SYNTHESIS OF A-23187 AND RELATED MODEL COMPOUNDS

Thesis by

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To Cheryl

and

To My Mother and the Memory of My Father

"A candle loses nothing by lighting another."

Anonymous

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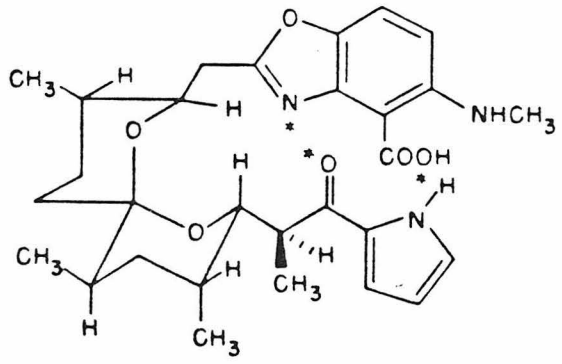
ABSTRACT

A-23187 is a calcium specific ionophore isolated from Streptomyces chartreusis. Syntheses of model systems containing the 1,7-dioxaspiro[5.5]undecane ring system and the total synthesis are discussed. Based on results from the total synthesis the absolute configuration of A-23187 is assigned.

A new ionophore, X-14547A, was recently discovered which, like A-23187, contains a pyrrole ketone subunit. New methodology designed to introduce the pyrrole unit via an N-protected 2-pyrrylcuprate is presented.



A-23187

[6S*-{6α(2S*,3S*),8β(R*),9β,11α}]-5-(Methylamino)-2-[{3,9,11-trimethyl-8-|1-methyl-2-oxo-2-(1H-pyrrol-2-yl)-ethyl|-1,7-dioxaspiro[5.5]undec-2-yl}methyl]-4-benzoxazole-carboxylic acid.

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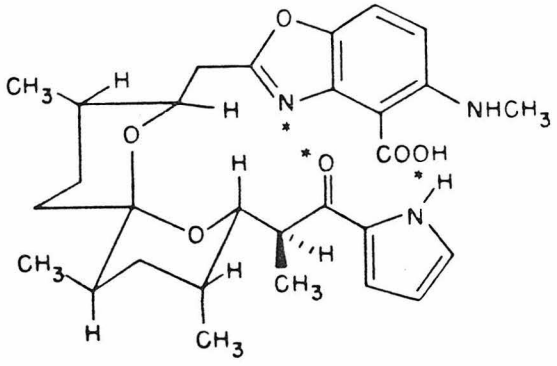
CHAPTER I

Chemistry and Biology of A-23187

Introduction

In the past ten years a large number of biologically interesting mold metabolites have been isolated.[1,2] Among these metabolites is a large and growing class known as the polyether antibiotics.[3] The ability of some of these to form lipid soluble complexes with cations and provide a vehicle to transport the cations across lipid barriers led to their being named ionophores.[4]

Several reviews have appeared on the topic of ionophores.[5-9] Recently, Westley published a review of the carboxylic acid ionophores in which he classifies them on the basis of structure.[2] The four classes are: monovalent polyethers, monovalent glycoside polyethers, divalent polyethers and divalent pyrrole ethers. A-23187 (1) is the only known member of the last class.



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Chemistry and Structure

Although A-23187 was isolated in 1972,[10] the structure was not determined until 1974. Proton and carbon-13 nuclear magnetic resonance and infrared spectroscopy indicate the presence of the pyrrole ketone and substituted benzoxazole side chains.[11,12] X-ray crystallography shows that the backbone is a 1,7-dioxaspiro[5.5]undecane ring system.[11,13] This makes A-23187 one of a small class of molecules to contain such a ring system, others being: Oscillotoxin A,[14] Aplysiatoxin,[15] Salinomycin,[16] Narasin,[17] Antibiotic B-41,[18] Milbemycin,[19] Oligomycin B,[20] and Rutamycin.[21]

X-ray studies of the calcium salt indicate that only four bonds have any rotational freedom[22] and that the

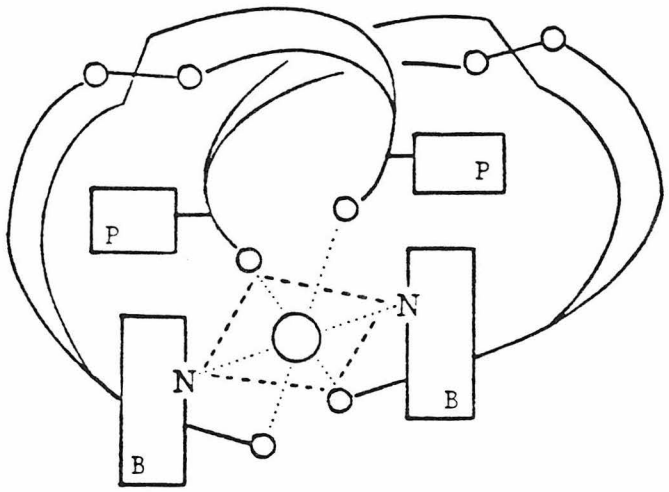


Figure 1

Divalent Ion Binding Selectivity

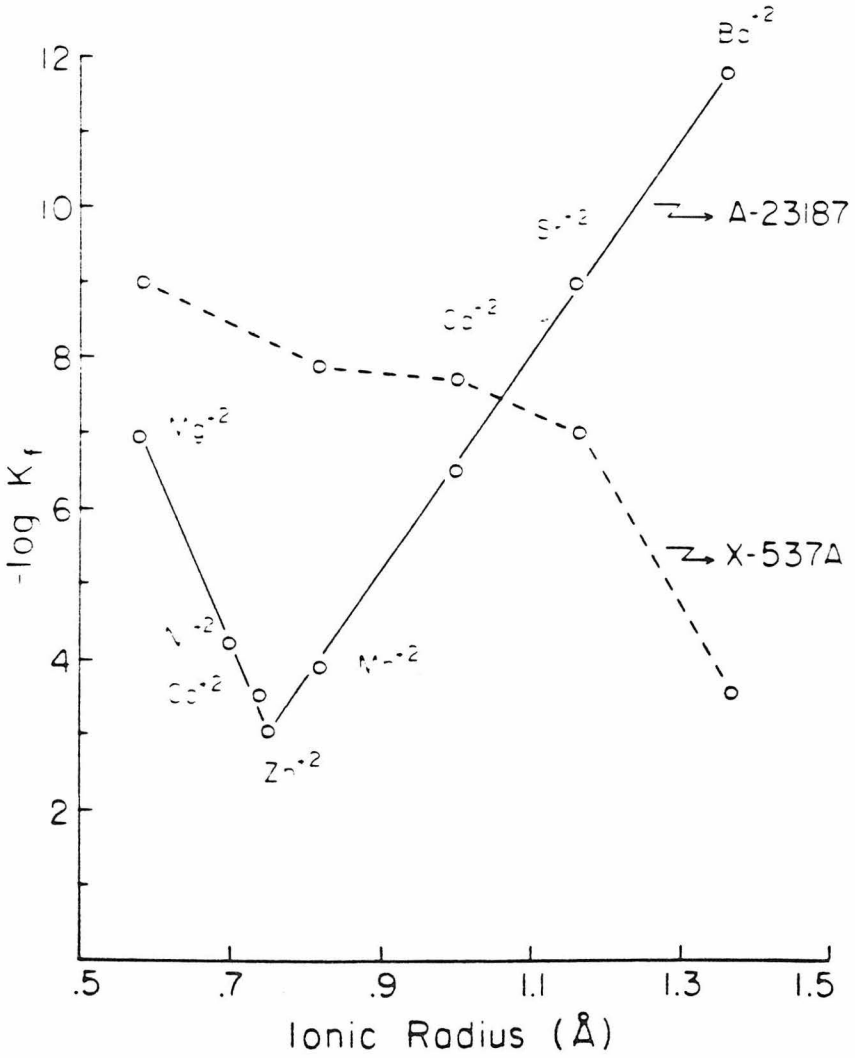


Figure 2

complex contains two molecules of A-23187 in an octahedral configuration surrounding one calcium ion.[13,22] NMR studies in solution (proton and carbon-13) also indicate the 2:1 octahedral complex with complexation occurring at the carboxylate, benzoxazole nitrogen and pyrrole carbonyl[22] (see Figure 1 and starred positions in structure 1).

Binding affinities reveal another unique feature which makes A-23187 especially useful for biochemical research.[23,24] A-23187 is very selective for divalent cations in the presence of monovalent cations. More specifically, it selects for calcium over other divalent species (see Figure 2).[25] Rigidity of the backbone structure is probably responsible for this by maintaining a cavity size which cannot vary over a large range of sizes.[22]

Biological Significance

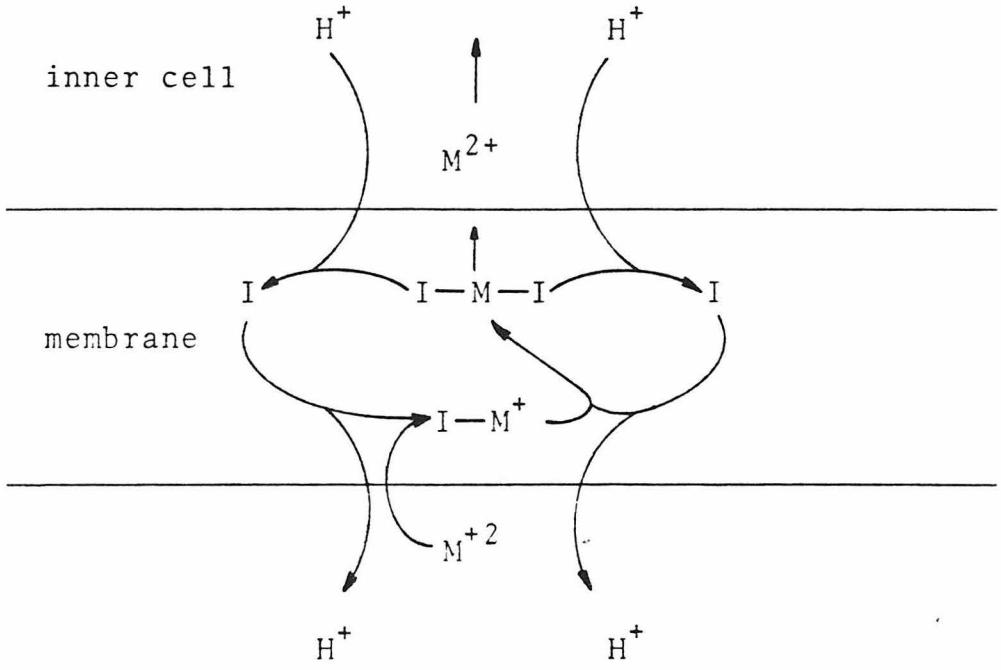
Among the divalent cations involved in physiological processes, calcium ion is perhaps the most ubiquitous in location and diverse in function. For example, alteration of cellular calcium levels is an important component of cellular control mechanisms. Especially sensitive are energized structures in cells such as mitochondria.[26] Calcium ion flow down concentration gradients is important

in muscle action.[27] Steady-state structures of cell membranes and walls, cell-cell conglomerates and structural units inside cells are also controlled by calcium mediated processes.[27] Evidence also exists that calcium is an important control mechanism in the synaptic transmission of nerve impulses, perhaps by mediating sodium and potassium gates.[28]

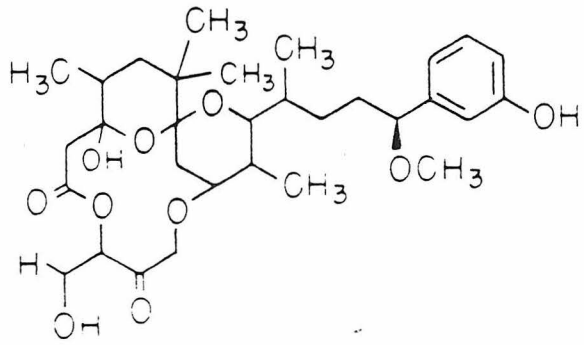
Clearly, any agent that influences the binding of membrane-bound or protein-bound calcium, or that alters the rate of transport of calcium across membranes would be a valuable biochemical probe. The ion specificity of A-23187, and its fluorescence (allowing for easy detection and analysis of its environment) make A-23187 a very potent probe into calcium mediated cell functions. As a consequence A-23187 is increasingly being used to study complex physiological processes such as secretion phenomena,[29] parthenogenesis,[30] membrane permeability,[24,31] lymphocyte transformation,[32] sperm motility,[33] glucogenesis,[34] and platelet function, structure and metabolism.[35]

Although nothing specific is known about the exact mechanism of calcium complexation and transport, several studies have shown that each calcium ion transported into the cell corresponds to an outward flux of two protons.[25] One mechanism to account for this is shown in Scheme 1.[36]

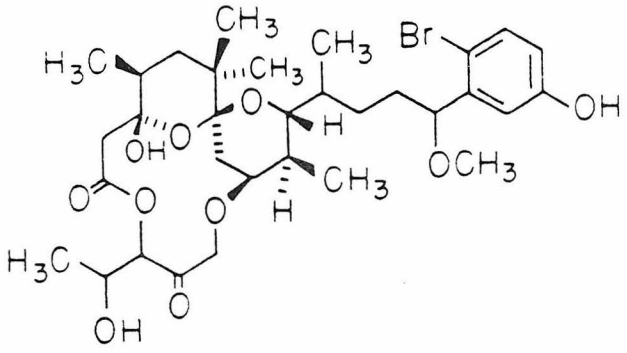
Scheme I



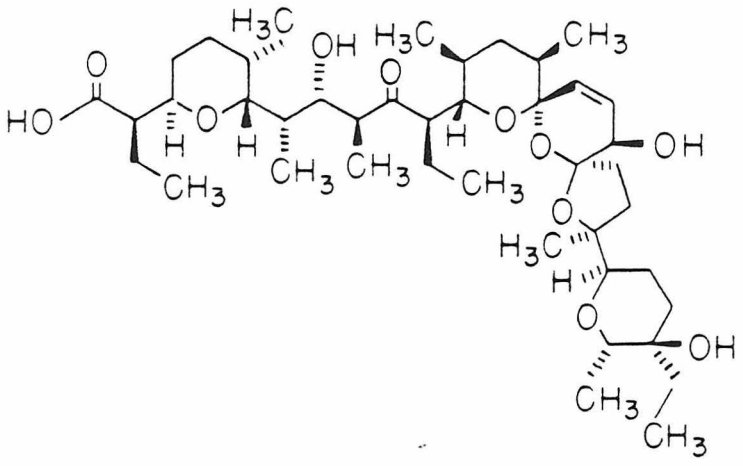
The 2:1 stoichiometry of the complex has recently been questioned. Hunt and his coworkers have evidence of an active transport species in a 1:1 ratio.[37,38] His results are based on NMR studies of the transport of praeseodymium ions across artificial lipid membranes. Most indications, however, are that, at least in vivo, the active transport species is a 2:1 complex.[12,25,39]



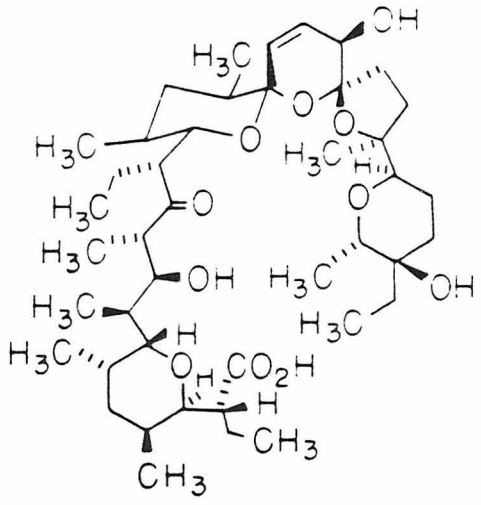
Oscillotoxin A



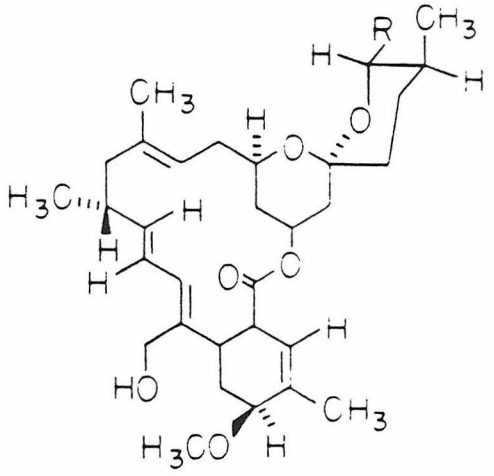
Aplysiatoxin



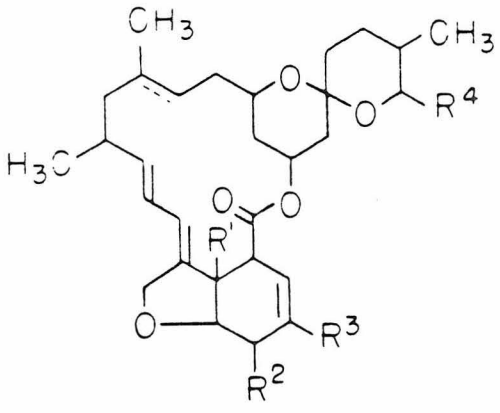
Salinomycin



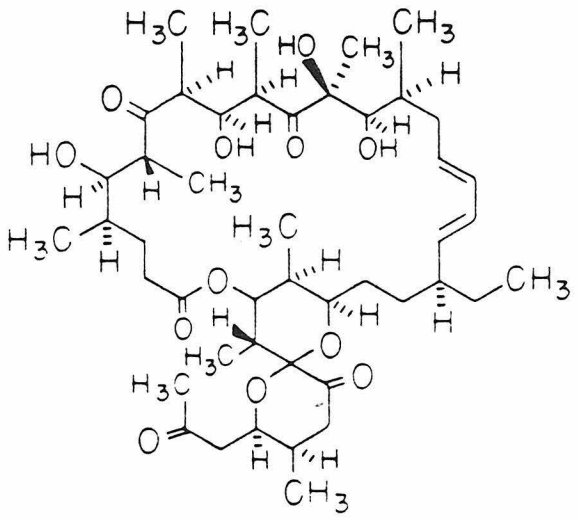
Narasin



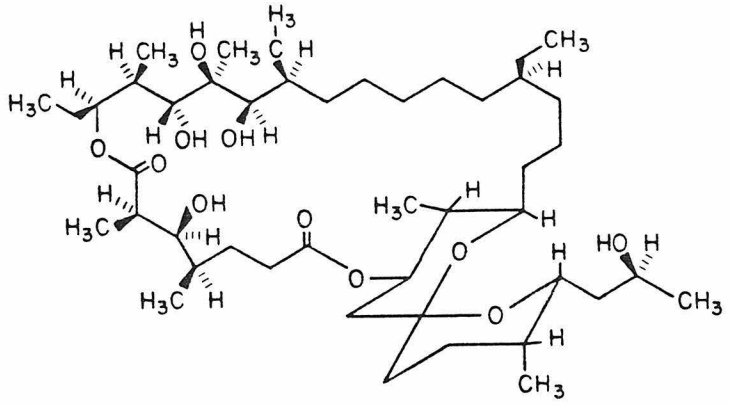
Milbemycin



Antibiotic B-41



Oligomycin B



Rutamycin

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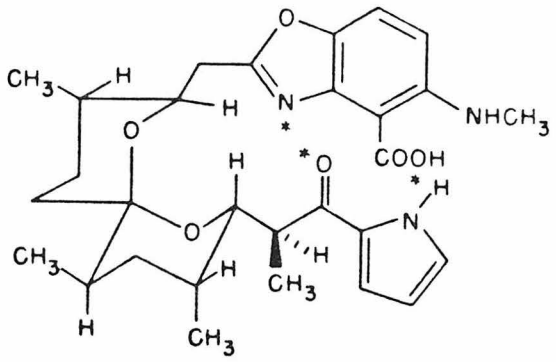
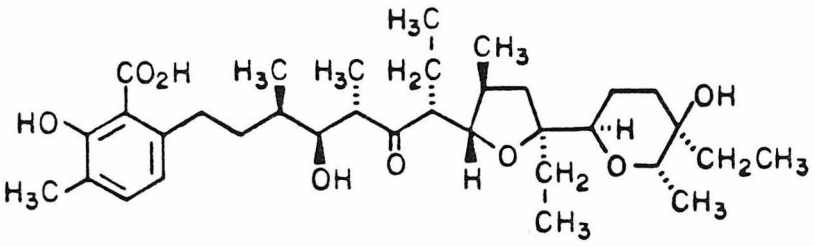
CHAPTER II

Synthesis of Model Compounds

Since their isolation, the polyether antibiotics have aroused much interest in the chemical and biochemical communities because of their interesting, highly complex structures and their ability to complex and transport a wide variety of cations across lipid barriers. The latter characteristic led to their being named ionophores.[1] Several reviews of the antibiotic ionophores are currently available.[2] Historically, three of the most important for clinical study have been A-23187 (1),[3] Lasalocid acid (2)[4] and Monensin (3).[5] Monensin has successfully been used as a poultry and livestock feed additive, greatly increasing weight gains,[6] while Lasalocid acid and A-23187 have proven useful in biochemical studies due to their ability to transport mono- and divalent ions, potent biological cations, across lipid membranes.[7,8]



1 (Calcimycin)



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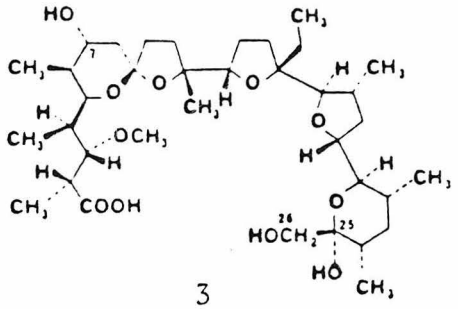


3

Since, as shown in Figure 1,[8] A-23187 is much more selective for calcium ions in the presence of other mono- and divalent cations than is Lasalocid acid, and since its fluorescence allows for easy detection and analysis, A-23187 has become a key biochemical tool for investigating calcium-mediated cellular phenomena.[9] As a result of this interest in A-23187, we felt that the synthesis of structurally related bidentate analogs would prove useful. Also, although the structure and relative stereochemistry have been firmly established by proton- and carbon-NMR and by X-ray analysis,[3,10-13] total synthesis would allow assignment of the absolute configuration of A-23187.

Divalent Ion Binding Selectivity

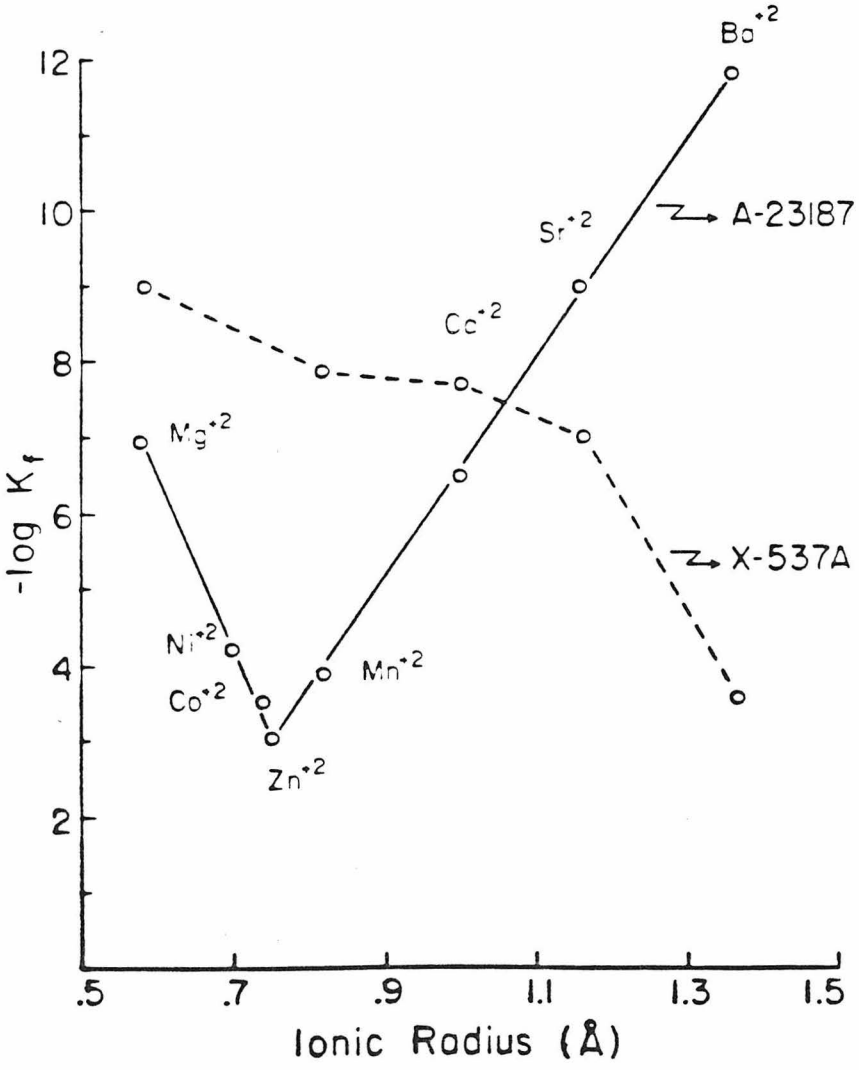
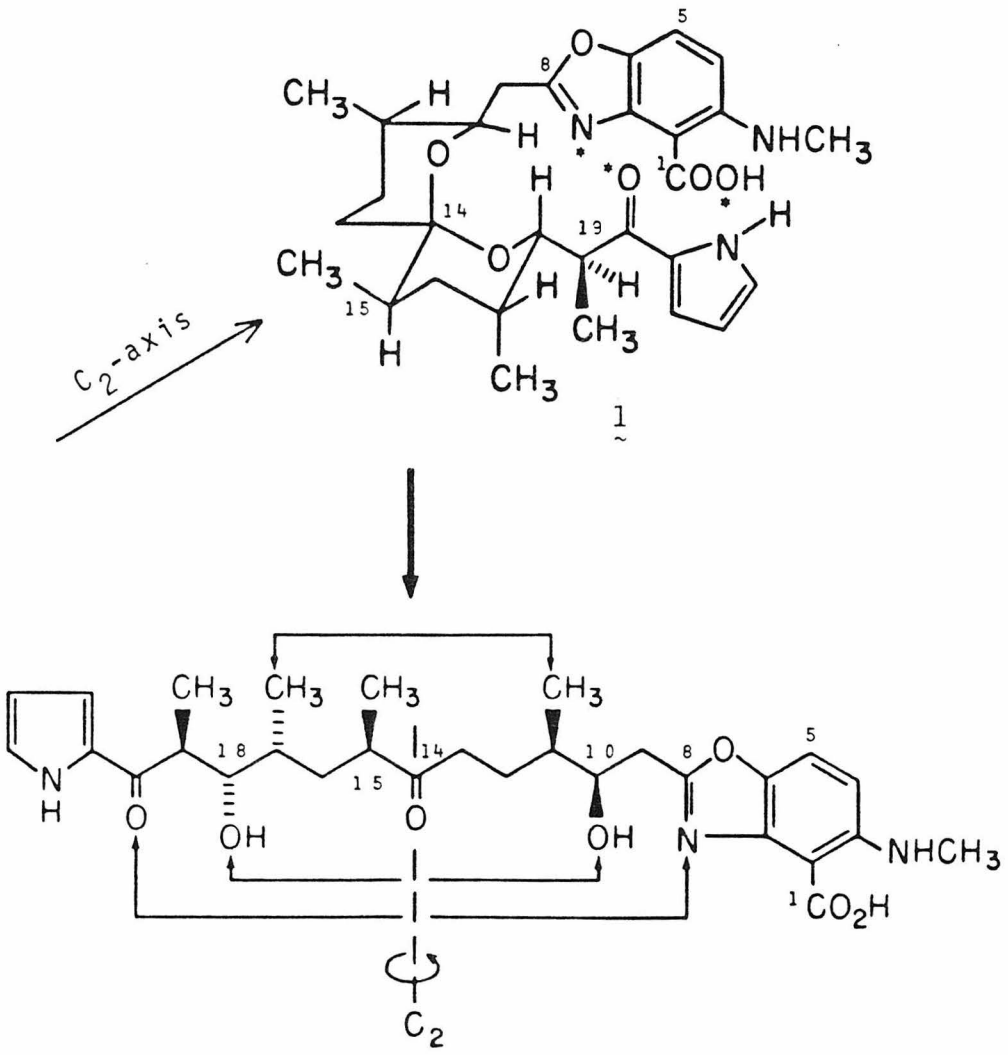


Figure 1

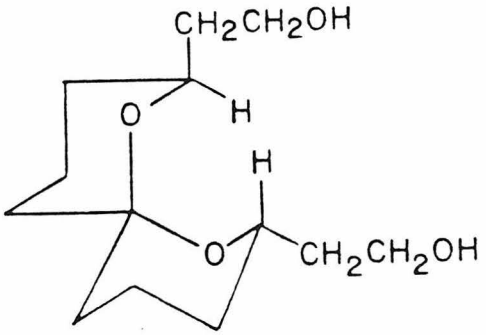
Our retrosynthetic planning for the total synthesis centered on the formation of the 1,7-dioxaspiro[5.5]undecane ring system. This rare structural feature affords a high degree of structural rigidity to A-23187 and is probably largely responsible for the observed complexation selectivity. The spirane system is also interesting since only a few other molecules contain it, most of them also ionophores isolated from mold metabolites: Salinomycin,[14] Narasin,[15] Milbemycin,[16] Antibiotic B-41,[17] Oligomycin B[18] and Rutamycin.[19] Two others, Aplysiatoxin[20] and Oscillotoxin,[21] have recently been isolated from marine sources.

The retrosynthetic plan as detailed in Scheme I immediately poses two problems. First, would internal ketalization occur to give the proper configuration at the spiro-carbon (C_{14}) and second, would the methyl group at C_{15} equilibrate to the equatorial configuration, thus allowing its introduction in a non-stereospecific reaction? An investigation of these concepts in models was deemed important, since not only would the results be applicable to the total synthesis of A-23187, but they could also be applied to the construction of bidentate analogs of narrowly defined cavity size, perhaps useful in ion-selective electrodes. Chiral synthesis could also afford ligands useful in asymmetric reductions.

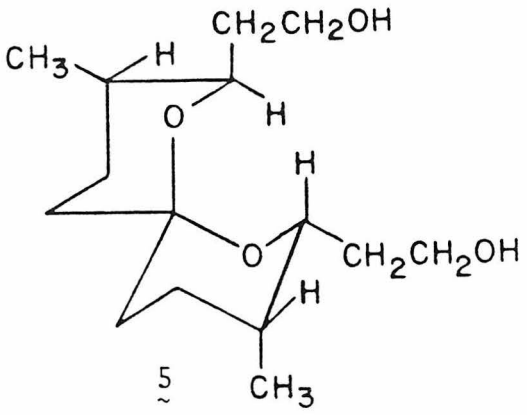
Scheme I



Hoping to utilize the latent C_2-axis of symmetry revealed in Scheme I, we chose spiranes 4 and 5 as our initial synthetic goals to test the spirane closure.



4

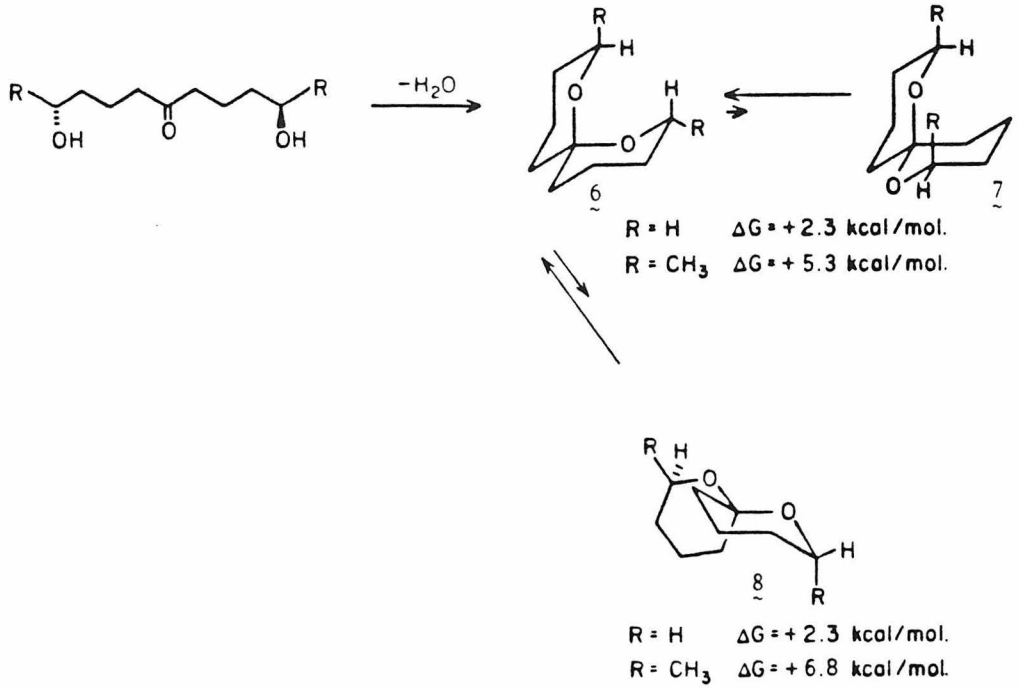


5

As depicted in Scheme II, closure of an acyclic ketone diol can give not only two configurational isomers, 6 ⇌ 7 but also two conformational isomers, 6 ⇌ 8. In determining which isomer would predominate, two considerations are of major importance. First are the steric interactions caused by axial substituents in a cyclohexane ring.[22] Second is the anomeric effect which favors the axial orientation of a polar group at C_2 of a pyran ring.[23] Using standard A values[22] and a value of 0.6 kcal/mole[24] for the anomeric effect, we calculated that the diaxial oxygen configuration (6) should be favored by at least 2.3 kcal/mole over the next most stable configuration, (7). Correspondingly, conformation 6 is also at least 2.3 kcal more stable than conformation 8 (see Appendix I for a more complete discussion).

Scheme II

Stereochemical Considerations



The synthesis of spiranes 4 and 5, to test the above hypothesis, followed the previously published route as depicted in Scheme III.[25,26] Thus, treatment of dihydroanisoles 9a and 9b with ozone and *in situ* reduction with lithium aluminum hydride gave the diols 10a and 10b.[27] Even though the reaction was carefully monitored by GLC, over-oxidation was still a major problem. Attempts to overcome this by using lower temperatures were moderately successful. By operating at -78°C and using high concentrations so that the intermediate ozonide precipitated

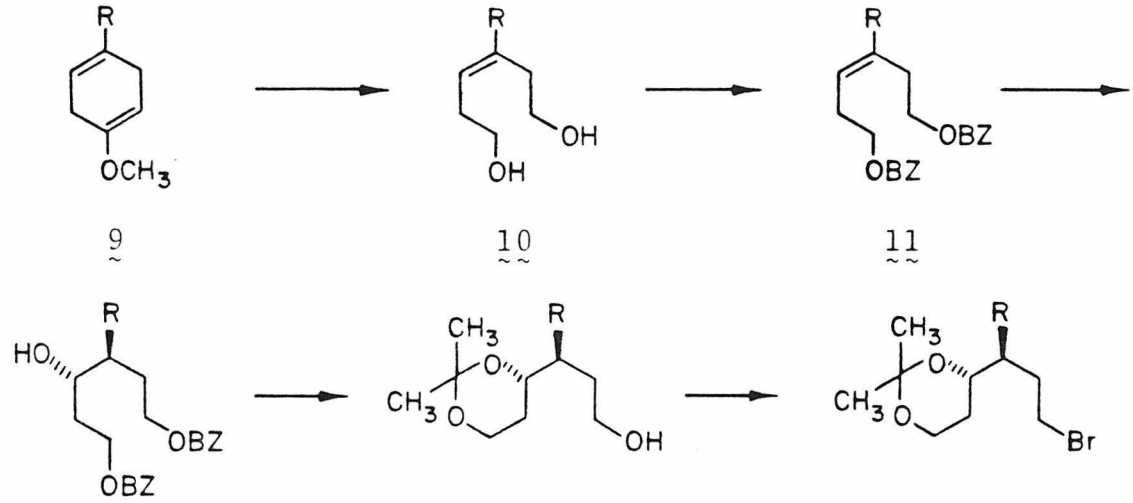
from solution, yields could be maximized at 50%. Protection of the diols by benzylation gave high yields of ethers 11a and 11b.[28] Hydroboration then gave alcohols 12a and 12b.[29] In series b, this reaction also served to cleanly establish the relative stereochemistry of the hydroxyl and methyl groups. Carbon-13 analysis indicated only one diastereomer. By using a chiral hydroborating agent we conceivably could produce chiral intermediates.[30] Direct conversion of alcohols 12a,b to the corresponding acetonide alcohols 13a and 13b was easily accomplished in high yield by hydrogenolysis in acetone over a palladium/carbon catalyst.[31] The bromides 14a and 14b were then formed by the method of Servis[32] in a 63% overall yield from diols 10a and 10b.

To assemble the backbone, we required an acyl anion equivalent. Investigation of Collman's reagent [$Na_2Fe(CO)_4$][33] or Masuyamo's reagent [$NCCH_2SC(S)N(CH_3)_2$][34] proved unsuccessful. Although 1,3-dithiane[35] gave acceptable yields, the anion of methyl methylthiomethyl sulfoxide proved superior in both yield and operational simplicity. Treatment of Ogura's reagent[36] with two equivalents of racemic bromide 14a or 14b and excess potassium hydride gave rise to racemic vinyl sulfides 16a,b and 17a,b. Isolation of these unexpected products was probably due to the presence of excess potassium hydride. Deprotonation of

Scheme III

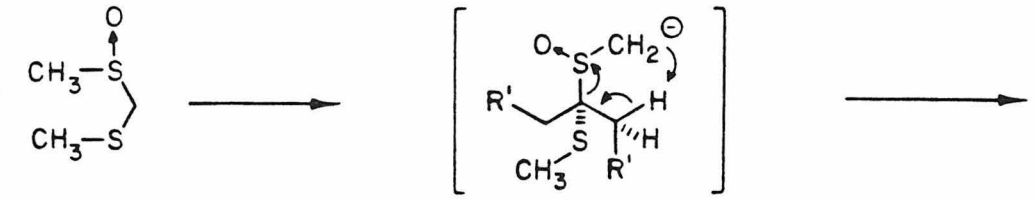
a, R = H; b, R = CH_3

BZ = CH_2Ph



9 10 11

12 13 14



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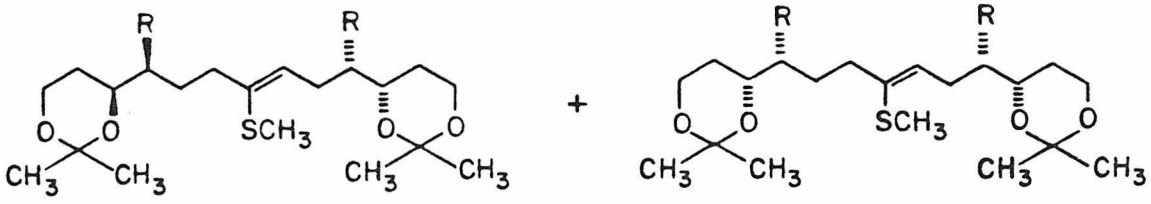


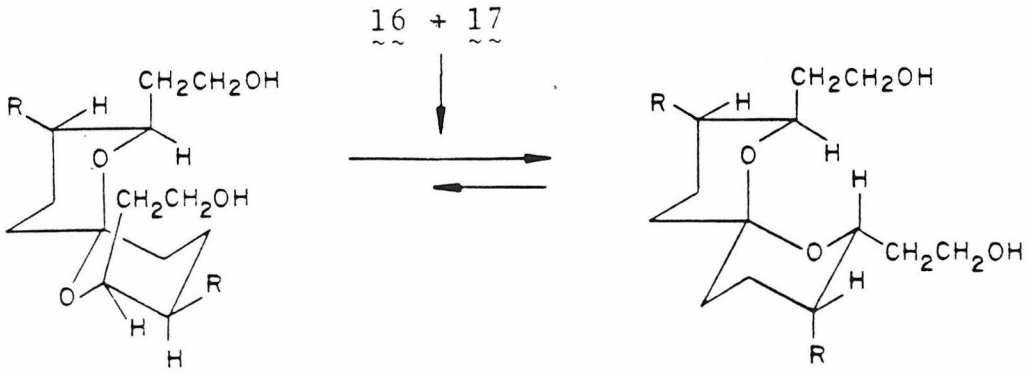
16 17

the initial bisalkylated product to 15 which could undergo subsequent intramolecular elimination to give the observed products and methylsulfenic acid is one reasonable explanation. Eliminations of this kind have recently been observed by Biellmann.[37]

We were now ready to test the intramolecular ketalization. Treatment of the 1:1 mixture of 16 and 17 with mercuric chloride in aqueous acetonitrile[38] could give rise to four possible diastereomers[39] as shown in Scheme IV. In the a series two compounds were isolated, A and B. Since only one of the four, namely 4a, has a C_2-axis of symmetry, then the seven-line carbon spectrum of the white crystalline A implies it has the structure as shown for 18. An X-ray analysis (Figure 2) confirmed this.[40] B, an oil, had a carbon spectrum consistent with a mixture of 18 and epi-18. The b series gave similar results, that is a white crystalline solid with an eight-line spectrum consistent with 5, confirmed by X-ray[40] (Figure 2), and an oil as a mixture of 19 and epi-19. We therefore concluded that, given the proper relative stereochemistry at the alcohol bearing centers, spirane closure would occur in a stereospecific manner.

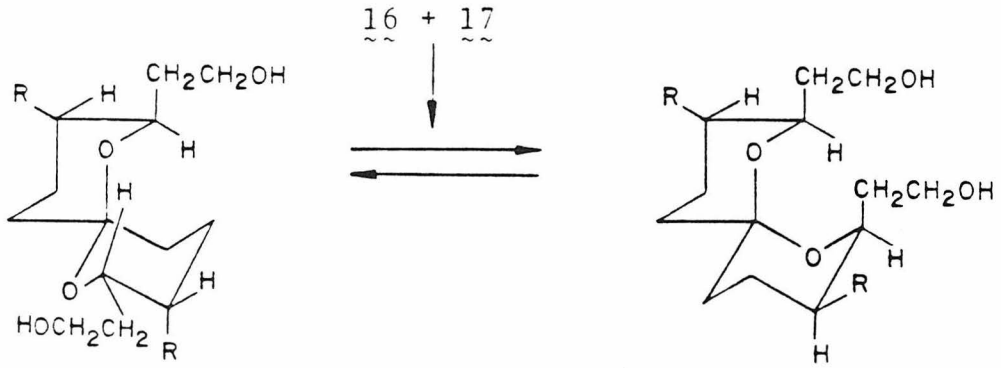
Next we investigated the equilibration of the methyl group at C_{15}. Although closure with the methyl group

Scheme IV



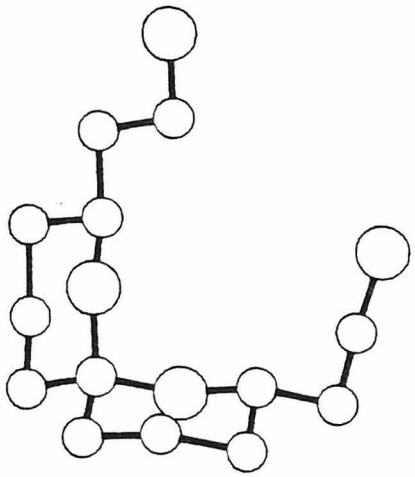
epi-4
epi-5

4, R = H
5, R = CH_3

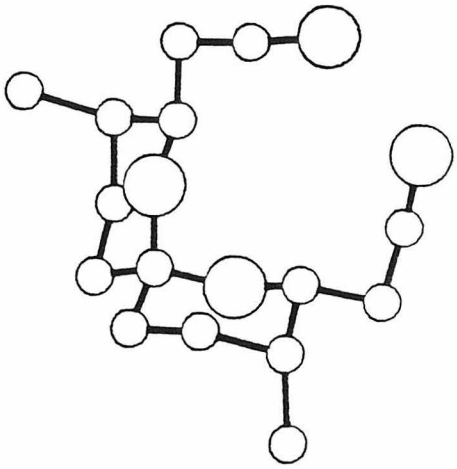


epi-18
epi-19

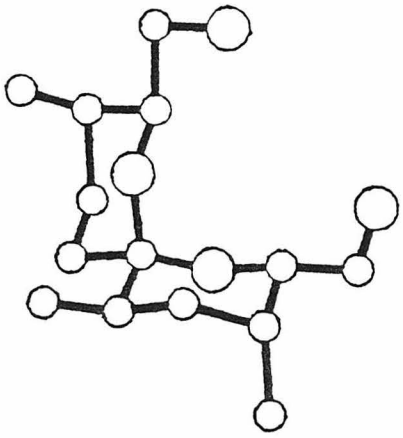
18, R = H
19, R = CH_3



4



5

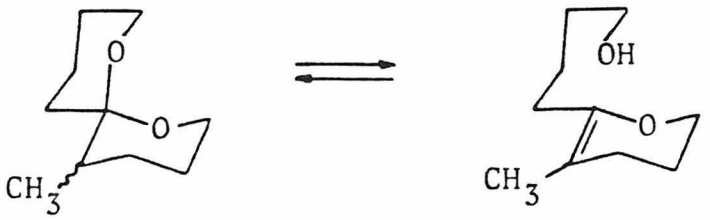


22a

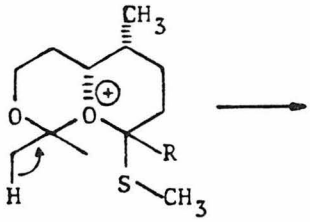
Figure 2. Computer generated ORTEP drawings of spiranes 4, 5 and 22a.

axial would lead to a severe 1,3-diaxial methyl-methyl interaction, we had no estimate for the offsetting A-1,2 strain due to an equatorial methyl. Based upon literature precedent[41] we believed that, even if closure should occur with the C_{15} methyl axial, acid-catalyzed equilibration could occur via a dihydropyran (eq 1).

Testing the equilibration of C_{15} required introduction of a methyl group at C_{15}. Repeated attempts to hydrolyze vinyl sulfides under acidic or neutral conditions[42] led only to isolation of spiranes presumably due to anchimeric-assisted hydrolysis (eq 2). In an



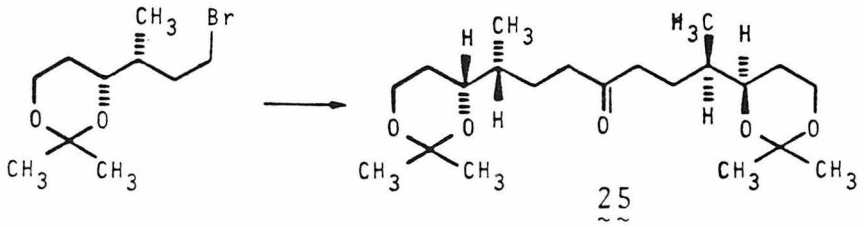
(1)



spiranes (2)

attempt to affect hydrolysis without proceeding through a carbocation, we treated 16 and 17 with lithium diphenylphosphide,[43] but recovered only starting material. To circumvent this problem we sought an alternate synthesis of ketone 25. Conversion of bromide 14b to the corre-

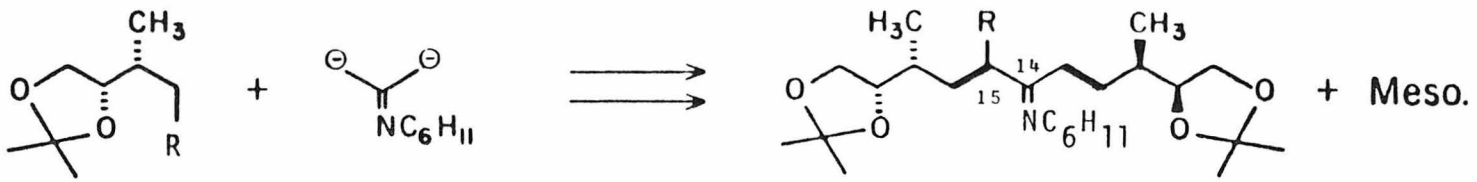
sponding lithium reagent[44] and quenching the reaction with carbon dioxide gave good yields of ketone 25 (eq 3). Attempts to monomethylate either the ketone or its corresponding dimethyl hydrazone,[45] however, were unsuccessful.



25 (3)

We next turned our attention to the route outlined in Scheme V. Conversion of known alcohol 20a to the bromide was accomplished as described previously.[32] The sequential bisalkylation and methylation of acetone imine 21 was conveniently carried out in a one-pot procedure. Alkylation of acetone cyclohexylimine (21) with two equivalents of bromide 20b in the presence of two equivalents of lithium diethylamide[46] gave the bisalkylated imine 22a. The imine could be isolated or deprotonated *in situ* by addition of another equivalent of base and then alkylated with methyl iodide. Acidic workup then yielded a crystalline spirane (48%) identified as 23a and an oil (23b) which carbon-13 analysis indicated to be a mixture of at least two different spiroketals (32%). X-ray analysis of the crystalline spirane con-

Scheme V

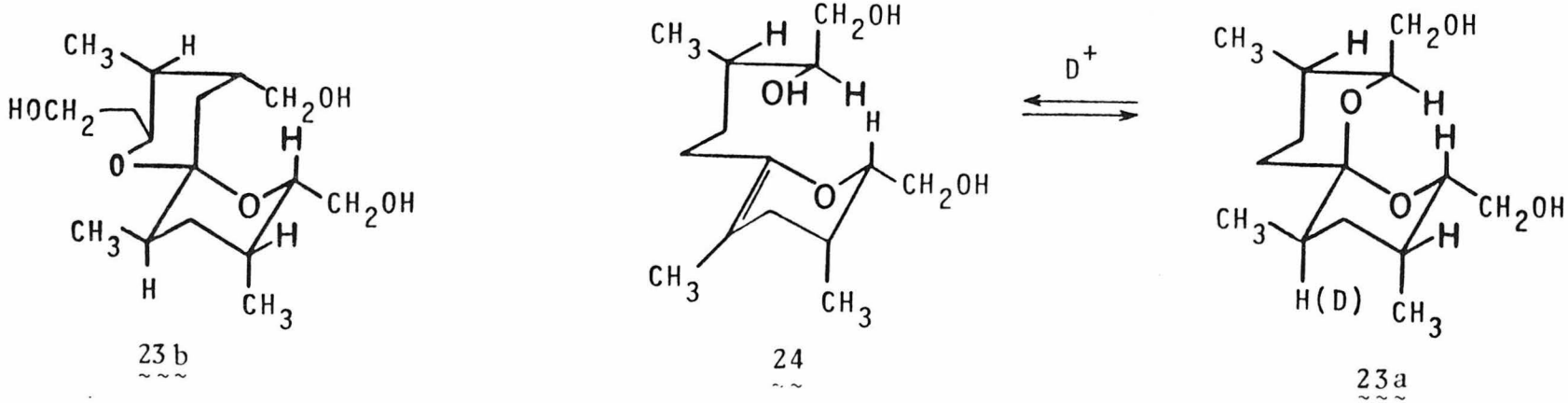


20a, R = OH
b, R = Br

21

22a, R = H
b, R = CH_3

+ Meso.



23b

24

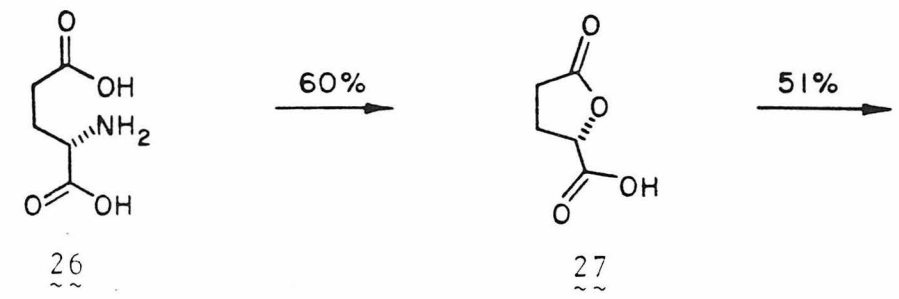
23a

firmed its assignment as structure 23a.[40] Treatment of 23a with DCl in deuterium oxide (see experimental) gave a single crystalline spirane in 80% yield. Carbon-13 and ^{1}H-NMR as well as mass spectral analysis indicated an average of 1.5 deuterium per molecule with complete incorporation at C_{15}. We therefore had convincing evidence that equilibration of the C_{15} methyl was possible. Further, whatever the magnitude of the A-1,2 strain (very obviously present from the deformations detectable in the X-ray structure), it is less than the 1,3-diaxial methyl interaction.

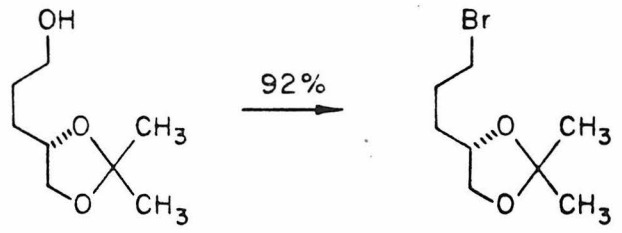
Having satisfied ourselves that the configuration at the spiro-center (C_{14}) could be controlled by the hydroxy-bearing stereocenters, and that the configuration of the methyl at C_{15} could be controlled by equilibration, we turned our attention to a chiral model synthesis.[26] We felt such ligands should be particularly successful as ligands for chiral reducing agents because: 1) they would have a C_2-axis of symmetry, 2) they would have high conformational rigidity.[47] Also, the chiral spiranes could be incorporated into crown ethers similar to Cram's chiral binaphthyls[48] (Figure 4).

The required chiral bromide (29) was prepared as shown in Scheme VI. Diazotization of S-glutamic acid (26) gave lactone 27.[49] Reduction to the triol with diborane[50] and ketalization with acetone and mineral acid

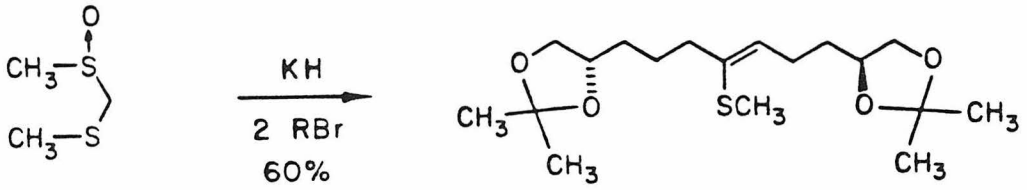
Scheme VI



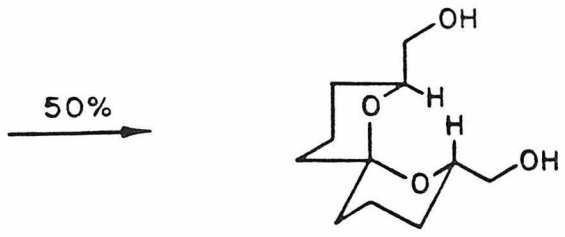
26 27



28 29



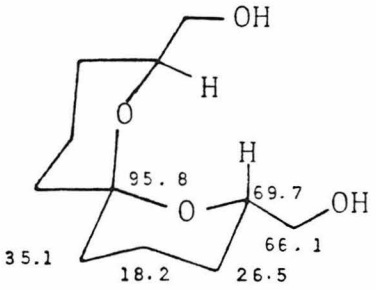
30



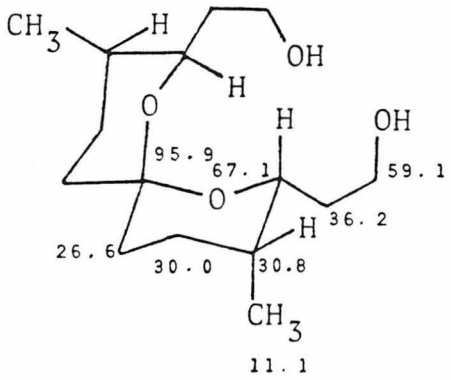
31

gave alcohol 28 in 40% yield from the amino acid. Careful control of the diazotization of glutamic acid was crucial in obtaining high optical yields of 28. The best optical yields were realized if lactone 27 was used without distillation (see experimental). Conversion to the bromide (29) followed standard procedures.[32] Alkylation of Ogura's reagent[36] with 29 gave vinyl sulfide 30 which was hydrolyzed with mercuric chloride[38] to give a mercury complex of spirane 31. X-ray analysis showed that mercury (as $HgCl_2$) had formed a linear complex with two molecules of 31.[40] Treatment with gaseous hydrogen sulfide sufficed to remove the mercury giving spirane 31 in 85% ee (see experimental). Alternatively the vinyl sulfide could be hydrolyzed with trifluoroacetic acid.[51] Carbon-13 and ^{1}H-NMR confirmed the symmetrical nature of 31. Studies are currently in progress to determine the utility of this chiral bidentate ligand for asymmetric hydrogenation catalysts.[52]

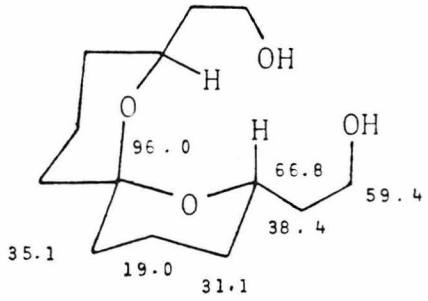
In conclusion, we have shown that the facile construction of spiroketals is possible by internal ketalization. Control of the stereochemistry of the hydroxyl-bearing centers allows complete control of the configuration of the spiro-carbon. Finally, a methyl group at C_{15} can be equilibrated to give the proper configuration at C_{15}. The application of these studies to the total synthesis of A-23187 will be reported shortly.[53]



31



5



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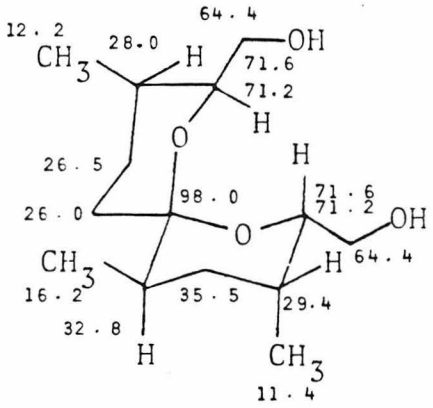
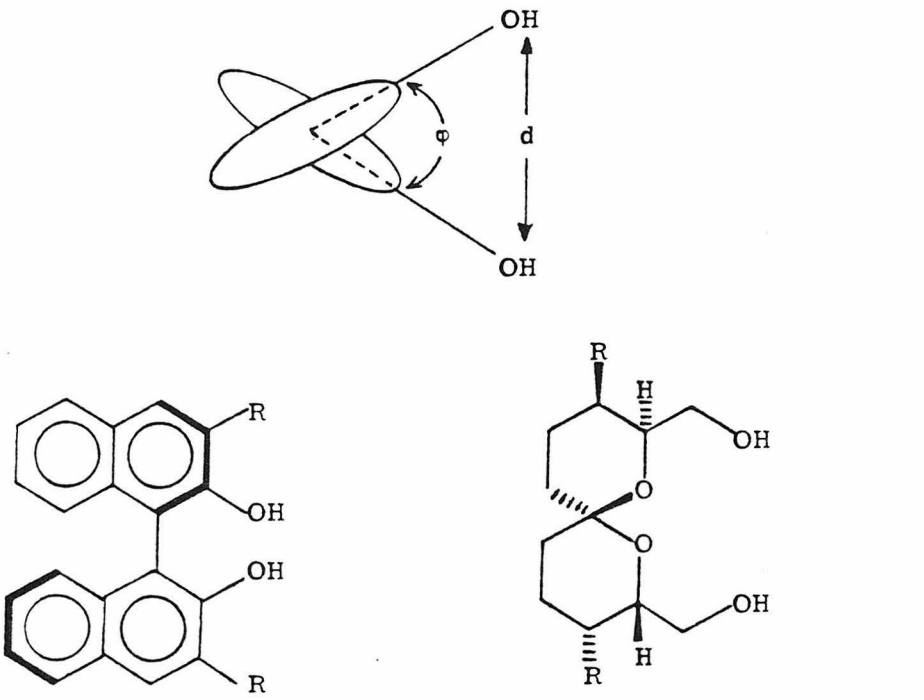


22a

Figure 3. ^{13}C-NMR chemical shifts of spiroketals.



ϕ = 80-85°; d = 3.4 Å ϕ = 85°; d = 3.2-7.5 Å

Figure 4. Comparison of spirane diols with Cram's binaphthyls.

Experimental Section

General. Diethyl ether, 1,2-dimethoxyethane (DME) and tetrahydrofuran (THF) were dried by distillation from benzophenone ketyl. Triethylamine, diisopropylamine and diethylamine were distilled from calcium hydride under nitrogen just prior to use. Dichloromethane was filtered through activity I alumina.

Oil dispersions of potassium hydride (24%), sodium hydride (50%) and lithium 2% sodium (50%) were washed free of oil with ether or pentane and dried under vacuum prior to use. All Grignard and alkyllithium reagents were standardized by the procedure of Watson and Eastham.[54]

Unless otherwise specified all reactions were run under an inert atmosphere of nitrogen.

Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-4210 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra were recorded on a Varian Associates Model T-60, A-60, or EM-390 spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet),

integration, coupling constants (Hz), and interpretation. Carbon-13 nuclear magnetic resonance spectra were recorded on a Varian Associates XL-100 (25.2 MHz) or T-60 (15.1 MHz) spectrometer and are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Mass spectra were recorded on a DuPont MS 21-492B mass spectrometer at 75 eV. Mass spectral analyses as well as combustion analyses were performed by Dr. Susan Rottschaeffer, Mrs. Jan Mitchell and Ms. Sally Muir of the California Institute of Technology Microanalytical Laboratory.

Analytical gas chromatographic analyses were performed on a Varian-Aerograph Model 1440 gas chromatograph equipped with a flame ionization detector using 2 m by 3.18 mm stainless steel columns of 10% Carbowax 20 M, or 10% SE-30 on 80-100 mesh DMCS Chromosorb W support.

1-Methoxy-4-methyl-1,4-cyclohexadiene (9b). The title compound was prepared by Birch reduction of 4-methylanisole according to the procedure of Pappas et al.,[55] in a 70% yield: bp 83-85°C (36 mm); IR (neat) 2820, 1690, 1663, 1450, 1385, 1217, 1172, 1010, 936, 775 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 5.30 (m, 1H vinyl), 4.49 (m, 1H, enol ether), 3.45 (s, 3H, $-OCH_3$), 2.62 (d, 4H, J = 1.5 Hz, allylic $-CH_2$), 1.65 (s, 3H, vinyl $-CH_3$).

(Z)-3-Methyl-3-hexen-1,6-diol (10b). A solution of

12.5 g (0.1 mol) of 1-methoxy-4-methyl-1,4-cyclohexadiene in ether (250 mL) was cooled to -78°C. Ozone (0.82 mmol/min) was bubbled through the stirred solution for 2 h. The course of the reaction was monitored by GLC (5% carbowax). After complete consumption of starting material, lithium aluminum hydride (5 g, 150 mmol) was added and stirring continued at -78°C for 2 h followed by warming to 25°C. After 3 h water (5 mL), 15% sodium hydroxide (5 mL) and then water (15 mL) were carefully added and the precipitate removed by filtration. Removal of solvent in vacuo gave a colorless oil which was distilled bulb-to-bulb at 120°C (0.01 mm) to yield 7.1 g (54%) of a clear, colorless oil: IR ($CHCl_3$) 3619, 3380, 2962, 1445, 1374, 1050, 877 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.65 (t, 1H, J = 8 Hz, vinyl), 3.68 (t, 2H, J = 6 Hz, $-OCH_2-$), 3.60 (t, 2H, J = 6 Hz, $-OCH_2-$), 2.67 (t, 4H, J = 6 Hz, allylic $-CH_2$), 1.75 (s, 3H, allylic CH_3); ^{13}C-NMR ($CDCl_3$) δ 134.5, 124.1, 62.0, 60.1, 35.0, 31.4, 23.4.

Anal. calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.61; H, 10.65.

(Z)-3-Methyl-1,6-bis(phenylmethoxy)-3-hexene (11b). To 6.0 g (0.25 mol) of oil-free sodium hydride suspended in THF (250 mL) at 0°C was added 14.7 g (0.113 mol) of diol 10b in THF (60 mL) with stirring. After gas evolution

ceased, 31.6 mL (0.25 mol) of benzyl chloride (filtered through alumina) in THF (60 mL) was added dropwise over 20 min. Following complete addition, a reflux condenser was attached and the suspension was heated at reflux for 12 h. Water (30 mL) was carefully added followed by removal of THF *in vacuo*. The residue was diluted with 150 mL hexane and the organic layer was washed successively with water and brine, and dried (Na_2SO_4). Filtration and solvent removal *in vacuo* afforded a yellow oil which was distilled bulb-to-bulb at 150°C (0.003 mm) to yield 27.7 g (79%) of a colorless oil: IR (CCl_4) 3064, 3030, 2860, 1491, 1450, 1360, 1203, 1100, 1028, 728, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.23 (s, 10H, Ar), 5.27 (t, 1H, J = 6 Hz, vinyl), 4.42 (s, 4H, $-OCH_2Ar$), 3.54 (t, 2H, J = 7.5 Hz, $-OCH_2-$), 3.43 (t, 2H, J = 7.5 Hz, $-OCH_2-$), 2.35 (t, 4H, J = 7.5 Hz, vinyl $-CH_2$), 1.74 (d, 3H, J = 1.2 Hz, vinyl $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 138.4, 133.9, 128.2, 127.5, 127.3, 122.8, 72.8, 70.1, 68.7, 32.4, 28.6, 23.9.

Anal. calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.20; H, 8.49.

(3*R**,4*R**)-4-Methyl-1,6-bis(phenylmethoxy)-3-hexanol (12b). To a solution of alkene 11b (27.7 g, 89 mmol) in THF (250 mL) at 0°C was added diborane in THF (90 mL, 96 mmol) over a 10 min period. After an additional 30 min the reaction was warmed to 25°C and stirred for 18 h,

then cooled in ice before careful addition of 3N sodium hydroxide (120 mL) and 30% hydrogen peroxide (60 mL). The reaction was warmed to 25°C and stirred 6 h then the product was isolated by partitioning between ether and water. The ether layer was washed with water and dried (Na_2SO_4). Filtration and solvent removal in vacuo gave a crude product which could be used directly or purified by silica gel chromatography (30% ether/hexane) to give 22 g (75%) of colorless oil: IR (CCl_4) 3527, 3064, 3035, 2860, 1491, 1450, 1360, 1203, 1095, 1028, 728, 695 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.31 (s, 10H, Ar), 4.50 (s, 4H, Ar-CH_2-O), 3.63 (t, 4H, J = 6 Hz, -OCH_2-), 3.40-3.80 (m, 1H, -OCH-), 2.90 (d, 1H, J = 3 Hz, -OH), 1.45-1.92 (m, 5H, -CH_2- and -$CHCH_3$), 0.88 (d, 3H, J = 7 Hz, -CH_3); ^{13}C-NMR ($CDCl_3$) δ 138.5, 128.3, 127.5, 73.2, 73.0, 69.3, 68.7, 36.1, 33.9, 33.3, 14.0.

Anal. calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: 76.63; H, 8.46.

(3R*)-3-[(4R*)-2,2-Dimethyl-1,3-dioxacyclohex-4-yl]-butanol (13b). A solution of 10 g (30 mmol) of dibenzyl ether 12b in acetone (200 mL) containing 10% palladium on charcoal (1.0 g) was hydrogenolyzed at 25-30 psi for 12 h on a Parr low-pressure hydrogenator. Catalyst

filtration and removal of solvent *in vacuo* gave a clear oil which was dissolved in a solution of acetone (20 mL) and benzene (30 mL) containing one crystal of p-toluenesulfonic acid and stirred for 5 h. Following addition of K_2CO_3, filtration and removal of solvent *in vacuo*, the residue was distilled bulb-to-bulb at 80°C (.005 mm) to yield 4.4 g (77%) of a colorless oil: IR (CCl_4) 3450, 2990, 2960, 2935, 2870, 1375, 1267, 1194, 1095, 966 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.41-3.98 (m, 5H, $-OCH_2-$ and -OCH-), 2.34 (broad s, 1H, -OH), 1.00-1.91 (m, 5H, $-CH_2-$, $-CHCH_3$), 1.37 (s, 3H, acetonide CH_3), 1.28 (s, 3H, acetonide CH_3), 0.98 (d, 3H, J = 7 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 98.4, 72.6, 60.7, 60.0, 35.4, 35.1, 29.8, 24.5, 19.8, 15.1.

Anal. calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 64.02; H, 10.34.

(3*R**)-1-Bromo-3-[(4*R**)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]butane (14b). Acetonide alcohol 13b (1.7 g, 9.1 mmol) was dissolved in methylene chloride (30 mL) and cooled in an ice bath. Next, with stirring, triethylamine (1.62 mL, 10.6 mmol) was added, followed by dropwise addition of methanesulfonyl chloride. After complete addition (*ca.* 5 min), the reaction was stirred for 1 h at 0°C during which time triethylamine hydrochloride precipitated. Dilution with dichloromethane (20 mL) followed by washing with water, drying (Na_2SO_4),

filtration, and removal of solvent in vacuo at 25°C gave the straw colored mesylate: IR (neat) 2990, 2963, 2868, 1453, 1365, 1193, 1168, 1097, 970, 940 cm^{-1}; ^{1}H-NMR (CCl_4) δ 4.25 (t, 2H, J = 6 Hz, $MsOCH_2$-), 3.80 (dd, 2H, J = 3, 6.5 Hz, $-OCH_2$-), 3.65 (m, 1H, -OCH-), 2.95 (s, 3H, $-SO_2CH_3$), 1.49-2.05 (m, 5H, $-CH_2$-, -CH-), 1.38 (s, 3H, acetonide CH_3), 1.28 (s, 3H, acetonide CH_3), 0.93 (d, 3H, J = 6 Hz).

The mesylate was dissolved in acetone (15 mL) and 2,2-dimethoxypropane (15 mL) and anhydrous lithium bromide (4.5 g, 54 mmol) were added and the resultant mixture heated at reflux for 5 h. The crude bromide was isolated by removing excess solvent in vacuo, dissolution of the residue in ether-hexane (1:1) and partitioning with water. The organic layer was dried (Na_2SO_4) filtered and solvent removed to give a yellowish oil which on distillation at 60°C (.03 mm) gave 1.65 g (78%) of an unstable colorless bromide: IR (CCl_4) 2960, 1502, 1375, 1265, 1215, 1195, 1168, 1100, 1063, 1000, 968 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.00 (t, 1H, J = 3.5 Hz, $-OCH_2$-), 3.83 (d, 1H, J = 3 Hz, $-OCH_2$-), 3.52-3.80 (m, 1H, -OCH-), 3.50 (t, 2H, J = 7.5 Hz, $BrCH_2$-), 1.08-2.10 (m, 5H, -CH- and $-CH_2$-), 1.42 (s, 3H, acetonide CH_3), 1.35 (s, 3H, acetonide CH_3), 0.90 (d, 3H, J = 6 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 98.2, 71.9, 60.0, 37.2, 36.4, 32.4, 31.3, 29.8, 28.4, 14.1.

Exact mass (75 eV) m/e, calcd. for $C_{10}H_{19}O_2Br$, M-CH_3: 235.033. Found: 235.031.

(2R*,8R*)-2,8-Bis-[(4R*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-5-(methylthio)-4-nonene (16b) and (2R*,8S*)-2-[(4R*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-8-[(4S*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-5-(methylthio)-4-nonene (17b). To a dry, three-neck, 100-mL, round-bottomed flask equipped with a reflux condenser, nitrogen inlet, rubber septum and magnetic stirring bar was added potassium hydride (24% in oil, 2.2 g, 56 mmol). The oil was removed by several washings with ether then THF (37 mL) was added. To the ice-cooled stirred suspension was added methyl methylsulfinylmethyl sulfide (0.86 mL, 6.9 mmol) dropwise over a 5 min period. After stirring 15 min, bromoacetonide 14b (3.5 g, 14 mmol) was added and stirring continued for 0.5 h at 0°C, 1 h at 25°C and 1 h at 45-55°C (oil bath). Excess hydride was quenched with moist ether and the crude product was isolated by ether extraction. Purification by chromatography (alumina activity III, hexane to 70% ether/hexane) gave pure vinyl sulfide (1.1 g, 75%) as a mixture of olefin isomers: IR (CCl_4) 2990, 2960, 2865, 1620, 1455, 1377, 1366, 1270, 1240, 1195, 1097, 970, 850 cm^{-1}; ^{1}H-NMR (CCl_4) δ 5.55 (t, 0.4H, J = 7 Hz, E-vinyl), 5.05 (t, 0.6H, J = 7 Hz, Z-vinyl), 3.89 (t, 2H, J = 3 Hz, -OCH_2-), 3.75 (d, 2H, J = 3 Hz,

-OCH_2-), 3.18-3.64 (m, 2H, -OCH-), 2.13 (s, 3H, -SCH_3), 1.1-1.8 (m, 10H, CH_3-CH-, -CH_2-, allylic CH_2-), 1.37 (s, 6H, acetonide CH_3), 1.28 (s, 6H, acetonide CH_3), 0.89 (d, 6H, J = 6 Hz, CH_3).

Exact mass (75 eV) m/e, calcd. for $C_{22}H_{40}O_4S$: 400.264. Found: 400.262.

(2R*,3R*,8R*,9R*)-2,8-Bis-(2-hydroxyethyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (5). To a solution of vinyl sulfide 16b and 17b (1.70 g, 4.25 mmol) in 75% aqueous acetonitrile (40 mL) was added mercuric chloride (2.8 g, 8.8 mmol) at 25°C. Within minutes a white precipitate had formed. The resultant suspension was stirred for 10 h, benzene (100 mL) was added and water was removed by azeotropic distillation (Dean Stark). Filtration and solvent removal gave a colorless oil. Chromatography on Silica Gel (1:1 ethyl acetate/hexane) gave an oil (0.33 g, 30%) which solidified on trituration with hexane, mp. 86-88°C (hexane): IR ($CHCl_3$) 3600, 3410, 2965, 2935, 1462, 1383, 1368, 1227, 1120, 1077, 1035, 982, 950, 884 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.01-4.35 (m, 6H, -OCH_2-, -OCH-), 2.72 (s, 2H, -OH), 1.07-2.26 (m, 14H, -CH- and -CH_2-), 0.94 (d, 6H, J = 6.8 Hz, -CH_3); ^{13}C-NMR ($CDCl_3$) δ 95.9, 67.1, 59.1, 36.2, 30.8, 30.0, 26.6, 11.1.

Anal. calcd. for $C_{15}H_{28}O_4$: C, 67.10; H, 10.36. Found: C, 66.92; H, 10.23.

(Z)-3-Hexen-1,6-diol (10a). The title compound was prepared according to the procedure described for diol 10b. Ozonolysis and reduction of dihydroanisole (11 g, 0.10 mol) gave diol 10a (4.6 g, 40%), bp. 80°C (0.1-0.05 mm): IR ($CHCl_3$) 3619, 3380, 2962, 1447, 1370, 1050, 870 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.56 (t, 2H, J = 4.5 Hz, vinyl), 4.06 (broad s, 2H, -OH), 3.51 (t, 4H, J = 6.5 Hz, $-CH_2O-$), 2.33 (t, 4H, J = 6 Hz, allylic CH_2-); mass spectrum (75 eV) m/e (rel intensity) 98 (13), 68 (100), 67 (48), 55 (39).

(Z)-1,6-Bis(phenylmethoxy)-3-hexene (11a). The title compound was prepared according to the procedure described for diether 11b. Benzylation of diol 10a (11.6 g, 0.10 mol) gave diether 11a (27.1 g, 92%), bp. 140°C (0.002 mm): IR (CCl_4) 3030, 2860, 1490, 1448, 1360, 1202, 1100, 1025, 723, 695 cm^{-1}; ^{1}H-NMR (CCl_4) δ 7.17 (s, 10H, Ar), 5.44 (t, 2H, J = 4.5 Hz, vinyl), 4.25 (s, 4H, Ar-CH_2O-), 3.35 (t, 4H, J = 6.5 Hz, $-OCH_2-$), 2.30 (d, t, 4H, J = 5.5, 6.5 Hz, allylic CH_2-); ^{13}C-NMR ($CDCl_3$) δ 128.29, 127.56, 72.9, 70.0, 28.2.

Exact mass (75 eV) m/e, calcd. for $C_{20}H_{24}O_2$, P-C_7H_7: 205.123. Found: 205.122.

4-Methyl-1,6-Bis(phenylmethoxy)-3-hexanol (12a). The title compound was prepared according to the procedure for alcohol 12b. Hydroboration of olefin 11a (27.1 g,

0.092 mol) gave alcohol 12a (31.0 g, 100%): IR (CCl_4) 3535, 2920, 2860, 1448, 1360, 1201, 1094, 1026, 725, 693 cm^{-1}; ^{1}H-NMR (CCl_4) δ 7.21 (s, 10H, Ar), 4.47 (s, 4H, $-OCH_2Ar$), 3.63 (t, 4H, J = 6.3 Hz, $-OCH_2-$), 3.32-3.54 (m, 1H, -OCH-), 3.10 (broad s, 1H, -OH), 1.34-1.92 (m, 6H, $-CH_2-$); ^{13}C-NMR ($CDCl_3$) δ 128.3, 127.6, 73.2, 72.9, 70.5, 68.8, 36.9, 34.5, 26.1; mass spectrum (75 eV) m/e (rel intensity) 208 (5), 108 (62), 107 (81), 91 (100), 79 (57), 77 (33).

3-(2,2-Dimethyl-1,3-dioxacyclohex-4-yl)propanol (13a). The title compound was prepared from alcohol 12a according to the procedure for acetonide 13b. Hydrogenation of alcohol 12a (9.4 g, 30 mmol) gave acetonide 13a (3.68 g, 72%), bp. 75°C (0.025 mm): IR (CCl_4) 3360, 2940, 2860, 1373, 1360, 1210, 1192, 1048, 963 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.35-4.10 (m, 6H, -OH, $-OCH_2-$, -OCH-), 1.4-1.9 (m, 6H, $-CH_2-$), 1.41 (s, 3H, acetonide CH_3), 1.35 (s, 3H, acetonide CH_3); ^{13}C-NMR ($CDCl_3$) δ 98.9, 69.6, 62.7, 60.5, 33.8, 32.2, 30.4, 29.1, 19.6.

1-Bromo-3-(2,2-dimethyl-1,3-dioxacyclohex-4-yl)-propane (14a). The title compound was prepared according to the procedure for bromide 14b. Reaction of alcohol 13a (3.68 g, 21.6 mmol) gave bromide 14a (3.73 g, 70%), bp. 50°C (0.03 mm).

Mesylate: IR (CCl_4) 2980, 2940, 2855, 1360, 1337,

1240, 1192, 1170, 1095, 963, 935, 855 cm^{-1}; ^{1}H-NMR (CCl_4) δ 4.16 (t, 2H, J = 6 Hz, $-SO_3CH_2-$), 3.82 (dd, 2H, J = 4.5, 8 Hz, $-OCH_2-$), 3.52-3.87 (m, 1H, -OCH-), 2.90 (s, 3H, CH_3SO_3-), 1.19-2.18 (m, 6H, $-CH_2-$), 1.35 (s, 3H, acetonide CH_3), 1.25 (s, 3H, acetonide CH_3).

Bromide was distilled bulb-to-bulb at 50°C (.03 mm) to give a colorless oil: IR (CCl_4) 2990, 2945, 2863, 1435, 1375, 1365, 1265, 1240, 1195, 1110, 1050, 967, 858 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.78 (dd, 2H, J = 4, 9.5 Hz, $-OCH_2-$), 3.55-3.95 (m, 1H, -OCH-), 3.33 (t, 2H, J = 6.5 Hz, $BrCH_2-$), 1.18-2.33 (m, 6H, $-CH_2-$), 1.33 (s, 3H, acetonide CH_3), 1.23 (s, 3H, acetonide CH_3); ^{13}C-NMR (d_6-acetone) δ 99.0, 68.9, 60.3, 35.8, 34.5, 32.2, 30.4, 29.5, 19.6.

Anal. calcd. for $C_9H_{17}BrO_2$: C, 45.58; H, 7.23. Found: C, 45.35; H, 6.94.

1,7-Bis-[(4R*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-4-methylthio-3-heptene (16a) and 1-[(4R*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-7-[(4S*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-4-methylthio-3-heptene (17a). The title compounds were prepared from bromide 14a according to the procedure for vinyl sulfides 16b and 17b. Alkylation of Ogura's reagent[36] (0.47 g, 3.8 mmol) with bromide 14a (1.9 g, 8.0 mmol) gave vinyl sulfides 16a and 17a. Purification by column chromatography on alumina (neutral, activity III, gradient from hexane to 70% ether/hexane)

gave a colorless oil (1.07 g, 76%): IR (CCl_4) 2995, 2950, 2870, 1455, 1430, 1375, 1365, 1270, 1197, 1162, 1097, 967, 870, 850 cm^{-1}; ^{1}H-NMR (CCl_4) δ 5.53 (t, 0.5H, J = 6.5 Hz, (E)-vinyl), 5.09 (t, 0.5H, J = 7 Hz, (Z)-vinyl), 3.50-4.14 (m, 6H, -OCH- and $-OCH_2-$), 2.15 (s, 3H, $-SCH_3$), 1.90-2.40 (m, 4H, allylic CH_2-), 1.40-1.85 (m, 10H, $-CH_2-$), 1.42 (s, 6H, acetonide CH_3), 1.35 (m, 10H, $-CH_2-$), 1.42 (s, 6H, acetonide CH_3), 1.35 (s, 6H, acetonide CH_3): ^{13}C-NMR ($CDCl_3$) δ 129.8, 122.2, 97.8, 68.5, 68.2, 67.8, 59.7, 36.6, 36.0, 35.7, 31.3, 29.9, 24.7, 24.2, 23.9, 19.2, 14.7.

Exact mass (75 eV) m/e, calcd. for $C_{20}H_{36}O_4S$: 372.233. Found: 372.235.

(2R*,8R*)-2,8-Bis-(2-hydroxyethyl)-1,7-dioxaspiro[5.5]-undecane (4) and (2R*,8S*)-2,8-Bis-(2-hydroxyethyl)-1,7-dioxaspiro[5.5]undecane (18). The title compounds were prepared from vinyl sulfides 16a and 17a as for the preparation of spirane 5. Hydrolysis of vinyl sulfides 16a and 17a (1.07 g, 2.88 mmol) and purification by chromatography on alumina (neutral, activity III, gradient elution from ether to 3% methanol/ether) gave (2R*,8R*), spirane 4 (0.317 g, 44.5%), mp. 97-98°C (hexane): IR (CCl_4) 3600-3100, 2930, 2860, 1430, 1275, 1195, 1140, 1110, 1085, 1075, 1050, 1030, 970, 900 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.80-4.20 (m, 6H, $-OCH_2-$ and -OCH-), 3.17 (broad s, 2H, -OH), 1.31-2.00 (m, 12H, $-CH_2-$); ^{13}C-NMR ($CDCl_3$) δ 96.0,

66.8, 59.4, 38.4, 35.1, 31.1, 19.0.

(2R*,8S*) Spiroketal 18 (20%) as an oil: IR ($CHCl_3$) 3610, 3600-3200, 2000, 2940, 2870, 1440, 1375, 1080, 1055, 900 cm^{-1}; ^{1}H-NMR (d_6-DMSO) δ 3.80-4.20 (m, 4H, -OCH-, -OH), 3.60 (t, 2H, J = 7 Hz, $-OCH_2-$), 3.45 (t, 2, J = 7 Hz, OCH_2), 1.00-2.00 (m, 1 H, $-CH_2-$); ^{13}C-NMR ($CDCl_3$) δ 97.8, 72.5, 70.3, 60.8, 60.6, 38.0, 36.0, 30.9, 30.7, 28.3, 19.5, 16.3

Anal. calcd. for $C_{13}H_{24}O_4$: C, 63.9; H, 9.9. Found: C, 64.1; H. 9.6.

(2R*,8R*)-2,8-Bis-[(4R*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-5-nonanone (25) and (2R*,8S*)-2-[(4R*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-8-[(4S*)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-5-nonanone. A 50% oil dispersion of lithium powder containing 2% sodium as an amalgam was placed in a three-neck, 50-mL, round-bottomed flask under an argon atmosphere and oil removed by washing with ether (4 x 20 mL). The powder (0.33 g, 47.5 mmol) was suspended in ether (10 mL), cooled to -10°C and bromide 14b (2.3 g, 9.1 mmol) was added in ether (10 mL) over 0.5 h. Stirring was continued for 2 h (analysis by GLC, 5% SE-30). The purple colored suspension was cooled to -20°C and carbon dioxide gas was passed through the reaction for 2 min (ca. 50 mL/min). The reaction was quenched by slowly adding it to

vigorously stirred ice-cold water (50 mL). Extraction with ether (80 mL), drying (Na_2SO_4), filtration and removal of solvent gave a yellow oil. Bulb-to-bulb distillation at 180°C (.03 mm) gave 1.01 g (60%) of a colorless oil: IR (CCl_4) 2995, 2975, 2870, 1712, 1456, 1378, 1368, 1270, 1240, 1197, 1098, 970, 804 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.87 (t, 2H, J = 3 Hz, $-OCH_2-$), 3.72 (d, 2H, J = 3.2 Hz, $-OCH_2-$), 3.34-3.72 (m, 4H, -OCH-), 2.37 (t, 4H, J = 6.5 Hz, $-COCH_2-$), 1.1-1.91 (m, 10H, -CH- and $-CH_2-$), 1.36 (s, 6H, acetonide CH_3), 1.26 (s, 6H, acetonide CH_3), 0.86 (d, 6H, J = 5.5 Hz, $-CH_3$); ^{13}C-NMR (d_6-acetone) δ 221.7, 98.3, 72.7, 60.2, 40.6, 38.1, 30.2, 28.9, 27.0, 19.5, 14.8.

Exact mass (75 eV) m/e, calcd. for $C_{22}H_{10}O_5$, M-CH_3: 369.264. Found: 369.264.

Treatment with 10% hydrochloric acid/THF at 25°C gave spiroketal 5, as characterized above.

(2R*)-1-Bromo-2-[(4R*)-2,2-dimethyl-1,3-dioxacyclopent-4-yl]propane (20b). The title compound was prepared by the method of Servis.[32] Reaction of alcohol 20a (5.9 g, 36.8 mmol) gave bromide 20b (7.06 g, 86%), bp. 54°C (4.0 mm).

Mesylate: IR (neat) 2980, 2956, 1455, 1350, 1212, 1170, 1057, 958, 850 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.10 (d, 2H, J = 6 Hz, $MSOCH_2-$), 3.87-4.18 (m, 2H, $-OCH_2-$), 3.45-3.84 (m, 1H, -OCH-), 2.99 (s, 3H, $-SO_2CH_3$), 1.67-2.28

(m, 1H, -CH-), 1.37 (s, 3H, acetonide CH_3), 1.30 (s, 3H, acetonide CH_3), 1.01 (d, 3H, J = 7.5 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 108.5, 75.6, 71.4, 66.7, 37.0, 35.9, 26.3, 25.0, 11.4.

Exact mass (75 eV) m/e, calcd. for $C_9H_{18}O_5S$: 238.089. Found: 238.087.

Bromide: Distillation at 73°C (.04 mm); IR (neat) 2980, 2935, 2875, 1450, 1375, 1365, 1254, 1210, 1150, 1060, 1000, 850 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.06 (A_2B pattern, 2H, $-OCH_2-$), 3.54-3.78 (m, 1H, -OCH-), 3.00-3.52 (A_2B pattern, $-CH_2Br$), 1.90 (m, 1H, -CH-), 1.40 (s, 3H, acetonide CH_3), 1.33 (s, 3H, acetonide CH_3), 1.07 (d, 3H, J = 6.9 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 108.8, 77.3, 66.9, 38.6, 36.4, 26.3, 25.2, 14.4.

Anal. calcd. for $C_8H_{15}BrO_2$: C, 43.07; H, 6.8. Found: C, 42.85; H, 6.76.

(2R*,3R*,5R*,6S*,8R*,9R*)-2,8-Bis(hydroxymethyl)-3,5,9-trimethyl-1,7-dioxaspiro[5.5]undecane (23a). A THF (20 mL) solution of diethylamine (5.36 mL, 51.8 mmol) in a three-neck, 100-mL round-bottomed flask (flask 1) equipped with a thermometer, septum, magnetic stirring bar, and nitrogen inlet was cooled to -20°C (internal temperature) and n-butyllithium in hexane (20.5 mL, 49.8 mmol) was added. After 0.5 h, hexamethylphosphoric acid triamide (1 mL) was added followed by the addition of acetone

cyclohexylimine (21)[56] (3.31 g, 23.8 mmol) at -20°C. The reaction was warmed to -5°C, stirred for 3 h then cooled to -60°C and bromide 20b (11.0 g, 47.3 mmol) in THF (12 mL) was added. Stirring was continued at -60°C for 1 h followed by warming to 25°C for 12 h.

To a separate three-neck, 250-mL round-bottomed flask (flask 2) equipped with a septum, magnetic stirring bar, thermometer and nitrogen inlet cooled to -20°C were added 1) diethylamine (2.69 mL, 26 mmol) in THF (20 mL) and 2) n-butyllithium in hexane (10.3 mL, 25.1 mmol). After 0.5 h, the solution was cooled to -50°C (internal). The alkylated imine (flask 1) was cooled to -50°C and transferred into flask 2 by cannula. Flask 1 was rinsed with THF (10 mL) which was also transferred to flask 2. The solution in flask 2 was stirred for 1 h at -50°C; then warmed to -5°C for 2 h followed by recooling to -50°C and methyl iodide (1.9 mL, 30.0 mmol) was added. After 1 h the reaction was warmed to 25°C and stirred for 12 h. Hydrolysis of imine 22b was accomplished by the addition of excess concentrated aqueous hydrochloric acid (20 mL) to the cooled reaction mixture followed by heating at reflux for 4 h. The desired spiranes were isolated by ether extraction (4 x 50 mL), drying (Na_2SO_4), filtration, and removal of solvent in vacuo to afford a yellow oil. Purification by column chromatography on

alumina (neutral, activity III, gradient from ether to 5% methanol/ether) gave two components. The less polar material (1.0 g, 48%) solidified by trituration with hexane mp. 75-77°C (hexane), was determined to be spiroketal 23a by ^{13}C-NMR analysis and later by X-ray crystallography. The minor component (0.62 g, 30%) was present as a more polar component which was presumed to be spiroketal 23b as a mixture of ketal isomers.

Imine 22a: IR (CCl_4) 2980, 2930, 2875, 1650, 1445, 1375, 1365, 1245, 1210, 1158, 1060, 860, 690 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.45-4.08 (m, 7H, -CHO-, $-CH_2O-$, -CHN-), 2.01-2.33 (m, 4H, $-CH_2-$, alpha to imine carbon), 1.13-1.95 (m, 16H, $-CH_2-$ and -CH-), 1.32 (s, 6H, acetonide CH_3), 1.25 (s, 6H, acetonide CH_3), 0.93 (d, 6H, J = 6 Hz, $-CH_3$).

Methylated imine 22b: IR (CCl_4) 2970, 2925, 2830, 1647, 1442, 1370, 1362, 1243, 1205, 1155, 1060, 853 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.32-4.05 (m, 7H, -CHO-, $-CH_2O-$, -CHN-), 1.90-2.42 (m, 3H, $-CH_2-$ and -CH- alpha to imine carbon), 1.10-1.90 (m, 16H, $-CH_2-$ and -CH-), 1.28 (s, 6H, acetonide CH_3), 1.23 (s, 6H, acetonide CH_3), 0.97 (d, 3H, J = 6.5 Hz, $-CH_3$), 0.92 (d, 3H, J = 6 Hz, $-CH_3$), 0.90 (d, 3H, J = 6 Hz, $-CH_3$).

Exact mass (75 eV) m/e, calcd. for $C_{26}H_{47}NO_4$: 437.352. Found: 437.354.

Spiroketal 23a: IR ($CHCl_3$) 3600, 3400, 2965, 2925,

1460, 1382, 1368, 1225, 1110, 1075, 1035, 980, 950 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.78-4.02 (m, 2H, -OCH-), 3.40-3.78 (m, 4H, $-OCH_2-$), 2.87 (broad s, 2H, -OH), 1.05-2.21 (m, 9H, $-CH_2-$ and -CH-), 0.88 (broad d, 9H, J = 6.5 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 98.0, 71.6, 71.2, 64.4 (two carbons), 35.5, 32.8, 29.4, 28.0, 26.5, 26.0, 16.2, 12.2, 11.4.

Anal. calcd. for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.76; H, 9.95.

Mass spectrum (75 eV) m/e (rel intensity): 258 (5), 244 (5), 227 (24), 213 (56), 195 (22), 184 (81), 145 (100).

Spiroketals 23b were isolated as an oil: IR ($CHCl_3$) 3590, 3420, 3000, 2960, 2935, 2875, 1450, 1375, 1210, 1110, 1070, 1015, 980, 945, 900, 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.31-4.33 (m, 8H, -OCH-, $-OCH_2OH$), 1.11-2.48 (m, 9H, -CH-, $-CH_2-$), 0.88 (d, 6H, J = 6.5 Hz, $-CH_3$), 0.78 (d, 3H, J = 6.5 Hz, $-CH_3$ alpha to spirocenter); ^{13}C-NMR ($CDCl_3$) δ 110.2, 108.1, 96.0 (indicates three different spiroketal carbons).

Equilibration studies on spiroketal 23a. To a solution of spiroketal 23a (0.22 g, 8.4 mmol) in THF (6 mL) was added deuterium chloride in deuterium oxide (2 mL, 38% solution). The mixture was heated at reflux for 18 h. Spiroketal was isolated as previously described for spirane 23a, to yield a white crystalline solid (80%) mp. 75-77°C (hexane): IR ($CHCl_3$) 3600, 3400, 2230, 2160, 1455, 1380, 1360, 1225,

1125, 1100, 1075, 1030, 980, 915 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.42-4.10 (m, 6H, $-CH_2O-$, -CHO-), 3.33 (broad s, 2H, -OH), 1.17-2.33 (m, 7-8H, $-CH_2-$, -CH-), 0.84 (broad d, 9H, J = 6.5 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 97.8, 71.5, 71.2, 64.55, 64.47, 35.4, 32.6 (triplet), 29.3, 28.0, 26.3, 26.1, 16.1 (broadened), 12.2, 11.4.

(5S)-5-Carboxy-oxacyclopentan-2-one (27). To (2S)-glutamic acid (100 g, 0.68 mol) in water (250 mL) was added concentrated hydrochloric acid (38%, 96 mL, 1 mol) and the resultant solution cooled to 0-5°C with an ice-salt bath. A solution of sodium nitrite (71 g, 1.03 mol) in water (150 mL) was added dropwise during 5 h at such a rate that the temperature did not exceed 5°C. After complete addition, the reaction mixture was warmed to 25°C and stirred 12 h. Concentration under reduced pressure at 40°C gave an oily residue that was dissolved in hot acetone and filtered to remove inorganic salts. Purification gave lactone 27 (65.7 g, 74%) bp. 155-160°C (0.1-0.2 mm, lit. 150-155°C at 0.2 mm); $[\alpha]_D$ = +12.5° (C = 3.25, ethanol).

3-[(4S)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]propanol (28). A solution of lactone 27 (48.3 g, 0.37 mol) in THF (100 mL) was added to a 2-liter, 3-neck, round-bottomed flask equipped with a septum, overhead mechanical stirrer, nitrogen inlet and reflux condenser and cooled to 0°C in an ice-salt bath. Diborane (1000 mL of a 1 M solution

in THF) was added slowly. After 50% addition (hydrogen evolution ceases), the rate of addition was increased. The reaction was heated to reflux for 20 h. Cooling was followed by destruction of excess borane with methanol (300 mL). After a further 5 h reflux, the reaction was concentrated by atmospheric distillation of THF, methanol and trimethylborate. The residue was redissolved in methanol (300 mL) and evaporated to dryness in vacuo; then benzene (300 mL), acetone (300 mL) and sulfuric acid (1 mL) were added. Stirring was continued for 12 h at which time potassium carbonate (30 g) was added to neutralize the acid. Filtration and removal of solvent in vacuo gave an oil which was distilled at 80-87°C (1 mm) to give 30 g (51%) of a clear colorless oil: IR (CCl_4) 3600-3200, 2980, 2940, 2870, 1470, 1450, 1375, 1365, 1245, 1210, 1155, 1050, 848 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.90-4.30 (m, 2H, -CH_2OH), 3.35-3.90 (m, 4H, -OCH_2-, -OCH-, -OH), 1.55-1.90 (m, 4H, -CH_2-), 1.34 (s, 3H, acetonide CH_3), 1.28 (s, 3H, acetonide CH_3); ^{13}C-NMR ($CDCl_3$) δ 108.6, 75.9, 69.3, 61.9, 30.3, 29.2, 27.0, 25.7; $[\alpha]_D$ = +7.1° (C = 1.747, CCl_4).

Anal. calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.01; 9.92.

1-Bromo-3-[(4S)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-

propane (29). The title compound was prepared by the method of Servis.[32] Reaction of alcohol 28 (12.3 g, 77 mmol) gave bromide 29 (12.12 g, 70%).

Mesylate: NMR (CCl_4) δ 4.25 (t, 2H, J = 6.5 Hz, $-SO_3CH_2-$), 3.85-4.32 (A_2B, 2H, $-OCH_2-$), 3.3-3.6 (m, 1H, -OCH-), 3.00 (s, 3H, $-SO_3CH_3$), 1.43-2.20 (m, 4H, $-CH_2-$), 1.37 (s, 3H, acetonide CH_3), 1.32 (s, 3H, acetonide CH_3).

Bromide was distilled at 56°C (0.07 mm) to give a colorless oil (70%): IR (CCl_4) 2980, 2935, 2870, 1455, 1430, 1245, 1205, 1150, 1100, 1060, 968, 852 cm^{-1}; ^{1}H-NMR (CCl_4) δ 3.78-4.18 (A_2B, 2H, $-OCH_2$), 2.90-3.61 (m, 1H, -OCH-), 3.44 (t, 2H, J = 6.5 Hz, $-SO_3CH_2-$), 1.34-2.20 (m, 4H, $-CH_2-$), 1.33 (s, 3H, acetonide CH_3), 1.27 (s, 3H, acetonide CH_3); ^{13}C-NMR ($CDCl_3$) δ 108.7, 75.1, 69.2, 32.8, 32.3, 29.3, 27.0, 25.6; $[\alpha]_D$ = -1° (C = 1.03, benzene).

Exact mass (75 eV) m/e, calcd. for $C_7H_{12}BrO_2$, M-CH_3: 207.003, 209.001. Found: 207.002, 209.002.

1,7-Bis-[(4S)-2,2-dimethyl-1,3-dioxacyclohex-4-yl]-5-(methylthio)-4-nonene (30). The title compound was prepared from bromide 29 according to the procedure for vinyl sulfides 16b and 17b. Alkylation of Ogura's reagent[36] (12.6 g, 0.102 mol) with bromide 29 (45.5 g, 0.204 mol) gave vinyl sulfide 30. Purification (neutral alumina, activity-III, gradient from hexane to 50% ether/hexane) afforded a 57% yield of an oil: IR (CCl_4)

2980, 2935, 2870, 1450, 1375, 1365, 1245, 1210, 1150, 1130, 1100, 1062, 855 cm^{-1}; ^{1}H-NMR (CCl_4) δ 6.35 (t, 0.5H, J = 7.5 Hz, E-vinyl), 5.02 (t, 0.5H, J = 7.0 Hz, Z-vinyl), 3.78-4.17 (A_2B, 4H, $-OCH_2-$), 3.38 (apparent t, 2H, J = 9.0 Hz, -OCH-), 2.03-2.48 (m, 4H, allylic CH_2-), 2.15 (s, 3H, $-SCH_3$), 1.30-1.78 (m, 6H, $-CH_2-$), 1.32 (s, 6H, acetonide CH_3), 1.27 (s, 6H, acetonide CH_3).

Anal. calcd. for $C_{18}H_{32}O_4$: C, 62.75; H, 9.35. Found: C, 63.02; H, 9.20.

(2S,8S)-2,8-Bis(hydroxymethyl)-1,7-dioxaspiro[5.5]-undecane (31). Vinyl sulfide 30 (300 mg, 0.87 mmol) was dissolved in trifluoroacetic acid (2 mL) and water (2 mL); then stirred overnight at 25°C. Benzene (30 mL) was added and water removed by azeotropic distillation. Dilution with ether, drying ($MgSO_4$), filtration and solvent removal in vacuo gave 368 mg of crude product. IR (CCl_4) 1780 cm^{-1}. Dissolution in 75% aqueous methanol (10 mL) containing potassium carbonate, refluxing for 3 h; then dilution with water and ether-methylene chloride (1:1) gave, after drying ($MgSO_4$), filtration and evaporation to dryness, 186 mg of an oil. Chromatography (neutral alumina, activity III, gradient from dichloromethane to 5% methanol/dichloromethane) mp. 96.0-96.5°C (ether): IR ($CHCl_3$) 3590, 3600-3200, 3000, 2940, 2870, 1450, 1430, 1380, 1370, 1280, 1220,

1200, 1155, 1080, 1040, 1010, 980 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.80 (broad s, 2H, -OH), 3.20-3.59 (m, 6H, $-OCH_2-$, -OCH-), 0.91-2.05 (m, 12H, $-CH_2-$); ^{13}C-NMR ($CDCl_3$) δ 95.9, 69.7, 66.1, 35.2, 26.4, 18.2; $[\alpha]_D$ = +60.5 (C = 0.81, chloroform).

Anal. calcd. for $C_{11}H_{22}O_4$: C, 61.09; H, 9.32. Found: C, 60.75; H, 8.95.

Optical purity of spiroketal (31). (+)-α-Methoxy-α-trifluoromethyl phenylacetic acid[57] (250 mg, 1.05 mmol) in thionyl chloride (2 mL) was refluxed for two days. Excess thionyl chloride was removed in vacuo and the residue was distilled bulb-to-bulb (125°C, 20 mm) to give the acid chloride: IR (CCl_4) 1785 cm^{-1}.

A solution of spiroketal 31 (43 mg, 0.2 mmol) in pyridine (1 mL) was reacted with the acid chloride (132 mg, 0.52 mmol) in carbon tetrachloride (1 mL). After stirring 12 h at 25°C the reaction mixture was diluted with ether (3 mL) and filtered through alumina (neutral, activity III) to give the diester: IR (CCl_4) 2950, 1751, 1450, 1270, 1243, 1187, 1172, 1125, 1022, 990, 720, 695 cm^{-1}; ^{1}H-NMR (CCl_4) δ 7.17-7.67 (m, 10H, Ar), 4.16 (d, 4H, J = 5 Hz, $-OCH_2-$), 3.66-4.16 (m, 2H, -OCH-), 3.52 (s, 6H, $-OCH_3$), 1.16-1.80 (m, 12H, $-CH_2-$); ^{19}F-NMR (207 MHz) gave two singlets separated by 9 Hz in a ratio of 9:1. $[\alpha]_D^{22}$ of spiroketal used was +55.6° (C = 0.1 g/

mL, $CHCl_3$). Therefore $[\alpha]_D^{22}$ = +69.5° for optically pure spiroketal.

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CHAPTER III

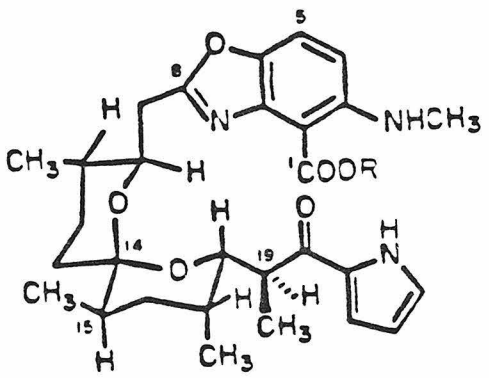
Synthesis of A-23187

Introduction

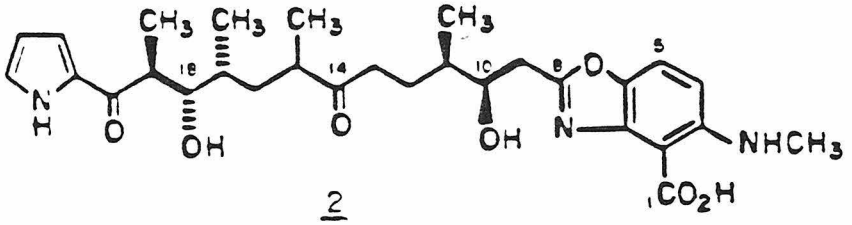
Having confirmed in models that control of the stereochemistry of C_{10} and C_{18} of diol 2 would ensure closure to the correct C_{14} spirane configuration for A-23187 (1a) and further, that the configuration of the methyl at C_{15} could be equilibrated during the acid-catalyzed closure of diol 2, we planned to utilize these results for the total synthesis of A-23187. Since we desired both a convergent and an asymmetric synthesis (so that the absolute configuration of A-23187 could be assigned[1]) we initially investigated the synthesis of diol ketone 3 and heterocycle 4 resulting from disconnection of the C_{12}-C_{13} bond as depicted in Scheme I. Subunit 4 was a likely candidate for chiral synthesis from chiral hydroxybutyric acid 14[2] (detailed in a later section). Resolution of 1a could then be accomplished by separation of diastereomers without requiring further chemical modification.

The synthesis of 3 posed an interesting problem being confronted increasingly more often in organic synthesis, namely, control of asymmetry in an acyclic unit.[3] Our strategy was to use a ring to control stereochemistry and then to free the desired acyclic piece. Accordingly, we chose diol 5 as our immediate target. Desulfurization would then yield acyclic 3 ($R_1 = R_2 = H$).

Scheme I



1a, R = H
1b, R = CH_3



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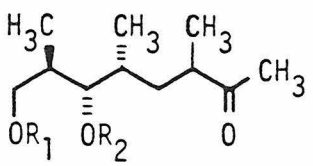

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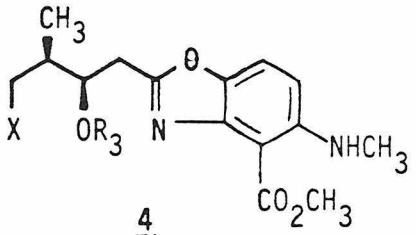

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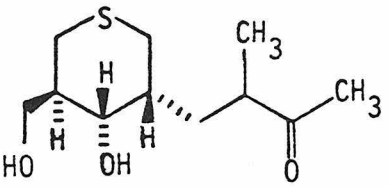
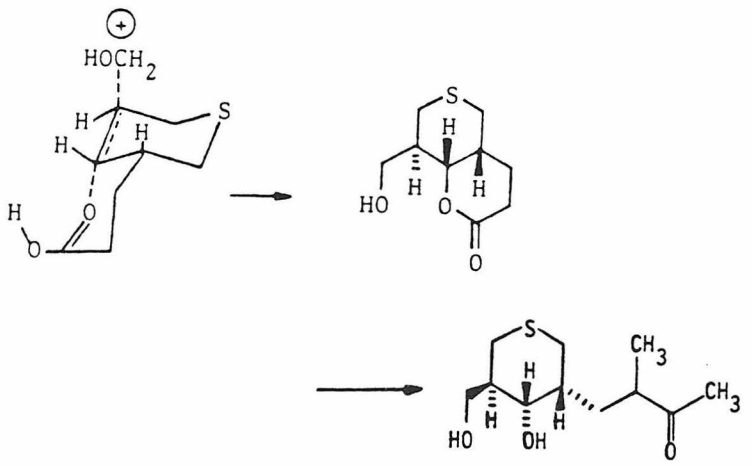


5

Discussion of Alkylation Approach

Starting from the known thiacyclohexanone 6b,[4] the enamine 7 was formed by standard methods.[5] Conversion to the olefin 9 was conveniently done in one pot, without isolation of intermediates, by treatment of enamine 7 with methyl acrylate[5] followed by hydroboration of enamine 8.[6] Acid-catalyzed elimination[6] of the intermediate α-amino alkyl borane gave olefin 9 in a 64% overall yield from 6b. Saponification[7] quantitatively gave the desired acid 10. Scheme II summarizes the above sequence.

We now faced the problem of introducing the elements $-CH_2OH$ and -OH across the double bond in a regio- and stereospecific fashion. Our initial plan was to utilize the acid side chain to direct attack[8] by an incoming electrophile as in equation 1. The lactone could then



(1)

5

Scheme II

6a, R = CO_2Me
b, R = H

7

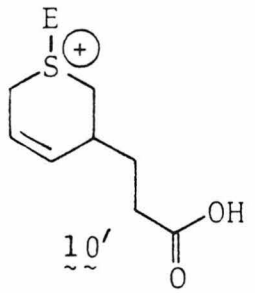
8

9

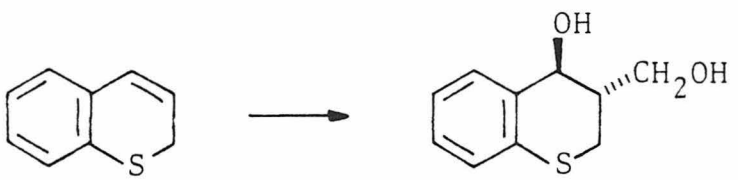
10

11a, R = H
b, R = CH_3

be methylated and treated with methyllithium[9] to give diol 5. Unfortunately, reaction of several electrophiles ($POCl_3$/DMF,[10] $CH_3COCl/AlCl_3$,[11] or Br_2[12]) with the acid 12, or the derived amide or ester, failed to yield any lactonic material. Likewise, attempted 1,3-dipolar cycloadditions failed to give any reaction.[13] The explanation for these negative results may be that the sulfur in 10 complexed with electrophiles to form 10', in which the olefin was sufficiently deactivated to prevent any further reaction. This is partially substantiated by the failure of attempts to cyclopropanate similar systems with dichlorocarbene.[14] Gaining some



10'



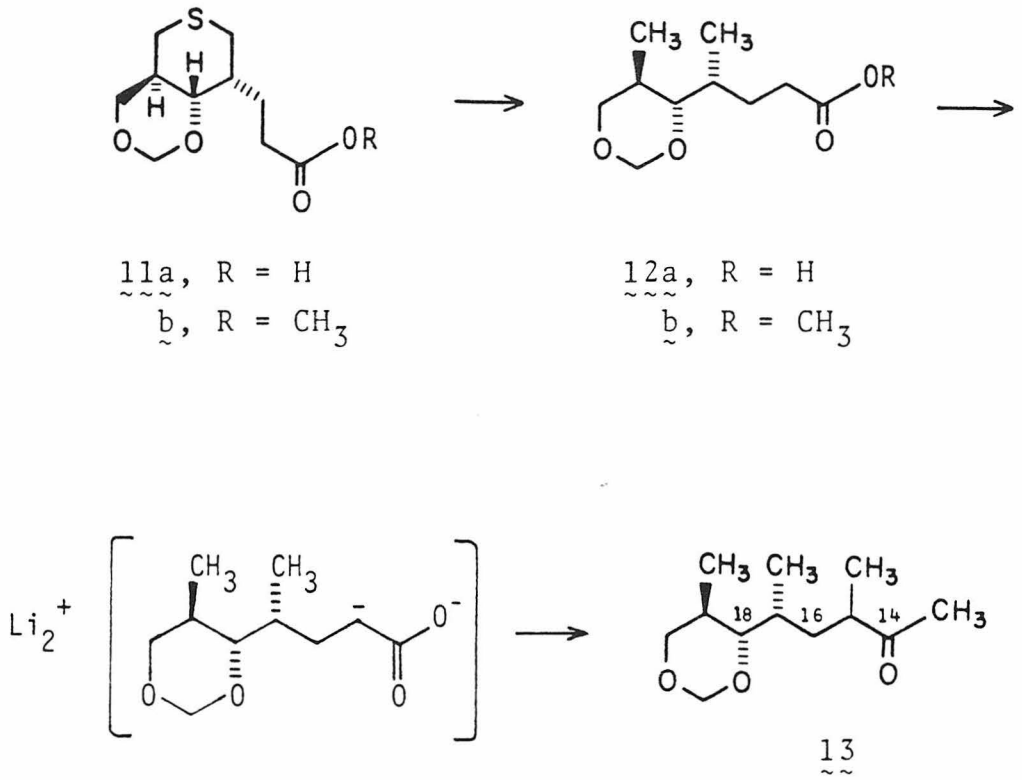
(2)

encouragement from a literature report that the Prins reaction in aqueous media was successful for a system similar to ours[15] (eq 2), we attempted to apply it to 10.

Treatment of 10 under standard Prins conditions[16] led to the isolation of small amounts of a crystalline material which we identified as 11a. After many attempts, we optimized the yield of 11a at approximately 25% by use of very carefully controlled conditions. Temperature and concentration as well as the scale of the reaction were found to be crucial factors in controlling the yield (see experimental). Esterification of the acid gave an oil, 11b, which could be purified by careful chromatography on a Waters' Prep 500. The formation of the dioxane, rather than a diol, probably arises from the high concentration of formaldehyde used giving formaldehyde dimer as the active electrophile rather than free monomer.[17]

Regio- and stereochemical assignments for 11b were made by proton and ^{13}C-NMR analysis of 11b and the desulfurized ester (12b).[18] ^{13}C-NMR spectra indicated that both 11b and 12b were diastereomerically homogeneous. The proton spectrum[19] of 11b (Figure 1) revealed a proton (3.85 δ) which was coupled to only two other protons (H_{17} and H_{19}). From the chemical shift and integration, this signal was determined to be a methine proton with an α-oxygen. This confirmed the regiochemistry as that shown in 11b since in the other regioisomer the corresponding proton would be coupled to three protons. Also, desulfurization did not effect the chemical shift

Scheme III



of this proton (Figure 1), consistent with structure 11b (one might expect a shift in the regioisomer since desulfurization would correspond to the loss of a β-sulfur atom). The stereochemistry was assigned by analysis of the coupling constants of H_{18} to H_{17} and H_{19} in 11b and 12b. In 11b, the coupling constants are 2.7 and 11.1 Hz, consistent with one trans-diaxial coupling and one cis-coupling (or trans-diequatorial). Removal of sulfur yields a compound which retains the diaxial coupling

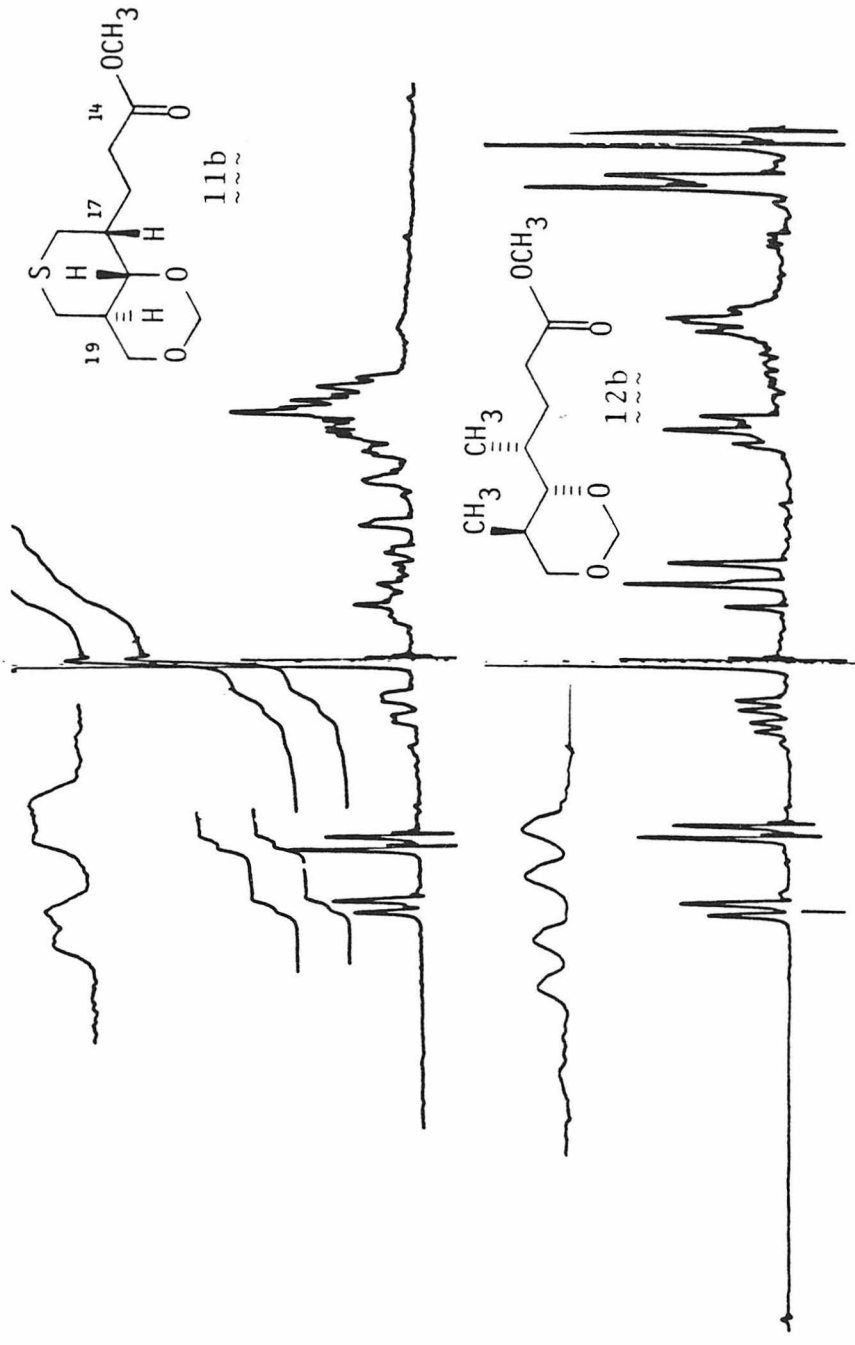


Figure 1. 90 MHz Proton Spectra of 11b and 12b.

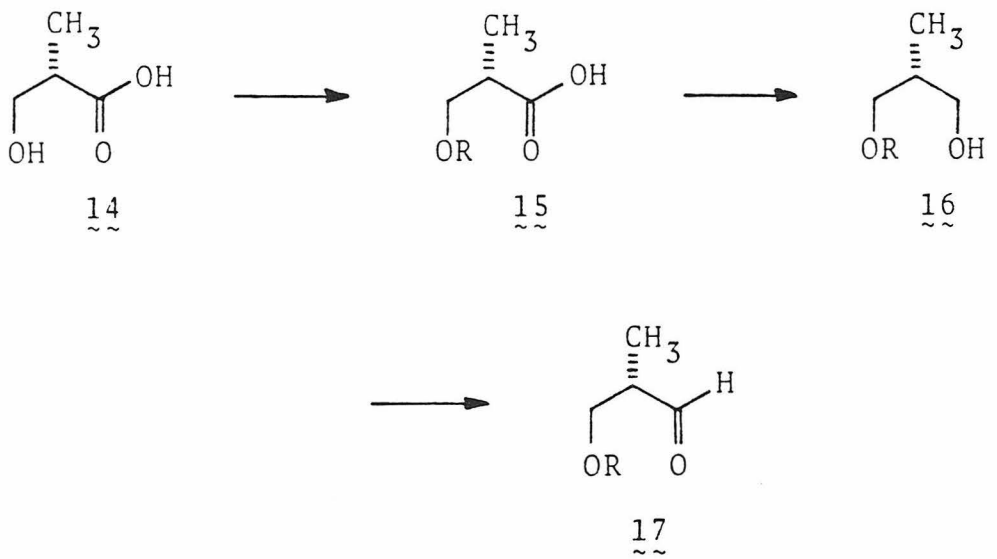
constant virtually unchanged (11.4 Hz) indicating it is probably present in the dioxane ring. The other coupling constant increases to 4.8 Hz from 2.7 Hz, consistent with a coupling between a ring proton and an acyclic proton. All these data, plus the fact that the Prins reaction is known to proceed with high trans selectivity,[16b,17,20] is consistent with the structure shown for 11b.

Three steps remained to convert 12b to 3: introduction of the methyl group at C_{15}, conversion of the ester to a methyl ketone and hydrolysis of the dioxane. The hydrolysis could be accomplished in quantitative yield by the method of Ness[21] but was postponed since the methylene acetal protecting group was useful to mask the diol function during subsequent transformations. Introduction of the two required methyl groups was readily accomplished in one pot from acid 12a. Hydrolysis of ester 12b by treatment with potassium hydroxide in methanol was quantitative. Then, in one pot, the dianion[22] was generated, quenched with one equivalent of methyl iodide and treated with methyllithium[23] to give methyl ketone 13 (Scheme III) in a 59% overall yield from ester 12b (a net yield from the known ketone 6 to 13 of 10%). Proton and ^{13}C-NMR spectral analysis of 13 revealed it to be a 1:1 mixture of diastereomers due to the newly intro-

duced asymmetric center at C_{15}.

With the piece corresponding to ketone 3 in hand, we investigated the synthesis of heterocycle 4. Since the required aromatic acid was not available at the time, we chose instead to utilize 2-methylbenzoxazole as a model. From literature precedent,[24] we felt that an aldol reaction of 2-lithiomethylbenzoxazole with aldehyde 17 should give the desired Cram product (19a). To test this hypothesis, the synthesis of aldehyde 17 was undertaken (Scheme IV).

Scheme IV



R = t-Bu(Ph)$_2$Si

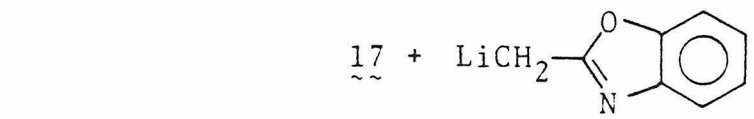
Protection of the known chiral hydroxy-isobutyric acid 14[2] was accomplished by silylation[25] to give the monoprotected acid 15. Reduction with borane-methyl-sulfide[26] quantitatively afforded the alcohol 16. Oxidation with Collins Reagent[27] gave aldehyde 17 in a 64% overall yield from 14. Proton NMR examination of alcohol 16 and aldehyde 17 in the presence of tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato], europium III[28] revealed them both to be enantiomerically pure (Appendix V).

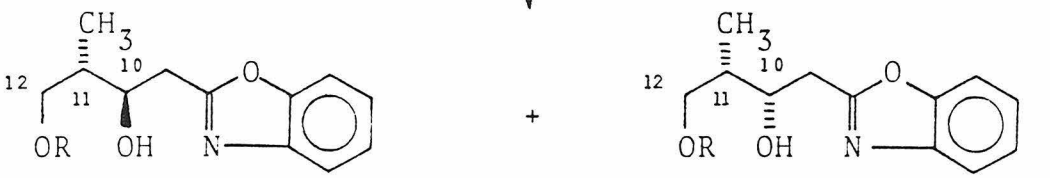
Then we investigated the generation of 2-lithio-methylbenzoxazole and its application in the aldol reaction. Surprisingly, little precedent for this kind of anion existed in the literature.[29] After some experimentation, we found that the success of the aldol depended on maintaining the anion at temperatures below -60°C, otherwise it degraded. Meyers has observed similar degradation with simple lithiooxazolines,[30] but only at higher temperatures. Disappointingly, the aldol reaction (Scheme V) was non-selective, giving an 85% yield of a 1:1 mixture of the Cram (19a) and anti-Cram (18a) products. Stereochemical assignments were made by converting the separated alcohols, high R_f and low R_f, into two conformationally locked acetonides, A and B respectively, via desilylation with

fluoride[31] and ketalization of the diols with acetone in the presence of p-toluenesulfonic acid. Application of the results from proton NMR studies of similar systems[19b,32] and proton NMR analysis of A and B (Figure 2) allowed us to assign the anti-Cram aldol product (18a) as the high R_f component and the Cram product (19a) as the low R_f component. Specifically, the C_{11}-methyl resonance for A was upfield (closer to TMS) from the corresponding resonance for B implying that the methyl was equatorial in A and axial in B.[19b] Similarly, the methine proton, H_{11}, in A was downfield from H_{11} in B indicating that H_{11} was axial in A but equatorial in B,[19b] consistent with the observations for the methyl resonances. Further, the methine proton H_{10} of acetonide A appeared as the X part of an ABMX pattern with a value for $J_{10,11}$ of 12.6 Hz (by computer analysis), consistent with a trans-diaxial coupling. The corresponding value in B was 7.2 Hz, consistent with an axial-equatorial coupling.[19a] Analysis of the chemical shifts and coupling constants for the axial and equatorial protons at C_{12} was also consistent with the structural assignments of A as anti-Cram derived acetonide 20 and B as Cram derived acetonide 21. All of these observations are summarized in Tables 1 and 2.

Next, we briefly explored methods to increase the yield of 19a. Changes of counter-ion from lithium to

Scheme V





18a, R = t-BuPh$_2$Si
18b, R = H

19a, R = t-BuPh$_2$Si
19b, R = H

20

21

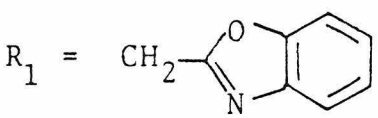


Table 1. Chemical Shift Analysis of 20 and 21.

Proton	δ[a] A	B	Conclusion
Methyl at C_{11}	0.80	1.13	equatorial methyl in A axial methyl in B
H_{10}	1.77	1.55	axial in A equatorial in B

[a]In ppm relative to tetramethylsilane internal standard, $CDCl_3$ soln, 90 MHz field strength.

Table 2. Coupling Constant Data of 20 and 21.

Potons Coupled		J (Hz)[a]	Conclusion
A	H_{10}-H_{11}	12.6	trans-diaxial
	H_{11}-H_{12} eq	6.0	axial-equatorial
	H_{11}-H_{12} ax	10.2	trans-diaxial
B	H_{10}-H_{11}	2.6	axial-equatorial
	H_{11}-H_{12} eq	2.7	equatorial-equatorial
	H_{11}-H_{12} ax	1.5	axial-equatorial

[a]By computer modeling.

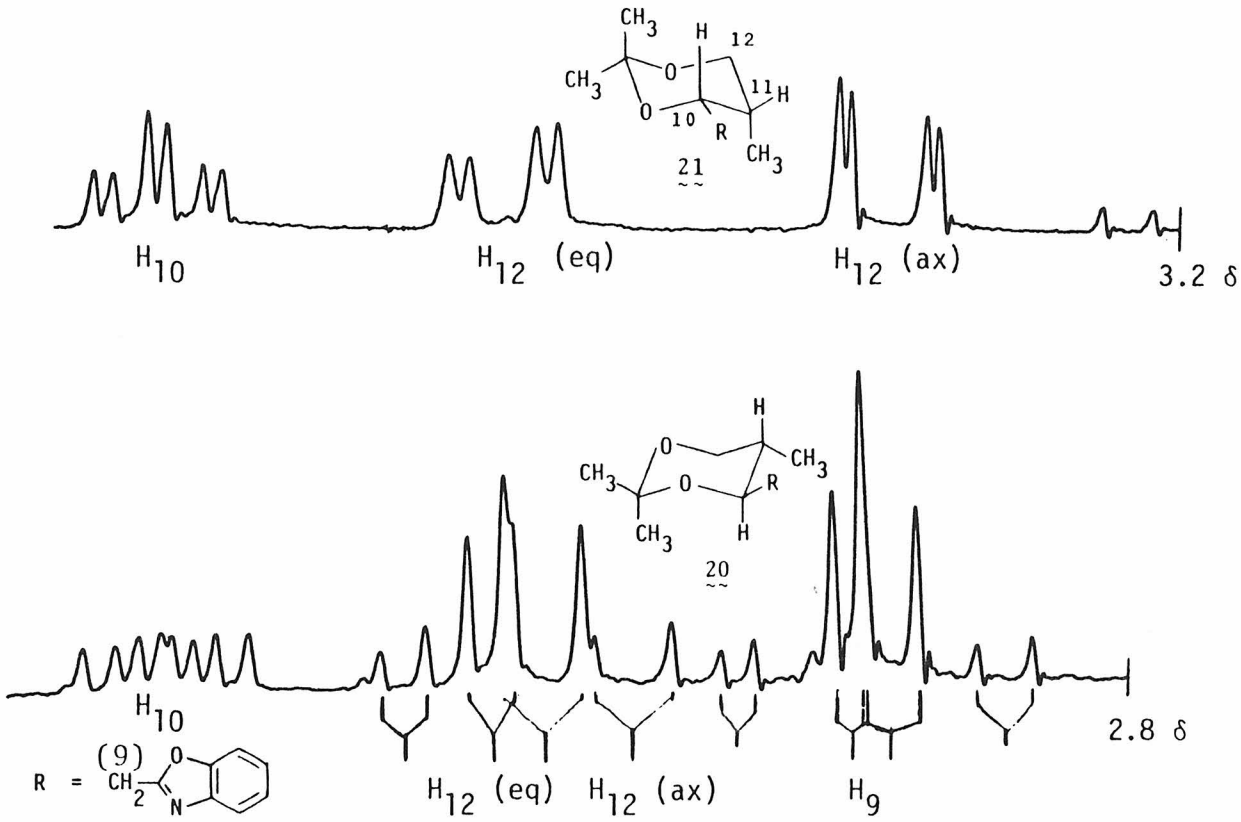
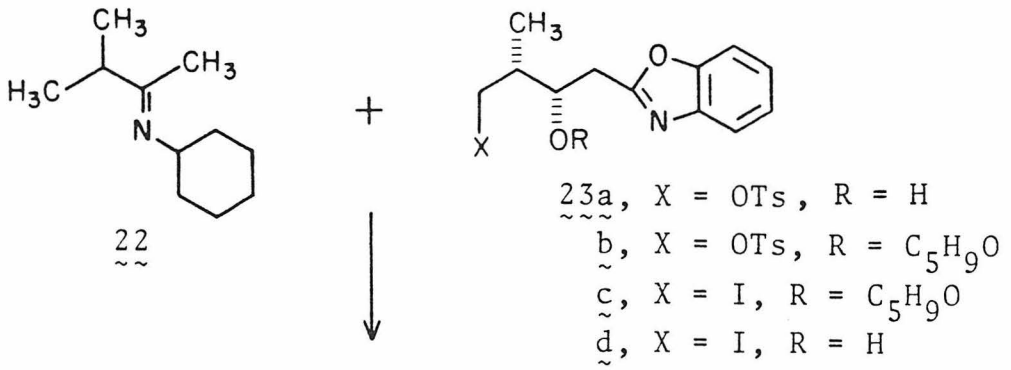


Figure 2. Expansion of the methylene and methine regions of the 90 MHz ^{1}H-NMR spectra for 20 and 21.

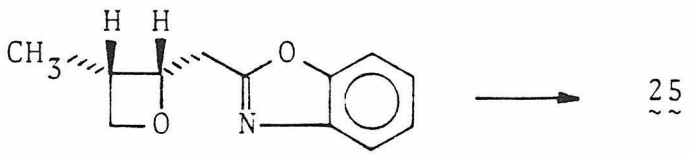
zinc as well as variation in temperature and solvent[24,32] gave no improvement in the ratio of 18a to 19a.[33] Dispensing with attempts at optimization, we turned our attention to the formation of the C_{12}-C_{13} bond. Encouraged by studies done by Stork[34] and Normant,[35] we believed that alkylation of the imine anion derived from 13 would afford the best yields of the desired mono-alkylation product corresponding to 2. Accordingly, 19b was converted to

Scheme VI



Ts = $-SO_2-C_6H_4-CH_3$

tosylate 23a[36] and the secondary hydroxyl was protected as a THP ether[37] to give tosylate 23b. In order to study the alkylation reaction, imine 22 was used as a model. Reaction of the imine anion derived by reaction of 22[35] and LDA with either tosylate 23b or iodide 23c[38] led only to the elimination product 24 (Scheme VI). Reasoning that if OTHP were converted to a poorer leaving group the elimination reaction might be prevented, we converted iodide 23d (from 23a[38]) to an alkoxide with sodium hydride. Unfortunately, after treatment with the anion of 22 only alcohol 25 and a small amount of diene 24 were isolated. Alcohol 25 probably arises by initial formation of oxetane 26 followed by proton transfer and elimination.



25

26

At this point, faced with a poor ratio in the aldol reaction and a low yield in the Prins reaction as well as difficulties with the final alkylation we decided to abandon further investigation of this approach to A-23187.

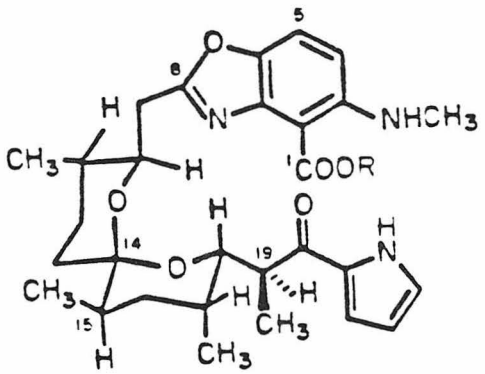
Rather, we turned our efforts toward the aldol approach outlined in Scheme VII.

Discussion of Aldol Approach

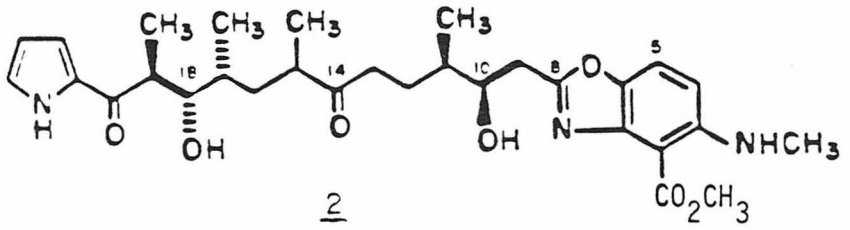
As in our previous approach, we again visualized that closure of diol 2 would give A-23187. Retrosynthetic aldol disconnection between C_9-C_{10} and C_{18}-C_{19} gave heterocyclic subunits 26 (R_1 = H) and 28 (R_4 = H) and the ketone 27 which possessed a C_2-axis of symmetry with respect to skeletal carbons C_{10}-C_{12} and C_{16}-C_{18} (Scheme VII). We felt that a chiral synthesis of 27 from chiral subunits 29 and 30 should be straightforward (Scheme VIII).[39,40] Also, literature precedent indicated that the aldol of the benzoxazole anion derived from 28 should favor the Cram product.[24,32] (The ratio was found to be 4:1, Cram/anti-Cram.[40]) Therefore, the success of the synthetic sequence seemed to hinge on whether an aldol reaction would establish the correct configurations of C_{18} and C_{19} relative to each other and relative to C_{17}.[41,42] To this end, we decided to pursue model studies designed to answer that question.

In the model studies we needed to investigate two problems: could the relative configurations of

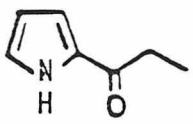
Scheme VII



1a, R = H
1b, R = CH_3



2



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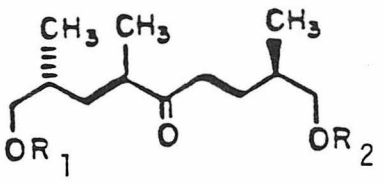
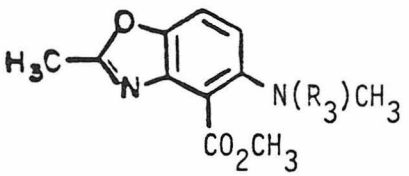
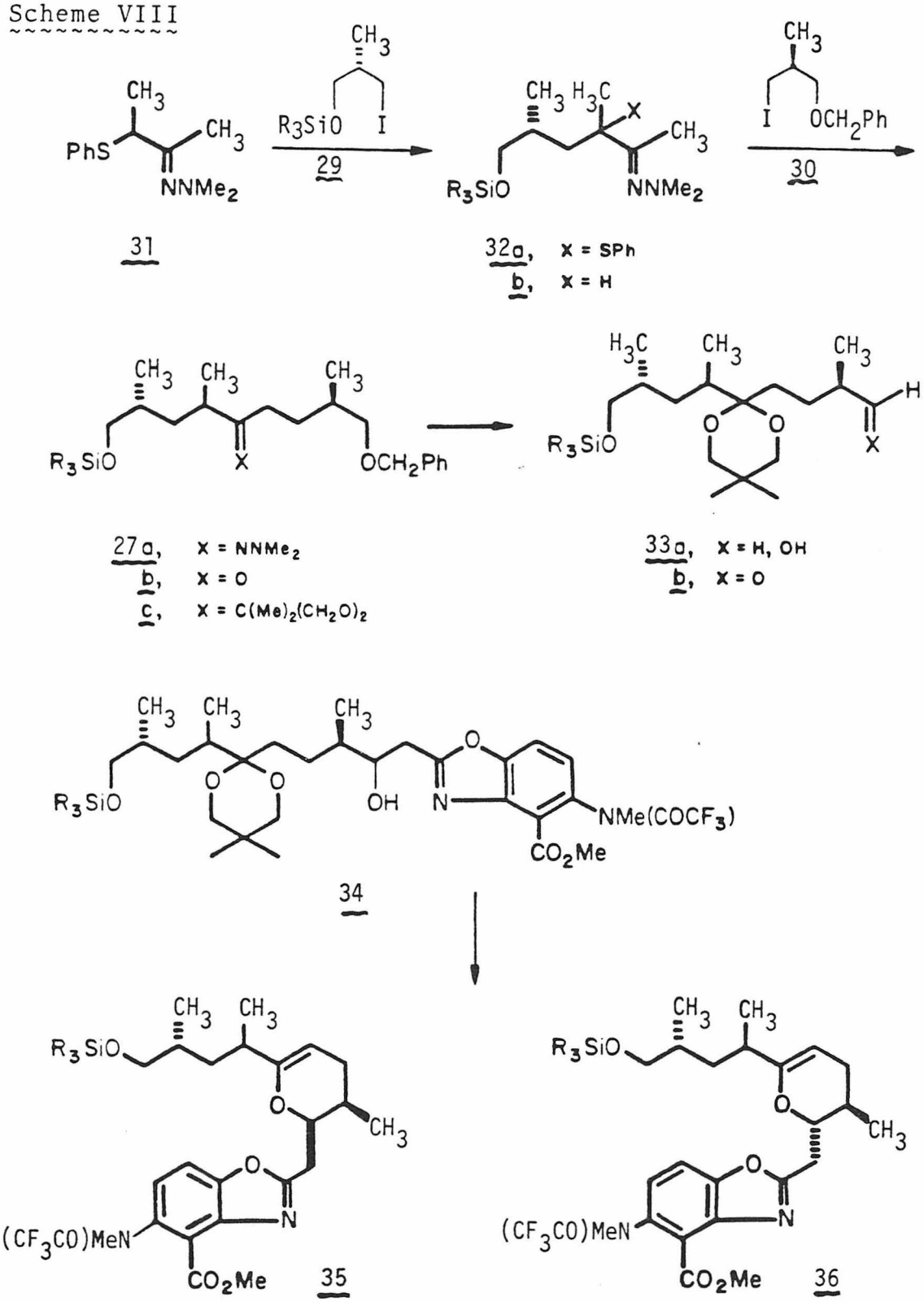


27

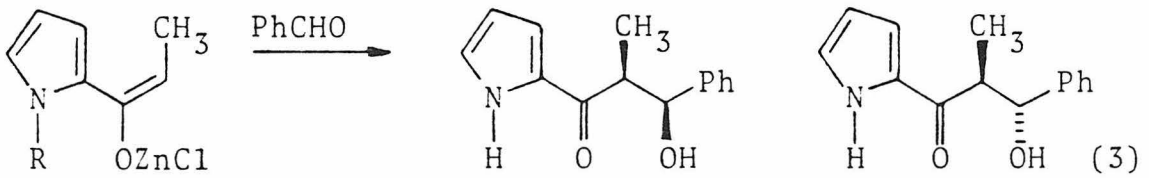


28

Scheme VIII


CH3
PhS
CH3
NNMe2
R3SiO
I
29
CH3 H3C
X
CH3
R3SiO
NNMe2
I
OCH2Ph
30
31
32a, X = SPh
b, X = H
CH3 CH3 CH3
R3SiO
X
OCH2Ph
H3C CH3 CH3
O O
H
27a, X = NNMe2
b, X = O
c, X = C(Me)2(CH2O)2
33a, X = H, OH
b, X = O
OH
N
NMe(COCF3)
CO2Me
34
(CF3CO)MeN
35
36

C_{18}-C_{19} (threo vs erythro, threo desired) be controlled and could the relative configurations of C_{17}-C_{18} (Cram vs anti-Cram, Cram desired) also be established. Initially, we studied the threo-erythro problem by using benzaldehyde as a model. We hoped that the known pyrrole 26 could be used, thereby avoiding the necessity of incorporating and later removing a protecting group. Using as an analogy the studies done by House[42] (in which he used the zinc enolate to obtain the thermodynamically favored threo product), we examined the zinc enolate of 26 (R = Zn) as shown in equation 3. As can be seen from Table 3, this was not a satisfactory solution since the erythro product predominated.

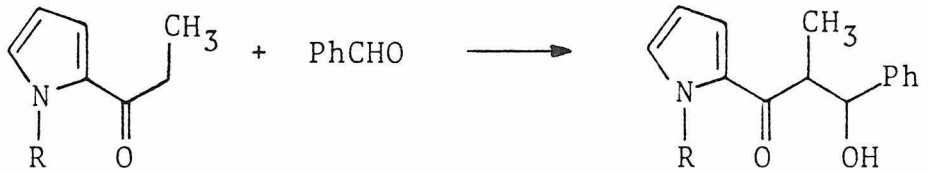


(3)

26 (R = H) erythro threo

The ratio of threo/erythro was independent of counter-ion (Zn vs Li) and was constant with time and temperature implying that the dianion probably forms a kinetic product[44] (enriched in erythro) which cannot equilibrate to the thermodynamically more stable threo product. In

Table 3. Aldol Studies of Threo vs Erythro Selectivity.

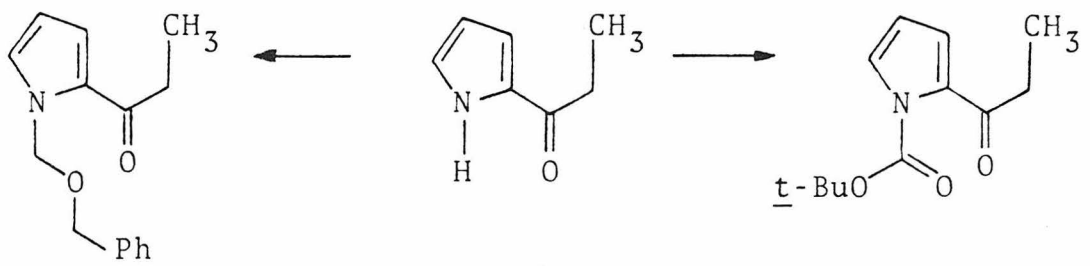


Pyrrole	R	Temp (°C)	$ZnCl_2$ (equiv)	Solvent[a]	Threo/Erythro[b]
1. 26	Zn	-78	--	A	1:3.0
2. 26	Zn	4	0.5	B	1:3.1
3. 26	Zn	4	0.5	C	1:3.2
4. 26	Zn	4	1.0	C	1:1.8
5. 37	BzO[c]	4	1.0	C	1:1.6
6. 37	BzO	4	1.0	D	1:1
7. 37	BzO	4	2.0	D	1:1
8. 38	t-BOC[d]	-78	--	B	1:3
9. 38	t-BOC	4	1.0	B	1:1
10. 38	t-BOC	4	1.0	C	3:1
11. 38	t-BOC	4	1.0	D	3:1

[a]A = THF, B = ether, C = ether/dimethoxyethane (1:1), D = ether/dimethoxyethane (1:2). [b]By NMR integration of the -OCH- doublets. [c]Benzyloxymethyl. [d]t-Butoxycarbonyl.

an attempt to solve the problem of non-equilibration of the dianion, we decided to investigate N-protected pyrroles. Since the ketalization step to close diol 2 would be acid catalyzed, we wanted to use a protecting group which would be removed under acidic conditions but stable to the conditions necessary for the aldol reaction. Pyrrole ketones 37 and 38 (readily available from 26[45]) were chosen to fulfill these conditions.

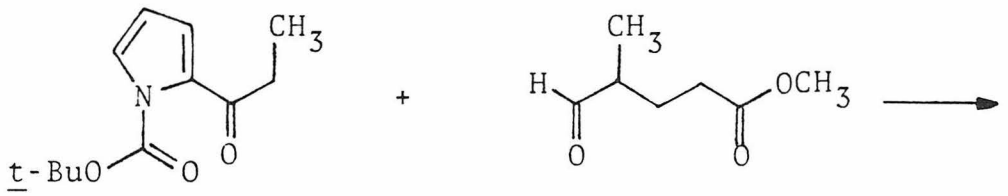
Initial experiments with benzaldehyde indicated that 38 gave the best threo/erythro ratio (ca. 3:1). To



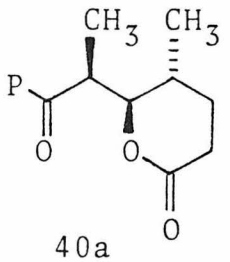
37 26 38

determine the effect of an asymmetric center next to the aldehyde (ie. Cram vs anti-Cram), we chose aldehyde 39[44b,46] as a model. Condensation of 39 with pyrrole ketone 38 gave the four lactonic products 40a, 40b, 40c and 40d, in order of elution on analytical HPLC (Scheme IX). Separation of the isomers, analysis of the proton NMR spectra and comparison with analogs of the Prelog-

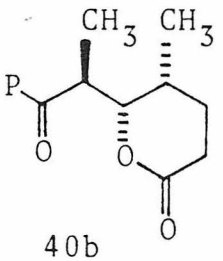
Scheme IX



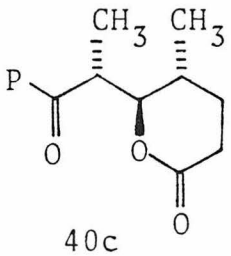
38 + 39 →



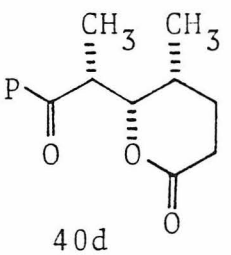
40a



40b

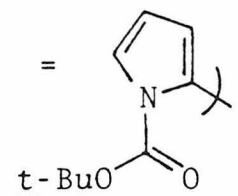


40c

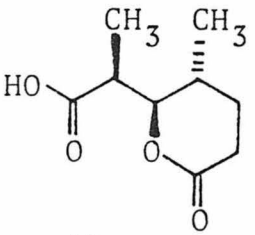


40d

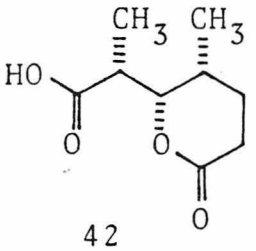
P =



Djerassi lactone and one of its isomers[44b] (41 and 42 respectively) allowed assignment of 40a as erythro-anti-Cram and 40b as threo-Cram. Several reactions were run to optimize the yield of 40b; the results are tabulated in Table 4. From the results summarized in the



41



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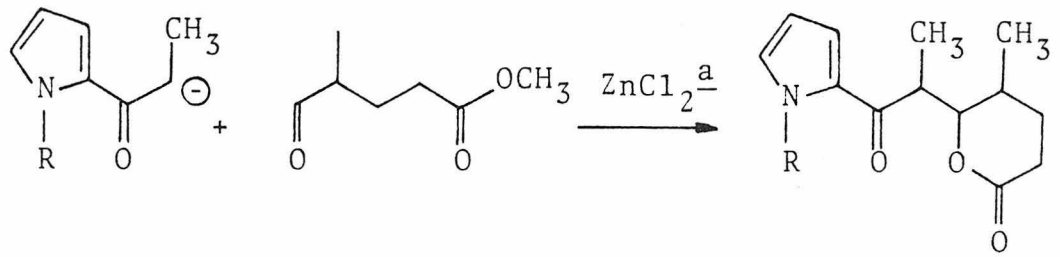
table, we chose the conditions of experiment 3. Before applying these results to the total synthesis, we investigated the stability of A-23187 to conditions necessary for the removal of the pyrrole protecting group. Treatment of an authentic sample of A-23187[47] with ion-exchange resin[48] (H^+ form) in refluxing toluene[49] convinced us of its stability to the conditions necessary for deprotection of the pyrrole.

The final steps for the total synthesis are outlined in Schemes X and XI. Treatment of a 4:1 mixture of pyrans 35 and 36 with fluoride ion effected not only silicon ether cleavage but also the removal of the trifluoroacetyl group in approximately 60% yield. Because the deprotected aromatic nitrogen might interfere with the oxidation

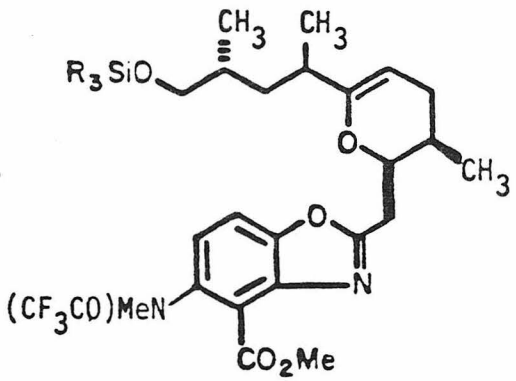
Table 4. Aldol Studies of Cram vs Anti-Cram Selectivity.



	Pyrrole	Solvent[b]	40a	40b	40c	40d[c]
1.	38	A	21	44	21	14
2.	38	B	26	32	19	23
3.	38	C	27	42	19	12
4.	R = t-Bu-OCH_2-	D	24	36	21	20
5.	37	D	20	32	25	23

[a]1 equivalent. [b]A = ether/dimethoxyethane (2:1), B = ether/dimethoxyethane (1:2), C = ether/dimethoxyethane (1:1), D = dimethoxyethane. [c]By HPLC.

Scheme X



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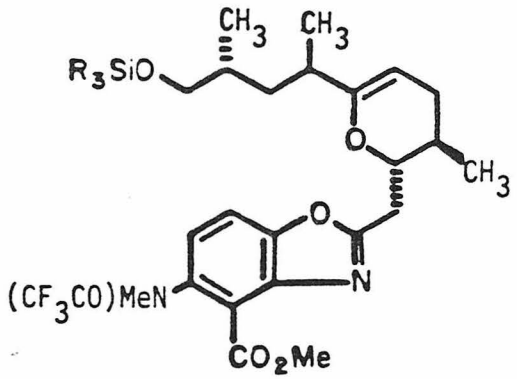

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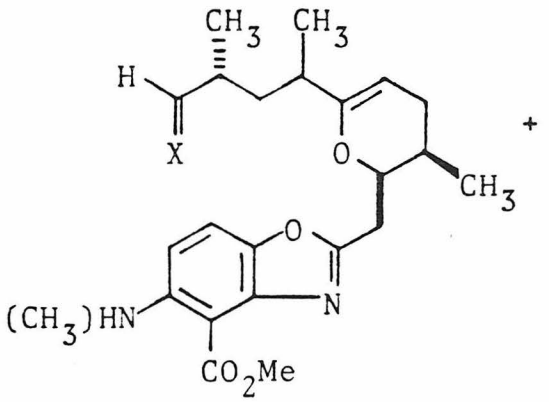
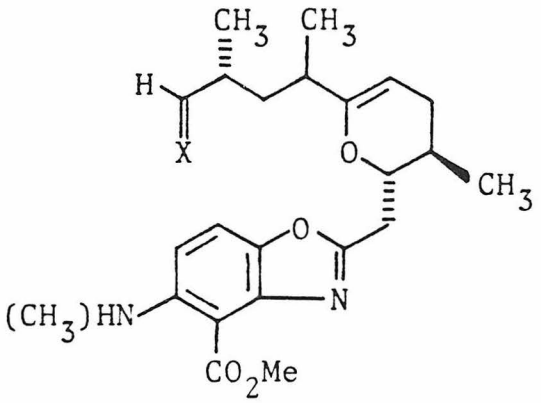
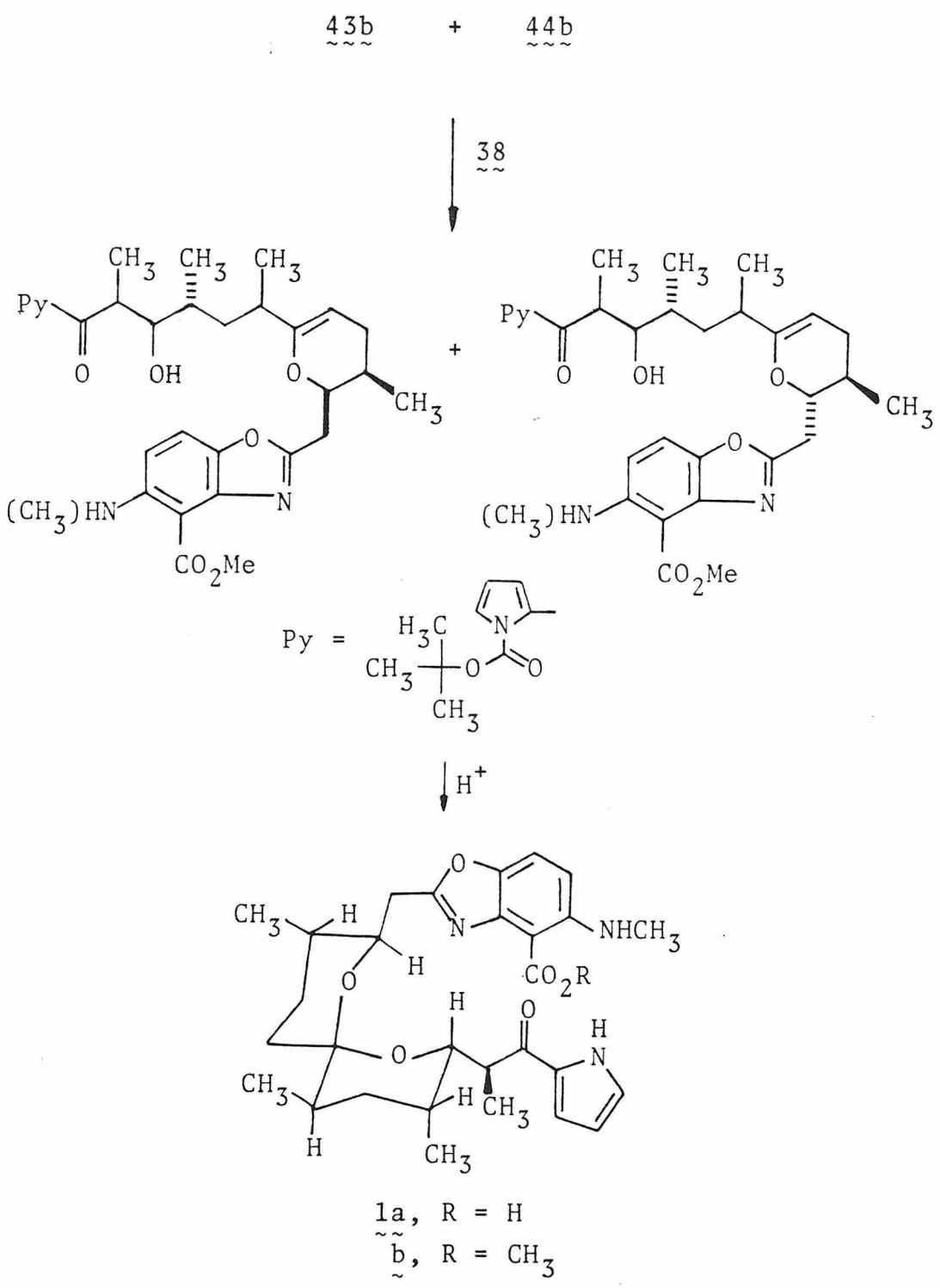


43a, X = H, OH
b, X = O



44a, X = H, OH
b, X = O

Scheme XI



1a, R = H
b, R = CH_3

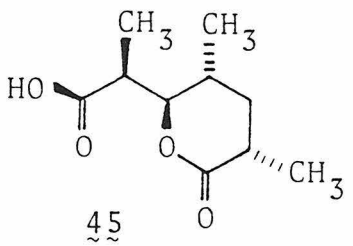
of alcohols 43a and 44a, we first investigated the stability of benzoxazole 28 (R_3 = H) (obtained from 28, R_3 = $COCF_3$, by fluoride treatment) to conditions of a Collins oxidation.[27] Since 28 (R_3 = H) was found to be stable, we proceeded to oxidize the mixture of 43a and 44a (4:1) to give aldehydes 43b and 44b. Condensation of the aldehydes with pyrrole ketone 38 gave an aldol mixture containing all eight possible diastereomers. The crude product was treated with ion-exchange resin[48] to give a mixture of eight spiroketals now lacking the pyrrole protecting group. Isolation of the major component (ca. 50% of the total) afforded a material (18%,[50] overall yield from aldehydes 43b and 44b) identical (IR, ^{1}H-NMR, MS, $[\alpha]_D$, HPLC) with an authentic sample of 1b.[51] Cleavage of the methyl ester by treatment with lithio-n-propylmercaptide[52] gave a crystalline acid in quantitative yield. Synthetic 1a, mp 184.5-186°C (lit mp 181-182),[1a] $[\alpha]_D^{24}$ -56° (C = 1.0 g/mL, $CHCl_3$)[53] was identical in all respects (IR, UV, MS, ^{1}H-NMR, ^{13}C-NMR, $[\alpha]_D$, mixed mp) to an authentic sample of A-23187 (Table 5). This total synthesis firmly established the absolute configuration of A-23187 as that depicted in structure 1a.

Table 5. Comparison of Data for Authentic and Synthetic A-23187.

	Authentic[1,53]	Synthetic
IR ($CHCl_3$)	1640 cm^{-1}	1640 cm^{-1}
	1690	1690
UV (ethanol)	204 mμ	208 mμ
	224	226
	278	279
	284-288 (sh)	284-288 (sh)
	379	377
mass spec (m/e)	523	523
	318	318
	206	206
	123	123
	94	94
mp	185-186	184.5-186
$[\alpha]_D^{24}$	-56°	-56°

Summary

In this chapter, two routes to A-23187 were discussed. The first route was unsuccessful due to low stereoselectivity in an aldol reaction and failure of a key alkylation step. This route was noteworthy, however, in that if the chirality of C_{18} were inverted and a methyl group were added to C_{15}, then acid 13 could be converted to the Prelog-Djerassi lactone 45,[54] a key intermediate in the synthesis of Methymicin.[54a]



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The second route, based on two key aldol reactions, was successfully accomplished to afford synthetic A-23187. Since this route started from chiral precursors of known configuration, the completion of the synthesis allowed assignment of the previously unknown absolute configuration of A-23187 as that depicted for 1a. Improvement of the second aldol should be investigated to increase the stereoselectivity of that step.

Experimental Section

General. Diethyl ether, tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were dried by distillation from benzophenone ketyl under nitrogen. Triethylamine diisopropylamine and pyrrole were dried by distillation under nitrogen from calcium hydride. Hexamethylphosphoric acid triamide was distilled from sodium metal and stored over 13X molecular sieves. Dichloromethane was filtered through activity I alumina prior to use. Ion-exchange[48] resin was washed with methanol and methanol removed by azeotropic distillation with toluene immediately prior to use. Methyl acrylate was distilled just prior to use.

All commercial alkyllithium reagents were titrated by the procedure of Watson and Eastham.[55]

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

Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-4210 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra were recorded on a Varian Associates EM-390 or T-60 spectrophotometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Proton data are reported as follows: chemical shift, multiplicity (s = singlet, d =

doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (Hz) and interpretation. Carbon-13 nuclear magnetic resonance spectra were recorded on a Varian Associates XL-100 (25.2 MHz) spectrometer and are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Mass spectra were recorded on a DuPont MS 21-492B mass spectrometer at 75 eV. Mass spectral analyses as well as combustion analyses were performed by the California Institute of Technology Microanalytical Laboratory.

Analytical gas chromatographic analyses were performed on a Varian-Aerograph Model 1440 gas chromatograph equipped with a flame ionization detector using 2 m by 3.18 mm stainless steel columns of 10% Carbowax 20 M or 10% SE-30 on 80-100 mesh DMCS Chromsorb W support. Analytical HPLC was performed on a Water's Associates high pressure liquid chromatograph equipped with ultraviolet and refractive index detectors using a 35 mm by 6 mm μ-porasil column.

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

2-(Methoxycarbonyl)-4-thiacyclohexan-1-one (6a).[4] Commercial reagent grade sodium methoxide (54.2 g, 1 mol) was suspended in reagent grade THF (400 mL) in a three-neck, 500-mL, round-bottomed flask equipped with a mechanical

stirrer, nitrogen inlet, reflux condenser and 150-mL constant-volume addition funnel and heated to reflux. Dimethyl-3,3'-thiodipropionate (100 g, 0.49 mmol) in THF (100 mL) was added over 1 h. The reaction was monitored by GLC (10% SE-30). After an additional 0.5 h at reflux the reaction mixture was cooled and THF removed *in vacuo*. The residue was added to acetic acid (130 mL) in ice-water (400 mL). Extraction with ether (4 x 200 mL), washing of the combined organics with water and saturated sodium bicarbonate (to remove acetic acid), drying (Na_2SO_4), filtration and removal of solvent *in vacuo* gave an oil. Distillation gave a 2.2 g forerun (70-98°C, 1 mm) and a major fraction (98-102°C), 48.5 g (58%): IR (neat) 2995, 2950, 2900, 2830, 1735, 1650, 1603, 1435, 1350, 1304, 1250, 1220, 1193, 1104, 1060, 830, 690, 670 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 12.16 (s, 0.5H, enolic form) 3.73 (s, 3H, $-OCH_3$), 2.48-3.68 (m, 6.5H); ^{13}C-NMR ($CDCl_3$) δ 203.3, 172.2, 97.2, 58.6, 52.4, 51.7, 43.5, 32.4, 30.7, 30.3, 24.6, 23.4.

4-Thiacyclohexan-1-one (6b). Keto-ester 6a (45.5 g, 0.26 mol) was added to a 500-mL round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. 10% Sulfuric acid in water (400 mL) was added and the heterogeneous mixture heated to reflux until carbon dioxide evolution ceased (*ca.* 3 h). Cooling caused formation of a white precipitate. The mixture was

extracted with ether (4 x 100 mL); then organics were combined, washed with water and dried (Na_2SO_4). Filtration and removal of solvent in vacuo gave a yellow solid which was sublimed at 85°C (30 mm) to give 23.8 g (80%) of a white solid, mp 62-63°C: IR ($CHCl_3$) 3025, 2980, 2930, 1718, 1430, 1378, 1300, 1299, 1275, 1228, 1130, 980, 655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.81 (A_2B_2 pattern); ^{13}C-NMR ($CDCl_3$) δ 207.6, 43.9, 30.0.

1-Pyrrolidin-1-yl-4-thia-1-cyclohexene (7). Ketone 6b (30.0 g, 0.26 mol) was dissolved in benzene (300 mL) and pyrrolidine (38.7 g, 0.54 mol) was added. The mixture was heated to reflux with azeotropic removal of water. After 5 h (GLC, 10% SE-30) benzene was removed by distillation. The residue was distilled 98-102°C (0.2 mm) to give 39.1 g (90%) of a colorless air and moisture sensitive liquid: IR ($CHCl_3$) 2980, 2920, 2870, 2815, 1630, 1410, 1385, 1345, 1300, 1285, 1165, 1138, 885 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.41 (t, 1H, J = 4.5 Hz, vinyl), 3.24 (d, 2H, J = 4.5 Hz, $-SCH_2-$ vinyl), 3.00 (t, 4H, J = 7.3 Hz, $-NCH_2-$), 2.61 (A_2B_2, 4H, SCH_2CH_2- vinyl), 2.68-2.00 (m, 4H, $-CH_2CH_2-$).

Methyl 3-(1-thia-4-cyclohexen-3-yl)propionate (9). Enamine 7 (32 g, 0.19 mol) in p-dioxane[56] (200 mL) in a three-neck 1000 mL round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, nitrogen inlet

and 150-mL constant-volume addition funnel was heated to reflux. Freshly distilled methyl acrylate (22 mL, 0.25 mol) in p-dioxane (30 mL) was added during 2 h. Reflux was continued an additional 14 h (GLC, 10% SE-30) followed by cooling to 25°C. Borane-methylsulfide (25 mL, 0.25 mol) in p-dioxane (50 mL) was added (mild exotherm) over 1 h with stirring. After stirring an additional 2 h, the mixture was cooled in an ice bath and propionic acid (56 mL, 0.75 mol) was slowly added (vigorous hydrogen gas evolution at beginning). When the initial reaction subsided, the cooling bath was removed and the mixture was heated to reflux for 9 h (GLC, 10% SE-30). Solvent was then removed in vacuo, the residue taken up in hexane (200 mL), washed with water and brine and dried (Na_2SO_4). Filtration, removal of solvent in vacuo and distillation at 75-80°C (0.05 mm) gave 25.4 g (72%) of a colorless oil: IR (CCl_4) 3015, 2955, 2920, 2880, 1735, 1434, 1320, 1245, 1210, 1193, 1160, 1020, 690, 680 cm^{-1}; ^{1}H-NMR (CCl_4) δ 5.45-5.86 (m, 2H, vinyl), 3.61 (s, 3H, $-OCH_3$), 3.03 (broad d, 2H, J = 3 Hz, $-SCH_2$ vinyl), 2.50-2.78 (m, 1H, vinyl CH-), 2.14-2.42 (m, 4H, $-SCH_2-$, $-CH_2CO_2Me$), 1.73 (t, 2H, J = 6 Hz, $-CHCH_2CH_2$); ^{13}C-NMR ($CDCl_3$) δ 173.4, 131.2, 124.1, 51.4, 33.9, 31.2, 30.0, 29.6, 25.3.

Anal. calcd. for $C_9H_{14}O_2S$: C, 58.03; H, 7.58. Found: C, 58.15; H, 7.70.

Enamine 8: IR (CCl_4) 2960, 2880, 2820, 1725 1625, 1434, 1300, 1240-1180, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.32 (t, 1H, J = 4 Hz, vinyl), 3.66 (s, 3H, $-OCH_3$), 1.50-3.11 (m, 22H).

Anal. (performed on a sample of 8 that had been hydrolyzed to ketone) calcd. for $C_9H_{14}O_3S$: C, 53.44; H, 6.98. Found: C, 53.20; H, 6.76.

IR ($CHCl_3$) 2950, 2910, 1725, 1700, 1430, 1365, 1310, 1265, 1190, 1165, 1110, 1015, 975, 825, 730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.63 (s, 3H, $-OCH_3$), 2.20-3.01 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 209.3, 178.8, 52.0, 44.1, 36.0, 31.3, 31.0, 24.5.

Hydrolysis of ester 9. Ester 9 (29.1 g, 0.16 mol) was dissolved in THF (70 mL) and sodium hydroxide (6.8 g, 0.17 mol) in water (100 mL) was added. The resulting biphasic mixture was stirred 1 h during which time the mixture became homogeneous. TLC (silica gel, 50% ethyl acetate/45% hexane/5% acetic acid) indicated consumption of ester (R_f = 0.55). After cooling the reaction in ice it was acidified with concentrated hydrochloric acid to pH 1. The acid was isolated by extraction into chloroform (4 x 100 mL), drying (Na_2SO_4), filtration and removal of solvent in vacuo to give 18.2 g (100%) of a waxy solid mp. 42-44°C: IR ($CHCl_3$) 3400-2400, 2990, 2910, 1720, 1700, 1432, 1405, 1270 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 11.65

(s, 1H, $-CO_2H$), 5.42-5.97 (m, 2H, vinyl), 3.00 (broad d, 2H, J = 3 Hz, $-SCH_2-$ vinyl), 2.70 (t, 1H, J = 8 Hz, -CH-), 2.13-2.52 (m, 4H, $-SCH_2-$ and $-CH_2CO_2-$), 1.50-1.95 (m, 2H, $-CHCH_2CH_2-$); ^{13}C-NMR ($CDCl_3$) δ 179.6, 131.2, 124.4, 33.8, 31.3, 29.7, 29.6, 25.3.

Anal. calcd. for $C_8H_{12}O_2S$: C, 55.82; H, 7.02. Found: C, 56.25; H, 7.16.

Methyl 2-(trans-1,8a-cis-6,8-oxa-3-thiaperhydronaphth-1-yl)propanoate (11b). In each of two 50-mL round-bottomed flasks was placed paraformaldehyde (9.0 g, 0.30 mol). To each was added H_2O (19 mL) followed by concentrated sulfuric acid (7 mL). The resulting mixtures were heated to 100°C and maintained at that temperature for 2 h during which time the formaldehyde depolymerized to give homogeneous solutions. After cooling to 70°C, olefinic acid 10 (5.0 g, 29 mmol) was added to each flask (ie., total of 10 g of acid). The reactions were maintained at 70°C until consumption of acid was complete (ca. 16-25 h) as indicated by TLC (silica gel, 50% ethyl acetate/45% hexane/5% acetic acid; olefinic acid: R_f = 0.66; product: R_f = 0.56). The two reactions were cooled, combined, diluted with water (50 mL) and extracted with ether (5 x 40 mL). Drying, (Na_2SO_4), filtering, and removing solvent gave a crude waxy material which could be purified by medium-pressure chromatography (silica

gel, ether) to give a solid acid (ca. 25%), mp 128.5-120°C (chloroform/hexane): IR ($CHCl_3$) 3400-2400, 3000, 2850, 1704, 1421, 1368, 1280, 1180, 1125, 1085, 1075, 1038, 1025, 933 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.80 (broad s, 1H, $-CO_2H$), 5.00 (d, 1H, J = 7 Hz, part of AB quartet, H_{eq}, $-OCH_2O-$), 4.62 (d, 1H, J = 7 Hz, part of AB quartet, H_{ax}, $-OCH_2O-$), 3.88 (dd, 1H, J = 2.7, 11.1 Hz, -OCH-), 2.90-3.50 (m, 2H, $-OCH_2-$), 1.65-2.85 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 179.1, 93.9, 82.8, 70.3, 37.3, 35.6, 32.3, 32.2, 28.5, 20.6.

Anal. calcd. for $C_{10}H_{16}O_4S$: C, 51.70; H, 6.94. Found: C, 51.37; H, 6.63.

A better purification procedure consisted of dissolving the crude acid 11a in methanol (50 mL) and p-toluenesulfonic acid (monohydrate) (0.1 g), heating to reflux for 1 h, removal of solvent in vacuo and chromatography on a Waters' Prep 500 (silica gel, 30% ethyl acetate/70% hexane) with recycle to give 3.3 g (23%) of ester 11b: IR ($CHCl_3$) 3000, 2950, 2905, 2845, 1720, 1430, 1365, 1270, 1223, 1167, 1123, 1085, 1070, 1027, 932, 905 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.99 (broad d, 1H, J = 7 Hz, part of AB quartet, H_{eq}, $-OCH_2O-$), 4.62 (d, 1H, J = 7 Hz, part of AB quartet, H_{ax}, $-OCH_2O-$), 3.86 (dd, 1H, J = 11.0, 2.5 Hz, -OCH-), 3.64 (s, 3H, $-OCH_3$), 3.13-3.40 (ABX, 2H, $-OCH_2-$), 2.00-3.00 (m, 10H, $-CH_2-$, -CH-); ^{13}C-NMR ($CDCl_3$) δ 173.4,

93.8, 82.7, 70.3, 51.4, 37.4, 35.6, 32.4, 32.0, 28.4, 20.7.

Anal. calcd. for $C_{11}H_{18}O_4S$: C, 53.65; H, 7.37. Found: C, 54.04; H, 7.50.

(3R*)-Methyl-3-[(4S*,5R*)-5-methyl-1,3-dioxacyclohex-4-yl]pentanoate (12b). The ester 11b (2.9 g, 11.7 mmol) in ethanol (70 mL) was treated with Raney-nickel (11 g) prepared from 1:1 nickel-aluminum alloy (22 g) by the method of Fieser and Fieser.[18] The mixture was heated to reflux and monitored by GLC (10% SE-30). After 5 h filtration through a celite pad, washing the filter cake with dichloromethane (3 x 20 mL), removal of solvent in vacuo and bulb-to-bulb distillation at 130°C (0.005 mm) gave 2.2 g (85%) of a colorless oil: IR ($CHCl_3$) 2970, 2940, 2850, 1725, 1455, 1435, 1380, 1260, 1240, 1175, 1085, 1030, 925 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.01 (d, 1H, J = 11 Hz, part of AB quartet, H_{eq}, $-OCH_2O-$), 4.48 (d, 1H, J = 11 Hz, part of AB quartet, H_{ax}, $-OCH_2O-$), 3.91 (dd, 1H, J = 12.0, 4.8 Hz, -OCH-), 3.64 (s, 3H, $-OCH_3$), 3.16 (t, 2H, J = 10.8 Hz, $-OCH_2-$), 2.31 (t, 2H, J = 6.9 Hz, $-CH_2CO_2-$), 1.68 (dt, 2H, J = 1.3, 5.4 Hz, $-CH_2CH_2CO_2-$), 0.9 (broad d, 3H, J = 6.3 Hz, acyclic CH_3), 0.63 (d, 3H, J = 6.6 Hz, cyclic CH_3); ^{13}C-NMR ($CDCl_3$) δ 173.8, 93.8, 84.6, 72.6, 51.4, 32.6, 31.9, 31.3, 29.0, 12.6, 12.2.

Anal. calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32.

Found: C, 60.93; H, 9.17.

(3R*)-3-[(4S*,5R*)-5-Methyl-1,3-dioxacyclohex-4-yl]-pentanoic acid (12a). To ester 12b (1.1 g, 4.9 mmol) in a 25-mL round-bottomed flask with reflux condenser was added potassium hydroxide in methanol (10 mL of a 0.82 M solution, 8.2 mmol). The solution was heated to 50°C for 1 h and cooled. Ethanol was removed in vacuo and the residue redissolved in water (10 mL). Aqueous concentrated hydrochloric acid was added to pH 1; then the acid was extracted into dichloromethane (4 x 20 mL). Drying (Na_2SO_4), filtration, removal of solvent in vacuo and distillation at 160°C (0.006 mm) gave 0.97 g (97%) of a colorless oil: IR ($CHCl_3$) 3340-2400, 2960, 2850, 1705, 1455, 1400, 1380, 1275, 1175, 1150, 1085, 1030, 960, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.98 (broad s, 1H, $-CO_2H$), 4.89 (broad d, 1H, J = 6 Hz, part of AB quartet, H_{eq}, $-OCH_2O-$), 4.54 (d, 1H, J = 6 Hz, part of AB quartet, H_{ax}, $-OCH_2O-$), 3.80 (dd, 1H, J = 4.8, 11.4 Hz, -OCH-), 3.14 (apparent t, 2H, J = 10 Hz, $-OCH_2-$), 2.33 (t, 2H, J = 7.3 Hz, $-CH_2CO_2-$), 1.41-2.19 (m, 4H, -CH- and $-CH_2CH_2CO_2-$), 0.94 (d, 3H, J = 7.2 Hz, ring CH_3), 0.67 (d, 3H, J = 6.9 Hz, acyclic CH_3).

Anal. calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.21; H, 8.90.

[3(R*,S*),5R*]-3-Methyl-[(4S*,5R*)-5-methyl-1,3-

dioxacyclohex-4-yl]hexan-2-one (13). To diisopropylamine (1.76 mL, 12 mmol) in THF (5 mL) at -10°C was added methyllithium (5.6 mL, 10 mmol) in ether. After stirring for 10 min acid 12a (0.894 g, 4.4 mmol) in THF (7 mL) was added over 0.5 h at -10°C, stirred for an additional 0.5 h and cooled to -30°C. Methyl iodide (0.67 mL, 11 mmol) was added (exotherm) with stirring over 5 min at -30°C then warmed to 25°C and stirred 1 h. The reaction flask was connnected to a vacuum pump and solvent removed in vacuo. The residue was redissolved in THF (6 mL) and cooled in an ice bath; methyllithium (2.6 mL, 4.4 mmol) in ether was added and the reaction warmed to 25°C. After 1 h (TLC, silica gel, 20% ethyl acetate/hexane, R_f = 0.34) the reaction was slowly added to vigorously stirred ice water. Extraction with ether (4 x 30 mL), drying (Na_2SO_4), filtration and removal of solvent gave a pale yellow oil which was purified by column chromatography (silica gel, 15% ethyl acetate/hexane) giving 13, 0.55 g (59%): IR ($CHCl_3$) 2970, 2930, 2850, 1705, 1455, 1380, 1230, 1175, 1090, 1070, 1030, 965, 925 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.00 (dd, 1H, J = 11, 1.2 Hz, part of AB quartet, H_{eq}, $-OCH_2O-$), 4.56 (dd, 1H, J = 11, 1.9 Hz, part of AB quartet, H_{ax}, $-OCH_2O-$), 3.80 (dd, 1H, J = 11, 5 Hz, -OCH-), 3.24 (d, 1H, J = 11 Hz, H_{eq}, $-OCH_2-$), 3.07 (d, 1H, J = 7 Hz, H_{ax}, $-OCH_2-$), 2.53 (m, 1H, $-CHCH_3$,

in ring), 2.10 (s, 3H, CH_3CO-), 1.1-2.0 (m, 5H, -CH- and $-CH_2$-), 1.05 (d, 1.5H, J = 7.5 Hz, $C\underline{H}_3CHCO$-), 1.03 (d, 1.5H, J = 7.2 Hz, $C\underline{H}_3CHCO$-), 0.90 (d, 3H, J = 6.8 Hz, ring CH_3), 0.66 (d, J = 6.8 Hz, acyclic CH_3); ^{13}C-NMR ($CDCl_3$) δ 212.0, 93.7 (84.7, 84.6), 72.5 (44.6, 44.4), (36.8, 36.6), 31.3, 30.8 (27.7, 27.6), (16.9, 16.4), (13.1, 12.8), 12.1.

Anal. calcd. for $C_{12}H_{22}O_3$: C, 67.26; H, 10.4. Found: 67.16; H, 10.2.

(S)-(+)-3-t-Butyldiphenylsiloxy-2-methylpropionic acid (15). S-(+)-hydroxyisobutyric acid[2] (5.0 g, 48 mmol) was dissolved in dry dimethylformamide (50 mL). Imidazole (10.1 g, 150 mmol) and t-butyldiphenylchlorosilane (14.6 g, 53 mmol) were added. After 16 h (TLC, silica gel, 30% ethyl acetate/hexane, R_f = 0.39), the reaction mixture was cooled in an ice bath and sodium hydroxide (5.0 g, 0.12 mol) in water (50 mL) was added. The aqueous layer was washed with ether (3 x 30 mL) then recooled, acidified with concentrated hydrochloric acid, and extracted with ether (4 x 50 mL). Drying (Na_2SO_4), filtration and removal of solvent in vacuo gave an oil (12.3 g, 75%) which crystallized on storage at -10°C, mp 52.5-53.5°C: IR ($CHCl_3$) 3400-2400, 3070, 2950, 2930, 2860, 1705, 1585, 1465, 1455, 1385, 1110, 820, 800, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.21 (broad s, 1H, $-CO_2H$), 7.54 (m, 4H, aromatic),

7.36 (m, 6H, aromatic), 3.76 (d, 1H, J = 7.5 Hz, $-OCH_2-$), 3.74 (d, 1H, J = 6.0 Hz, $-OCH_2-$), 3.67 (hextet, 1H, J = 6.7 Hz, -CH-), 1.13 (d, 3H, J = 7.0 Hz, $-CH_3$), 1.03 (s, 9H, t-butyl methyls); ^{13}C-NMR ($CDCl_3$) δ 180.8, 135.4, 133.1, 129.6, 127.5, 65.5, 42.2, 26.7, 19.2, 13.3; $[\alpha]_D$ = +10.37° (C = 1.09, $CHCl_3$).

Anal. calcd. for $C_{20}H_{26}O_3Si$: C, 70.13; H, 7.65. Found: C, 69.73; H, 7.70.

R-(+)-3-t-Butyldiphenylsiloxy-2-methylpropan-1-ol (16). Acid 15 (6.13 g, 17.9 mmol) was dissolved in ether (20 mL) and borane-dimethylsulfide (2 mL, 20 mmol) in ether (10 mL) was added dropwise at 0°C. After the initial reaction the borane was added faster. At the end of 3 h (TLC, silica gel, 30% ethyl acetate/hexane, R_f = 0.48) the reaction was added to ice water and extracted with ether (4 x 20 mL). The combined organics were washed with 4 N sodium hydroxide (aqueous), water and brine, dried (Na_2SO_4) and filtered. Removal of solvent in vacuo gave 5.54 g (94%) of a colorless oil: IR ($CHCl_3$) 3500, 3060, 3000, 2950, 2930, 2860, 1580, 1460, 1420, 1385, 1100, 1080, 1020, 920, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.45 (m, 4H, aromatic), 7.16 (m, 6H, aromatic), 3.61 (d, 2H, J = 5.0 Hz, $-CH_2OH$), 3.60 (d, 2H, J = 6.0 Hz, $-OCH_2-$), 2.40 (broad s, 1H, -OH), 1.91 (octet, 1H, J = 6.0 Hz, -CH-), 1.06 (s, 9H, t-butyl methyls), 0.83 (d,

3H, J = 6.3 Hz, $C\underline{H}_3CH$-); ^{13}C-NMR ($CDCl_3$) δ 135.4, 133.0, 129.6, 127.6, 68.5, 67.4, 37.3, 26.8, 19.2, 13.2; $[\alpha]_D$ = +7.43° (C = 1.09, $CHCl_3$), optically pure by ^{1}H-NMR/chiral shift reagent (tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato], europium (III) derivative) analysis of methyl doublet.[28]

S-(+)-2-t-Butyldiphenylsiloxy-1-methylpropionaldehyde (17). To an ice-cold solution of pyridine (39 mL, 0.48 mol) in dichloromethane (600 mL) was added chromium trioxide (24 g, 0.24 mmol). The orange solution was stirred 15 min then warmed to 25°C and stirred 0.5 h. Alcohol 16 (12.9 g, 39.4 mmol) in dichloromethane (10 mL) was added in one portion to the deep red solution. A black precipitate formed immediately. After 15 min the solution was decanted and solvent removed in vacuo. The residue was taken up in ether and filtered through florisil, eluting with ether. After removal of solvent in vacuo the residue was dissolved in toluene (20 mL) and solvent removed (to azeotropically remove pyridine). The toluene procedure was repeated again and after complete removal of solvent a white solid (10.46 g, 91%) was obtained, mp. 60-62.5°C: IR ($CHCl_3$) 3070, 2950, 2930, 2860, 1720, 1580, 1460, 1450, 1420, 1380, 1360, 1105, 1030, 1005, 995, 820, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.76 (d, 1H, J = 2.1 Hz, -COH), 7.64 (m, 4H, aromatic), 7.36 (m, 6H, aromatic),

3.80 (d, 2H, J = 5.4 Hz, $-OCH_2-$), 2.51 (m, 1H, -CH-), 1.07 (d, 3H, J = 6.3 Hz, $-CH_3$), 1.04 (s, 9H, t-butyl methyls); ^{13}C-NMR ($CDCl_3$) δ 203.9, 135.4, 132.9, 129.6, 127.5, 64.0, 48.7, 26.7, 19.2, 10.2; $[\alpha]_D$ = +25.93° (C = 1.08, $CHCl_3$). Optically pure by ^{1}H-NMR/chiral shift reagent analysis of methyl doublet.[28]

Anal. calcd. for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.65; H, 7.85.

(2S)-1-t-Butyldiphenylsiloxy-2-methyl-4-(1-oxa-3-azainden-2-yl)-3-butanol (18a, 19a). To a dry, three-necked 100-mL round-bottom flask equipped with a septum magnetic stirring bar, thermometer, nitrogen inlet and constant-volume addition funnel were added THF (20 mL) and diisopropylamine (5.3 mL, 3 mmol). The solution was cooled to -20°C and methyllithium (19.5 mL, 35 mmol) in ether was added over 20 min. After 15 min the colorless solution was cooled to -78°C (internal) and 2-methyl-benzoxazole (4.15 mL, 35 mmol) in THF (10 mL) was added dropwise over 15 min while maintaining an internal temperature below -70°C. Stirring was continued an additional 1 h during which time a yellow precipitate formed; then aldehyde 17 (9.67 g, 30.0 mmol) in THF (7 mL) was added over 5 min. The mixture was stirred 5 min followed by quenching with saturated ammonium chloride. The reaction was partitioned between water

(60 mL) and ether (4 x 50 mL). Combination of organics, washing with water and brine, drying (Na_2SO_4), filtration and removal of solvent gave 13 g of a crude product. Purification on a Waters' Prep 500 (10% ethyl acetate/hexane) gave 3S alcohol 19a (5.97 g, 43.4%): IR ($CHCl_3$) 3470, 3060, 3000, 2950, 2920, 2850, 1605, 1560, 1460, 1445, 1420 1385, 1235, 1100, 1010, 995, 900, 815, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.64 (m, 5H, aromatic), 7.36 (m, 9H, aromatic), 4.40 (m, 1H, -CHOH), 3.68 (d, 2H, J = 5.4 Hz, $-CH_2O-$), 3.58 (broad s, 1H, -OH), 3.05 (d, 1H, J = 2.2 Hz, $-CH_2-$ benzoxazole), 3.00 (s, 1H, $-CH_2-$ benzoxazole), 1.65-2.00 (m, 1H, -CH-), 1.06 (s, 9H, t-butyl methyls), 0.96 (d, 3H, J = 6.2 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 165.6, 150.4, 140.8, 135.4, 132.7, 129.6, 127.6, 124.3, 124.0, 119.4, 110.4, 71.0, 67.4, 39.6, 33.7, 26.9, 19.2, 11.0; $[\alpha]_D^{22}$ = -3.87° (C = 1.27, $CHCl_3$); HPLC (1 foot μ-porasil, 10% ethyl acetate/hexane): k = 3.5

Anal. calcd. for $C_{28}H_{33}NO_3Si$: C, 73.16; H, 7.24; N, 3.05. Found: C, 73.47; H, 7.42; N, 2.91.

3R alcohol 18a (4.95 g, 35%): IR same as 19a; ^{1}H-NMR ($CDCl_3$) δ 7.55 (m, 5H, aromatic), 7.34 (m, 9H, aromatic), 4.21 (q, 1H, J = 5.3 Hz, -OCH-), 4.04 (broad s, 1H, -OH), 3.73 (d, 1H, J = 5.3 Hz, $-OCH_2-$), 3.72 (d, 1H, J = 6.0 Hz, $-OCH_2-$), 3.10 (s, 1H, $-CH_2-$ benzoxazole), 3.03 (d, 1H, J = 2.2 Hz, $-CH_2-$ benzoxazole), 1.90 (heptet, 1H,

J = 6.0 Hz, -CH-), 1.07 (s, 9H, t-butyl CH_3), 0.97 (d, 3H, J = 6.6 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 165.2, 146.0, 140.7, 135.4, 132.8, 129.6, 127.5, 124.3, 123.9, 119.4, 110.2, 72.4, 67.2, 40.1, 33.9, 26.8, 19.2, 13.4; HPLC: k = 3.1.

Anal. calcd. for $C_{28}H_{33}NO_3Si$: C, 73.16; H, 7.24; N, 3.05. Found: C, 73.47; H, 7.42; N, 2.91.

(2S,3S)-2-Methyl-4-(1-oxa-3-azainden-2-yl)-1,3-butandiol (19b). To alcohol 19a (2.1 g, 4.6 mmol) in THF (4 mL) was added tetra-n-butylammonium fluoride (8 mL, 8 mmol) in THF. After 0.5 h solvent was removed in vacuo and the residue chromatographed on silica gel (ethyl acetate) to give an off-white solid (0.953 g, 94%), mp 102-104°C (1:1 ethyl acetate/hexane): IR ($CHCl_3$) 3600, 3450, 3000, 2970, 1610, 1570, 1455, 1345, 1160, 1145, 1100, 1030, 1005, 840 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.16-7.72 (m, 4H, aromatic), 4.30-4.59 (m, 1H, -OCH-), 4.01 (broad s, 1H, -OH), 3.80 (broad d, 2H, J = 5.4 Hz, $-OCH_2-$), 2.78-3.19 (m, 3H, -OH, $-CH_2-$ benzoxazole), 1.73-2.16 (m, 1H, -CH-), 1.00 (d, 3H, J = 7.2 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 165.3, 150.3, 140.5, 124.6, 124.2, 119.3, 110.2, 71.1, 66.0, 39.2, 33.2, 10.7; $[\alpha]_D$ = -24.22° (C = 1.09, $CHCl_3$).

Anal. calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.11; H, 7.02; N, 6.27.

(2S,3R)-2-Methyl-4-(1-oxa-3-azainden-2-yl)butan-1,3-

diol (18b). Prepared as for diol 19b. 18a (2.1 g) gave 0.95 g (94%): IR (see 19b); ^{1}H-NMR ($CDCl_3$) δ 7.16-7.72 (m, 4H, aromatic), 4.20 (q, 1H, J = 4.2 Hz, -OCH-), 3.58-3.76 (m, 3H, $-CH_2OH$), 3.08 (broad s, 2H, -OH and $-CH_2$- benzoxazole), 3.02 (d, 1H, J = 4.8 Hz, $-CH_2$- benzoxazole), 1.80-1.89 (m, 1H, -CH-), 0.93 (d, 3H, J = 7.5 Hz, CH_3).

(2S,3R)-2-Methyl-4-(1-oxa-2-azainden-2-yl)-1-p-toluenesulfonyloxybutan-3-ol (23a). Diol 18b (0.284 g, 1.28 mmol) was dissolved in pyridine (20 mL), cooled to 0°C and p-toluenesulfonylchloride (0.266 g, 1.4 mmol) was added. After 40 h (TLC, silica gel, 50% ethyl acetate/hexane, R_f = 0.30) the reaction (deep purple) was added to ice water (60 mL) and extracted with ether (4 x 30 mL). The combined organics were washed with 10% hydrochloric acid, water, brine and dried (Na_2SO_4). Filtration and removal of solvent gave a yellow oil (0.373 g, 78%): IR ($CHCl_3$) 3640-3200, 3000, 2930, 1610, 1595, 1565, 1450, 1355, 1240, 1185, 1170, 1090, 965, 935, 905, 830, 810, 655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.07-7.82 (m, 8H, aromatic), 4.09 (d, 2H, J = 4.5 Hz, $-OCH_2$-), 3.78-4.08 (m, 2H, -CHOH), 2.98 (s, 1H, $-CH_2$- benzoxazole), 2.91 (d, 1H, J = 4.5 Hz, $-CH_2$- benzoxazole), 2.30 (s, 3H, CH_3- aromatic), 1.74-2.03 (m, 1H, -CH-), 0.97 (d, 3H, J = 7.5 Hz, $-CH_3$).

(2S,3R)-3-(Oxacyclohex-2-yloxy)-2-methyl-4-(1-oxa-

2-azainden-2-yl)-1-p-toluenesulfonyloxybutane (23b). The crude tosylate 23a (0.341 g, 0.92 mmol) was dissolved in dichloromethane (2 mL), cooled to 0°C and dihydropyran (0.2 mL, 2.22 mmol) added. After addition of one crystal of p-toluenesulfonic acid the reaction was stirred 1 h (TLC, silica gel, 40% ethyl acetate/hexane, R_f = 0.27). The reaction was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate then dried (Na_2SO_4). Filtration and removal of solvent gave 0.415 g (92%) of a yellow oil: IR no -OH; ^{1}H-NMR ($CDCl_3$) δ 7.10-7.78 (m, 8H, aromatic), 4.50 (broad s, 1H, -OCHO-), 3.89-4.20 (m, 2H, $-CH_2-OSO_2-$), 3.17-3.81 (m, 3H, -OCH-, $-OCH_2$ of THP group), 3.17 and 3.03 (d, 2H, J = 5.4 Hz, $-CH_2-$ benzoxazole), 2.37 (s, 3H, CH_3- aromatic), 1.12-2.28 (m, 7H, -CH- and $-CH_2-$ of THP), 1.03 and 1.00 (d, J = 7.5 Hz, $-CH_3$).

(2S,3R)-4-Iodo-3-methyl-1-(1-oxa-2-azainden-2-yl)-2-butanol (23d). Tosylate 23a (0.977 g, 2.6 mmol) was dissolved in acetone (10 mL) and sodium iodide (1.51 g, 10 mmol) added. The mixture was stirred at 25°C for 17 h (TLC, silica gel, 50% ethyl acetate/hexane, R_f = 0.37). The iodide was isolated by filtration, rinsing the filter cake with ether and removal of solvent. The oil was redissolved in ether, washed with 10% sodium sulfite, dried (Na_2SO_4), filtered and ether removed to yield a

pale yellow oil (0.570 g, 67%): ^{1}H-NMR ($CDCl_3$) δ 7.07-7.68 (m, 4H, aromatic), 4.14 (broad s, 1H, -OH), 3.95 (doublet of triplets, 1H, J = 3.9, 7.8 Hz, -OCH-), 3.23-3.50 (m, 2H, $-CH_2I$), 2.66-3.10 (m, 2H, $-CH_2-$ benzoxazole), 1.32-1.73 (m, 1H, -CH-), 1.02 (d, 3H, J = 6.9 Hz).

1-(1-t-Butyloxycarbonyl-1-azacyclopenta-2,4-dien-2-yl)-1-propanone (38). To a three-neck 100-mL round-bottomed flask with a septum, nitrogen inlet, mechanical stirrer and constant-volume addition funnel were added potassium t-butoxide (2.58 g, 22 mmol) and THF (20 mL). The suspension was stirred with cooling to 0°C and pyrrole ketone 26[43] (2.46 g, 20 mmol) in THF (10 mL) was added over 10 min. After warming to 25°C and stirring for 1 h t-butyloxycarbonyl anhydride (5.1 mL, 22 mmol) in THF (30 mL) was added over 0.5 h (exotherm). The heterogeneous mixture was stirred an additional 2 h (TLC, silica gel, 40% ethyl acetate/hexane, R_f = 0.60); then water (50 mL) was added and the mixture partitioned between water and ether (4 x 50 mL). Drying (Na_2SO_4), filtration and removal of solvent gave an oil which was purified on a Waters' Prep 500 on silica gel eluting with 6% ethyl acetate/hexane to give 0.20 g of starting ketone and 3.51 g (85% based on recovered ketone 26) of a solid mp. 57.5-58.5°C: IR ($CHCl_3$) 2880, 1740, 1670, 1440, 1410, 1390, 1370, 1315, 1250, 1150, 1100, 1080,

1030, 925, 845 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.96 (dd, 1H, J = 1.4, 3.1 Hz, pyrrole C-5H), 6.70 (dd, 1H, J = 1.4, 3.7 Hz, pyrrole C-3H), 6.10 (dd, 1H, J = 3.1, 3.7 Hz, pyrrole C-4H), 2.73 (q, 2H, J = 7.5 Hz, $-CH_2-$), 1.56 (s, 9H, t-butyl CH_3), 1.17 (t, 3H, J = 7.5 Hz, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 191.9, 148.7, 133.8, 127.3, 119.9, 109.7, 84.6, 33.6, 27.5, 8.8.

Anal. calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68. Found: C, 64.51; H, 7.68.

1-(1-Phenylmethoxymethyl-1-azacyclopenta-2,4-dien-2-yl)-1-propanone (37). The title compound was prepared according to the procedure for ketone 38. To ketone 26 (2.46 g, 20 mmol) were added commercial potassium t-butoxide (2.50 g, 22 mmol) and chloromethylbenzyl ether (3.44 g, 22 mmol) to yield ketone 37. Purification by distillation at 120°C (0.006 mm) gave a colorless oil (4.90 g, 100%): IR ($CHCl_3$) 3000, 2960, 2900, 1665, 1550, 1480, 1430, 1310, 1250, 1220, 1100, 1040, 950, 755, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.32 (s, 5H, phenyl), 6.97-7.14 (m, 2H, pyrrole), 6.20 (dd, 1H, J = 3, 4.5 Hz, pyrrole), 5.81 (s, 2H, $-NCH_2O-$), 4.50 (s, 2H, $ArCH_2O-$), 2.83 (q, 2H, J = 6.9 Hz, CH_2CO-), 1.17 (t, 3H, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 191.9, 137.3, 130.2, 129.6, 128.2, 127.6, 119.8, 108.8, 77.0, 70.4, 32.3, 8.9.

Anal. calcd. for $C_{15}H_{17}NO_2$: C. 74.05; H, 7.04;

N, 5.76. Found: C, 74.20; H, 7.20; N, 5.76.

Pyrrole ketone enolate. General procedure for aldols. In a two-neck round-bottomed flask equipped with a magnetic stirring bar, septum and nitrogen inlet is placed diisopropylamine (1.2 equiv) and ether (2 mL/equiv of amine). The solution is cooled to 0°C and n-butyllithium (1.1 equiv) in hexane is added. After 15 min the solvent is removed in vacuo. The white powder is redissolved in ether (1 mL/equiv), cooled to -98°C and pyrrole ketone (1 equiv) in ether (2 mL/equiv) is added over 2 min. After 0.5 h, zinc chloride (1 equiv, freshly fused) in ether (2 mL/equiv) is added and the reaction warmed to 10°C to give a yellow solution. Dimethoxyethane (5 mL/equiv) is then added. Aldehyde (0.8 equiv) is added in dimethoxyethane (1 mL), the reaction is stirred 5 min and saturated ammonium chloride (1 mL/equiv) is added. The reaction is worked-up by diluting with ether; washing 1 x water, 1 x 10% hydrochloric acid, 1 x sodium bicarbonate; drying (Na_2SO_4); filtration and removal of solvent in vacuo.

Aldol condensation of ketone 37 with benzaldehyde. According to the general procedure, ketone 37 (0.249 g, 1.02 mmol) was added to benzaldehyde (0.1 mL, 1.0 mmol) to give 0.359 g (90%) of an aldol product. The crude product was purified by flash chromatography on silica

gel (25% ethyl acetate/hexane) TLC [silica gel, 25% ethyl acetate/hexane, R_f = 2.8 (threo), 2.6 (erythro)]: IR ($CHCl_3$) 3460, 3050, 3000, 2960, 2900, 1645, 1540, 1510, 1460, 1425, 1300, 1240, 1210, 1090, 1040, 970, 920, 740, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.41 (s, 10H, phenyl), 6.96-7.15 (m, 2H, pyrrole), 6.20 (dd, 1H, J = 2.1, 4.5 Hz, pyrrole), 5.76 (s, 0.6H, $-NCH_2O-$), 5.74 (s, 1.4H, $-NCH_2O-$), 5.13 (d, 0.3H, J = 3.5 Hz, erythro, -OCH-), 4.93 (d, 0.7H, J = 6.6 Hz, threo, -OCH-), 4.58 (s, 0.6H, $-OCH_2$-Ar), 4.36 (s, 1.4H, $-OCH_2$-Ar), 3.93 (broad s, 1H, -OH), 3.43 (dt, 0.7H, J = 3.6, 7.5 Hz, -CHCO-), 2.74 (dt, 0.3H, J = 2.4, 5.4 Hz), 1.22 (d, 1H, J = 7.5 Hz, CH_3-), 1.13 (d, 2H, J = 6.0 Hz, CH_3-).

Aldol condensation of ketone 38 with benzaldehyde. According to the general procedure, ketone 38 (0.222 g, 1.0 mmol) was added to benzaldehyde (0.1 mL, 1.0 mmol) to give 0.263 g (85%) of an aldol product. ^{1}H-NMR ($CDCl_3$) δ 7.33 (broad s, 5H, phenyl), 6.78-7.00 (m, 2H, pyrrole), 6.14 (t, 1H, J = 3 Hz, pyrrole), 5.23 (d, 0.25H, J = 1.5 Hz, -OCH-), 4.90 (d, 0.75, J = 7.8 Hz, -OCH-), 3.43 (pentet, 1H, J = 7.5 Hz, -CH-), 3.06 (broad s, 1H, -OH), 1.60 (s, 9H, t-butyl CH_3), 1.03 (d, 3H, J = 6.9 Hz, $-CH_3$); HPLC (10% ethyl acetate/hexane, 1 foot μ-porasil) k_{threo} = 4.2, $k_{erythro}$ = 6.1.

Aldol condensation of ketone 38 with Methyl 3-methyl-4-

oxopentanoate (39). According to the general procedure, ketone 38 (0.305 g, 1.37 mmol) was added to aldehyde 39 to give four lactones (0.267 g, 80%). HPLC (1 foot μ-porasil, 25% ethyl acetate/hexane) k_A = 2.46, k_B = 3.54, k_C = 4.30, k_D = 4.74). Isomers A and B were separated pure by chromatography on a Waters' Prep 500 (silica gel, 25% ethyl acetate/hexane). C and D were isolated as a mixture enriched in C.

40a: IR ($CHCl_3$) 3000, 2960, 2920, 1725, 1690, 1665, 1445, 1430, 1405, 1360, 1305, 1240, 1140, 1065, 1030, 945, 900, 840 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.43 (dd, 1H, J = 1.5, 3.1 Hz, pyrrole), 6.96 (dd, 1H, J = 1.5, 3.6 Hz, pyrrole), 6.22 (t, 1H, J = 3.4 Hz, pyrrole), 4.41 (dd, 1H, J = 2.2, 10.2 Hz, -OCH-), 3.20-3.88 (m, 2H, -C<u>H</u>CH_3), 2.48 (t, 2H, J = 6.0 Hz, -CH_2CO), 1.83-2.49 (m, 2H, CH_2), 1.56 (s, 9H, t-butyl CH_3), 1.48 (d, 3H, J = 6.6 Hz, acyclic -CH_3), 0.92 (d, 3H, J = 6.6 Hz, cyclic -CH_3).

40b: ^{1}H-NMR ($CDCl_3$) δ 7.43 (dd, 1H, J = 1.5, 3.1 Hz, pyrrole), 6.96 (dd, 1H, J = 1.5, 3.6 Hz, pyrrole), 6.22 (t, 1H, J = 3.4 Hz, pyrrole), 4.48 (dd, 1H, J = 5.1, 8.3 Hz, -OCH-), 3.15-3.49 (m, 2H, -C<u>H</u>CH_3), 2.46-2.60 (m, 2H, -CH_2CO), 1.58-2.03 (m, 2H, -CH_2-), 1.59 (s, 9H, t-butyl CH_3), 1.27 (d, 3H, J = 6.9 Hz, acyclic -CH_3), 1.04 (d, 3H, J = 6.3 Hz, cyclic -CH_3).

40c: ^{1}H-NMR ($CDCl_3$) δ 4.66 (dd, 1H, J = 1.5, 10.5 Hz,

-OCH-).

40d: ^{1}H-NMR ($CDCl_3$) δ 4.26 (dd, 1H, J = 4.5, 8.4, -OCH-).

Aldol condensation of ketone 37 with methyl-3-methyl-4-oxopentanoate (39). According to the general procedure ketone 37 (0.240 g, 0.99 mmol) was added to aldehyde 39 to give four lactones (0.311 g, 80%). Analysis of the four lactones was performed by HPLC analysis (1 foot μ-porasil, 25% ethyl acetate/hexane): k_A = 4.43, k_B = 6.07, k_C = 7.00, k_D = 7.50. By analogy, A was assigned as erythro/anti-Cram, and B was assigned as threo/Cram.

Methyl-5-(methylamino)-2-[{(5R)-2-[(2R)-1-hydroxy-2-methylpent-4-yl]-5-methyloxacyclohex-2-en-6-yl}methyl]-4-benzoxazole carboxylate (43a, 44a). Silyl ethers 35 and 36 (0.368 g, 0.49 mmol) were dissolved in THF (1 mL). Tetra-n-butylammonium fluoride (5 mL, 1 M, 5 mmol) in THF was added. TLC (silica gel, ethyl acetate, R_f = 0.72) showed a new spot which fluoresced, indicating removal of the trifluoroacetyl group. After 10 h three new components were present (R_f = 0.69, 0.64, 0.46). The hi-R_f spots were spiroketals. The lower R_f component was isolated by flash chromatography (silica gel, 50% ethyl acetate/49% hexane/1% triethylamine) to yield 75.8 mg (37%)[57] of an unstable oil: IR ($CHCl_3$) 3660, 3370, 3000, 2960, 2930, 1730, 1665, 1565, 1555, 1525, 1425, 1410, 1250, 1205, 1160, 1110, 1040, 925,

665 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.86 (broad s, 1H, NH), 7.54 (d, 1H, J = 9 Hz, Ar), 6.68 (d, 1H, J = 9 Hz, Ar), 5.52 (broad s, 1H, OH), 4.11-4.28 (m, 1H, vinyl), 3.96 (s, 3H, $-OCH_3$), 3.45-3.65 (m, 1H, -OCH-), 3.32 (d, 2H, J = 6.9 Hz, $-OCH_2-$), 3.05 (d, 3H, J = 3 Hz, $-NCH_3$), 2.91 (d, 2H, J = 6 Hz, $-CH_2-$ benzoxazole), 0.71-1.89 (m, 16H).

Exact mass (75 eV) m/e calcd. for $C_{23}H_{32}N_2O_6$: 432.226. Found: 432.229.

Methyl-5-(methylamino)-2-|{(5R)-2-[(2R)-2-methyl-1-oxopent-4-yl]-5-methyloxacyclohex-2-en-6-yl}methyl|-4-benzoxazolecarboxylate (43b, 44b). Pyridine (0.18 mL, 2.16 mmol) in dichloromethane (9 mL) was cooled to 0°C and chromium trioxide (0.108 g, 1.08 mmol) was added. After 10 min the orange solution was warmed to 25°C and stirred for 15 min. Alcohols 43a, 44a (0.0758 g, 0.18 mmol) in dichloromethane (1 mL) were added to the burgundy-colored solution. After 15 min the reaction was worked-up as for aldehyde 17 to give 49.9 mg (66%) of a colorless oil: IR ($CHCl_3$) 3350, 2990, 2950, 2930, 1730, 1720; 1670, 1560, 1520, 1430, 1410, 1250, 1160, 1130, 1085, 1040, 800 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.68 (d, 1H, J = 1.5 Hz, -CHO), 7.75 (broad s, 1H, NH), 7.54 (d, 1H, J = 9 Hz, Ar), 6.68 (d, 1H, J = 9 Hz, Ar), 4.11-4.28 (m, 1H, vinyl), 3.96 (s, 3H, OCH_3), 3.45-3.65 (m, 1H, -OCH-), 3.09 (d, 3H, J = 3 Hz, $-NCH_3$), 2.91 (d, 2H, J = 6 Hz, $-CH_2-$ benzoxazole), 0.69-2.00 (m, 16H).

Exact mass (75 eV) m/e, calcd. for $C_{23}H_{30}N_2O_6$: 430.210. Found: 430.209.

(2S)-Methyl-5-(methylamino)-2-|{(3R,6R,8S,9R,11R)-3,9,11-trimethyl-8-[(1S)-1-methyl-2-oxo-2-(1H-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undec-2-yl}methyl|-4-benzoxazolecarboxylate (1b). In a two-neck 25-mL round-bottomed flask, connected to a three-way valve and equipped with a septum and magnetic stirring bar, were placed diisopropylamine (0.15 mL, 1.1 mmol) and ether (2 mL). The solution was cooled to 0°C, n-butyllithium (0.69 mL, 1.0 mmol) in hexane was added and stirring continued for 15 min. After solvent removal in vacuo the residual white powder was dissolved in ether (2 mL), cooled to -98°C and ketone 38 (0.223 g, 1.0 mmol) in ether (2 mL) was added over 5 min. The yellow solution was stirred 0.5 h and zinc chloride (0.14 g, 1.0 mmol, freshly fused) in ether (2 mL) was added. Warming to 10°C was followed by dilution with dimethoxyethane (5 mL). Aldehydes 43 and 44 (0.050 g, 0.12 mmol) in dimethoxyethane (2 mL) were added, the reaction was stirred 5 min and saturated ammonium chloride (2 mL) was added. Workup was the same as in the general procedure. The crude product was dissolved in toluene (2 mL), Dowex resin[48] (2 g, sulfonic acid H^+ form) was added and the mixture was heated to 100°C for 8 h. The mixture was purified to isolate the major

component (flash chromatography, silica gel, gradient from 10% ethyl acetate/hexane to 50% ethyl acetate/hexane, TLC silica gel, 40% ethyl acetate/hexane, R_f = 0.17) as a yellow oil (11.2 mg, 18%[50] based on aldehyde) identified as A-23187 methyl ester by comparison with an authentic sample: IR ($CHCl_3$) 3440, 3360, 3000, 2960, 2930, 2870, 1710, 1670, 1635, 1555, 1520, 1450, 1430, 1415, 1405, 1305, 1250, 1160, 1130, 1070, 1000, 985, 890, 800 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 10.2 (broad s, 1H, pyrrole -NH), 7.84 (broad s, 1H, -NH), 7.62 (d, 1H, J = 9.0 Hz, benzoxazole aromatic), 6.89 (apparent triplet, 2H, J = 1.9 Hz, pyrrole), 6.65 (d, 1H, J = 9.0 Hz, benzoxazole aromatic), 6.13-6.27 (m, 1H, pyrrole), 4.10-4.21 (m, 1H, -OCH-), 3.97 (s, 3H, $-OCH_3$), 3.60 (dd, 1H, J = 2.1, 10.7 Hz, -OCH on pyrrole side), 2.61-3.40 (m, 3H, $-CH_2$- benzoxazole and -CHCO-), 2.92 (d, 3H, J = 3.6 Hz, $-NCH_3$), 0.78-2.09 (m, 21H); $[\alpha]_D^{23}$ = -10.0° (C = 0.011 g/mL, $CHCl_3$).

Anal. calcd. for $C_{30}H_{39}N_3O_6$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.11; H, 7.53; N, 8.04.

Exact mass (75 eV) m/e, calcd. for $C_{30}H_{39}N_3O_6$: 537.284. Found: 537.286.

The authentic sample was prepared by treating A-23187 with 20 equivalents of dimethylformamide dimethylacetal in toluene at 110°C for 10 h. Isolation was by chromatography on silica gel (ether). IR and NMR were identical.

$[\alpha]_D^{23}$ = -10.4° (C = 0.009 g/mL, $CHCl_3$).

(2S)-5-(Methylamino)-2-|{(3R,6R,8S,9R,11R)-3,9,11-trimethyl-8-[(1S)-1-methyl-2-oxo-2-(1H-pyrrol-2-yl)-ethyl]-1,7-dioxaspiro[5.5]undec-2-yl}methyl|-4-benzoxazolecarboxylic acid (1a). A-23187 methyl ester 1b (5.1 mg, 9.5 μ mole) was dissolved in hexamethylphosphoric triamide (1 mL) and lithio-n-propylmercaptide (0.12 mL, 0.038 mmol) in the same solvent was added at 25°C. After 3 h ether (10 mL) and ice cold water were added. The ether layer was washed several times with water, dried (Na_2SO_4), filtered and solvent removed. Trituration with hexane gave a solid. Recrystallization from hexane/acetone gave 4.8 mg (95%) as a cream colored solid, mp. 184.5-186°C (lit. 181-182°C):[1a] IR ($CHCl_3$) 3500-2600, 3440, 3350, 3000, 2960, 2940 1695, 1635, 1595, 1560, 1530, 1450, 1420, 1405, 1255, 1160, 1080, 1060, 1000, 985 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 13.2-12.0 (broad s, 1H, $-CO_2H$), 10.81 (broad s, 1H, pyrrole NH), 8.06 (broad s, 1H, NH), 7.59 (d, 1H, J = 9.3 Hz, benzoxazole aromatic), 7.06 (m, 1H, pyrrole), 6.94 (m, 1H, pyrrole), 6.73 (d, 1H, J = 9.3 Hz), 6.30 (m, 1H, pyrrole), 4.26 (dt, 1H, J = 3.1, 7.2 Hz, -OCH- benzoxazole side), 3.70 (dd, 1H, J = 2.1, 10.2 Hz, -OCH- pyrrole side), 2.73-3.45 (m, 3H, -CHCO- and $-CH_2-$ benzoxazole), 2.96 (s, 3H, NCH_3), 1.00-2.00 (m, 9H), 0.71-1.03 (m, 12H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 193.8, 168.0, 165.9, 150.6, 141.5, 140.5,

133.0, 124.4, 116.7, 116.25, 110.0, 108.2, 98.4, 97.6, 72.6, 68.3, 43.4, 35.0, 32.4, 32.2, 29.9, 28.6, 28.2, 25.7, 25.4, 16.1, 13.1, 11.35, 10.75; mixed mp. (182.5-184); $[\alpha]_D$ = -55° (C = 0.007 g/mL, $CHCl_3$) (lit. -56°C,[53] C = 0.01 g/mL, $CHCl_3$); mass spectrum (75 eV) m/e: 523.270 (calcd. 523.268), 479, 318, 274, 123.

Anal. calcd. for $C_{29}H_{37}N_3O_6$: C, 66.51; H, 7.13; N, 8.02. Found: C, 66.61; H, 6.96; N, 7.78.

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40. The synthesis of ketone 27 and the aldol to form 34 were carried out by Dr. William A. Kleschick.[58]

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46. The unstable aldehyde 39 was always distilled immediately prior to use. For its preparation see: W. H. Pirkle and W. V. Turner, J. Org. Chem., 40, 1617 (1975).

47. We are indebted to Dr. Manuel Debono of the Eli Lilly Company for a generous sample of A-23187.

48. Bio-Rad AG 50W-X8 20-50 mesh sulfonic acid H^+ form resin was used after washing with methanol and azeotropic removal of residual solvent with toluene.

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50. The yield was 23% based on aldehyde 38b being 80% of the mixture of aldehydes used.

51. An authentic sample of 1b was prepared from 1a by the method of Eschenmoser: H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, and A. Eschenmoser, Helv. Chim. Acta, 48, 1746 (1965).

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56. p-Dioxane was distilled from sodium-benzophenone ketyl.

57. In subsequent studies this yield could be improved to 60% by adding 0.1 equivalent of triethylamine to the reaction.

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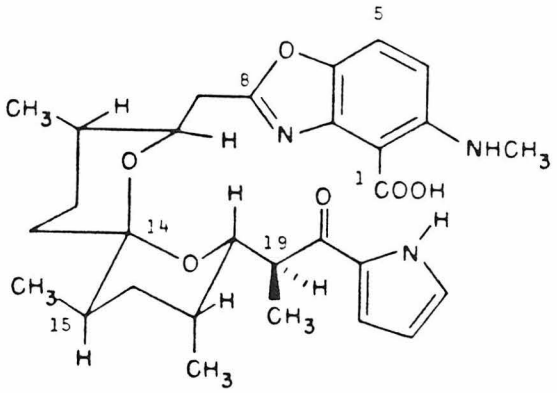
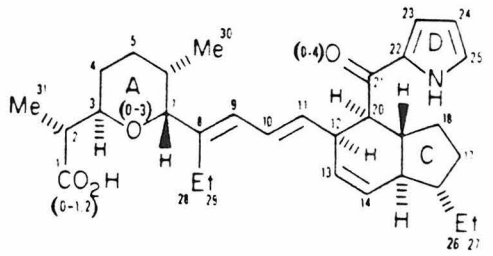
CHAPTER IV

Studies on Pyrroles

Besides A-23187, 1, only one other pyrrole containing ionophore is known, X-14547A (2).[1] Isolated by Westley and coworkers, its structure has been solved by X-ray analysis.[1] As investigations for new antibiotics possessing ion transporting qualities continue, new pyrrole containing molecules will undoubtedly be found. For this reason, general methodology for the introduction of a pyrrole unit is desirable.



1

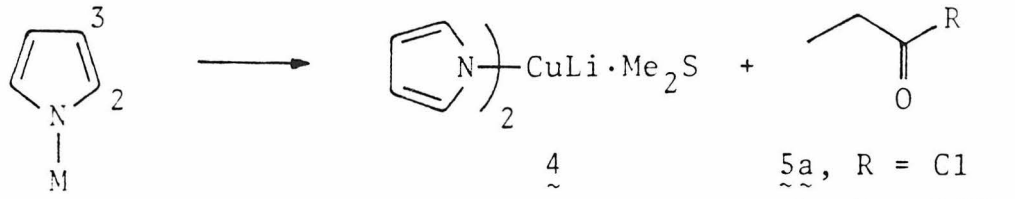


2

In general, pyrryllithium 3a alkylates on nitrogen and carbon.[2] Addition of esters or acid chlorides to 3a or 3b gives both C-2 and C-3 acylated products. To be useful, complete control of the regiochemistry (ie, alkylation or acylation at C-2) is important. Specifically, for both A-23187 and X-14547A, control of the acylation reaction is necessary. An initial investigation of the pyrrylcuprate 4, as shown is Scheme I, was less than satis-

factory. Although cuprates are known to give ketones by reaction with thioesters or acid chlorides,[3] cuprate 4 gave only poor yields of the desired pyrrole ketone 6.

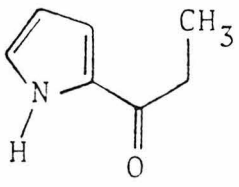
Scheme I



3a, M = Li
b, M = Mg

4

5a, R = Cl
b, R = SCH_3



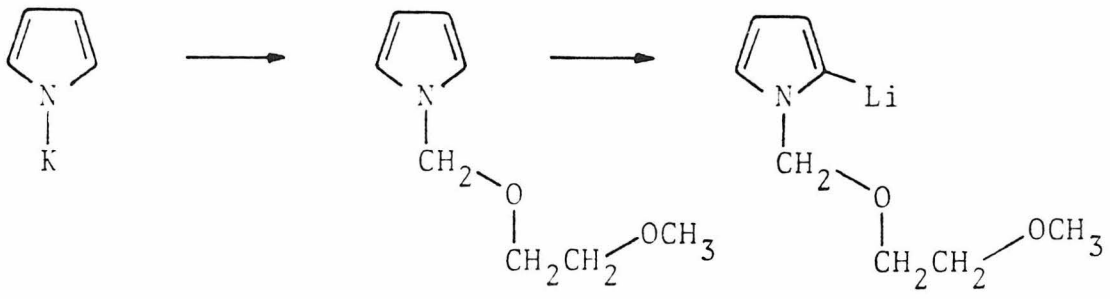
6

We therefore considered blocking the nitrogen and generating the 2-pyrryllithium with a strong base.

Such a blocking group, in order to be compatible with sensitive functionality generated during a synthesis, should be easily removed under mild conditions. A search

of the literature revealed that the only N-blocked pyrryllithium known was the N-methyl pyrrole.[4] Unfortunately, the methyl was not removable. However, based on studies by Sundberg[5] and Levy[6] with N-blocked indole systems, we chose to investigate the methoxyethoxymethyl (MEM) blocking group.[7] Treatment of pyrrole potassium[8] with MEM-Cl gave the protected pyrrole 7 as shown in Scheme II. Reaction of 7 with t-butyllithium under carefully controlled conditions[9] then gave good yields of the lithiated pyrrole 8 (see Table 1). Treatment of pyrryllithium 8, under con-

Scheme II



7 8

ditions which gave 65% lithiation (experiment 2), with electrophiles proceeded well as shown in Scheme III.

Table 1. Metalation of 7 and Quenching With CH_3OD.

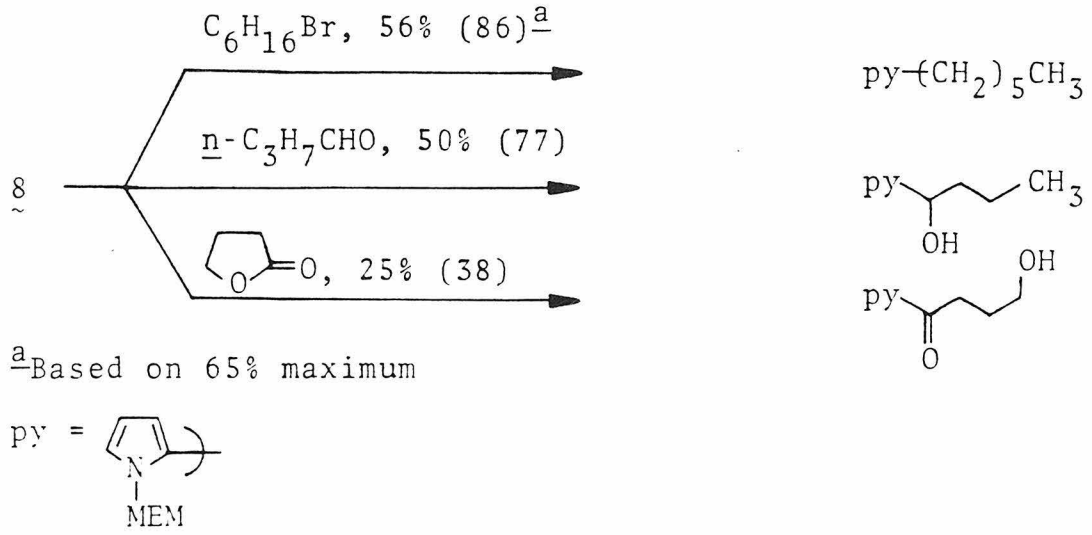
Experiment Base (equiv)	T (°C)	Solvent	% Mass Recovery	% Conversion[b]
1. t-BuLi (1.1)	4-25	ether[a]	80	68
2. t-BuLi (1.7)	-10-25	THF	60	65
3. n-BuLi (1.2)	-30	THF	c	--
4. t-BuLi (1.1)	-30	ether[a,d]	85	75
5. t-BuLi (2.0)	-30	ether[a,e]	80	100

[a] 8 is insoluble. [b] By mass-spectral analysis of $(M)^+$ and $(M+1)^+$. [c] n-Butyl incorporated into molecule. [d] 0.5 equiv of THF.[9] [e] 1.0 equiv of THF.[9]

Conversion to the cuprate 9 was affected by treatment with cuprous bromide-dimethyl sulfide.[4b,10] Reaction with t-butyl thiopropionate then gave a high conversion to pyrrole ketone 10 as shown in Scheme IV. Unfortunately, attempts to remove the MEM blocking group from any of the pyrroles under standard conditions was unsuccessful.[7]

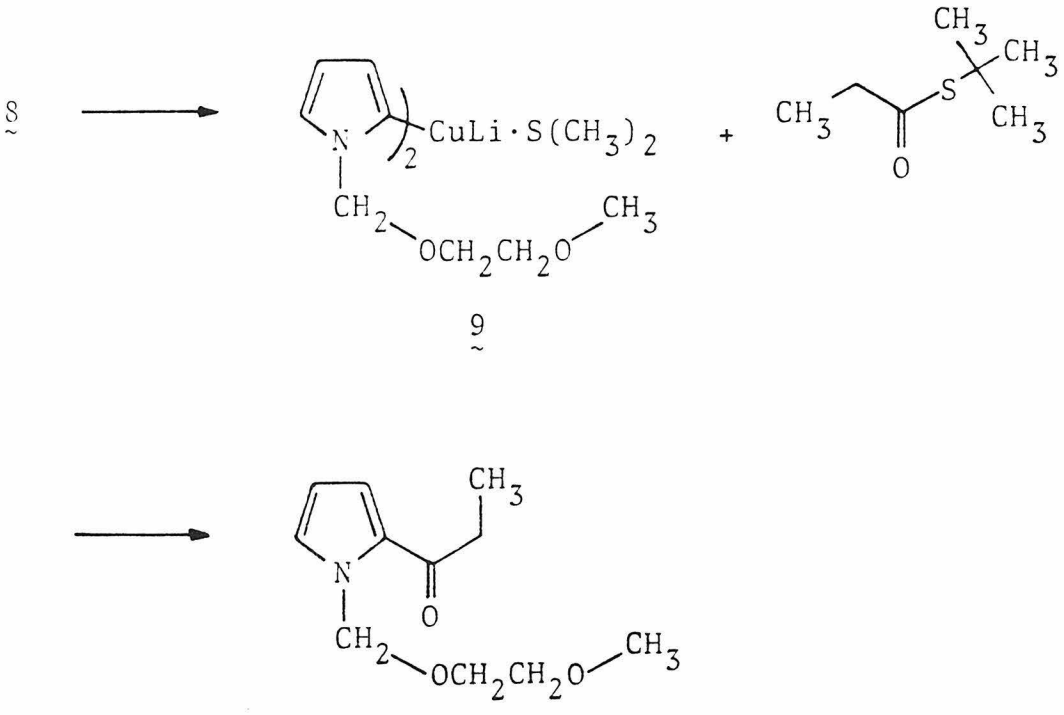
These studies demonstrate the feasibility of generating an N-blocked pyrryllithium or pyrrylcuprate and using it to introduce a pyrrole ring. Studies should be continued to develop a protecting group which can be easily and selectively removed.

Scheme III



[a]Based on 65% maximum

Scheme IV



Experimental Section

General. Diethyl ether and tetrahydrofuran (THF) were dried by distillation from benzophenone ketyl under nitrogen. Pyrrole was dried by distillation under nitrogen from calcium hydride.

All commercial alkyllithium reagents were titrated by the procedure of Watson and Eastham.[11]

Unless otherwise specified all reactions were run under an inert atmosphere of nitrogen.

Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-4210 or Perkin Elmer 727B spectrophotometer and are reported in cm^{-1}. Proton spectra were recorded on a Varian Associates EM-390 or T-60 spectrophotometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Proton data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (Hz) and interpretation. Carbon-13 nuclear magnetic spectra were recorded on a Varian Associates XL-100 (25.2 MHz) spectrometer and are reported in parts per million on the δ scale relative to tetramethylsilane internal standard.

Mass spectra were recorded on a DuPont MS 21-492B or a Kratos MS 25 (equipped with a DS 50S data system) mass spectrometer. Mass spectral analyses as well as combustion analyses were performed by the California Institute of Technology Microanalytical Laboratory.

1-[(2-Methoxyethoxy)methyl]azacyclopenta-2,4-diene(7). In a three-neck, 100 mL, round-bottomed flask with a magnetic stirring bar, nitrogen inlet, reflux condenser and constant-volume addition funnel were placed potassium metal (3.8 g, 0.098 mol) and THF (30 mL). The mixture was heated to reflux and freshly distilled pyrrole (6.7 mL, 0.097 mol) in THF (20 mL) was added over 10 min. A white precipitate began to form and hydrogen was evolved. Refluxing was continued until all the potassium was consumed (ca. 3 h). The suspension was cooled in an ice bath and MEM-chloride (10.3 mL, 0.09 mol), in THF (20 mL) was added over 20 min (mild exotherm). The cooling bath was removed and the reaction brought to 25°C. After 1 h the reaction (pumpkin colored) was filtered to remove salts. The THF was removed *in vacuo* and the residue dissolved in ether (100 mL). After washing the organics with water (2 x 20 mL), drying ($MgSO_4$), filtering and removing solvent *in vacuo* the oil was distilled to give a colorless oil, bp. 85-86°C (4 mm), 4.01 g (35%): IR (neat) 3100, 2930, 2810, 1490, 1450, 1365, 1270, 1100, 1080, 1070, 850,

730 cm^{-1}; NMR ($CDCl_3$) δ 6.79 (t, 2H, J = 1.1, pyrrole C-2H), 6.18 (t, 2H, J = 1.1, pyrrole C-3H), 5.23 (s, 2H, $-NCH_2O-$), 3.47 (s, 4H, $-OCH_2CH_2O-$), 3.29 (s, 3H, $-OCH_3$).

Lithiation of pyrrole 7. In a dry two-neck round-bottomed flask with a magnetic stirring bar, nitrogen inlet and septum were placed pyrrole 7 (1 equiv), ether (2 mL) and THF (1.1 equiv). The solution was cooled to -78°C and t-butyllithium (2.2 equiv, 1.30 M in pentane) was added. After stirring for 10 min the reaction was warmed to -30°C for 0.5 h, then cooled to -78°C. Quenching with CH_3OD indicated 99.7% metallation with 78% recovery of material.

Reactions with pyryllithium 8. All reactions were run with pyrryllithium generated in pure THF which gives only ca. 60% metallation. Yields should be higher utilizing the above lithiation procedure.

1-Bromohexane. 1-Bromohexane (0.13 mL, 0.9 mmol) was added to pyrryllithium in THF (3 mL) at -78°C, then warmed to 25°C for 8 h. Product isolation by ether dilution washing with water, drying (Na_2SO_4), filtration removal of solvent, and flash chromatography (silica gel, 17% ethyl acetate/hexane; TLC, R_f = 0.31) gave a colorless oil (120 mg, 56%): IR ($CHCl_3$) 3030, 2940, 2870, 1490, 1480, 1380, 1290, 1140, 1100, 1060, 870 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 6.64 (dd, 1H, J = 2.4, 1.5 Hz, pyrrole), 6.06 (t, 1H, J = 3 Hz,

pyrrole), 5.81-6.04 (m, 1H, pyrrole), 5.19 (s, 2H, $-NCH_2O-$), 3.47 (s, 4H, $-OCH_2CH_2O-$), 3.34 (s, 3H, $-OCH_3$), 2.57 (t, 2H, J = 8.1 Hz, pyrrole $-CH_2-$), 1.49--1.78 (m, 6H), 1.10-1.42 (m, 6H), 0.87 (t, 3H, J = 6 Hz, CH_3).

Anal. calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.55; H, 10.26; N, 5.97.

Butanal. Butanal (0.09 mL, 1.0 mmol) was added at -78°C, stirred 10 min and saturated ammonium chloride was added. The product was isolated as above. Flash chromatography (silica gel, 80% ether/hexane; TLC, R_f = 0.29) gave a colorless oil (92.1 mg, 50%): IR ($CHCl_3$) 3500, 3030, 2990, 2960, 2900, 1495, 1470, 1410, 1380, 1290, 1100, 1060, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.70 (dd, 1H, J = 2.4, 1.3 Hz, pyrrole), 6.20 (m, 1H, pyrrole), 6.10 (m, 1H, pyrrole), 5.36 (AB quartet, 2H, J = 10.5 Hz, $-NCH_2O-$), 4.70 (t, 1H, J = 6.0 Hz, pyrrole -CH-), 3.43 (s, 4H, $-OCH_2CH_2O-$), 3.26 (s, 3H, $-OCH_3$), 3.0 (broad s, 1H, -OH), 1.70-2.05 (m, 2H, $-OCHCH_2-$), 1.19-1.67 (m, 2H, $-CH_2-$), 0.95 (t, 3H, J = 7.2 Hz, $-CH_3$).

Anal. calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.84; H, 9.14; N, 6.25.

γ-Butyrolactone γ-Butyrolactone (0.07 mL, 0.9 mmol) was added at -78°C, stirred 10 min and quenched. Isolation as above and flash chromatography (silica gel, ethyl acetate; TLC, R_f = 0.25) gave a colorless oil (48.5 mg, 22%): IR ($CHCl_3$) 3640, 3450, 3010, 2940, 2890, 1730, 1650,

1540, 1480, 1420, 1300, 1220, 1090, 1050, 860 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.00-7.15 (m, 2H, pyrrole), 6.22 (dd, 1H, J = 3.0, 3.6 Hz), 5.74 (s, 2H, $-NCH_2O-$), 3.35-3.75 (m, 4H, OCH_2CH_2O and $-C\underline{H}_2-OH$), 3.32 (s, 3H, $-OCH_3$), 2.92 (t, 2H, J = 6.6 Hz, $-COCH_2-$), 2.48 (broad s, 1H, -OH), 1.95 (pentet, 2H, J = 6.6 Hz, $-\underline{C}H_2-CH_2OH$).

Anal. calcd. for $C_{12}H_{19}NO_4$: C, 59.72; H, 7.93; N, 5.80. Found: C, 59.83; H, 7.60; N, 5.91.

1-{[(2-Methoxyethoxy)methyl] azacyclopenta-2,4-dien-2-yl}-1-propanone (10). The pyrryllithium (0.54 mmol) was formed as in the general procedure. It was added to a solution of $CuBr \cdot Me_2S$ (0.052 g, 0.27 mmol) in ether (2 mL) and dimethylsulfide (1 mL) via cannula. After 10 min the reaction was warmed to 0°C for 0.5 h (greenish solution). t-Butylthiopropionate (0.09 mL, 0.57 mmol) was added. After 2 h the brown heterogeneous reaction was quenched with saturated ammonium chloride and product isolated by extraction with ether (3 x 30 mL). The organics were washed with 1:1 ammonia/saturated ammonium chloride (2 x 30 mL), water (1 x 30 mL), dried (Na_2SO_4) and filtered. Removal of solvent gave an oil which was purified by flash chromatography (silica gel, 30% ethyl acetate/hexane) to give 0.039 g (69%): IR ($CHCl_3$) 3010, 2940, 2880, 2820, 1650, 1525, 1460, 1410, 1375, 1295, 1220, 1130, 1085, 1050, 930 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.09

(t, 1H, J = 3 Hz, pyrrole), 6.99 (dd, 1H, J = 4.5, 1.5 Hz, pyrrole), 6.16 (dd, 1H, J = 4.5, 3 Hz), 5.79 (s, 2H, $-NCH_2O-$), 3.52 (A_2B_2, 4H, $-OCH_2CH_2O-$), 3.32 (s, 3H, $-OCH_3$), 2.78 (q, 2H, J = 7.2 Hz, pyrrole $-CH_2CO-$), 1.14 (t, 3H, J = 7.2 Hz, $-CH_2C\underline{H}_3$).

Anal. calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.12; N, 6.27.

References and Notes

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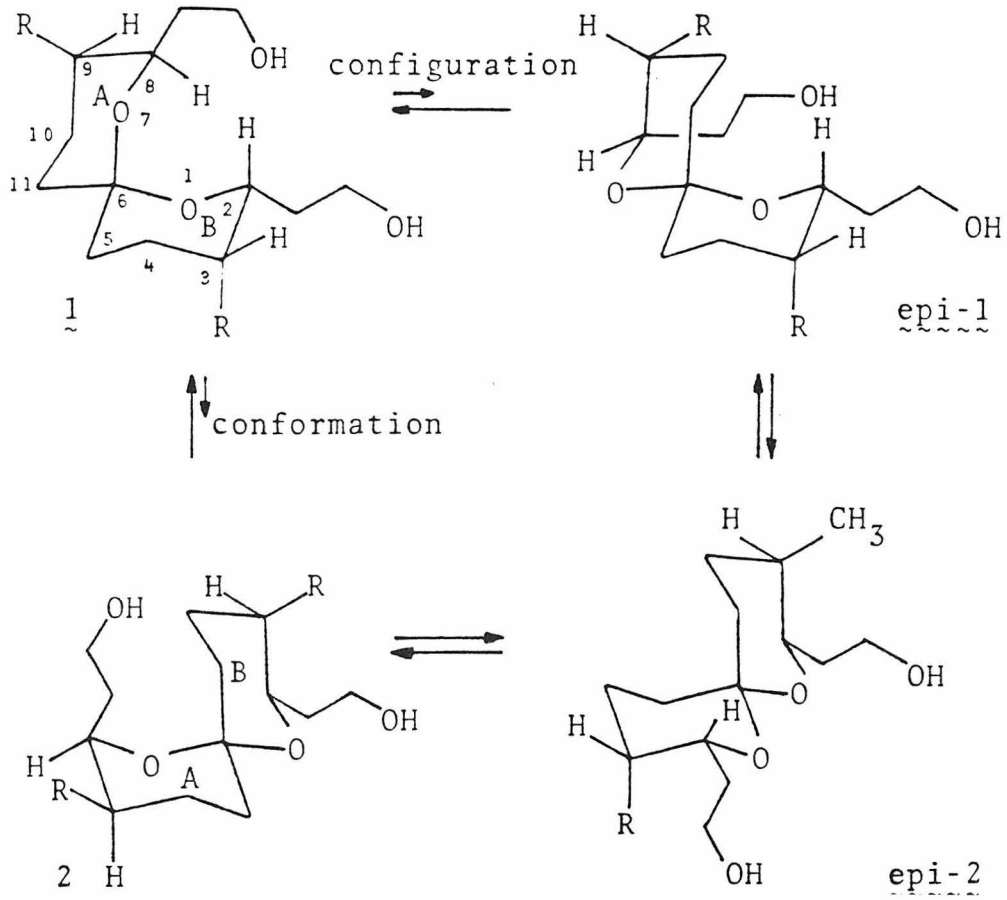
11. S. C. Watson and J. F. Eastham, J. Organomet. Chem., 9, 165 (1967).

APPENDIX I

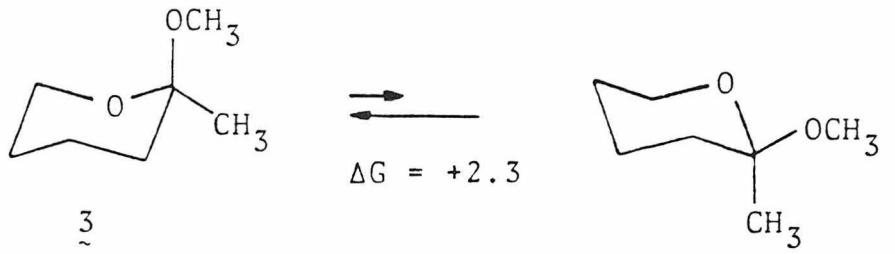
Thermochemical Estimates of 1,7-Dioxaxpiro[5.5]undecane Ring Systems

Thermochemical estimates for the relative stability of the spirane configurations and conformations are based on standard A-values for cyclohexanes.[1] Where necessary corrections have been applied for the anomeric effect.[2,3] These values come from the investigation of Gelin and coworkers on 2-alkoxy pyrans.[4] All numerical values in this section are free energy terms and are expressed in kcal/mol.

Scheme I



In the general case, spirane 1, R = H is a suitable example (Scheme I). If 1 is arbitrarily chosen as the ground state (zero level) then the relative stability of epi-1, 2, and epi-2 can be computed by tabulating changes using positive values for destabilizing and negative values for stabilizing effects relative to 1. For example, comparison of epi-1 (change of configuration at C-6) with 1 reveals two interactions not present in 1. Namely, at C-8 there is now an axial substituent. This costs a net of +3.0, +0.8 for one 1,3-diaxial carbon-hydrogen interaction (gauche butane) and +2.2[1] for one 1,3-diaxial C-O interaction. Also, examination of C-6 and use of 3 and 4 as models gives another +2.3[4] destabilizing effect (0.6



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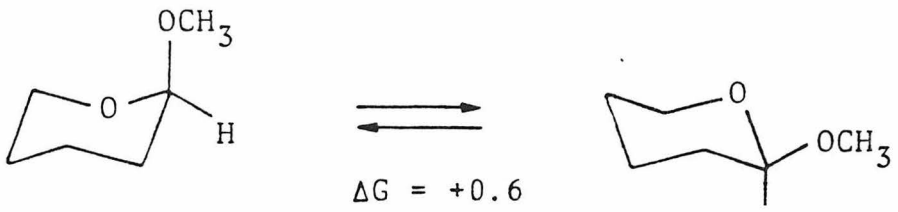
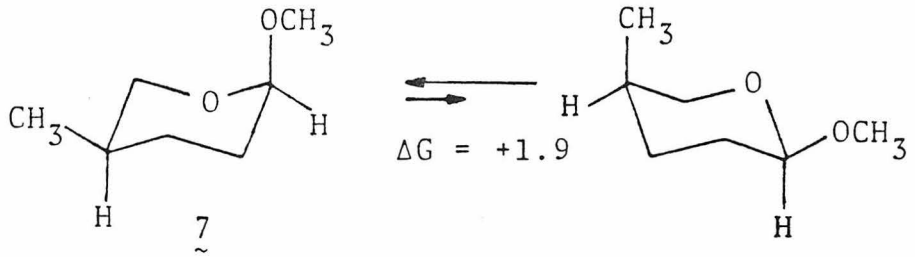


for the anomeric effect, 1.7 for an axial methyl) for a net of +5.3. This is summarized in Table 1.

For 1 going to 2 (conformational change in ring A) there is a change at C-2 and C-3. At C-2 there is now an axial methyl group 1,3-diaxial to a methylene. This is destabilizing by at least +4.5[1] (some estimates are as high as 5.5). Also, at C-6 there is again the anomeric effect of 0.6 + 1.7 or 2.3.[4] This gives a net destabilization of at least 6.8 as summarized in Table 1.

The rest of the calculations are summarized in Tables 1, 2 and 3. Some of these values deserve a somewhat expanded explanation. For example, for spirane 1 (R = CH_3) going to epi-1 a stabilizing interaction of 1.3 is realized by the change at C-9. Normally an axial-methyl to equatorial-methyl is worth 1.7 in stabilization, however, here only one gauche interaction is being relieved, worth 0.8. Also, using 7 and 4 as models we



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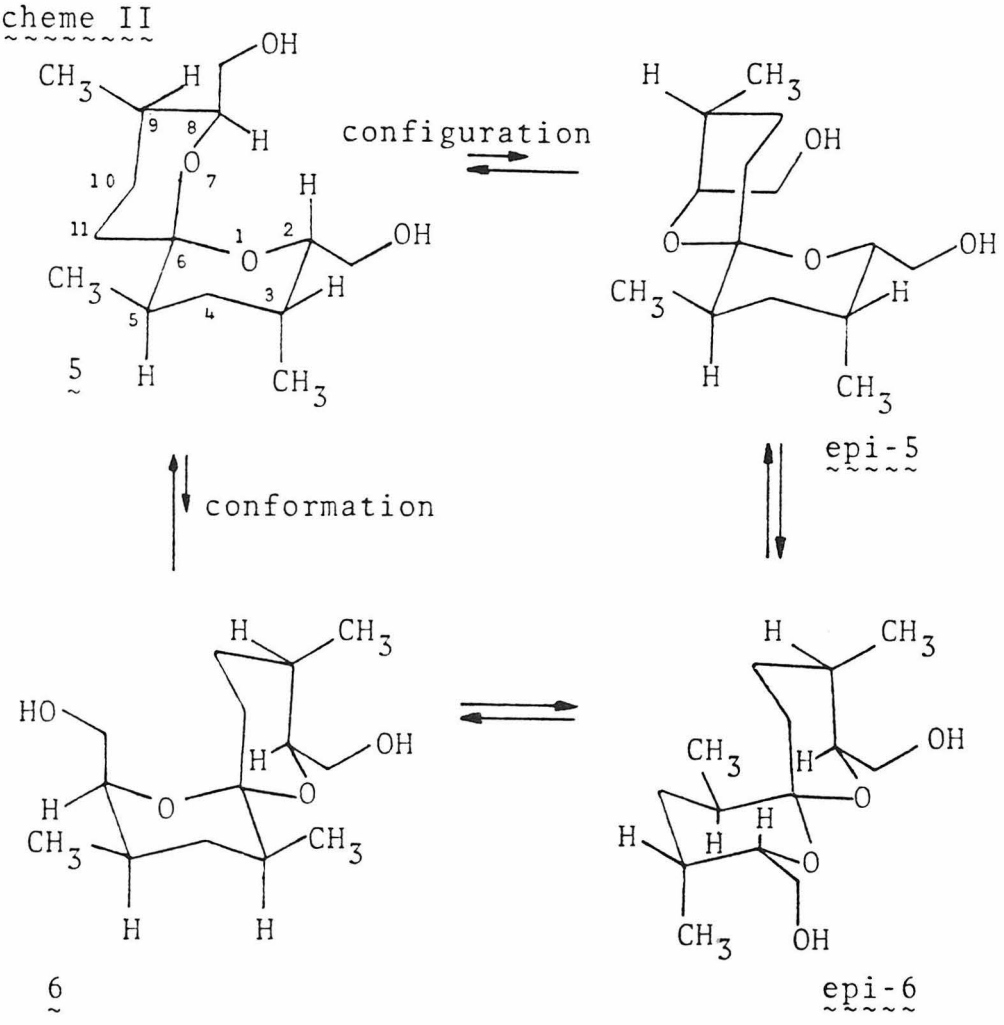
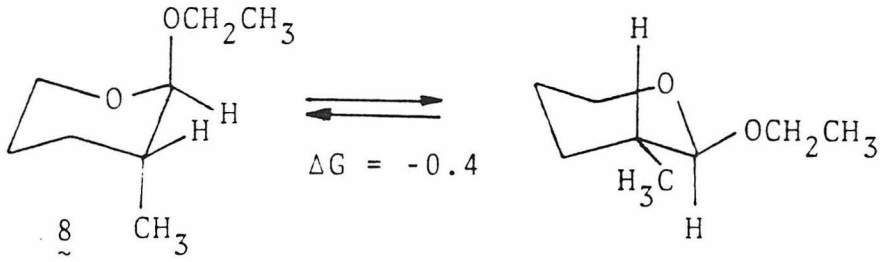
calculate that for a methyl 1,3-diaxial to an oxygen lone pair there is 1.9-0.6-0.8 or 0.5 worth of strain energy.

This gives a net of -0.8 + (-0.5) or -1.3 stabilization. For C-5 in the transformation of 5 to epi-5 (Scheme II) there is a stabilization of 0.5. This is because in 5

Scheme II



there is a trans-1,2 diequatorial methyl-methyl interaction (destablizing 5 by 0.8), but in epi-5 there is a trans-1,2 diequatorial methyl-oxygen interaction. Using 8 as a model and allowing 1.3 for the axial methyl to equatorial methyl



8

as well as 0.6 for the anomeric effect (as explained above) we get a net destabilization due to the methyl oxygen gauche interaction of -0.4-(-1.3 + 0.6) or 0.3. Thus, this interaction stabilizes epi-5 over 5 by 0.8-0.3 for a net of 0.5. Although the application of these models to such a rigid system as 5 is not without risk, the fact that we are not using absolute numbers but rather differences should tend to cancel most of the errors inherent in applying a conformationally mobile model to a conformationally locked system such as 5.

Since we are using only relative numbers, no inter-system comparison is possible [ie., epi-1 (R = CH_3) is not necessarily more stable than epi-1 (R = H)]. However in all three systems the desired isomer (1 and 5) is always favored by a substantial margin.

Table 1. (R = H)

Carbon No.	1	epi-1	2	epi-2
2	0	0	4.5	0
6	0	2.3	2.3	2 x 2.3
8	0	3.0	0	0
Net (relative to 1)	0	+5.3	+6.8	+4.6

Table 2. (R = CH_3)

Carbon No.	1	epi-1	2	epi-2
2	0	0	4.5	0
3	0	0	-1.3	0
6	0	2.3	2.3	2 x 2.3
8	0	3.0	0	0
9	0	-1.3	0	0
Net (relative to 1)	0	+4.0	+5.5	+4.6

Table 3.

Carbon No.	5	epi-5	6	epi-6
2	0	0	4.5	0
3	0	0	-1.3	0
5	0	-0.5	-0.5	0
6	0	2.3	2.3	2 x 2.3
8	0	3.0	0	0
9	0	-1.3	0	0
Net (relative to 5)	0	+3.3	+5.0	+4.6

References and Notes

1. E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co. Inc., New York, 1962.

2. (a) E. L. Eliel and C. A. Giza, J. Org. Chem., 33, 3754 (1968); (b) G. O. Pierson and O. A. Runquist, ibid., 33, 2572 (1968).

3. W. A. Szarek, Ed., "Anomeric Effect: Origin and Consequences," American Chemical Society, Washington, D. C., 1979.

4. M. Gelin, Y. Bahurel and G. Descotes, Bull. Soc. Chim. France, 3723 (1970).

APPENDIX II

^{13}C-NMR Spectral Catalog

for Chapter II

Discussion

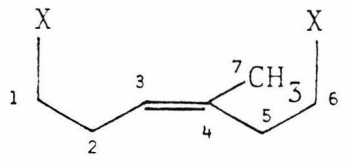
In general, assignments were made based on off-resonance decoupling experiments and chemical shift data of models available in the literature.[1] For 10 and 11 ambiguities in assignment were resolved by calculation based on a hydrocarbon substitution system utilizing equation 1[2] for the saturated carbons and the method of

$$\Delta_C\ (K) = B_S + D_2A_{S2} + D_3A_{S3} + D_4A_{S4} + \gamma_S N_{K3} + \Delta_S N_{K4} \qquad (1)$$

Roberts[3] for the unsaturated carbons. The results are tabulated in Table 1.

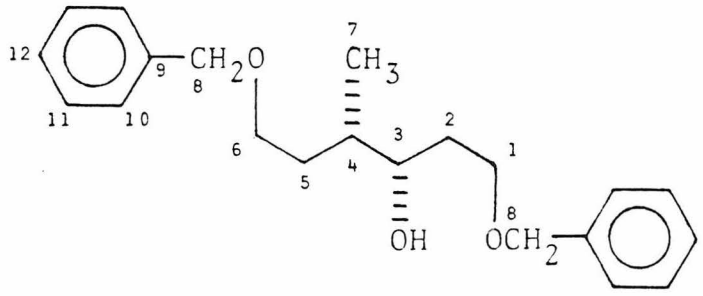
Assignments for 13 and 14 as well as for 20a and 20b were made by intersystem comparisons. The assignments for spiroketals were based on intersystem comparisons, related methyl cyclohexane systems,[4] multistriatin models,[5] heteroatom substituted cyclohexanes[6] and deuterium incorporation studies.[7]

All numerical values in this section are reported in parts per million on the δ scale relative to tetramethylsilane internal standard, and are reported as chemical shift and multiplicity.



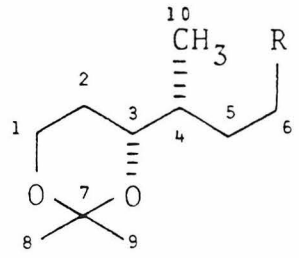
Carbon No.	Calc.	10 (X = OH)	11 (X = $O\overset{8}{C}H_2Ph$)
1	62.1	62.0, t	70.1, t
2	32.5	31.4, t	28.6, t
3	121.4	124.1, d	122.7, d
4	139.9	134.5, s	133.9, s
5	42.2	35.0, t	32.4, t
6	59.9	60.1, t	68.7, t
7	20.4	23.4, q	23.9, q
8	--	--	72.8, t
aromatic	--	--	138.9, s,[a] 127.3, d, 127.5, d, 128.2

[a]Ipso aromatic.

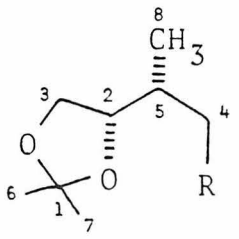


12

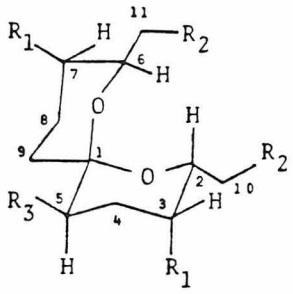
Carbon No.	δ
1, 6	68.7, t
2, 5	33.3, t; 33.9, t
3	69.3, d
4	36.1, d
7	14.01, q
8	72.3, t; 73.0, t
9	138.5, s
10, 11, 12	128.3, d; 127.5, d; 127.3, d



Carbon No.	R (δ) 13 OH	14 Br
1	59.4, t; 59.6, t	60.0, t
2	35.3, t	37.2, t
3	72.2, d	71.9, d
4	30.0, d	29.8, d
5	27.9, t	28.4, t
6	59.4, t; 59.6, t	59.4, t
7	98.1, s	98.2, s
8, 9	34.5, q; 19.3, q	13.4, q; 18.4, q
10	14.7, q	14.1, q



Carbon No.	R 20a -OH	(δ)9 OSO_2CH_3	20b Br
1	108.2, s	108.5, s	108.8, s
2	77.2, d	75.6, d	77.3, d
3	67.0, t	66.7, t	66.9, t
4	65.2, t	71.4, t	36.4, t
5	37.9, d	35.9, d	38.6, d
6	26.4, q	26.3, q	26.3, q
7	25.2, q	25.1, q	25.2, q
8	12.1, q	11.4, q	14.4, q
9	--	37.0, q	--



Carbon No.	4 R_1, H R_2, CH_2OH (12) R_3, H	5 CH_3 (13) CH_2OH (12) H	31 H OH H	22a CH_3 (13) OH CH_3 (14)
1	96.0, s	95.9, s	95.8, s	98.0, s
2	66.8, d	61.1, d	69.7, d	71.6, 71.2, d
3	31.1, t[a]	30.8, d	26.5, t[a]	28.0, 29.4, d
4	19.0, t[a]	30.0, t	18.2, t[a]	35.5, t
5	35.1, t[b]	26.6, t	35.1, t[b]	32.8, d[b]
6	66.8	67.1	69.7	71.6, 71.2, d
7	31.1	30.8	26.5	28.0, 29.4, d
8	19.0	30.0	18.2	26.5, t
9	35.1	26.6	35.1	26.0, t[b]
10	38.4, t	36.2, t	66.1, t	64.4, t
11	38.4	36.2	66.1	64.4, t
12	59.4, t	59.1, t	--	--
13	--	11.1, q	--	12.2, 11.4, q[c]
14	--	--	--	16.2, q[b]

[a]By analogy to methyl cyclohexanes.[2] [b]By deuteriation studies. [c]Resonance at 11.4 is on the dimethyl ring.[2]

References and Notes

1. G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," John Wiley and Sons, New York, 1972.
2. L. P. Linderman and J. Q. Adams, Anal. Chem., 43, 1245 (1971).
3. D. E. Dorman, M. Jautelat, and J. D. Roberts, J. Org. Chem., 36, 2757 (1971).
4. D. Doddrell, C. Charrier, B. L. Hawkins, W. O. Crain, Jr., L. Harris, and J. D. Roberts, Proc. Natl. Acad. Sci., 67, 1588 (1970); D. K. Dalling and D. M. Grant, J. Am. Chem. Soc., 89, 6612 (1967).
5. G. T. Pearce, W. E. Gore, and R. M. Silverstein, J. Mag. Res., 27, 497 (1977).
6. J. R. Demember, R. B. Greenwald, and D. H. Evans, J. Org. Chem., 42, 3518 (1977); J. A. Hirsch and E. Havinga, ibid., 41, 455 (1976).
7. The spiroketals 22a and 31 were refluxed with DCl/D_2O to give the C-5, C-9 deuteriated spiranes.

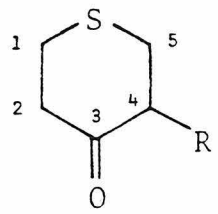
APPENDIX III

^{13}C-NMR Spectral Catalog for Chapter III

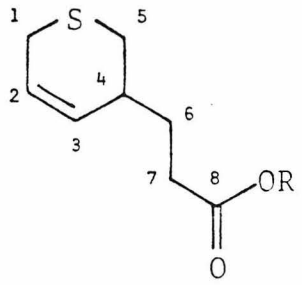
Discussion

Most assignments are based on chemical shift data,[1] off-resonance decoupling experiments and internal consistency within a sequence of transformation. For the sulfur containing molecules, reference was made to studies by Demember[2] and Hirsch.[3] Assignments for metadioxanes also utilized examples in the literature.[4]

All numerical values in this section are reported in parts per million on the δ scale relative to tetramethylsilane internal standard and are reported as chemical shift and multiplicity.

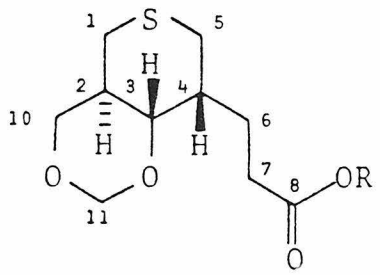


Carbon No.	R = H	R = $\overset{6}{CH_2}\overset{7}{CH_2}\overset{8}{CO_2}\overset{9}{CH_3}$
1	30.0, t	31.0, t
2	43.9, t	36.0, t
3	207.6, s	209.3, s
4	43.9	31.3, s
5	30.0	31.0, t
6	--	24.5, t
7	--	36.0, t
8	--	178.9, s
9	--	52.0, q

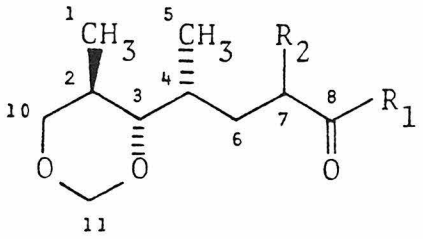


Carbon No.	R = CH_3 (9)	R = H
1	31.2, t	31.3, t
2	131.2, d; 124.1, d	131.2, d; 124.4, d
3	131.2, d; 124.1, d	131.2, d; 124.4, d
4	33.9, d	33.8, d
5	29.6, t[a]	29.6, t[a]
6	25.3, t	25.3, t
7	30.0, t	29.7, t[a]
8	173.4, s	179.6, s
9	51.4, q	--

[a]By comparison of R = CH_3 vs R = H.

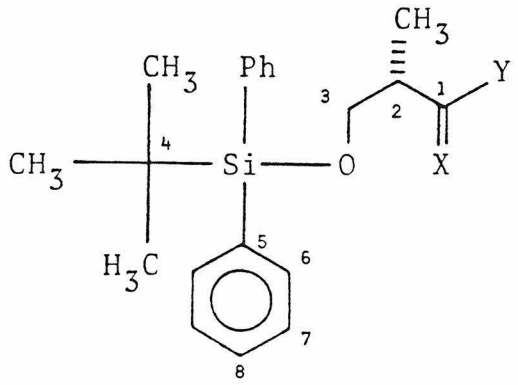


Carbon No.	R = H	R = CH_3 (9)
1	32.2, t; 32.3, t	32.4, t; 32.0, t
2	37.3, d	37.4, d
3	82.8, d	82.7, d
4	35.6, d	35.6, d
5	32.2, t; 32.3, t	32.4, d; 32.0, d
6	20.6, t	20.7, t
7	28.5, t	28.4, t
8	179.1, s	173.4, s
9	--	51.4, q
10	70.3, t	70.3, t
11	93.9, t	93.8, t



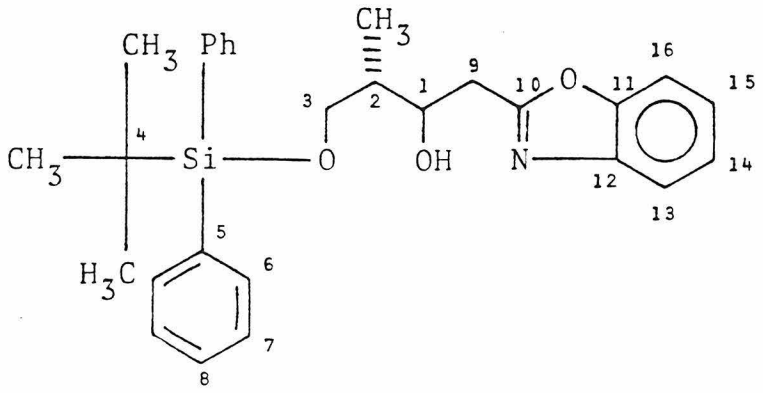
Carbon No.	R_1 = OCH_3 (9) R_2 = H	R_1 = CH_3 (12) R_2 = CH_3 (13)
1	12.2, q[a]	12.1
2	32.6, d	30.8
3	84.6, d	84.7, 84.6[b]
4	31.3, d	31.3
5	12.7, q[a]	13.0, 12.8[b]
6	29.0, t	36.8, 36.6[b]
7	31.9, t	44.6, 44.4[b]
8	173.7, s	212.0
9	51.4, q	--
10	72.6, t	72.5
11	93.8, t	93.7
12	--	27.7, 27.6[b]
13	--	16.9, 16.4[b]

[a]These assignments were made by comparison of the diastereomers (R_1 = R_2 = CH_3) with the ester (R_1 = OCH_3, R_2 = H) and assuming the farther a center was from the diastereomer center (C_7) the smaller the effect. [b]The multiplicity of resonances is due to the diastereomers caused by the introduction of the methyl at C_7.



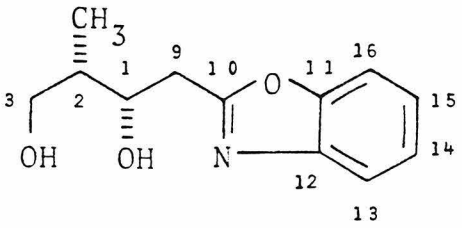
Carbon No.	X = O Y = OH	H, OH H	O H
1	180.7, s	68.5, t[a]	203.9, s
2	42.2, d	37.3, d	48.7, d
3	65.5, t	67.4, t[a]	64.0, t
4	19.2, s	19.2, s	19.2, s
5	133.1, s	133.0, s	132.9, s
6, 7, 8	135.4 129.6 127.5	135.4 129.6 127.6	135.4 129.6 127.5
CH_3 (2)	26.7, q	26.8, q	26.7, q
CH_3 (4)	13.3, q	13.2, q	10.3, q

[a]By comparison with aldol adducts 18a and 19a of Chapter 3.

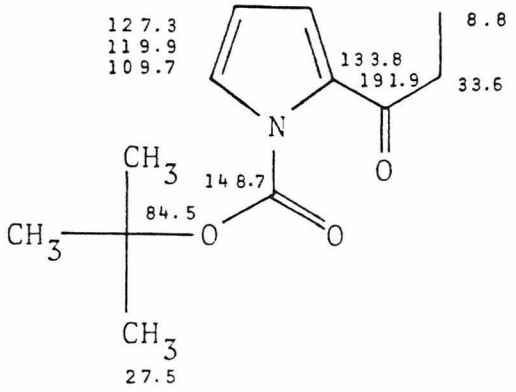


Alcohol Configuration At C-1

Carbon No.	α	β
1	72.4, d	71.0, d
2	40.1, d	39.6, d
3	67.2, t	67.4, t
4	19.2, s	19.2, s
5	132.8, s	132.7, s
6, 7, 8	135.4 129.6 127.5	135.4 129.6 127.6
9	33.9, t	33.7, t
10	165.2, s	165.6, s
11, 12	146.0, s 140.7, s	150.4, s 140.8, s
13, 14, 15, 16	124.3 123.9 119.4 110.2	124.3 124.0 119.4 110.2
CH_3 (2)	26.8, q	26.9, q
CH_3 (4)	13.4, q	11.0, q



Carbon No.	
1	71.1, d
2	39.2, d
3	66.0, t
9	33.2, d
10	165.4, s
11, 12	150.4, s; 140.6, s
13, 14, 15, 16	124.6, 124.2, 119.3, 110.2
CH_3 (2)	10.7, q


127.3
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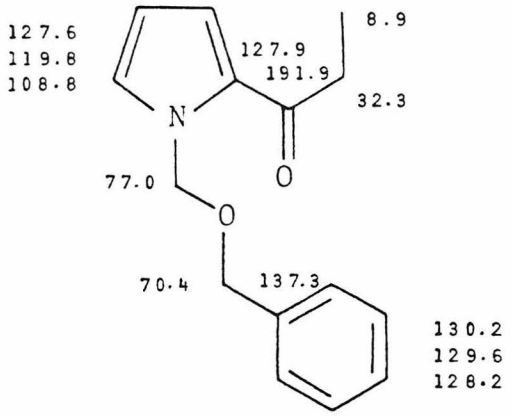
CH3
148.7
84.5
O
O
CH3
CH3
27.5


127.6
119.8
108.8
127.9
191.9
8.9
32.3
N
O
77.0
O
70.4
137.3
130.2
129.6
128.2

References and Notes

1. G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Crganic Chemists," John Wiley and Sons, New York, 1972.

2. J. R. Demember, R. B. Greenwald, and D. H. Evans, J. Org. Chem., 42, 3518 (1977).

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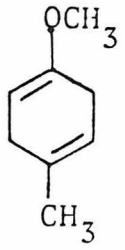
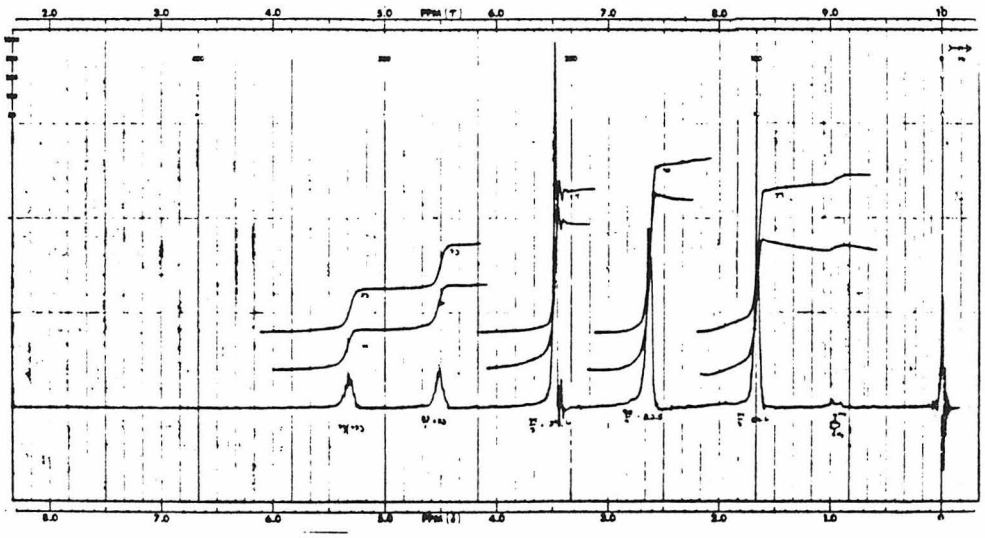
APPENDIX IV

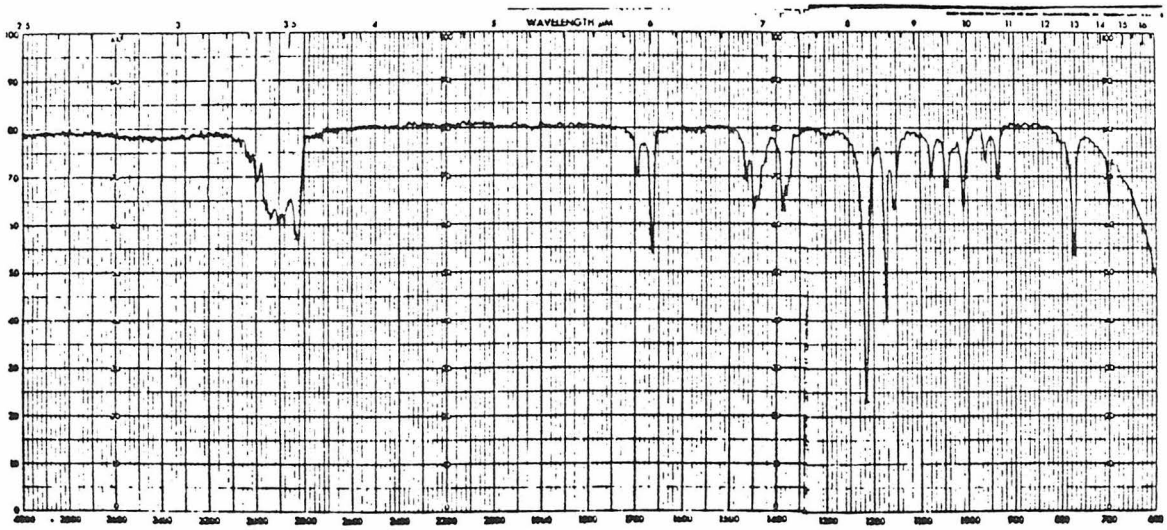
IR and ^{1}H-NMR Spectral Catalog for Chapter II

Page 38



9b





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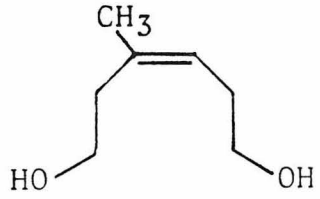
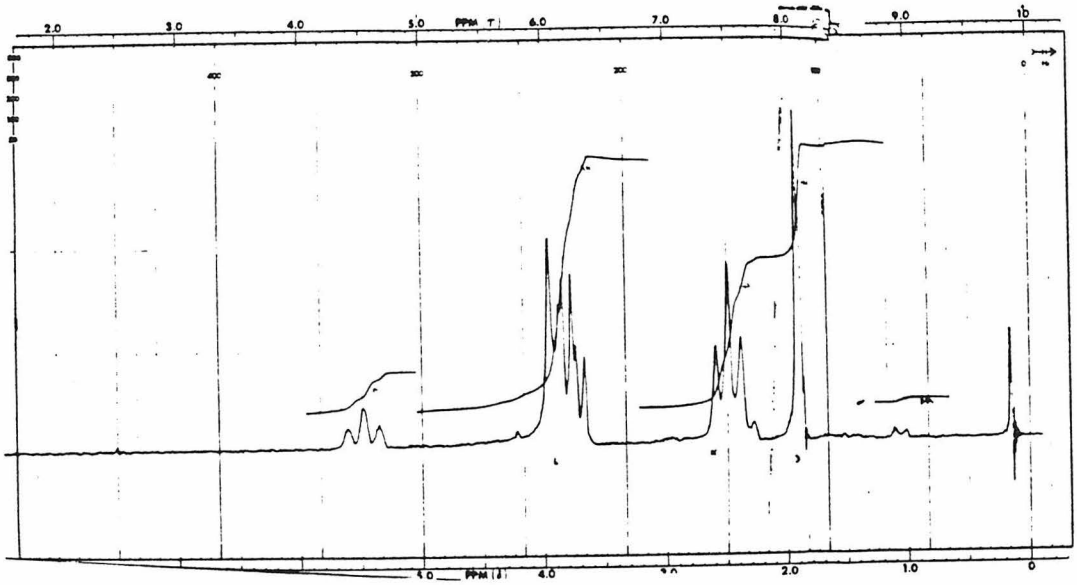
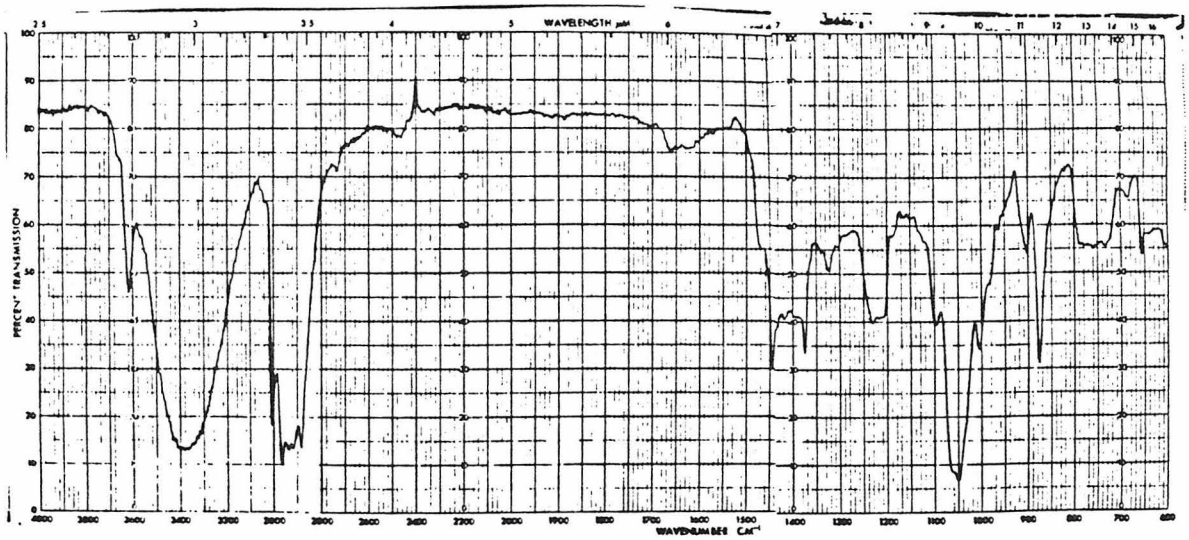

CH3
HO
OH

10b


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


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER Cm⁻¹

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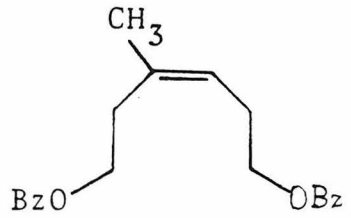
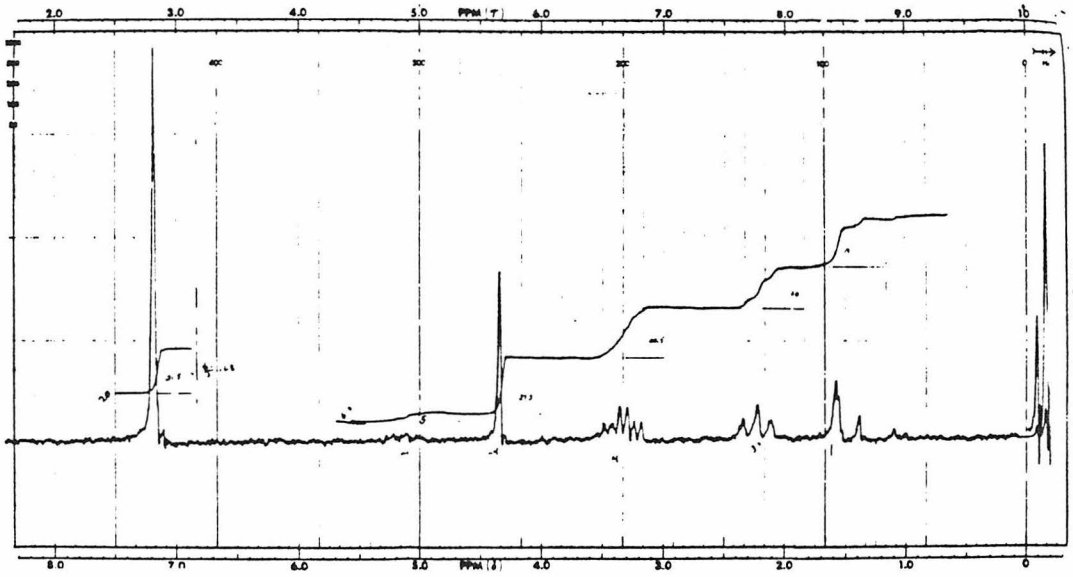
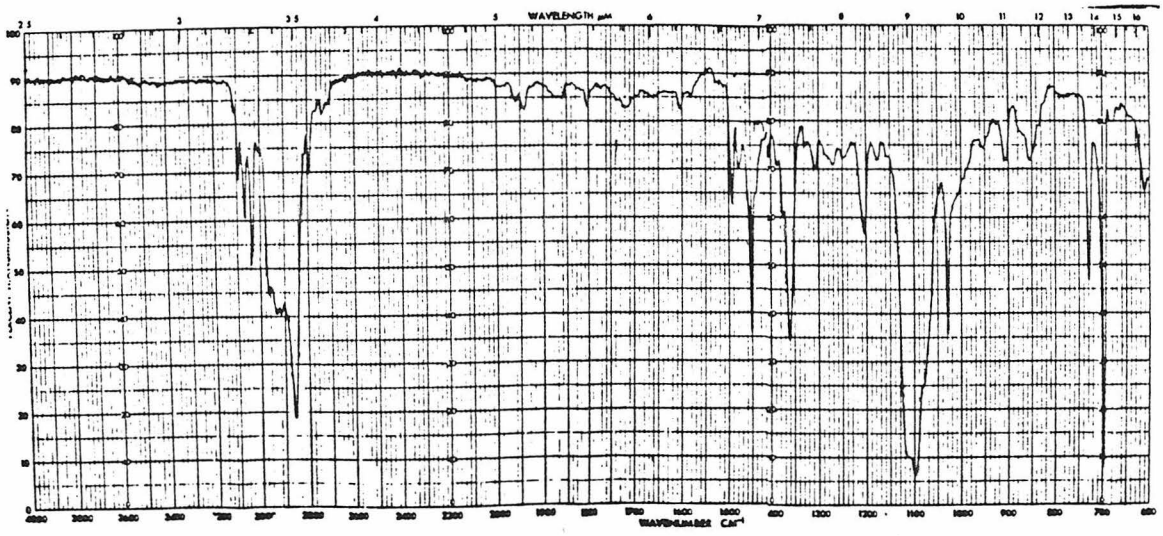
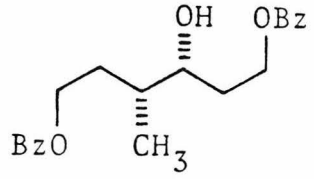


11b

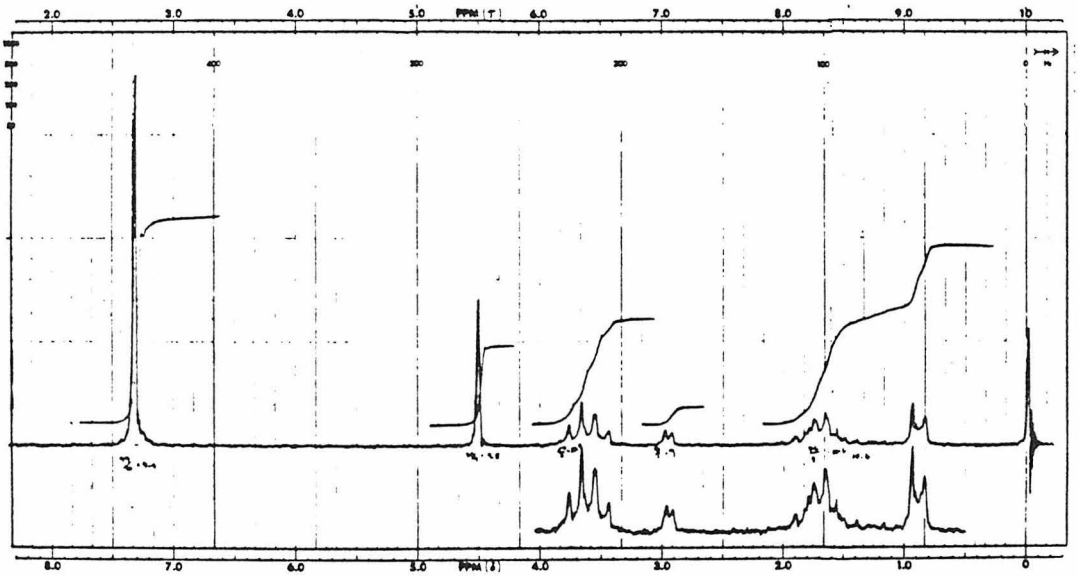


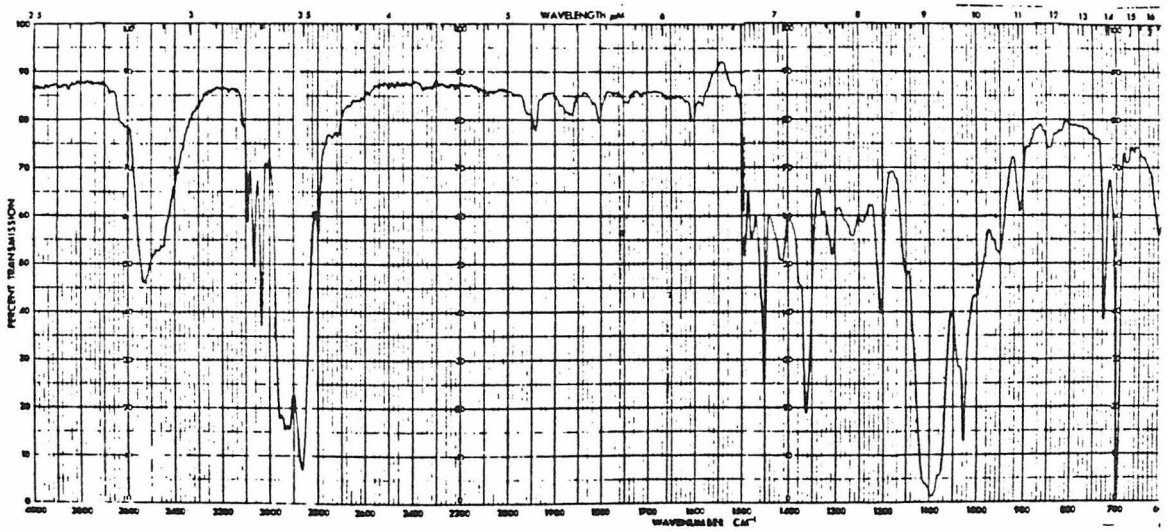


Page 40


OH
OBz
BzO
CH3

12b


PPM (τ)
PPM (δ)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM-1

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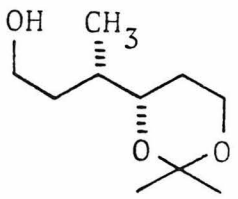
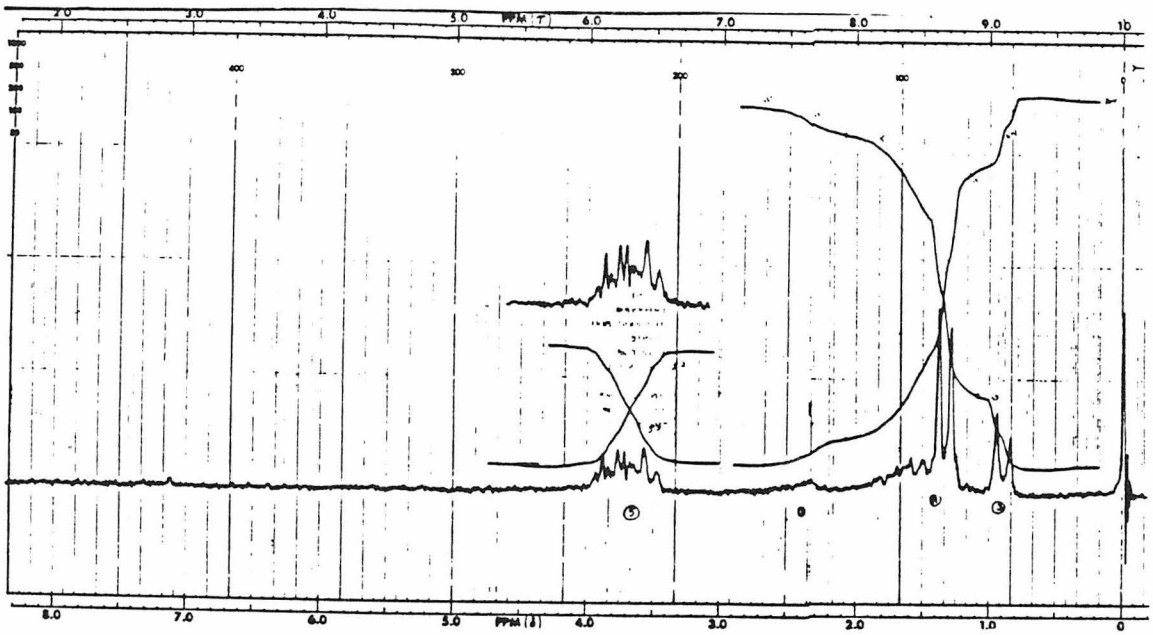

OH
CH3
O
O

13b


PPM (δ)
WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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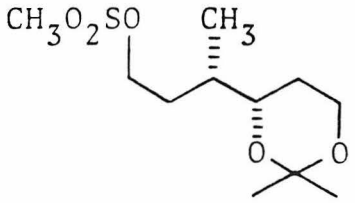

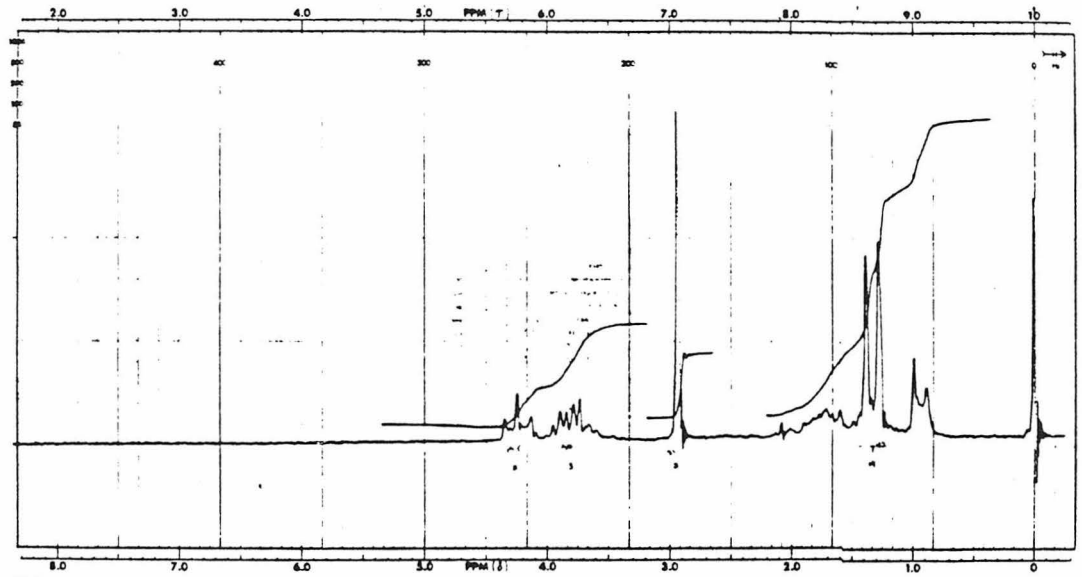

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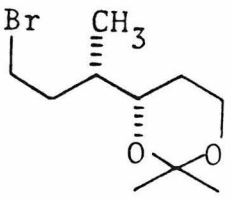
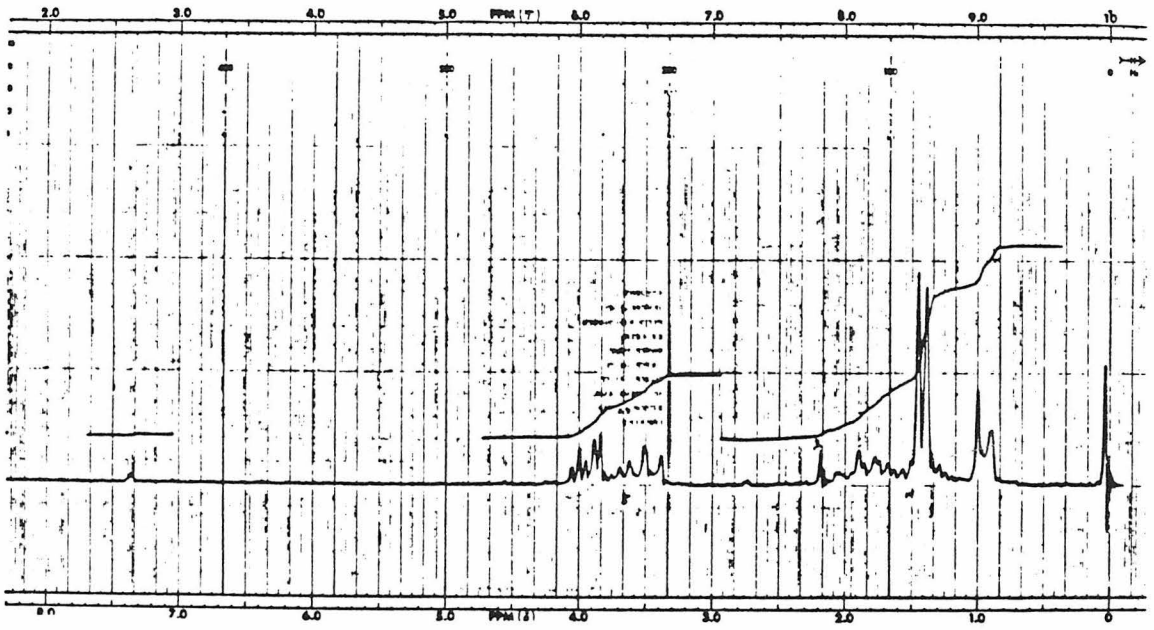
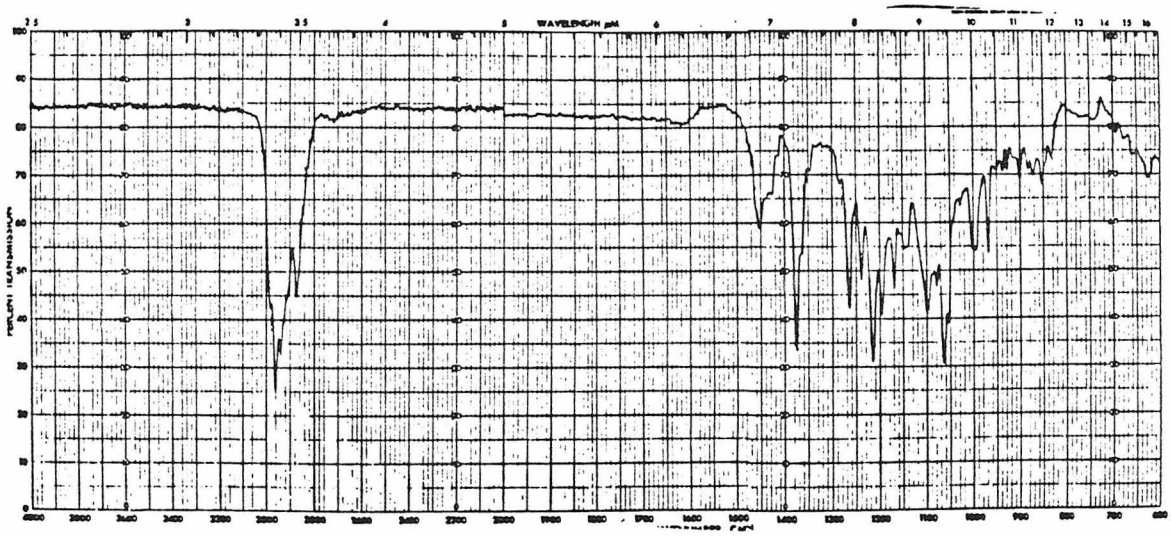


14b





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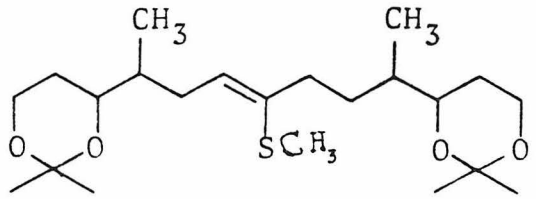
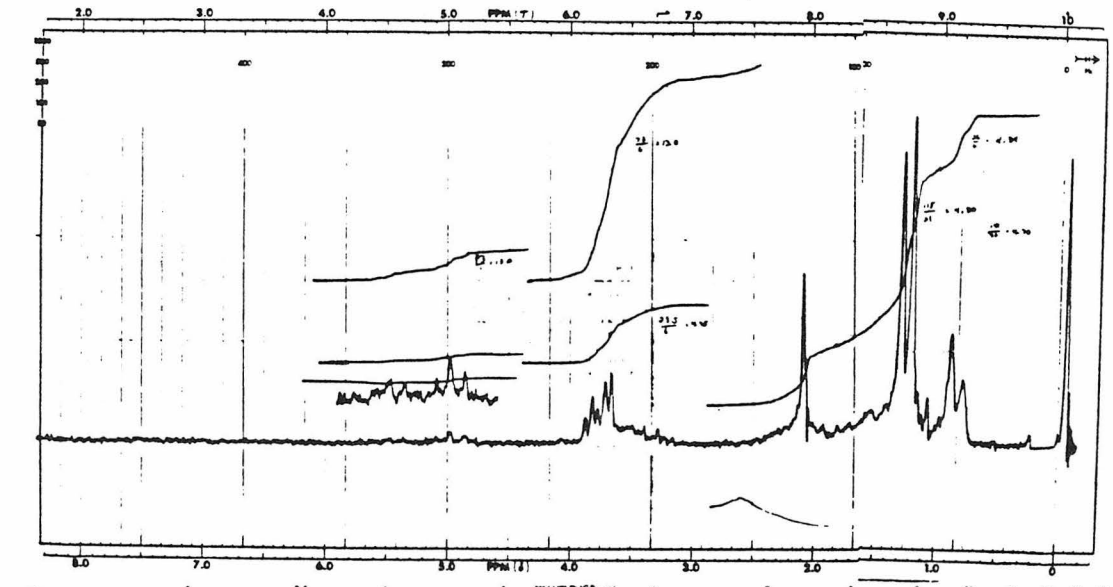
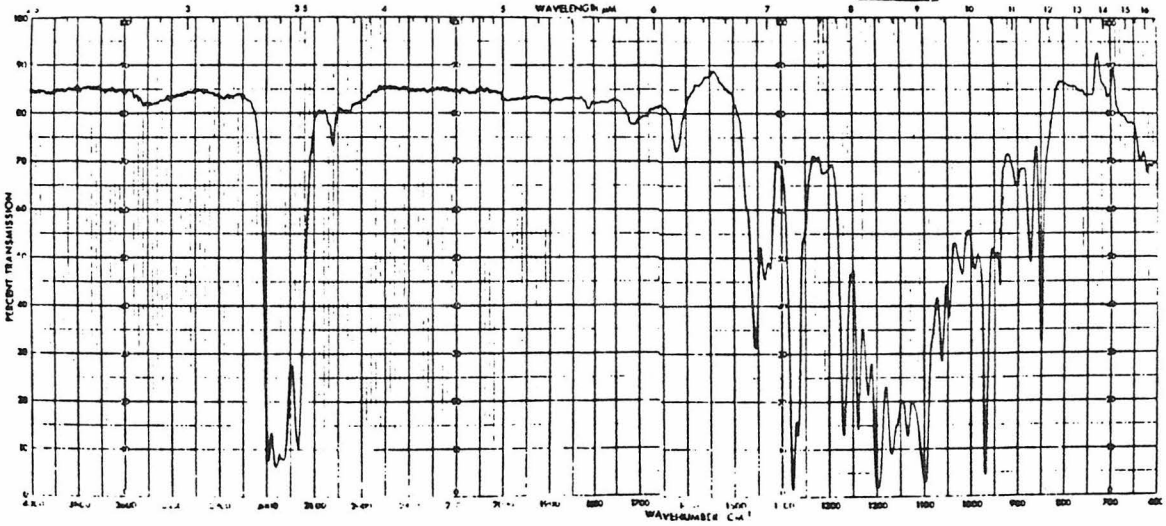
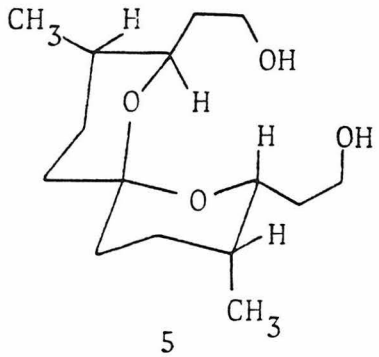


16b, 17b

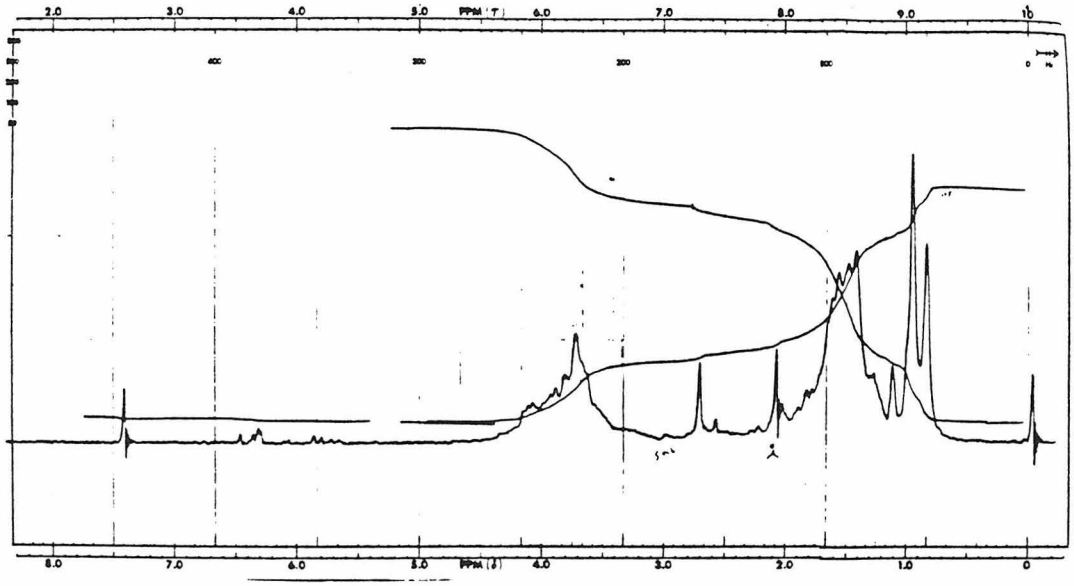


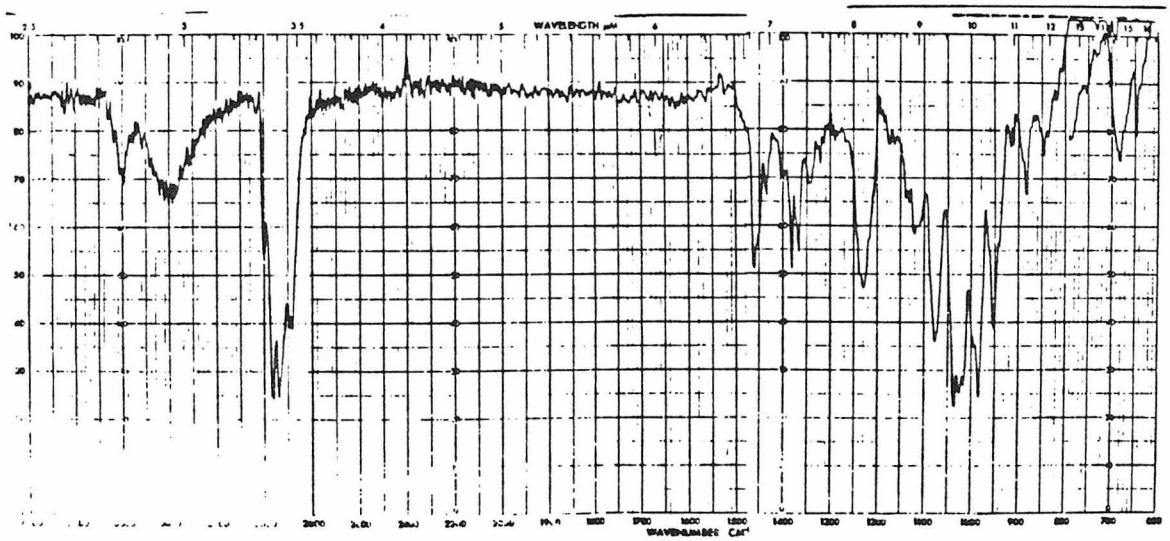


Page 45

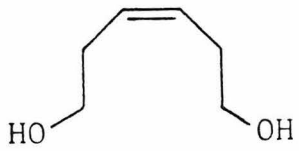

CH3
H
OH
O
H
H
OH
O
H
CH3

5

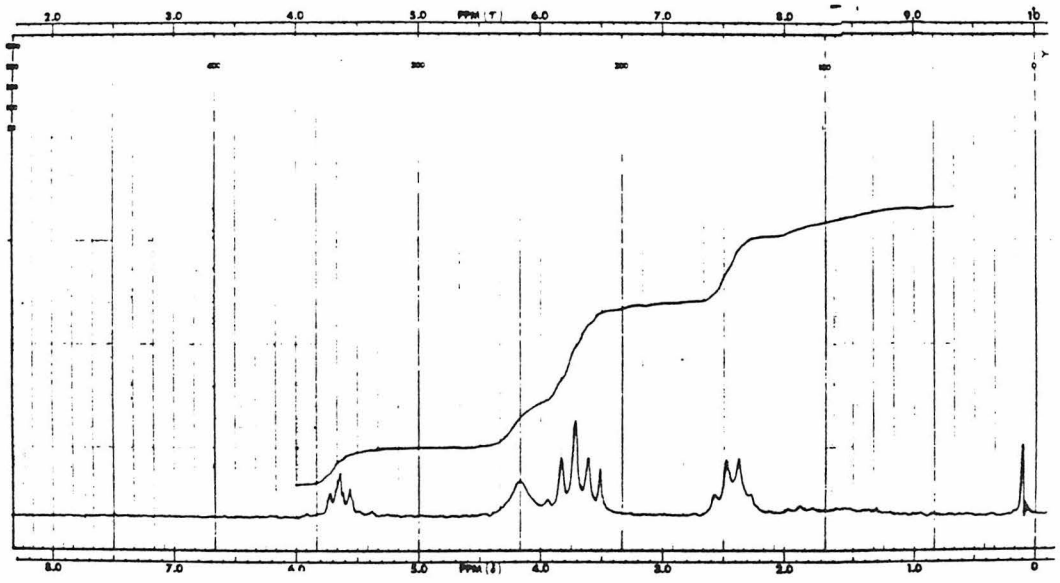

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
WAVENUMBER CM⁻¹

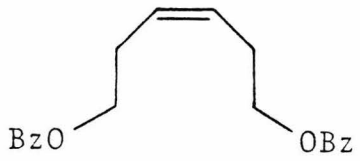
Page 46



10a

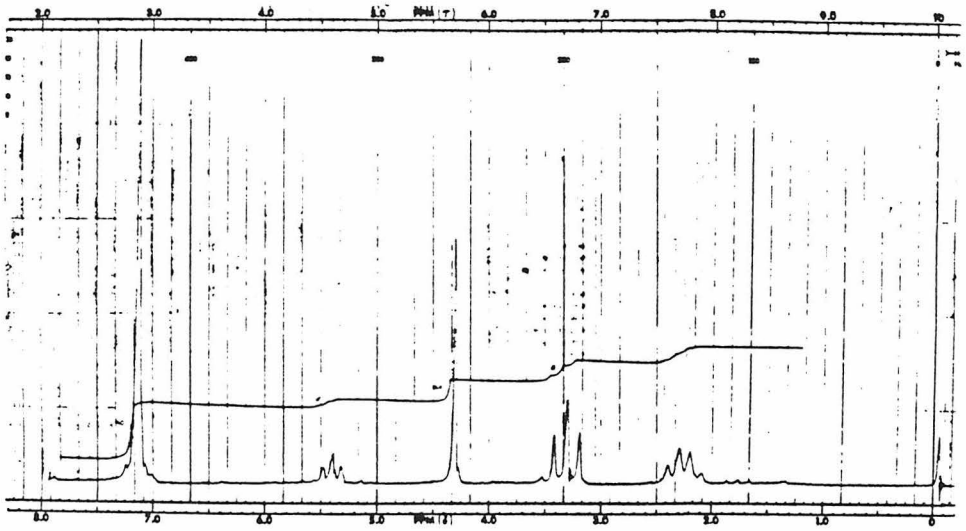


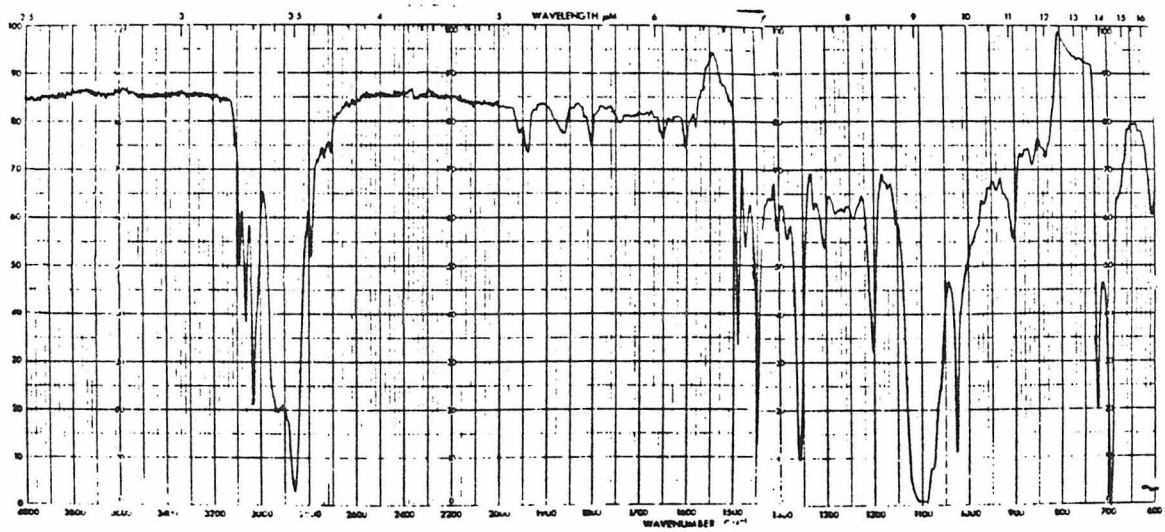
Page 46



11a

~~~

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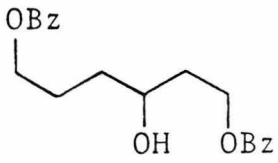
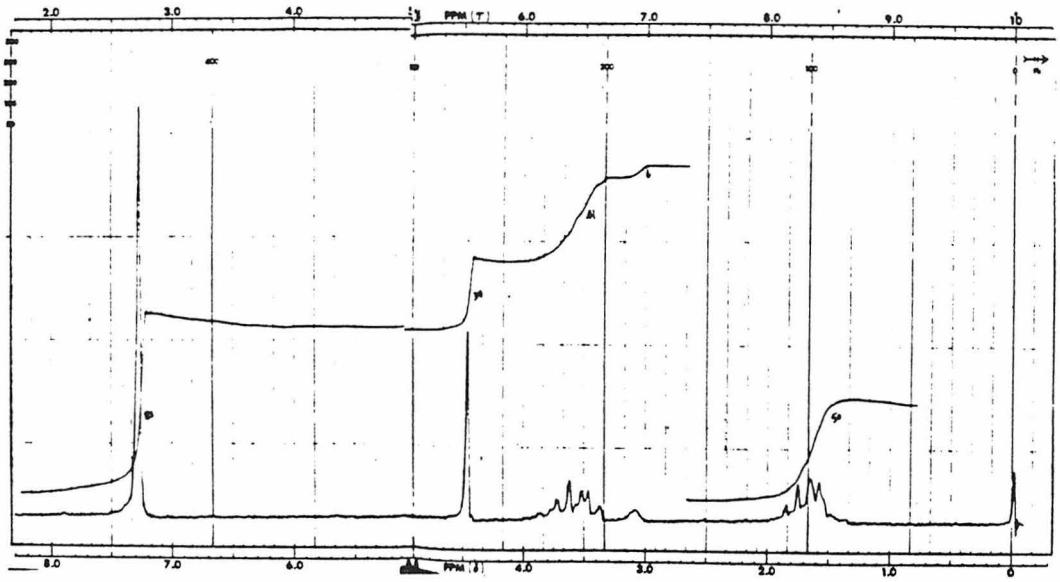
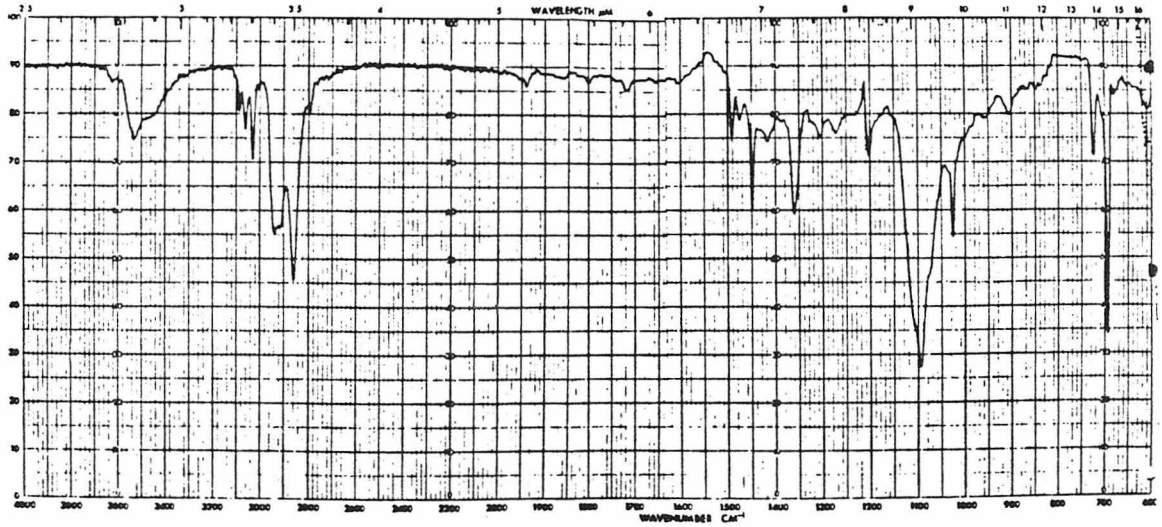
Page 46



12a





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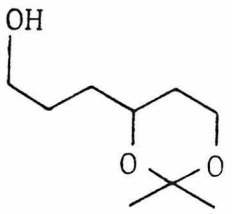
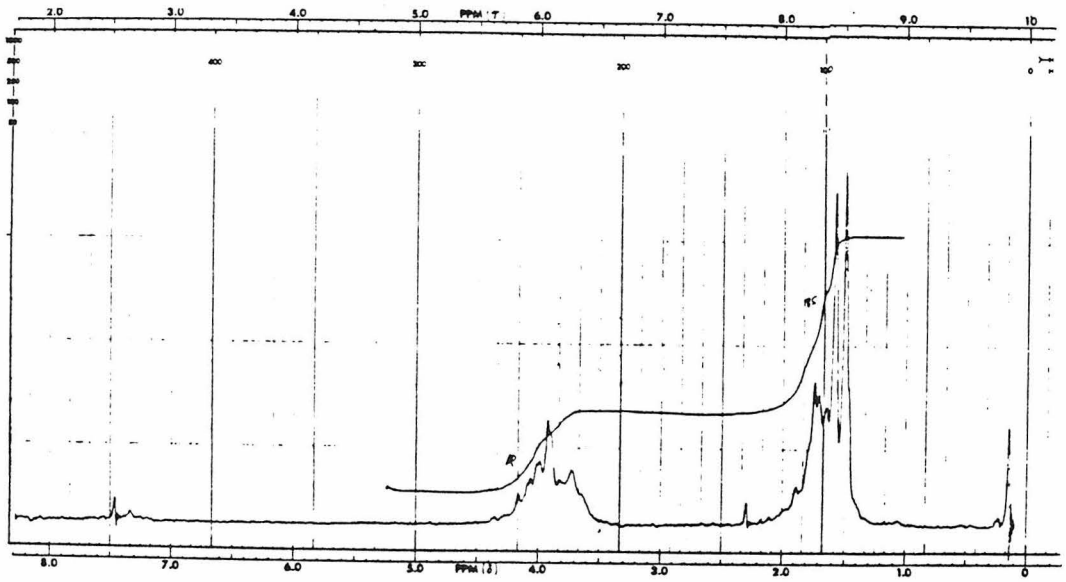
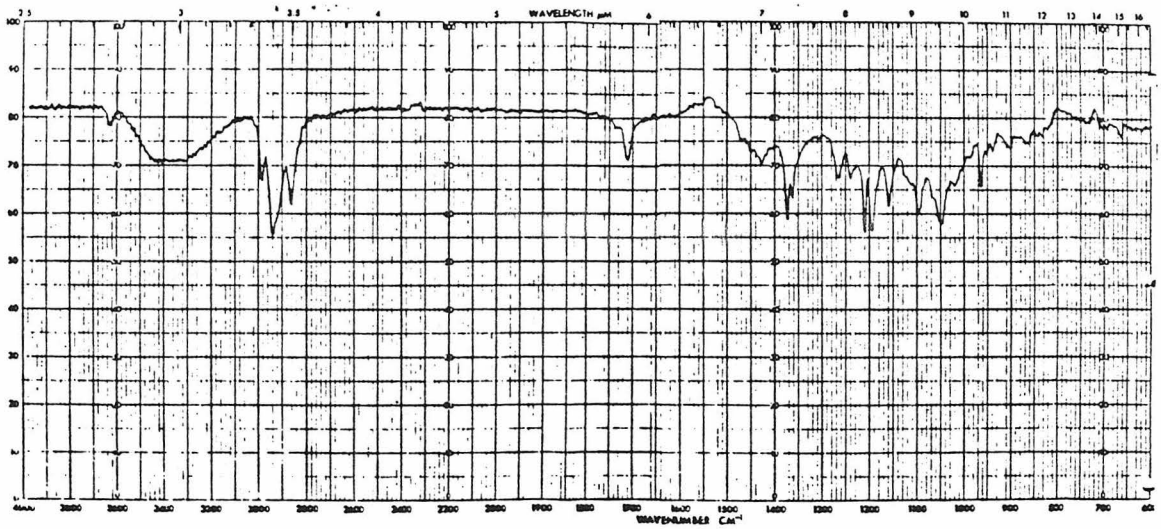
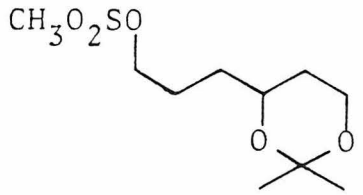

OH
O
O

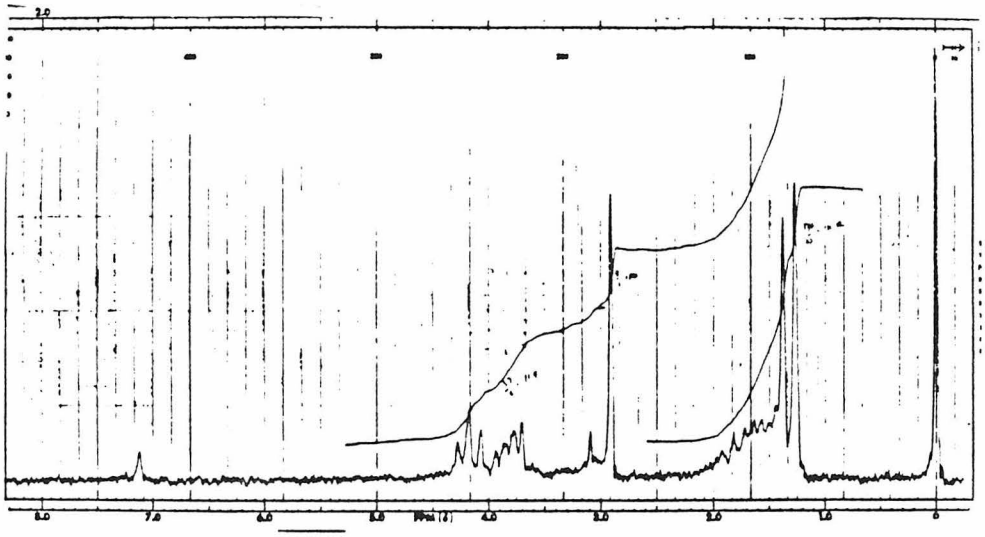
13a

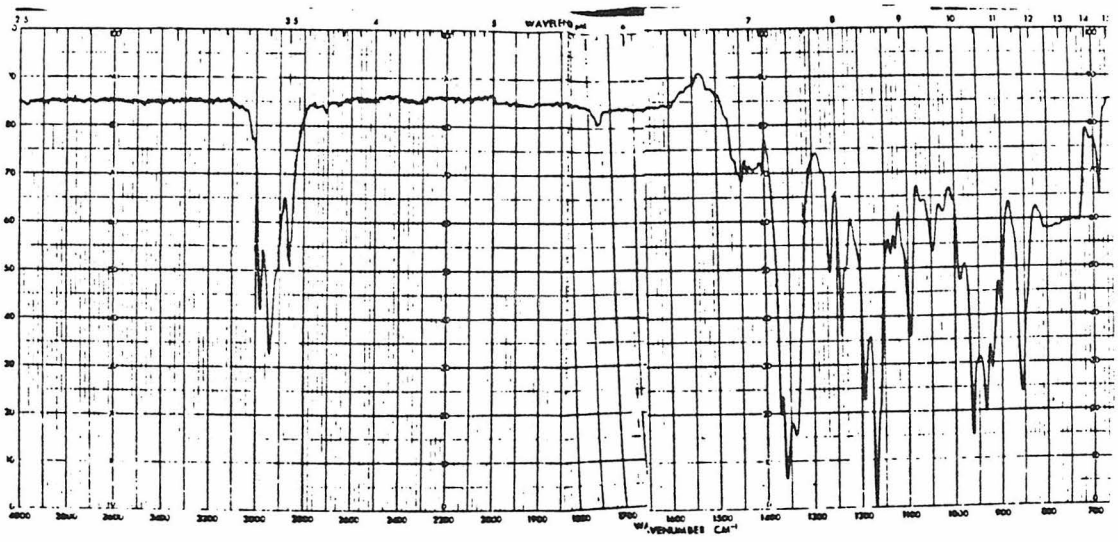

2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
WAVENUMBER CM⁻¹

Page 47







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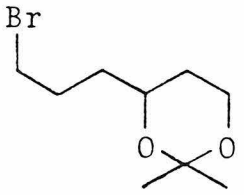
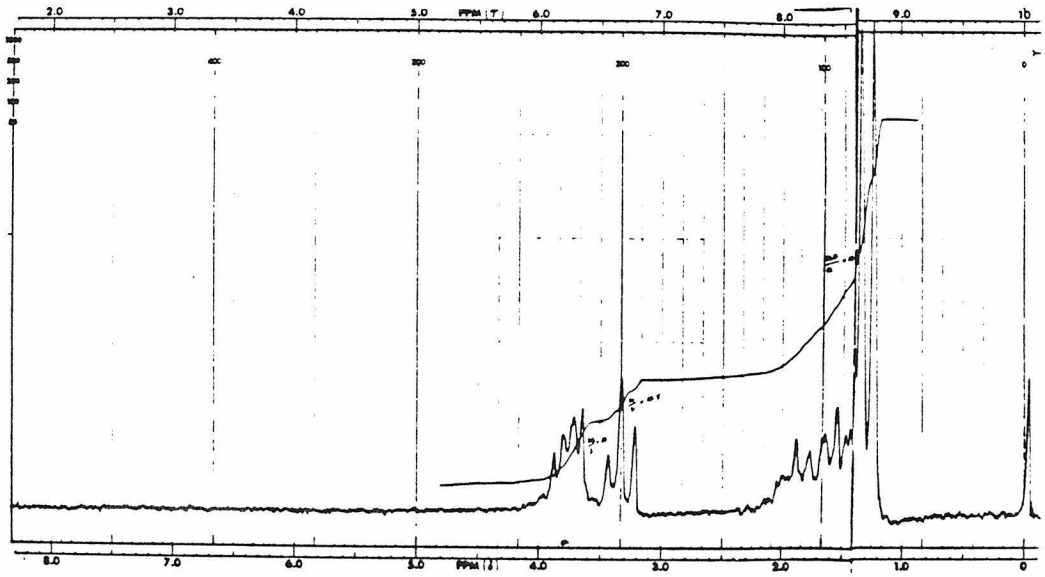
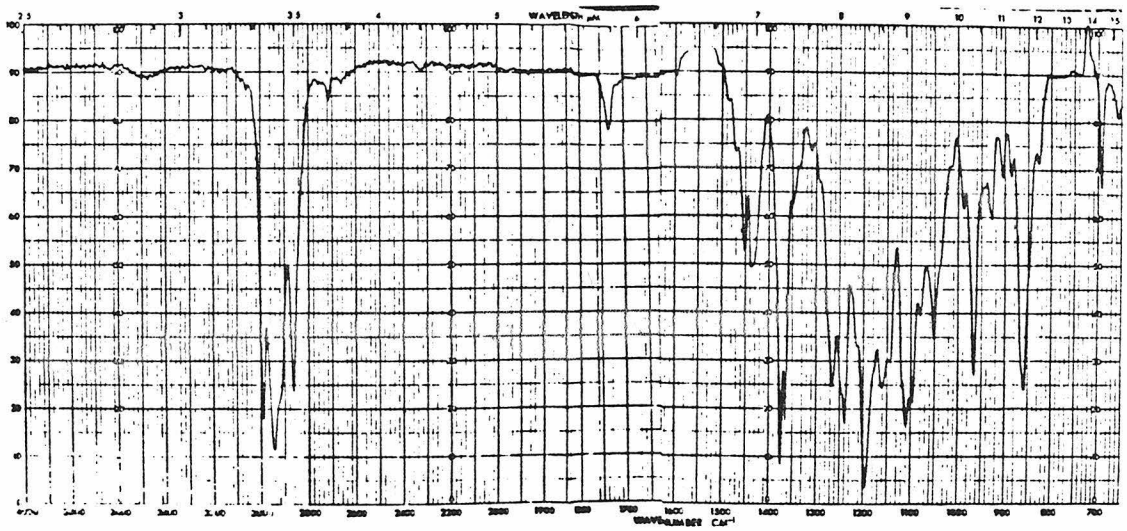


14a





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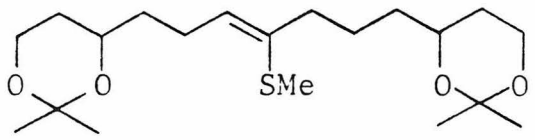
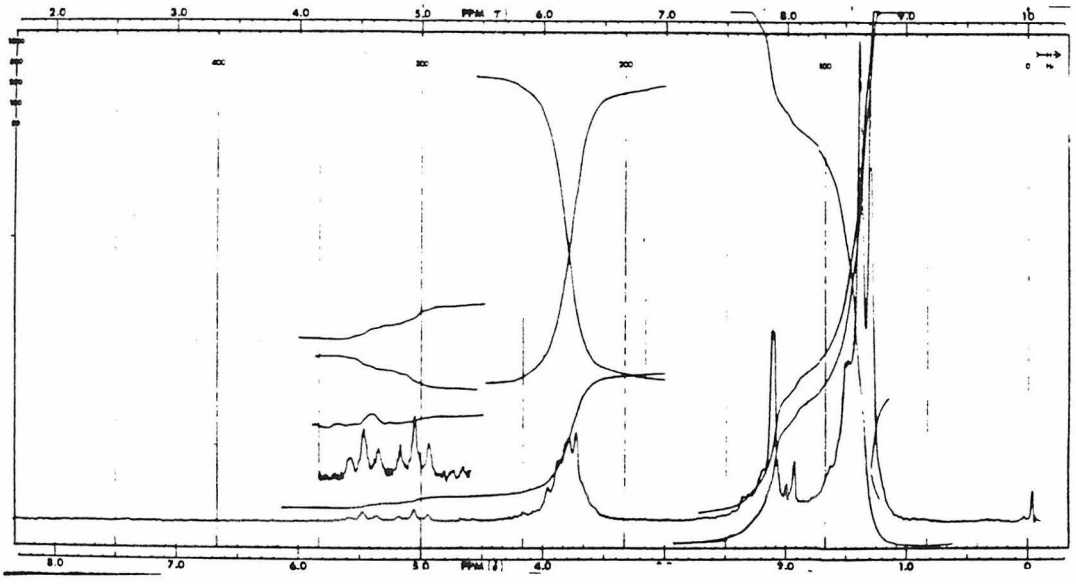
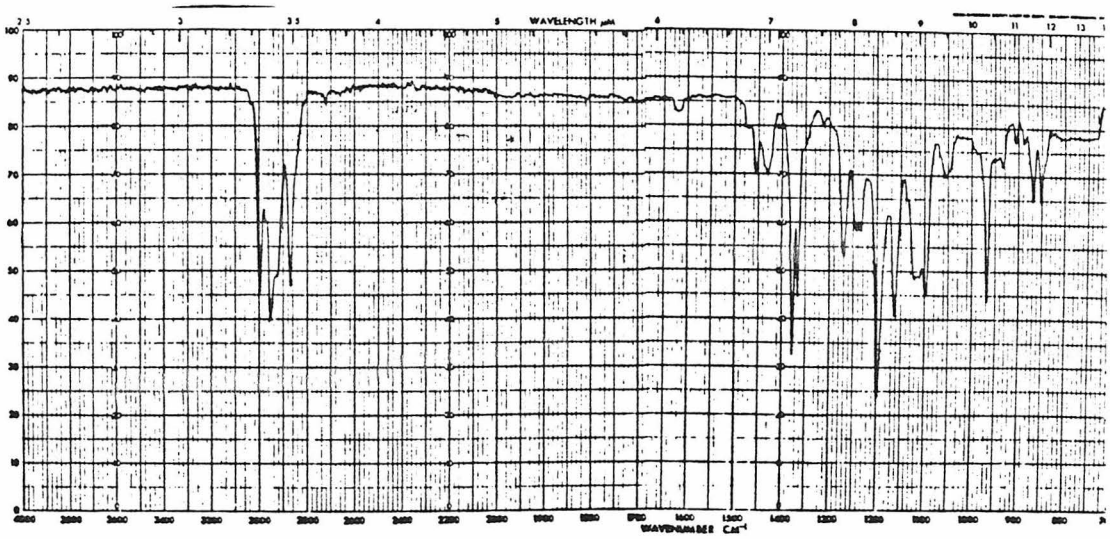


16a, 17a





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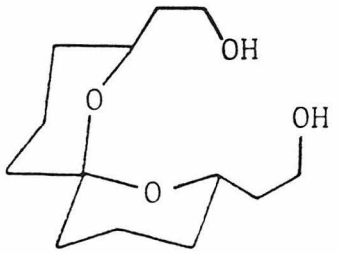
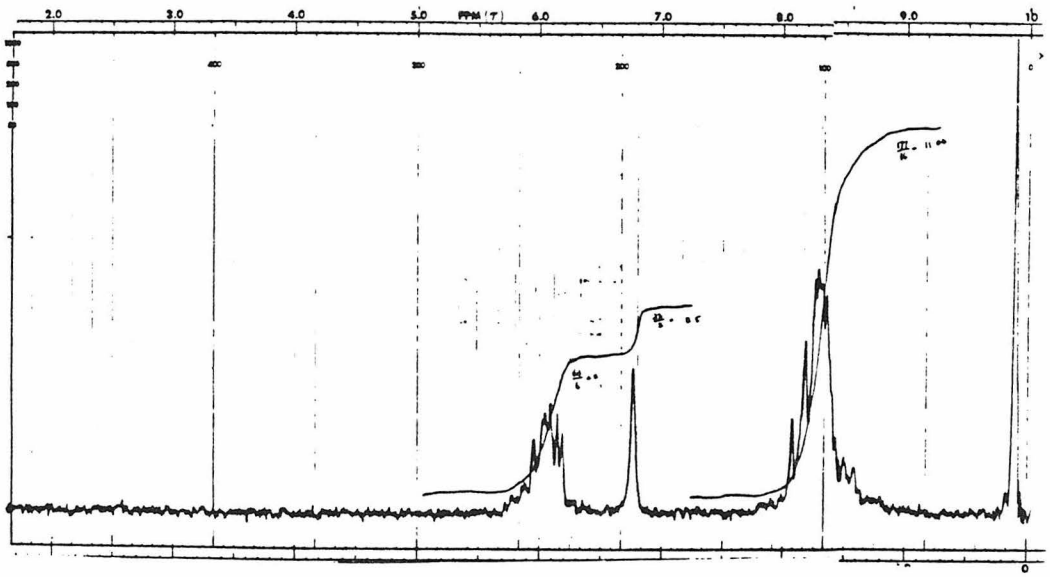
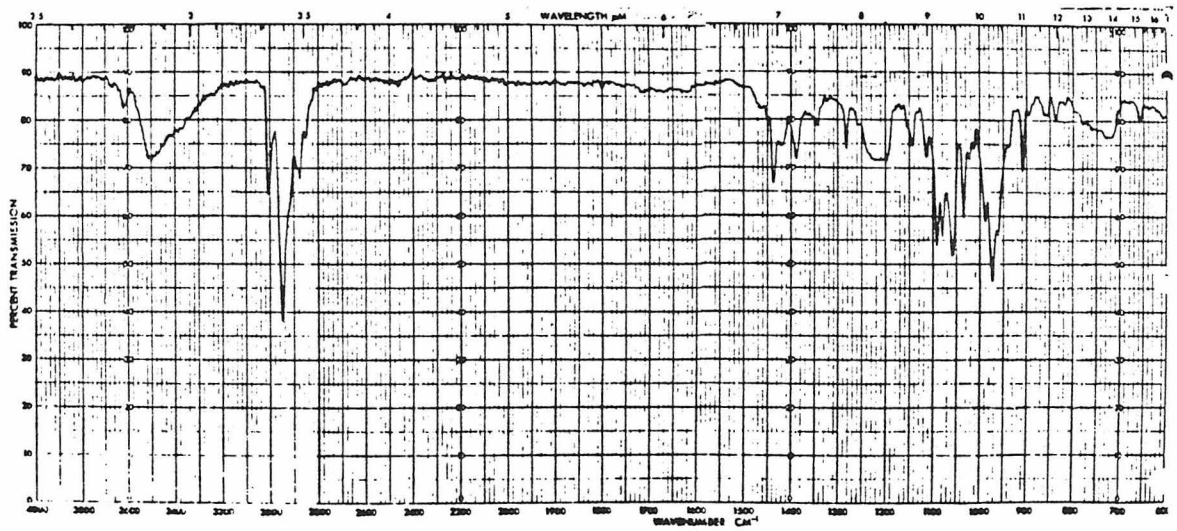

OH
O
OH
O

18


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


WAVELENGTH μM
PERCENT TRANSMISSION

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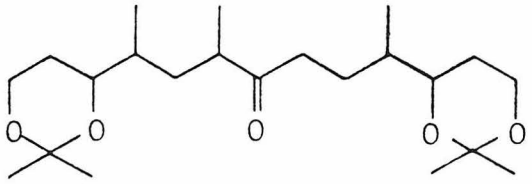
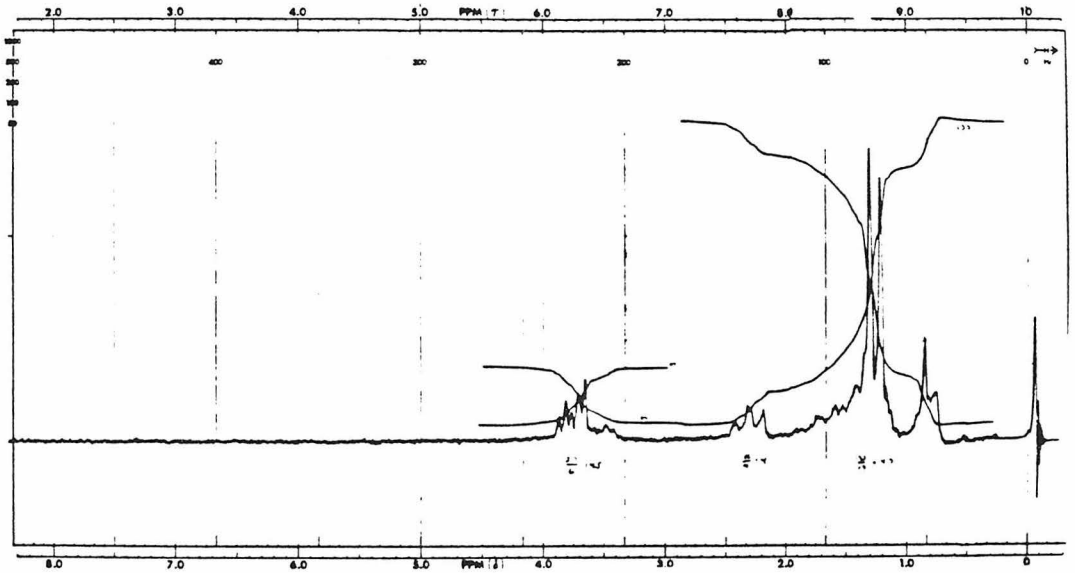
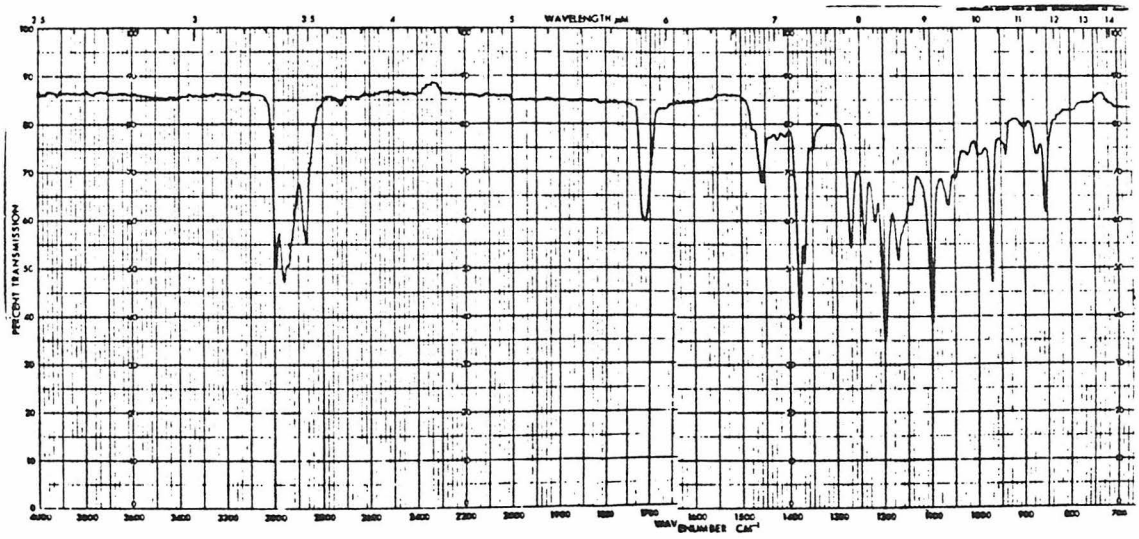


25





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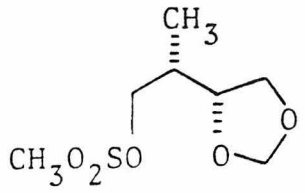
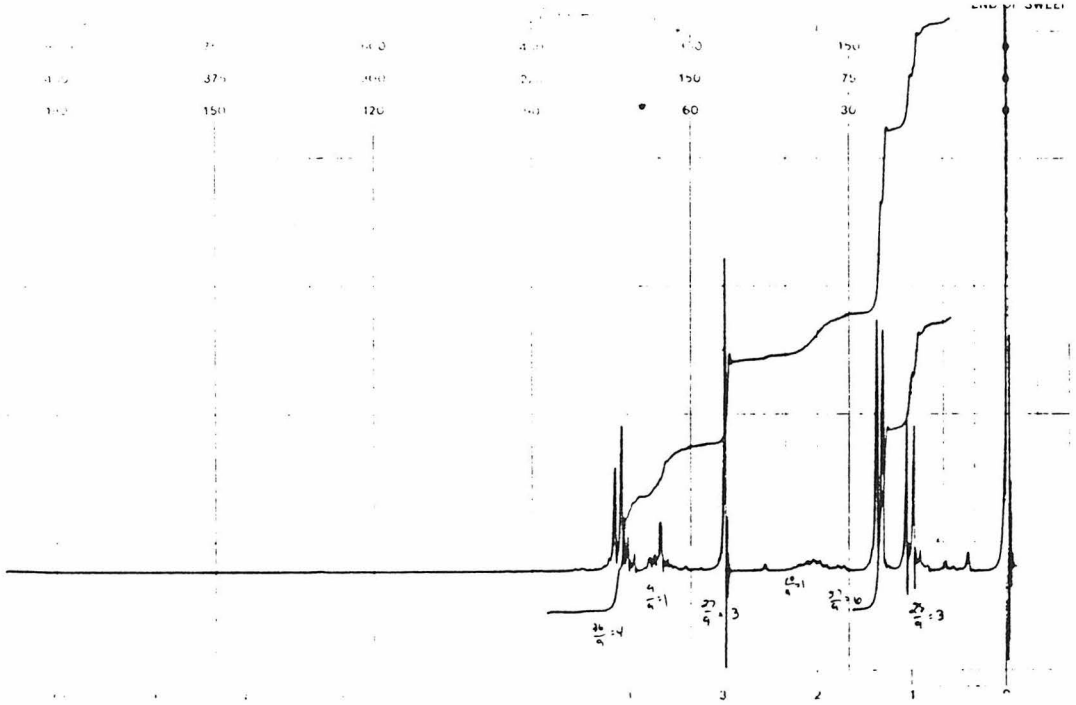
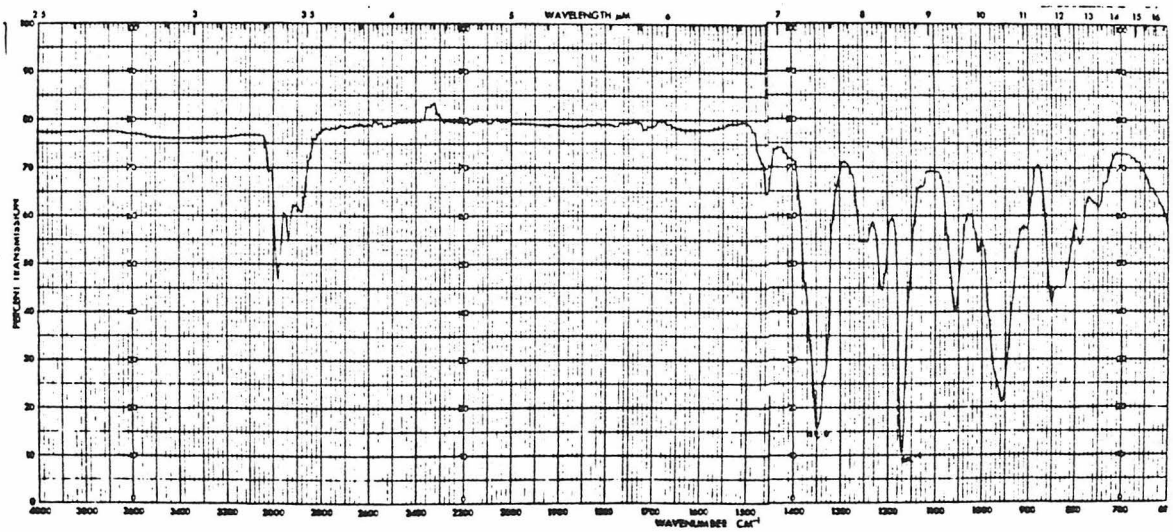

CH3
O
CH3O2SO
O




WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBERS CM⁻¹

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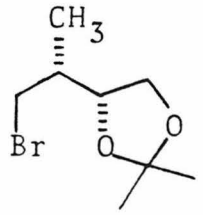
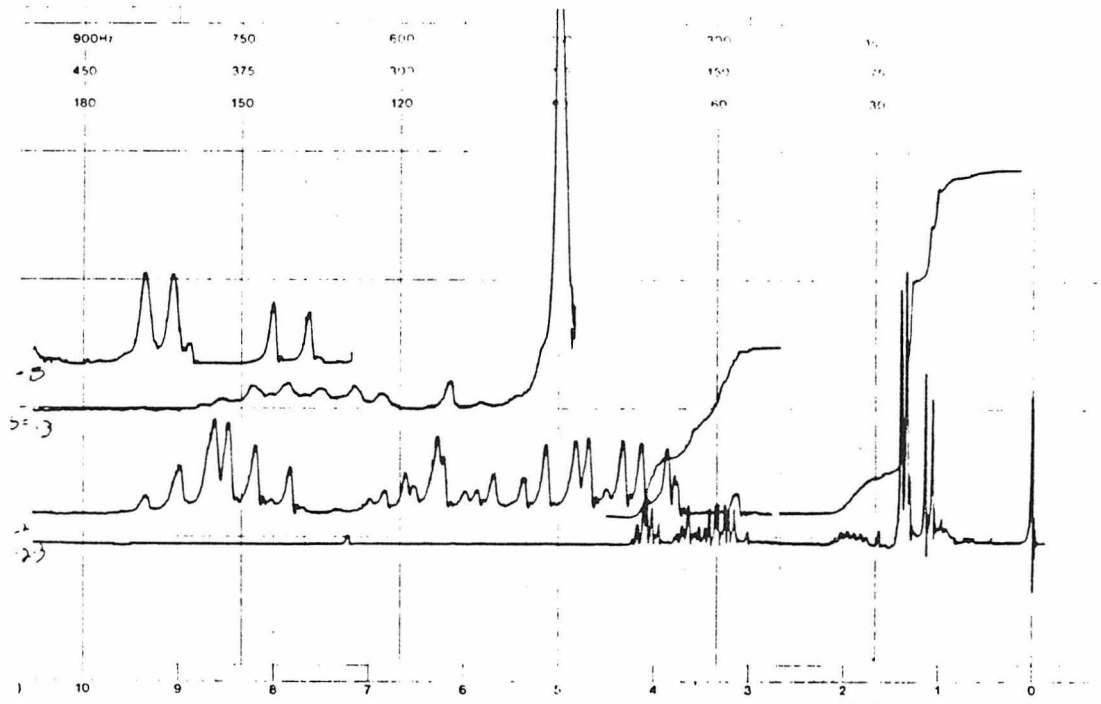
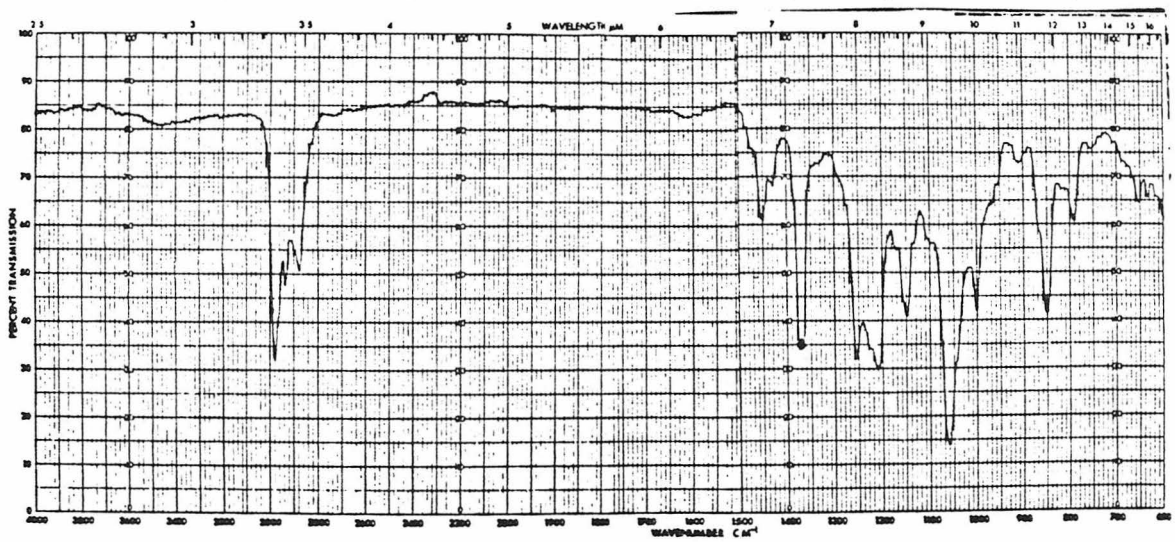

CH3
Br
O
O

20b


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


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

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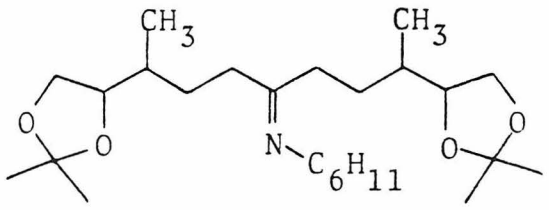
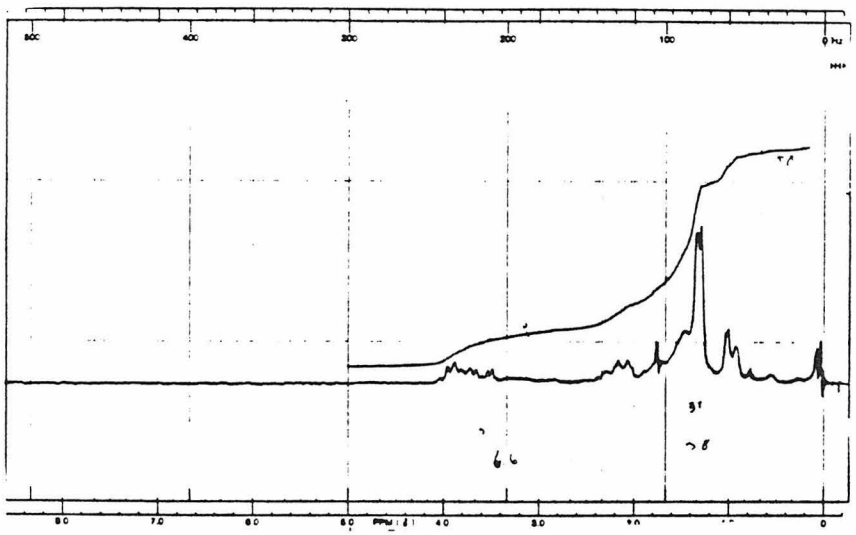
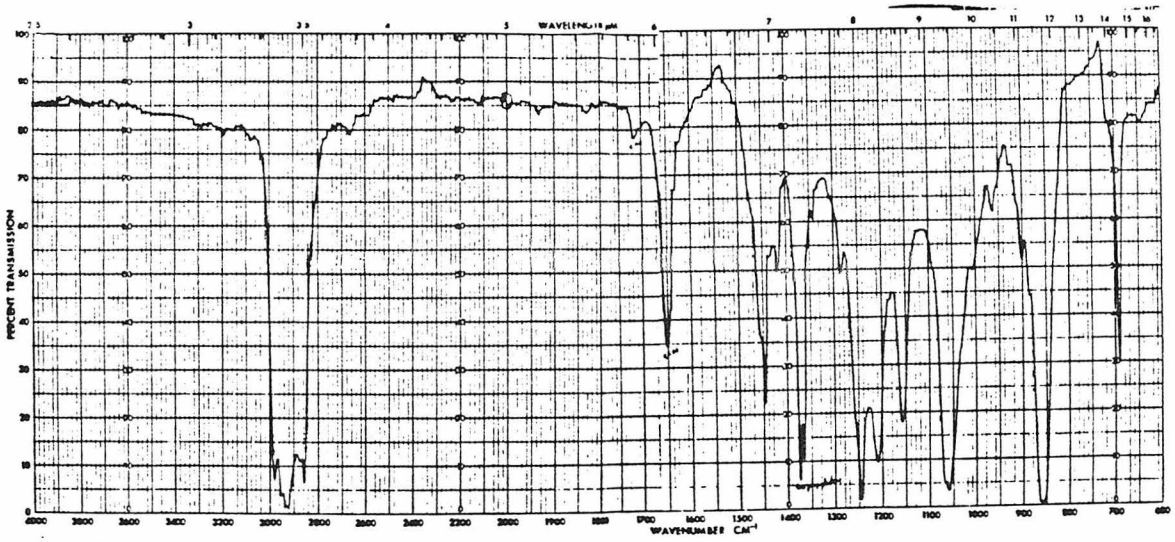


22a





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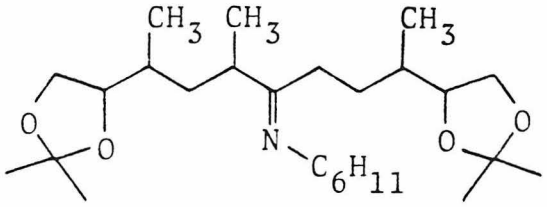
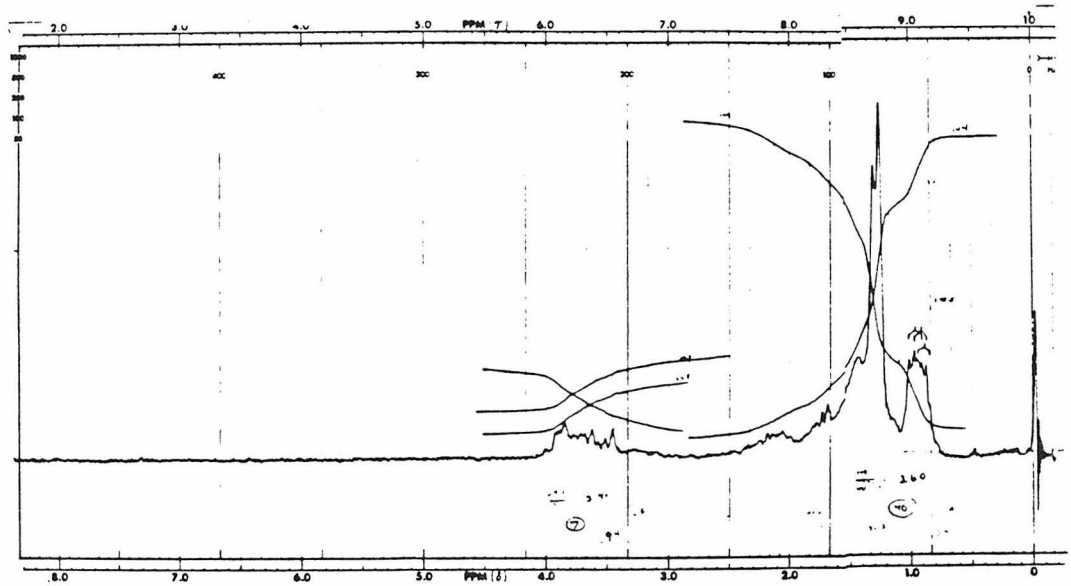
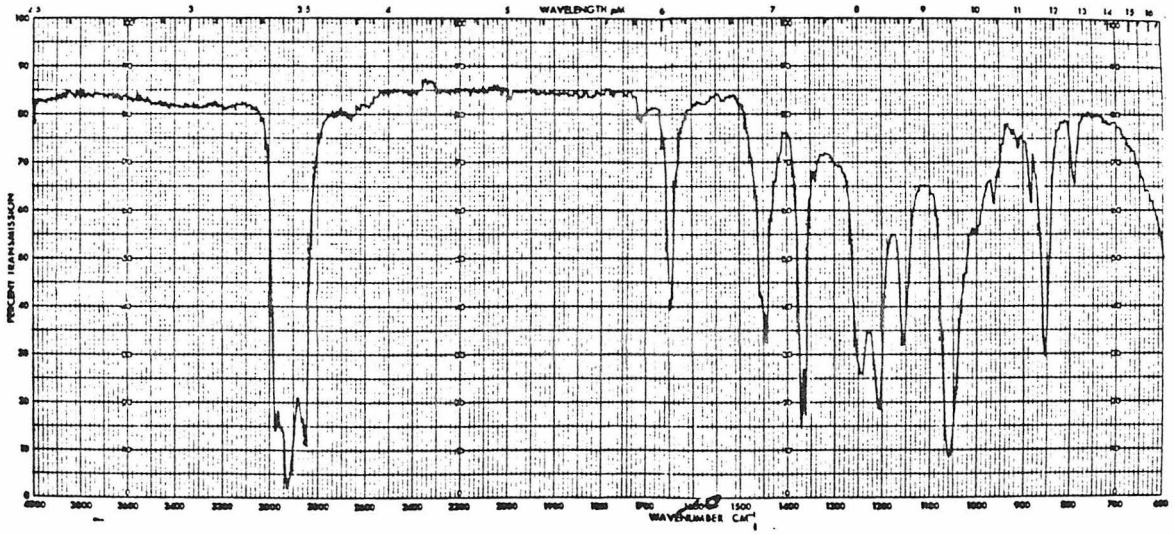
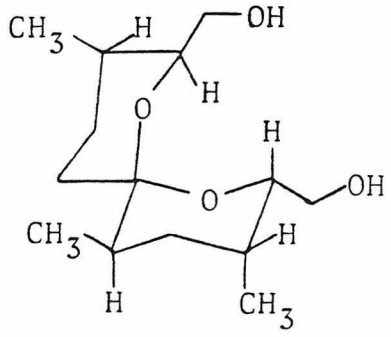

CH3
CH3
CH3
O
O
N
C6H11
O
O

22b

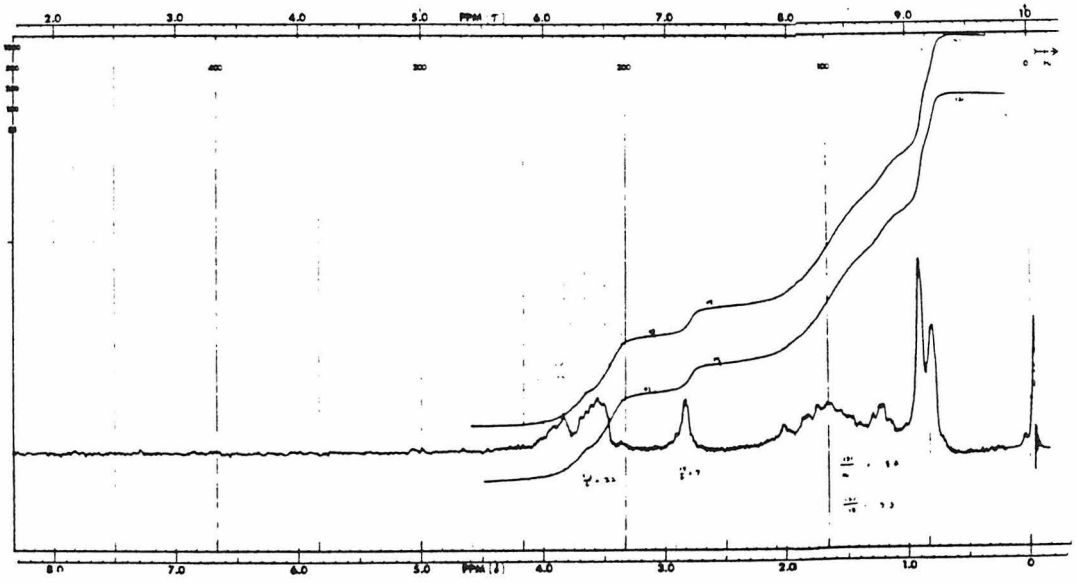

PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

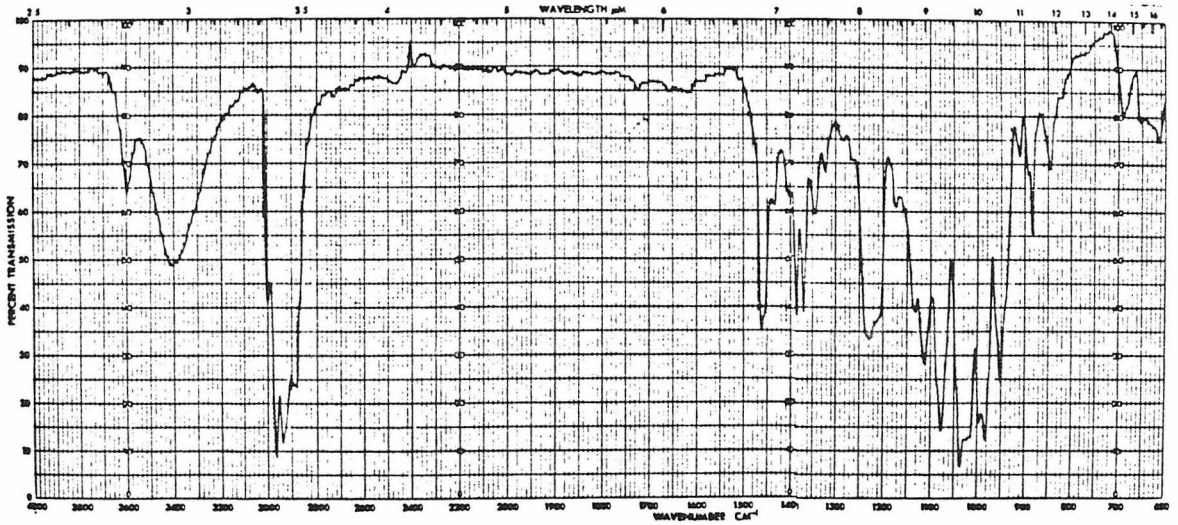

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER Cm-1

Page 52

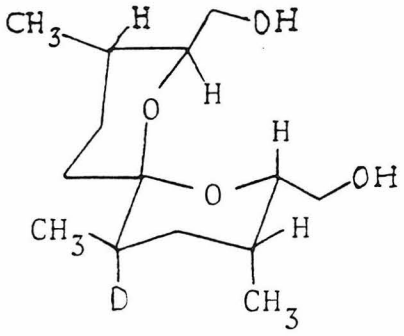

CH3
H
OH
H
O
H
O
OH
CH3
H
H
CH3

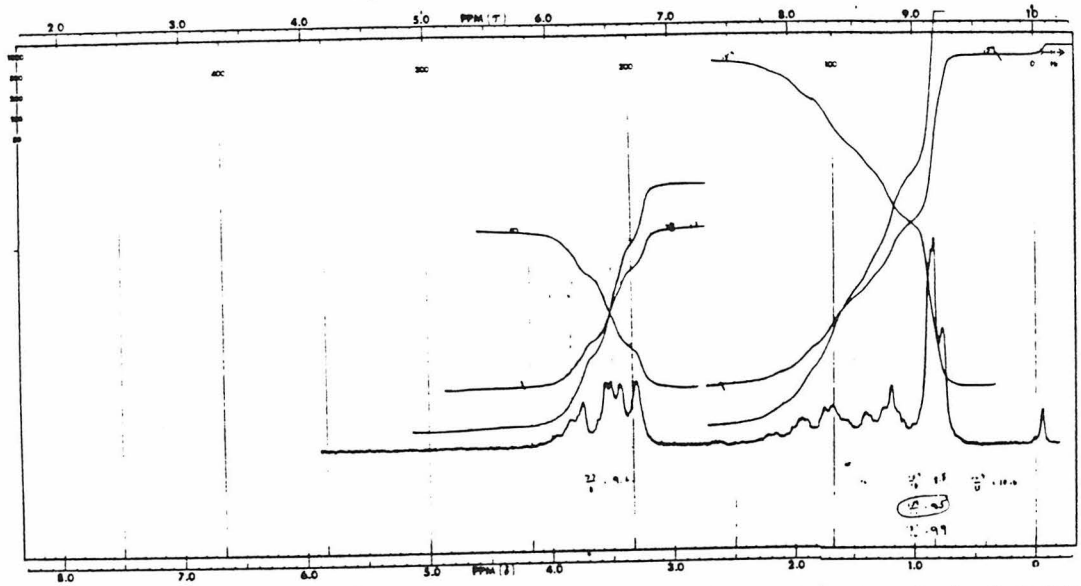
23a

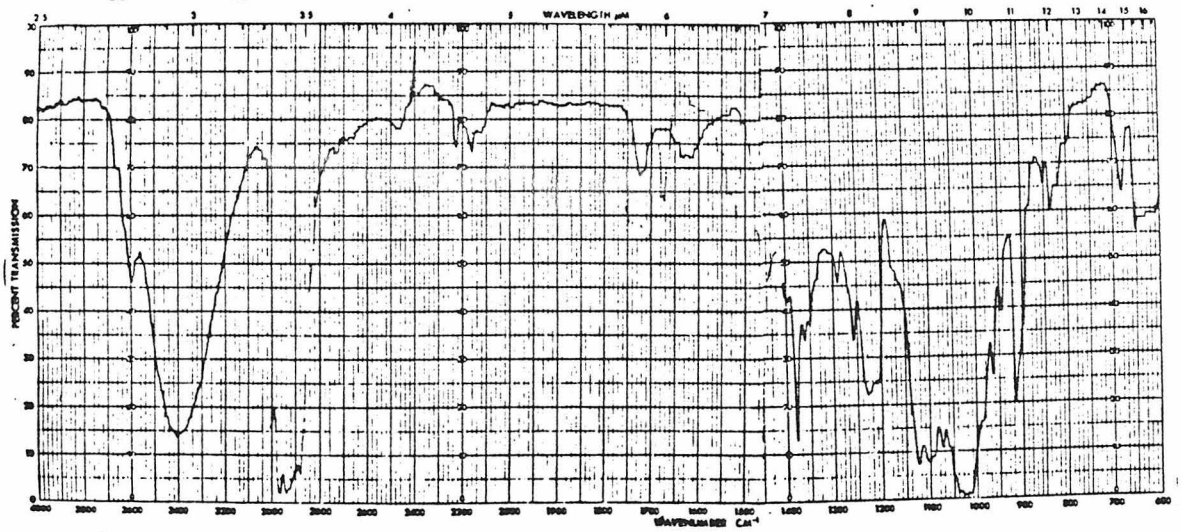

2.0
3.0
4.0
5.0
PPM (δ)
6.0
7.0
8.0
9.0
10
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹

Page 55


CH3
H
OH
O
H
H
O
OH
CH3
H
D
CH3


PPM (τ)
PPM (δ)


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER Cm-1

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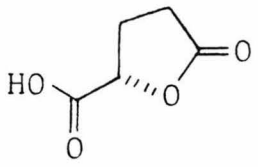
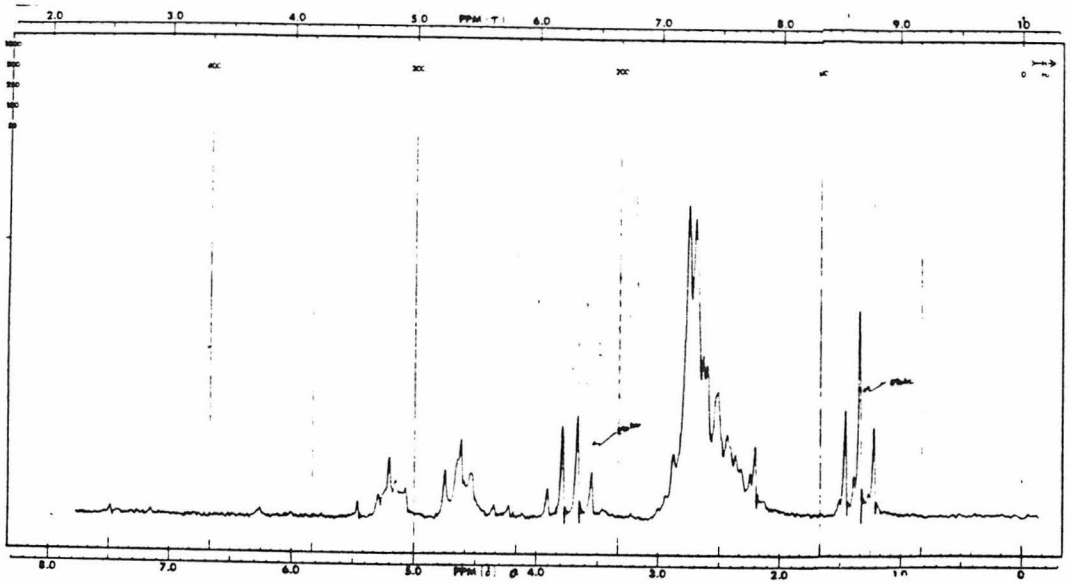

HO
O
O
O

27


PPM (δ)
PERCENT TRANSMISSION
WAVELENGTH μM
WAVENUMBER CM⁻¹

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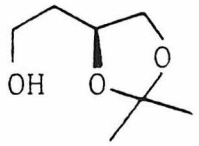

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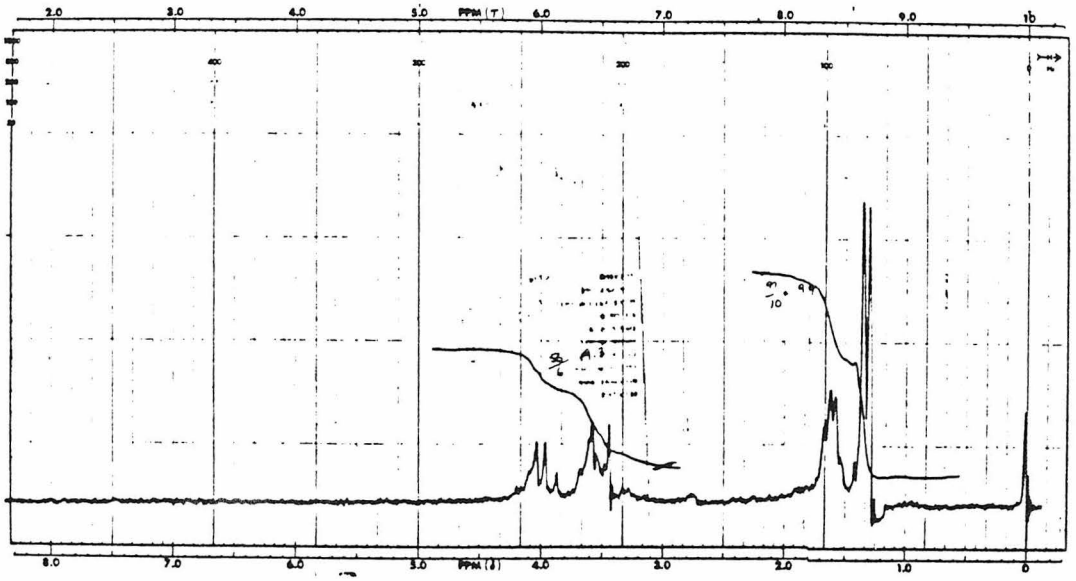

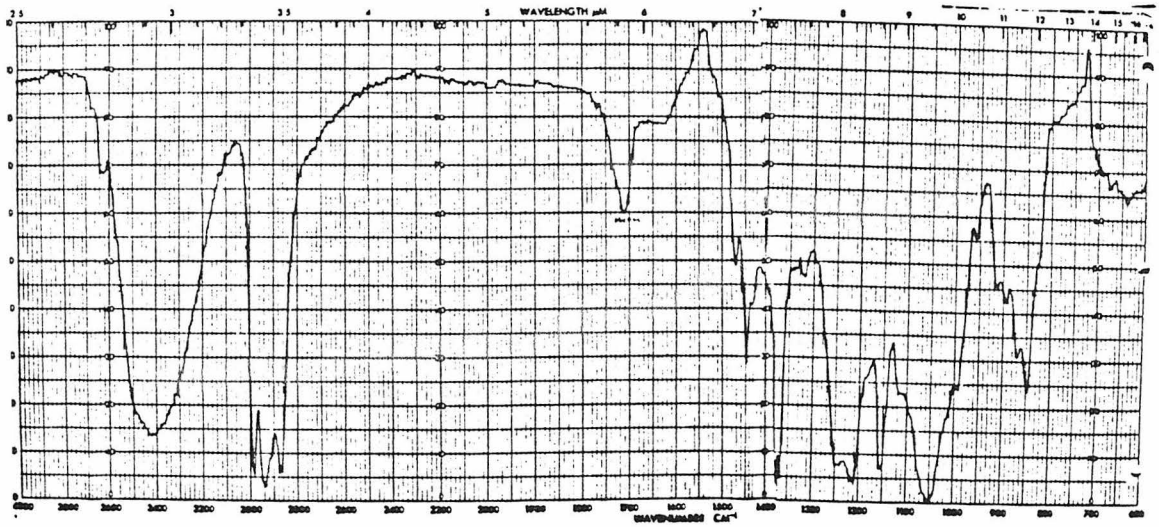

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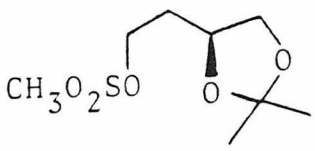
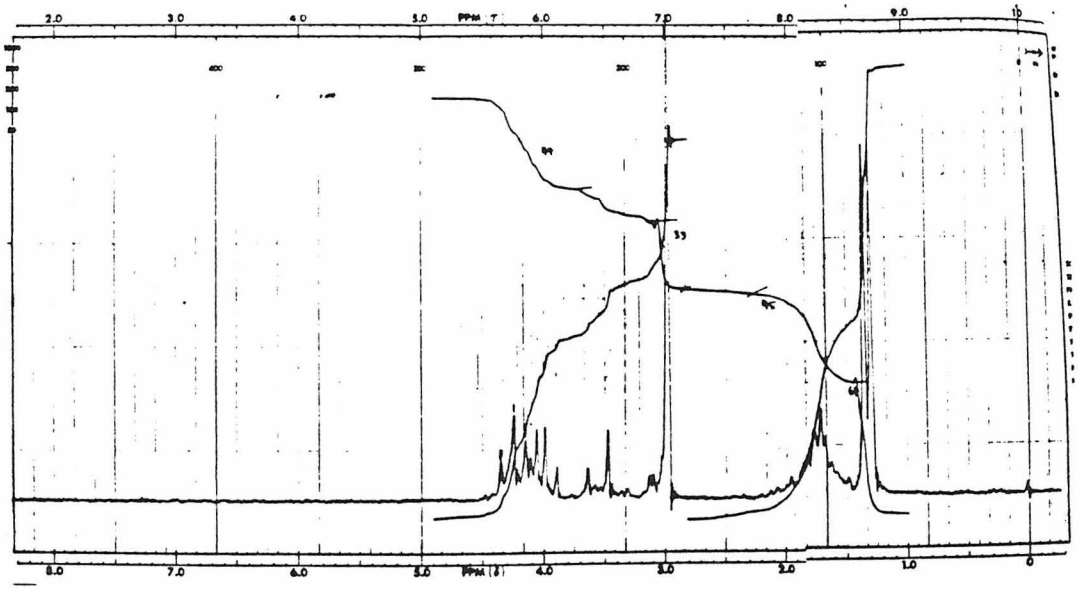
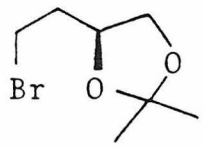
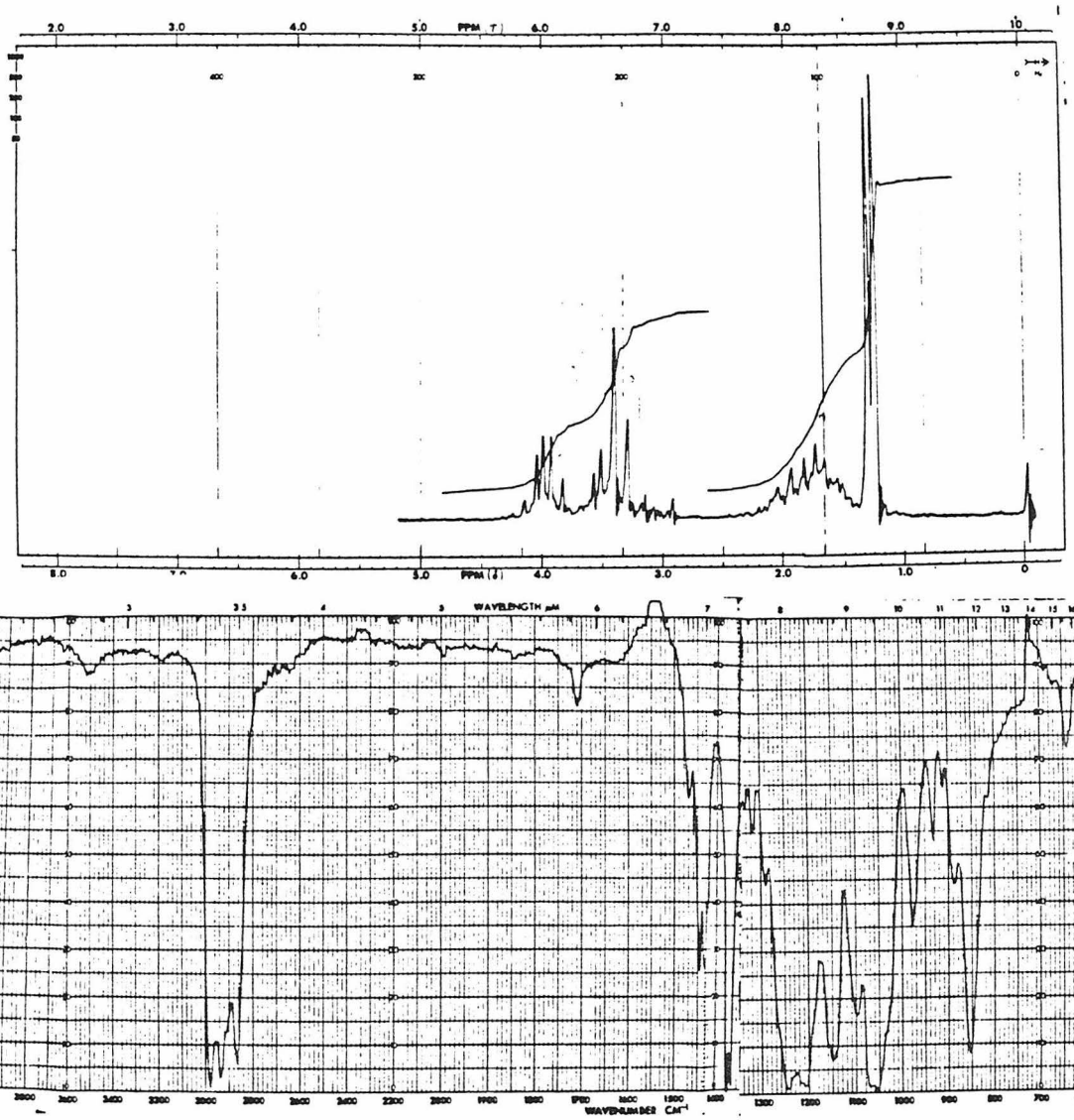

CH3O2SO
O
O


2.0
3.0
4.0
5.0
PPM
6.0
7.0
8.0
9.0
10
99
33
64
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Page 56


Br
O
O

29


PPM (τ)
PPM (δ)
WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION

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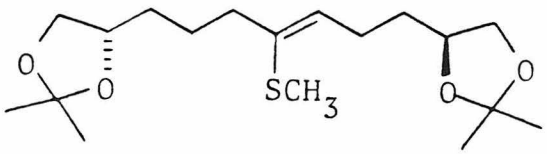
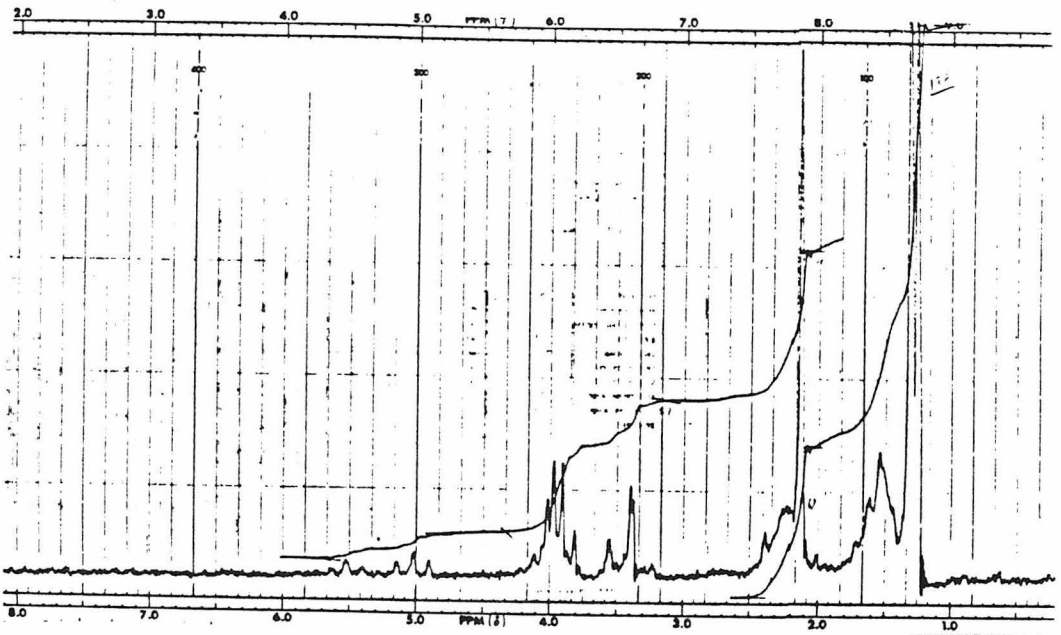
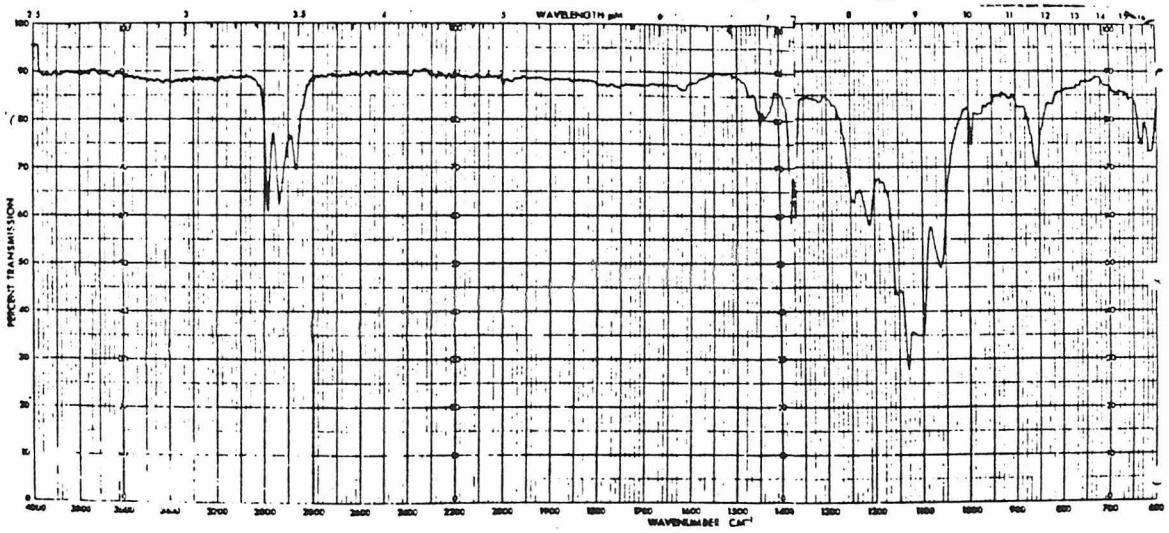

O
O
SCH3
O
O

30


2.0
3.0
4.0
5.0
6.0
7.0
8.0
PPM (δ)


PERCENT TRANSMISSION
WAVELENGTH μm
WAVENUMBER cm⁻¹

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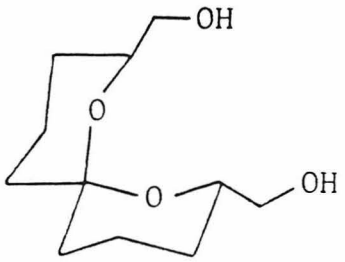
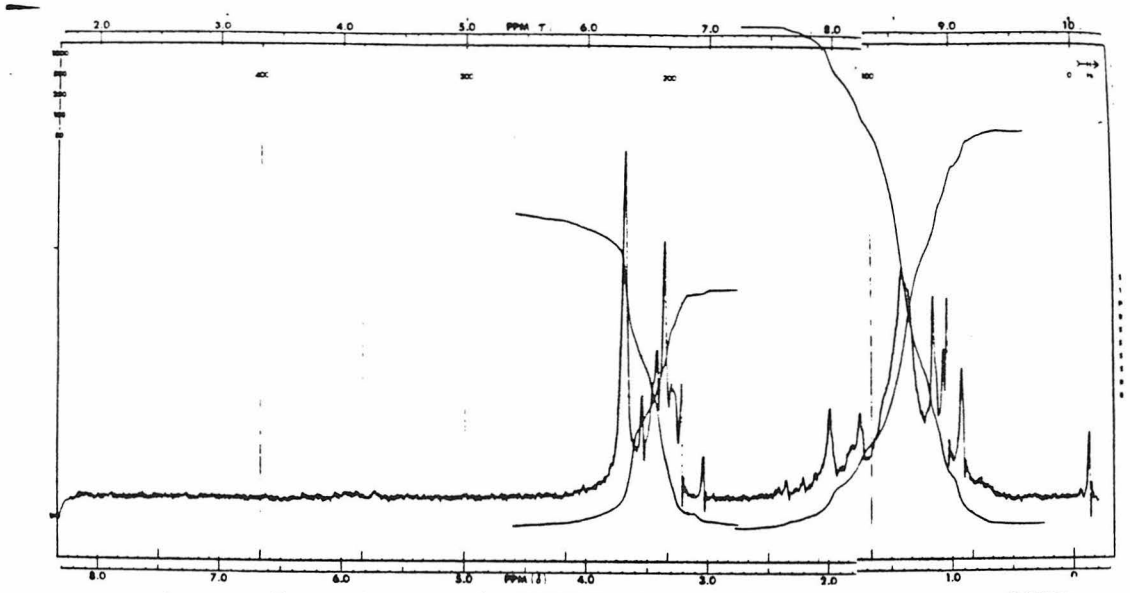


31



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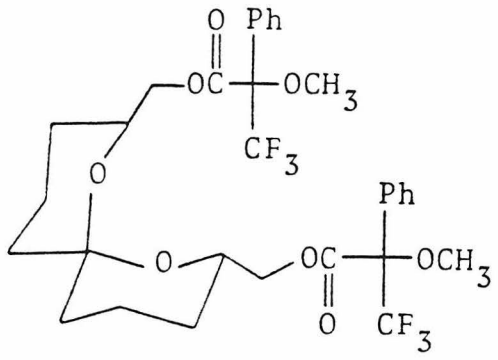
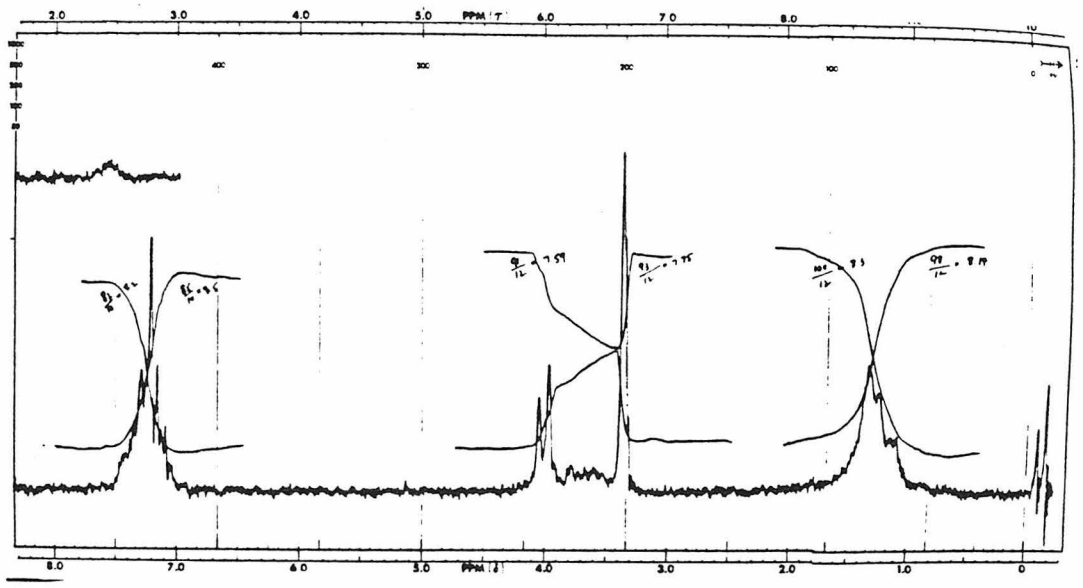
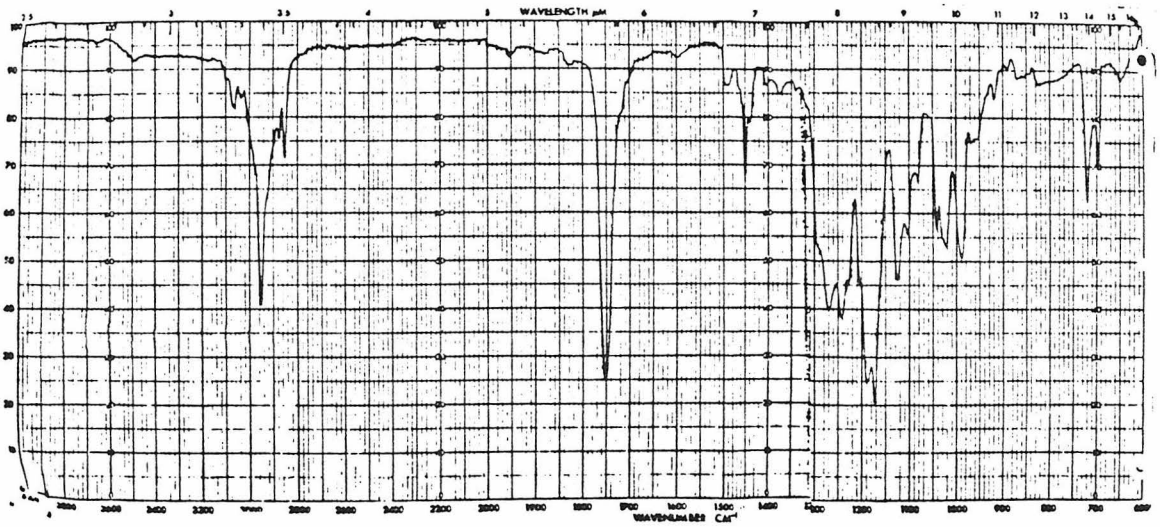
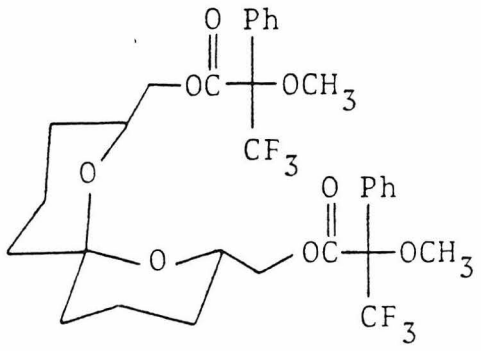
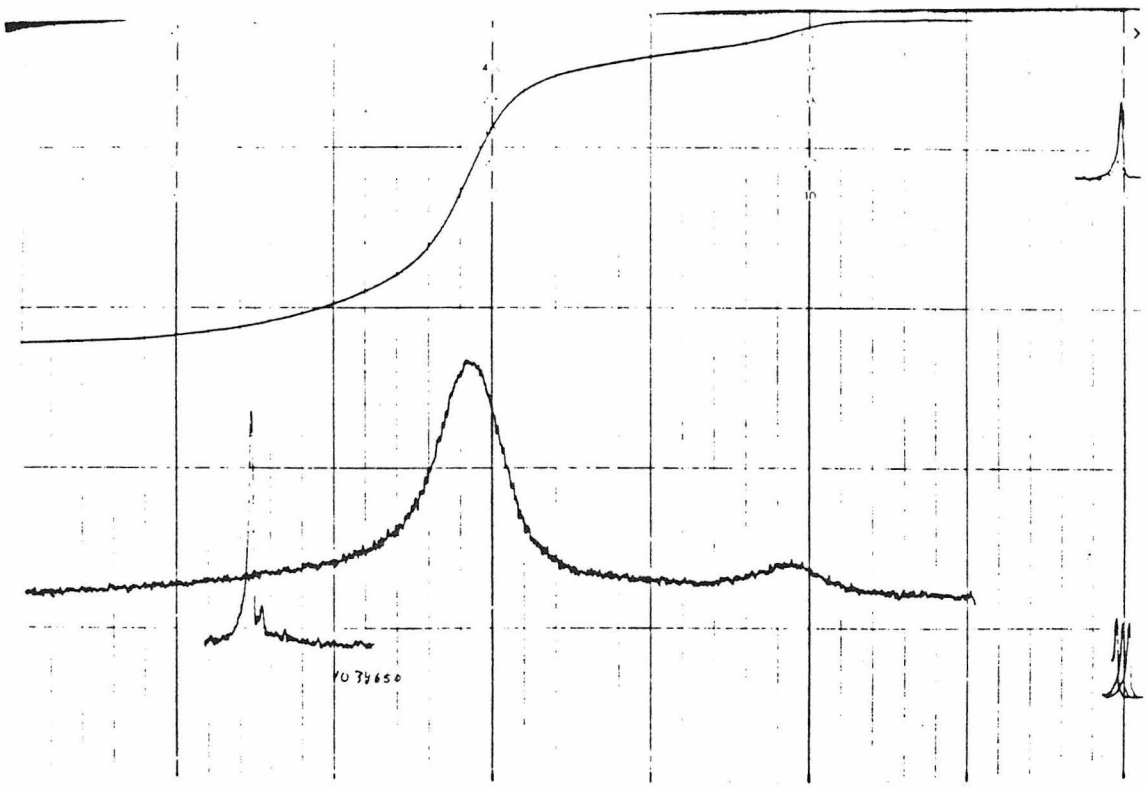

O
Ph
OC
OCH3
CF3
O
Ph
O
OC
OCH3
O
CF3


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


WAVELENGTH μm
WAVENUMBER CM-1



^{19}F-NMR

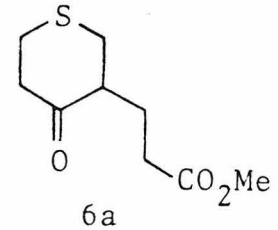


APPENDIX V

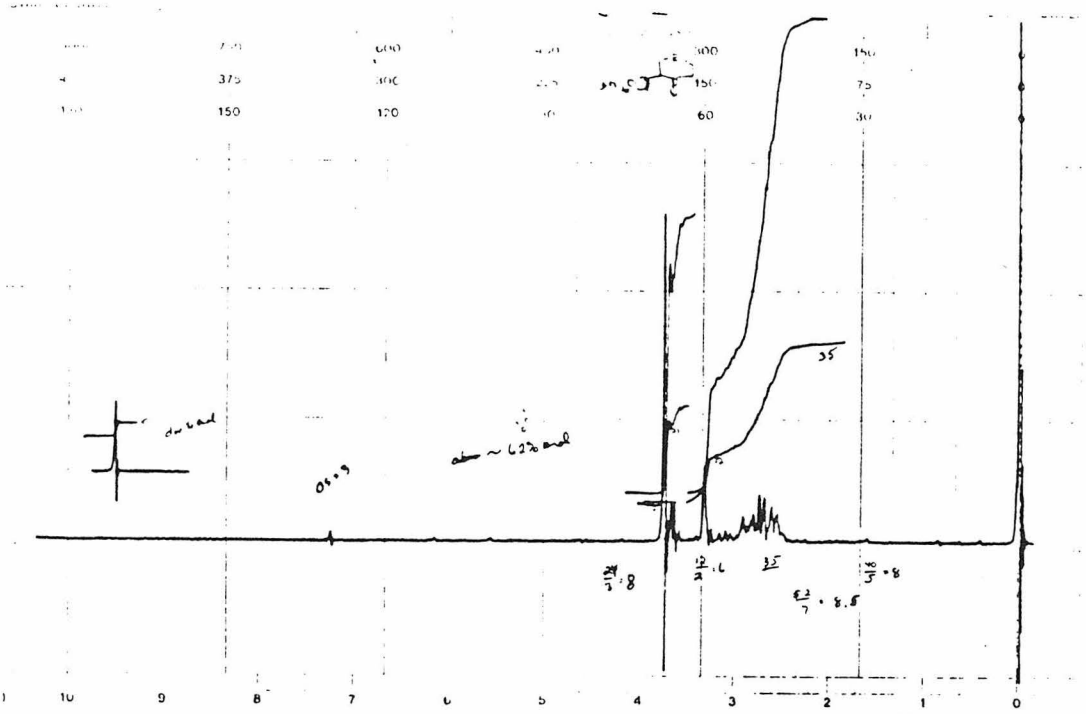
IR and ^{1}H-NMR Spectral Catalog

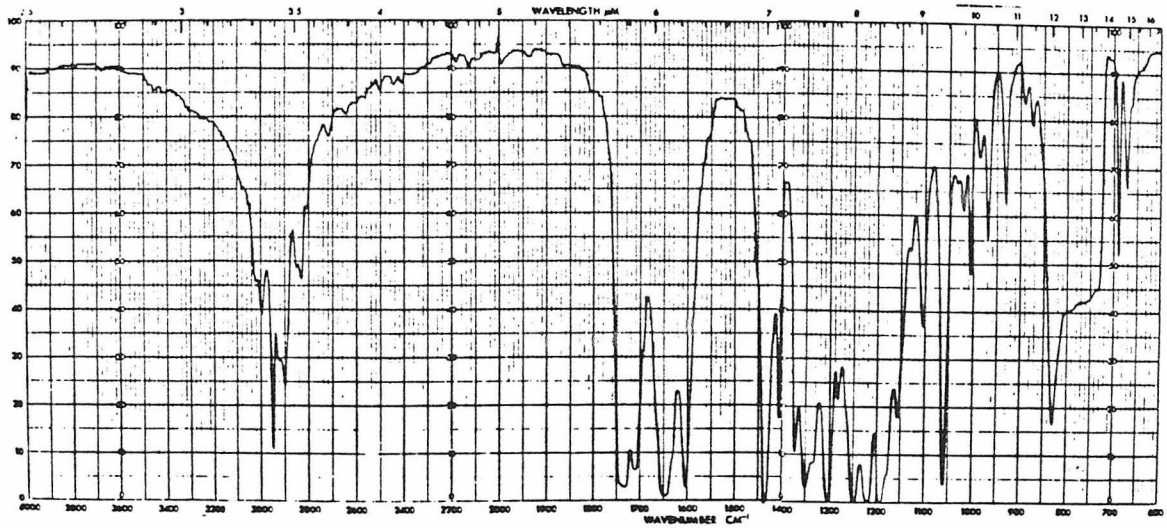
for Chapter III

Page 101



6a





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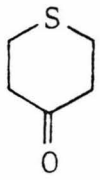
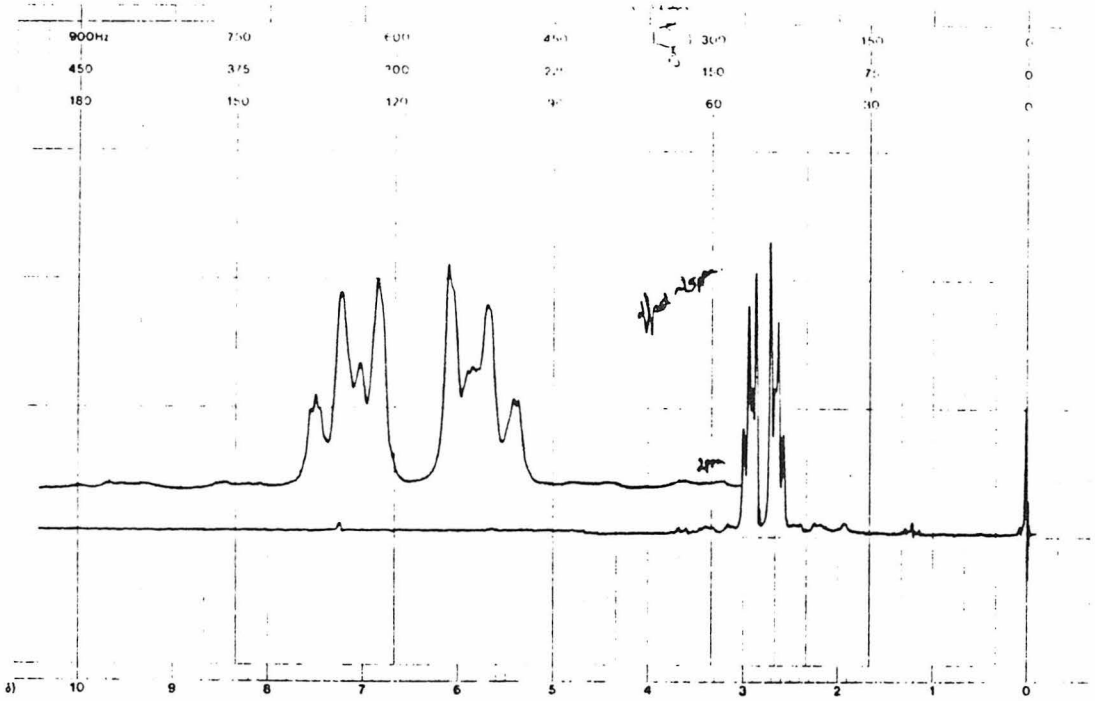
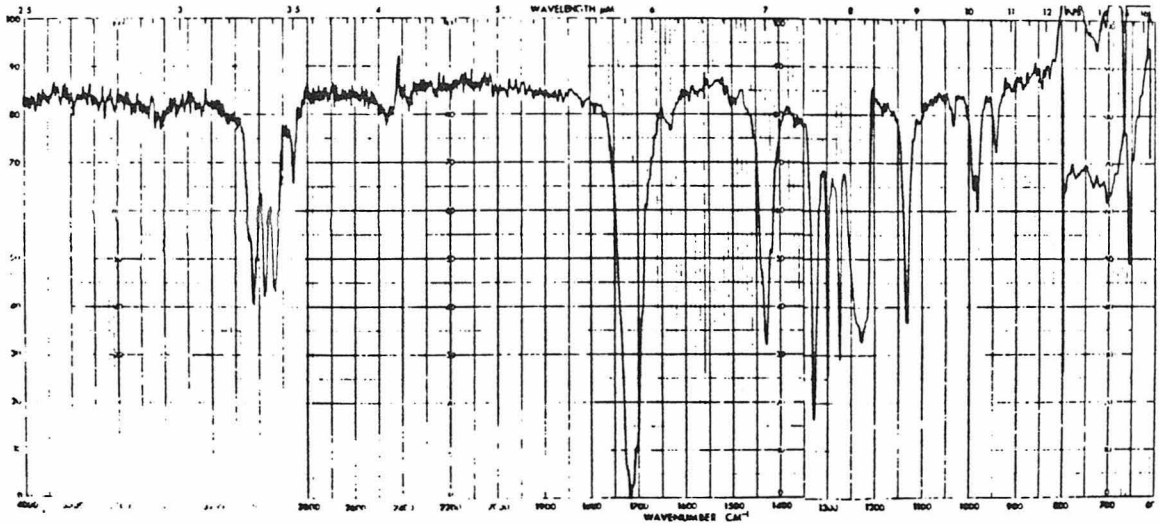


6b





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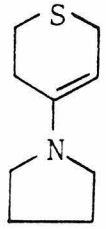

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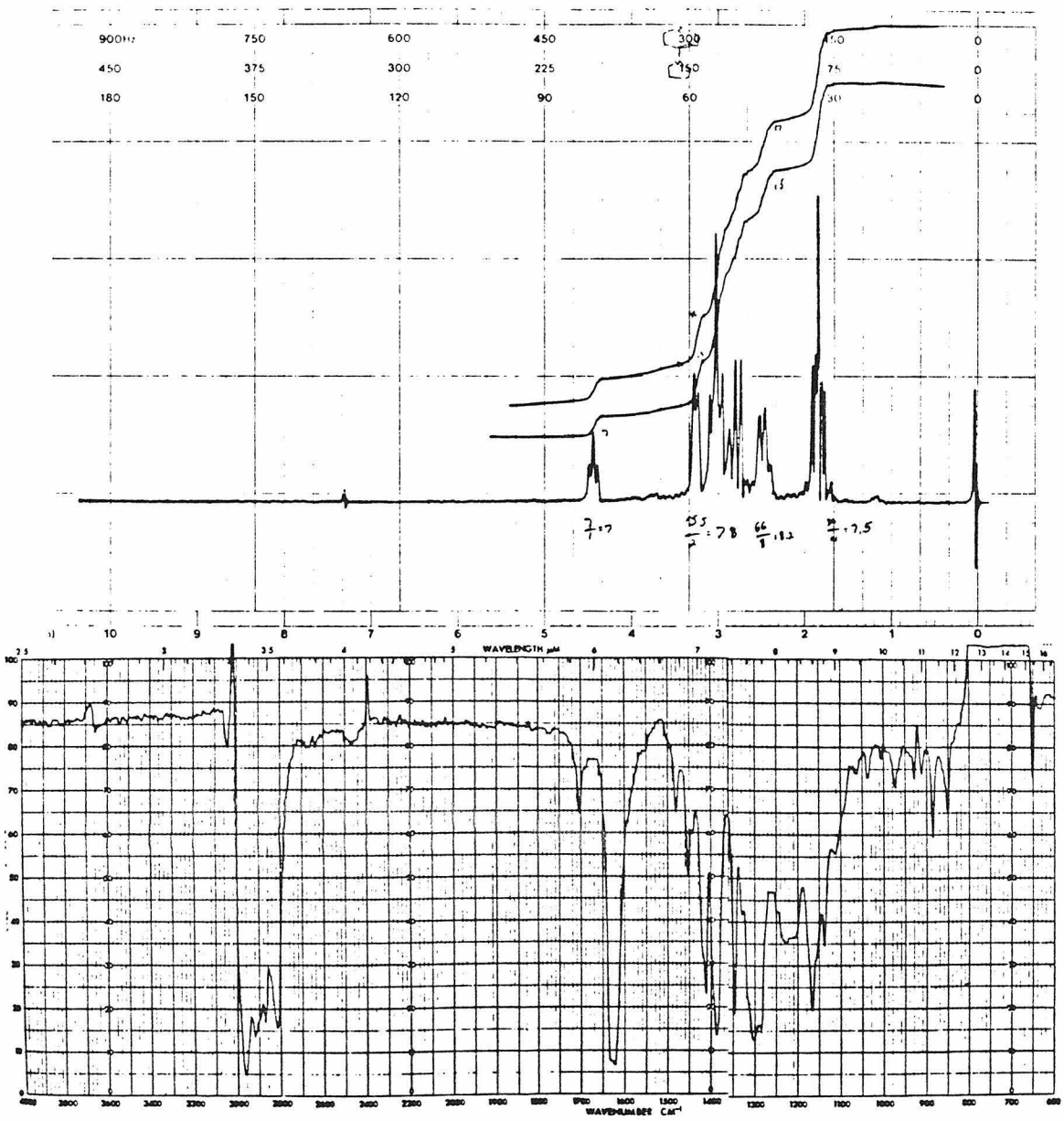
900Hz
750
600
450
300
450
375
300
225
150
180
150
120
90
60
10
9
8
7
6
5
4
3
2
1
0
WAVELENGTH μm
WAVENUMBER Cm⁻¹

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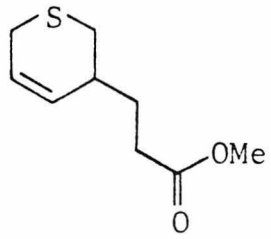

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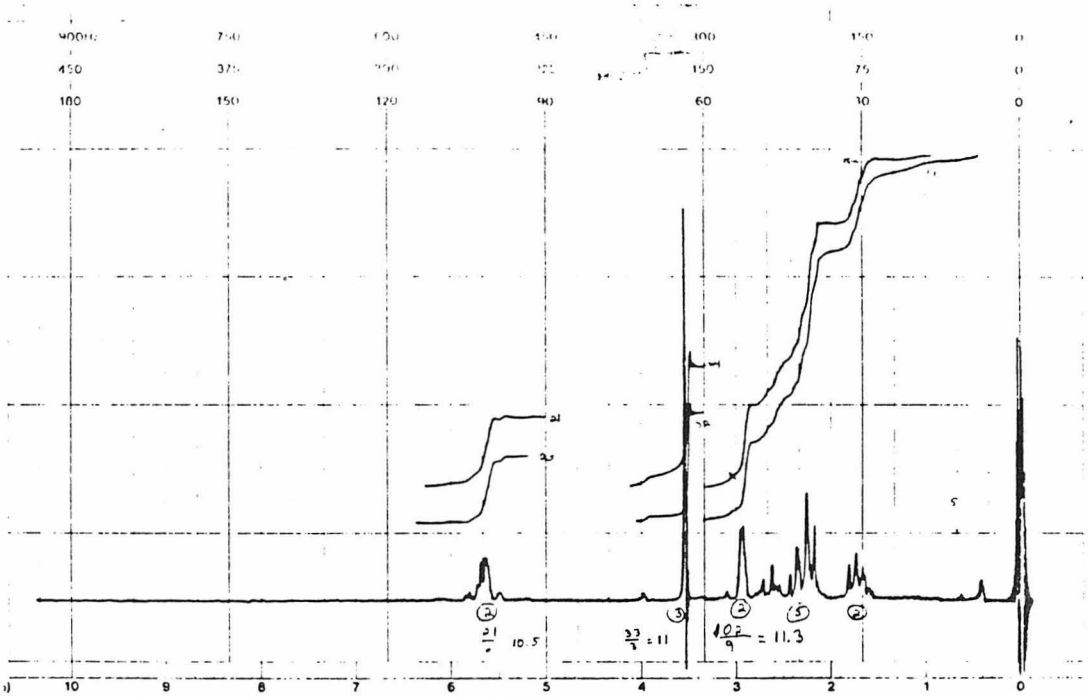

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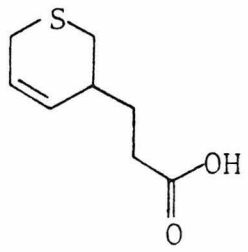
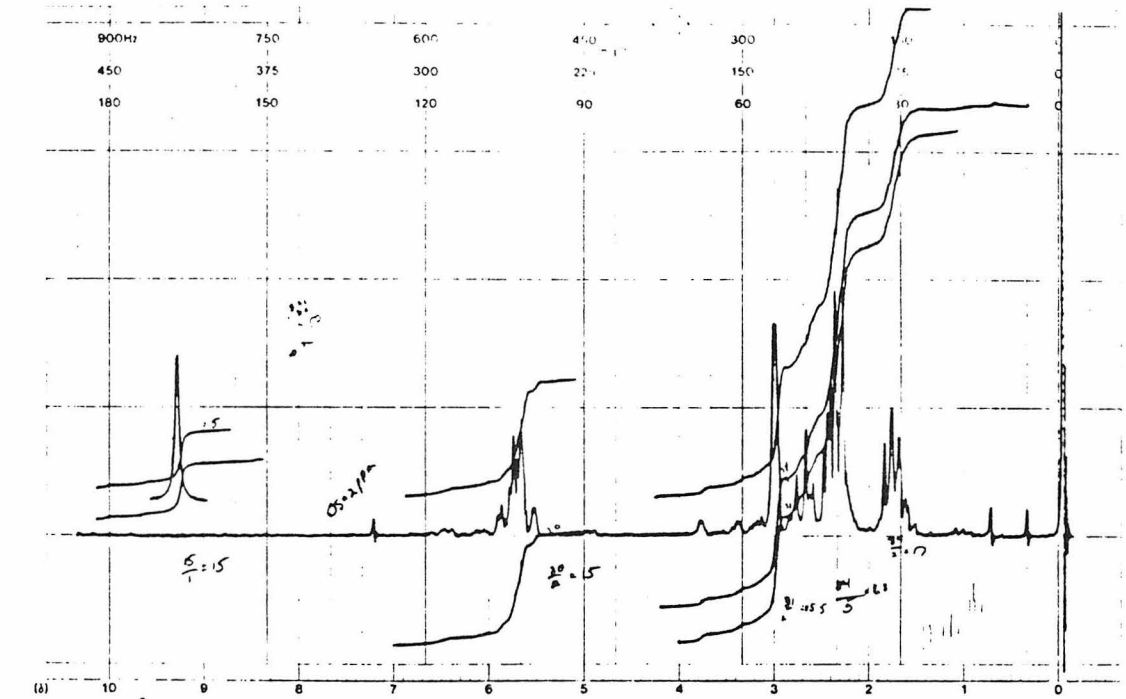
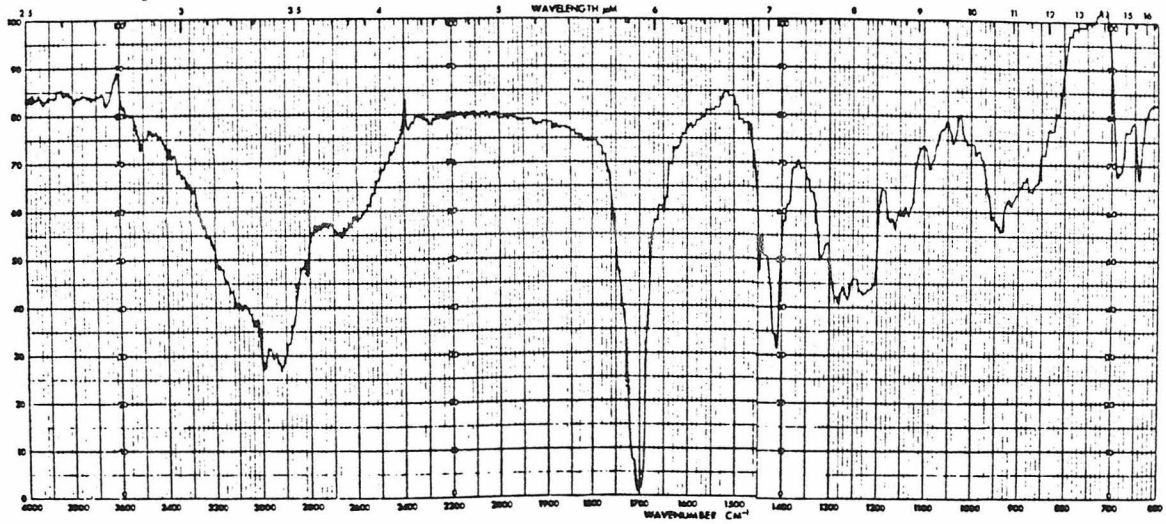

S
OH
O


900Hz
750
600
300
450
375
300
150
180
150
120
90
60
(δ)
10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
WAVENUMBER CM⁻¹

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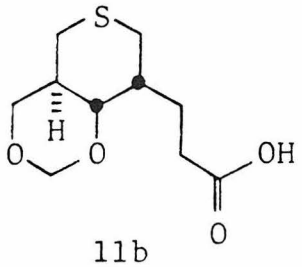
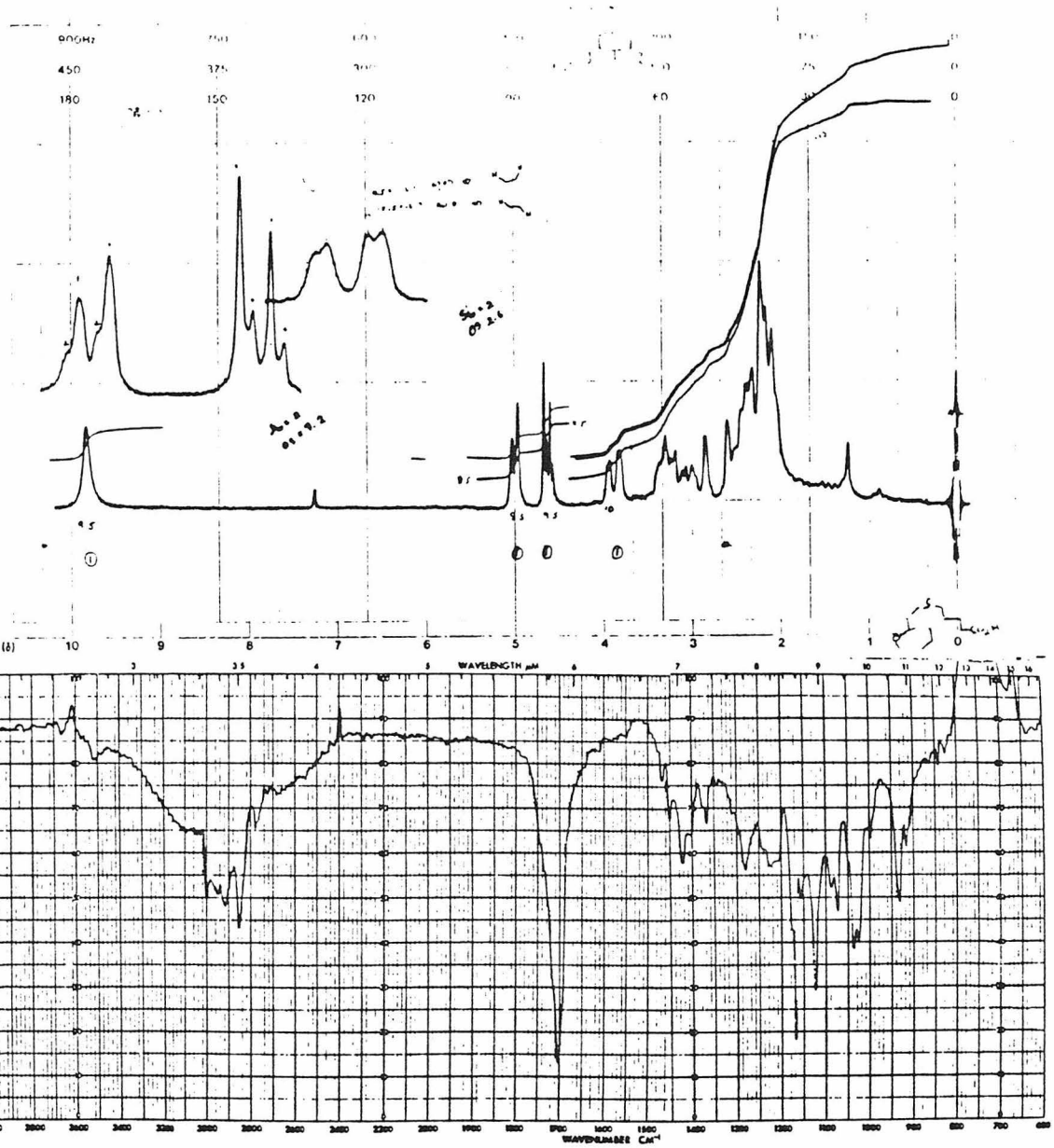
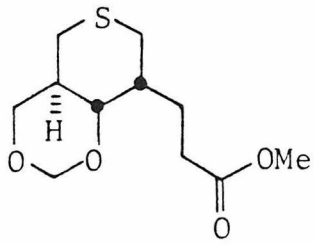

S
H
O
O
OH
O

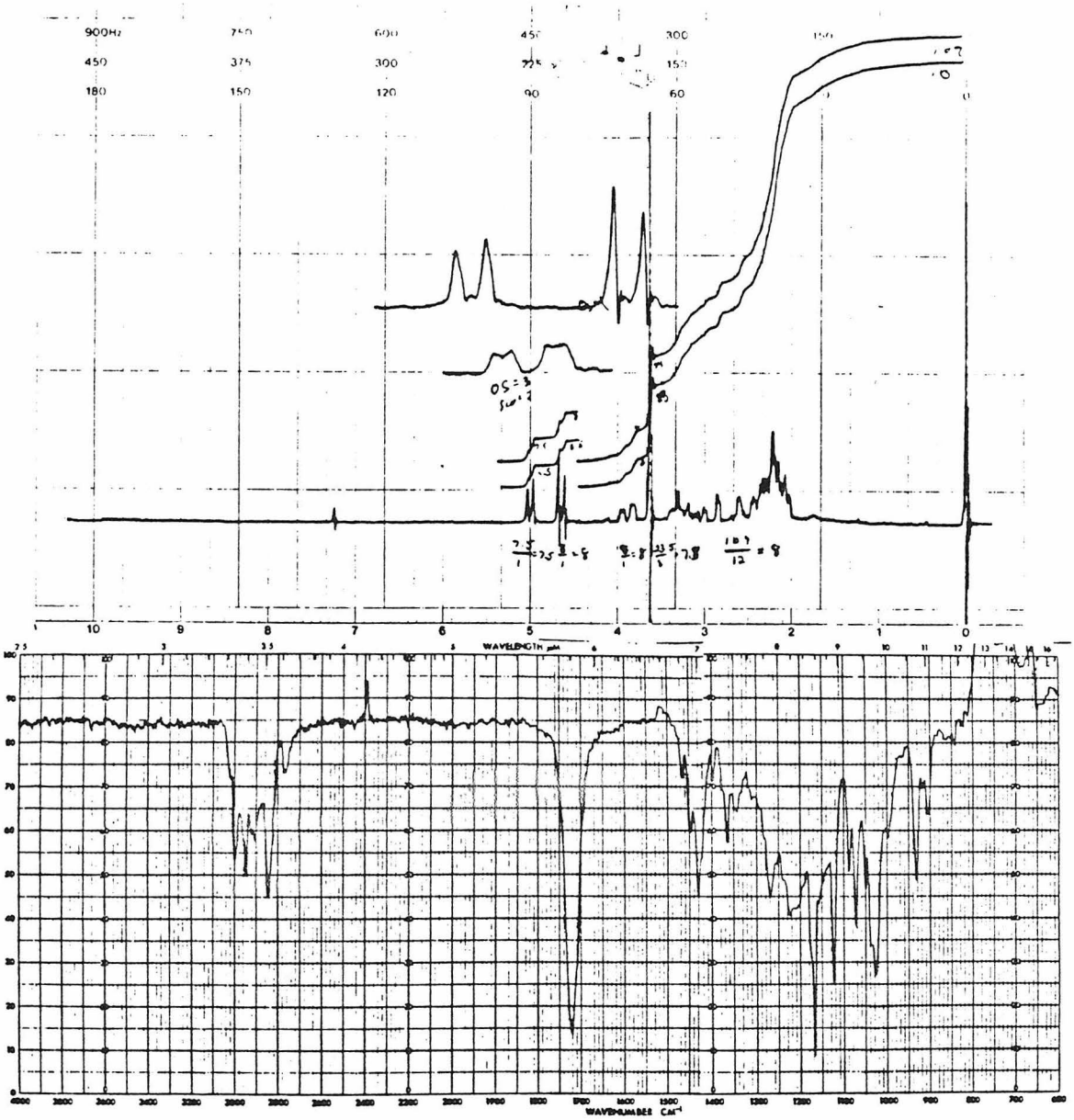
11b


900Hz
450
180
10
9
8
7
6
5
4
3
2
1
0
WAVELENGTH μM
WAVENUMBER Cm⁻¹

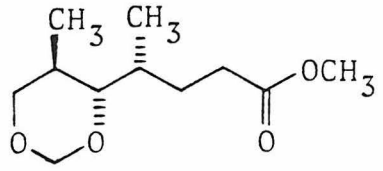
Page 107


S
H
O
O
OMe
O

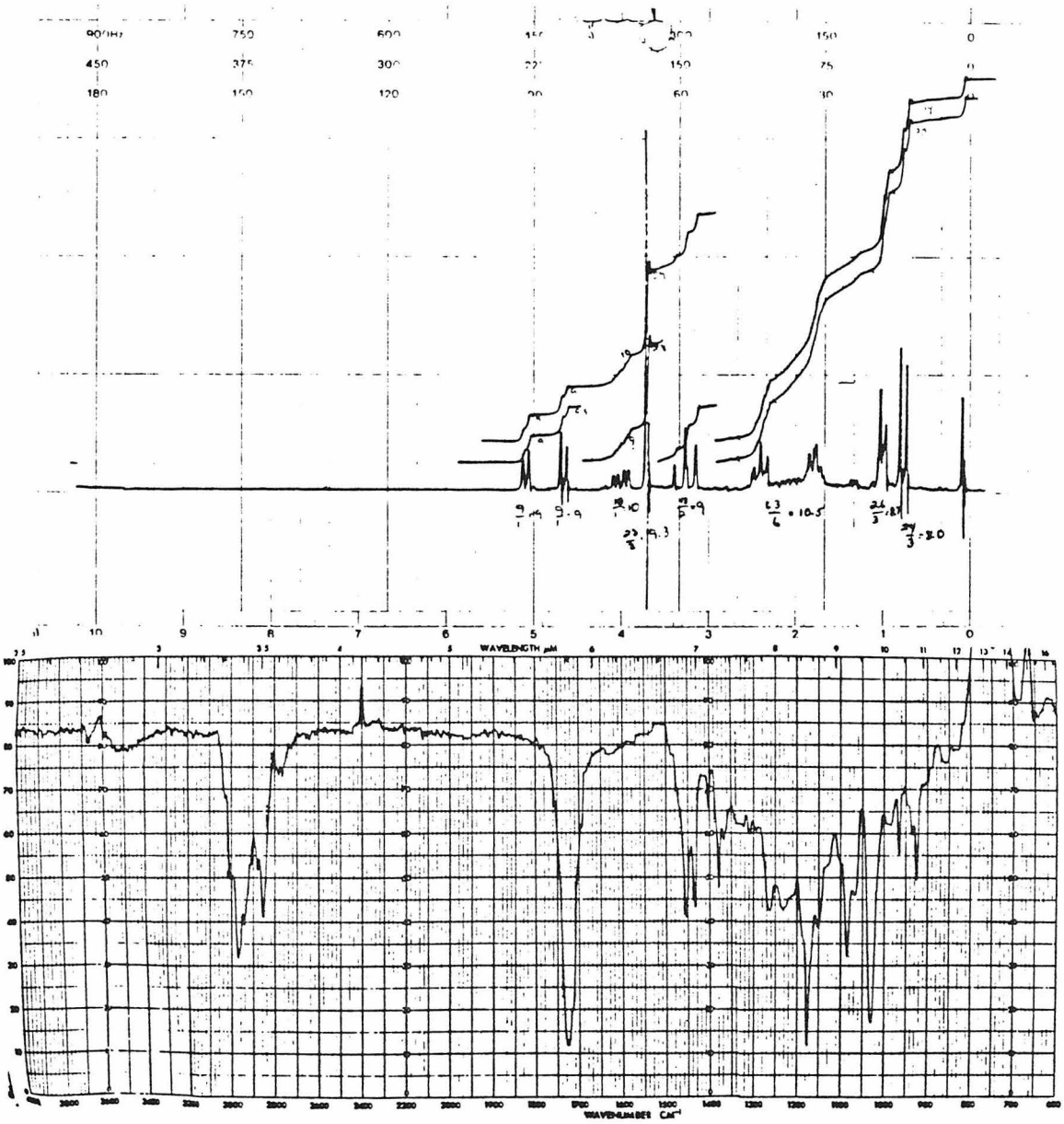
11a


900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
10
9
8
7
6
5
4
3
2
1
0
WAVELENGTH μm
WAVENUMBER Cm⁻¹

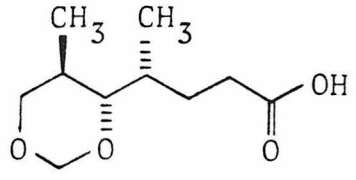
Page 108



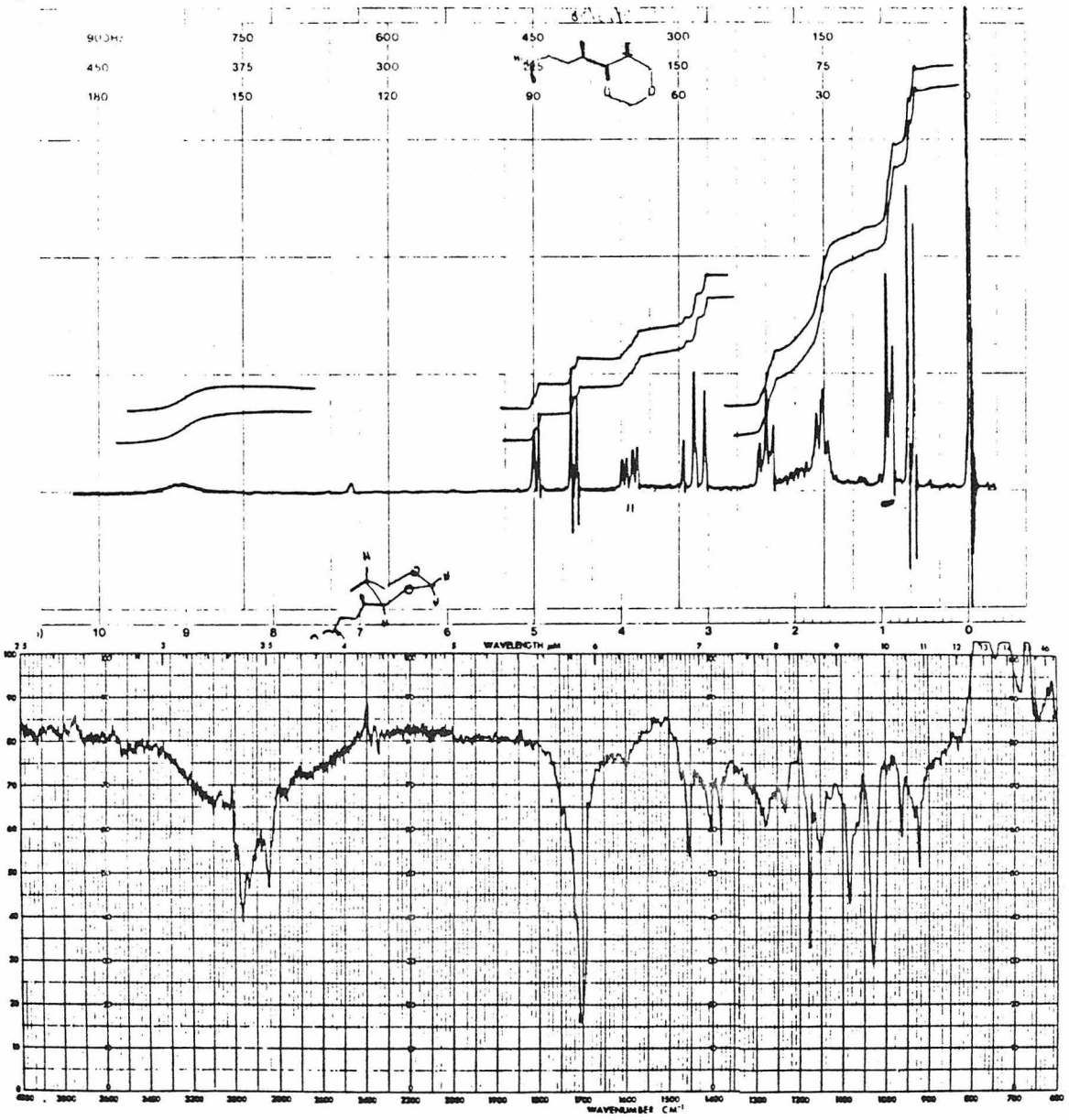
12b



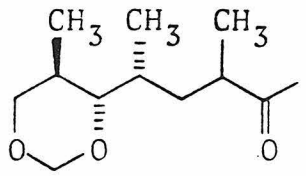
Page 109



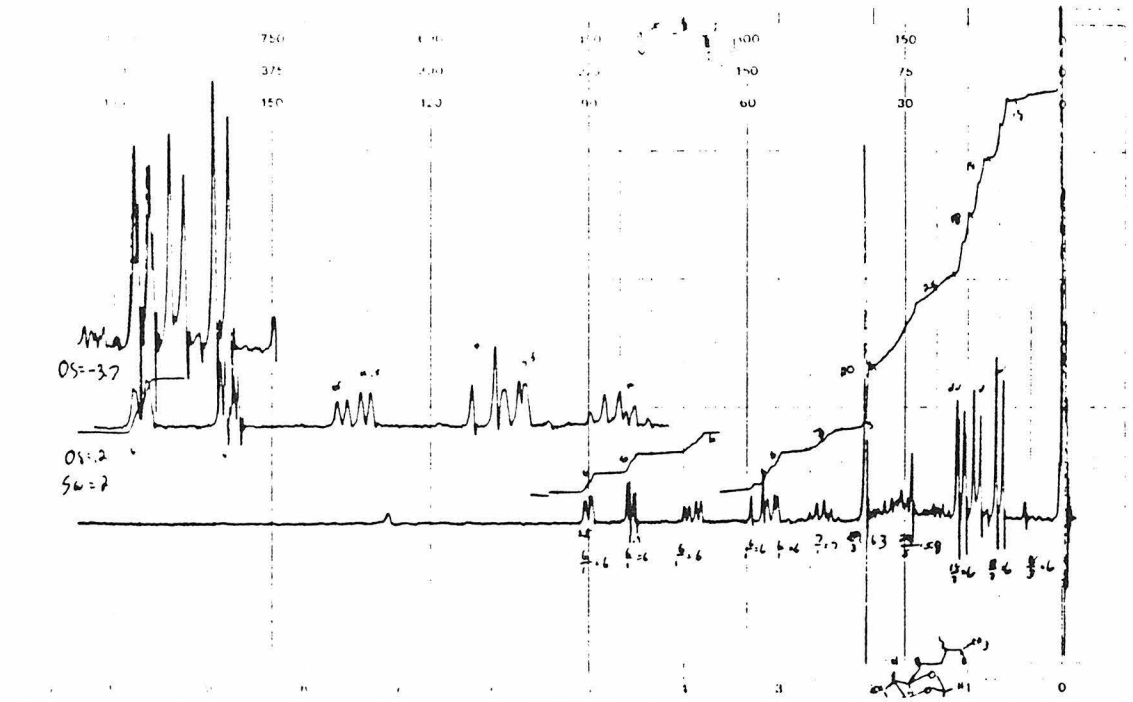
12a

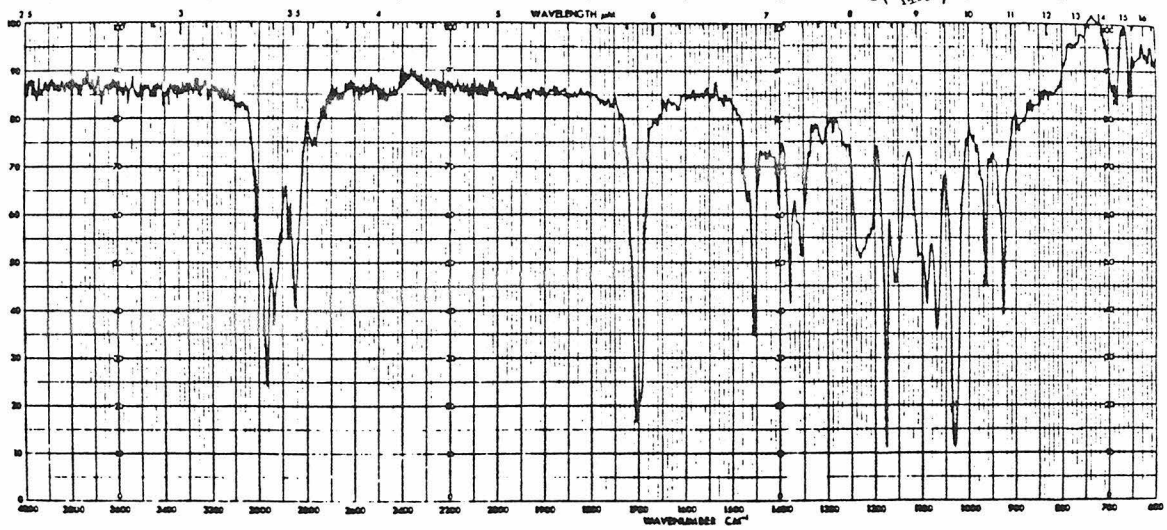


Page 109



13





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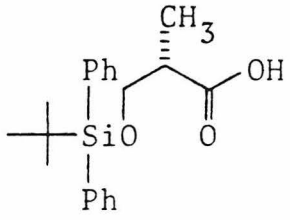
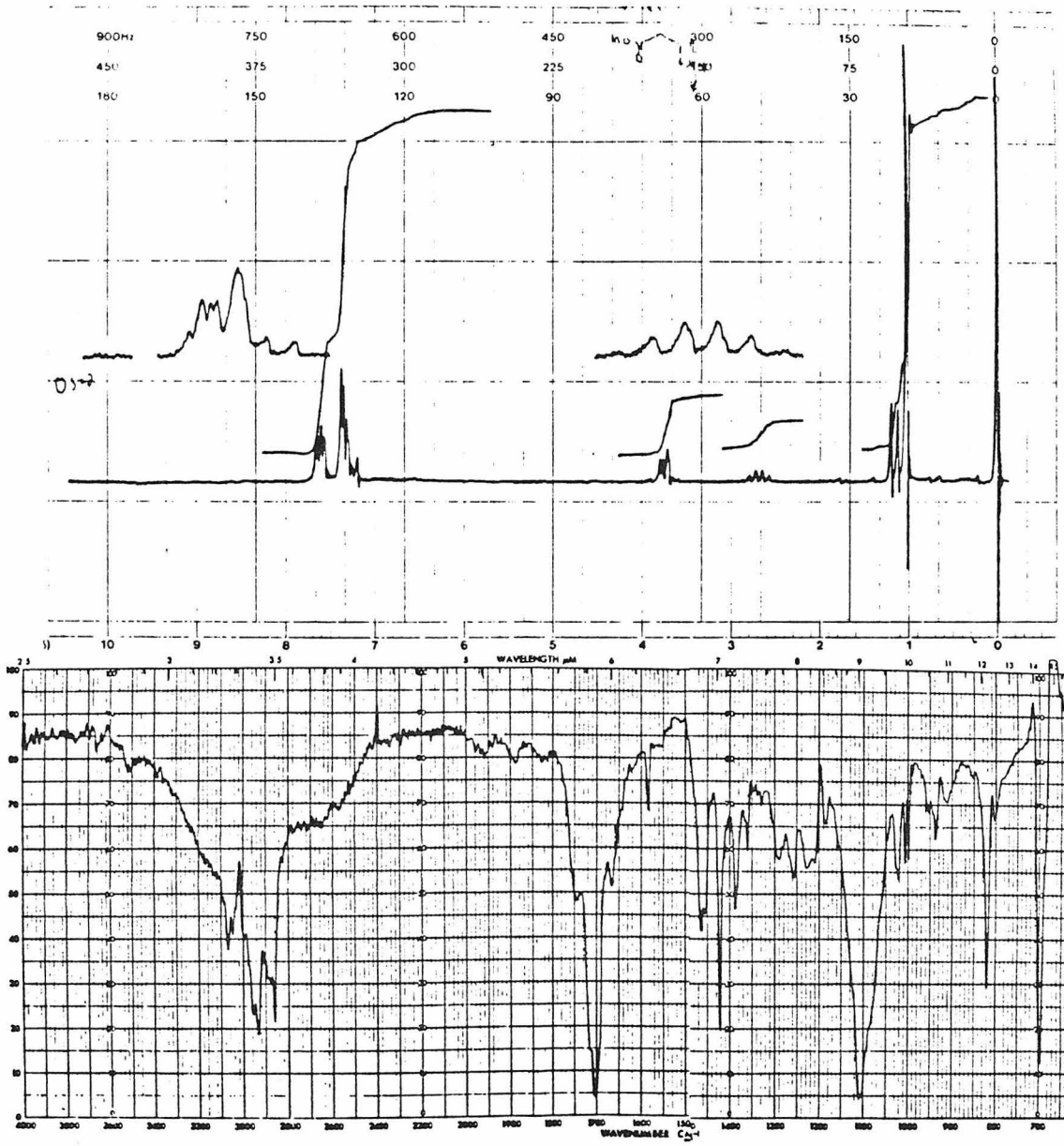
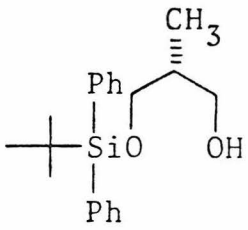

CH3
Ph
OH
SiO
O
Ph

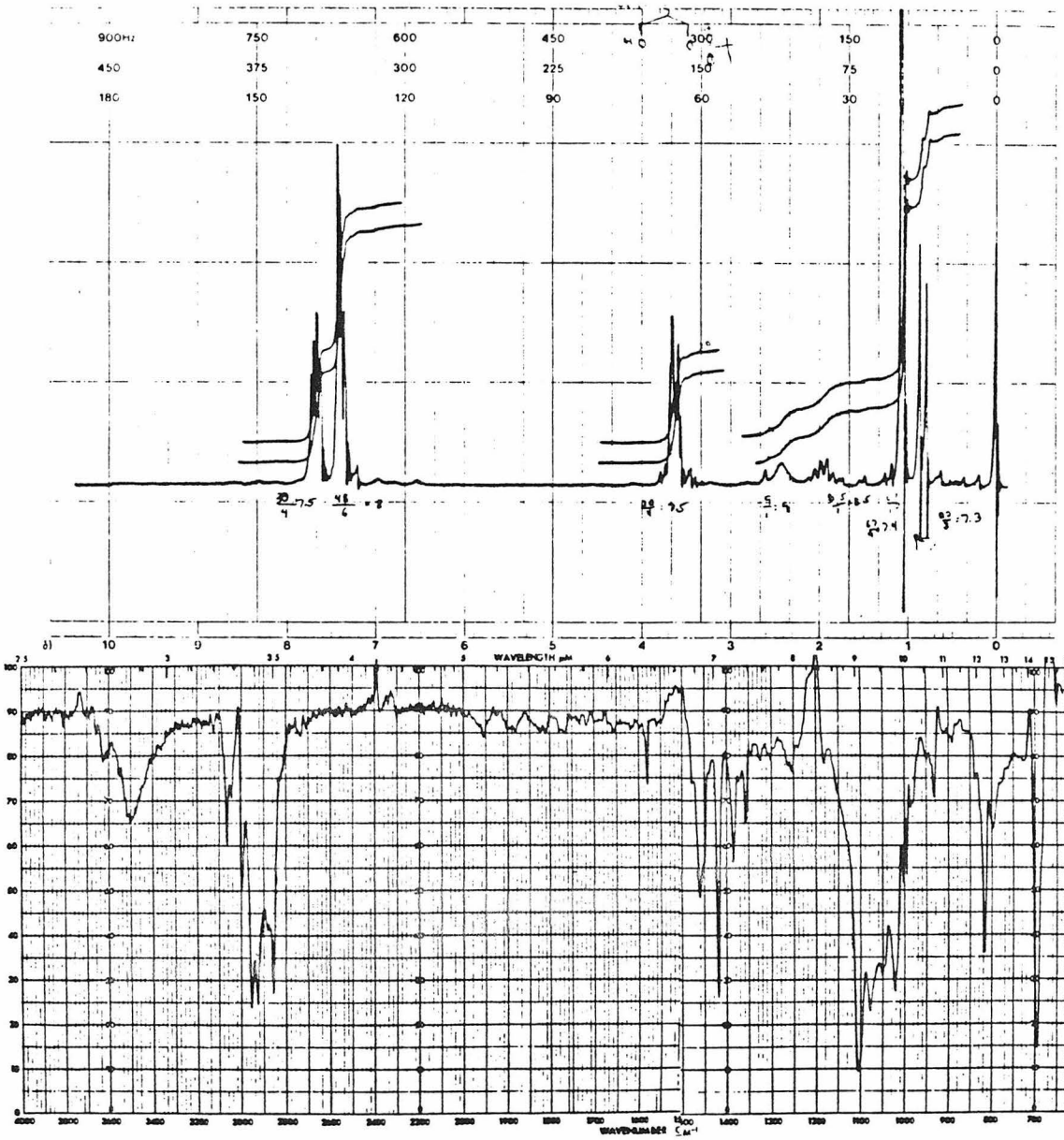
15


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

Page 112


CH3
Ph
SiO
OH
Ph

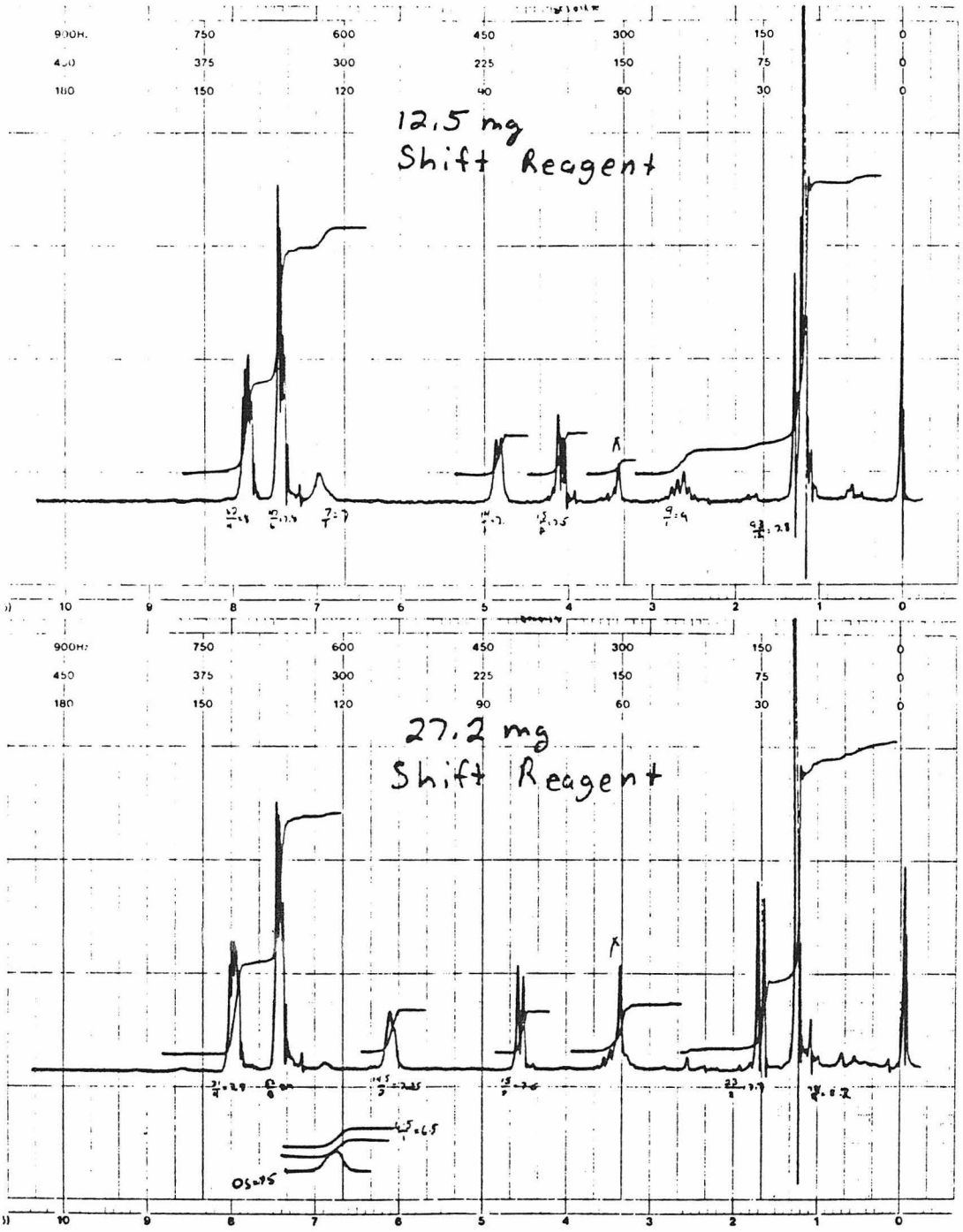
16


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

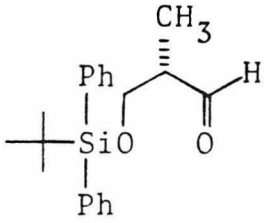
Page 113

16 +

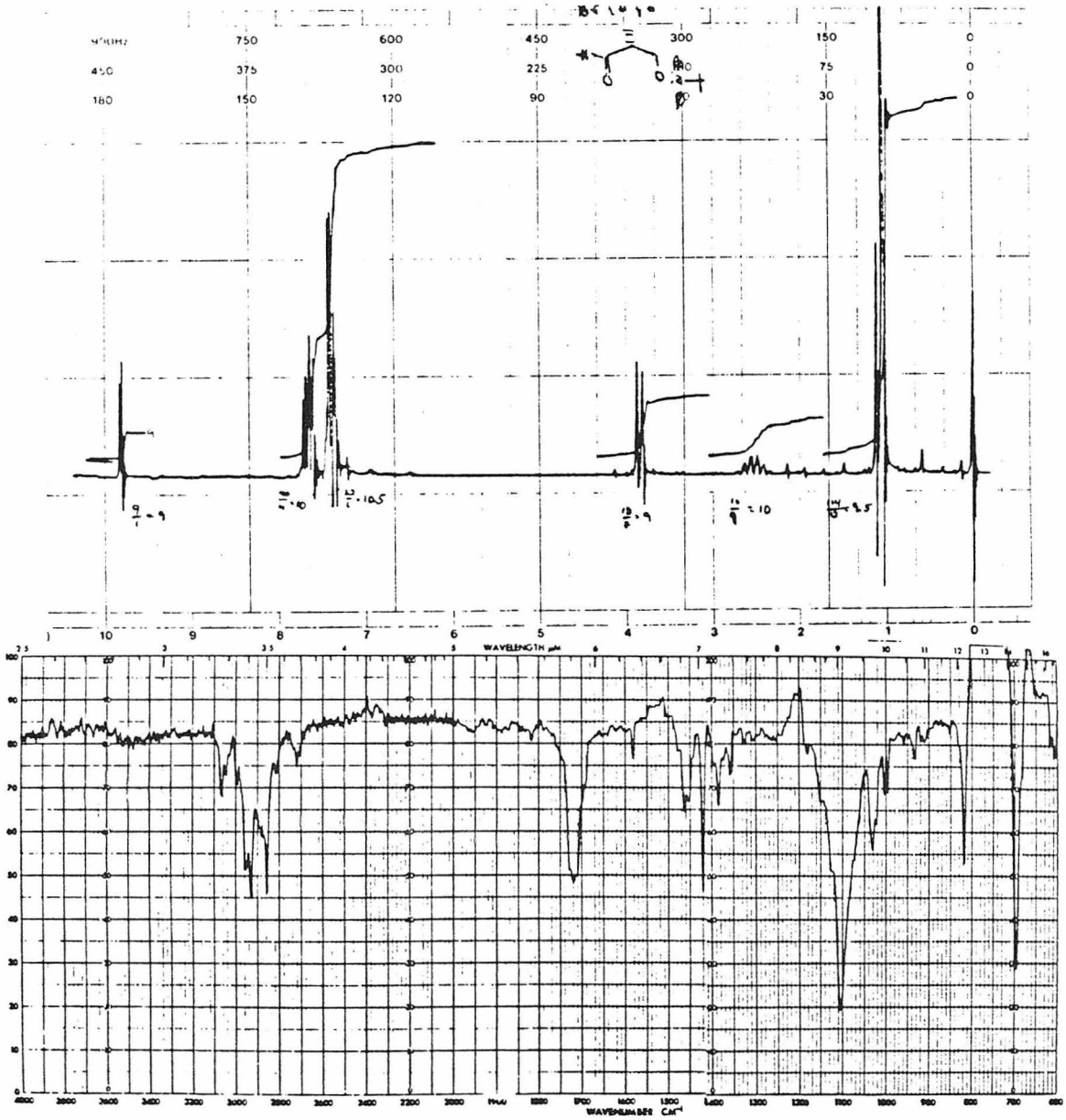
Chiral Shift Reag.



Page 113


CH3
Ph
H
SiO
O
Ph

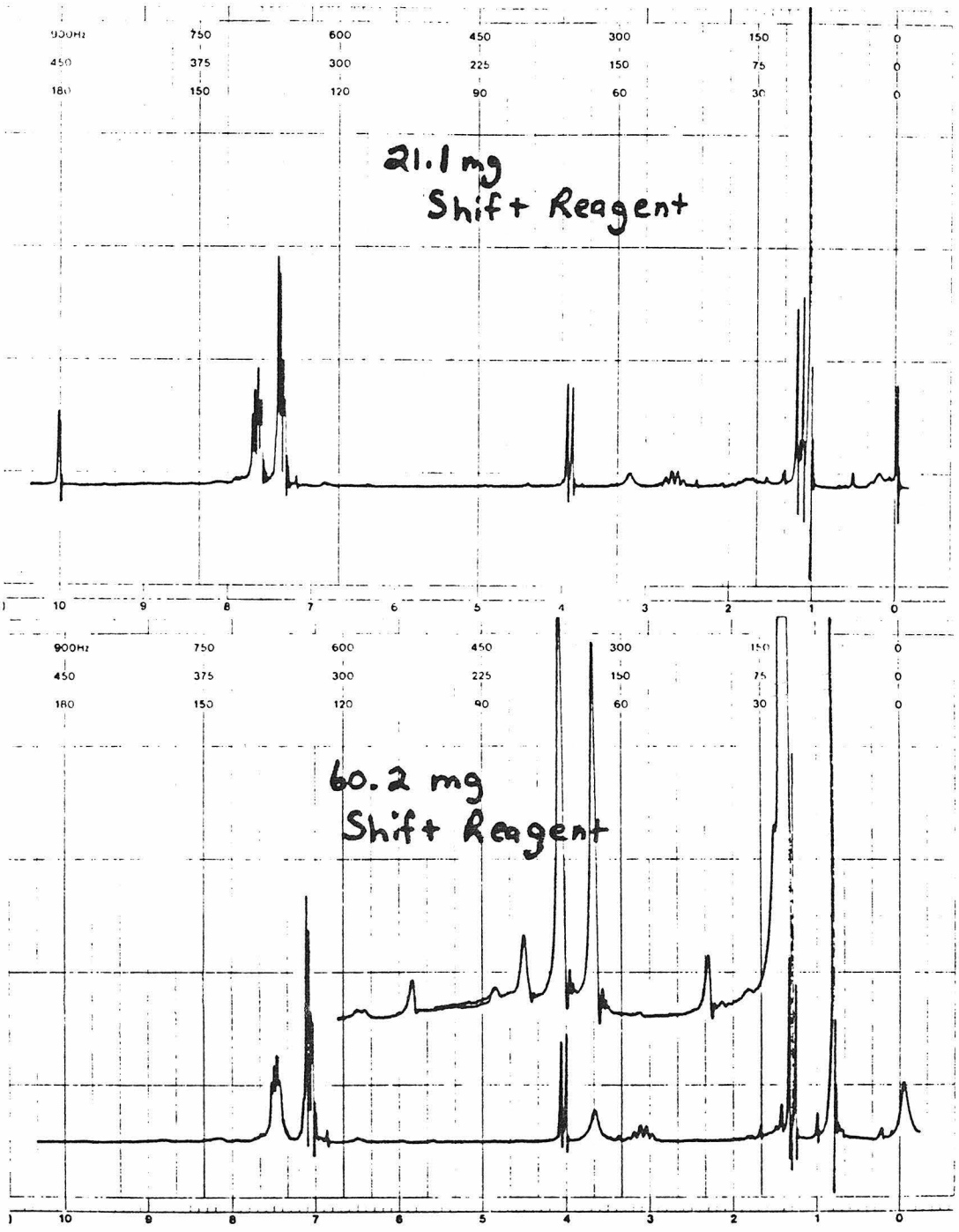
17


750
600
450
300
150
0
375
300
225
75
0
150
120
90
30
0
10
9
8
7
6
5
4
3
2
1
0
WAVELENGTH μm
WAVENUMBER cm⁻¹

Page 113

17 plus Chiral

Shift Reagent



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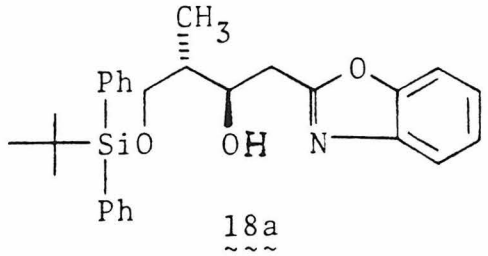
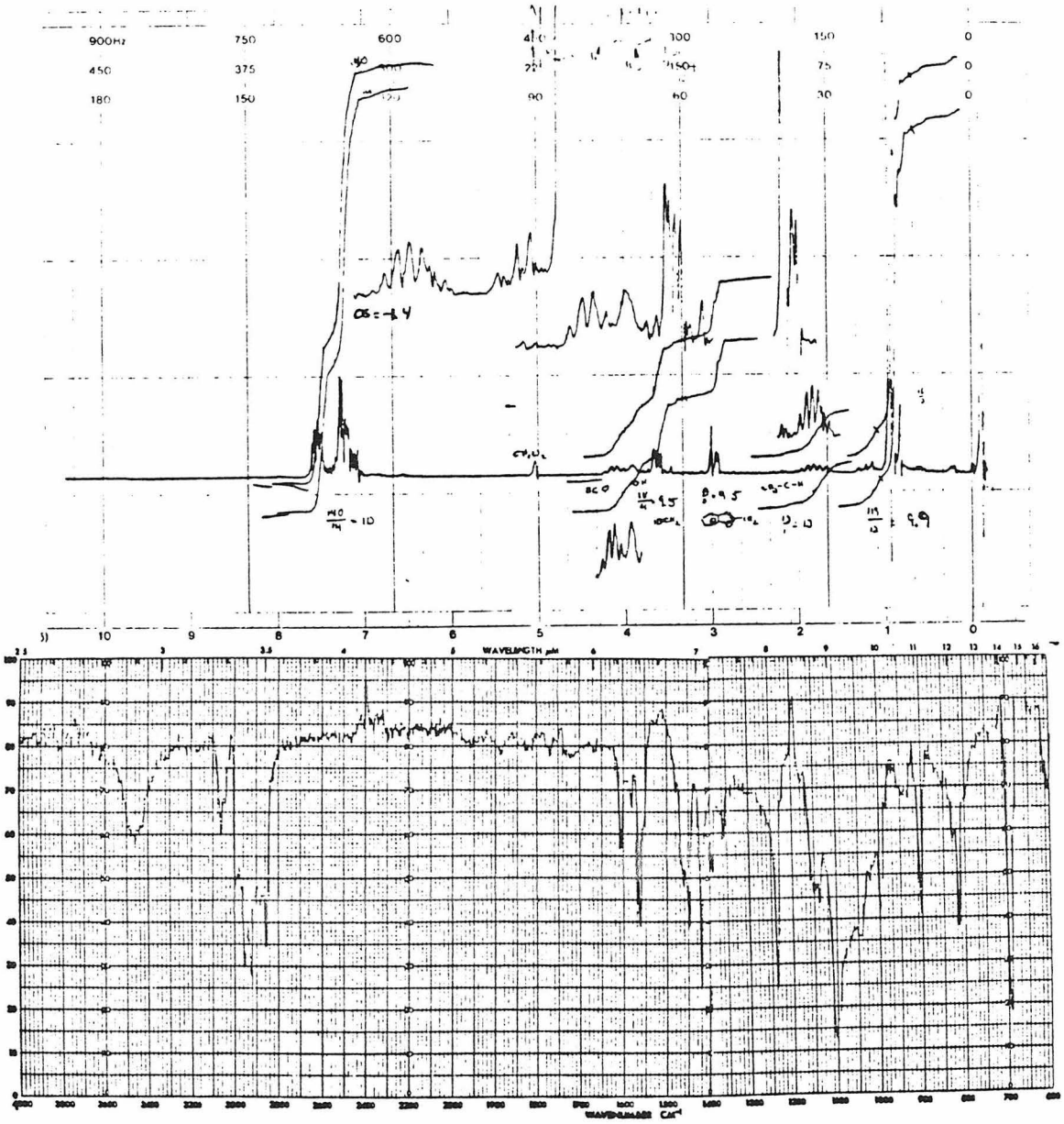
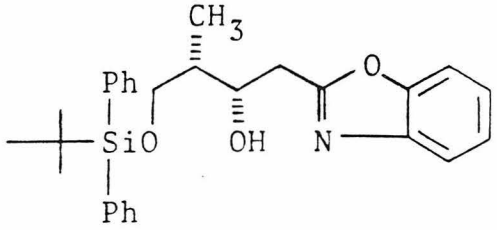

CH3
Ph
SiO
OH
N
O
Ph

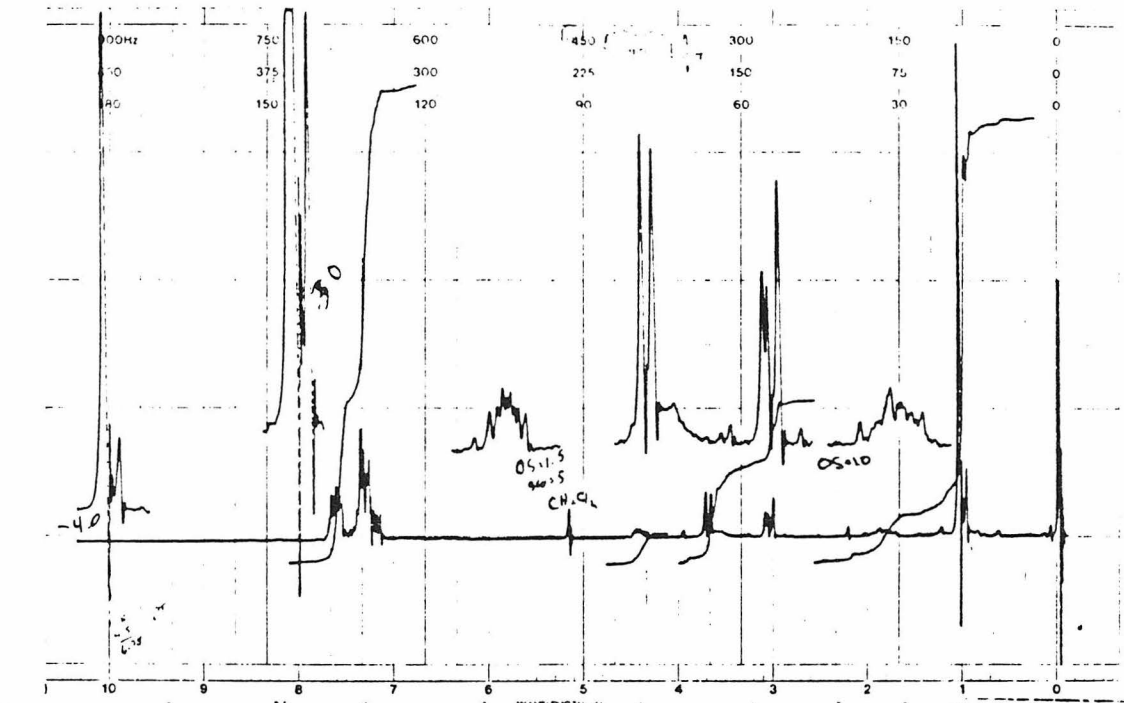
18a

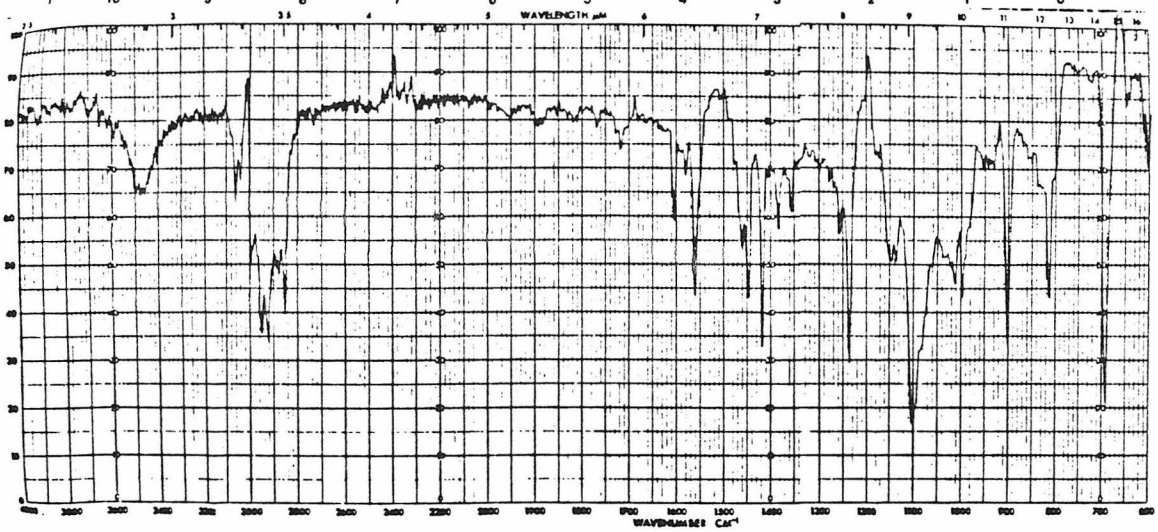

900Hz
450
180
750
375
150
600
300
150
100
50
150
75
30
0
0
0
WAVELENGTH μM
WAVENUMBER CM-1

Page 114



19a





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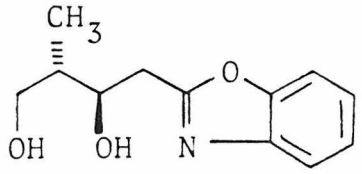
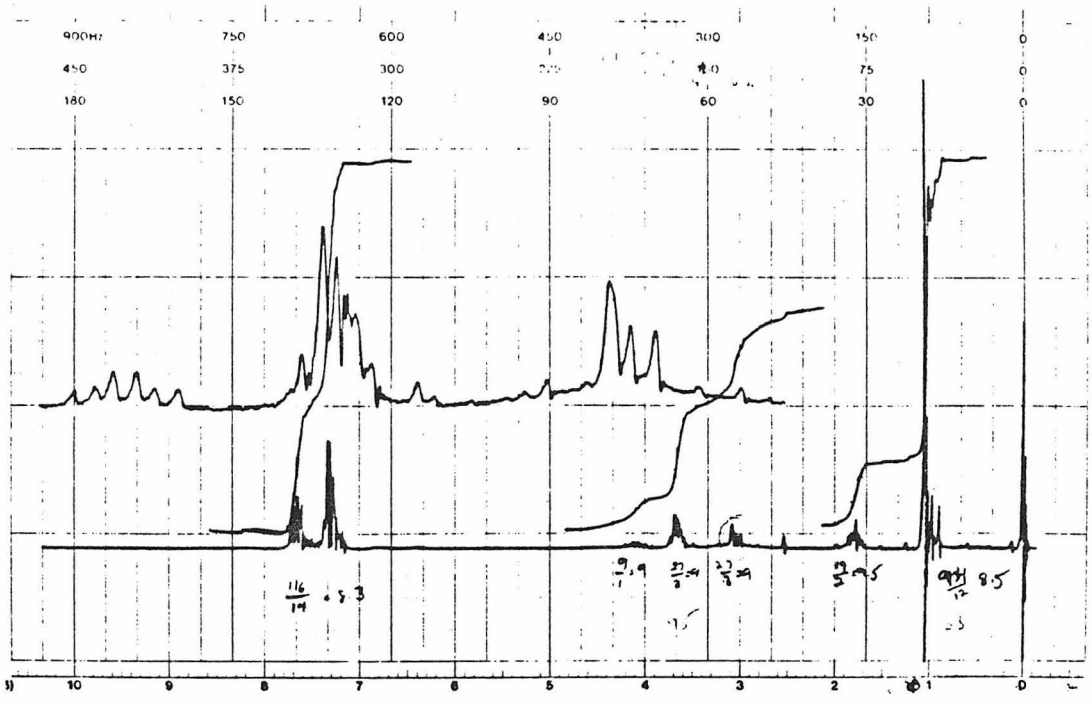

CH3
O
OH
OH
N

18b


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

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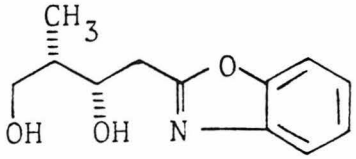
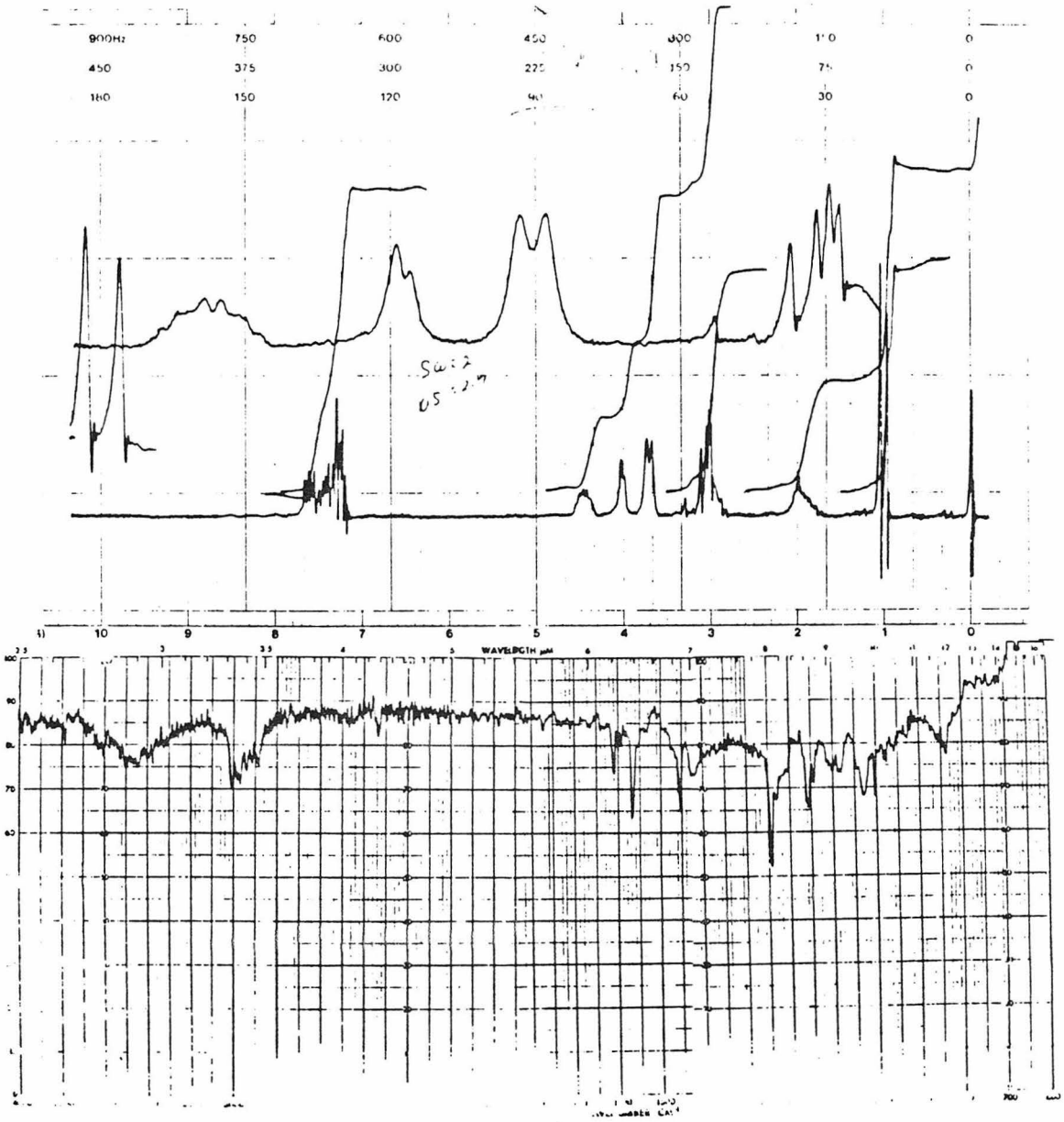
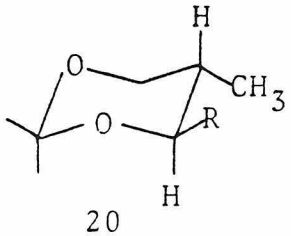

CH3
O
OH
OH
N

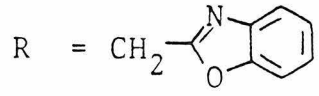
19b

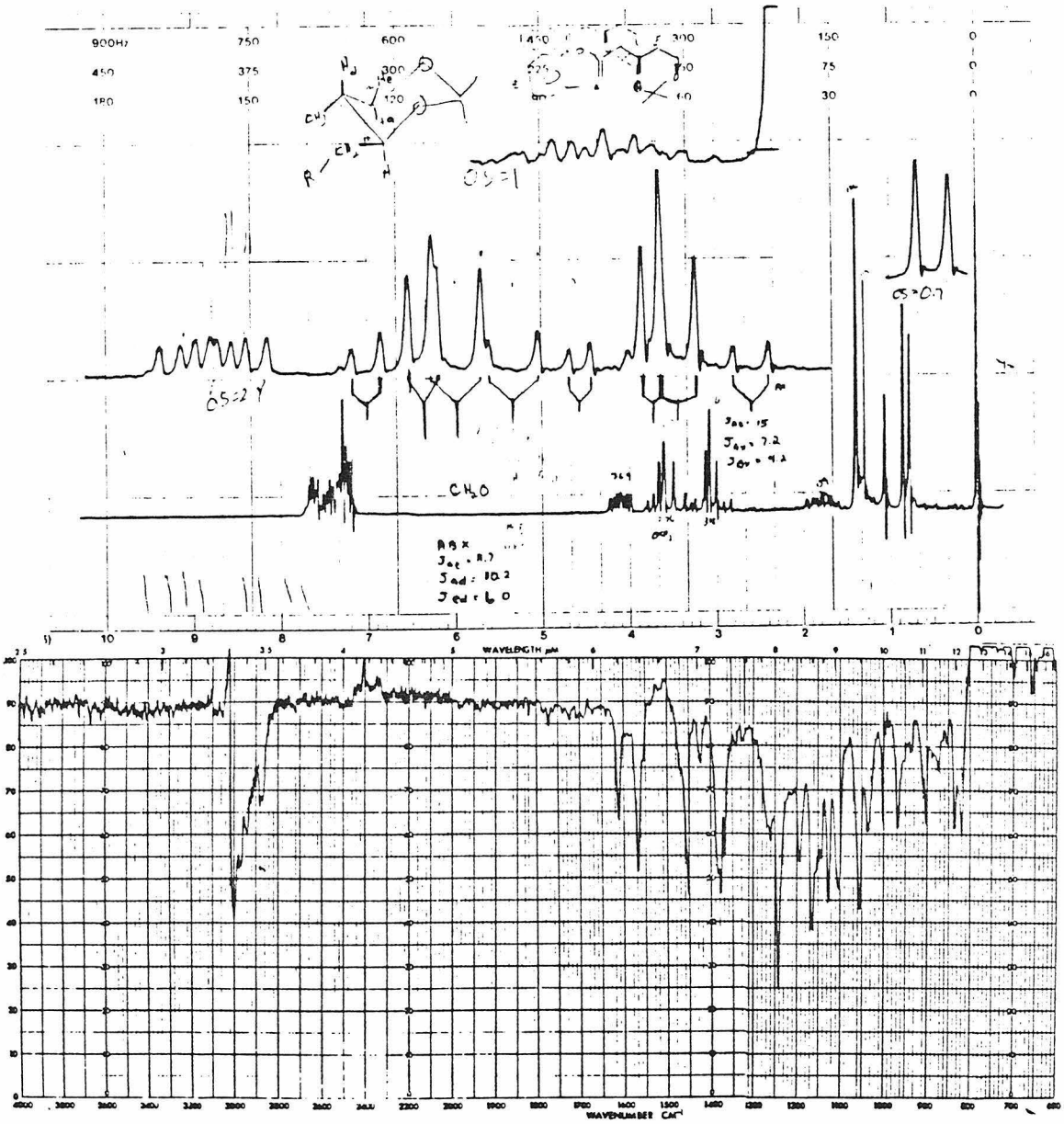

900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
10
9
8
7
6
5
4
3
2
1
0
WAVELENGTH

Page 80

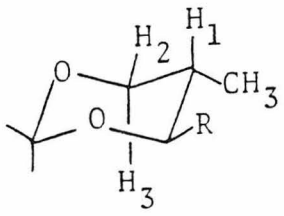


20

R = 

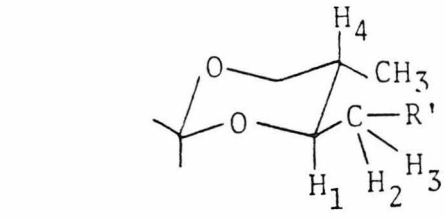

900Hz
750
600
450
375
300
180
150
120
CH2O
WAVELENGTH μM
WAVENUMBER CM⁻¹

Computer model of 20



η_1 = 167 (Hz)
η_2 = 336
η_3 = 318

$J_{1,2}$ = 6 (Hz)
$J_{1,3}$ = 10.2
$J_{2,3}$ = 11.7



η_1 = 369 (Hz)
η_2 = 265
η_3 = 281
η_4 = 159

$J_{1,2}$ = 10 (Hz)
$J_{1,3}$ = 4
$J_{1,4}$ = 12.6
$J_{2,3}$ = 15
$J_{2,4}$ = 0
$J_{3,4}$ = 0

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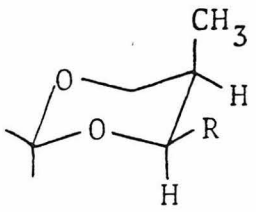
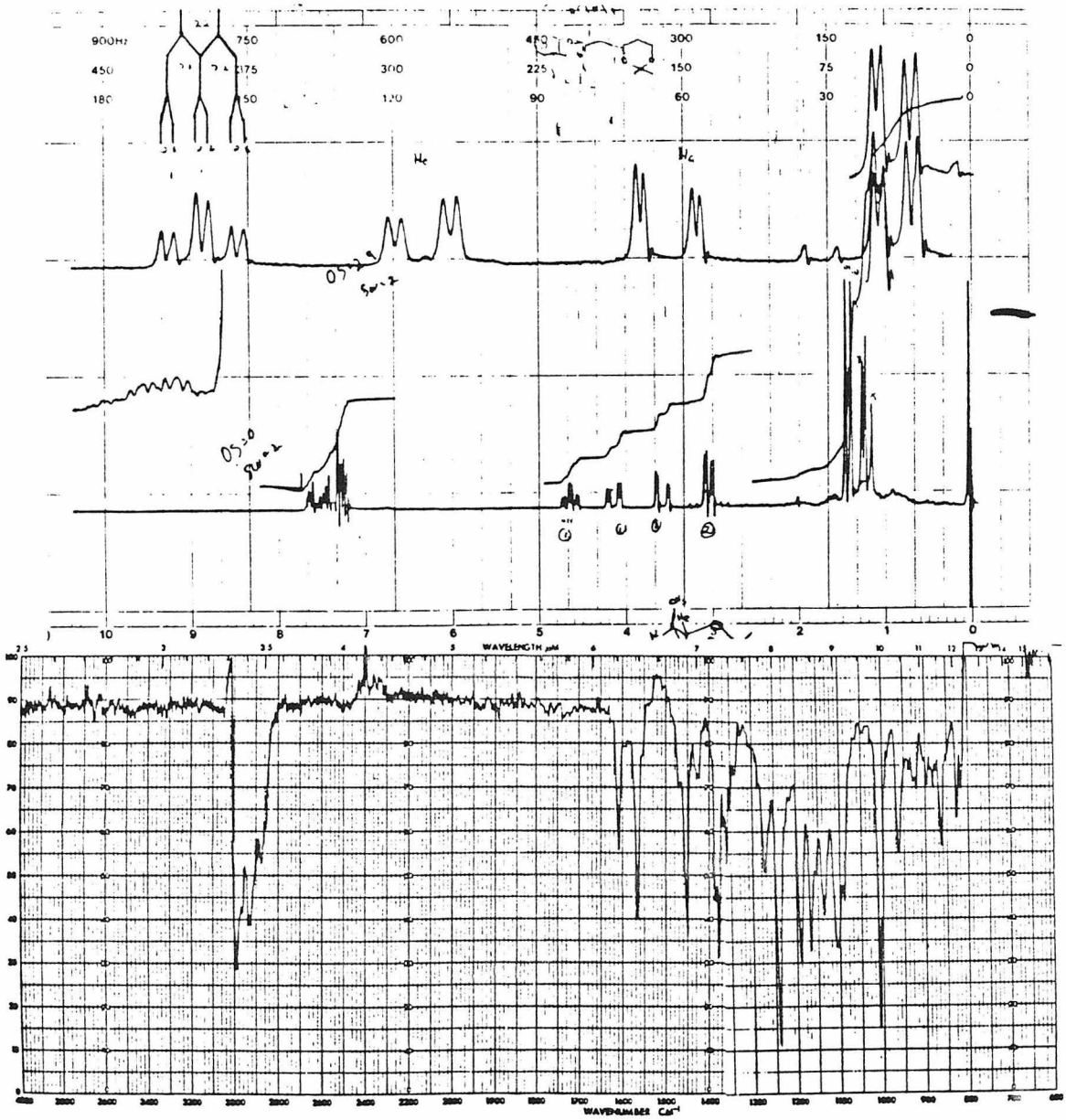
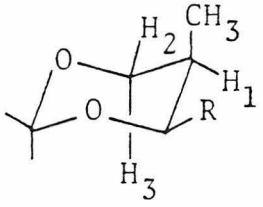

CH3
O
H
O
R
H

21

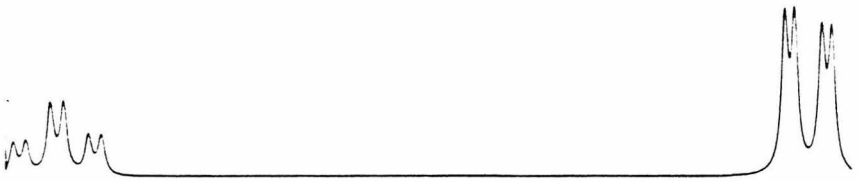

900Hz
450
180
750
375
150
600
300
120
450
225
90
300
150
60
150
75
30
0
0
0
Hc
Hc
WAVELENGTH μM
WAVENUMBER Cm-1

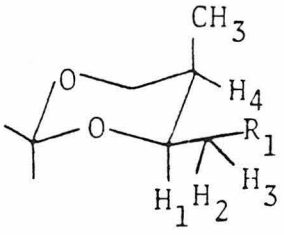
Computer Model of 21



n_1 = 140 (Hz)
n_2 = 372
n_3 = 321

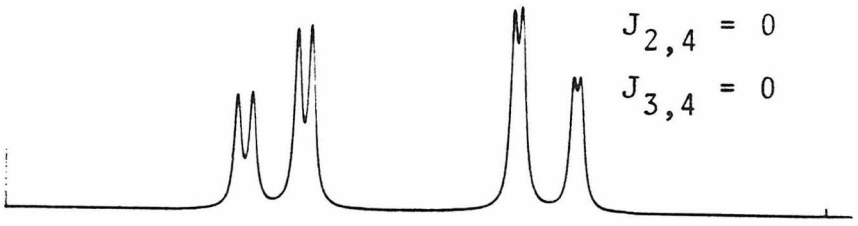
$J_{1,2}$ = 2.7 (Hz)
$J_{1,3}$ = 1.5
$J_{2,3}$ = 11.4





n_1 = 414 (Hz)
n_2 = 269
n_3 = 271
n_4 = 140

$J_{1,2}$ = 7.2 (Hz)
$J_{1,3}$ = 7.2
$J_{1,4}$ = 2.6
$J_{2,3}$ = 15
$J_{2,4}$ = 0
$J_{3,4}$ = 0



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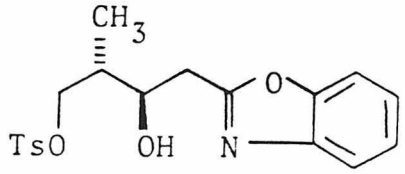
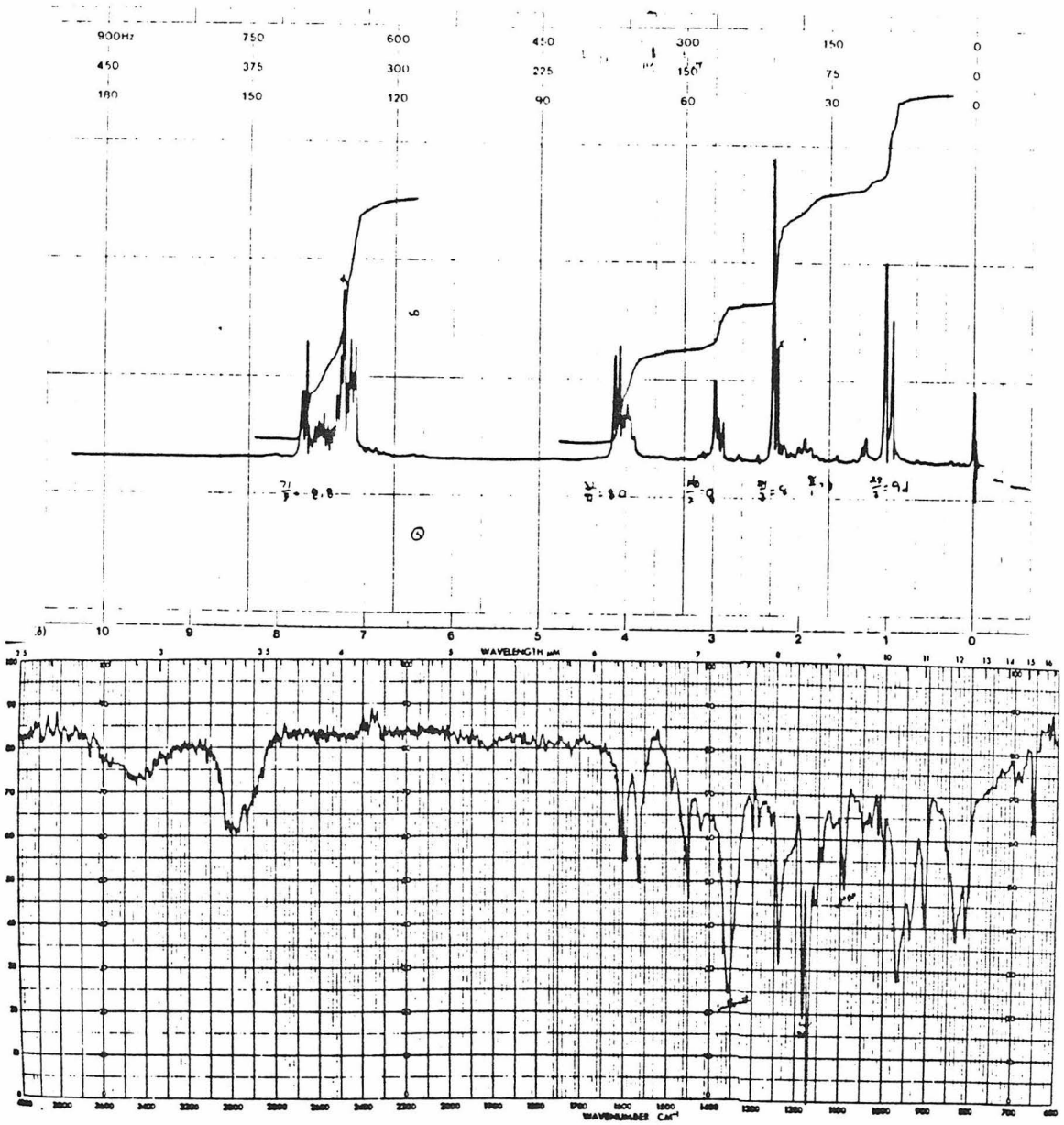

CH3
O
TsO
OH
N

23a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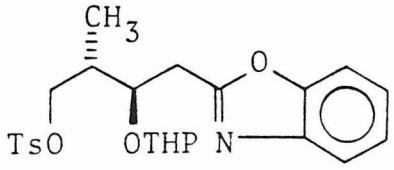
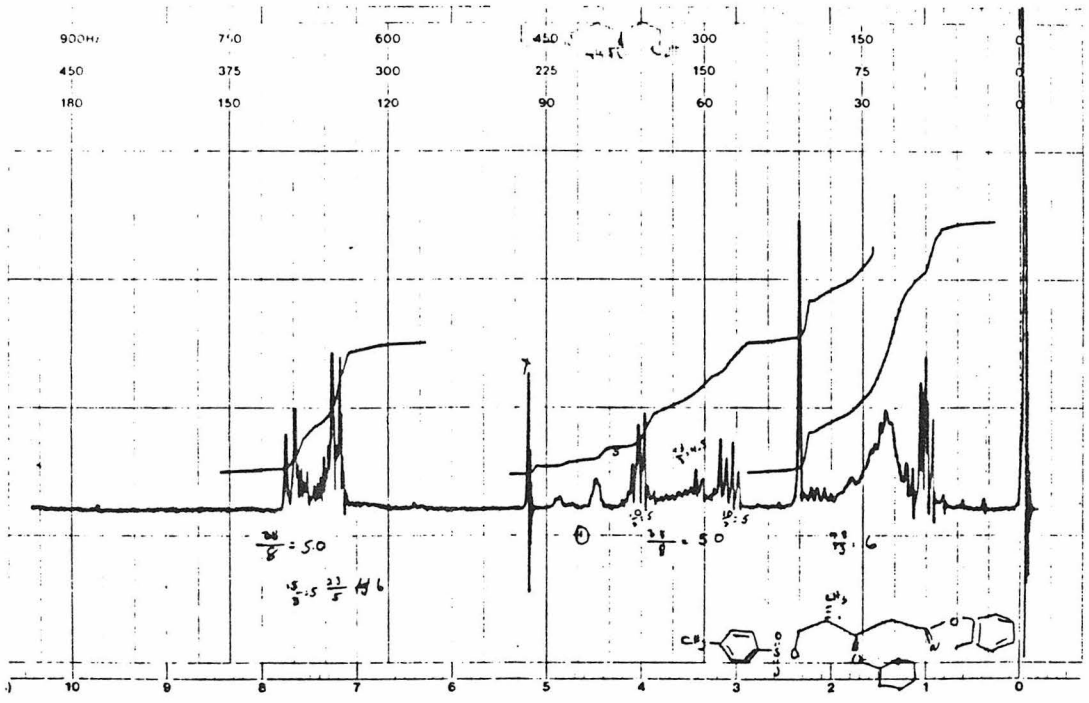
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
δ)
10
9
8
7
6
5
4
3
2
1
0
WAVELENGTH μm
WAVENUMBER Cm⁻¹

Page 117


CH3
O
TsO
OTHP
N

23b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90
300
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150
75
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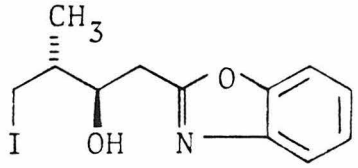
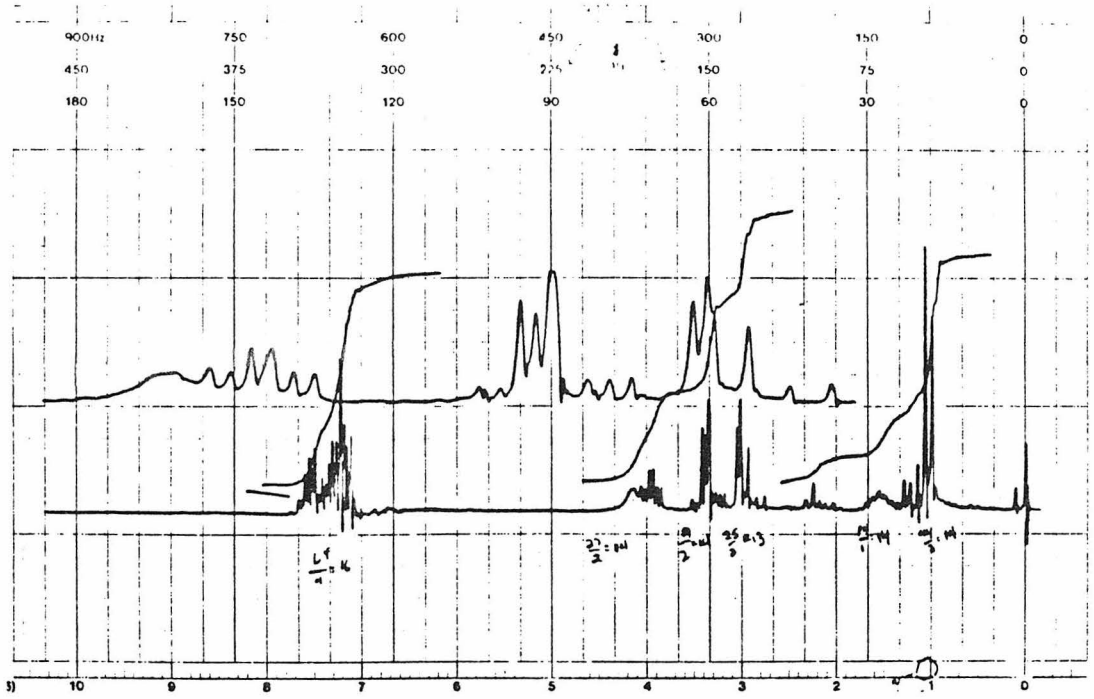
10
9
8
7
6
5
4
3
2
1
0

Page 118


CH3
O
I
OH
N

23d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150
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225
150
75
0
180
150
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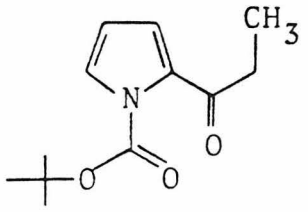
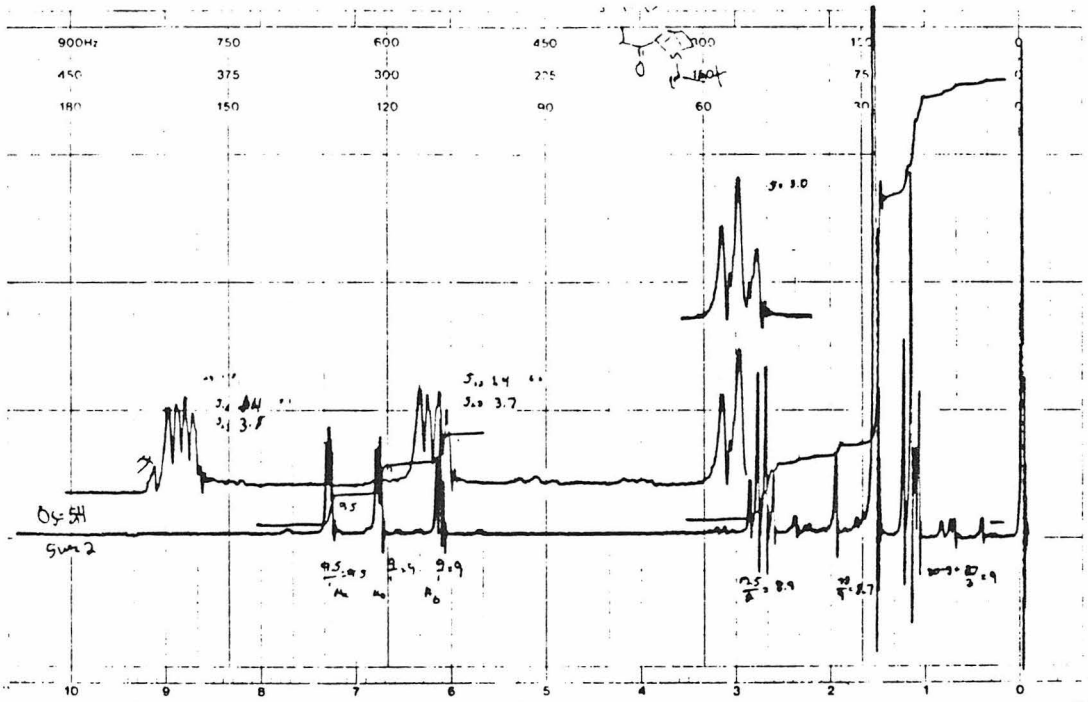
90
60
30
0
10
9
8
7
6
5
4
3
2
1
0

Page 119


CH3
N
O
O
O

38


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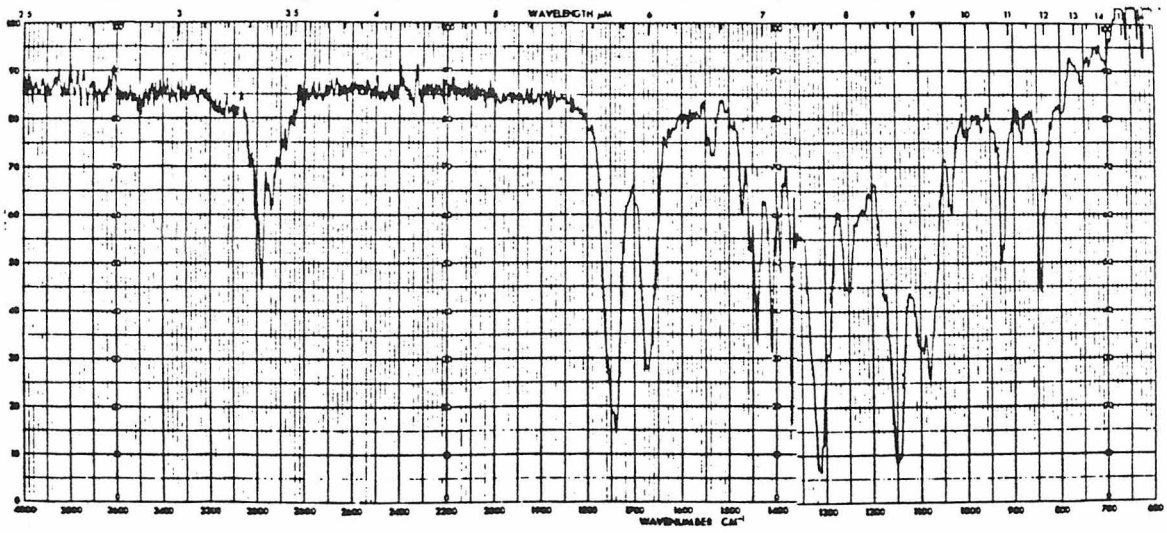
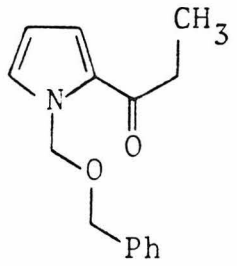
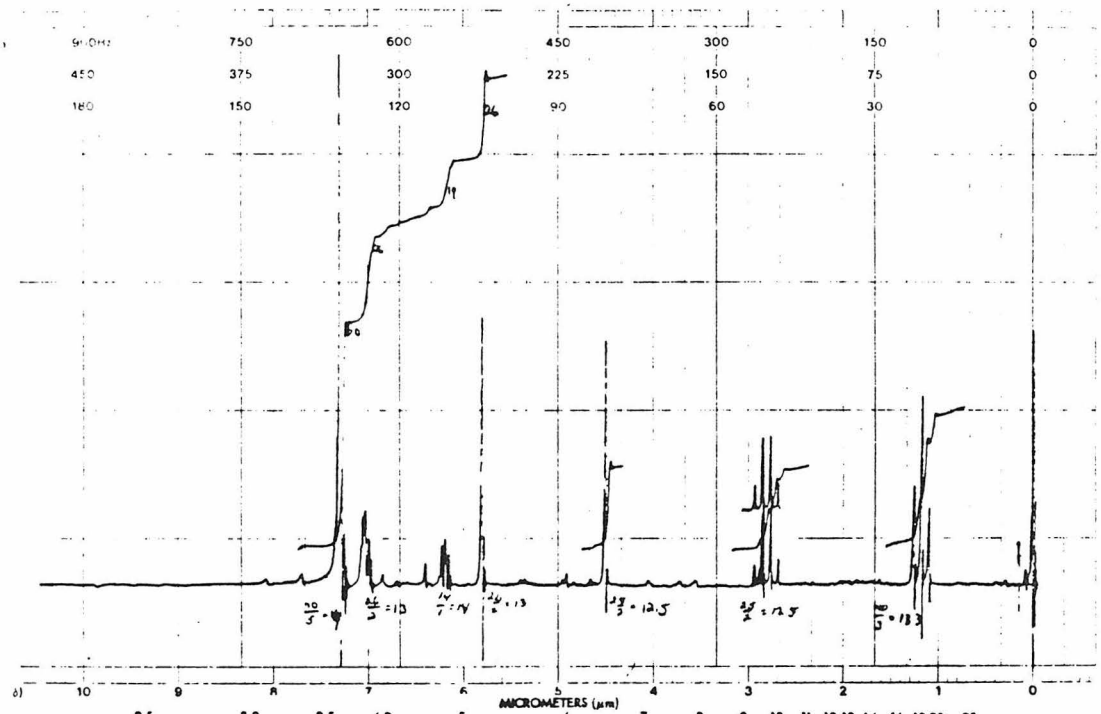
60
375
225
180
10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
WAVENUMBER CM⁻¹

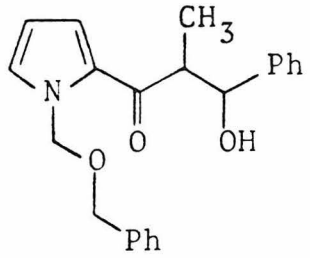
Page 120

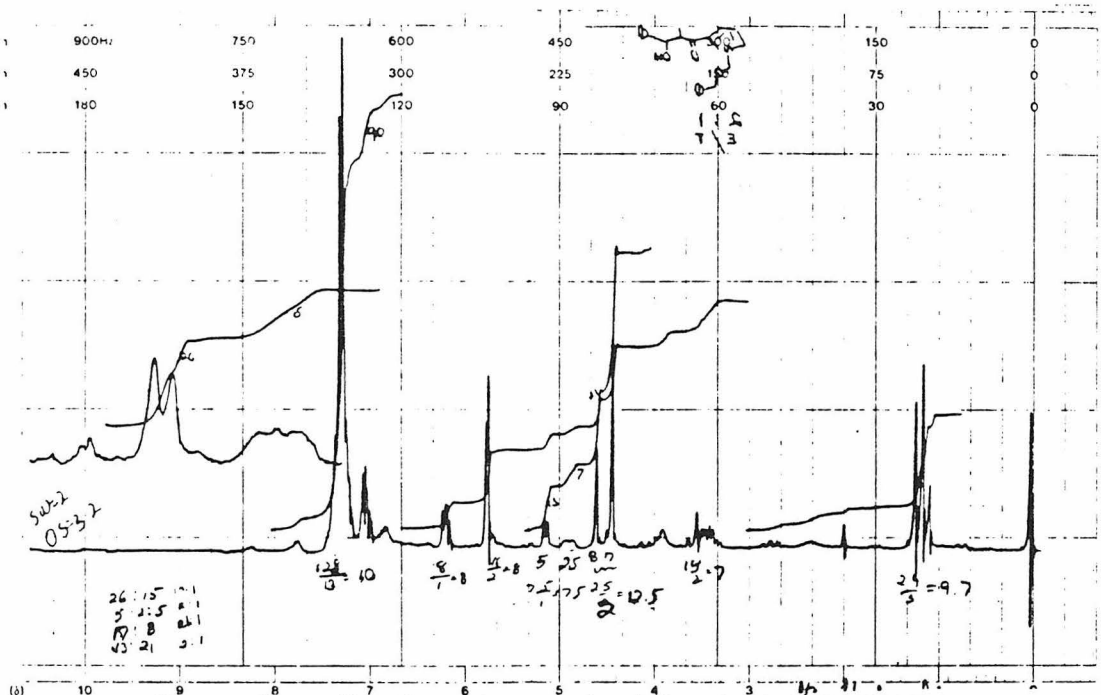

CH3
N
O
O
Ph

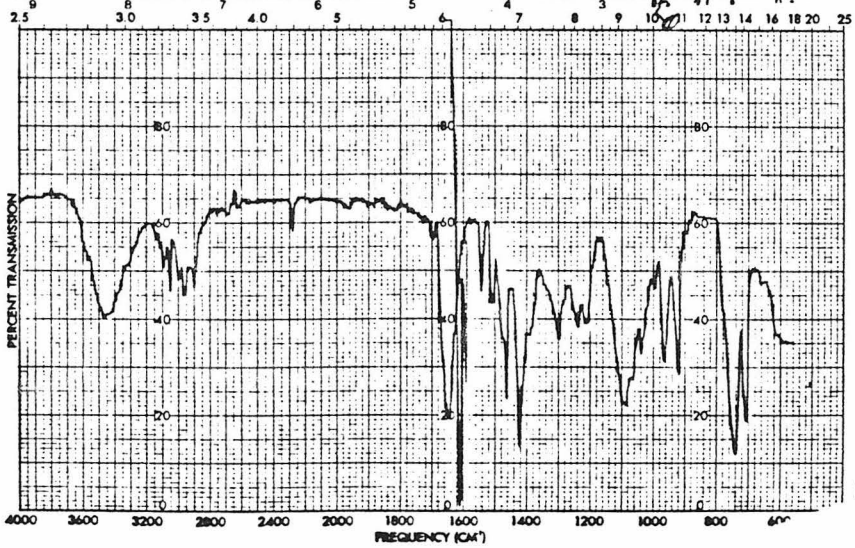
37


MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)

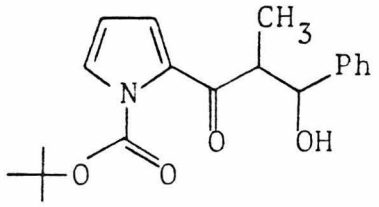
Page 121

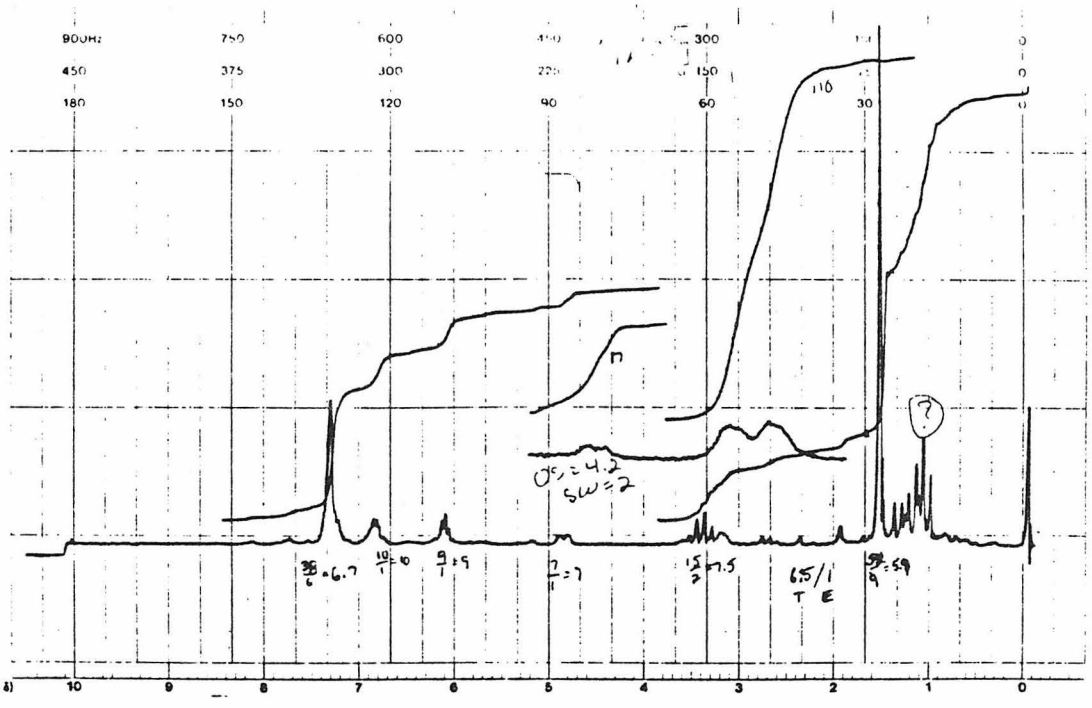

CH3
Ph
N
O
OH
O
Ph


900Hz
750
600
450
150
0
450
375
300
225
75
0
180
150
120
90
30
0
SWH-2
05-32
10
8
5
25
12.5
9.7
10
9
8
7
6
5
4
3
2
1
0
2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
16
18
20
25

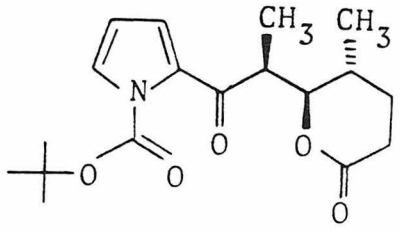

PERCENT TRANSMISSION
100
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)

Page 122

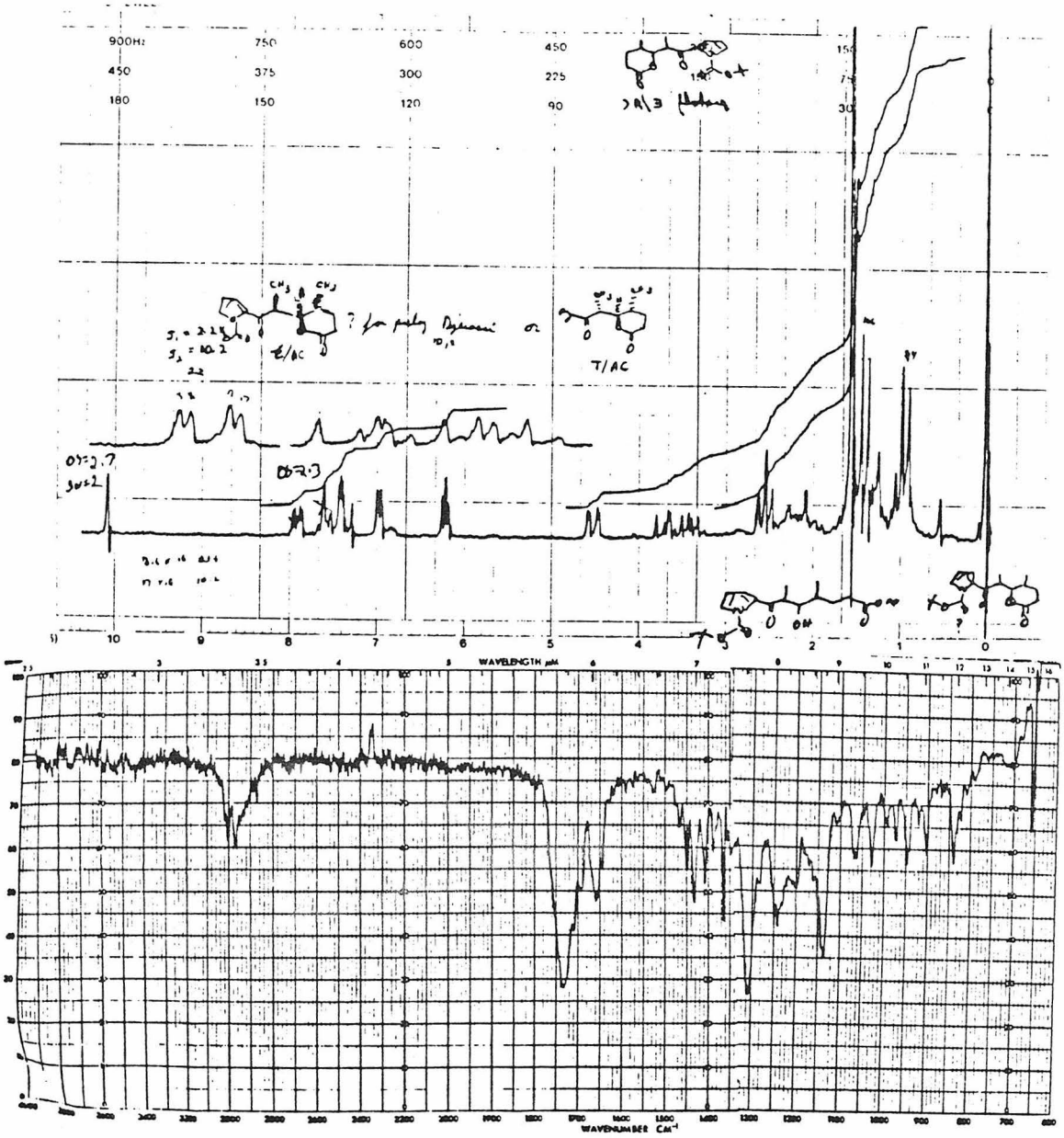

CH3
Ph
N
O
OH
O
O


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

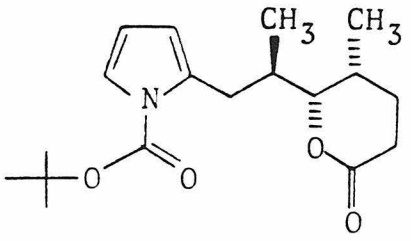
Page 122



40a


900Hz
750
600
450
450
375
300
225
180
150
120
90
T/AC
WAVELENGTH μM
WAVENUMBER CM⁻¹

Page 122



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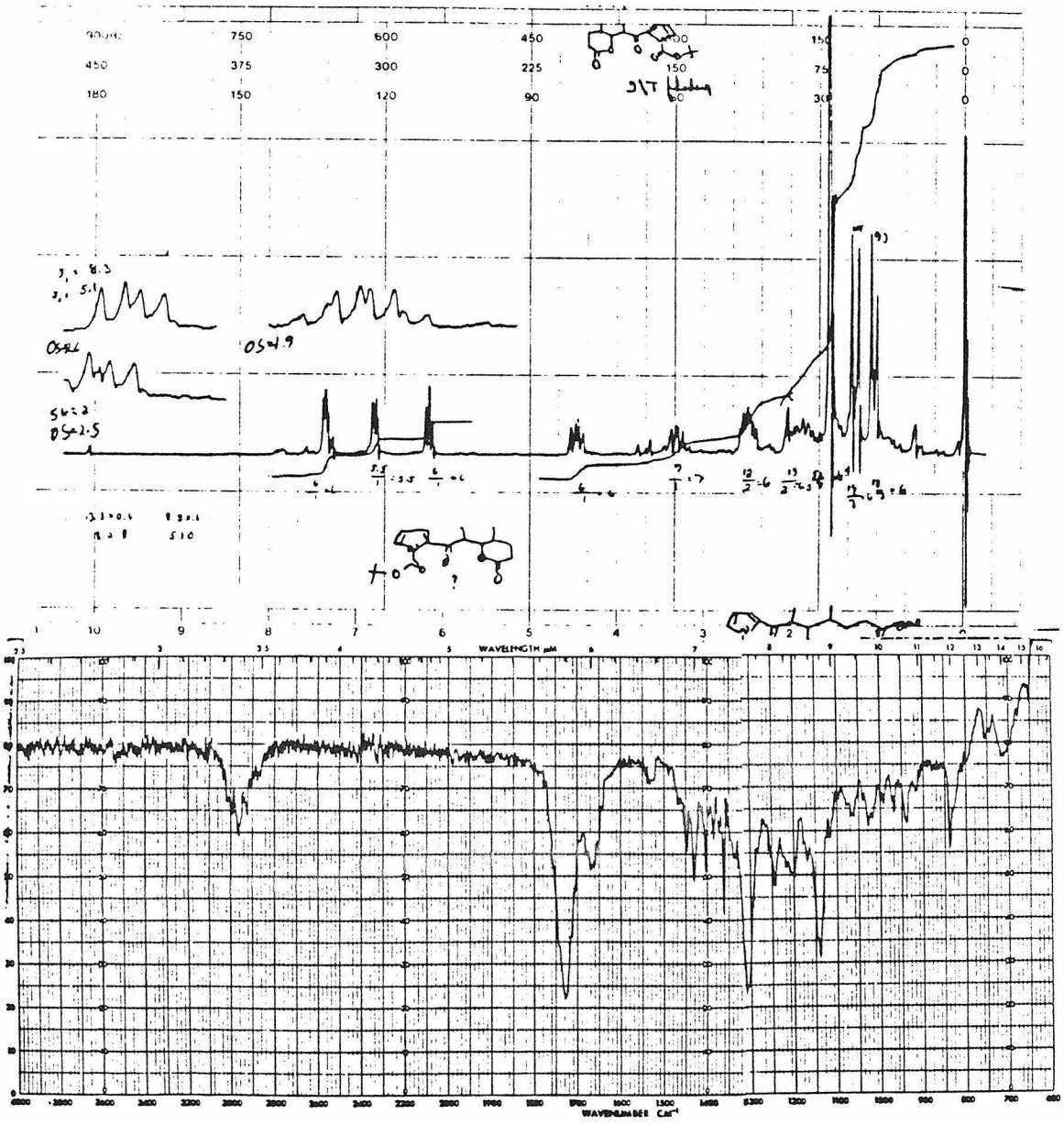
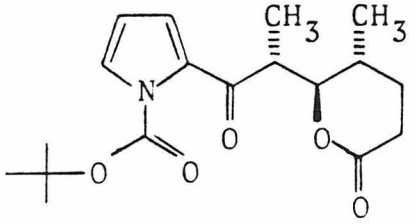
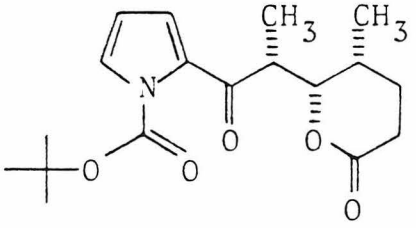


Page 122



40c

+



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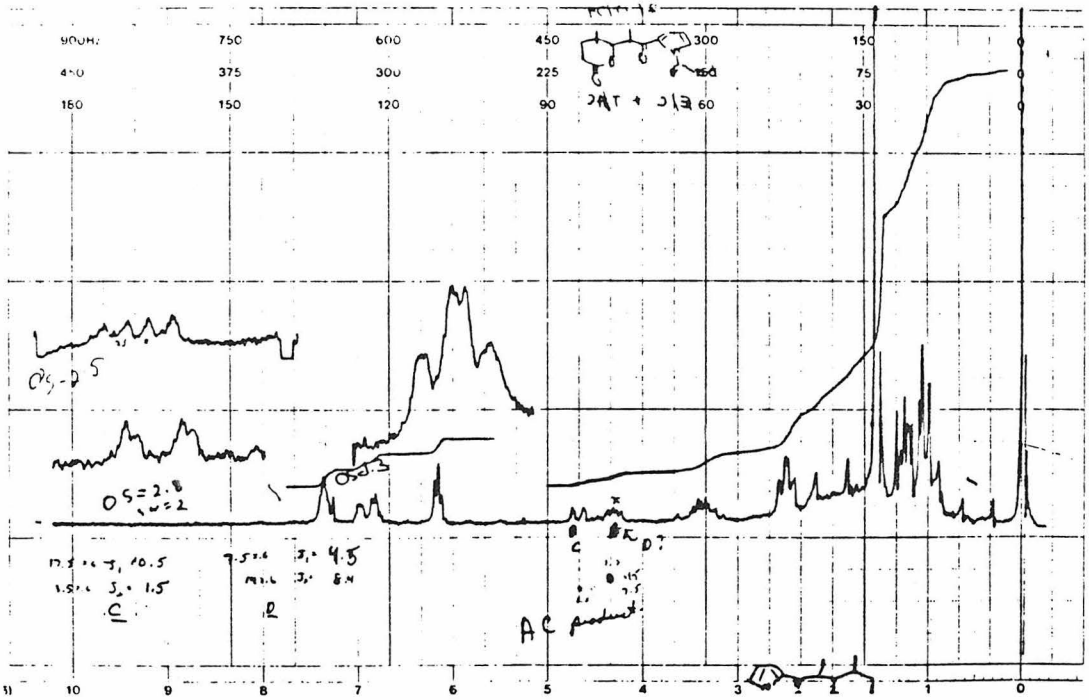
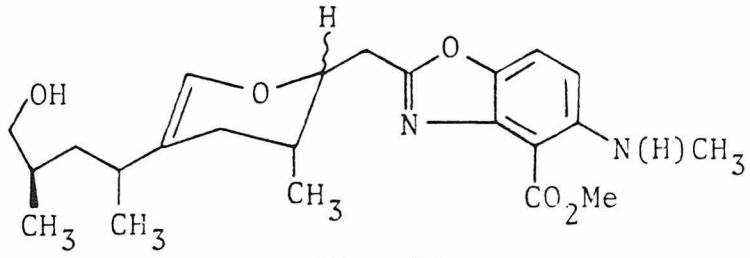
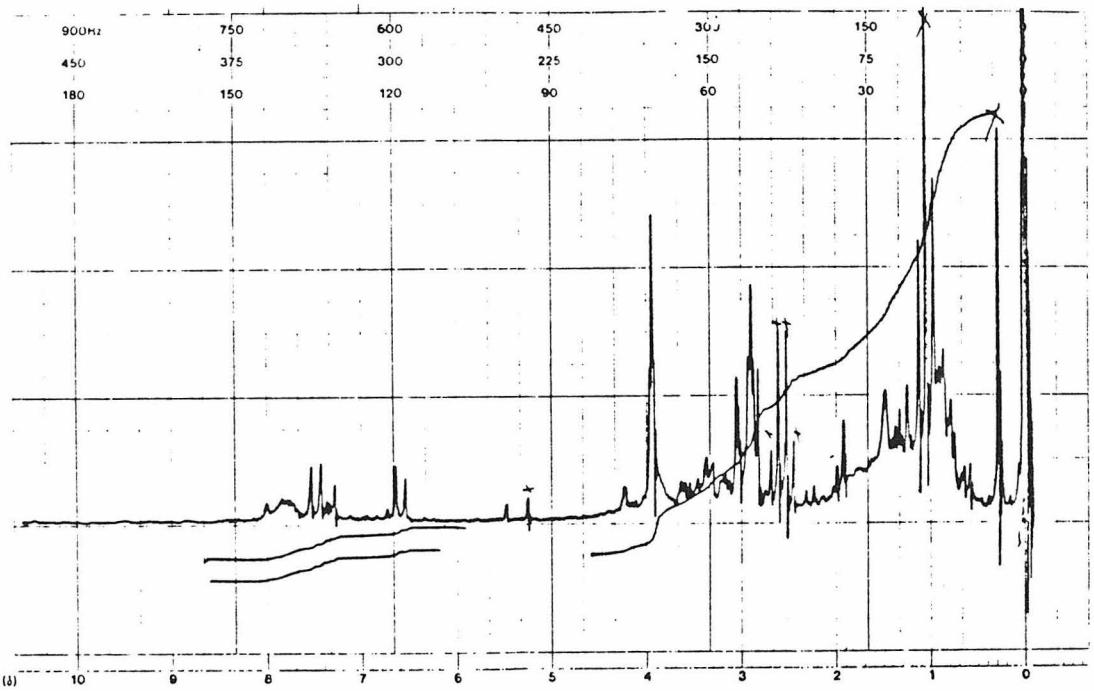
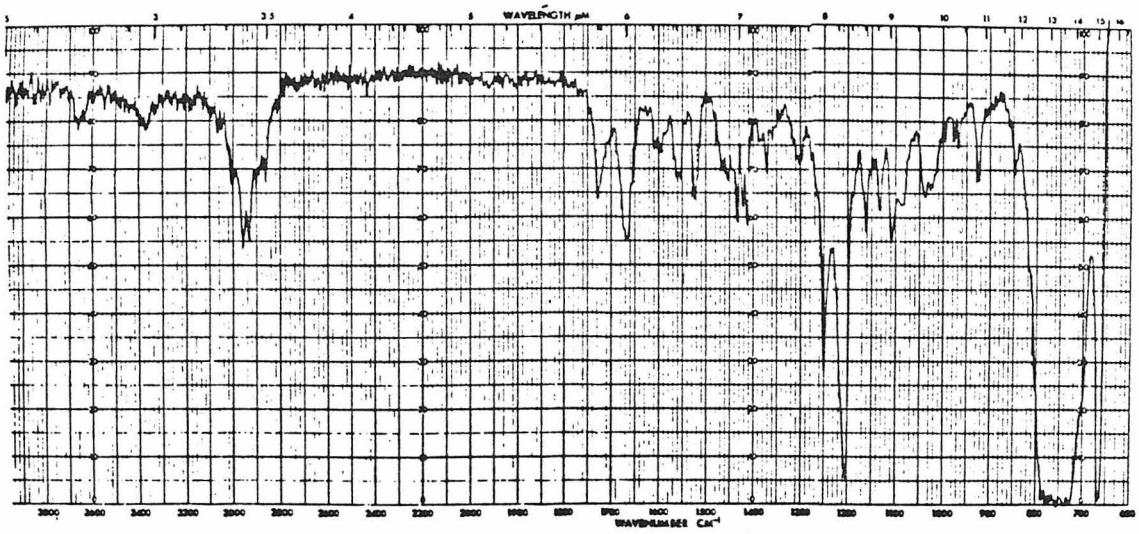


Page 124



43a, 44a





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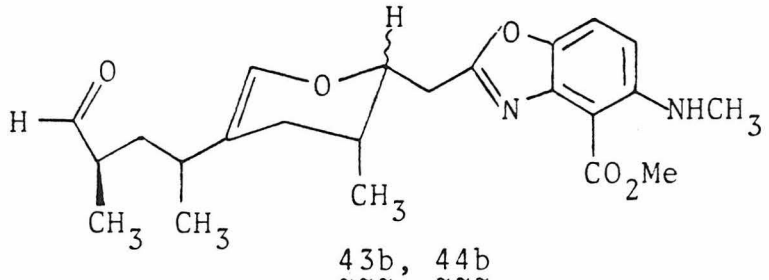

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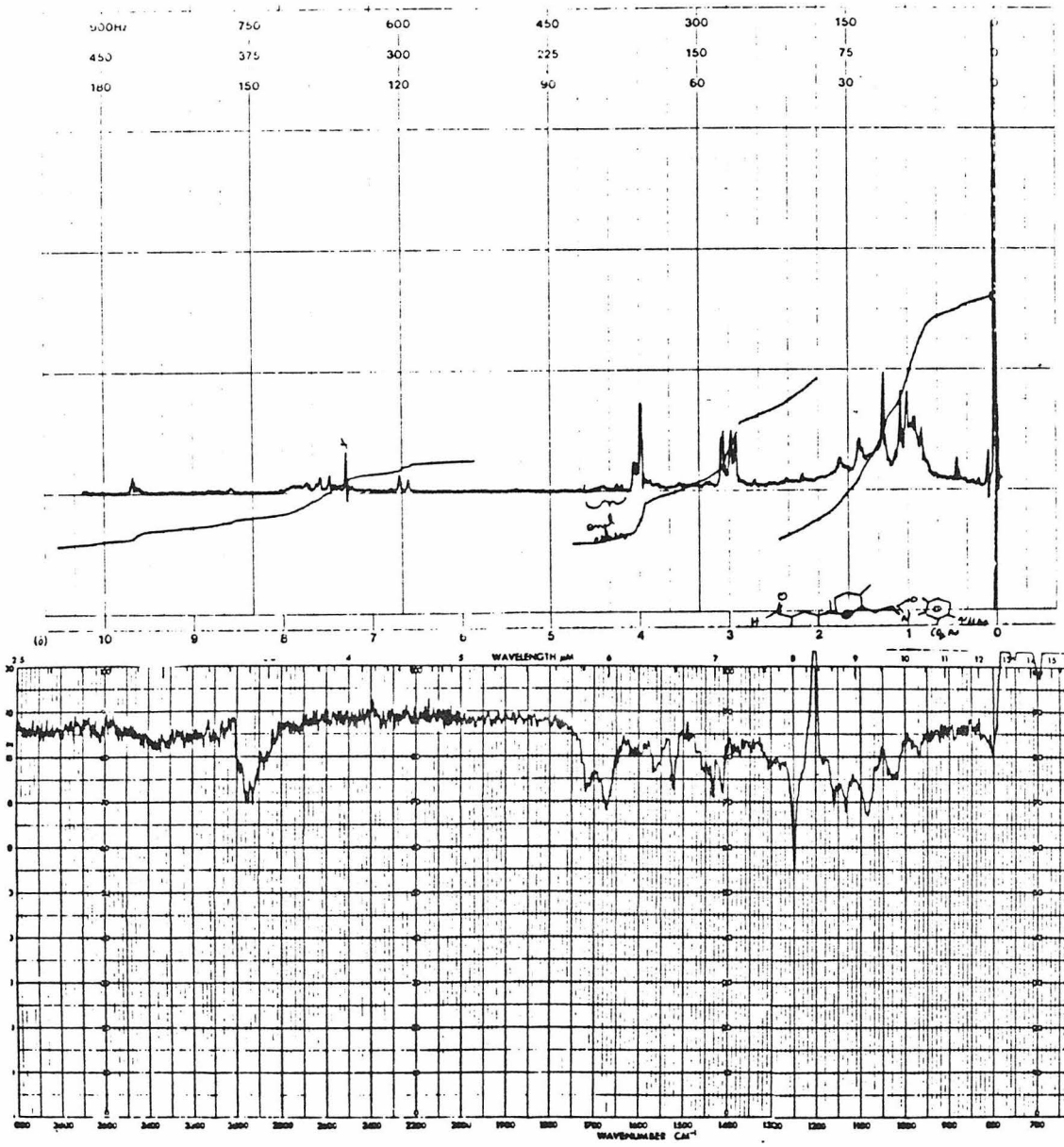

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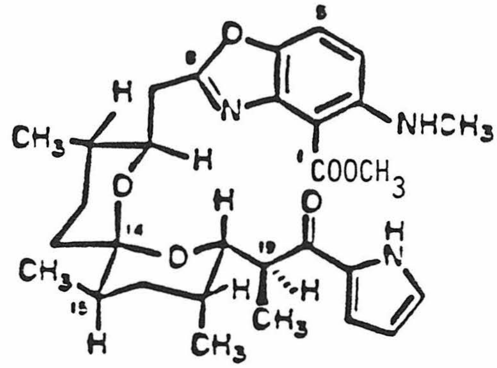
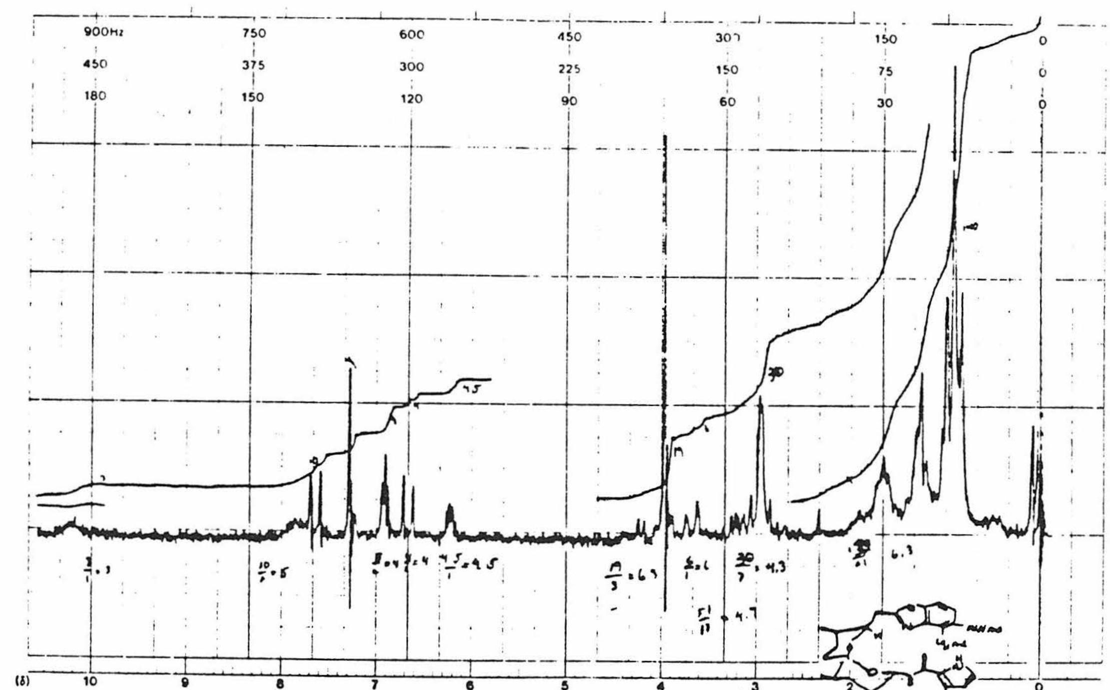
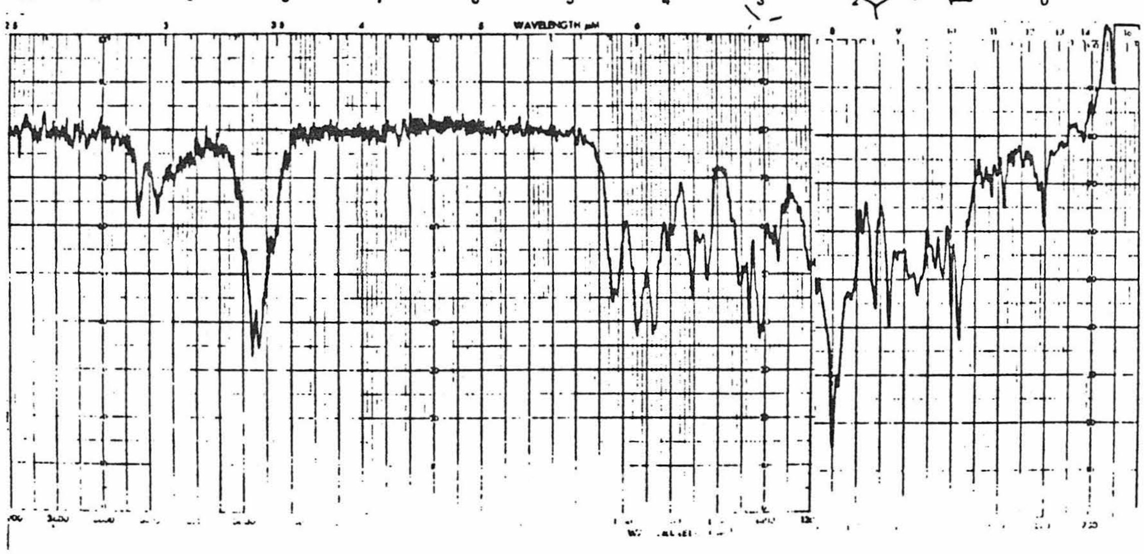


Authentic





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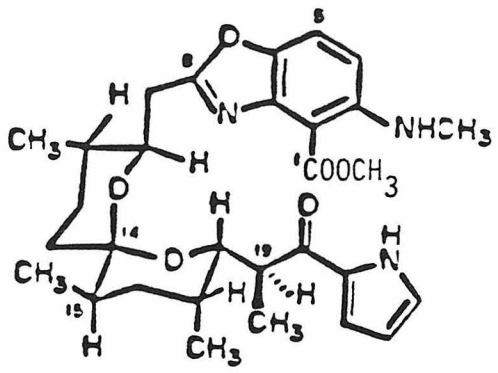
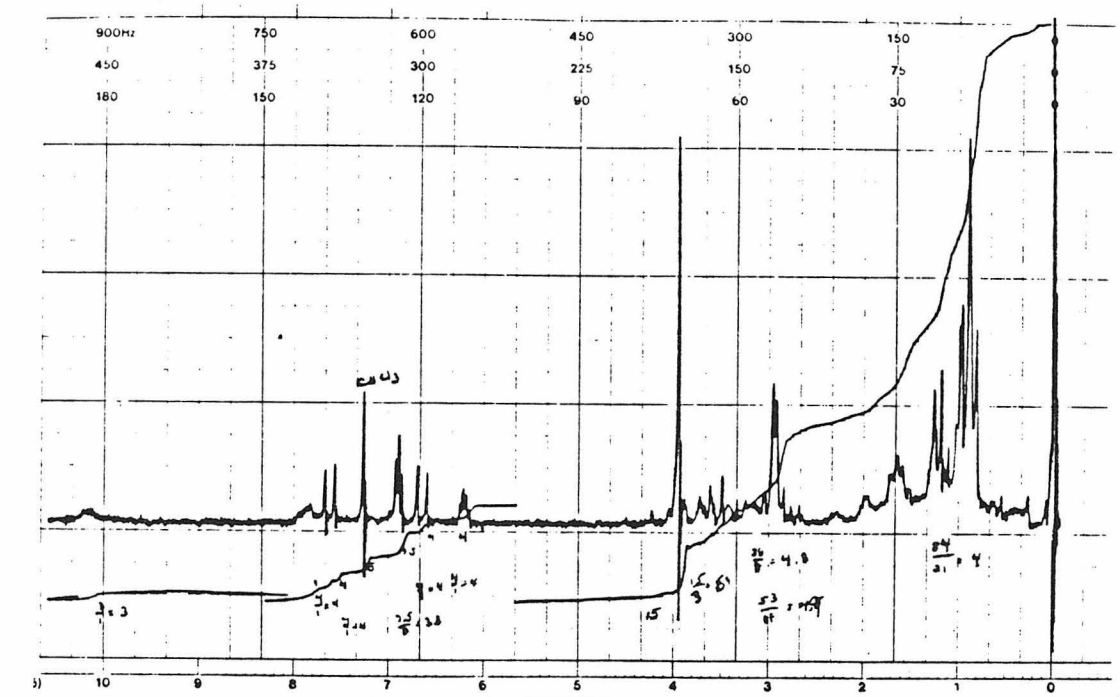
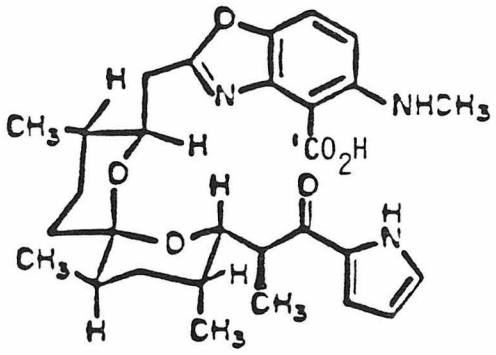
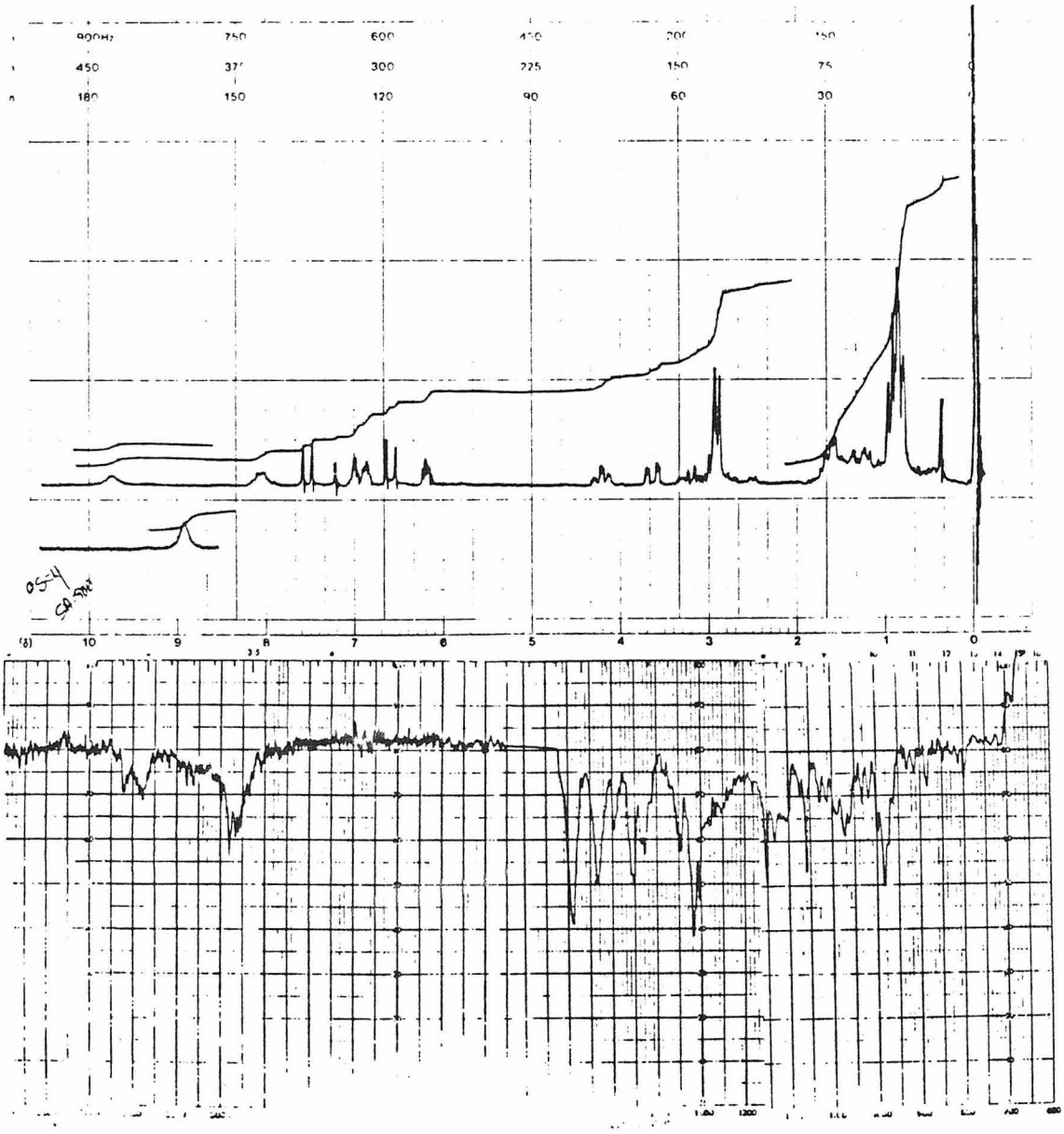


Synthetic 1b

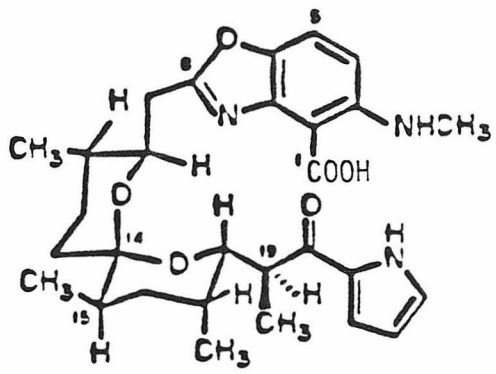



O
H
N
NHCH3
CH3
H
CO2H
O
H
O
O
H
N
CH3
H
CH3
H
CH3

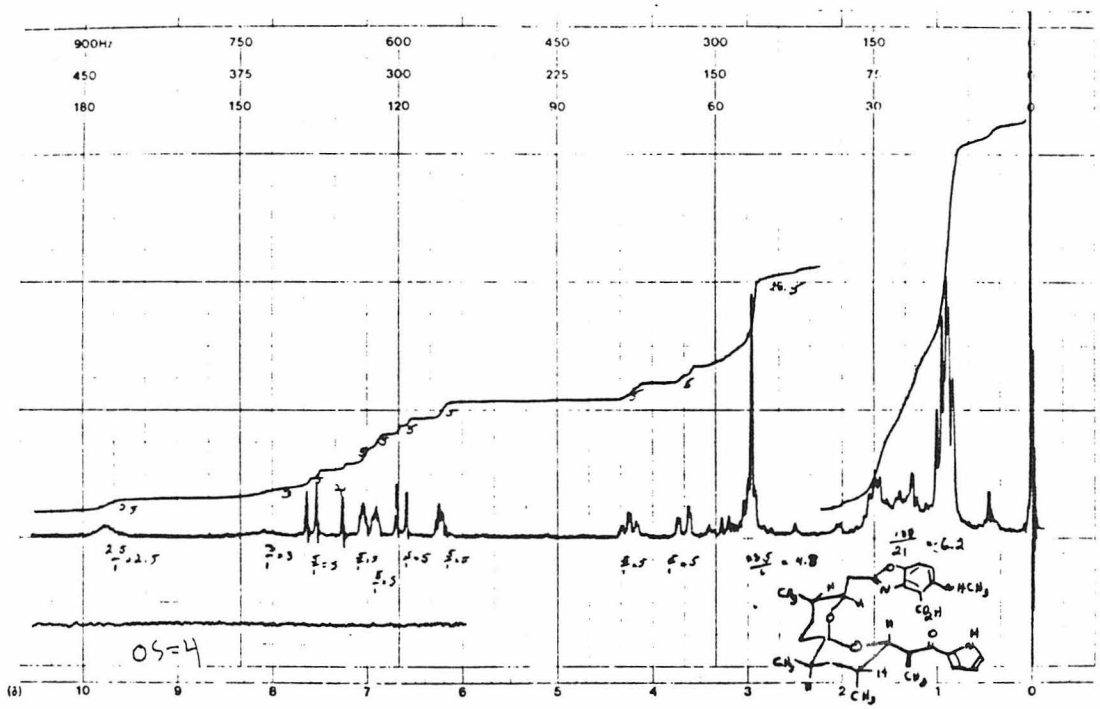
Authentic

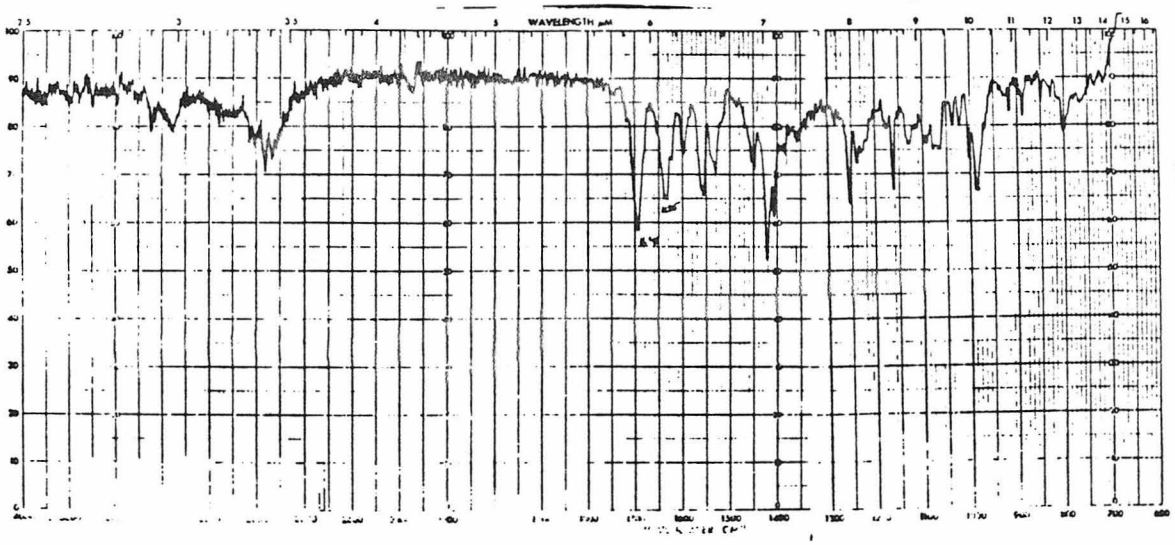

900Hz
750
600
450
375
300
225
180
150
120
90
60
30
(δ)
10
9
8
7
6
5
4
3
2
1
0

Page 128



Synthetic 1a

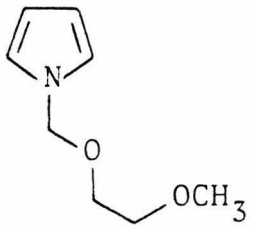




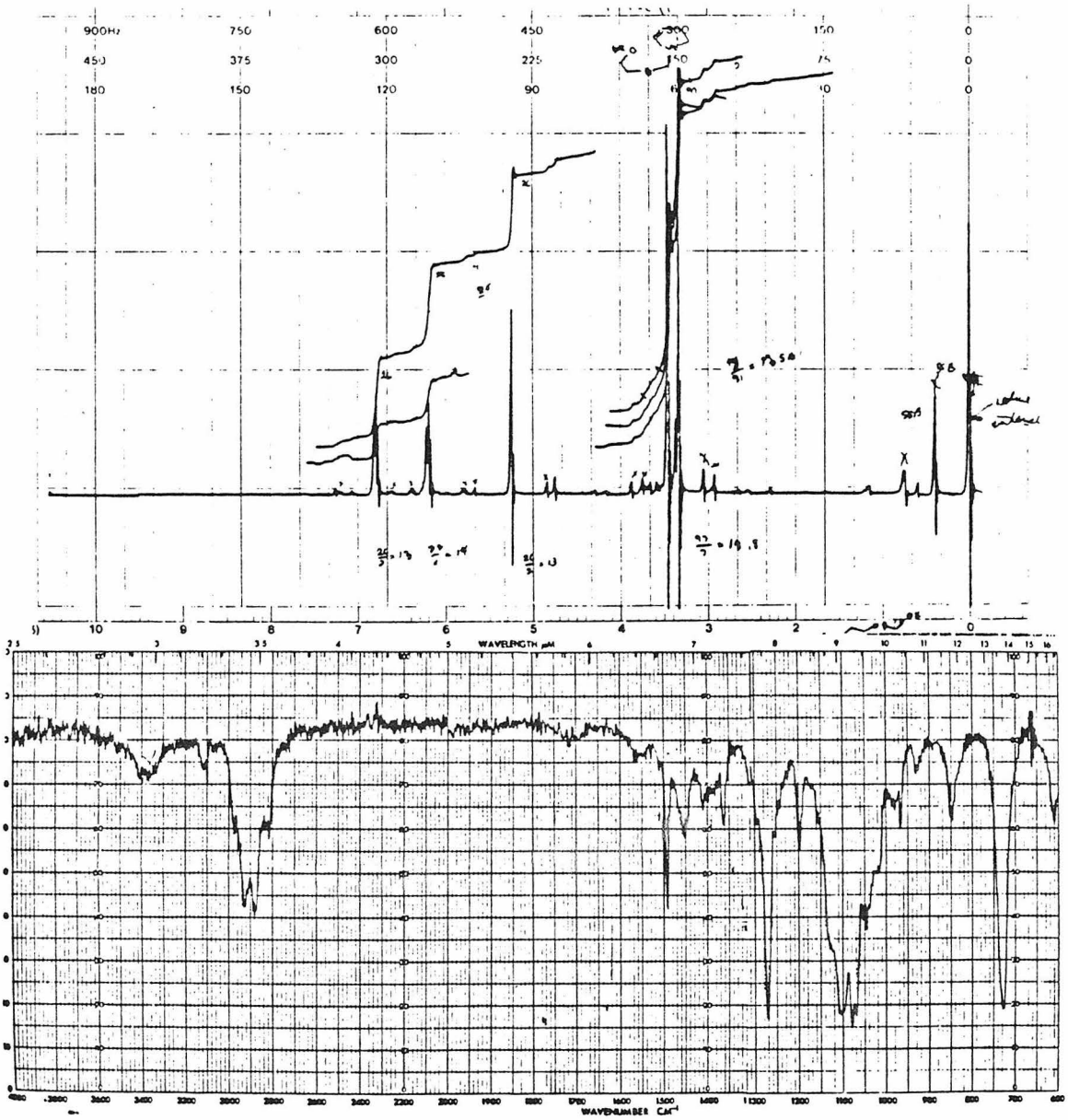
APPENDIX VI

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

Page 144


N
O
OCH3

7


900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
WAVELENGTH μM
WAVENUMBER CM⁻¹

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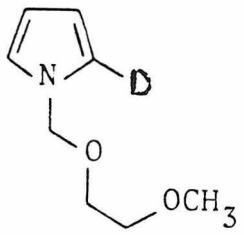
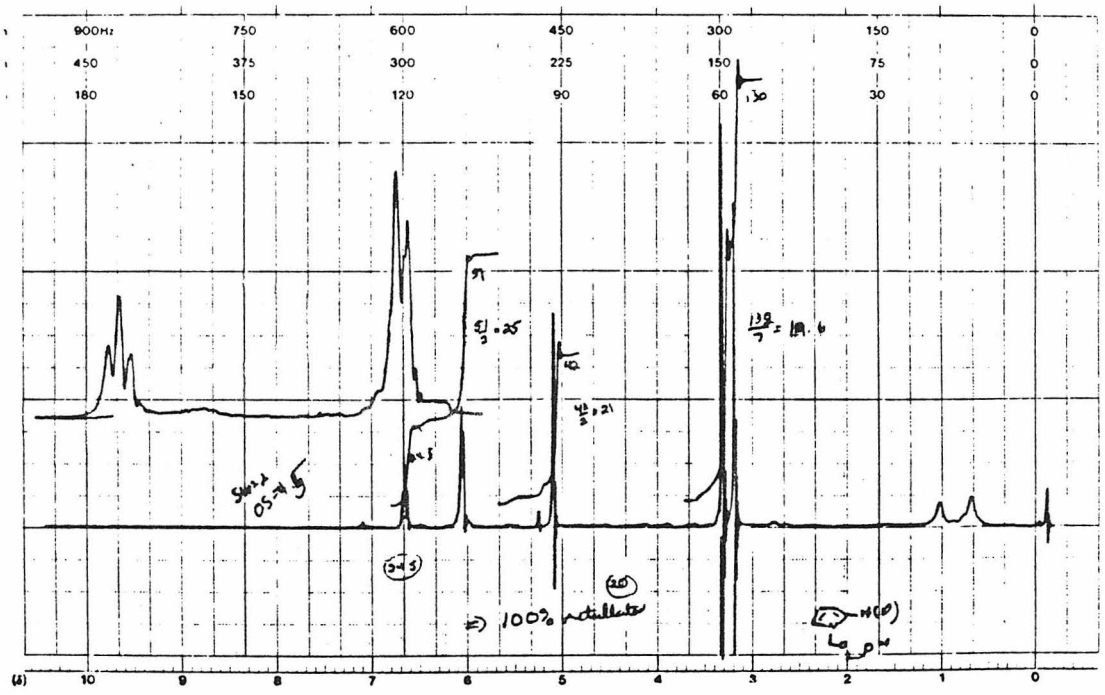
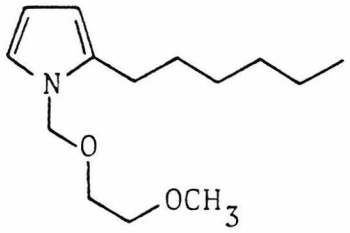
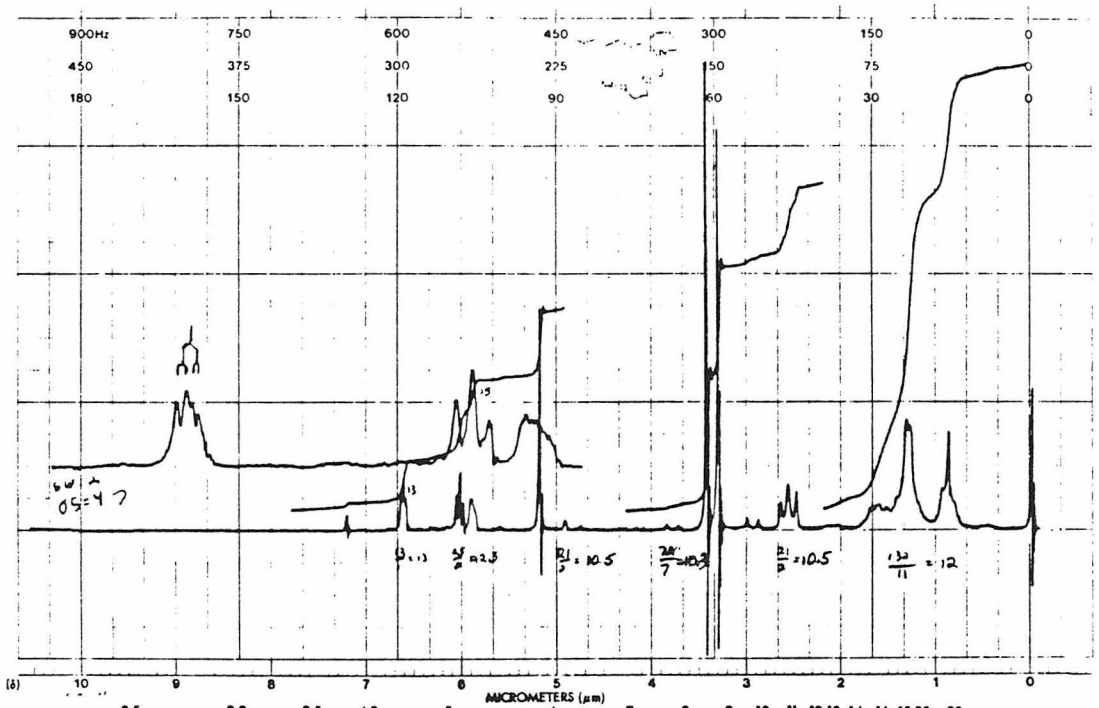

N
D
O
OCH3

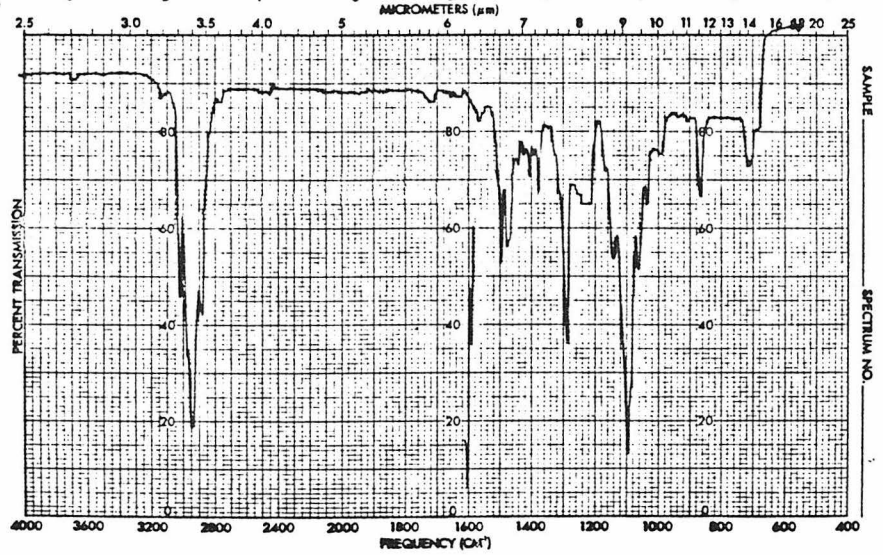
7


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

Page 145


N
O
OCH3


900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
(δ)
10
9
8
7
6
5
4
3
2
1
0
MICROMETERS (μm)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PERCENT TRANSMISSION
80
60
40
20
0
SAMPLE
SPECTRUM NO.
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3600
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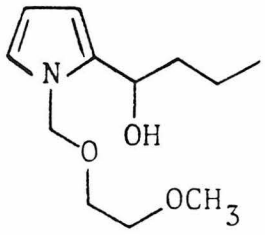
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM⁻¹)

Page 146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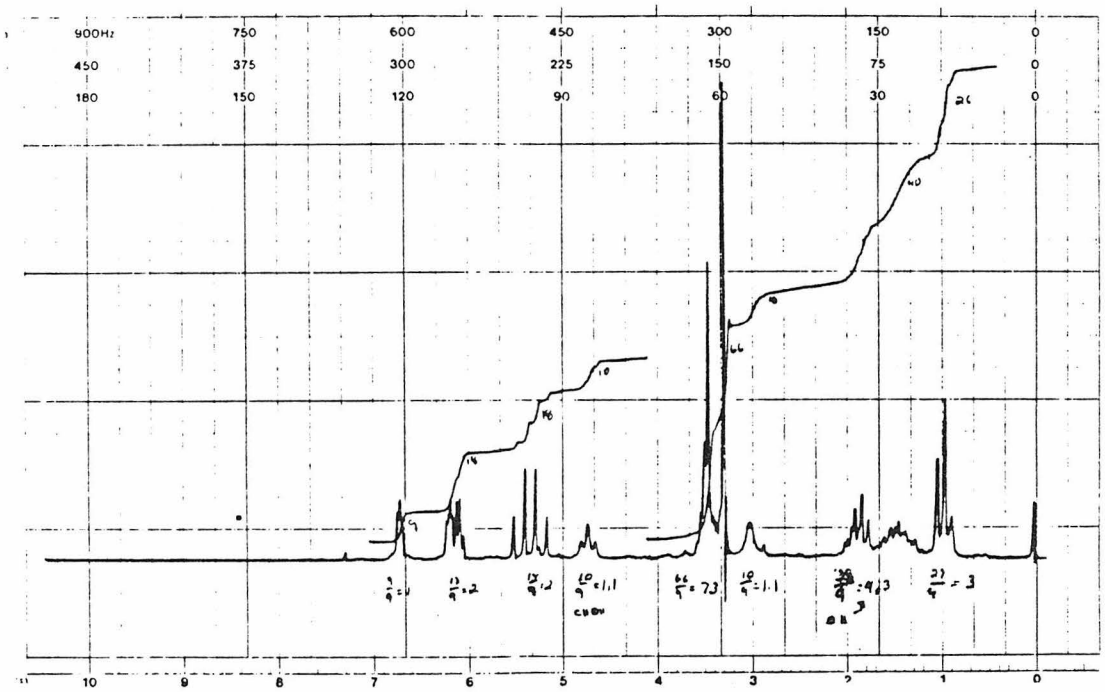
OCH3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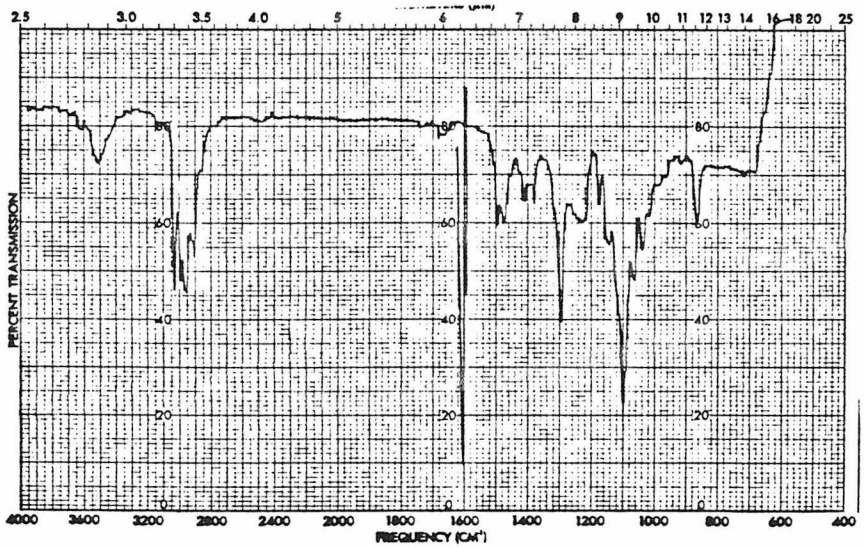
3
2
1
0


PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
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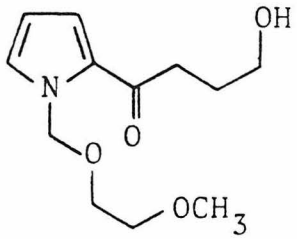
Page 146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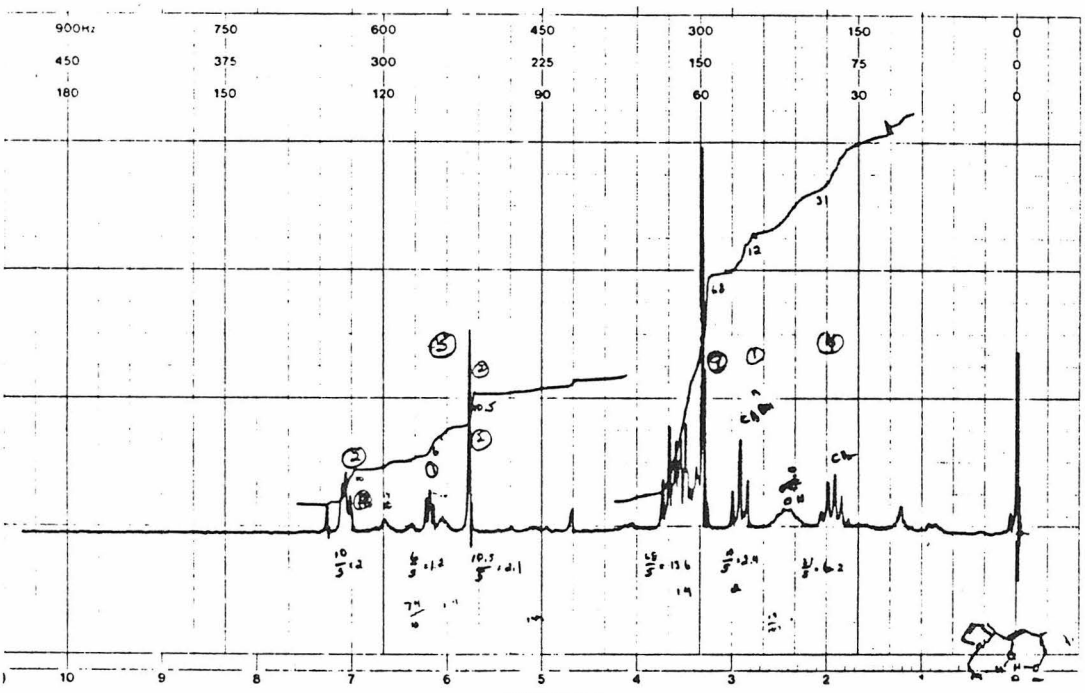
O
O
OCH3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3
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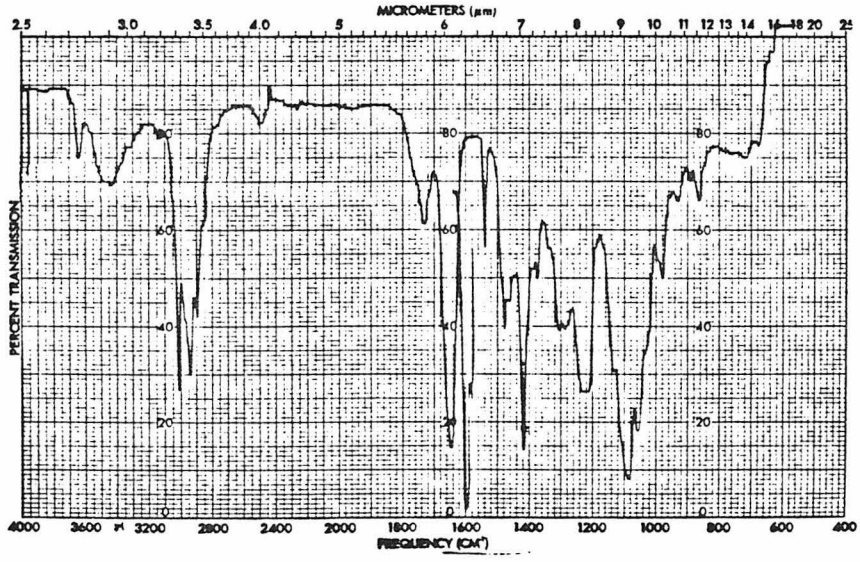
1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PERCENT TRANSMISSION
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80
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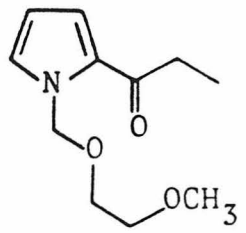
FREQUENCY (CM⁻¹)

Page 147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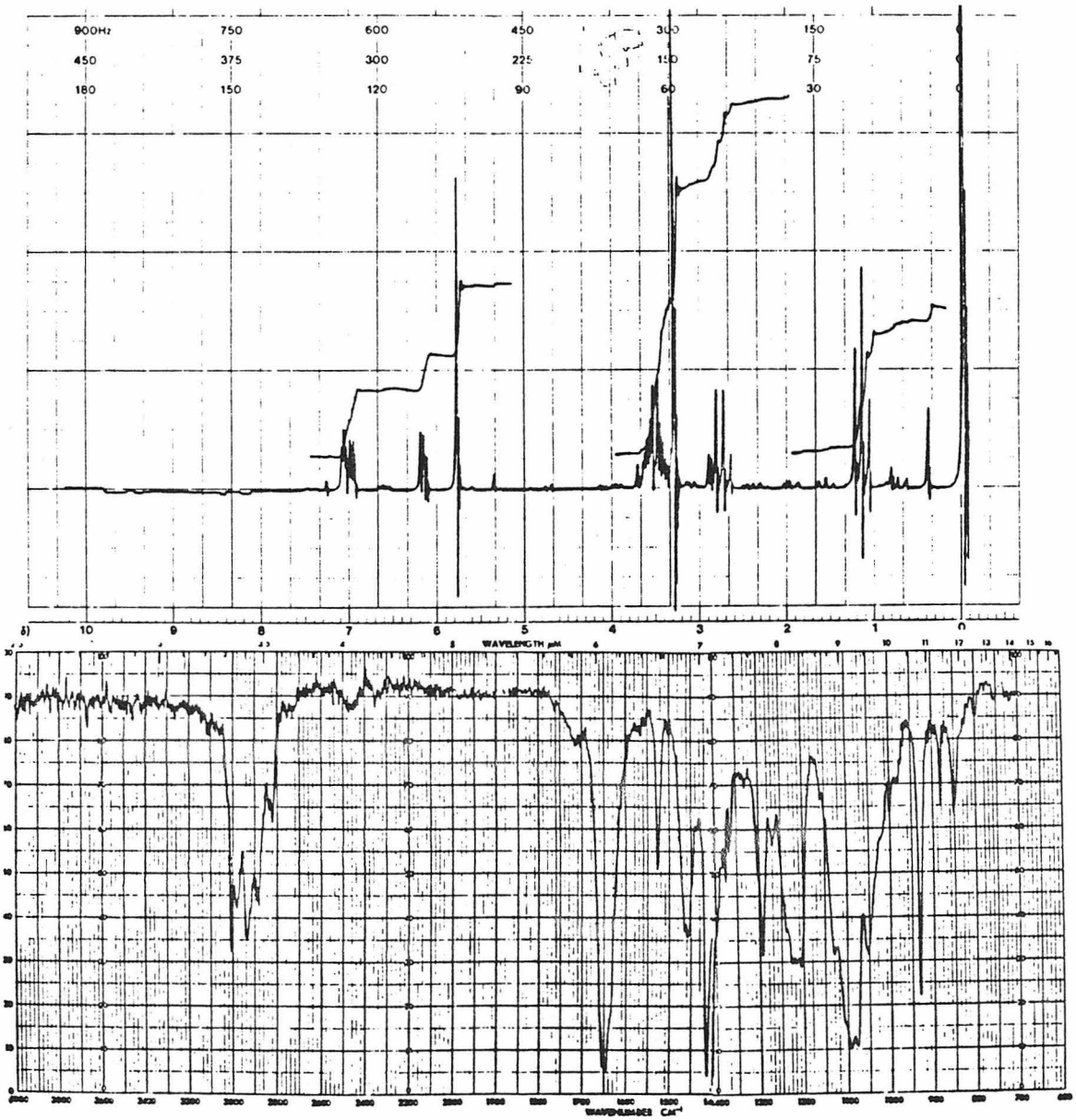
O
O
OCH3

10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90
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30
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9
8
7
6
5
4
3
2
1
0
WAVELENGTH μM
WAVENUMBER CM-1

PROPOSITIONS

ABSTRACTS

PROPOSITION I: The development of a new asymmetric ketone synthesis is suggested and its application to the synthesis of the cigarette beetle sex pheremone is proposed.

PROPOSITION II: The utilization of cuprate reagents for asymmetric synthesis is proposed.

PROPOSITION III: A modification of current therapeutic methods for the treatment of aphasia is suggested. The limitations and risks are discussed.

PROPOSITION IV: Synthesis of chamaecynone by an intramolecular Diels-Alder Reaction is proposed.

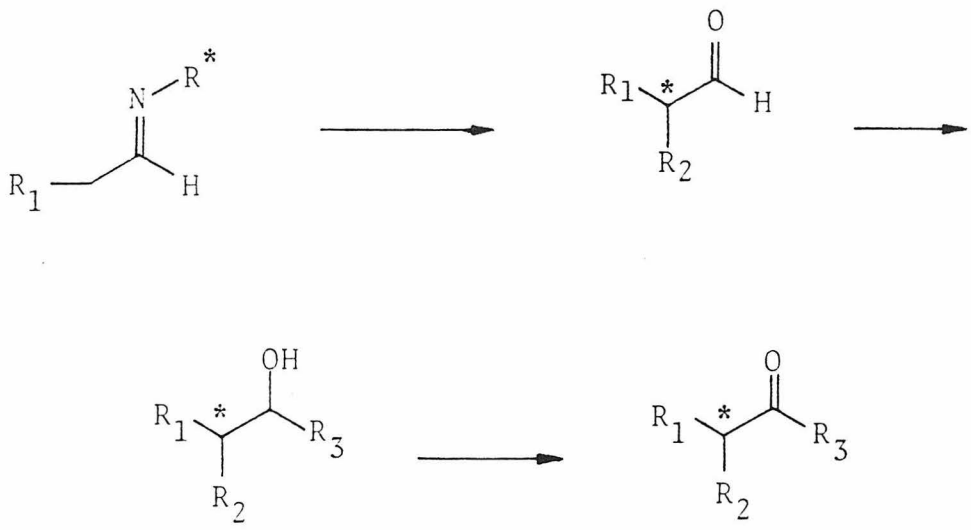
PROPOSITION V: A mechanism for the reaction of cuprates with propargylic alcohol derivatives is proposed.

PROPOSITION I

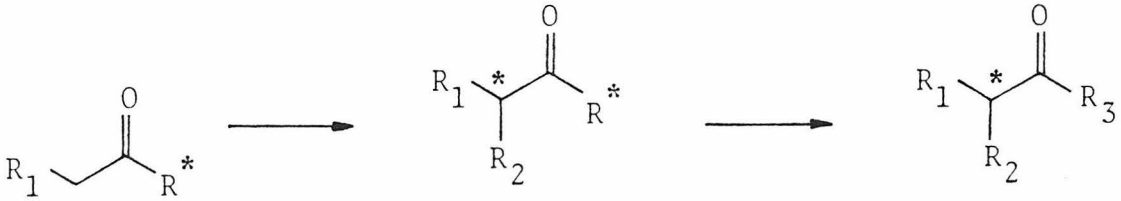
Abstract: The development of a new asymmetric ketone synthesis is suggested and its application to the synthesis of the cigarette beetle sex pheremone is proposed.

During the past few years much emphasis has been placed on asymmetric synthesis in organic chemistry.[1] As complexity of synthetic targets increased, the need to control the relative and the absolute configuration of newly introduced asymmetric centers became essential. Two basic strategies have been used to cope with asymmetry. The first was the use of readily available chiral synthons.[2] Several elegant syntheses have recently been reported which take advantage of this approach.[3-5] The major drawback is that often, the required chiral precursor was either not available in the correct chirality, or conversion of the available chiral precursor to the desired synthon was very laborious Therefore, much attention has recently been directed toward utilizing available chiral sources as recyclable ligands to induce chirality during bond forming reactions.[1] Among the most successful of these have been asymmetric hydrogenations[1c,b] and asymmetric alkylations.[1c,7] A new approach to asymmetric alkylations of acids and its application to the determin-

Scheme I



Scheme II

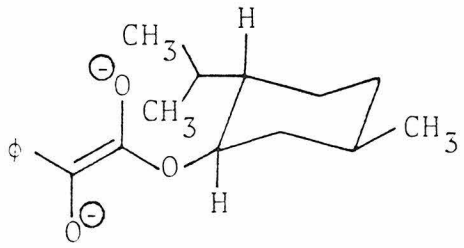


ation of the relative and absolute configurations of a new pheremone are the subject of this proposal.

During the past three to five years, amazing progress has been made in asymmetric alkylation reactions. By alkylating chiral imines or hydrazones derived from an aldehyde[7a] or a ketone[7b] and a chiral amine or hydrazine, enantiomeric excesses[8] in the range of 50-80% have been made routinely accessible. The problem with alkylating ketones, however, is that unless they are symmetrical or methyl ketones,[9] the regiochemistry of alkylation may be uncontrollable; making asymmetric alkylation of unsymmetrical ketones difficult. One way of avoiding this would be to alkylate an aldehyde, free the aldehyde, do a Grignard addition and oxidize (Scheme I). Synthetically, this procedure is unattractive due to the many steps (imine formation, alkylation, hydrolysis, grignard and oxidation) required to obtain the desired product. Alternatively, one could start with a chiral acid derivative, alkylate and then, in the case of an amide, add an alkyllithium[10] to directly obtain the desired ketone (Scheme II).

To date, only a few chiral acid derivatives have been utilized for asymmetric alkylations. The most successful (for asymmetric induction) of these have been the chiral oxazolines used by Meyers and coworkers.[1c,11] Although enantiomeric excesses of 70-80% were obtained, application

of this method suffers from the same disadvantage as does the aldehyde procedure, a long sequence from starting acid to desired ketone. Recently three more studies on asymmetric alkylation of acid derivatives have been described. Newcomb[12] used the dianion 1, but the optical yields were low (ca. 10-40% ee). Larcheveque[10] reported



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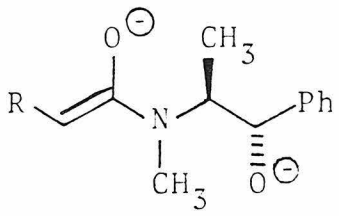
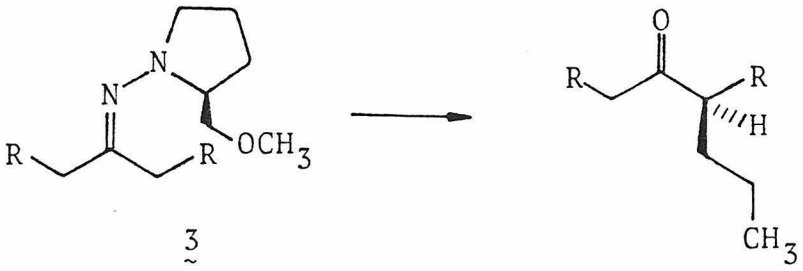


2

the alkylation of dianion 2 and then direct conversion to a ketone in 60-80% ee. While this is encouraging the optical yields are not high enough so as to be useful in a multistep synthesis or synthesis of pheremones where very high enantiomeric purity is required. The third method, pioneered by Schöllkopf,[13] gave high asymmetric induction, but was only applicable to amino acid synthesis.

Based on recent results of Enders,[14] in which symmetrical hydrazones like 3 could be alkylated in ≥98% ee (eq 1), the amide 4 is proposed as a possible solution for asymmetric alkylation of acids. Direct conversion of the amides to unsymmetrical ketones should then be possible,

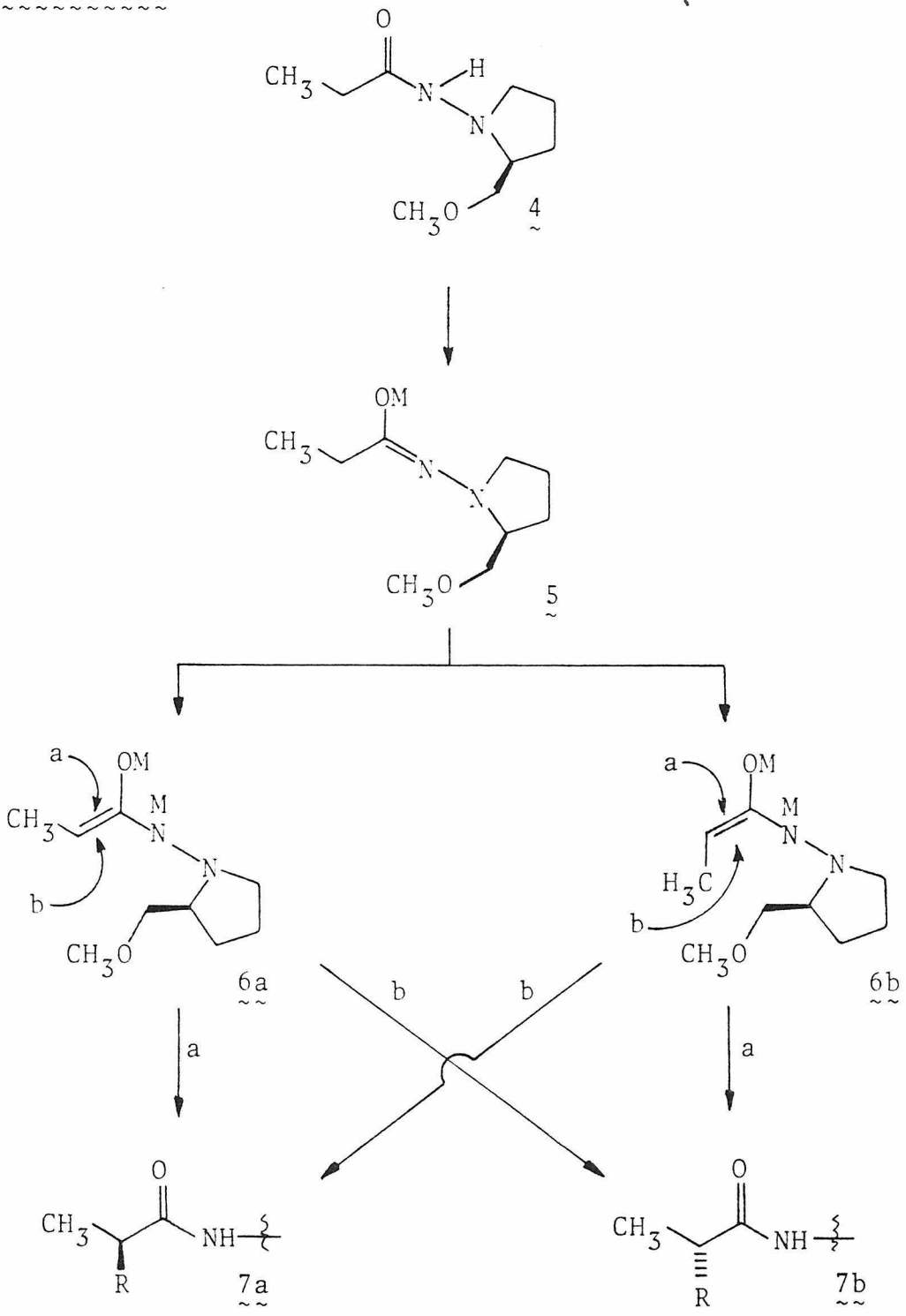


3 (1)

making unsymmetrical, chiral ketones readily available (Scheme III).

In such an asymmetric reaction, there are two components which control the level of asymmetric induction. The first is the enolate geometry (5a vs 5b) and the second is the enantioface selectivity in the alkylation step. From several studies in the literature,[11a,15] imines and hydrazones show a very strong preference for the geometry represented by 6a. If one assumes that the mono-anion 5 behaves like an imine,[16] then the second deprotonation should give 6a. Alkylation of 6a from the top face (a, from above the plane of the paper) would lead to 7a whereas attack from the bottom face (b, below the plane of the paper) would lead to diastereomer 7b. Again using Enders' examples as a model[14] (see structure 8), 7b should be obtained in very high enantiomeric yields.

Scheme III


O
CH3
N
H
N
CH3O
4
OM
CH3
N
N
CH3O
5
a
OM
M
CH3
N
N
b
CH3O
6a
a
OM
M
N
N
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NH
R
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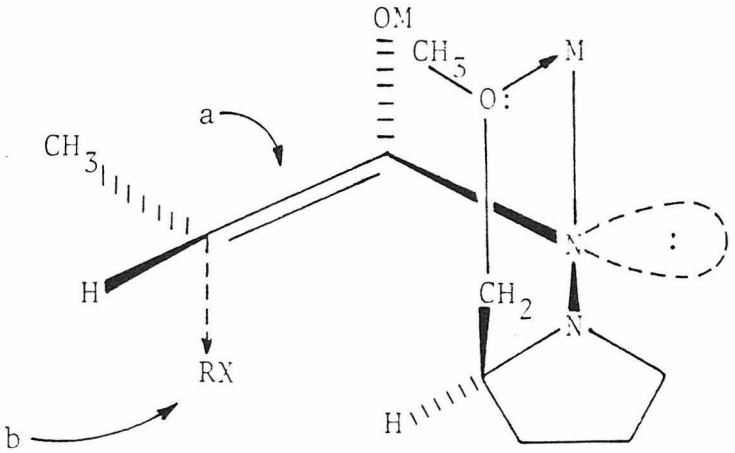
CH3
NH
R
7b

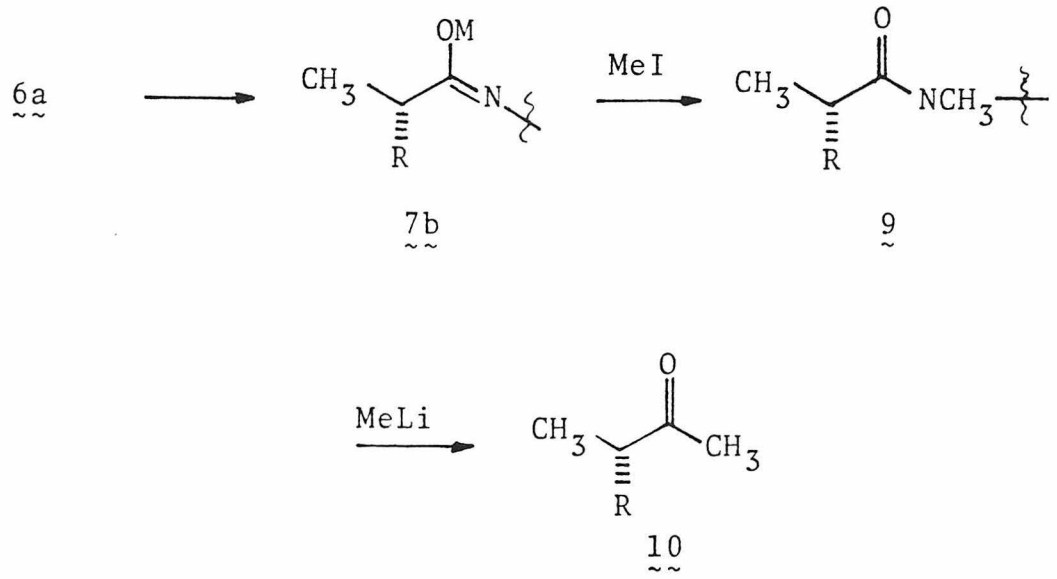


8

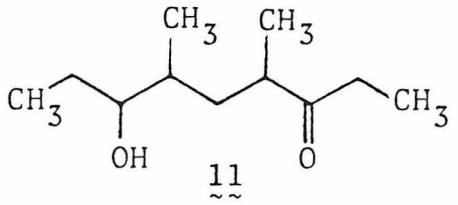
If the mono-anion resulting from alkylation of 6a were to be treated with methyl iodide followed by methyllithium[10] one should realize an essentially one-pot synthesis of chiral methyl ketone 10 (Scheme IV). Substitution of other lithium reagents would provide analogous chiral ketones. In going from propionic acid to higher homologs, the percent ee should increase since the ratio of 6a to 6b should be improved, while the enantioface selectivity would probably remain unchanged.

Several applications for this procedure can be envisioned. One of these is the synthesis of the sex

Scheme IV



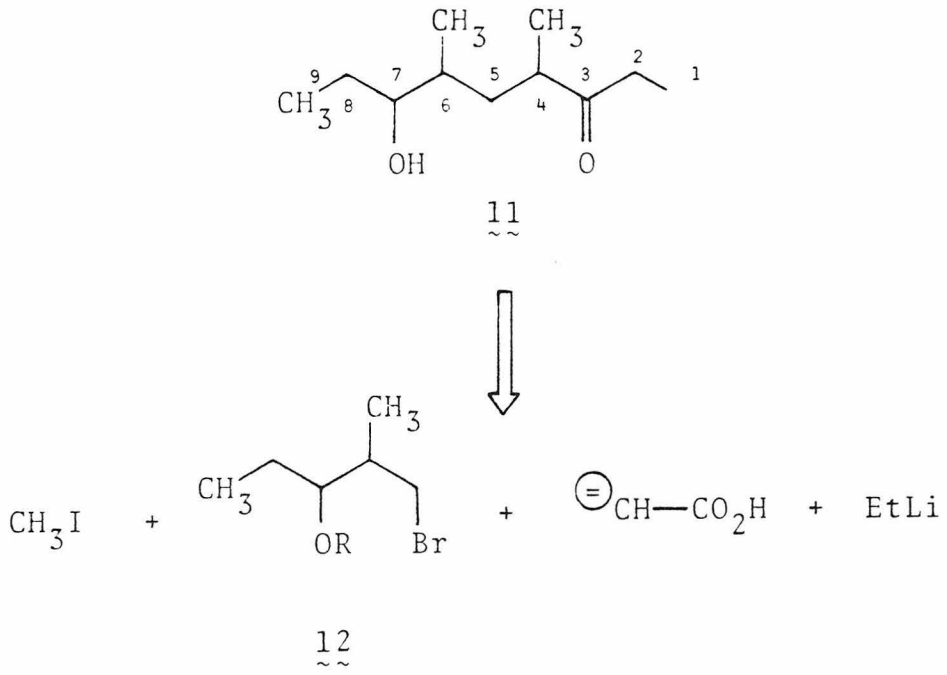
attractant (11), isolated from the female cigarette beetle (lasioderma serricorne F.).[18]



The cigarette beetle causes widespread damage to cured tobacco leaves. Since the use of pesticides is increasingly being discouraged, the use of pheremones for pest management is becoming more popular.[19] Because insects are frequently sensitive to changes in the diastereomeric (and enantiomeric) constitution of pheremones,[19a] com-

mercially produced pheremones must mimic the exact constitution of the naturally produced pheremone to be effective. An approach to the synthesis of the eight possible diastereomeric constituents of 1 is outlined retrosynthetically in Scheme V. Asymmetric alkylation of an amide could give either enantiomer at C_4 simply by

Scheme V

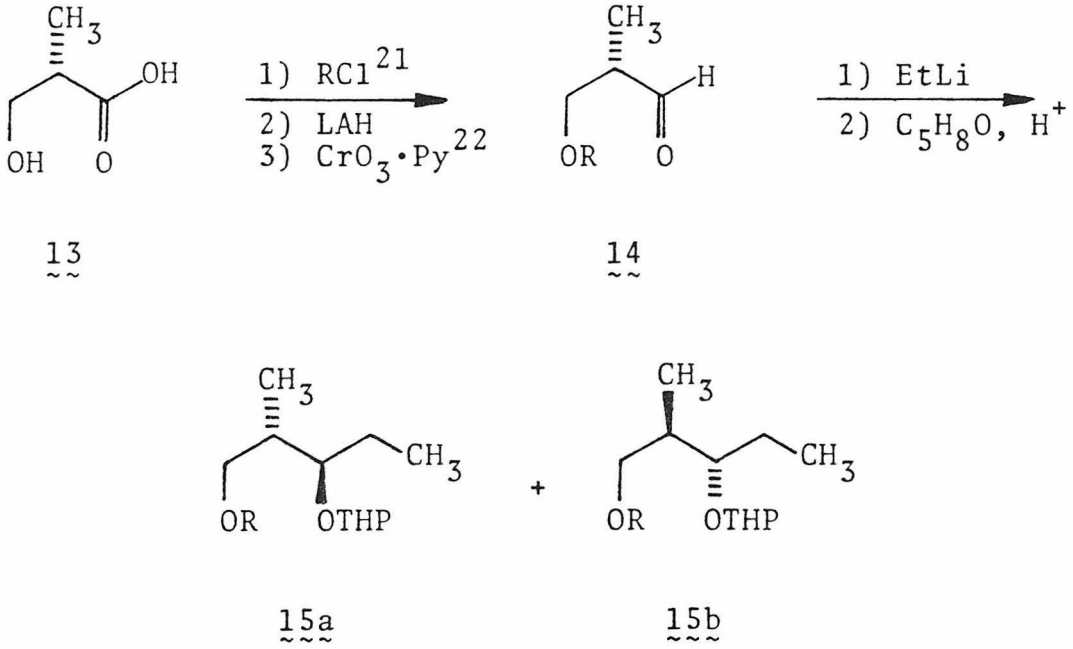


changing the order of alkylation (ie., introduce CH_3- or 12 first). Chiral halide 12 could be obtained by an addition of ethyllithium to chiral aldehyde 14[1d] (available from chiral acid 13[20]) to give the two diastereomers

15a and 15b which should be separable by chromatography (Scheme VI). As shown in Scheme VII, 17a,b (the enantiomers of 15a,b) should also be readily available from 13. Treatment of the silyl ethers with fluoride[21] would give the corresponding alcohols. Then mesylation and bromide exchange by the method of Servis[24] would give the required bromides.

The synthesis of (4R,6R,7R)-11 and (4S,6R,7R)-11 are detailed in Scheme VIII, as representative examples. Alkylation of amide 4 with bromide 18a followed by

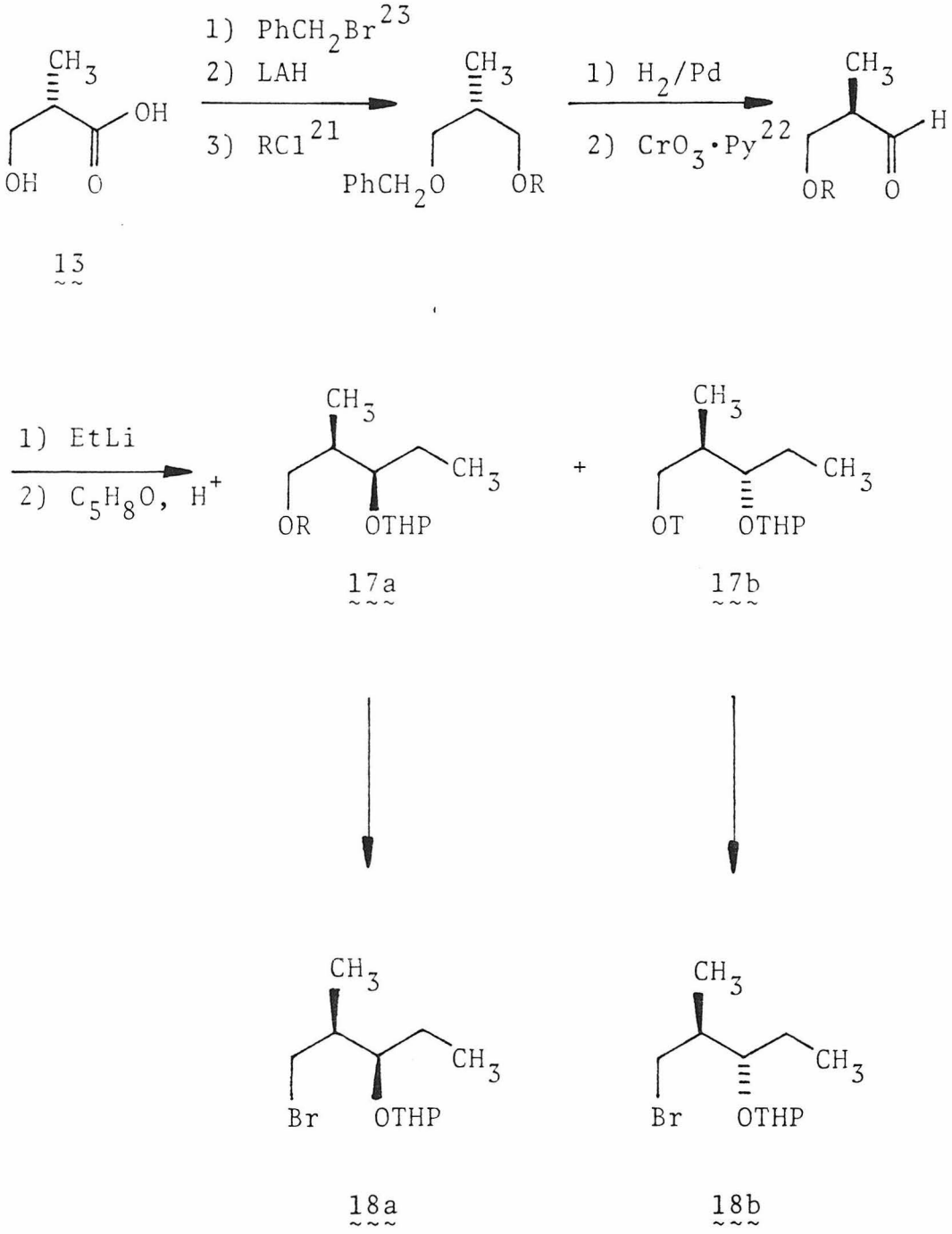
Scheme VI



13 14 15a 15b

R = $C_4H_9Ph_2Si$—

Scheme VII



13

17a

17b

18a

18b

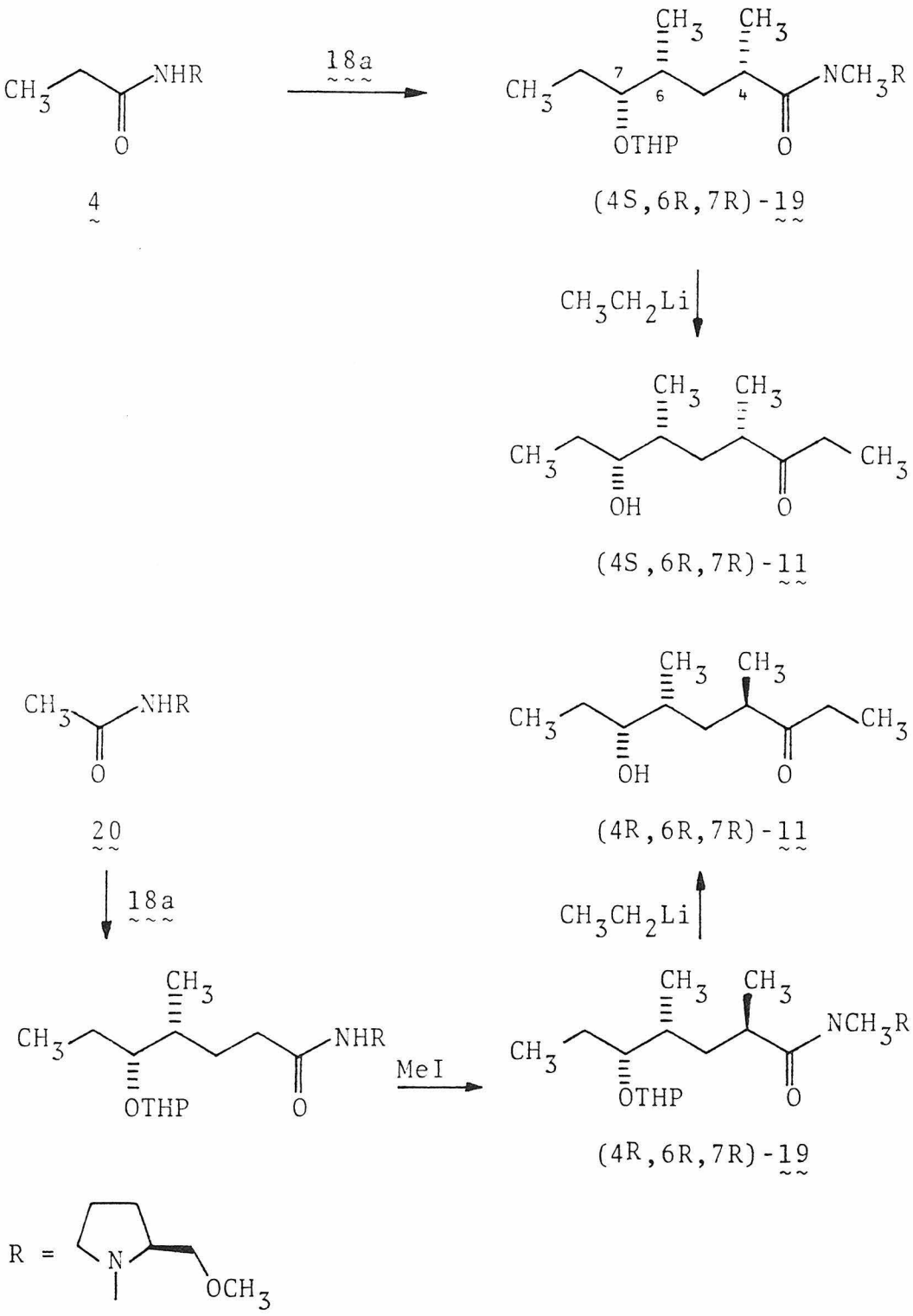
R = $C_4H_9Ph_2Si-$

quenching with methyl iodide should give (4S,6R,7R)-19. Addition of ethyllithium[10] and removal of the THP protecting group would yield (4S,6R,7R)-11. By using amide 20 and first alkylating with 18a followed by methyl iodide, (4R,6R,7R)-19 would be available. Reaction with ethyllithium would then yield (4 ,6R,7R)-11. In a similar fashion the other six diastereomers should be available.

Each synthesized diastereomer should be enantiomerically pure at C_6 and C_7. If the third center (C_4) were not adequately pure following the alkylation step, intermediate 19 could be purified by conventional chromatography[25] since this now involves merely a separation of diastereomers. Application of this method should supply large enough quantities of the eight diastereomers for biological testing of each pure diastereomer as well as mixtures.

The preparation of the pheremone 11 outlined above provides a reasonable beginning project for testing the applicability of the proposed asymmetric alkylation reaction. Applications to asymmetric aldol reactions might also be successful[26]

Scheme VIII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NHR
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4
18a
CH3
CH3
7
6
4
CH3
NCH3R
OTHP
O
(4S,6R,7R)-19
CH3CH2Li
CH3
CH3
CH3
OH
O
CH3
(4S,6R,7R)-11
CH3
NHR
O
20
CH3
CH3
CH3
OH
O
CH3
(4R,6R,7R)-11
18a
CH3CH2Li
CH3
CH3
NHR
OTHP
O
MeI
CH3
CH3
CH3
NCH3R
OTHP
O
(4R,6R,7R)-19
R =
N
OCH3

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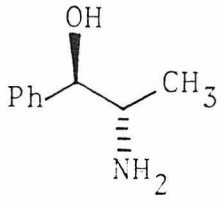
PROPOSITION II

Abstract: The utilization of cuprate reagents for asymmetric synthesis is proposed.

The 1,4 addition of cuprate reagents has proven extremely useful to the synthetic chemist.[1] During the last ten years several attempts have been made to induce asymmetry in the 1,4-addition reaction.[2-4] Addition of chiral complexing agents such as ephledrine (1)[2b] and sparteine (2)[2c] have met with only marginal success (6-10% ee). Preparation of "chiral-cuprates" such as 3[2a,f] have also not met with much success. The best results to date have been those of Kawana[2e] and Meyers[3] who chose to modify the enone partner. Meyers' oxazolines have routinely afforded 70% ee[5] or better. Unfortunately, the nucleophile must be an organolithium reagent, thus precluding any base sensitive functionality which may be present. Also, since this method relies on initial derivatization of an acid, it is not applicable to substrates like α,β-unsaturated ketones, thereby limiting its generality. While Kawana's method, using α,β-unsaturated esters derived from carbohydrates permits the use of the milder cuprate reagents, it too relies on derivatization of an acid. To overcome these

difficulties two new approaches to asymmetric cuprate reactions are proposed.



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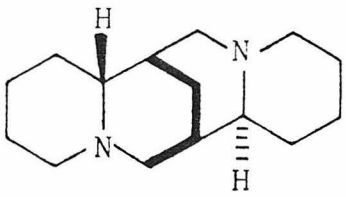

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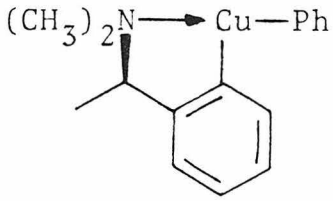

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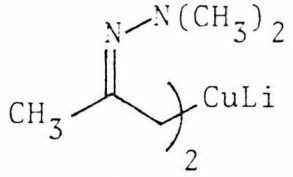
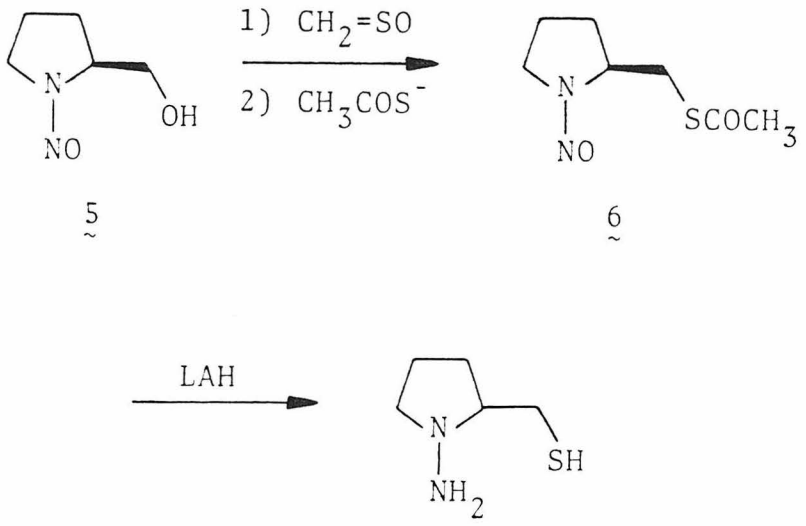
The first of these methods is based on a recent report by Corey and Enders.[6] They found that the cuprate (4) derived from dimethylhydrazone anions would undergo 1,4-addition to α,β-unsaturated ketones. If a chiral unit



4

could be incorporated into the hydrazone, asymmetric induction should result. The easiest way to incorporate chirality might be by use of the hydrazine 7, whose synthesis is depicted in Scheme I. Treatment of the known N-nitroprolinol[7] (5) with sulfene and displacement of the mesylate with thioacetic acid anion would give the

Scheme I

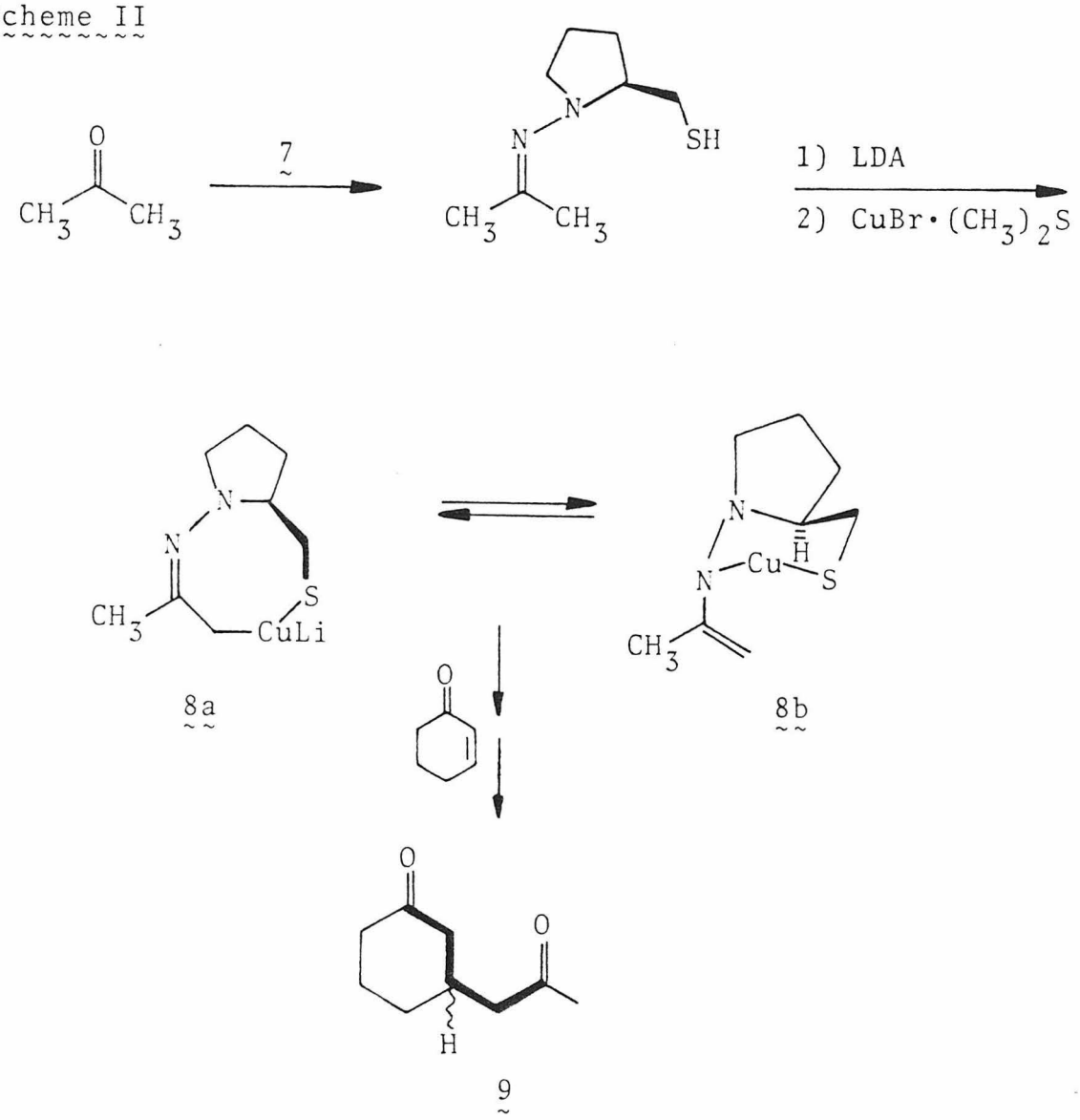


5 6 7

thioacetate 6, which would be reduced with lithium aluminum hydride[7] to yield the desired hydrazine 7. Hydrazone formation followed by deprotonation and transmetallation with $CuBr\cdot(CH_3)_2S$[8] should give a cuprate which would be capable of asymmetric conjugate additions. For example, if acetone were converted to cuprate 8, reacted with cyclohexenone and hydrolyzed,[7,9] the 1,5-dicarbonyl 9 would be obtained (Scheme II).

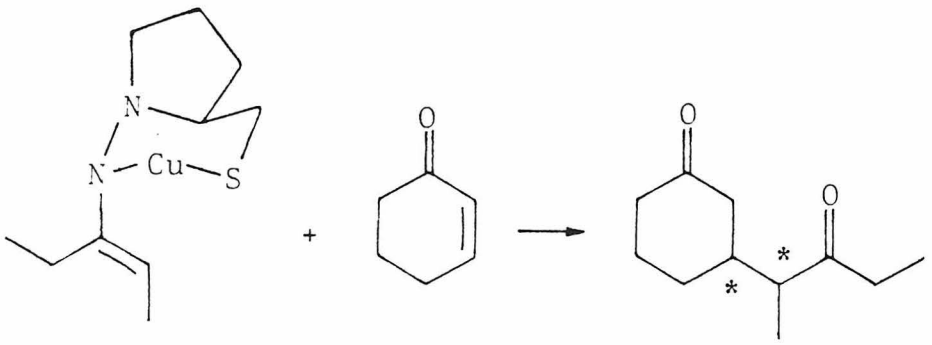
This approach to asymmetric cuprate reactions suffers from two basic problems. First is the lack of generality of cuprate substrates since only aldehydes and methyl or symmetrical ketones can be used. The product must there-

Scheme II



fore contain a carbonyl which, in some cases, might result in extra steps for its removal. If an unsymmetrical ketone were used, the regiochemistry of deprotonation, unless controlled, would give rise to more than one product. However, use of a symmetrical ketone would allow the possibility of introducing two asymmetric

centers in one C-C bond forming step as illustrated in equation 1. The second problem is that since the direction of equilibrium between 8a and 8b is unknown



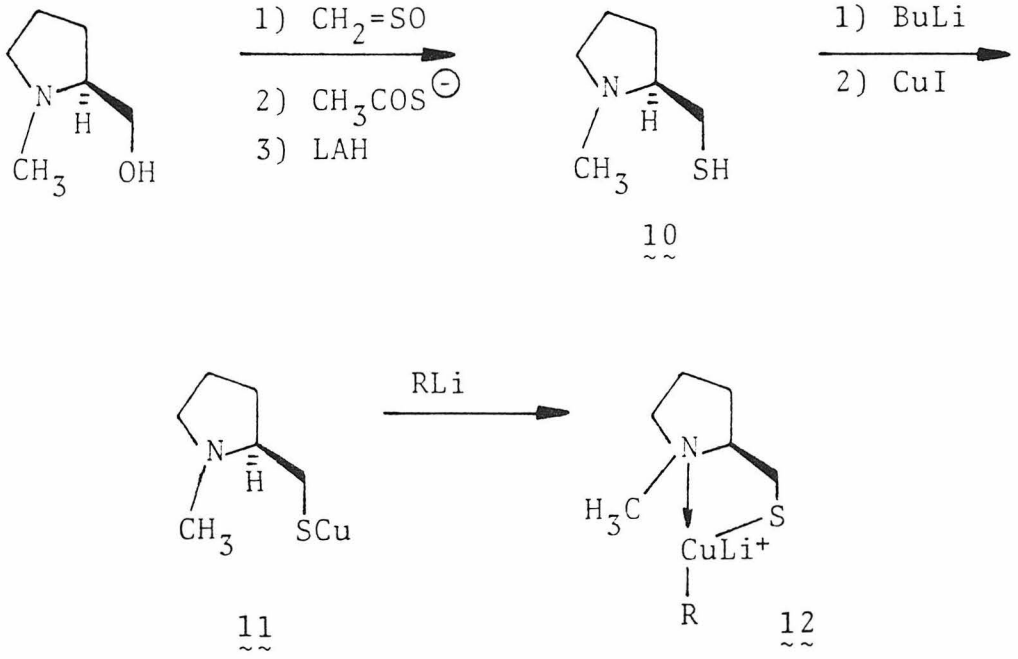
(1)

and since the mechanism of the cuprate 1,4-addition reaction is still in doubt,[1,10] no predictions as to direction or extent of asymmetric induction can easily be made a priori. Similar to this approach and suffering from the same faults, would be utilization of chiral imines rather than hydrazones (Scheme III).[11]

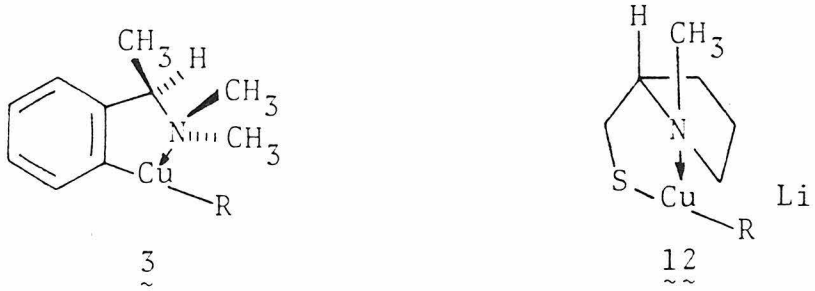
Scheme III

An alternative to the above method would be to use a cuprate derived from 10, the synthesis of which is displayed in Scheme IV. Mesylation of N-methylprolinol, displacement with thioacetic acid anion and reduction with lithium aluminum hydride would give the thiol 10. Formation of the lithium thiolate and quenching with cuprous iodide[12] would yield the copper reagent 11. Addition of an organometallic would then afford the mixed hetero cuprate reagent 12.

Scheme IV



Utilization of 11 would permit use of cuprates other than those derived from carbonyl containing reagents thereby increasing the generality of the method. As noted earlier, chiral cuprates similar to 12 (ie. 3[2a]) were investigated and found to give only low asymmetric yields. Comparison of 3 and 12, however, reveals that in 12 the copper is in a more highly ordered, less symmetric environment than in 3 (see Figure 1). The chiral environment of 3 is provided entirely by a methyl group which is two atoms removed from the copper center



3 12

Figure 1

whereas the chiral environment in 11 is provided by a cis-fused (3,3,0)-bicyclooctane. Again, as for systems like 8, the direction and magnitude of asymmetric induction are difficult to predict due to a lack of necessary information about the mechanism of the reaction.

Study of the above reactions should prove useful for organic synthesis. If successful, they would allow asymmetric synthesis of a wide range of molecules now constructed by cuprate additions.[1] Even if the asymmetric induction were low, the direction and magnitude of asymmetry could yield valuable information as to the mechanism of 1,4-addition.[13] For example, one proposed mechanism is e^- transfer followed by transfer of the alkyl group. From this mechanism one might expect fairly low levels of asymmetric induction. Alternatively, a mechanism involving a charge transfer complex followed by formation of a Cu^{III} intermediate has been proposed. Since the copper atom is effectively chiral, high levels of asymmetric induction might be expected from this mechanism.

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PROPOSITION III

Abstract: A modification of current therapeutic methods for the treatment of aphasia is suggested. The limitations and risks are discussed.

> "Communicate: 1) share, impart, partake...to make known: inform a person of...convey knowledge or information of...to send information or messages back and forth: speak, gesticulate or write to another to convey information: interchange thoughts...."[1]

For most of us communication is a way of life. We take for granted that everyone can learn to communicate. We assume that after a certain age communication will remain with us for life. The entire basis of civilization is founded on communication. Unfortunately, for a large number of the population, communication is extremely difficult. Even being understood may be impossible, yet these same people may be fully cognizant of their surroundings and what is being said to them. Unable to answer a question verbally, some may be able to answer in writing. Unable to name a common object (eg. a fork), some can describe its function (used to eat food; can be used to pick up food, etc.). Unable to verbally reply to a question (What is a ball?), they can pick the requested object out of a group of objects. This class of people

have one thing in common, they all suffer from a language disorder.

Language disorders can be subdivided into two broad categories, dysarthria and aphasia. Dysarthria is any one of a number of motor disorders which affect speech.[2] It can be further subdivided into subgroups, based on age of onset, etiology (cause), neuroanatomic area of impairment (part of central nervous system, CNS, affected), cranial nerve involvement, speech process involved or disease entity. All of the dysarthrias are similar in that they are motor dysfunctions caused by some form of injury or insult of the motor control processes of the CNS. Quite often they can be treated merely by a repetition type of therapy, similar to treatment given to paralysis victims. That is, as the impaired motor systems are called upon to do work, the patient can learn to regain control of the muscles. This may be the result of new neural connections being made in the CNS but no hard evidence of that is available. Aphasia, on the other hand, although also caused by CNS injury is ascribed to injury of higher sections of the brain, the so called speech centers.[3] Whereas dysarthria is characterized by impaired motor function, for example, difficulty in placement or movement of the tongue, weak or non-responsive jaw muscles, lack of control of the larynx

musculature, aphasics may show none of these symptoms. Aphasia, then, is a speech disorder characterized by inability to make a correct response despite the fact that, at least physically, the patient is capable of making the response. Three of the more common broad classifications of aphasia; Broca's aphasia, Wernicke's aphasia and amnesic aphasia; are represented in Table 1 to further clarify the problems suffered by aphasics.[4,5] The three examples are, of course, very simplified. None of them is usually manifested in a pure form. Also, depending on the severity of the insult to the CNS, aphasics may additionally suffer from dysarthria.

Aphasia is believed to be caused by an injury to speech centers, specifically areas in the left hemisphere. For many years scientists have believed that the brain is asymmetric, that the two halves perform different functions. By a series of ingenious techniques designed to feed information selectively to either the left or right hemisphere they have shown that, generally, the left hemisphere controls language and is better at discriminating letters and verbal features whereas the right hemisphere is better for nonsense figures, recognition of faces and spatial discrimination.[5,6] The left hemisphere, since it is the one which communicates, has also been designated as the dominant hemisphere.[7] That is,

Table 1[a]

Below is an outline of the characteristics of three common forms of aphasia. At the end of each description is an example of how each class might respond to a question.

Broca's aphasic: expressive disorder, poor articulation, telegraphic speech mostly of content words, impoverished or impaired grammar.

How was your Easter holiday?

"Uh, uh, uh, Easter...ho, ho, ho holiday...I like... eat turkey...many lights...people...very good."

The speech is labored and the patient is aware of his own deficit; may become depressed about it.

Wernicke's aphasia: impaired auditory language comprehension, fluently articulated but nonsensical speech.

How was your Easter holiday?

"Oh, yes, we have done it. Could be different but nevertheless done. Go, go, gone. And however successful, it still fails. I wish indeed. Good morning."

The patient is often unaware of his own deficit and will deny it vehemently.

Table 1 (continued)

Amnesic aphasia: Word finding difficulties, spoken and written, relatively intact auditory language comprehension.

What is this? (Display a fork.)

"It's a, ah, ah...(eating motions). It's a spoon. No. No. I mean it's a.... You eat with it, a, ah, I can say it."

If prompted with a question -- Is it a knife? -- he will say no, but if prompted with a clue -- "Use your knife and..." -- he can often complete the sentence.

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[a]The above examples are excerpted from ref. 5.

in order to express itself the right hemisphere must first communicate with the left which then communicates with the outside world (at least verbally). The evolutionary reason and actual physical causes for such a dominance of one hemisphere over another are currently unknown. Recently, morphological studies have uncovered a physical asymmetry between the two hemispheres.[8] Whether this asymmetry is inherent or develops due to some other factor is unknown.

Some of the most exciting results in the area of brain asymmetry come from studies of patients who have undergone a commissurotomy.[9] These are patients who have had the major communication link between the left and right hemispheres (the corpus callosum) surgically severed. These patients are interesting because there is now no communication between the left and right hemispheres. For example, if an object is placed in the patient's left hand (controlled by right hemisphere) while his eyes are closed and he is asked to name it he cannot because the left hemisphere (the one with speech) does not know what the object is. However, if the subject is then asked to pick that object out of a mixture of objects (still without looking) he can do it. By study of these patients Zaidel discovered that the right hemisphere is indeed capable of language but it is in an immature form.[5,10] For some reason, as we develop, the left hemisphere somehow shuts down development of language in the right side. From an evolutionary standpoint, this is probably quite useful since it prevents duplication of effort. Unfortunately, from the point of view of an aphasic it can be disasterous. The current therapy consists mostly of attempts to retrain the patient, which may or may not be successful. If the left hemisphere inhibition of the right hemisphere could be removed, perhaps the right

hemisphere could be trained to communicate. That is the subject of this proposal.

Recently several researchers have found that not only do neurons release neurotransmitters but they also release macromolecules.[11] Further, they have found that if the source of macromolecules is removed from an axon that axon dies.[12] The degeneration then continues down the neural chain. This degeneration has been applied to tracing neural pathways.[11c] One can conceive that the left hemisphere releases some form of inhibitory macromolecule which keeps the language centers of the right side shut down. Alternatively, the shutdown might be caused by release of inhibitory neural transmitters (such as gamma aminobutyric acid).[13] Under normal circumstances the fact that the right hemisphere lacks speech is unimportant. But, when the left hemisphere suffers injury to the speech areas then the inability becomes a disability. Even though the left hemisphere speech centers are disabled the right side centers may be unaffected, but they are still unuseable. If the inhibition could be removed perhaps the right side could be taught to speak.[14] At first, this seems like an insurmountable task due to the complexity of the human brain but it may not be as complex as it seems. The first task would be to locate the neuronal network responsible for the inhibition.

Second that network would have to be shut down without excessive damage to the surrounding CNS.

One promising new method for tracing neuronal paths might be applicable to locating the necessary network. Graybiel[11b] and others[15] have found that injections of radiolabeled amino acids are incorporated into the macromolecules which are transported by neurons. Injection of the active amino acids into the cellular matter of the left speech center or surrounding tissues might allow the mapping of the inhibitory network. In order to shut that network down two methods could be considered. Either a mechanical destruction by cutting or freezing could be used or a drug which inhibits neuronal transmission could be applied topically. Recent findings by Feldberg[16] indicate that the brain (at least for cats) is sensitive to the topical application of drugs. Studies have indicated that if the right hemisphere speech center could be freed from inhibition it would be capable of learning communication skills.[8,14,17]

The limitations and risks of the proposed studies are fairly obvious. The major limitation is suitable cases. The patients would have to be people who had suffered left hemisphere brain damage without corresponding right side damage. Additionally, they would have to be willing to risk more severe damage or possibly death. One

interesting possibility which would be more ethical than experimenting on human beings, would be to utilize primates or dolphins. Both of these species have been shown capable of communication. Studies to determine whether their brains are asymmetric in function might prove invaluable to further understanding of the human brain.

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14. Recent studies by Zaidel with split brain patients reveals that the right hemisphere can understand complex speech.[17a] Also, left side lesions in females, whose brains show less differentiation than males, are not as detrimental to speech as are similar lesions in men,[8,17b] indicating that perhaps the right side takes up some of the language function formerly controlled by the left side.

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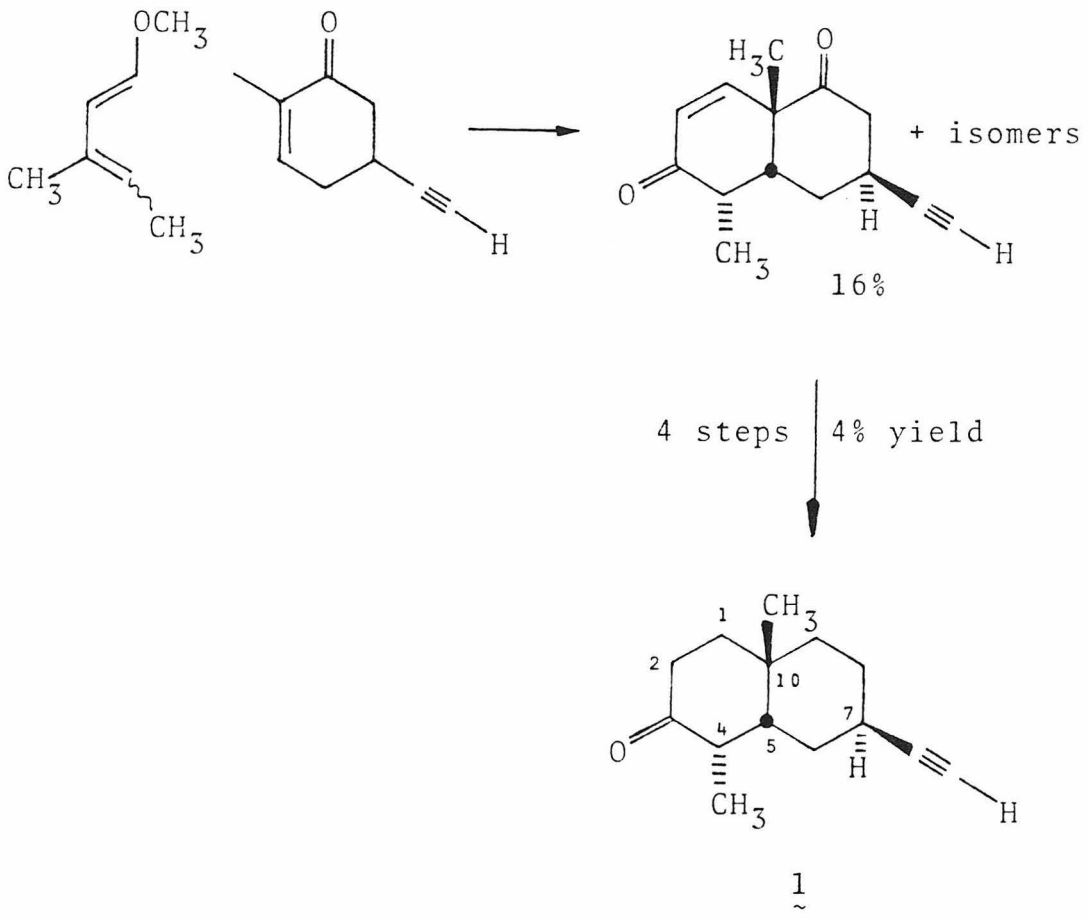
PROPOSITION IV

Abstract: Synthesis of chamaecynone by an intramolecular Diels-Alder Reaction is proposed.

Chamaecynone (1) was originally isolated from Chamaecyparis formosensis Matsum., Cupressaclae.[1] Investigation of the termite-resistant quality of the wood from this tree revealed that Chamaecynone was the active agent.[2] To date, two syntheses of this natural termiticide have been published.[3,4] The first,[3] based on modifying α-santonin, is inefficient from a standpoint of overall yield and number of steps required. Recently, a shorter route, based on an intermolecular Diels-Alder reaction (Scheme I), was published.[4] The cycloaddition, however, gave a low yield of a mixture of three diastereomers. Since intramolecular versions of the Diels-Alder reaction generally give better isomer ratios and higher yields than do the corresponding intermolecular counterparts, application of an intramolecular Diels-Alder approach to Chamaecynone is proposed.

The retrosynthetic approach to 1 (whose preferred conformation is 1'[5b]) is outlined in Scheme II.[5a] Disconnection of bonds a and b reveals that an intramolecular Diels-Alder could be used to control the

Scheme I



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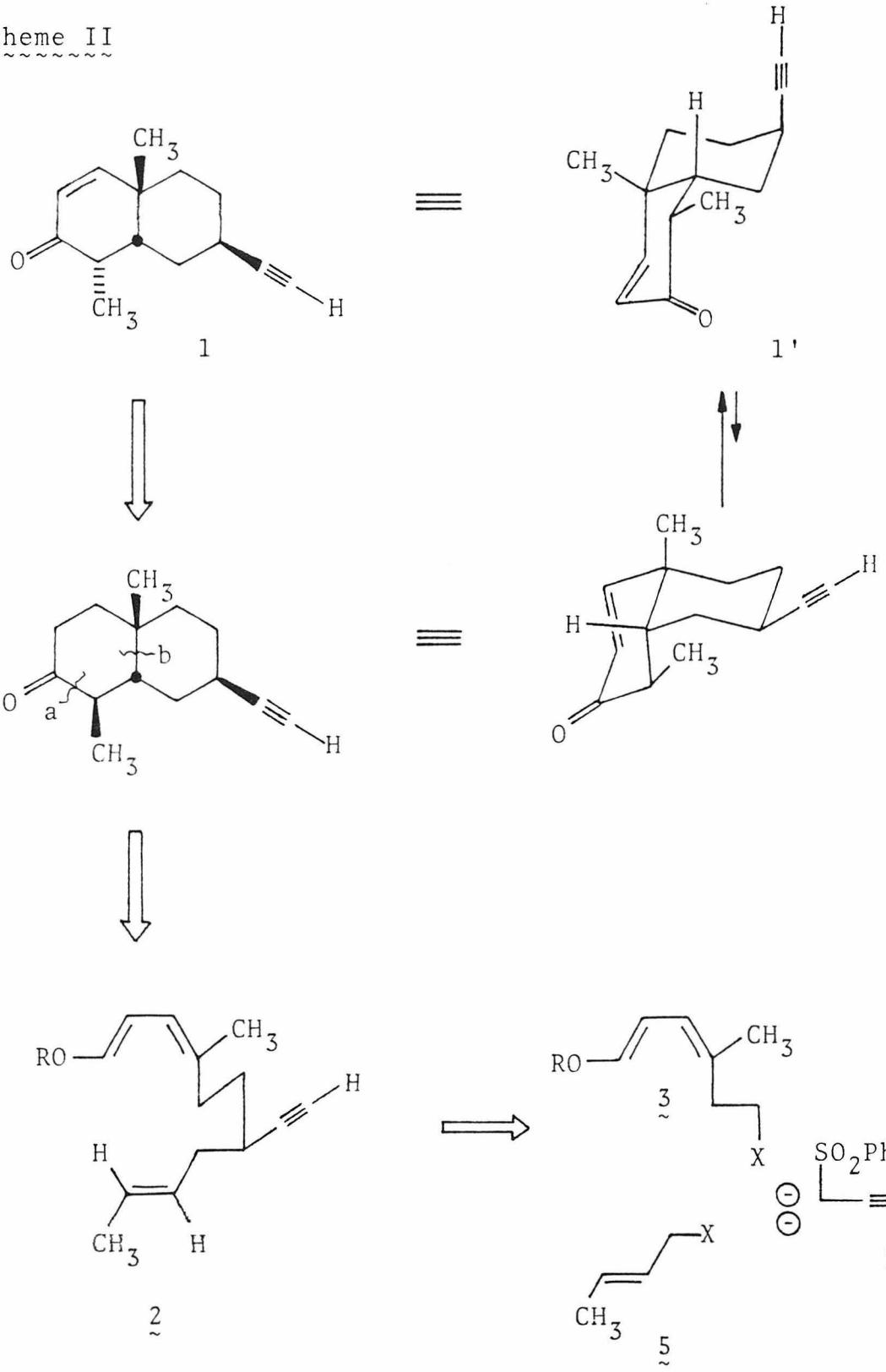
relative stereochemistry of three of the four required stereocenters (control of the fourth center, C_7, will be discussed below). Diene 2, could be obtained from diene 3, dianion 4 and olefin 5.

Since the key step in the proposed synthesis is the intramolecular cycloaddition, further discussion of the stereo- and regiochemical outcome of that reaction is important. During the last ten years, the intramolecular

Scheme II


CH3
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X
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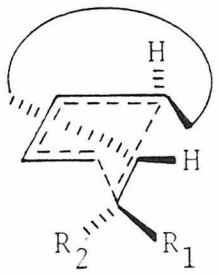
5

version of the Diels-Alder reaction has played a key part in many syntheses. Some of these applications have recently been reviewed by Oppolzer.[6] The most important aspect of the Diels-Alder is that four new stereocenters can be formed in one step. Due to steric constraints imposed by intramolecularity, the normal endo- and ortho rules[7] for predicting products do not always apply.[6a] Examination of the six possible transition states for an intramolecular Diels-Alder[6a] (Scheme III) reveals that for cis-dienes, the transition state leading to cis-fused rings (B), is favored over that leading to trans fused rings (A) even though B requires an exo transition state. Also, annelated (B) rather than bridged (C) adducts are generally favored.[6a] However, in the case of trans-dienes, either cis-(D) or trans-(E) fused rings may result, while bridged systems are generally not observed, presumably because transition state F is too strained. Therefore, control of the olefin geometries (i.e., $\underset{\sim}{2}$) would give the cis-fused decalin with the correct relative configurations at C_5 and C_{10}, with the configuration at C_4 controlled by equilibration.[5]

The last remaining consideration is the fate of the stereocenter at C_7. Although no close analogies exist, reports by Wilson[8] and more recently Taber[9] indicate that a stereocenter located on the carbon chain linking

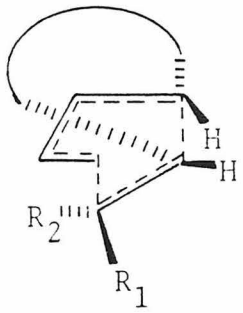
Scheme III

cis-dienes

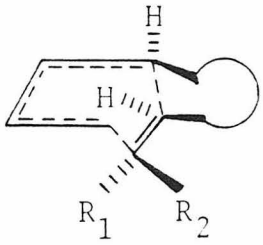


A (strained)

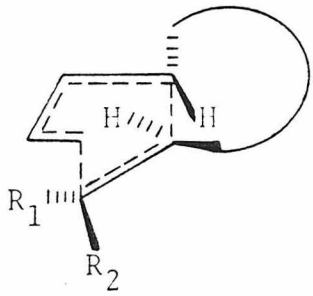
trans-dienes



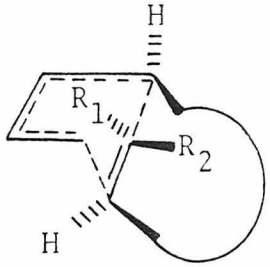
D



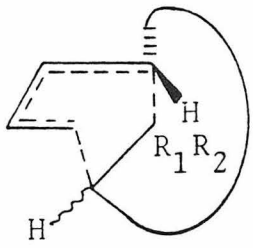
B (favored)



E



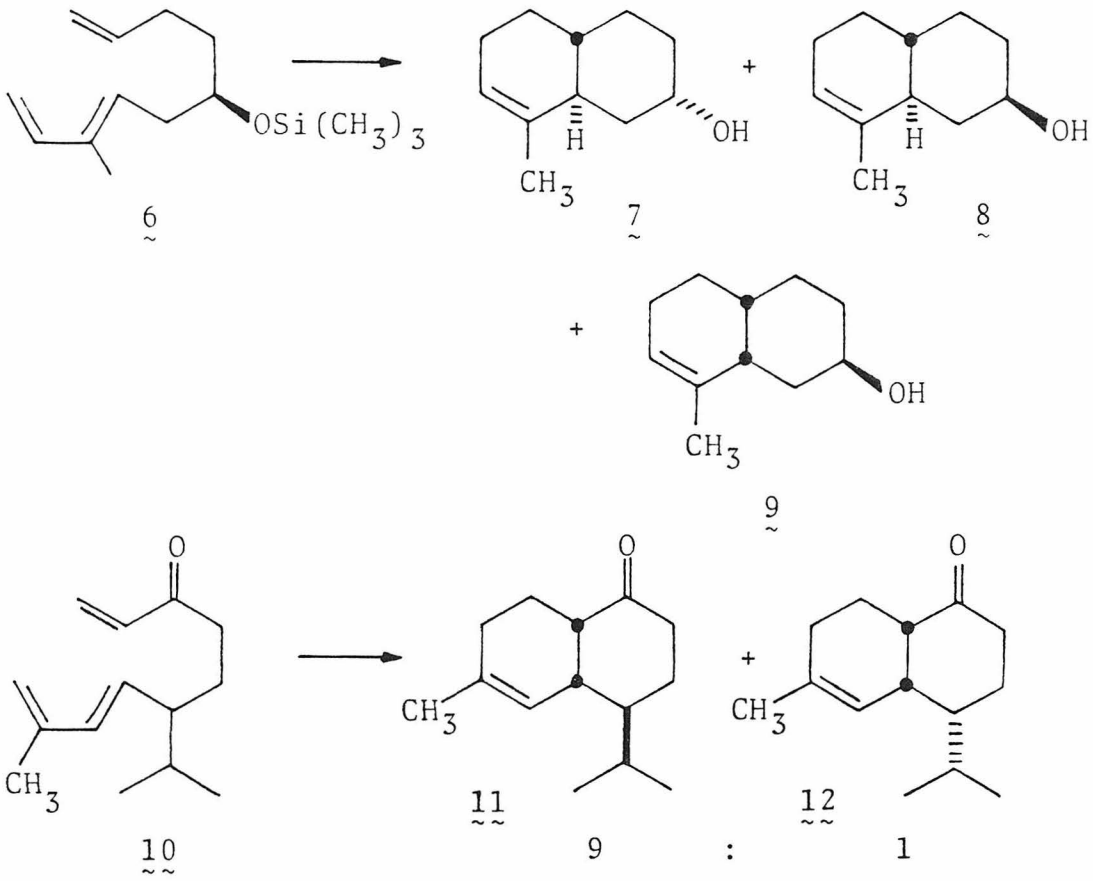
C



F (strained)

the diene and dienophile can have a profound effect on the configurations at the newly formed stereocenters. Thus, 6[8] gave both trans-fused products (7 and 8) but only one cis-fused product (9), while 10[9] gave only 11 and 12 (Scheme IV). Examination of models of 2 reveals that either the boat, or chair transition states should give the correct configurations at C_5, C_7 and C_{10} as shown in Scheme V.

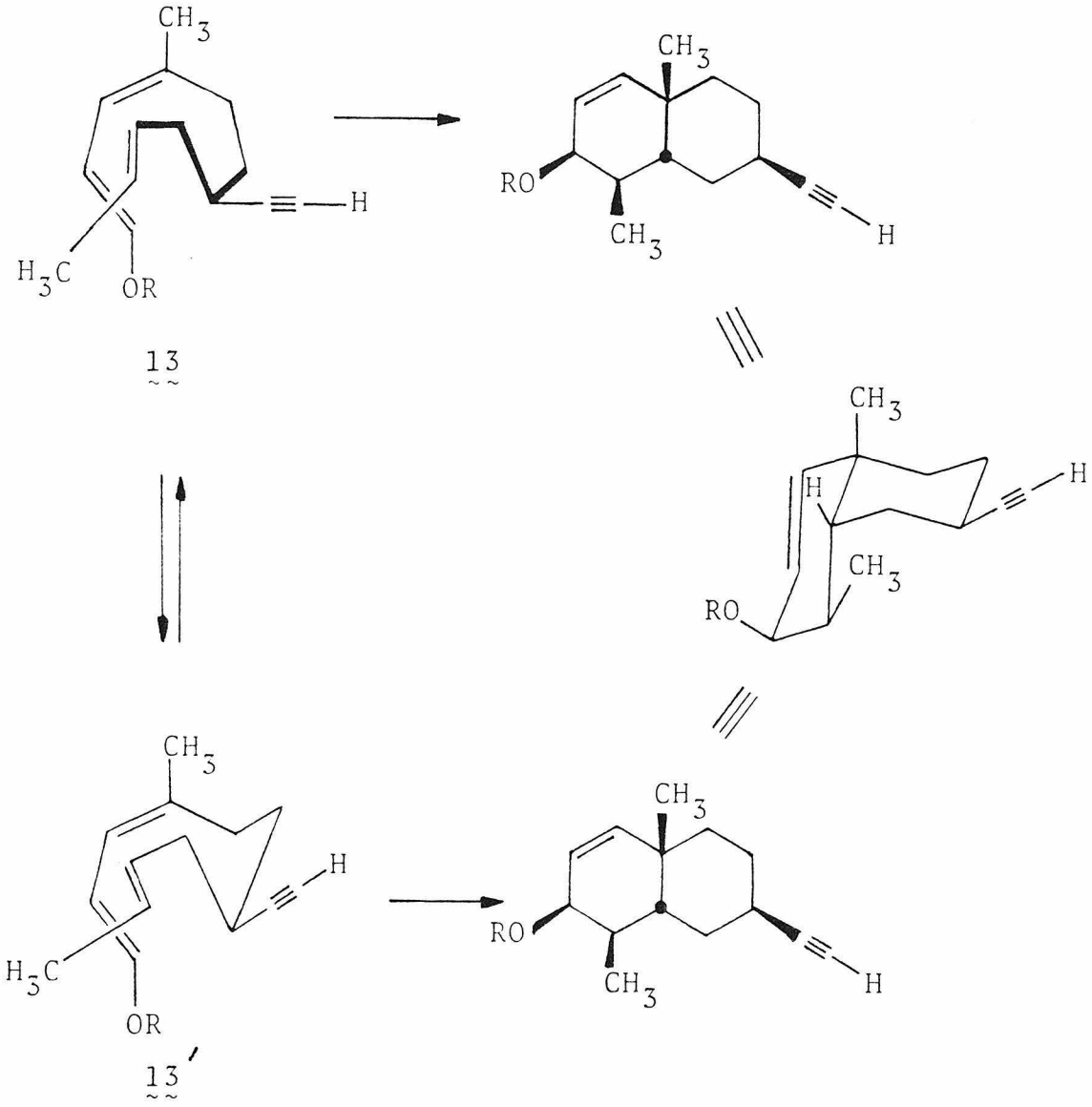
Scheme IV



6 7 8 9 10 11 12

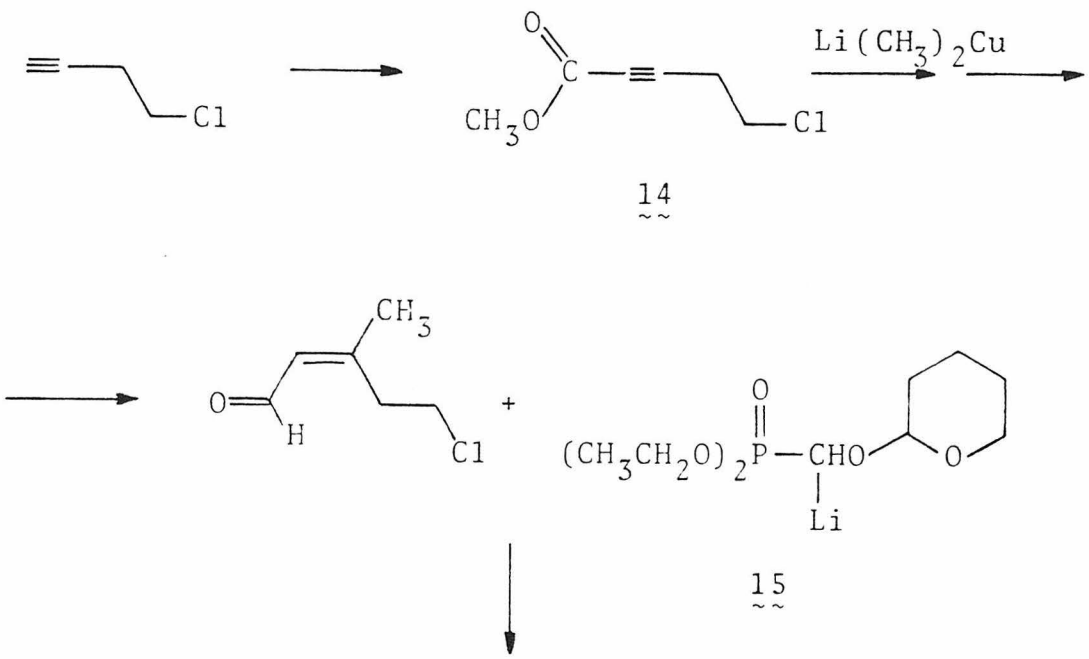
9 : 1

Scheme V



The synthesis of the diene component (3, R = C_5H_9O) is outlined in Scheme VI. Treatment of the anion of 3-chloro-1-butyne with diethyl carbonate should give the ester 14. Reaction of 14 with $Li(CH_3)_2Cu$,[10] reduction to the alcohol,[10] oxidation[11] and Wittig

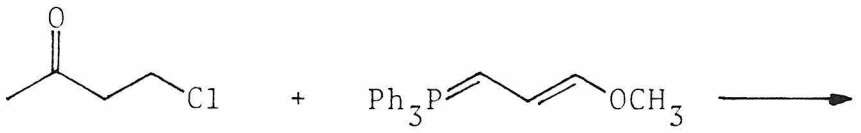
Scheme VI



reaction of the resulting Z-aldehyde with phosphonate 15[12] would yield diene 3, with the desired E,Z-diene-olefin predominating. If necessary, the intermediate 1,3-adducts from the phosphonate addition could be isolated and separated before elimination to give stereochemically pure 3. Alternatively, 3 (R = CH_3) could be prepared by Wittig reaction of 1-chloro-3-butanone with the ylide developed by Martin (Scheme VII).

The final steps of the synthesis could be completed

Scheme VII

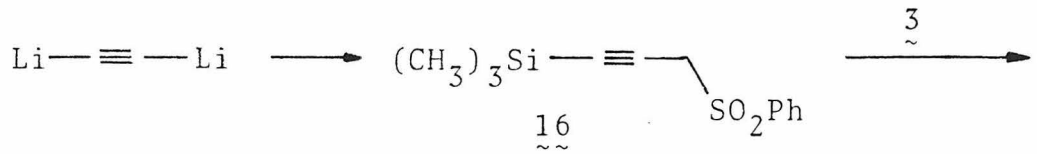


3 (R = CH_3)

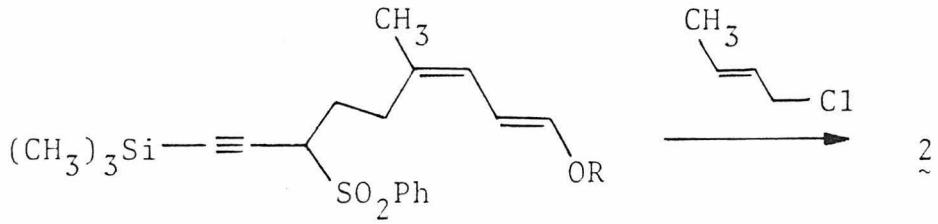
as outlined in Scheme VIII. Acetylene dianion could be alkylated by chloromethyl phenylsulfone[14] and trimethylsilylchloride to give acetylene 16. Anion formation and then quenching with 3[14] would give diene 17. Anion generation a second time and quenching with trans-1-chloro-2-butene would give the desired diene 2.[14] Removal of the sulfone group by Al(Hg) reduction,[15] Diels-Alder reaction and removal of silicon (nBuLi or F^-) would give the cis-decalin 18. Removal of the alcohol protecting group, oxidation and epimerization[5] would then afford Chamaecynone (1).

This approach to Chamaecynone is attractive because of the stereochemical control made possible by using an intramolecular Diels-Alder reaction. It is also efficient because of the high degree of convergency and the minimum amount of refunctionalization necessary.

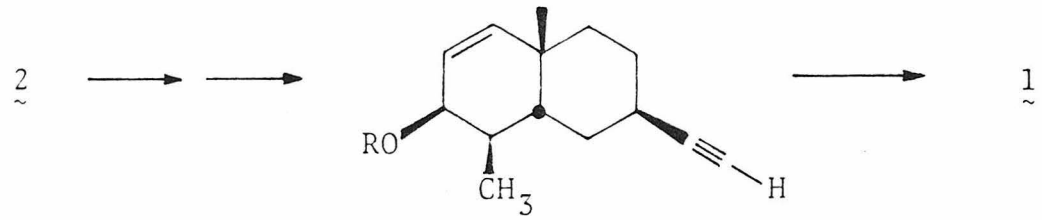
Scheme VIII



16



17



18

R = CH_3 or C_5H_9O

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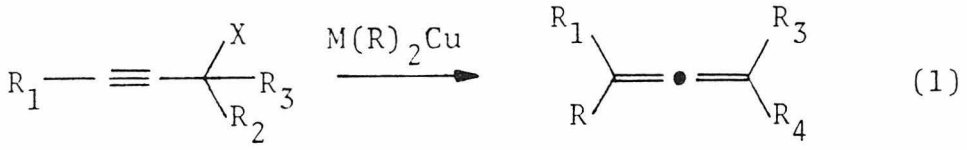
PROPOSITION V

Abstract: A mechanism for the reaction of cuprates with propargylic alcohol derivatives is proposed.

Organocopper and cuprate reagents have received a lot of attention. Due to their ability to form carbon-carbon bonds without disturbing sensitive functionality, they have proven extremely useful.[1] Unfortunately, the available information about the mechanism of these reactions has not kept pace with the information on synthetic applications.[1-4] The little that is available is often confusing and contradictory. Contributing to the confusion is the lack of careful systematic studies utilizing similar reagents, solvents and substrates. Also, different types of bond forming reactions seem to proceed by different mechanisms. For example, 1,4-conjugate addition seems to occur *via* an initially formed charge transfer complex followed by e^- transfer and alkyl migration.[5] Some authors also imply that a Cu^{III} intermediate may form but no firm evidence has been found to support such a claim.[2] Coupling with halides and tosylates, on the other hand, seems to proceed *via* a simple nucleophilic displacement, but the exact nature of the S_N2 process is not clear.[4] Some authors support a direct displacement of the leaving

group by the alkyl of the cuprate while others prefer to consider a S_N2 by copper to give a Cu^{III} intermediate which undergoes reductive elimination.[6] Compounding the confusion is the fact that variations in purification of reagents, differences in cuprate ligands and counterions, trace impurities, different solvents and inorganic salts can all have profound effects on the course of the reaction.[7]

One of the more interesting reactions now being utilized in cuprate chemistry is that of allene formation from propargylic alcohols and their derivatives as shown in equation 1 (X = leaving group). Several mechanisms

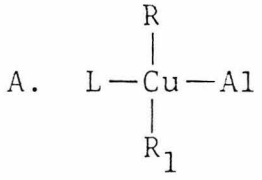
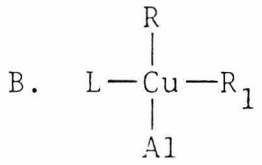
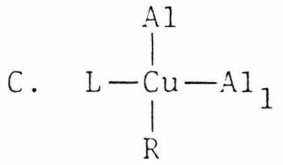
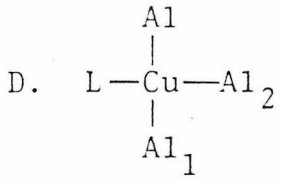


(1)

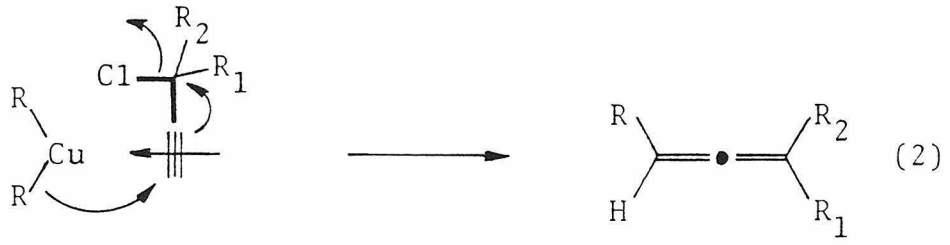
can be postulated which explain the overall transformation. Pasto, et al.,[8] postulated an initial charge transfer complex which then went to products (eq 2) via transfer of an alkyl group in an S_N2' type of reaction. Based on an analogous study of organoaurates,[9] Pasto ruled out an intermediate Cu^{III} intermediate (Scheme I).

However, studies by Crabbé[10] strongly implicated a

Scheme I

		Predict	Observe
A.		$RAl + R_1Al$	$RAl + R_1Al + RR_1$
B.		$RR_1 + R_1Al$	RR_1
C.		$Al\text{-}Al_1 + RAl_1$	RAl_1
D.		$AlAl_2 + Al_2Al_1$	no allenes

L = ligand, Al = allene, R - alkyl

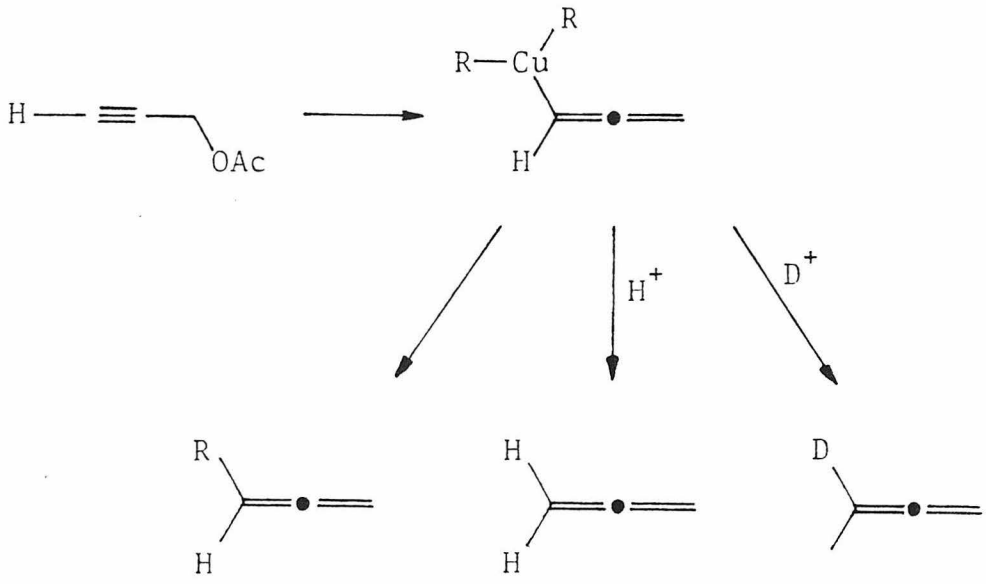


(2)

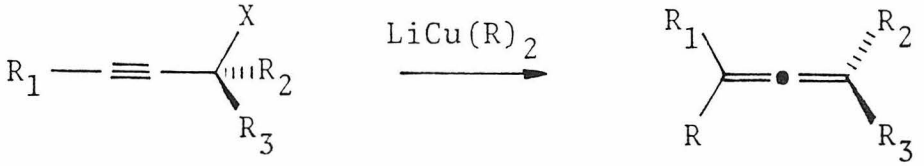
Cu^{III} intermediate. Crabbé found that if the reaction were carried out at low temperature and quenched, not only were the expected alkylated allenes observed but also reduced allenes were found. By changing the temperature and reaction time he could obtain varying ratios of alkylated or reduced allenes, the alkylated product being favored by longer reaction times or higher temperatures. Further, he showed that the proton source for the reduction did not originate from solvent or the cuprate reagent but from the quenching reagent (Scheme II). Crabbé therefore postulated an S_N2' reaction to give an initial Cu^{III} allene which could reductively eliminate or be quenched during workup.

A glaring inconsistency is readily apparent. Pasto's evidence precludes a Cu^{III} intermediate while Crabbé's evidence requires at least a metalloallene. To further compound the confusion Crabbé, Pasto and others have shown that if the carbon bearing the leaving group is

Scheme II



chiral,[8,10,11] a chiral allene results with the configuration of the major enantiomer best explained by a S_N2' reaction that proceeds in an anti manner (eq 3). To

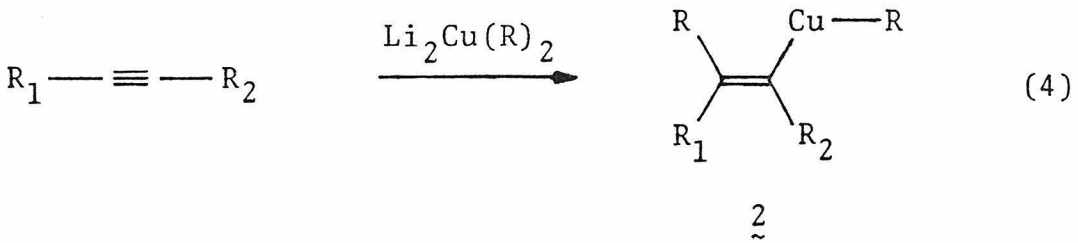


(3)

explain all of the available data an alternative mechanism is proposed which entails an initially formed vinyl-Cu^{III} intermediate as shown in Scheme III.[12]

This mechanism is consistent with the Pasto findings in that the results of the control experiments Pasto performed are not applicable. The results of Crabbé may be rationalized by supposing that at low temperature the rate of rotation (k_2,) and elimination (k_3,) for 1 are competitive with the alkylation path (k_1 and k_2). That is, this mechanism presumes the rate of alkyl transfer is more sensitive to temperature than is the rate of rotation and elimination, implying that (if this mechanism holds) alkyl transfer might be intermolecular.[13]

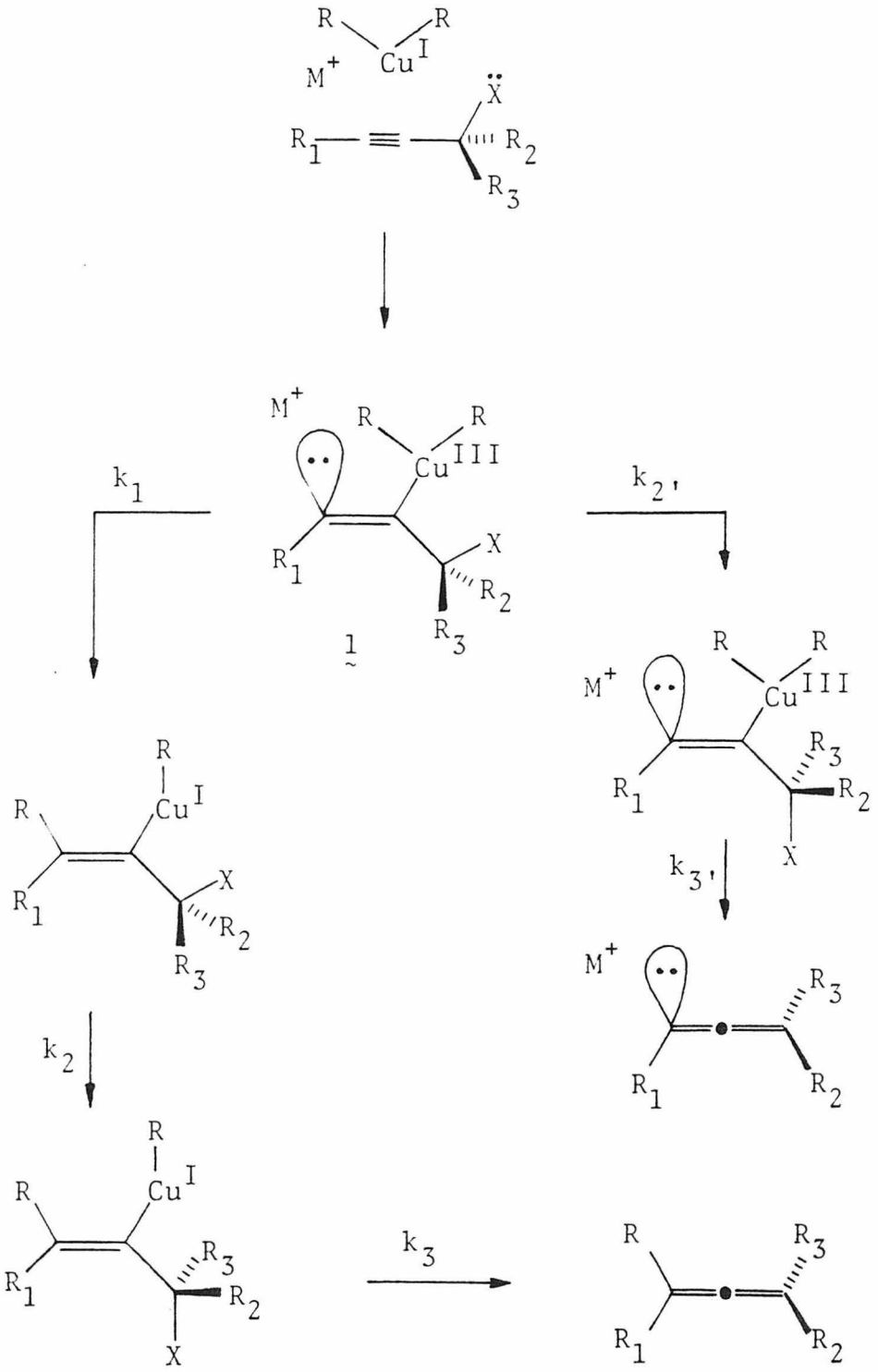
Other supportive evidence of this mechanism comes from studies of the reaction of cuprates with acetylenes. Several authors have shown that cuprates do indeed add to acetylenes in a cis fashion to give an intermediate vinyl cuprate (2) (eq 4). Also directive effects of acetals have been noted. Studies of the metallation



(4)

2

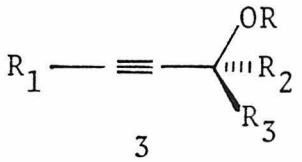
Scheme III


R
R
Cu I
M+
X
R1
R2
R3
M+
R
R
Cu III
R1
X
R2
R3
1
k1
k2'
R
Cu I
R
R1
X
R2
R3
M+
R
R
Cu III
R3
R1
R2
X
k3'
k2
M+
R3
R1
R2
R
Cu I
R
R1
R3
R2
X
k3
R
R3
R1
R2

of heterosubstituted aromatics and vinyl groups have also indicated a strong kinetic and syn-directing effect by heteroatoms.[14] That would explain the high levels of asymmetric induction possible.

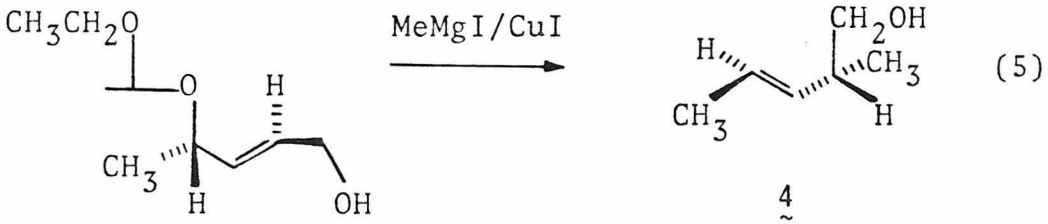
Further tests of the proposed mechanism are immediately obvious. If the alkylation step is indeed intermolecular then changes in concentration should have a dramatic effect on the rate of formation of the alkylated allene. Also, the intermediate vinyl anion could be trapped by reaction with carbonyls. Cuprates are known to be very unreactive toward ketones. Thus if the intermediate could be trapped that would be strong evidence against Crabbé's mechanism and in favor of Scheme III.[15] Another possible test might include low temperature Li, ^{1}H and ^{13}C-NMR examination of the allenes. Since both copper and lithium allenes should be readily available,[8,16] comparison of the experimental spectra with the authentic samples should be productive. Finally, an examination of a series of O-alkyl acetylenes (3) in which the relation between the level of asymmetric induction and the electron donating ability of the oxygen would allow a determination of the importance of the leaving group on the course of the reaction.[17]

Another interesting aspect of the proposed mechanism is that it could also be used to explain some of the



3

results in the reaction of cuprates with allylic alcohols and their derivatives.[18] For example, Claesson[18b] recently reported the reaction in equation 5. He postulated that the reaction went via a π-allyl Cu^{III}

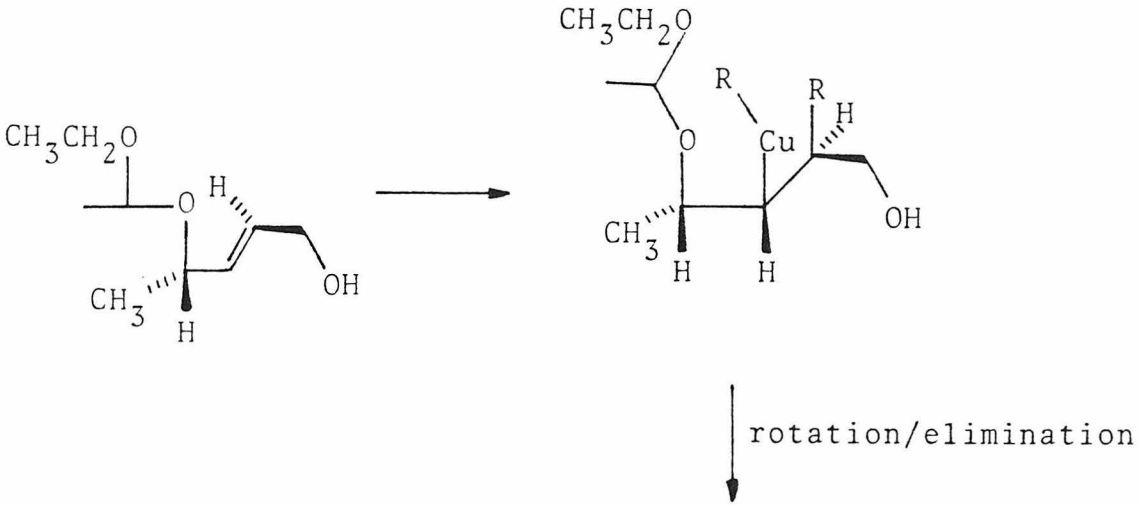


4 (5)

species, but the data are also consistent with an addition across the double bond followed by elimination (Scheme IV). To date however, no examples of cuprate addition to non-conjugated olefins have been observed.[19]

An alternative mechanism for propargylic displacements has been proposed. The new mechanism explains the available data and is amenable to experimental tests.

Scheme IV


CH3CH2O
O
H
CH3
H
OH
CH3CH2O
R
R
H
O
Cu
CH3
H
H
OH
rotation/elimination

4

References and Notes

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Tetrahedron Lett., 4615 (1975); J.-M. Dollat, J.-L. Luche, and P. Crabbé, J. Chem. Soc., Chem. Commun., 761 (1977).

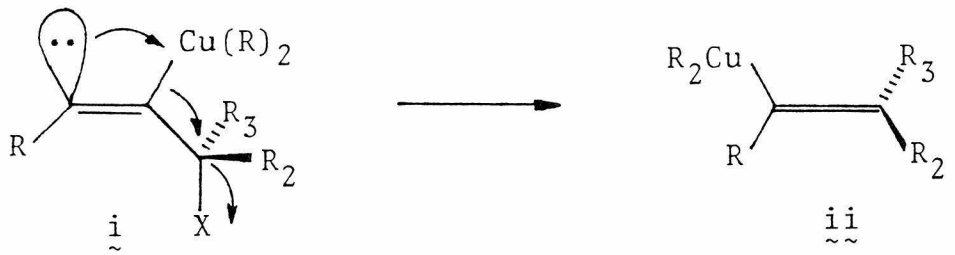
11. W. H. Pirkle and C. W. Boeder, J. Org. Chem., 43, 2091 (1978); W. H. Pirkle and C. W. Boeder, ibid., 43, 1950 (1978).

12. Note that the intermediate Cu^{III} postulated is different than that used in the control experiments by Pasto.[8]

13. Cu^{III} species, if they exist, have been suggested to be alkylating agents.[2]

14. (a) J. J. Eisch and J. H. Merkley, J. Am. Chem. Soc., 101, 1149 (1979); (b) J. J. Eisch, J. H. Merkley, and J. E. Galle, J. Org. Chem., 44, 587 (1979); (c) A. Alexakis, A. Commergon, J. Villiéras, and J. F. Normant, Tetrahedron Lett., 2313 (1976).

15. Even if the capture with carbonyls fails, that does not rule out Scheme III since the elimination reaction might be i → ii.



i ii

16. R. Bandov, F. Delbecq, and J. Gore, Tetrahedron Lett., 937 (1979).

17. By making the oxygen a better e^- donor the levels of asymmetric induction should increase because of the increase in the directing effect on the initial step of the reaction.

18. See: (a) R. J. Anderson, C. A. Henrick, and J. B. Siddall, J. Am. Chem. Soc., 92, 735 (1970); (b) A. Claesson and L.-I. Olsson, J. Chem. Soc., Chem. Commun., 621 (1979).

19. Addition of Grignard reagents across olefins which have a β-hydroxyl group has been reported.[13a,b]