I. ASYMMETRIC ALKYLATION REACTIONS OF CHIRAL IMIDE ENOLATES

II. EFFORTS DIRECTED TOWARD THE TOTAL SYNTHESIS OF (+)-MACBECIN I

Thesis by

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To My Parents

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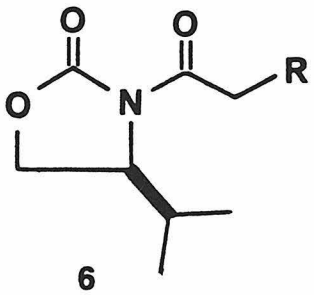
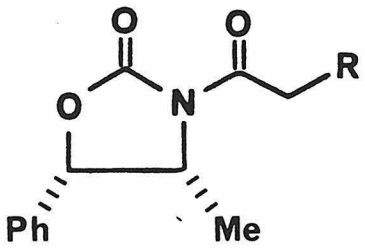
And finally, my heartfelt gratitude goes out to Dorothy Lloyd for her untiring diligence and expertise with regard to the technical preparation of this thesis.

ABSTRACT

The preparation of chiral N-acyl oxazolidones **6** and **7** from readily available amino acid precursors is described. Reaction of the alkali metal enolates derived from these chiral imides with alkyl halides and acid chlorides exhibit high levels of kinetic diastereoselection. Chromatographic enrichment



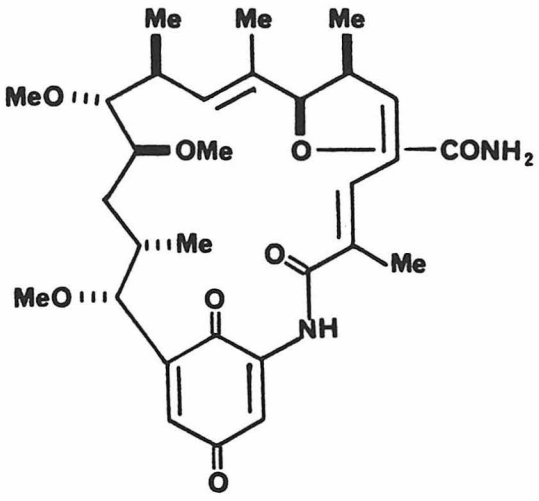
6



7

affords alkylated and acylated products of ≥99:1 diastereomeric purity. Non-destructive cleavage of the chiral auxiliary is accomplished by a variety of means to afford optically active products.

The use of chiral imides **6** and **7** in the synthesis of the ansa-antibiotic macbecin-I (**1**) is described. The synthesis makes use of the iterative application of highly stereoregulated aldol condensations of N-acyl oxazolidones for the construction of the ansa-bridge of **1**. This project has culminated in the preparation of the advanced acyclic intermediate **46**.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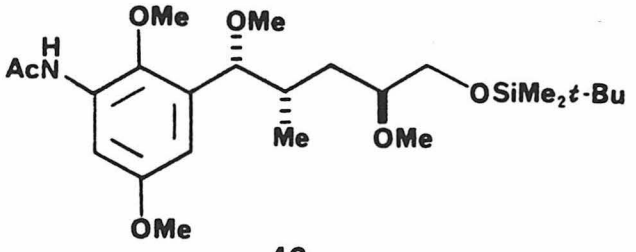
Me
Me
MeO
OMe
O
CONH2
Me
O
Me
MeO
O
NH
O

1


OMe
OMe
H
AcN
OSiMe2t-Bu
Me
OMe
OMe

46

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CHAPTER I

Asymmetric Alkylation Reactions of Chiral Imide Enolates

I. Introduction

The ability to control the stereochemical outcome of a variety of chemical reaction processes is rapidly becoming a necessity for the organic chemist endeavoring to efficiently synthesize those architecturally complex molecules which represent the frontier of modern synthetic organic chemistry.[1] These molecules present a stereochemical complexity as yet unrivaled in the realm of natural products. Given in Figure 1 is a representative sampling of some of these molecules which are of current scientific interest.

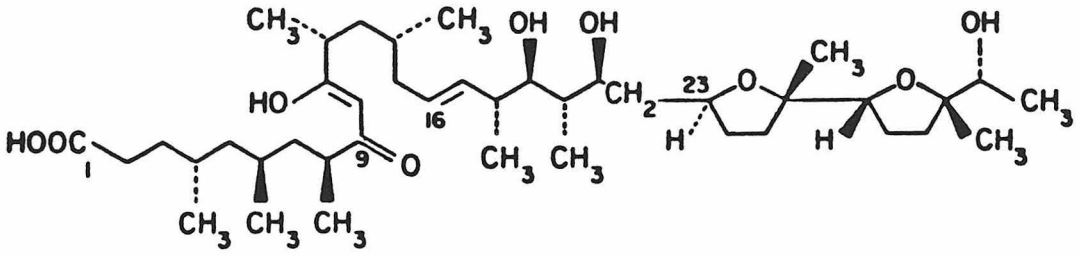
In the past, absolute stereochemical issues in chemical synthesis have typically been resolved in one of three ways:

1) By the use of "cycle-strategies", which take advantage of the well-known chemical biases present in four, five, and six-membered rings;

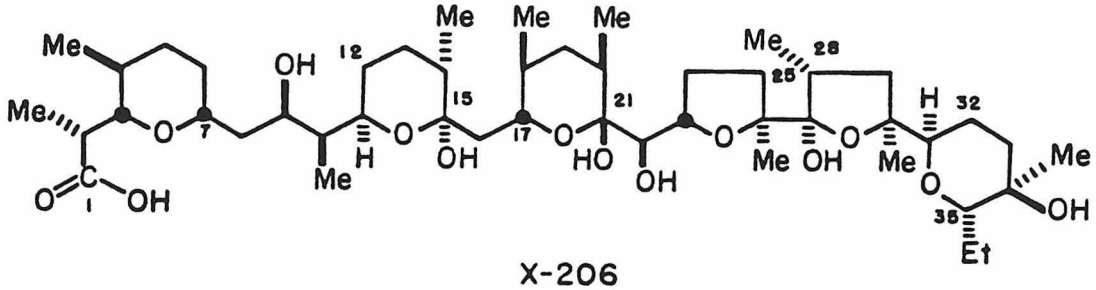
2) By relying upon relative asymmetric induction, whereby a resident chiral center already established in a molecule dictates the stereochemical consequences of chemistry nearby;

3) By tapping nature's "chiral pool" for readily available, optically active starting materials, such as sugars.

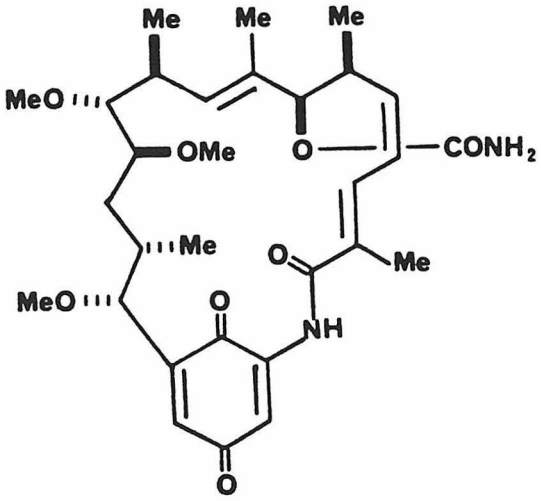
Since most synthetic approaches for the construction of macrolide antibiotics and polyether-based ionophores proceed through some advanced acyclic intermediate laden with pendant chirality,[2] "cycle-strategy" type syntheses



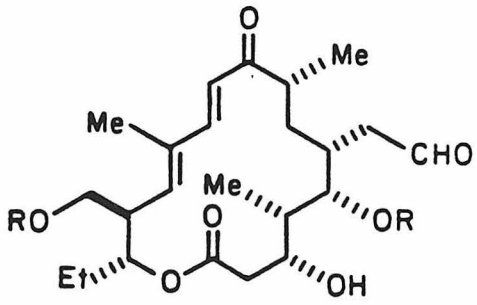
Ionomycin



X-206



Macbecin

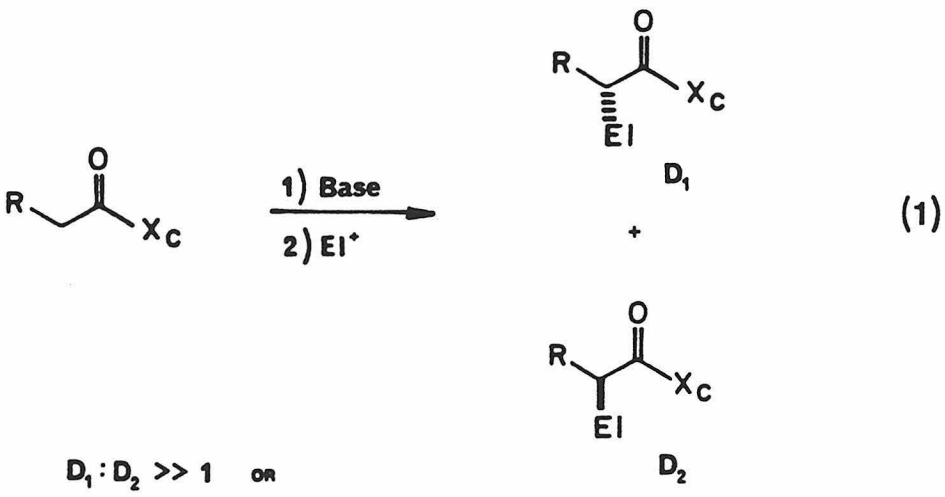


Tylosin

Figure 1

are generally unworkable.[3] Furthermore, the stereochemical richness of these molecules is usually beyond the scope of relative asymmetric induction, although the recent advances in this area by Kishi and co-workers are impressive.[4] However, there are a number of examples of the use of sugars as chiral templates in macrolide synthesis.[5]

We have sought a conceptually different approach to the stereochemical synthesis of large-ring or acyclic natural products. A very efficient method for the construction of these molecules could involve the use of a chiral enolate synthon. Such a synthon could be described as an enolate species bearing a removable chiral auxiliary (X_C) with which an approaching electrophile would react in such a way that the newly formed chiral center is generated in high optical purity (eq. 1). This strategy has received intensive investigation in recent years in a number of laboratories,[6] and has been a primary focus of research efforts in our own group.[7]

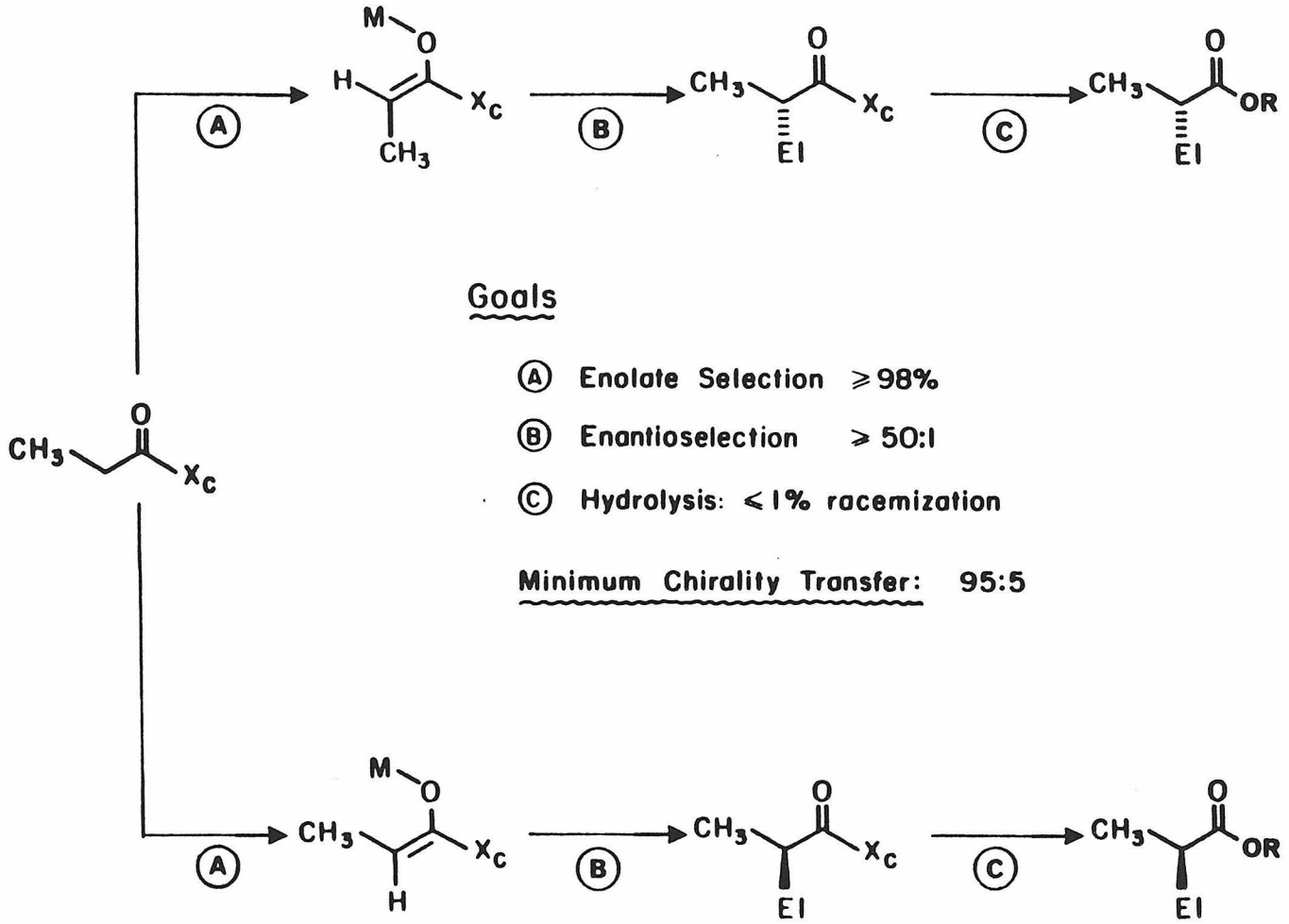


(1)

Inherent in this approach to acyclic stereochemical control are three independent problems of fundamental importance. These problems are outlined in Scheme I. Stereoselective enolization (step A) is a mandatory requirement for any chiral enolate synthon, since enolate geometry is directly transferable to product stereochemistry. Second, the chiral enolate must incorporate in its design sufficient diastereofacial bias so that an electrophile will approach a given face of the enolate system in a highly discriminating manner (step B). Finally, cleavage of the chiral auxiliary (step C) must proceed under sufficiently mild conditions so as to preclude or minimize the amount of racemization in the final product. In order to achieve useful levels of asymmetric induction in this overall process (e.g., $\geq$90% ee), margin for error in each of these individual steps is small indeed.

A consideration of the energetics for the kind of reaction selectivity outlined in Scheme I demonstrates the challenge faced by the organic chemist in designing a highly diastereoselective enolate synthon. Illustrated in Figure 2 is a graphic representation of the difference in transition state free energies ($\Delta\Delta G^{\dagger}$) required for a given ratio of reaction products (D_1 and D_2) from competing similar reactions. As can be seen, energetic demands increase exponentially with increasing reaction selectivity. Thus, for any chiral enolate synthon striving toward a synthetically practical level of stereoselection (e.g., a kinetic diastereoselectivity of $\geq$95:5), design requirements dictate a $\Delta\Delta G^{\dagger}$ of >1 kcal/mol for the competing transition states.

Scheme I


M
O
H
CH3
Xc
A
B
CH3
Xc
El
O
C
CH3
OR
El
Goals
A Enolate Selection ≥ 98%
B Enantioselection ≥ 50:1
C Hydrolysis: ≤ 1% racemization
Minimum Chirality Transfer: 95:5
O
CH3
Xc
M
O
CH3
Xc
H
A
B
CH3
Xc
El
O
C
CH3
OR
El

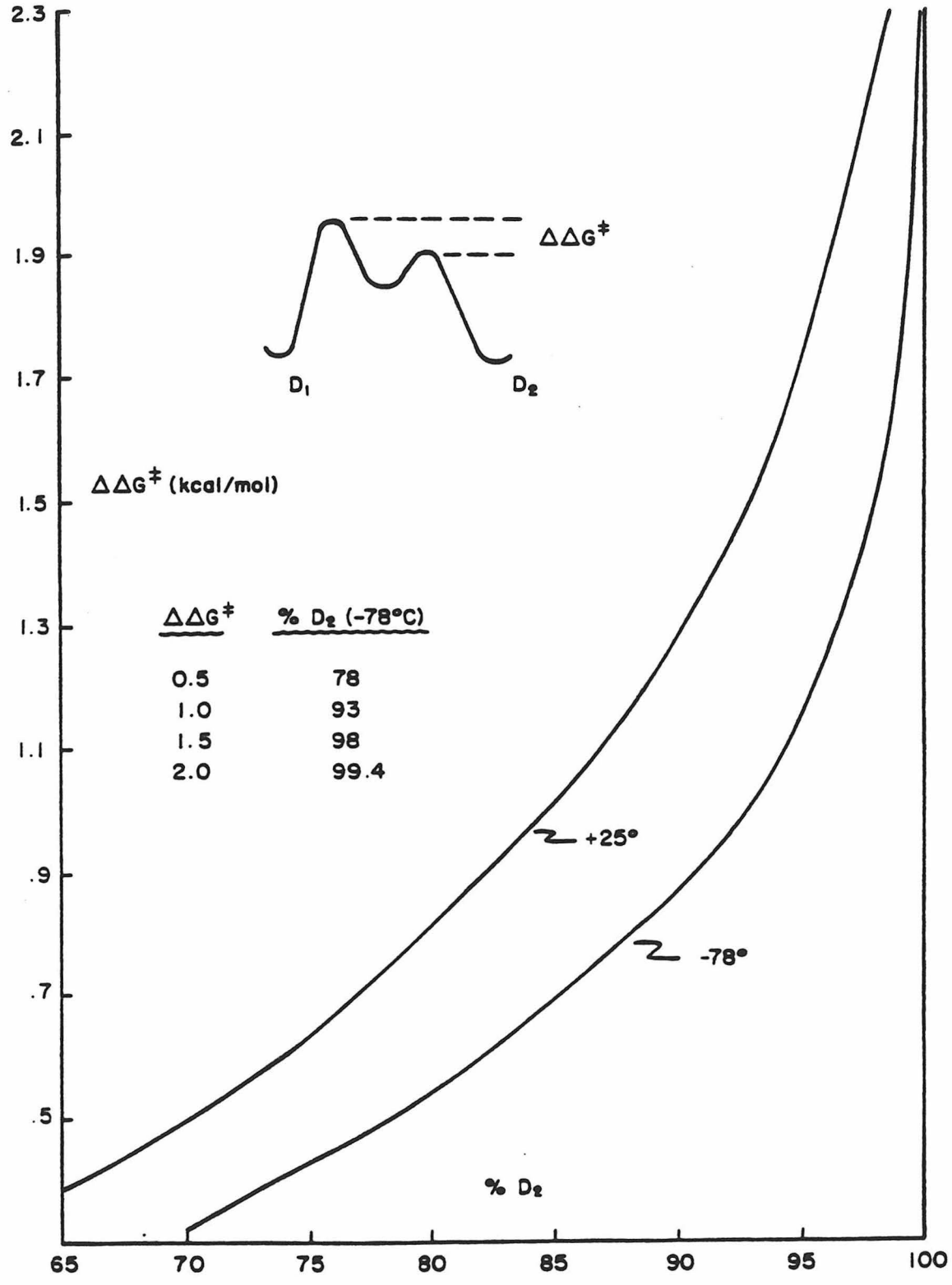

2.3
2.1
1.9
1.7
1.5
1.3
1.1
.9
.7
.5
ΔΔG‡ (kcal/mol)
ΔΔG‡
D1
D2
ΔΔG‡ % D2 (-78°C)
0.5 78
1.0 93
1.5 98
2.0 99.4
+25°
-78°
% D2
65
70
75
80
85
90
95
100

Figure 2

II. Chiral Enolate Design

As previously stated, stereoselective enolization plays a pivotal role in the success of any chiral enolate synthon. Although the chemical literature is replete with examples of the enolization process, the main features governing this transformation remain obscure. However, a number of observed trends have helped contribute to an empirical understanding of this ubiquitous chemical process.

Given in Table 1 are some representative examples of Z:E enolate ratios obtained upon kinetic enolization of various carboxylic acid derivatives with lithium diisopropylamide (eq. 2). Whereas ketone substrates (Entries A-D) seem to show a marked system dependence for enolate selection with LDA, both esters (Entries E-F) and dialkylcarboxamides (Entries G-H) exhibit definite enolate geometry preferences. The selective generation of the Z-enolate from dialkylcarboxamides with LDA can be rationalized on the grounds of a destabilizing $A_{1,3}$-steric interaction between the enolate methyl substituent and the nitrogen ligand R in the transition state leading to the E-isomer (Scheme II). Indeed, there is now experimental evidence that strongly suggests that enolization of N,N-dialkylpropionamides proceeds with exclusive generation of the Z- enolate isomer.[9,10]

Due in part to their selective enolization properties, we felt that dialkylcarboxamide substrates might prove to be attractive candidates for chiral enolate synthons. In theory, the two ligands on nitrogen could serve as convenient points of attachment for a resident chiral center. However, the availability of two rotameric forms to unsymmetrically N,N-disubstituted carboxamides presents problems of the type depicted in Scheme III. Each

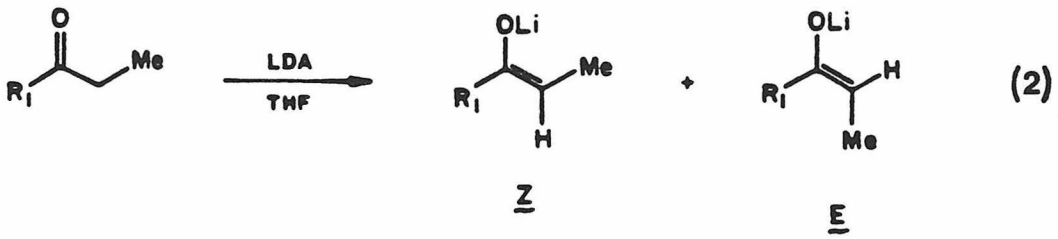
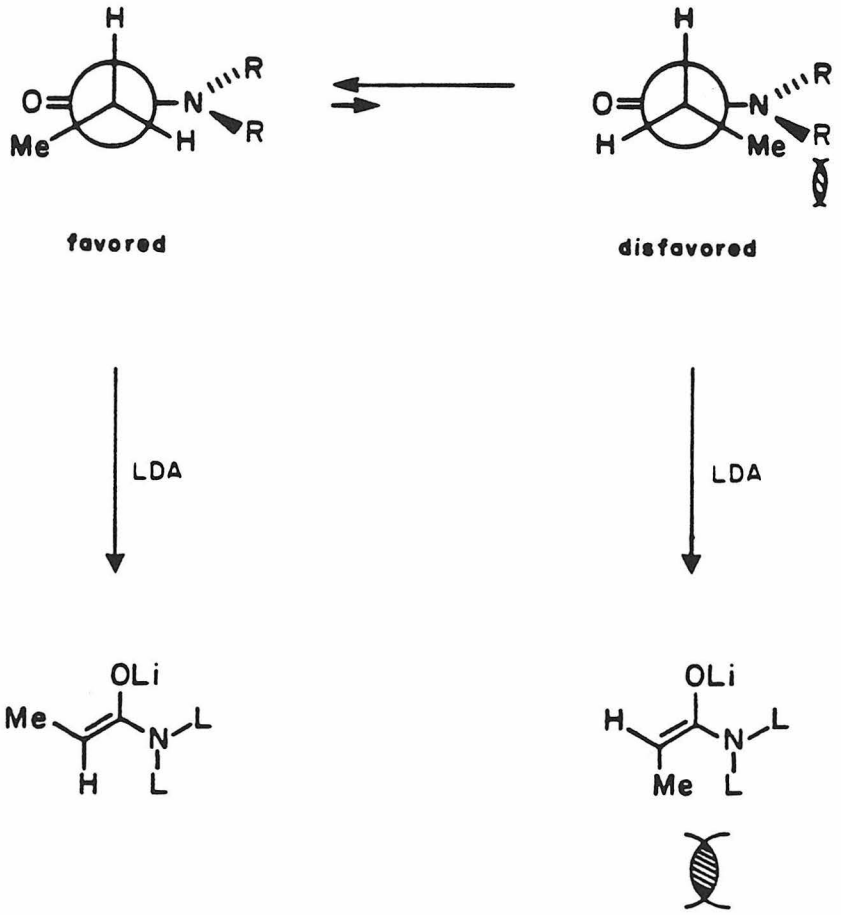


Table 1. Enolization of Representative Carboxylic Acid Derivatives With Lithium Diisopropylamide (eq. 2).

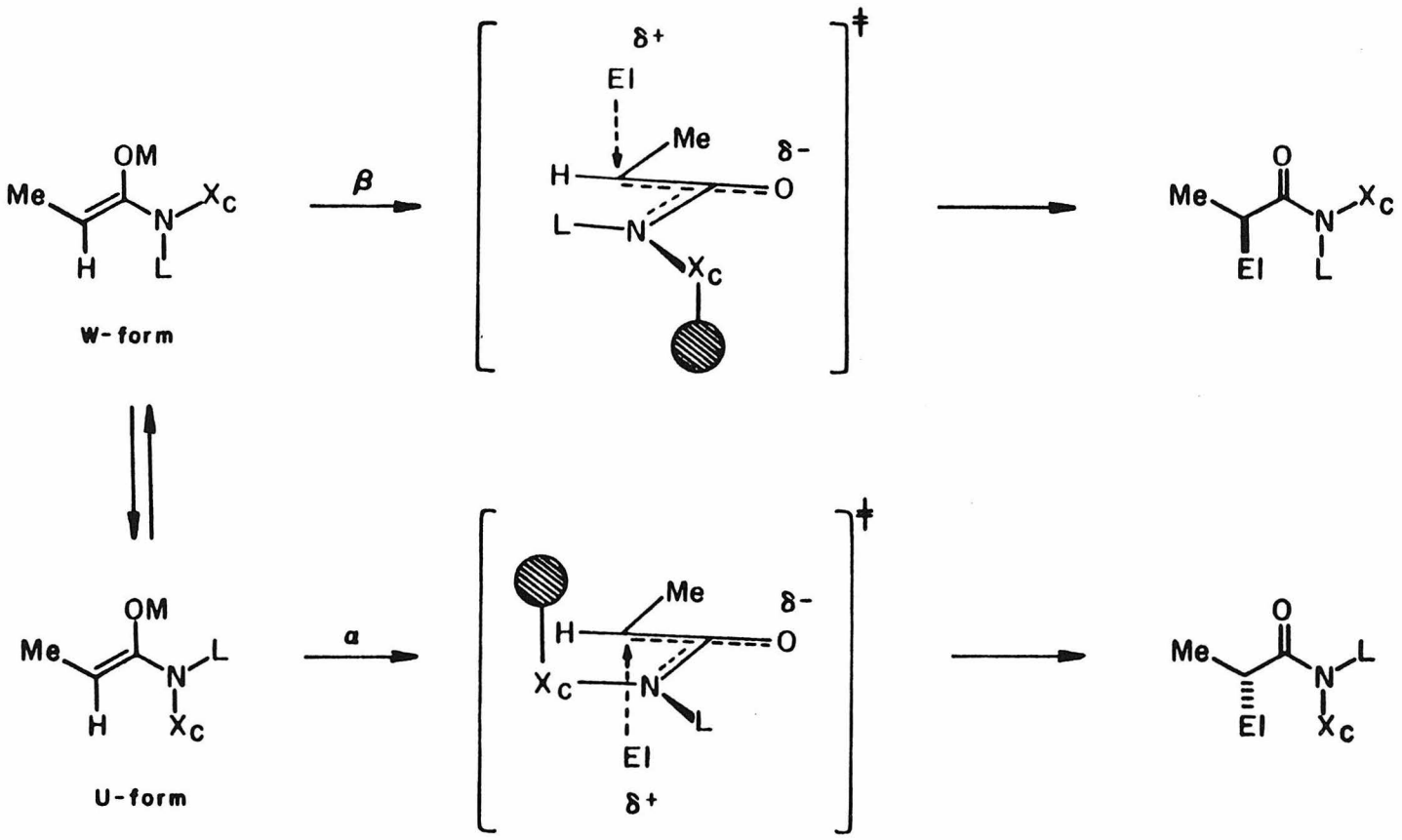
Entry	R_1	Z:E	Ref.
A	C_2H_5	30:70	8
B	i-C_3H_7	60:40	8
C	t-C_4H_9	98:2	8
D	C_6H_5	98:2	8
E	OCH_3	5:95	8
F	Ot-C_4H_9	5:95	8
G	$N(C_2H_5)_2$	97:3	9
H	$N(CH_2)_4$	97:3	9

rotameric form (W-form or U-form in Scheme III) presents to an approaching electrophile the opposite accessible enolate π-face than does its counterpart. This results in a diastereomeric ratio of products reflecting, at least in part, the relative ground state populations of the two rotameric forms. Therefore, an additional design requirement for practical asymmetric induction in these

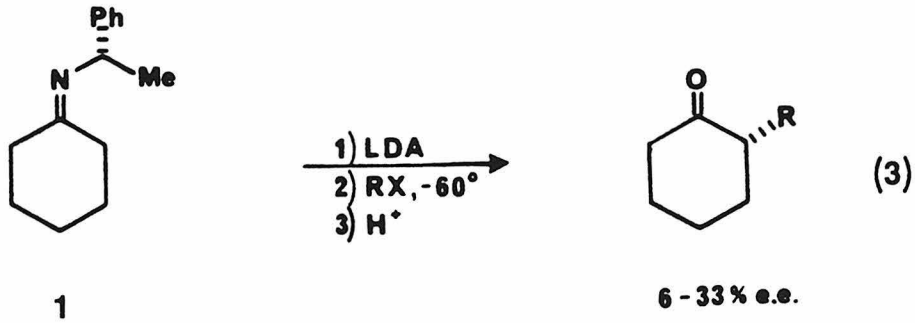
Scheme II

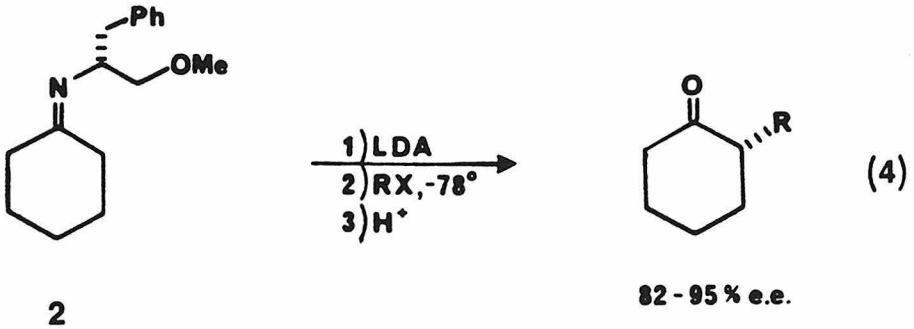


Scheme III


OM
Me
N
Xc
H
L
W-form
β
δ+
El
Me
δ-
H
O
L
N
Xc
‡
O
Me
N
Xc
El
L
OM
Me
N
L
H
Xc
U-form
α
δ+
Me
δ-
H
O
Xc
N
L
El
‡
O
Me
N
L
El
Xc

systems is needed. Previous efforts in this field have strongly implicated that successful asymmetric induction in chiral enolate synthons requires the establishment of a rigid enolate framework whereby rotational degrees-of-freedom have been severely restricted. Early work on the alkylation of chiral imines aptly demonstrates this point. Alkylation of the lithium enolate of 1 (eq. 3) with a variety of alkyl halides, followed by hydrolysis to the ketone afforded the alkylated cyclohexanones having optical purities of 6-33% ee.[11] However, alkylation of the lithium enolate of 2 (eq. 4), which now contains a chiral imine ligand bearing a coordinating methoxyl group, affords alkylated cyclohexanones of much greater optical purity, typically above 90% ee.[12] These results can be rationalized by invoking the internal chelate shown in Figure 3, a situation not possible for the enolate derived from imine 1. In





case after case, it has been shown that chiral enolates capable of establishing a rigid or fixed cyclic configuration, frequently through intramolecular coordination, produce alkylated products of much higher optical purities than those which cannot.[1]

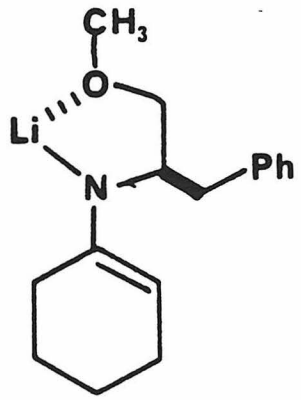
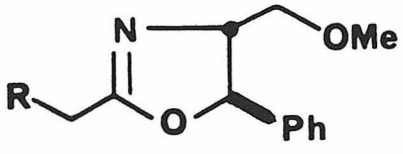


Figure 3

Two of the most successful chiral enolate synthons developed to date are shown below. Meyers' chiral oxazoline **3** enjoys the advantages of selective enolization (95:5 ratio of enolate isomers) and high diastereofacial



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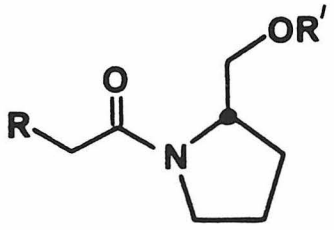
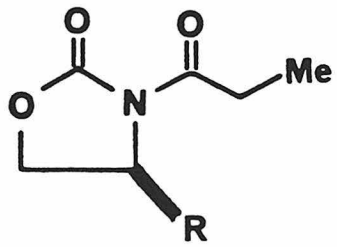


4

bias, but suffers from difficulty in removal of the chiral auxiliary.[6a] The proline-derived chiral amide **4** developed by Takacs and Evans exhibits highly stereospecific enolization and remarkable diastereoselection with electrophiles ($\geq$92:8), as well as mild hydrolytic behavior of the chiral amine auxiliary.[7a] The success of both of these synthons depends largely upon the cyclic, rigid nature of the chiral auxiliary, fixed either through covalent bonding, as in **3**, or internal chelation, as in **4**.

Based upon the ideas outlined in the preceding discussion, we felt that chiral N-acyl oxazolidones such as **5** would be highly attractive candidates for chiral enolate synthons. This chapter will describe, in full detail, our results regarding the synthesis and utility of these substrates in diastereoselective alkylation and acylation reactions.



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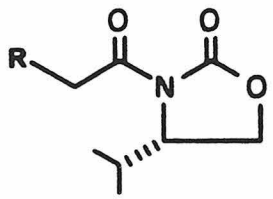
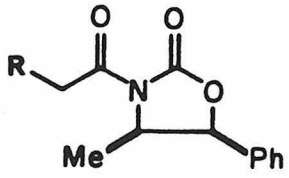
III. Results and Discussion

We have examined in some detail the reactions of the enolates derived from the chiral N-acyl oxazolidones **6** and **7** with a variety of electrophiles. Based upon the preceding discussion, it was our expectation that enolization of these imide substrates would produce metal-chelated Z-enolates such as **8**

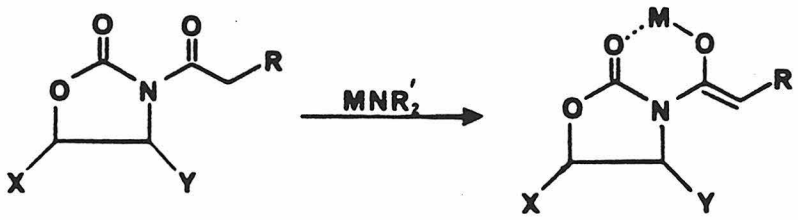


6



7

predominately, if not exclusively (eq. 5). Coordination of the oxazolidone ring carbonyl with the metal counterion via a six-membered ring chelate would impart a high degree of planarity to this system. In this configuration,



(5)

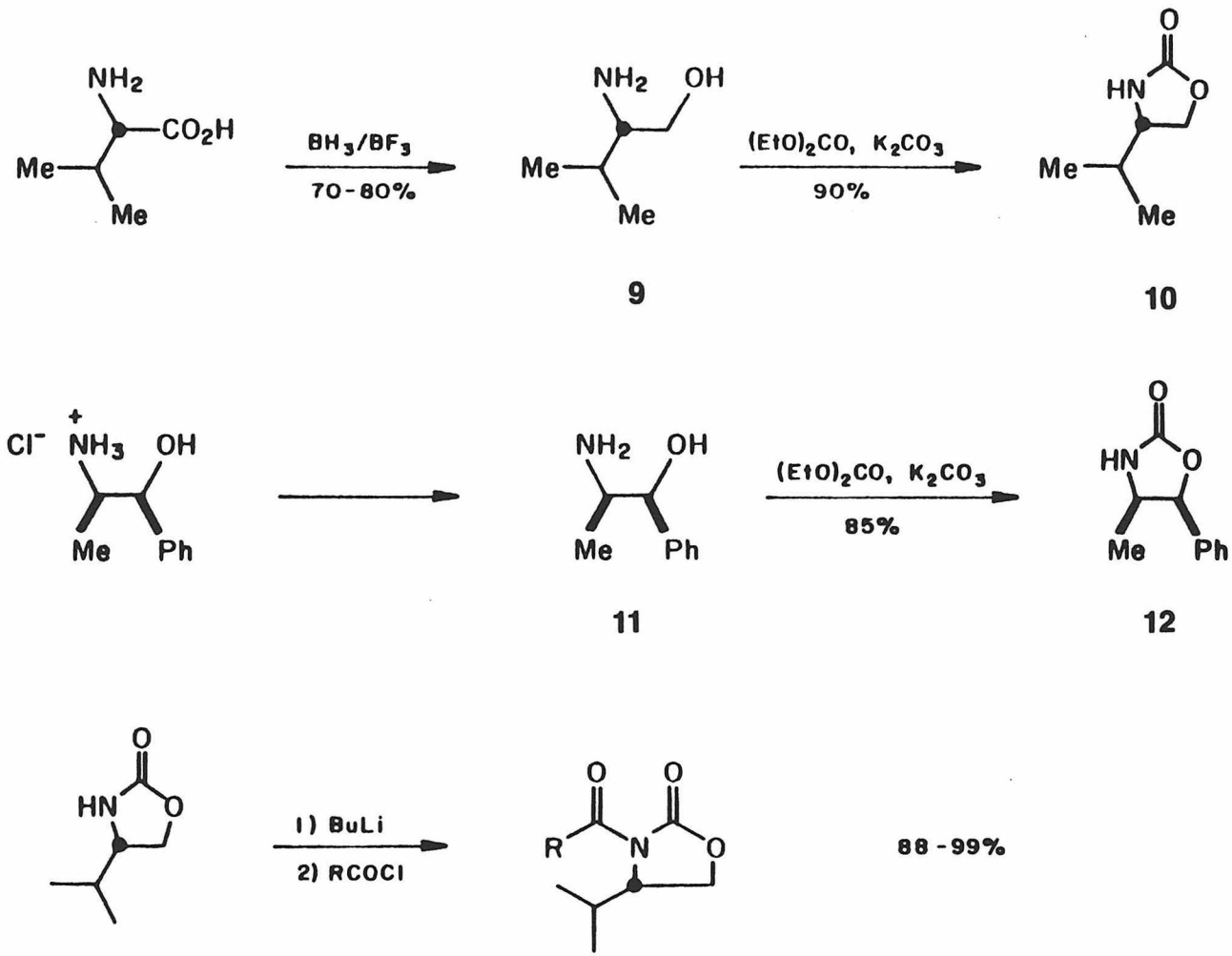
8a (X = H, Y = β-*i*-Pr)

8b (X = α-Ph, Y = α-Me)

chiral substitution on the oxazolidone ring would be expected to direct the approach of incoming electrophiles to the least hindered side. It was upon this hypothesis that this project was undertaken.

A. Synthesis of N-Acyl Oxazolidones. The synthesis of the N-acyl oxazolidones used in this study is outlined in Scheme IV. Commercially available amino acid (S)-valine can be reduced with borane[13] to provide the

Scheme IV


NH2
CO2H
Me
Me
BH3/BF3
70-80%
NH2 OH
Me
Me
9
(EtO)2CO, K2CO3
90%
O
HN
O
Me
Me
10
Cl⁻ NH3 OH
Me Ph
NH2 OH
Me Ph
11
(EtO)2CO, K2CO3
85%
O
HN
O
Me Ph
12
O
HN
O
1) BuLi
2) RCOCl
O O
R N O
88-99%

chiral amino alcohol **9** in good yield. Cyclization at 110-125°C with diethyl carbonate in the presence of a catalytic amount of potassium carbonate affords the (4S)-4-(2-propyl)-oxazolidine-2-one **10** (valine-oxazolidone, X_V) in >90% yield (mp 71-72°C). Similarly, the readily available amino alcohol norephedrine, **11**, is cyclized in high yield to furnish the (4R,5S)-4-methyl-5-phenyloxazolidine-2-one **12** (norephedrine-oxazolidine, X_n, mp 120-121°C). Both of these "parent" oxazolidones are white, crystalline compounds and can routinely be prepared on a large scale. The optical purities of these chiral auxiliaries were determined to be >99% by gas chromatographic analysis of the imides derived from the Mosher acid chloride.[14]

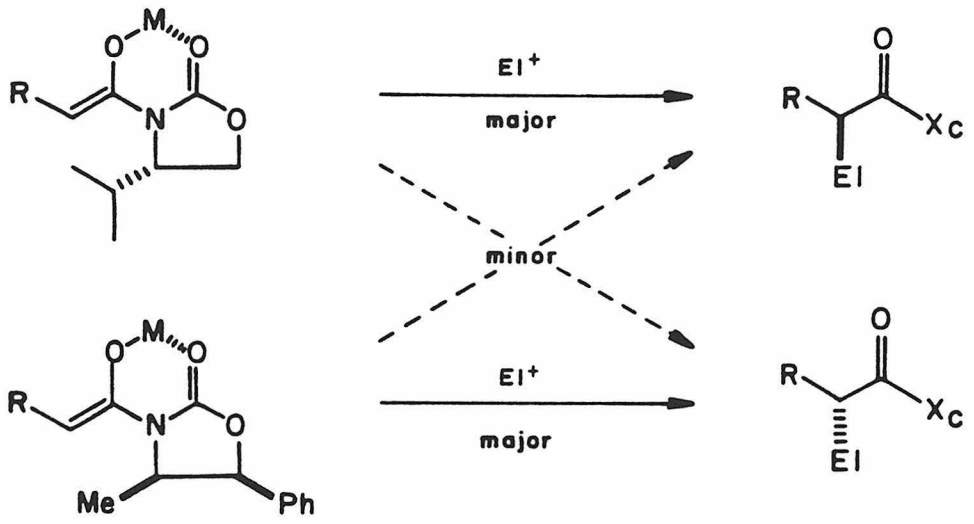
Acylation of the oxazolidones is accomplished by metalation at -78°C with n-butyllithium, followed by quenching of the anion with the desired acid chloride or anhydride. The N-acyl oxazolidones are isolated by reduced-pressure distillation or chromatography on silica gel.[15] All of these reactions can conveniently be carried out on multigram scales without loss of yield.

B. Alkylation Results. Imides **6** and **7** contain chiral auxiliaries having opposite configurations at C-4 of the oxazolidone ring. Since it is the sense of asymmetry at this center which dictates reaction stereoselectivity (vide infra), it was anticipated that these imides would exhibit complementary diastereoselection in the alkylation process (Scheme V). The results of the alkylations of the lithium enolates derived from imides **6** and **7** with a variety of alkyl halides are given in Table 2.[16]

Treatment of imides **6** or **7** with 1.1 equiv of lithium diisopropylamide in THF for 30 min at -78°C cleanly affords the respective lithium enolates. Although reaction of the lithium enolates with alkyl halides is sluggish at

-78°C (vide infra), synthetically useful yields of alkylated product are obtained upon warming the reaction to 0°C for 2-4 h. Whereas the data in Table 2 were determined from reactions employing 3 equivalents of electrophile unless otherwise noted, satisfactory yields can generally be

Scheme V



obtained by using 1.1 equivalent of alkyl halide. Diastereomer ratios (R:S) were determined by capillary gas chromatography (see Experimental Section).

A number of interesting points emerge from data in Table 2. Somewhat surprisingly, nearly identical levels of complementary diastereoselection are seen with the lithium enolates derived from imides **6** and **7**. Thus, it would appear that the methyl group of **7** and the isopropyl group of **6** impart essentially the same degree of π-facial bias to their

Table 2. Stereoselective Alkylations of the Lithium Enolates Derived From Imides **6** and **7**.[a]

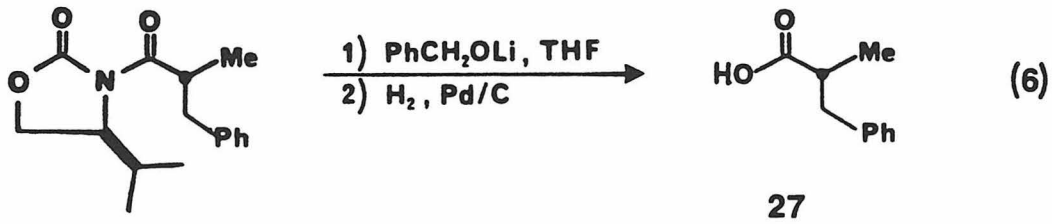
Entry	Imide	Electrophile[b]	Kinetic Ratio (R:S)[c]	Purified Ratio (R:S)[d]	Isolated Yield, %[e]	$[\alpha]_D$ (c, CH_2Cl_2) deg[f]		Mp °C (bp)
A	**6** (R = Me)	$PhCH_2Br$	> 99:1	>99:1	92 **(13)**	+9.42	(2.06)	Liquid
B	**7** (R = Me)	$PhCH_2Br$	2:98	< 1:99	78 **(14)**	+78.5	(1.68)	(150, 0.005 mm)
C	**6** (R = Me)	$CH_2=CHCH_2Br$	98:2	>99:1	71 **(15)**	+62.9	(3.48)	liquid
D	**7** (R = Me)	$CH_2=CHCH_2Br$[b]	2:98	< 1:99	75 **(16)**	+47.0	(2.36)	69-70
E	**6** (R = Me)	$CH_2=C(Me)CH_2Br$	98:2	>99:1	62 **(17)**	+71.4	(1.79)	liquid
F	**7** (R = Me)	$CH_2=C(Me)CH_2I$	3:97	< 1:99	73 **(18)**	+33.7	(5.90)	42-44
G	**6** (R = Me)	$PhCH_2OCH_2Br$[g,h]	98:2	99:1	77 **(19)**	+35.4	(2.88)	(180, 0.005 mm)
H	**7** (R = Me)	$PhCH_2OCH_3Br$[g,h]	2:98	< 1:99	72 **(20)**	+37.0	(2.07)	(180, 0.005 mm)
I	**6** (R = Me)	EtO_2CCH_2I[h]	95:5	>99:1	51 **(21)**	+48.7	(1.64)	(150, 0.005 mm)

Table 2. Continued

Entry	Imide	Electrophile[b]	Kinetic Ratio (R:S)[c]	Purified Ratio (R:S)[d]	Isolated Yield, %[e]	α_D (c, CH_2Cl_2) deg[f]		Mp (bp) °C
J	**7** (R = Me)	EtO_2CCH_2Br[h]	7:93	1:99	51 **(22)**	+35.7	(1.78)	(160, 0.005 mm)
K	**6** (R = Me)	CH_3CH_2I	94:6	>99:1	36 **(23)**	+61.6	(0.85)	liquid
L	**7** (R = Me)	CH_3CH_2I[h]	12:88	< 1:99	28 **(24)**	+54.7	(1.38)	71-72
M	**6** (R = Et)	CH_3I	11:89	1:99	86 **(23)**	+112.6	(4.10)	(180, 0.01 mm)
N	**7** (R = Et)	CH_3I[h]	87:13	>99:1	75 **(24)**	+6.1	(1.72)	65-66
O	**6** (R = n-C_8H_{17})	CH_3I	9:91	< 1:99	83 **(25)**	+83.3	(2.03)	(160, 0.008 mm)
P	**7** (R = n-C_8H_{17})	CH_3I[h]	89:11	>99:1	70 **(26)**	-1.41	(1.56)	42-43

[a]Results obtained from alkylation of the lithium enolates using 3 equiv of the indicated electrophile (THF, 0 °C, 2-4 h). [b]The number following the isolated yield is that assigned to the alkylated product. [c]Ratios determined by capillary GC (see Experimental). [d]Diastereomer resolution carried out by either flash chromatography or MPLC (see Experimental). [e]Yields reported for chromatographed material of diastereomer composition as noted in the preceeding column. [f]All rotations were determined in dichloromethane (c = g/100 mL). [g]Reaction carrfied out at -40° C. [h]See Ref. 16.

respective lithium enolates. It is instructive to note that kinetic selectivity of 98:2, which is typical for these enolates, represents a free energy difference in the transition states leading to diastereomeric products of over 2 kcal/mol at 0 °C. It must be noted, however, that the alkylation diastereomer ratios given in Table 2 are necessarily lower limits for enolate π-facial selectivity, due to the paucity of data relating to enolate geometry homogeneity. However, it can be safely assumed that enolization stereoselectivity under the described conditions must proceed with ≥100:1 selectivity for the Z-enolate. Evidence for this can be seen from Table 2, Entry A. Reaction of benzyl bromide with lithium enolate **8a** (enolate geometry inferred) at 0 °C proceeds with a kinetic diastereoselection of 120:1. Based upon this result, we feel confident in assuming that for all practical purposes we are dealing with a single enolate isomer. That enolization with LDA proceeds to afford the Z-enolate isomer can be inferred from the absolute stereochemistry of the newly created chiral center. Transesterification of the purified reaction product **13** was carried out in THF using lithium benzyloxide (vide infra), and the resulting benzyl ester was hydrogenolized to afford the known α-methylhydrocinnamic acid **27** in 91% overall yield (eq. 6). The optical rotation for this derived acid correlates very well with the highest reported literature rotation for the (R)-enantiomer.[17] This result is fully consistent with a metal-chelated (Z)-enolate (see **8a**) where diastereoface selection is dictated by the C_4-substituent on the oxazolidone ring. Indeed, the results of all of the alkylations carried out during the course of this study can be readily interpreted in a totally analogous manner. The hypothesis upon which this project was undertaken has thus been shown to be internally consistent.



(6)

13

27

$[\alpha]_D$ = -25.1° (neat)

Lit. $[\alpha]_D$ = -25.4° (neat)

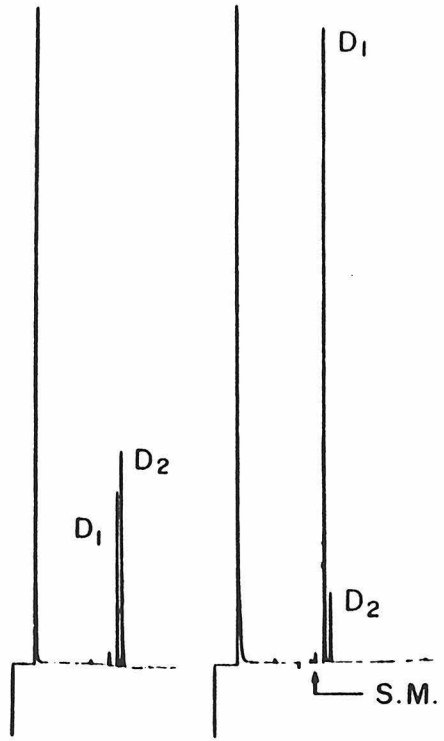
Data from Table 2 reveal other interesting points worth mentioning. There appears to be a general correlation between the steric demands of the electrophile and the corresponding alkylation stereoselectivity (compare Entries A or B with M and N). Enolate alkylations with the relatively small electrophile methyl iodide have been the least stereospecific processes encountered to date ($D_1:D_2 \cong 90:10$). Furthermore, one must employ alkylating agents that will react at a convenient rate at 0° C. As can be seen from Entries K and L, it is necessary to use a large excess of the relatively unreactive electrophile ethyl iodide in order to achieve even modest yields of alkylation product. Indeed, attempted alkylations using isobutyl iodide at 0° C for protracted time periods resulted in either recovered starting material and/or enolate decomposition products (vide infra).

In most cases, diastereomer resolution could be accomplished with high efficiency by chromatography on silica gel. This fortuitous finding permitted routine enrichment of nearly all unpurified diastereomeric mixtures to the $\geq$99:1 level. Only in cases where the substituents α to the acyl carbonyl are similar (i.e., methyl vs ethyl) were chromatographic resolutions poor.

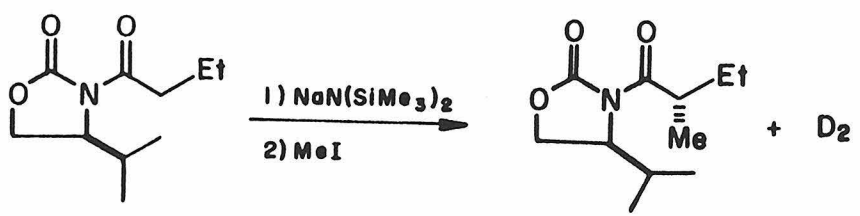
Shown in Figure 4 is a typical gas chromatographic trace from an alkylation diastereomer analysis. For comparison purposes, authentic mixtures of diastereomers were prepared from the racemic acids and analytical GC conditions for their separation were determined. In not a single case in this study were we unable to achieve complete diastereomer resolution by capillary GC.

C. Analysis of Reaction Parameters. In general, the reaction of the lithium enolates derived from chiral imides **6** and **7** in THF with most alkyl halides proceeds in good yield with a high degree of stereoselectivity. The notable exception to this observation is the relatively low diastereoselectivity (ca. 9:1) when methyl iodide is used as the electrophile. Due to the abundance of natural products containing a chiral methyl center, it was deemed important to attempt to improve the stereospecificity in the methylation reactions. Thus, a systematic investigation was undertaken in order to assess the relative influence of a number of reaction parameters on both the stereochemical consequences and chemical yields of these reactions.

It was felt that the nature of the enolate counterion might have an effect on both the nucleophilicity of the enolate as well as on the stereochemical outcome of the alkylations. An examination of different alkali-metal counterions showed this to be the case. The lithium, sodium, and potassium metal enolates of imides **6** and **7** were prepared by deprotonating with lithium diisopropylamide (LDA), sodium hexamethyldisilylamide (NHDS), and potassium hexamethyldisilylamide (KHDS) respectively (eq. 7). The comparative results of the alkylation of these enolates is given in Table 3.



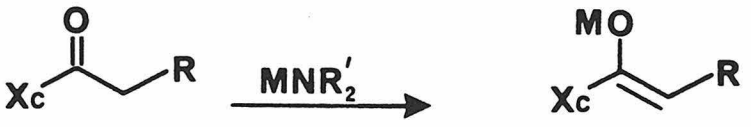
Column: 30 m x 0.25 mm SE-54
at 130°C



S.M. D_1

$D_1 : D_2 = 91 : 9$

Figure 4



(7)

Base	M	R'
LDA	Li	i-Pr
NHDS	Na	$SiMe_3$
KHDS	K	$SiMe_3$

We have found that both the sodium and potassium imide enolates afford satisfactory to excellent yields of alkylation products from reactions performed entirely at -78°C, even when relatively unreactive electrophiles are employed. Furthermore, it is generally observed that diastereoselection for the alkylation reaction is increased by ca. 5% under these conditions. For example, methylation of the lithium enolate derived from **7** (R = Et) at 0°C for 2 h affords a kinetic diastereomer ratio of 87:13 (Table 3, Entry J). The same reaction carried out at -78°C for 2 h employing the sodium enolate of **7** (R = Et) now provides a 93:7 ratio of diastereomers (Table 3, Entry K). This improvement in kinetic selectivity observed upon carrying out the alkylation at lower temperatures is very close to what would be predicted based upon the calculated $\Delta\Delta G^{\dagger}$ from the methylation reaction run at 0°C.

Other interesting points regarding the data in Table 3 bear mentioning. Whereas it is generally true that kinetic diastereoselectivity is improved by employing the more nucleophilic sodium enolates and performing the alkylations at -78°C, the effect seems to be more dramatic for the norephedrine-derived oxazolidone systems **7** than for those systems bearing the valine-derived chiral auxiliary (compare Entries D and H with J and K). Furthermore, it is interesting

Table 3. Counterion-Effects in Alkylations of Imide **6** and **7**.[a]

Entry	Imide	M	Electrophile	Alkylation Conditions	Kinetic Ratio (R:S)[b]	Yield, %[c]
A	**6** (R = Me)	Li	CH_2=$CHCH_2Br$	2 h/0 °C	98:2	71
B	**6** (R = Me)	Na	CH_2=$CHCH_2Br$	2 h/0 °C	96:4	80
C	**6** (R = Me)	Na	CH_2=$CHCH_2Br$	2 h/-78° C	99:1	29
D	**6** (R = Et)	Li	CH_3I	2 h/0 °C	11:89	90
E	**6** (R = Et)	K	CH_3I	2 h/0 °C	14:86	84
F	**6** (R = Et)	Li	CH_3I	2 h/-78° C; 1 h/0 °C	10:90	80
G	**6** (R = Et)	Na	CH_3I	2 h/-78° C; 1 h/0 °C	9:91	75
H	**6** (R = Et)	Na	CH_3I	3 h/-78° C	9:91	96
I	**6** (R = Et)	Na	CH_3I	2 h/-78° C; 1 h/RT	15:85	88
J	**7** (R = Et)	Li	CH_3I	2 h/0 °C	87:13	90
K	**7** (R = Et)	Na	CH_3I	2 h/-78° C	93:7	97

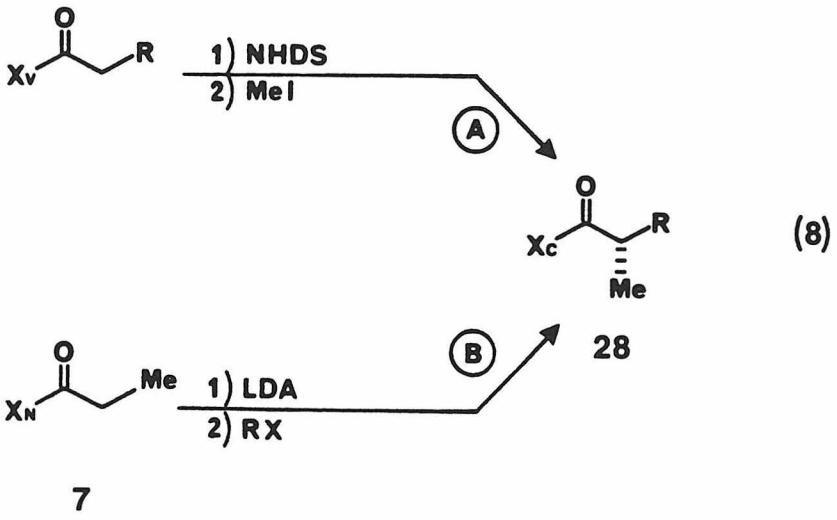
Table 3. Continued

Entry	Imide	M	Electrophile	Alkylation Conditions	Kinetic Ratio (R:S)[b]	Yield, %[c]
L	**7** (R = Me)	Li	CH_3CH_2I	2 h/0°C	88:12	28
M	**7** (R = Me)	Na	CH_3CH_2I	2 h/-78°C	94:6	--
N	**6** (R = n-C_8H_{17})	Li	CH_3I	2 h/0°C	9:91	83[d]
O	**6** (R = n-C_8H_{17})	Na	CH_3I	2 h/-78°C	7:93	98
P	**7** (R = n-C_8H_{17})	Li	CH_3I	2 h/0°C	88:11	70[d]
Q	**7** (R = n-C_8H_{17})	Na	CH_3I	2 h/-78°C	93:7	96

[a]All reactions carried out in THF. [b]Diastereomer ratios determined by capillary GC. [c]Determined by GC unless otherwise noted. [d]Isolated yield.

to note that under identical reaction conditions, the sodium or potassium enolates exhibit lower kinetic diastereoselectivity than do their lithium counterparts (see Table 3, Entries A and B, D and E). Finally, it has been demonstrated that the boron enolates (**8**, M = Bu_2B), obtained by reaction of imides **6** or **7** with dibutylboryl triflate in the presence of triethylamine, are totally unreactive with alkyl halides.[18] It would thus appear that the influence of different metal counterions in these systems resides primarily in determining the relative nucleophilicities of the derived enolates. As the degree of metal-oxygen bond covalency increases, as in going from sodium to lithium counterions, enolate reactivity is attenuated. However, there seems to be little disruption in the nature of the chelation control which is critical to these reactions. Even at higher temperatures (0 °C), the potassium and sodium enolates exhibit impressive levels of diastereoselection.

At the present time, the optimized protocol for alkylation with methyl iodide involves the use of sodium enolates in THF at -78 °C. Unfortunately, these conditions still yield diastereomer ratios little better than 90:10. However, an important point must be kept in mind. For a generalized α-substituted propionate such as **28** (eq. 8), there exists two independent pathways which ultimately lead to the same enantiomeric product. For the illustrated example, one could start with the appropriately acylated valine oxazolidone and, through the agency of the sodium enolate and methyl iodide at -78 °C, obtain the desired (2S)-2-methyl substituted imide **28** ($X_C = X_V$, Path A). Alternatively, the lithium enolate of the norephedrine derived propionate imide **7** could be alkylated with the appropriate alkyl halide RX to obtain product **28** with the same sense of chirality at C-2 (**28**, $X_C = X_n$, Path



B). Since pathway B will generally proceed with higher diastereoselectivity than pathway A, this option should be the procedure of choice for the creation of methyl-bearing chiral centers.

An investigation of reaction media was also undertaken in order to determine the influence of solvent in these alkylations. One would expect solvent participation to play a major role in any chelation-controlled reaction. In the event, valine-derived butyrate **6** (R = Et) was enolized with LDA and alkylated with methyl iodide in a variety of solvents (eq. 9). Diastereomer ratios and chemical yields were determined by capillary gas chromatography. The results of these studies are given in Table 4.

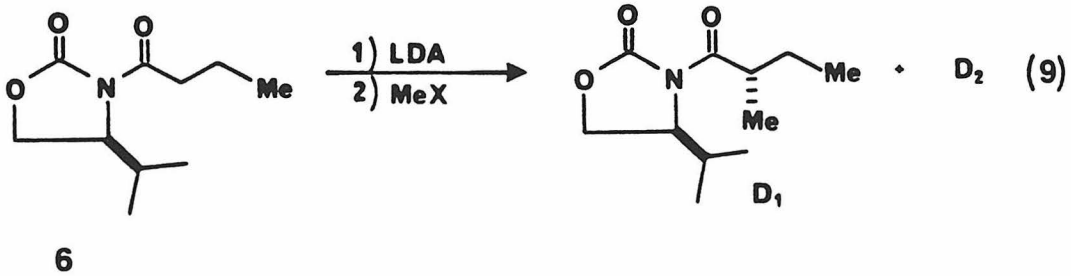


Table 4. Solvent Effect on Butyrate Methylation (eq. 9).[a]

Entry	Solvent	Kinetic Ratio[b] (R:S)	Recovered **6** (R = Et), %[d]
A	THF	11:89	3
B	Diethyl Ether	10:90	88
C	Benzene	9:91	94
D	Pentane	13:87[c]	49

[a]Alkylation of the lithium enolates, 0.5 M in the indicated solvent, using 1.1 equiv of CH_3I.[b]Alkylations performed at 0°C for 2 h. [c]Alkylation at RT for 2 h. [d]Determined by capillary GC.

Upon examination of the data in Table 4, it becomes immediately apparent that THF is the solvent of choice for these imide alkylations. Although a slight increase in kinetic diastereoselectivity is seen when either diethyl ether or benzene are used as solvents, chemical yields in these solvents fall dramatically (Table 4, Entries B and C). Pentane is not suitable for these reactions due to the insolubility of the lithium enolate in this solvent, even at room temperature.

A comparison of three different methylating agents is given below in Table 5. It appears that for methylations, electrophile structure plays only a minor role in determining reaction diastereoselection. Reactions using methyl iodide clearly give the highest yields of alkylation product, whereas reactions with methyl tosylate (Table 5, Entry B) afford only a trace of alkylated product.

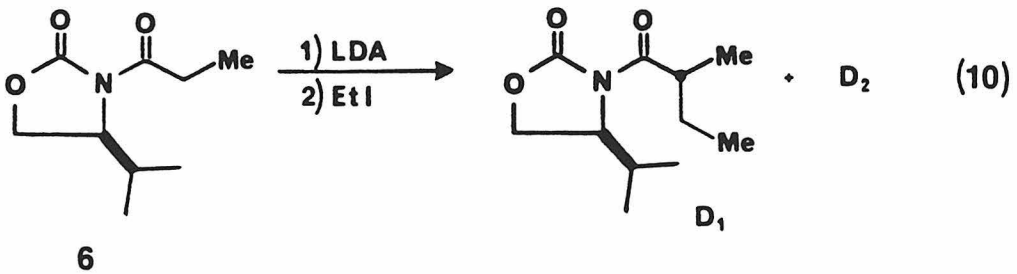
As previously stated, the relatively modest nucleophilicity of the

Table 5. Effect of Electrophile Structure on Butyrate Methylation (eq. 9).[a]

Entry	Electrophile	Kinetic Ratio[b] (R:S)	Recovered **6** (R = Et), %[c]
A	CH_3I	11:89	3
B	CH_3OTs	10:90	97
C	$Me_3O^+BF_4^-$	9:91	33

[a]Alkylations were carried out with the lithium enolates, 0.5 M in THF, using 1.1 equiv of the indicated electrophile. [b]Alkylations run for 2 h at 0°C. [c]Determined by capillary GC.

lithium enolates derived from chiral imides **6** and **7** requires the use of alkylating agents which react at a convenient rate at 0°C. Under standard conditions (0°C, 2 h, 1-3 equiv RX), alkylations using ethyl iodide proceed in poor yield (see Table 2, Entry K). It is well known that the solvent addend HMPT (hexamethylphosphoric triamide) accelerates the rate of a wide variety of polar reactions.[19] Thus, a study of the effects of added HMPT on the ethylation of lithium enolate **8a** was undertaken (eq. 10). The results of this investigation are given in Table 6.



(10)

Table 6. Temperature/Solvent Effects in Propionate Ethylation (eq. 10).[a]

Entry	Solvent System[b]	Temperature °C	Kinetic Ratio[d] (R:S)	Recovered **6** (R = Me), %[d]
A	THF	-78[c]	--	100
B	THF-HMPT	-78	87:13	75
C	THF	-50	--	99
D	THF-HMPT	-50	89:11	23
E	THF	0	90:10	76
F	THF-HMPT	0	90:10	3
G	THF	+25	94:6	3

[a]Alkylations were carried out with the lithium enolates, 0.5 M in THF, for 2 h, using 1.1 equiv of ethyl iodide. [b]3 Equiv HMPT added prior to alkylation where noted. [c]Alkylation time 4 h. [d]Determined by capillary GC.

Inspection of the data in Table 6 reveals that the addition of HMPT clearly increases the rate of the ethylation reaction. Whereas a quantitative yield of starting imide **6** (R = Me) is recovered after attempted ethylation at -78°C for 4 h in THF alone (Table 6, Entry A), the same reaction in the presence of 3 equivalents of HMPT proceeds to the extent of *ca.* 25% after only 2 h at -78°C (Table 6, Entry B). However, even at this temperature, diastereoselectivity is low. It is interesting to note that reactions in the presence of HMPT show an unusual *inverse* relationship between diastereoselectivity and temperature (Table 6; compare Entries B, D, and F). The reasons for this observation are unclear.

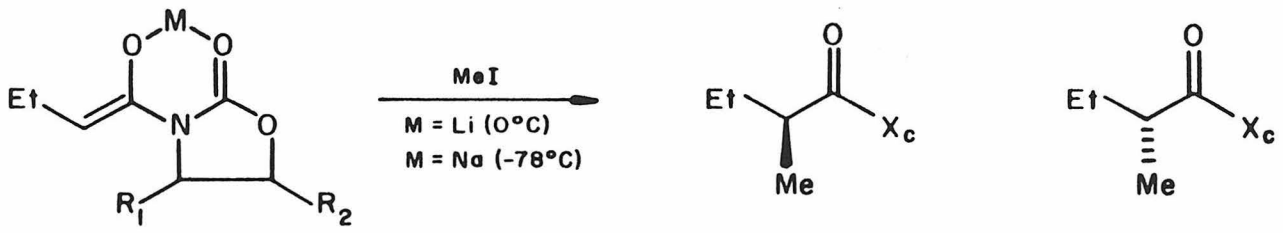
Finally, the nature of the chiral substitution pattern on the

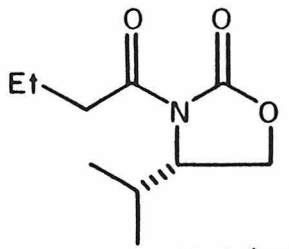
oxazolidone ring was briefly examined.[16] Methylation ratios of both the lithium and sodium enolates of four different N-butyryl oxazolidones were compared. The diastereomer ratios from these experiments are shown in Scheme VI.

A number of interesting points emerge from these results. First, deletion of the C-5 phenyl substituent from the norephedrine-derived oxazolidone provides chiral imide **30**. This system, bearing the lone C-4 methyl substituent, exhibits a kinetic diastereoselection in the methylation reactions nearly identical to those of **7** (R = Et). This result demonstrates that it is the C-4 substituent which plays the dominant role in dictating reaction diastereoselectivity. Second, a comparison between the valine-derived oxazolidone **6** (R = Et) and **30** provides calibration as to the influence of the size of the C-4 substituent on kinetic diastereoselection in these reactions. As can be seen from Scheme VI, the improvement in diastereomer ratios in going from a C-4 methyl substituent (**30**) to a C-4 isopropyl group (**6**) is small indeed, especially for the sodium enolates. It would therefore appear that a methyl group alone affords sufficient spatial demands to engender the high levels of diastereoselection seen in these imide systems. For this reason, it was felt that a t-butyl substituent at C-4 would provide little, if any, improvement in diastereomer ratios over the isopropyl or methyl substituted oxazolidones.

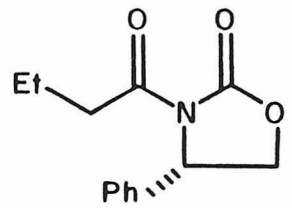
Interestingly, the chiral auxiliary which provided the lowest level of kinetic diastereoselection was the phenylglycine-derived oxazolidone imide **29**. The methylation results with this system show that a C-4 phenyl substituent is inferior to even a methyl group in providing enolate π-facial

Scheme VI

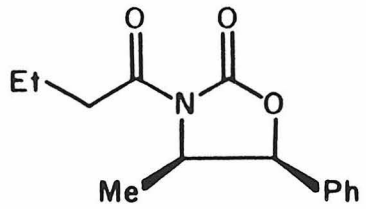




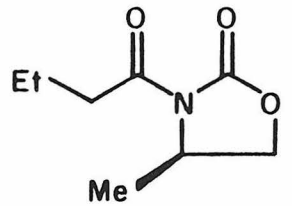
6 91:9 (Na) 90:10 (Li)



29 87:13 (Na) 81:19 (Li)

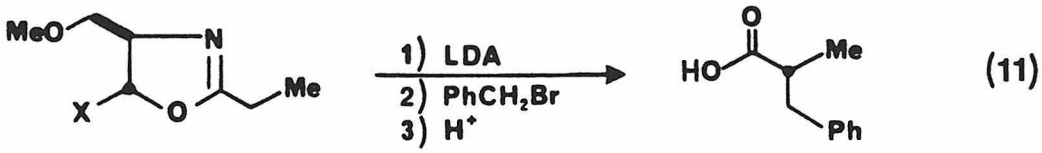


7 7:93 (Na) 13:87 (Li)



30 8:92 (Na) 14:86 (Li)

selectivity. This result is in sharp contrast to findings in Meyers' oxazoline system, which indicate that a phenyl ring is significantly more sterically demanding than a methyl group (eq. 11).[20] This discrepancy might be



(11)

74%e.e.(X = Ph)
47%e.e.(X = Me)

explicable when one considers the relative proximities of the chiral substituent in the auxiliary to the reacting enolate center. In imide oxazolidones, the C-4 substituent is clearly <u>closer</u> to the enolate carbon atom than is the C-5 substituent in oxazoline auxiliaries (Figure 5). Therefore the "steric effectiveness" of an oxazoline C-5 methyl group will be severely attenuated by the relatively large distance separating it from the

Figure 5

enolate π-system. Alternatively, the situation in the oxazolidone case places the C-4 substituent nearly on top of the enolate π-system. In this arrangement, a planar benzene ring might be able to adopt a configuration which is indeed less sterically demanding than that provided by a three-dimensional, space-filling methyl group.

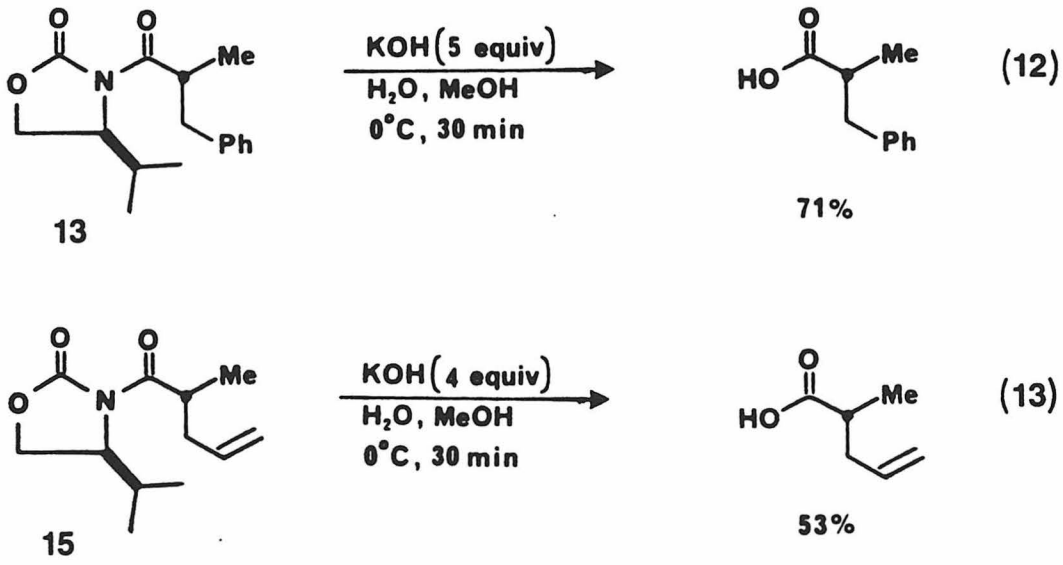
In summary, it would appear that the single most important factor responsible for determining the diastereoselectivity of N-acyl oxazolidone imide alkylations is the nature of the substitution on the oxazolidone ring. Other elements, such as enolate counterion, solvent, and electrophile structure, play only a small role in influencing reaction selectivity, but may become important in determining reaction kinetics. However, steric considerations remain the priority concern, and high levels of diastereoselection are seen in these systems as the result of the physical presence of an oxazolidone substituent as small as a methyl group.

D. Chiral Auxiliary Cleavage. The N-acyl oxazolidones **6** and **7** have been shown to exhibit very high levels of diastereoselection during the alkylation process. These chiral auxiliaries seem to serve admirably in directing both enolization stereoselectivity as well as π-facial selectivity in electrophilic attack by alkyl halides. What remains to be demonstrated in order to define the practicality of imides **6** and **7** as chiral α-substituted carboxylic synthons is the convenient removal of the chiral oxazolidone auxiliaries. During the course of this study, we have developed a number of mild chemical transformations which non-destructively cleave these chiral auxiliaries without producing racemization in the final product. The recovery of the intact auxiliary represents a "chiral economy" which further extends

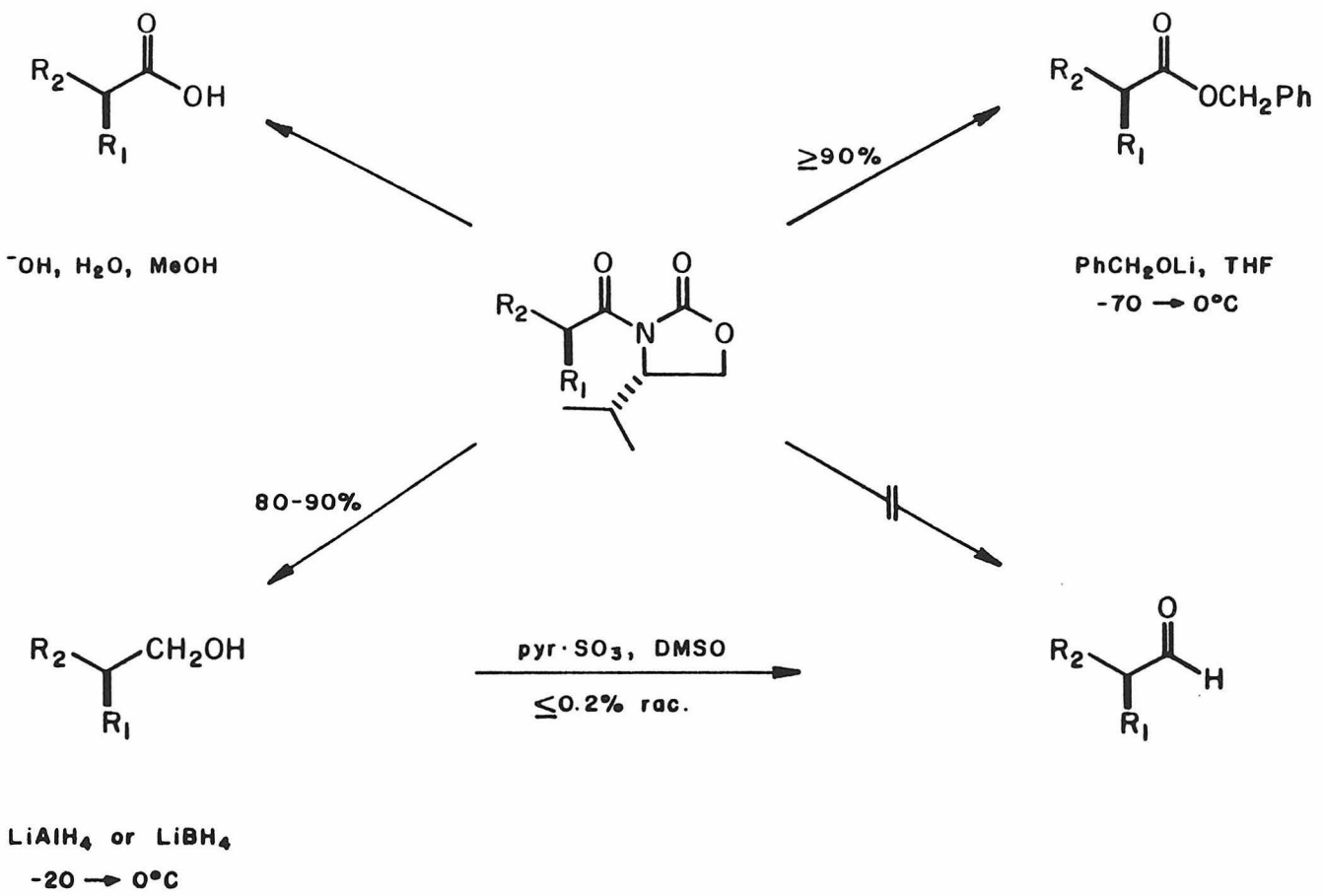
the usefulness of these reagents. Outlined in Scheme VII are the transformations that have been developed for these systems.

The success of the reactions shown in Scheme VII requires selective nucleophilic attack at the acyl carbonyl in preference to that of the oxazolidone carbonyl. While these reactions generally proceed as indicated, there is clearly a system dependence governing each transformation. If the steric requirements of R_1 and R_2 (Scheme VII) become too great, nucleophilic attack at the oxazolidone ring carbonyl becomes favored. This undesired side-reaction can usually be suppressed by a prudent choice between the various options to be described below.

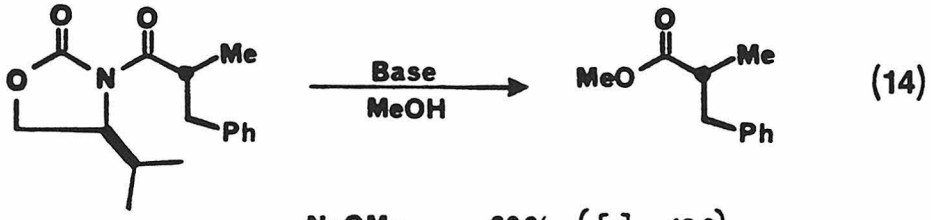
Base-catalyzed hydrolysis of the alkylated imides proceeds rapidly in methanol at 0°C. Yields for the free carboxylic acids are variable, however (eqs. 12 and 13).



Scheme VII


R2
R1
OH
O
OCH2Ph
≥90%
⁻OH, H2O, MeOH
PhCH2OLi, THF
-70 → 0°C
N
80-90%
CH2OH
pyr·SO3, DMSO
≤0.2% rac.
H
LiAlH4 or LiBH4
-20 → 0°C

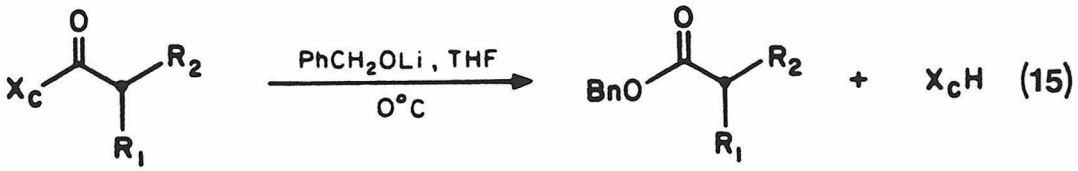
Formation of methyl esters from basic methanolic solutions also proceeds rapidly at 0°C, affording transesterified products in satisfactory yields (eq. 14). Admittedly, due to the capricious nature of both of these transformations, neither has found general use in our laboratories. However,



(14)

NaOMe	60%	($[\alpha]_D$ -48.0)
$Mg(OMe)_2$	71%	($[\alpha]_D$ -45.4)

we have discovered a reaction which consistently gives >90% isolated yields of transesterified product. Reaction of the alkylation products from either imide **6** or **7** with lithium benzyloxide in THF at 0°C affords high yields of the corresponding benzyl esters (eq. 15). Furthermore, it has been shown that essentially no racemization takes place during this process (vide infra). This transformation was performed on a number of the alkylation products, and the results are summarized in Table 7.



(15)

Table 7. Transesterification to Benzyl Esters (eq. 15).[a]

Entry	X_c	R_1	R_2	(R:S)[b]	Yield, %[c]	Configuration	$[\alpha]_D$ (c, CH_2Cl) deq	
A	VAL	$PhCH_2$	CH_3	>99:1	92	R	-26.8	(2.33)
B	NOR	CH_3	$PhCH_2$	< 1:99	92	S	+26.8	(5.93)
C	VAL	$CH_2=C(CH_3)CH_2$	CH_3	>99:1	93	R	+3.94	(5.86)
D	NOR	CH_3	$CH_2=C(CH_3)CH_2$	3:97	93	S	-3.70	(6.33)
E	VAL	$CH_2=CHCH_2$	CH_3	98:2	77[d]	R	-2.08	(17.7)
F	NOR	CH_3	$CH_2=CHCH_2$	< 1:99	86	S	+2.29	(14.7)
G	VAL	CH_3CH_2	CH_3	>99:1	89	R	-12.6	(6.38)
H	VAL	CH_3	CH_3CH_2	1:99	92	S	+12.5	(5.55)
I[e]	NOR	CH_3CH_2	CH_3	>99:1	93	R	-12.6	(2.85)
J[e]	NOR	CH_3	CH_3CH_2	< 1:99	90	S	+12.8	(2.16)

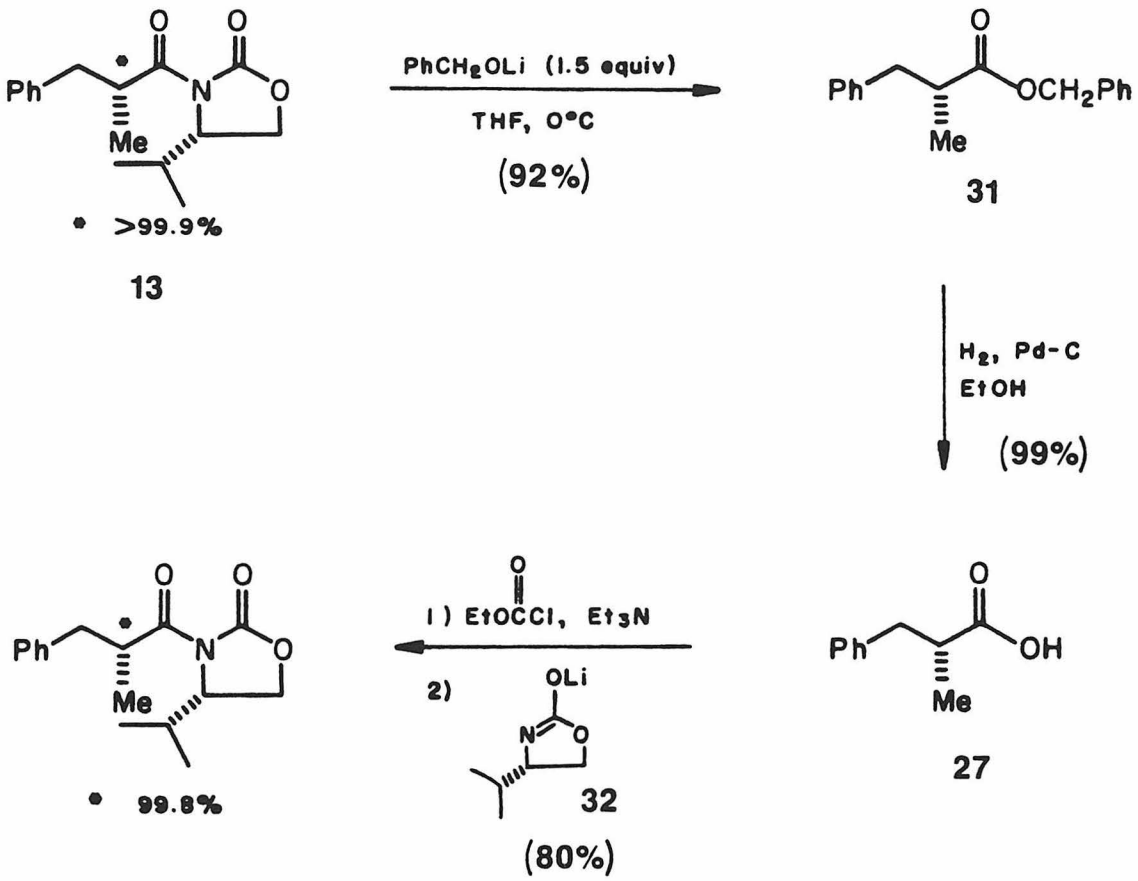
[a]Reactions carried out with 1.5 equiv of lithium benzyloxide in THF (ca. 0.3 M) at 0 °C for 1 h. [b]Diastereomer ratio prior to transesterification as determined by capillary GC. [c]Purified yields. [d]Reaction done in diethyl ether. [e]We thank Mr. D. J. Mathre for these results.

The reactions reported in Table 7 were carried out by adding the indicated alkylated imide to a cooled (0°C) THF solution of 2 equivalents of benzyl alcohol and 1.5 equivalents of n-butyllithium. The use of THF as a solvent is critical. Reactions run in diethyl ether result in markedly reduced yields of benzyl ester product (see Table 7, Entry E), as well as significant production of a byproduct identified as dibenzyl carbonate. The production of dibenzyl carbonate is best rationalized by competitive alkoxide attack at the oxazolidone ring carbonyl, and serves to illustrate the delicate balance frequently seen between nucleophilic attack at the two available carbonyl centers.

It was gratifying to see the high correlation between optical rotations of enantiomeric benzyl esters produced from transesterification of complementary alkylation products of valine and norephedrine-derived imides (Table 7). This result suggested that transesterification under these conditions proceeded without significant racemization. However, in order to provide definitive proof of this point, a rigorous racemization control experiment was conducted. This experiment is outlined in Scheme VIII.

Alkylation of lithium enolate **8a** with benzyl bromide affords **13**, which could be chromatographically resolved to high diastereomeric purity (**13r**:**13s** = 99.95:0.05). Transesterification with lithium benzyloxide in THF for 1 h at 0°C afforded benzyl ester **31** in 92% yield, which was hydrogenolized to the known (2R)-2-methyl hydrocinnamic acid **27** (vide supra). Treatment of this acid with ethyl chloroformate, followed by addition of the metalated valine-oxazolidone **32** afforded starting imide **13**. Diastereomer analysis (capillary GC) on the unpurified acylation product revealed a ratio **13r**:**13s**

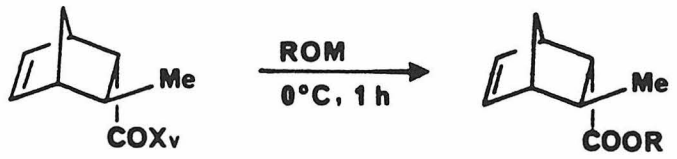
Scheme VIII



of 99.80:0.20. Thus, only 0.30% of racemization was obtained during this cycle, which sets an upper limit for epimerization during the transesterification step.

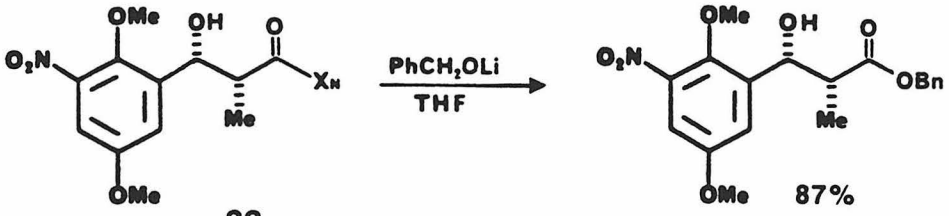
The cleavage of both the valine and the norephedrine oxazolidone auxiliaries with lithium benzyloxide in THF is a reaction that has found general synthetic utility in our laboratories. This reaction is applicable to imide products obtained from both alkylation reactions and aldol condensations.[22] Transformation to the benzyl ester has sometimes worked admirably in cases

where other reagents have failed (eq. 16).[21] The moderately sensitive aldol adduct **33** cleanly affords the benzyl ester under standard conditions (eq. 17).[22]



(16)

ROM = MeONa 44%
ROM = $PhCH_2OLi$ 96%



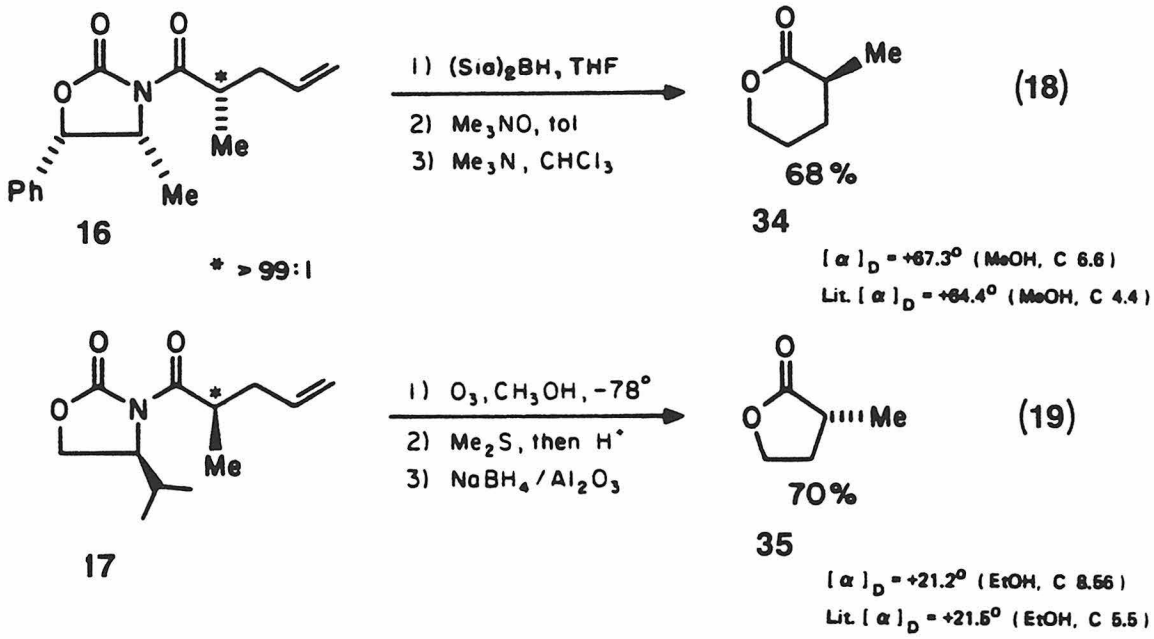
33

(17)

Unfortunately, attempts at using other alcohols in place of benzyl alcohol in these reactions fail. For example, when the reaction in equation 17 is carried out with lithium methoxide in THF at -20°C, only a 44% yield of methyl ester is obtained. The use of lithium ethoxide affords a 29% yield of product arising from attack at the oxazolidone ring carbonyl. The unparalleled success of benzyl alcohol in this reaction is mysterious, but might find explanation in some kind of unique aggregation phenomenon.[23]

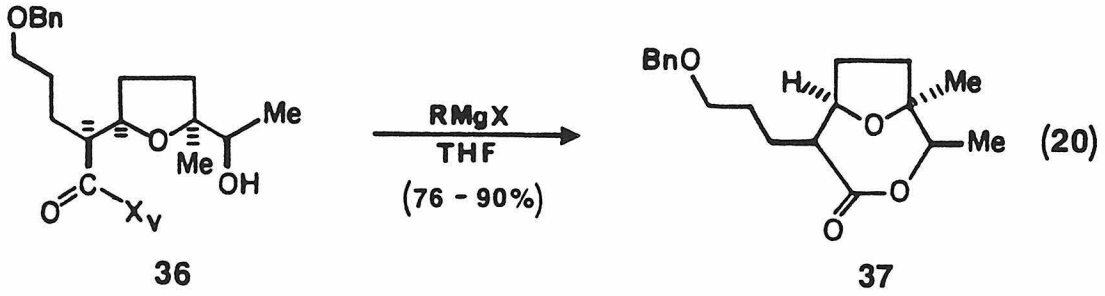
In contrast to the failure of alcohols other than benzyl alcohol to effect useful transesterifications, the intramolecular variant of this transformation proceeds quite smoothly. To demonstrate this point, as well as to provide further absolute configuration correlations, the allylated

propionates 16 and 17 were subjected to the reactions shown in equations 18 and 19 respectively. Thus, norephedrine imide 16 was hydroborated with disiamylborane (THF, 0°C for 1.5 h, RT for 30 min), and the resulting organo-



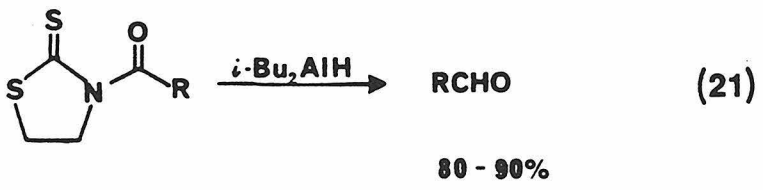
borane was oxidized with trimethylamine N-oxide in refluxing toluene. Addition of triethylamine and continued heating for 4 h effected cyclization, resulting in a 68% overall yield of (2S)-2-methylvalerolactone 34 after chromatography. The optical rotation for this (S)-lactone exceed the highest reported literature rotations calculated for the (R)-enantiomer.[6a] In addition, valine imide 17 was ozonized (-78 °C, MeOH) and the resultant aldehyde reduced with sodium borohydride to the carbinol, which spontaneously lactonized to (2R)-2-methyl butyrolactone 35 upon distillation.[16] The optical rotation for (R)-35 was also in good agreement with the highest literature value reported for this lactone.[17]

The observation that intramolecular oxazolidone cleavage is a viable reaction has prompted its use in synthetic projects currently underway in our laboratories. For example, in the context of an ionomycin total synthesis, the hydroxy imide **36** was cyclized in yields ranging from 76-90% by the agency of t-butyl Grignard in THF in the presence of lithium bromide (eq. 20).[24] That the seven-membered ring lactone **37** forms so readily is remarkable.



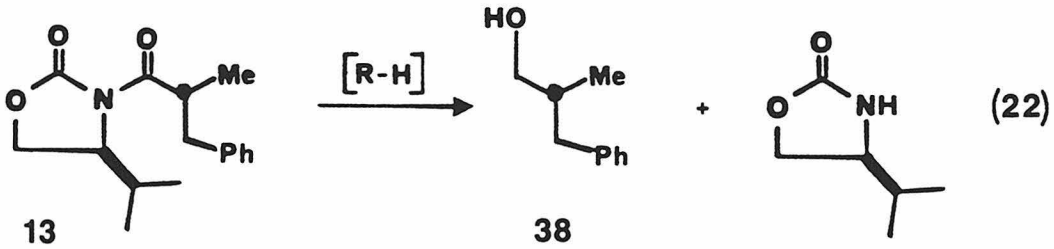
36 **37** (20)

As indicated in Scheme VII, we have been unable to find reducing conditions for the acyl carbonyl group which stop at the aldehyde oxidation state. We were hopeful that this transformation could be achieved, based upon the observation that reduction of 3-acyl-thiazolidine-2-thiones with diisobutyl aluminum hydride affords excellent yields of aldehydes (eq. 21).[25] However, the less basic oxazolidone carbonyl in our system appears to be unable to effectively stabilize the tetrahedral intermediate formed upon addition of 1 equivalent of DIBAL, and over-reduction to the primary alcohol was facile.



(21)

Alternatively, we have performed this operation by the two-step reduction-oxidation sequence shown in Scheme VII. We have found that reduction of oxazolidone imides with either lithium aluminum hydride (LAH) or lithium borohydride (LBH) in THF affords high yields of the primary alcohols without effecting reduction at the oxazolidone ring carbonyl. Given in Table 8 are the results on the effectiveness of various reducing agents in the reduction of benzylated valine imide **13** (eq. 22). Whereas the use of LAH affords both the highest yields and optical rotations of alcohol **38** (Table 8, Entries G-I), neither borane in THF (Table 8, Entries B and C) or sodium borohydride (Table 8, Entry J) are effective in this capacity.



13 **38** (22)

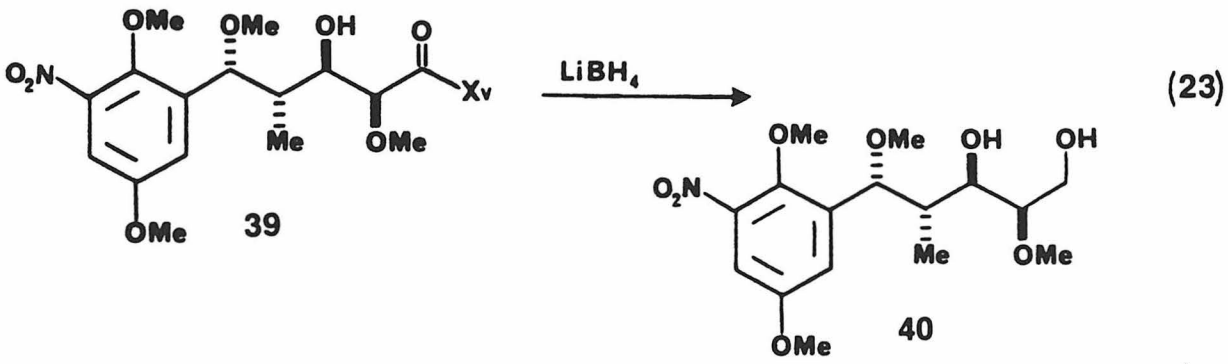
In Figure 6 are shown some representative imide reductions to primary alcohols which further serve as absolute configuration correlations. In all cases, the alcohol so obtained gave an optical rotation in excellent agreement with the highest known literature rotation reported for that compound. Furthermore, a nearly quantitative yield of the unreduced oxazolidone chiral auxiliary was recovered from each of these reductions.

We have also demonstrated that aldol adducts are viable substrates for these reductions. For example, treatment of aldol imide **39** with a solution of $LiBH_4$ in THF affords diol **40** in excellent yield (eq. 23).[30]

Table 8. Effectiveness of Reducing Agents in Imide Reduction (eq. 22).[a]

Entry	R-H (Equiv)[b]	Reaction[c] Conditions	Isolated Yield, %	$[\alpha]_D$ (c, CH_2Cl_2) deq
A	$(i\text{-Bu})_2AlH$ (3)	-78 °C, RT, overnight	49	+8.99 (1.29)
B	BH_3·THF (1)	-78 ° (2 h), 0 °C (45 min)	0	--
C	BH_3·THF (1)	overnight, RT	trace	--
D	$LiBH(Et)_3$ (1)	-78 °C (2 h), 0 °C (30 min)	10	--
E	$LiBH(Et)_3$ (5)	-78 °C, RT, overnight	70	+9.09 (0.61)
F	$LiBH_4$ (3)	RT (2 h)	78	+10.7 (0.65)
G	$LiAlH_4$ (3)	RT (2.5 h)	83	+11.0 (1.23)
H	$LiAlH_4$ (3)	RT (25 min)	86	+11.0 (1.15)
I	$LiAlH_4$ (3)	0 °C (25 min)	88	+10.3 (0.94)
J	$NaBH_4$ (3)	RT (2 h)	0	--

[a]13r:13s > 99:1. [b]Value in parenthesis is the number of molar equivalents of reducing agent used. [c]All reactions done in anhydrous THF, except Entry A, where diethyl ether was the solvent.



(23)

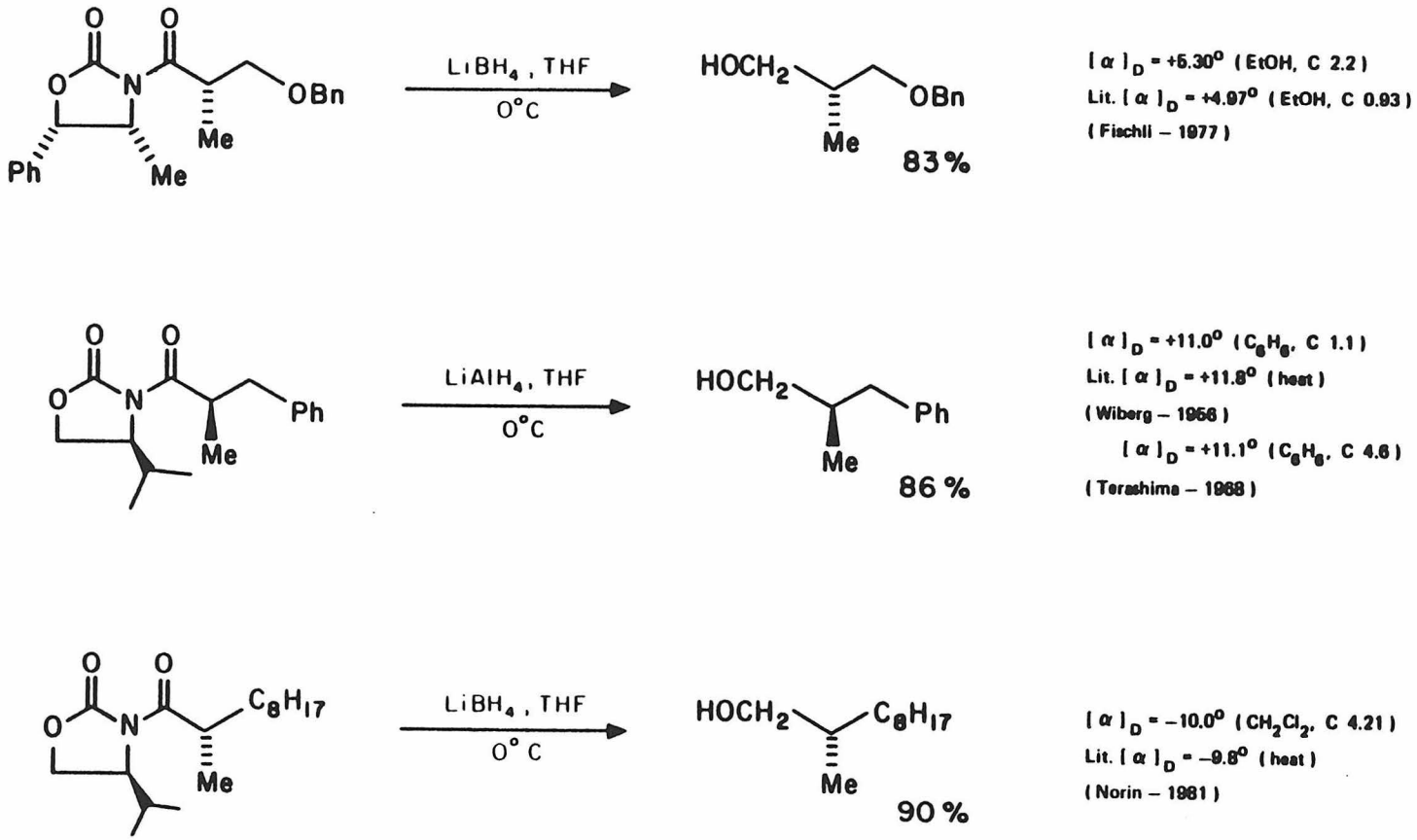


Figure 6. Representative Imide Reductions.

E. Acylation Results. Throughout the course of these investigations, it was observed that two minor byproducts were routinely formed during the alkylation reactions, and typically accounted for ca. 10% of all non-solvent peaks in the analytical GC trace. It was noted that these two byproducts, formed in approximately equal amounts, were present in all reactions, independent of which electrophile was used. These products could readily be separated by chromatography, and one of these compounds was so isolated from the products of an alkylation of the lithium enolate of valine-propionate **6** (R = Me). The spectral data obtained from this crystalline product were revealing. The ^{1}H NMR (90 MHz) indicated the presence of four methyl groups; a doublet, a triplet, and a set of two other doublets assignable to the isopropyl group on the oxazolidone ring. The ^{13}C NMR revealed a total of twelve carbons, three more than the starting imide **6** (R = Me). In addition, the infrared spectrum exhibited three different carbonyl frequencies. Although the second byproduct of the pair was not totally purified, the spectral characteristics of the impure sample indicated that it was a stereoisomer of the first compound. Based upon these observations, a tentative structural assignment was made, and is shown in Figure 7.

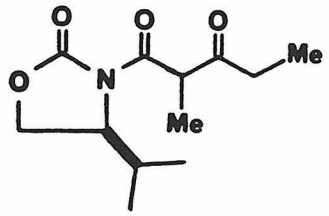
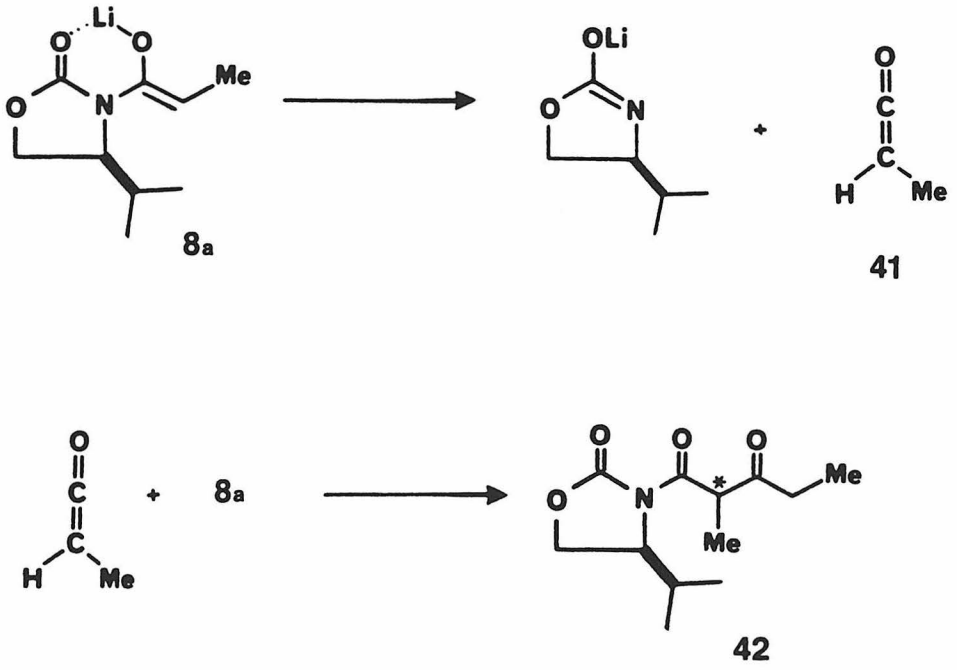


Figure 7. Possible Structure of Alkylation Byproduct.

The formation of β-keto imide products with the structure shown in Figure 7 can be explained by the sequence of events outlined in Scheme IX. Thermal fragmentation of lithium enolate **8a** occurs slowly at 0°C, affording the metalated valine oxazolidone and methyl ketene **41**. It would be expected that the highly energetic methyl ketene **41** would react immediately with remaining enolate **8a** in a stereorandom sense to produce roughly equal amounts of diastereomeric acylation products **42**. This mechanism would require the generation of one equivalent of valine oxazolidone **10** for

Scheme IX



*mixture of epimers

every equivalent of **42** formed. Reinspection of analytical GC traces from past alkylations revealed that this was indeed the case.

The mechanism in Scheme IV was further substantiated by the following experiment. A solution of lithium enolate **8a** in THF was generated with LDA at -78°C and allowed to warm to room temperature. After stirring at room temperature for 2 h, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the crude reaction product obtained after workup (89% mass balance) was analyzed by GC. The results of this experiment are shown in Figure 8. Clearly, the postulated β-keto

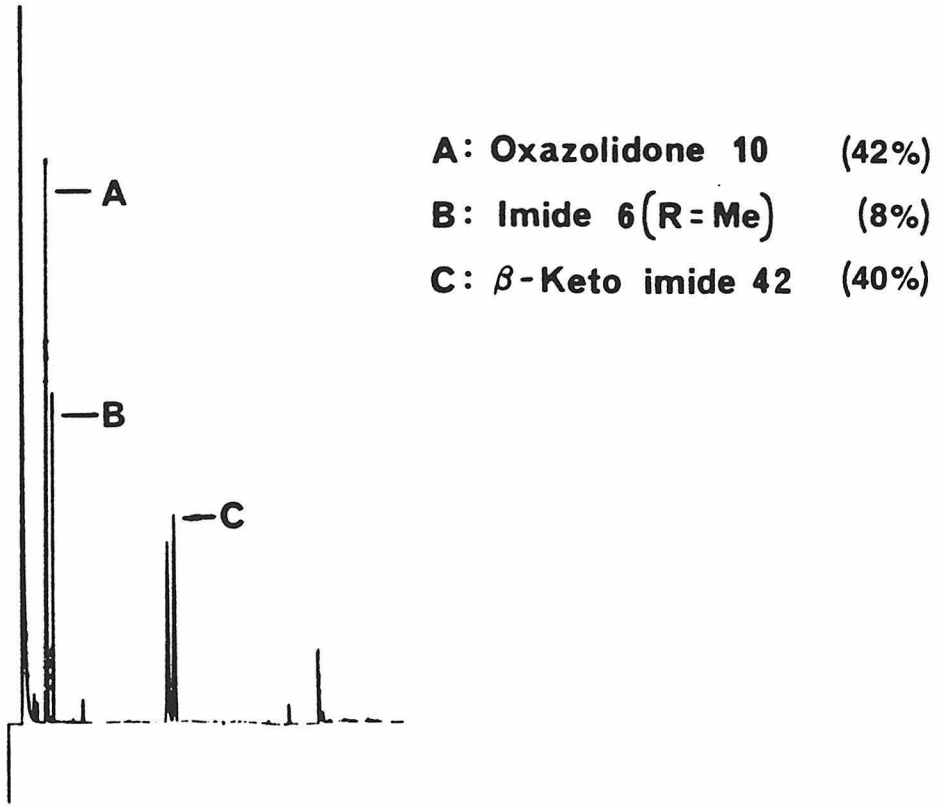
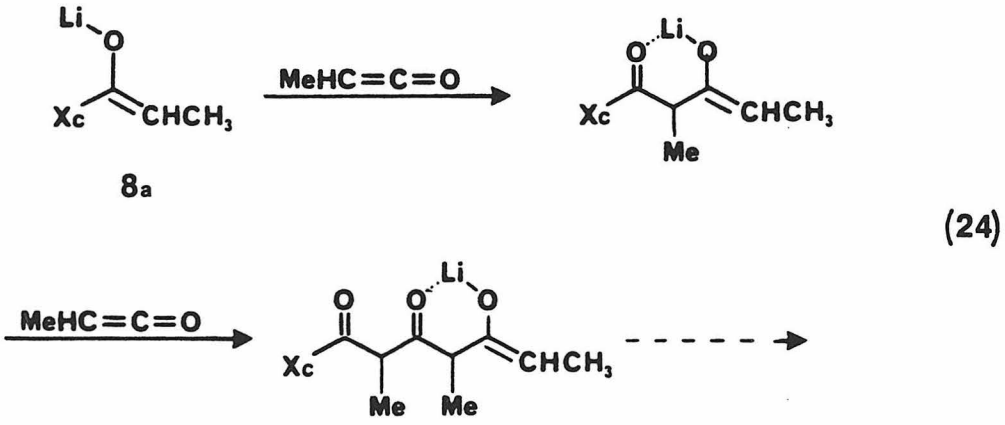


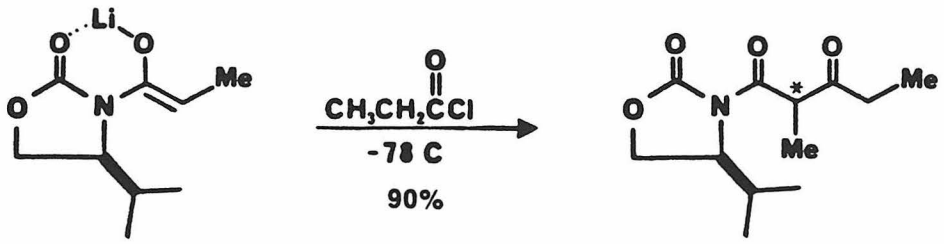
Figure 8. Analysis of Lithium-Enolate Breakdown.

imide peaks were cleanly generated in high yield (ca. 40%) under these conditions, along with the appropriate amount of valine oxazolidone. It is interesting to speculate that the 10% of other byproducts seen in this reaction (the longer retention time peaks in the trace above) might be the result of an additional molecule of methyl ketene adding to the enolate generated after attack of the first equivalent on **8a** (eq. 24).



(24)

Additional evidence for the proposed structure **42** was obtained from the following experiment. To a cooled (-78°C) solution of lithium enolate **8a** was added 1.2 equivalents of propionyl chloride (eq. 25). After stirring at -78°C for 2 h, the reaction was quenched and worked-up in the normal manner (see Experimental) to provide a white, crystalline powder (100% mass balance). Analysis of the unpurified reaction mixture by GC showed that this acylation reaction cleanly produced in high yield the same products as were seen from the thermal enolate decomposition experiment. Equally interesting, however, was the totally unexpected observation that this acylation proceeded with remarkable stereoselectivity, providing diastereomers of **42** in a ratio of 96:4. Since it was later shown that some thermal



(25)

* ≥ 96:4

racemization takes place under the conditions of the GC analysis,[31] this ratio represents a lower limit for the stereospecificity of this reaction.

The serendipitous discovery of β-keto imides systems such as **42** has opened a new avenue of investigation in our studies of chiral enolates. These systems exhibit a remarkable degree of stereochemical integrity. Racemization control experiments were carried out on purified diastereomer **42** (stereochemistry unknown) in dichloromethane at room temperature in the presence of 20 mol percent triethylamine. Under these conditions, it required over one week to reach an equilibrium value of diastereomers of ca. 3:2. The results of these studies are shown in Figure 9.

It was desired to determine whether the stereochemistry of the chiral center created during the acylation reaction was the same as that obtained from the alkylation experiments. Toward this end, an X-ray structure determination was carried out on the recrystallized product obtained from the quenching of lithium enolate **8a** with propionyl chloride (eq. 25).[32] Given in Figure 10 is the structure of the major diastereomer from this reaction. As can be seen, the absolute configuration at the C-2 center is **R**, consistent with the interpretation given for the alkylation reactions (vide

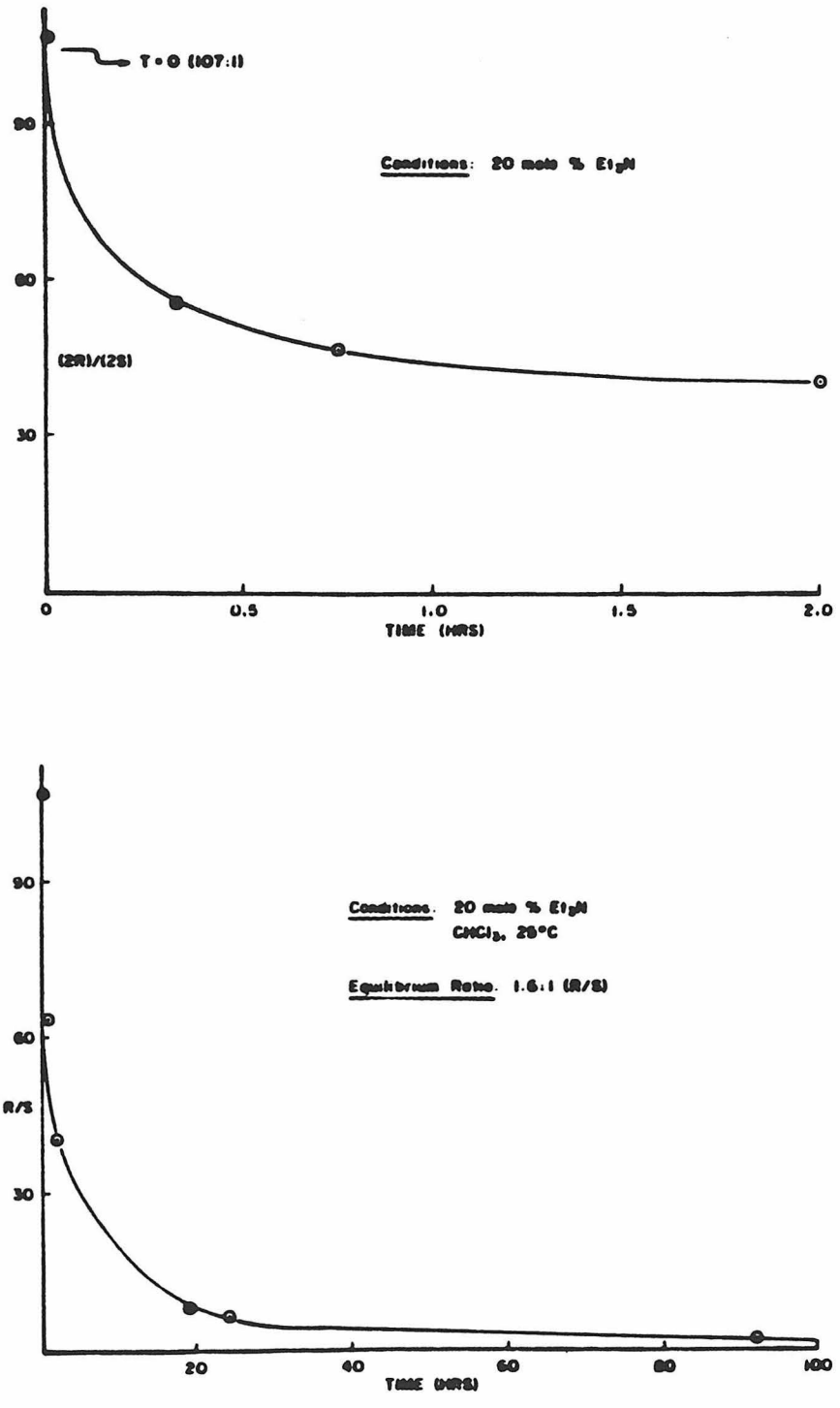


Figure 9. Racemization Curves for β-Keto Imide **42.**

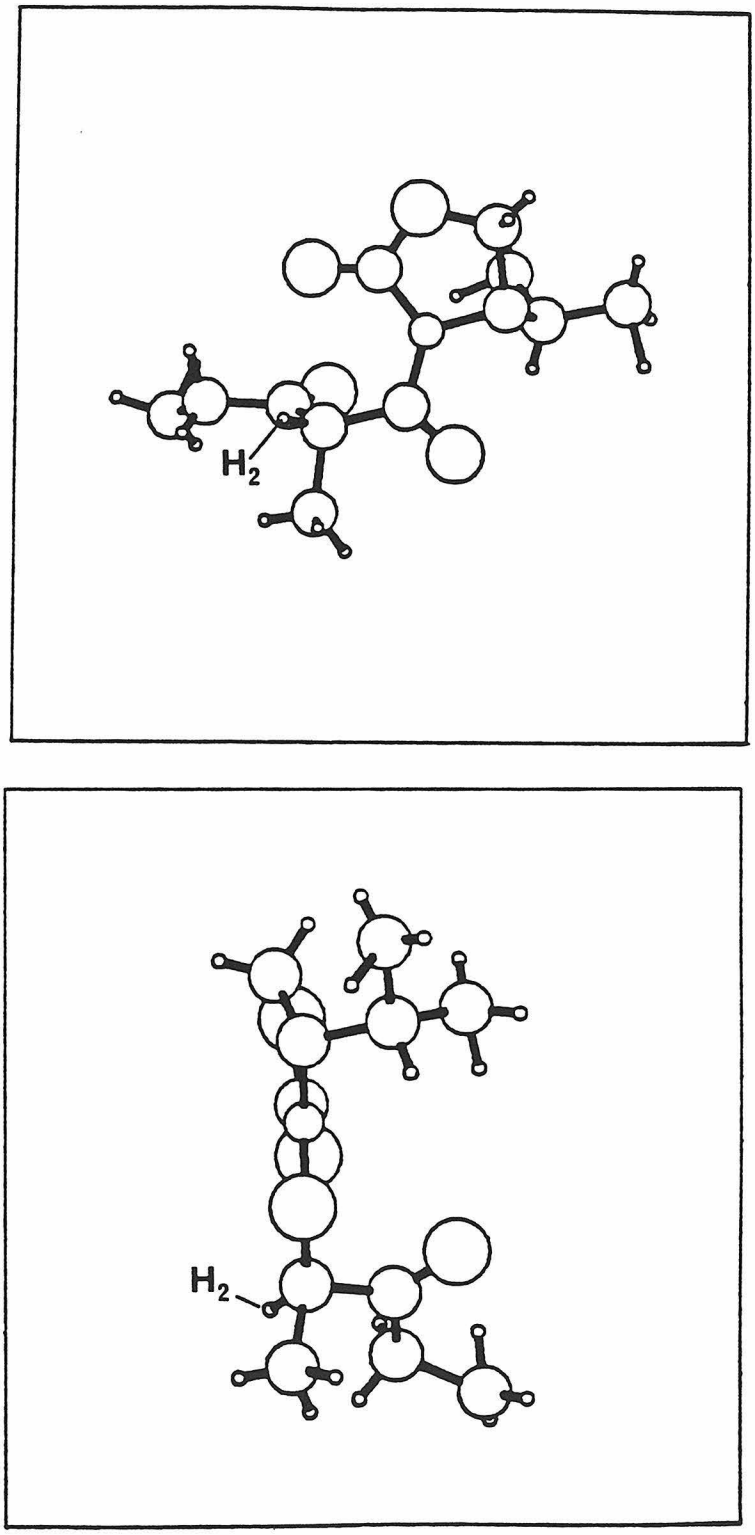


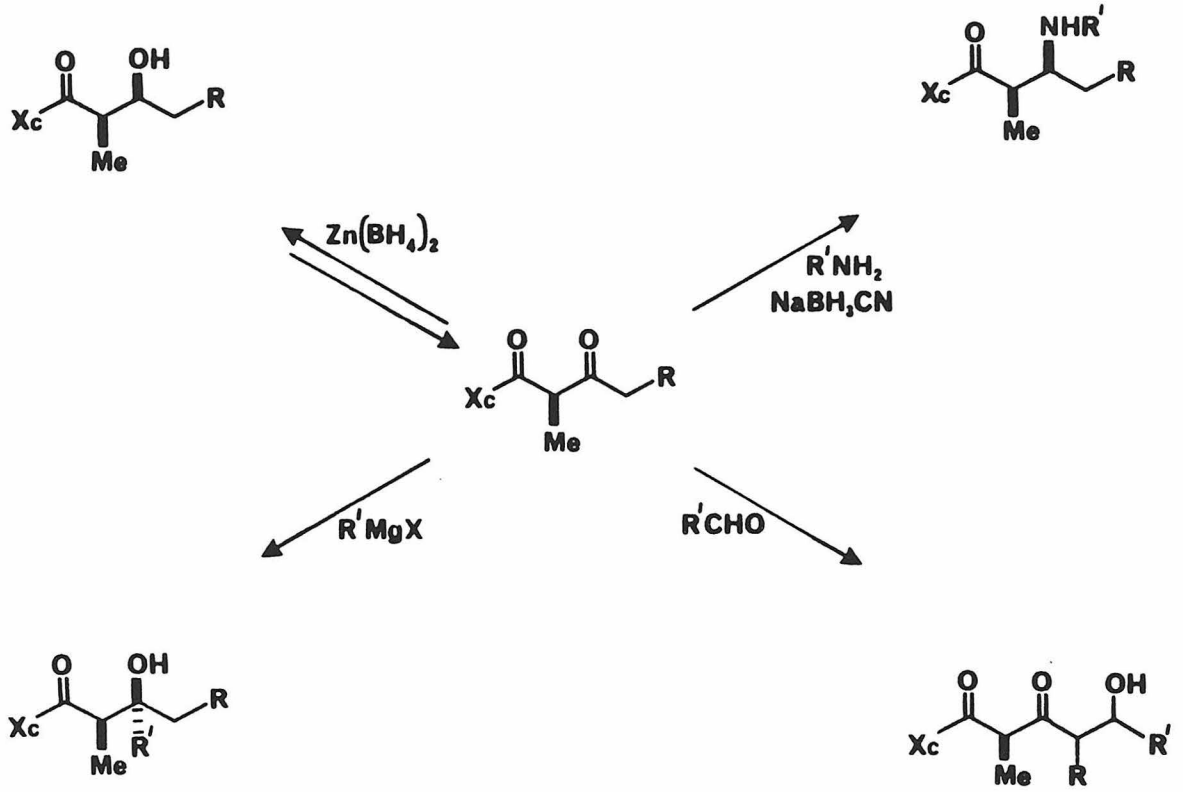
Figure 10. X-ray Structure of β-Keto Imide **42.**

supra). Thus, in analogy with alkyl halides, acid chlorides also react with imide-derived, metal-chelated Z-enolates from the least hindered side.

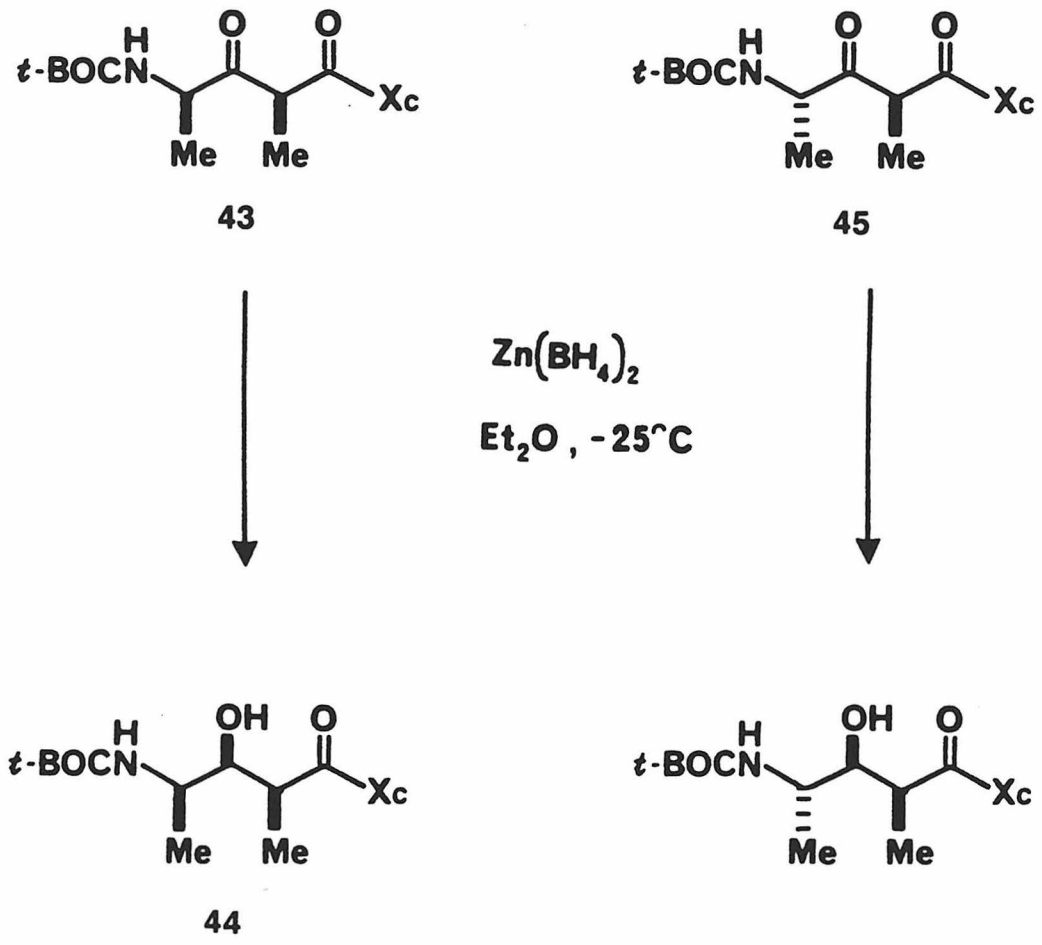
An examination of the X-ray structure reveals a possible reason for the reluctance of these systems toward epimerization. The enolizable methine proton (labeled H_2 in Figure 10) is oriented in a configuration which places the C-H bond orthogonal to either of the two carbonyl systems. Therefore, lack of sufficient σ-π orbital overlap may be responsible in part for the low kinetic acidity of these systems. Furthermore, the $A^{1,3}$-strain arguments given earlier to account for selective generation of (Z)-enolates from dialkylcarboxamides are also applicable here. Finally, it is interesting to note that the crystal structure of compound **42** shows the oxazolidone ring carbonyl opposed to the N-acyl carbonyl, an orientation which would be expected on the grounds of dipole repulsion.[33]

This new class of compounds, the β-keto imides, has the potential to extend the scope and practical utility of the oxazolidone based chiral enolate synthons. Outlined in Scheme X are just some of the possible useful transformations available to this system. Reduction with zinc borohydride affords high yields of β-hydroxy imides.[30] It has been shown that the stereochemistry of this reduction is determined solely by the configuration at the C-2 center, which directs hydride attack anti to that substituent in the chelated form to afford erythro products (Scheme X).[30,33] Additional studies carried out in other laboratories confirm this finding. Reduction of the diastereomeric β-keto imides **43** and **45** with zinc borohydride affords, in both cases, the 3-(S) alcohol (Scheme XI).[34] The stereochemically rich pentanoic acid derivative **44** is a useful fragment for the synthesis of bleomycin.

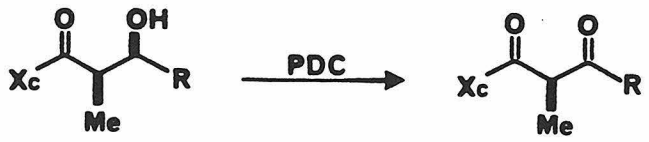
Scheme X



Scheme XI

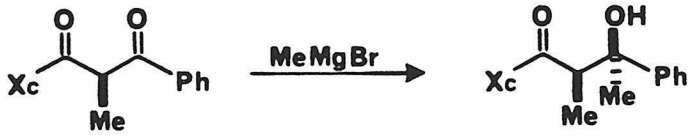


Conversely, oxidation of β-hydroxy imides, readily obtained through aldol condensations,[6b] should provide another entry into the β-keto imide manifold. It has been demonstrated that oxidation of aldol adducts with PDC cleanly affords the β-keto imides with <1% racemization at the C-2 center (eq. 26).[31]



(26)

Addition of organometallics to the β-keto imide systems might be expected to proceed in a stereoselective sense, giving rise to chiral tertiary alcohols (Scheme X). These compounds are the equivalent of an aldol adduct arising from the condensation of a ketone with chiral imide enolates, and would be difficult to prepare with high stereospecificity by other means. It has been shown that addition of methyl magnesium bromide to β-keto imide **46** affords a single stereoisomer, the absolute configuration of which has yet to be determined (eq. 27).[31]



46

(27)

Scheme X outlines other useful transformations open to the β-keto imides. Conceptually, reductive aminations to afford β-amino imides could serve as an entry into the β-lactams. Also, enolate chemistry of the distal methylene could become a very rapid route to acyclic carbon chains dense with stereochemistry. These projects, and others, are currently under investigation in our laboratories.

IV. Summary

The practical utility of N-acyl oxazolidones, derived from readily available chiral amino alcohols, as chiral enolate synthons has been demonstrated. The enolates derived from these systems exhibit a high degree of diastereoselectivity in reactions with alkyl halides and acid chlorides. Non-destructive removal of the oxazolidone chiral auxiliary by a variety of methods affords optical active compounds of high enantiomeric purity. Furthermore, recovery of the intact oxazolidone auxiliary permits economical recycling of the chiral moiety. These systems have already found application in the total synthesis efforts of natural products,[35] and have been recognized as valuable additions to the organic chemists repertoire of chiral enolate synthons.[36]

Experimental Section

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

Analytical gas-liquid chromatography was carried out on a Hewlett Packard 5880A Level 3 gas chromatograph equipped with a split mode capillary injection system and a flamed ionization detector, using a 25 m x 0.2 mm flexible fused silica capillary column wall-coated with Carbowax 20M or methyl silicone (SP-2100), or a 30 m x 0.32 mm fused silica capillary column

wall-coated with SE-54. Unless otherwise noted, injector and detector temperatures were 250°C. Chromatography on silica gel was performed using a forced flow[37] of the indicated solvent system on EM Reagents Silica Gel 60 (70-230 mesh), or for large scale preparative work on EM Reagents Silica Gel 60 (230-400 mesh). Medium pressure liquid chromatography (MPLC) was carried out using EM Reagents Lobar Silica Gel 60 prepacked columns (column size indicated) with a Fluid Metering Inc. Model RP-SY Lab Pump in conjunction with an ISCO Model UA-5 Absorbance/Fluoresence Monitor with Type 6 Optical Unit (2 mm path length cell, 15 μL volume). Analytical thick-layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Preparative thick-layer chromatography was performed using EM Reagents 2 mm silica gel 60-F plates (20 cm x 20 cm).

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, triethylamine, diisopropylethylamine, and boron trifluoride etherate were distilled from calcium hydride. Dimethyl sulfoxide, dimethylformamide, and hexamethylphosphoric triamide (HMPT) were distilled from calcium hydride and stored over activated 4 Å molecular sieves. Alkyl halides were passed down a column of activity I alumina immediately prior to use. All other reagents were used as received.

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

(2S)-2-Amino-3-methylbutanol [(S)-Valinol.] (9). A dry, 2-liter, three-

necked, round-bottomed flask equipped with a 250-mL pressure-equalizing addition funnel, mechanical stirrer, and a reflux condenser vented to a bubbler was flushed with nitrogen and charged with 100 g (0.86 mol) of (S)-valine and 250 mL of anhydrous tetrahydrofuran (THF). The addition funnel was charged with 115 mL (0.95 mol) of freshly distilled boron trifluoride etherate, which was added dropwise with stirring to the THF slurry over a 15-min period. After the addition was complete, the reaction mixture was heated to reflux and maintained at that temperature until all solids were dissolved (ca. 15 min). The addition funnel was then charged with 95 mL of a 10 M solution (0.95 mol) of borane-dimethyl sulfide complex, which was added to the externally heated reaction mixture at a rate which maintained a gentle reflux. During this addition, which required ca. 1 h, there was an exothermic evolution of hydrogen gas. Following the addition, heating at reflux was continued overnight (18 h). The clear, colorless reaction mixture was cautiously hydrolyzed by the dropwise addition of 84 mL of a 1:1 mixture of THF and water (addition time: 15 min), followed by the slow addition (15 min) of 700 mL of a 6 N aqueous solution of sodium hydroxide. After continued heating at reflux for an additional 4 h, the two-phase system was cooled, and the clear, upper organic layer was separated, and the milky, aqueous layer was exhaustively extracted with diethyl ether.[38] The combined organic phases were dried over anhydrous potassium carbonate, filtered, and concentrated on a rotary evaporator. The residue was distilled under reduced pressure to give 71 g (80%) of (S)-valinol (9), bp 90°C, 10 mm (Lit.[13] bp 78-79°C, 8 mm). IR ($CHCl_3$) 3700-2200, 1590, 1460, 1382, 1364 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.60 (d of d, 1, J = 4.5 Hz, 11 Hz, $-C\underline{H}_2OH$), 2.55 (m, 1, $-C\underline{H}-NH_2$), 2.10 (br

s, 3, -N<u>H</u>$_2$, -O<u>H</u>), 1.60 [m, 1, -C<u>H</u>(CH$_3$)$_2$]; $[\alpha]_D$ +17.2° (<u>c</u> 10.9, EtOH) [Lit.[13] $[\alpha]_D$ +16.4 (<u>c</u> 10.0 neat)].

(4S)-4-(2-Propyl)-oxazolidine-2-one [(S)-Valine Oxazolidone] (10). Into a dry 250-mL single-necked round-bottomed flask equipped for magnetic stirring was placed 59 g (0.57 mol) of (2S)-2-amino-3-methylbutanol, 77 mL (75 g, 0.63 mol) of diethyl carbonate, and <u>ca</u>. 4 g (~5 mol %) of anhydrous potassium carbonate. The flask was fitted with a short-path distillation head and the stirred reaction mixture was heated in an oil bath pre-equilibrated to 100°C. Heating was continued until ethanol distillation ceased (<u>ca</u>. 14 h). Upon cooling to room temperature, the contents of the flask solidified. The reaction product was dissolved in dichloromethane, filtered through a Celite pad, and concentrated <u>in vacuo</u> to give a colorless solid. Recrystallization from diethyl ether afforded 70 g (95%) of **10** as a white crystalline solid, mp 71-72°C. IR ($CHCl_3$) 3484, 3400-3200, 3030, 2980, 1755, 1215 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.77 (broad s, 1, -N<u>H</u>), 4.40 (t, 1, J = 9 H, C_5-<u>H</u>), 4.03 (d of d, 1, J = 6 Hz, 9 Hz, C_5-<u>H</u>), 3.60 (q, 1, J = 7 H, C_4-<u>H</u>), 1.70 [m, 1, $(CH_3)_2C\underline{H}$-], 0.94 [t, 6, J = 6 Hz, -CH($C\underline{H}_3$)$_2$]; ^{13}C NMR (CCl_4) δ 160.4, 68.2, 58.2, 32.6, 17.7, 17.5; $[\alpha]_D$ -16.6° (<u>c</u> 5.81, EtOH).

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

(4R,5S)-4-Methyl-5-phenyloxazolidine-2-one [Norphedrine Oxazolidone] (12). Into a dry 300-mL single-necked, round-bottomed flask equipped for magnetic stirring was placed 40.2 g (0.27 mol) of (1S,2R)-2-amino-2-phenylpropanol, 36 mL (35.1 g, 0.30 mol) of diethyl carbonate, and <u>ca</u>. 2 g (~5 mol %) of anhydrous potassium carbonate. The flask was fitted

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

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

General Procedure for the Acylation of Oxazolidones 10 and 12. A mechanically-stirred solution of the indicated oxazolidone in anhydrous tetrahydrofuran (0.2 → 0.3 M) under a nitrogen atmosphere is treated dropwise at -78° C with a solution of n-butyllithium in hexane (1.0 → 1.2 equiv) over 5-10 min.[40] After stirring an additional 20 min at -78° C, the appropriate acid chloride (1.2 equiv)[41] is added to the reaction mixture, either neat or as a THF solution. After the addition is complete, the reaction is allowed to warm to room temperature and stirred for an additional 1-2 h. The clear reaction mixture is then poured into an equal volume of a saturated aqueous solution of ammonium chloride and volatiles are removed by rotary evaporation. The

resulting aqueous residue is extracted three times with dichloromethane and the combined organic phases are washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The N-acyl oxazolidones are purified by vacuum distillation, column chromatography, or both.

(4S)-3-Propionyl-4-(2-propyl)-oxazolidine-2-one (**6**, R = Me). A solution of 3.0 g (23 mmol) of valine-oxazolidone **10** (ca. 0.25 M in THF) was metalated using 18.8 mL of a 1.49 M solution (28 mmol) of n-butyllithium in hexane and acylated with 2.43 mL (2.59 g, 28 mmol) of propionyl chloride according to the general procedure described above to afford 4.74 g (110% mass balance) of unpurified product. The title compound was isolated by chromatography on silica gel (250 g, 20% ethyl acetate:hexane) followed by molecular distillation (Kugelrohr, 140°C, 0.01 mm) to give 4.18 g (97%) of **6** (R = Me) as a clear, colorless oil. IR ($CHCl_3$) 3015, 2890, 1785, 1705, 1392, 1380, 1209 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.50-4.11 (m, 3, C_4-H, C_5-H_2), 2.90 (q, 2, J = 7 Hz, -CH_2CH_3), 2.33 [d of septets, 1, J = 7 Hz, 4 Hz, -$CH(CH_3)_2$], 1.14 (t, 3, J = 7 Hz, -CH_2CH_3), 0.94 [d, 3, J = 7 Hz, -$CH(CH_3)_2$], 0.90 [d, 3, J = 7 Hz, -$CH(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 174.0, 154.1, 63.4, 58.4, 29.1, 28.5, 17.9, 14.7, 8.4; $[\alpha]_D$ +97.3° (c 1.79, CH_2Cl_2).

Anal. calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.46; H, 8.29; N, 7.41.

(4R,5S)-3-Propionyl-4-methyl-5-phenyl-oxazolidine-2-one (**7**, R = Me). A solution of 4.68 g (26.4 mmol) of norephedrine-oxazolidone **12** (ca. 0.25 M in THF) was carefully metalated using 18.0 mL of a 1.47 M solution (26.4 mmol) of n-butyllithium in hexane and acylated with 2.8 mL (2.93 g, 31.7 mmol) of propionyl chloride according to the previously described procedure

to afford 6.08 g (99% mass balance) of unpurified product. The title compound was isolated by chromatography of silica gel (300 g, 20% ethyl acetate:hexane) followed by molecular distillation (Kugelrohr, 120° C, 0.006 mm) to give 5.73 g (93%) of **7** (R = Me) as a clear, colorless oil. IR ($CHCl_3$) 3030, 3000, 1780, 1705, 1455, 1370, 1350, 1197 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.28 (s, 5, aromatic H's), 5.65 (d, 1, J = 8 Hz, C_5-H), 4.70 (quintet, 1, J = 8 Hz, C_4-H), 2.84 (q, 2, J = 7 H, $-CH_2CH_3$), 1.10 (t, 3, J = 7 Hz, $-CH_2CH_3$), 0.83 (d, 3, J = 8 Hz, C_4-CH_3); ^{13}C NMR ($CDCl_3$) δ 173.7, 153.0, 133.5, 128.6, 125.6, 79.0, 54.7, 29.2, 14.5, 8.3; $[\alpha]_D$ +43.3° (c 3.61, CH_2Cl_2).

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

(4S)-3-Butyryl-4-(2-propyl)-oxazolidine-2-one (**6**, R = Et). A solution of 2.80 g (21.7 mmol) of valine-oxazolidone **10** (ca. 0.25 M THF) was metalated using 17.7 mL of a 1.47 M solution (26.0 mmol) of n-butyllithium in hexane and acylated with 2.7 mL (26.0 mmol) of butyryl chloride according to the previously described procedure to afford 4.10 g (95% mass balance) of unpurified product. The title compound was isolated by chromatography on silica gel (300 g, 20% ethyl acetate:hexane) followed by molecular distillation (Kugelrohr, 150°C, 0.005 mm) to give 4.01 g (93%) of **6** (R = Et) as a clear, colorless oil. IR ($CHCl_3$) 2970, 1780, 1700, 1384, 1209 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.54-4.04 (m, 3, C_4-H, C_5-H_2), 3.04-2.74 [d of t, 2, J = 7 Hz, 4 Hz, $-C(O)CH_2-$), 2.57-2.17 [d of septets, 1, J = 7 Hz, 4 Hz, $-CH(CH_3)_2$] 1.69 (sextet, 2, J = 7 Hz, $-CH_2CH_3$), 0.97 (t, 3, J = 7 Hz, $-CH_2CH_3$), 0.90 [d, 3, J = 7 Hz, $-CH(CH_3)_2$], 0.87 [d, 3, J = 7 Hz, $-CH(CH_3)_2$]; $[\alpha]_D$ +89.9° (c 3.80, CH_2Cl_2).

Anal. calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: 60.34; H, 8.59; N, 7.02.

General Procedure for the Alkylation of N-Acyl-Oxazolidones. The following alkylation reactions were carried out under a nitrogen atmosphere on scales ranging from 1-300 mmol at enolate concentrations of ca. 0.50 M. All reagent additions were made via hypodermic syringe. Alkylating agents were either freshly distilled or passed through a column of neutral alumina immediately prior to use.

Enolate Generation. A. Lithium Enolate. To a dry, nitrogen-filled, 100-mL single-necked flask equipped with a magnetic stirrer and rubber septum was added 20 mL of anhydrous tetrahydrofuran (THF) and 1.54 mL (11 mmol) of anhydrous diisopropylamine. After cooling to -78 °C, 7.5 mL of n-butyllithium (1.47 M in hexane) was added, at which point the cooling bath was removed and stirring was continued for ca. 10 min at ambient temperature. After re-cooling to -78 °C, a solution of the indicated N-acyl oxazolidone (10 mmol, 2 M in THF) was introduced, and after stirring for 30 min at -78 °C, the desired lithium enolate was ready for alkylation.

B. Sodium Enolate. Into a dry, 100-mL single-necked flask containing a magnetic stirrer was weighed 2.0 g (11 mmol) of sodium hexamethyldisilylamide[42] (NHDS) in a dry box. The flask was sealed with a rubber septum, removed from the dry box, and 20 mL of anhydrous tetrahydrofuran (THF) was added. Upon cooling to -78 °C, a solution of the indicated N-acyl oxazolidone (10 mmol, 2 M in THF) was introduced, and after stirring for 30 min at -78 °C, the desired sodium enolate was ready for alkylation.

C. Potassium Enolate. A stock solution of potassium hexamethyldisilyl-

amide (KHDS) in anhydrous tetrahydrofuran (0.5 M) was prepared according to the procedure of Brown.[42] Into a dry, 10-mL, single-necked flask equipped for magnetic stirring was weighed the indicated N-acyl oxazolidone (1 mmol). The flask was sealed with a rubber septum, purged with nitrogen, cooled to -78 °C, then treated with 2.2 mL (1.1 mmol) of the stock solution of KHDS in THF. After stirring for 30 min at -78 °C, the potassium enolate was ready for alkylation.

Enolate Alkylation. To the cold enolate solutions (-78 °C) prepared as described above were added the indicated electrophiles (1-10 equiv) neat via syringe. The amount of alkylating agent, as well as the temperature and duration of the alkylation reaction were variables specific to each experiment. The reactions were quenched by the addition of a saturated aqueous solution of ammonium chloride (1 mL per mmol enolate). Volatiles were removed in vacuo, and the resulting aqueous residue was extracted with dichloromethane (3x). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate (1x), brine (1x), and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded the unpurified alkylated products with excellent mass balance. Gas chromatographic analyses were performed on the unfractionated reaction products to determine the extent and diastereoselectivity of each alkylation reaction. Products were purified by either medium-pressure chromatography or flash chromatography as indicated in the following specific examples.

(4S)-3-[(2R)-2-Methyl-3-phenylpropionyl]-4-(2-propyl)-oxazolidine-2-one (13) (Table 2, Entry A). To a cooled (-78 °C) solution of lithium enolate **8a** (R = Me, 10 mmol, 0.5 M in THF) was added 3.60 mL (30 mmol) of benzyl

bromide. The reaction was brought to 0°C, stirred for 2 h, and the product was isolated according to the previously described procedure to give 5.70 g (93% mass balance) of unpurified product. Diastereomer analysis (SE-54, 140°C (10 min) → 200°C, t_r **13s** = 14.25 min, t_r **13r** = 14.59 min) afforded a ratio of **13r:13s** > 99:1. The product was purified by flash chromatography (300 g silica gel, 15% ethyl acetate:hexane, major diastereomer eluted second) to give 2.56 g (97%) of **13** as a colorless oil (**13r:13s** > 99:1). IR (CH_2Cl_2) 3070, 2990, 1782, 1704, 1389, 1241, 1211 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.22 (s, 5, aromatic H's), 4.50-3.93 (m, 4, C_4-H, C_5-H_2, -CHCH$_3$), 3.08 (d of d, 1, J = 14 Hz, 7 Hz, PhCH_2-), 2.57 (d of d, 1, J = 14 Hz, 7 Hz, PhCH_2-), 2.11 (d of septets, 1, J = 3 Hz, 7 Hz, -CH(CH$_3$)$_2$), 1.12 (d, 3, J = 7 Hz, -CHCH_3), 0.80 (d, 3, J = 7 Hz, -CH(CH_3)$_2$), 0.58 (d, 3, J = 7 Hz, -CH(CH_3)$_2$); $[\alpha]_D$ +9.42° (c 2.06, CH_2Cl_2).

Anal. calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.88; H, 7.73; N, 5.15.

(4R,5S)-3-[(2S)-2-Methyl-3-phenylpropionyl]-4-methyl-5-phenyloxazolidine-2-one (14) (Table 2, Entry B). To a cooled (-78°C) solution of lithium enolate **8b** (R = Me, 10 mmol, 0.5 M in THF) was added 3.60 mL (30 mmol) of benzyl bromide. The reaction was brought to 0°C, stirred for 2 h, and the product was isolated according to the previously described procedure to give 6.48 g (97% mass balance) of unpurified product. Diastereomer analysis (SE-54, 200°C, t_r **14r** = 10.35 min, t_r **14s** = 11.88 min) afforded a ratio of **14r:14s** = 2:98. The product was isolated by flash chromatography (300 g silica gel, 20% ethyl acetate:hexane, major diastereomer eluted second) followed by molecular distillation (Kugelrohr, 150°C, 0.005 mm) to give 2.52 g (78%) of

14 as a colorless oil (**14r:14s** > 1:99). IR (CH_2Cl_2) 3080, 2992, 1780, 1700, 1421, 1265, 895 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ7.43-7.03 (m, 10, aromatic H's), 5.57 (d, 1, J = 7 Hz, C_5-H), 4.70 (quintet, 1, J = 7 Hz, C_4-H), 4.12 (sextet, 1, J = 7 Hz, -CHCH$_3$), 3.10 (d of d, 1, J = 14 Hz, 7 Hz, PhCH$_2$-), 2.61 (d of d, 1, J = 14 Hz, 7 Hz, PhCH$_2$-), 1.28 (d, 3, J = 7 Hz, -CHCH$_3$), 0.70 (d, 3, J = 7 Hz, C_4-CH$_3$); $[\alpha]_D$ +78.5° (c 1.68, CH_2Cl_2).

Anal. calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.30; H, 6.69; N, 4.44.

(4S)-3-[(2R)-2-Methylpent-4-enoyl]-4-(2-propyl)-oxazolidine-2-one (15). (a) Lithium Enolate Alkylation (Table 2, Entry C). To a cooled (-78°C) solution of lithium enolate **8a** (R = Me, 10 mmol, 0.5 M in THF) was added 0.95 mL (11 mmol) of allyl bromide. The reaction was brought to 0°C, stirred for 2 h, and the product was isolated according to the previously described procedure to give 2.13 g (95% mass balance) of unpurified product. Diastereomer analysis (SE-54, 140°C, t_r **15s** = 3.78 min, t_r **15r** = 4.03 min) afforded a ratio of **15r:15s** = 98:2. The product was purified by MPLC (Merck Lobar C column) using ethyl acetate, dichloromethane, hexane (1:1:9; major diastereomer eluted second) to give 1.34 g (60%) of **15** as a colorless oil (**15r:15s** = 99:1). An identical reaction using 2.6 mL (30 mmol) of allyl bromide gave 1.78 g (79%) of **15** after chromatography (154:15s = 98:2).

b) Sodium Enolate Alkylation (Table 3, Entry B). To a cooled (-78°C) solution of sodium enolate **8a** (R = Me, 1 mmol, 0.5 M in THF) was added 0.10 mL (1.1 mmol) of allyl bromide. The reaction was brought to 0°C, stirred for 2 h, and the product was isolated according to the previously described procedure to afford 210 mg (93% mass balance) of unpurified product.

Diastereomer analysis as before revealed a ratio of **15r:15s** = 96:4 (80% yield by GC). An identical experiment performed entirely at -78°C for 2 h (Table 3, Entry C) gave a ratio of **15r:15s** = 99:1 (29% yield by GC). IR ($CHCl_3$) 3030, 2980, 1780, 1700, 1387, 1222 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.01-5.57 (m, 1, -C<u>H</u>=CH_2), 5.20-4.90 (m, 2, -CH=C<u>H_2</u>), 4.57-4.10 (m, 3, C_5-<u>H_2</u>, C_4-<u>H</u>), 3.87 (sextet, 1, J = 7 Hz, -C<u>H</u>CH_3), 2.71-2.00 [m, 3, -C<u>H_2</u>CH=CH_2, -C<u>H</u>$(CH_3)_2$], 1.14 (d, 3, J = 7 Hz, -CHC<u>H_3</u>), 0.90 [d, 3, J = 7 Hz, -CH(C<u>H_3</u>$)_2$), 0.87 [d, 3, J = 7 Hz, -CH(C<u>H_3</u>$)_2$]; $[\alpha]_D$ +62.2 (<u>c</u> 5.90, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.17; H, 8.60; N, 6.27.

(4S)-3[(2R)-2,4-Dimethylpent-4-enoyl]-4-(2-propyl)-oxazolidine-2-one (17) (Table 2, Entry E). To a cooled (-78°C) solution of lithium enolate **8a** (R = Me, 10 mmol, 0.5 <u>M</u> in THF) was added 3.1 mL (30 mmol) of 3-bromo-2-methyl-2-propene (methallyl bromide). The reaction was brought to 0°C, stirred for 2 h, and the product was isolated according to the previously described procedure to give 2.41 g (100% mass balance) of unpurified product. Diastereomer analysis (SE-54, 140°C, t_r **17s** = 3.20 min, t_r **17r** = 3.40 min) afforded a ratio of **17r:17s** = 98:2. The product was purified by MPLC (Merck Lobar <u>C</u> column, 15% ethyl acetate:hexane, major diastereomer eluted second) followed by molecular distillation (Kugelrohr, 150°C, 0.005 mm) to give 1.57 g (62%) of **17** as a colorless oil (**17r:17s** > 99:1). IR ($CHCl_3$) 3030, 2980, 1780, 1700, 1388, 1215 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.70 (br s, 2, -C=C<u>H_2</u>), 4.53-4.07 (m, 3, C_4-<u>H</u>, C_5-<u>H_2</u>), 3.96 (sextet, 1, J = 7 Hz, -C<u>H</u>CH_3), 2.51 (d of d, 1, J = 15 Hz, 8 Hz, -C<u>H_2</u>-), 2.29 [d of septets, 2, J = 3 Hz, 7 Hz, -C<u>H</u>$(CH_3)_2$], 2.02 (d of d, 1, J = 15 Hz, 8 Hz, -C<u>H_2</u>-), 1.76 (s, 3, CH_2=C-CH_3),

1.11 (d, 3, J = 7 Hz, -CHC$\underline{H}_3$), 0.89 (d, 3, J = 7 Hz, -CH(C$\underline{H}_3$)$_2$) , 0.89 (d, 3, J = 7 Hz, -CH(C$\underline{H}_3$)$_2$) , 0.83 (d, 3, J = 7 Hz, -CH(C$\underline{H}_3$)$_2$) ; $[\alpha]_D$ +71.4° ($\underline{c}$ 2.79, CH_2Cl_2).

Anal. calcd. for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84. Found: C, 63.30; H, 9.01.

(4R,5S)-3-((2S)-2,4-Dimethylpent-4-enoyl) -4-methyl-5-phenyloxazolidine-2-one 18 (Table 2, Entry F). To a cooled (-78° C) solution of lithium enolate **8b** (R = Me, 10 mmol, 0.5 M in THF) was added 3.10 mL (30 mmol) of 3-bromo-2-methyl-1-propene (methallyl bromide). The reaction was brought to 0° C, stirred for 2 h, and the product was isolated according to the previously described procedure to give 3.03 g (106% mass balance) of unpurified product. Diastereomer analysis (SE-54, 180° C, t_r **18r** = 6.06 min, t_r **18s** = 6.53 min) afforded a ratio of **18r:18s** = 3:97. The product was purified by MPLC (Merck Lobar C column, 20% diethyl ether:hexane, major diastereomer eluted second) to give 1.79 g (62%) of **18** as a low-melting, colorless solid, mp 42-44°C, (**18r:18s** < 1:99). A similar experiment using 2 equiv of 3-iodo-2-methyl-1-propene (methallyl iodide) as the alkylating agent (alkylation conditions: 1 h at -78°C, 2 h at ca -35°C) afforded 2.10 g (73%) of **18** (**18r:18s** < 1:99) after chromatography on silica gel. IR ($CHCl_3$) 3070, 2980, 2930, 1784, 1705, 1345, 1200 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.50-7.17 (m, 5, aromatic H's), 5.63 (d, 1, J = 7 Hz, C_5-H), 4.76 (quintet, 1, J = 7 Hz, C_4-H), 4.72 (br d, 2, J = 7 Hz, -C=C$\underline{H}_2$), 4.02 (sextet, 1, J = 7 Hz, -C$\underline{H}$CH$_3$), 2.53 (d of d, 1, J = 14 Hz, 7 Hz, -C$\underline{H}_2$-), 2.06 (d of d, 1, J = 14 Hz, 7 Hz, -C$\underline{H}_2$-), 1.77 (s, 3, -CH$_2$=CC$\underline{H}_3$), 1.17 (d, 3, J = 7 Hz, -CHC$\underline{H}_3$), 0.86 (d, 3, J = 7 Hz, C_4-C$\underline{H}_3$); $[\alpha]_D$ +33.7° ($\underline{c}$ 5.90, CH_2Cl_2).

Anal. calcd. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.97; H, 7.26; N, 5.05.

(4S)-3-[(2R)-2-Methylbutyryl]-4-(2-propyl)-oxazolidine-2-one 23 (Table 2, Entry K). To a cooled (-78°C) solution of lithium enolate **8a** (R = Me, 10 mmol, 0.5 M in THF) was added 3.10 mL (30 mmol) of ethyl iodide. The reaction was brought to 0°C, stirred for 2 h, and the product was isolated according to the previously described procedure to give 2.03 g (95% mass balance) of unpurified product. Diastereomer analysis (SE-54, 140°C, t_r **23s** = 2.44 min, t_r **23r** = 2.56 min) afforded a ratio of **23r:23s** = 94:6. The product was purified by MPLC (Merck Lobar C column, 17% ethyl acetate:hexane, major diastereomer eluted second) followed by molecular distillation (Kugelrohr, 165°C, 0.01 mm) to give 724 mg (34%) of **23** as a colorless oil (**23r:23s** = 94:6). An identical experiment using 8.00 mL (100 mmol) of ethyl iodide afforded 771 mg (36%) of diastereomerically pure **23** (23r:23s > 99:1) as an oil after chromatography. IR (CH_2Cl_2) 2970, 1778, 1700, 1382, 1208 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.57-4.10 (m, 3, C_5-H_2, C_4-H), 3.69 (sextet, 1, J = 7 Hz, -CHCH$_3$), 2.23 (d of septets, 1, J = 4 Hz, 7 Hz, -CH(CH$_3$)$_2$), 2.00-1.27 (m, 2, -CH$_2$CH$_3$), 1.13 (d, 3, J = 7 Hz, -CHCH$_3$), 0.94 (d, 3, J = 4 Hz, -CH(CH$_3$)$_2$), 0.93 (t, 3, J = 7 Hz, -CH$_2$CH$_3$), 0.87 (d, 3, J = 7 Hz, -CH(CH$_3$)$_2$); $[\alpha]_D$ +61.6° (c 8.50, CH_2Cl_2).

Anal. calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.09; H, 8.91; N, 6.65.

(4S)-3-[(2S)-2-Methylbutyryl]-4-(2-propyl)-oxazolidine-2-one (23) (Table 2, Entry M). **a) Lithium Enolate Alkylation.** To a cooled (-78° C) solution of lithium enolate **8a** (R = Et, 10 mmol, 0.5 M in THF) was added 1.90 mL (30

mmol) of methyl iodide. The reaction was brought to 0°C, stirred for 2 h, and the product was isolated according to the previously described procedure to give 2.12 g (100% mass balance) of unpurified product. Diastereomer analysis (SE-54, 130°C (8 min)→ 200°C, t_r **23s** = 2.77 min, t_r **23r** = 2.91 min) afforded a ratio of **23r:23s** = 11:89. The product was purified by MPLC (Merck Lobar B column, 17% ethyl acetate:hexane) to give 1.79 g (86%) of **23** as a colorless oil (**23r:23s** = 10:90). A similar reaction (1 mmol scale) using 1.1 equiv of methyl iodide (alkylation conditions: 2 h at -78°C, 1 h at 0°C) afforded a ratio of **23r:23s** = 10:90, in 80% yield by GC (Table 3, Entry F).

b) Sodium Enolate Alkylation (Table 3, Entry H). To a cooled (-78°C) solution of sodium enolate **8a** (R = Et, 10 mmol, 0.5 M in THF) was added 3.10 mL (50 mmol) of methyl iodide. The reaction was stirred at -78°C for 3 h, then worked up in the usual manner to give 2.10 g (99% mass balance) of unpurified product. Diastereomer analysis as described for the lithium enolate reaction revealed a product ratio of **23r:23s** = 9:91. Purification by MPLC (Merck Lobar C column, 10% THF:hexane, major diastereomer eluted second) and subsequent molecular distillation (Kugelrohr, 180°C, 0.01 mm) afforded 1.69 g (79%) of **23** as a colorless oil (**23r:23s** = 1:99). A similar reaction (1 mmol scale) using 1.1 equiv of methyl iodide (alkylation conditions: 2 h at -78°C, 1 h at 0°C) afforded a ratio of **23r:23s** = 9:91 in 75% yield by GC (Table 3, Entry G). IR (CH_2Cl_2) 3070, 2985, 1780, 1700, 1387, 1210 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.57-4.03 (m, 3, C_4-H, C_5-$\underline{H}_2$), 3.63 (sextet, 1, J = 7 Hz, -C$\underline{H}$CH$_3$), 2.00-1.27 (m, 2, -C$\underline{H}_2$CH$_3$), 1.30 (d, 3, J = 7 Hz, -CHC$\underline{H}_3$), 0.90 (d, 3, J = 7 Hz, -CH(C$\underline{H}_3$)$_2$), 0.88 (t, 3, J = 7 Hz, -CH$_2$C$\underline{H}_3$), 0.86 (d, 3, J = 7 Hz, -CH(C$\underline{H}_3$)$_2$); $[\alpha]_D$ +112.6° (c 4.10, CH_2Cl_2).

Anal. calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.73; H, 8.94; N, 6.64.

c) Potassium Enolate Alkylation (Table 3, Entry E). To a cooled (-78 °C) solution of potassium enolate **8a** (R = Et, 1 mmol, 0.5 M in THF) was added 68 μL (1.1 mmol) of methyl iodide. The reaction was brought to 0 °C, stirred for 2 h, then worked up in the usual manner to afford 201 mg (94% mass balance) of unpurified product. Diastereomer analysis as before revealed a ratio of **23r:23s** = 14:86. An identical reaction where alkylation was performed for 2 h at -78 °C, then 1 h at RT afforded a ratio of **23r:23s** = 15:85 (Table 3, Entry I).

Hydrolysis of (4S)-3-[(2R)-2-Methyl-3-phenylpropionyl]-4-(2-propyl)-oxazolidine-2-one (13) (eq. 12). A solution of 168 mg (0.61 mmol) of **13** in 3 mL of methanol at 0 °C was treated with 1.5 mL of a 2 N aqueous solution (3 mmol) of potassium hydroxide. After 15 min, no starting material was present by TLC. The reaction mixture was concentrated in vacuo, and the resulting aqueous residue was extracted three times with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give 70 mg (89%) of crystalline oxazolidone **10**.

The aqueous layer was acidified with an aqueous solution of concentrated hydrochloric acid, resulting in a voluminous white precipitate. Extraction with diethyl ether (3x), drying (Na_2SO_4), filtering, and concentration afforded 71 mg (71%) of 2-methyl-3-phenylpropionic acid **27** as a clear, colorless oil. ^1H NMR (90 MHz, $CDCl_3$) δ 10.32 (br s, 12, -OH), 7.37-7.03 (m, 5, aromatic H's), 3.27-2.50 (m, 3, $PhCH_2$-, -$CHCH_3$), 1.18 (d, 3, J = 7 Hz, -$CHCH_3$).

Methanolysis of (4S)-3-[(2R)-2-Methyl-3-phenylpropionyl]-4-(2-propyl)-

oxazolidine-2-one (13) (eq. 14). **a) Sodium Methoxide.** To a cooled (0°C) solution of 108 mg (2 mmol) of sodium methoxide in 4 mL of anhydrous methanol under nitrogen was added 550 mg (2 mmol) of imide **13** in 2 mL anhydrous methanol. After stirring for 20 min, no starting material was present by TLC. The reaction was quenched with pH 7 phosphate buffer and volatiles were removed in vacuo. The aqueous residue was extracted three times with diethyl ether, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 456 mg (74% mass recovery) of unpurified product. Purification by chromatography on silica gel (MPLC, Merck Lobar B column, 15% ethyl acetate:hexane) afforded 212 mg (60%) of the desired methyl ester. ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.39-7.02 (m, 5, aromatic H's), 3.60 (s, 3, CH_3O-), 3.22-2.49 (m, 3, $PhCH_2$-, -$CH$$CH_3$), 1.13 (d, 3, J = 6 Hz, -$CHCH_3$); $[\alpha]_D$ -48.0° (c 0.85, EtOH).

b) Magnesium Methoxide. To a cooled (0°C) solution of 4 mL of anhydrous methanol under nitrogen was rapidly added 0.70 mL of a 2.9 M solution (2 mmol) of methyl magnesium bromide in diethyl ether. To this solution was added 550 mg (2 mmol) of imide **13** in 2 mL of methanol. The reaction mixture was stirred for 1 h at 0°C, then warmed to room temperature and stirred for an additional 1 h. Product isolation (415 mg, 68% mass balance) and purification as before (MPLC, 15% ethyl acetate:hexane) afforded 253 mg (71% yield) of the desired methyl ester. The optical rotation of this material was $[\alpha]_D$ -45.4° (c 1.50, EtOH).

General Procedure for Transesterification (Benzyl Esters). The following reactions were performed under a nitrogen atmosphere in dry, single-necked, round-bottom flasks equipped for magnetic stirring and fitted

with septa. Benzyl alcohol was carefully purified and dried. All additions are made *via* hypodermic syringe. In a typical reaction, a solution of benzyl alcohol (2 equiv) in anhydrous tetrahydrofuran (ca 0.3 M) is cooled to 0 °C and treated with n-butyllithium (1.5 equiv in hexane). To this solution is added the indicated imide as a THF solution (ca 1 M), and stirring is continued at 0 °C for 1 h. The reaction is quenched by the addition of a saturated aqueous solution of ammonium chloride. Volatiles are removed by rotary evaporation, and the resulting oily aqueous residue is extracted three times with dichloromethane. The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the desired benzyl esters along with deacylated oxazolidinone. Purification of the esters was carried out by chromatography on silica gel as indicated in the following specific examples.

Benzyl (2R)-2-methyl-3-phenylpropionate (Table 7, Entry A). To a cooled solution (0 °C) of lithium benzyloxide in 20 mL of anhydrous THF (prepared from 0.8 mL of benzyl alcohol and 4.0 mL of a 1.47 M solution of n-butyllithium in hexane) was added 1.07 g (3.9 mmol) of imide **13** (**13r:13s** > 99:1) in 3 mL of THF. After stirring for 1 h at 0 °C, the reaction products were isolated according to the previously described procedure to afford 1.83 g (96% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 2.6% ethyl acetate:hexane) gave 0.90 g (92%) of the desired benzyl ester (**31**) as a colorless oil, >99% pure by GC (SE-54, 170 °C, t_r = 3.72 min). IR ($CHCl_3$) 3060, 2989, 1732, 1449, 1454, 1168 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.43-7.00 (m, 10, aromatic H's), 5.04 (s, 2, $PhCH_2O$-), 3.20-2.52 (m, 3, -$CHCH_3$, $PhCH_2CH$-), 1.17 (d, 3, J = 7 Hz, -CHCH); $[\alpha]_D$ -26.8 ° (c 2.33, CH_2Cl_2).

Anal. calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.43; H, 7.24.

Benzyl (2S)-2-methyl-3-phenylpropionate (Table 7, Entry B). To a cooled solution (0°C) of lithium benzyloxide in 20 mL of anhydrous THF (prepared from 0.87 mL of benzyl alcohol and 4.3 mL of a 1.47 M solution of n-butyllithium in hexane) was added 1.36 g (4.2 mmol) of imide **14** (**14r:14s** < 1:99) in 3 mL of THF. After stirring for 1 h at 0°C, the reaction products were isolated according to the previously described procedure to afford 2.23 g (98% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 3% ethyl acetate:hexane) gave 0.99 g (92%) of the desired benzyl ester as a colorless oil, >99% pure by GC. [Spectral data are identical to those reported for the (R)-enantiomer.] $[\alpha]_D$ +26.8° (c 5.93, CH_2Cl_2).

Anal. calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.44; H, 7.32.

Benzyl (2R)-2,4-dimethyl-4-pentenoate (Table 7, Entry C). To a cooled solution (0°C) of lithium benzyloxide in 20 mL of anhydrous THF (prepared from 0.73 mL of benzyl alcohol and 3.60 mL of a 1.47 M solution of n-butyllithium in hexane) was added 0.85 g (3.55 mmol) of imide **17** (**17r:17s** > 99:1) in 2 mL THF. After stirring for 1 h at 0°C, the reaction products were isolated according to the previously described procedure to afford 1.58 g (98% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 2.6% ethyl acetate:hexane) gave 0.72 g (93%) of the desired benzyl ester as a colorless oil, >99% pure by GC (SE-54, 130°C, t_r = 3.13 min). IR (CCl_4) 3085, 2982, 2949, 1737, 1455, 1160, 894, 692 cm^{-1};

^{1}H NMR (90 MHz, $CDCl_3$) δ 7.31 (s, 5, aromatic H's), 5.08 (s, 2, $PhCH_2O$-), 4.70 (br d, 2, J = 5 Hz, $CH_3C=CH_2$), 2.90-1.87 (m, 3, -CHCH_2-), 1.69 (s, 3, $CH_3C=CH_2$), 1.14 (d, 3, J = 7 Hz, -$CHCH_3$); $[\alpha]_D$ +3.94° (c 5.86, CH_2Cl_2).

Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.10; H, 8.41.

Benzyl (2S)-2,4-dimethyl-4-pentenoate (Table 7, Entry D). To a cooled solution (0°C) of lithium benzyloxide in 15 mL anhydrous THF (prepared from 0.73 mL of benzyl alcohol and 3.60 mL of a 1.47 M solution of n-butyllithium in hexane) was added 1.02 g (3.54 mmol) of imide **18** (**18r:18s** = 3:97) in 5 mL of THF. After stirring for 1 h at 0°C, the reaction products were isolated according to the previously described procedure to afford 1.75 g (98% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 3.3% ethyl acetate:hexane) gave 0.72 g (93%) of the desired benzyl ester as as colorless oil, 99% pure by GC. [Spectral data are identical to those reported for the (R)-enantiomer.] $[\alpha]_D$ -3.70° (c 6.33, CH_2Cl_2).

Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.38.

Benzyl (2R)-2-methyl-4-pentenoate (Table 7, Entry E). To a cooled solution (0°C) of lithium benzyloxide in 20 mL of anhydrous diethyl ether (prepared from 0.92 mL of benzyl alcohol and 4.53 mL of a 1.47 M solution of n-butyllithium in hexane) was added 1.00 g (4.44 mmol) of imide **15** (**15r:15s** = 98:2) in 5 mL of diethyl ether. After stirring for 1 h at 0°C, the reaction products were isolated according to the previously described procedure to afford 1.91 g (98% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 5% ethyl acetate:hexane) gave 0.70 g

(77%) of the desired benzyl ester as a colorless oil, 98% pure by GC (SE-54, 130°C, t_r = 4.42 min). IR (CH_2Cl_2) 3065, 2990, 1735, 1255, 1179 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.32 (s, 5, aromatic H's), 5.97-5.47 (m, 1, HC=CH_2), 5.09 (s, 2, PhCH_2O-), 5.06 (m, 1, HC=CH_2), 4.91 (br s, 1, HC=CH_2), 2.77-1.97 (m, 3, -CHCH_2-), 1.28 (d, 3, J = 7 Hz, -CHCH_3); $[\alpha]_D$ -2.08° (c 17.7, CH_2Cl_2).

Anal. calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.46; H, 7.84.

Benzyl (2S)-2-methyl-4-pentenoate (Table 7, Entry F). To a cooled solution (0°C) of lithium benzyloxide in 20 mL of anhydrous THF (prepared from 0.80 mL of benzyl alcohol and 4.0 mL of a 1.47 M solution of n-butyllithium in hexane) was added 1.05 g (3.84 mmol) of imide **16** (**16r:16s** < 1:99) in 5 mL THF. After stirring for 1 h at 0°C, the reaction products were isolated according to the previously described procedure to afford 1.85 g (98% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 2.6% ethyl acetate:hexane) gave 0.65 g (86%) of the desired benzyl ester as a colorless oil, <99% pure by GC. [Spectral data are identical to those reported for the (R)-enantiomer.] $[\alpha]_D$ +2.29° (c 14.7, CH_2Cl_2).

Anal. calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.69; H, 8.06.

Benzyl (2R)-2-methylbutyrate (Table 7, Entry G). To a cooled solution (0°C) of lithium benzyloxide in 15 mL of anhydrous THF (prepared from 0.60 mL of benzyl alcohol and 2.95 mL of a 1.47 M solution of n-butyllithium in hexane) was added 0.62 g (2.90 mmol) of imide **23** (**23r:23s** > 99:1) in 3 mL of

THF. After stirring for 1 h at 0° C, the reaction products were isolated according to the previously described procedure to afford 1.21 g (97% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 5% ethyl acetate:hexane) followed by molecular distillation (Kugelrohr, 75°C, 0.005 mm) gave 0.50 g (89%) of the desired benzyl ester as a colorless oil, >99% pure by GC (SE-54, 130°C, t_r = 2.47 min). IR (CH_2Cl_2) 3069, 2990, 1734, 1422, 1265, 897 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (s, 5, aromatic H's), 5.10 (s, 2, $PhCH_2O$-), 2.42 (sextet, 1, J = 7 Hz, $-CHCH_3$), 1.93-1.27 (m, 2, $-CH_2CH_3$), 1.15 (d, 3, J = 7 Hz, $-CHCH_3$), 0.88 (t, 3, J = 7 Hz, $-CH_2CH_3$); $[\alpha]_D$ -12.6° (c 6.38, CH_2Cl_2).

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-methylbutyrate (Table 7, Entry H). To a cooled solution (0°C) of lithium benzyloxide in 20 mL of anhydrous THF (prepared from 0.94 mL of benzyl alcohol and 4.65 mL of a 1.47 M solution of n-butyllithium in hexane) was added 0.97 g (4.55 mmol) of imide **23** (**23r:23s** = 1:99) in 5 mL of THF. After stirring for 1 h at 0°C, the reaction products were isolated according to the previously described procedure to afford 1.89 g (97% mass balance) of unpurified product. Chromatography on silica gel (MPLC, Merck Lobar B column, 5% ethyl acetate:hexane) followed by molecular distillation (Kugelrohr, 195°C, 15 mm) gave 0.80 g (92%) of the desired benzyl ester as a colorless oil, >99% pure by GC. [Spectral data are identical to those reported for the (R)-enantiomer.] $[\alpha]_D$ +12.5° (c 5.55, CH_2Cl_2).

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

Transesterification Racemization Control Experiment (Scheme VIII). Benzyl ester **31** was prepared in 92% yield by transesterification of imide **13** (**13r**:**13s** = 99.954:0.946) as described on p. 78. To a solution of 0.56 g (2.2 mmol) of this benzyl ester (**31**) in 5 mL of absolute ethanol was added 58.0 mg of 5% palladium on carbon. The reaction was placed under an atmosphere of hydrogen (1 atm) and stirred vigorously at room temperature. Hydrogen uptake was rapid (28 mL in 0.5 h), and after 1 h the reaction appeared complete by TLC. The reaction mixture was filtered through Celite and concentrated in vacuo to give 358 mg (99% mass balance) of unpurified product. This material was dissolved in diethyl ether and washed three times with a 10% aqueous solution of hydrochloric acid, then extracted three times with a 10% aqueous solution of sodium hydroxide. The combined basic fractions were made acidic (ca. pH 2) by the dropwise addition of concentrated aqueous hydrochloric acid and extracted three times with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 266 mg (74%) of carboxylic acid **27** as a colorless oil. ^{1}H NMR (90 MHz, $CDCl_3$) δ 10.32 (br s, 1, -OH), 7.37-7.03 (m, 5, aromatic H's), 3.27-2.50 (m, 3, $PhCH_2CH$-), 1.18 (d, 3, J = 7 Hz, $-CHCH_3$); $[\alpha]_D$ -25.1° (neat, 1 cm); Lit.[17] $[\alpha]_D$ -25.4° (neat, 1 cm).

To a cooled solution (0 °C) of 206 mg (1.26 mmol) of carboxylic acid **27** and 0.19 mL (138 mg, 1.36 mmol) of dry triethylamine in 10 mL of anhydrous THF under nitrogen was added 0.13 mL (148 mg, 1.36 mmol) of ethyl chloroformate. In another flask, a solution of 195 mg (1.51 mmol) of valine oxazolidone **10** in 7 mL of anhydrous THF was cooled to 0 °C and treated with 1 mL of a 1.47 M solution (1.47 mmol) of n-butyllithium in hexane, resulting

in immediate oxazolidone anion precipitation. Both of these solutions were allowed to stir at 0° C for 0.5 h, at which point the oxazolidone anion solution was cannulated into the mixed anhydride reaction, and the resulting clear solution was warmed to room temperature and stirred for 2 h. The reaction was quenched by the addition of aqueous pH 7 phosphate buffer, and volatiles were removed by rotary evaporation. The resulting aqueous residue was extracted three times with dichloromethane, and the combined organics phases were washed once with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 396 mg (99% mass balance) of a clear colorless oil. Gas chromatographic analysis (SE-54, 130° C→ 200° C) revealed an 81% yield of **13** (t_r **13s** = 6.04 min, t_r **13r** = 6.25 min) showing a diastereomer ratio of **13r:13s** = 99.801:0.199. This result demonstrated that racemization for the overall cycle is no more than 0.30%.

(2S)-2-Methyl Valerolactone (34). A dry, 250-mL three-necked round-bottomed flask equipped for magnetic stirring was fitted with a gas inlet valve, a reflux condenser topped with another gas inlet valve (closed), and a rubber septum, and the system was purged with nitrogen for 15 min. The flask was then cooled to -15° C (ice/methanol) and 1.1 mL of a 10 M solution (11 mmol) of borane-dimethyl sulfide complex was introduced via syringe, followed by the dropwise addition of 5.5 mL of a 4 M solution (2.2 mmol) of 2-methyl-2-butene in anhydrous THF. After stirring for 2 h at -15° C, a solution of 2.73 g (10 mmol) of (4R,5S)-3-[(2S)-methyl-4-pentenoyl]-4-methyl-5-phenyloxazolidine-2-one **16** (**16r:16s** < 1:99) in 5 mL of anhydrous THF was added dropwise. The reaction mixture was stirred at 0° C for 1.5 h,

then warmed to room temperature and stirred for an additional 30 min. At this point, the gas inlet valve was closed, and the system was evacuated (water aspirator) through the valve on the reflux condenser, and solvent and volatiles were evaporated with gentle heating. After reestablishing a nitrogen atmosphere, the viscous, clear, colorless organoborane was diluted with 50 mL of anhydrous toluene and treated with 3.69 g (33 mmol) of trimethylamine N-oxide dihydrate. The suspension was refluxed for 2-1/4 h, cooled to RT, and diluted with methanol. Solvents were removed in vacuo, and the resulting residue was dissolved in diethyl ether, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was dissolved in anhydrous chloroform and treated with ca. 0.5 mL (3.6 mmol) of triethylamine. The reaction mixture was stirred overnight at RT, then briefly brought to reflux (4 h). After cooling, volatiles were evaporated in vacuo and the residue was purified by chromatography on silica gel (300 g, 10% diethyl ether:dichloromethane) followed by molecular distillation (Kugelrohr, 200°C, 14 mm) to give 775 mg (68% overall yield from imide **16**) of lactone **34** as a clear, colorless oil. IR ($CDCl_3$) 2992, 1735, 1460, 1382, 1250, 1162, 1088 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.30 (t, 2, J = 6 Hz, C_5-$\underline{H}_2$), 2.83-2.33 (m, 1, C_2-$\underline{H}$), 2.33-1.36 (m, 4, C_3-$\underline{H}_2$, C_4-$\underline{H}_2$), 1.23 (d, 3, J = 6 Hz, -CHC$\underline{H}_3$); $[\alpha]_D$ +67.3° (c 6.60, CH_3OH); Lit.[6a] $[\alpha]_D$ (for R enantiomer) -58.1°, -64.4° (calculated).

Anal. calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.03; H, 8.79.

(2R)-2-Methyl-3-phenylpropanol 38. To a cooled (0°) slurry of 114 mg (3 mmol) of lithium aluminum hydride in 2 mL of anhydrous THF was added 287 mg (1.04 mmol) of (4S)-3-[(2R)-2-methyl-3-phenylpropionyl]-4-(2-

propyl)-oxazolidine-2-one **13** (**13r:13s** > 99:1) in 1 mL of THF. The reaction appeared complete by TLC after 10 min. After 25 min, the reaction was carefully quenched by the successive addition of 0.12 mL of water, 0.12 mL of 15% aqueous sodium hydroxide, and an additional 0.36 mL of water. The mixture was filtered, and the filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 276 mg (95% mass balance) of unpurified products. Chromatography on silica gel (25 g, 20% ethyl acetate:hexane) afforded 138 mg (88%) of alcohol **38** as a clear, colorless oil. IR ($CHCl_3$) 3700-3200, 2940, 1603, 1492, 1452, 1024, 693 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.12 (m, 5, aromatic H's), 3.44 (br d, 2, $-CH_2OH$), 2.73 (d of d, 1, J_{ba} = 13 Hz, 8 Hz), 1.91 (sextet, 1, J = 7 Hz, $-CHCH_3$), 0.90 (d, 3, J = 7 Hz, $-CHCH_3$); $[\alpha]_D$ +11.0° (c 1.12, C_6H_6); Lit.[27,28] for (S)-**38** -11.08° (c 4.6, C_6H_6).

Lithium Enolate Decomposition Study. To a cooled (-78°C) solution of 1.10 mmol of LDA in 2 mL of anhydrous THF was added 196 mg (1.06 mmol) of (4S)-3-propionyl-4-(2-propyl)-oxazolidine-2-one **6** (R = Me) in 1 mL of THF. The reaction was stirred for 30 min at -78°C, then allowed to warm to room temperature and stir for an additional 2 h. The reaction products were isolated in the manner described in the general alkylation procedure to afford 175 mg (89% mass balance) of a clear, slightly yellow oil. Gas chromatographic analysis (SE-54, 140°C) revealed the following product distribution: valine oxazolidone **10** (t_r = 1.68 min) 42%; 3-propionyl-valine oxazolidone **6** (R = Me) (t_r = 1.95 min) 8%; 3-(2-methyl-3-oxo-pentanoyl)-valine oxazolidone diastereomers **42a,42b** (t_r **42a** = 6.73, t_r **42b** = 7.01) 40% (**42a:42b** = 48:52).

Acylation Experiment of Valine Oxazolidone Lithium Enolate. To a cooled (-78°C) solution of lithium enolate **8a** (R = Me, 1.0 mmol) in 2 mL of anhydrous THF was added 0.1 mL (0.11 g, 1.15 mmol) of propionyl chloride. The reaction was stirred at -78°C for 2 h, and the reaction products were isolated in the manner described in the general alkylation procedure to afford 244 mg (100% mass balance) of a white solid (unpurified m.p. 114-121°C). Gas chromatographic analysis (SE-54, 140°C) revealed the following product distribution: 3-propionyl valine oxazolidone **6** (R = Me), 1.6%; 3-(2-methyl-3-oxo-pentanoyl)-valine oxazolidone diastereomers **42a** and **42b**, 92%, (**42a:42b** = 96:4). The major diastereomer was purified by recrystallization from diethyl ether: hexane to afford 216 mg (90%) of **42a** as a white crystalline solid, m.p. 131-132°C. IR ($CHCl_3$) 3070, 3005, 1782, 1725, 1707, 1392, 1255, 1220 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.47 (q, 1, J = 7 Hz, -C<u>H</u>CH_3), 4.49-4.02 (m, 3, C_4-<u>H</u>, C_5-$\underline{H_2}$), 2.67 (d of q, 2, J = 2 Hz, 7 Hz, -C<u>H_2</u>CH_3), 2.42 (d of septets, 1, J = 4 Hz, -C<u>H</u>$(CH_3)_2$), 1.36 (d, 3, J = 7 Hz, -CHC<u>H_3</u>), 1.18 (t, 3, J = 7 Hz, -CH_2C<u>H_3</u>), 0.92 (d, 6, J = 6 Hz, -CH(C<u>H_3</u>$)_2$); ^{13}C NMR ($CDCl_3$) δ 208.0, 169.9, 154.2, 63.7, 58.6, 52.4, 33.8, 28.3, 17.9, 14.6, 12.7, 7.5; $[\alpha]_D$ -17.2° (<u>c</u> 2.25, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.59; H, 7.91; N, 5.78.

Equilibration Study of β-Keto Imide 42 (Figure 9). A solution of 33 mg (0.14 mmol) of β-keto imide **42** (**42r:42s** > 99:1) in 2 mL of dicholormethane was treated with 4.2 μL (<u>ca.</u> 20 mole %) of triethylamine at room temperature. Equilibration was monitored by capillary GC (SE-54, 140°C, t_r **42r** = 6.73 min, t_r **42s** = 7.01 min). The following diastereomer ratios (**42r:42s**) were obtained:

t = 0 (107:1), 30 sec (73:1), 20 min (55:1), 45 min (47:1), 2 h (41:1), 19 h (7.78:1), 24 h (6.55:1), 92 h (2.13:1), 116 h (1.73:1), 141 h (1.65:1), 164 h (1.57:1), 190 h (1.59:1), 260 h (1.56:1). An equilibrium ratio of **42r:42s** = 61:39 was reached after 11 days.

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(16) Acknowledgment is due to my co-worker throughout this project, Mr. David J. Mathre, for the contribution of these results.

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CHAPTER II

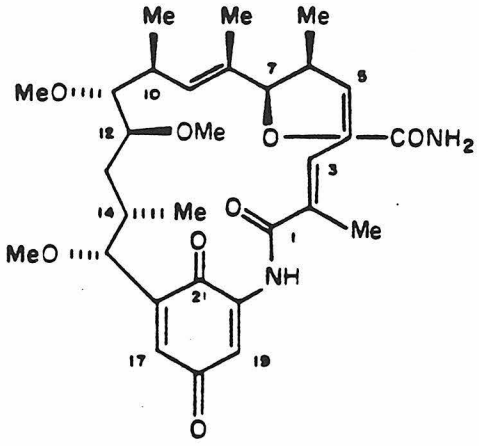
Efforts Directed Toward the Total Synthesis of (+)-Macbecin I

I. Introduction

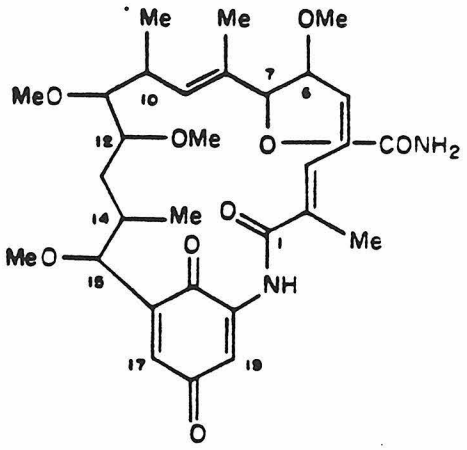
In 1980, Muroi and coworkers reported the isolation of two new antibiotics from the fermentation broth of Nocardia sp. No. C-14919.[1] These new antibiotics, named macbecin I and macbecin II, exhibited significant antibacterial, antifungal, and antiprotozoal activities.[1a] The structure of these compounds, including absolute stereochemistry, has recently been determined by X-ray crystallography.[2] Macbecins I and II belong to an ever-growing class of ansa-bridged quinone macrolides structurally related to the well-known rifamycins. Herbimycin[3] and geldanamycin[4] are two other known members of this class of compounds, although the absolute stereochemistry of the latter has not been determined. Representative structures of this family of antibiotics are shown in Figure 1.

Both macbecin I (1) and its associated hydroquinone macbecin II (1-H_2) are moderately active against gram-positive bacteria, fungi, and protozoa in vivo,[1b] and, in addition, show good antitumor activity against murine leukemia P-388 and melanoma B-16 in vivo.[1a] Unlike the ansamycin antibiotics however, macbecins I and II do not exhibit specific inhibition of prokaryotic DNA-dependent RNA polymerase or antitubulinic activity.[1a] Preliminary testing of herbimycin and geldanamycin indicates a common pharmacology for all of these compounds.[1a] The acute toxicities (LD_{50}) of the macbecins in mice are in the range of 25-100 mg/kg.[1b] These values are relatively low for antitumor antibiotics.

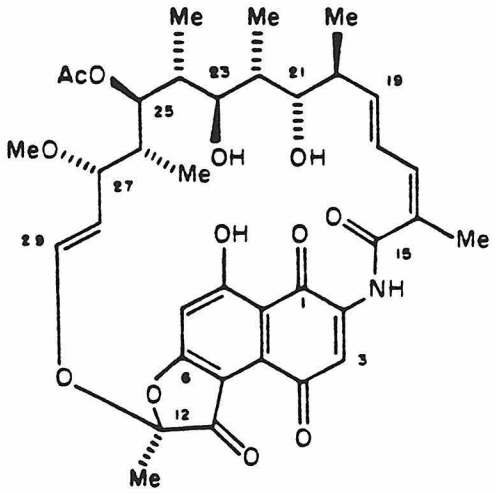
In conjunction with our interest in the stereoregulated construction of macrolide and polyether antibiotics, we undertook the enantioselective total synthesis of macbecin I. The synthetic strategy employed for the construction



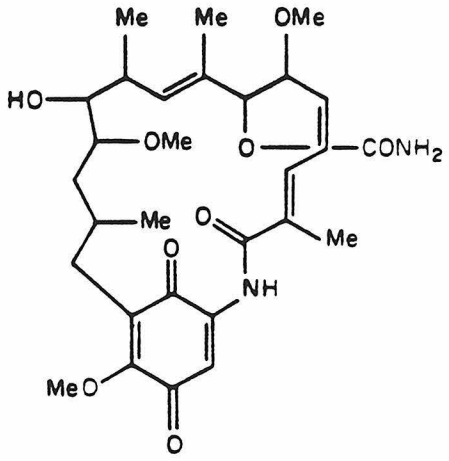
Macbecin I (1)



Herbimycin (1979)



Rifamycin-S



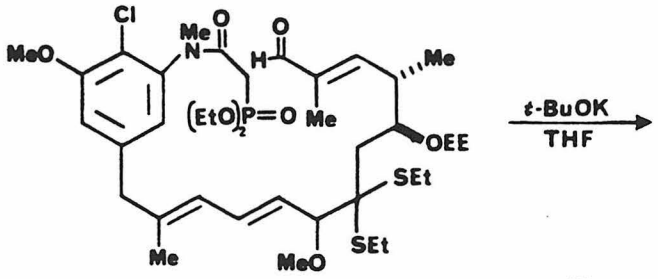
Geldanamycin (1970)

Figure 1. Representative Structures of Some Ansa-Bridge Macrolide Antibiotics.

of 1 enjoys sufficient flexibility to accommodate both the herbimycin and geldanamycin structures. This chapter will describe in full detail our efforts to date toward the synthesis of these molecules.

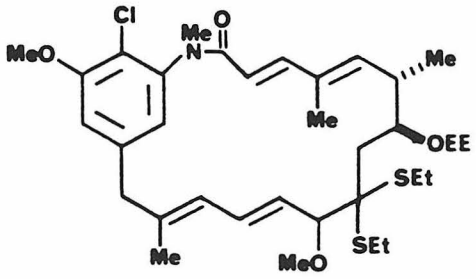
II. Synthetic Strategy

Our general synthetic approach to the construction of macbecin I is underscored by three major commitments. We have elected to construct the 16-membered ansa macrocycle by means of an intramolecular keto-phosphonate reaction of a suitable acyclic precursor. Conceptually, either the Δ(2-3)-bond or Δ(4-5)-bond could serve as convenient disconnection points for this process (Scheme I). The viability of such an approach has recently been demonstrated by Meyers in the context of an N-methylmaysenine total synthesis.[5] Cyclization of compound **2** under high-dilution conditions afforded a 74% yield of macrolactam **3** as a single olefin isomer (eq. 1). Further



2

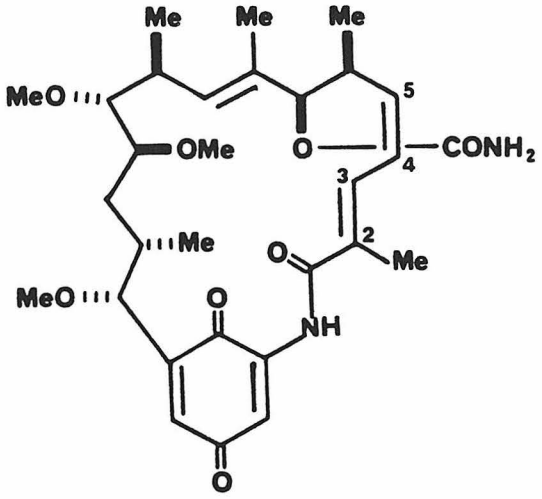
t-BuOK
THF

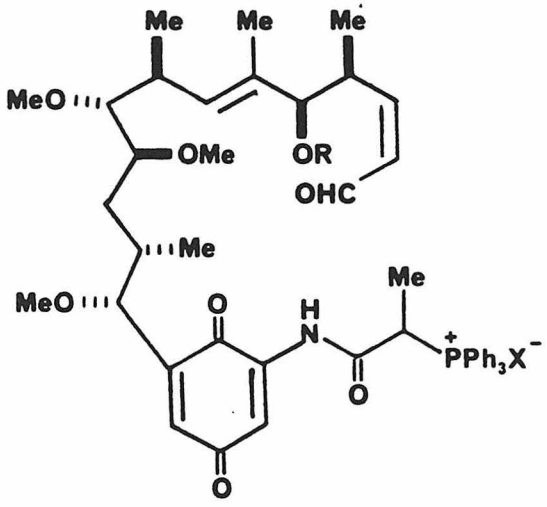


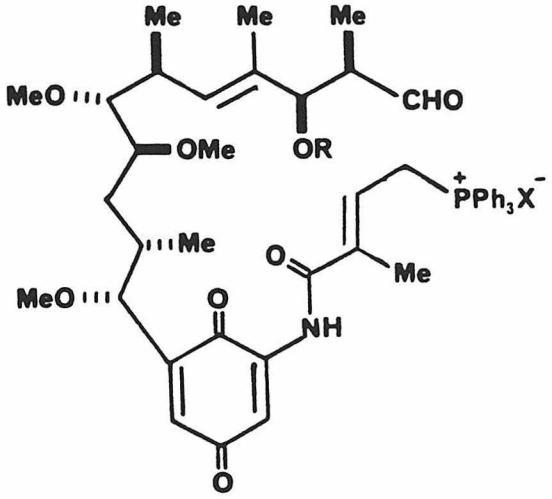
3 (74%)

(1)

Scheme I

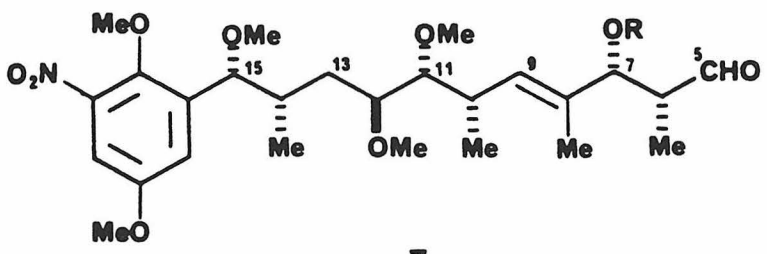

Me
Me
Me
MeO
OMe
O
CONH2
5
4
3
2
Me
Me
MeO
O
NH
O
O


Me
Me
Me
MeO
OMe
OR
OHC
Me
MeO
O
H
N
Me
O
PPh3X-
O

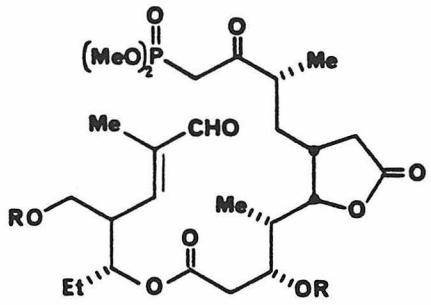

Me
Me
Me
MeO
CHO
OMe
OR
PPh3X-
Me
O
Me
MeO
O
NH
O

extension of this methodology to the macrolactone area can be found in Nicolaou's recent tylonolide synthesis.[6] Again, intramolecular Wittig reaction of **4** proceeds in excellent yield to provide the 16-membered lactone **5** (eq. 2). In contrast, macrolactonization of seco-acid **6** proceeds with modest yield (eq. 3).[7] Indeed, it is a general observation that construction of medium- and large-ring macrocycles <u>via</u> an internal keto-phosphonate reaction seems to be superior to any currently existing macrolactonization or macrolactamization procedure.

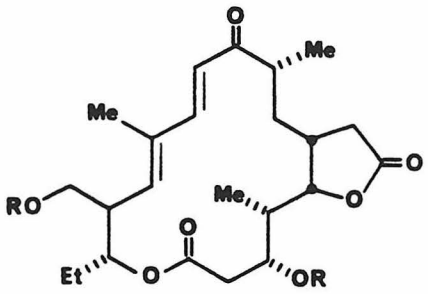
The second major commitment that we've embraced for the synthesis of macbecin I is the use of highly stereoselective aldol reactions to control the absolute stereochemistry of the seven chiral centers in **1**. Retro-Wittig (C_4-C_5) of macbecin I, followed by a re-packaging of the aromatic nucleus (<u>vide infra</u>), affords the advanced acyclic intermediate **7**. Inspection of this piece quickly reveals three obvious erythro-aldol bond constructions (C_6-C_7, C_{10}-C_{11}, C_{14}-C_{15}). The stereocenter at C_{12} will also be incorporated using aldol technology, where deoxygenation at C_{13} would provide the sole methylene unit in **1** (<u>vide infra</u>).



7

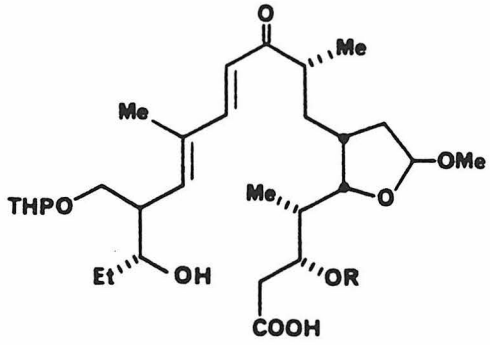


4



5 (80%)

(2)



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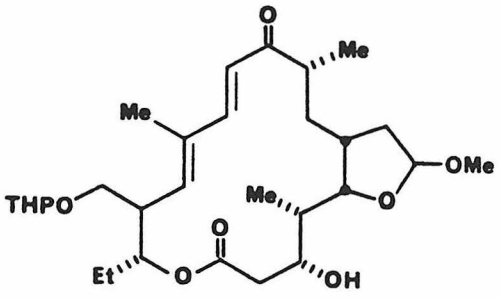
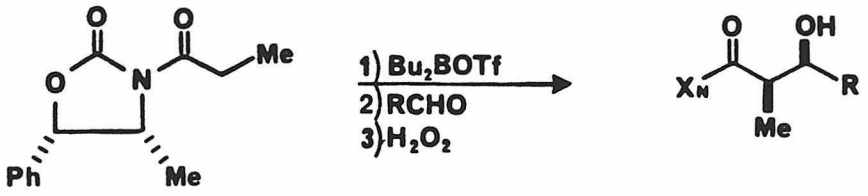


(32%)

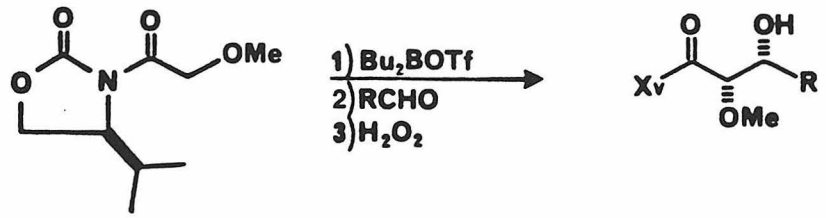
(3)

Stereochemical control in the aldol process is an area of intense current interest.[8] Research efforts in our own laboratories have resulted in the development of chiral imides **8** and **9**, whose derived boron enolates participate in highly stereoregulated aldol condensations.[9] Shown in Scheme II are the relevant aldol reactions of imides **8** and **9** which directly pertain to the absolute stereochemical control required for the construction of the acyclic intermediate **7**. Both N-acyl oxazolidones **8** and **9** have been shown to exhibit impressive levels of both relative and absolute diastereoselectivity with simple aldehydes, producing one of four possible stereoisomers with >99% selectivity.[9] The absolute stereochemistry of the major adduct, which

Scheme II



8

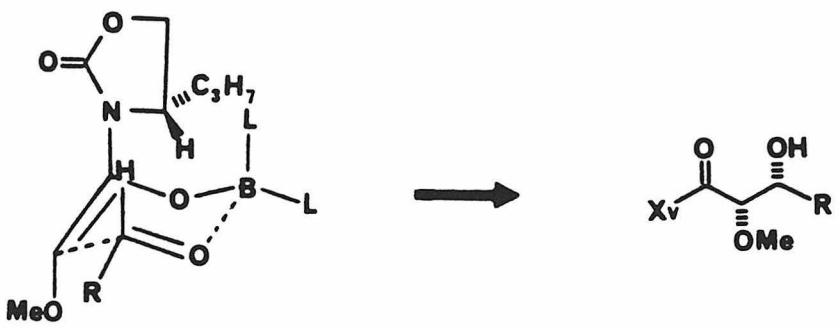


9

Erythro:Threo ≥ 100:1

Erythro A:Erythro B ≥ 500:1

is always an erythro isomer, is determined by the sense of chirality of the oxazolidone ring substituents. The proposed lowest-energy transition state which leads to production of the observed erythro enantiomer is illustrated in Figure 2 for chiral imide **9**. Enolization of imides **8** and **9** proceeds smoothly at -78°C upon treatment with di-n-butylboryl triflate and triethylamine



i

Figure 2. Chiral Imide Aldol Transition State.

to produce exclusively the Z-enolate.[10] Conventional wisdom describes the aldol condensation as proceeding through a six-membered, chair-like transition state in which the aldehyde substituent occupies a pseudo-equatorial position (see Fig. 2).[11] The oxazolidone auxiliary, once coordinately liberated from boron chelation by aldehyde displacement, would be expected to adopt the configuration shown in structure **i** (Fig. 2) on the basis of dipole-dipole interactions.[12] Thus, for the illustrated case, the (4S)-isopropyl substituent on the auxiliary severely blocks aldehyde approach from the α-face. The stereochemical outcome of aldol condensations employing

chiral imide **8** can be interpreted in a totally analogous fashion. Figure 3 illustrates the actual degree of stereoregulation that is routinely observed with these chiral enolate synthons.

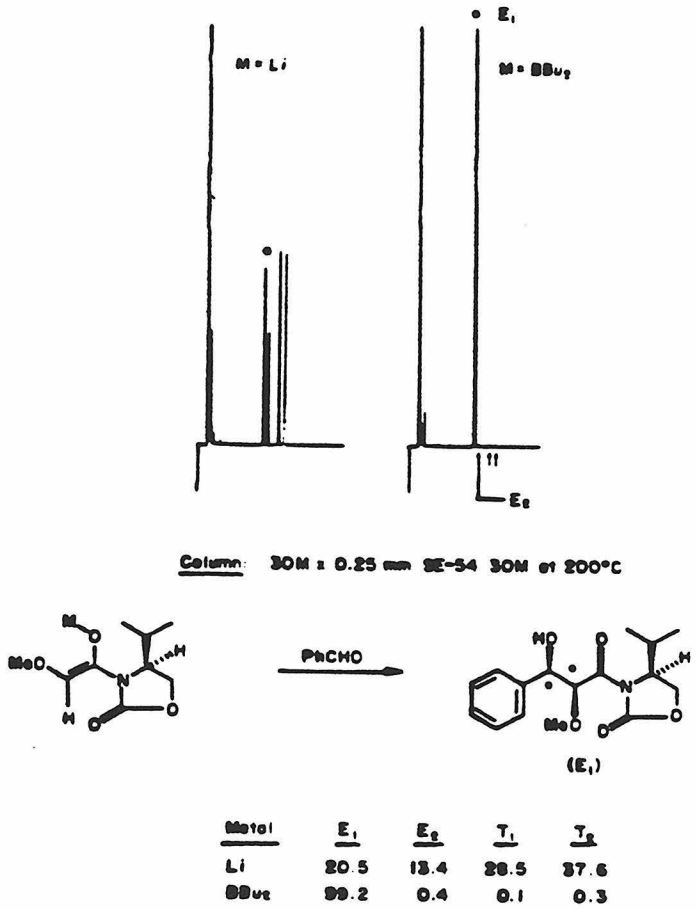
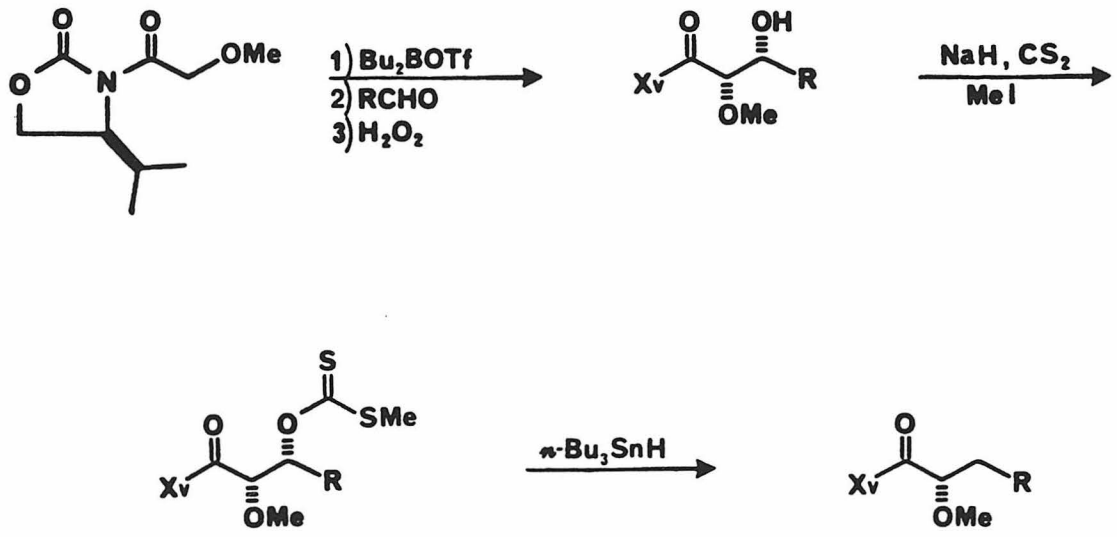


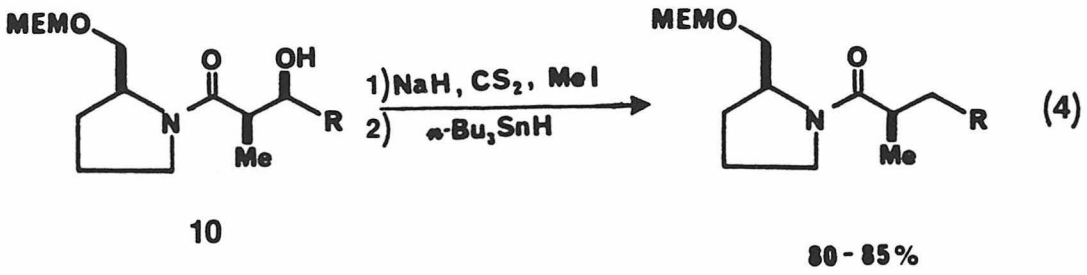
Figure 3. Gas chromatographic analysis of the aldol process with **9** (chromatograms of unpurified product mixtures).

As stated previously we envisioned the establishment of the chiral center at C-12 (see **7**) to proceed through an aldol condensation/deoxygenation sequence, as outlined in Scheme III. Tin hydride reduction of thiocarbonyl derivatives of secondary alcohols (Barton Deoxygenation)[13] has been shown to efficiently deoxygenate the β-hydroxyl of amide-derived aldol adducts.

Scheme III



Treatment of the xanthate derived from prolinol propionamide adduct **10** with tin hydride in refluxing toluene afforded the deoxygenated product in 80-85% yield (eq. 4).[14] Furthermore, the Barton procedure is known to be facilitated by the presence of a carbon-oxygen bond adjacent to the center to be deoxygenated,[15] as would be the case in this synthesis (See Scheme III).



10

80 - 85%

(4)

The third major commitment we've made in the synthesis of macbecin pertains to the handling of the quinone nucleus. We plan to carry the aromatic ring through the synthesis in the reduced form of a hydroquinone dimethyl ether. The amide nitrogen of macbecin will be incorporated into the starting material as a nitro group, as shown in Figure 4. Oxidation of hydroquinone dimethyl ethers to quinones can be accomplished in a number of ways,[16] and several examples of this kind of transformation can be found in the mitomycin literature.[17] Our primary concern involves the stability of

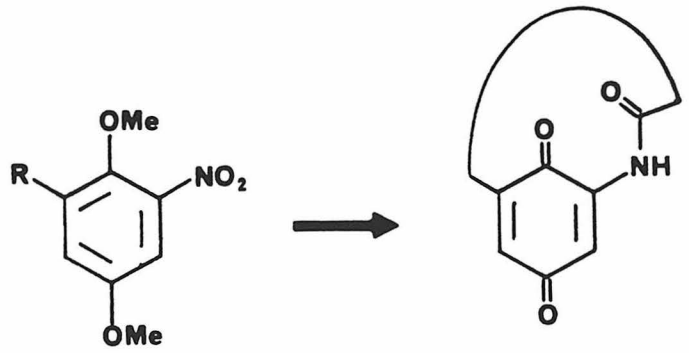


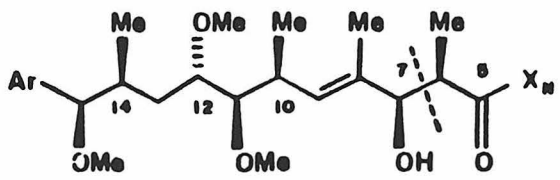
Figure 4

the aromatic nitro functionality to the various reducing conditions foreseen in the synthesis. For example, it is known that tri-n-butyltin hydride will reduce aromatic nitro compounds to the corresponding anilines,[13] although this process is not necessarily facile. Refluxing a mixture of 2-nitroflurene and three equivalents of tri-n-butyltin hydride in toluene for 22 h results in only ca. 50% reduction to the aniline.[18] It is hoped that favorable kinetics will prevent reduction at the electron-rich aromatic ring and allow facile deoxygenation in intermediates toward acyclic precursor **7**.

Shown in Scheme IV is a retrosynthetic plan for the assemblage of acyclic intermediate **7**. This target can be stereoselectively synthesized by the iterative application of four aldol condensations and one Wittig reaction. Each reaction contributes two carbons to the acyclic chain, and each aldol condensation establishes two stereocenters. All of the stereochemistry in macbecin will be derived from chiral imides **8** and **9**. Stereoselective generation of the Δ(8-9) E-trisubstituted olefin (Step B) finds ample precedent in the work of Kishi, who has demonstrated the conditions needed to prepare either olefin isomer selectively (Figure 5).[19]

The retrosynthetic analysis outlined in Scheme IV requires the formation of methyl ethers from aldol adducts at two different points; once after the first aldol (Step E) and again after the third aldol (Step C). Anticipating potential complications arising from the propensity of β-hydroxy carbonyl compounds to undergo retro-aldol reactions under anionic conditions, we sought a mild procedure for the O-methylation of simple aldol adducts. Among the mildest procedures known to effect this transformation is the use of silver (I) oxide and iodomethane.[20] In the event, β-hydroxy

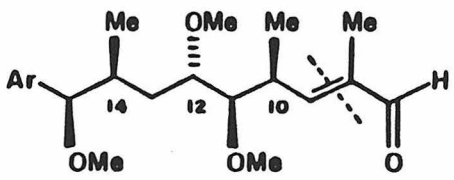
Scheme IV



7

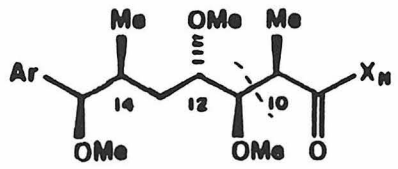
A

-8



11

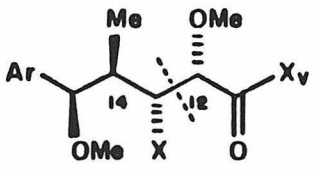
B



12

C

-8

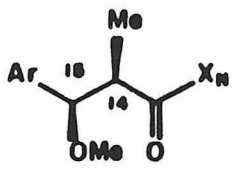


13 a, X = H

b, X = OH

D

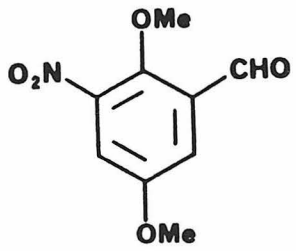
-9



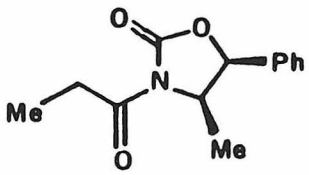
14

E

-8



15



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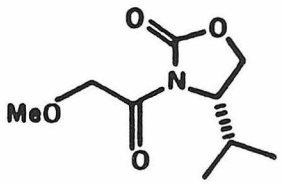

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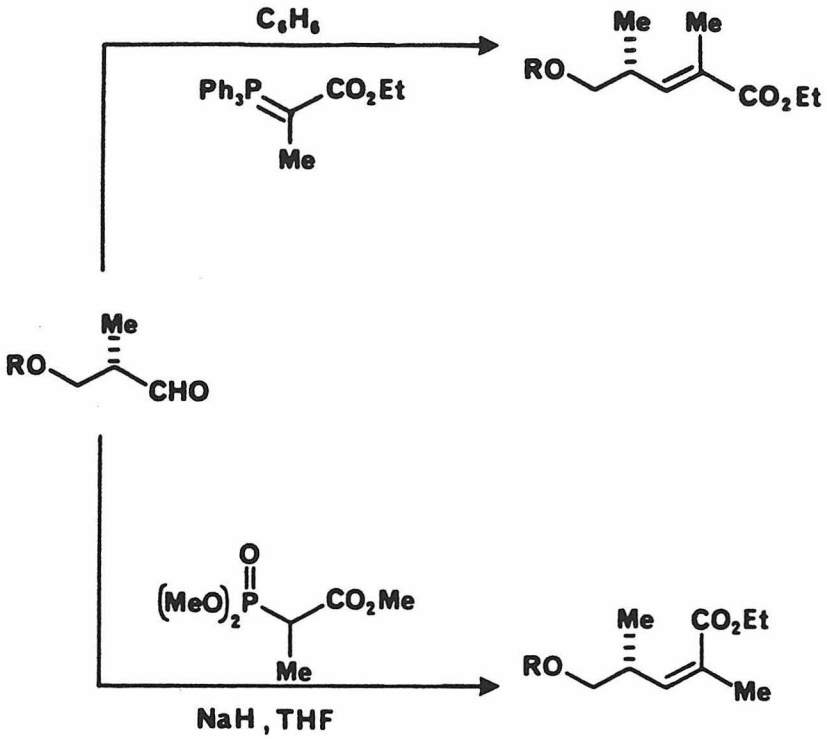
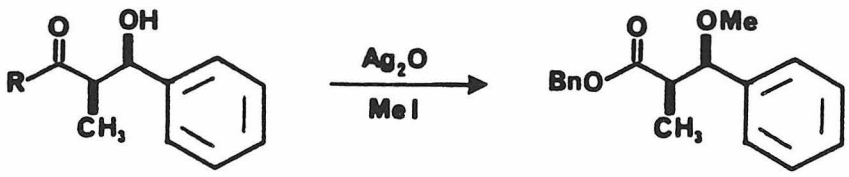


Figure 5. Trisubstituted olefin synthesis.

carbonyl compounds **16a** and **16b** were refluxed in iodomethane in the presence of Ag_2O (eq. 5). Under these conditions, imide **16a** showed significant amounts of products arising from aldol reversion.[18] However, benzyl ester **16b** was cleanly and quantitatively transformed into the desired methyl ether by this procedure. Furthermore, no racemization was detected for this process as evidenced by NMR and analytical GC.



(5)

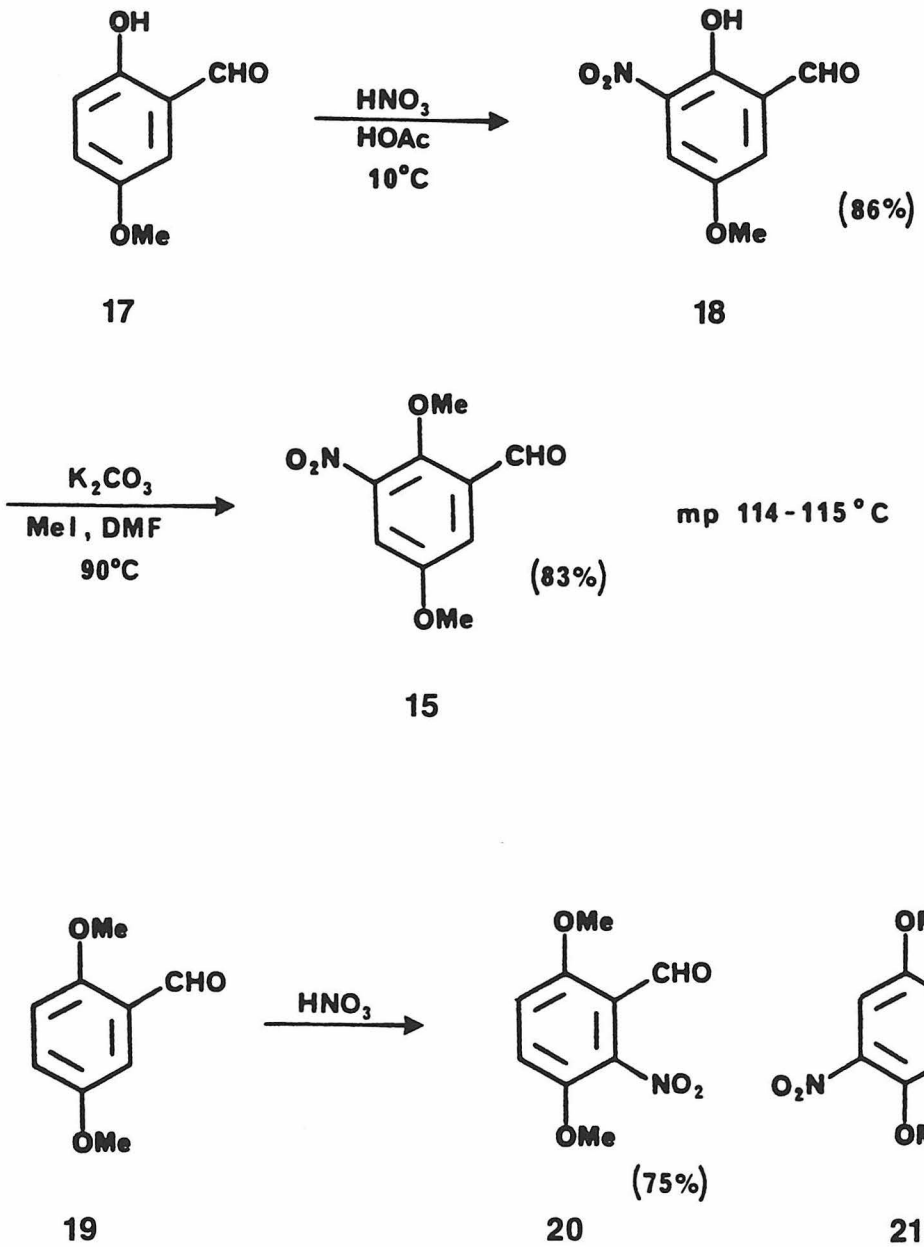
16 a (R = X_N)
b (R = OB_N)

III. Results and Discussion

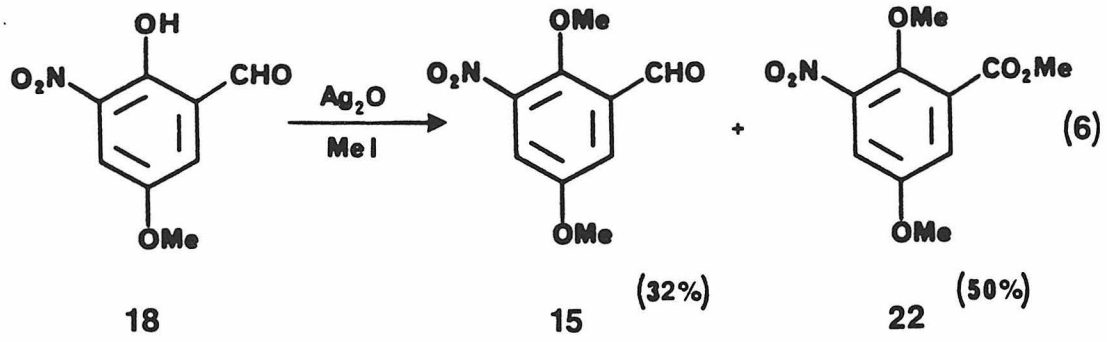
The synthesis of 2,5-dimethoxy-3-nitrobenzaldehyde **15**, the aromatic aldehyde chosen for the first aldol condensation, is given in Scheme V.[21] Nitration of the commercially available 2-hydroxy-5-methoxybenzaldehyde **17**[22] has been reported by Rubenstein to proceed upon treatment with 10 equivalents of nitric acid in glacial acetic acid.[23] All attempts to reproduce this experiment resulted in the rapid and exothermic over-oxidation of the initially formed nitration product by excess nitric acid. However, by reducing the amount of nitric acid used, **18** was produced in high yield. Thus, treatment of **17** with 1.1 equivalent of nitric acid in glacial acetic acid at 10-20°C resulted in an 86% yield of the bright yellow nitro-aromatic **18** (mp 129.5-130.5°C). Unfortunately, nitration of the significantly less expensive 2,5-dimethoxybenzaldehyde **19** produces none of the desired regioisomer, but rather a 3:1 mixture of C-6 and C-4 nitration products (Scheme V).[24]

Rubenstein also reports on the "quantitative" methylation of **18** using silver (I) oxide and iodomethane.[23] In our hands, this procedure affords only a 32% yield of the desired **15**, the major product being the methyl ester **22**

Scheme V

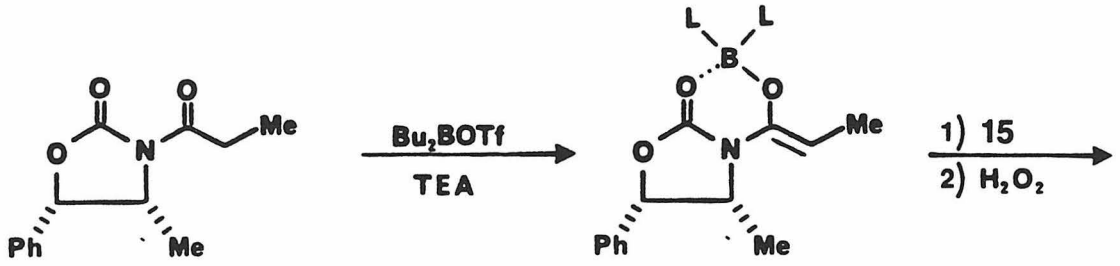

OH
CHO
OMe
HNO3
HOAc
10°C
O2N
(86%)
17
18
K2CO3
MeI, DMF
90°C
(83%)
mp 114-115°C
15
NO2
(75%)
(25%)
19
20
21

resulting from aldehyde oxidation (eq. 6). However, treatment of phenol **18** with potassium carbonate and iodomethane in N,N-dimethylformamide (DMF) at 90°C affords the desired dimethylhydroquinone **15** as tan needles in 83% yield (mp 114-115°C). Thus, aromatic aldehyde **15** can be conveniently synthesized in multi-gram quantities in two steps from commercially available starting material.

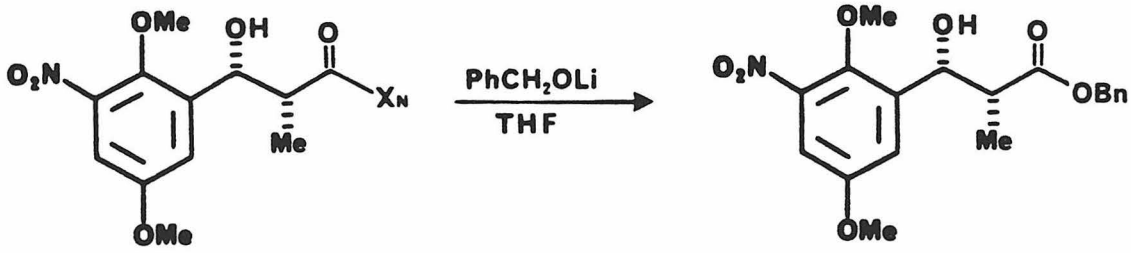


The first of the four aldol reactions that will ultimately yield macbecin incorporates carbon atoms 13 and 14 (macbecin numbering) and establishes their stereochemistry. Treatment of N-propionyl imide **8** with di-n-butylboryl triflate (1.1 equiv) and triethylamine (1.2 equiv) in dichloromethane (-78°C, 30 min; 0°C, 1 h) results in the formation of (Z)-boron enolate **23** (Scheme VI). Condensation with aromatic aldehyde **15** (-78°C, 30 min; 0°C, 1 h) affords, after oxidative removal of boron, the highly crystalline adduct **24** in 78-86% recrystallized yield (mp 204-206°C). The assignment of erythro stereochemistry to aldol adduct **24** can be made on the basis of its ^{1}H NMR, which exhibits a 3 Hz splitting of the benzylic $C_{3'}$

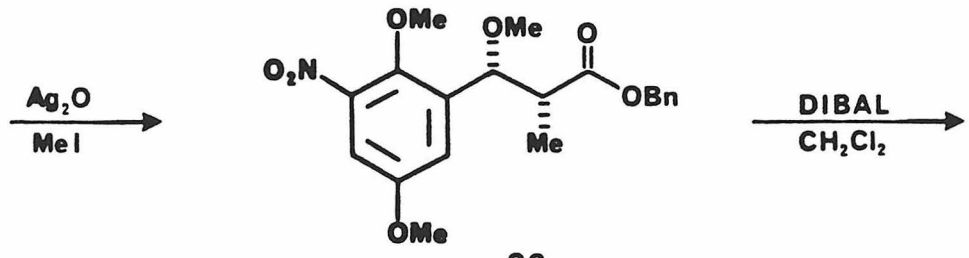
Scheme VI



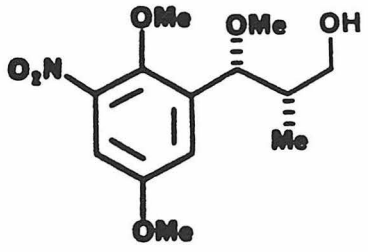
8 23



24 25



26



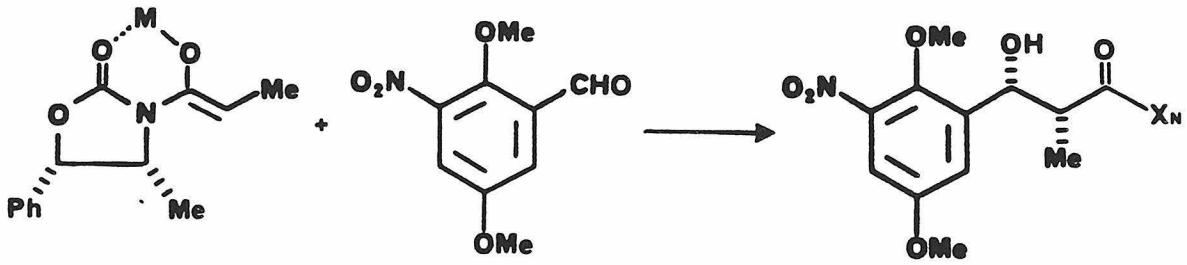
27

proton.[25] Gas chromatographic analysis on the derived trimethylsilyl ethers of the unpurified reaction product reveals that erythro isomer **24** is 98% pure, being contaminated by <2% of any other single isomer or byproduct. Shown in Figure 6 are the analytical GC traces for both the boron- and lithium-meditaed aldol reactions. As expected, the lithium enolate of **8** (LDA, -78°C, 30 min) reacts with aldehyde **15** to produce all four of the possible aldol diastereomers, although peak assignments were not determined.

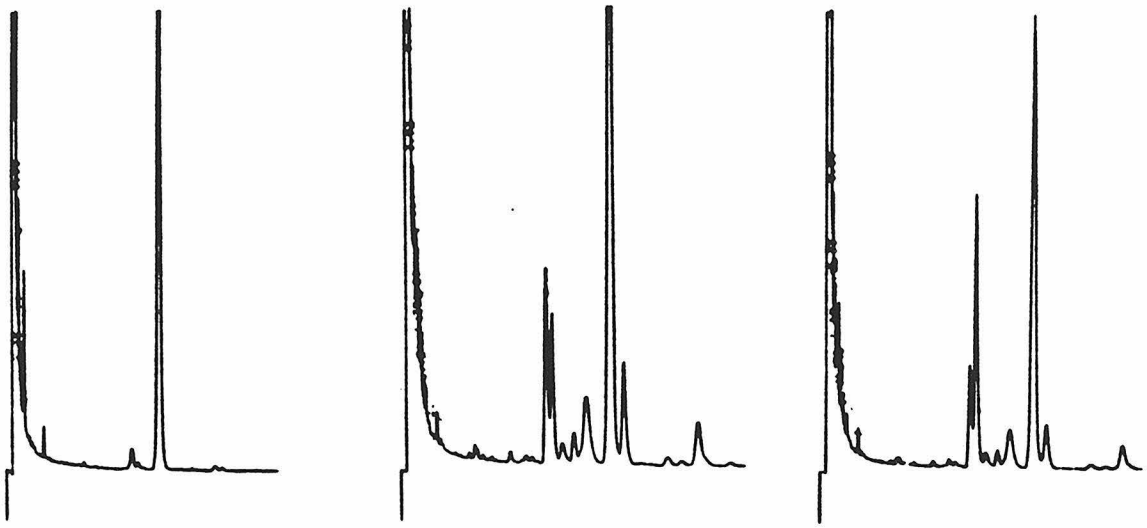
Transesterification of aldol imide **24** with 1.5 equivalent of lithium benzyloxide in THF at -20°C affords benzyl ester **25** in 87% yield after chromatography. However, due to difficulties in separating ester **25** from remaining benzyl alcohol in large scale reactions, the unpurified mixture obtained from this reaction was usually directly subjected to the methylation procedure previously described. Thus, ester **25** was heated at reflux in iodomethane in the presence of silver (I) oxide to provide methyl ether **26**, readily separable from benzyl methyl ether, in 86% purified yield.

Attempts to reduce ester **26** to the aldehyde oxidation state using 1 equivalent of diisobutylaluminum hydride (CH_2Cl_2, -78°C) met with only moderate success, as over-reduction to the primary alcohol was facile. In order to avoid having to chromatograph a potentially sensitive aldehyde, we elected to carry out a two-step, reduction-oxidation sequence. Thus, ester **26** was treated with 2.2 equivalents of DIBAL (CH_2Cl_2, -50°C, 2 h) to provide alcohol **27** as a single isomer (GC, NMR) in 95% yield after chromatography.

We have found it convenient for large-scale preparations to carry out the three-step transformation of aldol product **24** to alcohol **27** without the purification of any intermediates. In this way, a 93% overall yield of **27** was



15 24

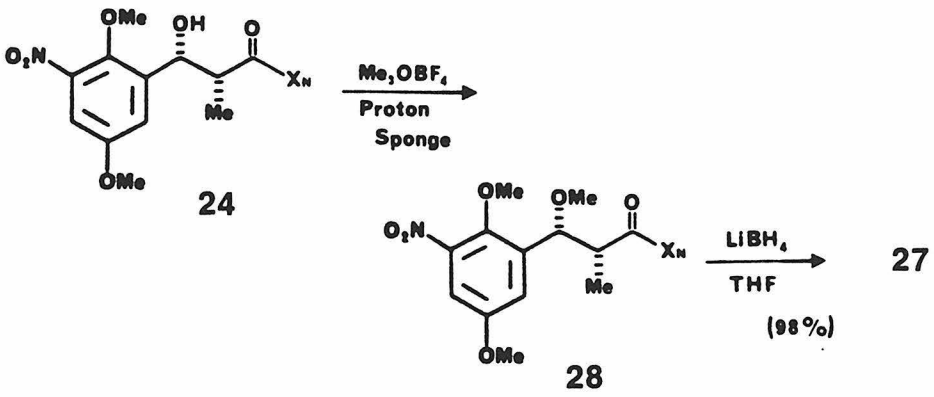


A: M = BBu_2 B: M = Li C: A + B

Figure 6. GC analysis of aldol condensation of imide **8** with aldehyde **15**.

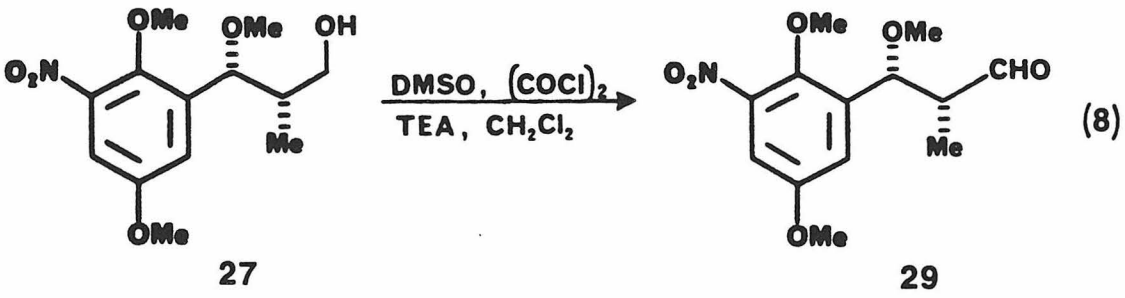
obtained starting from 15 mmol of adduct **24**.

A somewhat shorter route to alcohol **27** has recently been developed.[26] Treatment of aldol adduct **24** with trimethyloxonium tetrafluoroborate (4.5 equiv) in refluxing dichloromethane in the presence of [1,8-bis(dimethylamino)]naphthalene (Proton Sponge) produces methyl ether **28** in 70% yield after a week, along with some recovered **24** (eq. 7).[27] Reduction of **28** with lithium borohydride (THF, 0° → RT) affords a 98% yield of alcohol **27**, identical in all respects (GC, NMR, $(\alpha)_D$) to that obtained by the three-step sequence in Scheme VI.



(7)

We have found that the activated DMSO-based oxidations work admirably in providing rapid and clean generation of aldehydes from primary alcohols.[28] Caution must be exercised, however, in the handling of aldehydes sensitive to racemization or β-elimination. For these cases, best results have been obtained by using a modification of the Swern procedure.[29] Thus, treatment of alcohol **27** with oxalyl chloride-activated DMSO and triethylamine in dichloromethane produces a quantitative yield of aldehyde **29** after 30min → 1 h at ≤-50°C (eq. 8). No evidence of epimerization to the threo isomer or elimination to the α,β-unsaturated aldehyde was seen by ^1H NMR



27 29 (8)

(see Figure 7, Spectrum A). This is in contrast to the results obtained from oxidations using the pyridine-sulfur trioxide complex in DMSO at room temperature.[30] Under these conditions, up to ca. 30% of racemization to the threo aldehyde can occur (Figure 7, Spectrum B). Since aldehyde **29** is a low-melting solid (mp 77-79°C), recrystallization from ethyl acetate:hexane will often provide purified **29** as a single isomer. However, the product obtained from the Swern oxidation is sufficiently pure to be used directly in the subsequent aldol reaction.

The second aldol condensation in this synthesis of macbecin utilizes the valine-derived imide **9** and incorporates carbon atoms 11 and 12 in the straight chain, acyclic target **7**. This reaction is sensitive to a number of external variables, including reaction temperature, reaction time, solvent, and stoichiometry. For example, condensation of the boron enolate derived from imide **9** with aldehyde **29** in dichloromethane for 2 h at -78°C results in only a 40% yield of aldol adduct **30** (eq. 9), along with recovery of ca. 50% of racemized aldehyde **29** (erythro:threo = 60:40). Gradual warming of the

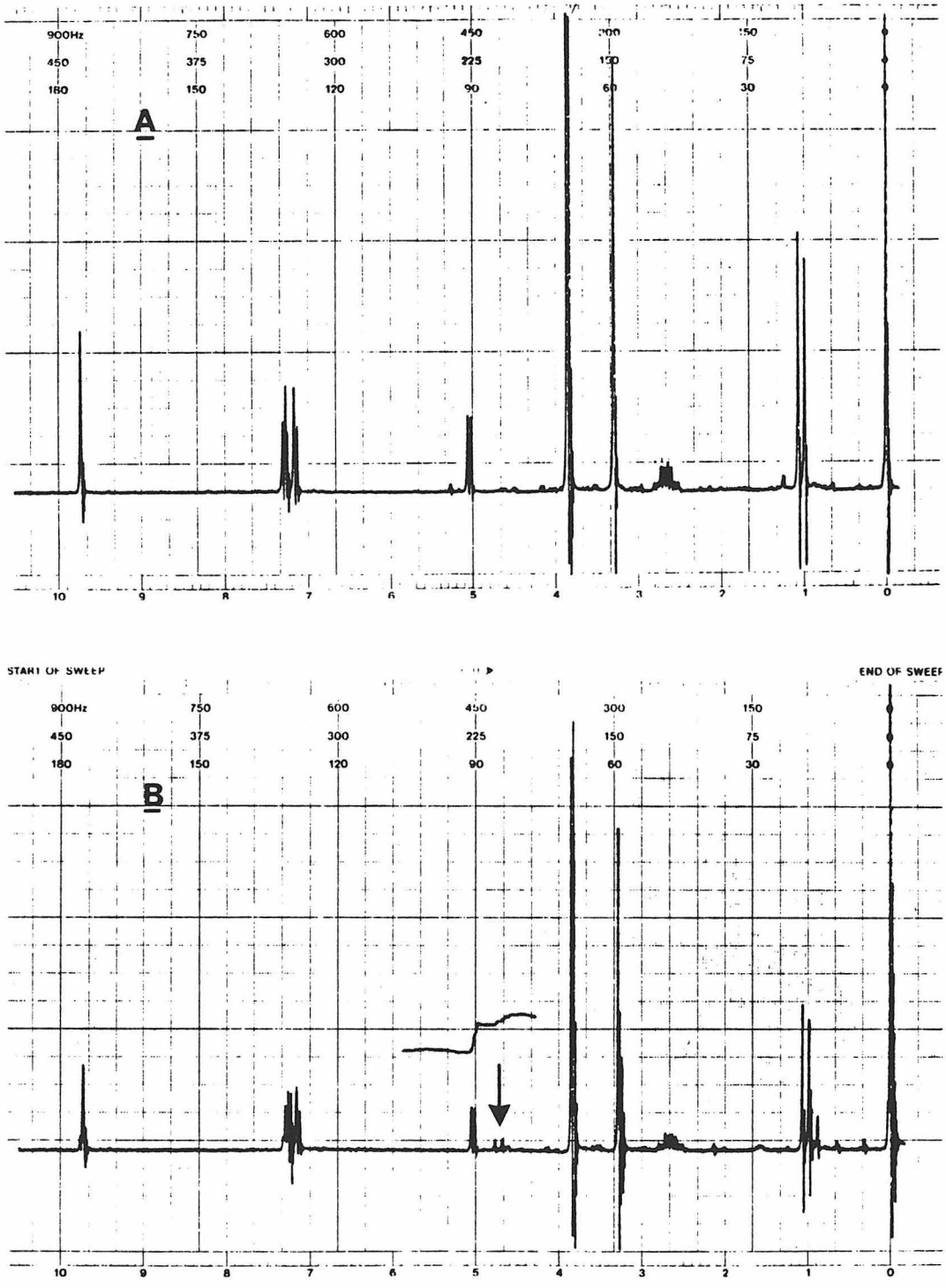
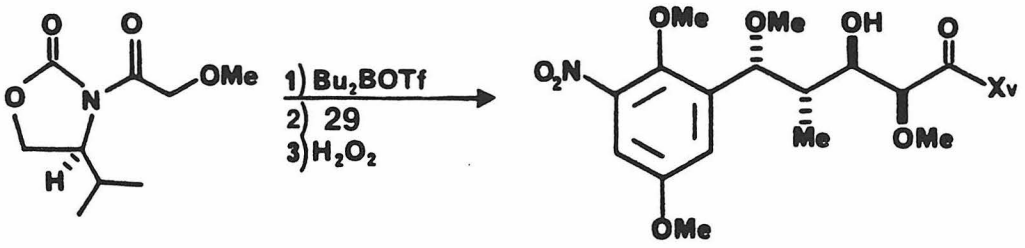
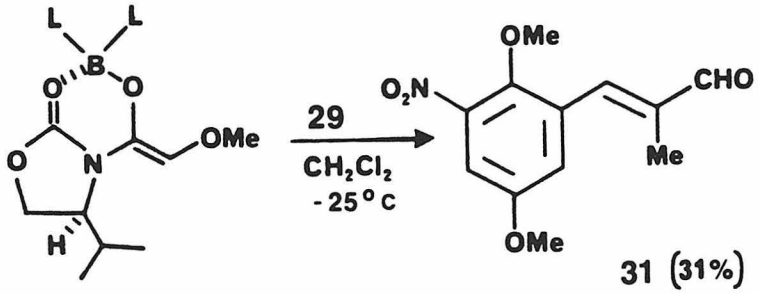


Figure 7. ^1H NMR (90 MHz, $CDCl_3$) of aldehyde **29** from: (A) DMSO, $(COCl)_2$ oxidation: (B) DMSO, $Pyr{\cdot}SO_3$ oxidation.



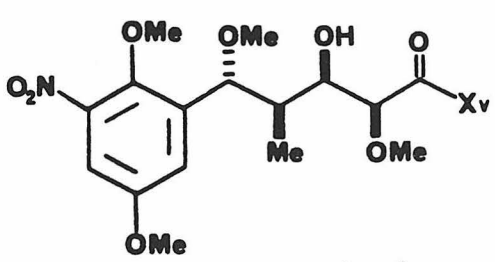
9 30 (9)

reaction from -78°C to room temperature over a period of 6 h increases yields of aldol product to 60-80%. However, if after aldehyde addition, the reaction is immediately warmed to -25°C and held there for 2 h, one realizes at 31% yield of the α,β-unsaturated aldehyde **31**,[31] a 33% yield of the aldol adduct derived from the threo aldehyde (**32**), and a 42% yield of the desired product **30** (eq. 10). Undoubtedly, the presence of the methoxyl substituent on the

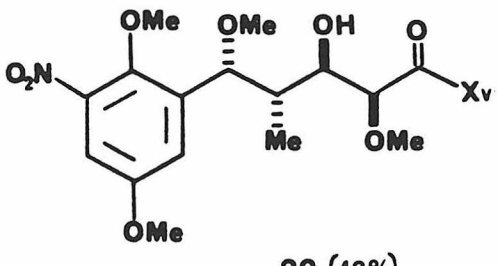


31 (31%)

(10)



32 (33%)



30 (42%)

enolate derived from **9** serves to attenuate the nucleophilicity of this species. Thus, the reaction of this enolate with aldehyde **29** is partitioning between competitive carbonyl addition and enolization pathways. We have found, however, that by employing <u>two</u> equivalents of boron-enolate at -78 → -30°C (3 h), one can obtain consistently high yields (80-85%) of aldol adduct **30** without loss of stereochemical integrity.

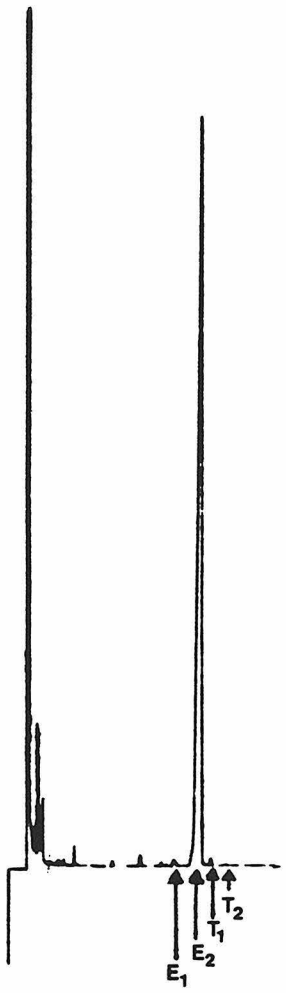
Shown in Figure 8 is the analytical GC trace of the silated reaction product obtained from the aldol condensation of aldehyde **29**.[32] Of the four stereoisomers possible from this reaction, the desired erythro isomer **30** is generated with >98% selectivity. A single recrystallization from carbon tetrachloride/hexane affords aldol adduct **30** with >99% purity by GC.

A brief examination was made on the influence of solvent in the stereochemical outcome of the aldol condensation of aldehyde **29**. The results of this study are given in Table 1. As is evident from the data, there appears

Table 1. Solvent Study for Aldol II (eq. 9).[a]

Entry	Solvent	E_1	E_2	T_1	T_2
A	CH_2Cl	0.9	97.7	0.6	0.7
B	Et_2O	1.1	94.6	3.4	0.9
C	Toluene	1.0	95.3	2.7	0.9

[a]Reaction stoichiometry: enolate:aldehyde = 1:1; reaction temperature was -78→ 0° C.



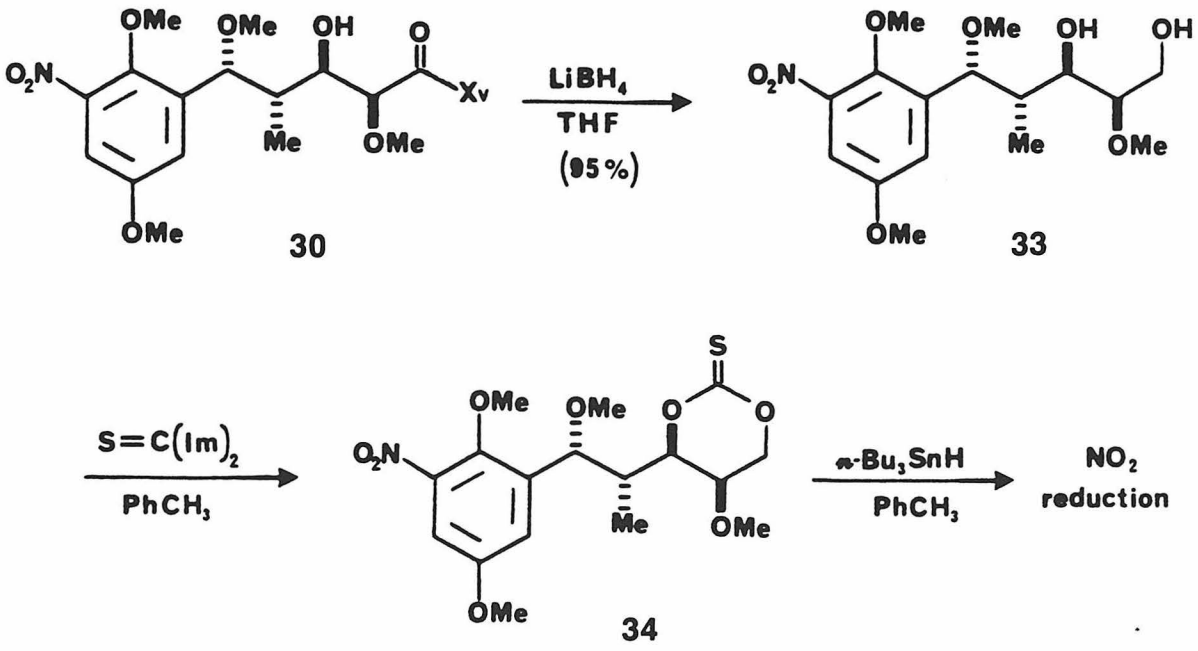
	SE-54 (30m) 250°C	
E_1	5.69	0.7%
E_2	6.36	98.6%
T_1	6.66	0.5%
T_2	7.45	0.2%

Figure 8. Analytical GC trace of aldol II (eq. 9)

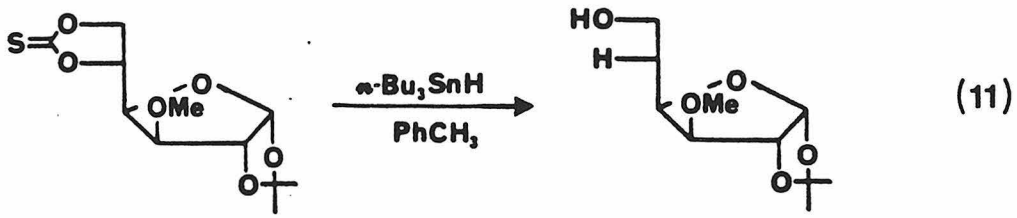
to be only a minor solvent effect in this reaction. Triethylamine hydrochloride precipitated out of solution in the reactions run in ether and toluene. It was gratifying to see that dichloromethane, which gives a homogeneous reaction mixture, is the medium in which this reaction proceeds with the greatest stereoselectivity.

With aldol adduct **30** in hand, our attention turned to the problem of deoxygenation at C-13. Wary of the propensity of **30** to retro-aldol, our initial plan involved reduction of **30** to diol **33**, followed by formation of the thiocarbonate derivative **34** (Scheme VII). Barton has demonstrated that cyclic thiocarbonates such as **34** react with tri-n-butyltin hydride to effect deoxygenation selectively at the secondary hydroxyl position.[33] For example, treatment of thiocarbonate **35** with tri-n-butyltin hydride in toluene under

Scheme VII



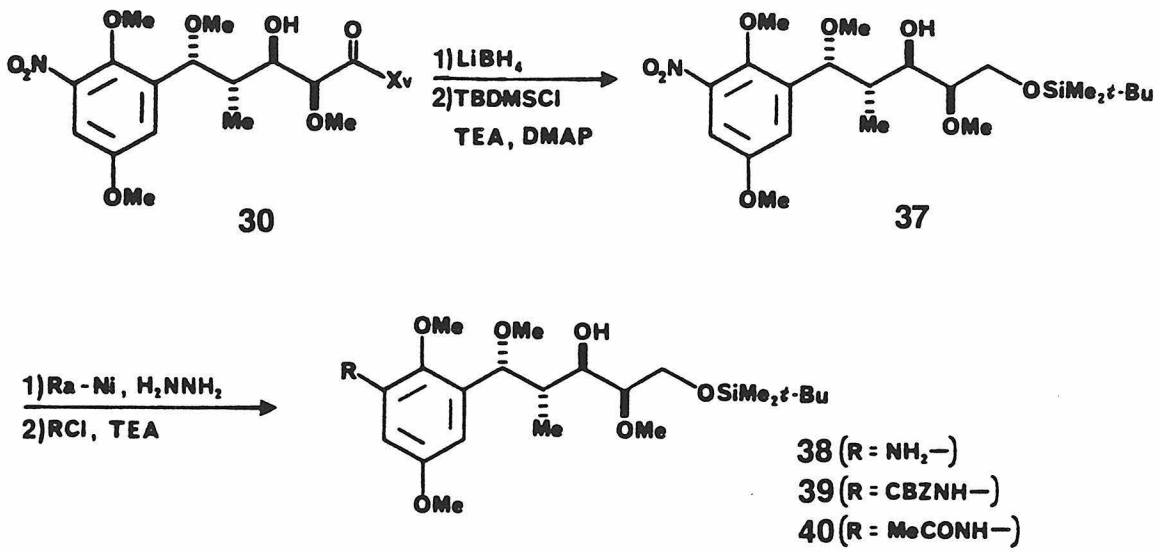
reflux gave, after alkaline hydrolysis, the 5-deoxy sugar **36** in 67% yield (eq. 11). None of the isomeric 6-deoxy sugar was detected. Unfortunately, thiocarbonate **34** proved unworkable, as treatment with tri-n-butyltin hydride in toluene engendered nitro-group reduction, along with the production of numerous uncharacterized byproducts.



35 **36** (67%) (11)

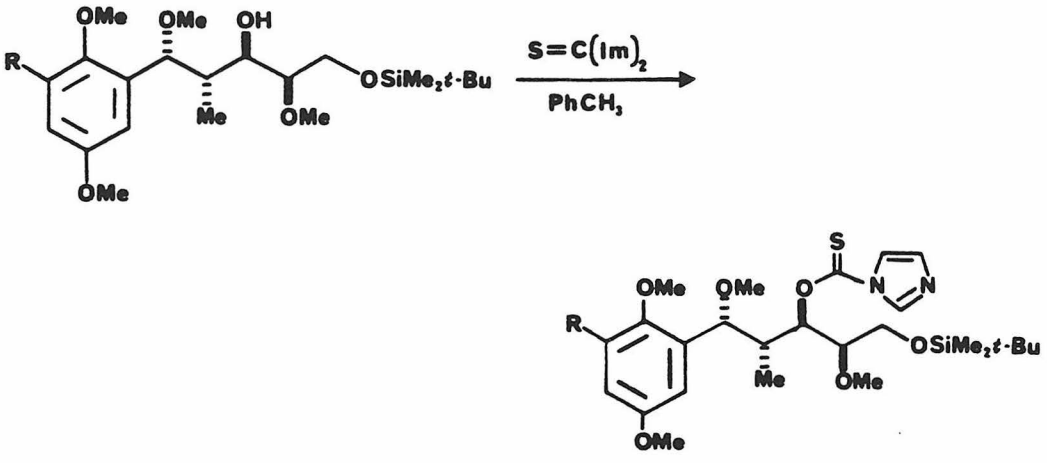
Abandoning thiocarbonate chemistry, we opted to protect the primary hydroxy group of **33** and concentrate on the deoxygenation of the isolated C-13 alcohol. Reduction of aldol adduct **30** with lithium borohydride in THF, followed by treatment with tert-butyldimethylsilyl chloride (CH_2Cl_2, TEA, DMAP, 0 → RT) affords mono-alcohol **37** in 55-70% overall yield (Scheme VIII). Alcohol **37** proved to be stubbornly resistant to derivatization, due most likely to the sterically congested environment around C-13 as well as the existence of a strong intramolecular hydrogen bond between the C-13 hydroxyl and the C-15 methoxyl group (see Appendix I). For example, prolonged treatment of **37** with sodium hydride, carbon disulfide, and methyl iodide (THF, reflux) failed to produce significant amounts of the desired xanthate derivative. Furthermore, a mixture of alcohol **37** and acetyl chloride (CH_2Cl_2, TEA,

Scheme VIII



DMAP, 25°) afforded none of the desired acetate. However, we were able to generate the thiocarbonylimidazole derivative **41** in good yield by refluxing a solution of a **37** with thiocarbonyldiimidazole in toluene (eq. 12). The success of this reaction is probably due to the planar nature of the imidazole reagent.

All attempts at the deoxygenation of substrate **41** met with failure. The initial product formed upon treatment of **41** with tri-n-butyltin hydride in refluxing toluene is the aniline **42**, the result of nitro-group reduction. Subsequent to that primary event, apparent deoxygenation takes place, albeit in low yield due to a host of competing side reactions. Photo-initiated (Pyrex filter) tinhydride reduction of **41** at room temperature in toluene in the presence of AIBN was ineffective, and at elevated temperatures, this



(12)

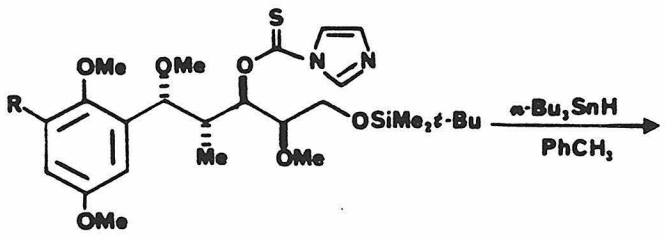
41 (R = NO_2–)
42 (R = NH_2–)
43 (R = CBZNH–)
44 (R = MeCONH–)

reaction follows the course of the thermal reduction. Attempted photochemical deoxygenation of **41** in HMPA:H_2O (95:5, Vycor filter)[34] rapidly produced unrecognizable polymer.

It would thus appear that our earlier hopes of being able to effect deoxygenation at C-13 without concomitant nitro-group reduction are unattainable. We therefore directed our studies to the deoxygenation of substrates in which the aromatic nitro-group has been pre-reduced and protected. Thus, treatment of alcohol **37** with Raney-nickel and hydrazine hydrate in refluxing methanol[35] rapidly produces aniline **38** in excellent yield (Scheme VIII). Direct derivatization of unpurified **38** with either benzyl chloroformate or acetyl chloride (CH_2Cl_2, TEA, DMAP, 0° → RT) affords compounds **39** and **40** in 75% and 90% overall yields respectively. Treatment of these compounds with thiocarbonyldiimidazole in refluxing toluene

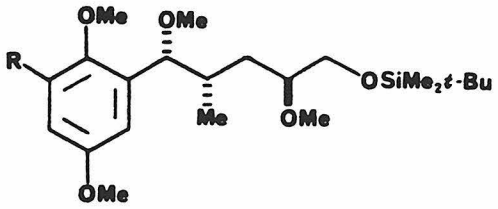
produces the reduction substrates **43** and **44** in good yield (eq. 12).

Both compounds **43** and **44** have proven to be viable substrates for carrying out the desired deoxygenation chemistry. However, treatment of the carbobenzoxy-protected aniline **43** with tri-n-butyltin hydride in refluxing toluene affords only a 29% yield of the desired deoxy-compound **45** (eq. 13). A major byproduct was isolated from this reaction which, although not fully characterized, appears to be the result of both deoxygenation at C-13 and loss of the CBZ-protecting group. This compound, which is definitely <u>not</u> the expected aniline, might possibly be some sort of diazo dimer.



(13)

43 (R = CBZNH—)
44 (R = MeCONH—)



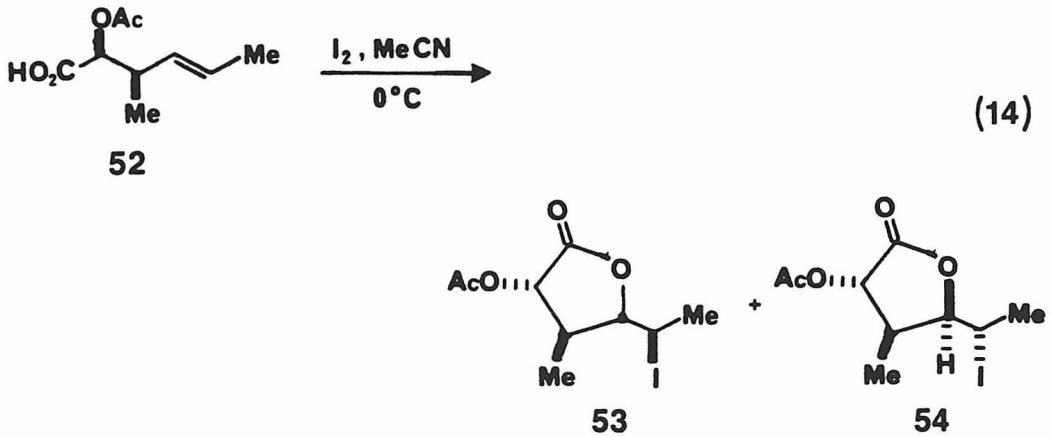
45 (R = CBZNH—)
46 (R = MeCONH—)

Final success in this deoxygenation was ultimately achieved through the use of compound **44**. The more robust acetate group easily survives the Barton reduction conditions, and deoxy-product **46** is obtained in 70% isolated yield from the reaction with tin hydride (eq. 13).

The deoxygenation product **46** is an advanced intermediate in our synthesis of macbecin I and incorporates three of the seven stereocenters in

this macrolide, as well as carbons 15-11 of the ansa bridge. By the route described, fragment **46** is produced in 16% overall yield from 2-hydroxy-5-methoxybenzaldehyde **17** in 14 steps, with an average yield per reaction of 88%. Although only two carbon-carbon bond forming reactions occur in this sequence (the two aldol condensations), functional group manipulations proceed in high yield, and many steps can usually be combined without purification of reaction intermediates. Indeed, the synthesis of the advanced intermediate **37**, representing ten steps into the sequence, can be carried out with only two chromatographies.

Due to our inability to effect tinhydride induced deoxygenation at C-13 without concurrent nitro-group reduction, we have sought alternatives which avoid these difficulties. One attractive approach to establishing the stereochemistry at C-12 without proceeding through aldol intermediates, and thereby obviating deoxygenation, is illustrated in Scheme IX. Iodolactonization of compounds such as **49** was expected to proceed to



(14)

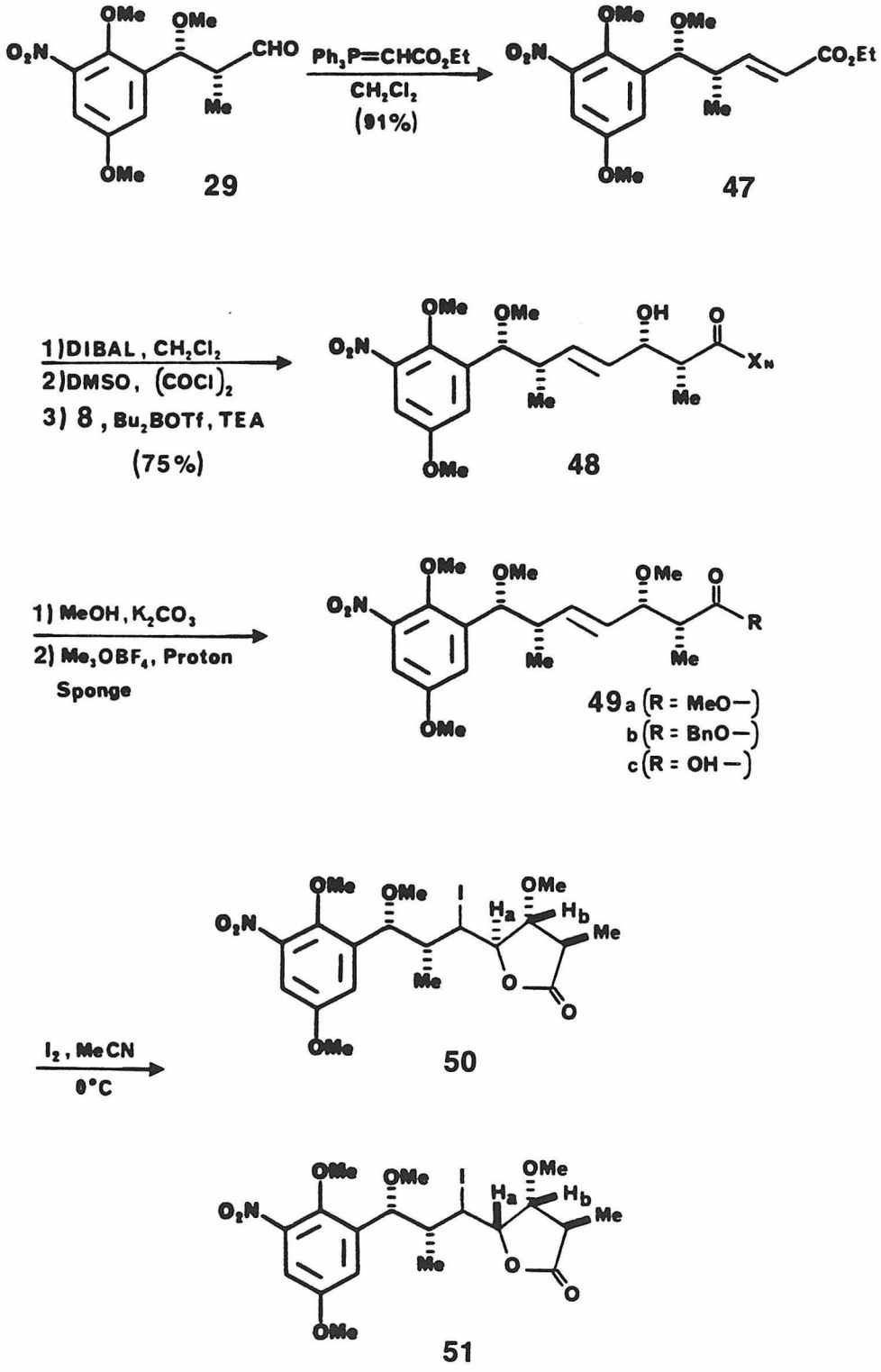
53:54 = 20:1

selectively generate the trans γ-lactone **50** under thermodynamic conditions, based upon the pioneering work of Bartlett in this area.[36] Bartlett has demonstrated that reaction at the unsaturated acid **52** with iodine in acetonitrile produces the trans- and cis-lactones **53** and **54** respectively, favoring the thermodynamically more stable trans isomer **53** by 20:1 (eq. 14). We set out to explore this reaction with substrates such as **49**. The reduction of the derived iodo lactone to the dehalogenated product was expected to proceed under conditions mild enough to permit nitro-group survival.

Two-carbon homologation of aldehyde **29** by Wittig reaction with carboethoxymethylene triphenylphosphine afforded the α,β-unsaturated ester **47** in 91% yield as a single olefin isomer.[26] Conversion of the ester functionality to an aldehyde through the normal reduction-oxidation sequence, followed by aldol condensation with the boron-enolate **23** affords aldol adduct **48** in 75% overall yield from **47**. Transesterification of adduct **48** (MeOH, K_2CO_3, 1 h, 0°C) followed by methyl ether formation as previously described produced substrate **49a** in 68-75% yield.

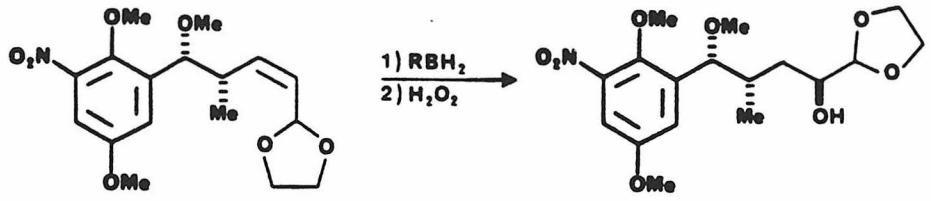
Under a variety of conditions, iodolactonization of ester **49a** with iodine in acetonitrile (0°C → 25°) produced a single compound. That **49a** had cyclized to produce the five-membered ring lactone and not the six-membered ring lactone was evidenced by ^1H NMR and IR. However, extensive decoupling and NOE experiments revealed that the product obtained from this reaction was the undesired cis-isomer **51**. Irradiation of the proton labeled H_a (Scheme IX) leads to enhancement of both proton H_b and the adjacent lactone methyl group, clearly indicative of the cis-product. Substrates **49b** and **49c** proved equally uncooperative, each also affording the γ-

Scheme IX


OMe
OMe
O2N
CHO
Me
OMe
29
Ph3P=CHCO2Et
CH2Cl2
(91%)
CO2Et
47
1)DIBAL, CH2Cl2
2)DMSO, (COCl)2
3) 8, Bu2BOTf, TEA
(75%)
OH
O
XN
48
1) MeOH, K2CO3
2) Me3OBF4, Proton Sponge
R
49a (R = MeO—)
b (R = BnO—)
c (R = OH—)
I
Ha
Hb
50
I2, MeCN
0°C
51

lactone with incorrect stereochemistry. Although the initial lack of success in these reactions is mysterious as well as disappointing, this avenue of research is currently under further investigation.

Another potential solution to this problem which was briefly examined involves the stereoselective hydroboration of the cis-olefin **55**. Ketal **55** could be conveniently synthesized from aldehyde **29** in 76% yield via the appropriate Wittig reaction.[26] $A_{1,3}$-strain arguments similar to those proposed by Kishi[37] would predict that hydroboration of **55** should occur from the α-face, giving rise to the desired stereochemistry at C-14 (eq. 15). Inductive electronic effects by the ketal group should favorably direct the regiochemistry of the hydroboration.[38]



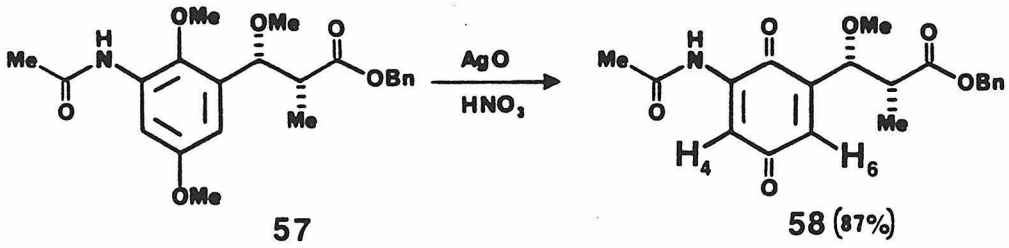
(15)

55 **56**

In the event, treatment of olefin **55** with thexyl borane in THF (0°C → RT) followed by oxidative removal of boron led to a plethora of unrecognizable products.[26] After the failure of a number of prospecting experiments to bear fruit, this route was discarded. At the moment, therefore, the initially deoxygenation pathway to fragment **46** appears to hold the most promise.

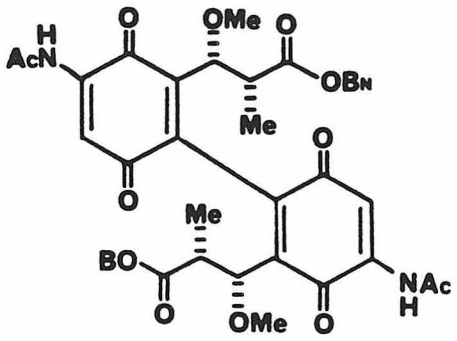
Before committing ourselves too deeply in this synthesis, we wished to demonstrate the viability of the proposed oxidative transformation of a hydroquinone dimethyl ether to a quinone (see Figure 4). Some of the more common reagents known to promote this type of oxidation are nitric acid,[16a] argentic oxide (AgO),[39] ceric ammonium nitrate,[40] and Freny's salt.[16b] We chose as a model system for studying this reaction the compound **57** (eq. 16), easily obtainable from the previously described ester **26** via nitro-group reduction (Ni, H_2NNH_2) and acylation (CH_3COCl, TEA) in 82% overall yield.

Brief exposure of **57** to 2.5 equivalents of ceric ammonium nitrate (CAN) in aqueous acetonitrile (30 min, RT) afforded after chromatography a 58% yield of the yellow quinone **58**, along with ca. 10% of another quinone product. The ^1H NMR spectrum of quinone **58** is instructive. The aromatic protons



57 **58** (87%) (16)

H_4 and H_6 (eq. 16) exhibit an AB splitting pattern with J_{AB} = 3 Hz. In addition, proton H_6 experiences an allylic coupling with the C_3-benzylic hydrogen (J = 2 Hz). This allylic coupling is absent in precursor **57**. The ^1H NMR spectrum of the byproduct obtained from this reaction exhibits no signal for H_6, a singlet for H_4, and a lack of allylic coupling to the benzylic proton. Based



59

Figure 8. Proposed byproduct from CAN oxidation of **57**.

upon these observations, we propose structure **59** for this compound (Figure 8). Dimers of this type are well-known byproducts of similar CAN oxidations.[40]

Although CAN is a satisfactory reagent for this transformation, the reagent of was found to be is silver (II) oxide (argentic oxide). The mixing of ester **57** with four equivalents of finely powdered AgO in dioxane at room temperature produces no reaction until a mineral acid is added. Addition of six equivalents of aqueous nitric acid resulted in the rapid and clean generation of quinone **58** (<5 min, 25°), which was obtained pure after chromatography in 87% yield. Interestingly, the use of perchloric acid instead of nitric acid proved unsatisfactory, producing numerous byproducts.

IV. Summary

Our efforts toward the total synthesis of the ansa-antibiotic macbecin I have culminated in the preparation of the advanced intermediate **46**. This

piece contains one-third of the carbon atoms comprising the ansa-bridge of both macbecin I and herbimycin. The efficient synthesis of **46** demonstrates the viability of constructing acyclic carbon chains rich in stereochemistry via an iterative aldol approach. Furthermore, the validity of the proposed final transformation to macbecin by oxidative demethylation of a hydroquinone precursor has been demonstrated. Efforts continue toward the ultimate completion of this synthesis of macbecin 1, as well as other members of this ansa-antibiotic family.

Experimental Section

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

Analytical gas-liquid chromatography was carried out on a Hewlett Packard 5880A Level 3 gas chromatograph equipped with a split mode capillary injection system and a flamed ionization detector, using a 25 m x 0.2 mm flexible fused silica capillary column wall-coated with Carbowax 20M or methyl silicone (SP-2100), or a 30 m x 0.32 mm fused silica capillary column

wall-coated with SE-54. Unless otherwise noted, injector and detector temperatures were 250°C. Chromatography on silica gel was performed using a forced flow[37] of the indicated solvent system on EM Reagents Silica Gel 60 (70-230 mesh), or for large scale preparative work on EM Reagents Silica Gel 60 (230-400 mesh). Medium pressure liquid chromatography (MPLC) was carried out using EM Reagents Lobar Silica Gel 60 prepacked columns (column size indicated) with a Fluid Metering Inc. Model RP-SY Lab Pump in conjunction with an ISCO Model UA-5 Absorbance/Fluoresence Monitor with Type 6 Optical Unit (2 mm path length cell, 15 μL volume). Analytical thick-layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Preparative thick-layer chromatography was performed using EM Reagents 2 mm silica gel 60-F plates (20 cm x 20 cm).

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, triethylamine, diisopropylethylamine, and boron trifluoride etherate were distilled from calcium hydride. Dimethyl sulfoxide, dimethylformamide, and hexamethylphosphoric triamide (HMPT) were distilled from calcium hydride and stored over activated 4 Å molecular sieves. Alkyl halides were passed down a column of activity I alumina immediately prior to use. All other reagents were used as received.

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

2-Hydroxy-5-methoxy-3-nitrobenzaldehyde (18). Attempts to prepare the title compound by the procedure of Rubenstein[23] were unqualified failures. The following modification proved successful. To a mechanically-stirred, cooled (10°C) solution of 30.4 g (0.20 mol) of 2-hydroxy-5-methoxybenzaldehyde[22] (17) in 150 mL of glacial acetic acid was added dropwise a solution of 14 mL of 70% nitric acid (0.22 mol) and 14 mL of glacial acetic acid. The addition was carried out at a rate which maintained the reaction temperature between 10° and 20°C. After approximately one-half of the nitric acid solution has been added, the product begins to separate out as a bright yellow precipitate. After the addition was complete, the reaction mixture was vigorously stirred at room temperature for 30 min, then poured into 200 mL of water. The aqueous layer was extracted with dichloromethane (3 x 75 mL), and the combined organic layers were washed with brine (1 x 75 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a yellow powder. This material was recrystallized from ethanol:water and dried in vacuo over phosphorous pentoxide for 12 h to give 33.9 g (86%) of **18** as bright yellow crystals, mp 129.5-130.5°C (Lit.[23] mp 132°C). IR ($CHCl_3$) 3400-3150, 3030, 1695, 1541, 1435, 1051 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 10.89 (s, 1, -OH), 10.46 (s, 1, -CHO), 7.82 (d, 1, J_{AB} = 3 Hz, C_4-H), 7.67 (d, 1, J_{BA} = 3 Hz, C_6-H), 3.86 (s, 3, $-OCH_3$).

Anal. calcd. for $C_8H_7NO_5$: C, 48.74; H, 3.58. Found: C, 49.06; H, 3.31.

2,5-Dimethoxy-3-nitrobenzaldehyde (15). A dry, 500-mL, single-necked, round-bottomed flask fitted with a magnetic spin bar and a reflux

condenser was charged with 25.6 g (0.13 mol) of 2-hydroxy-5-methoxy-3-nitrobenzaldehyde (**18**) and 22.0 g (0.16 mol) of anhydrous potassium carbonate. The system was purged with nitrogen, and 250 mL of dry N,N-dimethylformamide (DMF) was added. To the resulting blood-red slurry was added 50 mL (0.8 mol) of iodomethane, and the reaction mixture was heated to ca. 90°C. After 10 min, the blood-red solution changes to brown, indicating consumption of the phenolate anion. After cooling to room temperature, the reaction was poured into 200 mL of water and extracted with 1,1,1-trichlorethane (3 x 75 mL). The combined organic layers were washed once with water (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to a brown solid. This material was recrystallized from ethanol:water and dried in vacuo over phosphorous pentoxide for 12 h to give 22.9 g (83%) of **15** as tan needles, mp 114-115°C (Lit.[23] mp 113°C). IR ($CHCl_3$) 3035, 1699, 1539, 1488, 1425, 1220, 1050 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 10.37 (s, 1, -CHO), 7.59 (d, 1, J_{AB} = 1 Hz, C_4-H), 7.58 (d, 1, J_{BA} = 1 Hz, C_6-H), 4.00 (s, 3, $-OCH_3$), 3.87 (s, 3, $-OCH_3$); ^{13}C NMR (C_6D_6) δ 186.6, 116.5, 65.1, 55.4 (5 aromatic carbons obscured by C_6D_6 signals).

Anal. calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30. Found: C, 51.28; H, 4.29.

(4S)-3-(Methoxyacetyl)-4-(2-propyl)-oxazolidine-2-one (9). A solution of 2.98 g (23.1 mmol) of valine-oxzolidone[41] (ca. 0.25 M in THF) was metalated using 18.9 mL of a 1.47 M solution (27.8 mmol) of n-butyllithium in hexane and acylated with 2.5 mL (3.01 g, 27.7 mmol) of methoxyacetyl chloride according to the previously described procedure[41] to afford 5.69 g (95% mass balance) of unpurified product. The title compound was isolated by

chromatography on silica gel (400 g, 70-230 mesh, 40% ethyl acetate:hexane) followed by molecular distillation (Kugelrohr, 140°C, 0.005 mm) to give 3.72 g (80%) of **9** as a clear, colorless oil. IR ($CHCl_3$) 3025, 2970, 1782, 1720, 1390, 1200 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.56 (s, 2, $-C\underline{H}_2OCH_3$), 4.50-4.15 (m, 3, $C_4-\underline{H}$, $C_5-\underline{H}_2$), 3.42 (s, 3, $-CH_2OC\underline{H}_3$), 2.39 [d of septets, 1, J = 7 Hz, 3 Hz, $-C\underline{H}(CH_3)_2$], 0.94 [d, 3, J = 7 Hz, $-CH(C\underline{H}_3)_2$], 0.89 [d, 3, J = 7 Hz, $-CH(C\underline{H}_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 170.0, 154.2, 72.0, 64.7, 59.3, 58.2, 28.5, 17.8, 14.8; $[\alpha]_D$ +92.6° (c 5.5, CH_2Cl_2).

Anal. calcd.for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: 53.56; H,7.45; N, 6.82.

[4S-[3(2R,3R)]]-3-[3-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxy-2-methyl-1-oxopropyl)]-4-(1-methylethyl)-2-oxazolidinone (24). A cooled (-78°C) and stirred solution of 7.00 g (30 mmol) of norephedrine imide **8** in 60 mL of anhydrous dichloromethane under nitrogen was treated successively with 8.4 mL (33 mmol) of di-n-butylboron triflate[8e] and 5.1 mL (36 mmol) of triethylamine. The reaction was stirred at -78°C for 30 min, then warmed to 0°C and stirred for an additional 1 h. After re-cooling to -78°C, the reaction was treated with a solution of 6.34 g (30 mmol) of 2,5-dimethoxy-3-nitrobenzaldehyde (**15**) in 30 mL of dichloromethane. The reaction was stirred at -78°C for 30 min, then warmed to 0°C and stirred for an additional 1 h before being quenched by the addition of 60 mL of pH 7 phosphate buffer. This solution was diluted with 240 mL of methanol, cooled to 0°C, and treated with 90 mL of a 2:1 mixture of methanol and 30% hydrogen peroxide. After stirring for 1 h at room temperature, volatiles were removed in vacuo

and the resulting aqueous residue was extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed successsively with 5% aqueous sodium bicarbonate (1 x 30 mL) and brine (1 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to a pale yellow solid. Gas chromatographic analysis (SE-54, 250°C, injector 275°C, t_r = 3.91 min) of the silated unpurified aldol adduct showed it to be 97% one compound. Recrystallization from ethyl acetate:hexane gave 10.6 g (80%) of pure **24** (>99% by GC) as a very crystalline, yellow solid, mp 204-206°C, IR ($CHCl_3$) 3650-3300, 3040, 1786, 1678, 1532, 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.23 (m, 7, aromatic H's), 5.67 (d, 2, J = 7 Hz, C_5-H_2), 5.41 (t, 1, J = 3 Hz, C_3'-H), 4.80 (quintet, 1, J = 7 Hz, C_4-H), 4.06 (d of q, 1, J = 3 H, 7 Hz, C_2'-H), 3.84 (s, 3, -OCH_3), 3.83 (s, 3, -OCH_3), 3.79 (d, 1, J = 3 Hz, -OH), 1.20 (d, 3, J = 7 H, C_2'-CH_3), 0.90 (d, 3, J = 7 Hz, C_4-CH_3); ^{13}C NMR ($CDCl_3$) δ 177.5, 155.1, 143.3, 138.1, 133.0, 128.8, 125.6, 119.5, 109.0, 78.8, 68.2, 62.7, 56.1, 54.8, 42.4, 14.4, 10.8; $[\alpha]_D$ +35.3° (c 2.16, DMSO).

Anal. calcd. for $C_{22}H_{24}N_2O_8$: C, 59.46; H, 5.44. Found: C, 59.53; H, 5.32.

Benzyl (2R,3R)-3-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxy-2-methylpropionate (25). To a cooled (-20°C) solution of lithium benzyloxide in 2 mL of anhydrous THF (prepared from 0.20 mL (2.0 mmol) of benzyl alcohol and 1.0 mL of a 1.47 M solution (1.5 mmol) of n-butyllithium in hexane) under nitrogen was added dropwise a solution of 445 mg (1.0 mmol) of aldol adduct **24** in 5 mL of THF. The reaction was stirred at -20°C for 1.5 h, and then quenched by the addition of 10 mL of a saturated, aqueous solution of ammonium chloride. Volatiles were evaporated in vacuo, and the resulting aqueous residue was

extracted with dichloromethane (3 x 5 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 648 mg (98% mass balance) of a yellow oil. Chromatography on silica gel (MPLC, Merck Lobar B column, 20% ethyl acetate:hexane) afforded 326 mg (87%) of the desired benzyl ester **25** as a colorless oil. IR ($CHCl_3$) 3650-3300, 3030, 2955, 1720, 1533, 1230, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.21 (m, 7, aromatic H's), 5.40 (t, 1, J = 3 Hz, ArCHOH), 5.15 (s, 2, $PhCH_2O$-), 3.88 (s, 3, $-OCH_3$), 3.87 (s, 3, $-OCH_3$), 3.42 (d, 1, J = 3 Hz, -OH), 3.02 (d of q, 1, J = 3 Hz, 8 Hz, $-CHCH_3$), 1.09 (d, 3, J = 7 Hz, $-CHCH_3$).

Exact mass calcd. for $C_{19}H_{21}NO_7$: 375.1318. Found: 375.1325.

Benzyl (2R,3R)-3-(2,5-dimethoxy-3-nitrophenyl)-3-methoxy-2-methylpropionate (26). A well-stirred solution of 2.35 g (6.26 mmol) of alcohol **25** in 50 mL of iodomethane was heated to reflux and treated successively with ca. 1 g portions of silver(I) oxide every 24 h. The reaction was conveniently monitored by TLC, which indicated complete consumption of starting material after 4 days at reflux (a total of 5.54 g (23.9 mmol) of Ag_2O was used). The reaction was cooled to room temperature, filtered through Celite, and concentrated to an oil. Chromatography on silica gel (100 g, 25% diethyl ether:hexane) gave 2.09 g (86%) of the desired methyl ether as a colorless oil, bp 225°C (Kugelrohr, 0.005 mm). IR (CCl_4) 3140-2800, 1740, 1535, 1092, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.12 (m, 7, aromatic H's), 5.20 (d, 1, J_{AB} = 12 Hz, $PhCH_2O$-), 5.05 (d, 1, J_{BA} = 12 Hz, $PhCH_2O$-), 4.92 (d, 1, J = 5Hz, $ArCHOCH_3$), 3.82 (s, 3, $ArOCH_3$), 3.80 (s, 3, $ArOCH_3$), 3.20 (s, 3, $ArCHOCH_3$), 2.93 (d of q, 1, J = 5 Hz, 7 H, $-CHCH_3$), 1.14 (d, 3, J = 7 H, $-CHCH_3$); $[\alpha]_D$ +48.0° (c 2.04, CH_2Cl_2).

Anal. calcd. for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95. Found: C, 61.65; H, 5.91.

(2S,3R)-3-(2,5-Dimethoxy-2-nitrophenyl)-3-methoxy-2-methyl-1-propanol (27). To a cooled (-50°C) solution of 2.51 g (6.45 mmol) of ester **26** in 10 mL of anhydrous dichloromethane was added 14.2 mL of a 1 M solution (14.2 mmol) of diisobutylaluminum hydride (DIBAL) in dichloromethane. The reaction was stirred at -50°C for 2 h, and then carefully quenched by the dropwise addition of ca. 2 mL of methanol. To the flask was added 25 mL of a 0.5 M aqueous solution of sodium-potassium tartrate, and the two-phase mixture was stirred vigorously at room temperature until the upper aqueous layer was clear (ca. 1 h). Layers were separated, and the aqueous phase was extracted with dichloromethane (2 x 5 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give 2.51 g (100% mass balance) of a yellow oil. Chromatography on silica gel (175 g, 35% ethyl acetate:hexane) gave 1.75 g (95%) of alcohol **27** as a clear yellow oil, bp 225°C (Kugelrohr, 0.005 mm). IR (CCl_4) 3660-3200, 3060-2800, 1529, 1480, 1425, 1350, 1230, 1052 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.28 (d, 1, J_{AB} = 3 Hz, C_4'-H), 7.18 (d, 1, J_{BA} = 3 Hz, C_6'-H), 4.70 (d, 1, J = 5 H, ArCHOCH$_3$), 3.86 (s, 3, ArOCH$_3$), 3.83 (s, 3, ArOCH$_3$), 3.56 (br d, 2, J = 5 Hz, H$_2$COH), 3.29 (s, 3, ArCHOCH$_3$), 2.34 (br s, 1, H$_2$COH), 2.15-1.76 (m, 1, -CHCH$_3$), 0.91 (d, 3, J = 7 Hz, -CHCH$_3$); $[\alpha]_D$ +98.6° (c 0.96, CH_2Cl_2).

Anal. calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71. Found: C, 54.50; H, 6.92.

(2R,3R)-3-(2,5-Dimethoxy-3-nitrophenyl)-3-methoxy-2-methylpropanal (29). To a cooled (≤ -60 °C) solution of 0.76 mL (10.7 mmol) of anhydrous

dimethyl sulfoxide (DMSO) in 5 mL of anhydrous dichloromethane under nitrogen was added 0.55 mL (6.30 mmol) of oxalyl chloride. After two minutes, a solution of 1.38 g (4.84 mmol) of alcohol **27** in 10 mL of dichloromethane was added to the flask. After stirring at $\leq$-60 °C for an additional 15 min, 2.7 mL (19.4 mmol) of anhydrous triethylamine was added, resulting in the immediate precipitation of triethylamine hydrochloride. The reaction was maintained at $\leq$-60 °C and monitored by TLC, which showed complete consumption of starting material after 30 min. The reaction was quenched by the addition of 15 mL of pH 7 phosphate buffer, and the contents of the flask were transferred to a sepratory funnel. Layers were separated, and the aqueous phase was extracted with dichloromethane (2 x 5 mL). The combined organic phases were washed once with brine (5 mL), diluted with an equal volume of pentane, and dried over anhydrous sodium sulfate. After filtration, the solution was concentrated in vacuo to give a thick yellow oil which solidified upon standing. This solid was triturated with hexane, filtered, and dried under vacuum to give 1.34 g (98%) of aldehyde **29** as fine, yellow crystals, mp 77-79 °C. IR ($CHCl_3$) 3035, 2952, 2841, 1730, 1535, 1485, 1429, 1355, 1220 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.74 (s, 1, -CHO), 7.31 (d, 1, J_{AB} = 3 Hz, C_4'-H), 7.14 (d, 1, J_{BA} = 3 Hz, C_6'-H), 5.04 (d, 1, J = 4 Hz, $ArCHOCH_3$), 3.87 (s, 3, $ArOCH_3$), 3.83 (s, 3, $ArOCH_3$), 3.30 (s, 3, $ArCHOCH_3$), 2.67 (d of q, 1, J = 3 Hz, 7 Hz, $-CHCH_3$), 1.04 (d, 3, J = 7 Hz, $-CHCH_3$); $[\alpha]_D$ +50.9 ° (c 0.81, CH_2Cl_2).

Anal. calcd. for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05. Found: C, 55.24; H, 5.93.

(4S-[3(2S,3R,4S,5R)])-3-(2,5-Dimethoxy-3-nitrophenyl-2,5-dimethoxy-

3-hydroxy-4-methyl-1-oxopentyl)-4-(1-methylethyl)-2-oxazolidone (30). To a cooled (-78°C) solution of 1.90 g (9.46 mmol) of α-methoxy imide **9** in 20 mL of anhydrous dichloromethane under nitrogen was added 2.40 mL (9.50 mmol) of di-n-butylboron triflate[8e] and 1.44 mL (10.3 mmol) of freshly distilled triethylamine. After enolizing for 1 h at -78°C, a pre-cooled (-78°C) solution of 1.22 g (4.30 mmol) of aldehyde **29** in 4 mL of dichloromethane was added to the flask. The reaction temperature was maintained at -78°C for ca. 10 hours, then allowed to warm slowly overnight to a final temperature of -35°C. The reaction was quenched with 10 mL of pH 7 phosphate buffer and diluted with enough methanol to homogenize the solution (ca. 50 mL). This solution was cooled to 0°C and treated with 15 mL of a 2:1 mixture of methanol and 30% hydrogen peroxide. After stirring for 1 h at room temperature, volatiles were removed in vacuo and the resulting aqueous residue was extracted with dichloromethane (3 x 15 mL). The combined organic phases were washed successively with 5% aqueous sodium bicarbonate (1 x 10 mL) and brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to a pale-yellow foam. A small portion of this unpurified foam was silated (Me_3SiNEt_2, DMAP, CH_2Cl_2, RT, 1 h) and analyzed by capillary GC (SE-54, 250°C, injector temp. 275°C, 10 psi). The following distribution of aldol stereoisomers was observed: t_r = 5.69 min, 0.70%; t_r = 6.63 min, 98.6%; t_r = 6.99, 0.50%; t_r = 7.45 min, 0.19%. The yellow foam was chromatographed on silica gel (350 g of 70-230 mesh, 50% ethyl acetate:hexane) and recrystallized from carbon tetrachloride:hexane to give 1.66 g (80%) of aldol adduct **30** as an off-white powder (>99% pure by GC), mp 141-142°C. IR (CCl_4) 3590, 3050-2800, 1790, 1718, 1534, 1386,

1125, 1053 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.31 (d, 1, J_{AB} = 3 Hz, C_4"-H), 7.05 (d, 1, J_{BA} = 3 H, C_6"-H), 5.36 (d, 1, J = 1.5 Hz, C_2'-H), 5.29 (d, 1, J = 1.5 Hz, C_5'-H), 4.48 (d of t, 1, J = 1.5 Hz, 11 Hz, C_3'-H), 3.91 (d of d of d, 1, J = 9 Hz, 3.5 Hz, 2.5 Hz, C_4-H), 3.53 (s, 3, C_5"-OCH_3), 3.32 (d of d, 1, J = 9 Hz, 2.5 Hz, C_5-H_α), 3.13 (s, 3, C_2"-OCH_3), 3.11 (s, 3, C_2'-OCH_3), 3.10 (s, 3, C_5'-OCH_3), 3.00 (t, 1, J = 9 Hz, C_5-H_β), 2.62 (d, 1, J = 11 Hz, -OH), 2.38-2.27 (m, 2, C_4'-H, -C<u>H</u>Me_2), 1.06 (d, 3, J = 7 Hz, C_4'-CH_3), 0.55 (d, 3, J = 7 Hz, -CH<u>Me</u>$_2$), 0.38 (d, 3, J = 7 Hz, -CH<u>Me</u>$_2$); ^{13}C NMR (C_6D_6) δ 170.7, 155.5, 154.1, 145.2, 144.9, 139.5, 119.3, 108.0, 80.8, 77.4, 73.7, 63.6, 62.4, 591, 57.8, 57.6, 55.4, 42.5, 28.4, 17.5, 14.4, 9.2; $[\alpha]_D$ +98.3° (<u>c</u> 0.46, CH_2Cl_2).

<u>Anal.</u> calcd. for $C_{22}H_{32}N_2O_{10}$: C, 53.48; H, 7.01. Found: C, 53.74; H, 6.86.

(2R,3R,4S,5R)-1,3-Dihydroxy-2,5-dimethoxy-5-(2,5-dimethoxy-3-nitrophenyl)-4-methylpentane (33). To a cooled (0°C) solution of 310 mg (0.64 mmol) of aldol adduct **30** in 5 mL of anhydrous THF under nitrogen was added 0.8 mL of a 1 <u>M</u> solution (0.80 mmol) of lithium borohydride in THF (prepared from 82 mg of lithium borohydride and 3.7 mL of THF). The reaction was stirred at 0°C for 1 h, then warmed to room temperature and stirred for an additional 1 h before being quenched by the addition of 5 mL of a saturated aqueous solution of ammonium chloride. Volatiles were removed <u>in vacuo</u>, and the resulting aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to a thick oil. Chromatography on silica gel (25 g, 75% ethyl acetate:hexane) afforded 219 mg (95%) of diol **33** as a clear, yellow

oil. IR (CCl_4) 3700-3200, 2965, 2859, 1534, 1481, 1427, 1232, 1052 cm^{-1}; ^1H NMR (500 MHz, $C_{12}C_6$) δ 7.30 (d, 1, J_{AB} = 3 Hz, C_4'-H), 7.04 (d, 1, J_{BA} = 3 Hz, C_6'-H), 5.21 (d, 1, J = 2 H, C_5-H), 3.82 (t, 1, J = 9 Hz, C_3-H), 3.78 (m, 2, C_1-H_2), 3.61 (s, 3, C_5'-OCH_3), 3.12 (s, 3, C_2'-OCH_3), 3.10 (s, 3, C_2-OCH_3), 3.09 (s, 3, C_5-OCH_3), 3.06 (d of t, 1, J = 1 Hz, 5 Hz, C_2-H), 2.96 (br d, 1, J = 9 Hz, C_3-OH), 2.51 (br s, 1, C_1-OH), 2.08 (m, 1, C_4-H), 0.73 (d, 3, J = 8 Hz, C_4-CH_3); ^{13}C NMR (CCl_4) δ 154.7, 144.6, 144.0, 138.9,m 118.5, 107.5, 79.7, 76.8, 73.4, 62.2, 61.3, 57.8, 57.3, 55.4, 41.3, 9.1; $[\alpha]_D$ +83.0° (c 0.14, CCl_4).

(2R,3R,4S,5R)-1-t-Butyldimethylsilyloxy-2,5-dimethoxy-5-(2,5-dimethoxy-3-nitrophenyl)-3-hydroxy-4-methylpentane (37). A mixture of 189 mg (0.52 mmol) of diol **33**, 103 mg (0.68 mmol) of t-butyldimethylsilyl chloride (TBSCl), 0.1 mL (0.68 mmol) of freshly distilled triethylamine, and ca. 2 mg of 4-dimethylaminopyridine (DMAP) in 2.5 mL of anhydrous dichloromethane was stirred under nitrogen at room temperature. The reaction was sluggish under these conditions, and after 24 h an additional 50 mg (0.34 mmol) of TBSCl was added. After 48 h, the reaction appeared complete by TLC. The reaction mixture was diluted with 4 mL of saturated aqueous ammonium chloride, layers were separated, and the aqueous phase was extracted with dichloromethane (2 x 3 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to a yellow oil. Chromatography on silica gel (20 g, 20% ethyl acetate:hexane) followed by heating to 150°C under vacuum (0.01 mm) for 10 min (to remove remaining TBSCl) afforded 208 mg (84%) of the protected alcohol **37** as a clear, yellow oil. IR (CCl_4) 3595, 3040-2800, 1532, 1425, 1112, 1050, 1000 cm^{-1}; ^1H NMR

(500 MHz, C_6D_6) δ 7.32 (d, 1, J_{AB} = 3 Hz, C_4'-H), 7.03 (d, 1, J_{BA} = 3 Hz, C_6'-H), 5.27 (d, 1, J = 2 Hz, C_5-H), 3.89 (t, 1, J = 10 Hz, C_3-H), 3.84 (d of d, 1, J_{AB} = 6 Hz, 11 Hz, C_1-H), 3.81 (d of d, 1, J_{BA} = 6 Hz, 9 Hz, C_1-H), 3.58 (s, 3, C_5'-OCH_3), 3.30 (t, 1, J = 6 Hz, C_2-H), 3.15 (s, 3, C_2'-OCH_3), 3.12 (s, 3, C_2-OCH_3), 3.11 (s, 3, C_5-OCH_3), 2.48 (d, 1, J = 10 Hz, -OH), 2.16 (d of quintets, 1, J = 2 Hz, 10 Hz, C_4-H), 0.97 (s, 9, -C<u>Me</u>$_3$), 0.77 (d, 3, J = 7 Hz, C_4-CH_3), 0.09 (s, 3, -Si<u>Me</u>$_2$), 0.07 (s, 3, -Si<u>Me</u>$_2$); ^{13}C NMR (C_6D_6) δ 160.8, 124.6, 112.9, 86.2, 82.9, 78.0, 68.6, 67.6, 63.9, 62.9, 60.6, 47.4, 31.3, 14.8, -0.1; $[\alpha]_D$ +76.5° (<u>c</u> 0.12, CCl_4).

<u>Anal.</u> calcd. for $C_{22}H_{39}NO_8Si$: C, 55.79; H, 8.30. Found: C, 55.89; H, 8.32.

(2S,3R,4S,5R)-5-(3-N-Acetylamino-2,5-dimethoxyphenyl)-1-<u>t</u>-butyldimethylsilyloxy-2,5-dimethoxy-3-hydroxy-4-methylpentane (40). To 172 mg (0.36 mmol) of nitro alcohol **37** in a 25-mL, single-necked, round-bottomed flask was added 10 mL of a Raney-Nickel slurry in ethanol. The flask was fitted with a magnetic spin-bar and reflux condenser, treated with 1 mL of hydrazine hydrate[35] ($H_2NNH_2 \cdot x\ H_2O$, <u>ca.</u> 55% hydrazine, <u>ca.</u> 17 mmol), and heated to reflux. After 10 min, the reaction appears complete by TLC (R_f **37** = 0.58; R_f **38** = 0.35, 50% ethyl acetate:hexane). The reaction was cooled to room temperature, filtered through a pad of Celite, and concentrated to an air-sensitive oil which was used directly without further purification. ^1H NMR (90 MHz, $CDCl_3$) δ 6.34 (d, 1, J_{AB} = 3 H, C_4'-H), 6.24 (d, 1, J_{BA} = 3 Hz, C_6'-H), 4.98 (d, 1, J = 3 Hz, C_5-H), 3.86 (d of d, 1, J_{BA} = 11 Hz, 6 Hz, C_1-H), 3.82 (d of d, 1, J_{BA} = 11 Hz, 6Hz, C_1-H), 3.77-3.23 (br m, 4, C_3-H, -OH, $-NH_2$), 3.73 (s, 3, $ArOCH_3$), 3.71 (s, 3, $ArOCH_3$), 3.48 (s, 3,

C_2-OCH_3), 3.35 (d of t, 1, J = 1 Hz, 6 Hz, C_2-H), 3.31 (s, 3, C_5-OCH_3), 1.98 (m, 1, C_4-H), 0.90 (s, 9, -C<u>Me</u>$_3$), 0.79 (d, 3, J = 7 Hz, C_4-CH_3), 0.09 (s, 6, -Si<u>Me</u>$_2$).

A solution of the unpurified aniline **38** in 5 mL of anhydrous dichloromethane under nitrogen was treated with 0.15 mL (1 mmol) of freshly distilled triethylamine and cooled to 0°C. To the cooled and stirred solution was added 51 μL (0.72 mmol) of acetyl chloride, and the ice bath was removed and the reaction was allowed to warm to room temperature for 15 min, at which point the reaction appeared complete by TLC (R_f **40** = 0.18, 50% ethyl acetate:hexane). The reaction was quenched by the addition of 5 mL of pH 7 phosphate buffer, layers were separated, and the aqueous phase was extracted with dichloromethane (2 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated <u>in vacuo</u> to an oil. Chromatography of silica gel (15 g, 50% ethyl acetate:hexane) followed by drying under vacuum (170°C, 0.005 mm) afforded 157 mg (90% for two steps) of anilide **40** as a colorless oil. IR (CCl_4) 3600-3240, 2950, 1702, 1520, 1462, 1418, 1115, 1054, 1004, 839 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.49 (br d, 1, J_{AB} = 3 H, C_4'-H), 7.38 (br s, 1, CH_3CON<u>H</u>), 7.03 (d, 1, J_{BA} = 3 H, C_6'-H), 5.29 (d, 1, J = 2 Hz, C_5-H), 3.98 (br t, 1, J = 9 Hz, C_3-H), 3.90 (d of d, 1, J_{AB} = 10 Hz, 6 Hz, C_1-H), 3.86 (d of d, 1, J_{BA} = 10 Hz, 6 Hz, C_1-H), 3.47 (s, 3, C_2'-OCH_3), 3.39-3.32 (br m, 1, C_2-H), 3.34 (s, 3, C_5'-OCH_3), 3.28 (s, 3, C_2-OCH_3), 3.23 (s, 3, C_5-OCH_3), 2.70 (d, 1, J = 9 Hz, -OH), 2.22 (d of quintets, 1, J = 2 Hz, 8 Hz, C_4-H), 1.68 (s, 3, <u>C</u>H_3CONH), 0.97 (s, 9, -C<u>Me</u>$_3$), 0.94 (d, 3, J = 7 Hz, C_4-CH_3), 0.09 (s, 3, -Si<u>Me</u>$_2$), 0.08 (s, 3, -Si<u>Me</u>$_2$).

Exact mass calcd. for $C_{24}H_{43}NO_7Si$: 485.280. Found: 485.279.

1 H-Imidazole-1-carbothioic acid, O-[(2R,3R,4R,5R)-5-(3-N-acetylamino-2,5-dimethoxyphenyl)-1-t-butyldimethylsilyloxy-2,5-dimethoxy-4-methylpent-3-yl] ester (44). A mixture of 157 mg (0.32 mmol) of alcohol **40** and 186 mg (1.04 mmol) of thiocarbonyldiimidazole[42] in 10 mL of anhydrous toluene was refluxed for 15 h. The reaction was cooled, concentrated, and chromatographed on silica gel (15 g, ethyl acetate) to give 152 mg (79%) of **44** as a colorless oil. IR (CCl_4) 3440, 3400-3240, 3200-3300, 2940, 1700, 1615, 1600, 1520, 1465, 1285, 1055, 840 cm^{-1}; ^1H NMR (90 MHz, C_6D_6) δ 8.67 (s, 1, -N-C<u>H</u>=CHN-), 6.98 (br m, 1, -NCH=C<u>H</u>N-), 6.89 (d, 1, J_{BA} = 3 Hz, C_6'-H), 6.28 (d of d, 1, J = 9 Hz, 2 Hz, C_3-H), 4.56 (d, 1, J = 2 Hz, C_5-H), 3.76 (d, 2, J = 6 Hz, C_1-H_2), 3.53 (d of d, 1, J = 7 Hz, 2 Hz, C_2-H), 3.43 (s, 3, C_5'-OCH_2), 3.23 (s, 3, C_2'-OCH_3), 3.14 (s, 3, C_2-OCH_3), 3.08 (s, 3, C_5-OCH_3), 2.61 (m, 1, C_4-H), 1.60 (s, 3, <u>C</u>H_3CONH), 1.02 (d, 3, J = 8 Hz, C_4-CH_3), 0.94 (s, 9, -CMe_3), 0.02 (s, 3, -$SiMe_2$), 0.00 (s, 3, -$SiMe_2$).

Exact mass calcd. for $C_{28}H_{45}N_3O_7SSi$: 595.275. Found: 595.275.

(2S,4S,5R)-5-(3-N-Acetylamino-2,5-dimethoxyphenyl)-1-t-butyldimethylsilyloxy-2,5-dimethoxy-4-methylpentane (46). To a refluxing solution of 100 µL (0.38 mmol) of tri-n-butyltin hydride in 4 mL of anhydrous toluene under nitrogen was added a solution of 125 mg (0.21 mmol) of O-thiocarbonylimidazole anilide **44** in 5 mL of toluene over a 40-min period. After refluxing for 2.5 h, an additional 100 µL (0.38 mmol) of tri-n-butyltin hydride was added and the reaction was refluxed overnight (ca. 15 h). The reaction was cooled, concentrated in vacuo, chromatographed on silica gel (30 g, 35% ethyl acetate:hexane), and the product was isolated by preparative

TLC (20 x 20 cm silica gel, ethyl acetate) to afford 69 mg (70%) of deoxy-compound **46** as a colorless oil. IR (CCl_4) 3440, 3400-3250, 2940, 1700, 1515, 1460, 1415, 1100, 838 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.45 (br d, 1, J_{AB} = 3 Hz, C_4'-H), 7.35 (br s, 1, CH_3CONH), 6.90 (d, 1, J_{BA} = 3 Hz, C_6'-H), 4.38 (d, 1, J = 5 Hz, C_5-H), 3.62 (d of d, 1, J_{AB} = 10 Hz, 6 Hz, C_1-H), 3.52 (d of d, 1, J_{BA} = 10 Hz, 4 Hz, C_1-H), 3.42 (s, 3, C_5'-OCH_3), 3.33 (s, 3, C_2'-OCH_3), 3.32 (m, 1, C_2-H), 3.28 (s, 3, C_2-OCH_3), 3.17 (s, 3, C_5-OCH_3), 2.35 (m, 1, C_4-H), 1.75 (m, 1, C_3-H), 1.66 (s, 3, CH_3CONH), 1.53 (m, 1, C_3-H), 1.15 (d, 3, J = 7 Hz, C_4-CH_3), 0.95 (s, 9, -CMe_3), 0.04 (s, 3, -$SiMe_2$), 0.03 (s, 3, -$SiMe_2$); $[\alpha]_D$ +7.26° (c 0.46, CCl_4).

Exact mass calcd. for $C_{24}H_{43}NO_6Si$: 469.286. Found: 469.288.

(2R,3R)-Benzyl-3-(3-N-Acetylamino-2,5-dimethoxyphenyl)-3-methoxy-2-methylpropionate (57). To a refluxing mixture of 2.29 g (5.90 mmol) of nitro ester **26** in 30 mL of a Raney-Nickel slurry in ethanol was added 1 mL of hydrazine hydrate ($H_2NNH_2 \cdot x\ H_2O$, ca. 55% hydrazine, ca. 17 mmol). After 10 min at reflux, the reaction appeared complete by TLC. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo to an oil. This oil was immediately sealed under nitrogen and dissolved in 25 mL of anhydrous dichloromethane. After cooling to 0°C, the stirred solution was treated with 2.0 mL (14 mmol) of freshly distilled triethylamine and 1.0 mL (14 mmol) of acetyl chloride, resulting in an immediate precipitation of amine hydrochloride salts. The suspension was warmed to room temperature and stirred for 1 h, then quenched by the addition of 200 mL of water. Volatiles were removed in vacuo, and the aqueous residue was extracted with dichloro-methane (2 x 10 mL). The combined organic phases were washed once with a

0.1 N aqueous solution of hydrochloric acid, once with a 5% aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated to an oil. Chromatography on silica gel (150 g, 40% ethyl acetate:hexane) afforded 1.93 g (82% overall yield) of anilide **57** as a very thick yellow oil. IR (CCl_4) 3440, 3100-2800, 1738, 1701, 1520, 1460, 1418, 1242, 1095, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, 1, J = 2 Hz, C_4'-H), 7.70 (s, 1, CH_3CONH), 7.40-7.10 (m, 5, C_6H_5-), 6.63 (d, 1, J = 2 Hz, C_6'-H), 5.13 (1, d, J_{AB} = 12 Hz, $PhCH_2O$-), 4.99 (d, 1, J_{BA} = 12 Hz, $PhCH_2O$-), 4.77 (d, 1, J = 6 Hz, C_3-H), 3.77 (s, 3, $ArOCH_3$), 3.20 (s, 3, $ArOCH_3$), 2.95 (quintet, 1, J = 7 Hz, C_2-H), 2.22 (s, 3, CH_3CONH), 1.19 (d, 3, J = 7 Hz, C_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 173.8, 168.3, 156.2, 136.1, 132.6, 132.2, 128.4, 127.9, 108.3, 106.1, 78.8, 66.2, 61.3, 57.2, 55.6, 45.2, 24.8, 11.8.

Anal. calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78. Found: C, 65.74; H, 6.78.

(2R,3R)-Benzyl-3-(2-N-acetylamino-2,5-cyclohexadiene-1,4-dione-6-yl)-3-methoxy-2-methylpropionate (58). To a solution of 166 mg (0.41 mmol) of hydroquinone dimethyl ether **57** in 25 mL of dioxane was added 203 mg (1.64 mmol) of silver(II) oxide. To this stirred suspension was added 0.41 mL of a 6 N aqueous solution (6 equivs) of nitric acid, resulting in rapid coloration to yellow-green and visible consumption of most of the suspended AgO. After 5 min, the reaction appeared complete by TLC. The reaction was quenched by the addition of 20 mL of a 1:3 mixture of water and chloroform. The phases were separated, and the aqueous layer was extracted once with 5 mL of chloroform. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 205 mg of a red-yellow

oil. Chromatography on silica gel (10 g, 40% ethyl acetate:hexane) afforded 134 mg (87%) of quinone **58** as a yellow oil. IR ($CDCl_3$) 3390, 2950, 2255, 1725, 1651, 1611, 1500 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1, CH_3CONH), 7.53 (d, 1, J_{AB} = 3 Hz, C3'-H), 7.34 (s, 5, $-C_6H_5$), 6.67 (d of d, 1, J_{BA} = 3 Hz, 2 Hz, C5'-H), 5.22 (d, 1, J_{AB} = 12 Hz, $PhCH_2O$-), 5.10 (d, 1, J_{BA} = 12 Hz, $PhCH_2O$-), 4.75 (d of d, 1, J = 4 Hz, 2 Hz, ArCH-), 3.21 (s, 3, CH_3O-), 2.84 (d of q, 1, J = 4 Hz, 7 Hz, CH_3CH-), 2.25 (s, 3, CH_3CONH-), 1.13 (d, 3, J = 7 Hz, CH_3CH-); ^{13}C NMR ($CDCl_3$) δ 187.6, 182.7, 172.7, 169.7, 169.4, 142.8, 138.4, 135.8, 134.3, 128.5, 128.2, 114.6, 66.5, 58.2, 43.4, 24.8, 10.3.

Exact mass calcd. for $C_{20}H_{21}NO_6$: 371.137. Found: 371.137.

(2R,3R,4S,5R)-1-t-Butyldimethylsilyloxy-5-(3-N-carbobenzoxyamino-2,5-dimethoxyphenyl)-2,5-dimethoxy-3-hydroxy-4-methylpentane (39). To 195 mg (0.41 mmol) of nitro alcohol **37** in a 25-mL, single-necked, round-bottomed flask was added 10 mL of a Raney-Nickel slurry in ethanol. The flask was fitted with a magnetic spin-bar and reflux condenser, and treated with 1 mL of hydrazine hydrate ($H_2NNH_2 \cdot x\ H_2O$, ca. 55% hydrazine, ca. 17 mmol). The reaction was heated to reflux for 15 min, then cooled to room temperature, filtered through a pad of Celite, and concentrated to give 203 mg of an oil. This oil was immediately dissolved in 2 mL of anhydrous dichloromethane, cooled to 0°C under nitrogen, and treated with 143 µL (0.82 mmol) of diisopropylethylamine and 72 µL (0.45 mmol) of benzylchloroformate. A crystal of 4-dimethylaminopyridine (DMAP) was added, and the reaction was allowed to warm to room temperature and stir overnight. The contents of the flask were transferred to a separatory funnel, washed once with 4 mL of

1 N aqueous hydrochloric acid, once with 4 mL of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated to a pink oil. Chromatography on silica gel (20 g, 20% ethyl acetate:hexane) followed by vacuum drying (200°C, 0.005 mm, 1 h) gave 177 mg (75% overall yield) of N-protected alcohol **39** as a thick, sticky oil. ^{1}H NMR (500 MHz, C_6D_6) δ 8.30 (br s, 1, -NH), 7.29-7.00 (m, 7, aromatic H's), 5.24 (d, 1, J = 2.5 Hz, C_5-H), 5.08 (d, 1, J_{AB} = 13 Hz, $PhCH_2O$-), 5.05 (d, 1, J_{BA} = 13 Hz, $PhCH_2O$-), 3.96 (t, 1, J = 10 Hz, C_3-H), 3.89 (d of d, 1, J_{AB} = 11 Hz, 7 Hz, C_1-H), 3.86 (d of d, 1, J_{BA} = 11 Hz, 7 Hz, C_1-H), 3.48 (s, 3, C_5'-OCH_3), 3.35 (t, 1, J = 7 Hz, C_2-H), 3.26 (s, 3, C_2'-OCH_3), 3.21 (s, 3, C_2-OCH_3), 3.20 (s, 3, C_5-OCH_3), 2.54 (d, 1, J = 10 H, C_3-OH), 2.19 (d of quintets, 1, J = 8 Hz, 2 Hz, C_4-H), 1.02 (s, 9, -CMe_3), 0.98 (d, 3, J = 8 Hz, C_4-CH_3), 0.02 (s, 3, -$SiMe_2$), 0.01 (s, 3, -$SiMe_2$); $[\alpha]_D$ +13.0° (c 0.15, CCl_4).

Anal. calcd. for $C_{30}H_{47}NO_8Si$: C, 62.36; H, 8.20. Found: C, 62.41; H, 8.07.

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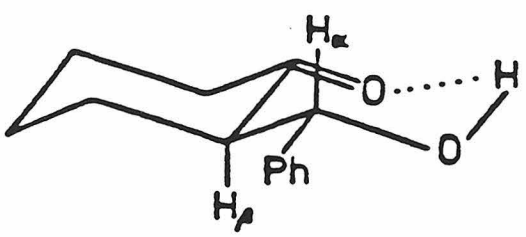
erythro diastereomer is equatorial and resonates at lower field with a coupling constant of $J_{\alpha,\beta}$ = 2-4 Hz.



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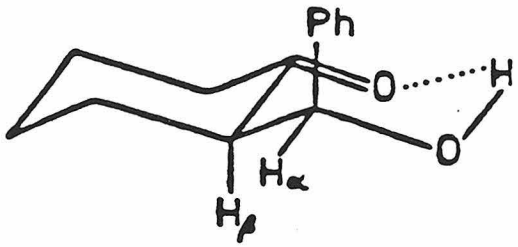

erythro

(26) I am indebted to Dr. Paul L. Ornstein, my coworker in the later stages of this project, for these results.

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(31) Olefin geometry inferred to be trans from ^{1}H NMR.

(32) The assignment of erythro/threo to the analytical GC peaks is strictly empirical and follows previously established trends.

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Khueng-Huu, Q. Synthesis **1977**, 774-776. (b) Kishi, T.; Tsuchiya, T.; Umezawa, S. Bull. Chem. Soc., Jpn **1979**, 52, 3015-3018.

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(41) See Experimental Section, Chapter I.

(42) Thiocarbonyldiimidazole was prepared according to the procedure of Pullukat, T. J.; Urry, G. Tetrahedron Lett. **1967**, 1953-1954. We found it necessary to sublime the product (90°C, 0.002 mm) in order to remove trimethylsilyl chloride.

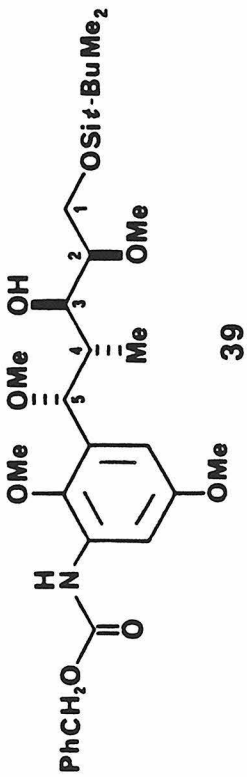
APPENDIX I

^{1}H NMR Decoupling Experiments of Compound **39**

The ^1H NMR spectra of many of the advanced intermediates described in this synthesis are characterized by a plethora of resonances in the range of 3-4 ppm. This is a result of the abundance of protons attached to oxygen-bearing carbon atoms, (i.e., H-C-O type systems). Indeed, fully 16 of the 25 hydrogen atoms of diol **33** fall into this category. Although fully resolved by high-field instrumentation (500 MHz), assignment of individual resonances is not trivial. In an attempt to unequivocally assign these resonances, as well as to possibly gain information as to the solution configuration of these acyclic compounds, a series of proton-decoupling experiments were performed. The results of these investigations are reported in this appendix.

Compound **39** was chosen as a suitable substrate for these decoupling experiments. Given in Figure 9 is the 500 MHz ^1H NMR of **39**. The four resonances labeled **A**, **B**, **C**, and **C_4-H** were irradiated, and the region between 4.5 ppm and 2 ppm was scanned. The information from these double-irradiation experiments has yielded the complete set of coupling constants between each pair of the adjacent protons on the five-carbon chain of **39** (vide infra).

Irradiation of the resonance labelled **A** results in the spectrum shown in Figure 10. Notable in this spectrum is the collapse of the hydroxyl doublet into a singlet. This result identifies **A** as the C_3-proton. Furthermore, lack


PhCH2O
H
N
O
OMe
OMe
OMe
OH
OMe
OSi t-BuMe2
Me
1
2
3
4
5

39

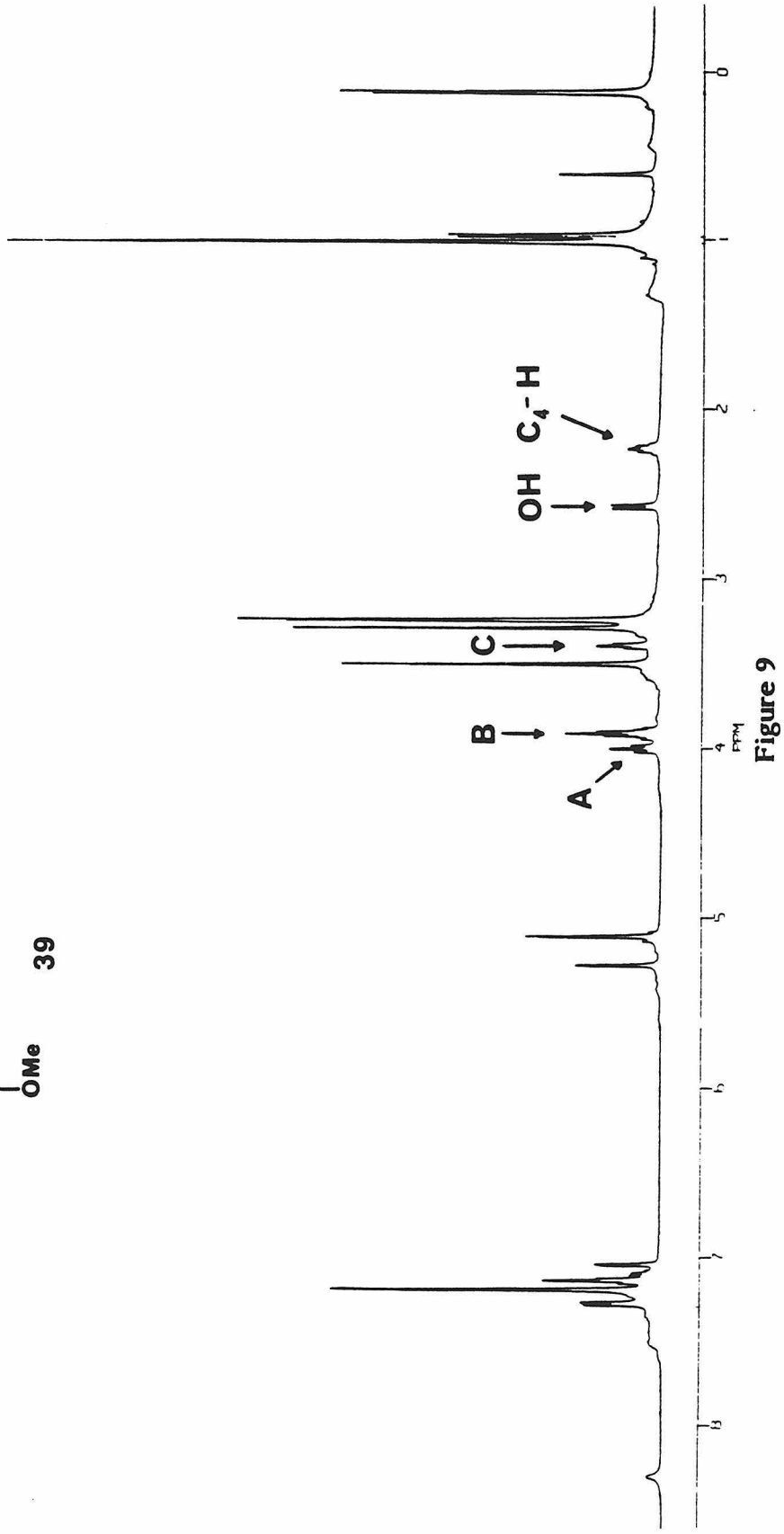

A
B
C
OH
C4-H
0
1
2
3
4
5
6
7
8
PPM

Figure 9

of any change in the **B** or **C** signals indicates that $J_{3,2}$ is zero, a finding that will be verified later. The C_4-H also shows a simplification from a complex multiplet to a doublet of quartets (this is clearer in expansions).

Irradiation at **B** provides the spectrum shown in Figure 11. The collapse of the **C** peak into a sharp singlet is consistent with the assignment of this signal to the C_2-proton and the **B** signal to the C_1-protons. The appearance of the C_2-proton as a singlet in this experiment supports the lack of coupling between the C_2 and C_3 protons.

That the above assignments are valid can be confirmed by irradiation at **C**, the resulting spectrum of which is illustrated in Figure 12. Simplification of the multiplet **B** to a clear AB quartet for the C_1-protons is the expected and observed result.

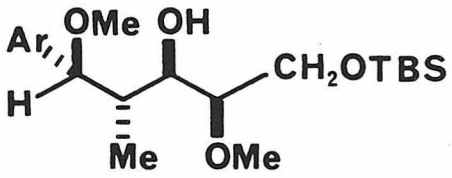
Finally, saturation of the C_4-H signal results in the conversion of the **A** triplet into a doublet, as shown in Figure 13. This further verifies signal **A** as the C_3-proton, as well as confirming the fact that $J_{2,3} = 0$. The observed triplet for C_3-H (**A**) is therefore the result of two equal splittings of this proton by the hydroxyl hydrogen and the C_4-hydrogen. Since the -OH doublet shows a 10 Hz coupling constant, one can assign a $J_{3,4} = 10$ Hz from this experiment.

Taken in total, these results now allow for the establishment of all the coupling constants along the acyclic carbon chain of **39**. The value for $J_{4,5}$ can be routinely measured from the normal NMR experiment and is equal to 2 Hz. By making use of the well-known Karplus correlations for vicinal proton relationships,[1] one can calculate the dihedral angle between each set of protons in **39**, and therefore approximate a solution conformation for this

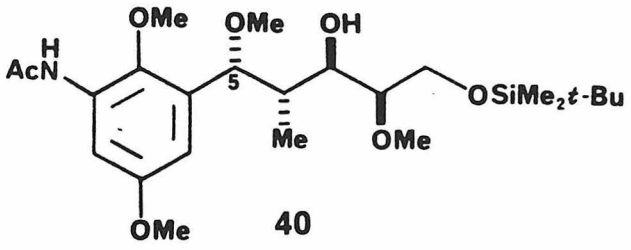
Proton Set	J	Calc. Angle
2,3	0 Hz	90°
3,4	10 Hz	180°
4,5	2 Hz	60°

compound. The calculated angles are shown above.

Although difficult to visualize without the aid of Dreiding models, these calculated angles result in what appears to be a very reasonable conformation for compound **39**. This conformation is approximated below. In this arrangement, the C_3-hydroxyl group is conveniently situated to allow for

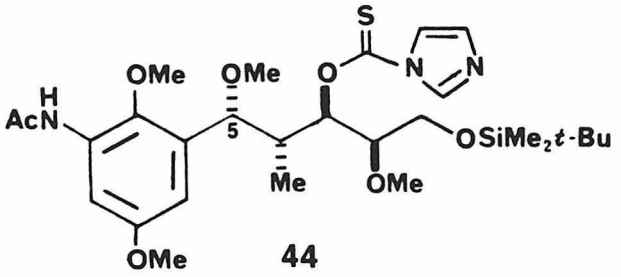


good hydrogen bonding to both the C_2- and C_5-methoxyl groups. Furthermore, it directs the smallest substituent on C_2, the proton, toward the vicinity of the C_4-methyl group. That a hydrogen bond does indeed exist between C_3-OH and C_5-OCH_3 is evidenced by the change in chemical shift of the benzylic C-5 proton upon derivatization of the C_3-hydroxyl. For example, this resonance occurs at δ 5.29 in alcohol **40**, but shifts upfield to δ 4.56 upon formation of the thiocarbonylimidazole derivative **44**.



40

C_5-H δ 5.29



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C_5-H δ 4.56

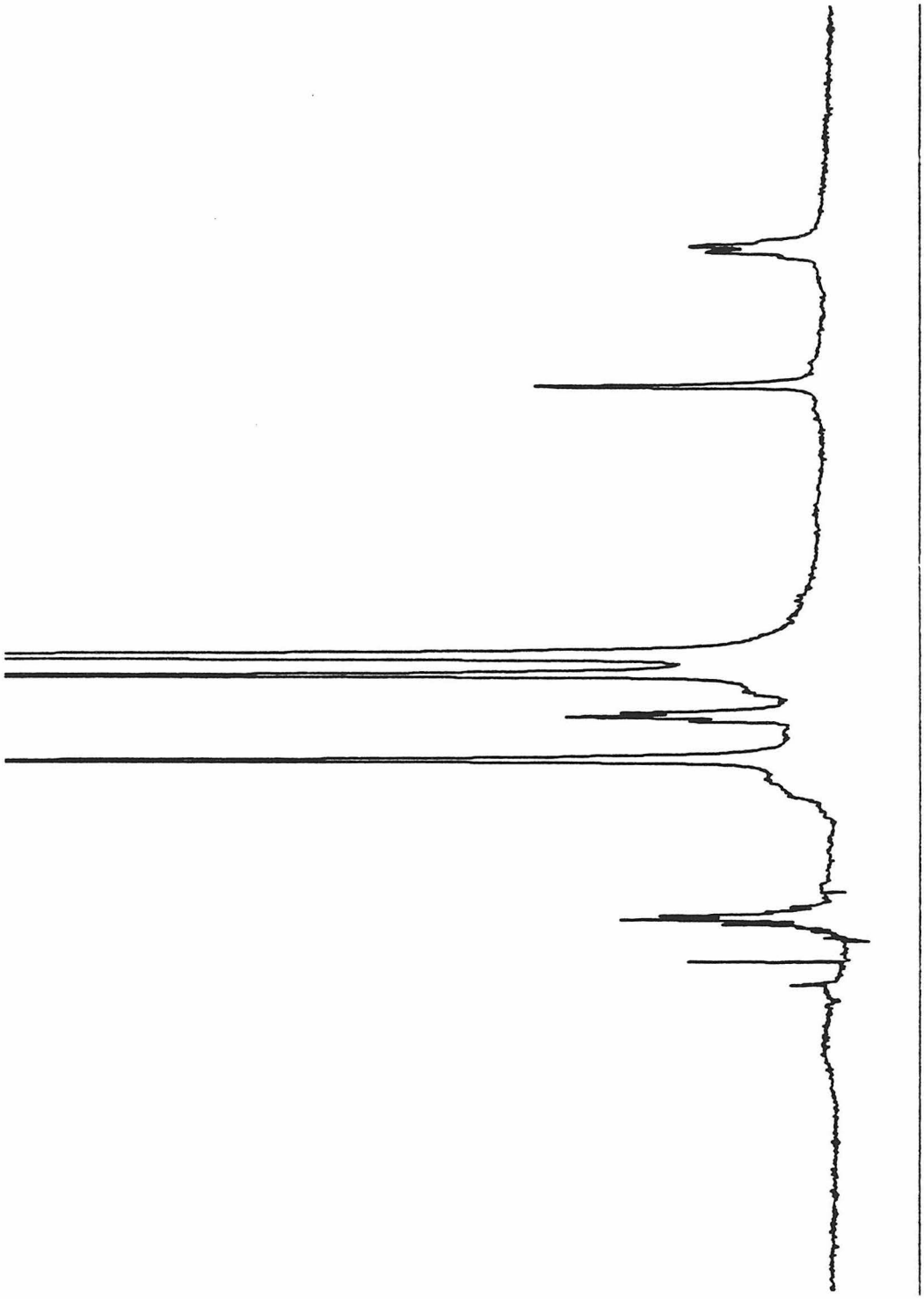

Figure 10

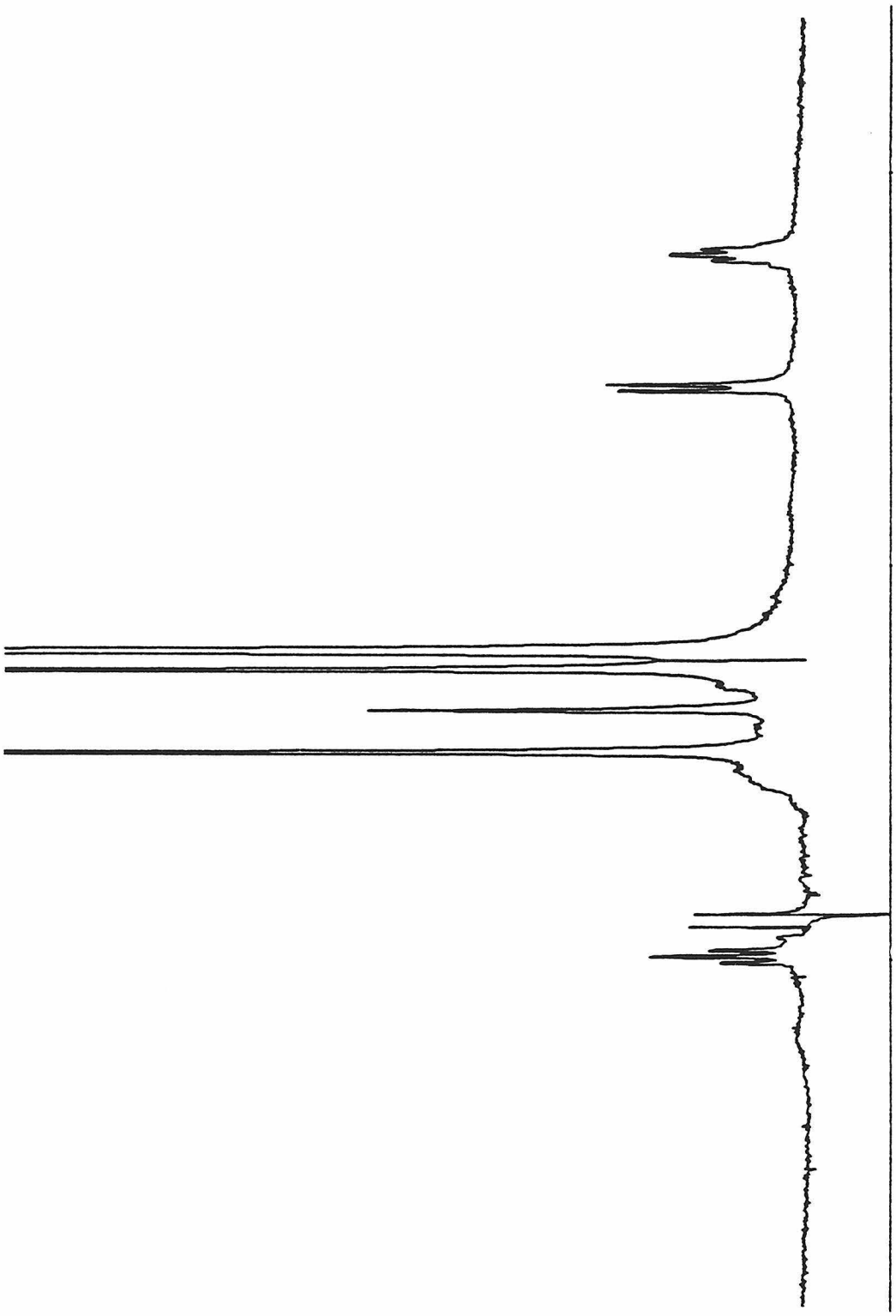

Figure 11

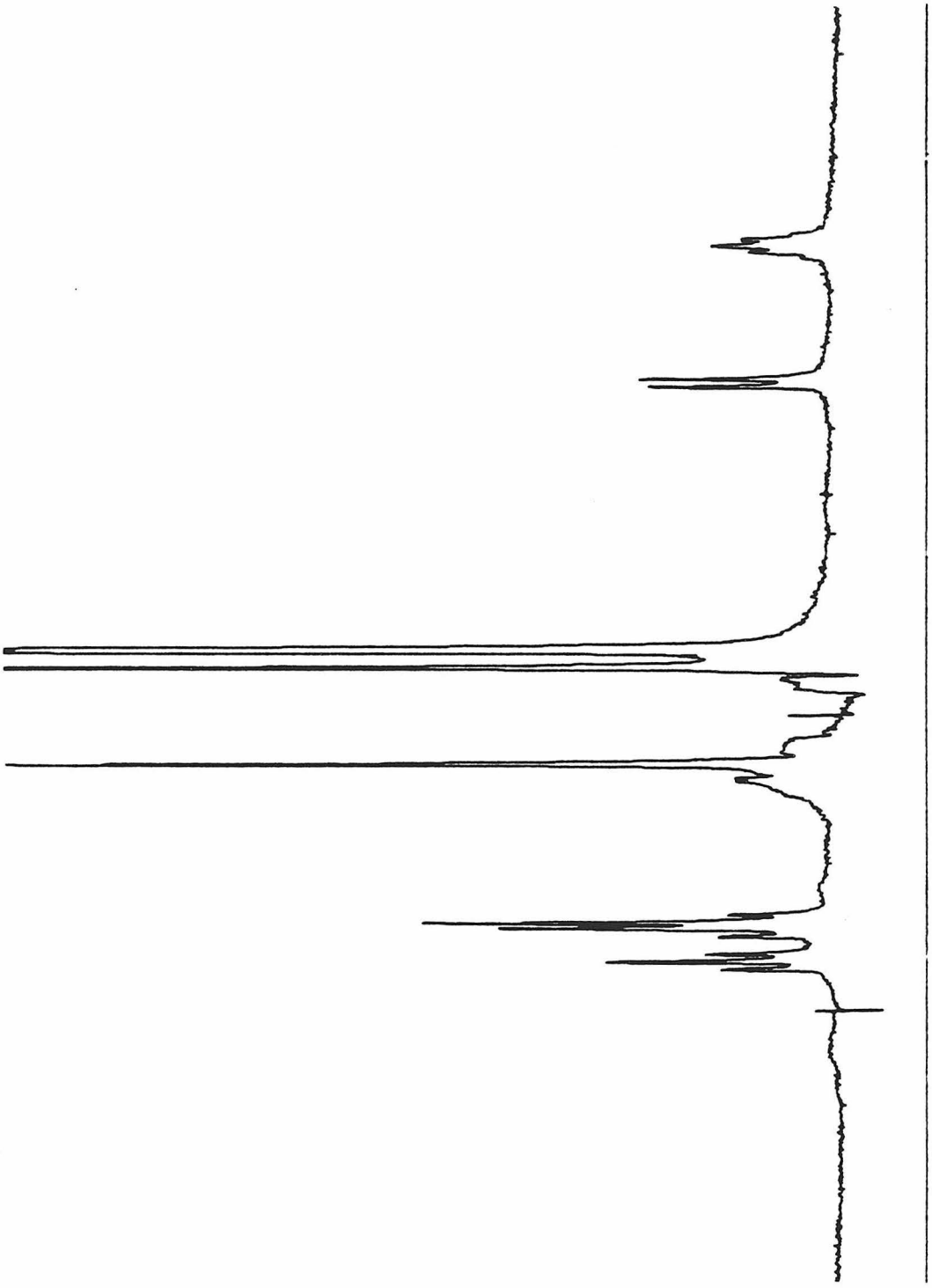

Figure 12

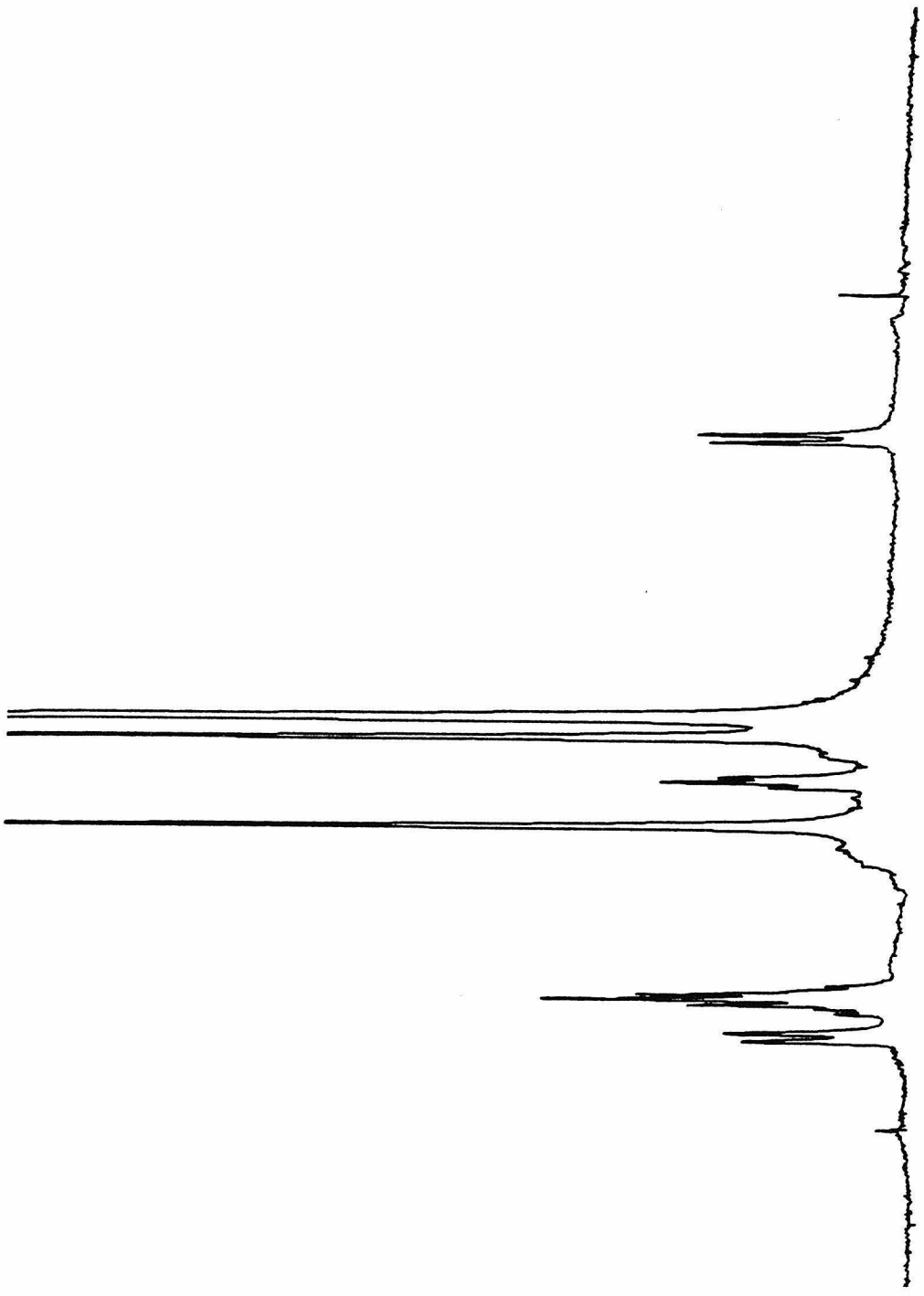

Figure 13

Reference

(1) Silverstein, R. M.; Bassler, G. C.; Morill, T. C. "Spectrometric Identification of Organic Compounds", 4th ed.; John Wiley and Sons: New York, 1981, Chapter 4.

APPENDIX II

IR annd ^{1}H NMR Spectral Catalog

For Chapter I

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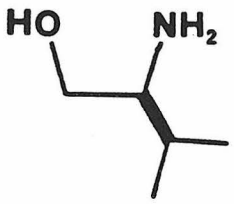

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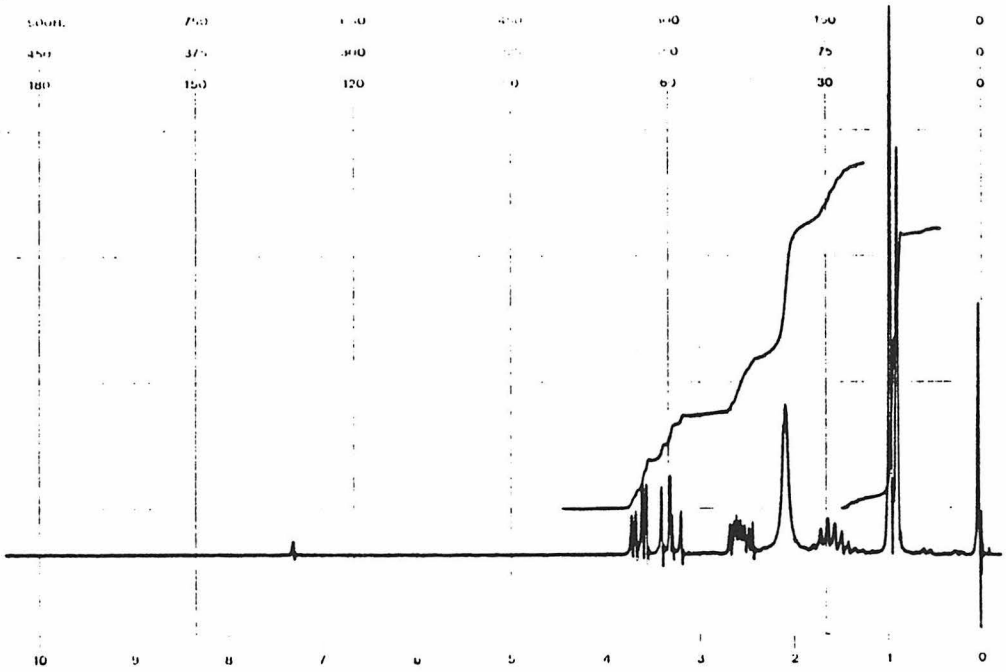

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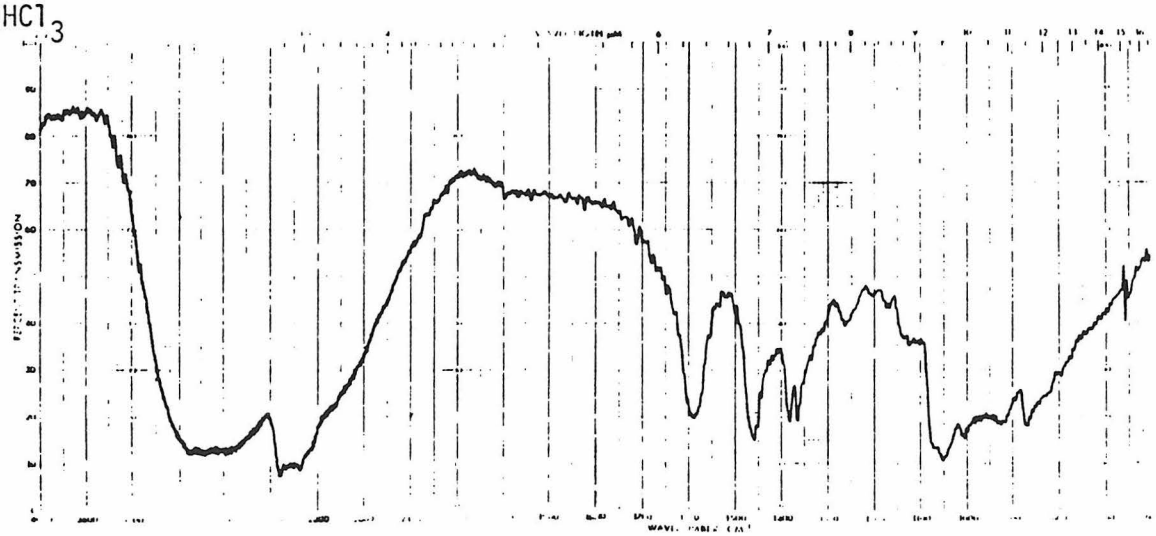

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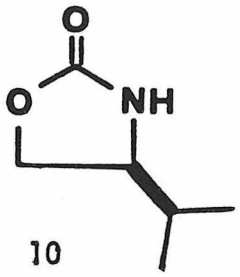

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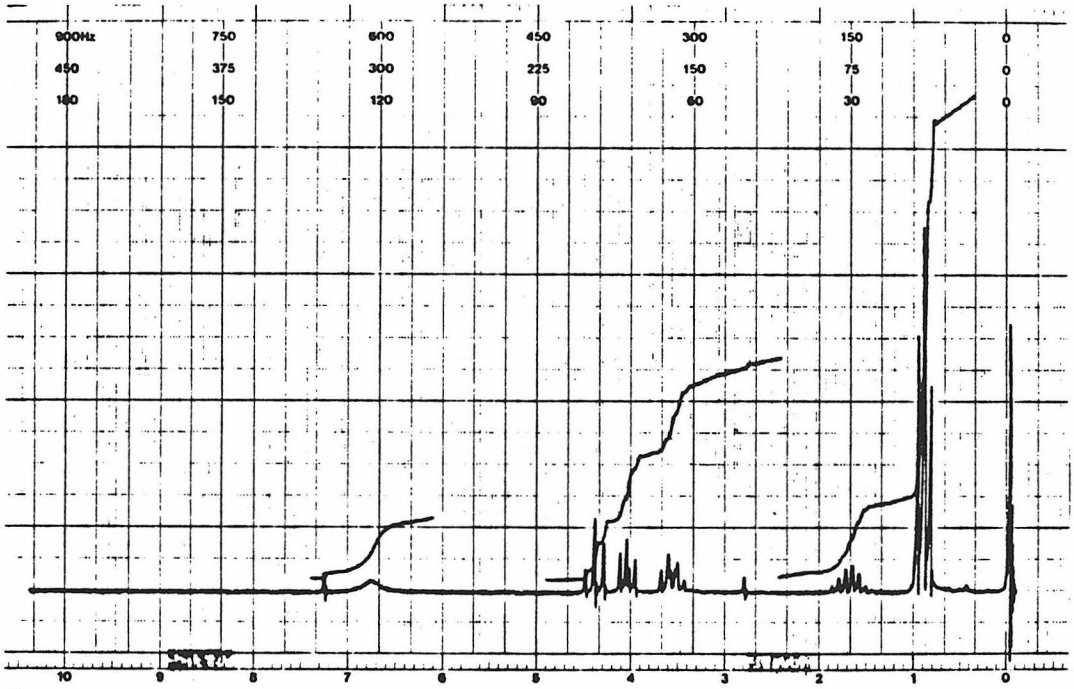

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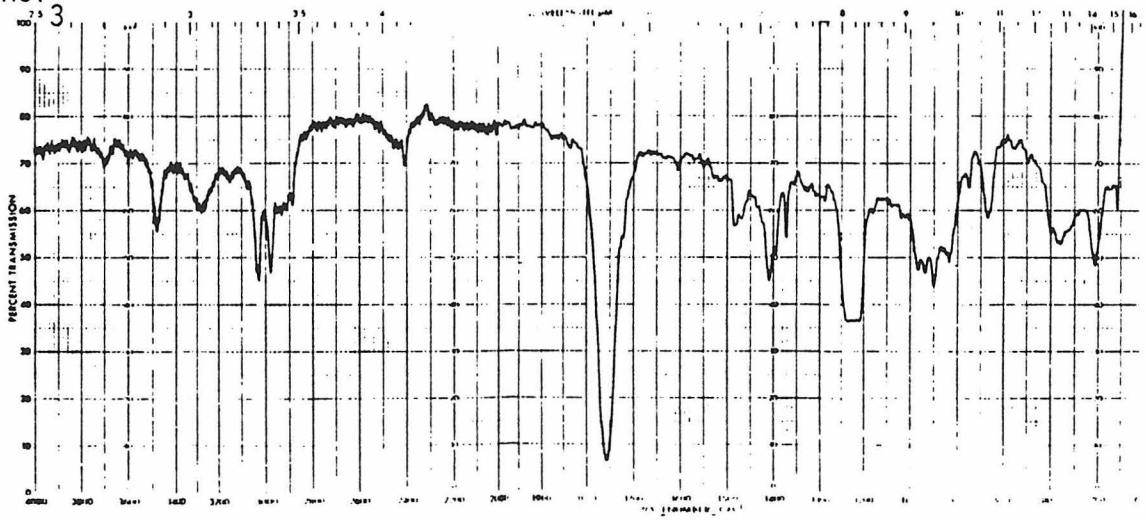

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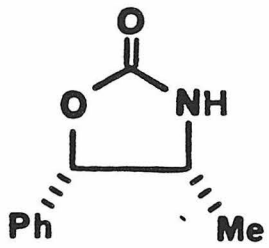

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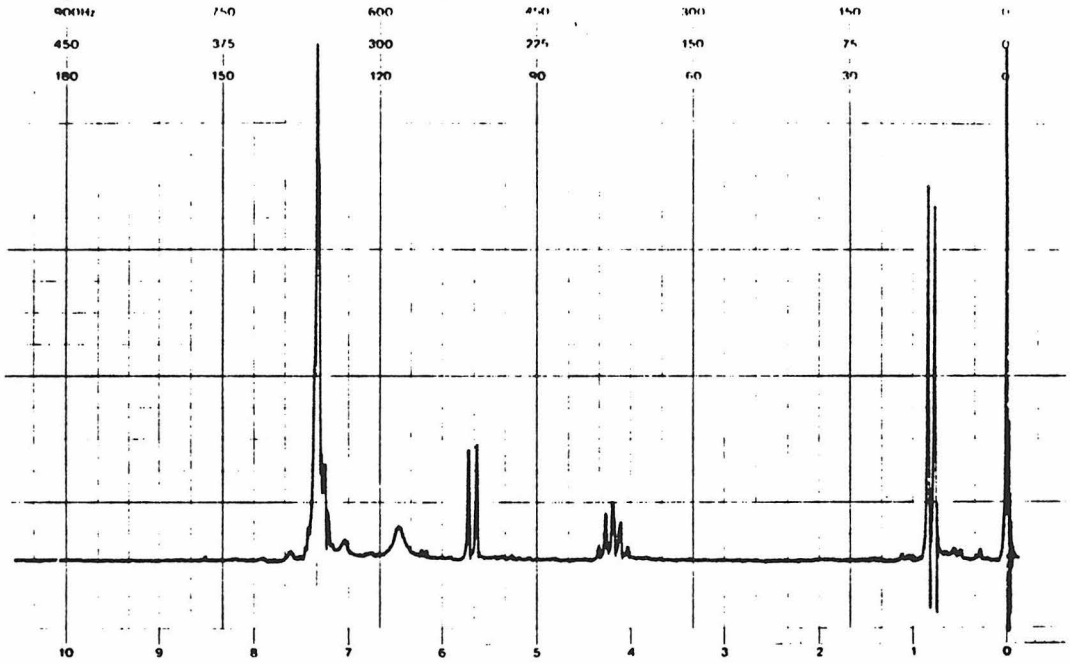

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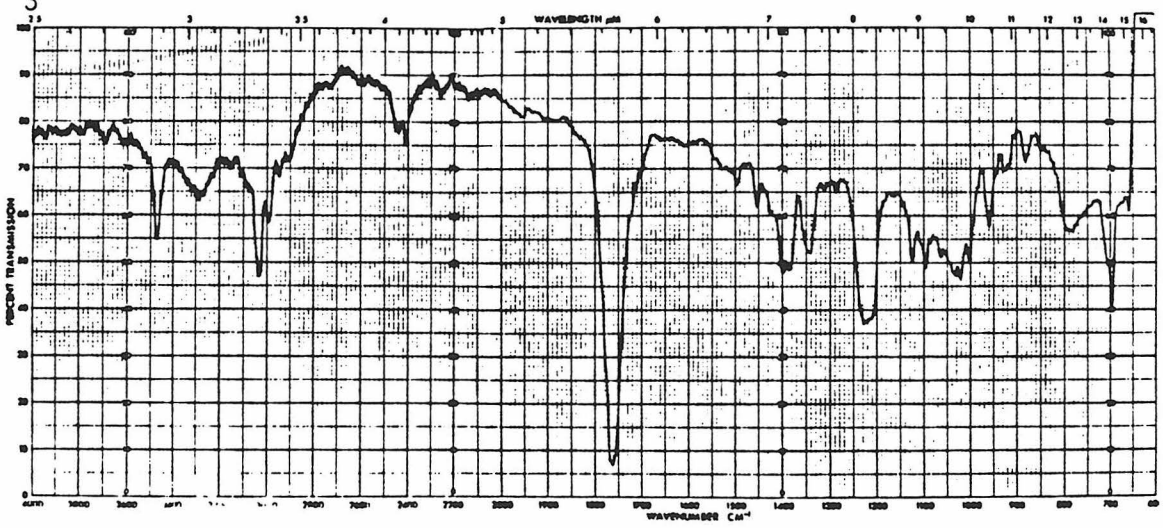

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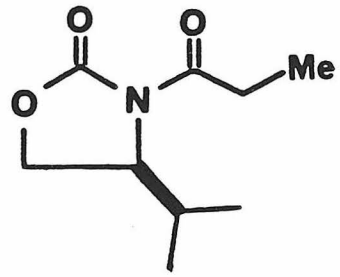

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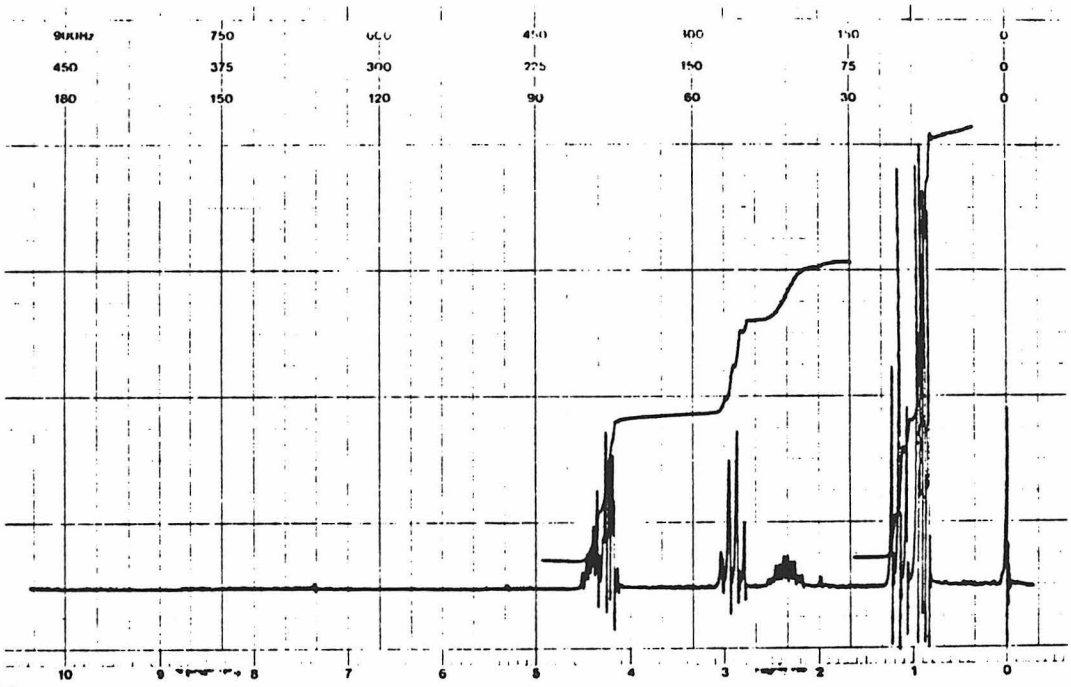

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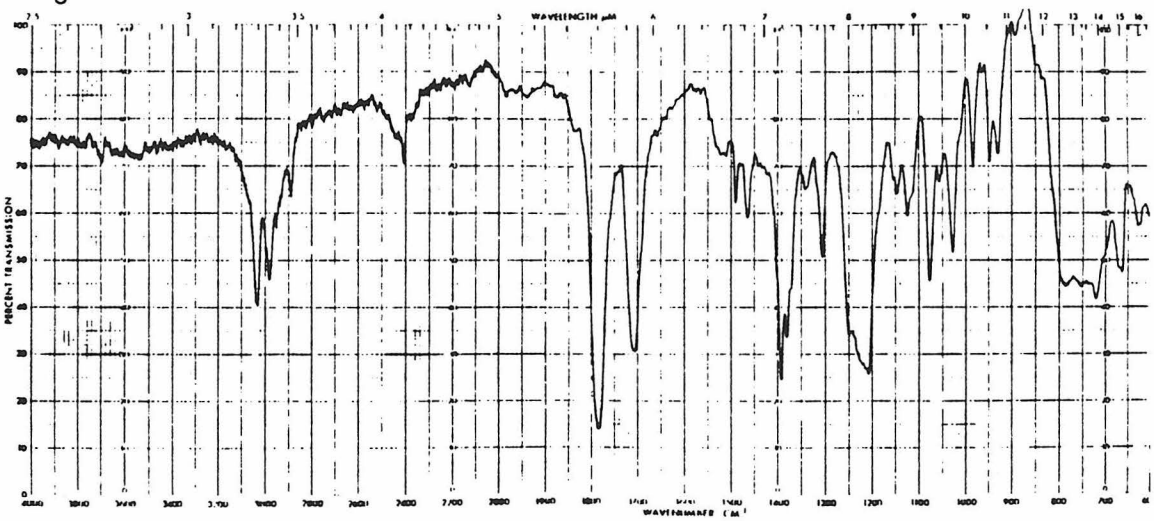

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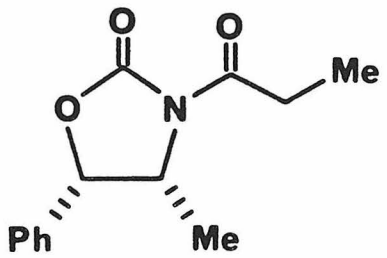

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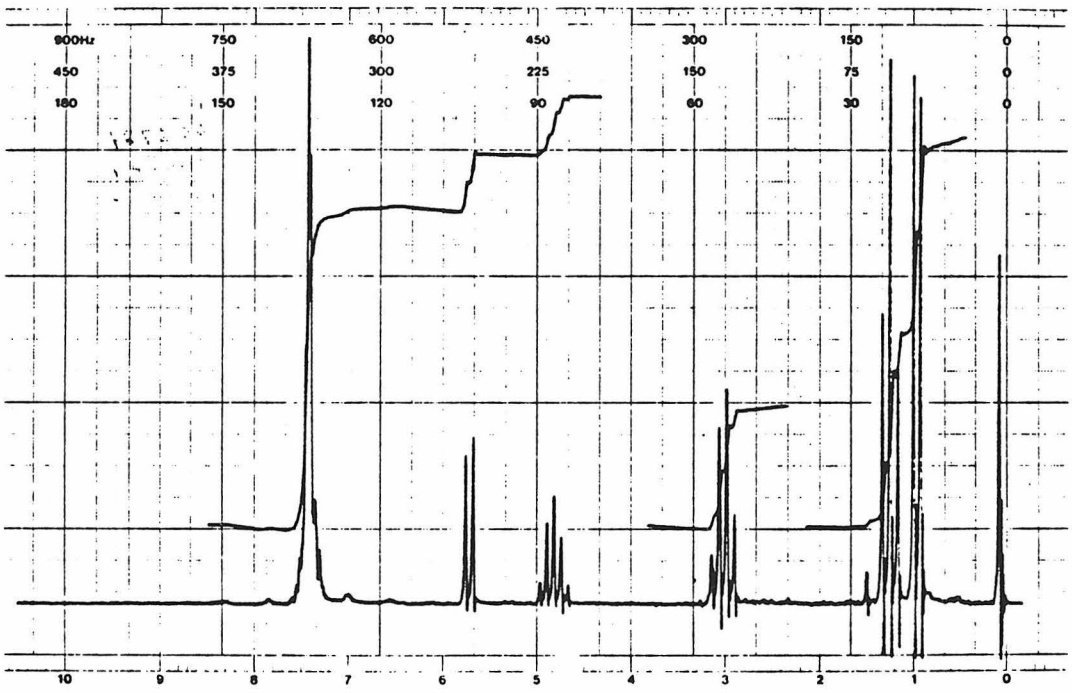

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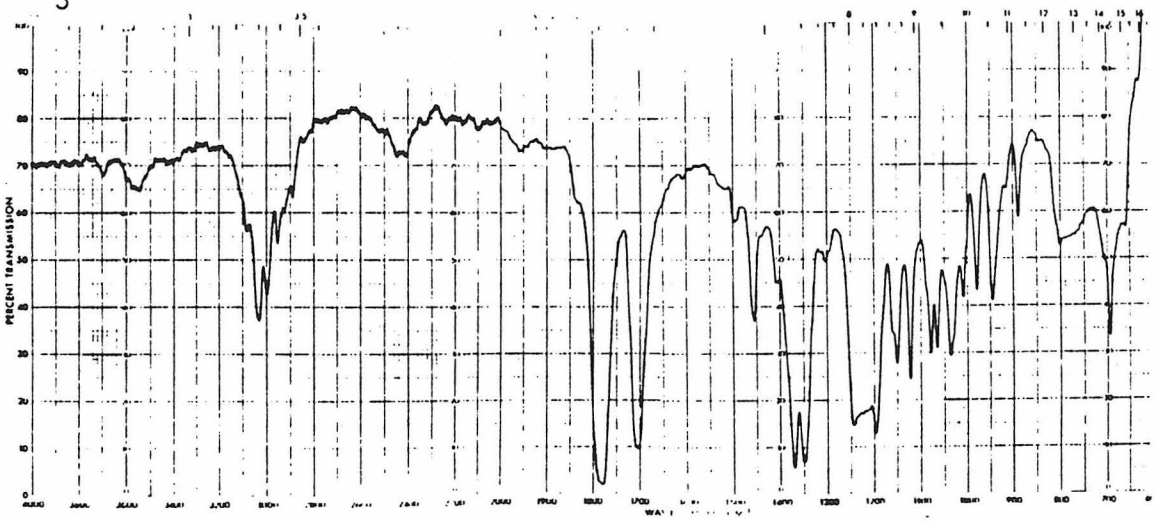

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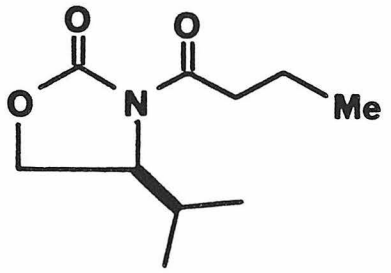

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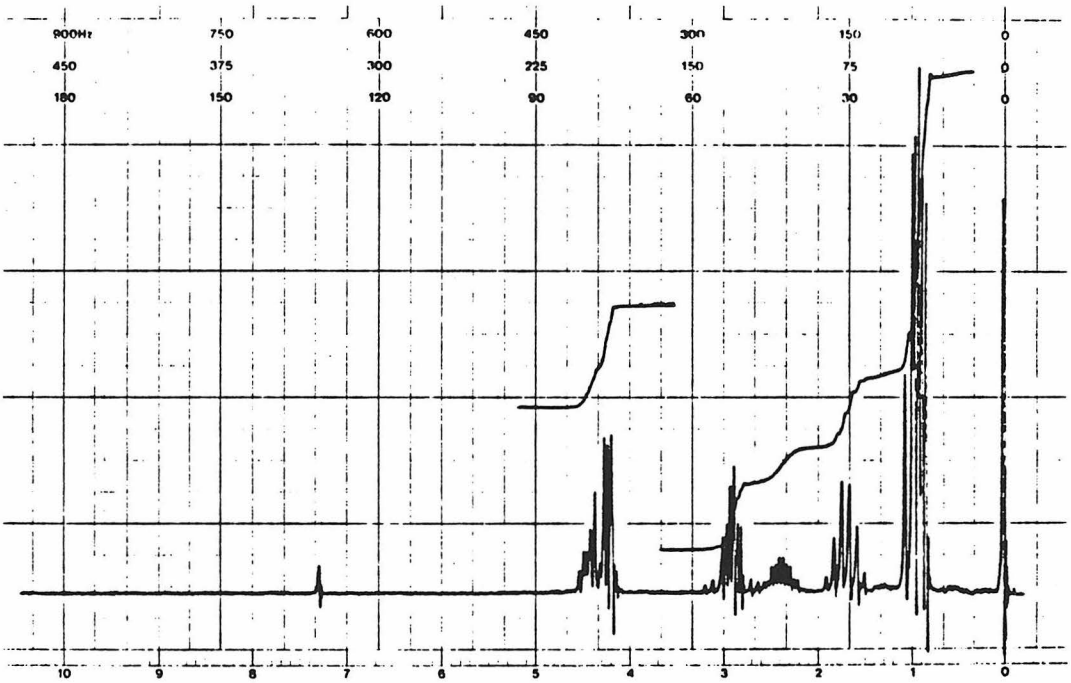

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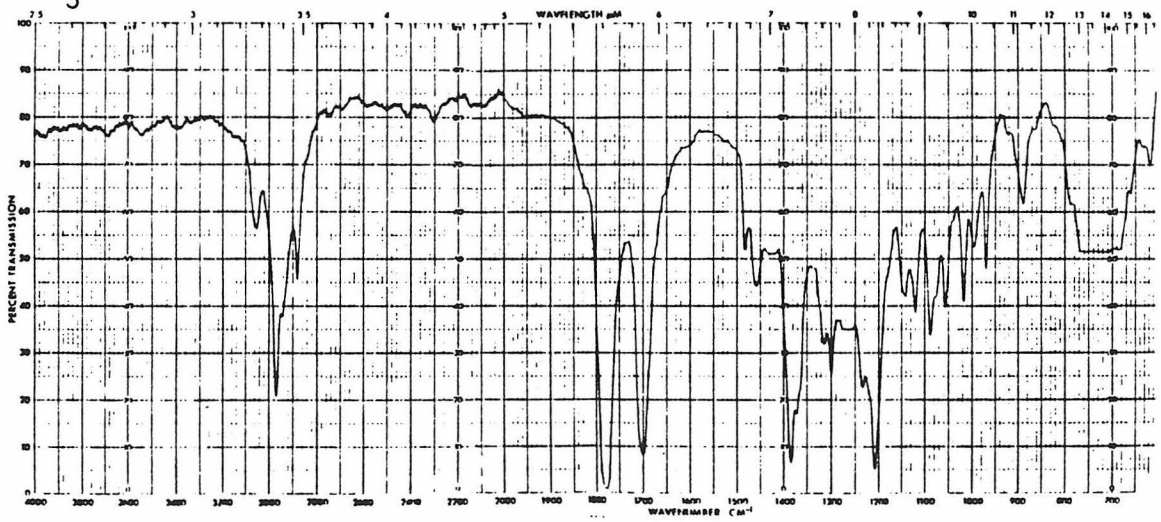

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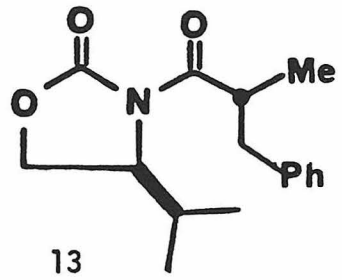

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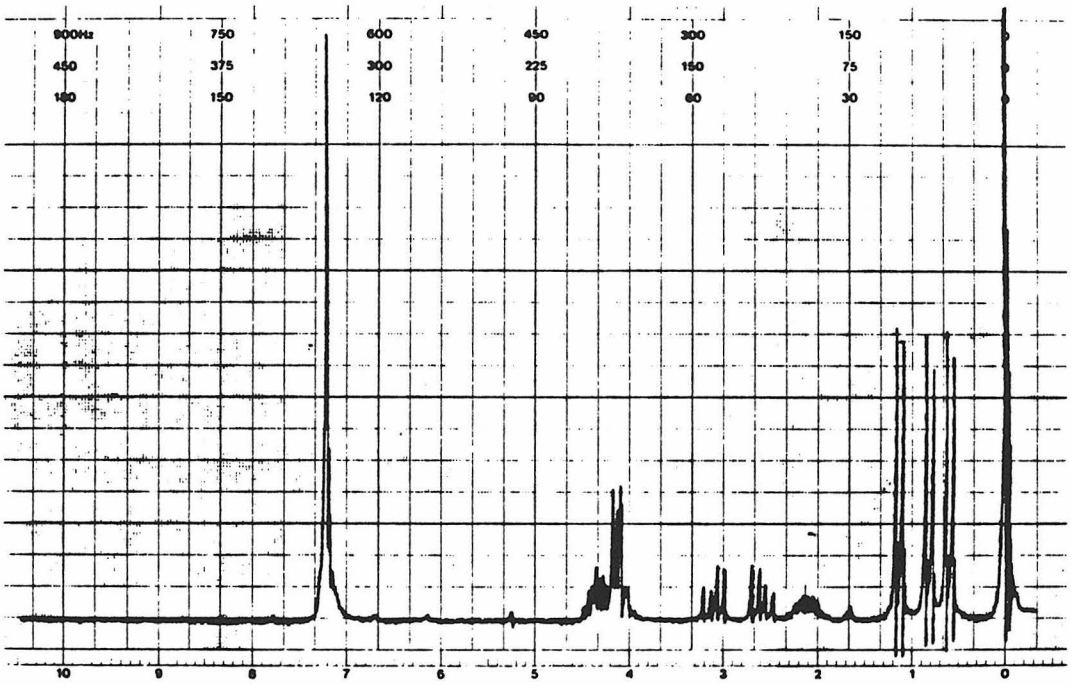

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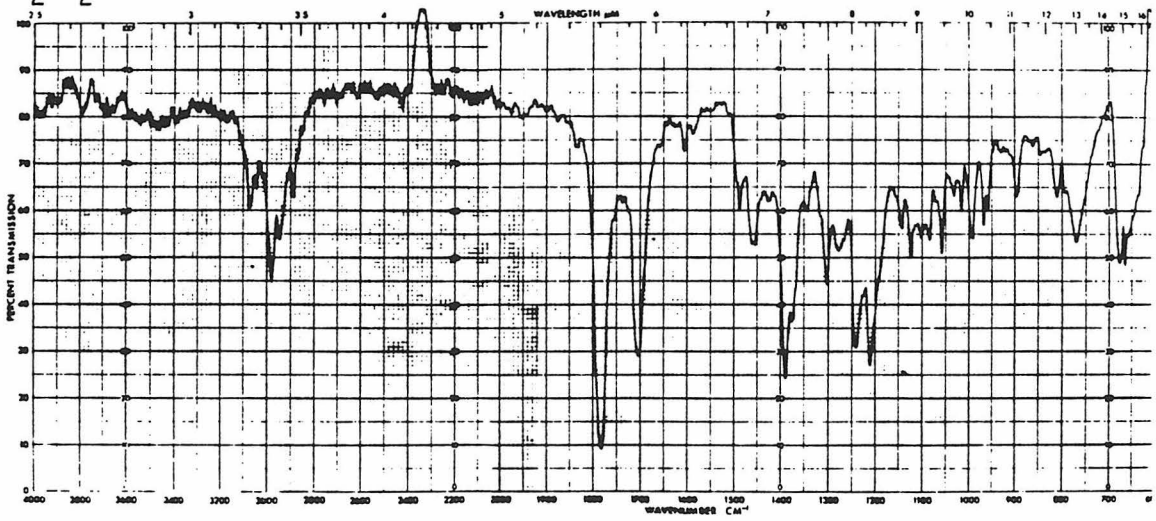

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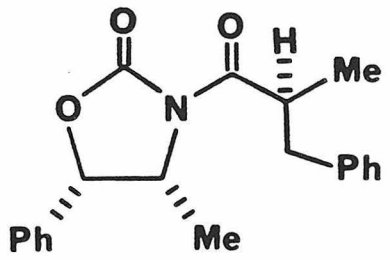

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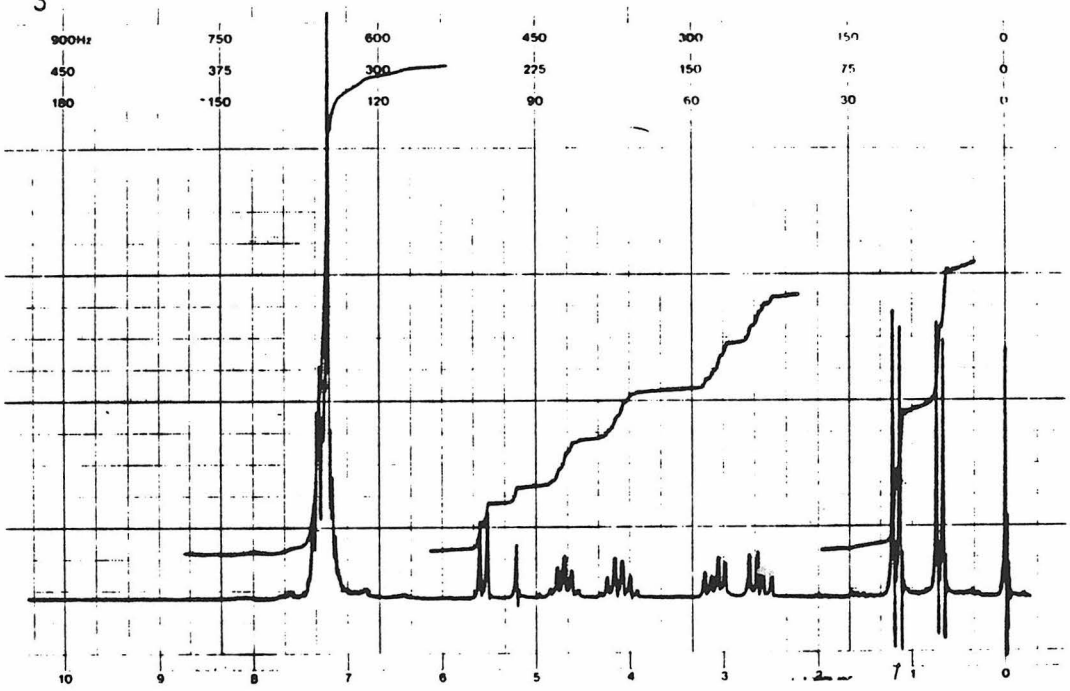

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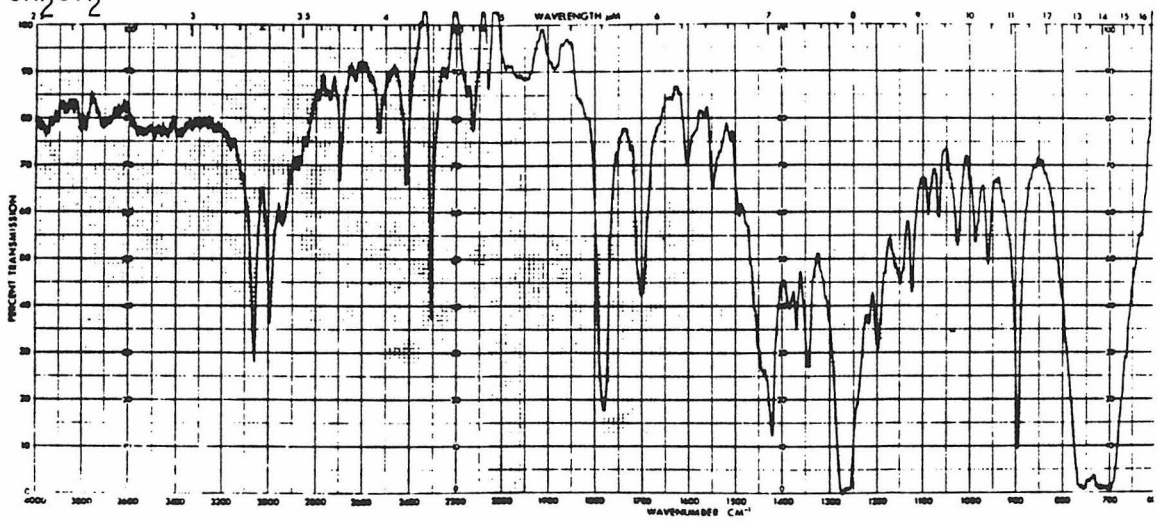

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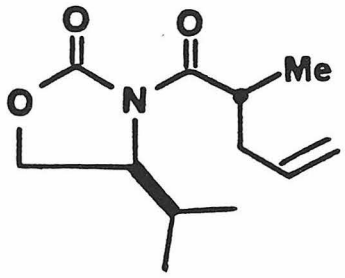

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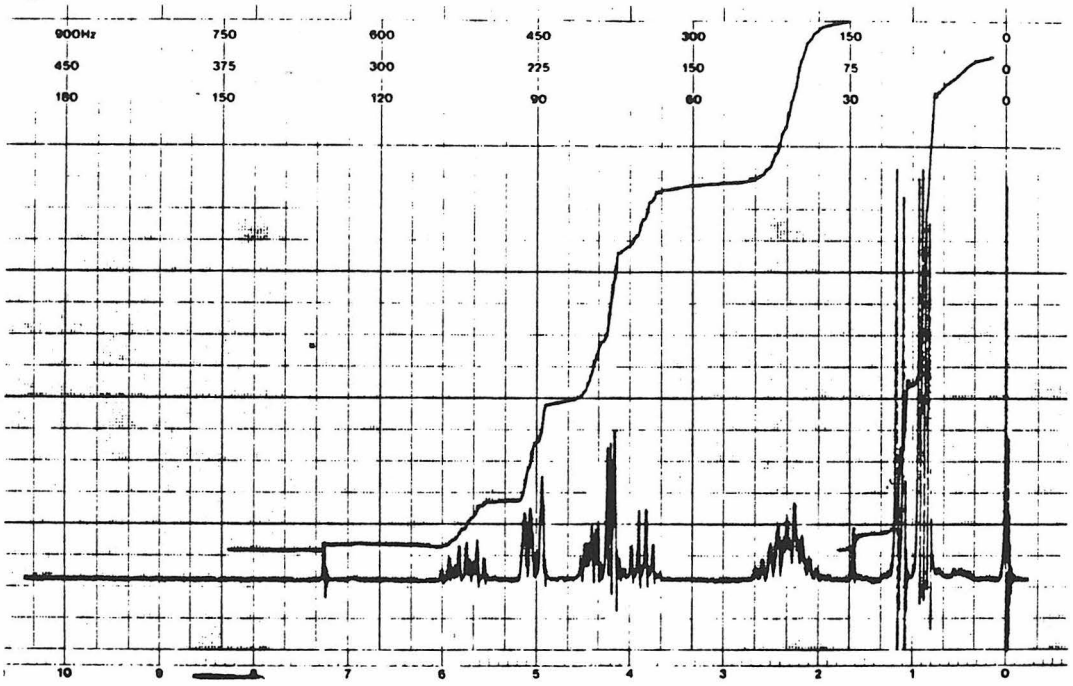

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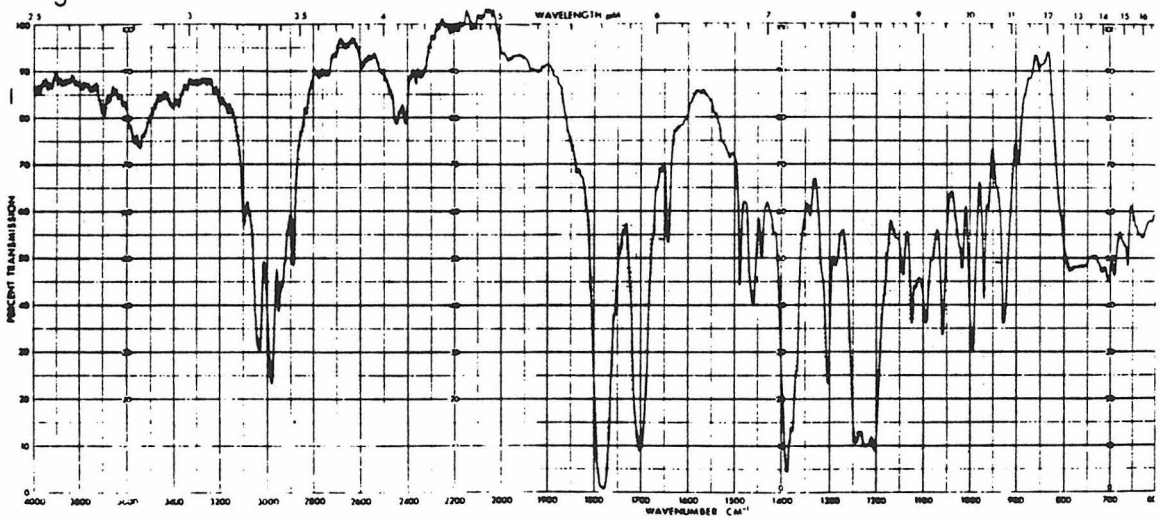

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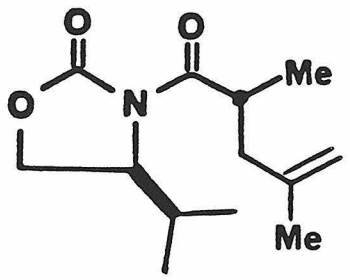

17

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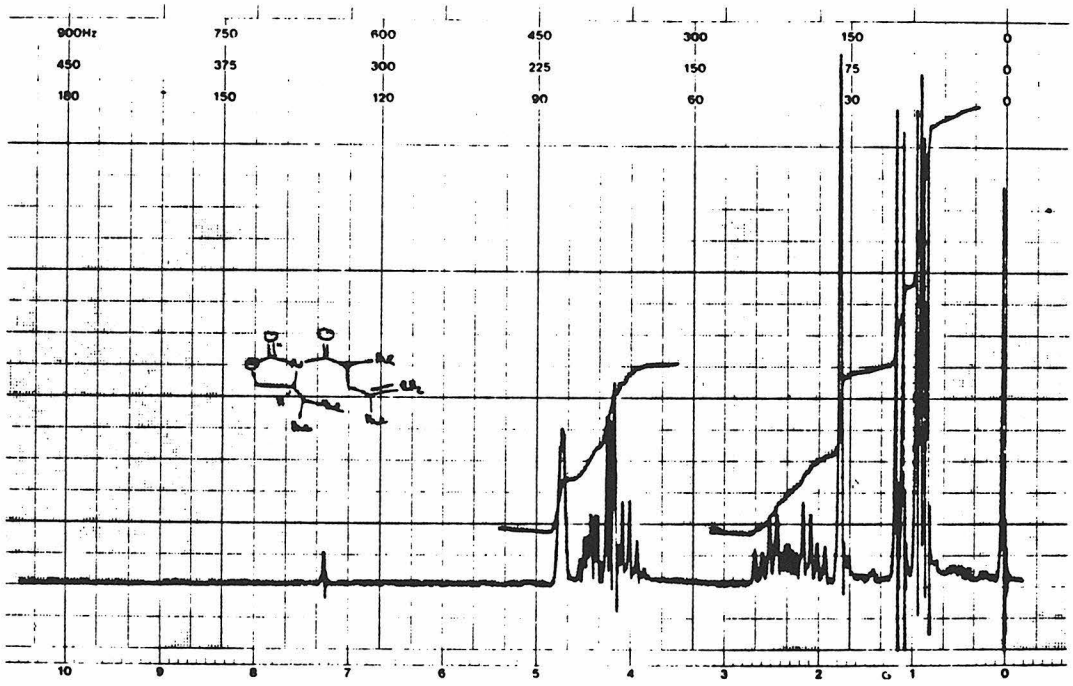

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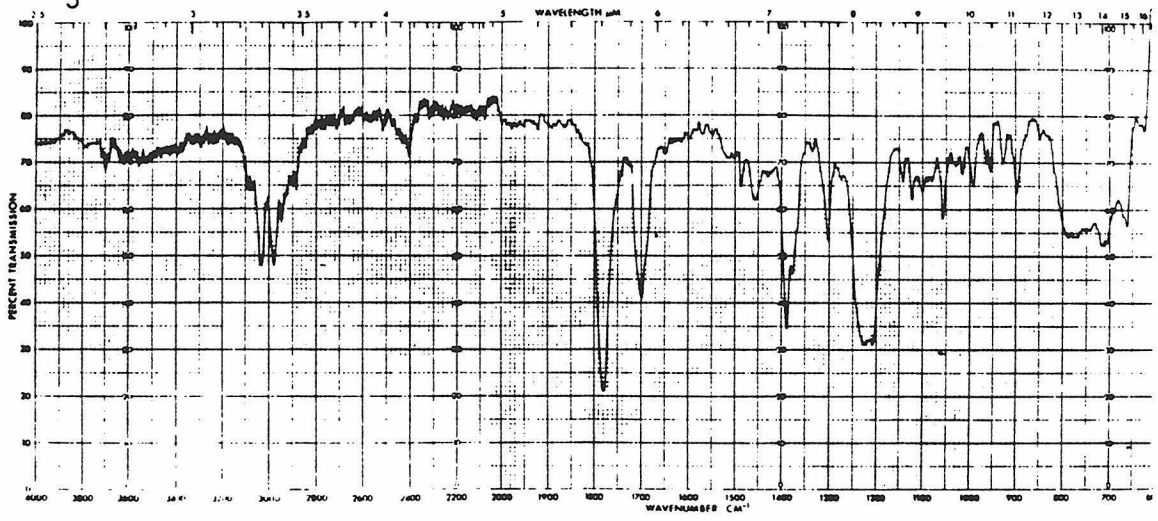

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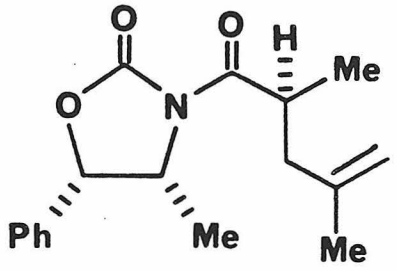

18

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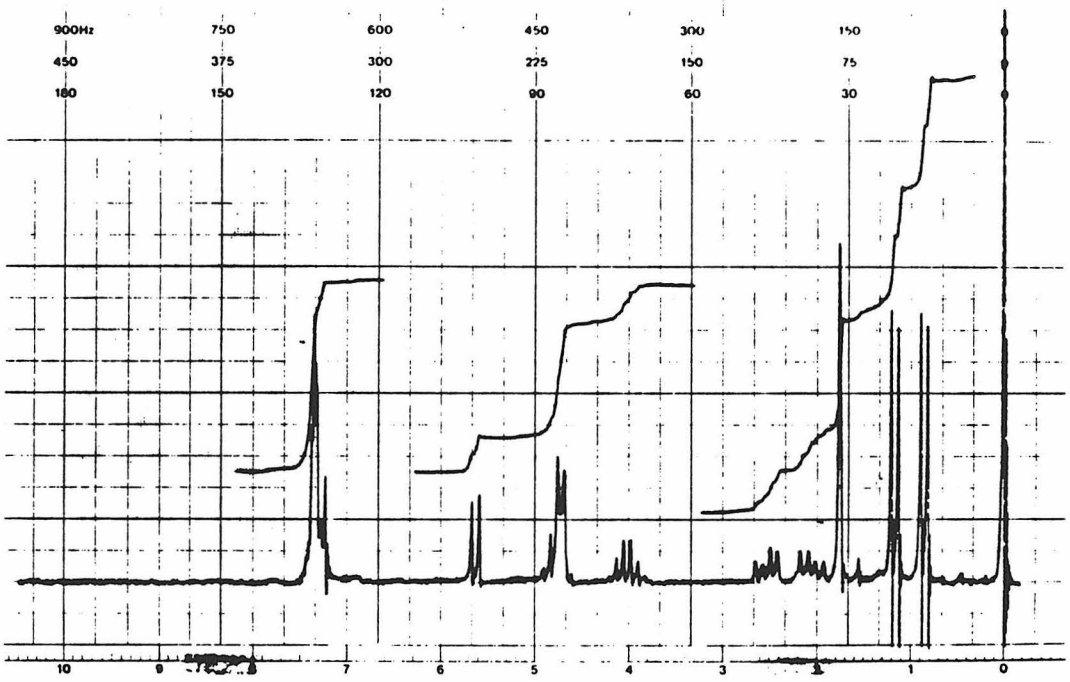

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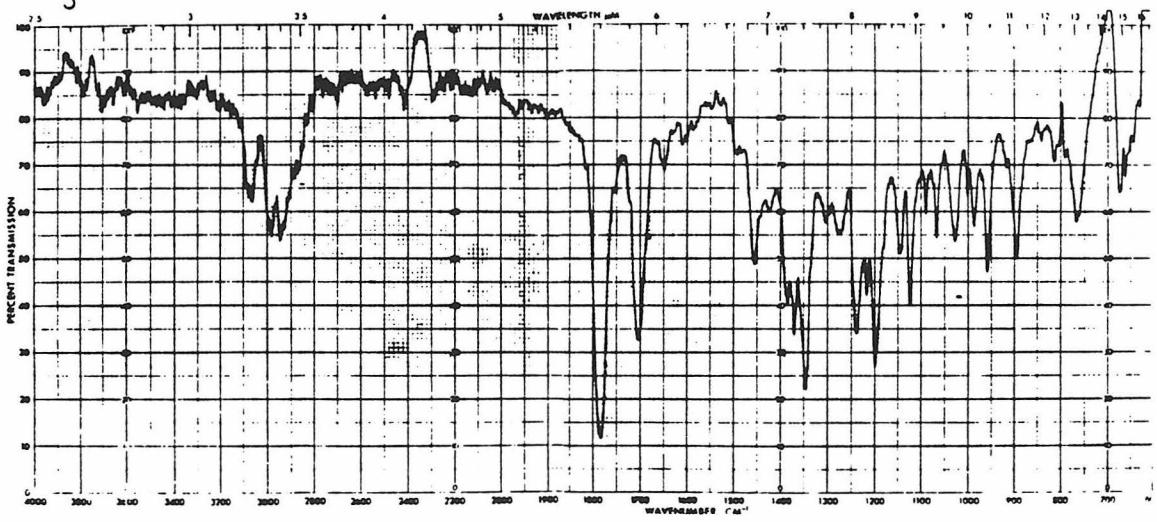

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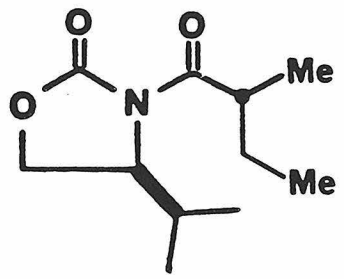

23(R)

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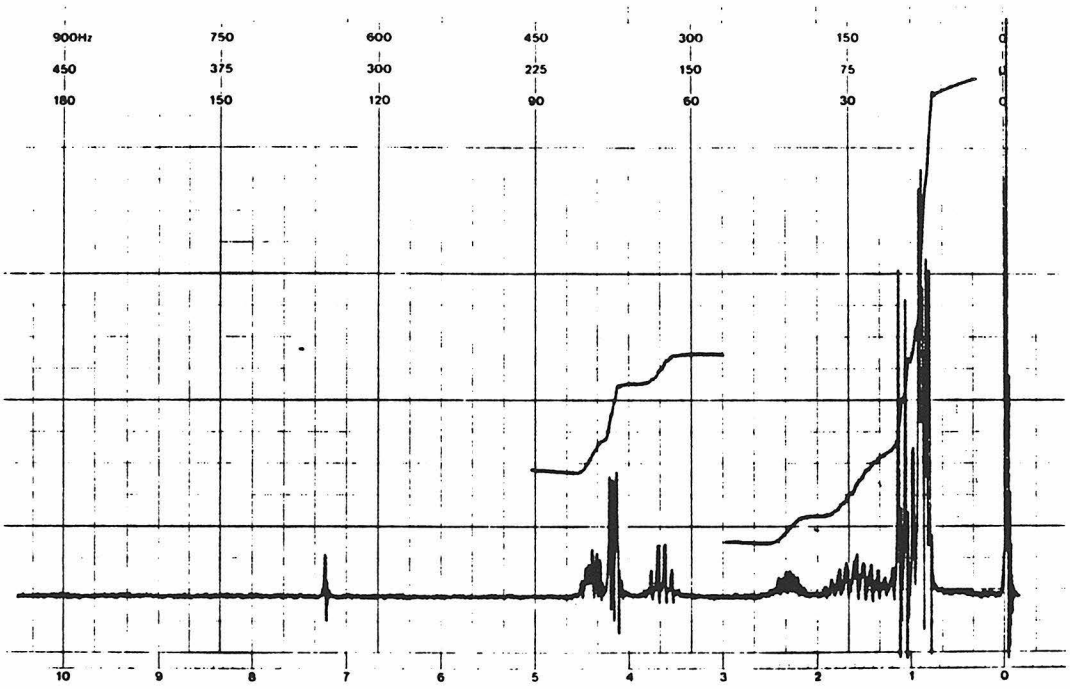

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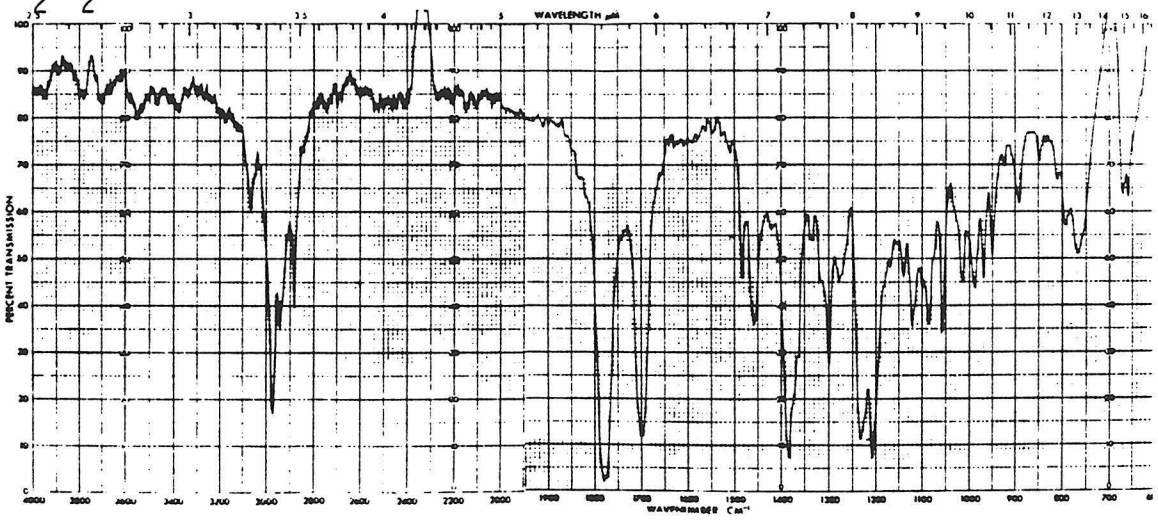

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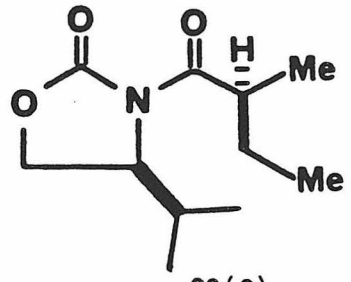

23(S)

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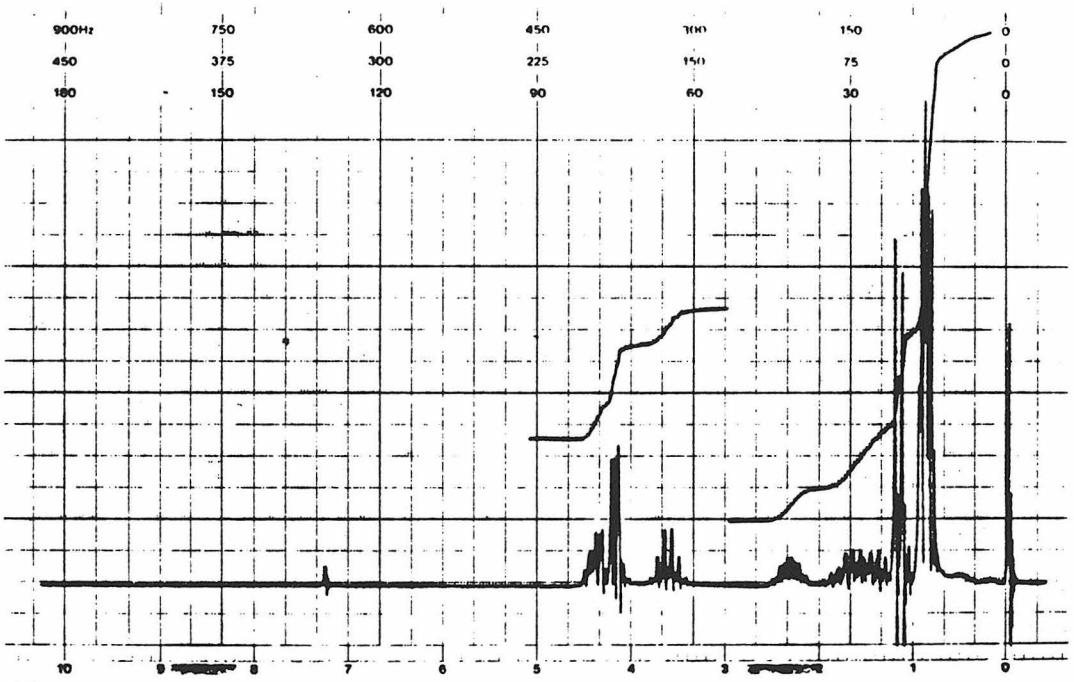

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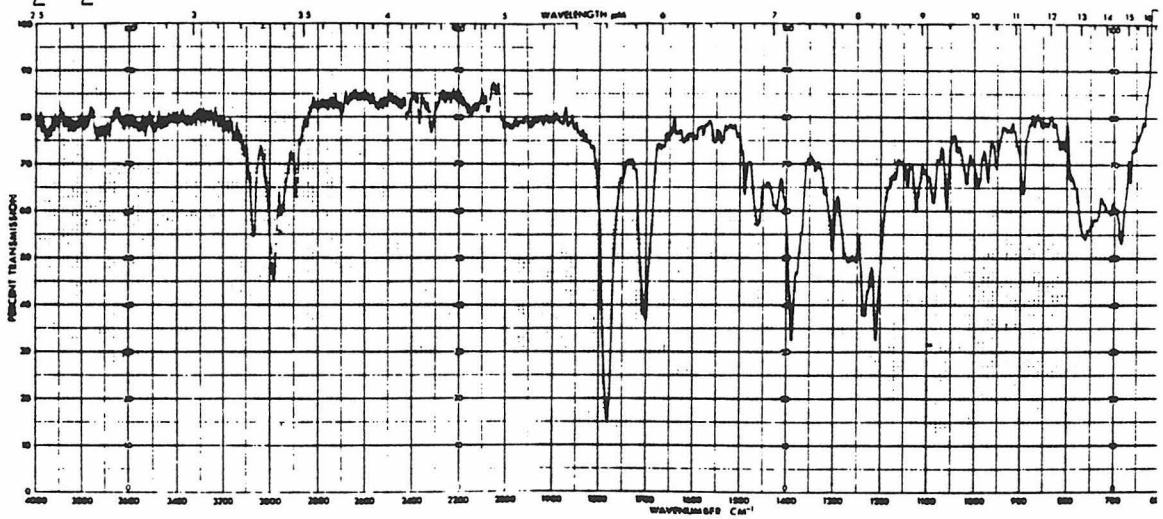

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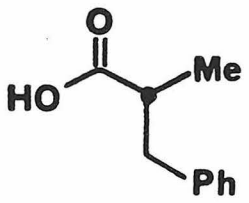

27

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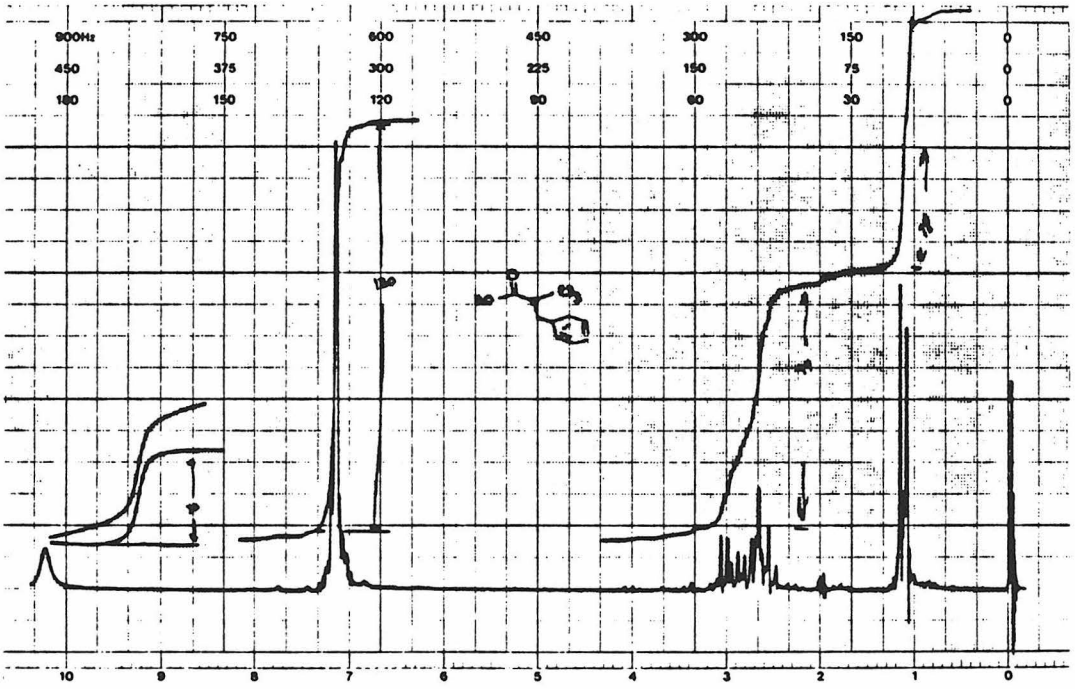

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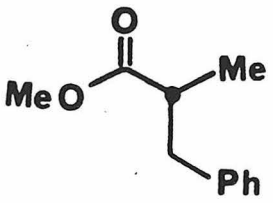

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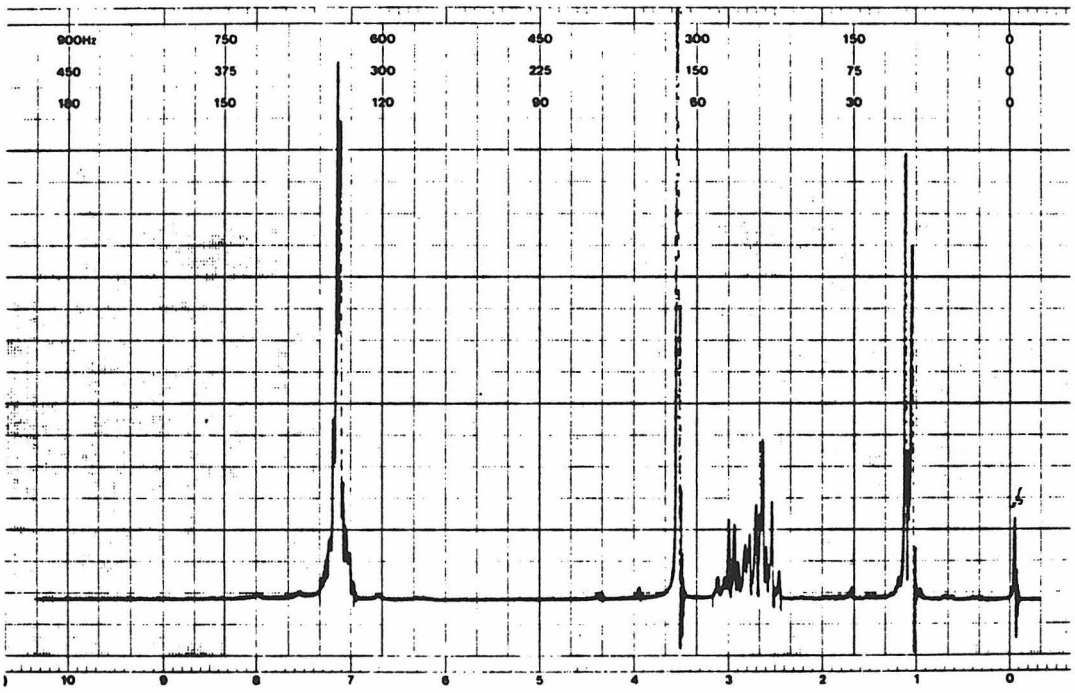

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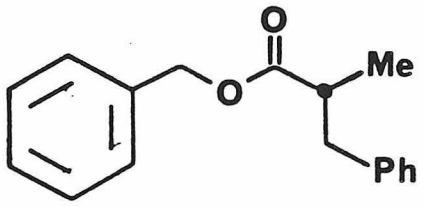

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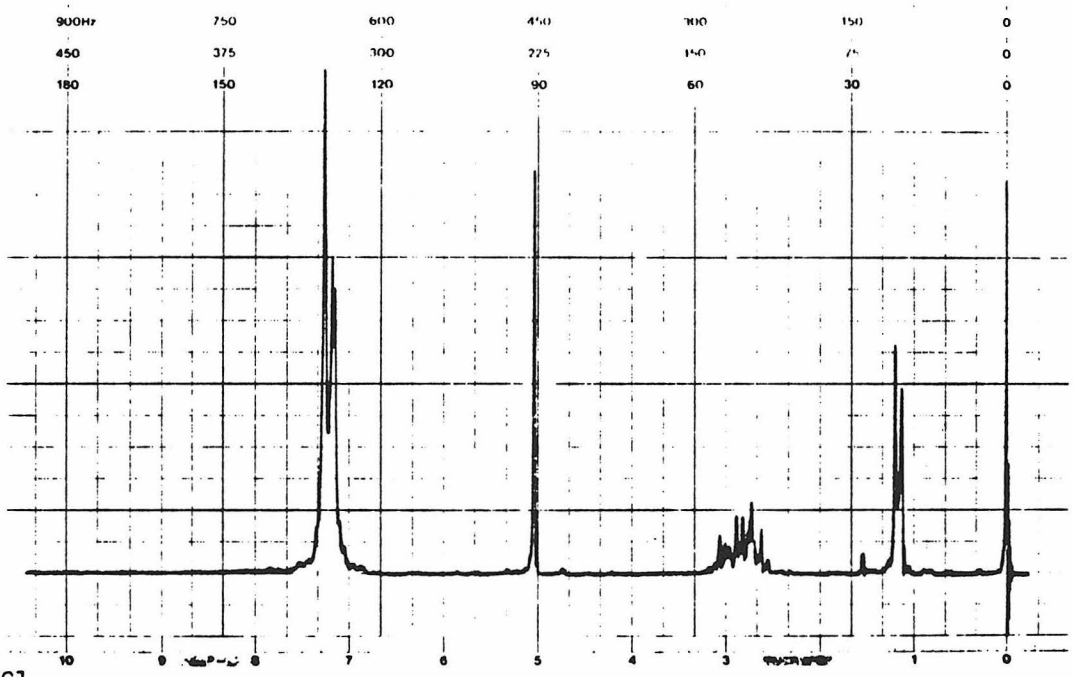

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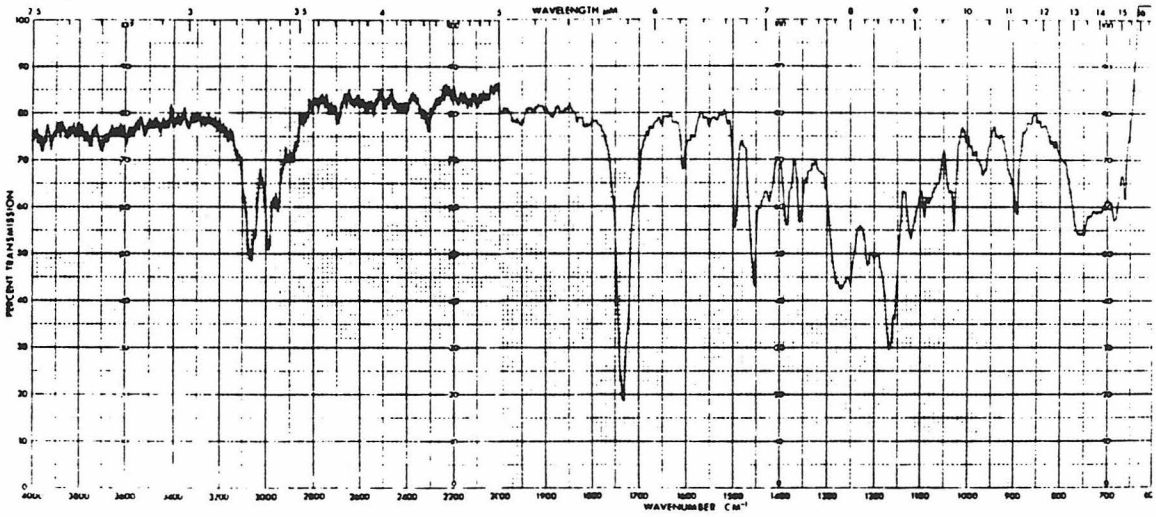

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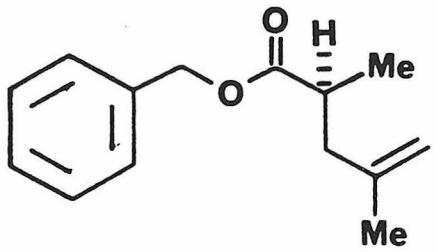

$CDCl_3$

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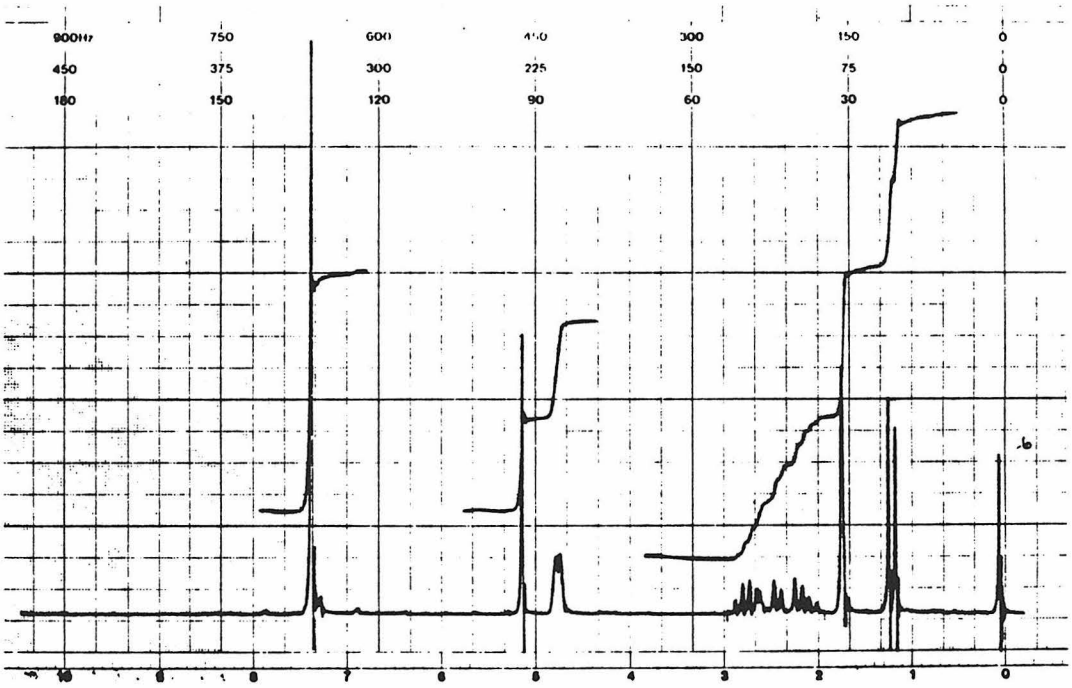
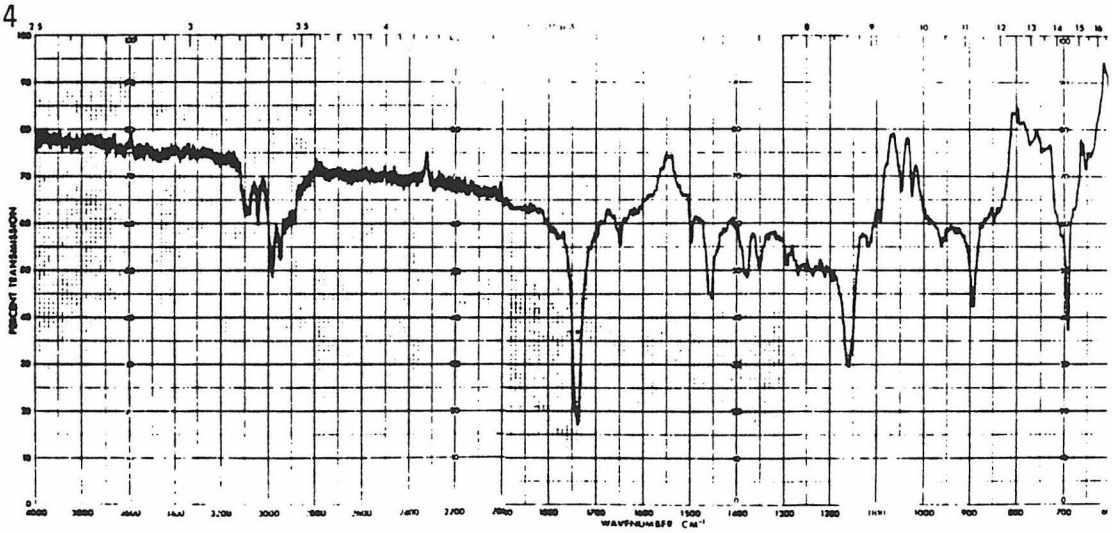


CCl_4



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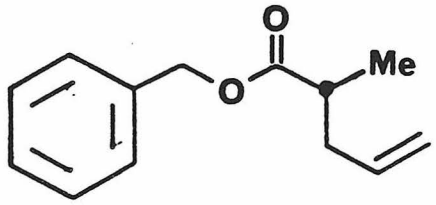

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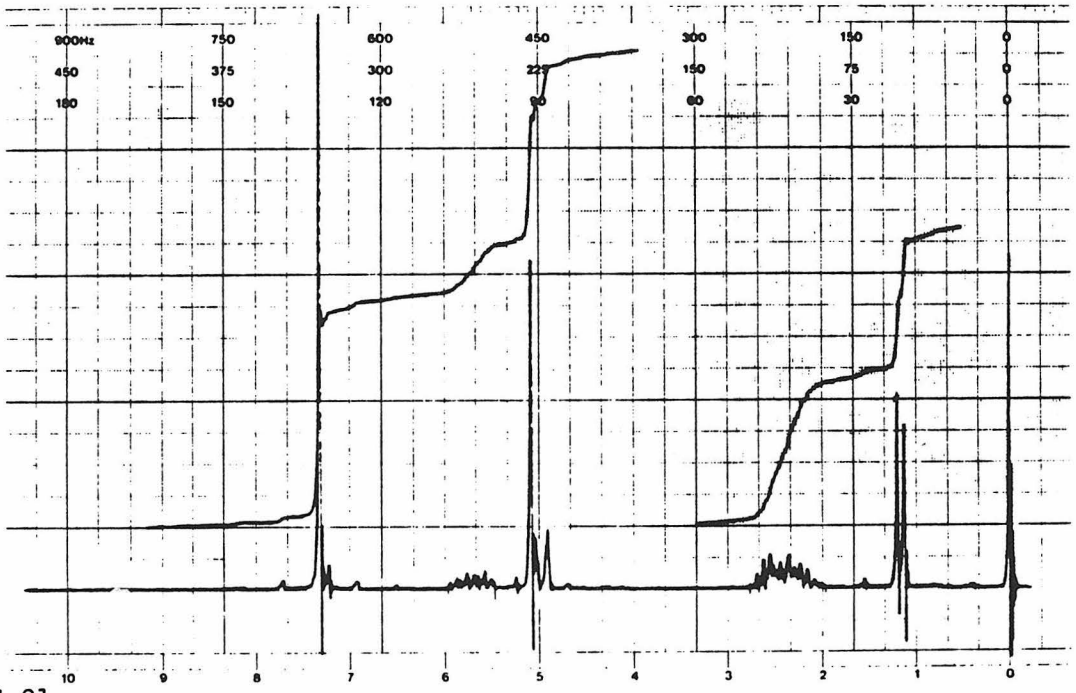

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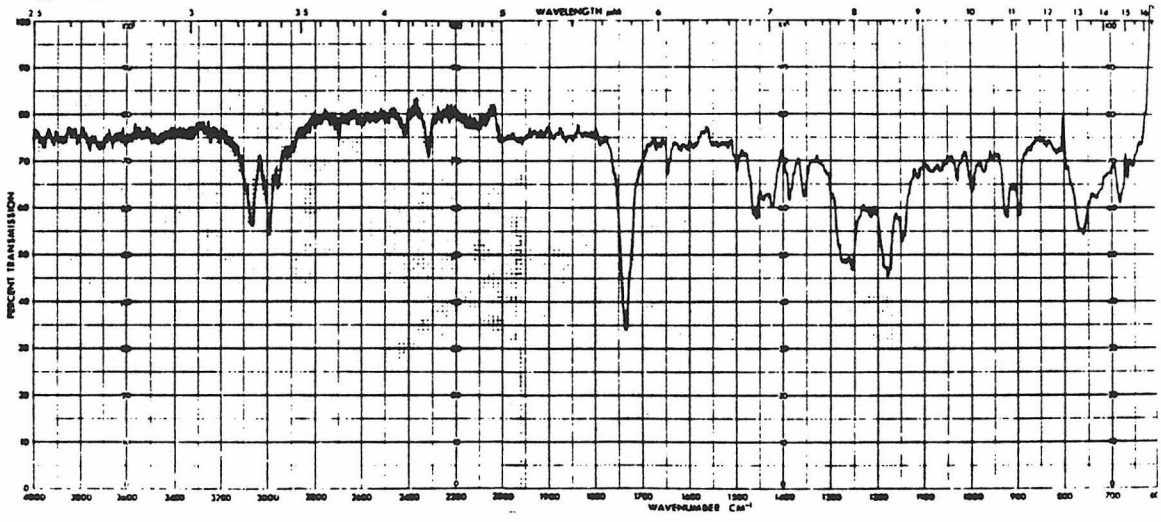

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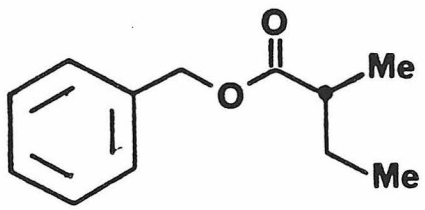

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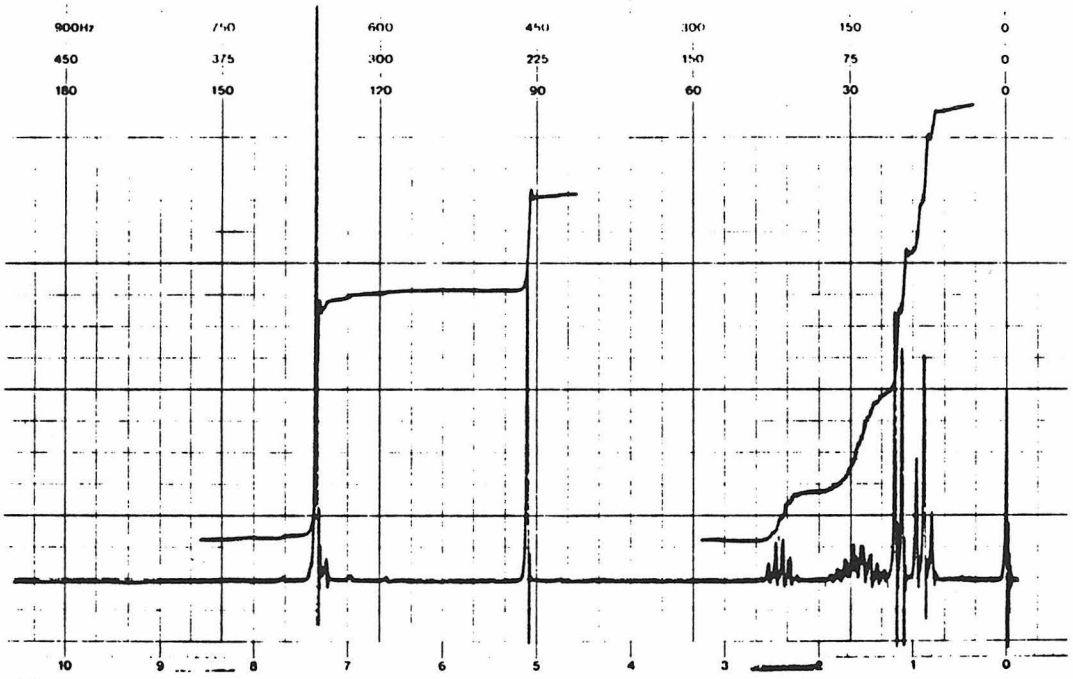

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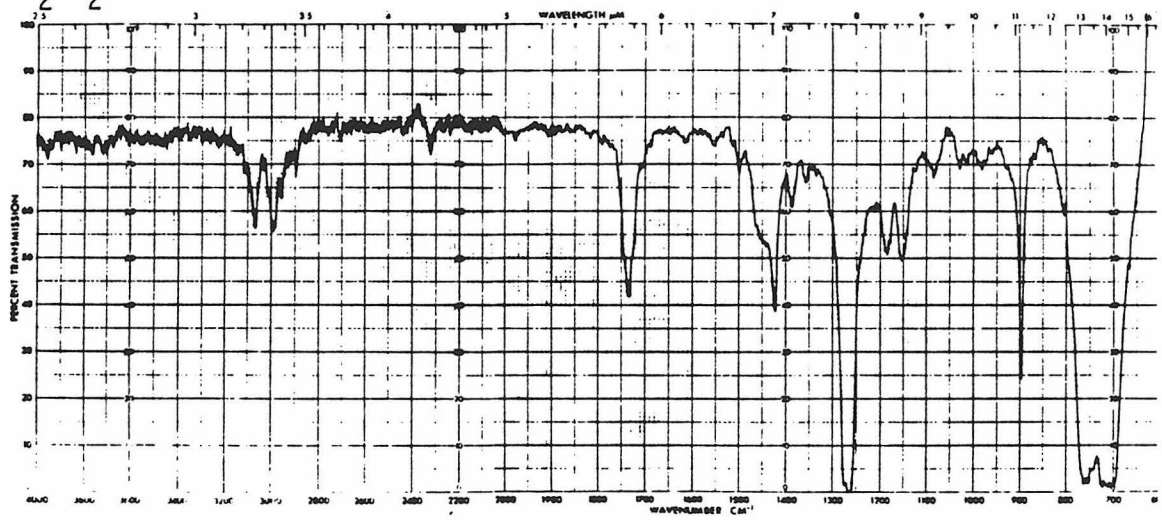

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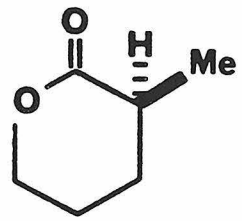

34

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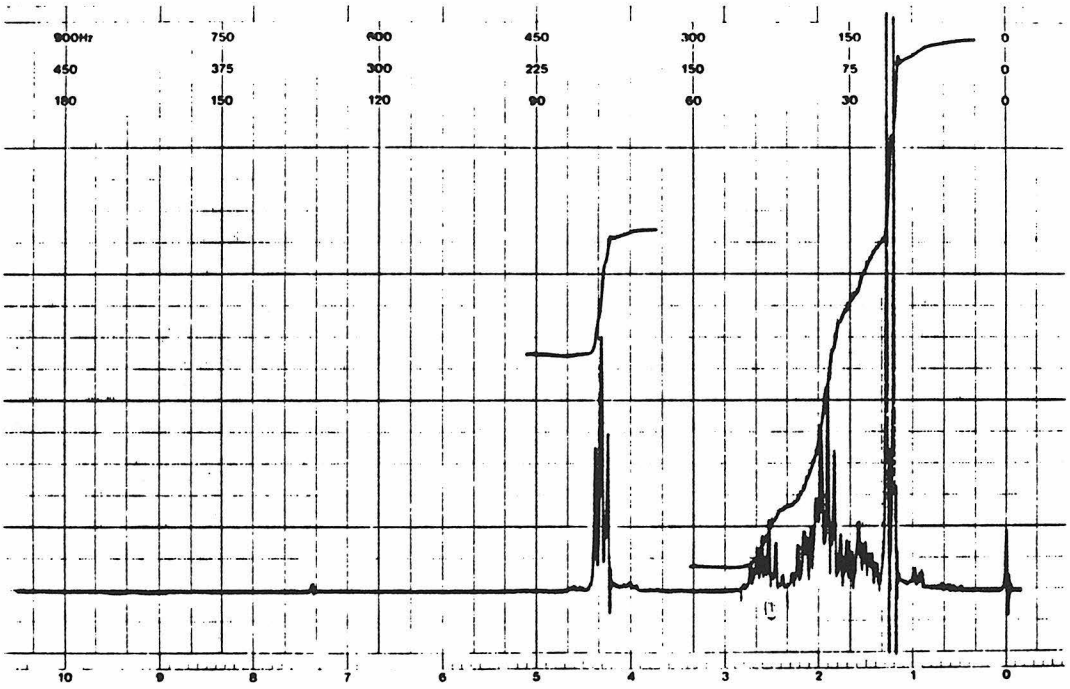

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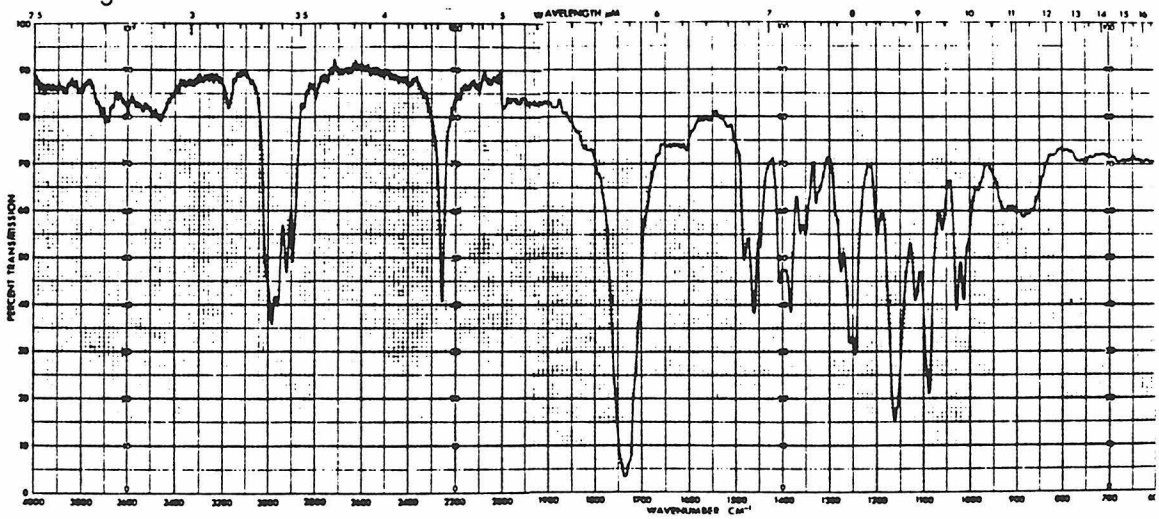

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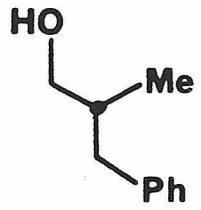

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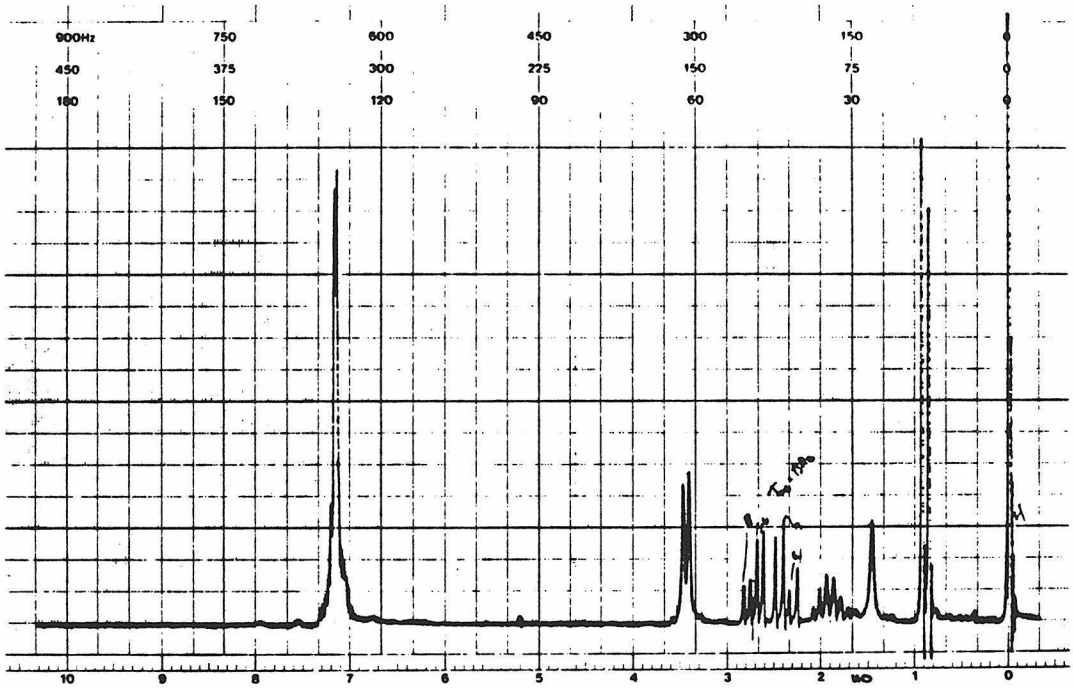

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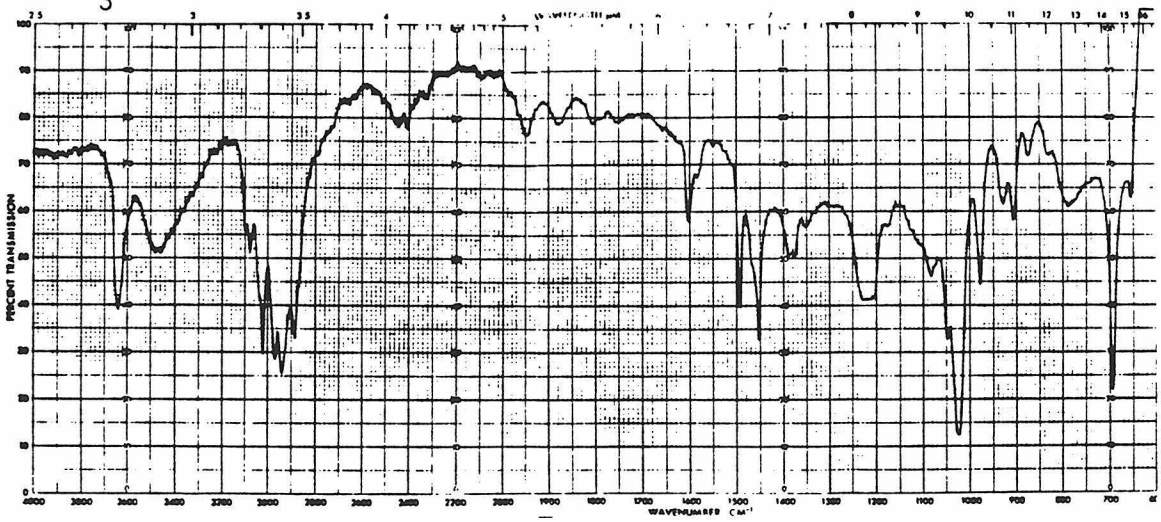

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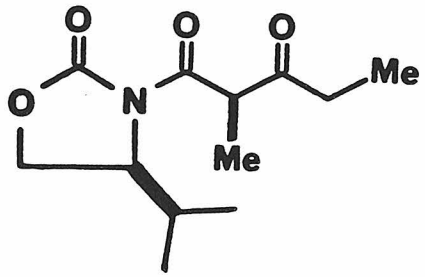

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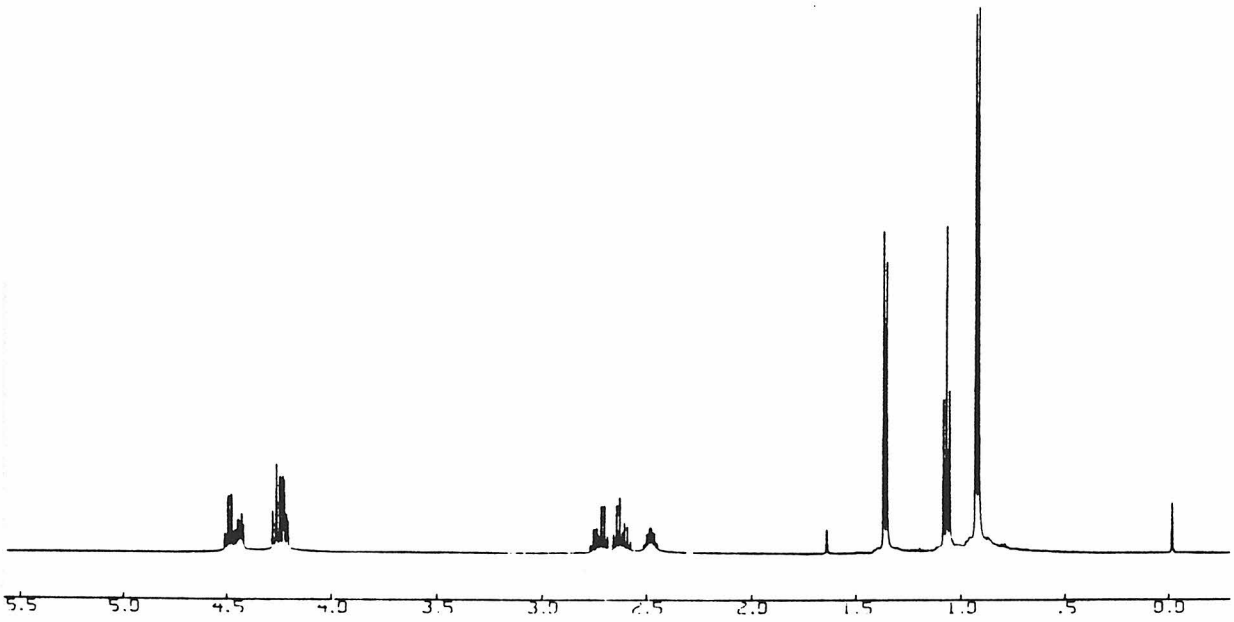

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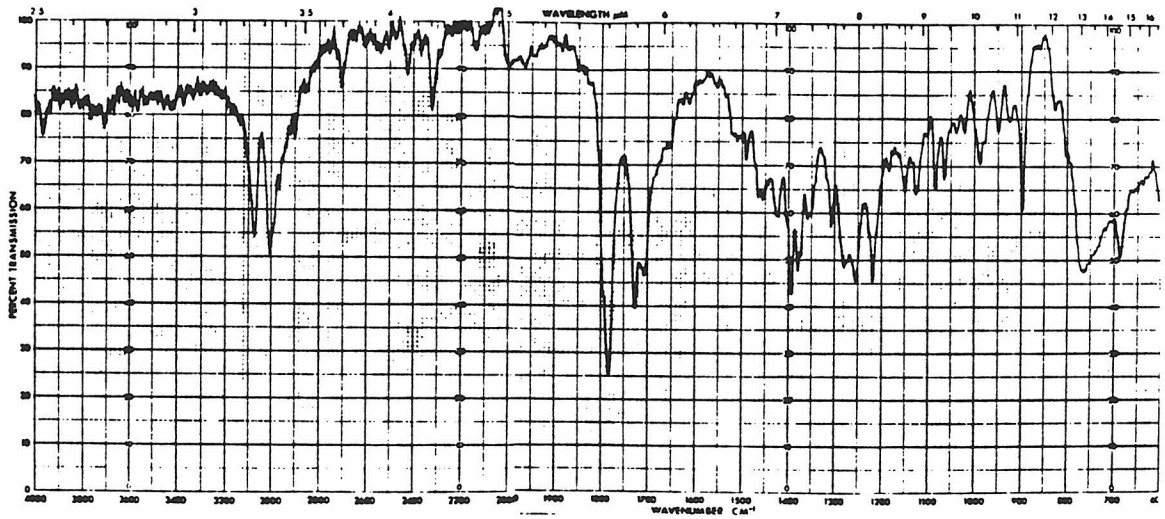

APPENDIX III

IR and NMR Spectral Catalog

For Chapter II

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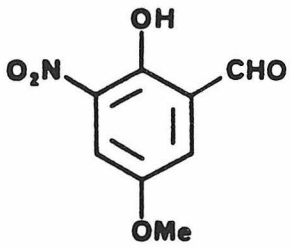

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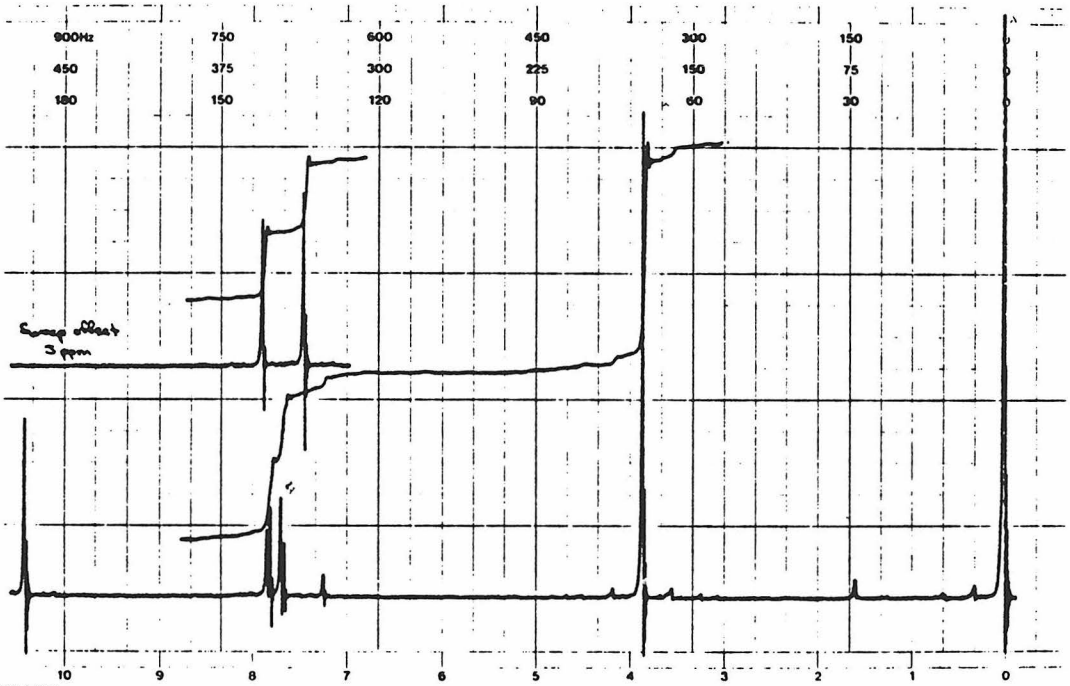

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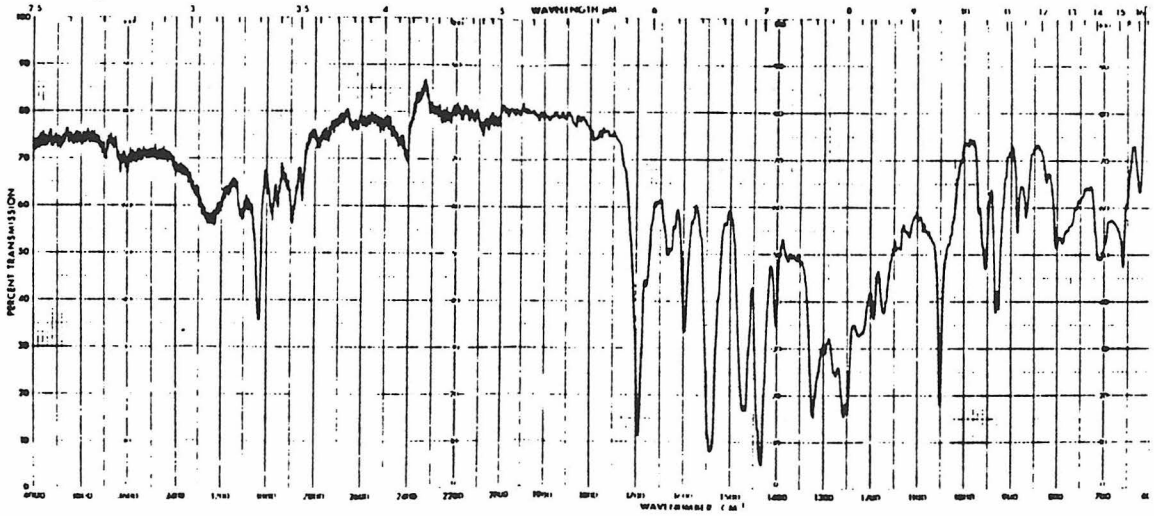

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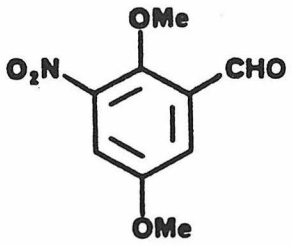

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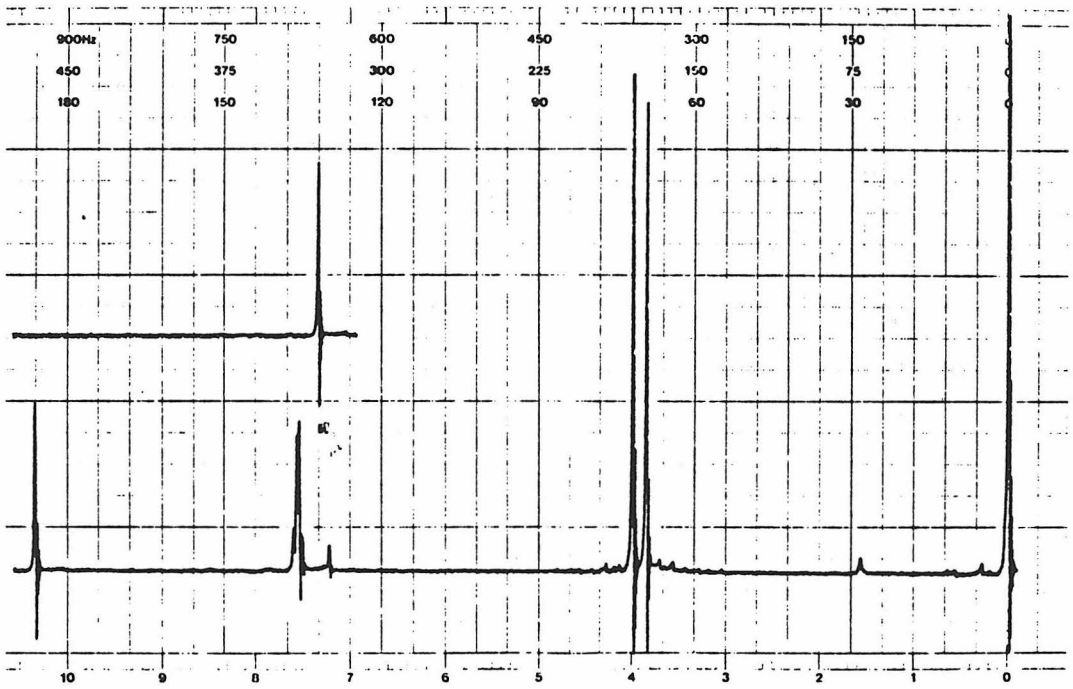

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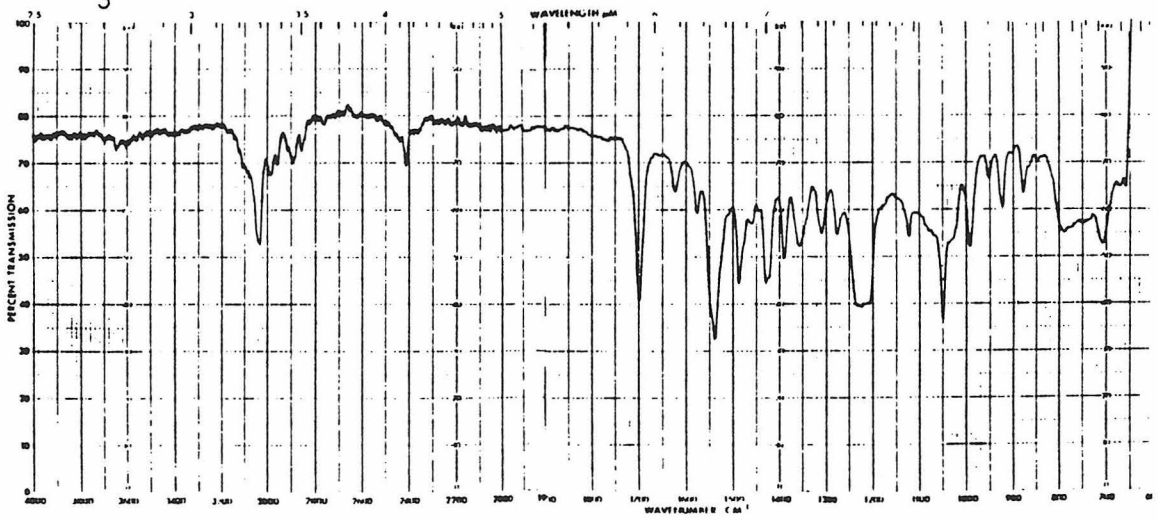

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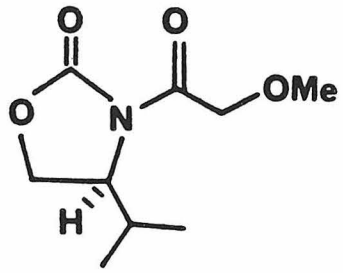

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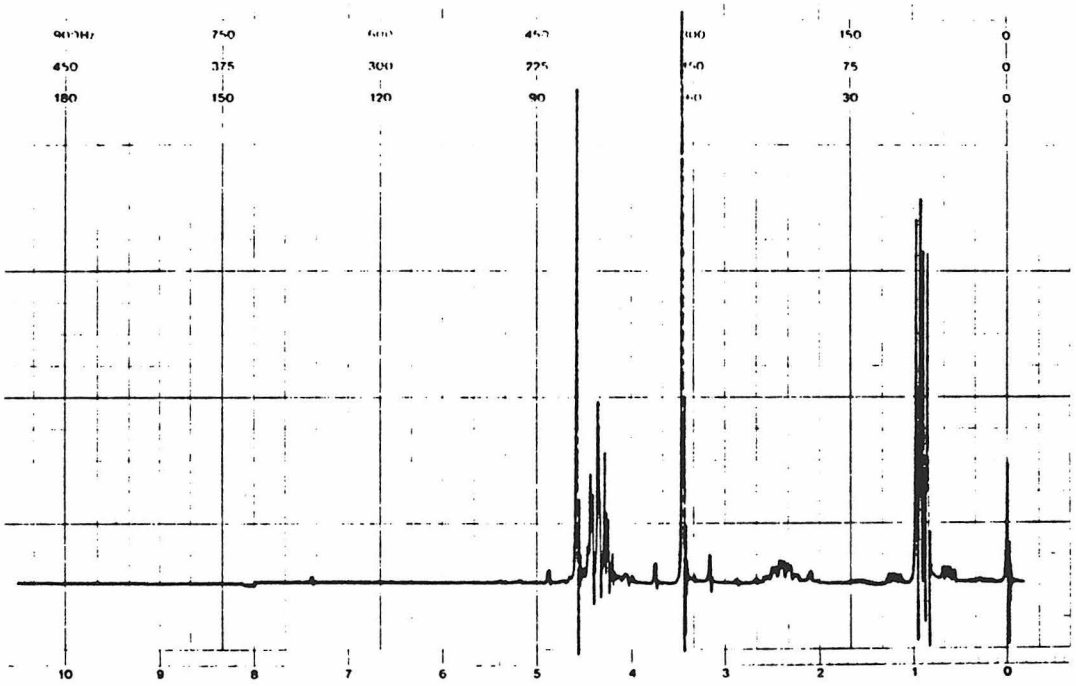

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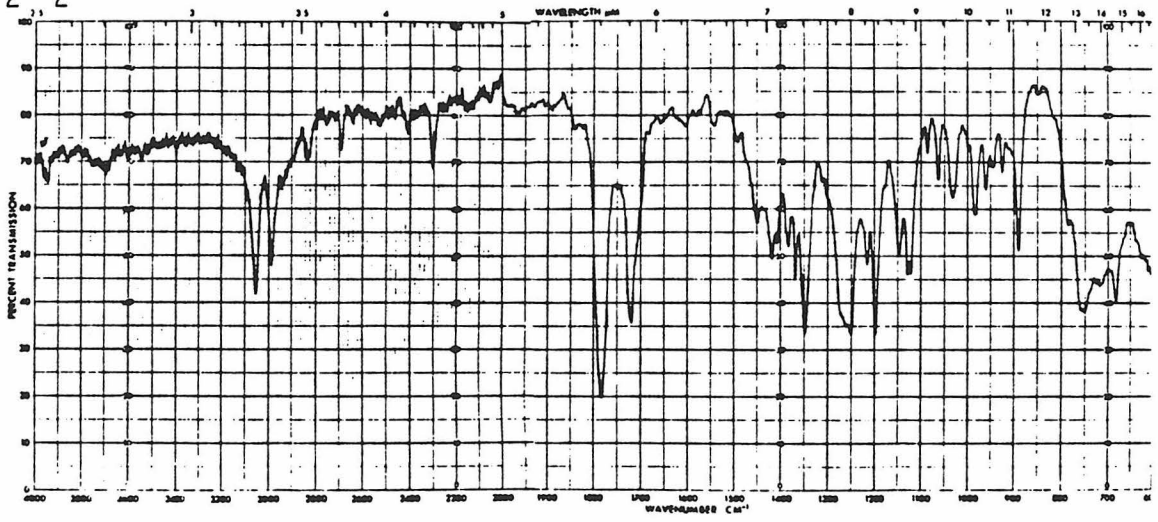

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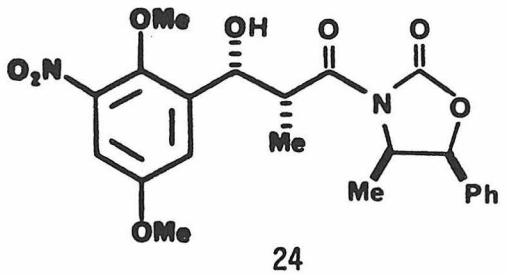

24

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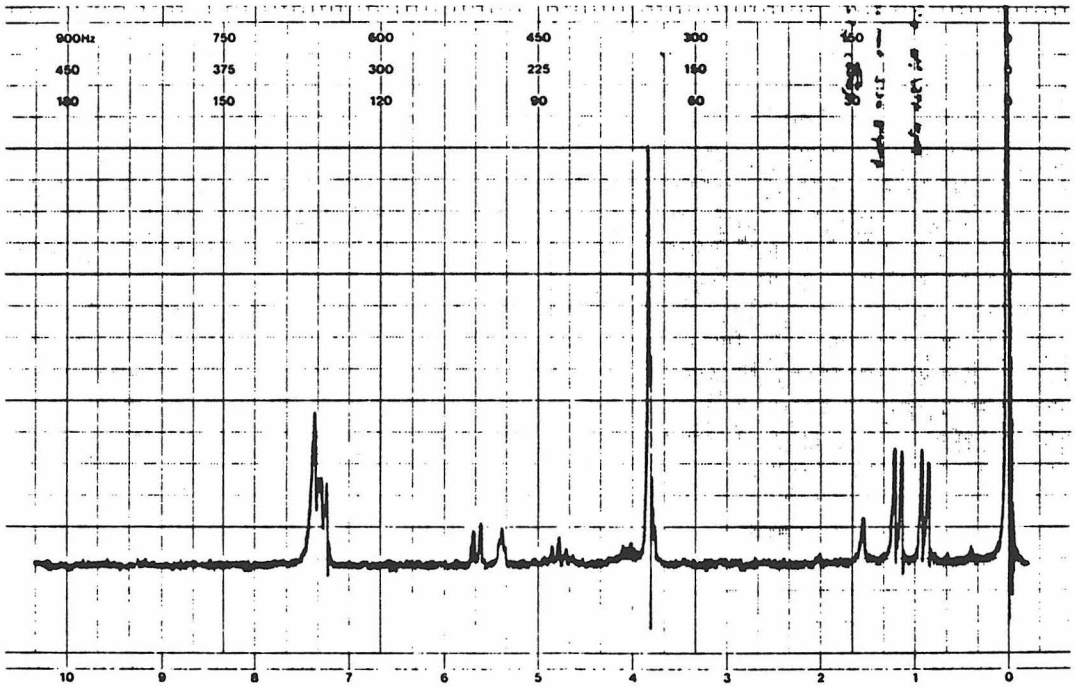

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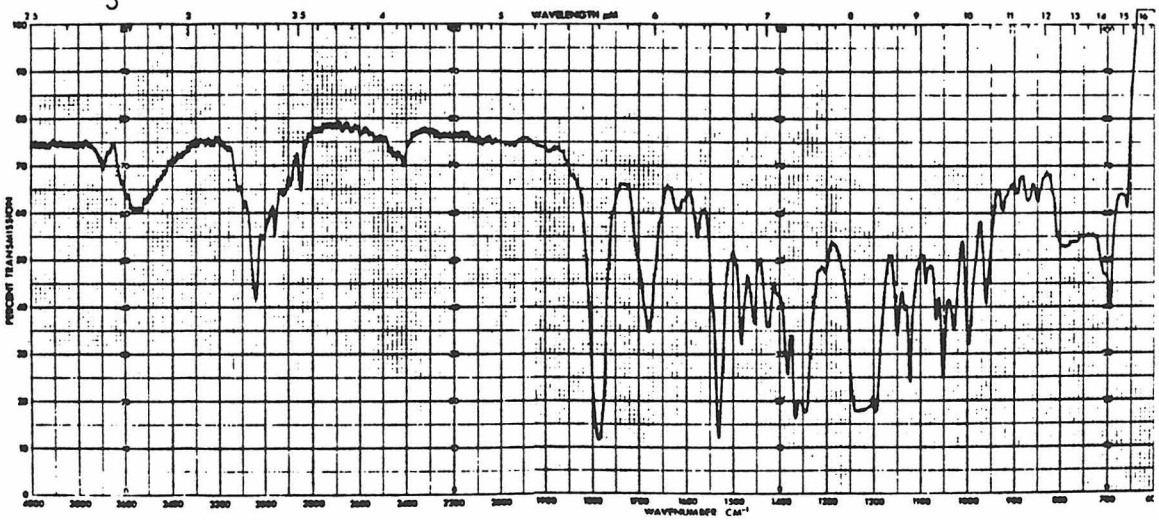

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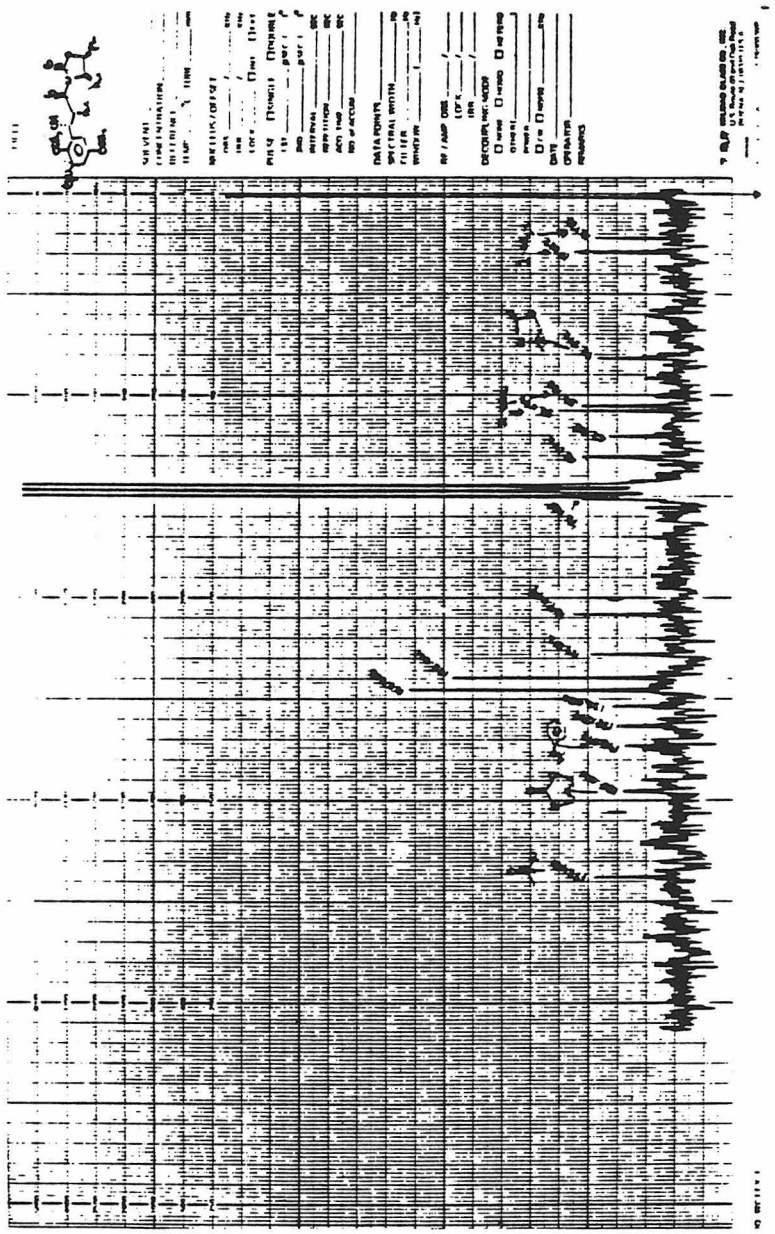
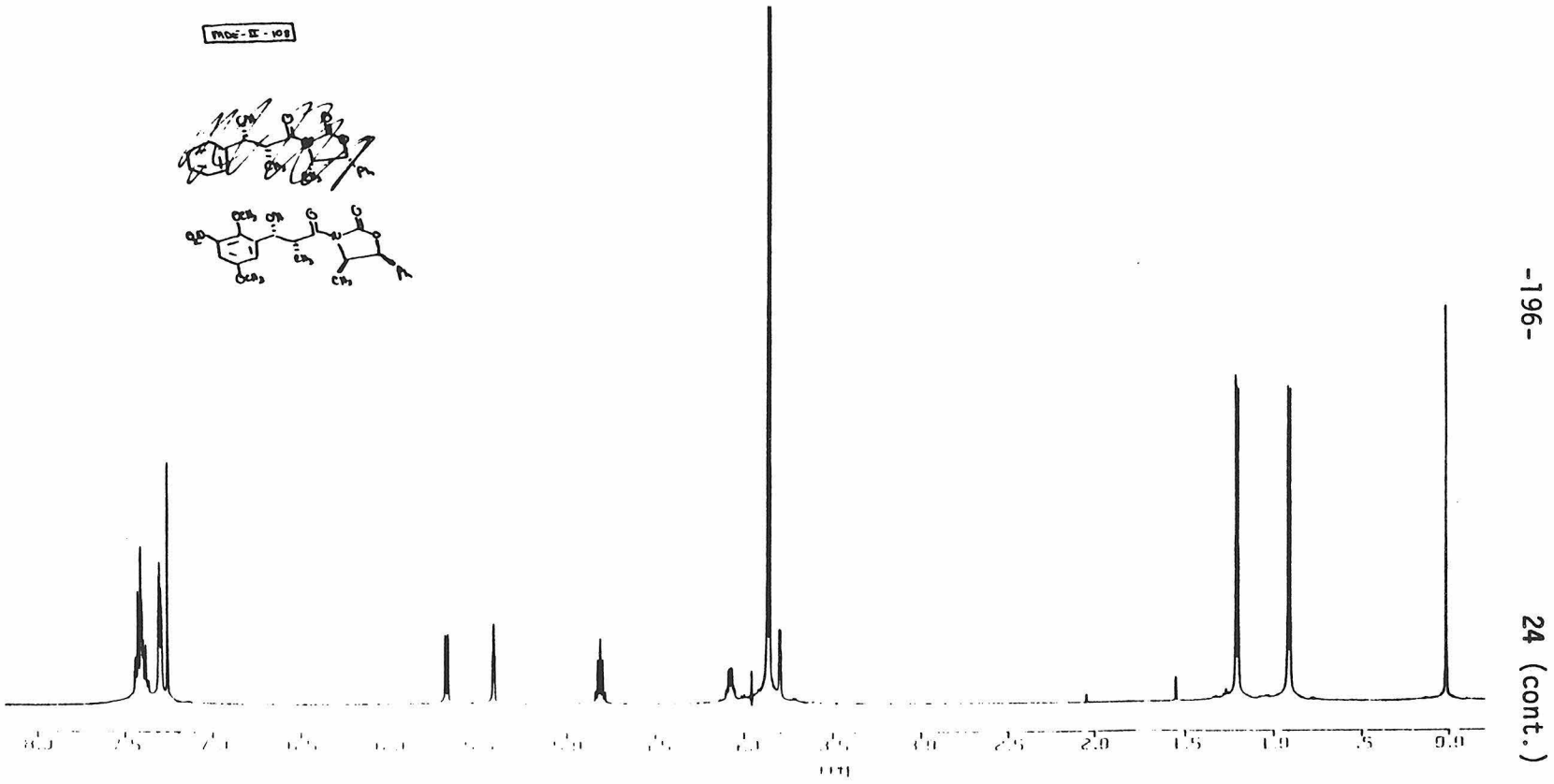


$CDCl_3$

24 (cont.)

$CDCl_3$



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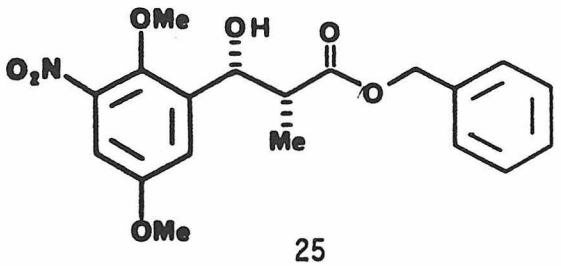

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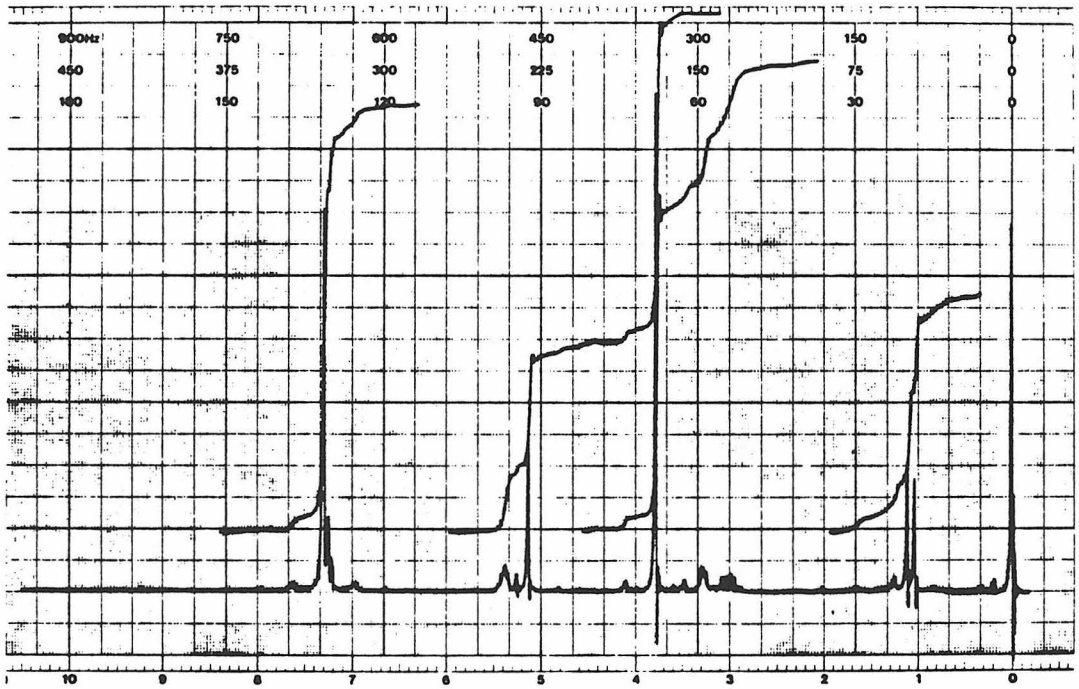

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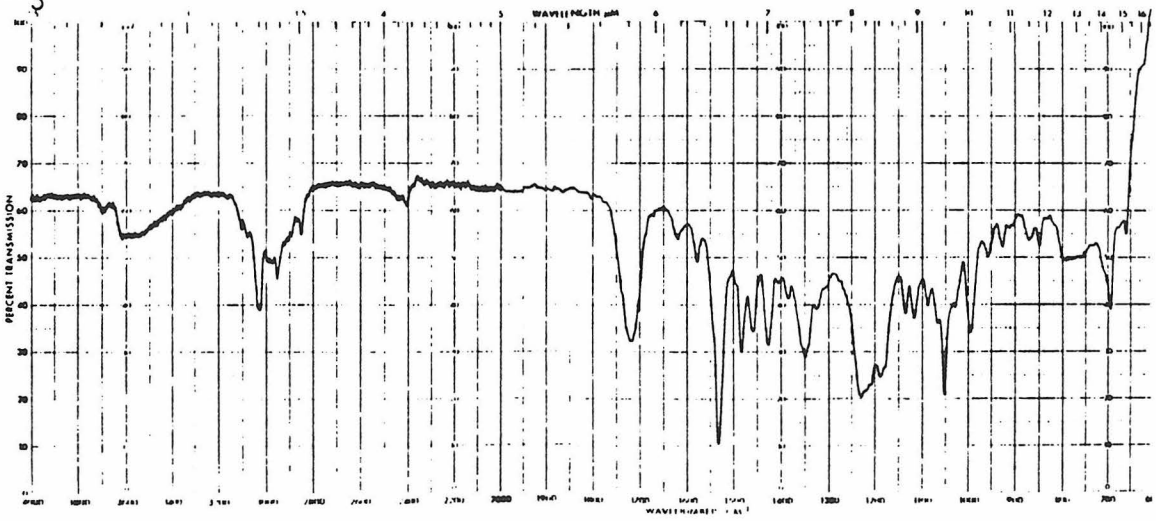

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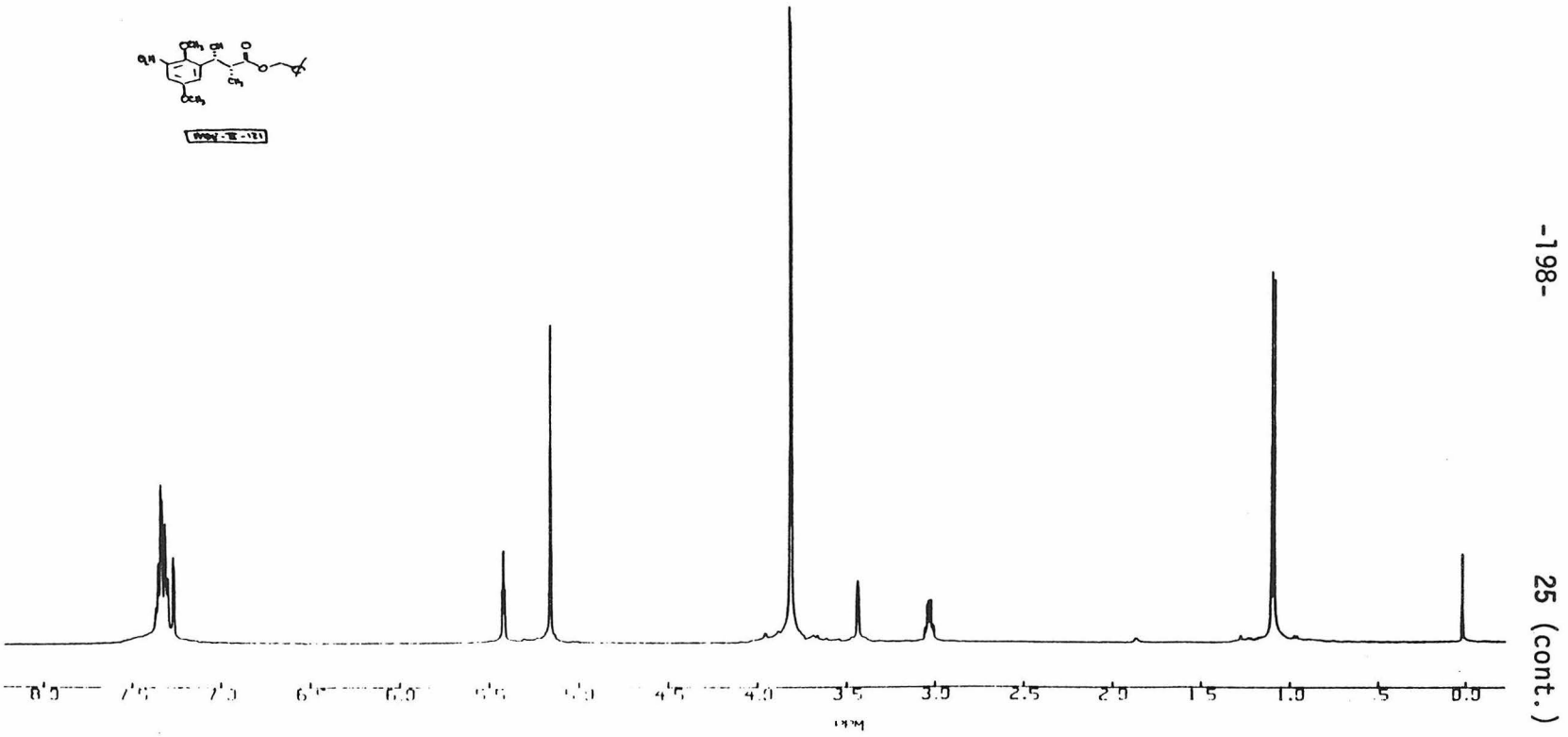

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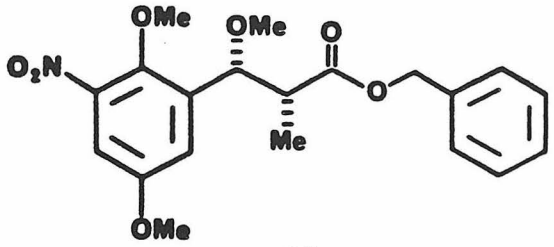

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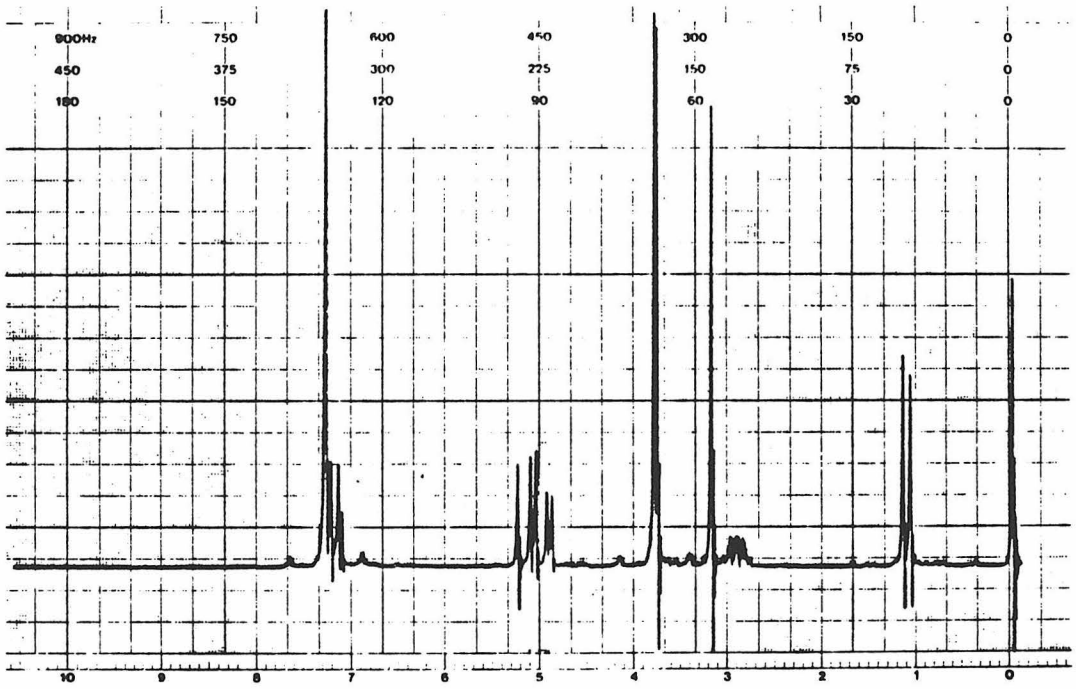

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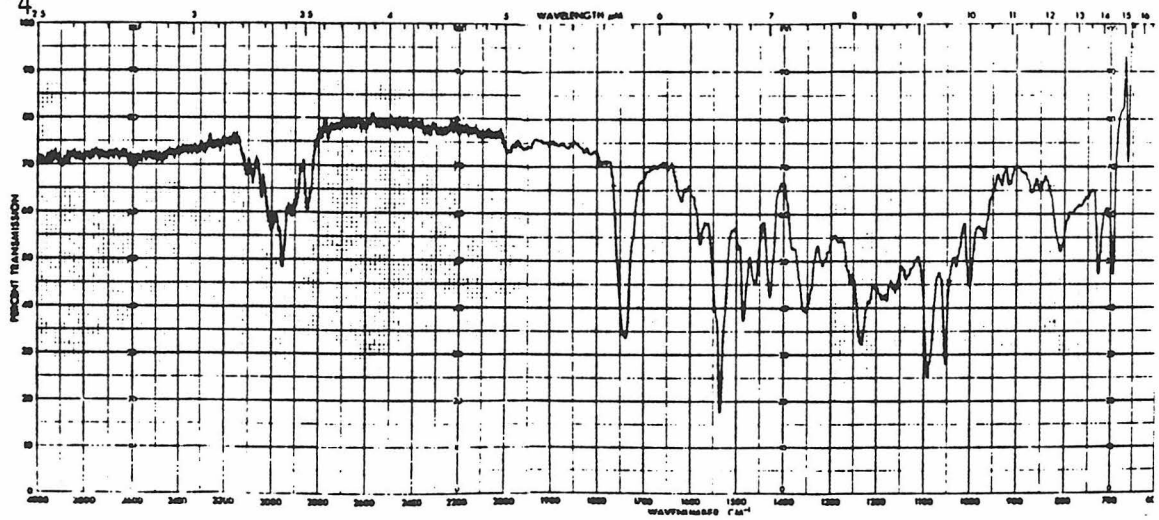

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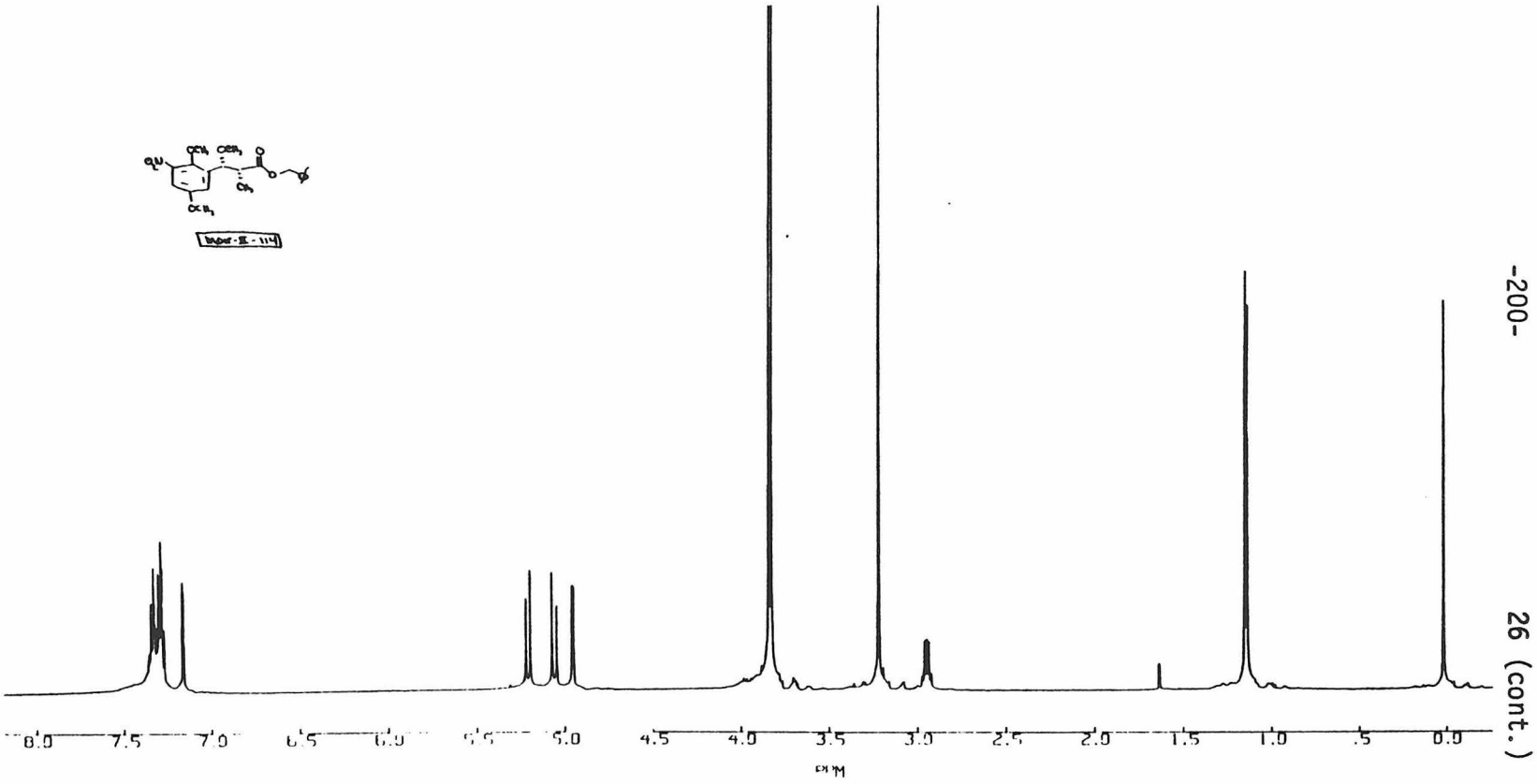

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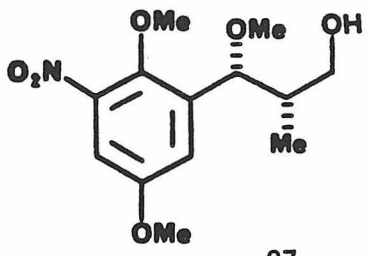

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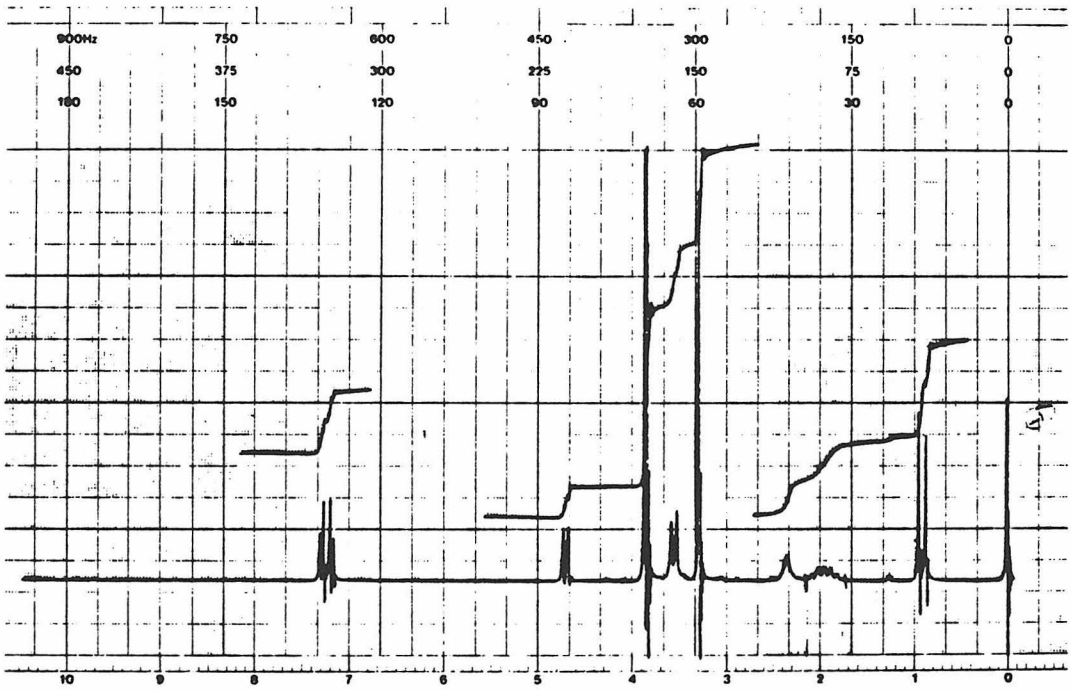

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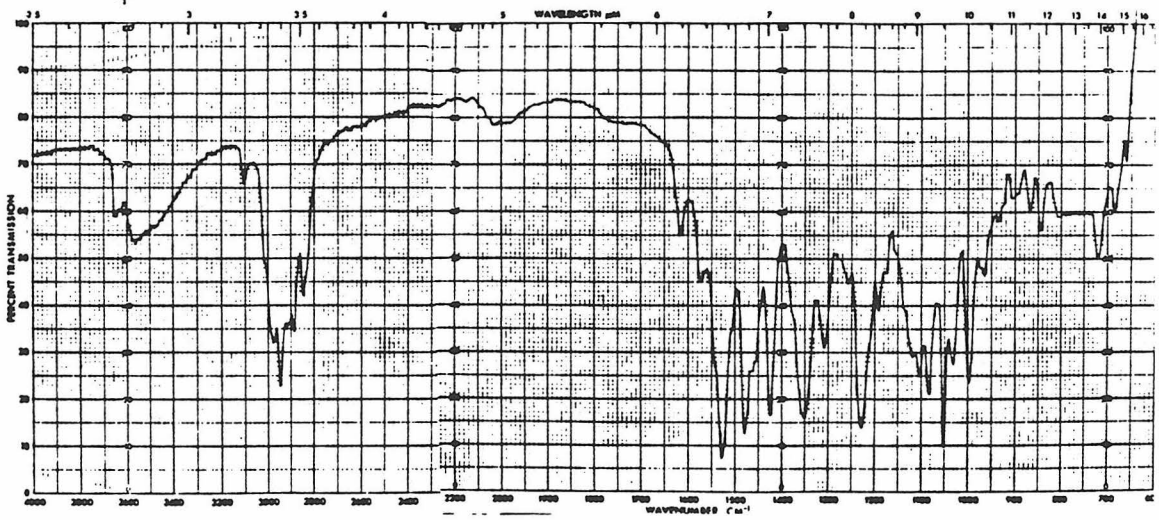

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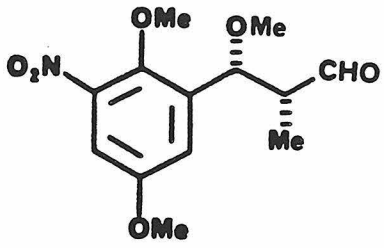

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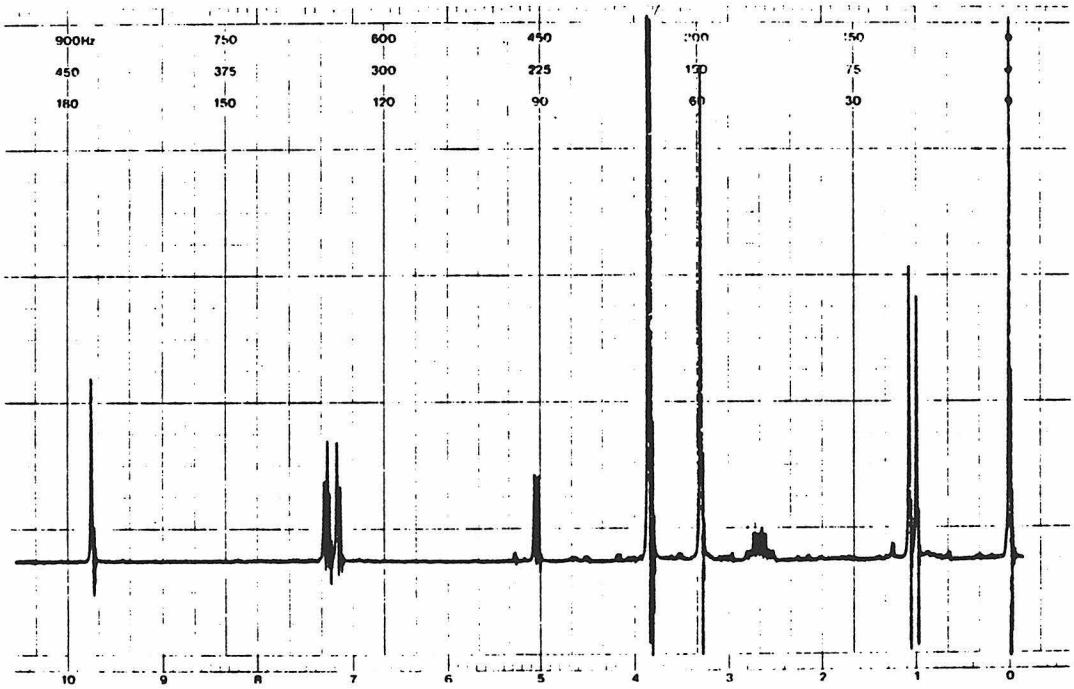

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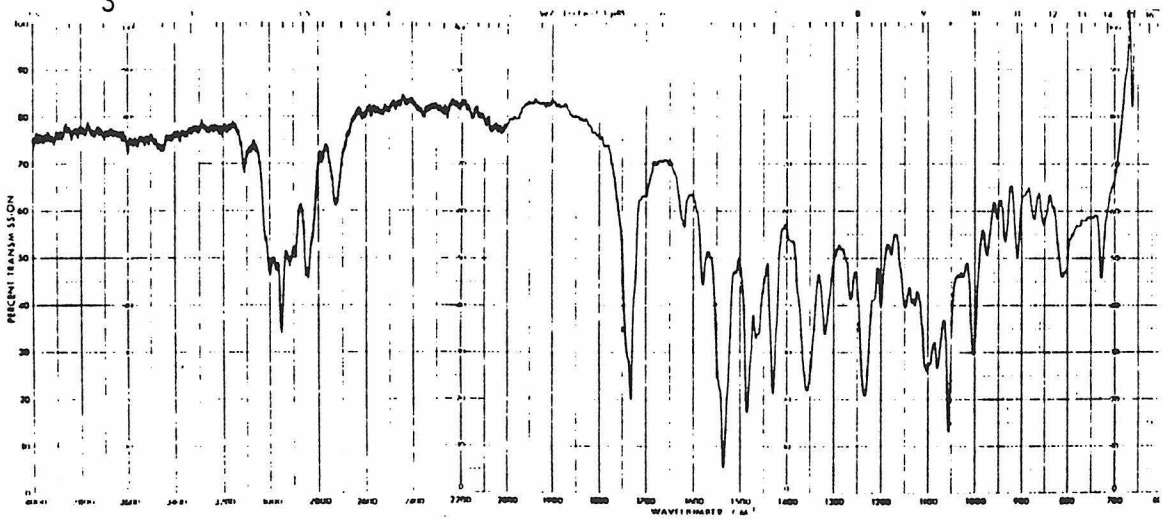

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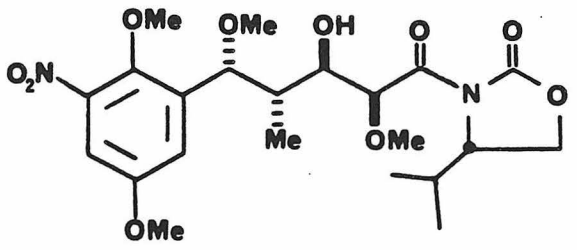

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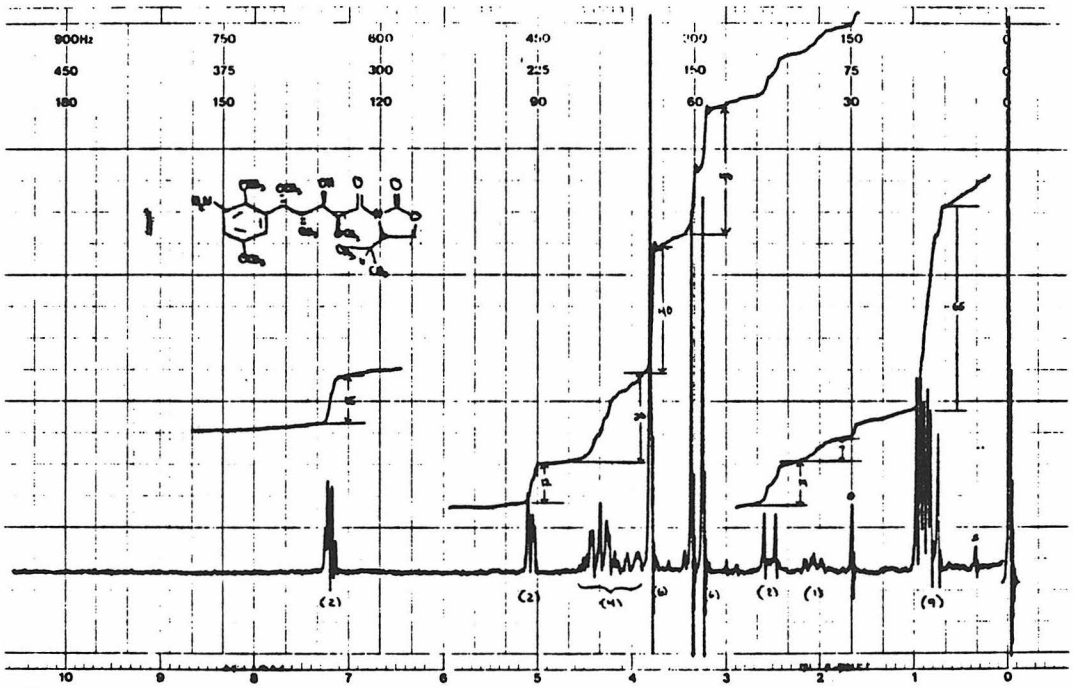

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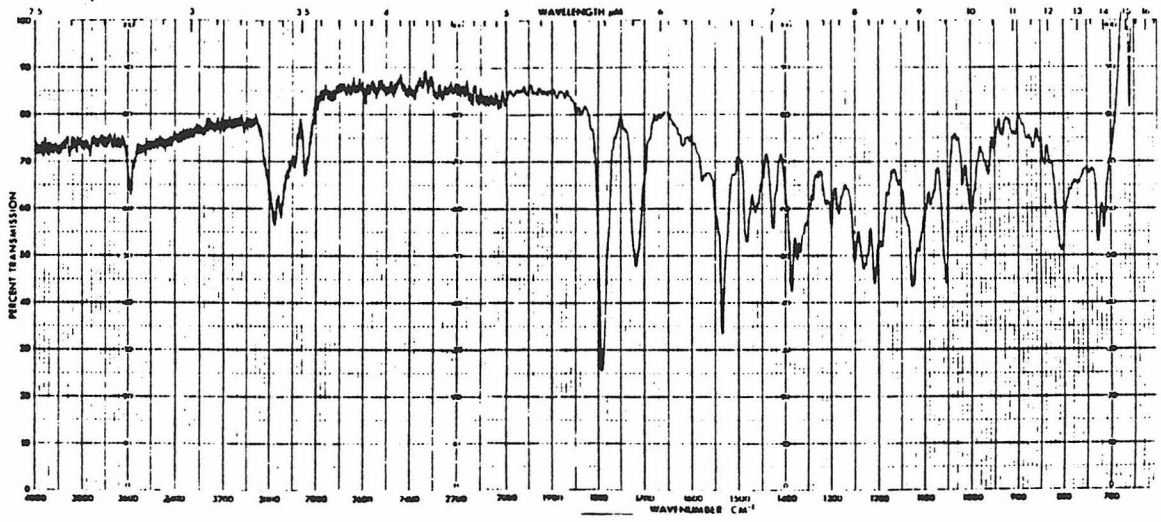

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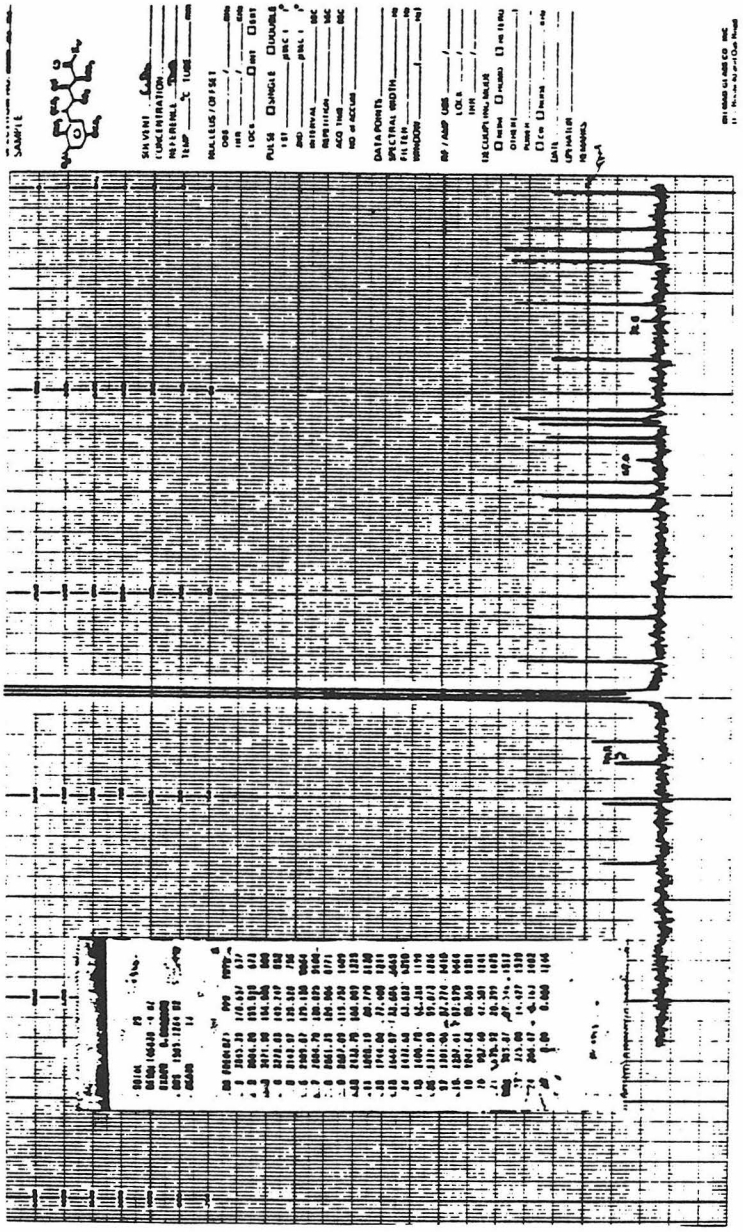
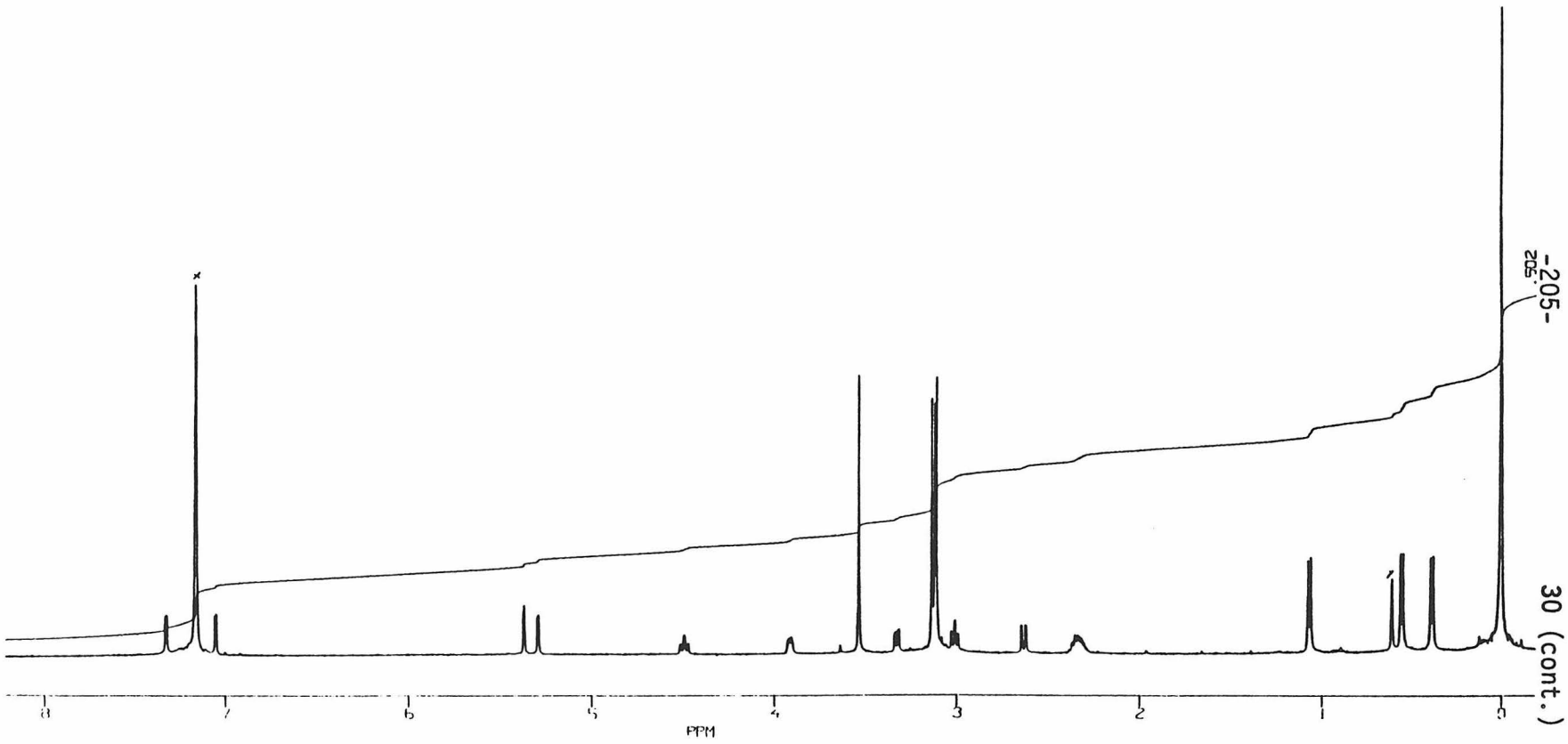


C_6D_6

C_6D_6



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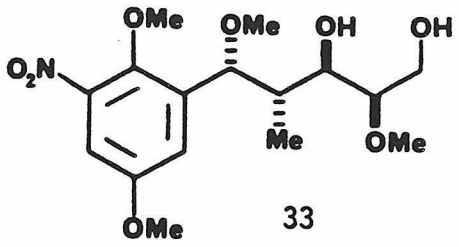

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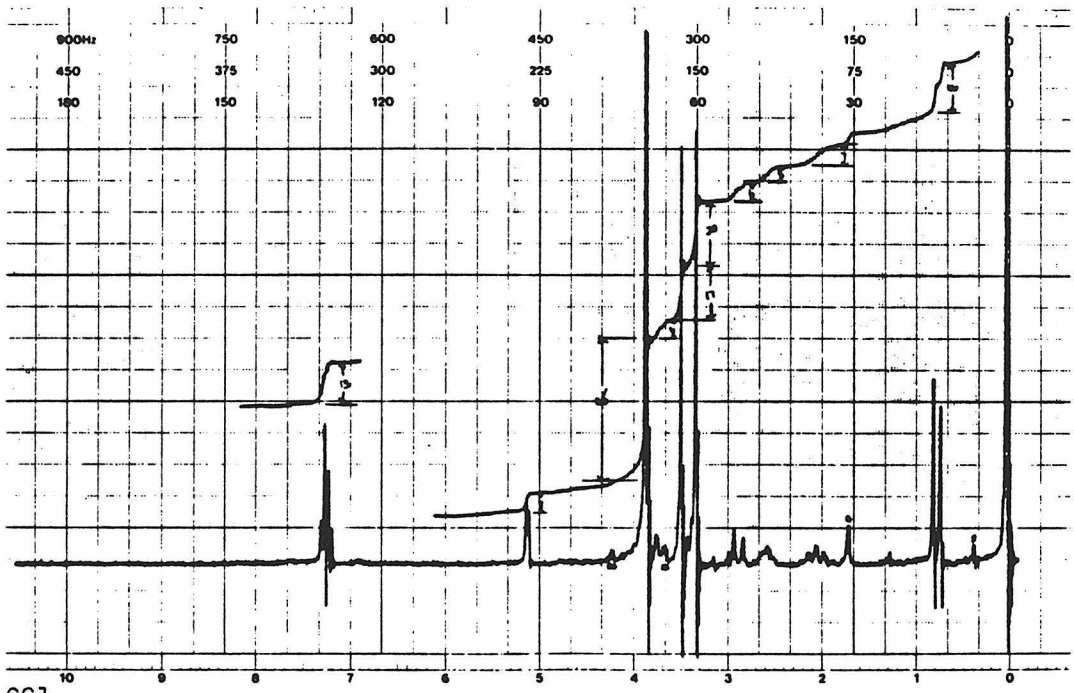

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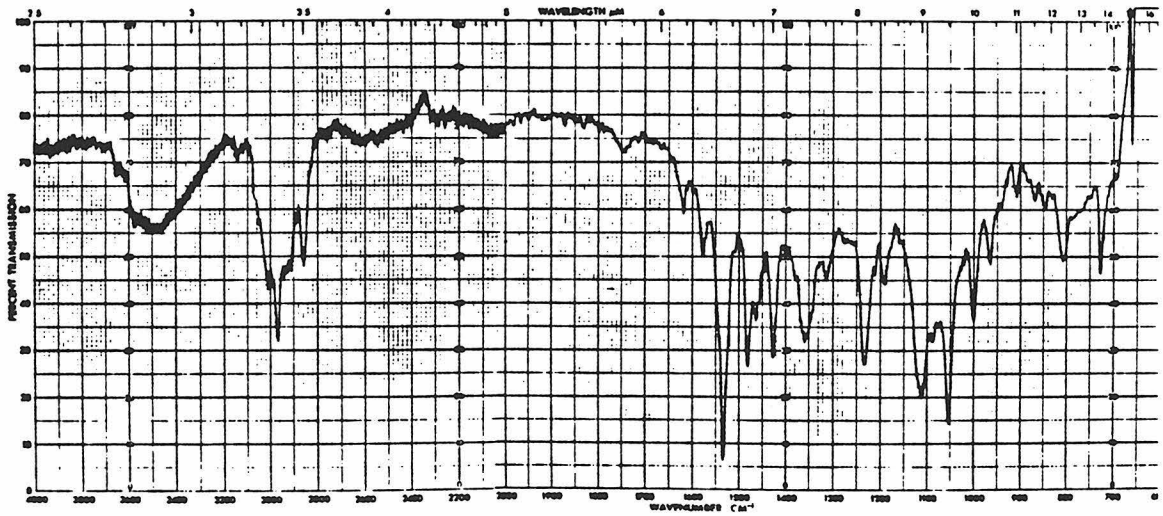

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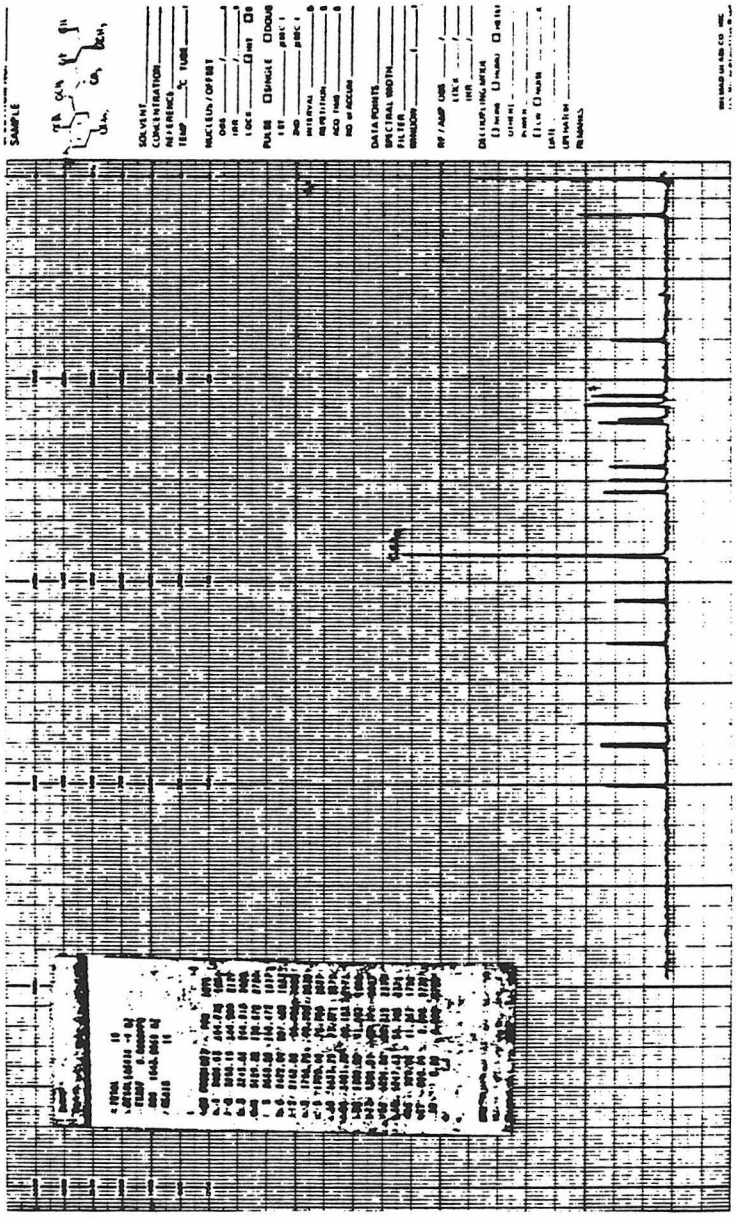

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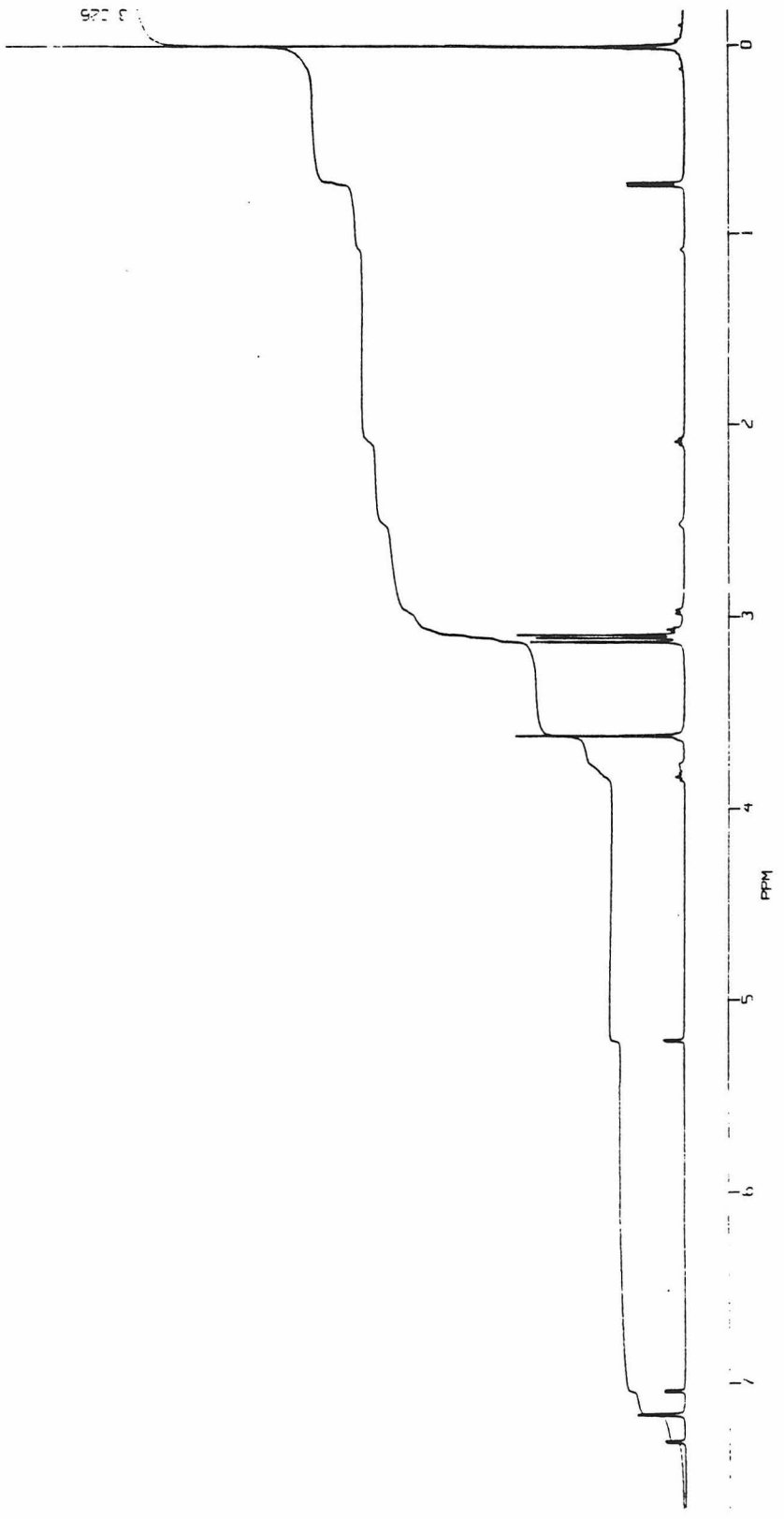

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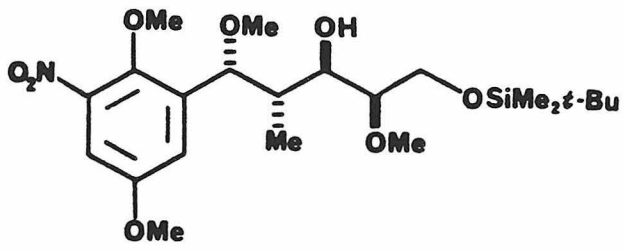

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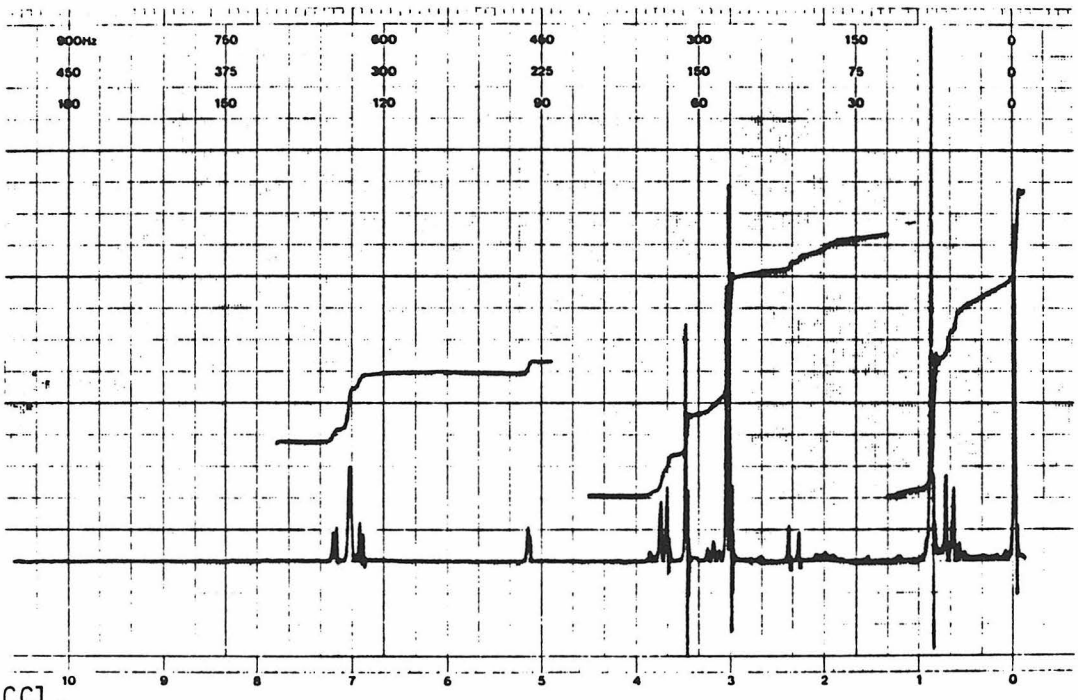

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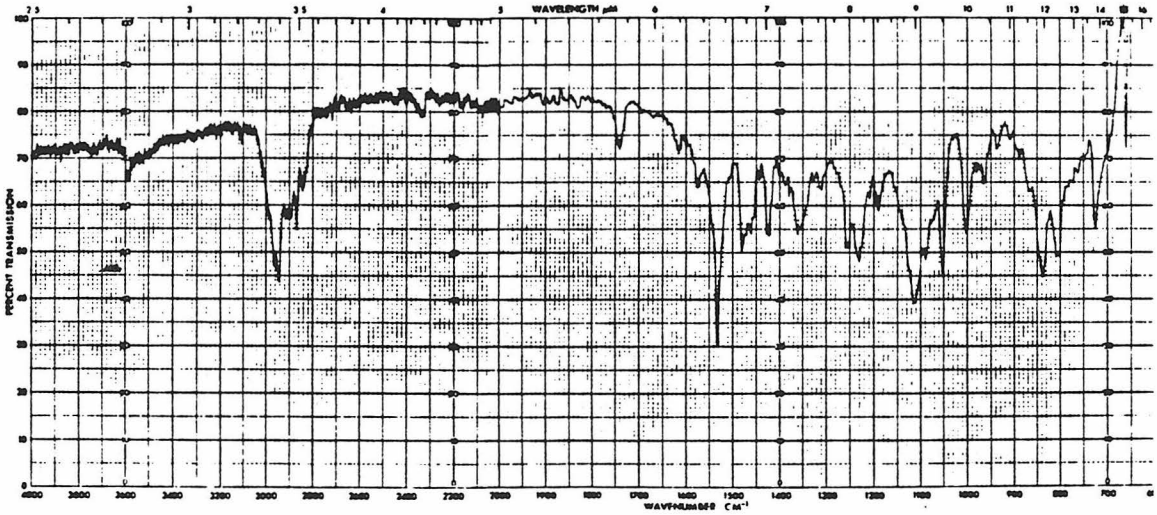

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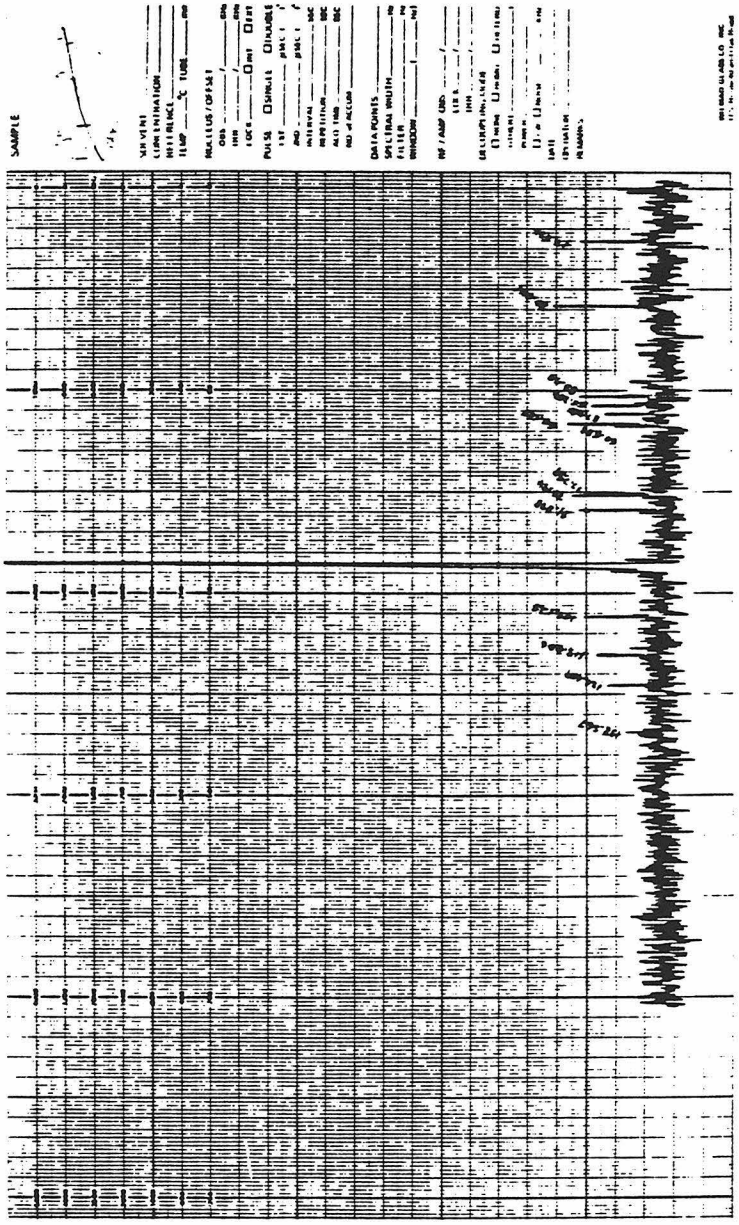

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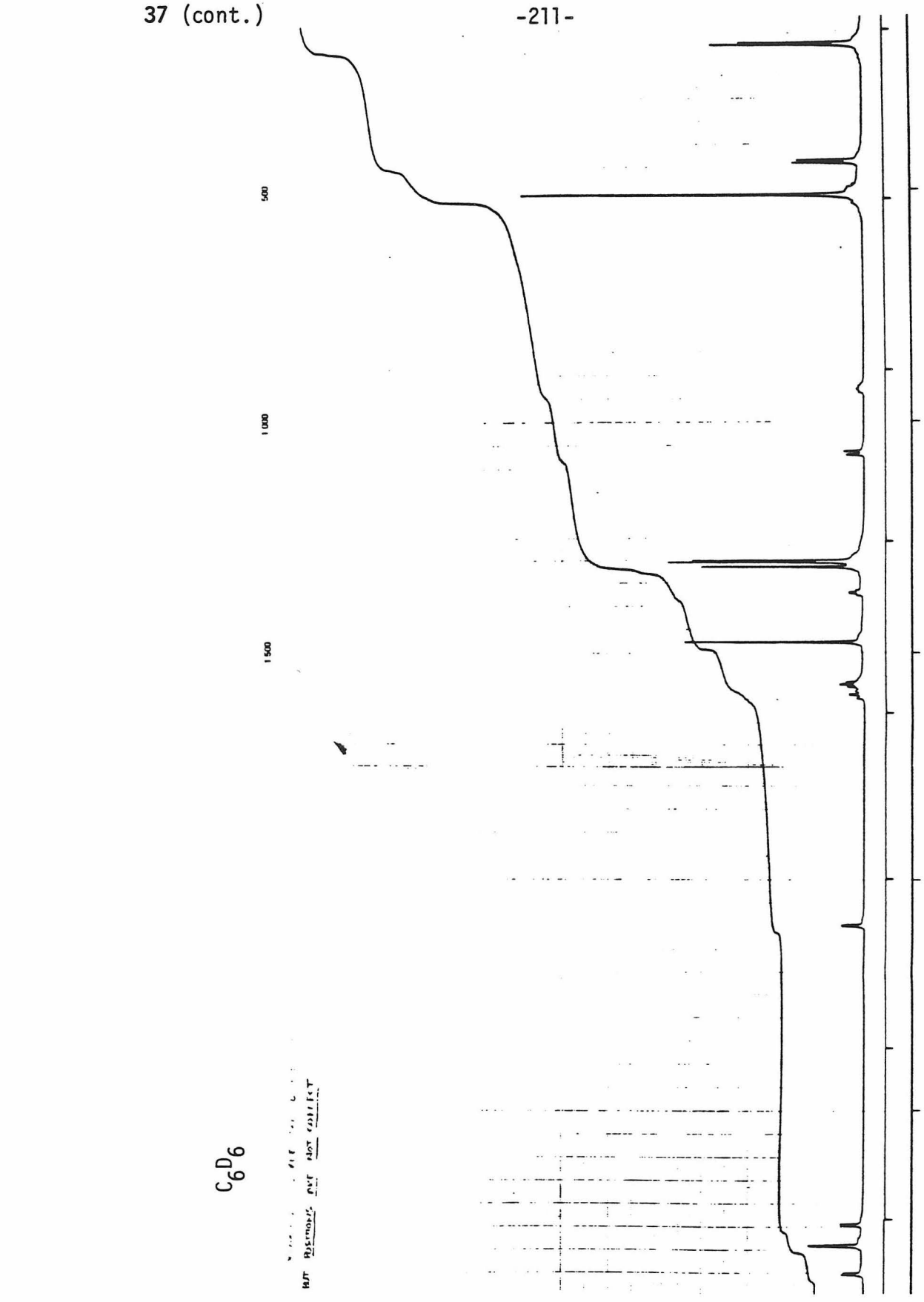

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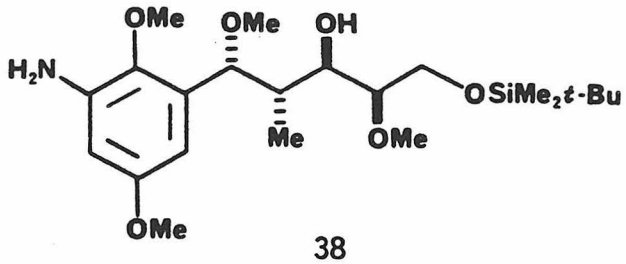

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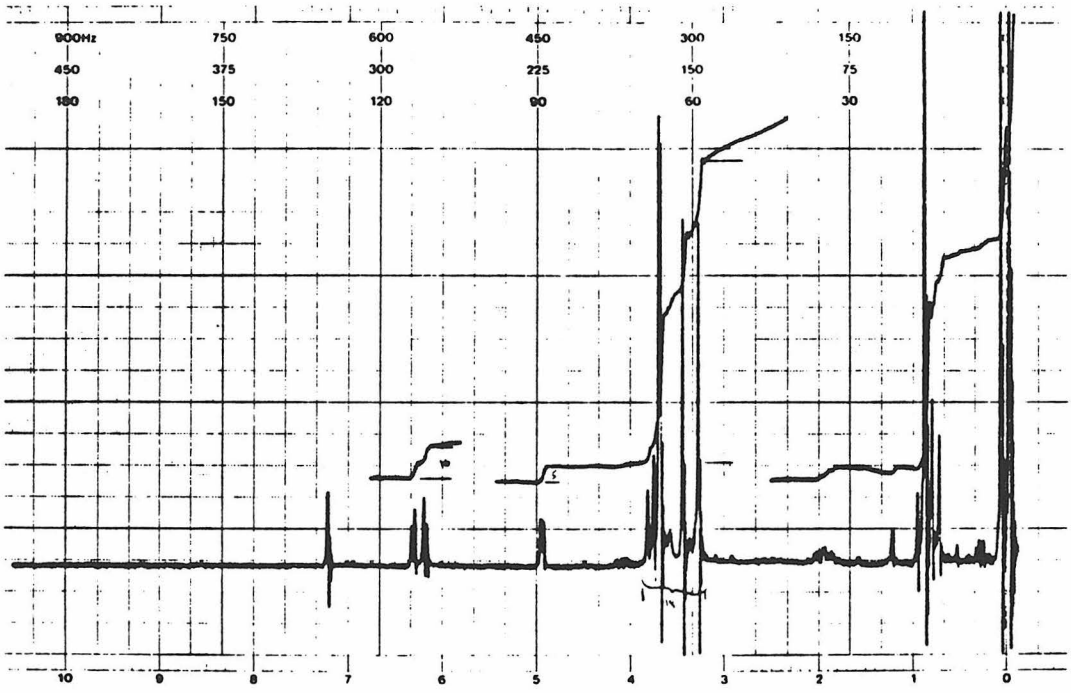

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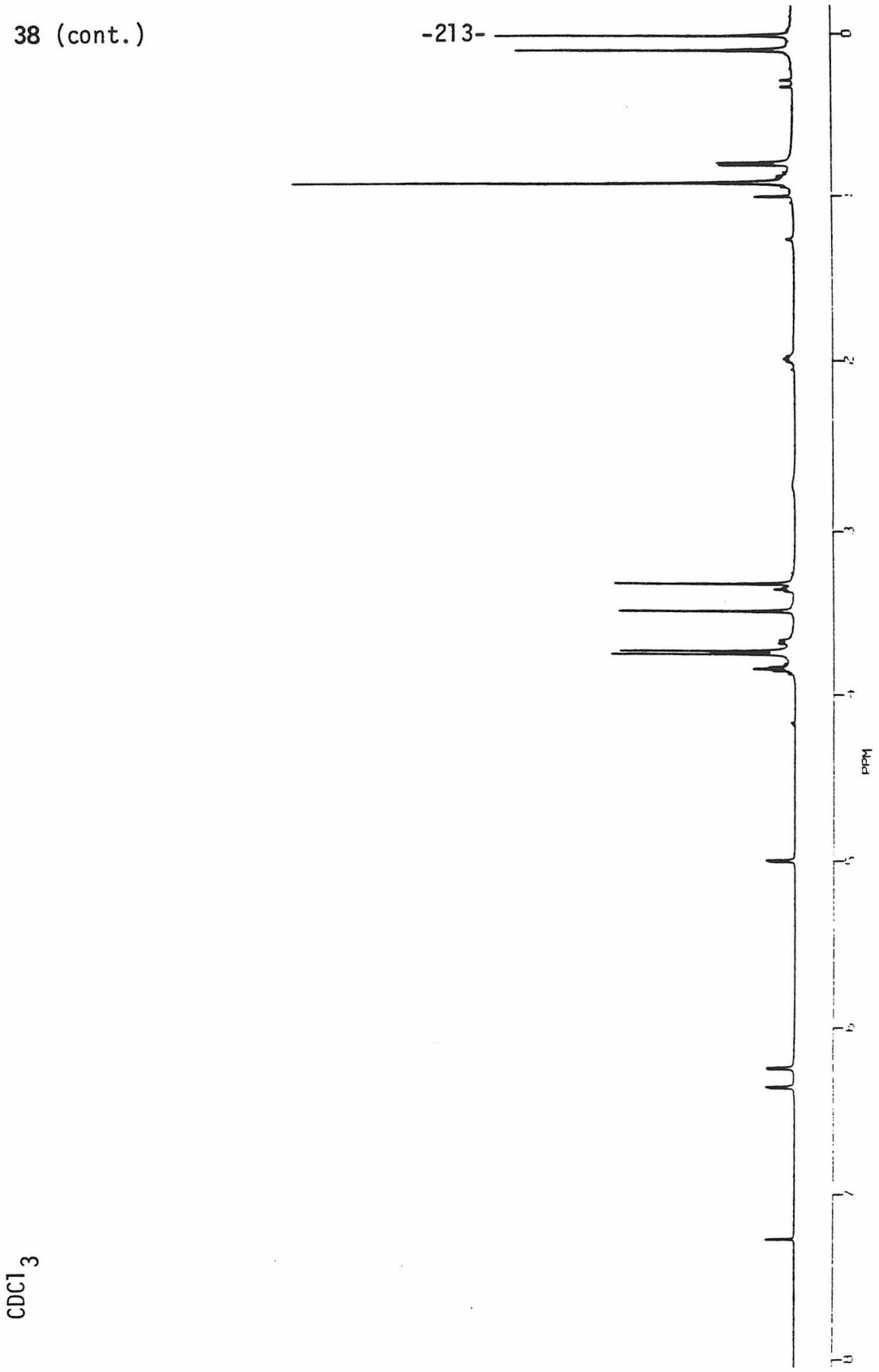

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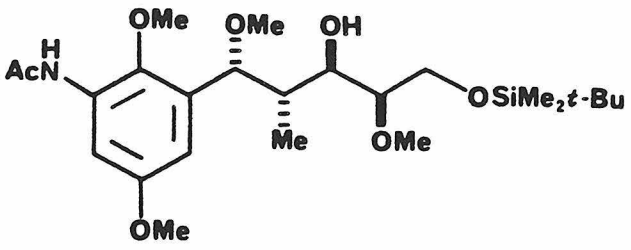

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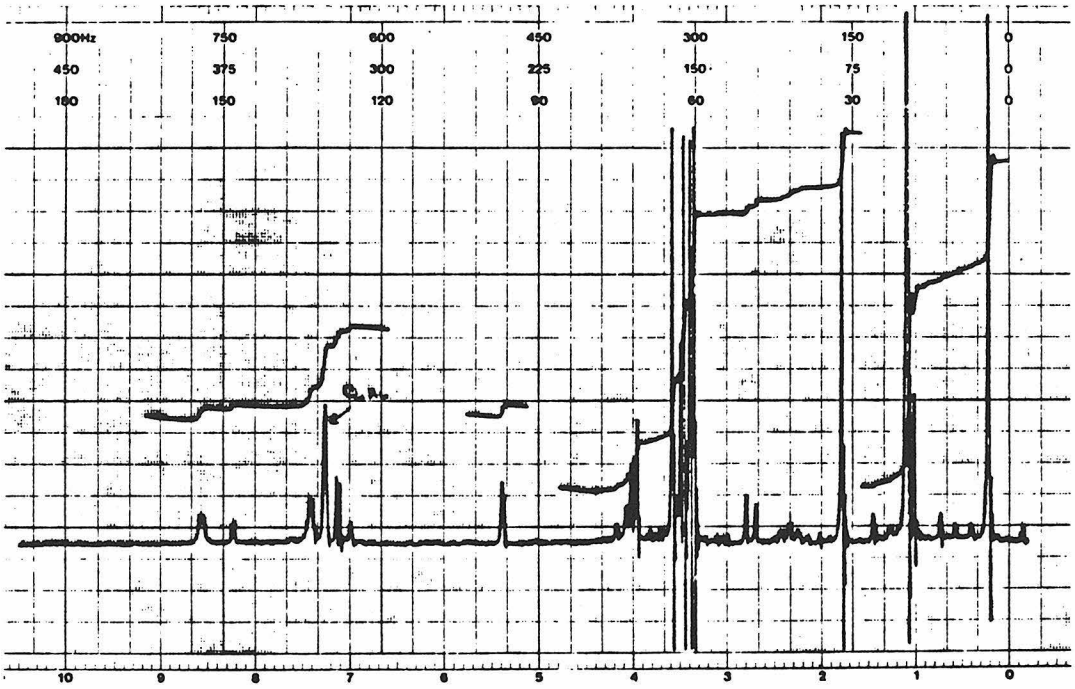

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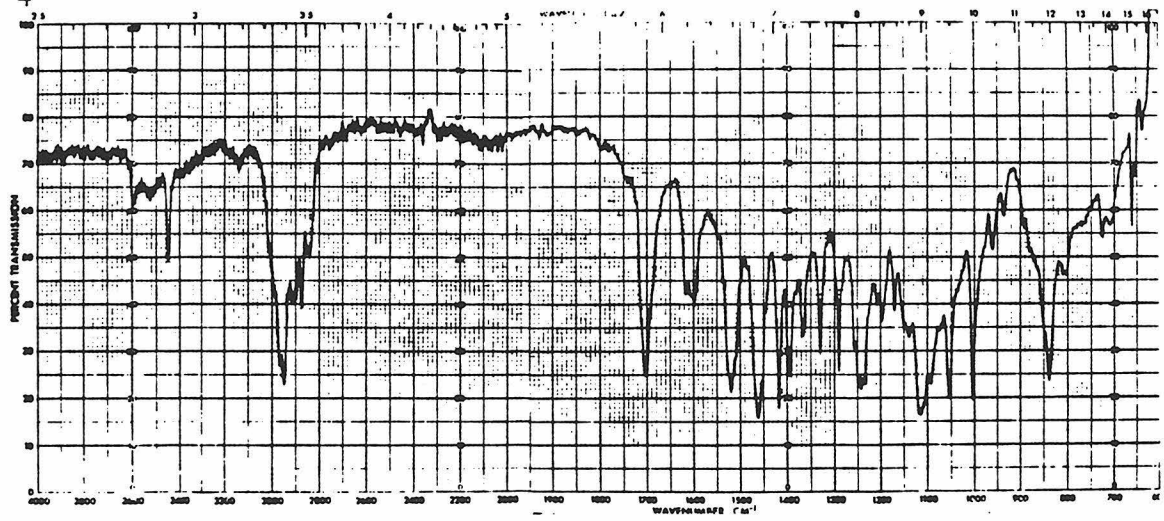

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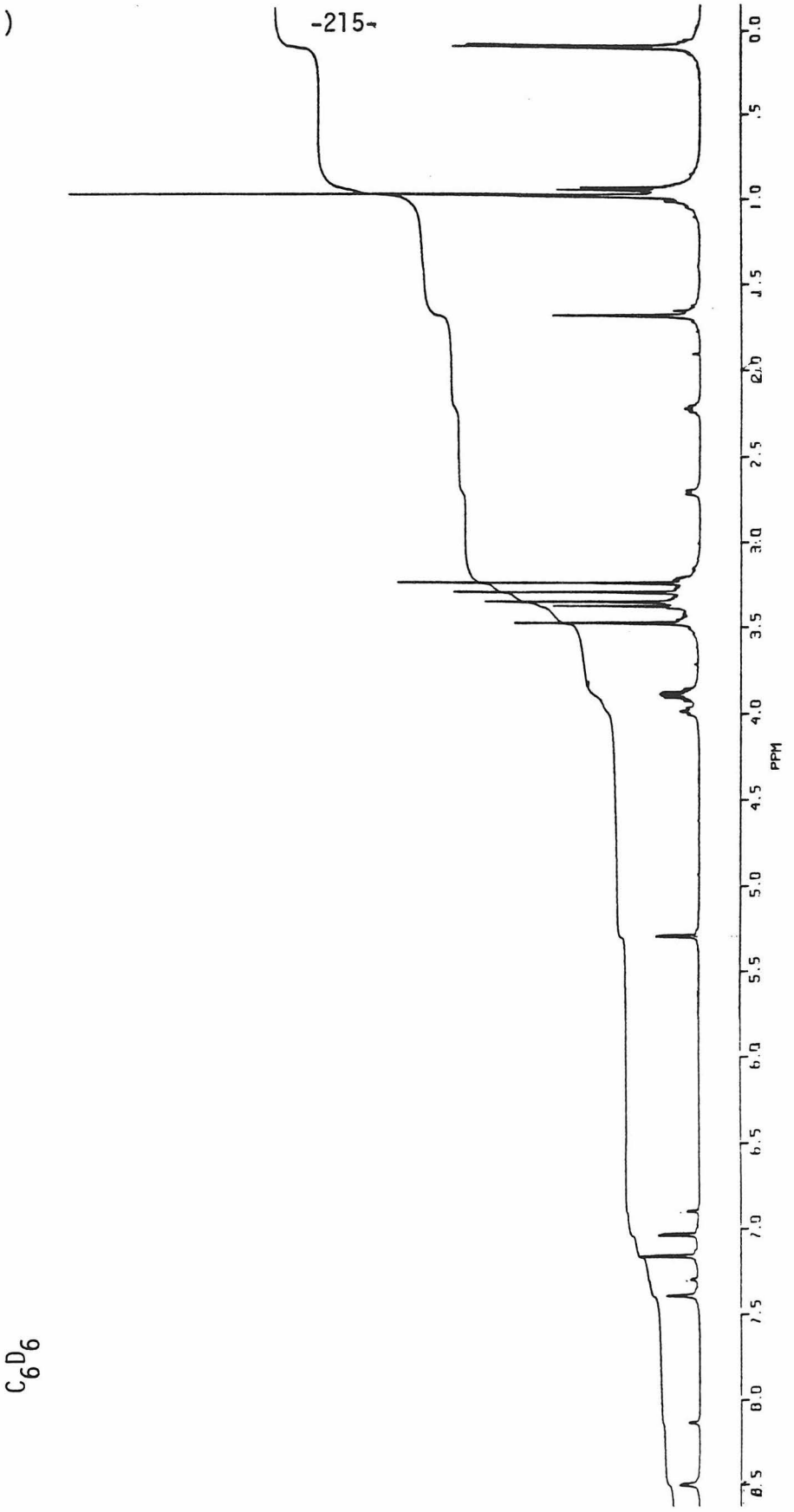

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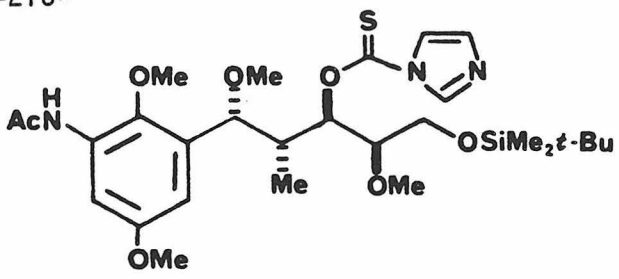

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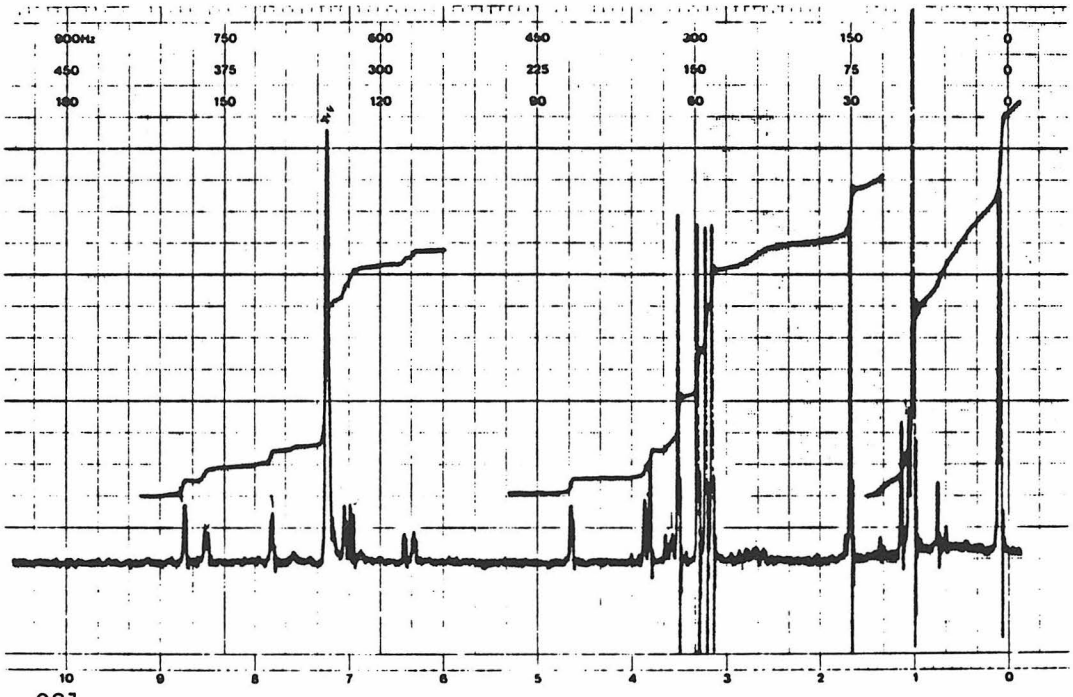

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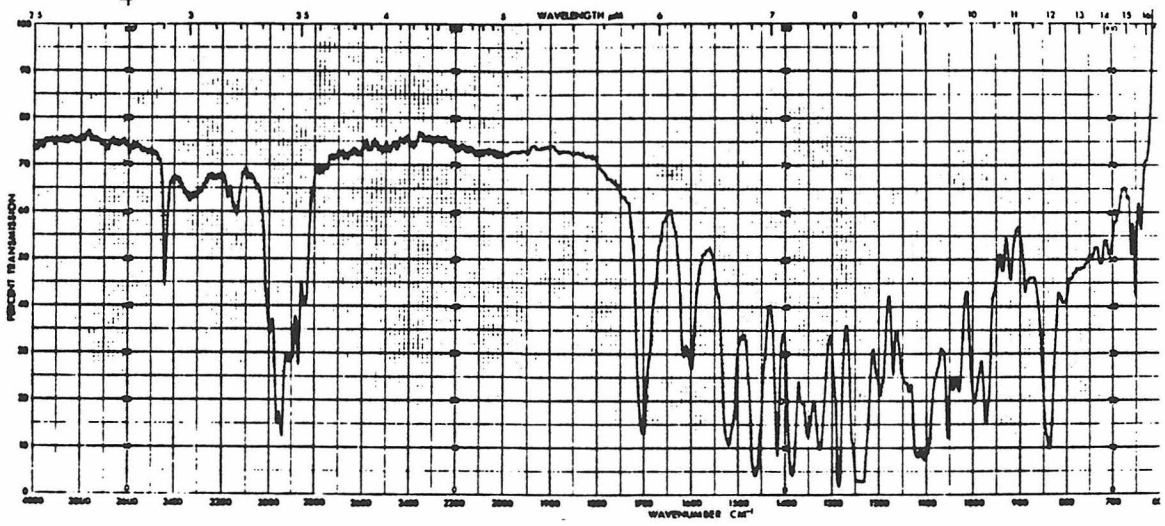

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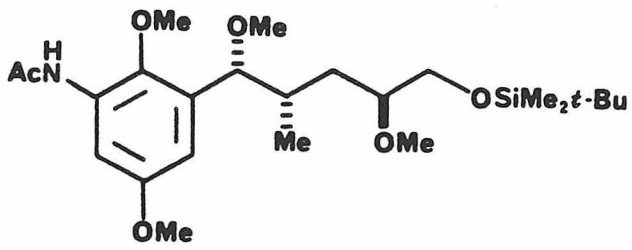

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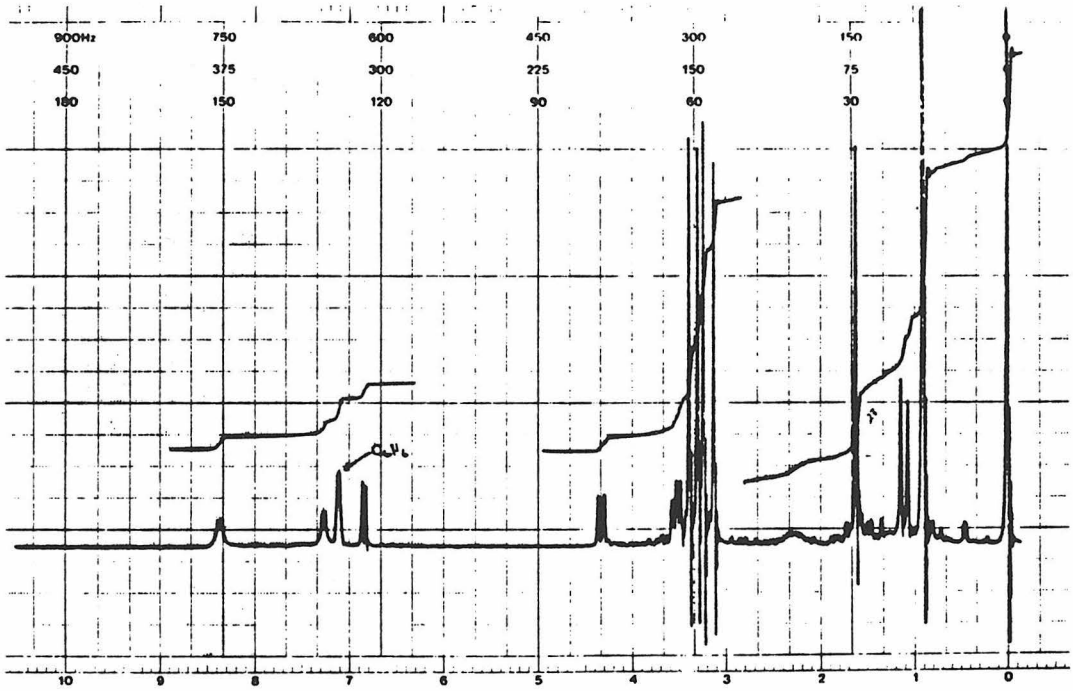

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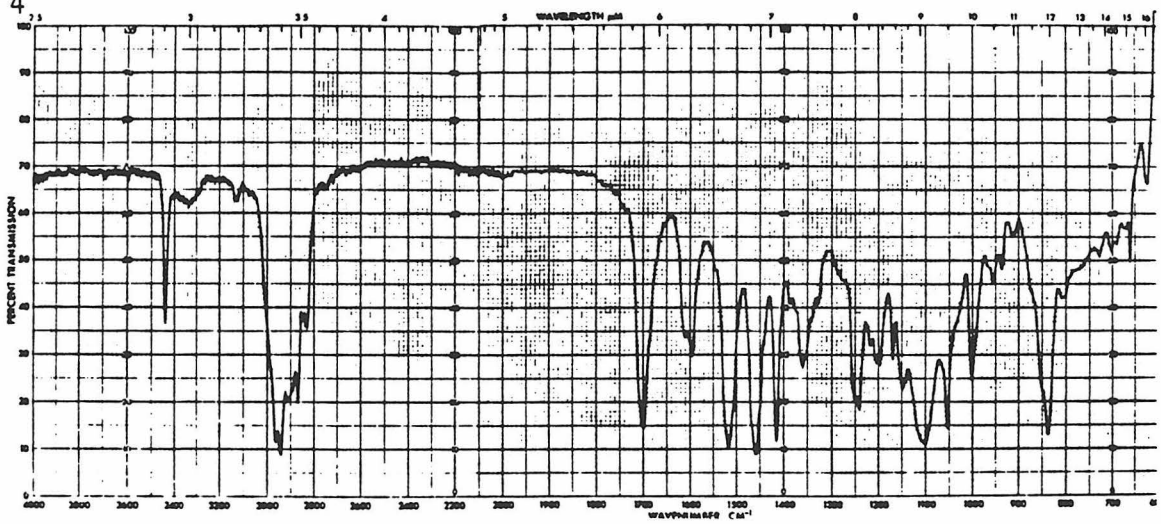

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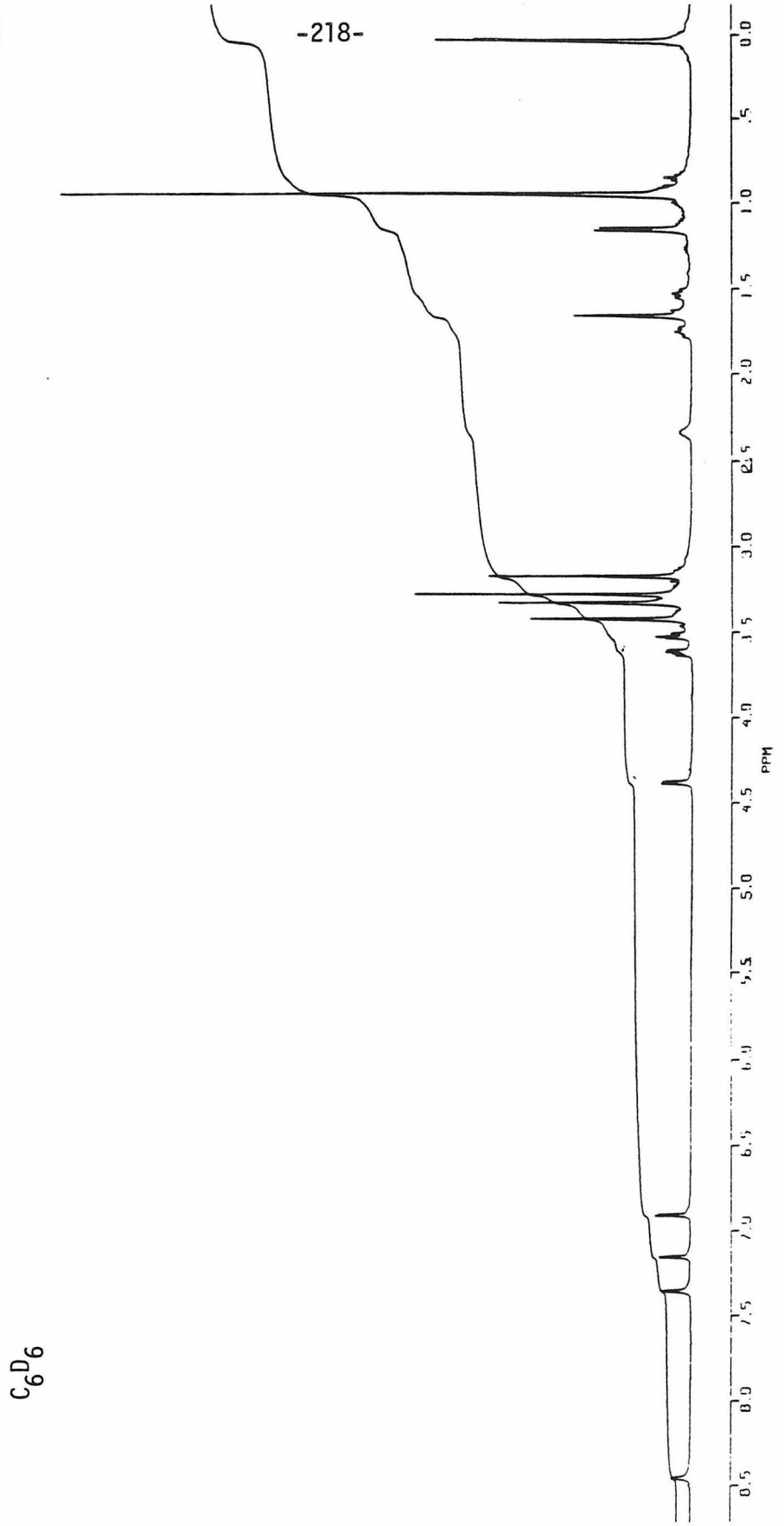

C_6D_6

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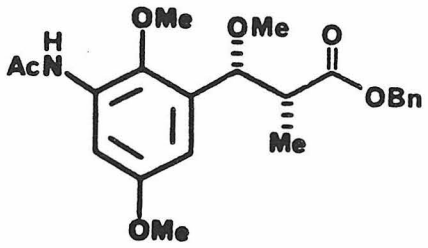

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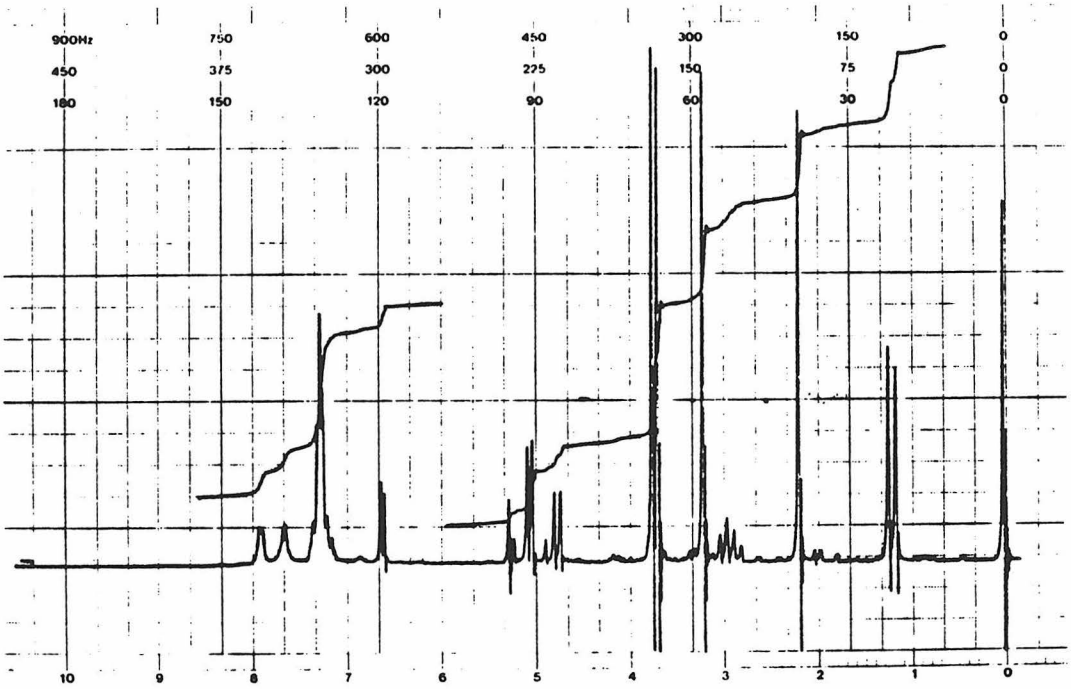

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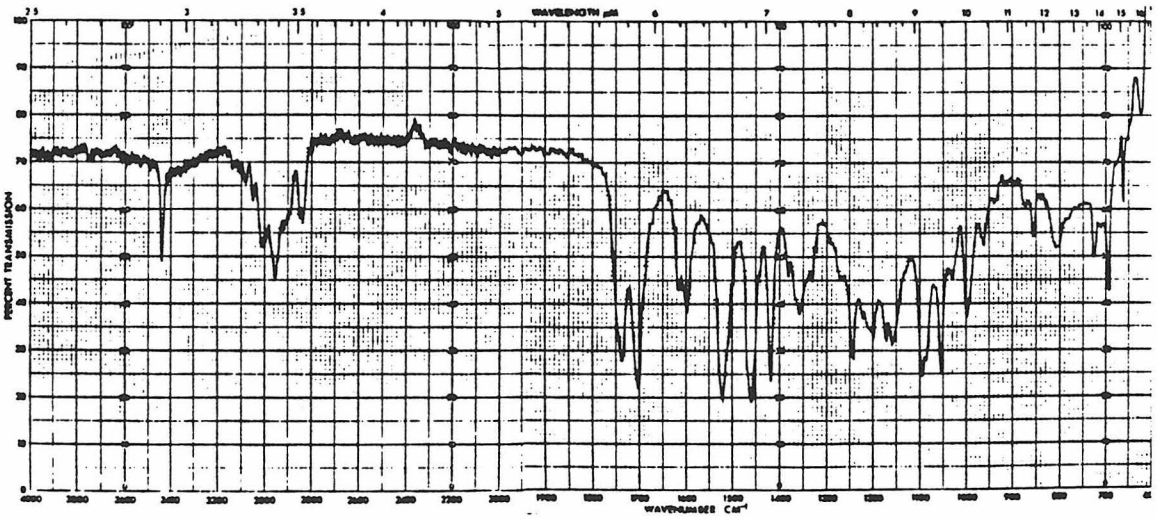

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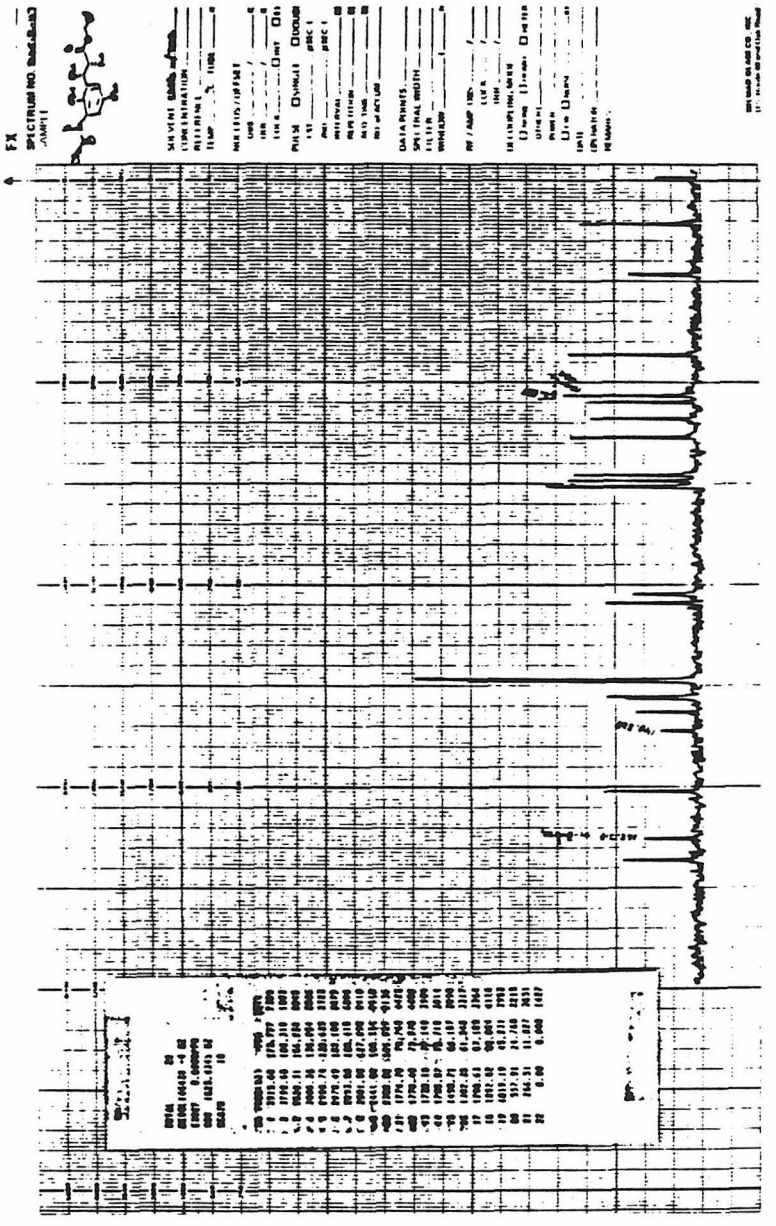

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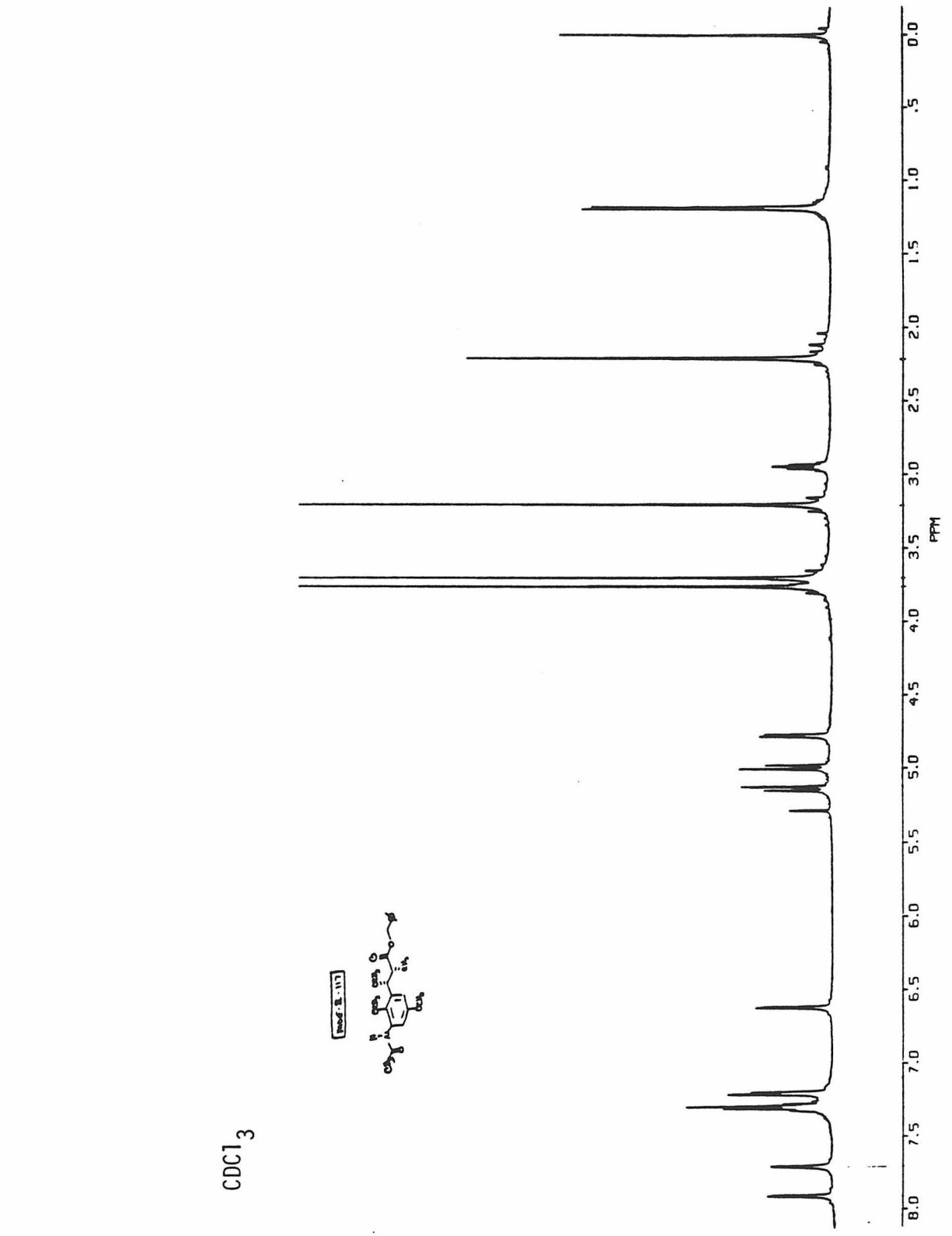

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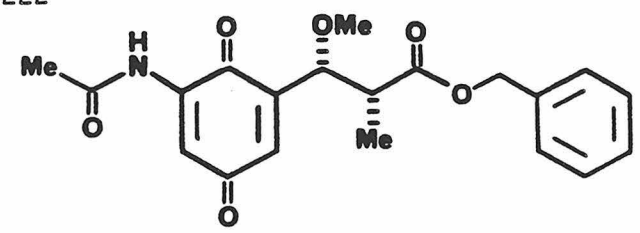

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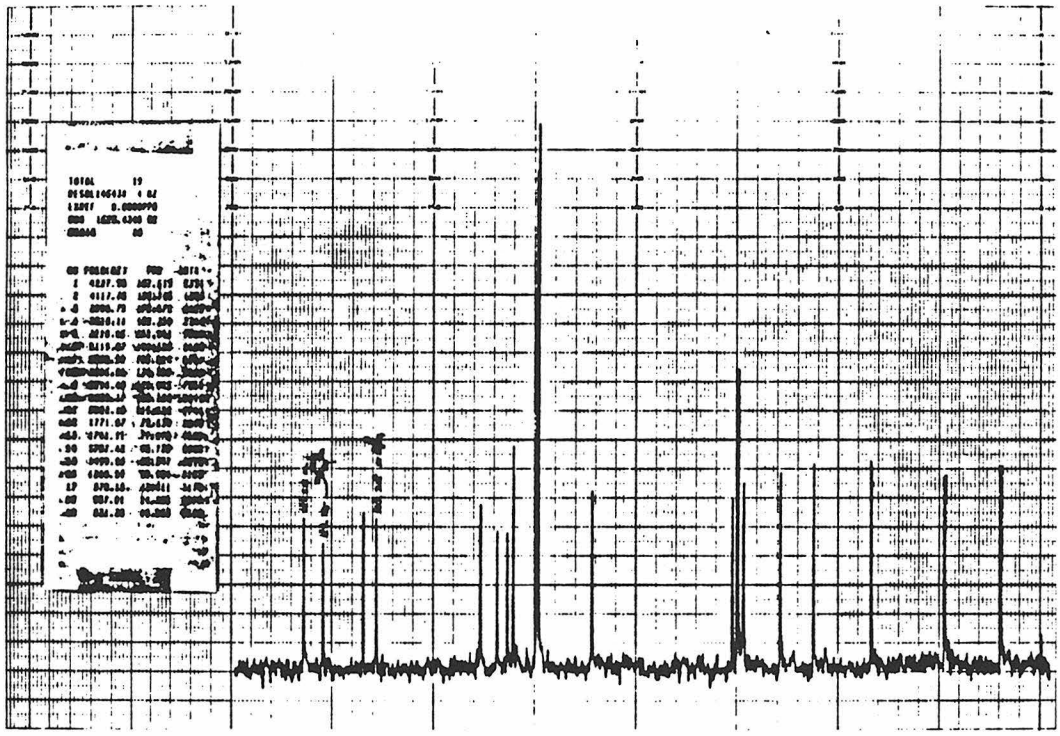

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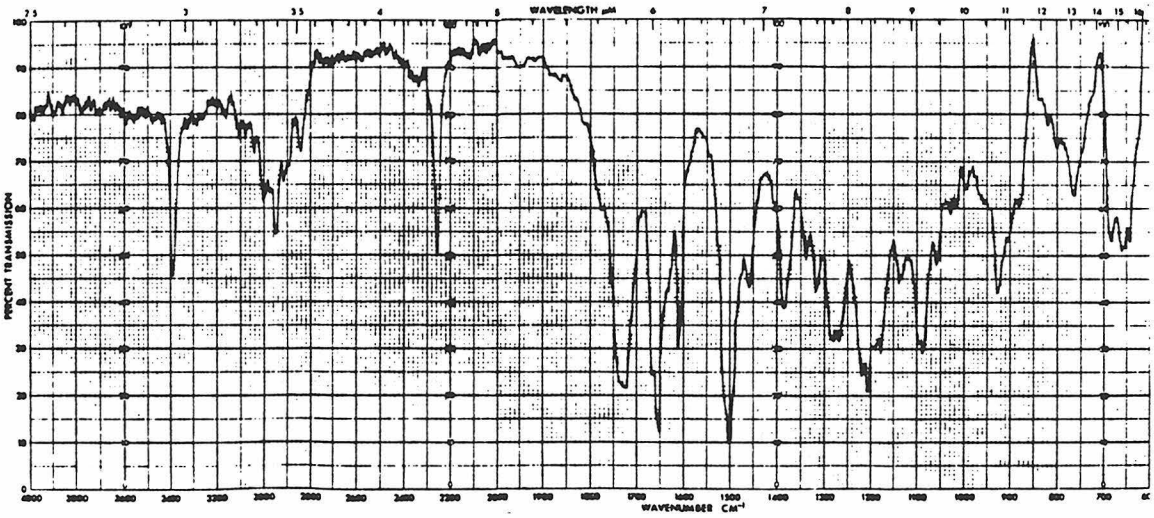
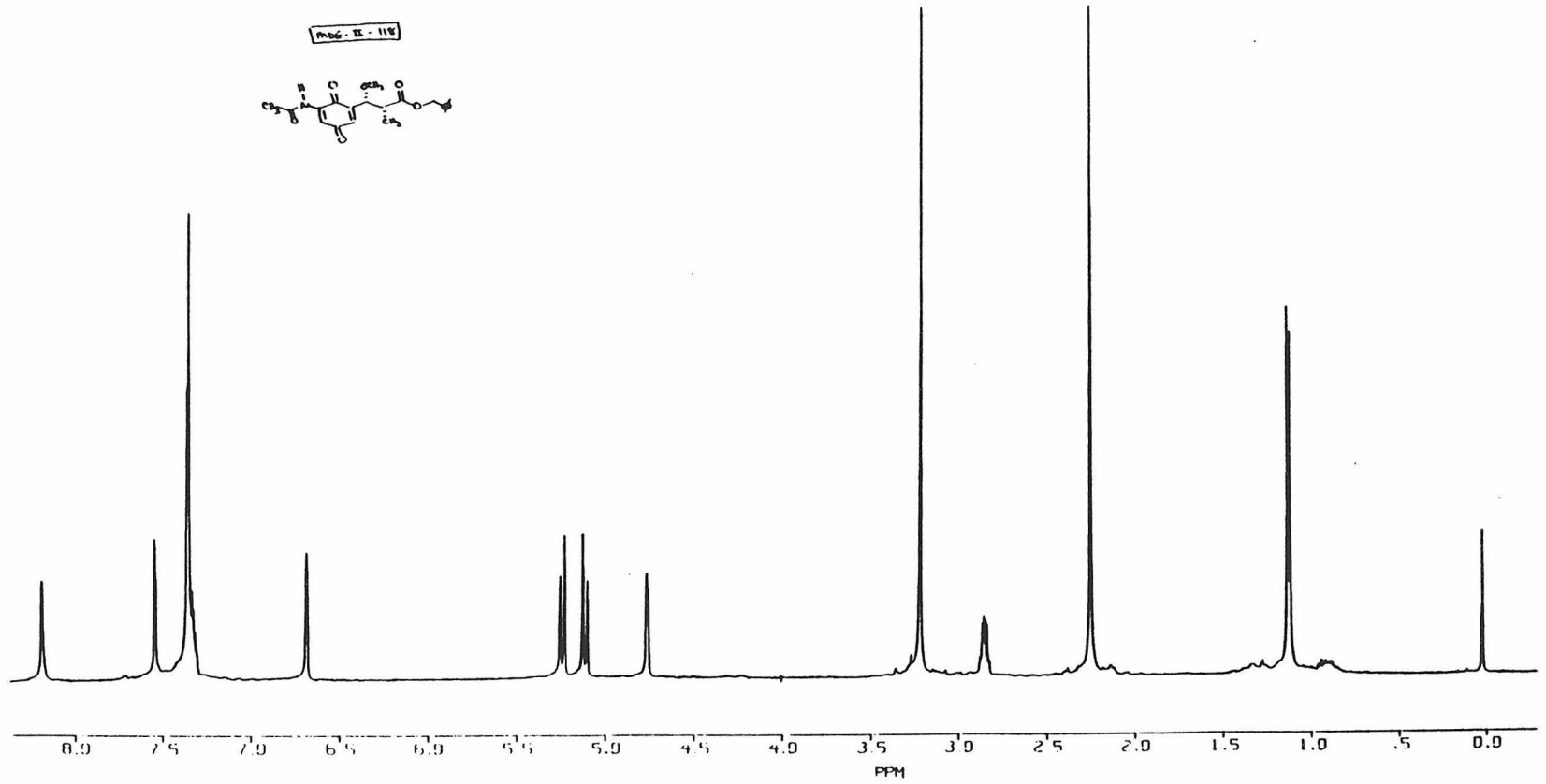


58 (cont.)

CCl_4



PROPOSITIONS

ABSTRACTS

PROPOSITION I: An examination of the catalysis of medium to large ring-forming reactions by cycloamyloses (cyclodextrins) is proposed.

PROPOSITION II: The use of ^{14}N-nuclear quadrupole resonance (NQR) is proposed to study the electron distribution in some organic conductors and semiconductors.

PROPOSITION III: An investigation of the iterative application of intramolecular oxirane ring-opening reactions is proposed. The use of α,β-epoxysilanes to direct the regiochemistry of these reactions is presented. Application to the synthesis of polyether antibiotics and novel heterocyclic structures is discussed.

PROPOSITION IV: The use of spin-saturation transfer in ^{13}C NMR is proposed to obtain kinetic data and thermodynamic parameters for the non-dissociative ligand rearrangement in zerovalent Group VI-B complexes $M(CO)_5PR_3$.

PROPOSITION V: An investigation of hydroxy-directed asymmetric induction in the oxidation of homoallylic alcohols by osmium tetroxide is proposed.

PROPOSITION I

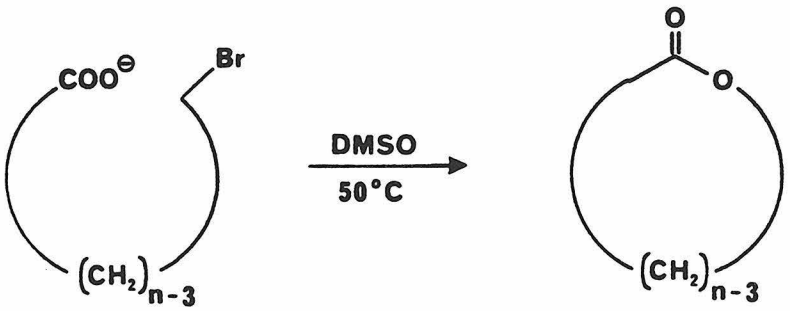
Abstract: An examination of the catalysis of medium to large ring-forming reactions by cycloamyloses (cyclodextrins) is proposed.

* * * * * * * *

The intramolecular reaction of bifunctional molecules to form cyclic structures is a transformation which has received considerable attention. A wide variety of systems have been examined, and studies include the cyclization of ω-bromoalkylamines[1] and ω-chloroalkylsulfides,[2] the lactonization of ω-hydroxy acids[3] and ω-bromoalkanoic acids,[4,5] and the formation of catechol polymethylene ethers from the corresponding ω-bromoalkoxy phenoxides.[5] These studies have helped contribute to an empirical understanding of the factors governing intramolecular reactivity.

By far, the most thorough study of this type is the kinetic analysis reported by Illuminati on the cyclization of a series of homologous ω-bromoalkanoic acids to form the corresponding 3- to 23-membered ring lactones (eq. 1).[5] A rate difference of over 10^6-fold has been found among members of this series, the fastest cyclization occurring for the 5-membered lactone ($k_{rel} = 2.8 \times 10^6$ sec^{-1}) and the slowest rate occurring for the 8-membered ring lactone ($k_{rel} = 1$). A plot of the first-order rate constants for lactonization versus ring size is shown in Figure 1.

The wide range of reactivities exhibited by the series of ω-bromoalkanoic acids toward lactonization has been attributed to both an



(1)

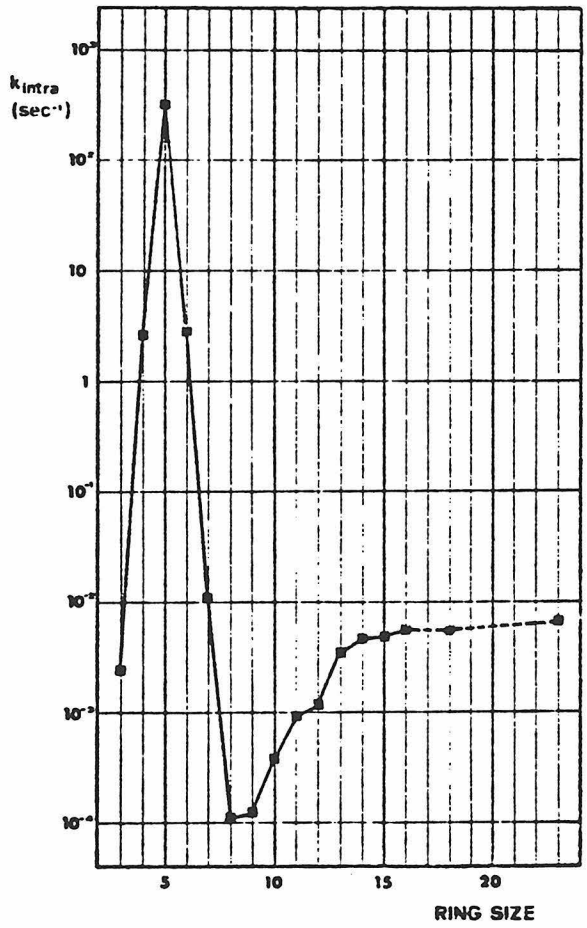


Figure 1. Reactivity plot for the formation of lactones in 99% DMSO at 50°C from the parent ω-bromoalkanote ions (from Ref. 5b).

enthalphy term ($\Delta H^{\dagger}$) associated with ring strain, and an entropy term ($\Delta S^{\dagger}$) associated with the probability of two ends of a linear chain being in proximity to react.[6] For example, a large $\Delta H^{\dagger}$ value is observed for the formation of the highly strained α-lactone ($\Delta H^{\dagger} = 22.0 \pm 0.24$ kcal/mol), which corresponds to a strain energy of ca. 8 kcal/mol.[5b] A similar strain is observed for the formation of the 8-membered ring lactone ($\Delta H^{\dagger} = 21.8 \pm 0.46$ kcal/mol), which appears to be the most strained term in the medium-ring series. The over 20-fold difference in rates between these two cyclizations is therefore a manifestation of the entropic factor. The $\Delta S^{\dagger}$ parameter drops from a value of -2.6 eu for the 3-membered ring to -9.2 eu for the 8-membered ring, and decreases to -23.8 for n = 23. Given in Table 1 are the kinetic data for the formation of 3- to 16-, 18-, and 23-membered lactones by the reaction shown in equation 1. It is interesting to note that a roughly inverse reactivity order for the ring-opening reaction of lactones compared to intramolecular cyclization has been reported.[7]

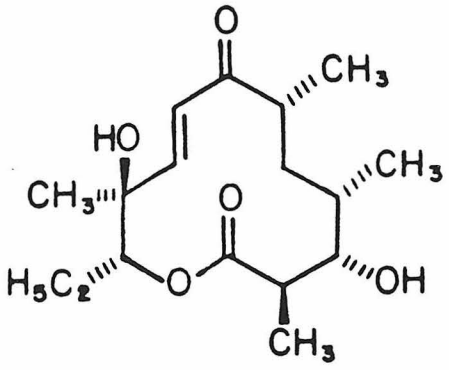
Further interest in the chemistry of medium- to large-ring lactones was generated by the discovery in the 1950's of a number of biological potent antibiotics from the fermentation broth of Streptomyces organisms.[8] These metabolites were shown to be structurally related, and each contains a lactone incorporated into a medium- or large-ring system. Examples of this growing class of compounds, called the macrolides, include methymycin (12-membered ring), erythromycin (14-membered ring), and tylosin (16-membered ring). The structures of these compounds are shown in Figure 2.

With the recognition of compounds such as the macrolides as viable synthetic targets, the need for acceptable methodology for the construction

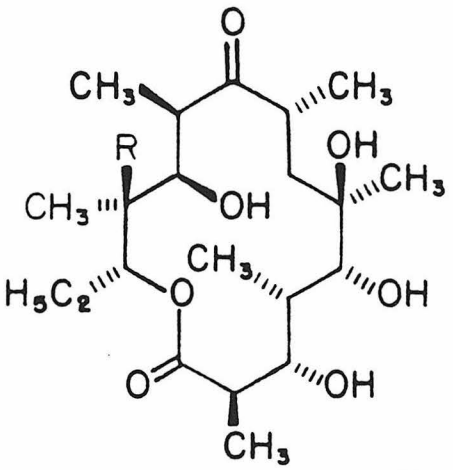
Table 1. Kinetic Data for the Formation of 3- to 16-, 18-, and 23-Membered Lactones from the Anions of the Parent ω-Bromo Acids in 99% Aqueous DMSO (from Ref. 5b).

n[a]	Temp, °C	k_{intra}, s^{-1} [b]	k_{rel} (at 50 °C)	EM, M[c]	$\Delta H^{\ddagger}$,[d] kcal/mol	$\Delta S^{\ddagger}$,[d] eu	r[d]
3	20.0	$(6.50 \pm 0.11) \times 10^{-5}$	21.7	1.23×10^{-2}	22.0 ± 0.24	−2.5 ± 0.76	0.9999
	35.0	$(4.44 \pm 0.03) \times 10^{-4}$					
	50.0	$(2.41 \pm 0.02) \times 10^{-3}$					
4	50.0	2.6	2.4×10^{4}	1.35×10			
5	50.0	3.1×10^{2}	2.8×10^{6}	1.60×10^{3}			
6	50.0	2.9	2.6×10^{4}	1.45×10			
7	20.0	$(6.17 \pm 0.17) \times 10^{-4}$	97.3	5.51×10^{-2}	17.4 ± 0.58	−13.6 ± 1.90	0.9987
	35.0	$(3.02 \pm 0.14) \times 10^{-3}$					
	50.0	$(1.08 \pm 0.02) \times 10^{-2}$					
8	40.0	$(3.88 \pm 0.04) \times 10^{-5}$	1.00	5.66×10^{-4}	21.8 ± 0.46	−9.2 ± 1.38	0.9995
	50.0	$(1.11 \pm 0.02) \times 10^{-4}$					
	60.0	$(3.17 \pm 0.06) \times 10^{-4}$					
	70.0	$(9.13 \pm 0.04) \times 10^{-4}$					
9	40.0	$(4.12 \pm 0.05) \times 10^{-5}$	1.12	6.33×10^{-4}	20.3 ± 0.36	−13.9 ± 1.10	0.9996
	50.0	$(1.24 \pm 0.03) \times 10^{-4}$					
	60.0	$(3.11 \pm 0.04) \times 10^{-4}$					
	70.0	$(7.96 \pm 0.07) \times 10^{-4}$					
10	35.0	$(9.19 \pm 0.04) \times 10^{-5}$	3.35	1.90×10^{-3}	17.4 ± 0.32	−20.5 ± 0.98	0.9997
	50.0	$(3.72 \pm 0.11) \times 10^{-4}$					
	65.0	$(1.26 \pm 0.02) \times 10^{-3}$					
11	35.0	$(2.38 \pm 0.08) \times 10^{-4}$	8.51	4.82×10^{-3}	16.4 ± 0.58	−21.9 ± 1.80	0.9986
	50.0	$(9.45 \pm 0.06) \times 10^{-4}$					
	65.0	$(2.80 \pm 0.09) \times 10^{-3}$					
12	20.0	$(6.49 \pm 0.07) \times 10^{-5}$	10.6	6.02×10^{-3}	17.6 ± 0.32	−17.6 ± 1.06	0.9995
	35.0	$(3.07 \pm 0.11) \times 10^{-4}$					
	50.0	$(1.18 \pm 0.02) \times 10^{-3}$					
13	20.0	$(2.82 \pm 0.01) \times 10^{-4}$	32.2	1.82×10^{-2}	15.3 ± 0.54	−22.5 ± 1.76	0.9994
	35.0	$(1.08 \pm 0.07) \times 10^{-3}$					
	50.0	$(3.57 \pm 0.02) \times 10^{-3}$					
14	20.0	$(4.00 \pm 0.03) \times 10^{-4}$	41.9	2.37×10^{-2}	14.8 ± 0.20	−23.6 ± 0.62	0.9999
	35.0	$(1.48 \pm 0.02) \times 10^{-3}$					
	50.0	$(4.65 \pm 0.02) \times 10^{-3}$					
15	20.0	$(3.52 \pm 0.05) \times 10^{-4}$	45.1	2.56×10^{-2}	16.1 ± 0.24	−19.5 ± 0.80	0.9998
	35.0	$(1.44 \pm 0.03) \times 10^{-3}$					
	50.0	$(5.01 \pm 0.07) \times 10^{-3}$					
16	20.0	$(3.60 \pm 0.03) \times 10^{-4}$	52.0	2.94×10^{-2}	16.8 ± 0.28	−17.0 ± 0.94	0.9997
	35.0	$(1.54 \pm 0.06) \times 10^{-3}$					
	50.0	$(5.77 \pm 0.08) \times 10^{-3}$					
18	20.0	$(4.42 \pm 0.08) \times 10^{-4}$	51.2	2.90×10^{-2}	15.4 ± 0.38	−21.2 ± 1.26	0.9995
	35.0	$(1.79 \pm 0.03) \times 10^{-3}$					
	50.0	$(5.68 \pm 0.09) \times 10^{-3}$					
23	40.0	$(3.01 \pm 0.04) \times 10^{-3}$	60.4	3.42×10^{-2}	14.5 ± 0.56	−23.8 ± 1.76	0.9987
	50.0	$(6.70 \pm 0.10) \times 10^{-3}$					
	60.0	$(1.30 \pm 0.03) \times 10^{-2}$					

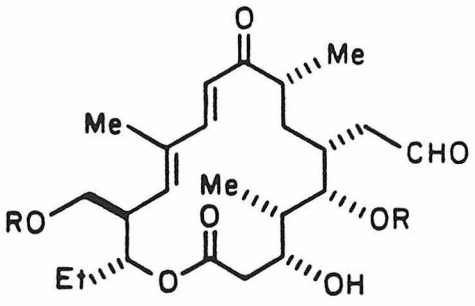
[a] Ring size of the ring to be formed. [b] Runs in duplicate or triplicate. [c] Calculated as k_{intra}/k_{inter}, where k_{inter} refers to the corresponding intermolecular counterpart. All rate constants at 50.0 °C. [d] $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were estimated from the least-squares slope and intercept of the Eyring plots, i.e., ln k_{intra}/T against $1/T$. The reported errors are expressed as 2σ (95% confidence limit), where σ is the pertinent standard error. The correlation coefficients (r) are also shown.



methymycin



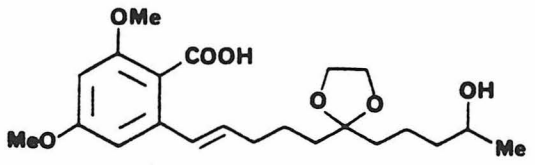
erythronomycin



Tylosin

Figure 2. Representative macrolides

of medium and large-ring lactones becomes apparent. Research efforts in this area have resulted in the development of a number of procedures designed to promote the intramolecular cyclization of bifunctional acyclic precursors. Three of the more general procedures for the synthesis of macrocyclic lactones are illustrated in Scheme I. The "double-activation" method of Corey and Nicolaou[9] (eq. 2) involves the prolonged heating of a 2-pyridinethiol ester under high-dilution conditions. This procedure has been used successfully in the synthesis of the 13-membered ring lactone zearalenene 1 (eq. 5),[10] but proceeded in <15% yield in a recently reported synthesis of (+)-tylonolide.[11] The method of Kruizinga and Kellogg[12] involves the cyclization of cesium carboxylates on ω-substituted alkanoic acids bearing a suitable leaving group (eq. 3). This procedure has also been applied to the synthesis of zearalenone with excellent results (eq. 5). Very recently, a "triphase catalytic cyclization" procedure has been reported which utilizes a polymer-bound phosphonium salt as the carboxylate counterion for the lactonization of ω-hydroxy alkanoic acids (eq. 4).[13]



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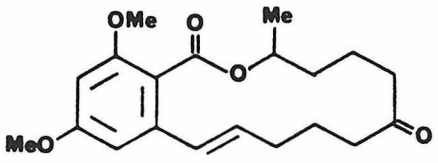
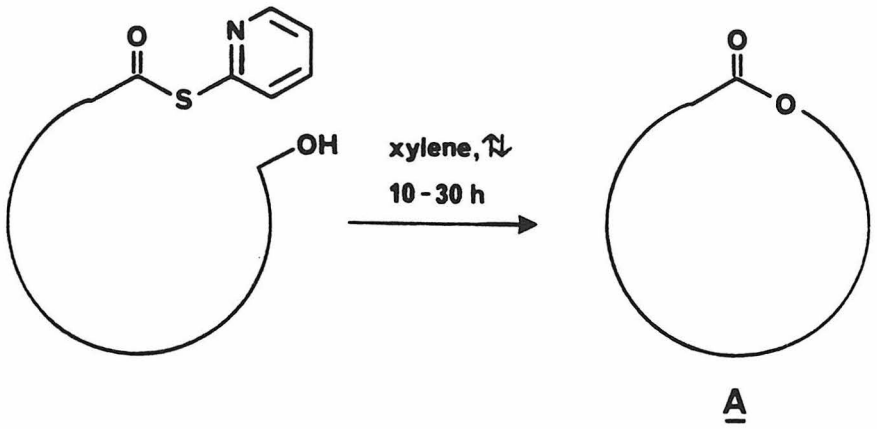


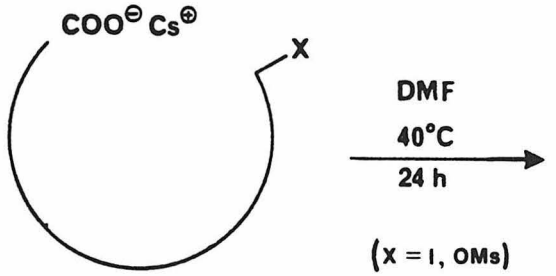
1

Corey-Nicolaou	75%
Kruizinga-Kellogg	80%

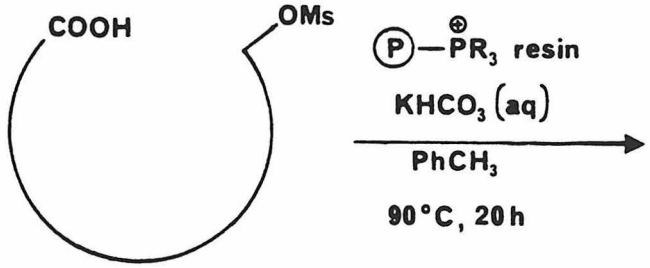
Scheme I



A (2)



A (3)



A (4)

All of these procedures have been systematically applied to the construction of a series of unsubstituted medium- to large-ring lactones. Given in Table 2 are the comparative results of these methodologies. It is clear from the data given in the table that existing methodology enables satisfactory construction of macrolactones of ring size >12 atoms, but offers little synthetic advantage for the construction of medium ring lactones containing 8-11 atoms.

The success of the three lactonization procedures described above can be attributed, at least in part, to their ability to attenuate the unfavorable entropic effects involved in forming a marocyclic system. For example, Corey and Nicolaou propose that electrostatic attraction brings the two ends of the bifunctional chain together to facilitate reaction, whereas Kruizinga and Kellogg advance the notion that the cesium cation serves as a "surface template" to bring the chain ends together (see Figure 3). In the triphasic

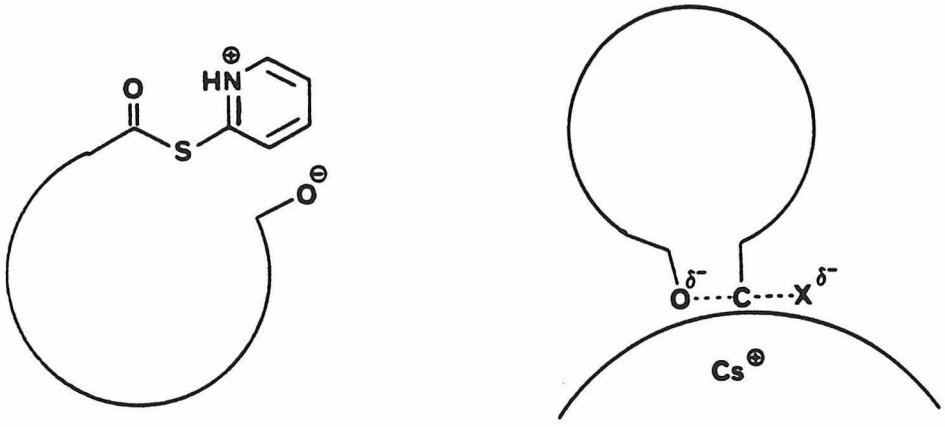


Figure 3

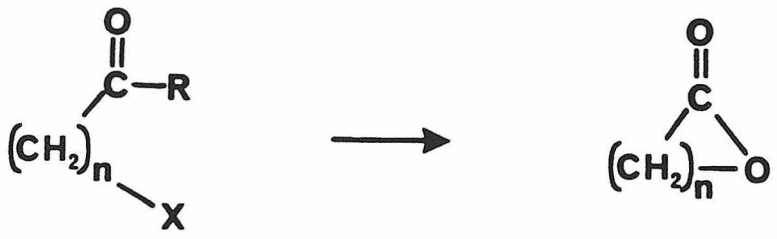


Table 2. Comparative macrolactonization results (% yield).[a]

n	Ring Size	Corey-Nicolaou[9] (R = S-Pyr, X = OH)	Kruizanga-Kellogg[12] (R = OH, X = I)	Triphase[13] (R = OH, X = OMe)
4	6	--	70	--
5	7	87 (71)[b]	[c]	--
6	8	--	--	--
7	9	25 (8)	--	0
8	10	--	0	--
9	11	--	23	--
10	12	64 (47)	33	47
11	13	76 (66)	62	66(68)
12	14	79 (68)	77	76
13	15	--	72	--
14	16	88 (80)	83	72
15	17	--	85	--

[a]Yields determined by GC. [b]Values in parentheses are isolated yields. [c]An 88% yield of dimer was formed in this case.

polymer-bound system of Reyen and Kimura, so called "kinetic isolation" of pendant groups serves to favor intramolecular cyclization over intermolecular dimerization.

One potentially attractive and experimentally simple method of overcoming entropic barriers in the cyclization of ω-substituted alkanoic acids could involve the use of cyclodextrins as reaction catalysts.[14] Cyclodextrins are cyclic oligosaccharides produced by Bacillus Macerans and are composed of from six to twelve α-1,4 linked glucose units.[15] X-ray crystallographic studies of α-cyclodextrin[16] (6 glucose residues) and β-cyclodextrin[17] (7 glucose units) have established the structure of these compounds as being rigid, torus-shaped molecules (Figure 4). The secondary hydroxyls of the glucose monomers are directed toward the open end of the

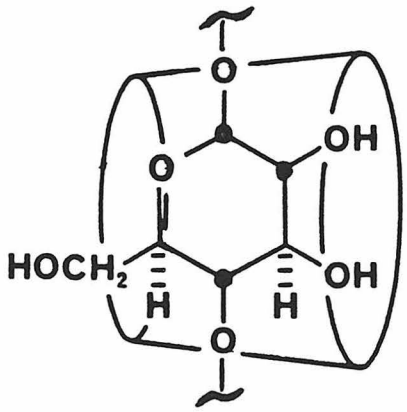


Figure 4. Cyclodextrin torus-structure

torus, where substantial hydrogen bonding helps maintain structural integrity. In this arrangement, the glucose C_3-H and C_5-H bonds are directed toward the interior of the torus-cavity, creating a hydrophobic pocket. It is this hydrophobic cavity that accounts for many of the interesting properties of the cyclodextrins. In Table 3 are given the approximate dimensions of the hydrophobic pocket for the three best characterized cyclodextrins.

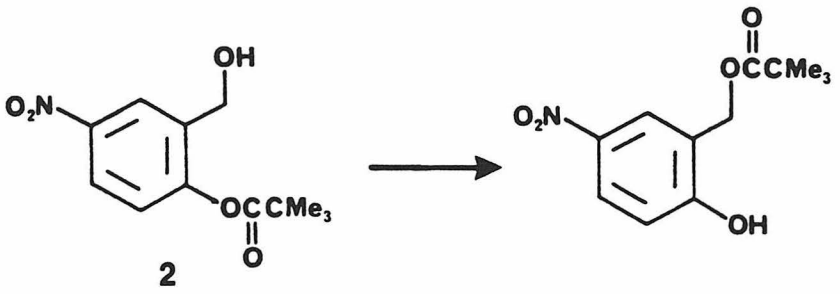
Table 3. Cyclodextrin cavity sizes (after ref. 15b).

Cyclodextrin	n[a]	Cavity Dimensions (A) Diameter	Depth
Cyclohexaamylose	6	4.5	6.7
Cycloheptaamylose	7	7.0	7.0
Cyclooctaamylose	8	8.5	7.0

[a]n is the number of glucose residues comprising the oligosaccharide.

It is well known that a hydrophobic molecule of appropriate size can fit into the cavity of cyclodextrins to form what are called "inclusion complexes". In this regard, the cyclodextrins have been classified as miniature enzyme models. They are known to catalyze the hydrolysis of a number of substrates, such as esters, amides, organophosphates, carbonates, and sulfates.[15a] The catalytic nature of the cyclodextrins in these hydrolyses are the result of a covalent participation of the secondary hydroxyl groups located at the large rim of the torus.

Cyclodextrins can also catalyze reactions in a non-covalent manner by influencing the relative populations of configurationally flexible molecules. For example, acyl transfer in compound **2** is accelerated by a factor of six when included within the cavity of α-cyclodextrin (eq. 6).[16] The authors attribute this rate enhancement to an increase in activation entropy and argue



(6)

that inclusion of **2** into α-cyclodextrin restricts rotational degrees of freedom of the hydroxymethyl side chain, orienting it in close proximity to the ester carbonyl (Fig. 5). Additional examples of rate enhancement in organic reactions can be found in the Diels-Alder literature. Breslow has

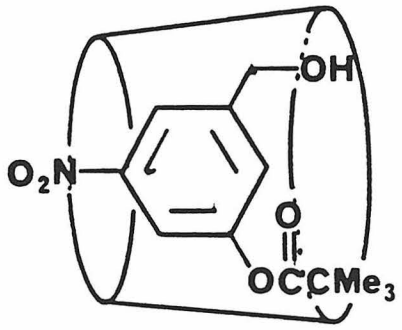
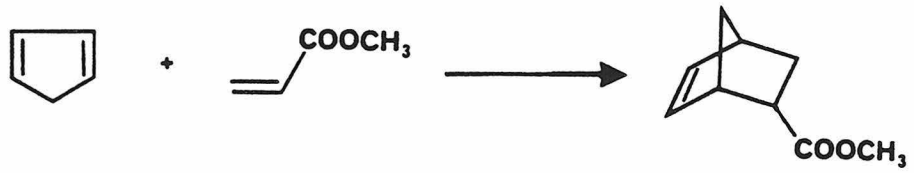


Figure 5

demonstrated a marked acceleration in the cycloaddition of cyclopentadiene and methyl acrylate in the presence of β-cyclodextrin (eq. 7).[17] Improved product yields for an intramolecular Diels-Alder reaction when performed in the presence of β-cyclodextrin have also been recently noted.[18]



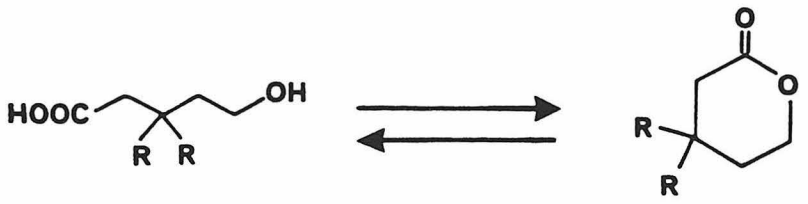
(7)

Solvent:	Isooctane	MeOH	H_2O	H_2O + β-Cyclodextrin
	1	13	733	1817

In light of the foregoing discussion, it seems reasonable to propose that cyclodextrins might catalyze the lactonization of ω-hydroxy acids in aqueous media. A hydrocarbon-like molecule dissolved in water is surrounded by water assemblies along its exposed surface, a situation that is very entropically unfavorable. Therefore, a hydrocarbon-like molecule will try to reduce these water assemblies by making contact at its surface with the surface of another hydrocarbon-like molecule. This can be accomplished by "self-solvation", i.e., coiling of the molecule around itself, or by the formation of micelles. In the presence of cyclodextrin, one might expect that hydrophobic recognition could occur between the hydrocarbon chain of a ω-hydroxyalkanoic acid and the hydrophobic cavity of the cyclodextrin. As a result of inclusion into a cyclodextrin, the two ends of the carbon chain would be situated in close proximity to one another, which would have a significant

effect on the rate at which these ends react. Therefore, as in the previously discussed lactonization procedures, cyclodextrin would serve to help overcome the unfavorable entropy terms associated with medium- to large-ring forming reactions. The overall process is illustrated in Scheme II for the formation of the 8-membered ring lactone.

The catalysis by cyclodextrin of the lactonization of medium- to large-rings would clearly be a conformational effect. That such effects would be important in this kind of reaction has already been demonstrated, and can be related to the well-known "gem-dimethyl effect".[19] For example, the equilibrium position of 5-hydroxypentanoic acid favors the open form by over 16:1 (eq. 8).[20] However, geminal substitution by methyl groups at the β-position perturb this equilibrium to now favor the lactone form by over 11:1.

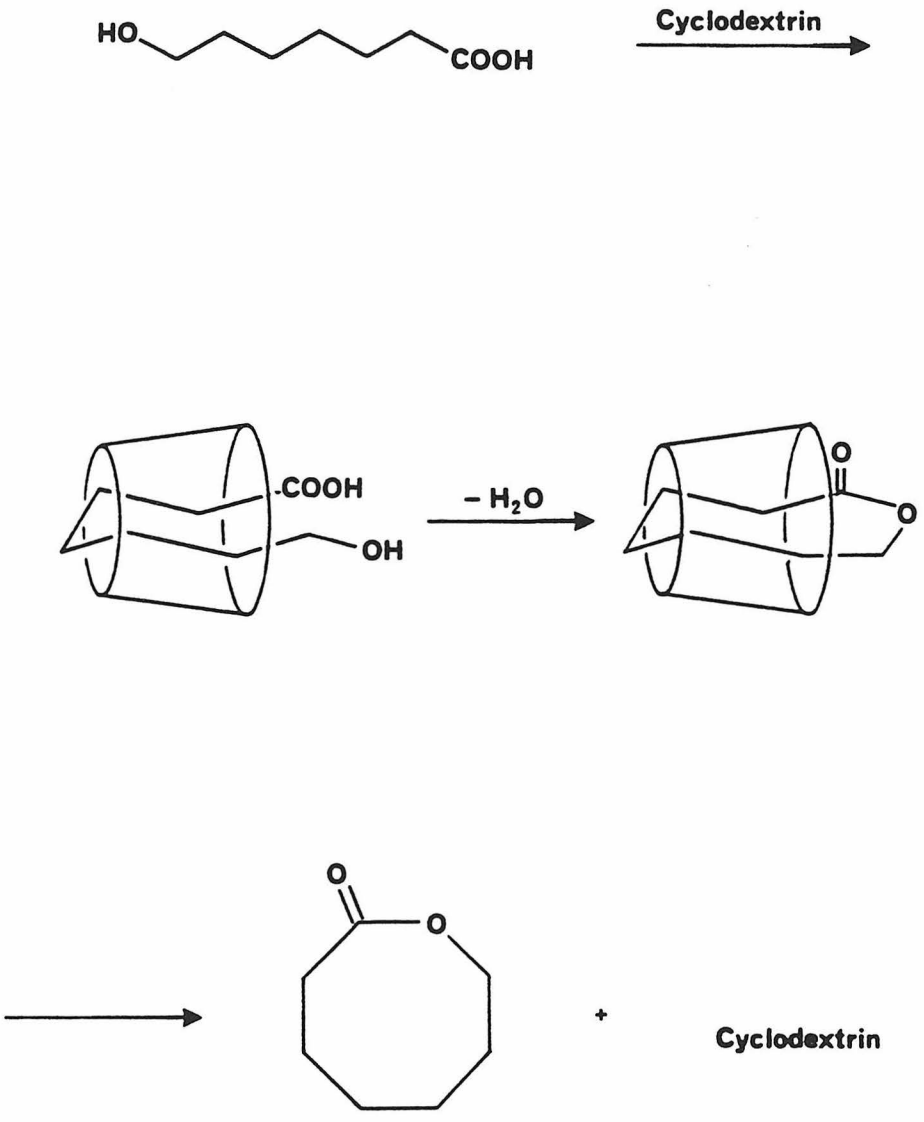


(8)

	K	k_{rel} (lactonization)
R = H	0.06	1
R = Me	11.1	2.9

Furthermore, the rate at which the substituted hydroxy-acid cyclizes is nearly three times that of the unsubstituted acid.[20] Indeed, rate enhancement by geminal substitution has been noted in the formation of medium- and large ring lactones.[21] Although the effect is generally small and

Scheme II



depends upon the location along the chain of the geminal substitution, lactonization rates for compound **3** are increased by over a factor of six when R = methyl.[21]

(9)

3	k_{rel}
R = H	1
R = Me	6.62

In summary, it is proposed that cyclodextrin could serve as a catalyst for the lactonization of ω-hydroxyalkanoic acids of varying chain-length in aqueous media. A study such as this need not be limited to lactonization, and an examination of the ring-closure kinetics of a number of suitably bi-functionalized carbon chains in the presence of cyclodextrins would be revealing. The availability of cyclodextrins possessing hydrophobic cavities of varying sizes adds to the flexibility of the proposed procedure. Unfortunately, due to the polyoxygenated nature of the macrolactone antibiotics, which renders the carbon backbone non-hydrophobic, this procedure would most likely be of little use to the natural product chemist. However, a study such as that proposed would add to our knowledge of intramolecular reactivity and the chemistry of medium- and large-ring compounds.

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PROPOSITION II

Abstract: The use of ^{14}N-nuclear quadrupole resonance (NQR) is proposed to study the electron distribution in some organic conductors and semiconductors.

* * * * * * * *

I. Introduction

The design and synthesis of organic materials exhibiting unusually high electrical conductivity is an area of research currently witnessing renewed interest.[1,2] Whereas the electrical conductivity of most organic materials is quite low ($\sigma < 10^{-10}\ \Omega^{-1}\ cm^{-1}$), certain strong π-molecular donor and acceptor molecules often react to form ion-radical salts and charge-transfer compounds which have considerably higher conductivities, often as high as $10^{-2}\ \Omega^{-1}\ cm^{-1}$. These materials, called "organic semiconductors", have been actively studied since the mid 1950's.[2] In the early 1960's, a powerful new π-molecular acceptor was discovered; tetracyano-p-quinodimethane (TCNQ, Fig. 1).[3] The TCNQ radical anion readily forms organic semiconductors with a large number of organic cations. In 1973, the TCNQ salt of tetrathiafulvalene (TTF) was prepared.[4,5] This salt was found to have a conductivity which increases dramatically below room temperature, rising as high as $10^{4}\ \Omega^{-1}\ cm^{-1}$ near 60°K -- high enough to be considered an "organic metal". This discovery excited both chemists and solid state physicists, and was responsible for bringing renewed interest in this field, along with early

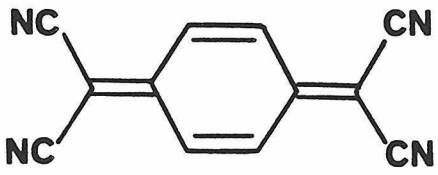


Figure 1. Tetracyano-p-quinodimethane.

hopes of generating organic solids exhibiting high-temperature superconductivity.[5,6]

Many questions regarding the factors responsible for high conductivity in organic insulators and conductors are still unanswered. There are currently a number of theories regarding these issues. It is the purpose of this proposition to suggest the use of nuclear quadrupole resonance (NQR) to provide direct experimental support for one of these theories.

II. Discussion

Since their discovery, a large number of investigators have examined the magnetic, electronic, optical, and structural properties of TCNQ salts.[1,6,7,12,14,18a,30] It was found that the high conductivity of some of these salts was associated with crystal structures in which the planar TCNQ molecules are packed face-to-face with segregated stacks of cations and TCNQ molecules.[7,8] The π-overlap between adjacent TCNQ molecules is strong along the stacking axis, causing their unpaired electron to be partially delocalized and enabling them to conduct in the direction of these one-

dimensional stacks.

Over 400 charge-transfer or radical-anion salts of TCNQ are now known.[3,7,9] Although the ideas presented below are generally applicable, this discussion will be limited to the simple salts of TCNQ (i.e., those with 1:1 stoichiometry of donor to acceptor) which form segregated cation and TCNQ stacks. This group of salts (which represent ~25% of the known TCNQ salts) can be subdivided into two categories on the basis of the magnitude of their conductivity at 300°K. Class I salts are characterized by low conductivity and high activation energy for electrical conduction. These salts are called "insulators", and include all of the alkali-metal salts, as well as a number of organic donor salts. Some Class I cations are listed in Table I. Class II salts are characterized by high conductivity and are called metallic. Some Class II cations are listed in Table II.

A number of theories have been proposed to explain the difference between Class I and Class II salts. For example, it has been suggested that distortions in the TCNQ stacks play an important role in the conductivity of these salts.[7,8,14] LeBlanc[15] has proposed that excitonic polarizability of the cations of Class II salts sufficiently screens the repulsive Coulombic interactions on the TCNQ stacks, making them small compared to the electronic bandwidth 4t (t is the charge transfer integral). Whereas these and other theories[17] have some grounds for support, they fail to explain the differences between some Class I and Class II salts. Indeed, some of these differences are not so easily found. For example, the difference between the NMP vs the NMAd salts of TCNQ is only one heterocyclic nitrogen, and yet their conductivities differ by five orders of magnitude (see Tables I and II).

Table I. Some Class I Cations: Powder Conductivity at 300°K and Peak Reductive Potentials, Ep.

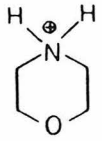
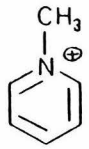
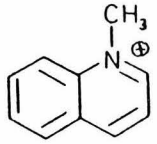
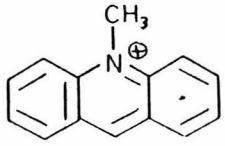
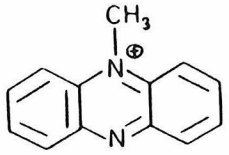
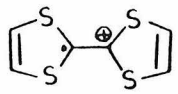
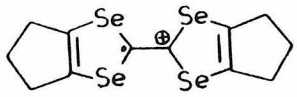
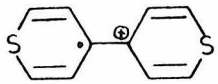
		σ (Ω^{-1} cm^{-1})	Ep (eV)	Ref.
	$Na^{\oplus}$	3×10^{-5}	-3.0	3
Triethylammonium (TEA)	$HN^{\oplus}(Et)_3$	10^{-9}	-2.8	3
Morpholinium (Morph)		10^{-9}	-2.8	3
N-Methylpyridinium (NMPy)		10^{-5}	-1.28	3
N-Methylpyrazinium (NMPyz)		3×10^{-8}	-0.73	10
N-Methylquinolinium (NMQn)		10^{-7}	-0.86	3
N-Methylacridinium (NMAd)		2×10^{-5}	-0.41	10

Table II. Some Class II Cations: Powder Conductivity at 300°K and Peak Reduction Potentials, Ep

		σ (Ω^{-1} cm^{-1})	Ep (eV)	Ref.
N-Methylphenazinium (NMP)		2	-0.11	10,11
Tetrathiafulvalinium (TTF)		10	+0.31	4,5
Hexamethylene-tetraselenafulvalinium (HMTSF)		25	+0.41	12
Δ4,4'-Bithiopyranium (BTP)		1	+0.08	13

Of all of the proposed theories regarding organic conduction, that first suggested by Soos,[14] and now being popularized by Torrance[1,18] seems the most reasonable. In the past, it has been generally assumed that simple TCNQ salts were fully ionic with $\rho = 1$ electron transferred from donor to TCNQ molecule. Torrance proposes that Class II conducting salts are characterized by a $\rho < 1$, i.e., incomplete charge transfer from donor to TCNQ. Thus, the TCNQ stacks of Class II salts can be viewed as containing both neutral $TCNQ^0$ and ionic $TCNQ^-$ molecules. In such a mixed valence stack, it would be possible to excite an electron from a $TCNQ^-$ molecule to an adjacent $TCNQ^0$ molecule. This is in contrast to the fully ionic $\rho = 1$ situation in Class I materials, where now an electron is transferred from one $TCNQ^-$ molecule to another $TCNQ^-$ molecule, thereby creating severe Coulombic repulsion or otherwise require highly correlated electron motion. These ideas are schematically represented in Figure 2.

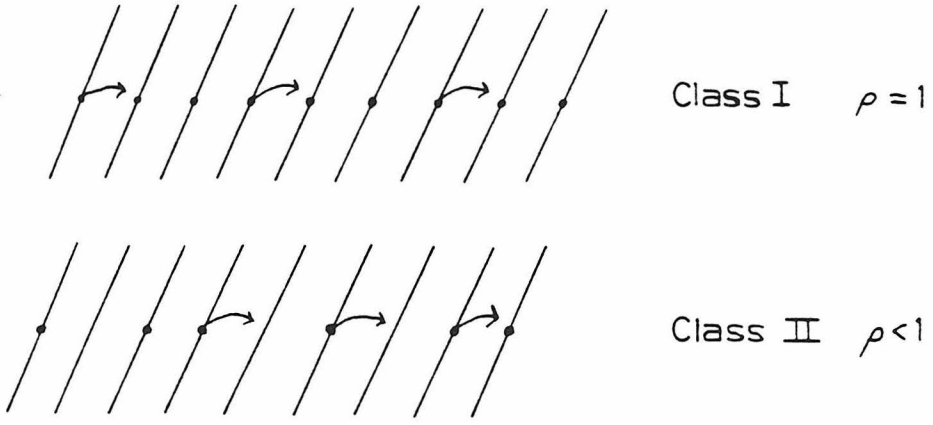


Figure 2. Schematic representation of Class I/Class II differences (after Ref. 1).

This theory suggests that complex TCNQ salts (i.e., those which which deviate from 1:1 stoichiometry, as for example TEA-$(TCNQ)_2$) should be good conductors because of the necessity of $\rho = 1/2$. Indeed, it was recognized very early that the conductivity of complex salts is generally much higher than the corresponding simple salts of the same donor.[6] Furthermore, a comparison of the optical absorption spectra of Class I, Class II, and complex TCNQ salts provides further support for this theory. As can be seen from Figure 3,[18a] the main features of the spectra of TTF- and NMP-TCNQ are nearly identical with those of TEA-$(TCNQ)_2$, but differ markedly from those of K(TCNQ). This similarity in spectra was a key piece of evidence in postulating incomplete charge transfer as an explanation of Class I/Class II conductivity differences.

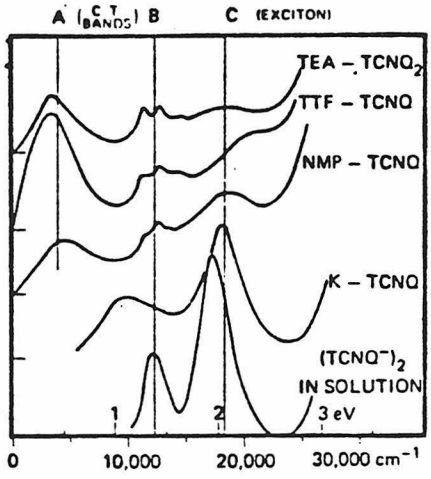


Figure 3. Powder absorption spectra of representative TCNQ salts.

The theory put forth by Torrance also suggests reasons for the differences in ρ values between Class I and Class II salts.[1,18] One can

envision that the electrons in a D-TCNQ salt are in equilibrium between a neutral and fully ionic structure:

$$D^0 + TCNQ^0 \underset{(I-A)}{\overset{E_M}{\rightleftharpoons}} D^+ + TCNQ^- \qquad (1)$$

Torrance suggests that the important factors in determining the position of the equilibrium in equation 1 are the electrostatic Madelung binding energy E_M which is gained when the crystal is ionic and the molecular energy of electron transfer I-A, which is related to the ionization potential of the donor and the electron affinity of the acceptor. There are large differences in both of these quantities between Class I and Class II salts. Class I salts are characterized by high Madelung energies[18b,19] and low ionization potentials (see Table I). Both of these energies tend to drive the equilibrium in equation 1 toward the ionic ground state with complete reduction of the TCNQ stacks and $\rho = 1$.[1]

On the other hand, Class II salts have Madelung energies typically ~2 eV lower than Class I salts,[18b,19] as well as ionization potentials ~2 eV higher (see Table II). Torrance therefore suggests that it is energetically favorable for Class II salts to form mixed valence stacks, and therefore have a $\rho < 1$.

Clearly, an experimental determination of ρ-values for TCNQ insulators and conductors would be highly desirable in light of the above discussion. Evidence for $\rho < 1$ in a few Class II TCNQ salts has been obtained from diffuse X-ray[20] and neutron-scattering[21] experiments. It is proposed

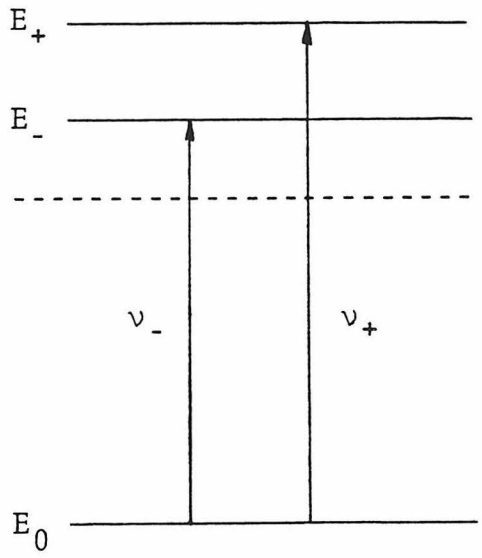
here that ^{14}N-nuclear quadrupole resonance would be a powerful tool for the investigation of organic conductors and semiconductors.

Nitrogen-14 NQR has been shown to be a very sensitive means of measuring the charge distribution in the cyano group[22,23] and can therefore provide relevant information regarding charge transfer phenomenon. For a nucleus with spin I = 1 (e.g., ^{14}N, 99.6% natural abundance) there are three energy levels for nuclear orientation in an asymmetric field gradient which are given by:[24]

$$E_{\pm} = \frac{e^2Qq}{4}(1 \pm \eta) \qquad (2)$$

$$E_0 = \frac{e^2Qq}{2} \qquad (3)$$

where eQ is the nuclear quadrupole moment, eq is the electric field gradient, and η is a parameter associated with the asymmetry of the electric field. Between these energy levels there are two transitions:



$$\nu_+ = \frac{3}{4}\frac{e^2Qq}{h}(1 + \frac{1}{3}\eta) \qquad (4)$$

$$\nu_- = \frac{3}{4}\frac{e^2Qq}{h}(1 - \frac{1}{3}\eta) \qquad (5)$$

The term

$$\left(\frac{e^2Qq}{h}\right)$$

is called the quadrupole coupling constant. This term can be determined directly from the measured values of ν_+ and ν_- and can be shown to be (from eqs. 4 and 5):

$$\left(\frac{e^2Qq}{h}\right) = \frac{2}{3}(\nu_+ + \nu_-)$$

Similarly, it can be shown that

$$\eta = \frac{3(\nu_+ - \nu_-)}{(\nu_+ + \nu_-)}$$

The Townes and Dailey theory[25] provides a satisfactory method of analysis of the electronic charge distribution in different compounds in terms of the electric field gradient measured by NQR at the site of the resonant nucleus. This theory (modified somewhat by Murgich and Pissanetzky)[22] gives the transition frequencies in a -C≡N group as

$$\nu_+ = \frac{3}{4}\left(\frac{e^2Qq_0}{h}\right)\left[2(1 - \alpha^2) + b\alpha^2 - A_2\right] + \delta\nu_+^m + \delta\nu_+^c \qquad (8)$$

$$\nu_{-} = \frac{3}{4}\left(\frac{e^2Qq_0}{h}\right)\left[2(1 - \alpha^2) + b\alpha^2 - A_1\right] + \delta\nu_{-}^{m} + \delta\nu_{-}^{c} \qquad (9)$$

where

α^2 = the s-character of the sp-hybrid

A_1 = population of the π_x-oribital

A_2 = population of the π_y-orbital

b = population of the σ-orbital

$\nu_{\pm}^{m}$ = contribution to $\nu_{\pm}$ by other charges on atoms in the molecule

$\nu_{\pm}^{c}$ = contribution to $\nu_{\pm}$ by other molecules in the crystal

(e^2Qq_0/h) = quadrupole coupling constant of ^{14}N nucleus with 1p-electron, usually taken as 10 MHz.[26]

Nitrogen-14 NQR experiments have been done on the neutral $TCNQ^0$ [27] and the $TCNQ^-$ anion.[22] In the electron-transfer process, one can assume that the σ-bond parameters α and b change much less than the π-bond parameters A_1 and A_2.[22] This is consistent with the small change in length observed for the -C≡N bond.[28] Thus, equations 8 and 9 demonstrate that ν_+ and ν_- are measures of A_2 and A_1 respectively. In order to determine the relative change in A_1 and A_2 in going from

$$TCNQ^0 \xrightarrow{e^-} TCNQ^-$$

one must have values for $\delta\nu_{\pm}^{m}$ and $\delta\nu_{\pm}^{c}$. These can be calculated in terms of a point-charge model, using the results of MO calculations and a Mulliken-type charge redistribution.[29] These calculations were done, and it was found that in K^+ $(TCNQ)^-$, the populations A_1 and A_2 are larger by 0.11 and 0.024 electrons, respectively, than in $TCNQ^0$.[22] These results are consistent with the fact that A_1, being the conjugated π_x-orbital, should exhibit a much greater increase in population than A_2, the non-conjugated π_y-orbital. It was concluded, therefore, that the total charge on the N atom is increased by 0.13 electrons in going from $TCNQ^0$ to the negative anion $TCNQ^-$. This is in excellent agreement with the MO calculations of Jonkman and Kommandeur,[29] which give an increase of charge on N of 0.14 electrons (Fig. 4). The experimental results of the ^{14}N-NQR experiments for $TCNQ^0$ and $TCNQ^-$ are given in Table III.

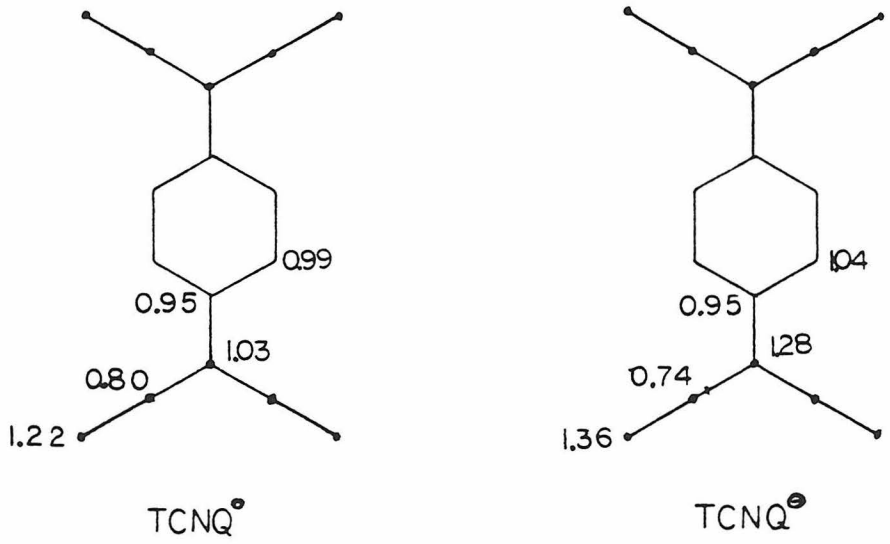


Figure 4. Charge densities in $TCNQ^0$ and $TCNQ^-$ (after Ref. 29).

Table III. ^{14}N-NQR results of $TCNQ^0$ and $TCNQ^-$.[a]

	ν_+ (kHz)	ν_- (kHz)	(e^2Qq/h) (kHz)	η (%)	A_1-A_2
K-TCNQ	2977.8 ± 0.1	2011.8 ± 0.3	3334	58.7	0.130
	2978.8 ± 0.1	2032.7 ± 0.2	3348	47.2	0.128
	2984.5 ± 0.1	2071.8 ± 0.2	3374	54.4	0.122
	2987.1 ± 0.1	2090.0 ± 0.2	3387	53.1	0.120
	2988.7 ± 0.1	2119.2 ± 0.2	3406	51.1	0.116
	2991.6 ± 0.1	2129.7 ± 0.2	3413	50.4	0.115
	3003.5 ± 0.1	2171.8 ± 0.2	3441	47.5	0.109
	3006.5 ± 0.1	2205.3 ± 0.2	3463	45.3	0.105
$TCNQ^0$	3151.6 ± 0.1	2888.7 ± 0.1	4021	13.1	0.035
	3142.9 ± 0.1	2879.5 ± 0.1			

[a]The eight sets of frequencies for $TCNQ^-$ are due to eight non-equivalent crystallographic nitriles. Averages are used for calculations. Same for $TCNQ^0$.

The value of (A_1-A_2) can be obtained by subtracting equation 9 from equation 8. This operation cancels the $\delta\nu_{\pm}^{m}$ and $\delta\nu_{\pm}^{c}$ terms, thereby eliminating the need to calculate them. Thus, the NQR experiment yields the difference in π_x-orbital population directly.

The application of ^{14}N-NQR to the study of organic conductors and semiconductors is now obvious. If the TCNQ stack of an organic conductor is indeed of mixed-valence and the equilibrium depicted in equation 1 is rapid on the NQR time scale, then one can expect to see a value of (A_1-A_2) somewhere between 0.035 (ρ = 0, $TCNQ^0$) and 0.118 (ρ = 1, $TCNQ^-$). Therefore, the value of ρ can be calculated from the experimentally determined (A_2-A_1) by

$$\rho = \frac{(A_2-A_1) - 0.035}{0.083} \qquad (10)$$

Conclusion

The use of ^{14}N-NQR spectroscopy to probe electron densities in TCNQ molecules seems to have significant applicability in the study of organic conductors and semiconductors. It is important to note that most NQR experiments are done at 77°K.[24] Fortunately, the best known organic metals have significant conductivity at this temperature (see Fig. 5). The application of ^{14}N-NQR to determine ρ values for a number of Class I and Class II TCNQ salts would provide experimental evidence for the theory of incomplete charge transfer currently being postulated for the difference between organic conductors and semiconductors.

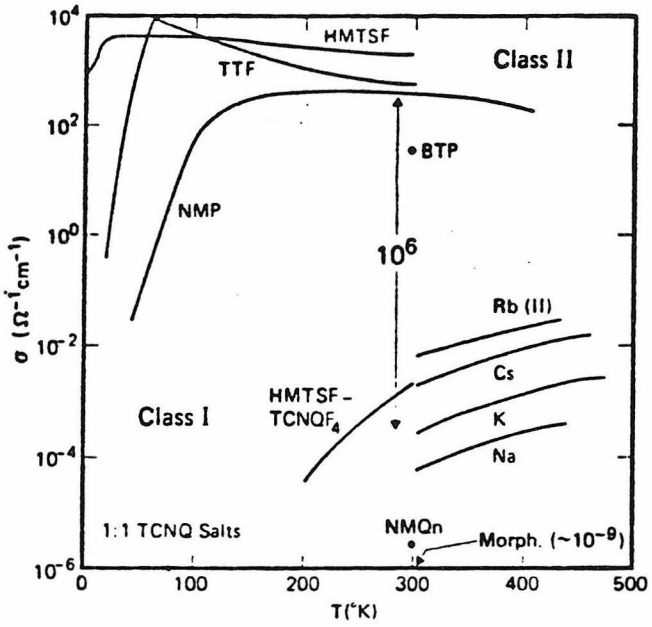


Figure 5. Single crystal dc conductivities for some 1:1 TCNQ salts (after Ref. 1).

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PROPOSITION III

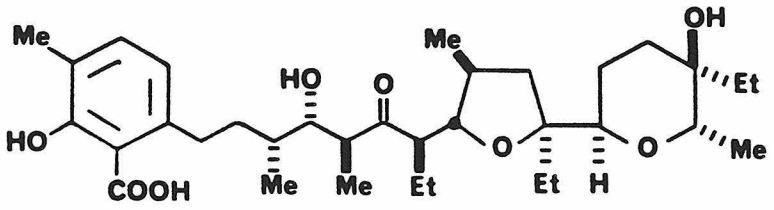
Abstract: An investigation of the iterative application of intramolecular oxirane ring-opening reactions is proposed. The use of α,β-epoxysilanes to direct the regiochemistry of these reactions is presented. Application to the synthesis of polyether antibiotics and novel heterocyclic structures is discussed.

* * * * * * * *

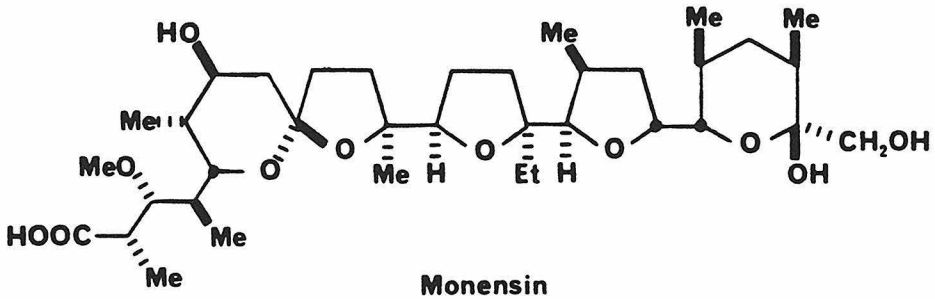
Over the last ten years the polyether antibiotics and ionophores have emerged to occupy a position of significance at the frontier of modern synthetic organic chemistry. Only recently have the necessary methodologies been developed which provide satisfactory solutions to the immense stereochemical problems presented by these complex structures, and a number of elegant syntheses within this class of compounds have been reported.[1] Given in Figure 1 are some representative examples of these types of structures.

Recently, Clardy et. al., have reported the isolation and structure determination of a new dinoflagellate toxin, brevetoxin B (BTX-B), whose structure is given in Figure 2.[2] This unprecendented structure represents a novel class of macromolecules which are composed of a single carbon chain locked into a rigid ladder-like structure consisting of contiguous trans-fused ether rings.

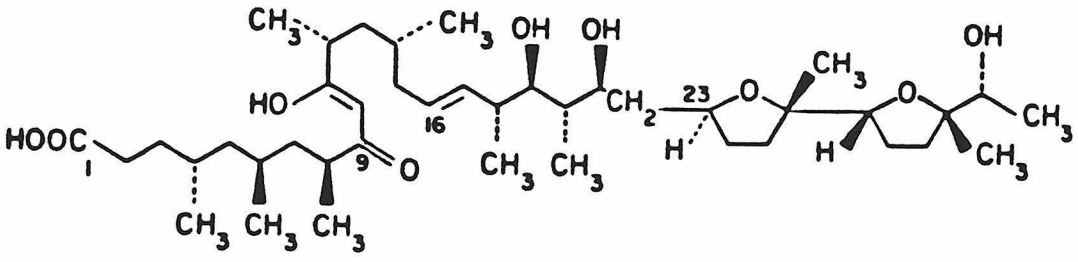
The polyether based molecules depicted in Figure 1 are structurally



Lasalocid A



Monensin



Ionomycin

Figure 1. Polyether based natural products.

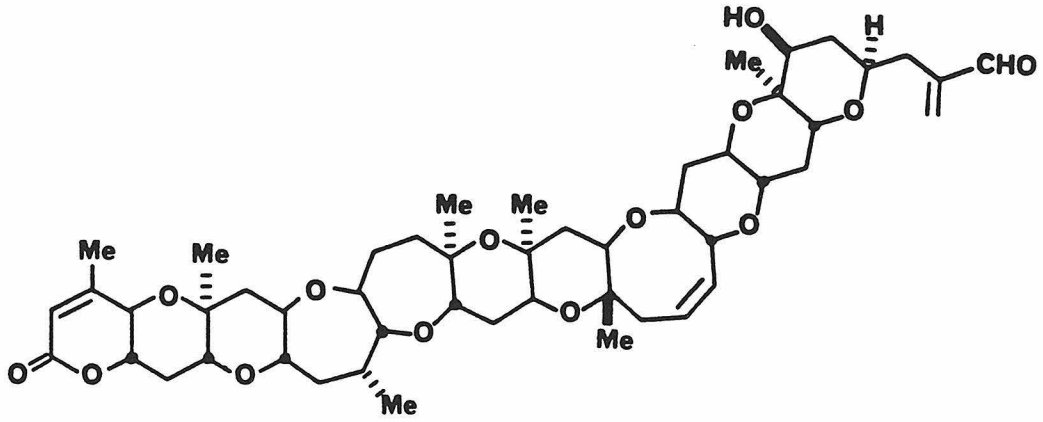
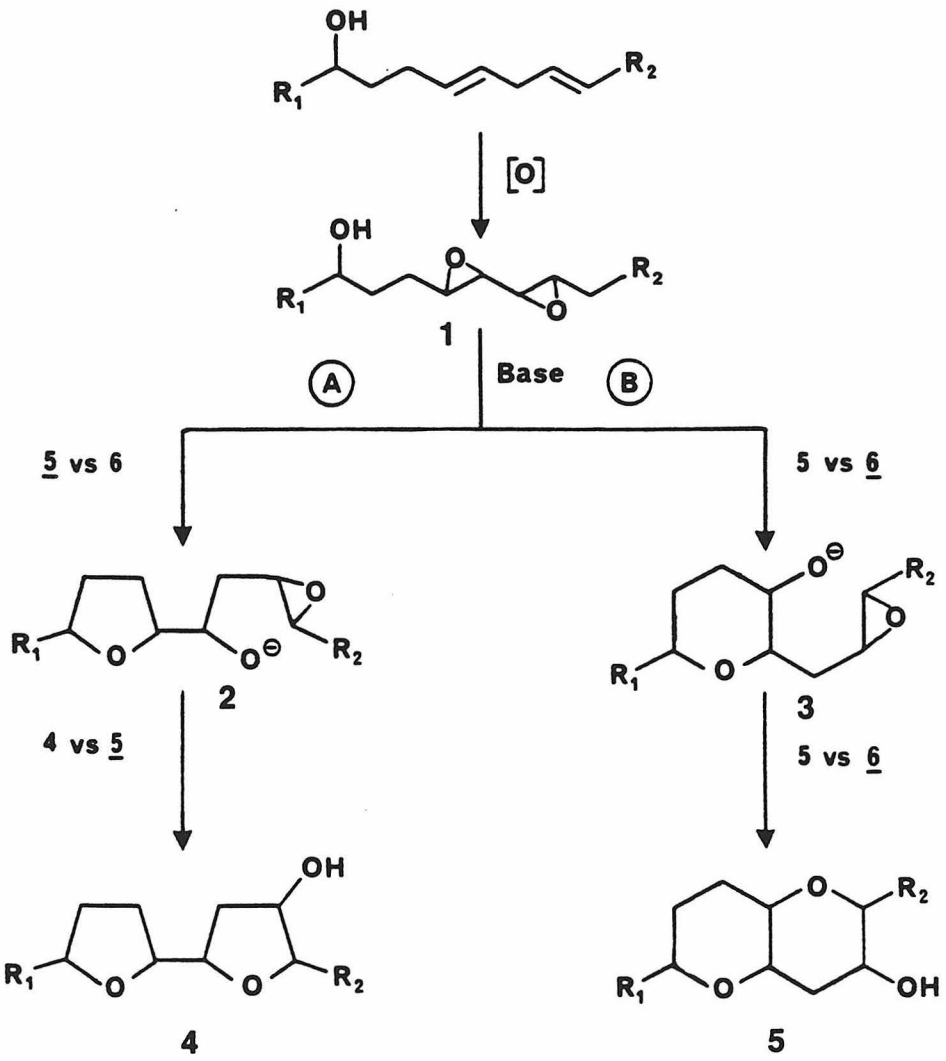
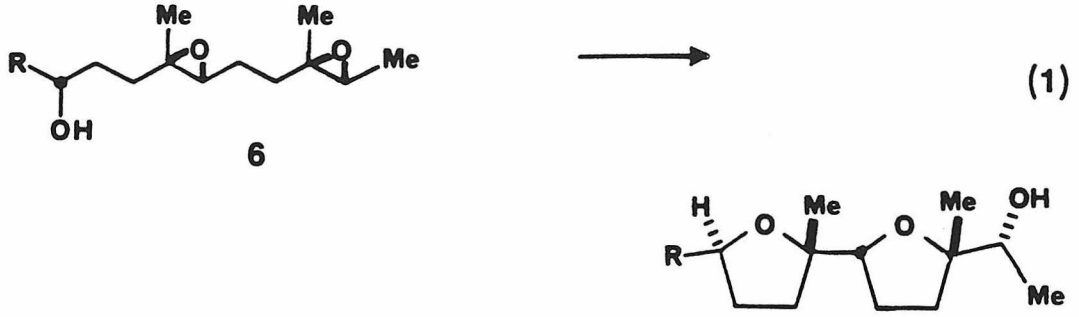


Figure 2. Brevetoxin-B (BTX-B).

related to the brevetoxins in that both of these classes of compounds are made up of a series of joined cyclic ethers. That this relationship is more than superficial is appreciated upon the realization that either of these types of structures could in theory be derived from a common acyclic precursor. Conceptually, the iterative application of an intramolecular epoxide ring-opening reaction could provide entry into one or the other of these two skeletal frameworks, as depicted in Scheme I. Treatment of the diepoxy-alcohol **1** with acid or base would effect intramolecular oxirane ring cleavage to afford either intermediate **2** (Path **A**) or **4** (Path **B**), depending upon the regiochemistry of the epoxide displacement. Similarly, further cyclization of the newly generated oxygen nucleophile with the remaining epoxide could produce structures **3** or **5**, again dependent upon the regioselectivity. Clearly, if one could control the regiochemical outcome of these kinds of reactions, this route could prove valuable in the synthesis of polyether-based natural products. For example, one might envision that elaboration of the linked tetrahydrofuran units which comprise the right-hand side of ionomycin (Fig. 1) could be conducted by the intramolecular poly-epoxide cyclization of a

Scheme I

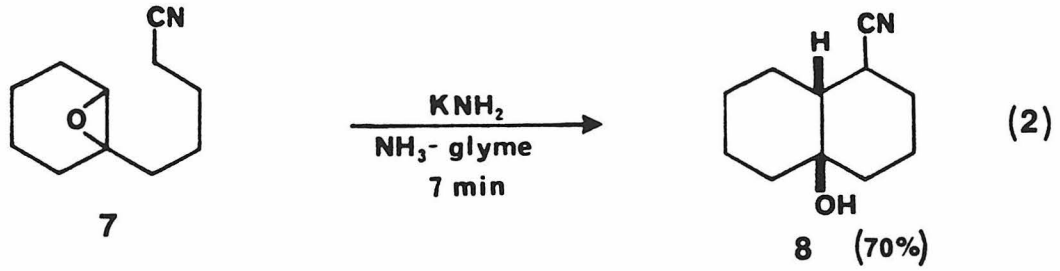

OH
R1
R2
[O]
OH
O
R1
R2
O
1
A
Base
B
5 vs 6
5 vs 6
R1
O
O⊖
R2
2
O⊖
R2
O
R1
O
3
4 vs 5
5 vs 6
OH
R1
O
O
R2
4
O
R2
R1
O
OH
5



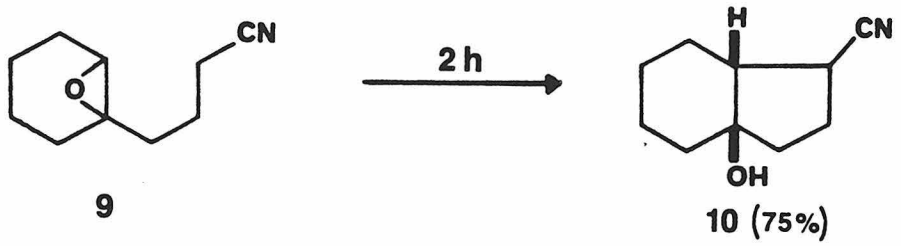
(1)

fragment such as **6** (eq. 1).

Although examples of the intramolecular ring-opening of epoxides are well-documented in the literature, few systematic investigations have been carried out which address the issue of regiochemistry in these reactions. Stork, et. al., have studied the intramolecular isomerization of epoxynitriles and have demonstrated that this reaction exhibits kinetic behavior dissimilar to other cyclizations involving S_N2-type transition states.[3] For example, base-catalyzed isomerization of the epoxy-nitrile **7** proceeds in 7 min to afford the 6-membered cyclization product **8** in ca. 70% yield (eq. 2), whereas compound **9** requires 2 h to achieve a 75% yield of the 5-membered ring cyclization product **10** (eq. 3). This observation is in contrast to a host of



(2)



9

10 (75%)

(3)

reactions involving the cyclization of bifunctional molecules, where usually the 5-membered ring products are kinetically favored.[4] This phenomenon has been attributed to unique geometric constraints imposed upon the system by the oxirane ring, and has been associated with the requirement of "colinear-attack" for S_N2-type displacements.[3] As shown in Figure 3, colinearity of the approaching nucleophile and a C-O bond is more easily achieved in cyclizations which yield 4- and 6-membered ring products than in those leading to 5-membered ring products. Indeed, in reactions where steric consideration were equal, Stork (and others) have observed exclusive

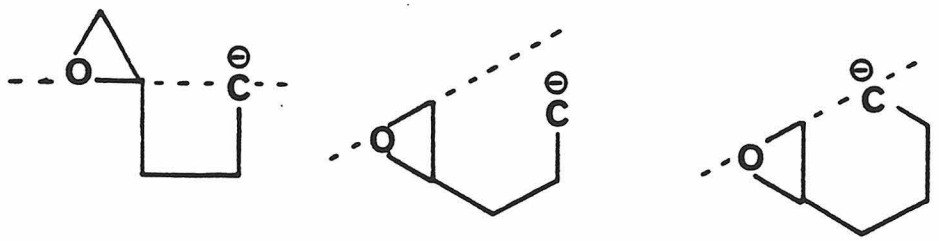
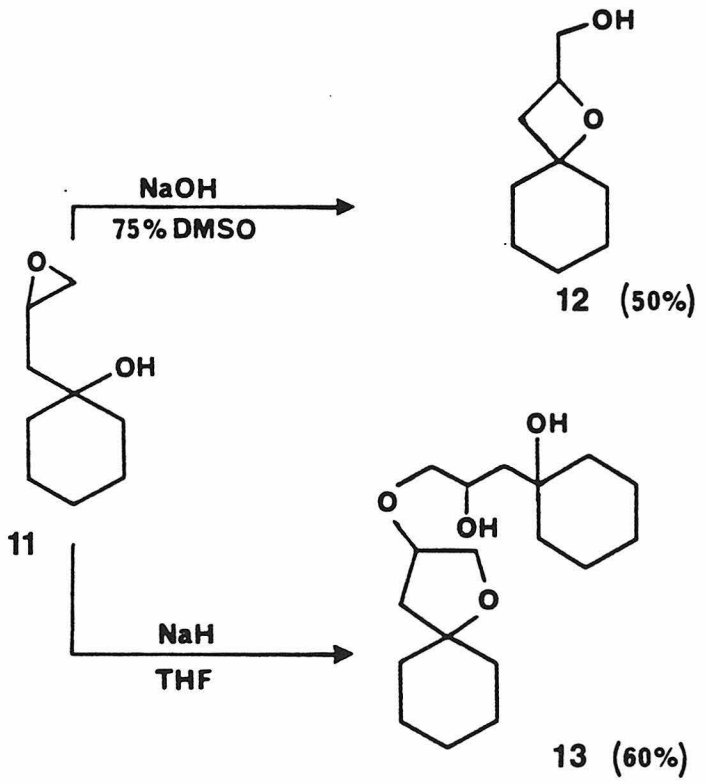


Figure 3. Colinearity

formation of 4-membered ring structures over their 5-membered ring counterparts. Other studies employing ester enolates have noted similar observations.[5]

An analogous study of the intramolecular isomerization of epoxy-alcohols, where now the incoming nucleophile is oxygen rather than carbon, has never been carried out. An investigation such as this would be required before an intramolecular poly-epoxide cyclization project was undertaken. Isolated cases throughout the literature have not addressed the issue of regiochemistry versus ring-size, and few cases have been looked at under a variety of conditions. However, one interesting study on the cyclization of 3,4-epoxy alcohols clearly demonstrates that more work is warranted in this area. Murai, et. al.,[6] have reported that treatment of



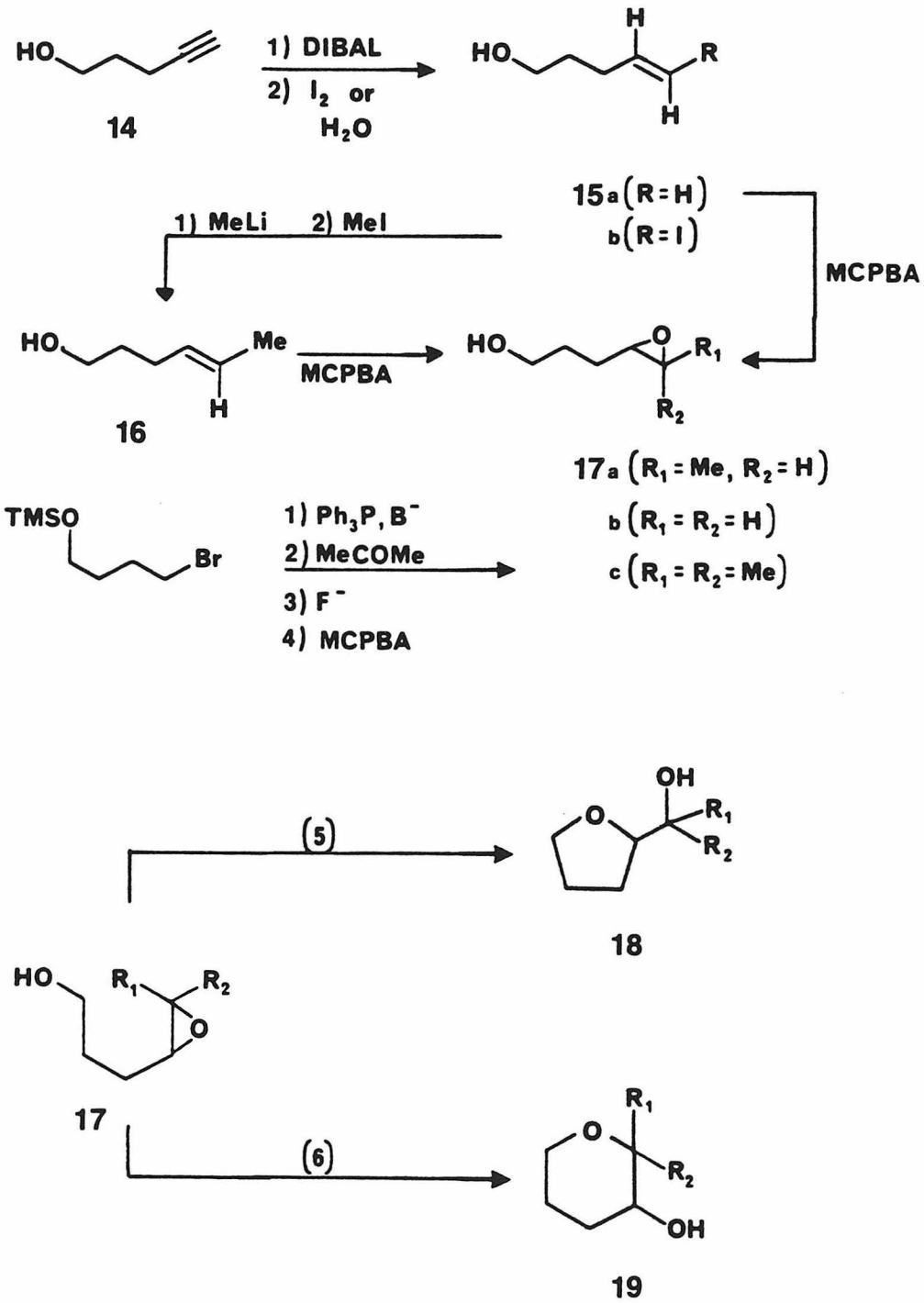
compound **11** with base in 75% aqueous dimethylsulfoxide resulted in cyclization only to the 4-membered ring product **12**. However, under anhydrous conditions, intramolecular cyclization occurred to give only the 5-membered ring product dimer **13**. Thus, it is clear that reaction conditions can effect the course of such intramolecular cyclizations, and it would be instructive to ferret out the factors governing their chemistry.

The simple preliminary experiments outlined in Scheme II would require examination before the investigation of more complicated polyepoxide systems. The synthesis of the necessary 4,5-epoxy alcohols **17a-c** is straightforward, starting with commercially available 4-pentyn-1-ol (**14**). The cyclization of substrates **17a-c** would be examined in an effort to determine the effect of various reaction conditions upon the regiochemistry of oxirane displacement. Critical issues to be looked at would include:

1) Catalyst effects (i.e., acid, base, Lewis acid, etc.)
2) Solvent effects (e.g., DMSO <u>versus</u> THF, etc.)
3) Counterion effects (K, Na, Mg...)

It is not unreasonable to expect differing modes of cyclization with differing nucleophilicities of the oxygen anion, as suggested by the work of Murai. For example, base-catalyzed isomerization in <u>aprotic</u> solvents of <u>low</u> solvating powers would involve attack by a highly nucleophilic oxygen, which would probably favor attack at the least substituted oxirane center, as in intermolecular cases. On the other hand, by attenuating the nucleophilicity of the oxygen anion by changing to a more <u>polar</u> solvent, the reaction might

Scheme II

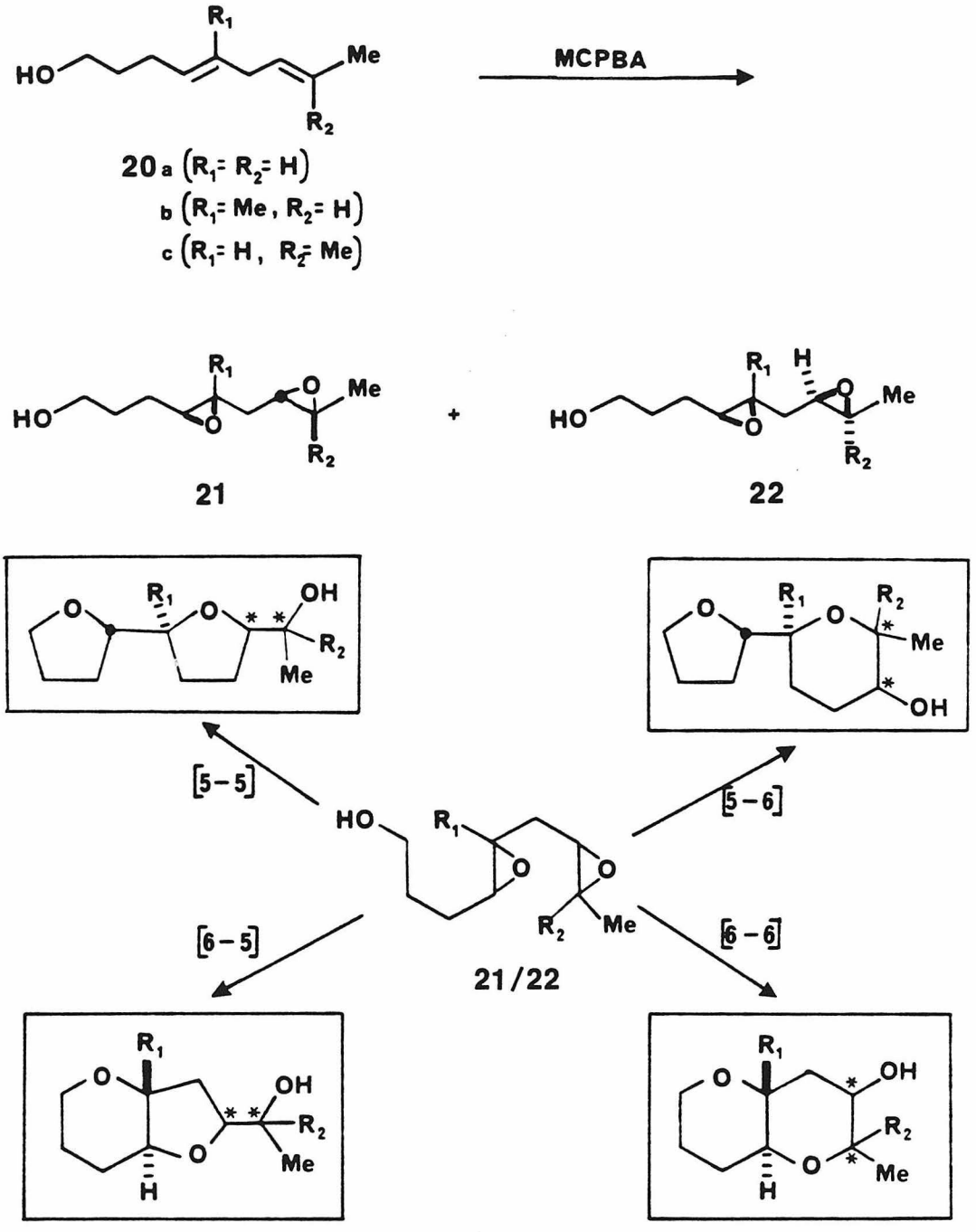

HO
1) DIBAL
2) I_2 or H_2O
H
R
14
15a (R=H)
b (R=I)
1) MeLi 2) MeI
MCPBA
Me
16
17a (R_1=Me, R_2=H)
b (R_1=R_2=H)
c (R_1=R_2=Me)
TMSO
Br
1) Ph_3P, B^-
2) MeCOMe
3) F^-
4) MCPBA
(5)
OH
18
17
(6)
19

be more sensitive to the "colinearity requirement" mentioned previously. Similar arguments would apply to effects due to counterion dependence. Experiments examining acid catalysis (H_3O^+, BF_3, etc.) would provide relevant information as to carbonium ion stability vs mode of cyclization. The results of these experiments would help to fill an existing void in our understanding of intramolecular epoxide cleavage.

With the results of the study outlined in Scheme II in hand, one would be better able to design a rational set of experiments for use in the more complicated di-epoxide cases. As illustrated in Scheme III, the situation rapidly becomes complex. Epoxidation of dienes **20a-c**[7] would be expected to produce a mixture of epoxide diastereomers **21** and **22**. Cyclization of these compounds could proceed along a number of differing paths, as shown.[8] In these cases, competition between cyclization to a 5- or 6-membered ring is examined. From these two possibilities, four reaction pathways are possible (i.e., (5-5), (5-6), (6-5) and (6-6)). These products are given in Scheme III.

For the simplest case (i.e., $R_1 = R_2 = H$), base catalyzed cyclization would be expected to proceed through the (5-5) manifold. This expectation is based upon the interesting observation that epoxidation of polymeric olefins such as **23** with peracid, followed by treatment with base, affords only the joined tetrahydrofuran products **24** (eq. 4).[9] However, in the more substituted cases, the situation is less clear. Unless conditions were found in the preliminary experiments which allow for complete control of any desired regiochemistry, it is most likely that substrates such as **21/22** would isomerize to provide a mixture of products resulting from a non-selective partitioning between reaction modes, probably being dependent upon the

Scheme III



*mixture of epimers

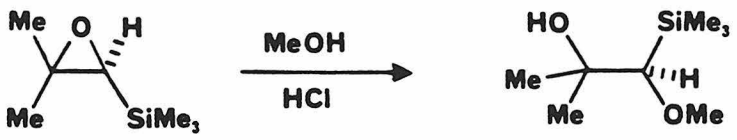
23

(4)

24

substitution pattern of the acyclic precursor. Nevertheless, a systematic study carried out on these types of substrates would provide additional information that currently awaits investigation.

Clearly, what is needed is the ability to direct the regiochemistry of the intramolecular displacement to effect whatever process is desired. A potential solution to this problem might be found in the synthetic exploitation of α,β-epoxysilanes. These versatile reagents are known to react with nucleophiles in acidic media exclusively at the α-carbon, forming the β-alcohols (eq. 5), which eliminate to olefins upon base treatment.[10] For example, exposure of the α,β-epoxysilane **25** to methanolic HCl affords compound **26** as the sole product. This remarkable result clearly demonstrates the high degree of regiochemical directivity imparted to an



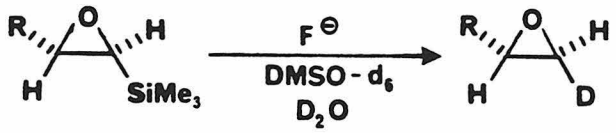
25 26

(5)

oxirane substituted with a trimethylsilyl group. The application of these findings to the problem of control of intramolecular epoxide cleavage is self-evident. For example, one would expect exclusive formation of the 6-membered ring product **28** upon treatment of epoxysilane **27** with mineral acid (Scheme IV). Removal of the trimethylsilyl group with cesium fluoride in DMSO follows the procedure of Magnus, who has successfully desilylated compounds such as **29** without effecting elimination to enol ethers (eq. 6).[11]

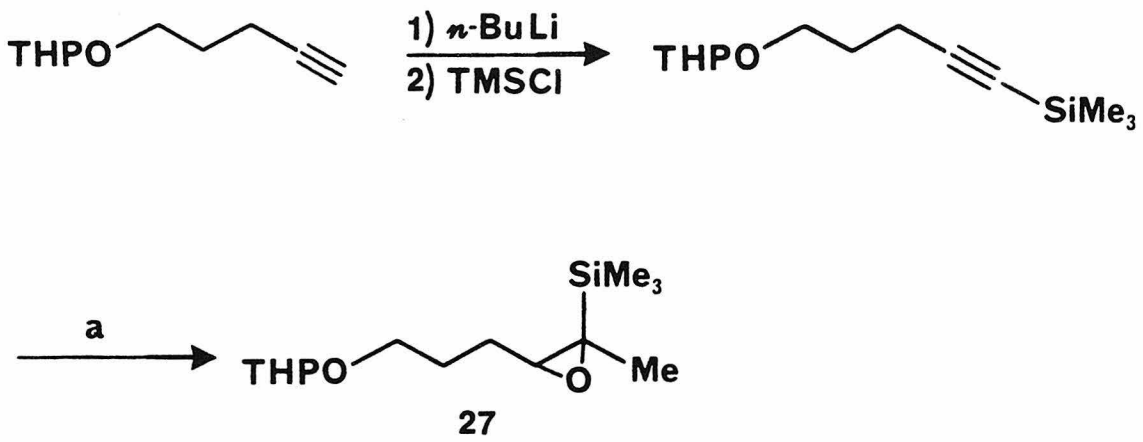
29 (6)

The resulting stereochemistry from this procedure is unknown, but might be expected to proceed with retention, as observed in the related fluoride-induced desilylation of α,β-epoxysilanes reported by Chan, et. al (eq. 7).[12]



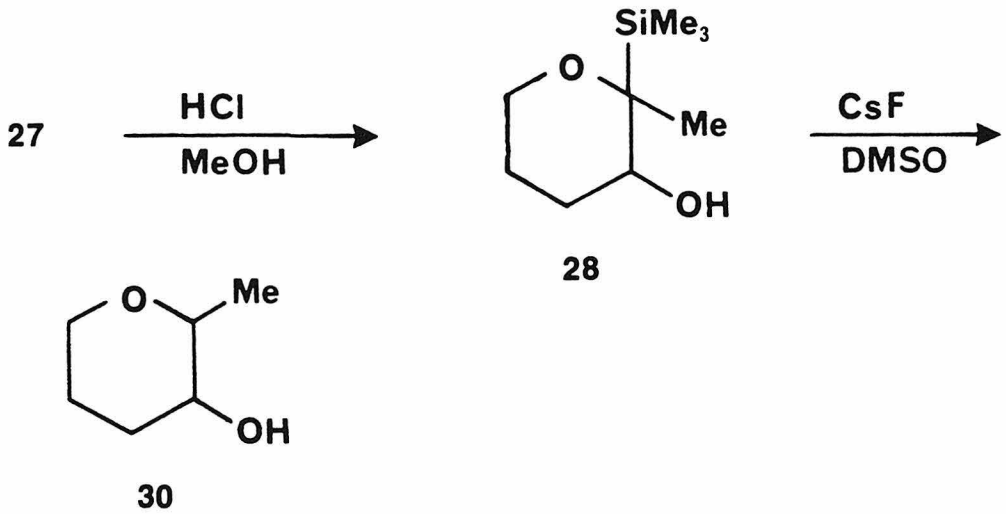
(7)

Scheme IV



27

a 1) DIBAL ; I_2 2) MeLi ; MeI 3) MCPBA

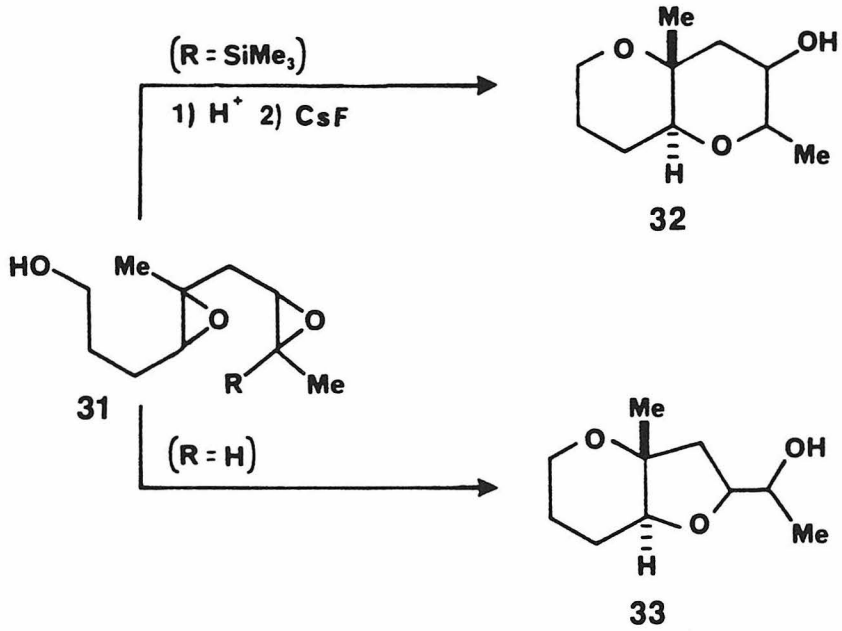


28

30

Certainly, experiments such as those in Scheme IV which address the issue of controlling the regiochemistry of ring-opening would be enlightening, especially with regard to poly-epoxide cases. For instance, controlled production of either the (6-6) isomer **32** or the (6-5) isomer **33** might be possible from acid treatment of precursor **31** by simply varying the nature of R (i.e., R = $SiMe_3$ versus R = H, eq. 8).

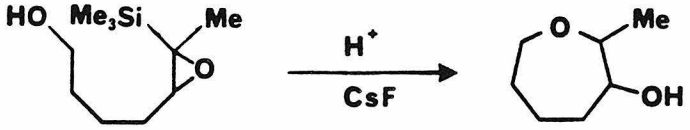
The ability to selectively produce compounds such as **32** bear relevance to synthetic studies on brevetoxin-B. Examination of the structure (see Fig. 2) reveals that application of poly-epoxide cyclizations to the construction of this carbon framework requires, for some of the rings, the preferred cyclization to form a 7-membered ring over a 6. A model system such as **34** would be



(8)

quite interesting to examine in this regard (eq. 9). The severe preference for nearly every intramolecular bifunctional cyclization to favor production of 6-membered ring products over the 7-membered counterparts is well-documented. It would be instructive to see if the directivity imparted on these reactions

by silicon is enough to override both the kinetic and thermodynamic preferences for formation of a 6-membered ring.



(9)

34

The experiments outlined in this proposal would lead to a better understanding of the underlying principles involved in the intramolecular isomerization of epoxy alcohols and polyepoxy alcohols. This isomerization bears relevance to the synthesis of many cyclic ether based natural products. Indeed, with the recent advent of methodologies allowing for stereospecific epoxidation of olefins,[13] these kinds of cyclizations could well become an important synthetic strategy for the organic chemist. The ability to direct the regiochemical course of these reactions by employing α,β-epoxysilanes would certainly add to the versatility of this method.

References and Notes

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PROPOSITION IV

Abstract: The use of spin-saturation transfer in ^{13}C NMR is proposed to obtain kinetic data and thermodynamic parameters for the non-dissociative ligand rearrangement in zerovalent Group VI-B complexes $M(CO)_5PR_3$.

* * * * * * * *

Stereochemical non-rigidity in six-coordinate octahedral complexes has been a long-recognized phenomenon.[1] Usually, the process by which ligand scrambling occurs is thought to proceed <u>via</u> a prior ligand dissociation mechanism.[2] However, there is a growing class of octahedral complexes where stereochemical non-rigidity due to a non-bond-breaking process has been demonstrated. The dihydrido complexes H_2ML_4 (M = Fe or Ru; L = phosphine or phosphite) have been shown to undergo such rearrangements.[3] It has also been observed that the cis → trans isomerization reactions of $Ru(CO)_4(SiMe_3)_2$ and $Os(CO)_4(SiMe_3)_2$ occur with no bond cleavage.[4]

Recently, Darensbourg has for the first time unambiguously established that internal ligand rearrangement in some zerovalent d^6 octahedral complexes containing monodentate ligands proceeds by a non-dissociative pathway as the lowest energy mechanism. The cis → trans isomerizations shown in equation 1 has been studied by infrared spectroscopy, and the kinetics have been worked out using this method.[5] When this reaction is carried out in a >90% ^{13}CO atmosphere, no incorporation of labeled carbon monoxide is evident in either the cis- or trans-complex, and no

formation of $Mo(CO)_4(^{13}CO)P\text{-}n\text{-}Bu_3$ is observed. Similarly, the isomerization of the labeled complexes in equation 2 have also been shown to undergo ligand isomerization via a non-dissociative mechanism.[6]

$$\underline{cis}\text{-}Mo(CO)_4(P\text{-}n\text{-}Bu_3)_2 \rightleftharpoons \underline{trans}\text{-}Mo(CO)_4(P\text{-}n\text{-}Bu_3)_2 \quad (1)$$

K_{eq} 85% $\underline{trans}$

$$\underline{cis}\text{-}M(CO)_4(^{13}CO)L \rightleftharpoons \underline{trans}\text{-}M(CO)_4(^{13}CO)L \quad (2)$$

M = Cr, Mo, W

L = $P(OMe)_3$, $P(n\text{-}Bu)_3$

Several mechanisms have been proposed to account for non-dissociative ligand scrambling in octahedral complexes. One of these, the so-called "Bailar Twist" proceeds through a trigonal prismatic intermediate as shown in Figure 1.[7] Variations on this mechanism include the Ray-Dutt[8] or Springer-Sievers[1a] processes. Rotation mechanisms involving bi-capped tetrahedral intermediates have also been proposed.[1d]

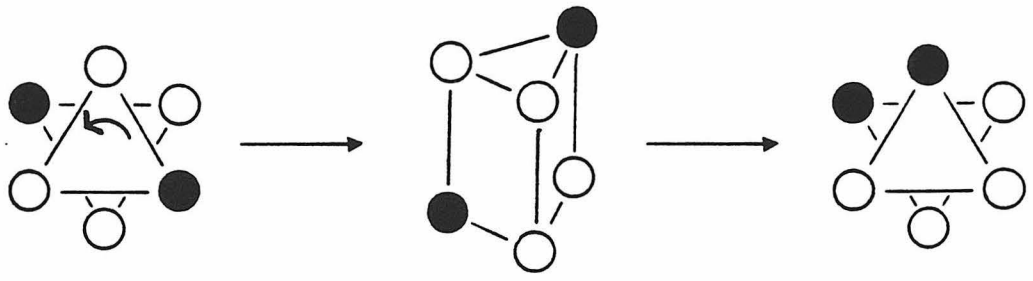

Figure 1. The Bailar Twist

For intramolecular rearrangements of the types illustrated in equations 1 and 2 to proceed through a trigonal prismatic intermediate as the lowest energy pathway is not unreasonable. Within the valence bond framework of constructing at the metal hybrid orbitals which maximize overlap with ligand orbitals, Hultgren has concluded that a trigonal prism configuration would have grater energy per bond, but the octahedron would have smaller inter-ligand repulsive forces.[9] Furthermore, in their pioneering study of the racemization and isomerization of tris-chelate complexes, Fay and Piper calculated the crystal field stabilization for d^6 O_h and D_{3h} geometries and found greater stabilization in the trigonal prismatic configuration.[10] The seemingly overwhelming preference for octahedral geometry in six-coordinate complexes is therefore probably a manifestation of ligand-ligand repulsions. In this regard, it is interesting to note that when triphenylphosphine is the non-carbonyl ligand in the reaction shown in equation 1, the isomerization proceeds through a dissociative mechanism.[5] Presumably, the more sterically demanding triphenylphosphine ligand destabilizes the trigonal prismatic intermediate enough to perturb the mechanism toward a bond-breaking process.

A kinetic study of the intramolecular rearrangements shown in equation 2 have not been carried out. Qualitative rate information has revealed a metal dependence on the relative energy barriers to this process. Interestingly, the relative ease of ligand scrambling for the Group VI-B metals follows the order of Cr < W < Mo, chromium being the fastest.[6a,c] Indeed, even with the triphenylphosphine complex, the reaction in equation 2 still proceeds through a non-dissociative pathway when the metal is chromium.[6c]

Based upon steric considerations alone, one would expect a greater ease of flexibility for a trigonal twist for the larger Mo and W species. Clearly, electronic effects are important in these processes. Reliable kinetic information to determine thermodynamic parameters would provide illuminating information regarding the energetics of these rearrangements. It is proposed here to use the technique of spin-saturation transfer in order to experimentally determine this information.

Forsen and Hoffman have described a nuclear magnetic double resonance method of measuring the rate of exchange between two non-equivalent sites in a molecule.[11] One site is saturated with a strong radio frequency magnetic field, and the other site is observed. Interchange between the two sites carries the saturation to the observed site, resulting in a decrease in the NMR signal of that site. From the amount of signal attenuation observed (and some measurable parameters (vide infra)) one can easily and accurately calculate rate constants. This technique has been successfully applied in the determination of the activation parameters for such fluxional molecules as cyclohexane-d_{11},[12] various cis- and trans-dimethylcyclohexanes,[13] and cis-decalin.[14]

The viability of this method for the study of chemical reaction dynamics requires a relationship between the T_1 spin-lattice relaxation time of the nucleus being saturated and the average lifetime with which that nucleus occupies the site in question (τ). Ideally, these two quantities should be approximately equal. The observed decrease in NMR signal due to spin-saturation transfer is related to the rate constant for exchange in the following way.[14] For two equally populated sites, A and B, when a strong

irradiating radio frequency is applied at site B at t = 0, the magnitization at site A decreases from an initial value of $M_z^A(O)$ to a value of $M_z^A(t)$ after a time t. The dependence of $M_z^A(t)$ on the lifetime in site A, τ_A, and the spin-lattice relaxation time T_1, is given by

$$M_z^A(t) = M_z^A(O)[(\tau_{1A}/\tau_A)\exp(-t/\tau_{1A}) + \tau_{1A}/T_{1A}] \tag{3}$$

where τ_{1A} is defined as

$$\tau_{1A}^{-1} = T_1^{-1} + \tau_A^{-1} \tag{4}$$

When $t \rightarrow \infty$, equation 3 becomes

$$M_z^A(\infty) = M_z^A(O)\tau_{1A}/T_1 \tag{5}$$

which upon substituting for τ_{1A} in equation 4 gives

$$\tau_A = \frac{M_z^A(\infty)T_1}{M_z^A(O) - M_z^A(\infty)} \tag{6}$$

$M_z^A(O)$ can be measured in the absence of irradiation at site B, and $M_z^A(\infty)$ can be measured in the presence of irradiation at site B, providing at least $5\tau_{1A}$ are waited after switching on the irradiation before measuring $M_z^A(\infty)$. There are a number of different pulse sequences which directly measure T_1.[15] The derived τ_A is related to the rate constant for exchange by simply $k_r = \tau_A^{-1}$.

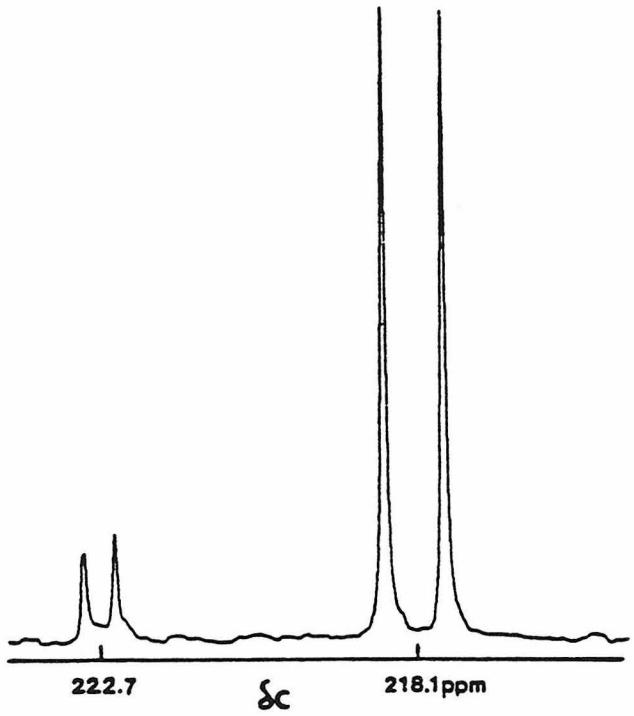

Figure 2. Natural abundance ^{13}C NMR of the carbonyl region of $Cr(CO)_5PPh_3$ at 80°C (from ref. 6c).

Shown in Figure 2 is the natural abundance ^{13}C NMR of the carbonyl region of $Cr(CO)_5PPh_3$. Signals for the axial and equatorial carbonyls are resolved by over 4 ppm [$\delta(C_{trans})$ 222.7 (J_{P-C} = 6.8 Hz); δ (C_{cis}) 218.1 (J_{P-C} = 13.2 Hz)]. Saturation at the signal for the axial carbonyl (222.7 ppm) would result in a diminution of the signal at 218.1 ppm representing the equatorial carbonyls. However, four carbonyl resonances are contributing to this signal, versus one for the axial carbonyl. Since equation 6 was derived for two equal populated states, an adjustment must be made. Multiplication of the observed decrease in $M_Z^A(\infty)$ by four is required in order to obtain the

correct lifetime for an equatorial carbonyl τ_A. Thus, equation 6 can be rewritten, and the rate constant for axial → equatorial exchange is then given by

$$k_r = \tau_A^{-1} = \frac{(1/4)\left(M_z^A(O)/M_z^A(\infty)\right) - 1}{T_1} \qquad (7)$$

As previously stated, this method is most accurate when $\tau_1 \cong \tau_A$. The spin-lattice relaxation time for metal-bound carbonyl carbons is quite large, usually between 100-200 sec.[16] The rate of ligand exchange in equation 2 (M = Cr) has been estimated at 3×10^5 sec^{-1} at 40°C with an E_a of <32 kcal $mole^{-1}$ but >16 kcal mol^{-1}.[17] Simple extrapolation reveals that a convenient temperature to do these experiments would be ca. 80°C, where $\tau_A \cong 130$ sec.. This would result in a $M_z^A(\infty)/M_z^A(O) \cong 0.40$, which is certainly within an accurately measurable range.

The technique of spin-saturation transfer would provide relevant and accurate rate information for the non-dissociative ligand rearrangements of the Group VI-B metal carbonyl systems depicted in equation 2. This procedure is superior to those involving ^{13}C labeled compounds, as no stereospecific syntheses of ^{13}C enriched samples are needed.[6] This technique could be used for all three metal systems in equation 2, even though the rates of exchange for the W or Mo complexes is slower than that of the Cr species. Indeed, previous applications of this procedure have determined rate constants covering a range of over half a million![12] The derived thermodynamic parameters would provide important information regarding the energetics of this theoretically interesting phenomenon.

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(17) See Ref. 6c. The authors estimated about a 20% error in the rate constant.

PROPOSITION V

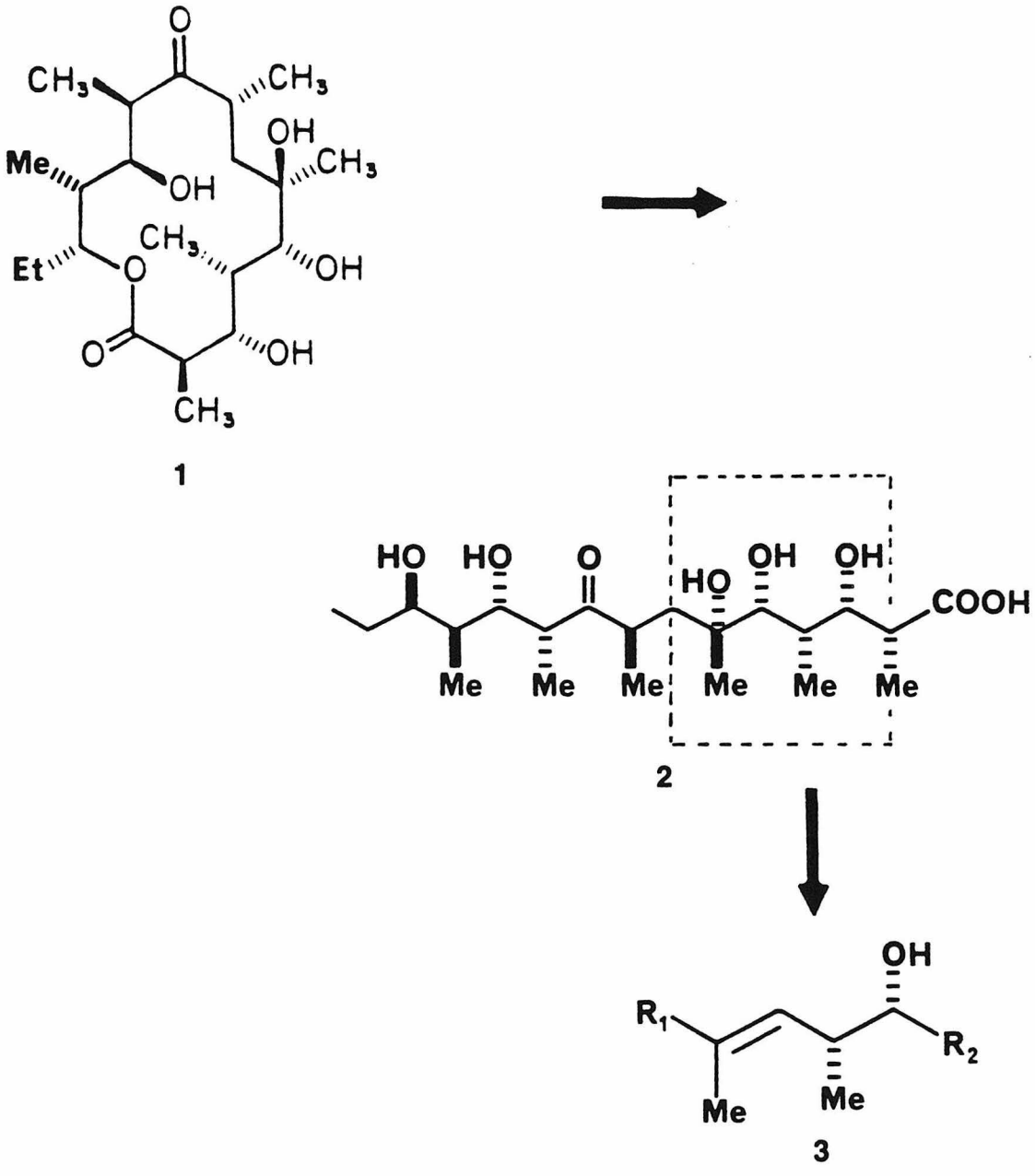
Abstract: An investigation of hydroxy-directed asymmetric induction in the oxidation of homoallylic alcohols by osmium tetroxide is proposed.

* * * * * * * *

The stereoselective establishment of a carbon-oxygen bond on an acyclic carbon backbone has received extensive investigation in recent years. The abundance of poly-hydroxylated natural products demands methodologies whereby the construction of chiral carbinol centers can be easily achieved. A number of elegant procedures which accomplish this goal, either directly or indirectly, have been reported.[1] These include the stereoselective reduction of carbonyl precursors,[2] the hydroboration of olefins with chiral borane reagents,[3] the conformationally directed epoxidation and hydroboration of chiral allylic alcohols,[4] and the asymmetric epoxidation of prochiral allylic alcohols.[5] The significance and utility of these procedures has been demonstrated by their repeated use in a number of synthetic projects.

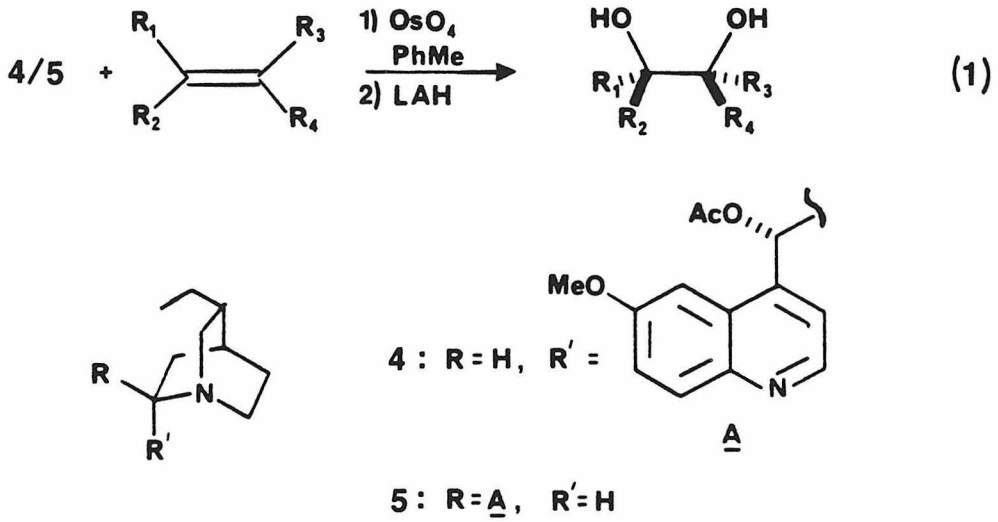
A logical and important extension of current methodology would be the development of a procedure whereby vicinal diols could be obtained in a stereospecific sense. A number of natural products contain 1,2-diol fragments, and such a procedure might find application in the synthesis of these molecules. Consider, for example, the structure of the important antibiotic aglycone erythronolide B (**1**, Scheme I). The derived seco-acid **2** exhibits a 1,3,4-triol sequence (in box) which conceivably could arise from an

Scheme I


O
CH3
CH3
OH
Me
CH3
OH
CH3
Et
O
OH
O
OH
CH3
1
HO
HO
O
HO
OH
OH
COOH
Me
Me
Me
Me
Me
Me
2
OH
R1
R2
Me
Me
3

asymmetric hydroxylation of olefin **3**.

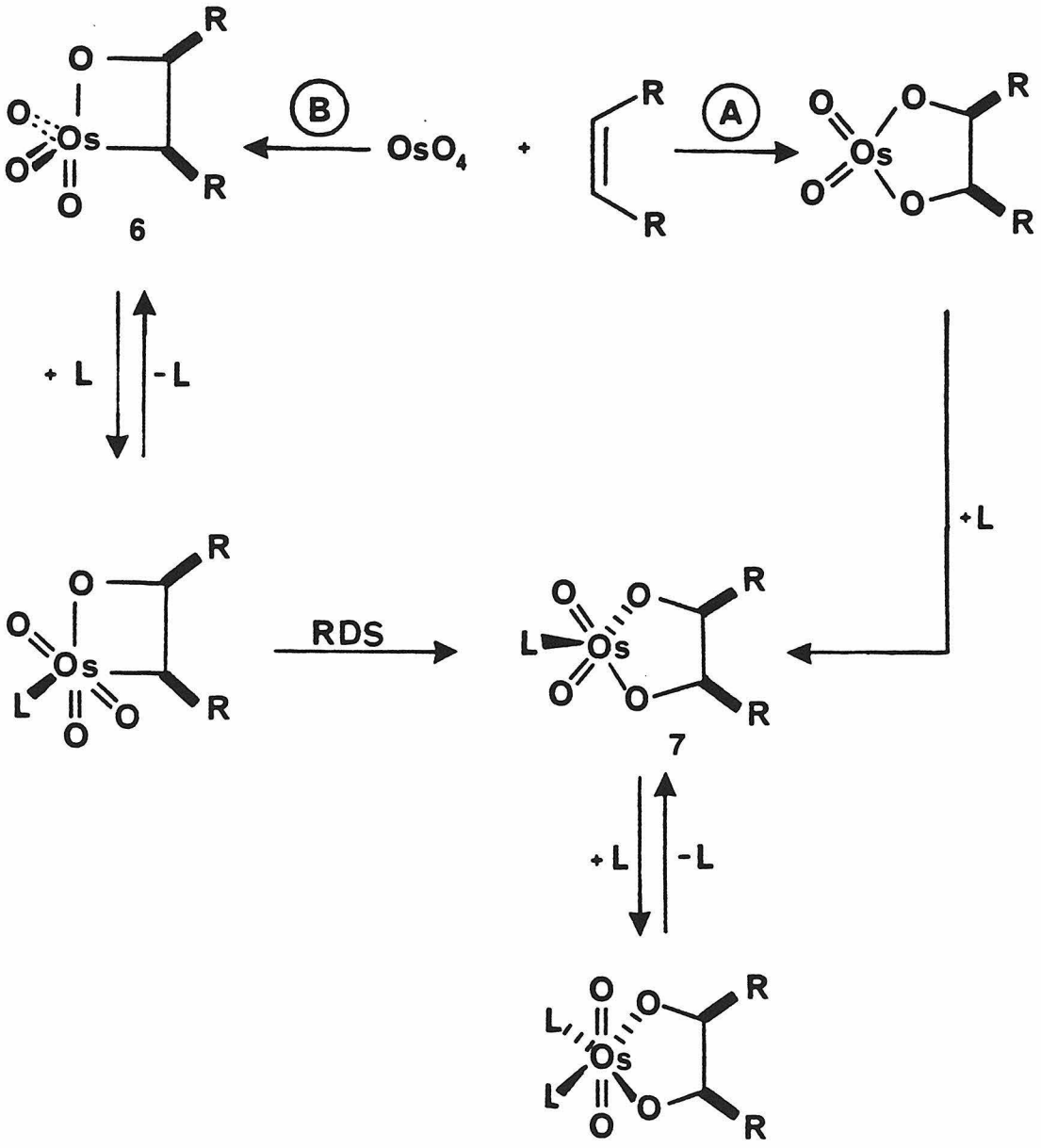
Certainly the most reliable method for the conversion of olefins to cis-vicinal diols involves the stoichiometric use of osmium tetroxide in pyridine.[5] Among the miriad applications of this reagent, however, there exists but a single report where an attempt has been made to influence the stereochemical course of this reaction. Sharpless has examined the cis-hydroxylation of prochiral olefins with osmium tetroxide in the presence of the chiral tertiary amine bases **4** and **5** (eq. 1).[6] Although the results were



encouraging, the enantiomeric excesses obtained (5-83%) were not synthetically useful. It is interesting to note that the diastereomeric quinuclidine bases **4** and **5** provided complimentary senses of asymmetric induction in this reaction.

The mechanism by which osmium tetroxide reacts with olefins is unknown. Proposed mechanisms include a direct (3+2) cycloaddition process[5] (Path A, Scheme II) and a stepwise process proceeding through the

Scheme II



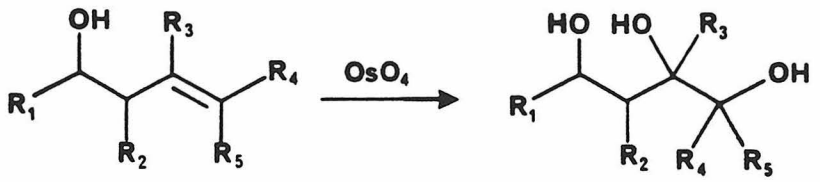
organoosmium intermediate **6** (Path B),[6,7] which ultimately rearranges in a rate-determining step to the osmate ester **7**, an intermediate also involved in Path A. Although distinguishing between these two possible mechanisms is difficult, general observations tend to support Path B.[7] However, the intimate involvement of donor ligands (e.g., pyridine) has been demonstrated.

In this proposal, exploratory experiments are given which attempt to define the degree to which one might expect to see relative asymmetric induction in the cis-hydroxylation of homoallylic alcohols (eq. 2). The rationale for these experiments are based on two assumptions:

1) The hydroxyl group is capable of coordinating to the metal center in OsO_4.

2) A cyclic transition state obtains, whereby chain substituents adopt positions of lowest steric congestion.

These assumptions have been invoked to explain the high levels of relative asymmetric induction seen in the vanadium-catalyzed epoxidations of homoallylic alcohols.[8]



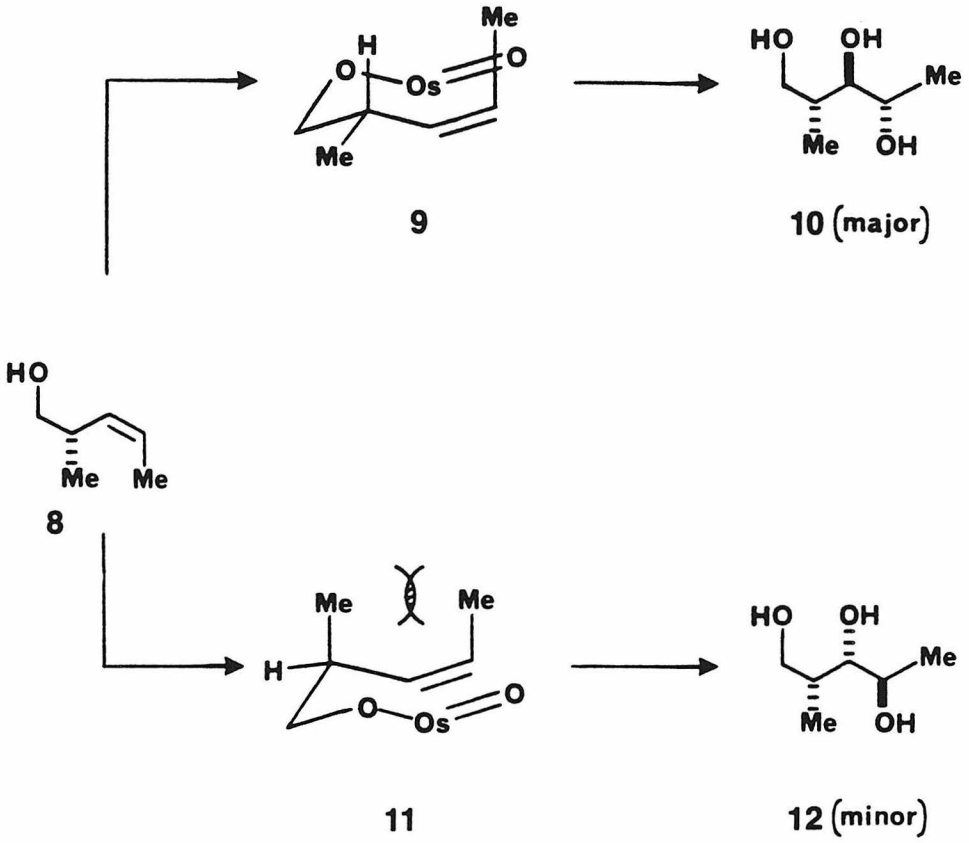
(2)

By way of illustration, consider the example outlined in Scheme III. Osmium tetroxide oxidation of **8** could proceed through two different "6-membered" chair-like transition states, **9** and **11**. Severe 1,3-diaxial substituent interactions in transition state **11** would disfavor this mode of reaction, and the triol **10** would be the expected product. Indeed, the vanadium-catalyzed epoxidation of **8** produces diastereomer **13** with >400:1 stereoselectivity (eq. 3).[8] This remarkable selectivity has been rationalized by arguments analogous to those presented here.

A variety of substituted homoallylic alcohols would be studied in order to asses the relative importance of a variety of substrate parameters. Initially, however, a number of predictions can be made based upon transition state models (Scheme IV). For example, the Z-olefin **8** would be expected to exhibit higher levels of asymmetric induction than the corresponding E-isomer **14**, which places the vinyl methyl group in a psuedo-equatorial position. Also, the threo-isomer **15** allows for both methyl groups to adopt equatorial conformations in a cooperative sense, whereas the erythro-isomer **16** requires at least one substituent to be axial. Furthermore, 1,1-disubstituted olefins such as **17** would be expected to be more sensitive to chirality at the hydroxyl-bearing center than at the allylic position, as the $R_1 \leftrightarrow R_5$ interactions of the former would be more severe than the R_3 or $R_4 \leftrightarrow R_5$ interactions of the latter. It is thus clear that the examination of a number of suitable substituted substrates would provide experimental evidence which would impact directly upon the viability of the proposed transition state arguments.

It is interesting to note that the predicted sense of asymmetric

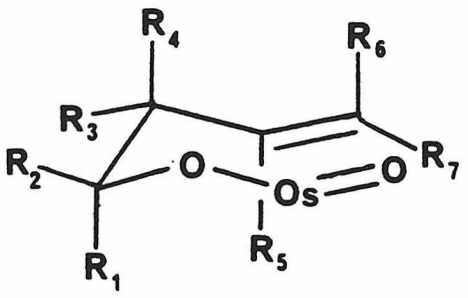
Scheme III



(3)

selectivity > 400:1

Scheme IV



8 14

15 16

17

induction in these reactions is opposite to that predicted by $A^{1,3}$-strain arguments.[9] As illustrated in Figure 1 for compound **8**, the preferred conformation places the larger group (i.e., hydroxy-methyl) blocking the top face, and would predict that attack of OsO_4 would occur from the least hindered bottom face. This would result in the production of triol **12** (Scheme

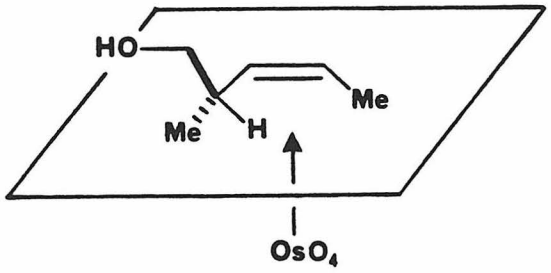


Figure 1. $A^{1,3}$-strain prediction

III), the minor product in the hydroxyl-directed manifold. Thus, it might be possible to obtain either triol diastereomer from the same starting olefin, as shown in Figure 2.

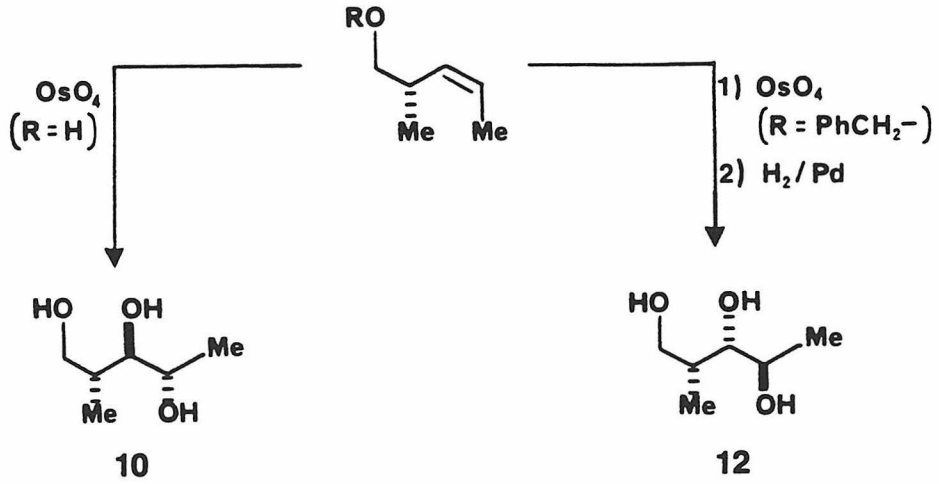
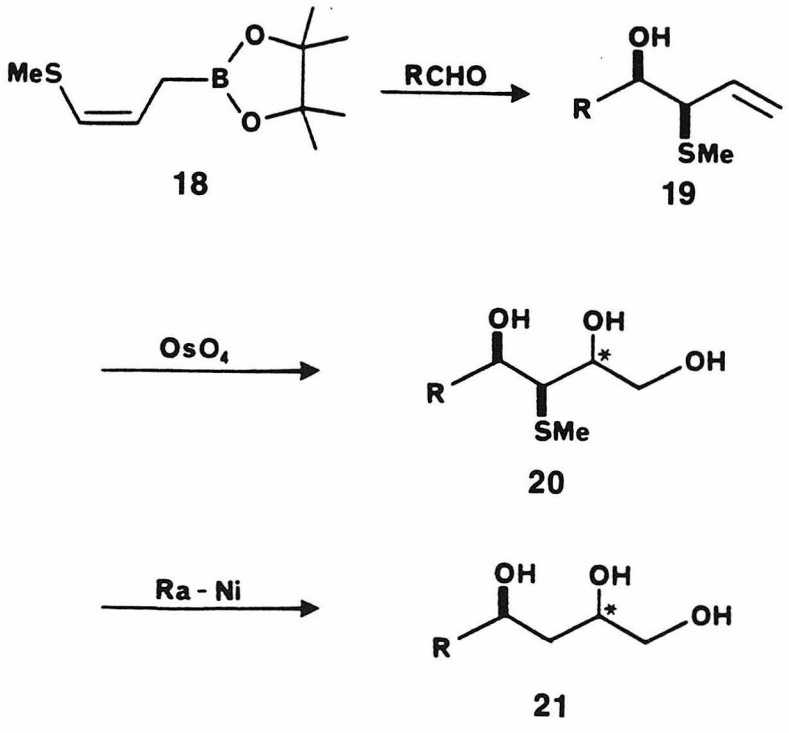


Figure 2

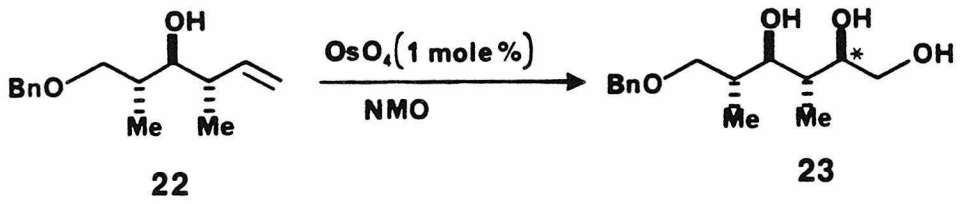
Another interesting idea in this area might involve the use of a removable chiral substituent to direct the stereochemistry of these oxidations. As outlined in Scheme V, erythro methyl sulfide **19** can be stereoselectively prepared from the condensation of the Z-γ-alkylthio-allylboronate **18** with an aldehyde following the procedure of Hoffmann.[10] Osmium tetroxide is known to be ineffective in the oxidation of sulfides.[11] Thus, treatment of the unsaturated sulfide **19** with OsO_4 would produce triol **20**, the stereochemistry of which would probably be dependent upon the nature of **R**. Reductive cleavage of the carbon-sulfur bond with Raney-Nickel affords triol **21**. Due to the ubiquity of 1,3-diol relationships in natural products, such a procedure might find synthetic applicability.

Scheme V



18 **19** **20** **21**

That the ideas put forth in this proposition are valid has recently been demonstrated by an observation in our own group.[12] Treatment of compound **22** with 1 mole % of OsO_4 in the presence of N-methylmorpholine-N-oxide[13] afforded triol **23**. Gas chromatographic analysis of the derived acetonide revealed a stereoselectivity of 78:22 at the indicated carbinol center. The major diastereomer obtained is that which is entirely consistent



22 **23**

*78:22

with the transition state model illustrated in Scheme IV, where all substituents are occupying equatorial positions.[14] That this reaction proceeds with such a high degree of stereoselectivity is remarkable, considering the fact that 50% aqueous acetone was employed as the solvent. This result suggests a strong interaction between OsO_4 and the secondary alcohol of **22**.

Based upon the above result and coupled with the observations of Mihelich[8] in the V^{+5}/THP epoxidations of similar systems, it is felt that the experiments described in this proposal have a high probability of success. This methodology would add to the ever-growing technology of asymmetric control in acyclic systems and could prove valuable to the synthetic organic chemist.

References and Notes

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