I. THE DIASTEREOSELECTIVE ALKYLATION OF CHIRAL 2-OXAZOLIDINONE IMIDE ENOLATES.

II. EFFORTS DIRECTED TOWARD THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF FERENSIMYCIN B.

Thesis by

David J. Mathre

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1985

(Submitted November 12, 1984)

ACKNOWLEDGEMENTS

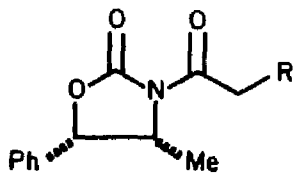
I would like to extend my deepest appreciation to Dave Evans--not only as a premier scientist and educator, but also as a friend. His continued support and encouragement finally brought this project to an end.

I also thank the members of the Evans group, both past and present, for providing a stimulating research environment, as well as for their friendship. I am especially grateful to Mike Ennis and Rick Polniaszek for their contributions to this project.

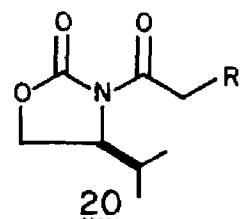
I wish to acknowledge and thank Bob Dow, Kevin Chapman, Vance Novack, and Ann Weber for proofreading various rough drafts of this manuscript. I also thank my father and brother Erik, for providing the computer and word processing program on which this thesis was typed.

ABSTRACT

The diastereoselective alkylation of chiral 2-oxazolidinone imide enolates is described. The requisite chiral N-acyl 2-oxazolidinones are prepared from readily available amino acid and amino alcohol precursors. The lithium and sodium enolates, derived from these chiral imides, react in a highly diastereoselective manner with a variety of electrophiles. Furthermore, the diastereomers are often separable by liquid chromatography affording products with a diastereomeric purity $\geq$ 99:1. Several methods are described for the non-destructive removal of the chiral auxiliary to afford enantiomerically pure alcohols, aldehydes, carboxylic acids, acid chlorides, esters, hydrazides, and ketones. Through the use of chiral imides **16** and **20** either of the enantiomeric products can be obtained.

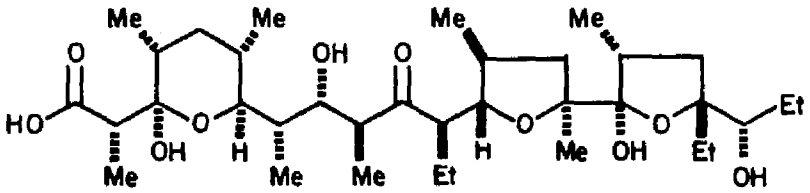


16

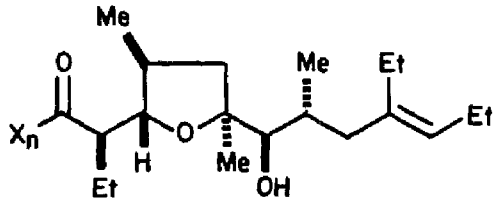


20

An approach to the enantioselective total synthesis of the polyether ionophore antibiotic ferensimycin B (**2**) is described. The synthesis employs the diastereoselective alkylation and aldol condensation of chiral 2-oxazolidinone imide enolates to both construct the carbon backbone and generate the necessary stereocenters. This research has culminated in the preparation of the advanced intermediate **49**.



2



49

An enantioselective total synthesis of (R) and (S)-thiorphan [N-(1-oxo-2-mercaptomethyl-3-phenylpropyl)glycine] via a six-step sequence is reported. The key step, establishing the absolute stereochemistry, is the diastereoselective alkylation of the enolate derived from chiral 2-oxazolidinone imide **16** (R = $PhCH_2$) or **20** (R = $PhCH_2$) with benzyl bromomethyl sulfide. The level of alkylation diastereoselection is in excess of 95:5.

TABLE OF CONTENTS

COMPOUND INDEX

CHAPTER I

DIASTEREOSELECTIVE ALKYLATION OF CHIRAL 2-OXAZOLIDINONE IMIDE ENOLATES

I. INTRODUCTION

Enantiomers can evoke diverse biological responses. (l)-Carvone smells like spearmint, whereas (d)-carvone smells like anise. One enantiomer of an insect pheromone can produce a hundred-fold greater response than the other enantiomer.[1] Only the (S)-enantiomer of the sedative thalidomide causes birth defects.[2] Investigations into the enantiotropic behavior of chiral molecules require that both enantiomers are available. The synthesis of chiral molecules is thus an important aspect of organic chemistry.

The synthesis of both simple and complex chiral molecules hinges on the ability to either acquire or create asymmetry. Chiral molecules can be prepared in three ways: 1) resolving racemic mixtures to afford enantiomers; 2) acquiring asymmetry from available chiral molecules; and 3) preparing chirality by asymmetric synthesis. Each approach is useful for preparing various types of chiral molecules.

The resolution of a racemic mixture is the classical method to obtain an optically active substance. Many resolution techniques are known.[3] But most are not general, and some only resolve a single racemic pair. Unless both enantiomers of a chiral molecule are needed, the resolution of a racemate wastes at least half of the mixture. Only if the racemic mixture is readily obtained and efficiently resolved, is resolution a useful method to procure chirality.

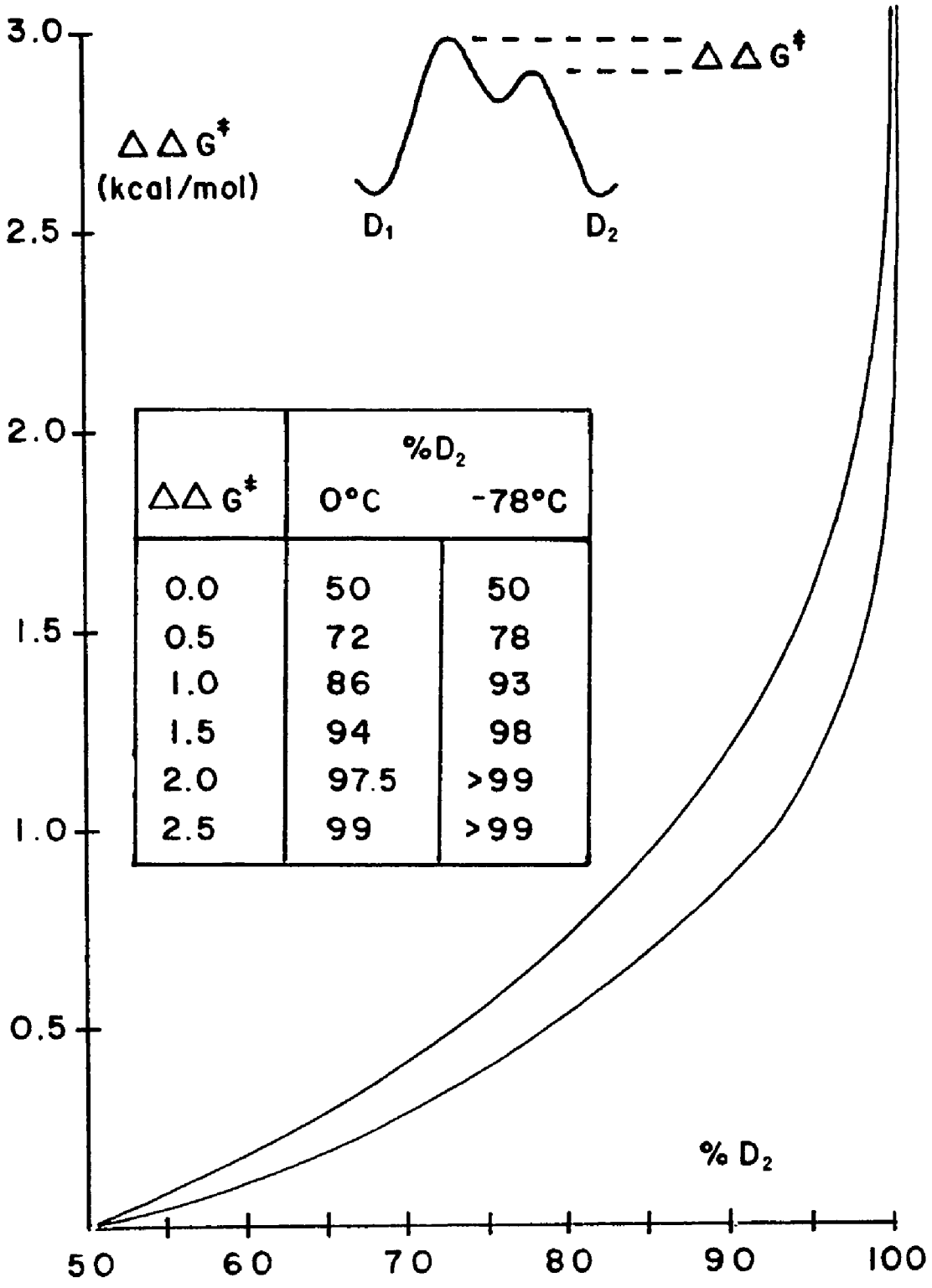
Nature produces a wide variety of chiral molecules.[4] This "chiral pool" is the origin of chirality for the preparation of numerous chiral molecules.[5] Natural products are an economical source of enantiomerically pure chiral precursors. But nature only produces one enantiomer

of most chiral precursors, thereby inhibiting the synthesis of both enantiomers of a chiral molecule.

Asymmetric synthesis is a more flexible approach for preparing chirality. Neither resolution techniques nor natural products that contain the desired chirality are necessary. Asymmetric synthesis creates new chirality under the influence exerted by existing chirality. The asymmetry that directs the creation of new chirality can either reside within the same molecule (intramolecular asymmetric induction) or be part of another molecule (intermolecular asymmetric induction). The methods of asymmetric synthesis have significantly improved over the last 50 years.[6] A better understanding of stereochemistry and reaction mechanisms now permits asymmetric reactions to be designed on a more rational basis.

Asymmetric synthesis embodies three modes of asymmetric induction: 1) the differential reaction of a chiral reagent with a prochiral substrate (stoichiometric asymmetric induction); 2) the differential reaction of an achiral reagent with a prochiral substrate under the influence exerted by a chiral catalyst (catalytic asymmetric induction); and 3) the differential reaction of an achiral reagent at a prochiral center within a chiral molecule (relative asymmetric induction). Each of these processes is kinetically controlled. Therefore, the extent of asymmetric induction is related to the difference in the activation energy ($\Delta\Delta G$) between the two competing pathways.[7]

In a simple approximation, as the ratio of the reaction products increases, the requisite difference in the activation energy of the competing transition states, $\Delta\Delta G$ increases in an exponential manner. This relationship is illustrated in Figure 1. For example, a 98:2



ΔΔG‡	%D2 0°C	%D2 -78°C
0.0	50	50
0.5	72	78
1.0	86	93
1.5	94	98
2.0	97.5	>99
2.5	99	>99

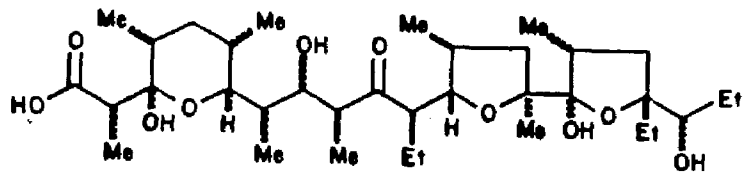
Figure 1 The Relationship Between Transition State Free Energies and Product Ratios.

product ratio at -78°C corresponds to a $\Delta\Delta G$ of 1.5 kcal/mol. The same product ratio at 25°C requires a $\Delta\Delta G$ of 2.5 kcal/mol. Although these requirements seem small, when compared with the typical carbon-carbon bond disassociation energy (2.5 kcal/mol vs 84 kcal/mol), they have proven significant for designing asymmetric biases that differentially control reactions occurring at prochiral reaction sites.

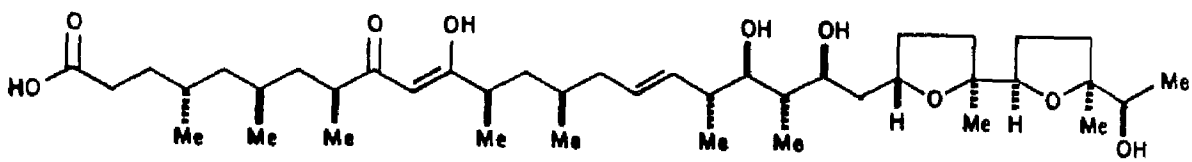
Macrolide and polyether ionophores often elicit significant antibacterial and antitumor activities.[8] This class of natural products, isolated from a variety of microbial sources, contains numerous stereocenters and oxygenated ligands on a carbon backbone. The architectural complexity of macrolide and polyether ionophores is illustrated in Figure 2.

The total synthesis of macrolide and polyether ionophores provides a critical method of evaluating the different approaches to asymmetric synthesis. Most synthetic pathways to these natural products proceed through acyclic intermediates containing numerous asymmetric centers. Reactions based on both catalytic and stoichiometric asymmetric induction, however, are more suited for preparing simple chiral molecules. Even relative asymmetric induction can become bogged down as the number and variety of stereocenters increase. Despite these difficulties, Kishi has made some significant advances in the use of relative asymmetric induction.[9]

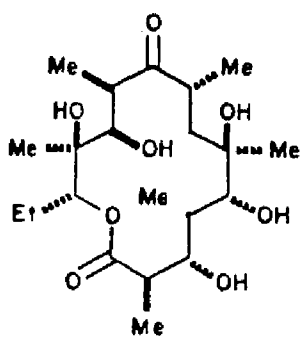
We, however, sought a more general approach to synthesize these complex natural products. Nature constructs the macrolide and polyether ionophores in a linear fashion, similar to the biosynthesis of fatty acids, from acetate, propanoate, and butanoate derived building blocks.[9]



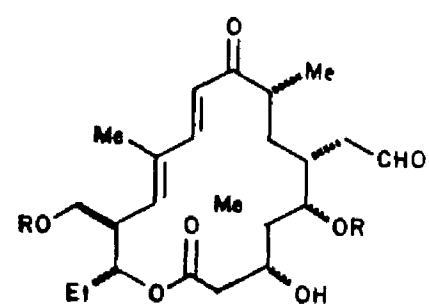
Ferensimycin B



Ionomycin



Erythronolide A

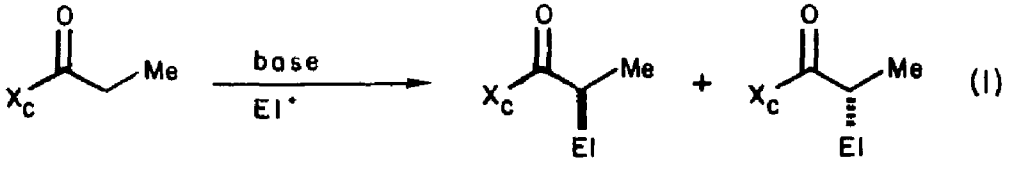


Tylosin

Figure 2 Macrolide and Polyether Ionophore Antibiotics.

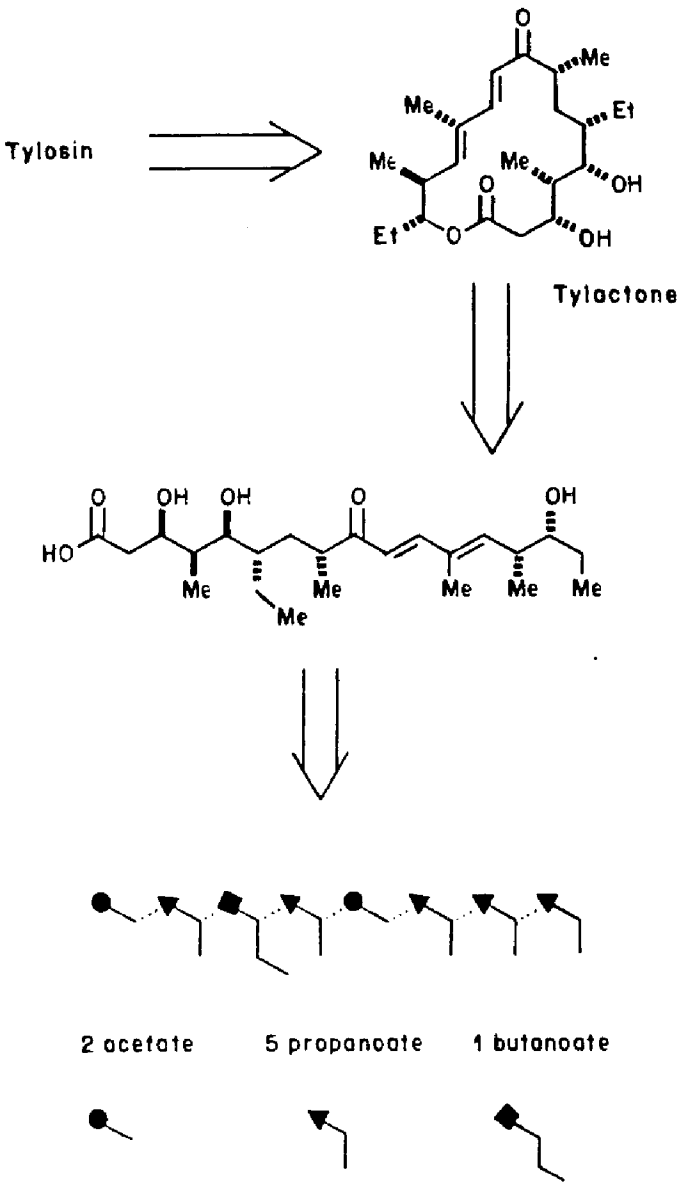
Scheme 1 illustrates the proposed biosynthesis of tylosin. A straightforward approach to their synthesis would be to mimic this process--a method, whereby both the carbon backbone is constructed, and the new stereocenters are set, independent of other stereochemistry in the molecule. This would necessitate a set of asymmetric carbon-carbon bond forming reactions based on chiral C_2, C_3, and C_4 precursors. An iterative series of these reactions would enable the synthesis of the macrolide and polyether ionophores, as well as related molecules not available from nature.

We envisioned using a chiral acyclic enolate synthon to mimic ionophore biosynthesis. A chiral enolate synthon is an enolate or an enolate equivalent to which an asymmetric bias is applied.[11] Attaching a removable chiral auxiliary (X_C) to an acyclic enolate precursor affords a chiral acyclic enolate synthon. The chiral auxiliary differentiates the prochiral π-faces of the enolate to the approaching electrophile, and thus favors one diastereomeric product (eq 1).



(1)

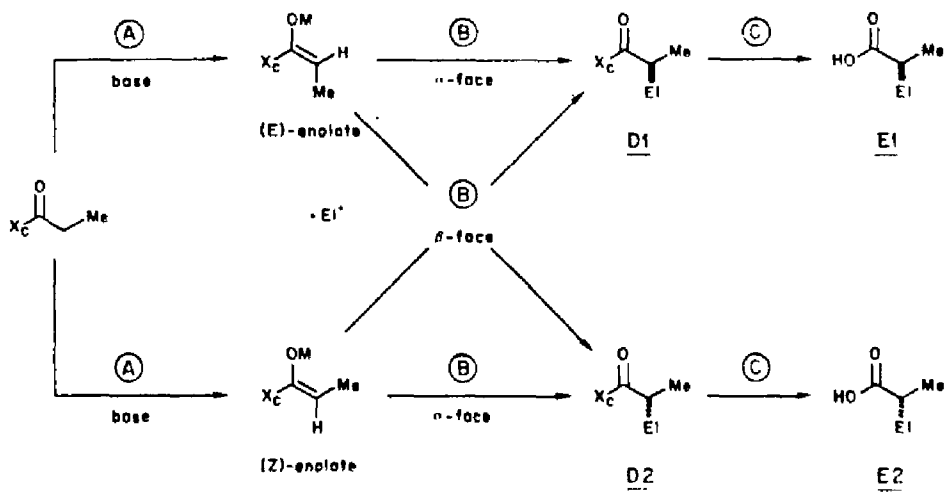
(D1 << D2) or (D1 >> D2) D1 D2



Scheme 1

II. DESIGN OF A CHIRAL ACYCLIC ENOLATE SYNTHON

The enantioselective alkylation of a chiral acyclic enolate synthon requires control over three individual steps. The overall process for alkylation of a chiral propanoate synthon is illustrated in Scheme 2. The stereochemisty of the product is directly related to both the geometry of the enolate and the chirality of the auxiliary. Therefore, both the generation of a single enolate isomer (Step A) and the alkylation of a single diastereoface of the enolate (Step B) is required to obtain a specific diastereomer. In order to be synthetically useful, both steps must be highly stereoselective. Finally, the chiral auxiliary must be removable under conditions that minimize racemization of the newly formed chiral center (Step C).

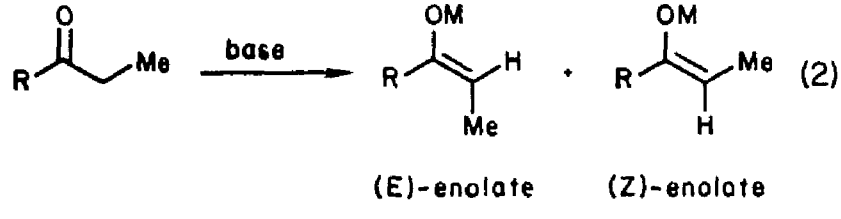


A) Stereoselective Enolization. B) Diastereoselective Alkylation. C) Chiral Auxiliary Removal

Scheme 2

For a chiral acyclic enolate synthon to be useful in an iterative sense, as would be required for the synthesis of the macrolide and polyether ionophores, the entire process must be highly enantioselective. Six repetitions of a 95:5 process decrease the proportion of the major stereoisomer below 75%. The attainment of an overall enantioselection of >95:5 for the alkylation of a chiral enolate synthon necessitates an enolate stereoselection of >98:2, an alkylation diastereoselection of >98:2, and less than 1% product racemization during removal of the chiral auxiliary. As previously indicated, a selectivity of 98:2 corresponds to a $\Delta\Delta G$ of 1.5 kcal/mol at -78°C, or 2.5 kcal/mol at 25°C.

The first reaction step to address for the design of a chiral acyclic enolate synthon is stereoselective enolization. Deprotonation of an acyclic carbonyl derivative can afford two geometrically isomeric enolates (eq 2). Although enolates play an important role in organic chemistry, the process of enolization is not fully understood. A number of the factors that control this transformation, however, are empirically known.



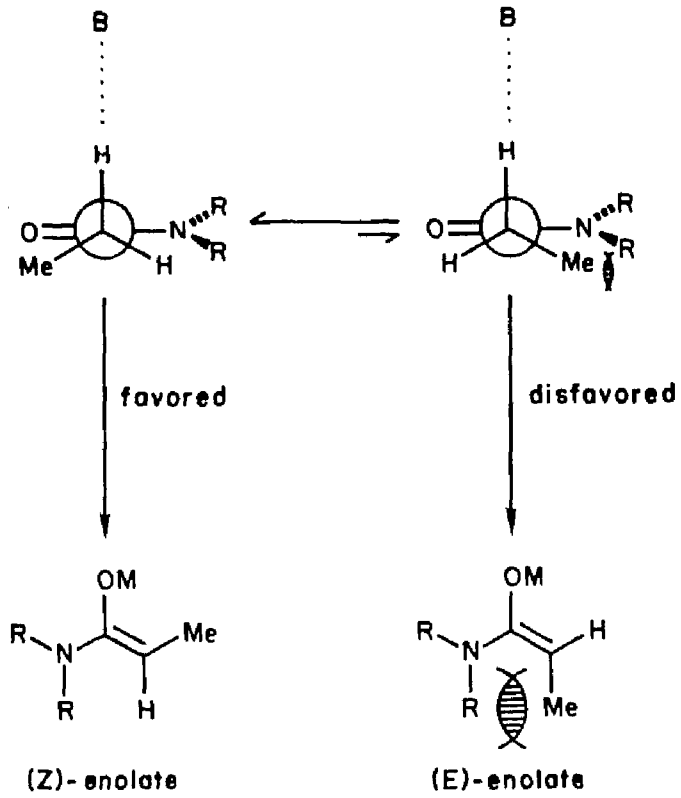
The kinetic ratio (E:Z) of enolate stereoisomers obtained by the deprotonation of various ester, ketone, and N,N-dialkylcarboxamides with lithium diisopropylamide (LDA) is summarized in Table 1. With ketone

substrates (Table 1 entries A-D), both the magnitude and the sense of enolate stereoselection depends on the size of the R substituent. Enolate stereoselection for esters (Table 1, entries E-F) and N,N-dialkylcarboxamides (Table 1, entries G-H), however, is independent of the R substituent. Esters preferentially (E:Z = 95:5) form the (E) enolate isomer, whereas N,N-dialkylcarboxamides exclusively (E:Z $\leq$ 3:97) afford the (Z) enolate isomer. The stereoselective generation of the (Z)-enolate isomer by deprotonation of N,N-dialkylcarboxamides with LDA can be rationalized on the basis of a developing $A_{1,3}$-steric interaction between the C-2 methyl and the nitrogen substituent R, in the transition state leading to the (E) enolate isomer (Scheme 3).

Table 1. Enolization of Esters, Ketones and N,N-Dialkylcarboxamides with Lithium Diisopropylamide (eq 2).

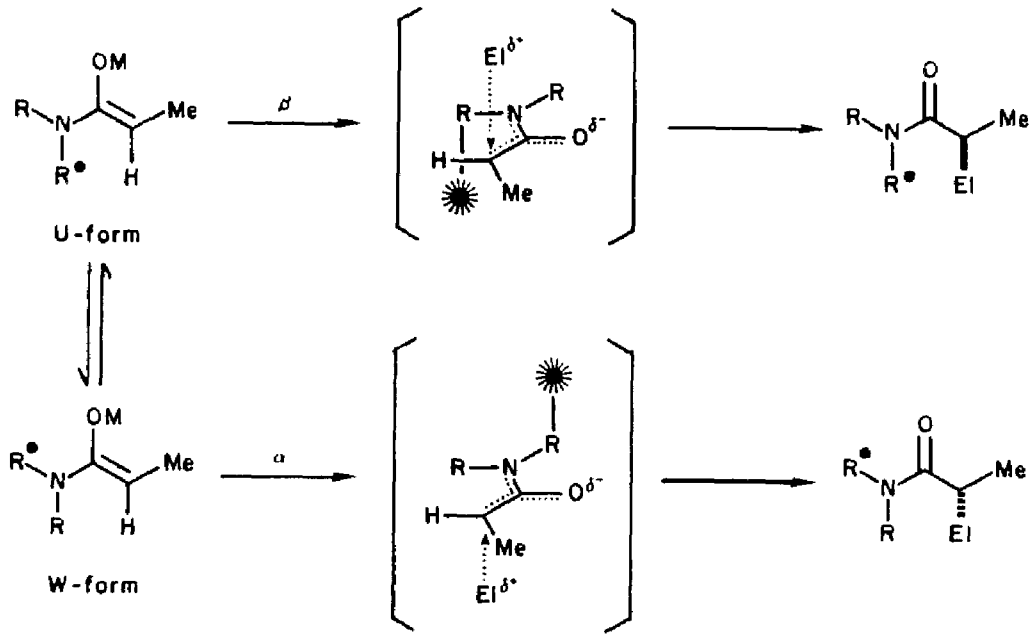
Entry	R	E:Z	Ref.
A	Et	70:30	12
B	i-Pr	40:60	12
C	t-Bu	$\leq$ 2:98	12
D	Ph	$\leq$ 2:98	12
E	MeO	95:5[a]	12
F	t-BuO	95:5[a]	12
G	Et_2N	$\leq$ 3:97	13
H	$[(CH_2)_4]N$	$\leq$ 3:97	13

a) For assignment of ester enolate configuration, the OLi group arbitrarily is given a higher priority than the OR group.



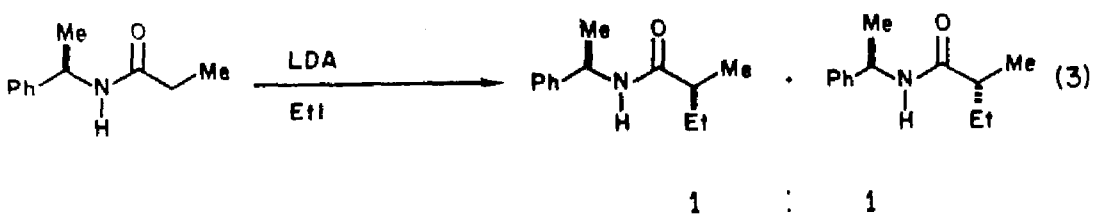
Scheme 3

Since N,N-dialkylcarboxamides satisfy the first design requirement, we elected to investigate chiral N,N-dialkylcarboxamides as potential chiral acyclic enolate synthon candidates. The two nitrogen substituents provide convenient locations to situate an asymmetric bias. Placement of the resident chirality on one of the nitrogen substituents, however, introduces the problem of amide rotational isomerization. The U-form and the W-form of the unsymmetrically N,N-disubstituted (Z)-carboxamide enolate favor opposite diastereofaces of the enolate to the approaching electrophile, and thereby lead to diastereomeric products (Scheme 4). Therefore, the level of alkylation diastereoselection will also depend on the proportion of the two rotameric forms present during alkylation.



Scheme 4

A chiral carboxamide enolate lacking preference for either rotameric form will be non-diastereoselective. Indeed, alkylation of the lithium enolate of N-[(R)-1-phenylethyl]propanamide with ethyl iodide affords a 1:1 mixture of diastereomers (eq 3).[14] Therefore, an additional design element is required to obtain a high level of alkylation diastereoselection: the selection and immobilization of a single amide rotational isomer.



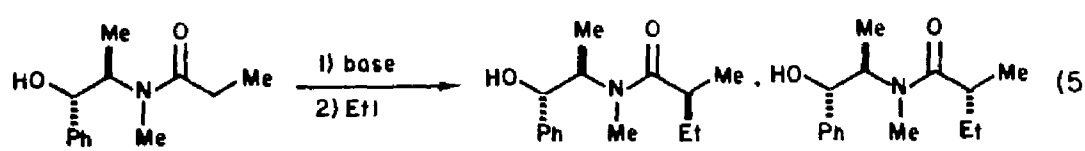
(3)

1 : 1

One method to selectively favor and immobilize one amide rotational isomer involves chelation. A chelating ligand (Y) is located on one of the nitrogen substituents. Only one of the amide rotational isomers places the chelating ligand in proximity to the enolate oxygen. The formation of a metal-centered chelate ring then immobilizes this amide conformation (eq 4).

(4)

Two different chiral N,N-disubstituted carboxamide systems employ chelation to inhibit amide rotational isomerization. Alkylation of the lithium enolate of (L)-ephedrine propanamide with ethyl iodide at -20°C affords a 76:24 ratio of diastereomers (eq 5).[15] The observed sense of diastereoselection is rationalized by the electrophile approaching the sterically less encumbered β-face of seven-membered chelated (Z) enolate **1.** Alkylation of the corresponding magnesium enolate at 25°C improves the diastereomer ratio to 95:5. Presumably, magnesium as the dication, forms a tighter, more stable chelated structure, with less conformational freedom.

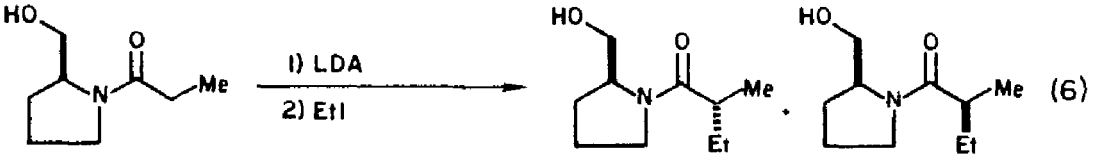


(5)

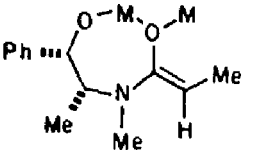
base = LDA 76 : 24

base = LDA·$MgBr_2$ 95 : 5

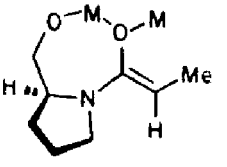
Both Takacs in our laboratories,[13,16] and Sonnet[14] have investigated the diastereoselective alkylation of carboxamides derived from (S)-prolinol. Alkylation of the lithium enolate of (S)-prolinol propanamide with ethyl iodide affords a 92:8 ratio of diastereomers (eq 6). In this case, the observed sense of diastereoselection is explained by the electrophile approaching the sterically less encumbered α-face of seven-membered chelated (Z) enolate **2**.



(6)



1



2

In both of these examples the resident chirality is located on the nitrogen substituent corresponding to the W-rotameric isomer. An examination of the two rotameric forms shows that the U-rotameric isomer places the resident chirality in closer proximity to the prochiral reaction site (Figure 3). Therefore, alkylation of the U-rotameric isomer should in principle be more diastereoselective than alkylation of the W-rotameric isomer. In order to selectively favor and immobilize the U-rotameric isomer, the chelating ligand and the resident chirality would have to be located on different nitrogen substituents (eq 7).

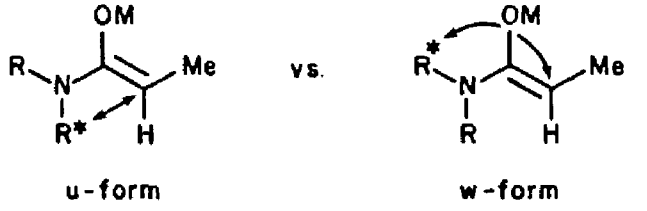
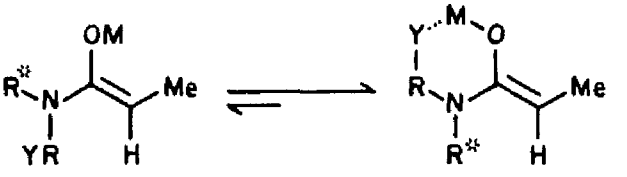
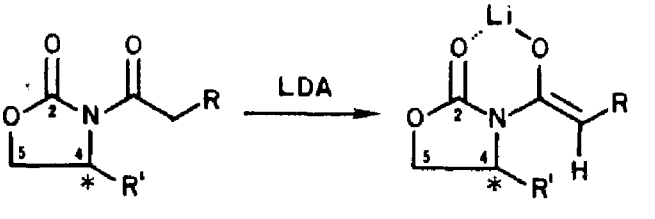


Figure 3 U- and W-Rotameric Forms of (Z) Carboxamide Enolates.

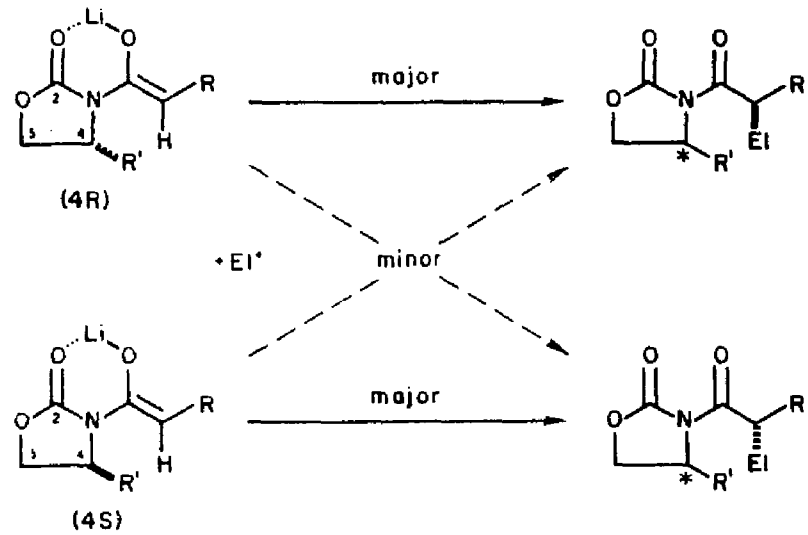


(7)

Based on the previous discussion, we envisioned that chiral 4-substituted 2-oxazolidinone imides **3** meet the design criteria for a chiral acyclic enolate synthon. Enolization of **3** should stereoselectively if not exclusively afford the metal-centered, six-membered chelated (Z) enolate **4** (eq 8). This conformationally rigid enolate structure places the oxazolidinone C-4 position in close proximity to the prochiral enolate reaction site. Introducing chirality at the C-4 position would be expected to differentially bias the two diastereofaces of the enolate. The electrophile approaching the least hindered diastereoface of the enolate would favor a single diastereomer (Scheme 5).



(8)

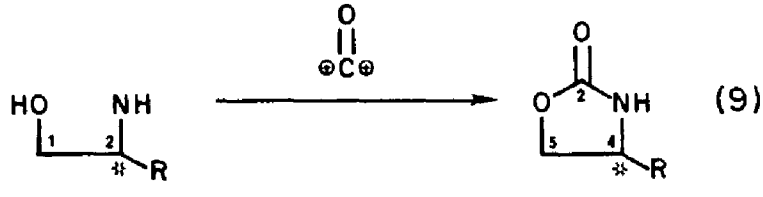


Scheme 5

In the following report, we discuss the synthesis and diastereoselective alkylation of chiral 4-substituted 2-oxazolidinone imides, as well as the transformation of the resultant alkylated products into useful chiral intermediates. The reported kinetic diastereoselection for alkylation of other chiral esters and N,N-dialkylcarboxamides is summarized in Appendix 1.

III. RESULTS AND DISCUSSION

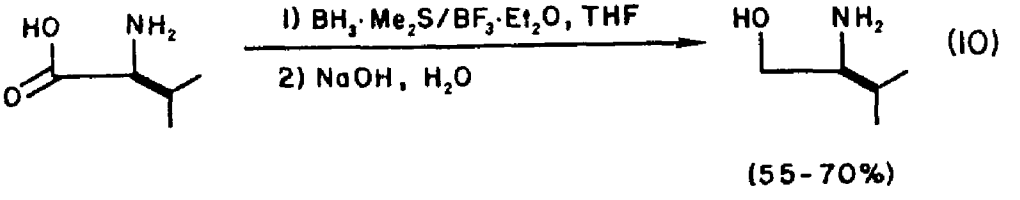
A. Preparation of the Chiral Auxiliary. Dyen has reviewed the synthesis and chemistry of 2-oxazolidinones.[17] Of the many synthetic approaches to this class of molecules, cyclization of chiral 2-substituted amino alcohols with carbonyl dication equivalents is especially well suited for preparing a variety of chiral 4-substituted 2-oxazolidinones (eq 9). The requisite chiral amino alcohols are commercially available, or easily prepared, either by reducing the corresponding amino acids with borane,[18] or by reducing the amino acid ester salts with sodium borohydride.[19]



(9)

Reduction of the amino acid (S)-valine with borane--dimethyl sulfide/boron trifluoride--diethyl etherate, following the procedure of Lane,[18] affords (2S)-2-amino-3-methyl-1-butanol [(S)-valinol] in 45-55% yield (eq 10). This procedure, however, also affords a considerable quantity of 4-methylmercapto-1-butanol, which interferes with isolation of the (S)-valinol. Brown has reported that the rate of amide reduction, with borane--dimethyl sulfide, is increased by removing the dimethyl sulfide from the reaction mixture.[20] We applied this modification to the reduction of (S)-valine. Thus, as borane--dimethyl sulfide is added to the mixture of (S)-valine and boron trifluoride--diethyl etherate in tetrahydrofuran (THF), both dimethyl sulfide and diethyl

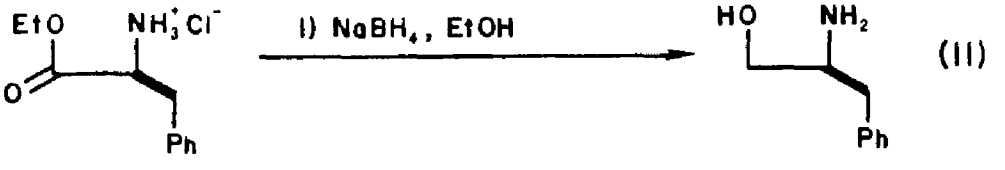
ether are removed by distillation. This both increases the rate of reduction and decreases the amount of biproduct formed. The modified reduction procedure, performed on large scale (1-8 mol), affords (S)-valinol in 55-70% yield.



(10)

(55-70%)

Alternately, chiral amino alcohols can be prepared by reducing the corresponding amino acid ester salts with sodium borohydride.[19] Although this procedure requires the additional step of preparing the amino acid ester salt, it uses the less expensive sodium borohydride as the reductant. Reduction of ethyl (S)-phenylalanine hydrochloride with sodium borohydride affords (2S)-2-amino-3-phenyl-1-butanol [(S)-phenylalaninol] in 63% yield (eq 11).[21]



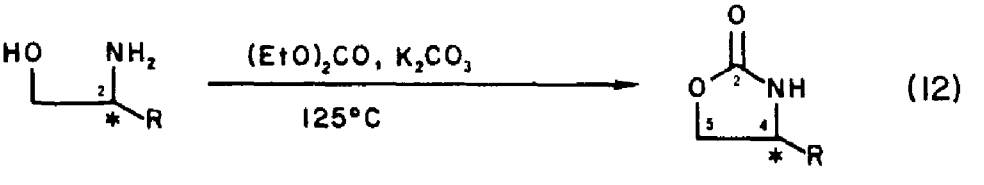
(11)

(64%)

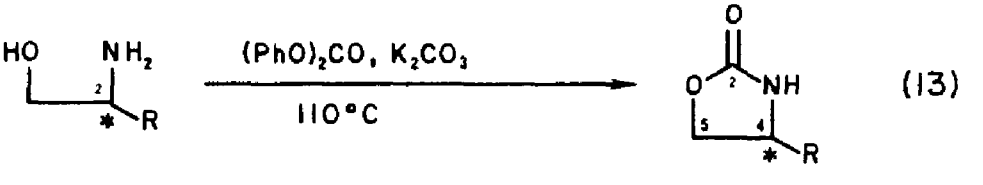
By examination of the ^{19}F NMR spectrum of amides derived from these chiral amino alcohols and Mosher's acid,[22] Meyers has demonstrated that less than 2% racemization occurs during either of these reduction procedures.[23] We show that the amount of racemization is actually less than 0.5%, based on the enantiomeric purity of chiral 2-oxazolidinones prepared from these amino alcohols.

Both (S)-phenylalaninol and (S)-valinol are derived from naturally occurring amino acids. In order for the proposed chiral auxiliary to induce either sense of asymmetry would require both C-4 configurations of the 4-substituted 2-oxazolidinone. Therefore, a source of (2R)-amino alcohols is necessary. Of the "unnatural" amino acids, as precursors to (2R)-amino alcohols, only (R)-phenylglycine is commercially available at reasonable cost. Fortunately, the amino alcohol (1S,2R)-2-amino-1-phenyl-1-propanol [(1S,2R)-norephedrine], resolved as its tartrate salt, also is commercially available.

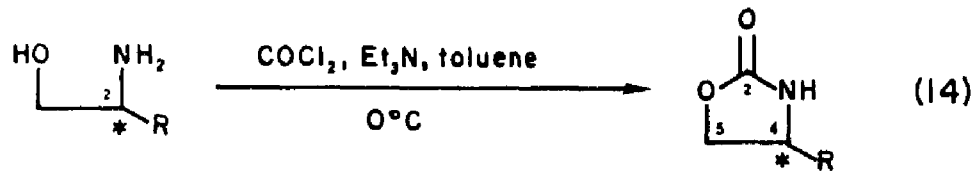
With both (2R)- and (2S)-amino alcohols at our disposal, we prepared a variety of (4R)- and (4S)-4-substituted 2-oxazolidinones. Three different carbonyl dication equivalents were employed to cyclize the amino alcohols: 1) diethyl carbonate (eq 12); 2) diphenyl carbonate (eq 13); and 3) phosgene (eq 14). The cyclization results are summarized in Table 2.[24] Other than (±)-4-methyl-2-oxazolidinone [(±)-alaninol 2-oxazolidinone, 5], all of the 2-oxazolidinones are colorless crystalline solids. The 2-oxazolidinones prepared for this investigation are illustrated in Figure 4.



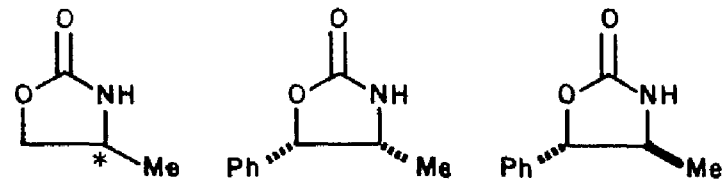
(12)



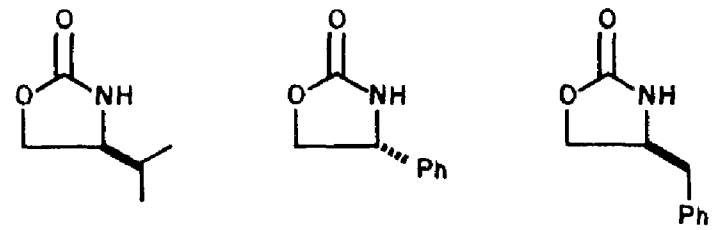
(13)



(14)



5 6 7



8 9 10

Figure 4. 2-Oxazolidinones.

Homeyer has reported that amino alcohols react with dialkyl carbonates in the presence of base to afford 2-oxazolidinones.[26] This is the basis for the first two cyclization procedures. The diethyl carbonate procedure is operationally very simple. A neat mixture of the amino alcohol, diethyl carbonate, and a catalytic amount of anhydrous potassium carbonate is heated at 125°C until two equivalents of ethanol distills from the reaction mixture. The product is separated from the

Table 2. Preparation of 2-Oxazolidinones.

Entry	Oxazolidinone	Method[a]	Yield	mp (bp)	$[\alpha]_{589}$
A	(±)-**5**	A	46%	(100°C, 12 mm)	-----
B	(4R,5S)-**6**	A	0-95%	121-122°C	+177.2° (c 2.21, $CHCl_3$)
C	(4R,5S)-**6**	B	82-95%	121-122°C	+177.2° (c 2.21, $CHCl_3$)
D	(4R,5S)-**6**	C	88%	121-122°C	+177.2° (c 2.21, $CHCl_3$)
E	(±)-**6**	C	73%	136°C	-----
F	(4S,5S)-**7**	A	90%	119-120°C	+15.7° (c 1.83, EtOH)
G	(4S)-**8**	A	85-95%	69-70°C	-16.6° (c 5.81, EtOH)
H	(±)-**8**	C	58%	64-65°C	-----
I	(4R)-**9**	A	79%	123.5-124.5°C	-58.6° (c 1.06, CH_2Cl_2)
J	(4S)-**10**	A	77%	82-83°C	+5.1° (c 0.76, EtOH)

a) A = diethyl carbonate (eq 12); B = diphenyl carbonate (eq 13); C = phosgene (eq 14).

potassium carbonate and purified by crystallization or reduced-pressure distillation. The reaction can easily be performed on a large scale (1-3 mol). Usually, the yield of 2-oxazolidinone obtained by the diethyl carbonate procedure (Table 2, entries F, G, I, and J) is good to excellent (79-95%). We attribute the poor yield (46%) of 2-oxazolidinone **5** (Table 2, entry A) to the water solubility of this product.

The reaction of (1S,2R)-norephedrine with diethyl carbonate (Table 2, entry B) presents a more serious problem. Normally, the yield of (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone [(4R,5S)-norephedrine 2-oxazolidinone, **6**] is very good (85-95%). Periodically, however, the reaction fails, affording neither product nor starting material. When this occurs, N-ethylnorephedrine 2-oxazolidinone and a polymer are formed. (1S,2R)-Norephedrine often takes longer to cyclize than other amino alcohols. The slower rate of cyclization for this amino alcohol may be the result of the developing cis steric interaction between the C-4 methyl and C-5 phenyl substituents in 2-oxazolidinone **6**. Raising the reaction temperature to 140-180°C in an attempt to accelerate the rate of cyclization only increases the amount of byproducts formed. Rather, we suggest that the reaction be maintained at 125°C, and that a full equivalent of potassium carbonate is used to catalyze this cyclization.

Because of the inconsistent yield of 2-oxazolidinone **6**, we investigated two other cyclization procedures. The diphenyl carbonate procedure for preparing 2-oxazolidinones is essentially the same as the diethyl carbonate procedure.[25] A neat mixture of amino alcohol and diphenyl carbonate in the presence of anhydrous potassium carbonate at 110°C reacts to afford the 2-oxazolidinone. The two equivalents of phenol formed during this reaction are removed from the product by extraction with aqueous base. The product is purified by crystallization. The reaction can be performed on a large scale (0.5-3 mol). Cyclization of (1S,2R)-norephedrine with diphenyl carbonate (Table 2, entry C) affords 2-oxazolidinone **6** in 82-93% yield. Despite the more involved work-up procedure, this is the preferred synthesis of the 2-

oxazolidinone derived from (1S,2R)-norephedrine.

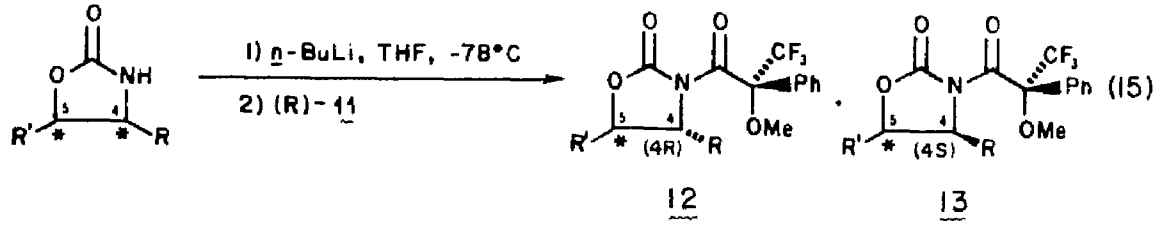
Phosgene also reacts with amino alcohols in the presence of base to afford 2-oxazolidinones.[27] Although phosgene is a gas at room temperature (bp 8°C), it can be supplied as a solution in toluene. The amino alcohol and triethylamine in toluene at 0°C react instantaneously with phosgene to afford the 2-oxazolidinone and a voluminous white precipitate of triethylamine hydrochloride. Unfortunately, the high reactivity of phosgene can lead to the formation of two byproducts: N-chloroformyl-2-oxazolidinone, and N,N-carbonyldi-2-oxazolidinone. Therefore, excess phosgene must be avoided. Cyclization of (1S,2R)-norephedrine with phosgene (Table 2, entry D) affords 2-oxazolidinone **6** in 88% yield. This is the method of choice for small scale cyclizations, when neat procedures are impractical.

B. Determination of the Enantiomeric Purity of Chiral 2-Oxazolidinones. The level of asymmetric induction exerted by a chiral auxiliary is directly proportional to the enantiomeric purity of the chiral auxiliary. An asymmetric reaction, 100% stereoselective, but whose directing chirality is only 75% enantiomerically pure, can only afford a chiral product 75% enantiomerically pure. Therefore, the enantiomeric purity of the chiral 2-oxazolidinone is of vital importance. The specific rotation of chiral 2-oxazolidinones is both solvent and concentration dependent. Thus, it is difficult to accurately relate the specific rotation and enantiomeric purity of chiral 2-oxazolidinones.

An alternate method of determining the enantiomeric purity of a chiral molecule involves preparation of a diasteromeric derivative. A chiral molecule of known enantiomeric purity is coupled, under non-

racemizing conditions, to the chiral molecule of unknown enantiomeric purity. The ratio of diastereomers in the resultant product is directly related to the enantiomeric purity of the two chiral molecules. To accurately reflect the enantiomeric purity, the two chiral molecules must completely react. Also, diastereomer resolution prior to analysis, must be prevented. Cognizant of these factors, diastereomeric derivatives are useful for determining, to a high degree of precision, the enantiomeric purity of chiral molecules.

We successfully employed this technique to determine the enantiomeric purity of chiral 2-oxazolidinones. Metalation of the chiral 2-oxazolidinone with n-butyllithium at -78°C, and N-acylation of the resultant anion with (2R)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride [(R)-Mosher's acid chloride, **11**][22] affords the diastereomers **12** and **13** (eq 15). The ratio of diastereomers (**12**:**13**) was measured by capillary GC and independently confirmed by HPLC. A standard mixture of diastereomers was prepared by coupling racemic 2-oxazolidinone to (R)-**11** or chiral 2-oxazolidinone to (±)-**11** in order to demonstrate that the analytical technique separated the diastereomers. The results are summarized in Table 3. In all cases, the diastereomer ratio (major:minor) is $\geq$ 200:1. Therefore, the enantiomeric purity of the chiral 2-oxazolidinones and their precursor amino alcohols is $\geq$ 99%.



(15)

12 13

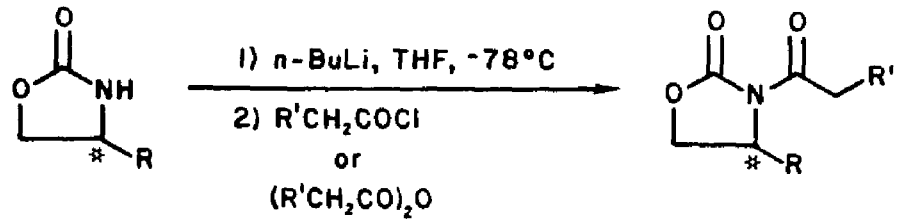
Table 3. Enantiomeric Purity of the 2-Oxazolidinones (eq 15).

Entry	2-Oxazolidinone	R	R'	Chirality	Ratio[a] 12:13	First Diastereomer to Elute[b] GC Carbowax 20M	GC DB-5	HPLC Silica gel
A	6	Me	Ph	(4R,5S)	$\geq$ 200:1	(4S)	----	(4S)
B	7	Me	Ph	(4S,5S)	$\leq$ 1:200	----	(4R)	(4S)
C	8	i-Pr	H	(4S)	$\leq$ 1:200	(4S)	----	(4S)
D	9	Ph	H	(4R)	$\geq$ 200:1	----	(4R)	(4S)
E	10	$PhCH_2$	H	(4S)	$\leq$ 1:200	----	(4R)	(4S)

a) Diastereomer ratio determined by capillary GC analysis of the unfractionated product. b) Chromatographic conditions for each separation are reported in the experimental section.

C. Preparation of N-Acyl 2-Oxazolidinones. N-Acyl 2-oxazolidinones are prepared in high yield from their respective "parent" 2-oxazolidinones (eq 16). Metalation of the 2-oxazolidinone with n-butyllithium at -78°C, followed by N-acylation of the resultant anion with the desired acid chloride or anhydride affords the N-acyl 2-oxazolidinone. The product is purified by reduced-pressure distillation, liquid chromatography on silica gel, or both, as indicated in the experimental section. The N-acylation results are summarized in Table 4. Most N-acyl 2-oxazolidinones are colorless crystalline solids. Figure 5 illustrates the structure of the N-acyl 2-oxazolidinones.

2-Oxazolidinones **6**, **7**, **9**, and **10** contain benzylic protons. Metalation of these 2-oxazolidinones with excess n-butyllithium results in benzylic deprotonation. After one equivalent of base is added, a deep burgundy color develops, indicating formation of the dianion. As the



(16)

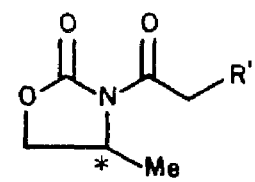
Table 4. Preparation of N-Acyl 2-Oxazolidonones (eq 16).

Entry	Imide	R'	Yield	mp (bp)	$[\alpha]_{589}$ (c)[a]
A	**14c**	Et	66%	(75°C, 0.005 mm)	-----
B	**16a**	H	93%	65.5-66°C	+47.6° (2.06)
C	**16b**	Me	94%	(135°C, 0.008 mm)	+43.4° (3.61)
D	**16c**	Et	87%	55.5-56°C	+40.4° (4.90)
E	**16d**	Me_2CH	90%	52-53°C	+38.5° (2.36)
F	**16e**	$CH_2=CHCH_2$	92%	59-60°C	+34.6° (1.35)
G	**16f**	Me_3C	87%	79-80°C	+36.3° (2.63)
H	**16g**	Ph	90%	101-102°C	+0.5° (0.97)
I	**16h**	$PhCH_2$	88%	95-96°C	+28.7° (0.45)
J	**16i**	$Me(CH_2)_7$	89%	41-42°C	+27.4° (3.03)
K	**16j**	1-Naphthyl	88%	103-104°C	-40.1° (0.584)
L	**16k**	MeO	80%	63-64°C	+30.4° (1.07)
M	**16l**	BnO	87%	99-100°C	+16.2° (2.47)
N	**18c**	Et	95%	(140°C, 0.01 mm)	+21.8° (2.95)
O	**20b**	Me	93%	(100°C, 0.01 mm)	+91.9° (0.377)
P[b]	**20c**	Et	93%	(150°C, 0.005 mm)	+89.9° (3.80)

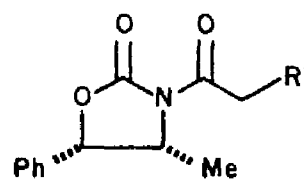
Table 4. Continued

Entry	Imide	R'	Yield	mp (bp)	$[\alpha]_{589}$ (c)[a]
Q	**20h**	$PhCH_2$	91%	63-64°C	+71.0° (4.61)
R	**20i**	$Me(CH_2)_7$	56%	(160°C, 0.008 mm)	+63.7° (2.07)
S	**22b**	Me	85%	76-77°C	-84.1° (1.44)
T	**22c**	Et	84%	50-51°C	-79.5° (2.21)
U	**24b**	Me	99%	44.5-45.5°C	+80.7° (1.00)
V	**24c**	Et	95%	(140°C, 0.01 mm)	+74.8° (1.34)

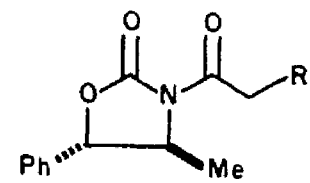
a) Specific rotation determined in dichloromethane (c = g/100 mL).
b) We thank Dr. M. D. Ennis for this result, ref. 29.



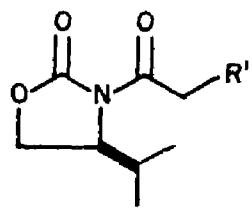
14



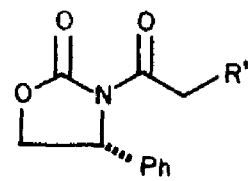
16



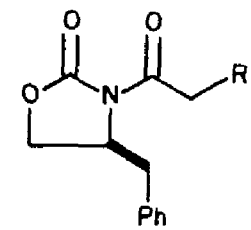
18



20



22



24

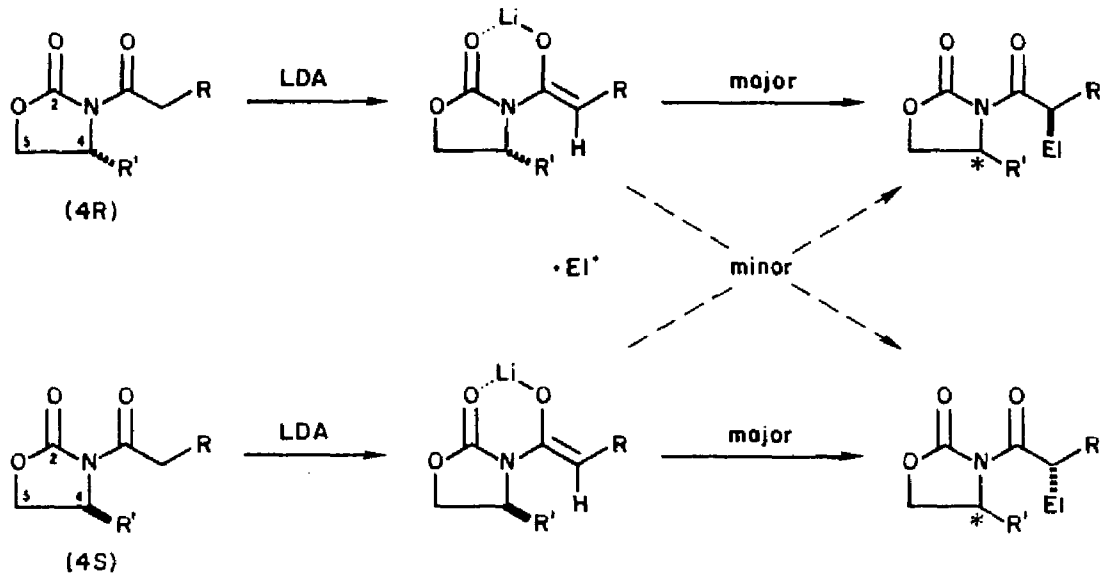
Figure 5. N-Acyl 2-Oxazolidinones.

dianion, 2-oxazolidinone **9** can racemize, and 2-oxazolidinones **6**, and **7** can epimerize. Dianion formation at -78°C is much slower than at 0°C. Therefore, at -78°C, a small excess of base can be tolerated. The color change can even be used as a titration indicator, provided the anion is immediately treated with the acylating agent.

D. Diastereoselective Alkylation of Chiral 2-Oxazolidinone Imide Enolates. Based on the discussion in section II, we expected that enolization of N-acyl 2-oxazolidinones would predominantly, if not exclusively, afford the six-membered chelated (Z) enolate isomer. Substitution at the C-4 position of the 2-oxazolidinone ring was anticipated to provide the enolate with a diastereofacial bias, and thereby direct the electrophile to approach the least hindered diastereoface. Therefore, it was our expectation that the (4R)- and (4S)-4-substituted 2-oxazolidinone imide enolates would lead to the opposite sense of chirality at the newly formed asymmetric center. The stereoselective enolization and diastereoselective alkylation of chiral N-acyl 2-oxazolidinones is illustrated in Scheme 6.

With a variety of enantiomerically pure N-acyl 2-oxazolidinones readily available, we investigated their use as chiral acyclic enolate synthons.[28] At the onset, we imposed three criteria with which to evaluate the alkylation results: 1) high levels of diastereoselection ($\geq$ 95:5); 2) synthetically useful rates of alkylation; and 3) the facile non-destructive removal of the chiral auxiliaries under non-racemizing conditions.

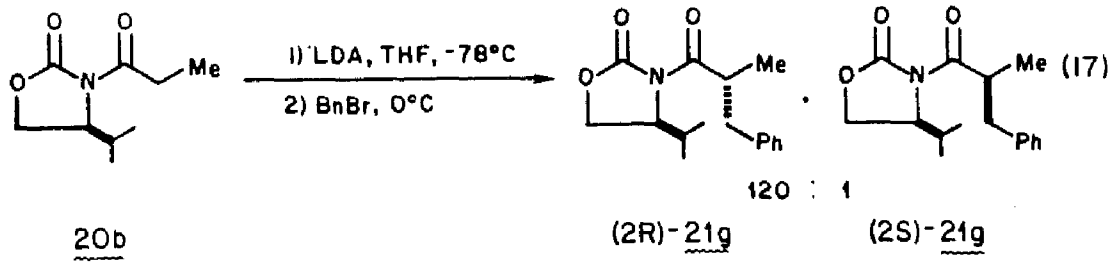
Alkylation results (diastereomer ratio and percent reaction) were determined by GC analysis of the unfractionated reaction mixture on



Scheme 6

commercially available fused-silica capillary columns (see Experimental Section). A standard mixture of diastereomers was prepared by N-acylation of the chiral 2-oxazolidinone with racemic acid chloride. In almost all instances, capillary GC provides baseline separation of the diastereomers. Under routine conditions, diastereomer ratios of >200:1 can be determined. This is significantly better precision than can be obtained by integration of NMR spectra.

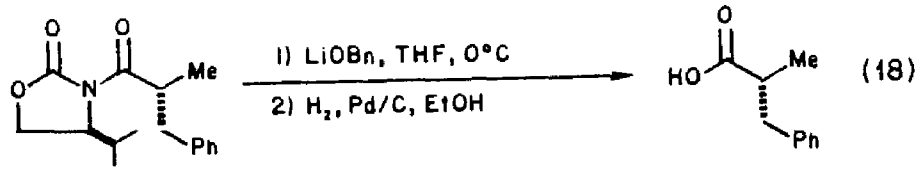
Deprotonation of imide **20b** with LDA (1.1 equiv) in THF for 0.5 h at -78°C cleanly affords the lithium enolate. Treatment of the lithium enolate with benzyl bromide (3 equiv) for 2-4 h at 0°C affords alkylated imide **21g** [(2R)-**21g**:(2S)-**21g** = 120:1] in 97% yield (eq 17).[29] Although the magnitude of alkylation diastereoselection is lower with other electrophiles, this ratio places a lower limit on enolization stereoselection. Therefore, we are confident that we are dealing essentially with a single enolate isomer.



(17)

20b (2R)-21g (2S)-21g

Transesterification (LiOBn, THF, 0°C, 0.5 h) of alkylated imide (2R)-**21g** followed by hydrogenolysis (H_2, 5% Pd on C, EtOH) of the resultant benzyl ester affords (2R)-2-methyl-3-phenylpropanoic acid **26g** ($[\alpha]_{589}$ = -25.1° (neat)) in 68% yield (eq 18).[29] The specific rotation corresponds in both magnitude and sign to the highest reported literature rotation for (2R)-acid **26g** ($[\alpha]_{589}$ = -25.4° (neat)).[30] The sense of diastereoselection is consistent with our proposed model--wherein the electrophile approaches the least hindered face of the six-membered chelated (Z) imide enolate (see Scheme 6). Therefore, the hypothesis upon which this project was undertaken is shown to be internally consistent.



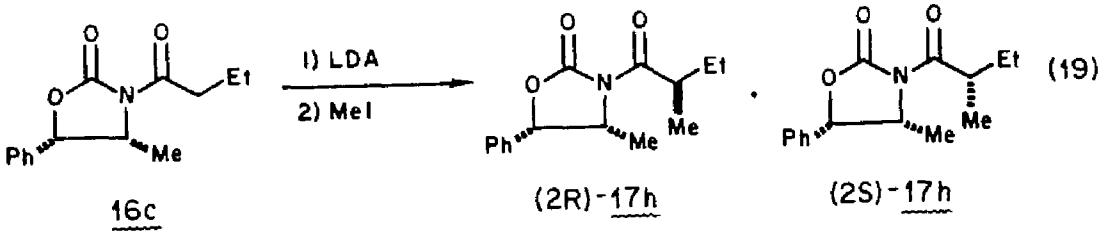
(18)

(2R)-21g (2R)-26g

$[\alpha]_{589}$ = -25.1° (neat)

Lit.[28] $[\alpha]_{589}$ = -25.4° (neat)

E. Analysis of Alkylation Reaction Parameters. The impressive level of diastereoselection in the previous example prompted us to delineate the full range of capabilities and limitations of this asymmetric alkylation reaction. Deprotonation (LDA, THF, -78°C, 0.5 h) of imide **16c** followed by alkylation with methyl iodide (3 equiv) at 0°C for 2 h affords alkylated imide **17h** [(2R)-**17h**:(2S)-**17h** = 87:13] in 75% yield (eq 19). The level of alkylation diastereoselection for this methylation reaction is lower than the previously described benzylation. Many natural products contain chiral methyl centers. Therefore, we were interested in improving the level of diastereoselection for the introduction of methyl centers.

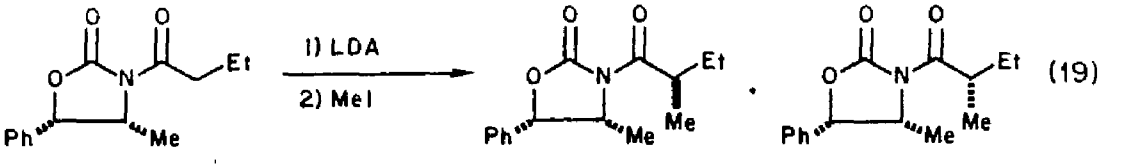


(19)

Several reaction parameters may influence the alkylation results. Base, solvent, and temperature are expected to affect the rate and stereoselectivity of enolization. We already have presented evidence that LDA in THF at -78°C cleanly deprotonates N-acyl 2-oxazolidinones to afford the six-membered chelated (Z) imide enolate. The relative stability of the chelate could influence both the nucleophilicity and the diastereoselectivity of the enolate. Chelate stability depends on the nature of the counterion, solvent, and temperature. The size of the C-4 substituent on the 2-oxazolidinone was anticipated to affect the magnitude of diastereoselection. Also, the nature of the electrophile and its leaving group could affect both the rate of alkylation and the level

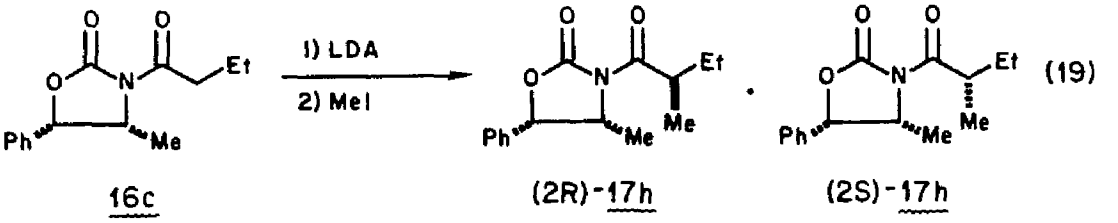
of diastereoselection. We investigated each of these reaction parameters in order to optimize both the yield and the diastereomeric purity of the alkylated product.

Alkylation of the enolate derived from imide **16c** with methyl iodide was chosen as the model reaction (eq 19). As previously noted, alkylation of the lithium enolate of **16c** with methyl iodide at 0°C affords an 87:13 ratio of diastereomers. This ratio corresponds to a $\Delta\Delta G^{\ddagger}$ of ca. 1.0 kcal/mol (see Figure 2). Thus, the same reaction performed at -78°C should improve the level of diastereoselection to ca. 93:7. Therefore, we investigated the effect of reaction temperature on alkylation diastereoselection and product yield. Imide **16c** was deprotonated with LDA (THF, -78°C, 0.5 h) and the resultant lithium enolate treated with methyl iodide (3 equiv) at a variety of temperatures (eq 19). The results are summarized in Table 5.



16c (2R)-17h (2S)-17h (19)

As expected, the level of kinetic diastereoselection increases by decreasing the reaction temperature. For example, alkylation of the lithium enolate derived from imide **16c** with methyl iodide at -20°C affords an 88:12 ratio of diastereomers (Table 5, entry C), whereas the same reaction performed at -78°C affords a 92:8 ratio of diastereomers. The rate of alkylation, however, significantly decreases at temperatures below -20°C. Only 5% of the enolate reacts after 2 h at -78°C. In terms of reaction rate and alkylation diastereoselection, the best



16c (2R)-17h (2S)-17h (19)

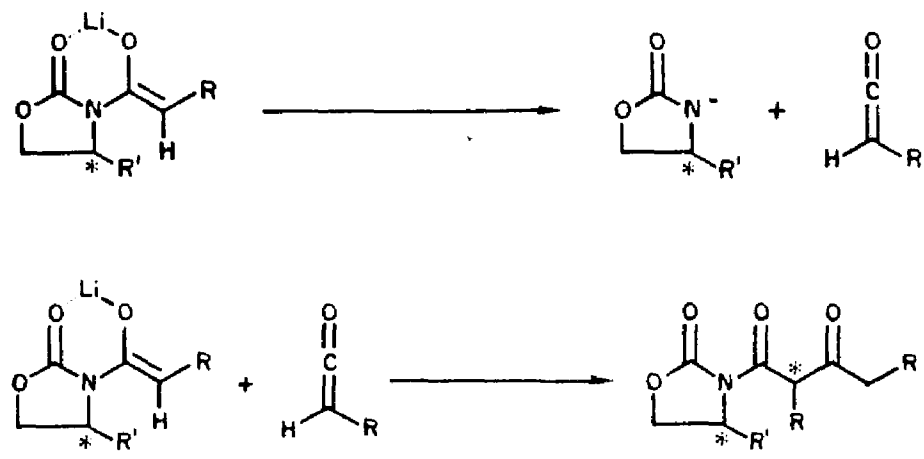
Table 5. Effect of Temperature on Alkylation Diastereoselection (eq. 19).

Entry	Alkylation Conditions	Ratio[a] 2R:2S	Yield[b]
A	-78°C, 2 h	92:8	(5%)
B	-50°C, 2 h	89:11	(57%)
C	-20°C, 2 h	88:12	(96%)
D	0°C, 1 h	87:13	(97%)

a) Diastereomer ratio determined by capillary GC analysis of the unfractionated product. b) Percentage of enolate alkylated as determined by capillary GC.

temperature for the alkylation of the lithium enolate derived from imide **16c** lies between -20°C and 0°C.

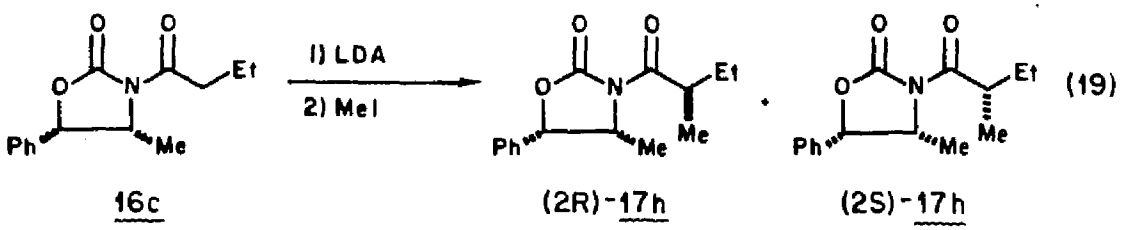
The lithium enolate derived from N-acyl 2-oxazolidinones is thermally unstable. At temperatures above 0°C, the lithium enolate decomposes at rates competitive with alkylation. Decomposition of the 2-oxazolidinone imide enolate affords the "parent" 2-oxazolidinone and a ketene derivative. The ketene in turn acylates the remaining enolate (Scheme 7).[28c] Thus, for each enolate molecule that decomposes, two are lost. Therefore, the enolate should be alkylated at the lowest temperature providing a useful yield of product.



Scheme 7

The solvent can play an important role in any chelation controlled reaction. It also may influence the state of enolate aggregation.[31] A decrease in solvent polarity should increase the relative stability of the chelate. This could, by decreasing the conformational mobility of the chelated imide enolate, increase the level of diastereoselection. But, a more stable chelate could also decrease the nucleophilicity of the enolate. With this in mind, we investigated the effect of reaction media on both alkylation diastereoselection and product yield. Imide **16c**, in a variety of solvents, was deprotonated (LDA, -78°C, 0.5 h) and the resultant lithium enolate treated with methyl iodide (3 equiv). The alkylation results are summarized in Table 6.

Decreasing the solvent polarity from THF, to diethyl ether, to toluene slightly increases the level of diastereoselection (Table 6, entries A, C, and D). The rate of alkylation, however, decreases drastically. Adding hexamethylphosphoric triamide (HMPT) to a solution of the preformed lithium enolate in THF slightly decreases the level of



16c (2R)-17h (2S)-17h (19)

Table 6. Effect of Solvent on Alkylation Diastereoselection (eq. 19).

Entry	Solvent	Alkylation Conditions	ratio[a] 2R:2S	Yield[b]
A	THF	0°C, 2 h	87:13	(97%)
B	THF, HMPT[c]	0°C, 2 h	83:17	(75%)
C	Et_2O	0°C, 2 h	88:12	(15%)
D	toluene	0°C, 2 h	90:10	(10%)

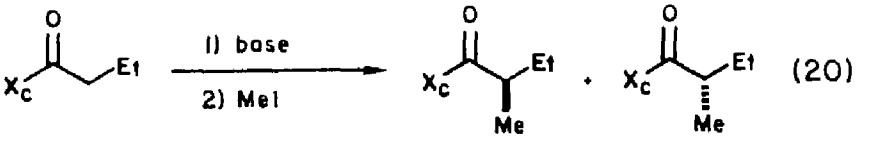
a) Diastereomer ratio determined by capillary GC analysis of unfractionated product. b) Percentage of enolate alkylated as determined by capillary GC. c) 3 equiv of HMPT (hexamethylphosphoric triamide) added to the preformed lithium enolate prior to alkylation.

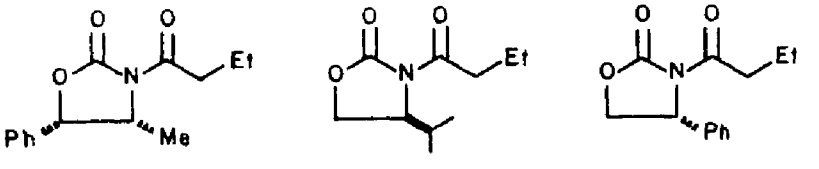
diastereoselection (Table 6, entry B). That the strongly coordinating HMPT barely decreases the level of diastereoselection demonstrates the high stability of the chelated imide enolate. From these data it is apparent that THF is the solvent of choice for the alkylation of 2-oxazolidinone imide enolates.

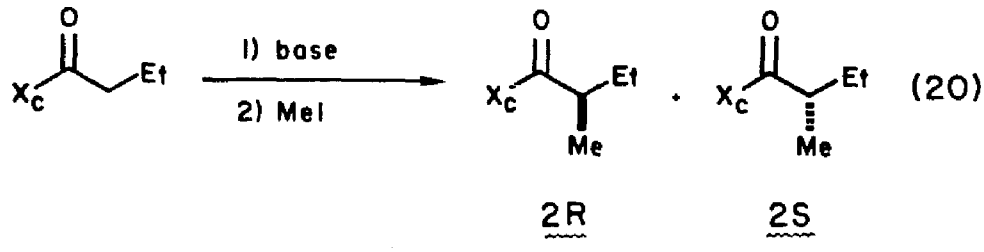
A major factor influencing chelate stability is the nature of the counterion. As previously noted, the stability of the chelate may affect both the nucleophilicity and the diastereoselectivity of the chelated imide enolate. By decreasing the stability of the chelate, the

nucleophilicity of the enolate should increase. Simultaneously, however, the conformational rigidity of the chelated intermediate may decrease, and thus reduce the the level of diastereoselection. Therefore, a compromise must be achieved between rate of alkylation and the level of diastereoselection. We examined a variety of alkali metal and alkaline earth cations in order to determine their effect on alkylation rate and product diastereoselection.

Imides **16c**, **20c**, and **22c** were deprotonated with lithium diisopropylamide (LDA), sodium hexamethyldisilylamide (NaHMDS), or potassium hexamethyldisilylamide (KHMDS) to afford their respective lithium, sodium, and potassium enolates. The magnesium enolate of imide **16c** was prepared by adding anhydrous magnesium bromide to the preformed lithium enolate. The various metal enolates were treated with 3 equiv of methyl iodide (eq 20). The alkylation results are summarized in Table 7.







(20)

Table 7. Effect of Cation on Alkylation Diastereoselection (eq. 20).

Entry	Imide	Base[a]	Alkylation Conditions	Ratio[b] 2R:2S	Yield[c]
A	**16c**	LDA	0°C, 2 h	87:13	75% (97%)
B	**16c**	NaHMDS	-78°C, 2 h	93:7	82% (93%)
C	**16c**	KHMDS	-78°C, 2 h	81:19	(95%)
D	**16c**	LDA, $MgBr_2$[d]	0°C, 2 h	94:6	(76%)
E	**20c**	LDA	0°C, 2 h	10:90	86% (99%)[e]
F	**20c**	NaHMDS	-78°C, 2 h	9:91	79% (99%)[e]
G	**20c**	KHMDS	-78°C, 2 h	14:86	(99%)
H	**22c**	LDA	0°C, 1 h	81:19	(85%)
I	**22c**	NaHMDS	-78°C, 1 h	87:13	(97%)
J	**22c**	KHMDS	-78°C, 1 h	76:24	(96%)

a) Enolization conditions: -78°C for 0.5 h with the indicated base (LDA = lithium diisopropylamide, NaHMDS = sodium hexamethyldisilylamide, KHMDS = potassium hexamethyldisilylamide. b) Diastereomer ratio determined by capillary GC analysis of the unfrationated product. c) Isolated yield of the major diastereomer. Yield in parentheses refers to the percentage of substrate alkylated. d) 1.1 equiv of anhydrous magnesium bromide was added to the preformed lithium enolate prior to alkylation. e) We thank Dr. M. D. Ennis for these results, ref. 29.

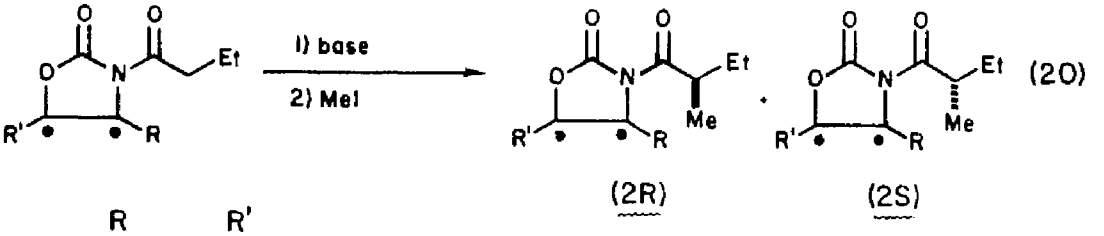
Both the sodium and potassium imide enolates react with methyl iodide at -78°C to afford the alkylated imide in good to excellent yield. Compared with the lithium enolate, not only is the sodium enolate more reactive, but it is also more diastereoselective. For example, treatment of the lithium enolate derived from imide **16c** with methyl iodide at 0°C affords an 87:13 ratio of diastereomers (Table 7, entry A), whereas the corresponding sodium enolate reacts with methyl iodide at -78°C to afford a 93:7 ratio of diastereomers (Table 7, entry B). With the valinol-derived imide **20c**, the percent increase in diastereoselectivity going from the lithium to the sodium enolate is not as dramatic as the norephedrine-derived imide **16c** (Table 7, compare entries A and B with E and F).

Potassium as the counterion, although more reactive than lithium, is significantly less diastereoselective than either lithium or sodium. Thus, alkylation of the potassium enolate derived from imide **16c** with methyl iodide at -78°C affords an 81:19 ratio of diastereomers (Table 7, entry C). Presumably, the potassium is less capable of forming a conformationally rigid chelated enolate, and thus is less diastereoselective. The sodium and potassium enolates are less thermally stable than the corresponding lithium enolate. At temperatures above -20°C, the sodium and potassium enolates decompose more rapidly than they react with methyl iodide.

The counterion affording the highest level of diastereoselection is magnesium. Alkylation of the magnesium enolate derived from imide **16c** with methyl iodide affords a 94:6 ratio of diastereomers (Table 7, entry D). The magnesium enolate, however, is less reactive than even the lithium enolate. Only 76% of the magnesium enolate is alkylated in 2 h

at 0°C. Presumably, magnesium as the dication forms a more stable chelate than alkali metal cations, and as such is less nucleophilic. The relative stability of the magnesium enolate also manifests itself by decreasing the rate of enolate decomposition. Despite the higher diastereoselectivity of the magnesium enolate, the lithium enolate at 0°C or the sodium enolate at -78° are better suited in terms of reaction rate, product yield, and alkylation diastereoselection.

The nature of the C-4 substituent on the 2-oxazolidinone ring was envisioned to play a major role in determining both the sense and the magnitude of alkylation diastereoselection. Since the C-4 position of the 2-oxazolidinone ring is in closer proximity to the prochiral reaction site than the C-5 position, substitution at the C-4 position was expected to have a greater influence over alkylation diastereoselection. In order to investigate the effect of the C-4 substituent, imide enolates derived from a variety of 2-oxazolidinones were alkylated with 3 equiv of methyl iodide (eq 20). The results are summarized in Table 8.



(20)

	R	R'
14c	Me(α)	H
16c	Me(α)	Ph(α)
18c	Me(β)	Ph(α)
20c	i-Pr(β)	H
22c	Ph(α)	H
24c	$PhCH_2$(β)	H

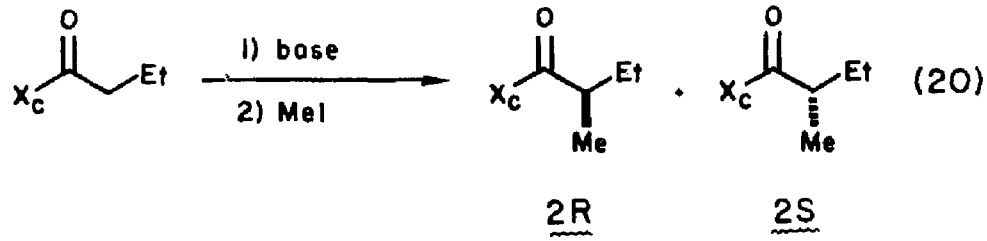


Table 8. Effect of 2-Oxazolidinone Structure on Alkylation Diastereoselection (eq 20).

Entry	Imide	2-Oxazolidinone R	R'	Chirality	Base[a]	Alkylation[b] Conditions	Ratio[c] 2R:2S	Yield[d]
A	**14c**	Me	H	(±)	LDA	0°C, 2 h	86:14	(99%)
B	**14c**	Me	H	(±)	NaHMDS	-78°C, 2 h	92:8	(92%)
C	**16c**	Me	Ph	(4R,5S)	LDA	0°C, 2 h	87:13	75% (97%)
D	**16c**	Me	Ph	(4R,5S)	NaHMDS	-78°C, 2 h	93:7	82% (93%)
E	**18c**	Me	Ph	(4S,5S)	LDA	0°C, 2 h	14:86	(98%)
F[e]	**20c**	i-Pr	H	(4S)	LDA	0°C, 2 h	10:90	86% (99%)
G[e]	**20c**	i-Pr	H	(4S)	NaHMDS	-78°C, 2 h	9:91	79% (99%)
H	**22c**	Ph	H	(4R)	LDA	0°C, 2 h	81:19	(85%)
I	**22c**	Ph	H	(4R)	NaHMDS	-78°C, 2 h	87:13	(97%)
J[f]	**24c**	$PhCH_2$	H	(4S)	LDA	-30°C, 2 h	6:94	

a) Enolization conditions: -78°C for 0.5 h with the indicated base (LDA = lithium diisopropylamide, NaHMDS = sodium hexamethyldisilylamide). b) Alkylation with 3 equiv of methyl iodide. c) Diastereomer ratio determined by capillary GC analysis of the unfractionated product. d) Isolated yield of major diastereomer; yield in paraentheses refers to the percentage of substrate alkylated. e) We thank Dr. M. D. Ennis for these results, ref. 29. f) We thank Mr. K. T. Chapman for this result, ref. 32.

The first observation to be made is that (4R)- and (4S)-4-substituted 2-oxazolidinones induce the opposite sense of asymmetry, thereby confirming one of the hypotheses of this project. The size of the C-4 substituent influences the level of diastereoselection. The magnitude of the difference, however, is not very large. For example, imide **14c** with a lone C-4 methyl substituent affords an 86:14 ratio of diastereomers (Table 8, entry A), whereas imide **20c** with a C-4 isopropyl substituent affords a 90:10 ratio of diastereomers (Table 8, entry F).

Interestingly, imide **22c** with a C-4 phenyl substituent affords an 81:19 ratio of diastereomers (Table 8, entry H). Thus, a phenyl substituent presents a smaller diastereofacial bias than a methyl substituent. Presumably, the planer phenyl ring adopts a conformation less sterically demanding than the three-dimensional methyl or isopropyl substituents.

Substitution at the C-5 position of the 2-oxazolidinone ring has little effect on the level of alkylation diastereoselection. For example, alkylation of the lithium enolate derived from imide **14c** (with a C-4 methyl substituent) affords an 86:14 ratio of diastereomers (Table 8, entry A), whereas alkylation of the lithium enolate derived from imide **16c** (with a C-4 methyl substituent and a cis C-5 phenyl substituent) affords an 87:13 ratio of diastereomers (Table 8, entry C), or alkylation of the lithium enolate derived from imide **18c** (with a C-4 methyl substituent and a trans C-5 phenyl substituent) affords an 86:14 ratio of diastereomers (Table 8, entry E).

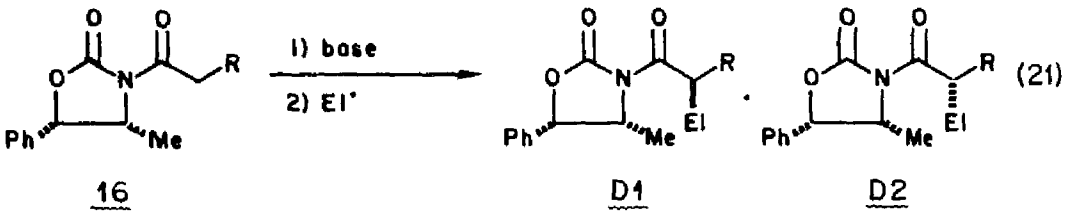
In summary, the C-4 substituent is the most important factor controlling the level of alkylation diastereoselection. Indeed, a methyl group in this position is sufficient to provide a high level of dia-

stereoselection. Imides derived from (4R,5S)-norephedrine 2-oxazolidinone **6** and (4S)-valinol 2-oxazolidinone **8** exhibit the best level of diastereoselection for their respective chiralities.

Finally, we treated the 2-oxazolidinone imide enolates with a variety of electrophiles in order to determine the effect electrophile structure plays on the rate of alkylation and the level of diastereoselection. The results obtained for alkylating enolates derived from imide **16** (eq 21) are summarized in Table 9. The corresponding results for alkylating enolates derived from imide **20** (eq 22) are summarized in Table 10.

Methyl iodide affords the lowest level of alkylation diastereoselection. Alkylation of these lithium imide enolates with methyl iodide affords a diastereoselection (**D1:D2**) of ca. 9:1. As previously noted, the corresponding sodium enolate exhibits a slightly higher level of diastereoselection with this electrophile. For example, alkylation of the lithium enolate derived from imide **16c** affords an 87:13 ratio of diastereomers (Table 9, entry K), whereas alkylation of the corresponding sodium enolate affords a 93:7 ratio of diastereomers (Table 9, entry L). The magnitude of improvement is not as great with the valinol-derived imides. Thus, alkylation of the lithium enolate derived from imide **20i** affords a 91:9 ratio of diastereomers (Table 10, entry J), whereas alkylation of the corresponding sodium enolate affords a 93:7 ratio of diastereomers (Table 10, entry K).

Alkyl halides other than methyl iodide are significantly less reactive with these enolates. For example, alkylation of the lithium enolate derived from imide **16b** (R = methyl) with ethyl iodide (3-10

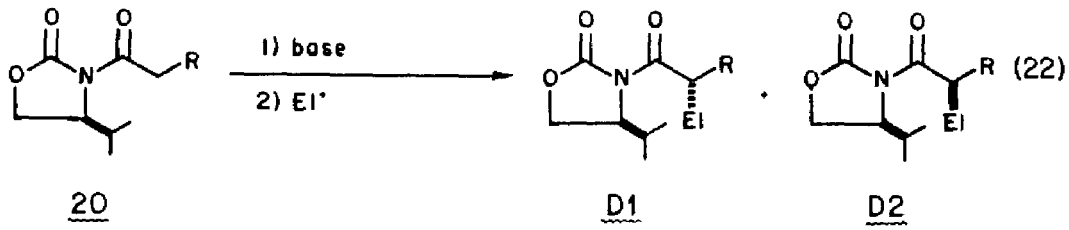


16 D1 D2 (21)

Table 9. Diastereoselective Alkylation of Imide Enolates Derived from **16** (eq 21).

Entry	Imide	R	Base[a]	Electrophile (equiv)	Alkylation Conditions	Ratio[b] D1:D2	Product	Yield[c]
A	**16b**	Me	LDA	EtI (3)	0°C, 2 h	91:9	**17a**	28%
B	**16b**	Me	NaHMDS	EtI (4)	-20°C, 2 h	94:6	**17a**	53%
C	**16b**	Me	LDA	CH_2=$CHCH_2Br$ (3)	0°C, 2 h	98:2	**17b**	75%
D	**16b**	Me	NaHMDS	CH_2=$CHCH_2I$ (2)	-78°C, 3 h	97:3	**17b**	83%
E[d]	**16b**	Me	LDA	CH_2=$C(CH_3)CH_2Br$ (3)	0°C, 2 h	97:3	**17c**	62%
F[d]	**16b**	Me	LDA	CH_2=$C(CH_3)CH_2I$ (2)	-78°C, 1 h, -35°C, 2 h	97:3	**17c**	73%
G	**16b**	Me	LDA	$BnOCH_2Br$ (2)	-45°C, 4 h	98:2	**17e**	72%
H	**16b**	Me	LDA	EtO_2CCH_2Br (3)	0°C, 2 h	93:7	**17f**	51%
I	**16b**	Me	LDA	BnBr (1.1)	0°C, 2 h	98:2	**17g**	73%
J	**16b**	Me	NaHMDS	BnBr (1.1)	-78°C, 3 h	98:2	**17g**	79%
K	**16c**	Et	LDA	MeI (3)	0°C, 2 h	87:13	**17h**	75%
L	**16c**	Et	NaHMDS	MeI (5)	-78°C, 3 h	93:7	**17h**	82%
M	**16d**	i-Pr	LDA	MeI (3)	-10°C, 2 h	87:13	**17i**	54%
N	**16f**	t-Bu	LDA	MeI (3)	-10°C, 2 h	94:6	**17j**	56%
O	**16h**	$PhCH_2$	LDA	$BnSCH_2Br$ (1.1)	-25°C, 2 h, 0°C, 2 h	98:2	**17k**	76%[e]
P	**16i**	n-C_8H_{17}	LDA	MeI (4)	0°C, 2 h	89:11	**17l**	70%
Q	**16i**	n-C_8H_{17}	NaHMDS	MeI (4)	-78°C, 2 h	94:6	**17l**	85%

a) Enolization conditions: -78°C for 0.5 h with the indicated base (LDA = lithium diisopropylamide, NaHMDS = sodium hexamethyldisilylamide). b) Diastereomer ratio determined by capillary GC analysis of the unfractionated product. c) Isolated yield of the major diastereomer (**D1:D2** $\geq$ 99:1 unless otherwise noted). d) We thank Dr. M. D. Ennis for these results. e) **D1:D2** = 98:2.



20 D1 D2 (22)

Table 10. Diastereoselective Alkylation of Imide Enolates Derived from **20** (eq 21).

Entry	Imide	R	Base[a]	Electrophile (equiv)	Alkylation Conditions	Ratio[b] D1:D2	Product	Yield[c]
A[d]	**20b**	Me	LDA	EtI (10)	0°C, 2 h	94:6	**21a**	36%
B	**20b**	Me	LDA	CH_2=$CHCH_2Br$ (3)	-10°C, 2 h	98:2	**21b**	75%
C[d]	**20b**	Me	LDA	CH_2=$C(CH_3)CH_2Br$ (3)	0°C, 2 h	98:2	**21c**	62%
D[e]	**20b**	Me	LDA	$PhCH$=$CHCH_2Br$ (1.5)	-40°C, 1 h, 0°C, 2 h	99:1	**21d**	84%
E	**20b**	Me	LDA	$BnOCH_2Br$ (2)	-45°C, 4h	98:2	**21e**	62-74%
F	**20b**	Me	LDA	EtO_2CCH_2Br (2)	-20°C, 2 h 0°C, 2 h	95:5	**21f**	51%
G[d]	**20b**	Me	LDA	BnBr (3)	0°C, 2 h	>99:1	**21g**	97%
H[d]	**20c**	Et	LDA	MeI (3)	0°C, 2 h	90:10	**21h**	86%
I	**20h**	$PhCH_2$	LDA	$BnSCH_2Br$ (1.1)	-20°C, 2 h	97:3	**21k**	83%[f]
J	**20i**	n-C_8H_{17}	LDA	MeI (3)	0°C, 2 h	91:9	**21l**	83%
K	**20i**	n-C_8H_{17}	NaHMDS	MeI (3)	-78°C, 2 h	93:7	**21l**	77%

a) Enolization conditions: -78°C for 0.5 h with the indicated base (LDA = lithium diisopropylamide, NaHMDS = sodium hexamethyldisilylamide). b) Diastereomer ratio determined by capillary GC analysis of the unfractionated product. c) Isolated yield of the major diastereomer (D1:D2 $\geq$ 99:1 unless otherwise noted). d) We thank Dr. M. D. Ennis for these results. e) We thank Mr. K. L. Dow for this result, ref. 34. f) D1:D2 = 98:2.

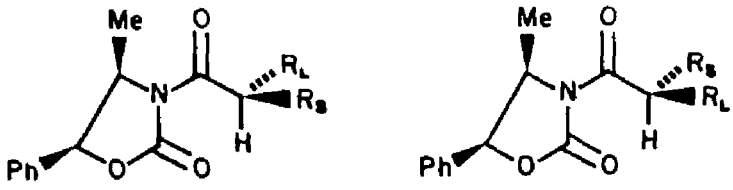
equiv) affords the alkylated product in 28% isolated yield (Table 9, entry A). Even with the more reactive sodium enolate, at -20°C, only 53% of the alkylated product is isolated (Table 9, entry B). Attempts to alkylate 2-oxazolidinone imide enolates with either n-butyl iodide or isobutyl iodide fail; only recovered starting materials and/or enolate decomposition products are isolated.

Allylic halides and benzyl bromide reacts with 2-oxazolidinone imide enolates to afford the alkylated products in moderate to excellent yields (62-97%). The level of alkylation diastereoselection (**D1:D2**) is consistently >95:5. With these more reactive electrophiles, both the lithium and the sodium enolates provide about the same level of diastereoselection. Alkylation of the sodium enolate, however, often improves the product yield.

Other reactive electrophiles that react with 2-oxazolidinone imide enolates include benzyl bromomethyl ether (Table 9, entry G; Table 10, entry E) and benzyl bromomethyl sulfide (Table 9, entry K; Table 10, entry I). In both cases, the level of alkylation diastereoselection (**D1:D2**) is $\geq$ 97:3. Alkylation of propanoate imides with benzyl bromomethyl ether affords chiral derivatives of 2-methyl-3-benzyloxypropanoic acid, a useful chiral precursor previously obtained by the microbial hydroxylation of 2-methylpropanoic acid.[33] We have employed (2S)-2-methyl-3-benzyloxy-1-propanol, derived from a diastereoselective imide alkylation, in the total synthesis of ionomycin.[34] Alkylation of 3-phenylpropanoate imides with benzyl bromomethyl sulfide affords chiral derivatives of 2-benzylthiomethyl-3-phenylpropanoic acid, which we have employed as precursors for the synthesis of both enantiomers of thiorphan (see Appendix 4).[35]

The diastereomeric imide alkylation products are easily separated by liquid chromatography on silica gel. This permits the major diastereomer to be isolated in a state of high diastereomeric purity (**D1:D2** $\geq$ 99:1). The capacity factor k' (defined as $(t_1 - t_0)/t_0$ where t_1 is the retention time of diastereomer 1 and t_0 is the retention time of an unretained compound) and the separation factor α (defined as k'_2/k'_1 where k'_1 and k'_2 are the capacity factors for diastereomers 1 and 2 respectively) for several pairs of diastereomers are recorded in Table 11. From the data in Table 11 several interesting trends are observed. The amount of separation depends on the difference in size between R and R'. Even when R = methyl and R' = ethyl, a reasonable diastereomer separation can be obtained. Also, the order of elution is regular. With alkylated (4R,5S)-norephedrine 2-oxazolidinone imides the (2R)-diastereomer elutes first. This information permits the minor diastereomer to be removed, in a predictable manner, by discarding or recycling the head or the tail of the chromatographic peak. Generally, we observed that diastereomers with an α >1.3 are readily separable by either "flash" chromatography or by MPLC (see Experimental Section).

Recently, Pirkle has reported that chiral 2-oxazolidinones can be used to resolve racemic primary amines *via* diastereomeric allophanate derivatives (**27** and **28**).[36] The diastereomers are separated by liquid chromatography on silica gel. Diastereomer **27** elutes before diastereomer **28**. The observed order of elution is rationalized in the following manner. The two diastereomers adopt the conformations shown in Figure 7. Dipole-dipole repulsion causes the two carbonyls to choose an antiperiplaner arrangement.[37] Hydrogen bonding between the NH and the 2-oxazolidinone carbonyl provides additional stabilization for this con-



(2R)-17 (2S)-17

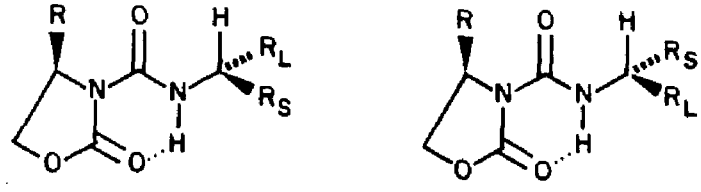
Figure 6. Alkylated N-Acyl 2-Oxazolidinone Diastereomers.

Table 11. HPLC Separation of Alkylated N-Acyl 2-Oxazolidinone Diastereomers (Figure 6).[a]

Entry	R_S	R_L	k' 2R	k' 2S	α
A	Me	Et	1.04	1.39	1.34
B	Me	$PhCH_2$	1.34	2.11	1.57
C	Me	$CH_2=CHCH_2$	0.96	1.53	1.59
D	Me	i-Pr	0.81	1.34	1.65
E	Me	t-Bu	0.53	1.05	1.94
F	Me	n-C_8H_{17}	0.39	1.05	2.69

a) HPLC conditions: 88:12 isooctane/ethyl acetate, 2.0 mL/min, 10 cm x 8mm, Waters Associates Radial Pak 5 μm silica gel column.

formation. This arrangement places the R and R_L substituents of diastereomer **27** on opposite faces of the molecule, and thus **27** is better able to "fend off" polar associations with silica gel than **28**. Therefore, diastereomer **27** is the first to elute.



27 28

Figure 7. Diastereomeric Allophanate Derivatives

A similar argument can be used to explain the order of elution for alkylated N-acyl 2-oxazolidinones. The two diastereomers adopt the conformation shown in Figure 6. Dipole-dipole repulsion maintains the two carbonyls in an anti-periplaner arrangement.[37] The (2R)-diastereomer places the R_L substituent anti to the resident chirality on the 2-oxazolidinone ring. Therefore, the (2R)-diastereomer, less able to associate with silica gel, elutes first.

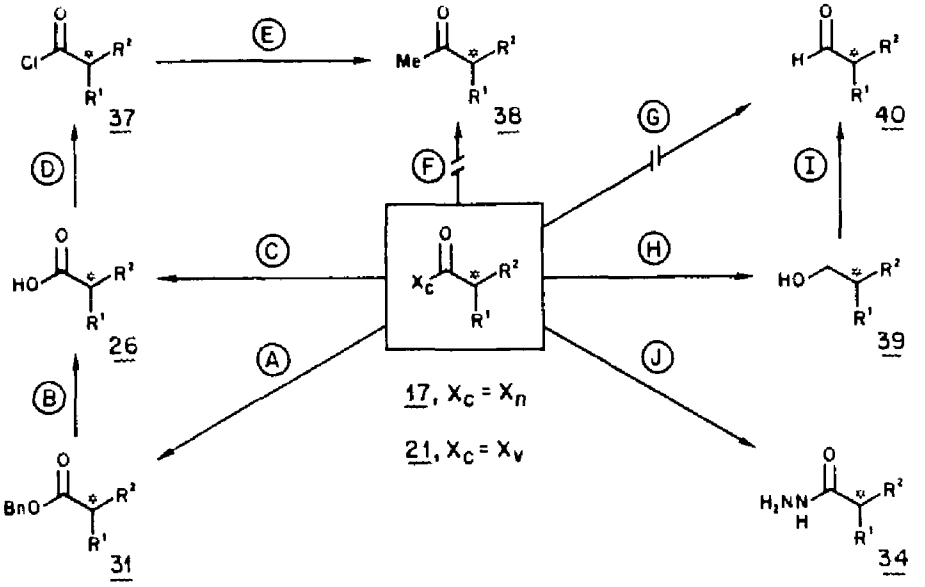
In summary, N-acyl 2-oxazolidinones are cleanly deprotonated with LDA or NaHMDS in THF at -78°C to afford the lithium or sodium enolate. Chiral 2-oxazolidinone imide enolates react with methyl iodide, allylic halides, benzyl bromide, and other reactive electrophiles in a highly diastereoselective manner. The C-4 substituent of the 2-oxazolidinone ring provides the asymmetric bias. A methyl group in this position is sufficient to provide a high level of diastereoselection. Either sense of asymmetric induction can be achieved by use of chiral 2-oxazolidinones derived from (1S,2R)-norephedrine or (2S)-valinol. The sodium enolate is more reactive, and when alkylated with methyl iodide more diastereoselective, than the corresponding lithium enolate. The resultant diastereomeric products can, in a predictable manner, be purified

to a high degree of diastereomeric purity by liquid chromatography on silica gel.

F. Removal of the Chiral Auxiliary. We have demonstrated that chiral N-acyl 2-oxazolidinones are alkylated in a highly diastereoselective fashion, and that the resultant products can be obtained in a diastereomerically pure state. The remaining criterion to be demonstrated is the selective removal of the chiral auxiliary from the alkylated product in a manner preserving the newly formed stereocenter. In terms of chiral economy, it also is useful if the chiral auxiliary can be recovered and recycled.

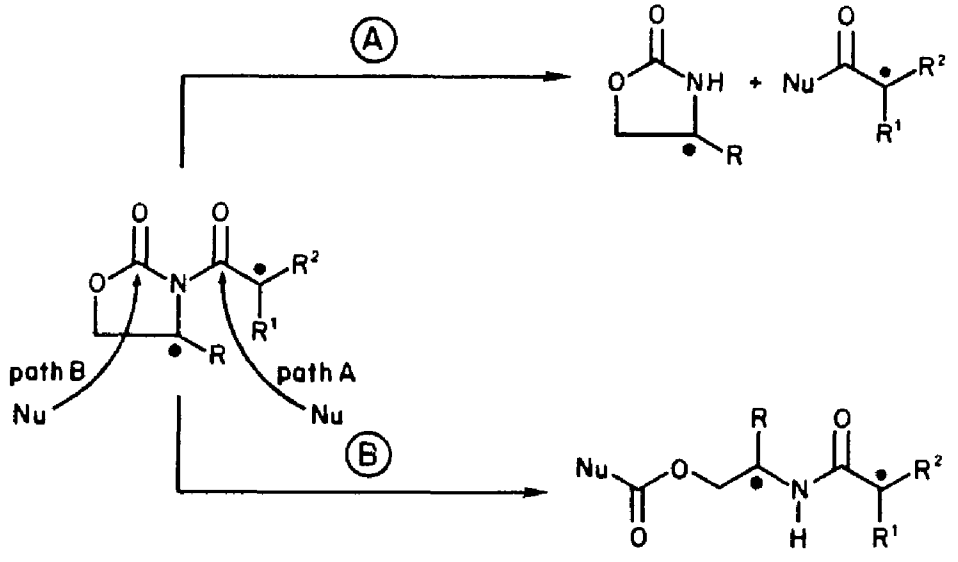
We have developed several convenient procedures for the nondestructive cleavage of the chiral auxiliary from alkylated N-acyl 2-oxazolidinones. The chiral product can be obtained in high yield in several different oxidation states. The amount of racemization is minimal. The various transformations for removing the chiral auxiliary are illustrated in Scheme 8.

The removal of 2-oxazolidinones from alkylated imides requires nucleophilic attack at the exocyclic imide carbonyl (Scheme 9, path A). Nucleophilic attack at the endocyclic 2-oxazolidinone carbonyl affords the ring opened product (Scheme 9, path B). Path A must be favored to obtain a high yield of the chiral product. Increasing the size of R^1 and R^2, however, can hinder nucleophilic attack at the exocyclic carbonyl, and thereby favor ring opening. Therefore, removal of the chiral auxiliary from the alkylated product is system dependent. We have found by careful choice of reaction conditions that ring opening can be minimized. The various methods of chiral auxiliary removal are described below.



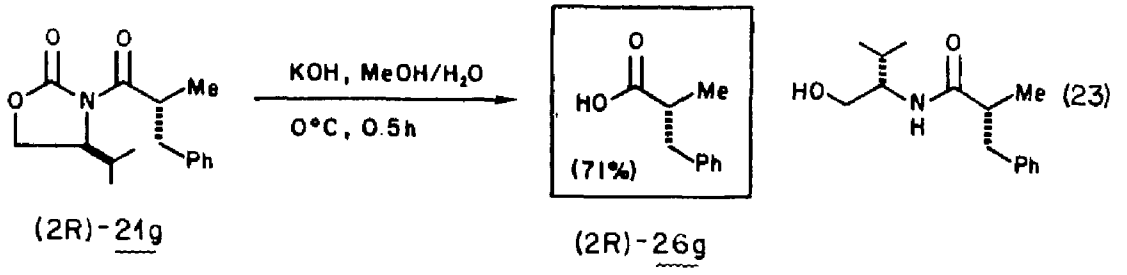
A) LiOBn, THF, 0°C B) H_2, 5%Pd/C, EtOH or 6M HBr in HOAc. C) KOH, MeOH/H_2O, 0°C. D) $(COCl)_2$, CH_2Cl_2, 0°C. E) $Cp_2Ti{=}CH_2$, CH_2Cl_2. F) MeMgBr, CH_2Cl_2. G) DIBAL, CH_2Cl_2. H) $LiAlH_4$ or $LiBH_4$, THF. I) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. J) H_2NNH_2, EtOH

Scheme 8

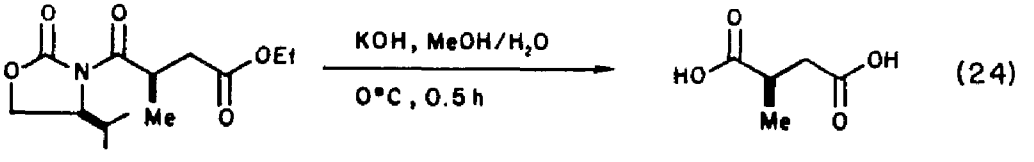


Scheme 9

The first removal technique investigated was base-catalyzed hydrolysis. Treatment of alkylated imide (2R)-**21g** with potassium hydroxide in methanol/water at 0°C affords (2R)-2-methyl-3-phenylpropanoic acid **26g** in 71% yield (eq 23).[29] The remainder of the product is the ring opened valinol amide. The hydrolysis of other alkylated imides affords similar mixtures. Only imides (2S)-**17f** and (2R)-**21f** are hydrolyzed to afford the resultant chiral acids in >90% yield (eqs 24 and 25). Presumably, the selectivity in this example is assisted by intramolecular formation of a cyclic anhydride, which then opens to afford the chiral 2-methylsuccinic acid **26f**.

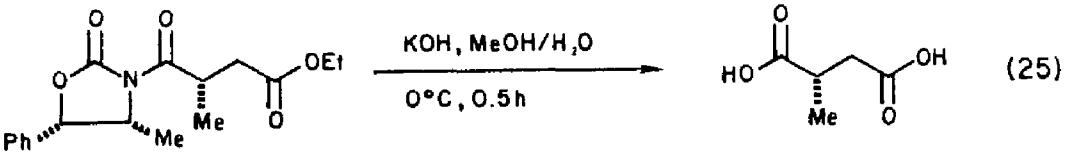


(2R)-21g (2R)-26g



(2R)-21f (2R)-26f (91%)

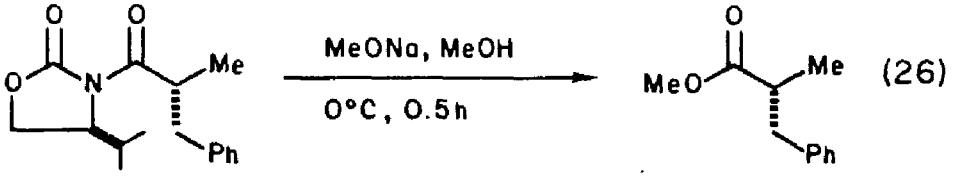
$[\alpha]_{589} = -15.0°$ (c 4.21, EtOH)



(2S)-17f (2S)-26f (95%)

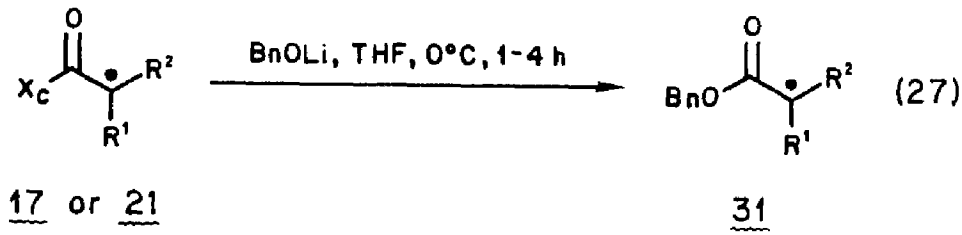
$[\alpha]_{589} = +15.7°$ (c 4.25, EtOH)

Transesterification was investigated as an alternate method for removing the chiral auxiliary from alkylated imides. The resultant chiral ester also is in the carboxylic acid oxidation state. Methanolysis of imide (2R)-**21g** (MeOH, NaOMe, 0°C) proceeds rapidly to afford methyl (2R)-2-methyl-3-phenylpropanoate **30g** in 60% yield (eq 26).[29] Unfortunately, as with base-catalyzed hydrolysis, ring opening also competes with this process. Similar mixtures are obtained with other alkylated imides. Other bases (LiOMe, KOMe, $Mg(OMe)_2$) do not significantly improve the results.

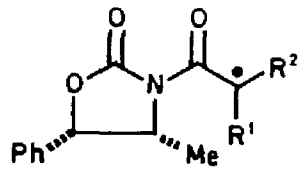


(2R)-21g (2R)-30g (60%)

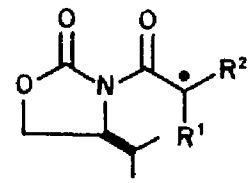
We found a transesterification reaction that consistently affords chiral esters in >90% yield. Treatment of the alkylated imide (ca. 0.3 M in THF, 0°C) with 1.5 equiv of lithium benzyloxide cleanly affords the corresponding benzyl ester (eq 27). The reaction conditions are relatively specific, and the reaction is only successful for preparing benzyl esters. But the process is successful with most alkylated imides and it causes minimal racemization (vide infra). The transesterification results for cleavage of various alkylated imides with lithium benzyloxide are summarized in Table 12.



17 or 21 — 31



17



21

Table 12. Transesterification of Alkylated 2-Oxazolidinone Imides to Afford Benzyl Esters (eq 27).[a]

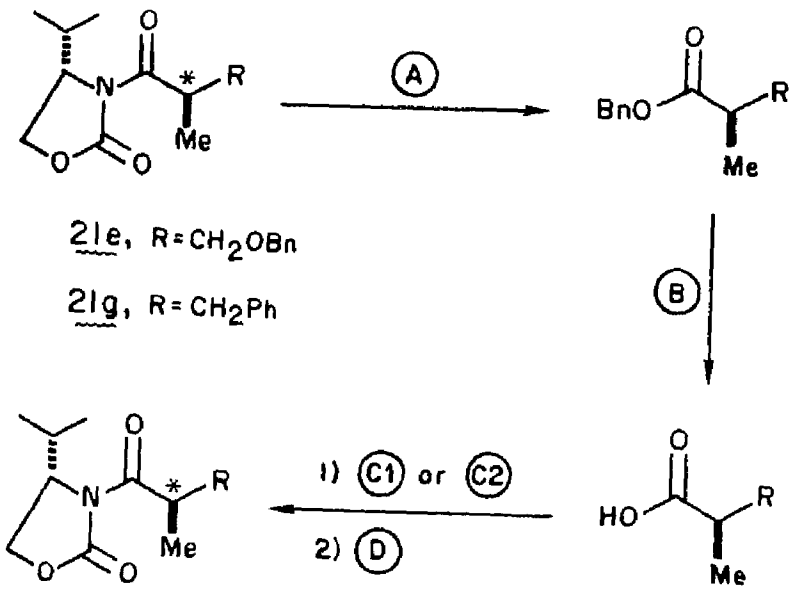
Entry	Imide	R_1	R_2	2R:2S[b]	Ester	Yield[c]	CONFIG	$[\alpha]_{589}$	(c, CH_2Cl_2)
A	**17a**	Me	Et	<1:99	**31a**	90%	S	+12.8°	2.16
B[d]	**21h**	Me	Et	<1:99	**31a**	92%	S	+12.5°	5.55
C	**17h**	Et	Me	>99:1	**31a**	93%	R	-12.6°	2.85
D[d]	**21a**	Et	Me	>99:1	**31a**	89%	R	-12.6°	6.38
E	**17b**	Me	CH_2=$CHCH_2$	<1:99	**31b**	86%	S	+2.3°	14.7
F[d]	**17c**	Me	CH_2=$C(CH_3)CH_2$	3:97	**31c**	93%	S	-3.7°	6.33
G[d]	**21c**	Me	CH_2=$C(CH_3)CH_2$	>99:1	**31c**	93%	R	+3.9°	5.86
H	**21e**	Me	$BnOCH_2$	>99:1	**31e**	96%	R	-3.5°	4.78
I	**17g**	Me	$PhCH_2$	<1:99	**31g**	92%	S	+26.8°	5.93
J[d]	**21g**	Me	$PhCH_2$	>99:1	**31g**	92%	R	-26.8°	2.33
K	**17k**	$PhCH_2$	$BnSCH_2$	98:2	**31k**	83%	R	+36.2°	0.86
L	**21k**	$PhCH_2$	$BnSCH_2$	2:98	**31k**	82%	S	-34.6°	2.46

a) Transesterification reaction performed with 1.5 equiv of lithium benzyloxide in THF (ca. 0.3 M) at 0°C for 1 h. b) Diastereomer ratio of alkylated imide prior to transesterification. c) Isolated yield of benzyl ester. d) We thank Dr. M. D. Ennis for these results, ref. 29.

The specific rotation for enantiomeric benzyl esters derived from alkylated imides is equal in magnitude and opposite in sign (Table 12). Since we already have shown that both norephedrine and valinol-derived chiral auxiliaries have equally high enantiomeric purities, the optical rotation results suggest--but do not prove--that negligible racemization occurs during transesterification.

An experiment was designed to assay the maximum amount of racemization that occurs during transesterification. The experiment, outlined in Scheme 10, consists of four separate reactions: 1) transesterification (1.5 equiv of LiOBn, THF, 0°C, 1 h) of an alkylated imide of known diastereomeric purity to afford the chiral benzyl ester (step A); 2) hydrogenolysis (5% Pd on C, H_2, EtOH or THF) of the benzyl ester to afford the chiral carboxylic acid (step B); 3) treatment of this acid with ethyl chloroformate (THF, Et_3N, -10°C, 0.5 h) or oxallyl chloride (CH_2Cl_2, 0°C, 4 h) (step C); and finally 4) treatment of the resultant carboethoxy mixed anhydride or acid chloride with the metalated (4S)-valinol 2-oxazolidinone (THF, -78°C, 0.5 h) to afford the starting alkylated imide (step D). The results are summarized in Table 13.

Performing the racemization assay on imide (2R)-**21g** (R = $PhCH_2$) with an initial diastereomer ratio [(2R)-**21g**:(2S)-**21g**] of >99.9:0.1 affords the alkylated imide with a final diastereomer ratio of 99.8:0.2 (Table 13, entry A). Thus, with this imide, less than 0.2% racemization occurs. This places an upper limit on the amount of racemization that occurs during transesterification. The same assay repeated with imide (2R)-**21e** (R = $BnOCH_2$) [(2R)-**21e**:(2S)-**21e** = 99.2:0.8] resulted in 1.8% and 1.6% racemization (Table 13, entries B and C). Thus, even with a system more prone to racemization, less than 2% of the stereochemistry



A) LiOBn, THF, 0°C, 1h. B) H_2, 5% Pd/C, EtOH or THF.

C1) EtO_2CCl, Et_3N, THF, -10°C. C2) $(COCl)_2$, CH_2Cl_2, 0°C.

D) 8, n-BuLi, THF, -78°C.

Scheme 10

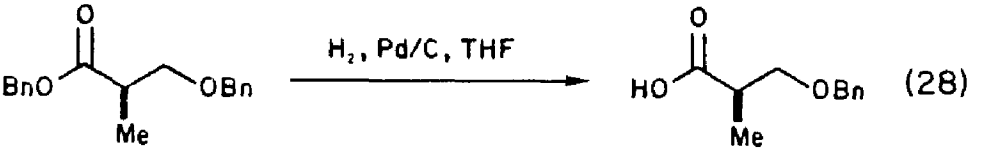
Table 13. Transesterification Racemization Assay (Scheme 10).

Entry	Imide	R	Diastereomer Ratio[a] Inital 2R:2S	Final 2R:2S	Percent Racemization
A[b]	**21g**	$PhCH_2$	99.9:0.1	99.8:0.2	0.2%
B	**21e**	$BnOCH_2$	99.2:0.8	98.3:1.7	1.8%
C[c]	**21e**	$BnOCH_2$	99.2:0.8	98.4:1.6[d]	1.6%

a) Diastereomer ratio determined by capillary GC analysis. b) We thank Dr. M. D. Ennis for this result, ref. 29. c) We thank Mr. J. R. Stille for this result, ref. 38. d) Acylation of the chiral acid chloride.

is eroded. Interestingly, the chiral acid chloride racemizes less than the chiral carboethoxy mixed anhydride.[38c]

The racemization assay also demonstrates a high-yield procedure for obtaining chiral carboxylic acids from alkylated imides: transesterification of the alkylated imide to give the benzyl ester followed by hydrogenolysis of the benzyl ester to afford the chiral carboxylic acid. This two-step sequence avoids the problem of 2-oxazolidinone ring opening encountered during base-catalyzed hydrolysis. The benzyl ester can even be selectively removed in the presence of a benzyl ether. For example, hydrogenolysis of benzyl (2R)-2-methyl-3-benzyloxypropanoate **31e** with 5% palladium on carbon in THF cleanly affords (2R)-2-methyl 3-benzyloxypropanoic acid **26e** in 98% yield (eq 28).



(28)

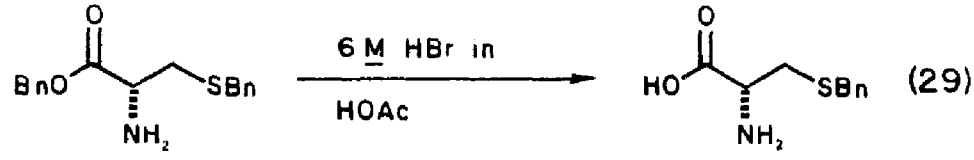
(2R)-31e

(2R)-26e

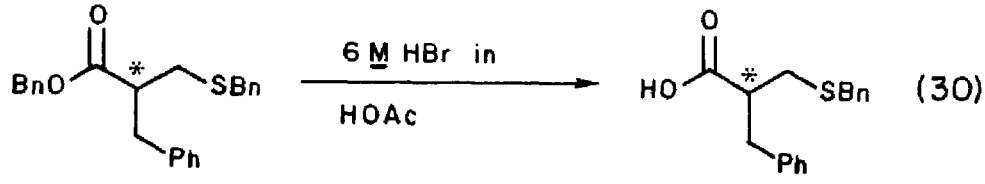
(98%)

We were unable to remove the benzyl ester from benzyl (2R)- or (2S)-2-benzylthiomethyl-3-phenylpropanoate **31k** by hydrogenolysis due to catalyst poisoning. Benzyl esters, however, also can be removed under acidic conditions. For example, Maclaren has reported that the benzyl ester of (S)-S-benzylcysteine, benzyl ester is selectively removed by treatment with anhydrous hydrogen bromide in glacial acetic acid (eq 29).[41] Applying this technique to (2R)-benzyl ester **31k** affords (2R)-2-benzylthiomethyl-3-phenylpropanoic acid **26k** ($[\alpha]_{589}$ = +54.1° (c 1.54,

EtOH)) in 85% yield (eq 30). Likewise, (2S)-benzyl ester **31k** affords (2R)-acid **26k** ($[\alpha]_{589}$ = -50.6° (c 1.57, EtOH)) in 83% yield.



(29)



(30)

31k

(2R)-26k (83%)

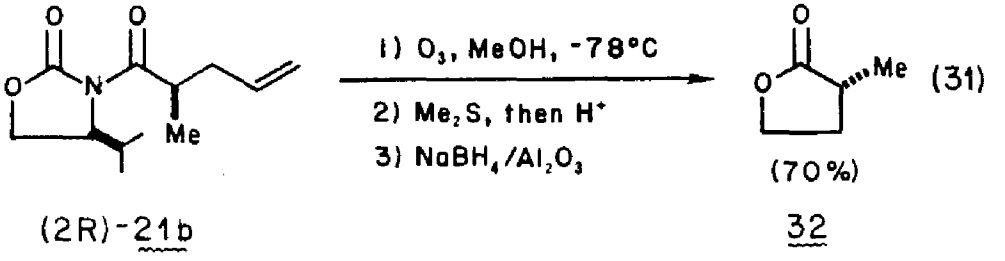
$[\alpha]_{589}$ = +54.1° (c 1.54, EtOH)

(2S)-26k (83%)

$[\alpha]_{589}$ = -50.6° (c 1.57, EtOH)

The lithium benzyloxide transesterification reaction is the only intermolecular transesterification reaction that consistently affords high yields of chiral esters. We, however, found that the intramolecular variant of the transesterification reaction is quite successful. The product from this reaction is the chiral 2-substituted lactone. Removal of the chiral auxiliary by intramolecular mediated transesterification requires the presence of a free hydroxyl in the substrate. The precursors we used to demonstrate these cyclizations are the allylated imides (2S)-**17b** and (2R)-**21b**.

Ozonolysis of imide (2R)-**21b** [(2R)-**21b**:(2S)-**21b** >99:1] in methanol at -78°C with Sudan Red III as an indicator[41] followed by dimethyl sulfide workup[42] gives a mixture of the aldehyde and the dimethyl acetal. Subjecting this mixture to hydrochloric acid in aqueous THF cleanly affords the aldehyde in 97% yield. Reduction of the resultant aldehyde with sodium borohydride on alumina[43] in diethyl ether gives the hydroxy imide, which spontaneously lactonizes upon distillation to give (2R)-2-methylbutyrolactone **32** ($[\alpha]_{589}$ = +21.2° (c 8.56, EtOH)) in 70% yield (eq 31). The specific rotation for (2R)-lactone **32** is in good agreement with the highest rotation reported in the literature for this lactone ($[\alpha]_{589}$ = +21.5° (c 5.5, EtOH)).[30]

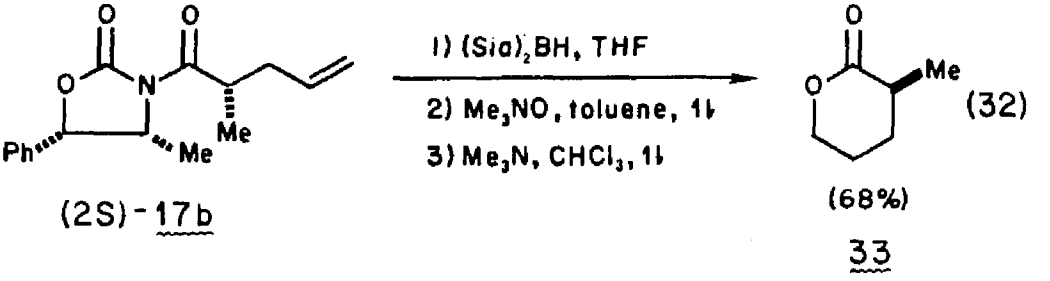


(31)

(2R)-21b

32

Hydroboration of imide (2S)-**17b** [(2R)-**17b**:(2S)-**17b** <1:99] with disiamylborane (THF, 0°C for 1.5 h then 25°C for 0.5 h) followed by oxidation of the resultant organoborane with triethylamine-N-oxide in refluxing toluene gives a mixture of the hydroxy imide and the lactone. Refluxing this mixture in the presence of excess triethylamine affords after chromatography (2S)-2-methylvalerolactone **33** ($[\alpha]_{589}$ = +67.3° (c 6.6, MeOH)) in 68% yield (eq 32).[29] The specific rotation for (2S)-lactone **33** exceeds the highest rotation reported in the literature for this lactone ($[\alpha]_{589}$ = +64.4° (c 4.4, MeOH)).[39]

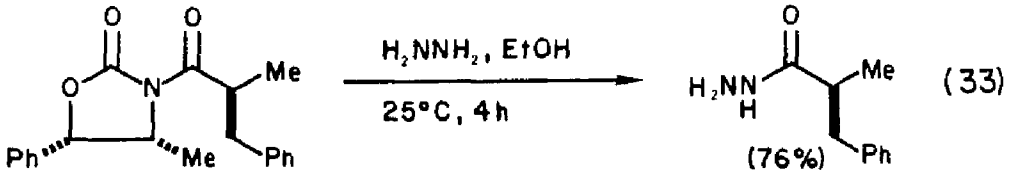


(2S)-17b

33

(32)

In addition to transesterification, the chiral product can be removed from the alkylated imide by transamination. Treatment of alkylated imide (2S)-**17g** [(2R)-**17g**:(2S)-**17g** <1:99] with anhydrous hydrazine in ethanol at 25°C for 4 h affords (2S)-2-methyl-3-propanoic acid, hydrazide **43g** in 76% yield (eq 33). Chiral hydrazides are potentially transformed via the acyl azide to chiral amides, amines, isocyanates, and urethanes (Scheme 11). These transformations are known to be free from racemization.[44]

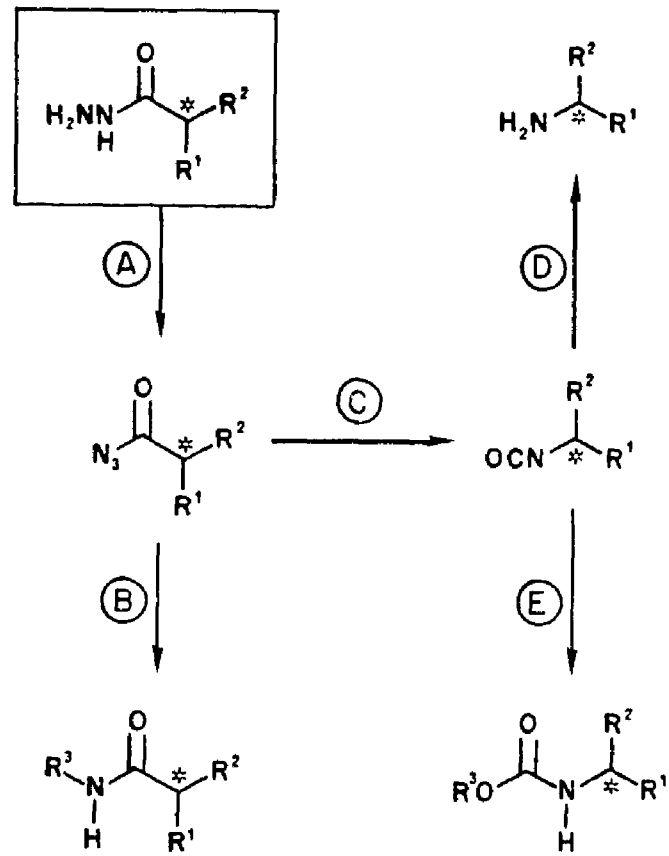


(2S)-17g

34

(33)

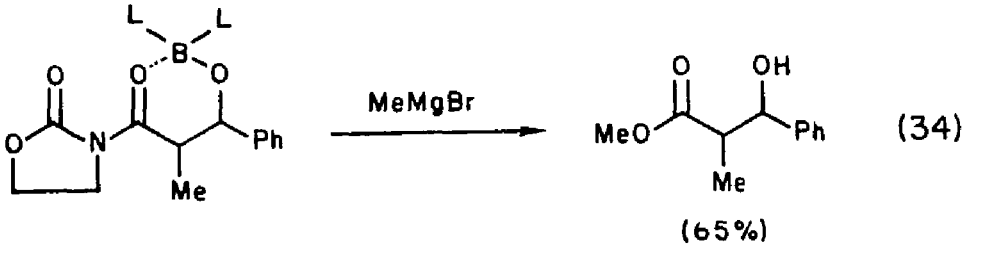
Cherpeck and Tannis, in our laboratories, have demonstrated that boron aldolates derived from N-acyl 2-oxazolidinones react with methylmagnesium bromide to afford the corresponding methyl ketone (eq 34).[45] We were interested in applying this transformation to the preparation of chiral ketones from alkylated imides. Treatment of alkylated imide (2S)-**17g** [(2R)-**17g**:(2S)-**17g** <1:99] with 1.1 equiv of methylmagnesium bromide in dichloromethane at 0°C for 3 h affords the ring-opened



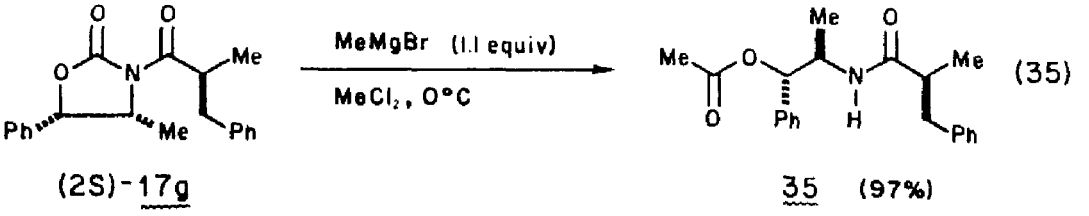
Scheme 11

norephedrine amide acetate **35** in 97% yield (eq 35). The structure of **35** was inferred by the presence of two carbonyl absorptions (1750 and 1685 cm^{-1}) in the IR spectrum, and the presence of two phenyl rings (7.2 and 7.1 ppm) and a methyl singlet (2.1 ppm) in the ^1H NMR spectrum. The same reaction repeated with excess methylmagnesium bromide in refluxing dichloromethane affords the ring-opened norephedrine amide **36** in 99% yield (eq 36). Presumably, the imide carbonyl is two hindered in the case of alkylated imides for the methylmagnesium bromide to approach the

imide carbonyl. Therefore, exclusive attack at the 2-oxazolidinone carbonyl cleanly affords the ring-opened product.



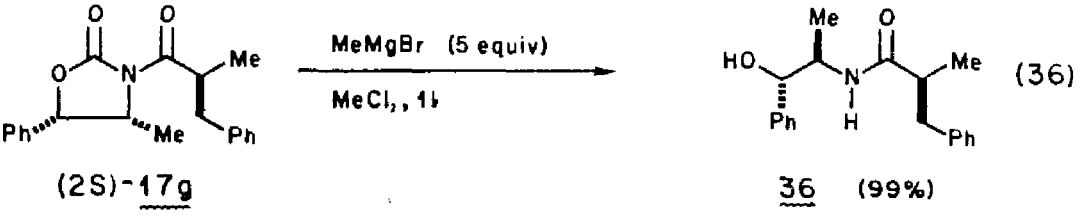
(34)



(2S)-17g

35 (97%)

(35)

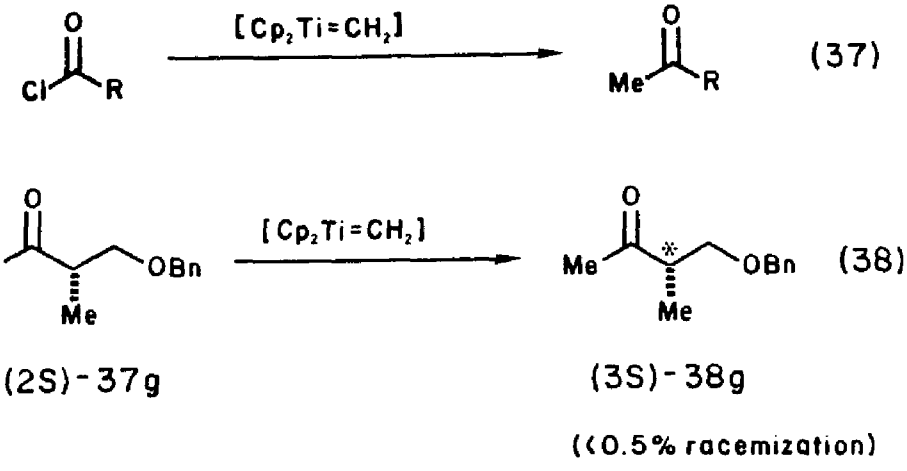


(2S)-17g

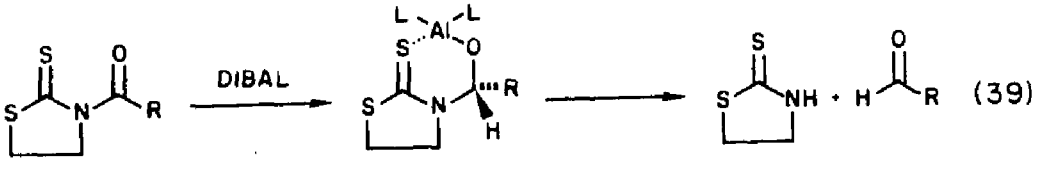
36 (99%)

(36)

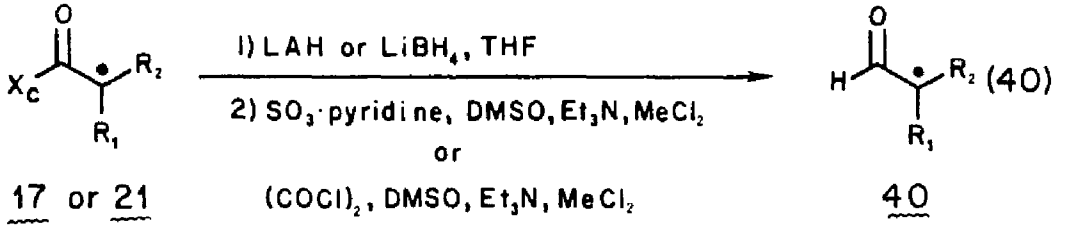
An alternate method is available to prepare chiral methyl ketones from the alkylated imides via an indirect route. Stille and Grubbs have demonstrated that the titanocene methylidene complex reacts with acid chlorides to afford methyl ketones (eq 37).[38] We already have shown that chiral acid chlorides can be prepared with less than 2% racemization. Reaction of (2R)-2-methyl-3-benzyloxypropanoic acid chloride **37g** with the titanocene methylidene complex affords (3R)-3-methyl-4-benzyloxy-2-butanone **38** with less than 0.5% additional racemization (eq 38).[38]



Mukaiyama has shown that N-acyl thiazolidine-2-thiones undergo reduction with diisobutylaluminum hydride (DIBAL) to afford the corresponding aldehyde (eq 39).[46] Chelation serves to stabilize the tetrahedral intermediate, and thus prevent over-reduction to the alcohol. We were interested in applying this transformation to the alkylated imides. Unfortunately, treatment of the alkylated imides with 1.1 equiv of DIBAL affords a mixture of starting material, aldehyde, and the over-reduced alcohol. Presumably, the 2-oxazolidinone is insufficiently basic to stabilize the tetrahedral intermediate.

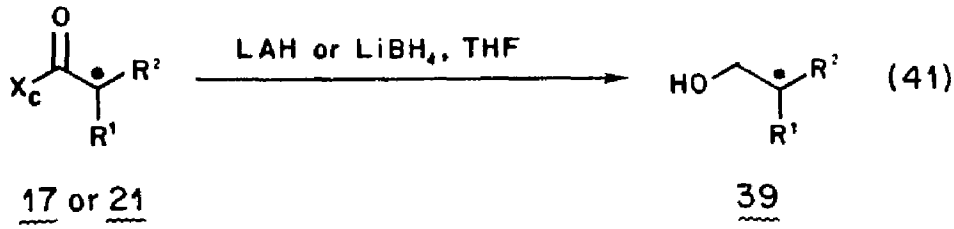


We have prepared chiral aldehydes from alkylated imides via a two-step reduction-oxidation process (eq 40). Reduction of alkylated imides with either lithium aluminum hydride (LAH) or lithium borohydride gives the chiral alcohol (vide infra). Oxidation of the resultant alcohol by the Parikh modification of the Moffet procedure (SO_3--pyridine, DMSO, Et_3N),[47] or the Swern procedure ($(COCl)_2$, DMSO, Et_3N)[48] affords the chiral aldehyde. Although chiral 2-substituted aldehydes are relatively prone to racemization, we have shown that these techniques usually limit the amount of racemization to under 0.5%.[29, 34, 37a]

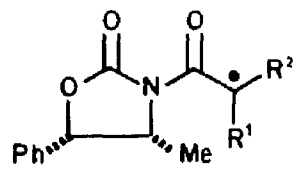


17 or 21 40

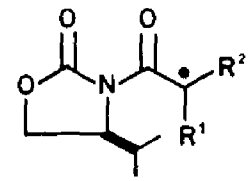
The alkylated imides are reduced with either LAH or lithium borohydride in THF to give the corresponding chiral primary alcohol **39** (eq 41). The reduction results are summarized in Table 14. The yield of alcohol ranges from 76-90%. Small amounts of the under-reduced aldehyde **40** as well as the ring-opened methyl amine **41** are responsible for the remainder of the product. Reduction at the 2-oxazolidinone carbonyl is minimized by maintaining the LAH reduction below 0°C, or the lithium borohydride reduction below 25°C. Other reductants such as borane, excess DIBAL, lithium triethylborohydride, or sodium borohydride do not afford significant yields of the chiral alcohol.



17 or 21 39



17



21

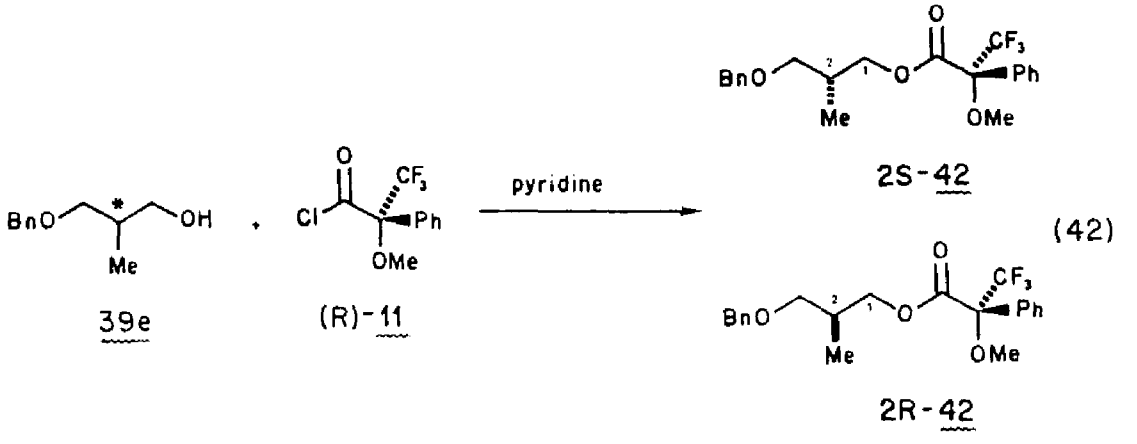
Table 14. Reduction of Alkylated 2-Oxazolidinone Imides (eq 41).

Entry	Imide	R1	R2	Ratio[a] 2R:2S	Reductant[b]	Conditions	Alcohol	CONFIG	Yield[c]	$[\alpha]_{589}$	(c, CH_2Cl_2)
A	**17e**	Me	$BnOCH_2$	<1:99	$LiBH_4$	0°C, 4 h	**39e**	S	88%	-4.2°	2.50
B	**21e**	Me	$BnOCH_2$	>99:1	$LiAlH_4$	0°C, 4 h	**39e**	R	76%	+5.3°[d]	2.20
C[e]	**21g**	Me	$PhCH_2$	>99:1	$LiBH_4$	25°C, 2 h	**39g**	R	78%	+10.7°[f]	0.94
D[e]	**21g**	Me	$PhCH_2$	>99:1	$LiAlH_4$	0°C, 0.5 h	**39g**	R	88%	+10.3°	1.15
E[e]	**21g**	Me	$PhCH_2$	>99:1	$LiAlH_4$	25°C, 0.5 h	**39g**	R	86%	+11.0°	0.65
F	**17i**	Me	$n\text{-}C_8H_{17}$	>99:1	$LiBH_4$	0°C, 4 h	**39i**	R	84%	+10.8°	4.37
G	**21i**	Me	$n\text{-}C_8H_{17}$	<1:99	$LiBH_4$	0°C, 4 h	**39i**	S	90%	-11.0°[g]	4.21

a) Diastereomer ratio of imide prior to reduction. b) One molar equiv, thus four hydride equivs. c) Isolated yield of alcohol. d) Lit. rotation +4.97° (0.93), ref. 33b. e) We thank Dr. M. D. Ennis for these results, ref. 29. f) Lit. rotation +11.8° (4.6), ref. 49. g) Lit. rotation -9.8° (neat), ref. 50.

The specific rotations for the various chiral alcohols are similar to the highest reported literature values (Table 13). The enantiomeric purity of (2R)- and (2S)-2-methyl-3-benzyloxy-1-propanol **39e** was confirmed by an alternate method. The Mosher ester of alcohol **39e** was prepared by the standard procedure (eq 42).[22] Neither capillary GC nor HPLC separates the diastereomers. The 500 MHz ^1H NMR spectra of (2R)-**42**

and (2S)-**42**, however, are sufficiently different to demonstrate that each enantiomer of the alcohol is >95% enantiomerically pure. Illustrated in Figure 8 is an expansion of the spectra showing the C-1 protons.



(42)

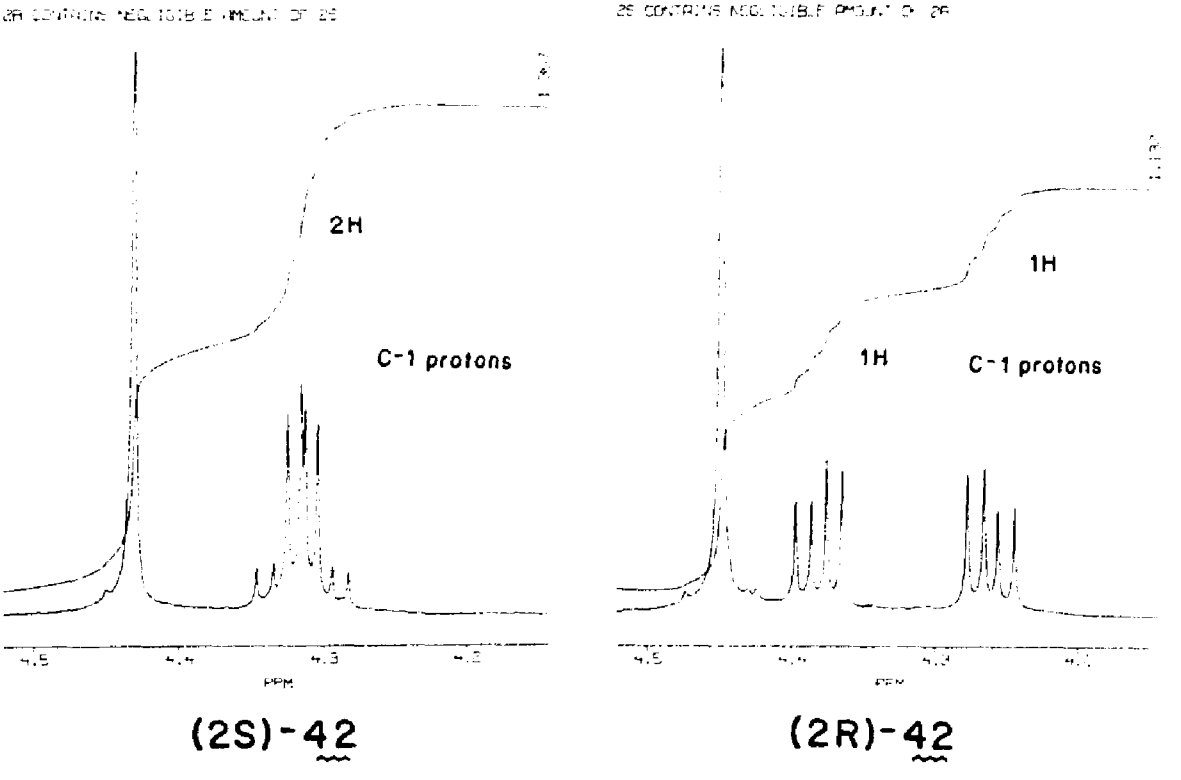


Figure 8 500 MHz ^{1}H NMR Spectra of (2R)- and (2S)-**42**

covered intact from each of these chiral auxiliary removal procedures. Usually, the chiral auxiliary is separated from the chiral product by liquid chromatography on silica gel. Further elution of the column with a more polar solvent removes the 2-oxazolidinone. Analysis of the Mosher imide derived from the recovered 2-oxazolidinone indicates that no racemization of the chiral auxiliary occurs during this process. Therefore, the chiral auxiliary can be recycled, invoking a form of chiral economy.

IV. SUMMARY

We have demonstrated that N-acyl 2-oxazolidinones, derived from readily available, enantiomerically pure, chiral amino alcohols, are useful chiral acyclic enolate synthons. Enolization of the N-acyl 2-oxazolidinone with either LDA or NaHMDS stereoselectively affords the six-membered chelated (Z) imide enolate. Chiral substitution at the C-4 position of the 2-oxazolidinone ring directs methyl iodide, allylic halides, benzyl bromide, or other reactive electrophiles to approach the least hindered diastereoface of the enolate. The kinetic alkylation diastereoselection is generally >95:5. The major diastereomer can, in a predictable manner, be isolated by liquid chromatography on silica gel, with a diastereomeric purity of $\geq$ 99:1. Non-destructive methods are available to remove the chiral auxiliary from the alkylated imide, and either directly or *via* further transformations afford chiral alcohols, aldehydes, amides, amines, carboxylic acids, carboxylic acid chlorides, esters, hydrazides, ketones, lactones, or urethanes in a state of high enantiomeric purity. In each case, the 2-oxazolidinone is recovered intact, permitting the economical recycling of the chiral auxiliary.

V. EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. IR spectra were recorded on a Beckman 4210 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Routine ^{1}H NMR spectra were recorded on a Varian Associates CFT-20 (80 MHz) or EM-390 (90 MHz) spectrometer. High field ^{1}H NMR spectra were recorded on a Varian Associates XL-200 (200 MHz), a Bruker WM-300 (300 MHz), or a Bruker WM-500 (500 MHz)[51] spectrometer. Chemical shifts are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant (Hz), integration and interpretation. ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz) or a Varian Associates XL-200 (50 MHz) spectrometer and are reported in ppm from internal tetramethylsilane on the δ scale. Multiplicities, when determined by off-resonance decoupling, are reported using the above format.

Optical rotations were determined with a Jasco DIP-181 digital polarimeter at 589, 577, 546, 435 and 365 nm. Data are reported as follows: $[\alpha]_{589}$, $[\alpha]_{577}$, $[\alpha]_{546}$, $[\alpha]_{435}$, $[\alpha]_{365}$, concentration (c g/100 mL) and solvent. When chloroform was used as the solvent, it was filtered through activity 1 alumina immediately prior to use.

Combustion analyses were performed by Galbraith Laboratories, Inc. (Knoxville, Tennessee), Mr. Lawrence Henling at the California Institute of Technology Microanalytical Laboratory, or Spang Microanalytical Laboratory (Eagle Harbor, Michigan).

Analytical gas chromatography (GC) was carried out on a Hewlett Packard 5880A gas chromatograph equipped with a split mode capillary injector and a flame ionization detector. Unless otherwise noted, hydrogen was used as the carrier gas. The following wall coated open tubular (WCOT) fused silica capillary columns were employed: 0.32 mm x 15 m and 0.32 mm x 30 m Carbowax 20M (J and W Associates), 0.32 mm x 30 m DB-1 (J and W Associates), 0.32 mm x 30 m DB-5 (J and W Associates), 0.31 mm x 25 m SE-54 (Hewlett Packard) and 0.21 mm x 25 m methyl silicone (Hewlett Packard). Specific GC conditions are reported in the following format: column, oven temperature, carrier gas flow rate, and retention time. Unless otherwise indicated, the injector and detector temperatures were 250°C.

Flash chromatography was performed according to the general procedure of Still,[52] employing EM Reagents Silica Gel 60 (40-63 μm). Data are reported as follows: column dimensions (d x l), elutant composition and order of elution. Medium pressure liquid chromatography (MPLC) was carried out on an MPLC apparatus consisting of a Chromatronix SV8031 Sample Injection Valve, a Fluid Metering Inc. model RP-SY Lab Pump and an ISCO model UA-5 UV (254 nm) Detector using the following EM Reagents prepacked LoBar LiChroprep Si 60 columns: column A (1.0 x 24 cm, 40-63 μm silica gel), column B (2.5 x 31 cm, 40-63 μm silica gel) and column C (3.7 x 44 cm, 63-125 μm silica gel). Specific MPLC conditions are reported as follows: column dimensions (d x l), elutant composition, elutant flow rate and order of elution. Analytical high performance liquid chromatography (HPLC) was carried out on a Waters Associates ALC 202/401 HPLC equipped with a model 6000 high pressure solvent pump, a model U6K injector and a differential UV detector (254 nm), using the following

columns: Waters Associates Radial Pak (8 mm x 10 cm, 5 μm silica gel) or (8 mm x 10 cm, 10 μm silica gel), DuPont Zorbax (4.6 mm x 25 cm, 5 μm silica gel), and Regis (4.6 mm x 25 cm, Pirkle[53] phenylglycine covalently bound to 5 μm aminopropyl silica gel). Specific HPLC conditions are reported as follows: column, elutant composition, elutant flow rate and retention volume (k'). Preparative HPLC was performed on a Waters Associates PrepLC/System 500 liquid chromatograph, equipped with a refractive index detector and using two PrepPak 500 silica gel cartridges (5 x 30 cm, 30μm silica gel). Specific HPLC conditions are reported using the above format. Unless otherwise noted, the substrate was introduced onto the HPLC as a concentrated solution through the solvent inlet port. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, iodine vapor, an aqueous cerium molybdate spray,[54] or an aqueous potassium permanganate spray.

When necessary, solvents and reagents were dried prior to use. Diethyl ether, dimethoxyethane (DME) and tetrahydrofuran (THF) were distilled from sodium-potassium alloy/benzophenone ketyl. Benzene and toluene were distilled from sodium/benzophenone ketyl. Boron trifluoride etherate, chlorotrimethylsilane, dichloromethane, diisopropylamine, diisopropylethylamine, hexamethyldisilylamine, and triethylamine were distilled from calcium hydride. Acetonitrile, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride and stored over 4A molecular sieves. Alkyl bromides and iodides were passed through a column of activity 1

alumina immediately prior to use. n-Butyllithium (Aldrich Chemical Co.) was standardized by double titration (total base - inorganic base = organic base).

Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon or nitrogen with rigid exclusion of moisture from reagents and glassware.

(2S)-2-Amino-3-methyl-1-butanol [(S)-Valinol].[18] Into an oven dried, 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a distillation head/reflux condenser, and a 250 mL pressure-equalizing addition funnel was introduced 234 g (2.00 mol) of (S)-valine ($[\alpha]_{589}$ = -27.4 (c 3.4, 6 N aqueous HCl), Aldrich Chemical Co.). The apparatus was flushed with nitrogen and the flask charged with 1-L of dry THF and 275 mL (318 g, 2.20 mol) of boron trifluoride diethyl etherate. The mixture was heated at reflux until the valine dissolved (0.5-1 h). Stirring was continued as 220 mL (10.0 M, 2.20 mol) of borane dimethyl sulfide was added dropwise over a 4 h period. External heating was adjusted to allow dimethyl sulfide and diethyl ether to distil from the reaction flask. **Caution: a large quantity of hydrogen is evolved during the addition.** After the addition was complete, the flask was charged with an additional 500 mL of dry THF. Distillation was continued until the temperature of the distillate rose to 64-65°C. The reaction mixture was then heated at reflux for 4 h. External heating was continued as the reaction mixture was hydrolyzed by the **cautious** dropwise addition of 250 mL of a 1:1 (v/v) mixture of THF and water over a 0.5 h period, followed by the addition of 1.5 L of a 5 M aqueous solution of sodium hydroxide over a 0.5 h period. After the additions were

complete, the two-phase reaction mixture was heated at reflux for an 8-h period. The reaction mixture was cooled to room temperature. A small amount of an amorphous solid was removed by filtration through a 2 cm pad of celite. The reaction mixture was transferred to a 6-L separatory funnel, and the two layers separated. The lower aqueous layer was extracted with four 1-L portions of diethyl ether. The etheral extracts were combined with the THF solution (upper phase). The water that separated at this point was combined with the aqueous phase. The organic solution was dried over anhydrous potassium carbonate, filtered, and the solvent removed *in vacuo*. The residue was distilled under reduced pressure to afford 82-113 g (40-55%) of (S)-valinol as a colorless liquid, bp 97-98°C (8 mm), [Lit.[18] bp 55-57°C (2 mm)], which may solidify upon standing, mp 27-29°C, [Lit.[55] mp 31-32°C]. An additional 25-40 g (12-19%) of (S)-valinol was obtained by continuously extracting the aqueous phase with dichloromethane for 4 days. IR (CH_2Cl_2) 3600-3040, 1580, 1460, 1220 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 3.60 (d of d, J = 4.5, 11 Hz, 1H, C_1-H), 3.26 (d of d, J = 9, 11 Hz, 1H, C_1-H), 2.6-2.4 (m, 1H, C_2-H), 2.35-2.15 (br s, 3H, OH, NH_2), 1.85-1.3 (m, 1H, C_2-CH), 1.90 (d, J = 6 Hz, 6H, $CH(CH_3)_2$); Specific rotation: $[\alpha]_{589}$ = +17.2° (*c* 10.9, EtOH), [Lit.[56] $[\alpha]_{589}$ = +18.5° (*c* 7.83, EtOH)].

General Procedure for the Preparation of 2-Oxazolidinones. A. Diethyl Carbonate Method.[25] A magnetically stirred mixture of the indicated amino-alcohol (1.0 equiv), diethyl carbonate (1.1 equiv) and anhydrous potassium carbonate (0.1 equiv), in a flask equipped for distillation through a 20-cm Vigreux column, is heated in an oil bath (intern-

al reaction temperature 125-126°C) until 2.0 equiv of ethanol is collected. The Vigreux column is removed for distillation of the last traces of ethanol. The reaction mixture is allowed to cool to room temperature, the product dissolved in dichloromethane or diethyl ether, and the solution filtered through a pad of celite. The filtrate is concentrated in vacuo and the residue purified by distillation or recrystallization to afford the indicated 2-oxazolidinones.

B. Diphenyl Carbonate Method.[26] A mechanically stirred mixture of the indicated amino-alcohol (1.0 equiv), diphenyl carbonate (1.1 equiv), and anhydrous potassium carbonate (1.1 equiv) is heated at 110°C (internal reaction temperature) for a 4-6 h period. The resultant mixture is allowed to cool to < 60°C. Excess diphenyl carbonate is hydrolyzed by addition of methanol (4-6 mL/mmol of initial diphenyl carbonate) and heating the mixture at reflux for 0.5 h. Sufficient water (4-6 mL/mmol of potassium carbonate) is added to dissolve the potassium carbonate and methanol is removed in vacuo. The product and phenol are extracted into dichloromethane (3 x 1 mL/mmol of expected 2-oxazolidinone). The combined extracts are washed with 2 M aqueous sodium hydroxide (3 x 1 mL/mmol of initial diphenyl carbonate, to remove the phenol), 1 M aqueous hydrochloric acid (1 x 0.5 mL/mmol of initial amino-alcohol), brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue is purified by recrystallization to afford the indicated 2-oxazolidinone.

C. Phosgene Method.[27] To a mechanically stirred, cooled (0°C) solution of the indicated amino-alcohol (1.0 equiv) and triethylamine (2.2 equiv) in toluene (1-2 mL/mmol of amino-alcohol) is added a toluene solution of phosgene (1.0 equiv) dropwise. The thick white mixture is

stirred at 0°C for 1 h. The mixture is filtered and the precipitate washed with warm ethyl acetate (3x). The combined filtrate and washings are concentrated *in vacuo* and the residue purified by recrystallization to afford the indicated 2-oxazolidinone.

(±)-4-Methyl-2-oxazolidinone [(±)-Alaninol 2-Oxazolidinone, (5, Table 2, Entry A)]. Diethyl Carbonate Method. A magnetically stirred mixture of 4.85 g (64.6 mmol) of (±)-alaninol, 9.0 mL (8.8 g, 74 mmol) of diethyl carbonate, and 0.2 g (0.14 mmol) of anhydrous potassium carbonate was heated at 125-126°C (internal reaction temperature) until 7.5 g (5.9 g, 130 mmol) of ethanol distilled (ca. 4 h). Isolation according to the general diethyl carbonate cyclization procedure gave 3.5 g (54% mass balance) of a pale yellow liquid. Distillation (Kugelrohr, 100 C, 12 mm) afforded 3.0 g (46%) of (±)-alaninol 2-oxazolidinone **5** as a mobile colorless liquid: IR (neat) 3600-3100, 2980, 1745, 1410, 1245, 1030 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 6.8 (br s, 1H, N-H), 4.6-4.3 (m, 1H, C_4-H), 4.2-3.8 (m, 2H, C_5-H_2), 1.33 (d, J = 6 Hz, 3H, C_4-CH_3); GC (30 m DB-5, 100 C, 94 cm/sec, t_r = 2.45 min); TLC (ethyl acetate, R_f = 0.45).

(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone [(4R,5S)-Norephedrine 2-Oxazolidinone, (6, Table 2, Entry B)]. Diethyl Carbonate Method. A magnetically stirred mixture of 35.2 g (0.233 mol) of (1S,2R)-norephedrine, 30 mL (30.3 g, 0.256 mol) of diethyl carbonate, and 5 g of anhydrous potassium carbonate was heated at 125-126°C (internal reaction temperature) until 30 mL of ethanol distilled (ca. 16 h). Isolation according to the general diethyl carbonate cyclization procedure gave 41 g

(99% mass balance) of a pale yellow solid. The product was recrystallized from toluene to afford 35 g (87%) of **6** as a white crystalline solid: mp 121-122°C (Lit.[57] 117°C); IR ($CHCl_3$) 3460, 3400-3200, 3020, 2980, 1760, 1450, 1380, 1350, 1220, 1125, 1000, 960, 690 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.33 (s, 5H, aromatic H's), 6.3-6.0 (br s, 1H, N-H), 5.67 (d, J = 7.5 Hz, 1H, C_5-H), 4.17 (qn, J = 7.0 Hz, 1H, C_4-H), 0.80 (d, J = 7.0 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 159.9, 135.0, 128.4, 125.9, 81.0, 52.4, 17.4; Specific Rotation $[\alpha]_{589}$ = +177.2°, $[\alpha]_{577}$ = +186.1°, $[\alpha]_{546}$ = +212.0°, $[\alpha]_{435}$ = +368.6°, $[\alpha]_{365}$ = +598.6° (c 2.21, $CHCl_3$), [Lit.[57] $[\alpha]_{589}$ = +158.4° (c 0.44, $CHCl_3$)]; GC (30 m DB-1, 150°C, 81 cm/sec, t_r = 4.31 min); TLC (ethyl acetate, R_f = 0.45).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.62; N, 7.90. Found: C, 67.42; H, 6.19; N, 7.87.

(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone [(4R,5S)-Norephedrine 2-Oxazolidinone, (6, Table 2, Entry C)]. Diphenyl Carbonate Method. A mechanically stirred mixture of 151 g (1.00 mol) of (1S,2R)-norephedrine ($[\alpha]_{589}$ = +33.4° (c 7, water) as the hydrochloride salt, Aldrich Chemical Co.), 236 g (1.10 mol) of diphenyl carbonate, and 152 g (1.10 mol) of anhydrous potassium carbonate, treated according to the general diphenyl carbonate cyclization procedure to give 195 g (110% mass balance) of a light-yellow solid. Recrystallization from toluene (600 mL, 3 crops) afforded 145-165 g (82-93%) of norephedrine 2-oxazolidinone **6** as a white crystalline solid, identical in all respects to the previously prepared material.

(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone [(4R,5S)-Norephedrine 2-Oxazolidinone, (6, Table 2, Entry D)]. Phosgene Method. A mechanically stirred solution of 82.0 g (0.542 mol) of (1S,2R)-norephedrine and 110 g (1.08 mol) of triethylamine in 400 mL of toluene was treated with 282 mL (1.92 M in toluene, 0.542 mol) of phosgene according to the general phosgene cyclization procedure to give 99.4 g (103% mass balance) of a pale yellow solid. Recrystallization from chloroform/diethyl ether 6- afforded 84.9 g (88%) of (4R,5S)-norephedrine 2-oxazolidinone **6** as a white crystalline solid, identical in all respects to the previously prepared material.

(±)-cis-4-Methyl-5-phenyl-2-oxazolidinone [(±)-Norephedrine 2-Oxazolidinone, (6, Table 2, Entry E)]. Phosgene Method. A magnetically stirred solution of 1.51 g (10.0 mmol) of (±)-norephedrine and 2.80 mL (2.03 g, 20.1 mmol) of triethylamine in 20 mL of toluene was treated with 8.3 mL (1.2 M in toluene, 10.0 mmol) of phosgene according to the general phosgene cyclization procedure to give 1.89 g (99% mass balance) of a yellow solid. Purification by flash chromatography (3 x 30 cm column, diethyl ether) afforded 1.39 g (73%) of (±)-norephedrine 2-oxazolidinone **6**, as a white crystalline solid: mp 136°C, [Lit[25]. mp 142-144°C]; IR ($CHCl_3$) 3460, 3030, 1765, 1230, 1210 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.30 (s, 5H, aromatic H's), 5.67 (d, J = 7.8 Hz, 1H, C_5-H), 4.17 (qn, J = 6.8 Hz, 1H, C_4-H), 0.82 (d, J = 6.8 Hz, 3H, C_4-CH_3); GC (30 m DB-5, 150°C, 94 cm/sec, t_r = 5.86 min); TLC (ethyl acetate, R_f = 0.45).

Anal. calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.62. Found: C, 67.64; H, 6.40.

(4S,5S)-4-Methyl-5-phenyl-2-oxazolidinone [(4S,5S)-Norpseudoephedrine 2-Oxazolidinone, (7, Table 2, Entry F)]. Diethyl Carbonate Method. A magnetically stirred mixture of 6.92 g (45.8 mmol) of (1R,2R)-norpseudoephedrine ($[\alpha]_{589}$ = -41.7° (c 7, water) as the hydrochloride salt, Aldrich Chemical Co.), 6.2 mL (6.1 g, 51 mmol) of diethyl carbonate, and 0.70 g (5.1 mmol) of anhydrous potassium carbonate was heated at 125-126°C (internal reaction temperature) until 5.4 mL (4.2 g, 91 mmol) of ethanol distilled (ca. 8 h). Isolation according to the general diethyl carbonate cyclization procedure gave 8.5 g (105% mass balance) of a pale yellow solid. Recrystallization from toluene (two crops) afforded 7.2 g (90% yield) of (4S,5S)-norpseudoephedrine 2-oxazolidinone **7** as a white crystalline solid: mp 119-120°C; IR (CH_2Cl_2) 3460, 3320-3200, 3060, 2990, 1770, 1450, 1420, 1400, 1320 cm^{-1}; ^1H NMR ($CDCl_3$/80 MHz) δ 7.35 (s, 5H, aromatic H's), 6.45-6.2 (br s, 1H, NH), 5.02 (d, J = 7.8 Hz, 1H, C_5-H), 3.82 (qn, J = 7.2 Hz, 1H, C_4-H), 1.40 (d, J = 7.0 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = +15.7°, $[\alpha]_{577}$ = +17.1°, $[\alpha]_{546}$ = +19.0°, $[\alpha]_{435}$ = +32.4°, $[\alpha]_{365}$ = +50.9° (c 1.83, EtOH); GC (30 m DB-5, 175°C, 86 cm/sec, t_r = 2.71 min); TLC (ethyl acetate, R_f = 0.52).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.86; H, 6.35.

(4S)-4-(1-Methylethyl)-2-oxazolidinone [(S)-Valinol 2-Oxazolidinone, (8, Table 2, Entry G)]. Diethyl Carbonate Method. A magnetically stirred mixture of 103 g (1.00 mol) of (S)-valinol, 133 mL (130 g, 1.10 mol) of diethyl carbonate, and 14 g (0.10 mol) of anhydrous potassium carbonate was heated at 125-126°C (internal reaction temperature) until 117 mL (92 g, 2.0 mol) of ethanol distilled (ca. 4-6 h). The resultant

mixture was cooled to room temperature, dissolved in diethyl ether (3 L), and the solution filtered through a 2 cm pad of celite to remove the potassium carbonate. The etheral solution was concentrated to a volume of ca. 1 L, slowly cooled to 0°C, and the product allowed to crystallize. Concentration of the mother liquors provided two additional crops of crystals. The total yield of (S)-valinol 2-oxazolidinone **8**, was 110-123 g (85-95%), as a white needles: mp 69-70°C, [Lit.[58] mp 71.5°C]; IR (CH_2Cl_2) 3480, 3340-3240, 3060, 2980, 1760, 1400, 1240 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 6.7 (br s, 1H, N-H), 4.42 (t, J = 8.6 Hz, 1H, C_5-H), 4.07 (d of d, J = 8.5, 6.5 Hz, 1H, C_5-H), 3.58 (d of t, J = 8.6, 6.5 Hz, 1H, C_4-H), 1.9-1.6 (m, 1H, C_4-CH), 0.95 (overlapping d's, J = 6.0 Hz, 6H, $CH(CH_3)_2$); Specific rotation $[\alpha]_{589}$ = -16.6°, $[\alpha]_{577}$ = -17.3°, $[\alpha]_{546}$ = -20.2°, $[\alpha]_{435}$ = -37.3°, $[\alpha]_{365}$ = -63.7° (c 5.81, EtOH); GC (30 m DB-5, 100°C, 94 cm/sec, t_r = 5.55 min); TLC (6:4 hexanes/ethyl acetate, R_f = 0.19).

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.80; H, 8.58. Found: C, 55.63; H, 8.53.

(±)-4-(1-Methylethyl)-2-oxazolidinone [(±)-Valinol 2-Oxazolidinone, (8, Table 2, Entry H)]. Phosgene Method. A magnetically stirred solution of 1.03 g (10.0 mmol) of (±)-valinol and 2.80 mL (2.03 g, 20.1 mmol) of triethylamine in 20 mL of toluene was treated with 8.3 mL (1.2 M in toluene, 10.0 mmol) of phosgene according to the general phosgene cyclization procedure to give 1.0 g (77% mass balance) of a yellow solid. Purification by flash chromatography (2 x 20 cm column, diethyl ether) afforded 0.75 g (58 %) of (±)-valinol oxazolidinone **8**, as a white

crystalline solid: mp 64-65 C; IR ($CHCl_3$) 3480, 3400-3200, 3020, 2970, 1755, 1405, 1230 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 6.7 (br s, 1H, N-H), 4.42 (t, J = 8.6 Hz, 1H, C_5-H), 4.07 (d of d, J = 8.5, 6.5 Hz, 1H, C_5-H), 3.58 (d of t, J = 8.6, 6.5 Hz, 1H, C_4-H), 1.9-1.6 (m, 1H, C_4-CH), 0.95 (overlapping d's, J = 6.0 Hz, 6H, $CH(CH_3)_2$); GC (30 m DB-5, 100°C, 94 cm/sec, t_r = 5.52 min); TLC (ethyl acetate, R_f = 0.49).

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.80; H, 8.58. Found: C, 55.61; H, 8.46.

(4R)-4-Phenyl-2-oxazolidinone [(4R)-Phenylglycinol 2-Oxazolidinone, (9, Table 2, Entry I)]. Diethyl Carbonate Method. A magnetically stirred mixture of 20.0 g (0.143 mol) of (R)-phenylglycinol ($[\alpha]_{589}$ = -31.7° (c 0.76, 1 N aqueous HCl), Aldrich Chemical Co.), 17.4 mL (17.0 g, 0.144 mol) of diethyl carbonate, and 2.1 g (15 mmol) of anhydrous potassium carbonate was heated at 125-126°C (internal reaction temperature) until 16 mL (13 g, 0.27 mol) of ethanol distilled (ca. 4h). Isolation according to the general diethyl carbonate cyclization procedure gave 19.8 g (85% mass balance) of a pink solid. Recrystallization from hexanes/chloroform afforded 18.5 g (79%) of (R)-phenylglycinol oxazolidinone **9** as a white crystalline solid: mp 123.5-124.5°C; IR ($CHCl_3$) 3440, 3300-3180, 2990, 1750, 1390, 1210, 1135 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.33 (s, 5H, aromatic H's), 6.3 (br s, 1H, N-H), 4.92 (d of d, J = 6.9, 8.9 Hz, 1H, C_4-H), 4.68 (t, J = 8.7 Hz, 1H, C_5-H), 4.12 (d of d, J = 6.9, 8.3 Hz, 1H, C_5-H); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 160.1, 139.8, 129.1, 128.6, 126.0, 72.5, 56.3; Specific rotation $[\alpha]_{589}$ = -58.6°, $[\alpha]_{577}$ = -62.0°, $[\alpha]_{546}$ = -70.7°, $[\alpha]_{435}$ = -121.6°, $[\alpha]_{365}$ = -196.4° (c 1.06, CH_2Cl_2); GC (30 m DB-5, 150°C, 94 cm/sec, t_r = 5.05

min); TLC (ethyl acetate, R_f = 0.46).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.20; H, 5.55; N, 8.56.

(4S)-4-Phenylmethyl-2-oxazolidinone [(S)-Phenylalaninol 2-Oxazolidinone, (10, Table 2, Entry J)]. Diethyl Carbonate Method. A magnetically stirred mixture of 2.05 g (13.6 mmol) of (S)-phenylalaninol, 1.80 mL (1.76 g, 14.9 mmol) of diethyl carbonate and 0.2 g (0.14 mmol) of anhydrous potassium carbonate was heated in an oil bath at 120-125°C until no amino alcohol remained as detected by TLC (ethyl acetate, R_f phenylalaninol = 0.01, R_f **10** = 0.43). Isolation according to the general diethyl carbonate cyclization procedure gave 2.3 g of a cloudy liquid. Purification by flash chromatography (3 x 30 cm column, diethyl ether) afforded 1.86 g (77 %) of (S)-phenylalaninol 2-oxazolidinone **10**, as a white crystalline solid: mp 82-83°C; IR ($CHCl_3$) 3460, 3020, 1760, 1400, 1220 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.4-7.1 (m, 5H, aromatic H's), 5.52 (br s, 1H, N-H), 4.6-4.3 (m, 1H, C_5-H), 4.2-3.9 (m, 2H, C_4-H, C_5-H), 2.88 (d, J = 6 Hz, 2H, C_4-CH_2); Specific rotation $[\alpha]_{589}$ = +5.1°, $[\alpha]_{577}$ = +5.5°, $[\alpha]_{546}$ = +6.1°, $[\alpha]_{435}$ = +8.0°, $[\alpha]_{365}$ = +9.1° (c 0.76, EtOH); GC (30 m DB-1, 175°C, 100 cm/sec, 2.13 min).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.62. Found: C, 67.83; H, 6.55.

General Procedure to Determine the Enantiomeric Purity of 4-Substituted-2-Oxazolidinones. The indicated 2-oxazolidinone is acylated with (R)-(-)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride **11**[22] ac-

cording to the general acylation procedure (vide infra). The ratio of imide diastereomers (**12**:**13**), which corresponds to the enantiomeric purity of the 2-oxazolidinone, is determined by GC and HPLC analysis of the unfractionated product. An authentic mixture of diastereomers is prepared from the indicated racemic 2-oxazolidinone and (R)-acid chloride **11** or from the indicated oxazolidinone and racemic acid chloride **11**.

Enantiomeric Purity of (4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone [(4R,5S)-Norephedrine 2-Oxazolidinone, (6, Table 3, Entry A)]. A solution of 44.6 mg (0.252 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** ($[\alpha]_{589}$ = +172.2° (c 2.21, $CHCl_3$)), (0.1 M in THF) was metalated with 0.16 mL (1.55 M in hexane, 0.248 mmol) of n-butyllithium and acylated with 0.053 mL (70 mg, 0.28 mmol) of (R)-acid chloride **11** according to the general acylation procedure to give 105 mg (107% mass balance) of unpurified product. Analysis by GC (30 m Carbowax 20M, 225°C, 94 cm/sec, t_r **12** = 22.89 min) indicated the presence of only diastereoisomer **12** (limits of detection > 200:1). HPLC analysis (8 mm x 10 cm Radial Pak (10 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' **12** = 2.59) also indicated the presence of only one diastereoisomer. A standard mixture of diastereomers was prepared from (±)-norephedrine 2-oxazolidinone **6** and (R)-acid chloride **11** by the some procedure. Analysis by GC (same conditions as above: t_r **13** = 21.97 min, t_r **12** = 22.89 min). HPLC analysis (same conditions as above: k' **13** = 2.32, k' **12** = 2.59, α = 1.12). TLC (8:2 hexanes/ethyl acetate R_f **13** = 0.57, R_f **12** = 0.67).

Enantiomeric Purity of (4S,5S)-4-Methyl-5-phenyl-2-oxazolidinone [(4S,5S)-Norpseudoephedrine 2-Oxazolidinone, (7, Table 3, Entry B)]. A solution of 177 mg (1.00 mmol) of (4S,5S)-norpseudoephedrine 2-oxazolidinone ($[\alpha]_{589}$ = +15.7° (c 1.83, EtOH)), (0.2 M in THF) was metalated with 0.45 mL (2.23 M in hexane, 1.00 mmol) of n-butyllithium and acylated with 0.20 mL (0.27 g, 1.06 mmol) of (R)-acid chloride **11** according to the general acylation procedure to give 0.40 g (101% mass balance) of unpurified product. Analysis by GC (30 m DB-5, 200°C, 83 cm/sec, t_r **13** = 8.23 min) indicated the presence of only diastereoisomer **13** (limits of detection > 200:1). HPLC analysis (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' **13** = 3.02) also indicated the presence of only one diastereomer. A standard mixture of diastereomers was prepared from (4S,5S)-norpseudoephedrine 2-oxazolidinone **7** and (±)-acid chloride **11** by the same procedure. Analysis by GC (same conditions as above: t_r **12** = 7.59 min, t_r **13** = 8.23 min). HPLC analysis (same conditions as above: k' **13** = 3.02, k' **12** = 3.95, α = 1.38). TLC (8:2 hexanes/ethyl acetate, R_f **13** = 0.29, R_f **12** = 0.23).

Enantiomeric Purity of (4S)-4-(1-Methylethyl)-2-oxazolidinone [(4S)-Valinol 2-Oxazolidinone, (8, Table 3, Entry C)]. A solution of 42.9 mg (0.333 mmol) of (4S)-valinol 2-oxazolidinone **8** ($[\alpha]_{589}$ = -16.6° (c 5.81, CH_2Cl_2)), (0.1 M in THF) was metalated with 0.24 mL (1.55 M in hexane, 0.37 mmol) of n-butyllithium and acylated with 0.069 mL (92 mg, 0.37 mmol) of (R)-acid chloride **11** according to the general acylation procedure to give 120 mg (104% mass balance) of unpurified product. Analysis by GC (30 m Carbowax 20M, 200°C, 96 cm/sec, t_r **13** = 9.04 min) indicated the presence of only diastereoisomer **13** (limits of detection

>200:1). HPLC analysis (8 mm x 10 cm Radial Pak (10 μm silica gel), 76:24 isooctane/ethyl acetate, 2.0 mL/min, k' **13** = 1.72) also indicated the presence of only one diastereoisomer **13**. A standard mixture of diastereomers was prepared from (±)-valinol 2-oxazolidinone **8** and (R)-acid chloride **11** by the same procedure. Analysis by GC (same conditions as above: t_r **13** = 9.04 min, t_r **12** = 9.53 min). HPLC analysis (same conditions as above: k' **13** = 1.72, k' **12** = 2.44, α = 1.42). TLC (8:2 hexanes/ethyl acetate, R_f **13** = 0.43, R_f **12** = 0.32).

Enantiomeric Purity of (4R)-4-Phenyl-2-Oxazolidinone [(4R)-Phenylglycinol 2-Oxazolidinone, (9, Table 3, Entry D)]. A solution of 163 mg (1.00 mmol) of (4R)-phenylglycinol 2-oxazolidinone **9** ($[\alpha]_{589}$ = -58.6° (c 1.06, CH_2Cl_2)), (0.2 M in THF) was metalated with 0.45 mL (2.23 M in hexane, 1.00 mmol) of n-butyllithium and acylated with 0.20 mL (0.27 g, 1.06 mmol) of (R)-acid chloride **11** according to the general acylation procedure to give 0.40 (105% mass balance) of unpurified product. Analysis by GC (30 m Carbowax 20M, 225°C, 93 cm/sec, t_r **12** = 20.12 min; 30 m DB-5, 200°C, 83 cm/sec, t_r **12** = 7.03 min) indicated the presence of only one diastereoisomer **12** (limits of detection > 200:1). HPLC analysis (8 mm x 10 cm Radial Pak (10 μm silica gel), 76:24 isooctane/ethyl acetate, 2.0 mL/min, k' **12** = 3.00) also indicated the presence of only diastereoisomer **12**. A standard mixture of diastereomers was prepared from (4R)-phenylglycinol 2-oxazolidinone **9** and racemic acid chloride **11** by the same procedure. GC (same conditions as above: Carbowax 20M, t_r **12** = 20.12 min, t_r **13** = 21.18 min; DB-5, t_r **12** = 7.03 min, t_r **13** = 7.42 min). HPLC (same conditions as above: k' **13** = 2.14, k' **12** = 3.00, α = 1.40). TLC (8:2 hexanes/ethyl acetate R_f **13** = 0.32, R_f **12** = 0.25).

Enantiomeric Purity of (4S)-4-Phenylmethyl-2-oxazolidinone [(4S)-Phenylalaninol 2-Oxazolidinone, (10, Table 3, Entry E)]. A solution of 177 mg (1.00 mmol) of (4S)-phenylalaninol 2-oxazolidinone **10** ($[\alpha]_{589}$ = +5.1° (c 0.76, ethanol)), (0.2 M in THF) was metalated with 0.45 mL (2.23 M in hexane, 1.00 mmol) of n-butyllithium and acylated with 0.20 mL (0.27 g, 1.06 mmol) of (R)-acid chloride **11** according to the general acylation procedure to give 0.40 g (101% mass balance) of unpurified product. Analysis by GC (30 m DB-5, 200°C, 83 cm/sec, t_r **13** = 10.78 min) indicated the presence of only one diastereoisomer **13**. HPLC analysis (8 mm x 10 cm Radial Pak (10 μm silica gel), 76:24 isooctane/ethyl acetate, 2.0 mL/min, k' **13** = 1.31) also indicated the presence of only one diastereoisomer. A standard mixture of diastereomers was prepared from (4S)-phenylalaninol 2-oxazolidinone **10** and racemic acid chloride **11** by the same procedure. GC (same conditions as above: t_r **12** = 10.52 min, t_r **13** = 10.78 min). HPLC (same conditions as above: k' **13** = 1.31, k' **12** = 1.78, α = 1.36). TLC (8:2 hexanes/ethyl acetate, R_f **13** = 0.39, R_f **12** = 0.32).

General Procedure for the N-Acylation of 2-Oxazolidinones. To a magnetically or mechanically stirred, cooled (-78°C) solution of the indicated 2-oxazolidinone, 0.1-1.0 M in THF, is added a hexane solution of n-butyllithium (1.0-1.2 equiv) over a 10-20 min period. After stirring for 0-20 min, the indicated acylating agent (acid chloride, anhydride or mixed anhydride; 1.0-1.2 equiv) is added either neat or as a THF solution. The reaction mixture is allowed to warm to room temperature and stirred for 0.5-1.0 h. Excess acylating agent is quenched by addition of 1 M aqueous potassium bicarbonate and stirring the two-phase

mixture for 0.5-1.0 h. The THF is removed *in vacuo* and the product extracted into dichloromethane (3x). The combined organic extracts are washed with brine, dried over anhydrous magnesium sulfate or sodium sulfate, and concentrated *in vacuo*. The N-acyl 2-oxazolidinone imides are purified by chromatography, molecular distillation or recrystallization.

Specific Information for the Acylation of (4R,5S)-Norephedrine 2-Oxazolidinone (6), (4S)-Phenylalaninol 2-Oxazolidinone (10), or (4R)-Phenylglycinol 2-Oxazolidinone (9). *n*-Butyllithium is added to the 2-oxazolidinone solution until the orange-red color of the dianion just persists. The acylating agent is added immediately to prevent epimerization at the benzylic carbon of norephedrine and phenylglycinol 2-oxazolidinones.

(±)-3-(1-Oxobutyl)-4-methyl-2-oxazolidinone (14c, Table 4, Entry A). A solution of 0.841 g (8.32 mmol) of (±)-alaninol 2-oxazolidinone 5 (0.42 *M* in THF) was metalated with 5.8 mL (1.57 *M* in hexane, 9.11 mmol) of *n*-butyllithium and acylated with 1.50 mL (1.47 g, 9.17 mmol) of butanoic anhydride according to the general acylation procedure to give 1.4 g (99% mass balance) of unpurified product. The title compound was isolated by flash chromatography (3 x 30 cm column, 7:3 hexanes/ethyl acetate) followed by molecular distillation (Kugelrohr, 75°C, 0.005 mm) to afford 0.937 g (66%) of **14c** as a colorless liquid: IR (CCl_4) 2980, 2940, 2880, 1795, 1710, 1390, 1340, 1210, 1135 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 4.7-4.3 (m, 2H, C_5-$\underline{H}_2$), 4.1-3.9 (m, 1H, C_4-$\underline{H}$), 2.87 (t, J = 7.5 Hz, 2H, $C_{2'}$-$\underline{H}_2$), 1.9-1.5 (m, 2H, $C_{3'}$-$\underline{H}_2$), 1.40 (d, J = 6.3 Hz, 3H, C_4-

$C\underline{H}_3$), 1.00 (t, J = 7.0 Hz, 3H, $C_{4'}$-$\underline{H}_3$); GC (30 m SE-54, 100°C, 54 cm/sec, t_r = 8.97 min); TLC (7:3 hexanes/ethyl acetate, R_f = 0.29).

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.65. Found: C, 56.18; H, 7.68.

(4R,5S)-3-(1-Oxoethyl)-4-methyl-5-phenyl-2-oxazolidinone (16a, Table 4, Entry B). A solution of 4.12 g (23.3 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.23 M in THF) was metalated with 14.0 mL (1.57 M in hexane, 22.0 mmol) of n-butyllithium and acylated with 1.88 g (23.9 mmol) of acetyl chloride according to the general acylation procedure to give 4.92 g (96% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 140°C, 0.006 mm) to afford 4.75 g (93%) of **16a** as a white crystalline solid: mp 65.5-66.0°C; IR (CCl_4) 2095, 1800, 1715, 1380, 1370, 1350, 1200, 1165 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.61 (d, J = 7.2 Hz, 1H, C_5-$\underline{H}$), 4.70 (qn, J = 6.8 Hz, 1H, C_4-$\underline{H}$), 2.48 (s, 3H, $C_{2'}$-$\underline{H}_3$), 0.88 (d, J = 6.8 Hz, 3H, C_4-$C\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = +47.6°, $[\alpha]_{577}$ = +49.9°, $[\alpha]_{546}$ = +57.0°, $[\alpha]_{435}$ = +101.3°, $[\alpha]_{365}$ = +172.8° (c 2.06, CH_2Cl_2); GC (30 m SE-54, 175°C, 49 cm/sec, t_r = 4.40 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 5.13); TLC (8:2 hexane/ethyl acetate, R_f = 0.39).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98. Found: C, 65.80; H, 6.20.

(4R,5S)-3-(1-Oxopropyl)-4-methyl-5-phenyl-2-oxazolidinone (16b, Table 4, Entry C). A mechanically stirred solution of 88.6 g (0.500 mol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.5 M in THF) was metalated with 290 mL (1.74 M in hexane, 0.505 mol) of n-butyllithium and acylated with 52 mL (55 g, 0.60 mol) of propanoyl chloride according to the general acylation procedure to give 124 g (106% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 135°C, 0.008 mm) to afford 110 g (94%) of **16b** as a colorless viscous liquid: IR (CH_2Cl_2) 2990, 1785, 1710, 1370, 1350, 1245, 1220, 1200, 1150, 1125 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.33 (s, 5H, aromatic H's), 5.63 (d, J = 7.2 Hz, 1H, C_5-H), 4.73 (qn, J = 6.8 Hz, 1H, C_4-H), 2.93 (q, J = 7.5 Hz, 2H, $C_{2'}$-H_2), 1.17 (t, J = 7.2 Hz, 3H, $C_{3'}$-H_3), 0.88 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 173.7, 153.0, 133.5, 128.6, 125.6, 79.0, 54.7, 29.2, 14.5, 8.3; Specific rotation $[\alpha]_{589}$ = +43.4°, $[\alpha]_{577}$ = +45.1°, $[\alpha]_{546}$ = +51.6°, $[\alpha]_{435}$ = +92.3°, $[\alpha]_{365}$ = +159.8° (c 3.61, CH_2Cl_2); GC (30 m SE-54, 175°C, 49 cm/sec, t_r = 5.75 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 2.62).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48. Found: C, 67.17; H, 6.64.

(4R,5S)-3-(1-Oxobutyl)-4-methyl-5-phenyl-2-oxazolidinone (16c, Table 4, Entry D). A mechanically stirred solution of 20.0 g (0.113 mol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.28 M in THF) was metalated with 80 mL (1.55 M in hexane, 0.124 mol) of n-butyllithium and acylated with 22.0 mL (21.3 g, 0.135 mol) of butanoic anhydride according to the general acylation procedure to give 30 g (108% mass balance) of unpuri-

fied product. The title compound was isolated by recrystallization from pentane/diethyl ether to afford 24.3 g (87%) of **16c** as a white crystalline solid: mp 55.5-56°C; IR (CH_2Cl_2) 2970, 2940, 2880, 1785, 1705, 1385, 1370, 1350, 1235, 1220, 1200, 1125 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 6.83 (s, 5H, aromatic H's), 5.62 (d, J = 7.2 Hz, 1H, C_5-H), 4.73 (qn, J = 6.8 Hz, 1H, C_4-H), 2.93 (t, J = 7.5 Hz, 1H, $C_{2'}$-H), 2.90 (t, J = 6.9 Hz, 1H, $C_{2'}$-H), 1.68 (m, 2H, $C_{3'}$-H_2), 0.98 (t, J = 7.0 Hz, 3H, $C_{4'}$-H_3), 0.88 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 172.9, 153.0, 133.5, 128.7, 125.7, 79.0, 54.7, 37.4, 17.8, 14.6, 13.6; Specific rotation $[\alpha]_{589}$ = +40.4°, $[\alpha]_{577}$ = +41.6°, $[\alpha]_{546}$ = +47.8°, $[\alpha]_{435}$ = +86.0°, $[\alpha]_{365}$ = +149.3° (c 4.9, CH_2Cl_2); GC (30 m SE-54, 200°C, 47 cm/sec, t_r = 5.06 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 1.93); TLC (7:3 hexanes/ethyl acetate, R_f = 0.36).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.20; H, 7.12.

(4R,5S)-3-(1-Oxo-3-methylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (16d, Table 4, Entry E). A solution of 8.86 g (50.0 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.20 M in THF) was metalated with 22.4 mL (2.23 M in hexane, 50.0 mmol) of n-butyllithium and acylated with 6.6 g (54.7 mmol) of 3-methylbutanoyl chloride according to the general acylation procedure to give 13.6 g (104% mass balance) of unpurified product. The title compound was purified by recrystallization from pentane/diethyl ether to afford 11.8 g (90%) of **16d** as a white crystalline solid: mp 52-53°C; IR (CH_2Cl_2) 3060, 2970, 1780, 1700, 1370,

1350, 1305, 1215, 1200, 1160 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.4 (s, 5H, aromatic H's), 5.70 (d, J = 7.2 Hz, 1H, C_5-H), 4.80 (qn, J = 6.8 Hz, 1H, C_4-H), 2.97 (d of d, J = 16.5, 7.5 Hz, 1H, $C_{2'}$-H), 2.73 (d of d, J = 16.5, 7.5 Hz, 1H, $C_{2'}$-H), 2.5-1.9 (m, 1H, $C_{3'}$-H), 1.02 (d, J = 7.2 Hz, 6H, $C_{3'}$-CH_3, $C_{4'}$-H_3), 0.92 (d, J = 6.8 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = +38.5°, $[\alpha]_{577}$ = +40.9°, $[\alpha]_{546}$ = +47.0°, $[\alpha]_{435}$ = +84.0°, $[\alpha]_{365}$ = +145.1° (c 2.36, CH_2Cl_2); GC (30 m DB-1, 175°C, 78 cm/sec, t_r = 4.45 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 1.50); TLC (8:2 hexanes/ethyl acetate, R_f = 0.69).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 69.06; H, 7.30.

(4R,5S)-3-(1-Oxo-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (16e, Table 4, Entry F). A solution of 7.21 g (40.7 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.14 M in THF) was metalated with 25.0 mL (1.55 M in hexane, 38.8 mmol) of n-butyllithium and acylated with 5.4 g (45.5 mmol) of 4-pentenoyl chloride according to the general acylation procedure to give 10.8 g (107% mass balance) of unpurified product. The title compound was isolated by flash chromatography (4 x 30 cm column, 7:3 hexanes/diethyl ether) to afford 9.26 g (92%) of **16e** as a white crystalline solid : mp 59-60°C; IR (CH_2Cl_2) 3060, 2990, 1780, 1700, 1370, 1350, 1200 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.35 (s, 5H, aromatic H's), 6.1-5.7 (m, 1H, $C_{4'}$-H), 5.60 (d, J = 7.2 Hz, 1H, C_5-H), 5.2-4.9 (m, 2H, $C_{5'}$-H_2), 4.73 (qn, J = 6.8 Hz, 1H, C_4-H), 3.2-3.0 (m, 2H, $C_{2'}$-H_2), 2.6-2.3 (m, 2H, $C_{3'}$-H_2), 0.90 (d, J = 6.8 Hz, 3H, C_4-H_3); Specific rotation $[\alpha]_{589}$ = +34.6°, $[\alpha]_{577}$ = +36.4°, $[\alpha]_{546}$ = +41.8°, $[\alpha]_{435}$ =

+74.9°, $[\alpha]_{365}$ = +129.8° (c 1.35, CH_2Cl_2); GC (30 m DB-5, 175°C, 85 cm/sec, t_r = 6.08 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 1.99); TLC (8:2 hexanes/ethyl acetate, R_f = 0.53).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61. Found: C, 69.54; H, 6.51.

(4R,5S)-3-(1-Oxo-3,3-dimethylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (16f, Table 4, Entry G). A solution of 8.86 g (50.0 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.2 M in THF) was metalated with 22.4 mL (2.23 M in hexane, 50.0 mmol) of n-butyllithium and acylated with 7.4 g (55.0 mmol) of 3,3-dimethylbutanoyl chloride according to the general acylation procedure to give 15.2 g (110% mass balance) of crude product. The title compound was purified by recrystallization from hexanes/ethyl acetate to afford 12.0 g (87%) of **16f** as a white crystalline solid: mp 79-80°C; IR (CH_2Cl_2) 3060, 2970, 1785, 1700, 1370, 1350, 1250, 1190, 1170, 1120 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.30 (s, 5H, aromatic H's), 5.60 (d, J = 7.2 Hz, 1H, C_5-H), 4.77 (qn, J = 6.8 Hz, 1H, C_4-H), 3.07 (d, J = 15 Hz, 1H, $C_{2'}$-H), 2.82 (d, J = 15 Hz, 1H, $C_{2'}$-H), 1.1 (s, 9H, $C_{3'}$-(CH_3)$_3$), 0.90 (d, J = 6.8 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = +36.3°, $[\alpha]_{577}$ = +38.8°, $[\alpha]_{546}$ = +44.3°, $[\alpha]_{435}$ = +78.4°, $[\alpha]_{365}$ = +133.5° (c 2.63, CH_2Cl_2); GC (30 m DB-1, 175°C, 78 cm/sec, t_r = 5.14 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 1.13); TLC (8:2 hexanes/ethyl acetate, R_f = 0.63).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.83; 7.57.

(4R,5S)-3-(1-Oxo-2-phenylethyl)-4-methyl-5-phenyl-2-oxazolidinone (16g, Table 4, Entry H). A magnetically stirred solution of 8.86 g (50.0 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.2 M in THF) was metalated with 22.4 mL (2.23 M in hexane, 50.0 mmol) of n-butyllithium and acylated with 8.5 g (55 mmol) of phenylacetyl chloride according to the general acylation procedure to give 15.1 g (105% mass balance) of crude product. The title compound was purified by recrystallization from hexanes/ethyl acetate to afford 13.4 g (90%) of **16g** as a white crystalline solid: mp 101-102°C; IR (CH_2Cl_2) 3060, 2990, 1780, 1710, 1355 cm^{-1}; ^1H NMR ($CDCl_3$/80 MHz) δ 7.3 (m, 10H, aromatic H's), 5.65 (d, J = 8 Hz, 1H, C_5-H), 4.75 (qn, J = 7 Hz, 1H, C_4-H), 4.3 (s, 2H, $C_{2'}$-H_2), 0.90 (d, J = 7 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = +0.5°, $[\alpha]_{577}$ = +0.5°, $[\alpha]_{546}$ = +0.5°, $[\alpha]_{435}$ = +0.6°, $[\alpha]_{365}$ = +0.8° (c 0.97, CH_2Cl_2); GC (30 m DB-5, 200°C, 83 cm/sec, t_r = 9.35 min), HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 3.07); TLC (8:2 hexanes/ethyl acetate, R_f = 0.47).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80. Found: C, 73.01; H, 5.77.

(4R,5S)-3-(1-Oxo-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (16h, Table 4, Entry I). A mechanically stirred, solution of 44.3 g (0.250 mol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.5 M in THF) was metalated with 147 mL (1.70 M in hexane, 0.250 mol) of n-butyllithium and acylated with 39.0 mL (44.3 g, 0.263 mol) of 3-phenylpropanoyl chloride according to the general acylation procedure to give 83.2 g (107% mass balance) of unpurified product. The title compound was purified by recrystallization from 9:1 hexanes/ethyl acetate (2 crops)

to afford 68.1 g (88%) of **16h** as a white crystalline solid: mp 95-96°C; IR (CH_2Cl_2) 3060, 3000, 1785, 1700, 1370, 1350, 1250 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.44-7.19 (m, 10H, aromatic H's), 5.63 (d, J = 7.5 Hz, 1H, C_5-H), 4.75 (qn, J = 6.9 Hz, 1H, C_4-H), 3.34 (m, 2H, $C_{2'}$-H_2), 3.06-3.00 (m, 2H, $C_{3'}$-H_2), 0.89 (d, J = 6.8Hz, 3H, C_4-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 172.1, 152.9, 140.4, 133.4, 128.7, 126.2, 125.6, 79.0, 54.7, 37.2, 30.3, 14.5; Specific rotation $[\alpha]_{589}$ = +28.7°, $[\alpha]_{577}$ = +28.9°, $[\alpha]_{546}$ = +32.9°, $[\alpha]_{435}$ = +60.1°, $[\alpha]_{365}$ = +106.7° (c 0.45, CH_2Cl_2); GC (30 m DB-1, 200°C, 86 cm/sec, t_r = 9.06 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 2.76); TLC (7:3 hexanes/ethyl acetate, R_f = 0.42).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19. Found: C, 73.85; H, 6.28.

(4R,5S)-3-(1-Oxodecyl)-4-methyl-5-phenyl-2-oxazolidinone (16i, Table 4, Entry J). A solution of 8.86 g (50.0 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.2 M in THF) was metalated with 32.3 mL (1.55 M in hexane, 50.1 mmol) of n-butyllithium and acylated with 9.80 mL (9.54 g, 50.0 mmol) of decanoyl chloride according to the general acylation procedure to give 16.8 g (101% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 150°C, 0.006 mm) to afford 14.8 g (89%) of **16i** as a colorless liquid which solidified on standing: mp 41-42°C; IR (CCl_4) 2940, 2870, 1790, 1705, 1380, 1370, 1345, 1220, 1200 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.62 (d, J = 7.2 Hz, 1H, C_5-H), 4.73 (qn, J = 6.8 Hz, 1H, C_4-H), 2.95 (m, 2H, $C_{2'}$-H_2), 1.65 (m, 2H, $C_{3'}$-H_2), 1.3 (br s, 12H,

aliphatic H's), 0.90 (m, 6H, C_4-$\underline{H}_3$, $C_{10'}$-$\underline{H}_3$); ^{13}C NMR (CCl_4/22.5 MHz) δ 171.8, 151.9, 133.9, 128.3, 125.6, 78.2, 54.1, 35.2, 31.7, 29.3, 29.1, 24.1, 22.5, 14.4, 14.0; Specific rotation $[\alpha]_{589}$ = +27.4°, $[\alpha]_{577}$ = +28.9°, $[\alpha]_{546}$ = +33.0°, $[\alpha]_{435}$ = +59.5°, $[\alpha]_{365}$ = +103.4° (c 3.03, CH_2Cl_2); GC (30 m DB-1, 200°C, 83 cm/sec, t_r = 10.38 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 1.08); TLC (85:15 hexanes/ethyl acetate, R_f = 0.36).

Anal. Calcd. for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82. Found: C, 72.75; H, 8.98.

(4R,5S)-3-(1-Oxo-2-(1-naphthyl)ethyl)-4-methyl-5-phenyl-2-oxazolidinone (16j, Table 4, Entry K). A solution of 8.86 g (50.0 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.2 M in THF) was metalated with 27.0 mL (1.76 M in hexane, 50.0 mmol) of n-butyllithium and acylated with 11.3 g (55.2 mmol) of 2-(naphth-1-yl)acetyl chloride according to the general acylation procedure to give 17.6 g (102% mass balance) of crude product. The title compound was purified by recrystallization from hexanes/ethyl acetate to afford 15.3 g (88%) of **16j** as a white crystalline solid: mp 103-104°C; IR (CH_2Cl_2) 3060, 2990, 1780, 1705, 1420, 1350 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 8.2-7.2 (m, 12H, aromatic H's), 5.45 (d, J = 7.2 Hz, 1H, C_5-$\underline{H}$), 4.9-4.7 (m, 3H, C_4-$\underline{H}$, $C_{2'}$-$\underline{H}_2$), 0.90 (d, J = 7 Hz, 3H, C_4-$C\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = -40.1°, $[\alpha]_{577}$ = -42.1°, $[\alpha]_{546}$ = -48.9°, $[\alpha]_{435}$ = -93.3°, $[\alpha]_{365}$ = -174.7° (c 0.584, CH_2Cl_2); GC (30 m DB-5, 250°C, (injector, detector = 275°C), 78 cm/sec, 8.01 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 3.88); TLC (8:2 hexanes/ethyl acetate, R_f = 0.40).

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.28; H, 5.59; N, 3.97.

(4R,5S)-3-(1-Oxo-2-methyoxyethyl)-4-methyl-5-phenyl-2-oxazolidinone (16k, Table 4, Entry L). A solution of 8.86 g (50.0 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.2 M in THF) was metalated with 22.4 mL (2.23 M in hexane, 50.0 mmol) of n-butyllithium and acylated with 5.0 mL (5.9 g, 55 mmol) of methoxyacetyl chloride according to the general acylation procedure to give 12.0 g (96% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 150°C, 0.02 mm) followed by recrystallization from pentane/diethyl ether to afford 10.0 g (80%) of **16k** as a white crystalline solid: mp 63-64°C; IR (CH_2Cl_2) 3060, 2990, 2940, 2830, 1780, 1720, 1450, 1405, 1380, 1370, 1350, 1215, 1200, 1150, 1130, 1120 cm^{-1}; ^1H NMR ($CDCl_3$/80 MHz) δ 7.35 (m, 5H, aromatic H's), 5.75 (d, J = 7.5 Hz, 1H, C_5-H), 4.80 (qn, J = 7.2 Hz, 1H, C_4-H), 4.65 (s, 2H, $C_{2'}$-H_2), 3.50 (s, 3H, OCH_3), 0.95 (d, J = 7.1 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = +30.4°, $[\alpha]_{577}$ = +31.6°, $[\alpha]_{546}$ = +36.2°, $[\alpha]_{435}$ = +66.0°, $[\alpha]_{365}$ = +116.8° (c 1.07, CH_2Cl_2); GC (30 m DB-5, 175°C, 85 cm/sec, t_r = 5.50 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 64:36 isooctane/ethyl acetate, 2.0 mL/min, k' = 3.11); TLC (8:2 hexanes/ethyl acetate, R_f = 0.19).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07. Found: C, 62.84; H, 6.08.

(4R,5S)-3-(1-Oxo-2-phenylmethoxyethyl)-4-methyl-5-phenyl-2-oxazolidinone (16l, Table 4, Entry M). A solution of 2.90 g (16.4 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.25 M in THF) was metalated with 10.5 mL (1.57 M in hexane, 16.5 mmol) of n-butyllithium and acylated with 3.00 g (16.2 mmol) of phenylmethoxyacetyl chloride according to the general acylation procedure to give 5.72 g (109% mass balance) of crude product. The title compound was isolated by flash chromatography (3 x 30 cm column, 8:2 hexanes/ethyl acetate) to afford 4.61 g (87%) of **16l** as a white crystalline solid: mp 99-100°C; IR ($CDCl_3$) 3040, 3000, 2930, 1785, 1725, 1380, 1350, 1260, 1220, 1205, 1150, 1125 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.33 (s, 10H, aromatic H's), 5.68 (d, J = 7.2 Hz, 1H, C_5-H), 4.75 (qn, J = 6.8 Hz, 1H, C_4-H), 4.71 (s, 2H, $C_{2'}$-H_2), 4.66 (s, 2H, OCH_2Ph), 0.93 (d, J = 6.8 Hz, 3H, C_4-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 169.8, 152.9, 137.2, 133.0, 128.8, 128.7, 128.4, 128.0, 125.6, 79.9, 73.4, 69.7, 54.4, 14.5; Specific rotation $[\alpha]_{589}$ = +16.2°, $[\alpha]_{577}$ = +17.0°, $[\alpha]_{546}$ = +19.7°, $[\alpha]_{435}$ = +35.8°, $[\alpha]_{365}$ = +64.8° (c 2.47, CH_2Cl_2); GC (30 m SE-54, 240°C, (injector, detector = 275°C), 71 cm/sec, t_r = 5.58 min); HPLC (8 mm x 10 cm Radial Pak (10 μm silica gel), 64:36 isooctane/ethyl acetate, 2.0 mL/min, k' = 0.95); TLC (8:2 hexanes/ethyl acetate, R_f = 0.29).

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89. Found: C, 70.06; H, 5.97.

(4S,5S)-3-(1-Oxobutyl)-4-methyl-5-phenyl-2-oxazolidinone (18c, Table 4, Entry N). A solution of 1.77 g (10.0 mmol) of (4S,5S)-norpseudoephedrine 2-oxazolidinone **7** (0.2 M in THF) was metalated with 4.5 mL (2.23 M in hexane, 10.0 mmol) of n-butyllithium and acylated with 1.2 mL

(1.2g, 12 mmol) of butanoyl chloride according to the general acylation procedure to give 2.5 g (100% mass balance) of unpurified product. The title compound was isolated by distillation (Kugelrohr, 140°C, 0.01 mm) to afford 2.35 g (95%) of **18c** as a colorless liquid: IR (neat) 2970, 2880, 1785, 1705, 1460, 1370, 1325, 1220, 1200 cm^{-1}; ^1H NMR ($CDCl_3$/80 MHz) δ 7.35 (m, 5H, aromatic H's), 5.07 (d, J = 4.5 Hz, 1H, C_5-H), 4.42 (d of q, J = 4.5 Hz, 6.8 Hz, 1H, C_4-H), 2.93 (t, J = 7.8 Hz, 2H, $C_{2'}$-H_2), 1.95-1.5 (m, 2H, $C_{3'}$-H_2), 1.60 (d, J = 6.8 Hz, 3H, C_4-CH_3), 1.00 (t, J = 7.5 Hz, 3H, $C_{4'}$-H_3); Specific rotation $[\alpha]_{589}$ = +21.8°, $[\alpha]_{577}$ = +23.1°, $[\alpha]_{546}$ = +27.3°, $[\alpha]_{435}$ = +56.3°, $[\alpha]_{365}$ = +112.2° (c 2.95, CH_2Cl_2); GC (30 m DB-5, 175°C, 86 cm/sec, t_r = 3.61 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel, 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 1.51); TLC (8:2 hexanes/ethyl acetate, R_f = 0.37).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.23; H, 6.81.

(4S)-3-(1-Oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (20b, Table 4, Entry 0). A mechanically stirred solution of 115 g (0.891 mol) of (S)-valinol 2-oxazolidinone **8** (0.9 M in THF) was metalated with 550 mL (1.76 M in hexane, 0.968 mol) of n-butyllithium and acylated with 100 mL (107 g, 1.18 mol) of propanoyl chloride according to the general acylation procedure to give 180 g (109% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 100°C, 0.01 mm) to afford 153 g (93%) of **20b** as a colorless liquid: IR (neat) 2970, 2880, 1785, 1705, 1385, 1370, 1245, 1210, 1070 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 4.6-4.1 (m, 3H, C_4-H, C_5-H_2), 2.95 (q, J = 7.6 Hz, 2H,

$C_{2'}$-$\underline{H}_2$), 2.57-2.22 (m, 1H, C_4-C$\underline{H}$), 1.18 (t, J = 7.6 Hz, 3H, $C_{3'}$-$\underline{H}_3$), 0.92 (overlapping d's, 6H, CH(C$\underline{H}_3$)$_2$); Specific rotation $[\alpha]_{589}$ = +91.9°, $[\alpha]_{577}$ = +96.0°, $[\alpha]_{546}$ = +109.5°, $[\alpha]_{435}$ = +186.2°, $[\alpha]_{365}$ = +293.9° (c = 0.377, CH_2Cl_2); GC (30 m DB-5, 100°C, 94 cm/sec, t_r = 7.16 min); TLC (8:2 hexanes/ethyl acetate, R_f = 0.49).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16. Found: C, 58.38; H, 8.30.

(4S)-3-(1-Oxo-3-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone (20h, Table 4, Entry Q). A mechanically stirred solution of 20.0 g (0.155 mol) of (S)-valinol 2-oxazolidinone 8 (0.31 $\underline{M}$ in THF) was metalated with 95.0 mL (1.70 $\underline{M}$ in hexane, 0.162 mol) of $\underline{n}$-butyllithium and acylated with 25.0 mL (28.4 g, 0.168 mol) of 3-phenylpropanoyl chloride according to the general acylation procedure to give 41.5 g (102% mass balance) of unpurified product. The title compound was purified by recrystallization from hexanes (750 mL, 2 crops) to afford 37.0 g (91%) of **20h** as a white crystalline solid: mp 63-64°C; IR (CH_2Cl_2) 3060, 2970, 1780, 1700, 1385, 1210 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.3-7.17 (m, 5H, aromatic H's), 4.41 (d of d of d, J = 8.5, 4.0, 3.2 Hz, 1H, C_4-$\underline{H}$), 4.24 (d of d, J = 9.3, 8.4 Hz, 1H, C_5-$\underline{H}$), 4.19 (d of d, J = 9.3, 3.2 Hz, 1H, C_5-$\underline{H}$), 3.30 (d of d of d, J = 17.5, 8.7, 6.9 Hz, 1H, $C_{2'}$-$\underline{H}$), 3.22 (d of d of d, J = 17.5, 8.5, 7.2 Hz, 1H, $C_{2'}$-$\underline{H}$), 3.1-2.9 (m, 2H, $C_{3'}$-$\underline{H}_2$), 2.4-2.3 (m, 1H, C_4-C$\underline{H}$), 0.90 (d, J = 7.4 Hz, 3H, CH(C$\underline{H}_3$)), 0.84 (d, J = 7.4 Hz, 3H, CH(C$\underline{H}_3$)); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 172.3, 154.0, 140.5, 128.5, 126.1, 63.4, 58.4, 37.0, 30.4, 28.4, 17.9, 14.6; Specific rotation $[\alpha]_{589}$ = +71.0°, $[\alpha]_{577}$ = +74.1°, $[\alpha]_{546}$ = +84.2°, $[\alpha]_{435}$ = +143.4°, $[\alpha]_{365}$ = +225.3° ($\underline{c}$ 4.61, CH_2Cl_2); GC (30 m DB-1, 175°C, 83 cm/sec, t_r =

4.75 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 4.86); TLC (8:2 hexanes/ethyl acetate, R_f = 0.47).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 69.17; H, 7.42.

(4S)-3-(1-Oxodecyl)-4-(1-methylethyl)-2-oxazolidinone (20i, Table 4, Entry R). A mechanically stirred solution of 3.10 g (24.0 mmol) of (S)-valinol 2-oxazolidinone **8** (0.33 M in THF) was metalated with 15.5 mL (1.61 M in hexane, 25.0 mmol) of n-butyllithium and acylated with 5.00 g (26.2 mmol) of decanoyl chloride according to the general acylation procedure to give 8.3 g (122% mass balance) of unpurified product. The title compound was isolated by flash chromatography (3 x 30 cm column, 7:3 hexanes/diethyl ether) followed by molecular distillation (Kugelrohr, 160°C, 0.008 mm) to afford 3.83 g (56%) of **20i** as a colorless liquid: IR (CH_2Cl_2) 3070, 2980, 2940, 2880, 1785, 1705, 1390, 1210 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 4.4-4.1 (m, 3H, C_4-H, C_5-H_2), 3.0-2.8 (m, 2H, $C_{2'}$-H_2), 2.6-2.3 (m, 1H, C_4-CH), 1.6 (m, 2H, $C_{3'}$-H_2), 1.30 (br s, 12H, aliphatic H's), 0.91 (m, 9H, $CH(CH_3)_2$, $C_{10'}$-H_3); Specific rotation $[\alpha]_{589}$ = +63.7°, $[\alpha]_{577}$ = +66.7°, $[\alpha]_{546}$ = +75.7°, $[\alpha]_{435}$ = +128.8°, $[\alpha]_{365}$ = +202.8° (c 2.07, CH_2Cl_2); GC (25 m Carbowax 20M, 175°C, 50 cm/sec, t_r = 13.09 min); TLC (7:3 hexanes/diethyl ether, R_f = 0.17).

Anal. Calcd. for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31. Found: C, 68.06; H, 10.35.

(4R)-3-(1-Oxopropyl)-4-phenyl-2-oxazolidinone (22b, Table 4, Entry S). A solution of 2.00 g (12.3 mmol) of (R)-phenylglycinol 2-oxazolidinone **9** (0.25 M in THF) was metalated with 8.0 mL (1.53 M in hexane, 12.2 mmol) of n-butyllithium and acylated with 1.1 mL (1.2 g, 12.6 mmol) of propanoyl chloride according to the general acylation procedure to give 2.7 g (100% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 155°C, 0.01 mm) to afford 2.30 g (85%) of **22b** as a colorless liquid which crystallized on standing: mp 76-77°C; IR (CCl_4) 1795, 1720, 1380, 1200 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.38 (d of d, J = 9.0, 4.2 Hz, 1H, C_4-H), 4.62 (t, J = 9.0 Hz, 1H, C_5-H), 4.22 (d of d, J = 9.0, 3.7 Hz, 1H, C_5-H), 2.92 (q, J = 7.5 Hz, 2H, $C_{2'}$-H_2), 1.10 (t, J = 7.5 Hz, 3H, $C_{3'}$-H_3); Specific rotation $[\alpha]_{589}$ = -84.1°, $[\alpha]_{577}$ = -89.1°, $[\alpha]_{546}$ = -102.3°, $[\alpha]_{435}$ = -185.8°, $[\alpha]_{365}$ = -316.8°, (c 1.44, CH_2Cl_2); GC (30 m DB-1, 175°C, 104 cm/sec, t_r = 1.63 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 6.99); TLC (8:2 hexanes/ethyl acetate, R_f = 0.29).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.83; H, 6.03; N, 6.33.

(4R)-3-(1-Oxobutyl)-4-phenyl-2-oxazolidinone (22c, Table 4, Entry T). A solution of 5.00 g (30.7 mmol) of (R)-phenylglycinol 2-oxazolidinone **9** (0.3 M in THF) was metalated with 20.0 mL (1.60 M in hexane, 32.0 mmol) of n-butyllithium and acylated with 5.2 mL (5.0 g, 32 mmol) of butanoic anhydride according to the general acylation procedure to give 6.7 g (94% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 150°C, 0.005 mm) to

afford 6.0 g (84%) of **22c** as a colorless liquid which crystallized upon standing: mp 50-51°C; IR (CH_2Cl_2) 3050, 2970, 1780, 1705, 1380, 1330, 1200 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.28 (s, 5H, aromatic H's), 5.28 (d of d, J = 9.0, 4.0 Hz, 1H, C_4-H), 4.57 (t, J = 9.0 Hz, 1H C_5-H), 4.15 (d of d, J = 9.0, 3.9 Hz, 1H, C_5-H), 2.82 (t, J = 7.5 Hz, 2H, $C_{2'}$-H_2), 1.60 (m, 2H, $C_{3'}$-H_2), 0.90 (t, J = 7.5 Hz, 3H, $C_{4'}$-H_3); Specific rotation $[\alpha]_{589}$ = -79.5°, $[\alpha]_{577}$ = -83.6°, $[\alpha]_{546}$ = -87.0°, $[\alpha]_{435}$ = -173.6°, $[\alpha]_{365}$ = -296.8° (c 2.21, CH_2Cl_2); GC (30 m DB-1, 175°C, 104 cm/sec, t_r = 2.12 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 5.57); TLC (8:2 hexanes/ethyl acetate, R_f = 0.35).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48. Found: C, 67.19; H, 6.56.

(4S)-3-(1-Oxopropyl)-4-phenylmethyl-2-oxazolidinone (24b, Table 4, Entry U). A solution of 17.7 g (100 mmol) of (4S)-phenylalaninol 2-oxazolidinone **10** (0.2 M in THF) was metalated with 65 mL (1.69 M in hexane, 110 mmol) of n-butyllithium and acylated with 9.6 mL (10.2 g, 110 mmol) of propanoyl chloride according to the general acylation procedure to give 23.5 g (101% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 140°C, 0.008 mm) to afford 23.0 g (99%) of **24b** as a colorless liquid which crystallized on standing: mp 44.5-45.5°C; IR (CH_2Cl_2) 3050, 2980, 1780, 1700, 1385, 1375, 1240, 1210, 1080 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.2 (m, 5H, aromatic H's), 4.8-4.5 (m, 1H, C_4-H), 4.13 (d, J = 6.8 Hz, 2H, C_4-CH_2Ph), 3.27 (d of d, J = 14.1, 3.7 Hz, 1H, C_5-H), 2.93 (q, J = 7.8 Hz,

2H, $C_{2'}$-$\underline{H}_2$), 2.77 (d of d, J = 13.9, 9.9 Hz, 1H, C_5-$\underline{H}$), 1.18 (d, J = 3H, $C_{3'}$-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 173.9, 153.4, 135.4, 129.4, 128.9, 127.2, 66.2, 55.0, 37.8, 29.1, 8.3; Specific rotation $[\alpha]_{589}$ = +80.7°, $[\alpha]_{577}$ = +84.4°, $[\alpha]_{546}$ = +95.6°, $[\alpha]_{435}$ = +162.2°, $[\alpha]_{365}$ = +254.3° (c 1.00, CH_2Cl_2); GC (30 m DB-1, 175°C, 100 cm/sec, t_r = 2.44 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 4.85); TLC (8:2 hexanes/ethyl acetate, R_f = 0.37).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48. Found: C, 66.73; H, 6.51.

(4S)-3-(1-Oxobutyl)-4-phenylmethyl-2-oxazolidinone (24c, Table 4, Entry V). A solution of 1.77 g (10.0 mmol) of (4S)-phenylalaninol 2-oxazolidinone **10** (0.2 M in THF) was metalated with 4.5 mL (2.23 M in hexane, 10.0 mmol) of n-butyllithium and acylated with 1.2 mL (1.2 g, 12 mmol) of butanoyl chloride according to the general acylation procedure to give 2.5 g (100% mass balance) of unpurified product. The title compound was isolated by distillation (Kugelrohr, 140°C, 0.01 mm) to afford 2.35 g (95%) of **24c** as a colorless liquid; IR (neat) 2980, 2950, 2890, 1790, 1705, 1455, 1390, 1365, 1215, 1090 cm^{-1}; ^1H NMR ($CDCl_3$/80 MHz) δ 7.30 (m, 5H, aromatic H's), 4.65 (m, 1H, C_4-$\underline{H}$), 4.18 (d, J = 6.0 Hz, 2H, C_4-$C\underline{H}_2$), 3.32 (d of d, J = 13.2, 4 Hz, 1H, C_5-$\underline{H}$), 2.92 (t, J = 8 Hz, 2H, $C_{2'}$-$\underline{H}_2$), 2.77 (d of d, J = 13.2, 9.0 Hz, 1H, C_5-$\underline{H}$), 1.75 (m, 2H, $C_{3'}$-$\underline{H}_2$), 1.05 (t, J = 8z, 3H, $C_{4'}$-$\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = +74.8°, $[\alpha]_{577}$ = +78.1°, $[\alpha]_{546}$ = +88.8°, $[\alpha]_{435}$ = +150.7°, $[\alpha]_{365}$ = +235.7° (c 1.34, CH_2Cl_2); GC (30 m DB-5, 175°C, 86 cm/sec, t_r = 4.95 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 3.79); TLC (8:2 hexanes/ethyl acetate,

R_f = 0.29).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.13; H, 7.03.

(4R,5S)-3-((2E)-1-Oxo-2-butenyl)-4-methyl-5-phenyl-2-oxazolidinone (16m). A solution of 1.00g (5.64 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.38 M in THF) was metalated with 3.4 mL (1.61 M in hexane, 5.47 mmol) of n-butyllithium and acylated with 0.58 mL (0.63 g, 6.0 mmol) of crotonyl chloride according to the general acylation procedure to give 1.41 g (101% mass balance) of unpurified product. The title compound was isolated by flash chromatography (3 x 30 cm column, 7:3 hexanes/diethyl ether) to afford 1.21 g (87%) of **16m** as a white crystalline solid: mp 65-66°C; IR (CCl_4) 2990, 1790, 1690, 1645, 1350, 1240, 1195, 1150, 1125, 1045 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.45-7.30 (m, 5H, aromatic H's), 7.28 (d of q, J = 15.5, 1.7 Hz, 1H, $C_{2'}$-H), 7.17 (d of q, J = 15.5, 6.8 Hz, 1H, $C_{3'}$-H), 5.68 (d, J = 7.2 Hz, 1H C_5-H), 4.81 (qn, J = 6.8 Hz, 1H C_4-H), 1.96 (d of d, J = 6.9, 1.7 Hz, 3H, $C_{4'}$-H_3), 0.92 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 164.6, 153.0, 146.5, 133.5, 128.6, 125.7, 122.0, 79.0, 54.8, 18.5, 14.6; Specific rotation $[\alpha]_{589}$ = +32.4°, $[\alpha]_{577}$ = +33.3°, $[\alpha]_{546}$ = +37.9°, $[\alpha]_{435}$ = +64.7°, $[\alpha]_{365}$ = +110.4° (c 1.63, CH_2Cl_2); GC (30 m DB-1, 175°C, 104 cm/sec, t_r = 3.55 min); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 3.08); TLC (8:2 hexanes/diethyl ether, R_f = 0.26).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16. Found: C, 68.82; H, 6.14.

(4R,5S)-3-((2R)-1-Oxo-2-bromopropyl)-4-methyl-5-phenyl-2-oxazolidinone (16n) and (4R,5S)-3-((2S)-1-Oxo-2-bromopropyl)-4-methyl-5-phenyl-2-oxazolidinone (16o). A solution of 8.86 g (50.0 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.2 M in THF) was metalated with 27 mL (1.76 M in hexane, 50.0 mmol) of n-butyllithium and acylated with 9.4 g (55 mmol) of (±)-2-bromopropanoyl chloride according to the general acylation procedure to give 17.2 g (110% mass balance) of the unpurified products. The two diastereomers were separated by flash chromatography (6 x 30 cm column, 9:1 hexanes/ethyl acetate, **16n** elutes first) to afford 6.6 g (85%) of **16n** as a white crystalline solid and 7.0 g (90%) of **16o** as a white crystalline solid.

16n: mp 88-89°C; IR (CH_2Cl_2) 3060, 2995, 1785, 1710, 1420, 1370 cm^{-1}; ^1H NMR ($CDCl_3$/80 MHz) δ 7.35 (m, 5H, aromatic H's), 6.9-6.65 (m, 2H, C_5-H, $C_{2'}$-H), 4.78 (qn, J = 7 Hz, 1H, C_4-H), 1.87 (d, J = 7.2 Hz, 3H, $C_{3'}$-H_3), 0.95 (d, J = 7 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = +9.3°, $[\alpha]_{577}$ = +10.0°, $[\alpha]_{546}$ = +11.2°, $[\alpha]_{435}$ = +19.8°, $[\alpha]_{365}$ = +36.6° (c 0.485, CH_2Cl_2); GC (The diastereomers epimerize under the conditions required for GC analysis); HPLC (8 mm x 10 cm Radial Pak (5 µm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 0.96); TLC (8:2 hexanes/ethyl acetate, R_f = 0.73).

16o: mp 99-100°C; IR (CH_2Cl_2) 3060, 2990, 1785, 1710, 1420, 1370 cm^{-1}; ^1H NMR ($CDCl_3$/80 MHz) δ 7.35 (m, 5H, aromatic H's), 5.9-5.6 (m, 2H, C_5-H, $C_{2'}$-H), 4.83 (qn, J = 7 Hz, 1H, C_4-H), 1.85 (d, J = 6.8 Hz, 3H, $C_{3'}$-H_3), 0.91 (d, J = 7 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = +8.8°, $[\alpha]_{577}$ = +9.0°, $[\alpha]_{546}$ = +10.1°, $[\alpha]_{435}$ = +18.0°, $[\alpha]_{365}$ = +34.3° (c 0.714, CH_2Cl_2); GC (The diastereomers epimerize under the conditions required for GC analysis); HPLC (8 mm x 10 cm Radial Pak (5 µm silica

gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 4.52); TLC (8:2 hexanes/ethyl acetate, R_f = 0.46).

(4R,5S)-3-(1-Oxo-2-(2,5-dimethylpyrrol-1-yl)ethyl)-4-methyl-5-phenyl-2-oxazolidinone (16p). To a mechanically stirred, cooled (-5°C) solution of 3.28 g (21.4 mmol) of (2,5-dimethylpyrrol-1-yl)acetic acid (0.5 M in THF) was added 3.00 mL (2.18 g, 21.5 mmol) of triethylamine and 2.05 mL (2.33 g, 21.4 mmol) of ethyl chloroformate. The thick-white mixture was stirred at -5°C for 0.5 h followed by the addition via cannula of a solution of the metalated 2-oxazolidinone, prepared previously from 3.79 g (21.4 mmol) of (4R,5S)-norephedrine 2-oxazolidinone **6** (0.5 M in THF) and 12.7 mL (1.69 M in hexane, 21.5 mmoL) of n-butyllithium. The reaction mixture was stirred at 0°C for 4 h, then worked-up according to the general acylation procedure (under an atmosphere of nitrogen) to give 7.2 g (108% mass balance) of unpurified product contaminated with (4R,5S)-3-(1-ethoxy-1-oxomethyl)-4-methyl-5-phenyl-2-oxazolidinone. The title compound was isolated by flash chromatography (5 x 20 cm column, 75:25 hexanes/ethyl acetate) to afford 2.51 g (38%) of **16p** as a white crystalline solid: mp 154-155°C; IR (CH_2Cl_2) 3060, 2990, 1785, 1770, 1410, 1370, 1345, 1200 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.33 (m, 5H, aromatic H's), 5.73 (s, 2H, aromatic H's), 5.68 (d, J = 7.2 Hz, 1H, C_5-H), 5.06 (d, J = 2 Hz, 2H, $C_{2'}$-H_2), 4.72 (qn, J = 6.8 Hz, 1H, C_4-H), 2.28 (s, 6H, $C_{2''}$-CH_3, $C_{5''}$-CH_3), 0.92 (d, J = 6.8 Hz, 3H, C_4-CH_3); Specific rotation $[\alpha]_{589}$ = -24.8°, $[\alpha]_{577}$ = -26.2°, $[\alpha]_{546}$ = -30.2°, $[\alpha]_{435}$ = -54.8°, $[\alpha]_{365}$ = -92.0° (c 1.36, CH_2Cl_2); GC (30 m DB-1, 250°C, (injector, detector = 275°C), 89 cm/sec, t_r = 1.93 min); HPLC (8 mm x 10

cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' = 4.47); TLC (7:3 hexanes/ethyl acetate, R_f = 0.43).

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45. Found: C, 69.39; H, 6.58.

Sodium Hexamethyldisilylamide.[59] The following reaction and subsequent manipulations of the product were performed with careful exclusion of moisture and oxygen. A magnetically stirred mixture of 25 g (1.04 mol) of oil free sodium hydride and 211 mL (161 g, 1.00 mol) of hexamethyldisilylamine in 800 mL of dry toluene was heated at reflux for 18 h. The hot, dark mixture was filtered through a 2 cm pad of celite. The pale yellow filtrate was concentrated *in vacuo* to afford 145-170 g (79-93%) of the title compound as a white crystalline solid. The product was transferred and stored in a dry box.

Potassium Hexamethyldisilylamide.[59] The following reaction and subsequent manipulations of the product were performed with careful exclusion of moisture and oxygen. A magnetically stirred mixture of 1.77 g (44.0 mmol) of oil free potassium hydride and 7.11 g (44.0 mmol) of hexamethyldisilylamine in 50 mL of dry toluene was heated at reflux for 8 h. The hot, dark mixture was filtered through a 1 cm pad of celite. The pale yellow solution was concentrated *in vacuo* to afford 7.81 g (88%) of the title compound as a white crystalline solid. The product was stored in a dry box. Stock solutions were prepared in THF, benzene or toluene and titrated prior to use.

Benzyl Bromomethyl Ether (45). The title compound was prepared by an adaptation of the procedure of Conner et al.,[60] substituting anhydrous hydrogen bromide for anhydrous chloride. The product was distilled under reduced pressure through a 20-cm vacuum-jacketed Vigreux column. The forerun (bp 80-85°C, 0.6 mm), constituting ca. 40-50% of the crude product, was shown to be mainly benzyl bromide. The product **45** (40-50%), was then collected as a colorless liquid (bp 80-85°C, 0.01 mm). Benzyl bromomethyl ether, which fumes in air, was stored at -10°C under an atmosphere of argon. **45**: ^{1}H NMR ($CDCl_3$/90 MHz) δ 7.40 (s, 5H, aromatic H's), 5.70 (s, 2H, -OC$\underline{H_2}$Br), 4.70 (s, 2H, PhC$\underline{H_2}$O-).

Benzyl Chloromethyl Sulfide (46a). Anhydrous hydrogen chloride was bubbled through a magnetically stirred,cooled (-10°C) solution of 25.0 g (0.278 mol) of s-trioxane in 100 g (0.805 mol) of benzyl thiol until saturated (ca. 1h). After an additional period of 12 h at room temperature, the reaction mixture was dried over anhydrous calcium chloride. The product was decanted from the calcium chloride and distilled through a 5-cm vigreux column to afford 101 g (73%) of **46a** as a colorless liquid: bp 74-76°C, 0.01 mm, (Lit.[61] bp 102°C, 2 mm); ^{1}H NMR (CCl_4/90 MHz) δ 7.2 (s, 5H, aromatic H's), 4.40 (s, 2H, SC$\underline{H_2}$Cl), 3.80 (s, 2H, PhC$\underline{H_2}$S).

Benzyl Bromomethyl Sulfide (46b). The title compound was prepared following the procedure of Hollowood et. al.[62] The product was purified by molecular distillation (Kugelrohr, 140°C, 0.01 mm) to afford **46b** (92%) as a colorless liquid, which solidified below -10°C: ^{1}H NMR (CCl_4/90 MHz) δ 7.27 (s, 5H, aromatic H's), 4.33 (s, 2H, SC$\underline{H_2}$Br), 3.82 (s, 2H, PhC$\underline{H_2}$S).

General Procedure for the Alkylation of 2-Oxazolidinone Imide Enolates. Alkylation reactions are performed on scales ranging from 1 mmol to 0.5 mol at enolate concentrations of 0.1-1.0 M in THF. Electrophiles are either freshly distilled or passed through a column of neutral activity 1 alumina immediately prior to use.

Enolate Generation. A. Lithium Enolate. To a magnetically stirred, cooled (-5°C) solution of diisopropylamine (1.1 equiv, 0.5-1.0 M in THF) is added a hexane solution of n-butyllithium (1.1 equiv). The colorless solution of lithium diisopropylamide (LDA) is stirred at -5°C for 0.5 h then cooled to -78°C. The indicated N-acyl 2-oxazolidinone (1.0 equiv, 1-5 M in THF) is added dropwise. After stirring at -78°C for 0.5 h, the desired lithium enolate is ready for alkylation.

Enolate Generation. B. Sodium Enolate. To a magnetically stirred, cooled (-78°C) solution of sodium hexamethyldisilylamide (1.1 equiv, weighed and transferred in a dry box, 0.5 M in THF) is added the indicated N-acyl 2-oxazolidinone imide (1.0 equiv, 1-5 M in THF) dropwise. After stirring at -78°C for 0.5 h the desired sodium enolate is ready for alkylation.

Enolate Generation. C. Potassium Enolate. To a magnetically stirred, cooled (-78°C) solution of the indicated 3-acyl 2-oxazolidinone imide (1.0 equiv, 0.5-1 M in THF) is added a solution of potassium hexamethyldisilylamide (1.1 equiv, 0.5-1 M in benzene, THF or toluene) dropwise. After stirring at -78°C for 0.5 h the potassium enolate is ready for alkylation.

Enolate Generation. D. Magnesium Enolate. To a solution of the lithium enolate (prepared as described above) is added a solution of anhydrous magnesium bromide (1.1 equiv, 1.0 M in 1:1 benzene/diethyl

ether). After stirring at -78°C for 0.5 h the desired magnesium enolate is ready for alkylation.

Enolate Alkylation. To the magnetically stirred, cooled (-78°C) solution of the metal enolate, prepared as described above, is added the indicated electrophile (1-10 equiv, neat or 2-5 M in THF) dropwise. Electrophile quantity, as well as reaction temperature and time, are variables specific to each experiment. The reaction is quenched by the addition of 3 M aqueous ammonium chloride. Volatiles are removed *in vacuo* and the product extracted into dichloromethane (3x). The combined organic layers are successively washed with 1 M aqueous sodium bisulfate or hydrochloric acid (2x), 1 M aqueous potassium bicarbonate (2x), and brine (1x), dried over anhydrous magnesium sulfate or sodium sulfate, and concentrated *in vacuo*. Alkylation diastereoselection, as well as the extent of reaction, is determined by GC analysis of the unfractionated product. The product is purified by chromatography, molecular distillation or recrystallization as indicated in the following examples.

(4R,5S)-3-((2S)-1-Oxo-2-methylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17a, Table 9, Entry A). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 1.55 mL (1.12 g, 11.1 mmol) of diisopropylamine and 6.8 mL (1.61 M in hexane, 10.9 mmol) of *n*-butyllithium] (0.2 M in THF) was used to enolize 2.34 g (10.0 mmol) of **16b**. The resultant lithium enolate was alkylated with 2.4 mL (4.7 g, 30 mmol) of ethyl iodide according to the general alkylation procedure for 2 h at 0°C to give 2.39 g (92% mass balance) of

unpurified product. Analysis by GC (30 m DB-1, 175°C, 91 cm/sec) afforded a 9:91 ratio of (2R)-**17a** (t_r = 4.44 min) to (2S)-**17a** (t_r = 4.69 min), and indicated the presence of both **6** (t_r = 2.59 min, ca. 34%) and unreacted **16b** (t_r = 3.74 min, ca. 10%). The title compound was isolated by MPLC (column C, 8:2 hexanes/diethyl ether, 10 mL/min, (2S)-**17a** elutes second) to afford 734 mg (28%) of (2S)-**17a** as a white crystalline solid [(2R)-**17a**:(2S)-**17a** < 1:99]: mp 71-72°C; IR (CH_2Cl_2) 3060, 2980, 2950, 1785, 1700, 1390, 1370, 1350, 1240, 1200 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.53 (d, J = 7.2 Hz, 1H, C_5-H), 4.67 (qn, J = 6.8 Hz, 1H, C_4-H), 3.60 (q, J = 6.8 Hz, 1H, $C_{2'}$-H), 2.1-1.3 (m, 2H, $C_{3'}$-H_2), 1.13 (d, J = 7.5 Hz, 3H, $C_{2'}$-CH_3), 0.93 (t, J = 7.5 Hz, 3H, $C_{4'}$-H_3), 0.85 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR (CCl_4/22.5 MHz) δ 175.5, 151.4, 133.8, 128.2, 125.4, 77.9, 54.1, 38.4, 26.6, 16.2, 14.4, 11.2; Specific rotation $[\alpha]_{589}$ = +54.7°, $[\alpha]_{577}$ = +58.9°, $[\alpha]_{546}$ = +67.2°, $[\alpha]_{435}$ = +117.9°, $[\alpha]_{365}$ = 197.7° (c 1.38, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12, 2.0 mL/min, k' (2R)-**17a** = 1.05, k' (2S)-**17a** = 1.41, α = 1.34).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 69.09; H, 7.36.

(4R,5S)-3-((2S)-1-Oxo-2-methylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17a, Table 9, Entry B). Sodium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of 0.243 g (1.33 mmol) of sodium hexamethyldisilylamide (0.25 M in THF) was used to enolize 0.261 g (1.12 mmol) of **16b**. The resultant sodium enolate was alkylated with 0.40 mL (0.78 g, 5.0 mmol) of ethyl iodide according to the general alkylation procedure for 2 h at -20°C to give 0.272 g (76% mass balance) of unpuri-

fied product. Analysis by GC (30 m SE-54, 200°C, 48 cm/sec) afforded a 6:94 ratio of (2R)-**17a** (t_r = 8.31 min) to (2S)-**17a** (t_r = 8.66 min), and indicated the presence of unreacted **16b** (t_r = 5.75 min, ca. 20%). The title compound was isolated by flash chromatography (2 x 30 cm column, 9:1 hexanes/ethyl acetate, (2S)-**17a** elutes second) to afford 194 mg (53%) of (2S)-**17a** [(2R)-**17a**:(2S)-**17a** = 2:98] as a white crystalline solid.

(4R,5S)-3-((2S)-1-Oxo-2-methyl-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (17b, Table 9, Entry C). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 3.10 mL (2.24 g, 22.1 mmol) of diisopropylamine and 14.2 mL (1.55 M in hexane, 22.0 mmol) of n-butyllithium] (0.66 M in THF) was used to enolize 4.60 g (19.7 mmol) of **16b**. The resultant lithium enolate was alkylated with 5.1 mL (7.1 g, 59 mmol) of allyl bromide according to the general alkylation procedure for 3 h at 0°C to give 5.28 g (98% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C, 79 cm/sec) afforded a 2:98 ratio of (2R)-**17b** (t_r = 5.04 min) to (2S)-**17b** (t_r = 5.45 min), and indicated the presence of both **6** (t_r = 2.18 min, ca. 11%) and unreacted **16b** (t_r = 4.42 min, ca. 2%). The title compound was isolated by MPLC (column C, 85:15 hexanes/ethyl acetate, 10 mL/min, (2S)-**17b** elutes second) to afford 4.06 g (75%) of (2S)-**17b** as a white crystalline solid [(2R)-**17b**:(2S)-**17b** < 200:1]: mp 69-70°C; IR (CCl_4) 3000, 2950, 1795, 1705, 1385, 1370, 1345, 1245, 1200, 1125 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3 (m, 5H, aromatic H's), 6.0-5.7 (m, 1H, $C_{4'}$-H), 5.55 (d, J = 7.6 Hz, 1H, C_5-H), 5.2-4.8 (m, 2H, $C_{5'}$-H_2), 4.67 (qn, J = 6.8

Hz, 1H, C_4-H), 3.73 (septet, J = 6.7 Hz, 1H, $C_{2'}$-H), 2.6-1.9 (m, 2H, $C_{3'}$-H_2), 1.15 (d, J = 7.2 Hz, 3H, $C_{2'}$-CH_3), 0.83 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 174.8, 151.4, 135.1, 133.7, 128.2, 125.4, 116.7, 77.9, 54.2, 37.8, 36.7, 16.3, 14.4; Specific rotation $[\alpha]_{589}$ = +47.0°, $[\alpha]_{577}$ = +48.2°, $[\alpha]_{546}$ = +55.1°, $[\alpha]_{435}$ = +96.7°, $[\alpha]_{365}$ = +162.3° (c 2.36, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' (2R)-**17b** = 0.97, k' (2S)-**17b** = 1.55, α = 1.60).

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01. Found: C, 70.55; H, 7.16.

(4R,5S)-3-((2S)-1-Oxo-2-methyl-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (17b, Table 9, Entry D). Sodium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of 12.3 g (67.1 mmol) of sodium hexamethyldisilylamide (0.93 M in THF) was used to enolize 14.1 g (60.6 mmol) of **16b**. The resultant sodium enolate was alkylated with 11.0 mL (20.3 g, 121 mmol) of allyl iodide according to the general alkylation procedure for 3 h at -78°C to give 17.2 g (104% mass balance) of unpurified product. Analysis by GC (25 m SE-54, 175°C, 37 cm/sec) afforded a 7:93 ratio of (2R)-**17b** (t_r = 7.97 min) to (2S)-**17b** (t_r = 8.66 min). The title compound was purified by recrystallization from pentane (3x) to afford 13.7 g (83%) of (2S)-**17b** as a white crystalline solid [(2R)-**17b**:(2S)-**17b** < 1:200], identical in all respects to the previously prepared material.

(4R,5S)-3-((2S)-1-Oxo-2-methyl-3-phenylmethoxypropyl)-4-methyl-5-phenyl-2-oxazolidinone (17e, Table 9, Entry G). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 2.1 mL (1.52 g, 15.0 mmol) of diisopropylamine and 9.3 mL (1.61 M in hexane, 15.0 mmol) of n-butyllithium] (0.5 M in THF) was used to enolize 3.15 g (13.5 mmol) of **16b**. The resultant lithium enolate was alkylated with 3.8 mL (5.4 g, 27 mmol) of benzyl bromomethyl ether **45** according to the general alkylation procedure for 2 h at -20°C to give 6.1 g (124% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 150°C for 10 min, 20°C/min to 225°C, 83 cm/sec) afforded a 4:96 ratio of (2R)-**17e** (t_r = 18.31 min) to (2S)-**17e** (t_r = 19.08 min), and indicated the presence of unreacted **16b** (t_r = 5.99 min, ca. 5%). The title compound was isolated by MPLC (column C, 8:1:1 hexanes/diethyl ether/dichloromethane to afford 3.42 g (72%) of (2S)-**17e** as a colorless oil [(2R)-**17e**:(2S)-**17e** = 1:99]: IR (CCl_4) 2990, 2940, 2870, 1790, 1700, 1385, 1370, 1340, 1235, 1200, 1120, 1090 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.13 (m, 10H, aromatic H's), 5.45 (d, J = 7.2 Hz, 1H, C_5-H), 4.63 (qn, J = 6.9 Hz, 1H, C_4-H), 4.40 (s, 2H, OCH_2Ph), 4.07 (m, 1H, $C_{2'}$-H), 3.67 (d of d, J = 9.0, 7.5 Hz, 1H, $C_{3'}$-H), 3.45 (d of d, J = 9.0, 6.0 Hz, 1H, $C_{3'}$-H), 1.12 (d, J = 6.9 Hz, 3H, $C_{2'}$-CH_3), 0.92 (d, J = 6.9 Hz, 3H, C_4-CH_3); ^{13}C NMR (CCl_4/22.5 MHz) δ 174.1, 151.9, 138.2, 133.7, 128.2, 127.9, 127.1, 125.6, 78.0, 72.6, 72.1, 54.1, 38.0, 14.4, 13.7; Specific rotation $[\alpha]_{589}$ = +37.0°, $[\alpha]_{577}$ = +37.3°, $[\alpha]_{546}$ = +42.6°, $[\alpha]_{435}$ = +73.6°, $[\alpha]_{365}$ = +119.4° (c 2.07, CH_2Cl_2).

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 70.36; H, 6.79. Found: C, 70.62; H, 6.78.

(4R,5S)-3-((2S)-1,4-Dioxo-2-methyl-4-ethoxy)-4-methyl-5-phenyl-2-oxazolidinone (17f, Table 9, Entry H). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 2.3 mL (1.6 g, 16 mmol) of diisopropylamine and 10 mL (1.61 M in hexane, 16.1 mmol) of n-butyllithium] (0.37 M in THF) was used to enolize 3.43 g (14.7 mmol) of **16b**. The resultant lithium enolate was alkylated with 4.9 mL (7.4 g, 44 mmol) of ethyl 2-bromoacetate according to the general alkylation procedure for 2 h at 0°C to give 3.95 g (84% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 200°C, 88 cm/sec) afforded a 7:93 ratio of (2R)-**17f** (t_r = 5.75 min) to (2S)-**17f** (t_r = 6.28 min), and indicated the presence of both unreacted **16b** (t_r = 1.70 min, ca. 8%) and an unidentified material (t_r = 3.42 min, ca. 17%). The title compound was isolated by MPLC (column C, 8:2 hexanes/diethyl ether, 10 mL/min) to afford 2.40 g (51%) of (2S)-**17f** as a colorless liquid [(2R)-**17f**:(2S)-**17f** = 1:99]: IR (CCl_4) 2990, 1795, 1740, 1705, 1370, 1345, 1250, 1190, 1120, 1030 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.28 (s, 5H, aromatic H's), 5.57 (d, J = 7.2 Hz, 1H, C_5-H), 4.63 (qn, J = 6.8 Hz, 1H, C_4-H), 4.2-3.9 (m, 3H, $C_{2'}$-H, OCH_2CH_3), 2.80 (d of d, J = 18, 10 Hz, 1H, $C_{3'}$-H), 2.30 (d of d, J = 18, 5 Hz, 1H, $C_{3'}$-H), 1.23 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 0.98 (d, J = 7.0 Hz, 3H, $C_{2'}$-CH_3) 0.87 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR (CCl_4/22.5 MHz) δ 174.8, 170.4, 152.9, 133.8, 128.2, 125.5, 78.0, 59.6, 54.3, 37.4, 33.9, 17.0, 14.1, 13.9; Specific rotation $[\alpha]_{589}$ = +35.7°, $[\alpha]_{577}$ = +36.8°, $[\alpha]_{546}$ = +41.9°, $[\alpha]_{435}$ = +70.3°, $[\alpha]_{365}$ = +110.7° (c 1.78, CH_2Cl_2).

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63. Found: C, 64.03; H, 6.63.

(4R,5S)-3-((2S)-1-Oxo-2-methyl-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (17g, Table 9, Entry I). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 1.9 mL (1.4 g, 14 mmol) of diisopropylamine and 8.6 mL (1.57 M in hexane, 13.5 mmol) of n-butyllithium] (0.11 M in THF) was used to enolize 2.91 g (12.5 mmol) of imide **16b**. The resultant lithium enolate was alkylated with 1.6 mL (2.3 g, 13.5 mmol) of benzyl bromide according to the general alkylation procedure for 2 h at 0°C to give 4.07 g (101% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 225°C, 77 cm/sec) afforded a 2:98 ratio of (2R)-**17g** (t_r = 4.33 min) to (2S)-**17g** (t_r = 4.99 min). The title compound was isolated by flash chromatography (3 x 30 cm column, 85:15 hexanes/ethyl acetate, (2S)-**17g** eluted second) to afford 2.93 g (73%) of (2S)-**17g** as a viscous colorless oil [(2R)-**17g**:(2S)-**17g** < 1:99]: IR (CCl_4) 1790, 1705, 1340, 1190 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.2 (s, 5H, aromatic H's), 6.7 (s, 5H, aromatic H's), 5.47 (d, J = 7.2 Hz, 1H, C_5-H), 4.63 (qn, J = 6.8 Hz, 1H, C_4-H), 4.0 (m, 1H, $C_{2'}$-H), 3.05 (d of d, J = 13.5, 6.4 Hz, 1H, $C_{3'}$-H), 2.58 (d of d, J = 13.5, 8.1 Hz, 1H, $C_{3'}$-H), 1.08 (d, J = 6.9 Hz, 3H, $C_{2'}$-CH_3), 0.65 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR (CCl_4/22.5 MHz) δ 175.2, 151.8, 138.9, 133.7, 129.0, 128.3, 128.0, 125.9, 125.5, 78.1, 54.1, 39.7, 39.1, 16.1, 14.2; Specific rotation $[\alpha]_{589}$ = +78.5° (c 1.68, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (10 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' (2R)-**17g** = 1.27, k' (2S)-**17g** = 2.02, α = 1.59).

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found: C, 74.50; H, 6.55.

(4R,5S)-3-((2S)-1-Oxo-2-methyl-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (17g, Table 9, Entry J). Sodium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of 10.5 g (57.3 mmol) of sodium hexamethyldisilylamide (0.85 M in THF) was used to enolize 12.0 g (51.4 mmol) of imide **16b**. The resultant sodium enolate was alkylated with 7.4 mL (10.6 g, 62.2 mmol) of benzyl bromide according to the general alkylation procedure for 3 h at -78°C to give 17.9 g (108% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 225°C, 77 cm/sec) afforded a 2:98 ratio of (2R)-**17g** (t_r = 4.33 min) to (2S)-**17g** (t_r = 4.99 min). The title compound was isolated by MPLC (column C, 7:3 hexanes/diethyl ether, 10 mL/min, (2S)-**17g** eluted second) in two portions to afford 13.1 g (79%) of (2S)-**17g** as a viscous colorless liquid [(2R)-**17g**:(2S)-**17g** < 1:99], identical in all respects to the previously prepared material.

(4R,5S)-3-((2R)-1-Oxo-2-methylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17h, Table 9, Entry K). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 2.00 mL (1.44 g, 14.3 mmol) of diisopropylamine and 8.8 mL (1.61 M in hexane, 14.2 mmol) of n-butyllithium] (0.43 M in THF) was used to enolize 3.19 g (12.9 mmol) of imide **16c**. The resultant lithium enolate was alkylated with 2.4 mL (5.5 g, 39 mmol) of methyl iodide according to the general alkylation procedure for 2 h at 0°C to give 3.25 g (96% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C, 93 cm/sec) afforded an 87:13 ratio of (2R)-**17h** (t_r = 4.54 min) to (2S)-**17h** (t_r = 4.67 min). The title compound was isolated by MPLC (column C, 85:15 hexanes/diethyl ether, 11 mL/min, (2R)-**17h** eluted first) to afford 2.51 g (75%)

of (2R)-**17h** as a white crystalline solid [(2R)-**17h**:(2S)-**17h** >99:1]: mp 65-66°C; IR (CH_2Cl_2) 2980, 2950, 2880, 1780, 1700, 1385, 1370, 1345, 1235, 1200, 1125 cm^{-1}; ^1H NMR (CCl_4/90 MHz) 7.3 (s, 5H, aromatic H's), 5.55 (d, J = 7.2 Hz, 1H, C_5-H), 4.66 (qn, J = 6.8 Hz, 1H, C_4-H), 3.56 (septet, J = 6.9 Hz, 1H, $C_{2'}$- H), 2.0-1.2 (m, 2H, $C_{3'}$-H_2), 1.13 (d, J = 7.5 Hz, 3H, $C_{2'}$-CH_3), 0.90 (t, J = 7.5 Hz, 3H, $C_{4'}$-H_3), 0.85 (d, J = 6.8 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 176.0, 152.0, 133.1, 128.0, 125.2, 78.1, 54.1, 38.6, 25.9, 16.0, 13.8, 11.0; Specific rotation $[\alpha]_{589}$ = +6.1°, $[\alpha]_{577}$ = +7.3°, $[\alpha]_{546}$ = +8.2°, $[\alpha]_{435}$ = +18.1°, $[\alpha]_{365}$ = +42.6° (c 1.72, CH_2Cl_2).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 69.11; H, 7.24.

(4R,5S)-3-((2R)-1-Oxo-2-methylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17h, Table 9, Entry L). Sodium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of 11.0 g (60.0 mmol) of sodium hexamethyldisilylamide (0.64 M in THF) was used to enolize 1.1 g (45.0 mmol) of imide **16c**. The resultant sodium enolate was alkylated with 16 mL (36 g, 260 mmol) of methyl iodide according to the general alkylation procedure for 3 h at -78°C to give 11.5 g (97% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C, 106 cm/sec) afforded a 94:6 ratio of (2R)-**17h** (t_r = 3.98 min) to (2S)-**17h** (t_r = 4.07 min). The title compound was isolated by MPLC (column C, 95:5 hexanes/THF, 10 mL/min, (2R)-**17h** eluted first) in three portions to afford 9.7 g (82%) of (2R)-**17h** as a white crystalline solid [(2R)-**17h**:(2S)-**17h** > 99:1], identical in all respects to the previously prepared material.

(4R,5S)-3-((2R)-1-Oxo-2-methylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17h, Table 7, Entry C). Potassium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of 0.207 g (0.838 mmol) of imide **16c** (0.1 M in THF) was enolized with 2.0 mL (0.50 M in THF, 1.0 mmol) of potassium hexamethyldisilylamide and alkylated with 0.24 mL (0.55 g, 3.9 mmol) of methyl iodide according to the general alkylation procedure for 2 h at -78°C to give 0.20 g (91% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C, 93 cm/sec) afforded an 81:19 ratio of (2R)-**17h** (t_r = 4.54 min) to (2S)-**17h** (t_r = 4.67 min).

(4R,5S)-3-((2R)-1-Oxo-2-methylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17h, Table 7, Entry D). Magnesium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 0.15 mL (0.112 g, 1.10 mmol) of diisopropylamine and 0.72 mL (1.53 M in hexane, 1.11 mmol) of n-butyllithium] (0.2 M in THF) was used to enolize 0.250 g (1.00 mmol) of imide **16c**. After 0.5 h at -78°C a solution of anhydrous magnesium bromide (ca. 210 mg, 1.14 mmol) in 5 mL of 1:1 benzene/diethyl ether was added. The resultant magnesium enolate was alkylated with 0.2 mL (0.57 g, 4 mmol) of methyl iodide according to the general alkylation procedure for 2 h at 0°C to give 0.21 g (78% mass balance) of unpurified product. Analysis by GC (30 m SE-54, 175°C, 48 cm/sec) afforded a 94:6 ratio of (2R)-**17h** (t_r = 8.31 min) to (2S)-**17h** (t_r = 8.66 min) and indicated the presence of unreacted **16c** (t_r = 5.75 min). No enolate decomposition products were observed.

(4R,5S)-3-((2R)-1-Oxo-2,3-dimethylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17i, Table 9, Entry M). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 0.175 mL (0.126 g, 1.25 mmol) of diisopropylamine and 0.77 mL (1.61 M in hexane, 1.24 mmol) of n-butyllithium] (0.1 M in THF) was used to enolize 0.297 g (1.14 mmol) of imide **16d**. The resultant lithium enolate was alkylated with 0.21 mL (0.48 g, 3.37 mmol) of methyl iodide according to the general alkylation procedure for 2 h at -10°C to give 0.33 g (105% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C, 83 cm/sec) afforded a 87:13 ratio of (2R)-**17i** (t_r = 4.98 min) to (2S)-**17i** (t_r = 5.30 min), and indicated the presence of both **6** (t_r = 2.15 min, ca. 6%) and unreacted imide **16d** (t_r = 4.33 min, ca. 11%). The title compound was isolated by MPLC (column B, 9:1 hexanes/ethyl acetate, 5 mL/min, (2R)-**17i** eluted first) to afford 0.173 g (54%) of **17i** as a colorless oil [(2R)-**17i**:(2S)-**17i** > 991): IR (CH_2Cl_2) 3060, 2995, 1780, 1700, 1420, 1380, 1270, 890 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.33 (m, 5H, aromatic H's), 5.62 (d, J = 7.2 Hz, 1H, C_5-H), 4.73 (qn, J = 6.8 Hz, 1H, C_4-H), 3.60 (qn, J = 7.0 Hz, 1H, $C_{2'}$-H), 2.2-1.7 (m, 1H, $C_{3'}$-H), 1.13 (d, J = 7.2 Hz, 3H, $C_{2'}$-CH_3), 1.0-0.8 (m, 9H, C_4-CH_3, $C_{3'}$-CH_3, $C_{4'}$-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 176.7, 152.7, 133.4, 128.6, 125.6, 78.7, 55.0, 43.7, 30.7, 21.2, 18.6, 14.3, 13.6; Specific rotation $[\alpha]_{589}$ = -8.3°, $[\alpha]_{577}$ = -8.4°, $[\alpha]_{546}$ = -8.9°, $[\alpha]_{435}$ = -13.7°, $[\alpha]_{365}$ = 14.5° (c 2.42, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' (2R)-**17i** = 0.82, k' (2S)-**17i** = 1.53, α = 1.84).

(4R,5S)-3-((2R)-1-Oxo-2,3,3-trimethylbutyl)-4-methyl-5-phenyl-2-oxazolidinone (17j, Table 9, Entry N). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 0.165 mL (0.119 g, 1.18 mmol) of diisopropylamine and 0.73 mL (1.61 M in hexane, 1.18 mmol) of n-butyllithium] (0.1 M in THF) was used to enolize 0.295 g (1.07 mmol) of imide **16f**. The resultant lithium enolate was alkylated with 0.20 mL (0.46 g, 3.2 mmol) of methyl iodide according to the general alkylation procedure for 2 h at -10°C to give 0.307 g (101% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C, 83 cm/sec cm/sec) afforded a 94:6 ratio of (2R)-**17j** (t_r = 5.76 min) to (2S)-**17j** (t_r = 6.33 min), and indicated the presence of **6** (t_r = 2.15 min, ca. 4%). The title compound was isolated by MPLC (column B, 85:15 hexanes/diethyl ether, 5 mL/min, (2R)-**17j** eluted first) to afford 0.172 g (56%) of (2R)-**17j** as a white crystalline solid [(2R)-**17j**:(2S)-**17j** > 99:1]: mp 82-83°C; IR (CH_2Cl_2) 3050, 2980, 1775, 1695, 1380, 1365, 1340, 1240, 1190 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.5 (s, 5H, aromatic H's), 5.60 (d, J = 7.2 Hz, 1H, C_5-H), 4.75 (qn, J = 6.8 Hz, 1H, C_4-H), 3.68 (q, J = 7.0 Hz, 1H, $C_{2'}$-H), 1.13 (d, J = 7.5 Hz, 3H, $C_{2'}$-CH_3), 1.03 (s, 9H, $C_{3'}$-$(CH_3)_3$), 0.90 (d, J = 7.5 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 176.4, 153.0, 133.4, 128.7, 125.6, 78.5, 55.1, 44.9, 33.5, 27.4, 14.3, 12.9; Specific rotation $[\alpha]_{589}$ = -13.1°, $[\alpha]_{577}$ = -13.3°, $[\alpha]_{546}$ = -15.0°, $[\alpha]_{435}$ = -25.8°, $[\alpha]_{365}$ = -36.0° (c 3.60, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' (2R)-**17j** = 0.55, k' (2S)-**17j** = 1.06, α = 1.93).

(4R,5S)-3-((2R)-1-Oxo-2-phenylmethylthiomethyl-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (17k, Table 9, Entry 0). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 9.5 mL (6.9 g, 67.8 mmol) of diisopropylamine and 40 mL (1.69 M in hexane, 67.6 mmol) of n-butyllithium] (0.5 M in THF) was used to enolize 20.0 g (64.6 mmol) of imide **16h**. The resultant lithium enolate was alkylated with 10.6 mL (15.5 g, 71.3 mmol) of benzyl bromomethyl sulfide **46b** according to the general alkylation procedure for 2 h at -25°C and 2 h at 0°C to give 31.3 g (108% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 200°C for 10 min, 25°C/min to 275°C, (injector and detector = 300°C), 90 cm/sec) afforded a 98:2 ratio of (2R)-**17k** (t_r = 17.92 min) to (2S)-**17k** (t_r = 18.12 min), and indicated the presence of both **6** (t_r = 1.19 min, ca. 5%) and unreacted **16h** (t_r = 8.60 min, ca. 8%). The title compound was isolated by chromatography (Waters Prep-500, two 5 x 30 cm columns, hexanes/ethyl acetate (adjusted to TLC R_f = 0.09), 250 mL/min) in three portions to afford 21.8 g (76%) of (2R)-**17k** as a colorless, viscous oil [(2R)-**17k**:(2S)-**17k** = 98:2]: IR (neat) 3030, 2920, 1780, 1700, 1490, 1450, 1380, 1340, 1190, 1120 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.42-7.20 (m, 15H, aromatic H's), 5.18 (d, J = 7.0 Hz, 1H, C_5-H), 4.61-4.52 (m, 2H, C_4-H, $C_{2'}$-H), 3.77 (d, J = 13.5 Hz, 1H, SCH(H)Ph), 3.72 (d, J = 13.5 Hz, 1H, SCH(H)Ph), 2.91 (d of d, J = 13.0, 8.8 Hz, 1H, $C_{3'}$-H), 2.86 (d of d, J = 13.0, 7.3 Hz, 1H, $C_{3'}$-H), 2.83 (d of d, J = 13.8, 9.9 Hz, 1H, $C_{2'}$-CH(H)S), 2.53 (d of d, J = 13.7, 5.0 Hz, 1H, $C_{2'}$-CH(H)S), 0.89 (d, J = 6.5 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 174.5, 152.6, 138.2, 138.0, 133.1, 129.1, 128.9, 128.6, 128.4, 126.9, 126.6, 125.5, 78.7, 55.0, 44.6, 39.0, 35.9, 32.2, 14.4; Specific rotation $[\alpha]_{589}$ = +70.6°, $[\alpha]_{577}$ = +74.2°, $[\alpha]_{546}$ =

+84.5°, $[\alpha]_{435}$ = +150.0°, $[\alpha]_{365}$ = +253.1° (c 1.42, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' (2R)-**17k** = 1.98, k' (2S)-**17k** = 1.69, α = 1.17); TLC (7:3 hexanes/ethyl acetate, R_f = 0.44).

Anal. Calcd. for $C_{27}H_{27}NO_3S$: C, 72.78; H, 6.11. Found: C, 73.03; H, 6.07.

(4R,5S)-3-((2R)-1-Oxo-2-methyldecyl)-4-methyl-5-phenyl-2-oxazolidinone (17l, Table 9, Entry P). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 1.60 mL (1.16 g, 11.4 mmol) of diisopropylamine and 7.0 mL (1.61 M in hexane, 11.3 mmol) of n-butyllithium] (0.2 M in THF) was used to enolize 3.39 g (10.2 mmol) of imide **16i**. The resultant lithium enolate was alkylated with 2.6 mL (5.9 g, 42 mmol) of methyl iodide according to the general alkylation procedure for 2 h at 0°C to give 3.67 g (104% mass balance) of unpurified product. Analysis by GC (30 m SE-54, 200°C, 75 cm/sec) afforded a 89:11 ratio of (2R)-**17l** (t_r = 14.19 min) to (2S)-**17l** (t_r = 14.55 min). The title compound was isolated by MPLC (column C, 7:3 hexanes/diethyl ether,10 mL/min, (2R)-**17l** eluted first) to afford 2.45 g (70%) of (2R)-**17l** as a white crystalline solid [(2R)-**17l**:(2S)-**17l** > 200:1]: mp 42-43°C; IR (CH_2Cl_2) 3060, 2990, 2940, 2860, 1780, 1700, 1340, 1200 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.53 (d, J = 7.2 Hz, 1H, C_5-H), 4.63 (qn, J = 6.9 Hz, 1H, C_4-H), 3.60 (q, J = 7.0 Hz, 1H, $C_{2'}$-H), 1.27 (br s, 14H, aliphatic H's), 1.13 (d, J = 7.0 Hz, 3H, $C_{2'}$-CH_3), 0.87 (m, 6H, C_4-CH_3, $C_{10'}$-H_3); Specific rotation $[\alpha]_{589}$ = -1.4°, $[\alpha]_{577}$ = -0.4°, $[\alpha]_{546}$ = -0.6°, $[\alpha]_{435}$ = +1.9°, $[\alpha]_{365}$ =

+13.6° (c 1.6, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12, 2.0 mL/min, k' (2R)-**171** = 0.40, k' (2S)-**171** = 1.06, α = 2.65).

Anal. Calcd. for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04. Found: C, 73.18; H, 9.25.

(4R,5S)-3-((2R)-1-Oxo-2-methyldecyl)-4-methyl-5-phenyl-2-oxazolidinone (171, Table 9, Entry Q). Sodium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of 0.25 g (1.37 mmol) of sodium hexamethyldisilylamide (0.1 M in THF) was used to enolize 0.406 g (1.23 mmol) of imide **16i**. The resultant sodium enolate was alkylated with 0.31 mL (0.71 g, 5.0 mmol) of methyl iodide according to the general alkylation procedure for 2 h at -78°C to give 0.421 g (99% mass balance) of unpurified product. Analysis by GC (30 m SE-54, 200°C, 75 cm/sec) afforded a 94:6 ratio of (2R)-**171** (t_r = 14.17 min) to (2S)-**171** (t_r = 14.53 min). The title compound was isolated by flash chromatography (2 x 30 cm column, 85:15 hexanes/ethyl acetate, (2R)-**171** eluted first) to afford 0.361 g (85%) of (2R)-**171** as a white crystalline solid [(2R)-**171**:(2S)-**171** > 200:1], identical in all respects to the previously prepared material.

(4S)-3-((2R)-1-Oxo-2-methyl-4-pentenyl)-4-(2-methylethyl)-2-oxazolidinone (21b, Table 10, Entry B). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 4.4 mL (3.2 g, 31 mmol) of diisopropylamine and 20.0 mL (1.55 M in hexane, 31.0 mmol) of n-butyllithium] (1.0 M in THF) was used to enolize 5.21 g (28.1 mmol) of imide **20b**. The resultant lithium enolate was alkylated with 7.3 mL (10 g, 84 mmol) of allyl bromide according to the general alkylation procedure for 2 h at -10°C to give 6.04 g (95% mass balance) of

unpurified product. Analysis by GC (30 m DB-1, 125°C, 85 cm/sec) afforded a 98:2 ratio of (2R)-**21b** (t_r = 5.71 min) to (2S)-**21b** (t_r = 5.12 min). The title compound was isolated by MPLC (column C, 9:1 hexanes/diethyl ether, 10 mL/min, (2R)-**21b** eluted second) to afford 4.52 g (75%) of (2R)-**21b** as a colorless liquid [(2R)-**21b**:(2S)-**21b** > 99:1]: IR (CH_2Cl_2) 3060, 2970, 2940, 2880, 1780, 1700, 1385, 1300, 1240, 1220, 1210 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 6.0-5.5 (m, 1H, $C_{4'}$-H), 5.2-4.9 (m, 2H, $C_{5'}$-H_2), 4.5-4.1 (m, 3H, C_4-H, C_5-H_2), 3.85 (m, J = 7.0 Hz, 1H, $C_{2'}$-H), 2.7-2.0 (m, 3H, C_4-CH, $C_{3'}$-H_2), 1.13 (d, J = 7.0 Hz, 3H, $C_{2'}$-CH_3), 0.95 (d, J = 6.8 Hz, 3H, CH(CH_3), 0.89 (d, J = 6.8 Hz, 3H, CH(CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 176.2, 153.7, 135.3, 117.0, 63.2, 58.4, 38.3, 37.2, 28.5, 17.9, 16.2, 14.7; Specific rotation $[\alpha]_{589}$ = +62.9°, $[\alpha]_{577}$ = +65.2°, $[\alpha]_{546}$ = +73.9°, $[\alpha]_{435}$ = +126.3°, $[\alpha]_{365}$ = +199.1° (c 3.48, CH_2Cl_2).

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50. Found: C, 64.17; H, 8.60.

(4S)-3-((2R)-1-Oxo-2-methyl-3-phenylmethoxypropyl)-4-(2-methylethyl)-2-oxazolidinone (21e, Table 10, Entry E). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 15.4 mL (11.1 g, 110 mmol) of diisopropylamine and 65 mL (1.70 M in hexane, 110 mmol) of n-butyllithium] (1 M in THF) was used to enolize 18.5 g (100 mmol) of **20b**. The resultant lithium enolate was alkylated with 28 mL (40 g, 200 mmol) of benzyl bromomethyl ether **45** according to the general alkylation procedure for 4 h at -45°C, then 1 h at 0°C. To the reaction mixture was added 24 mL (24 g, 300 mmol) of dry

pyridine and 19 mL (20.5 g, 200 mmol) of acetic anhydride. The mixture was stirred for 4 h at room temperature. The mixture was transferred to a 1-L flask, cautiously diluted with 250 mL of 2 M aqueous potassium bicarbonate, and stirred at room temperature until the evolution of carbon dioxide ceased (ca. 2 h). The mixture was concentrated in vacuo and the product extracted into dichloromethane (3 x 200 mL). The combined organic extracts were washed with water (2x), 1 M aqueous hydrochloric acid (2x), 1 M aqueous potassium bicarbonate, and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. Analysis by GC (30 m DB-1, 100°C for 2 min, 20°C/min to 200°C, 88 cm/sec) afforded a 98:2 ratio of (2R)-**21e** (t_r = 9.85 min) to (2S)-**21e** (t_r = 9.63 min). The title compound was isolated in two portions by flash chromatography (7 x 70 cm column, 95:5 hexanes/tetrahydrofuran) to afford 18.9-22.6 g (62-74%) of **21e** as a colorless oil [(2R)-**21e**:(2S)-**21e** = 99:1]: IR (CH_2Cl_2) 3060, 2980, 1780, 1705, 1390, 1235, 1210 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.2 (s, 5H, aromatic H's), 4.45 (s, 2H, $OC\underline{H}_2Ph$), 4.5-4.0 (m, 4H, C_4-$\underline{H}$, C_5-$\underline{H}_2$, $C_{2'}$-$\underline{H}$), 3.70 (d of d, J = 8.4, 7.5 Hz, 1H, $C_{3'}$-$\underline{H}$), 3.50 (d of d, J = 8.4, 5.7 Hz, 1H, $C_{3'}$-$\underline{H}$), 2.32 (m, 1H, C_4-$C\underline{H}$), 1.13 (d, J = 6.8 Hz, 3H, $C_{2'}$-$C\underline{H}_3$), 0.87 (d, J = 6.5 Hz, 3H, $CH(C\underline{H}_3)$), 0.82 (d, J = 6.9 Hz, 3H, $CH(C\underline{H}_3)$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 175.3, 153.8, 138.2, 128.2, 127.5, 73.0, 72.7, 63.2, 58.4, 38.3, 28.3, 17.8, 14.6, 13.7; Specific rotation $[\alpha]_{589}$ = +35.4°, $[\alpha]_{577}$ = +36.6°, $[\alpha]_{546}$ = +41.9°, $[\alpha]_{435}$ = +73.0°, $[\alpha]_{365}$ = +120.7° (c 2.88, CH_2Cl_2); TLC (7:3 hexanes/ethyl acetate, R_f = 0.33).

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59. Found: C, 66.72; H, 7.64.

(4S)-3-((2R)-1,4-Dioxo-2-methyl-4-ethoxybutyl)-4-(2-methylethyl)-2-oxazolidinone (21f, Table 10, Entry F). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 2.3 mL (1.7 g, 16 mmol) of diisopropylamine and 10.1 mL (1.61 M in hexane, 16.3 mmol) of n-butyllithium] (0.3 M in THF) was used to enolize 2.67 g (14.5 mmol) of imide **20b**. The resultant lithium enolate was alkylated with 3.4 mL (6.2 g, 29 mmol) of ethyl 2-iodoacetate according to the general alkylation procedure for 2 h at -20°C then 2 h at 0°C to give 4.42 g (112% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C, 78 cm/sec) afforded a 95:5 ratio of (2R)-**21f** (t_r = 2.81 min) to (2S)-**21f** (t_r = 2.69 min). The title compound was isolated by MPLC (column C, 7:3 hexanes/diethyl ether, 10 mL/min, (2R)-**21f** eluted second) to afford 2.0 g (51%) of **(2R)-21f** as a colorless liquid [(2R)-**21f**:(2S)-**21f** > 100:1]: IR (CCl_4) 2980, 1795, 1735, 1700, 1380, 1255, 1190 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 4.45 (d of d of d, J = 9.0, 4.0, 3.0 Hz, 1H, C_4-H), 4.28 (d of d, J = 9.8, 9.5 Hz, 1H, C_5-H), 4.24 (d of d, J = 9.8, 3.0 Hz, 1H, C_5-H), 4.16 (d of d of q, J = 10.0, 4.7, 7.0 Hz, 1H, $C_{2'}$-H), 4.10 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 2.89 (d of d, J = 17, 1.0 Hz, 1H, $C_{3'}$-H), 2.42 (d of d, J = 17.0, 4.7 Hz, 1H, $C_{3'}$-H), 2.38 (m, 1H, C_4-CH), 1.23 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 1.18 (d, J = 7.0 Hz, 3H, $C_{2'}$-CH_3), 0.94 (d, J = 7.0 Hz, 3H, $CH(CH_3)$), 0.91 (d, J = 7.0 Hz, 3H, $CH(CH_3)$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 175.9, 171.6, 153.6, 63.2, 60.4, 58.6, 37.8, 34.4, 28.2, 17.9, 17.1, 14.5, 14.2; Specific rotation $[\alpha]_{589}$ = +48.7°, $[\alpha]_{577}$ = +51.2°, $[\alpha]_{546}$ = +59.3°, $[\alpha]_{435}$ = +102.2°, $[\alpha]_{365}$ = +169.3° (c 1.64, CH_2Cl_2).

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80. Found: C, 57.67; H, 7.93.

(4S)-3-((2S)-1-Oxo-2-phenylmethylthiomethyl-3-phenylpropyl)-4-(2-methylethyl)-2-oxazolidinone (21k, Table 10, Entry I). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 15.4 mL (11.1 g, 110 mmol) of diisopropylamine and 65 mL (1.69 M in hexane, 110 mmol) of n-butyllithium] (0.75 M in THF) was used to enolize 26.1 g (100 mmol) of imide **20b**. The resultant lithium enolate was alkylated with 23.9 g (110 mmol) of benzyl bromomethyl sulfide **46b** according to the general alkylation procedure for 2 h at -20°C to give 53.0 g (133% mass balance) of unpurified product. Analysis by GC (30 m DB-1, 175°C for 5 min, 20°C/min to 250°C, 60 cm/sec) afforded a 3:97 ratio of (2R)-**21k** (t_r = 11.74 min) to (2S)-**21k** (t_r = 11.53 min), and indicated the presence of unreacted **20b** (t_r = 4.17 min, ca. 10%). The title compound was isolated by chromatography (Waters Prep-500, two 5 x 30 cm silica gel columns, 87:13 hexanes/ethyl acetate, 250 mL/min) in two portions to afford 33.1 g (83%) of (2S)-**21k** as a viscous colorless liquid [(2R)-**21k**:(2S)-**21k** = 2:98]: IR (neat) 3040, 2980, 2940, 1780, 1700, 1495, 1455, 1390, 1300, 1250, 1200, 1100, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.30-7.16 (m, 10H, aromatic H's), 4.60 (m, 1H, $C_{2'}$-H), 4.27 (d of d of d, J = 8.5, 3.8, 2.5, 1H, C_4-H), 4.09 (d of d, J = 9.3, 2.7 Hz, 1H, C_5-H), 3.92 (d of d, J = 9.3, 8.7 Hz, 1H, C_5-H), 3.76 (d, J = 14.0 Hz, 1H, SCH(H)Ph), 3.70 (d, J = 14.0 Hz, 1H, SCH(H)Ph), 2.90 (d of d, J = 13.0, 8.0 Hz, 1H, $C_{3'}$-H), 2.80 (d of d, J = 13.5, 10.0 Hz, 1H, $C_{2'}$-CH(H)S), 2.78 (d of d, J = 13.0, 7.5 Hz, 1H, $C_{3'}$-H), 2.50 (d of d, J = 13.5, 4.5 Hz, 1H, $C_{2'}$-CH(H)S), 2.37 (d of septet, J = 3.8, 7.1 Hz, 1H, C_4-CH$(CH_3)_2$), 0.91 (d, J = 7.1 Hz, 3H, CH(CH_3)), 0.89 (d, J = 7.1 Hz, 3H, CH(CH_3)); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 174.6, 153.7, 138.2, 138.0, 129.1, 128.9, 128.4, 126.8, 126.5, 63.2, 58.7, 44.4, 38.7, 35.7,

32.3, 28.5, 17.9, 14.8; Specific rotation $[\alpha]_{589}$ = -29.1° (c 2.34, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min, k' (2S)-**21k** = 3.26; TLC (7:3 hexanes/ethyl acetate, R_f = 0.54).

Anal. Calcd. for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85. Found: C, 69.62; H, 6.85.

(4S)-3-((2S)-1-Oxo-2-methyldecyl)-4-(2-methylethyl)-2-oxazolidinone (21l, Table 10, Entry J). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 0.16 mL (0.116 g, 1.14 mmol) of diisopropylamine and 0.71 mL (1.61 M in hexane, 1.14 mmol) of n-butyllithium] (0.1 M in THF) was used to enolize 0.289 g (1.02 mmol) of imide **20i**. The resultant lithium enolate was alkylated with 0.25 mL (0.57 g, 4.0 mmol) of methyl iodide according to the general alkylation procedure for 2 h at 0°C to give 0.324 g (107% mass balance) of unpurified product. Analysis by GC (20 m Carbowax 20M, 175°C, 40 cm/sec) afforded a 9:91 ratio of (2R)-**21l** (t_r = 10.58 min) to (2S)-**21l** (t_r = 10.26 min), and indicated the presence of unreacted **20i** (t_r = 13.09 min, ca. 4%). The title compound was isolated by flash chromatography (3 x 30 cm column, 8:2 hexanes/diethyl ether) to afford 0.251 g (83%) of (2S)-**21l** as a colorless liquid [(2R)-**21l**:(2S)-**21l** < 1:99]: IR (CH_2Cl_2) 3060, 2970, 2940, 2860, 1780, 1700, 1385, 1210 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 4.4-4.1 (m, 3H, C_4-H, C_5-H_2), 3.6-3.4 (m, 1H, $C_{2'}$-H), 2.5-2.3 (m, 1H, C_4-CH), 1.3 (s, 14H, aliphatic H's), 1.12 (d, J = 7.0 Hz, 3H, $C_{2'}$-CH_3), 0.90 (m, 9H, $CH(CH_3)_2$, $C_{10'}$-H_3); Specific rotation $[\alpha]_{589}$ = +83.3°, $[\alpha]_{577}$ = +87.0°, $[\alpha]_{546}$ = +98.6°, $[\alpha]_{435}$ = +166.2°,

$[\alpha]_{365}$ = +258.1° (c 2.03, CH_2Cl_2).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 68.65; H, 10.51. Found: C, 68.67; H, 10.37.

(4S)-3-((2S)-1-Oxo-2-methyldecyl)-4-(2-methylethyl)-2-oxazolidinone (21l, Table 10, Entry K). Sodium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of 2.0 g (11 mmol) of sodium hexamethyldisilylamide (0.2 M in THF) was used to enolize 2.85 g (10.0 mmol) of imide **20i**. The resultant sodium enolate was alkylated with 2.5 mL (5.7 g, 40 mmol) of methyl iodide according to the general alkylation procedure for 2 h at -78°C to give 2.64 g (88% mass balance) of unpurified product. Analysis by GC (20 m Carbowax 20M, 175°C, 40 cm/sec) afforded a 7:93 ratio of (2R)-**21l** (t_r = 10.56 min) to (2S)-**21l** (t_r = 10.23 min), and indicated the presence of unreacted **20i** (t_r = 13.05 min, ca. 2%). The title compound was isolated by flash chromatography (4 x 30 cm column, 8:2 hexanes/diethyl ether) to afford 2.29 g (77%) of **(2S)-21l** as a colorless liquid [(2R)-**21l**:(2S)-**21l** < 200:1], identical in all respects to the previously prepared material.

(4R)-3-((2R)-1-Oxo-2-methylbutyl)-4-phenyl-2-oxazolidinone (23h, Table 8, Entry H). Lithium Enolate Alkylation. A magnetically stirred, cooled (-78°C) solution of LDA [prepared from 0.13 mL (0.095 g, 0.94 mmol) of diisopropylamine and 0.62 mL (1.52 M in hexane, 0.94 mmol) of n-butyllithium] (0.1 M in THF) was used to enolize 0.199 g (0.908 mmol) of imide **22c**. The resultant lithium enolate was alkylated with 0.24 mL (0.55 g, 3.9 mmol) of methyl iodide according to the general alkylation procedure for 2 h at 0°C to give 0.19 g (85% mass balance) of unpurified

product. Analysis by GC (25 m Carbowax 20M, 200°C, 30 cm/sec Helium) afforded an 81:19 ratio of (2R)-**23h** (t_r = 9.42 min) to (2S)-**23h** (t_r = 9.58 min), and indicated the presence of unreacted **22c** (t_r = 10.56 min, ca. 14%). An analytical sample was purified by MPLC (column B, 7:3 hexanes/diethyl ether) to afford (2R)-**23h** as a white crystalline solid [(2R)-**23h**:(2S)-**23h** > 99:1]: mp 80-81°C; IR (CCl_4) 2980, 2940, 1795, 1715, 1380, 1325, 1230, 1200, 1050 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.40 (d of d, J = 9.0, 4.0 Hz, 1H, C_4-H), 4.62 (t, J = 9.0 Hz, 1H, C_5-H), 4.18 (d of d, J = 9.0, 4.0, 1H, C_5-H), 3.65 (q, J = 6.9 Hz, 1H, $C_{2'}$-H), 1.9-1.2 (m, 2H, $C_{3'}$-H_2), 1.12 (d, J = 7.1 Hz, 3H, $C_{2'}$-CH_3), 0.90 (t, J = 7.5 Hz, 3H, $C_{4'}$-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 176.4, 153.4, 139.4, 129.1, 128.6, 125.7, 69.8, 57.7, 39.3, 26.1, 16.8, 11.6.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.29; H, 6.97.

General Procedure for Transesterification (Benzyl Ester). To a magnetically stirred, cooled solution of benzyl alcohol (2.0 equiv, distilled) in anhydrous THF (ca. 0.3 M) is added a hexane solution of n-butyllithium (1.5 equiv). To this solution is added a solution of the indicated imide (1.0 equiv, ca. 1 M in THF). The reaction mixture is stirred at 0°C until no imide remains as detected by TLC (ca. 1-4 h). The reaction is quenched by the addition of 3 M aqueous ammonium chloride. Volatiles are removed in vacuo and the product (along with benzyl alcohol and the 2-oxazolidinone) extracted into dichloromethane. The combined organic extracts are dried over anhydrous magnesium sulfate and

concentrated *in vacuo*. The benzyl ester is isolated by liquid chromatography as indicated in the following examples. Further elution with a more polar solvent (ethyl acetate or diethyl ether) allows recovery of the 2-oxazolidinone.

Benzyl (2R)-2-Methylbutanoate (31a, Table 12, Entry C). To a magnetically stirred, cooled (0°C) solution of lithium benzyloxide in 40 mL of THF [prepared from 0.65 mL (0.68 g, 6.3 mmol) of benzyl alcohol and 2.9 mL (1.61 *M* in hexane, 4.7 mmol) of *n*-butyllithium) was added 0.824 g (3.15 mmol) of **17h** [(2R)-**17h**:(2S)-**17h** > 99:1] in 10 mL of THF. After stirring at 0°C for 2 h, the reaction products were isolated according to the general transesterification procedure. The title compound was isolated by MPLC (column B, 9:1 hexanes/diethyl ether, 5 mL/min) to afford 0.561 g (93%) of (2R)-benzyl ester **31a** as a colorless liquid: IR (CH_2Cl_2) 3070, 2990, 1730, 1420, 1265, 900 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.0 (s, 2H, $OC\underline{H}_2Ph$), 2.3 (sextet, J = 7 Hz, 1H, C_2-$\underline{H}$), 1.9-1.3 (m, 2H, C_3-$\underline{H}_2$), 1.1 (d, J = 7 Hz, 3H, C_2-$C\underline{H}_3$), 0.85 (t, J = 8 Hz, 3H, C_4-$\underline{H}_3$); $[\alpha]_{589}$ = -12.6', $[\alpha]_{577}$ = -13.0', $[\alpha]_{546}$ = -15.1', $[\alpha]_{435}$ = -23.4', $[\alpha]_{365}$ = - 50.4' (*c* 2.85, CH_2Cl_2); TLC (8:2 hexanes/ethyl acetate, R_f = 0.65).

Anal. calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.78; H, 8.23.

Benzyl (2S)-2-Methylbutanoate (31a, Table 12, Entry A). To a magnetically stirred, cooled (0°C) solution of lithium benzyloxide in 10 mL of THF [prepared from 0.21 mL (0.22 g, 2.0 mmol) of benzyl alcohol and 0.93 mL (1.61 *M* in hexane, 1.5 mmol) of *n*-butyllithium) was added

0.259 g (0.992 mmol) of **17a** [(2R)-**17a**:(2S)-**17a** < 1:99] in 3 mL of THF. After stirring for 2 h at 0°C, the reaction products were isolated according to the general transesterification procedure. The title compound was isolated by MPLC (column B, 9:1 hexanes/diethyl ether, 5 mL/min) to afford 0.171 g (90%) of (2S)-benzyl ester **31a** as a colorless liquid: IR (CH_2Cl_2) 3070, 2990, 1730, 1420, 1265, 900 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3 (s, 5H, aromatic H's), 5.0 (s, 2H, $OC\underline{H}_2Ph$), 2.3 (sextet, J = 7 Hz, 1H, C_2-$\underline{H}$), 1.9-1.3 (m, 2H, C_3-$\underline{H}_2$), 1.1 (d, J = 8 Hz, 3H, C_2-$C\underline{H}_3$), 0.85 (t, J = 7 Hz, 3H, C_4-$\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = +12.8°, $[\alpha]_{577}$ = +13.2°, $[\alpha]_{546}$ = +15.1°, $[\alpha]_{435}$ = +24.8°, $[\alpha]_{365}$ = +40.4°, (c 2.16, CH_2Cl_2); TLC (8:2 hexanes/ethyl acetate, R_f = 0.61).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.91; H, 8.32.

Benzyl (2R)-2-Methyl-3-benzyloxypropanoate (31e, Table 12, Entry H). To a magnetically stirred, cooled (0°C) solution of lithium benzyloxide in 80 mL of THF [prepared from 8.2 mL (8.6 g, 79 mmol) of benzyl alcohol and 35 mL (1.70 M in hexane, 60 mmol) of n-butyllithium] was added 12.2 g (39.7 mmol) of **21e** [(2R)-**21e**:(2S)-**21e** 99.2:0.8) in 20 mL of THF. After stirring at 0°C for 1 h the reaction products were isolated according to the general transesterification procedure. The title compound was isolated by flash chromatography (5 x 45 cm column, 9:1 hexanes/THF) to afford 10.9 g (96%) of (2R)-benzyl ester **31e** as a colorless liquid. Further elution of the column with diethyl ether afforded 4.3 g (84%) of (4S)-valinol 2-oxazolidinone.

(2R)-**31e**: IR (CCl_4) 2960, 1740, 1450, 1245, 1170 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) 7.31, 7.29 (2s, 10H, aromatic H's), 5.1 (s, 2H, $COC_2\underline{H}_2Ph$), 4.5 (s, 2H, $CH_2OC\underline{H}_2Ph$), 3.4 (m, 2H, C_3-$\underline{H}_2$), 2.8 (q, J = 7 Hz, 1H, C_2-$\underline{H}$), 1.2 (d, J = 7 Hz, C_2-$C\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = -3.46°, $[\alpha]_{577}$ = -3.56°, $[\alpha]_{546}$ = -4.06°, $[\alpha]_{435}$ = -6.51°, $[\alpha]_{365}$ = -8.67°, (c 4.78, EtOH); GC (30 m DB-1, 200°C, 78 cm/sec, t_r = 3.43 min); TLC (8:2 hexanes/ethyl acetate, R_f = 0.42).

(2R)-2-Methyl-3-benzyloxypropanoic acid (26e). A mixture of 9.48 g (33.3 mmol) of (2R)-benzyl ester **31e** and 200 mg of 5% Pd on carbon in 90 mL of THF at 25°C under an atmosphere of hydrogen was stirred until 750 mL (ca. 1 equiv) of hydrogen had been absorbed (ca. 10 h). The solution was filtered through a pad of celite, and the celite washed with diethyl ether. The combined filtrates were concentrated in vacuo to afford 6.34 g (98%) of (2R)-acid **26e** as a colorless liquid: IR (neat) 3400-2400, 1715, 1450, 1100 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 10.3 (br s, 1H, $CO_2\underline{H}$), 7.3 (s, 5H, aromatic H's), 4.5 (s, 2H, $OC\underline{H}_2Ph$), 3.6 (m, 2H, C_3-$\underline{H}_2$), 2.8 (m, 1H, C_2-$\underline{H}$), 1.2 (d, J = 7 Hz, 3H, C_2-$C\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = -10.5°, $[\alpha]_{577}$ = -11.5°, $[\alpha]_{546}$ = -12.9°, $[\alpha]_{435}$ = -22.6°, $[\alpha]_{365}$ = -35.7° (neat, d = 1.095 g/mL).

Determination of the Extent of Racemization During Transesterification and Hydrogenolysis. Method 1. (2R)-Acid **26e** was prepared in two steps from imide **21e** [(2R)-**21e**:(2S)-**21e** = 99.2:0.8) as described in the previous two experiments. To a magnetically stirred solution of 89.9 mg (0.463 mmol) of (2R)-acid **26e** in 1.0 mL of dichloromethane was added

0.20 mL (0.29 g, 2.3 mmol) of oxallyl chloride. The mixture was stirred at 25°C for 6 h, then concentrated *in vacuo* to afford 98.5 mg (100% mass balance) of (2R)-acid chloride **37e** as a colorless oil. The acid chloride was immediately used in the next part of the experiment.

To a magnetically stirred, cooled (-78°C) solution of 0.104 g (0.789 mmol) of (4S)-valinol 2-oxazolidinone **8** in 10 mL of THF was added 0.40 mL (1.70 M in hexane, 0.68 mmol) of n-butyllithium. The mixture was stirred for 0.5 h followed by the addition of (2R)-acid chloride **37e**. The mixture was stirred for 0.5 h at -78°C then quenched by the addition of 3 M aqueous ammonium chloride. The mixture was concentrated *in vacuo* and the product extracted into dichloromethane. The combined organic extracts were washed with aqueous potassium bicarbonate and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford 0.20 g of a colorless oil. Analysis of the unfractionated reaction mixture by capillary GC (30 m DB-1, 100°C for 2 min, 20°C/min to 200°C, 89 cm/sec) afforded a 97.5:2.5 ratio of (2R)-**21e** (t_r = 9.87 min) to (2S)-**21e** (t_r = 9.66 min).

In two separate experiments[38] the acid chloride was prepared at 0°C for 4 h and 5 h. The acid chloride was acylated as above to afford a 98.4:1.6 and 98.1:1.9 ratio of (2R)-**21e** to (2S)-**21e**, respectively.

Determination of the Extent of Racemization During Transesterification and Hydrogenolysis. Method 2. (2R)-Acid **26e** was prepared from imide **21e** [(2R)-**21e**:(2S)-**21e** = 99.2:0.8) as described in the previous experiments. To a magnetically stirred, cooled (0°C) solution of 0.101 g (0.520 mmol) of (2R)-acid **26e** and 55 μL (58 mg, 0.57 mmol) of triethylamine in 10 mL of THF was added 55 μL (62 mg, 0.58 mmol) of ethyl

chloroformate. A white precipitate immediately formed. The mixture was stirred for 0.5 h at 0°C then cooled to -78°C.

In a separate flask, 0.59 mL (1.70 M in hexane, 1.00 mmol) of n-butyl-lithium was added to a magnetically stirred, cooled (-78°C) solution of 0.130 g (1.00 mmol) of (4S)-valinol 2-oxazolidinone **8** in 10 mL of THF. After 0.5 h, the solution of the metalated 2-oxazolidinone was added dropwise via cannula to the solution of the mixed anhydride. The reaction mixture was stirred for 0.5 h at -78°C then allowed to warm to 0°C over a 1-h period. The reaction was quenched by addition of half-saturated aqueous ammonium chloride. The mixture was concentrated in vacuo and the product extracted into dichloromethane. The combined organic extracts were washed with aqueous sodium bisulfate, aqueous potassium bicarbonate, and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 0.25 g of a colorless oil. Analysis of the unfractionated reaction mixture by capillary GC (same conditions as the previous experiment) afforded a 98.3:1.7 ratio of (2R)-**21e** to (2S)-**21e**.

(4S)-3-((2R)-1,4-Dioxo-2-methylbutyl)-4-(2-methylethyl)-2-oxazolidinone (21m). Ozone was bubbled through a magnetically stirred, cooled (-78°C) solution of 2.51 g (11.1 mmol) of imide **21b** [(2R)-**21b**:(2S)-**21b** = 99.8:0.2) and ca. 10 mg of Sudan Red III in 50 mL of methanol until the red color of the indicator changed to yellow. The solution was purged with argon then quenched by the addition of 5 mL (4.3 g, 68 mmol, excess) dimethyl sulfide. The mixture was allowed to warm to 25°C and stirred overnight. The reaction mixture was concentrated in vacuo to afford a mixture of the product and the corresponding dimethylacetal.

The mixture was dissolved in 50 mL of THF and 20 mL of 1 M aqueous hydrochloric acid. After 0.5 h the mixture was concentrated in vacuo and the product distilled (Kugelrohr, 150°C, 0.005 mm) to afford 2.45 g (97%) of imide **21m** as a colorless oil: IR ($CDCl_3$) 3170, 2980, 2840, 2740, 1780, 1725, 1700, 1390, 1300, 1250, 1205 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 9.72 (s, 1H, C<u>H</u>O), 4.6-4.0 (m, 4H, C_4-<u>H</u>, C_5-<u>H</u>$_2$, $C_{2'}$-<u>H</u>), 3.08 (d of d, J = 18.0, 9.0 Hz, 1H, $C_{3'}$-<u>H</u>), 2.55 (d of d, J = 18.0, 5.0 Hz, 1H, $C_{3'}$-<u>H</u>), 2.5-2.2 (m, 1H, C_4-C<u>H</u>), 1.20 (d, J = 7.0 Hz, 3H, $C_{2'}$-C<u>H</u>$_3$), 0.95, 0.90 (overlapping d's, J = 6.8 Hz, 6H, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 199.9, 175.7, 153.6, 63.2, 58.6, 47.8, 32.3, 28.1, 17.9, 16.9, 14.4.

(2R)-2-Methyl-4-hydroxybutanoic acid, lactone (2-Methylbutyrolactone, 32). A mixture of 1.47 g (6.49 mmol) of imide **21m** and 6.5 g (containing ca. 6.5 mmol of BH_4^-) of sodium borohydride on alumina[43] in 40 mL of anhydrous diethyl ether was stirred at 25°C for 0.5 h. The mixture was filtered, and the alumina washed with anhydrous diethyl ether. The combined filtrate and washings were concentrated in vacuo to afford 1.35 g of a pale yellow oil. Distillation (Kugelrohr, 170°C, 60 mm) afforded 0.455 g (70%) of (2R)-lactone **32** as a colorless liquid: IR (neat) 2980, 2950, 2920, 2890, 1780, 1455, 1380, 1370, 1170, 1025, 910 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 4.5-4.0 (m, 2H, C_4-<u>H</u>$_2$), 2.8-2.3 (m, 2H, C_2-<u>H</u>, C_3-<u>H</u>), 2.2-1.8 (m, 1H, C_3-<u>H</u>), 1.3 (d, J = 6 Hz, 3H, C_2-C<u>H</u>$_3$); Specific rotation $[\alpha]_{589}$ = +21.2° (<u>c</u> 8.5, EtOH), Lit.[30] specific rotation of (2S)-**32** $[\alpha]_{589}$ = -21.5° (<u>c</u> 5.5, EtOH).

Anal. Calcd. for $C_5H_8O_2$: C, 47.60; H, 6.55. Found: C, 47.44; H, 6.47.

(2R)-2-Methylsuccinic acid (26f). To a magnetically stirred, cooled (0°C) solution of 1.39 g (5.13 mmol) of imide **21f** [(2R)-**21f**:(2S)-**21f** > 99:1] in 50 mL of methanol was added 10 mL of 6 M aqueous potassium hydroxide. After 2 h no imide **21f** remained as detected by TLC. The methanol was removed in vacuo and the aqueous solution washed with dichloromethane. Concentration of the dichloromethane washings afforded 0.64 g (96%) of (4S)-valinol 2-oxazolidinone **8**. The aqueous solution was acidified with 6 M aqueous hydrochloric acid and the water removed in vacuo. The solid residue was washed with diethyl ether to dissolve the product. Concentration of the diethyl ether solution afforded 0.62 g (91%) of (2R)-acid **26f** as a white crystalline solid: mp 112-113°C; ^{1}H NMR ($CDCl_3$/90 MHz) δ 9.6-9.0 (br s, 2H, $CO_2\underline{H}$), 3.1-2.4 (m, 3H, C_2-$\underline{H}$, C_3-$\underline{H}_2$), 1.3 (d, J = 7 Hz, 3H, C_2-$\underline{H}$); Specific rotation $[\alpha]_{589}$ = +15.7° (c 4.25, EtOH).

Anal. Calcd. for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.64; H, 6.19.

(2S)-2-Methylsuccinic acid (26f). To a magnetically stirred, cooled (0°C) solution of 1.83 g (5.71 mmol) of imide **17f** [(2R)-**17f**:(2S)-**17f** < 1:99] in 50 mL of methanol was added 10 mL of 6 M aqueous potassium hydroxide. After 2 h no imide **17f** remained as detected by TLC. The methanol was removed in vacuo and the aqueous solution washed with dichloromethane. Concentration of the dichloromethane washings afforded 0.95 g (94%) of (4R,5S)-norephedrine 2-oxazolidinone **6**. The aqueous solution was acidified with 6 M aqueous hydrochloric acid and the water removed in vacuo. The solid residue was washed with diethyl ether to dissolve the product. Concentration of the diethyl ether solution

afforded 0.72 g (95%) of (2S)-acid **26f** as a white crystalline solid: mp 109-110°C; ^{1}NMR ($CDCl_3$/90 MHz) δ 9.6-9.0 (br s, 2H, $CO_2\underline{H}$), 3.1-2.4 (m, 3H, C_2-$\underline{H}$, C_3-$\underline{H}_2$), 1.3 (d, J = 7 Hz, 3H, C_2-$\underline{H}$); Specific rotation $[\alpha]_{589}$ = -15.0° (c 4.21, EtOH).

Anal. Calcd. for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.64; H, 6.19.

(2R)-2-Methyl-3-benzyloxy-1-propanol (39e). Lithium Borohydride Reduction. To a magnetically stirred, cooled (0°C) solution of 0.788 g (2.23 mmol) of imide **17e** [(2R)-**17e**:(2S)-**17e** < 1:99] in 5 mL of THF was added 2.3 mL (1 M in THF, 2.3 mmol) of lithium borohydride. After 2 h no imide **17e** remained as detected by TLC. The reaction was cautiously quenched by the addition of 1 M aqueous hydrochloric acid. The mixture was concentrated in vacuo and extracted with dichloromethane. The combined organic extracts were washed with 1 M aqueous hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 0.73 g of a colorless oil. The title compound was isolated by flash chromatography (3 x 30 cm column, 75:25 hexanes/ethyl acetate) to afford 0.346 g (88%) of (2R)-alcohol **39e** as a colorless liquid: IR (CH_2Cl_2) 3640, 3540, 3060, 2970, 1265, 1090 cm^{-1}; ^{1}H NMR (CCl_4/90 MHz) δ 7.2 (s, 5H, aromatic H's), 4.4 (s, 2H, $OC\underline{H}_2Ph$), 3.7-3.3 (m, 4H, C_1-$\underline{H}_2$, C_3-$\underline{H}_2$), 2.47 (br s, 1H, $O\underline{H}$), 2.1 (m, 1H, C_2-$\underline{H}$), 0.9 (d, J = 8 Hz, 3H, C_2-$C\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = -4.2° (c 2.5, EtOH); GC (30 m DB-1, 120°C, 86 cm/sec, t_r = 4.07 min); TLC (85:15 dichloromethane/diethyl ether, R_f = 0.32).

(2S)-2-Methyl-3-benzyloxy-1-propanol (39e). Lithium Aluminum Hydride Reduction. To a magnetically stirred, cooled (-78°C) solution of 15.3 g (50.0 mmol) of imide **21e** [(2R)-**21e**:(2S)-**21e** > 99:1] in 100 mL of THF was added 50 mL (1 M in THF, 50 mmol) of lithium aluminum hydride dropwise over a 15-min period. After 0.5 h the mixture was allowed to warm to 25°C then stirred for 2 h. The mixture was recooled to -78°C then cautiously quenched with 1.9 mL of water, 1.9 mL of 2 M aqueous sodium hydroxide, and 5.7 mL of water. The mixture was allowed to warm to 25°C and stirred for 1 h. The mixture was filtered through a sintered glass filter and the precipitate washed with diethyl ether. The filtrate and washings were concentrated in vacuo. The product was isolated by flash chromatography (7 x 70 cm column, 85:15 dichloromethane/diethyl ether) to afford after distillation (Kugelrohr, 90°C, 0.01 mm) 6.8 g (76%) of (2S)-alcohol **39e** as a colorless liquid. Further elution with diethyl ether afforded 4.8 g (74%) of (4S)-valinol 2-oxazolidinone **8**.

(2S)-**39e**: IR (CH_2Cl_2) 3640, 3540, 3060, 2970, 1265, 1090 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.2 (s, 5H, aromatic H's), 4.4 (s, 2H, $OC\underline{H}_2Ph$), 3.7-3.3 (m, 4H, C_1-$\underline{H}_2$, C_3-$\underline{H}_2$), 2.47 (br s, 1H, O$\underline{H}$), 2.1 (m, 1H, C_2-$\underline{H}$), 0.9 (d, J = 8 Hz, 3H, C_2-$C\underline{H}_3$); Specific rotation $[\alpha]_{589}$ = +5.3° (c 2.2, EtOH), Lit.[64] $[\alpha]_{589}$ = +4.97° (c 0.9, EtOH); GC (30 m DB-1, 120°C, 86 cm/sec, t_r = 4.07 min); TLC (85:15 dichloromethane/diethyl ether, R_f = 0.32).

Determination of the Enantiomeric Purity of (2R)-2-Methyl-3-benzyloxy-1-propanol (39e). To a magnetically stirred, cooled (0°C) solution of 41 mg (0.228 mmol) of (2R)-alcohol **39e** in 0.5 mL of pyridine was

added 54 μL (72 mg, 0.286 mmol) of (2R)-acid chloride **11**. The mixture was stirred at 25°C for 1 h. The reaction mixture was diluted with water and the product extracted into dichloromethane. The combined organic extracts were washed with 1 M aqueous hydrochloric acid, saturated aqueous potassium bicarbonate, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 110 mg of a colorless oil. Analysis of the unfractionated product by capillary GC (DB-1, DB-5, or Carbowax 20M) did not separate the diastereomers. Analysis of the unfractionated product by 500 MHz ^{1}H NMR indicated the absence of the (2S) diastereomer [(2R)-**39e**:(2S)-**39e** > 97:3) (Figure 8).

Determination of the Enantiomeric Purity of (2S)-2-Methyl-3-benzyloxy-1-propanol (39e). To a magnetically stirred, cooled (0°C) solution of 58 mg (0.322 mmol) of (2S)-alcohol **39e** in 0.5 mL of pyridine was added 76 μL (102 mg, 0.403 mmol) of (2R)-acid chloride **11**. The mixture was stirred at 25°C for 1 h. The reaction mixture was diluted with water and the product extracted into dichloromethane. The combined organic extracts were washed with 1 M aqueous hydrochloric acid, saturated aqueous potassium bicarbonate, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 135 mg of a colorless oil. Analysis of the unfractionated product by capillary GC (DB-1, DB-5, or Carbowax 20M) did not separate the diastereomers. Analysis of the unfractionated product by 500 MHz ^{1}H NMR indicated the absence of the (2R) diastereomer [(2R)-**39e**:(2S)-**39e** < 3:97) (Figure 8).

(2R)-2-Methyl-1-decanol (391). Lithium Borohydride Reduction. To a magnetically stirred, cooled (0°C) solution of 1.57 g (4.54 mmol) of **171** [(2R)-**171**:(2S)-**171** > 99:1] in 20 mL of THF was added 0.12 g (5.5 mmol) of lithium borohydride. After 3 h no imide **171** was detected by TLC. The reaction was cautiously quenched by the addition of 1 M aqueous hydrochloric acid. The mixture was concentrated *in vacuo* then extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous potassium bicarbonate and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford 1.56 g of a colorless oil. The product was isolated by flash chromatography (3 x 30 cm column, 8:2 hexanes/diethyl ether) followed by distillation (Kugelrohr, 160°C, 15 mm) to afford 0.653 g (84%) of (2R)-alcohol **391** as a colorless liquid. Further elution of the column with diethyl ether afforded 0.80 g (99%) of (4R,5S)-norephedrine 2-oxazolidinone **6**.

(2R)-**391**: IR (CH_2Cl_2) 3630, 2960, 2940, 2860, 1465, 1030 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 3.5-3.3 (m, 2H, C_1-H), 2.2 (br s, 1H, OH), 1.7-1.2 (br, 15H, aliphatic H's), 1.0-0.8 (m, 6H, C_2-CH_3, C_{10}-H_3); Specific rotation $[\alpha]_{589}$ = +10.8°, $[\alpha]_{577}$ = +11.4°, $[\alpha]_{546}$ = +12.9°, $[\alpha]_{435}$ = +21.3°, $[\alpha]_{365}$ = +32.3° (*c* 4.37, CH_2Cl_2); TLC (8:2 hexanes/ethyl acetate, R_f = 0.32).

Anal. Calcd. for $C_{11}H_{24}O$: C, 76.74; H, 13.95. Found: C, 76.77; H, 14.08.

(2S)-2-Methyl-1-decanol (391). Lithium Borohydride Reduction. To a magnetically stirred, cooled (0°C) solution of 1.23 g (4.15 mmol) of **211** [(2R)-**211**:(2S)-**211** < 1:99] in 20 mL of THF was added 0.12 g (5.5

mmol) of lithium borohydride. After 3 h no imide **211** was detected by TLC. The reaction was cautiously quenched by the addition of 1 M aqueous hydrochloric acid. The mixture was concentrated in vacuo then extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous potassium bicarbonate and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 1.13 g of a colorless oil. The product was isolated by flash chromatography (3 x 30 cm column, 8:2 hexanes/diethyl ether) followed by distillation (Kugelrohr, 160°C, 15 mm) to afford 0.643 g (90%) of (2S)-alcohol **391** as a colorless liquid. Further elution of the column with diethyl ether afforded 0.72 g (85%) of (4S)-valinol 2-oxazolidinone **8**.

(2R)-**391**: IR (CH_2Cl_2) 3630, 2960, 2940, 2860, 1465, 1030 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 3.5-3.3 (m, 2H, C_1-H), 2.2 (br s, 1H, OH), 1.7-1.2 (br, 15H, aliphatic H's), 1.0-0.8 (m, 6H, C_2-CH_3, C_{10}-H_3); Specific rotation $[\alpha]_{589}$ = -10.0°, $[\alpha]_{577}$ = -11.1°, $[\alpha]_{546}$ = -12.6°, $[\alpha]_{435}$ = -21.1°, $[\alpha]_{365}$ = -32.2° (c 4.21, CH_2Cl_2); TLC (8:2 hexanes/ethyl acetate, R_f = 0.32).

Anal. Calcd. for $C_{11}H_{24}O$: C, 76.74; H, 13.95. Found: C, 76.67; H, 13.97.

(2S)-2-Methyl-3-phenylpropanoic acid, hydrazide (34g). A magnetically stirred solution of 1.92 g (5.94 mmol) of imide **17g** [(2R)-**17g**:(2S)-**17g** < 1:99] and 0.5 mL (0.5 g, 15.6 mmol) of anhydrous hydrazine in 10 mL of anhydrous ethanol was stirred at 25°C for 4 h. The mixture was concentrated in vacuo (30°C at 30 mm then 30°C at 0.1 mm) and the residue dissolved in anhydrous diethyl ether. The solution was

saturated with anhydrous hydrochloric acid. The mixture was filtered and the precipitate washed with diethyl ether. (The combined filtrate and washings were concentrated *in vacuo* to afford after recrystallization from toluene 0.72 g (69%) of (4R,5S)-norephedrine 2-oxazolidinone **6**). The precipitate was treated with saturated aqueous potassium bicarbonate then extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford 0.810 g (76%) of (2S)-hydrazide **34g** as a white solid: ^{1}H NMR ($CDCl_3$/500 MHz)δ 7.20 (m, 5H, aromatic H's), 6.60 (br s, 1H, $H_2NN(\underline{H})CO$), 3.76 (br s, 2H, $\underline{H}_2NN(H)CO$), 2.95 (d of d, J = 14, 8 Hz, 1H, C_3-$\underline{H}$), 2.70 (d of d, J = 14, 6 Hz, 1H, C_3-$\underline{H}$), 2.40 (m, 1H, C_2-$\underline{H}$), 1.20 (d, J = 7 Hz, 3H, C_2-$C\underline{H}_3$); GC (30 m DB-1, 200°C for 10 min, 20°C/min to 275°C, 89 cm/sec, t_r = 18.51 min).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.36; H, 7.86. Found: C, 67.31; H, 7.83.

VI. NOTES AND REFERENCES.

(1) For a review of chiral insect pheromones see: Rossi, R. Synthesis **1978**, 413-434.

(2) Blaschke, G.; Kraft, H. P.; Fickentscher, K.; Kohler, F. Arzneim-Forsch. **1979**, 29, 1640.

(3) (a) Newman, P. "Optical Resolution Procedures for Chemical Compounds;" Optical Resolution Information Center: Riverdale, New York; 1981; Vol. 1, Amines and Related Compounds; Vol. 2, Acids; Vol. 3, Alcohols, Phenols, Thiols, Aldehydes, and Ketones. (b) For a review of chromatographic methods see: Blaschke, G. Agnew. Chem. Int. Ed. Engl. **1980**, 19, 13-24.

(4) Klyne, W.; Buckingham, J. "Atlas of Stereochemistry. Absolute Configuration of Organic Molecules;" Oxford University Press: New York, 1974.

(5) (a) Hanessian, S. Acc. Chem. Res. **1979**, 12, 159. (b) Fraser-Reid, B.; Anderson, R. C. in "Progress in the Chemistry of Natural Products;" Herz, W.; Grisebach, H.; Kirby, G. W. Eds.; Springer-Verlag: New York, 1980; Vol. 39.

(6) Reviews of Asymmetric Synthesis: (a) Morrison, J. D.; Mosher, H.S. "Asymmetric Organic Reactions;" American Chemical Society: Washington, D. C., 1971. (b) ApSimon, J. W.; Seguin, R. P. Tetrahedron **1979**, 35, 2797-2842. (c) Bartlett, P. A. Tetrahedron **1980**, 36, 2-72.

(7) Izumi, Y.; Tai, A. "Stereo-differentiating Reactions: The Nature of Asymmetric Reactions;" Academic Press: New York, 1977, p 181.

(8) For recent reviews of macrolide and polyether ionophore antibiotics see: (a) Westley, J. W. Adv. Appl. Microbiol. **1977**, 22, 177. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. Agnew. Chem. Int. Ed. Engl. **1977**, 16, 585-607. (c) Westley, J. W., Ed. "Polyether Antibiotics;" Marcel Dekker, Inc.: New York, 1982; Vol. I. Biology, Vol. 2. Chemistry.

(9) (a) Johnson, M. R.; Nakata, T.; Kishi, Y. Tetrahedron Lett. **1979**, 4343-4346. (b) Johnson, M. R.; Kishi, Y. Ibid. **1979**, 4347-4350. (c) Hasan, I.; Kishi, Y. Ibid. **1980**, 4229-4232.

(10) (a) Westley, J. W. Antibiotics **1981**, 4, 41-73. (b) O'Hagan, D.; Robinson, J. A.; Turner, D. L. J. Chem. Soc. Chem. Commun. **1983**, 1337-1340.

(11) For a review of chiral enolates see: Evans, D. A. in "Asymmetric Synthesis," Morrison, J. D. Ed.; Academic Press, Inc.: New York, 1983; Vol. 3, Chapter 1.

(12) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. A.; Sohn, J. E.; Lampe, J. J. Org. Chem. **1980**, 45, 1066.

(13) Takacs, J. M.; Ph. D. Thesis, California Institute of Technology, 1981.

(14) Sonnet, P. E.; Heath, R. R. J. Org. Chem. **1980**, 45, 3139-3141.

(15) Larchereque, M.; Ignatova, E.; Cuvigny, T. Tetrahedron Lett. **1978**, 3961-3964.

(16) Evans, D. A.; Takacs, J. M. Tetrahedron Lett. **1980**, 21, 4233-4236.

(17) Dyen, M. D.; Swern, D. Chem. Rev. **1967**, 67, 197-246.

(18) Lane, C. F. U.S. Patent 3,935,280; Chem. Abstr. **1976**, 84, 13510D.

(19) Seki, H.; Koga, K.; Matsuo, H.; Ohki, S.; Matsuo, I.; Yamada, S. Chem. Pharm. Bull. **1965**, 13, 995-1000.

(20) Brown, H. C.; Choi, Y. M; Narasimhan, S. J. Org. Chem. **1982**, 47, 3153-3163.

(21) (a) Bisaha, J. Research Report, California Institute of Technology, 1983. (b) Evans, D. A.; Bisaha, J. Unpublished results.

(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. **1969**, 34, 2543-2549.

(23) Poindexter, G. S.; Meyers, A. I. Tetrahedron Lett. **1977**, 3527-3528.

(24) Satisfactory spectral and analytical data were obtained for all new compounds reported herein.

(25) Homeyer, A. H. U.S. Patent, 2,399,118; Chem. Abstr. **1946**, 40, 4084^{6}.

(26) Evans, D. A.; Sjogren, E. Unpublished results.

(27) Close, W. J. J. Org. Chem. **1950**, 15, 1131-1134.

(28) Use of chiral 2-oxazolidinones in asymmetric synthesis: (a) Aldol: Evans, D. A.; Bartroli, X. B.; Shih, T. L. J. Am. Chem. Soc. **1981**, 103, 2876. (b) Alkylation: Evans, D. A.; Ennis, M. D.; Mathre, D. J. J. Am. Chem. Soc. **1982**, 104, 1734. (c) Acylation: Evans, D.; A.; Ennis, M. D.; Le, T. L. J. Am. Chem. Soc. **1984**, 106, 1154. (d) Diels--Alder: Evans, D. A.; Bisaha, J.; Chapman, K. T. J. Am. Chem. Soc. **1984**, 106, 0000.

(29) I thank my co-worker throughout this project, Dr. M. D. Ennis, for the contribution of these results: (a) Ennis, M. D. Ph.D. Thesis, California Institute of Technology, 1983. (b) Evans, D. A.; Ennis, M. D. Unpublished results.

(30) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. Agnew. Chem. Int. Ed. Engl. **1979**, 18, 63-65.

(31) Jackman, L. M.; Lang, B. C. Tetrahedron **1977**, 33, 2737-2769.

(32) Evans, D. A.; Chapman, K. T. Unpublished results.

(33) Preparation of (2S)-2-methyl-3-hydroxypropanoic acid by the bacteriological hydroxylation of 2-methylpropanoic acid: (a) Goodhue, C. T.; Schaeffer, J. R. Biotechnol. Bioeng. **1971** 13, 203. Transformation of the (2S)-acid to derivatives of both the (2R)- and (2S)-acid: (b) Branca, Q.; Fischli, A. Helv. Chem. Acta **1977**, 60, 925-944. (c) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. J. Org. Chem. **1976**, 41, 3503-3511.

(34) Evans, D. A.; Dow, R. L. Unpublished results.

(35) Evans, D. A.; Mathre, D. J. J. Org. Chem. submitted.

(36) Pirkle, W. H.; Simmons, K. A. J. Org. Chem. **1983**, 48, 2520-2527.

(37) The X-ray crystal structure of N-acyl 2-oxazolidinones demonstrates the anti-periplaner arrangement of the two carbonyls: see (a) Bartroli, X. B. Ph.D. Thesis, California Institute of Technology, 1983. (b) Ref. 29a.

(38) (a) Stille, J. R.; Grubbs, R. H. J. Am. Chem. Soc. **1983**, 105, 1664-1665. (b) Grubbs, R. H.; Stille, J. R. Unpublished results. (c) The amount of racemization depends on the reaction conditions for preparing the acid chloride: 4 h at 0°C, 1.6% racemization; 5 h at 0°C, 2.2% racemization; 6 h at 25°C, 3.4% racemization.

(39) Meyers, A. I.; Yamamoto, Y.; Mihelich, E. D.; Bell, R. A. J. Org. Chem. **1980**, 45, 2792-2796.

(40) Maclaren, J. A.; Savige, W. E.; Swan, J. M. Aust. J. Chem. **1958**, 11, 345-359.

(41) Veysoglu, T.; Mitscher, L. A.; Swaze, J. K. Synthesis **1980**, 807-810.

(42) Pappas, J. J.; Keaveny, W. P.; Gancher, E.; Berger, M. Tetrahedron Lett. **1966**, 4273-4278.

(43) Santaniello, E.; Ponti, F.; Manzocchi, A. Synthesis **1978**, 891-892.

(44) (a) Greenstein, J. P.; Winitz, M. "Chemistry of Amino Acids;" John Wiley and Sons: New York, 1961; Vol.2. (b) March, J. "Advanced Organic Chemistry," 2nd ed.; McGraw-Hill: New York, 1977; p 963. (c) Klausner, V. S.; Bodanszky, M. Synthesis **1974**, 549.

(45) (a) Cherpeck, R. Ph.D. Thesis, California Institute of Technology, 1980. (b) Tannis, S. P. Research Report, California Institute of Technology, 1980.

(46) (a) Izawa, T.; Mukaiyama, T. Chem. Lett, **1977**, 1443. (b) Izawa, T.; Mukaiyama, T. Ibid. **1978**, 409. (c) Izawa, T.; Mukaiyama, T. Bull. Soc. Chem. Jpn. **1979**, 52, 555.

(47) Parikh, J. R.; Doering, W. J. Am. Chem. Soc. **1967**, 89, 5505.

(48) Mancuso, A. J.; Huang, S.; Swern, D. J. Org. Chem. **1978**, 43, 2480.

(49) Terashima, S.; Yamada, S.-I. Chem. Pharm. Bull. **1968**, 16, 1953-1971.

(50) Bystrom, S.; Hogberg, H.-E.; Norin, T. Tetrahedron **1981**, 37, 2249-2254.

(51) Southern California Regional NMR Facility.

(52) Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem, **1978**, 43, 2923-2925.

(53) (a) Pirkle, W. H.; Hoekstra, M. S. J. Org. Chem. **1974**, 39, 3904-3906. (b) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. J. Am. Chem. Soc. **1981**, 103, 3964-3966.

(54) Cerium molybdate TLC spray: Ammonium molybdate (75 g), ceric sulfate (2.5 g) in 500 mL of 10% aqueous sulfuric acid.

(55) Karren, P.; Portmann, P.; Suter, M. Helv. Chem. Acta, **1949**, 32, 1156-1157.

(56) (a) Rubinstein, H.; Feibush, B.; Gil-Av, E. J. Chem. Soc. Perkin II **1973**, 1973, 2094-2097. (b) Tseng, C. C.; Terashima, S.; Yamada, S.-I. Chem. Pharm. Bull. **1977**, 25, 29-40.

(57) Fodor, G.; Stefanovosky, J.; Kurtev, B. Montash Chem. **1967**, 98, 1027-1042.

(58) Iwakura, Y.; Hayashi, K.; Inagaki, K. Makromol. Chem. **1967**, 104, 56-65.

(59) (a) Kruger, C. R.; Niederprum, H. Inorg. Synth. **1966**, 8, 15-19. (b) Wannagat, U.; Niederprum, H.; Chem. Ber. **1961**, 94, 1540.

(60) Conner, D. S.; Klein, G. W.; Taylor, G. N. Org. Synth. **1972**, 52, 17-19.

(61) Wood, J. L.; du Vigneaud, V. J. Biological Chem. **1939**, 131, 267-271.

(62) Hollowood, J.; Jansen, A. B. A.; Southgate, P. J. J. Med. Chem. **1967**, 10, 863-867.

(63) Rossi, R.; Diversi, P.; Ingrosso, G. Ital. Gazz. Chem. **1967**, 97, 1391-1399.

(64) Naguoka, H.; Kishi, Y. Tetrahedron **1981**, 37, 3873-3888.

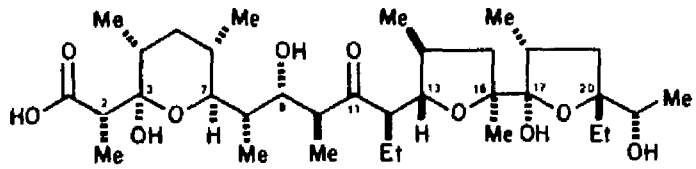
CHAPTER 2

EFFORTS DIRECTED TOWARD THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF FERENSIMYCIN B

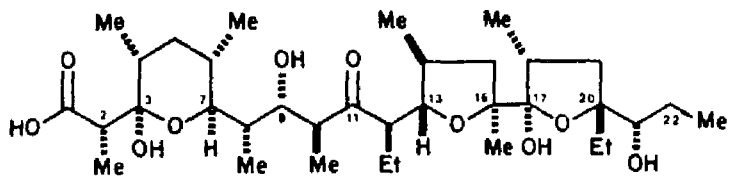
I. INTRODUCTION.

In 1982, Kusakabe and co-workers reported the isolation and characterization of two new polyether ionophore antibiotics, ferensimycin A (**1**) and ferensimycin B (**2**).[1] Since 1951, more than 75 members of this important family of natural products have been isolated.[2] Polyether ionophores are characterized as relatively large, stereochemically complex carboxylic acids that possess multiple ether linkages, usually as tetrahydrofuran and tetrahydropyran rings (Figure 1).[3] Especially noted for their ability to extract inorganic cations into non-polar organic solvents, polyether ionophores are important tools in the study of cation transport.[4] As antibiotics, polyether ionophores inhibit the growth of Gram-positive bacteria, are effective in the treatment of poultry coccidosis, and improve the utilization of feed among ruminants.[5] Ever since the structure of monensin was elucidated by X-ray crystallography,[6] synthetic chemists have been intrigued by the architectural complexity of polyether ionophores. Not only do polyether ionophores present challenging targets for total synthesis,[7] but they also provide the incentive for developing new stereo-, regio-, and chemoselective reactions. In conjunction with our interest in the development of methodology for asymmetric synthesis,[8] and the construction of both macrolide and polyether ionophore antibiotics,[9] we undertook the enantioselective total synthesis of ferensimycin B (**2**).

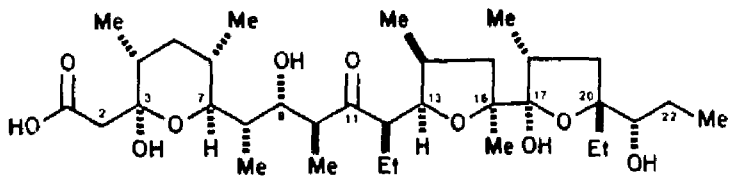
The ferensimycins were isolated from the fermentation broth of Streptomyces sp. No. 5057.[1] Their relative structures (excluding C-2 and C-21 stereochemistry) were elucidated by mass, ^{1}H NMR, and ^{13}C NMR



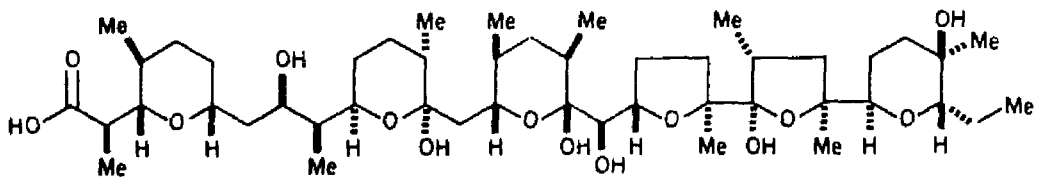
Ferensimysin A (1)



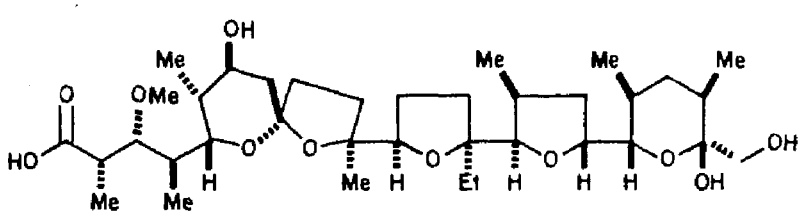
Ferensimysin B (2)



Lysocellin (3)



X-206



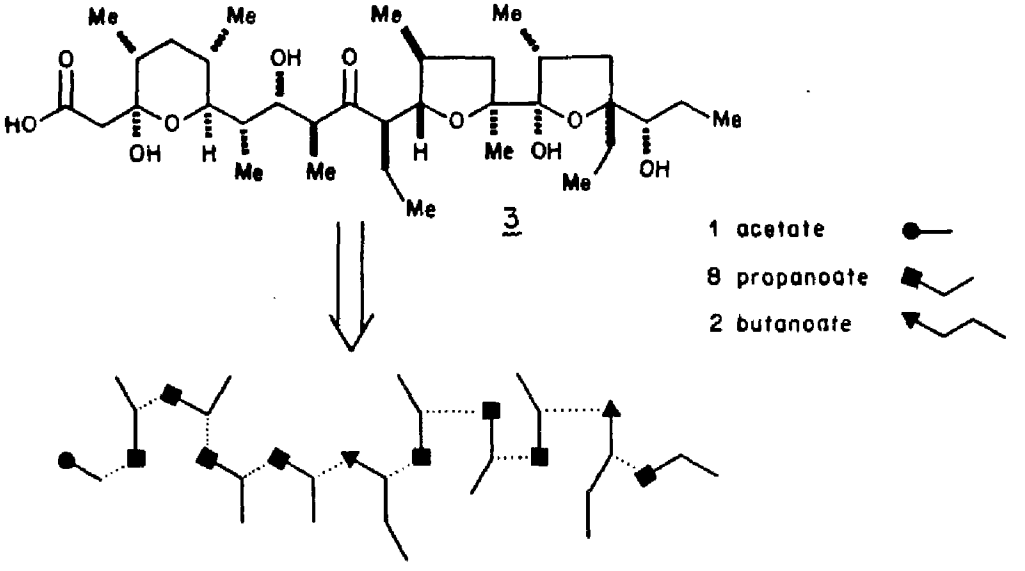
Monensin A

Figure 1. Various Polyether Ionophore Antibiotics.

spectroscopy. Westley (unpublished) has established, by X-ray crystallography, the stereochemistry of 1 at C-1 and C-21 to both be (S).[10] Structurally, the ferensimycins are closely related to lysocellin (**3**), **2** differing from **3** only in the substitution at C-2. Both the relative stereochemistry and the absolute configuration of **3** have been determined by X-ray crystallography.[11] By analogy, ferensimycin B (**2**) is presumed to possess the same absolute configuration as ferensimycin A (**1**) and lysocellin (**3**). The stereochemistry of **2** at C-2 is assigned as (S) based on the nearly identical chemical shifts in the ^{13}C NMR spectra of **1** and **2** for the carbon signals at and around C-2. Likewise, the stereochemistry of **2** at C-21 is assigned as (S) by comparison of the ^{13}C NMR spectra of **2** and **3**. The enantioselective total synthesis of ferensimycin B would test the validity of these assignments.

The structural homology of the ferensimycins and lysocellin suggests that they arise *via* similar biochemical pathways. The carbon framework of polyether ionophores is constructed from simple acetate, propanoate, and butanoate building blocks.[12] For example, by feeding *Streptomyces cacaoi* var. *asoensis* labeled $R^{13}CO_2H$ precursors, Otake has demonstrated that lysocellin is assembled from one acetate, eight propanoate, and two butanoate units (Scheme 1).[13] Less is known, however, about how the stereochemistry is generated during polyether biosynthesis.

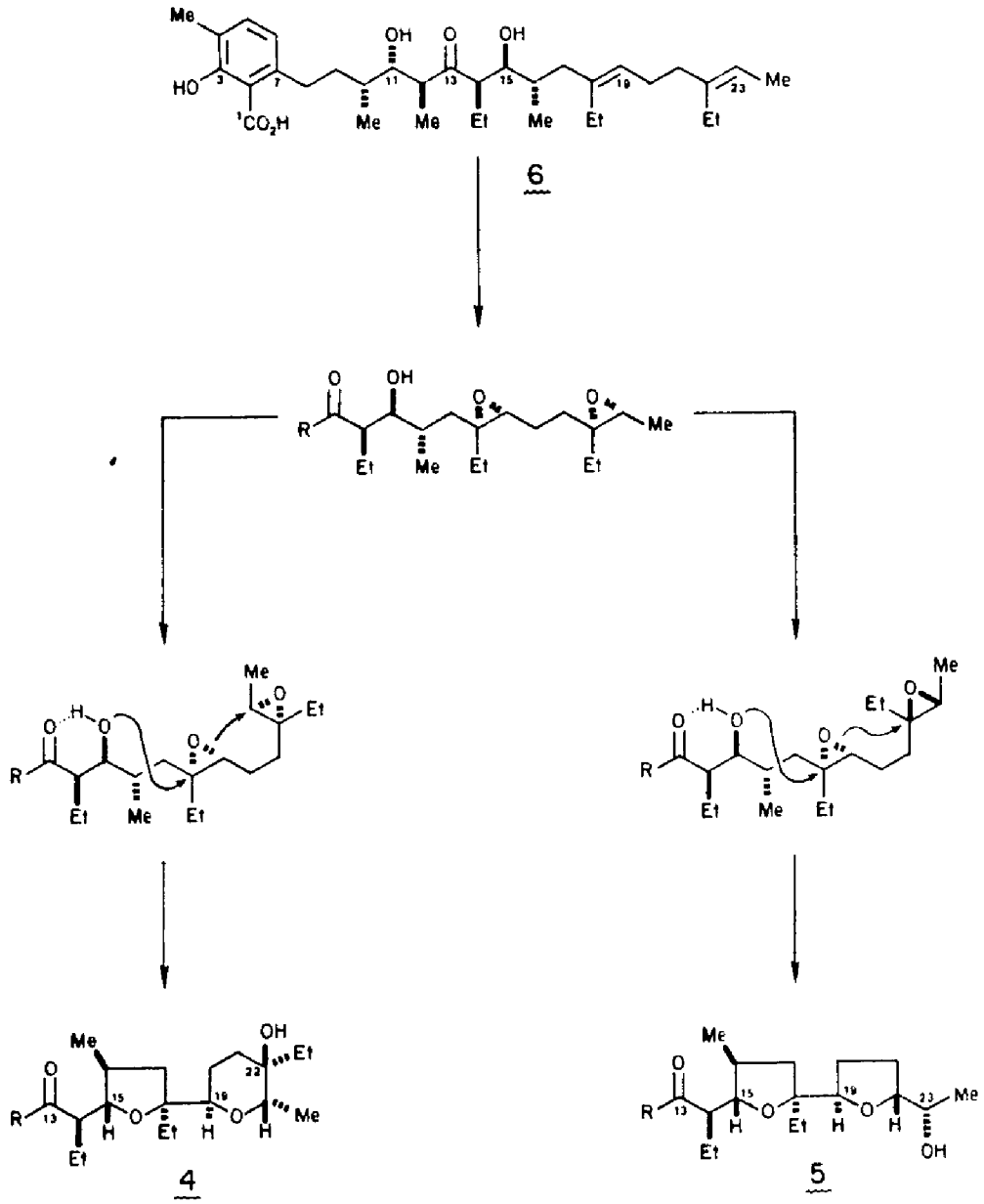
Westley has proposed a biochemical pathway that accounts for the stereochemistry of the two ether rings in lasalocid A (**4**) and isolasalocid A (**5**).[14] According to his hypothesis, **4** and **5** are both derived from diene **6**. As illustrated in Scheme 2, stereoselective diepoxidation



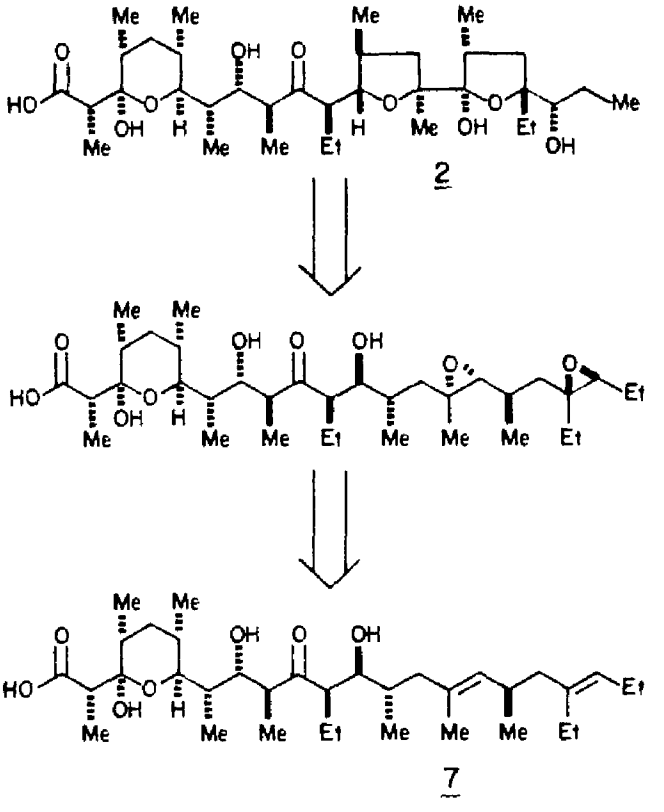
Scheme 1

of diene **6** followed by acid catalyzed cyclization can afford either **4** or **5**. Support for this biochemical pathway is provided by Hutchinson, who, by feeding double labeled $R^{13}C^{18}O_2H$ precursors to Streptomyces lasaliensis, has shown that ^{18}O is introduced into **4** at C-1, C-3, C-11, C-13, and C-15, but not at C-19 and C-22.[15] The absence of labeled oxygen at C-19 and C-22 would be expected if diene **6** is an intermediate. Presumably, the oxygen at these two positions is obtained from molecular oxygen.[16] The same diene--diepoxide or the analogous triene--triepoxide pathway has been proposed by Cane et al. as the final step in the biosynthesis of over 30 polyether ionophores.[12c]

We envisioned employing a similar diene--stereoselective epoxidation--acid catalyzed cyclization route as a key reaction sequence to construct the B and C rings of ferensimycin B (**2**). A retrosynthetic analysis of **2**, that reveals the requisite diene intermediate (**7**), is illustrated in Scheme 3. Since this approach closely resembles the



Scheme 2



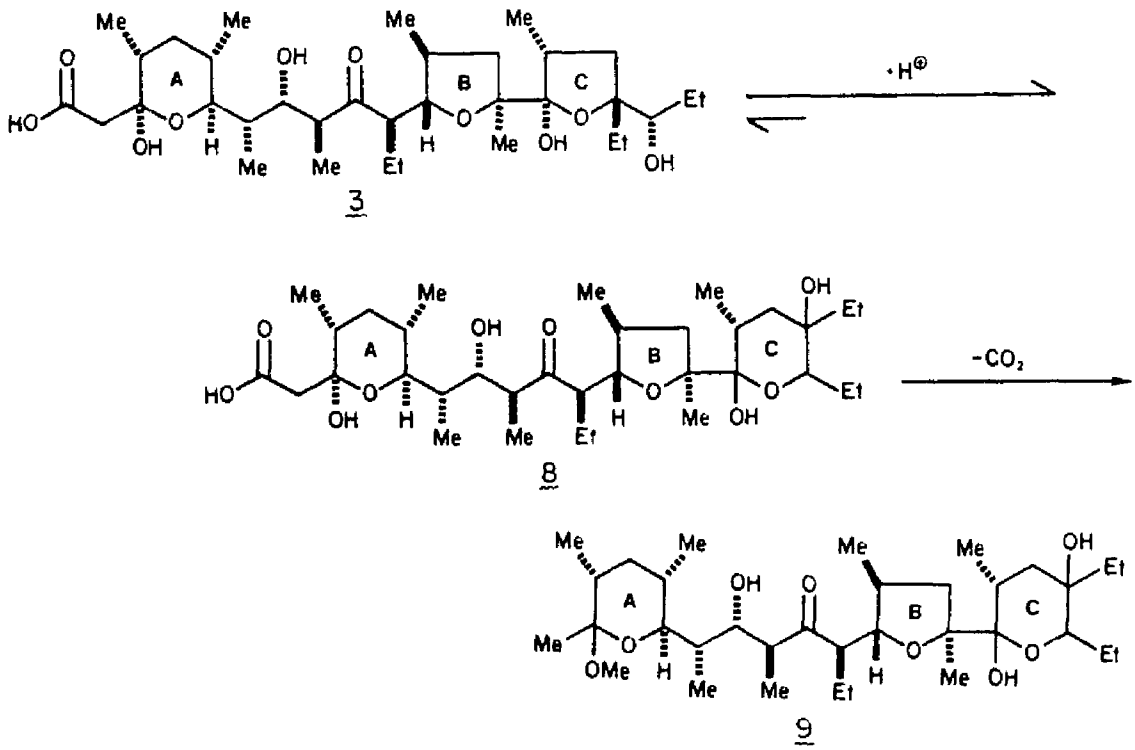
Scheme 3

proposed biosynthetic pathway, diene 7 or related molecules could be used to study the final stages of polyether biosynthesis.

The synthetic strategy we chose for the construction of ferensimycin B (**2**) is sufficiently flexible to accommodate both ferensimycin A (**1**) and lysocellin (**3**). This chapter will describe our efforts directed toward the enantioselective total synthesis of **2**: 1) the preparation of a C-11 to C-23 diene intermediate; 2) a study of the stereoselective epoxidation of bishomoallylic alcohols; and 3) the preparation of the B tetrahydrofuran ring of ferensimycin B <u>via</u> a stereoselective epoxidation--acid catalyzed cyclization sequence.

II. SYNTHETIC DESIGN.

An examination of the structure of ferensimycin B (Figure 1) reveals that it possesses 16 chiral centers and three ether rings (two of which are hemiketals). Although little is known about the chemistry of ferensimycins A and B, it presumably is similar to that of lysocellin (3). Koenuma has reported that **3** is degraded by both acidic and strongly basic conditions.[17] Under acidic conditions (cat. HOAc, MeOH), the five-membered hemiketal C ring of **3** initially isomerizes to the corresponding six-membered hemiketal **8** (Scheme 4). This is followed by the gradual decarboxylation of C-1 and methylation of the C-3 hydroxyl group to afford **9**. Acetylation of the C-21 hydroxyl group of **3**, how-



Scheme 4

ever, prevents acid catalyzed isomerization. Therefore, in our synthesis of ferensimycin B, we will need to either avoid acidic conditions, or protect the C-21 hydroxyl group when the five-membered hemiketal C ring is present.

As the sodium or silver salt, however, lysocellin is stable. This suggests that metal complexation imparts stability to lysocellin, as well as to ferensimycins A and B. Shown in Figure 2 is the silver salt of lysocellin. Six of the oxygen atoms are coordinated to the silver. Presumably, coordination between O(8) and Ag as well as a hydrogen bond between O(1) and O(9) prevent isomerization of the five-membered hemiketal C ring.

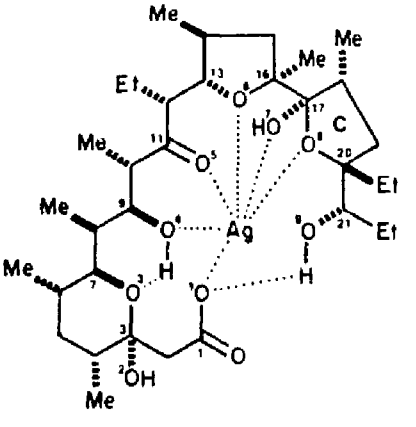
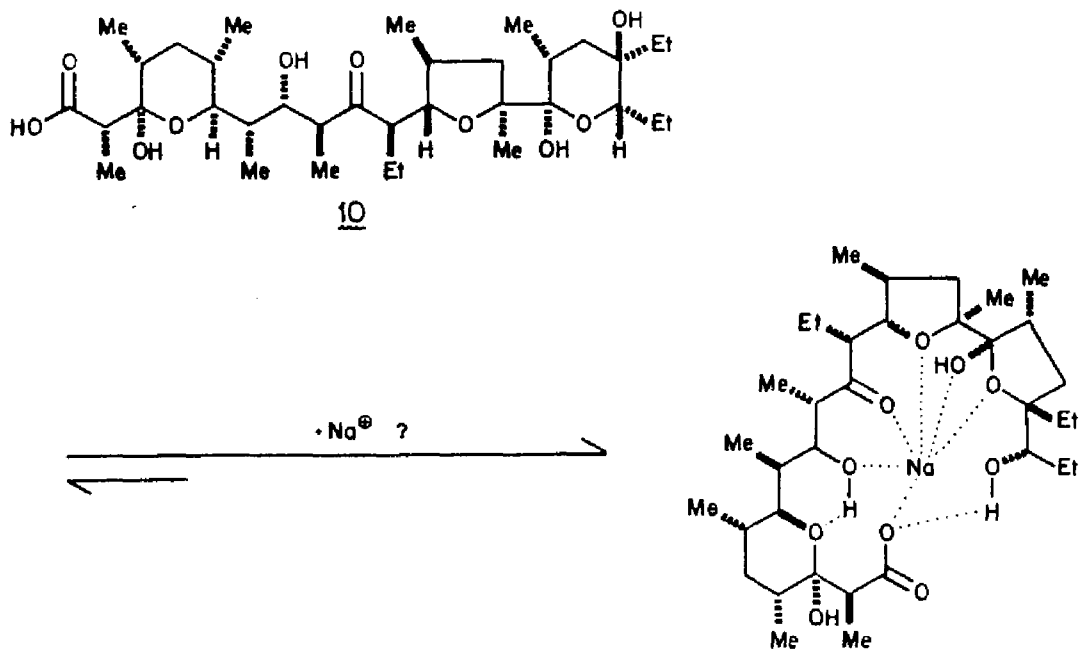


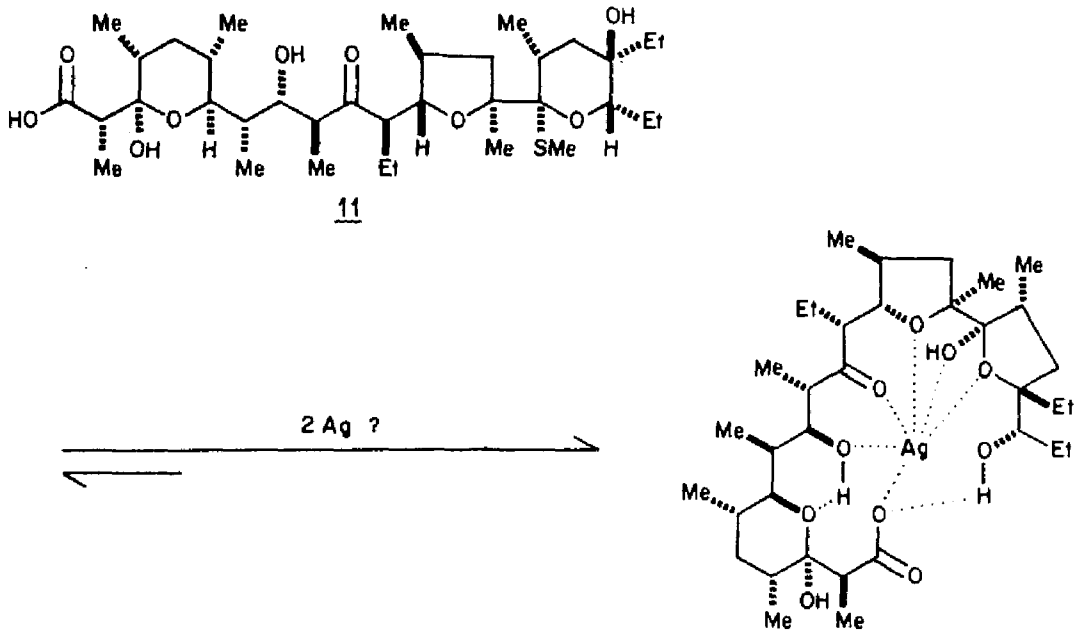
Figure 2. The Silver Salt of Lysocellin.

The reversibility of the five- to six-membered hemiketal ringisomerization will be an important aspect of our synthetic plan. Presently, we do not know whether the stability of the metal complex is sufficient to reverse the equilibrium in favor of the five-membered hemiketal (Scheme 5). We intend to examine this point with an authentic sample of lysocellin or ferensimycin B. Alternatively, we may be able to employ a mixed thioketal, such as **11**, and use silver ion complexation to drive the equilibrium to the desired five-membered hemiketal (Scheme 6).



Scheme 5

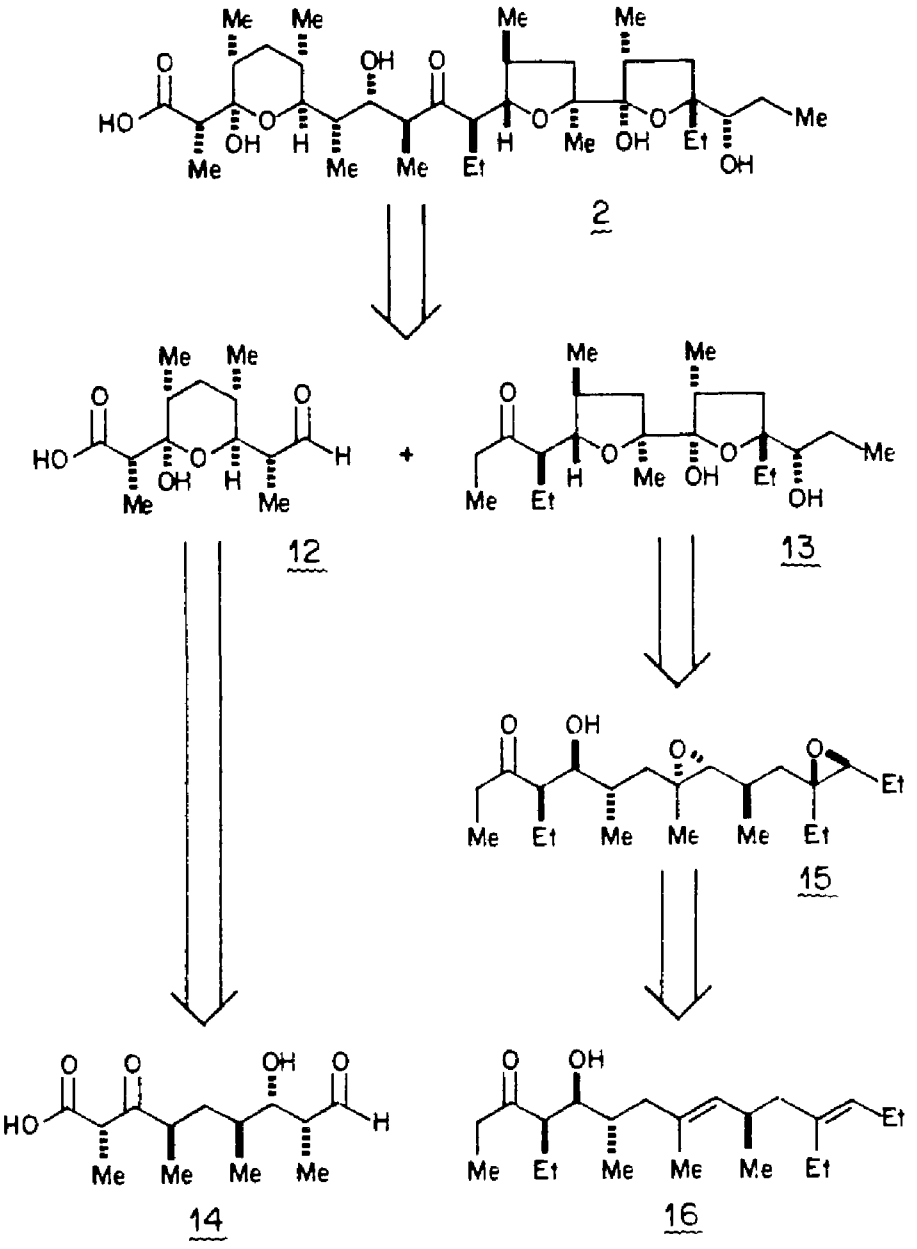
An initial retrosynthetic analysis of ferensimycin B reveals two acyclic targets **14** (left-hand segment) and **16** (right-hand segment) of similar stereochemical complexity (Scheme 7). The major C-9/C-10 bond disconnection is predicated on the total synthesis of lasalocid A by



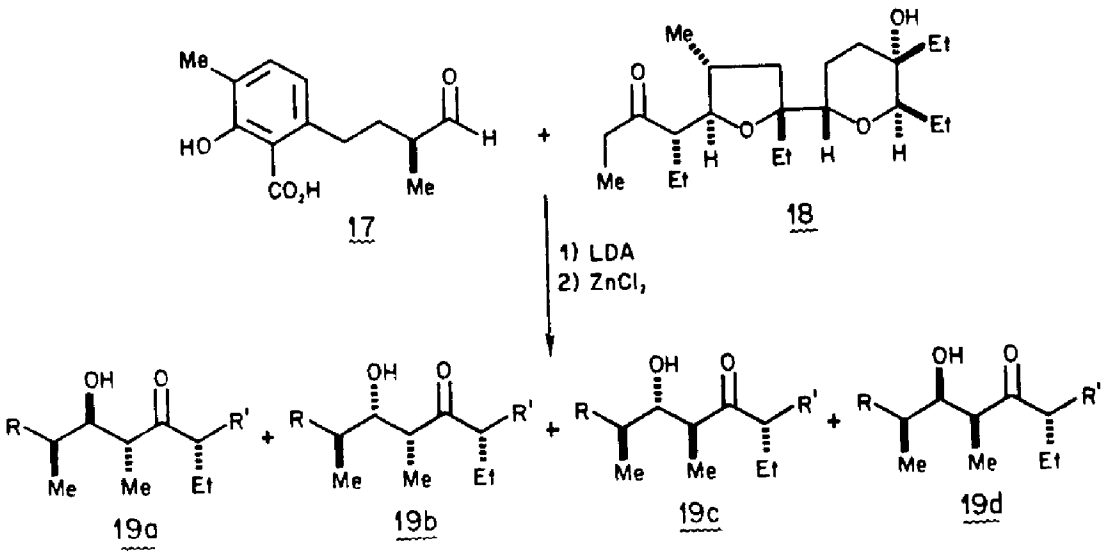
Scheme 6

both Ireland[18] and Kishi.[19] Unfortunately, the level of diastereoselection they observed for this mixed aldol condensation is far from optimal. For example, condensation of the zinc enolate derived from ketone **18** with aldehyde **17** affords a 61:20:11:7 mixture of the four possible enantio-lasalocid A diastereomers **19a**, **19b**, **19c**, and **19d** (Scheme 8).[20] Currently, we are investigating methods to improve the diastereoselection for this crucial bond construction.[21]

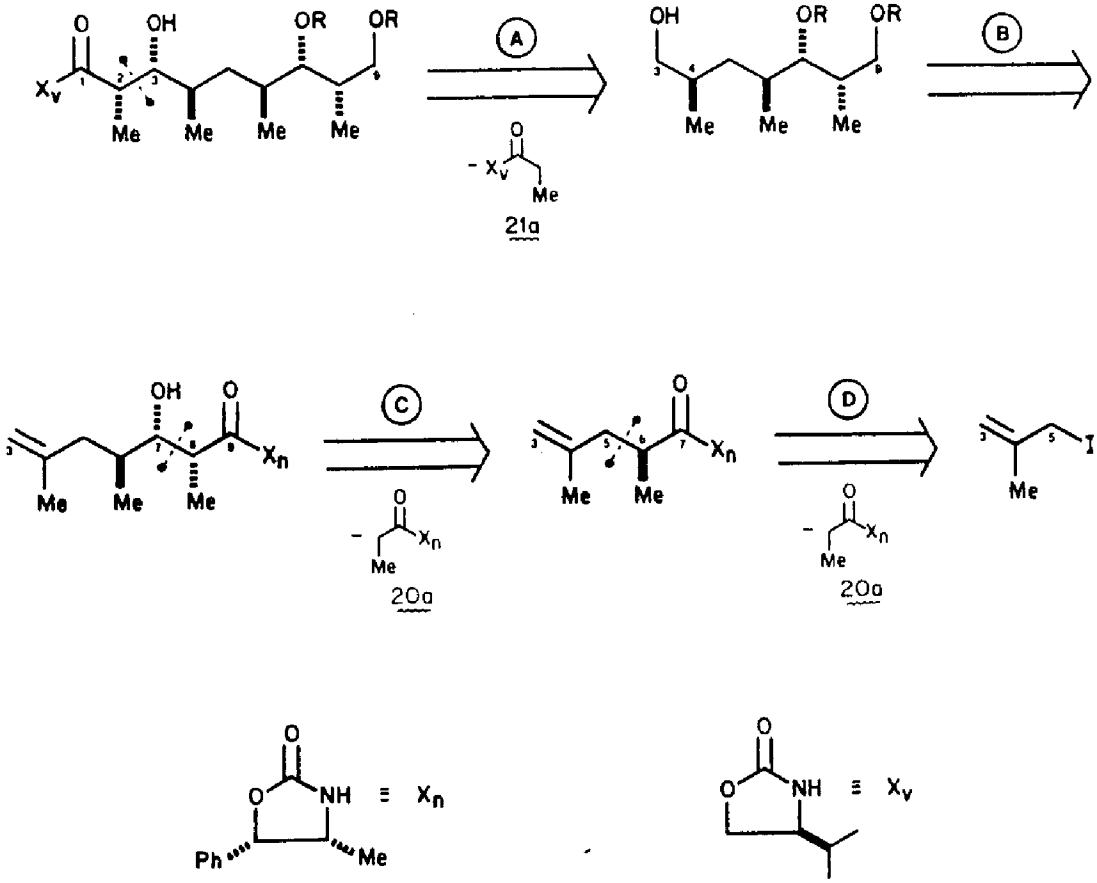
Shown in Scheme 9 is a retrosynthetic plan for the construction of the left-hand segment of ferensimycin B.[21] This target can be stereoselectively prepared by the application of two asymmetric aldol condensations (Steps A and C), one asymmetric alkylation (Step D), and one directed hydroboration (Step B). The chirality for the asymmetric aldol condensations and the asymmetric alkylation will be derived from chiral 2-oxazolidinone imides **20a** and **21a**.



Scheme 7

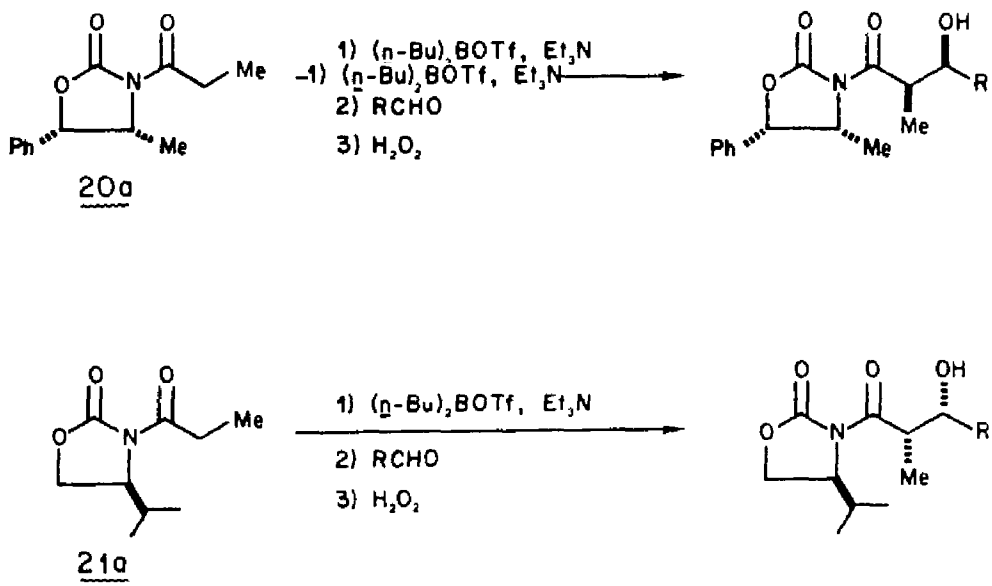


Scheme 8



Scheme 9

The diastereoselective alkylation of chiral 2-oxazolidinone imide enolates, described in Chapter 1, provides an efficient method of generating chiral 2-substituted carboxylic acid derivatives.[8b] We also have developed a highly stereoregular aldol condensation using the same 2-oxazolidinone chiral auxiliaries.[8a] Illustrated in Scheme 10 are the relevant aldol condensations required for the construction of the C-2/C-3 and C-7/C-8 bonds in the left-hand segment of ferensimycin B. The boron enolates derived from imides **20a** and **21a** (n-Bu_2BOTF, Et_3N, CH_2Cl_2, $-78°C$) react with aldehydes to afford one of the four possible diastereomers with greater than 99% stereoselectivity. Depending on the chirality of the C-4 2-oxazolidinone substituent, either erythro diastereomer can be obtained. The proposed transition state leading to the observed major diastereomer is illustrated in Figure 3 for chiral imide **20a**.[22b]



Scheme 10

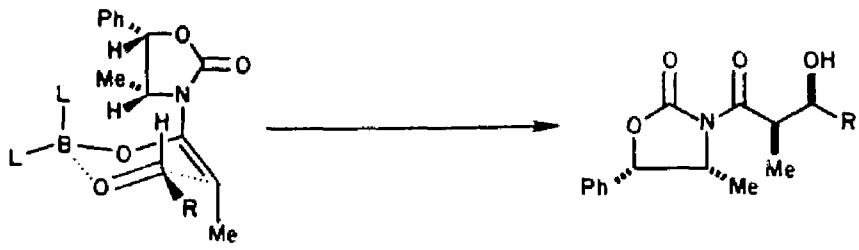
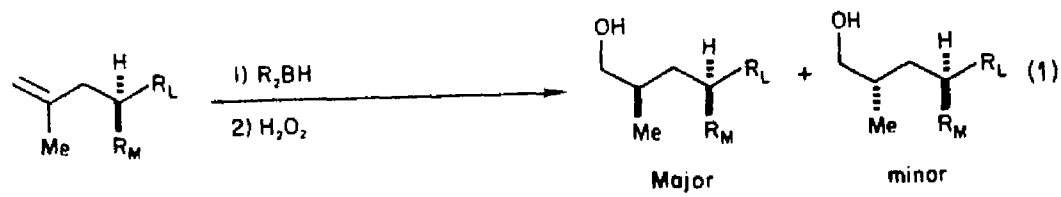
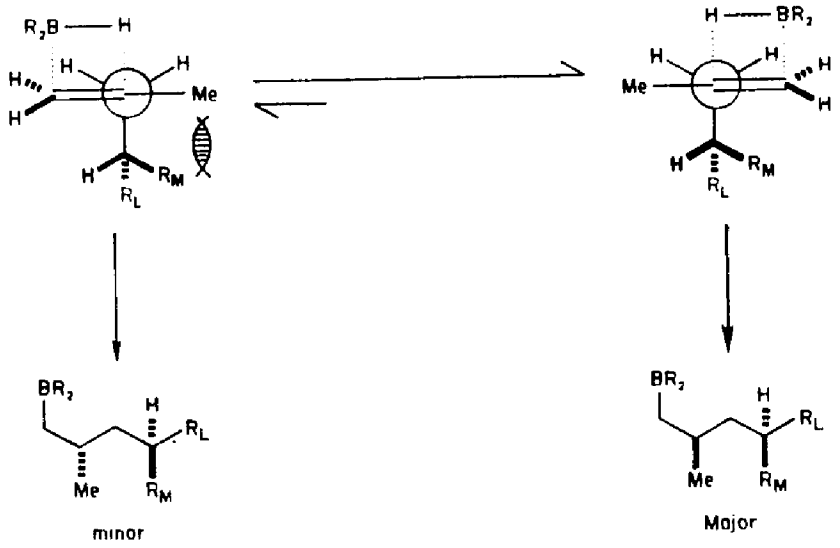


Figure 3. Chiral 2-Oxazolidinone Imide Boron Aldol Transition State.

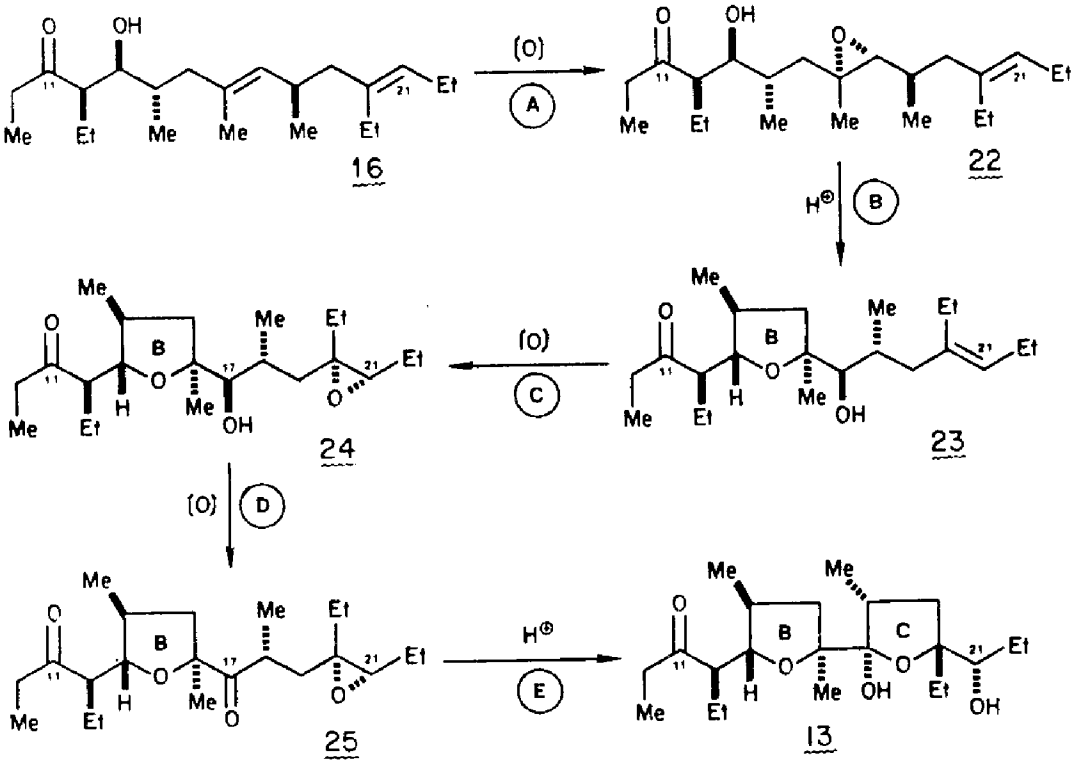
The stereochemisty at C-4 (Scheme 9, Step B) will be induced by a directed hydroboration. Bartrolli, in our laboratories, has demonstrated 1,3 asymmetric induction for the hydroboration of chiral terminal olefins (Eq 1).[22] The level of chirality transfer (ranging from 60:40 to 91:9) depends mainly on the steric difference between R_M and R_L (R_L is larger than R_M). A proposed transition state, leading to the major diastereomer, is illustrated in Scheme 11.[8a]



As previously noted, we envisioned employing a diastereoselective epoxidation--acid catalyzed cyclization sequence to establish the stereochemisty of the B and C rings of ferensimycin B. This approach, illustrated in Scheme 12 for the synthesis of **13** from diene **16**, involves two directed epoxidations (Steps A and C), two acid catalyzed cyclizations (Steps B and E), and one 2° alcohol to ketone oxidation (Step D). The two directed epoxidations will be responsible for generating the



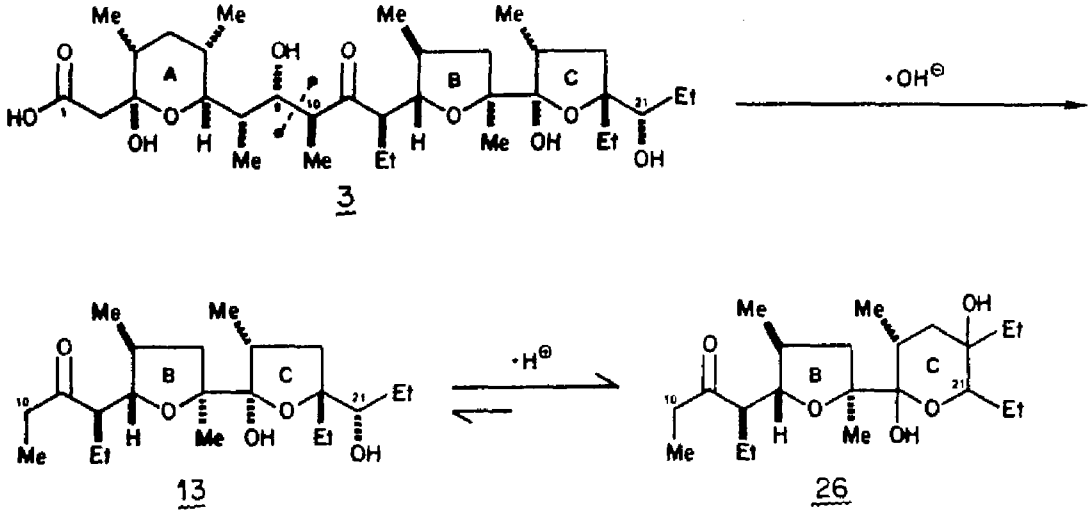
Scheme 11



Scheme 12

stereochemistry at C-16, C-20, and C-21, and thus are crucial to the outcome of this synthetic plan.

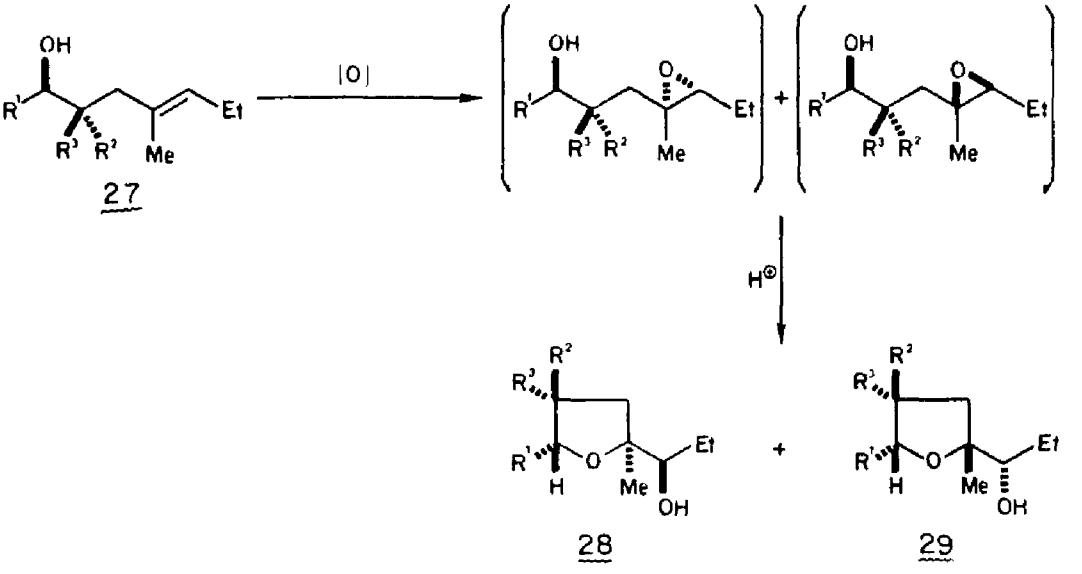
The right-hand segment of ferensimycin B, **13**, has been obtained as the neutral product from the basic (NaOH, dioxane/H_2O) degradation of lysocellin (**3**) (Scheme 13).[17] As previously noted for **3**, the five-membered hemiketal C ring of **13** undergoes acid catalyzed isomerization to the six-membered hemiketal **26**. Therefore, we will need to carefully monitor the transformation from epoxy-ketone **25** to **13** (Scheme 12, Step E) in order to prevent isomerization to **26**. Otherwise, regeneration of the five-membered hemiketal ring at a later stage would be necessary (vide supra). Alternatively, the second epoxidation sequence (see Scheme 12, Steps C, D, and E) could be postponed until after the right- and left-hand segments are coupled. This would permit metal ion complexation to protect the desired five-membered hemiketal ring as it is formed.



Scheme 13

Kishi[23] has demonstrated that the Sharpless procedure ($VO(acac)_2$, t-BuOOH) for the directed epoxidation of allylic and homoallylic alcohols[24] can be extended to bishomoallylic alcohols. Furthermore, with chiral bishomoallylic alcohols, he observed significant levels of diastereoselection (Scheme 14). Treatment of the resultant epoxyalcohols with acetic acid exclusively affords the diastereomeric tetrahydrofurans. Summarized in Table 1 are the data Kishi reported for the epoxidation--acid catalyzed cyclization of various bishomoallylic alcohols.[23] The level of diastereoselection for the vanadium catalyzed epoxidations ranges from 86:14 (Table 1, Entry C) to 95:5 (Table 1, Entry D). The sense of diastereoselection, which depends on the chirality of the directing hydroxyl group, is the same as that required for the construction of the B and C rings of ferensimycin B (compare Schemes 12 and 14).

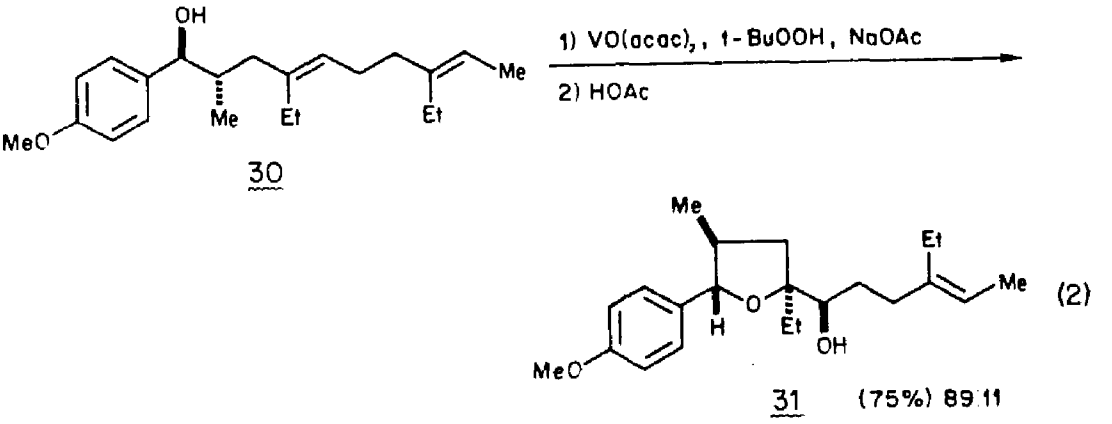
Kishi has applied the vanadium catalyzed epoxidation--acid catalyzed cyclization sequence to stereoselectively prepare a tetrahydrofuran ring in his synthesis of lasalocid A.[19] The relevant reaction is illustrated in Eq 2. In this example, he obtained an 89:11 ratio of tetrahydrofuran diastereomers from diene **30**. Significantly, the isolated olefin does not undergo epoxidation. The close similarity between diene **16** and diene **30** gave us confidence that we would be able to prepare the B and C rings of ferensimycin B, as illustrated in Scheme 12.



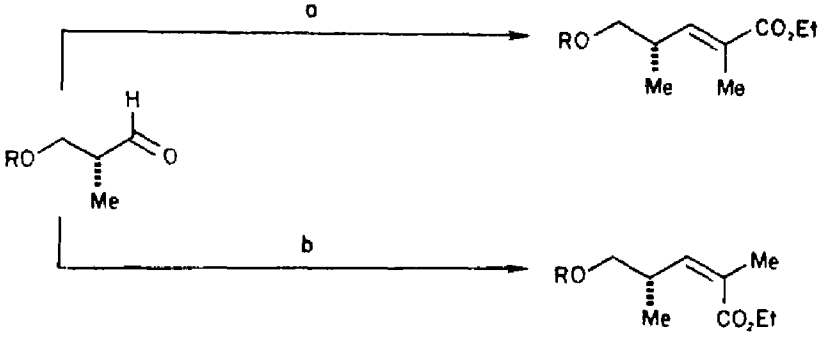
Scheme 14

Table 1. Epoxidation of Bishomoallylic Alcohols (Scheme 14).[23]

Entry	Substrate	R^1	R^2	R^3	[O]	Ratio 28:29
A	**27a**	i-Pr	H	H	MCPBA	50:50
B	**27a**	i-Pr	H	H	$VO(acac)_2$, t-BuOOH	90:10
C	**27b**	i-Pr	Me	H	$VO(acac)_2$, t-BuOOH	86:14
D	**27c**	i-Pr	H	Me	$VO(acac)_2$, t-BuOOH	95:5
E	**27d**	p-MeOPh	H	H	$VO(acac)_2$, t-BuOOH	89:11
F	**27e**	p-MeOPh	Me	H	$VO(acac)_2$, t-BuOOH	89:11

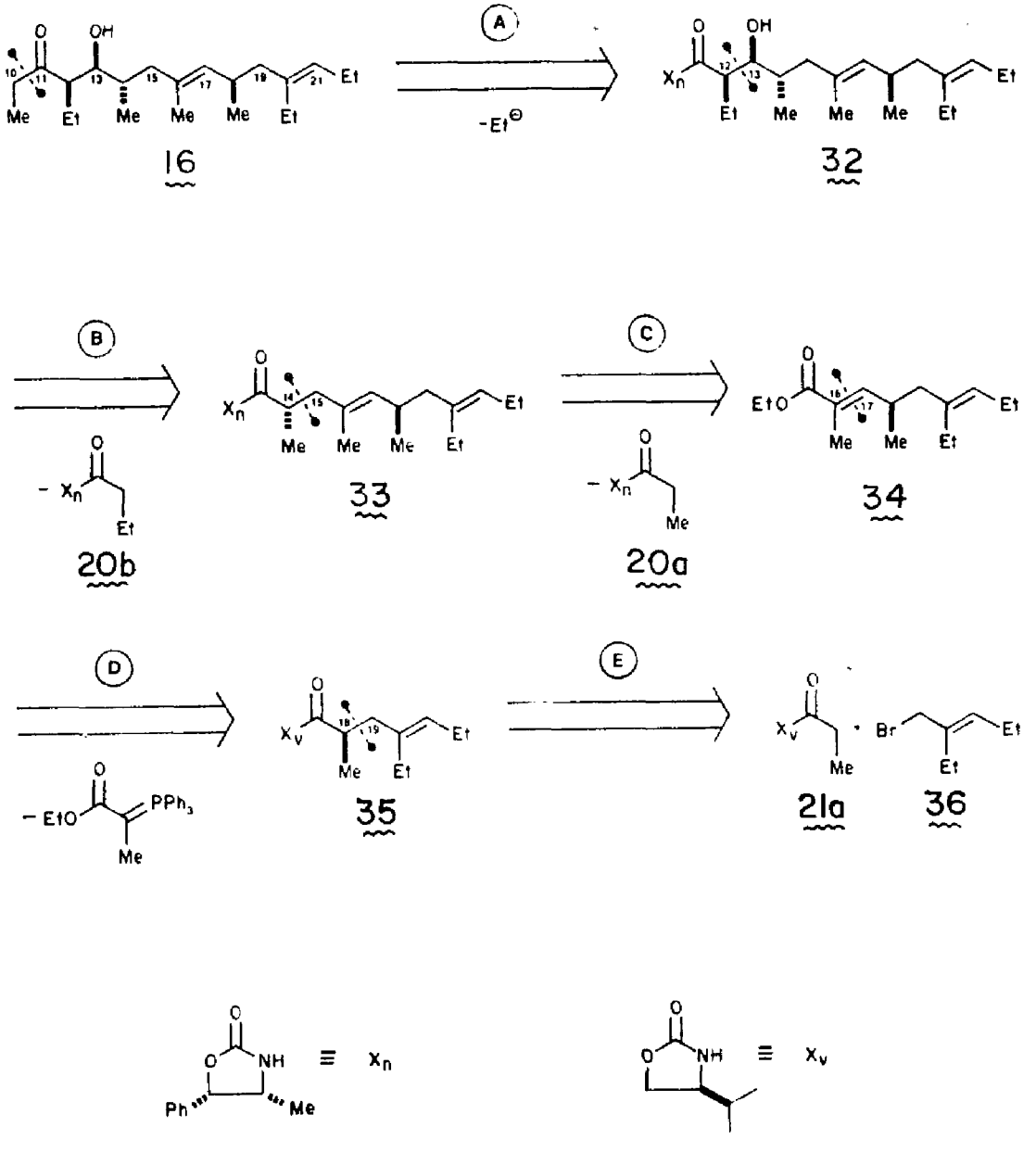


Shown in Scheme 15 is a retrosynthetic plan for the construction of diene **16.** This target can be stereoselectively prepared by the application of one asymmetric aldol condensation (Step B), two asymmetric alkylations (Steps C and E), and one stereoselective Wittig condensation (Step D). The chirality for the asymmetric aldol condensation and the asymmetric alkylations will be derived from chiral 2-oxazolidinone imides **20a, 20b,** and **21a.** The stereoselective generation of the Δ(16-17) (E)-trisubstituted olefin (Step D) is precedented by the work of Kishi, who has demonstrated conditions for preparing either olefin isomer stereoselectively (Scheme 16).[25]



(a) $Ph_3P{=}(Me)CO_2Et$, C_6H_6. (b) $(MeO)_2P(O)CH(Me)CO_2Et$, NaH, THF

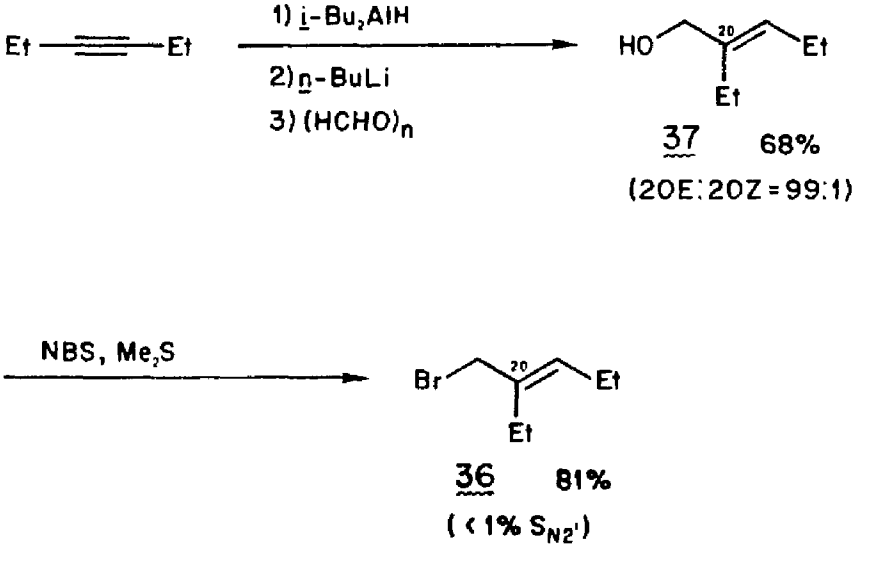
Scheme 16



Scheme 15

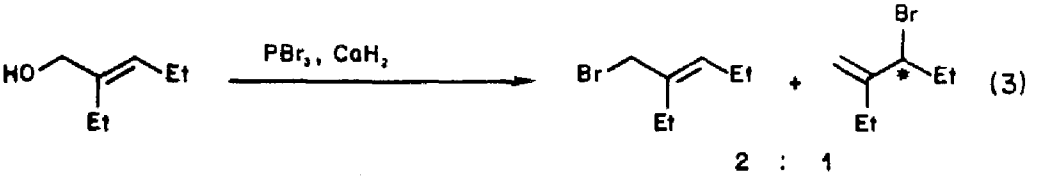
III. RESULTS AND DISCUSSION.

A. Construction of Diene (32, see Scheme 15). The synthesis of (E)-3-bromomethyl-3-hexene (**36**), the trisubstituted allylic bromide needed for the first asymmetric alkylation, is shown in Scheme 17.[26] The requisite allylic alcohol, (E)-3-hydroxymethyl-3-hexene (**37**), is prepared by modification of the Zweifel hydroalumination procedure.[27] Thus, hydroalumination of 3-hexyne with diisobutylaluminum hydride (DIBAL), metalation of the resultant cis-vinylalane with n-butyllithium, and subsequent treatment of the vinylalanate complex with paraformaldehyde affords allylic alcohol **37** in 68% yield as a colorless liquid. Analysis of the product by capillary GC reveals a 99:1 ratio of (2OE)-**37** to (2OZ)-**37**. Although the yield is only moderate, the reaction is readily performed on a large scale (> 1 mol), the reagents are inexpensive, and the reaction affords a product of high stereochemical purity.

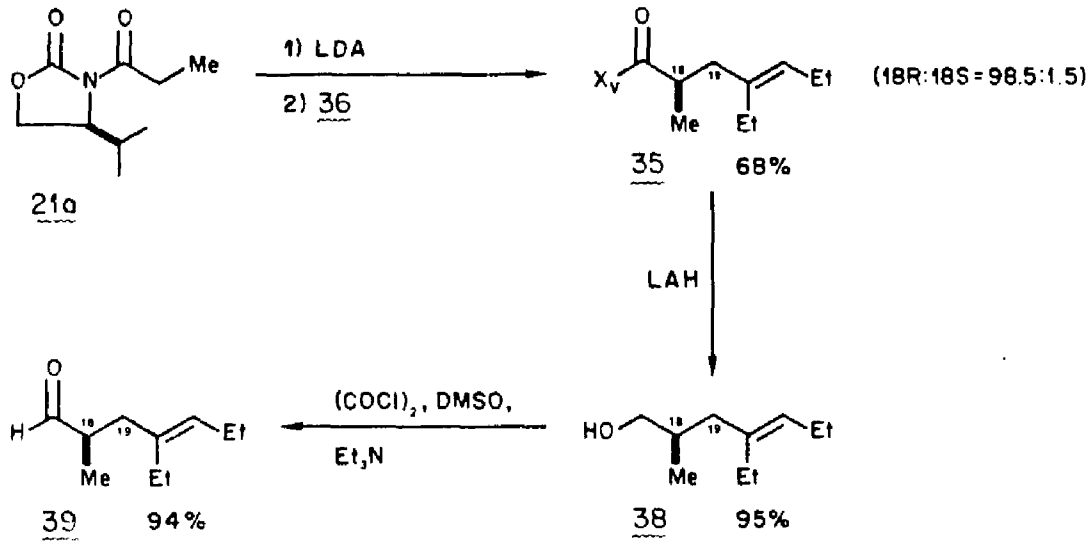


Scheme 17

Initially, we attempted to transform allylic alcohol **37** to allylic bromide **36** by treatment with phosphorus tribromide in the presence of calcium hydride (eq 3).[28] Unfortunately, these conditions afford a 2:1 mixture of the desired allylic bromide to the isomeric $S_{N2'}$ derived allylic bromide. Corey has reported that the complex obtained from N-bromosuccinimide (NBS) and dimethyl sulfide cleanly transforms allylic alcohols to their respective allylic bromides.[29] Accordingly, treatment of allylic alcohol **37** with the NBS--dimethyl sulfide complex affords, after simple filtration through silica gel, allylic bromide **36** in 81% yield as a colorless liquid. Analysis of the product by capillary GC reveals less than 1% of the isomeric allylic bromide. Although relatively stable at room temperature, allylic bromide **36** undergoes isomerization and decomposition upon distillation, even at reduced pressures.



The first of the two asymmetric alkylations constructs the C-18/C-19 bond and establishes the C-18 stereochemistry (Scheme 18). Enolization of imide **21a** with lithium diisopropylamide (LDA, 1.1 equiv, -78°C, 0.5 h) and subsequent treatment of the resultant lithium enolate with allylic bromide **36** (2 equiv, -35°C, 18 h) affords alkylated imide (18R)-**35** along with a minor amount of (18S)-**35**.[8b] Analysis of the unfractionated product by capillary GC reveals a 98.5:1.5 ratio of (18R)-**35** to (18S)-**35**. Product isolation by liquid chromatography (Waters Prep-500)

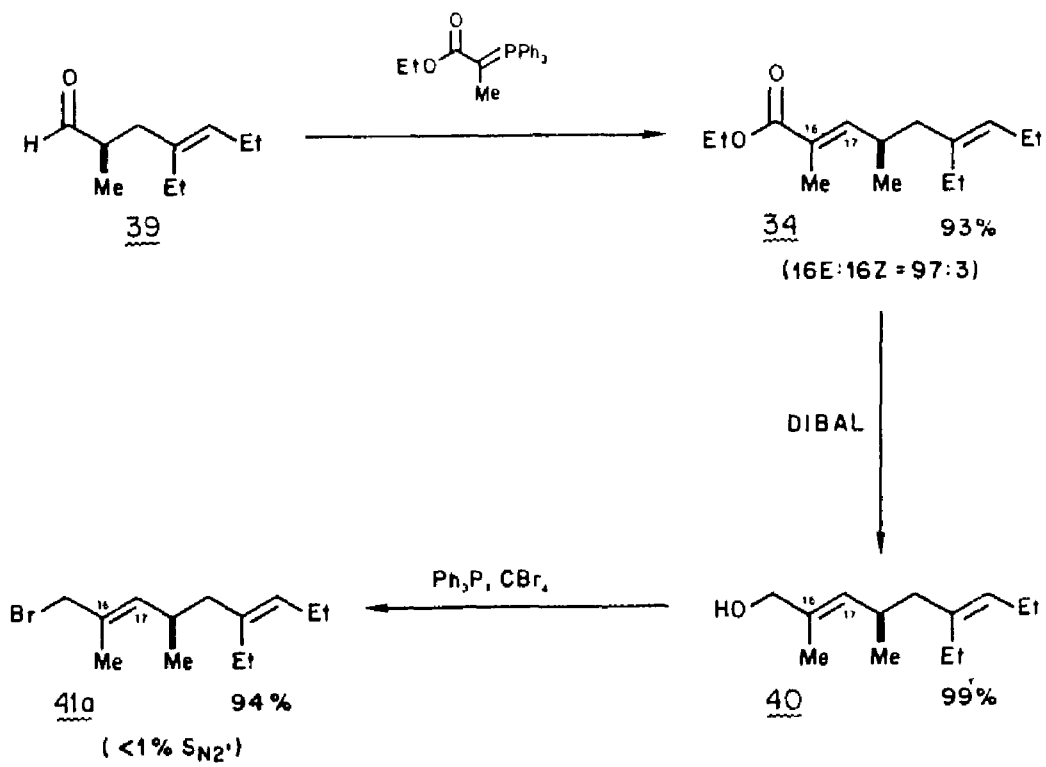


Scheme 18

affords alkylated imide (18R)-**35** in 68% yield as a colorless oil [(18R)-**35**:(18S)-**35** > 99:1].

Previous attempts to reduce alkylated imides to the aldehyde oxidation state with DIBAL (1 equiv, CH_2Cl_2, -78°C) have proven unsuccessful.[30] Therefore, we chose the two-step reduction-oxidation sequence to transform alkylated imide (18R)-**35** to aldehyde **39**.[8b] Reductive cleavage of the chiral auxiliary from alkylated imide (18R)-**35** with lithium aluminum hydride (LAH, 4 hydride equiv, THF, 0°C, 3 h) affords, after product isolation by liquid chromatography, alcohol **38** in 95% yield as a colorless liquid. After evaluating several oxidation procedures,[22b, 30] we found that the modified Swern procedure is the method best suited for preparing chiral aldehydes sensitive to racemization.[31] Thus, treatment of alcohol **38** with oxallyl chloride, dimethyl sulfoxide (DMSO), and triethylamine (CH_2Cl_2, -60°C to -30°C, 0.75 h) affords aldehyde **39** in 94% yield as a colorless liquid.

The second trisubstituted olefin [Δ(16,17)] is stereoselectively constructed *via* a Wittig reaction as illustrated in Scheme 19. Carboethoxyethylidene triphenylphosphorane has been shown to react with chiral 2-substituted aldehydes with a negligible amount of racemization and with a high degree of stereoselectivity to afford (E)-trisubstituted olefins.[22b, 23, 32, 33] Accordingly, treatment of aldehyde **39** with the stabilized phosphorane (1.2 equiv, CH_2Cl_2, 40°C, 12 h) affords ester (16E)-**34** and a minor amount of the diastereomeric product (16Z)-**34** in a combined yield of 93%. Analysis of the unfractionated product by capillary GC reveals a 97:3 ratio of (16E)-**34** to (16Z)-**34**. The same reaction performed in refluxing benzene (4 h) affords a 95:5 ratio of (16E)-**34** to

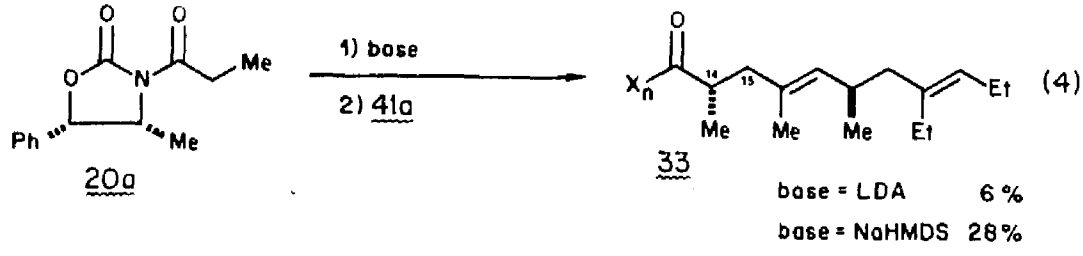


Scheme 19

(16Z)-**34**. Although the diastereomers are separable by careful liquid chromatography, we chose to remove the minor olefin isomer at a later stage (vide infra).

Reduction of ester **34** [(16E)-**34**:(16Z)-**34** = 97:3] with DIBAL (2.2 equiv, CH_2Cl_2, -78°C to -20°C, 2 h) followed by an aqueous sodium potassium tartrate workup affords allylic alcohol **40** in 99% yield as a colorless liquid. Initially, we attempted to transform allylic alcohol **40** to allylic bromide **41a** by the previously described NBS--dimethyl sulfide procedure.[29] Unfortunately, with this allylic alcohol, these conditions afford an intractable mixture of several isomeric allylic bromides. After evaluating several other procedures, we found the triphenylphosphine--carbon tetrabromide method to be well suited for this transformation.[36] Thus, treatment of allylic alcohol **40** with triphenylphosphine and carbon tetrabromide in acetonitrile rapidly affords allylic bromide **41a** in 94% yield. Analysis of the product by capillary GC reveals less than 1% of the isomeric $S_{N2'}$ derived allylic bromide.

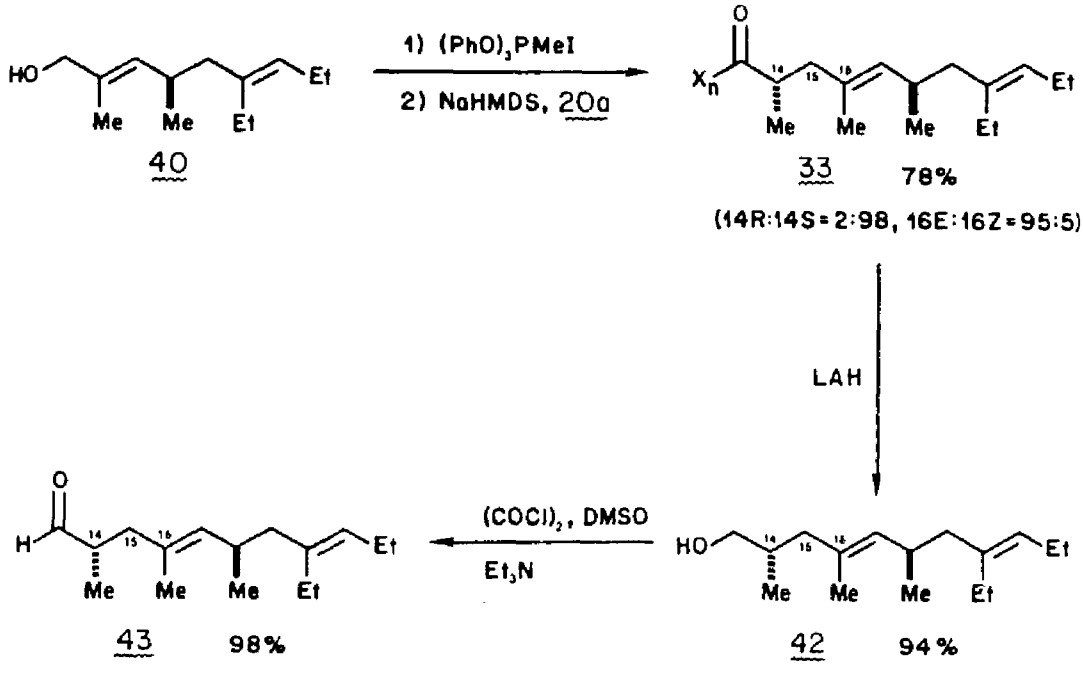
The second asymmetric alkylation constructs the C-14/C-15 bond and establishes the C-14 stereochemistry. Unfortunately, treatment of the lithium enolate derived from imide **20a** with allylic bromide **41a** (2 equiv, -78°C to 0°C, 4 h) affords alkylated imide **33** in a mere 6% yield (eq 4). Even treatment of the more reactive sodium enolate, prepared from imide **20a** and sodium hexamethyldisilylamide (NaHMDS, 1.1 equiv, -78°C to -40°C, 4 h) affords the desired product in only 28% yield. Although the allylic bromide could be recovered and recycled, we desired a more reactive electrophile, and therefore decided to prepare the corresponding allylic iodide **41b**.



(4)

Rydon has reported that methyl triphenoxyphosphonium iodide transforms alcohols, including allylic alcohols, to their respective iodides.[37] Although the original procedure called for the alcohol and phosphonium iodide to be heated in refluxing benzene, Moffet has reported that the reaction proceeds at room temperature if performed in dimethylformamide (DMF).[38] Accordingly, treatment of allylic alcohol **40** [(16E)-**40**:(16Z)-**40** = 97:3] with freshly prepared methyl triphenoxyphosphonium iodide[33] (1.1 equiv, DMF, 20°C, 20 min) affords allylic iodide **41b** along with a minor amount of diphenyl methylphosphonate (112% mass balance). Analysis of the product by ^{1}H NMR spectroscopy reveals a 95:5 ratio of (16E)-**41b** to (16Z)-**41b** and ca. 10% of the phosphonate. While the phosphonate can be removed by simple filtration of the mixture through alumina, this results in a considerable amount (10-40%) of olefin isomerization. Allylic iodide **41b** undergoes facile acid, heat, iodine, and light catalyzed isomerization. Therefore, it is imperative to use the product immediately, without further purification.

Allylic iodide **41b** functions admirably in the second asymmetric alkylation (Scheme 20). Enolization of imide **20a** with NaHMDS (1.1 equiv, -78°, 0.5 h) and subsequent treatment of the resultant sodium enolate with allylic iodide **41b** (0.33 equiv, -30°C, 4 h) affords alkylated imide (14S,16E)-**33** along with minor amounts of two diastereomeric products. The large excess of enolate (3 equiv) relative to electro-



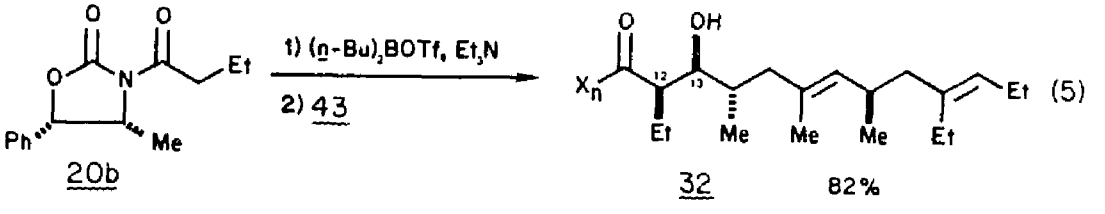
Scheme 20

phile is necessary to obtain a reasonable product yield. Analysis of the unfractionated product by capillary GC reveals a 93:7 ratio of the major diastereomer (14S,16E)-**33** to the minor diastereomers (14R,16E)-**33** and (14S,16Z)-**33**. Product isolation by liquid chromatography (Waters Prep-500) affords alkylated imide **33** in 78% yield (based on allylic alcohol **40**). The product, however, still contains the minor diastereomers. These are removed at a later stage.

The two-step reduction-oxidation sequence is repeated to transform alkylated imide **33** to aldehyde **43**. Thus, reductive cleavage of the chiral auxiliary from alkylated imide **33** with LAH (4 hydride equiv, THF, 0°C, 3 h) affords, after product isolation by liquid chromatography, alcohol **42** in 94% yield as a colorless liquid. One of the minor diastereomers, presumably (14R)-**42** is removed during product isolation.

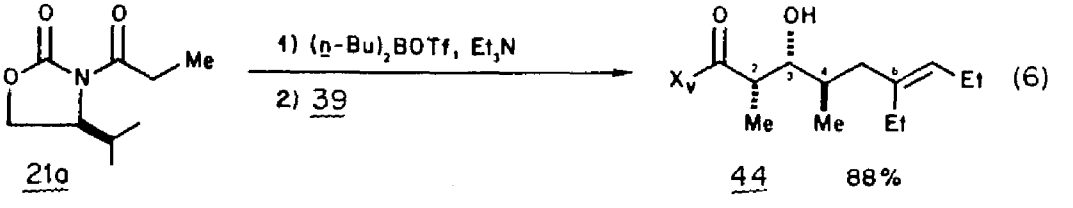
Analysis of the resultant product by capillary GC reveals a 97:3 ratio of diastereomers. Treatment of alcohol **42** with oxallyl chloride, DMSO, and triethylamine (CH_2Cl_2, -60°C to -30°C, 0.5 h) affords aldehyde **43** in 98% yield. Analysis of the product by capillary GC reveals a 97:3 ratio of diastereomers.[39]

An asymmetric aldol condensation constructs the C-12/C-13 bond and establishes the stereochemistry at C-12 and C-13.[8a] Enolization of imide **20b** with di-*n*-butylboryl triflate and triethylamine (CH_2Cl_2, -78°C for 0.5 h then 0°C for 1 h) and subsequent treatment of the resultant boron enolate with aldehyde **43** (-78°C to 0°C, 2.5 h) affords, after oxidative workup, diene **32** along with minor amounts of several diastereomers (eq 5). Analysis of the unfractionated product, as its trimethylsilyl derivative (Et_2NSiMe_3, DMAP, CH_2Cl_2, 4 h), by capillary GC reveals a 2.6:4.2:92.8:0.4 mixture of diastereomers. Product isolation by liquid chromatography (MPLC) affords diene **32** in 82% yield as a viscous colorless oil (0:4:96:0). The identity of the remaining minor diastereomer is unknown.



(5)

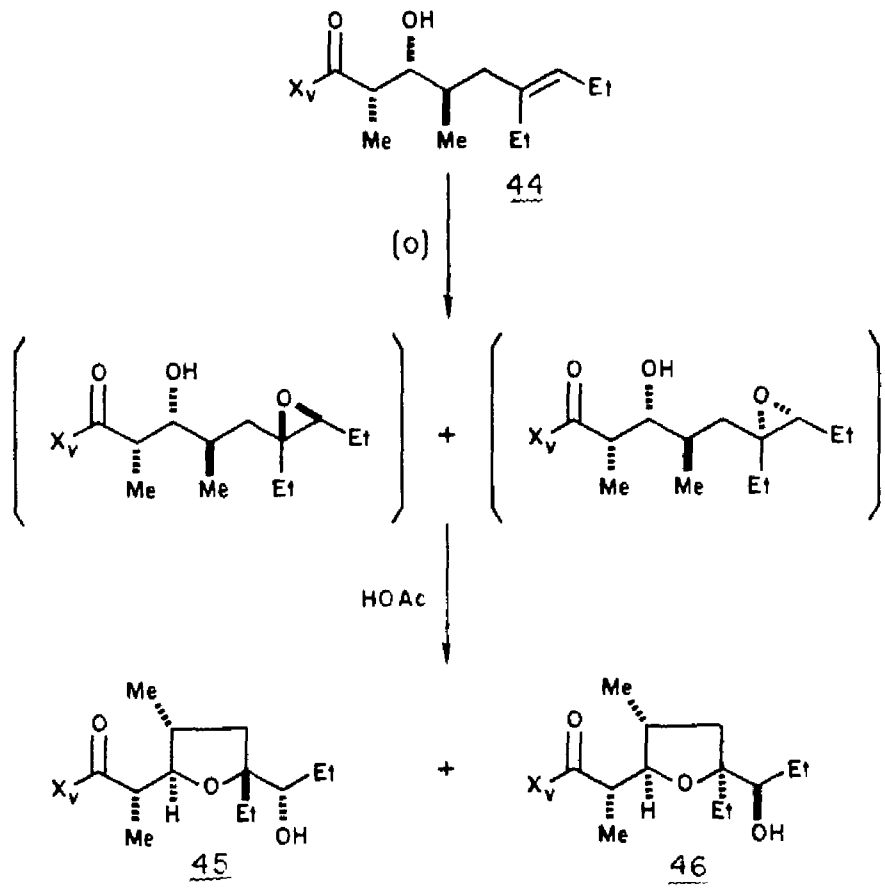
B. The Stereoselective Epoxidation of Bishomoallylic Alcohols: A Model Study. We prepared bishomoallylic alcohol **44** as a model substrate for the evaluation of the epoxidation--acid catalyzed cyclization sequence. Thus, enolization of imide **21a** with di-n-butylboryl triflate and triethylamine (CH_2Cl_2, -78°C for 0.5 h then 0°C for 1 h) and subsequent treatment of the resultant boron enolate with aldehyde **39** (-78°C to 0°C, 4 h) affords, after oxidative workup, bishomoallylic alcohol **44** in 88% yield (eq 6). Analysis of the trimethylsilylated derivative (Et_2NSiMe_3, DMAP, CH_2Cl_2, 4 h) reveals the presence of only one diastereomer (limits of detection $\geq$ 100:1). Bishomoallylic alcohol **44** possesses the same relative (although opposite absolute) stereochemistry as diene **32**.



21a 44 88% (6)

Kishi has reported that m-chloroperbenzoic acid (MCPBA) exhibits negligible diastereoselection for the epoxidation of chiral bishomoallylic alcohols (see Table 1, Entry A).[25] Therefore, for identification purposes, we employed MCPBA to prepare a standard mixture of tetrahydrofuran diastereomers **45** and **46** from bishomoallylic alcohol **44** (Scheme 21). Accordingly, treatment of bishomoallylic alcohol **44** with MCPBA (1.2 equiv, CH_2Cl_2, -20°C to 25°C, 4 h) followed by acetic acid (3 equiv, 0.5 h) affords tetrahydrofurans **45** and **46**. Analysis of the unfractionated product by capillary GC reveals a 23:77 ratio of **45** to **46**. The diastereomers are readily separable by liquid chromatography to

afford **45** in 19% yield (**45**:**46** > 99:1) and **46** in 72% yield (**45**:**46** < 1:99). Presumably, the C-4 methyl group is responsible for the observed diastereoselection in a manner analogous to the transition state shown in Scheme 11.[22b]



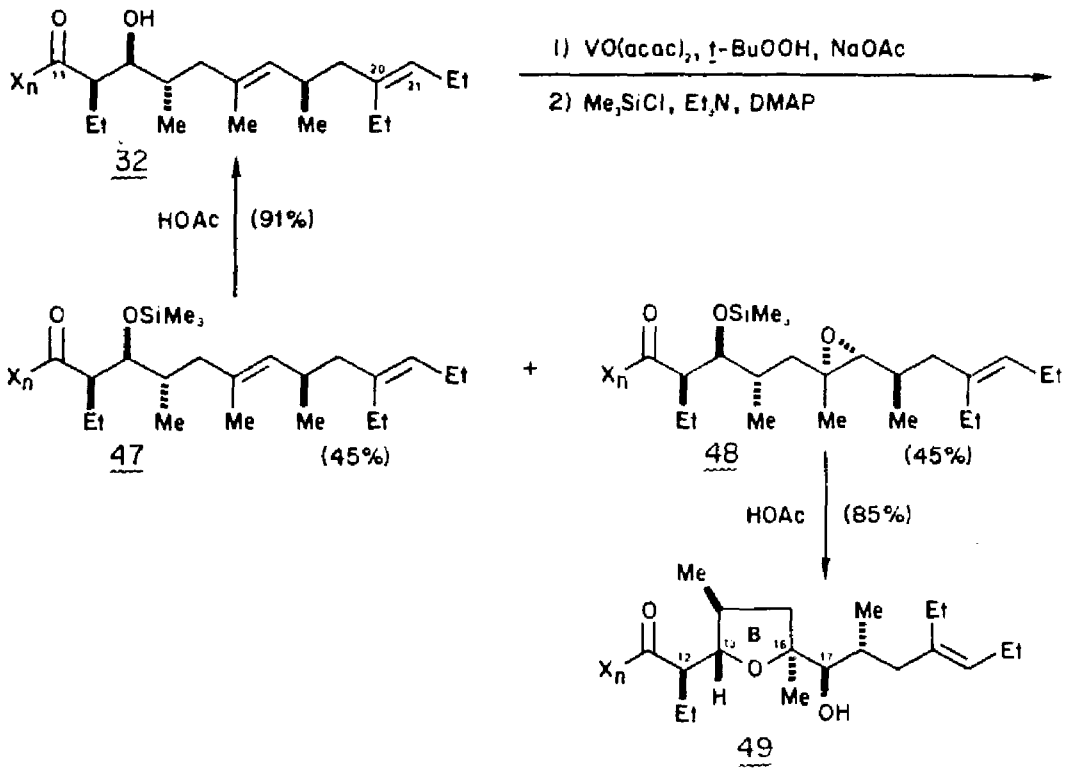
	45		46
(o) = t-BuOOH, VO(acac),	92	:	8
(o) = MCPBA	23	:	77

Scheme 21

The identity of the two tetrahydrofuran diastereomers was determined by nuclear Overhauser enhancement (NOE) difference spectroscopy. Irradiation of the C-3 proton of tetrahydrofuran **45** affords a positive enhancement of the signal for the C-7 proton. This indicates that these two groups reside on the same side of the tetrahydrofuran ring. In the case of tetrahydrofuran **46**, irradiation of the C-3 proton does not result in a signal enhancement for the C-7 proton. Therefore, tetrahydrofurans **45** and **46** are assigned the structures illustrated in Scheme 21.

In contrast to the above MCPBA epoxidation results, the vanadium catalyzed t-butylhydroperoxide epoxidation--acid catalyzed cyclization sequence favors tetrahydrofuran **45**. For example, treatment of bishomoallylic alcohol **44** with anhydrous t-butylhydroperoxide[40] (1.2 equiv) in the presence of a catalytic amount of vanadyl acetylacetonate (0.1 equiv, 25°C, 2 h) followed by acetic acid (3 equiv) and dimethyl sulfide (excess, to decompose the remaining peroxide) affords tetrahydrofurans **45** and **46**. Analysis of the unfractionated product by capillary GC reveals a 92:8 ratio of **45** to **46**. Product isolation by liquid chromatography affords tetrahydrofuran **45** in 74% yield (**45**:**46** >99:1).

C. Stereoselective Preparation of the B Tetrahydrofuran Ring. The first stereoselective epoxidation--acid catalyzed cyclization sequence constructs what will become the B tetrahydrofuran ring of ferensimycin B (Scheme 22). The presence of the Δ(20,21) double bond in diene **32** dictates that carefully controlled conditions be employed for this transformation in order to prevent over-oxidation. Accordingly, treatment of diene **32** with anhydrous t-butylhydroperoxide (1.1 equiv),



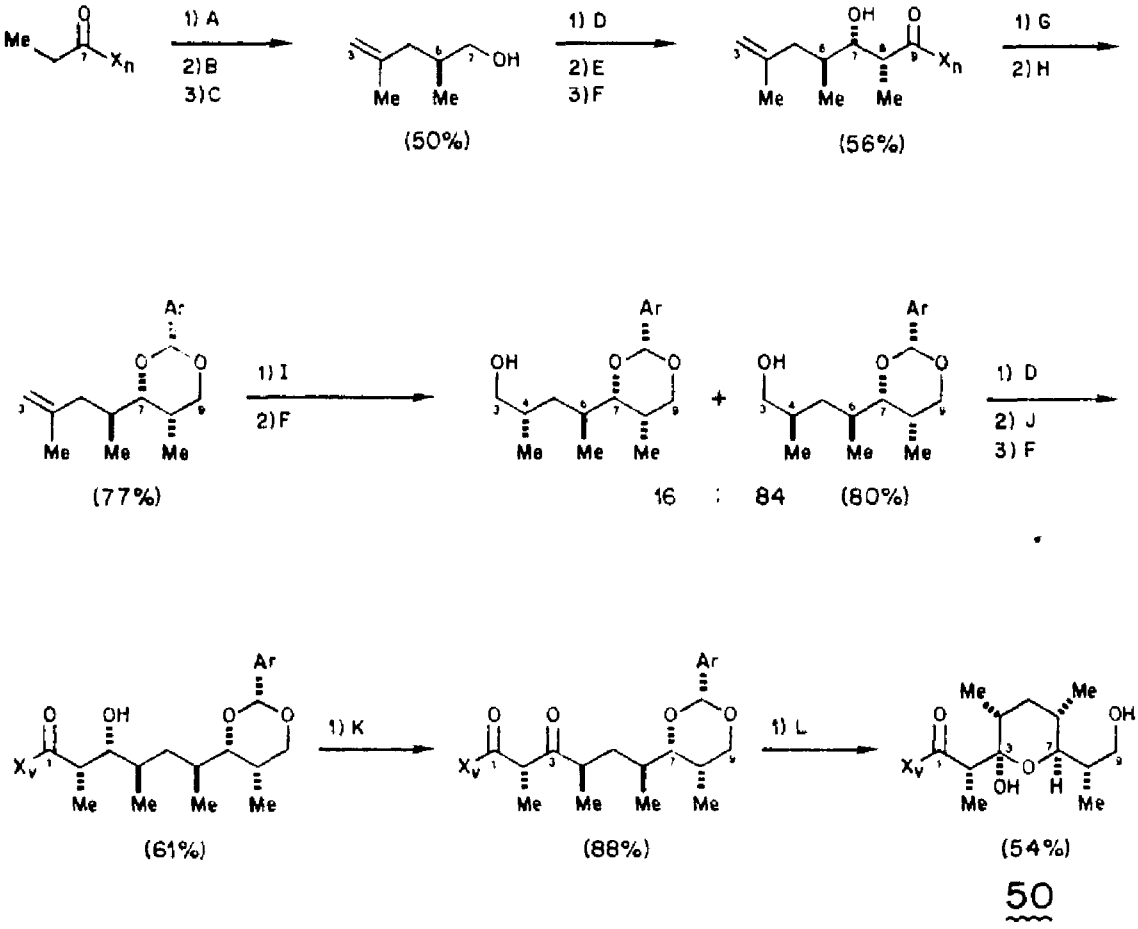
Scheme 22

vanadyl acetylacetonate (0.1 equiv), and anhydrous sodium acetate (10 equiv) in benzene for 1.5 h at 25°C, followed by chlorotrimethylsilane (10 equiv), triethylamine (10 equiv), and DMAP (1 equiv) for 0.5 h at 25°C affords, after isolation by liquid chromatography, trimethylsilylated diene **47** in 45% yield and trimethylsilylated epoxide **48** in 45% yield. Treatment of trimethylsilylated epoxide **48** with acetic acid in THF/water (1:5:3) for 4 h at 25°C affords tetrahydrofuran **49** in 85% yield. Analysis of the product by capillary GC, HPLC, and high field NMR spectroscopy reveals the presence of only one diastereomer. Presumably, any minor diastereomers are removed during liquid chromatographic product isolation. Treatment of trimethylsilylated diene **47** with acetic

acid in THF/water (1:5:3) for 4 h at 25°C affords diene **32** in 91% yield. Therefore, based on recovered diene **32**, tetrahydrofuran **49** is obtained in an overall yield of 55%. Attempts to improve the yield by increasing the amount of either the t-butylhydroperoxide or the vanadium catalyst have proven unsuccessful. Rather, several unidentified byproducts, presumably a result of diepoxidation, are formed.

The stereochemistry of tetrahydrofuran **49** was investigated by NOE difference spectroscopy. Irradiation of the C-13 proton affords a positive enhancement of the signal for the C-17 proton. In addition, irradiation of the C-16 methyl protons affords a small positive enhancement of the signal for the C-12 protons. These results are in agreement with the structure proposed for tetrahydrofuran **49**.

D. Construction of the Left-Hand Half of Ferensimycin B. Recently, Polniaszek in our laboratories has constructed an intermediate (**50**) corresponding to the left-half of ferensimycin B.[21] The synthesis basically follows the plan previously outlined in Scheme 9. The results are shown in Scheme 23.


1) A
2) B
3) C
(50%)
1) D
2) E
3) F
(56%)
1) G
2) H
1) I
2) F
(77%)
16 : 84
(80%)
1) D
2) J
3) F
1) K
(61%)
(88%)
1) L
(54%)
50


NH ≡ Xn
Ph
Me
NH ≡ Xv

Scheme 23

IV. SUMMARY

Our efforts, directed toward the enantioselective total synthesis of ferensimycin B, have culminated in the preparation of two advanced intermediates **49** and **50**. The synthesis of both **49** and **50** demonstrates the utility of chiral 2-oxazolidinones as synthons for the construction of acyclic stereochemistry. Furthermore, we have shown that the vanadium catalyzed directed epoxidation--acid catalyzed cyclization sequence is successful for the preparation of the B tetrahydrofuran ring. Intermediate **49**, corresponding to the right-hand half of ferensimycin B, is prepared in ten steps in an overall yield of 18%. Likewise, intermediate **50**, corresponding to the left-hand half of ferensimycin B, is prepared in ten steps in an overall yield of 5%.[21] Efforts continue toward the ultimate completion of this synthesis: 1) the stereoselective preparation of the five-membered hemiketal C ring; 2) the preparation of ethyl ketone **13**; and 3) the stereoselective coupling of the left- and right-hand segments.

V. EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. IR spectra were recorded on a Beckman 4210 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Routine ^{1}H NMR spectra were recorded on a Varian Associates CFT-20 (80 MHz) or EM-390 (90 MHz) spectrometer. High field ^{1}H NMR spectra were recorded on a Varian Associates XL-200 (200 MHz), a Bruker WM-300 (300 MHz), or a Bruker WM-500 (500 MHz)[41] spectrometer. Chemical shifts are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant (Hz), integration and interpretation. ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz) or a Varian Associates XL-200 (50 MHz) spectrometer and are reported in ppm from internal tetramethylsilane on the δ scale. Multiplicities, when determined by off-resonance decoupling, are reported using the above format.

Optical rotations were determined with a Jasco DIP-181 digital polarimeter at 589, 577, 546, 435 and 365 nm. Data are reported as follows: $[\alpha]_{589}$, $[\alpha]_{577}$, $[\alpha]_{546}$, $[\alpha]_{435}$, $[\alpha]_{365}$, concentration ($\underline{c}$ = g/100 mL) and solvent. When chloroform was used as the solvent, it was filtered through activity 1 alumina immediately prior to use.

Combustion analyses were performed by Galbraith Laboratories, Inc., (Knoxville, Tennessee) or Mr. Lawrence Henling at the California Institute of Technology Microanalytical Laboratory.

Analytical gas chromatography (GC) was carried out on a Hewlett Packard 5880A gas chromatograph equipped with a split mode capillary injector and a flame ionization detector. Hydrogen was used as the carrier gas. The following wall coated open tubular (WCOT) fused silica capillary columns were employed: 0.32 mm x 15 m and 0.32 mm x 30 m Carbowax 20M (J and W Associates), 0.32 mm x 30 m DB-1 (J and W Associates), 0.32 mm x 30 m DB-5 (J and W Associates), 0.31 mm x 25 m SE-54 (Hewlett Packard) and 0.21 mm x 25 m methyl silicone (Hewlett Packard). Specific GC conditions are reported in the following format: column, oven temperature, carrier gas flow rate, and retention time. Unless otherwise indicated, the injector and detector temperatures were 250°C.

Flash chromatography was performed according to the general procedure of Still,[42] employing EM Reagents Silica Gel 60 (40-63 μm). Data are reported as follows: column dimensions (d x l), elutant composition and order of elution. Medium pressure liquid chromatography (MPLC) was carried out on an MPLC apparatus consisting of a Chromatronix SV8031 Sample Injection valve, a Fluid Metering Inc. model RP-SY Lab Pump and an ISCO model UA-5 UV (254 nm) detector using the following EM Reagents prepacked LoBar LiChroprep Si 60 columns: column A (1.0 x 24 cm, 40-63 μm silica gel), column B (2.5 x 31 cm, 40-63 μm silica gel) and column C (3.7 x 44 cm, 63-125 μm silica gel). Specific MPLC conditions are reported as follows: column dimensions (d x l), elutant composition, elutant flow rate and order of elution. Analytical high performance liquid chromatography (HPLC) was carried out on a Waters Associates ALC 202/401 HPLC equipped with a model 6000 high pressure solvent pump, a model U6K injector and a differential UV detector (254 nm), using the following columns: Waters Associates Radial Pak (8 mm x 10 cm, 5 μm silica gel) or

(8 mm x 10 cm, 10 μm silica gel) and DuPont Zorbax (4.6 mm x 25 cm, 5 μm silica gel). Specific HPLC conditions are reported as follows: column, elutant composition, elutant flow rate and retention volume (k'). Preparative HPLC was performed on a Waters Associates PrepLC/System 500 liquid chromatograph, equipped with a refractive index detector and using two PrepPak 500 silica gel cartridges (5 x 30 cm). Specific HPLC conditions are reported using the above format. Unless otherwise noted, the substrate was introduced onto the HPLC as a concentrated solution through the solvent inlet port. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, iodine vapor, an aqueous cerium molybdate spray, or an aqueous potassium permanganate spray.

When necessary, solvents and reagents were dried prior to use. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium--potassium alloy/benzophenone ketyl. Benzene and toluene were distilled from sodium/benzophenone ketyl. Boron trifluoride--diethyl etherate, chlorotrimethylsilane, dichloromethane, diisopropylamine, hexamethyldisilylamine, and triethylamine were distilled from calcium hydride. Acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride and stored over 4A molecular sieves. Unless otherwise noted, alkyl bromides and iodides were passed through a column of activity 1 alumina immediately prior to use. n-Butyllithium (Aldrich Chemical Co.) was standardized by double titration (total base - inorganic base = organic base).

Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon or nitrogen with rigid exclusion of moisture from reagents and glassware.

(3E)-3-Hydroxymethyl-3-hexene (37). A mechanically stirred solution of 182 mL (132 g, 1.60 mol) of 3-hexyne (Farchan Chemical) and 1.60 L (1.0 M in hexane, 1.60 mol) of diisobutylaluminum hydride was heated at 50-60°C for a 4 h period. The colorless solution was cooled to room temperature, followed by the addition of 1.00 L (1.60 M in hexane, 1.60 mol) of n-butyllithium over a 40 min period (slightly exothermic, temperature rose to 30-35°C). The thick, pale yellow mixture was stirred at room temperature for 0.5 h. The precipitate was dissolved by the dropwise addition of 130 mL (ca. 1.6 mol) of THF (slightly exothermic, temperature rose to 30-35°C). To the pale yellow solution was added 53 g (1.76 mol) of paraformaldehyde (dried in vacuo over phosphorus pentoxide) in portions over a 2 h period (at a rate to maintain the temperature below 30°C). **Caution: Do not add all of the paraformaldehyde in one portion; the reaction may become uncontrollable after an induction period.** The reaction mixture was stirred at room temperature for 16 h. The mixture is cooled to 0°C and quenched by the cautious addition of 1.5 L of 6 N aqueous sulfuric acid over a 2 h period. During the initial phase of the addition, a large quantity of gas is evolved. The two phases were separated and the lower aqueous phase extracted with three 500 mL portions of dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford 250 g of a pale yellow oil. Distillation through a 20-cm Vigreux column afforded a 50 g forerun (bp 45-60°C, 10 mm) which consisted of 37

(ca. 50%) contaminated with 3-methylbutanol and n-pentanol, followed by 125 g (68%) of the title compound as a colorless liquid (bp 63-64°C, 10 mm. Analysis by GC (30 m DB-5, 50°C, 32 cm/sec) afforded a 99:1 ratio of (3E)-**37** (t_r = 9.06 min) to (3Z)-**37** (t_r = 9.33 min).

(3E)-**37**: IR (neat) 3500-3100, 2960, 2940, 2880, 1460, 1360, 1075, 1030, 1005, 850 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 5.37 (br t, J = 7.2 Hz, 1H, C_4-H), 4.00 (s, 2H, C_3-CH_2OH), 2.2-1.9 (m, 5H, OH, C_2-H_2, C_5-H_2), 0.99, 0.97 (overlapping t's, J = 7.5, 7.5 Hz, 6H, C_1-H_3, C_6-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 140.2, 128.0, 66.8, 21.1, 20.7, 14.4, 13.4.

(3E)-3-bromomethyl-3-hexene (36). To a mechanically stirred, cooled (0°C) suspension of 39.2 g (0.220 mol) of N-bromosuccinimide (recrystallized from water, dried in vacuo over phosphorus pentoxide) in 500 mL of dichloromethane was added 16.2 mL (13.7 g, 0.221 mol) of dimethyl sulfide dropwise over a 15 min period. The resultant yellow precipitate was stirred at 0°C for 15 min, cooled to -30°C, and followed by the addition of 22.8 g (0.200 mol) of allylic alcohol **37** dropwise over a 15 min period. After an additional 15 min at -30°C and 3 h at 0°C, the mixture was sequentially washed with cold water (3 x 300 mL) and brine (300 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 37 g of a yellow oil. The unpurified product was diluted with pentane, filtered through 40 g of silica gel, and concentrated in vacuo to afford 28.7 g (81%) of **36** as a colorless liquid. Analysis by GC (30 m DB-5, 75°C, 37 cm/sec) afforded a 99:1 ratio of (3E)-**36** (t_r = 4.61 min) to (3Z)-**36** (t_r = 4.81 min) and indicated the presence of less than 1% of the S_N2' product (t_r = 3.52 min).

(3E)-**36**: IR (neat) 2980, 2945, 2880, 1460, 1440, 1380, 1215, 1200 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 5.58 (br t, J = 7.2 Hz, 1H, C_4-H), 3.96 (s, 2H, CH_2Br), 2.4-1.9 (m, 4H, C_2-H_2, C_5-H_2), 1.03, 1.00 (overlapping t's, J = 7.2, 7.8 Hz, 6H, C_1-H_3, C_6-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 137.1, 133.2, 39.3, 21.3, 21.3, 13.9, 13.0.

(4S)-3-((2R,4E)-1-Oxo-2-methyl-4-ethylhept-4-enyl)-4-(1-methylethyl)-2-oxazolidinone (35). A magnetically stirred, cooled (-78°C) solution of lithium diisopropylamide [LDA, prepared from 14.0 mL (10.1 g, 100 mmol) of diisopropylamine and 57 mL (1.76 M in hexane, 100 mmol) of n-butyllithium] (0.5 M in THF) was used to enolize 18.5 g (100 mmol) of imide **21a**. After stirring for 0.5 h at -78°C, the resultant lithium enolate was treated with 35 g (198 mmol) of allylic bromide **36** for 18 h at -35°C. The reaction was quenched by addition of half-saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the product extracted into dichloromethane (3x). The combined organic extracts were successively washed with 1 M aqueous sodium bisulfate, 1 M aqueous potassium bisulfate (2x), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 55 g of a yellow oil. Analysis by GC (30 m DB-1, 150°C, 104 cm/sec) afforded a 98.5:1.5 ratio of (2R)-**35** (t_r = 6.80 min) to (2S)-**35** (t_r = 5.98 min). The title compound was isolated by liquid chromatography (Waters Prep-500, two 5 x 30 cm silica gel columns, 9:1 hexanes/ethyl acetate, 250 mL/min, minor isomer eluted first) in two portions to afford 18.3 g (65%) of (2R)-**35** as a colorless liquid [(2R)-**35**:(2S)-**35** > 99:1]: IR (neat) 2970, 2940, 2880, 1780, 1700, 1455, 1385, 1300, 1240, 1200 cm^{-1}; ^1H NMR ($CDCl_3$/200 MHz) δ 5.13 (br t, J = 7.2 Hz, 1H, $C_{5'}$-H), 4.50-4.42 (m, 1H, C_4-H),

4.31-4.15 (m, 2H, C_5-$\underline{H}_2$), 4.01 (septet, J = 7.0 Hz, $C_{2'}$-$\underline{H}$), 2.53 (d of d, J = 13.4, 7.1 Hz, 1H, $C_{3'}$-$\underline{H}$), 2.34-2.26 (m, 1H, C_4-C$\underline{H}$), 2.12-1.92 (m, 5H, $C_{3'}$-$\underline{H}$, $C_{4'}$-C$\underline{H}_2$, $C_{6'}$-$\underline{H}_2$), 1.10 (d, J = 6.7 Hz, 3H, $C_{2'}$-C$\underline{H}_3$), 1.00-0.83 (m, 12H, CH(C$\underline{H}_3$)$_2$, $CH_2C\underline{H}_3$, C_7-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 177.1, 153.7, 137.6, 128.7, 63.1, 58.4, 40.8, 35.9, 28.5, 22.7, 20.9, 17.9, 16.6, 14.7, 14.5, 13.2; Specific rotation $[\alpha]_{589}$ = +60.8°, $[\alpha]_{577}$ = +63.4°, $[\alpha]_{546}$ = +72.4°, $[\alpha]_{435}$ = +123.5°, $[\alpha]_{365}$ = +195.2°, (c 1.68, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 9:1 isooctane/ethyl acetate, 4.0 mL/min) k' = 2.48; TLC (8:2 hexanes/ethyl acetate) R_f = 0.54.

Anal. Calcd. for $C_{16}H_{27}NO_3$: C, 68.28; H, 9.67; N, 5.00. Found: C, 68.37; H, 9.59; N, 4.99.

Mixed fractions from the previous chromatography were purified by MPLC (column B, 9:1 hexanes/ethyl acetate, 4 mL/min) to afford 150 mg (0.5%) of (2S)-**35** as a colorless liquid [(2R)-**35**:(2S)-**35** = 1:99]: IR (neat) 2970, 2940, 2880, 1780, 1700, 1460, 1385, 1300, 1240, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$/90 MHz) δ 5.1 (br t, J = 7.2 Hz, 1H, $C_{5'}$-$\underline{H}$), 4.5-4.3 (m, 1H, C_4-$\underline{H}$), 4.3-4.1 (m, 2H, C_5-$\underline{H}_2$), 3.95 (septet, J = 7.0 Hz, 1H, $C_{2'}$-$\underline{H}$), 2.6-2.2 (m, 2H, C_4-C$\underline{H}$, $C_{3'}$-$\underline{H}$), 2.1-1.8 (m, 5H, $C_{3'}$-$\underline{H}$, $C_{4'}$-C$\underline{H}_2$, $C_{6'}$-$\underline{H}_2$), 1.17 (d, J = 7.2 Hz, 3H, $C_{2'}$-C$\underline{H}_3$), 1.0-0.8 (m, 12H, CH(C$\underline{H}_3$)$_2$, $CH_2C\underline{H}_3$, $C_{7'}$-$\underline{H}_3$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 177.2, 153.7, 137.6, 128.5, 63.2, 58.5, 39.9, 35.9, 28.5, 22.9, 20.9, 17.9, 17.4, 14.6, 14.6, 13.3; Specific rotation $[\alpha]_{589}$ = +84.0°, $[\alpha]_{577}$ = +87.1°, $[\alpha]_{546}$ = +99.4°, $[\alpha]_{435}$ = +169.0°, $[\alpha]_{365}$ = +268.7°, (c 1.80, CH_2Cl_2).

Anal. Calcd. for $C_{16}H_{27}NO_3$: C, 68.28; H, 9.67; N, 5.00. Found: C, 68.37; H, 9.59; N, 4.92.

(2R,4E)-2-methyl-4-ethylhept-4-en-1-ol (38). To a magnetically stirred, cooled (0°C) suspension of 1.90 g (50.1 mmol) of lithium aluminum hydride in 60 mL of THF was added a solution of 12.3 g (43.7 mmol) of alkylated imide (2R)-**35** in 40 mL of THF dropwise over a 0.5 h period. The mixture was stirred for 3 h at 0°C. Excess hydride was decomposed by the cautious addition of 10 mL of ethyl acetate. The aluminum salts were dissolved in 100 mL of 6 M aqueous hydrochloric acid and the product extracted into dichloromethane (3x). The combined organic extracts were sequentially washed with 1 M aqueous hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 16 g of a pale yellow oil. Flash chromatography (6 x 25 cm column, 85:15 hexanes/ethyl acetate) followed by distillation (Kugelrohr, 95°C, 3 mm) afforded 6.45 g (95%) of **38** as a colorless liquid. Further elution of the column with ethyl acetate afforded 4.8 g (85%) of (4S)-valinol derived 2-oxazolidinone.

38: IR (neat) 3500-3200, 2970, 2940, 2880, 1460, 1375, 1030 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 5.06 (br t, J = 7.2 Hz, 1H, C_5-H), 3.4 (br s, 2H, C_1-H_2, (with D_2O, d, J = 6 Hz)), 2.2-1.5 (m, 8H, OH, C_2-H, C_3-H_2, C_4-CH_2, C_6-H_2), 1.1-0.8 (m, 9H, C_2-CH_3, CH_2CH_3, C_7-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 138.9, 128.1, 68.6, 41.1, 33.9, 22.9, 20.9, 16.8, 14.8, 13.3; Specific rotation $[\alpha]_{589}$ = -1.22°, $[\alpha]_{577}$ = -1.65°, $[\alpha]_{546}$ = -2.13°, $[\alpha]_{435}$ = -4.41°, $[\alpha]_{365}$ = -8.90°, (neat, d = 0.84 g/mL); GC (30 m DB-5, 75°C, 33 cm/sec) t_r = 15.69 min; TLC (8:2 hexanes/ethyl acetate) R_f = 0.41.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.82; H, 12.77.

(2R,4E)-2-Methyl-4-ethylhept-4-enal (39). To a magnetically stirred, cooled (-60°C) solution of 3.0 mL (3.03 g, 38.8 mmol) of dimethyl sulfoxide in 30 mL of dichloromethane was added 1.9 mL (2.76 g, 21.8 mmol) of oxalyl chloride dropwise *via* syringe (exothermic, gas evolved) followed after 5 min by 2.78 g (17.8 mmol) of alcohol **38.** The resultant white mixture was stirred for 15 min at -60°C followed by the addition of 7.5 mL (5.45 g, 53.8 mmol) of triethylamine. The thick white mixture was warmed to -30°C and stirred for 45 min. The reaction mixture was partitioned between pentane and water. The pentane solution was sequentially washed with 1 *M* aqueous sodium bisulfate (2x), water (2x), and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 2.9 g of a colorless liquid. The title compound was purified by flash chromatography (4 x 25 cm column, 98:2 hexanes/ethyl acetate) followed by distillation (Kugelrohr, 110°C, 10 mm) to afford 2.58 g (94%) of **39** as a colorless liquid: IR (neat) 2980, 2940, 2880, 2720, 1730, 1460, 1440, 1375, 785 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 9.6 (d, J = 2 Hz, 1H, C*H*O), 5.13 (br t, J = 7.2 Hz, 1H, C_5-*H*), 2.6-2.3 (m, 2H, C_2-*H*, C_3-*H*), 2.2-1.8 (m, 5H, C_3-*H*, C_4CH_2, C_6-H_2), 1.2-0.8 (m, 9H, C_2-CH_3, CH_2CH_3, C_7-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 204.9, 136.7, 129.1, 44.5, 37.8, 22.9, 21.0, 14.6, 13.4, 13.1; Specific rotation $[\alpha]_{589}$ = -16.2°, $[\alpha]_{577}$ = -18.5°, $[\alpha]_{546}$ = -22.5°, $[\alpha]_{435}$ = -59.8°, $[\alpha]_{365}$ = -190.9°, (neat, d = 0.84 g/mL); GC (30 m DB-5, 75°C, 32 cm/sec) t_r = 10.72 min; TLC (98:2 hexanes/ethyl acetate) R_f = 0.18.

Ethyl 2-(Triphenylphosphoranylidene)propanoate (Carboethoxyethylidene triphenylphosphorane). A magnetically stirred mixture of 65.6 g (0.250 mol) of triphenylphosphine and 32.5 mL (45.3 g, 0.250 mol) of

ethyl 2-bromopropanoate was heated at 85°C for 20-30 min (until the mixture began to turn dark red). After cooling to room temperature, the reaction mixture was dissolved in 500 mL of dichloromethane. The solution was sequentially washed with 2.5 M aqueous potassium hydroxide (3 x 100 mL) and water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was dissolved in 250 mL of hot ethyl acetate, slowly cooled to room temperature and the product allowed to crystallize, affording 66 g (73%) of the phosphorane as a yellow crystalline solid: ^{1}H NMR (CDC_3/90 MHz) δ 7.8-7.3 (m, 15H, aromatic H's), 3.8 (br q, J = 7 Hz, 2H, $OC\underline{H}_2CH_3$), 1.2 (d, J = 14 Hz, 3H, $CC\underline{H}_3$), 0.8-0.5 (br s, 3H, $OCH_2C\underline{H}_3$).

Ethyl (2E,4R,6E)-2,4-Dimethyl-6-ethylnon-2,6-dienoate (34). A magnetically stirred solution of 30 g (83 mmol) of carboethoxyethylidene triphenylphosphorane and 10.4 g (67.7 mmol) of aldehyde **39** in 50 mL of dichloromethane was heated at 40°C for 12 h. The mixture was cooled to room temperature and added directly to the top of a 6 x 25 cm column of silica gel. The column was eluted with 95:5 hexanes/ethyl acetate to afford 14.9 g (93% mass balance) of **34** as a colorless liquid. Analysis by GC (30 m DB-5, 100°C for 5 min, 25°C/min to 200°C, 33 cm/sec) afforded a 97:3 ratio of (2E)-**34** (t_r = 9.78 min) to (2Z)-**34** (t_r = 9.14 min).

In a separate experiment, run in refluxing benzene, a 95:5 ratio of (2E)-**34** to (2Z)-**34** was obtained. The two isomers were separated by MPLC (1.55 g sample, column C, 98:2 hexanes/ethyl acetate, 10 mL/min, (2E)-**34** elutes second) followed by distillation (Kugelrohr, 100°C, 0.008 mm) to

afford 1.26 g (81%) of (2E)-**34** as a colorless liquid [(2E)-**34**:(2Z)-**34** > 99:1] and 25 mg of (2Z)-**34** as a colorless liquid [(2E)-**34**:(2Z)-**34** = 2:98].

(2E)-**34**: IR (neat) 2970, 2940, 2880, 1715, 1650, 1460, 1365, 1270, 1250, 1210, 1125, 1105, 785 cm^{-1}; ^1H NMR ($CDCl_3$/200 MHz) δ 6.54 (br d, J = 9.9 Hz, 1H, C_3-H), 5.07 (br t, J = 7.0 Hz, 1H, C_7-H), 4.22 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.66 (d of q, J = 10, 7 Hz, 1H, C_4-H), 2.06-1.92 (m, 6H, C_5-H_2, C_6-CH_2, C_8-H_2), 1.82 (s, 3H, C_2-CH_3), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.99-0.88 (m, 9H, C_4-CH_3, C_6-CH_2CH_3, C_9-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 168.3, 147.9, 137.8, 128.6, 126.1, 60.3, 43.6, 32.0, 23.0, 21.0, 19.6, 14.6, 14.4, 13.3, 12.5; Specific rotation $[\alpha]_{589}$ = -18.6°, $[\alpha]_{577}$ = -20.6°, $[\alpha]_{546}$ = -23.1°, $[\alpha]_{435}$ = -40.7°, $[\alpha]_{365}$ = -66.0°, (neat, d = 0.884 g/mL); TLC (95:5 hexanes/ethyl acetate) R_f = 0.29.

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.80; H, 10.92.

(2Z)-**34**: ^1H NMR ($CDCl_3$/200 MHz) δ 5.63 (br d, J = 9.6 Hz, 1H, C_3-H), 5.03 (br t, J = 7.2 Hz, 1H, C_7-H), 4.17 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.4-3.1 (m, 1H, C_4-H), 2.1-1.9 (m, 6H, C_5-H_2, C_6-CH_2, C_8-H_2), 1.85 (s, 3H, C_2-CH_3), 1.28 (t, J = 7.0 Hz, OCH_2CH_3), 1.0-0.8 (m, 9H, C_4-CH_3, C_6-CH_2CH_3, C_9-H_3).

(2E,4R,6E)-2,4-Dimethyl-6-ethylnon-2,6-dien-1-ol (40). To a mechanically stirred, cooled (-78°C) solution of 11.8 g (49.5 mmol) of **34** [(2E)-**34**:(2Z)-**34** = 97:3] in 100 mL of dichloromethane was added 110 mL (1.0 M in hexane, 110 mmol) of diisobutylaluminum hydride dropwise over

a 1 h period. After 0.5 h at -78°C and 1 h at -20°C the reaction was quenched by the cautious addition of 20 mL of methanol followed by 240 mL of 0.5 M aqueous sodium potassium tartrate. The resultant thick white mixture was stirred at room temperature until two clear homogeneous phases were obtained (ca. 6 h). The layers were separated, and the aqueous phase extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 9.9 g (102% mass balance) of a colorless liquid. Molecular distillation (Kugelrohr, 110°C, 0.08 mm) afforded 9.6 g (99%) of allylic alcohol **40**. Analysis by GC (30 m DB-5, 150°C, 31 cm/sec) afforded a 97:3 ratio of (2E)-**40** (t_r = 4.29 min) to (2Z)-**40** (t_r = 3.98 min). An analytical sample was obtained after purification by MPLC (column B, 9:1 hexanes/ethyl acetate, 3 mL/min, (2Z)-**40** eluted first) to afford (2E)-**40** as colorless liquid [(2E)-**40**:(2Z)-**40** > 99:1]: IR (neat) 3500-3200, 2980, 2880, 1460, 1375, 1070, 1010 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 5.17 (br d, J = 9 Hz, 1H, C_3-H), 5.03 (br t, J = 7 Hz, 1H, C_7-H), 3.93 (br d, J = 5 Hz, 2H, C_2-H_2), 2.52 (d of q, J = 10, 7 Hz, 1H, C_4-H), 2.2-1.8 (m, 7H, OH, C_5-H_2, C_6-CH_2, C_8-H_2), 1.63 (s, 3H, C_2-CH_3), 1.1-0.8 (m, 9H, C_4-CH_3, C_6-CH_2CH_3, C_9-H_3); ^{13}C NMR ($CDCl_3$/50 MHz) δ 138.53 (s, C_2), 133.03 (s, C_6), 132.98 (d, C_8), 127.96 (d, C_3), 60.03 (t, C_1), 44.36 (t, C_5), 30.51 (d, C_4), 22.9 (t, C_6-CH_2), 20.9 (t, C_8), 20.4 (q, C_2-CH_3), 14.7, 13.8, 13.3 (q, q, q, C_4-CH_3, C_6-CH_2CH_3, C_9); Specific rotation $[\alpha]_{589}$ = +4.61°, $[\alpha]_{577}$ = +4.73°, $[\alpha]_{546}$ = +5.52°, $[\alpha]_{435}$ = +14.0°, $[\alpha]_{365}$ = +32.0°, (neat, d = 0.841 g/mL); TLC (8:2 hexanes/ethyl acetate) R_f = 0.46.

Anal. Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.68; H, 12.30.

(2E,4R,6E)-1-Bromo-2,4-dimethyl-6-ethylnon-2,6-diene (41a). To a magnetically stirred mixture of 1.96 g (10.0 mmol) of allylic alcohol **40** [(2E)-**40**:(2Z)-**40** = 97:3] and 5.25 g (20.0 mmol) of triphenylphosphine in 20 mL of acetonitrile was added 6.63 g (20.0 mmol) of carbon tetrabromide (sublimed prior to use). The triphenylphosphine dissolved and the mixture turned orange in an exothermic reaction. After 15 min the reaction was quenched by addition of 1 mL of methanol. The mixture was stirred for 0.5 h then partitioned between pentane and water. The aqueous phase was extracted with pentane (3x). The combined organic extracts were sequentially washed with water and brine, filtered through 15 g of silica gel, and concentrated <u>in vacuo</u> (< 1 mm, 30°C, until no bromoform is detected by GC or ^{1}H NMR) to afford 2.32 g (90%) of allylic bromide **41a** as a colorless liquid: ^{1}H NMR ($CDCl_3$/90 MHz) δ 5.35 (br d, J = 9 Hz, 1H, C_3-<u>H</u>), 5.02 (br t, J = 7.2 Hz, 1H, C_7-<u>H</u>), 3.92 (s, 2H, C_2-<u>H</u>$_2$), 2.47 (d of q, J = 10, 7 Hz, 1H, C_4-<u>H</u>), 2.2-1.8 (m, 6H, C_5-<u>H</u>$_2$, C_6-C<u>H</u>$_2$, C_8-<u>H</u>$_2$), 1.72 (s, 3H, C_2-C<u>H</u>$_3$), 1.0-0.8 (m, 9H, C_4-C<u>H</u>$_3$, C_6-CH$_2$C<u>H</u>$_3$, C_9-<u>H</u>$_3$); GC (30 m DB-1, 150°C, 35 cm/sec) t_r = 4.47 min; TLC (9:1 hexanes/ethyl acetate) R_f = 0.80.

Methyltriphenoxyphosphonium iodide.[38] A magnetically stirred mixture of 9.2 mL (21.0 g, 148 mmol) of methyl iodide and 26 mL (30.8 g, 99.3 mmol) of triphenyl phosphite was heated at reflux in an oil bath at 120°C. The pot temperature rose from 65 to 115°C over a 24 h period. After cooling to room temperature, 100 mL of diethyl ether was added and the two-phase mixture stirred until the lower phase solidified. The etheral solution was discarded and the solid exhaustively washed with hot, anhydrous ethyl acetate. Excess ethyl acetate was removed <u>in vacuo</u>

to afford 34 g (75%) of the title compound as a yellow crystalline solid: ^{1}H NMR (Dry $CDCl_3$/90 MHz) δ 7.45 (s, 10H, aromatic H's), 3.15 (d, J = 17 Hz, 3H, $C\underline{H}_3$). The product was handled and stored with rigorous protection from moisture and light in a dry box. If prior to use, the phosphonium iodide turned brown or ^{1}H NMR analysis indicated the presence of $(PhO)_2P(O)CH_3$ [δ 1.8 (d, J = 18 Hz)], it was washed with hot, anhydrous ethyl acetate.

(2E,4R,6E)-1-Iodo-2,4-dimethyl-6-ethylnon-2,6-diene (41b). To a magnetically stirred, cooled (20°C) solution of 18.4 g (40.7 mmol)of methyltriphenoxyphosphonium iodide in 40 mL of dimethylformamide was added 8.00 g (40.7 mmol) of allylic alcohol **40** [(2E)-**40**:(2Z)-**40** = 97:3] dropwise over a 5 min period. After 20 min at room temperature the mixture was partitioned between pentane (100 mL) and cold 1 M aqueous sodium hydroxide (100 mL). The aqueous layer was extracted with two portions of pentane. The combined organic extracts were sequentially washed with cold 1 M aqueous sodium hydroxide (1 x 100 mL), cold water (1 x 100 mL), and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford 14.0 g (112% mass balance) of a pale yellow liquid. ^{1}H NMR analysis afforded a 95:5 ratio of (2E)-**41b** to (2Z)-**41b** and indicated the presence of ca. 10% of $(PhO)_2P(O)CH_3$. ^{1}H NMR ($CDCl_3$/90 MHz) δ 5.43 (br d, J = 9 Hz, 1H, C_3-$\underline{H}$), 5.03 (br t, J = 7.2 Hz, 1H, C_7-$\underline{H}$), 3.89 (s, 2H, C_2-$\underline{H}_2$), 2.47 (d of q, J = 10, 7 Hz, 1H, C_4-$\underline{H}$), 2.2-1.8 (m, 6H, C_5-$\underline{H}_2$, C_6-$C\underline{H}_2$, C_8-$\underline{H}_2$), 1.72 (s, 3H, C_2-$C\underline{H}_3$), 1.0-0.8 (m, 9H, C_4-$C\underline{H}_3$, C_6-$CH_2C\underline{H}_3$, C_9-$\underline{H}_3$). In a separate experiment it was observed that the $(PhO)_2P(O)CH_3$ could be removed from the allylic alco-

hol by passing a pentane solution of the mixture through a silica gel column. However, between 5 and 40% olefin isomerization occurred. The unpurified product is therefore used immediately in the next experiment, without further purification, in order to avoid excessive olefin isomerization.

(4R,5S)-3-((2S,4E,6R,8E)-1-Oxo-2,4,6-trimethyl-8-ethylundec-4,8-dienyl)-4-methyl-5-phenyl-2-oxazolidinone (33). A magnetically stirred, cooled (-78°C) solution of 22.4 g (122 mmol) of sodium hexamethyldisilylamide (0.75 M in THF) was used to enolize 28.5 g (122 mmol) of imide **20a**. After stirring for 0.5 h at -78°C, the resultant sodium enolate was alkylated with ca. 12.5 g (40.7 mmol) of allylic iodide **41a** for 0.5 h at -78°C then 4 h at -30°C. The reaction was quenched by the addition of half-saturated aqueous ammonium chloride. Volatiles were removed *in vacuo* and the product extracted into dichloromethane (3x). The combined organic extracts were sequentially washed with 1 M aqueous sodium bisulfate, 1 M aqueous potassium bicarbonate and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 41 g of a yellow oil. This material was prepurified by flash chromatography (8 x 25 cm silica gel column, 9:1 hexanes/ethyl acetate) to afford 28 g of a colorless oil. The title compound was isolated by chromatography (Waters Prep-500, two 5 x 30 cm silica gel columns, 95:5 hexanes/ethyl acetate, 250 mL/min) in two portions to afford 26 g (78% based on allylic alcohol **40**) of a colorless liquid. Analysis by GC (30 m DB-5, 250°C, 78 cm/sec) indicated the product to be ca. 93% alkylated imide **33** (t_r = 5.69 min), and contain ca. 7% of two unidentified minor isomers (t_r = 4.90 min, 5.45 min). An analytical sample was prepared by MPLC

(column C, 95:5 hexanes/ethyl acetate, 10 mL/min, minor isomers elute first) to afford alkylated imide **33** as a colorless liquid (>99% **33**): IR (CH_2Cl_2) 3060, 2979, 2940, 2880, 1780, 1700, 1450, 1385, 1370, 1340, 1240, 1200, 1120 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.4-7.2 (m, 5H, aromatic H's), 5.658 (d, J = 7.2 Hz, 1H, C_5-H), 5.034 (br t, J = 7.2 Hz, 1H, $C_{9'}$-H), 4.952 (br d, J = 9.4 Hz, 1H, $C_{5'}$-H), 4.779 (qn, J = 6.8 Hz, 1H, C_4-H), 3.98-3.91 (m, 1H, $C_{2'}$-H), 2.53-2.45 (m, 1H, $C_{6'}$-H), 2.03-1.85 (m, 8H, $C_{3'}$-H_2, $C_{7'}$-H_2, $C_{8'}$-CH_2, $C_{10'}$-H_2), 1.656 (d, J = 1.5 Hz, 3H, $C_{4'}$-CH_3), 1.092 (d, J = 6.8 Hz, $C_{2'}$-CH_3), 0.942, 0.926 (overlapping t's, J = 8.0, 8.2 Hz, 6H, $C_{8'}$-CH_2CH_3, $C_{11'}$-H_3), 0.865, 0.856 (overlapping d's, J = 6.8, 7.0 Hz, C_4-CH_3, $C_{6'}$-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 176.9, 152.7, 138.7, 134.6, 133.7, 130.1, 128.7, 127.7, 125.8, 78.7, 54.8, 44.7, 43.9, 35.9, 30.9, 22.9, 20.9, 16.2, 15.7, 14.8, 13.3; Specific rotation $[\alpha]_{589}$ = +22.9°, $[\alpha]_{577}$ = +23.8°, $[\alpha]_{546}$ = +27.6°, $[\alpha]_{435}$ = +50.9°, $[\alpha]_{365}$ = +92.1°, (c 5.77, CH_2Cl_2); HPLC (8 mm x 10 cm Radial Pak (5 m silica gel), 96:4 isooctane/ethyl acetate, 2.0 mL/min) k' = 5.01, note: k' minor isomers = 2.28, 4.48; TLC (8:2 hexanes/ethyl acetate) R_f = 0.64.

Anal. Calcd. for $C_{26}H_{37}NO_3$: C, 75.87; H, 9.06; N, 3.40. Found: C, 75.80; H, 8.91; N, 3.40.

(2S,4E,6R,8E)-2,4,6-Trimethyl-8-ethylundec-4,8-dienyl-1-ol (42). To a magnetically stirred, cooled (-30°C) solution of 75 mL (1.0 M in THF, 75 mmol) of lithium aluminum hydride was added a solution of 21.5 g (52.4 mmol) of alkylated imide **33** (93% by GC) in 50 mL of THF dropwise over a 0.5 h period. The reaction mixture was allowed to warm to room

temperature over a 2 h period. After recooling to -10°C, the excess lithium aluminum hydride was quenched by the cautious dropwise addition of 10 mL of ethyl acetate followed by 150 mL of 2 M aqueous hydrochloric acid. The product was extracted into dichloromethane. The combined organic extracts were sequentially washed with 1 M aqueous hydrochloric acid and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give 23.0 g of a mixture of norephedrine oxazolidinone and the product as a white solid and a colorless liquid. The liquid was purified by flash chromatography (6 x 25 cm silica gel column, 9:1 hexanes/ethyl acetate) followed by molecular distillation (Kugelrohr, 110°C, 0.01 mm) to afford) 11.8 g (94%) of alcohol **42** as a colorless liquid. Analysis by GC (30 m DB-5, 150°C, 30 cm/sec) indicated the product to be ca. 97% **42** (t_r = 10.34 min) and contain ca. 3% of an unidentified minor isomer. The solid, when combined with material obtained by eluting the column with diethyl ether, afforded 7.4 g (80%) of norephedrine-derived 2-oxazolidinone. An analytical sample of **42** was obtained after purification by MPLC (column B, 9:1 hexanes/ethyl acetate, 4 mL/min) followed by molecular distillation (Kugelrohr, 110°C, 0.01 mm) to afford a colorless liquid (>99% major isomer by GC): IR (neat) 3500-3200, 2970, 2940, 2880, 1450, 1380, 1040 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 5.03 (br t, J = 7.2 Hz, 1H, C_9-H), 4.92 (d, J = 9.2 Hz, 1H, C_5-H), 3.5 (br s, 2H, C_1-H_2), 2.5 (d of q, J = 10, 7 Hz, 1H C_6-H), 2.2-1.7 (m, 10H, OH, C_2-H, C_3-H_2, C_7-H_2, C_8-CH_2, C_{10}-H_2), 1.58 (s, 3H, C_4-CH_3), 1.1-0.8 (m, 12H, C_2-CH_3, C_6-CH_3, C_8-CH_2CH_3, C_{11}-H_3); ^{13}C NMR ($CDCl_3$/50 MHz) 138.77 (s), 133.45 (d), 131.60 (s), 127.63 (d), 68.68 (t), 44.90 (t), 44.60 (t), 33.60 (d), 30.73 (d), 22.82 (t), 20.84 (q, t), 16.59 (q), 16.04 (q), 14.72 (q), 13.26 (q); Specific rotation $[\alpha]_{589}$ = +13.6°, $[\alpha]_{577}$ =

+15.2°, $[\alpha]_{546}$ = +17.4°, $[\alpha]_{435}$ = +37.3°, $[\alpha]_{365}$ = +75.0°, (neat, d = 0.847 g/mL); TLC (8:2 hexanes/ethyl acetate) R_f = 0.47.

Anal. Calcd. for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.52; H, 12.60.

(2S,4E,6R,8E)-2,4,6-Trimethyl-8-ethylundec-4,8-dien-1-al (43). To a magnetically stirred, cooled (-60°C) solution of 0.86 mL (0.95 g, 12.1 mmol) of dimethyl sulfoxide in 12 mL of dichloromethane was added 0.53 mL (0.77 g, 6.1 mmol) of oxalyl chloride dropwise via syringe (exothermic, gas evolved) followed after 5 mL by 1.31 mL of alcohol **42**. The resultant white mixture was stirred for 15 min at -60°C followed by the addition of 2.3 mL (1.65 g, 16.5 mmol) of triethylamine. The thick white mixture was warmed to -30°C and stirred for 0.5 h. The reaction mixture was partitioned between pentane and water. The pentane solution was sequentially washed with 1 M aqueous sodium bisulfate (2x), water (2x), and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford 1.28 g (98%) of aldehyde **43** as a colorless liquid. Analysis by GC (30 m DB-5, 150°C, 30 cm/sec) indicated the product to be ca. 97% **43** (t_r = 8.09 min) and contained ca. 3% of an unidentified minor isomer (t_r = 7.17 min). The aldehyde was used immediately without purification to avoid epimerization. ^1H NMR ($CDCl_3$/90 MHz) δ 9.53 (d, J = 2 Hz, 1H, C$\underline{H}$O), 4.97 (br t, J = 7.2 Hz, 1H, C_9-$\underline{H}$), 4.87 (d, J = 9.2 Hz, 1H, C_5-$\underline{H}$), 2.6-2.2 (m, 2H, C_2-$\underline{H}$, C_6-$\underline{H}$), 2.1-1.7 (m, 8H, C_3-$\underline{H}_2$, C_7-$\underline{H}_2$, C_8-C$\underline{H}_2$, C_{10}-$\underline{H}_2$), 1.57 (s, 3H, C_4-C$\underline{H}_3$), 1.1-0.8 (m, 12H, C_2-C$\underline{H}_3$, C_6-C$\underline{H}_3$, C_8-CH$_2$C$\underline{H}_3$, C_{11}-$\underline{H}_3$).

(4R,5S)-3-((2R,3S,4S,6E,8R,10E)-1-Oxo-2,10-diethyl-3-hydroxy-4,6,8-trimethyltridec-8,10-dienyl)-4-methyl-5-phenyl-2-oxazolidinone (32). To a magnetically stirred, cooled (-78°C) solution of 2.55 g (10.3 mmol) of imide **20b** (0.8 M in dichloromethane) was added 2.86 mL (3.12 g, 11.4 mmol) of di-n-butylboryl triflate dropwise over a 5 min period. After 5 min, 1.72 mL (1.25 g, 12.3 mmol) of triethylamine was added. The mixture was stirred at 0°C for 1 h then recooled to -78°C. To the boryl enolate solution was added 1.95 g (8.25 mmol) of aldehyde **43** (97:3 ratio by GC) dropwise over a 5 min period. After 0.5 h at -78°C and 2 h at 0°C the reaction was quenched by the addition of 10 mL of aqueous pH 7 phosphate buffer in 30 mL of methanol followed by 10 mL of 30% aqueous hydrogen peroxide in 30 mL of methanol. The mixture was stirred at 0°C for 2 h. The mixture was concentrated in vacuo and the product extracted into dichloromethane. The combined organics were sequentially washed with 1 M aqueous potassium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford 4.95 g (124% mass balance) of a colorless viscous oil. Analysis by GC (trimethylsilylated sample (Et_2NSiMe_3, DMAP, CH_2Cl_2, 4 h), 30 m DB-5, 250°C, 71 cm/sec, (injector, detector = 275°C)) afforded a 2.6:4.2:92.9:0.4 mixture of diastereomers (t_r = 10.94, 12.47, 12.86, 15.93 min respectively) and indicated the presence of ca. 25% of imide **20b** (t_r = 1.04 min). Analysis by HPLC (8 mm x 10 cm Waters Radial Pak (5 μm silica gel), 85:15 isooctane/ethyl acetate, 1.0 mL/min) afforded the following order of elution: k' **20b** = 1.20, k' minor isomer = 1.53, k' minor isomer = 2.06, k' minor isomer = 2.33, k' **32** = 2.76. MPLC separation of the crude mixture (column C, 85:15 hexanes/ethyl acetate, 10 mL/min) afforded 0.19 g (9.7%) of recovered aldehyde **43** (mixture of diastereomers at C_2, GC (30

m DB-5, 150°C, 31 cm/sec, t_r (2R)-**43** = 7.87 min, ca. 39%; t_r (2S)-**43** = 8.00 min, ca. 61%)), 0.85 g of a mixture of imide **20b** and the minor isomers, and 3.27 g (82%) of **32** as a colorless oil (GC, same conditions as above, 4:96 ratio of t_r = 12.47 min to t_r = 12.86 min): IR (CH_2Cl_2) 3540 (br), 3060, 2980, 2940, 2880, 1785, 1690, 1460, 1385, 1370, 1340, 1235, 1200 cm^{-1}; ^1H NMR ($CDCl_3$ /500 MHz) δ 7.4-7.2 (m, 5H, aromatic H's), 5.658 (d, J = 7.2 Hz, 1H, C_5-H), 5.074 (br t, J = 7.1 Hz, 1H, $C_{11'}$-H), 4.950 (br d, J = 9.0 Hz, $C_{7'}$-H), 4.779 (qn, J = 7.1 Hz, 1H, C_4-H), 3.98-3.91 (m, 1H, $C_{2'}$-H), 2.52-2.45 (m, 2H, $C_{3'}$-H, $C_{8'}$-H), 2.03-1.85 (m, 12H, OH, $C_{2'}$-CH_2, $C_{4'}$-H, $C_{5'}$-H_2, $C_{9'}$-H_2, $C_{10'}$-CH_2, $C_{12'}$-H_2), 1.660 (s, 3H, $C_{6'}$-CH_3), 1.090 (d, J = 7.1 Hz, 3H, C_4-CH_3), 0.95-0.84 (m, 15H, $C_{2'}$-CH_2CH_3, $C_{4'}$-CH_3, $C_{8'}$-CH_3, $C_{10'}$-CH_2CH_3, $C_{13'}$-H_3); ^{13}C NMR ($CDCl_3$/50 MHz) δ 176.65 (s), 152.72 (s), 138.82 (s), 133.91 (d), 133.15 (s), 131.59 (s), 128.84 (d), 128.77 (d), 127.59 (d), 125.64 (d), 78.74 (d), 76.74 (d), 55.08 (d), 46.44 (d), 43.53 (t), 34.36 (d), 30.78 (d), 22.83 (t), 20.92 (q), 20.87 (t), 19.14 (t), 15.94 (q), 15.33 (q), 14.75 (q), 14.50 (q), 13.27 (q), 11.73 (q); Specific rotation $[\alpha]_{589}$ = +3.33°, $[\alpha]_{577}$ = +3.49°, $[\alpha]_{546}$ = +4.33°, $[\alpha]_{435}$ = +9.67°, $[\alpha]_{365}$ = +21.9° (c 3.90, CH_2Cl_2); TLC (7:3 hexanes/ethyl acetate) R_f = 0.59.

Anal. Calcd. for $C_{30}H_{45}NO_4$: C, 74.50; H, 9.38; N, 2.90. Found: C, 74.30; H, 9.13; N, 2.86.

(4S)-3-((2S,3R,4R,6E)-1-Oxo-2,4-dimethyl-3-hydroxy-6-ethylnon-6-enyl)-4-(1-methylethyl)-2-oxazolidinone (44). To a magnetically stirred, cooled (-78°C) solution of 0.932 g (5.03 mmol) of imide **21a** in 10 mL of dichloromethane was added 1.30 mL (1.42 g, 5.17 mmol) of di-n-

butylboryl triflate. After 10 min, 0.84 mL (0.61 g, 6.0 mmol) of triethylamine was added and the mixture warmed to 0°C. The solution was stirred for 0.5 h and cooled to -78°C, followed by the addition of 0.92 g (6.0 mmol) of aldehyde **39**. After 0.5 h at -78°C and 1.5 h at 0°C the reaction was quenched by the addition of 5 mL of pH 7 aqueous phosphate buffer in 15 mL of methanol followed by 5 mL of 30% aqueous hydrogen peroxide in 15 mL of methanol. The mixture was stirred for 2 h at 0°C, concentrated in vacuo and the product extracted into dichloromethane. The combined organic extracts were sequentially washed with 1 M aqueous potassium bicarbonate and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 1.85 g (108% mass balance) of a white solid. Analysis of the unfractionated product by GC (trimethylsilyl derivative (Et_2NSiMe_3, DMAP, CH_2Cl_2), 30 m DB-5, 175°C, 83 cm/sec) indicated the presence of only one diastereoisomer (t_r = 17.57 min, > 99%). Recrystallization from pentane/ethyl acetate (3 crops) afforded 1.51 g (88%) of **44** as a white crystalline solid: ^1H NMR ($CDCl_3$/90 MHz) δ 5.10 (br t, J = 7.0 Hz, 1H, $C_{7'}$-H), 4.5-4.1 (m, 3H, C_4-H, C_5-H_2), 3.9 (d of q, J = 2.5, 7.0 Hz, 1H, $C_{2'}$-H), 3.5 (m, 1H, $C_{3'}$-H), 3.0 (d, J = 3 Hz, 1H, OH), 2.5-1.4 (m, 8H, C_4-CH_2, $C_{4'}$-H, $C_{5'}$-H_2, C_6-CH_2, $C_{8'}$-H_2), 1.1 (d, J = 7.0 Hz, 3H, $C_{2'}$-CH_3), 1.1-0.8 (m, 12H, $CH(CH_3)_2$, $C_{6'}$-CH_2CH_3, $C_{9'}$-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 177.9, 153.6, 139.1, 128.2, 75.7, 63.4, 58.4, 40.3, 39.9, 34.0, 28.5, 22.9, 21.0, 17.9, 15.3, 14.8, 13.4; TLC (7:3 hexanes/ethyl acetate) R_f = 0.55.

Anal. Calcd. for $C_{19}H_{33}NO_4$: C, 67.21; H, 9.80; N, 4.14. Found: C, 67.28; H, 9.70; N, 4.02.

(2S)-3-((2S)-1-Oxo-2-methyl-2-((3R,5R)-3-methyl-5-ethyl-5-((1S)-1-hydroxypropyl)tetrahydrofuran-2-yl)-4-(1-methylethyl)-2-oxazolidinone (45) and (2S)-3-((2S)-1-Oxo-2-methyl-2-((3R,5S)-3-methyl-5-ethyl-5-((1R)-1-hydroxypropyl)tetrahydrofuran-2-yl)-4-(1-methylethyl)-2-oxazolidinone (46). Vanadyl acetylacetonate--t-butylhydroperoxide epoxidation. To a magnetically stirred solution of 260 mg (0.766 mmol) of **44** and 20 mg (0.075 mmol) of vanadyl acetylacetonate (recrystallized, Alfa) in 5 mL of benzene was added 0.22 mL (4.5 M in benzene, 0.99 mmol) of t-butylhydroperoxide. The blue-green solution turned dark red, then slowly faded to yellow-orange. After 2 h the reaction was quenched by the addition of 0.1 mL of acetic acid and 0.05 mL of dimethyl sulfide. The mixture was stirred at room temperature for 0.5 h. The product was extracted into dichloromethane, sequentially washed with 1 M aqueous hydrochloric acid, 1 M aqueous potassium bicarbonate, and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to give 0.21 g (80%) mass balance of a colorless oil. Analysis of the unfractionated product by GC (30 m DB-5, 200°C, 82 cm/sec) afforded a 92:8 ratio of **45** (t_r = 6.88 min) to **46** (t_r = 6.44 min). The product was isolated by flash chromatography (2 x 25 cm column, 7:3 hexanes/ethyl acetate) to afford 0.194 g (74%) of **45** as a colorless liquid (**45**:**46** > 99:1): ^{1}H NMR ($CDCl_3$/90 MHz) δ 4.6-4.2 (m, 3H, C_4-H, C_5-H_2), 4.0 (d of q, J = 2.5, 7.0 Hz, 1H, $C_{2'}$-H), 3.8-3.6 (m, 2H, $C_{3'}$-H, $C_{7'}$-H), 2.6-1.3 (m, 9H, C_4-CH, $C_{4'}$-H, $C_{5'}$-H_2, $C_{6'}$-CH_2, $C_{7'}$-OH, $C_{8'}$-H_2), 1.2 (d, J = 7.0 Hz, 3H, $C_{2'}$-CH_3), 1.1-0.8 (m, 12H, $CH(CH_3)_2$, $C_{6'}$-CH_2CH_3, $C_{9'}$-H_3); TLC (7:3 hexanes/ethyl acetate) R_f = 0.22.

(2S)-3-((2S)-1-Oxo-2-methyl-2-((3R,5R)-3-methyl-5-ethyl-5-((1S)-1-hydroxypropyl)tetrahydrofuran-2-yl)-4-(1-methylethyl)-2-oxazolidinone (45) and (2S)-3-((2S)-1-Oxo-2-methyl-2-((3R,5S)-3-methyl-5-ethyl-5-((1R)-1-hydroxypropyl)tetrahydrofuran-2-yl)-4-(1-methylethyl)-2-oxazolidinone (46). m-Chloroperbenzoic Acid Epoxidation. To a magnetically stirred, cooled (-20°C) solution of 252 mg (0.741 mmol) of **44** was added 200 mg (ca. 80%, 0.93 mmol) of m-chloroperbenzoic acid in 4 portions over a 0.5 h period. The reaction mixture was stirred at -20°C for 0.5 h then allowed to warm to room temperature. After 4 h, the resultant mixture of epoxides were converted to the corresponding tetrahydrofurans by addition of 0.1 mL of acetic acid and stirring the mixture for 0.5 h. The solution was diluted with dichloromethane, washed with 1 M aqueous potassium carbonate to remove the excess acid, washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 0.24 g of a colorless liquid. Analysis of the unfractionated product by GC (30 m DB-5, 200°C, 82 cm/sec) afforded a 23:77 ratio of **45** (t_r = 6.88 min) to **46** (t_r = 6.44 min). The product was isolated by flash chromatography (2 x 25 cm column, 7:3 hexanes/ethyl acetate) to afford 0.192 g (72%) of **46** as a colorless liquid (**45:46** < 1:99) and 0.051 g (19%) of **45** as a colorless liquid (**45:46** > 99:1).

46: ^{1}H NMR ($CDCl_3$/90 MHz) δ 4.6-4.2 (m, 3H, C_4-H, C_5-H_2), 4.1 (d of q, J = 2.5, 7.0 Hz, 1H, $C_{2'}$-H), 3.8-3.4 (m, 2H, $C_{3'}$-H, $C_{7'}$-H), 2.5-2.1 (m, 5H, C_4-CH, $C_{4'}$-H, $C_{5'}$-H_2, $C_{7'}$-OH), 1.8-1.1 (m, 7H, $C_{2'}$-CH_3, $C_{6'}$-CH_2, $C_{8'}$-H_2), 1.0-0.8 (m, 12H, $CH(CH_3)_2$, $C_{6'}$-CH_2CH_3, $C_{9'}$-H_3); TLC (7:3 hexanes/ethyl acetate) R_f = 0.31.

(4R,5S)-3-((2R)-1-Oxo-2-ethyl-2-((2R,3S,5S)-3,5-dimethyl-5-((1R, 2R,4E)-1-hydroxy-2-methyl-4-ethyl-hept-4-enyl)tetrahydrofuran-2-yl)-4-methyl-5-phenyl-2-oxazolidinone (49). Vanadyl acetylacetonate--t-butylhydroperoxide epoxidation. To a magnetically stirred mixture of 0.520 g (1.08 mmol) of **gt**, 28.5 mg (0.108 mmol) of vanadyl acetylacetonate and 0.25 g of anhydrous sodium acetate in 5 mL of anhydrous benzene at 25°C was added 0.27 mL (4.5 M in benzene, 1.22 mmol) of anhydrous t-butylhydroperoxide. The mixture turned dark red. After 1 h (pale yellow), the reaction was quenched by the addition of 2 mL of a 1:1 mixture of triethylamine and chlorotrimethylsilane. The mixture was stirred for 18 h at 25°C, diluted with dichloromethane, washed with cold water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford 0.77 g of a yellow oil. This material was purified by flash chromatography (3 x 25 cm, 95:5 hexanes/ethyl acetate) to afford 0.26 g (45%) of trimethylsilylated diene **47** [treatment with 5:3:1 THF/water/acetic acid afforded 0.215 g (91%) of **32**] followed by 0.26 g (45%) of trimethylsilylated epoxide **48** [treatment with 5:3:1 THF/water/acetic acid afforded 0.208 g (85%) of **49** as a colorless oil].

49: ^{1}H NMR ($CDCl_3$ + D_2O/500 MHz) δ 7.3-7.5 (m, 5H, aromatic H's), 5.61 (d, J = 7.2 Hz, 1H, C_5-H), 5.11 (t, J = 7.2 Hz, 1H, $C_{5'''}$-H), 4.79 (qn, J = 7.0 Hz, C_4-H), 4.17 (m, 1H, $C_{2'}$-H), 3.66 (d of d, J = 9.5, 6.0 Hz, 1H, $C_{2''}$-H), 3.39 (br d, J = 4 Hz, 1H, $C_{1'''}$-H), 2.4-1.3 (m, 12H, $C_{2'}$-CH_2, $C_{3''}$-H, $C_{4''}$-H_2, $C_{2'''}$-H, $C_{3'''}$-H_2, $C_{4'''}$-CH_2, $C_{6'''}$-H_2), 1.19 (s, 3H, $C_{5''}$-CH_3), 1.05 (d, J = 6.2 Hz, 3H, $C_{3''}$-CH_3), 0.97-0.89 (m, 15H, C_4-CH_3, $C_{2'}$-CH_2CH_3, $C_{2'''}$-CH_3, $C_{4'''}$-CH_2CH_3, $C_{7'''}$-H_3); ^{13}C NMR ($CDCl_3$/50 MHz) δ 174.37 (s), 152.89 (s), 138.95 (s), 133.26 (s), 128.72 (d), 128.17 (d), 125.64 (d), 86.11 (d), 85.17 (s), 80.99 (d), 78.61 (d),

55.22 (d), 48.37 (d), 41.88 (t), 38.73 (t), 36.98 (d), 32.73 (d), 24.79 (q), 22.59 (t), 22.06 (t), 20.89 (t), 17.89 (q), 17.03 (q), 14.73 (q), 14.52 (q), 13.37 (q), 11.82 (q); TLC (8:2 hexanes/ethyl acetate) R_f = 0.30.

Anal. calcd. for $C_{30}H_{45}NO_4$: C, 72.11; H, 9.08; N, 2.80. Found: C, 72.12; H, 8.99; N, 2.78.

VI. NOTES AND REFERENCES.

(1) Kusakabe, Y.; Mizuno, T.; Kawabata, S.; Seto, H.; Otake, N. J. Antibiot. **1982**, 35, 1119-1129.

(2) Westley, J. W., Ed. "Polyether Antibiotics;" Marcel Dekker, Inc.: New York, 1982; Vol. I, Introduction.

(3) The polyether ionophore antibiotics discussed in this chapter are numbered according to the system proposed by Westley: Westley, J. W. J. Antibiot. **1976**, 29, 584-586.

(4) Taylor, R. W.; Kauffman, R. F.; Pfeiffer, D. R. In "Polyether Antibiotics;" Westley, J. W. Ed.; Marcel Dekker, Inc.: New York, 1982; Vol. I, Chapter 4.

(5) Liu, C.-M. In "Polyether Antibiotics;" Westley, J. W. Ed.; Marcel Dekker, Inc.: New York, 1982; Vol. I, Chapter 3.

(6) Agtarap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. J. Am. Chem. Soc. **1967**, 89, 5737-5739.

(7) For a review of the syntheses of polyether ionophores see: Kishi, Y. In "Polyether Antibiotics;" Westley, J. W. Ed.; Marcel Dekker, Inc.: New York, 1982; Vol. II, Chapter 1.

(8) Use of chiral 2-oxazolidinones in asymmetric synthesis: (a) Aldol: Evans, D. A.; Bartroli, X. B.; Shih T. L. J. Am. Chem. Soc. **1981**, 103, 2876. (b) Alkylation: Evans, D. A.; Ennis, M. D.; Mathre, D. J. J. Am. Chem. Soc. **1982**, 104, 1734. (c) Acylation: Evans, D. A.; Ennis, M. D.; Le, T. L. J. Am. Chem. Soc. **1984**, 106, 1154. (d) Diels--Alder: Evans, D. A.; Bisaha, J.; Chapman, K. T. J. Am. Chem. Soc. **1984**, 106, 4261-4263.

(9) (a) A-23187: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. J. Am. Chem. Soc. **1979**, 101, 6789. (b) Tylosin: Bartroli, X. B. Ph.D. Thesis, California Institute of Technology, 1984. (c) Ionomycin: Shih, T. L. Ph.D Thesis, California Institute of Technology, 1984. (d) Macbecin: Ennis, M. D. Ph.D. Thesis, California Institute of Technology, 1983.

(10) See Ref. 1, "note added in proof."

(11) (a) Ebata, E.; Kasahara, H.; Sekine, K.; Inoue, Y. J. Antibiot. **1975**, 28, 118-121. (b)

(12) For recent reviews of polyether biosynthesis see: (a) Westley, J. W. In "Antibiotics;" Corcoran, J. W. Ed.; Springer-Verlag: Berlin, 1981; Vol. 4, pp 41-73. (b) Hutchinson, C. R. Acc. Chem. Res. **1983**, 16, 7-14. (c) Cane, D. E.; Celmer, W. D.; Westley, J. W. J. Am. Chem. Soc. **1983**, 105, 3594-3600.

(13) Otake, N.; Seto, H.; Koenuma, M. Agric. Biol. Chem. **1978**, 42, 1879-1886.

(14) (a) Westley, J. W.; Evans, Jr., R. H.; Harvey, G.; Pitcher, R. G.; Pruess, D. L.; Stempel, A.; Berger, J. J. Antibiot. **1974**, 27, 288-297. (b) Westley, J. W.; Blount, J. F.; Evans, Jr., R. H.; Stempel, A.; Berger, J. Ibid. **1974**, 27, 597-604.

(15) Hutchinson, C. R.; Sherman, M. M.; Vederas, J. C.; Nakashima, T. T. J. Am. Chem. Soc. **1981**, 103, 5953-5956.

(16) In related studies, both Cane and Ajaz have shown that labeled molecular oxygen (^{18}O) is incorporated by Streptomyces cinnamonesis during the biosynthesis of monensin A at the positions corresponding to a triene--triepoxide pathway: (a) Cane, D. E.; Liang, T.-C.; Hasler, H. J. Am. Chem. Soc. **1981**, 103, 5962-5965.

(b) Ajaz, A. A.; Robinson, J. A. J. Chem. Soc., Chem. Commun. **1983**, 679-680.

(17) Koenuma, M.; Otake, N. J. Antibiot. **1977**, 30, 819-828.

(18) (a) Ireland, R. E.; Thaisrivongs, A.; Wilcox, C. S. J. Am. Chem. Soc. **1980**, 102, 1155-1157. (b) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. J. Am. Chem. Soc. **1983**, 105, 1988-2006.

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

(20) Fitzsimmons, B. J. Ph.D. Thesis, California Institute of Technology, 1983.

(21) I thank Dr. Richard Polniaszek, my co-worker on this project, for these results.

(22) (a) Evans, D. A.; Bartroli, X. B. Tetrahedron Lett. **1982**, 807-810. (b) Bartroli, X. B. Ph.D. Thesis, California Institute of Technology, 1984.

(23) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. Tetrahedron Lett. **1978**, 2741-2744.

(24) (a) Sharpless, K. B.; Michaelson, R. C. J. Am. Chem. Soc. **1973**, 95, 6136-6137. (b) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson R. C.; Cutting, J. D. J. Am. Chem. Soc. **1974**, 96, 5254-5255. (c) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. J. Am. Chem. Soc. **1981**, 103, 6237-6240.

(25) Kishi, Y.; Johnson M. R. Tetrahedron Lett. **1979**, 4347-4350.

(26) Satisfactory elemental analyses and spectra data were obtained for

all new compounds reported herein.

(27) (a) Zweifel, G.; Steele, R. B. J. Am. Chem. Soc. **1967**, 89, 2754-2755. (b) Zweifel, G.; Steele, R. B. J. Am. Chem. Soc. **1967**, 89, 5085-5086.

(28) (a) Corey, E. J.; Cane, D. E.; Libit, L. J. Am. Chem. Soc. **1971**, 93, 7016-7021. (b) Trost, B. M.; Bogdanowicz, M. J.; Frazee, W. J.; Salzmann, T. N. J. Am. Chem. Soc. **1978**, 100, 5512-5525.

(29) Corey, E. J.; Kim, C. U.; Takeda, M. Tetrahedron Lett. **1972**, 4339-4342.

(30) Ennis, M. D. Ph.D. Thesis, California Institute of Technology, 1983.

(31) Mancuso, A. J.; Huang, S.-L.; Swern, D. J. Org. Chem. **1978**, 43, 2480-2482.

(32) Nicolaou, K. C.; Davia, M. R.; Seitz, S. P. J. Am. Chem. Soc. **1982**, 104, 2027-2029.

(33) Evans, D. A.; Dow, R. L. Unpublished results.

(34) When the reaction was performed with commercial (Aldrich Chemical Co.) carboethoxyethylidene triphenylphosphorane, a gross excess (up to 5 equiv) of this reagent was required in order to drive the reaction to completion. The commercial phosphorane was shown to be contaminated with triphenylphosphine and triphenylphosphine oxide. Therefore we prepared our own phosphorane (see Experimental Section) for these experiments.

(35) Wilson, K. E.; Seidner, R, T. Masamune, S. J. Chem Soc. Chem. Commun. **1970**, 213-214.

(36) Hooz, J.; Gilani, S. S. H. Can. J. Chem. **1968**, 46, 86-87.

(37) Landeuer, S. R.; Rydon, H. N. J. Chem. Soc. **1953**, 2224-2234.

(38) Verheyden, J. P. H.; Moffet, J. G. J. Org. Chem. **1970**, 35, 2319-2326.

(39) We presume that the remaining minor diastereomer is (14S,16Z)-**43**. This assignment is based on the observation that the capillary GC retention time for the minor diastereomer is significantly different than those obtained for either (14S,16E)-**43** or (14R,16E)-**43**. Epimerization of (14S,16E)-**43** affords a standard mixture of (14S,16E)-**43** and (14R,16E)-**43**.

(40) Sharpless, K. B.; Verhoeven, T. R. Aldrichimica Acta **1979**, 12, 63-74.

(41) Southern California Regional NMR facility.

(42) Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, 43, 2923-2925.

APPENDIX 1

THE DIASTEREOSELECTIVE ALKYLATION OF CHIRAL ESTER AND CARBOXAMIDE ENOLATES. A TABULATION OF LITERATURE EXAMPLES.[9]

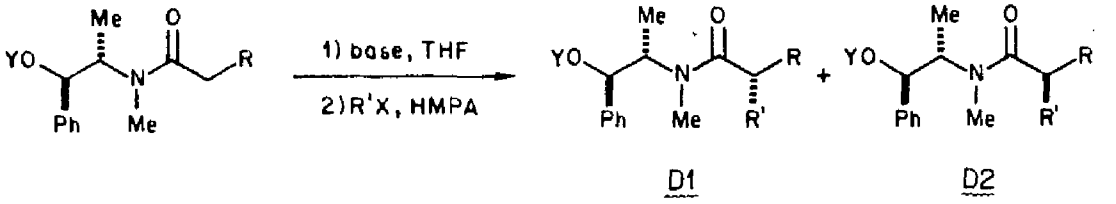
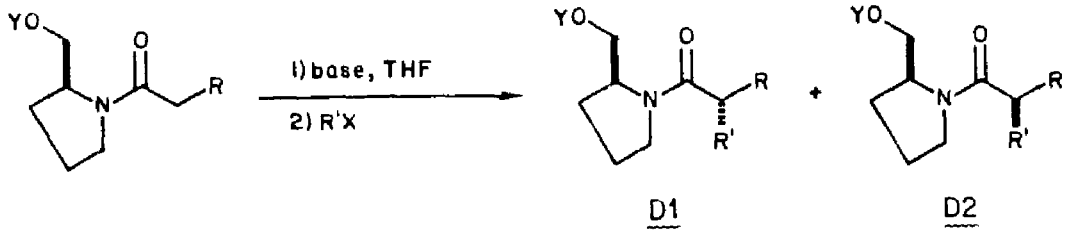
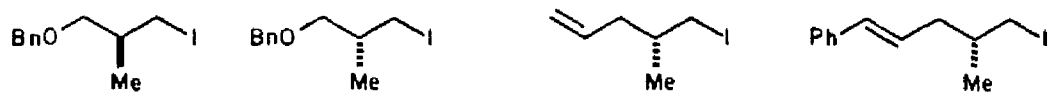


Table 1. Diastereoselective Alkylation of (-)-Ephedrine Amide Enolates.

Entry	Y	R	Base	R'X	Alkylation Conditions	Ratio[a] **D1:D2**	Yield	Ref.
A	H	Me	LDA	EtI	10°C, 2 h	76:24	95%	1
B	Me	Me	LDA	EtI	-40°C, 2 h	65:35	98%	1
C	H	Me	LDA, $MgBr_2$	EtI	25°C, 12 h	90:10	75%	1
D	H	Me	LDA	i-hexI	10°C, 2 h	80:20[b]	---	1
E	H	Me	LDA, $MgBr_2$	i-hexI	25°C, 12 h	88:12[b]	90%	1
F	H	Me	LDA, $MgBr_2$	n-BuI	25°C, 12 h	>95:5	95%	1
G	H	Et	LDA, $MgBr_2$	n-BuI	25°C, 12 h	>90:10	93%	1
H	H	Et	LDA, $MgBr_2$	BnCl	25°C, 12 h	>99:1	95%	1
I	H	n-C_8H_{17}	t-BuLi	MeI	-100°C, 0.5 h	81:19[c]	---	2
J	Me	n-C_8H_{17}	t-BuLi	MeI	-100°C, 0.5 h	16:84[c]	---	2

a) Unless otherwise noted, the diastereomer ratio (**D1:D2**) was determined by ^{13}C NMR. b) The diastereomer ratio was inferred fromthe specific rotation of the chiral acid obtained by hydrolysis of the alkylated amide. c) The diastereomer ratio was determined by capillary GC analysis of the alkylated amide.





1 2 3 4

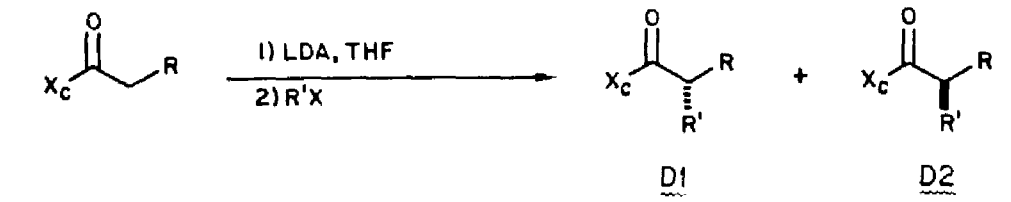
Table 2. Diastereoselective Alkylation of (S)-Prolinol Amide Enolates.

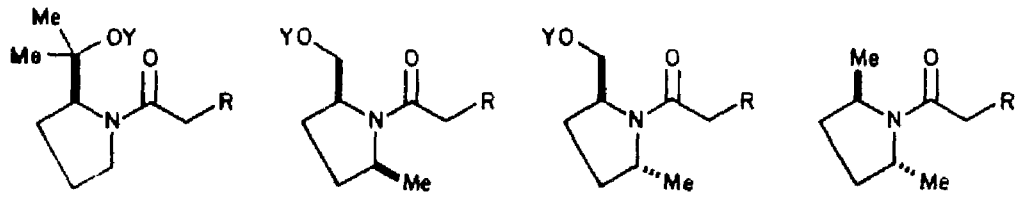
Entry	Y	R	Base	R'X	Alkylation Conditions	Ratio[a] D1:D2	Yield	Ref.
A	H	Me	LDA	EtI	25°C	92:8	98%	3
B	H	Me	LDA	n-BuI	25°C	94:6	99%	3
C	H	Me	t-BuLi	n-$C_8H_{17}I$	-100°C	83:17	---	2
D	H	Me	LDA, KH	n-$C_8H_{17}I$	-78°C[b]	94:6	78%	3
E	H	Me	LDA	i-BuI	-100°C[b]	97:3	89%	3
F	H	Me	LDA	CH_2=$CHCH_2Br$	-100°C[b]	96:4	98%	3
G	H	Me	LDA	BnBr	-100°C	88:12	75%	3
H	H	Me	LDA	1	-100°C[b]	97:3	59%	3
I	H	Me	LDA, KH	2	-78°C[b]	98:2	78%	3
J	H	Me	LDA, KH	3	-78°C[b]	97:3	52%	3
K	H	Me	LDA, KH	4	-78°C[b]	99:1	83%	4
L	H	Et	LDA	MeI	-100°C[b]	94:6	98%	3
M	H	n-C_8H_{17}	t-BuLi	MeI	-120°C	90:10	---	2

Table 2. Continued

Entry	Y	R	Base	R'X	Alkylation Conditions	Ratio[a] **D1:D2**	Yield	Ref.
N	H	n-C_8H_{17}	t-BuLi	EtI	-100°C	84:16	---	2
O	H	n-C_8H_{17}	t-BuLi	n-BuI	-100°C	76:24	---	2
P	H	CH_2=$CH(CH_2)_7$	LDA	EtI	-100°C[b]	90:10	---	5
Q	Me	Me	LDA	EtI	-78°C	22:78	---	3
R	Et	Me	LDA	EtI	-78°C	19:81	---	3
S	TBS[c]	Me	LDA	EtI	-78°C	23:77	---	3
T	TBS[c]	Me	LDA	CH_2=$CHCH_2Br$	-78°C	38:62	---	3
U	MEM[d]	Me	LDA	EtI	-78°C	22:78	---	3
V	MEM[d]	Me	LDA	CH_2=$CHCH_2Br$	-78°C	29:71	---	3
W	MEM[d]	CH_2=$CH(CH_2)_7$	LDA	EtI	-78°C[b]	13:87	---	5
X	MEM[d]	CH_2=$CH(CH_2)_7$	LDA	Me	-78°C[b]	21:79	---	5

a) Diastereomer ratio (**D1:D2**) determined by capillary GC. b) HMPA (2 equiv) added to the preformed enolate prior to addition of the electrophile. c) TBS = t-$Bu(Me)_2Si$. d) MEM = $MeOCH_2CH_2OCH_2$.



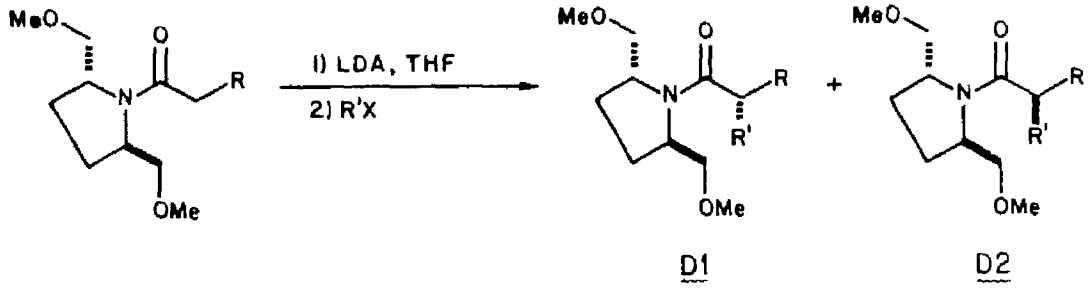


5 6 7 8

Table 3. Diastereoselective Alkylation of Substituted Pyrrolidine Amide Enolates.

Entry	Amide	Y	R	R'X	Alkylation Conditions	Ratio[a] D1:D2	Ref.
A	5	H	Me	EtI	25°C	89:11	3
B	5	TBS[b]	Me	EtI	-78°C	8:92	3
C	6	H	Me	EtI	25°C	95:5	3
D	6	TBS[b]	Me	EtI	-78°C	39:61	3
E	7	H	Me	EtI	25°C	76:24	3
F	7	TBS[b]	Me	EtI	-78°C	1:99	3
G	8	---	Me	EtI	-78°C	95:5[c]	6
H	8	---	Et	MeI	-78°C	88:12[c]	6

a) Unless otherwise noted, the diastereomer ratio (D1:D2) was determined by capillary GC. b) TBS = t-Bu(Me)$_2$Si. c) Diastereomer ratio determined by ^{13}C NMR.



D1 D2

Table 4. Diastereoselective Alkylation of (2R,5R)-Disubstituted Pyrrolidine Amide Enolates.

Entry	R	R'X	Alkylation Conditions	Ratio[a] D1:D2	Yield	Ref.
A	Me	EtI	-78°C	>95:5	87%	6
B	Me	n-BuI	-78°C	>95:5	81%	6
C	Me	CH_2=$CHCH_2Br$	-78°C	>95:5	81%	6
D	Me	BnBr	-78°C	>95:5	80%	6
E	Me	$BnOCH_2Cl$	-78°C	>95:5	74%	6
F	Me	$TBSO(CH_2)_3Br$[b]	-78°C	>95:5	78%	6
G	Et	MeI	-78°C	>95:5	91%	6
H	n-Bu	MeI	-78°C	>95:5	81%	6
I	$PhCH_2$	MeI	-78°C	>95:5	76%	6
J	n-$C_{16}H_{33}$	MeI	-78°C	>95:5	61%	6

a) Diastereomer ratio determined by ^{13}C NMR. b) TBS = t-$Bu(Me)_2Si$.

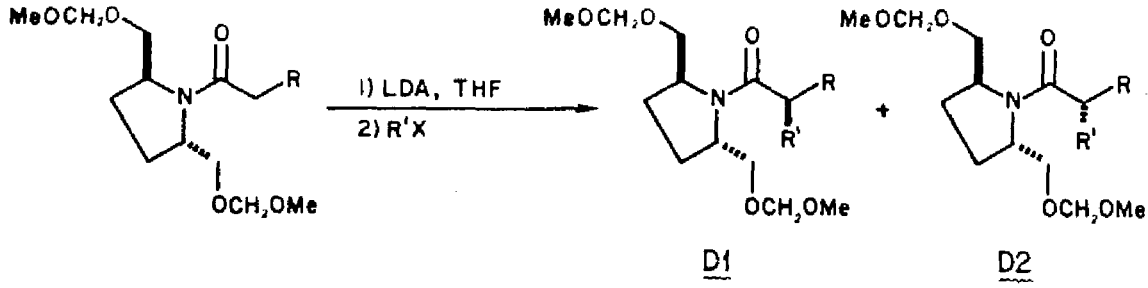


Table 5. Diastereoselective Alkylation of (2S,5S)-Disubstituted Pyrrolidine Amide Enolates.

Entry	R	R'X	Alkylation Conditions	Ratio[a] D1:D2	Yield	Ref.
A	Me	EtI	-78°C	>99:1	79%	6
B	Me	n-BuI	-78°C	>99:1	79%	6
C	Me	n-$C_8H_{17}I$	-20°C	>99:1	75%	6
D	Me	BnBr	-78°C	98:2	87%	6
E	Et	MeI	-78°C	>99:1	77%	6
F	n-Bu	MeI	-78°C	>99:1	70%	6
G	n-C_8H_{17}	MeI	-78°C	>99:1	73%	6
H	$PhCH_2$	MeI	-78°C	99:1	83%	6

a) Diastereomer ratio determined by ^{13}C NMR.

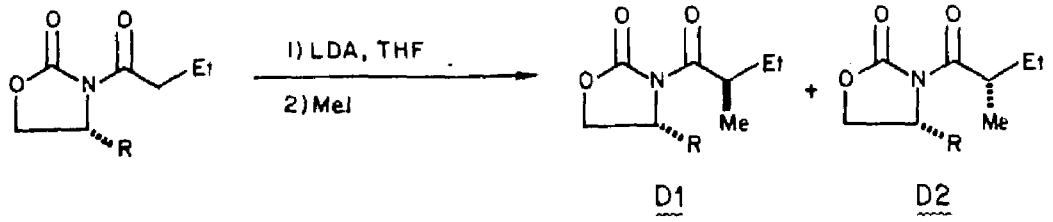


Table 6. Diastereoselective Alkuylation of Chiral 4-Substituted 2-Oxazolidinone Imide Enolates.

Entry	R	Alkylation Conditions	Ratio[a] **D1:D2**	Ref.
A	Me	-30°C, 12 h	88:12	7
B	Et	-30°C, 12 h	90:10	7
C	i-Pr	-30°C, 12 h	91:9	7
D	Ph	-30°C, 12 h	81:19	7
E	c-hex	-30°C, 12 h	86:14	7
F	$PhCH_2$	-30°C, 12 h	94:6	7
G	p-$MeOPhCH_2$	-30°C, 12 h	94:6	7
H	p-$ClPhCH_2$	-30°C, 12 h	94:6	7
I	c-$hexCH_2$	-30°C, 12 h	95:5	7

(a) Diastereomer ratio (**D1:D2**) determined by capillary GC.

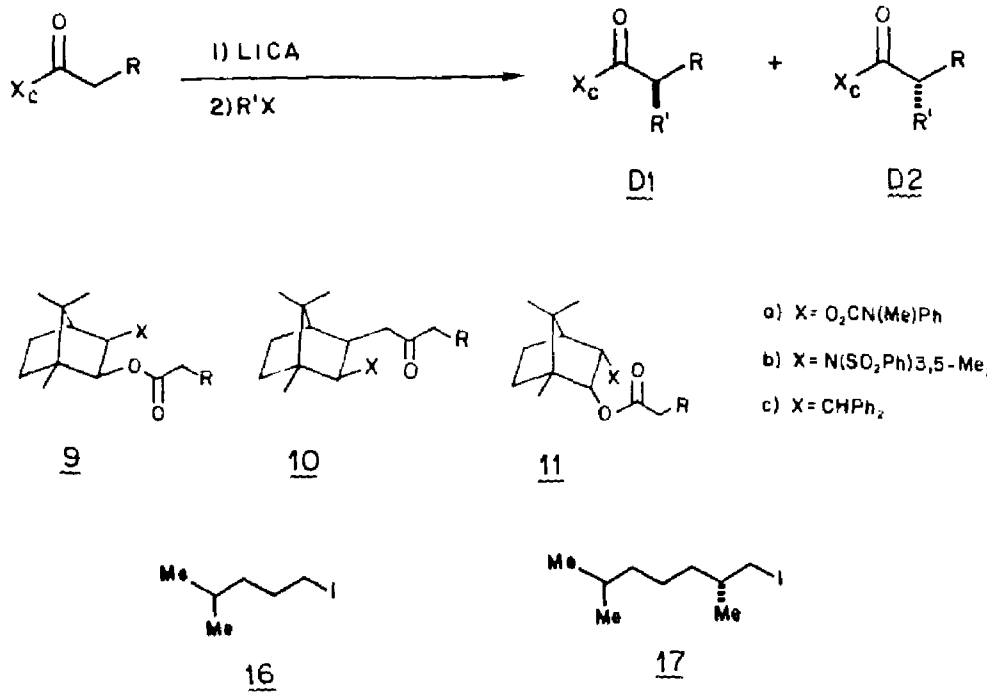


Table 7. Diastereoselective Alkylation of Chiral Ester Enolates.

Entry	Ester	R	R'X	Alkylation[a] Conditions	Ratio[b] D1:D2	Ref.
A	**9a**	Me	n-$C_{16}H_{33}I$	A	93:7	8b
B	**9a**	Me	i-BuI	A	93:7	8b
C	**9a**	Me	i-BuI	B	28:72	8b
D	**9a**	Me	CH_2=$CHCH_2Br$	A	93:7	8b
E	**9a**	Me	BnBr	A	94:6[c]	8b
F	**9a**	Me	BnBr	B	30:70[c]	8b
G	**9a**	n-Bu	BnBr	A	93:7	8b
H	**9a**	n-$C_{16}H_{33}$	MeI	A	90:10	8a
I	**9a**	CH_2=$CHCH_2$	MeI	A	90:10	8b
J	**9a**	CH_2=$CHCH_2$	BnBr	A	93:7	8b

Table 7. Continued.

Entry	Ester	R	R'X	Alkylation Conditions[a]	Ratio[b] D1:D2	Ref.
K	**9a**	$PhCH_2$	Me	A	>95:5	8b
L	**9a**	$PhCH_2$	n-BuI	A	89:11	8b
M	**9a**	$PhCH_2$	n-BuI	B	15:85	8b
N	**9a**	$PhCH_2$	CH_2=$CHCH_2Br$	A	93:7	8b
O	**9b**	Me	n-$C_{14}H_{29}I$	A	>98:2	8a
P	**9b**	Me	n-$C_{14}H_{29}I$	B	4:96	8b
Q	**9b**	Me	BnBr	A	98:2	8d
R	**9b**	Me	BnBr	B	24:76	8d
S	**9b**	BnO	EtI	A	12:88	8e
T	**9b**	BnO	EtI	B	7:93	8e
U	**9c**	Me	BnBr	A	90:10	8d
V	**9c**	Me	BnBr	B	19:81	8d
W	**10a**	Me	n-$C_{16}H_{33}I$	A	6:94	8b
X	**10a**	Me	BnBr	A	14:86[c]	8b
Y	**10a**	n-$C_{16}H_{33}$	Me	A	17:83	8b
Z	**10a**	$PhCH_2$	Me	A	19:81[c]	8b
AA	**11b**	Me	n-$C_{14}H_{29}I$	A	<3:97	8b
BB	**11b**	Me	n-$C_{14}H_{29}I$	B	98:2	8b
CC	**11b**	Me	**16**	A	2:98	8c
DD	**11b**	Me	**16**	B	94:6	8c
EE	**11b**	Me	**17**	A	3:97	8c
FF	**11b**	Me	BnBr	A	3:97	8d
GG	**11b**	Me	BnBr	B	95:5	8d

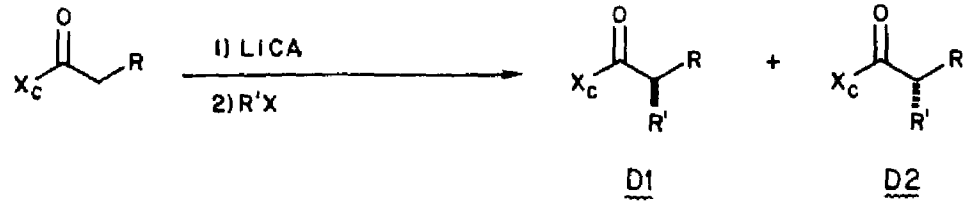
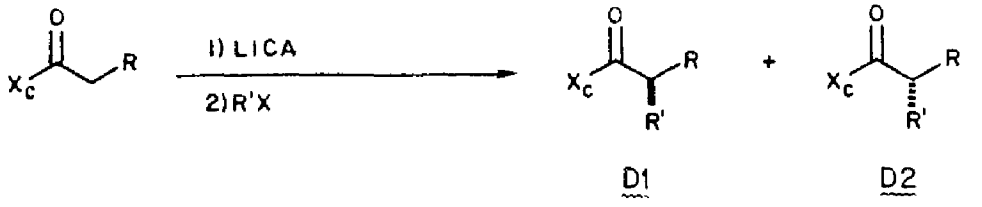
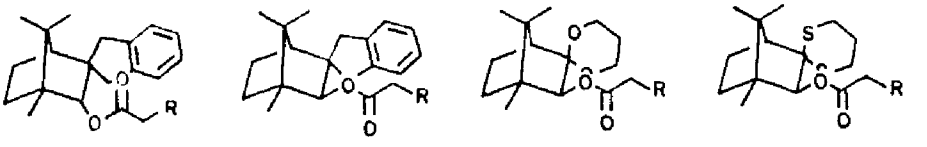


Table 7. Continued.

Entry	Ester	R	R'X	Alkylation[a] Conditions	Ratio[b] **D1:D2**	Ref.
HH	**11b**	BnO	MeI	A	88:12	8e
II	**11b**	BnO	MeI	B	91:9	8e
JJ	**11b**	BnO	EtI	A	88:12	8e
KK	**11b**	BnO	EtI	B	95:5	8e
LL	**11b**	BnO	n-$C_{10}H_{21}$	A	91:9	8e
MM	**11b**	BnO	n-$C_{10}H_{21}$	B	93:7	8e

(a) A = The lithium enolate was generated in THF with lithium isopropylcyclohexylamide (LICA) for 0.5 h at -78°C; To the lithium enolate solution was added 2.2 equiv of HMPA and the electrophile; enolate alkylation was allowed to proceed at -78°C to -40°C. B = The lithium enolate was generated in 4:1 THF/HMPA with LICA for 0.5 h at -78°C, then alkylated as above. (b) Unless otherwise noted, the diastereomer ratio (**D1:D2**) was determined by HPLC. (c) Diastereomer ratio determined by ^{1}H NMR.





12 13 14 15

Table 8. Diastereoselective Alkylation of Chiral Ester Enolates.

Entry	Ester	R	R'X	Alkylation[a] Conditions	Ratio[b] **D1:D2**	Ref.
A	**12**	Me	BnBr	A	16:84	8d
B	**12**	Me	BnBr	B	70:30	8d
C	**13**	Me	BnBr	A	81:19	8d
D	**13**	Me	BnBr	B	43:57	8d
E	**14**	Me	BnBr	A	35:65	8d
F	**14**	Me	BnBr	B	58:42	8d
G	**15**	Me	BnBr	A	14:86	8d
H	**15**	Me	BnBr	B	69:31	8d

(a) A = The lithium enolate was generated in THF with lithium isopropylcyclohexylamide (LICA) for 0.5 h at -78°C; To the lithium enolate solution was added 2.2 equiv of HMPA and the electrophile; enolate alkylation was allowed to proceed at -78°C to -40°C. B = The lithium enolate was generated in 4:1 THF/HMPA with LICA for 0.5 h at -78°C, then alkylated as above. (b) The diastereomer ratio (**D1:D2**) was determined by HPLC.

NOTES AND REFERENCES.

(1) (a) Larcheveque, M.; Ignatova, E.; Cuvigny, T. Tetrahedron Lett. **1978**, 3961-3964. (b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. J. Organomet. Chem. **1979**, 177, 5-15.

(2) Sonnet, P. E.; Heath, R. R. J. Org. Chem. **1980**, 45, 3137-3139.

(3) (a) Takacs, J. M.; Ph.D. Thesis, California Institute of Technology, 1981. (b) Evans, D. A.; Takacs, J. M. Tetrahedron Lett. **1980**, 21, 4233-4236.

(4) Evans, D. A.; Dow, R. L. Unpublished results.

(5) Sonnet, P. E.; Heath, R. R. J. Org. Ecology **1982**, 8, 41-53.

(6) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y. Tetrahedron Lett. **1984**, 25, 857-860.

(7) Evans, D. A.; Chapman, K. T. Unpublished results.

(8) (a) Abe, E.; Helmchen, G.; Heiligenmann, G. Tetrahedron Lett. **1980**, 21, 1137-1140. (b) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. Agnew. Chem. Int. Ed. Engl. **1981**, 20, 207-208. (c) Helmchen, G.; Schmierer, R. Tetrahedron Lett. **1983**, 24, 1235-1238. (d) Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I. Tetrahedron Lett. **1983**, 24, 3213-3216. (e) Helmchen, G.; Wierzchowski, R. Agnew. Chem. Int. Ed. Engl. **1984**, 23, 60-61.

(9) For a tabulation of the diastereoselective alkylation of other chiral enolates including Meyer's chiral oxazolines see: Ref. 3a, Appendix 1.

APPENDIX II

THE ENANTIOSELECTIVE SYNTHESIS OF (R) AND (S)-THIORPHAN, AN ENKEPHALINASE INHIBITOR.[1]

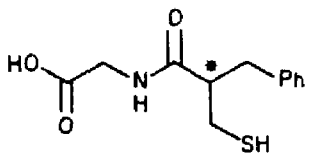
ABSTRACT.

The enantioselective synthesis of (R) and (S)-thiorphan (**1**) *via* a six-step sequence is reported. The key step, establishing the absolute stereochemistry in the target molecule, is the diastereoselective alkylation of the chiral 2-oxazolidinone imide enolates **6** and **7** with benzyl bromomethyl sulfide (**5b**). The level of diastereoselection is in excess of 95:5. Full experimental details are provided for the preparation of the 2-oxazolidinone chiral auxiliaries **3a** and **4a**.

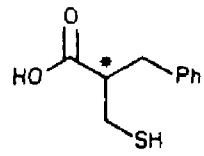
INTRODUCTION.

The endogenous opioid pentapeptides, leucine and methionine-enkephalin are neurotransmitters involved with the induction of analgesia.[2] Hydrolysis of the enkephalin Gly^3-Phe^4 bond by a membrane-bound metalloendopeptidases, "enkephalinase," located near the enkephalin and opioid receptors, has been postulated to mediate enkephalin-induced analgesia.[3] Thiorphan [(±)-N-(1-oxo-2-mercaptomethyl-3-phenylpropyl)glycine] (**1**) is reported to inhibit enkephalinase,[4] extend the duration of analgesia induced by enkephalin analogs or noxious stimuli,[5] and induce analgesia itself.[6] Several related zinc-containing metallopeptidases, including angiotensin converting enzyme (ACE), also are reported to be inhibited by (±)-**1**.[6,7] Both enantiomers of thiorphan were required to evaluate the absolute stereochemical requirements of thiorphan mediated--enkephalin and ACE--inhibition, as well as thiorphan induced analgesia.[8] Therefore, we developed a practical, enantioselective synthesis of both (R) and (S)-thiorphan, that enjoys sufficient flexibility to be directly applicable for the construction of chiral thiorphan homologs.

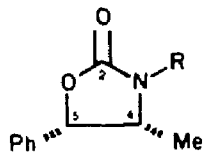
By inspection, the enantioselective synthesis of thiorphan reduces to the construction of a suitably protected form of (R) and (S)-2-mercaptomethyl-3-phenylpropanoic acid (**2**) (eq 1). This 2-substituted carboxylic acid was envisioned as being directly accessible <u>via</u> the chiral enolate methodology developed in our laboratories.[9] The chiral 2-oxazolidinone imide enolates **6** and **7**, illustrated in Scheme 1, would serve as practical precursors to (R) and (S)-thiorphan, respectively.



(±)-1



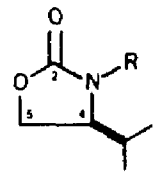
(±)-2 (1)



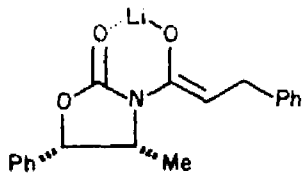
3 (X_n)

a, R = H

b, R = $COCH_2CH_2Ph$



4 (X_v)

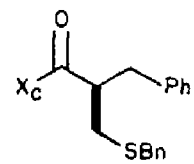


6

+ XCH_2SCH_2Ph

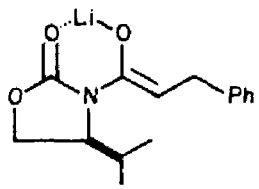
5a, X = Cl

5b, X = Br

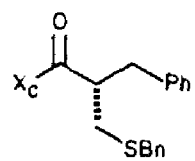


8a, $X_c = X_n$

8b, $X_c = X_v$



7



9a, $X_c = X_n$

9b, $X_c = X_v$

Scheme 1

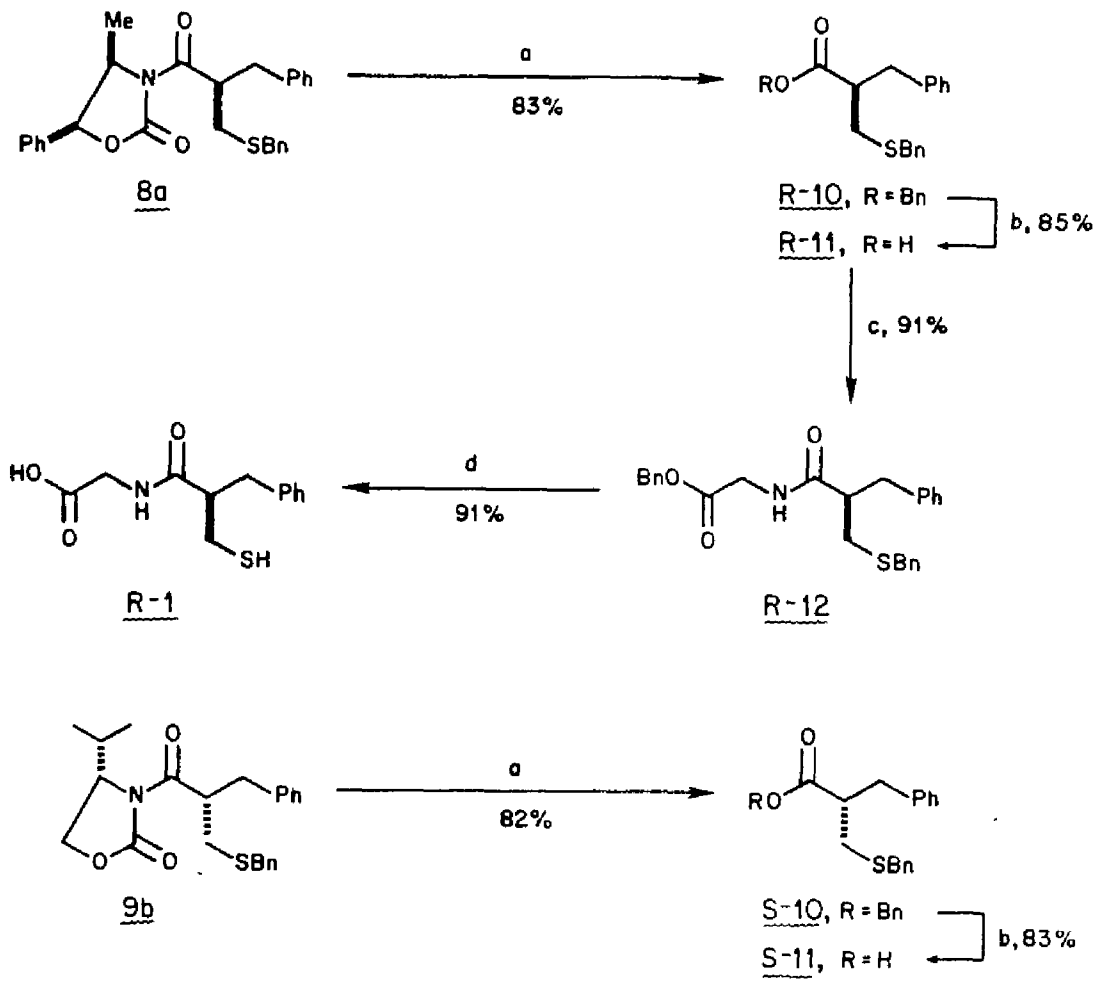
RESULTS AND DISCUSSION.

The requisite chiral 2-oxazolidinones **3a** and **4a** are prepared from their respective amino alcohols and a carbonyl dication equivalent.[10] (1S,2R)-Norephedrine, commercially available as the hydrochloride salt,[11] can be transformed into 2-oxazolidinone **3a** by treatment with phosgene,[12] diethyl carbonate,[13] or diphenyl carbonate. After evaluating several carbonyl dication equivalents, we found that the diphenyl carbonate procedure described herein, is the most reliable method for preparing **3a** on a laboratory scale (up to 3 mol). Norephedrine-derived 2-oxazolidinone **3a** produced *via* this procedure, and purified by simple crystallization [mp 121-122°C (Lit.[12] mp 117°C)] is afforded in 82-95% yield. (S)-Valinol,[14] on the other hand, is most conveniently transformed into 2-oxazolidinone **4a** with diethyl carbonate. This procedure affords valinol-derived 2-oxazolidinone **4a**, after purification by simple crystallization [mp 69-70°C (Lit.[15] mp 71.5°C)], in 85-95% yield. The enantiomeric purity of the chiral 2-oxazolidinones, prepared by the above procedures, was shown to be >99%.[16]

The chiral 2-oxazolidinones **3a** and **4a** are conveniently metalated with *n*-butyllithium and N-acylated with 3-phenylpropanoyl chloride to afford the crystalline imides **3a** (mp 95-96°C) and **4a** (mp 63-64°C) in 89% and91% yields, respectively.[17] Initial attempts to alkylate lithium enolate **6** with benzyl chloromethyl sulfide (**5a**)[18] were unsuccessful (Scheme 1). Only recovered starting material and enolate decomposition products were detected.[19] We found that the more reactive benzyl bromomethyl sulfide (**5b**),[20] however, functions admirably.

Enolization of imide **3b** with lithium diisopropylamide (LDA) and subsequent treatment of the resultant lithium enolate **6** with 1.1 equiv of alkyl bromide **5b** (2 h at -25°C, 2 h at 0°C) affords alkylated imide **8a** along with a minor amount of the diasteromeric alkylation product **9a**. Analysis of the unfractionated product by capillary GC indicated a 98:2 ratio of **8a** to **9a**. In addition to the product, both imide **3b** (ca. 8%) and 2-oxazolidinone **3a** (ca. 5%) were also detected. Product isolation by liquid chromatography (Waters Prep-500) affords **8a** in 76% yield as a viscous colorless oil (**8a**:**9a** = 98:2). Although the use of excess electrophile (2-5 equiv) improves the extent of enolate alkylation, the remaining electrophile complicates product isolation. Alkylation of the corresponding sodium enolate derived from imide **3b** [$NaN(SiMe_3)_2$] decreases both the level of alkylation diastereoselection and the yield of isolated product. The other diastereomeric imide **9b** is obtained by alkylation of lithium enolate **7**. Thus, treatment of lithium enolate **7** with 1.1 equiv of alkyl bromide **5b** (2 h at -25°C) affords a 3:97 ratio of **8b** to **9b**. Product isolation by liquid chromatography (Waters Prep-500) affords **9b** in 83% yield as a viscous colorless oil (**8b**:**9b** = 2:98).

The completion of the synthesis of (R)-thiorphan is illustrated in Scheme 2. Based on prior experience, we were not surprised that direct hydrolysis (KOH, $EtOH/H_2O$, 0°C) of alkylated imide **8a** to carboxylic acid **R-11** was unsuccessful. Only products resulting from attack at the urethane (ring) carbonyl and base catalyzed retro-Michael elimination of benzyl thiol were obtained. We have observed that the relative rates of nucleophilic attack at either carbonyl function depend on a subtle interplay of electronic and steric effects. For example, with two C-2 imide substituents with steric requirements greater or equal to methyl



a) LiOBn, THF, -10°C. b) 6 M HBr, HOAc, 50°C. c) $(PhO)_2P(O)N_3$, Et_3N, $BnO_2CCH_2NH_2$, DMF, -10°C. d) Na (5 equiv), NH_3/THF, -33°C.

Scheme 2

groups, direct basic hydrolysis strongly prefers attack at the endocyclic (ring) carbonyl. Fortunately, we have found that transesterification of alkylated imides with lithium benzyloxide selectively removes the alkylated product from the chiral auxiliary. This reaction exhibits less substrate dependency, and is quite reliable.[9a] Accordingly, treatment of alkylated imide **8a** with lithium benzyloxide (1.5 equiv, THF,

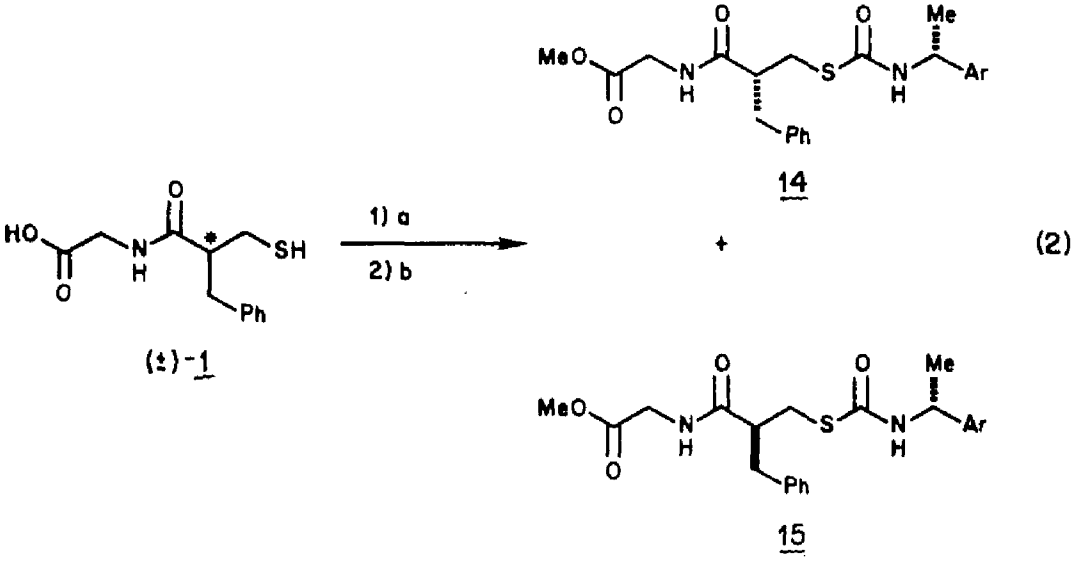
-10°C to 0°C) affords, after purification by liquid chromatography, benzyl ester **R-10** ($[\alpha]_{589}$ = +36.2° (*c* 0.86, CH_2Cl_2)) in 83% yield. The accompanying norephedrine-derived 2-oxazolidinone **3a** also can be recovered and recycled. Treatment of alkylated imide **9b** with lithium benzyloxide (1.5 equiv, THF, 0°C) affords, after purification by liquid chromatography, the enantiomeric benzyl ester **S-10** ($[\alpha]_{589}$ = -34.6° (*c* 2.46, CH_2Cl_2)) in 82% yield.

In direct analogy to the racemization-free debenzylesterification of (S)-S-benzylcysteine benzyl ester,[21] treatment of benzyl ester **R-10** with anhydrous hydrogen bromide in glacial acetic acid affords carboxylic acid **R-11** ($[\alpha]_{589}$ = 54.1° (*c* 1.54, abs. EtOH)) in 85% yield. Similar treatment of benzyl ester **S-10** affords the enantiomeric carboxylic acid **S-11** ($[\alpha]_{589}$ = -50.6° (*c* 1.57, abs. EtOH)) in 83% yield. Diphenylphosphoryl azide was employed to affect the peptide bond construction between **R-11** and benzyl glycinate.[22] Thus, treatment of carboxylic acid **R-11**, the *p*-toluenesulfonate salt of benzylglycinate, and triethylamine in dimethylformamide (DMF) with diphenylphosphoryl azide (4 h at -10°C and 18 h at 0°C) affords, after purification by flash chromatography,[23] the benzyl ester of (R)-S-benzylthiorphan (**R-12**) in 91% yield as a crystalline solid (mp 72-73°C, $[\alpha]_{589}$ = +25.2° (*c* 1.61, abs. EtOH)). Performing the same reaction with carboxylic acid **S-11** affords the enantiomeric benzyl ester **S-12** in 85% yield as a crystalline solid (mp 73.5-74°C, $[\alpha]_{589}$ = -24.5° (*c* 1.82, abs. EtOH)).

Bis-debenzylation of **R-12** under carefully controlled dissolving metal conditions completes the synthesis.[24] Thus, **R-12** in liquid ammonia/THF (1:1) is treated with 5 equiv of sodium metal over a 15-min

period. The heterogeneous blue solution is maintained at -33°C foran additional 15 min, then is quenched by the addition of anhydrous ammonium chloride. Product isolation affords (R)-thiorphan (**R-1**) in 91% yield as a viscous colorless oil which slowly crystallized on standing (mp 108-110°C, $[\alpha]_{589}$ = -40.1° (c 2.25, abs. EtOH)). In a similar manner, bis-debenzylation of **S-12** affords (S)-thiorphan (**S-1**) in 96% yield (mp 110-111°C, $[\alpha]_{589}$ = +39.6° (c 2.78, EtOH)). During the optimization of this reductive debenzylation, we noted that when less than 5 equiv of sodium metal are employed, a mixture of thiorphan and S-benzylthiorphan is obtained. The use of a large excess of sodium metal, however, results in a significant decrease in the isolated yield of thiorphan.

The complementary specific rotations (-40.1°, +39.6°) for (R) and (S)-thiorphan are within experimental error. This demonstrates a good degree of internal consistency in regard to the overall diastereoselection and racemization (or lack thereof) during the synthesis of each enantiomer. Nonetheless, we desired an independent, unequivocal assessment of enantiomeric purity. (±)-Thiorphan methyl ester reacts with (R)-1-(1-naphthyl)ethyl isocyanate (**13**) to afford the diastereomeric thiourethanes **14** and **15** (eq 2).[25] Although the thiourethane diastereomers are not separable by HPLC on conventional supports, they are resolved on a Pirkle covalent phenylglycine column (α = 1.46).[26] The same derivatization process and HPLC analysis established a lower limit of ca. 95% enantiomeric purity for both **R-1** and **S-1**. Peak broadening in this analysis prevents a more accurate assessment of enantiomeric purity.



a) $BF_3 \cdot OEt_2$, MeOH, 50°C. b) (R)-13, K_2CO_3, C_6H_6, 80°C.

BIOLOGICAL STUDIES.

Although a detailed biochemical evaluation of (R) and (S)-thiorphan will be reported elsewhere,[8] the interesting conclusions drawn from this study are noteworthy. First, synthetic (S)-thiorphan is approximately twenty-four-fold more effective as an ACE inhibitor than(R)-thiorphan. The low levels of ACE inhibition observed for (R)-thiorphan could largely, if not exclusively, be the result of enantiomeric contamination. In contrast, both enantiomers of thiorphan exhibit similar levels of inhibition of enkephalinase A. Finally, the analgesic properties reported for (±)-thiorphan,[6] are mainly associated with the (R) enantiomer.

EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. IR spectra were recorded on a Beckman 4210 spectrometer and are reported in reciprocal centimeters. ^{1}H NMR spectra were recorded on a Varian Associates EM-390 (90 MHz) or a Bruker WM-500 (500 MHz) spectrometer.[27] Chemical shifts are reported in ppm from tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and b = broad), coupling constant (Hz), integration and interpretation. ^{13}C NMR were recorded on a JEOL FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Optical rotations were determined with a Jasco DIP-181 digital polarimeter. Data are reported as follows: specific rotation ($[\alpha]$), concentration ($\underline{c}$ = g/100 mL), and solvent.

Combustion analyses were performed by Galbraith Laboratories. Inc., (Knoxville, Tennessee) or by Mr. Lawrence Henling at the California Institute of Technology Microanalytical Laboratory.

Analytical gas chromatography (GC) was carried out on a Hewlett Packard 5880A gas chromatograph equipped with a split mode capillary injector and flame ionization detector. Hydrogen was used as the carrier gas. The following wall coated open tubular (WCOT) fused silica capillary columns were employed: 30 m x 0.32 mm DB-1 (J and W Associates) and 30 m x 0.32 mm DB-5 (J and W Associates). Specific GC conditions are reported as follows: column, oven temperature, carrier gas flow rate, and retention time. Unless otherwise noted, the injector and detector temperatures were 250°C.

Flash chromatography was performed according to the general procedure of Still[23] employing EM Reagents silica gel 60 (40-63 μm). Analytical high performance liquid chromatography (HPLC) was carried out on a Waters Associates ALC 202/401 HPLC equipped with a model 6000 high pressure solvent pump, a model U6K injector and a differential UV (254 nm) detector, and using the following columns: Waters Radial Pak (8 mm x 10 cm, 5 μm silica gel) or a Regis (4.6 mm x 25 cm, Pirkle phenylglycine covalently bound to 5 μm aminopropyl silica gel).[26] Specific HPLC conditions are reported as follows: column, elutant composition, elutant flow rate, and retention volume (k'). Preparative HPLC was performed on a Waters Associates PrepLC/System 500 liquid chromatograph equipped with a refractive index detector and using two PrepPak 500 silica gel cartridges (5 x 30 cm). Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates.

When necessary, solvents were dried prior to use. Tetrahydrofuran (THF) and benzene were distilled from sodium/benzophenone ketyl. Boron trifluoride--diethyl etherate and diisopropylamine were distilled from calcium hydride. Dimethylformamide (DMF) was distilled from calcium hydride and stored over 4A molecular sieves. *n*-Butyllithium was standardized by double titration (total base - inorganic base = organic base).

Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon or nitrogen with rigid exclusion of moisture.

(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone (3a). A mechanically stirred mixture of 151 g (1.00 mol) of (1S,2R)-norephedrine ($[\alpha]_{589}$ =

+33.4° (c 7, water) as the hydrochloride salt, Aldrich Chemical Co.), 236 g (1.10 mol) of diphenyl carbonate, and 152 g (1.10 mol) of anhydrous potassium carbonate was heated at 110°C for 4-6 h. The resultant mixture was cooled to < 60°C. Excess diphenyl carbonate was hydrolyzed by addition of 600 mL of methanol and heating the mixture at reflux for 0.5 h. Sufficient water (400-600 mL) was added to dissolve the potassium carbonate. Methanol was removed *in vacuo*. The product and phenol were extracted into dichloromethane (3 x 1 L). The combined extracts were washed with 2 M aqueous sodium hydroxide (3 x 1 L) to remove the phenol, 1 M aqueous hydrochloric acid (1 x 1 L), and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 195 g (110% mass balance) of a light yellow solid. Recrystallization from toluene (600 mL, 3 crops) afforded 145-165 g (82-93%) of 2-oxazolidinone **3a** as a white crystalline solid: mp 121-122°C (Lit.[12] 117°C); IR ($CHCl_3$) 3460, 3400-3200, 3020, 2980, 1760, 1450, 1380, 1350, 1220, 1125, 1000, 960, 690 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.33 (s, 5H, aromatic H's), 6.3-6.0 (br s, 1H, N-H), 5.67 (d, J = 7.5 Hz, 1H, C_5-H), 4.17 (qn, J = 7.0 Hz, 1H, C_4-H), 0.80 (d, J = 7.0 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 159.9, 135.0, 128.4, 125.9, 81.0, 52.4, 17.4; Specific Rotation $[\alpha]_{589}$ = +177.2°, $[\alpha]_{577}$ = +186.1°, $[\alpha]_{546}$ = +212.0°, $[\alpha]_{435}$ = +368.6°, $[\alpha]_{365}$ = +598.6° (c 2.21, $CHCl_3$), [Lit.[12] $[\alpha]_{589}$ = +158.4° (c 0.44, $CHCl_3$)]; GC (30 m DB-1, 150°C, 81 cm/sec) t_r = 4.31 min; TLC (ethyl acetate), R_f = 0.45.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.62; N, 7.90. Found: C, 67.42; H, 6.19; N, 7.87.

(4S)-4-(1-Methylethyl)-2-oxazolidinone (4a). Into a 500-mL flask equipped with a 20-cm Vigreux column was introduced 103 g (1.00 mol) of (S)-valinol,[14] 133 mL (130 g, 1.10 mol) of diethyl carbonate, and 14 g (0.10 mol) of anhydrous potassium carbonate. The magnetically stirred mixture was heated at 125-126°C (internal reaction temperature) until 117 mL (92 g, 2.0 mol) of ethanol distilled (ca. 4-6 h).[28] The resultant mixture was cooled to room temperature, dissolved in diethyl ether (3 L), and the solution filtered through a 2 cm pad of celite to remove the potassium carbonate. The etheral solution was concentrated to a volume of ca. 1 L, slowly cooled to 0°C, and the product allowed to crystallize. Concentration of the mother liquors provided two additional crops of crystals. The total yield of 2-oxazolidinone **4a**, was 110-123 g (85-95%), as white needles: mp 69-70°C, [Lit.[15] mp 71.5°C]; IR (CH_2Cl_2) 3480, 3340-3240, 3060, 2980, 1760, 1400, 1240 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 6.7 (br s, 1H, N-H), 4.42 (t, J = 8.6 Hz, 1H, C_5-H), 4.07 (d of d, J = 8.5, 6.5 Hz, 1H, C_5-H), 3.58 (d of t, J = 8.6, 6.5 Hz, 1H, C_4-H), 1.9-1.6 (m, 1H, C_4-CH), 0.95 (overlapping d's, J = 6.0 Hz, 6H, $CH(CH_3)_2$); Specific rotation $[\alpha]_{589}$ = -16.6°, $[\alpha]_{577}$ = -17.3°, $[\alpha]_{546}$ = -20.2°, $[\alpha]_{435}$ = -37.3°, $[\alpha]_{365}$ = -63.7° (c 5.81, EtOH); GC (30 m DB-5, 100°C, 94 cm/sec) t_r = 5.55 min; TLC (6:4 hexanes/ethyl acetate) R_f = 0.19.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.80; H, 8.58. Found: C, 55.63; H, 8.53.

Benzyl Chloromethyl Sulfide (5a). Anhydrous hydrogen chloride was bubbled through a magnetically stirred, cooled (-10°C) solution of 25.0 g (0.278 mol) of s-trioxane in 100 g (0.805 mol) of benzyl thiol until

saturated (ca. 1h). After an additional period of 12 h at room temperature, the reaction mixture was dried over anhydrous calcium chloride. The product was decanted from the calcium chloride and distilled through a 5-cm Vigreux column to afford 101 g (73%) of **5a** as a colorless liquid: bp 74-76°C, 0.01 mm, (Lit.[18] bp 102°C, 2 mm); ^{1}H NMR (CCl_4/90 MHz) δ 7.2 (s, 5H, aromatic H's), 4.40 (s, 2H, SCH_2Cl), 3.80 (s, 2H, $PhCH_2S$).

Benzyl Bromomethyl Sulfide (5b). The title compound was prepared following the procedure of Hollowood et al.[20] The product was purified by molecular distillation (Kugelrohr, 140°C, 0.01 mm) to afford **5b** (92%) as a colorless liquid, which solidified below -10°C: ^{1}H NMR (CCl_4/90 MHz) δ 7.27 (s, 5H, aromatic H's), 4.33 (s, 2H, SCH_2Br), 3.82 (s, 2H, $PhCH_2S$).

(4R,5S)-3-(1-Oxo-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (3b). A mechanically stirred, cooled (-78°C) solution of 44.3 g (250 mmol) of 2-oxazolidinone **3a** (0.5 M in THF), was metalated with 150 mL (1.70 M in hexane, 255 mmol) of n-butyllithium (until the orange-red color of the dianion just persisted) and acylated immediately with 39.0 mL (44.3 g, 263 mmol) of freshly distilled 3-phenylpropanoyl chloride. The reaction mixture was warmed to 0°C and stirred for 0.5 h. Excess acid chloride was hydrolyzed by addition of 100 mL of 1 M aqueous potassium carbonate and stirring the resultant two-phase mixture for 1 h at room temperature. Volatiles were removed in vacuo and the product extracted into dichloromethane (3x). The combined organic extracts were successively washed with water and brine, dried over anhydrous

magnesium sulfate, and concentrated *in vacuo* to give 83.2 g of a yellow solid. Recrystallization from hexanes/ethyl acetate (3 crops) afforded 69.1 g (89%) of **3b** as a white crystalline solid: mp 95-96°C; IR (CH_2Cl_2) 3060, 3000, 1785, 1700, 1370, 1350, 1250 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.44-7.19 (m, 10H, aromatic H's), 5.63 (d, J = 7.5 Hz, 1H, C_5-H), 4.75 (qn, J = 6.9 Hz, 1H, C_4-H), 3.34 (m, 2H, $C_{2'}$-H_2), 3.06-3.00 (m, 2H, $C_{3'}$-H_2), 0.89 (d, J = 6.8 Hz, 3H, C_4-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 172.1, 152.9, 140.4, 133.4, 128.7, 126.2, 125.6, 79.0, 54.7, 37.2, 30.3, 14.5; Specific rotation $[\alpha]_{589}$ = +28.7°, $[\alpha]_{577}$ = +28.9°, $[\alpha]_{546}$ = +32.9°, $[\alpha]_{435}$ = +60.1°, $[\alpha]_{365}$ = +106.7 (c 0.45, CH_2Cl_2); GC (30 m DB-1, 200°C, 86 cm/sec) t_r = 9.06 min; HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min) k' = 2.76; TLC (7:3 hexanes/ethyl acetate) R_f = 0.42.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19. Found: C, 73.85; H, 6.28.

(4S)-3-(1-Oxo-3-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone (4b). A mechanically stirred, cooled (-78°C) solution of 20.0 g (155 mmol) of 2-oxazolidinone **4a** (0.3 M in THF), was metalated with 95 mL (1.70 M in hexane, 162 mmol) of n-butyllithium and acylated with 28.4 g (168 mmol) of freshly distilled 3-phenylpropanoyl chloride. The reaction mixture was warmed to 0°C and stirred for 0.5 h. Excess acid chloride was hydrolyzed by the addition of 100 mL of 1 M aqueous potassium carbonate and stirring the resultant two-phase mixture for 1 h at room temperature. Volatiles were removed *in vacuo* and the product extracted into dichloromethane (3x). The combined organic extracts were successively washed with water and brine, dried over anhydrous magnesium sul-

fate, and concentrated *in vacuo* to give 41.5 g of a pale-yellow solid. Recrystallization from hexanes afforded 37.0 g (91%) of **4b** as a white crystalline solid: mp 63-64°C; IR (CH_2Cl_2) 3060, 2970, 1780, 1700, 1385, 1210 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.3-7.17 (m, 5H, aromatic H's), 4.41 (d of d of d, J = 8.5, 4.0, 3.2 Hz, 1H, C_4-H), 4.24 (d of d, J = 9.3, 8.4 Hz, 1H, C_5-H), 4.19 (d of d, J = 9.3, 3.2 Hz, 1H, C_5-H), 3.30 (d of d of d, J = 17.5, 8.7, 6.9 Hz, 1H, $C_{2'}$-H), 3.22 (d of d of d, J = 17.5, 8.5, 7.2 Hz, 1H, $C_{2'}$-H), 3.1-2.9 (m, 2H, $C_{3'}$-H_2), 2.4-2.3 (m, 1H, C_4-CH), 0.90 (d, J = 7.4 Hz, 3H, $CH(CH_3)$), 0.84 (d, J = 7.4 Hz, 3H, $CH(CH_3)$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 172.3, 154.0, 140.5, 128.5, 126.1, 63.4, 58.4, 37.0, 30.4, 28.4, 17.9, 14.6; Specific rotation $[\alpha]_{589}$ = +71.0°, $[\alpha]_{577}$ = +74.1°, $[\alpha]_{546}$ = +84.2°, $[\alpha]_{435}$ = +143.4°, $[\alpha]_{365}$ = +225.3° (*c* 4.61, CH_2Cl_2); GC (30 m DB-1, 175°C, 83 cm/sec) t_r = 4.75 min; HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min) k' = 4.86; TLC (8:2 hexanes/ethyl acetate) R_f = 0.47.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 69.17; H, 7.42.

(4R,5S)-3-((2R)-1-Oxo-2-phenylmethylthiomethyl-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (8a). A magnetically stirred, cooled (-78°C) solution of lithium diisopropylamide (LDA, prepared from 9.5 mL (6.9 g, 67.8 mmol) of diisopropylamine and 40 mL (1.69 *M* in hexane, 67.6 mmol) of *n*-butyllithium), (0.5 *M* in THF), was used to enolize 20.0 g (64.6 mmol) of **3b**. After stirring for 0.5 h at -78°C the resultant lithium enolate was alkylated with 10.6 mL (15.5 g, 71.3 mmol) of benzyl

bromomethyl sulfide (**5b**) for 2 h at -25°C and 2 h at 0°C. The reaction was quenched by addition of half-saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the product extracted into dichloromethane (3x). The combined organic extracts were successively washed with 1 M aqueous sodium bisulfate (2x), 1 M aqueous potassium bicarbonate (2x), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 31.3 g of a yellow oil. Analysis by GC (30 m DB-1, 200°C for 10 min, 25°C/min to 275°C, (injector and detector = 300°C), 90 cm/sec) afforded a 98:2 ratio of **8a** (t_r = 17.92 min) to **9a** (t_r = 18.12 min), and indicated the presence of both 2-oxazolidinone **3a** (t_r = 1.19 min, ca. 5%) and imide **3b** (t_r = 8.60 min, ca. 8%). HPLC analysis (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min) indicated k' **8a** = 1.98, k' **9a** = 1.69, α = 1.17. The title compound was isolated by liquid chromatography (Waters Prep-500, two 5 x 30 cm silica gel columns, ca. 9:1 hexanes/ethyl acetate (adjusted to TLC R_f = 0.09), 250 mL/min) in three portions to afford 21.8 g (76%) of **8a** as a colorless oil (**8a**:**9a** = 98:2): IR (neat) 3030, 2920, 1780, 1700, 1490, 1450, 1380, 1340, 1190, 1120 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.42-7.20 (m, 15H, aromatic H's), 5.18 (d, J = 7.0 Hz, 1H, C_5-H), 4.61-4.52 (m, 2H, C_4-H, $C_{2'}$-H), 3.77 (d, J = 13.5 Hz, 1H, SCH(H)Ph), 3.72 (d, J = 13.5 Hz, 1H, SCH(H)Ph), 2.91 (d of d, J = 13.0, 8.8 Hz, 1H, $C_{3'}$-H), 2.86 (d of d, J = 13.0, 7.3 Hz, 1H, $C_{3'}$-H), 2.83 (d of d, J = 13.8, 9.9 Hz, 1H, $C_{2'}$-CH(H)S), 2.53 (d of d, J = 13.7, 5.0 Hz, 1H, $C_{2'}$-CH(H)S), 0.89 (d, J = 6.5 Hz, 3H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 174.5, 152.6, 138.2, 138.0, 133.1, 129.1, 128.9, 128.6, 128.4, 126.9, 126.6, 125.5, 78.7, 55.0, 44.6, 39.0, 35.9, 32.2, 14.4; Specific rotation $[\alpha]_{589}$ = +70.6°, $[\alpha]_{577}$ = +74.2°, $[\alpha]_{546}$ = +84.5°, $[\alpha]_{435}$ =

+150.0°, $[\alpha]_{365}$ = +253.1° (c 1.42, CH_2Cl_2); TLC (7:3 hexanes/ethyl acetate) R_f = 0.44.

Anal. Calcd. for $C_{27}H_{27}NO_3S$: C, 72.78; H, 6.11. Found: C, 73.03; H, 6.07.

(4S)-3-((2S)-1-Oxo-2-phenylmethylthiomethyl-3-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinones (9b). A magnetically stirred, cooled (-78°C) solution of LDA (prepared from 15.4 mL (11.1 g, 110 mmol) of diisopropylamine and 65 mL (1.69 M in hexane, 110 mmol) of n-butyllithium), (0.75 M in THF), was used to enolize 26.1 (100 mmol) of **4b**. After stirring for 0.5 h at -78°C the resultant lithium enolate was alkylated with 23.9 g (110 mmol) of benzyl bromomethyl sulfide (**5b**) for 2 h at -20°C. The reaction was quenched by addition of half-saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the product extracted into dichloromethane (3x). The combined organic extracts were successively washed with 1 M aqueous sodium bisulfate (2x), 1 M aqueous potassium bicarbonate (2x), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 53.0 g of a yellow oil. Analysis by GC (30 m DB-1, 175°C for 5 min, 20°C/min to 250°C, 60 cm/sec) afforded a 3:97 ratio of **8b** (t_r = 11.74 min) to **9b** (t_r = 11.53 min), and indicated the presence of imide **4b** (t_r = 4.17 min, ca. 10%). The title compound was isolated by liquid chromatography (Waters Prep-500, two 5 x 30 cm silica gel columns, 87:13 hexanes/ethyl acetate, 250 mL/min) in two portions to afford 33.1 g (83%) of **9b** as a viscous colorless liquid (**8b**:**9b** = 2:98): IR (neat) 3040, 2980, 2940, 1780, 1700, 1495, 1455, 1390, 1300, 1250, 1200, 1100, 700 cm^{-1}; ^1H NMR ($CDCl_3$/500

MHz) δ 7.30-7.16 (m, 10H, aromatic H's), 4.60 (m, 1H, $C_{2'}$-H), 4.27 (d of d of d, J = 8.5, 3.8, 2.5, 1H, C_4-H), 4.09 (d of d, J = 9.3, 2.7 Hz, 1H, C_5-H), 3.92 (d of d, J = 9.3, 8.7 Hz, 1H, C_5-H), 3.76 (d, J = 14.0 Hz, 1H, SCH(H)Ph), 3.70 (d, J = 14.0 Hz, 1H, SCH(H)Ph), 2.90 (d of d, J = 13.0, 8.0 Hz, 1H, $C_{3'}$-H), 2.80 (d of d, J = 13.5, 10.0 Hz, 1H, $C_{2'}$-CH(H)S), 2.78 (d of d, J = 13.0, 7.5 Hz, 1H, $C_{3'}$-H), 2.50 (d of d, J = 13.5, 4.5 Hz, 1H, $C_{2'}$-CH(H)S), 2.37 (d of septet, J = 3.8, 7.1 Hz, 1H, C_4-CH$(CH_3)_2$), 0.91 (d, J = 7.1 Hz, 3H, CH(CH_3)), 0.89 (d, J = 7.1 Hz, 3H, CH(CH_3)); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 174.6, 153.7, 138.2, 138.0, 129.1, 128.9, 128.4, 126.8, 126.5, 63.2, 58.7, 44.4, 38.7, 35.7, 32.3, 28.5, 17.9, 14.8; Specific rotation $[\alpha]_{589}$ = -29.1° (c 2.34, CH_2Cl_2); HPLC analysis (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min) k' **9b** = 3.26; TLC (7:3 hexanes/ethyl acetate) R_f = 0.54.

Anal. Calcd. for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85. Found: C, 69.62; H, 6.85.

Benzyl (2R)-2-Phenylmethylthiomethyl-3-phenylpropanoate (R-10). To a magnetically stirred, cooled (-10°C) solution of lithium benzyloxide (prepared from 3.7 mL (3.87 g, 35.8 mmol) of benzyl alcohol and 15.6 mL (1.69 M in hexane, 26.4 mmol) of n-butyllithium), (0.5 M in THF) was added a solution of 7.86 g (17.6 mmol) of **8a** in 20 mL of THF over a 0.5-h period. The reaction mixture was warmed to 0°C, stirred for 1.5 h, and then quenched by addition of half-saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the product extracted into dichloromethane (3x). The combined organic extracts were successively washed with water and brine, dried over anhydrous magnesium sulfate, and

concentrated *in vacuo* to give 11.2 g of a yellow oil. The title compound was isolated by flash chromatography (5 x 30 cm silica gel column, 9:1 hexanes/ethyl acetate) to afford 5.5 g (83%) of benzyl ester **R-10** as a colorless liquid. Further elution of the column with ethyl acetate afforded 2.3 g (75%) of 2-oxazolidinone **3a**.

R-10: IR (neat) 3070, 3040, 1735, 1600, 1490, 1450, 1210, 1160, 690 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 7.3-6.9 (m, 15H, aromatic H's), 5.0 (s, 2H, $OC\underline{H}_2Ph$), 3.6 (s, 2H, $SC\underline{H}_2Ph$), 3.0-2.3 (m, 5H, C_2-$\underline{H}$, C_2-$C\underline{H}_2S$, C_3-$\underline{H}_2$); Specific rotation $[\alpha]_{589}$ = +36.2°, $[\alpha]_{577}$ = +39.0°, $[\alpha]_{546}$ = +43.7°, $[\alpha]_{435}$ = +76.4°, $[\alpha]_{365}$ = +126.6° (*c* 0.856, CH_2Cl_2); GC (30 m DB-1, 200°C for 6 min, 25°C/min to 275°C, (injector, detector = 300°C), 63 cm/sec) t_r = 10.80 min; HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min) k' = 0.56; TLC (8:2 hexanes/ethyl acetate) R_f = 0.50.

Anal. Calcd. for $C_{24}H_{24}O_2S$: C, 76.56; H, 6.42. Found: C, 76.52; H, 6.37.

Benzyl (2S)-2-Phenylmethylthiomethyl-3-phenylpropanoate (S-10). To a magnetically stirred, cooled (-10°C) solution of lithium benzyloxide (prepared from 10.3 mL (10.8 g, 99.5 mmol) of benzyl alcohol and 44 mL (1.69 *M* in hexane, 75.0 mmol) of *n*-butyllithium), (0.75 *M* in THF) was added a solution of 19.8 g (49.7 mmol) of **9b** in 50 mL of THF over a 0.5 h period. The reaction mixture was warmed to 0°C and stirred for 3 h. The reaction was quenched by addition of half-saturated aqueous ammonium chloride. Volatiles were removed *in vacuo* and the product extracted into dichloromethane (3x). The combined organic extracts were

successively washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 28.4 g of a yellow oil. The title compound was isolated by liquid chromatography (Waters Prep-500, two 5 x 30 cm silica gel columns, 95:5 hexanes/ethyl acetate, 250 mL/min) to afford 15.3 g (82%) of benzyl ester **S-10** as a colorless liquid. Further elution with ethyl acetate afforded 4.8 g (75%) of 2-oxazolidinone **4a**.

S-10: IR (neat) 3070, 3040, 2920, 1735, 1490, 1450, 1160, 695 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.4-6.9 (m, 15H, aromatic H's), 5.0 (s, 2H, OCH_2Ph), 3.5 (s, 2H, SCH_2Ph), 2.9-2.2 (m, 5H, C_2-H, C_2-CH_2S, C_3-H_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) 173.7, 138.3, 138.0, 135.7, 128.9, 128.4, 128.1, 126.9, 126.5, 66.4, 47.6, 37.8, 36.3, 32.4; Specific rotation $[\alpha]_{589}$ = -34.6° (*c* 2.46, CH_2Cl_2); GC (30 m DB-1, 200°C for 6 min, 25 °C/min to 275°C, (injector, detector = 300°C), 94 cm/sec) t_r = 9.66 min; HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 88:12 isooctane/ethyl acetate, 2.0 mL/min) k' = 0.56; TLC (8:2 hexanes/ethyl acetate) R_f = 0.50.

Anal. Calcd. for $C_{24}H_{24}O_2S$: C, 76.56; H, 6.42. Found: C, 76.82; H, 6.51.

(2R)-2-Phenylmethylthiomethyl-3-phenylpropanoic acid (R-11). A magnetically stirred solution of 2.01 g (5.35 mmol) of benzyl ester **R-10** in 9 mL of 6 *M* anhydrous hydrogen bromide in glacial acetic acid was stirred at 50°C for 15 min. The reaction mixture was diluted with 20 mL of water and extracted with dichloromethane (4 x 20 mL). The combined organic extracts were concentrated *in vacuo*. The residue was diluted with toluene (50 mL) and concentrated *in vacuo* three times to remove acetic acid. The residue was dissolved in 1 *M* aqueous potassium hydrox-

ide, washed with dichloromethane, acidified to pH 1 with concentrated aqueous hydrochloric acid, and extracted with dichloromethane. The combined organic extracts were concentrated in vacuo afforded 1.31 g (85%) of carboxylic acid **R-11** as a colorless oil. An analytical sample was purified by molecular distillation (Kugelrohr, 140°C, 0.01 mm): IR (neat) 3400-2400, 1710, 1600, 1490, 1450, 1235, 690 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 11.4 (br s, 1H, $CO_2\underline{H}$), 7.1 (m, 10H, aromatic H's), 3.6 (s, 2H, $SC\underline{H}_2Ph$), 3.0-2.3 (m, 5H, C_2-$\underline{H}$, C_2-$C\underline{H}_2S$, C_3-$\underline{H}_2$); Specific rotation $[\alpha]_{589}$ = +54.1°, $[\alpha]_{577}$ = +55.3°, $[\alpha]_{546}$ = +64.5°, $[\alpha]_{435}$ = +113.2°, $[\alpha]_{365}$ = +189.6° (c 1.54, abs. EtOH).

Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.34. Found: C, 71.58; H, 6.52.

(2S)-2-Phenylmethylthiomethyl-3-phenylpropanoic acid (S-11). A magnetically stirred solution of 9.13 g (24.2 mmol) of benzyl ester **S-10** in 35 mL of 6 M anhydrous hydrogen bromide in glacial acetic acid was stirred at 50°C for 20 min. The reaction mixture was diluted with 35 mL of water and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were concentrated in vacuo. The residue was diluted with toluene (100 mL) and concentrated in vacuo three times to remove acetic acid. The residue was dissolved in 1 M aqueous potassium hydroxide, washed with dichloromethane, acidified to pH 1 with concentrated aqueous hydrochloric acid, and extracted with dichloromethane. The combined organic extracts were concentrated in vacuo afforded 5.77 g (83%) of carboxylic acid **S-11** as a pale-yellow oil. An analytical sample was purified by molecular distillation (Kugelrohr, 140°C, 0.01 mm): IR

(neat) 3500-2500, 1710, 1495, 1455, 1240, 700 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 9.7-9.3 (br s, 1H, $CO_2\underline{H}$), 7.2 (s, 10H, aromatic H's), 3.6 (s, 2H, $SC\underline{H}_2Ph$), 3.0-2.5 (m, 5H, C_2-$\underline{H}$, C_2-$C\underline{H}_2S$, C_3-$\underline{H}_2$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 180.1, 138.0, 137.9, 128.8, 128.5, 127.0, 126.6, 47.4, 37.3, 36.5, 31.8; Specific rotation $[\alpha]_{589}$ = -50.6° (c 1.57, abs. EtOH).

Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.34. Found: C, 71.12; H, 6.29.

Benzyl N-[(2R)-2-phenylmethylthiomethyl-3-phenylpropanoyl)glycinate [(2R)-S-Benzylthiorphan, benzyl ester, (R-12)]. To a magnetically stirred, cooled (-30°C) solution of 1.66 g (5.79 mmol) of carboxylic acid **R-11** and 2.15 g (6.37 mmol) of the p-toluenesulfonate salt of benzyl glycinate in 15 mL of anhydrous dimethylformamide was added 1.37 mL (1.75 g, 6.36 mmol) of diphenylphosphoryl azide followed by 1.77 mL (1.29 g, 12.7 mmol) of triethylamine. The reaction mixture was stirred for 4 h at -10°C, then overnight at room temperature. The resultant mixture was diluted with 1,1,1-trichloroethane (100 mL) and successively washed with water (3x), 1 M aqueous potassium hydroxide (3x), 1 M aqueous sodium bisulfate (2x), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 3.5 g of a pale yellow oil. The title compound was isolated by flash chromatography (5 x 20 cm silica gel column, 7:3 hexanes/ethyl acetate) to afford 2.28 g (91%) of benzyl ester **R-12** as a white solid. An analytical sample was recrystallized from hexanes/ethyl acetate: mp 72-73°C; IR (CH_2Cl_2) 3440, 3050, 2990, 1750, 1680, 1270, 1250 cm^{-1}; ^1H NMR (CCl_4/90 MHz) δ 7.3-6.9 (m, 15H, aromatic H's), 6.0 (br t, J = 6 Hz, 1H, N-$\underline{H}$), 5.0 (s, 2H, $OC\underline{H}_2Ph$), 3.8 (m, 2H, $NC\underline{H}_2CO$), 3.5 (s, 2H, $SC\underline{H}_2Ph$), 2.9-2.2 (m, 5H, C_2'-

H, $C_{2'}$-CH_2S, $C_{3'}$-H_2); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 173.6, 169.5, 138.9, 138.5, 135.1, 128.9, 128.5, 127.5, 126.4, 67.1, 49.7, 41.3, 38.3, 37.0, 33.3; Specific rotation $[\alpha]_{589}$ = +25.2°, $[\alpha]_{577}$ = +26.7°, $[\alpha]_{546}$ = +30.6°, $[\alpha]_{435}$ = +53.6°, $[\alpha]_{365}$ = +89.8° (c 1.61, abs. EtOH); GC (30 m DB-1, 275°C, (injector, detector = 300°C), 86 cm/sec) t_r = 6.19 min; HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 64:36 isooctane/ethyl acetate, 2.0 mL/min) k' = 0.77; TLC (7:3 hexanes/ethyl acetate) R_f = 0.25.

Anal. Calcd. for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28. Found: C, 72.14; H, 6.35.

Benzyl N-((2S)-2-phenylmethylthiomethyl-3-phenylpropanoyl)glycinate, [(2S)-S-Benzylthiorphan, benzyl ester, (S-12)]. To a magnetically stirred, cooled (-30°C) solution of 5.70 g (19.9 mmol) of carboxylic acid **S-11** and 7.43 g (22.0 mmol) of the p-toluenesulfonate salt of benzyl glycinate in 50 mL of anhydrous dimethylformamide was added 4.7 mL (6.0 g, 21.8 mmol) of diphenylphosphoryl azide followed by 6.1 mL (4.4 g, 44 mmol) of triethylamine. The reaction was stirred for 4 h at -10°C, then overnight at room temperature. The resultant mixture was diluted with 1,1,1-trichloroethane (100 mL) and successively washed with water (3x), 1 M aqueous potassium hydroxide (2x), 1 M aqueous sodium bisulfate (2x), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 10.6 g of a yellow oil. The title compound was isolated by liquid chromatography (Waters Prep-500, two 5 x 30 cm silica gel columns, 9:1 hexanes/ethyl acetate, 250 mL/min) to afford 7.34 g (85%) of benzyl ester **S-12** as a white solid. An analyt-

3070, 3040, 2930, 1750, 1660, 1450, 1180, 700 cm^{-}; ^{1}H NMR ($CDCl_3$/90 MHz) δ 7.5-7.0 (m, 15H, aromatic H's), 5.7 (br t, J = 6 Hz, 1H, N-H), 5.1 (s, 2H, OCH_2Ph), 3.9 (m, 2H, $NHCH_2CO$), 3.6 (s, 2H, SCH_2Ph), 2.9-2.1 (m, 5H, $C_{2'}$-H, $C_{2'}$-CH_2S, $C_{3'}$-H_2); Specific rotation $[\alpha]_{589}$ = -24.5°, $[\alpha]_{577}$ = -26.2°, $[\alpha]_{546}$ = -29.6°, $[\alpha]_{435}$ = -52.3°, $[\alpha]_{365}$ = -87.9° (c 1.82, abs. EtOH); GC (30 m DB-1, 275°C, (injector, detector = 300°C), 86 cm/sec) t_r = 6.14 min; HPLC (8 mm x 10 cm Radial Pak (5 μm silica gel), 64:36 isooctane/ethyl acetate, 2.0 mL/min) k' = 0.77; TLC (7:3 hexanes/ethyl acetate) R_f = 0.25.

Anal. Calcd. for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28. Found: C, 72.23; H, 6.35.

N-((2R)-1-Oxo-2-mercaptomethyl-3-phenylpropyl)glycine, [(2R)-Thiorphan, (R-1)]. To a magnetically stirred, cooled (-33°C) solution of 0.462 g (1.07 mmol) of benzyl ester **R-12** in 20 mL of THF and 30 mL of anhydrous ammonia (distilled from sodium) was added 0.13 g (5.8 mmol) of sodium in six portions over a 0.5 h period. After the reaction mixture had remained dark-blue for 10-15 min, the reaction was quenched by addition of 0.37 g (6.9 mmol) of ammonium chloride. The ammonia was evaporated under a stream of nitrogen, and the THF removed in vacuo. The residue was dissolved in 5 mL of 1 M aqueous potassium hydroxide and washed with diethyl ether to remove toluene and dibenzyl. The aqueous solution was cooled to 0°C, acidified to pH 1 with concentrated aqueous hydrochloric acid, and the product extracted into diethyl ether. The etheral solution was dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 0.246 g (91%) of (2R)-thiorphan **R-1** as a colorless oil which slowly solidified upon standing: mp 108-110°C; ^{1}H

NMR ($CDCl_3$/500 MHz) δ 7.16-7.09 (m, 5H, aromatic H's), 6.72 (br s, 1H, N-H), 4.05 (d of d, J = 15, 5 Hz, 1H, NCH(H)CO), 3.85 (d of d, J = 15, 5 Hz, 1H, NCH(H)CO), 2.95-2.50 (m, 5H, $C_{2'}$-H, $C_{2'}$-CH_2S, $C_{3'}$-H_2), 1.67 (br t, J = 7 Hz, 1H, S-H); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 147.7, 172.6, 138.2, 128.8, 128.5, 126.7, 52.8, 41.4, 38.0, 26.0; Specific rotation $[\alpha]_{589}$ = -40.1° (c 2.25, abs. EtOH); TLC (98:2 ethyl acetate/acetic acid) R_f = 0.31.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; S, 12.66. Found: C, 56.71; H, 6.19; S, 12.88.

N-((2S)-1-Oxo-2-mercaptomethyl-3-phenylpropyl)glycine, [(2S)-Thiorphan, (S-1)). To a magnetically stirred, cooled (-33°C) solution of 4.33 g (10.0 mmol) of benzyl ester **S-12** in 100 mL of THF and 100 mL of anhydrous ammonia (distilled from sodium) was added 0.92 g (40 mmol) of sodium in ca. six portions over a 0.5 h period. After the reaction mixture had remained dark-blue for 10-15 min the reaction was quenched by addition of 2.14 g (40 mmol) of ammonium chloride. The ammonia was evaporated under a stream of nitrogen and the THF was removed in vacuo. The residue was dissolved in 20 mL of 1 M aqueous potassium hydroxide and washed with diethyl ether to remove toluene and dibenzyl. The aqueous solution was cooled to 0°C, acidified to pH 1 with concentrated aqueous hydrochloric acid, and the product extracted into diethyl ether. The etheral solution was dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 2.43 g (96%) of (2S)-thiorphan **S-1** as a colorless oil, which slowly solidified: mp 110-111°C; IR (neat) 3500-2500, 1740, 1650, 1540, 1210, 700 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 9.2 (br

s, 1H, $CO_2\underline{H}$), 7.2 (m, 5H, aromatic H's), 6.3 (br t, J = 6 Hz, 1H, N-$\underline{H}$), 4.1 (d of d, J = 18, 6 Hz, 1H, NC$\underline{H}$(H)CO), 3.8 (d of d, J = 18, 6 Hz, 1H, NCH($\underline{H}$)CO), 3.0-2.4 (m, 5H, $C_{2'}$-$\underline{H}$, $C_{2'}$-$C\underline{H}_2$S, $C_{3'}$-$\underline{H}_2$), 1.6 (br t, J = 9 Hz, S-$\underline{H}$); Specific rotation $[\alpha]_{589}$ = +39.6° (c 2.78, abs. EtOH); TLC (98:2 ethyl acetate/acetic acid) R_f = 0.31.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; S, 12.66. Found: C, 56.79; H, 6.00; S, 12.53.

Determination of the Enantiomeric Purity of (R) and (S)-Thiorphan. A magnetically stirred solution of 89.5 mg (353 μmol) of (±)-thiorphan, 44 μL (51 mg, 360 μmol) of boron trifluoride--diethyl etherate in 5 mL of anhydrous methanol was heated at 50°C for 4 h (until no starting material remained by TLC analysis). The mixture was diluted with dichloromethane, washed with 1 M aqueous potassium carbonate, water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 102 mg (108% mass balance) of (±)-thiorphan, methyl ester as a pale yellow oil.

A mixture of 27 mg (100 μmol) of (±)-thiorphan, methyl ester, 20 mg (100 μmol) of (R)-1-(1-naphthyl)ethyl isocyanate (**13**),[11] and 10 mg of anhydrous potassium carbonate in 2 mL of benzene was heated at 80°C for 4 h (until no starting material remained by TLC analysis). The mixture was diluted with dichloromethane, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 50 mg (106% mass balance) of a mixture of thiourethane diastereomers **14** and **15**. The unfractionated product was analyzed by HPLC (Regis, 4.6 mm x 25 cm, Pirkle chiral phases covalently bound to 5 μm aminopropyl silica gel; 84:16 isooctane/isopropanol; 4.0 mL/min) k' **14** = 8.16, k' **15** =

11.91; α = 1.46).

The reactions were repeated separately with (2R) and (2S)-thiorphan **1**. HPLC analysis of the unfractionated product obtained from (2R)-thiorphan (**R-1**), showed a $\geq$ 95:5 ratio of **14** to **15**. Likewise, HPLC analysis of the unfractionated product obtained from (S)-thiorphan (**S-1**), showed a $\leq$ 5:95 ratio of **14** to **15**. Therefore, the enantiomeric ratio of the synthetic (2R) and (2S)-thiorphan is > 95:5.

NOTES AND REFERENCES

1. An edited version of this paper has been submitted for publication: Evans, D. A.; Mathre, D. J.; Scott, W. L. J. Am. Chem. Soc.

2. (a) Smith, T. W.; Wilkinson, S. In "The Chemical Regulation of Biological Mechanisms," Creighton, A. M.; Turner, S. Eds.; The Royal Society of Chemistry, London, 1981, pp 230-254. (b) Miller, R. J. In "Handbook of Psychopharmacology," Iversen, L. L.; Iversen, S. D.; Snyder, S. H. Ed.; Plenum: New York, 1983; Vol. 16, Chapter 2, and references contained therein.

3. (a) Malfroy, B.; Swerts, J. P.; Guyon, A.; Rogues, B. P.; Schwartz, J. C. Nature **1978**, 276, 523. (b) Gorenstein, C.; Synder, S. H. Life Sci. **1979**, 25, 2065.

4. (a) Llorens, C.; Gacel, G.; Swerts, J.-P.; Perdrisot, R.; Fournie-Zaluski, M.-C.; Schwartz, J.-C.; Roques, B. P. Biochem. Biophys. Res.Commun. **1980**, 96, 1710-1716. (b) Patey, G.; De La Baume, S.; Schwartz, J.-C.; Gros, C.; Roques, B.; Fournie-Zaluski, M.-C.; Soroca-Lucas, E. Science **1981**, 212, 1153-1155. (c) Roques, B. P.; Fournie-Zaluski, M. C.; Florentin, D.; Waksman, G.; Sassi, A.; Chaillet, P.; Collado, H.; Costentin, J. Life Sciences **1982**, 31, 1749-1752. (d) Zhang, A.-Z.; Yang, H.-Y. T.; Costa, E. Neuropharmacology **1982**, 21, 625-630. (e) Chaillet, P.; Marcais-Collado, H.; Costentin, J.; Yi, C.-C.; de la Baume, S.; Schwartz, J.-C. Eur. J. Pharmac. **1983**, 86, 329-336.

5. (a) Chipkin, R. E.; Latranyi, M. Z.; Iorio, L. C.; Barnett, A. Eur. J. Pharmac. **1982**, 83, 283-288. (b) Chipkin, R. E.; Latranyi, M. B.; Iorio, L. C. Life Sciences **1982**, 31, 1189-1192. (c)

Greenburg, R.; O'Keefe, E. H.; Life Sciences **1982**, 31, 1185-1188.

6. Roques, B. B.; Fournie-Zaluski, M. C.; Soroca, E.; Lecomte, J. M.; Malfroy, B.; Llorens, C.; Schwartz, J.-C. Nature **1980**, 288, 286-288.

7. (a) Mumford, R. A.; Zimmerman, M.; ten Broeke, J.; Taub, D.; Joshua, H.; Rothrock, J. W.; Hirshfield, J. M.; Springer, J. P.; Patchett, A. A. Biochem.Biophys. Res. Commun. **1982**, 109, 1303-1309. (b) Almenoff, J.; Orlowski, M. Biochemistry **1983**, 22, 590-599. (c) Almenoff, J.; Orlowski, M. J. Neurochem. **1984**, 42, 151-157.

8. Scott, W. L.; Mendelsohn, L. G.; Cohen, M. L.; Frederickson, R. C. A.; Evans, D. A. Life Sciences **1984**, manuscript submitted.

9. (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. J. Am. Chem. Soc. **1982**, 104, 1737-1739. (b) For a general review of the utility of these chiral auxiliaries for asymmetric synthesis see: Evans, D. A. Aldrichimica Acta **1982**, 15, 23.

10. For a general review of the synthesis and chemistry of 2-oxazolidinones see: Dyen, M. E.; Swern, D. Chem. Rev. **1967**, 67, 197.

11. Purchased from Aldrich Chemical Co.

12. (a) Newman, M. S.; Kutner, A. J. Am. Chem. Soc. **1951**, 73, 4199. (b) Fodor, G.; Stefanovsky, J.; Kurtev, B. Montash Chem. **1967**, 98, 1027-1042.

13. Homeyer, A. H. U. S. Patent 2,399,118. Chemical Abstracts **1946**, 40, 4084[6].

14. (S)-Valinol can either be purchased from Aldrich Chemical Co. or prepared by the reduction of (S)-valine with borane--dimethyl

sulfide/boron trifluoride--diethyl etherate as described in the following patent: Lane, C. F. U. S. Patent 3,935,280. Chemical Abstracts **1976** 84, 135101p.

15. Iwakura, Y.; Hayashi, K.; Inagaki, K. Makromol. Chem. **1967**, 104, 56-65.

16. The enantiomeric purity of the 2-oxazolidinones employed in this study were determined to be > 99% by capillary GC analysis of the imides derived from the Mosher acid chloride: Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. **1969**, 34, 2543-2549.

17. Evans, D. A.; Bartroli, J.; Shih, T. J. Am. Chem. Soc. **1981**, 103, 2127-2129.

18. Wood, J. L.; du Vigneaud, V. J. Biological Chem. **1939**, 131, 267-271.

19. Evans, D. A.; Ennis, M. D.; Le, T. L. J. Am. Chem. Soc. **1984**, 106, 1184.

20. Hollowood, J.; Jansen, A. B. A.; Southgate, P. J. J. Med. Chem. **1967**, 10, 863-867.

21. Maclaren, J. A.; Savige, W. E.; Swan, J. M. Aust. J. Chem. **1958**, 11, 345-359.

22. Shiori, T.; Ninomiya, K.; Yamada, S.-I. J. Am. Chem. Soc. **1972**, 94, 6203-6205.

23. Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, 43, 2923-2925.

24. Schon, I.; Szirtes, T.; Uberhardt, T. J. Chem. Soc. Chem. Commun. **1982**, 639-640.

25. Pirkle, W. H.; Hoekstra, M. S. J. Org. Chem. **1974**, 39, 3904-3906.

26. Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. J. Am.

Chem. Soc. **1981**, 103, 3964-3966.

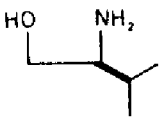
27. Southern California Regional NMR Facility.

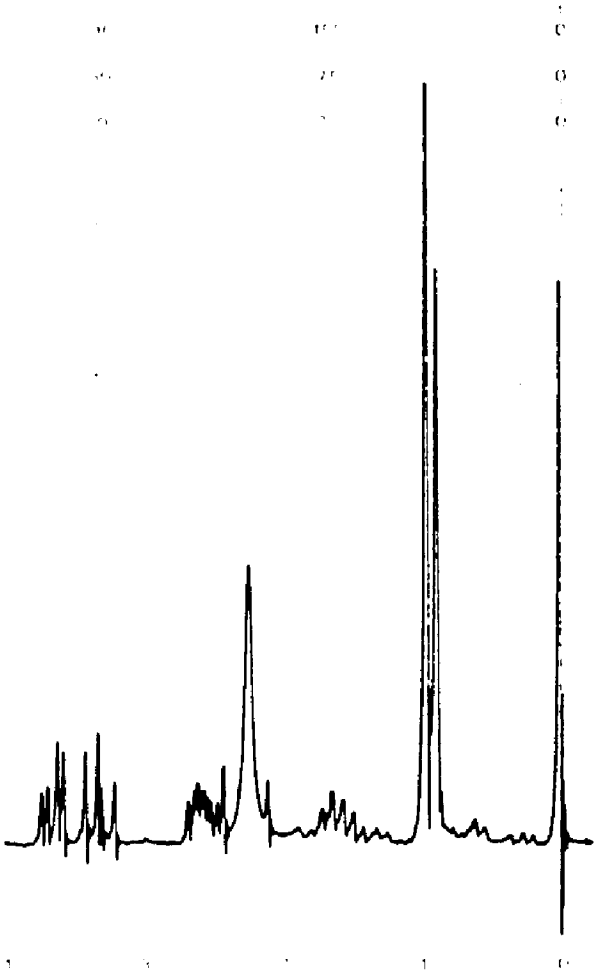
28. It may be necessary to remove the Vigreux column to distil the last traces of ethanol.

APPENDIX III

IR ^{1}H NMR, AND ^{13}C NMR SPECTRAL CATALOG FOR CHAPTER 1

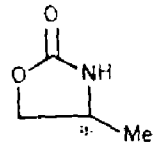
Compound (S)-Valinol

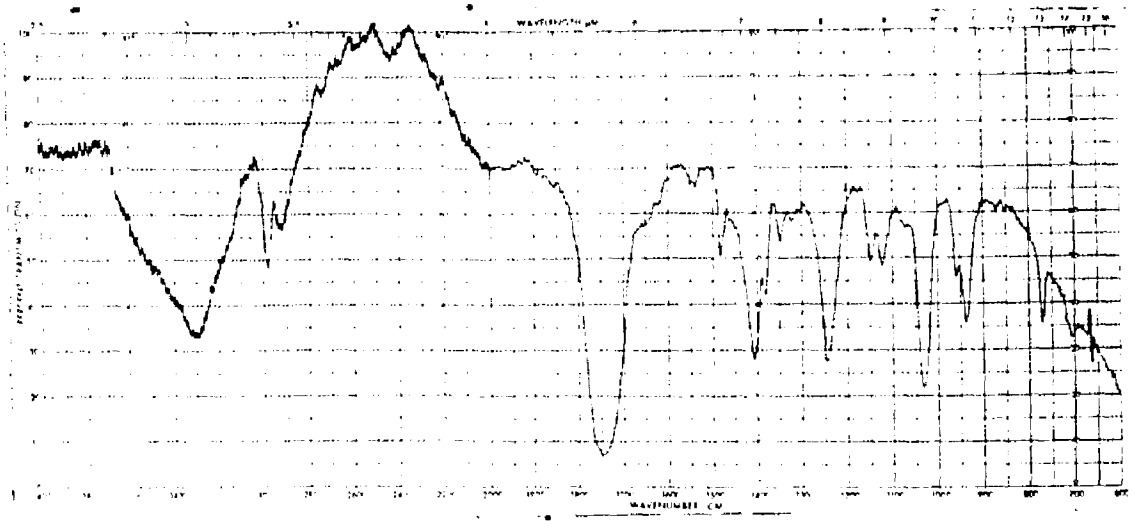




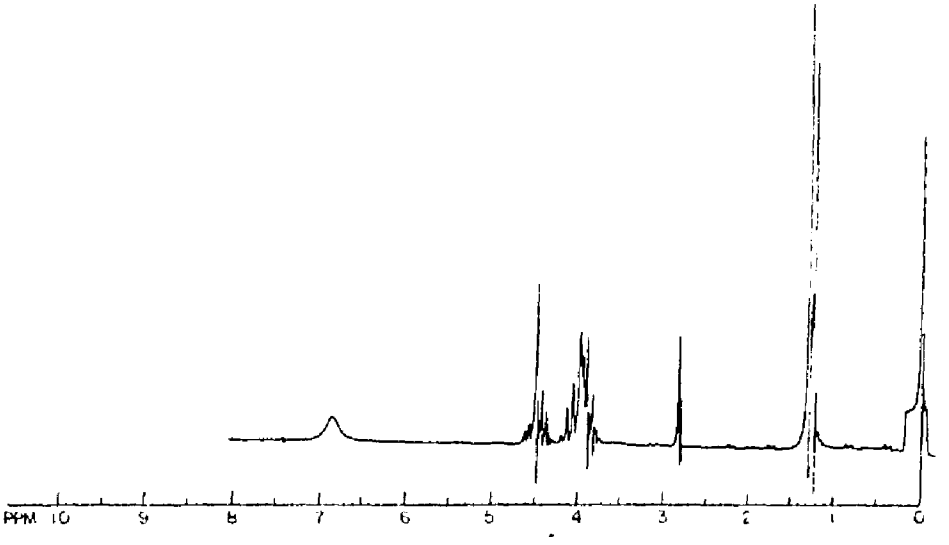
^{1}H NMR 90 MHz $CDCl_3$

Compound (±)-**5**



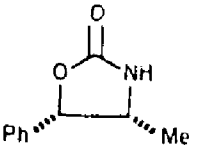


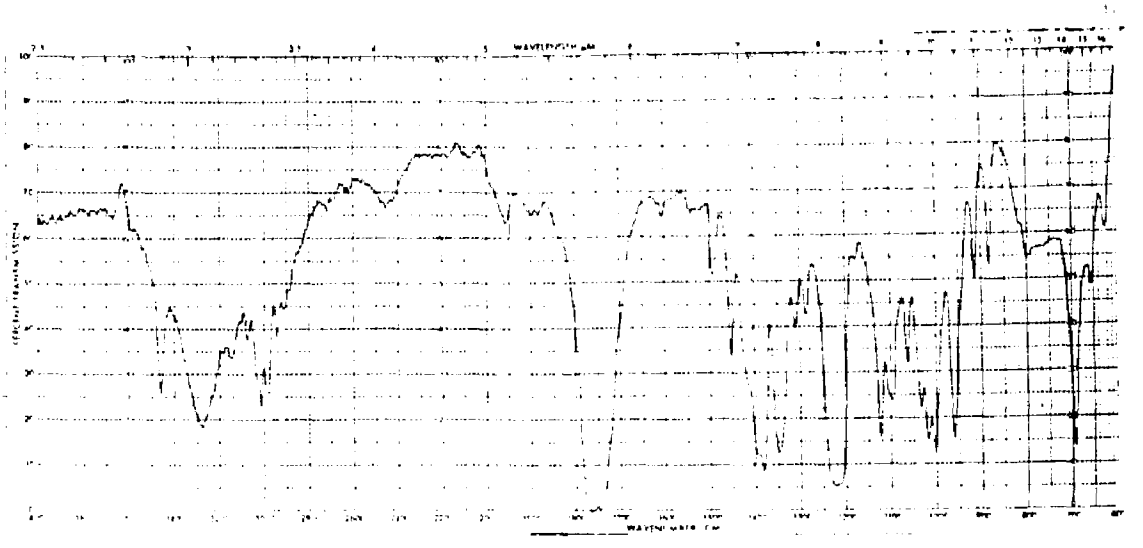
IR (neat)



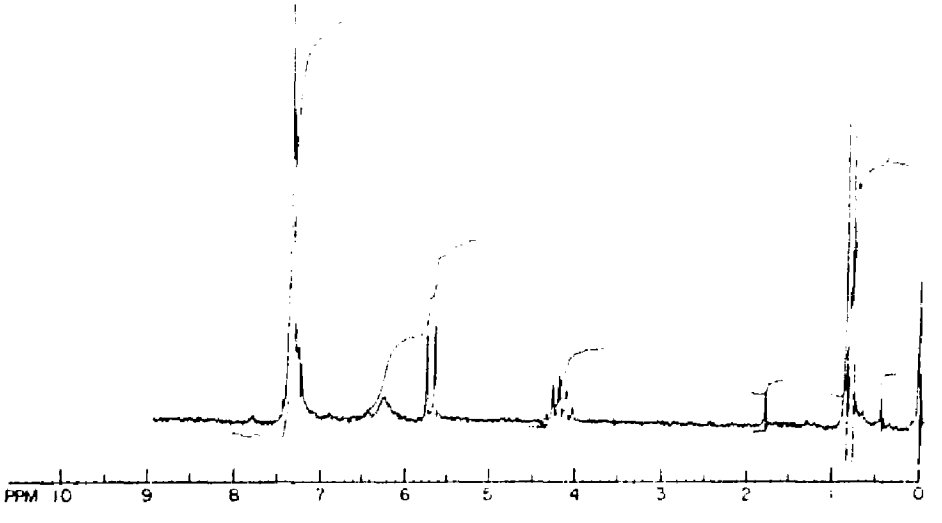
^{1}H NMR (90 MHz/$CDCl_3$)

Compound **6**



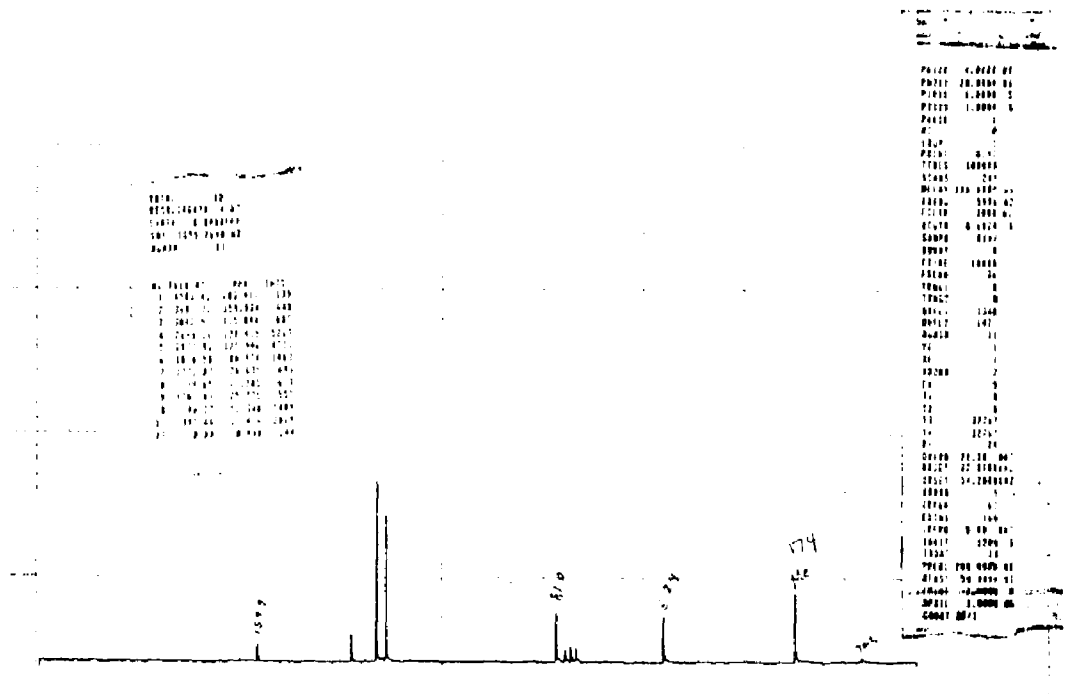


IR ($CHCl_3$)



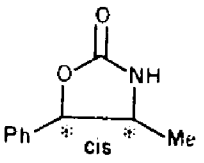
^1H NMR (90 MHz/$CDCl_3$)

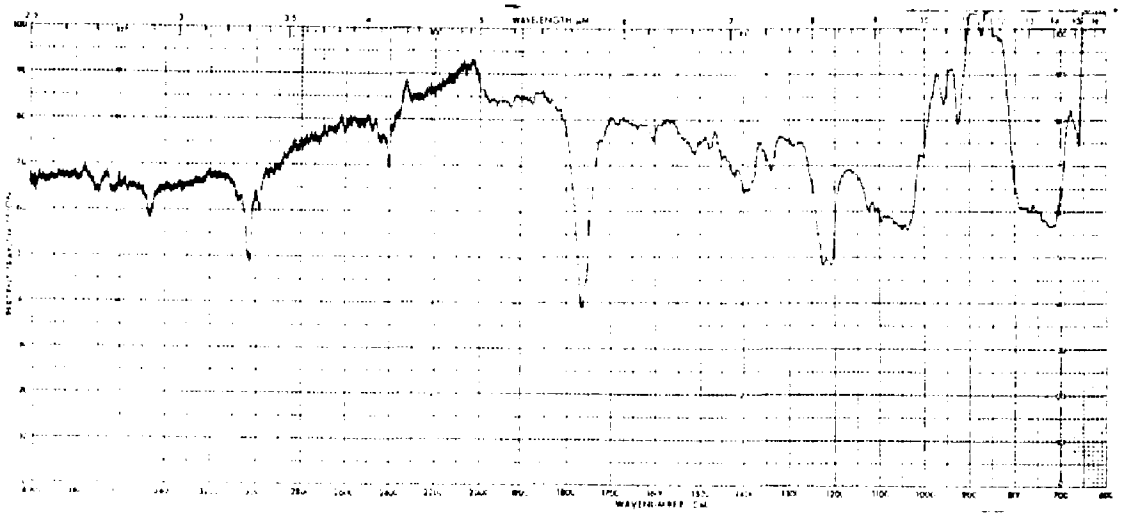
Compound **6** continued.



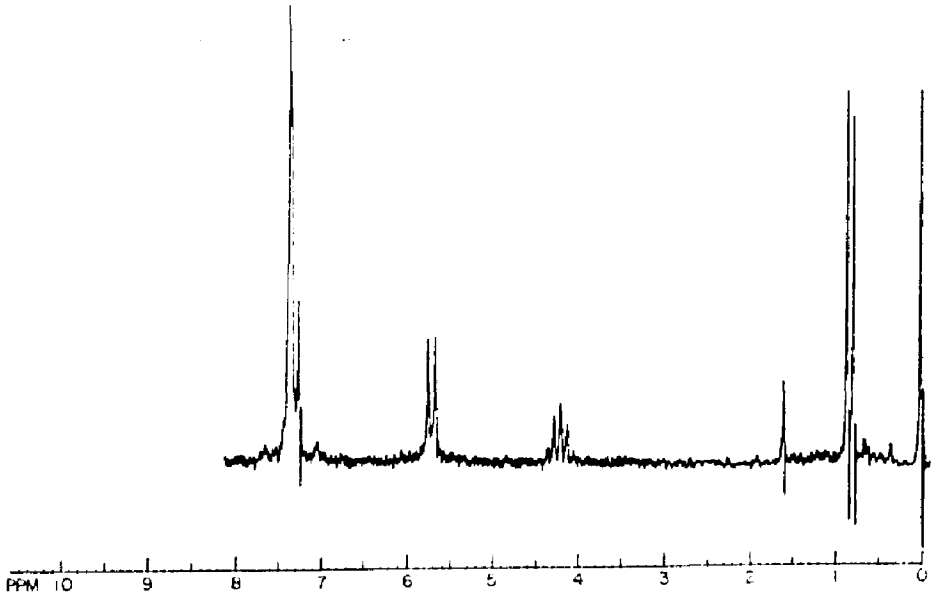
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound (±)-**6**



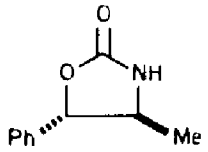


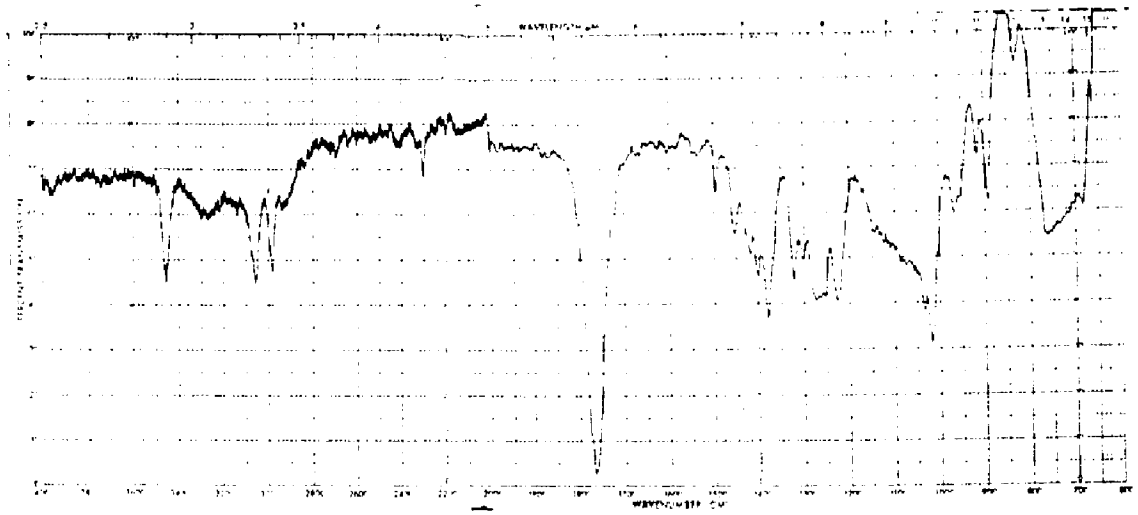
IR ($CHCl_3$)



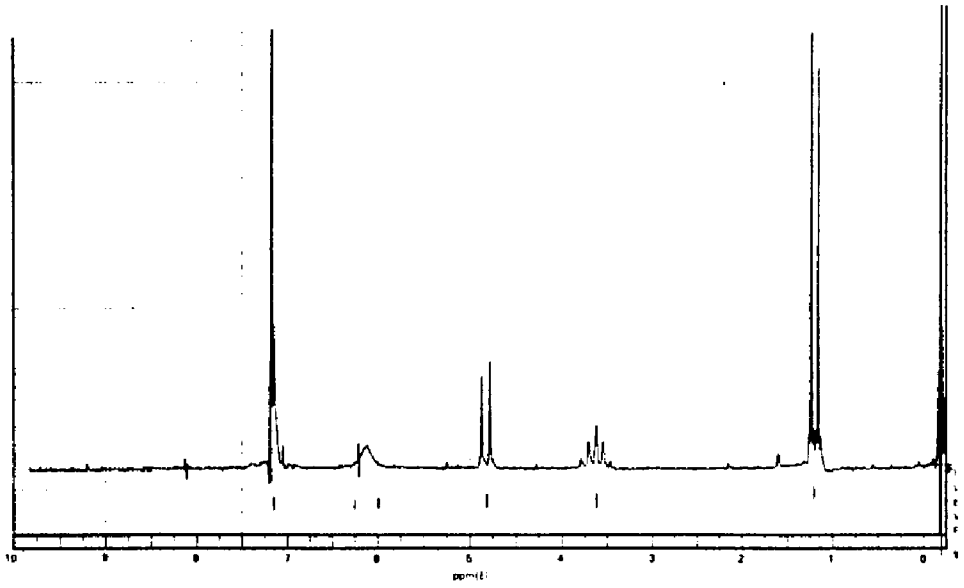
^1H NMR (90 MHz/$CDCl_3$)

Compound 7



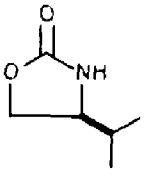


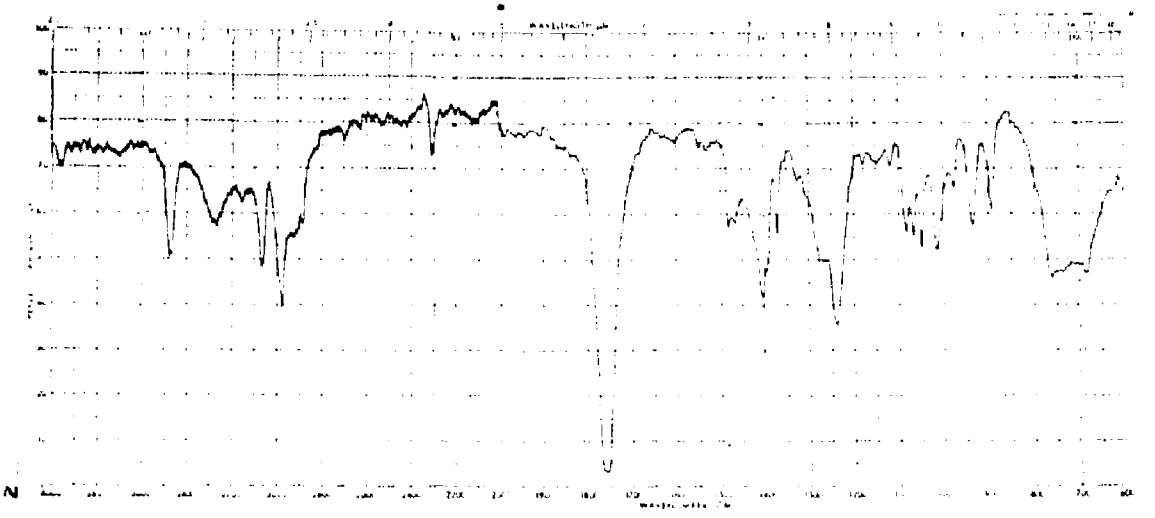
IR (CH_2Cl_2)



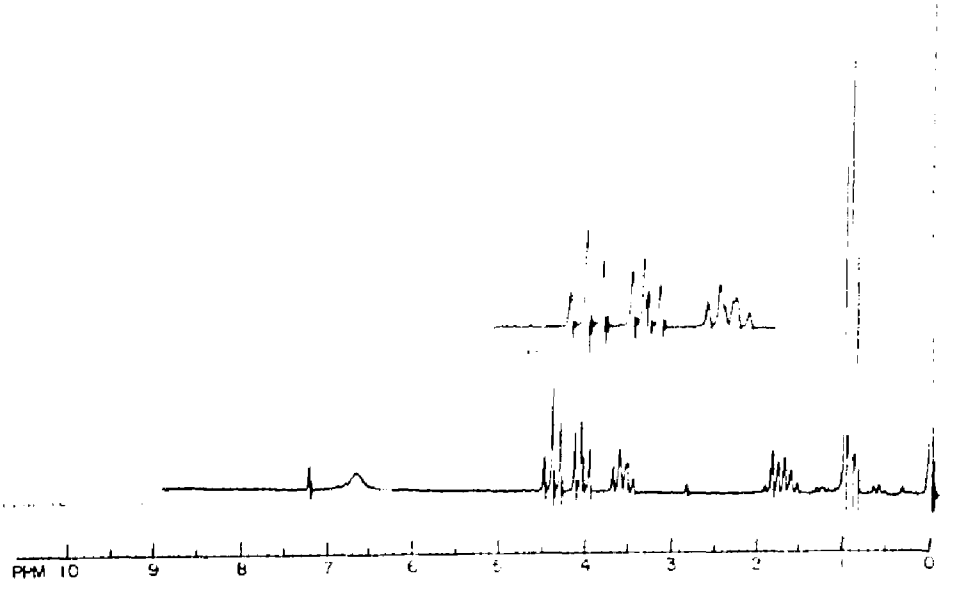
^1H NMR (90 MHz/$CDCl_3$)

Compound 8



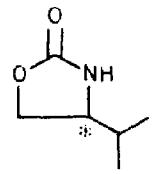


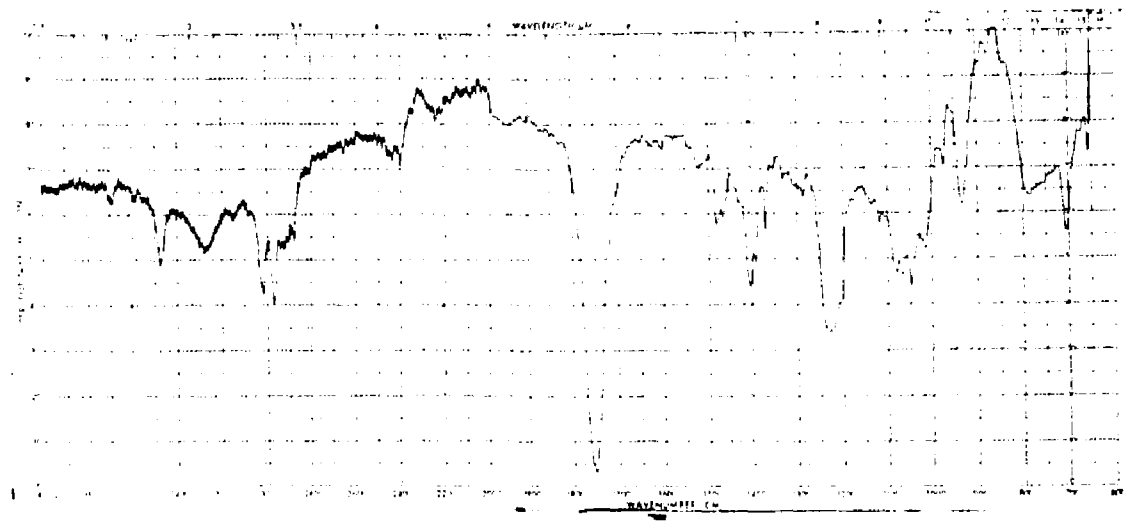
IR (CH_2Cl_2)



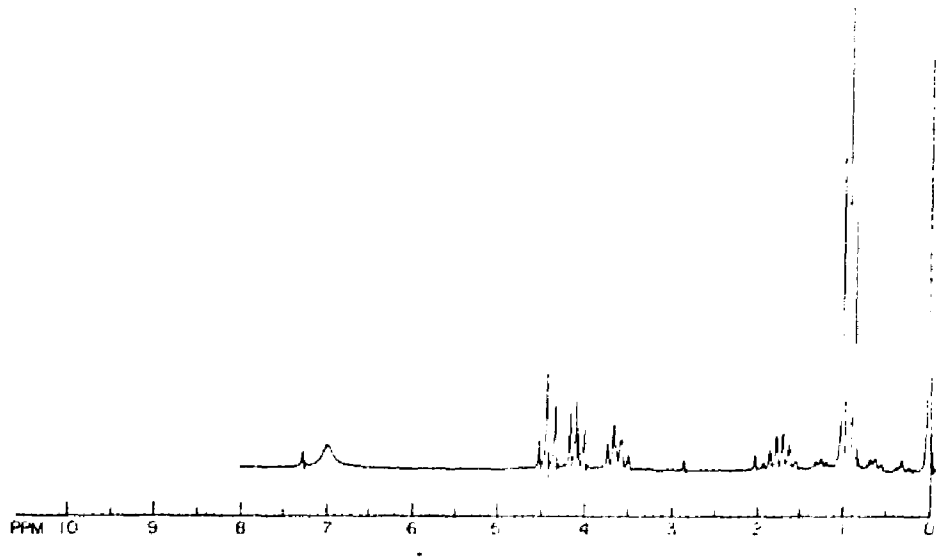
^1H NMR (90 MHz/$CDCl_3$)

Compound (±)-**8**



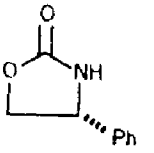


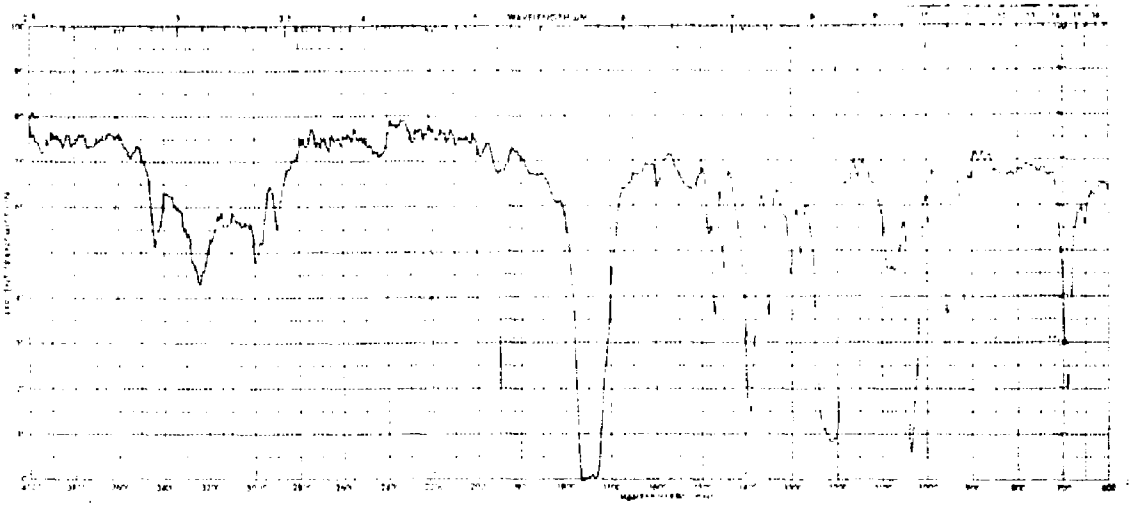
IR ($CHCl_3$)



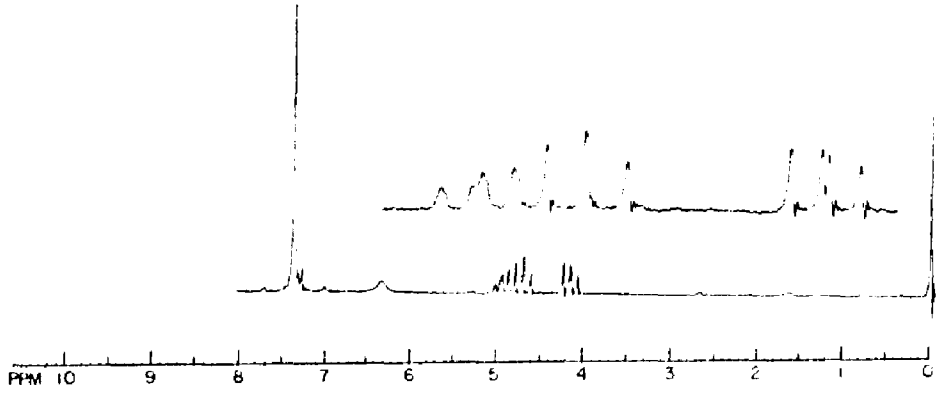
^1H NMR (90 MHz/$CDCl_3$)

Compound **9**



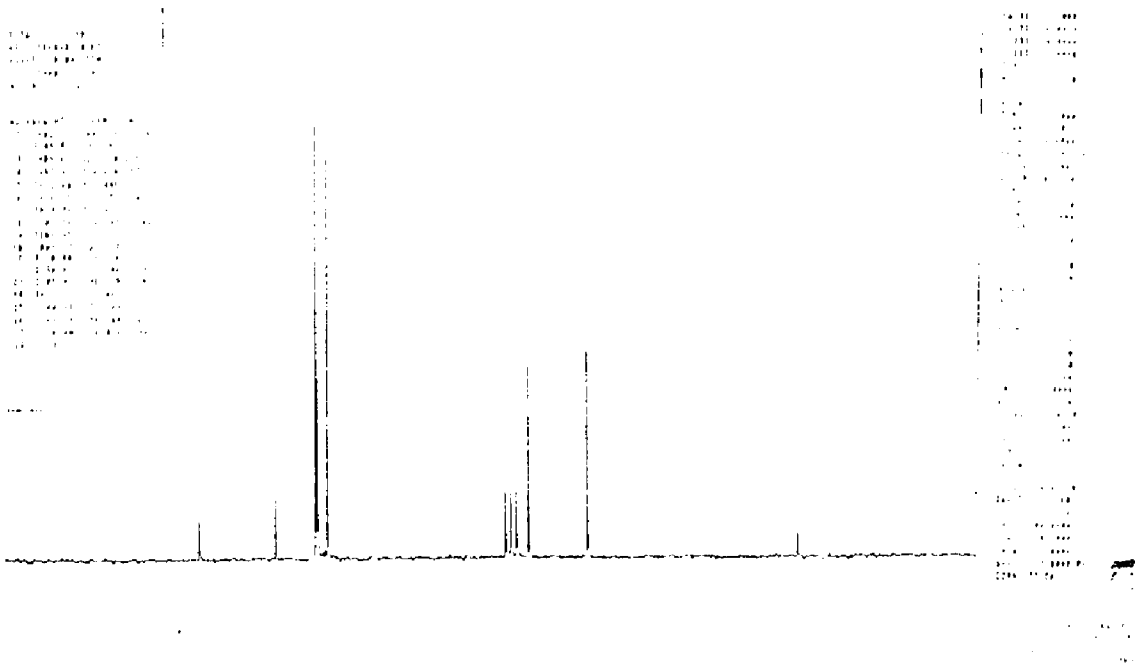


IR ($CHCl_3$)



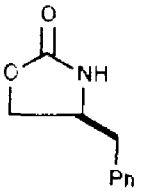
^1H NMR (90 MHz/$CDCl_3$)

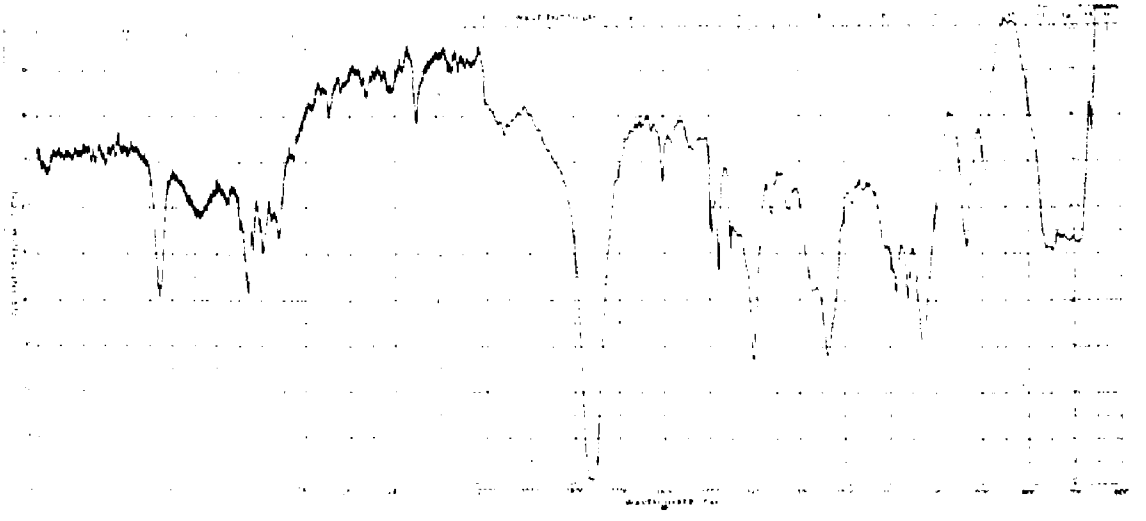
Compound **9** continued.



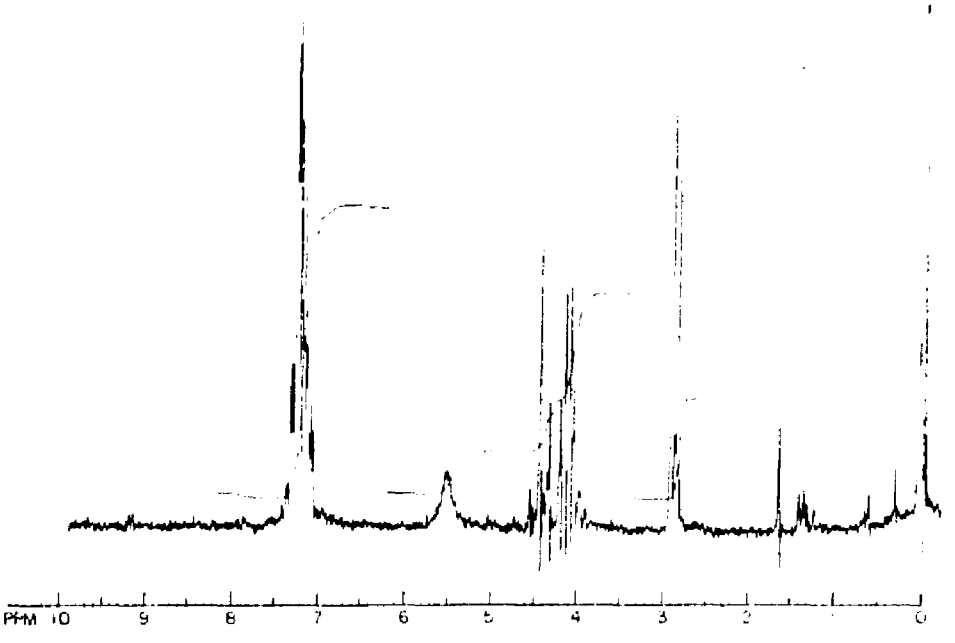
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **10**



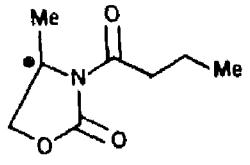


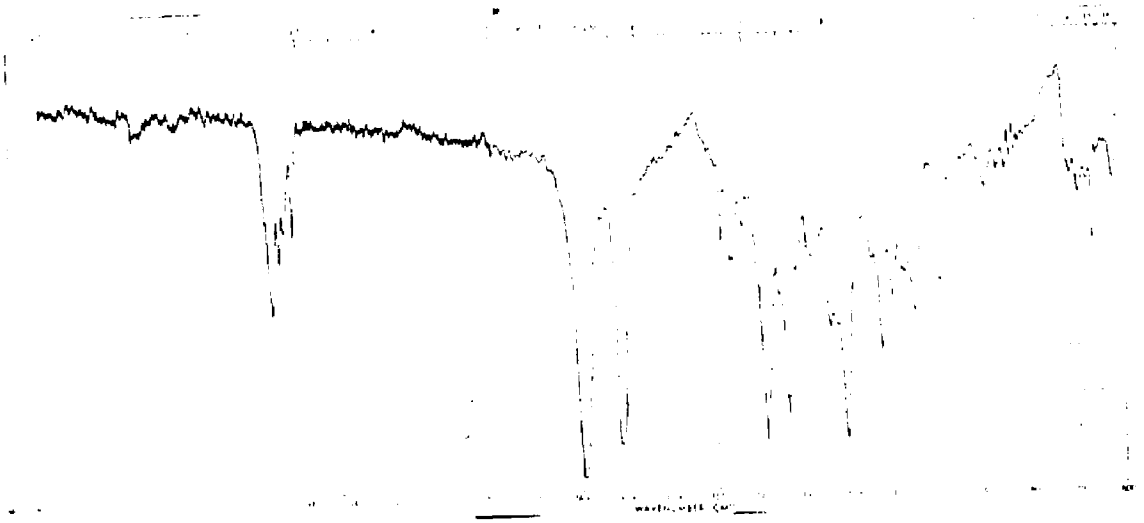
IR ($CHCl_3$)



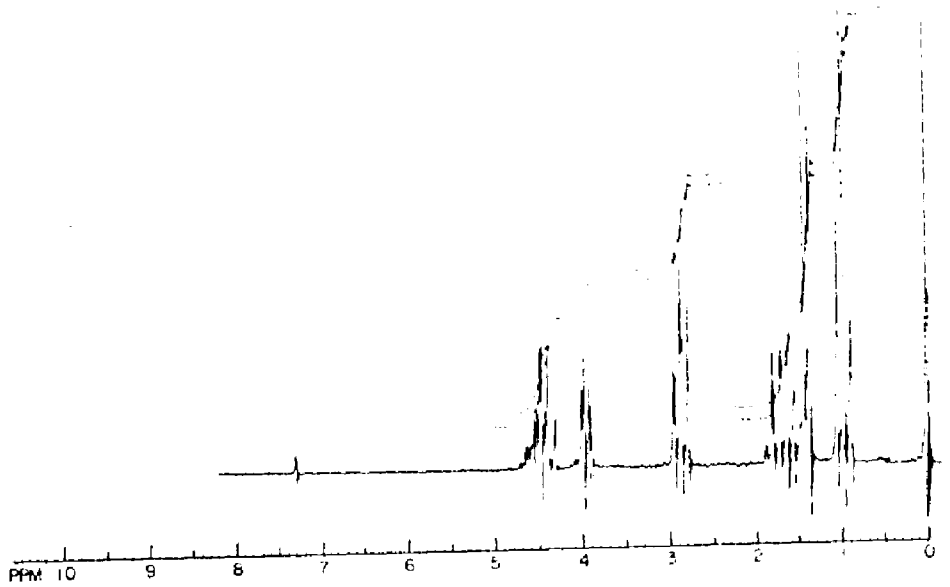
^1H NMR (90 MHz/$CDCl_3$)

Compound **14c**



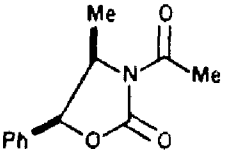


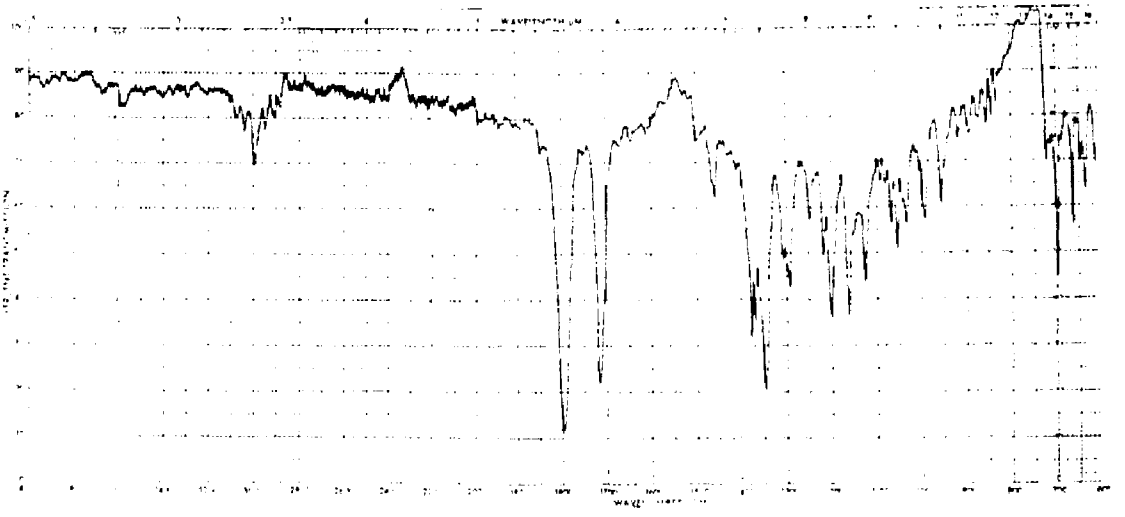
IR (CCl_4)



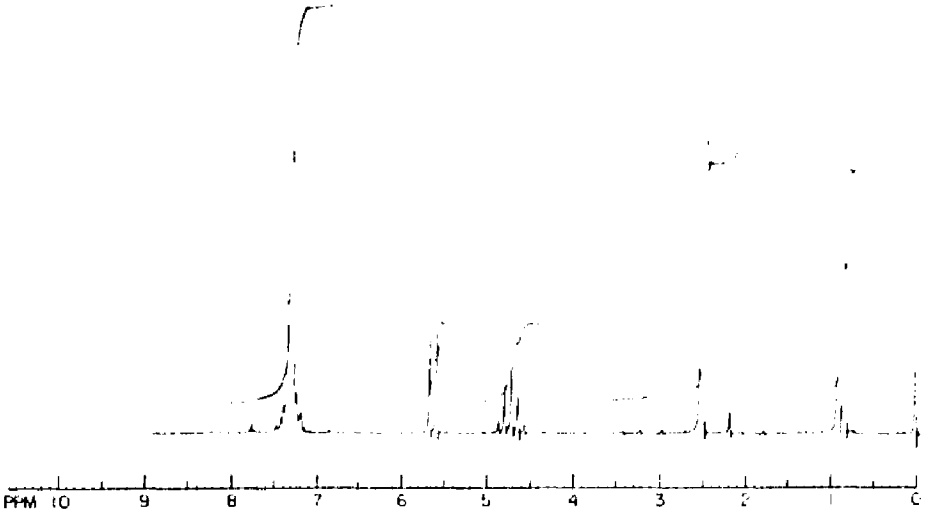
^1H NMR (90 MHz/$CDCl_3$)

Compound **16a**



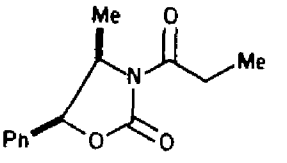


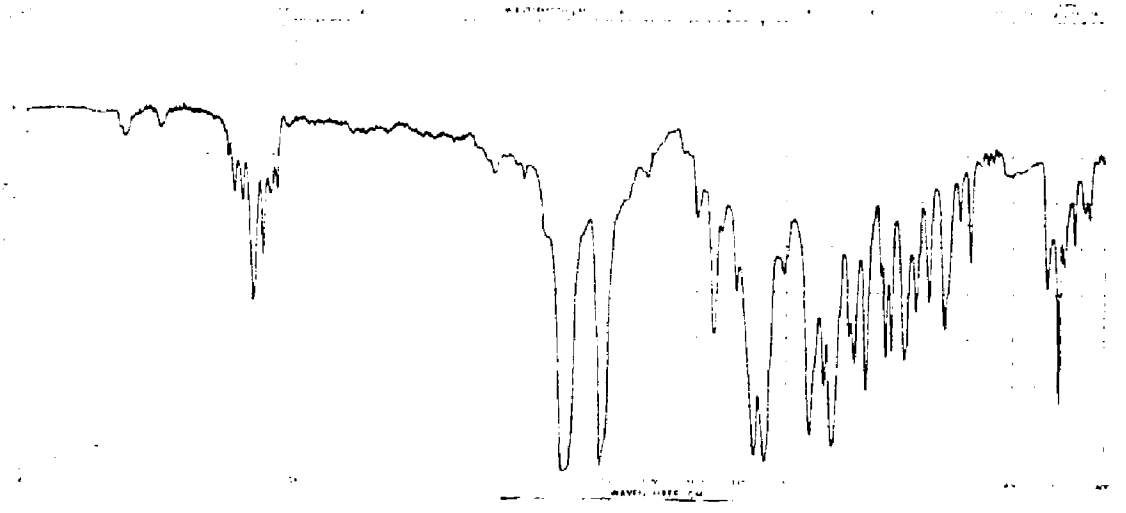
IR (CCl_4)



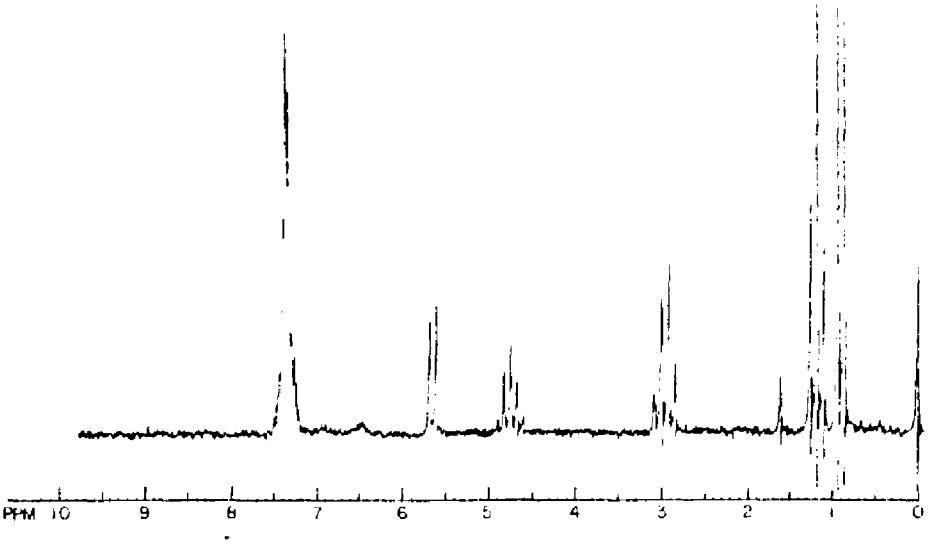
^1H NMR (90 MHz/$CDCl_3$)

Compound **16b**



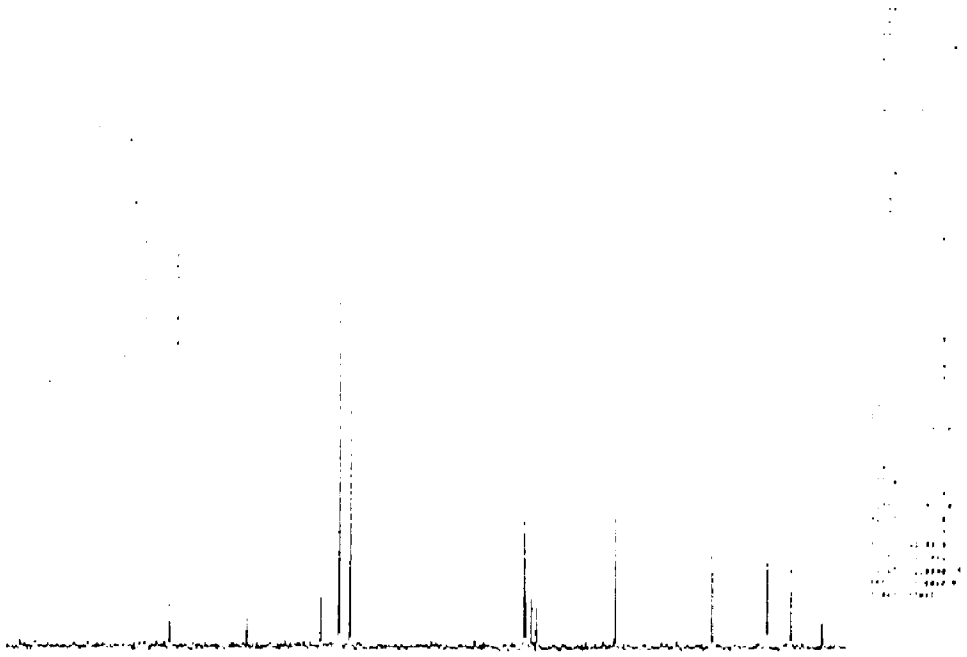


IR (CH_2Cl_2)



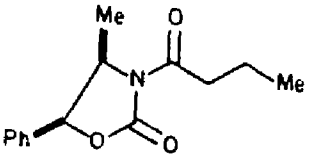
^1H NMR (90 MHz/$CDCl_3$)

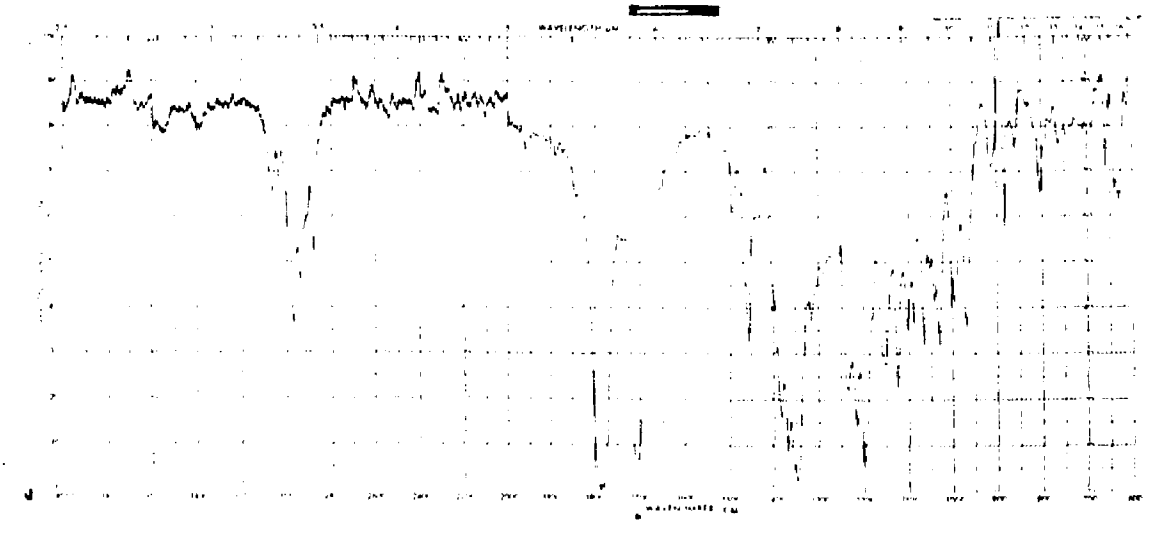
Compound **16b** continued.



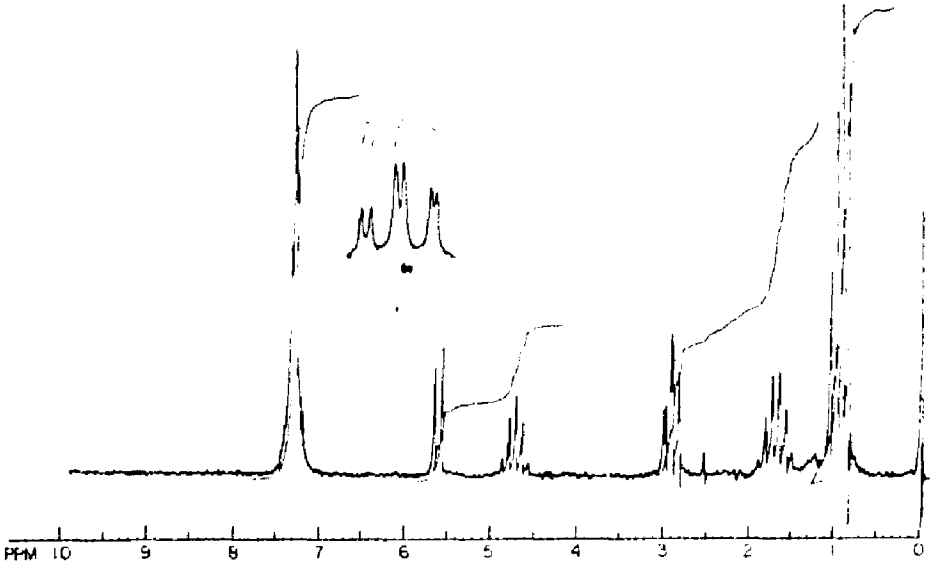
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **16c**



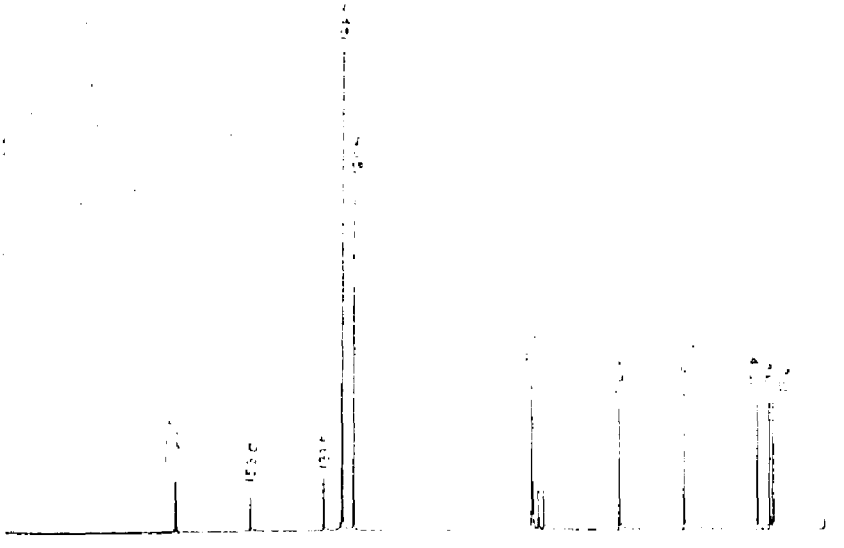


IR (CH_2Cl_2)



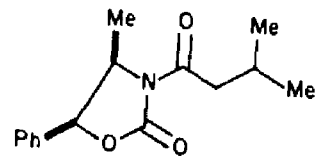
^1H NMR (90 MHz/$CDCl_3$)

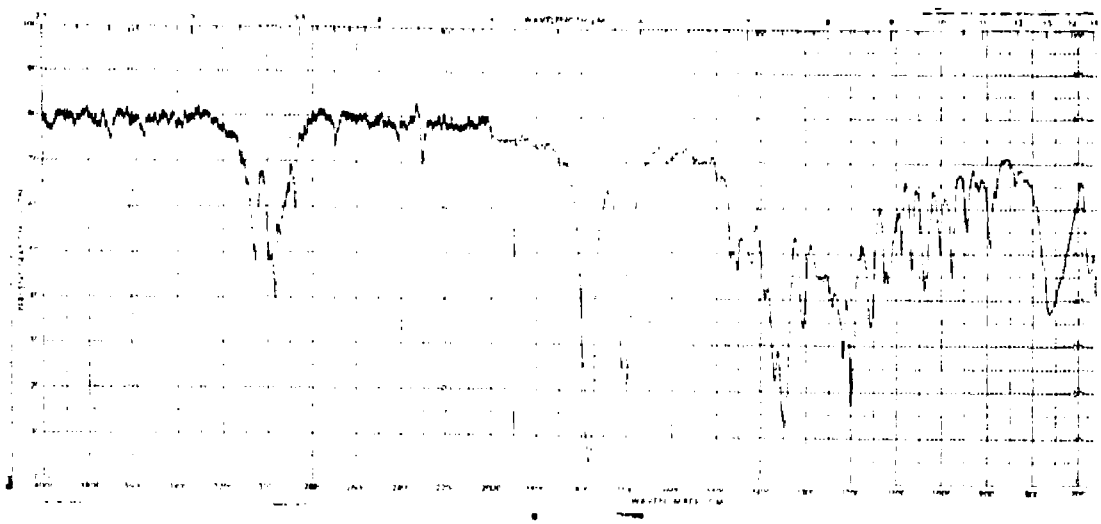
Compound **16c** continued.



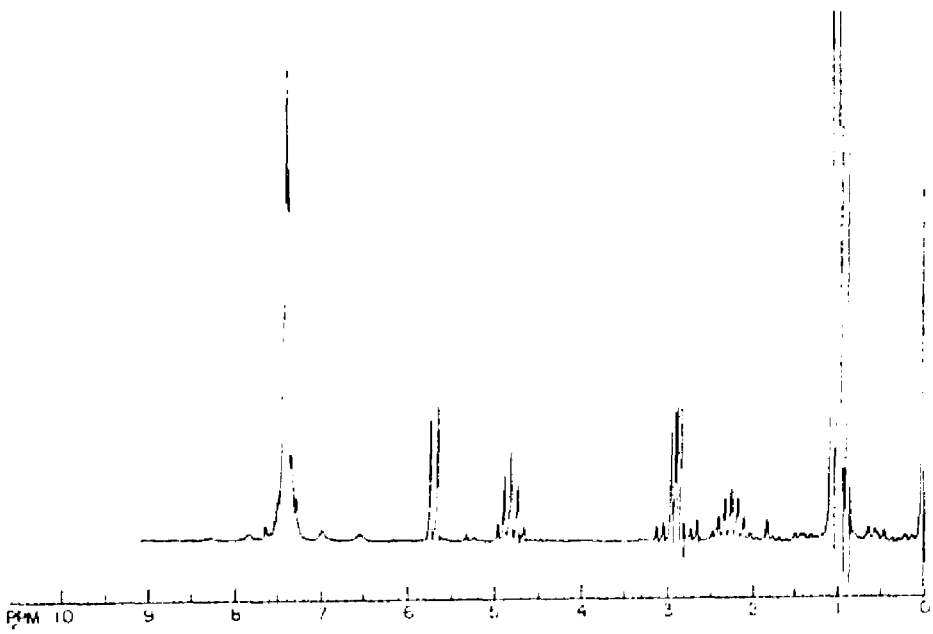
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **16d**



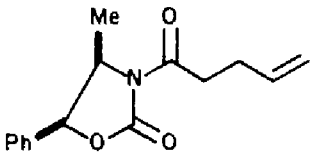


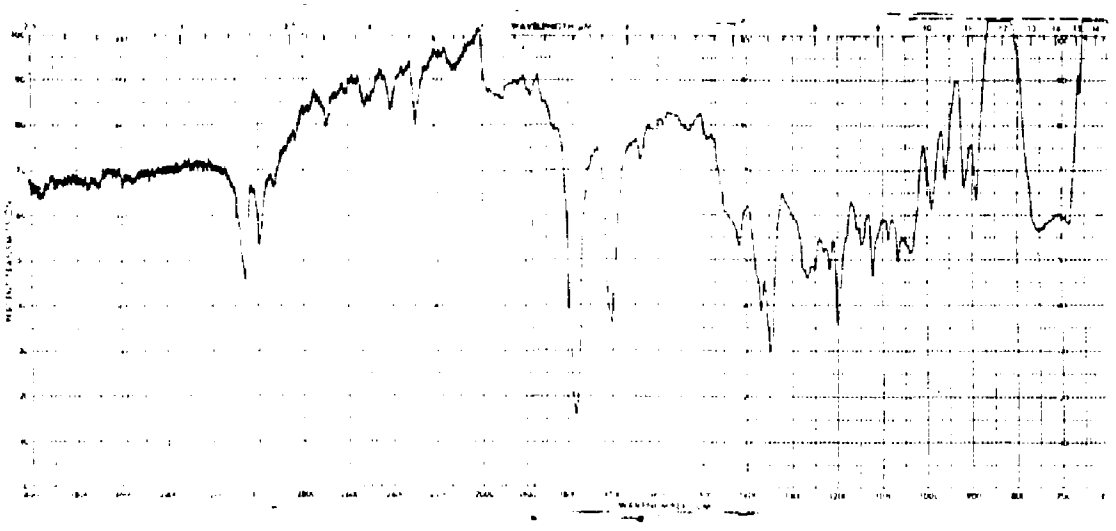
IR (CH_2Cl_2)



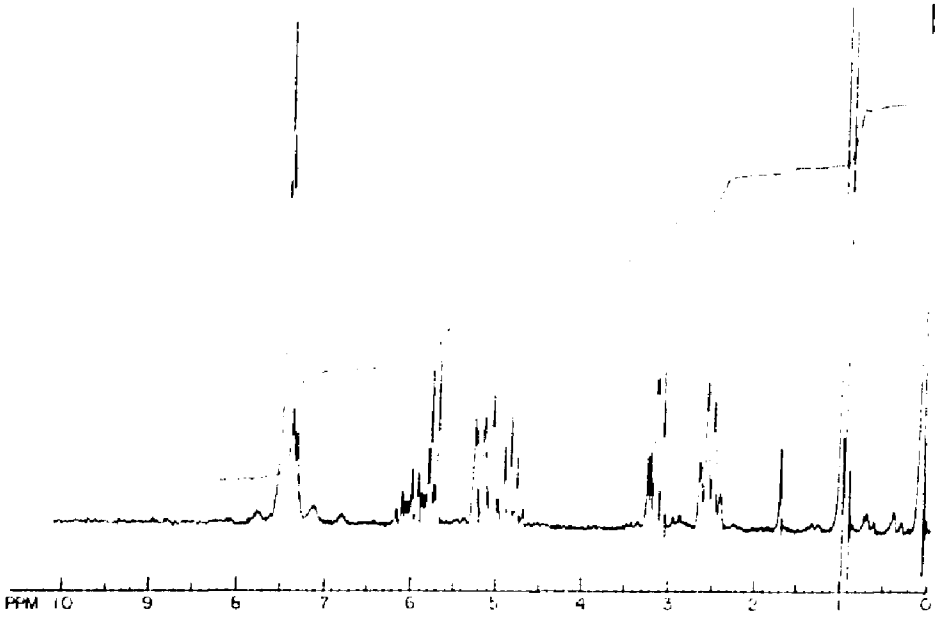
^1H NMR (90 MHz/$CDCl_3$)

Compound **16e**



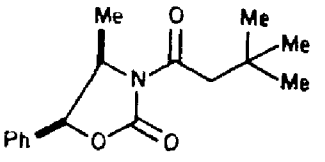


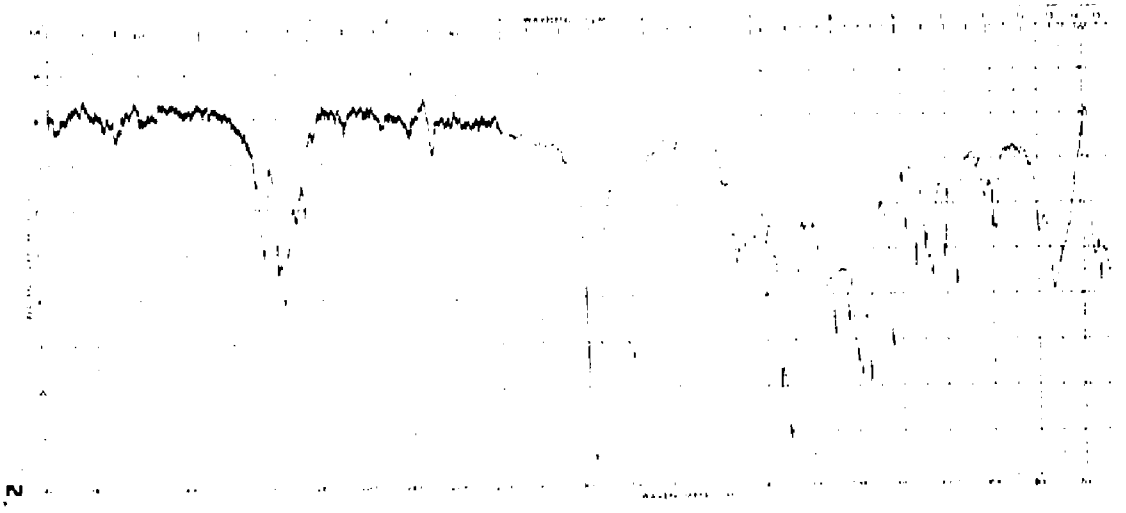
IR (CH_2Cl_2)



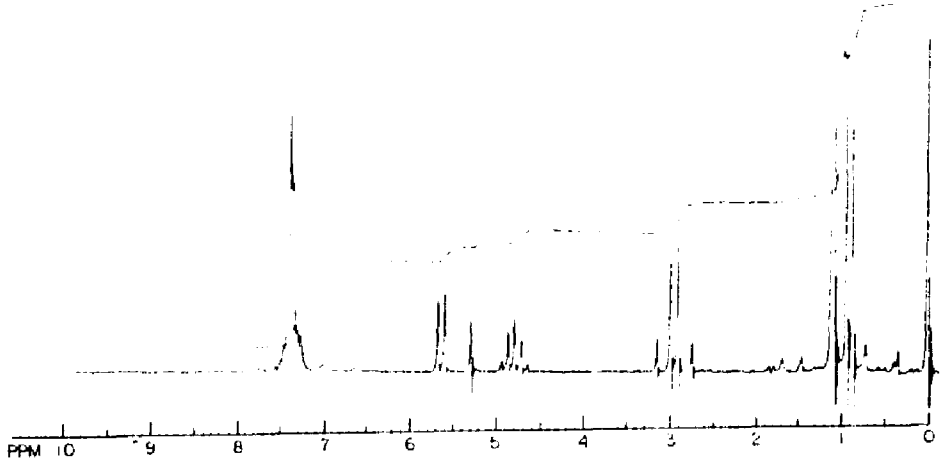
^1H NMR (90 MHz/$CDCl_3$)

Compound **16f**



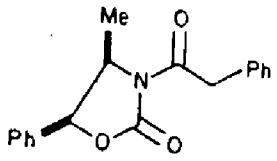


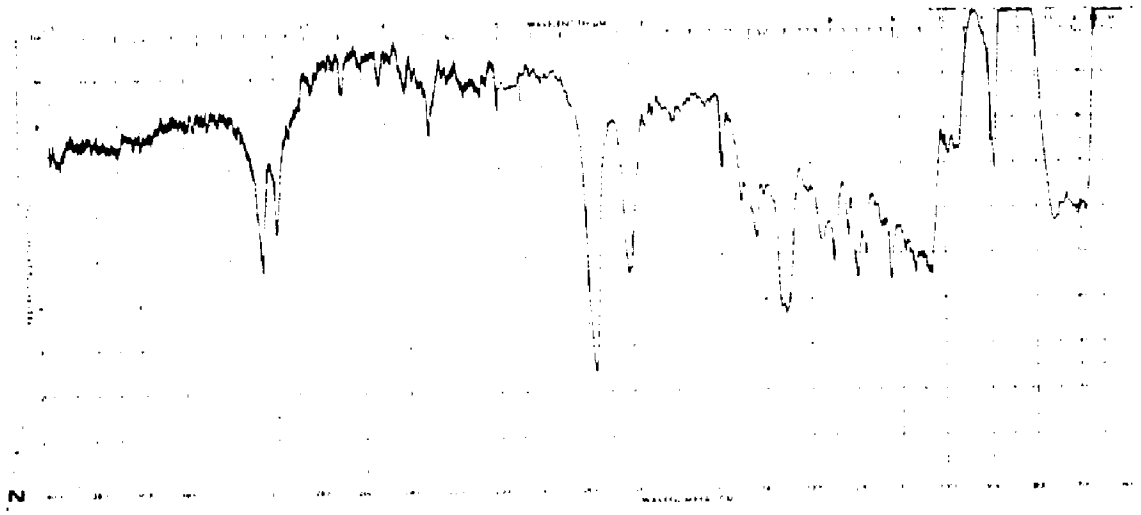
IR (CH_2Cl_2)



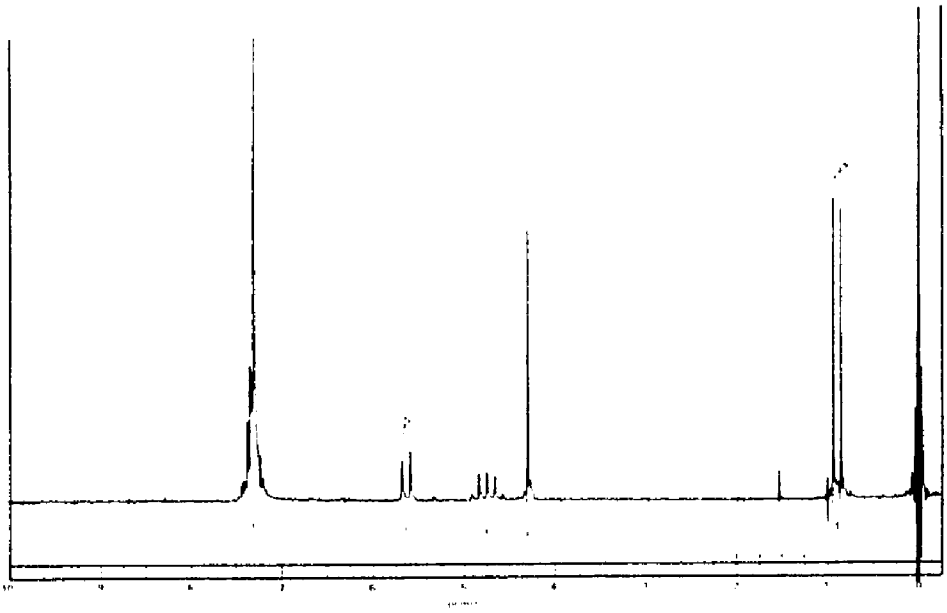
^1H NMR (90 MHz/$CDCl_3$)

Compound **16g**



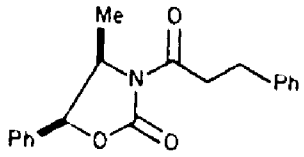


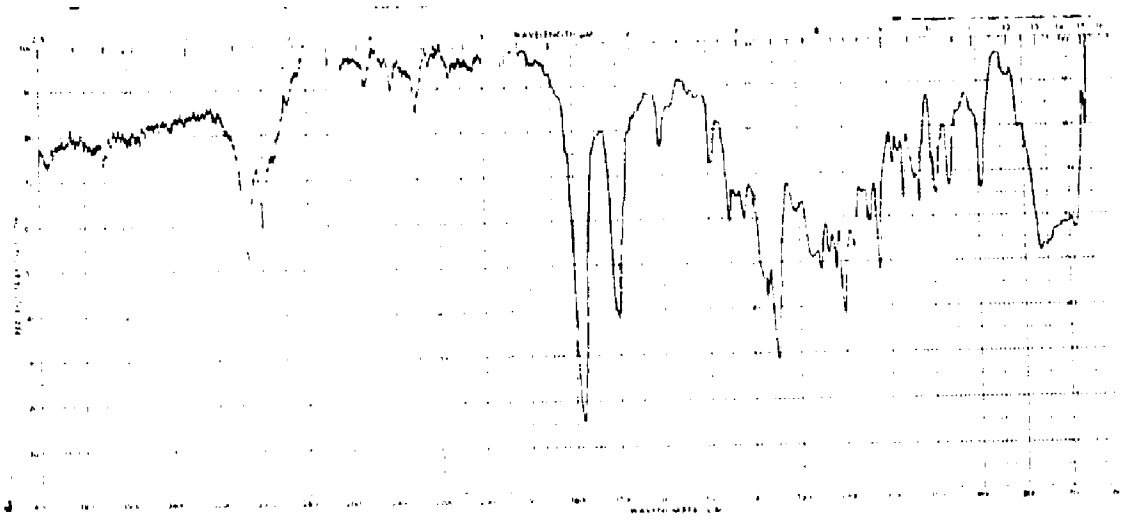
IR (CH_2Cl_2)



^1H NMR (90 MHz/$CDCl_3$)

Compound **16h**

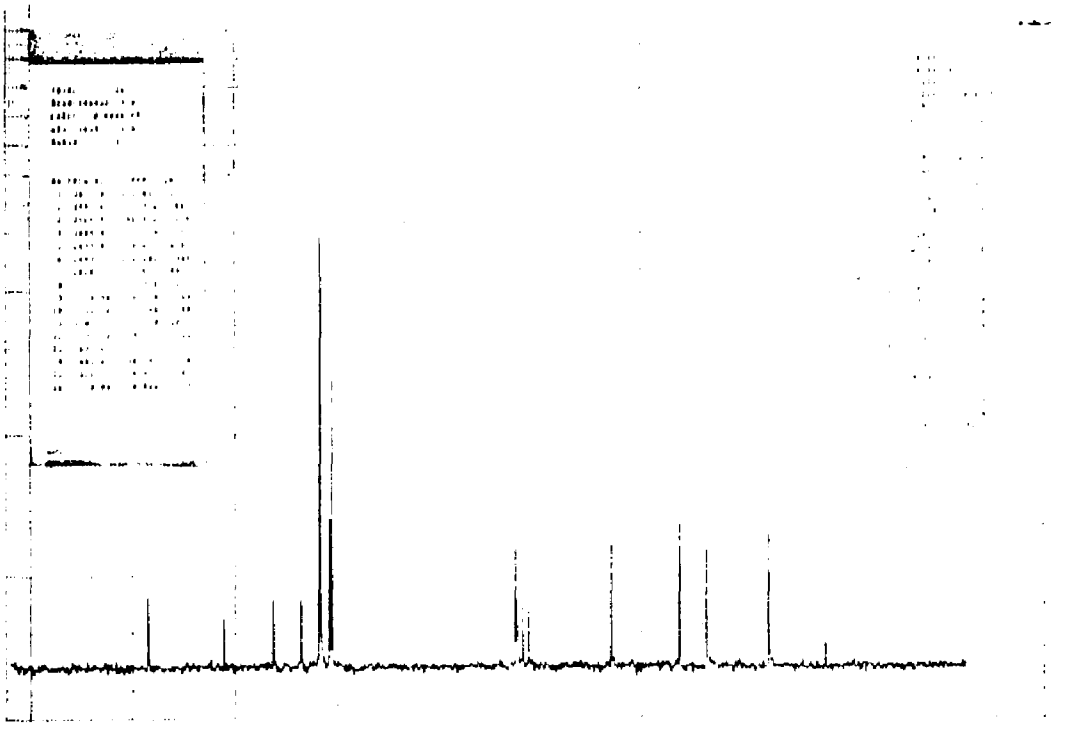




IR (CH_2Cl_2)

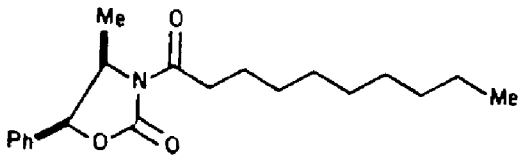
^1H NMR (500 MHz/$CDCl_3$)

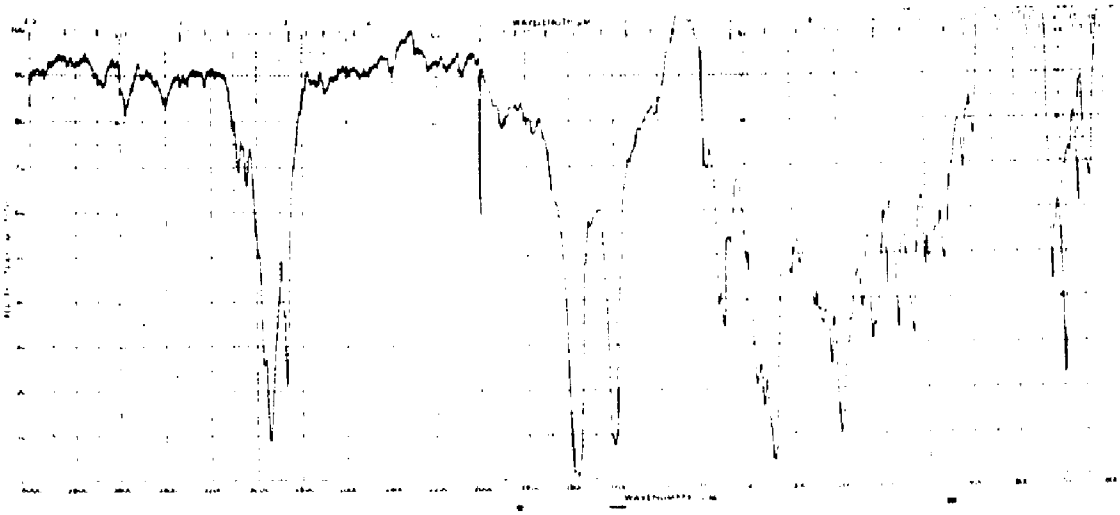
Compound **16h** continued.



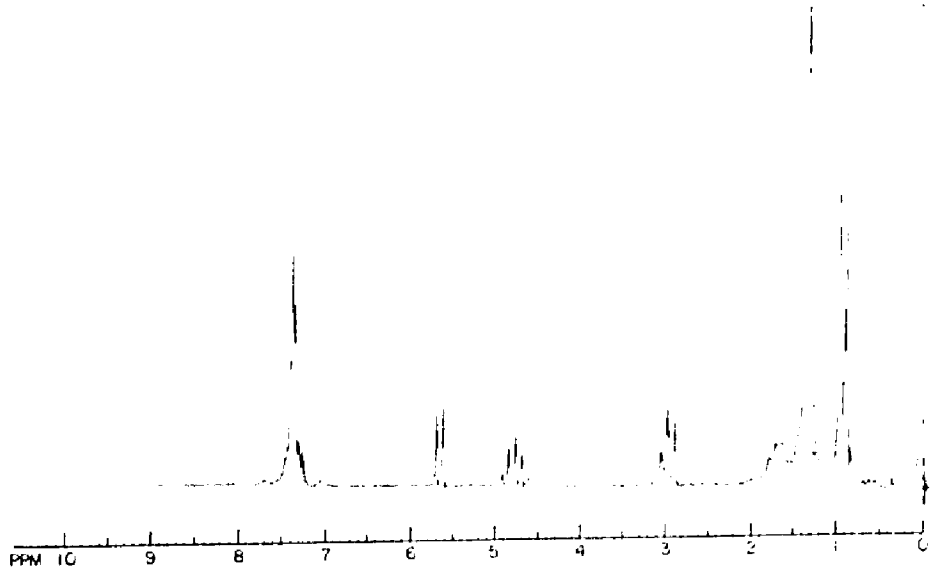
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **16i**



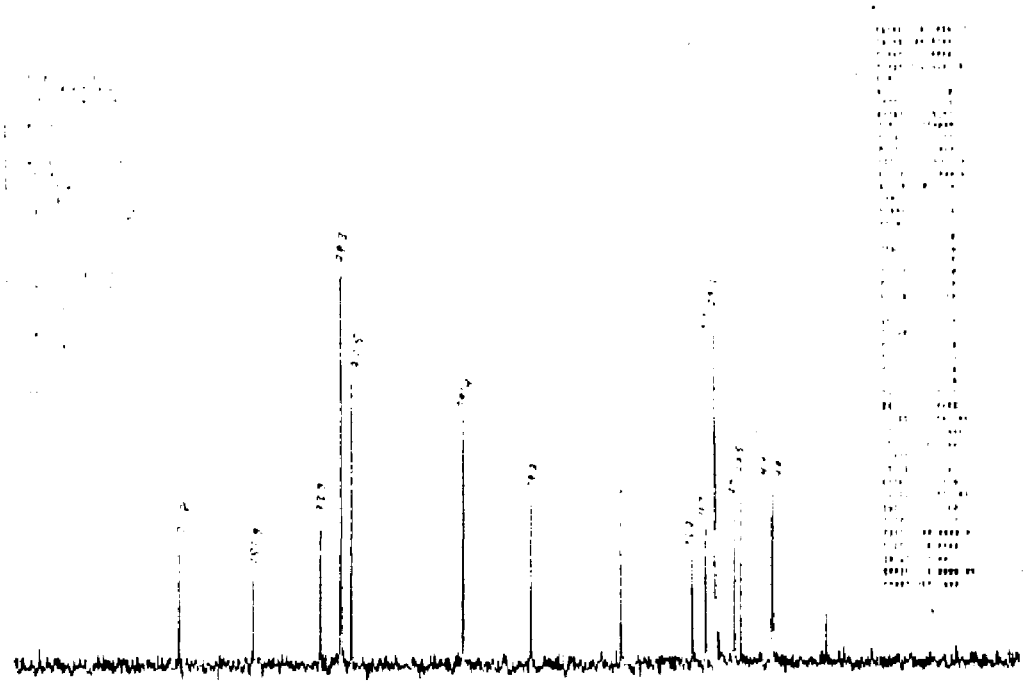


IR (CCl_4)



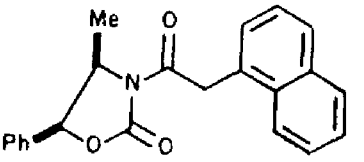
^1H NMR (90 MHz/$CDCl_3$)

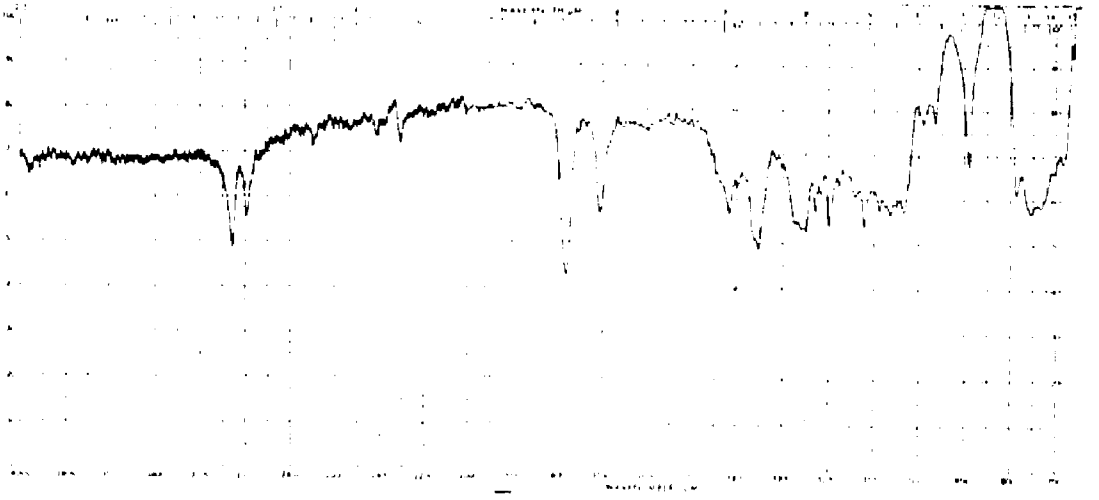
Compound **16i** continued.



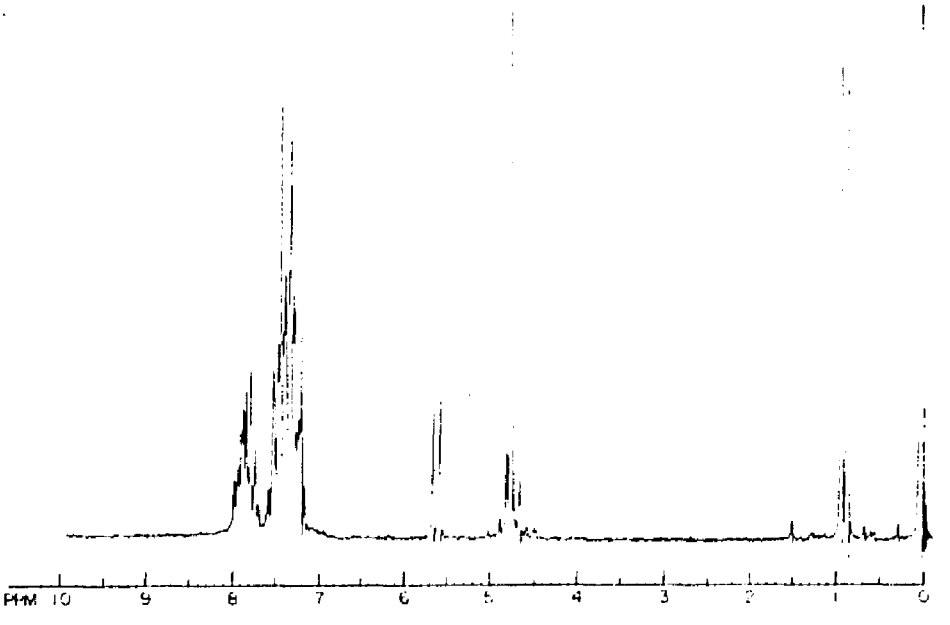
^{13}C NMR (22.5 MHz/CCl_4)

Compound **16j**



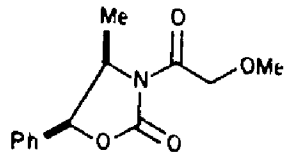


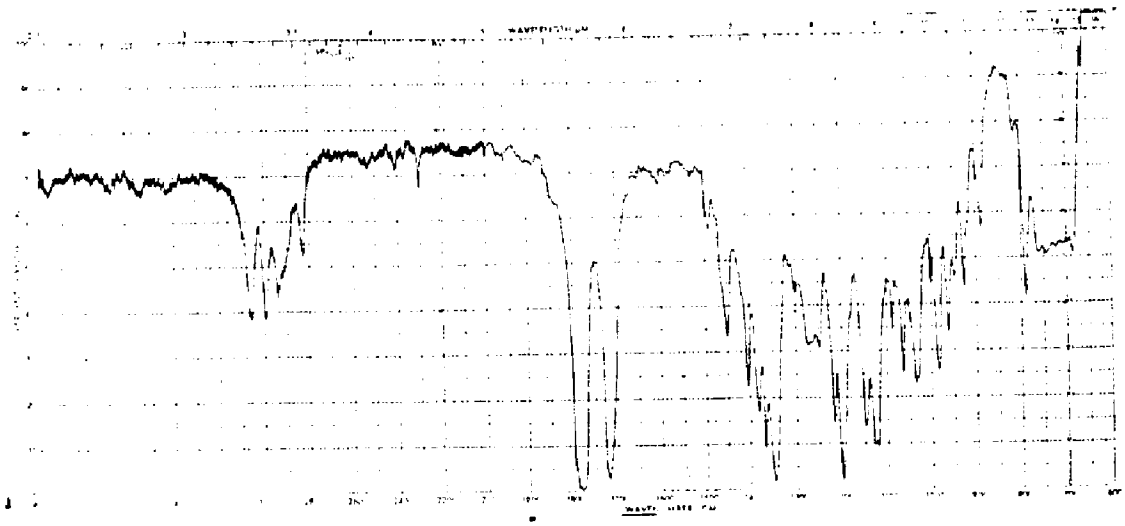
IR (CH_2Cl_2)



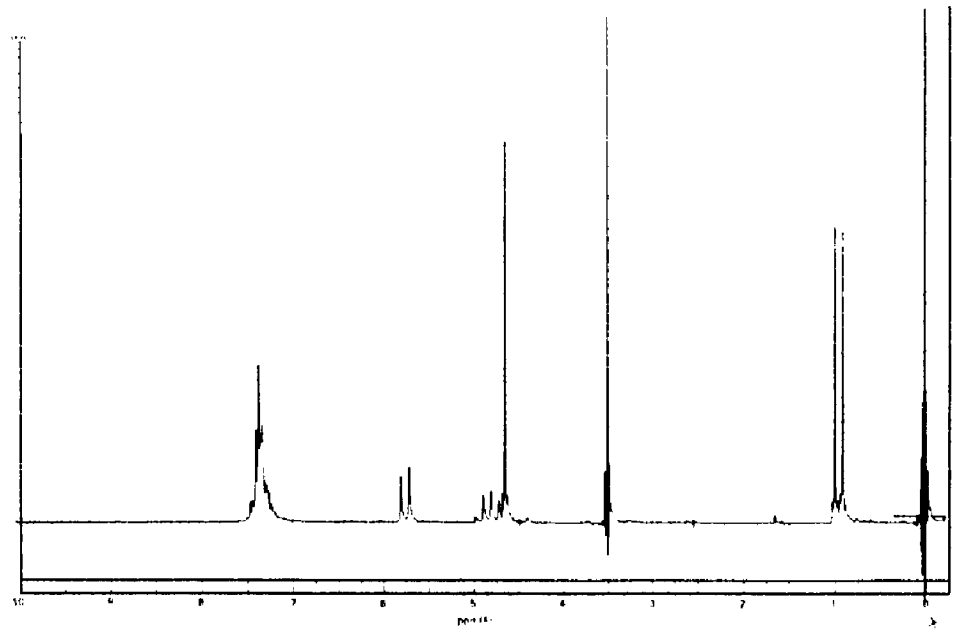
^1H NMR (90 MHz/$CDCl_3$)

Compound **16k**



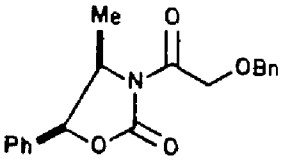


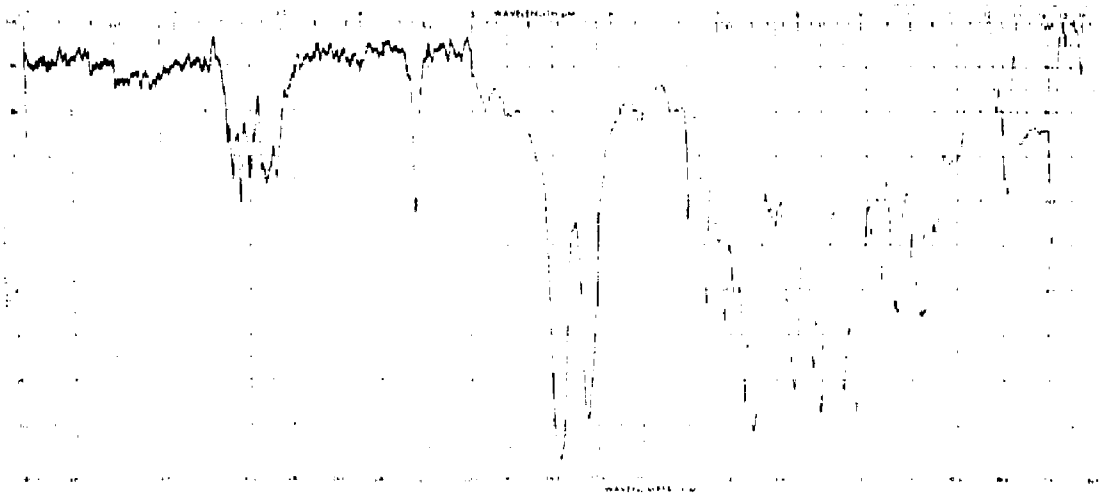
IR (CH_2Cl_2)



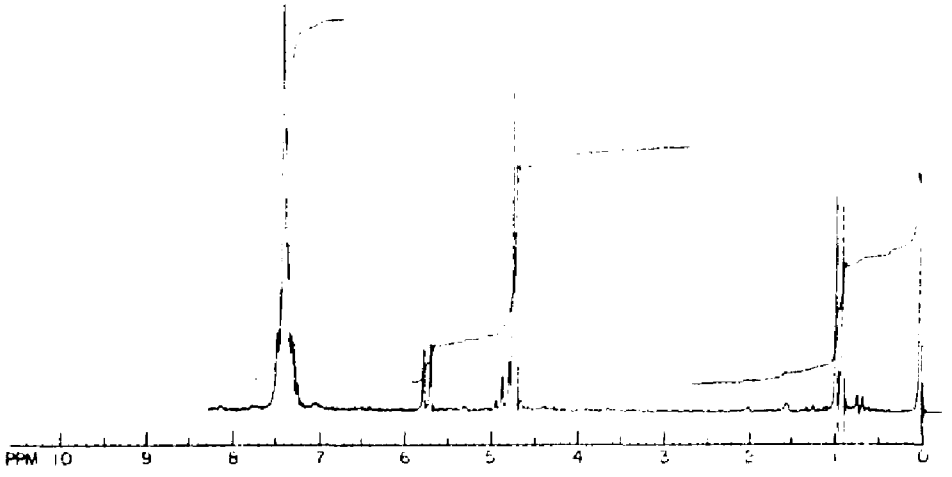
^1H NMR (90 MHz/$CDCl_3$)

Compound **161**



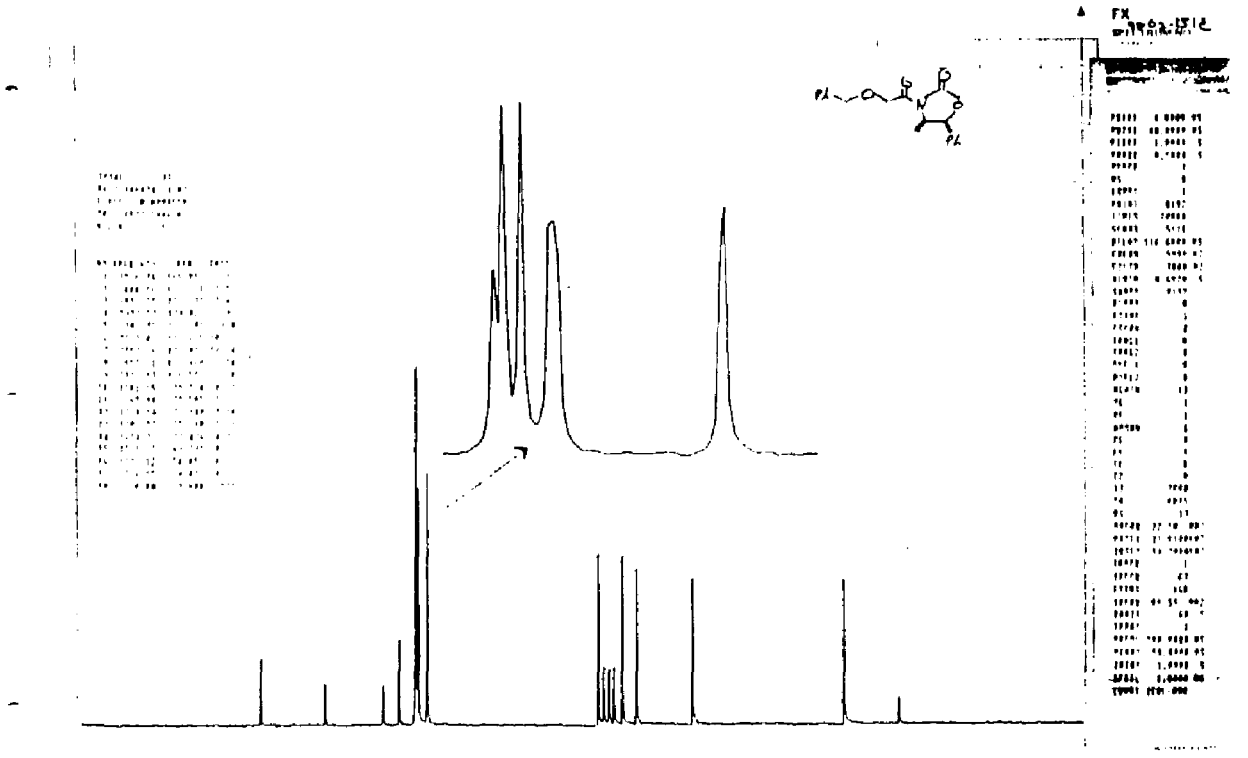


IR ($CHCl_3$)



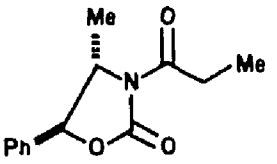
^1H NMR (90 MHz/$CDCl_3$)

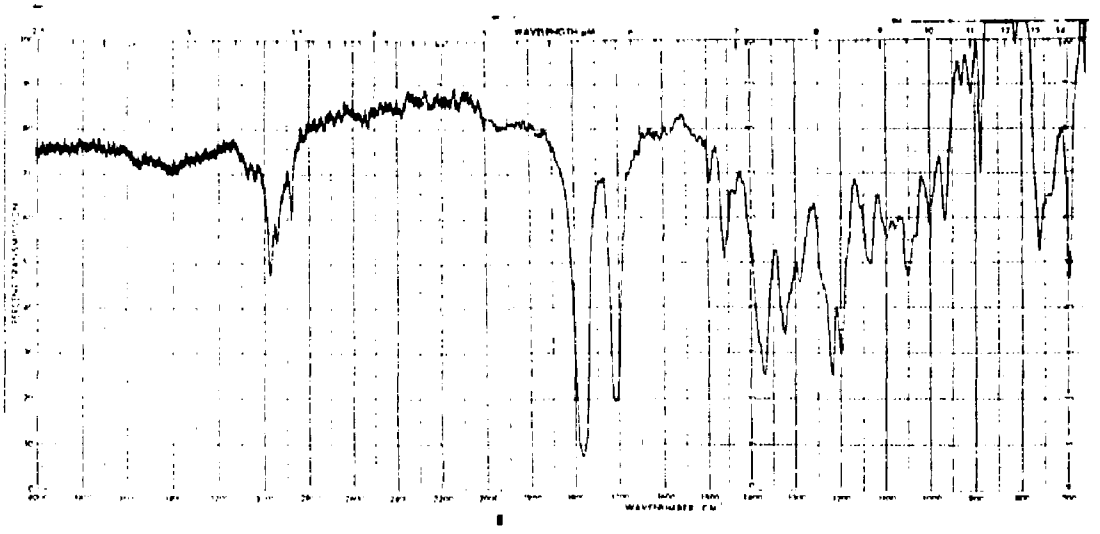
Compound **161** continued.



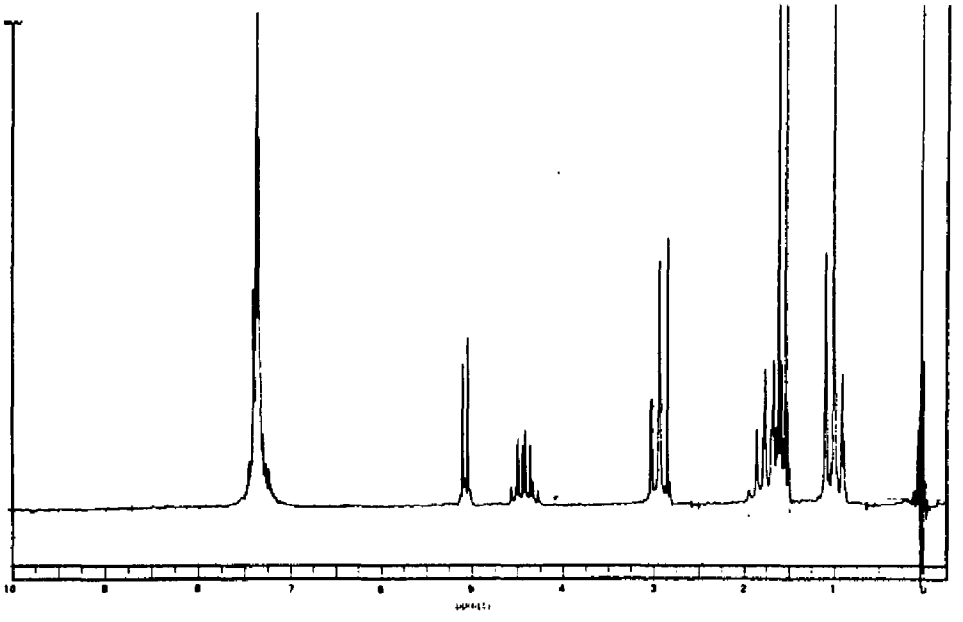
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **18c**



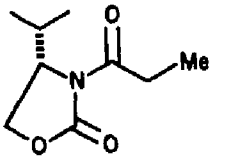


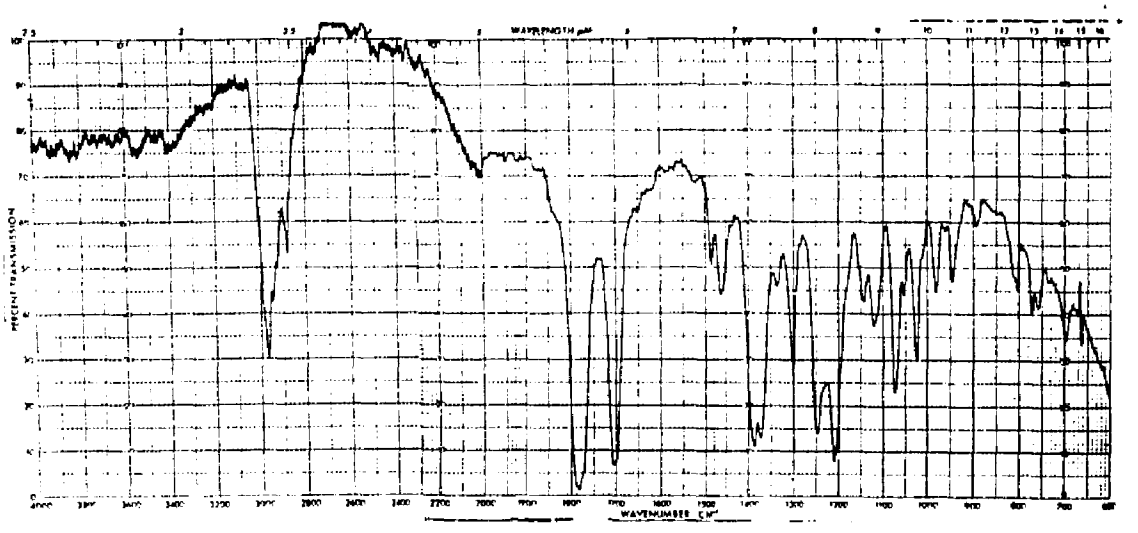
IR (neat)



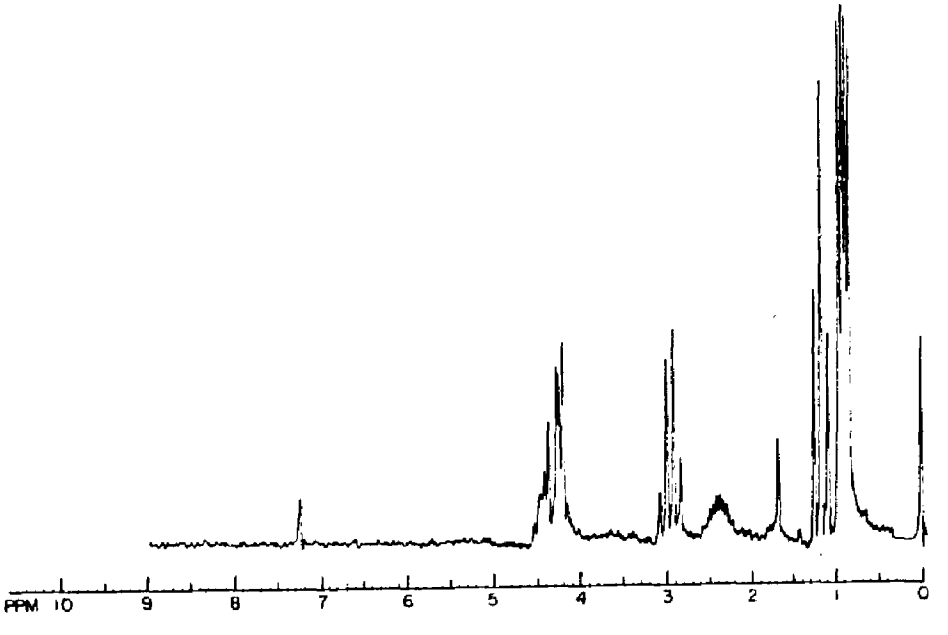
^1H NMR (90 MHz/$CDCl_3$)

Compound **20b**



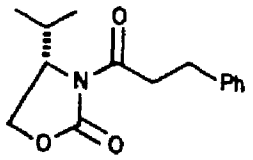


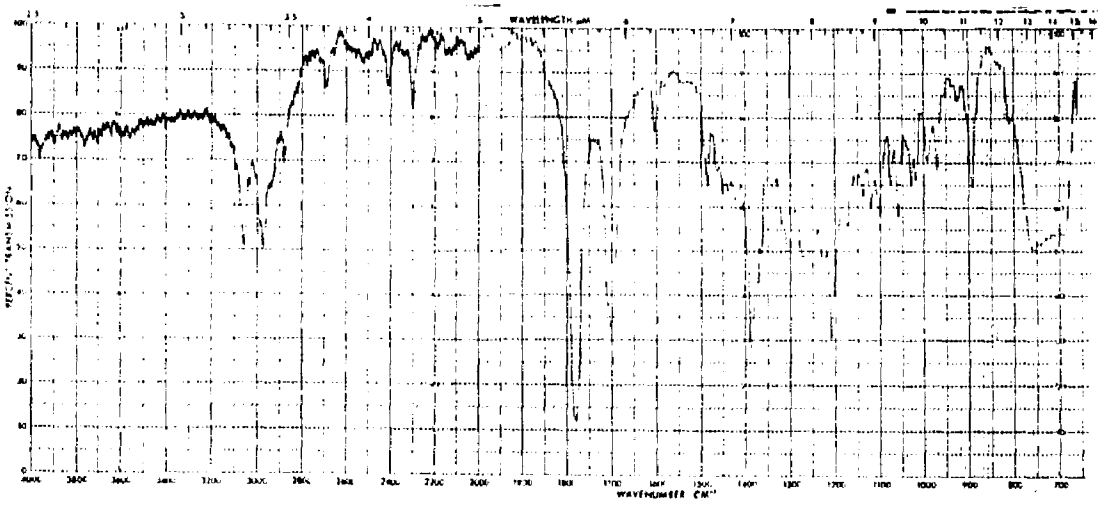
IR (neat)



^1H NMR (90 MHz/$CDCl_3$)

Compound **20h**

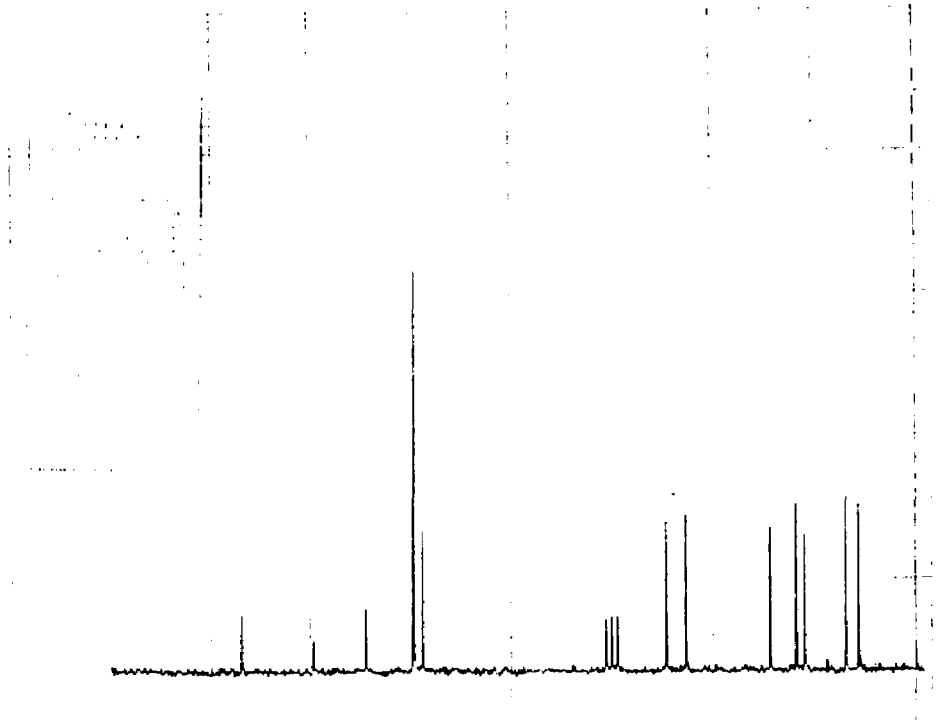




IR (CH_2Cl_2)

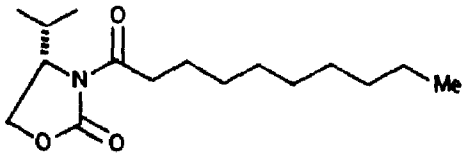
^1H NMR (500 MHz/$CDCl_3$)

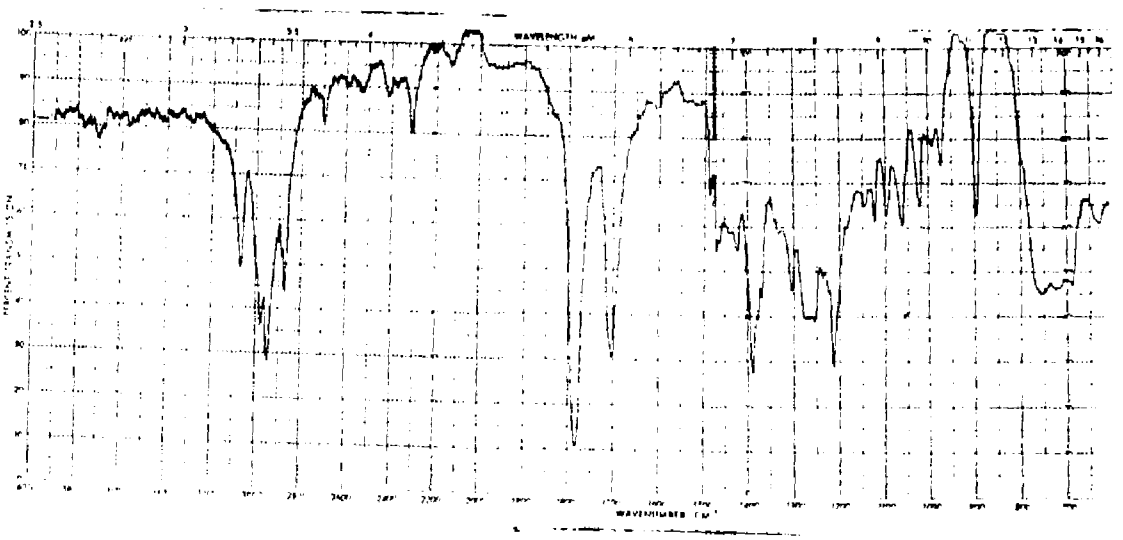
Compound **20h** continued.



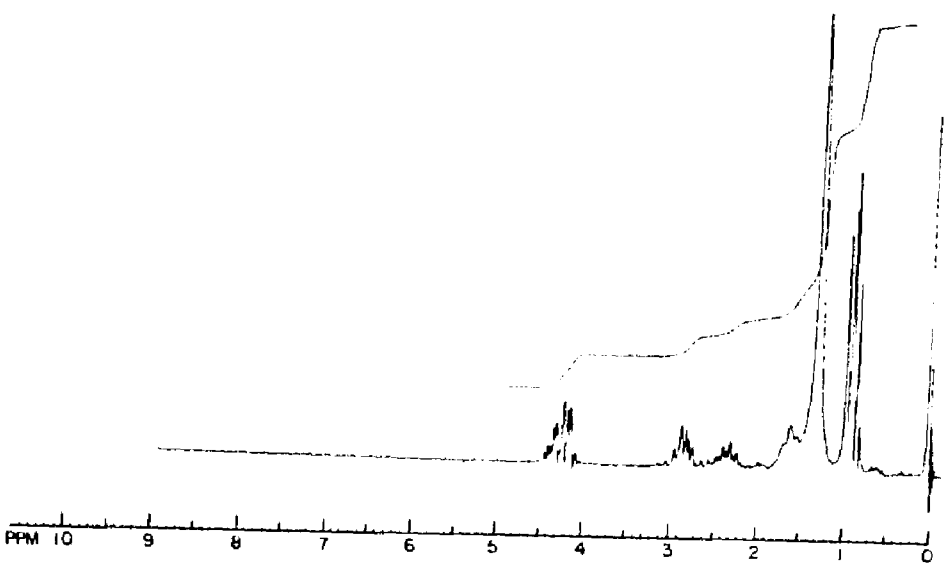
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **20i**



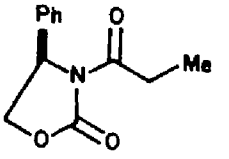


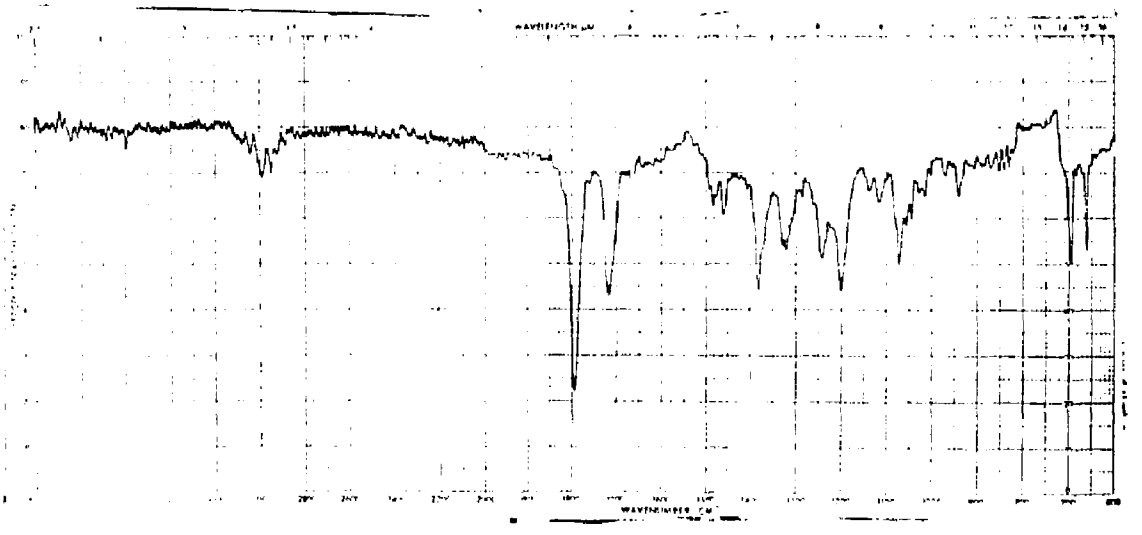
IR (CH_2Cl_2)



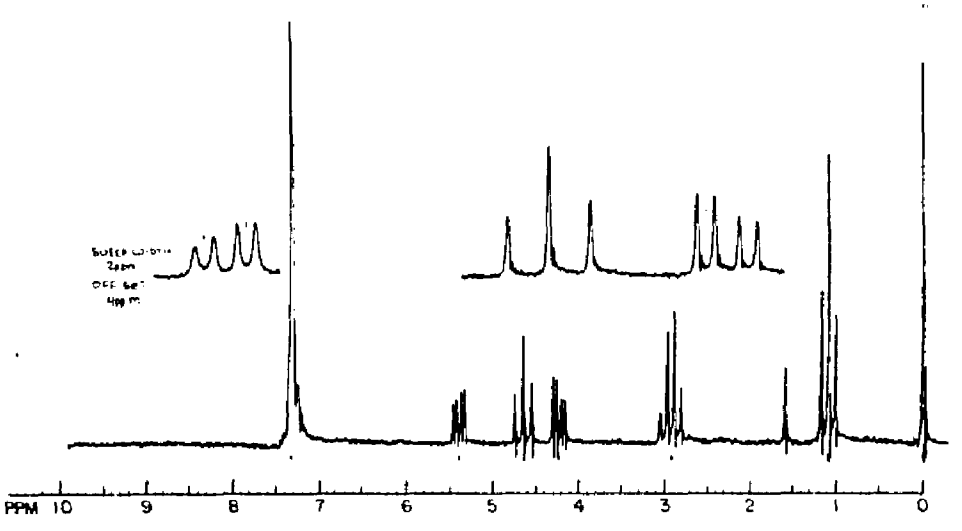
^1H NMR (90 MHz/CCl_4)

Compound **22b**



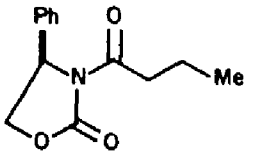


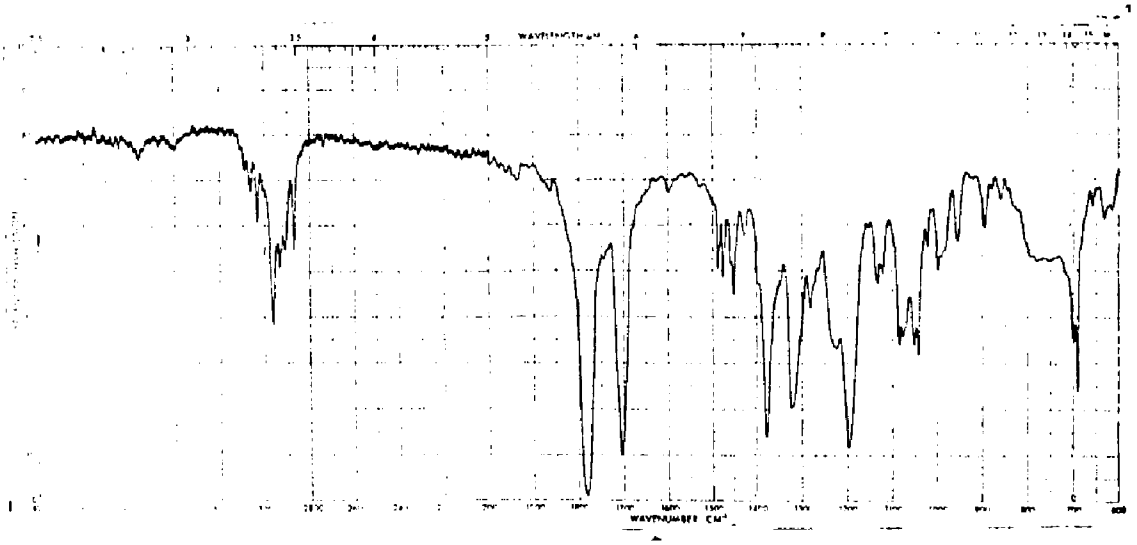
IR (CCl_4)



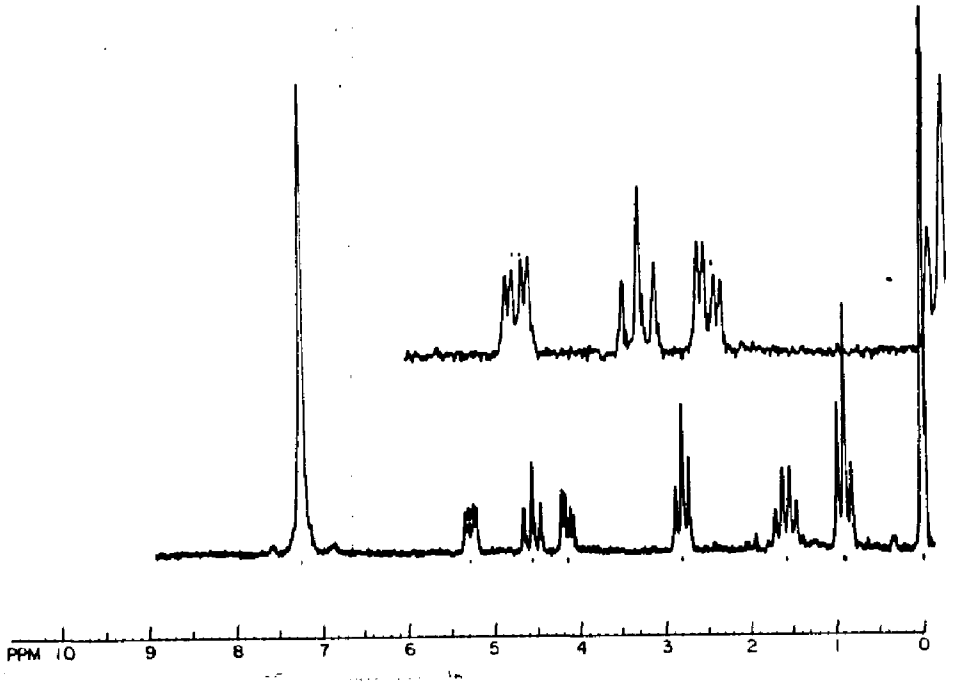
^1H NMR (90 MHz/$CDCl_3$)

Compound **22c**



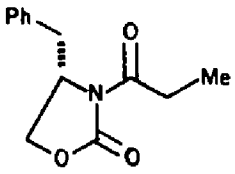


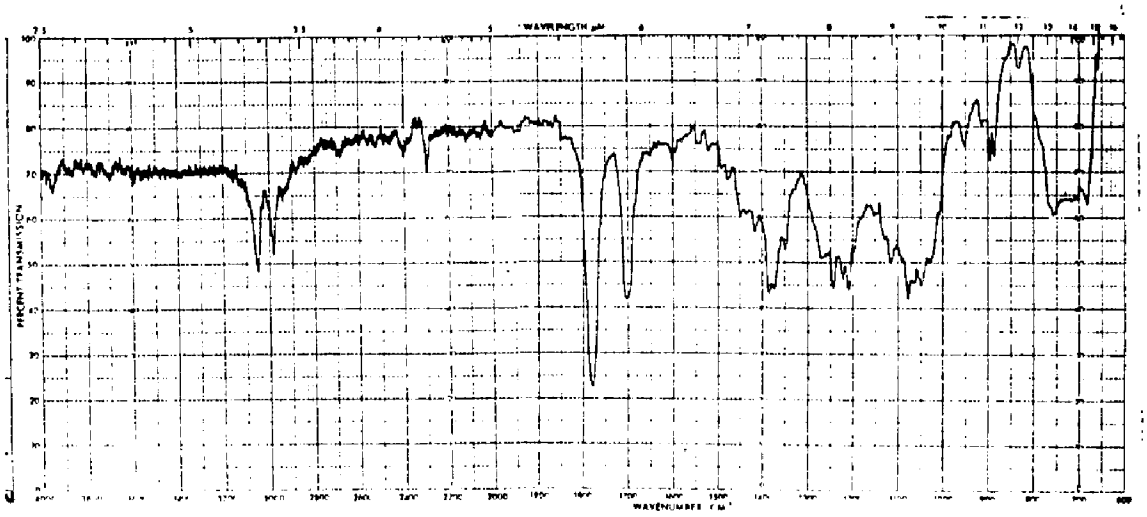
IR (CH_2Cl_2)



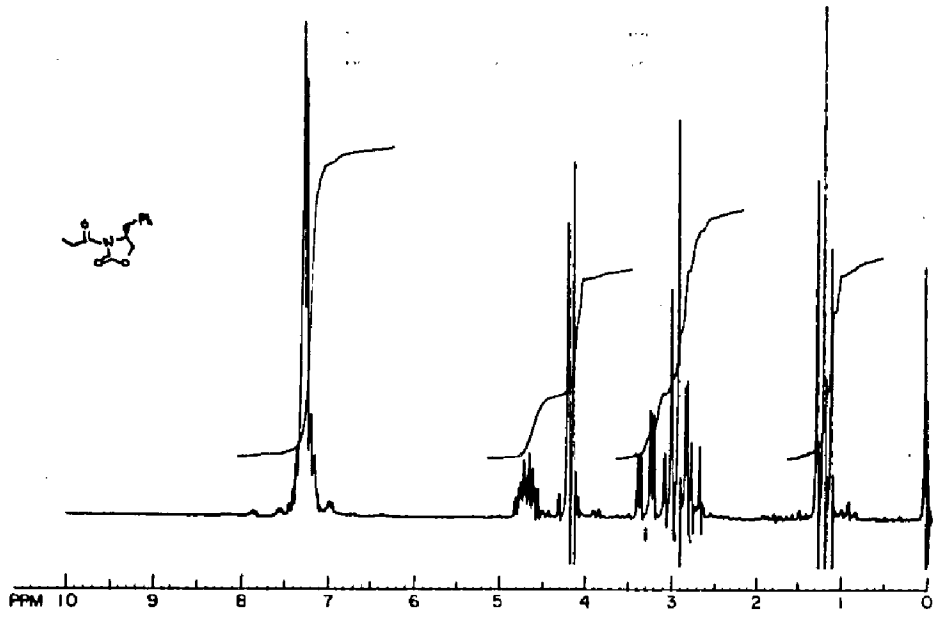
^1H NMR (90 MHz/CCl_4)

Compound **24b**



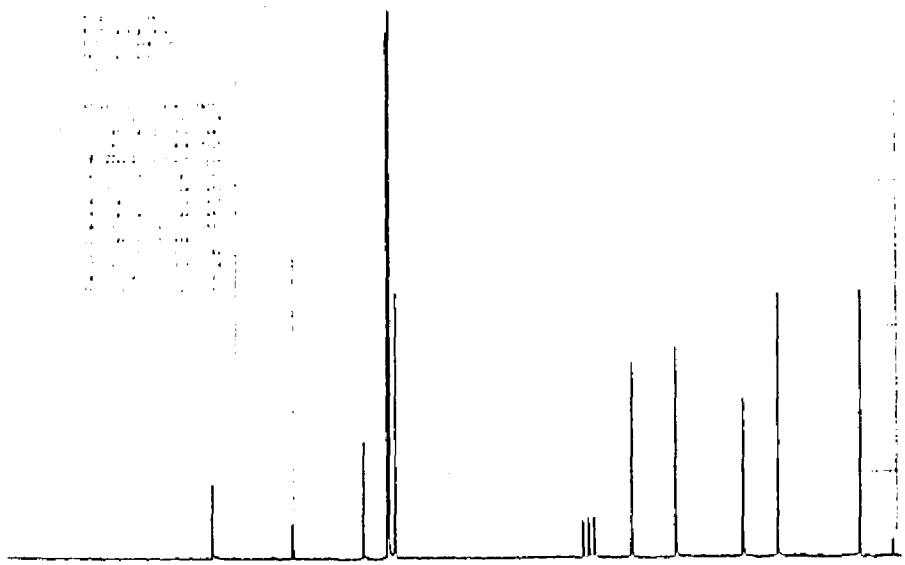


IR (CH_2Cl_2)



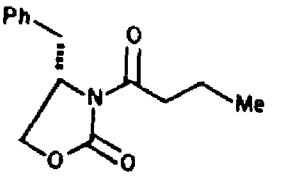
^1H NMR (90 MHz/$CDCl_3$)

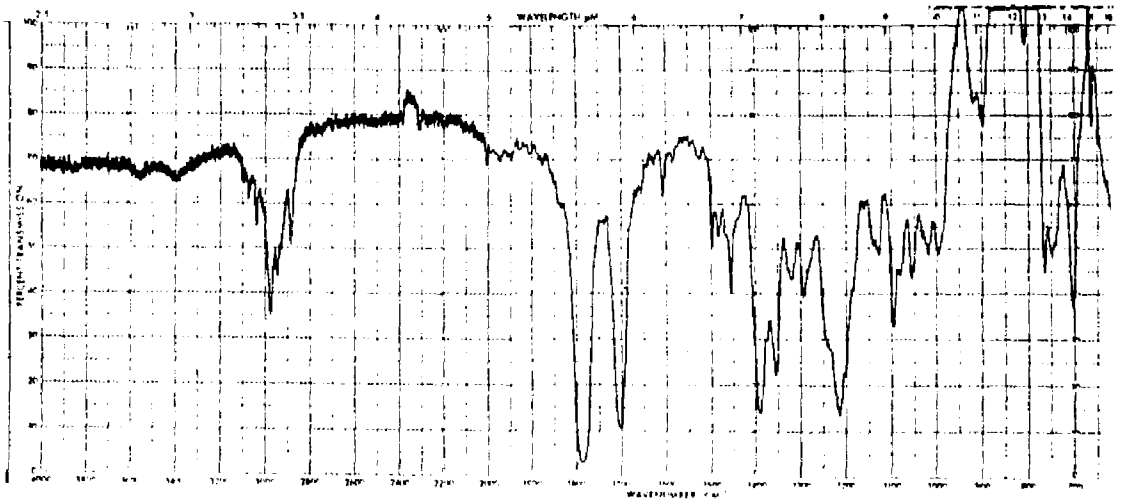
Compound **24b** continued.



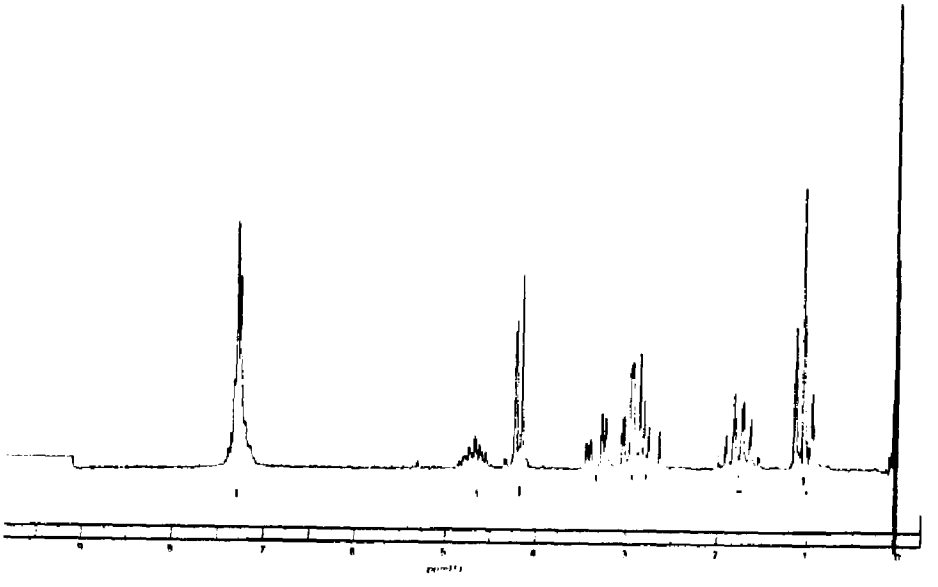
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **24c**



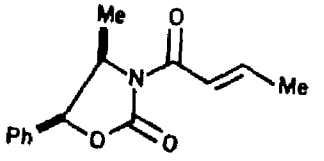


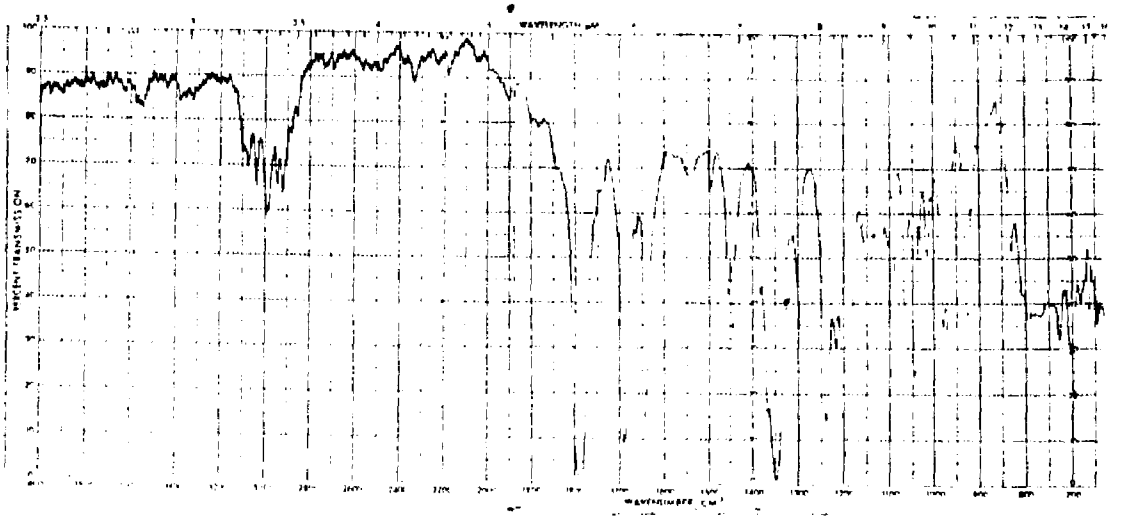
IR (neat)



^1H NMR (90 MHz/$CDCl_3$)

Compound **16m**

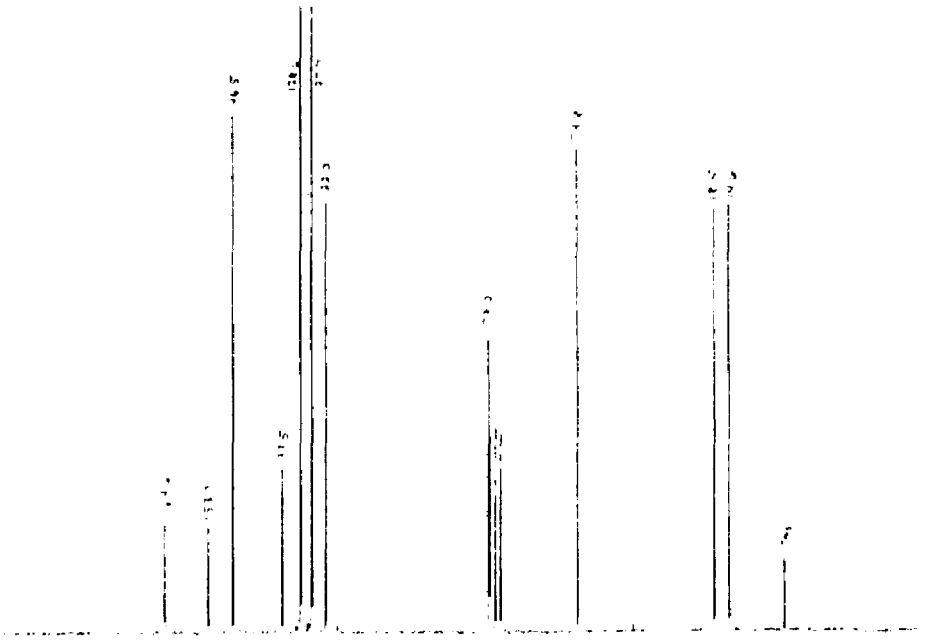




IR (CCl_4)

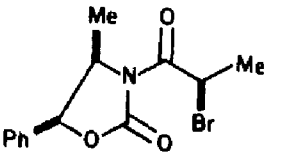
^1H NMR (500 MHz/$CDCl_3$)

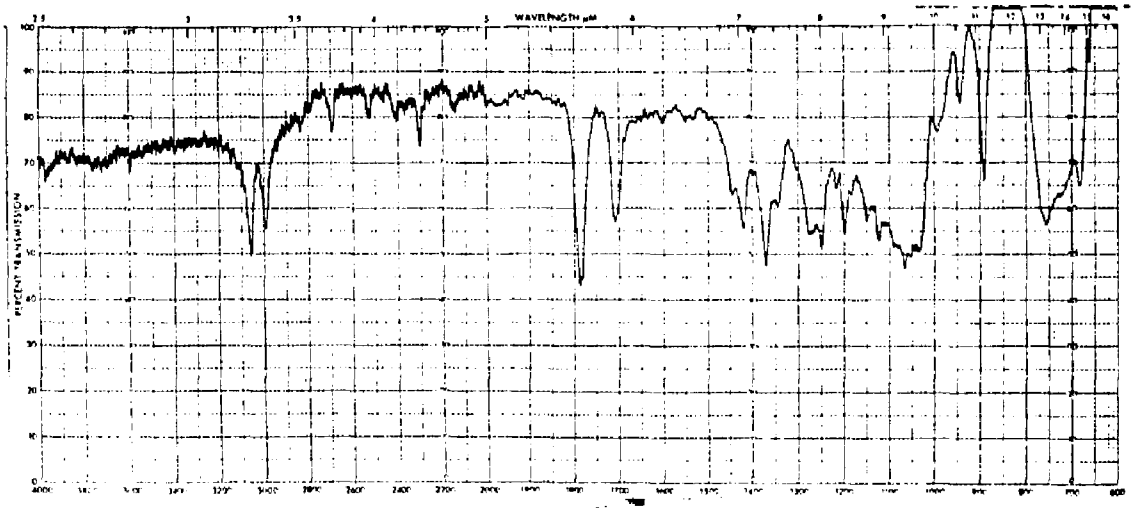
Compound **16m** continued.



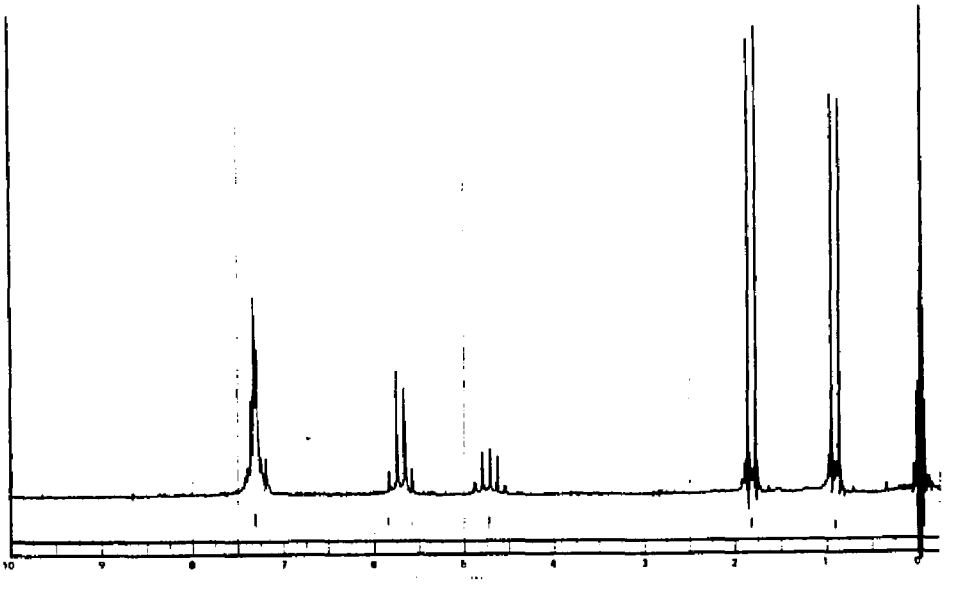
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **16n**



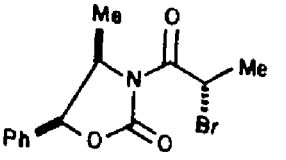


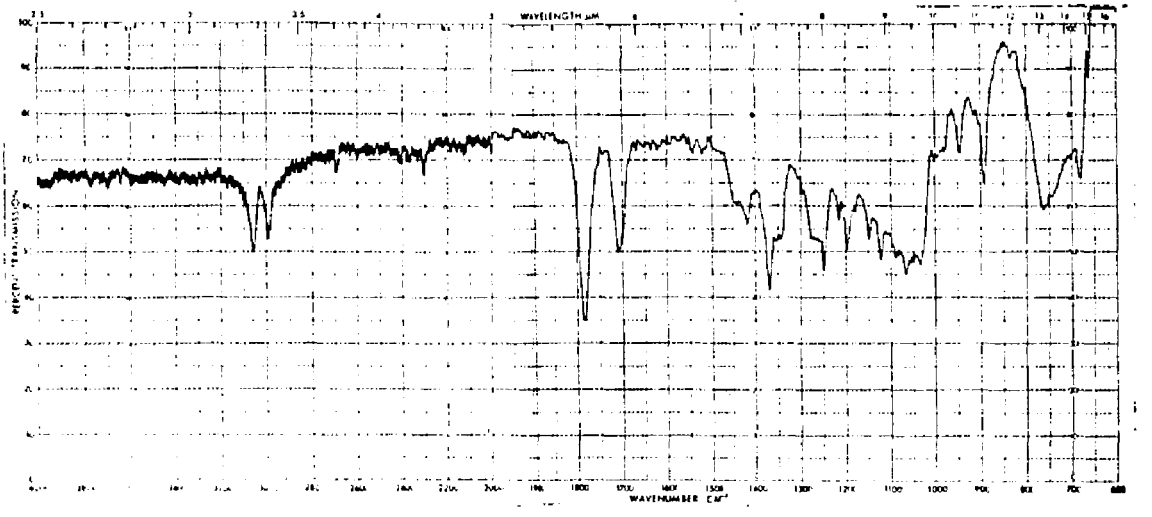
IR (CH_2Cl_2)



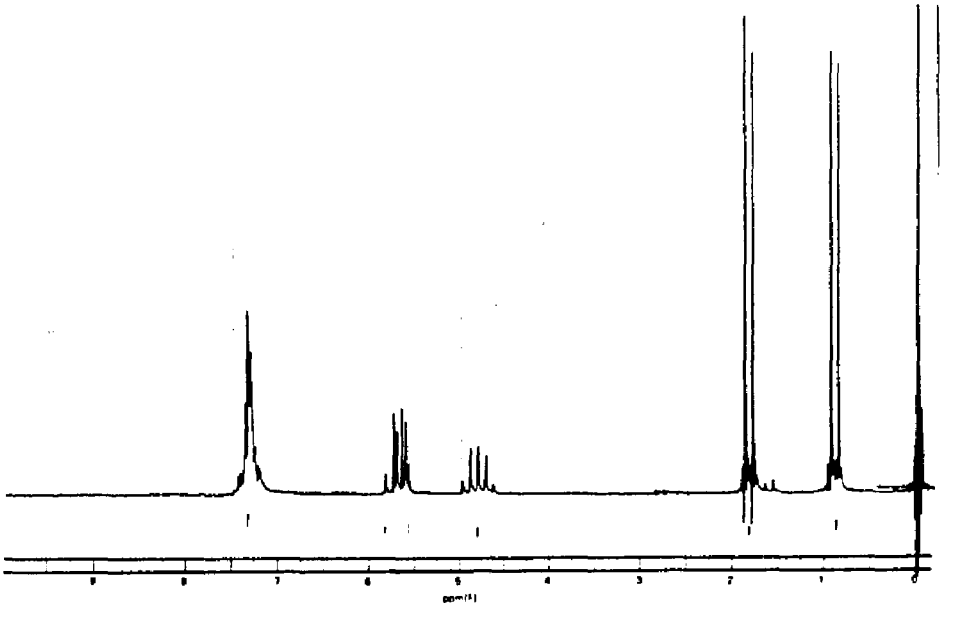
^1H NMR (90 MHz/$CDCl_3$)

Compound **16o**



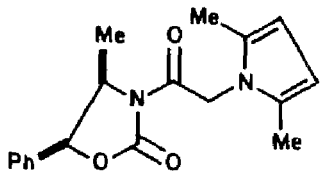


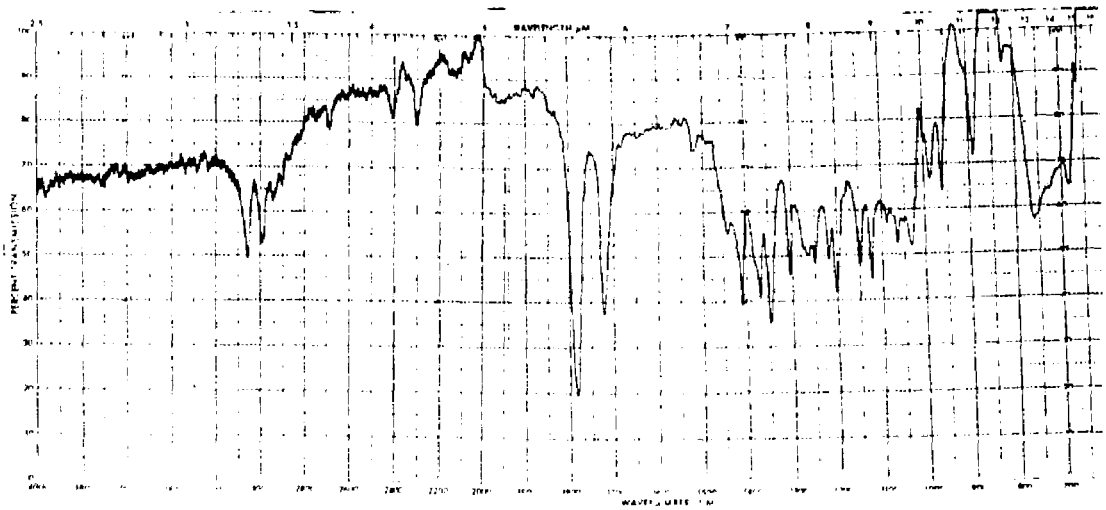
IR (CH_2Cl_2)



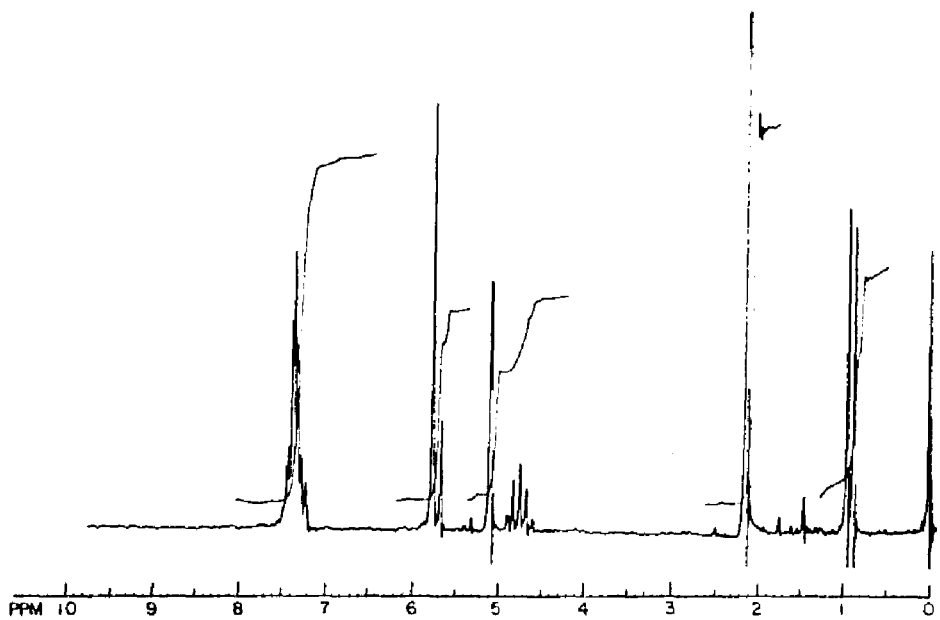
^1H NMR (90 MHz/$CDCl_3$)

Compound **16p**



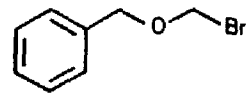


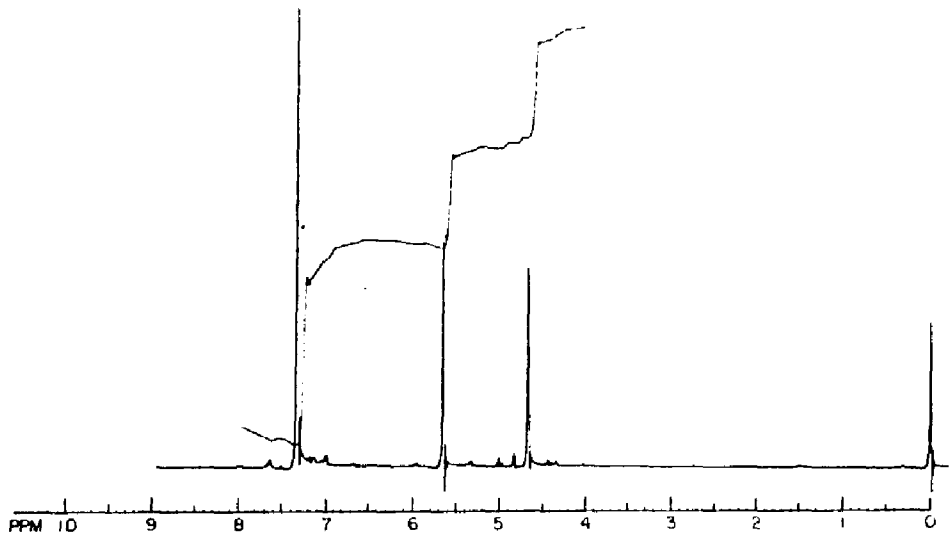
IR (CH_2Cl_2)



^1H NMR (90 MHz/$CDCl_3$)

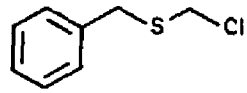
Compound **45**

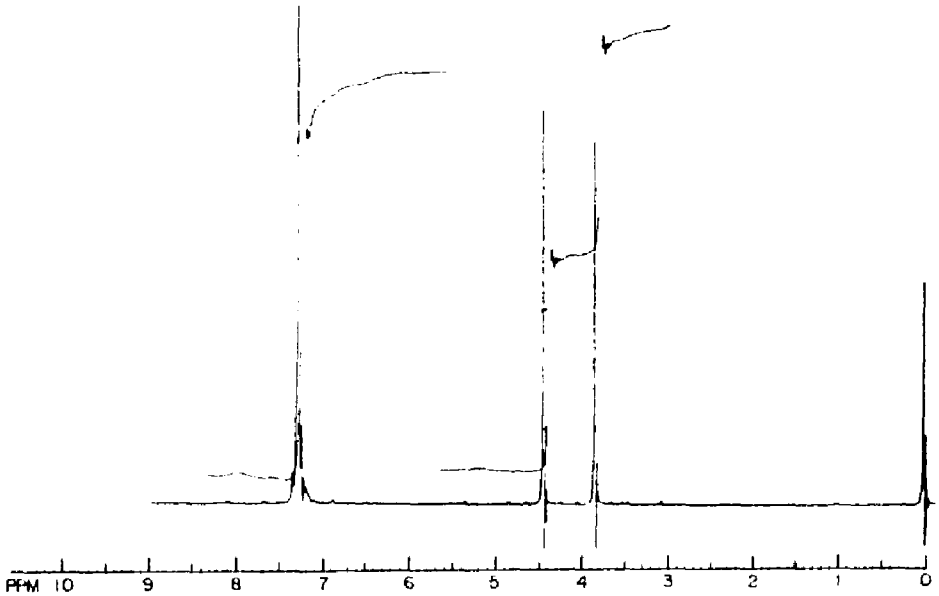




^1H NMR (90 MHz/$CDCl_3$)

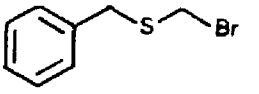
Compound **46a**

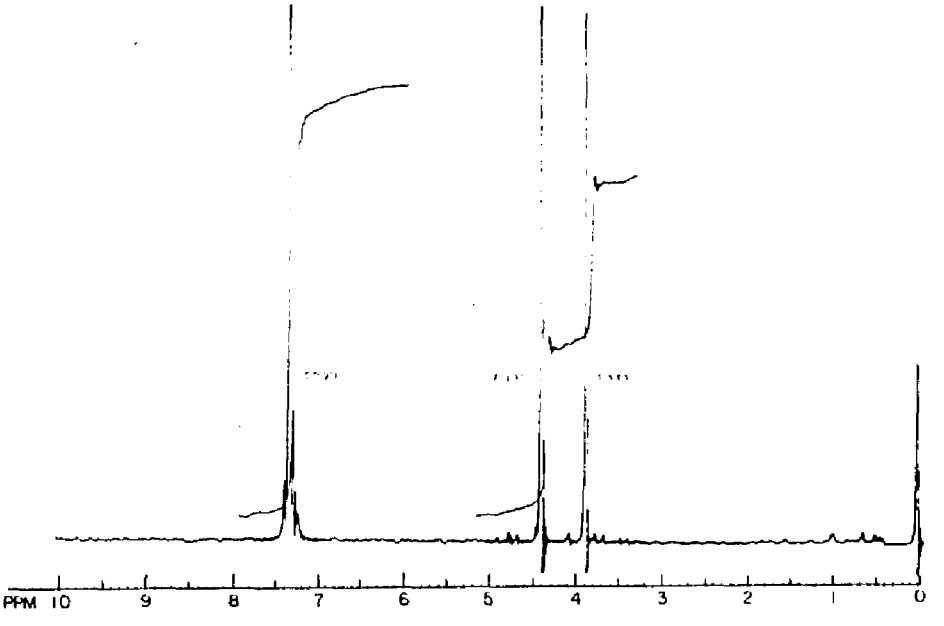




^{1}H NMR (90 MHz/CCl_4)

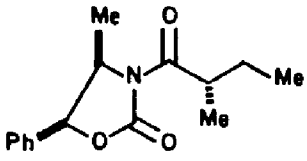
Compound **46b**

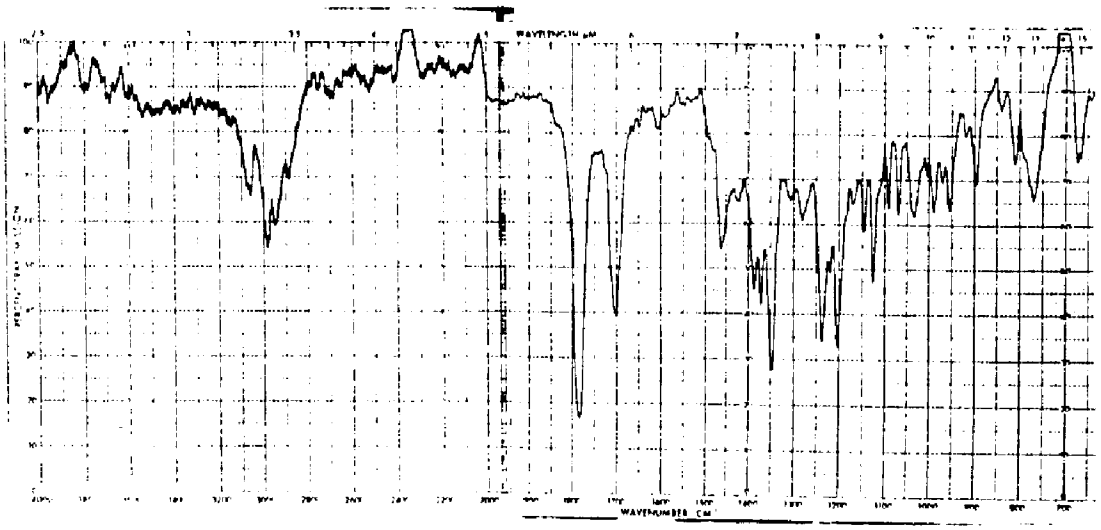




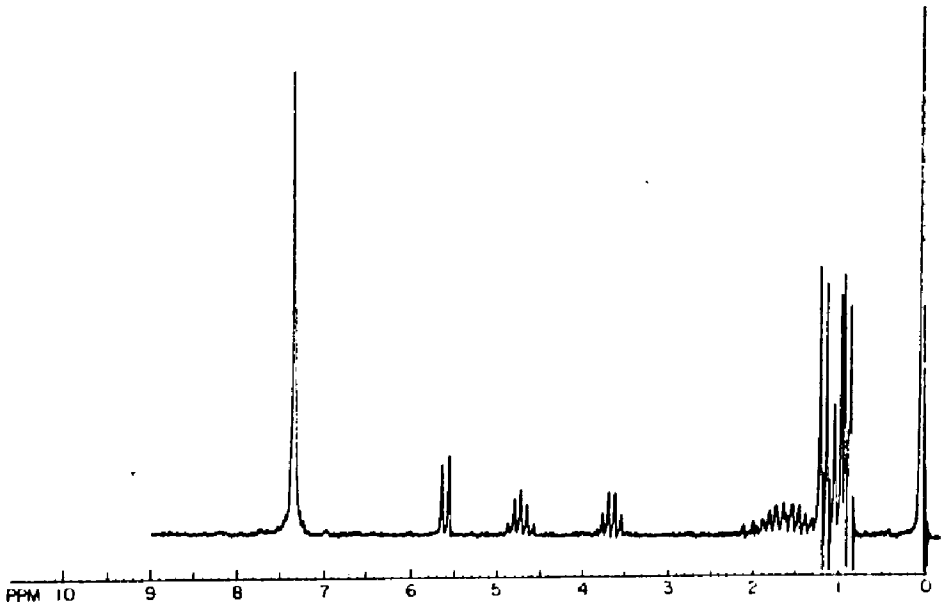
^1H NMR (90 MHz/CCl_4)

Compound **17a**



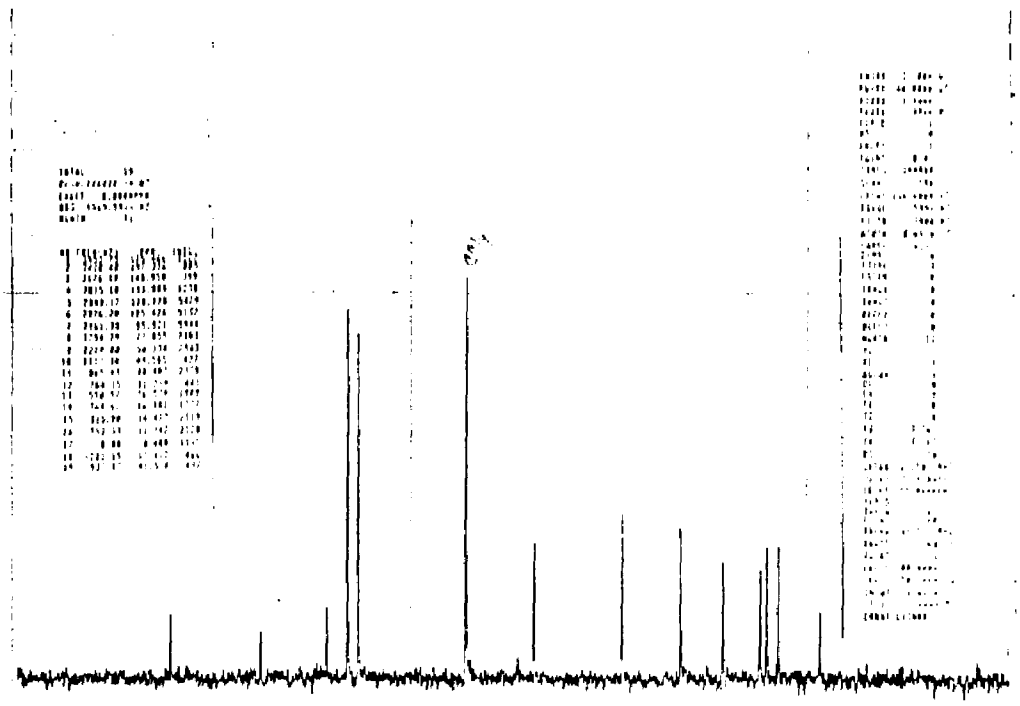


IR (CH_2Cl_2)



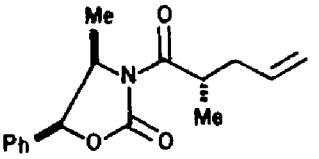
^1H NMR (90 MHz/CCl_4)

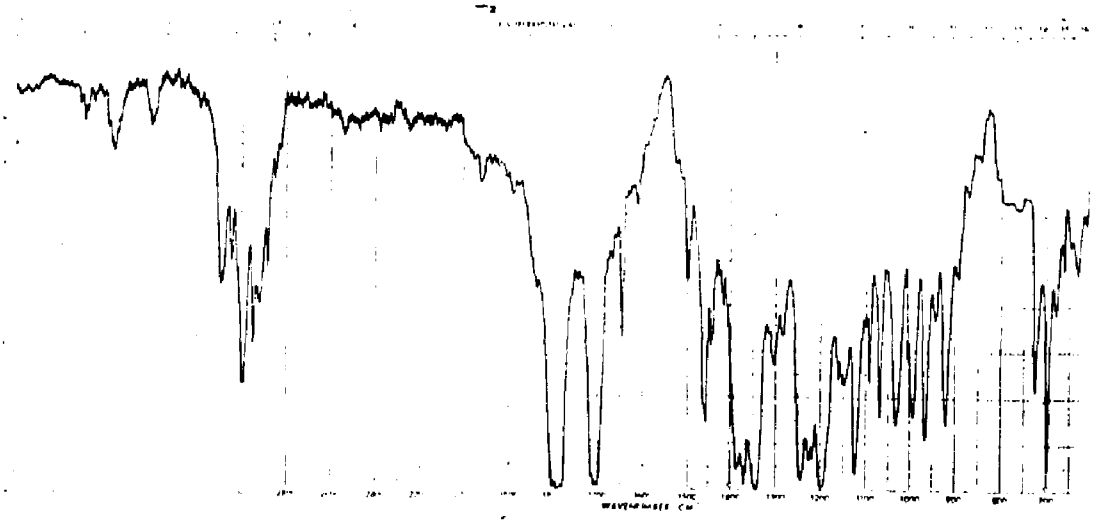
Compound **17a** continued.



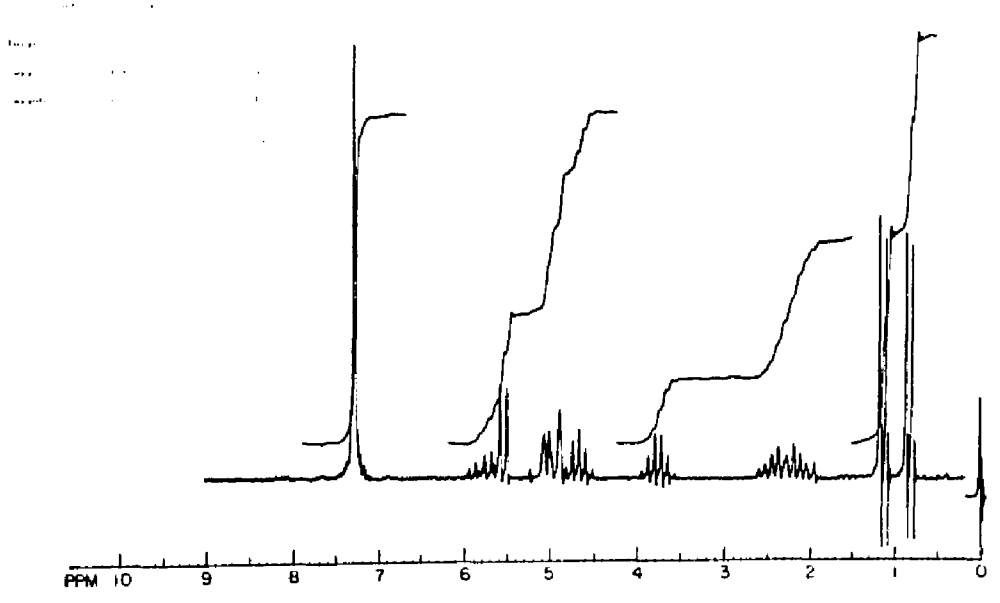
^{13}C NMR (22.5 MHz/CCl_4)

Compound **17b**



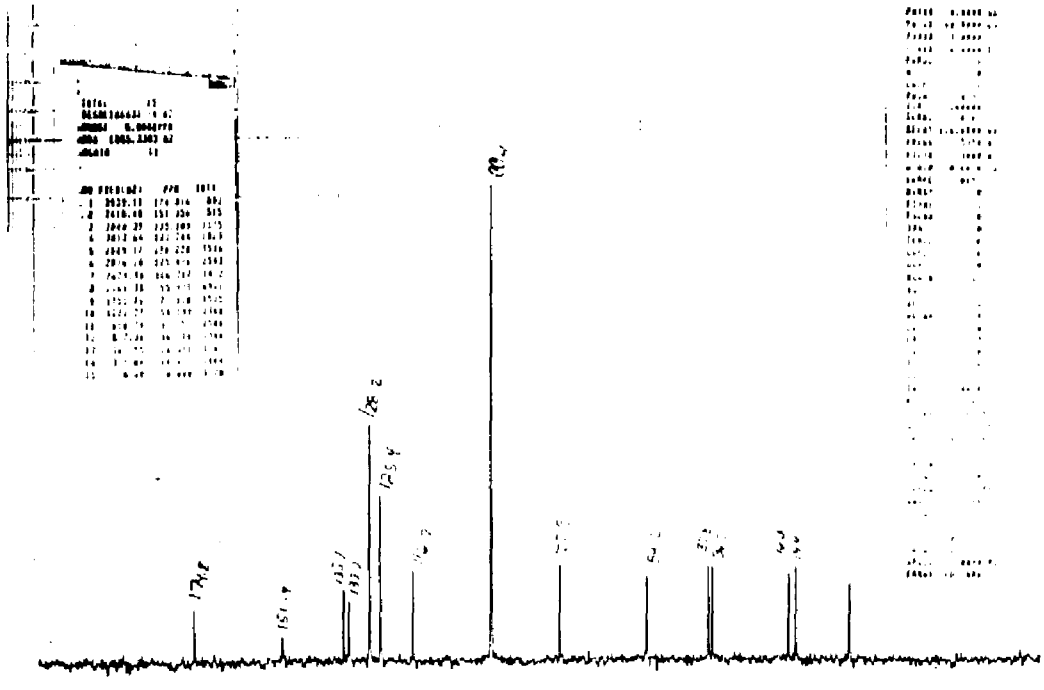


IR (CCl_4)



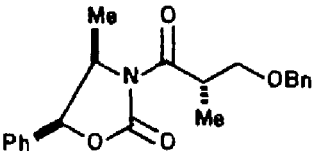
^1H NMR (90 MHz/$CDCl_3$)

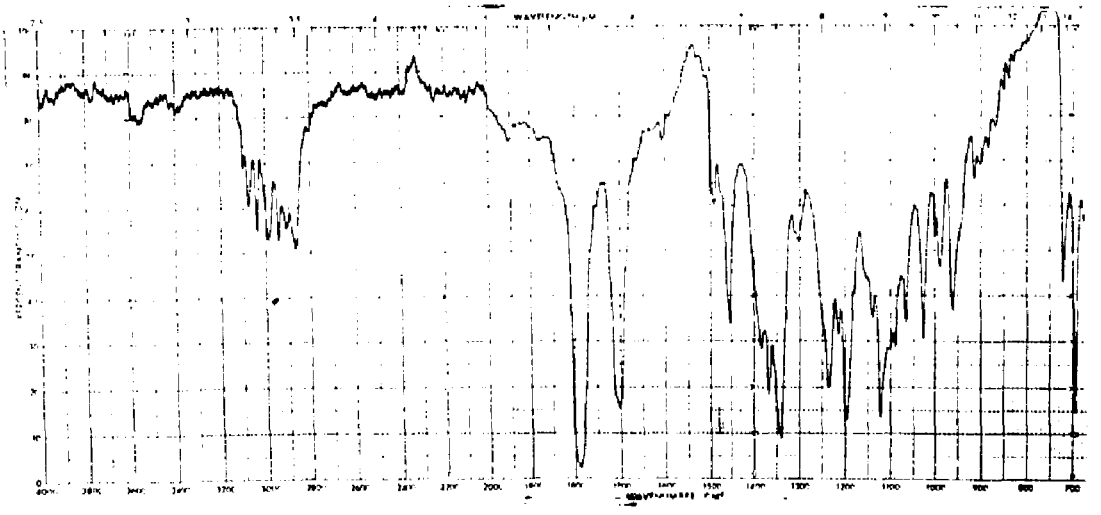
Compound **17b** continued.



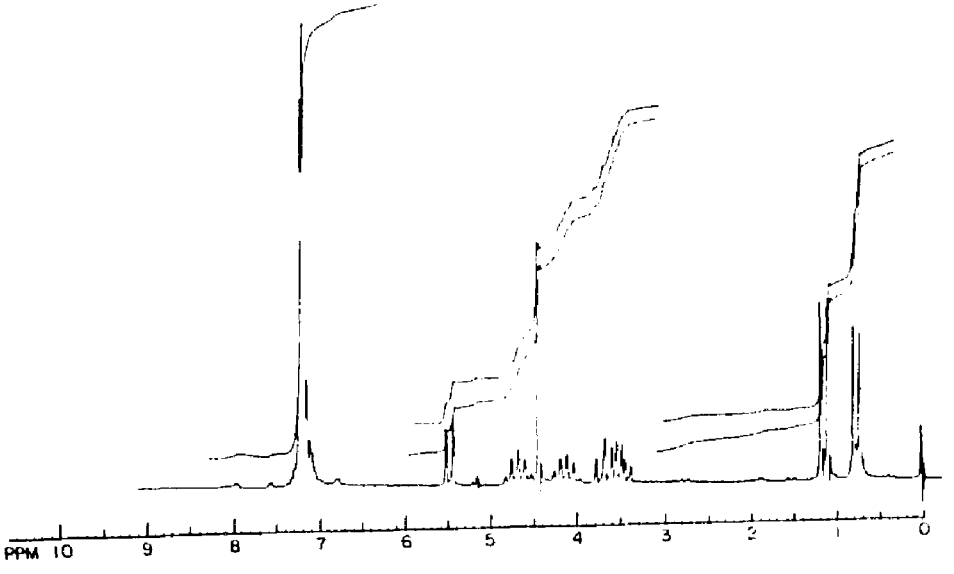
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **17e**



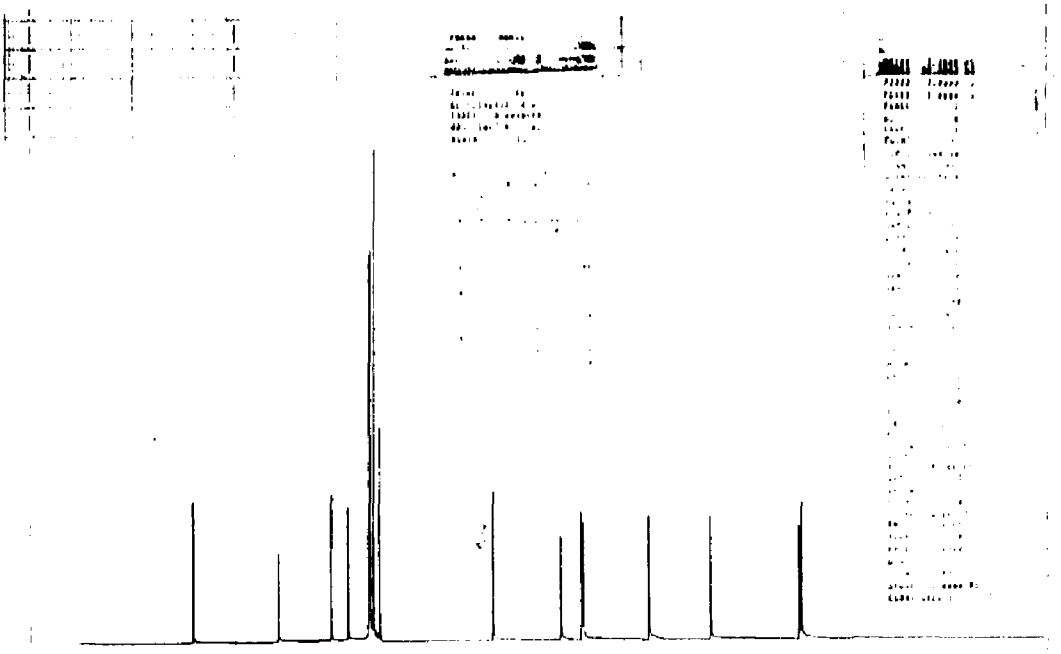


IR (CCl_4)



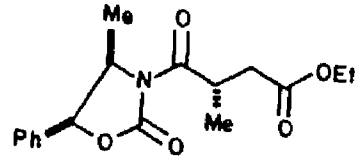
^1H NMR (90 MHz/CCl_4)

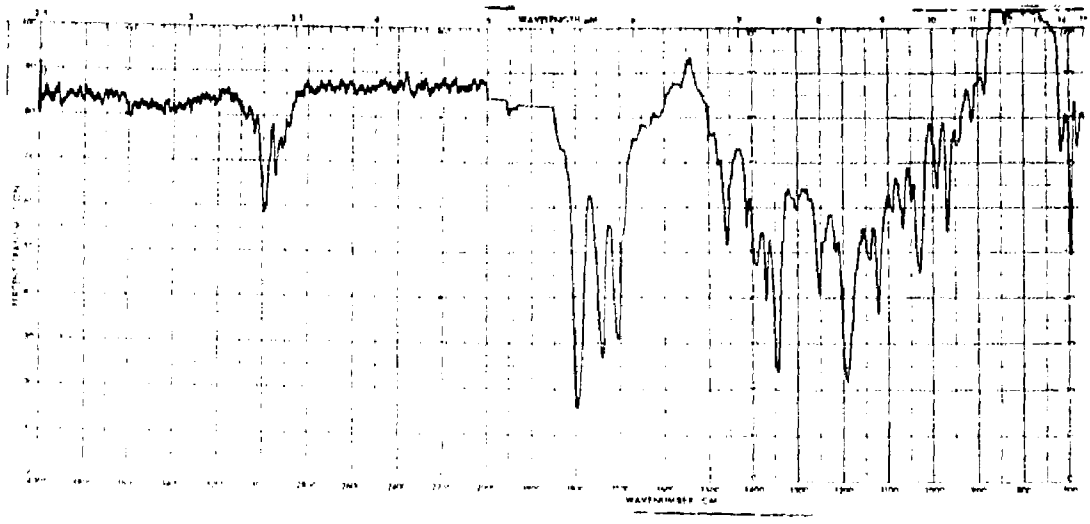
Compound **17e** continued.



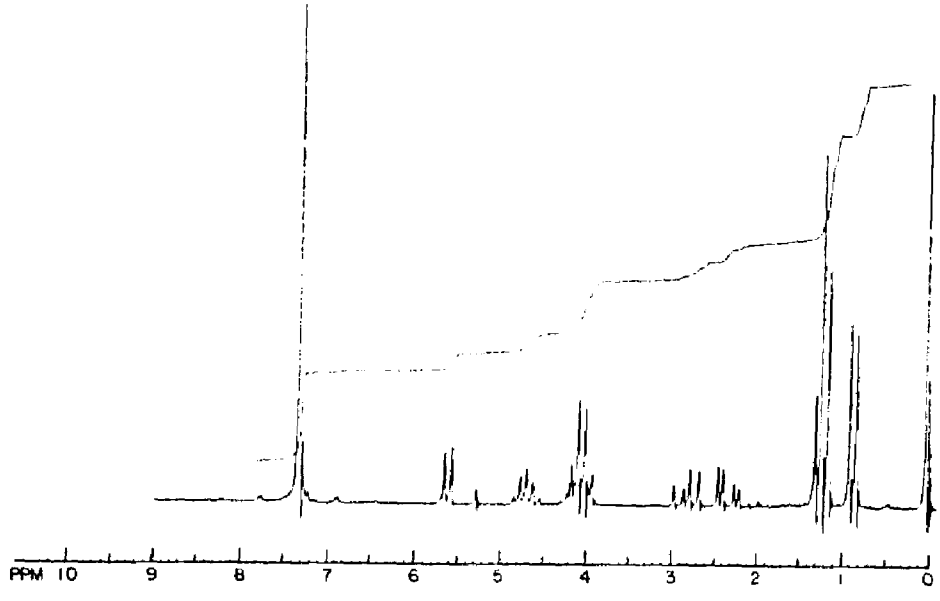
^{13}C NMR (22.5 MHz/CCl_4)

Compound **17f**



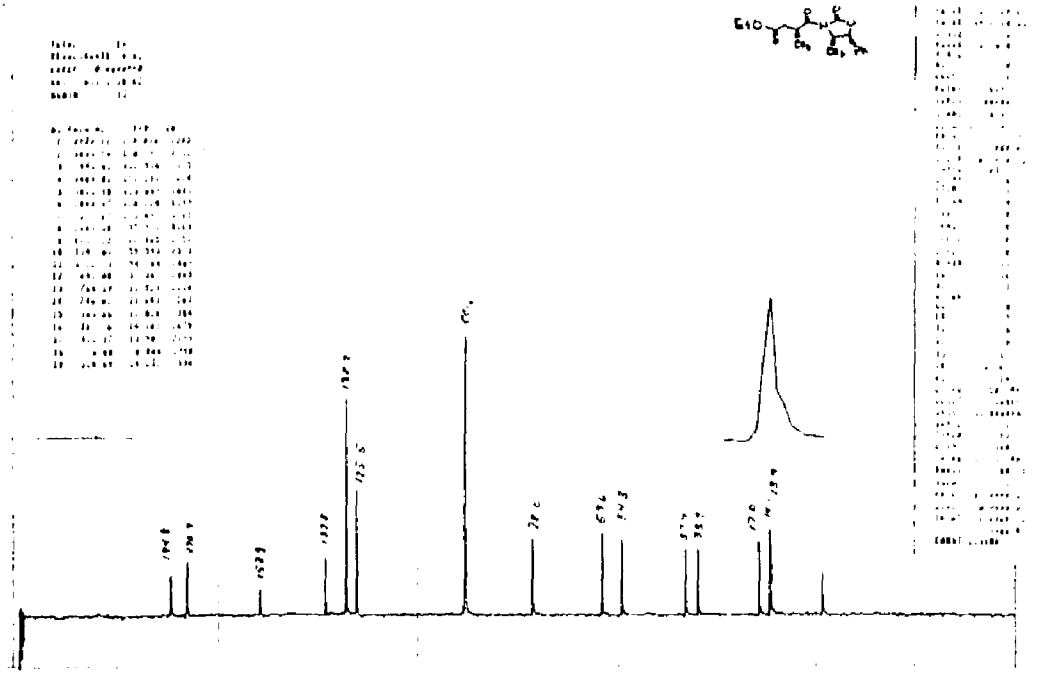


IR (CCl_4)



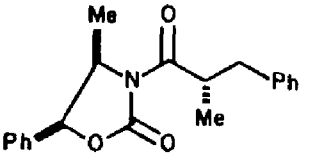
^1H NMR (90 MHz/CCl_4)

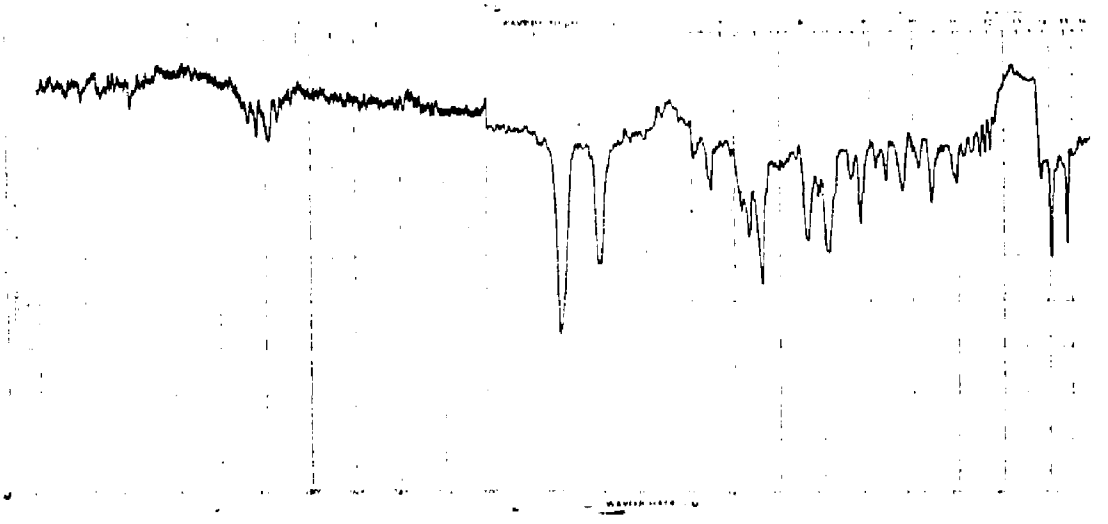
Compound **17f** continued.



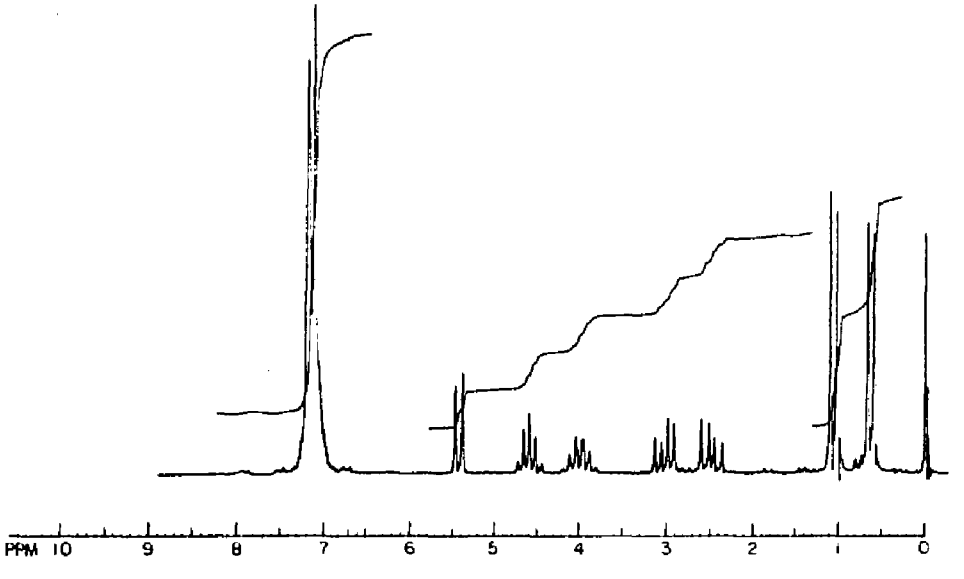
^{13}C NMR (22.5 MHz/CCl_4)

Compound **17g**



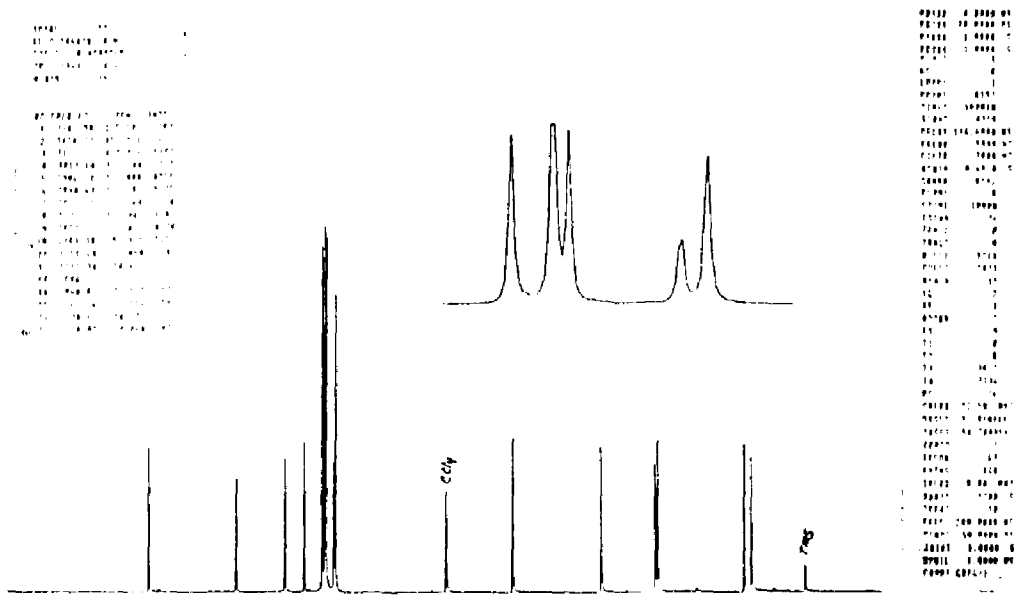


IR (CCl_4)



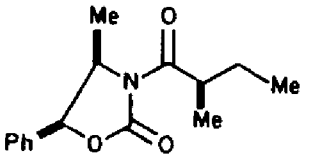
^1H NMR (90 MHz/CCl_4)

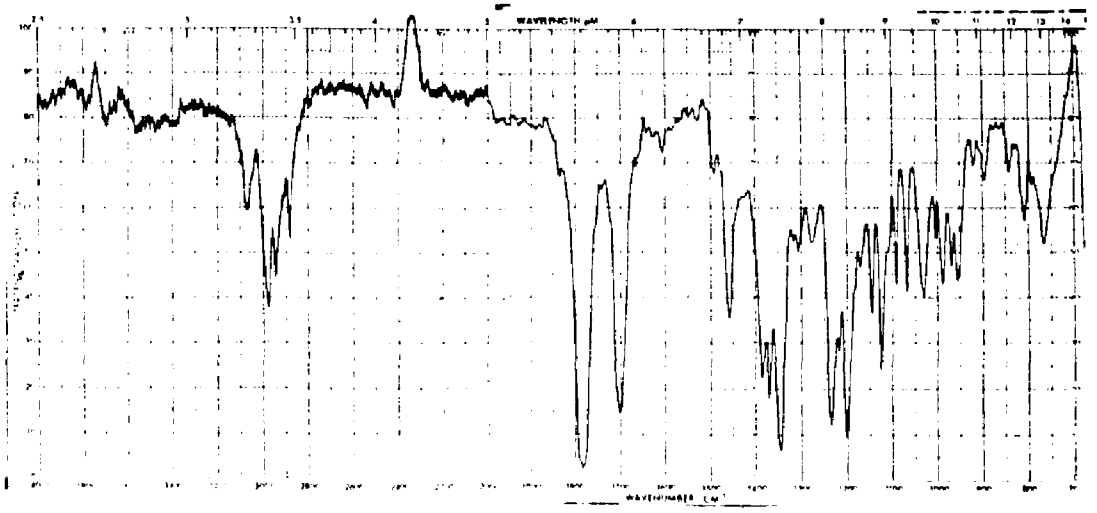
Compound **17g** continued.



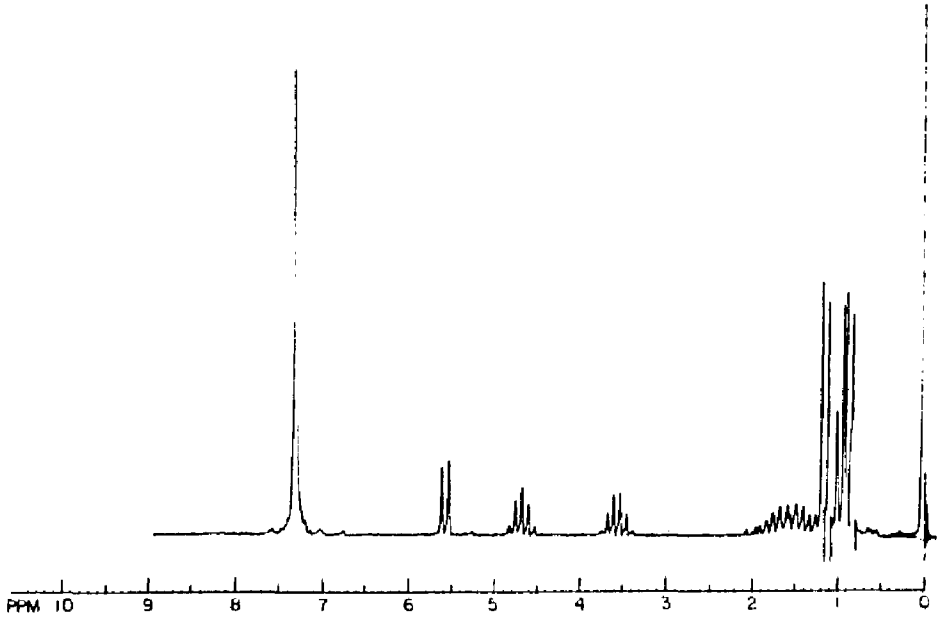
^{13}C NMR (22.5 MHz/CCl_4)

Compound **17h**



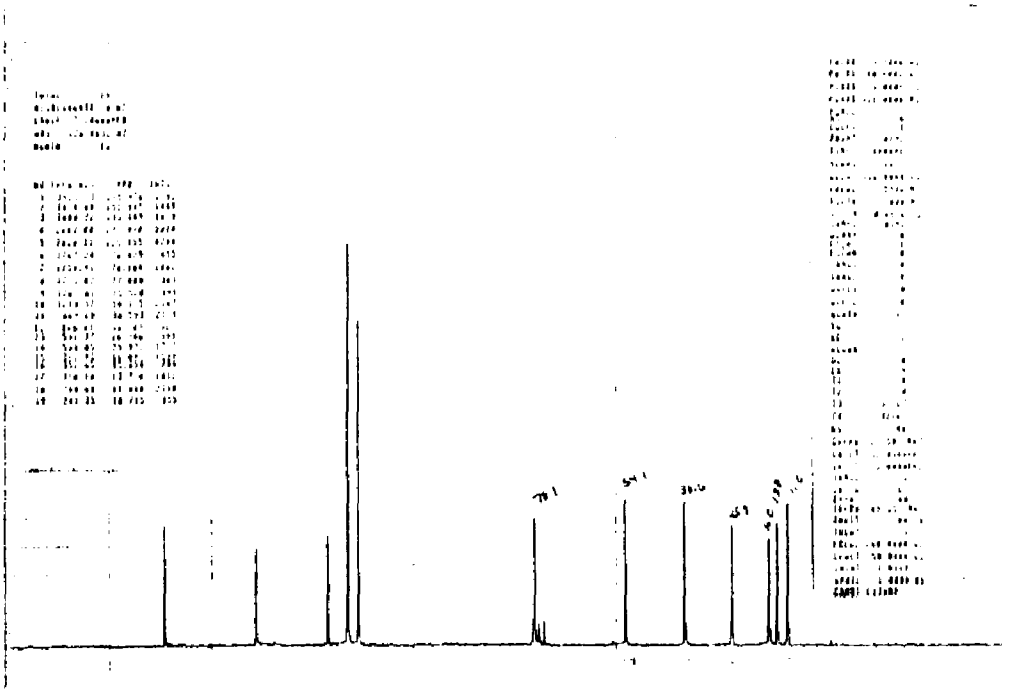


IR (CH_2Cl_2)



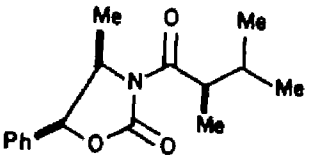
^1H NMR (90 MHz/CCl_4)

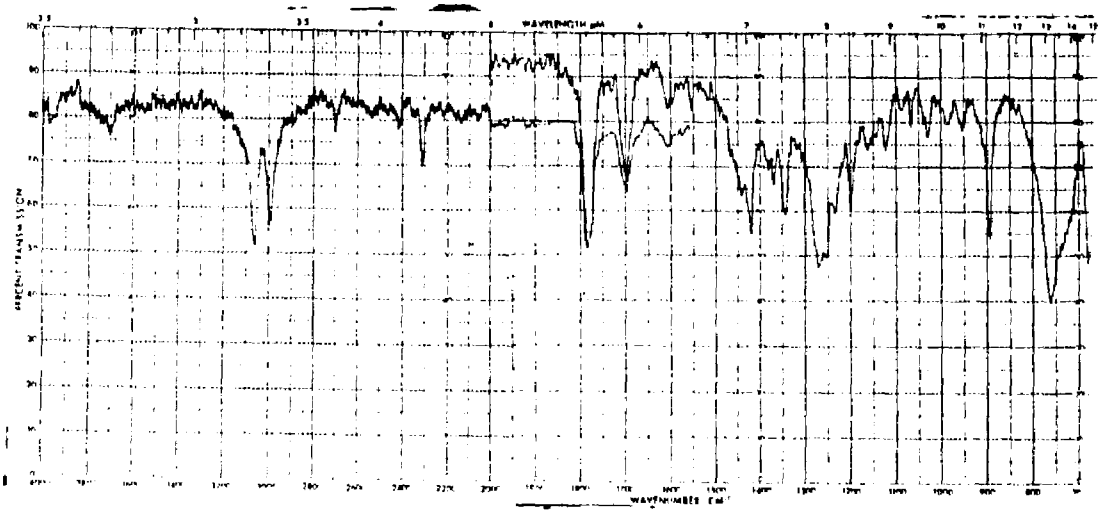
Compound **17h** continued.



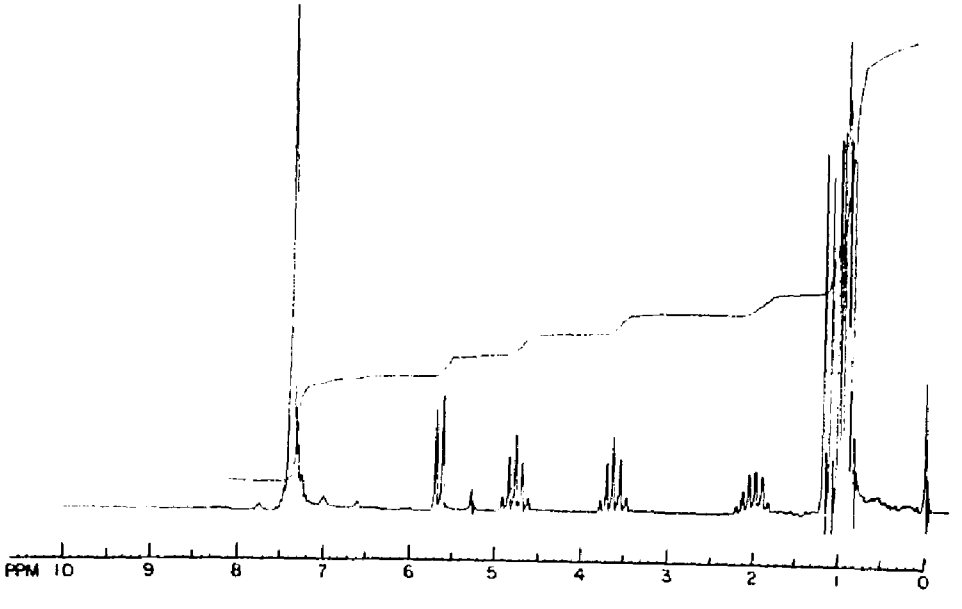
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **17i**



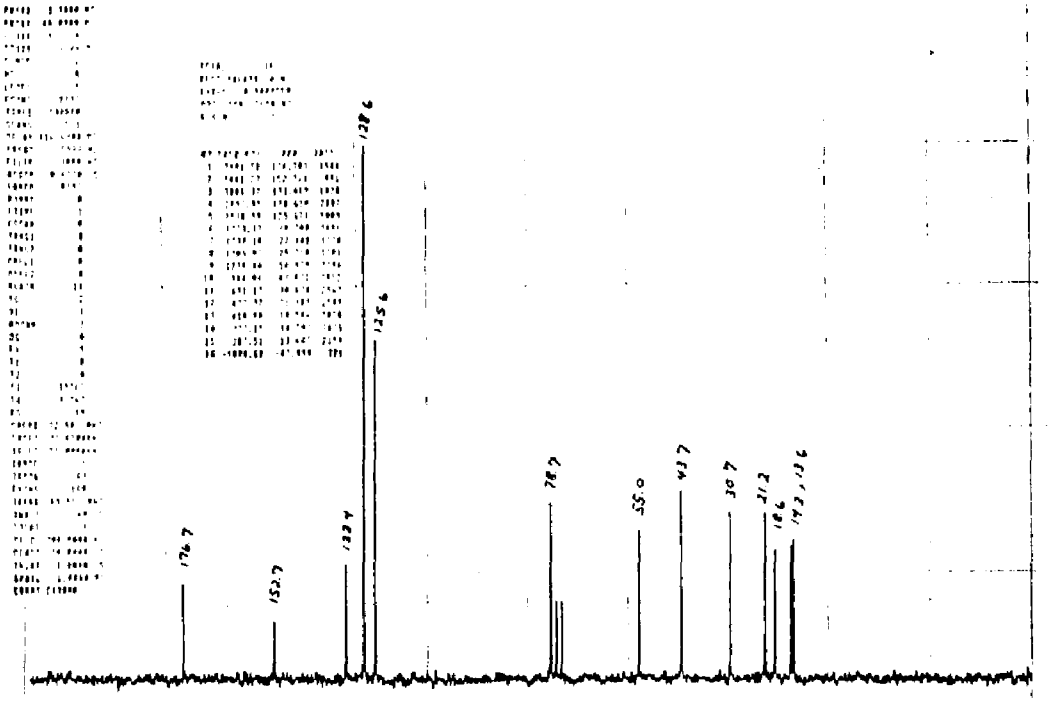


IR (CH_2Cl_2)



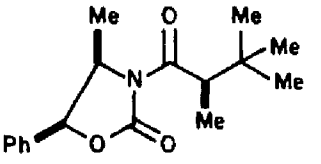
^1H NMR (90 MHz/$CDCl_3$)

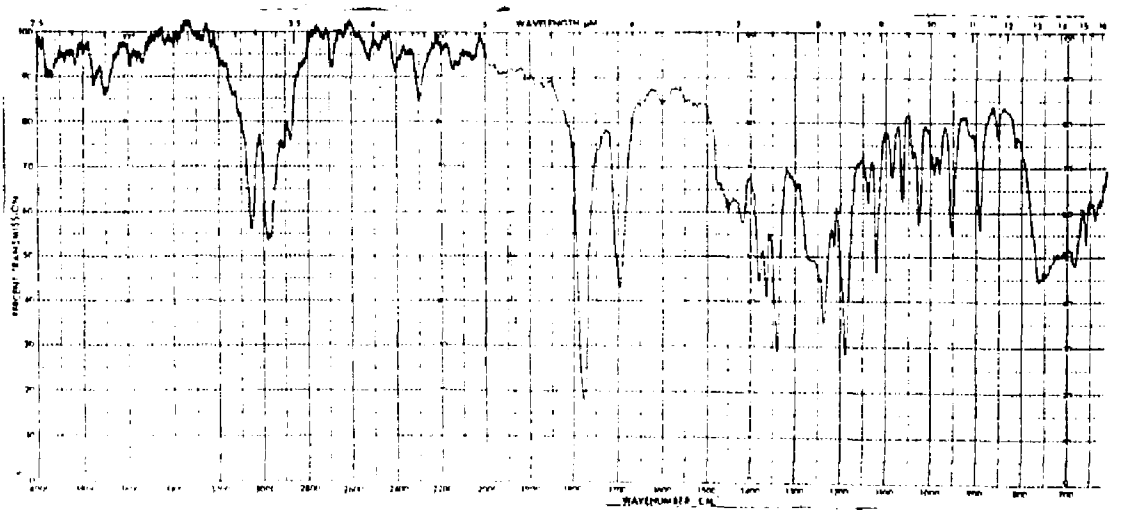
Compound **17i** continued.



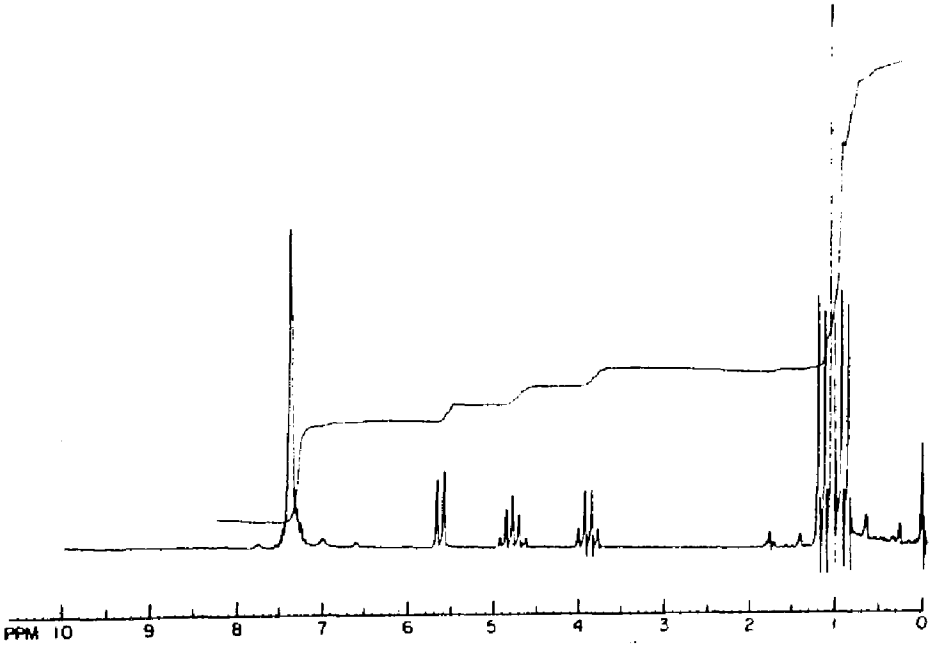
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **17j**



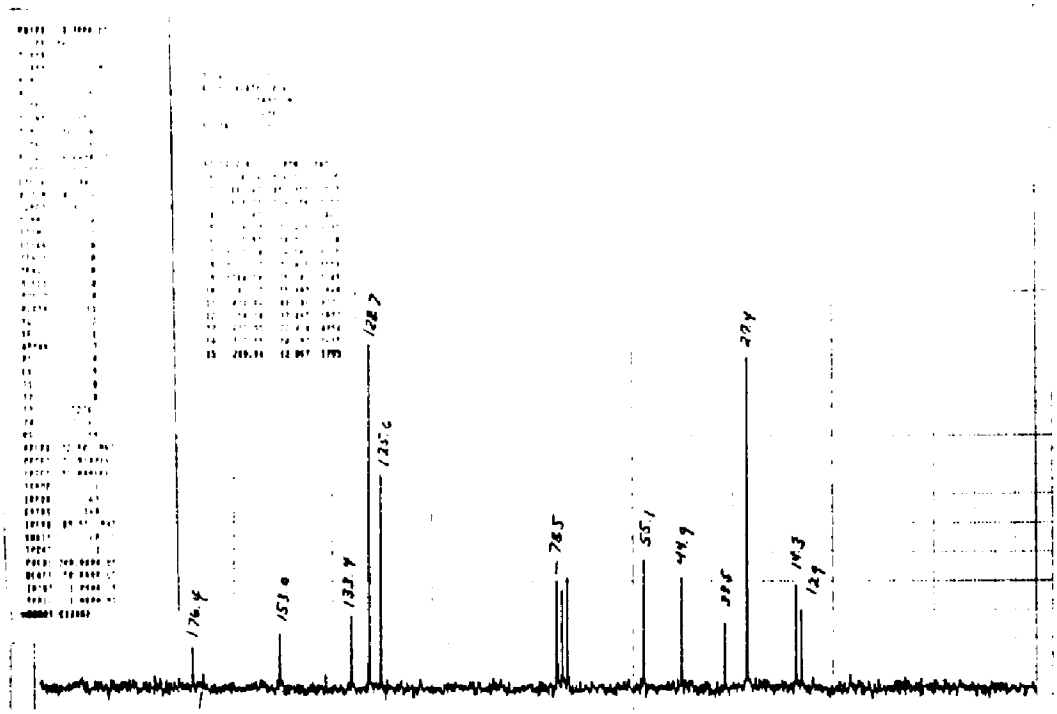


IR (CH_2Cl_2)



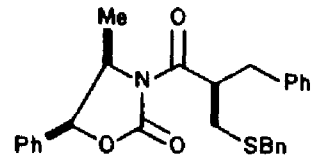
^1H NMR (90 MHz/$CDCl_3$)

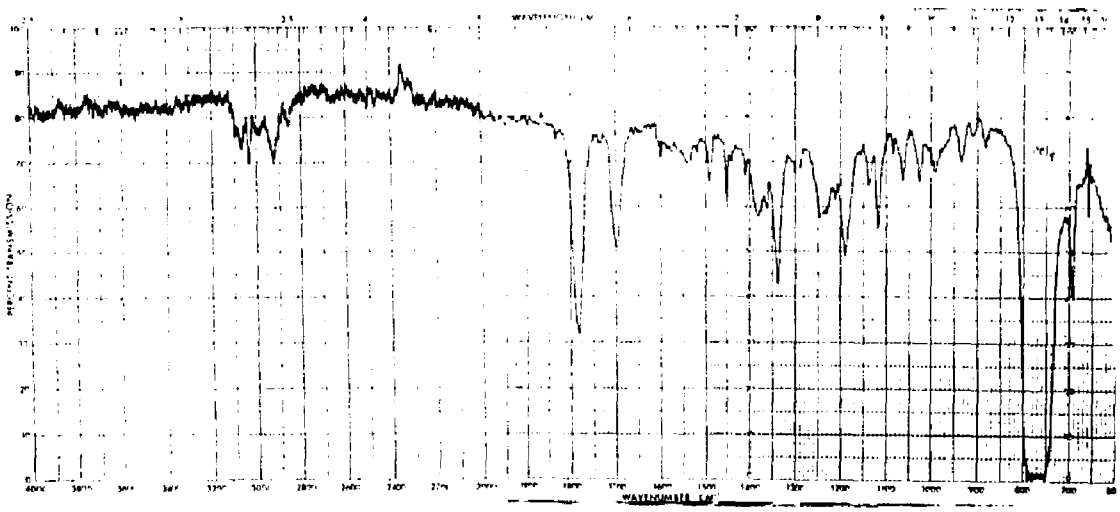
Compound **17j** continued.



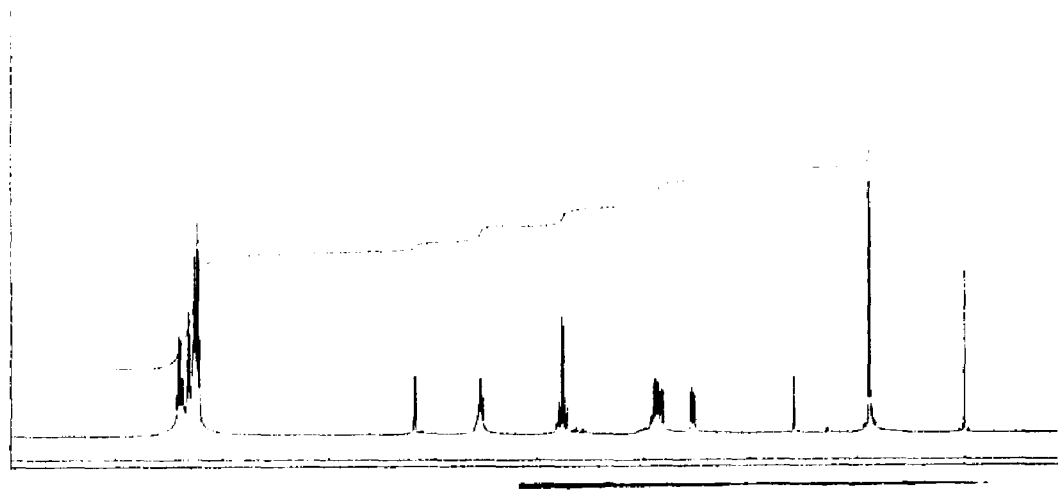
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **17k**



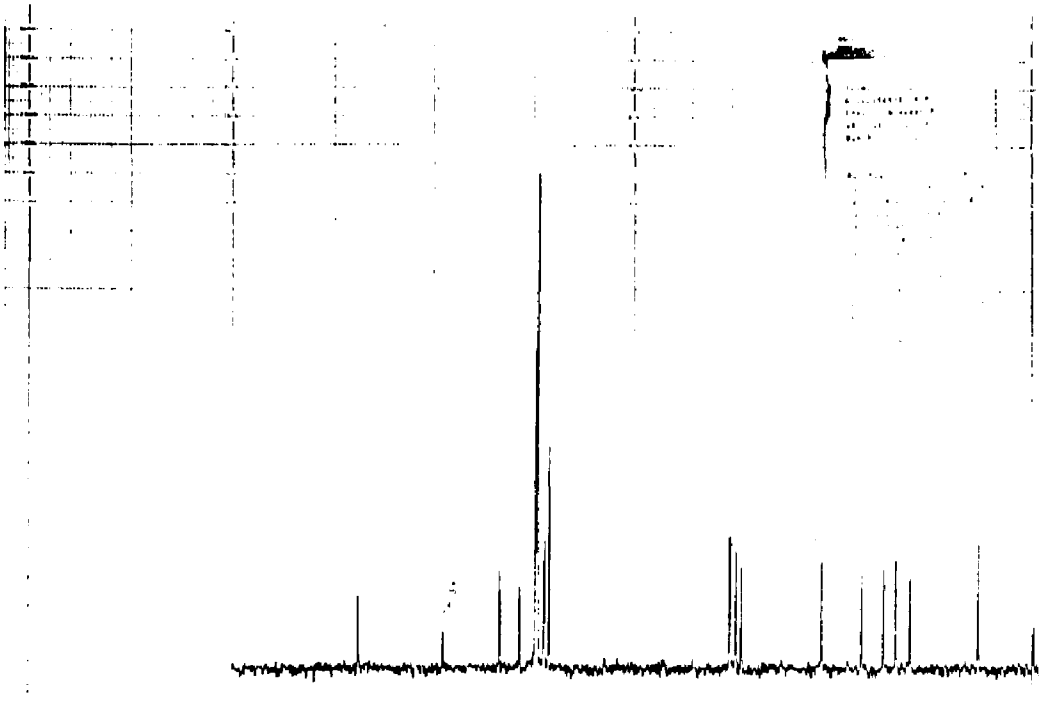


IR (neat)



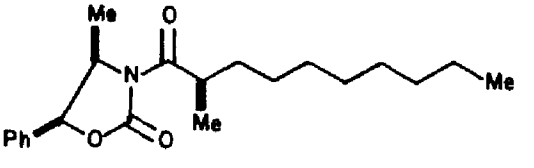
^{1}H NMR (500 MHz/$CDCl_3$)

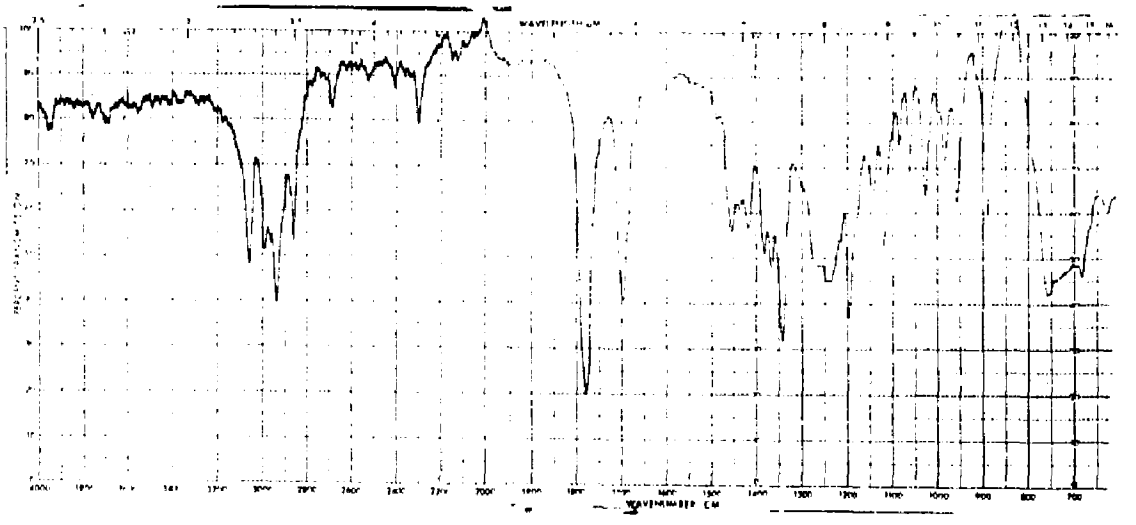
Compound **17k** continued.



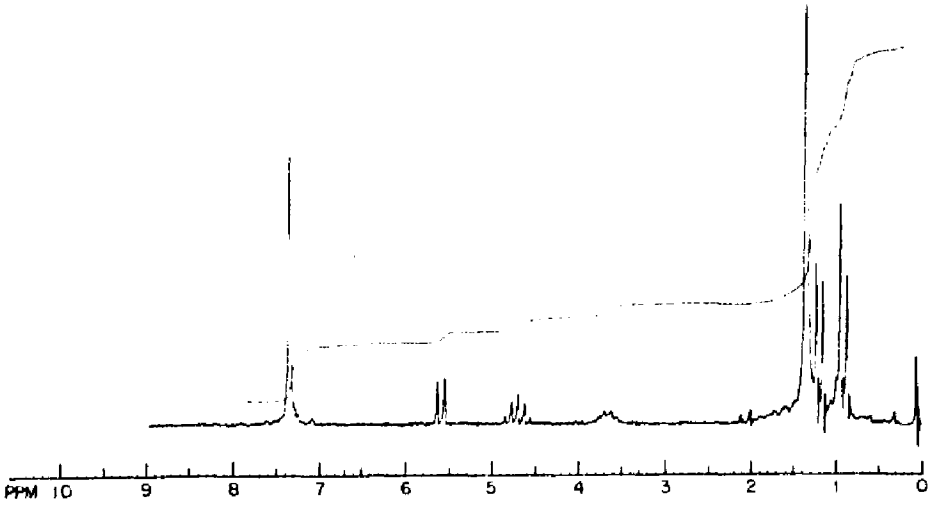
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **171**



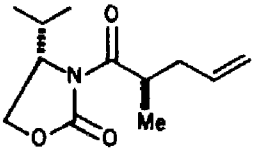


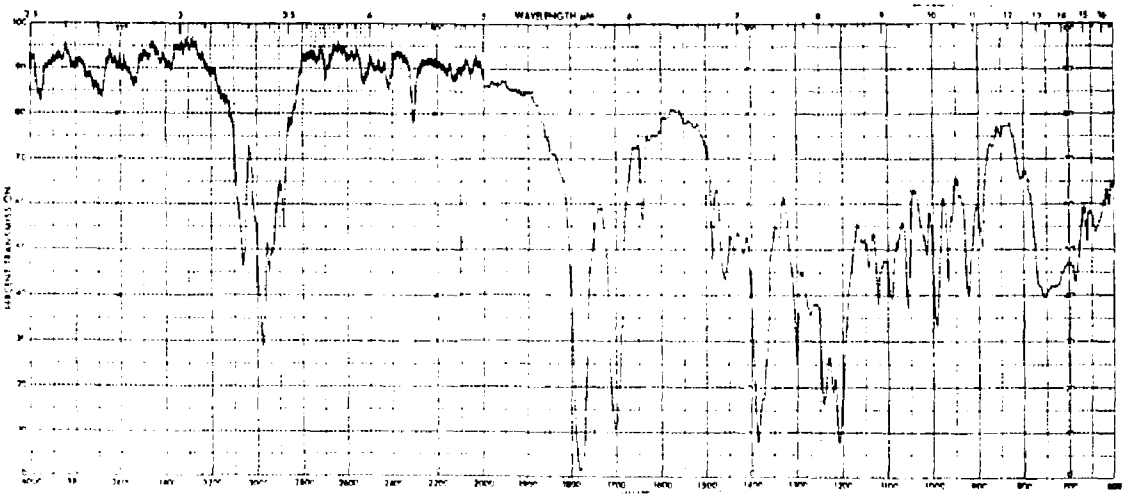
IR (CH_2Cl_2)



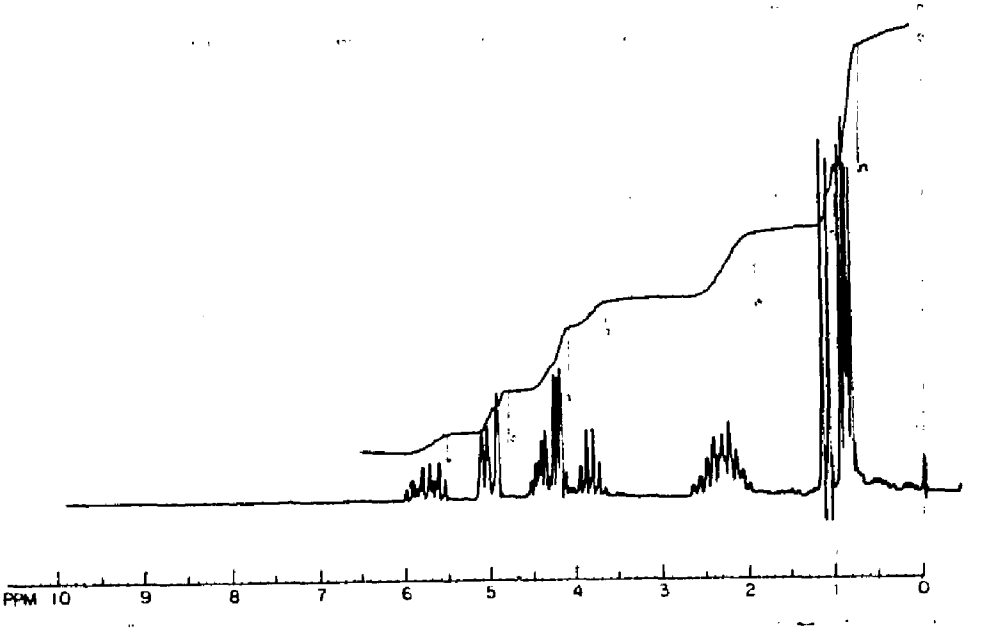
^1H NMR (90 MHz/CCl_4)

Compound **21b**



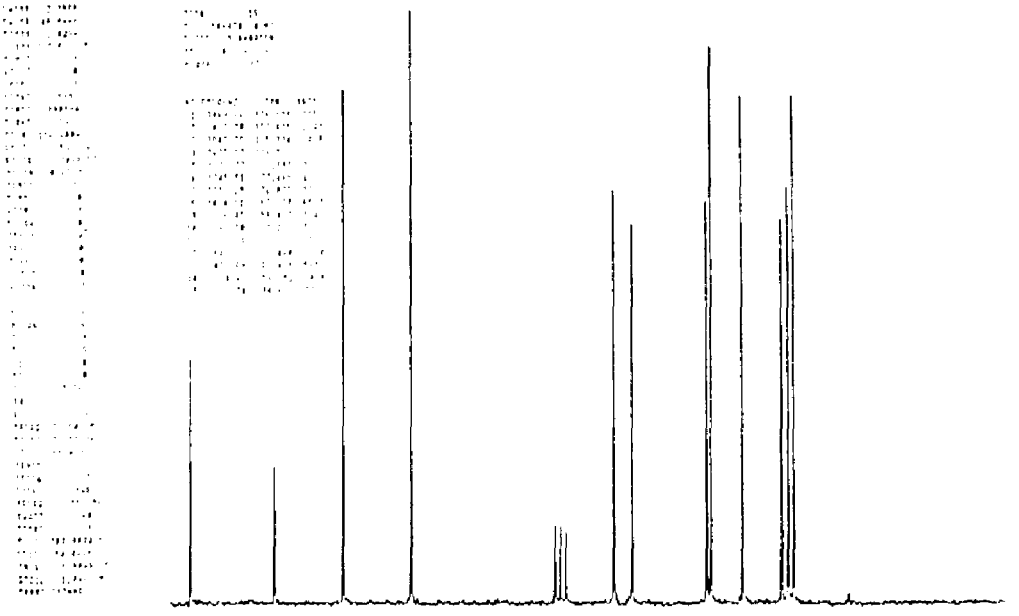


IR (CH_2Cl_2)



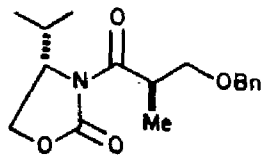
^1H NMR (90 MHz/$CDCl_3$)

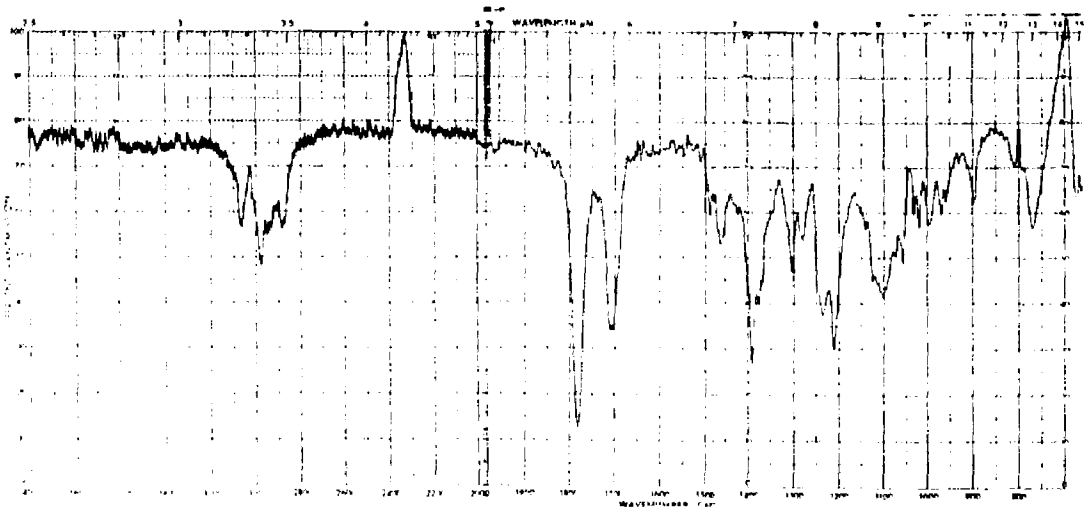
Compound **21b** continued.



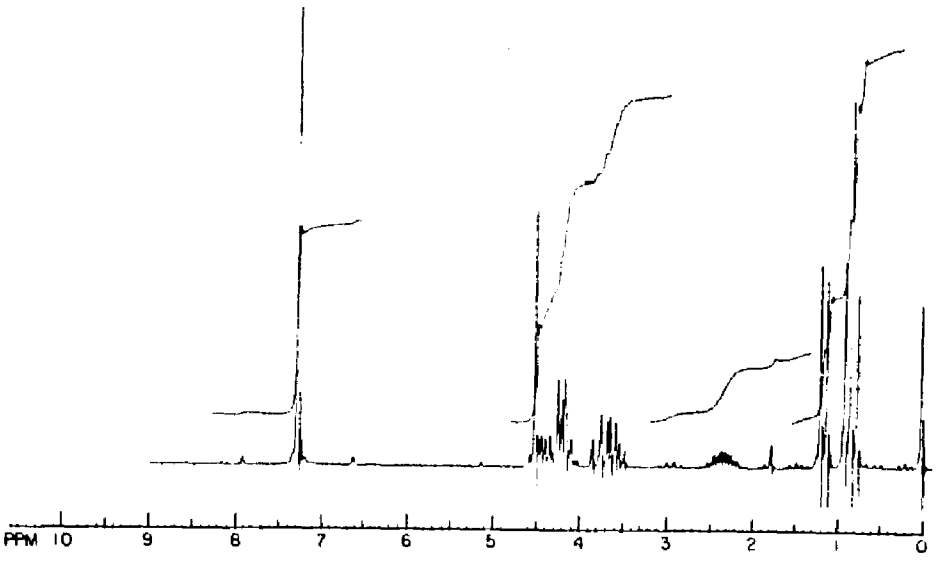
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **21e**



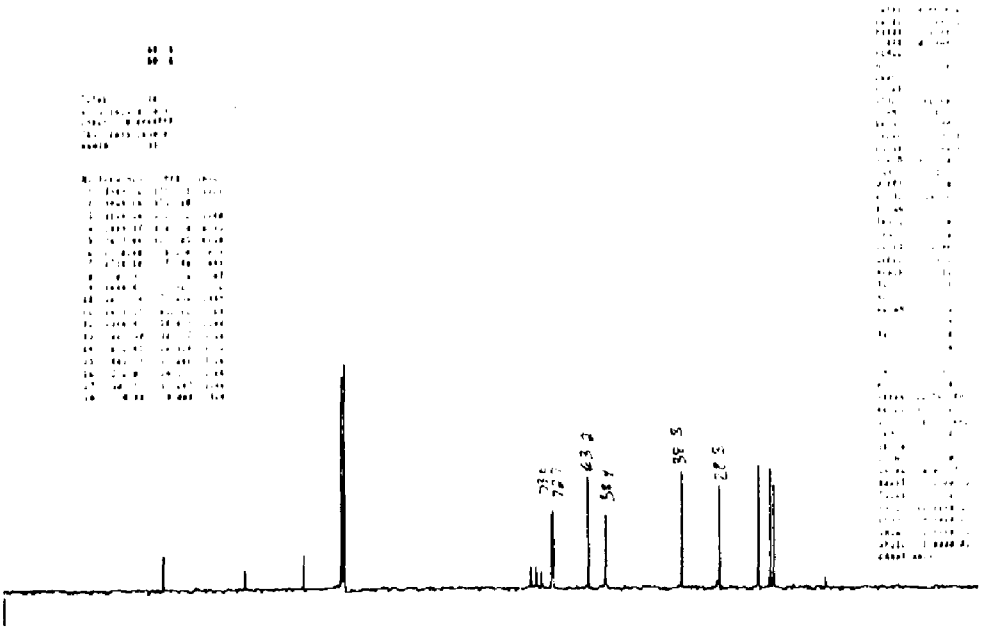


IR (CH_2Cl_2)



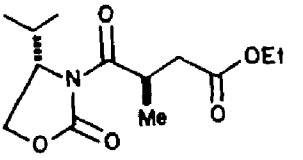
^1H NMR (90 MHz/$CDCl_3$)

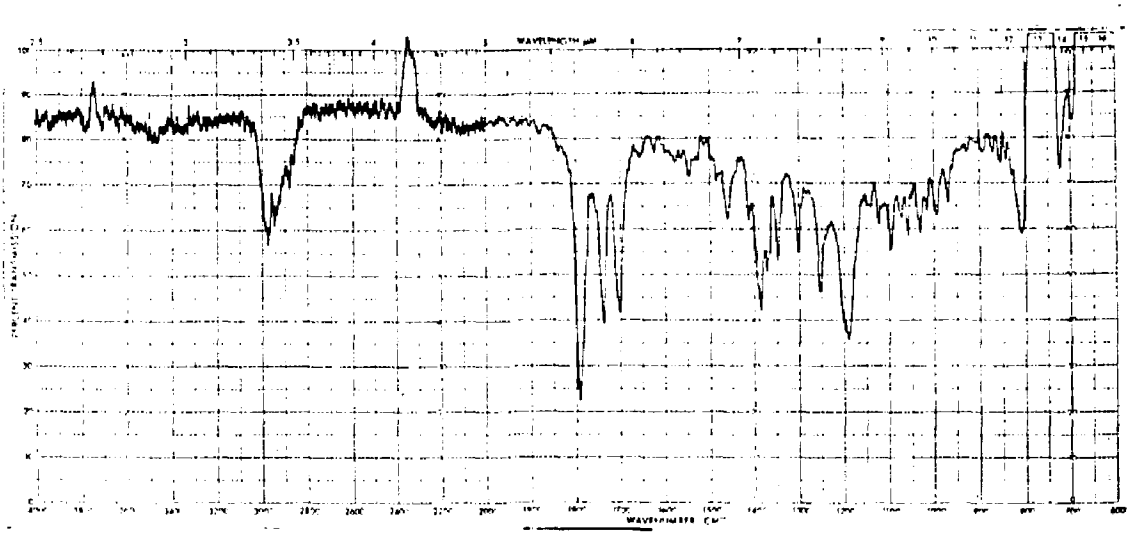
Compound **21e** continued.



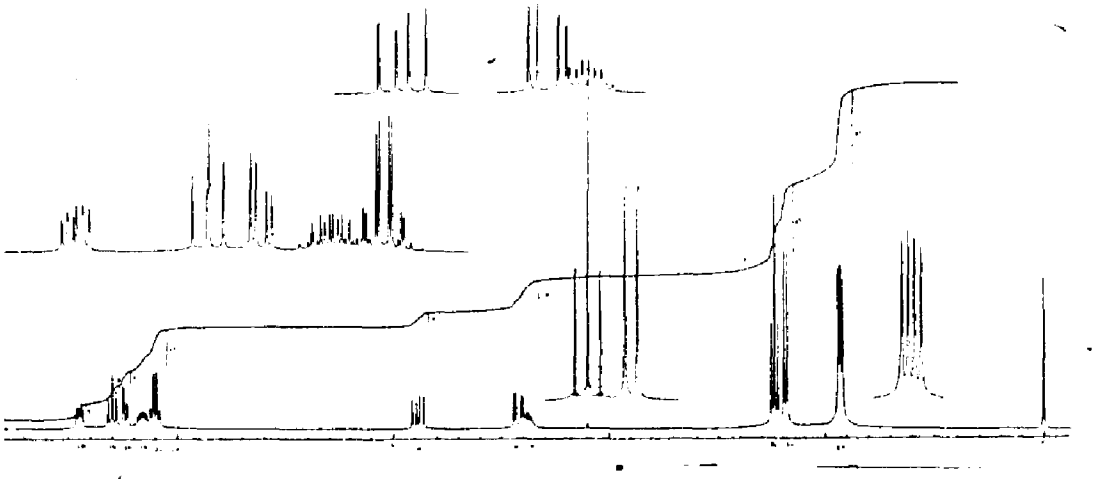
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **21f**



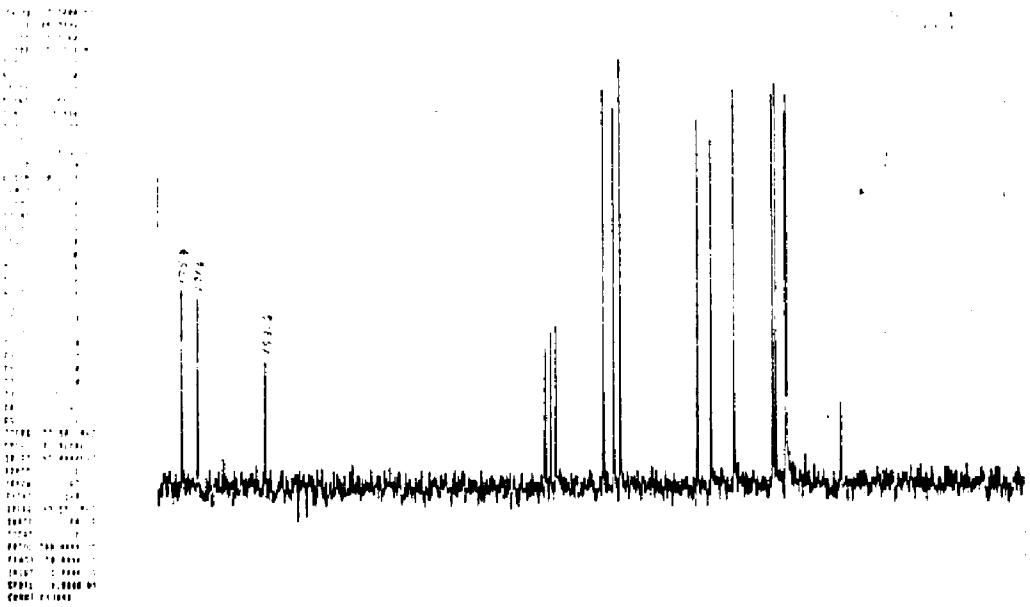


IR (CCl_4)



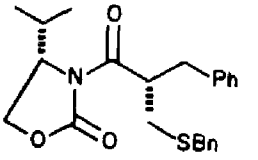
^1H NMR (500 MHz/$CDCl_3$)

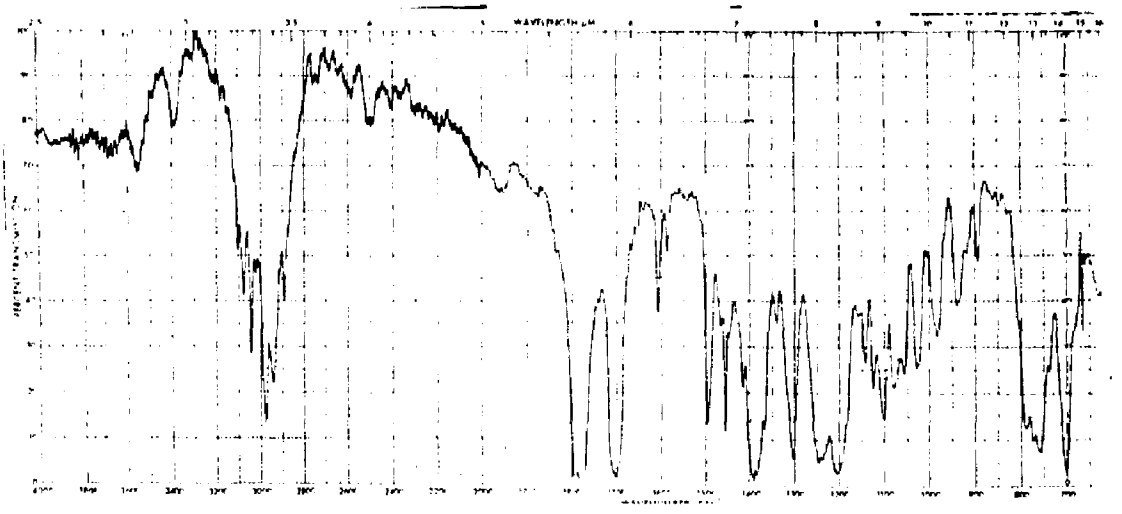
Compound **21f** continued.



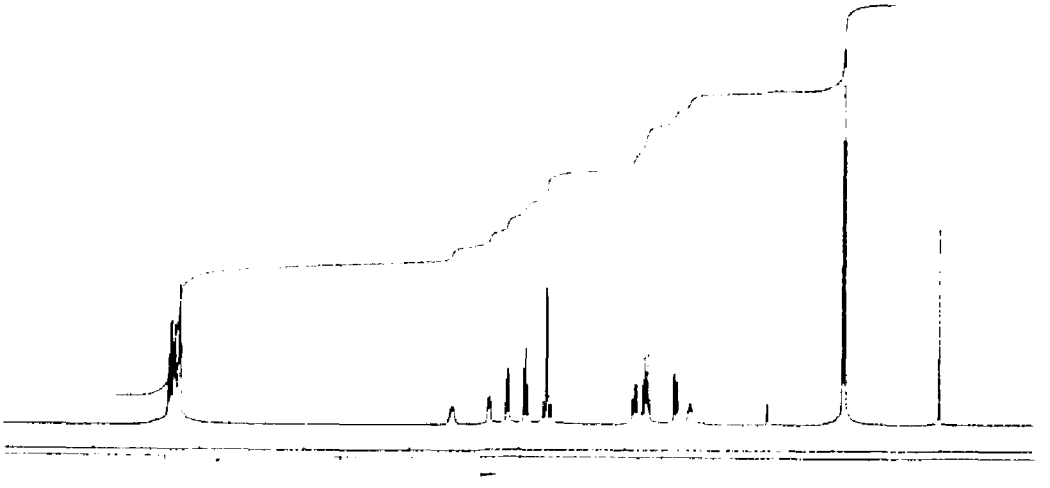
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **21k**



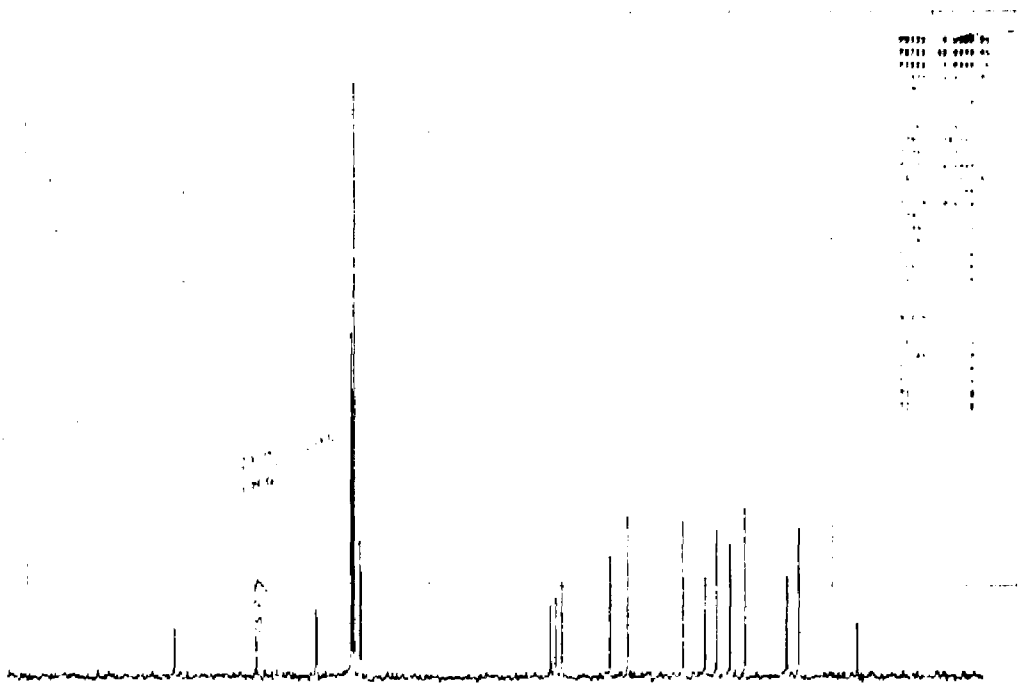


IR (neat)



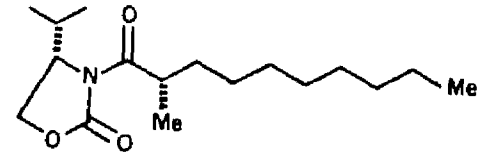
^{1}H NMR (500 MHz/$CDCl_3$)

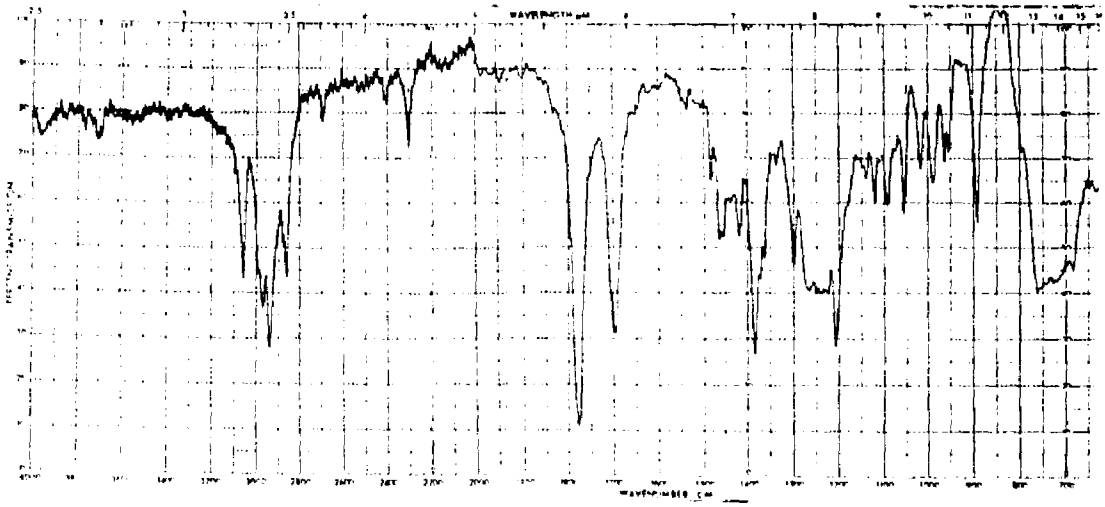
Compound **21k** continued.



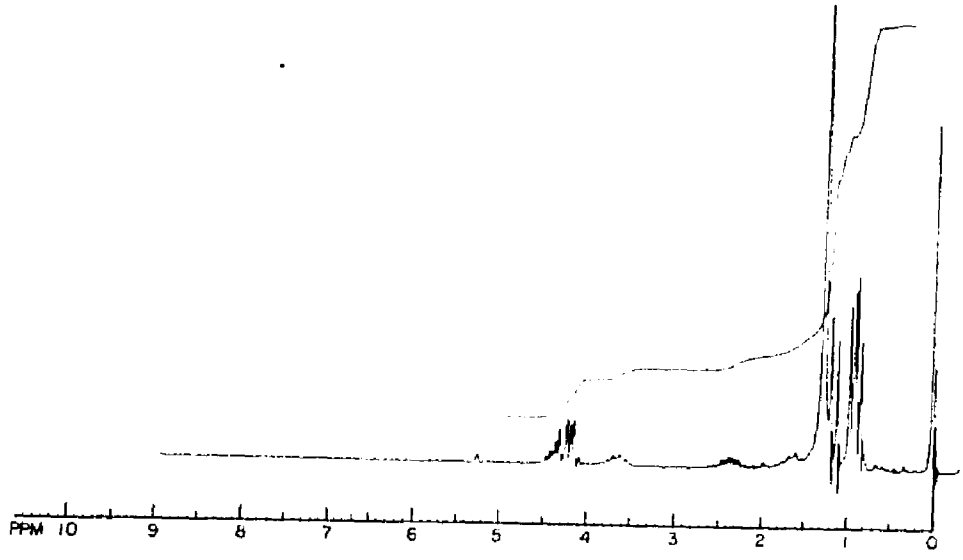
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **211**



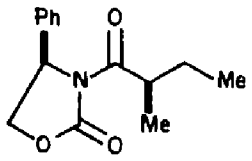


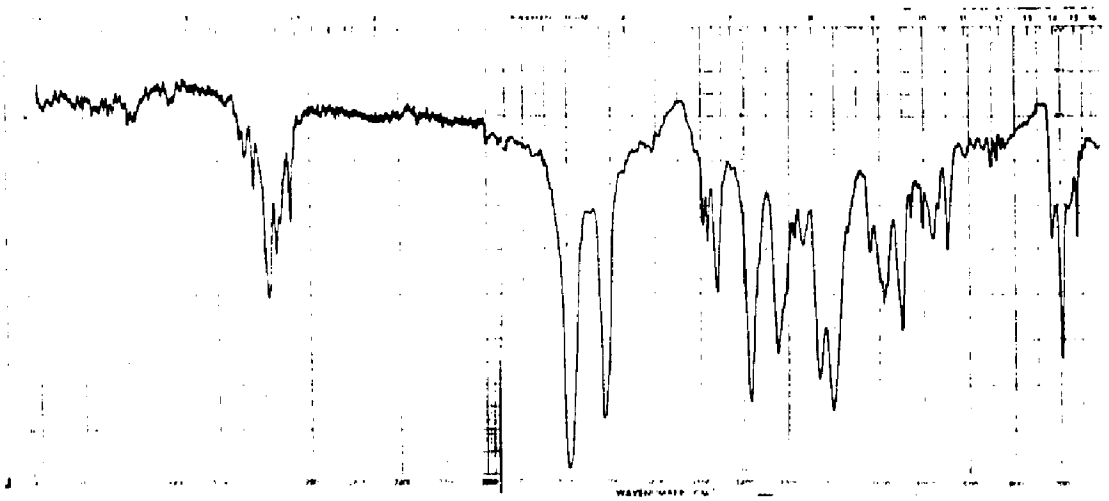
IR (CH_2Cl_2)



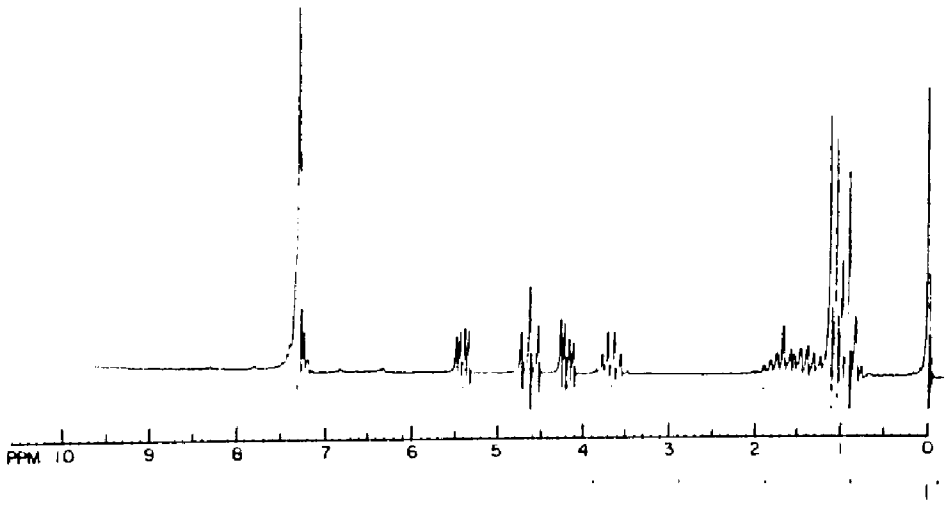
^1H NMR (90 MHz/CCl_4)

Compound **23h**



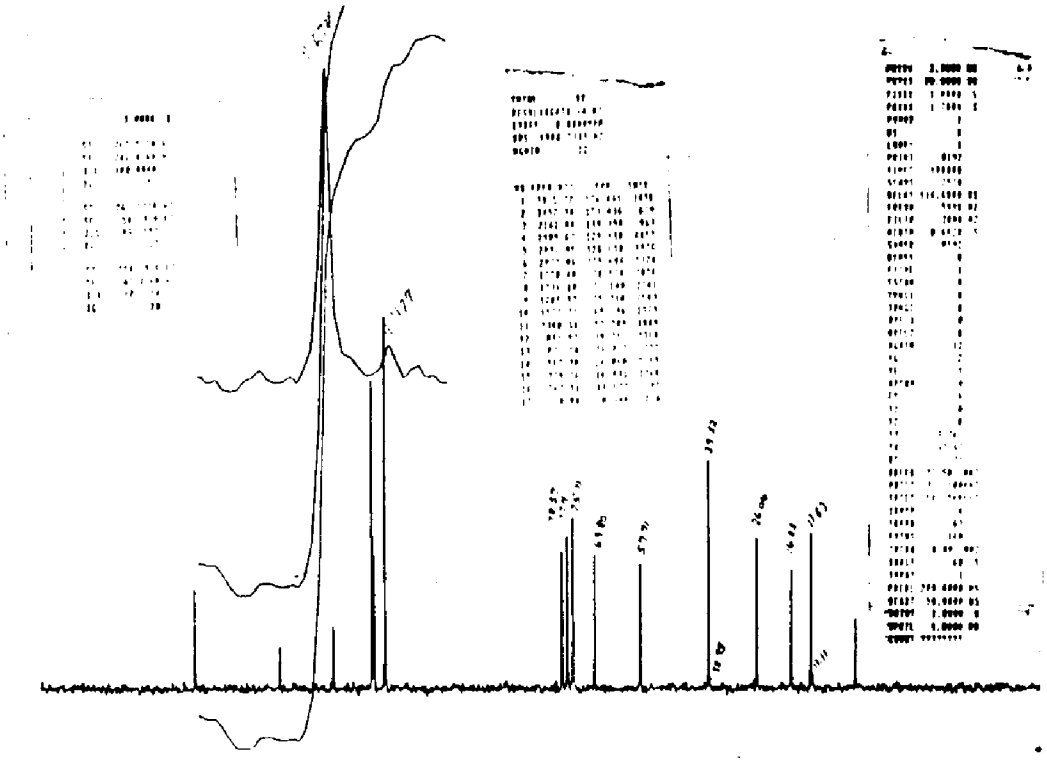


IR (CCl_4)



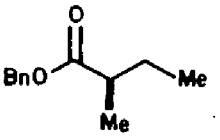
^1H NMR (90 MHz/$CDCl_3$)

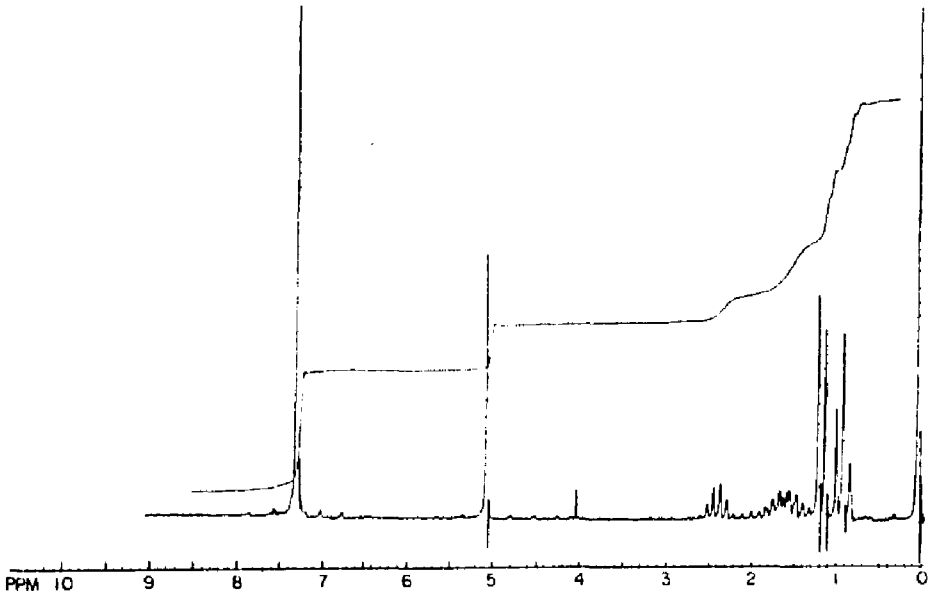
Compound **23h** continued.



^{13}C NMR (22.5 MHz/$CDCl_3$)

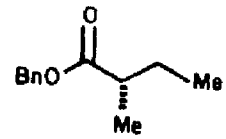
Compound (2R)-**31a**

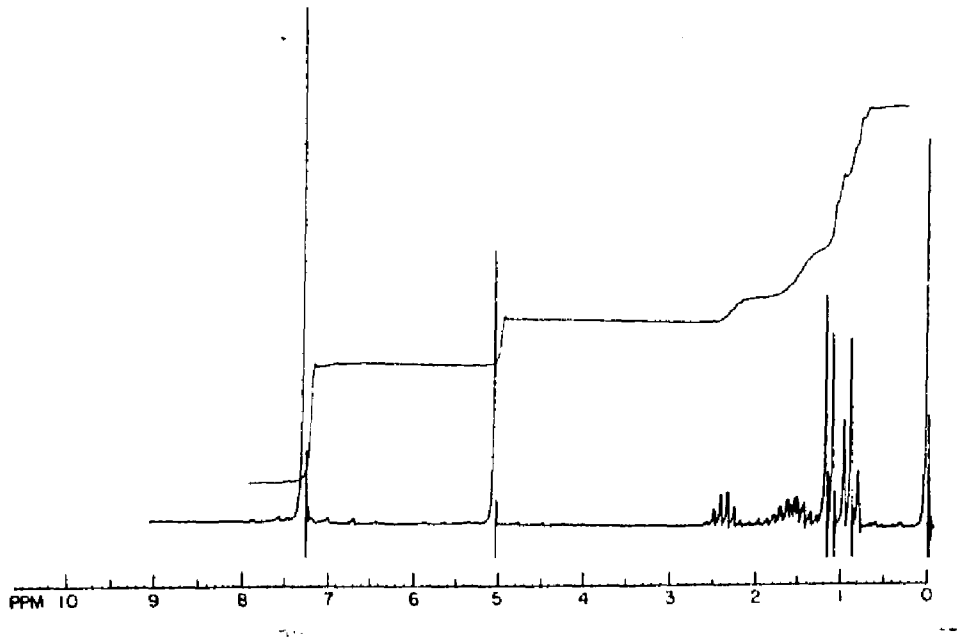




^1H NMR (90 MHz/$CDCl_3$)

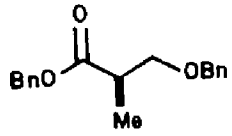
Compound (2S)-**31a**

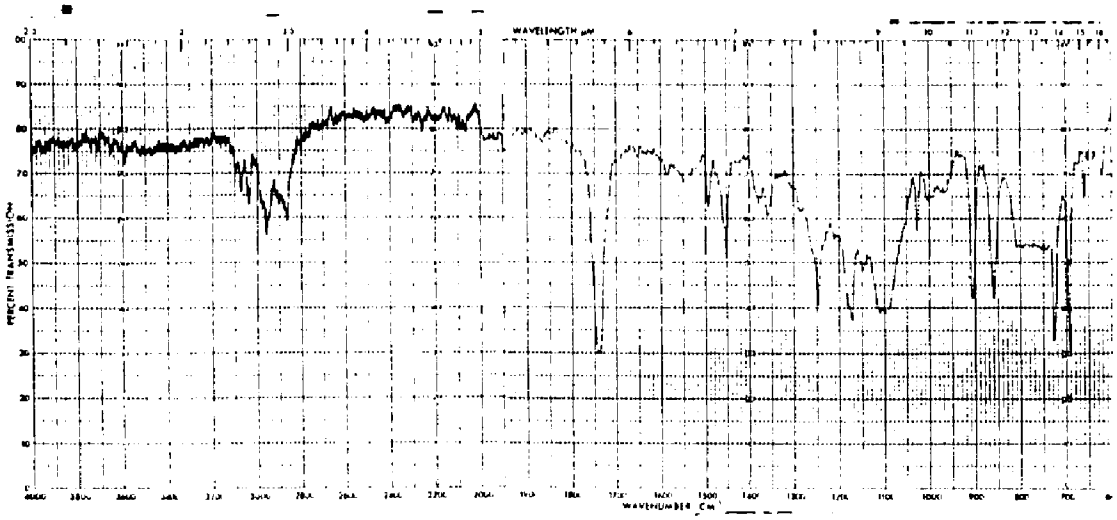




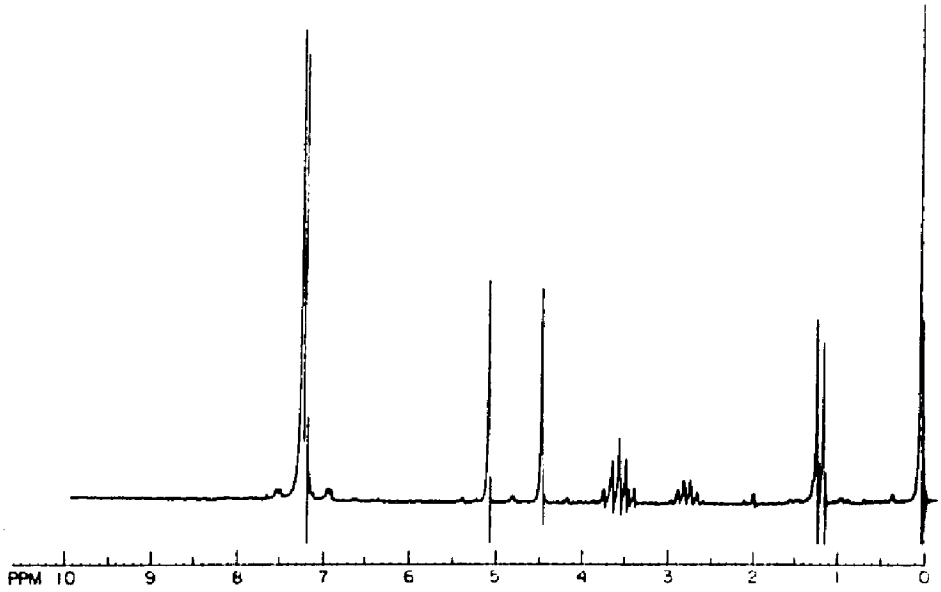
^1H NMR (90 MHz/$CDCl_3$)

Compound **31e**



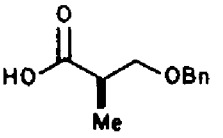


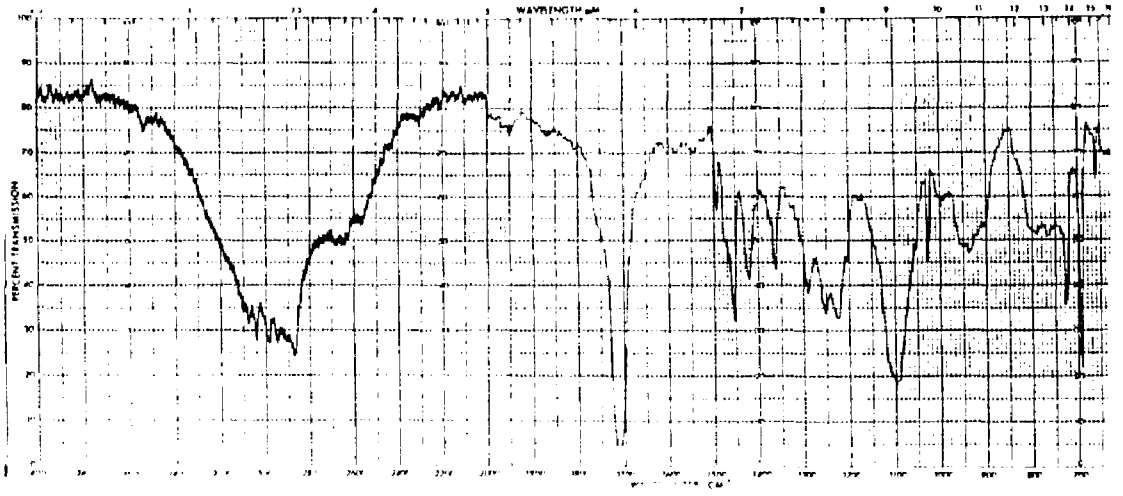
IR (CCl_4)



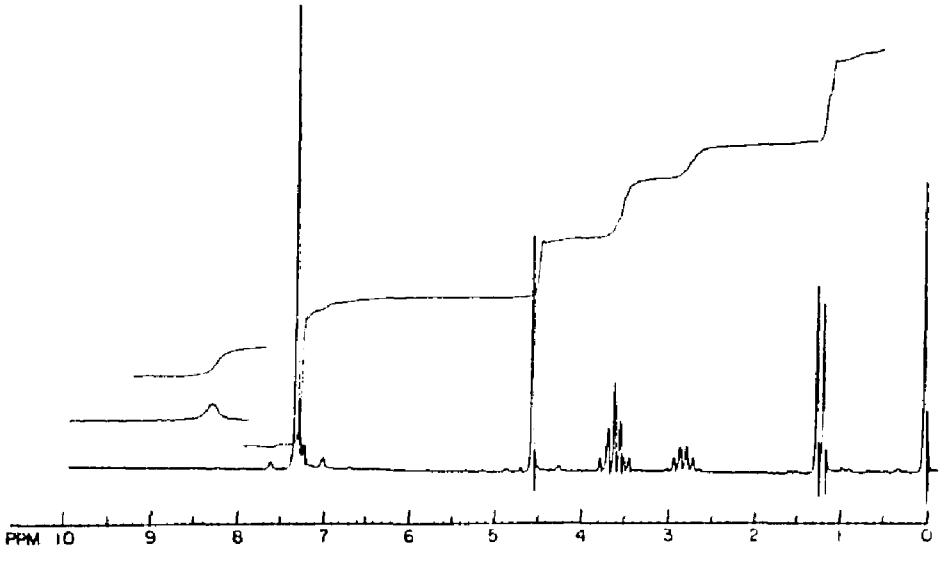
^1H NMR (90 MHz/$CDCl_3$)

Compound **26e**



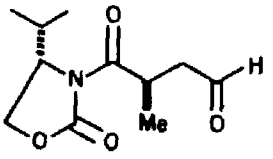


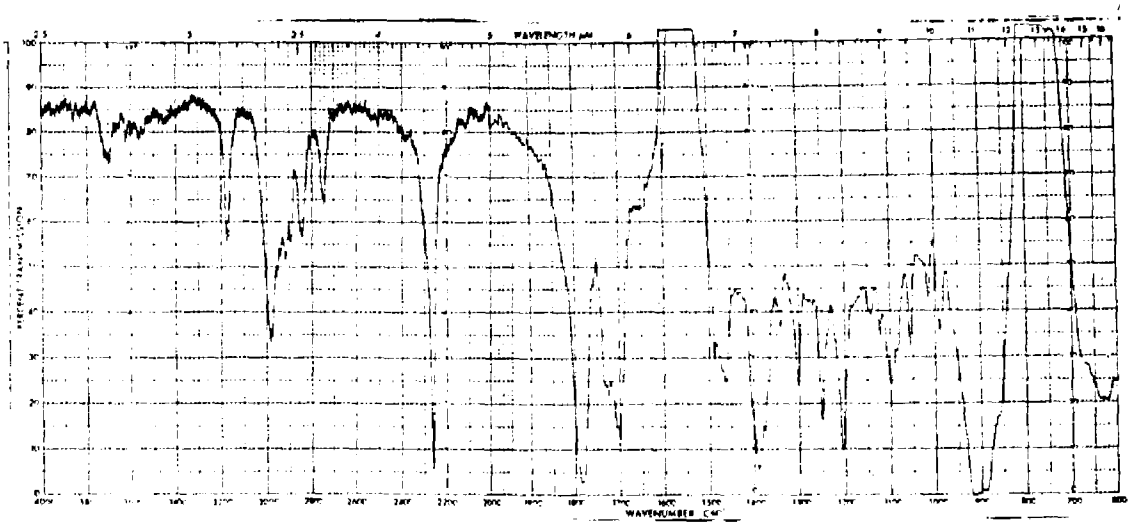
IR (neat)



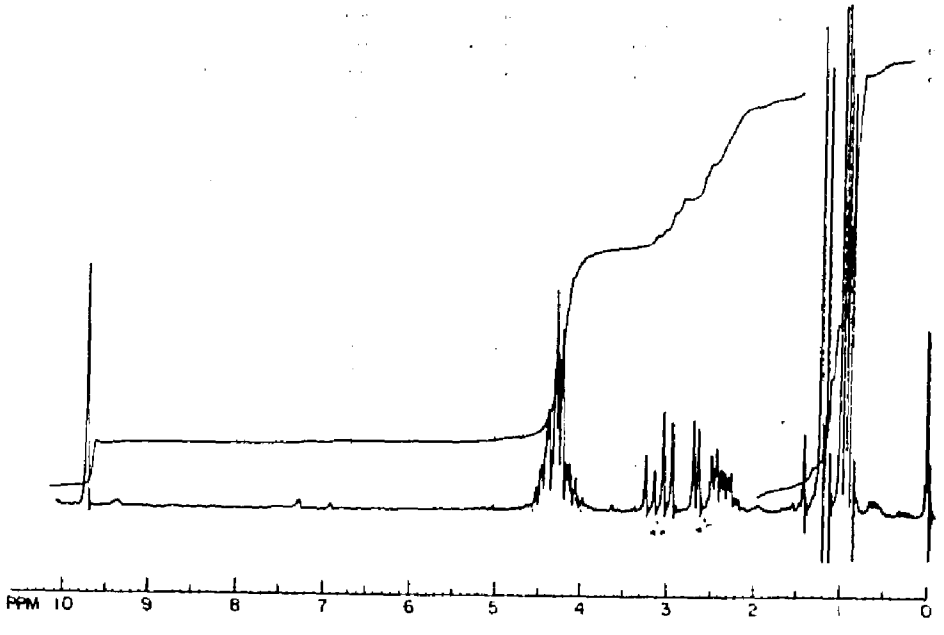
^1H NMR (90 MHz/$CDCl_3$)

Compound **21m**



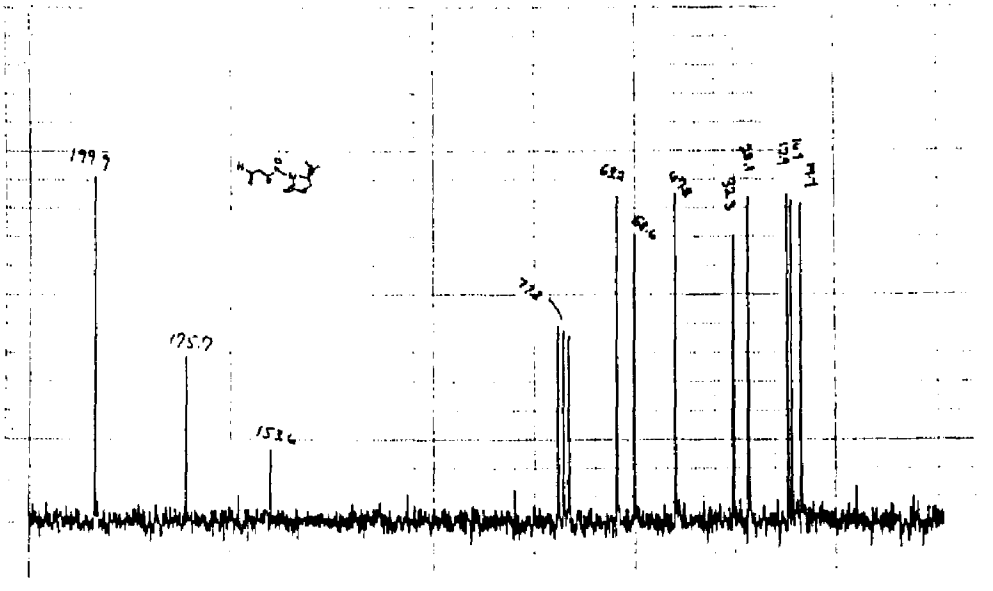


IR ($CDCl_3$)



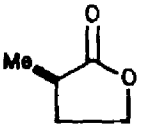
^1H NMR (90 MHz/$CDCl_3$)

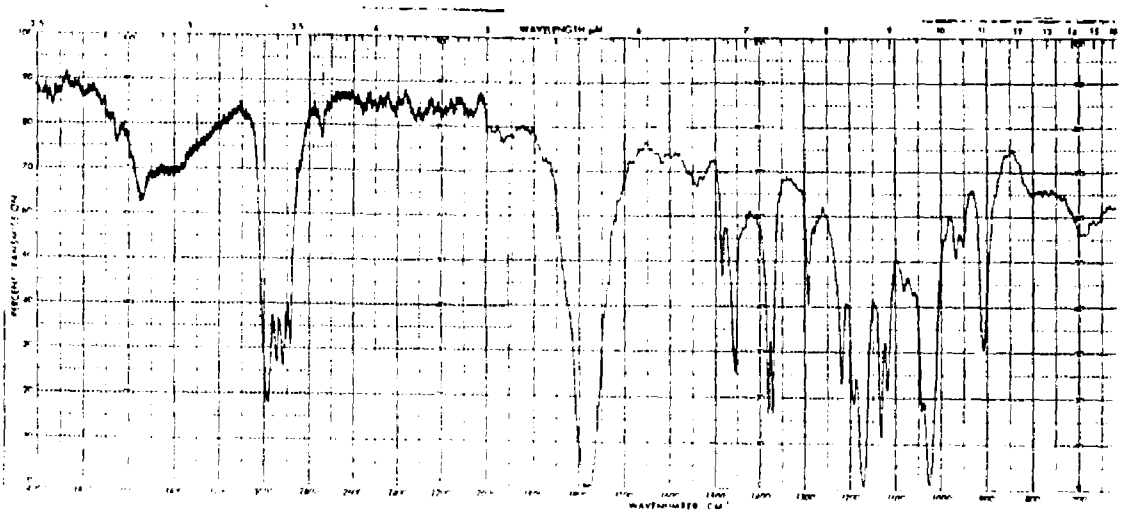
Compound **21m** continued.



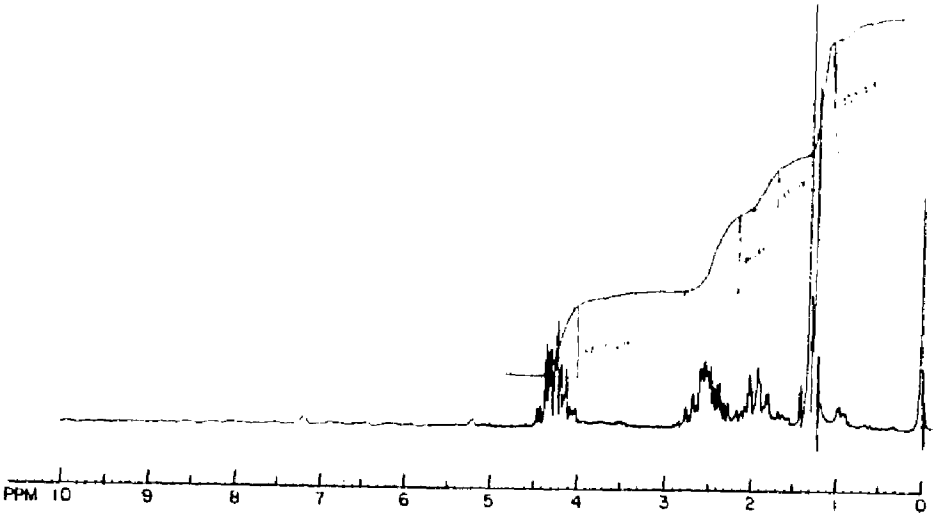
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **32**



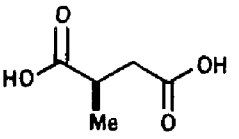


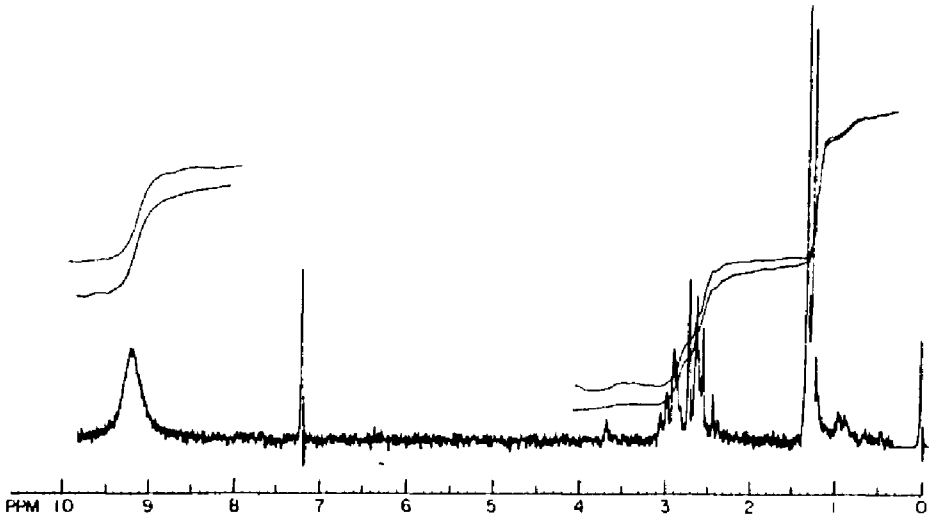
IR (neat)



^1H NMR (90 MHz/$CDCl_3$)

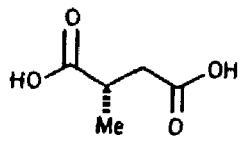
Compound (2R)-**26f**

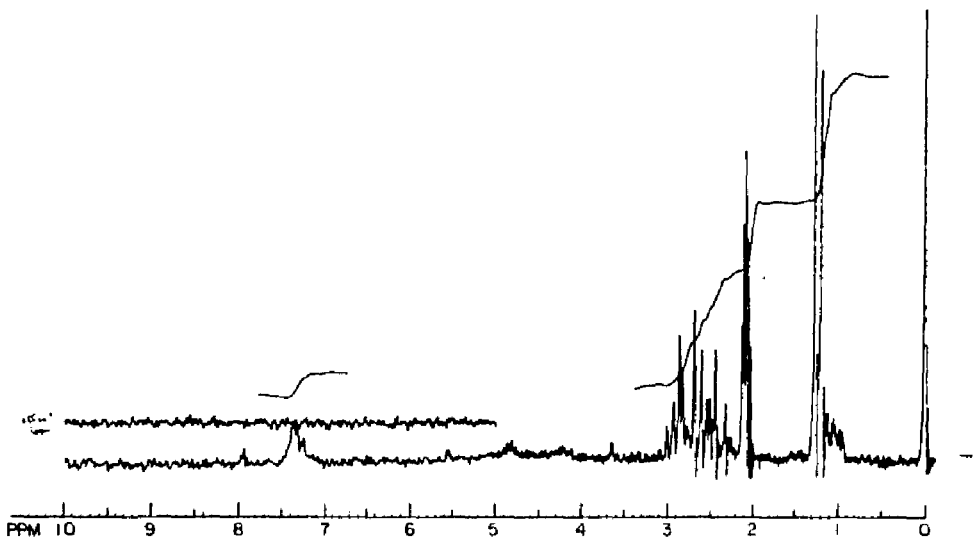




^1H NMR (90 MHz/$CDCl_3$)

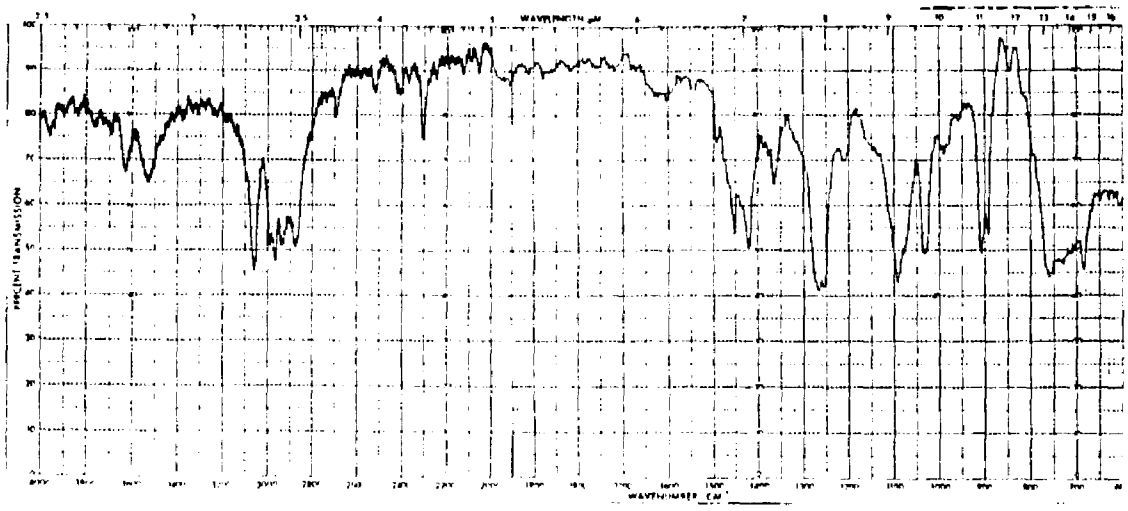
Compound (2S)-**26f**



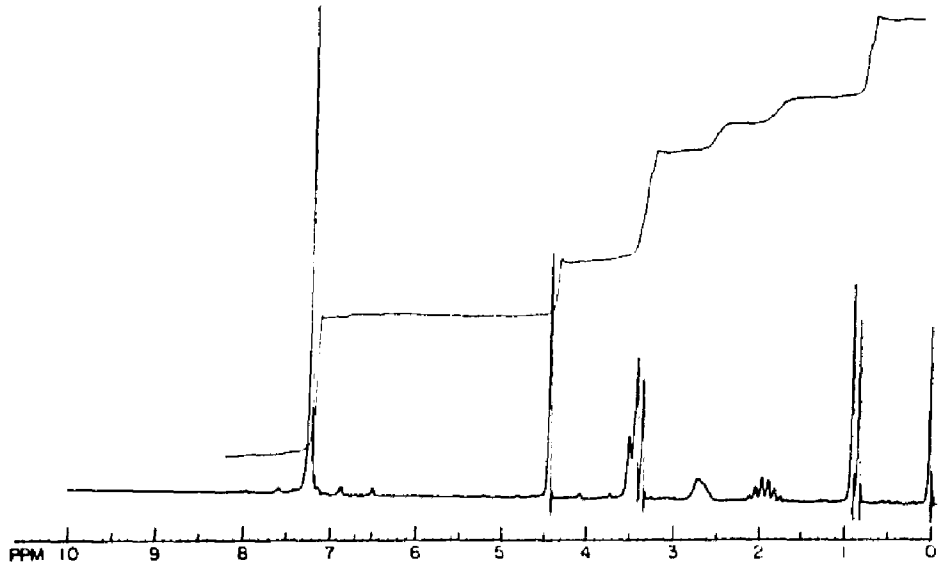


^1H NMR (90 MHz/$CDCl_3$)

Compound (2R)-**39e**

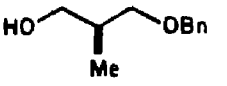


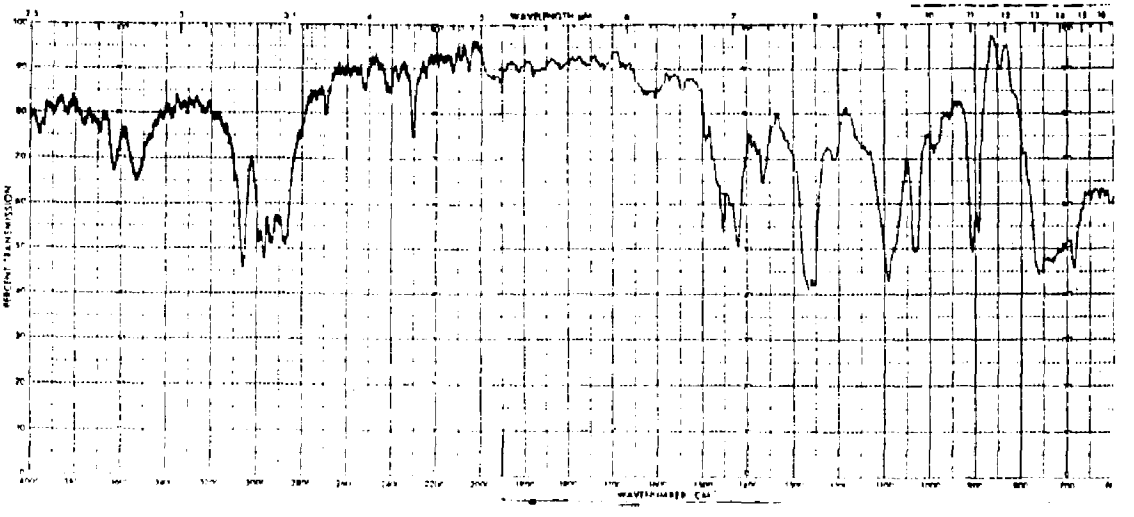
IR (CH_2Cl_2)



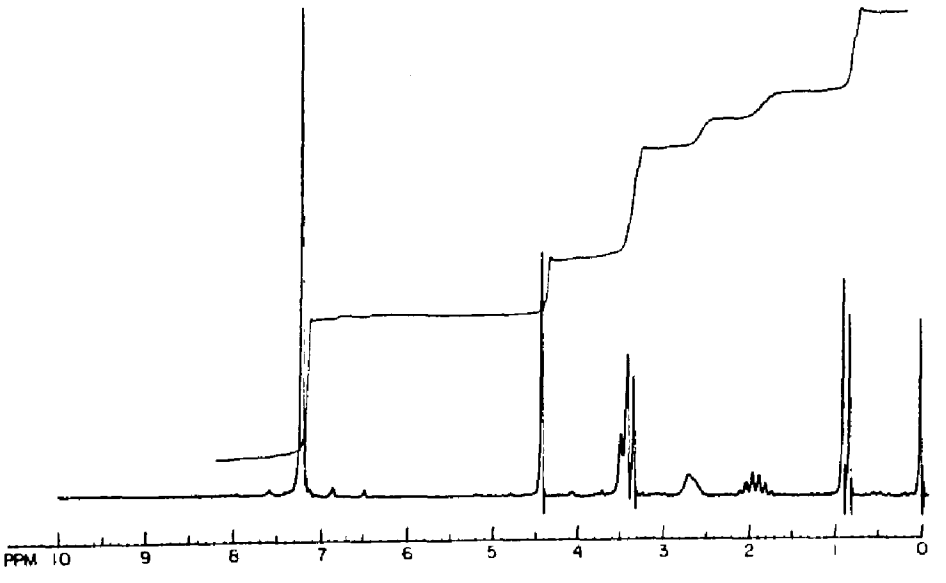
^1H NMR (90 MHz/CCl_4)

Compound (2S)-**39e**



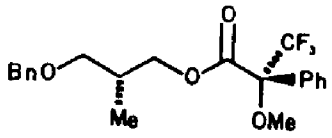


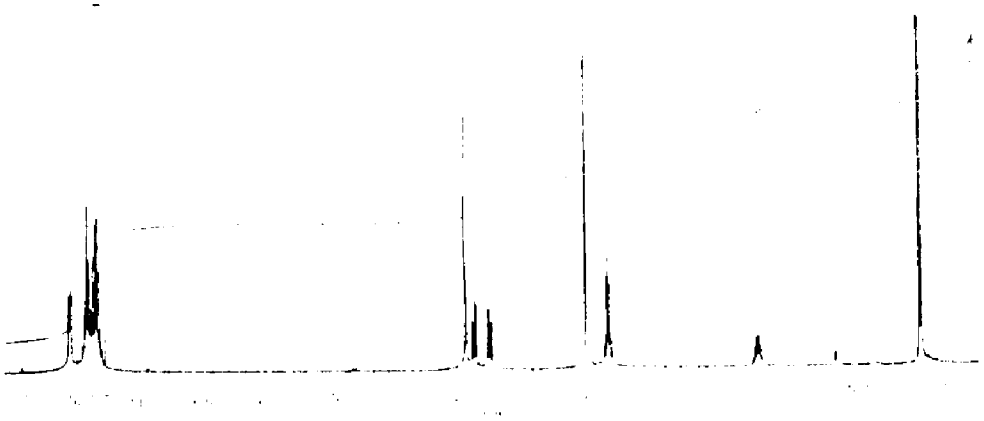
IR (CH_2Cl_2)



^1H NMR (90 MHz/CCl_4)

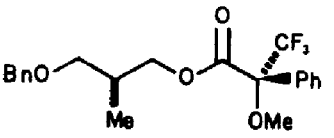
Compound (2R)-**42**

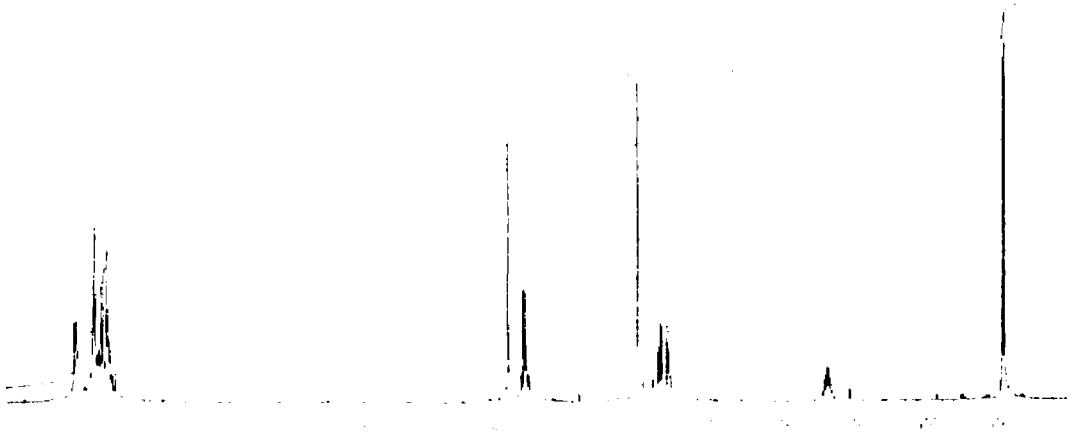




^1H NMR (500 MHz/$CDCl_3$)

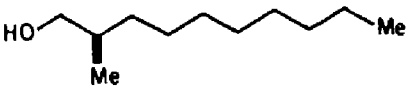
Compound (2S)-**42**

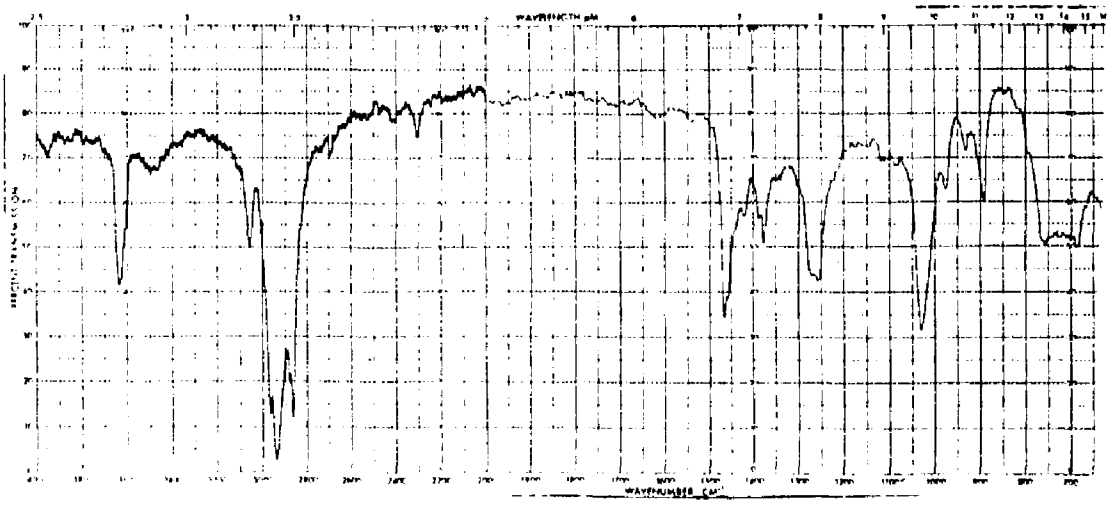




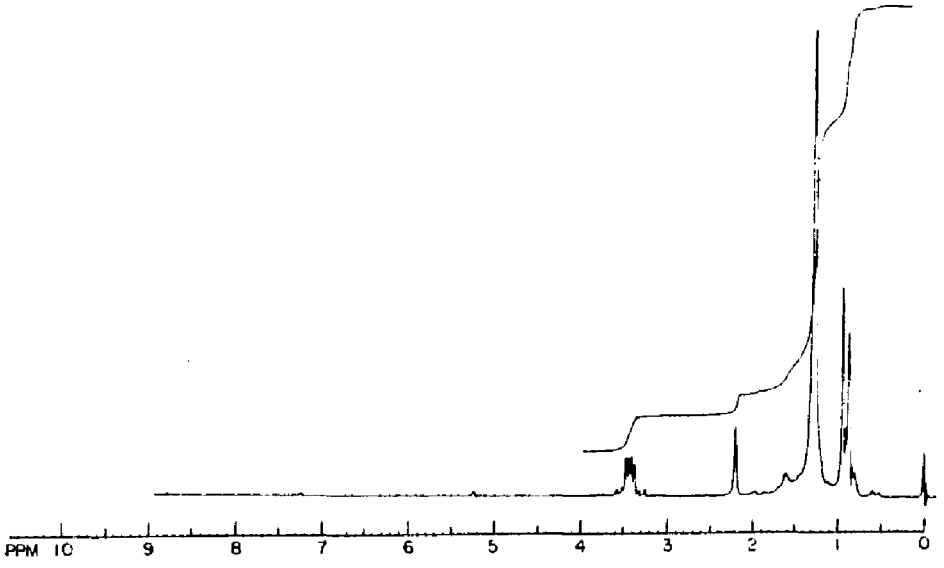
^{1}H NMR (500 MHz/$CDCl_3$)

Compound (2R)-391



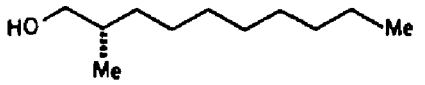


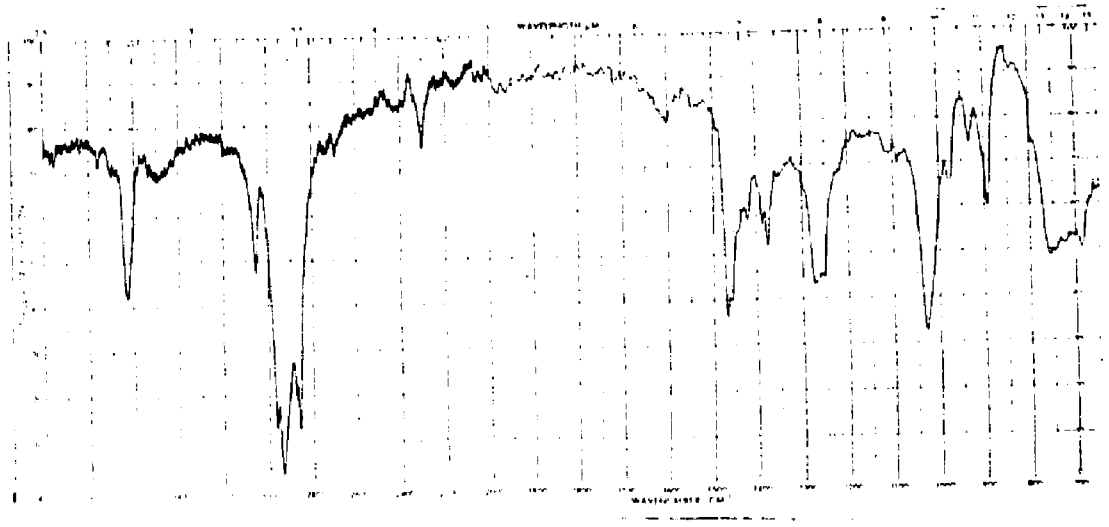
IR (CH_2Cl_2)



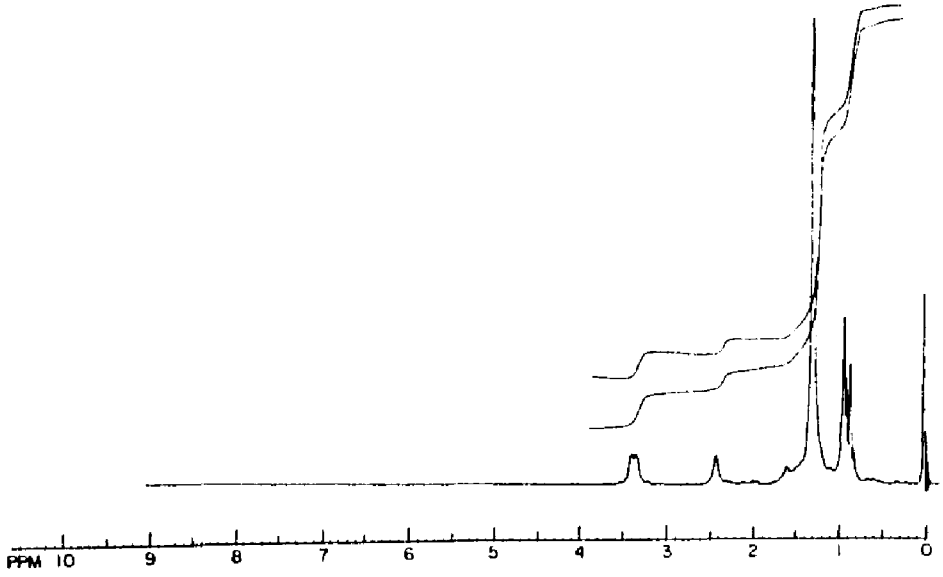
^1H NMR (90 MHz/$CDCl_3$)

Compound (2S)-**391**



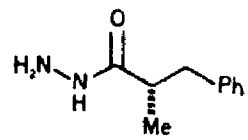


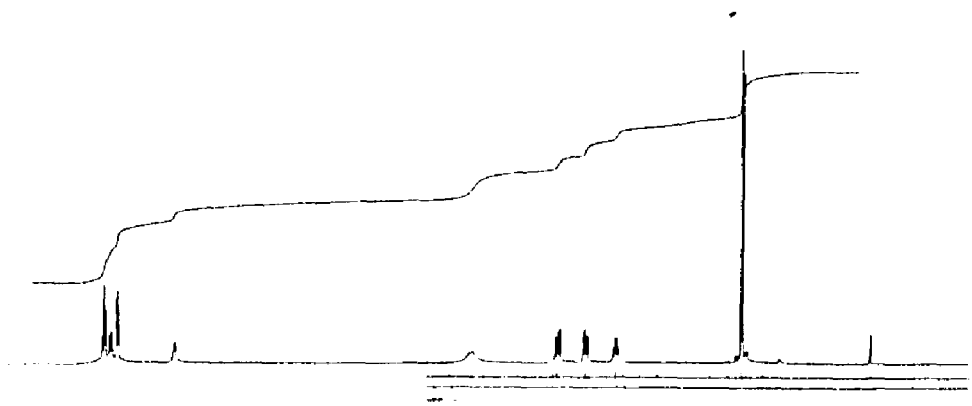
IR (CH_2Cl_2)



^1H NMR (90 MHz/$CDCl_3$)

Compound **34g**



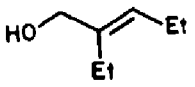


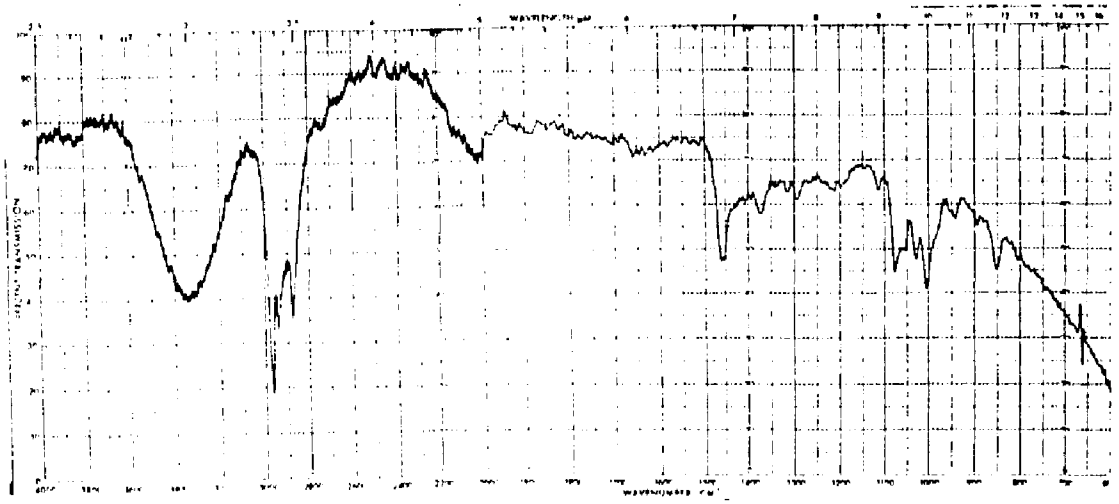
^{1}H NMR (500 MHz/$CDCl_3$)

APPENDIX IV

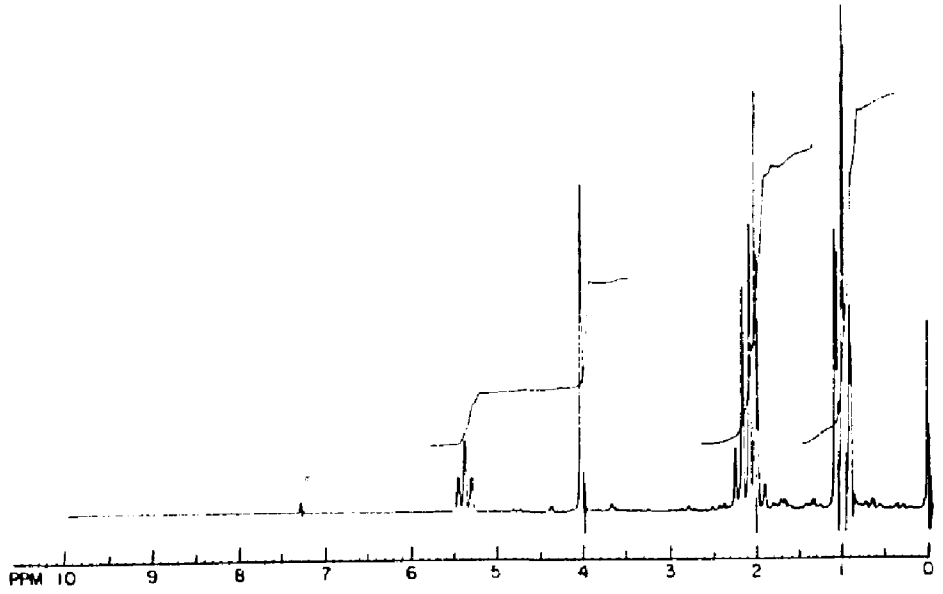
IR ^{1}H NMR, AND ^{13}C NMR SPECTRAL CATALOG FOR CHAPTER 2

Compound **37**



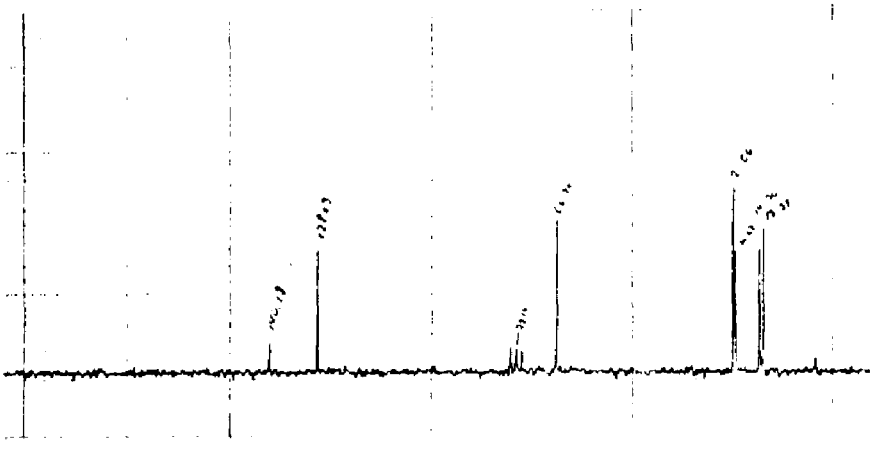


IR (neat)



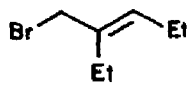
^{1}H NMR (90 MHz/$CDCl_3$)

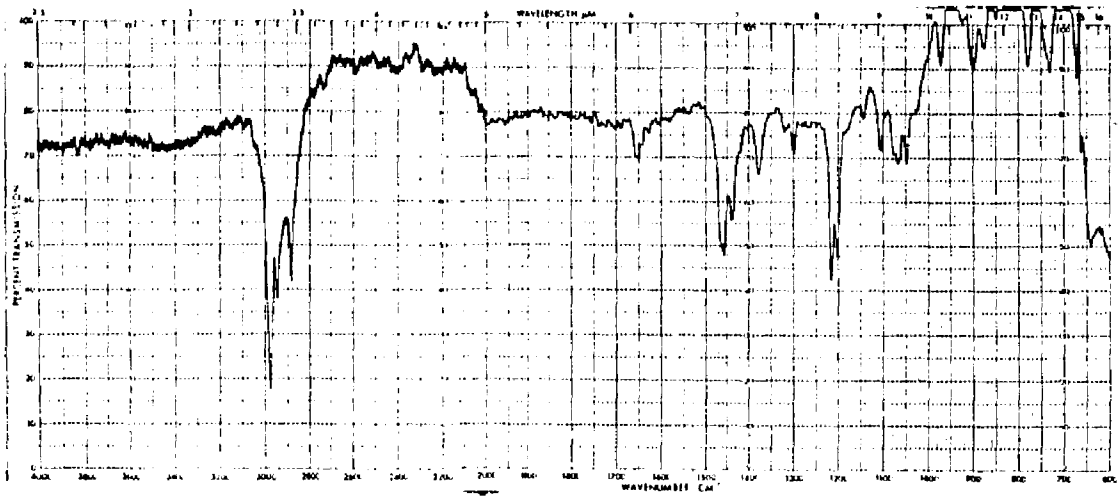
Compound **37** continued.



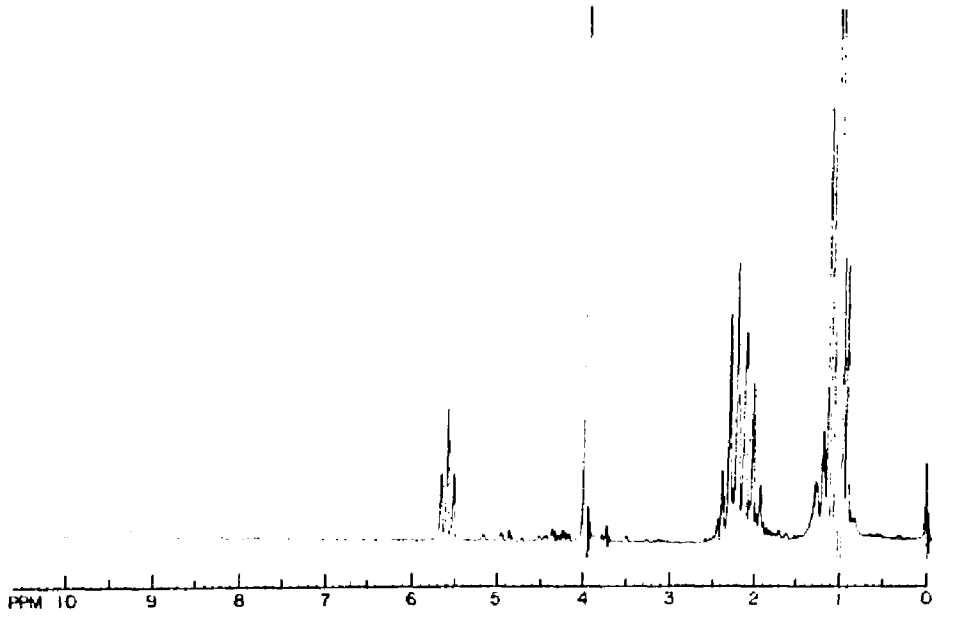
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **36**



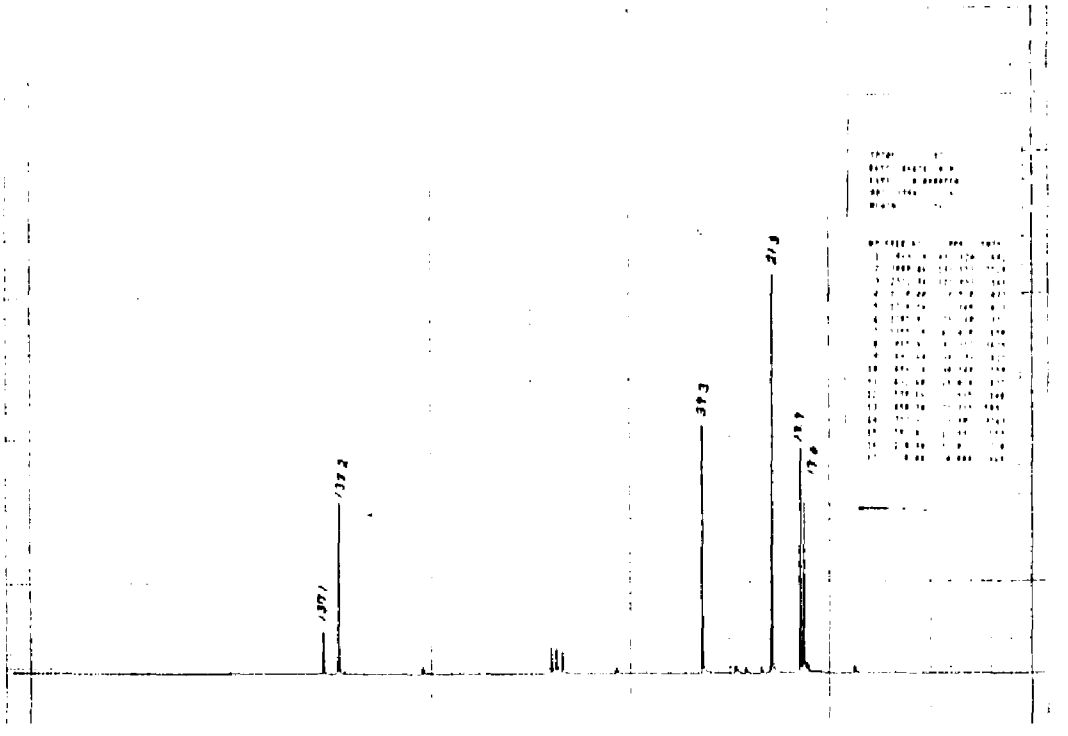


IR (neat)



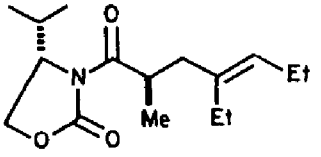
^1H NMR (90 MHz/$CDCl_3$)

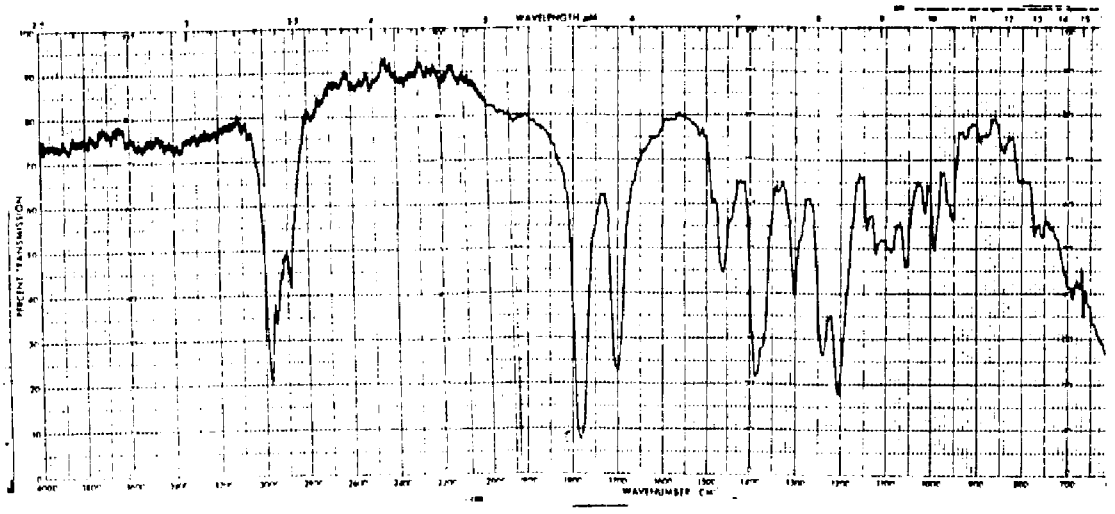
Compound **36** continued.



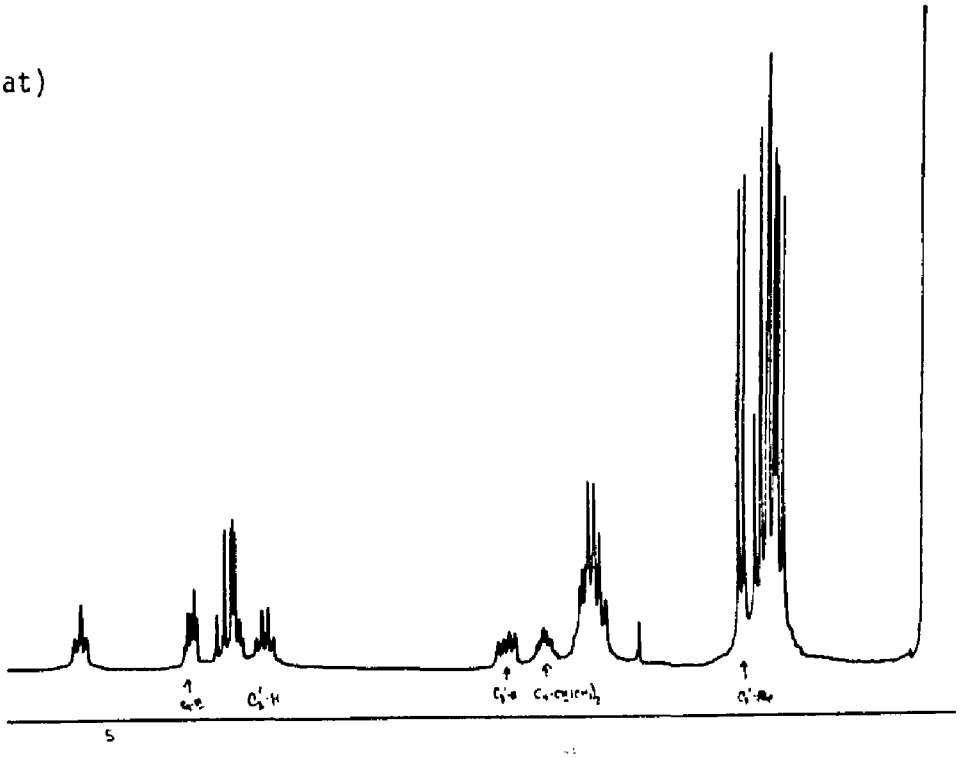
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound (2R)-35



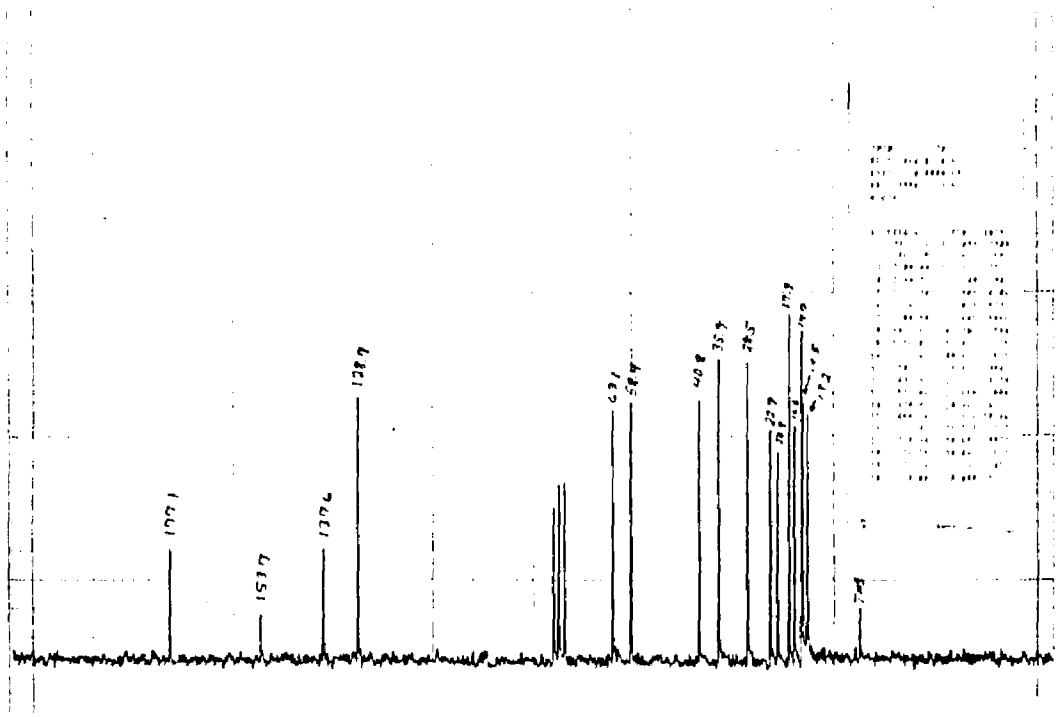


IR (neat)



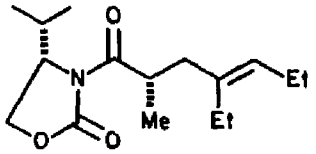
^1H NMR (200 MHz/$CDCl_3$)

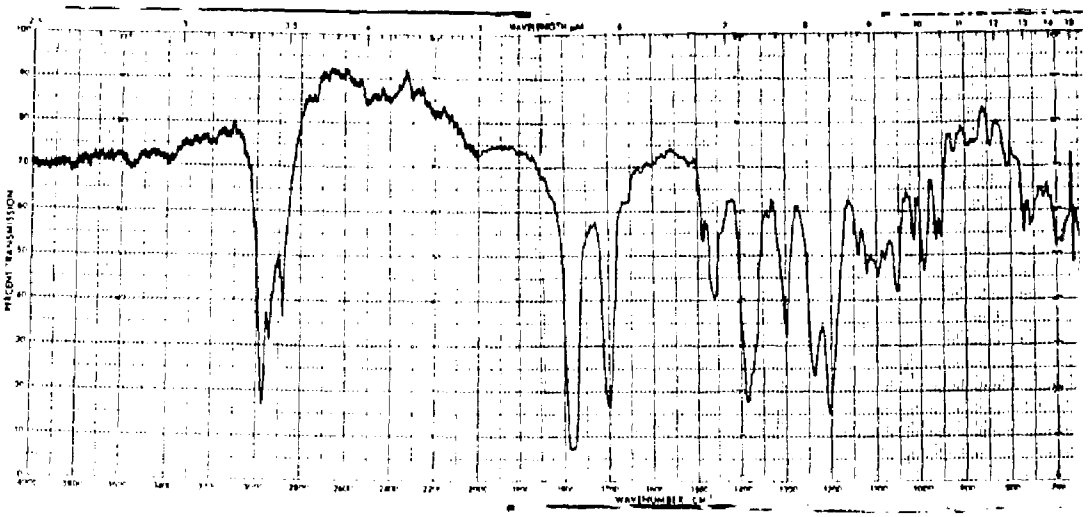
Compound (2R)-**35** continued.



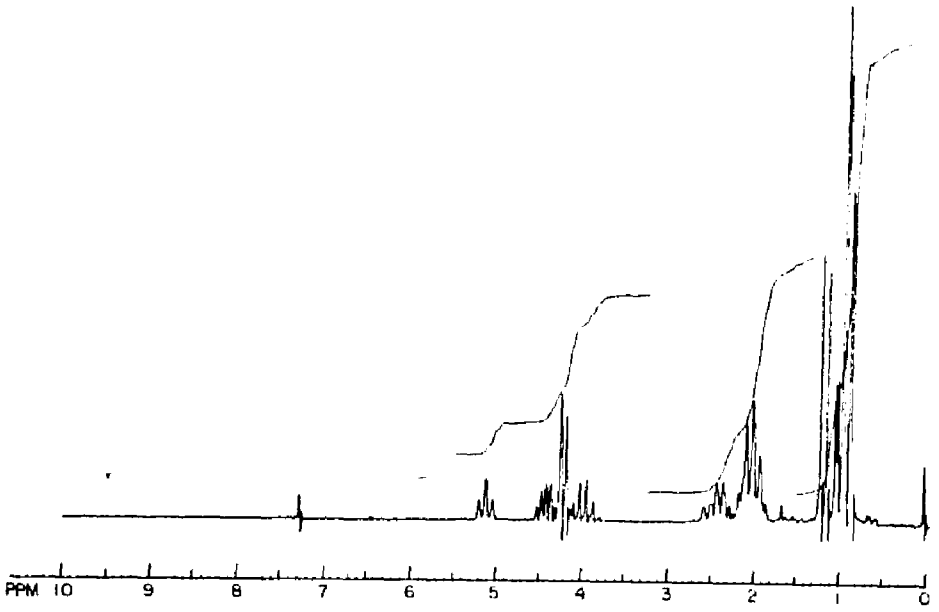
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound (2S)-**35**



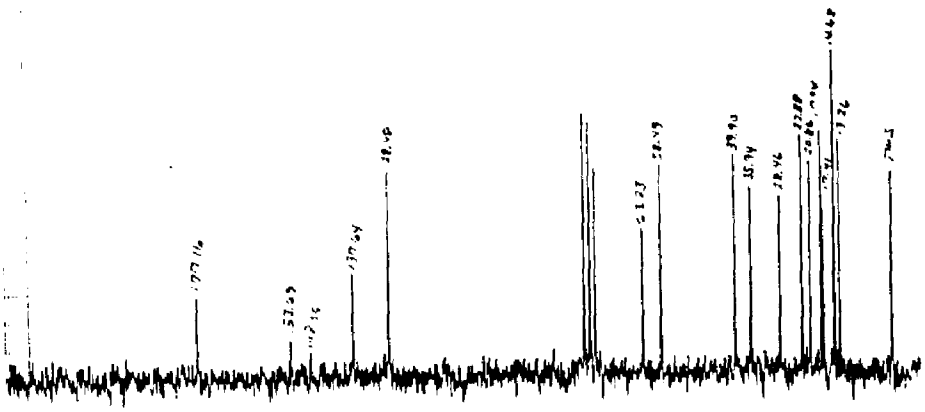


IR (neat)



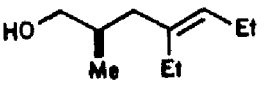
^1H NMR (90 MHz/$CDCl_3$)

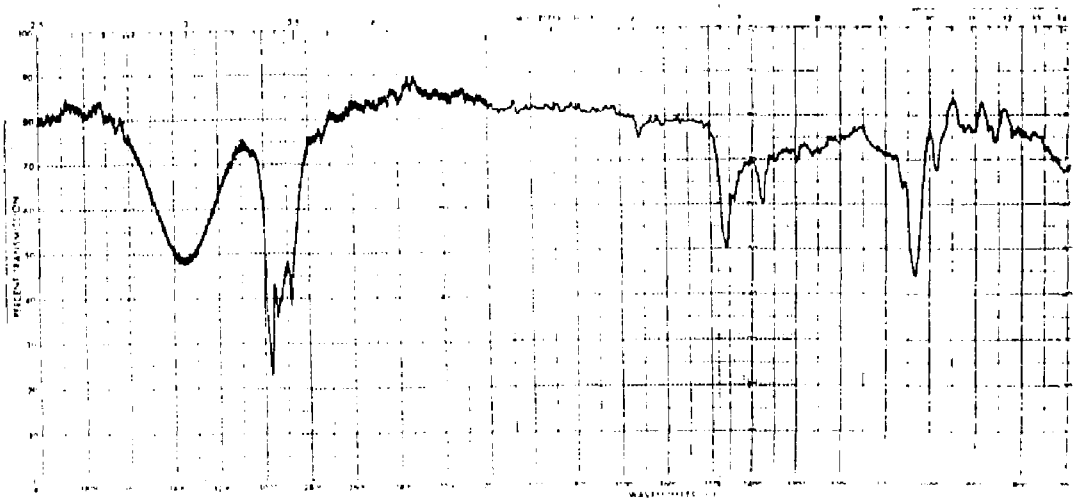
Compound (2S)-**35** continued.



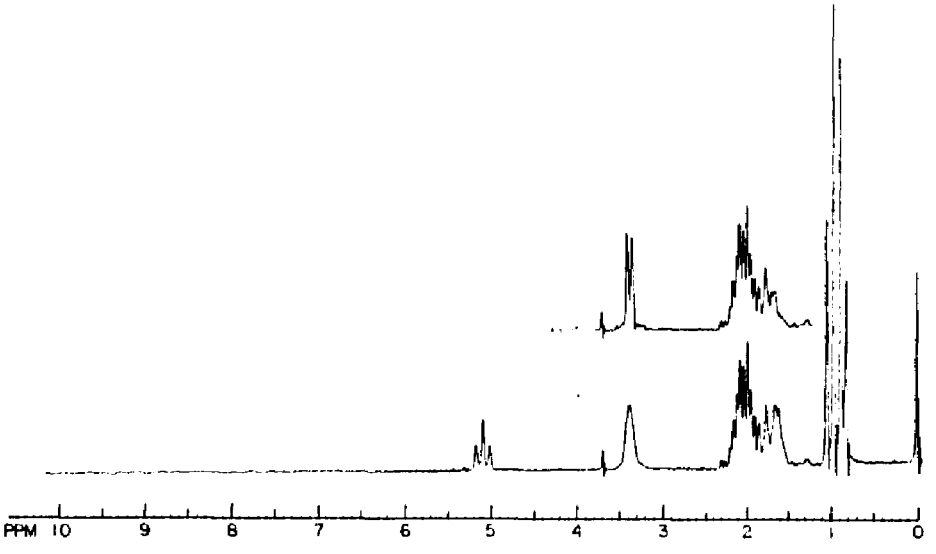
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **38**



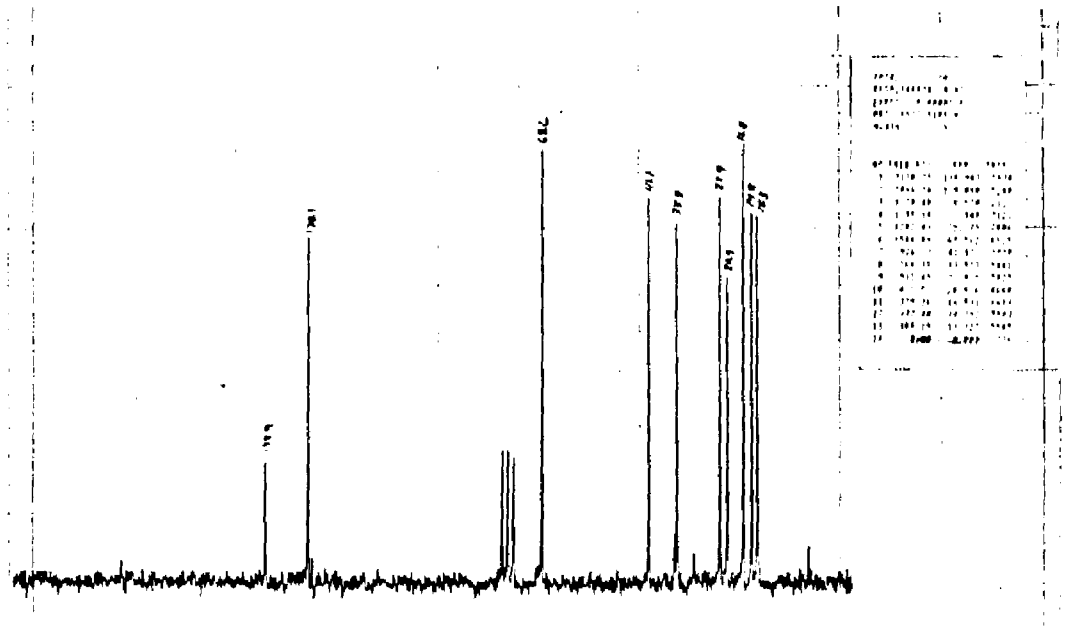


IR (neat)



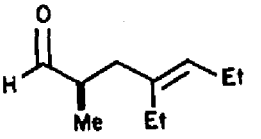
^1H NMR (90 MHz/CCl_4)

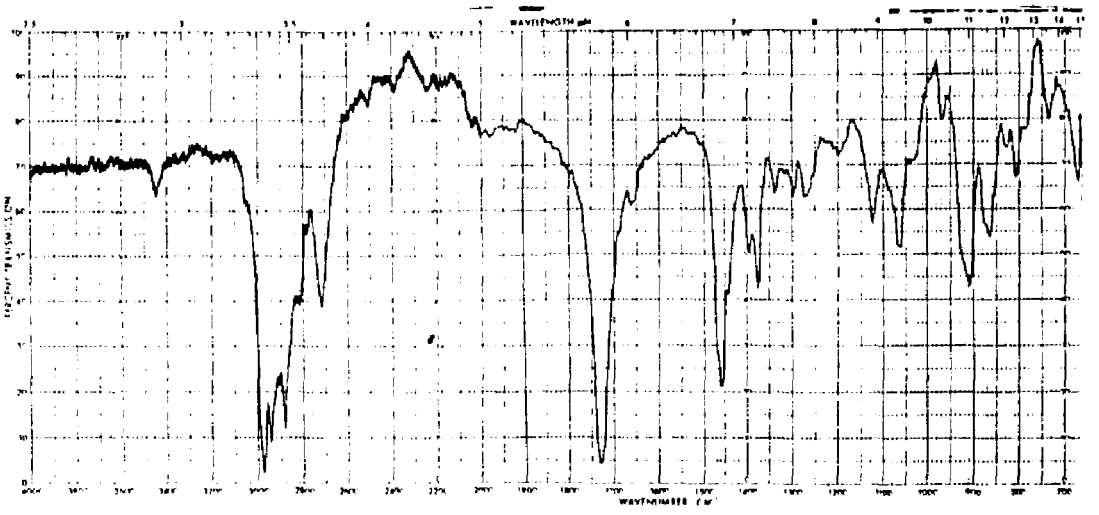
Compound **38** continued.



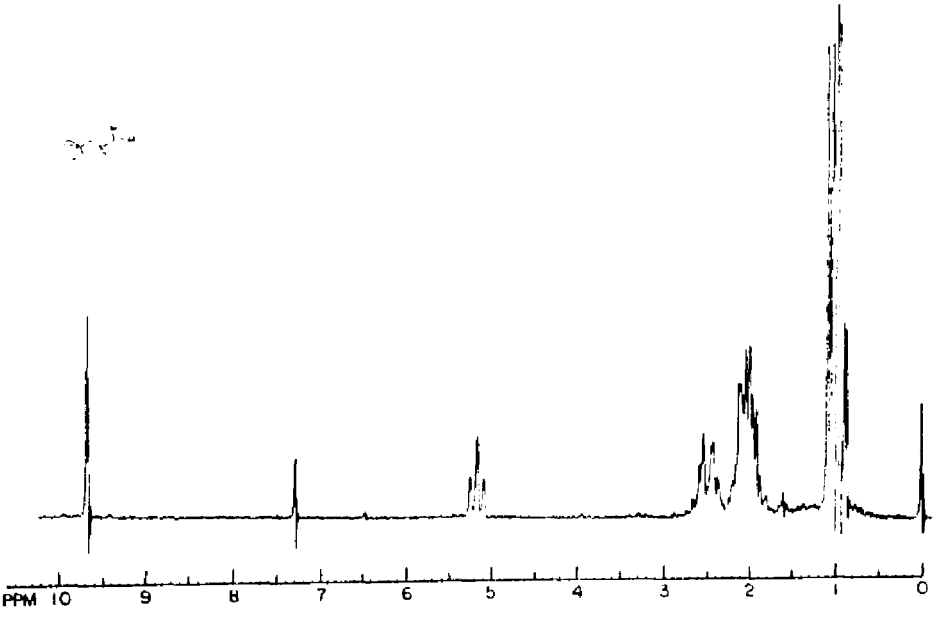
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **39**



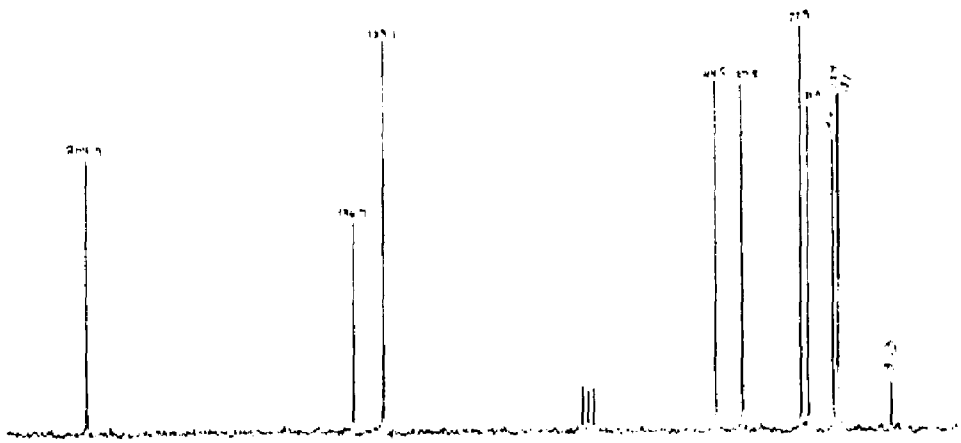


IR (neat)



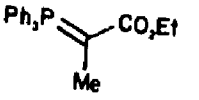
^1H NMR (90 MHz/CCl_4)

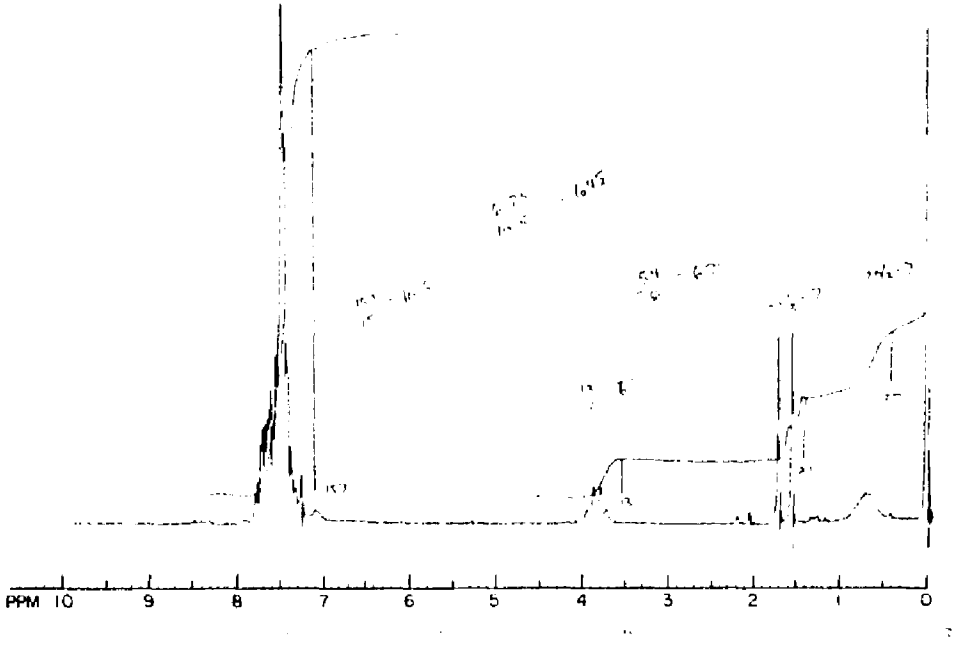
Compound **39** continued.



^{13}C NMR (22.5 MHz/$CDCl_3$)

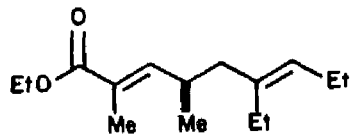
Compound

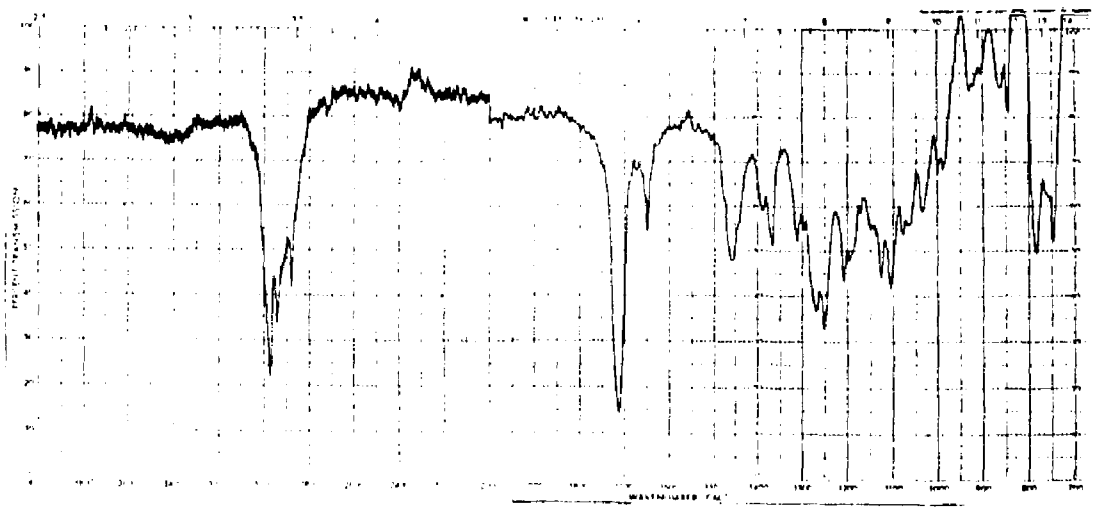




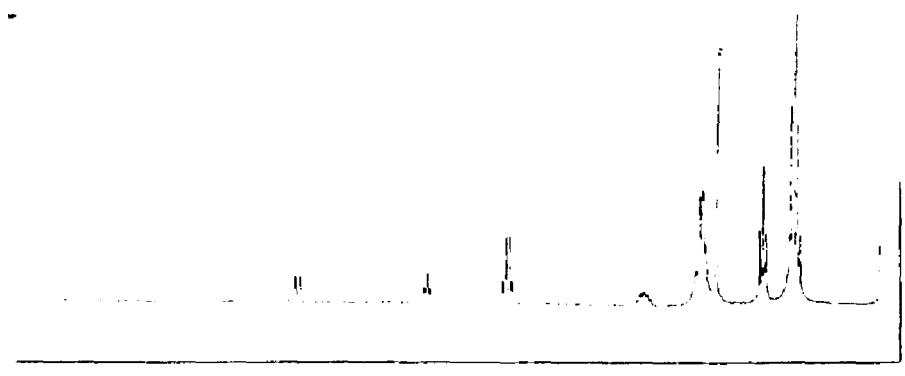
^1H NMR (90 MHz/$CDCl_3$)

Compound (2E)-**34**



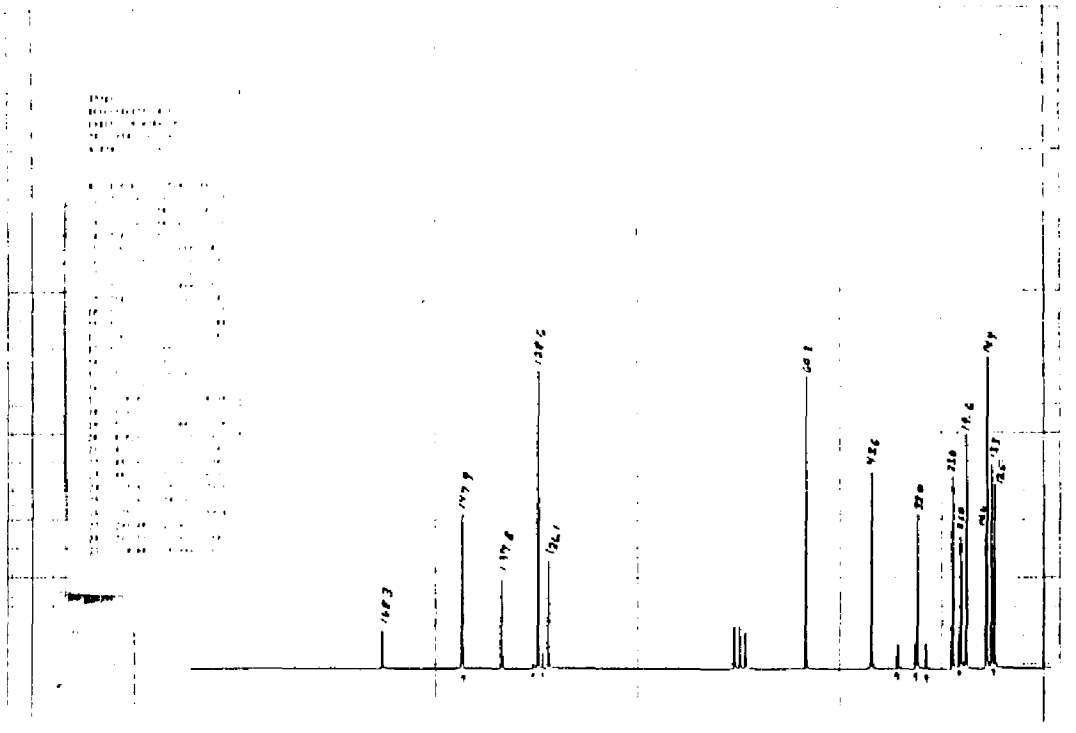


IR (neat)



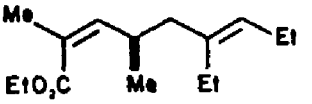
^1H NMR (200 MHz/$CDCl_3$)

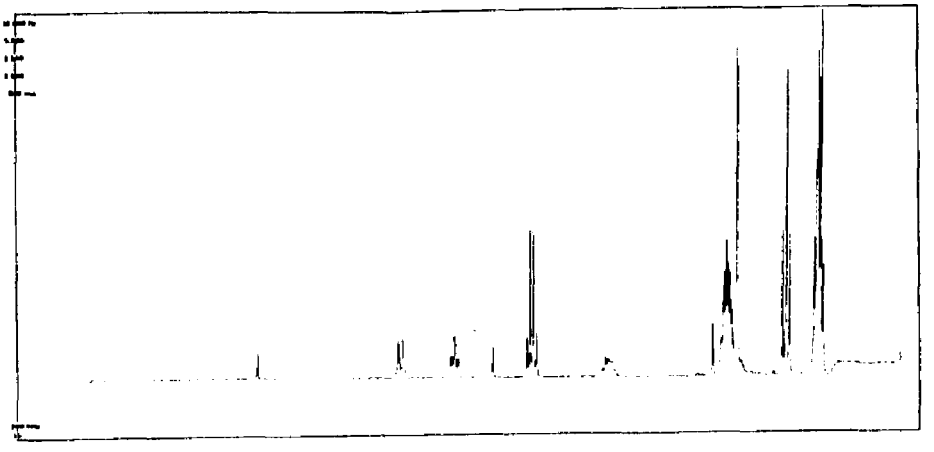
Compound (2E)-**34** continued.



^{13}C NMR (22.5 MHz/$CDCl_3$)

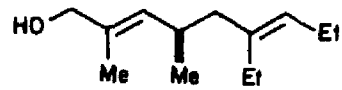
Compound (2Z)-**34**

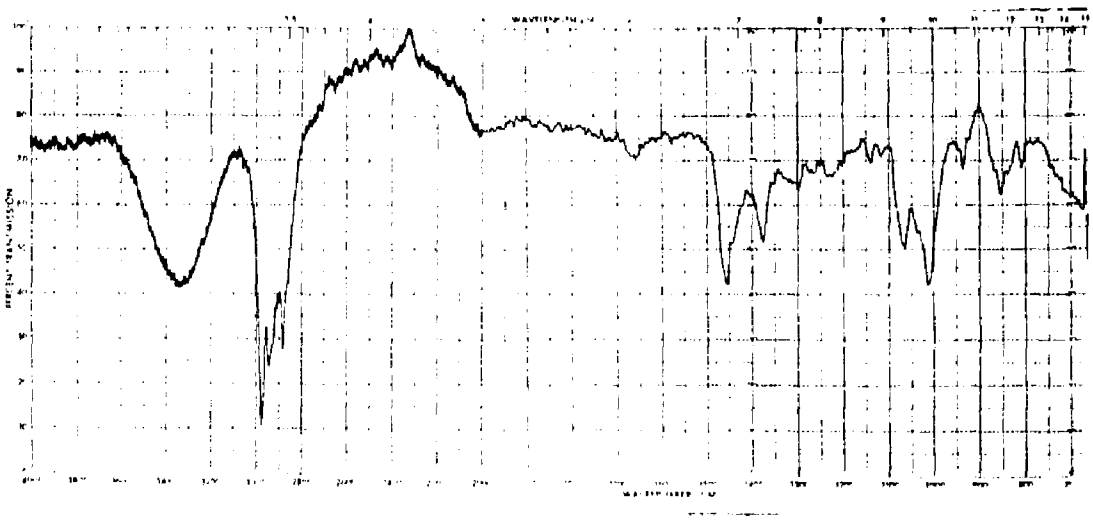




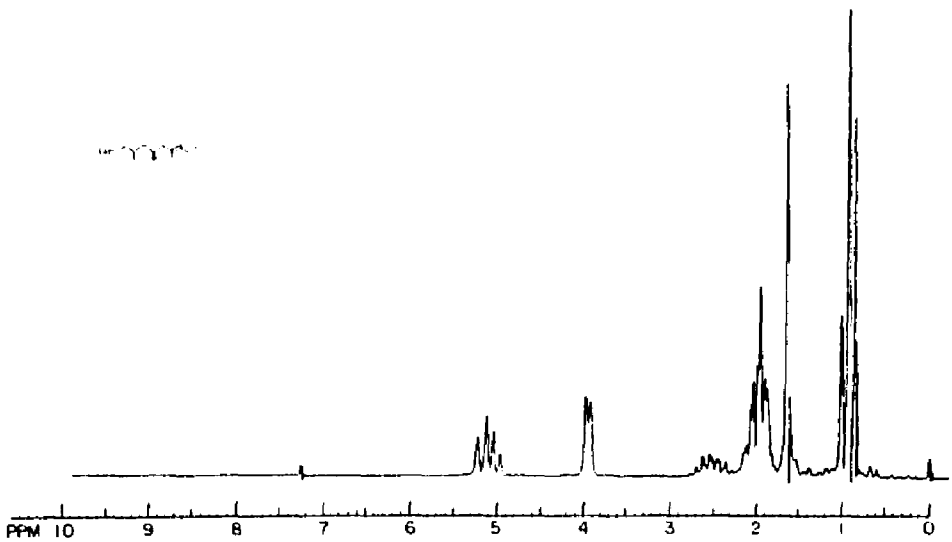
^{1}H NMR (200 MHz/$CDCl_3$)

Compound **40**



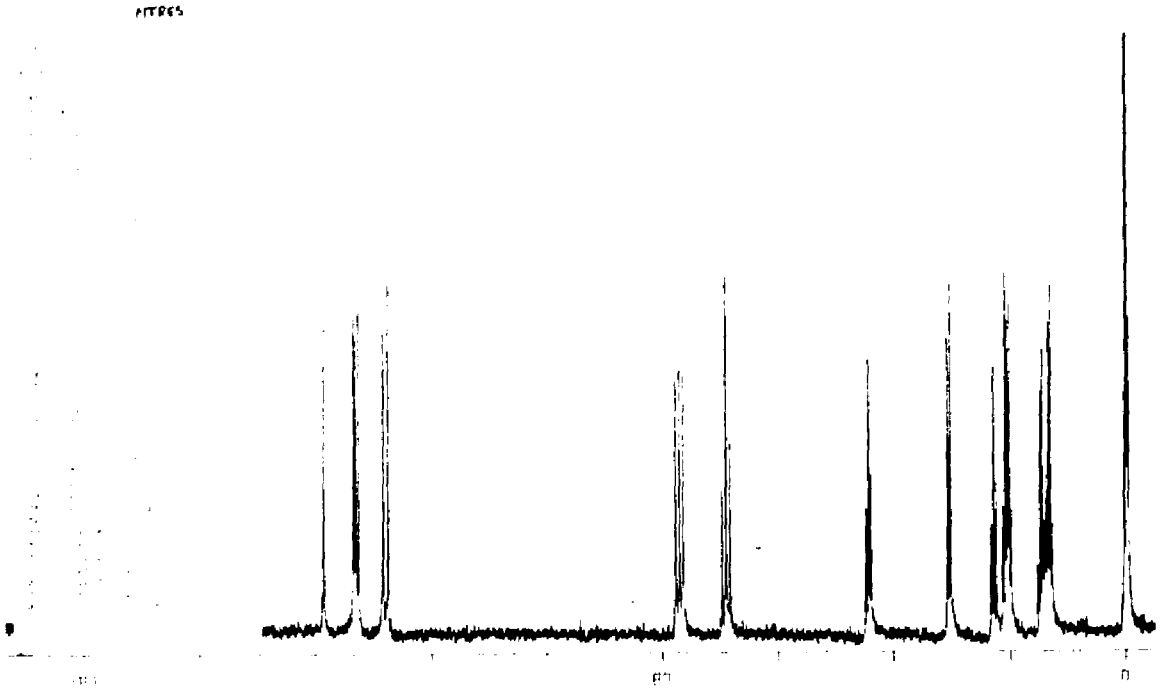


IR (neat)



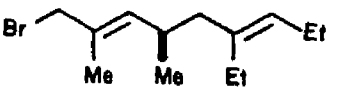
^1H NMR (90 MHz/$CDCl_3$)

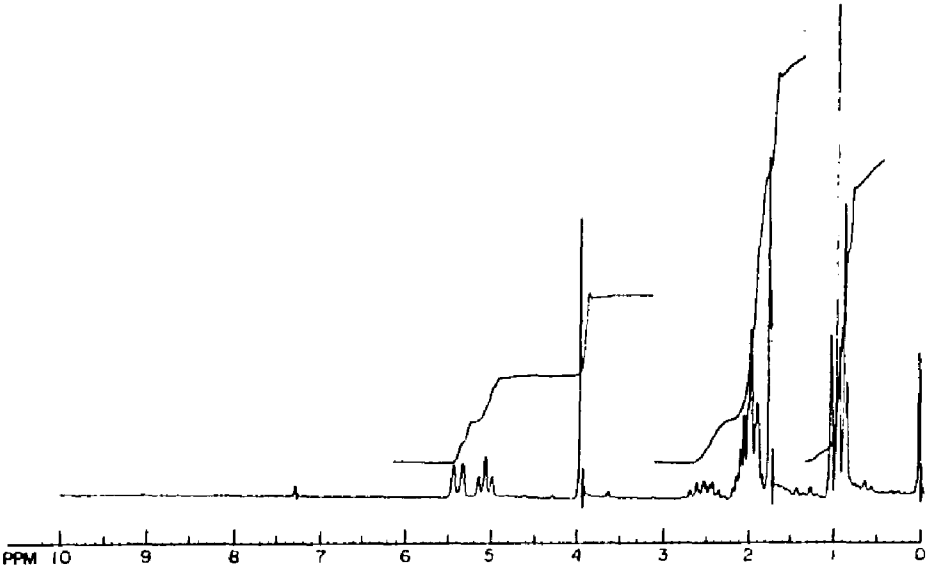
Compound **40** continued.



^{13}C NMR (50 MHz/$CDCl_3$)

Compound **41a**

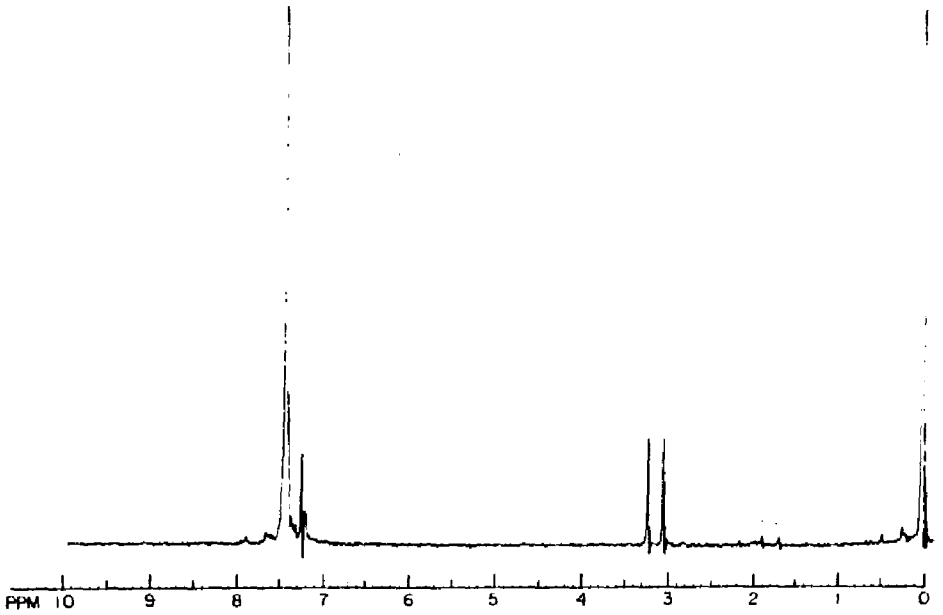




^1H NMR (90 MHz/$CDCl_3$)

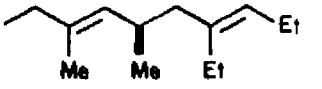
Compound

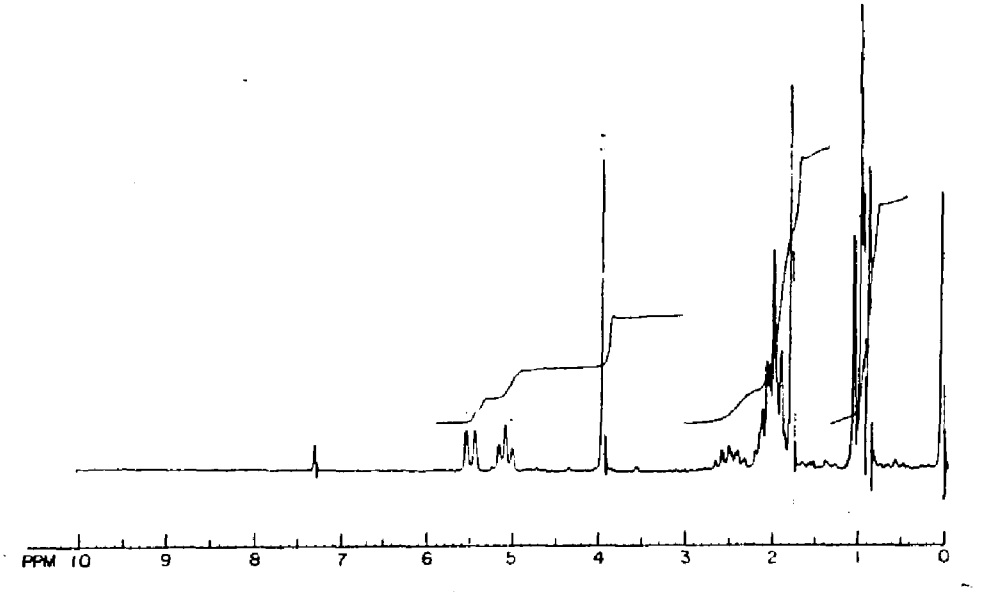
$(PhO)_2MePI$



^1H NMR (90 MHz/$CDCl_3$)

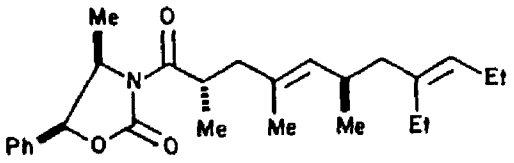
Compound **41b**

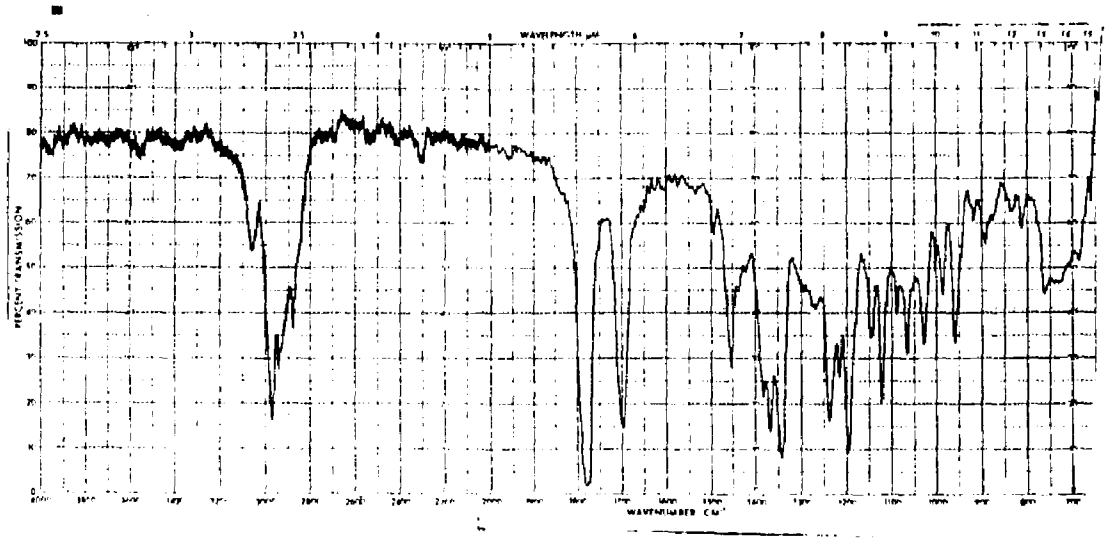




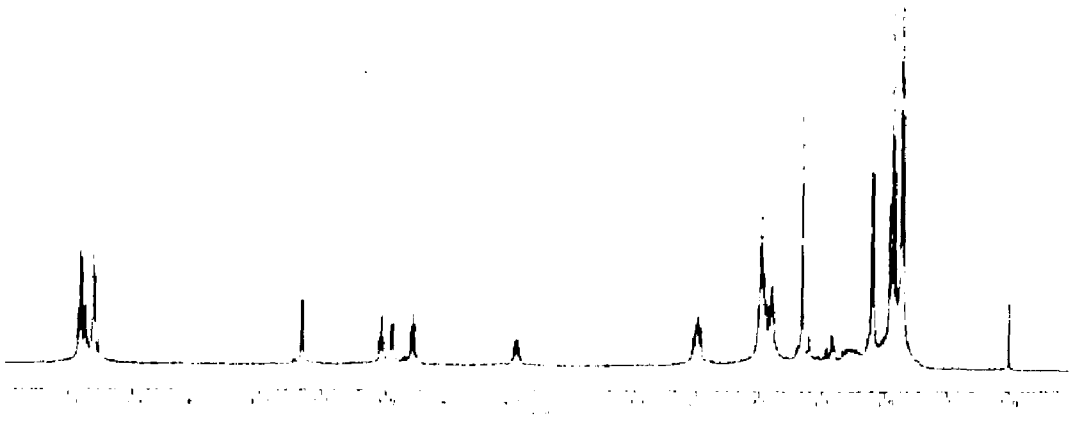
^{1}H NMR (90 MHz/$CDCl_3$)

Compound **33**



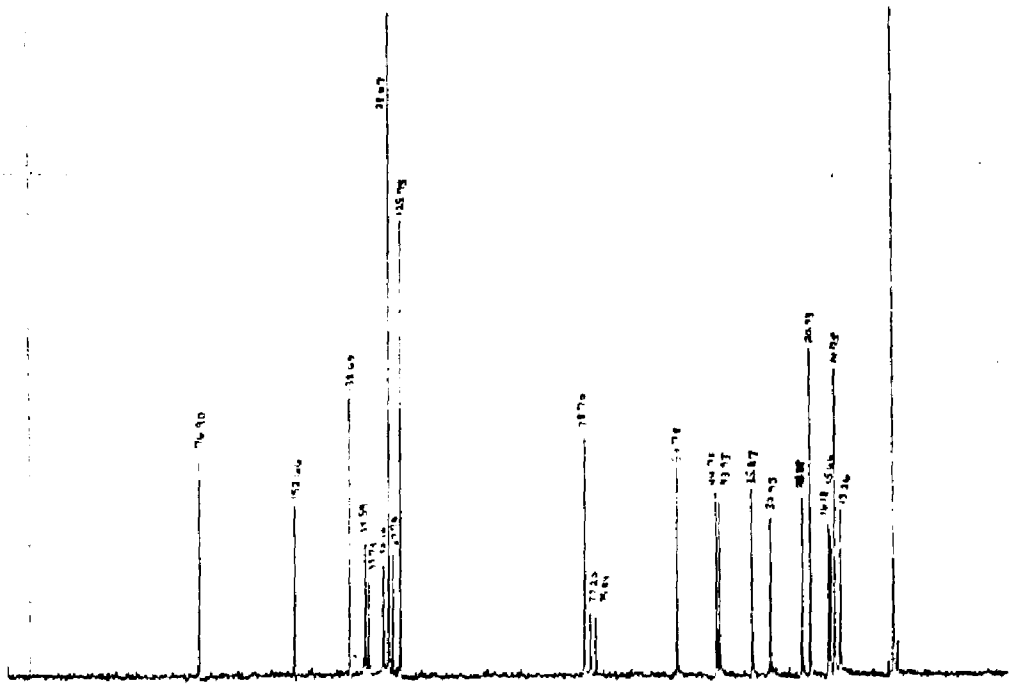


IR (CH_2Cl_2)



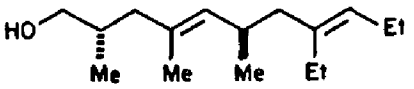
^1H NMR (500 MHz/$CDCl_3$)

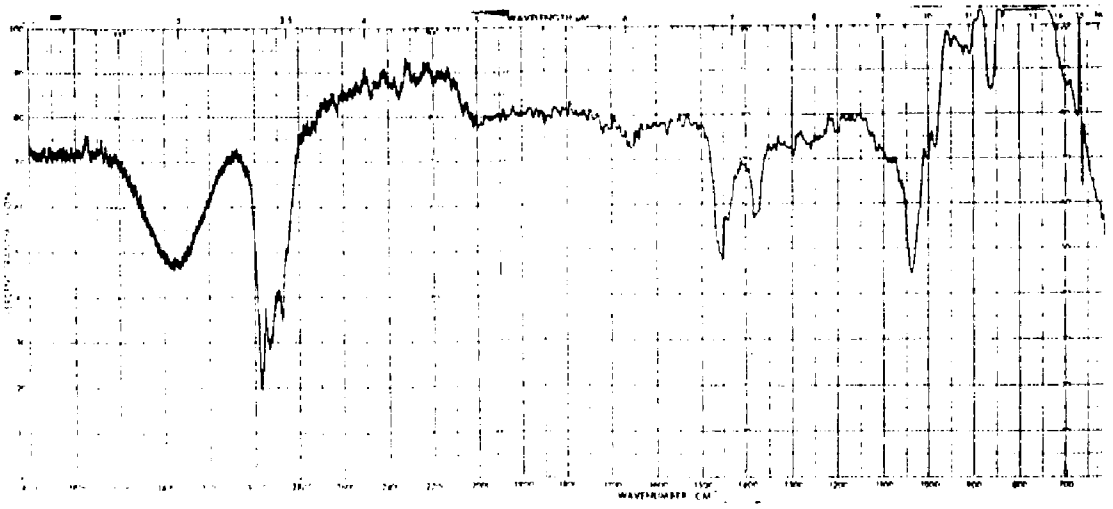
Compound **33** continued.



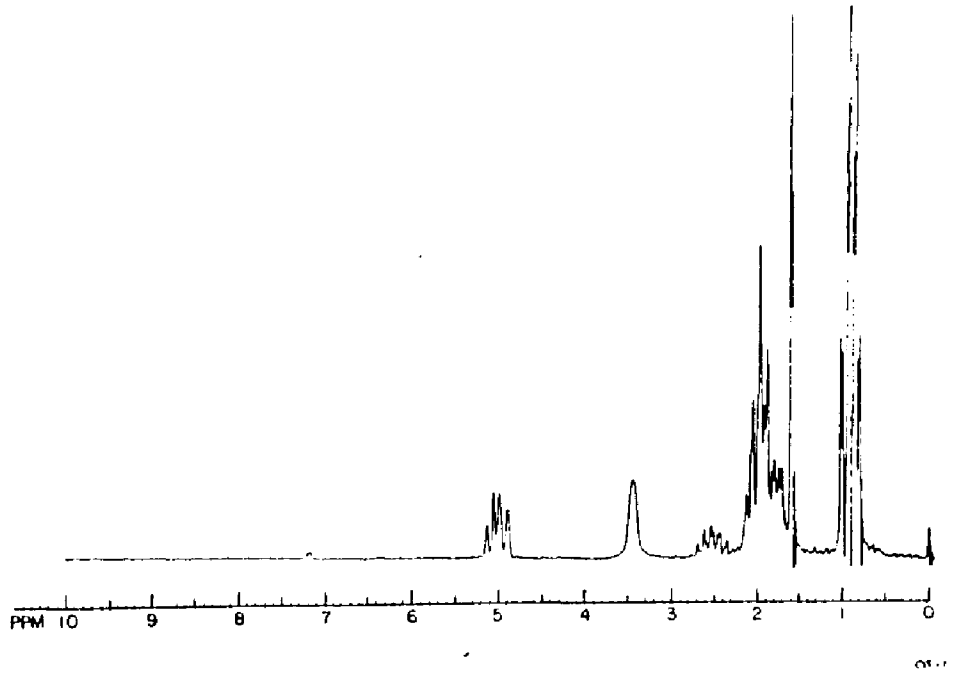
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **42**



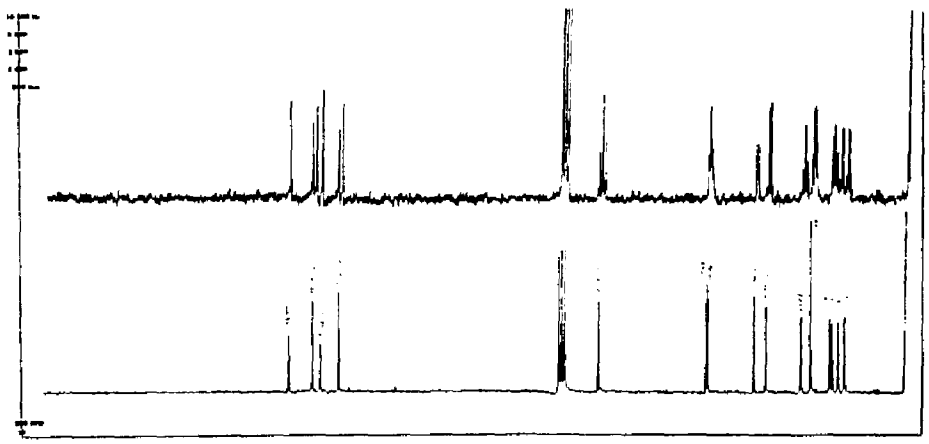


IR (neat)



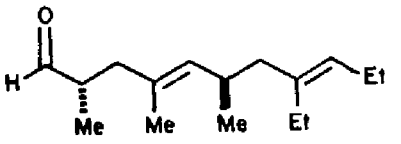
^1H NMR (90 MHz/$CDCl_3$)

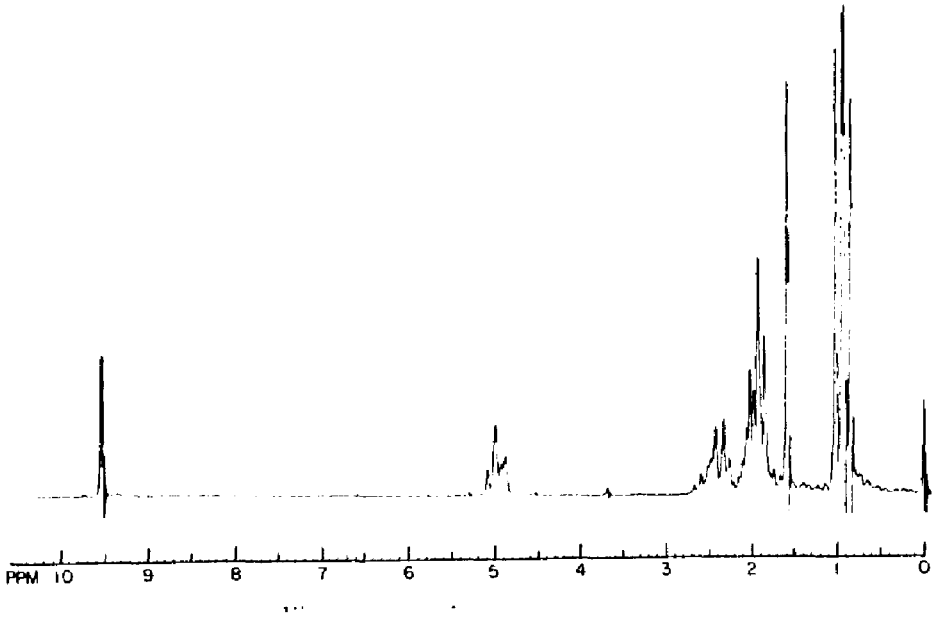
Compound **42** continued.



^{13}C NMR (50 MHz/$CDCl_3$)

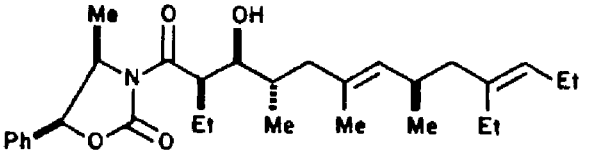
Compound **43**

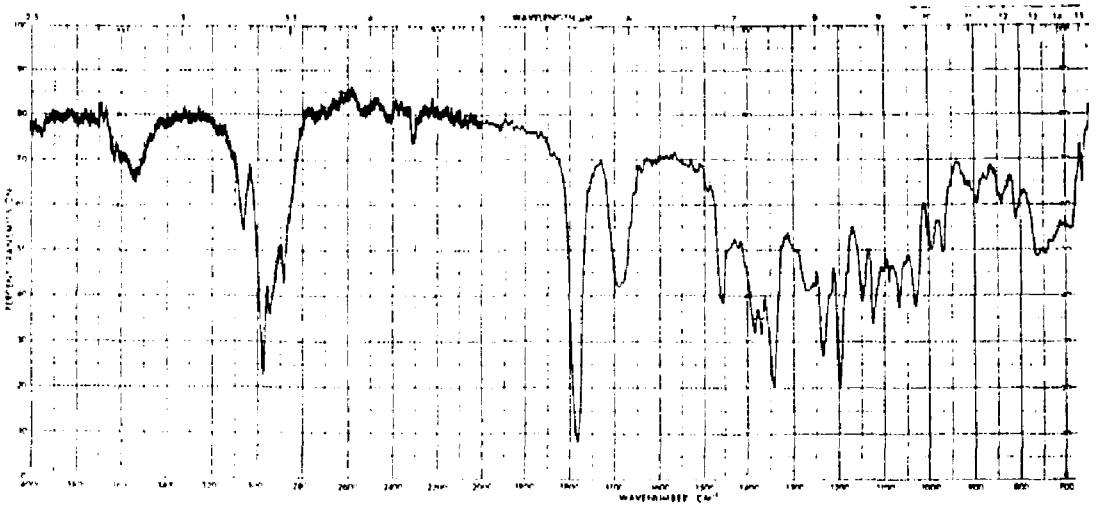




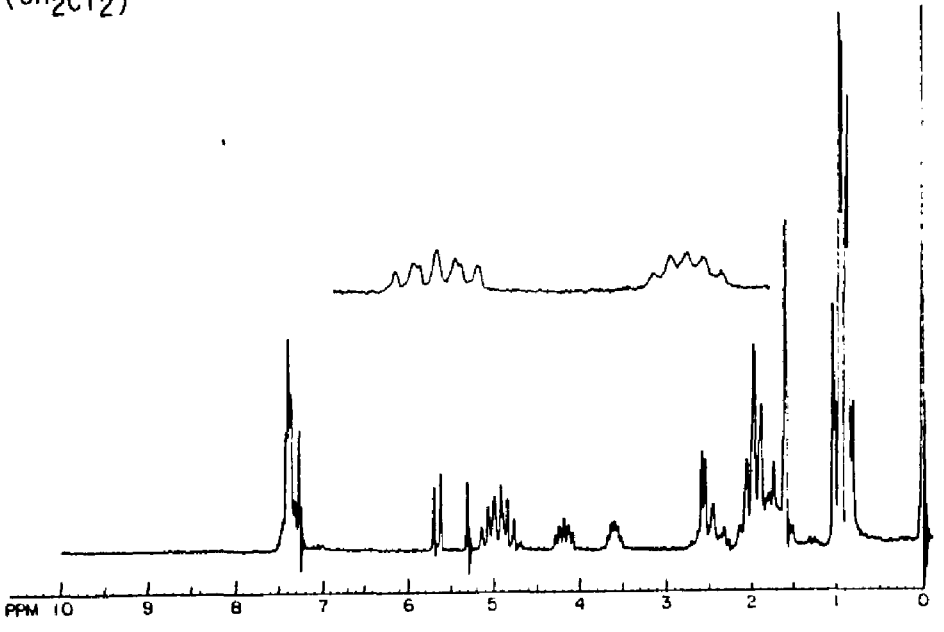
^1H NMR (90 MHz/$CDCl_3$)

Compound **32**



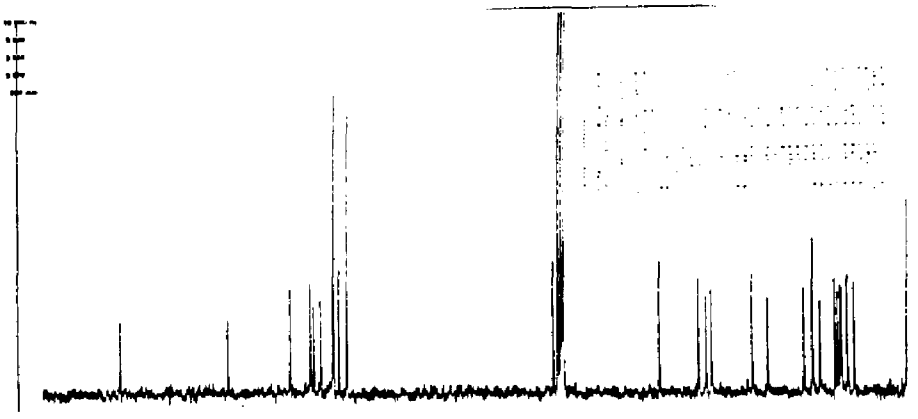


IR (CH_2Cl_2)



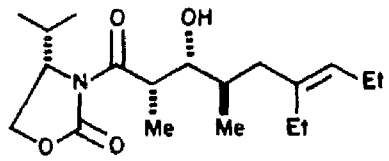
^1H NMR (90 MHz/$CDCl_3$)

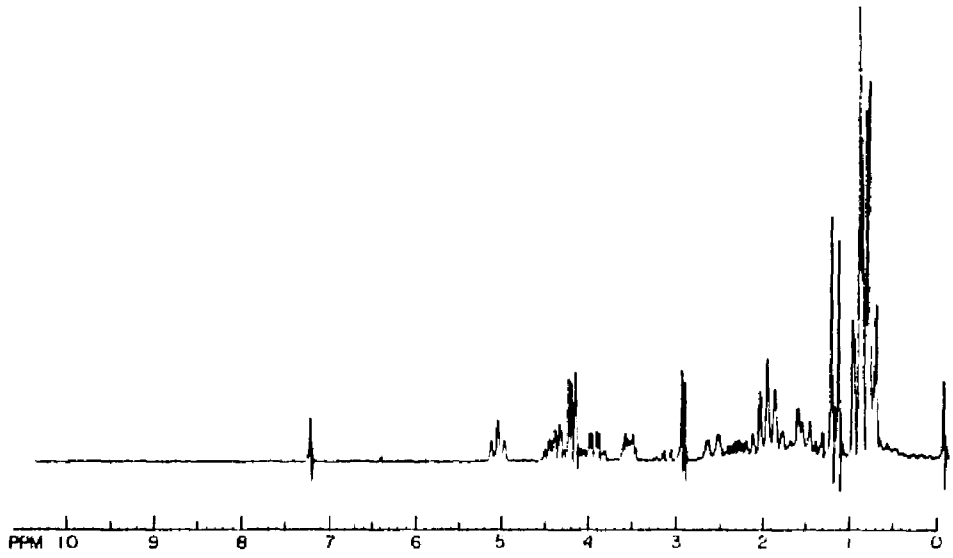
Compound **32** continued.



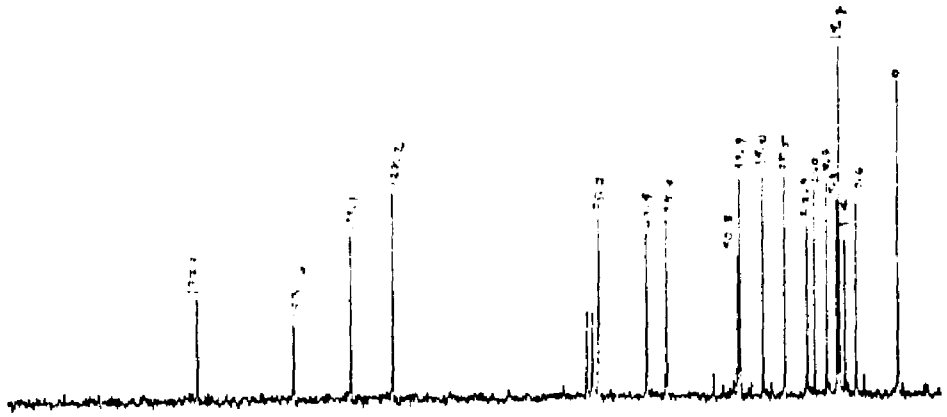
^{13}C NMR (50 MHz/$CDCl_3$)

Compound **44**



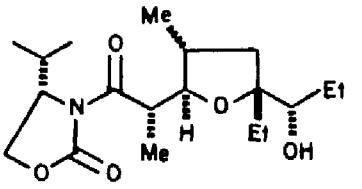


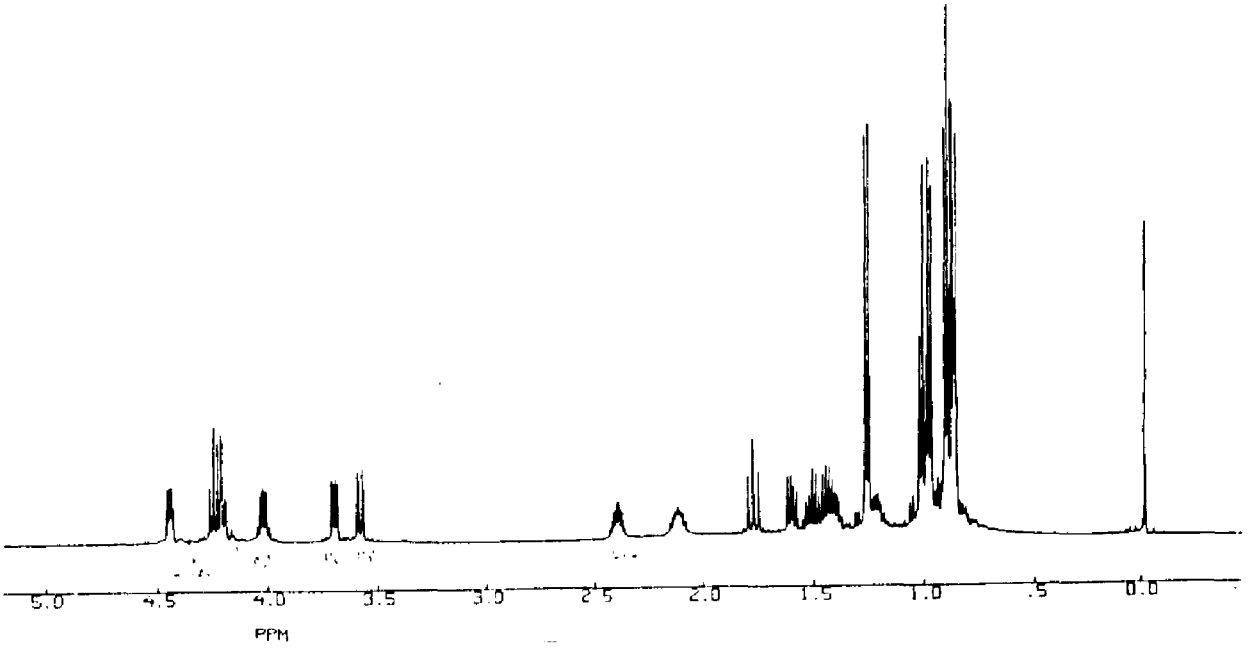
^{1}H NMR (90 MHz/$CDCl_3$)



^{13}C NMR (22.5 MHz/$CDCl_3$)

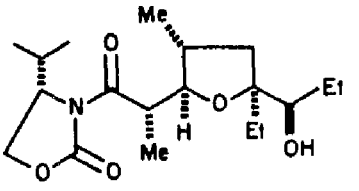
Compound **45**

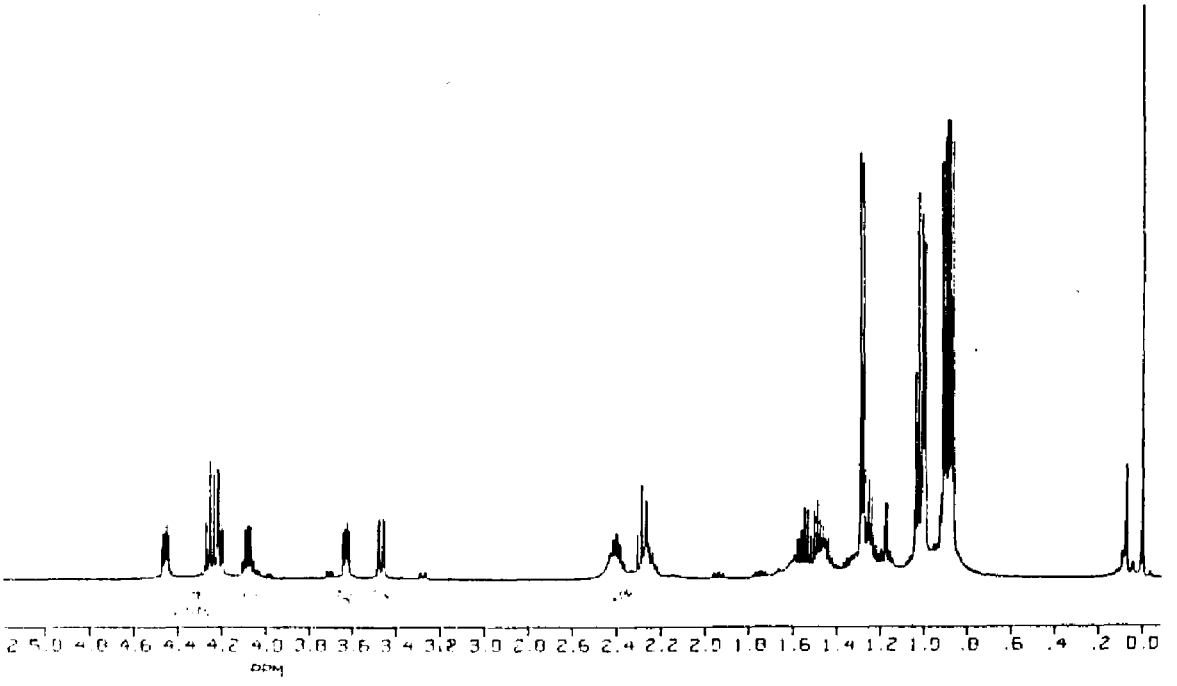




^1H NMR (500 MHz/$CDCl_3$)

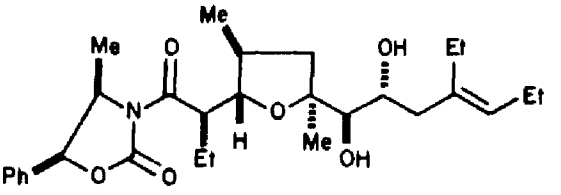
Compound **46**

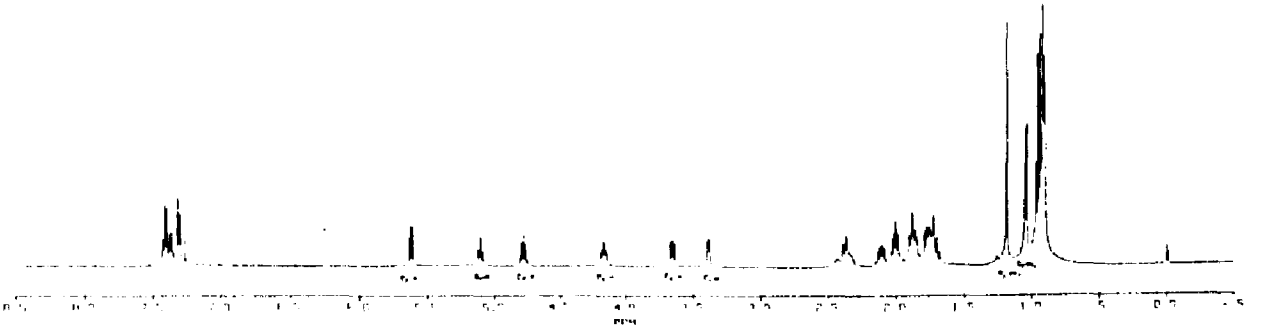




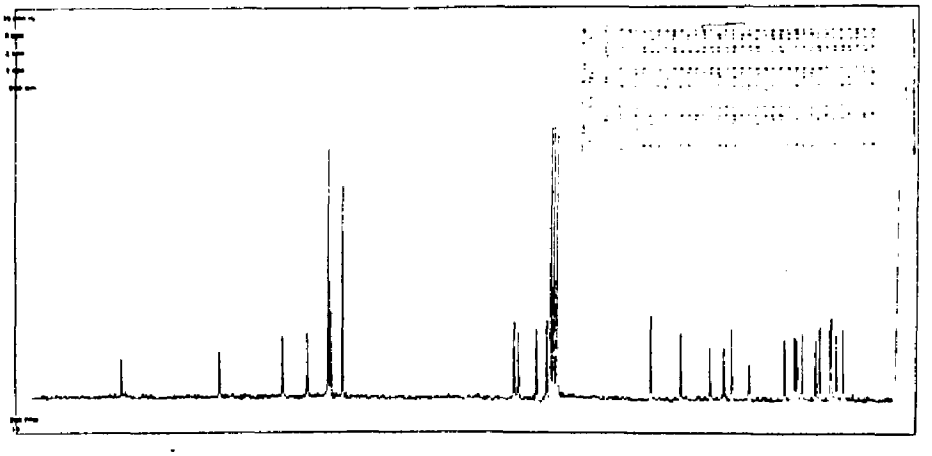
^1H NMR (500 MHz/$CDCl_3$)

Compound **49**





^{1}H NMR (500 MHz/$CDCl_3$)

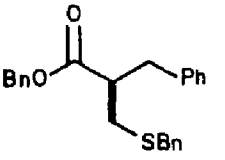


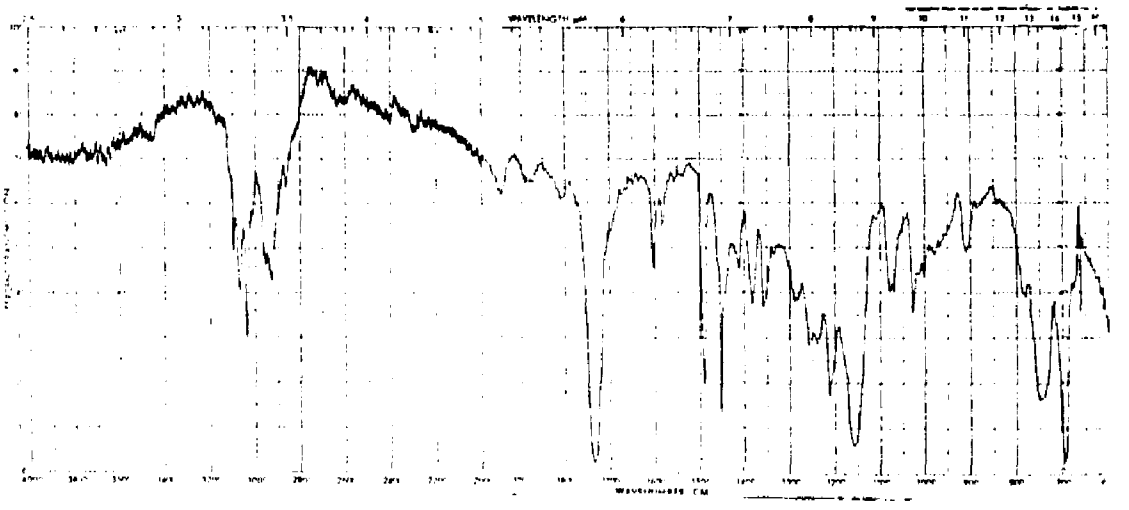
^{13}C NMR (50 MHz/$CDCl_3$)

APPENDIX V

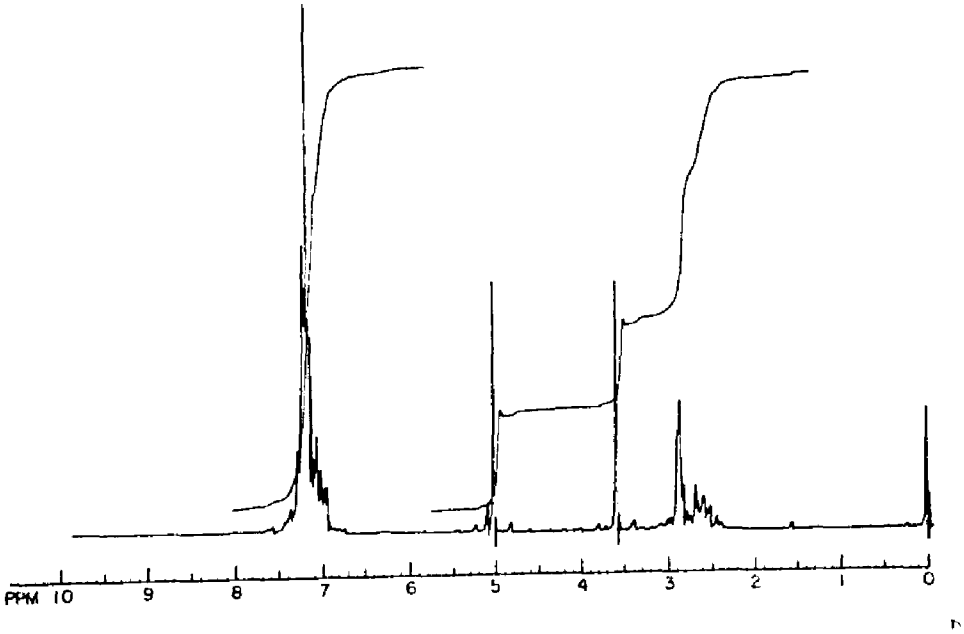
IR ^{1}H NMR, AND ^{13}C NMR SPECTRAL CATALOG FOR APPENDIX II

Compound **R-10**



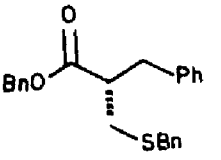


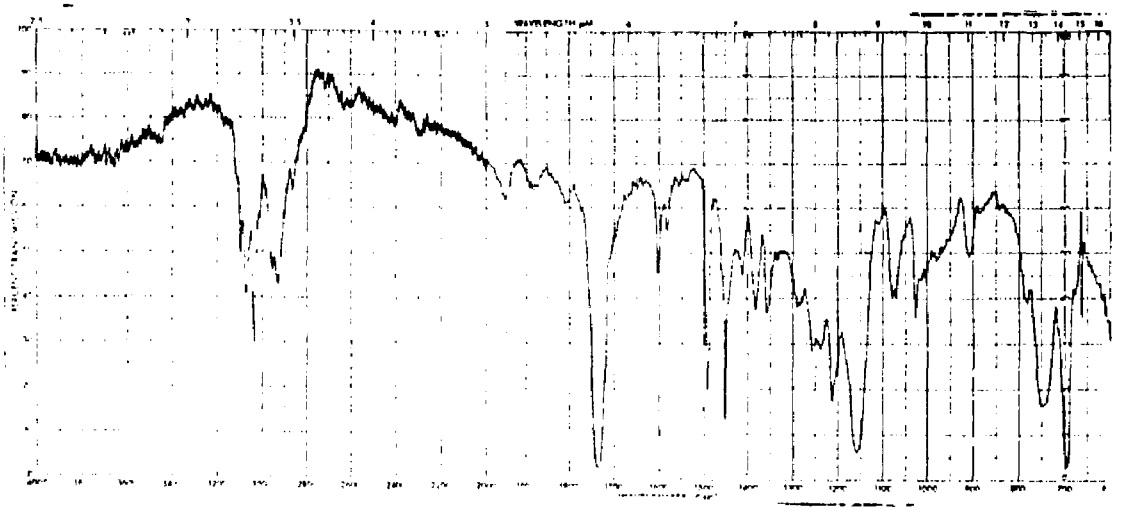
IR (neat)



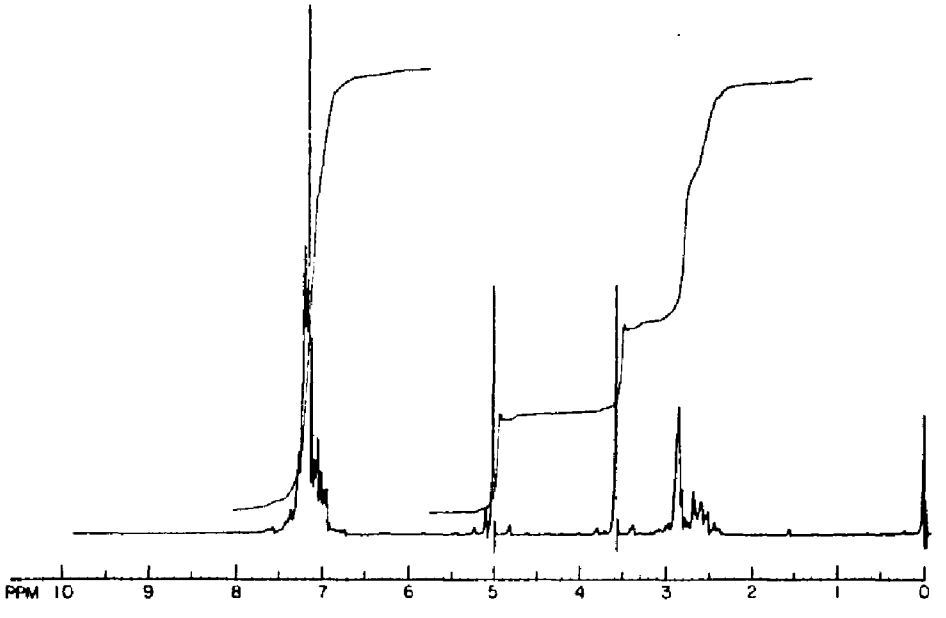
^1H NMR (90 MHz/$CDCl_3$)

Compound **S-10**



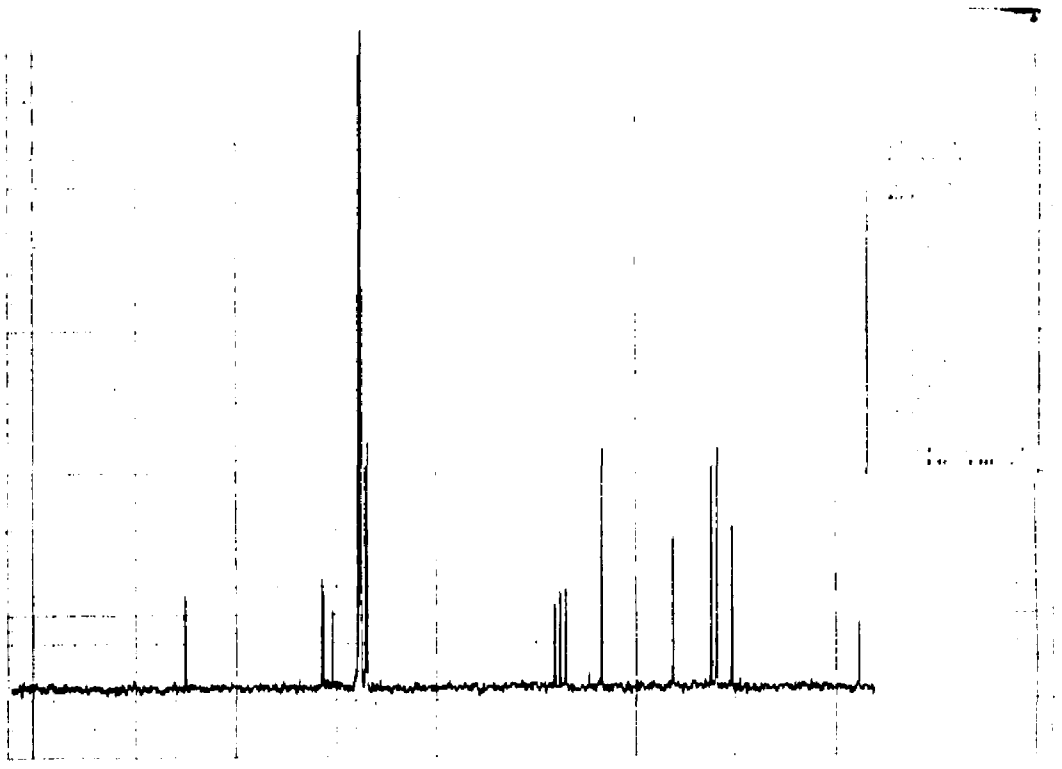


IR (neat)



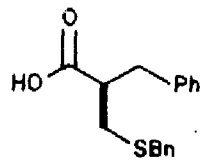
^1H NMR (90 MHz/CCl_4)

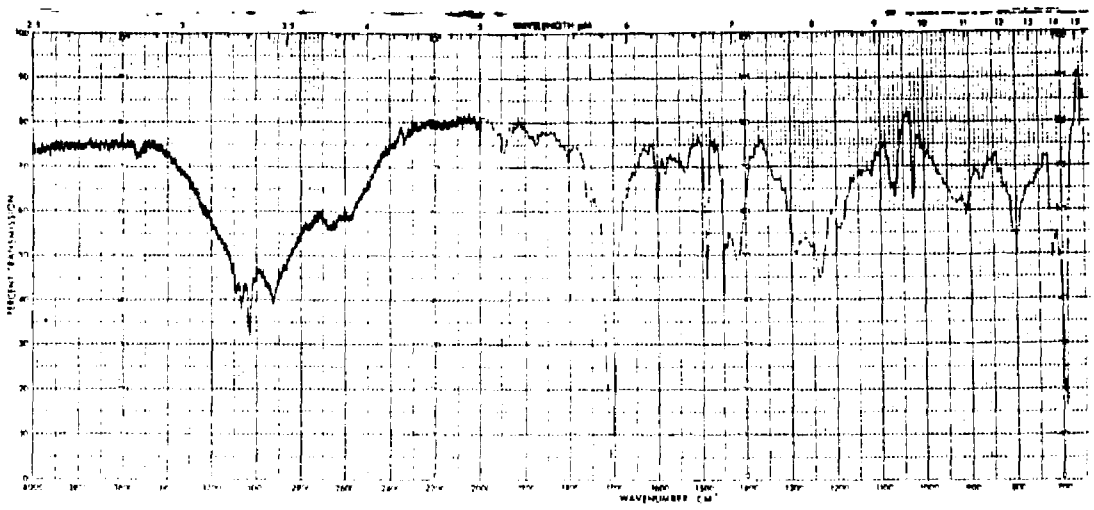
Compound **S-10** continued.



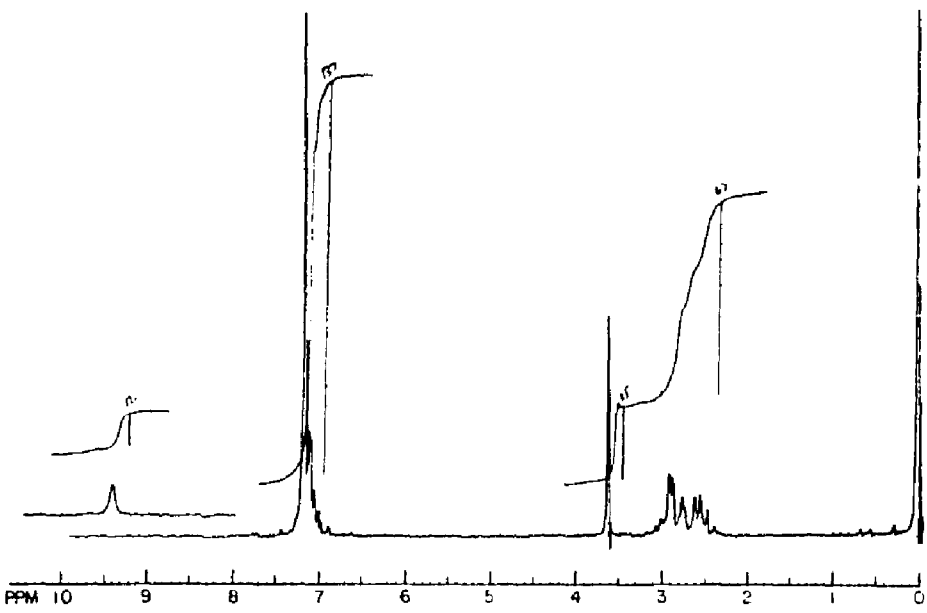
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **R-11**



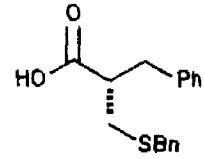


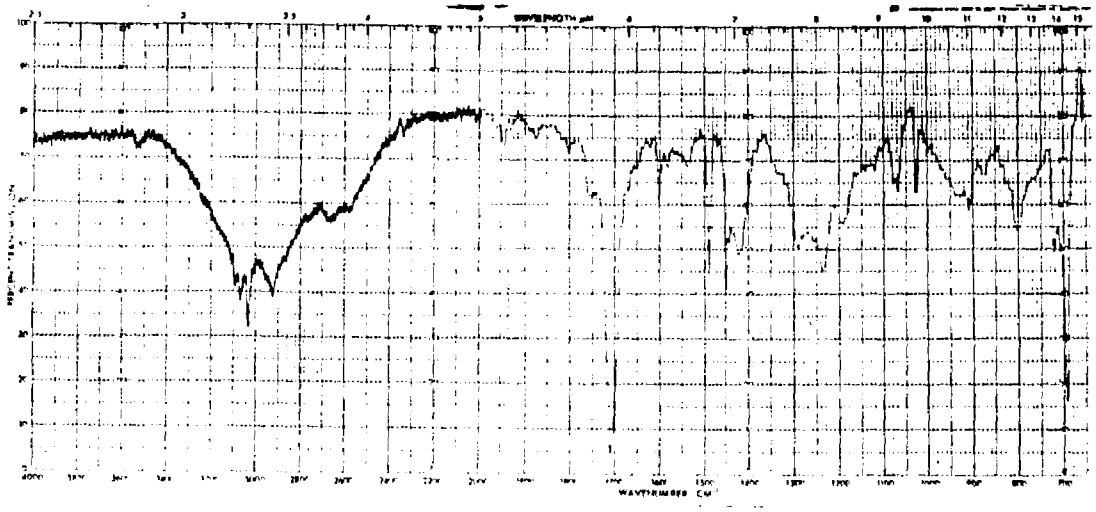
IR (neat)



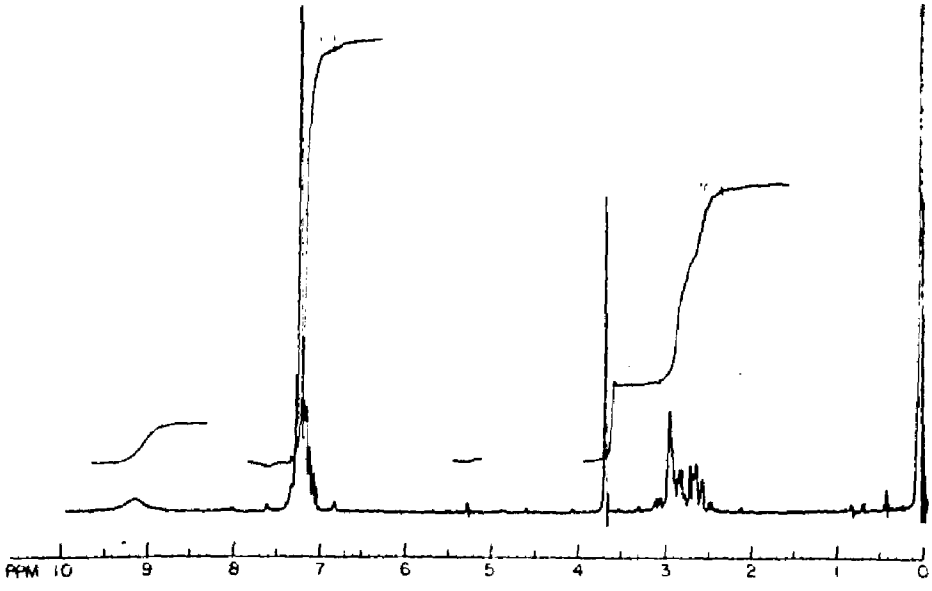
^1H NMR (90 MHz/CCl_4)

Compound S-11



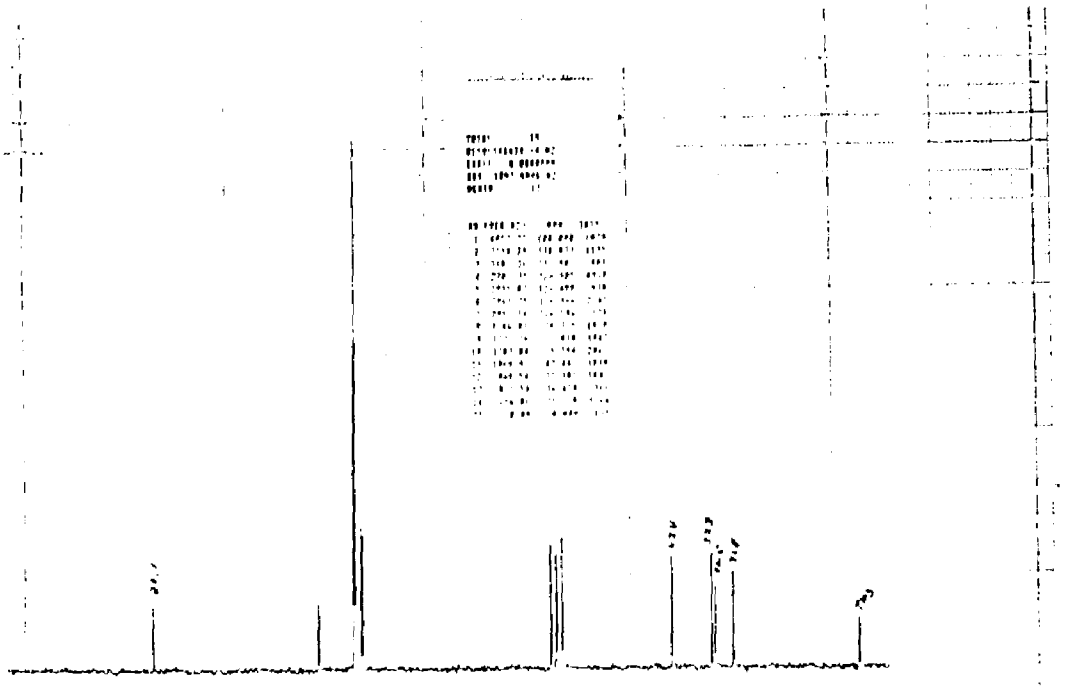


IR (neat)



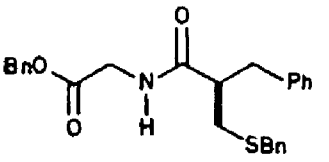
^1H NMR (90 MHz/CCl_4)

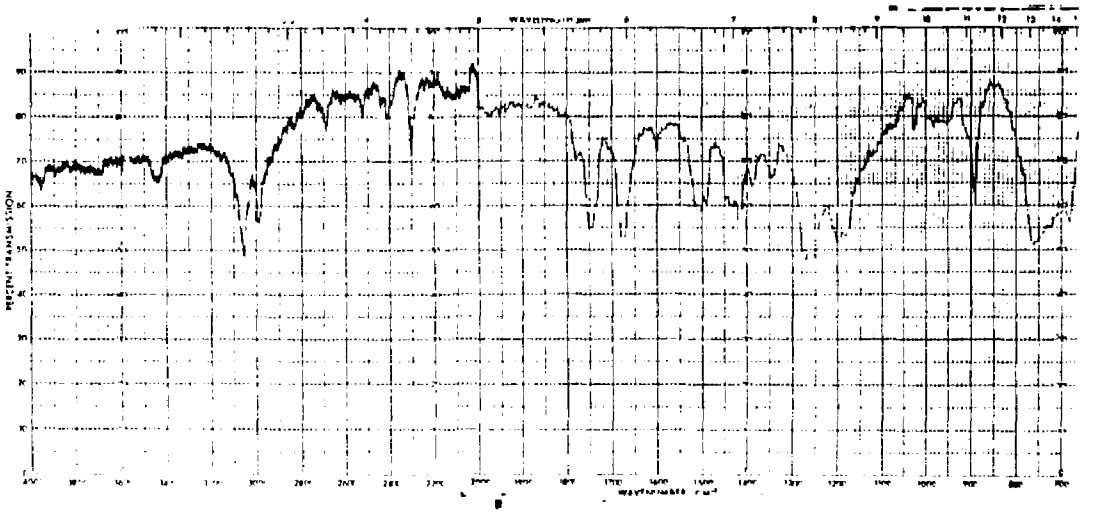
Compound S-11 continued.



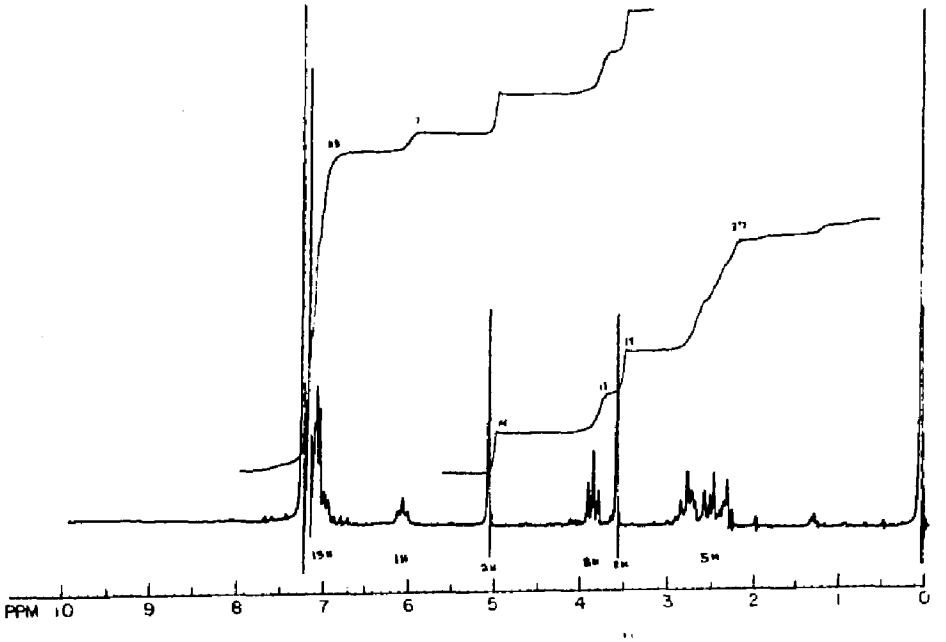
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **R-12**



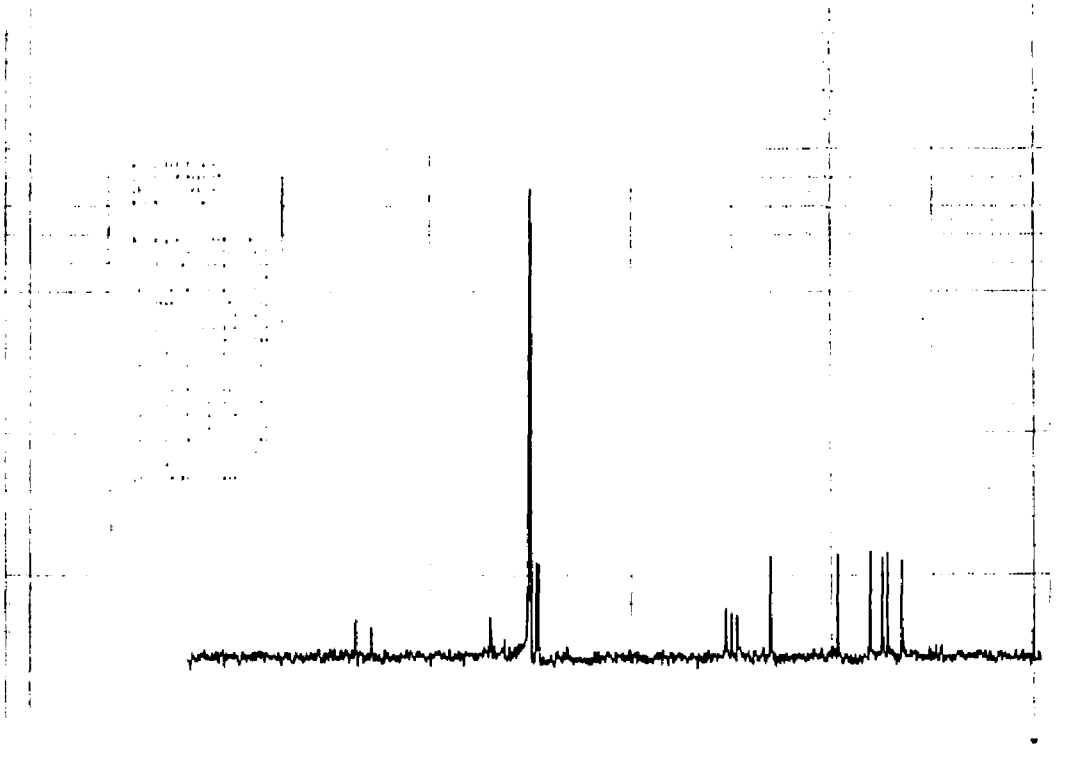


IR (CH_2Cl_2)



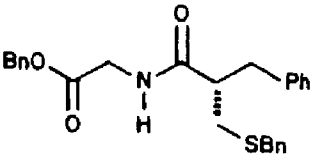
^1H NMR (90 MHz/CCl_4)

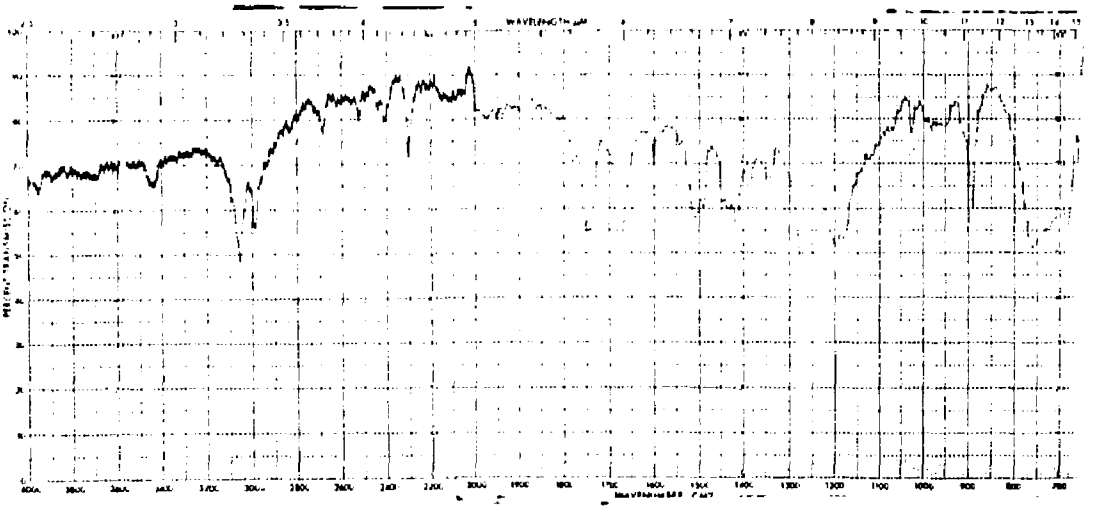
Compound **R-12** continued.



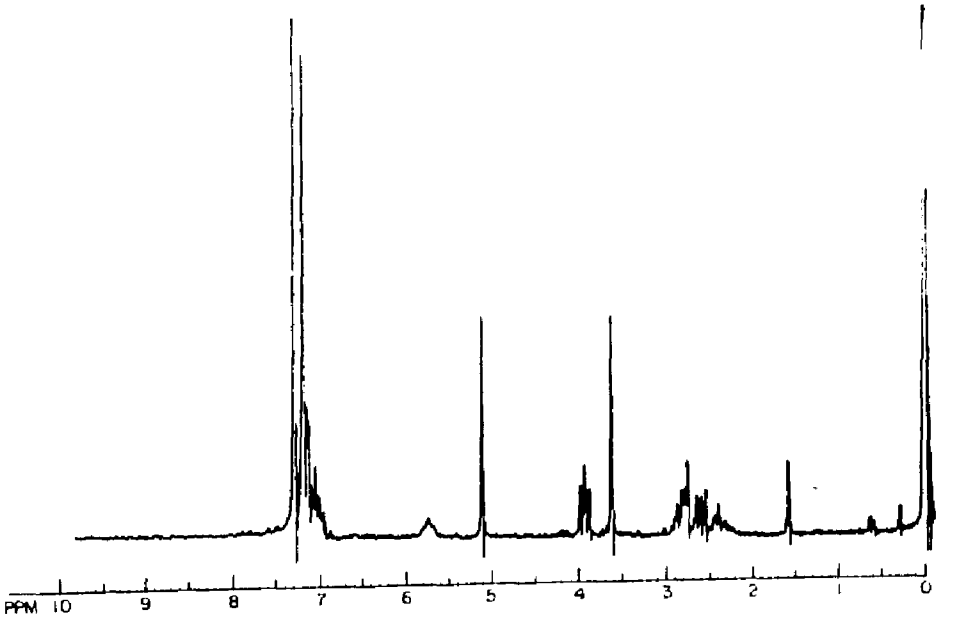
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound **S-12**



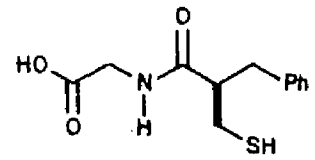


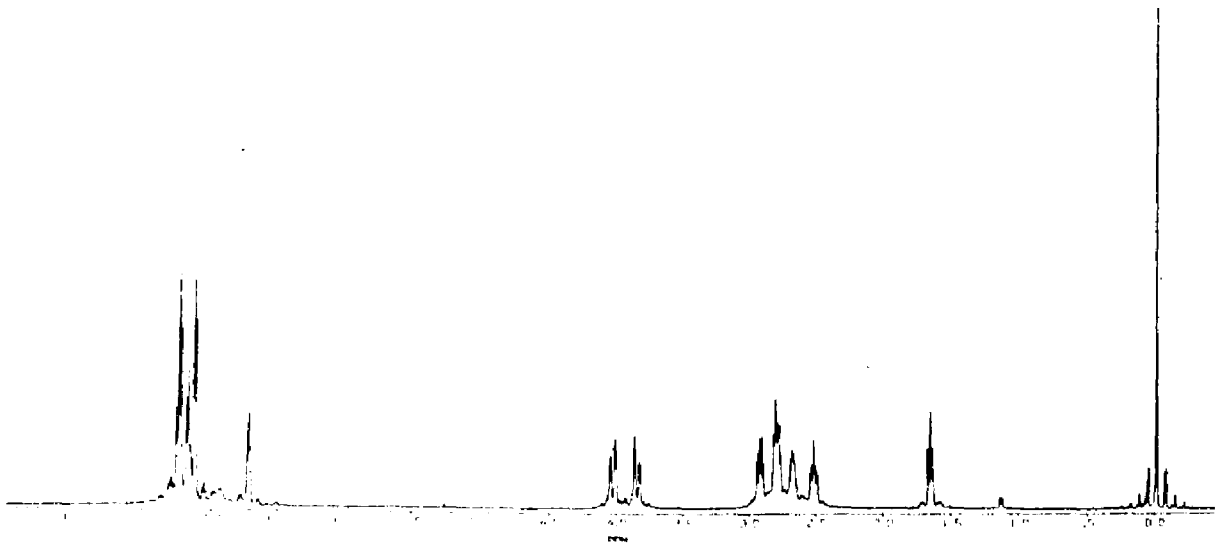
IR (neat)



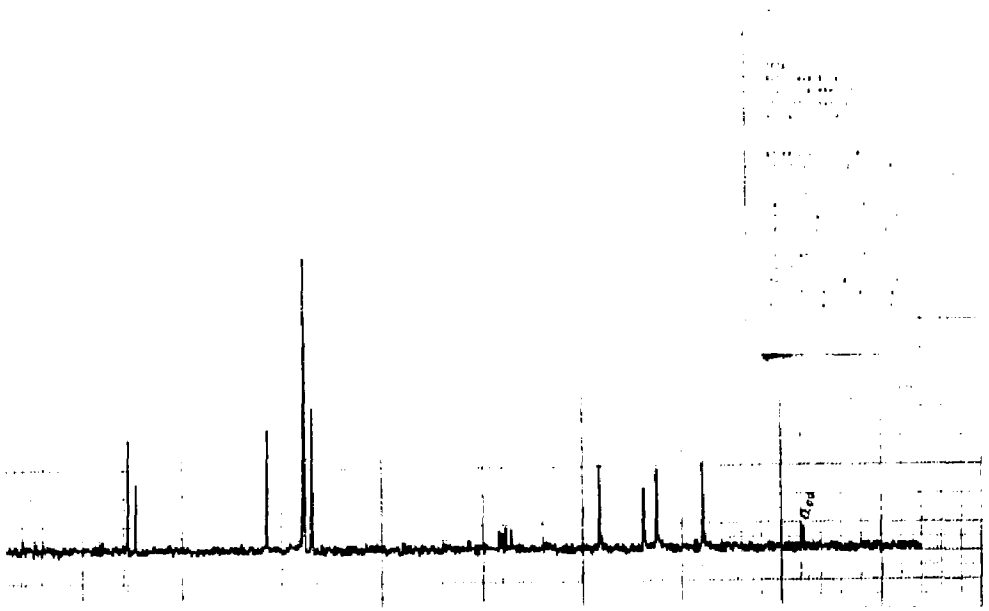
^1H NMR (90 MHz/$CDCl_3$)

Compound **R-1**



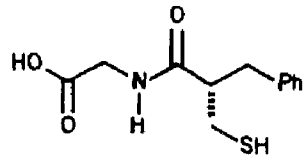


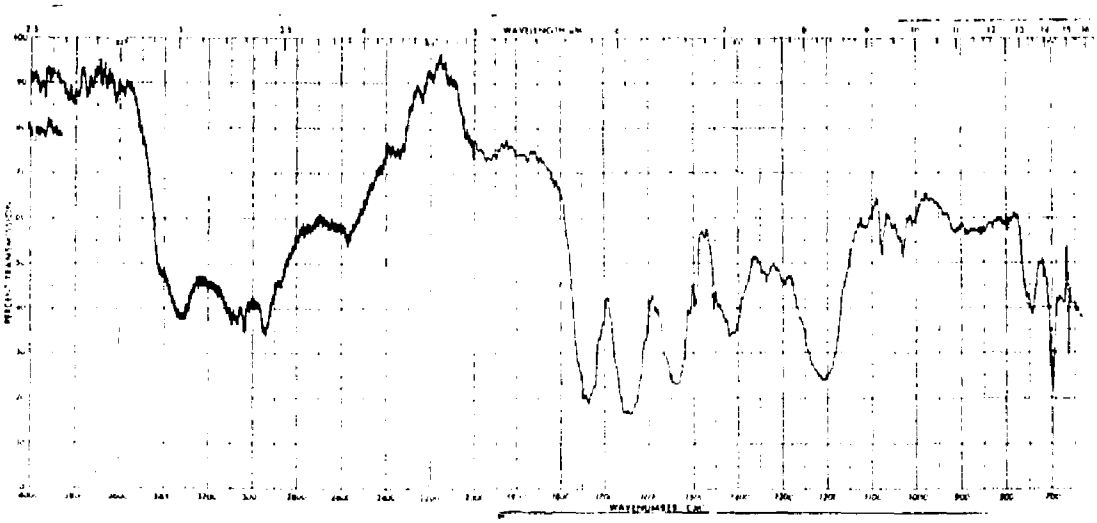
^{1}H NMR (500 MHz/$CDCl_3$)



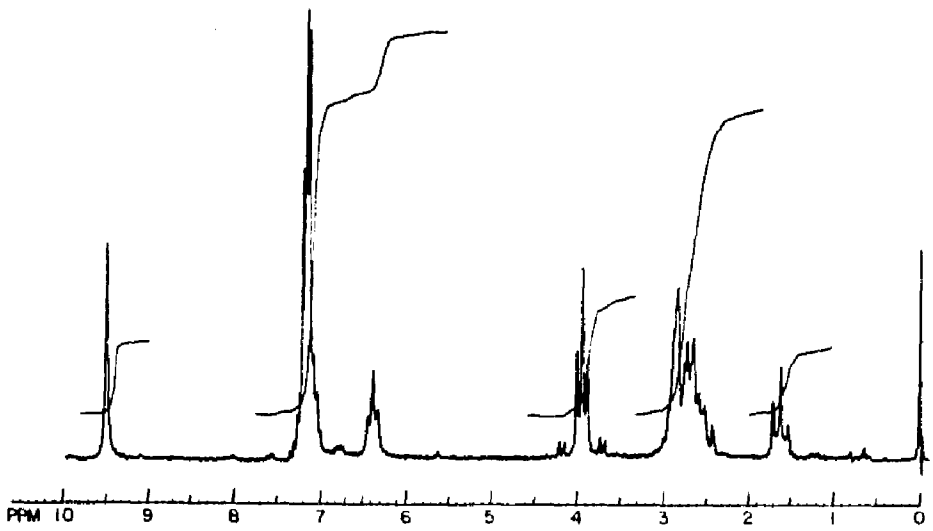
^{13}C NMR (22.5 MHz/$CDCl_3$)

Compound S-1





IR (neat)



^1H NMR (90 MHz/$CDCl_3$)

PROPOSITIONS

PROPOSITION 1. The isolation and structural characterization of bacteriocin JH1000, a small peptide antibiotic effective against Streptococcus mutans strains responsible for human dental caries, is proposed.

PROPOSITION 2. Two thiorphan analogs are proposed to investigate thiorphan induced analgesia. ^{19}F NMR topography is proposed to map the in vivo distribution of both enantiomers of a fluorine containing thiorphan derivative. A photoactivated analog of thiorphan, capable of covalently binding to the receptors for analgesia is proposed to determine if thiorphan binds to an opiate receptor.

PROPOSITION 3. The use of labeled metabolites is proposed to study the biosynthesis of the brevetoxins, an unusual family of polyether marine toxins isolated from the "red tide" dinoflagellate Ptychodiscus brevis Davis.

PROPOSITION 4. The use of a labeled precursor is proposed to determine whether the epoxidation of 5-hexen-2-one with potassium peroxymonosulfate is inter- or intramolecular. If the reaction is shown to be intramolecular, experiments are proposed to investigate internal asymmetric induction in the peroxymonosulfate epoxidation of chiral 1,5- and 1,6-enones.

PROPOSITION 5 Experiments are proposed to investigate the epoxidation step in the biosynthesis of polyether ionophore antibiotics.

PROPOSITION 1

ABSTRACT. The isolation and structural characterization of bacteriocin JH1000, a small peptide antibiotic effective against Streptococcus mutans strains responsible for human dental caries, is proposed.

****

Streptococcus mutans, a bacteria indigenous to the oral cavity, is generally accepted as the principle etiological agent of dental caries in humans.[1] In 1969, Kelstrup and Gibbons reported that some strains of S. mutans, isolated from humans and rodents, produced an exocellular bacteriocin effective against other S. mutans strains.[2] Of 143 strains of S. mutans investigated by Rogers, 70% produced one or more bacteriocins.[3] Based on their size and the effect various proteases exert on their antibacterial activity, the bacteriocins are assumed to be proteins. Only a few of the S. mutans bacteriocins have been isolated and purified, and none have had their structure elucidated.

Paul and Slade reported the isolation of a bacteriocin from S. mutans strain E14 (serotype c) with a mw of 20,000 daltons.[4] Bacteriocin E14 is mainly active against S. mutans serotypes a, c, d, g, l, and o. Both trypsin and pronase inhibit its activity. Ikeda et al. reported the isolation of a different bacteriocin from S. mutans strain C3603 (serotype c).[5] Bacteriocin C3603 is a basic protein with a pI value of 10 and a mw of 4800 daltons. It is mainly active against S. mutans serotypes b, c, e, and f. Pronase, papian, phospholipase C,

trypsin and α-amylase had no effect on its activity, whereas both α-chymotrypsin and pancreatin partially inhibit its activity. These workers also demonstrated that bacteriocin C3603 is an effective anti-caries agent. Bacteriocin C3603 fed to rats previously infected with S. mutans PS-14 had significantly fewer caries than those not treated with the antibiotic.

Recently, Hillman et al. have reported that S. mutans strain JH1000 produces a bacteriocin with novel properties.[6] Unlike the previous two bacteriocins, this antibiotic is active against 124 of 125 strains of S. mutans tested, and also is active against a variety of other Gram-positive bacteria. Both trypsin and pronase inhibit the antibacterial activity of a cell-free solution of bacteriocin JH1000, whereas DNase, RNase, lipases, thermolysin, and lysozyme had no effect on its activity. Surprisingly, experiments with dialysis membranes indicate that the mw of the antibiotic is < 1000 daltons. Bacteriocin JH1000, however, has not been isolated and purified.

The unusually small size of bacteriocin JH1000--probably less than ten amino acids in length--indicates its potential for purification and sequencing. I propose to isolate and identify the structure of bacteriocin JH1000. With its structure known, bacteriocin JH1000 could be prepared on a large scale in the laboratory, and its use as a direct anticaries agent evaluated. Furthermore, its mode of antibacterial activity could be investigated.

Before the structure of bacteriocin JH1000 can be determined, it will be necessary to obtain the peptide antibiotic in a pure form. The following isolation and purification sequence is based on the observed properties of the bacteriocin. The efficiency of the sequence would be

evaluated by assaying for antibacterial activity. Initially, the small size of the bacteriocin would be exploited to separate it from larger proteins. Both dialysis and gel-filtration chromatography separate molecules on the basis of size. As previously noted, bacteriocin JH1000 passes through a dialysis membrane. Therefore, dialysis would be the first purification technique evaluated.

Trypsin inhibits the antibacterial activity of bacteriocin JH1000. This indicates that the molecule contains lysine or arginine, and thus possesses a basic side chain. Therefore, ion-exchange chromatography or electrophoresis could be employed to further purify the bacteriocin. By judicious use of one or more of the separation techniques, it should be possible to obtain a pure sample of the bacteriocin.

Once purified, the structure of the bacteriocin would be determined by classical means, such as the Edman degradation procedure.[7] Based on its small size, bacteriocin JH1000 could be a cyclic peptide, similar to the decapeptide antamanide[8] or the pentapeptide gramacidin S.[9] Both antamanide and the gramacidins are peptide ionophores. Like bacteriocin JH1000, gramacidin S is an antibiotic active against Gram-positive bacteria. If bacteriocin JH1000 is a cyclic peptide, it would be necessary to open the chain prior to sequencing. Presumably, trypsin could be employed for this purpose. The small peptide antibiotics often contain unnatural (D)-amino acids. Therefore, the absolute stereochemistry of the amino acids in bacteriocin JH1000 would also be determined.

Interestingly, the biosynthesis of ionophore peptide antibiotics is independent of the usual protein biosynthetic pathway, involving ribosomal, messenger, and transfer-RNA. Rather, a multienzyme complex,

utilizing a mechanism related to fatty acid biosynthesis is employed.[10] Since bacteriocin JH1000 is a relatively small peptide, its biosynthesis may also involve a similar nonribosomal mechanism.

Hillman et al. have shown that S. mutans JH1000 and a tetracycline resistant strain JH1001 both possess plasmid DNA.[6a] By using the plasmids from S. mutans JH1001, they were able to induce tetracycline resistance into S. mutans GS5 (previously tetracycline sensitive). Half of the transformants also produced a bacteriocin with the same spectrum of activity as bacteriocin JH1000. Presumably, the plasmid is responsible for JH1000 bacteriocin. Therefore, depending on which method of protein synthesis is employed for the construction of bacteriocin JH1000, the plasmid would either contain a gene for the synthesis of the bacteriocin, or a gene for the nonribosomal enzymes responsible for the synthesis of the bacteriocin.

By knowing the structure of bacteriocin JH1000, it would be possible to construct a sequence of radiolabeled complementary DNA corresponding to the bacteriocin. This sequence could then be employed to detect if the bacteriocin gene is present in the JH1000 plasmid, and thus indicate which method of protein synthesis is responsible for the construction of the bacteriocin. Alternatively, S. mutans JH1000 could be feed an antibiotic known to inhibit ribosomal protein synthesis, such as chloramphenicol or puromycin. If bacteriocin JH1000 continues to be produced, a nonribosomal enzyme system is probably responsible for its synthesis. This information would be important if an in vivo technique were to be employed for the preparation of bacteriocin JH1000 on a large scale.

REFERENCES

(1) (a) Krass, B.; Jordan, H. V.; Edwardsson, S.; Svensson, I.; Tvell, L. Arch. Oral Biol. **1968**, 13, 911-918. (b) Loesche, W.; Rowan, J.; Straffon, L. H.; Loos, P. J. Infect. Immun. **1975**, 11, 1252-1260. (c) Loesche, W.; Straffon, L. H. Infect. Immun. **1979**, 26, 498-507.

(2) Kelstrup, J.; Gibbons, R. J. Arch. Oral Biol. **1969**, 14, 251-258.

(3) (a) Rogers, A. H. Arch. Oral Biol. **1976**, 21, 99-104. (b) Rogers, A. H. Arch. Oral Biol. **1976**, 21, 243-249.

(4) Paul, D.; Slade, H. D. Infect. Immun. **1975**, 12, 1375-1385.

(5) Ikeda, T.; Iwanami, T.; Hirasawa, M,; Watanabe, C.; McGhee, J. R.; Shiota, T. Infect. Immun. **1982**, 35, 861-868.

(6) (a) Hillman, J. D.; Johnson, K. P.; Yaphe, B. I. J. Dent. Res. **1983**, 62, 241. (b) Hillman, J. D.; Johnson, K. P.; Yaphe, B. I. Infect. Immun. **1984**, 44, 141-144.

(7) Needleman, S. B., Ed. in "Advanced Methods in Protein Sequence Determination;" Springer-Verlag: Berlin, 1977.

(8) Wieland, T.; Luben, G.; Ottenheym, H.; Faesel, J.; DeVries, J. X.; Konz, W.; Prux, A.; Schmid, J. Agnew. Chem. **1968**, 80, 209.

(9) Hotchkiss, R. D. Adv. Enzymol. **1944**, 4, 153.

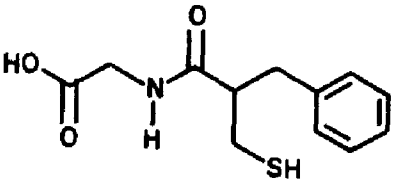
(10) Perlman, D.; Bodanszky, M. Ann. Rev. Biochem. **1977**, 40, 499-464.

PROPOSITION 2

ABSTRACT. Two thiorphan analogs are proposed to investigate thiorphan induced analgesia. ^{19}F NMR topography is proposed to map the *in vivo* distribution of both enantiomers of a fluorine containing thiorphan derivative. A photoactivated analog of thiorphan, capable of covalently binding to the receptors for analgesia is proposed to determine if thiorphan binds to an opiate receptor.

****

The endogenous opioid pentapeptides, leucine and methionine-enkephalin are neurotransmitter candidates thought to be responsible for the induction of analgesia.[1] In the absence of a specific uptake mechanism, hydrolysis of the enkephalin Gly^3-Phe^4 bond by a membrane-bound metalloendopeptidase, "enkephalinase," is postulated to mediate enkephalin induced analgesia.[2] Racemic thiorphan [(±)-1] is reported to inhibit enkephalinase,[3] extend the duration of analgesia induced by enkephalin analogs or noxious stimuli,[4] and even induce analgesia itself.[5] Recently, Scott et al. have reported that (S)-thiorphan is slightly more effective (ca. three-fold) an inhibitor of purified enkephalinase A than (R)-thiorphan.[6] Surprisingly, (R)-thiorphan is significantly more potent an analgesic in the hot plate test than (S)-thiorphan. Therefore, a mechanism other than enkephalinase inhibition may be responsible for the analgesic properties of thiorphan.



1

Several explanations can be advanced for the apparent dissociation of antinociception from enkephalinase inhibition. It is possible that (R) and (S)-thiorphan are metabolized at different rates *in vivo*. Both enantiomers of thiorphan, however, retain their ability to inhibit purified enkephalinase A, even after prolonged preincubation with rat brain homogenate.[6] Alternatively, (R)-thiorphan could be a stereospecific agonist for one of the opiate receptors. Naloxone, an opiate antagonist, mediates thiorphan induced analgesia.[5] It is unclear, however, whether naloxone prevents thiorphan, the enkephalins, or both from binding to an opiate receptor. The following two sets of experiments are designed to determine if thiorphan induces analgesia by binding to an opiate receptor.

Several opiate receptors have been proposed; however, only two--the μ and k-receptors--are thought to be directly involved with the induction of analgesia.[7] The opiate receptors are highly stereospecific: (-)-morphine induces analgesia, while (+)-morphine exhibits essentially no antinociceptive activity. The stereospecificity of the opiate receptors could explain why only (R)-thiorphan induces analgesia.

If (R)-thiorphan stereospecifically binds to an opiate receptor, then its *in vivo* distribution should correspond to the distribution of the opiate receptor. The distribution of (S)-thiorphan, on the other hand, should more closely resemble the distribution of enkephalinase.

In the CNS, the distribution of enkephalinase and the opiate receptors are similar, both having their highest concentration in the striatum.[8] This is not the case, however, in other regions of the body. High levels of enkephalinase are found in the lung and thyroid with low levels in the ileum, while high levels of opiate receptors are found in the ileum.[9, 10] By mapping the distributions of (R) and (S)-thiorphan, and comparing this with the differential distributions of enkephalinase and the opiate receptors, it should be possible to determine if the distribution of (R)-thiorphan corresponds to that of the opiate receptors, and the distribution of (S)-thiorphan corresponds to that of enkephalinase.

I propose to prepare both enantiomers of a fluorine containing thiorphan analog (2), and to employ ^{19}F NMR topography to map their distributions in vivo. NMR topography can be employed to map the two- and three-dimensional distribution of a drug within a living animal.[11] Fluorine is chosen to label the thiorphan because of the high sensitivity of ^{19}F NMR (second only to ^{1}H NMR), and the low natural abundance of other fluorine-containing molecules within the body.[12] ^{19}F NMR topography could also be employed to map the distributions of enkephalinase and the opiate receptors by using fluorine-containing analogs of the enkephalins and the opiates, respectively.

Smith and Wilkinson have shown that the antinociceptive activity of enkephalin analogs increases by placing an electron-withdrawing substituent on the Phe^4 phenyl ring (Figure 1).[1a] For example, a p-chloro and p-nitro substituent increases the antinociceptive activity eight and twenty-eight-fold, respectively, as compared to the parent unsubstituted

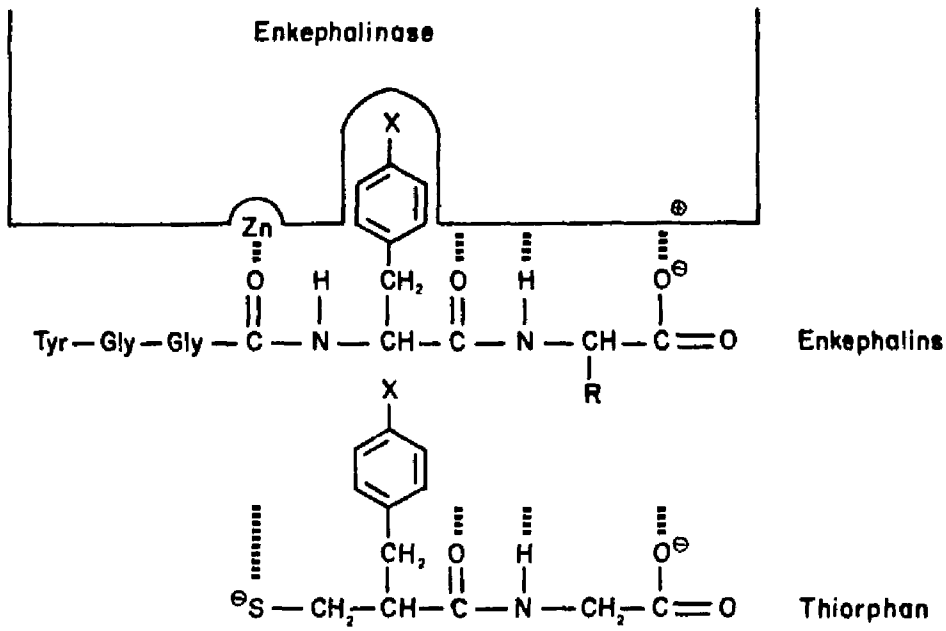
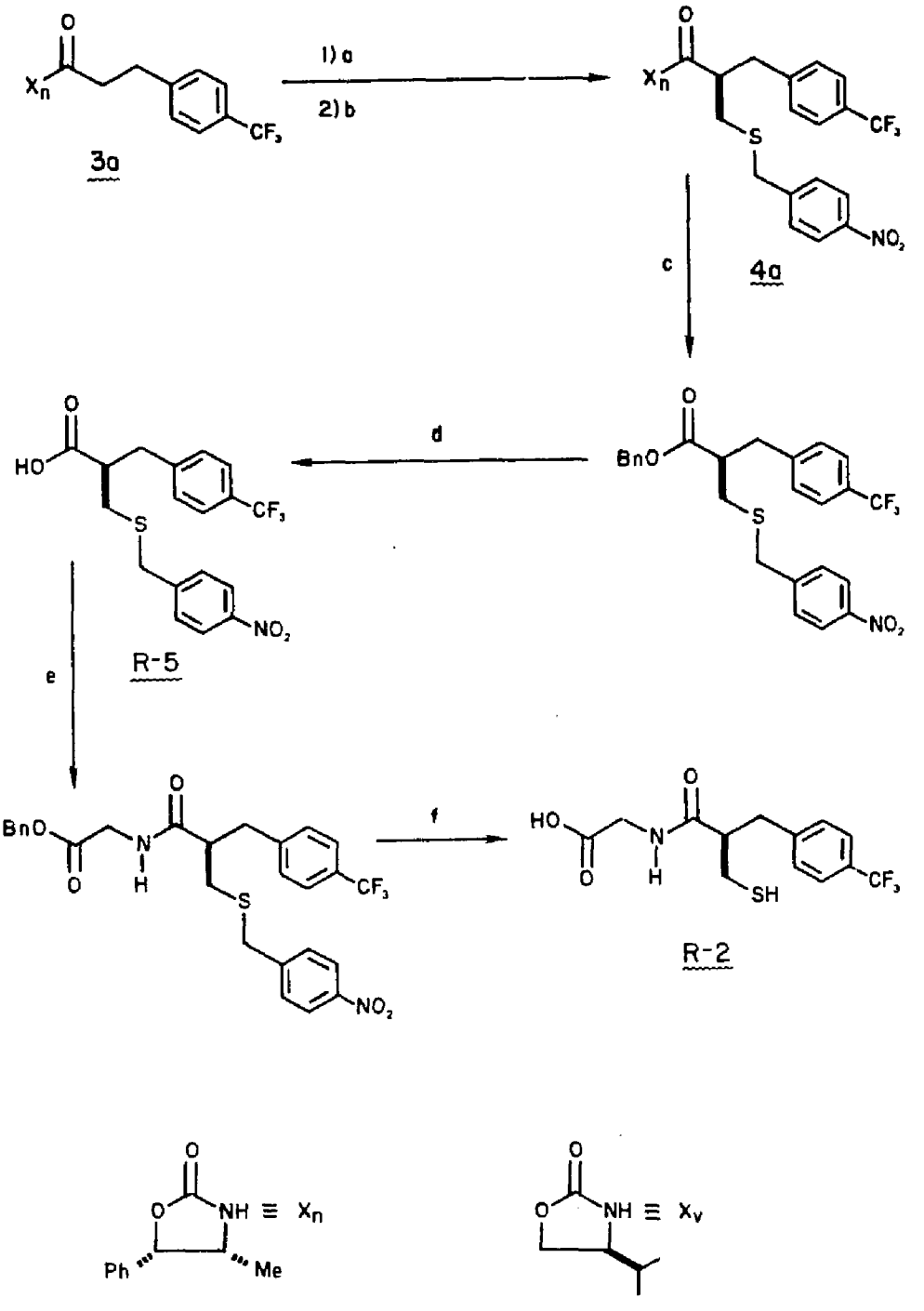


Figure 1. Binding of Enkephalins and Thiorphan to Enkephalinase.

enkephalin. Therefore, an electron-withdrawing p-triflurometliyl substituent on the phenyl ring of thiorphan would be expected to increase its antinociceptive activity.

A synthetic plan for the preparation of (R) and (S)-**2** is shown in Scheme 1. The synthesis closely resembles the method we employed to construct both enantiomers of thiorphan.[13] The major bond construction, generating the chirality, is based on the diastereoselective alkylation of chiral 2-oxazolidinone imide enolates.[14] Alkylation of the lithium enolate derived from imide **3a** with bromomethyl p-nitrobenzyl sulfide[15] would afford alkylated imide **4a**. Transbenzylesterification of **4a** (LiOBn, THF)[13] followed by acid-catalyzed hydrolysis of the resultant benzyl ester (6 M HBr in HOAc)[16] would afford acid (R)-**5**. Condensation of (R)-**5** with benzyl glycinate [$(PhO)_2P(O)N_3$, Et_3N, DMF][17] followed by deprotection [Pd/C, H_2, 10 equiv 1 N HCl][18] would afford (R)-**2**. The



a) LDA, THF. b) p-NO_2PhCH_2S CH_2Br. c) LiOBn, THF. d) 6M HBr in HOAc. e) $(PhO)_2P(O)N_3$, $BnO_2CH_2NH_2$, Et_3N, DMF. f) Pd/C, H_2, 10 equiv 1N HCl.

Scheme 1

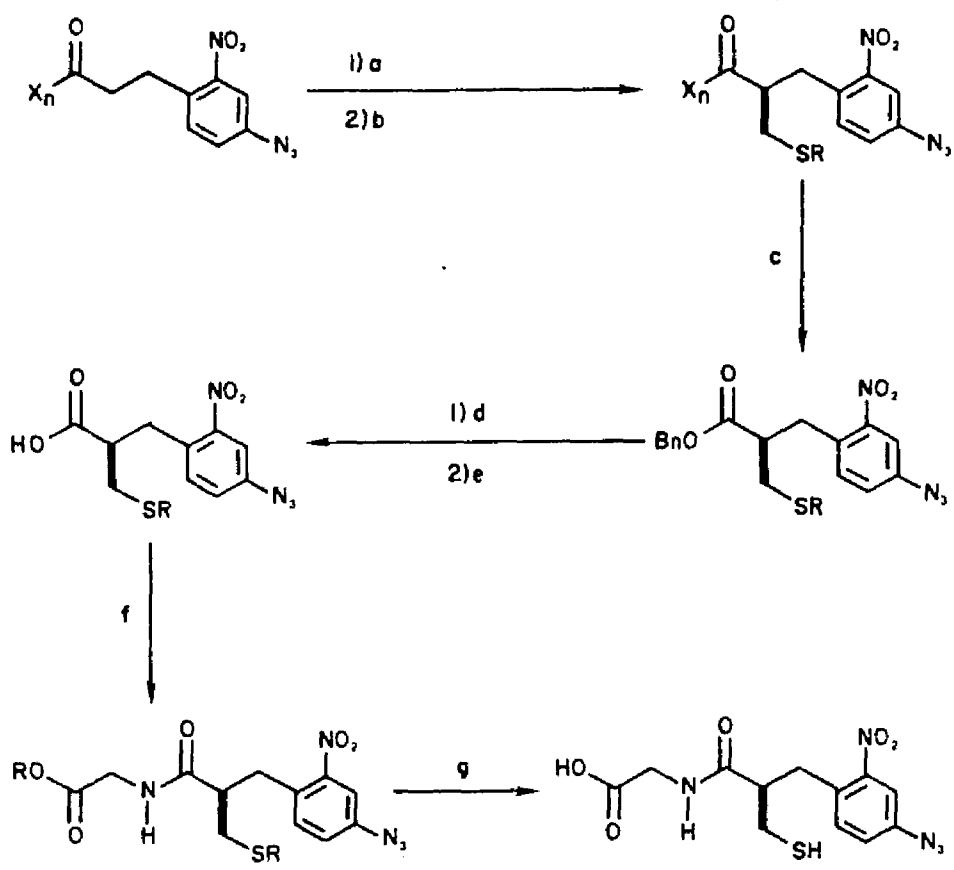
p-nitrobenzyl group is chosen to protect the sulfur since it can be removed by catalytic hydrogenation under acidic conditions.[18] The alternate dissolving metal reduction conditions, employed for the construction of thiorphan, potentially would remove fluorine from the trifluoromethyl substituent. The enantiomeric (S)-**2** could be prepared by substituting the norephedrine-derived 2-oxazolidinone (X_n) shown in Scheme 1 with the (S)-valinol derived 2-oxazolidinone (X_v).

The two enantiomers, (R) and (S)-**2** would first be assayed for enkephalinase inhibition and analgesia in the hot plate test on rats. Assuming that the structure-activity relationship is similar to thiorphan, (i.e., (R)-**2** induces analgesia, while (S)-**2** is mainly responsible for enkephalinase inhibition) the in vivo distribution of (R) and (S)-**2** in rats would be determined by ^{19}F NMR topography. Since (R)-thiorphan also inhibits angiotensin converting enzyme (ACE),[6] it would be necessary to pretreat the animal with captopril, a selective inhibitor of ACE.[1a] ^{19}F NMR topography could also be employed to measure the rate the drugs are distributed throughout the body. This information could then be correlated with the onset of analgesia.

Presuming that the above set of experiments indicate that (R)-**2** binds to an opiate receptor, the following set of experiments are designed to identify and possibly isolate the receptor. Toward this purpose, I propose to synthesize a ^{14}C labeled, photoactivated[19] thiorphan analog [(R)-**6**] that is capable of covalently binding to the opiate receptor.

A synthetic plan for the construction of (R)-**6** is shown in Scheme 2. As before, the synthesis closely resembles the method we employed to construct both enantiomers of thiorphan.[13] Since both the nitro and

azido substituents are labile to reduction, the protecting groups would be removed under acidic conditions.



a) LDA,THF. b) RCH_2SCH_2Br. c) LiOBn, THF. d) 6 M HBr in HOAc. e) K_2CO_3, RBr. f) $(PhO)_2P(O)N_3$, $RO_2CCH_2NH_2$, Et_3N, DMF. g) H^+

Scheme 2

The photoactivated analog (R)-**6** would first be assayed for analgesia in the hot plate test on rats. Those tissues, previously shown to have a high affinity for (R)-**2**, would then be treated with (R)-**6** and exposed to light. Fractionation of the tissue would allow the isolation and identification of those components binding to the thiorphan analog. A comparison could then be made with previously isolated opiate receptors.[7]

REFERENCES

(1) For a review of the chemistry and pharmacology of enkephalins, see: (a) Smith, T. W.; Wilkinson, S. In "The Chemical Regulation of Biological Mechanisms," Creighton, A. M.; Turner, S. Eds.; The Royal Society of Chemistry: London, 1981, pp 230-254. (b) Miller, R. J. In "Handbook of Psychopharmacology," Iversen, L. L.; Iversen, S. D.; Snyder, S. H. Ed.; Plenum: New York, 1983; Vol. 16, Chapter 2, and references contained therein.

(2) (a) Malfroy, B.; Swertz, J. P.; Guyon, A.; Roques, B. D.; Schwartz, J. C. Nature **1978**, 276, 523. (b) Gorenstein, C.; Snyder, S. H. Life Sci. **1979**, 25, 2065.

(3) (a) Llorens, C.; Gacel, G.; Swerts, J.-P.; Perdrisot, R.; Fournie-Zaluski, M.-C.; Schwartz, J.-C.; Roques, B. P. Biochem. Biophys. Res.Commun. **1980**, 96, 1710-1716. (b) Patey, G.; De La Baume, S.; Schwartz, J.-C.; Gros, C.; Roques, B.; Fournie-Zaluski, M.-C.; Soroca-Lucas, E. Science **1981**, 212, 1153-1155. (c) Roques, B. P.; Fournie-Zaluski, M. C.; Florentin, D.; Waksman, G.; Sassi, A.; Chaillet, P.; Collado, H.; Costentin, J. Life Sciences **1982**, 31, 1749-1752. (d) Zhang, A.-Z.; Yang, H.-Y. T.; Costa, E. Neuropharmacology **1982**, 21, 625-630. (e) Chaillet, P.; Marcais-Collado, H.; Costentin, J.; Yi, C.-C.; de la Baume, S.; Schwartz, J.-C. Eur. J. Pharmac. **1983**, 86, 329-336.

(4) (a) Chipkin, R. E.; Latranyi, M. Z.; Iorio, L. C.; Barnett, A. Eur. J. Pharmac. **1982**, 83, 283-288. (b) Chipkin, R. E.; Latranyi, M. B.; Iorio, L. C. Life Sciences **1982**, 31, 1189-1192. (c) Greenburg, R.; O'Keefe, E. H.; Life Sciences **1982**, 31, 1185-1188.

(5) Roques, B. B.; Fournie-Zaluski, M. C.; Soroca, E.; Lecomte, J. M.; Malfroy, B.; Llorens, C.; Schwartz, J.-C. Nature **1980**, 288, 286-288.

(6) Scott, W. L.; Mendelsohn, L. G.; Cohen, M. L.; Frederickson, R. C. A.; Evans, D. A. Life Sciences **1984**, manuscript submitted.

(7) For a review of opiate receptors, see: (a) Snyder, S. H.; Pasternak, G. W.; Pert, C. B. in "Handbook of Psychopharmacology," Iversen, L. L.; Iversen, S. D.; Snyder, S. H. Eds.; Plenum Press: New York, 1975; Vol. 5, Ch. 6. (b) Robson, L. E.; Paterson, S. J.; Kosterlitz, H. W. in "Handbook of Psychopharmacology," Iversen, L. L.; Iversen, S. D.; Snyder, S. H. Eds.; Plenum Press: New York, 1983; Vol. 17, Ch 2.

(8) (a) Malfroy, B.; Swertz, J. P.; Llorens, C.; Schwartz, J. C. Neurosci. Lett. **1979**, 11, 329-334. (b) Gorenstein, C.; Snyder, S. H. Proc. R. Soc. London Ser. B **1980**, 210, 123-132.

(9) Horens, C.; Schwartz, J.-C. Eur. J. Pharmacol. **1981**, 69, 113-116.

(10) Pert, C. B.; Snyder, S. H. Proc. Nat. Acad. Sci. (USA) **1973**, 70, 2243-2247. See also ref. 7.

(11) For reviews of NMR imaging techniques, see:(a) Bottomley, P. A. Rev. Sci. Instrum. **1982**, 53, 1319-1337. (b) Hoult, D. I.; Phil, D. in "An Overview of NMR in Medicine"; National Institute of Health: Washington, D. C., 1981.

(12) Holland, G. N.; Bottomley, P. A.; Hinshaw, W. S. J. Mag. Res. **1977**, 28, 133-136.

(13) Evans, D. A.; Mathre, D. J.; Scott, W. L. J. Am. Chem. Soc. submitted. See also Mathre, D. J. Ph.D. Thesis, California

Institute of Technology, 1985, Appendix 2.

(14) Evans, D. A.; Ennis, M. D.; Mathre, D. J. J. Am. Chem. Soc. **1982**, 104, 1737-1739.

(15) Paquette, L. A.; Wittenbrook, L. S.; Schreiber, K. J. Org. Chem. **1968**, 33, 1080-1083.

(16) Maclaren, J. A.; Savige, W. E.; Swan, J. M. Aust. J. Chem. **1958**, 11, 345-359.

17) Shiori, T.; Ninomiya, K.; Yamada, S.-I. J. Am. Chem. Soc. **1972**, 94, 6203-6205.

(18) Berse, C.; Boucher, R.; Piche, L. J. Org. Chem. **1957**, 22, 805.

(19) Fleet, G. W. J.; Knowles, J. R.; Porter, R. R. Biochem. J. **1972**, 128, 499-508.

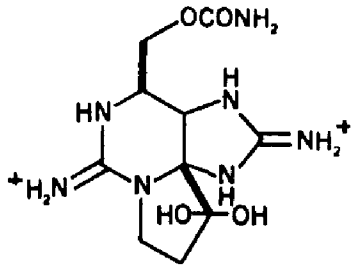
PROPOSITION 3

ABSTRACT. The use of labeled metabolites is proposed to study the biosynthesis of the brevetoxins, an unusual family of polyether marine toxins isolated from the "red tide" dinoflagellate Ptychodiscus brevis Davis.

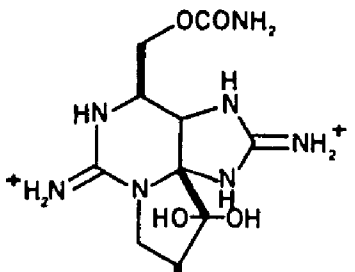
****

The marine phenomenon known as "red tide" is caused by the rapid growth, or bloom, of unicellular dinoflagellate algae. Dinoflagellate blooms by Ptychodiscus brevis Davis (Gymnodium brevis Davis), along the Florida coast and in the Gulf of Mexico, are responsible for massive fish kills, mollusk poisoning, human food poisoning, and human respiratory ailments.[1] Several dinoflagellate toxins have been isolated, including saxitoxin (**1**), gonyautoxin (**2**), and two phosphorus containing molecules **3** and **4**. Recently, three members of an entirely new family of dinoflagellate toxins, the brevetoxins (**5a-c**), have been isolated from P. brevis.[2] Unlike saxitoxin and gonyautoxin, which are water soluble and block the sodium channels, the brevetoxins are lipid-soluble neurotoxins that activate the sodium channels.[1b]

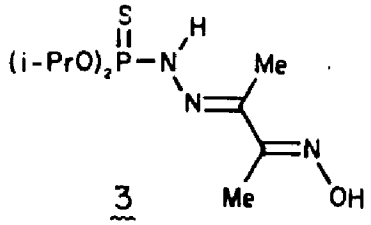
The brevetoxins represent a unique class of natural products. The structure of brevetoxin B (**5b**) was elucidated by X-ray crystallography.[2a] Soon thereafter, the structures of brevetoxins A (**5a**) and C (**5c**) were determined by high field ^{1}H and ^{13}C NMR spectroscopy.[2b, 2c] Structurally, the brevetoxins are characterized by a long carbon chain



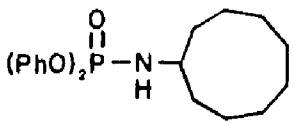
1



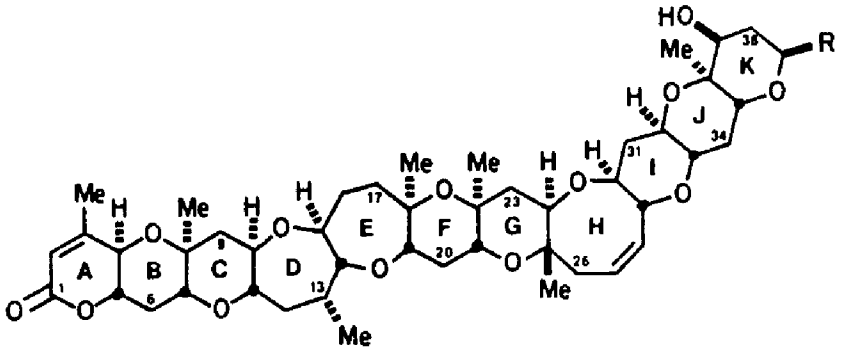
2



3



4



5a, R = CH_2–C(=CH_2)–CH_2OH

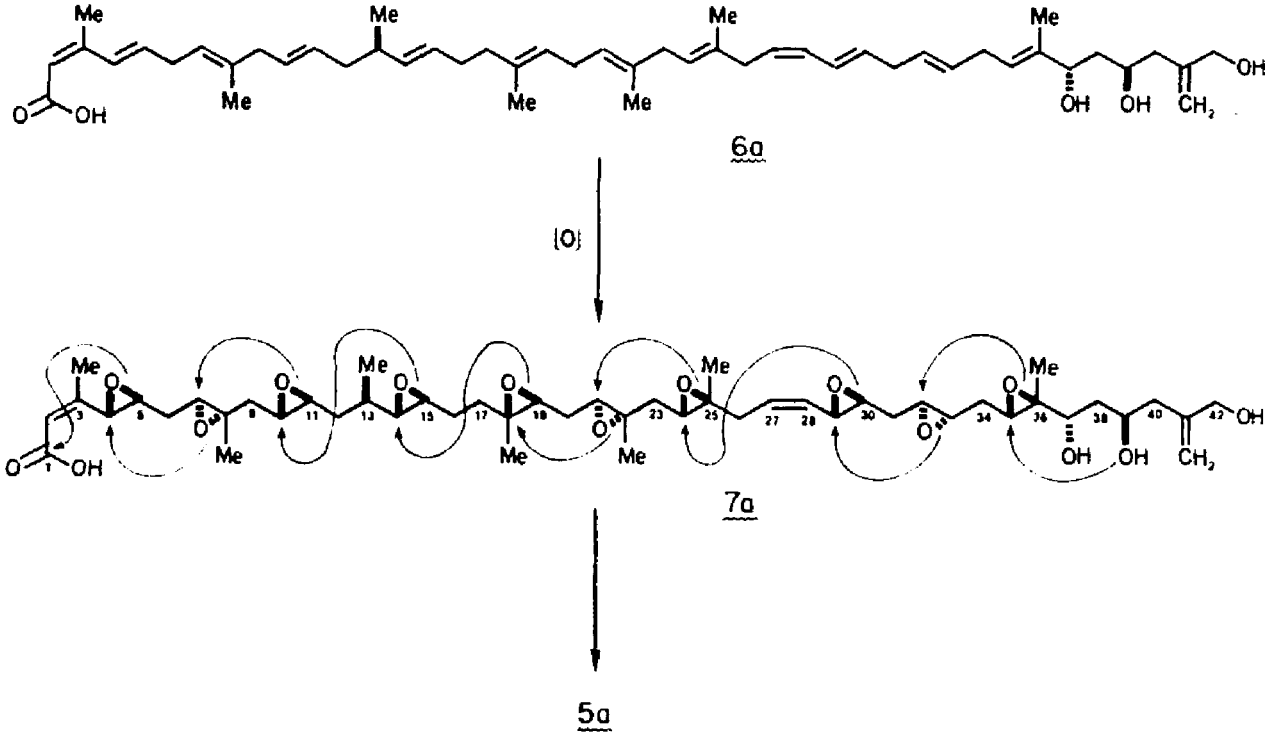
5b, R = CH_2–C(=CH_2)–CHO

5c, R = CH_2–C(=CH_2)–CH_2Cl

Figure 1. Dinoflagellate Toxins

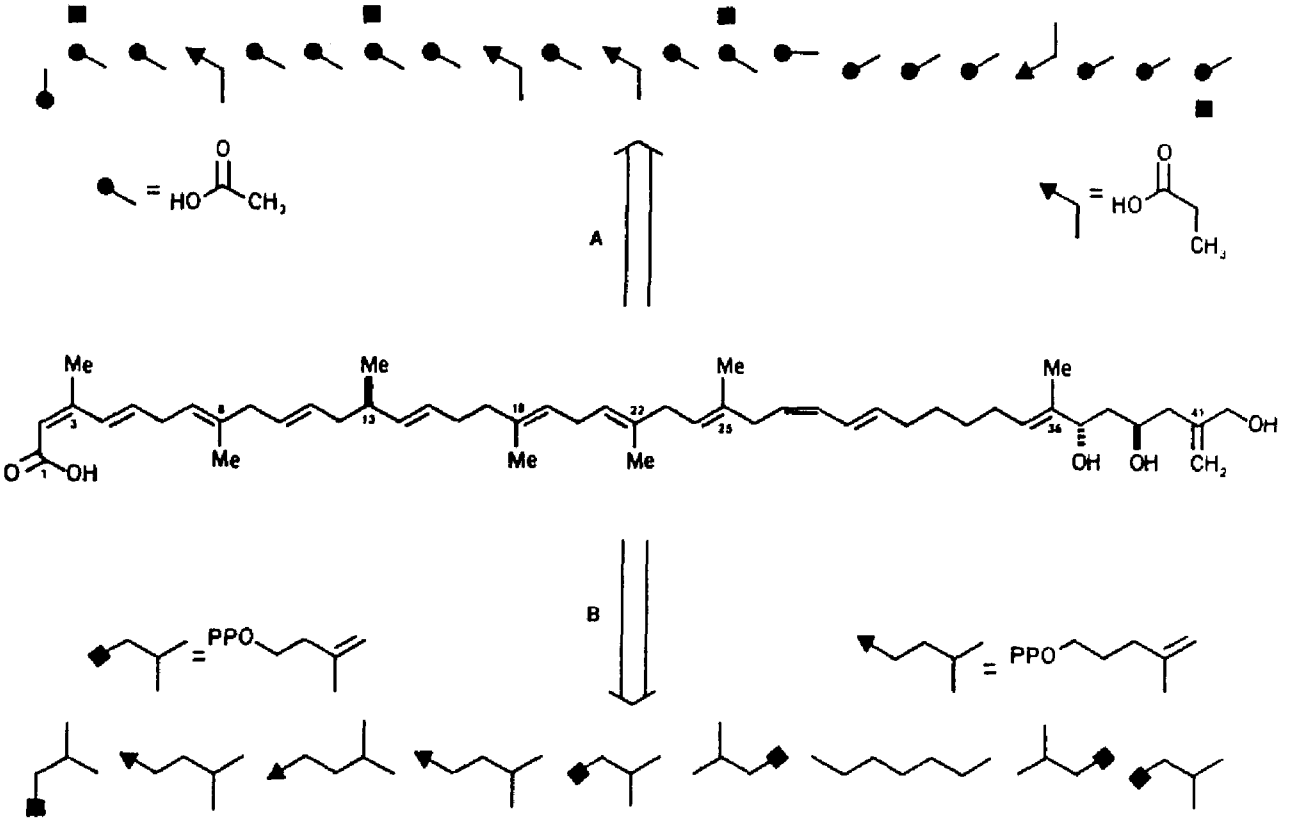
locked into a rigid ladder-like skeleton, consisting of 11 contiguous trans-fused ether rings. Other than their structure and acute toxicity, little is known about these molecules.

A plausible biosynthetic pathway that accounts for the stereochemistry at the numerous oxygen centers in brevetoxin A (**5a**) is illustrated in Scheme 1. The ten di- and trisubstituted (E) olefins of polyene **6a** are stereoselectively epoxidized from the (si,si) face to afford polyepoxide **7a**, which then undergoes a chain of epoxide ring-opening cyclizations to give **5a**. Cane et al. have proposed a similar scheme to account for the stereochemistry of most polyether ionophore antibiotics.[3]



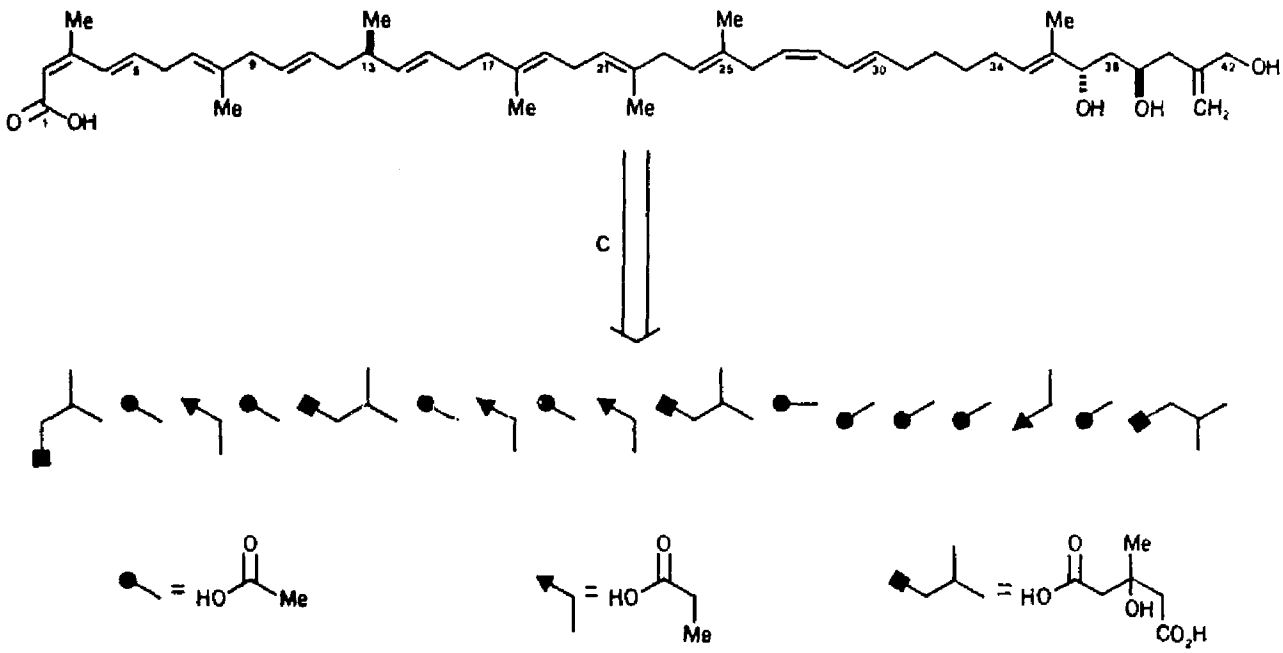
Scheme 1

The biosynthesis of the postulated polyene intermediate **6a**, however, is not immediately obvious. One possibility is that the carbon framework is constructed in a linear manner, analogous to the biosynthesis of fatty acids, from simple acetate and propanoate building blocks (Scheme 2, Path A). The carbon backbone of the polyether ionophore antibiotics is constructed in this fashion.[4] This pathway, however, does not account for the methyl substituents at C-3, C-13, and C-25, nor the methylene substituent at C-41. Presumably, these C_1 substituents could be derived from methionine or malonyl CoA (vide infra). Alternatively, polyene **6a** could be constructed via an isoprene pathway (Scheme



Scheme 2

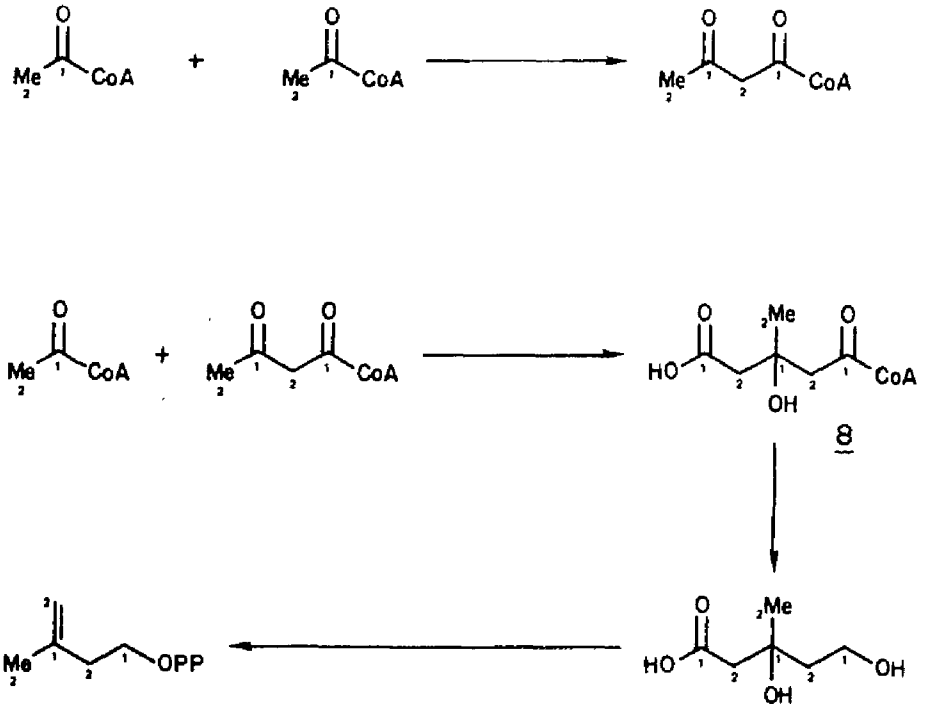
2, Path B). This pathway, however, would require the incorporation of three unusual C_6 isoprene homologs.[5] A third possibility, related to the first, is a linear polyketide synthesis from acetate, propanoate, and 3-hydroxy-3-methylpentan-1,5-dioate **8** building blocks (Scheme 3, Path C).



Scheme 3

I propose to use labeled metabolites to differentiate between the three biosynthetic pathways leading to polyene **6a**. Cultures of *P. brevis* would be grown in the presence of various ^{13}C labeled precursors, and the resultant brevetoxins isolated according to the reported procedure.[2] The incorporation of the labeled precursors would then be determined by ^{13}C NMR spectroscopy.

Initially, the incorporation of [1-^{13}C]- and [2-^{13}C]acetate would be evaluated. The specific positions predicted to be enriched by incorporation of various labeled precursors are shown in Table 1 (X = enrichment, 0 = no enrichment, U = unknown). The transformation of labeled acetate to isopentenyl pyrophosphate and 3-hydroxy-3-methylpentan-1,5-dioate (**8**), required for Paths B and C, respectively, is illustrated in Scheme 4. By examining the enrichment, or lack thereof, at C-20, C-23, C-37, C-38, C-22(Me), and C-36(Me), by incorporation of [1-^{13}C]- and [2-^{13}C]acetate, it would be possible to differentiate Paths A and C from Path B. Confirmation of Paths A and C would be provided by evaluating the incorporation of [3-^{13}C]propanoate at C-8(Me), C-18(Me), C-22(Me), and C-36(Me). Path B would be confirmed by evaluating the incorporation of [5-^{13}C]melvalonate at C-1, C-20, C-27, C-38, and C-39.



Scheme 4

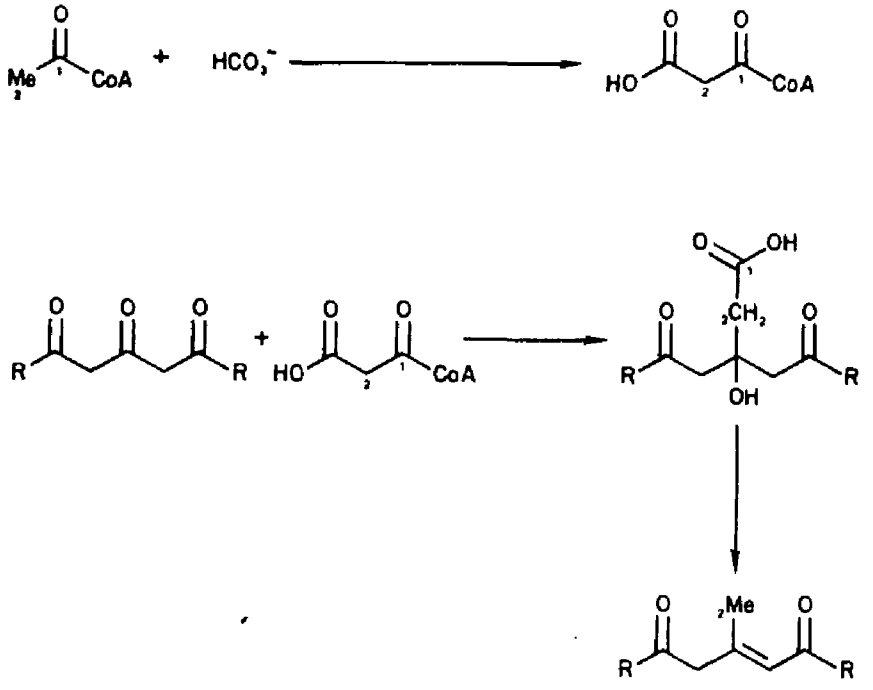
Table 1. Predicted Enrichment Pattern for Incorporation of ^{13}C Labeled Precursors.

Carbon/ Path	[1-^{13}C]-acetate			[2-^{13}C]-acetate			[3-^{13}C]-propanoate			[5-^{13}C]-melvalonate			[^{13}C]-methionine		[2-^{13}C]-acetate		[3-^{13}C]-serine		[^{13}C]-B	
	A	B	C	A	B	C	A	B	C	A	B	C	A1	A2	A2	C	A2	C	B	C
C-1	X	X	X	O	O	O	O	O	O	O	X	O	O	O					X	X
C-2	O	O	O	X	X	X	O	O	O	O	O	O	O	O					X	X
C-3	X	X	X	O	O	O	O	O	O	O	O	O	O	O					X	X
C-4	O	O	O	X	X	X	O	O	O	O	O	O	O	O					X	X
C-5	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	O
C-6	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	O
C-7	U	U	U	U	U	U	O	O	O	O	O	O	O	O					U	O
C-8	U	U	U	U	U	U	O	O	O	O	O	O	O	O					U	O
C-9	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	O
C-10	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	O
C-11	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	X
C-12	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	X
C-13	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	X
C-14	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	X
C-15	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	O
C-16	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	O
C-17	U	U	U	U	U	U	O	O	O	O	O	O	O	O					U	O
C-18	U	U	U	U	U	U	O	O	O	O	O	O	O	O					U	O
C-19	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	O
C-20	O	X	O	X	O	X	O	O	O	O	X	O	O	O					X	O
C-21	U	O	U	U	X	U	O	O	O	O	O	O	O	O					X	O
C-22	U	X	U	U	O	U	O	O	O	O	O	O	O	O					X	O
C-23	X	O	X	O	X	O	O	O	O	O	O	O	O	O					X	X
C-24	O	O	O	X	X	X	O	O	O	O	O	O	O	O					X	X
C-25	X	X	X	O	O	O	O	O	O	O	O	O	O	O					X	X
C-26	O	O	O	X	X	X	O	O	O	O	O	O	O	O					X	X
C-27	X	X	X	O	O	O	O	O	O	O	X	O	O	O					X	O
C-28	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	O
C-29	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	O
C-30	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	O
C-31	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	O
C-32	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	O
C-33	X	U	X	O	U	O	O	O	O	O	O	O	O	O					U	O
C-34	O	U	O	X	U	X	O	O	O	O	O	O	O	O					U	O
C-35	U	O	U	U	X	U	O	O	O	O	O	O	O	O					X	O
C-36	U	X	U	U	O	U	O	O	O	O	O	O	O	O					X	O
C-37	X	O	X	O	X	O	O	O	O	O	O	O	O	O					X	O
C-38	O	X	O	X	O	X	O	O	O	O	X	O	O	O					X	O
C-39	X	X	X	O	O	O	O	O	O	O	X	O	O	O					X	X
C-40	O	O	O	X	X	X	O	O	O	O	O	O	O	O					X	X
C-41	X	X	X	O	O	O	O	O	O	O	O	O	O	O					X	X
C-42	O	O	O	X	X	X	O	O	O	O	O	O	O	O					X	X
C-3(Me)	U	O	U	U	X	X	O	O	O	O	O	O	X	O	X	X	X	O	X	X
C-8(Me)	U	O	U	U	U	U	X	O	X	O	O	O	O	O	O	O	O	O	U	O
C-13(Me)	U	O	U	U	U	X	O	O	O	O	O	O	X	O	X	X	X	O	U	X
C-18(Me)	U	O	U	U	U	O	X	O	X	O	O	O	O	O	O	O	O	O	U	O
C-22(Me)	U	O	U	U	X	O	X	O	X	O	O	O	O	O	O	O	O	O	X	O
C-25(Me)	U	O	U	U	X	X	O	O	O	O	O	O	X	O	X	X	X	O	X	X
C-36(Me)	U	O	U	U	X	O	X	O	X	O	O	O	O	O	O	O	O	O	U	O
C-41(CH_2)	U	O	U	U	X	X	O	O	O	O	O	O	X	O	X	X	X	O	X	X

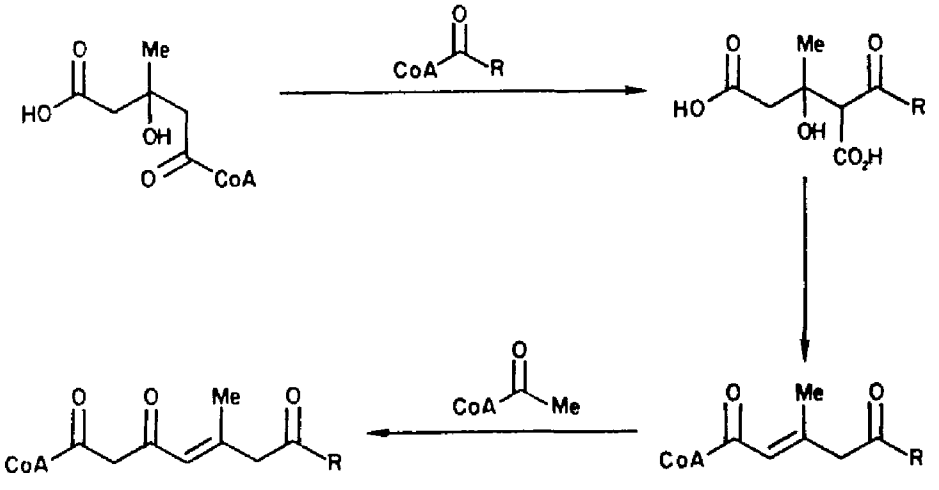
A distinction between Paths A1, A2, and C could be made by determining the source of the C_1 substituents at C-3, C-13, C-25, and C-41. In Paths A1 and A2 they are introduced by methylation of the polyketide chain, whereas in Path C they are incorporated as part of the polyketide chain. The source of the methyl groups in Path A1 is methionine. Therefore, Path A1 can be differentiated from Paths A2 and C by evaluating the incorporation of [^{13}C]methionine.

Recently, while investigating the biosynthesis of virginiamycin, Kingston et al. uncovered a new polyketide methylation reaction.[6] As illustrated in Scheme 5, the methyl group of acetate (*via* malonyl CoA) provides the source of the new carbon atom. Unfortunately, the incorporation of [2-^{13}C]acetate would not distinguish between Paths A2 and C. The two pathways, however, could be differentiated by using [3-^{13}C]serine as a delayed source of [2-^{13}C]acetate. In Path A2, the C-3, C-13, C-25, and C-41 substituents are introduced after the polyketide chain is formed,and therefore, with a delayed source of [2-^{13}C]acetate, would be expected to be enriched to a greater extent than the polyketide chain.

In conclusion, it is necessary to comment about Path C. Rather than only incorporating acetate and propanoate building blocks, 3-hydroxy-3-methylpentan-1,5-dioate (**8**) (or an equivalent) is introduced into the polyketide chain. This process is illustrated in Scheme 6. The incorporation of fully labeled **8** as indicated in Table 1 would be evaluated to confirm this possibility.



Scheme 5



Scheme 6

REFERENCES

(1) (a) Shimizu, Y. in "Marine Natural Products, Volume 1," Scheuer, P. J. Ed.; Academic Press: New York, 1978; pp 1-47. (b) Taylor, D. L.; Seliger, H. H., Eds. in "Toxic Dinoflagellate Blooms;" Elsevier: North Holland, New York, 1979.

(2) (a) Lin, Y. Y.; Risk, M.; Ray, S. M.; Van Egen, P.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. J. Am. Chem. Soc. **1981**, 103, 6773-6775. (b) Golik, J.; James, J. C.; Nakanishi, K. Tetrahedron Lett. **1982**, 23, 2535-2538. (c) Chou, H.-N.; Shimizu, Y. Tetrahedron Lett. **1982**, 23, 5521-5524.

(3) Cane, D. E.; Celmer, W. D.; Westley, J. W. J. Am. Chem. Soc. **1983**, 105, 3594-3600.

(4) (a) Westley, J. W. in "Antibiotics, Volume 4;" Corcoran, J. W. Ed.; Springer-Verlag: Berlin, 1981; pp 41-73. (b) Hutchinson, C. R. Acc. Chem. Res. **1983**, 16, 7-14.

(5) Koyama, T.; Katsuki, Y.; Oyura, K. Bioorg. Chem. **1983**, 12, 58-70, and references contained therein.

(6) Kingston, D. G. I.; Kolpak, M. X.; LeFevre, J. W.; Borup-Grochtmann, I. J. Am. Chem. Soc. **1983**, 105, 5106-5110.

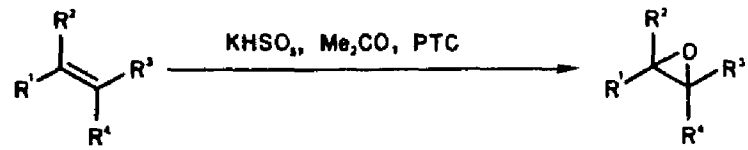
PROPOSITION 4

ABSTRACT. The use of a labeled precursor is proposed to determine whether the epoxidation of 5-hexen-2-one with potassium peroxymonosulfate is inter- or intramolecular. If the reaction is shown to be intramolecular, experiments are proposed to investigate internal asymmetric induction in the peroxymonosulfate epoxidation of chiral 1,5- and 1,6-enones.

****

The stereoselective generation of carbon-oxygen bonds is an important aspect in the construction of poly-hydroxylated natural products. A variety of procedures to accomplish this goal have been reported.[1] Significant among these are the stereoselective epoxidation of chiral allylic,[2] homoallylic,[3] and bishomoallylic alcohols,[4] as well as the asymmetric alkylation of prochiral allylic alcohols.[5] The overall utility of these epoxidation procedures has been demonstrated by their use in numerous synthetic projects.

Recently, potassium peroxymonosulfate ($KHSO_5$), in the presence of acetone and under neutral conditions, has been shown to epoxidize a wide variety of olefins (Scheme 1).[6] The peroxymonosulfate--acetone system is both highly reactive and stereoselective. For example, (E)-cinnamic acid, a substrate not epoxidized by either alkaline hydrogen peroxide or m-chloroperbenzoic acid, reacts with potassium peroxymonosulfate in the presence of acetone to afford the trans epoxide. The reaction condi-

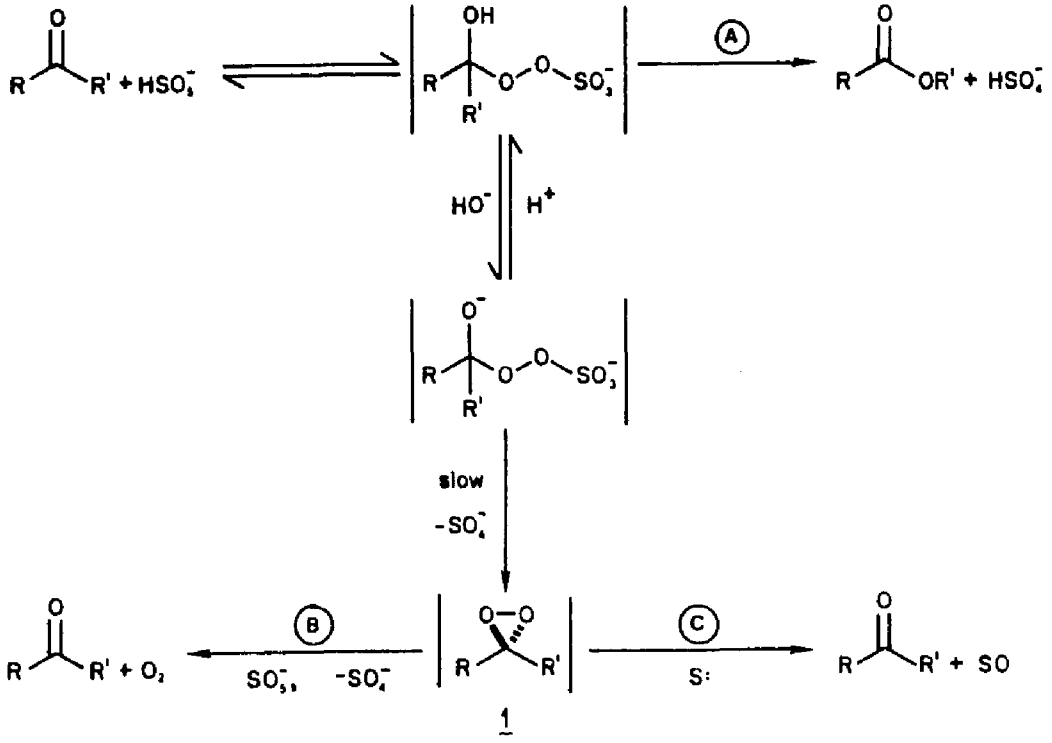


R^1	R^2	R^3	R^4	YIELD
Ph	H	H	CO_2H	95%
Ph	H	CO_2H	H	>90%
H	$-(CH_2)_4-$		H	98%
H	$-(CH_2)_{10}-$		H	85%
n-C_8H_{17}	H	H	H	72%

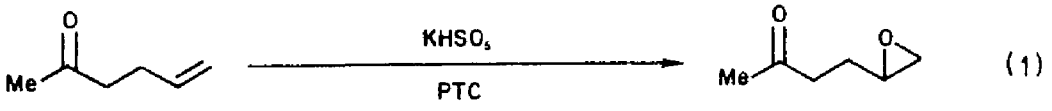
Scheme 1

tions are both mild (pH = 7-8, 2-10°C) and versatile. Water soluble olefins are epoxidized in aqueous solution; non-aqueous soluble olefins are epoxidized under biphasic conditions via phase transfer catalysis (PTC). In the absence of a ketone, potassium peroxymonosulfate does not react with olefins. Kinetic experiments suggest that dioxirane 1 is the reactive intermediate responsible for peroxymonosulfate epoxidations, and that the ketone merely acts to catalyze the process (Scheme 2).[7]

The epoxidation of 5-hexen-2-one with potassium peroxymonosulfate does not require acetone (Eq 1).[6] Presumably, the ketone present within this substrate is sufficient to catalyze the reaction. It is not known, however, whether the oxygen is transferred inter- or intramolecularally. The use of an [^{18}O]-labeled substrate is proposed to answer this question. A study would then be undertaken to determine both the minimum and the optimum number of connective atoms between ketone and olefin necessary for intramolecular oxygen transfer.[8] If the reaction is shown to be intramolecular, it would be interesting to investigate the potential for generating epoxide stereochemistry by relative asymmetric induction.[9]

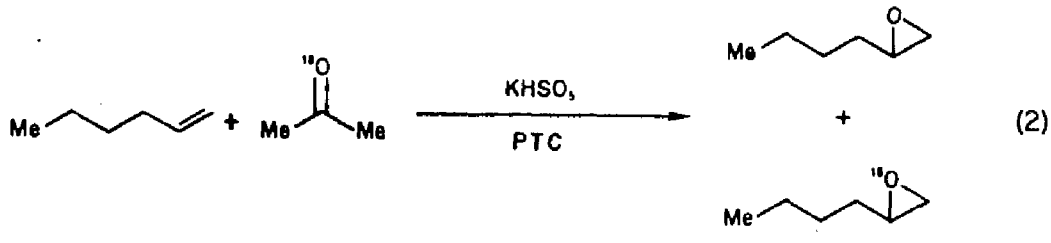

R
R' + HSO5-
OH
R'
O
O
SO3-
A
OR' + HSO4-
HO-
H+
slow
-SO4-
B
SO5-, -SO4-
C
S:
R' + O2
R' + SO
1

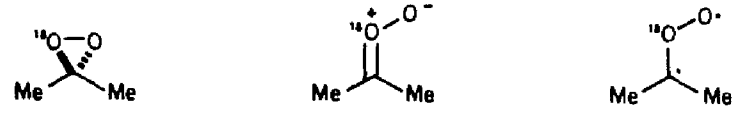
Scheme 2


Me
KHSO5
PTC
Me

(1)

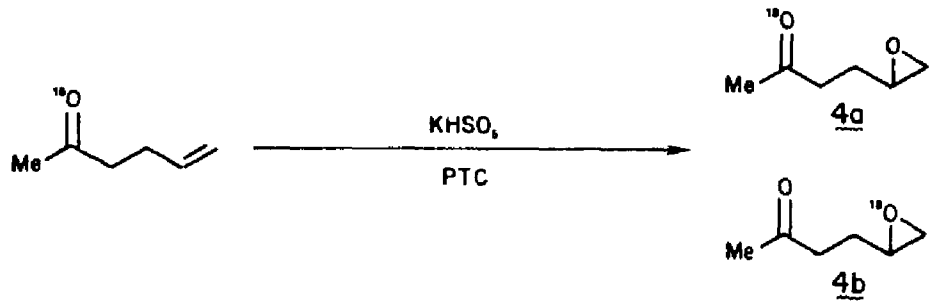
Initially, an experiment would be performed to demonstrate that acetone catalyzed peroxymonosulfate epoxidations proceed via a dioxirane intermediate. Assuming a negligible isotope effect, either of the oxygen atoms of dioxirane 1 could be incorporated into the olefin. Therefore, treatment of 1-hexene with potassium peroxymonosulfate in the presence of [^{18}O]acetone should afford a 1:1 mixture of labeled to unlabeled 1,2-epoxyhexane (Eq 2). Two alternate reactive intermediates, the carbonyl oxide **2** or the methylene peroxide biradical **3**, would give only unlabeled epoxide.[6]



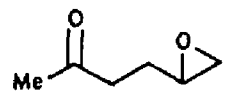


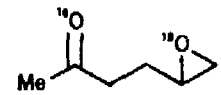
1 2 3

The epoxidation of [^{18}O]-5-hexen-2-one with potassium peroxymonosulfate, in the absence of acetone, would be investigated to determine whether the oxygen is transferred inter or intramolecularally (Eq 3). The intramolecular transfer of oxygen would afford a 1:1 mixture of **4a** to **4b**. The intermolecular transfer of oxygen, in addition to **4a** and **4b**, would afford **4c** and **4d**. The presence of **4c** and **4d** could readily be determined by mass spectrometry.



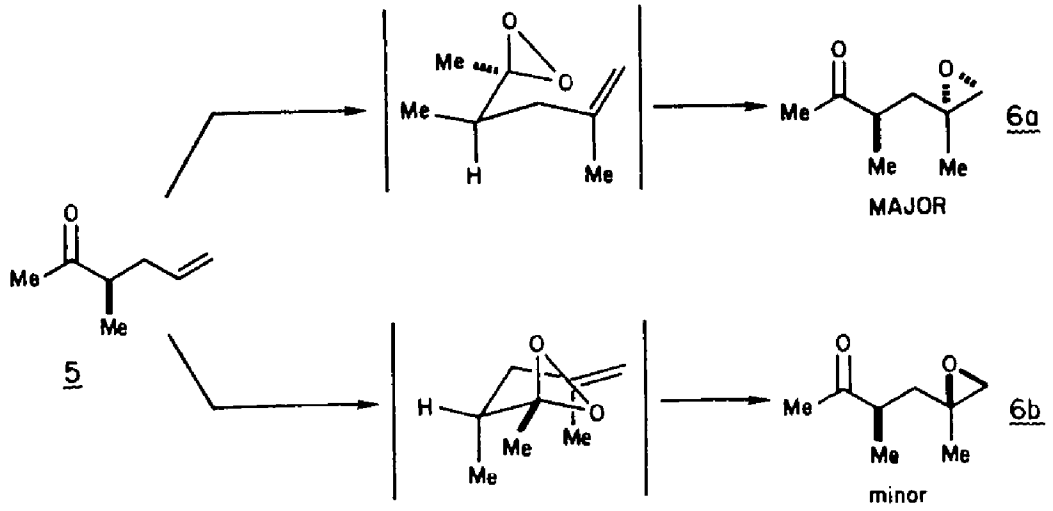
(3)



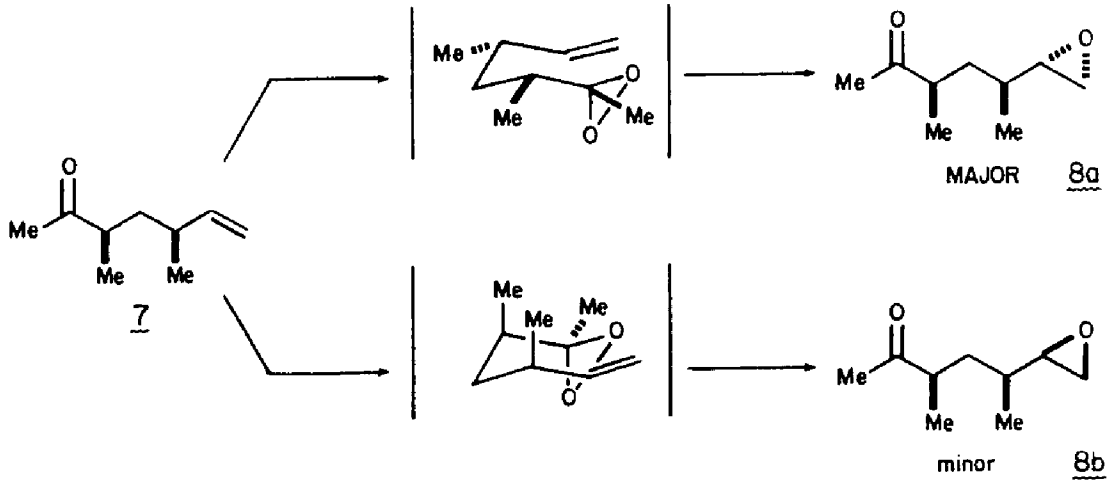


If the epoxidation of 5-hexen-2-one is shown to proceed via an intramolecular oxygen transfer, it would be interesting to investigate the potential for internal asymmetric induction. The epoxidation of (3R)-3,5-dimethyl-5-hexen-2-one (**5**) with potassium peroxymonosulfate can afford two diastereomeric epoxides **6a** and **6b** (Scheme 3). The transition state leading to **6b** would be destabilized in respect to the transition state leading to **6a** due to an unfavorable 1,3 diaxial methyl-methyl interaction. Therefore, **6a** is predicted to be the major epoxide diastereomer.

Likewise, the epoxidation of (3R,5S)-3,5-dimethyl-6-hepten-2-one (**7**) with potassium peroxymonosulfate can afford two diastereomeric epoxides **8a** and **8b** (Scheme 4). The transition state leading to **8b** would be destabilized with respect to the transition state leading to **8a** due to an unfavorable 1,3 diaxial methyl-methyl interaction. Therefore, **8a** is predicted to be the major epoxide diastereomer.

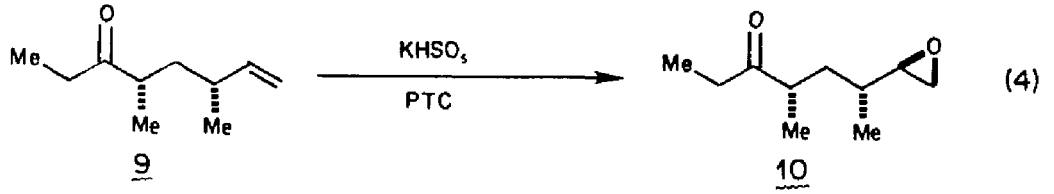


Scheme 3



Scheme 4

By analogy to the epoxidation of **7**, the epoxidation of (4S,6R)-4,6-dimethyl-7-octen-3-one (**9**) with potassium peroxymonosulfate should preferentially afford epoxide **10** (Eq 4). Treatment of **10** with tin tetrachloride previously has been shown to afford α-multistriatin (**11**), a component of the European elm bark beetle aggregation pheromone (Eq 5).



9 10 (4)

10 11 (5)

NOTES AND REFERENCES.

(1) For a review of asymmetric synthesis, see: Morrison, J. D.; Mosher, H. S. in "Asymmetric Organic Reactions;" American Chemical Society: Washington, D. C., 1976.

(2) Peroxy-acid epoxidations: (a) Johnson, M. R.; Nakata, T.; Kishi, Y. Tetrahedron Lett. 1979, 4343-4346. (b) Johnson, M. R.; Kishi, Y. Tetrahedron Lett. **1979**, 4347-4350. (c) Hasan, I.; Kishi, Y. Tetrahedron Lett. 1980, 21, 4229-4232. Vanadium catalyzed t-butylhydroperoxide epoxidations: (d) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. J. Am. Chem. Soc. **1974**, 96, 5254. (e) Rossiter, B. E.; Verhoven, T. R.; Sharpless, K. B. Tetrahedron Lett. **1979**, 4733-4737. (f) Mihelich, E. D. Tetrahedron Lett. **1979**, 4729-4732.

(3) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. J. Am. Chem. Soc. **1981**, 103, 7690-7692.

(4) (a) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. Tetrahedron Lett. **1978**, 2741-2744. (b) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. J. Am. Chem. Soc. **1978**, 100, 2933-2935.

(5) (a) Katsuki, T.; Sharpless, K. B.; J. Am. Chem. Soc. **1980**, 102, 5974-5976. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. J. Am. Chem. Soc. **1981**, 103, 464-465.

(6) (a) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. Photochem. Photobiol. **1979**, 30, 63-70. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. J. Org. Chem. **1980**, 45, 4758-4760. (c) Cicala, G.; Curci, R.; Fiorentino, M.; Larichiuta, O. J. Org. Chem. **1982**, 47, 2670-2673. (d) Curci, R.; Fiorentino,

M.; Serio, M. R. J. Chem. Soc. Chem. Commun. **1984**, 155-156.

(7) Gallopo, A. R.; Edwards, J. O. J. Org. Chem. **1981**, 46, 1684-1688.

(8) The intramolecular epoxidation of peroxyarachidonic acid involves a 16 1/2-membered transition state: Corey, E. J.; Niwa, H.; Falck, J. R. J. Am. Chem. Soc. **1979**, 101, 1586. Rebek, however, has shown that a peroxyketal-$(CH_2)_n$-olefin undergo intramolecular epoxidation when $n \geq 2$: Rebek, Jr., J. Heterocycles **1981**, 15, 517.

(9) For a review of relative asymmetric induction, see: Bartlett, P. A. Tetrahedron **1980**, 35, 3-72.

(10) (a) Gore, W. E.; Pearce, G. T.; Silverstein, R. M. J. Org. Chem. **1976**, 41, 2797. (b) Cernigliaro, G. J.; Kocienski, P. J. J. Org. Chem. **1977**, 42, 3622. (c) Bartlett, P. A.; Myerson, J. J. Org. Chem. **1979**, 44, 1625. For other routes to α-multistriatin, see Ref. 9.

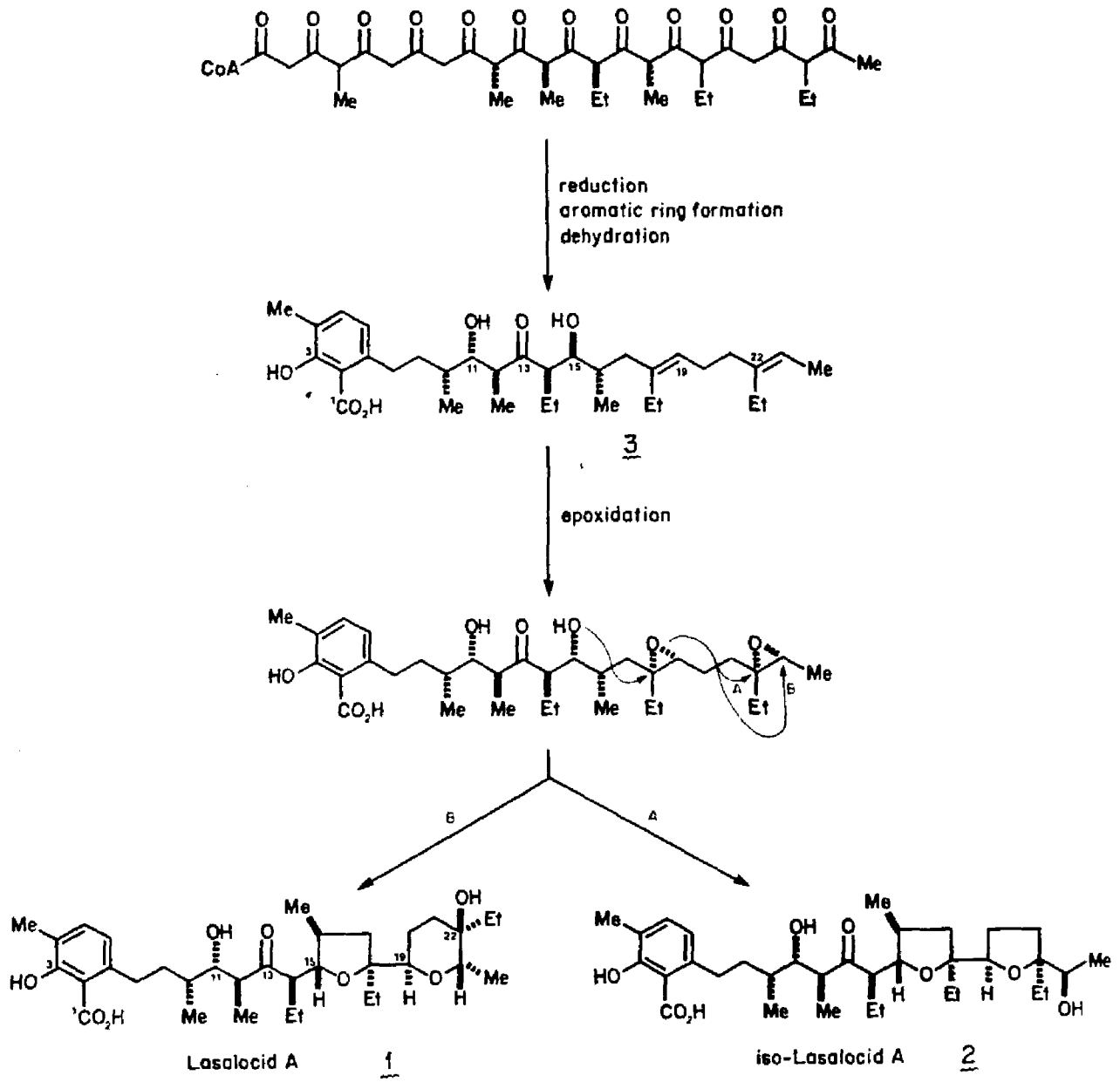
PROPOSITION 5

ABSTRACT. Experiments are proposed to investigate the epoxidation step in the biosynthesis of polyether ionophore antibiotics.

****

Most investigations into the biosynthesis of polyether ionophore antibiotics have focused on establishing the identity and location of precursor incorporation.[1] This is routinely accomplished by feeding antibiotic-producing cultures various labeled precursors and analyzing the incorporation pattern in the resultant antibiotic.[2] Numerous studies of this type have shown that polyether ionophores are derived from simple acetate, propanoate, and butanoate building blocks. Therefore, the biosynthesis of this family of natural products is thought to proceed *via* a polyketide pathway, in a manner analogous to fatty acid biosynthesis. Less, however, is known about the steps involved in transforming the polyketide intermediate to the polyether ionophore antibiotic--especially those steps responsible for generating the numerous stereocenters.[1c]

Based on the isolation of lasalocid A (**1**) and isolasalocid (**2**) from the same fermentation broth, Westley has proposed a biochemical pathway whereby both molecules are derived from a common precursor.[3] According to his hypothesis, illustrated in Scheme 1, the polyketide backbone is constructed and transformed into diene **3**.[4] Stereoselective diepoxidation followed by acid catalyzed cyclization then affords either **1** or **2**.

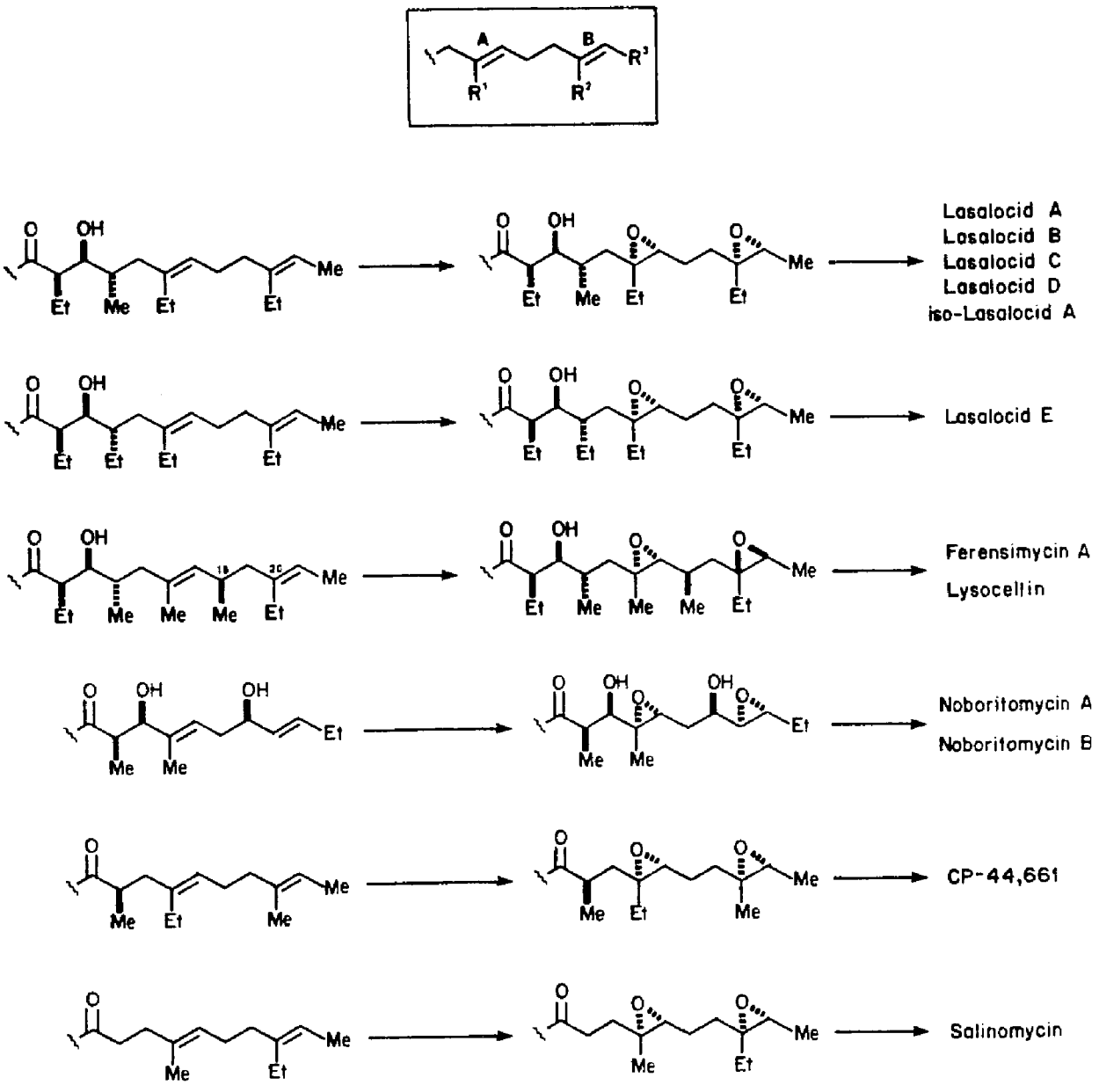

reduction
aromatic ring formation
dehydration
3
epoxidation
B
A
Lasalocid A 1
iso-Lasalocid A 2

Scheme 1

Support for this proposal is provided by Hutchinson, who, by feeding double labeled $R^{13}C^{18}O_2H$ precursors to Streptomyces lasaliensis, has shown that ^{18}O is introduced at C-1, C-3, C-11, C-13, and C-15, but not at C-19 or C-22.[5] The absence of labeled oxygen at C-19 and C-22 is the result predicted assuming a diene--diepoxide pathway. Presumably, the oxygen at these two positions is obtained from molecular oxygen.[6] The same diene--diepoxide or an analogous triene--triepoxide pathway has been proposed by Cane et al. as the final step in biosynthesis of over 30 polyether ionophore antibiotics.[1d]

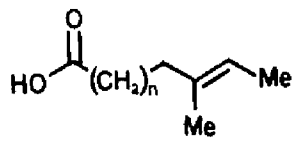
One method of investigating the epoxidation step in polyether ionophore biosynthesis is to feed the antibiotic-producing organism labeled diene or triene precursor. The isolation of labeled antibiotic would provide further conformation of this pathway.[7] Alternatively, the epoxidation of simple olefinic substrates by polyether ionophore-producing organisms could be investigated.

An examination of the proposed diene and diepoxide intermediates, illustrated in Scheme 2, indicates a high degree of stereochemical homology.[1d] Other than the Δ(20-21) double bond in the intermediate leading to ferensimycin A and lysocellin, all of the olefins are epoxidized from the (re,re) face of the double bond. Presumably, the same--or a very similar--epoxidase is responsible for these stereoselective epoxidations.[8] It would be interesting to investigate whether the bacteria responsible for the synthesis of these polyether ionophores are capable of stereoselectively epoxidizing simple olefinic substrates.

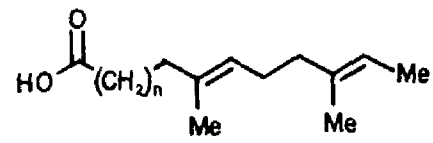

A
B
R³
R¹
R²
Me
Et
OH
O
Lasalocid A
Lasalocid B
Lasalocid C
Lasalocid D
iso-Lasalocid A
Lasalocid E
Ferensimycin A
Lysocellin
Noboritomycin A
Noboritomycin B
CP-44,661
Salinomycin

Scheme 2

Initial experiments would involve feeding ^{14}C labeled olefins, such as **4** and **5**, to a salinomycin producing culture, and assaying the fermentation broth for labeled products. The resultant labeled products would be analyzed to determine whether the substrate is epoxidized or degraded. By using substrates lacking a hydroxyl substituent it may be possible to isolate the resultant mono- or diepoxide. Information concerning the recognition requirements of the epoxidase would be gained by varying the chain length of **4** and **5**.

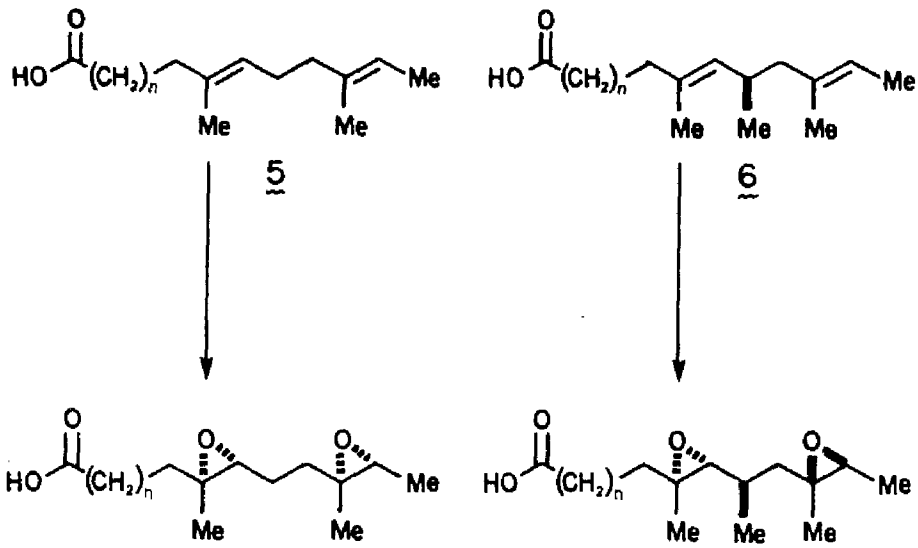


4



5

Contingent on the previous experiments being successful, a further set of experiments would be conducted to investigate the reversal in epoxidation stereochemistry in the case of ferensimycin A and lysocellin. A comparison of the structures of the diene precursors in Scheme 2 suggests that the C-18 methyl substituent may be responsible for the reversal in epoxidation stereochemistry. If this is the case, then feeding diene **5** and **6** to a lysocellin producing culture should afford diastereomeric diepoxides (Scheme 3).



Scheme 3

If polyether ionophore producing organisms are shown to stereoselectively epoxidize simple olefinic substrates, work would be directed at isolating the epoxidase system.[9] The stereoselective epoxidation of simple di- and trisubstituted (E) olefins to give products of high enantiomeric purity is generally difficult to accomplish.[10] Therefore, the isolation of an enantioselective epoxidase for di- and trisubstituted (E) olefins could be synthetically useful.

NOTES AND REFERENCES:

(1) For recent reviews of polyether ionophore biosynthesis, see: (a) Westley, J. W. in "Antibiotics," Corcoran, J. W. Ed.; Springer-Verlag: Berlin, 1981; Vol. 4, pp. 41-73. (b) Liu, C.-M. in "Polyether Antibiotics;" Westley, J. W. Ed.; Marcel Dekker, Inc.: New York, 1982; Vol. 1, Chapter 3. (c) Hutchinson, C. R. Acc. Chem. Res. **1983**, 16, 7-14. (d) Cane, D. E.; Celmer, W. D.; Westley, J. W. J. Am. Chem. Soc. **1983**, 105, 3594-3600.

(2) For relevant examples, see:(a) Westley, J. W.; Evans, R. H.; Harvey, G.; Pitcher, R. G.; Pruess, D. L.; Stempel, A.; Berger, J. J. Antibiot. **1974**, 27, 288-297. (b) Otake, N.; Seto, H.; Koenuma, M. Agric. Biol. Chem. **1978**, 42, 1879-1886. (c) Cane, D. E.; Liang, T. C.; Hasler, H. J. Am. Chem. Soc. **1981**, 103, 5962-5965.

(3) (a) Westley, J. W.; Blount, J. F.; Evans, R. H.; Stempel, A.; Berger, J. J. Antibiot. **1974**, 27, 597. (b) Westley, J. W.; Benz, W.; Donahue, J.; Evans, R. H.; Scott, C. G.; Stempel, A.; Berger, H. J. Antibiot. **1974**, 27, 744.

(4) It is not clear whether the polyketide chain is constructed then transformed via a reduction and dehydration sequence as shown in Scheme 1, or if the reduction and dehydration steps are performed as each acetate, propanoate, or butanoate segment is coupled to the carbon framework.

(5) Hutchinson, C. R.; Sherman, M. M.; Vederas, J. C.; Nakashima, T. T. J. Am. Chem. Soc. **1981**, 103, 5953-5956.

(6) In related studies, both Cane and Ajaz have shown that labeled molecular oxygen (^{18}O) is incorporated by Streptomyces cinnamonesis during the biosynthesis of monensin A at the positions corresponding to a triene--triepoxide pathway: (a) Ref. 2c. (b) Ajaz, A. A.; Robinson, J. A. J. Chem. Soc., Chem. Commun. **1983**, 679-680.

(7) An enantioselective total synthesis of the triene precursor to monensin is currently in progress. The in vivo transformation of this precursor to monensin will be evaluated in collaboration with Professor David Cane: Evans, D. A.; DiMare, M. unpublished results.

(8) Several organisms have been reported that enantioselectively epoxidize terminal olefins: (a) Ishikura, T.; Foster, J. W. Nature (London) **1961**, 192, 892. (b) Klug, M. J.; Markoretz, A. J. J. Bacteriol. **1968**, 96, 1115. (c) May, S. W.; Schwartz, R. D. J. Am. Chem. Soc. **1974**, 96, 4031. (d) May, S. W.; Steltenkamp, M. S.; Schwartz, R. D.; McCoy, C. J. J. Am. Chem. Soc. **1976**, 99, 7856-7858. (e) May, S. W.; Gordan, S. L.; Steltenkamp, M. S. J. Am. Chem. Soc. **1977**, 100, 2017.

(9) For a review of enzymatic epoxidation reactions, see:May, S. W. Enzyme Microb. Technol. **1979**, 1, 15-22.

(10) For the enantioselective epoxidation of allylic alcohols, see:(a) Katsuki, T.; Sharpless, K. B. J. Am. Chem. Soc. **1980**, 102, 5974-5976. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. J. Am. Chem. Soc. **1981**, 103, 464-465.