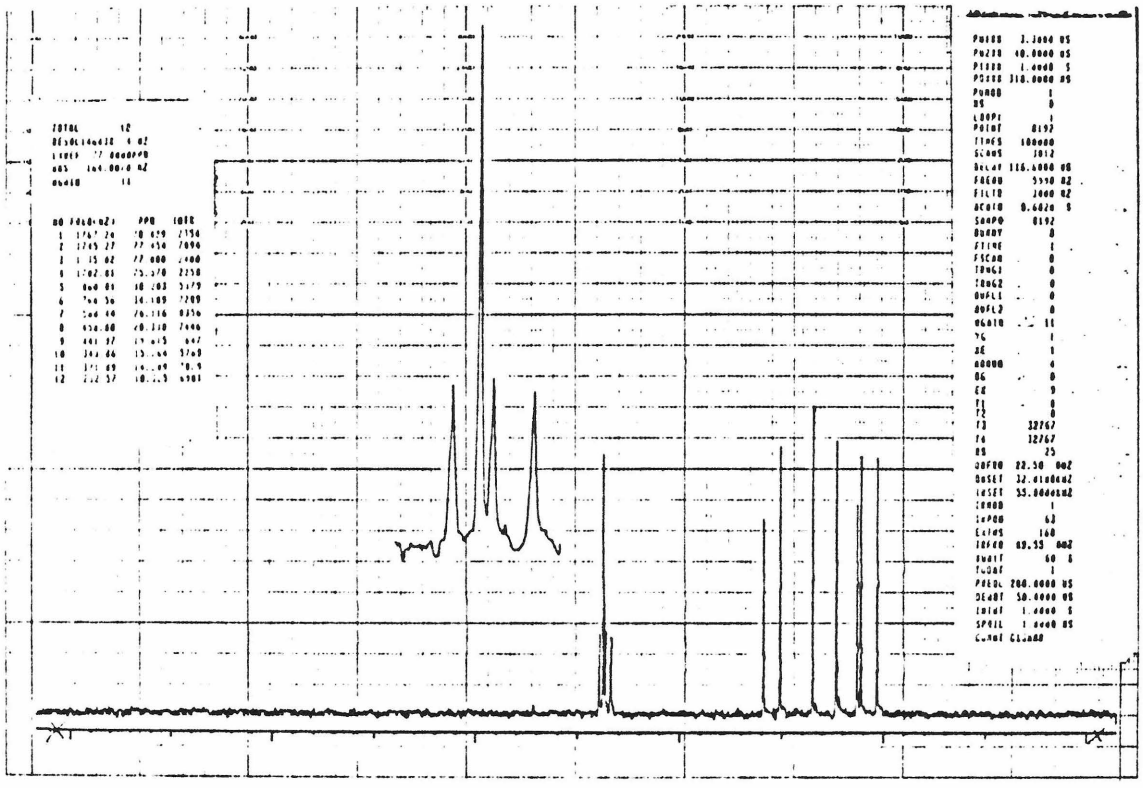

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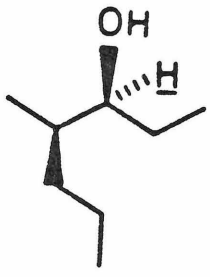
ppm (500 MHz)	int
3.3255	8.040
3.3328	8.144
3.3359	7.679
3.3432	15.469
3.3505	7.689
3.3536	7.809
3.3609	7.641



80

500 MHz ^{1}H NMR of carbinol region from 80.

VIII. PROPOSITIONS

ABSTRACTS

PROPOSITION I

The use of well-defined dicyclopentadienyl titanium (II) and zirconium (II) complexes is proposed as a method for synthetically attractive intramolecular pinacol coupling with potential control of stereochemistry.

PROPOSITION II

The use of mono-cyclopentadienyl metal complexes with dicoordinating chiral (Z) amide enolates is proposed as a method for the asymmetric preparation of threo aldol diastereomers.

PROPOSITION III

The application of catalysts, which promote the stereoregular polymerization of propylene, to the synthesis of diastereomerically pure, enantiomerically pure or enriched synthons for potential use in the synthesis of natural products is proposed.

PROPOSITION IV

Approaches to the formation of (N)acyloxazolidines with a trans-2,4-disubstitution pattern from aminoalcohols and aldehydes are proposed. These chiral heterocyclic amides should give high levels of asymmetric induction upon alkylation of the derived enolates.

PROPOSITION V

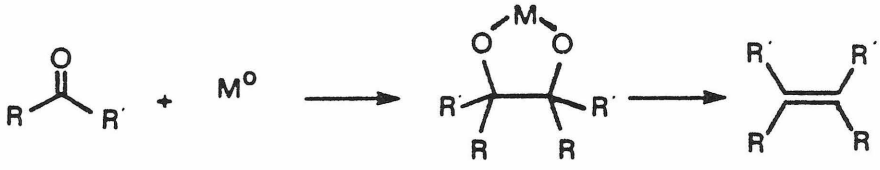
The use of ^{6}Li NMR to examine the complexation between lithium ions and strongly coordinating anions in solution is proposed.

PROPOSITION I

The use of well-defined dicyclopentadienyl titanium (II) and zirconium (II) complexes is proposed as a method for synthetically attractive intramolecular pinacol coupling with potential control of stereochemistry.

* * * * * * * *

The pinacol coupling of carbonyl compounds (Equation 1) is a valuable reaction for the formation of carbon-carbon bonds possessing 1,2 dioxygen functionality.[1] The reaction has however received little use in synthesis. Its major

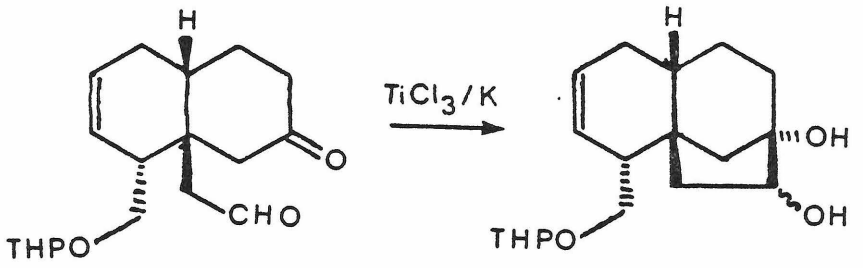


(1)

application has been the preparation of highly strained tetrasubstituted olefins by over-reduction of the initial pinacol product.[2] Application to the synthesis of diols is complicated by the lack of stereocontrol in the reaction and by the obtention of statistical product mixtures in mixed carbonyl couplings.

The intramolecular coupling of dicarbonyl compounds to form cyclic diols and olefins overcomes the problem of nonidentical carbonyl groups. An especially appealing aspect of the intramolecular reaction is that cyclic olefins are obtained in good to excellent yields over the range of three- to twenty-membered rings.[3,4]

Recent advances in pinacol technology involve low-valent titanium species which are defined only in terms of synthetic preparation. McMurray's $TiCl_3/LiAlH_4$ reagent[3] couples carbonyls to the olefin except in cases where strained bridgehead olefins would result. Corey has examined a number of milder reduced titanium preparations for the pinacol coupling to diols.[5] $TiCl_4/Mg(Hg)$ gave best results for intermolecular couplings while $CpTiCl_3/LiAlH_4$ was preferred for difficult intramolecular pinacol cyclizations. In the application to the synthesis of gibberellic acid these preparations proved unsatisfactory for the conversion of ketoaldehyde 1 to the diol 2 (Equation 2).[6] The more vigorous $TiCl_3/K$ was required.

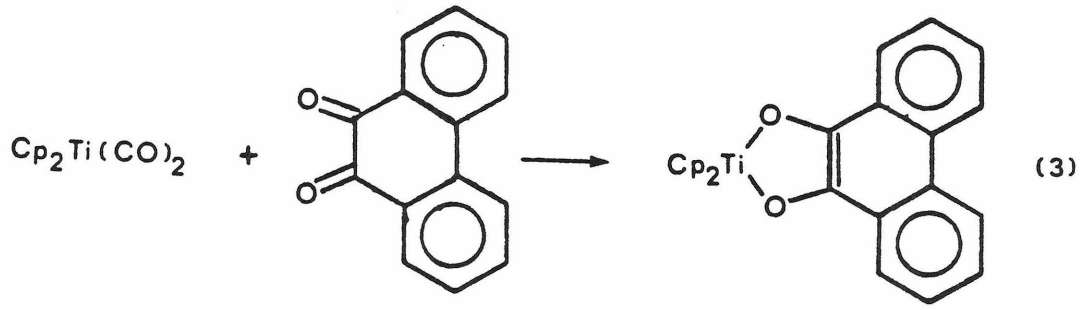


(2)

In the model studies Corey also investigated titanocene [$Cp_2Ti(II)$] prepared by the method of Rausch and Alt[7] but a complex mixture of products from which only 10% of the pinacol was isolated quenched further interest in the "titanocene" reagent. Rausch and co-workers subsequently concluded that their "titanocene" was a complex mixture of ill-defined titanium species.[8]

In spite of the undefined nature of these pinacol reagents they have proven useful within the limitations mentioned. The utility of the pinacol reaction should be further enhanced by the use of defined low-valent organometallic complexes. The dicarbonyl derivatives of titanocene and zirconocene (3a,b) are known and readily prepared from the corresponding commercially available dichlorides and a reducing agent under an atmosphere of carbon monoxide.[9,10] These carbonyl-stabilized metal complexes are monomeric and well-characterized.[11] The carbon monoxide ligands are easily displaced by other ligands such as acetylenes and olefins which may dimerize to form metalocycles.

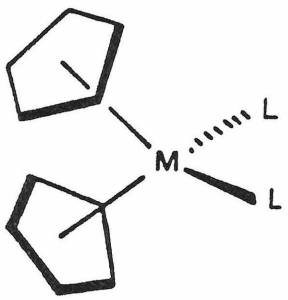
A diketone has also been used to displace the carbon monoxide ligands with oxidation of the metal and reduction of the ketone (Equation 3).[12] Intermolecular pinacol coupling of diethylketomalonate by $Cp_2Ti(CO)_2$ (3a) has been reported.[13]



(3)

Recently complexes containing phosphine[14] and phosphite[15] ligands have also been prepared (3c-e). Carbon monoxide displaces these ligands to form the corresponding dicarbonyl complexes.

Slow addition of diketones or dialdehydes to solutions of such complexes should readily form the pinacol metalate. These metal dialkoxides should be inert to the reaction conditions and readily hydrolyzed with water to diols and metal oxides. In THF solutions other functionality in the molecule such as THP or benzyl ether and polysubstituted olefins should be inert.



3 a M = Ti L = CO[9]

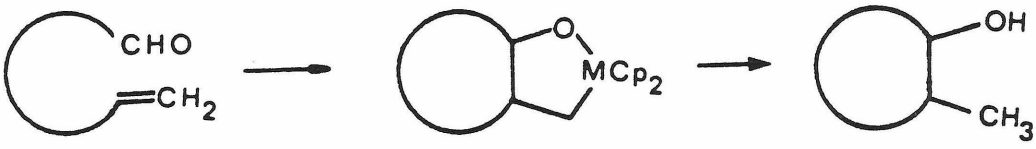
b M = Zr L = CO[10]

c M = Ti L = $P(OMe)_3$[15]

d M = Zr L = $P(OMe)_3$[15]

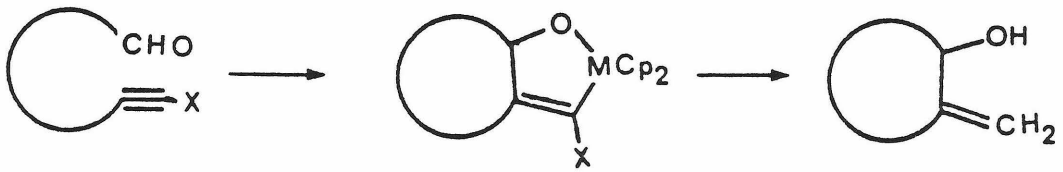
e M = Zr L = $P(CH_2Ph)_3$[14]

The intramolecular coupling of diolefins to form bicyclic metalocycles has been reported with the reduced zirconium complex 6e.[13] It would be interesting to intramolecularly couple an olefin with an aldehyde (Equation 4).



(4)

A similar coupling of an acetylene with an aldehyde (Equation 5) would give an allylic alcohol after hydrolysis.



(5)

These ring-forming bond constructions are not easily achieved with present technology.

The possibility of stereocontrol during bond formation arises from observations on stereocontrol in zirconium-mediated aldol condensation in which aldehydes appear to coordinate presenting the hydrogen substitutent towards the metal pocket (Figure 1).[15] In the low-valent metal

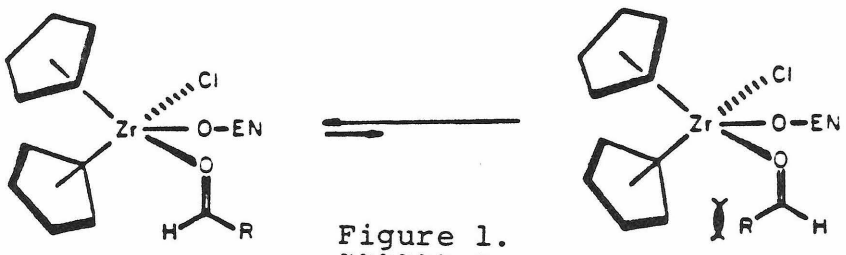
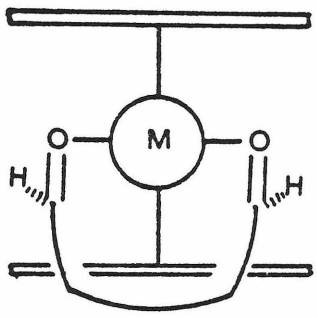


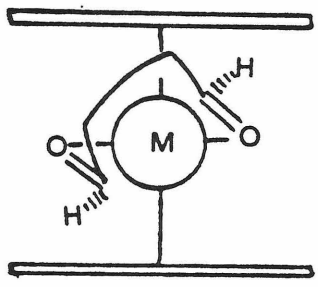
Figure 1.

complexes a second aldehyde should coordinate in a similar fashion. Bond formation from a syn-parallel orientation of the aldehydes would predict the cis diol (Figure 2)



CIS

Figure 2.

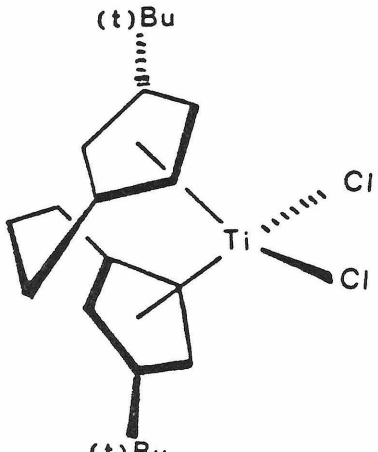


TRANS

Figure 3.

while the skewed anti-parallel orientation would give the trans diol, Figure 3. The relative competition of these transition states will be primarily affected by the chain connecting the aldehydes but also by the metal-ring distance (0.15 Å shorter for titanium than for zirconium) and by substituents on the cyclopentadienyl rings.

The asymmetric bent sandwich complex of Ti (4) has been prepared and resolved. The corresponding dicarbonyl compound should form without incident. The steric demand of the appended (t)butyl groups should exert a significant chiral bias in the skew anti-parallel transition state



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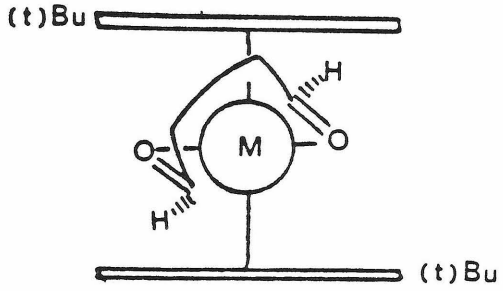

TRANS

Figure 4.

(Figure 4). This should result in significant asymmetric induction for the trans pinacol product. The steric demand of these groups may also influence the competition between cis and trans forming transition states in favor of the trans isomers.

The stereochemistry of the aldehyde-olefin and aldehyde-acetylene couplings should be influenced in a similar manner.

Cyclic cis diols in the absence of ring substitution possess asymmetry only due to ring conformations which usually interconvert easily. It is doubtful that substituents in the pinacol ring would be significantly impacted by the metal-centered chiralty. Thus asymmetric induction is only

to be expected with cyclic trans diols.

A variety of ring sizes will be investigated with full stereochemical characterization of the diol products. Those cases which afford good yields of the trans diols will be the subject of asymmetric synthesis with a resolved chiral metal complex.

As a result of this work, pinacol-type couplings should become synthetically attractive as stereocontrolled ring forming reactions.

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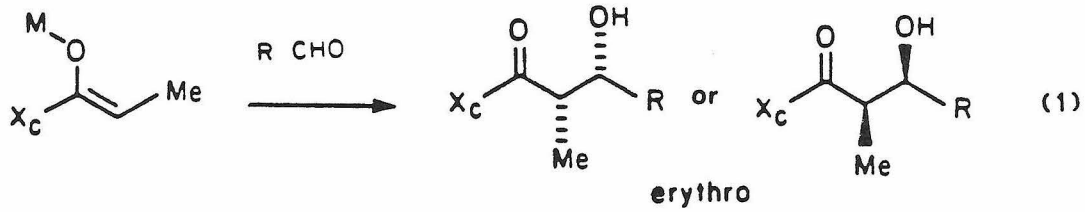
PROPOSITION II

The use of mono-cyclopentadienyl metal complexes with dicoordinating chiral (Z) amide enolates is proposed as a method for the asymmetric preparation of threo aldol diastereomers.

* * * * * * * *

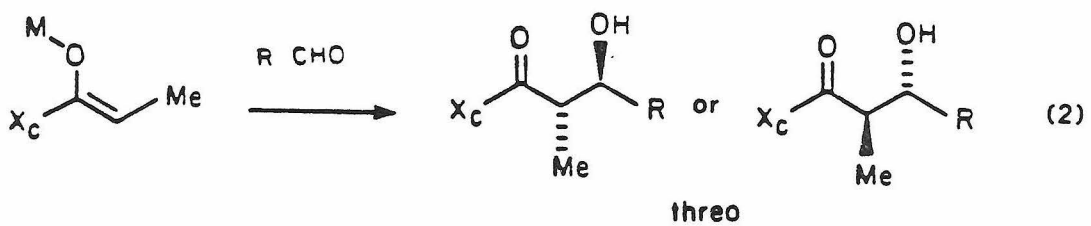
Recent work in aldol stereoregulation has led to selective methodology for the preparation of erythro stereochemistry with high levels of asymmetric induction.[1,2] The successful approaches have introduced a chiral bias (X_c)



(1)

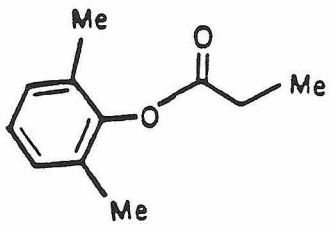
into aldol condensations already shown to be erythro diastereoselective with achiral enolate systems.

Progress with asymmetric induction in the threo manifold has been less successful. Heathcock's threo

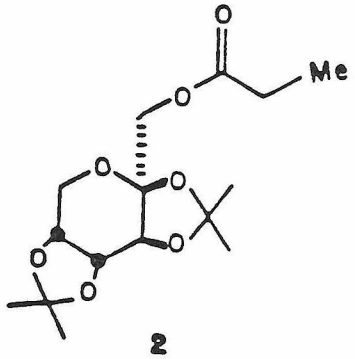


(2)

selective enolates derived from phenolic esters such as 1 do not lend themselves readily to the introduction of a chiral auxiliary.[3] With achiral aliphatic esters the lithium enolates give low levels of erythro-threo diastereosection.[4]



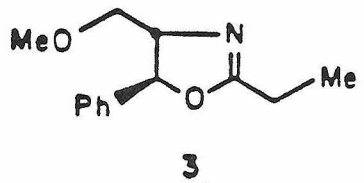
1



2

The lithium enolate of the sugar-derived 2 gave excellent asymmetric induction between the threo diastereomers (0%/60%) but 40% of the product were the two erythro diastereomers.[5]

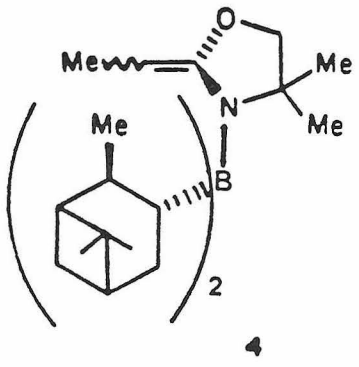
Meyer's chiral oxazoline 3 as its lithium azenolate gave with isobutyraldehdye 75% of a single threo diastereomer which could be purified from the diastereomeric impuries by chromatography.[6]



3

More recently Meyers and Yamamoto have used an achiral oxazoline in conjunction with a chiral boron triflate reagent.[7] The resulting boron azenolate 4 afforded threo aldol diastereomers with moderate enantiomeric excess (77% to 85%) contaminated by only 5 to 10% of the erythro

diastereomers. The use of metal-centered chirality is an important feature for future progress with asymmetric aldol condensations but this feature is attractive only when the asymmetric induction is near 100% since the chiral auxiliary is removed before it can be used as a resolving agent to remove the small amounts of undesired stereoisomers.



4

During the development of bis-(cyclopentadienyl) zirconium dichloride as an erythro-selective moderator for aldol condensations we developed a transition state model which predicted that mono-cyclopentadienyl complexes with otherwise similar structural features should induce threo stereochemistry from cis (Z) enolates[1] (Figure 1). In

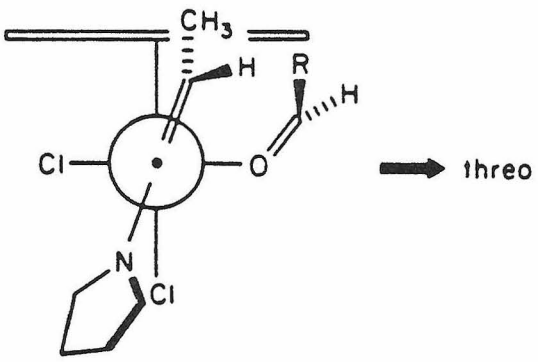
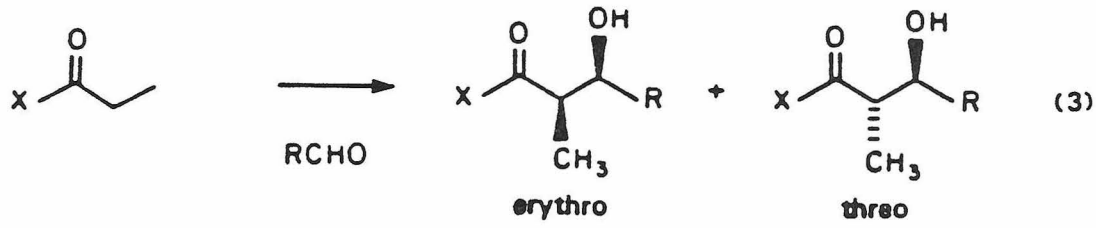


Figure 1.

qualitative experiments using mono-cyclopentadienyl titanium trichloride as the metal additive these predictions were born out (Table 1).



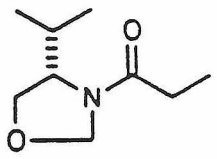
(3)

Table 1. Aldol Diastereoselection: $CpTiCl_3$ Mediated Condensations[a,b]

Carbonyl Substrate	Enolate Configuration	Aldehyde	Metal	Erythro	Threo
	cis/trans				
X=(t)BuO	5/95	R=C_6H_5-	Li	34	66
			Cp_2ZrCl_2	75	25
			$CpTiCl_3$	84	16
		R=(i)C_3H_7-	Li	40	60
			Cp_2ZrCl_2	73	27
			$CpTiCl_3$	87	13
X= 	>98/2	R=C_6H_5-	Li	60	40
			Cp_2ZrCl_2	95	5
			$CpTiCl_3$	27	73
		R=(i)C_3H_7-	Li	78	22
			Cp_2ZrCl_2	96	4
			$CpTiCl_3$	9	91

[a]Equation 3. [b]Taken from Ref. 1.

With the enolate of chiral amide 5, $CpTiCl_3$ again induced 90% threo diastereomers in the aldol condensation with isobutyraldehyde; however on further examination both diastereomers were present in approximately equal amounts. In this proposal are outlined further experiments to exploit these initial observations and to develop a solution to the problem of asymmetric induction of threo diastereomers.



5

The first priority will be to develop a substitute for the $CpTiCl_3$ reagent. The ready availability of the +3 oxidation state of titanium makes one electron chemistry a potentially serious problem.[8] Under conditions where titanium enolates may have been formed, coupling to give succinic acid derivatives was observed.[9] The low recovery of products in our cases with $CpTiCl_3$ may be the result of competing radical pathways siphoning off the enolate reagent. The reactions were examined only for the known aldol products.

Since the +3 oxidation state of zirconium is not easily attained[8], mono-cyclopentadienyl zirconium trichloride ($CpZrCl_3$) would be an obvious choice. The corresponding permethylated complex (Cp^*ZrCl_3) should also be considered. Neither is commercially available; however both have been

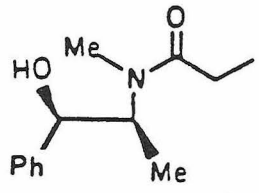
prepared. A Dupont patent claims $CpZrCl_3$ prepared by the oxidation of Cp_2ZrCl_2 with chlorine in methylene chloride solution.[10] The permethylated derivative has been prepared from zirconium tetrachloride and Cp*Li.[11]

Given a supply of the mono-cyclopentadienyl complex the achiral reaction would be optimized for yield and stereoselectivity. A special consideration will be the optimum stoichiometry of the metal additive. Excess metal complex may be detrimental to threo diastereoselection due to prior complexation with the aldehyde. Such complexes might react via bimetallic extended transition states (Figure 2) expected to give the erythro diastereomer.[12]

Figure 2.

The chiral bias in the bis-cyclopentadienyl zirconium-mediated aldol condensations is provided by a nonobvious steric interaction of the chiral auxiliary with the Cp ligands. On removing one of the Cp ligands the transition state becomes much more open and less well-defined. The loss of all asymmetric induction was not surprising.[1] A more obvious chiral bias might be generated by chelation of the chiral auxiliary to the metal center. Such an approach has been used in the asymmetric alkylation of amide enolates derived from the ephedrine amide 6[13] and the prolinol amide 7.[14]

Conditions which favor the formation of a tight chelate ring lead to the highest levels of asymmetric induction in the alkylation reaction. These two hydroxy amides as well as the valinol-derived hydroxy amide 8 should be suitable



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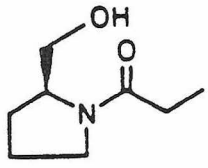

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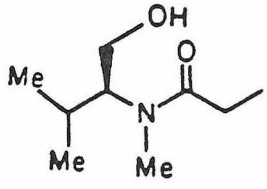


8

for investigations into threo asymmetric induction. The amide functionality should insure the formation of the required Z (cis) enolate geometry. Exchange of the lithium dianions with the cyclopentadienyl metal complex should give an intramolecularly coordinated complex. Coordination of the aldehyde gives the transition state depicted in Figure 3. The threo selectivity should be maintained. With the chiral auxiliary tied to the metal center the asymmetric induction should increase and the dependence on aldehyde structure should diminish. The absolute configuration of the aldol stereocenters from this transition state is illustrated by

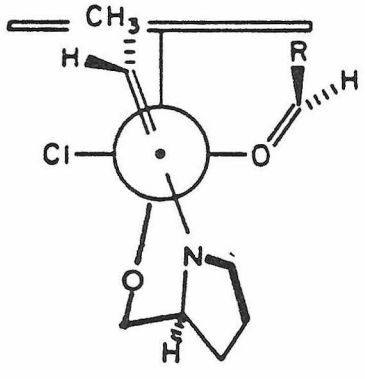
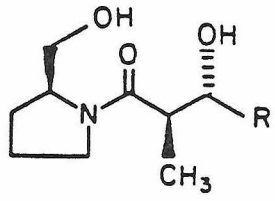


Figure 3.

hydroxy amide 9, the expected major product, from the reaction with isobutryaldehyde.



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The transition state depicted in Figure 3 is formally a $14e^-$ transition state. The remaining coordination sites are filled by solvent. The presence of alternate coordination sites on the metal is of some concern; however these sites provide opportunities for substitution and coordination of other ligands, polydentate alkoxy ethers for example, which may influence the overall aldol stereoselection. The presence of asymmetric centers in these addends would afford an opportunity to examine cooperative and competitive double asymmetric induction.

This approach should provide asymmetric induction in the formation of threo aldol adducts with results at least competitive with and potentially much better than the technology presently available.

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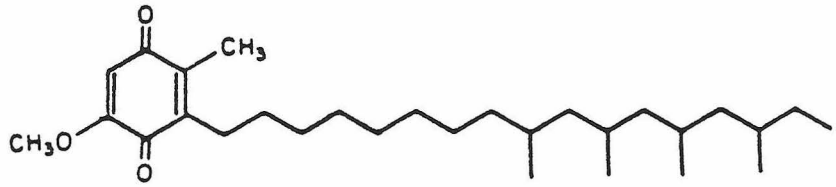
PROPOSITION III

The application of catalysts, which promote the stereoregular polymerization of propylene, to the synthesis of diastereomerically pure, enantiomerically pure or enriched synthons for potential use in the synthesis of natural products is proposed.

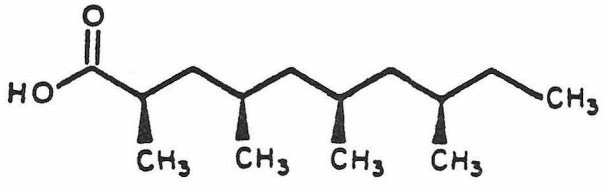
* * * * * * * *

There are a number of natural products which contain segments of polypropylene whose synthetic challenge resides in the control of relative and absolute stereochemistry. A few examples of such natural products are mavioquinone (1),[1]



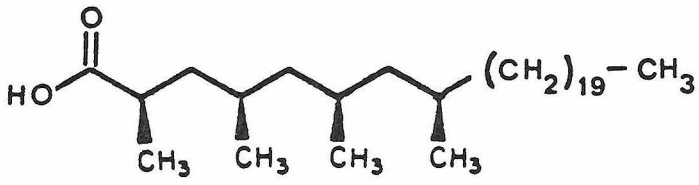
1

the branched fatty acids of the preen gland wax of waterfowl,[2] of which acid 2 is a member, the myocerosic acids obtained as characteristic lipids of various strains of tubercle



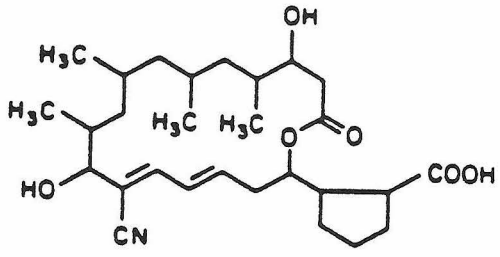
2

bacilli of which ester 3 is a member,[3] and borrelidin (4) a macrocyclic lactone.[4]



3

In most cases where the stereochemistry is known, the units are isotactic i.e. the pendent methyl groups are aligned on the same side of the carbon chain when the extended chain structure is drawn. As shown for fatty acid 2 stereocenters occur on alternate carbons and all stereocenters possess the same configuration. In those cases such as quinone 1 where the configurations have not been determined, biosynthetic considerations favor the isotactic structure.[1b,5]



4 BORRELIDIN

Isotactic polypropylene is similarly a long-carbon-carbon chain with stereocenters bearing methyls on alternate carbons. Within a given polymer chain all stereocenters possess the same configuration.[6] A chain and its enantiomer differ only in the polymer end groups and thus each asymmetric carbon is effectively achiral. Isotactic polypropylene has been produced for about 25 years.[8] Its discovery

was hailed as revolutionary in significance. Ziegler and Natta shared a Nobel prize for their work on the transition metal catalysts which produce these crystalline polymers.

In spite of 30 years of intense investigations the mechanism of the polymerization is still poorly understood and especially with regard to the stereoregulating features the catalytic site remains a black box.[9,10]

The stereoselective catalysts are almost always heterogenous systems with a variety of catalytic sties. Polymerization occurs by the overall incorporation of a propylene unit into a metal-carbon bond at the catalytic site. The stereochemistry of this bond construction is independent of the stereochemistry present in the polymer chain;thus each catalytic site represents a center for asymmetric induction.[8] This induction is determined only by metal-centered steric effects. The various sites have differing steric requirements. The addition of hindered amines or weak lewis bases such as ethers or esters decreases the polymerization rate but increases the isotacticity of the resulting polymer. It appears that slower, more stereospecific sites are sterically hindered. The added bases tend to poison less hindered, less stereospecific catalytic sites first.

The asymmetric induction at individual sites can be very impressive but since the overall product is effectively achiral little effort has been made to resolve the catalytic sites. The symmetry of the polymer chain also necessitates indirect methods for the analysis of asymmetric induction. Polymerization of racemic α-olefins bearing a chiral stereocenter adjacent to the double bond occurs with partial resolution of the side-chain stereocenter.[11] Incorporation of a homologous resolved α-olefin in the polymerization process results in co-polymerization with the monomer possessing the same configuration at the chiral center in preference to its enantiomer. The configurational excess of 15% to 25% obtained from this procedure is remarkably high considering the remoteness of the catalytic site from the α-chiral center of the monomers.

One approach to resolving the active sites involves the addition of a chiral ether or ester which presumably coordinates to one chirality of catalytic site in preference to the enantiomeric site.[8] As yet this approach has had little success but the analysis requires an indirect method such as that described above.

Limiting the degree of polymerization would produce short fragments wherein the end groups remain significant with respect to the bulk of the oligiomer and would allow

a more direct assessment of the asymmetric induction in such a polymerization.

Suitable end group functionality could be introduced by oxidation of the metal-carbon bond remaining after the polymerization has been discontinued. Methodology exists for the formation of alcohols and halides.[12] Bifunctional polymers could be formed by priming the catalytic sites with an alkyl group possessing a terminal protected alcohol function. The mono- and bi-functional fragments could be incorporated into larger molecules such as compounds 1-4.

The most significant problem for the synthetic use of this method deals with the control of the degree of polymerization. In most polymerizations a smooth distribution of oligiomers around an average size is obtained. For synthetic applications a very sharp distribution around four or five monomer units would be ideal. Two or three propylene unit oligiomers would also be useful with significant asymmetric induction.

A sharp distribution might be achieved by using catalysts which only slowly polymerize propylene, by limiting the amount of propylene available and by controlling the length of reaction time. In this regard it is interesting to note some details from the biosynthesis of the branched fatty acid 1 which is biosynthezised from

propionyl CoA by the fatty acid synthetase complex.[13] This complex is present in most cells for the production of linear fatty acids from acetyl CoA. The degree of oligomerization is highly selective for eight units of acetyl CoA to form palmitic acid[14] but accepts only four units of propionyl CoA to form 2.[13a] The enzyme specificity is a function of competing rates of oligiomerization and cleavage from the enzyme.[14] The cleavage rate is fairly slow and constant as a function of chain length, while the oligiomerization is rapid for the first units and falls drastically at the observed levels of polymerization. The reason for this change is not known but corresponds roughly with the spiralization of the secondary structure of the branched hydrocarbon chain of polypropylene.[15] The added steric hindrance at the enzyme catalytic site which occurs as the chain spirals over is one possible explanation. Such a mechanism would have a direct application to the catalytic sites for propylene polymerization.

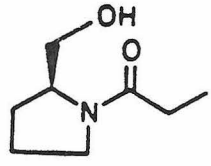
Such a change in rate of polymerization has been observed qualitatively for propylene incorporation by an homogenous alkyl lutetium complex.[16] The hindered stereo-selective sites of heterogenous catalysts should also show a rate dependence with added steric hindrance to the approach of additional monomer.

Small amounts of other chain size oligiomers should be separable by distillation for the range of oligiomers of interest here. The stereochemistry present in these by-products should also be valuable thus helping to recover some of the expense of such a separation.

The stereochemical purity of the functionalized polymer segments will be analyzed by capillary gas chromatography.[2] The degree of stereoselection is an important parameter used to compare various Ziegler-Natta catalysts. Since this stereoselectivity depends on the metal center and not on the polymer side chain the stereoselection observed in short segments should be representative of larger polymers obtained from the same catalysts. The use of capillary gas chromatography should allow at least a ten-fold improvement in the detection of diastereomeric polymers over the best available present technology, ^{13}C NMR.[17] An improvement in analytical capability would allow greater control over the factors which influence polymer stereoregulation. This technique would be valuable even in the absence of useful control of the oligiomer distribution.

The functionalized polymer fragments can also be resolved into the optical antipodes for incorporation into synthetic targets. Alcohols will be resolved by formation of the urethane derivative with a chiral amine and

chromatographic separation of the diastereomers.[18] Bromides or iodides will be extended one propylene unit by alkylation with a chiral propionyl enolate such as that derived from the prolinol amide 5.[19] Careful control of the alkylation conditions should result in two diastereomers possessing the same chirality at the α-methyl stereocenter and opposite chirality at the other stereocenters of the acyl fragment. These will be resolved by liquid chromatography. Hydrolysis of the amide occurs readily for these types of hydroxy amides.



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The formation of chiral derivatives should allow the asymmetric induction of the catalytic sites to be observed directly. With this analytical tool we would then further explore the influence of chiral additives on the polymerization process. This should lead to the development of chiral additives which are very hindered for one chirality of the active sites but unhindered for the enantiomeric sites. Thus one set of sites should remain active while the other set would be selectively poisoned. The enantiomerically enriched polymer segments would be even more valuable as synthons in total synthesis. The bifunctional segments would allow either sense of isotactic chirality to be obtained from the same catalyst system since the configuration would be reversed by simple protection-deprotection

of the functionalized end groups.[20]

Since the criteria defined in this proposal are very different from those normally required of polymerization catalysts it is probable that the present highly stereoselective catalysts will not be useful. A corollary is that many systems which were unacceptable as polymerization catalysts may show the desired behavior. The overall approach will concentrate on stereoselectivity (both relative and absolute) first, control of chain-length distribution second and the introduction of mono and difunctionality third.

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PROPOSITION IV

Approaches to the formation of (N)acyloxazolidines with a trans-2,4-disubstitution pattern from aminoalcohols and aldehydes are proposed. These chiral heterocyclic amides should give high levels of asymmetric induction upon alkylation of the derived enolates.

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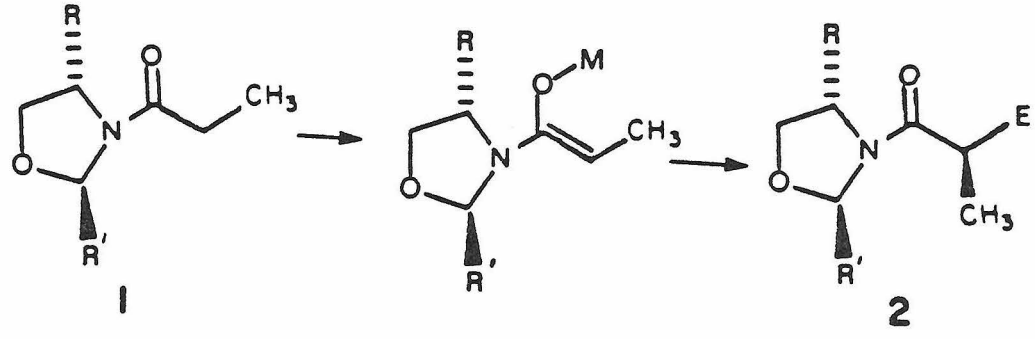
Chiral enolates derived from trans-2,4-disubstituted (N)acyloxazolidines (1) should afford excellent levels of useful asymmetric induction upon alkylation (Equation 1) for

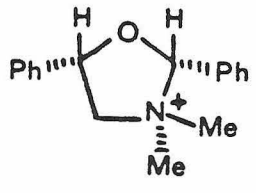


(1)

the following reasons.[1,2] The rigid five-membered ring will direct the selective formation of the Z enolate configuration during enolization with LDA. The trans substituents on the ring provide cooperative steric bias to the diastereotopic faces of the enolate. Based on a model study by

Takacs,[1] diastereoselection on the order of 65:1 and greater should be expected without rigorous control of the alkylation conditions. The amide enolate is highly nucleophilic and should react with a wide variety of electrophiles. The initial chirality is readily available from amino acids. And the latent hydroxyl protected within the heterocyclic ring can participate in the acid-catalyzed hydrolysis of the alkylated amide to afford the carboxylic acid.[2]

Despite several decades of research involving amino-alcohol-aldehyde co-condensations, no trans-2,4-disubstituted (N)acyl oxazolidines have been reported.[3] The major reason for this must be the inherent preference of 1,3 disubstituted five-membered rings to possess the cis configuration,[4] however very little work has been published with respect to stereochemistry in 2,4 disubstituted oxazolidines.[5] Compound 3 has been demonstrated to possess the cis-2,4-configuration.[6]



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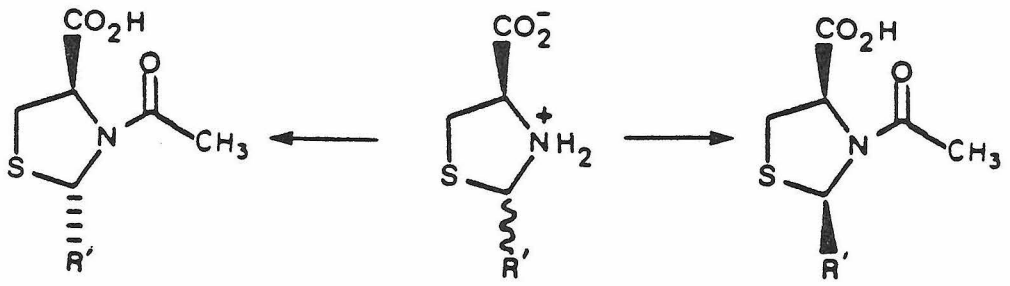
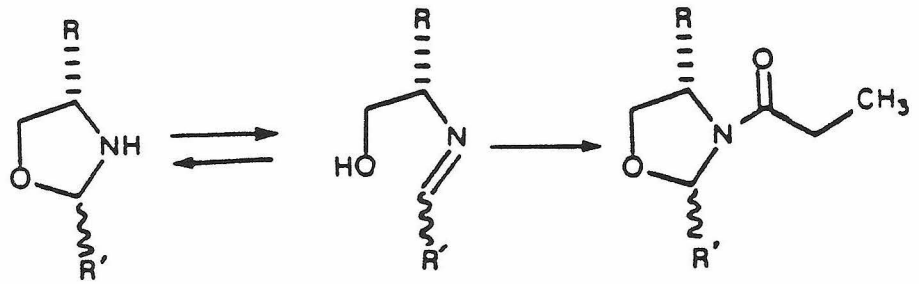
For the related thiazolidine ring system more work has been published. The cis preference is still observed.[7] Interestingly in a recent study[8] it was found that upon acylation of the thiazolidine ring either the cis or the trans configuration can prevail depending on the reaction conditions (Equation 2). High temperatures favor the cis configuration while basic conditions at ambient temperature favor the trans configuration.



(2)

The oxazolidines are generally prepared by azeotropic removal of water from a mixture of the aminoalcohol and carbonyl substrate.[9] The free oxazolidine 4 exists in equilibrium with the acyclic Schiff base 5.[10] Acyclation locks the cyclic form to give the (N)acyloxazolidine 6 (Equation 3).

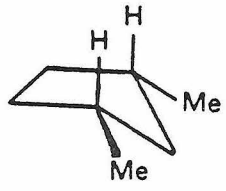


(3)

4 5 6

We propose to investigate the configuration ratio of both the free oxazolidines 4 and the acylated products 6 for a variety of R and R' substituents. The acylations will be conducted under a variety of conditions in an effort to maximize the trans configuration in analogy to the results reported for thiazolidines. Acylation of the aminoalcohols

prior to condensation with the aldehydes should give amidoalcohols. The condensation of the amidoalcohols with aldehydes should also afford (N)acyloxazolidines[11] but perhaps with differing stereochemical results. The cis preference of 1,3 disubstituted five-membered rings occurs because both substituents can achieve equatorial orientations in the envelope conformation as illustrated for the parent 1,3 dimethylcyclopentane (7).[4] The presence of sp^2 hybridized atoms in the ring does little to affect this conformational preference.



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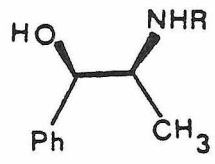
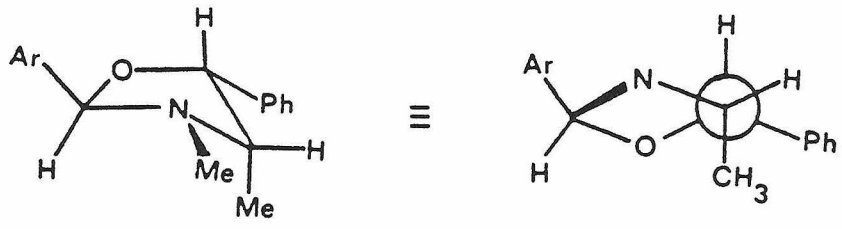
Neelakantan has observed that ephedrine (8a) condenses with aromatic aldehydes to afford the trans-2,4-relationship.[12] This can be interpreted in terms of $A_{1,2}$ strain between the cis substituents at the 4- and 5- positions of the ephedrine oxazolidine 9. This strain forces the smaller substituent into an axial orientation on the



8 a R=Me
b R=H
c R=COC$_2$H$_5$



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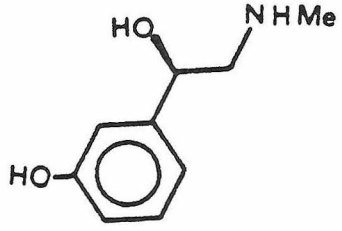
envelope flap carbon. This directs the aromatic substituent at the 2-position trans to the other ring substituents. The trans stereochemistry is general for aromatic aldehydes and has been confirmed by an X-ray structure of the p-bromobenzaldehyde adduct.[13] Acetaldehyde however forms both cis and trans oxazolidines with ephedrine. That the methyl substituent at the 4-position was essential for stereospecific ring formation was verified by the mixture of ring diastereomers obtained in the condensation of benzaldehyde with phenylephrine (10).[12]



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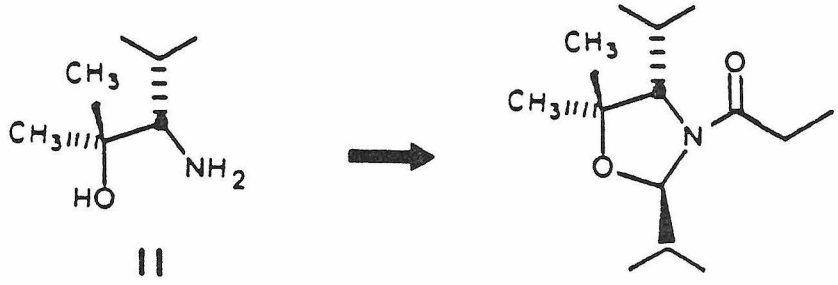
We postulate that the same trans ring stereochemistry observed with ephedrine (8a) will occur with norephedrine (8b) and (N)acylnorephedrine (8c). In the asymmetric alkylation the additional substituent at the 5-position should have a minor but reinforcing effect on the overall chiral bias provided by the oxazolidine to the diastereospecific faces of the derived enolates.

One possible complication would be proton exchange from the 2-position of the aromatic oxazolidines under the strongly basic conditions required for enolate formation.[14] Replacement of the aromatic aldehyde by isobutyraldehyde should decrease the acidity of this

position without adversely affecting the stereoselectivity of the ring formation.

The steric bias of the 4-position can be increased by the use of aminoacid-derived chirality. The aminoalcohol 11 should be readily available from valine. The additional methyl group at the 5-position of the derived acyloxazolidine 12 should occupy an equatorial orientation and have



11 12

little effect on the 2-position stereochemistry or on the chiral bias provided to the derived enolate.

The experiments outlined in this proposal should lead to a better understanding of the stereochemistry of substituted oxazolidine rings. The practical application of these chiral auxiliaries should allow convenient asymmetric alkylations with exceptionally high levels of asymmetric induction.

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PROPOSITION V

The use of ^{6}Li NMR to examine the complexation between lithium ions and strongly coordinating anions in solution is proposed.

* * * * * * * *

Nuclear Magnetic Resonance is a valuable tool since it provides direct information about the solution structure and environment of the nuclei under investigation. ^{7}Li NMR has aided in understanding the structure of alkyl lithium aggregates[1] and the solvation of lithium cations.[2] A number of drawbacks hinder the wider use of Li NMR. The total range of lithium chemical shifts is less than 10 ppm.[3] The nuclear quadrupole moment of ^{7}Li results in substantial line broadening due to quadrupolar relaxation in nonsymmetric electronic environments.[4] The small chemical shift range means that subtle structural information about the lithium environment may be masked by the line broadening which occurs.

The ^{6}Li nucleus has an almost negligible quadrupole moment. ^{6}Li has been said to behave essentially as a spin-1/2 nucleus in solution. As such it is expected to

"afford narrow high-resolution spectra even for larger nonsymmetric molecules."[5] The ^{6}Li nucleus is less abundant than ^{7}Li and much less sensitive and therefore more difficult to detect. The magnetic properties of the lithium isotopes are compared in Table 1 to the more commonly observed

Table 1. Nuclear Properties of ^{1}H, ^{6}Li, ^{7}Li, and ^{13}C[a]

Isotope	^{1}H	^{6}Li	^{7}Li	^{13}C
Natural Abundance, %	99.8	7.4	92.6	1.1
Nuclear Spin I	1/2	1	3/2	1/2
NMR Frequency (MHz) at Field Strength (kG)				
21.138	90	13.2	35.0	22.7
51.672	220	32.4	85.5	55.3
117.44	500	73.5	194.5	125.5
Relative Sensitivity				
Constant H[b]	1.0	0.008	0.294	0.016
Constant ν[c]	1.0	0.392	1.94	0.252
Magnetic Moment (Magnetons)	2.97	0.82	3.26	0.70
Quadrupole Moment (Barns)	-	0.0008	-0.04	-

[a]Data taken from Ref. 6. [b]H = magnetic field. [c]ν = frequency.

nuclei ^{1}H and ^{13}C.

Recent advances in instrumentation have more than overcome the problems associated with ^{6}Li. Thus at 117 kG (500 MHz ^{1}H) ^{6}Li gives far better signal strength than ^{13}C at the usual 21 kG (90 MHz ^{1}H). At 117 kG the chemical shift range spans 700 Hz so that resolution similar to 90 MHz ^{1}H NMR spectra should be obtainable.

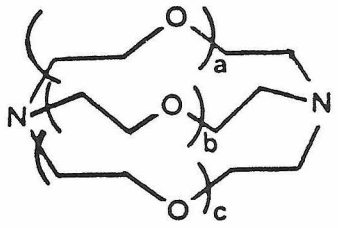
We originally proposed[7] the use of ^{6}Li NMR in conjunction with ^{1}H and ^{13}C NMR to investigate the solution structure of several lithium reagents including lithium ester enolates[8] and Meyers' asymmetric lithium oxazolinate.[9] Although some of the mechanistic questions have been resolved,[10] the interaction of lithium cation with strongly coordinating anions remains a topic of considerable interest.

The use of ^{6}Li NMR is being reported more often and in greater variety.[11,12] One recent study further demonstrates the advantages of ^{6}Li.[12] The solution structure of propyl lithium had previously been studied by ^{7}Li NMR.[12a] A single lithium resonance at 320°K had a line width of 2 Hz. Upon cooling to 180°K the line width gradually broadened to over 60 Hz. Recently this system was reinvestigated by ^{6}Li NMR.[12b] At 180°K the spectrum displayed five sharp lines with line widths of 0.5 Hz to 2 Hz over a span of 33 Hz. The five lines correlate with different

aggregates of the organolithium reagent. The quadrupolar line broadening of ^{7}Li had obscured the finer details of the complexation phenomenon.

Our understanding of a number of lithium-containing systems would be enhanced by the information available from ^{6}Li NMR studies. The systems described below are representative.

Complex formation between lithium cations and various cryptands has been studied as a function of solvent by ^{7}Li NMR.[13] Lithium complexes of larger cryptands such as C222 and C221 exhibit a broad averaged signal consistent with fast exchange between complexed and free lithium in solution. As the proportion of cryptand to Li^{+} is increased the chemical shift varies from that of the free Li^{+} to that of the cryptated lithium ion. In strongly coordinating solvents such as Me_2SO and water there is little or no effect on the lithium chemical shift with these added cryptands. This indicates that the large cryptands do not competitively solvate the lithium ions in these solvents.



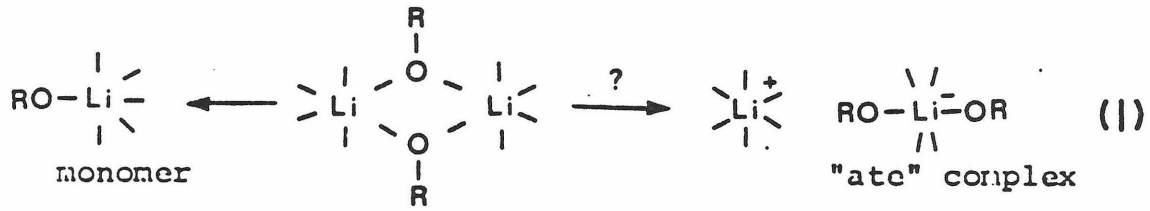
C222	a = b = c = 2
C221	a = b = 2, c = 1
C211	a = 2, b = c = 1

With the smaller cryptand C211, the lithium does not exchange between the cryptand and solvent environments on the NMR time scale. Distinct signals were observed for free and cryptand encapsulated ions in all solvents including Me_2SO and water. The lithium chemical shift of the cryptate complex was unaffected by solvent or by a change in the counterion. In order to avoid line broadening effects all counterions were nonnucleophilic ions with diffuse electronic charges such as ClO_4^- and BF_4^-.

The narrow line widths of ^6Li resonances should allow the same experiments to be conducted in the presence of strongly coordinating anions such as alkoxides or enolates. Given the understanding of the cryptand-cation complexation in the presence of diffuse counterions the differences observed in this system would give important insight into the nature and strength of metal-alkoxide coordination as a function of solvent.

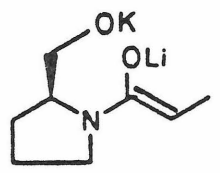
Metal alkoxides and enolates occur as aggregates in solvents of low to moderate polarity.[14,15] Aggregation of lithium enolates has also been studied by ^7Li NMR.[15] Aggregation in these species occurs through bridging oxygens.[16] With the addition of high polarity solvents such as Me_2SO and $(Me_2N)_3PO$ (HMPA) the chemical properties of the aggregates change.[17] One view is that monomeric species

result. An alternative view is that one lithium ion is removed from the aggregate leaving an "ate" complex with different chemical properties than the neutral aggregate. These possibilities are outlined schematically in Equation 1.



(1)

"Ate" complex formation on addition of polar aprotic solvents may explain the increase in diastereoselectivity observed with the alkylation of the dianion 1 in the presence of HMPA.[18] The two alternatives of Equation 1 should be distinguishable by ^{6}Li NMR.



1

Mulzer has presented evidence which he interprets as indicating that C211 does not complex lithium ions in competition with the lithium dienolate of phenylacetic acid.[19] Direct observation by ^{6}Li NMR should be able to verify or disprove this speculation.

The insight gained from an understanding of the behavior of the lithium ions in these systems should be applicable to many other systems in which chelation or coordination to lithium ions is believed to be important.

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