Use of Enantioselective Aldol Condensations: Efforts Directed Towards the Total Synthesis of Ionomycin

Thesis by

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To My Parents and My Sister

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I would like to express my sincere gratitude and thanks to Dave Evans for his patience and encouragement during my stay at Caltech. His friendship, support, and insight have helped my development as a scientist and as an individual. His sage advice, "...it is always better to deal with decisions from a position of strength because more options will be available..." will always be remembered.

I would like to thank all the members of the Evans' group for their help and inspiration, especially John, Charlie, Terry, Pete, Scott, Mike Ennis, and Carl. Special acknowledgment is reserved for Bob Dow, Xavi, and Bob Zahler (my collaborators in our research projects) for their contributions and invaluable criticisms. In addition, my thanks to Joe Dellaria and Paul Ornstein for reading and correcting the rough drafts of my thesis. I would like to thank Dr. Dan Straus of Professor Grubbs' research group for showing me how to prepare the Tebbe reagent.

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Finally, my thanks to Dot for her help in the preparation of the manuscript.

ABSTRACT

The amino acid derived N-acyl oxazolidones were found to be excellent chiral enolate synthons in the aldol condensation.[1] The dialkylboron enolates of these imides exhibit very high levels of asymmetric induction and diastereoselection. However, the use of N-acetyl oxazolidones resulted in much lower diastereoselection. In these cases, substitution of N-acetyl oxazolidones with N-α-thiomethylacetyl oxazolidones (followed by Raney Nickel desulfurization) restored the high level of stereoselection.

Application of this methodology to the total synthesis of ionomycin is described.

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CHAPTER I

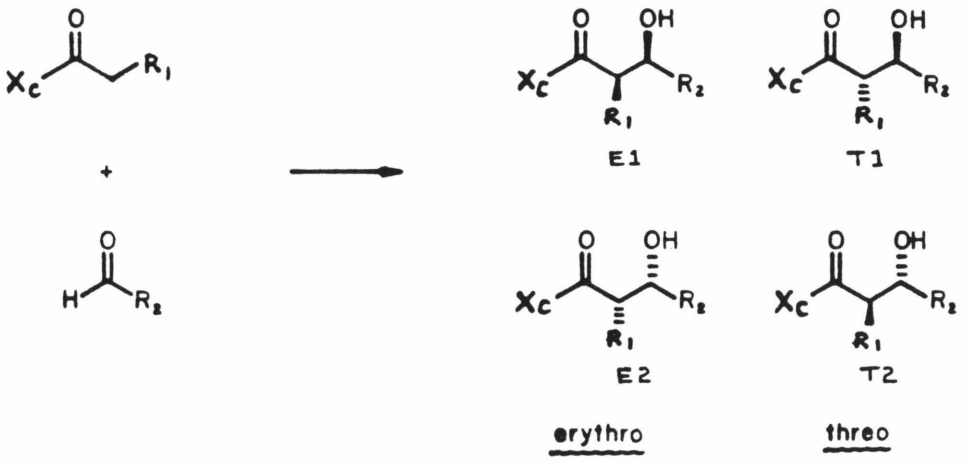
Enantioselective Aldol Condensations:

The Development of A Chiral Acetate Anion Equivalent

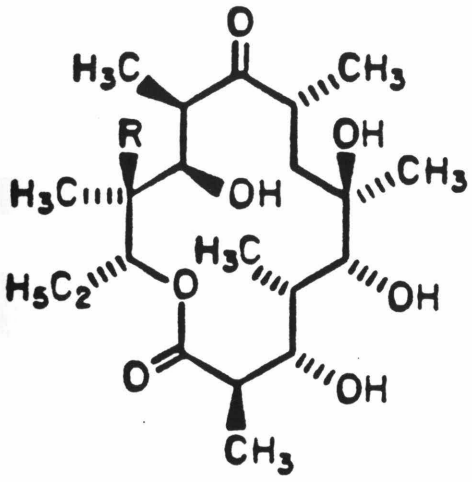
Introduction

The development of general stereoregulated carbon-carbon bond-forming reactions has been the focus of our research efforts over the last six years.[2] This interest has been prompted by the recent emergence of challenging, architecturally diverse, and stereochemically rich examples from the class of macrolide and ionophore antibiotics shown in Figure 1. Synthesis of these natural products has posed the task of controlling the generation of stereochemistry in acyclic molecules where conventional reaction methodology offers little help. The problem of acyclic stereocontrol has been addressed most notably by Sharpless,[3] in his asymmetric epoxidation studies; Kishi,[4] in his hydroboration examples; and Bartlett,[5] in a general review.

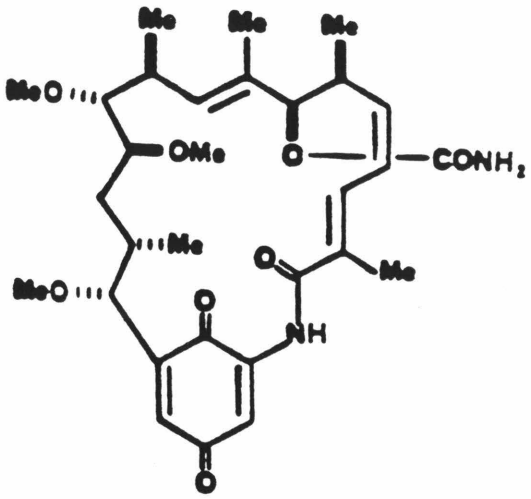
Complimenting these contributions, investigations in our laboratories produced a novel class of chiral carboxylic acid enolate synthons. A general survey exploring their reactivity with alkyl halide electrophiles has shown that high kinetic diastereoselections (>90-98%) could be obtained.[6] Concurrently, the reaction of these chiral enolates with aldehydes in the aldol condensation (eq. 1) was examined with the expectation of equally high stereoselectivity.



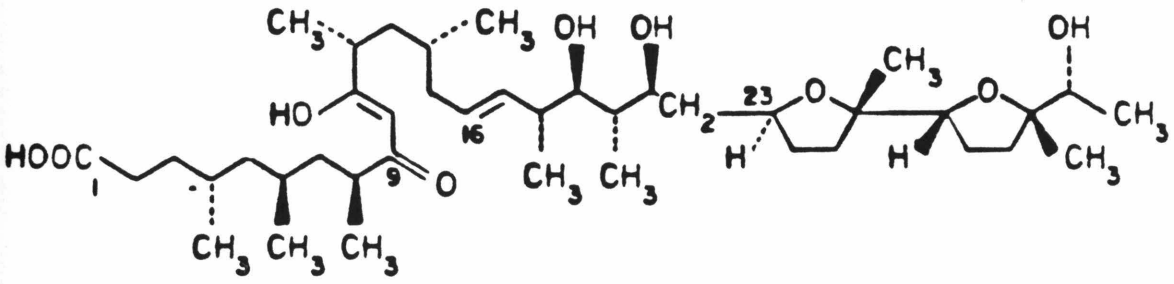
(1)



R = OH, Erythronolide A
R = H, Erythronolide B



Macbecin



Ionomycin

Figure 1

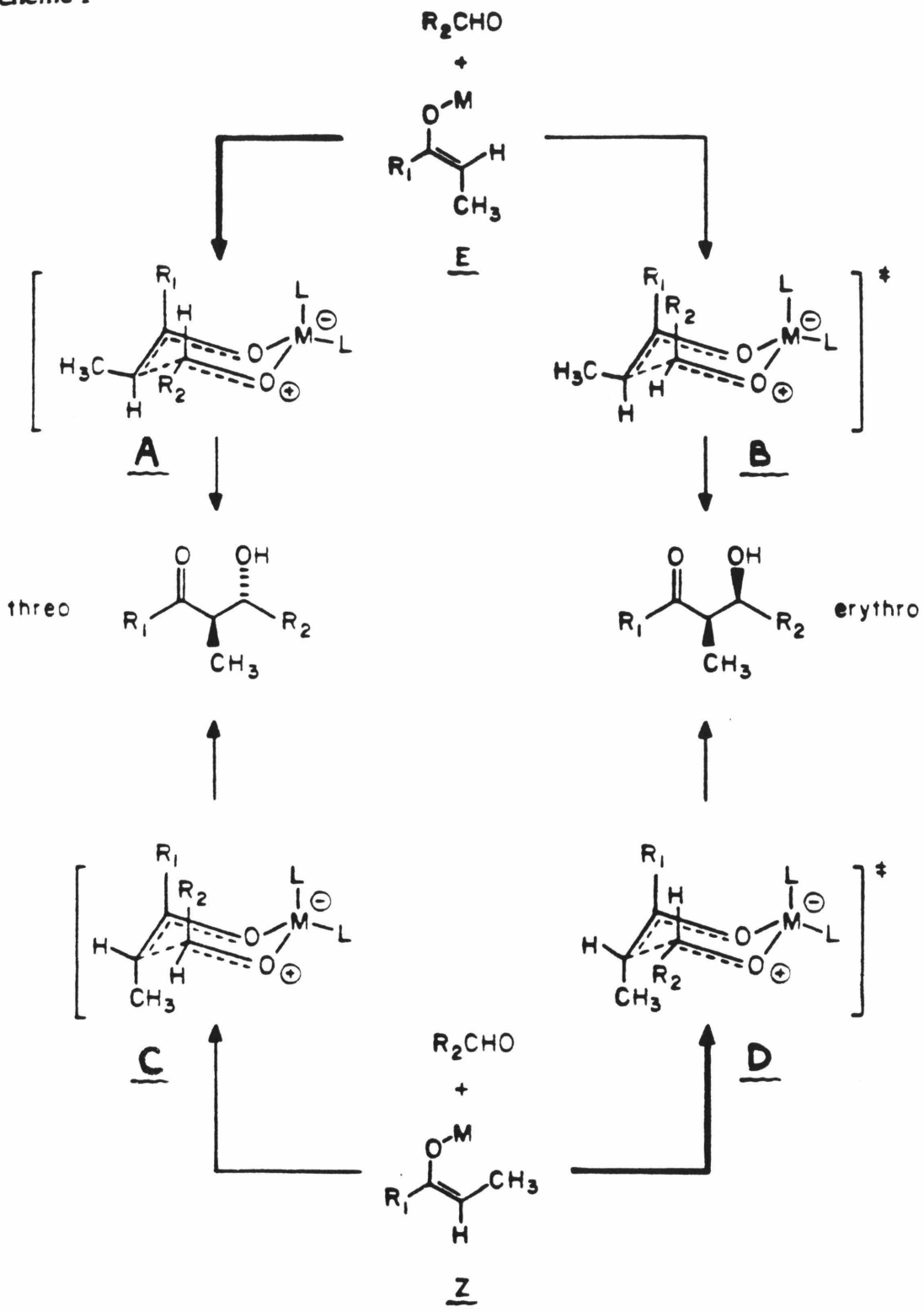
Our goal was to develop highly diastereoselective ($E_1 + E_2$ vs $T_1 + T_2$) and enantioselective (E_1 vs E_2, T_1 vs T_2) aldol methodology. The substituents in both X_C (chiral auxiliary) and R_1 (H, CH_3, alkyl) were varied in probing the aldol mechanism utilizing these enolates. In addition, the use of heteroatom (halogen, -OR, -SR) substituents for R_1 was examined. The results of these investigations will constitute the subject of this thesis.

The Stereoselection Problem in the Aldol Condensation. The aldol reaction constitutes one of the most direct and versatile means of assembling 1,3-dioxygen relationships in organic molecules. The ubiquity of this reaction in natural products biosynthesis has stimulated the development of stereoregulated aldol processes which has been a topic of intense interest and numerous reviews.[7]

The mechanistic aspects of most current interest are the stereochemical issues which regulate both reaction diastereoselection and enantioselection. As depicted in equation (1), four possible diastereomers could be produced from the formation of two new stereocenters. These diastereomers were assigned the erythro (E_1,E_2) and threo (T_1,T_2) designations following the convention outlined by Heathcock.[8]

The issue of aldol diastereoselection has been addressed by Zimmerman,[9] who proposed a cyclic six-membered, chair-like transition state for the aldol process (Scheme I). This model, along with results obtained by Dubois[10] and Heathcock[8] from lithium enolates of known geometry, have projected that kinetic aldol diastereoselection is closely associated with enolate geometry. On the basis of this model, one would predict that a cis or Z enolate would react with the aldehyde through the preferred transition state, **D**, which minimizes steric nonbonded interactions (R_2 vs L), leading to mainly erythro

Scheme I



products. Likewise, the trans or E enolates should lead via transition state A to predominantly threo products. Results of experiments[8,10,26] have supported these predictions.

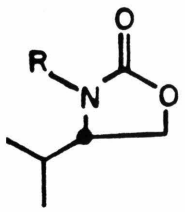
Examination of the proposed model also revealed that a design for enantioselection (E_1 vs E_2, T_1 vs T_2) necessitates the inclusion of a resident chiral center in the propionate synthon (e.g., within R_1) which would sterically bias an otherwise facially indiscriminent enolate.

Therefore, the design of a stereoselective aldol reaction must utilize a synthon possessing the following attributes:

1) The synthon must give a single enolate of high homogeneity (>95%).
2) The synthon must contain a proximal asymmetric center which will strongly direct electrophile approach from only one of the diastereofaces of the enolate nucleophile

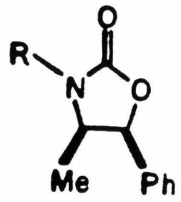
These criteria were met by the chiral oxazolidone imides (Fig. 2) developed in our laboratories. These imides are readily obtained from the N-acylation of oxazolidones derived from commercially available, optically pure α-amino acids and amino alcohols (Scheme II). This scheme permits a wide choice of acyl appendages with the chirality contained within a recyclable oxazolidone subunit.

Upon treatment with alkali metal amide bases or dialkylboryl triflates in conjunction with trialkylamine bases, a highly stereoselective enolization of these acyl imides may be achieved.[6] The selection towards the formation of the Z enolate may be rationalized using the same allylic strain model



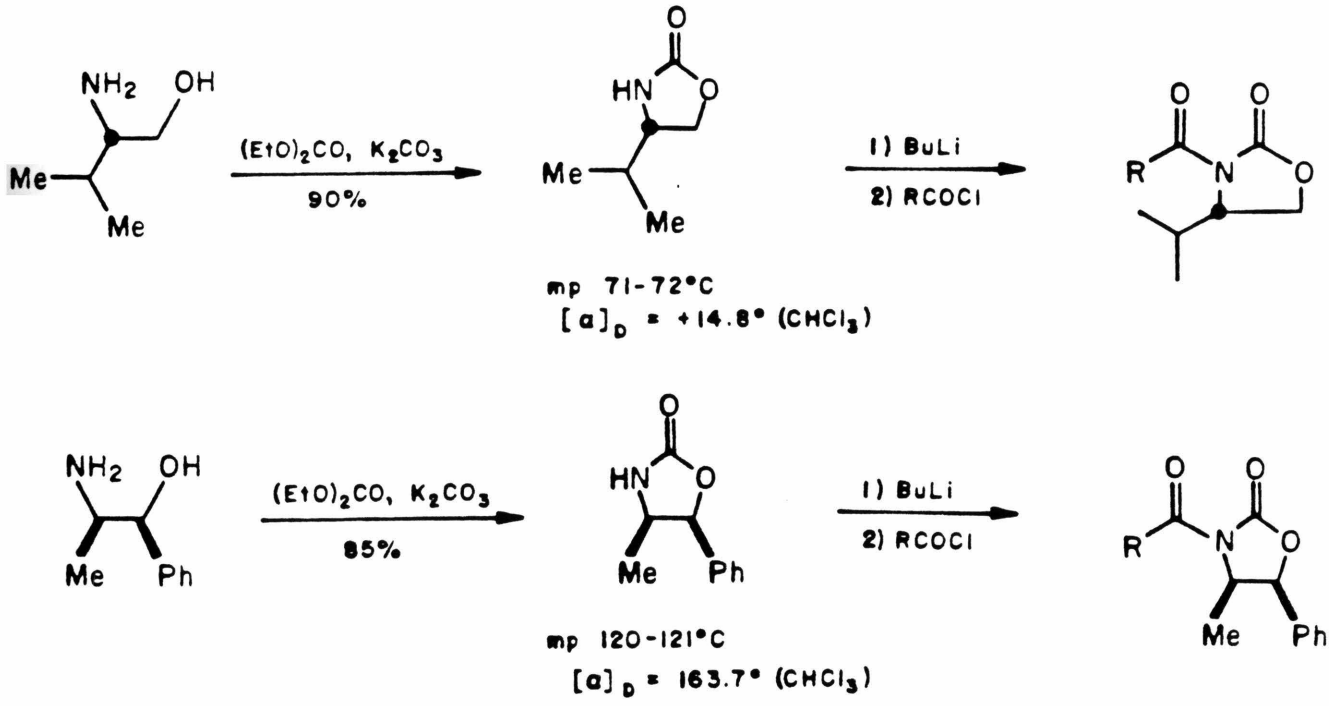
1

a, R = H
b, R = C(O)Et
c, R = C(O)Me
d, R = $C(O)CH_2SMe$
e, R = $C(O)CH_2X$, X = Cl, Br
f, R = $C(O)CH_2OR$
g, R = $C(O)CH{=}CHCH_3$



2

Figure 2

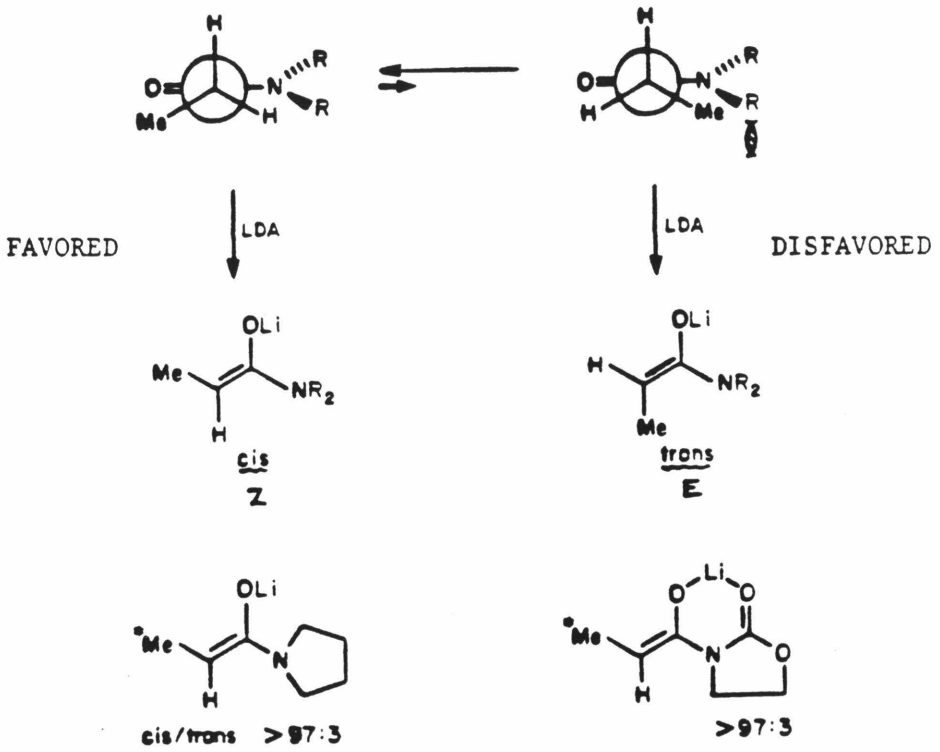


CHIRAL AUXILIARY SYNTHESIS

Scheme II

(Details of the syntheses of these imides have been disclosed; see ref. 6a, p. 15-17, 64-65).

Scheme III



proposed to explain the enolization of amide systems[11] (Scheme III).

Having established that these acyl imides are prime candidates for chiral ester enolate synthons, we considered the choice of metal counterion which would maximize the aldol stereoselectivity. The degree of stereoselection has been found to be highly dependent on the role of the metal counterion. In general, enolates of metals from group I and II of the periodic table, as well as zinc, and aluminum exhibit much lower aldol stereoselectivity than those enolates derived from boron.[12] This observation has been correlated to the metal-oxygen bond lengths in these enolates. The shorter boron-oxygen bonds

and the covalently bound alkyl ligands appear to amplify the steric control factors presented in the Zimmerman model. Therefore, the boron enolates of some representative acyl oxazolidone imides were condensed with a series of model aldehydes to determine the stereoselection of these synthons. Cases with aldehydes containing an adjacent asymmetric center[13] were included to measure the Cram[14] versus anti-Cram product ratio. These studies would reveal whether the resident chiral centers in both reaction partners would interact in a cooperative, antagonistic, or independent manner in directing the formation of the new stereocenters.

Discussion and Results

An extensive amount of research has been done in our laboratories determining the optimum conditions for effecting stereoselective boron aldol condensations.[2b] These conditions (-78°C, CH_2Cl_2, 1.1 equiv. dibutylboryl trifluoromethanesulfonate, 1.2 equiv. Hunig's base) generated the Z enolates of the acyl imides shown in Figure 2. The results of the aldol condensations of these enolates with representative aldehydes are shown in Tables 1,[1] 2,[1] and 3.[15]

The diastereomeric product distributions were determined using capillary column gas chromatography. The analyses were carried out on trimethylsilyl derivatives of unpurified aldol products. Each product's retention time was compared to that of the diastereomers obtained from the corresponding kinetic lithium aldol condensation. Representative traces of these gas chromatographic comparisons are shown in Figure 3. These results demonstrate that the boron aldol's diastereoselection is markedly superior to that obtained by lithium enolates.

Table 1.* Aldol Condensations of 1b and 2b with Representative Aldehydes (Scheme IV).

Entry	Imide	R_1CHO	Erythro Selection $E_1:E_2$[a]	Aldol Adduct Yield, %[b]	5b (6b) Overall Yield, %[c]	5b (6b) $[\alpha]^{25}$ (c, g/mL)[d]
A	1b	Me_2CHCHO	497:1	3, 78	5b, 69	-7.9° (5.7, $CHCl_3$)
B	2b	Me_2CHCHO	< 1:500	4, 91	6b, 68	+7.7° (5.4, $CHCl_3$)
C	1b	n-C_4H_9CHO	141:1	3, 75	5b, 68	+14.9° (6.6, CH_2Cl_2)
D	2b	n-C_4H_9CHO	< 1:500	4, 95	6b, 71	-15.0° (5.0, CH_2Cl_2)
E	1b	C_6H_5CHO	> 500:1	3, 88	5b, 81	-23.1° (3.2, $CHCl_3$)
F	2b	C_6H_5CHO	< 1:500	4, 89	6b, 60	+23.2° (3.2, $CHCl_3$)

[a]Determined by capillary gas chromatography on silylated adducts. In all cases the threo-aldol adducts constituted < 1% of total reaction mixture. The limits of detection by this method appear to be approximately 500:1. [b]Yields reported are after recrystallization (entries A, D, E, F) or chromatography (entries B, C). [c]Values refer to overall isolated yields of 5b (6b) for the aldol process, hydrolysis, and diazomethane treatment. [d]Optical purities >99% in all cases.

*The results in this table were supplied courteously by my colleague, Javier Bartroli.

Scheme IV

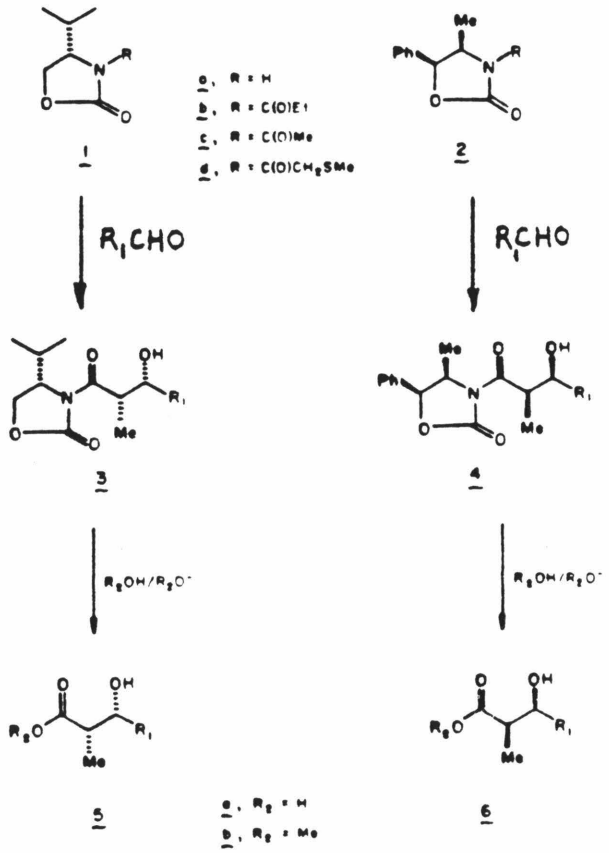


Table 2. Aldol Condensations of Ic and Id with Representative Aldehydes (Scheme V).

Entry	Imide	R_1CHO	Ratio 11a:12a[a]	(Yield)[i]	$[\alpha]_D^{25}$ 13	Optical Purity 13:14[c]	(Yield)[k]
A	Id	Me_2CHCHO	98.4:1.6	(57%)	-42.1° (1.8)[d]	97.8:2.2	(79%)
B	Ic	Me_2CHCHO	52:48				
C	Id	n-C_3H_7CHO	98.9:1.1	(51%)	-27.3° (2.1)[e]	99.4:0.6	(68%)
D	Ic	n-C_3H_7CHO	63:37				
E	Id	CH_3CHO	99.6:0.4	(46%)	-45.8° (1.7)[f]	99.9:0.1	(50%)
F	Ic	CH_3CHO	72:28				
G	Id	C_6H_5CHO	92.4:7.6	(-)[h]	-17.1° (0.1)[g]	92.4:7.6[h]	(69%)
H	Ic	C_6H_5CHO	62:38				
I	2d	CH_3CHO	< 1:99[j]	(62%)	+45.9° (1.4)	<1:99	(62%)

[a]Determined by GLC. [b]All rotations were carried out in $CHCl_3$ except for the C_6H_5CHO case. EtOH was used instead. [c]Inferred from the ratios of 11a and 12a after chromatographic purification. [d]Literature rotation: $[\alpha]_D$ -24.7° (c 0.98, $CHCl_3$) (ref. 23a); $[\alpha]_D$ -40.3° (c 4.6, $CHCl_3$) (ref. 35). [e]Literature rotation: $[\alpha]_D$ -28° (c 2.0, $CHCl_3$) (ref. 23b). [f]Value is $[\alpha]_D$ of methyl ester of 13 from methanolysis of 11a and 12a. Literature rotation for methyl ester of 14: $[\alpha]_D$ +33.3° (c 1.2, $CHCl_3$) (ref. 23c). [g]Literature rotation for antipode 14: $[\alpha]_D$ +18.9° (c 5.15, EtOH) (ref. 22) $[\alpha]_D$ -18.9° (c 2.3, EtOH) (ref. 23d). [h]Products 11a and 12a, $R_1 = C_6H_5$, are not stable on silica gel. The crude product from desulfurization was hydrolyzed directly to the acid. [i]Ratio refers to structures 11 and 12 with the norephedrine chiral auxiliary in place of the valine oxazolidone. [j]Values refer to overall isolated yields of 11a (12a) for the aldol process and desulfurization. [k]Values refer to isolated yield of 13 (14) from hydrolysis (methanolysis).

Scheme V

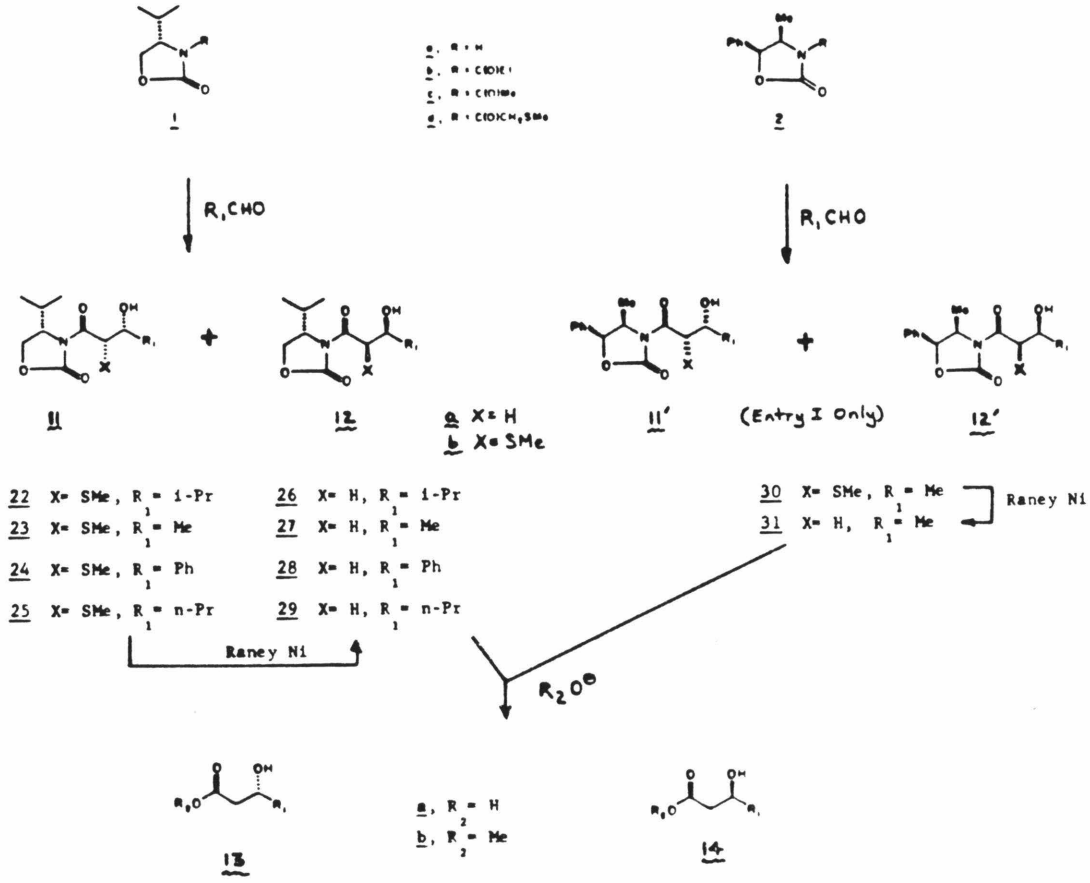


Table 3. Aldol Reactions of α-Heteroatom Substituted Enolates.[15]

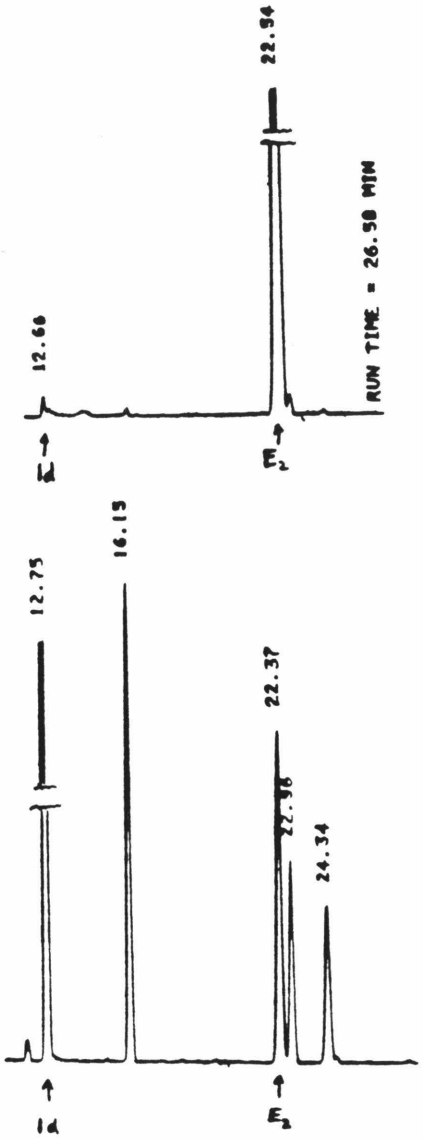
18 **19**

15, Y = OMe, **a**, $X_C = X_V$
b, $X_C = X_N$

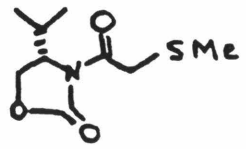
16, Y = -OCH_2Ph, $X_C = X_N$

17, Y = -Cl, $X_C = X_V$

Entry	Imide	RCHO	**18:19**	Yield
A	**15b**	ϕCHO	1.9:98.6	89.2%
B	**15b**	iPrCHO	1.4:98.6	76.7%
C	**15a**	ϕCHO	98.2:1.8	91%
D	**15a**	iPrCHO	98.9:1.1	73%
E	**16**	ϕCHO	97.3:2.7	76.5%
F	**16**	iPrCHO	98.1:0.9	--
G	**17**	ϕCHO	95.4:4.6	49%
H	**17**	iPrCHO	95.7:4.3	39%



Boron Aldol



+

n-butyraldehyde

Lithium Aldol

Carbowax 25 meter 170°C

Figure 3

Tables 1 and 2 represent the highest asymmetric induction cases ever measured; utilizing the capillary GC technique whose resolution is in the range of 500:1.

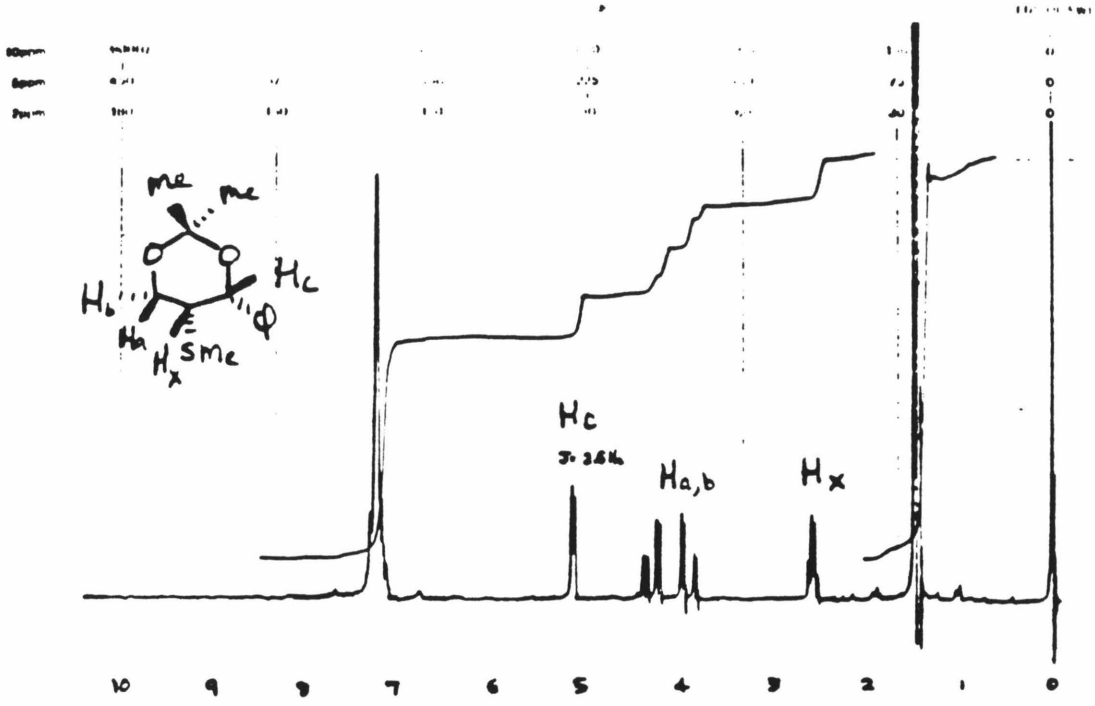
For the cases shown in Table 2, the products obtained from imide **1c** were compared to that obtained from **1d** after desulfurization. It may be noted that imide **1c** gave poor diastereoselection compared to imides substituted at the α-position (i.e., **1b, 1d**). Such a substitution dependence in another enolate system has been noted.[16] The mechanistic implication of this observation will be discussed in the section on mechanism.

Absolute Configuration of the New Stereocenters. The aldol adducts of **1b** and **2b** with representative aldehydes were hydrolyzed to give the corresponding β-hydroxy carboxylic acids and the free oxazolidones **1a** and **2a**. These acids were then converted to their methyl esters with diazomethane in ether. Relative erythro stereochemistry was assigned by ^{1}H NMR spectroscopy.[17,18] The absolute stereochemistry at the C2-methyl-bearing center was correlated to known acids by the work of Heathcock[19] and McGee.[20]

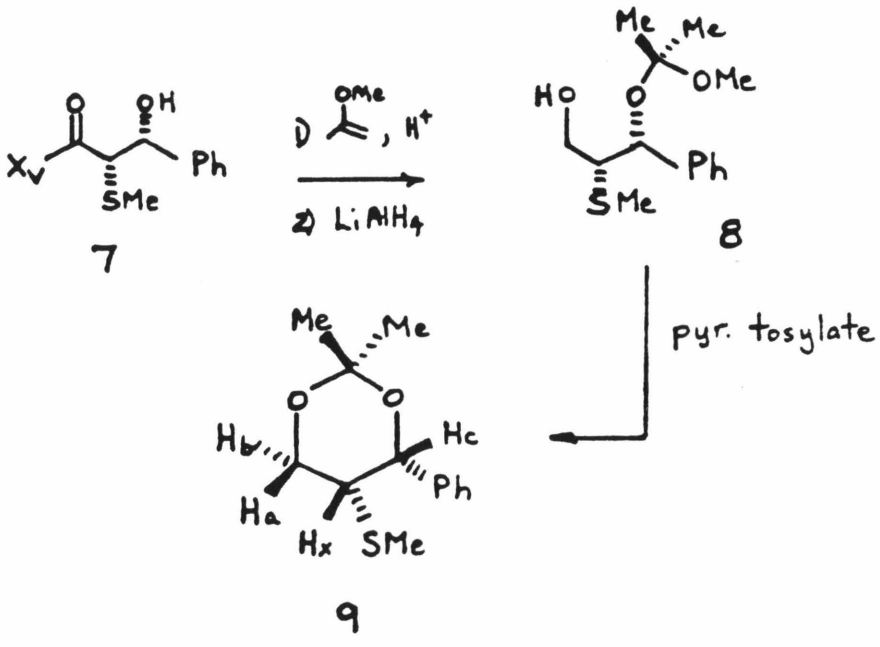
Evidence for the same erythro relationship in the aldol adducts of **1d** and **2d** was obtained from the ^{1}H NMR spectrum (Fig. 4) of the acetonide, **9**, derived from the benzaldehyde adduct, **1**, shown in Scheme VI. The observed coupling constants of J_{ax} = 2.6 Hz, J_{bx} = 3.3 Hz, and J_{cx} = 2.6 Hz are consistent with the values expected for protons in a gauche relationship in a cyclohexane chair model.[21] Final correlation of absolute stereochemistry was obtained by desulfurization of the aldol products with Raney Nickel, followed by hydrolysis to the known β-hydroxy acids.[22,23]

These correlations determined that for the general aldol reaction shown in Scheme VII, the (S)-valinol derived oxazolidone synthon will produce the product having the absolute stereochemistry shown in **20**. The

Figure 4



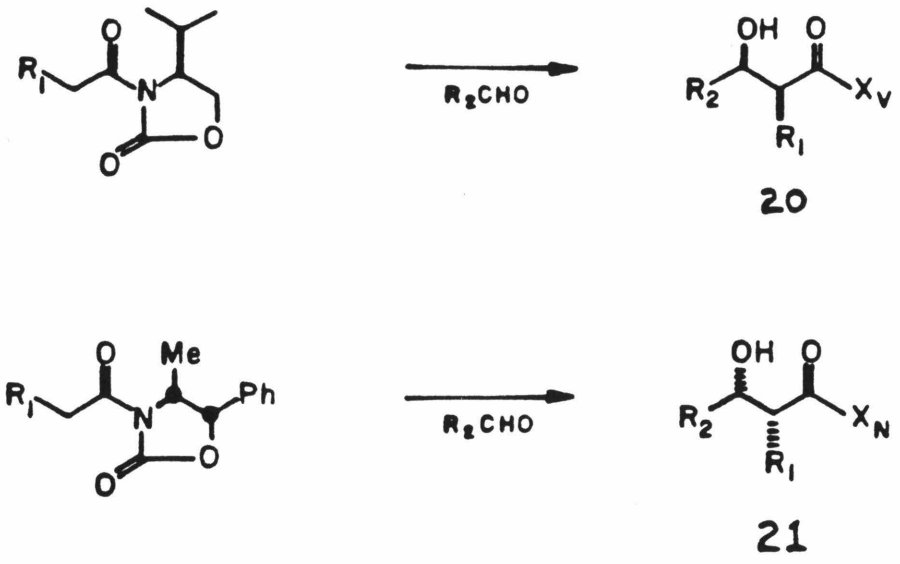
Scheme VI



complimentary (1S,2R) norephedrine oxazolidone will induce the opposite absolute stereochemistry shown in product 21.

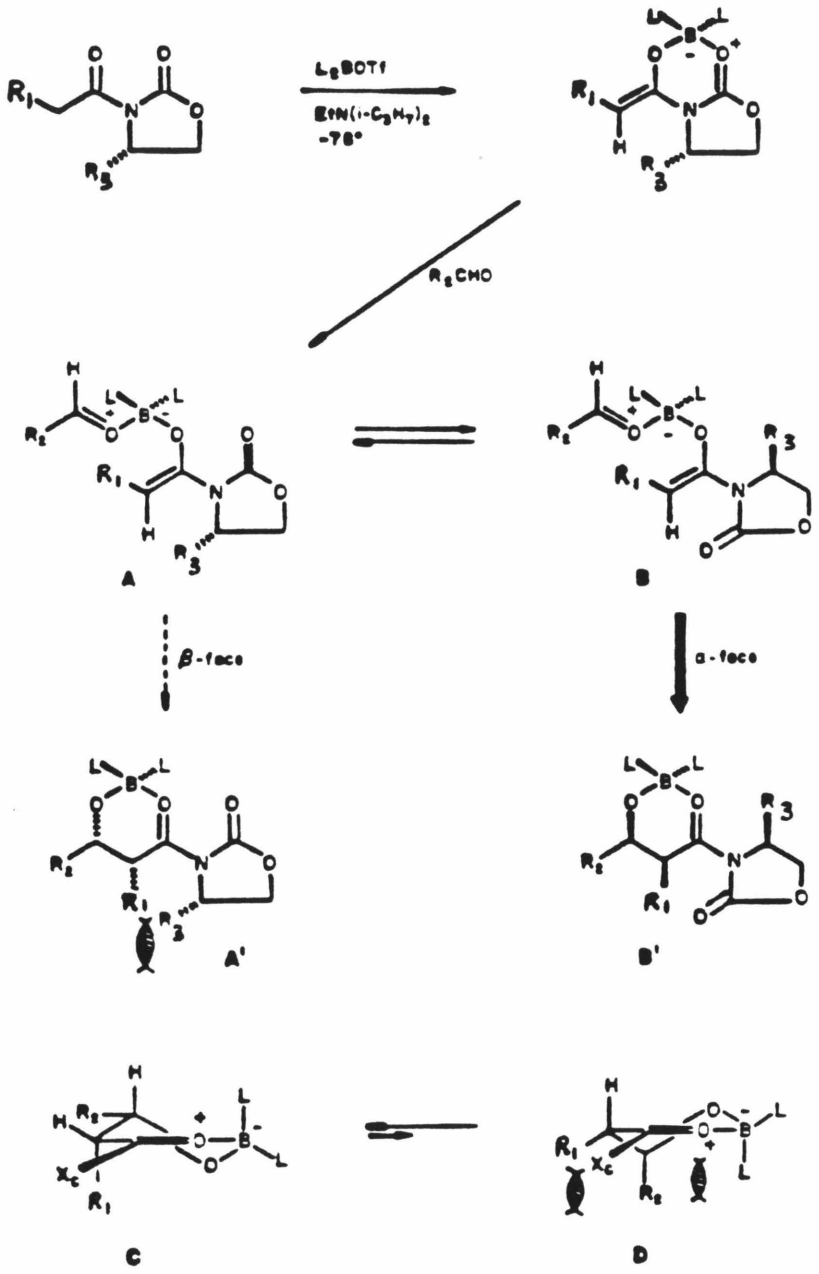
Rigorous correlation of the stereochemistry of the products derived from enolates containing other structural permutations (i.e., R_1 = Cl, -OR, $-(CH_2)_nOBn$) have not been made. However, one may presume by analogy that the above observations are general. The validity of this presumption is being tested by the application of these systems in natural product synthesis.

Scheme VII



Mechanistic Model. The establishment of the stereochemical outcome of the aldol reactions of these chiral imides led us to propose the mechanistic rationalization shown in Scheme VIII. Initial coordination of the aldehyde with the preformed boron enolate would lead to a complex having two

Scheme VIII



possible conformations (A and B). During the conversion of these conformers to the respective erythro products A' and B', the developing imide resonance[24] would be expected to lock the chiral auxiliary in the in-plane conformations shown.

Subsequently, the developing allylic strain ($R_1 \leftrightarrow$ i-Pr) would destabilize the transition state leading to A', favoring formation of B'. In addition, examination of models revealed a strong conformational bias in the product. Conformation **C** should be favored over **D**, since the 1,3 diaxial $R_2 \leftrightarrow$ **L** and $R_1 \leftrightarrow X_C$ interactions present in **D** is not present in conformation **C**. This bias would be translated into the transition states leading to the products. The importance of these factors seemed to be borne out by the fact that chiral imide, **1c**, lacking the $R_1 \leftrightarrow X_C$ interaction, showed poor diastereoselection in the aldol reaction.

In contrast, the high stereoselectivity obtained with imides **1b** and **1d** with enantioselections of $\geq$99%, translates to a $\Delta\Delta G^{\dagger}$ at -78°C of $\sim$3 kcal/mol.

Aldol Condensations with Chiral Aldehydes. One of the first attempts to correlate the stereochemical results of nucleophilic addition to aldehyde carbonyl groups containing an adjacent stereocenter was the empirical rule of Professor Cram.[14] Since the publication of Cram's rule in 1952, there have appeared other models (Felkin, Anh) which are supported by ab initio calculations. All of these models have been discussed by Evans in a review.[25] Regardless of which model was used to predict the diastereofacial bias present in the aldehyde, the products were given the Cram (C) and anti-Cram (A) designations.

In general, a survey[26] of examples of achiral enolate reactions with

chiral aldehydes has shown Cram:anti-Cram selectivity to fall in the range of 3-5:1 ($\Delta\Delta G^{\dagger}$ at -78°C of <0.7 kcal/mol). However, diastereoselections as high as 45:1 has been observed in cases where double asymmetric induction occurred in a cooperative sense. For other cases where the two resident chiral centers interacted in an antagonistic sense, lower diastereoselectivity was noted. Examination of the data shown in Table 4 reveals a general trend of predictability for cases involving the chiral imide enolates. The observed diastereoselections were solely determined by the enolate's alpha-substitution and chirality.

For example, entries A and B list C:A ratios of 2-3:1. This reaction diastereoselection is due to the induction from the aldehyde's chirality since imide 1c and 2c are nonselective (Table 2). The highly specific Cram selection exhibited by entry C confirmed the importance of enolate alpha-substitution in determining diastereoselection. Entries D and E illustrate the role of the imide's chirality by producing the expected Cram and anti-Cram adducts respectively from the same aldehyde. These predictions were based on which chiral auxiliary was used in the propionate enolate. The predominance of anti-Cram products in the other cases (Entries F, G, I, J) implied that the role of the aldehyde chirality is small compared to the influence exerted by the imide enolates.

Figure 5

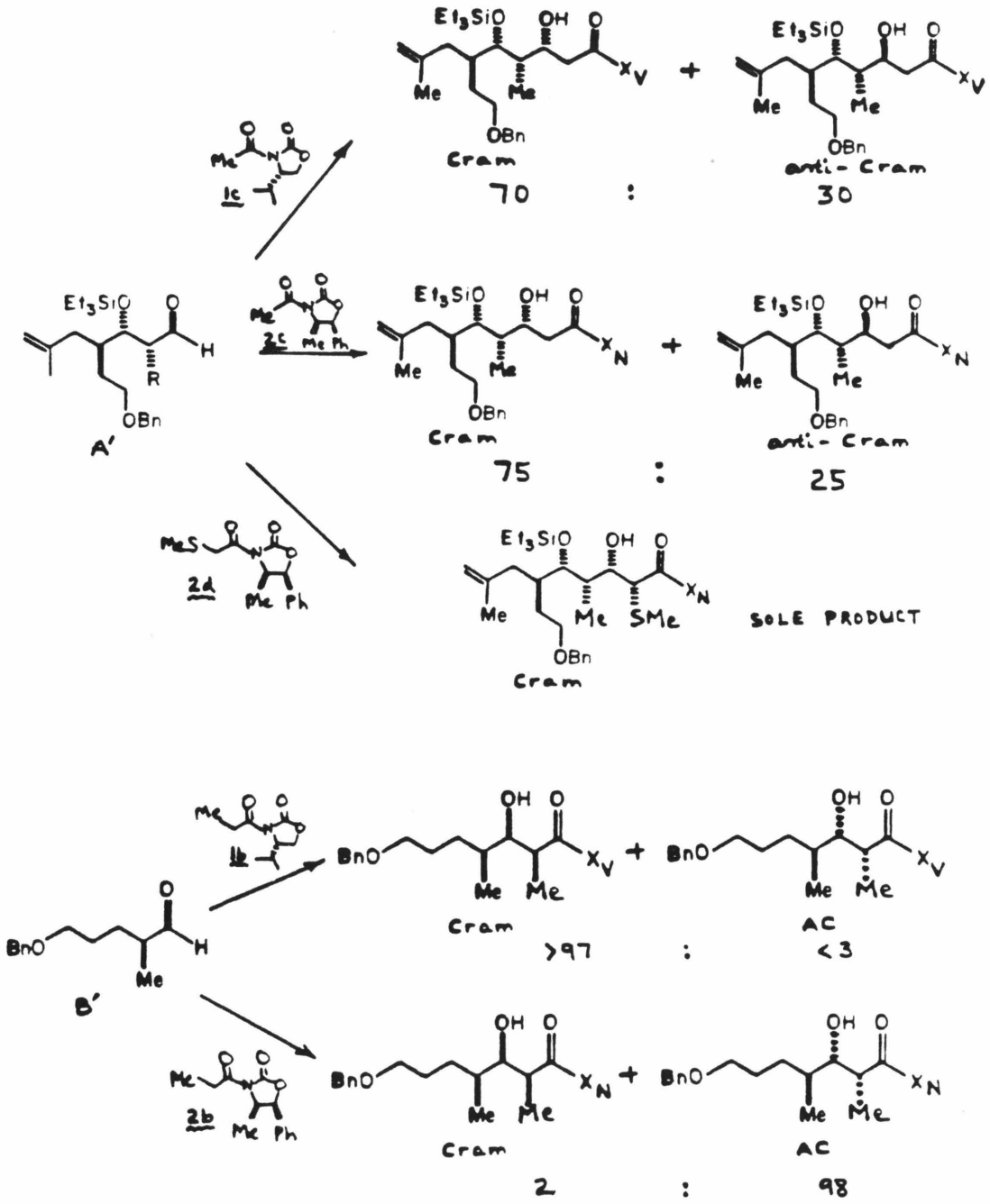

Et3SiO
OH
O
Me
Me
OBn
Cram
anti-Cram
70 : 30
1c
A'
R
H
2c Me Ph
75 : 25
MeS
2d
Me Ph
SOLE PRODUCT
BnO
B'
1b
>97 : <3
2b
2 : 98
AC

Figure 5 (continued)

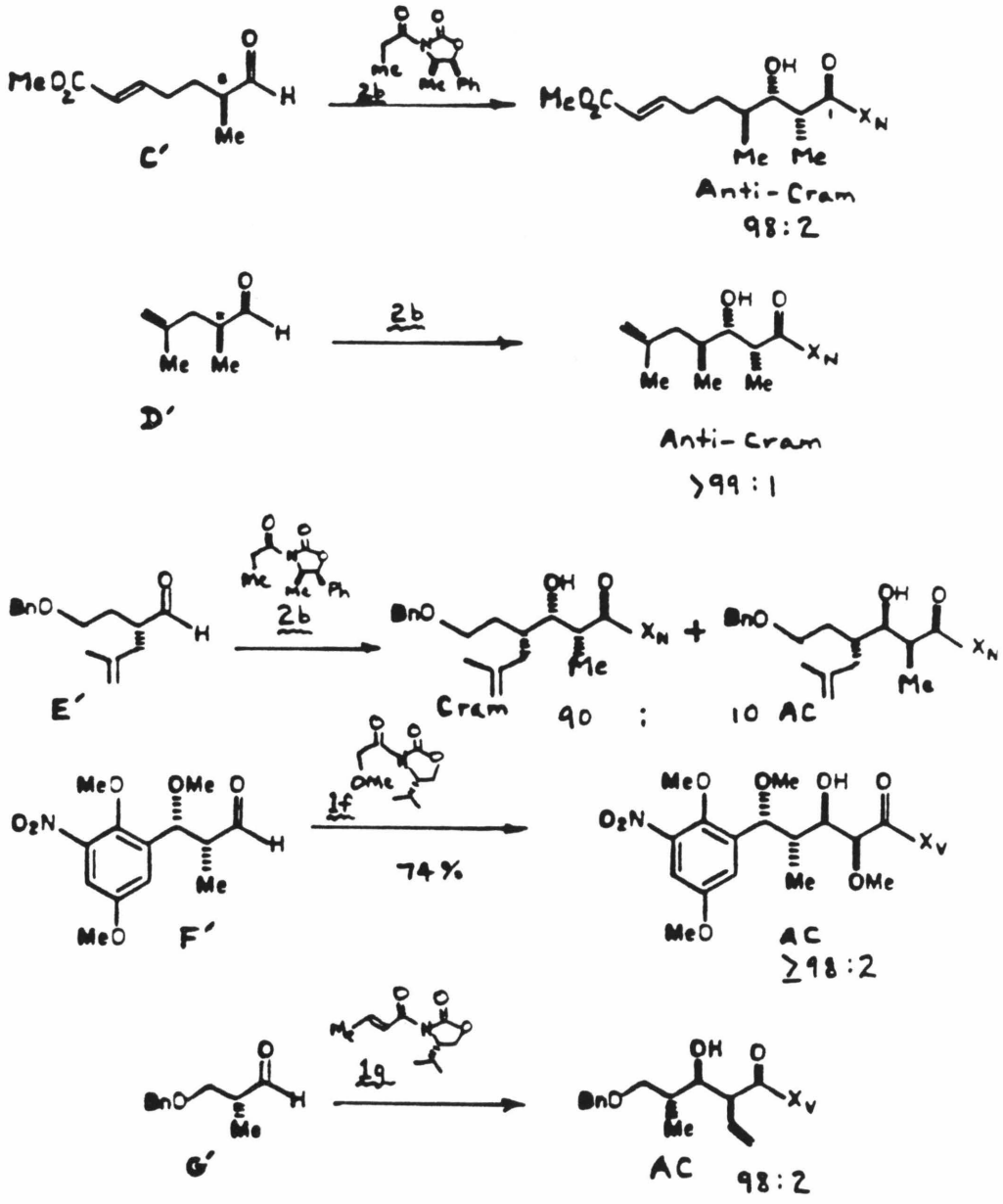


Table 4. Aldols with Chiral Aldehydes (Fig. 5).

Entry	Imide	RCHO	Cram:anti-Cram	Reference
A	**1c**	A'	70:30	27
B	**2c**	A'	75:25	27
C	**2d**	A'	Only Cram isolated	27
D	**1b**	B'	$\geq$ 97:3	29
E	**2b**	B'	2:98	30
F	**2b**	C'	98:2	30
G	**2b**	D'	$<$ 1:99	32
H	**2b**	E'	90:10	29
I	**1f**	F'	$\leq$ 2:98	31
J	**1g**	G'	2:98	28

Summary

The readily available oxazolidones **1a** and **2a** have been shown to be versatile chiral auxiliaries. When appended to higher homologues of acetic acid (via acylation), they are able to direct the aldol condensation with aldehydes in a highly stereoregulated and predictable fashion. The control exerted by the chirality at the oxazolidone appears to take precedence over all other factors including existing chirality in the aldehyde partners. Experiments with the N-acetyl oxazolidones (**1c**, **2c**) and their derivatives (**1d**, **2d**, etc.) have shown that α-substitution is essential for high levels of stereoselection.

Imides **1d** and **2d** formally represent "chiral acetate equivalents"[33] when coupled with the subsequent desulfurization procedure. These imides and resulting aldol products enjoy the advantage of ease of further transformation to other derivatives without loss of optical activity. This was evidenced by the optical rotations of the synthesized β-hydroxy carboxylic acids which exceeded or matched those reported in the literature.

An added advantage of these imide systems is the recyclability of the oxazolidones freed by subsequent transformations (reduction, hydrolysis, etc.) of the products. These features all combine to ensure their further widespread applications in natural product synthesis.

Experimental Section

Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman 4210 spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm on the δ scale from internal tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant (Hz), and interpretation. 500 MHz ^{1}H NMR spectra were recorded on a Bruker WM-500 Spectrometer at the Southern California Regional NMR Facility. ^{13}C NMR spectra were recorded on a Varian Associates XL-100 (25.2 MHz) or a JEOL-FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Mass spectral analyses were performed by the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln, on a Kratos MS-50 TA spectrometer. Combustion analyses were performed by either Spang Microanalytical Laboratory (Eagle Harbor, Michigan) or Galbraith Laboratolries, Inc. (Knoxville, Tennessee). Optical rotations were recorded on a Jasco DIP-181 digital polarimeter at the sodium D line and are reported as follows: $(\alpha)_D$, concentration ($\underline{c}$ = g/100 mL, and solvent).

Analytical gas-liquid chromatography was carried out on a Hewlett Packard 5880A Level 3 gas chromatograph equipped with a split mode capillary injection system and a flamed ionization detector, using a 25 m x 0.02 mm flexible fused silica capillary column wall-coated with Carbowax 20M or methyl silicone (SP-2100), or a 30 m x 0.32 mm fused silica capillary column

wall-coated with SE-54. Unless otherwise noted, injector and detector temperatures were 250°C. Flash chromatography on silica gel was performed using a forced flow[34] of the indicated solvent system on EM Reagents Silica Gel 60 (70-230 mesh), or for large scale preparative work on EM Reagents Silica Gel 60 (230-400 mesh). Medium pressure liquid chromatography (MPLC) was carried out using EM Reagents Lobar Silica Gel 60 prepacked columns (column size indicated) with a Fluid Metering Inc. Model RP-SY Lab Pump in conjunction with an ISCO Model UA-5 Absorbance/Fluoresence Monitor with Type 6 Optical Unit (2 mm path length cell, 15 μL volume). Analytical thick-layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Preparative thick-layer chromatography was performed using EM Reagents 2 mm silica gel 60-F plates (20 cm x 20 cm).

Unless otherwise stated, all solvents and reagents were dried or freshly distilled prior to use. Tetrahydrofuran (THF), diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, triethylamine, diisopropylethylamine, and boron trifluoride etherate were distilled from calcium hydride. Dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPT) were distilled from calcium hydride and stored over activated 4 Å molecular sieves. Reagent grade dimethyl sulfoxide was dried[36] with activated 4 Å sieves and used as received. Alkyl halides were passed down a column of activity I alumina immediately prior to use. All other reagents were used as received.

Unless otherwise noted, all non-aqueous reactions were carried out under a dry nitrogen atmosphere using oven-dried glassware.

2-Thiomethylacetic acid is available commercially from Fluka. It can also be readily prepared from monochloroacetic acid and potassium methane thiolate.

2-Thiomethylacetic Acid. To a solution of 64 g (0.67 mol) of monochloroacetic acid and 38 g (0.67 mol) of potassium hydroxide in 750 mL of (5:1) ethanol-water was added a cooled (0°C) yellow solution of 25 g (0.52 mol) of methanethiol in 200 mL of (9:1) ethanol-water containing 38 g (0.67 mol) of potassium hydroxide. The clear solution was heated at reflux for 18 h, after which a white precipitate (KCl) was deposited along the walls of the flask. The solvent was removed in vacuo and the white residual solid was dissolved in 250 mL of water. Upon acidification with 10 mL of concentrated. sulfuric acid, a white precipitate (K_2SO_4) was formed and was removed by filtration. Extraction of the filtrate with ethyl acetate (3 x 200 mL) and evaporation of the solvent in vacuo afforded 30 g of a yellow oil. Distillation of the oil afforded 27.3 g of pure 2-thiomethylacetic acid (49.5% yield based on methanethiol), bp 104-107°C (6 mm Hg).

2-Thiomethylacetyl Chloride. To 8.9 g (7.5 mmol) of 2-thiomethylacetic acid was added 6 mL (8.2 mmol) of thionyl chloride. After stirring at room temperature overnight (12 h) protected from moisture by a calcium chloride-packed tube, the resulting orange solution was distilled to afford 7.1 g (76%) of light yellow liquid acid chloride, bp 54-55°C (14 mm Hg).

(+)-(4S)-3-[(2-Thiomethyl)-acetyl]-4-(2-propyl)-oxazolidine-2-one (1d). To a cooled solution (-78°C) of 7.2 g (55.8 mmol) of (+)-(4S)-(2-propyl)-oxazolidine-2-one (**1a**) in 120 mL of anhydrous THF under an argon atmosphere was added 41 mL of a 1.5 M solution of n-butyllithium in hexane (61.5 mmol,

1.1 equiv.) to form the conjugate base. The milky slurry was stirred for 2.5 h before 7.1 g (57 mmol, 1.04 equiv.) of 2-thiomethylacetyl chloride was added in one portion. The slurry dissolved instantly to a clear orange solution. After stirring an additional hour at -78°C, the reaction was quenched with 20 mL of saturated aqueous ammonium chloride, and the THF was removed in vacuo at room temperature. The resultant concentrate was taken up in ether and extracted successively with aqueous sodium bicarbonate, water, brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by flash chromatography (400 g silica gel, 6 x 40 cm column, 15% ethyl acetate: CH_2Cl_2, 100 mL fractions) afforded 9.6 g (80%) of purified product as a viscous yellow oil: IR (neat) 2975, 2938, 2885, 1782, 1695, 1487, 1466, 1392, 1368, 1323, 1211, 1173, 1141, 1123, 1100, 1059, 1027, 972, 771, 756, 712, 690, 660, 635 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (d, 3H, J = 7 Hz), 0.94 (d, 3H, J = 7 Hz), 2.10 (s, 3H, $-SCH_3$), 2.22 (m, 1H, J = 3 Hz), 3.62 (AB, 2H, J = 13 Hz, $-C\underline{H}_2SCH_3$), 4.27 (m, 3H). $[\alpha]_D^{25}$ = +81.9 (c 1.7, CH_2Cl_2). R_f = 0.48 (silica gel, 50% ethyl acetate:hexane).

Anal. calcd. for $C_9H_{15}NO_3S$: C, 49.75; H, 6.96; N, 6.45. Found: C, 49.80; H, 6.98; N, 6.32.

(+)-(4S)-3-Acetyl-4-(2-propyl)-oxazolidine-2-one (1c). Prepared as described for **1d** using acetyl chloride. Chromatographic purification (MPLC, Merck size C Lobar silica gel column, ethyl acetate:hexanes, 1:2, 25 mL fractions) of ca. 8 g of material afforded 6 g (75%) of product as a colorless oil: IR (neat) 2980, 2950, 2890, 1790, 1710, 1490, 1469, 1391, 1378, 1367, 1340, 1310, 1212, 1153, 1129, 1120, 1062, 1041, 1018, 982, 970, 960, 773, 763, 758, 730, 643, 620 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (d, 3H, J = 7 Hz), 0.93 (d, 3H,

J = 7 Hz), 2.35 (m, 1H, J = 3 Hz, -CHMe$_2$), 2.50 (s, 3H, -COCH$_3$), 4.32 (m, 3H, -O-CH$_2$-CH-N). $(\alpha)_D^{25}$ = +98.4° (c 2.57, CH_2Cl_2). R_f = 0.46 (silica gel, 50% ethyl acetate:hexane).

Anal. calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.13; H, 7.76; N, 8.19.

(+)-(4R,5S)-3-[(2-Thiomethyl)-acetyl]-4-methyl-5-phenyloxazolidine-2-one (2d). To a cooled solution (-78°C) of 5.7 g (32.2 mmol) of (+)-(4R,5S)-4-methyl-5-phenyloxazolidine-2-one (**2a**) in 100 mL of anhydrous THF under an argon atmosphere was added dropwise 20.0 mL of a 1.5 m solution of n-butyllithium in hexane (32 mmol, 1 equiv) to form the conjugate base. Whenever a slight excess of n-butyllithium was used, a pink solution resulted from the formation of the 3,5-dilithium dianion of oxazolidinone **2a**. This undesirable result was avoided by using exactly one equivalent of base utilizing the appearance of color for determination of the titration endpoint. To the stirred solution of the conjugate base of oxazolidinone **2a** was added in one portion 4.05 g (32.5 mmol, 1 equiv) of 2-thiomethylacetyl chloride. After stirring an additional 30 min, the THF was removed in vacuo at room temperature. The resultant concentrate was taken up in methylene chloride and washed successively with water, brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by flash chromatography (250 g silica gel, 6 x 40 cm column, ether, 150 mL fractions) afforded 8.2 g crystalline product. Recrystallization from ethanol (30 mL) afforded 7 g (82.5%) of pure product: mp 83-84°C; IR (nujol) 2940, 2870, 1780, 1700, 1459, 1377, 1352, 1295, 1204, 1175, 1120, 1092, 1071, 1032, 989, 970, 778, 761, 737, 702 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ (TMS) 0.89 (d, 3H, J = 6 Hz),

2.15 (s, 3H, -S$\underline{CH_3}$), 3.70 (s, 2H, -$\underline{CH_2}$SMe), 4.75 (m, 1H, -C$\underline{H}$-Me), 5.65 (d, 1H, J = 6 Hz, -$\underline{CH}$Ph), 7.35 (s, 5H, phenyl protons). $[\alpha]_D^{25}$ = +15.67° (c 2.45, CH_2Cl_2). R_f = 0.57 (silica gel, 50% ethyl acetate:hexane).

Anal. calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.77; H, 5.61; N, 5.30.

(+)-(4R,5S)-3-Acetyl-4-methyl-5-phenyloxazolidine-2-one (2c). Prepared as described for **2d** using acetyl chloride. Purification by flash chromatography (120 g silica gel, 3 x 40 cm column, ether-CH_2Cl_2 1:1, 20 mL fractions) of ca. 3 of material afforded 1.8 g purified product (73%) as a crystalline solid: mp 65-66°C; IR (nujol) 2920, 2875, 1770, 1705, 1450, 1367, 1338, 1278, 1193, 1150, 1118, 1040, 1018, 981, 949, 760, 731, 699, 630, 611 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.85 (d, 3H, J = 6 Hz), 2.41 (s, 3H, -CO$\underline{CH_3}$), 4.61 (m, 1H, -$\underline{CH}$Me), 5.55 (d, 1H, J = 6 Hz, -$\underline{CH}$Ph), 7.27 (s, 5, phenyl protons). $[\alpha]_D^{25}$ = +46.3° (c 1.99, CH_2Cl_2).

Anal. calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.67; H, 5.94; N, 6.33.

General Procedure for the Boron Enolate Aldol Condensation with Aldehydes. The condensations were run on a 0.5-10 mmol scale, with concentration of N-acyl oxazolidinone in methylene chloride of ca. 0.3 M.

Into a dry, 3-necked flask equipped with a magnetic spin bar was weighed 1.0 mmol of oxazolidinone (**1d, 2d** or **1c, 2c**). The flask was flushed with argon and sealed with a rubber septum. Methylene chloride (3 mL) was added, and the solution cooled to -78°C. Di-n-butylboryl trifluoromethanesulfonate (0.27 mL, 1.1 mmol) was added, followed immediately by 0.21 mL (1.2 mmol) of diisopropylethylamine. The light orange solution was stirred at -78°C for

30 min and 1 h at 0°C. The solution was then cooled back to -78°C and 1.0-10 equivalents of freshly distilled aldehyde was added in one portion. After stirring the mixture for 30 min at -78°C and 1 h at 0°C, 1 mL of pH 7 phosphate buffer was added to quench the reaction. Methanol (5 mL) was then added followed by 1 mL of 30% hydrogen peroxide and the mixture was stirred at 0°C for 1 h. The mixture was transferred to a separatory funnel containing aqueous sodium bicarbonate (5%) and extracted with methylene chloride. After drying the organic extracts over anhydrous sodium sulfate and evaporation of the solvent in vacuo, a 90-100% mass recovery of products was obtained as a yellow oil. The ratio of diastereomeric aldol adducts was determined by capillary column gas chromatographic analysis of a sample of the crude product mixture after silylation with excess N,N-diethylaminotrimethylsilane and N,N-dimethylaminopyridine in methylene chloride (1 h at room temperature).

(+)-(4S)-3-[(2S,3R)-3-Hydroxy-4-methyl-2-thiomethylpentanoyl]-4-(2-propyl)-oxazolidine-2-one (22) (Table 2, Entry A). The indicated compound, **22** was prepared according to the general procedure described for boryl enolate condensations. From 1.01 g (4.66 mmol) of imide **1d**, and 0.5 mL (0.39 g, 5.5 mmol) of isobutyraldehyde was obtained 1.31 g (97% mass balance) of unpurified aldol adduct. Diastereomer analysis (30 meter SE-54, 185°C, t_r: 9.36; 10.10; 10.27; 11.80 min) gave a ratio of 0.96:98.98:0.0:0.04 respectively. Purification by flash chromatography (60 g silica gel, 3 x 40 cm column, ether, 10 mL fractions) afforded 1.14 g (84%) of **22** as a white crystalline solid: mp 51-52°C; IR (CCl_4) 3530, 2975, 2940, 2885, 1780, 1689, 1469, 1392, 1375, 1343, 1331, 1304, 1210, 1180, 1144, 1126, 1098, 1056, 1025, 1010, 974, 772, 758,

715, 680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 0.98 (dd, 12H, isopropyl methyls), 1.82 (m, 1H, -CHOHCHMe$_2$), 2.13 (s, 3H, -SMe), 2.31 (m, 1H, -NCHCHMe$_2$), 2.85 (s, 1H, -OH), 3.82 (dd, 1H, J = 8 Hz, 4 Hz, -CHOH), 4.38 (m, 3H, -OCH$_2$CHN), 4.92 (d, 1H, J = 8 Hz, CHSMe); ^{13}C NMR ($CDCl_3$) δ (TMS) 12.22, 14.56, 16.12, 17.81, 19.56, 20.15, 28.40, 30.74, 39.25, 47.51, 58.16, 63.23, 72.20, 153.44, 170.01. $[\alpha]_D^{25}$ = +45.6° (c 0.79, CH_2Cl_2). R_f = 0.40 (silica gel, 50% ethyl acetate:hexane).

Anal. calcd. for $C_{13}H_{23}NO_4S$: C, 53.95; H, 8.01; N, 4.84. Found: C, 53.74; H, 7.90; N, 4.70.

(+)-(4S)-3-[(2S,3R)-3-Hydroxy-2-thiomethylbutanoyl]-4-(2-propyl)-oxazolidine-2-one (23) (Table 2, Entry E). The general procedure described for boryl enolate condensations was employed, using 1.4 g (6.5 mmol) of imide **1d**, and 0.5 mL (0.39 g, 8.9 mmol) of acetaldehyde. Purification of 1.57 g (92%) of aldol adduct by flash chromatography (as **22**) afforded 1.15 g (70%) of **23** (diastereomer analysis on 25 meter Carbowax 20M, 145°C, gave a ratio of 99.6:0.4) as an oil: IR (neat) 3520, 2970, 2940, 2884, 1776, 1689, 1483, 1468, 1460, 1386, 1371, 1318, 1300, 1206, 1140, 1121, 1113, 1054, 1020, 974, 943, 787, 760, 711 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (d, 6H, J = 7 H), 1.20 (d, 3H, J = 6 Hz), 2.10 (s, 3H, -SCH$_3$), 2.29 (m, 1H, -CHMe$_2$), 3.17 (s, 1H, -OH), 4.2 (m, 4H), 4.50 (d, 1H, J = 7.5 Hz, -CHSMe). $[\alpha]_D^{25}$ = +71.31° (c 2.06, CH_2Cl_2). R_f = 0.45 (silica gel, ether).

Anal. calcd. for $C_{11}H_{19}NO_4S$: C, 50.56; H, 7.33; N, 5.36. Found: C, 50.29; H, 7.02; N, 5.23.

(+)-(4S)-3-[(2S,3R)-3-Hydroxy-3-phenyl-2-thiomethylpropionyl]-4-(2-propyl)-oxazolidine-2-one (24) Table 2, Entry G). The general procedure de-

scribed for boryl enolate condensations was employed, using 1.26 g (5.8 mmol) of imide **1d** and 0.68 mL (0.71 g, 6.7 mmol) of benzaldehyde. Diastereomer analysis (25 meter Carbowax 20 M, 200°C, t_r: 19.82; 20.59; 24.71; 28.13 min) gave a ratio of 0.0:96.72:0.0:3.28 respectively. After flash chromatography (as **22**), 1.41 g (75%) of **24** (as a 73:27 mixture of diastereomers t_r = 20.59, 28.13 min respectively by VPC analysis; apparently the aldol product is not stable to silica gel chromatography) was obtained (an oil). The following physical data are of this 73:27 mixture of diastereomers. IR (CCl_4) 3500, 2975, 2939, 2882, 1780, 1690, 1490, 1466, 1453, 1421, 1390, 1370, 1350, 1304, 1208, 1141, 1122, 1104, 1062, 1023, 974, 919, 872, 842, 772, 710, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (TMS) 0.89 (d, 6H, J = 7 Hz, -CH$\underline{Me}_2$), 2.16 (s, 3H, -S$\underline{Me}$), 2.27 (m, 1H, -C$\underline{H}Me_2$), 3.4 (s, 1H, -OH), 4.1 (m, 3H), 5.06 (ABq, 2H, J_{ab} = 8.5 Hz), 7.3 (m, 5H, aromatic protons); ^{13}C NMR (major diastereomer) (CCl_4) δ (TMS) 12.74, 14.50, 17.55, 28.07, 51.60, 57.64, 62.58, 70.64, 126.99, 127.51, 127.83, 140.70, 152.46, 169.03. $(\alpha)_D^{25}$ = +55.75° (c 0.85, CH_2Cl_2). R_f = 0.37 (silica gel, 50% ethyl acetate:hexane).

Anal. calcd. for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55; N, 4.33. Found: C, 59.46; H, 6.53; N, 4.29.

(+)-(4S)-3-[(2S,3R)-3-Hydroxy-2-thiomethylhexanoyl]-4-(2-propyl)-oxazolidine-2-one (25) (Table 2, Entry C). The general procedure described for boryl enolate condensations was employed, using 0.96 g (4.4 mmol) of imide **1d**, and 0.55 mL (0.45 g, 6.2 mmol) of butyraldehyde. Diastereomer analysis (25 meter Carbowax 20 M, 170°C, t_r: 16.15; 22.37; 22.86; 24.34 min) gave a ratio of 0.3:1.3:98.1:0.3 respectively. Flash chromatographic purification (as **22**) of 1.23 g (96%) of aldol adduct afforded 1.1 g (85%) of **25**

as an oil (no change in ratio of diastereomers by VPC): IR (neat) 3460, 2980, 2950, 2890, 1783, 1695, 1490, 1470, 1461, 1391, 1379, 1373, 1306, 1212, 1210, 1208, 1148, 1130, 1101, 1062, 1025, 978, 853, 794, 770, 718 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.95 (d, 6H, -C<u>H</u>Me_2), 1.45 (m, 4H, methylenes), 2.13 (s, 3H, -S<u>C</u>H_3), 2.31 (m, 1H, -<u>C</u>HMe_2), 2.72 (s, 1H, -O<u>H</u>), 3.88 (m, 1H, -C<u>H</u>-OH), 4.3 (m, 3H), 4.58 (d, 1H, J = 6.5 Hz, -C<u>H</u>SMe); ^{13}C NMR (CCl_4) δ (TMS) 12.29, 13.92, 14.50, 17.62, 18.86, 28.16, 36.42, 49.42, 57.75, 62.82, 67.83, 152.89, 169.73. $[\alpha]_D^{25}$ = +64.5° (<u>c</u> 1.2, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{13}H_{23}NO_4S$: C, 53.95; H, 8.01; N, 4.84. Found: C, 53.97; H, 7.86; N, 4.71.

Preparation of Raney Nickel and Desulfurization of Aldols. The procedure described in <u>Organic Syntheses</u> (<u>Org. Syn. Coll.</u>, Vol. III, p. 76) was used with the modification of maintaining the temperature of the reaction between 50 and 90°C during the addition of Raney Nickel alloy (<u>ca.</u> 100 g scale) to the sodium hydroxide solution. The freshly-made Raney Nickel's activity could be adjusted to specifically remove the sulfur without hydrogenolytic side reactions by proper choice of reaction solvent and temperature. Typically, <u>ca.</u> 1 g of the fresh batch of Raney Nickel was allowed to react with <u>ca.</u> 0.5 mmol of aldol substrate in CH_2Cl_2 (or more polar solvents) at 0°C (or higher) until thin layer chromatography showed the reaction to be completed. The reactivity of the Raney Nickel was found to increase with an increase of the polarity of the solvent employed (acetone, ethanol). Once calibrated, the activity of the metal remains constant over a period of several weeks to months when stored at temperatures below 0°C under ethanol.

(+)-(4S)-3-[(3S)-3-Hydroxy-4-methylpentanoyl]-4-(2-propyl)-

oxazolidine-2-one (26) (Table 2 Entry A). To 1.09 g (3.8 mmol) of **22** in 50 mL of acetone at room temperature was added ca. 9 g (8-10 wet weight equiv) of Raney Nickel-ethanol slurry. The mixture was vigorously stirred at 60°C for 20 min under a nitrogen atmosphere. Thin layer chromatographic analysis showed absence of starting substrate (R_f **22** = 0.40, silica gel, 50% ethyl acetate:hexane). The mixture was cooled to room temperature and filtered through celite. Evaporation of the solvent in vacuo afforded 0.81 g of product. Diastereomer analysis (30 meter SE-54, 175°C, t_r major = 3.87 min, t_r minor = 3.63 min) gave a ratio of 97.8:2.2. Flash chromatographic purification (40 g silica gel, 3 x 40 cm column, 1:4 ether: CH_2Cl_2, 10 mL fractions) gave 0.62 g (68%) of purified product as a solid: mp 40-41°C; IR (neat) 3520, 2970, 2880, 1782, 1697, 1486, 1467, 1458, 1390, 1372, 1302, 1209, 1142, 1122, 1097, 1059, 1020, 971, 874, 773, 758, 704 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (m, 12H, isopropyl methyls), 1.60 [m, 1H, -CHOHCH(Me_2)], 2.35 (m, 1H, -CHNCHMe_2), 2.63 (d, 1H, -OH), 2.91 (d, 2H, J = 6 Hz, -$COCH_2$-), 3.66 (m, 1H, -CHOH), 4.22 (m, 3H); ^{13}C NMR (CCl_4) δ (TMS) 14.63, 17.49, 17.75, 18.53, 28.22, 33.36, 39.60, 58.01, 62.89, 72.31, 153.28, 172.33. $[\alpha]_D^{25}$ = +33.7° (c 2.42, CH_2Cl_2). R_f **26** = 0.32 (silica gel, 30% ethyl acetate:hexane).

Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.17; H, 8.84; N, 5.88.

(+)-(4S)-3-[(3R)-3-Hydroxybutanoyl]-4-(2-propyl)-oxazolidine-2-one (27) (Table 2, Entry E). Desulfurization of 1.15 g (4.4 mmol) of **23** and flash chromatographic purification (as **26**) gave 0.62 g (66%) of **27** as an oil. Diastereomer analysis (25 meter Carbowax 20 M, 145°C, t_r minor = 12.50

min, t_r major = 12.96 min) gave a ratio of 0.4:99.6. IR (CCl_4) 3500, 2970, 2939, 2880, 1780, 1700, 1484, 1466, 1458, 1386, 1302, 1241, 1206, 1141, 1122, 1110, 1056, 1020, 971, 938, 772, 761, 750, 710 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (d, 3H, J = 6.5 Hz), 0.93 (d, 3H, J = 6.5 Hz), 1.21 (d, 3H, J = 6 Hz, -CHOH$\underline{CH_3}$), 2.37 (m, 1H, -C$\underline{H}Me_2$), 2.73 (broad s, 1H, -O$\underline{H}$), 2.94 (d, 2H, J = 6 Hz, -CO$\underline{CH_2}$), 4.2 (m, 4H). $[\alpha]_D^{25}$ = +38.6° ($\underline{c}$ 1.51, CH_2Cl_2). R_f = 0.18 (silica gel, 30% ethyl acetate:hexane).

Anal. calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.97; H, 7.89; N, 6.60.

(+)-(4S)-3-[(3S)-3-Hydroxy-3-phenylpropionyl]-4-(2-propyl)-oxazolidine-2-one (28) (Table 2, Entry G). Desulfurization of 1.41 g (4.4 mmol) of **24** and flash chromatographic purification (as **26**) gave 0.183 g (15%) of product. Diastereomer analysis (30 meter SE-54, 180°C, t_r minor = 10.39 min, t_r major = 10.95 min) gave a ratio of 27.4:72.6. The following physical data is of this diastereomeric mixture. IR (CCl_4) 3500, 2975, 2940, 2880, 1789, 1700, 1690, 1487, 1455, 1390, 1375, 1302, 1207, 1141, 1120, 1106, 1060, 1027, 970, 787, 762, 698 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.85 (m, 6H, isopropyl CH_3's), 2.30 (m, 1H, -C$\underline{H}Me_2$), 3.2 (m, 3H, -COC$\underline{H_2}$ and O$\underline{H}$), 4.2 (m, 3H), 5.05 (m, 1H, -C$\underline{H}$OHPh), 7.23 (m, 5H, aromatic protons). $[\alpha]_D^{25}$ = +44.6° ($\underline{c}$ 1.31, CH_2Cl_2). R_f = 0.27 (30% ethyl acetate:hexane). Note: The title compound **28** is unstable to silica gel (low yield is due to decomposition during chromatography). When aldol product **24** was directly treated with Raney nickel without any prior contact with silica gel (chromatography purification) a 92.4:7.6 mixture of diastereomers (**28**: epimer of **28** respectively) was obtained.

Anal. calcd. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C,

65.24; H, 6.88; N, 5.13.

(+)-(4S)-3-[(3R)-3-Hydroxyhexanoyl]-4-(2-propyl)-oxazolidine-2-one (29) (Table 2, Entry C). Desulfurization of 1.09 g (3.8 mmol) of **25** and flash chromatographic purification (as **26**) gave 0.68 g (60%) of product as an oil. Diastereomer analysis (30 meter SE-54, 150°C, t_r minor = 10.39 min, t_r major = 10.82 min) gave a ratio of 0.6:99.4: IR (CCl_4) 3500, 2975, 2943, 2882, 1785, 1700, 1470, 1390, 1378, 1305, 1210, 1145, 1122, 1060, 1020, 973, 775, 756, 711 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (d, 3H, J = 6 Hz), 0.94 (d, 3H, J = 6 Hz), 1.40 (m, 4H, -$\underline{CH_2CH_2}CH_3$), 2.37 (m, 1H, -$\underline{CH}Me_2$), 2.79 (d, 1H, -O$\underline{H}$), 2.91 (d, 2H, J = 6 Hz, -$COCH_2$-), 3.9 (broad m, 1H, -$\underline{CH}$OH), 4.3 (m, 3H). $[\alpha]_D^{25}$ = +40.6° (c 2.20, CH_2Cl_2). R_f = 0.29 (silica gel, 30% ethyl acetate:hexane).

Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.31; H, 8.58; N, 5.73.

(+)-(4R,5S)-3-[(2R,3S)-3-Hydroxy-2-thiomethylbutanoyl]-4-methyl-5-phenyl-oxazolidine-2-one (30) (Table 2, Entry I). The title compound **30**, was prepared according to the general procedure described for boryl enolate condensations. From 0.98 g (3.71 mmol) of imide **2d**, and 0.4 mL (0.31 g, 7.1 mmol) of acetaldehyde, 1.4 g of unpurified aldol adduct was obtained. Diastereomer analysis (30 meter SE-54, 200°C, t_r: 8.81; 10.54; 11.08; 11.33 min) gave a ratio of 0.2:97.2:2.1:0.5 respectively. The crude product was flash chromatographed (70 g silica gel, 3 x 40 cm column, 1:1 ether: CH_2Cl_2, 10 mL fractions) to afford 0.84 g (74%) of **30** as an oil: IR (neat) 3500, 2990, 2940, 1780, 1692, 1456, 1368, 1221, 1200, 1148, 1124, 1068, 1040, 1001, 974, 802, 766, 731, 697 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.85 (d, 3H, J = 6 Hz,

-NCH$\underline{CH_3}$), 1.22 (d, 3H, J = 6 Hz, -CHOHC$\underline{H_3}$), 2.11 (s, 3H, -S$\underline{Me}$), 2.9 (s, 1H, -O$\underline{H}$), 4.1 (m, 1H, -C$\underline{H}$OH), 4.49 (d, 1H, J = 7 Hz, -C$\underline{H}$SMe), 4.77 (m, 1H, J = 6 Hz, -NC$\underline{H}$Me), 5.65 (d, 1H, 6 Hz, -O-C$\underline{H}$Ph), 7.3 (s, 5, aromatic protons). $[\alpha]_D^{25}$ = +5.41° (c 1.15, CH_2Cl_2). R_f = 0.53 (silica gel, 50% ether:dichloromethane). Note: Product is unstable to silica gel.

(+)-(4R,5S)-3-[(3S)-3-Hydroxybutanoyl]-4-methyl-5-phenyloxazolidine-2-one (31). The aldol condensation was performed on a 3.8 mmol scale of imide **2d** with acetaldehyde. The product, **30**, was subjected to desulfurization without prior chromatography using 50 mL of CH_2Cl_2 and 24 g of Raney Nickel slurry in ethanol at0°C for 30 min. Diastereomer analysis (30 meter SE-54, 200°C, t_r = 4.83 min) detected only one single isomer. Flash chromatographic purification (60 g silica gel, 3 x 40 cm column, 1:4 ether: CH_2Cl_2, 10 mL fractions) gave 0.62 g (62% overall yield) of **31** as a white solid: mp 67-68°C; IR (CCl_4) 3490, 2980, 2940, 1986, 1974, 1950, 1790, 1700, 1458, 1355, 1244, 1219, 1198, 1154, 1123, 1090, 1068, 1038, 1031, 1002, 971, 936, 849, 785, 755, 698 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (d, 3H, J = 6 Hz, -N-C$\underline{H}$Me), 1.2 (d, 3H, J = 6 Hz, -CHOHC$\underline{H_3}$), 2.8 (d, 1H, -O$\underline{H}$), 2.95 (m, 2H, -COC$\underline{H_2}$-), 4.15 (m, 1H, -C$\underline{H}$OH), 4.8 (m, 1H, J = 6 Hz, -NC$\underline{H}$Me), 5.62 (d, 1H, J = 6 Hz, -$\underline{CH}$Ph), 7.3 (s, 5H, aromatic protons). $[\alpha]_D^{25}$ = +71.8° (c 1.46, CH_2Cl_2). R_f = 0.40 (silica gel, 1:1 ether:dichloromethane).

Anal. calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.73; H, 6.43; N, 5.36.

Imide 26 and Epimer (Table 2, Entry B). A 1.0 mmol scale boron enolate aldol condensation of imide **1c** with isobutyraldehyde was carried out

following the described general procedure. Diastereomer analysis of the unpurified products (30 meter SE-54, 175°C, t_r major = 3.87 min, t_r minor = 3.63 min) gave a ratio of 52:48.

Imide 27 and Epimer (Table 2, Entry F). A 1.0 mmol scale boron enolate aldol condensation of imide 1c with acetaldehyde was carried out. Diastereomer analysis of the unpurified products (25 meter Carbowax 20M, 145°C, t_r minor = 12.50 min, t_r major = 12.96 min) gave a ratio of 72:28.

Imide 28 and Epimer (Table 2, Entry H). A 1.0 mmol scale boron enolate aldol condensation of imide 1c with benzaldehyde was carried out. Diastereomer analysis of the unpurified products (30 meter SE-54, 180°C, t_r minor = 10.39 min, t_r major = 10.95 min) gave a ratio of 62:38.

Imide 29 and Epimer (Table 2, Entry D). A 1.0 mmol scale boron enolate aldol condensation of imide 1c with n-butyraldehyde was carried out. Diastereomer analysis of the unpurified products (30 meter SE-54, 150°C, t_r minor = 10.39 min, t_r major = 10.82 min) gave a ratio of 63:37.

General Procedure for the Hydrolysis of Imides 26, 28, and 29. To a cooled (0°C) solution of 1.0 mmol of imide 11a in 4 mL of methanol was added 2 mL of a 2 N aqueous KOH solution. After stirring at 0°C for 1 h, 5 mL of saturated brine was added. The solution was extracted 3-times with CH_2Cl_2 to remove the freed chiral oxazolidinone. Acidification of the basic aqueous layer with 6 N HCl and subsequent extraction with ethyl acetate afforded the acid in 80-90% yield. The acid was purified by bulb-to-bulb distillation at reduced pressure (see Table 2). Treatment of the acid with excess diazomethane in ether at 20°C afforded the methyl ester. The methyl ester was purified via bulb-to-bulb distillation at reduced pressure.

(-)-(3S)-3-Hydroxy-4-methylpentanoic Acid (Table 2, Entry A). Hydrolysis of 613.2 mg (2.52 mmol) of imide **26** in 25 mL of methanol with 5 mL of a 2 N aqueous KOH solution according to the described general procedure afforded 265 mg (79%) of acid (via distillation at 100°C, 0.1 mm Hg; purity ≥ 95% by ^{1}H NMR). The ^{1}H NMR (90 MHz, $CDCl_3$) and IR (neat) spectra were consistent with the assigned structure; $[\alpha]_D^{25}$ = -42.1° (c 1.8, $CHCl_3$); literature rotations $[\alpha]_D^{25}$ = -24.7° (c 0.98, $CHCl_3$ (ref. 23a) and $[\alpha]_D^{25}$ = -40.3° (c 4.6, $CHCl_3$) (ref. 35). Optical rotation of the derived methyl ester (purity ≥ 95% by ^{1}H NMR): $[\alpha]_D^{25}$ = -40.5° (c 4.84, $CHCl_3$).

(-)-(3R)-3-Hydroxyhexanoic Acid (Table 2, Entry C). Hydrolysis of 375 mg (1.5 mmol) of imide **29** in 15 mL of methanol with 3.1 mL of a 2 N KOH solution according to the described general procedure afforded 139 mg (68%) of acid (via distillation at 100°C, 0.1 mm Hg; purity ≥ 95% by ^{1}H NMR). The ^{1}H NMR (90 MHz, $CDCl_3$) and IR (neat) spectra were consistent with the assigned structure; $[\alpha]_D^{25}$ = -27.3° (c 2.1, $CHCl_3$); literature rotation $[\alpha]_D^{25}$ = -28° (c, 2.0, $CHCl_3$) (ref. 23b). Optical rotation of the derived methyl ester (purity ≥ 95% by ^{1}H NMR): $[\alpha]_D^{25}$ = -23.6° (c 8.71, $CHCl_3$).

(-)-(3S)-3-Hydroxy-3-phenylpropionic Acid (Table 2, Entry G). Hydrolysis of 207 mg (0.75 mmol) of imide **28** in 7 mL of methanol with 1.5 mL of a 2 N KOH solution according to the described general procedure afforded 86 mg (69%) of acid: mp 107-109°C (lit. mp 110°C, ref. 22). The ^{1}H NMR (90 MHz, $CDCl_3$) and IR spectra were consistent with that reported in the literature (ref. 22); $[\alpha]_D^{25}$ = -17.1° (c 4.1, EtOH); literature rotation $[\alpha]_D^{25}$ = -18.9 (c 2.3, EtOH) (ref. 23d). Optical rotation of

the derived methyl ester (purity ≥95% by NMR): $[\alpha]_D^{25}$ = -18.4° (c 3.3, EtOH).

Methanolysis of Imides 27 and 31. Due to the water solubility of β-hydroxybutyric acid, imides **27** and **31** were transesterified with sodium methoxide in methanol to afford the corresponding methyl ester as follows. To a cooled (0°C) solution of 1.5 mmol of imide **27** (**31**) in 4 mL of methanol was added a solution of 90 mg (1.7 mmol) of $NaOCH_3$ in 5 mL of methanol. After stirring for 15 min, the methanol was removed in vacuo at 20°C. The residue was filtered through 6 g of silica gel (1.5 x 30 cm column) with 60 mL of CH_2Cl_2. Evaporation of the solvent and bulb-to-bulb distillation (bp 76-77°C/20 mm Hg) of the residue gave 76-108 mg (40-60%) of pure methyl ester as an oil. The ^1H NMR (90 MHz, CCl_4) and IR (neat) spectra of the esters from **27** and **31** were consistent with their assigned structures. Due to the absence of any spurious signals in the esters' NMR spectra their purity may be assessed to be ≥95%. Optical rotation of (+)-(3S)-3-hydroxybutanoic acid, methyl ester from **31**: $[\alpha]_D^{25}$ = +45.9° (c 1.4, $CHCl_3$). Literature rotation $[\alpha]_D^{25}$ = +33.3 (c 1.2, $CHCl_3$) (ref. 23c). Optical rotation of (-)-(3R)-3-hydroxybutanoic acid, methyl ester from **27**: $[\alpha]_D^{25}$ = -45.8° (c 1.7, $CHCl_3$).

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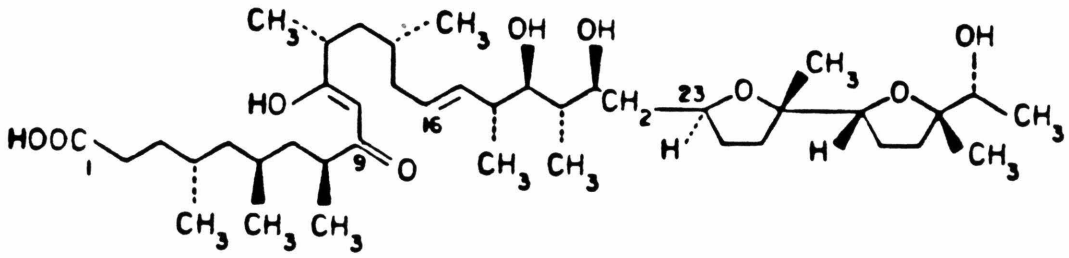
CHAPTER II

Progress Towards The Total Synthesis of (-)-Ionomycin

I. Introduction

Ionomycin,[1] **71**, is a recent addition to the class of polyether antibiotics.[2] Its isolation from the fermentation medium of Streptomyces conglobatus was first reported in 1975 by Meyers.[1a] Initial studies[1b] have shown that ionomycin exhibits the ability to transport divalent cations across solvent barriers. Its calcium specificity and ionophoric capacity exceeded that of A-23187 (calcimycin)[3] according to experiments in rat liver mitochondria.[1d]



Ionomycin **71**

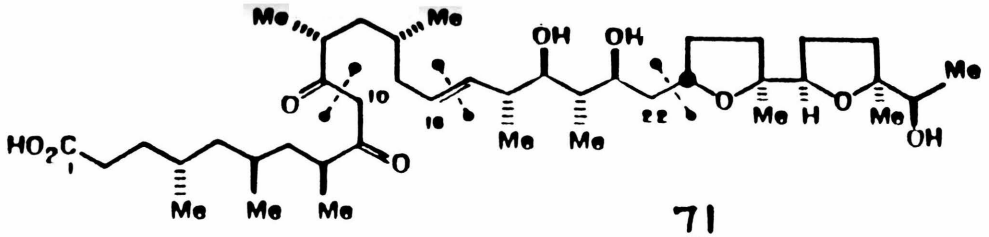
Figure 1

The chemical structure and the absolute stereochemistry of ionomycin was revealed in 1979 via X-ray crystallography of the calcium and cadmium complexes.[1c] Prominent structural features include fourteen asymmetric centers and an enolizable β-diketone function. The latter functionality accounts for ionomycin's intense ultraviolet absorption (280 nm) and its propensity to form neutral 1:1 complexes with divalent cations.

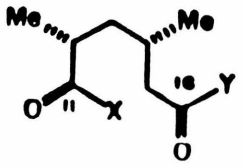
Ionomycin's diverse functionality and rich stereochemistry provide the opportunity to test the chiral imide technology developed in our laboratories. In conjunction with this interest we undertook an enantioselective total synthesis of (-)-ionomycin. This chapter will describe our efforts toward this goal.

II. Synthetic Strategy

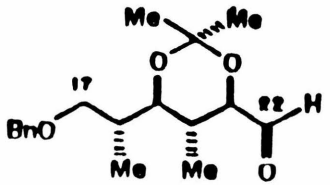
The synthetic challenges presented by any complex molecule can be subdivided into two categories; control of functional group reactivity and control of relative and absolute stereochemistry during the bond forming sequences. Our general plan for ionomycin is outlined in Scheme I. The proposed disconnections lead to four fragments (**A** through **D**). These subgoals, with their reactive functions suitably protected, may be assembled efficiently and convergently at the appropriate stages. The final phase will involve unmasking the protected functional groups leading to the enantiomerically pure (-)-ionomycin. This strategy packages the stereochemical issues within each fragment. An enantioselective synthesis of these subunits would solve the stereochemical requirements of ionomycin except for the C23 stereocenter. The generation of this stereocenter will be discussed in the section concerned with the coupling of fragments **A** and **B**. The assemblage of the four subunits was envisioned to involve Wittig olefination reactions connecting C22-C23 and C16-C17, the latter utilizing the Schlosser modification[4] to achieve the trans (E) double bond configuration present in ionomycin. The final bond connection leading to the fully assembled carbon backbone was to be an aldol



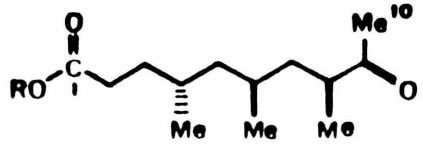
71



C C_{11}-C_{16}

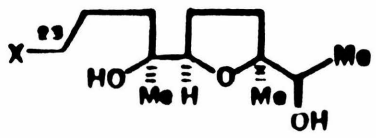


B C_{17}-C_{22}



D C_1-C_{10}

Scheme 1



A C_{23}-C_{32}

condensation between the D subunit (as a ketone enolate) and the C11-C32 subunit containing a C11 aldehyde function. A subsequent oxidation of the hydroxyl function at C11 of the aldol adduct would provide the fully assembled structure having the correct oxidation state. Removal of the three protecting groups would then yield the free carboxylic acid **71**. The successes and modifications of these approaches will be discussed in later sections of this report.

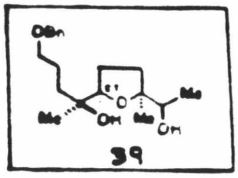
The immediate problem of obtaining the requisite fragments A-D in enantiomerically pure forms can be solved by several means. One approach along classical lines[5] would involve exploiting the well-known chemical biases present in small rings to control relative stereochemistry. This "cycle strategy" based on relative asymmetric induction would rely on a key controlling stereocenter tapped either from nature's existing chiral pool or through the chemical resolution of a racemate. However, in view of the acyclic stereochemical nature of our target structures, such an approach would be unwieldy. Another possible approach utilizes the existing chirality of carbohydrates and sugars.[6] Through extensive refunctionalizations one may modify optically pure sugars to the appropriate target fragments. Such tactics, although workable, do not directly address the more general issue of acyclic stereochemical control.

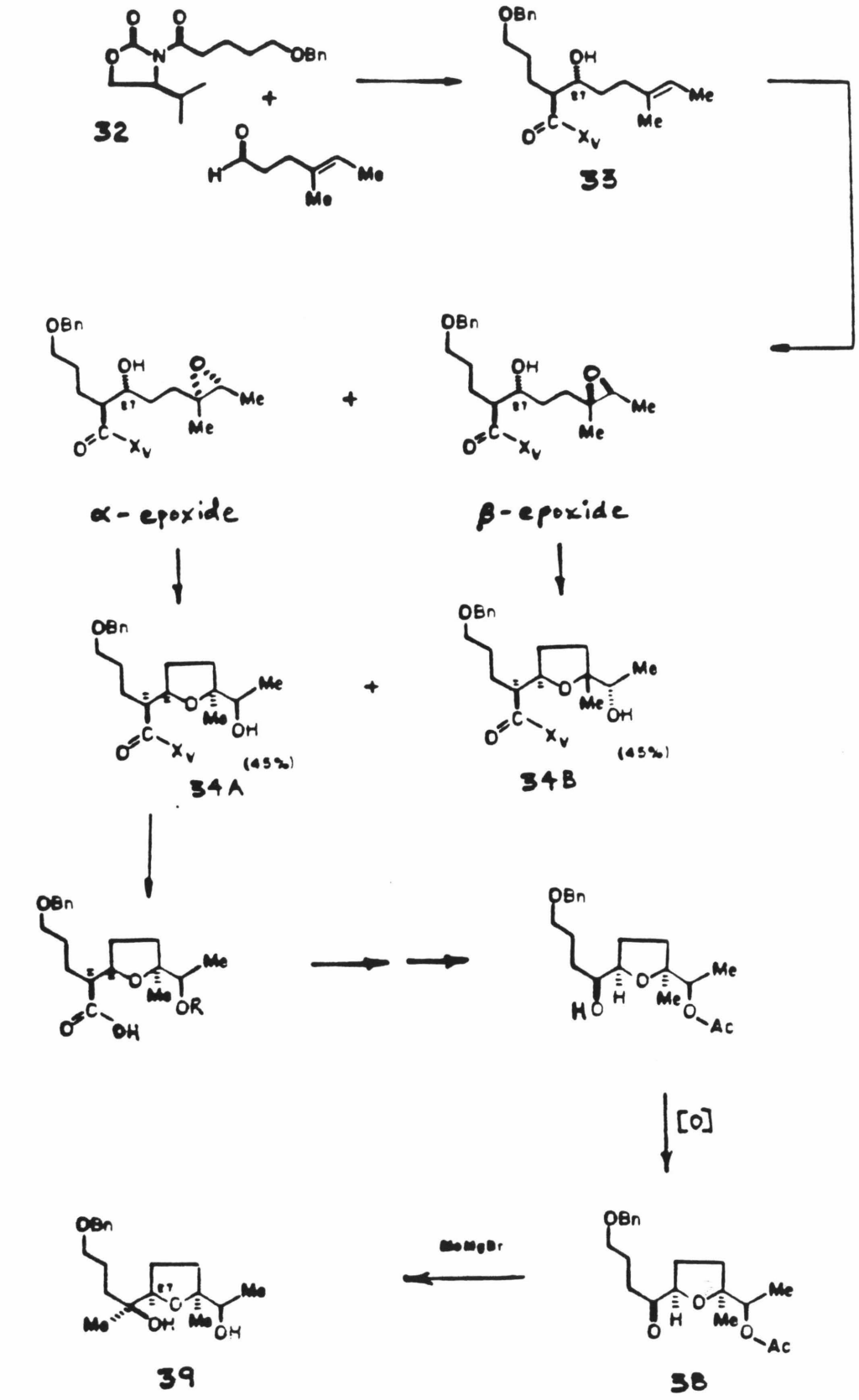
Ideally, the most direct means of attacking this problem would be to generate the stereocenters during the bond-forming steps of the reactions. Such an approach has recently become technically viable with the development of enantioselective aldol and alkylation reactions.[7] In conjunction with our interest in this area we committed ourselves to utilizing the chiral imide

methodology (vide infra) in designing enantioselective routes to fragments A-D. Since the chiral imides provide ready access to either enantiomeric forms (of A-D) this synthetic strategy will enjoy the flexibility of accommodating any stereochemical variants of ionomycin as well.

Subunit A (C23-C32) 39. The synthon representing the C23-C32 subunit of ionomycin was envisioned to consist of the intact remote tetrahydrofuran ring attached to a portion that will be eventually cyclized to produce the central tetrahydrofuran moiety. As shown in Scheme II, this synthon bearing four asymmetric centers will have the C27 stereocenter as the key controlling resident chirality. An enantioselective aldol condensation between imide **32** and (E)-4-methyl-4-hexenal was projected[8] to afford adduct **33** containing the desired C27 stereocenter. This hydroxy stereocenter may provide sufficient directivity in the epoxidation of the tri-substituted olefin to provide the desired α-epoxide. Acid catalyzed cyclization should produce the requisite furan diastereomer **34a**. Elaboration of **34a** to synthon **39** will involve four steps: hydrolytic cleavage of the chiral auxiliary to give the carboxylic acid; protection of the 2° alcohol function; a formal carboxy inversion[9] to decarboxylate the extra carbon fragment and introduce the requisite oxygen function; and oxidation of the alcohol to ketone **38**. The chelation-controlled addition of methyl Grignard to ketone **38** should in analogy to literature examples[10] proceed to give synthon **39**. The hydroxyl groups of **39** will then be inactivated by silylation. Hydrogenolysis of the benzyl ether will allow one to refunctionalize the resulting primary alcohol to a phosphonium salt (via mesylation, iodide substitution, and reaction with triphenylphosphine) in preparation for an eventual coupling with the next subunit.

Scheme II


OBn
Me
Me
OH
Me
OH
39


32
33
α-epoxide
β-epoxide
34A
(45%)
34B
(45%)
[O]
MeMgBr
38
39

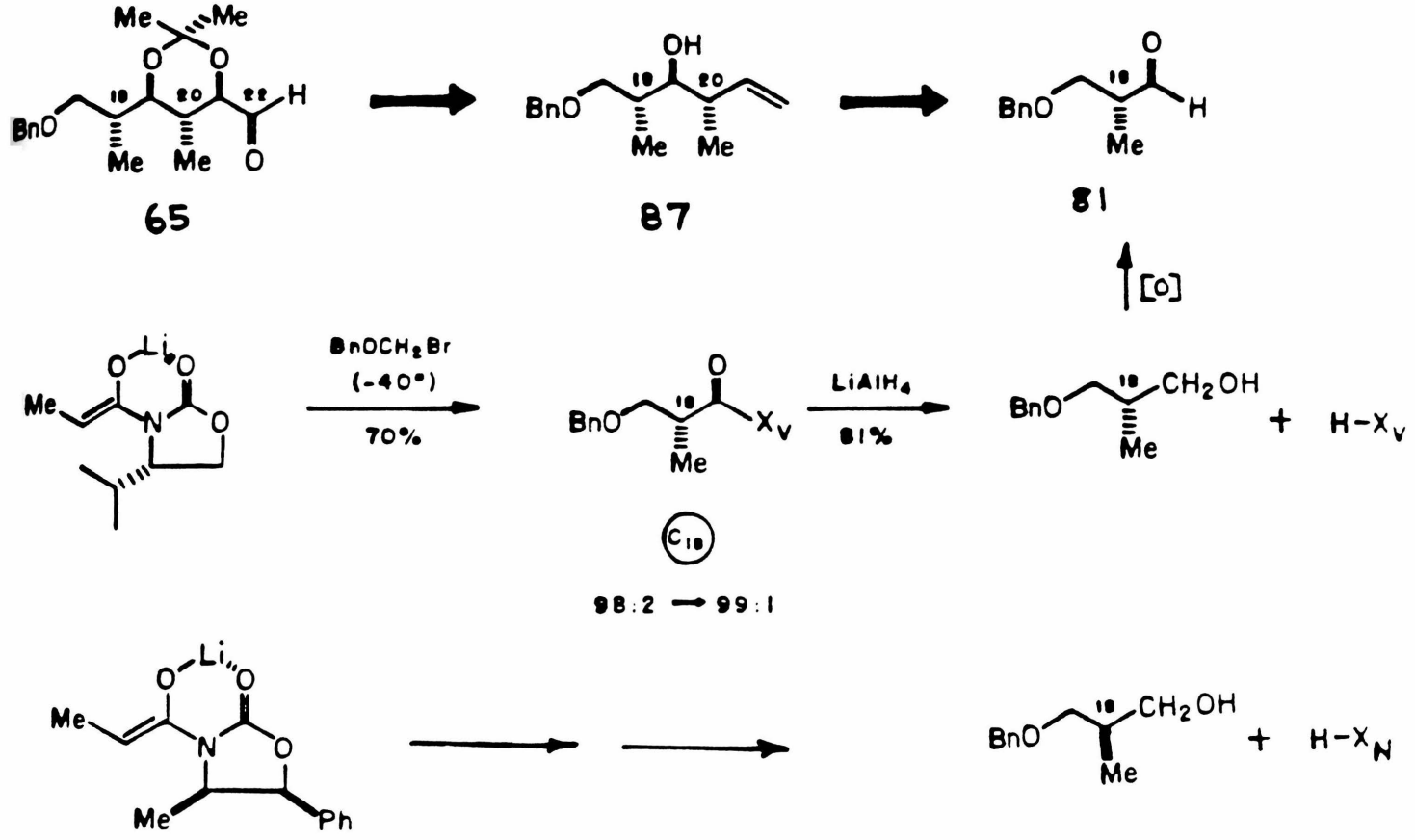
Subunit B (C17-C22) 65. The central right quarter segment of ionomycin containing four stereocenters is represented by synthon **65** as shown in Scheme III. The C19 and C21 hydroxyl functions are protected as the acetonide. With C17 blocked as a benzyl ether one may envision a facile coupling of this synthon at C22 with an alkylidene phosphorane derived from **39**.

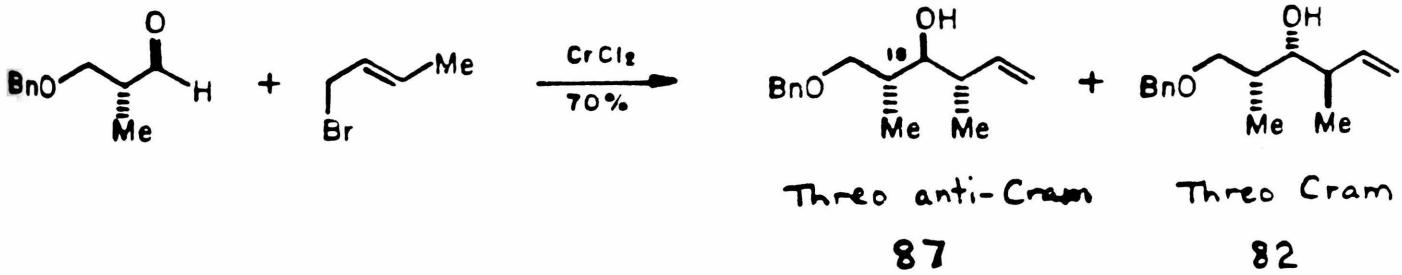
Examination of the relative stereochemistry of **65** reveals a threo or anti relationship between the hydroxyl and methyl groups. By recognizing the C19 hydroxyl stereocenter as a possible key control element in the stereoselective oxygenation of C21 and C22 one may retrosynthetically arrive at the homoallylic alcohol **87**. A further Δ(19-20) bond disconnection was projected based on the assumption that one may selectively regenerate the threo relationship from the addition of an organometallic crotyl anion species to aldehyde **81**. This assumption has literature precedence from the work of Hiyama and Nozaki[11] in which the addition of chromium(II) crotyl anions to various aldehydes resulted in the formation of threo adducts. In this case, the addition of a chromium(II) crotyl anion to aldehyde **81** will result in threo-Cram (**82**) and anti-Cram (**87**) products. The extent of selectivity in this addition will be examined.

The strategic plan for the construction of synthon **65** is ultimately based on the ready availability of aldehyde **81** in optically pure form. Although a classical source of this aldehyde exists (refunctionalization of (S)-(+)-β-hydroxyisobutyric acid[12] from the culture medium of Pseudomonas putida), we have an alternative synthetic route that is more convenient. Investigations by Mathre[13] in our laboratories revealed that the lithium

Scheme III

$C_{17}-C_{22}$ Synthon





Threo anti-Cram

87

Threo Cram

82

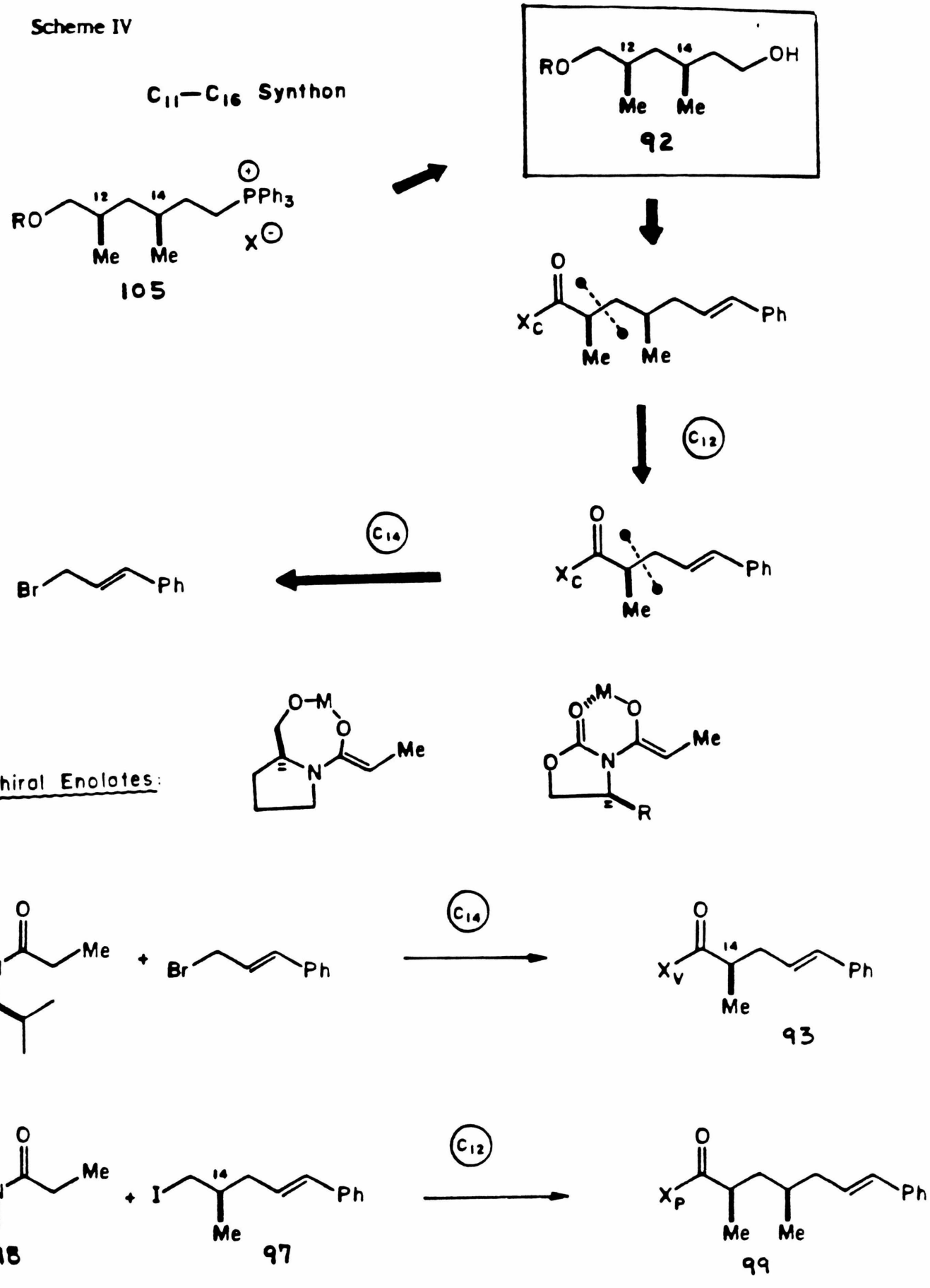
R. Dow[34]

enolates of imide **1b** may be alkylated by bromomethylbenzyl ether with high diastereoselection (>96% d.e.). The resulting alkylated product may be reduced to afford the optically active alcohol which upon Swern[14] oxidation provides the desired aldehyde **81**. The use of the complementary norephedrine-derived imide enolate will provide ready access to the enantiomer of **81**.

Subunit C (C11-C16) 92. Our general plan for the construction of ionomycin calls for the formation of the Δ(16-17) bond via a Schlosser-Wittig reaction followed by an aldol condensation at C10-C11. This designated the central left subunit to be represented by synthon **92** (Scheme IV). The primary hydroxyl function at C16 can easily be converted to the requisite phosphorane while the desired aldehyde function at C11 may be unmasked by the removal of the protecting group followed by a Swern oxidation. Retrosynthetically, the two stereocenters will be produced utilizing chiral alkylation technology.[15] The alkylation of imide **1b** with allylic halides has been shown to produce the requisite (R) absolute stereochemistry[15b] for C14. Therefore, alkylation with 1-bromo-3-phenyl-2-propene should provide **93**. Elaboration of **93** to iodide **97** and subsequent alkylation with the more reactive prolinol amide[16] will complete the formation of the two stereocenters of subunit C. Finally, the chiral auxiliary will be hydrolyzed off and the resulting carboxylic acid reduced to a primary alcohol. After blocking the C11 hydroxyl group as a silyl ether, the C16 reactive function may be unmasked via ozonolysis of the double bond followed by a reductive ($NaBH_4$) workup to afford synthon **92**.

Subunit D (C1-C10) 64. The last subunit containing the C1-C10

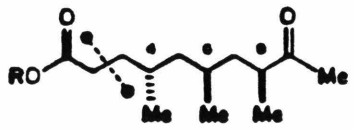
Scheme IV


C11—C16 Synthon
RO
12
14
OH
Me
Me
92
PPh3
X⊖
105
O
XC
Ph
C12
C14
Br
Chiral Enolates:
O-M
N
R
1b
HOCH2
93
98
97
99
XV
XP

backbone of ionomycin is represented by synthon **64** as shown in Scheme V. Exemplary features of this fragment are three methyl stereocenters two of which are far removed from the reactive functional groups. In keeping with our goal of generating each stereocenter *via* a highly stereoselective process we select to control these centers by introducing oxygen functionality at key sites within the synthon. An initial disconnection at Δ(C2-C3) trims **64** into a more symmetrical precursor **106**. Conceptually introducing a hydroxyl group at either C5 or C7 leads to intermediate **108** or **107** respectively. Route **A** which centers on **108** will exploit a recently discovered example of (1,3) induction *via* the stereoselective hydroboration[17] of intermediate **109** to induce the C8 methyl stereocenter of **110**. Intermediate **109** was retrosyntheticaly analyzed back to a series of aldol and alkylation reactions utilizing imide **1b** (*vide infra*, Scheme V).

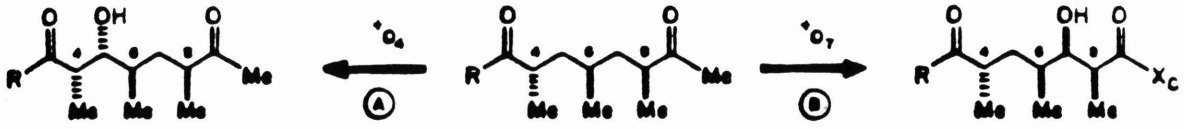
Equally attractive was route **B** which takes advantage of an alkylation result reported by Grieco[18] in which a lactone analogous to **50** was alkylated with a selectivity of >95:5 in favor of the α-isomer. Lactone **50** was envisioned to be readily derived from diol **49** which retrosynthetically is available from an aldol reaction between imide **1b** and aldehyde **47**. Aldehyde **47** can be traced back to a common intermediate, imide **32**, which was the starting material used for the construction of subunit **A**. The balance of choice was tipped in favor of route **B** in view of the ready availability of starting material **32**. In addition, the lower expected hydroboration selectivity (85:15)[17] *versus* the alkylation selectivity (>95:5) decided the issue. Final elaboration of lactone **51** to synthon **64** is shown in Scheme VI. It was assumed that a selective reduction of the lactone carbonyl in the

Scheme V



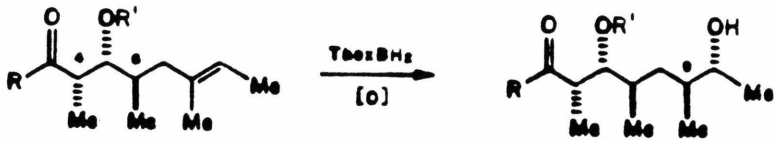
64

C_1–C_{10} Synthon

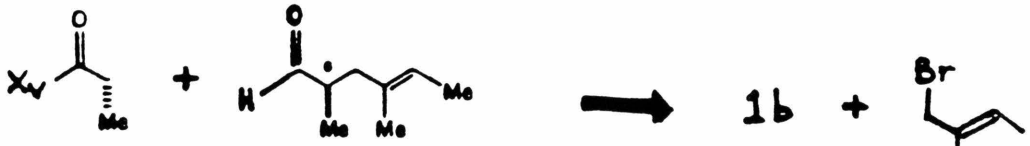


108 106 107

C_8-Induction from (A)



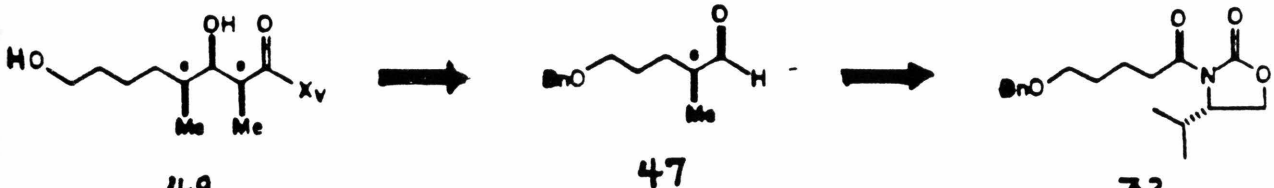
109 110



1b 111 1b

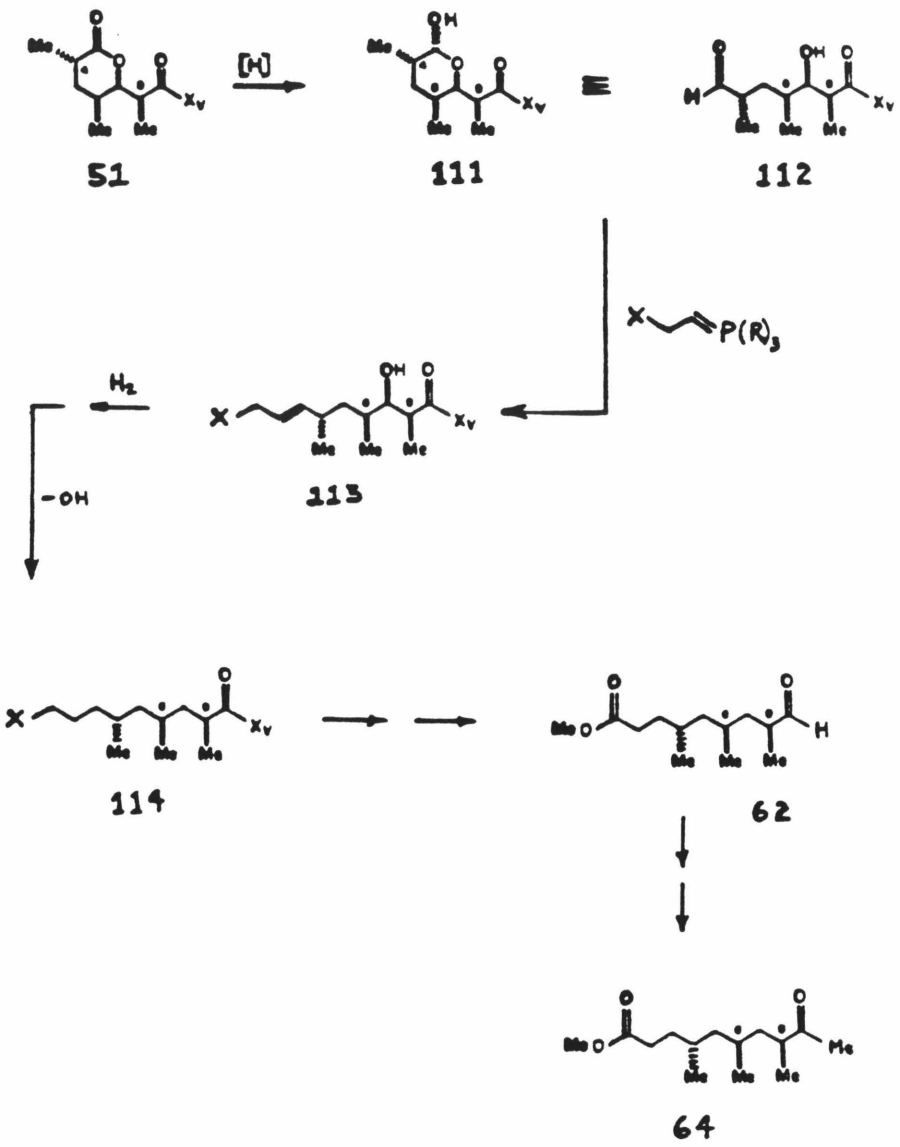
C_4-Induction from (B)

50 51



49 47 32

Scheme VI



presence of the imide carbonyl would be possible leading to lactol **111**. Treatment of lactol **111** with a suitable phosphorous ylid (to append the two-carbon fragment) would in principle form adduct **113** via **112**, the open form of lactol **111**. Subsequent hydrogenation of the double bond followed by a Barton deoxygenation[19] would lead to intermediate **114**. Further functional group manipulation would afford aldehyde **62** which upon reaction with lithium dimethylcuprate followed by an oxidation would produce synthon **64**.

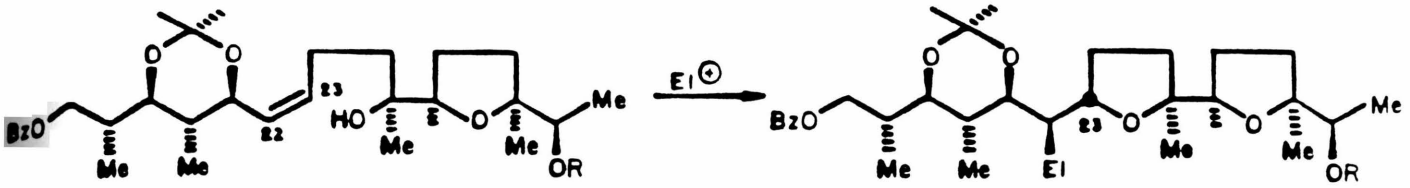
Coupling of Subunits A and B. The stereochemistry at C23. The

stereoselective control of thirteen of ionomycin's asymmetric centers has been outlined in the strategy for the synthesis of subunits **A-D** (vide infra). The remaining C23 stereocenter will now be addressed. An electrophile-mediated cyclization of the C26 hydroxyl function with a Δ(22-23) Z olefin was preconceived to form the second tetrahydrofuran ring. The stereoselection for this process was to be directed by the mutually cooperative controlling C26 and C21 stereocenters as shown in Scheme VII. Examination of possible transition state models indicated that the approach of the activating electrophile will be highly biased. The subsequent backsided displacement of the electrophile by the C26 hydroxyl group should proceed in the manner favoring the correct stereoselection. An analogous cyclization has been provided by Tanaka[20] which illustrates the C26 → C23 chirality transfer's viability. Additional support to the concept of the acetonide moiety (C19-C21) presenting a good stereofacial bias may be found in the examples of olefin epoxidation.[21] Based upon these considerations, a well-precedented Wittig olefination reaction joining subunits **A** and **B** should secure the right-hand half of ionomycin.

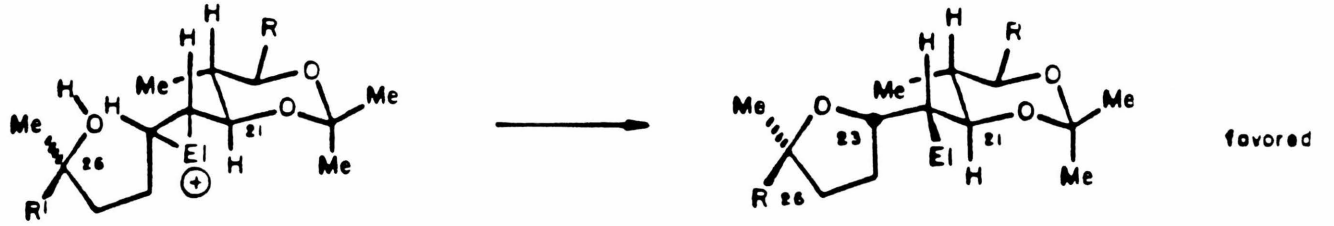
Final Synthon Assemblage. The union of the right half (C17-C32) of ionomycin with subunit **C** (C11-C16) may be regarded as an exercise in olefin synthesis. Specifically in our case, a trans or E olefin at Δ(16-17) is required (Fig. 2). A variety of approaches is available. The first potential method to be examined will be the Schlosser-Wittig reaction.[4] A model study to this effect has been attempted (Scheme VIII) where synthon **105** (subunit **C**) was condensed with isobutyraldehyde to produce mainly the desired E olefin in good yield.[34] Should the actual system prove unsatisfactory, we have at our

Scheme VII

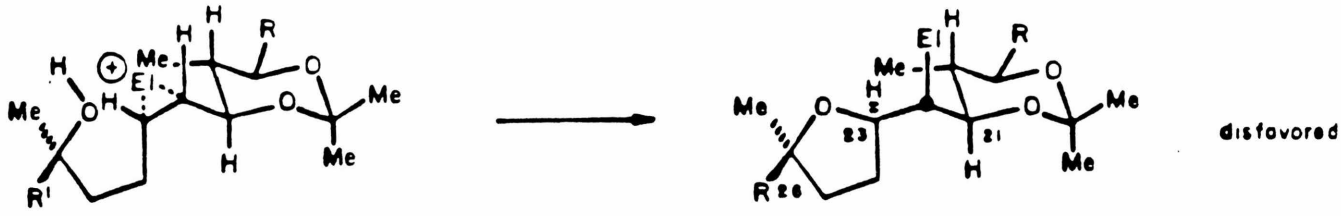
C_{23} – DIASTEREOSELECTION



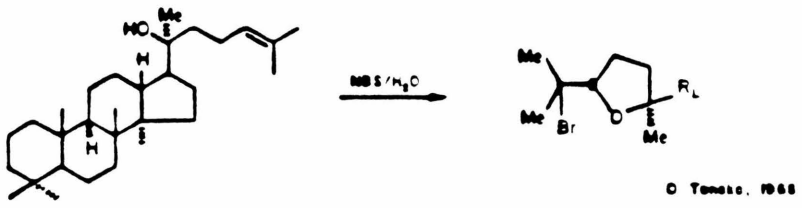
a, El = Br, HgX
b, El = H



favored



disfavored



O Tomas, 1968

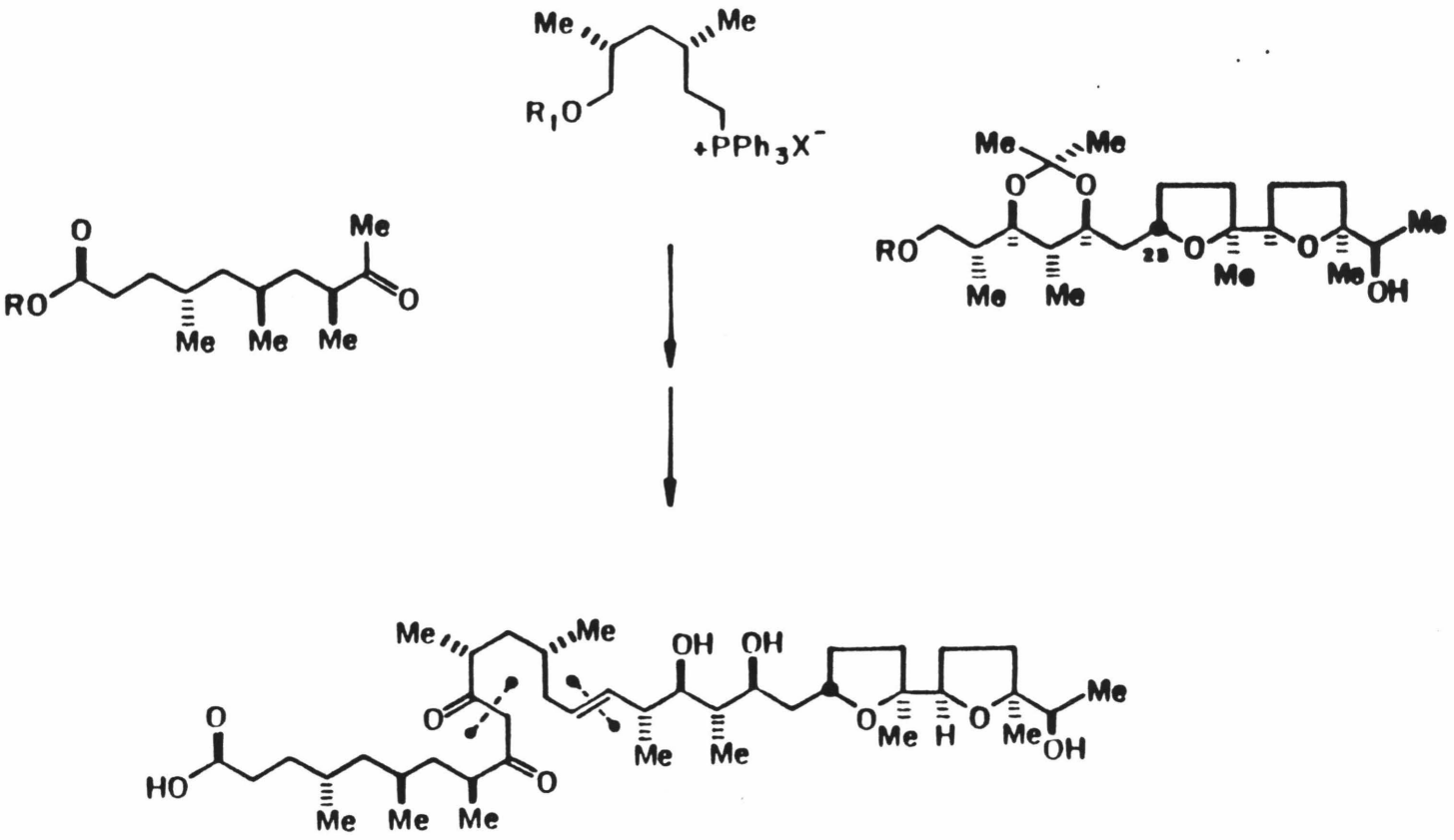
Blocks for $C_{26} \rightarrow C_{23}$ chirality transfer

mCPBA $\beta:\alpha = 9:1$

mCPBA only β

Blocks for $C_{21} \rightarrow C_{23}$ chirality transfer

Final Synthon Assemblage



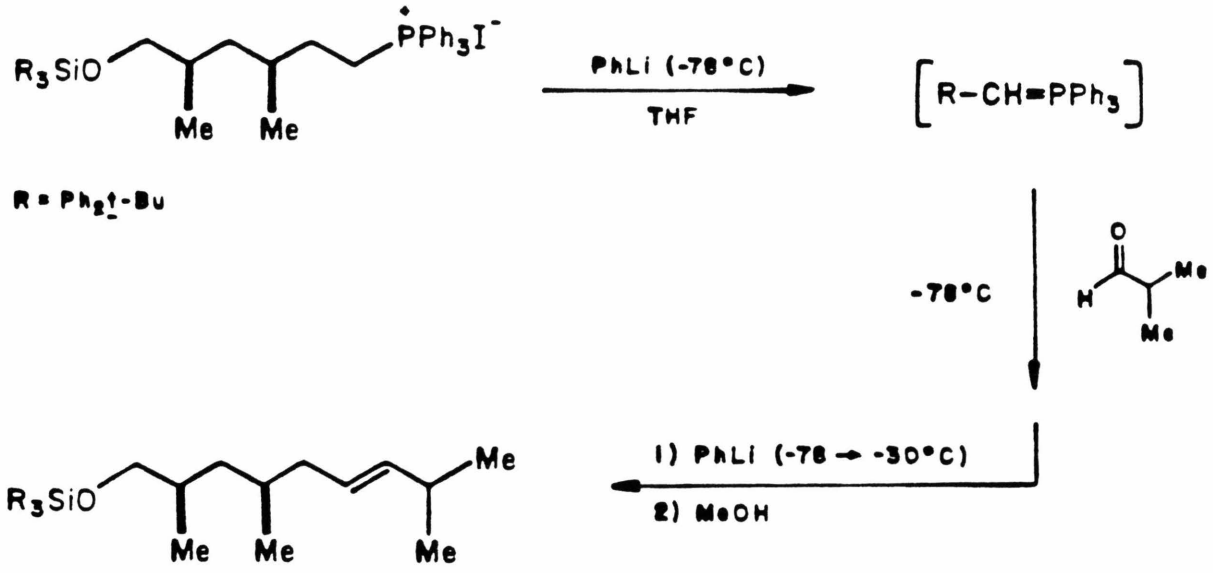
Ionomycin

Figure 2

Scheme VIII

C_{16}-C_{17} Bond Construction

Model Studies: Schlosser-Wittig



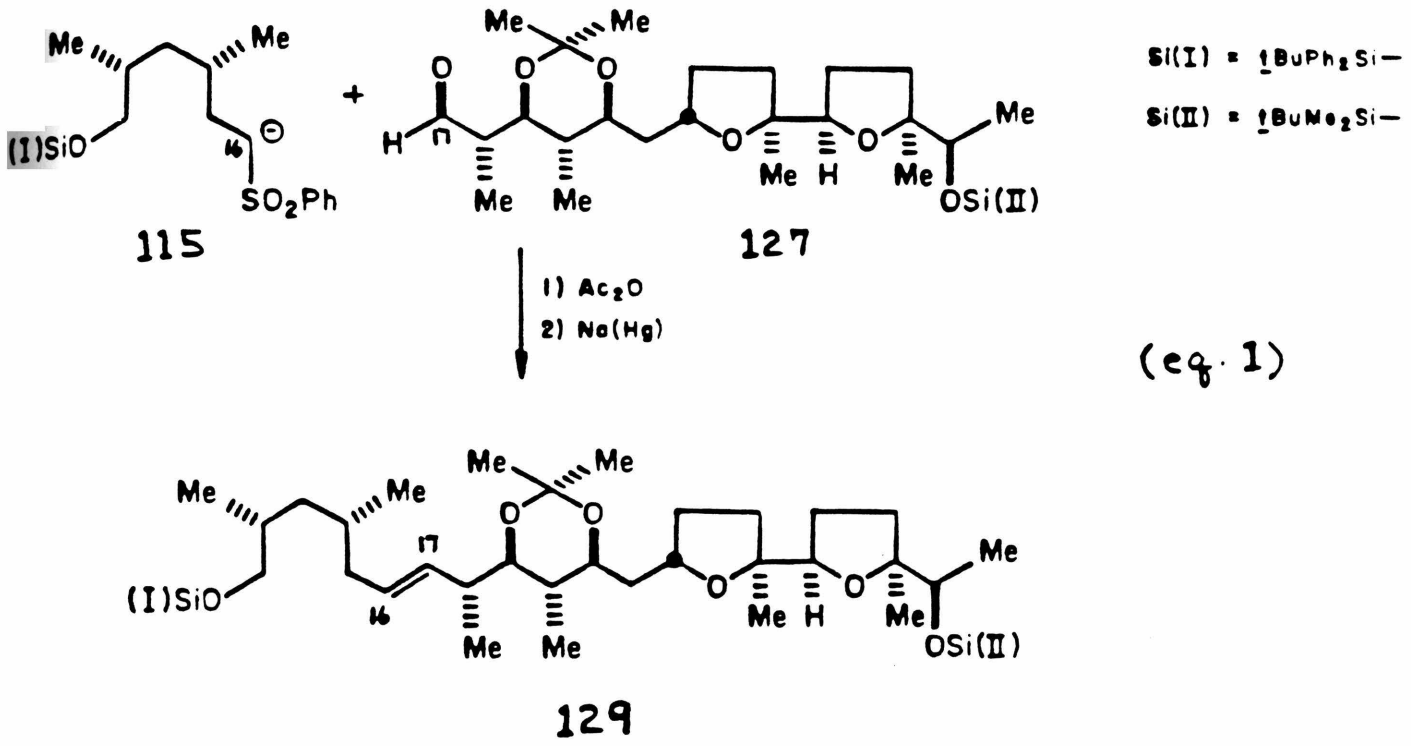
R. Dow[34]

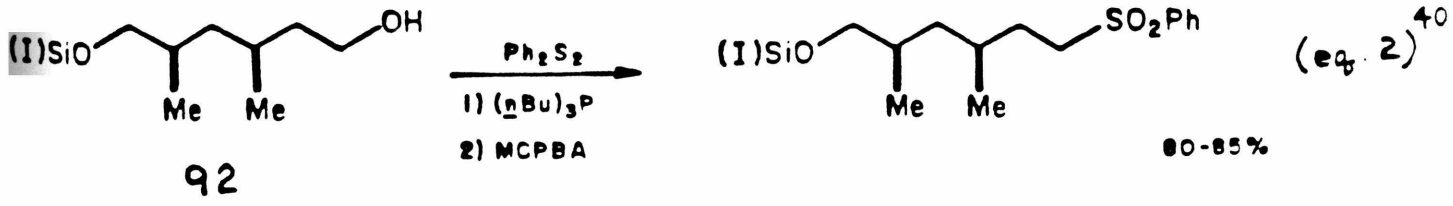
disposal two alternative plans. The first alternative will be the sulfone-mediated condensation and reductive elimination sequence of Kocienski et. al.[22] (Scheme IX). Sulfone **115** should be easily obtainable from synthon **92** as indicated in equation 2 (Scheme IX). The second alternative which utilizes aldol methodology in olefin synthesis[23] has high general applicability in view of the impressive levels of regioselection possible for this reaction.[24] A relevant analogy for this transformation is provided in Scheme X.

The final bond connection which assembles the entire carbon backbone of ionomycin is illustrated in Scheme XI. From prior investigations[25] in our laboratories we were confident that a regioselective enolization of synthon **64** could be effected. Subsequent aldol condensation with aldehyde **116** followed by an oxidation[26] would provide **74**. The integrity of **74** with fourteen stereocenters established as in ionomycin can then be probed by direct comparison with an authentic sample obtained by protecting the appropriate functional groups of ionomycin. The sequential protection of the appropriate functional group is depicted in Scheme XII. Starting with the natural product provided generously by Squibb we begin by freeing the carboxylic acid with 1 N hydrochloric acid. Esterification with diazomethane will be followed by treatment with 2,2-dimethoxypropane to form acetonide **73**. Silylation with t-butyldimethylsilyl triflate will complete the protection sequence and provide authentic samples for comparison. Ultimately, these three blocking groups will be removed in reverse order to afford (-)-ionomycin.

Scheme IX

C_{16}-C_{17} Bond Construction

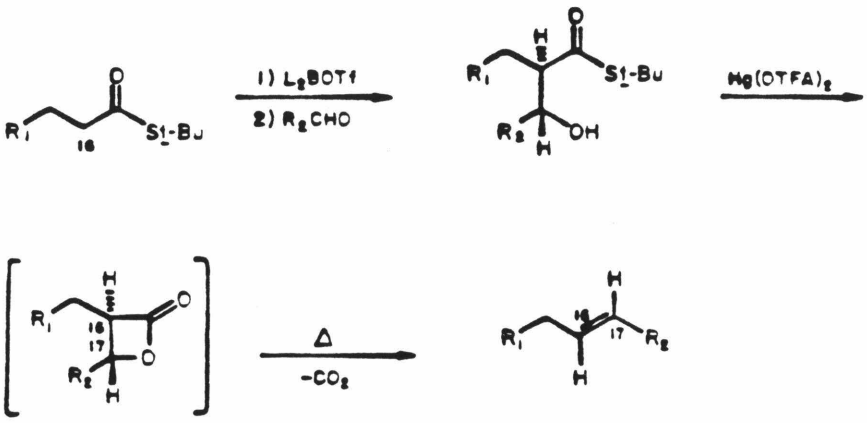




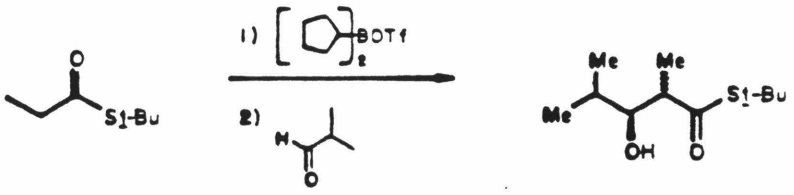
R. Dow [34]

Scheme X

TRANS-OLEFINS VIA ALDOL CONDENSATION

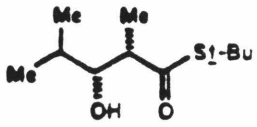


Aldol Stereochemistry



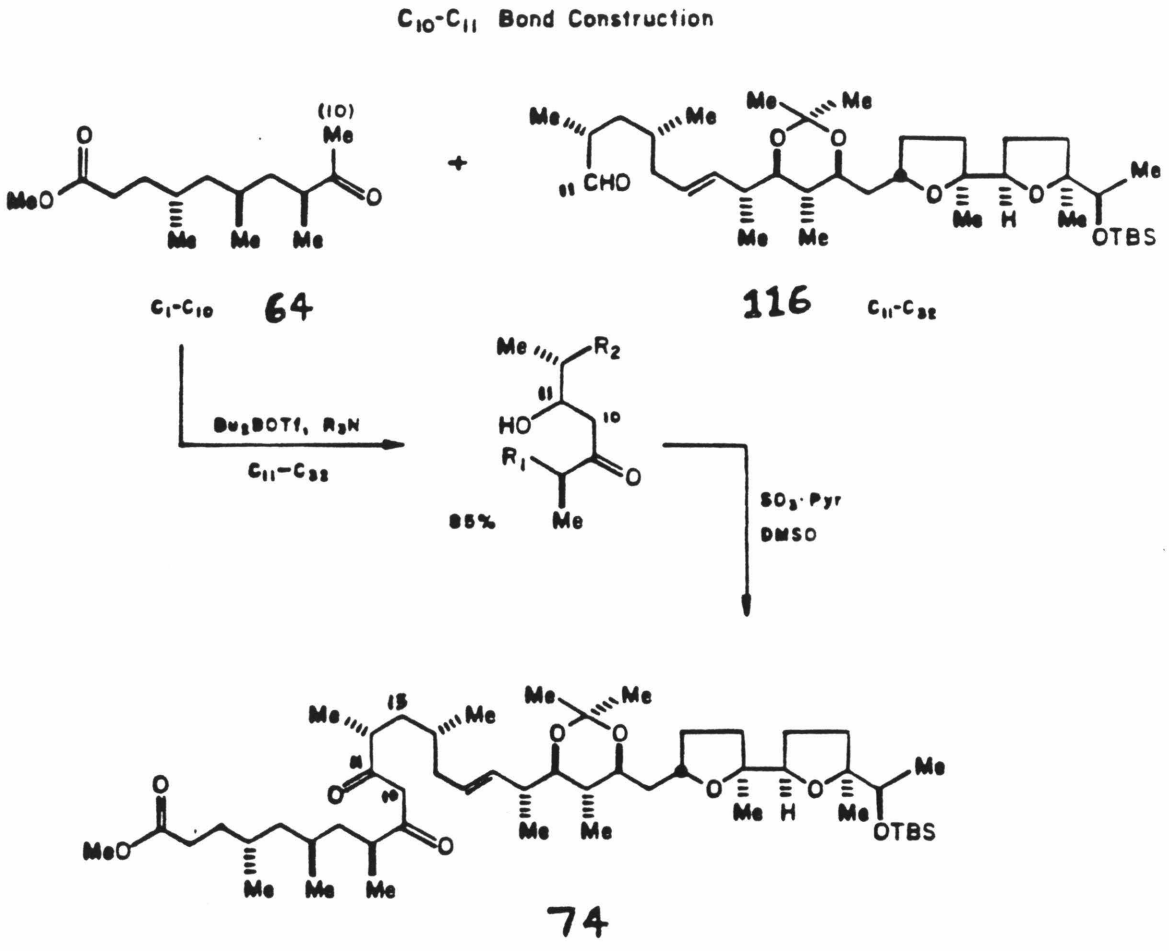
Threo

Ratio: T:E = 95:5

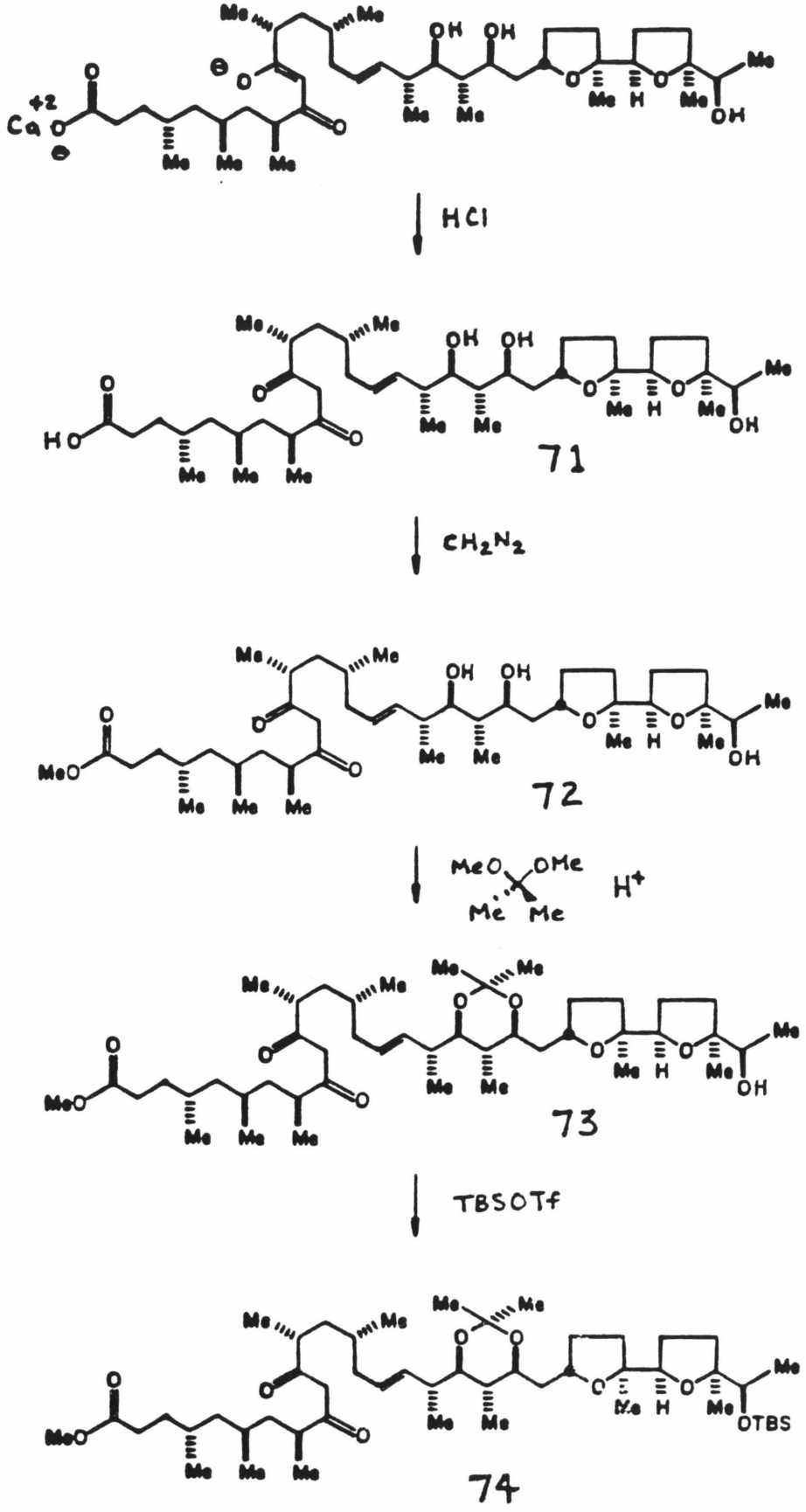


Erythro

Scheme XI


C10-C11 Bond Construction
(10)
Me
MeO
Me Me Me
C1-C10
64
+
Me Me
Me Me
11 CHO
Me Me
O O
O
Me H
Me
OTBS
116
C11-C32
Me R2
11
HO
10
R1
O
Me
85%
Bu2BOTf, R3N
C11-C32
SO3·Pyr
DMSO
15
Me Me
11
10
O
MeO
Me Me Me
Me Me
Me H
Me
OTBS
74

Scheme XII

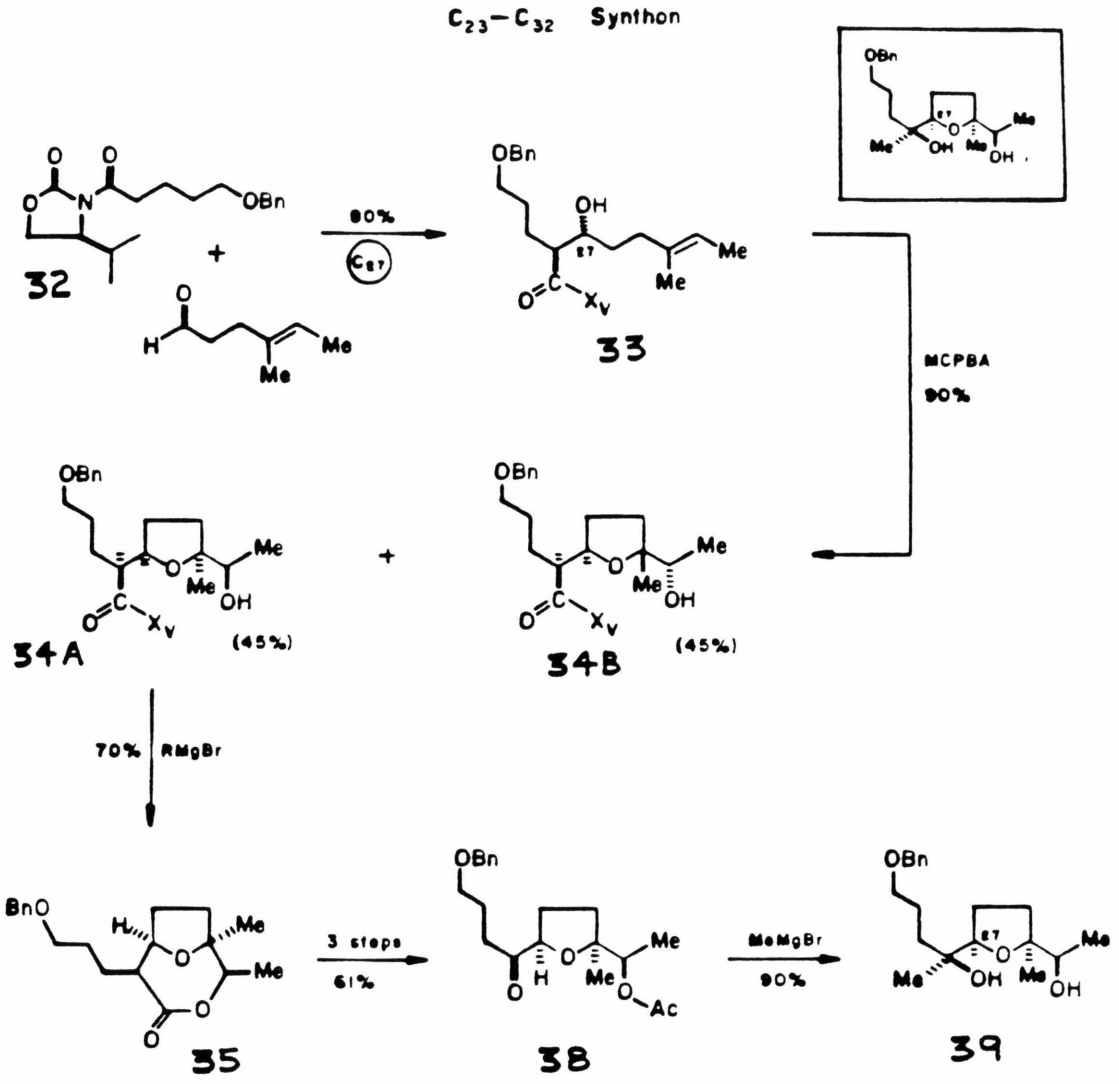


III. Results and Discussion

The strategic outline as described was implemented successfully for the construction of subunits **A-D**. Several technical difficulties did surface which were solved by novel tactics developed in the course of the synthetic effort.

Subunit A (C23-C32). The synthesis of synthon **39** is illustrated in Scheme XIII. The starting material, imide **32**, is obtained from the acylation of oxazolidone **1a**[27] with 5-benzyloxypentanoyl chloride[28] in 75% yield. Aldol condensation between the boron enolate of **32** and (E)-4-methyl-4-hexenal[29] proceeded in 80% yield to afford **33** with a diastereoselectivity of 97:3. Efforts in model systems to utilize the C27 hydroxyl stereocenter in a directed vanadium-catalyzed[30] t-butylhydroperoxide epoxidation produced mixtures favoring the undesired β-epoxide by 4:1 (Scheme XIV). Attempts to invert the β-epoxide's configuration following the procedure of Kishi[31] was met with little success. In view of the fact that the epoxidation could not be favorably directed, we were compelled to accept a non-selective but still efficient conversion of **33** to a 1:1 mixture of tetrahydrofurans **34a** and **34b**. Thus, treatment of the unpurified aldol adduct **33** with m-chloroperbenzoic acid (MCPBA) in ethyl acetate followed by the addition of glacial acetic acid to catalyze the cyclization resulted in the generation of three of the four stereocenters of synthon **39** in 36% overall yield. Tetrahydrofuran **34a** was readily separated from **34b** by flash chromatography on silica gel. The next transformation required the removal of the chiral auxiliary (X_V). Attempts at hydrolysis with aqueous hydroxide produced mainly amide products resulting from nucleophilic attack at the oxazolidone carbonyl. This problem appears

Scheme XIII


C23–C32 Synthon
32
80%
33
MCPBA
90%
34A
(45%)
34B
(45%)
70% RMgBr
35
3 steps
61%
38
MeMgBr
90%
39

Scheme XIV

Model System Studies at Directed Epoxidation

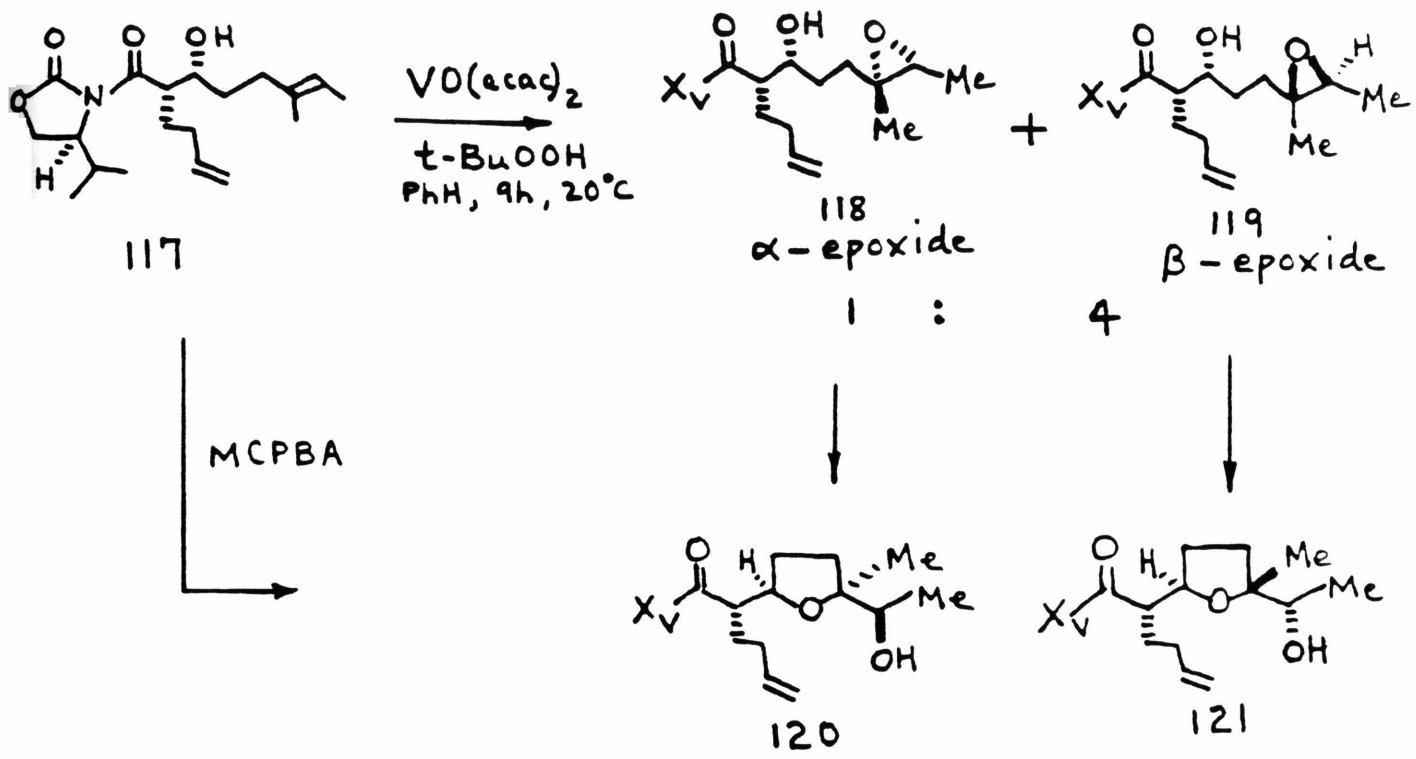


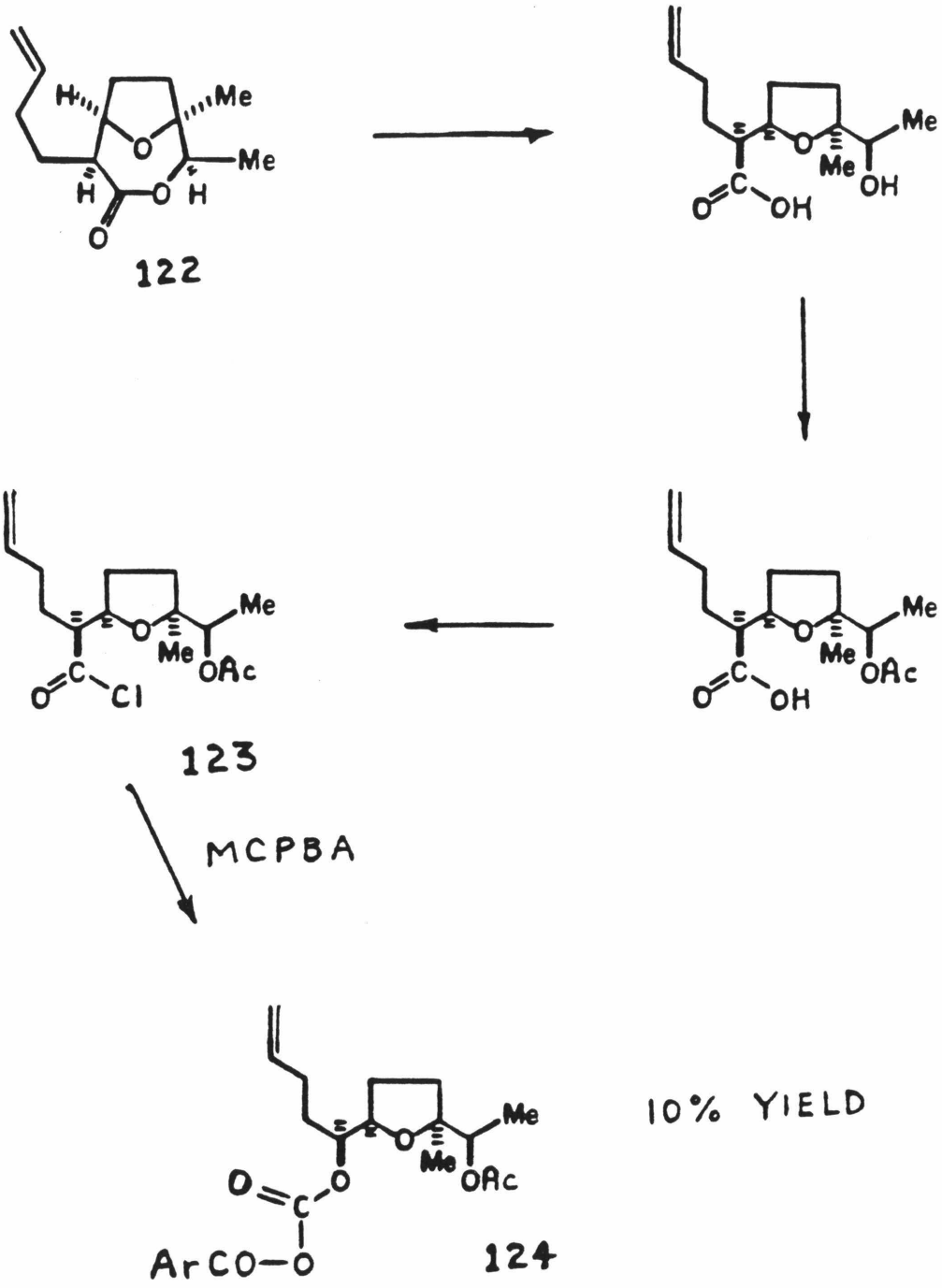
Table 1. MCPBA Results.

Temp (time)	Solvent	α : β : 117
0°C (9h)	CH_2Cl_2	1: 1: 0
0°C (9 h)	EtOH	1: 1: 0
-78°C (9 h)	CH_2Cl_2	19: 27: 51
-78°C (9 h)	EtOH	7: 13: 79

to manifest itself in cases where a large degree of α-substitution provides increased steric resistance to the approach of nucleophiles to the imide carbonyl. Fortunately, the presence of the C31 hydroxyl function in **34a** provided an intramolecular means to cleave off the chiral auxiliary. Treatment of **34a** with an equivalent of Grignard reagent at -78°C generated the magnesium alkoxide which cyclized smoothly to lactone **35** in 70% yield. This intramolecular trans-acylation concept has been applied in the synthesis of subunit C (vide infra) and has subsequently become incorporated as a design criteria in later generation chiral auxiliaries (Appendix II). When tetrahydrofuran **34b** was subjected to the same reaction conditions that transformed **34a** to **35**, largely starting material was isolated upon workup. This provided the assignment of stereochemistry to both diastereomers since the hydroxyl and carboxyl functions in **34b** are constrained spatially so as to preclude cyclization.

At this point our strategy (Section II, Scheme II) calls for the decarboxylation of the carboxyl function that has served to establish the key C27 stereochemistry. A model study investigating the viability of the carboxy-inversion approach is shown in Scheme XV. Lactone **122** was hydrolyzed with aqueous 2 N potassium hydroxide to the corresponding carboxylic acid. When the hydroxyl group was blocked as an acetate function the carboxylic acid at C26 was then converted to acid chloride **123**. Treatment of **123** with MCPBA was hoped to effect the carboxy-inversion reaction analogous to the examples of Denny[9a] and Suginome.[9b] Although this conversion was eventually realized, the yield of **124** remained an unacceptably low 10%. The impracticality demonstrated by this model

Scheme XV

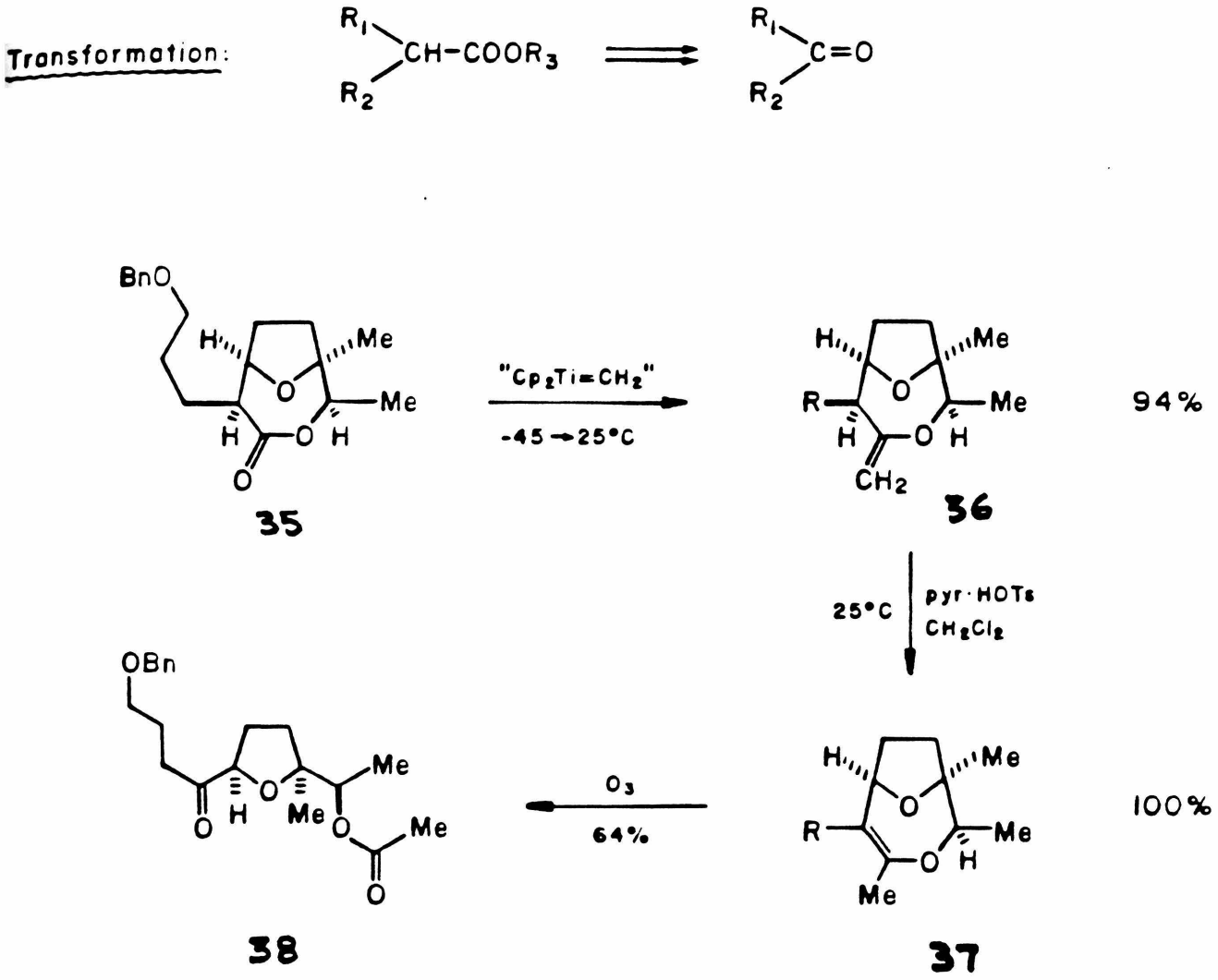


study compelled us to seek an alternative.

The critical transformation is illustrated at the top of Scheme XVI. Conceptually the most direct means would involve enolization, trapping the enolate as a ketene acetal, and ozonolysis. Therefore model lactone **122** was treated with lithium diisopropylamide and trimethylsilyl chloride in hopes of generating the ketene enol silyl ether. Unfortunately none could be isolated. Undaunted by these results we recognized that the desired transformation can be analogously effected through enol ether **37** (Scheme XVI). Thus, treatment of lactone **35** with 1.4 equivalents of Tebbe's reagent[32] at -45°C afforded enol ether **36** in high yield. Mild acid-catalyzed rearrangement of the exocyclic double bond to afford the thermodynamically favored endocyclic enol ether **37** proceeded in quantitative yields. Ozonolysis of **37** in the presence of red Sudan 7B dye[33] led to ketone **38** in 64% yield. The establishment of the last stereocenter in synthon **39** was accomplished by the addition of methylmagnesium bromide to **38** (Scheme XIII). Chelation-controlled[10] addition afforded a 6:1 mixture of diols in 90% yield. Synthon **39** was then converted to the requisite phosphonium salt intermediate as shown in Scheme XVII. The hydroxyl functions were blocked with t-butyldimethylsilyl trifluoromethanesulfonate (TBS triflate). Hydrogenolysis of the benzyl ether with palladium proceeded smoothly to afford alcohol **41** in quantitative yield. The corresponding iodide, **43**, was obtained via the mesylate in 99% overall yield from **41**. Treatment of the iodide with triphenylphosphine produced the phosphonium salt in 78% yield.

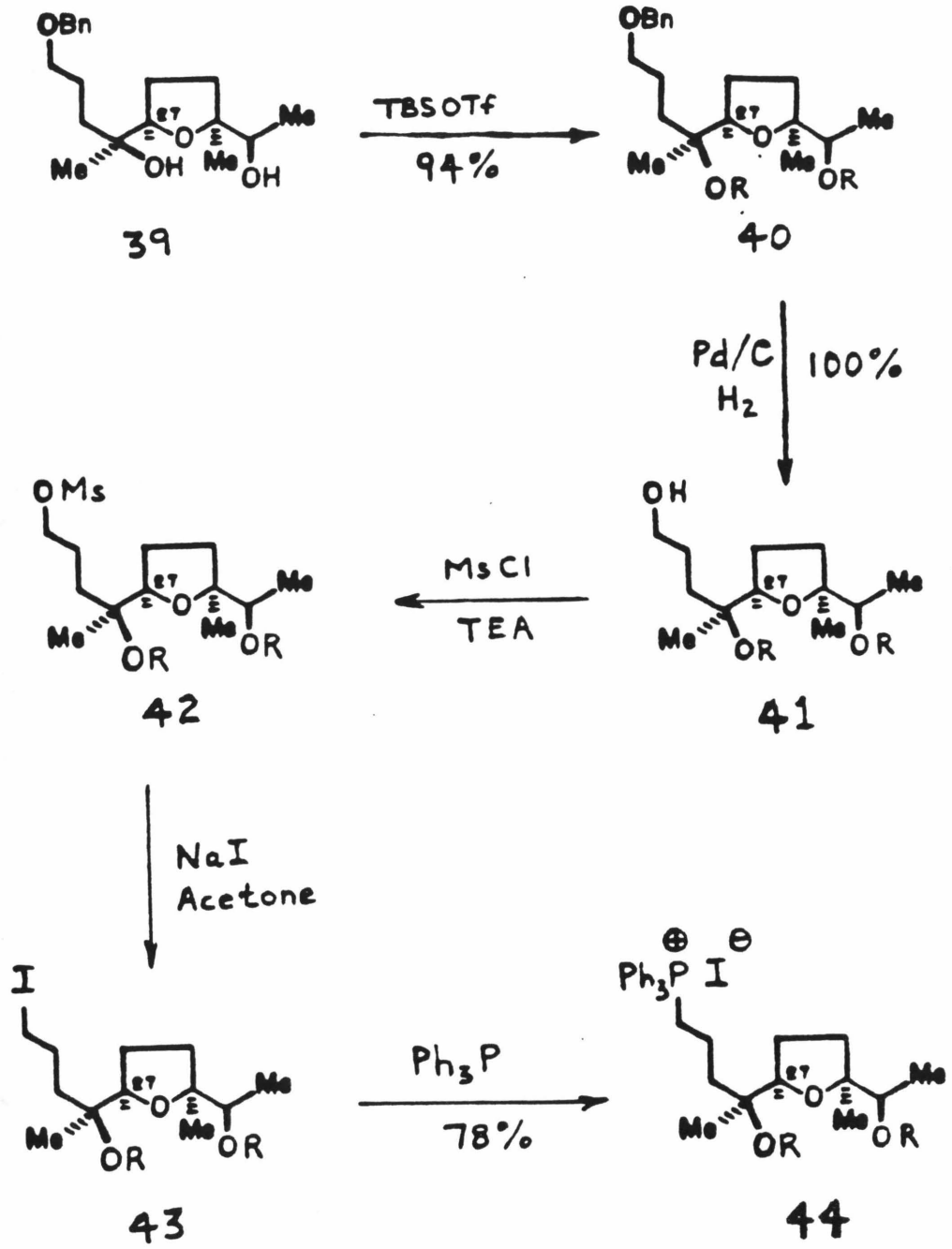
Subunit B (C17-C22) 65.[34] The construction of the C19 and C20 stereocenters via the chromium(II) crotyl anion addition to aldehyde **81** was attempted. Model studies condensing crotyl bromide and **81** resulted in a 60:40 ratio of

Scheme XVI


Transformation:
R1
CH-COOR3
R2
C=O
BnO
Me
Me
H
O
H
O
O
35
"Cp2Ti=CH2"
-45→25°C
R
CH2
36
94%
25°C
pyr·HOTs
CH2Cl2
OBn
O
H
Me
O
Me
38
O3
64%
37
100%

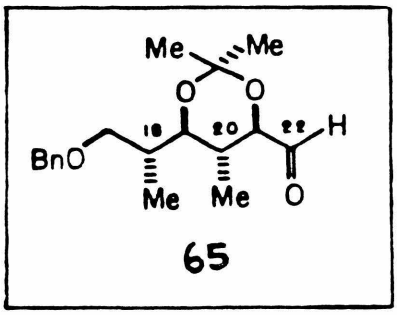
Scheme XVII

R = tBuMe$_2$Si—

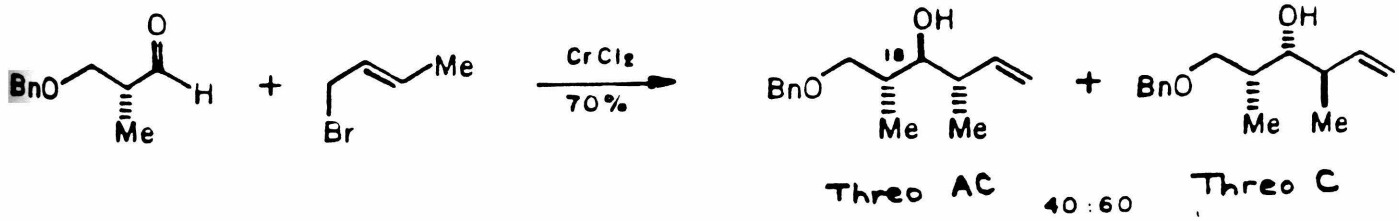


threo-Cram: threo anti-Cram products (Scheme XVIII). Since the desired threo anti-Cram product proved to be the minor constituent in the mixture, this approach was abandoned. A novel solution to the threo relative stereochemistry problem in this subunit is presented in Scheme XIX. An aldol condensation of crotonate imide[35] **125** with aldehyde **81** was projected to lead to erythro adduct **83**. A simple rotation of the Δ(C19-C20) bond reveals the latent threo-relationship of **83** required for elaboration to synthon **87** (Scheme XIX). Upon enolization with di-n-butylboron triflate and triethylamine base in dichloromethane, imide **125** condensed with **81** to afford a white crystalline adduct **83**. Reduction of the corresponding preformed boron complex of **83** with $LiBH_4$ afforded diol **84**. Subsequent mono-tosylation and lithium triethylborohydride reduction produced the desired synthon **87**.

Scheme XVIII



65

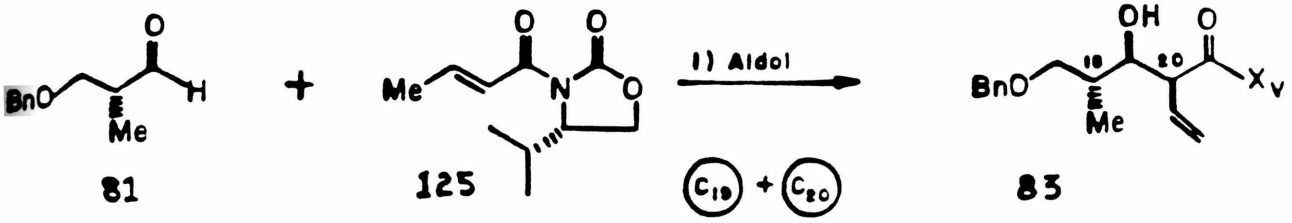


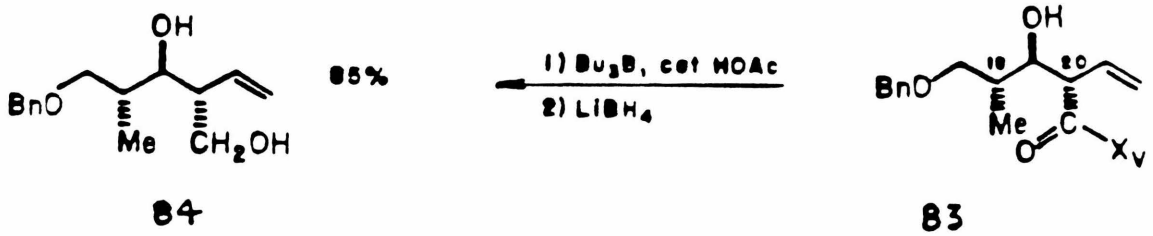
Threo AC 40:60 Threo C

R. Dow[34]

Scheme XIX

$C_{17}-C_{22}$ Sython





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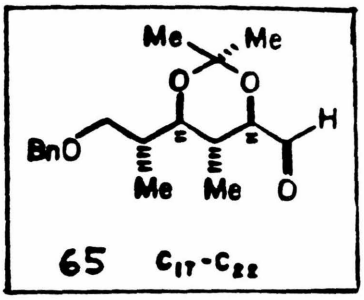
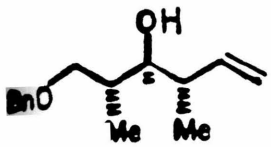
The introduction of the remaining two hydroxyl functions and final elaboration to subunit **65** is shown in Scheme XX. Cis-hydroxylation with catalytic amounts of osmium tetroxide and N-methylmorpholine-N-oxide afforded a 78:22 mixture of which the desired isomer **88** is the major component. The minor isomer **89** was speculated to be convertible to **65** at the final stage based on the assumption that the peripheral substituents of the six-membered acetonide ring will prefer the all-equatorial configuration shown. The mixture of triols **88** and **89** was treated with 1.5 equivalents of t-butyldiphenylsilyl chloride, triethylamine, and a catalytic amount of N,N-dimethylaminopyridine in dichloromethane at 0°C to selectively block the primary alcohol function. Ketalization with 2,2-dimethoxypropane and camphor sulfonic acid was followed by the removal of the silyl group with tetra-n-butylammonium fluoride to afford **91** in 99% yield. Finally, oxidation of **91** afforded aldehyde **65** (96%).

Subunit C (C11-C16) 92.[34] The synthesis of this subunit proved to be a straightforward exercise following the strategy outlined in Section II. Imide **1b** was enolized and alkylated with 1-bromo-3-phenyl-2-propene to afford almost exclusively diastereomer **93** (Scheme XXI). Reduction with lithium aluminum hydride (LAH) provided the primary alcohol precursor to iodide **97**. Subsequent transformation utilizing conventional means produced the iodide in 66% overall yield from **93**. Alkylation of the prolinol-derived amide[15a] **98** with iodide **97** afforded a 36:1 selection favoring the desired expected product **99**. The chiral auxiliary was then removed by acid-catalyzed hydrolysis. The corresponding carboxylic acid **100** was reduced with LAH to alcohol **101**. The hydroxyl function was protected with t-butyldiphenylsilyl chloride before the olefin was ozonized to unmask the oxygen functionality at C16. The ozonolysis

Scheme XX

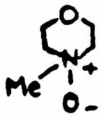


65 C_{17}-C_{22}

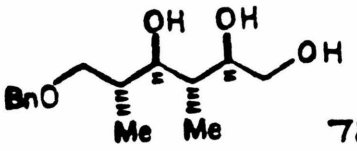


87

OsO_4



Acetone

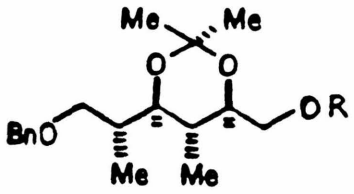


88

78 : 22 (epi-C21)

DMAP, Et_3N

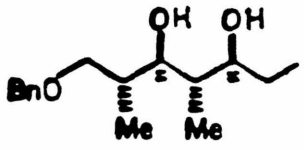
$Ph_2(t\text{-}Bu)SiCl$



90

CSA

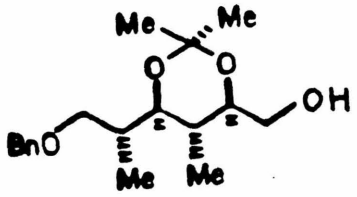
98 %



80

89 % overall

$n\text{-}Bu_4N^+F^-$

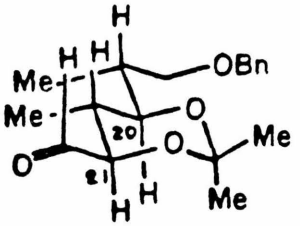


91

DMSO

$pyr.\text{-}SO_3$

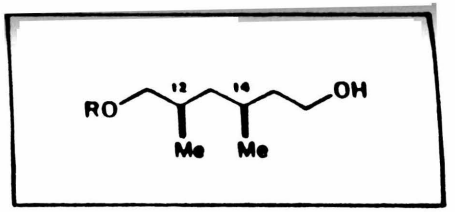
96 %

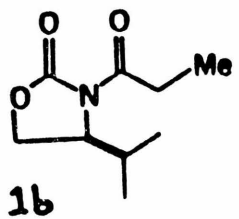


65

R. Dow[34]

Scheme XXI



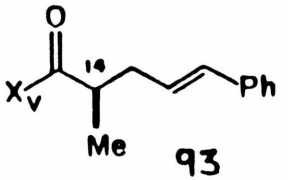


1b

LDA, THF

Br Ph

C_{14} ≥99:1



93

84%

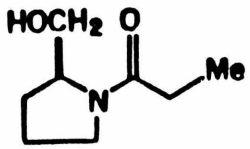
1) $LiAlH_4$

2) MsCl, Et_3N

3) NaI

97

66% I

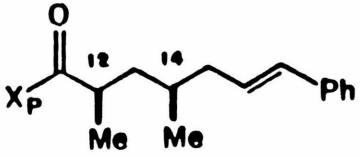


98

KH, LDA

I

C_{12} 36:1

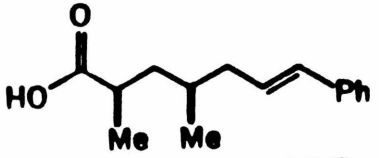


99

83%

1.0 N HCl

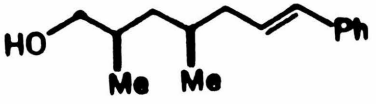
115°C, 8 h



100

91%

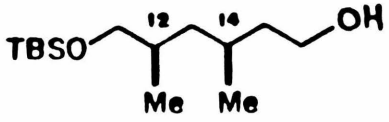
$LiAlH_4$



101

1) $Ph_2(t\text{-}Bu)SiCl$

2) O_3; $NaBH_4$

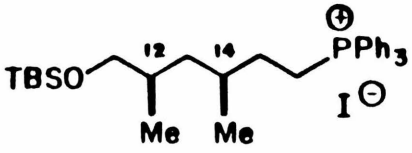


92

1) MsCl

2) NaI

3) Ph_3P



105

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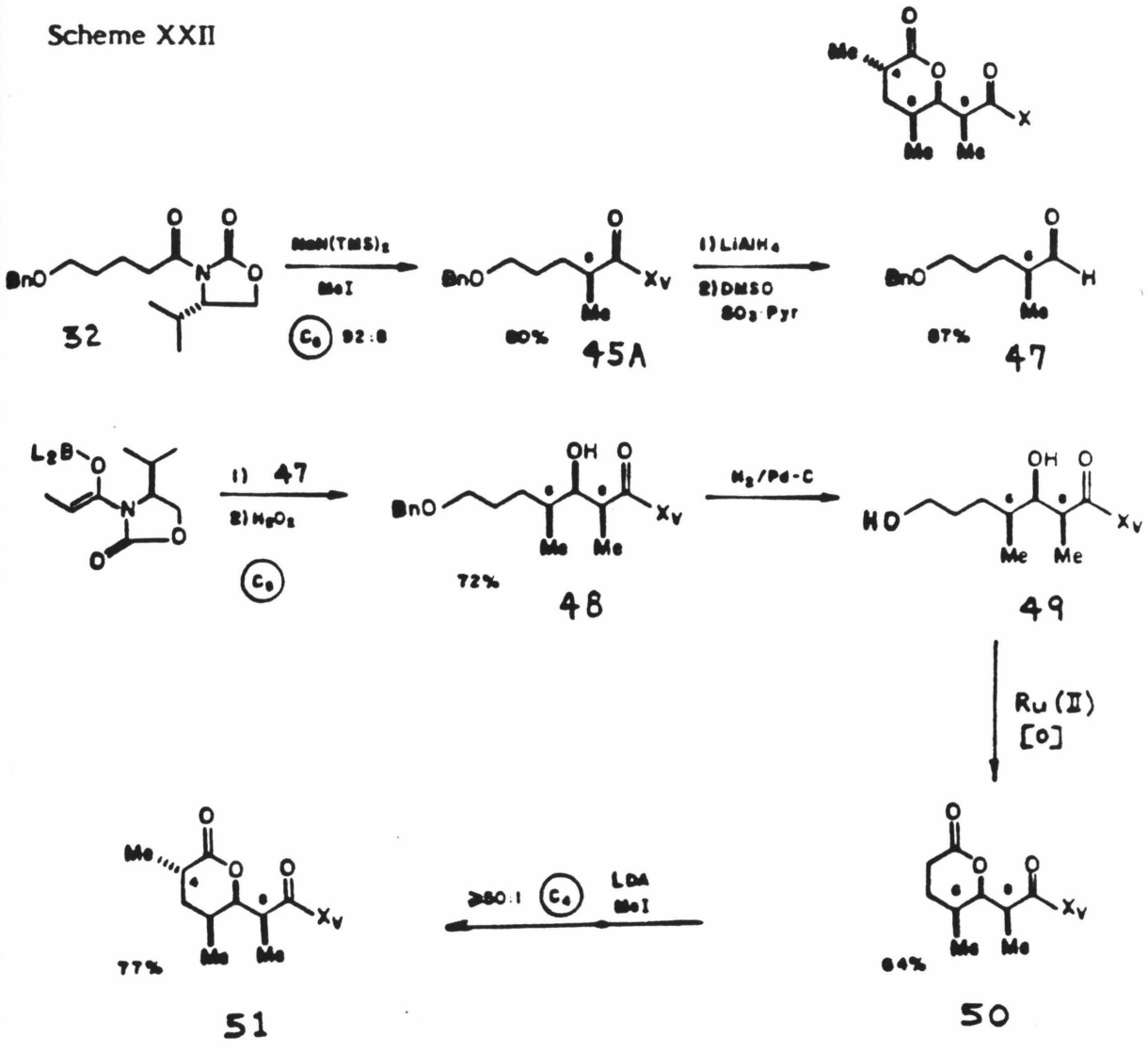
was followed by a sodium borohydride reductive workup to afford synthon **92**. Conversion of **92** to phosphonium salt **105** proceeded smoothly following established methods (vide infra). The overall yield of **105** from **100** was 62%.

Subunit D (C1-C10) 64. The major task involved with the construction of **64** proved to be the orchestration of functional group transformations. The three stereocenters were efficiently and easily established in the synthesis of lactone **51** (Scheme XXII). Methylation of imide **32** produced a 92:8 mixture of diastereomers favoring the desired isomer **45a**. Subsequent reduction (LAH) cleaving off the chiral auxiliary and oxidation provided the optically active (84% ee) aldehyde, **47**. Aldol condensation of the boron enolate of 1b with **47** afforded adduct **48** with a diastereoselection of 97:3.[36] Hydrogenolysis of the benzyl group proceeded smoothly to afford the highly crystalline diol **49**. This provided a convenient point to isolate **49** from the minor isomeric products generated in all prior steps through a simple recrystallization. A one-pot two- step oxidation of diol **49** to lactone **50** was achieved using the Sharpless procedure.[37] Enolization and alkylation of **50** resulted in a stereoselection of $\geq$50:1 to afford lactone **51** as a crystalline solid. This selection was projected by assuming that the enolate would prefer the equatorial orientation of the large substituent (R_L) exhibiting a diastereofacial bias through the axial methyl substituent (bottom of Scheme XXII).

With lactone **51** in hand, our plan was to chain-extend at C3 by a two-carbon unit followed by a deoxygenation of the C7 oxygen function (Section II). Although the selective reduction of the lactone carbonyl in the presence of the imide was easily accomplished using disiamylborane,[38] the resulting

Scheme XXII

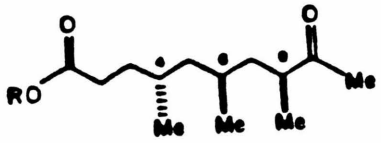


C_4-Asymmetric Induction

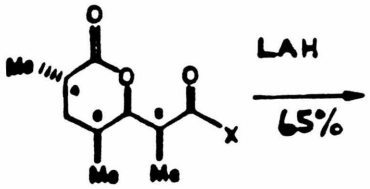
lactol **111** (Scheme VI) failed to undergo reaction with any phosphorous ylid. This obstacle was circumvented by reducing the lactone-imide with LAH to triol **52** (Scheme XXIII). Exploiting the proximity of the C7 and C9 hydroxyl groups one was able to effect a regioselective ketalization leading to acetonide **53** in 65% overall yield. Subsequent oxidation to the corresponding aldehyde and chain extension with carbomethoxymethylene triphenylphosphorane produced intermediate **55** in excellent yield. The double bond was hydrogenated and the ketal was then removed to afford diol **57**. Selective protection of the primary hydroxyl function was achieved with t-butyldimethylsilyl chloride. The required deoxygenation at C7 was accomplished using the Barton[19] procedure. Treatment of **58** with sodium hydride, carbon disulfide, and methyl iodide afforded the xanthate which was reduced with tri-n-butyltin-hydride to **60** in 80% overall yield. This advanced intermediate was easily converted to ketone **64** in four steps: desilylation with fluoride ion; oxidation to aldehyde **62**; nucleophilic addition of a methyl group with lithium dimethylcuprate to afford a 1:1 mixture of isomers at C9; and final oxidation of the C9 hydroxyl stereocenter to the ketone.

Assemblage of C17-C32 Synthon. The successful construction of the four subunits sets the stage for their assembly. According to plan, aldehyde **65** was condensed with phosphorane **126** under "salt-free" conditions[39] to afford a 97:3 ratio of Z:E olefinic products (Scheme XXIV). The silyl blocking groups were removed with fluoride ions and the resulting diol was cyclized with mercuric acetate to intermediate **68**. This intramolecular cyclization proceeded with a diastereoselection of $\geq$13:1 in favor of the correct C23 stereochemistry. Evidence for the integrity of this stereocenter

Scheme XXIII

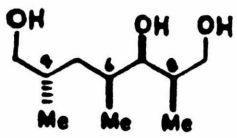


64



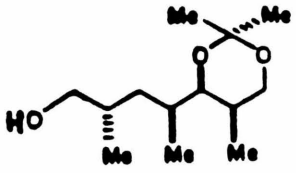
51

LAH, 65%



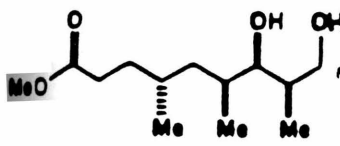
52

Acetone, H^+, 100%



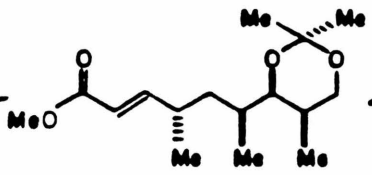
53

$pyr.\cdot SO_3$, DMSO, 91%



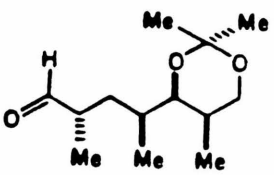
57

98%
1) H_2, Pt
2) H^+, MeOH, 100%



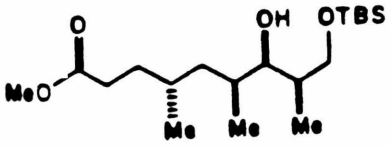
55

$R_3P{=}CHCO_2Me$, 90-99%



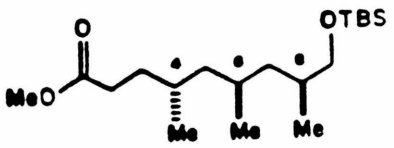
54

90% TBSCl



58

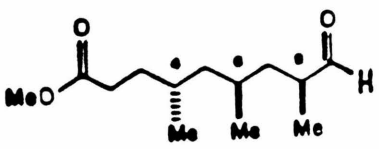
MeI,
1) NaH, CS_2
2) Bu_3SnH



60

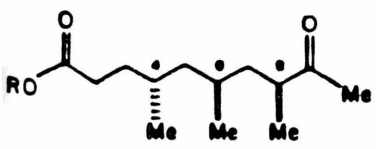
80% (2 steps)

1) $n\text{-}Bu_4N^+F^-$, 98%
2) DMSO/pyr.-SO_3, 95%



62

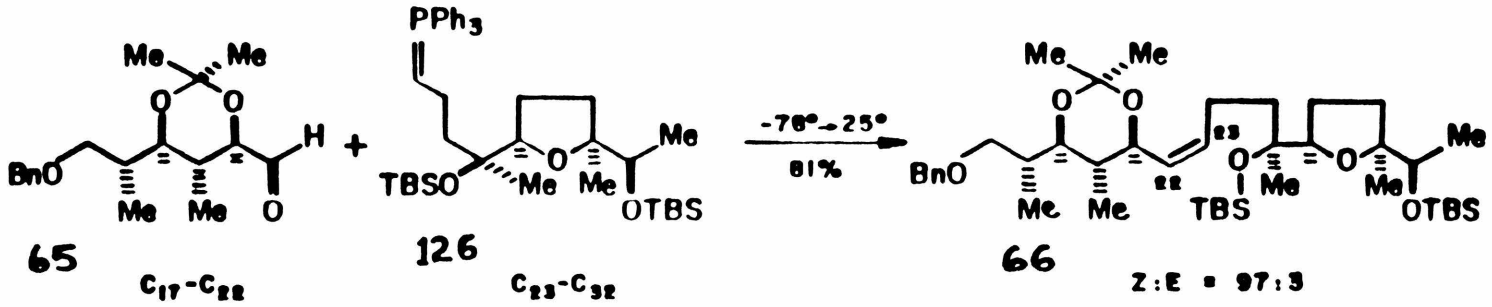
1) $LiCuMe_2$, 87%
2) DMSO/pyr.-SO_3, 90%

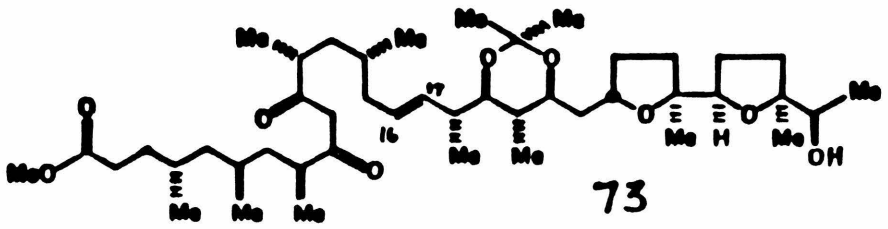


64

Scheme XXIV

Assemblage of C_{17}-C_{32} Synthon

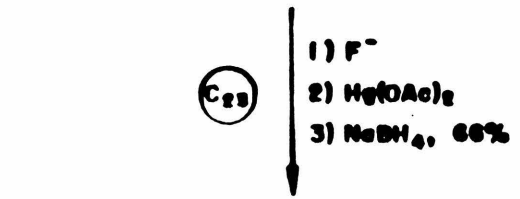


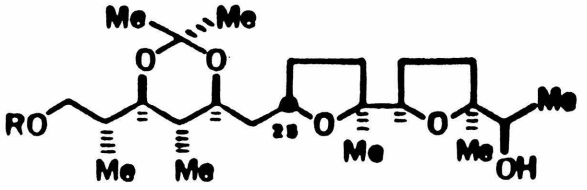


From Ionomycin (Scheme XII)

i) OsO_4, $NaIO_4$ → cleavage of Δ(16-17) bond

2) LAH → reduction



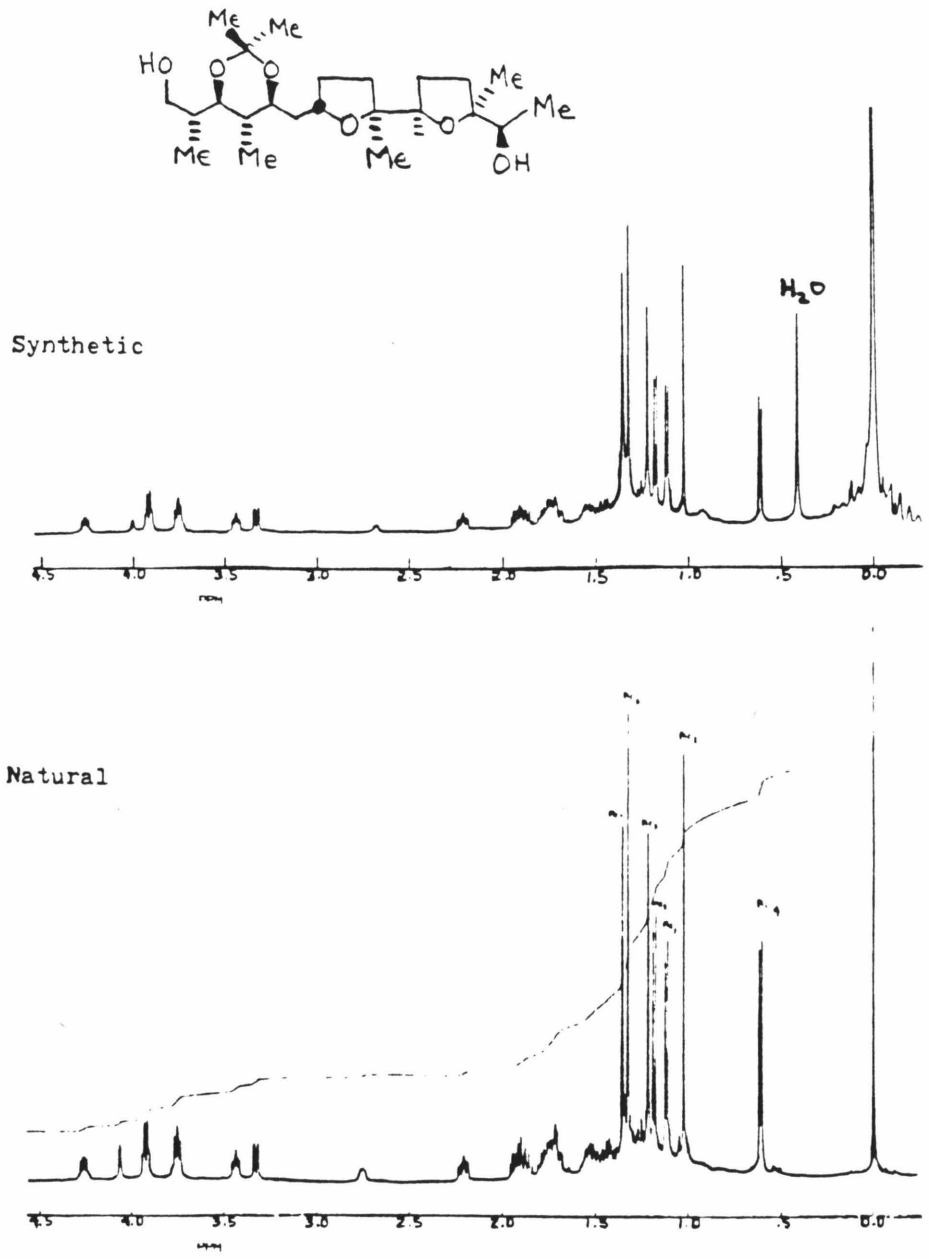


R = Bn → R = H

68 75

as projected (Section II, Scheme VII) was obtained when a comparison of the spectroscopic characteristics (IR, 500 MHz ^{1}H NMR, $(\alpha)_D$, ^{13}C NMR) of synthetic **75** matched those of a sample of **75** derived from the degradation of natural ionomycin. The particularly diagnostic ^{1}H NMR (500 MHz) spectrum of both "natural" and synthetic **75** is illustrated in Figure 3.

Final Assemblage of 74 (C1-C32)[34] Despite the spectacular success enjoyed in the model system (Section II, Scheme VIII), the attempts to couple subunit **C** (C11-C16) with intermediate **127** via a Schlosser modified Wittig reaction resulted in low yields of the desired product (a 60:40 cis:trans isomer ratio was obtained). Therefore, the second approach utilizing sulfone **115** (Scheme XXV) was tried and found to be viable. Thus, the two-step procedure afforded an 86:14 mixture of E:Z olefinic products in 80% yield. This mixture was treated with a dilute THF solution of tetra-n-butyl-ammonium fluoride at 25°C which selectively removed the silyl group at the least hindered alcohol function (C11 primary-OH). The E olefinic product was then isolated from the Z isomer by silica gel flash chromatography. Swern[14] oxidation of **130** afforded aldehyde **116** (Scheme XXVI) which when condensed with the boron enolate of ketone **64** produced a (1:1) mixture of aldol adducts at C11 in 75-85% yield. At this point a variety of oxidation procedures were tried to convert the aldol adducts to **74**. To date the most promising approach utilizes the Swern oxidation which produced mainly intermediate **132** (Fig. 4). It appears that the initial oxidation of the aldol adducts proceeds to **74** which competitively reacts with the chlorodimethyl-sulfonium species to produce the C10 dichloro-substituted compound **132**. When **132** was treated with zinc-copper couple in aqueous dioxane a smooth

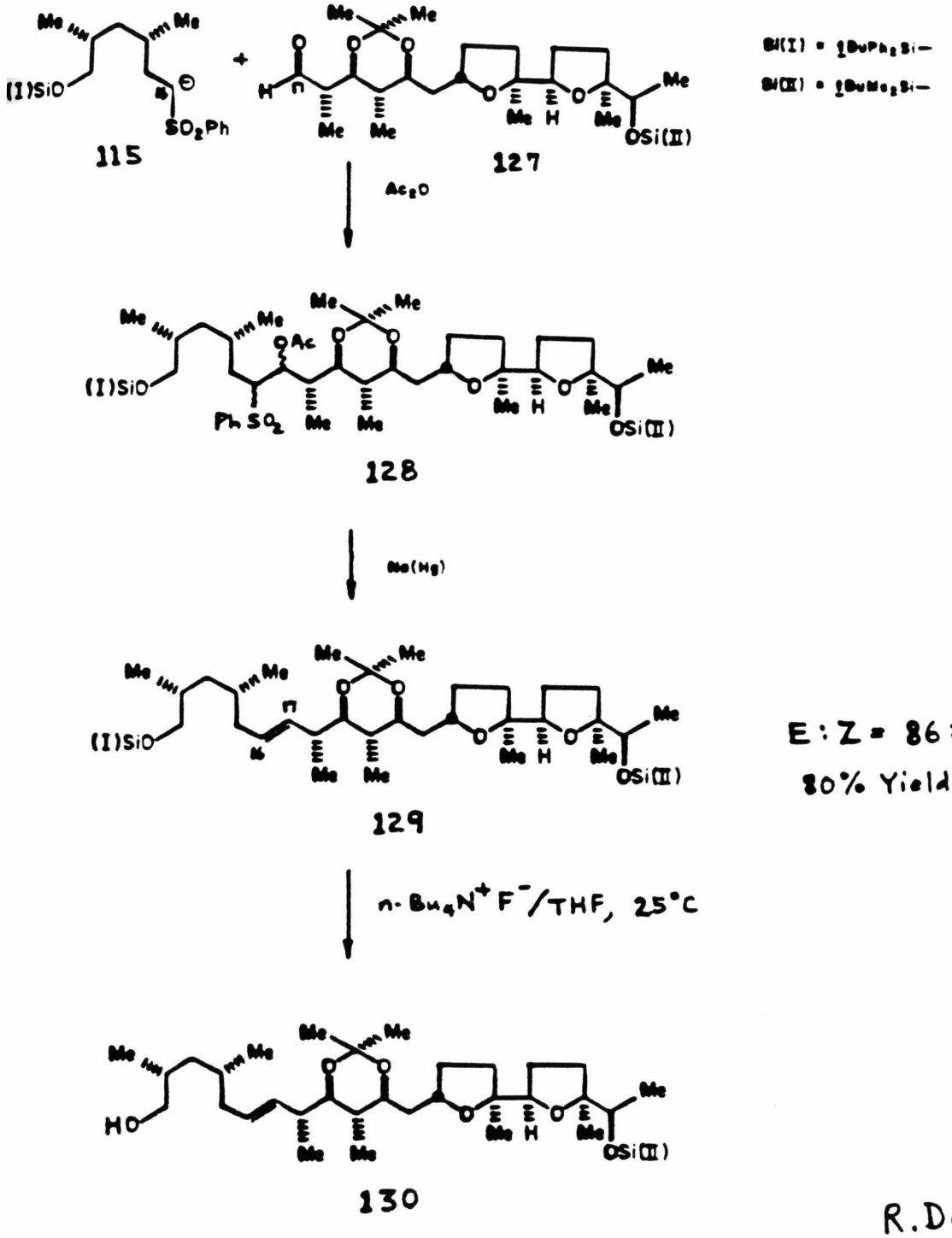


500 MHz NMR Spectra (benzene-d_6), TMS reference.

Figure 3

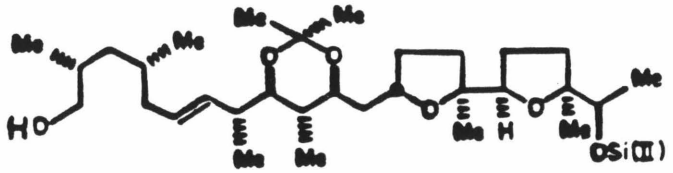
Scheme XXV

C_{16}-C_{17} Bond Construction



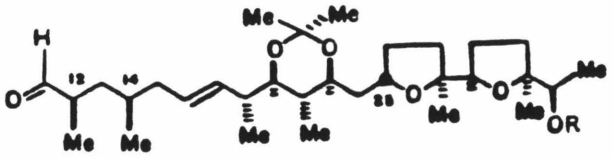
R. Dow[34]

Scheme XXVI

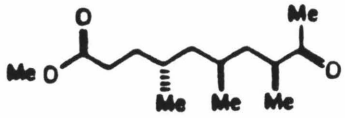


130

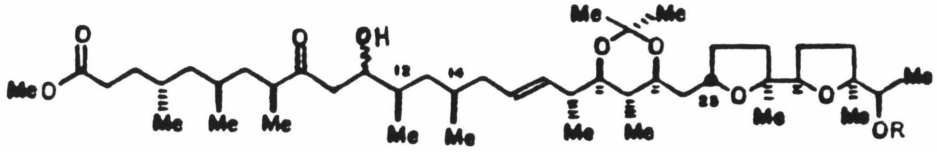
DMSO | ClCOCOCl



116

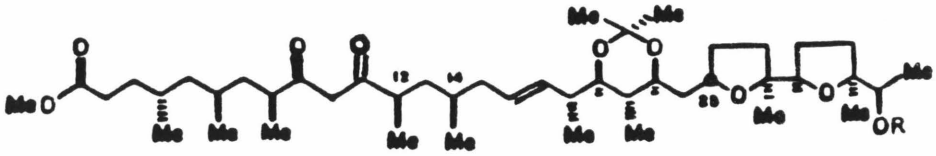


Bu_2BOTf, R_3N



[O]

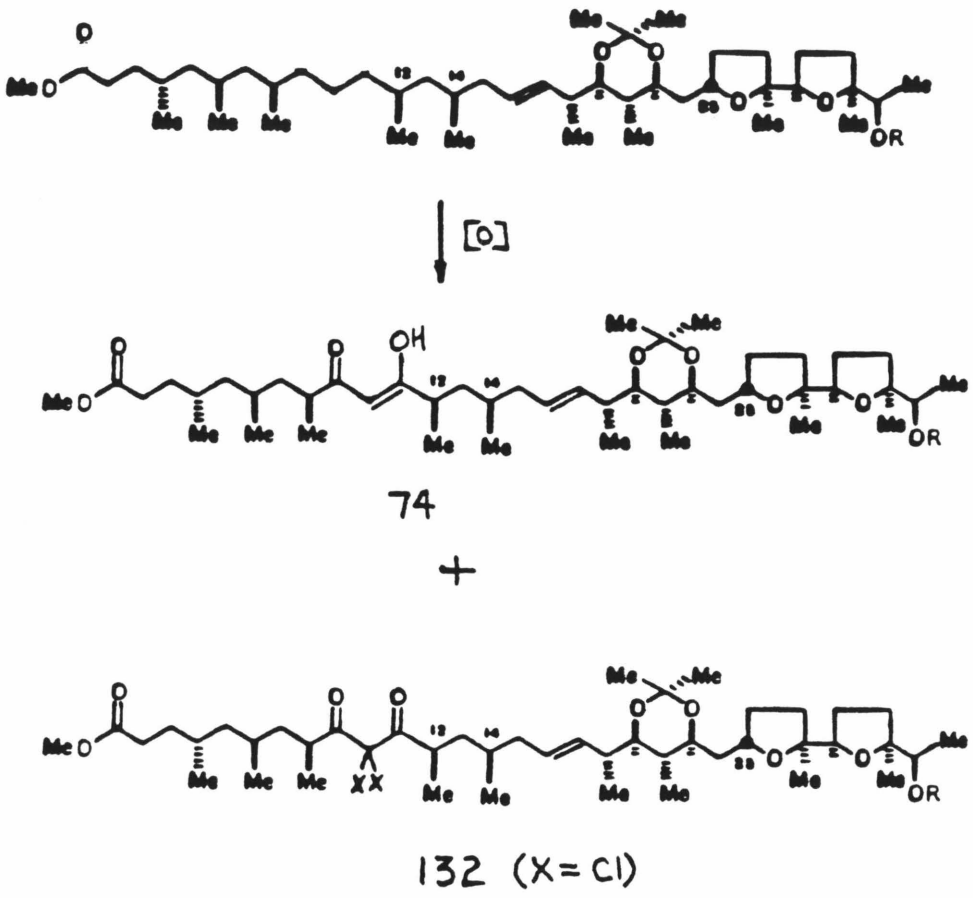
R = -Si t-BuMe$_2$



74

R. Dow[34]

Figure 4



74

+

132 (X = Cl)

R. Dow [34]

reduction to **74** occurs. Therefore this two step process established the correct oxidation state at C11 leading to synthetically derived ionomycin containing three protecting groups. The authenticity of synthetic **74** was determined by matching its 500 MHz ^{1}H NMR and IR spectrum with those of naturally derived **74**.

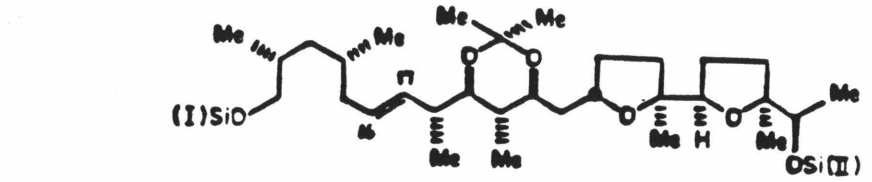
Derivatization and Deprotection Studies of (-)-Ionomycin. In conjunction with our intent to synthesize (-)-ionomycin, we initiated a series of experiments which would enable us to check the authenticity of the subunit synthesized and to determine which blocking groups one may incorporate into structure **74**. A 1 g sample of the calcium salt of (-)-ionomycin was obtained as a gift from Squibb Inc. The free acid[1] was obtained by shaking a hexane solution of the calcium complex with 1 N aqueous hydrochloric acid (Scheme XII, Section II). Treatment of the acid with diazomethane produced the methyl ester **72** in quantitative yield. The ester was then treated with 2,2-dimethoxypropane and pyridinium tosylate to afford derivative **73**. Silylation of the C31 hydroxyl function was achieved by treatment of **73** with TBS triflate followed by a dilute solution of tetra-n-butylammonium fluoride to desilylate the enol silyl ethers at C9 or C11 providing an authentic sample of **74** (see Scheme XXVI). Each derivative was purified and fully characterized including satisfactory C and H combustion analyses. The Δ(16-17) olefinic bond of **73** was cleaved by osmium tetroxide-sodium periodate to provide an authentic fragment (**75**) of the right half of ionomycin. This was used to check the prediction of the C23 stereocenter set via the intramolecular cyclization reaction (vide infra).

The final phase of this project involved the experiments which determined

the suitability of the protecting groups chosen for use in the subunits which must be removed after assemblage of the entire backbone structure of ionomycin. Derivative **74** was desilylated with a dilute THF solution of hydrogen fluoride-pyridine complex at 25°C to afford **73** in 91% yield. The lack of epimerization of the potentially labile stereocenters at C8 and C12 was established by examination of the 500 MHz ^{1}H NMR spectrum of **73**. The acetonide function's removal was investigated in a series of experiments. Dilute aqueous acids (15% aqueous trifluoroacetic acid, 2 M HCl/THF, H_2O/THF-pyridinium tosylate, 70% acetic acid, oxalic acid/THF-H_2O, ethylene glycol/DME-toluene sulfonic acid) are ineffective in the removal of the ketal. By thin layer chromatographic analysis these systems were slow (weeks) and many side-products were formed when the temperature of these reactions was raised above 50°C. Lewis acid catalysis was also tried with no success. When a 1,2-dimethoxyethane or methylene chloride solution of **73** was stirred with wet magnesium sulfate or calcium chloride no reaction was observed after three days. The use of boron trifluoride-etherate resulted in the destruction of the substrate. Effective conditions were found using methanol as the solvent and a variety of acids (trifluoroacetic acid, Dowex resin, pyridinium tosylate) as catalyst that will remove the ketal in a period of less than 20 h. However, the resulting methyl ester **76** was found to have undergone epimerization under these mild conditions. The evidence for this was found by a careful comparison of the 500 MHz ^{1}H NMR spectrum of **72** and **76** (iso-ionomycin, methyl ester) in which the methyl region as well as the chemical shifts of the low field protons do not match. A more distinct mismatch was found when **76** was hydrolyzed with lithium hydroxide to the carboxylic acid and treated with

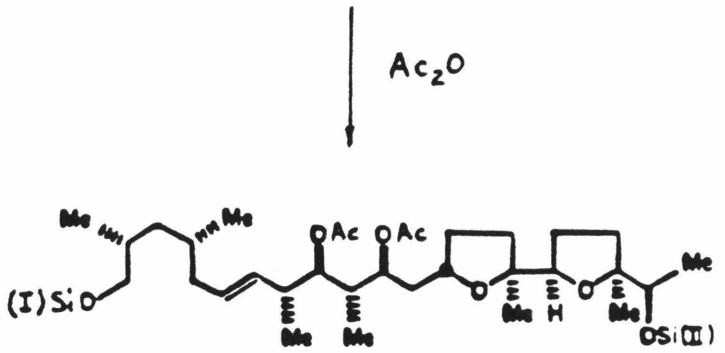
Ca^{+2} ions to form the calcium complex. The NMR spectrum of this complex (iso-ionomycin, calcium complex) was markedly different from that of the sample provided by Squibb. To check that epimerization was indeed responsible for such discrepancies a control experiment was done in which **72** was subjected to the deketalization conditions (methanolic pyridinium tosylate, 20°C, 17 h). Upon workup a methyl ester that was identical in spectral and physical properties to **76** was obtained. It was apparent given these results that an alternative protecting group must be considered which may be exchanged for the acetonide function at the stage before the final aldol condensation (Scheme XXVII). Thus intermediate **129** may be deketalized to afford diol **131**. A possible acetylation of the diol is proposed which should survive the boron aldol condensation and subsequent oxidation. Finally treatment of the methyl ester with lithium hydroxide should hydrolyze all the ester groups present in the structure. The proper conditions for the hydrolysis of methyl ester **72** has already been found. (-)-Ionomycin was recovered when a dimethoxyethane solution of **72** was treated at 20°C for 1 h with 1 N aqueous lithium hydroxide followed by acidification with 1 N HCl. No sign of base-catalyzed epimerization was found when the 500 MHz ^1H NMR spectrum of the recovered ionomycin and natural ionomycin were compared.

Scheme XXVII

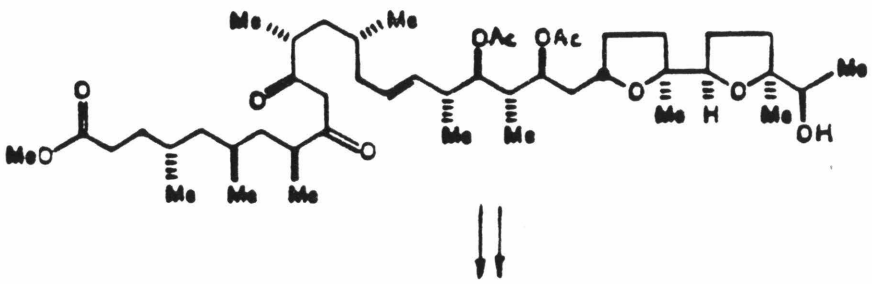


129

131



132



Ionomycin

IV. Summary

The enantioselective alkylation and aldol methodology developed in our laboratories have provided the means to the efficient synthesis of subunits **A-D**. To date, we have successfully constructed **74**, an advanced intermediate containing all the stereochemistry and the entire carbon backbone of (-)-ionomycin. Efforts are continuing toward the ultimate completion of this project.

Experimental Section

Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman 4210 spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm on the δ scale from internal tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant (Hz), and interpretation. 500 MHz ^{1}H NMR spectra were recorded on a Bruker WM-500 Spectrometer at the Southern California Regional NMR Facility. ^{13}C NMR spectra were recorded on a Varian Associates XL-100 (25.2 MHz) or a JEOL-FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Mass spectral analyses were performed by the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln, on a Kratos MS-50 TA spectrometer. Combustion analyses were performed by either Spang Microanalytical Laboratory (Eagle Harbor, Michigan) or Galbraith Laboratories, Inc. (Knoxville, Tennessee). Optical rotations were recorded on a Jasco DIP-181 digital polarimeter at the sodium D line and are reported as follows: $[\alpha]_D$, concentration ($\underline{c}$ = g/100 mL), and solvent.

Analytical gas-liquid chromatography was carried out on a Hewlett Packard 5880A Level 3 gas chromatograph equipped with a split mode capillary injection system and a flamed ionization detector, using a 25 m x 0.02 mm flexible fused silica capillary column wall-coated with Carbowax 20M or methyl silicone (SP-2100), or a 30 m x 0.32 mm fused silica capillary collumn

wall-coated with SE-54. Unless otherwise noted, injector and detector temperatures were 250°C. Flash chromatography on silica gel was performed using a forced flow[41a] of the indicated solvent system on EM Reagents Silica Gel 60 (70-230 mesh), or for large scale preparative work on EM Reagents Silica Gel 60 (230-400 mesh). Chromatography column dimensions are reported within parentheses following the type of solid support used. Medium pressure liquid chromatography (MPLC) was carried out using EM Reagents Lobar Silica Gel 60 prepacked columns (column size indicated) with a Fluid Metering Inc. Model RP-SY Lab Pump in conjunction with an ISCO Model UA-5 Absorbance/Fluoresence Monitor with Type 6 Optical Unit (2 mm path length cell, 15 μL volume). Analytical thick-layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Preparative thick-layer chromatography was performed using EM Reagents 2 mm silica gel 60-F plates (20 cm x 20 cm).

Unless otherwise stated, all solvents and reagents were dried or freshly distilled prior to use. Tetrahydrofuran (THF), diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, triethylamine, diisopropylethylamine, and boron trifluoride etherate were distilled from calcium hydride. Dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPT) were distilled from calcium hydride and stored over activated 4 Å molecular sieves. Reagent grade dimethyl sulfoxide was dried[41b] with activated 4 Å sieves and used as received. Alkyl halides were passed down a column of activity I alumina immediately prior to use. All other reagents were used as received.

Unless otherwise noted, all non-aqueous reactions were carried out

under a dry nitrogen atmosphere using oven-dried glassware.

5-Benzyloxy-1-pentanol.[42] To a 2-L round-bottom flask equipped with a mechanical stirrer and reflux condenser was added 20 g (0.42 mol) of 50% sodium hydride-oil dispersion and 400 mL of cyclohexane. This heterogeneous mixture was stirred vigorously while 42 mL (0.40 mol) of commercially available 1,5-pentanediol was added over a period of 5 min. After heating the slurry at reflux for 4 h, the grey alkoxide was cooled to 25°C. Cautious addition of 96 mL (0.81 mol) of benzyl bromide over a 5-10 min period was followed by refluxing the stirred mixture an additional 18 h. The cooled solution was then poured into a separatory funnel containing 200 mL of water to dissolve the white precipitate (NaBr). The organic layer was washed with 2 x 100 mL of a 2% aqueous solution of potassium hydroxide. The combined aqueous washes were extracted with 200 mL of ether. The combined organic layers were dried over anhydrous magnesium sulfate, concentrated in a rotary evaporator and distilled at reduced pressure to afford 56.1 g (72%) of 5-benzyloxy-1-pentanol (bp 138-140°C, 1 mm Hg) as a colorless oil: IR (neat) 3400, 3109, 3080, 3045, 2950, 2880, 1960, 1880, 1820, 1715, 1499, 1457, 1368, 1209, 1100, 905, 730, 690 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.49 (m, 6H), 2.60 (s, 1H, -O<u>H</u>), 3.40 (t, 2H, J = 6 Hz, HOC<u>H</u>$_2$-), 3.45 (t, 2H, J = 6 Hz, RO-C<u>H</u>$_2$-), 4.40 (s, 2H, PhC<u>H</u>$_2$O-), 7.20 (s, 5H).

5-Benzyloxypentanoic Acid.[28] To a 2-L Erlenmeyer flask was added 56 g of 5-benzyloxypentanol and 700 mL of reagent acetone. While cooling the solution in an ice bath, a solution of Jones reagent (40 g CrO_3 in 150 mL of water and 35 mL of conc. H_2SO_4) was added at a rate which maintained the reaction temperature at <u>ca.</u> 25°C. Upon completion of addition, the ice

bath was removed and the reaction stirred at 20°C for 30 min. Isopropanol was then added to quench excess oxidant. The acetone was concentrated in vacuo to give the dark green chromium salts which were hydrolyzed with 650 mL of water. The carboxylic acid was extracted with ether, and the combined ethereal layers were extracted with 3 x 100 mL of 2 N KOH. The aqueous extracts containing the carboxylate salt was washed with 2 x 100 mL of CH_2Cl_2 to remove organic impurities. Reacidification of the aqueous layer with conc. HCl was followed by ether extraction. The ethereal solution was dried ($MgSO_4$) and concentrated in vacuo to afford 43.2 g of product (72%) as a yellow oil: IR (neat) 3055, 2950, 2880, 1710, 1495, 1452, 1413, 1367, 1245, 1210, 1175, 1100, 1024, 925, 730 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.67 (m, 4H), 2.30 (t, 2H, J = 6 Hz, -CH_2CO_2H), 3.40 (t, 2H, J = 6 Hz, RO-CH_2), 4.40 (s, 2H), 7.20 (s, 5H), 11.63 (s, 1H, -CO_2H). The title compound was carried on to the subsequent experiment without further characterization.

5-Benzyloxypentanoyl Chloride.[28] To 50.6 g (0.24 mol) of 5-benzyloxypentanoic acid in a 500 mL flask, protected from moisture by a calcium chloride drying tube, was added 200 mL of carbon tetrachloride. This solution was cooled to 0°C before 43 mL (0.49 mol) of oxalyl chloride was added. The reaction was stirred at 0°C for 2 h and 20°C for 4 h. Excess oxalyl chloride and solvent was removed on a rotary evaporator. To the residue was added 200 mL of methylene chloride followed by a second concentration to ensure the removal of volatile by-products. The residue was maintained at reduced pressure (<1 mm Hg) on a rotary evaporator for 10 h to afford 54 g (98%) of acid chloride as a clear yellow oil: IR (neat) 3070, 3040, 2950, 2870, 1804, 1738, 1495, 1452, 1403, 1364, 1241, 1208, 1110, 1029, 950, 736, 698 cm^{-1}; ^1H

NMR (90 MHz, CCl_4) δ (TMS) 1.73 (m, 4H), 2.87 (t, 2H, J = 6 Hz, -$C\underline{H}_2$COCl), 3.40 (t, 2H, J = 4.5 Hz, ROC$\underline{H}_2$-), 4.41 (s, 2H, PhC$\underline{H}_2$-), 7.2 (s, 5H, aromatic H). The title compound was carried on to the subsequent experiment without further characterization.

(+)-(4S)-3-[5-Benzyloxypentanoyl]-4-(2-propyl)-oxazolidine-2-one (32). The title compound was prepared as described for (+)-4-(4S)-3-(2-thiomethyl)-acetyl-4-(2-propyl)-oxazolidine-2-one,[43] using 50 g (0.22 mol) of 5-benzyloxy-pentanoyl chloride and 28 g (0.22 mol) of (S)-valine oxazolidone (**1a**).[27] Flash chromatographic purification (300 g silica gel, 5.5 x 42 cm, 1:4 ethyl acetate:hexane, 175 mL fractions) of 4 x 18 g portions of material afforded 52.4 g (75%) of product as a colorless oil: IR (neat) 2958, 2860, 1776, 1695, 1480, 1445, 1380, 1294, 1240, 1200, 1095, 1018, 729, 688 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.83 (d, 3H, J = 4.5 Hz, -$C\underline{H}_3$), 0.90 (d, 3H, J = 4.5 Hz, -$C\underline{H}_3$), 1.66 (m, 4H, -$C\underline{H}_2C\underline{H}_2$-), 2.30 (m, 1H, -$C\underline{H}(CH_3)_2$), 2.87 (t, 2H, J = 6 Hz, -C(O)$C\underline{H}_2$-), 3.43 (t, 2H, J = 6 Hz, ROC$\underline{H}_2$-), 4.15 (m, 3H), 4.40 (s, 2H, Ph$C\underline{H}_2$O-), 7.21 (s, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) 14.49, 17.81, 21.06, 28.01, 28.85, 34.64, 57.64, 62.32, 69.41, 72.33, 126.99, 127.77, 138.49, 152.66, 171.63; $[\alpha]_D^{25}$ = +43.8° (c 3.15, CH_2Cl_2).

Anal. calcd. for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.65; H, 7.78; N, 4.30.

(+)-(4S)-3-[(2S,3R,6E)-2-(3-Benzyloxypropyl)-3-hydroxy-6-methyl-oct-6-enoyl]-4-(2-propyl)-oxazolidine-2-one (33). Into a 250-mL 3-necked flask equipped with a 2-way stopcock valve, a magnetic spin bar, and a thermometer was weighed 8.24 g (25.8 mmol) of acyl oxazolidone **32**. Oxygen was excluded by the sequential evacuation and filling of the rubber septum-sealed system

with argon (3 times). Freshly distilled dichloromethane (70 mL) was added and the mixture was cooled to-78°C. To this solution was added dropwise, 7.5 mL (30.6 mmol, 1.2 equiv) of di-n-butylboryl trifluoromethanesulfonate.[44] Any precipitate formed during this addition was allowed to dissolve by briefly warming the system to -40°C. Triethylamine (5.68 mL, 40.8 mmol, 1.5 equiv) was then added at a rate which maintained the internal temperature below -65°C. The solution was stirred at -78°C for 30 min and 1 h at 0°C to form the boryl enolate. To this cooled (-78°C) solution was added 3 g (26.8 mmol) of freshly distilled (E)-4-methyl-4-hexenal[29] in a single portion. After 30 min at -78°C and 1 h at 0°C, 50 mL of a pH 7 phosphate buffer was added to quench the reaction. A pre-cooled (-20°C) mixture of 100 mL of methanol and 20 mL of a 30% hydrogen peroxide solution was then added to oxidize the boron complexes. After stirring at 0°C for 1 h the reaction mixture was transferred to a separatory funnel containing 150 mL of a 5% sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to afford 11.3 g (100% mass balance) of material. Diastereomer analysis (SE-54, 220°C, t_r major = 16.81 min, t_r minor = 17.39 min) gave a ratio of 96.8:3.2. Flash chromatographic purification (300 g silica gel, 5.5 x 42 cm, 1:4 ethyl acetate:hexane, 175 mL fractions) afforded 7.6 g (68%) of product (R_f = 0.50, silica gel, 50% ethyl acetate:hexane, minor isomer not resolved) as a colorless oil: IR (CCl_4) 3500, 2975, 2940, 2880, 1780, 1695, 1452, 1389, 1302, 1205, 1102, 1056, 1018 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.84 (d, 3H, J = 5 Hz, -C$\underline{H}_3$), 0.90 (d, 3H, J = 6 Hz, -C$\underline{H}_3$), 1.53 (m, 9H, -C$\underline{H}_2$C$\underline{H}_2$-, -CMe=CHC$\underline{H}_3$), 1.58 (s, 3H,-C(C$\underline{H}_3$)=CHCH$_3$),

2.0 (t, 2H, J = 8 Hz, -$\underline{CH}_2CH=CR_2$), 2.21 (m, 1H, -$\underline{CH}(CH_3)_2$), 2.60 (d, 1H, J = 3 Hz, -$\underline{OH}$), 3.40 (t, 2H, J = 6 Hz, ROC$\underline{H}_2$-), 3.67 (m, 1H, -$\underline{CH}$(OH)-), 4.2 (m, 4H), 4.40 (s, 2H, PhC$\underline{H}_2$-O-), 5.15 (m, 1H, vinyl H), 7.21 (s, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) 13.19, 14.43, 15.53, 17.87, 23.85, 27.23, 28.01, 31.71, 35.81, 46.92, 58.10, 62.26, 69.47, 71.36, 72.40, 118.21, 127.18, 127.83, 134.98, 138.29, 153.05, 174.82; $[\alpha]_D^{25}$ = +34.1° (c 2.59, CH_2Cl_2).

Exact mass calcd. for $C_{25}H_{37}NO_5$: 431.2672. Found: 431.2659.

(+)-(4S)-3-[5-Benzyloxy-(2S)-2-{(2R,5S)-5-methyl-5-[(1R)-1-hydroxyethyl]-tetrahydrofuranyl}-pentanoyl]-4-(2-propyl)-oxazolidine-2-one (34a). The unpurified product, **33**, of the aldol condensation, 31 g (71.9 mmol), was dissolved in 300 mL of ethyl acetate. To this cooled solution (0°C) was added a solution of 39 g (180 mmol) of 80% pure technical grade m-chloroperoxybenzoic acid (MCPBA) dissolved in 100 mL of ethyl acetate. The reaction was stirred at 20°C for 24 h before 65 mL of acetic acid was added. After an additional 10 h at 20°C the excess MCPBA was consumed by the addition of 35 mL of dimethyl sulfide followed by stirring overnight. The solvent was removed <u>in vacuo</u>. The resulting white solid (m-chlorobenzoic acid) and oily products were taken up in 500 mL of ether. All acidic by-products were neutralized using 200 mL of water followed by cautious addition of solid sodium bicarbonate. Successive extraction of the ethereal solution with water and saturated brine removed most of the acids and dimethyl sulfoxide. The ethereal solution was dried (anhydrous $MgSO_4$) and concentrated <u>in vacuo</u> to give a golden oil. Flash chromatographic purification (300 g silica gel, 5.5 x 42 cm, 1:4 ether:dichloromethane, fractions monitored through a UV detector, two major bands **34a** and **34b** with

34a eluting first), in 7 g batches, afforded 14.5 g of **34a** (45%) as a colorless oil. Note: all of the fractions were checked by gas chromatography for the presence of lactone **35** before being discarded. IR (neat) 3510, 2975, 2949, 2882, 1780, 1694, 1488, 1452, 1387, 1372, 1365, 1300, 1235, 1205, 1097, 1020, 734, 696 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.83 [d, 3H, J = 6 Hz, $-CH(C\underline{H}_3)CH_3$], 0.90 [d, 3H, J = 6 Hz, $-CH(CH_3)C\underline{H}_3$], 1.02 (d, 3H, J = 7 Hz, $-C(OH)H-C\underline{H}_3$), 1.08 (s, 3H, $R_3C-C\underline{H}_3$), 1.7 (m, 9H, $-C\underline{H}_2-$), 2.28 (s, 1H, $-O\underline{H}$), 3.40 (t, 2H, J = 6 Hz, $-OC\underline{H}_2R$), 3.53 [q, 1H, J = 7 Hz, $-CH(OH)CH_3$], 4.2 (m, 5H), 4.40 (s, 2H, $PhC\underline{H}_2O-$), 7.2 (s, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) 14.49, 17.42, 17.81, 22.55, 26.32, 26.84, 28.20, 28.85, 30.41, 45.10, 58.03, 62.32, 69.34, 71.68, 72.33, 77.92, 86.04, 126.86, 127.12, 127.77, 138.42, 152.66, 173.71; $[\alpha]_D^{25}$ = +34.2° (c 3.2, CH_2Cl_2); R_f = 0.36 (silica gel, 1:4 ether:CH_2Cl_2).

Anal. calcd. for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13. Found: C, 67.00; H, 8.27; N, 3.28.

(+)-(4S)-3-[5-Benzyloxy-(2S)-2-{(2R,5R)-5-methyl-5-[(1S)-1-hydroxyethyl]-tetrahydrofuranyl}-pentanoyl]-4-(2-propyl)-oxazolidine-2-one (34b). The title compound, **34b**, 14 g (45%) was isolated in the chromatographic purification of **34a**. IR (neat) 3500, 2978, 2940, 2884, 1780, 1690, 1641, 1486, 1450, 1383, 1362, 1299, 1240, 1220, 1200, 1120, 1089, 1054, 908, 748, 703 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.83 [d, 3H, J = 6 Hz, $-CH(C\underline{H}_3)CH_3$], 0.90 [d, 3H, J = 6 Hz, $-CH(CH_3)C\underline{H}_3$], 1.0 [d, 3H, J = 6 Hz, $-CH(OH)C\underline{H}_3$], 1.0 (s, 3H, $R_3C-C\underline{H}_3$), 1.7 (m, 8H, $-C\underline{H}_2-$), 2.30 [m, 1H, $-C\underline{H}(CH_3)CH_2$], 2.4 (s, 1H, $-O\underline{H}$), 3.36 (t, 2H, J = 6 Hz, $-OC\underline{H}_2-$), 3.57 [q, 1H, J = 6 Hz, $-C\underline{H}(OH)CH_3$], 4.2 (m, 5H), 4.40 (s, 2H, $-OC\underline{H}_2Ph$), 7.2 (s, 5H, aromatic H);

^{13}C NMR (CCl_4) δ (TMS) 14.69, 17.35, 17.87, 23.59, 26.06, 27.16, 28.53, 30.22, 45.75, 58.23, 62.39, 69.47, 71.75, 72.40, 81.04, 86.04, 126.92, 127.18, 127.83, 138.49, 152.98, 173.45; $(\alpha)_D^{25}$ = +64.6° (c 1.56, CH_2Cl_2); R_f = 0.24 (silica gel, 1:4 ether:CH_2Cl_2).

Anal. calcd. for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13. Found: C, 67.12; H, 8.29; N, 3.24.

(1S,2R,5S,6R)-1,2-Dimethyl-5-(3-benzyloxypropyl)-3,9-dioxabicyclo-[4.2.1]nonan-4-one (35). To a cooled solution (-78°C) of 9.75 g (21.8 mmol) of tetrahydrofuran diastereomer **34a** in 220 mL of anhydrous tetrahydrofuran (THF) was added dropwise, 10 mL (24 mmol) of a 2.4 M solution of phenyl magnesium bromide in ether[45] to form the magnesium alkoxide. The solution was stirred at -78°C for 2 h before 1.5 g (17.2 mmol) of anhydrous LiBr was added. After stirring an additional 24 h at 20°C, thin layer chromatographic analysis (silica gel, 1:4 ether:CH_2Cl_2, R_f **34a** = 0.36, R_f **35** = 0.71) showed only a trace of starting material left. The solvent was removed in vacuo and the residue was flash eluted through a column of silica gel (200 g, 5.5 x 42 cm) eluting with 2 L of dichloromethane followed by 1 L of 1:1 ether:dichloromethane. The solvents were removed in vacuo to afford the unpurified lactone. Chromatographic purification (MPLC, Merck size C Lobar silica gel column, 5% ether:dichloromethane, 20 mL fractions) afforded 5.5 g (79%) of pure product as a colorless oil. IR (neat) 2990, 2955, 2875, 1731, 1464, 1451, 1383, 1213, 1178, 1088, 1062, 891, 733, 695 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.18 (d, 3H, J = 6.5 Hz, -O-CHCH_3), 1.20 (s, 3H, -C-CH_3), 1.3-2.4 (m, 8H, -CH_2-), 2.76 (t, 1H, J = 6.5 Hz, -CH_2CHC(O)-), 3.40 (t, 2H, J = 5 Hz, ROC$H_2$$CH_2$-), 4.06 (dd, 1H, J = 8.3 Hz, J = 1 Hz,

tetrahydrofuranyl methine), 4.39 (q, 1H, J = 6.5 Hz, $-CO_2-C\underline{H}CH_3$), 4.41 (s, 2H, $PhC\underline{H}_2O-$), 7.20 (s, 5H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.86 (d, 3H, J = 6.5 Hz, $-CHC\underline{H}_3$), 0.92 (s, 3H, quarternary $-C\underline{H}_3$), 1.08 (dt, 2H, J_d = 5.5 Hz, J_t = 12.5 Hz, $-CH_2-C\underline{H}_2-CHCO_2-$), 1.34 (m, 1H), 1.67 (m, 3H), 1.97 (m, 2H), 2.72 [t, 1H, J = 6.5 Hz, $-CH_2-C\underline{H}C(O)-$], 3.30 (m, 2H, $PhCH_2OC\underline{H}_2-$), 3.98 (d, 1H, J = 8.3 Hz, tetrahydrofuranyl methine), 4.08 (q, 1H, J = 6.5 Hz, $-CO_2-C\underline{H}CH_3$), 4.31 (s, 2H, $PhC\underline{H}_2O-$), 7.10 (t, J = 7.3 Hz), 7.18 (t, J = 7.5 Hz), 7.32 (d, J = 7.3 Hz); ^{13}C NMR (CCl_4) δ (TMS) 18.00, 23.53, 26.00, 27.23, 28.98, 30.48, 51.86, 69.67, 72.33, 77.73, 82.34, 84.48, 126.92, 127.12, 127.83, 138.49, 172.48; $[\alpha]_D^{25}$ = +59.5° (c 1.99, CH_2Cl_2).

Anal. calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.52; H, 8.15.

(1S,2R,5S,6R)-1,2-Dimethyl-5-(3-benzyloxypropionyl)-4-methylidene-3,9-dioxabicyclo[4.2.1]nonane (36). A solution of 4.5 g (14.2 mmol) of bicyclic lactone **35** in 57 mL of anhydrous THF under an argon atmosphere was cooled to -45°C with an acetonitrile-dry ice bath. To this solution was added 0.7 mL of freshly distilled pyridine followed by a cooled solution (-45°C) of 6.1 g (19.3 mmol) of Tebbe's reagent[32] in 28 mL of anhydrous toluene. The reaction temperature was maintained at -45°C for 40 min then allowed to warm to 20°C over 2 h. After an additional 45 min at 20°C, the red solution was cooled to 0°C and quenched cautiously with 6 mL of a 15% aqueous sodium hydroxide solution. The evolution of methane gas was accompanied by a change in color to a blue solution over 1 h at 20°C. Ether (60 mL) was added and the resulting slurry was filtered through 300 g of neutral activity III alumina (5.5 x 42 cm column) using 1 L of hexane followed

by 500 mL of ether. Evaporation of the solvent in vacuo afforded 4.2 g (94%) of product as a yellow oil. IR (neat) 2990, 2950, 2880, 1649, 1470, 1458, 1381, 1367, 1351, 1253, 1099, 1078, 1046, 1025, 980, 854, 731 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.05 (s, 3H), 1.11 (d, 3H, J = 7 Hz, -OCH-C$\underline{H}_3$), 1.2-2.3 (m, 8H), 2.66 (q, 1H, J = 6 Hz, allylic H), 3.33 (t, 2H, J = 6 Hz, $PhCH_2OC\underline{H}_2$-), 3.56 (q, 1H, J = 7 Hz, -OC$\underline{H}CH_3$), 4.20 (m, 1H, tetrahydrofuranyl methine), 4.22 (s, 1H, vinyl H), 4.38 (s, 2H, $PhC\underline{H}_2O$-), 4.48 (s, 1H, vinyl H), 7.21 (s, 5H, aromatic H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 1.04 (s, 3H), 1.07 (d, 3H, J = 7 Hz, -OCHC$\underline{H}_3$), 1.24-1.55 (m, 4H), 1.64 (m, 1H), 1.77 (m, 1H), 2.04 (m, 1H), 2.18 (m, 1H), 2.78 (dt, 1H, J_d = 8 Hz, J_t = 7 Hz, allylic H), 3.25 (m, 2H, $PhCH_2OC\underline{H}_2CH_2$-), 3.70 (q, 1H, J = 7 Hz, -OC$\underline{H}CH_3$), 4.30 (m, 1H, tetrahydrofuranyl methine), 4.32 (s, 2H, $PhC\underline{H}_2O$-), 4.35 (s, 1H, vinyl H), 4.73 (s, 1H, vinyl H), 7.11 (t, 1H, J = 7.5 Hz), 7.19 (t, 2H, J = 7.5 Hz), 7.27 (d, 2H, J = 7 Hz); ^{13}C NMR (CCl_4) δ (TMS) 17.87, 23.33, 27.42, 27.62, 27.81, 31.19, 48.61, 69.67, 72.40, 78.44, 86.17, 88.38, 99.11, 126.99, 127.77, 138.42, 166.56; $[\alpha]_D^{25}$ = +42.4° (c 1.04, CH_2Cl_2); R_f = 0.57(not stable to silica gel; gets converted to **37**, 1:4 ether:CH_2Cl_2).

Anal. calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.80; H, 8.80.

(1S,2R,6R)-(Z)-1,2,4-Trimethyl-5-(3-benzyloxypropyl)-3,9-dioxabicyclo[4.2.1]non-4-ene (37). To 4.0 g (12.6 mmol) of **36** in 68 mL of dichloromethane was added 0.59 g (2.3 mmol) of anhydrous pyridinium tosylate. After stirring the solution at 20°C for 6 h, the solvent was removed in vacuo. The residue was taken up in ether, filtered to remove the pyridinium tosylate, and extracted successively with 5% aqueous sodium carbonate, water, and

brine. The ethereal solution was dried (anhydrous Na_2SO_4) and concentrated in vacuo to afford 4 g (100%) of **37** as an oil. A small portion (100 mg) was flash chromatographed (10 g silica gel, 20% ethyl acetate:hexane) to provide an analytical sample. IR (neat) 2984, 2950, 2870, 1710, 1680, 1492, 1454, 1442, 1378, 1364, 1301, 1274, 1239, 1200, 1186, 1145, 1115, 1097, 1069, 1026, 884, 726, 680 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.09 (d, 3H, J = 7 Hz, -OCHC$\underline{H}_3$), 1.10 (s, 3H), 1-2.4 (m, 8H), 1.69 (s, 3H, vinylic methyl, 3.36 (t, 2H, J = 6 Hz, $PhCH_2OC\underline{H}_2CH_2$-), 3.42 (q, 1H, J = 7 Hz, -OC$\underline{H}CH_3$), 4.20 (dd, 1H, J = 3 Hz, 9 Hz, allylic methine), 4.40 (s, 2H, $PhC\underline{H}_2O$-), 7.21 (s, 5H); ^{13}C NMR (CCl_4) δ (TMS) 17.48, 18.46, 23.33, 28.46, 28.85, 31.00, 33.60, 68.43, 72.27, 79.16, 85.33, 125.88, 126.92, 127.70, 138.36, 150.51; $[\alpha]_D^{25}$ = +53.3° (c 2.16, CH_2Cl_2); R_f = 0.57 (silica gel, 1:4 ether:CH_2Cl_2).

Anal. calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.95; H, 8.92.

(2R,5S)-2-(1-Oxo-4-benzyloxybutyl)-5-methyl-5-[(1R)-1-acetoxyethyl]-tetrahydrofuran (38). To 1.6 g (5.06 mmol) of **37** in 40 mL of dichloromethane was added 6 mg of Sudan 7B dye.[33] This solution was protected from moisture with a calcium chloride-packed drying tube and cooled to -78°C. A gaseous solution of ozone in oxygen (prepared employing a Welsbach ozone generator) was then bubbled through until the red color of the indicator dye was discharged. The flow of ozone was terminated and 8 mL of dimethyl sulfide was added. After 1 h at -78°C and 1 h at 20°C, the solvent was removed in vacuo. The residue was taken up in ether and extracted with water and brine to remove dimethyl sulfoxide. The ethereal solution was dried (anhydrous Na_2SO_4) and concentrated to give 1.5 g of unpurified

product (GC analysis, 30 meter DB-1, 225°C, t_r = 3.77 min, shows 75-80% purity). A small sample (100 mg) was flash chromatographed (7 g silica gel 1 x 30 cm, 5% ether:CH_2Cl_2, 0.3 mL fractions) to give analytically pure material. It was noted that upon prolong exposure to silica gel, the α-stereocenter proximal to the ketone was epimerized to give a 1:1 mixture of diastereomers. IR (CCl_4) 2985, 2950, 2878, 1736, 1719, 1451, 1374, 1245, 1099, 1060, 1029 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ(TMS) 1.17 (s, 3H), 1.20 (d, 3H, J = 7 Hz, -OCHC<u>H</u>$_3$), 1.3-2.3 (m, 6H), 1.92 [s, 3H, -OC(O)C<u>H</u>$_3$], 2.58 [t, 2H, J = 7 Hz, -CH_2C<u>H</u>$_2$C(O)-], 3.40 (t, 2H, J = 6 Hz, -OC<u>H</u>$_2$$CH_2$-), 4.22 (m, 1H, tetrahydrofuranyl methine), 4.40 (s, 2H, PhC<u>H</u>$_2$O-), 4.80 [q, 1H, J = 7 Hz, -C<u>H</u>(CH$_3$)OC(O)CH$_3$], 7.21 (s, 5H); ^{13}C NMR (CCl_4) δ(TMS) 15.27, 20.67, 21.84, 23.01, 28.40, 33.53, 34.31, 68.69, 72.27, 73.44, 82.92, 85.13, 127.12, 127.77, 138.23, 168.12, 208.42; $[\alpha]_D^{25}$ = +24.0° (<u>c</u> 0.99, CH_2Cl_2); R_f = 0.48 (silica gel, 1:4 ether:CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.86; H, 8.04.

(2R,5S)-2-[(2S)-2-Hydroxy-5-benzyloxy-2-pentyl]-5-methyl-5-[(1R)-1-hydroxyethyl]-tetrahydrofuran (39). The unpurified keto-ester **38**, 1.5 g (4.3 mmol) was taken up in 4 mL of distilled dichloromethane and added, dropwise, to a cooled (-78°C) solution of 25 mL of dichloromethane and 24 mL of a 2.8 <u>M</u> solution of methylmagnesium bromide in ether (from Aldrich Chemical Co.). After 8 h at -78°C, the reaction was stirred an additional 2 h at 20°C. The solution was then cooled (-78°C) before a saturated aqueous solution of ammonium chloride was added to quench the excess Grignard reagent. The product was isolated from an aqueous workup by ether

extraction (3 x 100 mL). The ethereal extracts were combined and dried over anhydrous sodium sulfate. The entire procedure was repeated on the same scale. The combined unpurified product (ca. 3 g) was flash chromatographed (125 g silica gel, 4 x 40 cm, 1:1 ether:dichloromethane, 8 mL fractions) to give 1.78 g (55%) of **39** (eluting last) and 0.30 g (9%) of another isomer (eluting first) as oils (64% overall yield from **36**): IR (neat) 3420, 2984, 2950, 2880, 1498, 1456, 1379, 1108, 1085, 1031, 1019, 911, 738, 699 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.03 (d, 3H, J = 6.5 Hz, $-OCHC\underline{H}_3$), 1.06 (s, 3H, tetrahydrofuranyl methyl), 1.18 (s, 3H, $-C(OH)C\underline{H}_3$), 1.2-2.3 (m, 8H, $-C\underline{H}_2-$), 3.37 (t, 2H, J = 6.5 Hz, $PhCH_2OC\underline{H}_2-$), 3.7 (m, 2H, methines), 3.9 (br s, 2H, $-O\underline{H}$'s), 4.40 (s, 2H, $PhC\underline{H}_2O-$), 7.20 (s, 5, aromatic H's); ^1H NMR (500 MHz, benzene d_6) δ (TMS) 1.03 (s, 3H, tetrahydrofuranyl methyl), 1.08 (d, 3H, J = 6.5 Hz, $-OCHC\underline{H}_3$), 1.28 (m, 1H), 1.33 (s, 3H), 1.38 (m, 1H), 1.47 (m, 1H), 1.58 (m, 1H), 1.63 (m, 1H), 1.74 (m, 1H), 2.09 (m, 1H), 2.20 (m, 1H), 3.28 (t, 2H, J = 6.5 Hz, $PhCH_2OC\underline{H}_2-$), 3.70 (dd, 1H, J = 7 Hz, 8 Hz, tetrahydrofuranyl methine), 3.75 (br s, 1H, OH), 3.87 (q, 1H, J = 6.5 Hz, $-OC\underline{H}CH_3$), 4.30 (s, 2H, $-OC\underline{H}_2Ph$), 4.32 (br s, 1H, OH), 7.1-7.3 (m, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) 18.13, 23.72, 23.92, 24.37, 26.26, 30.41, 35.42, 70.38, 72.46, 72.72, 72.98, 83.83, 86.11, 127.12, 127.90, 138.29; $[\alpha]_D^{25} = -7.29^\circ$ (c 3.38, CH_2Cl_2).

Anal. calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.53; H, 9.17.

(2R,5S)-2-[(2S)-2-t-Butyldimethylsilyloxy-5-benzyloxy-2-pentyl-5-methyl-5-[(1R)-1-t-butyldimethylsilyloxyethyl]-tetrahydrofuran (40). To a cooled solution (0°C) of 1.37 g (4.23 mmol) of **39** in 10 mL of dichloromethane under an argon atmosphere was added 2.4 mL (17.3 mmol) of triethylamine

followed by 2.4 mL (10.9 mmol) of t-butyl-dimethylsilyl trifluoromethanesulfonate (TBS triflate).[46] After 2 h at 0°C, the reaction was quenched with 10 mL of a saturated aqueous sodium bicarbonate solution. The dichloromethane layer was concentrated in vacuo. The residue was chromatographed (80 g silica gel, 4 x 46 cm, dichloromethane, UV detector used to monitor product fractions) to afford 2.19 g (94%) of bis-silylated product **40** as a colorless oil: IR (neat) 2964, 2940, 2895, 2868, 1460, 1370, 1254, 1100, 1074, 1004, 837, 810, 773, 731, 693 cm^{-1}; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.07 (s, 6H, silyl -CH_3), 0.17 (s, 6H, silyl -CH_3), 0.96 (s, 9H, t-butyl group), 1.0 (s, 9H, t-butyl group), 1.17 (s, 3H), 1.20 (s, 3H), 1.25 (d, 3H, J = 6.5 Hz, ≡SiOC<u>H</u>CH_3), 1.2-2 (m, 8H, methylenes), 3.34 (br t, 2H, RO<u>CH_2</u>CH_2-), 3.70 (q, 1H, J = 6.5 Hz, ≡SiOC<u>H</u>CH_3), 3.83 (m, 1H, tetrahydrofuranyl methine), 4.41 (s, 2H, -OC<u>H_2</u>Ph), 7.2 (m, 5H, aromatic H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.069 (s, 3H), 0.075 (s, 3H), 0.169 (s, 3H), 0.174 (s, 3H), 0.97 (s, 9H), 1.01 (s, 9H), 1.175 (s, 3H), 1.19 (s, 3H), 1.27 (d, 3H, J = 6.5 Hz, ≡SiOCHC<u>H_3</u>), 1.57 (m, 2H), 1.7-1.9 (m, 6H), 3.35 (m, 2H, -OC<u>H_2</u>CH_2-), 3.70 (q, 1H, J = 6.5 Hz, ≡SiOC<u>H</u>CH_3), 3.86 (t, 1H, J = 7 Hz, tetrahydrofuranyl methine), 4.35 (s, 2H, PhC<u>H_2</u>O-), 7.1-7.3 (m, 5H); ^{13}C NMR (CCl_4) δ (TMS) -5.00, -3.96, -2.08, 17.74, 18.26, 18.59, 23.01, 23.85, 25.74, 36.13, 36.85, 70.32, 72.33, 73.57, 76.10, 82.99, 84.74, 126.92, 127.77; $[\alpha]_D^{25}$ = -3.73° (<u>c</u> 3.91, CH_2Cl_2); R_f = 0.66 (silica gel, 10% ether:CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{31}H_{58}O_4Si_2$: C, 67.58; H, 10.61. Found: C, 67.69; H, 10.51.

(2R,5S)-2-[(2S)-2-<u>t</u>-Butyldimethylsilyloxy-5-hydroxy-2-pentyl]-5-

methyl-5-{(1R)-1-t-butyldimethylsilyloxyethyl}tetrahydrofuran (41). To 1.8 g (3.27 mmol) of benzyl ether **40** in 40 mL of ethyl acetate was added 0.30 g of a 10% palladium on carbon hydrogenolysis catalyst. This mixture was loaded into a Parr hydrogenation apparatus and maintained under 4 atm of hydrogen for 19 h at 20°C. The mixture was filtered through celite to remove the catalyst. Evaporation of the solvent in vacuo gave 1.51 g (100%) of pure product: IR (neat) 3360, 2965, 2942, 2890, 2868, 1473, 1461, 1371, 1258, 1252, 1102, 1065, 1009, 835, 772 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ(TMS) 0.03 (s, 3H), 0.05 (s, 3H), 0.10 (s, 6H), 0.88 (s, 18H, t-butyl groups), 1.10 (d, 9H), 1.3-1.9 (m, 8H), 2.77 (s, 1H, -OH), 3.50 (t, 2H, J = 6 Hz, $HOCH_2$-), 3.52 (q, 1H, J = 6 Hz, ≡SiO-CHCH$_3$), 3.80 (t, 1H, J = 6 Hz, tetrahydrofuranyl methine); ^{13}C NMR (CCl_4) δ(TMS) -5.00, -3.96, -2.08, 17.74, 18.26, 18.65, 23.01, 35.74, 25.87, 26.58, 36.00, 36.59, 62.58, 73.44, 76.10, 82.66, 84.94; $(\alpha)_D^{25}$ = -4.60° (c 1.77, CH_2Cl_2); R_f = 0.44 (silica gel, 20% ether:CH_2Cl_2). The title compound was carried on to the subsequent experiment without further characterization.

(4S)-4-t-Butyldimethylsilyloxy-4-{(2R,5S)-5-methyl-5-{(1R)-1-t-butyldimethylsilyloxyethyl}-tetrahydrofuran-2-yl}-1-pentyl Methanesulfonate (42). To a cooled solution (0°C) of 1.5 g (3.25 mmol) of alcohol **41** in 18 mL of dichloromethane was added 0.92 mL (6.6 mmol) of triethylamine and 0.46 mL (5.94 mmol) of methanesulfonyl chloride. After 3 h, the solvent was removed in vacuo. The residue was taken up in ethyl acetate and extracted with ice water. The organic layer was dried (anhydrous $MgSO_4$) and filtered. Evaporation of the solvent in vacuo gave 1.88 g of unpurified **42** (R_f = 0.73, silica gel, 20% ether:CH_2Cl_2). IR (neat) 2968, 2945, 2898, 2870, 1474, 1463,

1361, 1259, 1252, 1179, 1102, 1071, 971, 835, 772 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.05 (m, 12H, silyl methyls), 0.85 (s, 18H, t-butyl groups), 1.03 (s, 3H), 1.06 (d, 3H, J = 6 Hz), 1.10 (s, 3H), 1.3-2.0 (m, 8H), 2.81 (s, 3H, $C\underline{H}_3SO_3$-), 3.50 (q, 1H, J = 6 Hz), 3.75 (t, 1H, J = 6 Hz, tetrahydrofuranyl methine), 4.10 (t, 2H, J = 6 Hz, CH_3SO_2-$OC\underline{H}_2$-). This material was carried on without purification to the next reaction.

(2R,5S)-2-{(2S)-2-t-Butyldimethylsilyloxy-5-iodo-pent-2-yl}-5-methyl-5-{(1R)-1-t-butyldimethylsilyloxyethyl}-tetrahydrofuran (43). The unpurified mesylate **42** (1.88 g) derived from 1.5 g (3.25 mmol) of alcohol **41** was dissolved in 40 mL of anhydrous acetone. To this solution was added 9.3 g of anhydrous sodium iodide, 0.37 g of sodium bicarbonate, and 2 drops of diisopropylethylamine. After protecting from light by aluminum foil, the reaction was allowed to stir for 18 h (20°C), the acetone was removed in vacuo, and the residue taken up in ethyl acetate. After filtration through celite the solvent was concentrated in vacuo. Flash chromatographic purification (50 g silica gel, 3 x 30 cm, 20% ethyl acetate:hexane, 8 mL fractions) of the residue afforded 1.84 g (99% overall from **41**) of the unstable iodide **43** (stored in a foil-wrapped container at -20°C): IR (CCl_4) δ 2967, 2940, 2895, 2869, 1471, 1460, 1370, 1361, 1252, 1100, 1004, 832, 770 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.03 (s, 3H), 0.05 (s, 3H), 0.10 (s, 6H), 0.88 (s, 9H, t-butyl group), 0.89 (s, 9H, t-butyl group), 1.07 (s, 3H), 1.13 (d, 3H, J = 6 Hz, $\equiv SiO$-$CHC\underline{H}_3$), 1.14 (s, 3H), 1.2-2.1 (m, 8H), 3.18 (t, 2H, J = 6 Hz, $RC\underline{H}_2I$), 3.42 (q, 1H, J = 6 Hz, $\equiv SiOC\underline{H}CH_3$), 3.8 (t, 1H, J = 6 Hz, tetrahydrofuranyl methine); ^{13}C NMR (CCl_4) δ (TMS) -5.00, -3.96, -2.08, 6.56, 17.74, 18.26, 18.65, 22.94, 25.74, 25.87, 27.55, 36.00, 41.20, 73.44, 75.84,

82.86, 85.00; $[\alpha]_D^{25}$ = -3.1° (c 5.5, CH_2Cl_2); R_f = 0.75 (silica gel, 20% EtOAc:hexane).

Anal. calcd. for $C_{24}H_{51}IO_3Si_2$: C, 50.51; H, 9.01. Found: C, 50.63; H, 8.86.

(4S)-4-t-Butyldimethylsilyloxy-4-{(2R,5S)-5-methyl-5-[(1R)-1-t-butyldimethylsilyloxyethyl]-tetrahydrofuran-2-yl}-1-pentyltriphenylphosphonium Iodide (44). To a solution of 1.3 g (4.96 mmol) of triphenylphosphine and 0.14 mL of diisopropylethylamine in 20 mL of distilled toluene and 20 mL of distilled acetonitrile was added 1.84 g (3.22 mmol) of iodide **43**. The reaction mixture was heated to 75°C under a nitrogen atmosphere for 54 h. The solution was cooled and the solvents removed in vacuo with the appropriate care to exclude moisture from the hygroscopic residue. The gummy residue was transferred to a 50 mL centrifuge test tube with dichloromethane. The solvent was evaporated under a stream of dry nitrogen at 80°C. The phosphonium salt was then washed with 3 x 50-mL portions of dry hexane to remove excess triphenylphosphine. The resulting white hygroscopic solid was dried under vacuum at 60°C for 10 h to give 2.1 g (78%) of **44**: mp 76-81°C; ^{1}H NMR (90 MHz, benzene-d_6) δ (TMS) 0.20 (s, 12H), 0.90 (s, 9H), 1.01 (s, 9H), 1.19 (s, 3H), 1.23 (s, 3H), 1.35 (d, 3H, J = 6 Hz), 1.2-2.5 (m, 8H), 3.8 (m, 3H), 4.5 (br m, 1H), 7.25 (br m), 7.85 (br m).

Anal. calcd. for $C_{42}H_{66}IO_3PSi_2$: C, 60.56; H, 7.99. Found: C, 60.21; H, 7.78.

(4S)-3-[(2S)-2-Methyl-5-benzyloxypentanoyl]-4-(2-propyl)-oxazolidine-2-one (45a). To 7.15 g (22.4 mmol) of **32** in 100 mL of anhydrous tetrahydrofuran (THF) at -78°C was added a cooled (-78°C) solution of 5.0 g (27.3

mmol) of sodium hexamethyldisilylamide[47] in 30 mL of THF. After 2 h at -78°C, 15 mL (240 mmol) of methyl iodide (freshly filtered through a column of activity I alumina) was added dropwise to the enolate solution. The reaction mixture was maintained at -78°C for 12 h before 40 mL of a saturated aqueous ammonium chloride solution was added. The solution was warmed to room temperature and transferred to a separatory funnel containing 300 mL of water. The aqueous layer was extracted with ether. The combined ethereal layers were dried (anhydrous $MgSO_4$) and concentrated to afford 7.4 g of unpurified alkylated products. Diastereomer analysis (10 meters Carbowax 20M, 200°C, t_r **45a** = 9.67 min, t_r **45b** = 10.51 min) gave a ratio of **45a:45b** = 92.4:7.6. The desired product **45a** was purified to 99% d.e. by MPLC (Merck Lobar size C silica gel column, 50% ether:hexane, 20 mL fractions) to afford 5.9 g (79%) of **45a** (eluting first) and 0.6 g (8%) of a mixture of **45a** and **45b**. This procedure was subsequently scaled up (40 mmol) resulting in a slight loss of diastereoselectivity to give a ratio of **45a:45b** of 89:11. This mixture may be carried on without purification in subsequent transformations. The purified product **45a** was characterized: IR (neat) 2974, 2950, 2882, 2870, 1782, 1701, 1456, 1389, 1366, 1300, 1243, 1206, 1100, 1059, 1029, 1019, 991, 968, 738, 697 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.83 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)_2$], 0.89 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)_2$], 1.13 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)C(O)X_V$], 1.3-1.9 (m, 4H, $-C\underline{H}_2C\underline{H}_2-$), 2.30 (m, 1H, J = 7 Hz, isopropyl methine), 3.33 (t, 2H, J = 6 Hz, $-CH_2C\underline{H}_2OBn$), 3.67 [q, 1H, J = 7 Hz, $-C\underline{H}(CH_3)C=O$], 3.9-4.3 (m, 3H, oxazolidinone H), 4.39 (s, 2H, $PhC\underline{H}_2O-$), 7.2 (s, 5H); ^{13}C NMR (CCl_4) δ (TMS) 14.56, 17.81, 17.94, 27.23, 28.07, 29.76, 36.98, 57.71, 62.26, 69.86, 72.33, 127.05, 127.83, 138.55, 152.40, 175.60; $[\alpha]_D^{25}$ = +74.4° (c 2.32,

CH_2Cl_2); R_f = 0.61 (silica gel, ether).

Anal. calcd. for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16. Found: C, 68.70; H, 7.82.

(-)-(2S)-5-Benzyloxy-2-methyl-1-pentanol (S)-46. To a cooled solution (-78°C) of 10 g (30 mmol) of **45a** (98% d.e.) in 80 mL of anhydrous THF was added 35 mL of a 1 M solution of lithium aluminum hydride in THF. The solution was then warmed to 20°C for 1 h. The excess hydride reagent was quenched with ice and the resultant salts were dissolved upon the addition of a 10% aqueous solution of hydrochloric acid. The desired alcohol was extracted with ether, the ethereal extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was flash chromatographed (120 g silica gel, 4.5 x 40 cm, ether, collecting the UV active band) to give 5.5 g (88%) of pure product as a colorless oil. IR (neat) 3400, 2940, 2879, 1452, 1363, 1098, 1027, 733, 694 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.88 (d, 3H, J = 6 Hz, $-CHCH_3$), 1-1.7 (m, 5H), 2.4 (s, 1H, -OH), 3.31 (m, 4H, $-CH_2OH$, $-CH_2OCH_2Ph$), 4.40 (s, 2H, $PhCH_2O-$), 7.2 (s, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) 16.64, 26.90, 29.50, 35.29, 67.00, 70.19, 72.46, 126.99, 127.12, 138.29; $[\alpha]_D^{25}$ = -7.9° (c 2.11, CH_2Cl_2; 98% ee based on GLC analysis of the **45a:45b** mixture reduced); R_f = 0.51 (silica gel, ether). The title compound was carried on to the subsequent experiment without further characterization.

(2S)-5-Benzyloxy-2-methylpentanal (S)-47. To a cooled solution (0°C) of 2.0 g (9.6 mmol) of alcohol **(S)-46** and 15.0 mL (108 mmol) of triethylamine in 30 mL of anhydrous dimethyl sulfoxide (DMSO) was added in one portion a solution of 8.0 g (50.3 mmol) of sulfur trioxide-pyridine complex[48] in 30 mL of DMSO.[14] The cooling bath was removed and the mixture was stirred at

20°C for 1 h. At the end of this period, the reaction mixture was poured into a separatory funnel containing ice-water and ether. The aqueous layer was separated and extracted with several portions of ether. The combined ethereal extracts were washed successively with water and brine, dried (anhydrous $MgSO_4$), and the solvent was removed in vacuo. The residue was flash filtered through a dichloromethane-packed silica gel column (20 g, 2.5 x 30 cm) with dichloromethane. Evaporation of the solvent in vacuo afforded 1.9 g (96%) of product as a yellow oil. The aldehyde was dried under vacuum at 20°C for 6 h: IR (CCl_4) 2950, 2870, 2720, 1730, 1498, 1456, 1398, 1365, 1262, 1209, 1100, 1030, 790 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.09 (d, 3H, J = 6 Hz, $-CH_3$), 1.2-1.9 (m, 4H, methylene), 2.27 (m, 1H, methine), 3.40 (t, 2H, J = 6 Hz, $-OCH_2CH_2-$), 4.4 (s, 2H, $PhCH_2O-$), 7.2 (s, 5H), 9.50 (d, 1H, J = 2 Hz, -CHO); R_f = 0.75 (silica gel, 20% ether:CH_2Cl_2). The title compound was carried on to the subsequent experiment without further characterization.

(4S)-3-[(2S,3R,4S)-2,4-Dimethyl-3-hydroxyl-7-benzyloxyheptanoyl]-4-(2-propyl)-oxazolidine-2-one (48). The procedure for the boron enolate aldol condensation used in the preparation of **33** was employed. A solution of 1.7 g (9.2 mmol) of (4S)-3-propionyl-4-(2-propyl)-oxazolidine-2-one[49] in 27 mL of dichloromethane was enolized with 2.3 mL (9.2 mmol) of di-n-butylboryl triflate and 1.4 mL (10.1 mmol) of triethylamine at -78°C for 1 h. The aldehyde **(S)-47**, 1.9 g (9.2 mmol, 89% ee), was then added in one single portion. After 30 min at -78°C and 90 min at 0°C the reaction was quenched with 10 mL of pH 7 phosphate buffer. The usual oxidative workup (50 mL of methanol and 10 mL of 30% H_2O_2) at 0°C for 1 h was followed by dichloromethane extraction

(2 x 75 mL, as described for **33**). Evaporation of the dichloromethane extracts in vacuo afforded 3.52 g (98% mass balance) of unpurified products. Diastereomer analysis (DB-1, 225°C, t_r major = 9.57 min, t_r minor = 8.84 min) afforded a ratio of 91.4:7.6. Since the aldehyde had an optical purity of 89% ee, this ratio translates to an erythro enantioselectivity of 97:3 for this aldol condensation. Chromatographic purification (MPLC, Merck size C Lobar silica gel column, 15% ether:dichloromethane, 15 mL fractions) gave 2.59 g (72%) of the desired product (eluting last, ≥95% pure by GC) as a thick colorless oil: IR (CCl_4) 3420, 2976, 2958, 2888, 1785, 1695, 1490, 1458, 1389, 1302, 1208, 1144, 1105, 1060, 1018, 990, 969 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.90 (m, 9H, isopropyl methyls, $-CH_2CHCH_3$), 1.17 (d, 3H, J = 6 Hz, $-C(O)CHCH_3-$), 1.5 (m, 5H), 2.28 (m, 1H, isopropyl methine), 2.62 (d, 1H, J = 5 Hz, -OH), 3.40 (t, 2H, J = 6 Hz, $-CH_2CH_2OBn$), 3.5 (m, 1H, -CHOH-), 3.7-4.35 (m, 4H, oxazolidinone H and $-C(O)CH(CH_3)-$), 4.40 (s, 2H, $PhCH_2O-$), 7.2 (s, 5H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.41 (d, 3H, J = 7 Hz, isopropyl methyl), 0.51 (d, 3H, J = 7 Hz, isopropyl methyl), 1.13 (d, 3H, J = 6.5 Hz, $-CH_2CH(CH_3)-$), 1.28 (m, 1H), 1.37 (d, 3H, J = 6.5 Hz, $-CH(CH_3)C=O$), 1.61 (m, 2H), 1.72 (m, 2H), 2.08 (m, 1H, isopropyl methine), 2.83 (s, 1H, -OH), 3.26 (t, 1H, J = 6 Hz, $-CH_2OC(O)N-$), 3.32 (t, 2H, J = 4 Hz, $-OCH_2CH_2-$), 3.39 (dd, 1H, J = 2 Hz, 6 Hz, $-CHCH(OH)CH(CH_3)-$), 3.86 (broad t, $-CH_2OC(O)N-$), 3.92 (m, 1H, $-CH_2CHN-$), 4.26 (dq, 1H, $-C(O)CHCH_3-$), 4.35 (s, 2H, $PhCH_2O-$), 7.11 (t, 1H, J = 7.5 Hz), 7.22 (t, 2H, J = 7.5 Hz), 7.33 (d, 2H, J = 7 Hz); ^{13}C NMR (CCl_4) δ (TMS) 11.70, 14.56, 15.01, 17.74, 26.71, 28.01, 29.37, 35.03, 39.51, 57.58, 62.45, 69.99, 72.33, 126.86, 127.05, 127.83, 138.55, 152.20, 176.96; $[\alpha]_D^{25}$ = +41.9° (c 3.74, CH_2Cl_2); R_f = 0.49 (silica gel, 20%

ether:CH_2Cl_2).

Anal. calcd. for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50. Found: C, 67.34; H, 8.31.

(4S)-3-[(2S,3R,4S)-2,4-Dimethyl-3,7-dihydroxyheptanoyl]-4-(2-propyl)-oxazolidine-2-one (49). The aldol adduct **48** (7.8 g) was first flash chromatographed (220 g silica gel, 5.5 x 4 cm, 15% ether:dichloromethane, collecting the UV active band) to remove impurities that could poison the hydrogenolysis catalyst. A solution of 5 g (12.8 mmol) of **48** in 250 mL of ethanol and 1.0 g of 10% palladium on carbon was agitated under 4 atm of hydrogen in a Parr apparatus. The extent of reaction was monitored by thin layer chromatography (R_f **48** = 0.41, R_f **49** = 0.09, silica gel, 50% EtOAc:hexane). After 4 h at 20°C, the catalyst was removed by filtration through celite. The solvents were removed in vacuo to give an oil which solidified upon standing. Recrystallization from dichloromethane:hexane gave 2.24 g as a first crop. The mother liquor was concentrated and the residue flash chromatographed (50 g silica gel, 3 x 44 cm, 500 mL of ether followed by 500 mL of acetone, 125 mL fractions) to give an additional 1.72 g of product. The two samples were combined to give 3.96 g (98%) of **49**. A subsequent recrystallization from dichloro-methane:hexane afforded 3.5 g of product (>99% pure by GC) as long colorless needles, mp 84-85°C. IR (neat) 3430, 2978, 2950, 2889, 1780, 1695, 1460, 1387, 1301, 1210, 1120, 1059, 990, 778, 710 cm^{-1}; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.50 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)_2$], 0.60 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)_2$], 1.15 [d, 3H, J = 6 Hz, $-CH_2CH(C\underline{H}_3)CH(OH)-$], 1.40 [d, 3H, J = 7 Hz, $-C(O)CH(CH_3)-$], 1.9-0.9 (m, 5H), 2.14 (m, 1H, J = 7 Hz, isopropyl methine), 2.5 (br s, 1H, $-O\underline{H}$), 3.2

(br s, 1H, -OH), 3.55 (m, 3H, -CHOH-, -CH_2OH), 3.8-4.5 (m, 4H, oxazolidinone H, -C(O)CH(CH_3)-); ^{13}C NMR (benzene-d_6) δ (TMS) 13.30, 14.53, 15.05, 17.59, 28.44, 30.07, 30.39, 36.11, 40.85, 58.34, 62.82, 63.02, 74.84, 153.67, 177.39; ^{13}C NMR ($CHCl_3$) δ (TMS) 12.02, 14.69, 15.08, 17.94, 28.33, 29.18, 29.83, 35.35, 39.90, 58.36, 62.97, 63.36, 74.67, 153.57, 177.61; $[\alpha]_D^{25}$ = +53.3° (c 1.25, CH_2Cl_2).

Anal. calcd. for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03. Found: C, 59.77; H, 8.89.

(4S)-3-{(2S)-2-[(5S,6R)-5-Methylvalerolacton-6-yl]-propionyl}-4-(2-propyl)-oxazolidine-2-one (50). To a solution of 2 g (6.6 mmol) of **49** in 70 mL of anhydrous acetone was added 2 g (17.1 mmol) of N-methylmorpholine N-oxide and 70 mg of tris(triphenylphosphine)ruthenium(II) chloride.[37] After several minutes the yellow solution became darker and a gummy precipitate was seen coating the wall of the reaction flask. An additional 2 g of N-methyl-morpholine N-oxide and 70 mg of ruthenium catalyst was added after 3 h at 20°C. The reaction was stirred for an additional 15 h before the solvent was removed in vacuo. The residue was introduced onto a silica gel column (60 g, 3 x 30 cm, packed in dichloromethane) with dichloromethane and flash eluted with 50% ethyl acetate:hexane. Three fractions (125 mL, 250 mL, and 200 mL, respectively) were collected. Evaporation of fraction 2 afforded 1.5 g (75%) of solid product. Recrystallization from ether afforded 1.2 g of **50** as colorless needles, mp 126-127°C. IR (nujol) 2940, 2870, 1780, 1735, 1690, 1460, 1385, 1361, 1320, 1297, 1238, 1201, 1139, 1122, 1100, 1068, 1013, 984, 964, 932, 910, 689 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ (TMS) 0.91 (m, 9H, isopropyl methyl and lactonic methyl), 1.40 (d, 3H, J = 6 Hz,

-CH(C$\underline{H}_3$)C(O)-), 1.65 (m, 1H, -$CH_2C\underline{H}$(CH_3)-), 2.25 (m, 3H, -C(O)$CH_2C\underline{H}_2$-, isopropyl methine), 2.54 (t, 2H, J = 7 Hz, -$C\underline{H}_2$C(O)O-), 4.0-4.7 (m, 4H, oxazolidinone H, -$C\underline{H}$(CH_3)C(O)X_Y); ^{13}C NMR ($CDCl_3$) δ (TMS) 12.74, 14.62, 16.05, 17.87, 26.39, 27.16, 28.27, 39.90, 58.16, 63.30, 82.60, 105.61, 153.11, 171.44, 174.17; $(\alpha)_D^{25}$ = +56.3° (c 1.23, CH_2Cl_2); R_f = 0.27 (silica gel, 50% EtOAc:hexane).

Anal. calcd. for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80. Found: C, 60.30; H, 7.79.

(4S)-3-[(2S)-2-{(3S,5S,6R)-3,5-Dimethylvalerolacton-6-yl}-propionyl)-4-(2-propyl)-oxazolidine-2-one (51). To a solution of 4.8 mmol of lithium diisopropylamide (2.9 mL of a 1.65 M solution of n-butyllithium in hexane and 0.73 mL (5.2 mmol) of diisopropylamine) in 7 mL of anhydrous THF at -78°C was added a solution of 1.12 g (3.8 mmol) of **50** in 3 mL of THF. The lactone was enolized over 2 h at -78°C before 3 mL (48 mmol) of iodomethane and 0.96 mL (5.5 mmol) of hexamethylphosphoric triamide (HMPT) was added. After 7 h (-78°C), 10 mL of a saturated aqueous ammonium chloride solution was added, and the reaction mixture was warmed to 20°C. The aqueous solution was extracted with ether. The ethereal extracts were combined, extracted with water, dried (anhydrous Na_2SO_4), and concentrated in vacuo to afford 1.16 g of a solid. Diastereomer analysis (10 meter Carbowax 20 M, 225°C, t_r major = 3.51 min, t_t minor = 3.69) gave a ratio of ≥97:3. Recrystallization from carbon tetrachloride:hexane (1:2) gave 0.92 g (78%) of **51** as white rhombic crystals, mp 94-95°C. IR (CCl_4) 2975, 2945, 2884, 1783, 1736, 1692, 1458, 1390, 1320, 1301, 1208, 1110, 1095, 991 cm^{-1}; ^{1}H NMR (90

MHz, CCl_4) δ (TMS) 0.93 [m, 9H, isopropyl methyl and $-CH_2CH(C\underline{H}_3)CHO-$], 1.27 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)CO_2-$], 1.40 [d, 3H, J = 6.5 Hz, $-CH(C\underline{H}_3)C(O)X_V$], 1.8 (m, 2H), 2-2.7 (m, 3H), 3.9-4.6 (m, 5H); ^{1}H NMR (500 MHz, benzene-d_6) δ (TMS) 0.42 (d, 3H, J = 7 Hz, isopropyl methyl), 0.52 (d, 3H, J = 7 Hz, isopropyl methyl), 0.72 (d, 3H, J = 7.2 Hz, $-CHC\underline{H}_3CO_2-$), 1.11 [d, 3H, J = 7 Hz, $-CH_2-CH(C\underline{H}_3)CH(OR)-$], 1.28 (m, 2H, $-CH_2-$), 1.51 [d, J = 6.8 Hz, $-CH(C\underline{H}_3)COX_V$], 2.05 [m, 2H, $-C\underline{H}(CH_3)CH(OR)-$ and isopropyl methine], 2.23 (m, 1H, J_{H-CH_3} = 7.2 Hz, α-lactonic methine), 3.34 (dd, 1H, J = 8.5, 9.0 Hz, proton anti to the isopropyl unit on the oxazolidinone ring), 3.46 (dd, 1H, J = 3, 9 Hz, proton syn to isopropyl unit in oxazolidinone ring), 3.98 (m, 1H, $-C\underline{H}N-$), 4.40 [dq, 1H, J_{H-CH_3} = 6.8 Hz, J = 10 Hz, $-CH(OR)C\underline{H}(CH_3)COX_V$], 4.52 [dd, 1H, J = 2.5, 10 Hz, $-C\underline{H}(OC(O)-)CH(CH_3)-$]; ^{13}C NMR ($CDCl_3$) δ (TMS) 11.83, 14.69, 16.12, 17.81, 27.94, 28.27, 31.26, 35.87, 40.36, 58.23, 63.36, 83.96, 153.24, 173.91, 174.23; $[\alpha]_D^{25}$ = +53.7° (c 0.795, CH_2Cl_2); R_f = 0.47 (silica gel, 50% EtOAc:hexane).

Anal. calcd. for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09. Found: C, 61.67; H, 7.90.

(2R,3R,4S,6S)-3,7-Dihydroxy-2,4,6-trimethyl-1-heptanol (52). To 80 mL of a 1 M THF solution of lithium aluminum hydride cooled to -78°C was added, via a cannula, a cooled solution (-78°C) of 2.5 g (8.03 mmol) of **51** in 20 mL of THF. After 1 h at -78°C the reaction mixture was warmed to 20°C over 2 h, and then stirred an additional 8 h. The mixture was cooled (0°C) before 5 mL of water was cautiously added to quench excess hydride reagent. This was followed successively by 5 mL of a 15% aqueous sodium hydroxide

solution and 10 mL of water. The resulting white slurry was transferred to an extraction thimble and continuously extracted with ether for 24 h in a Soxhlet extractor. The ethereal extract was concentrated in vacuo. The residue was triturated with dichloromethane to give a white solid. The solid was washed with dichloromethane and dried under vacuum to give 1 g (65%) of triol **52**: mp 110-111°C; ^{1}H NMR (90 MHz, CD_3OD) δ (TMS) 0.9 (m, 9H, methyl), 1.0-2.0 (m, 5H), 3.2-3.7 (m, 5H), 4.75 (s, 4H, -OH); R_f = 0.10 (silica gel, 75% EtOAc:hexane). The title compound was carried on to the subsequent experiment without further characterization.

(4R,5R)-2,2,5-Trimethyl-4-[(2S,4S)-4-methyl-5-hydroxypent-2-yl]-1,3-dioxacyclohexane (53). To a solution of 352 mg (1.85 mmol) of **52** in 40 mL of anhydrous acetone and 10 mL of toluene was added 700 mg of Dowex 50 X 12-100 ion-exchange resin[48] (pre-washed with 3 x 20 mL of anhydrous methanol). The mixture was heated at 110°C for 1 h utilizing a Dean-Stark trap filled with anhydrous $MgSO_4$ to remove moisture. The solution was then cooled, filtered, and the solvent evaporated to give 426 mg (100%) of acetonide **53** as a colorless liquid: IR (CCl_4) 3440, 3000, 2975, 2939, 2878, 1462, 1381, 1370, 1273, 1250, 1238, 1202, 1180, 1141, 1120, 1101, 1039, 1010, 982, 965, 938, 908, 864, 855 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ (TMS) 0.85 (d, 6H, J = 7 Hz), 1.0 (d, 3H, J = 7 Hz), 1.30 (s, 3H, acetonide methyl), 1.35 (s, 3H, acetonide methyl), 1.0-1.9 (m, 5H), 2.4 (br s, 1H, -OH), 3.2-4.0 (m, 5H); ^{13}C NMR (CCl_4) δ (TMS) 10.33, 15.40, 18.78, 29.63, 31.26, 32.49, 34.18, 66.48, 68.50, 76.23, 98.07; $[\alpha]_D^{25}$ = -37.4° (c 1.99, CH_2Cl_2); R_f = 0.52 (silica gel, 75% EtOAc:hexane).

Anal. calcd. for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.63; H,

11.25.

(4R,5R)-2,2,5-Trimethyl-4-[(2S,4S)-4-methyl-5-oxopent-2-yl]-1,3-dioxacyclohexane (54). The procedure for the oxidation of alcohol **46** was employed in the preparation of the title compound. The reaction was carried out at 20°C utilizing the following quantities of reagent: 426 mg (1.85 mmol) of **53**, 3.1 mL of triethylamine, 1.55 g of pyridine-sulfur trioxide complex, and 12 mL of dimethyl sulfoxide (DMSO). The usual workup gave 386 mg (91%) of aldehyde **54**: IR (neat) 2960, 2939, 2905, 2845, 2680, 1705, 1444, 1365, 1352, 1258, 1239, 1220, 1189, 1167, 1130, 1090, 999, 970, 950, 921, 891, 841 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.86 [d, 3H, J = 6 Hz, $-CH_2CH(C\underline{H}_3)-$], 0.95 (d, 3H, J = 7 Hz, acetonide methyl), 1.06 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)CHO$], 1.30 (s, 3H), 1.33 (s, 3H), 1.1-1.8 (m, 4H), 2.35 [m, 1H, $-C\underline{H}(CH_3)CHO$], 3.4 (dd, 1H, J = 9, 3 Hz), 3.43 (dd, 1H, J = 12, 2 Hz), 3.90 (dd, 1H, J = 12, 3 Hz), 9.57 (d, 1H, J = 2 Hz, $-C\underline{H}O$); $[\alpha]_D^{25} = -19.1°$ (c 2.40, CH_2Cl_2). This material was used in the subsequent experiment immediately without further purification to avoid epimerization of the stereocenter adjacent to the aldehyde function.

(4S,6S)-4-Methyl-6-[(4R,5R)-2,2,5-trimethyl.-1,3-dioxacyclohex-4-yl]-hept-2-enoic Acid, Methyl Ester (55). To a solution of 386 mg (1.69 mmol) of **54** in 10 mL of dichloromethane was added 4 g (12.0 mmol) of (carbomethoxymethylene)-triphenylphosphorane. After 8 h at 20°C, the solvent was removed in vacuo. The residue was flash filtered through a silica gel column (60 g, 3 x 30 cm) with dichloromethane. Evaporation of the solvent gave 434 mg (90%) of **55** as a solid, mp 54-55°C. GC analysis (10 meter Carbowax 20 M, 130°C, t_r E = 8.2 min, t_r Z = 6.7 min) gave an E:Z ratio of 96:4: IR (CCl_4) 3000,

2968, 2940, 2880, 2870, 1727, 1653, 1456, 1433, 1376, 1360, 1272, 1198, 1174, 1140, 1098, 1007, 980, 960, 930 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.88 [d, 3H, J = 6.5 Hz, $-CH_2CH(C\underline{H}_3)-$], 0.99 (d, 3H, J = 7 Hz, acetonide methyl), 1.05 (d, 3H, J = 7 Hz, $-CHC\underline{H}_3CH=C=$), 1.29 (s, 3H), 1.31 (s, 3H), 1.1-1.8 (m, 4H), 2.4 (m, 1H, vinylic methine), 3.35 (dd, 1H, J = 9, 2 Hz), 3.47 (dd, 1H, J = 10, 2 Hz), 3.64 (s, 3H, $-CO_2\underline{Me}$), 3.90 (dd, 1H, J = 11, 3 Hz), 5.69 (dd, 1H, J = 15, 1.5 Hz, $=C\underline{H}CO_2Me$), 6.8 (dd, 1H, J = 15, 7 Hz, $-C\underline{H}=CHCO_2Me$); ^{13}C NMR (CCl_4) δ (TMS) 10.31, 15.25, 17.59, 18.63, 29.62, 29.70, 31.57, 32.80, 37.00, 50.54, 66.27, 75.75, 98.00, 118.58, 153.93, 165.20; $[\alpha]_D^{25}$ = -15.2° (c 0.410, CH_2Cl_2); R_f **E-55** = 0.35, **Z-55** = 0.46 (silica gel, 20% EtOAc:hexane).

Anal. calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.85; H, 9.90.

(4R,6S)-4-Methyl-6-[(4R,5R)-2,2,5-trimethyl-1,3-dioxacyclohex-4-yl]-heptanoic Acid, Methyl Ester (56). A solution of 434 mg (1.53 mmol) of **55** in 15 mL of ethyl acetate and 200 mg of platinum (IV) oxide was hydrogenated under 3 atm of hydrogen in a Parr apparatus for 2 h. The catalyst was then removed by filtration through 2.5 g of silica gel (15 mL sintered glass funnel). Evaporation of the solvent gave 428 mg (98%) of **56** as an oil: IR (CCl_4) 3001, 2970, 2940, 2880, 1741, 1460, 1439, 1380, 1367, 1273, 1252, 1202, 1178, 1100, 1010, 980, 962, 933, 850 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.82 [d, 3H, J = 6 Hz, $-CH_2CH(C\underline{H}_3)CH_2-$], 0.83 [d, 3H, J = 7 Hz, $-CH_2CH(C\underline{H}_3)C(-OR)H-$], 0.95 (d, 3H, J = 7 Hz, acetonide methyl), 1.25 (s, 3H, acetonide methyl), 1.30 (s, 3H, acetonide methyl), 1.50 (m, 7H), 2.20 (t, 2H, J = 6.5 Hz, $-C\underline{H}_2CO_2CH_3$), 3.30 (dd, 1H, J = 9, 3 Hz), 3.42 (dd, 1H, J = 12, 2 Hz), 3.59 (s, 3H, $-CO_2C\underline{H}_3$),

3.90 (dd, 1H, J = 11, 3 Hz); ^{13}C NMR (CCl_4) δ (TMS) 10.27, 15.21, 18.26, 18.72, 28.98, 29.63, 31.26, 31.45, 33.21, 37.76, 50.63, 66.35, 76.10, 97.94, 172.02; $[\alpha]_D^{25}$ = -31.6° (c 2.70, CH_2Cl_2); R_f **56** = 0.65 (silica gel, 50% EtOAc:hexane). The title compound was carried on to the subsequent experiment without further characterization.

(4S,6S,7R,8R)-7,9-Dihydroxy-4,6,8-trimethylnonanoic Acid, Methyl Ester (57). To a solution of 414 mg (1.45 mmol) of **56** in 25 mL of anhydrous methanol was added 2.5 g of Dowex 50 X 12-200 ion-exchange resin[48] (pre-washed with 3 x 20 mL of methanol). The mixture was stirred at 20°C for 9 h, the resin was removed by filtration, and the solvent was removed in vacuo to give 362 mg (100%) of **57** as a white solid, mp 65-66°C; IR (CCl_4) 3340, 2970, 2944, 2922, 2890, 2860, 1736, 1473, 1453, 1438, 1419, 1383, 1330, 1318, 1271, 1252, 1218, 1195, 1171, 1145, 1118, 1098, 1070, 1042, 981, 934, 890, 882 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.7-1.1 (m, 11H), 1.3-2.0 (m, 5H), 2.3 (t, 2H, J = 7 Hz, -C<u>H</u>$_2$CO$_2$Me), 2.7 (br s, 2H, -O<u>H</u>), 3.45 (dd, 1H, J = 8, 3 Hz, -CH(CH$_3$)C<u>H</u>(OH)CH(CH$_3$)-), 3.65 (s, 3H, -CO$_2$C<u>H</u>$_3$), 3.67 (br d, 2H, -C<u>H</u>$_2$OH); $[\alpha]_D^{25}$ = -36.3° (c 0.820, CH_2Cl_2); R_f **57** = 0.15 (silica gel, 50% EtOAc:hexane).

Anal. calcd. for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64. Found: C, 63.53; H, 10.56.

(4S,6S,7R,8S)-7-Hydroxy-4,6,8-trimethyl-9-{({1,1-dimethylethyl}dimethylsilyl)oxy)-nonanoic Acid, Methyl Ester (58). To a solution of 362 mg (1.47 mmol) of **57** in 5 mL of dichloromethane was added 480 mg (2.94 mmol) of t-butyldimethylsilyl chloride, 10 mg 4-N,N-dimethylaminopyridine, and 0.5 mL of triethylamine. The reaction was stirred at 20°C for 1 h, and

then introduced directly onto a solvent-packed column of silica gel (70 g, 3 x 30 cm, 10% ethyl acetate:hexane). The product was flash eluted with 1 L of 10% ethyl acetate:hexane followed by 500 mL of 20% ethyl acetate:hexane (8 mL fractions). The bis-silylated product eluted first and the fractions (#43-80) containing the monosilylated product **58** were combined and concentrated to give 476 mg (90%) of light yellow oil: IR (CCl_4) 3520, 2968, 2942, 2870, 1742, 1471, 1460, 1438, 1380, 1258, 1173, 1088, 1021, 1008, 971, 839 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.07 (s, 6H, $=Si(C\underline{H}_3)_2$), 0.8-1.2 (m, 20H), 1.3-1.85 (m, 5H), 2.11 (s, 1H, -O<u>H</u>), 2.25 (t, 2H, J = 7 Hz, $-CH_2C\underline{H}_2CO_2Me$), 3.30 (dd, 1H, J = 7.5, 3 Hz, -C<u>H</u>(OH)-), 3.59 (s, 3H, $-CO_2C\underline{H}_3$), 3.60 (d, 2H, J = 4 Hz, $-C\underline{H}_2OSiR_3$); ^{13}C NMR (CCl_4) δ (TMS) -5.72, 10.20, 14.88, 18.00, 18.65, 25.73, 29.44, 31.26, 32.82, 33.14, 36.39, 40.16, 50.62, 67.85, 172.27; $[\alpha]_D^{25}$ = -20.8° (<u>c</u> 1.64, CH_2Cl_2); R_f **58** = 0.63, R_f bis-silylated **57** = 0.72 (silica gel, 50% EtOAc:hexane).

<u>Anal.</u> calcd. for $C_{19}H_{39}O_4Si$: C, 63.46; H, 10.93. Found: C, 63.40; H, 11.03.

(4S,6S,7R,8S)-7-[(S-Methyl-dithiocarbonyl)oxy]-4,6,8-trimethyl-9-[({1,1-dimethyl ethyl}dimethylsilyl)oxy]-nonanoic Acid, Methyl Ester (59). An oil-free suspension of sodium hydride in 5 mL of anhydrous THF was prepared by washing 800 mg of a 50% oil dispersion of sodium hydride with 3-10 mL portions of THF. To this hydride suspension was added a solution of 300 mg (0.83 mmol) of **58** in 5 mL of THF followed by 6 mL of carbon disulfide. The slurry was stirred for 30 min before 10 mL of iodomethane was added. After 20 h, the mixture was filtered through celite. The concentrated filtrate was taken up in ether, washed with water, dried ($MgSO_4$), and

reconcentrated in vacuo to give 711 mg of a red oil (by TLC to consist of mainly **59**; R_f **59** = 0.43, silica gel, 15% EtOAc:hexane). A small amount was flash chromatographed (10 g silica gel, 1.5 x 30 cm, 5% ethyl acetate:hexane) to provide a pure sample of **59** as a yellow oil: IR (CCl_4) 2965, 2942, 2870, 1744, 1464, 1458, 1440, 1390, 1383, 1364, 1257, 1252, 1222, 1175, 1110, 1051, 1049, 840 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.03 (s, 6H -$SiMe_2$), 0.85-1.0 (m, 18H), 1.0-1.7 (m, 6H), 1.8-2.4 (m, 3H), 2.52 (s, 3H, -SCH_3), 3.48 (dd, 2H, J = 6, 2 Hz, -CH_2OSiR_3), 3.59 (s, 3H, -OCH_3), 5.79 (t, 1H, J = 5.5 Hz, -$CH(OCS_2Me)$); $[\alpha]_D^{25}$ = -31.5° (c 1.35, CH_2Cl_2). The title compound was carried on to the subsequent reaction without further characterization due to apparent instability to silica gel.

(4S,6S,8S)-9-[({1,1-Dimethylethyl}dimethylsilyl)oxy]-4,6,8-trimethylnonanoic Acid, Methyl Ester (60). To a solution of the unpurified xanthate ester **59** (derived from 300 mg (0.83 mmol) of **58**) in 12 mL of toluene was added 10 mg of 2,2'-azobis(2-methylpropionitrile) and 2 mL of tri-n-butyltin hydride. The mixture was heated to 120-125°C for 12 h. The solvent was removed in vacuo. The residue was flash chromatographed (30 g silica gel, 2 x 30 cm, 200 mL hexane, 15% ethyl acetate:hexane, 10 mL fractions) to remove the tin by-products which eluted first (fractions 10-25) and to afford 230 mg (80% overall from **58**) of purified **60** as a colorless liquid: IR (neat) 2965, 2940, 2872, 1745, 1472, 1464, 1458, 1439, 1380, 1258, 1170, 1095, 837, 772 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.02 (s, 6H, $=Si(CH_3)_2$), 0.8-1.1 (m, 18H), 1.1-1.8 (m, 8H), 2.2 (t, 2H, J = 7 Hz, -CH_2CO_2Me), 3.35 (dd, 2H, J = 5, 2 Hz, -CH_2OSiR_3), 3.55 (s, 3H, -CO_2CH_3); ^{13}C NMR (CCl_4) δ (TMS) -5.52, 17.48, 18.13, 18.98, 20.08, 25.80, 27.23,

29.44, 31.19, 32.56, 32.82, 41.72, 44.13, 50.56, 67.78, 172.15; $[\alpha]_D^{25}$ = -17.5° (c 4.19, CH_2Cl_2); R_f **60** = 0.44; R_f tin compounds = 0.64 (silica gel, 15% EtOAc:hexane). The title compound was carried on to the subsequent experiment without further characterization.

(4S,6S,8S)-9-Hydroxy-4,6,8-trimethylnonanoic Acid, Methyl Ester (61). To 230 mg (0.67 mmol) of **60** was added 5 mL of a 0.4 M solution of tetra-n-butylammonium fluoride[50] in THF. After 19 h, the solvent was removed in vacuo. The residue was taken up in dichloromethane and flash chromatographed (12 g silica gel, 2 x 30 cm, 15% ethyl acetate:hexane, 10 mL fractions) to give 151 mg (98%) of **61** as a clear liquid: IR (neat) 3440, 2968, 2882, 2860, 1742, 1458, 1439, 1380, 1255, 1173, 1112, 1040, 987 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.80-0.95 (m, 9H), 0.9-1.8 (m, 9H), 1.92 (s, 1H, -OH), 2.27 t, 2H, J = 7 Hz, $-CH_2CO_2Me$), 3.35 (d, 2H, J = 5.5 Hz, $-CH_2OH$), 3.60 (s, 3H, $-CO_2CH_3$); ^{13}C NMR (CCl_4) δ (TMS) 17.42, 19.24, 20.41, 27.23, 29.31, 31.13, 32.17, 32.69, 41.14, 44.26, 50.82, 66.94, 172.80; $[\alpha]_D^{25}$ = -26° (c 3.3, CH_2Cl_2); R_f = 0.49 (silica gel, 50% EtOAc:hexane).

Exact mass calcd. for $C_{13}H_{26}O_3$: 230.1882. Found: 230.1874.

(4S,6S,8S)-9-Oxo-4,6,8-trimethylnonanoic Acid, Methyl Ester (62). The procedure for the oxidation of alcohol **46** was employed in the preparation of the title compound. The following quantities of reagents were used: 148 mg (0.64 mmol) of **61**, 6 mL of DMSO, 0.94 mL of triethylamine, 0.90 g of sulfur trioxide-pyridine complex. The usual workup afforded 140 mg (95%) of **62** as a yellow liquid: IR (neat) 2968, 2940, 2880, 2720, 1740, 1456, 1439, 1380, 1256, 1171, 1116 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.85 (d, 6H, J = 6 Hz, C4 and C6 methyls), 1.05 (d, 3H, J = 7 Hz, $-HC(CH_3)CHO$), 1.0-1.8 (m,

8H), 2.23 (t, 2H, J = 7 Hz, -C<u>H</u>$_2$CO$_2$Me), 2.30 [m, 1H, -C<u>H</u>(CH$_3$)CHO], 3.60 (s, 3H, -CO$_2$C<u>H</u>$_3$), 9.50 (d, 1H, J = 2 Hz, -C<u>H</u>O); ^{13}C NMR (CCl$_4$) δ (TMS) 14.04, 18.98, 19.56, 27.55, 29.31, 31.06, 32.30, 38.73, 43.54, 44.06, 50.63, 172.15, 201.59. The title compound was carried on to the subsequent experiment without further characterization.

(4S,6S,8S,9S)-9-Hydroxy-4,6,8-trimethyldecanoic Acid, Methyl Ester and Epimer at C9 (63a,b). A solution of lithium dimethylcuprate was generated at 0°C using 600 mg (2.92 m equiv. wt.) of copper (I) bromide-methyl sulfide complex[51] in 5 mL of ether and 4.0 mL (5.6 mmol) of a 1.4 <u>M</u> ethereal solution of methyllithium. After 15 min the yellow solution was cooled (-78°C) before a solution of 140 mg (0.61 mmol) of aldehyde **62** in 1 mL of ether was added. The reaction was quenched with a saturated aqueous ammonium chloride solution after 1 h at -78°C. The blue aqueous solution was extracted with ether, and the ethereal extracts were combined, dried ($MgSO_4$), and evaporated to afford an oil. Flash chromatographic purification (10 g silica gel, 1.5 x 30 cm, 10% ether:dichloromethane, 5 mL fractions) afforded 130 mg (87%) of purified products (R_f **63a** = 0.54, R_f **63b** = 0.47, silica gel, 50% EtOAc:hexane). Diastereomer analysis (DB-1, 150°C, t_r **63a** = 3.96 min, t_r **63b** = 4.12 min) gave a ratio of **63a:63b** = 55:45: ^{1}H NMR (90 MHz, CCl$_4$) δ (TMS) 0.85 (m), 1.03 [d, J = 7 Hz, CH(C<u>H</u>$_3$)CH(OH)CH$_3$], 1.06 [d, J = 7 Hz, -CH(C<u>H</u>$_3$)CH(OH)CH$_3$], 1.15-1.80 (m), 2.1 (s, -O<u>H</u>), 2.25 (t, J = 6 Hz, -C<u>H</u>$_2$CO$_2$Me), 3.56 [m, -C<u>H</u>(OH)CH$_3$], 3.60 (s, -CO$_2$<u>Me</u>). The title compounds were carried on to the subsequent experiment without further characterization.

(4S,6S,8S)-9-Oxo-4,6,8-trimethyldecanoic Acid, Methyl Ester (64). The

procedure used for the oxidation of alcohol **46** was followed in the preparation of the title compound. To 39.1 mg (0.16 mmol) of diastereomers **63a** and **63b** in 1 mL of DMSO was added 0.28 mL of triethylamine followed by a solution of 260 mg of sulfur trioxide-pyridine complex in 1 mL of DMSO. The usual workup and flash chromatographic purification (10 g silica gel, 1.5 x 30 cm, 10% ethyl acetate:hexane, 3 mL fractions) afforded 35 mg (90%) of **64** as a clear oil. IR (CCl_4) 2975, 2940, 2880, 1740, 1718, 1461, 1441, 1382, 1360, 1174 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.86 (d, 3H, J = 6.5 Hz; d, 3H, J = 6.5 Hz, C_4 and C_6 methyls), 1.05 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)COCH_3$], 1.06 (m, 2H), 1.2-1.8 (m, 6H), 2.05 (s, 3H, $-COC\underline{H}_3$), 2.27 (t, 2H, J = 7 Hz, $-CH_2C\underline{H}_2CO_2Me$), 2.52 [m, 1H, $-CH(CH_3)COMe$], 3.60 (s, 3H, $-CO_2Me$); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.70 (d, 3H, J = 6.5 Hz), 0.72 [d, 3H, J = 6.5 Hz, $-CH(C\underline{H}_3)CH_2-$], 0.85 [d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)COCH_3$], 0.89 (m, 2H), 1.38 (m, 4H), 1.57 (m, 2H), 1.76 (s, 3H, $-COC\underline{H}_3$), 2.15 (dt, 2H, J = 8.5, 2 Hz, $-CH_2C\underline{H}_2CO_2Me$), 2.32 [m, 1H, $-C\underline{H}(CH_3)COCH_3$], 3.38 (s, 3H, $-CO_2\underline{Me}$); ^{13}C NMR (CCl_4) δ (TMS) 17.03, 19.11, 19.69, 21.78, 27.21, 28.01, 29.44, 31.19, 32.36, 40.94, 44.45, 50.69, 172.22, 198.02; $[\alpha]_D^{25}$ = -14.5° (c 1.22, CH_2Cl_2); R_f = 0.28 (silica gel, 20% EtOAc:hexane).

Anal. calcd. for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.42; H, 10.86.

(4R,5R,6R)-2,2,5-Trimethyl-4-formyl-6-[(2R)-3-benzyloxy-2-propyl] -1,3-dioxacyclohexane (65). The procedure used for the oxidation of **46** was employed in the preparation of the title compound. To 200 mg (0.65 mmol) of **91**[52] in 3 mL of DMSO was added 0.66 mL of triethylamine and a solution of 640 mg sulfur trioxide-pyridine complex in 3 mL of DMSO. The usual workup

after 1 h at 20°C gave 190 mg (96%) of aldehyde **65** (R_f = 0.62, silica gel, 20% ether:CH_2Cl_2) as an oil: ^{1}H NMR (90 MHz, CCl_4) δ (TMS) 0.85 [d, 3H, J = 6.5 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$-] , 0.95 [d, 3H, J = 7 Hz, -CH(OR)CH($C\underline{H}_3$)-] , 1.38 (s, 6H, acetonide geminal $-CH_3$), 1.6-2.3 (m, 2H, methine), 3.05-3.70 [m, 4H, $PhCH_2OC\underline{H}_2$-, -C<u>H</u>(OR)] , 4.40 (s, 2H, $PhC\underline{H}_2O$-), 7.20 (s, 5H, aromatic H), 9.35 (d, 1H, J = 3 Hz, -C<u>H</u>O). The title compound was carried on to the subsequent experiment without further characterization.

C17-C32 Synthon 66. To a solution of 582 mg (0.70 mmol) of phosphonium salt **44** in 5.4 mL of toluene was added 1.45 mL (0.83 mmol) of a 0.575 <u>M</u> solution of sodium hexamethyldisilylamide[47] in toluene. After 15 min at 20°C, the orange solution was cooled to -78°C for 30 min. A solution of 200 mg (0.65 mmol) of aldehyde **65** in 0.200 mL of toluene was added. After 15 min, the cooling bath was removed and the reaction mixture was stirred an additional 5 h at 20°C. The triphenylphosphine oxide was precipitated by the addition of hexane. The mixture was filtered through celite, the filtrate was concentrated <u>in vacuo</u>, and the residue flash chromatographed (10 g silica gel, 1.5 x 30 cm, dichloromethane) to afford 424 mg (89%) of **66** as a light yellow oil. Diastereomer analysis (SE-54, 260°C, t_r major = 15.14 min, t_r minor = 14.12 min) gave a ratio of Z:E isomer of 97.3:2.7: IR (neat) 2966, 2944, 2868, 1460, 1378, 1371, 1258, 1204, 1170, 1100, 1049, 1008, 990, 939, 912, 887, 836, 810, 772, 732, 695, 681, 662 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ (TMS) 0.05 (m, 12H, $-Si\underline{Me}_2$), 0.70 (d, 3H, J = 6 Hz), 0.89 (s, 18H, t-butyl groups), 1.0 (d, 3H, J = 7 Hz), 1.06 (s, 3H), 1.13 (s, 3H), 1.29 (s, 3H, acetonide geminal methyl), 1.39 (s, 3H, acetonide geminal methyl), 1.4-2.3 (m, 10H), 3.1-4.2 (m, 6H), 4.4 (s, 2H, $PhC\underline{H}_2O$-), 5.0-5.6 (m, 2H, olefinic H), 7.2 (s, 5H, aromatic H); ^{1}H

NMR (500 MHz, benzene-d_6) δ (TMS) 0.07 [s, 6H, =Si($C\underline{H}_3$)$_2$], 0.15 [s, 3H, -Si($C\underline{H}_3$)$_2$], 0.17 [s, 3H, =Si($C\underline{H}_3$)$_2$], 0.83 [d, 3H, J = 7 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)CH(OR)$-], 0.98 (s, 9H, t-BuSi≡), 1.02 (s, 9H, t-BuSi≡), 1.18 (s, 3H, methyl in tetrahydrofuran ring), 1.18 (d, 3H, J = 7 Hz, methyl in acetonide ring), 1.19 [s, 3H, $-C(OSiR_3)C\underline{H}_3$-], 1.27 [d, 3H, J = 6 Hz, $-CH(C\underline{H}_3)OSiR_3$-], 1.49 (s, 3H, axial methyl in acetonide ring), 1.53 (s, 3H, equatorial methyl in acetonide ring), 1.60 [m, 1H, $-CCH_3(OSiR_3)C\underline{H}_2$-], 1.75 [m, 3H, tetrahydrofuranyl methylene and $-CCH_3(OSiR_3)C\underline{H}_2$-], 1.85 (m, 2H, tetrahydrofuranyl methylene), 2.27 (m, 2H, methine), 2.34 (m, 2H, $-C\underline{H}_2CH=CH$-), 3.39 [dd, 1H, J = 9, 7 Hz, $PhCH_2OC\underline{H}(H)$-], 3.57 [dd, 1H, J = 10, 2 Hz, $BnOCH_2$-$CH(CH_3)C\underline{H}(OR)$-], 3.69 [q, 1H, J = 6Hz, $-C\underline{H}(CH_3)OSiR_3$], 3.83 (dd, 1H, J = 9, 6 Hz, $PhCH_2OC\underline{H}_2$-), 3.89 (t, 1H, J = 7 Hz, tetrahydrofuranyl methine), 4.33 (d, 1H, J = 12 Hz, $PhC\underline{H}_2O$-), 4.36 (d, 1H, J = 12 Hz, $PhC\underline{H}_2O$-) 4.44 [dd, 1H, J = 10, 8 Hz, $-C\underline{H}(OR)CH=CH$-], 5.48-5.59 (m, 2H, J_{cis} = 11 Hz, $-C\underline{H}=C\underline{H}$-), 7.09 (t, 1H, J = 7.5 Hz), 7.18 (t, 2H, J = 7.5 Hz), 7.31 (br d, 2H, J = 7.5 Hz); ^{13}C NMR (CCl_4) δ (TMS) -5.00, -3.96, -2.01, 12.02, 15.99, 17.74, 18.26, 18.59, 19.24, 22.23, 22.98, 25.74, 25.87, 30.02, 34.18, 35.81, 36.13, 40.03, 70.45, 70.97, 72.66, 73.57, 76.10, 77.34, 82.60, 84.87, 97.35, 126.86, 127.77, 129.59, 132.83, 138.62; $[\alpha]_D^{25}$ = +6.59° (c 2.78, CH_2Cl_2).

Anal. calcd. for $C_{42}H_{76}O_6Si_2$: C, 68.80; H, 10.45. Found: C, 68.94; H, 10.40.

C17-C32 Synthon 67. To a solution of 2.5 g (9.56 mmol) of anhydrous tetra-n-butylammonium fluoride[50] in 4 mL of THF in a resealable tube was added a solution of 550 mg (0.75 mmol) of **66** in 6 mL of THF. The mixture

was heated to 80°C for 36 h in the sealed tube. The solvent was then removed in vacuo. The residue was introduced onto a silica gel column (40 g, 3 x 40 cm, packed in hexane) and flash eluted with 50% ethyl acetate:hexane (100 mL fractions). Concentration of the product-containing fractions (#2-5) afforded 356 mg (94%) of diol **67** as a liquid: IR (neat) 3410, 2980, 2945, 2882, 1656, 1498, 1455, 1380, 1350, 1255, 1205, 1172, 1130, 1103, 1080, 1046, 1030, 1011, 995, 940, 911, 891, 735, 697 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.71 [d, 3H, J = 6 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$-], 0.96 (d, 3H, J = 7 Hz, acetonide methyl), 1.05 [d, 3H, J = 6 Hz, $-CH(OH)C\underline{H}_3$], 1.09 (s, 3H, tetrahydrofuranyl methyl), 1.20 [s, 3H, $-CH_2C(OH)C\underline{H}_3$-], 1.30 (s, 3H, axial acetonide methyl), 1.40 (s, 3H, equatorial acetonide methyl), 0.9-2.3 (m, 10H), 3.10-3.80 (m, 6H), 4.10 [dd, 1H, J = 10, 8 Hz, $-C\underline{H}(OR)CH=CH$-], 4.40 (s, 2H, $PhC\underline{H}_2O$-), 5.0-5.70 (m, 2H, $-C\underline{H}=C\underline{H}$), 7.21 (s, 5H, aromatic H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.74 (d, 3H, J = 6.6 Hz, acetonide methyl), 1.00 [d, 3H, J = 6.3 Hz, $C\underline{H}_3CH(OH)$-], 1.02 (s, 3H, tetrahydrofuranyl methyl), 1.18 [d, 3H, J = 7.1 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$-], 1.2-1.3 (m, 2H), 1.31 [s, 3H, $-CH_2C(OH)C\underline{H}_3$-], 1.40 (s, 3H, axial acetonide methyl), 1.45 (m, 1H), 1.53 (s, 3H, equatorial acetonide methyl), 1.59 (m, 1H), 1.85 (m, 1H), 2.00 (m, 1H), 2.14 (m, 1H), 2.2-2.3 (m, 3H), 3.38 (dd, 1H, J = 9.2 Hz, 7.1 Hz), 3.44 (dd, 1H, J = 2.0, 10.2 Hz), 3.68 (dd, 1H, J = 6.6, 7.7 Hz), 3.80 [q, 1H, J = 6.3 Hz, $CH_3C\underline{H}(OH)$-], 3.82 (dd, 1H, J = 6.1, 7.7 Hz), 4.32 (dd, 1H, J = 7.7, 10.2 Hz), 4.36 (ABq, 2H, J_{AB} = 12.2 Hz, $PhC\underline{H}_2O$-), 5.49 (m, 2H, vinyl H), 7.08-7.33 (m, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) 11.96, 15.86, 18.13, 19.17, 22.23, 24.09, 24.32, 26.26, 29.96, 30.41, 34.18, 35.87, 38.15, 70.38, 70.90, 72.72, 73.11, 77.33, 83.64, 86.11, 97.55, 126.86, 127.77, 129.59,

133.35, 138.55; $[\alpha]_D^{25}$ = +15.7° (c 2.40, CH_2Cl_2). The title compound was carried on to the subsequent experiment without further characterization.

Bis-Tetrahydrofuran Synthon 68. To a cooled solution (-78°C) of 356 mg (0.71 mmol) of **67** in 14 mL of dichloromethane was added 460 mg (1.4 mmol) of mercuric acetate. The heterogeneous mixture was warmed to 20°C over 6 h and stirred at 20°C an additional 7 h. A solution of 1.7 g of sodium borohydride, 2.5 mL of a 15% aqueous sodium hydroxide solution, 5 mL of water, and 30 mL of methanol was prepared and added in one portion to the cooled reaction mixture (-78°C). The mixture was stirred at 20°C for 30 min before adding 50 mL of water and extracting with ether (3 x 100 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated in vacuo to afford 347 mg of unpurified products. Diastereomer analysis (SE-54, 250°C, t_r major = 3.99 min, t_r minor = 4.97 min) gave a ratio of 93:7. Diastereoselection as high as 96.8:3.2 has been observed in smaller scale cyclization reactions.

The unpurified product was chromatographed (25 g silica gel, 2 x 30 cm, 20% ether: dichloromethane, 8 mL fractions, major diastereomer eluted first in fractions 11-17) to afford 301 mg (85%) of **68** as a colorless oil: IR (CCl_4) 3440, 2974, 2940, 2875, 1451, 1385, 1302, 1264, 1245, 1203, 1173, 1123, 1100, 1075, 1029, 1012, 999, 990, 982, 978, 916, 881 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.80 (d, 3H, J = 6 Hz, $PhCH_2OCH_2CH\underline{Me}$), 0.96 (d, 3H, J = 6 Hz, acetonide $-CH_3$), 1.0 [d, 3H, J = 6.5 Hz, $-CH(C\underline{H_3})OH$], 1.05 [s, 3H, $CH_3CH(OH)C(C\underline{H_3})O-$], 1.20 (s, 3H, central tetrahydrofuranyl methyl), 1.26 (s, 3H, axial acetonide methyl), 1.35 (s, 3H, equatorial acetonide methyl), 1.3-2.3 (m, 12H), 3.1-4.2 (m, 8H), 4.4 (s, 2H, $PhC\underline{H_2}O-$),7.21 (s, 5H, aromatic H);

^{1}H NMR (500 MHz, benzene-d_6) δ (TMS) 0.66 (d, 3H, J = 6.6 Hz, acetonide methyl), 1.05 (s, 3H, terminal tetrahydrofuranyl methyl), 1.12 (d, 3H, J = 6.4 Hz, $C\underline{H}_3CH(OH)$-), 1.17 (d, 3H, J = 7.1 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$-), 1.20-1.28 (m, 1H), 1.29 (s, 3H, central tetrahydrofuranyl methyl), 1.35 (s, 3H, axial acetonide methyl), 1.35-1.41 (m, 1H), 1.45 (s, 3H, equatorial acetonide methyl), 1.46-1.61 (m, 3H), 1.72 (m, 2H), 1.79 (m, 1H), 1.91 (m, 1H), 2.00 (m, 1H), 2.20 (m, 2H), 3.33 (dd, 1H, J = 2.0, 10.2 Hz), 3.40 (dd, 1H, J = 7.7, 8.7 Hz), 3.45 (m, 1H), 3.80 (d, 1H, J = 8.7 Hz), 3.80 (dd, 1H, J = 9.2, 11.2 Hz), 3.95 (q, 1H, J = 6.4 Hz, $CH_3C\underline{H}(OH)$-), 4.1 (br s, 1H, -OH), 4.25 (m, 1H, central tetrahydrofuranyl methine), 4.38 (ABq, 2H, J_{AB} = 9.2 Hz, $PhC\underline{H}_2O$-), 7.09-7.33 (m, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) 12.09, 15.99, 17.68, 19.11, 24.31, 25.87, 27.42, 30.02, 30.41, 30.74, 34.05, 34.77, 35.29, 38.86, 70.90, 71.94, 72.72, 77.47, 77.73, 83.70, 86.82, 97.16, 126.86, 127.83, 138.62; $[\alpha]_D^{25}$ = -7.24° (c 1.57, CH_2Cl_2); R_f = 0.54 (silica gel, 50% ether:dichloromethane).

Anal. calcd. for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.52.

Note: the other minor diastereomer can be isolated in the later chromatography fractions (#18+, not characterized).

Bis-Tetrahydrofuran Synthon 69. To a cooled (0°C) solution of 305 mg (0.60 mmol) of **68** in 12 mL of dichloromethane under nitrogen was added 1.2 mL (8.6 mmol) of freshly distilled triethylamine and 0.75 mL (3.4 mmol) of t-butyldimethylsilyl trifluoromethanesulfonate.[46] After 1.5 h at 0°C, the reaction was quenched with 10 mL of a saturated aqueous sodium bicarbonate solution, and stirred an additional 1 h at 20°C. The two phases were separated and the aqueous phase was extracted with dichloromethane (3 x 50

mL). The combined dichloromethane extracts were dried (anhydrous $MgSO_4$) and concentrated in vacuo. The residue was flash chromatographed (10 g silica gel, 1.5 x 30 cm, ether) collecting the UV active fraction. Evaporation of the solvent in vacuo afforded 374 mg (100%) of product as a yellow oil: IR (neat) 2970, 2945, 2869, 1460, 1452, 1377, 1370, 1258, 1205, 1175, 1100, 1029, 921, 831, 810, 772, 734, 695 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.05 (s, 6H, $-Si(C\underline{H}_3)_2-$), 0.79 (d, 3H, J = 6 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)-$), 0.89 (s, 9H, t-butyl group), 0.96 (d, 3H, J = 7 Hz, $C\underline{H}_3CH(OH)-$), 1.05 (s, 6H, quarternary tetrahydrofuranyl methyls), 1.10 (d, 3H, acetonide methyl), 1.25 (s, 3H, axial acetonide methyl), 1.31 (s, 3H, equatorial acetonide methyl), 1.4-2.2 (m, 12H), 3.05-4.20 (m, 7H), 4.39 (s, 2H, $PhC\underline{H}_2O-$), 7.2 (s, 5H, aromatic H); ^{13}C NMR (CCl_4) δ (TMS) -5.00, -4.03, 12.02, 15.99, 18.00, 18.13, 19.04, 23.40, 25.74, 26.45, 29.96, 31.19, 34.05, 34.83, 35.29, 35.87, 38.73, 70.97, 72.01, 72.59, 73.24, 76.36, 77.40, 82.73, 83.83, 84.74, 97.03, 126.79, 127.70, 138.55. $[\alpha]_D^{25}$ = -16.6° (c 0.976, CH_2Cl_2); R_f = 0.76 (silica gel, 50% ether:dichloromethane). The title compound was carried on to the subsequent experiment without further characterization.

Bis-Tetrahydrofuran Synthon 70. A solution of 55.2 mg (89.2 μmol) of **69** and 20 mg of 10% palladium-on-carbon in 4 mL of acetone was stirred at 20°C under 1 atmosphere of hydrogen for 3 h. Thin layer chromatographic analysis (R_f **69** = 0.76, R_f **70** = 0.47, 50% ether:dichloromethane) showed reaction to be complete. The catalyst was removed via filtration through celite. Evaporation of the solvent in vacuo afforded 44.5 mg (94%) of **70** as an oil: IR (CCl_4) 3440, 2970, 2950, 2870, 1462, 1379, 1260, 1206, 1178, 1100, 1050, 1044, 920, 838, 832, 775 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS)

0.05 [s, 6H, -Si($C\underline{H}_3$)$_2$-], 0.77 (d, 3H, J = 6.5 Hz), 0.87 (s, 9H, t-butyl group), 1.02 (d, 3H), 1.05 (s, 6H, tetrahydrofuranyl methyls), 1.09 (d, 3H), 1.30 (s, 3H, axial acetonide methyl), 1.31 (s, 3H, equatorial acetonide methyl), 1.4-2.1 (m, 12H), 3.3-4.2 (m, 7H); ^{13}C NMR (CCl_4) δ (TMS) -4.94, -3.96, 12.02, 15.40, 17.81, 18.20, 18.78, 19.11, 23.53, 25.74, 26.51, 30.09, 31.45, 34.57, 35.42, 35.87, 38.60, 62.58, 71.94, 73.37, 76.10, 79.42, 82.92, 83.83, 84.87, 97.42; $[\alpha]_D^{25}$ = -23.3° (c 1.47, CH_2Cl_2). The title compound was carried on to the next assembly stage without further characterization.

Chemical Transformations of Ionomycin and Derivatives

Ionomycin, Free acid (71). The calcium complex[53] of ionomycin (100 mg) was dissolved in hexane (15 mL) and shaken with 1 N aqueous HCl (15 mL). The hexane was separated and evaporated in vacuo to afford the free acid (100 mg) as an oil; IR (neat) 3400, 2960, 2930, 2862, 1728, 1710, 1608, 1459, 1375, 1074 cm^{-1}; ^{1}H NMR (90 MHz, benzene-d_6) δ (TMS) 0.80 (s), 0.87 (s), 0.97 (s), 1.00 (s), 1.04 (s), 1.13 (s), 1.23 (s), 1.30 (d, J = 6.5 Hz), 1.2-2.6 (m), 3.35-4.20 (m, 5H), 5.43 (s, 1H, vinylic enol H), 5.25-5.90 (m, 2H, vinyl protons); ^{1}H NMR (500 MHz, benzene-d_6) δ (TMS) 0.75 (d, 3H, J = 6.4 Hz), 0.83 (d, 6H, J = 6.9 Hz),0.90 (d, 3H, J = 6.5 Hz), 0.98 (s, 3H), 0.99-1.05 (m, 4H), 1.07 (d, 3H, J = 6.5 Hz), 1.10 (2d, 6H, J = 6.6, 6.7 Hz), 1.18-1.24 (m, 3H), 1.25 (s, 3H), 1.30 (d, 3H, J = 6.9 Hz), 1.31-1.60 (m, 6H), 1.68-1.84 (m, 5H), 1.85-2.20 (m, 4H), 2.11 (m, 1H, J = 3.7, 8.5, 12.5 Hz), 2.25 (m, 3H), 2.37 (m, 2H), 2.45 (m, 1H), 3.48 (dd, 1H, J = 3.1, 8.8 Hz), 3.70 (dd, 1H, J = 6.5, 8.4 Hz), 3.84 (q, 1H, J = 6.5 Hz, C31 methine), 3.97 (m, 1H, J = 2.1, 7.1, 9.3 Hz), 4.07 (m, 1H), 5.46 (s, 1H, vinylic enol H), 5.49 (m, 1H, C16 vinylic H), 5.76

(dd, 1H, J = 8.5, 15.4 Hz, C17 vinylic H); $[\alpha]_D^{25}$ = -6.8° (c 0.15, CH_2Cl_2). The title compound has been characterized fully as the calcium complex.[53]

Ionomycin, Methyl Ester (72). A solution of 1 g (9.7 mmol) of N-nitroso-N-mehylurea, 20 mL of ether, and 20 mL of a 15% aqueous sodium hydroxide solution was heated to 60°C in a diazomethane generating kit (Aldrich Diazald Kit). The distilled ethereal solution of diazomethane (ca. 10 mL) was collected at 0°C and added in one portion to 50 mg (70.5 μmmol) of **71**. After exactly 15 s, a few drops of glacial acetic acid was added to quench the excess diazomethane and the solvent was removed in vacuo to afford 50 mg (98%) of methyl ester. Thin-layer chromatographic analysis (silica gel; R_f of three minor impurities = 0.44, 0.36, 0.29; R_f **72** = 0.22, 50% ethyl acetate:hexane) showed small traces of by-products. Note: an extended reaction period (30 min) with excess diazomethane produces more of these impurities as well as another major product[54] (R_f = 0.15, 50% ethyl acetate:hexane). The ester was flash chromatographed (10 g silica gel, 1.5 x 30 cm, 40% ethyl acetate:hexane, 5 mL fractions) to yield 28 mg of an analytically pure sample: IR (neat) 3440, 2974, 2940, 2880, 1740, 1610, 1455, 1440, 1385, 1170, 1120, 1072, 1028, 989, 975, 910 cm^{-1}; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.69 (s), 0.72 (s), 0.80 (s), 0.83 (s), 0.90 (s), 0.99 (s), 1.01 (s), 1.10 (s), 1.15 (s), 1.30 (d, 3H, J = 7 Hz), 1.20-2.60 (m), 3.37 (s, 3H, $-CO_2\underline{Me}$), 3.40-4.15 (m, 5H), 5.44 (s, 1H, vinylic enol H), 5.25-5.95 (m, 2H, vinyl H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.725 (d, 3H, J = 6.0 Hz), 0.785 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.4 Hz), 0.905 (d, 3H, J = 6.4 Hz), 0.96 (t, 2H, J = 6.4 Hz), 1.01 (s, 3H), 1.04 (m, 1H), 1.06-1.10 [3 overlapped d (3 lines), 9H], 1.17 (s, 3H), 1.23 (m, 1H), 1.35 (d, 3H, J = 6.7 Hz), 1.29-1.45

(m, 4H), 1.48-1.57 (m, 5H), 1.57-1.75 (m, 6H), 1.81 (m, 1H), 1.84-1.94 (m, 2H), 2.01 (m, 1H), 2.08 (m, 1H), 2.16 (m, 2H), 2.37 (m, 2H), 2.43 (m, 1H), 3.37 (br s, 1H, -O<u>H</u>), 3.40 (s, 3H, $-CO_2C\underline{H}_3$), 3.52 (dd, 1H, J = 2.6, 8.8 Hz, C27 methine), 3.69 (dd, 1H, J = 6.7, 8.2 Hz, C19 methine), 3.79 [q, 1H, J = 6.3 Hz, $-C\underline{H}(CH_3)OH$], 3.88 (m, 1H, J = 1.8, 7.4, 9.2 Hz, C21 methine), 4.00 (m, 1H, C23 methine), 5.43 (m, 1H, C16 vinyl H), 5.45 (s, 1H, vinylic enol H), 5.84 [dd, 1H, J = 8.6, 15.1 Hz (trans vinylic coupling), C17 vinyl H); ^{13}C NMR (benzene-d_6) δ (TMS) 13.00, 17.94, 18.72, 18.85, 19.17, 19.50, 19.82, 23.53, 25.54, 27.81, 28.20, 29.83, 31.13, 31.32, 31.84, 32.49, 32.82, 34.05, 40.49, 40.62, 40.81, 41.20, 41.33, 42.50, 42.63, 44.71, 51.01, 73.24, 76.62, 79.22, 81.49, 83.96, 85.52, 86.95, 97.68, 133.61, 173.58, 198.73, 198.86; $[\alpha]_D^{25} = -10.9°$ (<u>c</u> 0.795, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{42}H_{74}O_9$: C, 69.77; H, 10.32. Found: C, 69.81; H, 10.23.

Ionomycin, Methyl Ester, C19-C21 Acetonide, (73). To 50 mg (69.2 μmol) of methyl ester **72** in a nitrogen-filled flask was added 5 mL of 2,2-dimethoxypropane and 10 mg of pyridinium tosylate (p-toluenesulfonate). After 10 h at 20°C, thin-layer chromatographic analysis (silica gel, 50% ethyl acetate:hexane R_f **73** = 0.58, R_f by-product = 0.70) showed no starting material was left (R_f **72** = 0.22). The solid pyridinium tosylate was removed by filtration through a glass sintered funnel, and the dimethoxypropane was removed <u>in vacuo</u>. The residue was flash chromatographed (10 g silica gel, 1.5 x 30 cm, 15% ethyl acetate:hexane, UV active fraction collected) to afford 46 mg (87%) of pure **73** as a colorless oil: IR (neat) 3460, 2980, 2945, 2920, 2882, 2860, 1741, 1610, 1460, 1440, 1379, 1304, 1265, 1204, 1173, 1129,

1075, 1070, 1030, 1014, 979, 930, 905, 868 cm^{-1}; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.68 (d, 3H, J = 6 Hz), 0.73 (d, 3H, J = 6 Hz), 0.80 (d, 3H, J = 6 Hz), 0.88 (d, 3H, J = 6 Hz), 1.05 (s, C30 methyl), 1.12 (overlapped set of 4 methyl doublets), 1.23 (part of a methyl doublet), 1.35 (s, 6H, 2 overlapped methyls, axial acetonide methyl and C26 methyl), 1.50 (s, 3H, equatorial acetonide methyl), 1.2-2.5 (m), 3.40 (s, 3H, $-CO_2C\underline{H}_3$, 3.2-4.3 (m, 5H), 5.41 (s, 1H, vinylic enol H), 5.15-5.85 (m, 2H, vinyl H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.66 (d, 3H, J = 6.5 Hz), 0.72 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.5 Hz), 0.86 (d, 3H, J = 6.5 Hz), 0.96 (t, 2H, J = 7.3 Hz), 1.05 (s, 3H), 1.08 (d, 3H, J = 6.3 Hz), 1.05 (m, 1H), 1.09 (d, 3H, J = 6.5 Hz), 1.12 (d, J = 6.5 Hz), 1.21 (d, 3H, J = 6.9 Hz), 1.25 (m, 2H), 1.34 (s, 3H), 1.36 (s, 3H, axial acetonide methyl), 1.40 (m, 3H), 1.49 (s, 3H, equatorial acetonide methyl), 1.50-1.65 (m, 6H), 1.65-1.80 (m, 2H), 1.80-1.87 (m, 3H), 1.87-1.95 (m, 1H), 2.01 (m, 2H), 2.13-2.23 (m, 4H), 2.35 (m, 3H), 3.28 (dd, 1H, J = 2.2, 9.8 Hz, C27 methine), 3.39 (s, 3H, $-CO_2\underline{Me}$), 3.54 (m, 1H, J = 2.7, 8.2, 10.9 Hz, C21 methine), 3.81 (dd, 1H, J = 7.1, 8.2 Hz, C19 methine), 3.93 [q, 1H, J = 6.5 Hz, $CH_3C\underline{H}(OH)-$], 4.12 (br s, 1H, -OH), 4.23 (m, 1H, C23 methine), 5.34 (m, 1H, C16 vinyl H), 5.44 (s, 1H, vinylic enol H), 5.73 [dd, 1H, J = 9.2, 15.3 Hz (trans vinylic coupling), C17 vinyl H); ^{13}C NMR (benzene-d_6) δ (TMS) 11.63, 18.26, 18.72, 18.91, 19.17, 19.56, 24.63, 26.32, 27.90, 28.16, 29.78, 30.43, 30.88, 31.10, 31.23, 31.80, 32.74, 35.12, 36.69, 38.91, 39.82, 40.44, 40.66, 41.33, 42.48, 44.78, 50.83, 72.20, 78.06, 78.63, 84.22, 84.44, 87.47, 97.68, 97.87, 130.43, 133.32, 173.78, 199.11, 199.60; $[\alpha]_D^{25} = -25^\circ$ (c 0.24, CH_2Cl_2).

Anal. calcd. for $C_{45}H_{78}O_9$: C, 70.83; H, 10.30. Found: C, 70.68; H,

10.32.

Ionomycin, Methyl Ester; C19-C21 Acetonide; C31 O-t-Butyldimethylsilyl Ether (74). To a cooled solution (0°C) of 31.9 mg (41.8 μmol) of **73** in 1 mL of dichloromethane under argon was added a premixed solution of 50 μL triethylamine (358 μmol) and 25 μL (114 μmol) of t-butyldimethylsilyl trifluoromethanesulfonate.[46] Thin-layer chromatographic analysis (silica gel, 15% ethyl acetate:hexane, R_f **73** = 0.07, R_f **74** = 0.34) after 1 h showed that all of **73** was reacted. The reaction was quenched with 100 μmol of methanol (5 min, 20°C) and the solvent was removed in vacuo. The residue was dissolved in 5 mL of anhydrous THF under argon and 1 mL of a 0.15 M anhydrous tetra-n-butylammonium fluoride solution in THF was added. After 9 h at 20°C, the solvent was removed in vacuo and the residue was flash chromatographed (10 g silica gel, 1.5 x 30 cm, 5% ethyl acetate:hexane, collecting the UV active fractions) to afford 33.5 mg (91%) of **74** as a clear oil: IR (neat) 2976, 2950, 2885, 2872, 1746, 1610, 1462, 1440, 1380, 1373, 1363, 1258, 1204, 1175, 1099, 1063, 1048, 990, 971, 926, 914, 834, 811, 774, 662 cm^{-1}; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.06 (s, 6H, -Si$\underline{Me}_2$-), 0.67 (d, 3H, J = 6.5 Hz), 0.70 (d, J = 4 Hz), 0.80 (d, J = 6 Hz), 0.85 (d, J = 6 Hz), 0.95 (s, 9H, t-butyl group), 1.05 (d, J = 7 Hz), 1.19 (d, J = 7 Hz), 1.20 (s), 1.25 (s), 1.30 (s, axial acetonide methyl), 1.50 (s, equatorial acetonide methyl), 1.4-2.50 (m), 3.27 (dd, 1H, J = 3, 9.5 Hz, C27 methine), 3.38 (s, 3H, -$CO_2\underline{Me}$), 3.50 (m, 1H, C21 methine), 3.75 [q, 1H, J = 6 Hz, $CH_3\underline{C}H$(OH)-], 3.90 (t, 1H, J = 7 Hz, C19 methine), 4.30 (m, 1H, C23 methine), 5.15-5.85 (m, 2H, vinyl H), 5.40 (s, 1H, vinylic enol H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.07 (s, 3H, -SiC$\underline{H}_3$=), 0.08 (s, 3H, silyl -CH_3), 0.67 (d, 3H, J = 6.4 Hz), 0.72 (d, 3H,

J = 6.4 Hz), 0.79 (d, 3H, J = 6.5 Hz), 0.86 (d, 3H, J = 6.4 Hz), 0.95 (m, 2H), 0.97 (s, 9H, t-butyl group), 1.04 (m, 1H), 1.077 (d, 3H, J = 7.0 Hz), 1.081 (d, 3H, J = 7.0 Hz), 1.21 (s, 3H), 1.22 (d, 3H, J = 6.4 Hz), 1.28 (s, 3H), 1.29 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H, axial acetonide methyl), 1.40 (m, 2H), 1.51 (s, 3H, equatorial acetonide methyl), 1.52-1.65 (m, 4H), 1.65-1.87 (m, 8H), 1.93-2.02 (m, 5H), 2.05 (m, 1H), 2.16 (m, 2H), 2.30-2.42 (m, 4H), 3.29 (dd, 1H, J = 2.1, 9.7 Hz, C27 methine), 3.40 (s, 3H, $-CO_2C\underline{H}_3$), 3.54 (m, 1H, J = 2.7, 8.5, 10.6 Hz, C21 methine), 3.76 [q, 1H, J = 6.4 Hz, $CH_3C\underline{H}$(OSi-t-butyl Me_2)-], 3.96 (t, 1H, J = 7.5 Hz, C19 methine), 4.37 (m, 1H, C23 methine), 5.34 (m, 1H, C16 vinyl H), 5.42 (s, 1H, vinylic enol H), 5.73 [dd, 1H, J = 9.6, 14.9 Hz (trans vinylic coupling), C17 vinylic H); ^{13}C NMR (benzene-d_6) δ (TMS) -4.68, -3.77, 11.70, 18.20, 18.72, 18.91, 19.04, 19.17, 19.63, 24.11, 26.13, 27.10, 28.20, 29.83, 30.48, 31.32, 31.84, 32.82, 35.48, 36.46, 36.78, 38.99, 39.97, 40.49, 40.68, 41.33, 42.50, 44.78, 50.95, 72.33, 73.96, 77.40, 78.18, 83.51, 84.68, 85.46, 97.61, 97.87, 125.56, 130.43, 133.22, 173.45, 198.41, 198.93; $[\alpha]_D^{25}$ = -26.9° (c 0.985, CH_2Cl_2).

Anal. calcd. for $C_{51}H_{92}O_9Si$: C, 69.82; H, 10.57. Found: C, 69.94; H, 10.33.

Degradation of Ionomycin [The **C17-C32** Fragment (**75**)]. To a solution of 83 mg (0.11 mmol) of **73** in 4 mL of THF was added 1 mL of water, 0.8 mL (0.11 mmol) of an aqueous 0.135 M osmium tetroxide[55] solution, and 0.44 g (2.1 mFW) of sodium periodate ($NaIO_4$). After 9 h at 20°C, thin-layer chromatographic analysis (silica gel, 20% ether:dichloromethane) indicated the complete consumption of starting material (R_f **73** = 0.52) and the presence of four major products (R_f = 0.08, 0.15, 0.24, 0.37, respectively).

The milky reaction solution was then filtered to remove the inorganic salts and the ethereal filtrate was washed with 5 mL of an aqueous 10% sodium sulfite solution. The ethereal extract was saved and the aqueous extract was acidified with acetic acid and re-extracted with dichloromethane (3 x 25 mL). The combined organic extracts were evaporated in vacuo to afford 81 mg of a mixture of products. The unpurified mixture was subjected to an ethereal solution containing excess diazomethane for 5 min to esterify any carboxylic acid functionality present in the mixture. The solvent was evaporated in vacuo and the residue was introduced with dichloromethane onto two preparative thick-layer plates (2 mm thickness, silica gel). The plates were developed (25% ether:dichloromethane) and three major bands (R_f = 0.26, 0.34, and 0.43 respectively) were extracted. The product present in the band with R_f = 0.26 was extracted from the silica gel with 40% methanol:dichloromethane. GC analysis (25 meter SE-54, 225°C, t_r minor = 2.13 min, t_r major = 2.57 min) gave a ratio of 1:3 for the two components. ^{1}H NMR (90 MHz, benzene-d_6) indicated the presence of an aldehyde [δ (TMS) 9.7 ppm (d, J = 2 Hz)] and carbomethoxy [3.39 ppm (s)] protons in addition to signals corresponding to a fragment possessing the furan portions of the right-half of ionomycin. From the NMR integration, the minor component (GC analysis) was assigned to be the aldehyde and the major component the methyl ester at the C17 terminus of the C17-C32 fragment of ionomycin. This mixture of aldehyde and methyl ester (13.7 mg, 0.03 mmol) of the C17-C32 fragment was stirred at 20°C for 1.5 h with 1.0 mL (1 mmol) of a 1.0 M ethereal solution of lithium aluminum hydride. Ethyl acetate (0.5 mL) was then added, followed by 0.5 mL of water, and 1 mL of a 15% sodium hydroxide solution. Ether extraction

afforded 12 mg of product **75** as an oil: IR (CCl_4) 3440, 2980, 2945, 2883, 1458, 1420, 1379, 1334, 1303, 1270, 1262, 1250, 1204, 1176, 1128, 1119, 1109, 1074, 1041, 1035, 1027, 1015, 998, 989, 919 cm^{-1}; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.62 (d, 3H, J = 6 Hz, C20 methyl), 1.02 (s, 3H, C30 methyl), 1.10 (d, 3H, J = 6 Hz, C18 methyl), 1.15 (d, 3H, J = 6.5 Hz, C31 methyl), 1.20 (s, 3H, C26 methyl), 1.30 (s, 3H, axial acetonide methyl), 1.35 (s, 3H, equatorial acetonide methyl), 1.40-2.30 (m, 11H), 2.65 (m, 1H), 3.25-4.40 (m, 8H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.61 (d, 3H, J = 6.6 Hz, C20 methyl), 1.02 (s, 3H, C30 methyl), 1.12 (d, 3H, J = 6.6 H, C18 methyl), 1.18 (d, 3H, J = 7.3 H, C31 methyl, 1.22 (s, 3H, C26 methyl), 1.20-1.58 (m, 6H), 1.33 (s, 3H, axial acetonide methyl), 1.35 (s, 3H, equatorial acetonide methyl), 1.67-1.82 (m, 3H), 1.82-1.95 (m, 2H), 2.20 (m, 1H), 2.75 (br d, 1H, -O<u>H</u>), 3.32 (dd, 1H, J = 2.1, 10.4 Hz, C27 methine), 3.43 (m, 1H, C21 methine), 3.75 (m, 2H, dd superimposed on a q, J_{dd} = 6.8, 8.4 Hz, J_q = 7.3 Hz, C31 and C19 methines), 3.92 (ABq, 2H, J_{AB} = 6.3 Hz, C17 methylene), 4.07 (br s, 1H, OH), 4.26 (m, 1H, C23 methine); ^{13}C NMR (CCl_4) δ (TMS) 12.15, 15.79, 17.42, 18.91, 24.11, 26.06, 27.23, 29.50, 30.09, 30.35, 31.32, 34.64, 34.96, 39.06, 62.71, 72.14, 72.79, 77.27, 79.22, 83.77, 84.03, 86.69, 97.42; $[\alpha]_D^{25}$ = -8.43° (<u>c</u> 0.695, CH_2Cl_2). The title compound was not further characterized because it has been correlated to compound **68** in the subsequent experiment.

Synthetic 75 (Fragment **C17-C32**). To a solution of 31 mg (61.9 μmol) of **68** in 10 mL of ethyl acetate was added 10 mg of 10% palladium-on-carbon. The reaction was stirred under 1 atmosphere of hydrogen at 20°C for 1 h. GC analysis (25 meter SE-54, 225°C, t_r **68** = 9.94 min, t_r **75** = 2.39 min)

shows complete reaction with one major product that was 98% pure. The catalyst was removed by filtration through celite and evaporation of the solvent in vacuo afforded 25 mg of synthetic **75** (99%) as an oil. All physical and spectroscopic properties (IR, ^{1}H NMR (90, 500 MHz), ^{13}C NMR, $[\alpha]_D^{25}$ ($\pm 0.1^\circ$) were identical to that of naturally derived **75**.

Desilylation of 74. Commercially available hydrogen fluoride-pyridine complex (Aldrich) was diluted to provide a stock solution as follows: 1 mL of HF-pyridine, 20 mL of freshly distilled pyridine, 7 mL of anhydrous THF were mixed under argon in a polyethylene bottle sealed with a rubber stopper. Plastic disposable syringes were used to transfer this solution. To 4.5 mg (5.13 μmol) of **74** in a dry polyethylene bottle under nitrogen was added 4.0 mL of the diluted HF-pyridine solution. After 58 h at 20°C, thin-layer chromatographic analysis (silica gel, 20% ethyl acetate:hexane, R_f **74** = 0.51, R_f **73** = 0.25) indicated the absence of starting material **74**. A saturated solution of sodium bicarbonate was cautiously added at 0°C to quench the acid. The mixture was extracted with ether (3 x 15 mL), dried (anhydrous $MgSO_4$), and the solvent was evaporated in vacuo to afford a yellow residue. Flash chromatographic purification (5 g silica gel, 1.5 x 30 cm, 20% ethyl acetate:hexane, collecting the UV active fraction) afforded 3.7 mg (91%) of product which gave a ^{1}H NMR (500 MHz, benzene-d_6) spectrum identical in all respect to that of **73** derived from **72**.

Deketalization of 73 to 76 (Isoionomycin, Methyl Ester). To a solution of 4.1 mg (5.4 μmol) of **73** in 2 mL of anhydrous methanol was added 50 mg (0.2 mmol) of pyridinium p-toluenesulfonate (pyridinium tosylate). The solution was stirred at 20°C for 44 h (or 40°C for 16 h) before ethyl acetate

(10 mL) and water (10 mL) were added. The ethyl acetate extracts were combined and washed with a saturated sodium bicarbonate solution. The ethyl acetate was removed in vacuo and the residue was taken up in hexane and filtered (sintered glass filter). The filtrate was evaporated in vacuo to afford 3.6 mg (93%) of **76** as an oil: IR (neat) 3420, 2968, 2920, 2860, 1732, 1600, 1451, 1430, 1375, 1318, 1255, 1165, 1075, 1030, 985, 972, 915, 909 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.72 (d, 3H, J = 6.1 Hz), 0.78 (d, 3H, J = 6.8 Hz), 0.80 (d, 3H, J = 7.0 Hz), 0.90 (d, 3H, J = 6.9 Hz), 0.96 (t, 2H, J = 6.6 Hz), 1.00 (s, 3H), 1.07 (d,3H, J = 6.8 Hz), 1.08 (d, 3H, J = 7.1 Hz), 1.09 (d, 3H, J = 6.8 Hz), 1.10 (m, 1H), 1.16 (s, 3H), 1.21 (m, 2H), 1.26-1.45 (m, 6H), 1.35 (d, 3H, J = 6.8 Hz), 1.45-1.75 (m, 10H), 1.77-1.94 (m, 3H), 1.98-2.10 (m, 2H), 2.17 (m, 2H), 2.34-2.40 (m, 2H), 2.44 (m, 1H), 3.40 (s, 3H, -CO_2Me), 3.53 (dd, 1H, J = 2.3, 8.6 Hz), 3.68 (dd, 1H, J = 6.6, 8.2 Hz), 3.78 (q, 1H, J = 6.3 Hz), 3.87 (m, 1H, J = 2.0, 7.4, 10.2 Hz), 3.96 (m, 1H), 4.10 (br s, 1H, -OH), 4.20 (br s, 1H, -OH), 5.43 (m, 1H), 5.44 (s, 1H, vinylic enol H), 5.85 (dd, 1H, J = 15.6, 8.1 Hz). Comparison of the ^1H NMR (500 MHz, benzene-d_6) spectrum of **76** and **72** indicated that the two are structurally different. Note: isomer **76** appears to be unstable to silica gel. All attempts at chromatographic purification (HPLC, flash) lead to very poor mass recovery. The title compound **76** was also obtained as the major product from the treatment of 6.6 mg of **73** in 2 mL of methanol with 100 μL of trifluoroacetic acid at 40°C for 14 h. The control experiment in which **72** was subjected to the above conditions ($MeOH/H^+$) resulted in the transformation of **72** to **76**.

Exact mass calcd. for $C_{42}H_{74}O_9$: 722.5335. Found: 723.5387 (MH^+, FAB analysis).

Hydrolysis of 76 to Carboxylic Acid 77. To 6.5 mg (9 μmol) of **76** in 600 μL of distilled 1,2-dimethoxyethane was added 100 μL of water followed by 150 μL of a 1 N lithium hydroxide solution. After 1.25 h at 20°C, 600 μL of 1 N hydrochloric acid was added followed by 10 mL of ethyl acetate and 5 mL of water. The two phases were separated and the ethyl acetate extract was evaporated in vacuo. The residue was flash chromatographed (4 g silica gel, 1.5 x 30 cm, eluting first with 10 mL of ethyl acetate; then 20 mL of anhydrous acetone) collecting the major product in the acetone fraction. The ethyl acetate fraction contained the minor by-products (TLC R_f = 0.38, 0.52, 0.58, 0.70; R_f **77** = 0.21, silica gel, 50% ethyl acetate:hexane). Evaporation of the acetone in vacuo afforded 4.7 mg (74%) of a white solid (TLC, R_f = 0.0-0.10, 50% ethyl acetate:hexane, streak similar to that exhibited by the calcium complex of ionomycin). This solid complex (of Ca^{+2} from the silica gel), **78**, was taken up in 10 mL of hexane and shaken with 7 mL of 1 N HCl. Evaporation of the hexane in vacuo afforded 4.7 mg of **77** as an oil: ^{1}H NMR (500 MHz, benzene-d_6) δ (TMS) 0.75 (d, 3H, J = 6.6 Hz), 0.83 (d, 6H, J = 6.2 Hz), 0.90 (d, 3H, J = 6.6 Hz),0.99 (s, 3H), 1.02 (m, 4H), 1.07 (d, 3H, J = 6.6 Hz), 1.10 (d, 3H, J = 6.6 Hz), 1.11 (d, 3H, J = 6.7 Hz), 1.22 (m, 2H), 1.24 (s, 3H), 1.30 (d, 3H, J = 6.7 Hz), 1.31-1.59 (m, 7H), 1.67-1.82 (m, 5H, 1.87-2.2 (m, 4H), 2.11 (m, 1H, J = 4.0, 9.0, 12.5 Hz), 2.25 (m, 3H), 2.36 (m, 2H), 2.45 (m, 1H), 3.48 (dd, 1H, J = 3.0, 8.9 Hz), 3.70 (dd, 1H, J = 7.0, 8.0 Hz), 3.84 (q, 1H, J = 6.2 Hz, C31 methine), 3.97 (m, 1H, J = 3.0, 7.0, 10.0 H), 4.15 (m, 1H), 5.46 (s, 1H, vinylic enol H), 5.48 (m, 1H, C16 vinylic H), 5.76 (dd, 1H, J = 8.5, 15.5 Hz, C17 vinylic H). The title compound was not further characterized.

Complexation of 77 with Ca^{+2} (78). A solution of buffered (pH 9)

calcium(II) ions was prepared by dissolving 1.47 g (0.01 FW) of $CaCl_2 \cdot 2\ H_2O$, 2.07 g (0.01 mol) of 2-(cyclohexylamino)ethanesulfonic acid (CHES), and 6 mL of 1 N LiOH in 100 mL of water. To 4.7 mg of **77** in 10 mL of dichloromethane was added 10 mL of the buffered calcium chloride solution. The mixture was stirred vigorously at 20°C for 12 h. The dichloromethane was separated from the aqueous phase and evaporated in vacuo to afford 4.7 mg of **78** as a white solid: ^{1}H NMR (500 MHz, benzene-d_6) δ (TMS) 0.60 (d, 3H, J = 7.0 Hz), 0.84 (m, 2H), 0.97 (s, 3H), 1.07 (s, 3H), 1.08 (d, 3H, J = 6 Hz), 0.90-1.40 (m, 8H), 1.12 (d, 3H, J = 6.5 Hz), 1.14 (d, 3H, J = 6.4 Hz), 1.18 (d, 3H, J = 6.6 Hz), 1.20 (d, 3H, J = 6.6 Hz), 1.25 (d, 3H, J = 6.5 Hz), 1.27 (d, 3H, J = 7.0 Hz), 1.48 (m, 1H), 1.60-1.70 (m, 2H), 1.70-1.80 (br m, 1H), 1.92 (br m, 1H), 1.98-2.05 (m, 3H), 2.05-2.28 (m, 3H), 2.29-2.37 (m, 3H), 2.37-2.52 (m, 4H), 2.58 (dt, 1H, J = 3.0,12.0 Hz), 3.25 (dd, 1H, J = 2.5, 10.3 Hz), 3.35 (dd, 1H, J = 5.5, 10.5 Hz), 3.58 (m, 1H), 3.82 (m, 1H), 4.78 (q, 1H, J = 6.4 Hz, C31 methine), 5.40 (s, 1H, vinylic enol H), 5.62 (dd, 1H, J = 9.5, 15.50 Hz, C17 vinylic H), 5.72 (m, 1H, C16 vinylic H).

Exact mass calcd. for $C_{41}H_{70}O_9{}^{40}Ca$: 746.4646. Found: 709.5258 ($M-{}^{40}Ca+3H^+$, FAHR analysis).

Hydrolysis of 72 to Ionomycin (71). To a solution of 3.1 mg (4.3 μmol) of methyl ester **72** in 300 μL of distilled 1,2-dimethoxyethane was added 50 μL of water and 75 μL of a 1 N solution of lithium hydroxide. After 1 h at 20°C, the reaction was quenched with 200 μL of 1 N HCl, and extracted with ether (2 x 10 mL). The ethereal extracts were evaporated in vacuo to afford 2.1 mg (69%) of an oil whose ^{1}H NMR (500 MHz, benzene-d_6) spectrum was identical to that of **71** (derived from the calcium salt provided by Squibb).

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(26) The oxidation of aldol adducts to beta-diketones has been investigated by Smith, III, A. B. See: Smith, III, A. B.; Levenberg, P. Synthesis **1981**, 567-570.

(27) See Appendix I (this thesis).

(28) 5-Benzyloxypentanoyl chloride was prepared from the corresponding acid by treatment with oxalyl chloride. The carboxylic acid is available from the Jones oxidation of 5-benzyloxy-1-pentanol; a known compound (Ref. 42) for which we have developed a more convenient preparation as described in the experimental section.

(29) (a) Obtained by reduction of the ethyl ester of 4-methyl-4-hexenoic acid with lithium aluminum hydride followed by pyridinium chlorochromate oxidation. See: Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Petersen,

M. R. J. Am. Chem. Soc. **1970**, 92, 741-743. (b) Bertelo, C.A.; Schwartz, J. Ibid. **1976**, 98, 262-264.

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(31) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. J. Am. Chem. Soc. **1978**, 100, 2933-2935.

(32) Tebbe's reagent as prepared by established procedure was found to be ~90% pure. Stored and handled in a dry box. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. J. Am. Chem. Soc. **1978**, 100, 3611. (b) Tebbe, F. N.; Parshall, G. W.; Ovenall, D. W.; Ibid. **1979**, 101, 5074. (c) Klabunde, U.; Tebbe, F. N.; Parshall, G. W.; Harlow, R. L. J. Mol. Cat. **1980**, 8, 37.

(33) Commerically available from Aldrich Chemical Co. Used as an indicator during the ozonolysis of olefins. See: Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. Synthesis **1980**, 807-810.

(34) I am indebted to Robert Dow, my coworker, in this project for these results.

(35) The crotonate imides have been extensively utilized by E. Sjogren in his work on β-lactams. Evans, D. A.; Sjogren, E. Unpublished results.

(36) The methylated isomer **45a** was purified by MPLC to ≥98% d.e. before reduction and oxidation to (S)-**47**. Subsequent aldol condensation and diastereomer analysis (capillary GC) determined the diastereoselectivity to be 97:3.

(37) The procedure employed by Sharpless was used: Sharpless, K. B.;

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(43) See Experimental Section of Chapter I (this thesis).

(44) Inoue, T.; Mukaiyama, T. Bull. Chem. Soc. Jpn. **1980**, 53, 174-178.

(45) Commercially available Grignard reagent from Aldrich Chemical Co. was titrated before use.

(46) TBS triflate (FW 264, d 1.2) was prepared according to: Corey: E. J.; Cho, H.; Rucker, C.; Hua, D. H. Tetrahedron Lett. **1981**, 22, 3455-3458.

(47) Brown, C. A. J. Org. Chem. **1974**, 39, 3913-3918.

(48) Commercially available from Aldrich Chemical Co.

(49) See: Ennis, M. D. Ref. 15b, p 66.

(50) Commercially available (Fluka Chemical Co.) tetra-n-butylammonium fluoride trihydrate (FW 315.52) was dried under vacuum at 75°C for 12

h. A resealable tube was fashioned from a thick-walled 25 mm OD glass tube and a right angle side-arm vacuum valve equipped with a Teflon ^{R} plug and Viton ^{R} O-ring seal (Kontes Glass Co.).

(51) House, H. O.; Chu, C-Y.; Wilkins, J. M.; Umen, M. J. J. Org. Chem. 1975, 40, 1460-1469.

(52) See: Dow, R. Ph.D. Thesis, California Institute of Technology, 1985.

(53) See Ref. 1c.

(54) ^{1}H NMR (90 MHz, benzene-d_6) of this product shows two methoxyl signals at $_{\delta}$ (TMS) 3.40 and 3.90 ppm. No further characterization was attempted.

(55) Pappo, R.; Allen, Jr., D. S.; Lemieux, R. U.; Johnson, W. S. J. Org. Chem. 1956, 21, 478.

APPENDIX I. Procedure for the Preparation of Chiral Oxazolidones

(4S)-4-(2-Propyl)-oxazolidine-2-one [(S)-Valine Oxazolidone]. Into a dry 250-mL single-necked round-bottomed flask equipped for magnetic stirring was placed 59 g (0.57 mol) of (2S)-2-amino-3-methylbutanol, 77 mL (75 g, 0.63 mol) of diethyl carbonate, and ca. 4 g (~5 mol %) of anhydrous potassium carbonate. The flask was fitted with a short-path distillation head and the stirred reaction mixture was heated in an oil bath pre-equilibrated to 100°C. Heating was continued until ethanol distillation ceased (ca. 14 h). Upon cooling to room temperature, the contents of the flask solidified. The reaction product was dissolved in dichloromethane, filtered through a Celite pad, and concentrated in vacuo to give a colorless solid. Recrystallization from diethyl ether afforded 70 g (95%) of 1a as a white crystalline solid, mp 71-72°C. IR ($CHCl_3$) 3484, 3400-3200, 3030, 2980, 1755, 1215 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.77 (broad s, 1, -NH), 4.40 (t, 1, J = 9 H, C_5-H), 4.03 (d of d, 1, J = 6 Hz, 9 Hz, C_5-H), 3.60 (q, 1, J = 7 H, C_4-H), 1.70 [m, 1, $(CH_3)_2CH$-], 0.94 [t, 6, J = 6 Hz, $-CH(CH_3)_2$]; ^{13}C NMR (CCl_4) δ 160.4, 68.2, 58.2, 32.6, 17.7, 17.5; $[\alpha]_D$ -16.6° (c 5.81, EtOH).

Anal. calcd. for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.46; H, 8.30; N, 10.77.

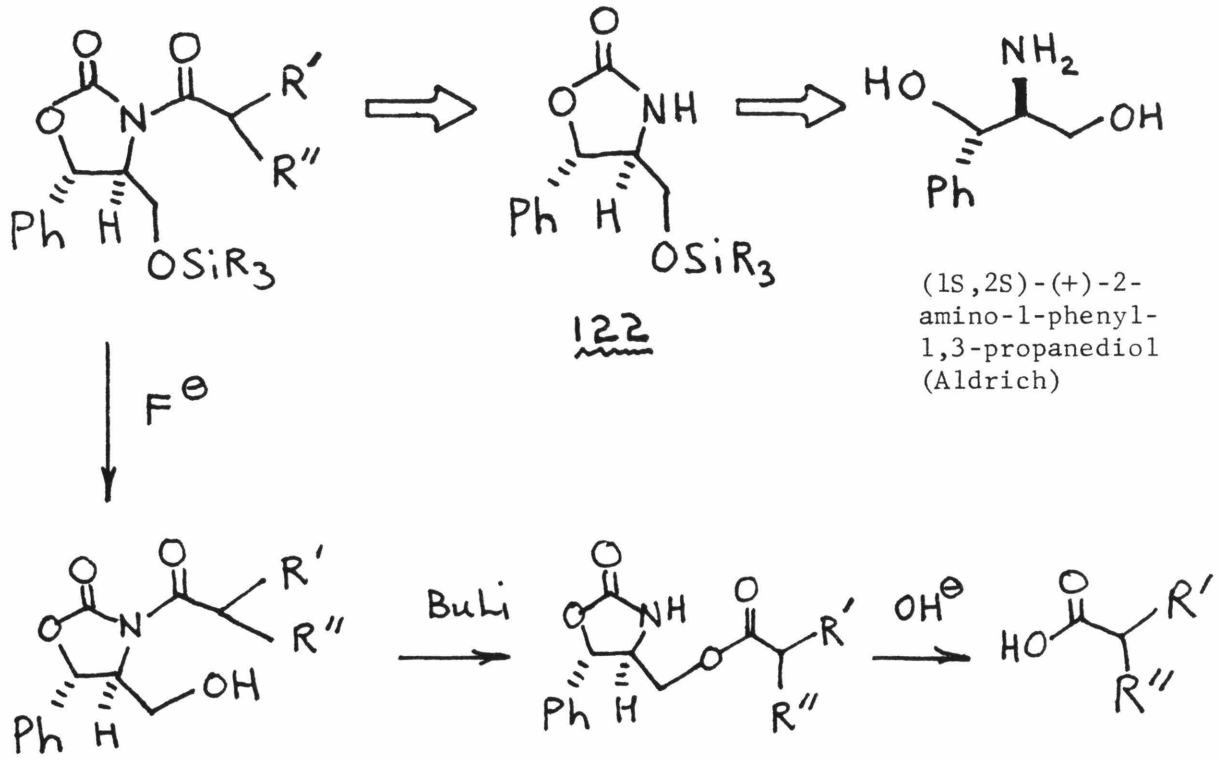
(4R,5S)-4-Methyl-5-phenyloxazolidine-2-one [Norphedrine Oxazolidone]. Into a dry 300-mL single-necked, round-bottomed flask equipped for magnetic stirring was placed 40.2 g (0.27 mol) of (1S,2R)-2-amino-2-phenylpropanol, 36 mL (35.1 g, 0.30 mol) of diethyl carbonate, and ca. 2 g (~5 mol %) of anhydrous potassium carbonate. The flask was fitted

for distillation through a 12" Vigreux column and placed in an oil bath pre-equilibrated to 150° C. The stirred solution was heated until ethanol distillation ceased (overnight). Upon cooling to room temperature, the contents of the flask solidified. The reaction product was dissolved in dichloromethane (200 mL), washed once with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a colorless solid. Recrystallization from toluene afforded 40.8 g (85%) of 2a as a white, crystalline solid, mp 120-122° C (Lit.[39] mp 116-117° C). IR ($CHCl_3$) 3462, 3400-3100, 2990, 1755, 1400, 1388, 1350, 1235 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.30 (s, 5, aromatic H's), 6.4 (b, 1, -NH), 5.67 (d, 3, J = 8 Hz, C_5-H), 4.20 (quintet, 1, J = 7 Hz, C_4-H), 0.80 (d, 3, J = 7 Hz, C_4-CH_3); ^{13}C NMR ($CDCl_3$) δ 159.9, 135.0, 128.4, 81.0, 52.4, 17.4; $[\alpha]_D$ +177.2° (c 2.21, $CHCl_3$) [Lit.[5] $[\alpha]_D$ +158.4° (c 0.44, $CHCl_3$)].

Anal. calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.42; H, 6.19; N, 7.87.

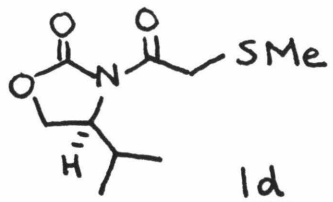
APPENDIX II. Scheme for Second Generation of Chiral Oxazolidones

SCHEME FOR A SECOND GENERATION CHIRAL AUXILIARY WHICH CONTAINS AN INTRAMOLECULAR ASSIST TOWARDS REMOVAL



J. Bisahas
E. Sjogren

APPENDIX III. Selected IR and NMR Spectral Catalog for Chapter I



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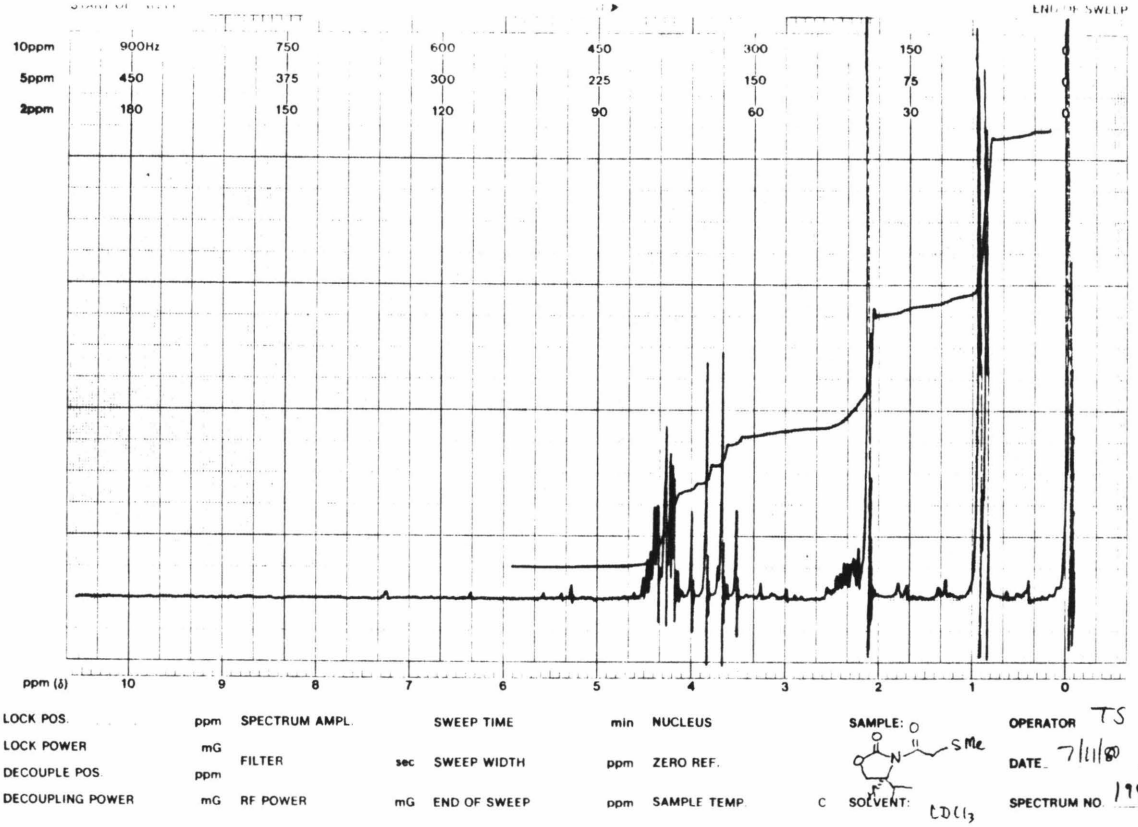

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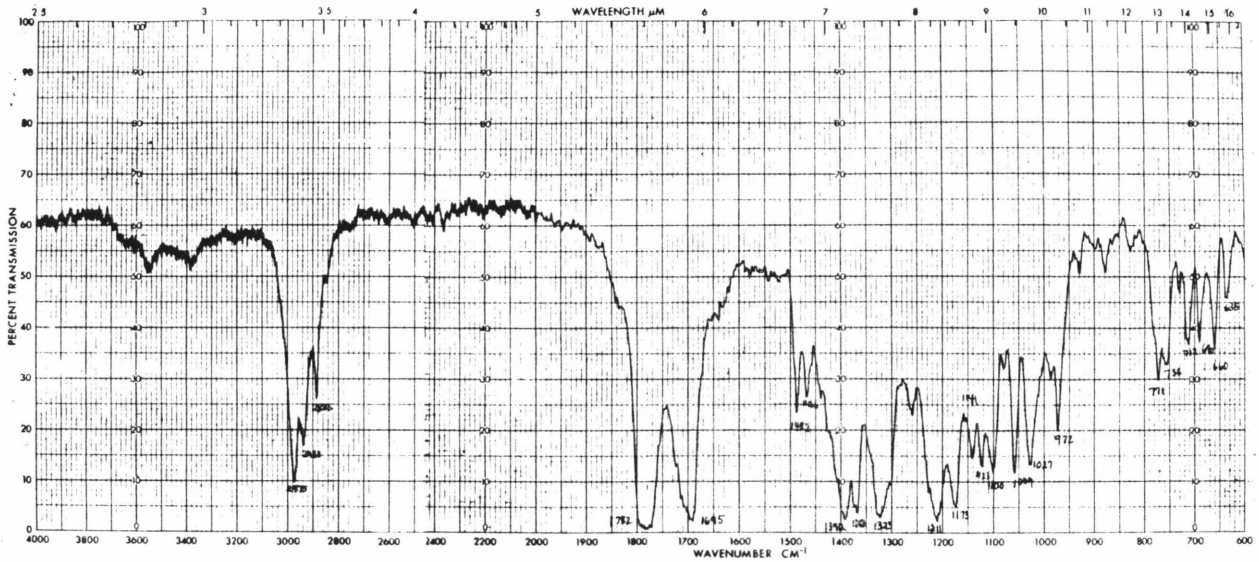

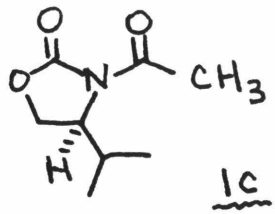

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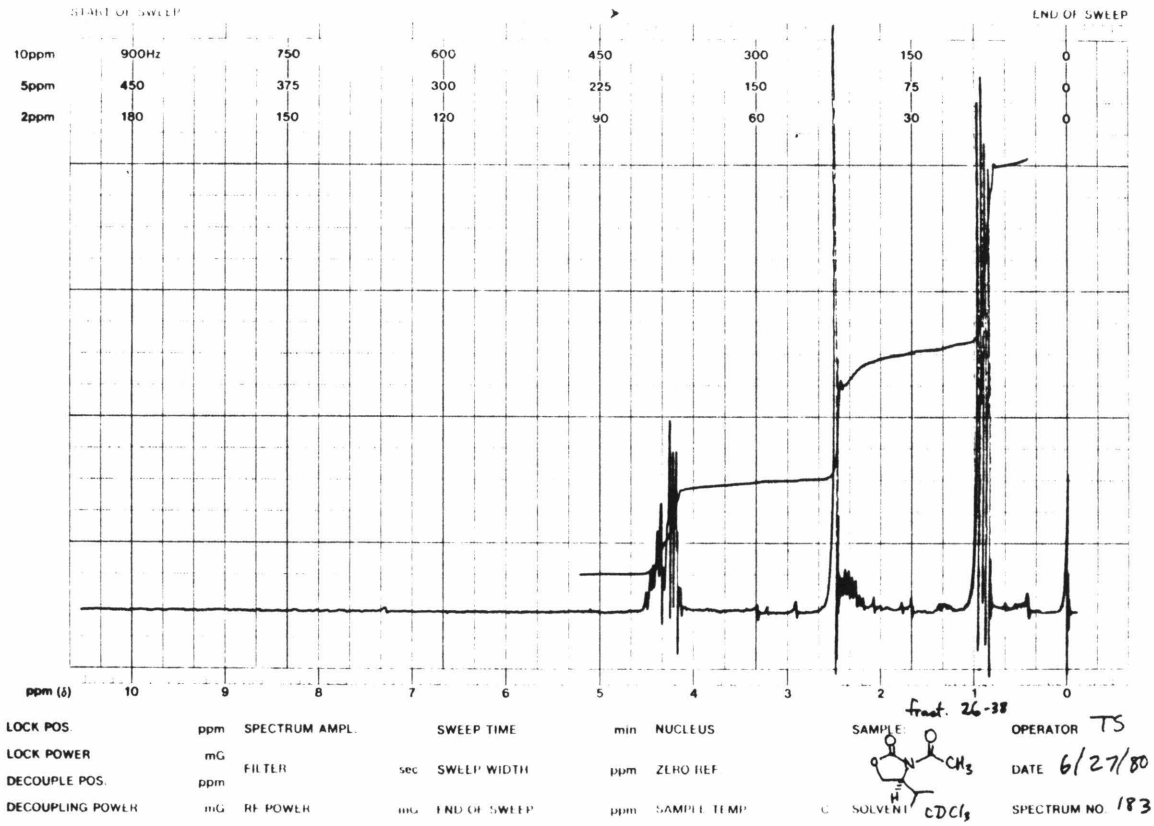

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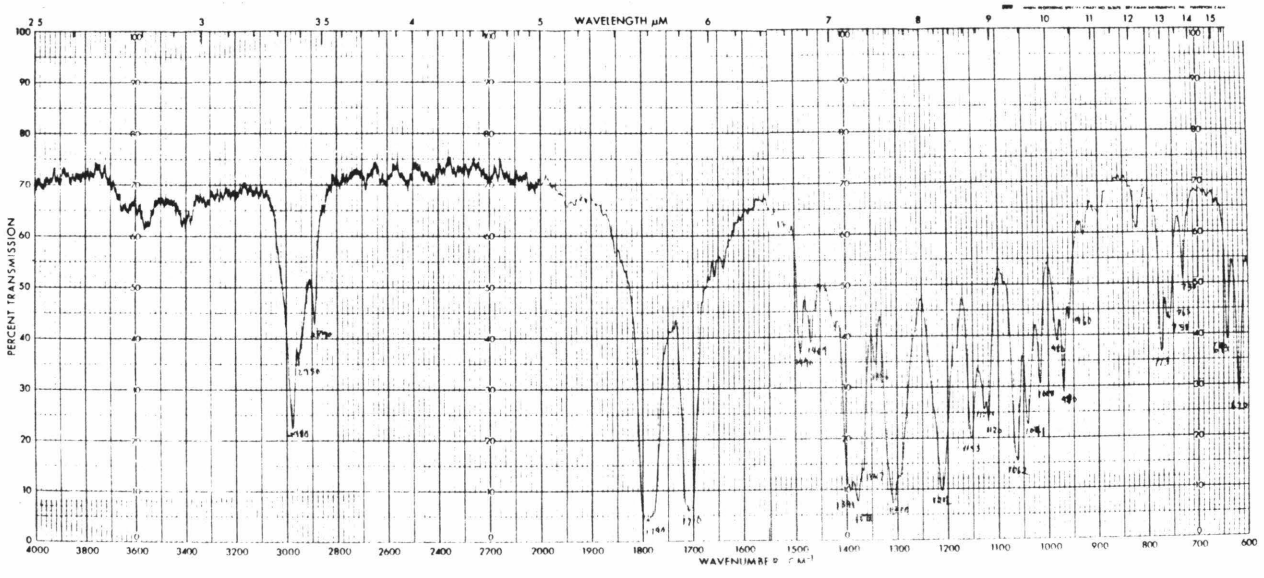

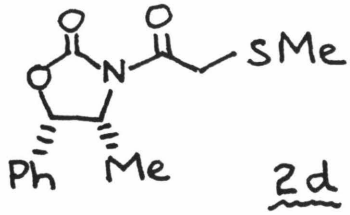

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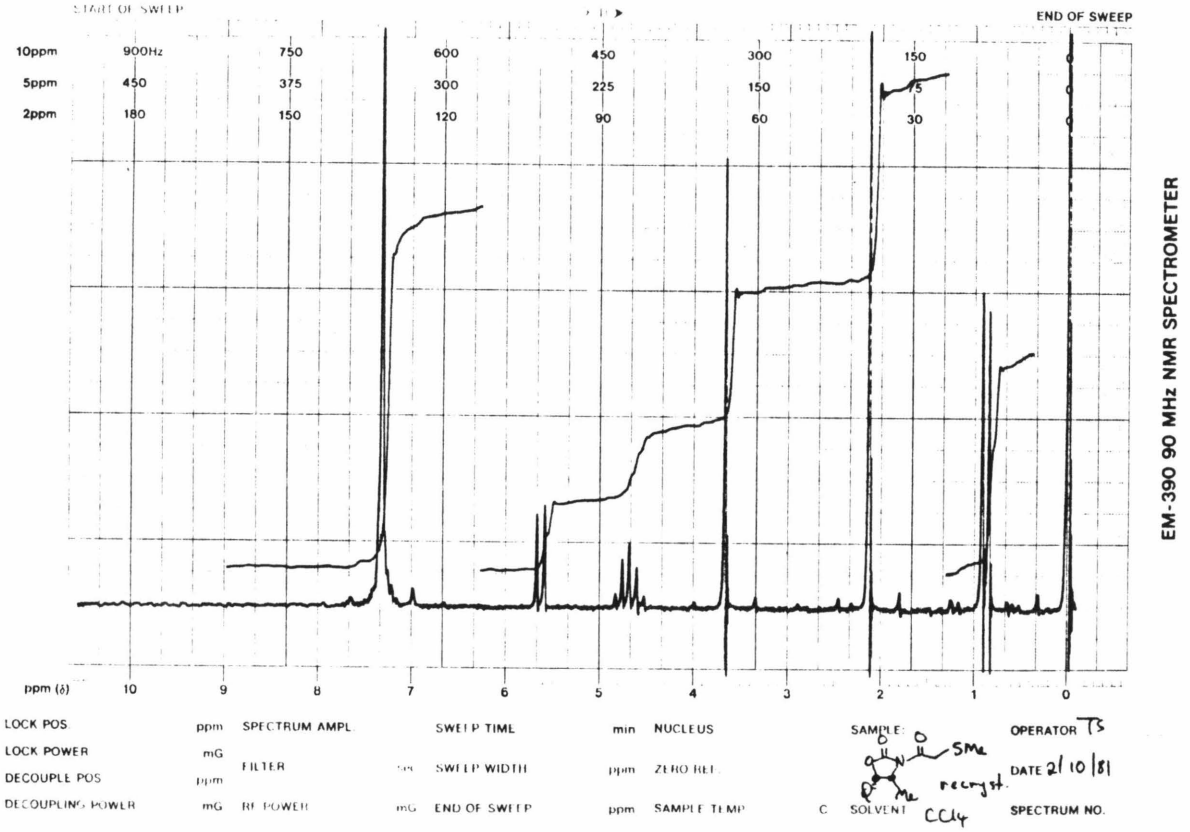

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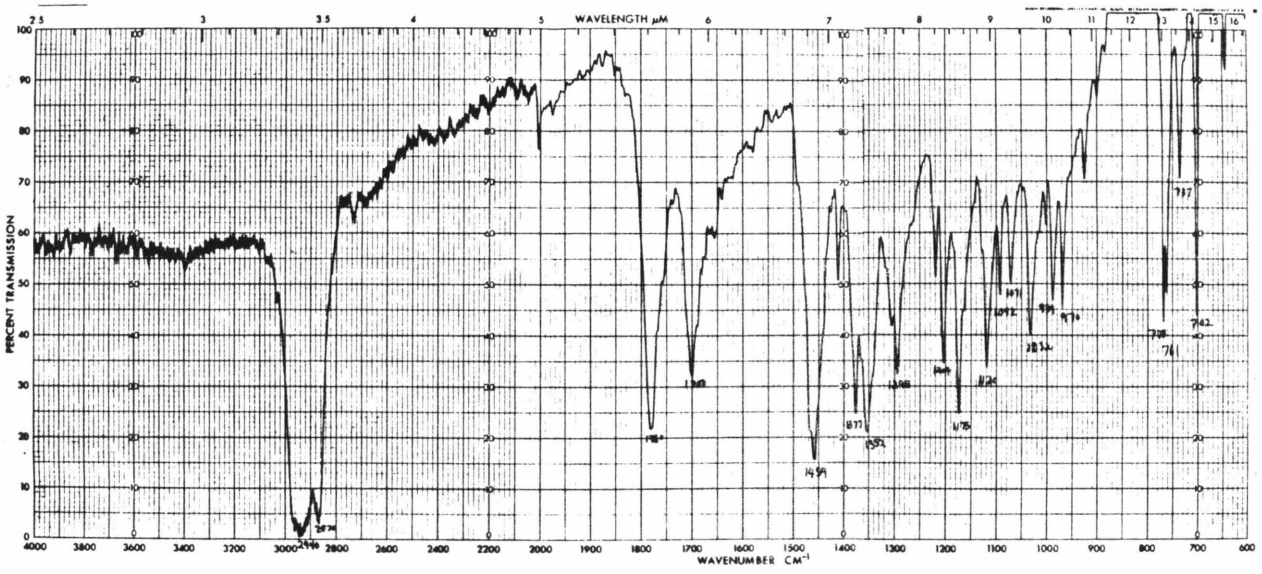

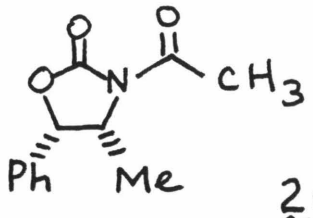

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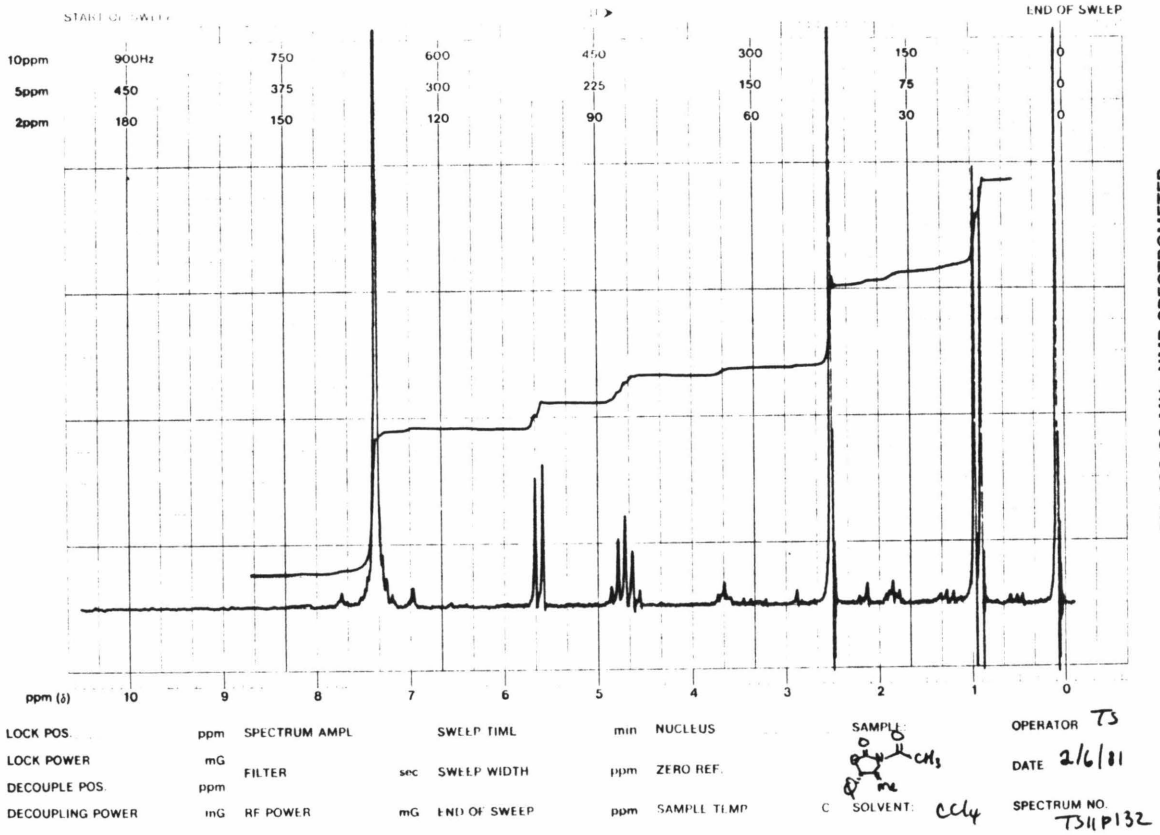

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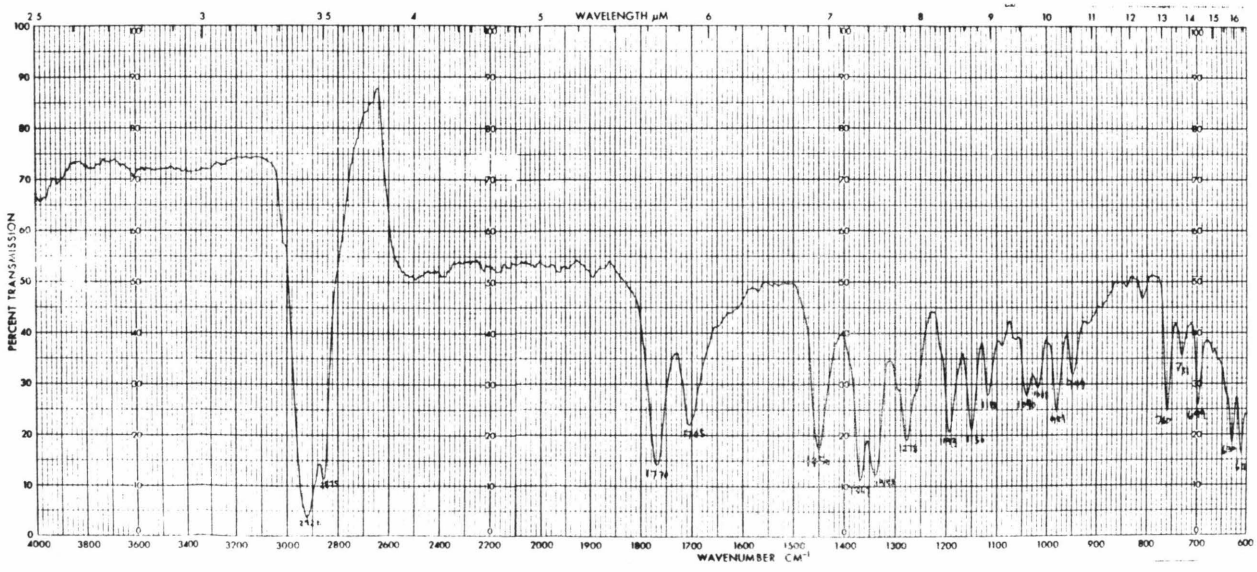

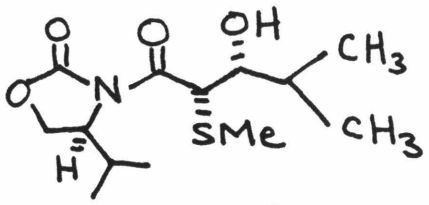

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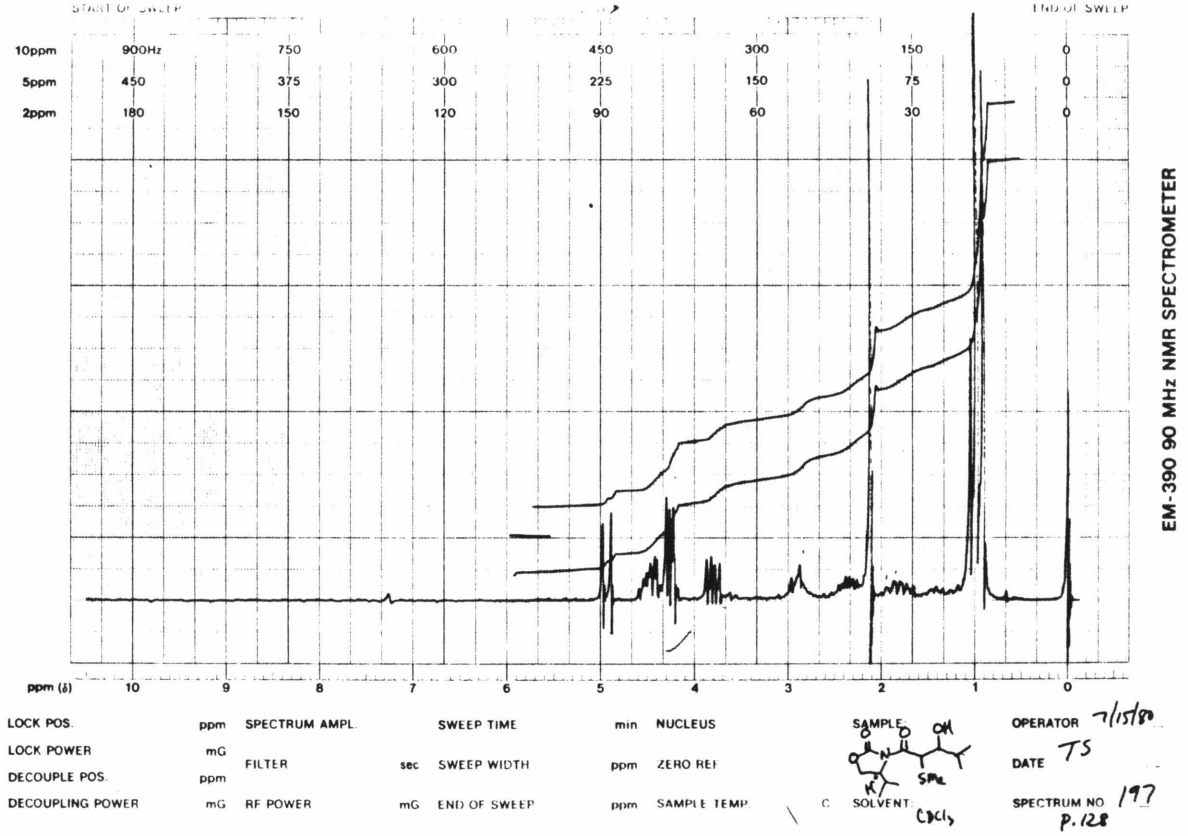

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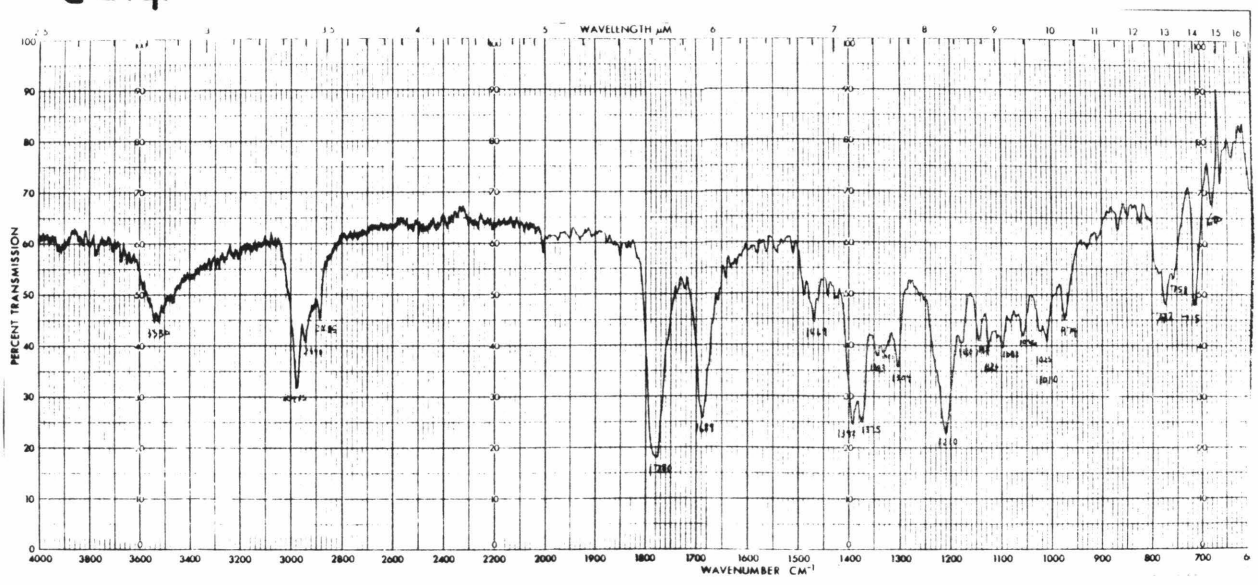

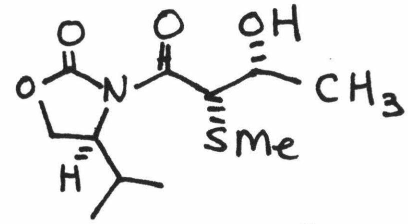

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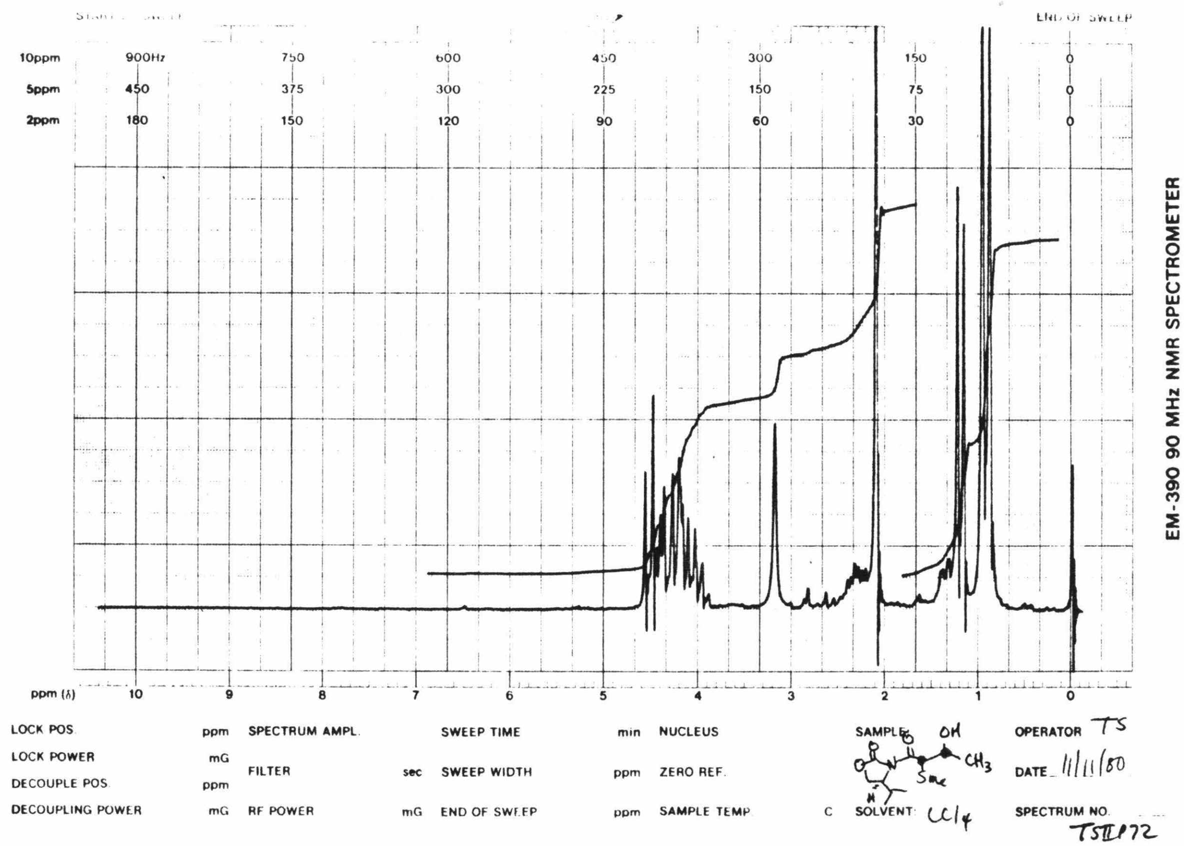
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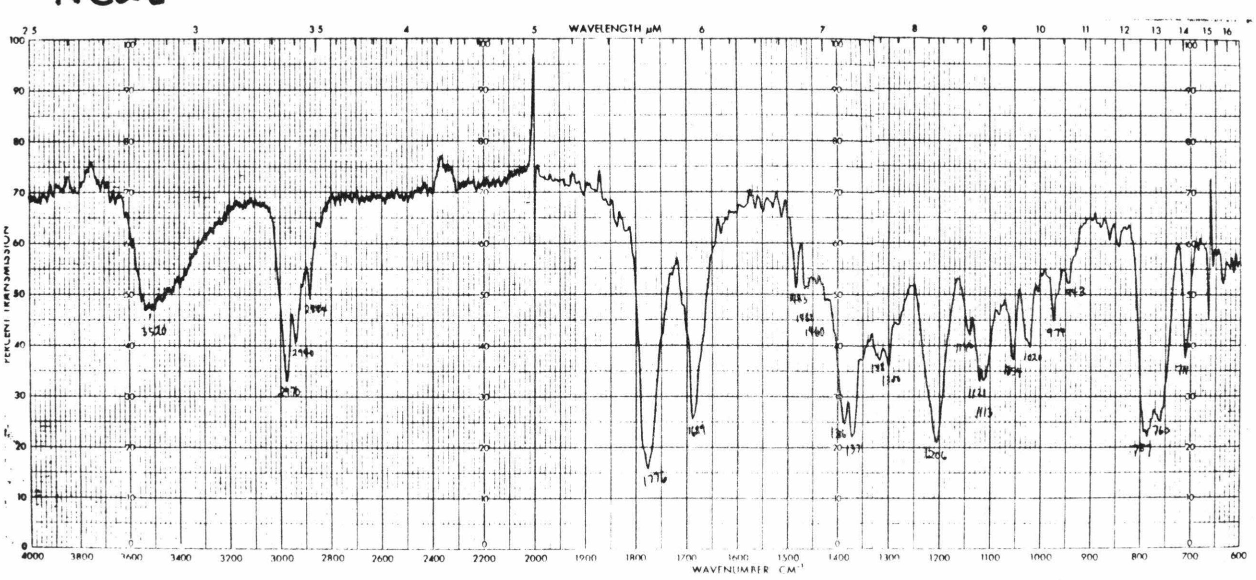
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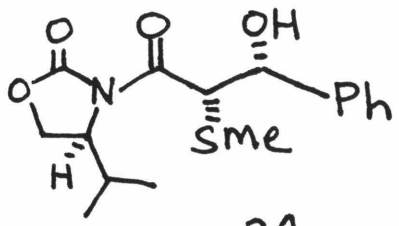

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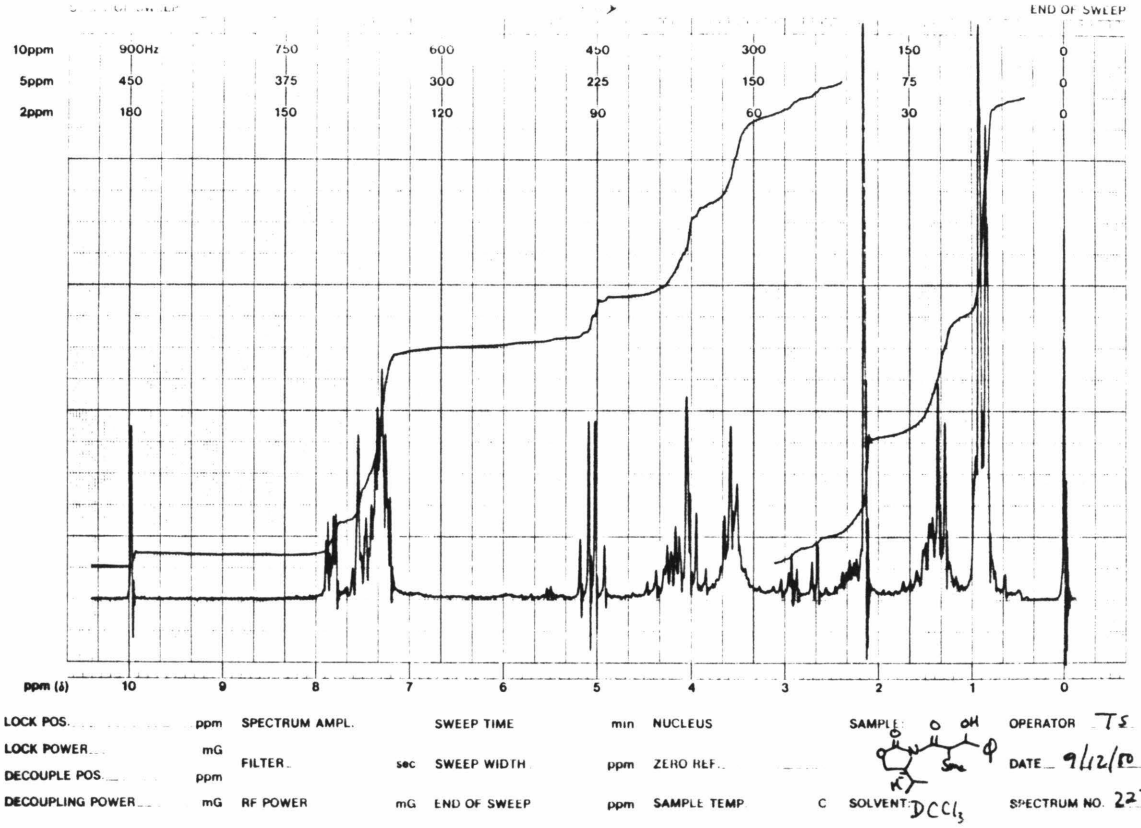

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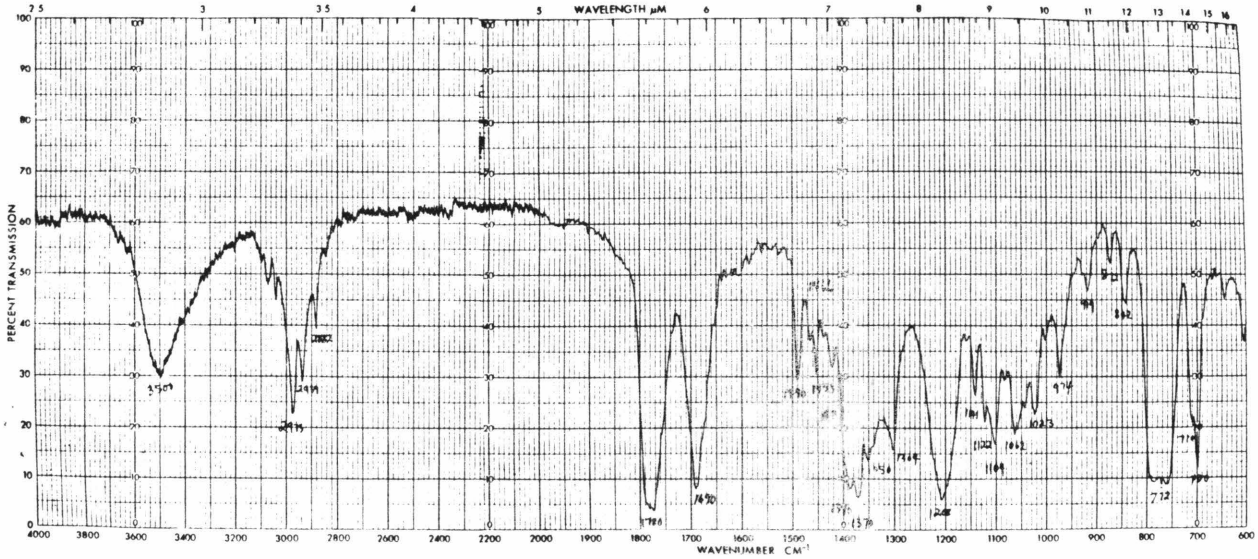

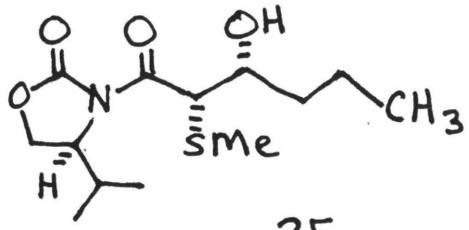

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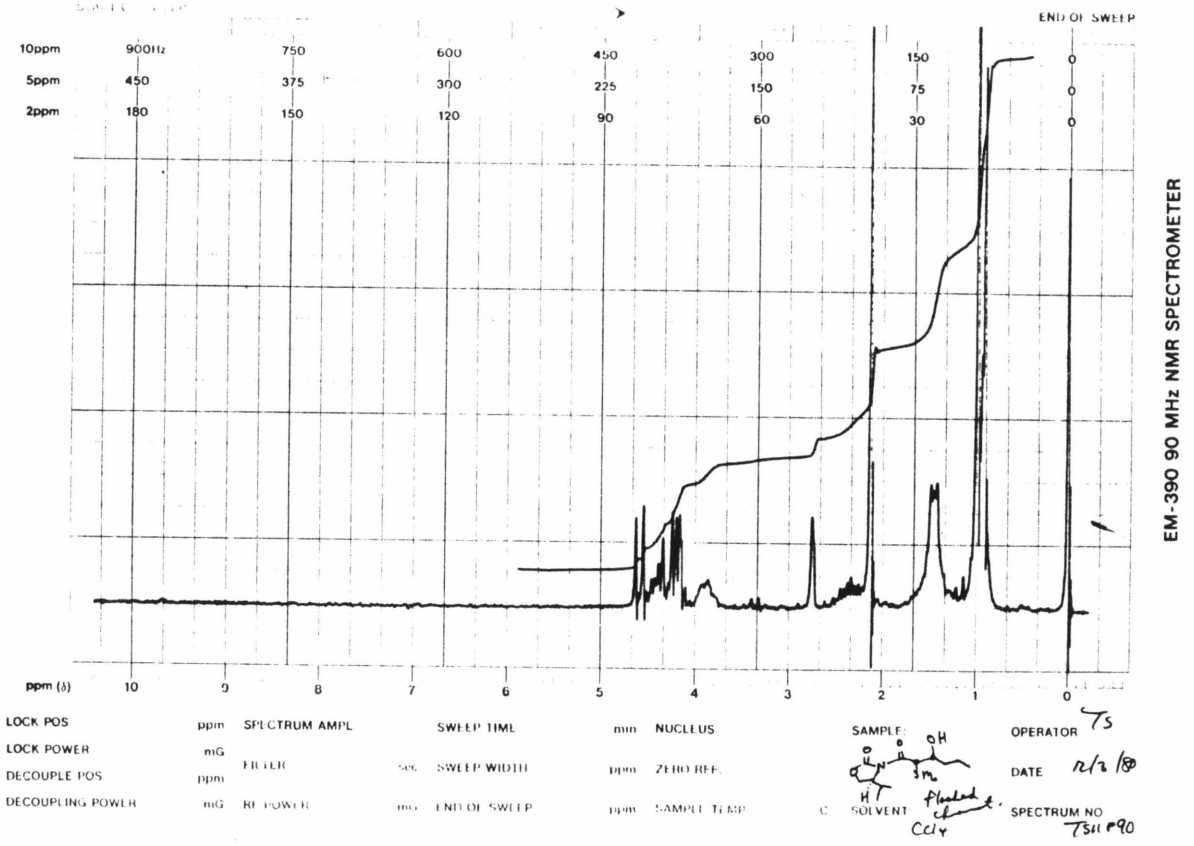
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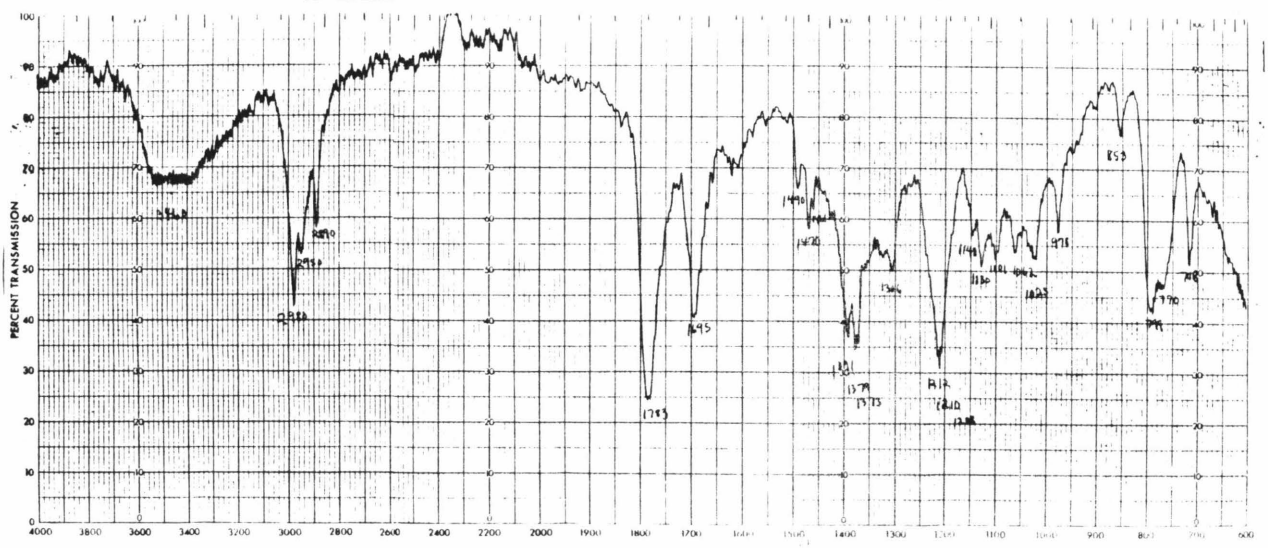
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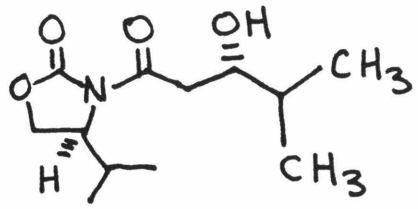

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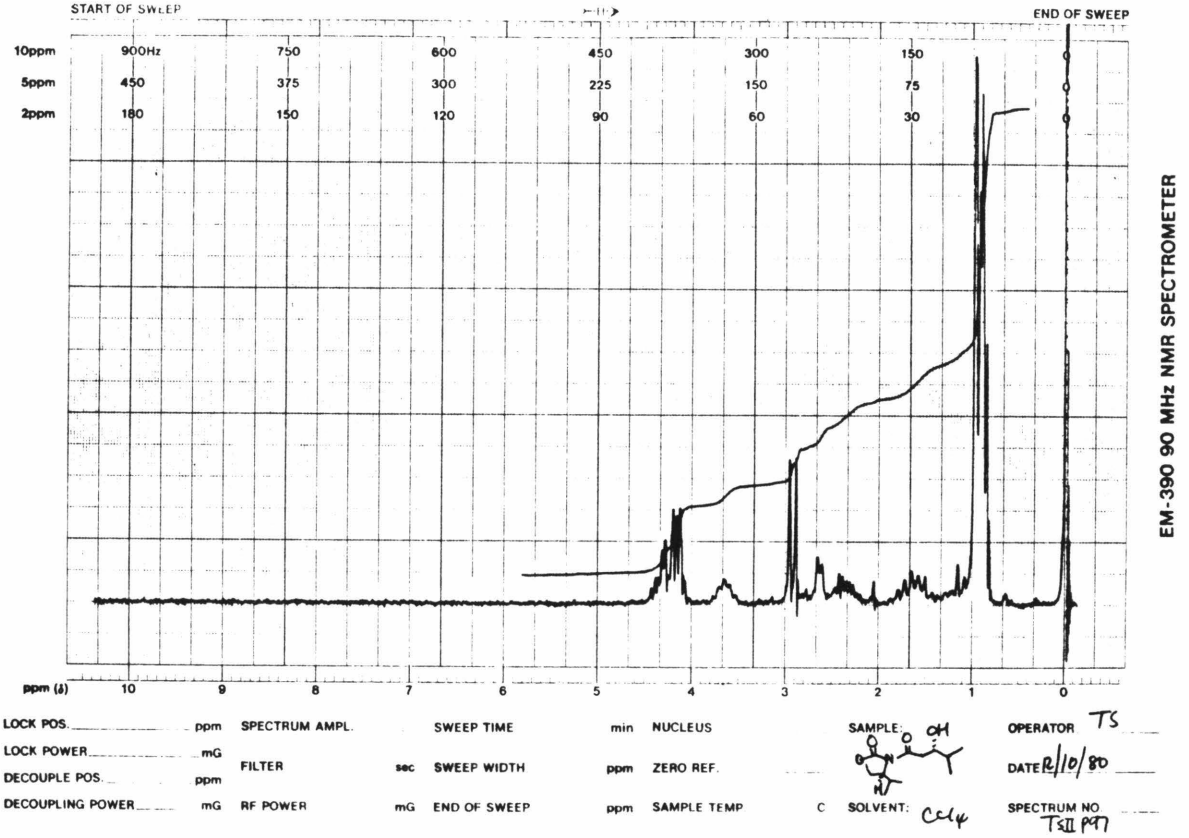
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ppm (δ)
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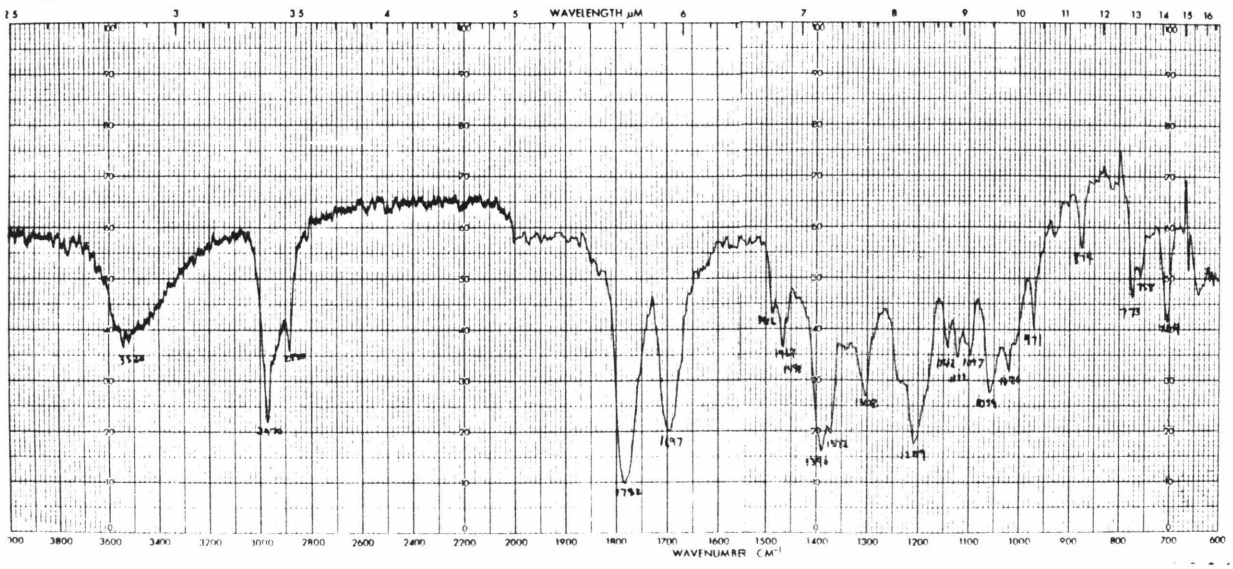
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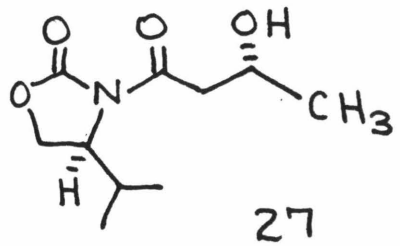

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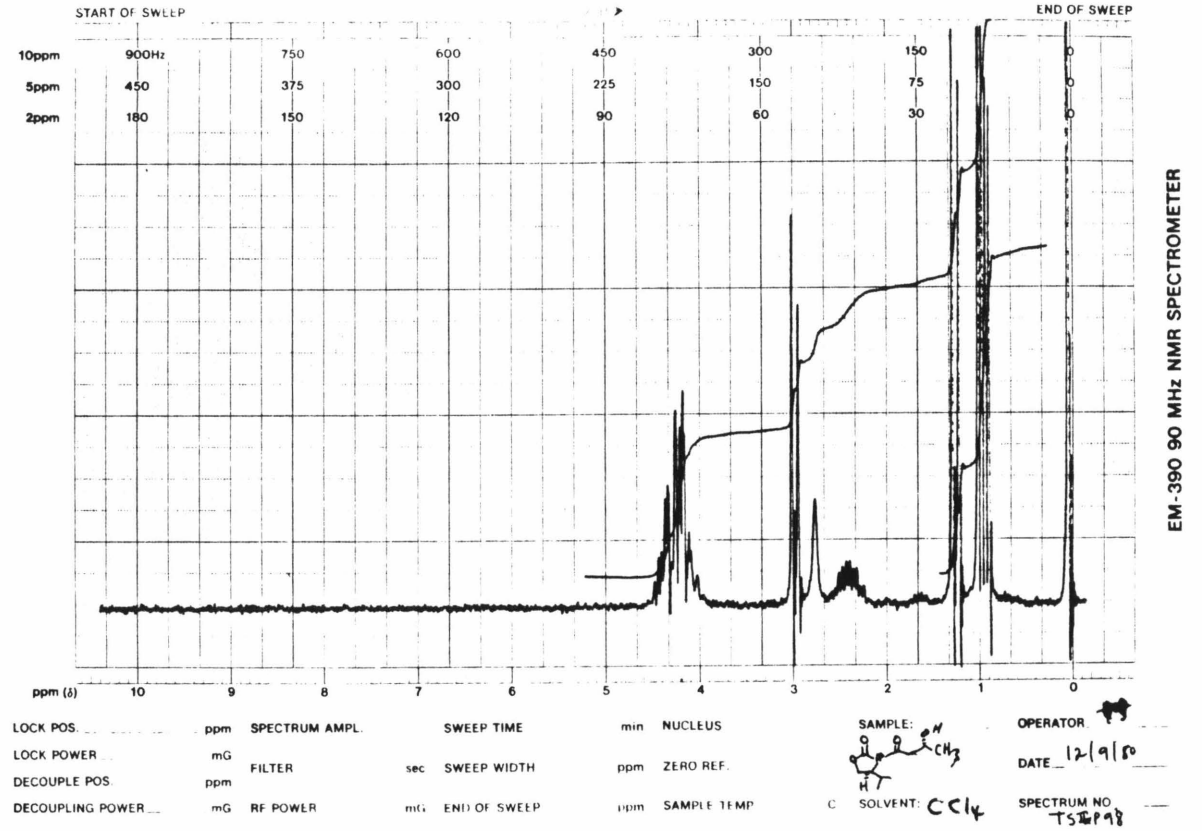
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90
300
150
60
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
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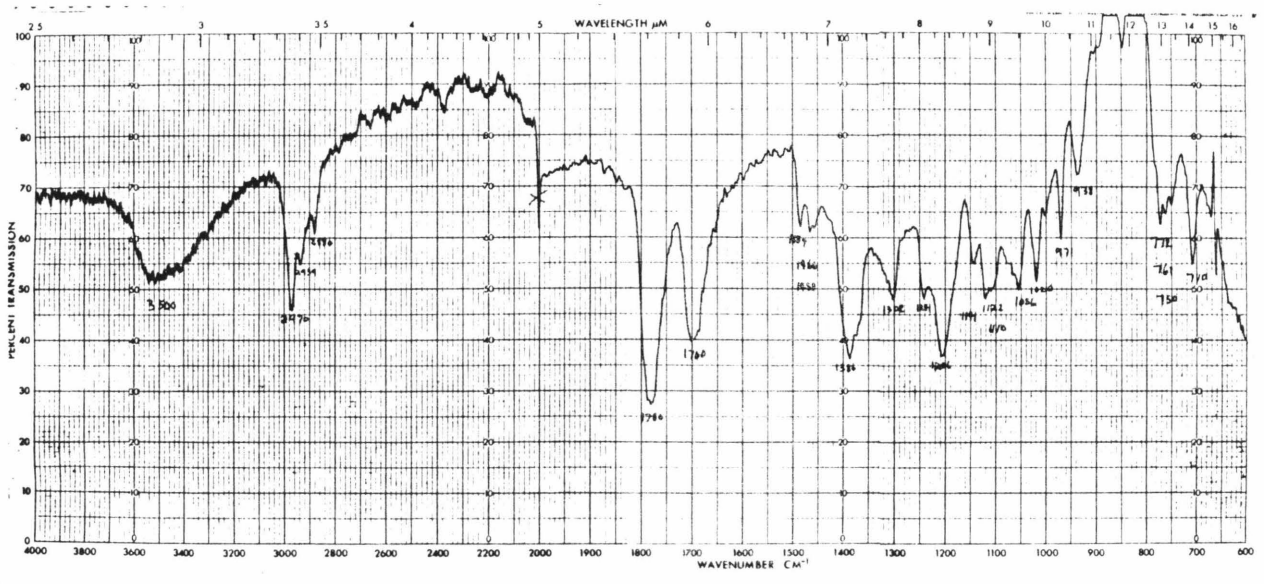
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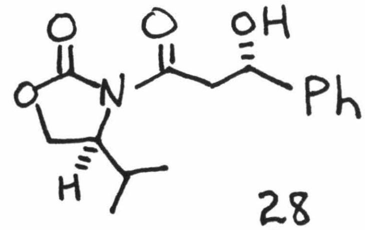
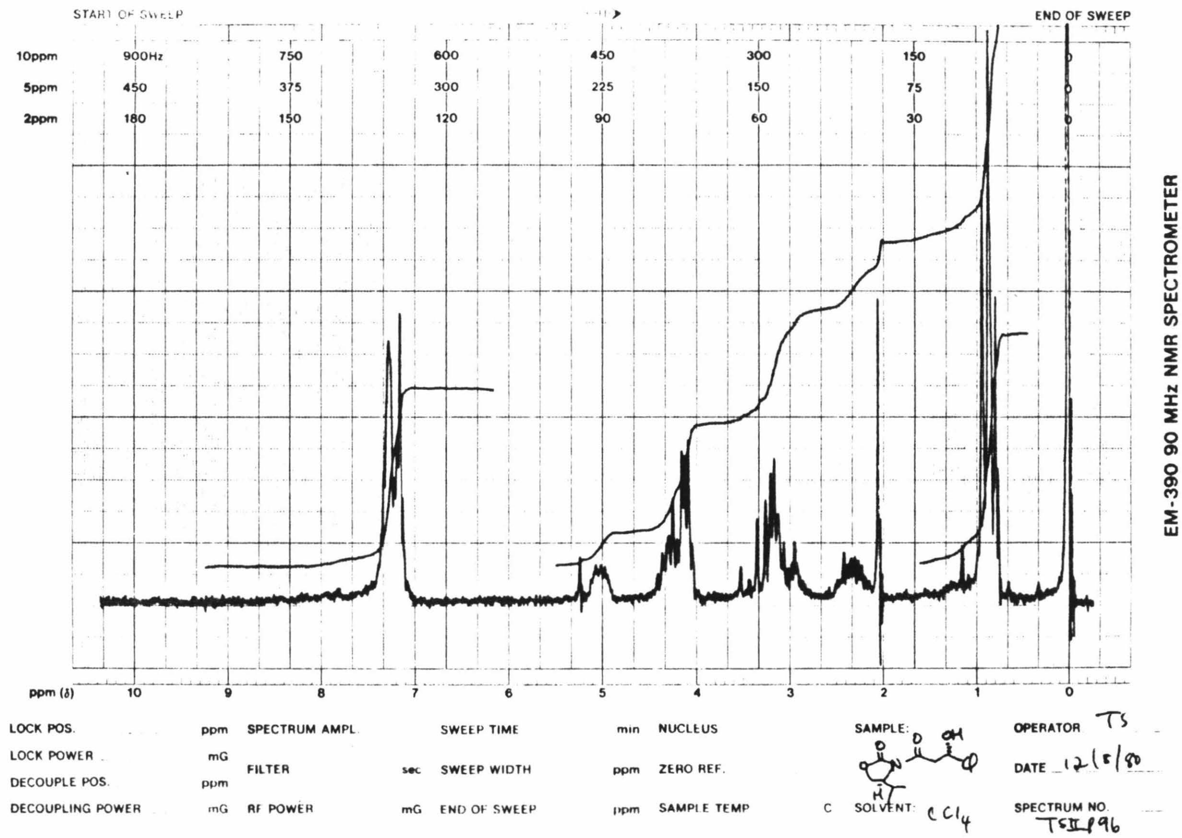
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600

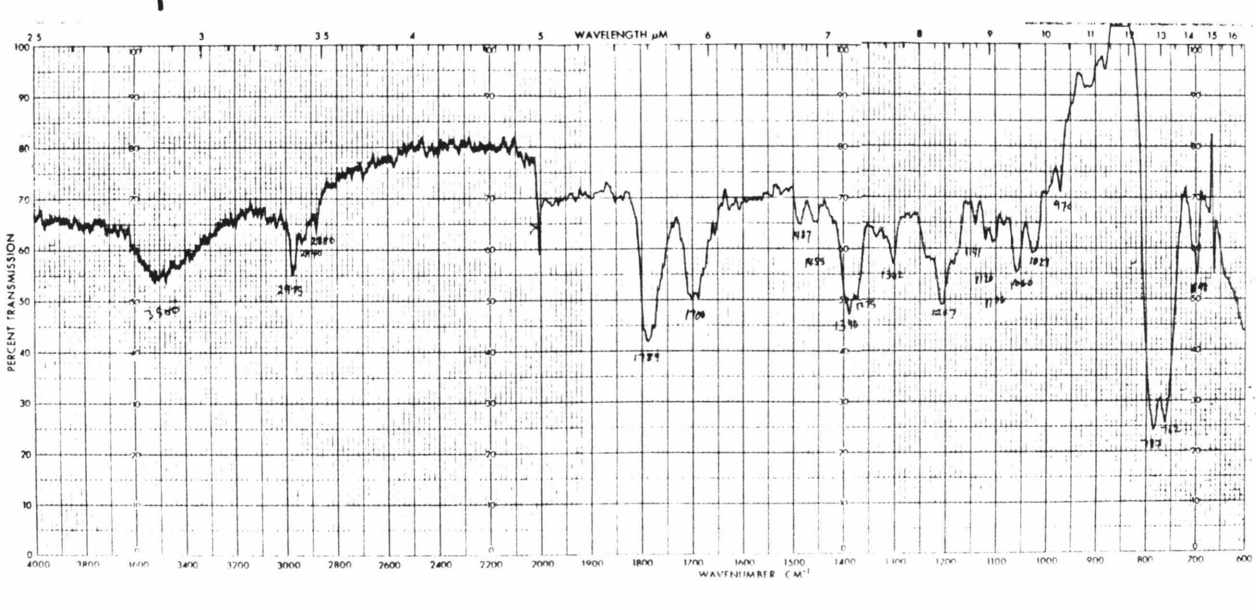

O
O
OH
O
N
Ph
H

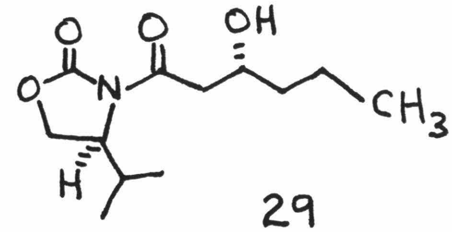
28

CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
LOCK POS.
ppm
SPECTRUM AMPL.
SWEEP TIME
min
NUCLEUS
SAMPLE:
OPERATOR TS
LOCK POWER
mG
FILTER
sec
SWEEP WIDTH
ppm
ZERO REF.
DATE 12/5/80
DECOUPLE POS.
ppm
DECOUPLING POWER
mG
RF POWER
mG
END OF SWEEP
ppm
SAMPLE TEMP
C
SOLVENT: CCl4
SPECTRUM NO.
TSII 96

CCl_4

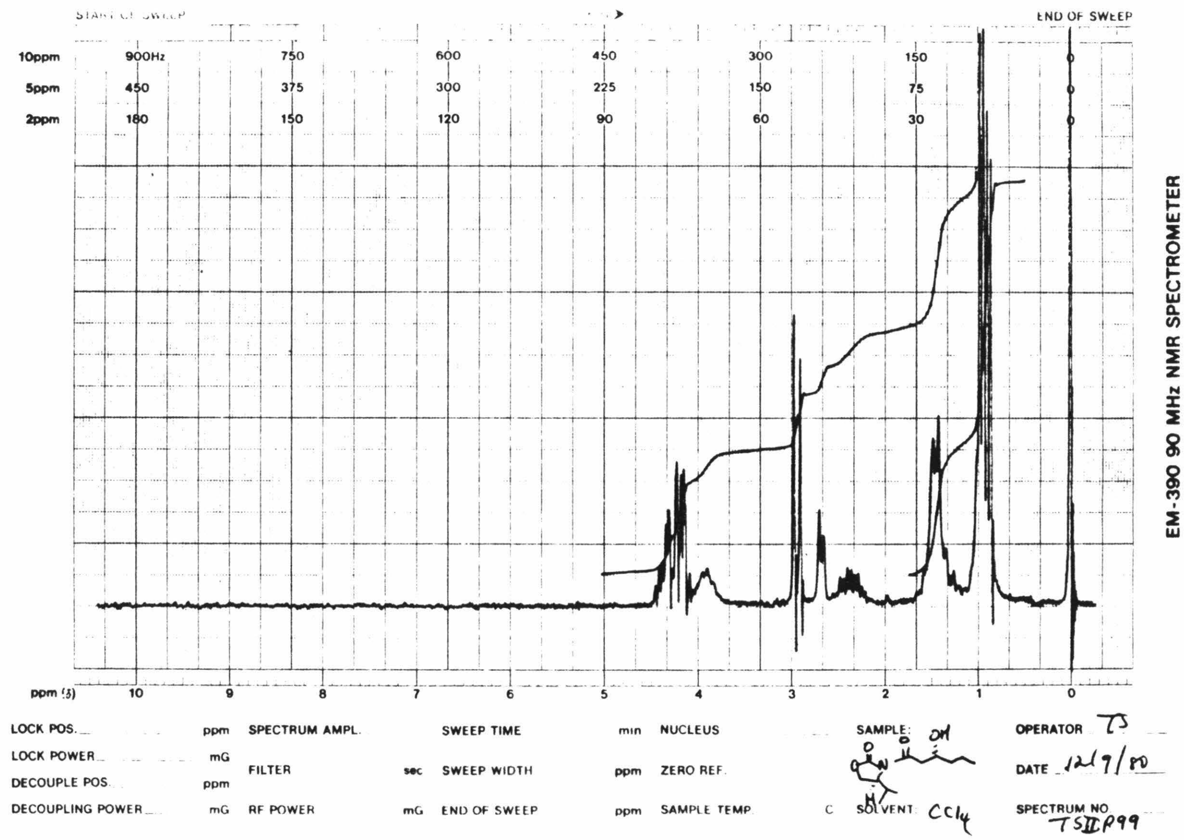

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
3500
2975
1789
1700
1390
1302
1207
976
757
742



OH
CH3

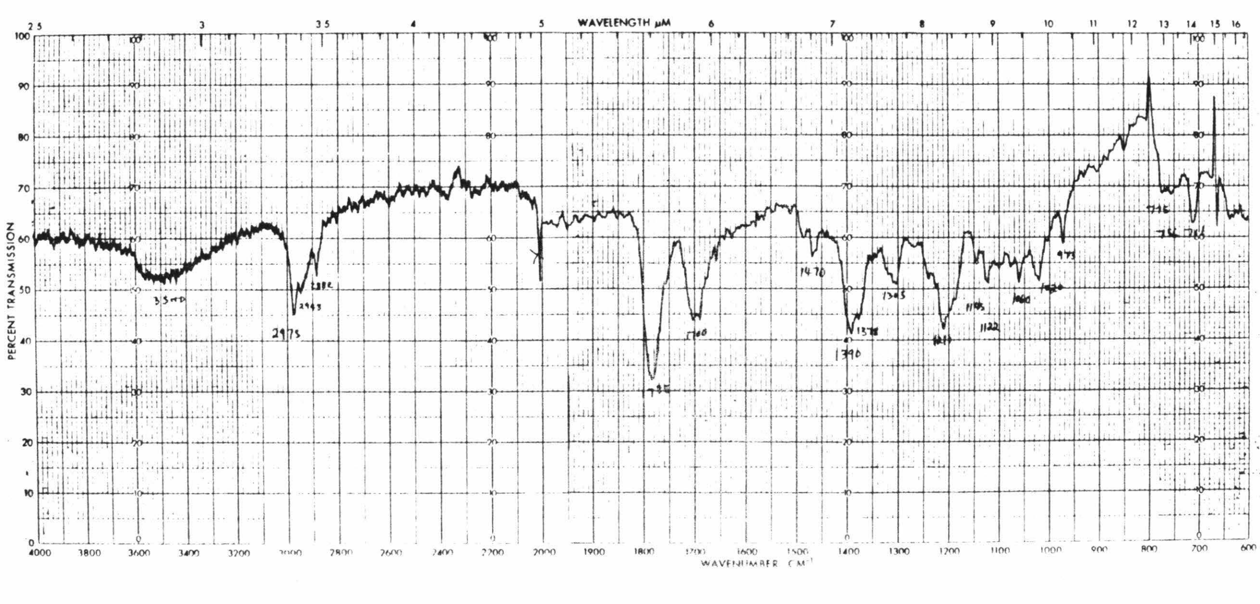
29

CCl4

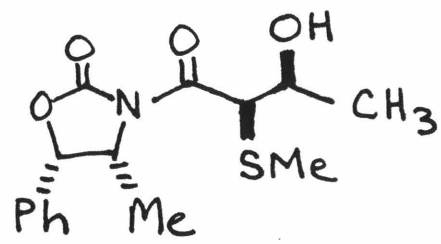


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS.
LOCK POWER
DECOUPLE POS.
DECOUPLING POWER
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP.
SAMPLE:
SOLVENT: CCl4
OPERATOR TS
DATE 12/9/80
SPECTRUM NO TSIIP99

CCl4

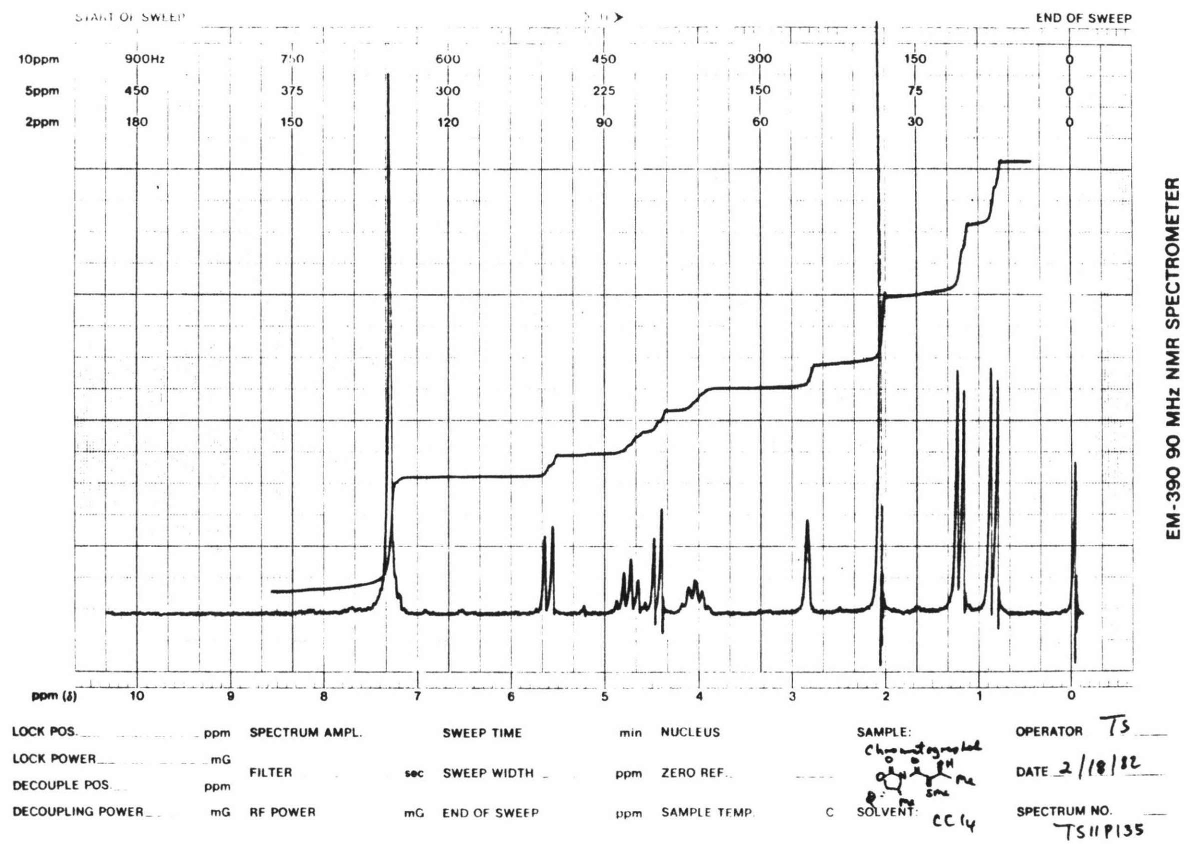


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
3540
2975
2945
2880
1795
1700
1470
1390
1378
1345
1211
1185
1122
1060
1024
975

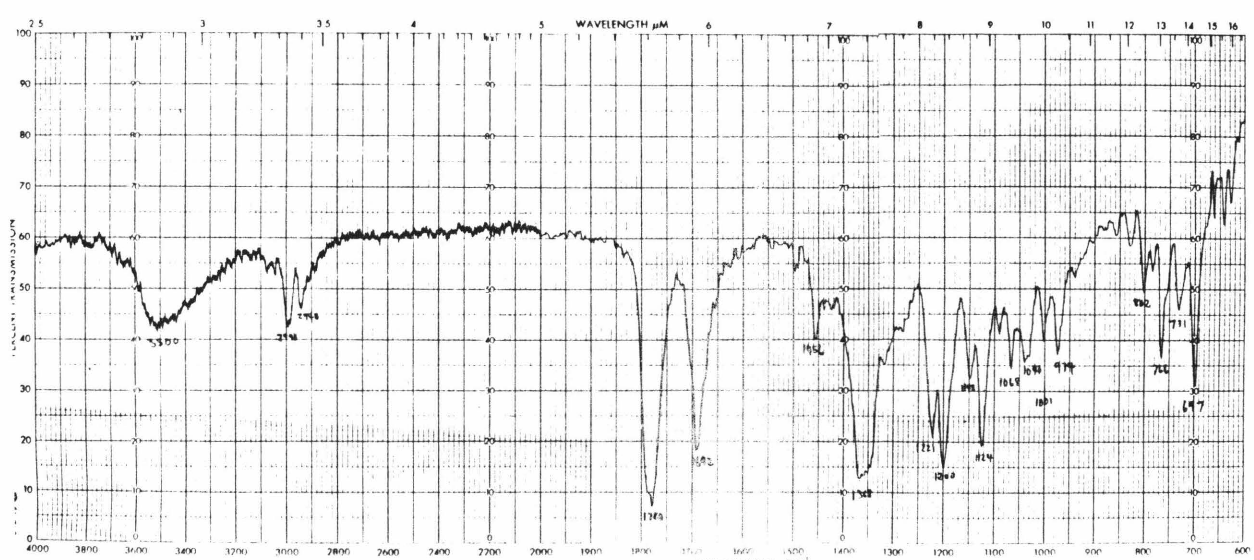

OH
CH3
SMe
Ph
Me

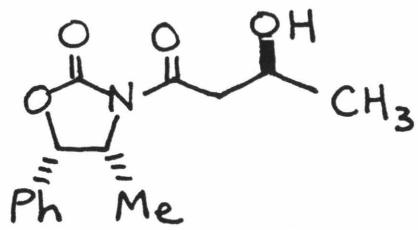
CCl4

30


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS.
LOCK POWER
DECOUPLE POS.
DECOUPLING POWER
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP.
SAMPLE: Chromatographed
SOLVENT: CCl4
OPERATOR TS
DATE 2/18/82
SPECTRUM NO. TS11P135

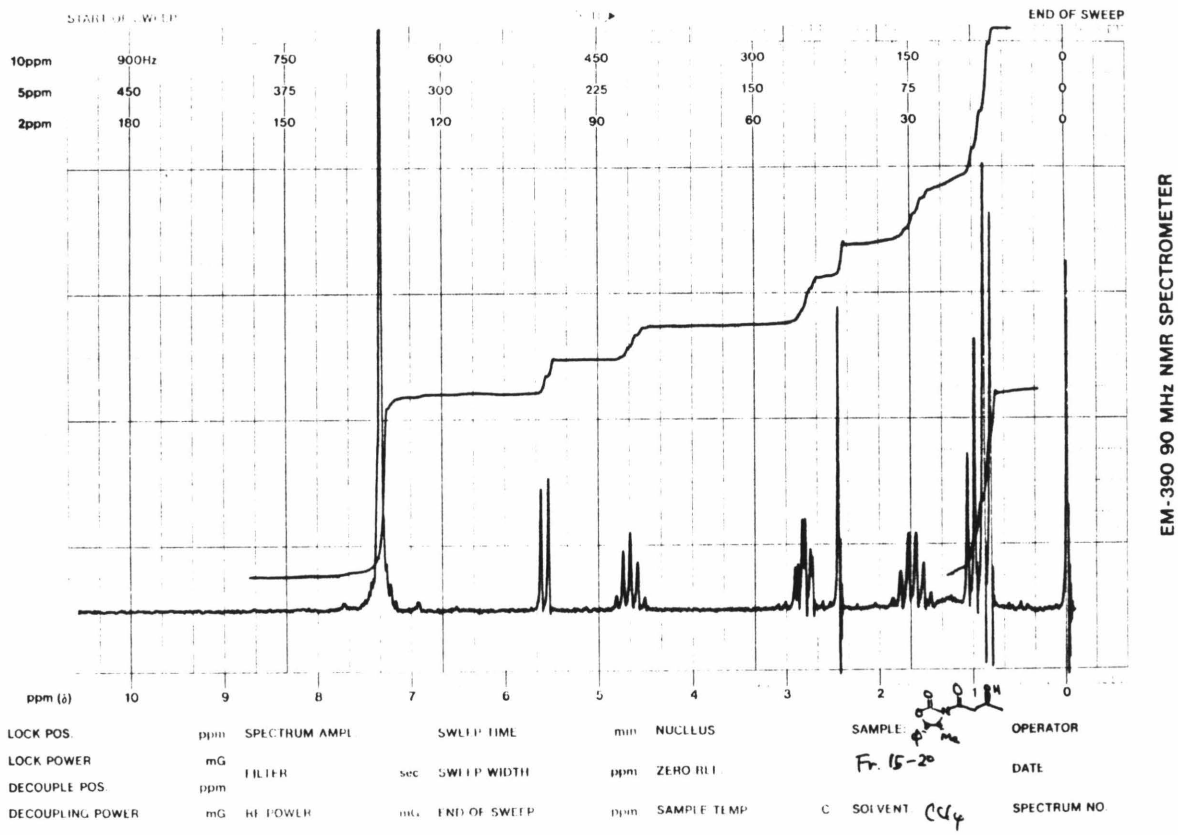
Neat


WAVELENGTH μM
3300
2978
1784
1682
1452
1368
1221
1200
1124
1068
1001
974
862
766
731
697

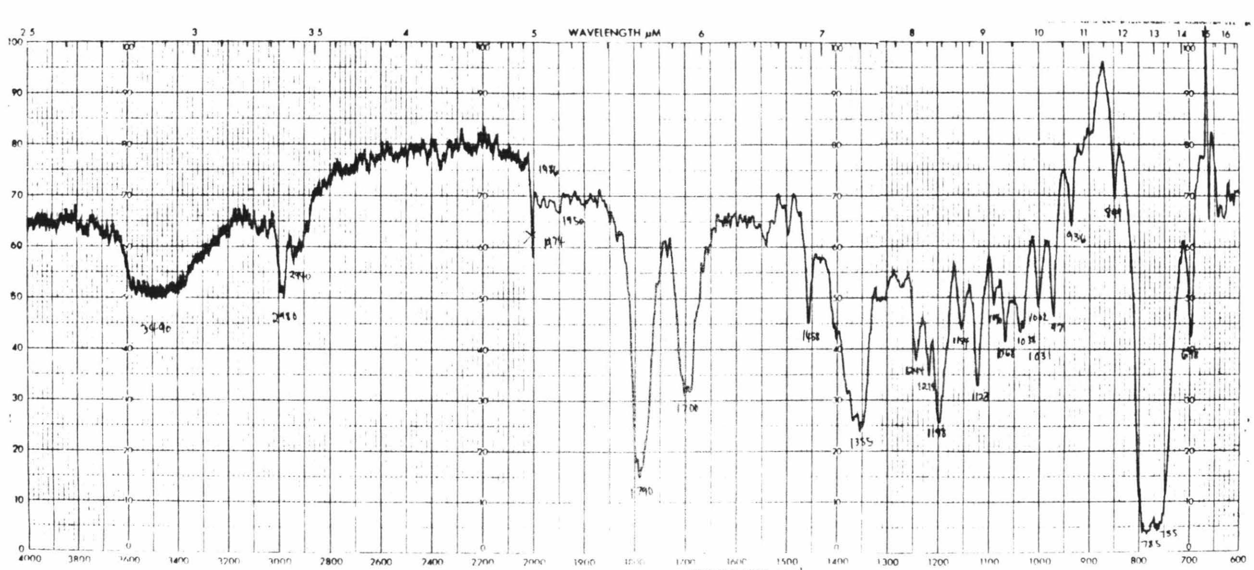

O
O
OH
O
N
CH3
Ph
Me

31

CCl4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
LOCK POS.
ppm
SPECTRUM AMPL
SWEEP TIME
min
NUCLEUS
SAMPLE:
OPERATOR
LOCK POWER
mG
FILTER
sec
SWEEP WIDTH
ppm
ZERO REF
Fr. 15-20
DATE
DECOUPLE POS.
ppm
DECOUPLING POWER
mG
RF POWER
mG
END OF SWEEP
ppm
SAMPLE TEMP
C
SOLVENT
CCl4
SPECTRUM NO.

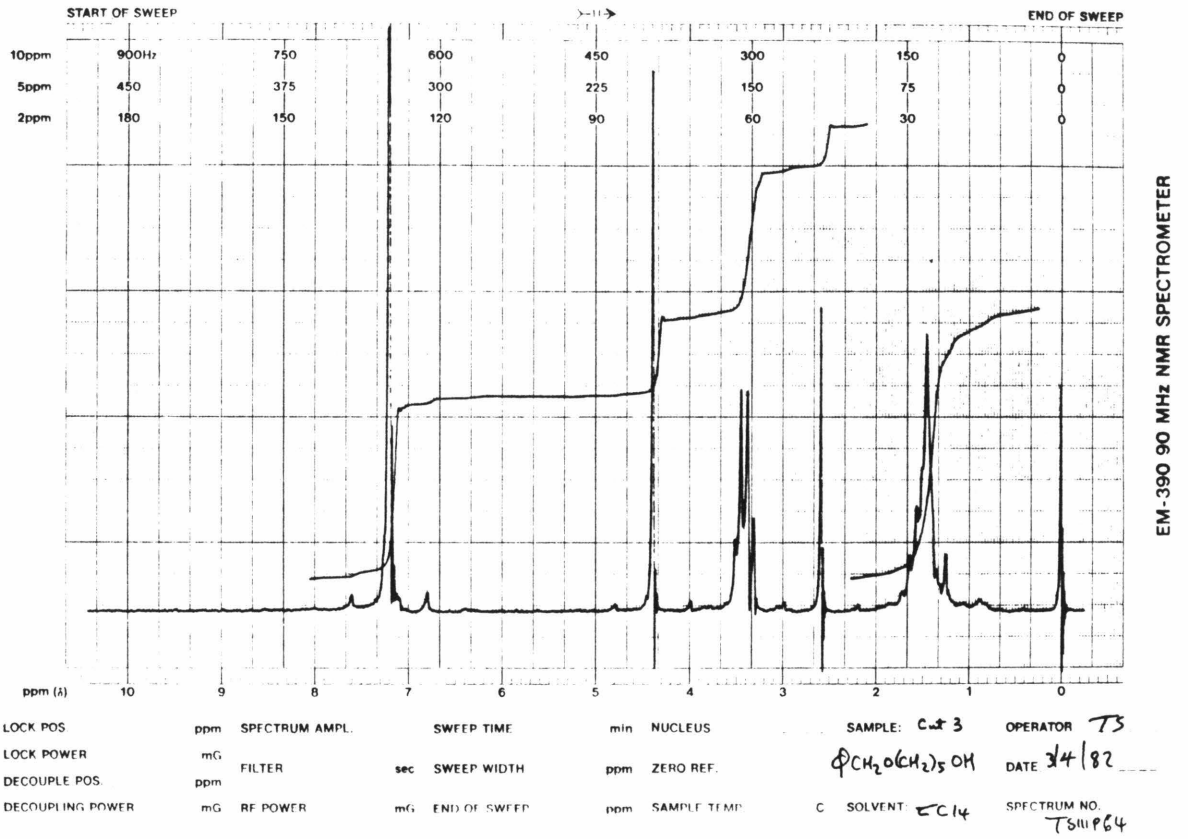
CCl4


WAVELENGTH μM
3490
2980
2940
1984
1956
1974
1790
1700
1458
1355
1244
1219
1198
1194
1152
1118
1068
1036
1062
1031
971
936
844
785
755
698
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1500
1400
1300
1200
1100
1000
900
800
700
600

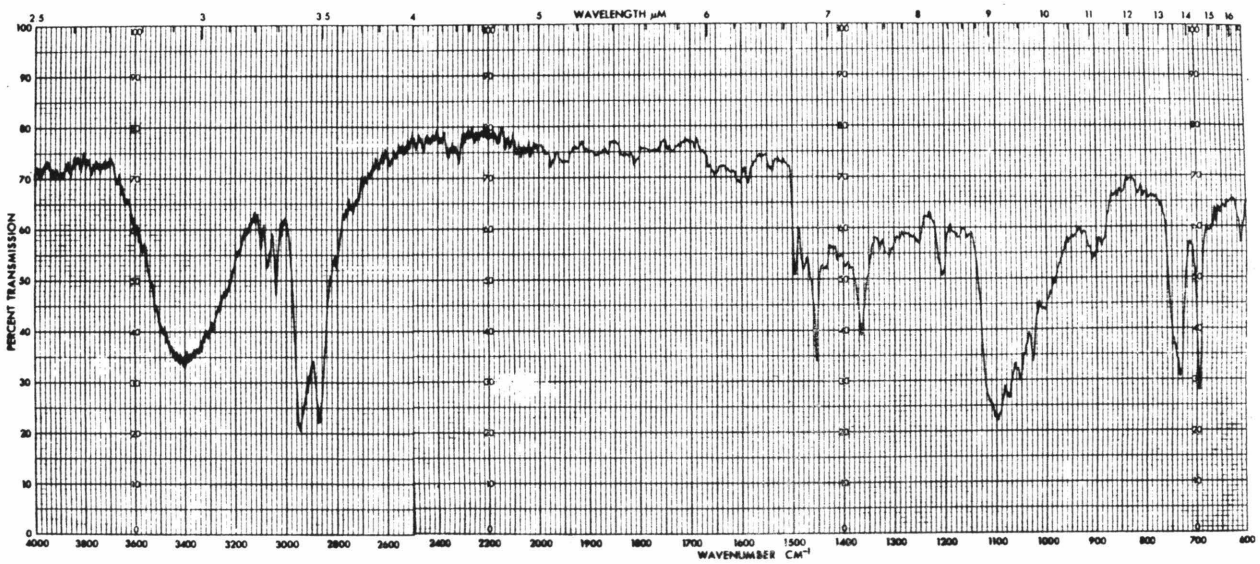
APPENDIX IV. Selected IR and NMR Spectral Catalog for Chapter II

$PhCH_2O(CH_2)_5OH$

CCl_4

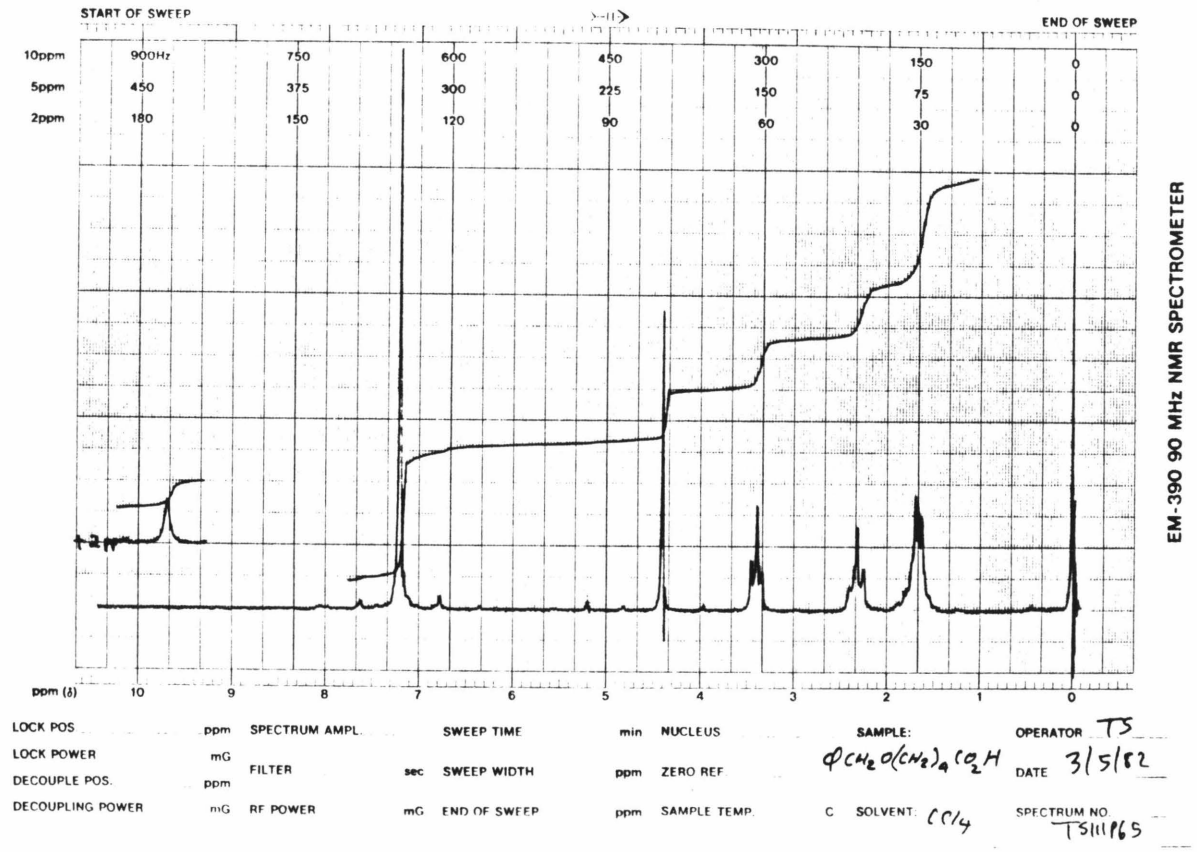


Neat

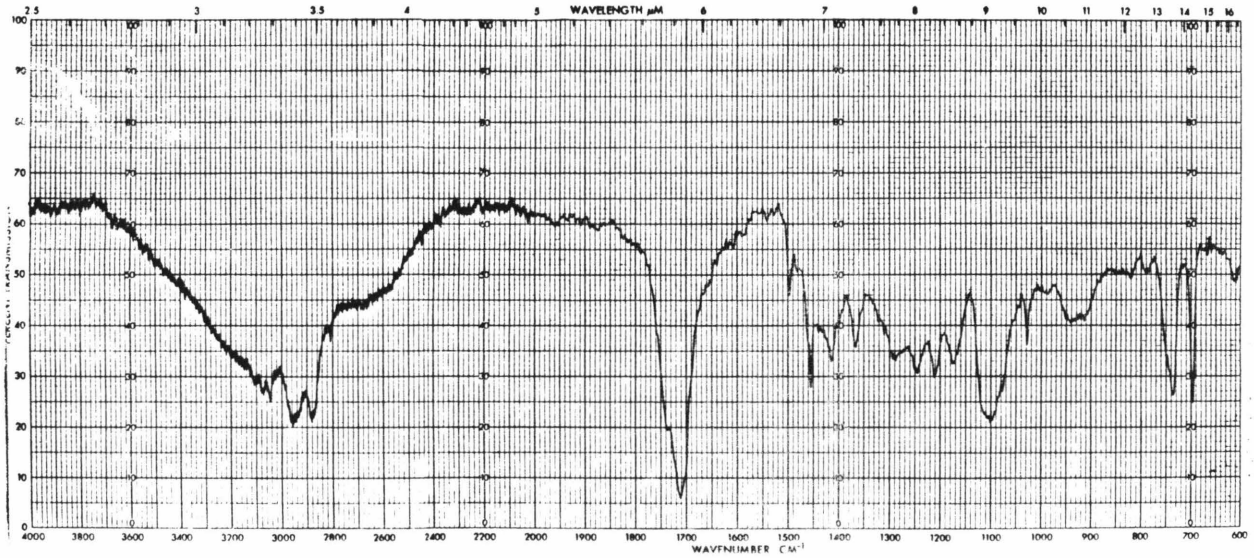


$PhCH_2O(CH_2)_4CO_2H$

CCl_4

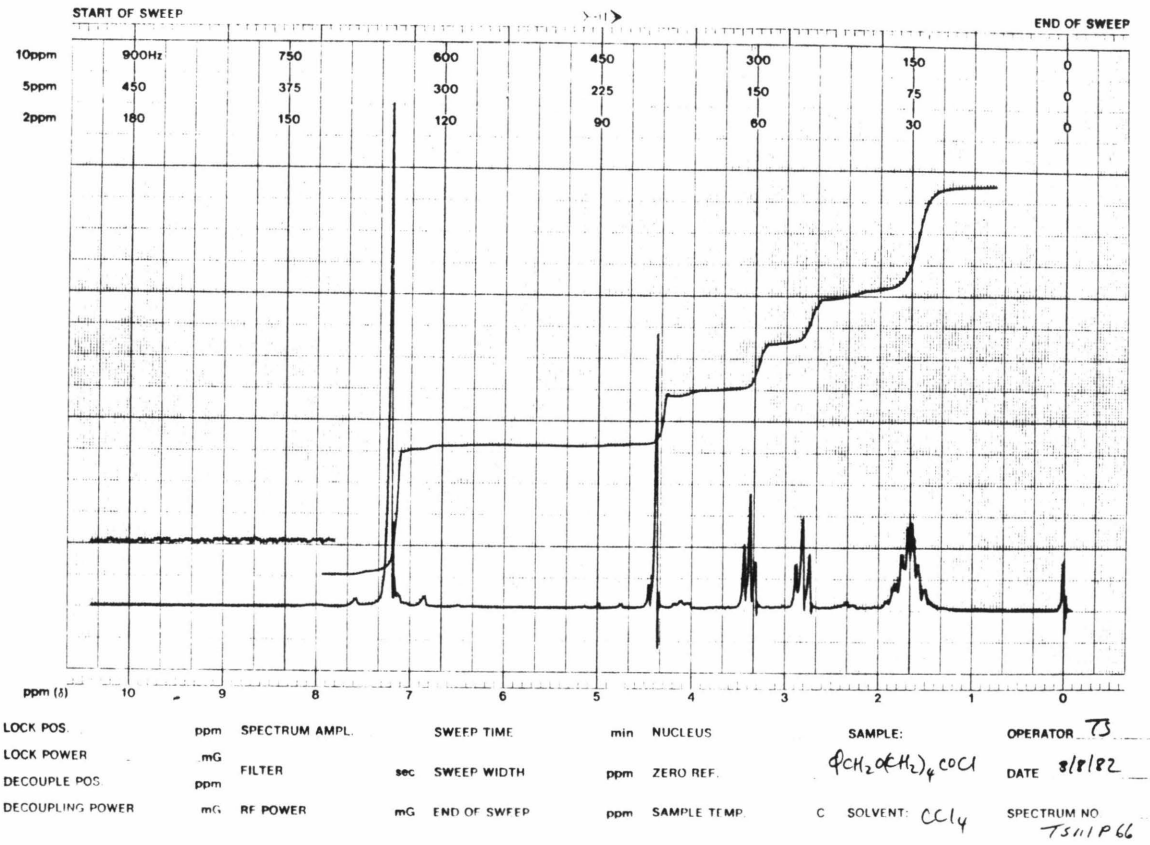


Neat

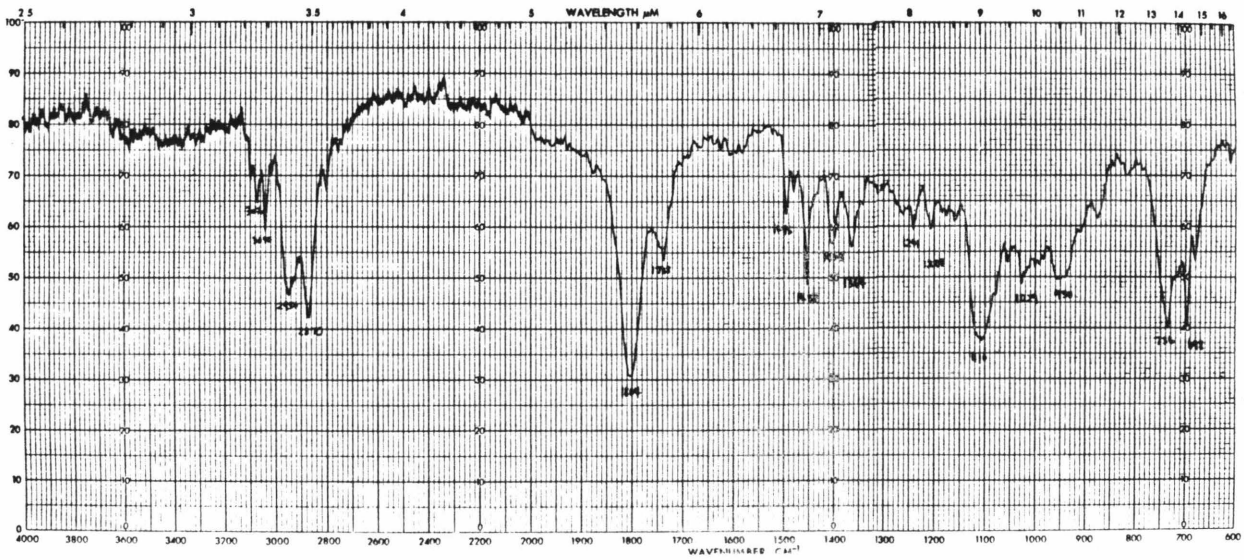


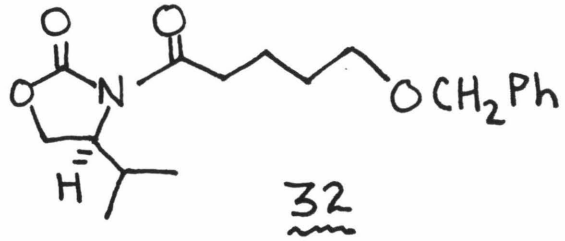
$PhCH_2O(CH_2)_4COCl$

CCl_4



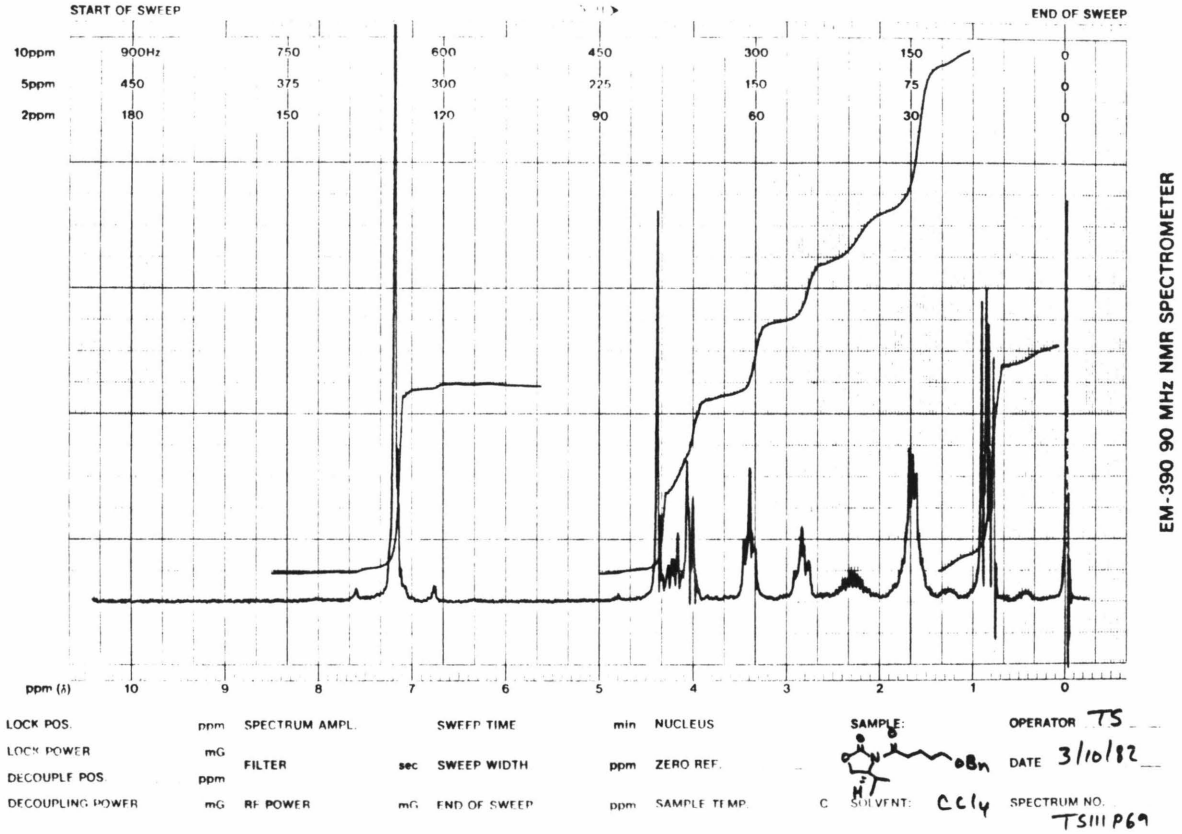
Neat



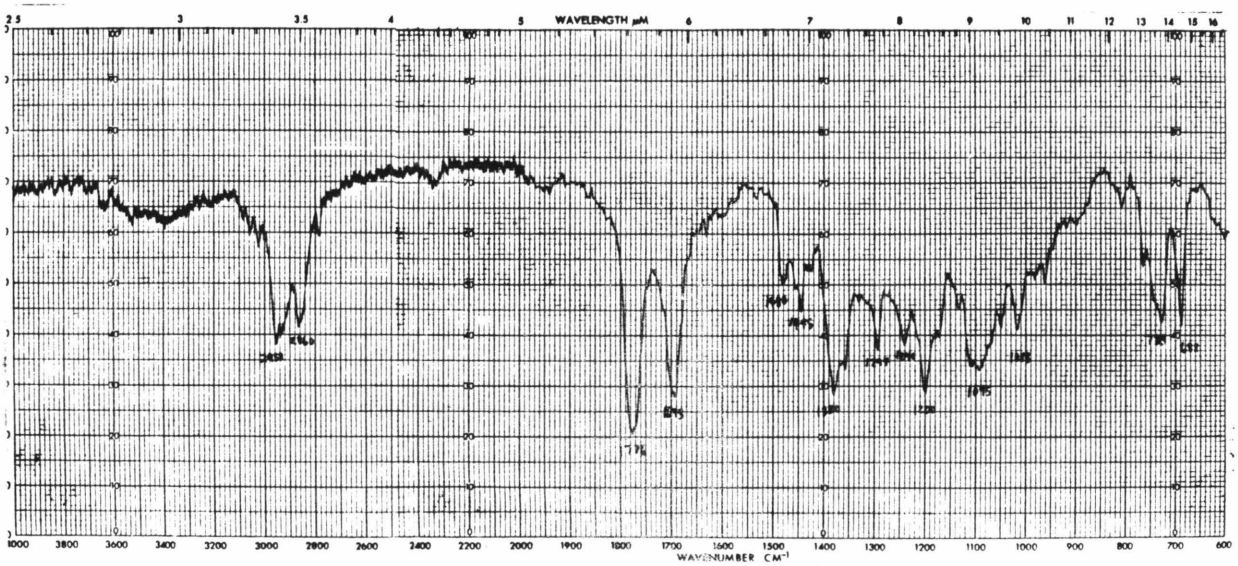

O
O
N
O
OCH2Ph
H

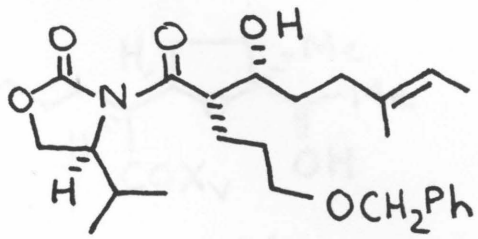
32

CCl4


START OF SWEEP
END OF SWEEP
10ppm 900Hz 750 600 450 300 150 0
5ppm 450 375 300 225 150 75 0
2ppm 180 150 120 90 60 30 0
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm SPECTRUM AMPL.
LOCK POWER mG FILTER
DECOUPLE POS. ppm
DECOUPLING POWER mG RF POWER
SWEEP TIME min NUCLEUS
sec SWEEP WIDTH ppm ZERO REF.
mG END OF SWEEP ppm SAMPLE TEMP. C
SAMPLE:
OBn
OPERATOR TS
DATE 3/10/82
SOLVENT: CCl4
SPECTRUM NO. TS111 P69

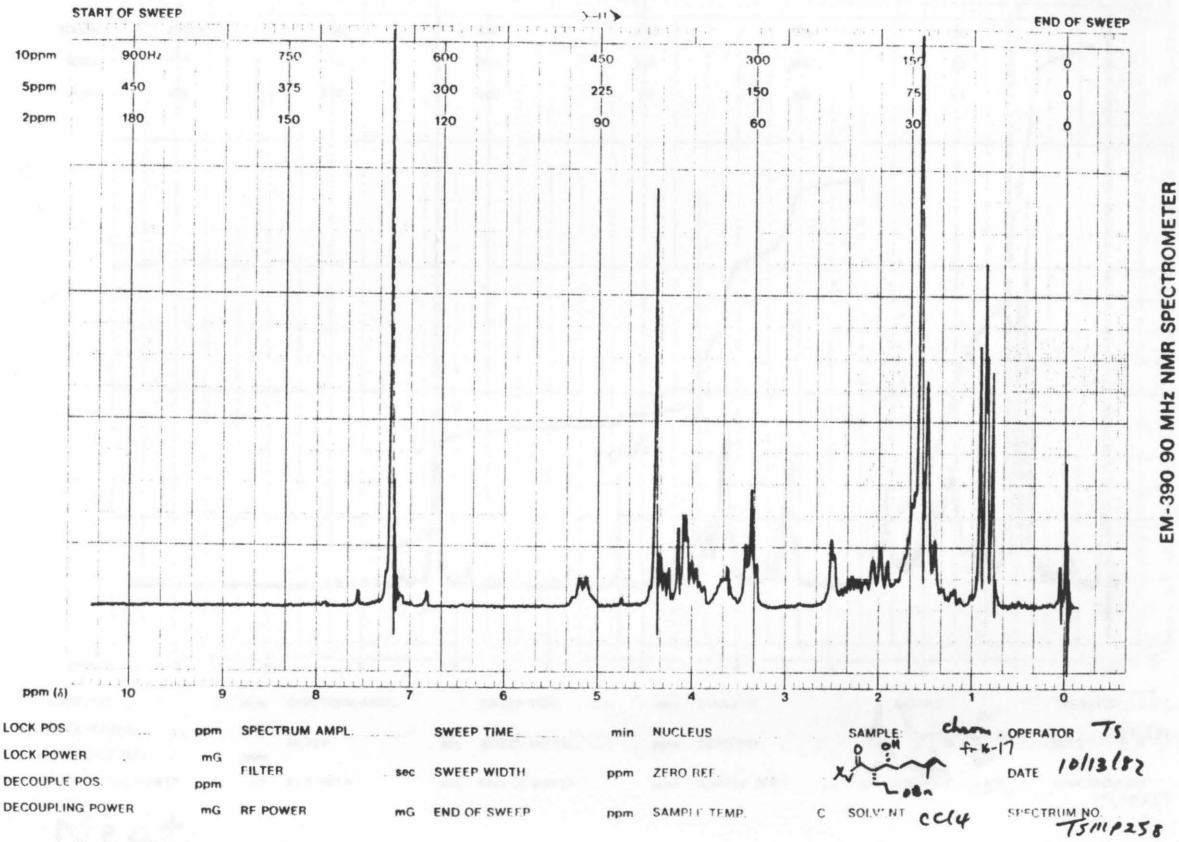
Neat


WAVELENGTH μM
WAVENUMBER CM-1

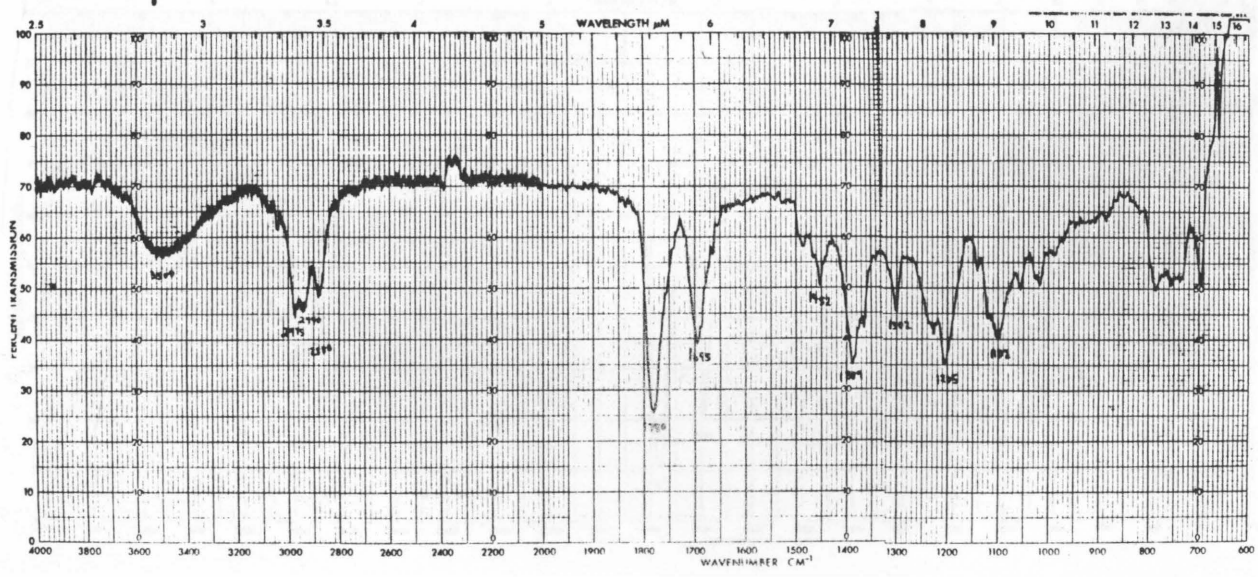

O
O
OH
N
O
H
OCH2Ph

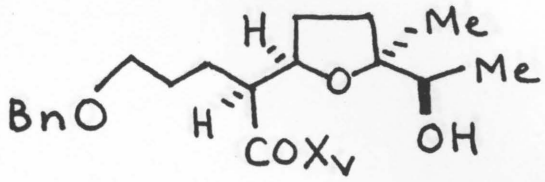
33

CCl_4


START OF SWEEP
END OF SWEEP
10ppm 900Hz 750 600 450 300 150 0
5ppm 450 375 300 225 150 75 0
2ppm 180 150 120 90 60 30 0
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm SPECTRUM AMPL. SWEEP TIME min NUCLEUS
LOCK POWER mG
DECOUPLE POS. ppm FILTER sec SWEEP WIDTH ppm ZERO REF.
DECOUPLING POWER mG RF POWER mG END OF SWEEP ppm SAMPLE TEMP. C SOLVENT CCl4
SAMPLE: chrom. fr 16-17
OPERATOR TS
DATE 10/13/82
SPECTRUM NO. TS11P258

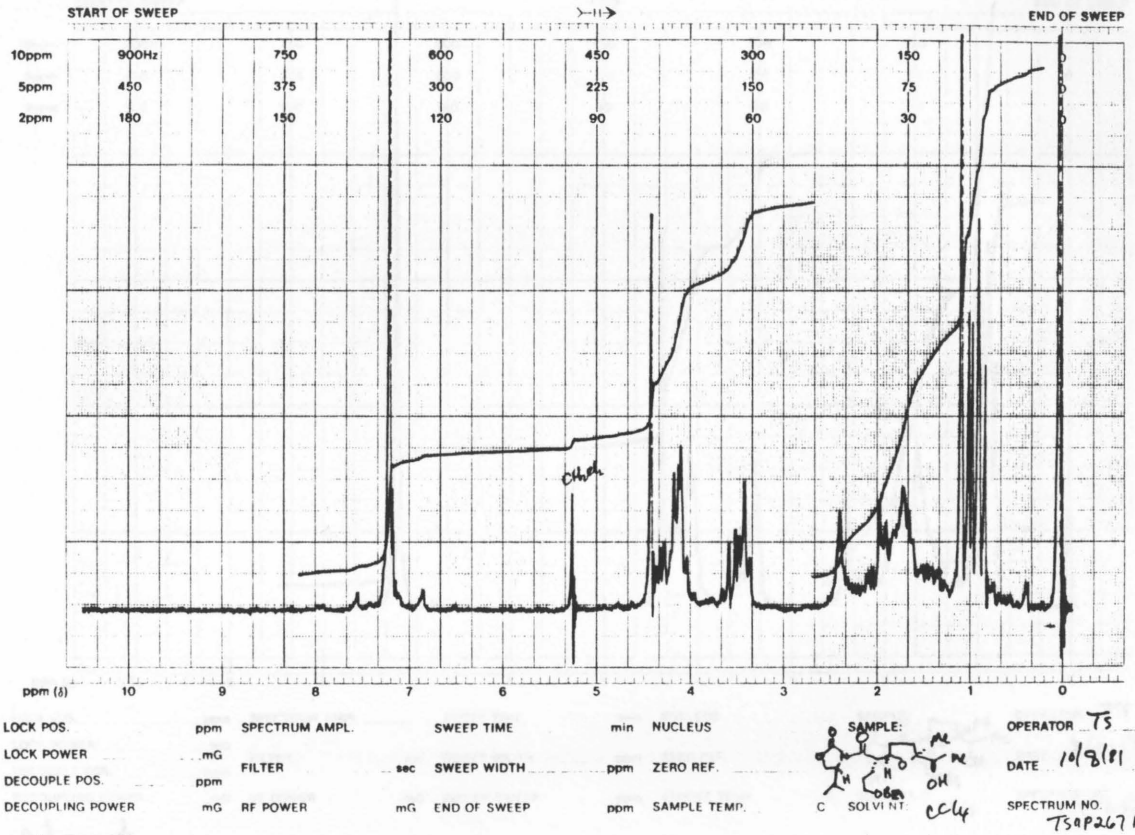
CCl_4


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM-1



34a

CCl_4



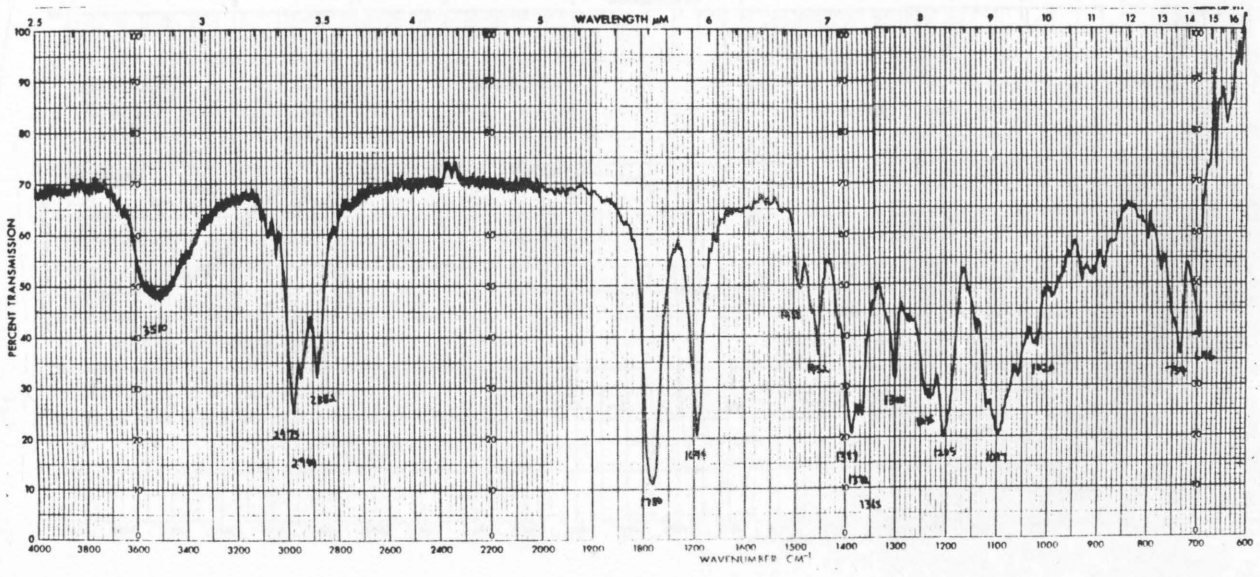
LOCK POS. ppm SPECTRUM AMPL. SWEEP TIME min NUCLEUS SAMPLE: OPERATOR TS

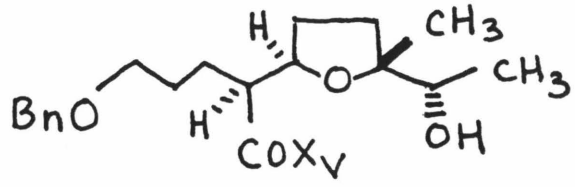
LOCK POWER mG FILTER sec SWEEP WIDTH ppm ZERO REF. DATE 10/8/81

DECOUPLE POS. ppm

DECOUPLING POWER mG RF POWER mG END OF SWEEP ppm SAMPLE TEMP. C SOLVENT CCl_4 SPECTRUM NO. TSAP267A

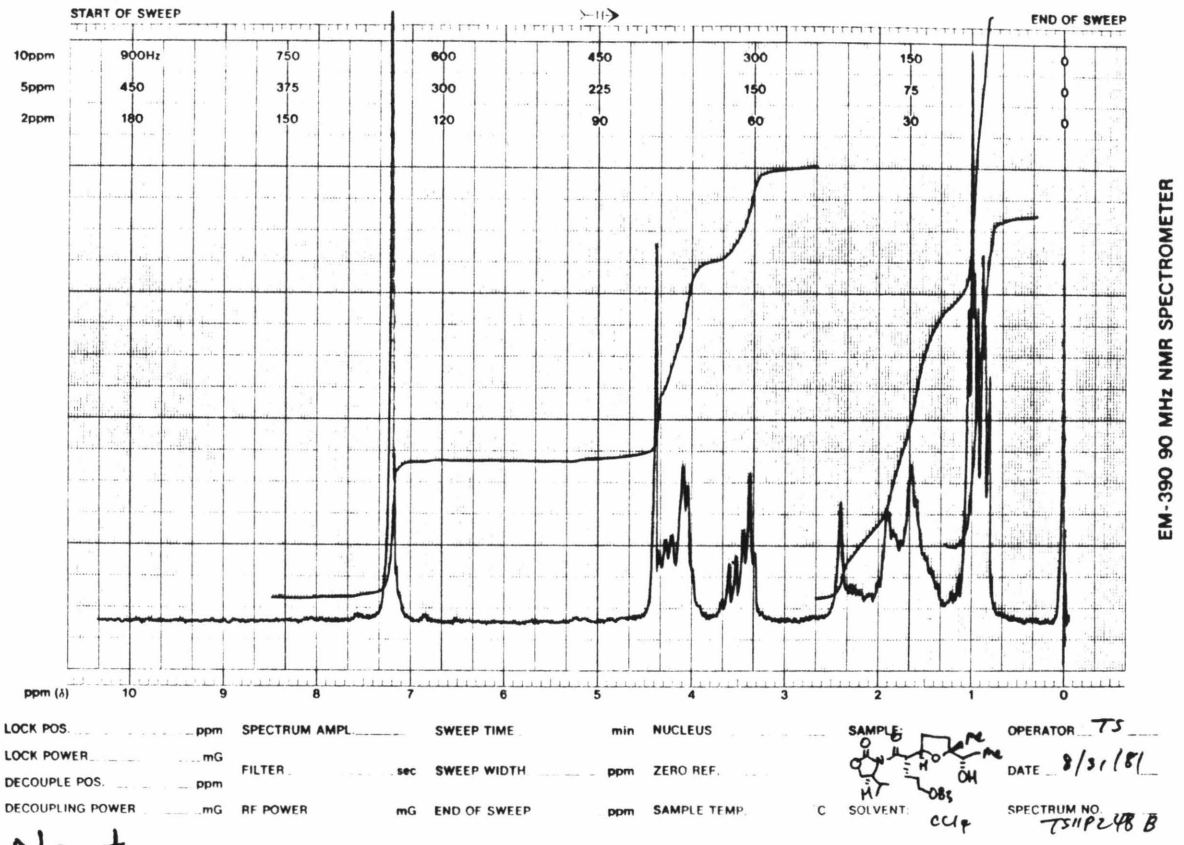
Neat



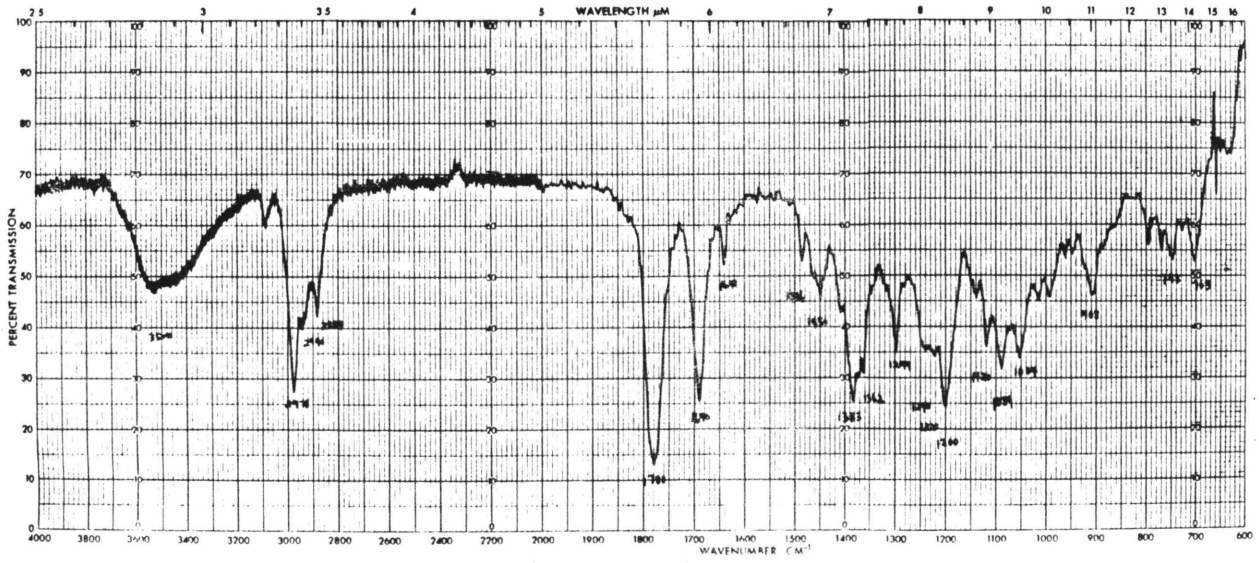


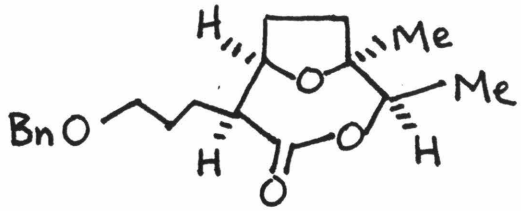
34b

CCl4



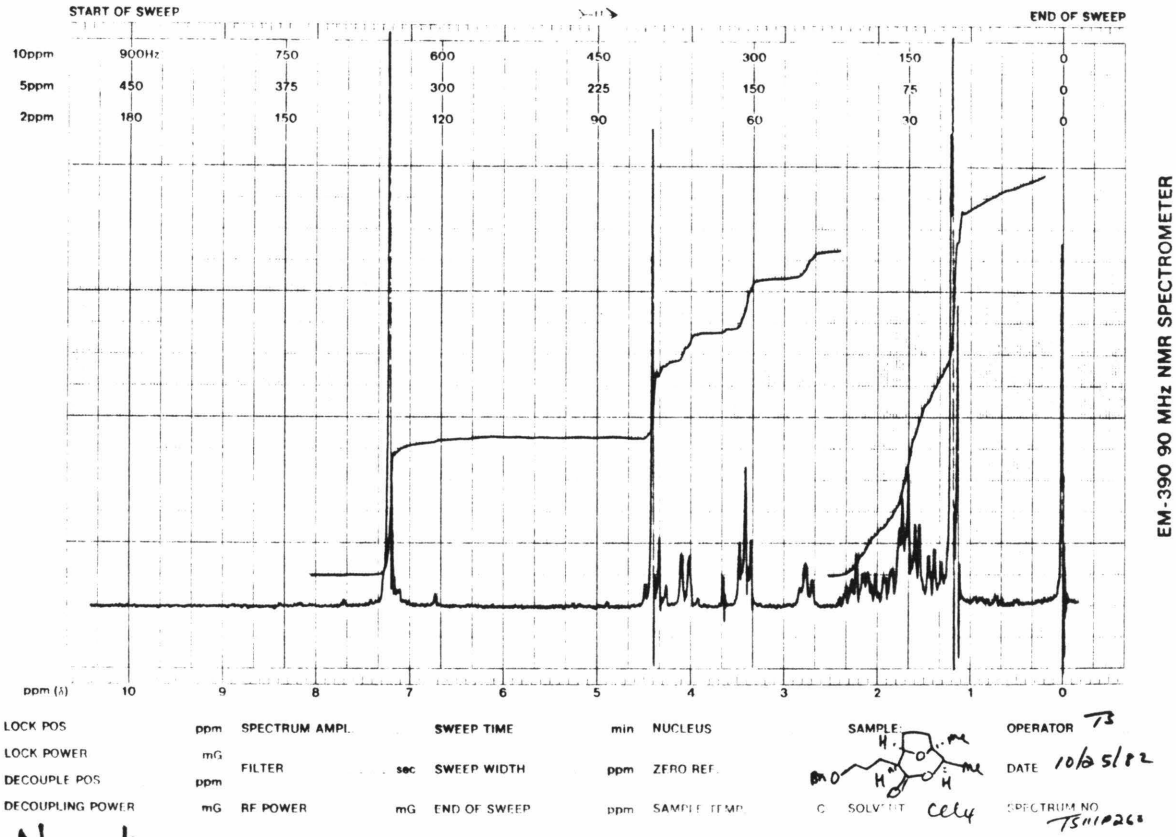
Neat



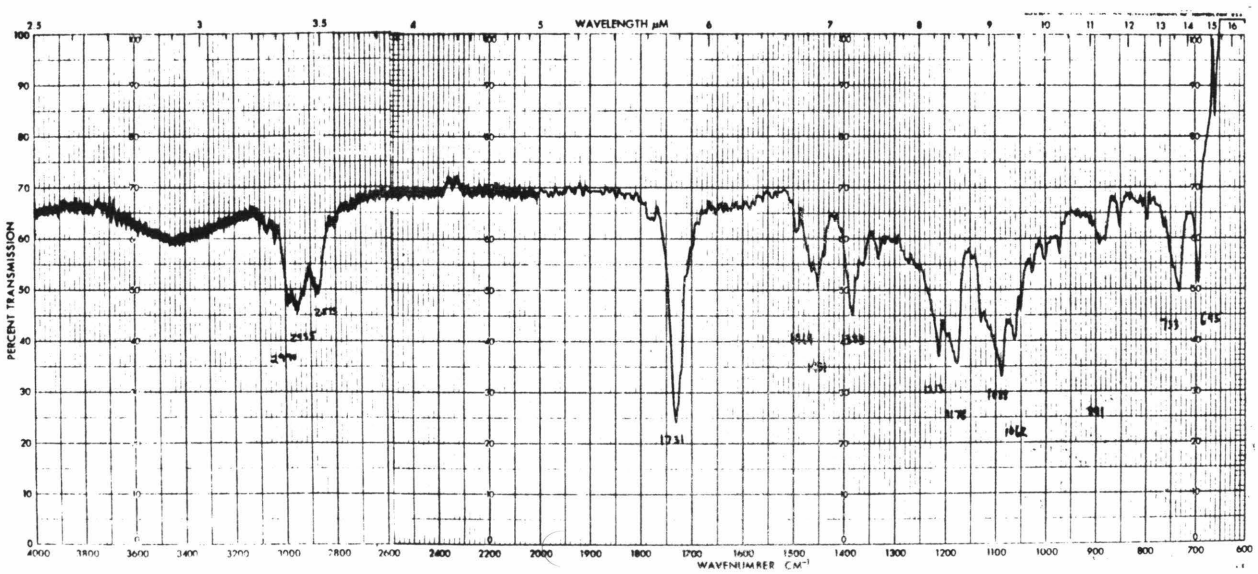

H
Me
Me
BnO
H
O
H
O

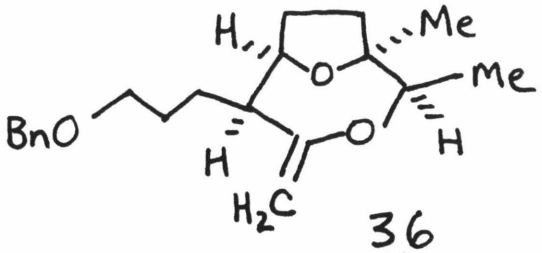
35

CCl4


START OF SWEEP
END OF SWEEP
10ppm 900Hz 750 600 450 300 150 0
5ppm 450 375 300 225 150 75 0
2ppm 180 150 120 90 60 30 0
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
LOCK POS ppm SPECTRUM AMPL SWEEP TIME min NUCLEUS SAMPLE OPERATOR TB
LOCK POWER mG
DECOUPLE POS ppm FILTER sec SWEEP WIDTH ppm ZERO REF DATE 10/15/82
DECOUPLING POWER mG RF POWER mG END OF SWEEP ppm SAMPLE TEMP C SOLVENT CCl4 SPECTRUM NO TS11P26
EM-390 90 MHz NMR SPECTROMETER

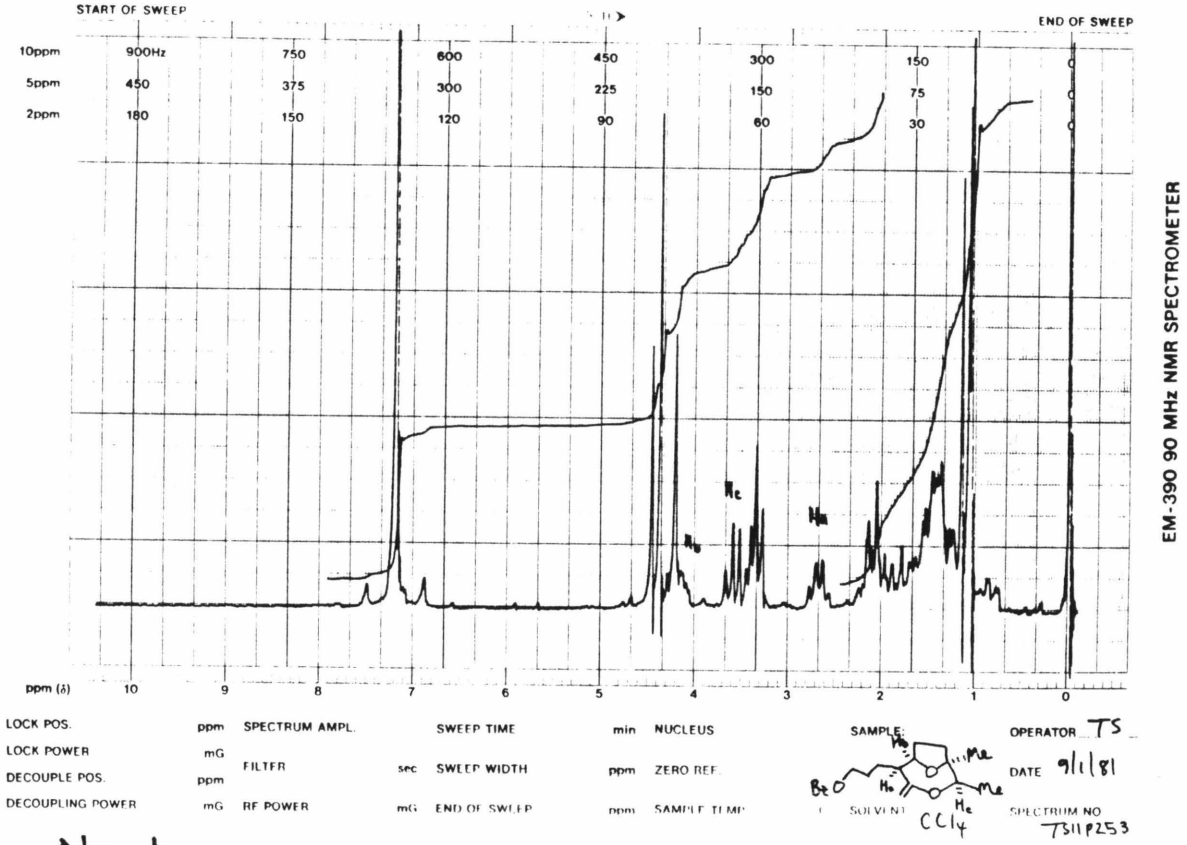
Neat


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600
2.5 3 3.5 4 5 6 7 8 9 10 11 12 13 14 15 16

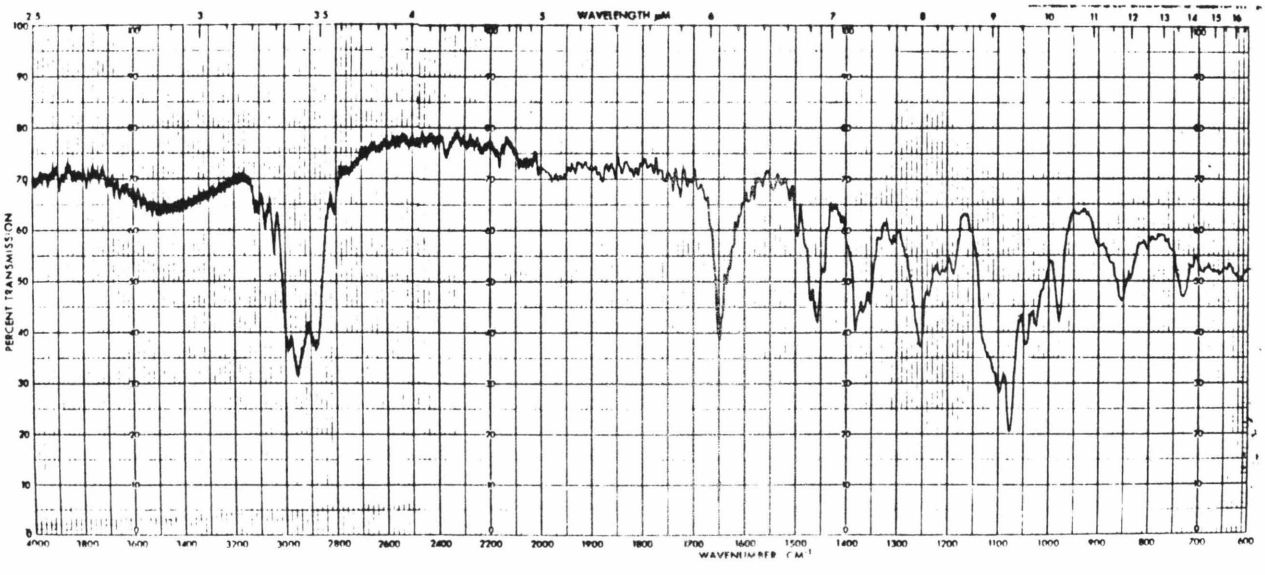

H
Me
O
Me
BnO
O
H
H
H2C

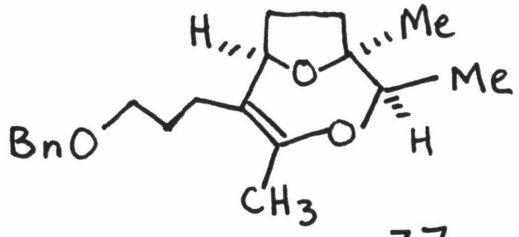
36

CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
LOCK POS.
LOCK POWER
DECOUPLE POS.
DECOUPLING POWER
ppm
mG
ppm
mG
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
min
sec
mG
NUCLEUS
ZERO REF.
SAMPLE TEMP.
ppm
ppm
SAMPLE:
SOLVENT
CCl4
OPERATOR TS
DATE 9/1/81
SPECTRUM NO
T311P253
EM-390 90 MHz NMR SPECTROMETER

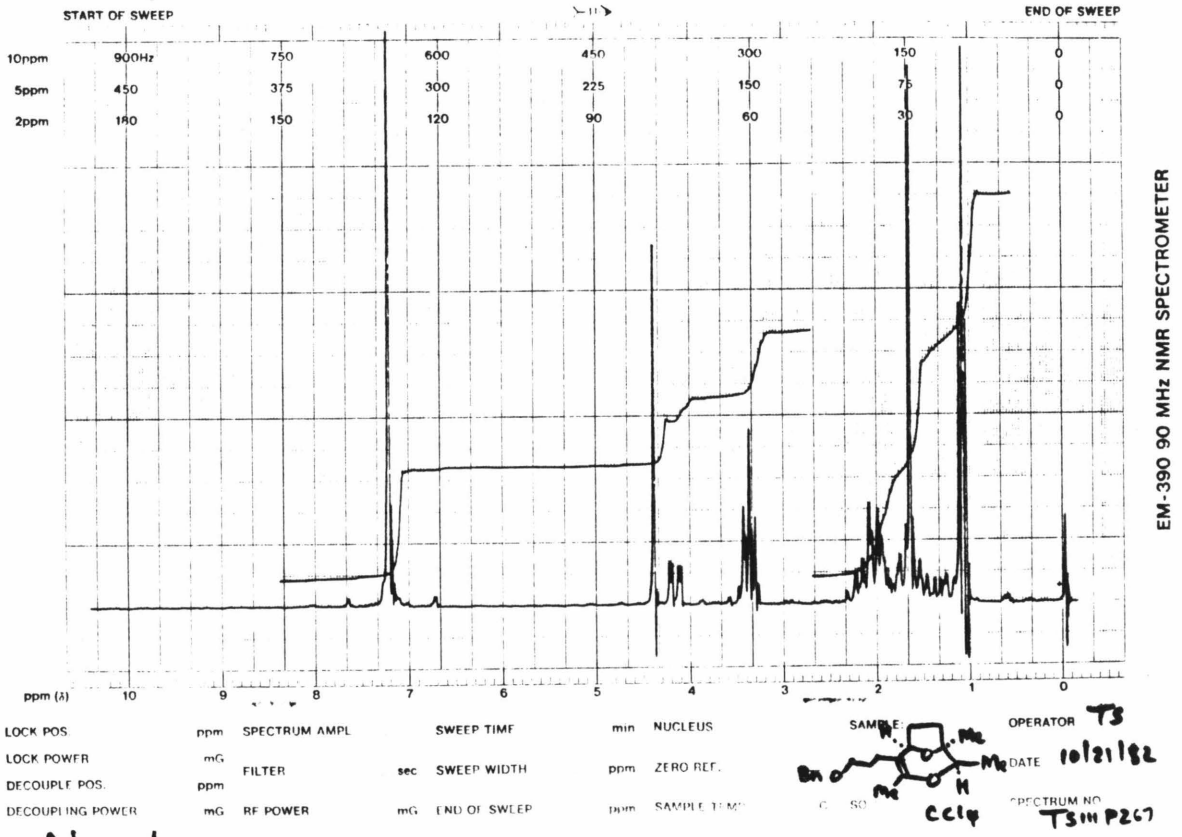
Neat


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM-1

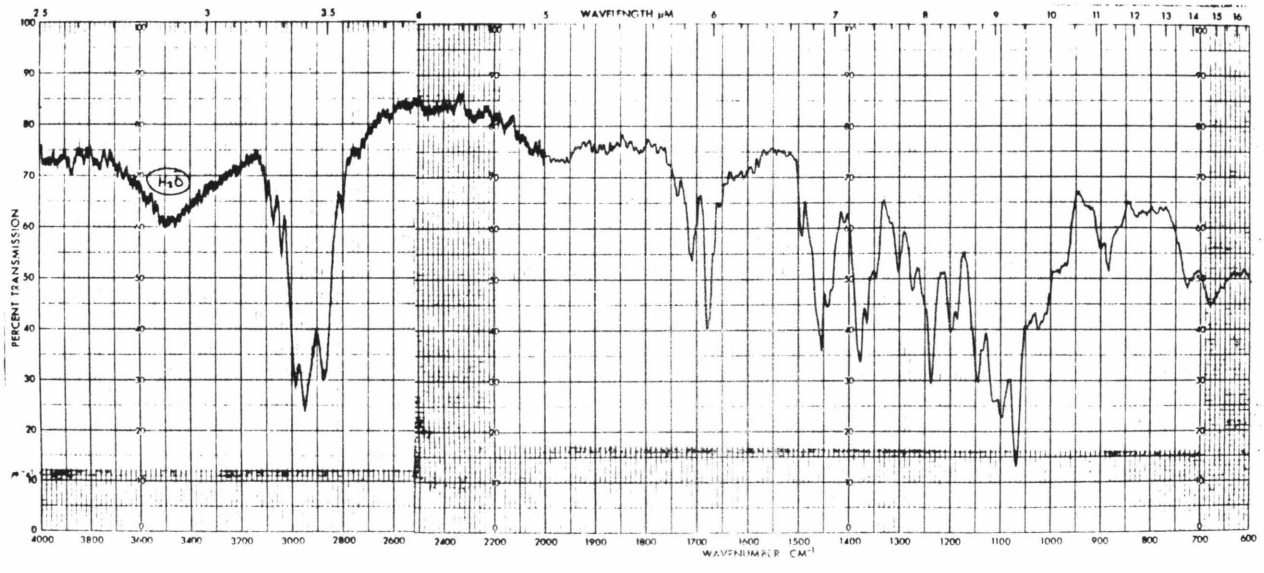

H
Me
Me
O
O
BnO
H
CH3

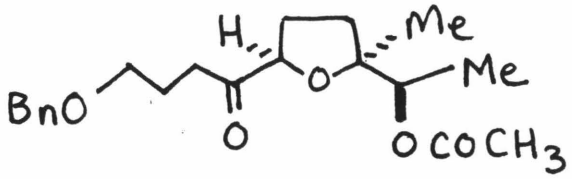
37

CCl_4


START OF SWEEP
END OF SWEEP
10ppm 900Hz 750 600 450 300 150 0
5ppm 450 375 300 225 150 75 0
2ppm 180 150 120 90 60 30 0
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm SPECTRUM AMPL SWEEP TIME min NUCLEUS
LOCK POWER mG FILTER sec SWEEP WIDTH ppm ZERO REF.
DECOUPLE POS. ppm
DECOUPLING POWER mG RF POWER mG END OF SWEEP ppm SAMPLE TEMP
SAMPLE:
OPERATOR TS
DATE 10/21/82
SPECTRUM NO. TSIH P267
CCl4

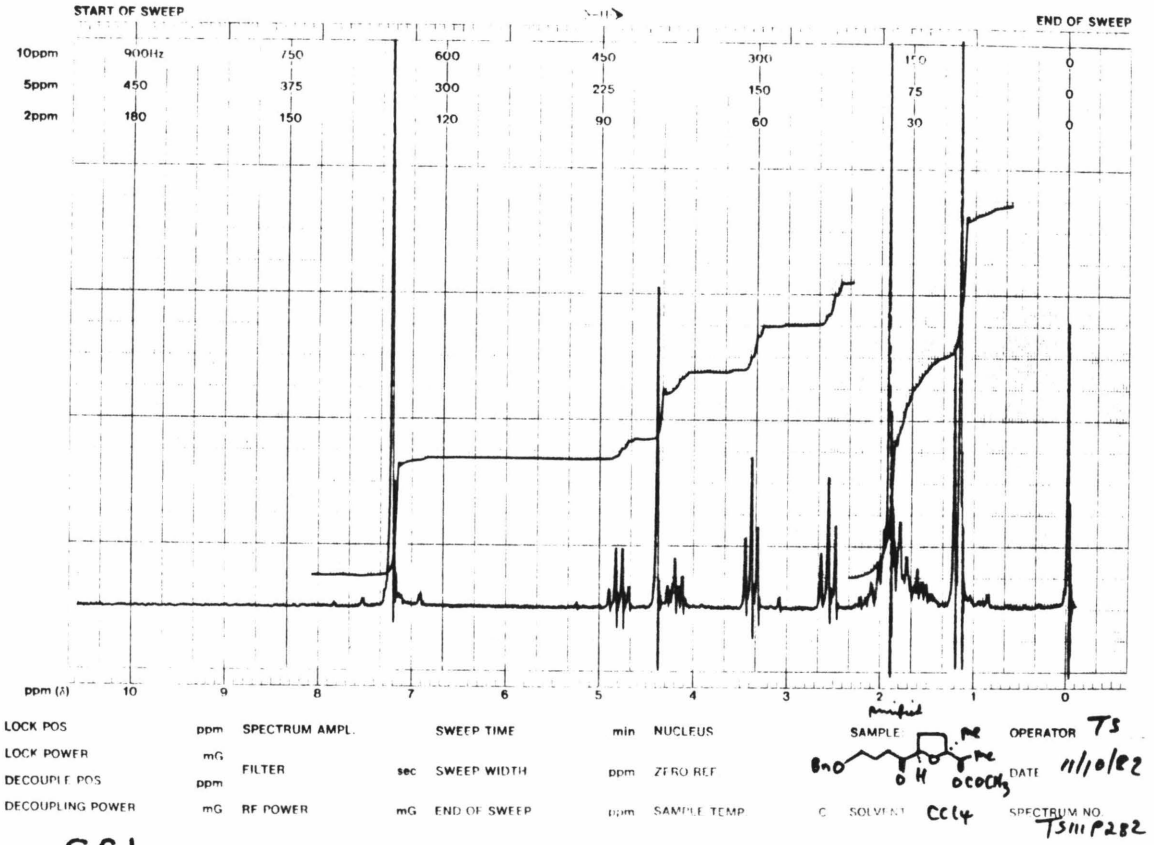
Neat


WAVELENGTH μM
PERCENT TRANSMISSION
H2O
WAVENUMBER CM-1
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600

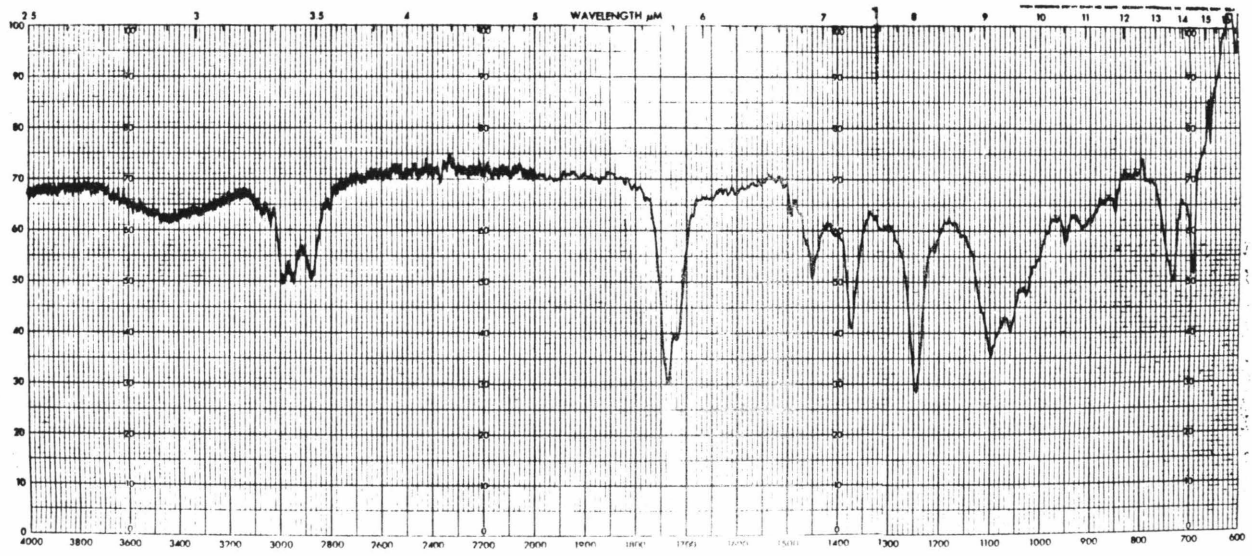

H
Me
Me
BnO
O
O
O COCH3

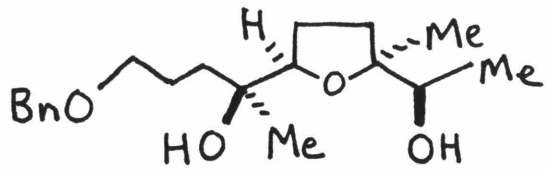
38

CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
ppm
SPECTRUM AMPL.
SWEEP TIME
min
NUCLEUS
SAMPLE
OPERATOR Ts
LOCK POWER
mG
DECOUPLE POS
ppm
FILTER
sec
SWEEP WIDTH
ppm
ZERO REF
DATE 11/10/82
DECOUPLING POWER
mG
RF POWER
mG
END OF SWEEP
ppm
SAMPLE TEMP.
C
SOLVENT CCl4
SPECTRUM NO. TS111P282

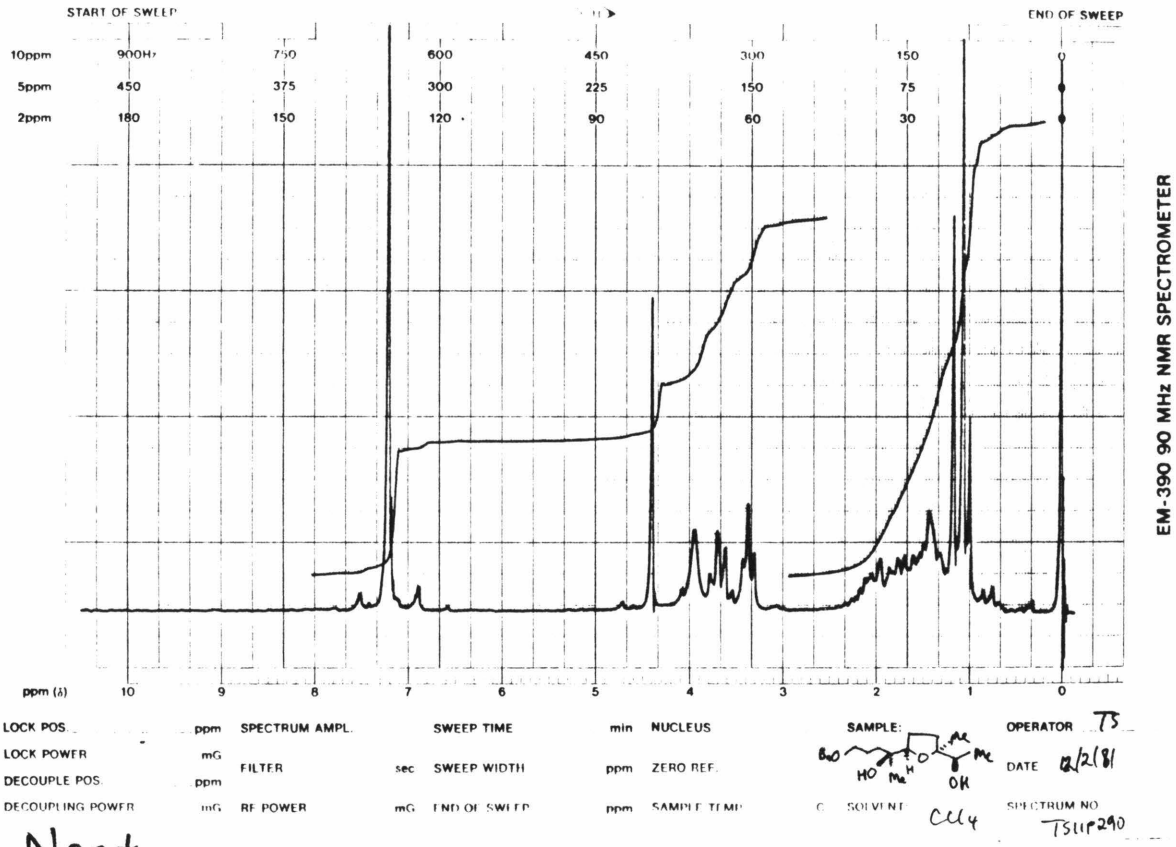
CCl_4


WAVELENGTH μM
2.5
3
3.5
4
5
6
7
8
9
10
11
12
13
14
15
100
90
80
70
60
50
40
30
20
10
0
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1300
1200
1100
1000
900
800
700
600

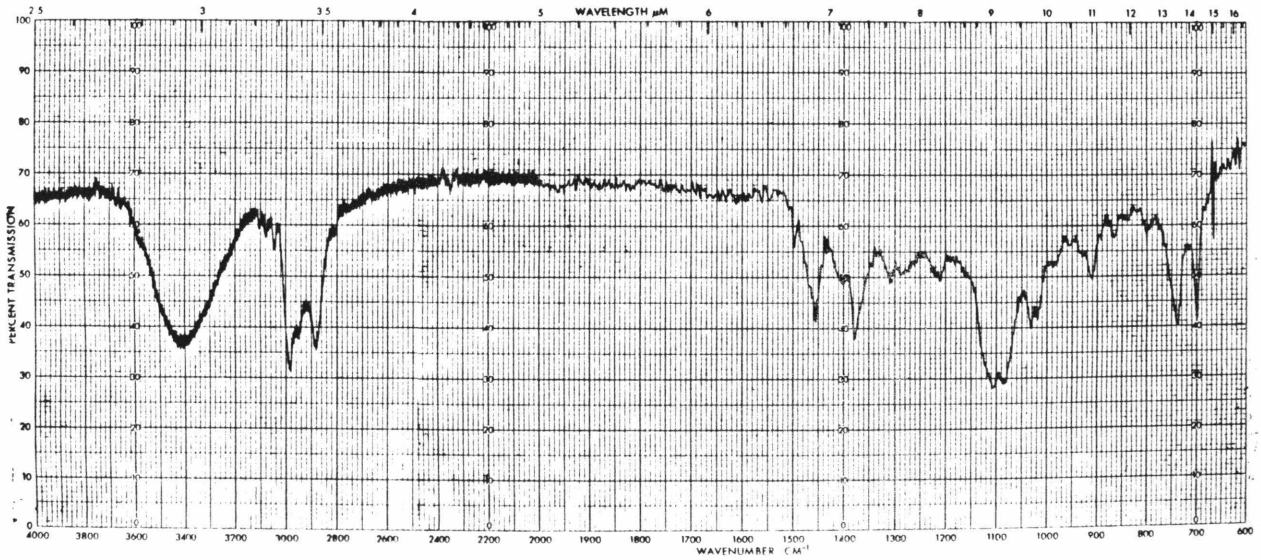

H
Me
Me
O
BnO
HO
Me
OH

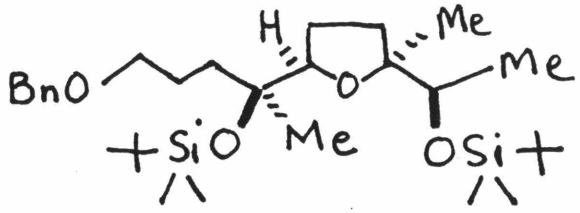
39

CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
150
75
30
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm
LOCK POWER mG
DECOUPLE POS. ppm
DECOUPLING POWER mG
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME min
sec SWEEP WIDTH ppm
mG END OF SWEEP ppm
NUCLEUS
ZERO REF.
SAMPLE TEMP.
SAMPLE:
OPERATOR TS
DATE 12/2/81
SOLVENT CCl4
SPECTRUM NO. TS11P290

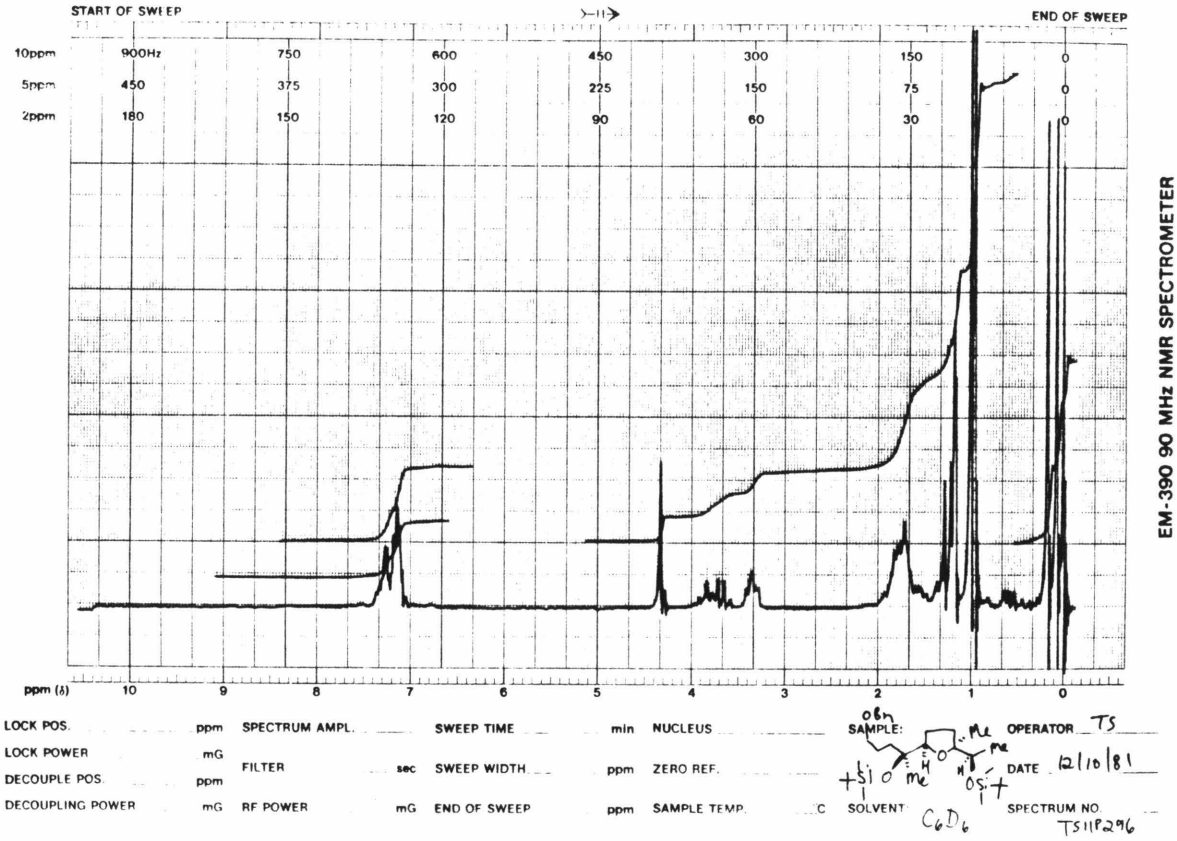
Neat


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

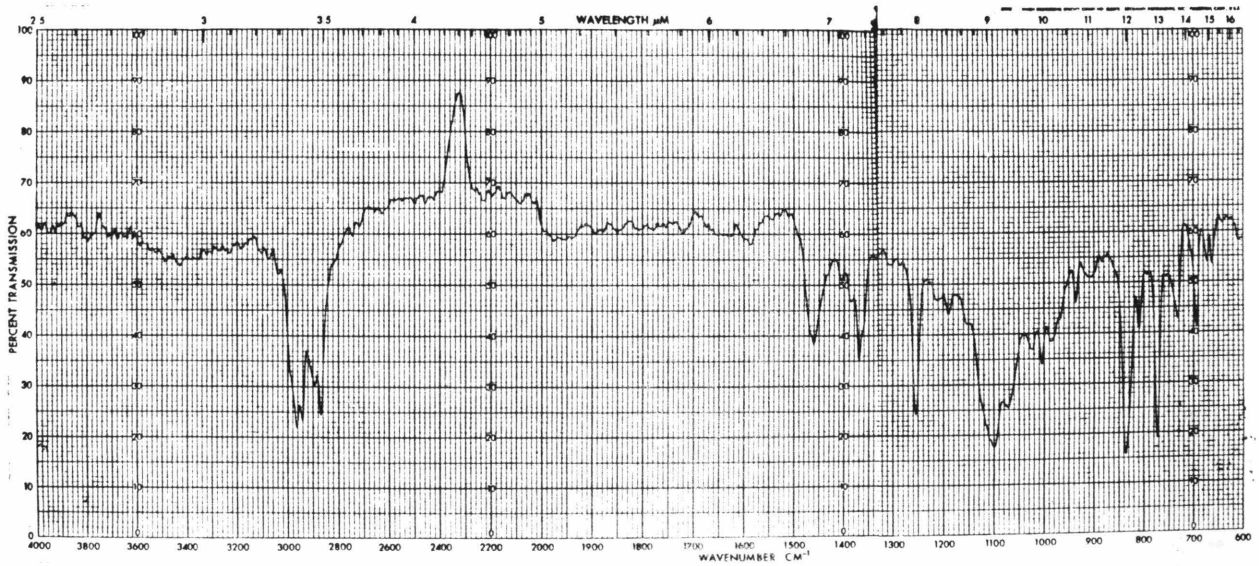


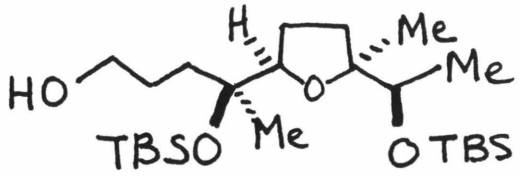
40

Benzene-d_6



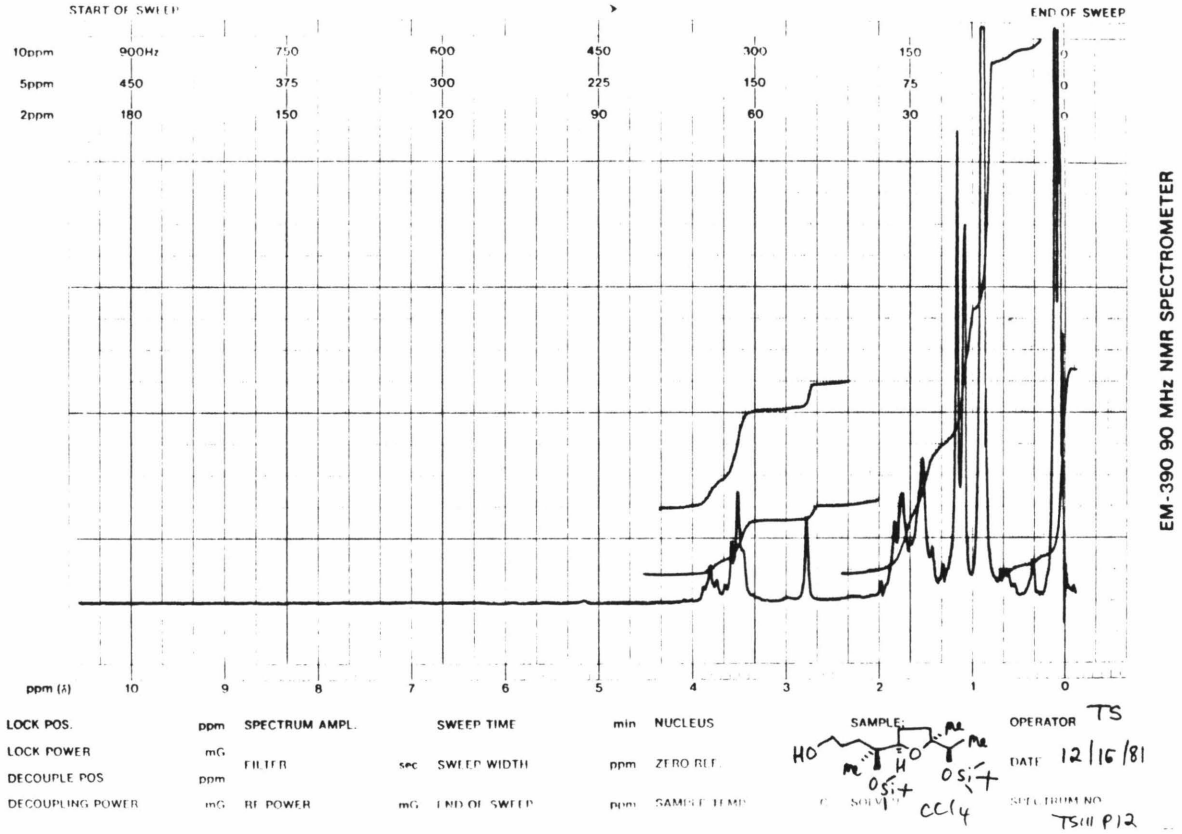
Neat



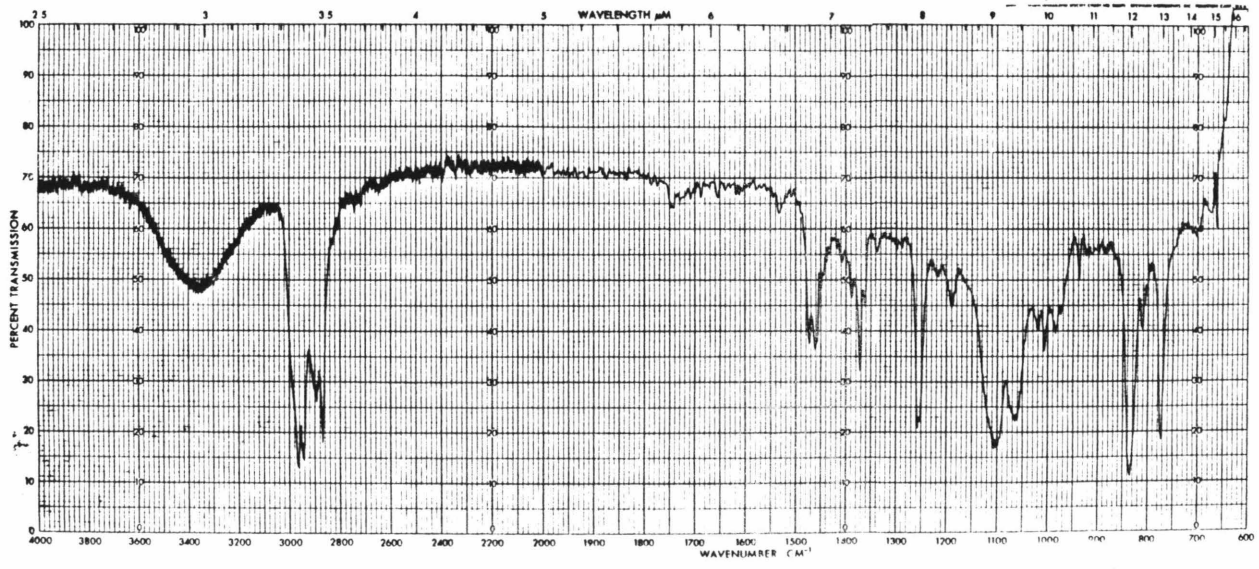

H
Me
HO
Me
O
TBSO
Me
OTBS

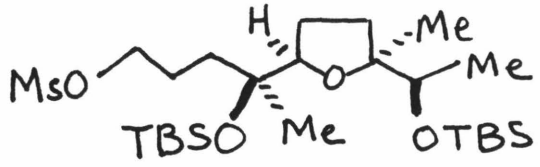
41

CCl_4


START OF SWEEP
END OF SWEEP
10ppm 900Hz 750 600 450 300 150
5ppm 450 375 300 225 150 75
2ppm 180 150 120 90 60 30
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm SPECTRUM AMPL. SWEEP TIME min NUCLEUS
LOCK POWER mG
DECOUPLE POS ppm FILTER sec SWEEP WIDTH ppm ZERO REF.
DECOUPLING POWER mG RF POWER mG END OF SWEEP ppm SAMPLE TEMP.
SAMPLE:
OPERATOR TS
DATE 12/16/81
CCl4
SPECTRUM NO. TS(II) P12

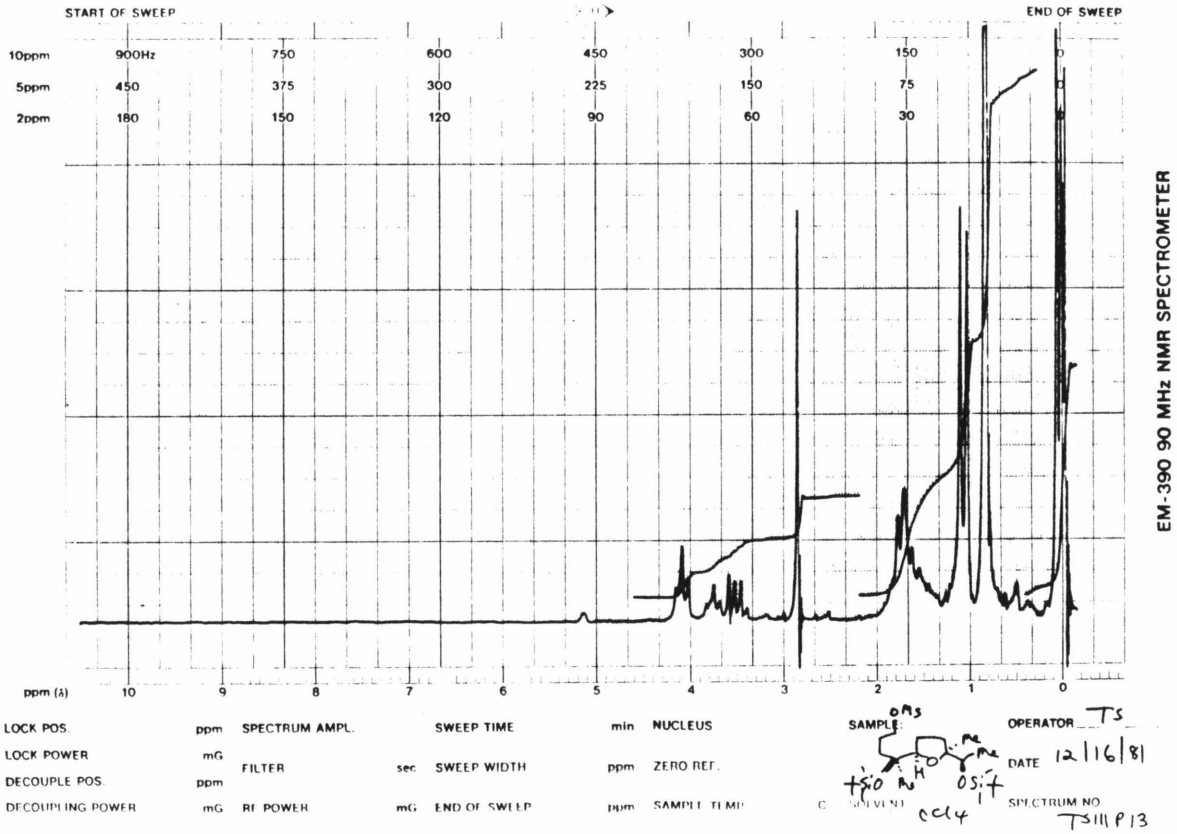
Neat


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

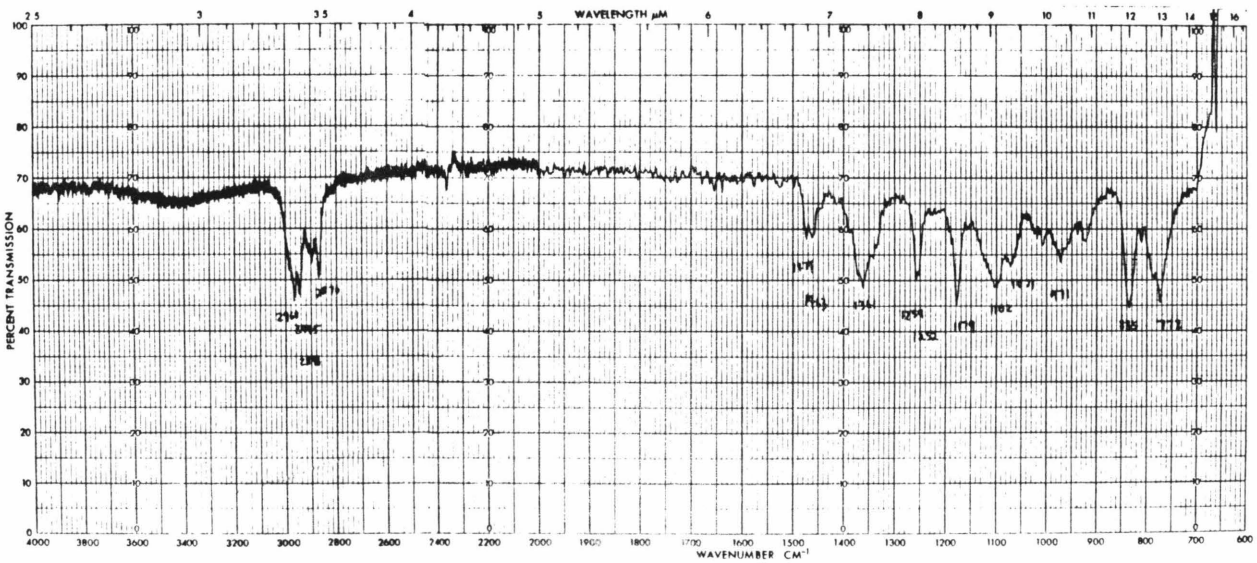

H
Me
MsO
Me
TBSO
Me
OTBS

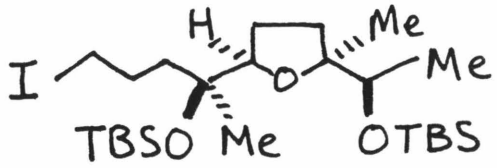
42

CCl_4


START OF SWEEP
END OF SWEEP
10ppm 900Hz 750 600 450 300 150
5ppm 450 375 300 225 150 75
2ppm 180 150 120 90 60 30
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm SPECTRUM AMPL. SWEEP TIME min NUCLEUS
LOCK POWER mG FILTER sec SWEEP WIDTH ppm ZERO REF.
DECOUPLE POS. ppm
DECOUPLING POWER mG RF POWER mG END OF SWEEP ppm SAMPLE TEMP
SAMPLE:
OPERATOR Ts
DATE 12/16/81
SOLVENT ccl4
SPECTRUM NO Ts111P13

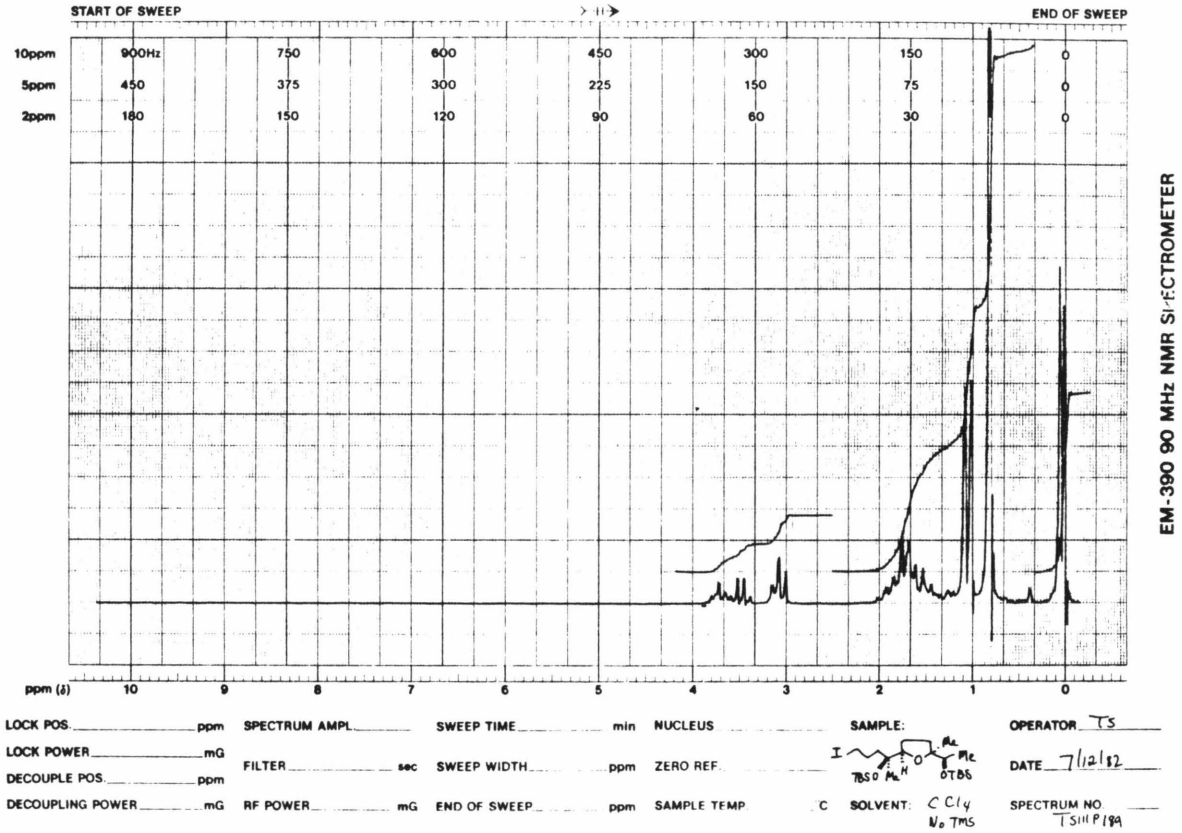
Neat


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

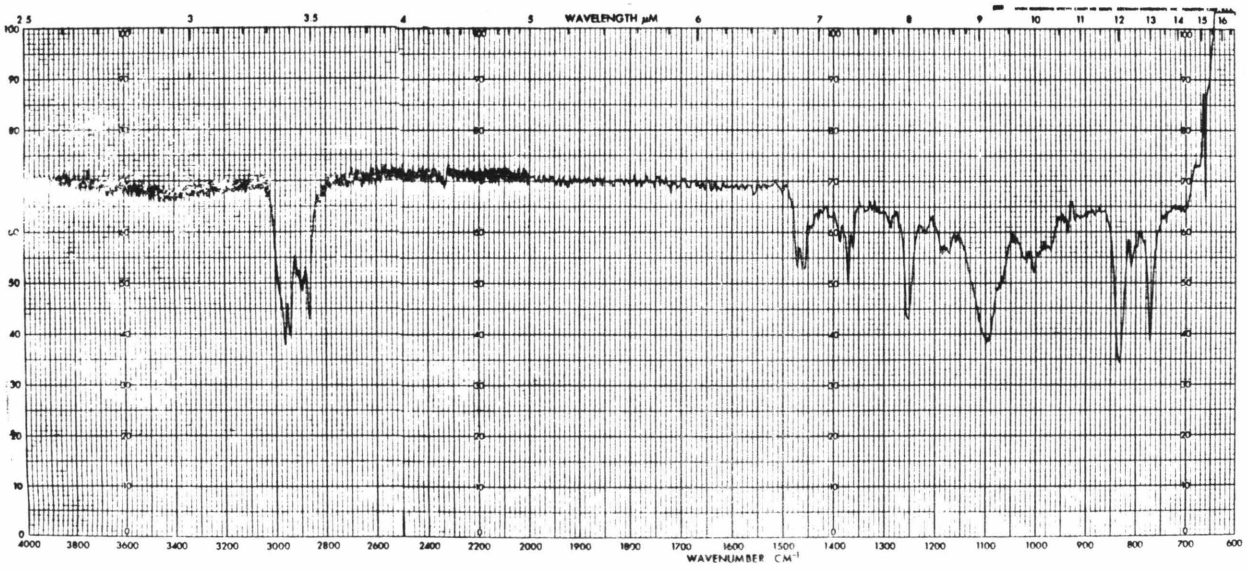

H
Me
I
O
Me
TBSO Me
OTBS

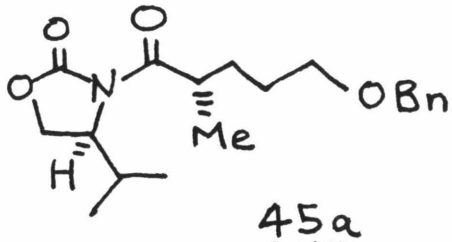
43

CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm
LOCK POWER mG
DECOUPLE POS. ppm
DECOUPLING POWER mG
SPECTRUM AMPL.
FILTER sec
RF POWER mG
SWEEP TIME min
SWEEP WIDTH ppm
END OF SWEEP ppm
NUCLEUS
ZERO REF.
SAMPLE TEMP. C
SAMPLE:
SOLVENT: CCl4 No TMS
OPERATOR TS
DATE 7/12/82
SPECTRUM NO. TS111P189

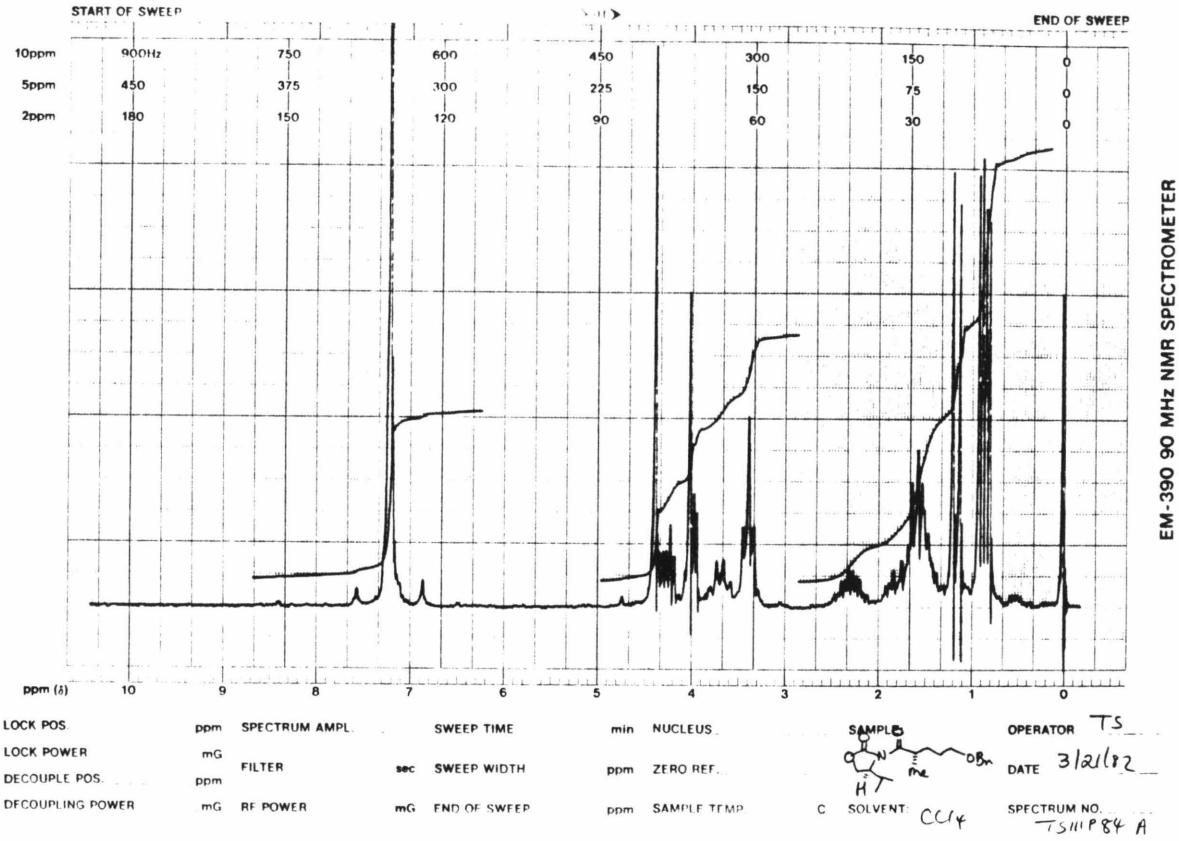
CCl_4


WAVELENGTH μM
2.5
3
3.5
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
WAVENUMBER CM⁻¹

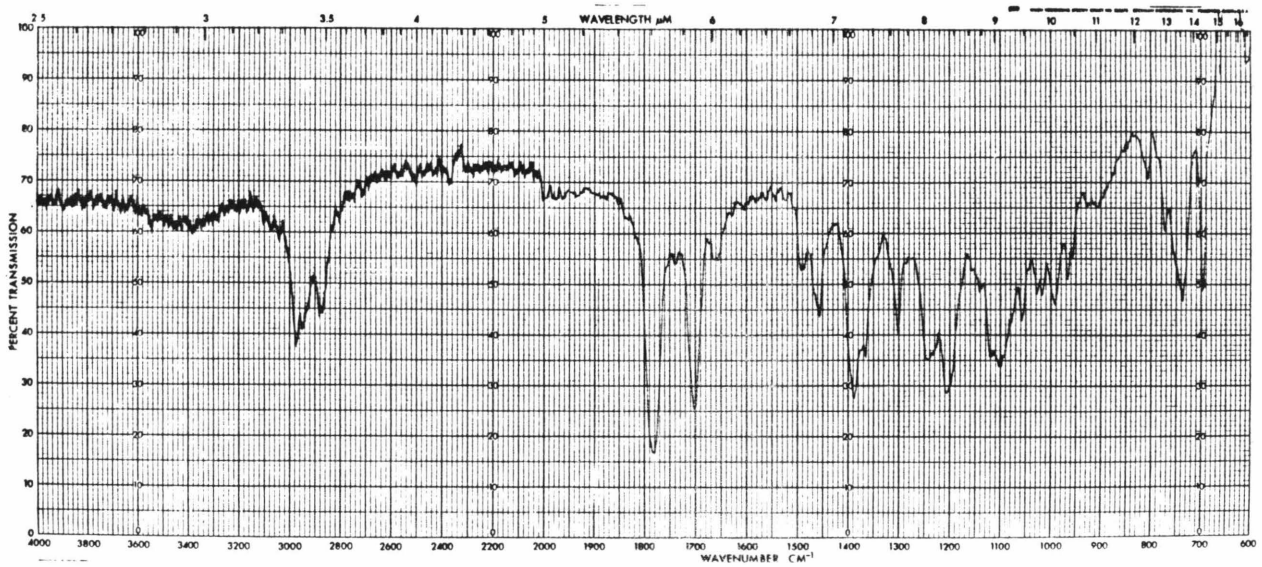


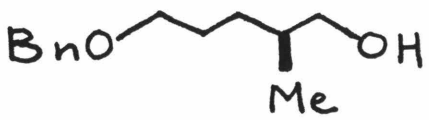
45a

CCl_4



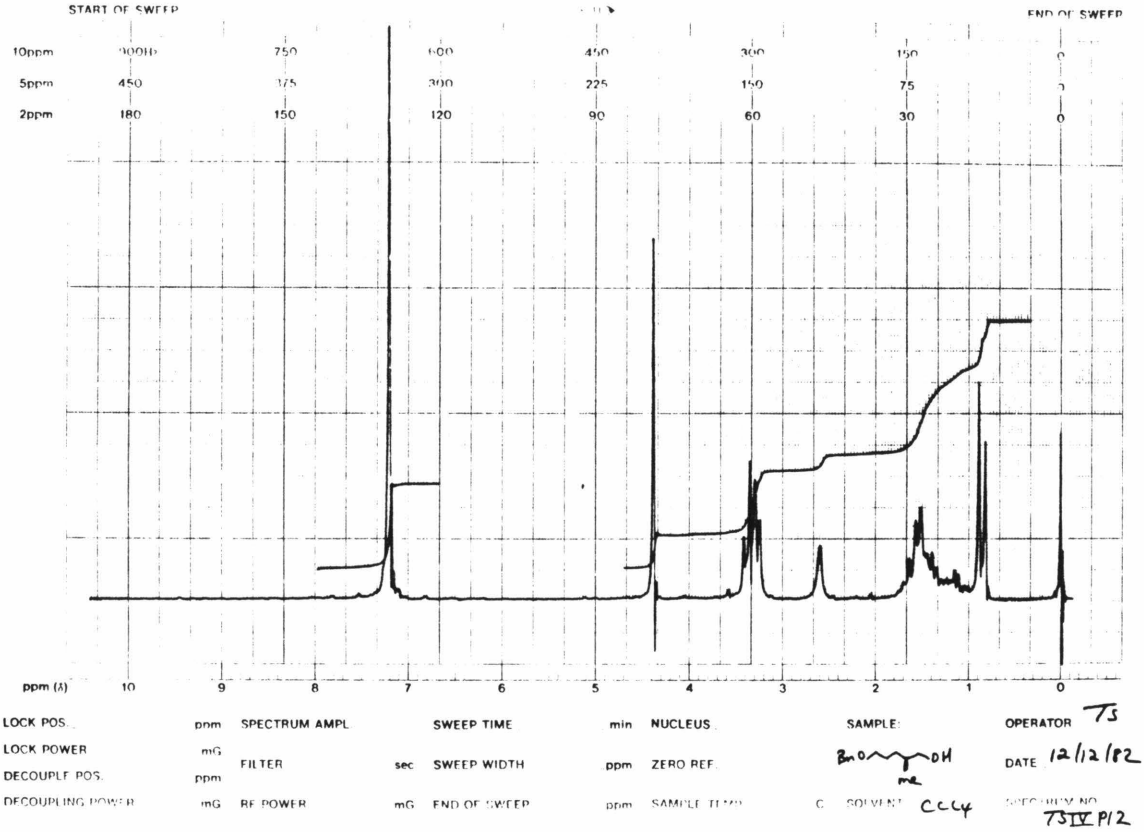
Neat





46

CCl_4



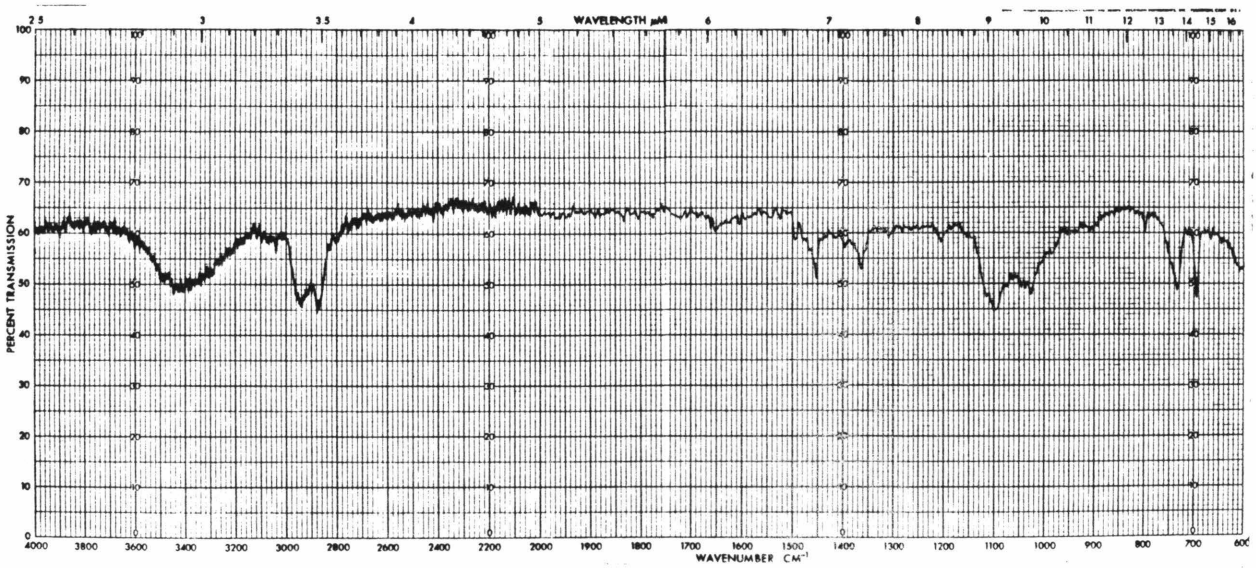
TS

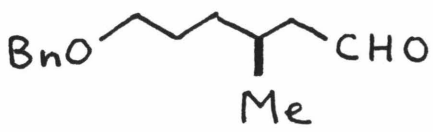
12/12/82

CCl_4

73IV P12

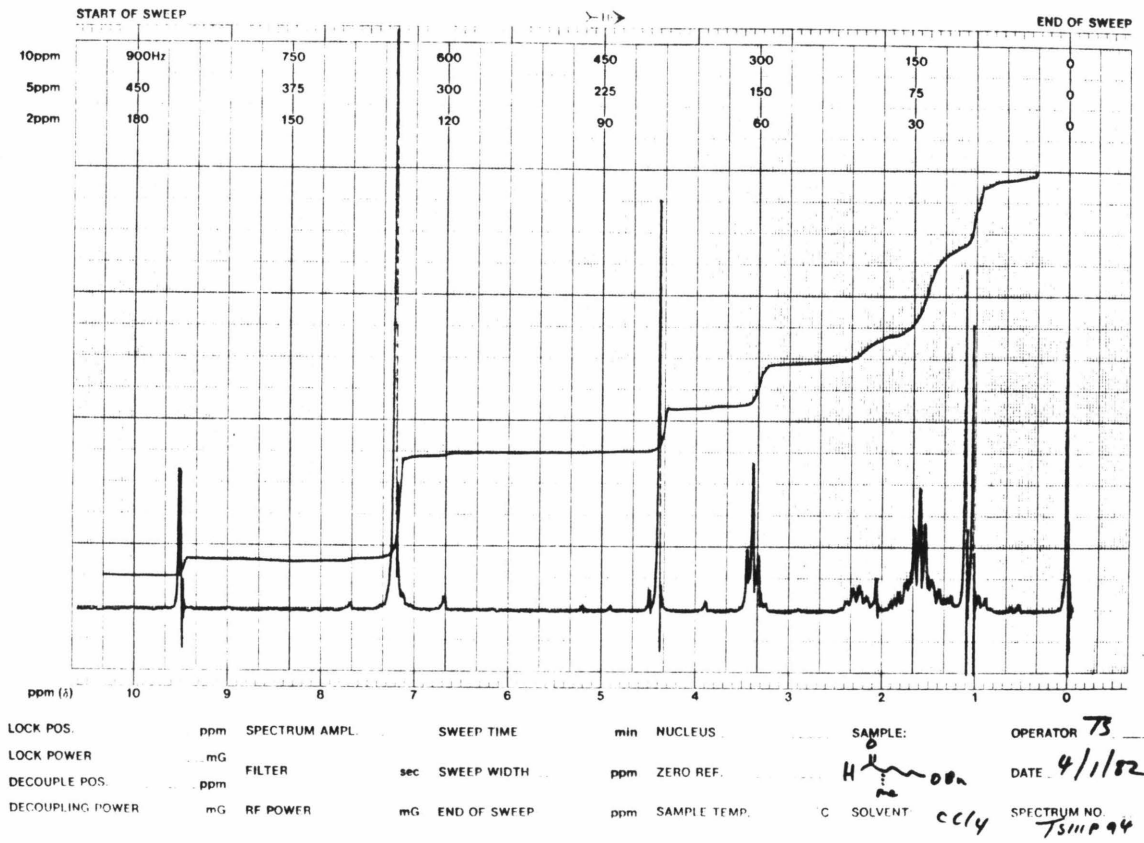
Neat



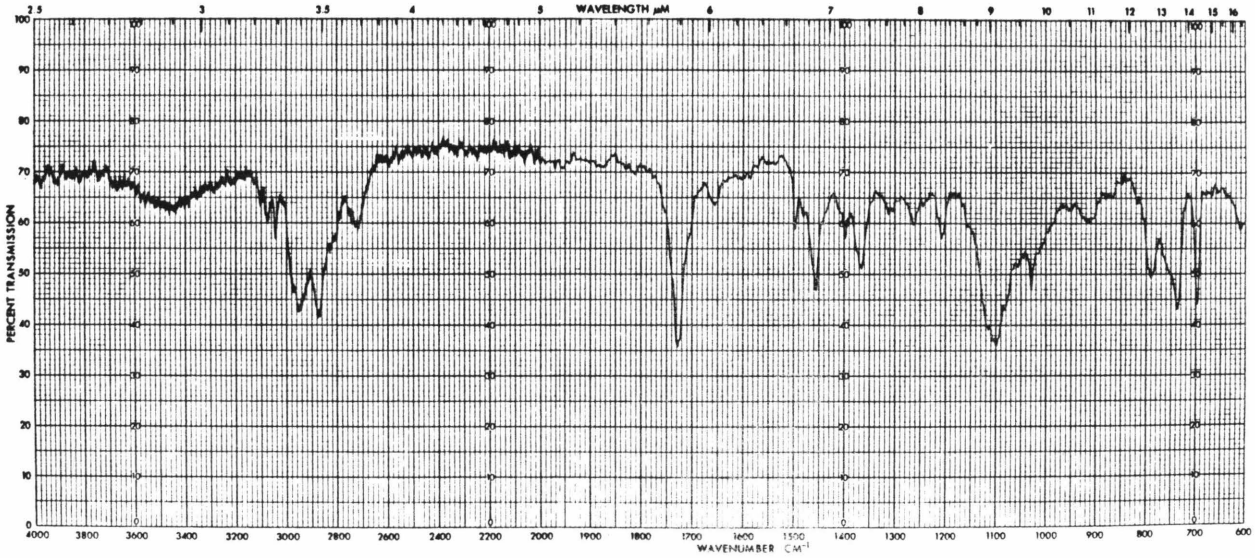

BnO
CHO
Me

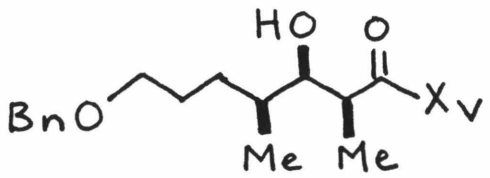
47

CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm
LOCK POWER mG
DECOUPLE POS. ppm
DECOUPLING POWER mG
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME min
sec SWEEP WIDTH
mG END OF SWEEP
NUCLEUS
ppm ZERO REF.
ppm SAMPLE TEMP. °C
SAMPLE:
SOLVENT CCl4
OPERATOR TS
DATE 4/1/82
SPECTRUM NO. TS111P94

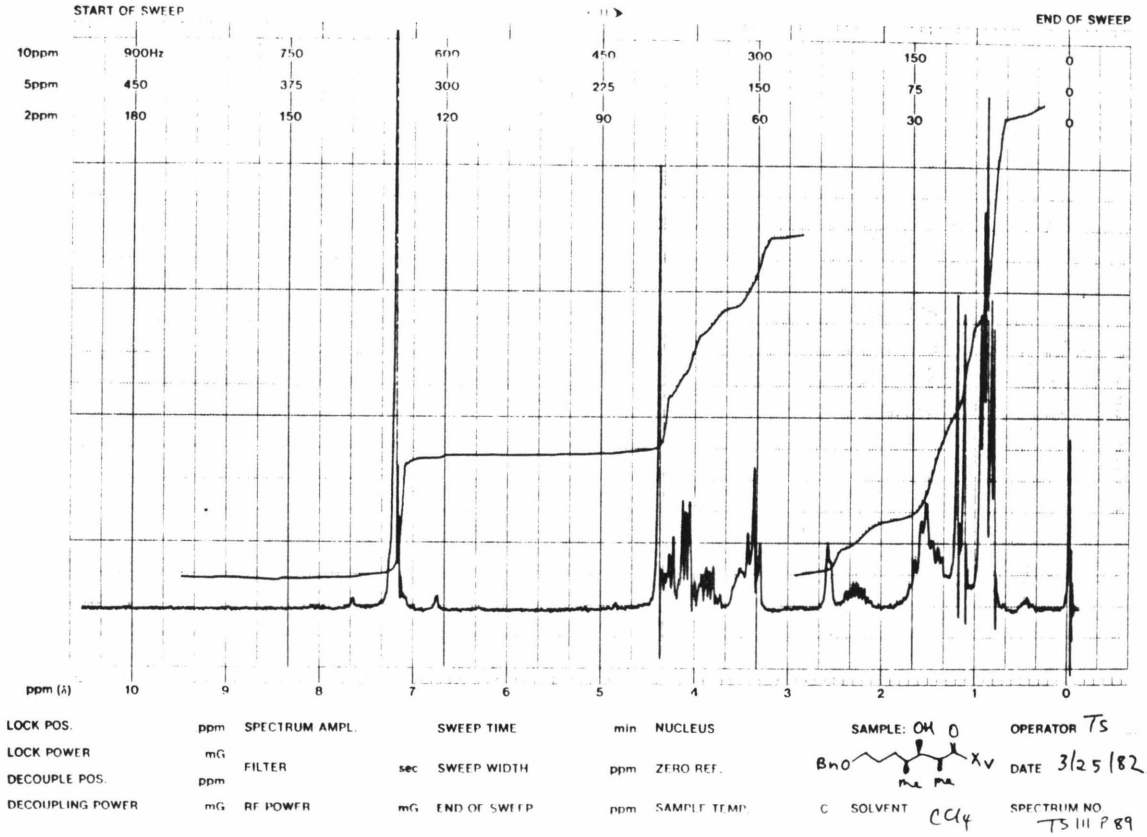
CCl_4


WAVELENGTH μM
2.5
3
3.5
4
5
6
7
8
9
10
11
12
13
14
15
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
WAVENUMBER CM⁻¹

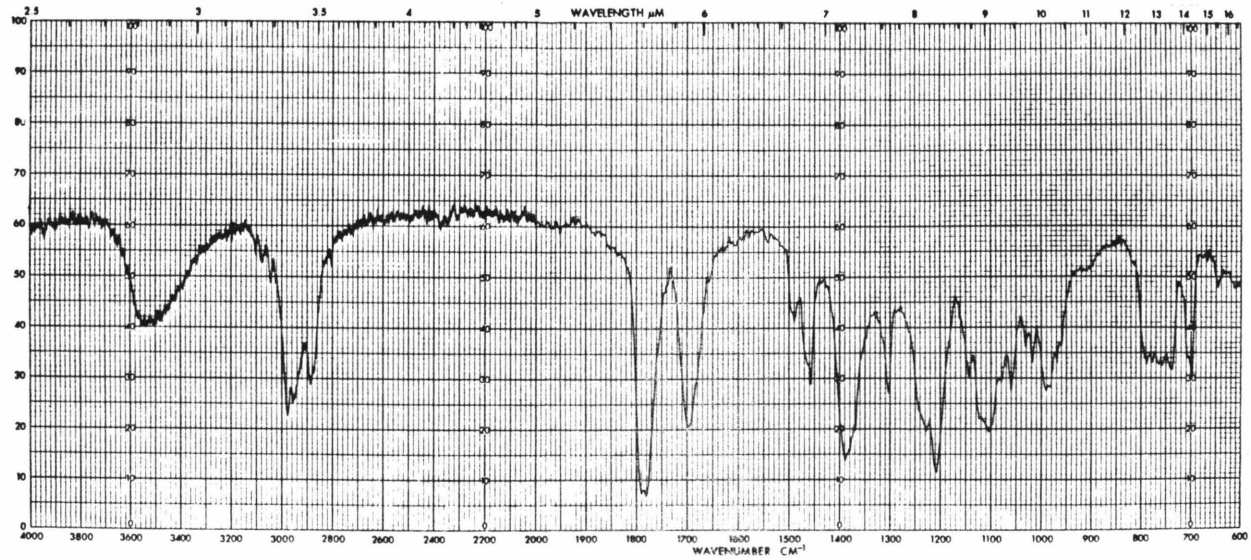

HO
O
BnO
Xv
Me
Me

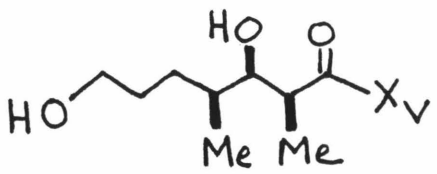
CCl_4

48


START OF SWEEP
END OF SWEEP
10ppm 900Hz 750 600 450 300 150 0
5ppm 450 375 300 225 150 75 0
2ppm 180 150 120 90 60 30 0
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS. ppm SPECTRUM AMPL.
LOCK POWER mG
DECOUPLE POS. ppm FILTER
DECOUPLING POWER mG RF POWER
SWEEP TIME min NUCLEUS
sec SWEEP WIDTH ppm ZERO REF.
mG END OF SWEEP ppm SAMPLE TEMP. C SOLVENT CCl4
SAMPLE: OH O BnO Xv Me Me
OPERATOR TS
DATE 3/25/82
SPECTRUM NO. TS III P89

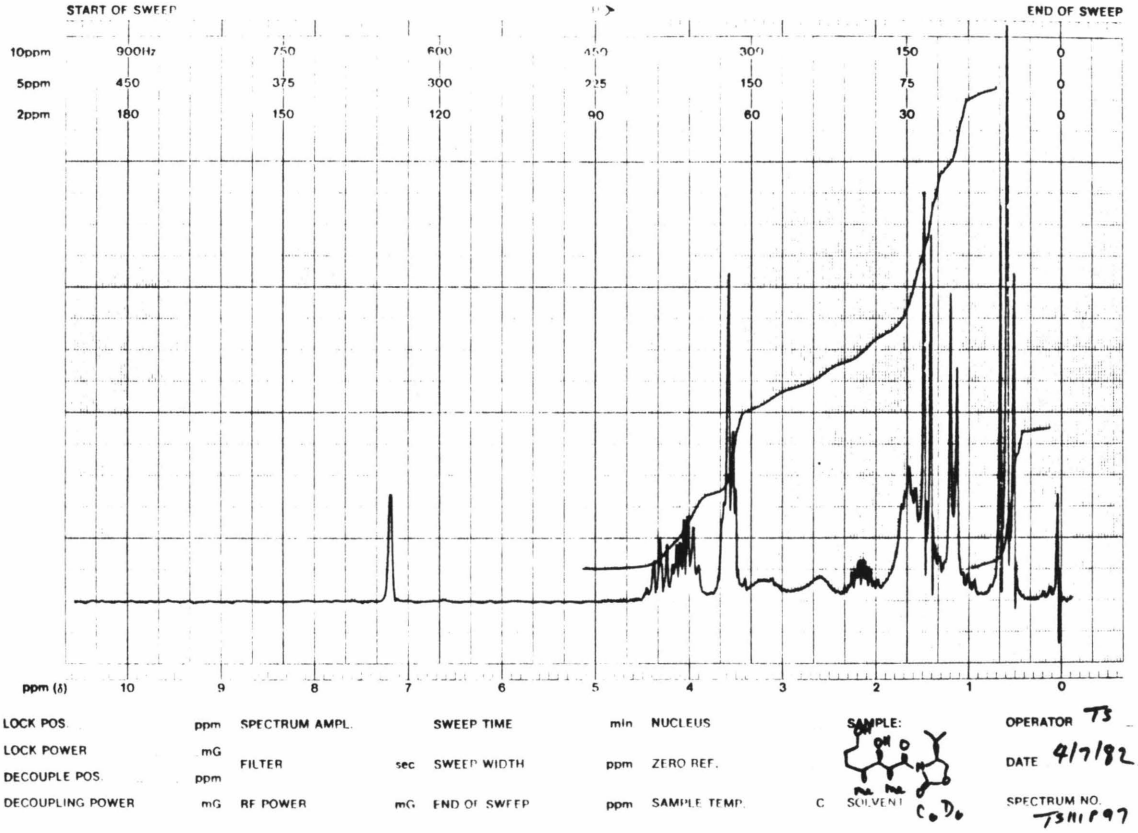
CCl_4


WAVELENGTH μM
WAVENUMBER CM⁻¹

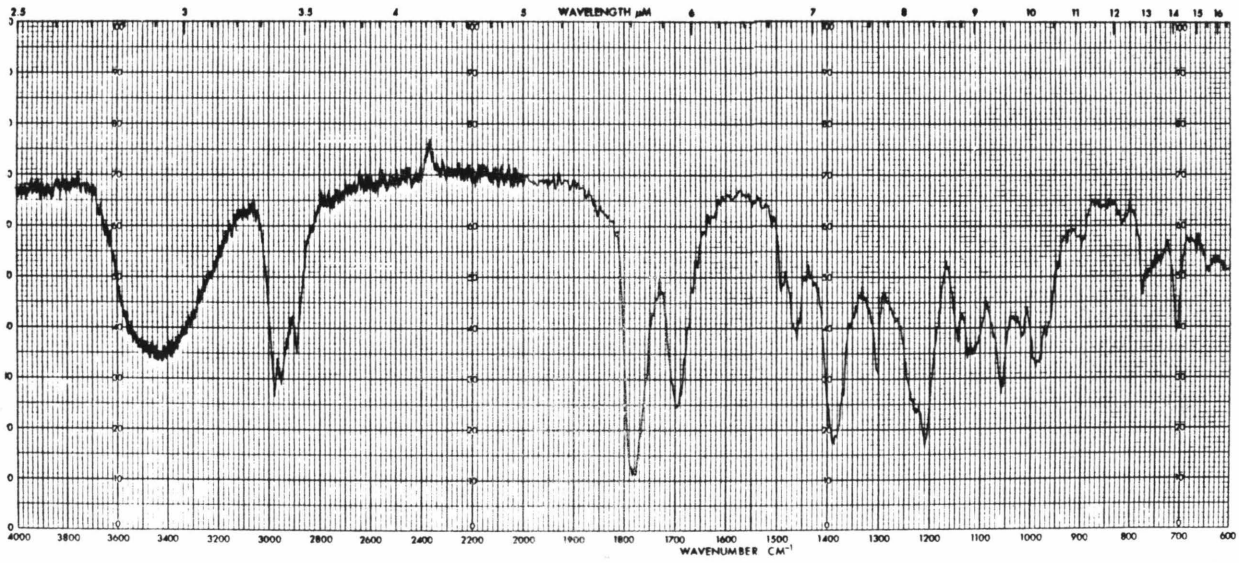


49

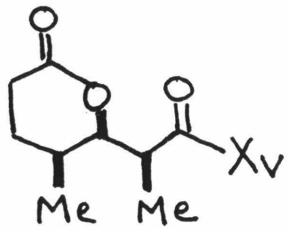
Benzene-d_6



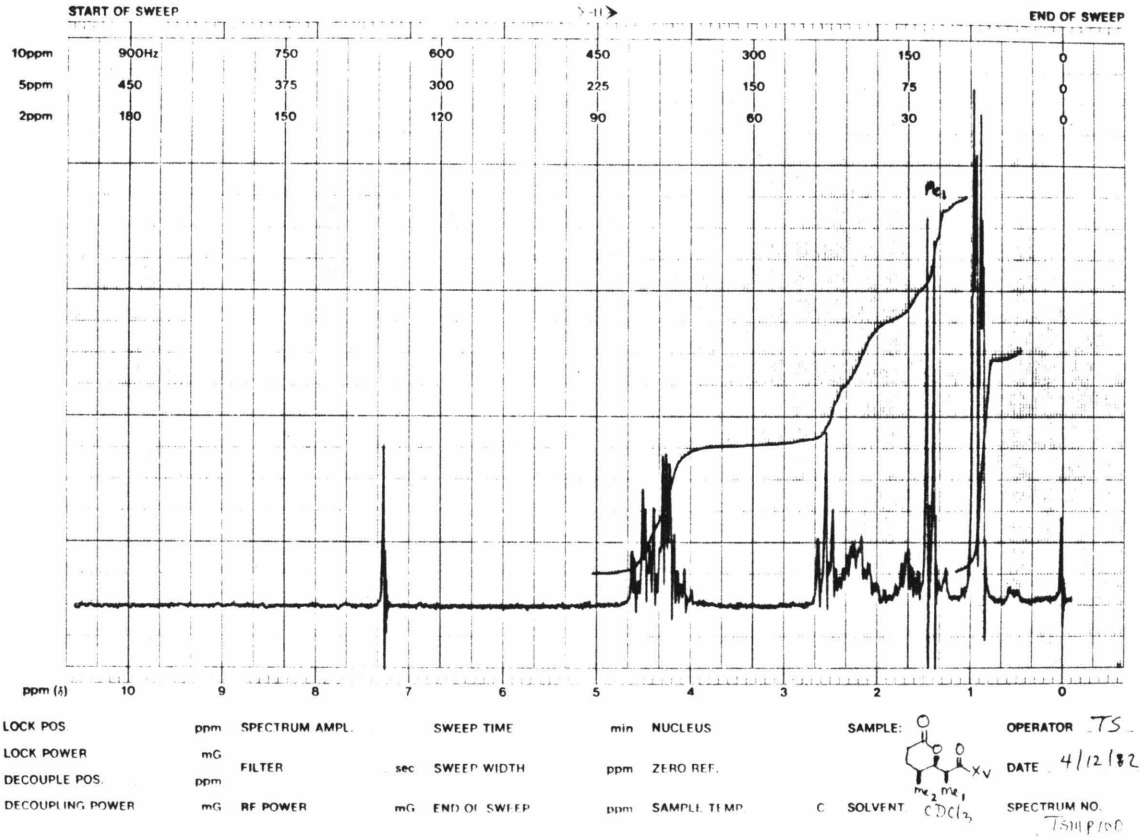
Neat



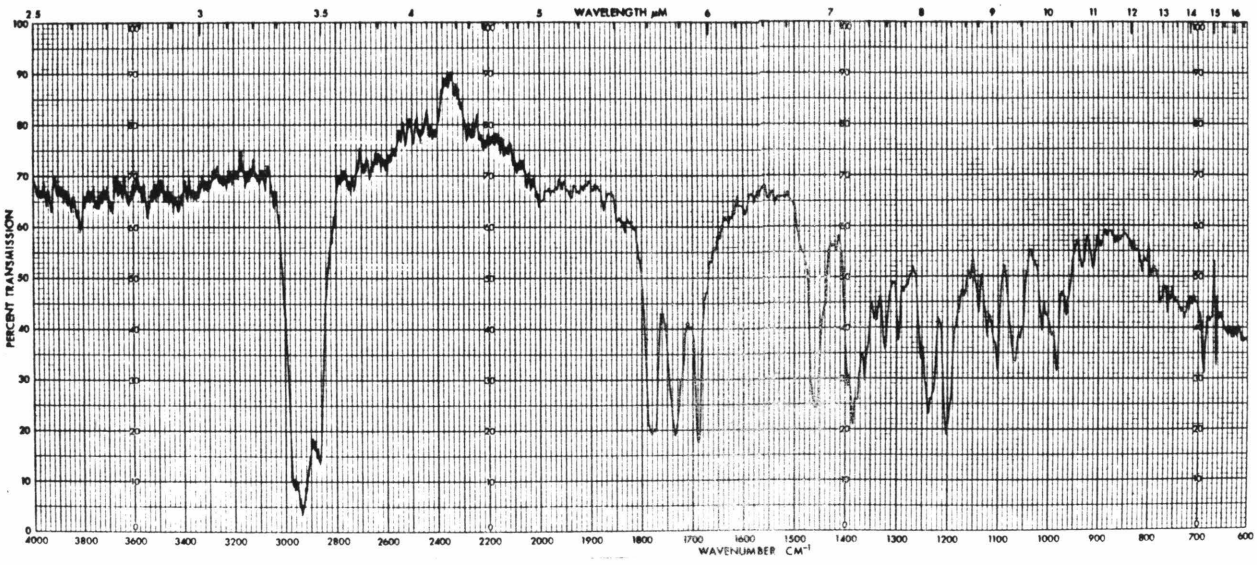
50

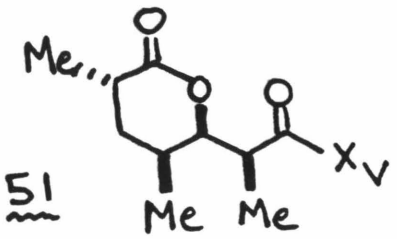


$CDCl_3$



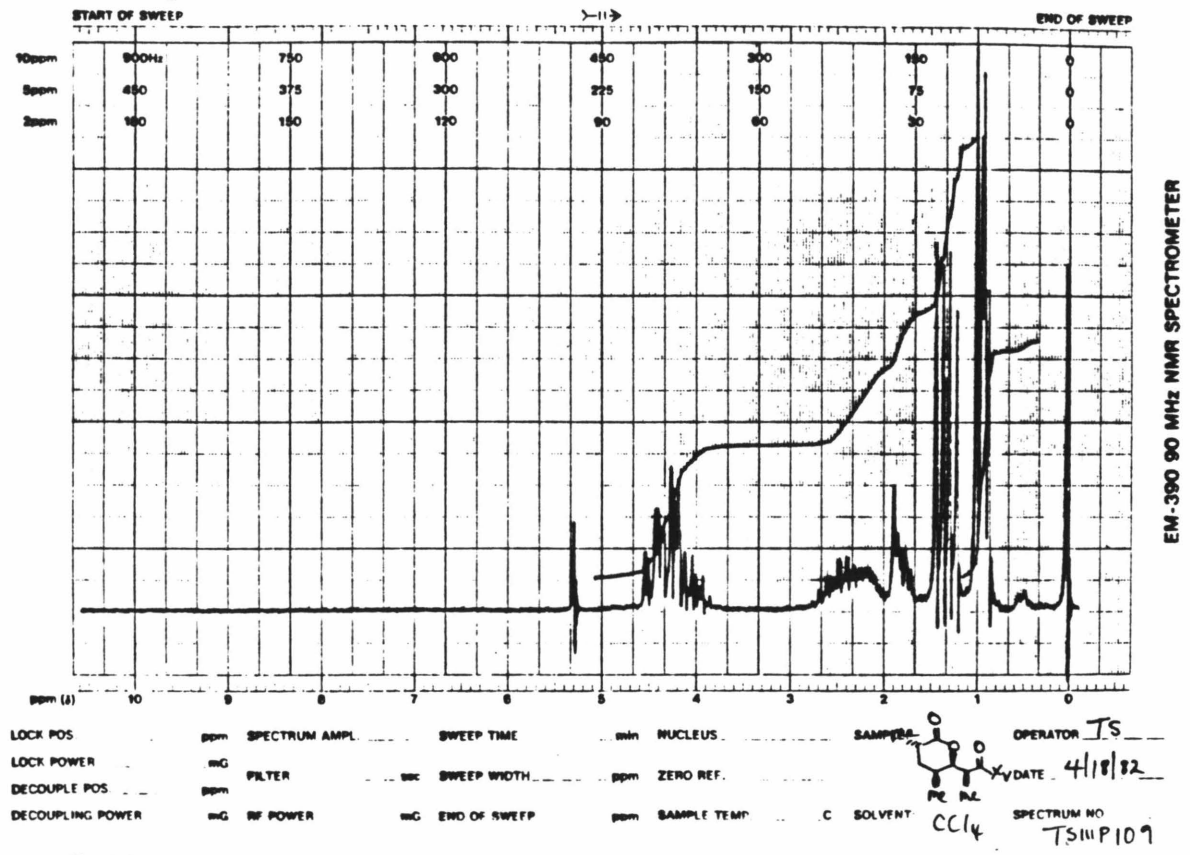
Nujol



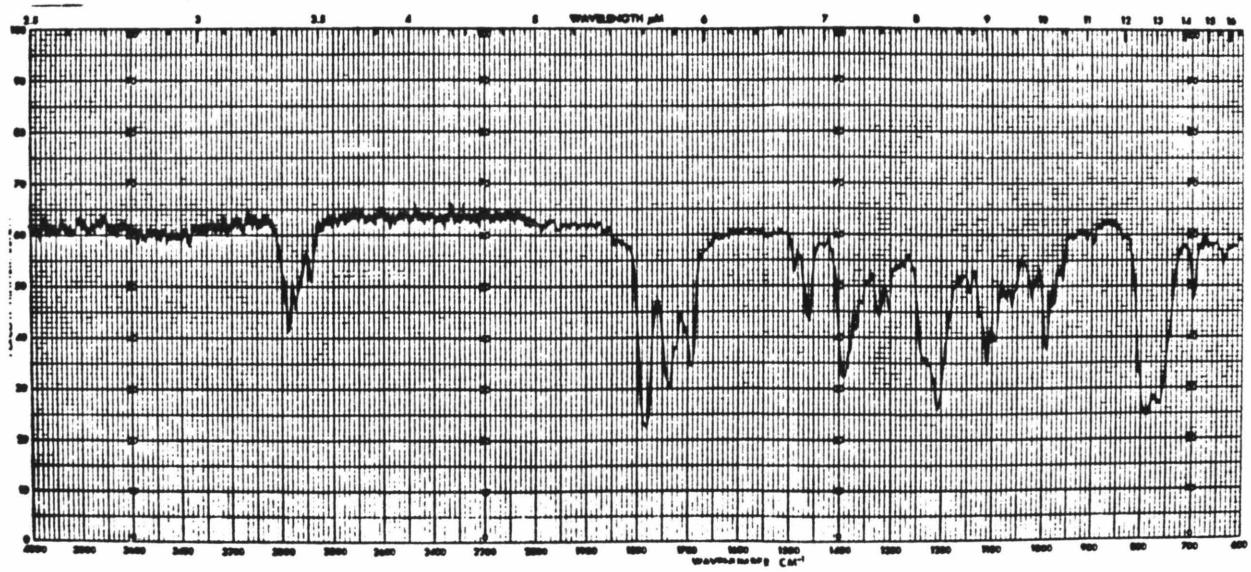

Me
X
V
Me
Me

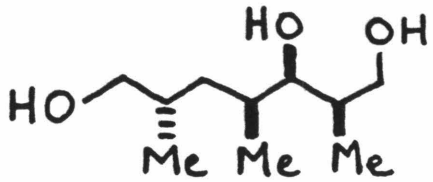
51

CCl_4


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP
SOLVENT
OPERATOR TS
DATE 4/18/82
SPECTRUM NO TSIIIP109

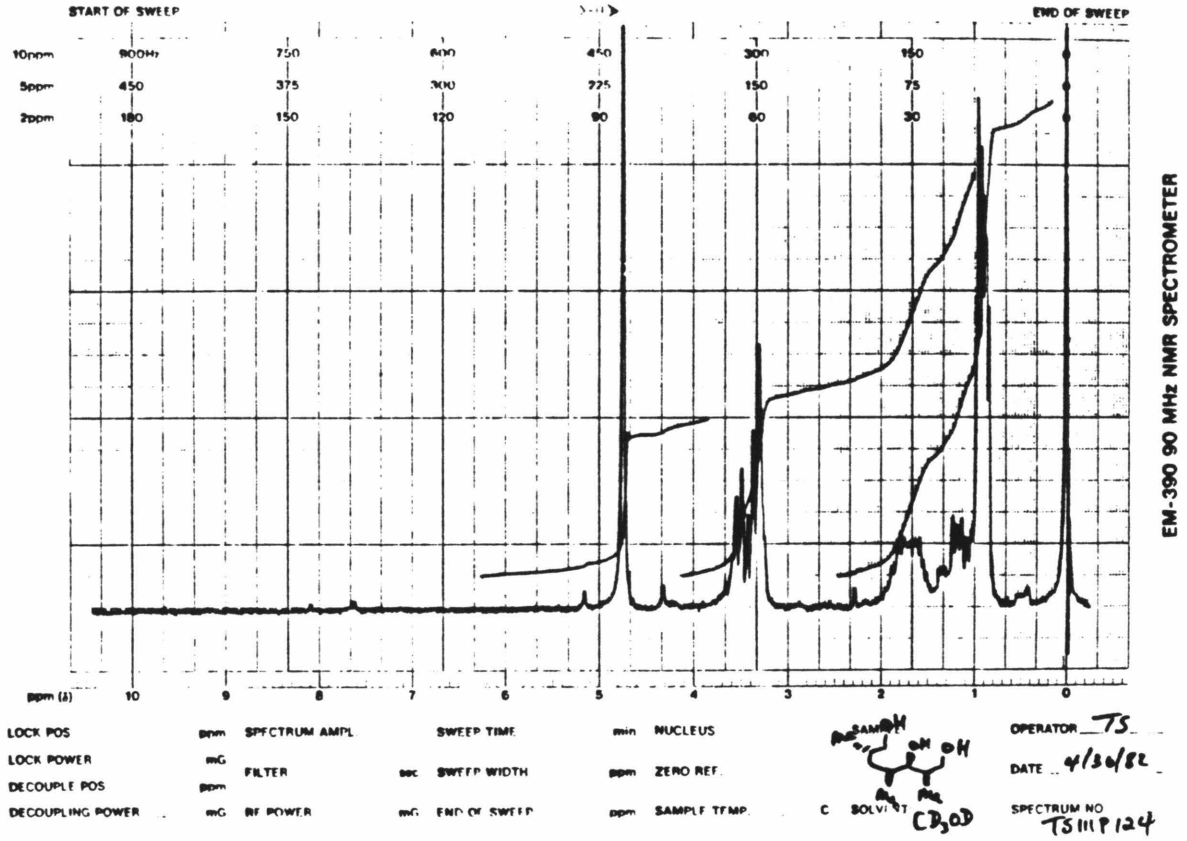
CCl_4

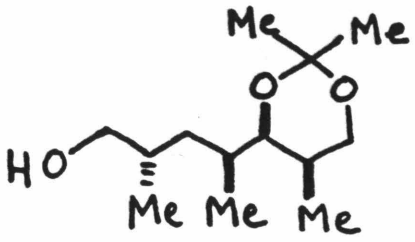

WAVELENGTH μM
WAVENUMBER CM⁻¹


HO
OH
HO
Me Me Me

52

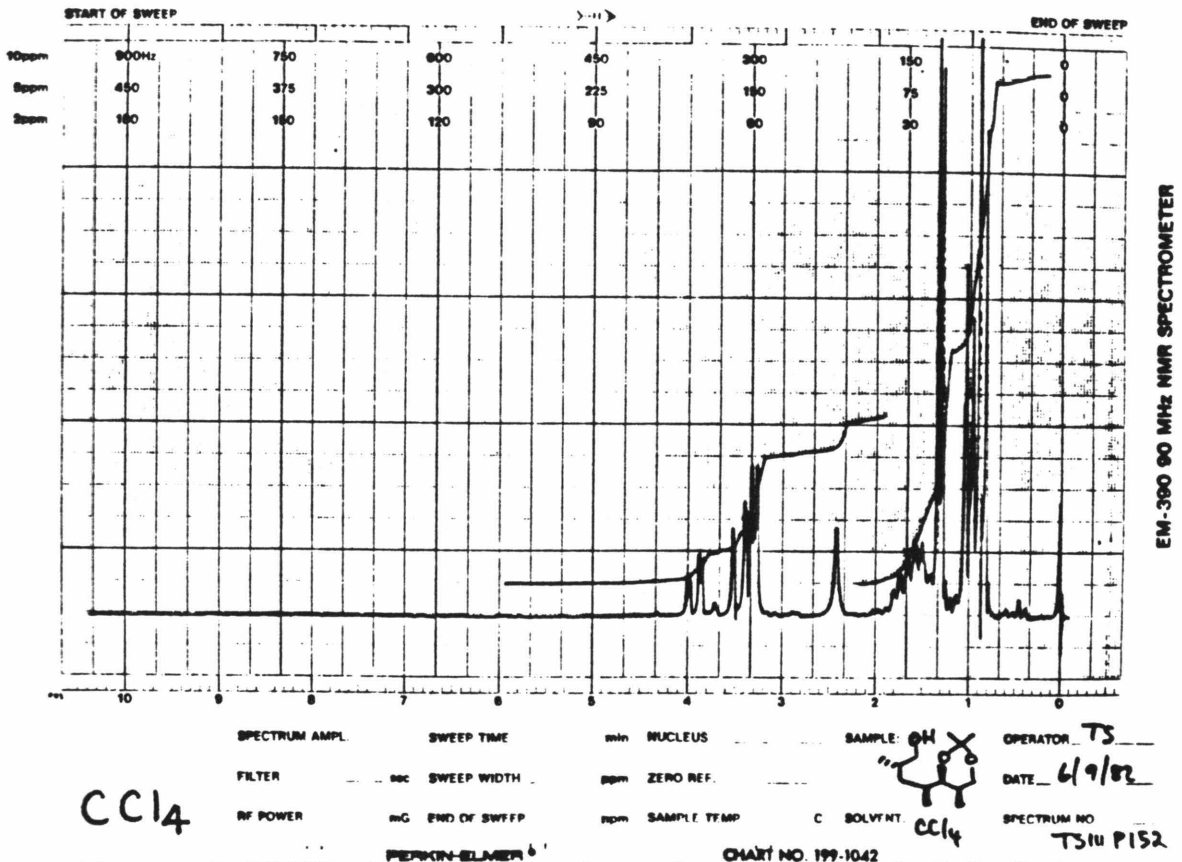
MeOH-d_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
750
600
450
300
150
450
375
300
225
150
75
180
150
120
90
60
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP.
SOLVENT
CD3OD
OPERATOR TS
DATE 4/30/82
SPECTRUM NO TS111P124

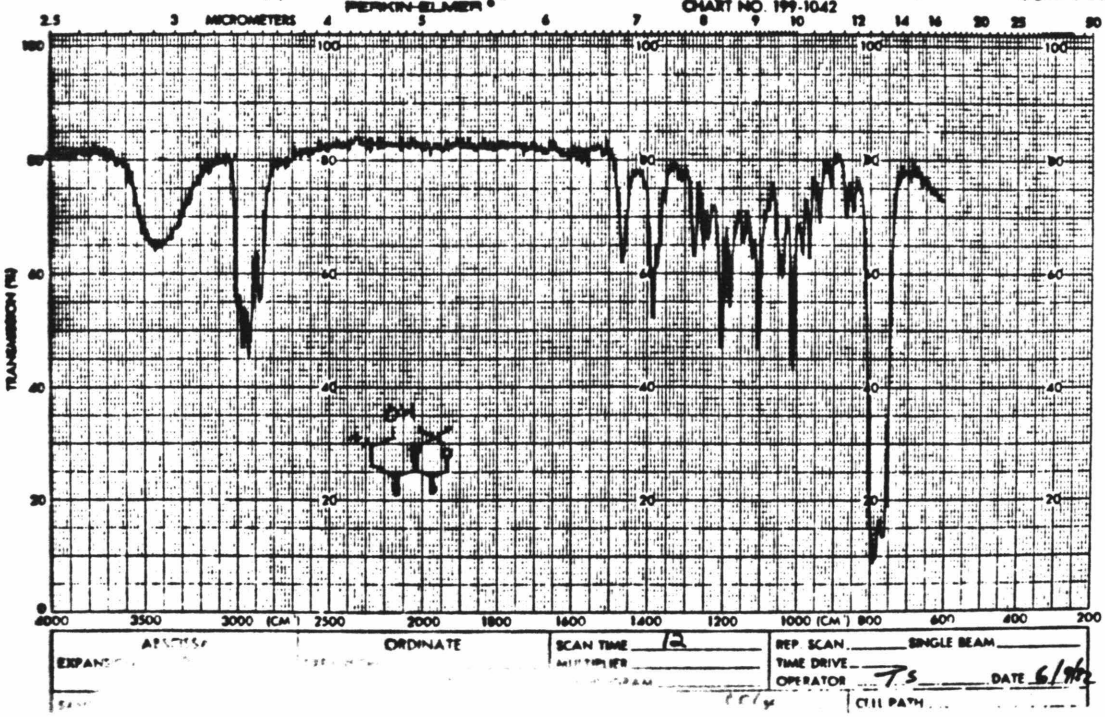

Me
Me
O
O
HO
Me Me Me

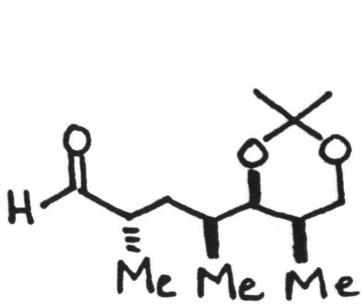
CCl_4

53


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
SPECTRUM AMPL.
SWEEP TIME
min
NUCLEUS
SAMPLE:
OPERATOR TS
FILTER
sec
SWEEP WIDTH
ppm
ZERO REF.
DATE 6/9/82
RF POWER
mG
END OF SWEEP
ppm
SAMPLE TEMP
C
SOLVENT CCl4
SPECTRUM NO
TS111 P152

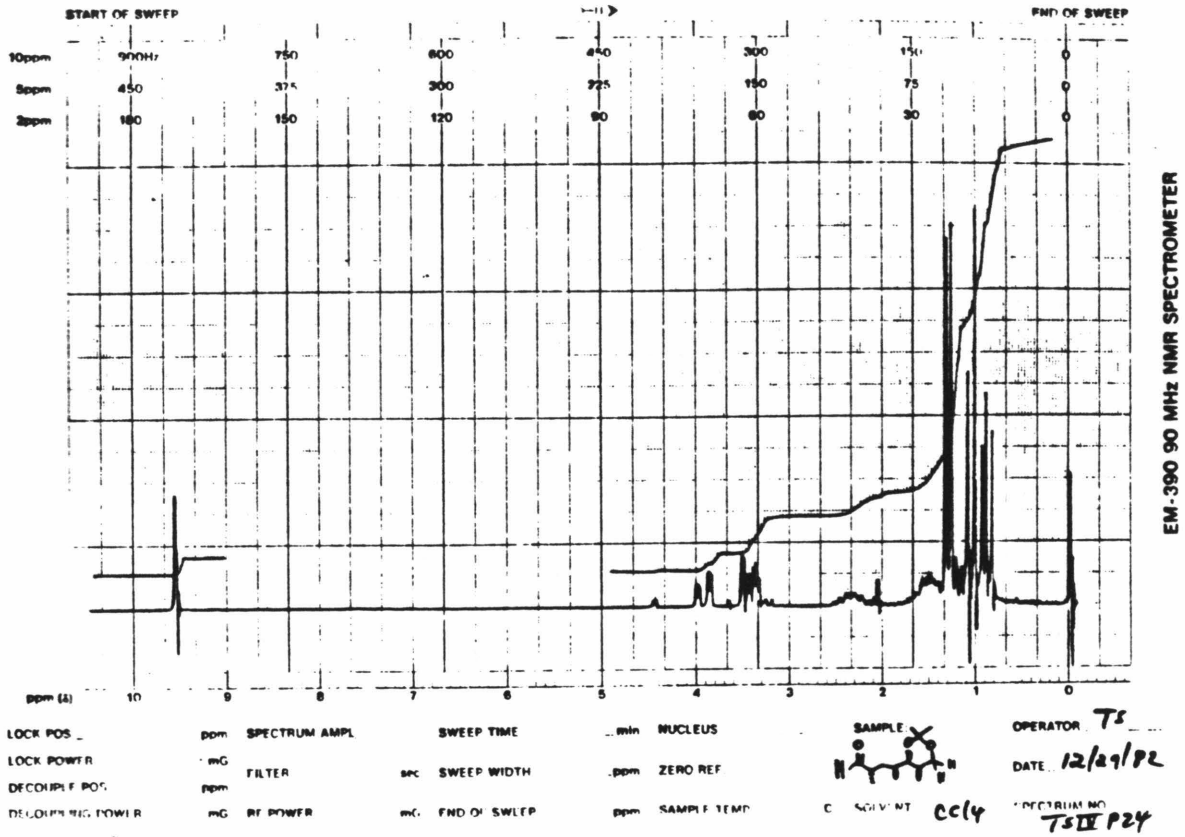
CCl_4


PERKIN-ELMER
CHART NO. 199-1042
MICROMETERS
TRANSMISSION (%)
(CM⁻¹)
ABSCISSA
ORDINATE
SCAN TIME 12
REP. SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR TS
DATE 6/9/82
CELL PATH



54

CCl_4



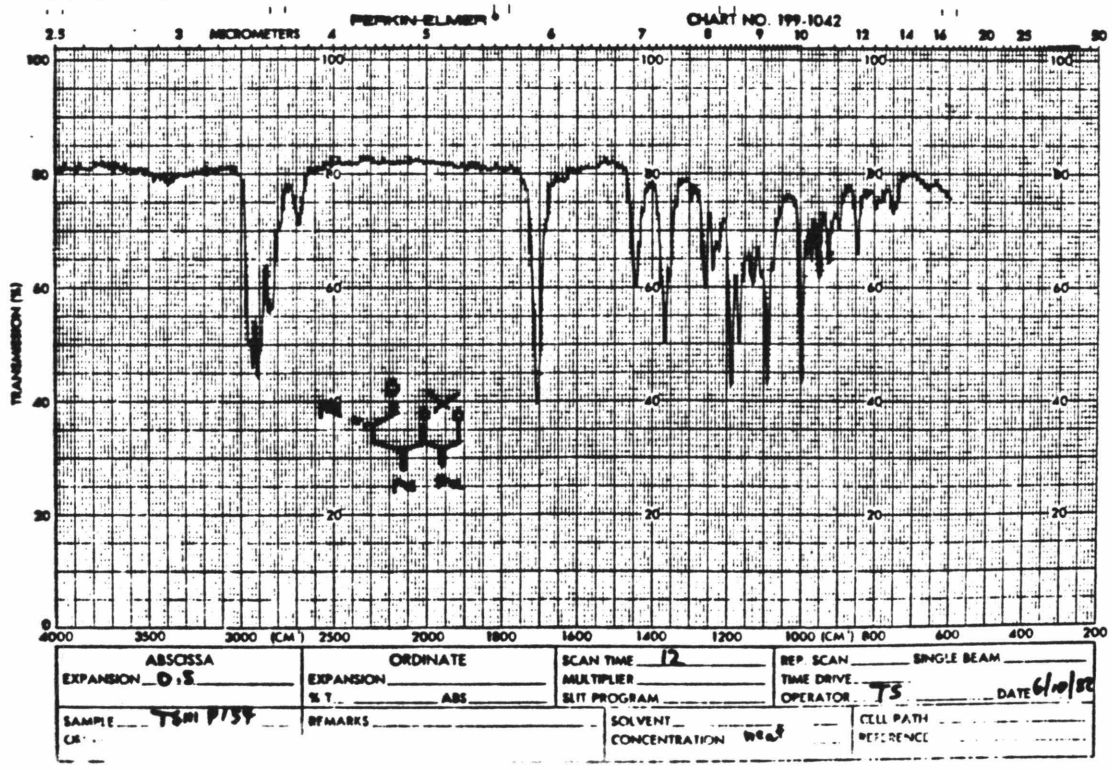
OPERATOR TS

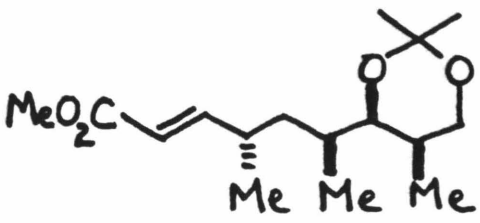
DATE 12/29/82

CCl_4

TSIII P24

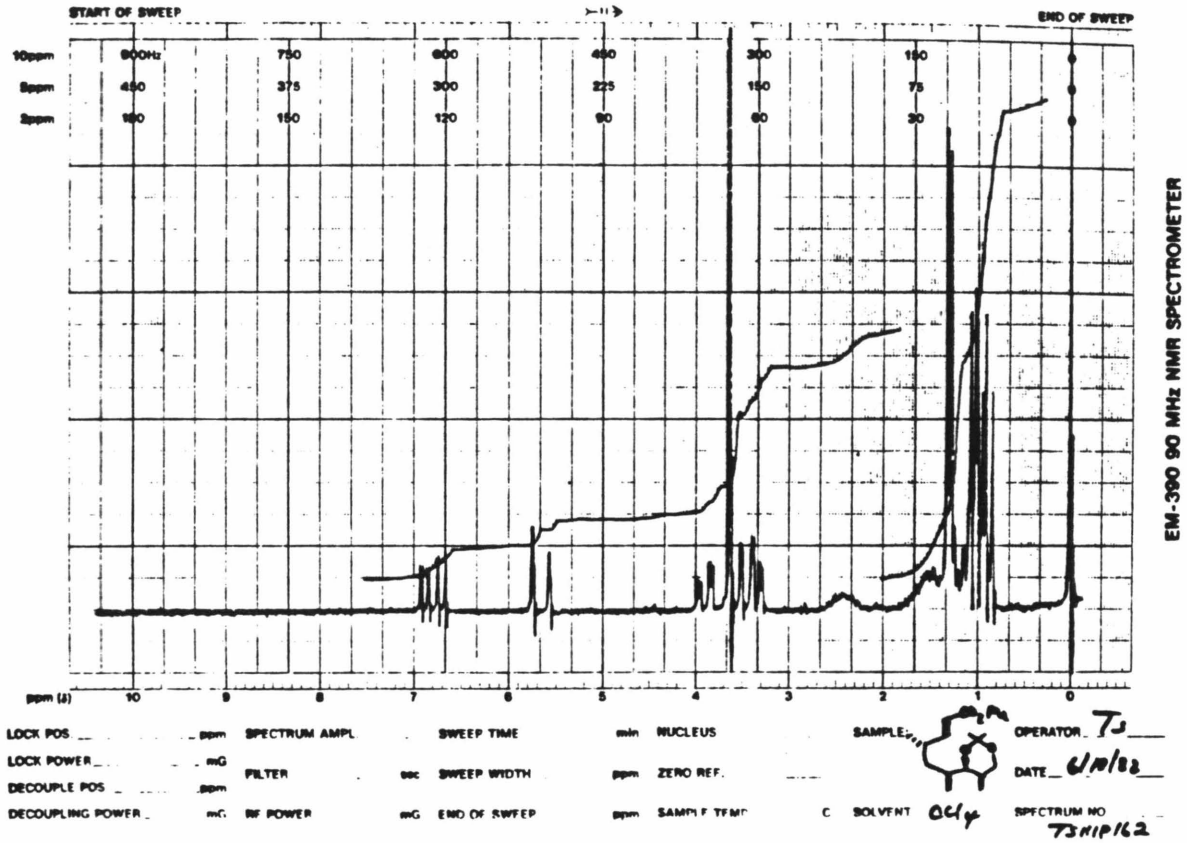
Neat



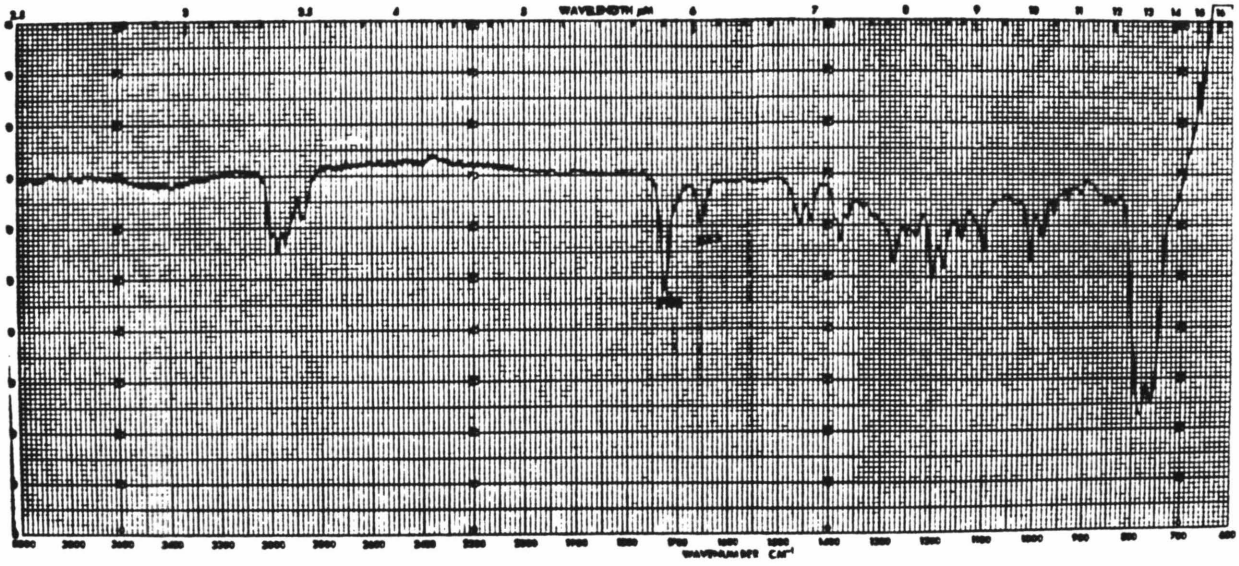

MeO2C
Me Me Me

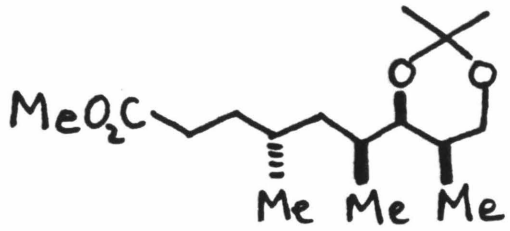
CCl4

55


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE
SOLVENT CCl4
OPERATOR TJ
DATE 4/11/82
SPECTRUM NO
TJNIP162

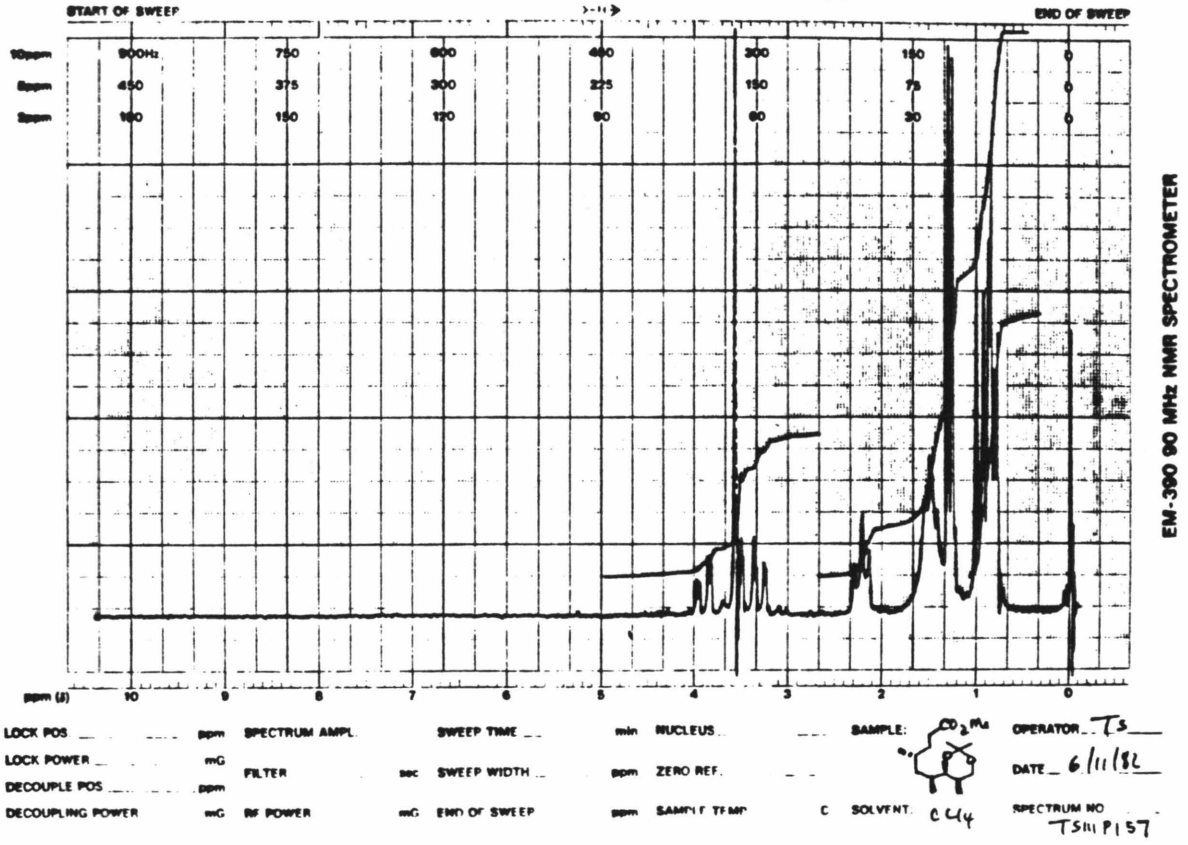
CCl4


WAVELENGTH μm
WAVENUMBER CM-1

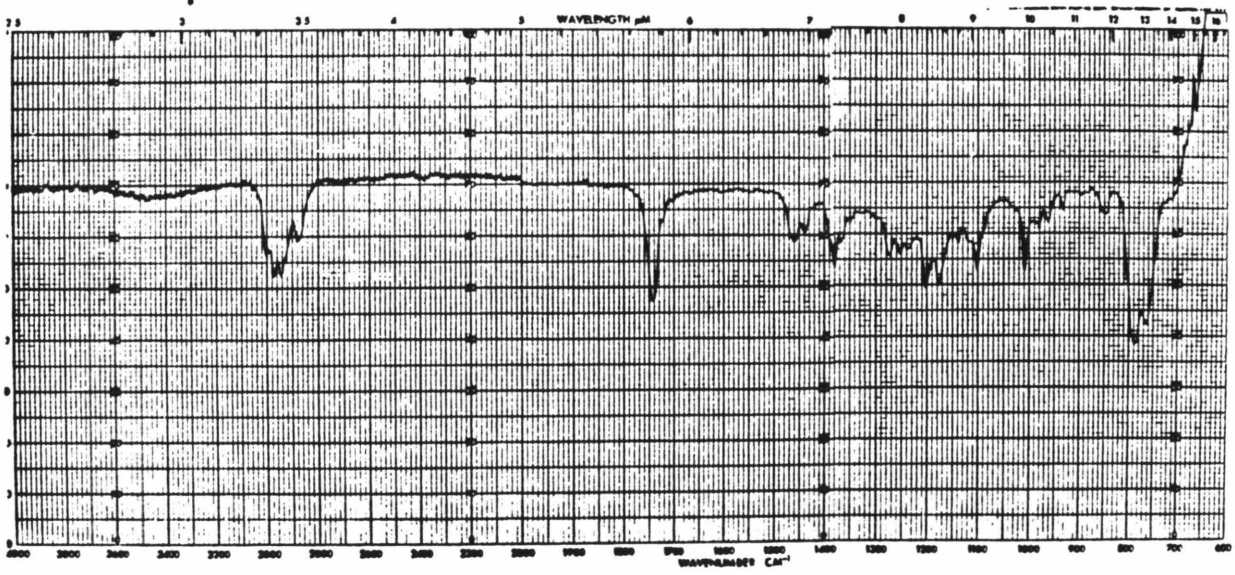

MeO2C
Me Me Me

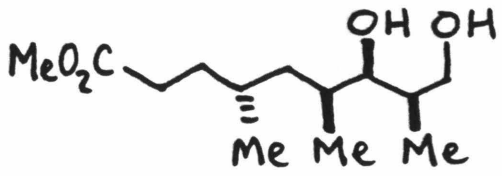
CCl_4

56


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP
SAMPLE:
SOLVENT
OPERATOR
DATE
SPECTRUM NO

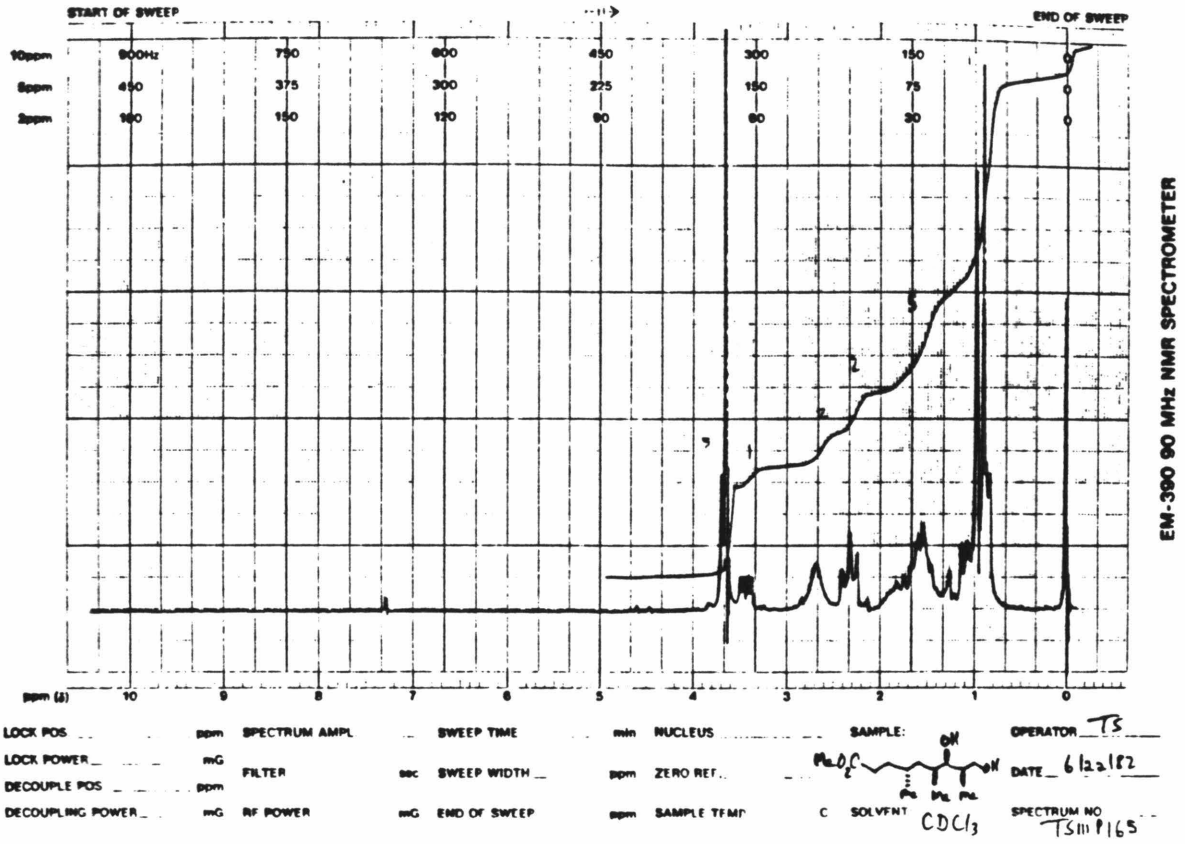
CCl_4


WAVELENGTH μM
WAVENUMBER cm⁻¹

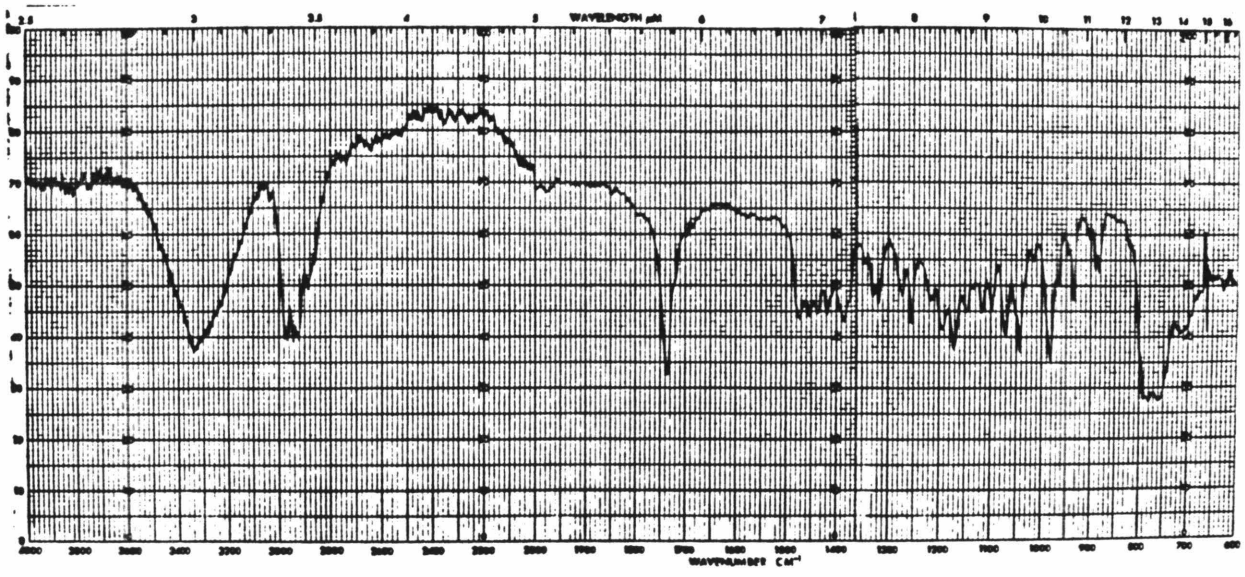


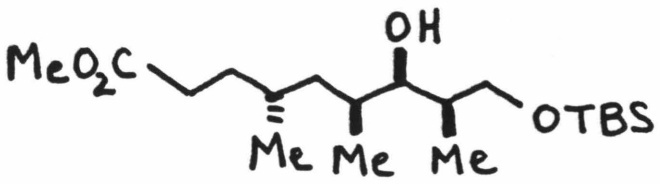
$CDCl_3$

57



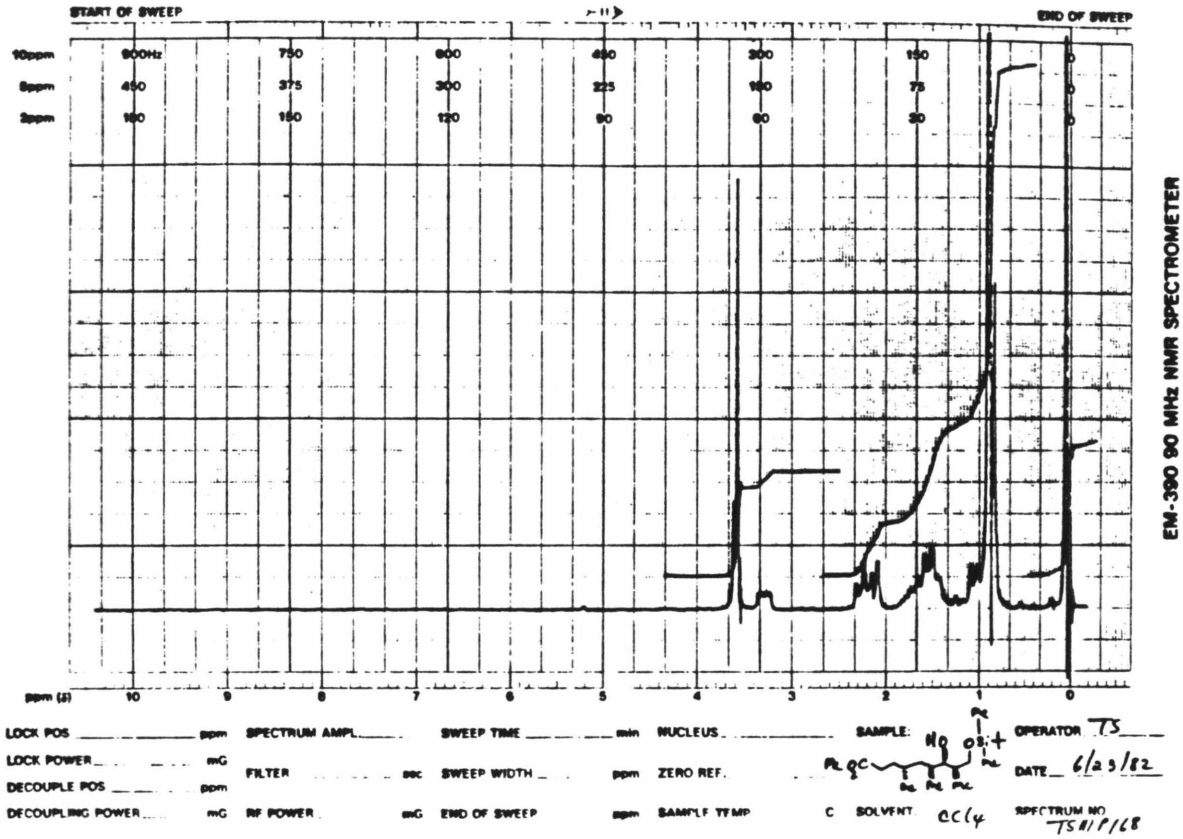
CCl_4



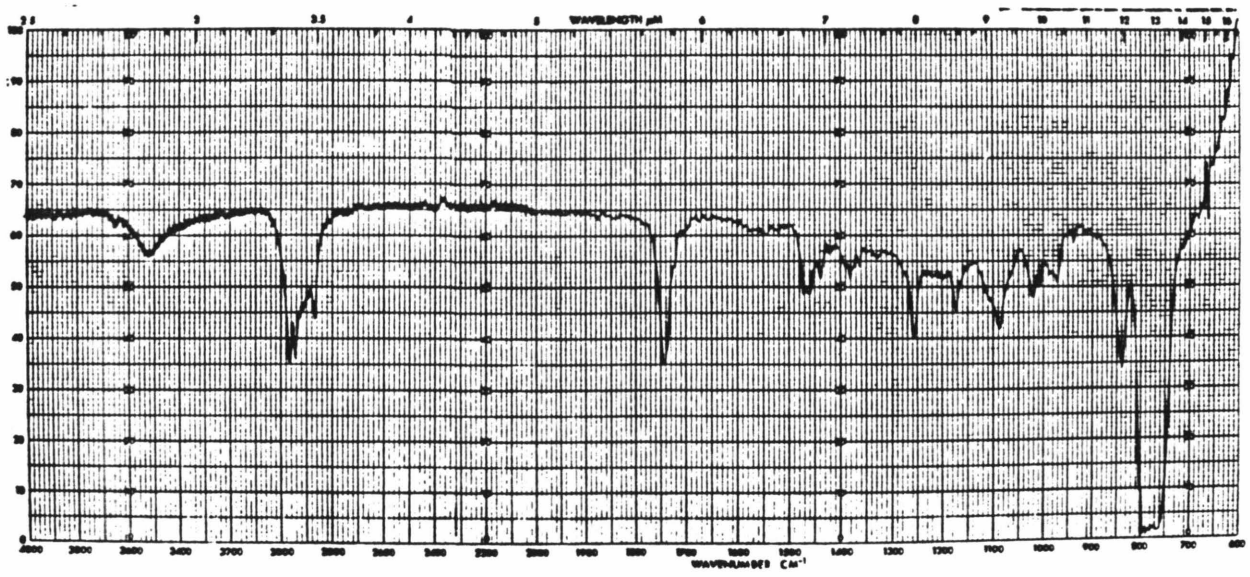

MeO2C
OH
OTBS
Me Me Me

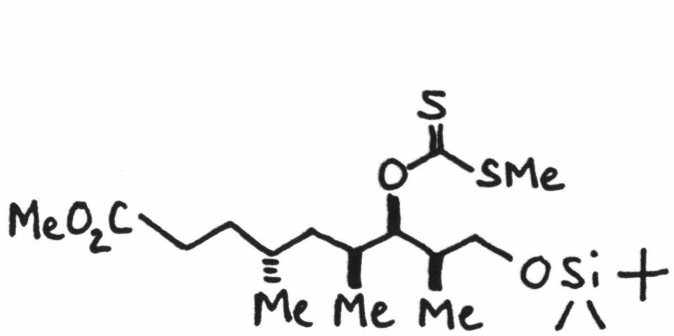
CCl4

58


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP
SAMPLE:
SOLVENT CCl4
OPERATOR TS
DATE 6/23/82
SPECTRUM NO TS11P/68

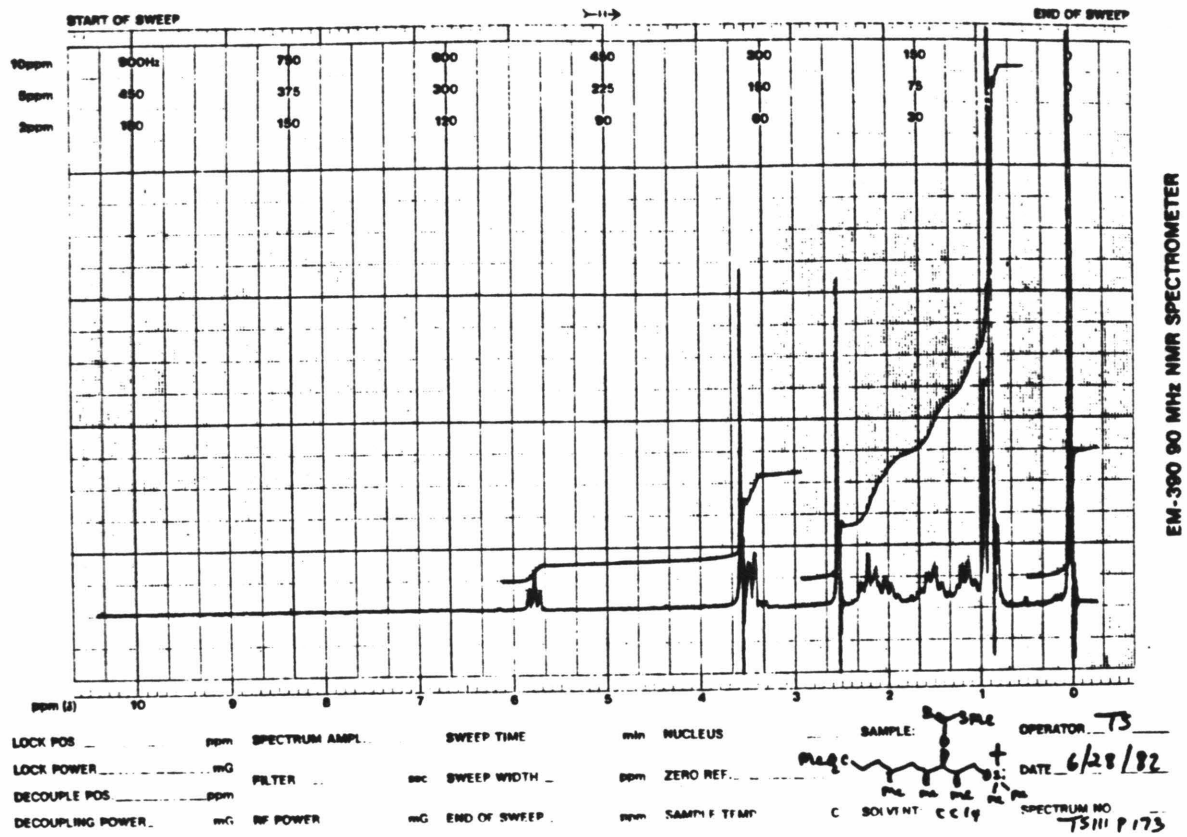
CCl4


WAVELENGTH μM
WAVENUMBER CM⁻¹

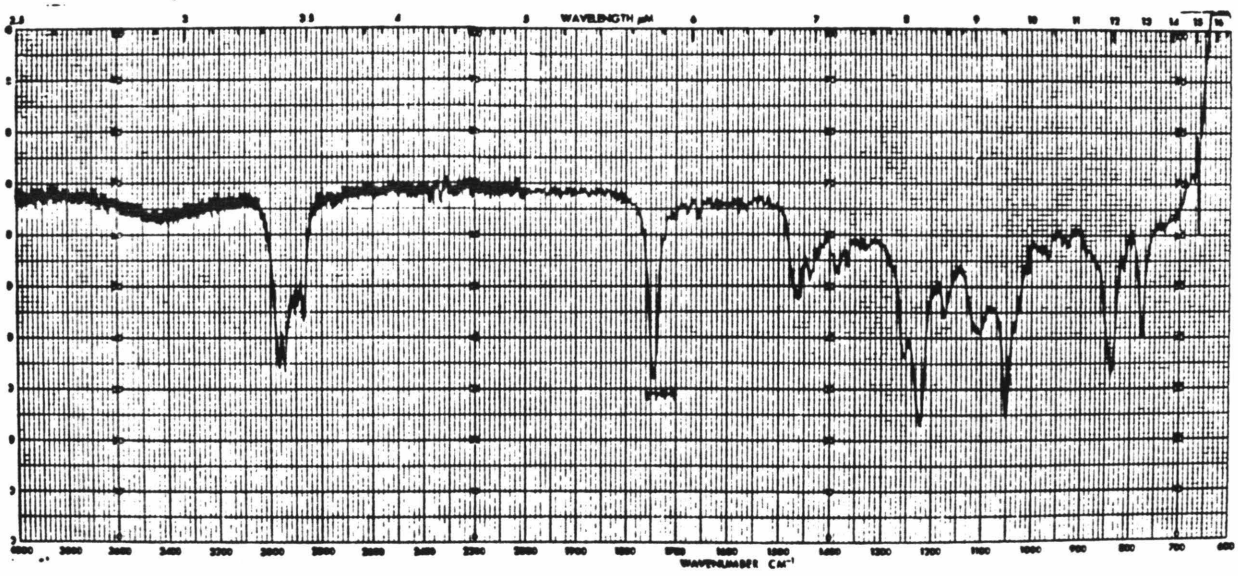

S
SMe
O
MeO2C
Me Me Me
OSi +

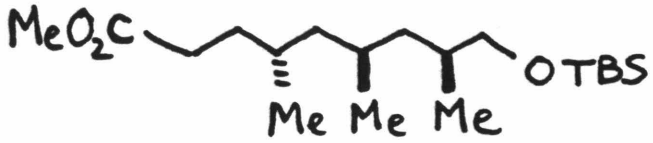
CCl4

59

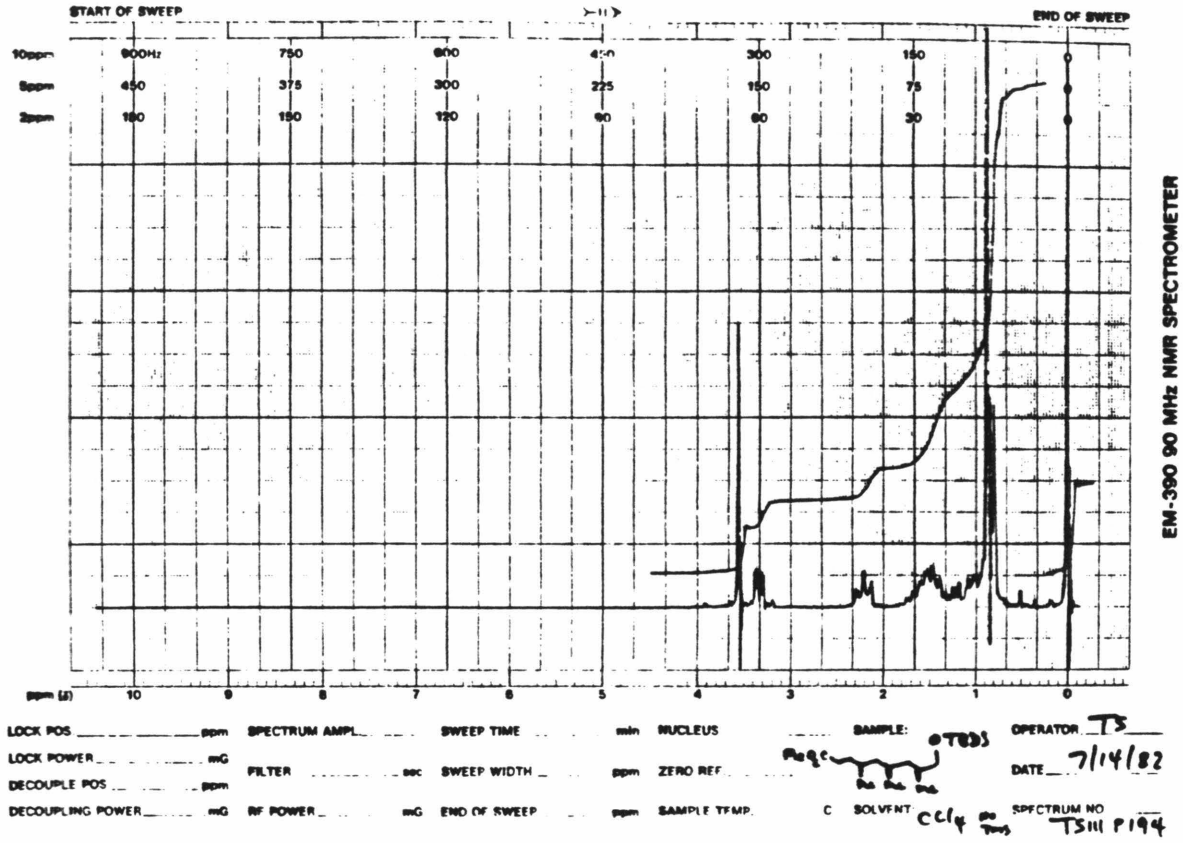

START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP
SAMPLE:
SOLVENT CCl4
OPERATOR TS
DATE 6/28/82
SPECTRUM NO TS111 P173

CCl4

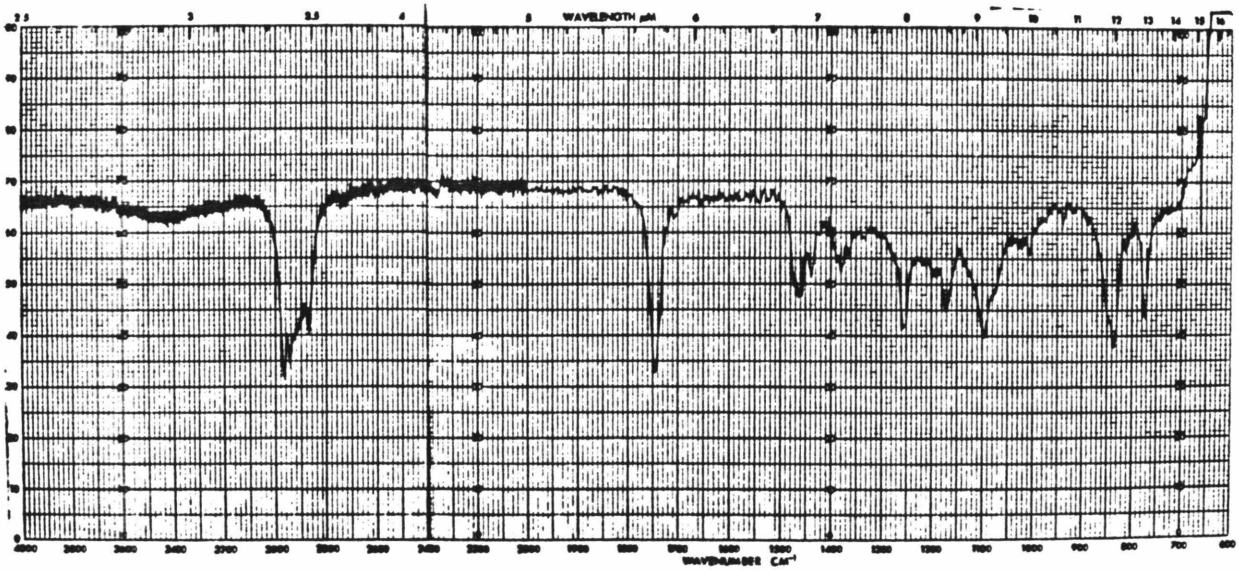

WAVELENGTH μM
WAVENUMBER CM⁻¹

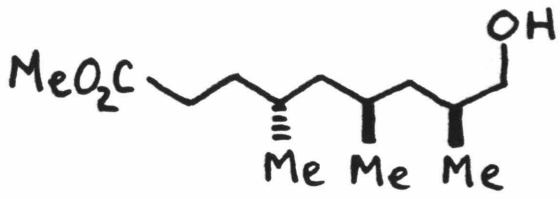

MeO2C
OTBS
Me Me Me

CCl_4 60


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF
SAMPLE TEMP.
SAMPLE:
OTBS
SOLVENT
CCl4
OPERATOR TS
DATE 7/14/82
SPECTRUM NO TS111 P194

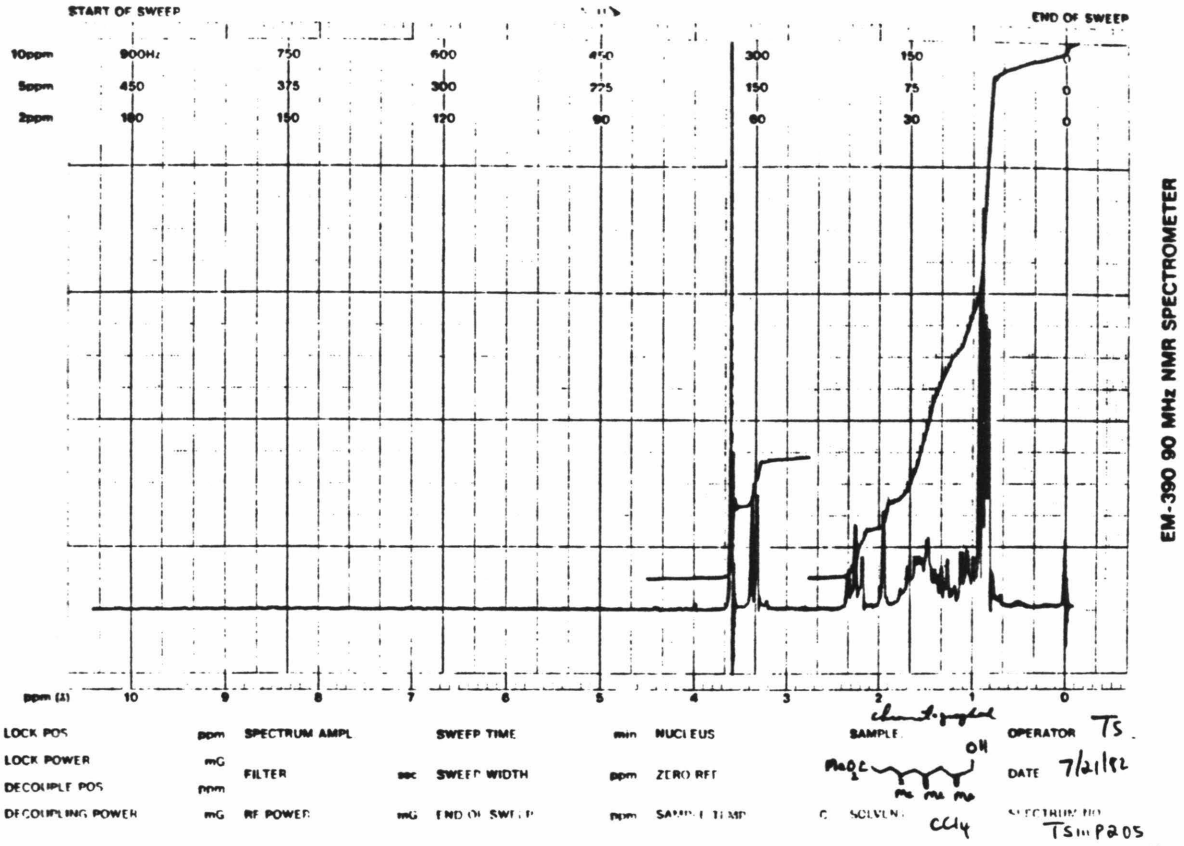
Neat


WAVELENGTH

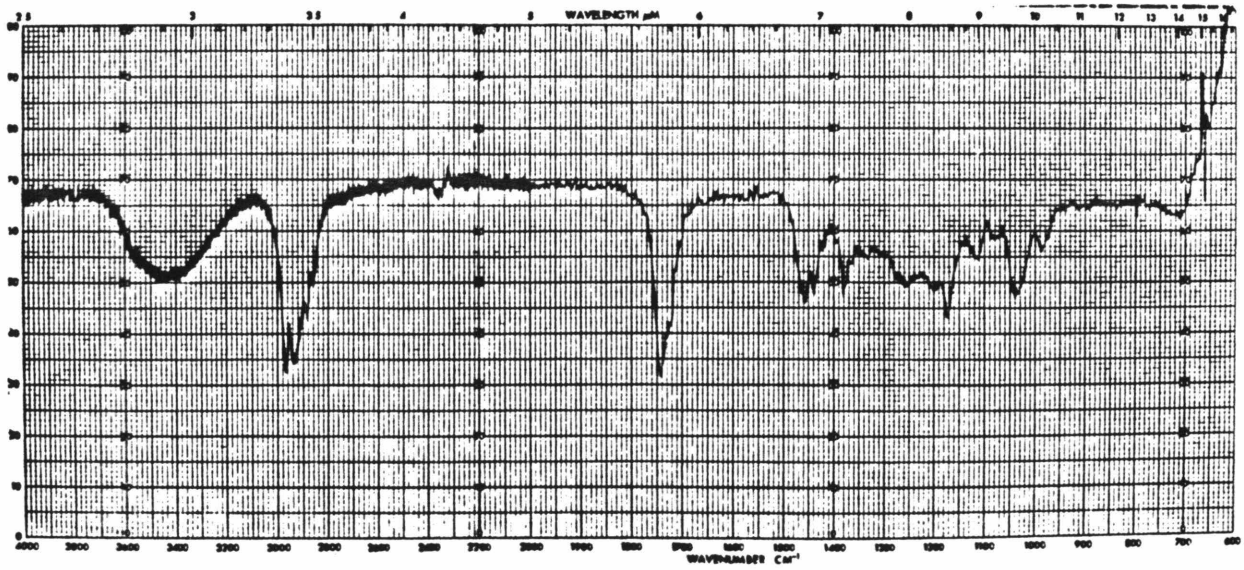

MeO2C
OH
Me Me Me

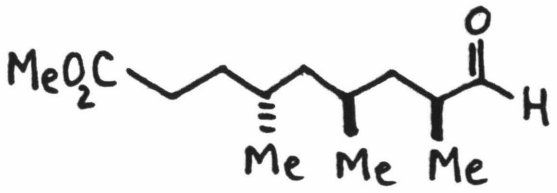
CCl4

61


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
150
75
30
0
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
ppm
mG
ppm
mG
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
min
sec
mG
NUCLEUS
ZERO REF
ppm
SAMPLE
OPERATOR
DATE
SOLVENT
CCl4
Ts
7/21/82
Ts in P205

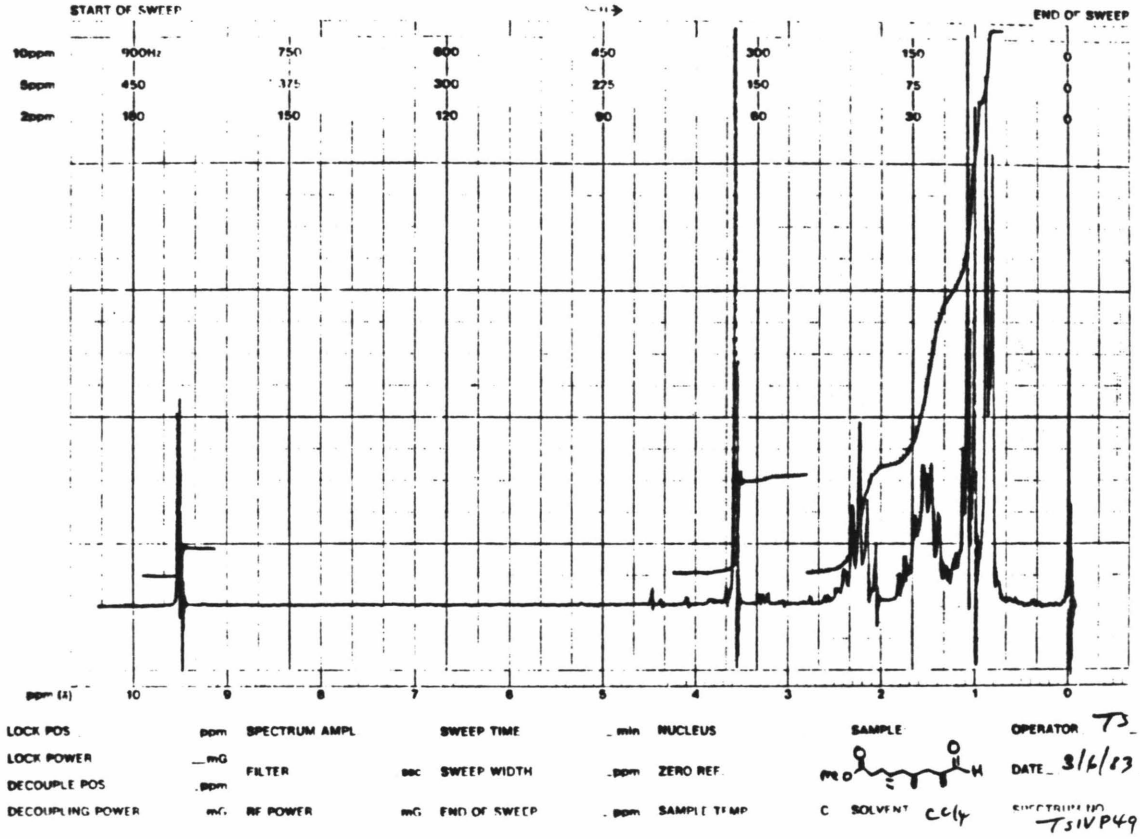
Neat


WAVELENGTH μM
WAVENUMBER cm⁻¹

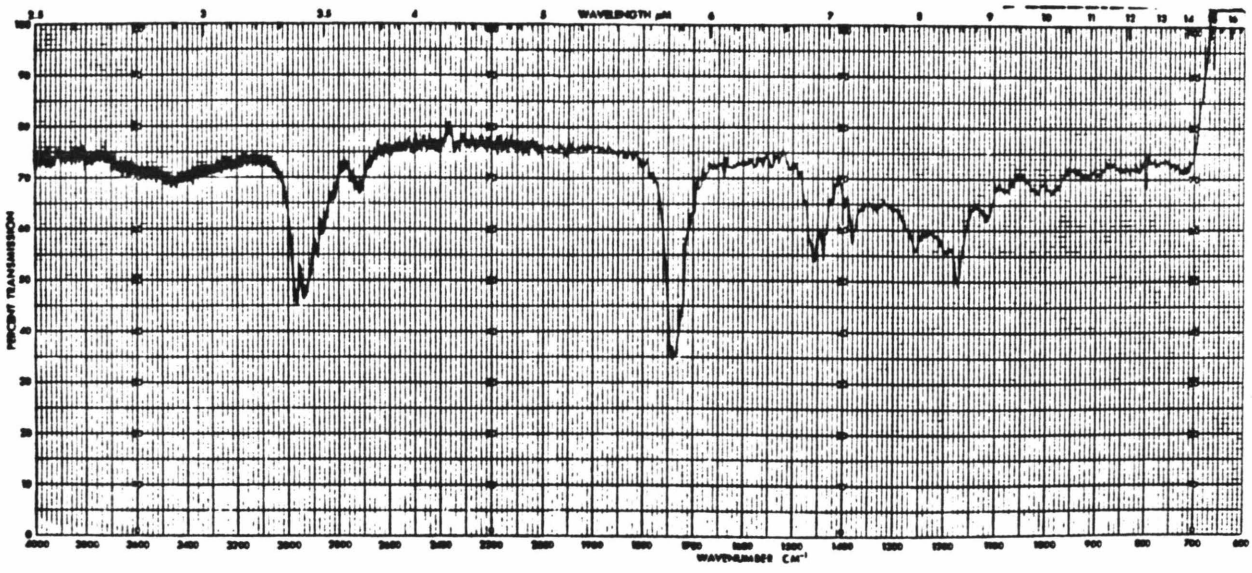

MeO2C
O
H
Me Me Me

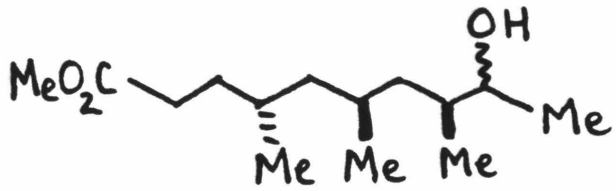
CCl4

62


START OF SWEEP
END OF SWEEP
10ppm
8ppm
2ppm
900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
ppm
SPECTRUM AMPL
SWEEP TIME
min
NUCLEUS
SAMPLE
OPERATOR TS
LOCK POWER
mG
FILTER
sec
SWEEP WIDTH
ppm
ZERO REF
DATE 3/6/83
DECOUPLE POS
ppm
DECOUPLING POWER
mG
RF POWER
mG
END OF SWEEP
ppm
SAMPLE TEMP
C
SOLVENT CCl4
TS1VP49

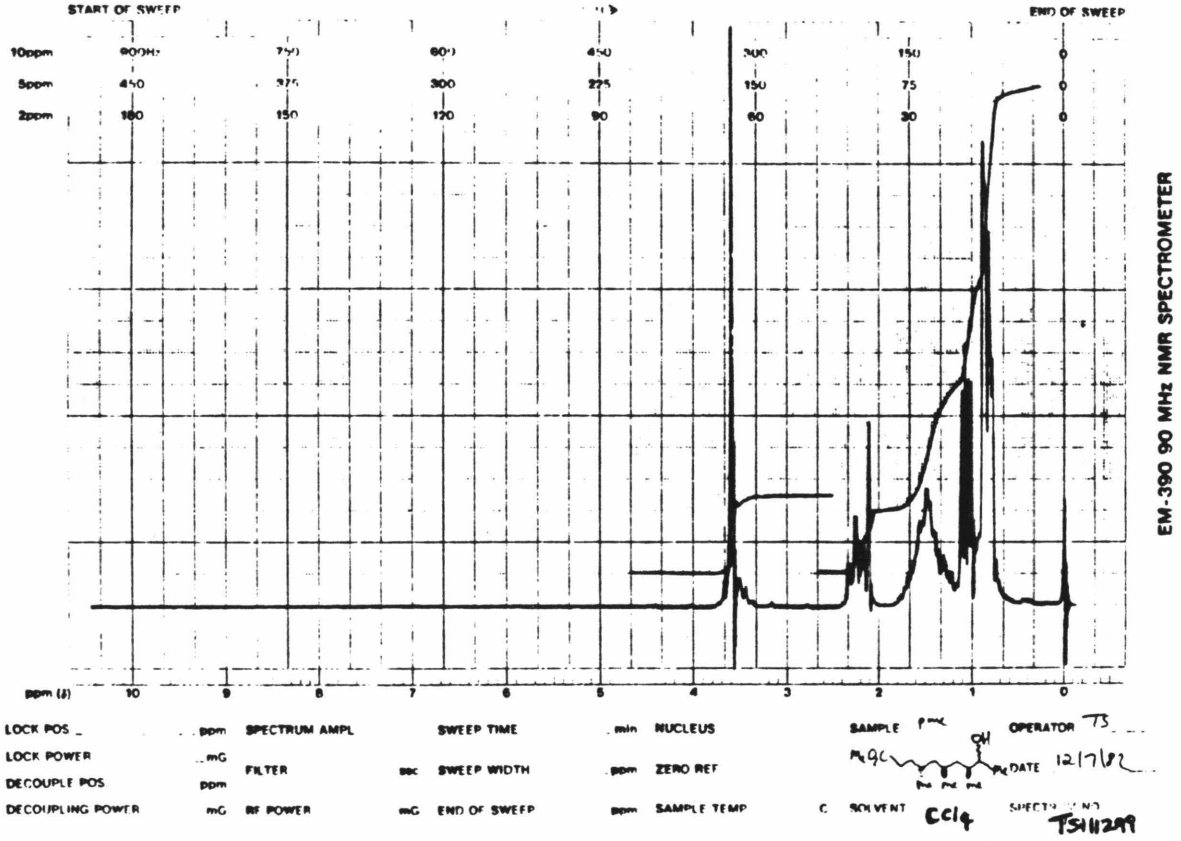
Neat

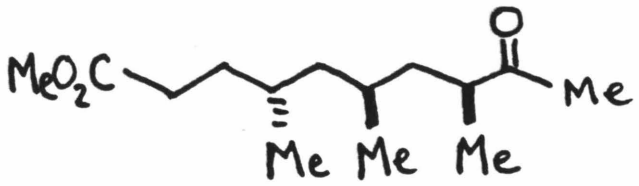

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM-1


OH
MeO2C
Me
Me Me Me

63 a,b

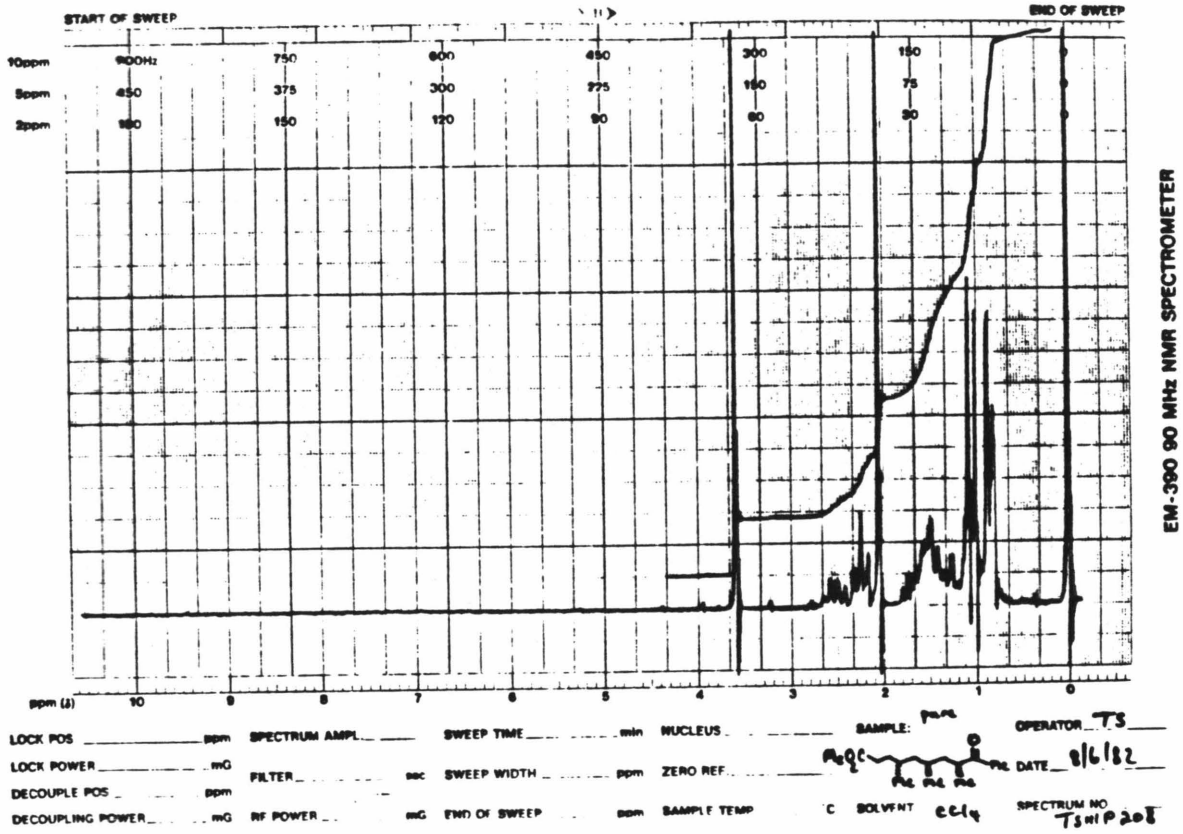
CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
ppm (δ)
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF
SAMPLE TEMP
SAMPLE
OPERATOR
DATE
SOLVENT
CCl4
TSH1299

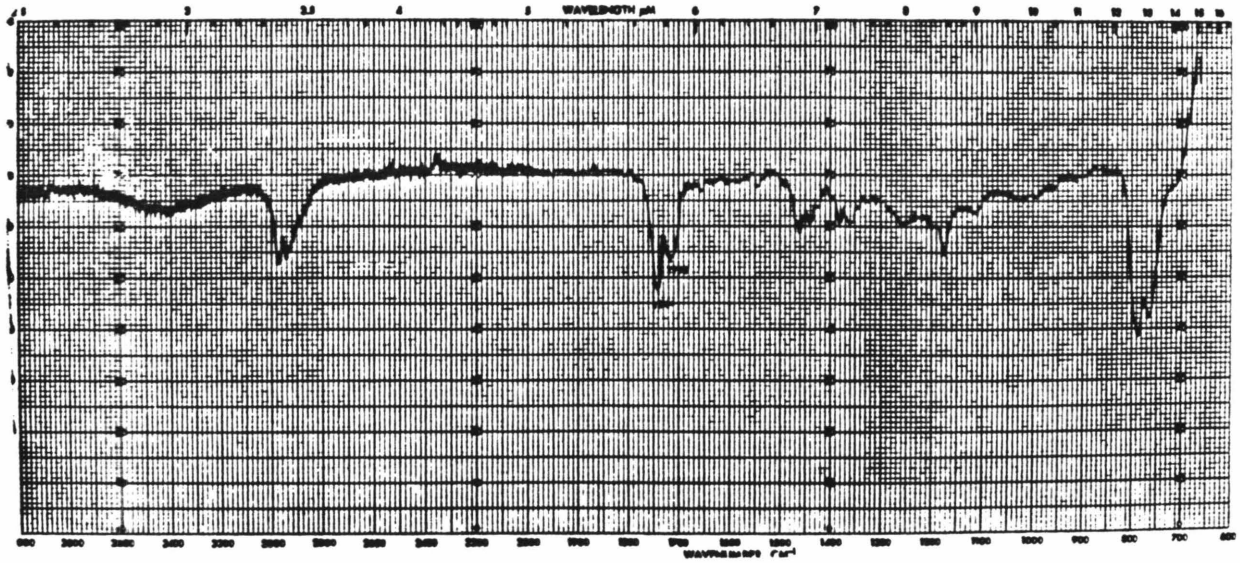

MeO2C
O
Me
Me Me Me

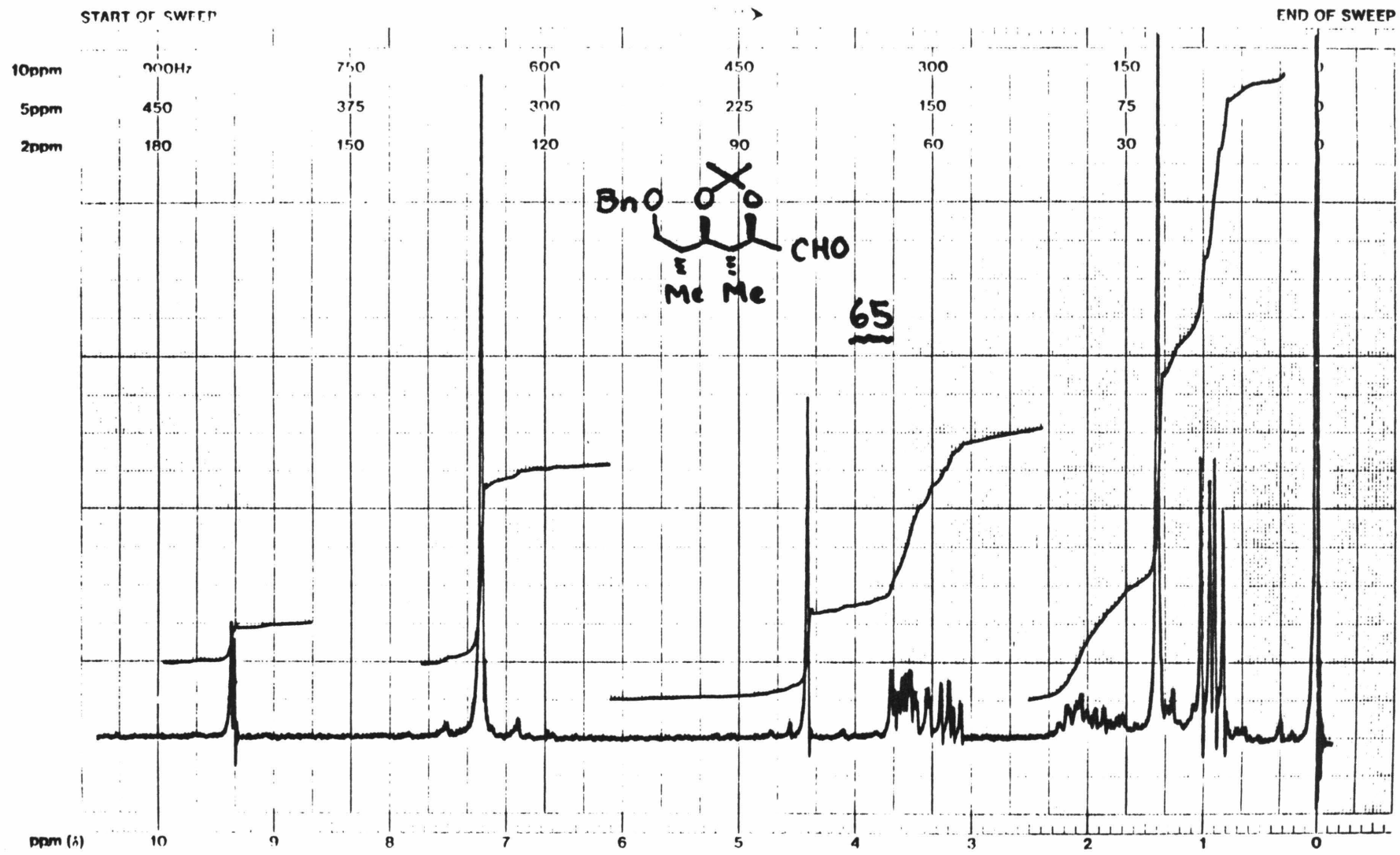
CCl_4

64


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF
SAMPLE TEMP
SAMPLE:
SOLVENT
OPERATOR
DATE
SPECTRUM NO

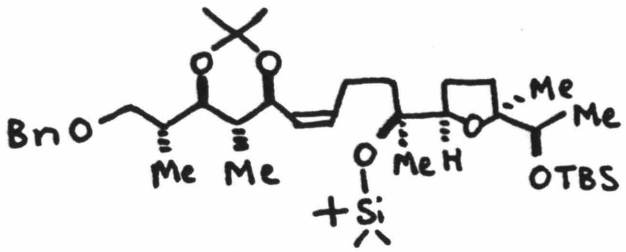
CCl_4


WAVELENGTH μM
WAVENUMBER cm⁻¹



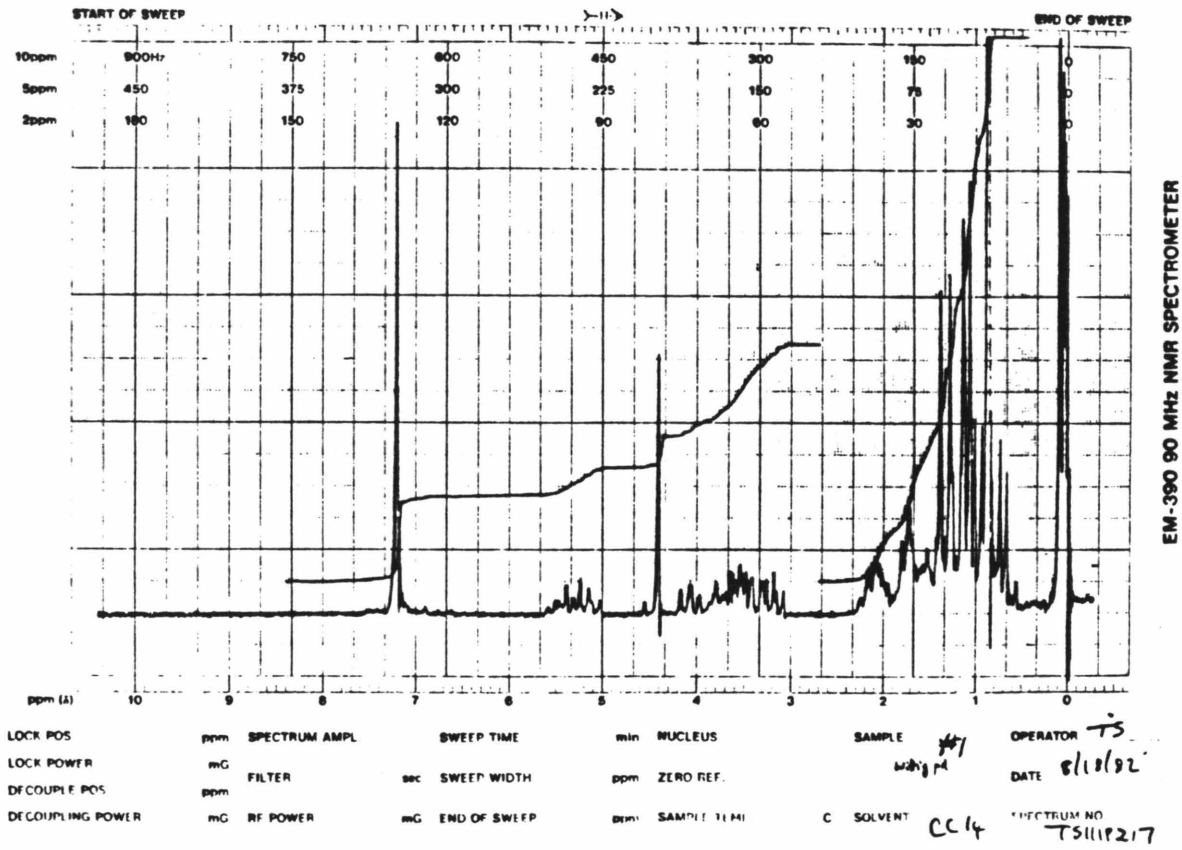
EM-390 90 MHz NMR SPECTROMETER

LOCK POS.	ppm	SPECTRUM AMPL.		SWEEP TIME	min	NUCLEUS	SAMPLE:	OPERATOR	Ts
LOCK POWER	mG	FILTER							
DECOUPLE POS.	ppm		sec	SWEEP WIDTH	ppm	ZERO REF.		DATE	12/22/81
DECOUPLING POWER	mG	RF POWER	mG	END OF SWEEP	ppm	SAMPLE TEMP.	C SOLVENT	CCl4	SPECTRUM NO.	TS111 P19

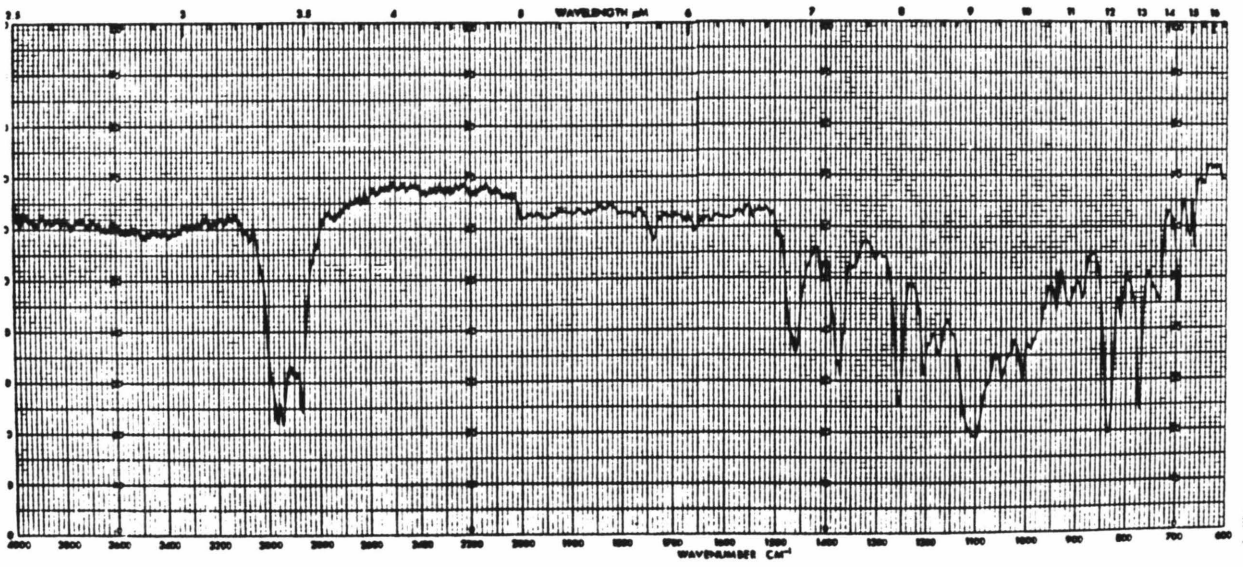

BnO
Me
Me
O
Me
H
O
Si
Me
Me
OTBS

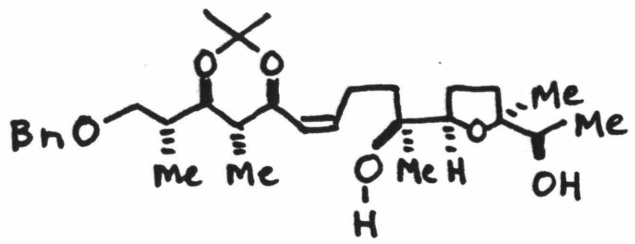
CCl_4

66


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
ppm
mG
ppm
mG
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
sec
mG
min
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ppm
ZERO REF.
SAMPLE
SOLVENT
CCl4
OPERATOR
TS
DATE
8/18/92
TS111217

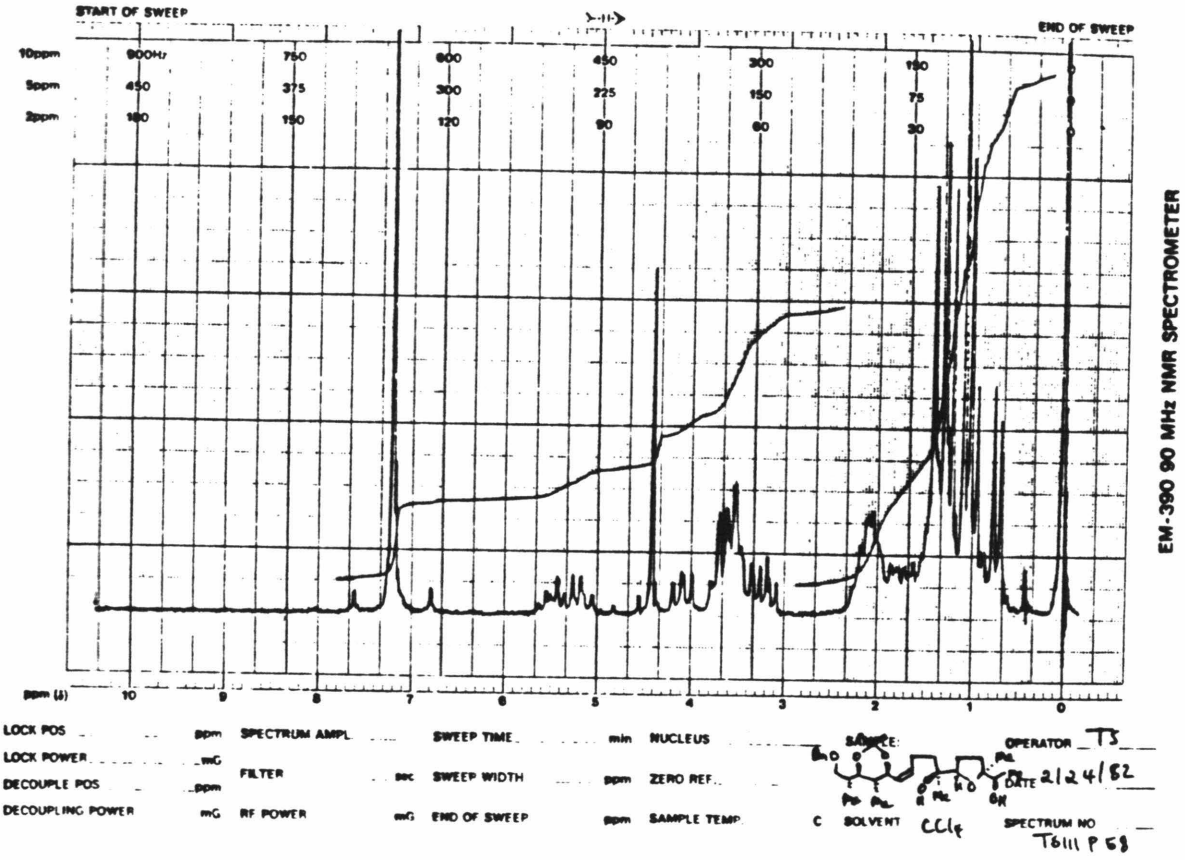
Neat


WAVELENGTH μM
WAVENUMBER Cm⁻¹

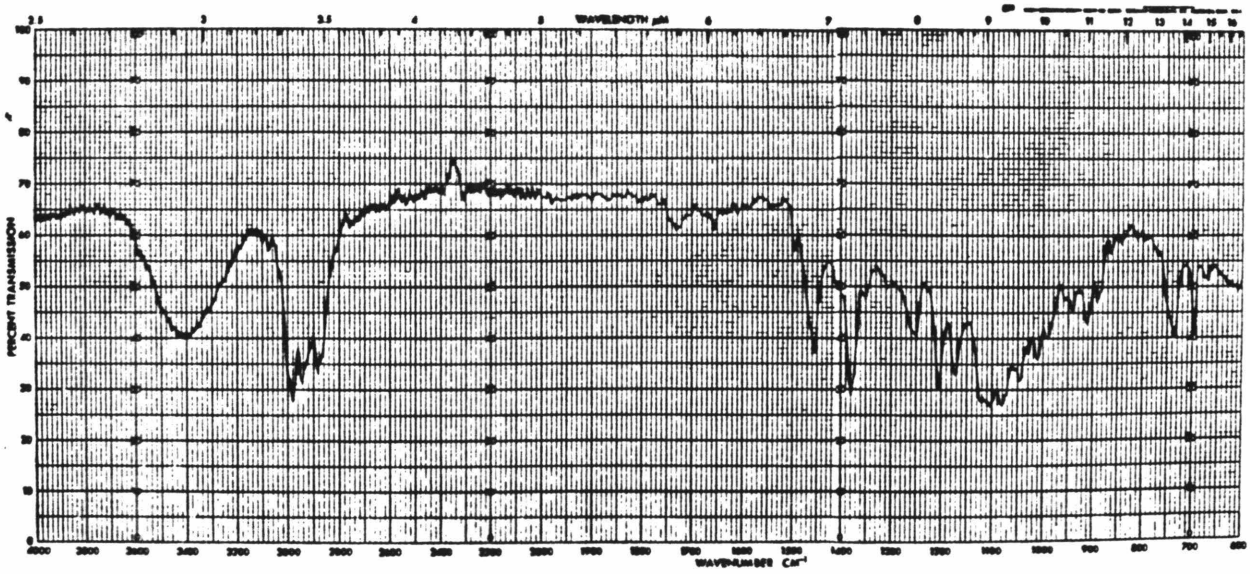

BnO
Me Me
O
O
O
Me H
H
Me
Me
OH

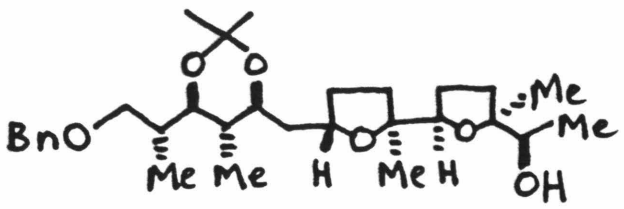
67

CCl_4

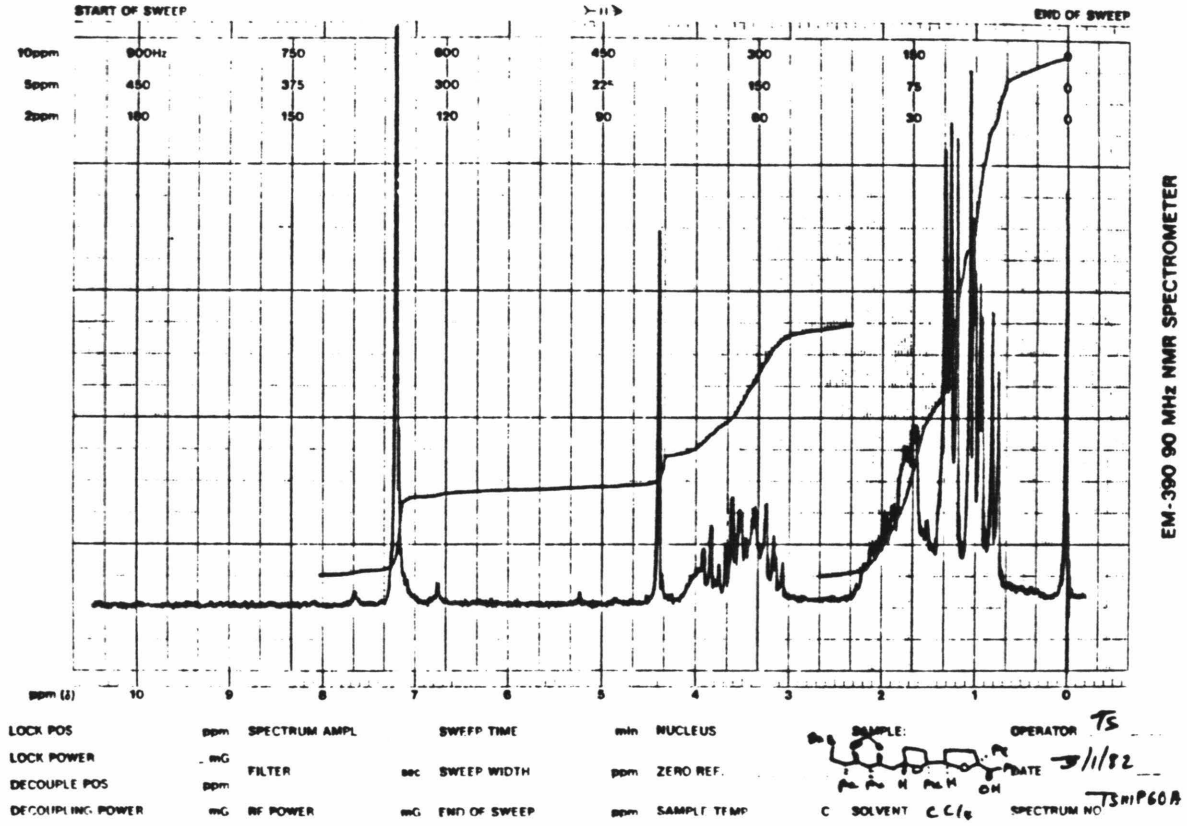

START OF SWEEP
END OF SWEEP
10ppm
9ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS ppm
LOCK POWER mG
DECOUPLE POS ppm
DECOUPLING POWER mG
SPECTRUM AMPL
FILTER sec
RF POWER mG
SWEEP TIME min
SWEEP WIDTH ppm
END OF SWEEP ppm
NUCLEUS
ZERO REF.
SAMPLE TEMP C
SOLVENT CCl4
OPERATOR TS
DATE 2/24/82
SPECTRUM NO T6111 P 58

Neat

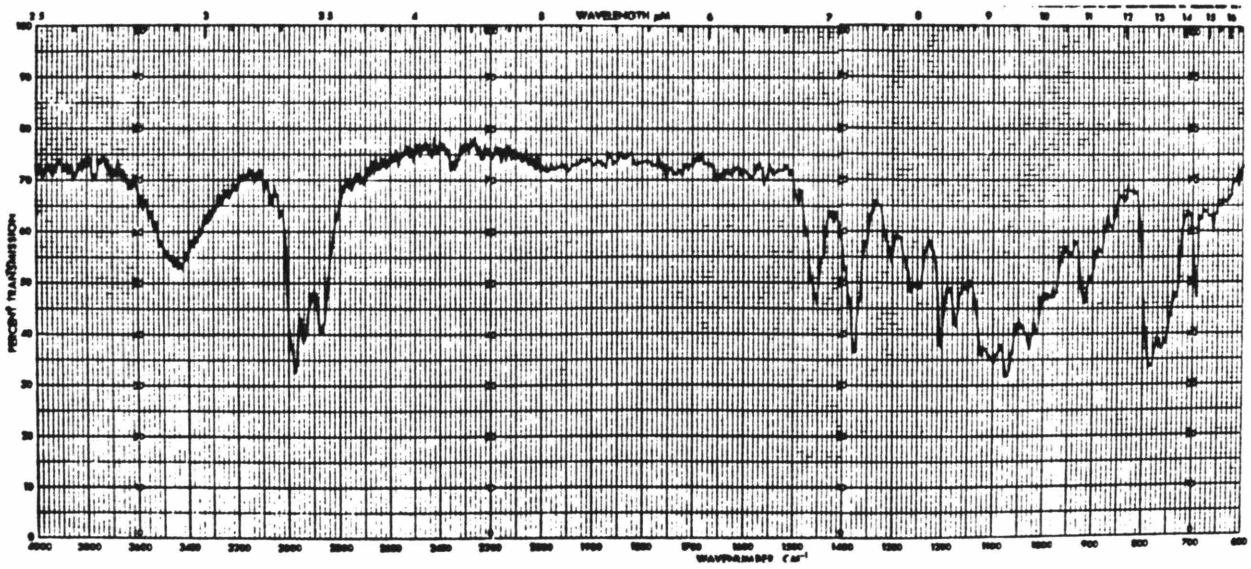

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER cm⁻¹

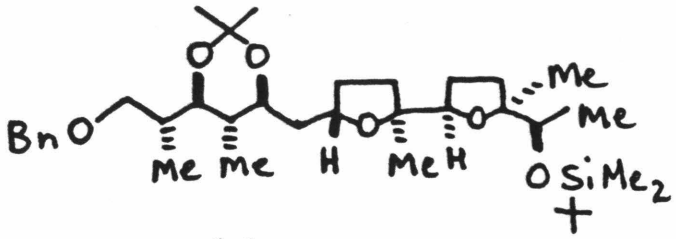

BnO
Me Me H Me H
OH
Me
Me

CCl_4 68


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF.
SAMPLE TEMP
SAMPLE:
OPERATOR TS
DATE 3/11/82
SOLVENT CCl_4
SPECTRUM NO TSN1P60A

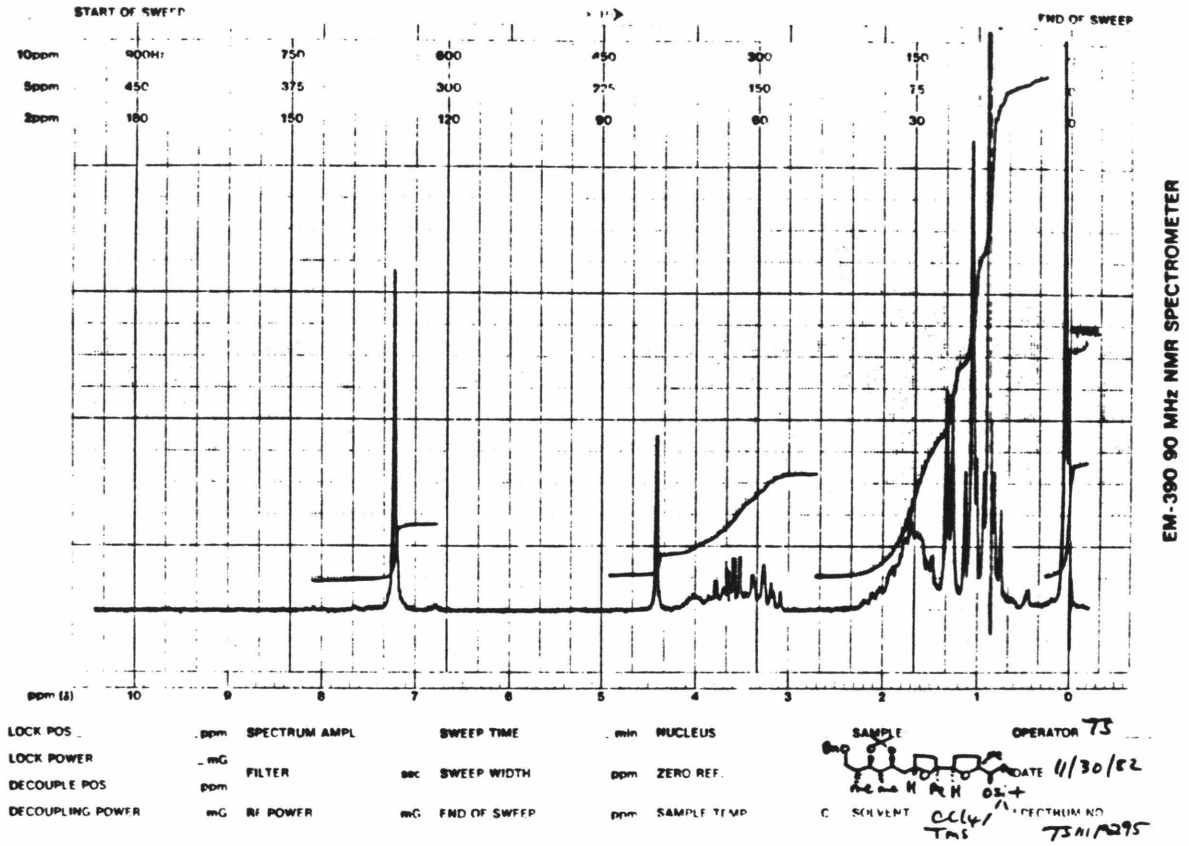
CCl_4


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER cm⁻¹

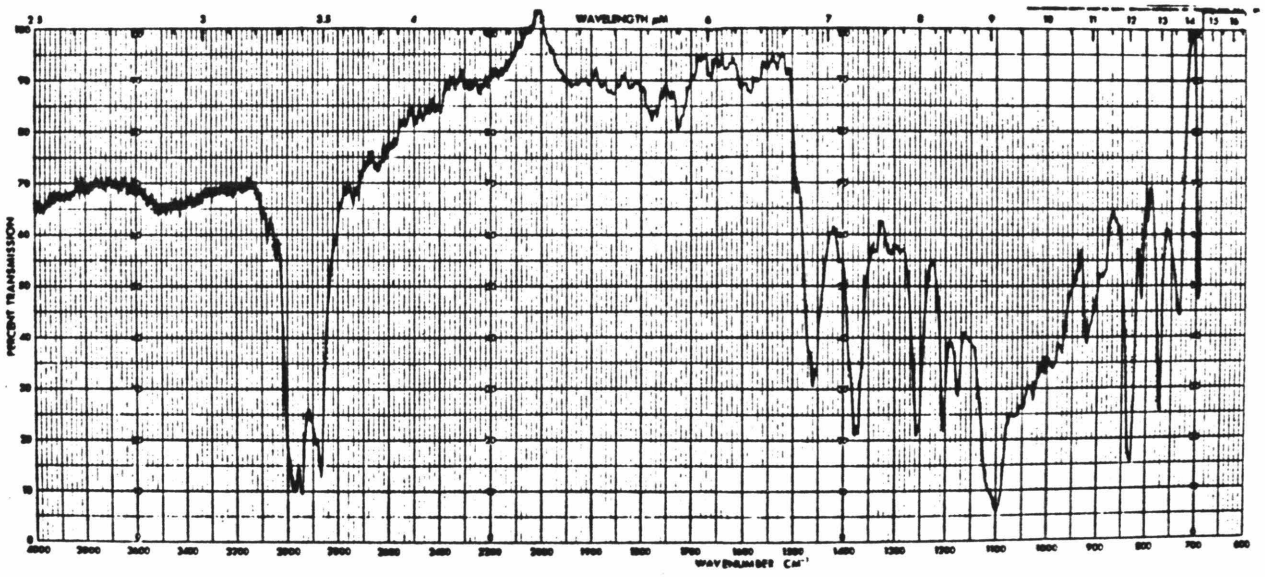

BnO
Me
Me
Me Me
H
MeH
OSiMe2
+

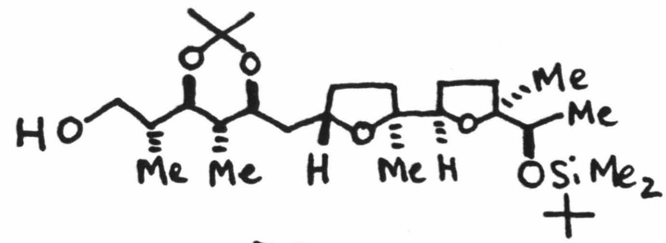
69

CCl_4


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
150
75
30
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
EM-390 90 MHz NMR SPECTROMETER
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
ppm
mG
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
min
sec
mG
NUCLEUS
ZERO REF.
SAMPLE TEMP.
SAMPLE
OPERATOR TS
DATE 11/30/82
SOLVENT CCl4/TMS
SPECTRUM NO. TS11/295

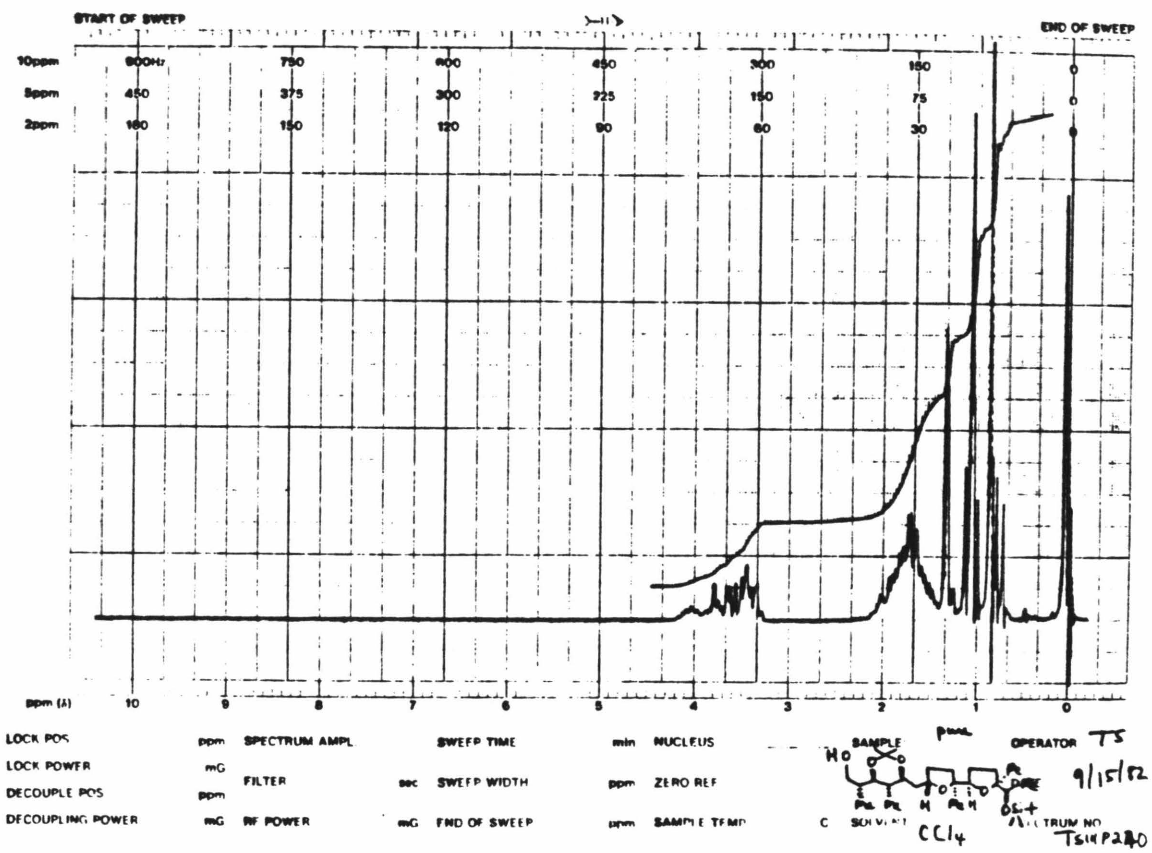
Neat


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER Cm⁻¹

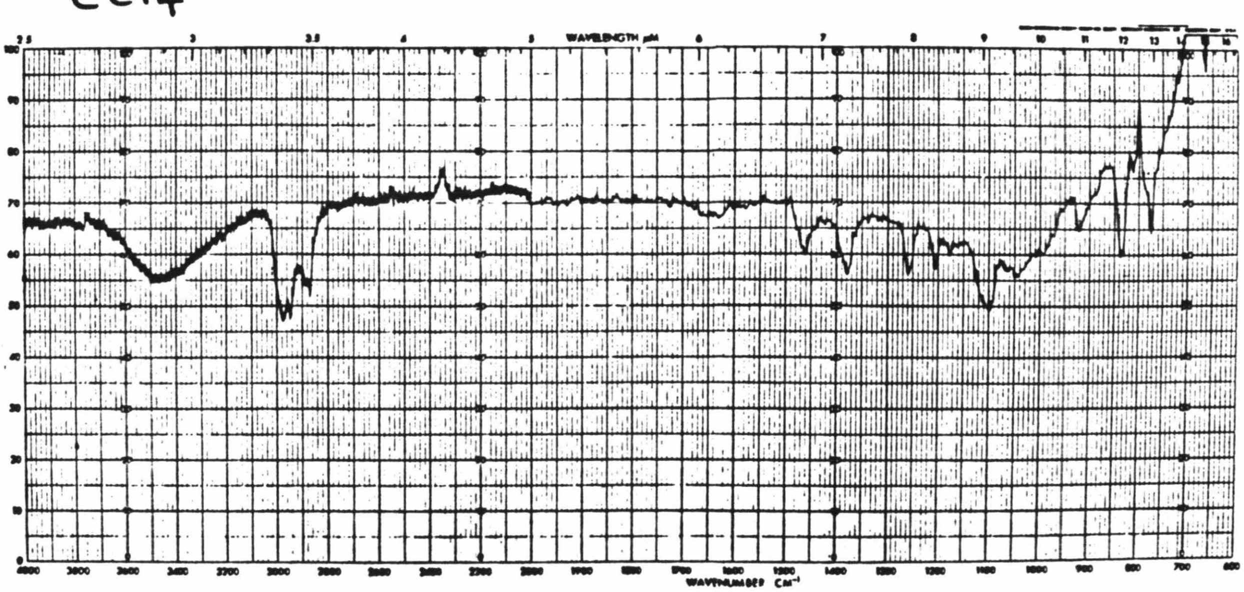


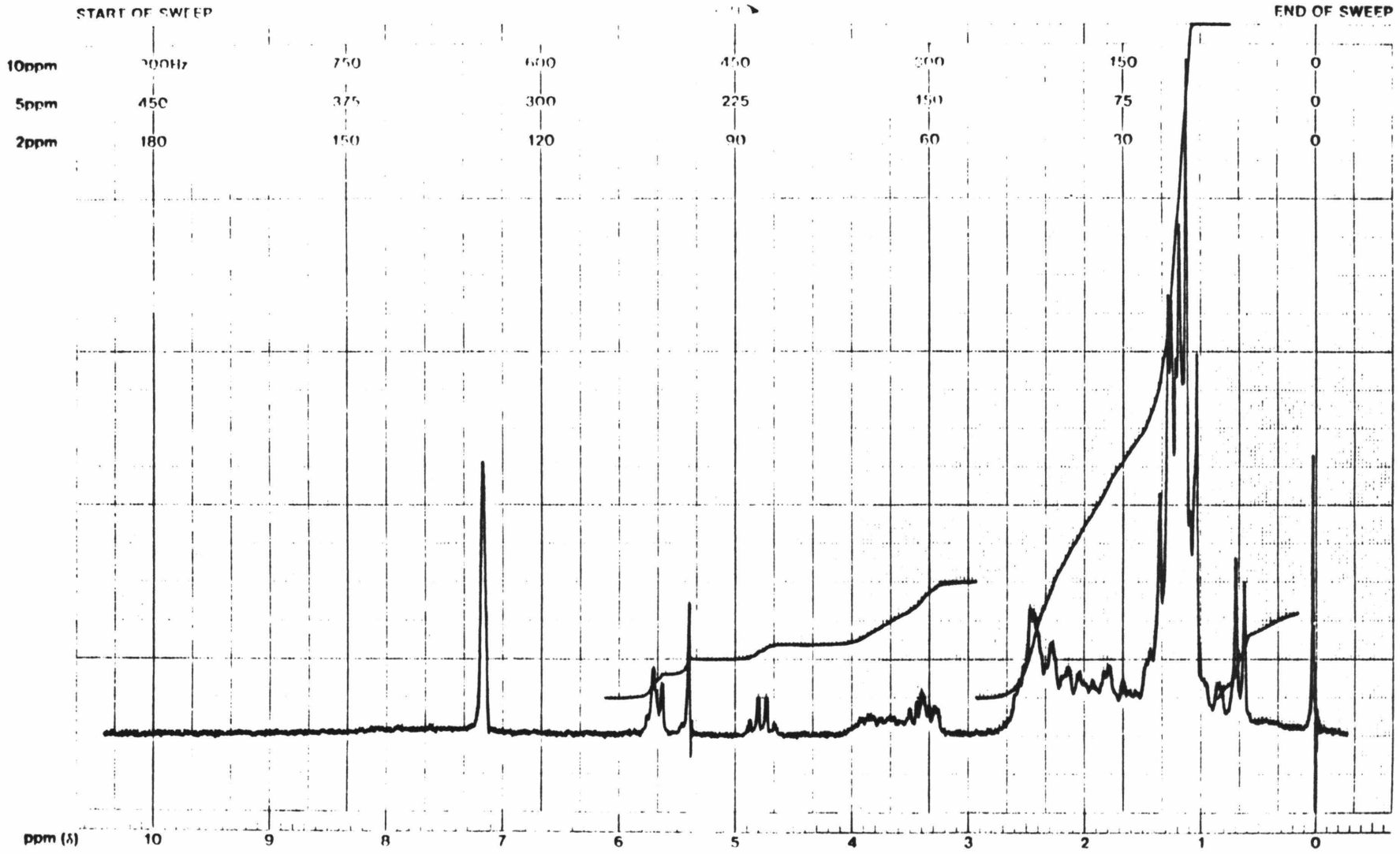
CCl$_4$

70


START OF SWEEP
END OF SWEEP
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
LOCK POS
LOCK POWER
DECOUPLE POS
DECOUPLING POWER
SPECTRUM AMPL
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
NUCLEUS
ZERO REF
SAMPLE TEMP
SAMPLE
SOLVENT CCl4
OPERATOR TS
9/15/82
SPECTRUM NO TSIIP240

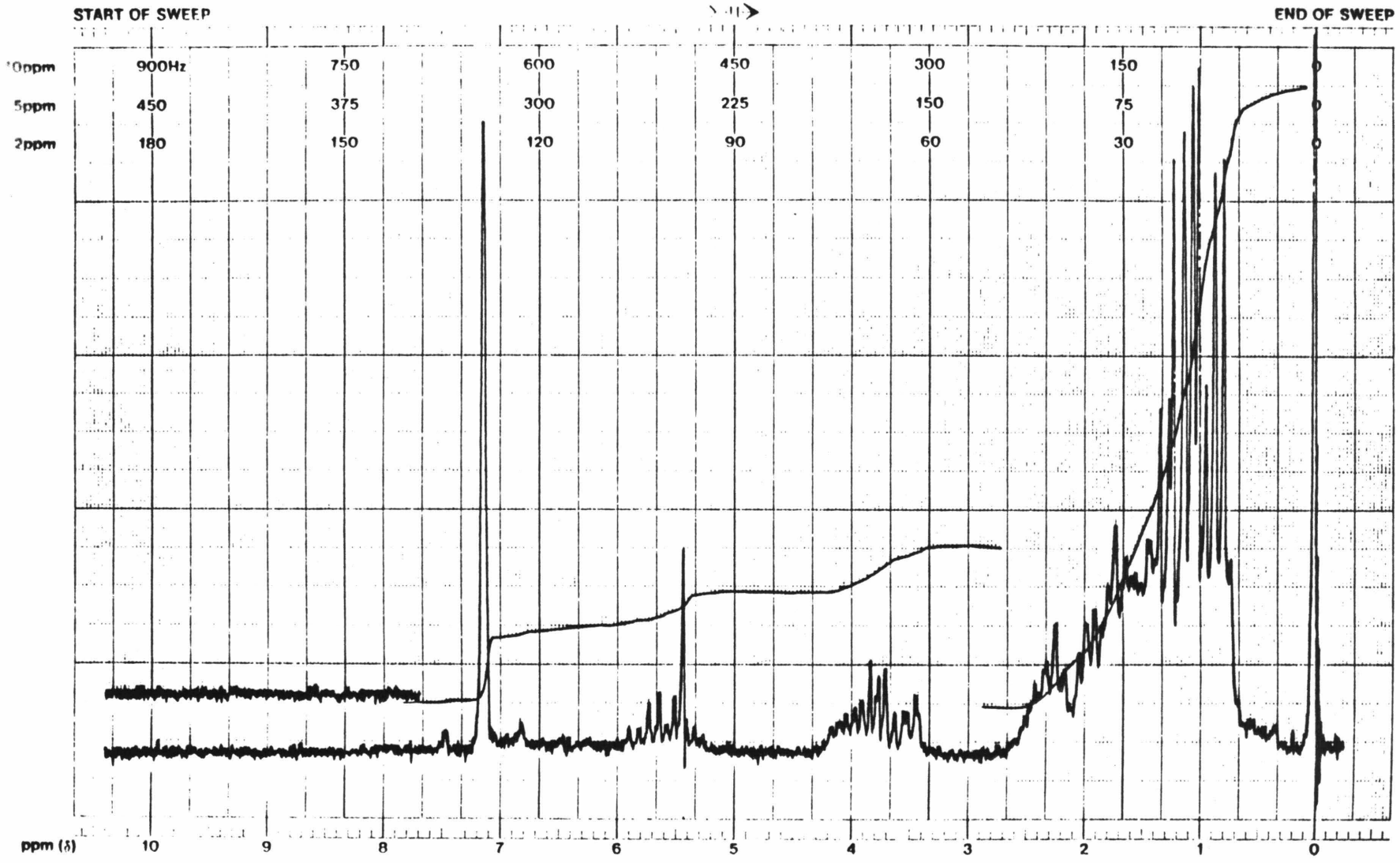
CCl$_4$


WAVELENGTH μM
WAVENUMBER CM⁻¹

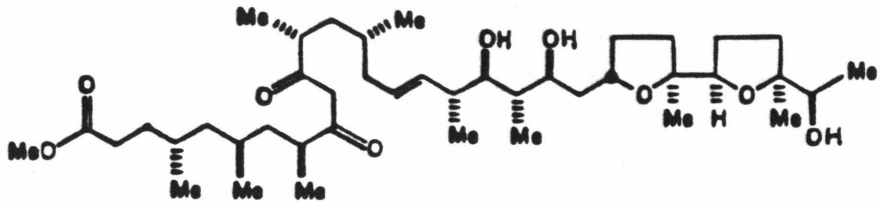


EM-390 90 MHz NMR SPECTROMETER

IONOMYCIN, CALCIUM SALT (Benzene-d_6)

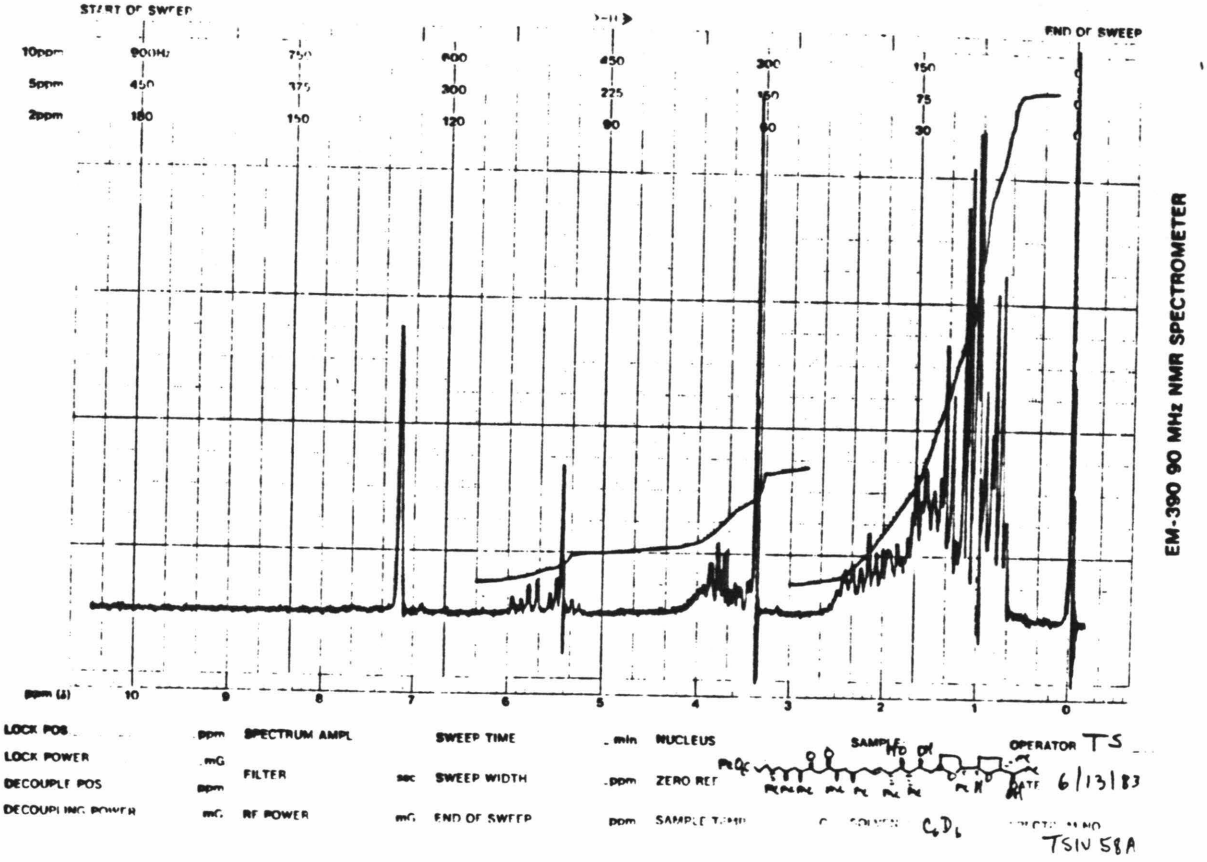


IONOMYCIN, FREE ACID (Benzene-d_6)

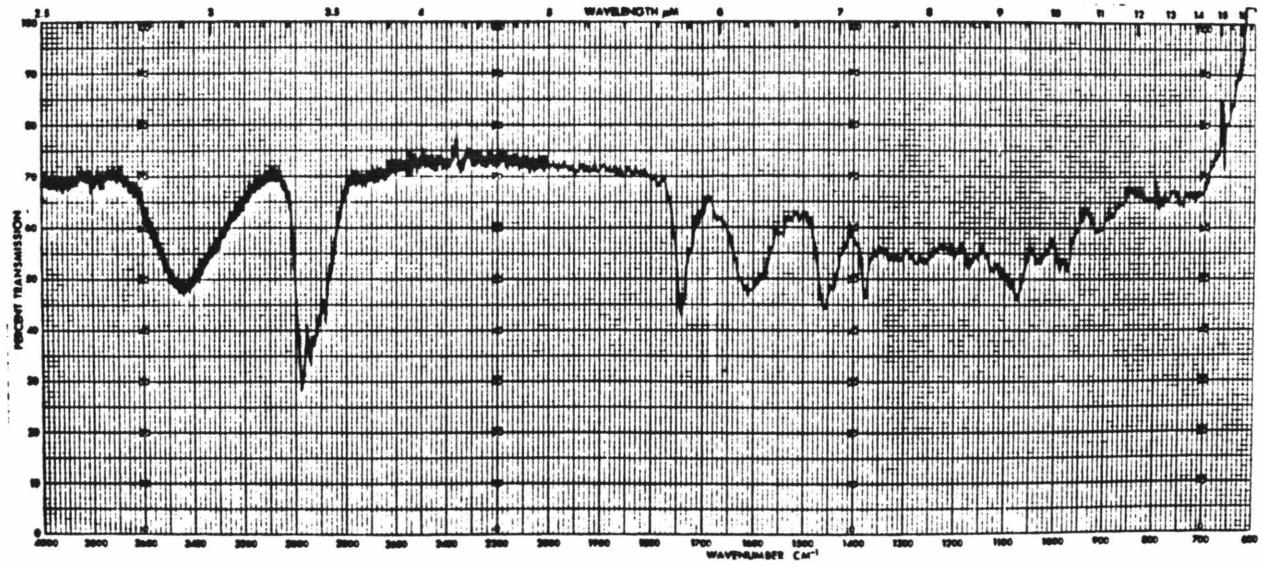


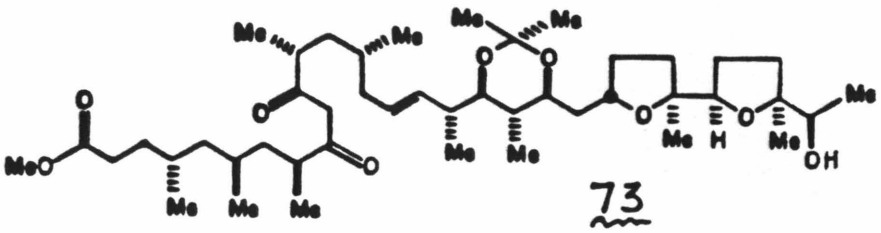
72

Benzene-d6



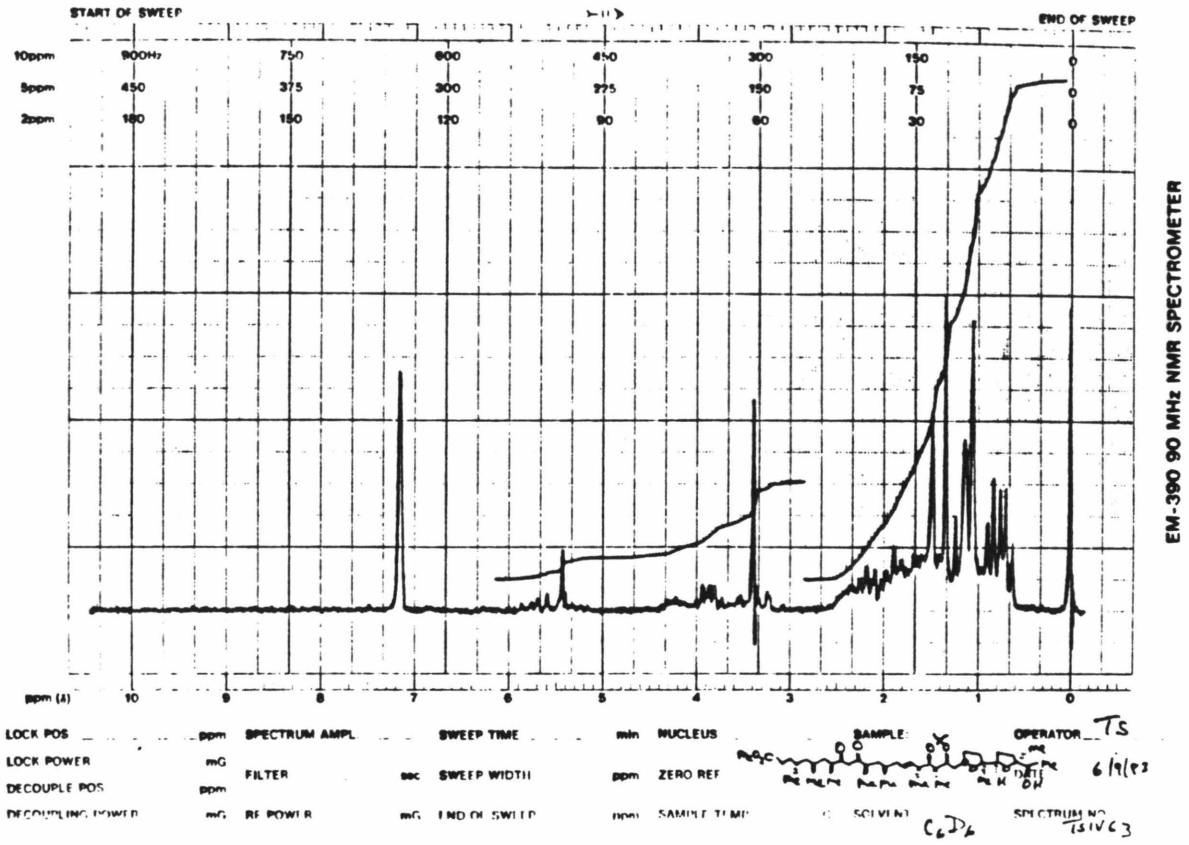
Neat



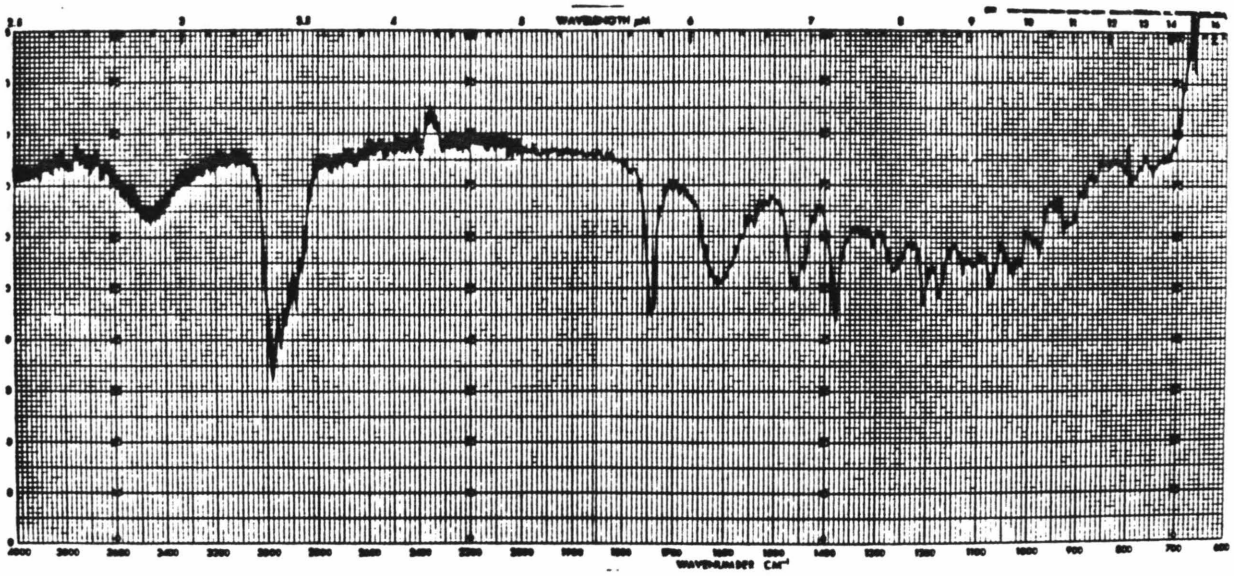


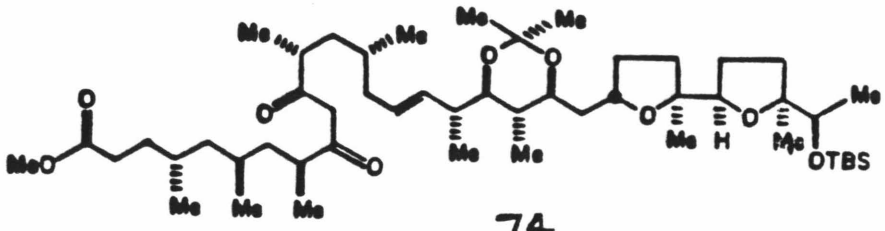
73

Benzene-d_6



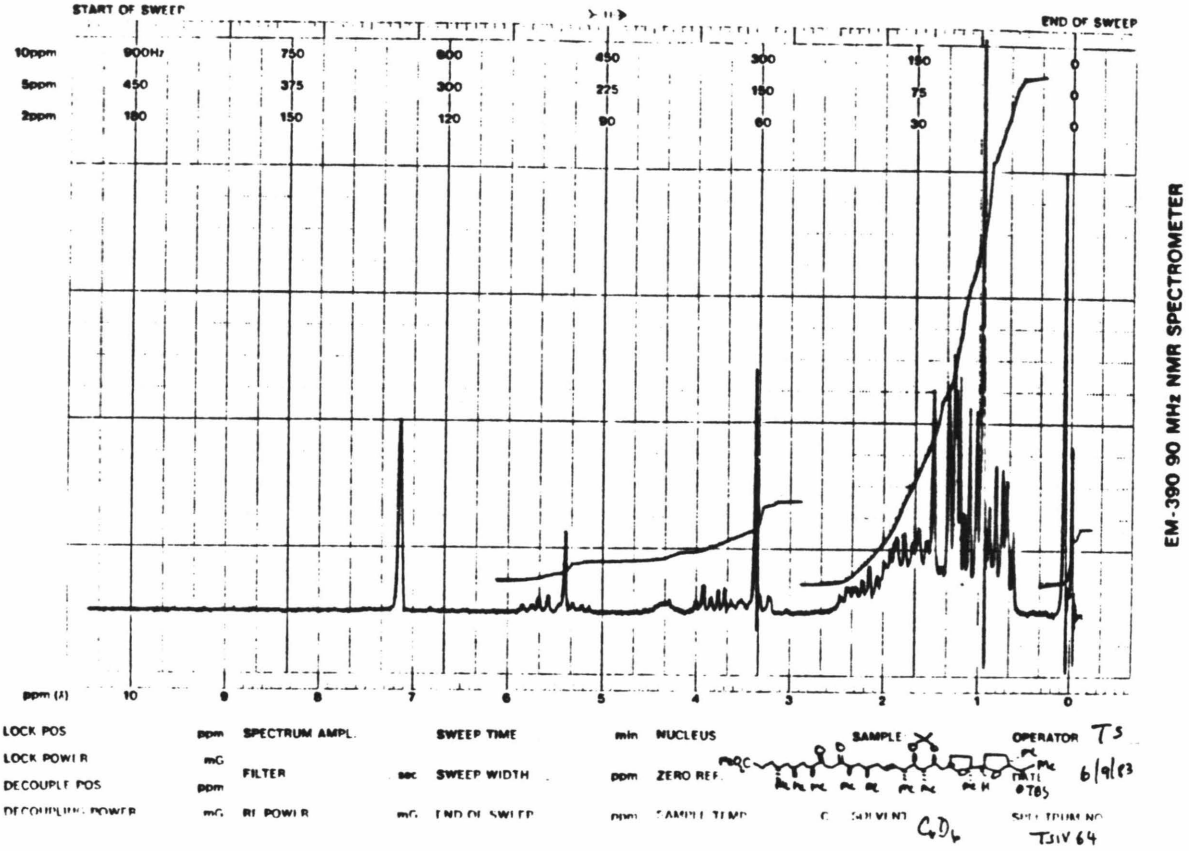
Neat



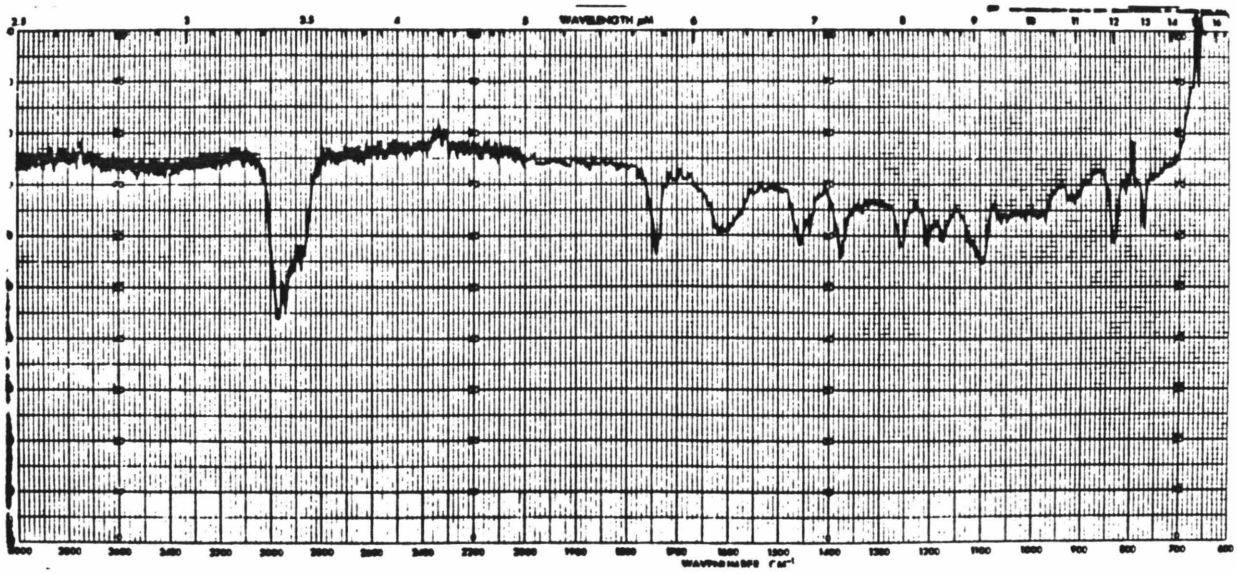


74

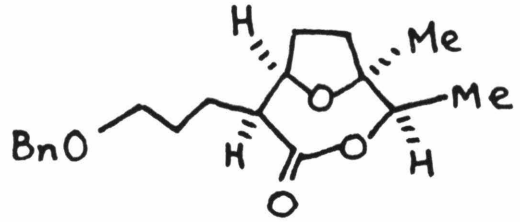
Benzene-d_6



Neat

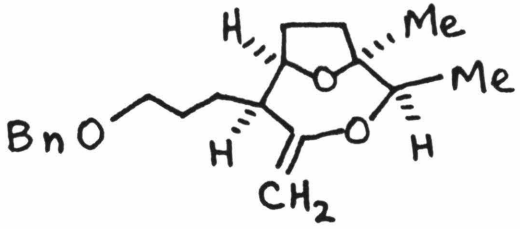


APPENDIX V. Selected 500 MHz NMR Spectral Catalog for Chapter II



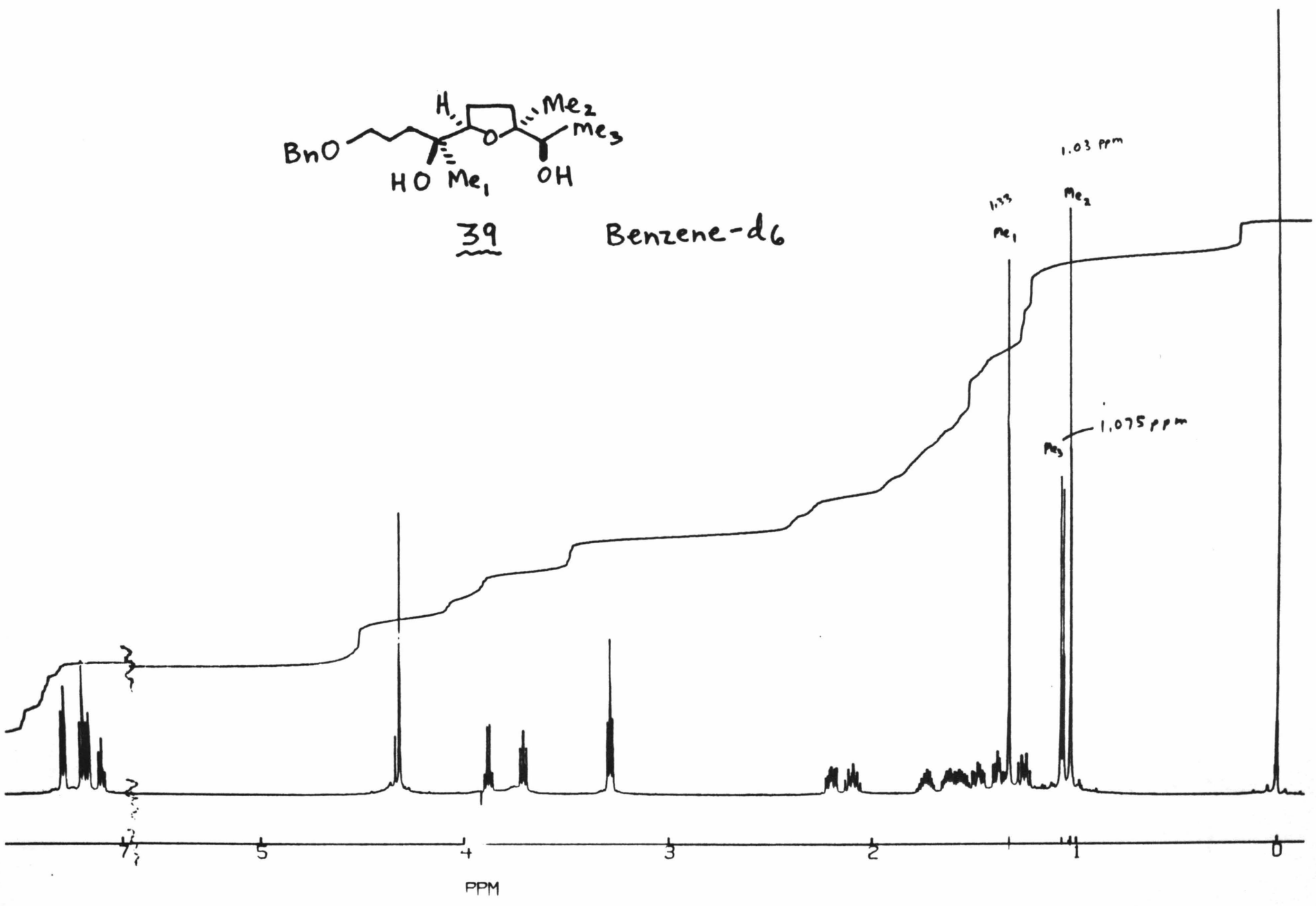
35

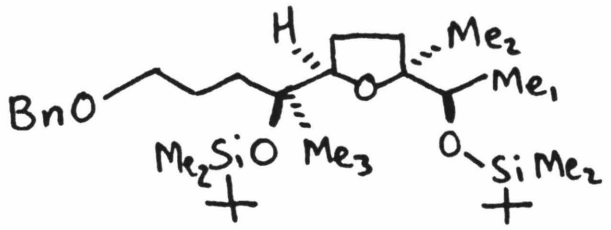
Benzene-d_6



36

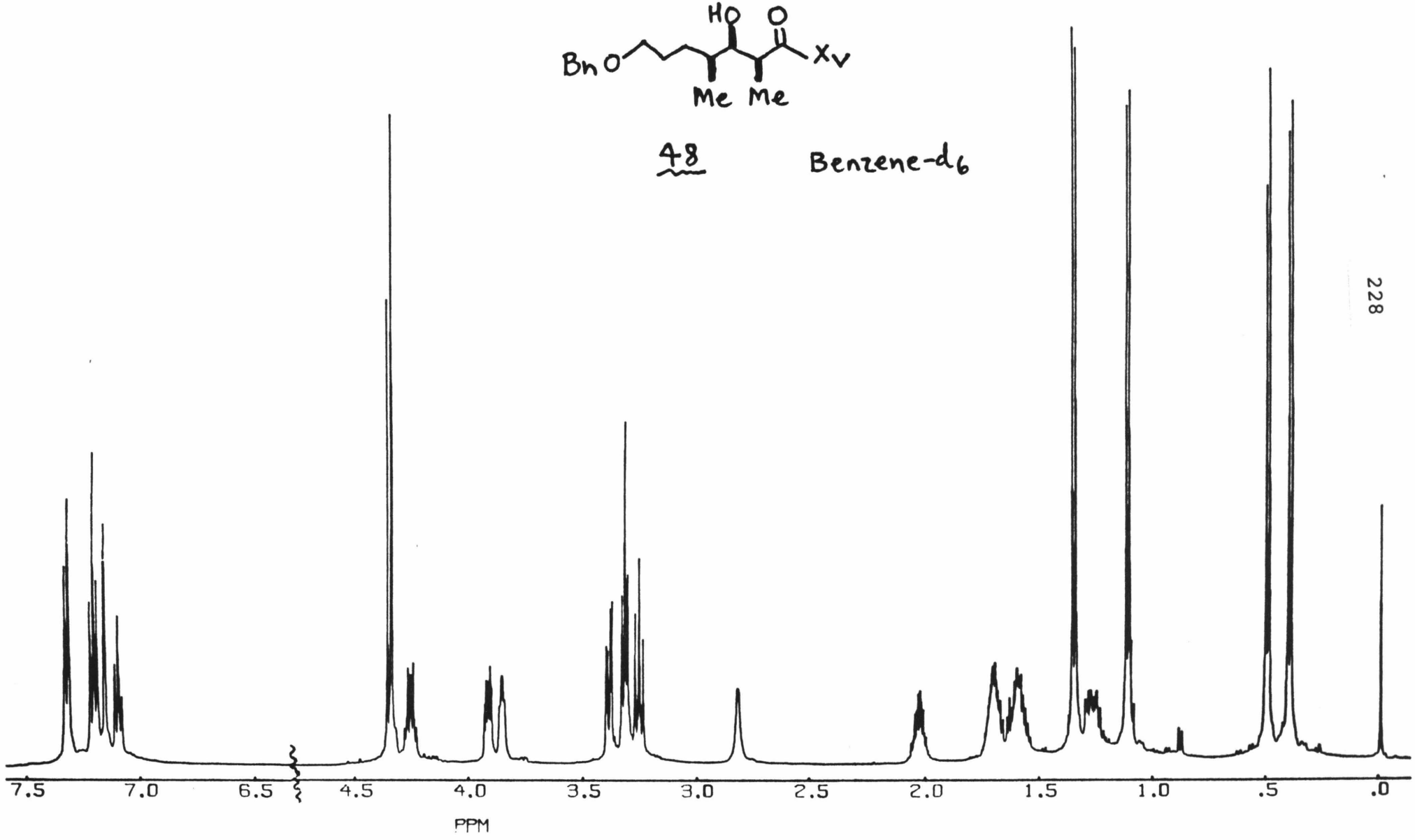
Benzene-d6

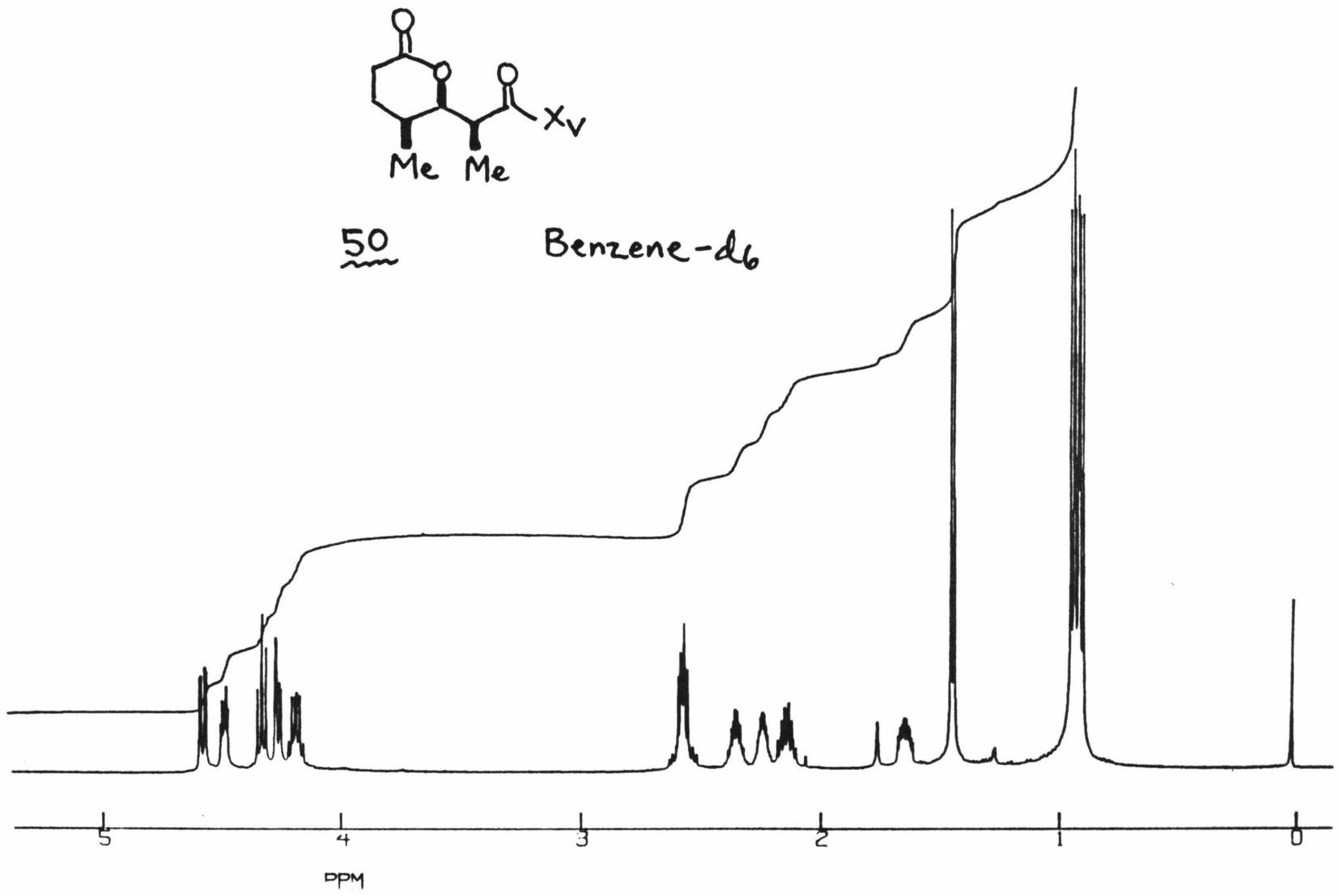

BnO
H
Me2
Me3
HO
Me1
OH
39
Benzene-d6
1.03 ppm
Me2
1.133
Me1
1.075 ppm
Me3
5
4
3
2
1
0
PPM

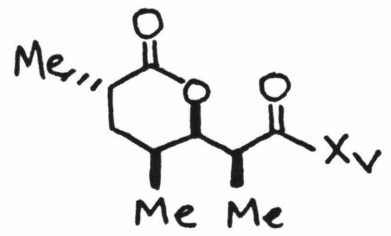


40

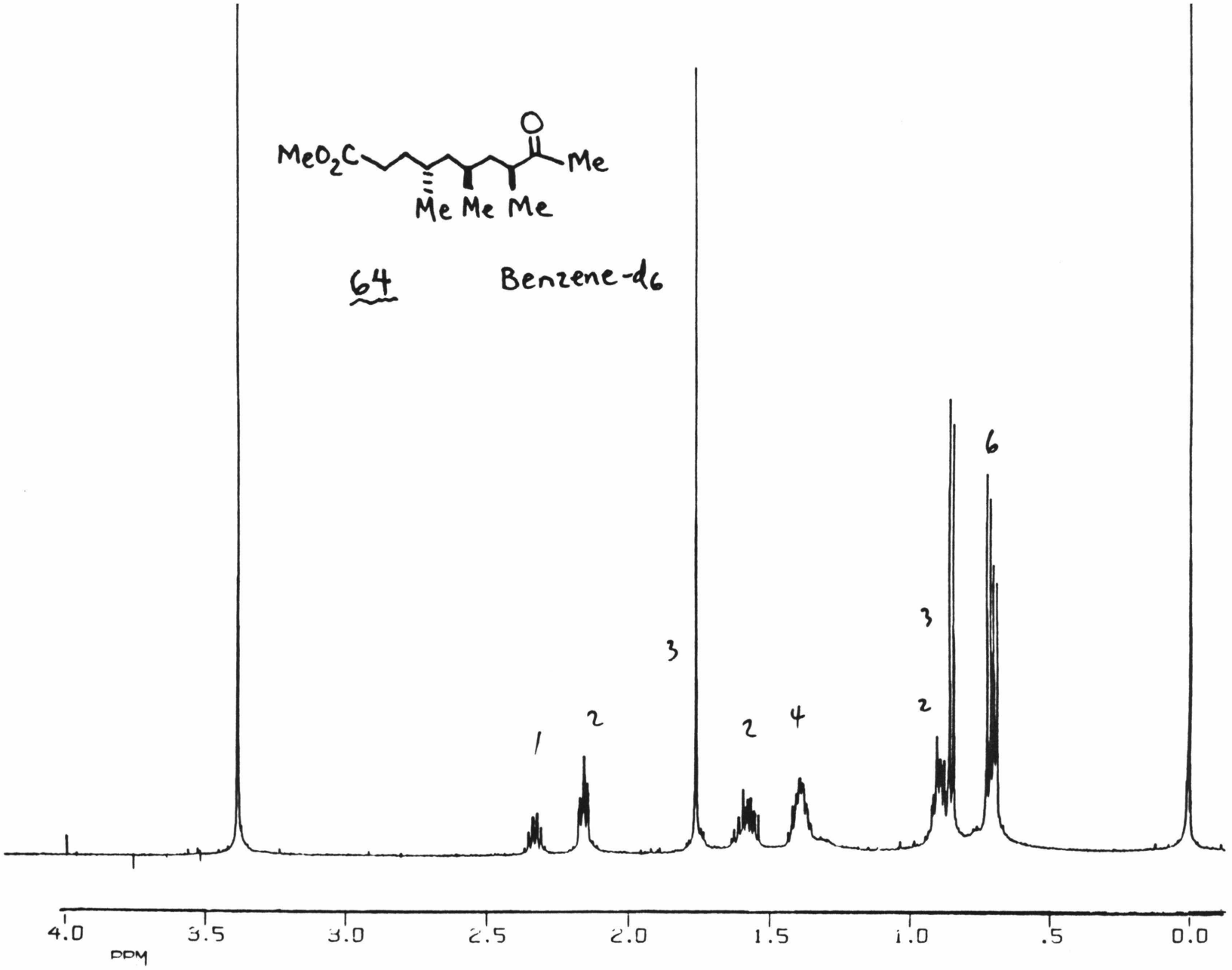
Benzene-d_6


HO
O
BnO
Xv
Me Me
48
Benzene-d6
228
7.5
7.0
6.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
.0
PPM


Me Me
Xv
50
Benzene-d6
5
4
3
2
1
0
PPM



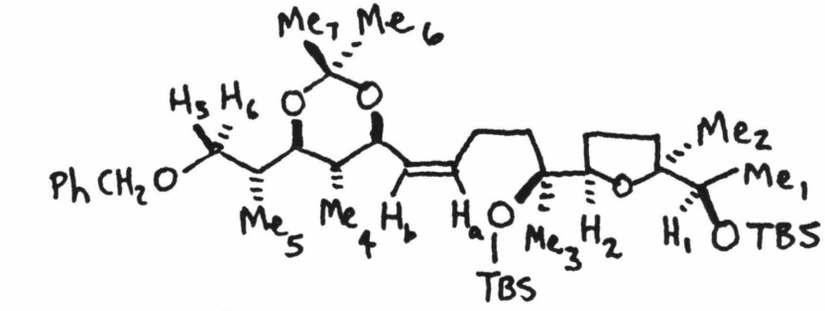
51 Benzene-d6


MeO2C
Me
Me Me Me
64
Benzene-d6
1
2
3
2
4
3
2
6
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

Decoupled Spectrum

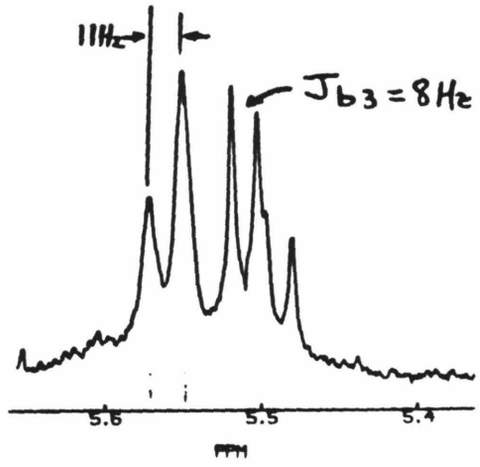
Irradiated 2.2-2.4ppm

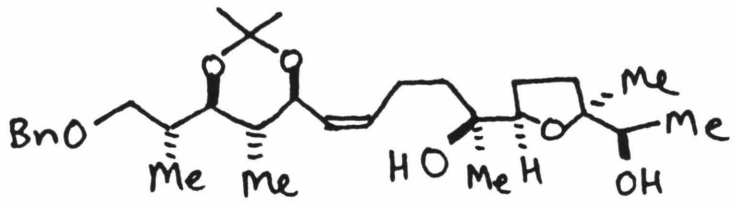
$J_{a,b}$ = 11 Hz



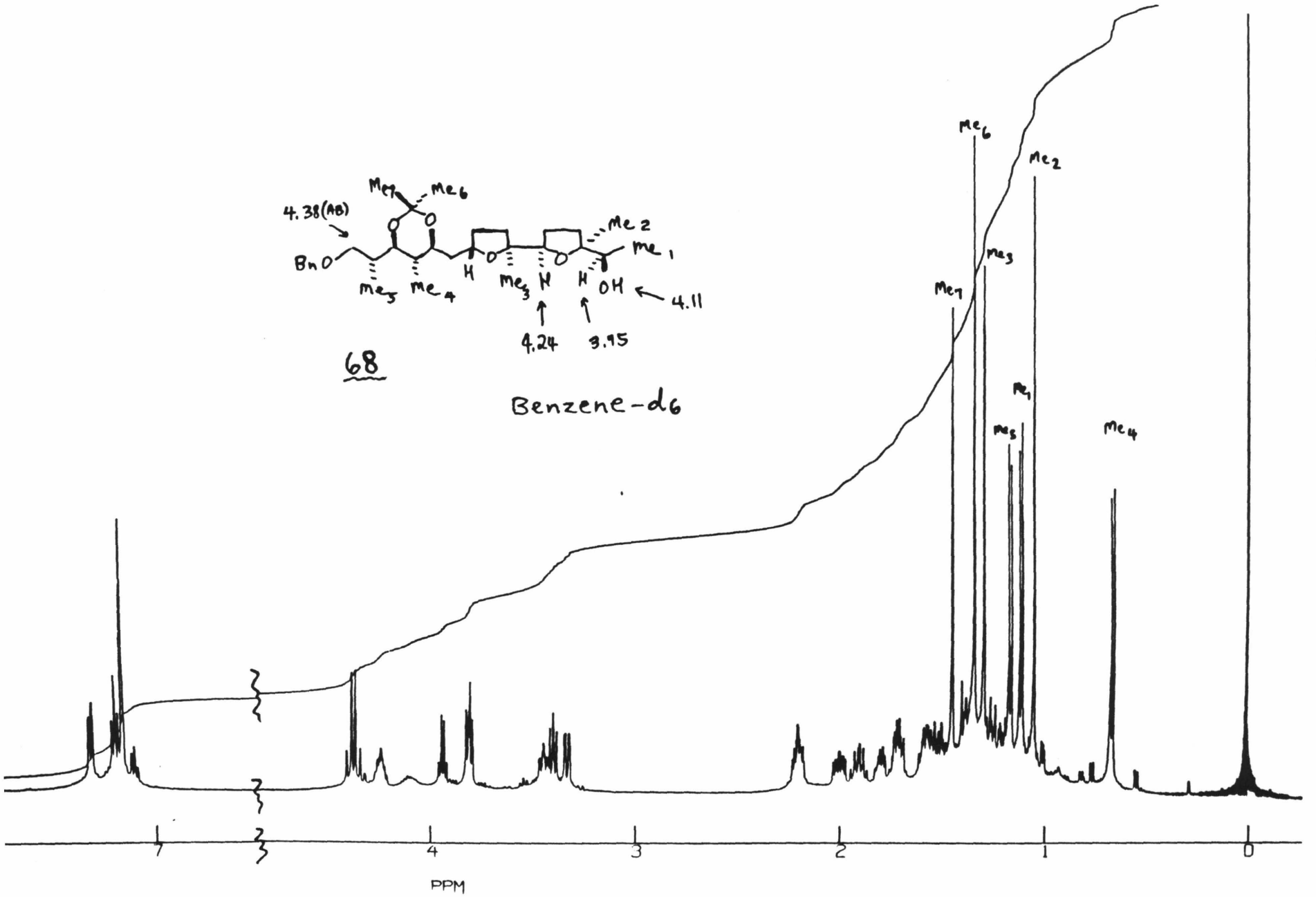
66

Benzene-d6

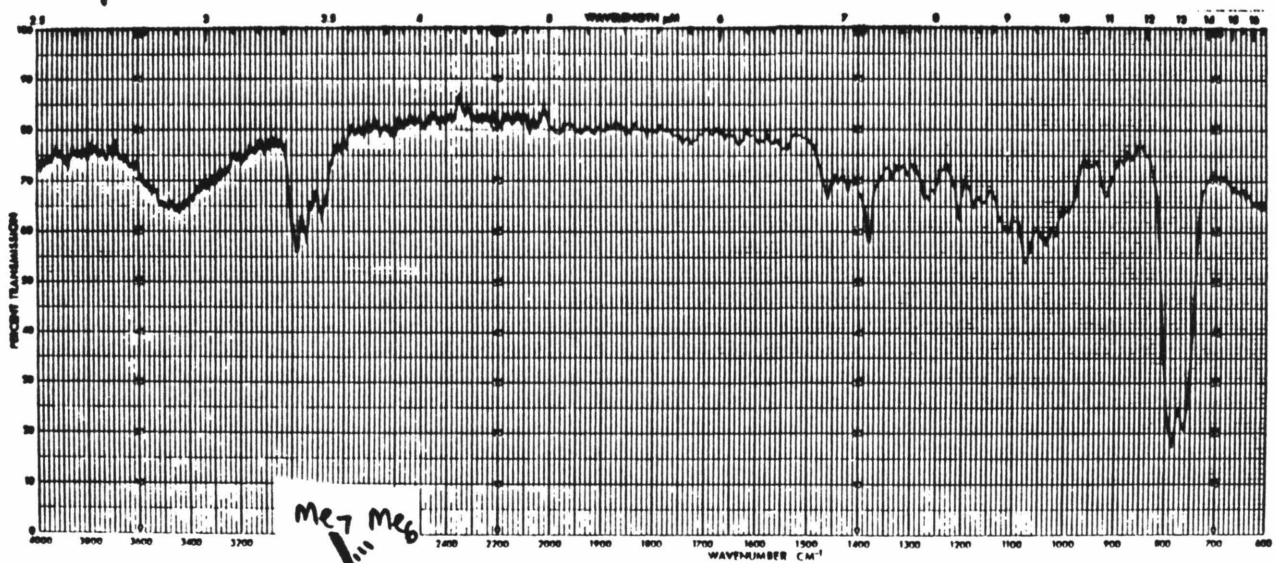


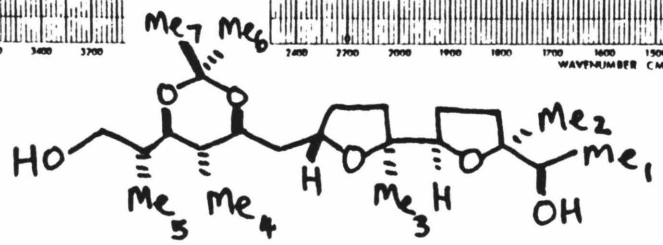


67 Benzene-d_6


4.38(AB)
BnO
Me7
Me6
Me2
Me1
Me5
Me4
Me3
H
H
H
OH
4.11
4.24
3.95
68
Benzene-d6
Me6
Me2
Me7
Me3
Me1
Me5
Me4
7
4
3
2
1
0
PPM

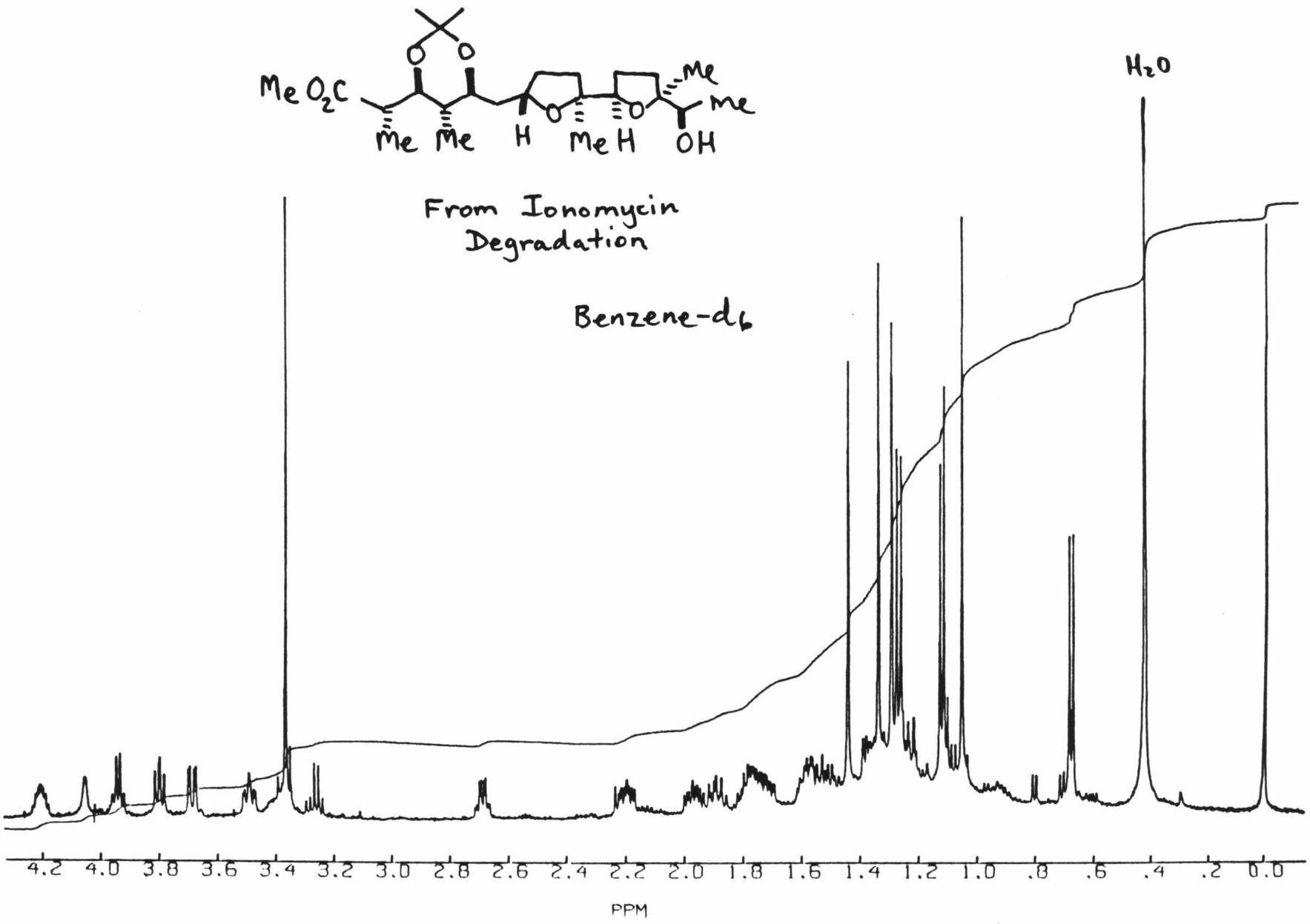
CCl_4

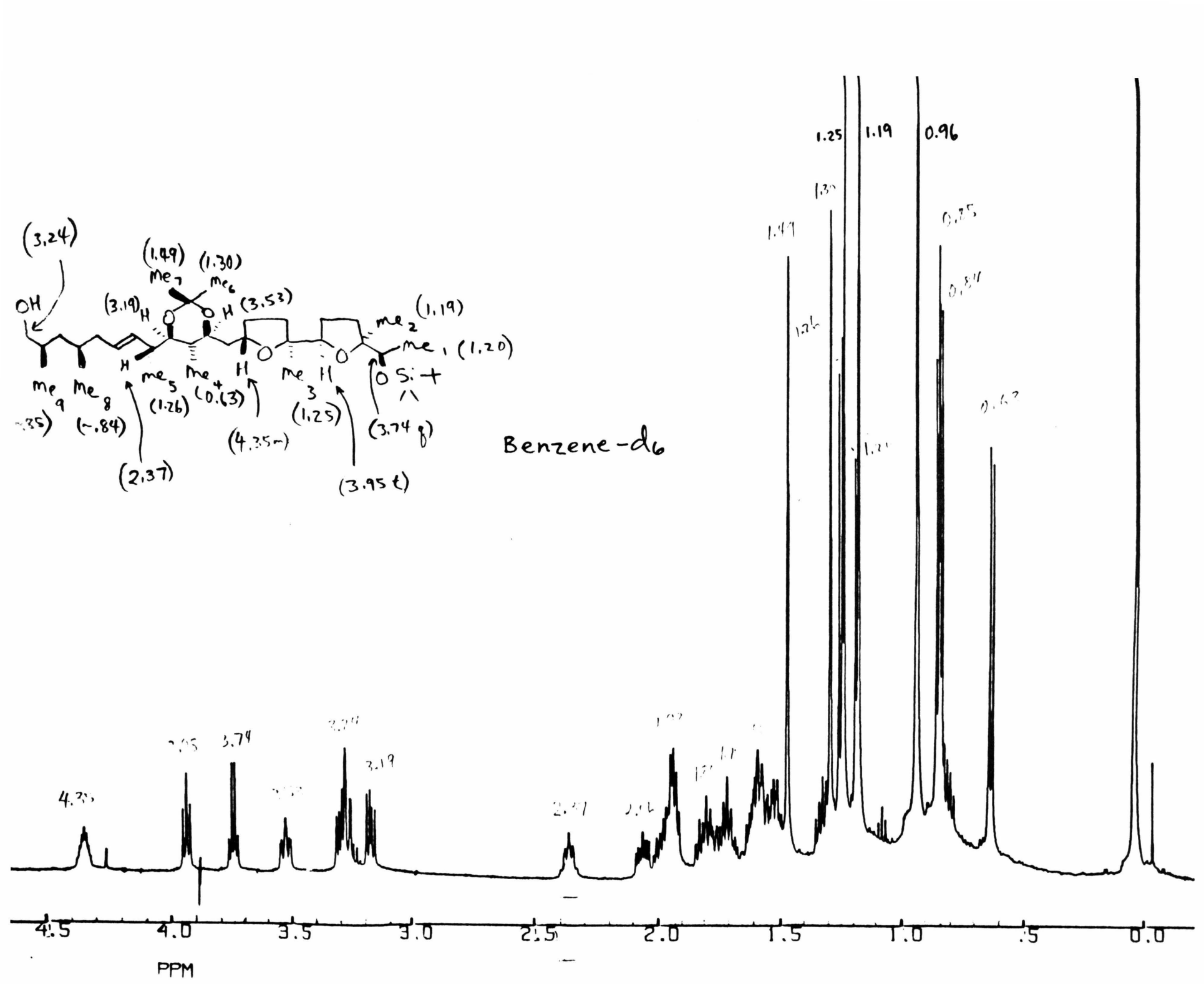


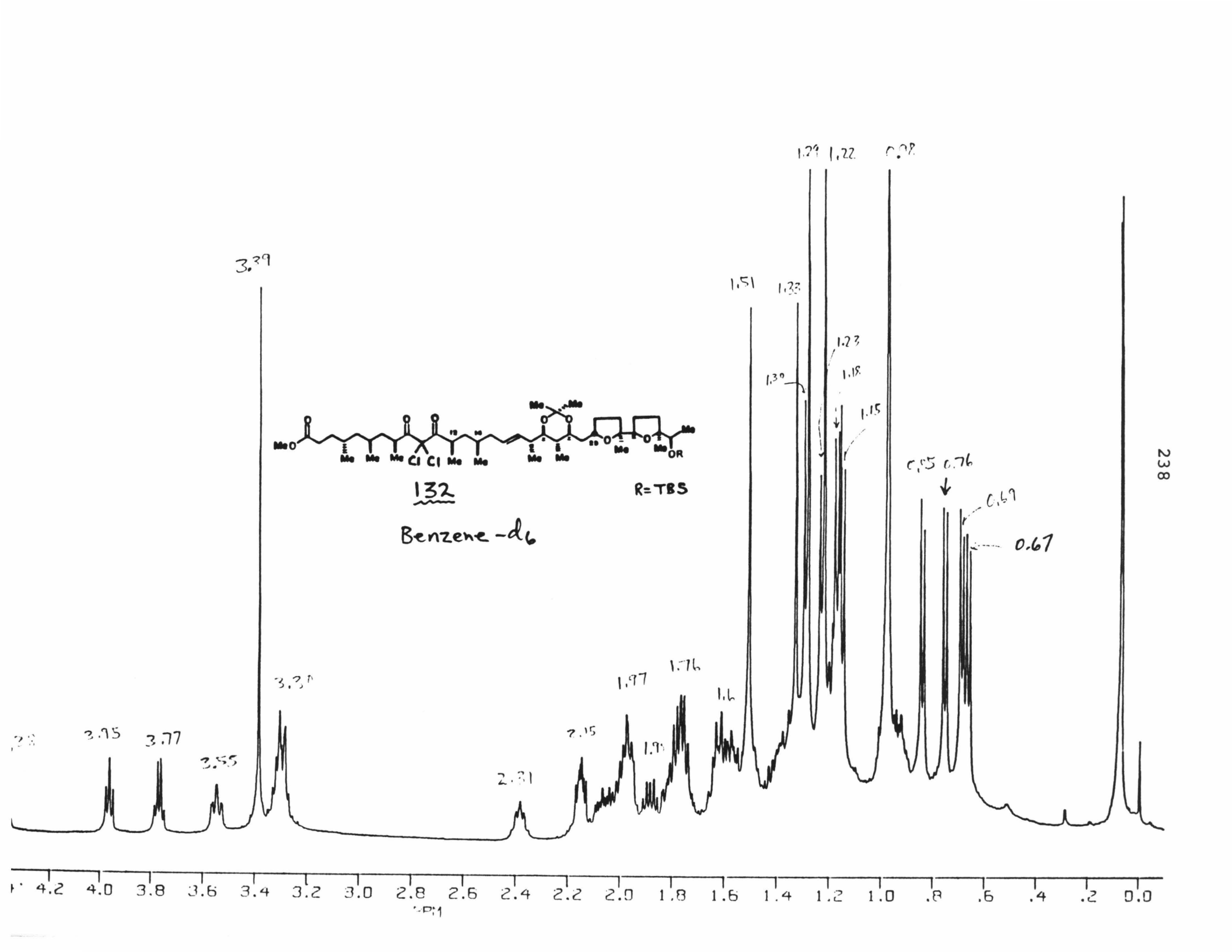


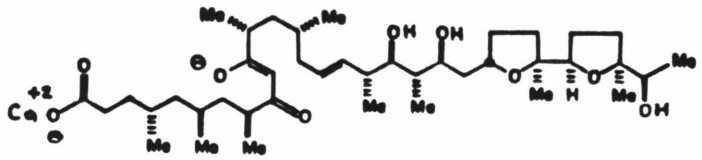
75

Benzene-d_6


MeO2C
Me
Me
Me
H
Me
H
OH
Me
H2O
From Ionomycin
Degradation
Benzene-d6
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
.4
.2
0.0
PPM

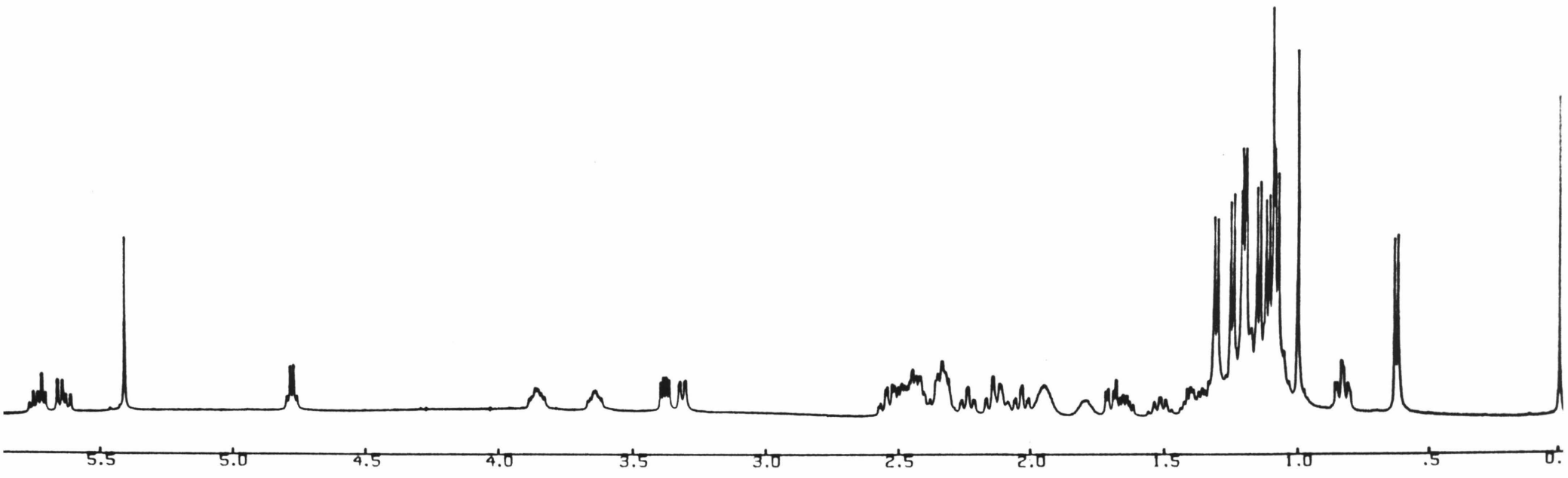

(3.24)
OH
(1.09)
(1.30)
Me7
Me6
(3.19)
H
O
H
(3.53)
Me2
(1.19)
Me1 (1.20)
H
Me5
(1.26)
Me4
(0.63)
H
Me3
H
(1.25)
O Si +
Me9
Me8
(~.84)
(2.37)
(4.35 m)
(3.95 t)
(3.74 q)
Benzene-d6
1.25
1.19
0.96
4.35
3.74
3.19
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

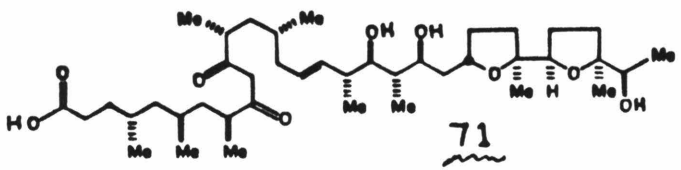

3.39
1.51
1.33
1.29
1.22
1.23
1.18
1.15
1.30
0.98
0.95
0.76
0.69
0.67
3.95
3.77
3.55
3.31
2.31
2.15
1.97
1.76
1.6
238
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
.4
.2
0.0
PPM
132
R=TBS
Benzene-d6



Calcium Salt

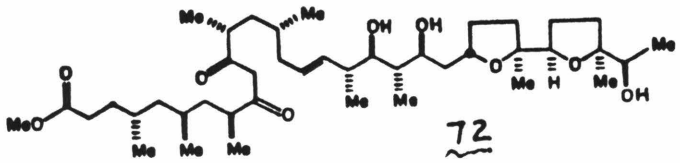
Benzene-d_6





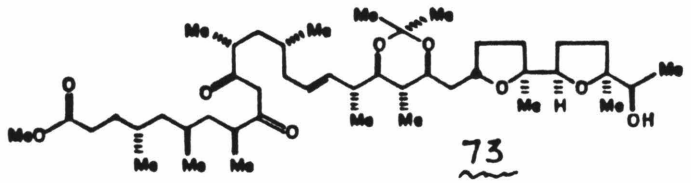
71

Benzene-d_6



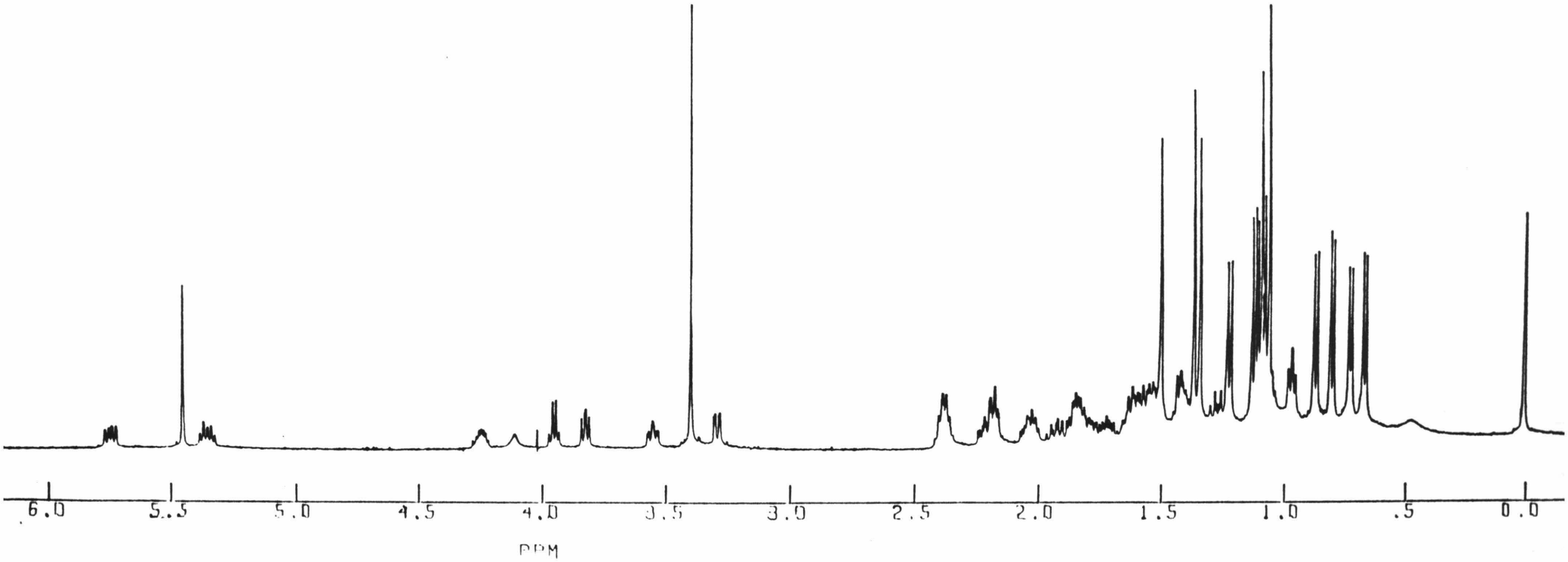
72

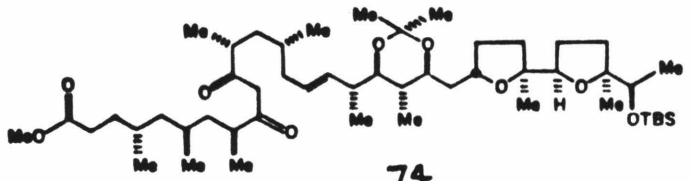
Benzene-d_6



73

Benzene-d_6





74

Benzene-d_6

243

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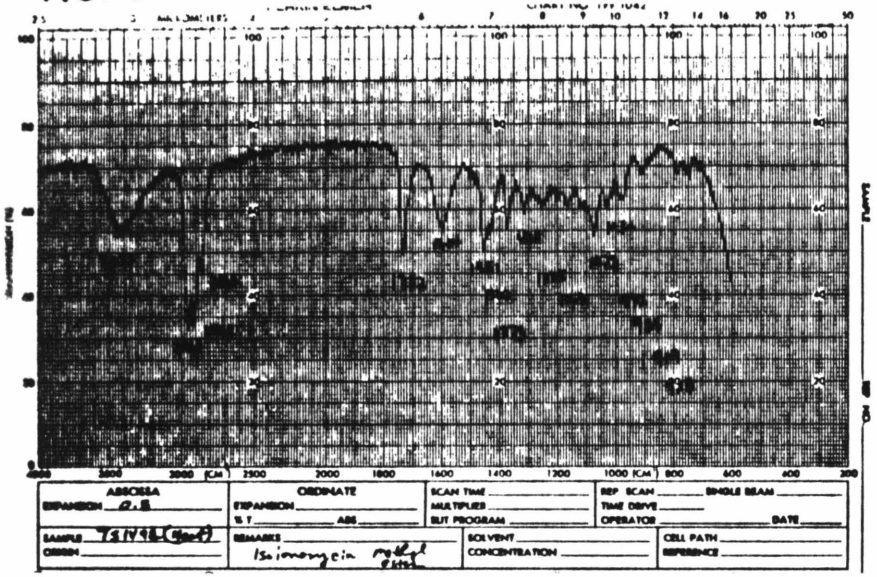
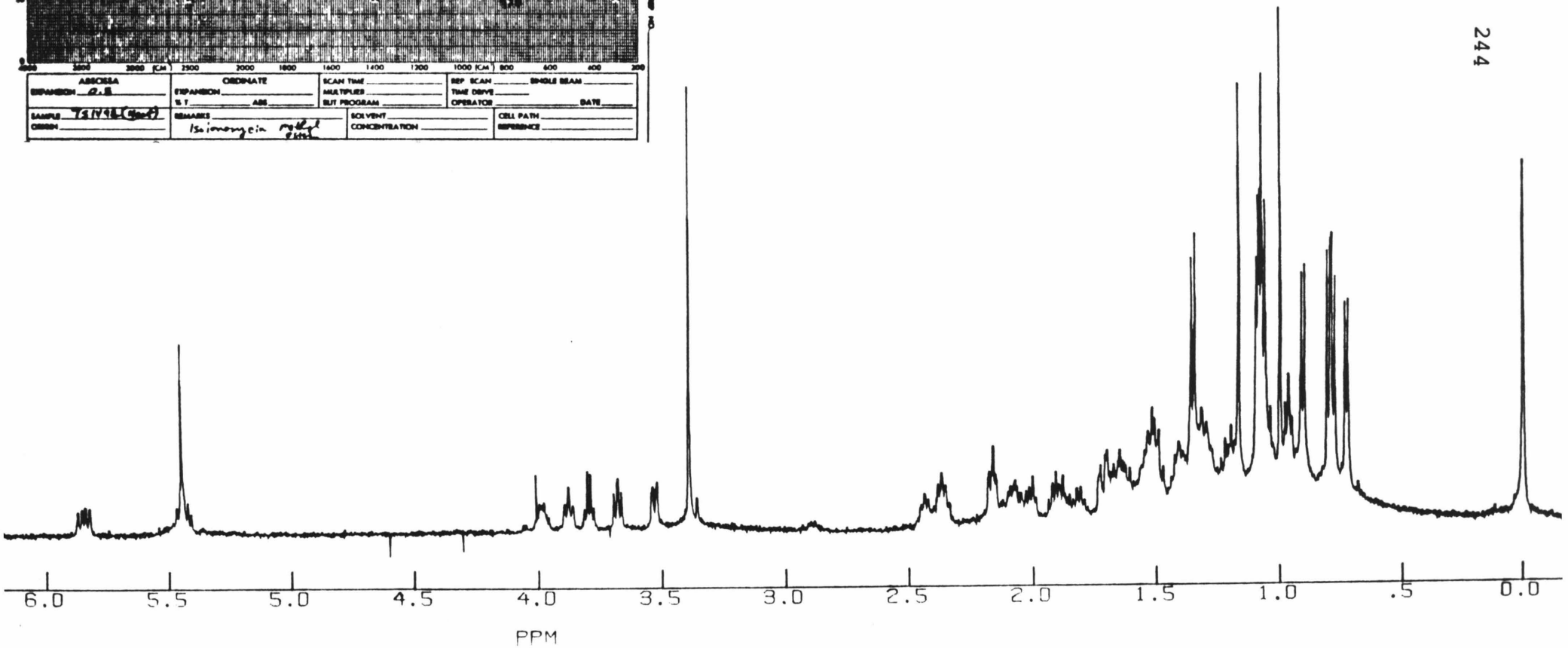
PPM

Neat



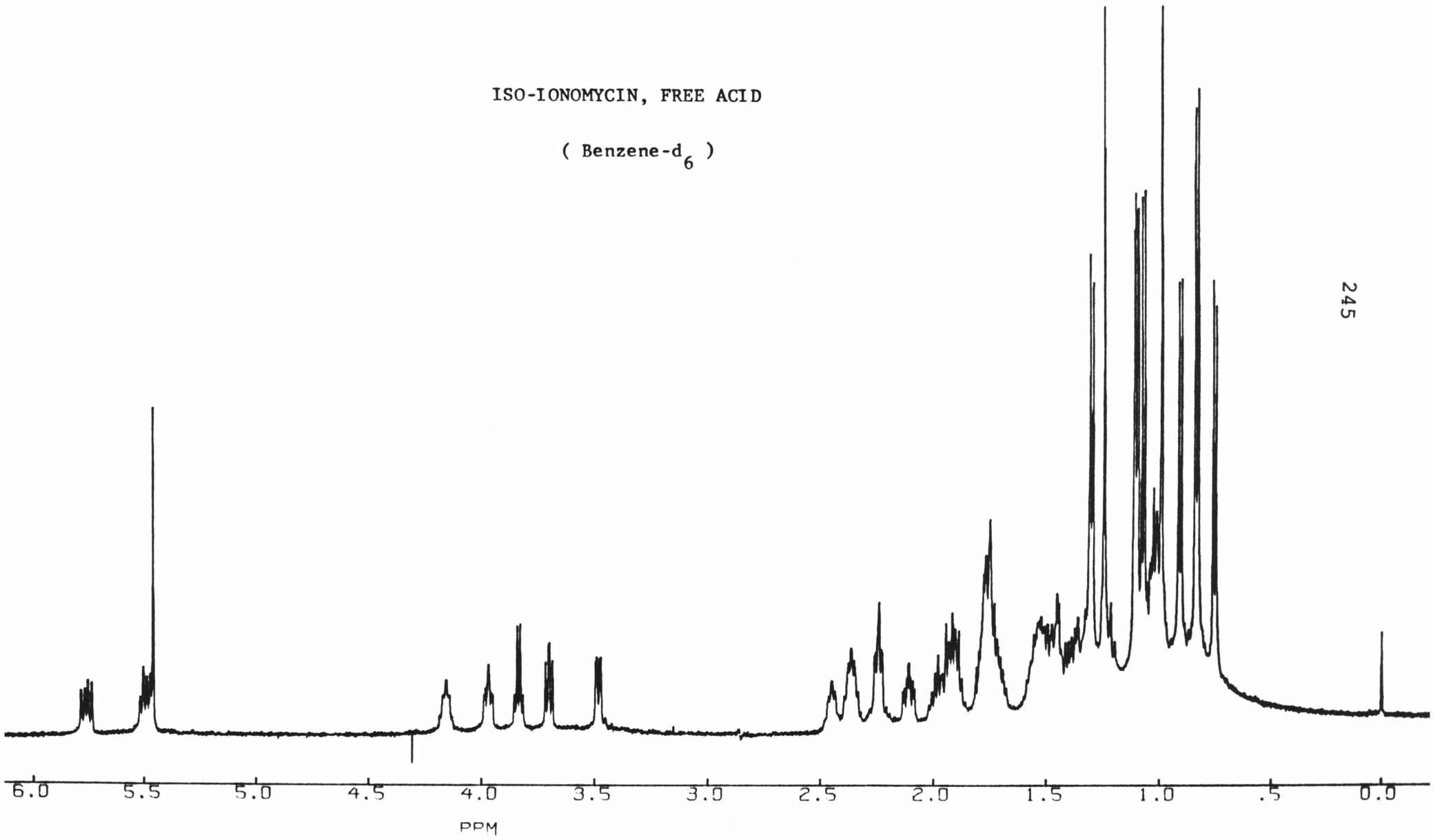
ISO-IONOMYCIN, METHYL ESTER

(Benzene-d_6)



ISO-IONOMYCIN, FREE ACID

(Benzene-d_6)



ISO-IONOMYCIN, CALCIUM SALT

(Benzene-d_6)