THE TOTAL SYNTHESIS OF A-23187 AND RELATED ENANTIOSELECTIVE ALDOL CONDENSATIONS

Thesis by

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To Sherri

and

to my parents

To Be a Scientist

Most of us have harbored at one time in our lives the romantic image of the scientist in a white lab coat working on some exciting project. While a scientist's lot is not always as glamorous as it seems, this profession does have its own unique satisfactions.

There is an overwhelming reward which every scientist will find at one time or another...the sheer blinding excitement of discovery, the uncovering of something which was hidden until his work was begun and now is revealed, the unbelievable gratification of tackling a difficult problem and hanging on through months or years of hard, disappointing, difficult work until the answer is in his hands.

This one thing alone, most scientists would agree, will compensate for everything else....

Alan E. Nourse

ACKNOWLEDGEMENTS

I would like to thank Dave Evans for his guidance and interest in my development as a scientist during my tenure at Caltech. His enthusiasm for chemistry, his encouragement in times of adversity, and his vast knowledge of chemistry combine to create a stimulating and rewarding research environment.

My stay at Caltech has been enriched in many ways by all the members of the Evans group, but I extend a special thanks to Jim Takacs, Dave Hart, and Scott Biller for their numerous contributions to my educational development. I also thank my coworkers, Cliff Sacks, Bill Kleschick, Ernst Vogel, and John Nelson, because without their collaboration the work described here could not have been accomplished. Also, thank you Sherri for always being a constant source of encouragement.

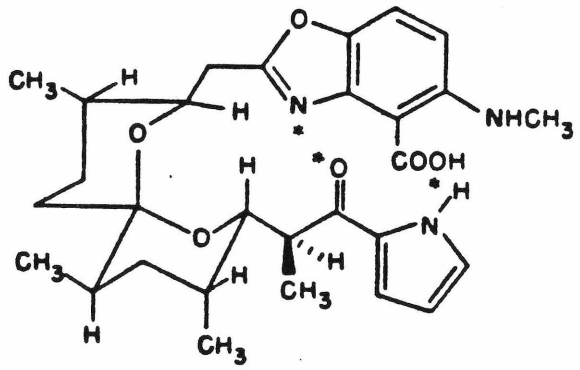
I wish to express my appreciation to the National Institutes of Health, California Institute of Technology, and Dave Evans for financial assistance.

Finally, a special word of thanks is extended to Dot Lloyd for a superb job in constructing this thesis.

ABSTRACT

A-23187 is a calcium specific ionophore which was isolated from Streptomyces chartreusis. The total synthesis of A-23187 and synthesis of related diacid ionophores are discussed.

The synthetic approach used for A-23187 required stereoselective aldol condensations. In this regard, the development of enantioselective aldol condensations with boron enolates is detailed. The general applications of such condensations are also discussed.



A-23187

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

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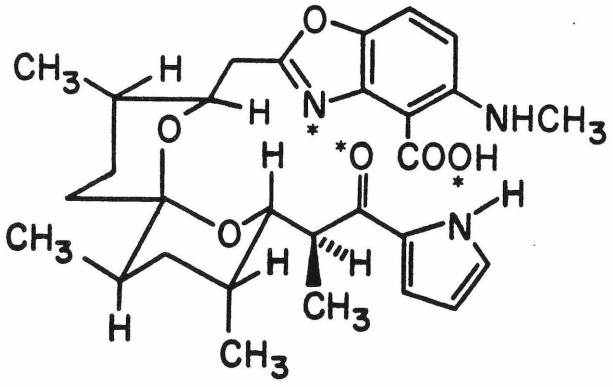
CHAPTER I

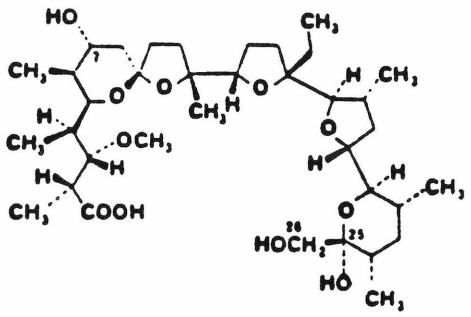
Total Synthesis of A-23187

Introduction

The rapid expansion in the number of new polyether antibiotics has served to increase the general interest in these compounds.[1] This class of structurally-unique antibiotics characteristically form lipophilic metal ion complexes which are effective in ion transport across lipid barriers.[2] Accordingly, extensive literature is accumulating on the biochemical applications of these ionophores,[1,3] which now number over forty. Nonetheless, three members have received considerable attention clinically, A-23187 (1a),[4] monensin (10),[5] and lasalocid (X-537A, 11).[6] Among these ionophores, A-23187 appears to be unique in its divalent cation transport selectivity, vide infra. This report elaborates on our communication[7] reporting the first total synthesis and the absolute configuration of A-23187.



1a



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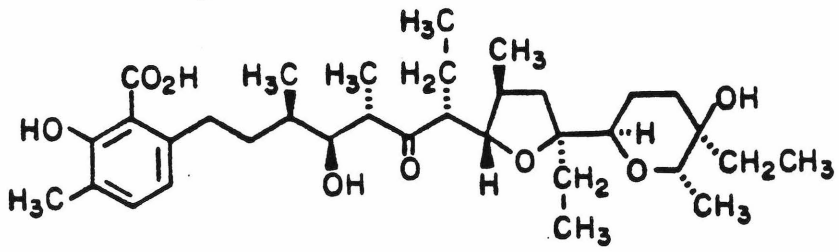

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The ionophore A-23187 (calcimycin) was isolated from cultures of Streptomyces Chartreusensis in 1972[8] and its structure (but not absolute configuration) was determined by X-ray and combined spectroscopic techniques two years later.[4] In contrast to other ionophores, A-23187 does not bind alkali metal cations and it displays good selectivity among divalent cations based on ionic radius (Figure 1).[9]

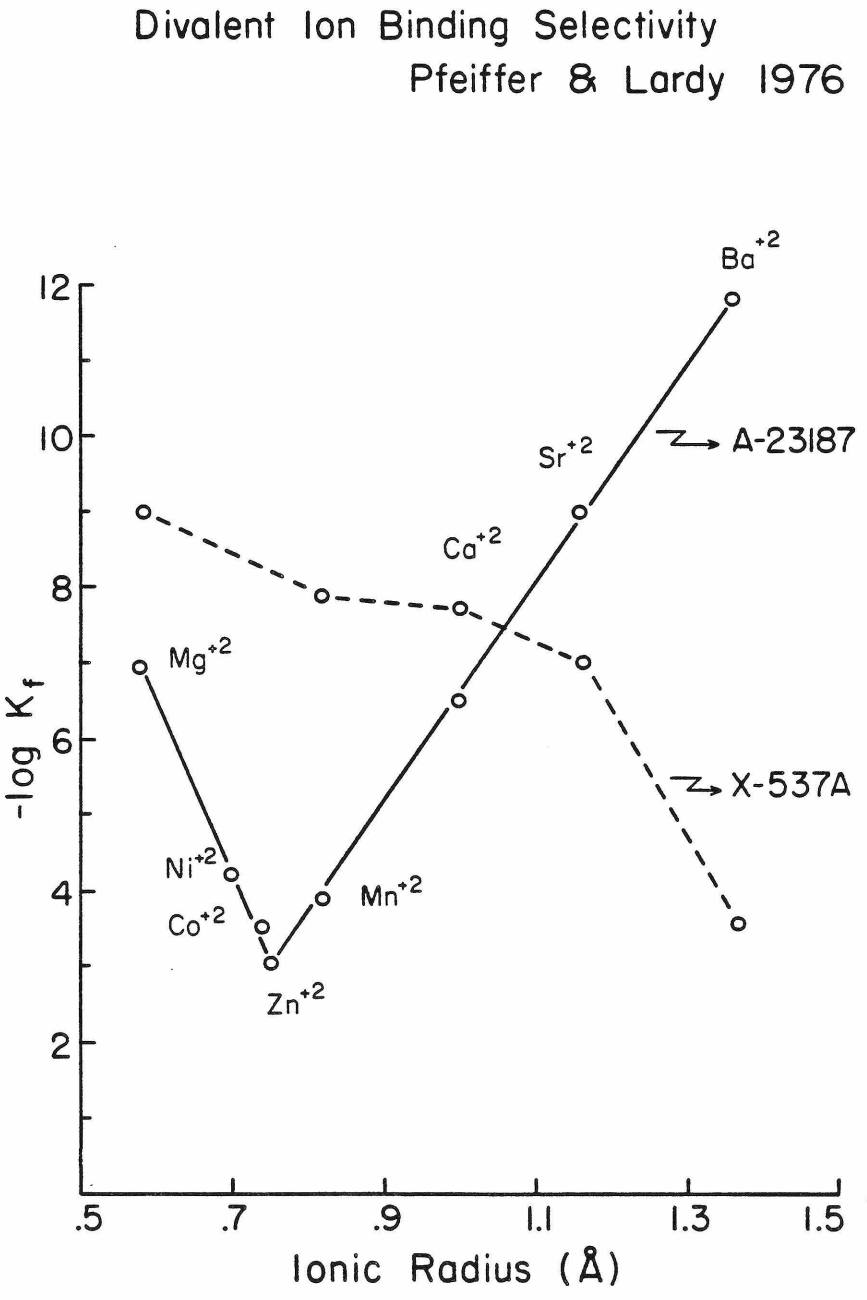
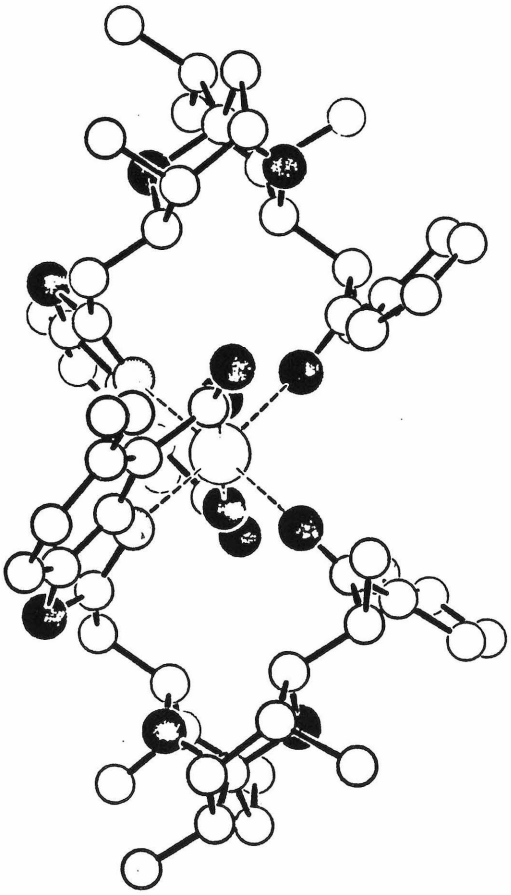
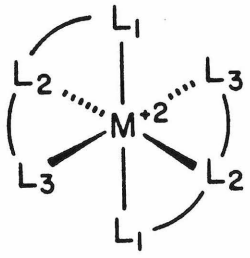


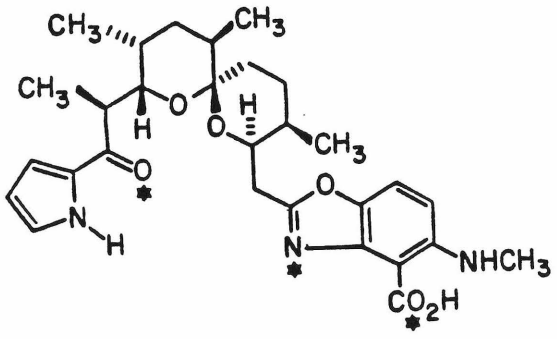
Figure 1

The 1,7-dioxaspiro[5,5]undecane backbone provides a rigid chelating cavity which is probably responsible for the ion

selectivity exhibited by A-23187. The X-ray structure of the calcium complex (Figure 2) indicates a 2:1 ionophore-cation complex with binding at the benzoxazole nitrogen, the carboxylate, and the pyrrole carbonyl oxygen (starred positions in 1a).[10] The ion specificity of A-23187 and its easy







A-23187

Figure 2

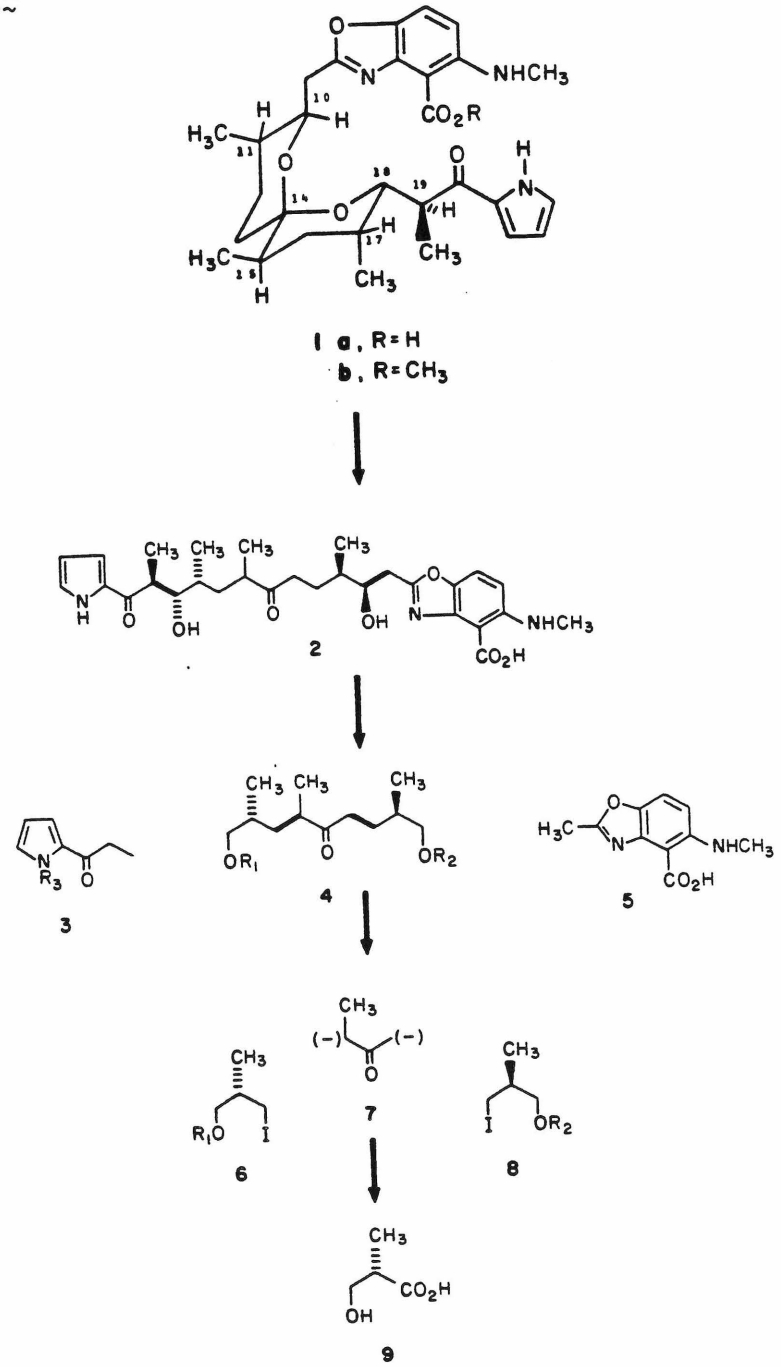
detection by fluorescence make it a useful biochemical tool for monitoring ion transport; consequently, evidence is mounting on its utility as an effective probe for the involvement of metal ions in physiological processes.[1,3]

The unique architectural features of the polyether antibiotics are synthetically challenging and provide the opportunity for new synthetic developments. In A-23187 the prominent structural feature is the 1,7-dioxaspiro[5.5]-undecane ring system (see 1a). This spirane system is contained by only a few other molecules, most of them also ionophores isolated from mold metabolites: Salinomycin,[11a] Narasin,[11b] Milbemysin,[11c] Antibiotic B-41,[11d] Oligomycin B,[11e] and Rutamycin.[11f] Two others, Aplysiatoxin[11g] and Oscillotoxin,[11h] have recently been isolated from marine sources. Our retrosynthetic planning will center on the formation of this rare spirane system.

In a retrosynthetic analysis of A-23187 a key element to be recognized is the latent C_2-axis of symmetry which relates the stereocenters C-18 and C-17 to C-11 and C-10 (Scheme I). This axis is easily seen by opening the spiroketal 1a to the potential keto diol precursor 2. Based upon the anomeric effect and related stereochemical considerations,[12] we projected that the 1,7-dioxaspiro[5.5]-undecane ring system in 1, with the requisite C-14 stereochemistry, would be readily attained from 2 via acid-catalyzed

ring closure (Scheme I). We also assumed that stereochemical

Scheme I



control of the C-15 methyl-bearing stereocenter need not be addressed in the synthesis of 2 since acid-catalyzed equilibration of this center during the spirocyclization should afford the desired equatorial methyl diastereoisomer, vide infra.

With these considerations in mind, intermediate 2 should be accessible from the heterocyclic precursors 3 and 5 and the ketone 4 via sequential aldol condensations. The application of these aldol condensations to the assemblage of intermediate 2 would create two new hydroxyl-bearing stereocenters (cf 2, C-10 and C-18). With the C_2 symmetry element in 2, proper stereochemical relationships at both C-10 and C-18 can be projected from the established stereocenters C-11 and C-17 via a Cram's rule argument. This stereochemical prediction is outlined in Figure 3 for a general nucleophile (Nu) using the Felkin model for 1,2-asymmetric induction.[13] Assuming non-perpendicular nucleophilic attack, transition state T_1 is favored due to minimal steric interaction between the incoming nucleophile (Nu) and substituents at the chiral center (Nu $\longleftrightarrow$ H for T_1, Nu $\longleftrightarrow$ CH_3 for T_2).[13] The favored transition state T_1 gives the Cram's-rule product, which contains the stereochemical relationship needed for the natural product (OH and CH_3 cis). Thus, the major aldol condensation products should have the correct absolute

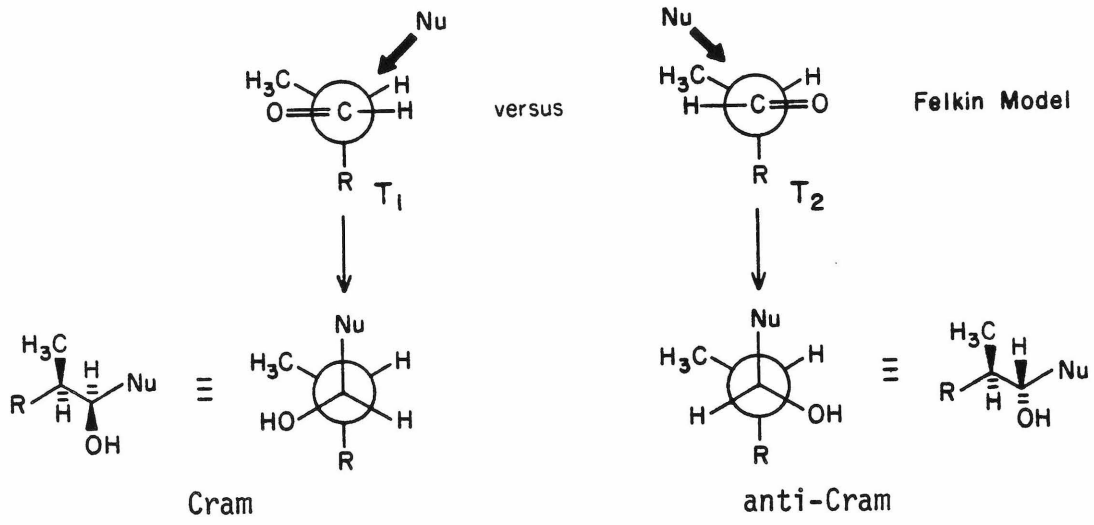


Figure 3

configurations at stereocenters C-10 and C-18. As a footnote, there are two sequences in which the aldol condensations could be undertaken. Both routes were examined and the advantages and shortcomings of each will be outlined, *vide infra*. Additionally, the aldol condensation establishing the C-18 stereocenter would also introduce the C-19 methyl-bearing stereocenter. Based on prior art, the construction of the threo relationship between C-18 and C-19 needed for A-23187 *via* a kinetic aldol condensation requires a trans-enolate.[14]

Intermediate ketone 4 could be constructed through alkylations of butanone (or an operational equivalent) with iodides 6 and 8 (Scheme I). By virtue of the C_2-axis of symmetry, with respect to skeletal carbons C-10 ⟶ C-12 and C-16 ⟶ C-18, the chiral centers in 6 and 8 could be secured from the same four carbon unit, (S)-(+)-β-hydroxyisobutyric acid 9.[15] With this analysis in mind, herein is described the total synthesis and the absolute configuration of the ionophore A-23187.

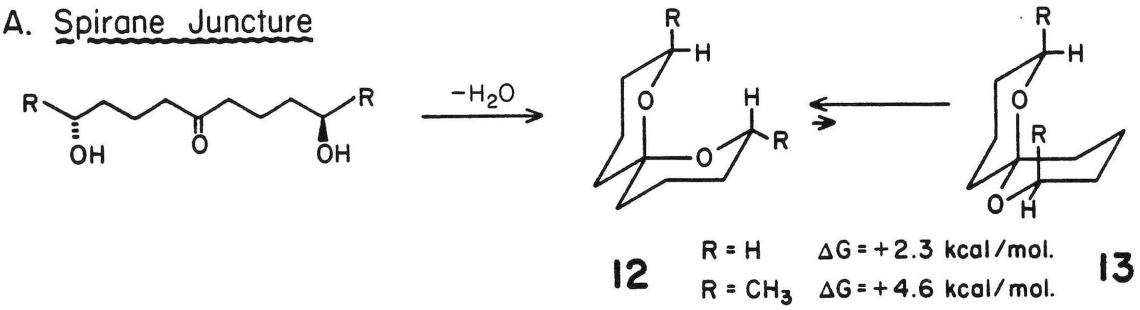
Results and Discussion

Spirane Model Studies. Prior to initiating the total synthesis of A-23187, the final stages of the projected synthetic plan which involve the formation of the stereocenters C-14 (spirane juncture) and C-15 (methyl-bearing stereocenter, cf. 1, Scheme I) warranted model studies to test the assumptions made in the retrosynthetic analysis. Concerning the C-14 spirocenter, the closure of an acyclic ketone diol can give two configurational isomers, 12⇄13, as well as two conformational isomers, 12⇄14 (Scheme II). In calculations to determine the predominant isomer, the anomeric effect[16] and 1,3-diaxial steric interactions were given major consideration. Using standard A values for a cyclohexane system[17] and a value of 0.6 kcal/mole[16b] for the anomeric effect, the diaxial oxygen configuration

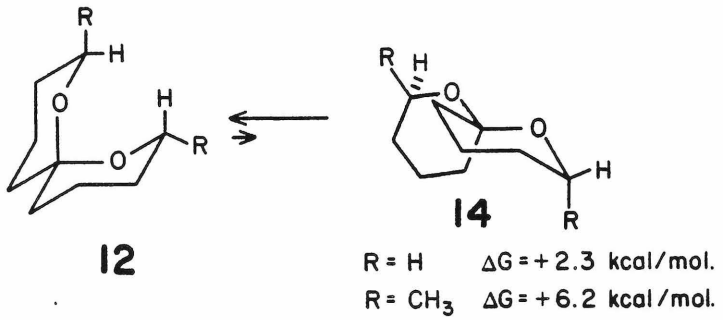
Scheme II

Stereochemical Considerations

A. Spirane Juncture



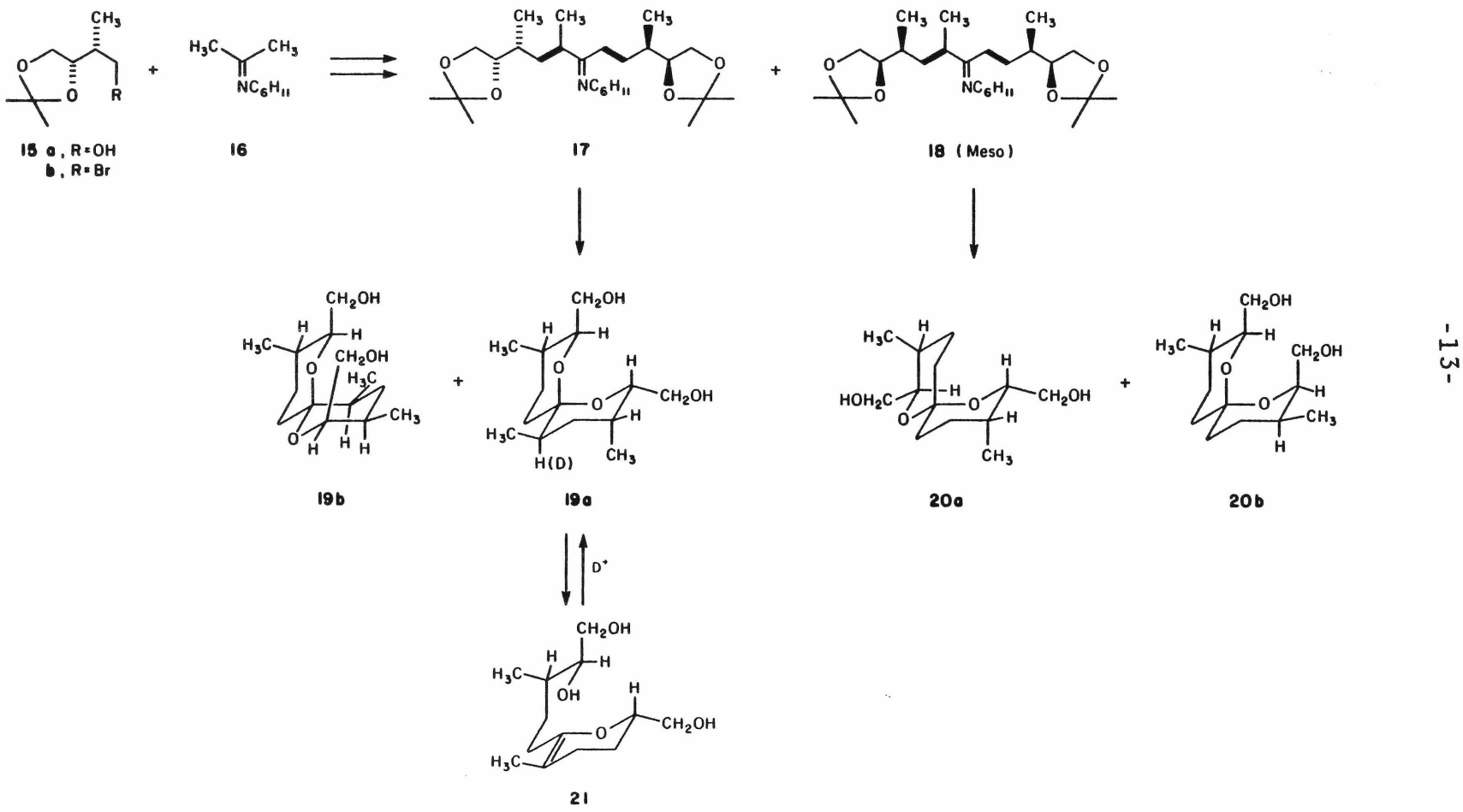
B. Spirane Conformation



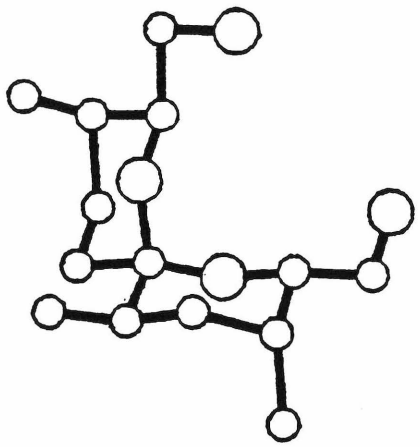
(12) was calculated to be favored by at least 2.3 kcal over the next most stable configuration, (13). Correspondingly, conformation 12 is also at least 2.3 kcal more stable than conformation 14. It is noteworthy that the most stable isomer 12 is the same configuration and conformation as that of A-23187.

In order to test these calculations and previous assumptions concerning the C-15 stereocenter, the imines 17 and 18 were prepared and cyclized to examine stereochemical consequences of spirane closure and possible methyl equilibration at the C-15 stereocenter (Scheme III).[51] The known alcohol 15a[18] was converted to the corresponding mesylate and displaced with lithium bromide in acetone-dimethoxypropane to give bromide 15b.[18] The acetone imine 16 could be sequentially bisalkylated with 15b and methylated conveniently in a one-pot procedure. Alkylation of acetone cyclohexylimine 16 with two equivalents of bromide 15b in the presence of two equivalents of lithium diethylamide,[19] followed by deprotonation with another equivalent of base and then alkylation with methyl iodide gave a 1:1 mixture of imines 17 and 18 (stereochemically undefined at C-15). Closure of this mixture could give rise to four diastereoisomers with respect to the C-14 stereocenter: two from 17 (19a, 19b) and two from 18 (20a, 20b). Acidic workup of the imine reaction mixture yielded a crystalline spirane (48%) identified by ^{13}C NMR and X-ray analysis[20] (Figure 4) as 19a[21] (from 17) mp 75-77°C, and an oil (32%) identified by ^{13}C NMR analysis as a mixture of diastereoisomers 20a and 20b (from 18, Scheme III). This spirane closure confirms the stereochemical calculations and earlier observations[22] that, given the proper

Scheme III



relative configurations at the hydroxyl-bearing centers, spirane closure occurs in a stereoselective manner.



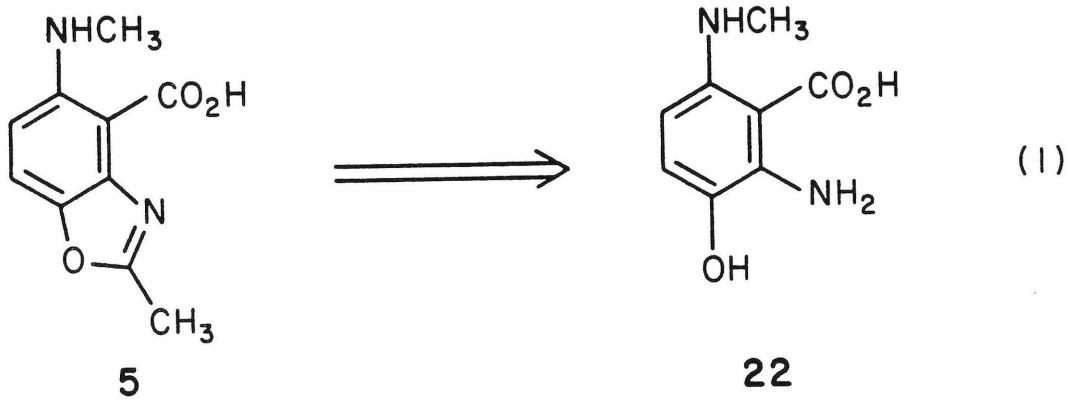
19a

Figure 4

To test the equilibration of the C-15 methyl group, treatment of 19a with DCl in deuterium oxide gave back the same spirane (80%) as a crystalline solid. ^{13}C, ^{1}H NMR and mass spectral analysis indicated an average of 1.5 deuterium per molecule with complete deuteration at C-15. These data conclusively indicate that equilibration of the C-15 methyl is possible. Presumably, this equilibration proceeds through a monocyclic intermediate such as dihydropyran 21 (Scheme III). Having confirmed that the configuration at the spirocenter (C-14) could be controlled and the

configuration of the methyl at C-15 could be equilibrated, our attention was directed to the total synthesis of A-23187.

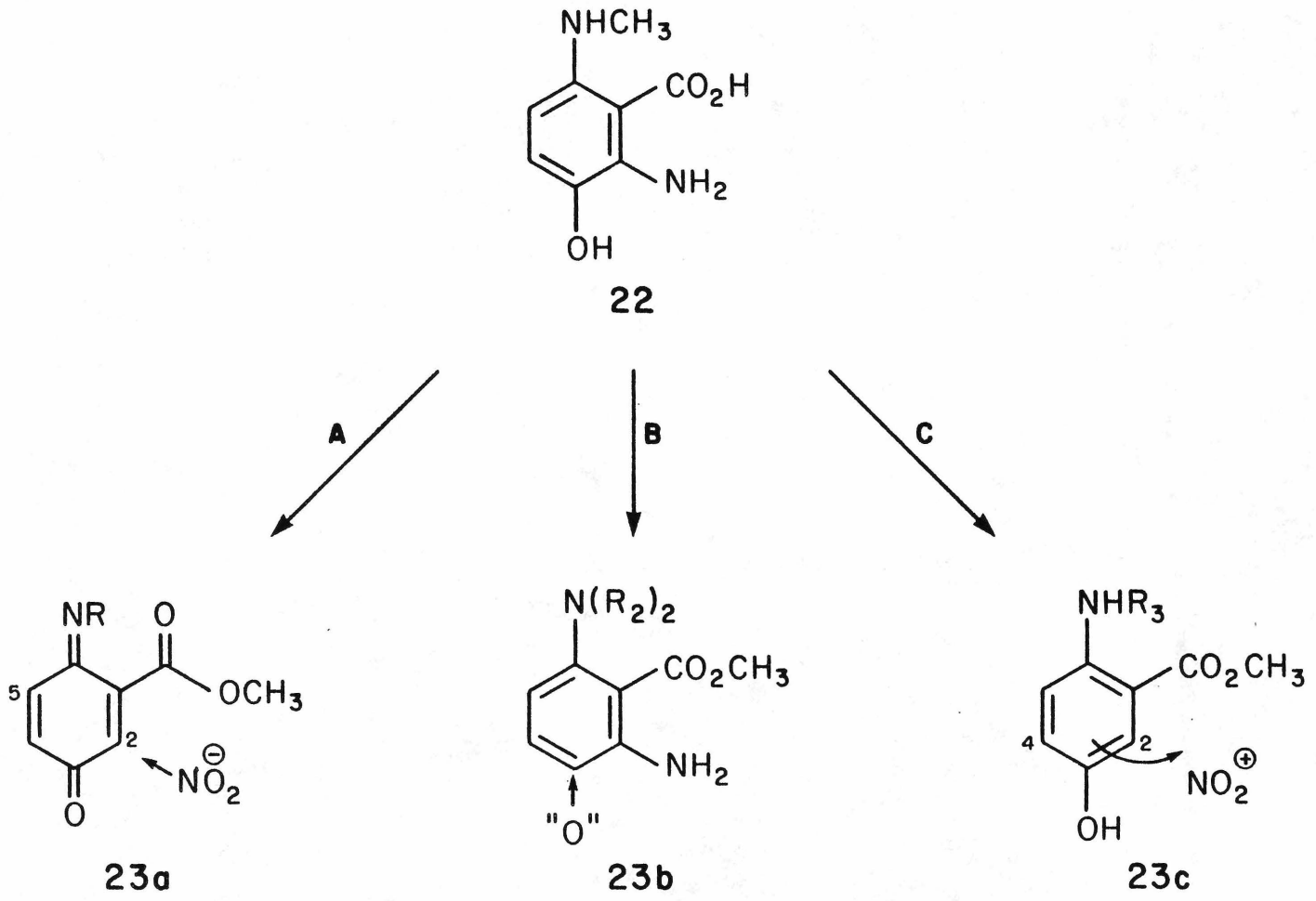
Synthesis of Benzoxazole (5). Based upon the ample literature precedent which documents the transformation of 2-aminophenols to benzoxazoles,[23] the synthesis of 5 was reduced to an examination of potential routes to the requisite aminophenol 22 (eq. 1). The problems inherent



5 22 (1)

with the synthesis of 22 include the contiguous 1,2,3,4-substitution pattern and the diverse functionality. Both of these factors seem to preclude traditional aromatic substitution reactions, which tend to be non-regioselective. Nonetheless, the diverse functionality does provide several options to explore (Scheme IV). The selection of precursors 23a, b, c was based upon previously designed syntheses of 23a-c or closely-related analogues and potential chemical

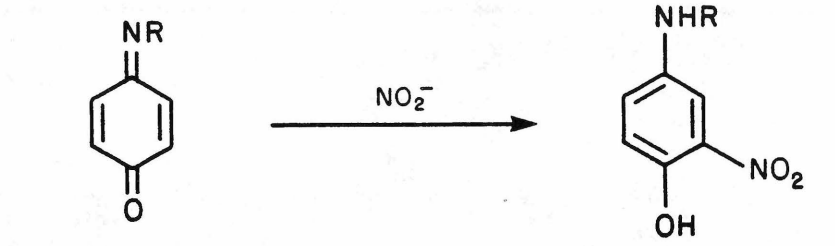
Scheme IV


NHCH3
CO2H
NH2
OH
22
A
B
C
NR
O
OCH3
5
2
NO2
O
23a
N(R2)2
CO2CH3
NH2
"O"
23b
NHR3
CO2CH3
4
2
NO2
OH
23c

transformations for the introduction of the final substituent, as outlined below.

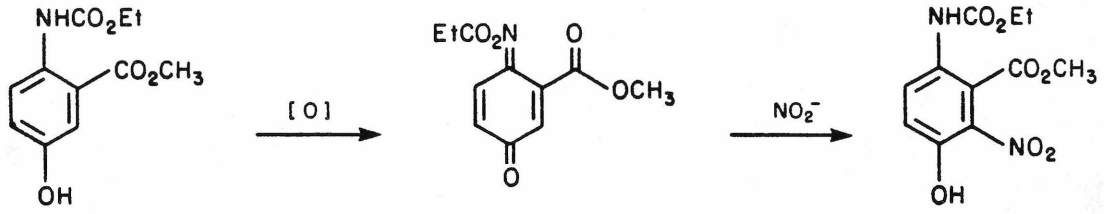
Route A would require the introduction of nitrogen via regioselective, nucleophilic 1,4-addition to quinone imide 23a (Scheme IV). Based on Adams's detailed studies with quinone imides, it was known that most nucleophiles added 1,4 with respect to the imide (substitution @ C-2 rather than C-5, Scheme IV).[24] However, Adams also found that amine nucleophiles were non-selective in their reactivity with quinone imides (1,2-addition, 1,4-addition, and overaddition).[24] Thus, the nitrite ion was selected as the nitrogen nucleophile since it could easily be reduced to an amine function. Model studies to test this approach were conducted with the known quinone imides 24a, b (Scheme V).[24] Under conditions found to promote 1,4-addition of nitrite to methylvinylketone ($NaNO_2$, DMSO, HOAc, 25°C), only modest success (20-30% desired nitrophenol 25a, b, Scheme V) was realized. Efforts to increase the nucleophilicity of the nitrite ion (KNO_2 and 18-crown-6 or elevated temperatures) failed to increase the yield of nitrophenol 25. Hoping that the electronic effects of an electron-withdrawing substituent (CO_2Me) would enhance 1,4-addition, attempts were made to synthesize quinone imide 23a by oxidation (Ag_2O, benzene) of the corresponding

Scheme V



24 **a**, R = SO_2Ph
b, R = CO_2Et

25 **a**, R = SO_2Ph
b, R = CO_2Et

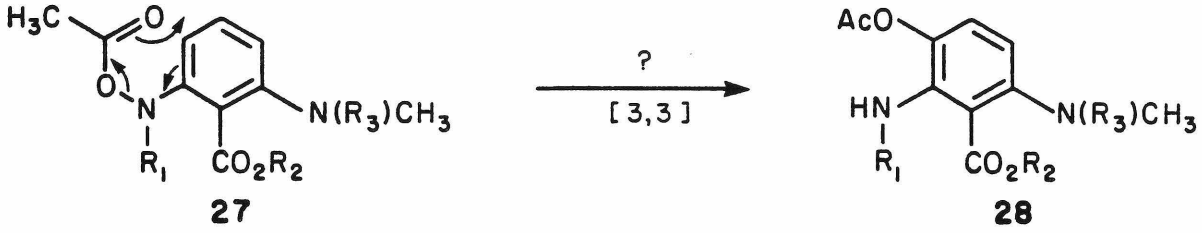


23d **23a** **26**

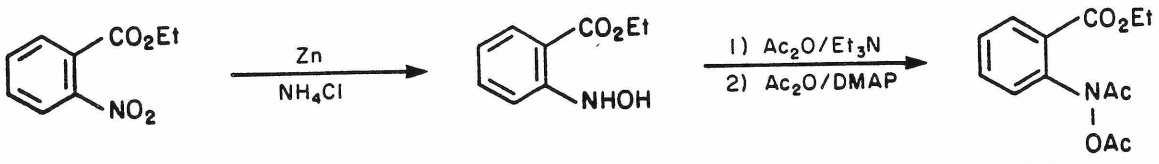
amidophenol (23d, Scheme V). However, imide 23a could not be successfully isolated. Attempted *in situ* generation of 23a (Ag_2O, benzene, 50°C)[25] followed by nitrite addition failed to produce any discernible nitrophenol 26 (Scheme V).

Another route to 22 (B) would require the introduction of the hydroxyl function as a final step (Scheme IV). The [3,3] sigmatropic rearrangement of acylated phenylhydroxylamines is such a hydroxylation procedure which produces α-aminophenols in good yields (see 31b, 33b, Scheme VI).[26] In general, these rearrangements have been limited to substrates bearing little or no functionality on the aromatic ring. However, the requisite intermediate 27, to produce 28, is highly-functionalized (Scheme VI). *A priori*, the effects of these substituents upon the sigmatropic rearrangement was not predictable; thus, several relevant model studies were conducted. The phenylhydroxylamine 30a was prepared by reduction of ethyl 2-nitrobenzoate (29) with zinc in the presence of ammonium chloride.[27] The hydroxylamine 30a was monoacylated with acetic anhydride and triethylamine in THF followed by acylation with acetic anhydride and 4-dimethylaminopyridine in dichloromethane[28] to afford the diacetylated hydroxylamine 32a in 60% overall yield. Thermal rearrangement of 32a gave less than 10% of the protected aminophenol 33a in contrast to the 70-90%

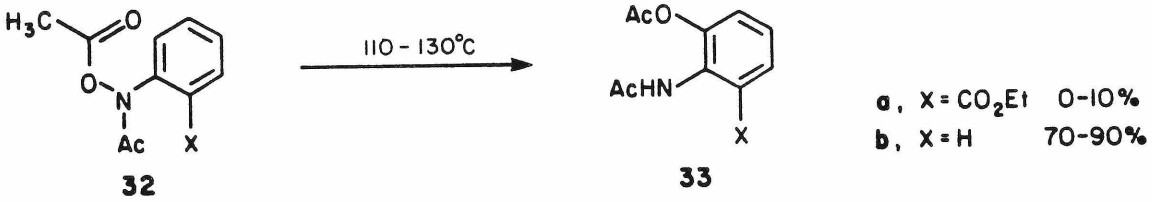
Scheme VI



27 28

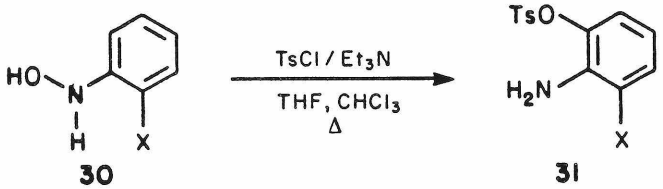


29 30a 32a



32 33

a, X = CO_2Et 0-10%
b, X = H 70-90%



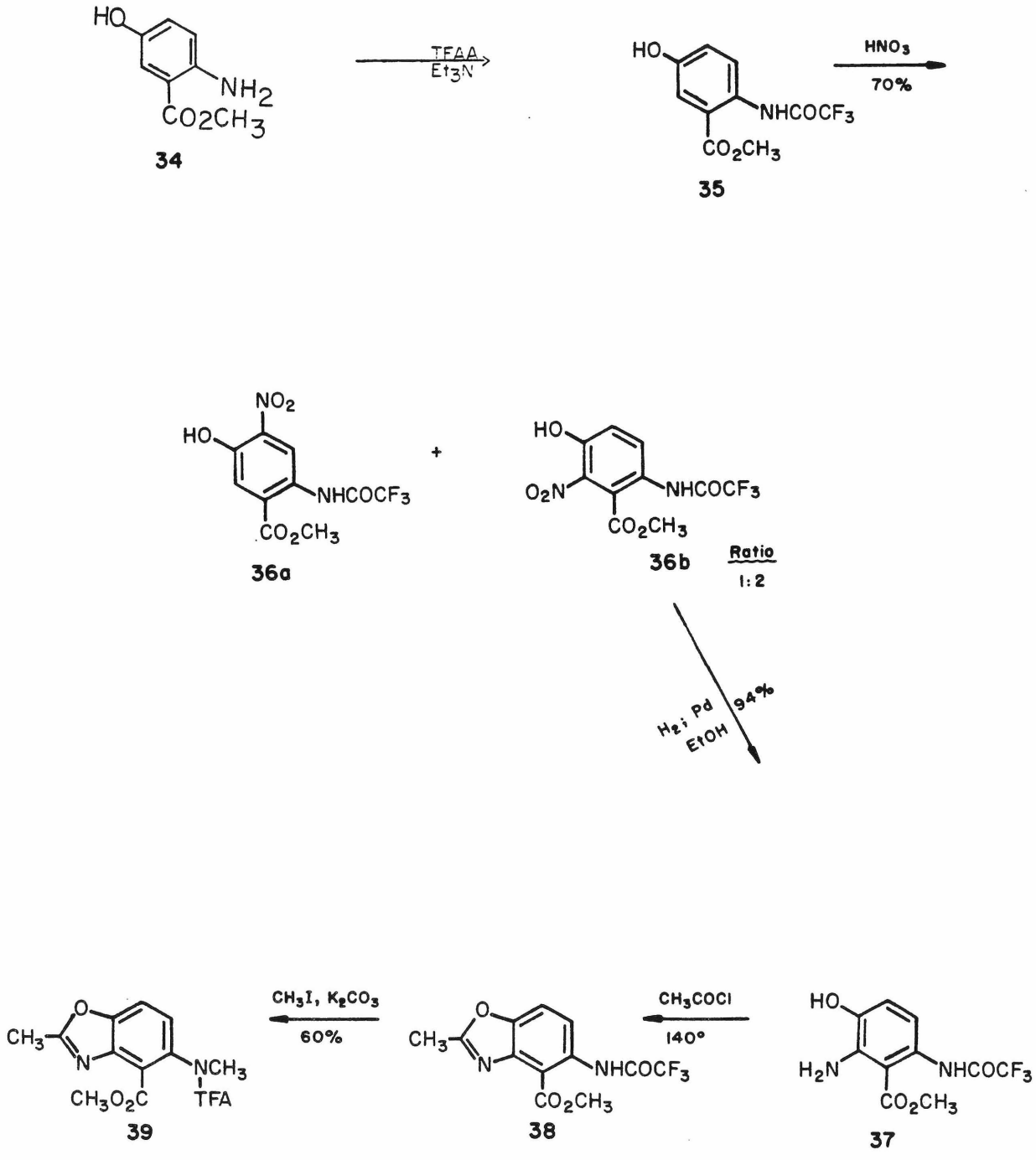
30 31

a, X = CO_2Et 20%
b, X = H 80%

yields for the rearrangement of 32b to 33b.[26a] In a related procedure the free hydroxylamines 30a and 30b underwent rearrangement when treated with tosyl chloride/triethylamine and subsequent heating in $CHCl_3$/THF.[26b] Under these conditions 30b afforded 31b in 80% yield, but the model system 30a gave only a 20% yield of aminophenol 31a (Scheme VI). Several other experiments in this area failed to produce acceptable yields of substituted aminophenols. We conclude that the carboxylic ester ortho to the hydroxylamine substituent imparts either electronic or steric factors upon the reaction which greatly reduce the amount of rearranged products formed.

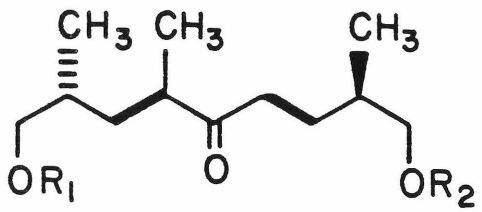
A practical synthesis of the benzoxazole moiety 5 was finally developed by relying on the introduction of nitrogen via electrophilic aromatic substitution (route C, Scheme IV). A priori, we had anticipated that mononitration of 23c would show a greater propensity for substitution at C-4 rather than sterically-hindered C-2 (the requisite substitution site for benzoxazole 5); thus, we had neglected the nitration route C. These misgivings turned out to be unfounded. The known methyl 5-hydroxyanthranilate 34[29] was trifluroacylated with TFAA/pyridine to give phenol 35, mp 136-138°C (Scheme VII). Nitration of 35 with 1 equiv of HNO_3 in ether afforded a 2:1 mixture of the desired nitro-

Scheme VII


HO
NH2
CO2CH3
34
TFAA
Et3N
HO
NHCOCF3
CO2CH3
35
HNO3
70%
NO2
HO
NHCOCF3
CO2CH3
36a
+
HO
O2N
NHCOCF3
CO2CH3
36b
Ratio
1:2
H2; Pd
EtOH
94%
CH3
O
N
NCH3
CH3O2C
TFA
39
CH3I, K2CO3
60%
CH3
O
N
NHCOCF3
CO2CH3
38
CH3COCl
140°
HO
H2N
NHCOCF3
CO2CH3
37

phenol 36b, mp 121-124°C, and the corresponding 4- nitro-isomer 36a, mp 96-98°C. The mixture was readily separated by silica gel chromatography to provide 36a and 36b in pure form. In order to test the directing effects of the carboxyl group in the nitration, the free acid of 35 was nitrated under identical conditions. The same 2:1 mixture of 2-nitro and 4-nitro isomers was obtained in 90% yield. Catalytic reduction (10% Pd/C) of 36b gave aminophenol 37, mp 157-158°C, which was closed to 2-methylbenzoxazole 38, mp 150-151.5°C, with acetyl chloride in refluxing xylene.[23d] Methylation with CH_3I/K_2CO_3 in acetone afforded the suitably protected benzoxazole 39, mp 97-98°C, in 60% overall yield from 37 (Scheme VII).

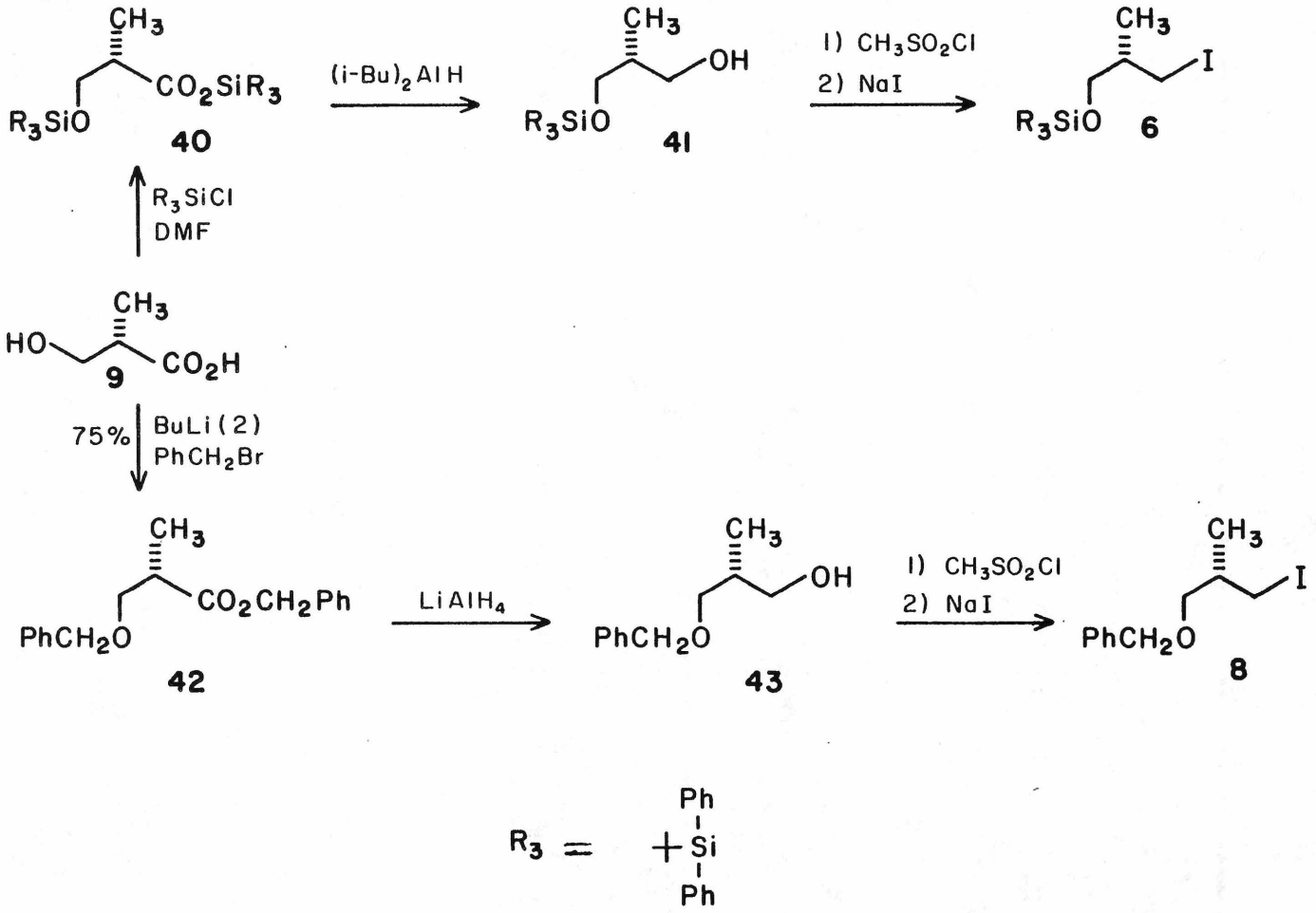
Synthesis of Ketone (4).[51] Based on the previously elaborated symmetry elements present in ketone 4, its construction via common chiral subunits and enolate technology was relatively straightforward. The absolute



4

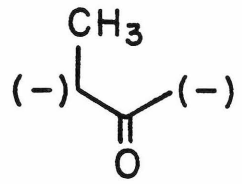
configurations at methyl-bearing stereocenters C-11 and C-17 were secured from the chiral iodides 6 and 8 derived from (S)-(+)-β-hydroxyisobutyric acid 9 (Scheme VIII). The protecting groups R_1 and R_2 for the chiral iodides were chosen with primary consideration for stability to strong base and ease of selective removal under mild conditions. Initial efforts with R_1 as t-butyldimethylsilyl[30] or methoxyethoxymethyl (MEM)[31] were unsatisfactory due to instability on silica gel or incomplete functionalization. Subsequently, the t-butyldiphenylsilyl[32] group provided a suitable alternative for R_2 in 6. The hydroxy acid 9 was bis-silylated with t-butyldiphenylchlorosilane to give silyl ether silyl ester 40 which, without purification, was reduced with diisobutylaluminum hydride to alcohol 41 (Scheme VIII, 50% overall yield from 9). The mesylate of 41 was formed with methanesulfonyl chloride and triethylamine in dichloromethane[18] and subsequent displacement with sodium iodide in refluxing acetone afforded iodide 6 ($[\alpha]_D^{23}$ + 3.80° (c 0.413, $CHCl_3$)) in 91-96% yield. Based on literature precedent for the facile and selective removal of the benzyl group via catalytic hydrogenolysis, it was chosen as the protecting group R_2 in iodide 8. Consequently known alcohol 43,[33] prepared via ester 42, was converted to iodide 8 ($[\alpha]_D^{23}$ +9.98 (c 0.239, $CHCl_3$)) in 84-91% yield under conditions analogous to those described for the preparation of 6 (Scheme VIII).

Scheme VIII



$R_3 =$

The synthesis of ketone 4 from 6 and 8 required a suitably-masked butanone equivalent to 7, which allowed sequential, regioselective deprotonation. Initial studies con-



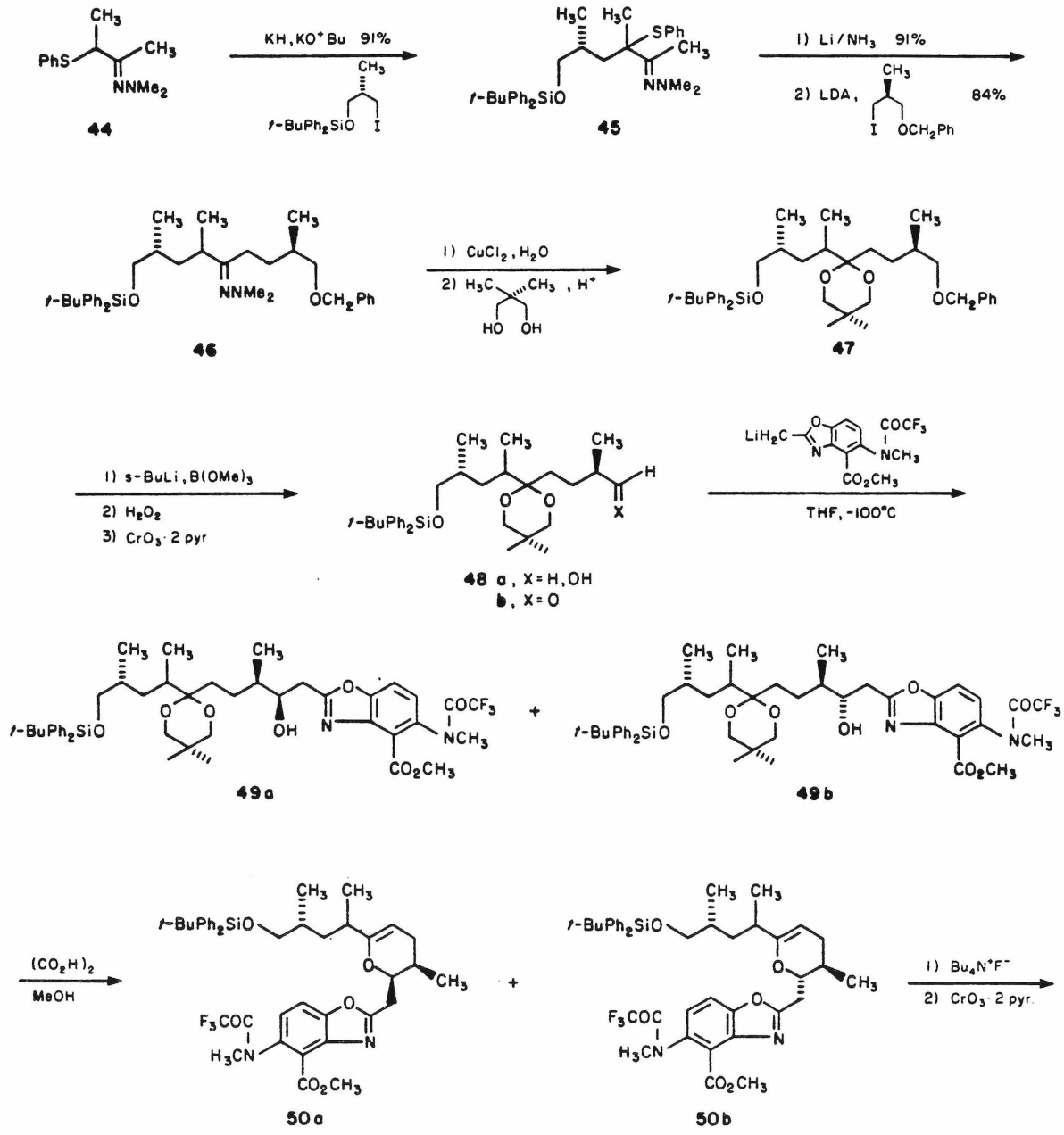
7

ducted with several carbonyl substrates, to determine an equivalent for 7, led to two additional considerations. First, highly reactive oxygen nucleophiles, which might cleave the silyl protecting group in 6, must not be present. Secondly, the equivalent must be activated towards alkylation with the relatively poor (less reactive than isobutyl halides) alkylating agents 6 and 8. With these points in mind we chose hydrazone 44 as our 2-butanone equivalent (Scheme IX). Hydrazone 44 was prepared from phenylthioacetone[34] by treatment with Me_2NNH_2 and subsequent methylation with KH/CH_3I/THF in 77% overall yield. Initial attempts to form the S-stabilized anion of 44 (KH, THF, 23°C; EtMgBr, THF, 23°C; i-C_3H_7NMgI, Ether, 23°C) were not successful, leading to deprotonation at the 1-CH_3. Ultimately, the anion was formed with KH in refluxing THF containing a catalytic amount of potassium t-butoxide.

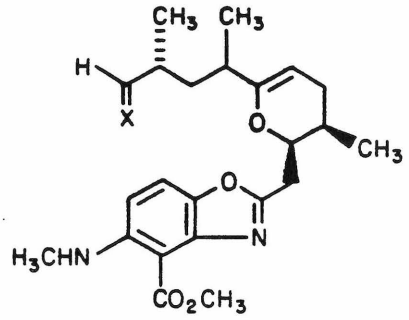
Subsequent alkylation of the anion, thus formed, with iodide 6 gave hydrazone 45 in 91% yield (Scheme IX). Hydrazone 45 was desulfurized with two equivalents of lithium in refluxing ammonia and the lithium anion (LDA, 0°C) of the resulting hydrazone alkylated with iodide 8 to afford 46 in 80% yield from 45. Hydrolysis of hydrazone 46 was accomplished using cupric chloride in aqueous THF at pH 7.[35] The resultant ketone was protected as the corresponding ketal with 2,2-dimethylpropane-1,3-diol in refluxing benzene containing a trace of p-toluenesulfonic acid. Ketal 47 was isolated in 77% overall yield from 46 as a 1:1 mixture of α-methyl diastereoisomers (C-15). This stereochemical ambiguity will be corrected in the spiroketalization step, vide supra.

A-23187 Aldol Approach A.[51] The first sequence of aldol condensations used to synthesize A-23187 was the connection of ketone subunit 4 and benzoxazole 5 followed by the incorporation of pyrrole ketone 3 (Scheme I). In preparation for the aldol condensation with the lithium anion of benzoxazole 39, the cleavage of the benzyl ether in ketal 47 by hydrogenolysis was attempted (Scheme IX). Under neutral or acidic conditions predominant side reactions were observed that involved the loss of the ketal functionality in alcohol 48a. This was facilitated by intramolecular participa-

Scheme IX

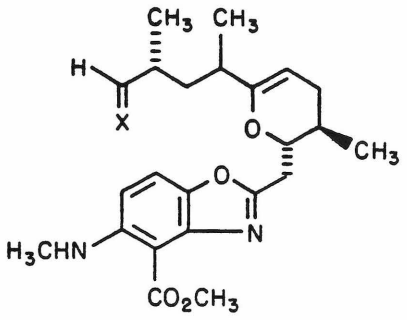

KH, KO*Bu 91%
1) Li/NH3 91%
2) LDA, 84%
1) CuCl2, H2O
2) H+
1) s-BuLi, B(OMe)3
2) H2O2
3) CrO3·2 pyr
THF, -100°C
(CO2H)2
MeOH
1) Bu4N+F-
2) CrO3·2 pyr
44
45
46
47
48 a, X=H,OH
b, X=O
49a
49b
50a
50b

Scheme IX - continued

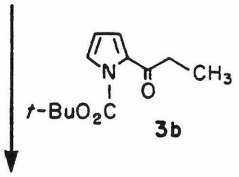


51a, X=H,OH
52a, X=O

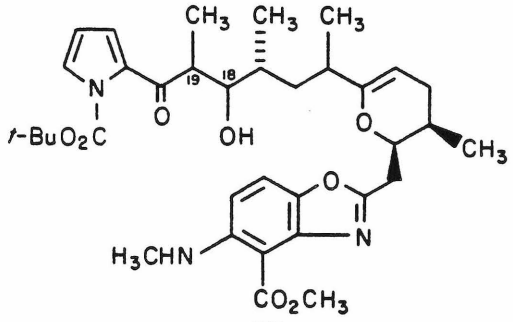
+



51b, X=H,OH
52b, X=O

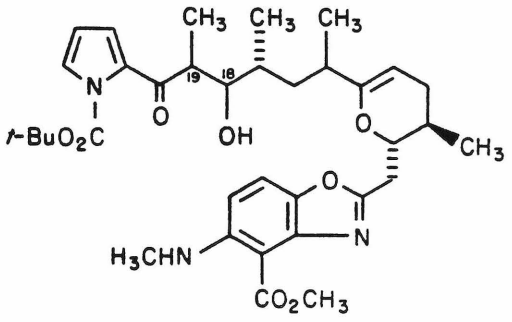


3b



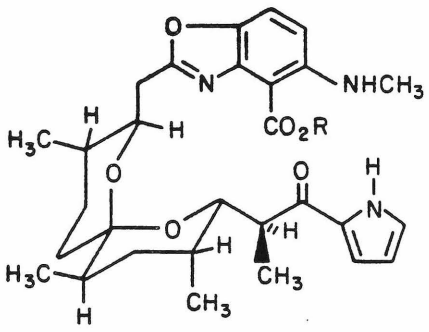
53a

+



53b

Acidic
Resin
Toluene, 100°C

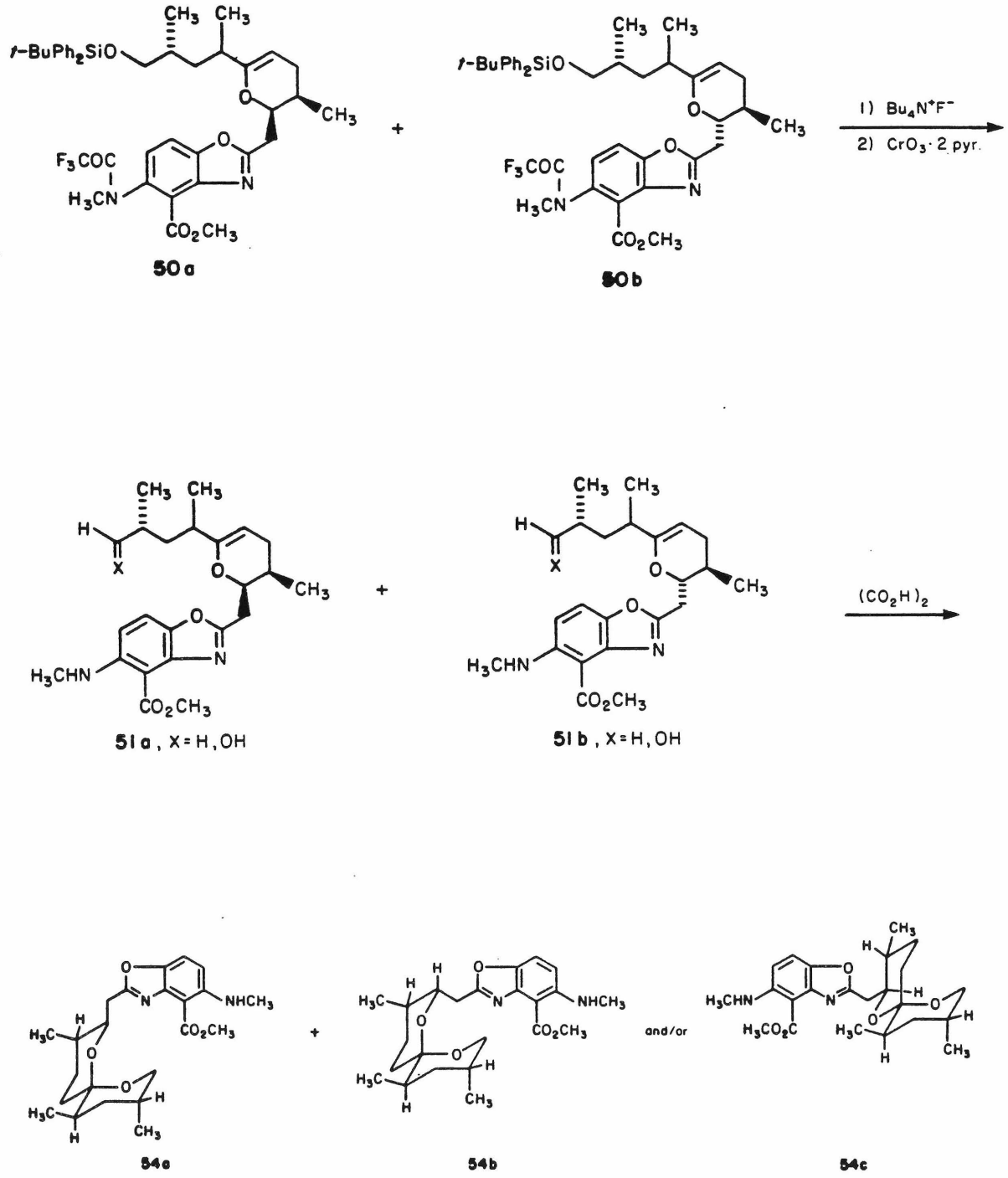


1a, R=H
b, R=CH_3

tion of the free hydroxy group in 48a. Catalytic hydrogenolysis of benzyl ether 47 under basic conditions (10% Pd/C in ethanol containing 0.2 equiv Na_2CO_3 or diisopropylethylamine) was successful, but proved to be sluggish and required large mole ratios of catalyst to substrate. Debenzylation of 47 to alcohol 48a was successfully accomplished by benzylic metalation with sec-butyllithium (-78°C)[36] followed by trapping of the benzyl anion with trimethyl borate and oxidation with basic hydrogen peroxide (Scheme IX). Unpurified alcohol 48a was oxidized with chromium trioxide-pyridine[37] to aldehyde 48b and condensed at -100°C with the lithium anion of benzoxazole 39 (LDA, THF, -100°C) for 3 min to afford an 88:12 mixture, as determined by analytical HPLC, of diastereoisomers 49a and 49b (33% overall yield from ketal 47). The stereochemistry of the major product was assigned in accordance with Cram's rule, vide supra, and spectral evidence, vide infra. In order to protect the free hydroxyl group during subsequent transformations, aldol adducts 49a and 49b were cyclized with oxalic acid in methanol to dihydropyrans 50a and 50b in 87% yield. The utilization of stronger acids for dihydropyran formation led to decomposition of the substrate.

The stereochemistry of the condensation products 49a and 49b was proven by spectral analysis of the cyclization products, spiroketals 54a, 54b, and 54c (Scheme X). The

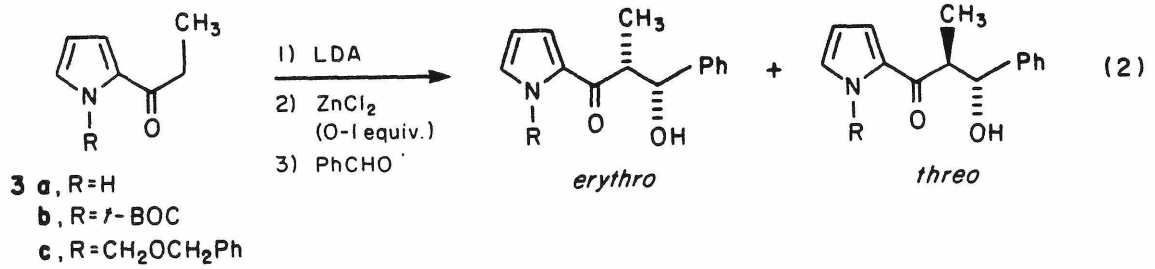
Scheme X


t-BuPh2SiO
CH3 CH3
CH3
F3COC
H3CN
CO2CH3
50a
50b
1) Bu4N+F-
2) CrO3·2 pyr.
H
X
H3CHN
51a, X=H,OH
51b, X=H,OH
(CO2H)2
NHCH3
H3C
54a
54b
and/or
H3CO2C
54c

mixture of dihydropyrans 50a and 50b, formed from 49a and 49b as outlined above, was treated with tetra-n-butylammonium fluoride to produce alcohols 51a and 51b (Scheme X). Without purification the alcohols were treated with acidic ion exchange resin in dichloromethane to yield a mixture of spiroketals. After separation by analytical HPLC, the major spiroketal was assigned structure 54a (from the Cram aldol adduct). This assignment was based on the methine carbinol resonance in the ^{1}H NMR which compared favorably in multiplicity and coupling constant with the analogous resonance in A-23187. The minor spiroketal displayed a complicated ^{1}H NMR spectrum and a structural distinction could not be made between 54b and 54c or a mixture of both (54b and 54c are from the anti-Cram aldol adduct), vide supra. With the successful connection of subunits 39 and 48b (Scheme IX), we focused our attention on the second aldol condensation.

In the final aldol condensation involving the chiral aldehyde 52 and the ethyl ketone 3b, two new stereocenters are created (cf 53, C-18 and C-19, Scheme IX). The success of this synthetic sequence hinged on establishing the correct configuration of C-18 and C-19 relative to each other (threo vs erythro, threo desired) and relative to the preexisting stereocenter C-17 (Cram vs anti-Cram). In order to achieve the proper relative stereochemistry at C-18

and C-19 in a highly stereoselective manner under conditions of kinetic control, it was necessary to obtain a convenient source of the trans-enolate of the pyrrole ethyl ketone 3a (eq. 2). Since the formation of a clean trans-enolate of ketone 3a was not anticipated, an alternative solution was to obtain the thermodynamically favored threo-product under equilibrating conditions, thereby putting no conditions on enolate geometry. Both the kinetic and thermodynamic aldol options were explored.



3 a, R=H
b, R=t-BOC
c, R=CH_2OCH_2Ph

(2)

Initial attempts to utilize the dianion of ketone 3a (with benzaldehyde as the electrophile) failed to give the desired threo-product (eq. 2). Even the zinc enolate (zinc enolates were used by House[38] to obtain the thermo-

dynamically favored threo aldol adducts) gave predominantly the erythro-adduct. The ratio of threo/erythro (ca 1:3 by ^{1}H NMR was independent of counterion (Zn, Li) and was constant with time and temperature. This implies the dianion probably forms a kinetic product (enriched in erythro) which cannot equilibrate to the threo diastereoisomer.

To circumvent the difficulties encountered with the dianion, we investigated acid-labile N-protecting groups, which would be removed under the acidic conditions of the spiroketalization. The N-protected pyrrole ketones 3b and 3c (readily available from 3a) were chosen for study (eq. 2). Aldol condensations with the lithium enolates derived from 3b and 3c (LDA, -78°C) and benzaldehyde (under potentially equilibrating conditions: 2 min, -78°C) gave predominantly the erythro-aldol adduct (erythro:threo, 70:30 by ^{1}H NMR). However, by using equilibrating conditions analogous to House, the zinc enolate of 3b was condensed with benzaldehyde to give mainly the threo-adduct (threo: erythro, 70:30 by ^{1}H NMR, see eq. 2).

The model aldehyde 55[39] was then used to explore the Cram vs anti-Cram issue. Condensation of 55 with the zinc enolate of 3b afforded four lactone diastereoisomers (Scheme XI, 56a-d). The diastereoisomers were separated by HPLC and stereochemical assignments made by comparison of the ^{1}H NMR spectra with analogs of the Prelog-Djerassi

Scheme XI

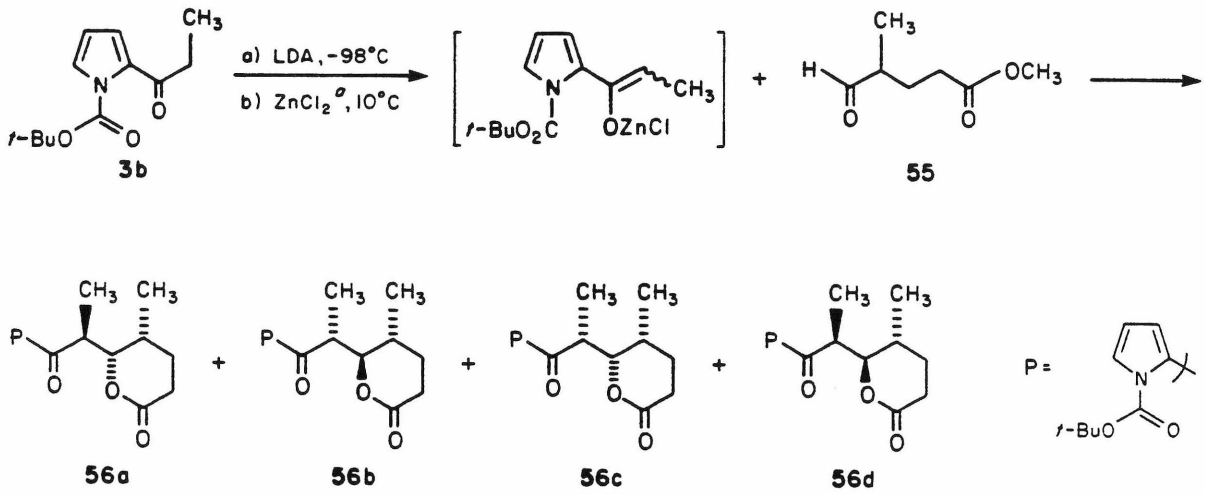
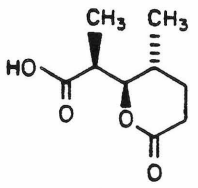
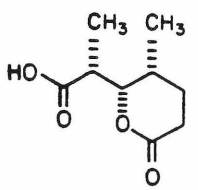


Table I Aldol Studies of Cram vs Anti-Cram Selectivity
Scheme XI

Pyrrole	$ZnCl_2$ (equiv)	Solvent[a]	56a	56b	56c	56d[b]
1. 3b	1.0	A	44	21	14	21
2. 3b	1.0	B	32	19	23	26
3. 3b	1.0	C	42	19	21	27

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


57a


57b

lactone and an isomer (57a and 57b).[39] Various reaction conditions were studied with the results summarized in Table I. Under the most selective conditions found, the desired threo-Cram stereorelationship is over 40% of the mixture of diastereoisomers (entries 1 and 3).

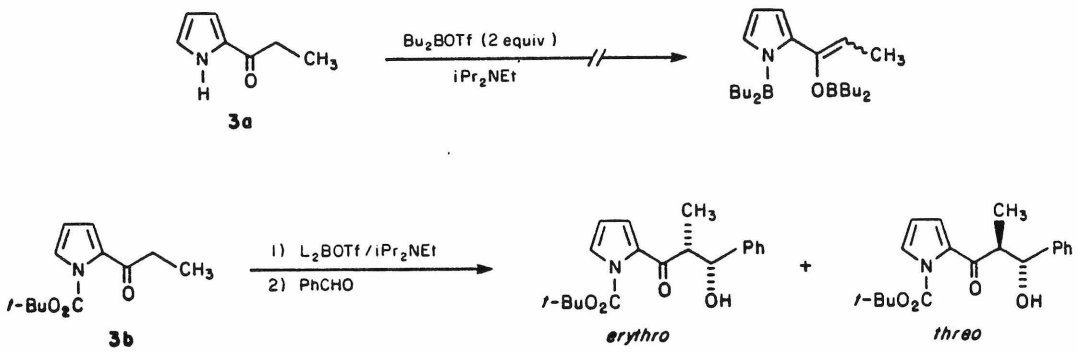
In order to prepare the requisite aldehyde 52, dihydropyrans 50a and 50b were desilylated with tetra-n-butylammonium fluoride (Scheme IX). This also conveniently liberated the secondary amine function to give alcohols 51a and 51b. After purification, the alcohols were oxidized with Collins reagent[37] to provide the corresponding aldehydes 52a and 52b (45% overall yield). Under the conditions described above (Table I, entry 3), condensation of aldehydes 52a and 52b with the zinc enolate of ketone 3b (LDA, -78°C; $ZnCl_2$, 10°C) afforded aldol adducts 53a and 53b. The unpurified condensation products were treated with acidic ion-exchange resin in toluene (100°C) to induce the following events: (a) spiroketal formation; (b) equilibration of the diastereoisomeric C-15 methyl groups; and (c) removal of the pyrrole protecting group. The major product isolated by flash chromatography[40] was A-23187 methyl ester 1b, $[\alpha]_D^{23}$ -10° (c 0.011, $CHCl_3$), in 23% overall yield from aldehyde 52a. A sample of 1b prepared from the natural product[41] was identical in all respects (IR, NMR, $[\alpha]_D$, HPLC) with the synthetic material.

Conversion to the free acid 1a was carried out in quantitative yield with lithium n-propylmercaptide in HMPA.[42] Synthetic 1a, mp 184.5-186°C, $[\alpha]_D^{23}$ -56° (c 0.010, $CHCl_3$) was identical in all respects (IR, UV, MS, ^1H NMR, ^{13}C NMR, $[\alpha]_D$, mixture mp)[43] with an authentic sample of A-23187. This establishes the absolute configuration of A-23187 as that depicted in structure 1a (Scheme IX).

A-23187 Aldol Approach B. In the first synthetic route to A-23187 described above, two major difficulties were encountered; namely, in establishing the threo-Cram stereorelationship (C-17, C-18, C-19) and an unsatisfactory yield in the desilylation of 50 with, possibly, minor loss of stereochemical integrity. Additional studies were undertaken to more fully understand these issues. The basic strategy previously outlined was followed with emphasis being placed on the more challenging of the two problems; namely, the threo-Cram stereorelationship (C-17, C-18, C-19).

Initial efforts to stereoselectively establish the stereocenters C-18 and C-19 were concerned with using pyrrole ketones 3a and 3b in the recently developed boron aldol condensation.[44] The boron dianion of 3a (Scheme XII) would not form; therefore, the studies were concentrated on 3b. The dibutylboron enolate of 3b was formed under the reported conditions[44] and condensed with benzaldehyde

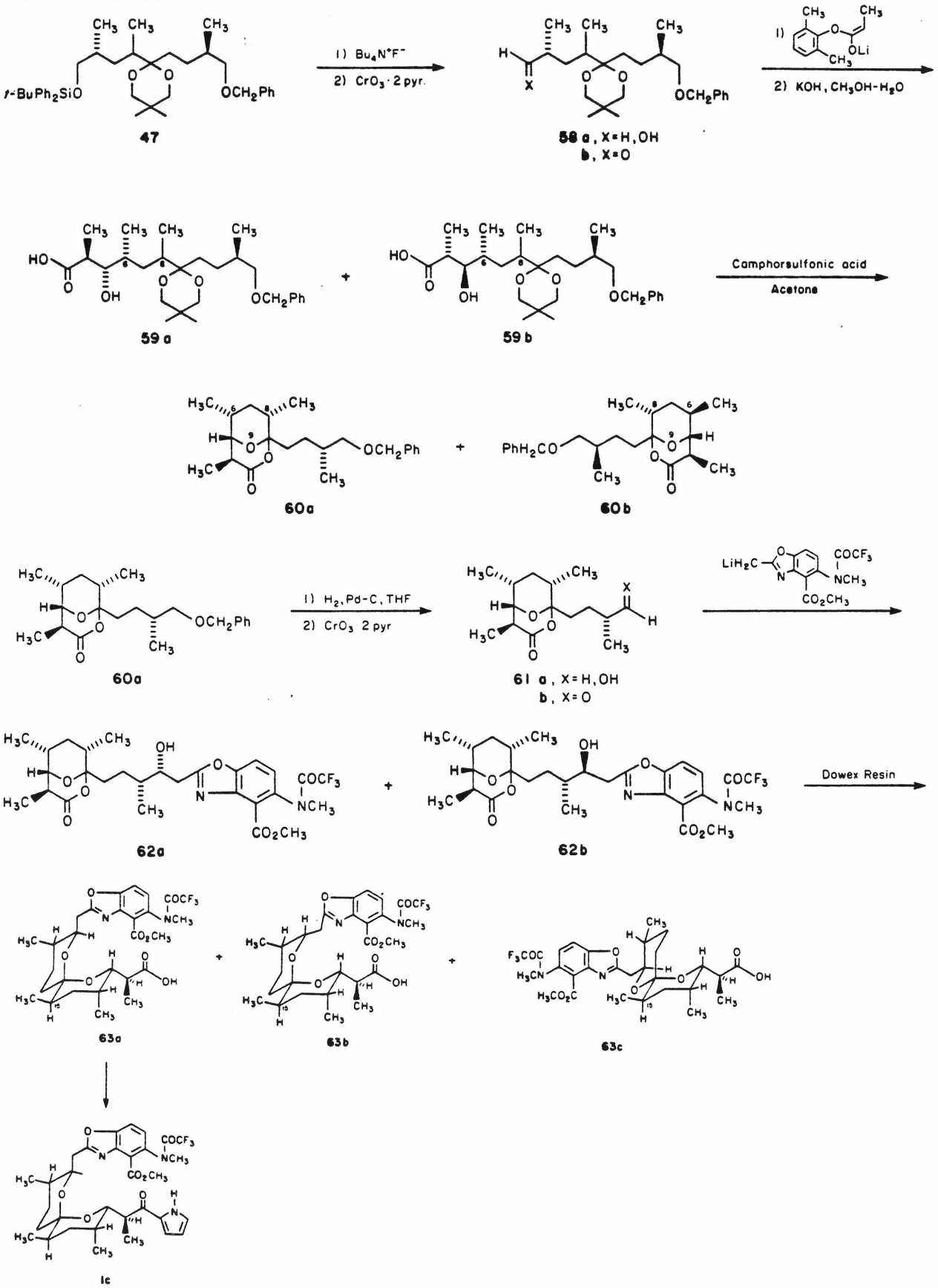
Scheme XII



to give exclusively the erythro-aldol adduct (>97:3 by ^{1}H NMR, Scheme XII). The more sterically demanding dicyclopentyl boron enolate was also condensed with benzaldehyde to give predominantly the erythro-product (erythro:threo, 55:45 by ^{1}H NMR). Failure of the boron aldol condensations to give the desired threo product focused attention on reversing the order of the aldol condensations necessary to construct A-23187. This would allow for desilylation with no other sensitive functionality present (compare Schemes IX and XIII) and for the introduction of the threo-Cram stereochemistry via a more threo-selective ketone (or equivalent) than 3.

Accordingly, ketal 47 was desilylated with tetra-n-butylammonium fluoride (Scheme XIII) to afford alcohol 58a in 81% yield, effectively solving the desilylation difficulties mentioned above. Alcohol 58a was oxidized with Collins reagent[37] to aldehyde 58b and condensed with the lithium enolate of 2,6-dimethylphenyl propionate, a threo-

Scheme XIII


1) Bu4N+F-
2) CrO3·2pyr.
2) KOH, CH3OH-H2O
Camphorsulfonic acid
Acetone
1) H2, Pd-C, THF
2) CrO3 2pyr
Dowex Resin
47
58 a, X=H, OH
b, X=O
59 a
59 b
60a
60b
61 a, X=H, OH
b, X=O
62a
62b
63a
63b
63c
Ic

selective ester recently reported by Heathcock and co-workers.[45] The unpurified aldol mixture was hydrolyzed with KOH in aqueous methanol[45] to afford diastereoisomeric acids 59a and 59b.[46] As expected, only the threo-aldol adducts were observed; however, obtaining a quantitative ratio between Cram and anti-Cram diastereoisomers was complicated by the 1:1 mixture of diastereoisomers at C-8, (Scheme XIII, 59a and 59b), vide supra. The acids 59a and 59b were then cyclized to lactones 60a and 60b with camphorsulfonic acid in acetone. The mixture of diastereoisomers was readily separated by medium pressure liquid chromatography (MPLC) to give pure lactones 60a (33% from alcohol 58a) and 60b (11% from alcohol 58a) in a ratio of 3:1 (threo-Cram: threo-anti-Cram).** The stereochemistry of the lactones was assigned by analogy to the results of Heathcock and spectral data. The bridgehead proton in 60a appears as a doublet at δ3.71 ($J = 5$ Hz) and in 60b it appears as a singlet at δ3.60. An examination of Dreiding models indicates approximately 90° angles between the bridgehead proton and both adjoining protons in 60b and a 90° angle between the bridgehead proton and only

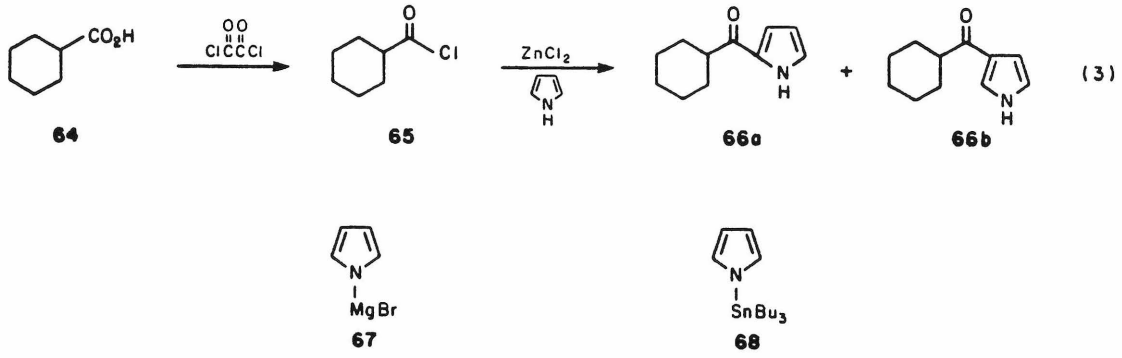
**This represents a substantial improvement in establishing the threo-Cram stereorelationship from 44% to 75% of the total mixture of diastereoisomers.

one of the adjoining protons in 60a. These dihedral angles can account for the doublet observed for the 5-H in lactone 60a and the singlet observed for the 5-H in lactone 60b. In addition, in the closure of the two aldol adducts 59a and 59b to the bicyclic system, the C-6 methyl is equatorially disposed in 60a and axially-oriented in 60b. Consequently, the signal for the C-6 methyl group in 60b is deshielded in the ^{1}H NMR relative to 60a because of its interaction with the 9-oxygen atom. Finally, the C-8 methyl group was equilibrated to the equatorial diastereoisomer in analogy to the previously discussed C-15 methyl equilibration, vide supra.

Catalytic hydrogenolysis of the benzyl ether in pure lactone 60a with 5% Pd-C in THF[47] (Scheme XIII) presented none of the difficulties observed earlier with ketal 47. Alcohol 61a was oxidized with Collins reagent[37] to aldehyde 61b and condensed at -100°C with the lithium anion of benzoxazole 39 (LDA, THF, -100°C) for 3 min to afford a mixture of aldol adducts 62a and 62b. In contrast to the 88:12 ratio observed earlier in the condensation of aldehyde 48 with 39, a 50:50 mixture, as determined by analytical HPLC, of condensation adducts 62a and 62b was obtained with aldehyde 61b. Apparently, subtle changes in the structure relatively distant from the site of nucleophilic addition dramatically influence the Cram,

anti-Cram selectivity. The addition of HMPA to disrupt any coordination between the lactone moiety and the lithiated benzoxazole afforded no aldol adducts but rather led to decomposition of the benzoxazole subunit. Thus, the aldol adducts 62a and 62b were cyclized with acidic ion-exchange resin to effect the following transformations: (a) spiroketal formation and (b) equilibration of the C-15 methyl group to the equatorial diastereoisomer (Scheme XIII). As anticipated, this closure afforded a mixture of the spiroketals 63a (from the Cram aldol adduct) and 63b and 63c (from the anti-Cram aldol adduct) in 75% yield. These stereochemical assignments were based on the model spirane studies and A-23187 aldol route A.

The critical incorporation of pyrrole to effectively complete the synthesis of A-23187 (see 1c, Scheme XIII) was first examined with the model compound, cyclohexanecarboxylic acid (64). The acid was treated with oxalyl chloride in refluxing benzene to afford acid chloride 65 (eq. 3). Subsequent acylation of pyrryl Grignard 67[48] with 65 gave an unacceptable ratio of N-acylated to 2-acylated pyrrole. However, $ZnCl_2$ catalyzed acylation of pyrrole with 65 afforded a 4:1 ratio of 66a:66b in 90% yield. The mixture was readily separated by MPLC to give acyl pyrrole 66a in nearly 60% yield. Attempted $ZnCl_2$ catalyzed acylation of pyrrole with the acid chlorides



of spiroketals 63b and 63c afforded no discernible acylpyrroles. Apparently, the metal catalyst is complexed by the ionophoric spiroketal 63 and no acylation occurs.[49] A pyrrole moiety was sought which was activated toward acylation without a metal which could be complexed by the spiroketal system. The stannyl pyrrole 68 appeared to be the answer because treatment with acetyl chloride reportedly gave 2-acetylpyrrole in 45% yield.[50] However, model studies with propionyl chloride and acid chloride 65 afforded only small amounts of 2-acylated pyrrole contaminated with N- and 3-acylated pyrroles. More importantly, the acid chloride of spiroketal 63a when treated with stannyl pyrrole 68 failed to give any pyrrole incorporation.

Although the pyrrole acylation attempts failed, the alternate route did improve the threo-Cram selectivity and eliminated desilylation difficulties encountered in the first synthesis of A-23187. Moreover, the second route provides easy access to diacid ionophores in good overall yield.

Summary

The enantioselective total synthesis and absolute configuration of A-23187 were reported. The latent C_2-axis of symmetry present in the molecule was effectively used to secure two chiral centers from (S)-(+)-β-hydroxyisobutyric acid. These centers were then utilized in controlling the formation of nearly all other stereocenters. The major stereochemical control problem encountered was the establishment of a threo-Cram stereorelationship (cf 2, C-17, C-18, C-19). A satisfactory solution was achieved using zinc enolate technology and later improved upon by employing a threo-selective ester aldol. Nevertheless, the establishment of the threo-Cram stereorelationship in a highly stereoselective manner remains as a general problem. Finally, a synthetic route was developed to afford diacid ionophores in good yield.

Experimental Section

General. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz), integration, and interpretation. ^{13}C magnetic resonance spectra were recorded on a JEOL-FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Multiplicities are reported using the format given above. Mass spectra were recorded on a Dupont 21-492B spectrometer by the California Institute of Technology Microanalytical Laboratory. Combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan and the California Institute of Technology Microanalytical Laboratory.

Medium pressure chromatography was performed using EM Laboratories LoBar silica gel 60 prepacked columns on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP Lab Pump. Analytical HPLC was performed on

a Water's Associates Model ALC 202/401 high pressure liquid chromatograph equipped with a Model 6000 pump and ultraviolet and refractive index detectors.

Diethyl ether, tetrahydrofuran (THF), and benzene were dried by distillation from benzophenone ketyl under nitrogen. Triethylamine, diisopropylamine, and pyrrole were dried by distillation under nitrogen from calcium hydride. Dichloromethane and chloroform were filtered through activity I alumina prior to use. All commercial alkyllithium reagents were titrated by the procedure of Watson and Eastham.[52]

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

Ethyl 2-hydroxyaminobenzoate (30a). Ethyl 2-nitrobenzoate (5.0 g, 25.6 mmol) was reduced with zinc (10.0 g, 152.9 mmol) in the presence of ammonium chloride to afford the title compound[27] as a yellow solid. Recrystallization from chloroform-pet ether gave 2.8 g hydroxylamine 30a (60%) as white needles: mp 68-70°C (lit.[27] mp 72-73°C); IR (CH_2Cl_2) 3545, 3325, 2975, 1680, 1600, 1570, 1480, 1365, 1310, 1240, 1160, 1140, 1085 cm^{-1}; ^1H NMR (d_6-DMSO) δ 9.20 (1 H, broad s, -O<u>H</u> or N<u>H</u>), 8.90 (1 H, broad s, -O<u>H</u> or -N<u>H</u>), 7.82 (1 H, d of d, J = 8 Hz, 1 Hz, aromatic H), 7.67-7.17 (2 H, m, aromatic H's), 6.92-6.68 (1 H, m, aromatic H), 4.28 (2 H, q, J = 7 Hz, -C<u>H</u>$_2$CH$_3$), 1.35 (3 H, t, J = 7 Hz, -CH$_2$C<u>H</u>$_3$).

Ethyl 2-(N-acetoxyacetamido)benzoate (32a). To a solution of hydroxylamine 30a (1.5 g, 8.3 mmol) and triethylamine (1.1 g, 10.9 mmol) in THF (25 mL) at 0°C was added dropwise acetic anhydride (0.92 g, 9.0 mmol). After 30 min the ice bath was removed, and the reaction mixture stirred for 3 h at 25°C. The mixture was partitioned between ether and 10% hydrochloric acid solution. The ether layer was then washed successively with saturated sodium bicarbonate and brine solutions. The ether layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford 1.4 g (76%) of the mono-acetyl derivative of hydroxylamine 30a as a light-yellow solid: IR (CH_2Cl_2) 3280, 2980, 1755, 1685, 1600, 1575, 1480, 1365, 1305, 1220, 1200, 1160, 1140, 1085, 1020 cm^{-1}; ^1H NMR (d_6-DMSO) δ 10.9 (1 H, s, -NHOAc), 7.92 (1 H, d of d, J = 8 Hz, 2 Hz, aromatic H), 7.58 (1 H, m, aromatic H), 7.30-6.90 (2 H, m, aromatic H's), 4.35 (2 H, q, J = 7 Hz, $-OCH_2CH_3$), 2.25 (3 H, s, $-OC(O)CH_3$), 1.32 (3 H, t, J = 7 Hz, $-OCH_2CH_3$). To a solution of the mono-acetylated material (0.45 g, 2.0 mmol) prepared above and 4-dimethylaminopyridine (1.22 g, 10.0 mmol) in dichloromethane (10 mL) at 0°C was added dropwise acetic anhydride (0.80 g, 7.8 mmol). After 30 min the ice bath was removed, and the reaction mixture stirred for 2 h at 25°C. The mixture was partitioned between dichloromethane and 10% hydrochloric acid solution. The organic layer was washed

successively with saturated sodium bicarbonate and brine solutions. The dichloromethane layer was dried (Na_2SO_4) and concentrated *in vacuo* to give 500 mg of a light-yellow oil. Purification by MPLC (Merck Lobar size B, 50% EtOAc-hexane) gave 326 mg (62%) of **32a** as a colorless oil: IR (CCl_4) 2980, 1795, 1720, 1700, 1600, 1450, 1365, 1290, 1255, 1175, 1130 cm^{-1}; ^1H NMR (CCl_4) δ 7.98-7.80 (1 H, m, aromatic H), 7.63-7.28 (3 H, m, aromatic H's), 4.26 (2 H, q, J = 7 Hz, $-OC\underline{H}_2CH_3$), 2.07 (3 H, s, $-OC(O)C\underline{H}_3$), 1.90 (3 H, broad s, $-NC(O)C\underline{H}_3$), 1.35 (3 H, t, J = 7 Hz, $-OCH_2C\underline{H}_3$).

Exact mass (75 eV) *m/e* calcd. for $C_{13}H_{15}NO_5$: 265.095. Found: 265.095.

Ethyl 2-amino-3-(4-toluenesulfonyl)benzoate (31a). To a solution of hydroxylamine **30a** (1.2 g, 6.6 mmol) and triethylamine (0.67 g, 6.6 mmol) in THF (100 mL) at 0°C was added a solution of *p*-toluenesulfonyl chloride (1.26 g, 6.6 mmol) in chloroform (50 mL) dropwise. After 10 min the ice bath was removed, and the mixture heated to the reflux temperature. After 5 h the reaction mixture was cooled, filtered, and the filtrate concentrated *in vacuo* to give 3.9 g of a dark red oil. The oil was extracted with hot hexane several times. The combined hexane extracts were concentrated *in vacuo* to afford 2.1 g of a light red oil. Purification by MPLC (Merck Lobar size B, 60% dichloromethane-hexane) gave 450 mg (20%) of **31a** as a light-yellow

oil: IR ($CDCl_3$) 3510, 3380, 2980, 2930, 1685, 1615, 1580, 1550, 1460, 1370, 1300, 1265, 1250, 1195, 1180, 1160, 1085, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (3 H, m, aromatic H's), 7.23 (2 H, d, J = 8 Hz, tosyl aromatic H's), 7.03 (1 H, d of d, J = 8 Hz, 2 Hz, aromatic H's), 6.43 (1 H, d of d, J = 8 Hz, aromatic H's), 5.85 (2 H, broad s, $-N\underline{H}_2$), 4.23 (2 H, q, J = 7 Hz, $-OC\underline{H}_2CH_3$), 2.42 (3 H, s, tosyl $C\underline{H}_3$), 1.32 (3 H, t, J = 7 Hz, $-OCH_2C\underline{H}_3$).

Exact mass (75 eV) m/e calcd. for $C_{16}H_{17}NSO_5$: 335.083. Found: 335.080.

Ethyl 2-amino-3-(4-nitrobenzenesulfonyl)benzoate (69). To a solution of hydroxylamine 30a (1.2 g, 6.6 mmol) and triethylamine (0.67 g, 6.6 mmol) in THF (80 mL) at 0°C was added a solution of p-nitrobenzenesulfonyl chloride (1.47 g, 6.6 mmol) in chloroform (50 mL) dropwise. After 2 h at 0°C, the reaction mixture was filtered, and the filtrate concentrated in vacuo to give 2.81 g of a dark red oil. Purification by MPLC (Merck Lobar size B, 60% dichloromethane-hexane) afforded 534 mg (22%) of 69 as a light yellow oil: IR (film) 3500, 3380, 3110, 2980, 1685, 1615, 1580, 1530, 1460, 1380, 1370, 1350, 1305, 1265, 1250, 1195, 1160, 1085, 855, 760, 750, 740, 730, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (2 H, d, J = 9 Hz, tosyl aromatic H's), 8.07 (2 H, d, J = 9 Hz, tosyl aromatic H's), 7.79 (1 H, d of d, J = 8 Hz, 2 Hz, aromatic H's), 7.13 (1 H, d of d,

8 Hz, 2 Hz, aromatic H's), 6.50 (1 H, d of d, J = 8 Hz, aromatic H's), 4.27 (2 H, q, J = 7 Hz, $-OC\underline{H}_2CH_3$), 1.37 (3 H, t, J = 7 Hz, $-OCH_2C\underline{H}_3$).

Exact mass (75 eV) m/e calcd. for $C_{15}H_{14}N_2S'O_7$: 366.053. Found: 366.050.

2-Amino-5-hydroxybenzoic acid (70). The diazonium salt of aniline (30 g, 0.32 mol) and m-hydroxybenzoic acid were coupled according to the literature procedure[53] to give 76.5 g (98%) of an intermediate azo compound: ^{1}H NMR ($CDCl_3$, d_6-DMSO) δ 8.96 (2 H, broad s, $-CO_2\underline{H}$, $-O\underline{H}$), 8.07-7.30 (6 H, m, aromatic H's), 7.18-6.93 (2 H, d of d, J = 9 Hz, 3 Hz, aromatic H's), which was reduced to the title compound by the following modified literature procedure.[54] To a dark red solution of the azo intermediate (5.0 g, 20.7 mmol) in 10% sodium hydroxide (45 mL) was gradually added sodium dithionite (8.3 g, 47.7 mmol) with vigorous stirring. The reaction mixture was stirred occasionally over a 45 min period, cooled to 15°C, and carefully acidified with concentrated hydrochloric acid (9.4 mL). The resulting precipitate was collected, dried in vacuo, and recrystallized from water to give 2.2 g (70%) of 70 as purple crystals: mp 244-245°C (lit.[53] 252°C); IR (nujol) 3280-2100 (broad), 3220, 1650, 1600, 1560, 1495, 1370, 1360, 1340, 1300, 1290, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, d_6-DMSO) δ 8.30-6.70 (4 H, broad s, $-CO_2\underline{H}$, $-N\underline{H}_2$, $-O\underline{H}$), 7.15 (1 H, d, J = 3 Hz, aromatic H),

6.78 (1 H, d of d, J = 3 Hz, 9 Hz, aromatic H), 6.58 (1 H, d, J = 9 Hz, aromatic H).

Methyl 2-amino-5-hydroxybenzoate (34). 2-Amino-5-hydroxybenzoic acid (4.7 g, 30.7 mmol) was esterified with methanol (39 mL) and sulfuric acid (10 mL) according to the published procedure[29] to give 4.3 g (84%) of the title compound 34 as a brown solid. The ester was sufficiently pure to proceed with the next transformation, but could be purified by recrystallization from aqueous methanol, if necessary. A sample so purified gave ester 34 as a light tan solid: mp 156-157°C (lit.[29] 154-155°C); ^{1}H NMR (d_6-DMSO) δ 8.67 (1 H, broad s, -OH), 7.12 (1 H, d, J = 3 Hz, aromatic H), 6.82 (1 H, d of d, J = 3 Hz, 9 Hz, aromatic H), 6.65 (1 H, d, J = 9 Hz, aromatic H), 6.03 (2 H, broad s, $-NH_2$), 3.72 (3 H, s, $-CO_2CH_3$).

Methyl 2-N-trifluroacetylamino-5-hydroxybenzoate (35). A 500-mL flask equipped with an addition funnel was charged with ether (300 mL), aromatic amine 34 (4.30 g, 25.7 mmol), and cooled to 0°C. The addition funnel was charged with ether (50 mL), trifluroacetic anhydride (7.80 mL, 55.2 mmol), pyridine (4.50 mL, 55.6 mmol), and this mixture added dropwise to the stirred reaction over a 20 min period. Pyridinium trifluroacetate precipitated immediately and continued to form throughout the entire reaction period. After the addition was complete the mixture was warmed to

25°C and stirred for 20 h. The reaction mixture was filtered and the filtrate washed with 10% hydrochloric acid and brine solutions. An equal volume of brine was added to the ether layer and the two-phase system stirred for 45 min. The ether layer was dried ($MgSO_4$) and concentrated in vacuo to give 6.30 g (92%) of a light-brown solid. Purification by MPLC (Merck Lobar size C, 20% EtOAc-hexane) gave 6.10 g (90%) of 35 as a light-tan solid: mp 136-138°C; IR (CH_2Cl_2) 3575, 3230, 1720, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, d_6-DMSO) δ 11.9 (1 H, broad s), 9.5 (1 H, broad s), 8.35 (1 H, d, J = 9 Hz, aromatic H), 7.51 (1 H, d, J = 3 Hz, aromatic H), 7.09 (1 H, d of d, J = 3 Hz, 9 Hz, aromatic H), 3.93 (3 H, s, $-CO_2CH_3$).

Anal. calcd. for $C_{10}H_8NO_4F_3$: C, 45.64; H, 3.06; N, 5.32. Found: C, 45.82; H, 3.22; N, 5.34.

Methyl 6-N-trifluroacetylamino-3-hydroxy-2-nitrobenzoate (36b). A solution of phenol 35 (4.85 g, 18.4 mmol) in 17.8 mL of nitric acid-ether solution (7 mL of 70% Mallinckrodt nitric acid dissolved in 95 mL of anhydrous ether, 19.3 mmol nitric acid, 1.05 equiv) was stirred for 60 min at room temperature. The reaction mixture was partitioned between ether and brine. The ether layer was washed with 10% sodium sulfite and extracted with 5% sodium bicarbonate (3 x 125 mL). The combined bicarbonate extracts were cooled to 0°C and acidified to pH 2 with 20% hydrochloric

acid solution. The resultant solution was saturated with salt and extracted with ethyl acetate (3 x 200 mL). The combined extracts were dried (Na_2SO_4) and filtered. Removal of solvent *in vacuo* gave 4.3 g of a yellow-brown solid containing (TLC, silica gel, 25% EtOAc-hexane) the nitrophenols **36b** (R_f = 0.11) and **36a** (R_f = 0.25). Purification by column chromatography (silica gel, 70:1 ratio, $CHCl_3$) gave 2.7 g (48%) of a pale-yellow solid (**36b**) and 0.9 g (16%) of a bright-yellow solid (**36a**).

36b: mp 121-124°C; IR ($CDCl_3$) 3380, 3300, 1730, 1720, 1550, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.5 (2 H, broad s, -NH, -OH), 8.38 (1 H, d, J = 9 Hz, aromatic H), 7.33 (1 H, d, J = 9 Hz, aromatic H), 3.92 (3 H, s, $-CO_2CH_3$).

Anal. calcd. for $C_{10}H_7N_2O_6F_3$: C, 38.98; H, 2.29; N, 9.09. Found: C, 39.16; H, 2.34; N, 9.21.

36a: mp 96-98°C; IR (CH_2Cl_2) 3270, 3230, 1720, 1700, 1540, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.5 (1 H, broad s), 9.5 (1 H, broad s), 9.42 (1 H, s, aromatic H), 7.93 (1 H, s, aromatic H), 4.00 (3 H, s, $-CO_2CH_3$).

Anal. calcd. for $C_{10}H_7N_2O_6F_3$: C, 38.98; H, 2.29; N, 9.09. Found: C, 39.27; H, 2.44; N, 9.21.

Methyl 2-amino-6-N-trifluroacetylamino-3-hydroxybenzoate (**37**). A solution of nitrophenol **36b** (4.30 g, 14.0 mmol) in ethanol (140 mL) was reduced with H_2 (1 atm) and 10% Pd/carbon (500 mg, MCB). Hydrogen uptake was monitored, and

the reaction stopped when the theoretical amount was consumed. The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give 3.63 g (94%) of aminophenol **37** as a light-yellow solid: mp 157-158°C; IR (nujol) 3500, 3380, 3360, 1705, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, d_6-DMSO) δ 11.7 (1 H, broad s), 9.5 (1 H, broad s), 7.55 (1 H, d, J = 9 Hz, aromatic H), 6.86 (1 H, d, J = 9 Hz, aromatic H), 5.8 (2 H, broad s, $-NH_2$), 3.96 (3 H, s, $-CO_2CH_3$).

Exact mass (75 eV) *m/e* calcd. for $C_{10}H_9N_2O_4F_3$: 278.050. Found: 278.052.

Methyl 2-methyl-5-N-trifluroacetylamino-4-benzoxazole-carboxylate (38). A 100-mL flask equipped with a reflux condenser was charged with aminophenol **37** (0.630 g, 2.27 mmol), acetyl chloride (0.38 mL, 5.34 mmol), and o-xylene (50 mL). To completely dissolve **37** the suspension was *gradually* heated over a 30 min period to the reflux temperature of xylene. After 45 min the solution was cooled to room temperature, and the xylene removed *in vacuo* to afford a dark brown solid containing benzoxazole **38** (TLC, silica gel, 75% EtOAc-hexane, R_f = 0.19) along with minor impurities. Purification by MPLC (Merck Lobar size B, 60% EtOAc-hexane) gave 546 mg (80%) of benzoxazole **38** as a light yellow solid: mp 150-151.5°C; IR ($CDCl_3$) 3140, 1725, 1690, 1570; ^1H NMR ($CDCl_3$) δ 12.2 (1 H, broad s, $-NHCOCF_3$), 8.74 (1 H, d, J = 9 Hz, aromatic H), 7.75

(1 H, d, J = 9 Hz, aromatic H), 4.11 (3 H, s, $-CO_2C\underline{H}_3$), 2.70 (3 H, s, $-N{=}C(CH_3)\underline{CH}_3$).

Anal. calcd. for $C_{12}H_9N_2O_4F_3$: C, 47.69; H, 3.00; N, 9.27. Found: C, 47.61; H, 2.93; N, 9.19.

The benzoxazole 38 need not be purified at this stage and can be successfully methylated with subsequent purification of the resulting benzoxazole 39 in the same overall yield.

Methyl 2-methyl-5-N-methyl-N-trifluroacetylamino-4-benzoxazolecarboxylate (39). To a solution of benzoxazole 38 (0.535 g, 1.77 mmol) in acetone (60 mL) were added anhydrous potassium carbonate (1.80 g, 13.0 mmol) and methyl iodide (1.80 mL, 28.9 mmol). The mixture was slowly warmed over a 30 min period to the reflux temperature of acetone. After 30 min the reaction mixture was cooled to room temperature, filtered, and the filtrate concentrated in vacuo. The residue was taken up in EtOAc, filtered, and the filtrate concentrated in vacuo to give 490 mg yellow oil containing (TLC, silica gel, 75% EtOAc-hexane, R_f = 0.29) benzoxazole 39 accompanied by minor impurities. Purification by MPLC (Merck Lobar size B, 50% EtOAc-hexane) gave 406 mg (73%) of benzoxazole 39 as an off-white solid: mp 97-98°C; IR ($CDCl_3$) 1725, 1695, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (1 H, d, J = 9 Hz, aromatic H), 7.22 (1 H, d, J = 9 Hz, aromatic H), 3.99 (3 H, s, $-CO_2C\underline{H}_3$), 3.33, 3.49 (3 H, s,

-NC$\underline{H}_3$(COCF_3)), 2.70 (3 H, s, -N=C(-C$\underline{H}_3$)-).

Anal. calcd. for $C_{13}H_{11}N_2O_4F_3$: C, 49.38; H, 3.51; N, 8.86. Found: C, 49.69; H, 3.71; N, 8.80.

Erythro-1-(1-t-butyloxycarbonyl-1-azacyclopenta-2,4-dien-2-yl)-3-hydroxy-2-methyl-3-phenyl-1-propanone (Scheme XII, 71E). Kinetic enolization[55] of 0.446 g (2.0 mmol) of 1-(1-t-butyloxycarbonyl-1-aza-cyclopenta-2,4-dien-2-yl)-1-propanone[56] with 0.310 g (2.4 mmol) of diisopropylethylamine and 0.603 g (2.2 mmol) of di-n-butylboryl triflate in 5 mL ether at -78°C for 45 min was followed by aldol condensation and MoOPH workup with 0.22 g (2.0 mmol) of benzaldehyde to yield 0.723 g (>100%) of a light yellow oil. No threo-aldol adduct 71T was detected by ^{1}H NMR of the unpurified product, vide infra. The product was chromatographed at medium pressure over silica gel (hexane, ethyl acetate) to give 0.47 g (70%) of erythro-aldol adduct 71E as a colorless oil: IR (CCl_4) 3500, 2980, 2940, 1750, 1700, 1650, 1440, 1410, 1370, 1310, 1150, 945, 845, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (broad s, 5, phenyl), 7.28-7.15 (m, 1, pyrrole), 6.78-6.70 (m, 1, pyrrole), 6.15-6.05 (m, 1, pyrrole), 5.19 (d, J = 4 Hz, 1, -CHC$\underline{H}$OH), 3.64 (broad s, 1, -O$\underline{H}$), 3.40 (d of q, J = 7 Hz, 4 Hz, 1, $CH_3C\underline{H}CHOH$), 1.57 (s, 9, t-butyl CH_3's), 1.13 (d, J = 7 Hz, 3, $C\underline{H}_3CH$-). In the threo-aldol adduct[56] the signal for $CH_3CHC\underline{H}OH$ (carbinol center proton) appears at δ 4.90 (d,

J = 8 Hz). These spectra are identical with those reported in the literature[56] for this compound.

2,2-Dimethyl-1,3-propane ketal of (2R,4R,8R) and (2R,4S,8R)-9-benzyloxy-1-hydroxy-2,4,8-trimethylnonan-5-one (58a). A solution of silyl ether 47 (1.02 g, 1.61 mmol), dry Et_3N (0.58 mL, 4.17 mmol), and tetra-n-butylammonium fluoride (8.05 mL, 1 M, 8.05 mmol) in dry THF (33 mL) was stirred at room temperature for 10 h. The THF was removed by evaporation and the residue partitioned between 0.1% Et_3N-CH_2Cl_2 and saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with 0.1% Et_3N-CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil containing (TLC, silica gel, 25% EtOAc-hexane) the mixture of diastereoisomeric alcohols 58a (R_f = 0.21) and impurities (R_f = 0.49 and 0.04). Flash chromatography on florisil eluting with EtOAc-Et_3N-hexane (gradient from 5% EtOAc to 25% EtOAc) gave 514 mg (81%) of alcohols 58a as a colorless oil: IR (film) 3400, 2960, 2870, 1095 cm^{-1}; ^1H NMR (CCl_4) δ 7.22 (5 H, s, aromatic H), 4.38 (2 H, s, OCH_2Ph), 3.19-3.35 (8 H, m, $HOCH_2CH$-, $PhCH_2OCH_2$-, and $-OCH_2C(CH_3)_2CH_2O$-), 2.00 (1 H, broad s, -OH), 1.71-0.73 (24 H, m, $CH_3CHCH_2CHCH_3$, $-CH_2CH_2CHCH_3$, and $(CH_3)_2C(CH_2O)_2$).

Exact mass (75 eV) m/e calcd. for $C_{24}H_{40}O_4$: 392.293. Found: 392.290.

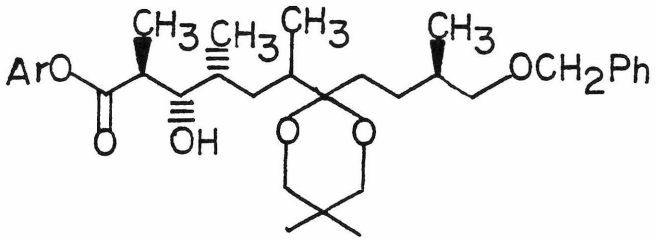
2,2-Dimethyl-1,3-propane ketal of (2R,4R,8R) and (2R,4S,8R)-9-benzyloxy-5-oxo-2,4,8-trimethylnonanal (58b). Pyridine (1.68 mL, 20.8 mmol) in dichloromethane (24 mL) was cooled to 0°C and chromium trioxide (1.04 g, 10.4 mmol) was added. After 5 min the orange solution was warmed to room temperature and stirred for 15 min. After the addition of Celite (5.0 g), alcohols 58a (0.514 g, 1.31 mmol) in dichloromethane (6 mL) were added to the burgundy-colored solution. After 25 min the solution was decanted and the Celite washed thoroughly with dichloromethane. The solvent was removed in vacuo, the residue was taken up in ether, and filtered through florisil and eluted with ether. Removal of solvent in vacuo gave 450 mg (88%) of aldehydes 58b as a colorless oil: IR (film) 2950, 2860, 2700, 1718, 1450, 1390, 1370, 1360, 1090, 735, 695 cm^{-1}; ^1H NMR (CCl_4) δ 9.52 (1 H, d, -CHO), 7.23 (5 H, s, aromatic H), 4.40 (2 H, s, $-OCH_2Ph$), 3.33-3.18 (6 H, m, $PhCH_2OCH_2$-, $-OCH_2C(CH_3)_2CH_2O$-), 2.42-0.6 (24 H, m, $CH_3\dot{C}HCH_2\dot{C}HCH_3$, $-CH_2CH_2\dot{C}HCH_3$, and $(CH_3)_2C(CH_2O)_2$).

Exact mass (75 eV) m/e calcd. for $C_{24}H_{38}O_4$: 390.277. Found: 390.277.

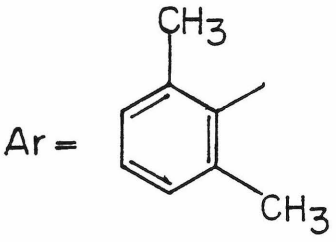
2,2-Dimethyl-1,3-propane ketal of (2S,3S,4R,10R) and (2R,3R,4R,10R)-2,6-dimethylphenyl 11-benzyloxy-3-hydroxy-7-oxo-2,4,6,10 tetramethylundecanoate (72a,b). To a solution of diisopropylamine (0.23 mL, 1.61 mmol) in THF

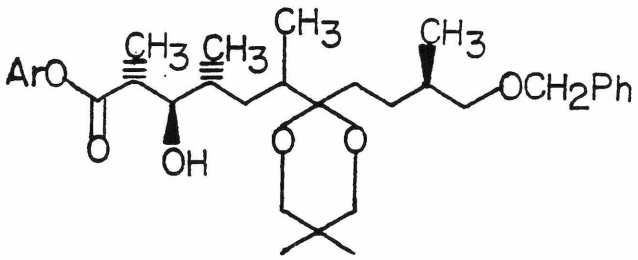
(1.3 mL) at 0°C, n-butyllithium in hexane (1.08 mL, 1.49 M, 1.61 mmol) was added dropwise. After 10 min the solution was cooled to -78°C and 2,6-dimethylphenyl propionate (0.271 g, 1.52 mmol) in THF (1.3 mL) was added dropwise. After 30 min, unpurified aldehydes 58b (0.570 g, 1.46 mmol) in THF (1.9 mL) were added in one portion, the reaction mixture was stirred for 45 sec, and saturated ammonium chloride (3 mL) was added. After warming to room temperature, the reaction mixture was diluted with H_2O and extracted three times with ether. The combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo to give 781 mg (92%) of a colorless oil containing (TLC, silica gel, 25% EtOAc-hexane, R_f = 0.38) condensation adducts 72a and 72b: IR (film) 3460, 2960, 2860, 1750, 1460, 1395, 1375, 1360, 1260, 1170, 1160, 1150, 1140, 1095, 770, 735, 700 cm^{-1}; ^1H NMR (CCl_4) δ 7.20 (5 H, m, aromatic H), 6.94 (3 H, s, aromatic H), 4.40 (2 H, m, $-OCH_2Ph$), 3.90-3.03 (7 H, m, $-CH_2OCH_2Ph$, $-OCH_2C(CH_3)_2CH_2O-$, $-CHCH(OH)CH-$), 3.00-2.30 (2 H, m, -OH and $OCCHCH_3$), 2.10 (6 H, s, aromatic $-CH_3$'s), 2.20-0.60 (27 H, m, $OCCHCH_3$, $CH_3CHCH_2CHCH_3$, $-CH_2CH_2CHCH_3$, $(CH_3)_2C(CH_2O)_2$). The ratio of condensation adducts 72a and 72b was shown to be approximately 3:1 by analytical HPLC (μ-porasil, 3.9 mm x 30 cm, 15% ether-hexane, 4.0 mL/min). A better determination of this ratio was achieved after closure to lactone 60.

An exact mass determination on this aldol adduct failed under all conditions due to decomposition of the parent.



72a





72b

2,2-Dimethyl-1,3-propane ketal of (2S,3S,4R,10R) and (2R,3R,4R,10R)-11-benzyloxy-3-hydroxy-7-oxo-2,4,6,10-tetramethylundecanoic acid (59a,b). A solution of unpurified esters 72a,b (0.048 g, 0.085 mmol) and KOH (0.11 mL, 2 N, 0.213 mmol) in 0.5 mL CH_3OH was stirred at room temperature for 5 h. TLC indicated starting material remained (silica gel, 25% EtOAc-hexane, R_f = 0.38). Additional KOH (0.06 mL, 2 N, 0.12 mmol) was added and stirring continued for 2 h. The reaction mixture was diluted with H_2O, cooled to 0°C, acidified with 10% HCl to Congo Red, and saturated with salt. The solution was extracted with EtOAc, the combined extracts dried (Na_2SO_4), and the solvent removed

in vacuo to give 31.0 mg of a colorless oil containing the acids 59a and 59b: IR (film) 3400, 3300-2500 (broad), 1705, 1090 cm^{-1}; ^1H NMR (CCl_4) δ 7.23 (5 H, s, aromatic H's), 6.70 (1 H, broad s, $-CO_2\underline{H}$), 4.41 (2 H, s, $-OC\underline{H}_2Ph$), 3.73-3.00 (7 H, m, $-OC\underline{H}_2C(CH_3)_2C\underline{H}_2O-$, $-C\underline{H}_2OCH_2Ph$, $CH_3\underline{C}H\underline{C}HOH$), 2.50 (1 H, broad s, $-O\underline{H}$), 2.22-0.57 (28 H, m, $OC\underline{C}H\underline{C}H_3$, $(C\underline{H}_3)_2-C-(CH_2O)_2$, $-C\underline{H}_2C\underline{H}_2\underline{C}H\underline{C}H_3$, $C\underline{H}_3\underline{C}H\underline{C}H_2\underline{C}H\underline{C}H_3$). The acids could not be purified on silica gel due to closure to lactones 60a and 60b. Repeated attempts to determine an exact mass failed, but subsequent compounds were fully characterized and confirm the presence of these acids.

(1S,4S,5S,6R,8S) and (1R,4S,5R,6R,8R)-1-[(2R)-1-benzyloxy-2-methylbutan-4-yl]-3-oxo-4,6,8-triemthyl-2,9-dioxabicyclo[3.3.1]nonane (60a,b). A solution of unpurified acids 59a, 59b (0.739 g, 1.59 mmol) from the previous experiment and camphorsulfonic acid (0.180 g, 0.78 mmol) in acetone (27 mL) was stirred for 15 h at 25°C. The acetone was removed in vacuo and the residue partitioned between dichloromethane and saturated sodium bicarbonate. The bicarbonate layer was extracted twice more with dichloromethane, the combined organic extracts were dried (Na_2SO_4), and the solvent removed in vacuo to give 480 mg of a yellow oil containing lactones 60a, 60b (TLC, silica gel, 25% EtOAc-hexane, R_f = 0.32, 0.37). Medium

pressure liquid chromatography on silica gel (Merck Lobar size A, 15% EtOAc-hexane) gave 187 mg (36% from aldehyde 58b over three steps) of lactone 60a as a colorless oil, 60a: IR (film) 2960, 2930, 2870, 1730, 1450, 1375, 1265, 1090, 990, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (5 H, s, aromatic H's), 4.47 (2 H, s, $-OCH_2Ph$), 3.71 (1 H, d, J = 5 Hz, H-C-O), 3.28 (2 H, d of d, J = 6 Hz, $CH_3CHCH_2OCH_2Ph$), 2.49 (1 H, q, J = 7.5 Hz, $OCCHCH_3$), 2.32-1.08 (9 H, m, $CH_3CHCH_2CHCH_3$, $-CH_2CH_2CHCH_3$), 1.40 (3 H, d, J = 7.5 Hz, $OCCHCH_3$), 0.98-0.72 (9 H, m, $CH_3CHCH_2CHCH_3$, $-CH_2CHCH_3$); ^{13}C NMR ($CDCl_3$) δ 172.7, 138.8, 128.3, 127.5, 107.5, 78.8, 75.8, 73.0, 38.0, 34.6, 33.5, 33.3, 33.1, 32.2, 26.1, 19.8, 16.9, 15.9

Exact mass (75 eV) m/e calcd. for $C_{22}H_{32}O_4$: 360.230. Found: 360.231.

Anal. calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.40; H, 8.88.

and 63 mg (12% from aldehyde 58b over three steps) of lactone 60b as a colorless oil. 60b: IR (film) 2960, 2925, 2865, 1730, 1455, 1375, 1270, 1250, 1085, 980, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (5 H, s, aromatic H's), 4.45 (2 H, s, $-OCH_2Ph$), 3.60 (1 H, s, H-C-O-), 3.27 (2 H, d, J = 6 Hz, $-CH_2OCH_2Ph$), 2.34 (1 H, q, J = 7.5 Hz, $OCCHCH_3$), 2.18-1.00 (9 H, m, $CH_3CHCH_2CHCH_3$, $-CH_2CH_2CHCH_3$),

1.38 (3 H, d, J = 7.5 Hz, OCCHC$\underline{H}_3$), 1.12 (3 H, d, J = 7 Hz, -OCHCHC$\underline{H}_3$), 0.92 (3H, d, J = 7 Hz, -OCCHC$\underline{H}_3$), 0.88 (3 H, d, J = 7 Hz, -CH_2CH_2CHC$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 172.7, 138.8, 128.3, 127.5, 108.0, 79.5, 75.6, 73.0, 40.1, 35.0, 33.5, 32.8, 31.8, 29.8, 26.1, 19.8, 18.5, 17.4, 16.1.

Exact mass (75 eV) m/e calcd. for $C_{22}H_{32}O_4$: 360.230. Found: 360.230.

Analytical HPLC analysis (Water's Radial Pak, silica gel, 8 mm x 10 cm, 15% ether-hexane) of the purified lactones showed each lactone to be only one diastereoisomer. This conclusion was confirmed by ^{13}C NMR spectra of the individual lactones. The isolated ratio of pure lactone 60a (from the Cram aldol product) to pure lactone 60b (from the anti-Cram aldol product) was 3:1, in line with Heathcock's observations.[4,5] Combined yield of pure lactones 60a,60b was 44% from alcohols 58a over a total of four steps.

(1S,4S,5S,6R,8S)-1-[(2R)-1-hydroxy-2-methylbutan-4-yl]-3-oxo-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonane (61a). A solution of benzyl ether 60a (0.120 g, 0.33 mmol) in THF (3 mL) was treated with H_2 at 50 psi with 5% Pd-C (Engelhard) as catalyst (70 mg) for 24 h. Filtration through Celite and removal of solvent in vacuo gave 88.2 mg (98%) of a colorless oil containing (TLC, silica gel, 50% EtOAc-hexane, R_f = 0.31) alcohol 61a: IR (film) 3450, 2970,

2960, 2940, 2880, 1730, 1460, 1380, 1280, 1270, 1255, 970 cm^{-1}; ^1H NMR (CCl_4) δ 3.67 (1 H, d, J = 5 Hz, $\underline{H}\dot{C}O$), 3.35 (2 H, d, J = 6 Hz, $-C\underline{H}_2OH$), 3.18 (1 H, broad s, $-O\underline{H}$), 2.68-1.00 (10 H, m, $OC\dot{C}\underline{H}CH_3$, $-C\underline{H}_2C\underline{H}_2\dot{C}\underline{H}CH_3$, $CH_3\dot{C}\underline{H}C\underline{H}_2\dot{C}\underline{H}CH_3$), 1.35 (3 H, d, J = 7.5 Hz, $OC\dot{C}HC\underline{H}_3$), 0.93 (3 H, d, J = 7 Hz, $-C\underline{H}_3$), 0.90 (6 H, d, J = 7 Hz, 2 $-C\underline{H}_3$'s).

Exact mass (75 eV) m/e calcd. for $C_{15}H_{26}O_4$: 270.183. Found: 270.182.

(1S,4S,5S,6R,8S)-1-[(2R)-2-methyl-1-oxo-butan-4-yl]-3-oxo-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonane (61b). To a solution of pyridine (0.42 mL, 5.20 mmol) in dichloromethane (6.2 mL) cooled to 0°C was added chromium trioxide (0.260 g, 2.60 mmol). After 5 min the orange solution was warmed to room temperature and stirred for 15 min. After the addition of 1.23 g Celite, alcohol 61a (0.088 g, 0.327 mmol) in dichloromethane (2.2 mL) was added to the burgundy-colored solution. After 25 min the reaction mixture was worked up as for aldehydes 58b to give 56 mg (64%) of aldehyde 61b as a colorless oil: IR (film) 2960, 2930, 2880, 2720, 1730, 1715, 1460, 1375, 1265, 1250, 990, 970 cm^{-1}; ^1H NMR (CCl_4) δ 9.58 (1 H, d, J = 2 Hz, $-C\underline{H}O$), 3.63 (1 H, d, J = 5 Hz, $\underline{H}\dot{C}$-O-), 2.68-1.00 (10 H, m, O-$C\dot{C}\underline{H}CH_3$, $-C\underline{H}_2C\underline{H}_2\dot{C}\underline{H}CH_3$, $CH_3\dot{C}\underline{H}C\underline{H}_2\dot{C}\underline{H}CH_3$), 1.35 (3 H, d, J = 7.5 Hz, $C\underline{H}_3\dot{C}HCO_2$-), 1.10 (3 H, d, J = 7 Hz, $C\underline{H}_3\dot{C}HCHO$), 0.92 (3 H, d, J = 7 Hz, $-C\underline{H}_3$), 0.89 (3 H, d, J = 7 Hz, $-C\underline{H}_3$).

Exact mass (75 eV) m/e calcd. for $C_{15}H_{24}O_4$: 268.167. Found: 268.167.

Methyl 5-N-methyl-N-trifluroacetylamino-2-|{(1R,2R) and (1S,2R)-4-[(1S,4S,5S,6R,8S)-3-oxo-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-1-yl]-1-hydroxy-2-methylbutan-1-yl}methyl|-4-benzoxazolecarboxylate (62a,b). To a solution of diisopropylamine (0.0336 mL, 0.240 mmol) in THF (0.6 mL) cooled to 0°C was added n-butyllithium in hexane (0.16 mL, 1.49 M, 0.240 mmol) dropwise. After 10 min the solution was cooled to -100°C, a precooled (-100°C) solution of benzoxazole 39 (0.073 g, 0.230 mmol) in THF (0.7 mL) was added dropwise over 3 min and stirred for 10 min. Aldehyde 61b (0.056 g, 0.209 mmol) in THF (0.7 mL) was added in one portion and the reaction mixture rapidly stirred for 3 min. The reaction mixture was quenched with saturated ammonium chloride (2 mL), warmed to room temperature, and diluted with H_2O. After extraction three times with ether, the combined extracts were dried (Na_2SO_4), and solvent removed in vacuo to give 114 mg of an orange-yellow oil. Medium pressure liquid chromatogrpahy on silica gel (Merck Lobar size A, gradient elution from 15% EtOAc-hexane to 50% EtOAc-hexane) gave 68 mg (56%) of condensation products 62a and 62b as a light yellow oil: IR (film) 3420, 2960, 2930, 2880, 1730, 1715, 1695, 1610, 1605, 1565, 1480, 1455, 1430, 1290, 1270, 1250, 1220, 1205, 1150, 1050, 1010, 990, 970,

950, 820, 800, 780, 760, 690, 680 cm^{-1}; ^1H NMR (CCl_4) δ 7.57 (1 H, d, J = 9 Hz, aromatic H), 7.17 (1 H, d, J = 9 Hz, aromatic H), 3.90 (3 H, s, $-CO_2CH_3$), 3.61 (1 H, d, J = 4 Hz, $HC(-O-)$), 3.40 and 3.21 (3 H, s, CH_3NCOCF_3), 4.30-2.80 (4 H, m, $-CH_2C=N-$, $-OH$, $CH_3CHCHOH$), 2.50-1.00 (10 H, m, $O=CCHCH_3$, $-CH_2CH_2CHCH_3$, $CH_3CHCH_2CHCH_3$), 1.30 (3 H, d, J = 7 Hz, $O=CCHCH_3$), 1.10-0.72 (9 H, m, $CH_3CHCH_2CHCH_3$, $CH_3CHCHOH$).

Exact mass (75 eV) m/e calcd. for $C_{28}H_{35}N_2O_8F_3$: 584.235. Found: 584.235.

HPLC analysis (Waters'Radial Pak, silica gel, 8 mm x 10 cm, 50% EtOAc-hexane) indicated a 1:1 mixture of Cram (62a) and anti-Cram (62b) condensation products (35% isolated yield from lactone 60a over three steps).

Methyl 5-N-methyl-N-trifluroacetylamino-2-{[(3R,8S,9R,11R)-3,9,11-trimethyl-8-[(2S)-carboxyethan-2-yl]-1,7-dioxaspiro[5.5]undecan-2-yl}methyl]-4-benzoxazolecarboxylate (63a,b,c). A 25-mL flask was charged with aldol adducts 62a and 62b (0.066 g, 0.113 mmol), dichloromethane (3 mL), Dowex H^+ Resin (sulfonic acid form, 1.0 g)[57] and stirred for 21 h at room temperature. After heating at the reflux temperature for 2 h, the mixture was filtered to remove the resin and the solvent removed in vacuo to give 52 mg (80%) of a light yellow oil containing (TLC, silica gel, 4% HOAc - 48% EtOAc - 48% hexane) three spiroketals: IR

(film) 3400-2500 (broad), 1720, 1695, 1560, 1480, 1455, 1420, 1295, 1220, 1205, 1155, 1050, 1020, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80-7.65 (1 H, m, aromatic H), 7.30-7.10 (1 H, m, aromatic H), 3.96 (3 H, s, $-CO_2CH_3$), 3.31 (3 H, s, $-N(COCF_3)CH_3$), 4.10-3.00 (4 H, m, $-OCH$, $-OCH$, $-CH_2C=N$), 2.70-2.40 (1 H, m, $-CHCH_3CO$), 2.10-0.60 (21 H, m, $CH_3CHCH_2CH_2C-$, $-CCH(CH_3)CH_2CH(CH_3)CHCHCH_3$).

Exact mass (75 eV) m/e calcd. for $C_{28}H_{35}N_2O_8F_3$: 584.235. Found: 584.235.

The desired spiroketal 63a could be separated from the undesired spiroketals (63b and 63c) by prep TLC (one-half of an analytical TLC plate, 25% EtOAc, 3% acetic acid, 72% hexane; R_f (63a) = 0.20, R_f (63b,63c) = 0.40).

Methyl 5-N-methyl-N-trifluoroacetylamino-2-[{(3R,8S,9R,11R)-3,9,11-trimethyl-8-[(2S)-carbomethoxyethan-2-yl]-1,7-dioxaspiro[5.5]undecan-2-yl}methyl]-4-benzoxazolecarboxylate (73a-c). A solution of spiroketals 63a, 63b, and 63c (20 mg, 0.034 mmol) and the dimethylacetal of dimethylformamide (8.1 mg, 0.068 mmol) in dichloromethane (1 mL) was heated to the reflux temperature. After 90 min, the reaction solution was cooled and partitioned between 1,1,1-trichloroethane and saturated brine solution. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 19.4 mg of a yellow oil. Purification by HPLC (Waters' Radial Pak, silica gel, 8 mm x 10 cm, 25% EtOAc-Hexane) afforded

17.1 mg of a mixture of the three esterified spiroketals 73a, 73b, 73c as a colorless oil: IR ($CHCl_3$) 2970, 2950, 1735, 1705, 1570, 1465, 1445, 1430, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (1 H, m, aromatic H), 7.24 (1 H, m, aromatic H), 4.00 (3 H, s, $-CO_2C\underline{H}_3$), 3.74 (3 H, s, $-CO_2C\underline{H}_3$), 3.37 (3 H, s, $-N(COCF_3)C\underline{H}_3$), 4.10-2.90 (4 H, m, $-OC\underline{H}$, $-OC\underline{H}$, $-C\underline{H}_2C{=}N$), 2.55 (1 H, m, $-C\underline{H}CH_3CO$), 2.10-0.60 (21 H, m, $C\underline{H}_3C\underline{H}C\underline{H}_2C\underline{H}_2C-$, $-CC\underline{H}(C\underline{H}_3)C\underline{H}_2C\underline{H}(C\underline{H}_3)CHCHC\underline{H}_3$).

Exact mass (75 eV) m/e calcd. for $C_{29}H_{37}N_2O_8F_3$: 598.250. Found: 598.251.

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43. It should be noted that the optical rotation reported for 1a is incorrect. The correct rotation (M. Debono, Eli Lilly) is $[\alpha]_D^{25}$ -56° (c 0.01, $CHCl_3$). We have found that the optical rotation, $[\alpha]_D^{22}$ is markedly concentration dependent ($CHCl_3$): c 0.028 (-58.6°),

c 0.014 (-58.3°), c 0.010 (-56.0°), c 0.007 (-54.8°), c 0.005 (-53.4°), c 0.003 (-45.1°), c 0.001 (-36.1°) (c g/mL).

44. Evans, D. A.; Vogel, E.; Nelson, J. V. J. Am. Chem. Soc. 1979, 101, 6120-6123; Masmune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. Tetrahedron Lett. 1979, 1665-1668.

45. Heathcock, C. H.; Pirrung, M. C. J. Org. Chem. 1980, 45, 1727-1728.

46. Condensation of the boron enolate of t-butylthiopropionate with aldehyde 58b gave high threo, erythro selectivity (threo, as expected); however, the Cram, anti-Cram selectivity was poor (approx. 60:40, Cram: anti-Cram).

47. Ioannou, P. V.; Dodd, G. H.; Golding, B. T. Synthesis 1979, 939-941.

48. (a) Bean, G. P. J. Heterocyclic Chem. 1965, 2, 473-474; Clezy, P. S.; Daikiw, V. Austral. J. Chem. 1971, 24, 2665-2677; (b) Castro, A. J.; Deck, J. F.; Ling, N. C.; Marsh, J. P.; Means, G. E. J. Org. Chem. 1965, 30, 344-350.

49. It has been reported that by removing the benzoxazole unit in spiroketal 63a, the acid chloride of the resulting spiroketal will acylate pyrryl Grignard 67 in 50% yield. Grieco, P.; personal communication.

50. Pommier, J. C.; Lucas, D. J. Organomet. Chem. 1973, 57, 139-153.

51. The synthesis of ketone 4 and the aldol to form 50 (route A) were carried out by Dr. William A. Kleschick;[7] the aldol to form 1a (route A), the model studies with pyrrole ketone 3, and the spirane model studies were carried out by Dr. Clifford E. Sacks.[7]

52. Watson, S. L.; Eastham, J. F. J. Organomet. Chem. 1967, 9, 165-168.

53. Limpricht, H. Justus Liebigs Ann. Chem. 1891, 263, 224-245.

54. Fieser, L. F. "Organic Syntheses"; Blatt, A. H., Ed. Wiley: New York, 1943; pp. 35-42.

55. For a complete description of the boron aldol condensation, see the experimental section of Chapter II.

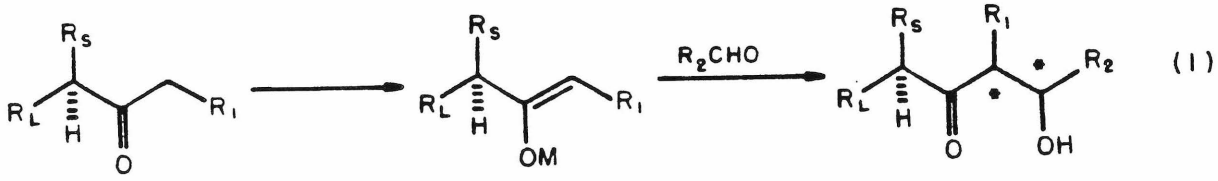
56. Sacks, C. E. Ph.D. Thesis, California Institute of Technology, 1980, pp. 119-120.

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

CHAPTER II

Enantioselective Aldol Condensations

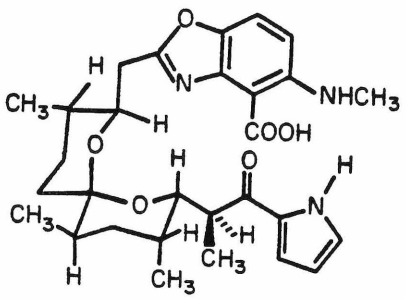
In the course of trying to establish the C_{17}, C_{18}, and C_{19} stereocenters (threo-Cram) in A-23187 (Scheme I), our interests were focused on the development of a suitable asymmetric aldol condensation. Since the aldol process generally forms at least one new chiral center, several approaches to asymmetric induction in the aldol condensation have already been explored (Appendix I). One of these approaches utilizes a resident chiral center in the enolate system to induce chirality at the newly generated centers of asymmetry (eq. 1).



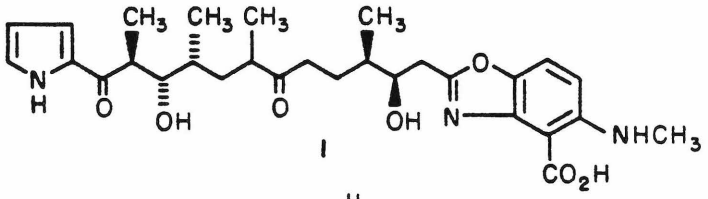
(1)

In 1976, Seebach documented the first example of this type of asymmetric induction for lithium enolates (R_1 = H, R_S = Me, R_L = Et).[1] Recently, Heathcock has reported enhanced diastereoselection for a more sterically biased lithium enolate (R_1 = Me, R_S = $OSiMe_3$, R_L = t-Bu).[2] With the high erythro,threo-diastereoselection observed in the aldol condensations of boron enolates,[11,13] it was of considerable interest to us to determine whether boron enolates would also exhibit enhanced diastereo-

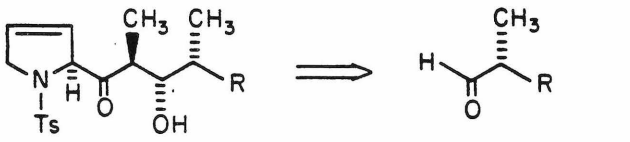
Scheme I



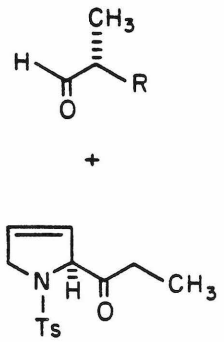
A-23187



1

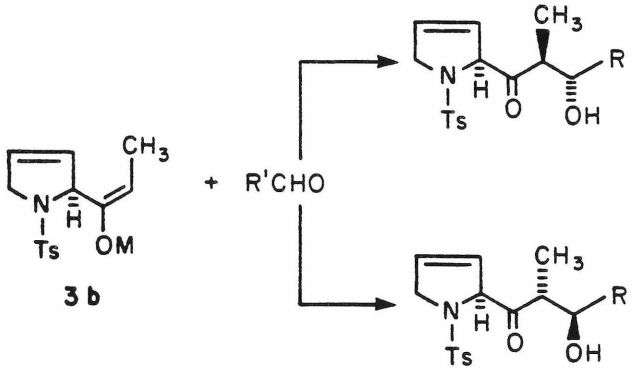


2



3a

1,4 Induction

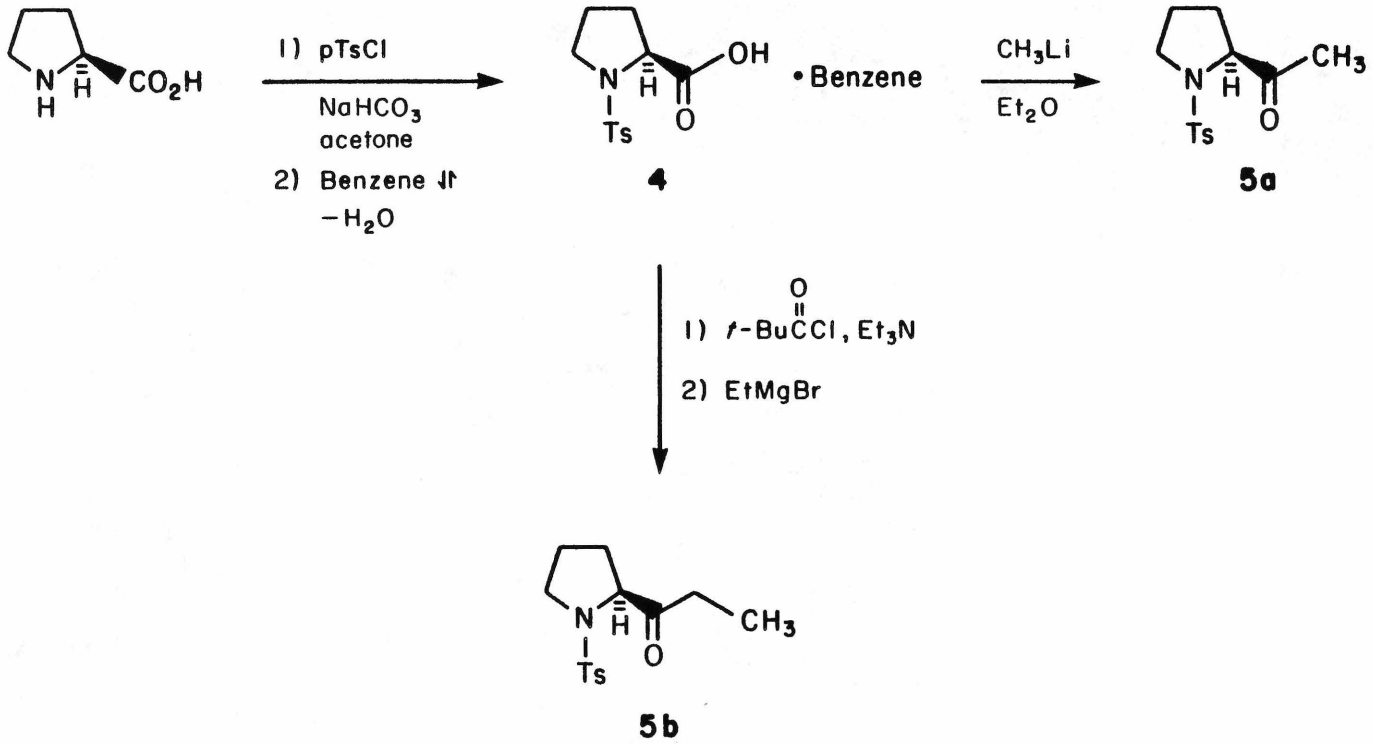


3b

selection of the type illustrated (eq. 1). A successful asymmetric aldol condensation of this type would have widespread applications, but its immediate use in solving the threo-Cram stereochemical problem in the total synthesis of A-23187 is shown in Scheme I. The pyrrolidine subunit 3a could serve as the resident chiral center in the enolate, 3b, as well as a precursor to pyrroles. In accordance with these studies, the development of transition state models which correlate the steric effects of ligands R_S (small) and R_L (large) with the sense of chirality transfer to the newly created centers of asymmetry would be instructive for future synthetic planning, just as Cram's Rule has been in the area of 1,2-asymmetric induction.[3]

Model studies addressing the feasibility of this asymmetric aldol approach were conducted with the chiral pyrrolidine ketones 5a and 5b. These ketones could be synthesized optically pure from (S)-proline (Scheme II). (S)-proline was protected as the sulfonamide 4 (p-TsCl, $NaHCO_3$, H_2O),[4] which was purified as the crystalline benzene solvate, mp 92-96°C.[4] The acid 4 when treated with methyllithium in ether afforded the methyl ketone 5a. Purification by medium pressure liquid chromatography (MPLC) gave ketone 5a as a white crystalline solid, mp 59-60.5°C, $[\alpha]_D$ = -155.6° (C = 0.0447 g/mL, $CHCl_3$). Treatment of acid 4 with trimethylacetyl chloride and triethylamine

Scheme II


1) pTsCl
NaHCO3
acetone
2) Benzene ⇃
−H2O
• Benzene
CH3Li
Et2O
4
5a
1) t-BuCCl, Et3N
2) EtMgBr
5b

in THF followed by ethylmagnesium bromide in ether[5] gave ketone 5b. Purification by MPLC afforded ethyl ketone 5b as white needles, mp 73-74.5°C, $[\alpha]_D$ = -157.8° (C = 0.0203 g/mL, $CHCl_3$).

In order to look for possible metal-center effects in the asymmetric aldol process, both the lithium and boron enolates derived from ketones 5a and 5b were condensed with representative aldehydes (eq. 2, 3). The lithium (LDA) and boron (L_2BOTf, iPr_2NEt) enolates 6, from methyl ketone 5a, afforded the aldol condensation adducts 7a,b and 8a,b upon reaction with benzaldehyde and isobutyraldehyde (eq. 2). The diastereoisomeric ratios 7:8 summarized in Table I were determined by analytical HPLC of the unpurified aldol adducts. The absolute configurations of the new carbinol stereocenters were determined by preparative HPLC separation of the diastereoisomeric aldol adducts 7 and 8, followed by Baeyer-Villiger oxidation of the major diastereoisomer, 7a or 7b, from each experiment to the optically pure β-hydroxy acids, (R)-9a, $[\alpha]_D$ = +21° (EtOH, C = 0.0148 g/mL) and (R)-9b, $[\alpha]_D$ = +40.5° ($CHCl_3$, C = 0.0063 g/mL) of known absolute configuration.[6,7] The boron enolate 6 (M = Bu_2B) derived from ketone 5a exhibited good asymmetric induction (7:8; from 3:1 to 5:1), while the corresponding lithium enolate 6 (M = Li) gave nearly a 1:1 ratio of aldol adducts 7:8.

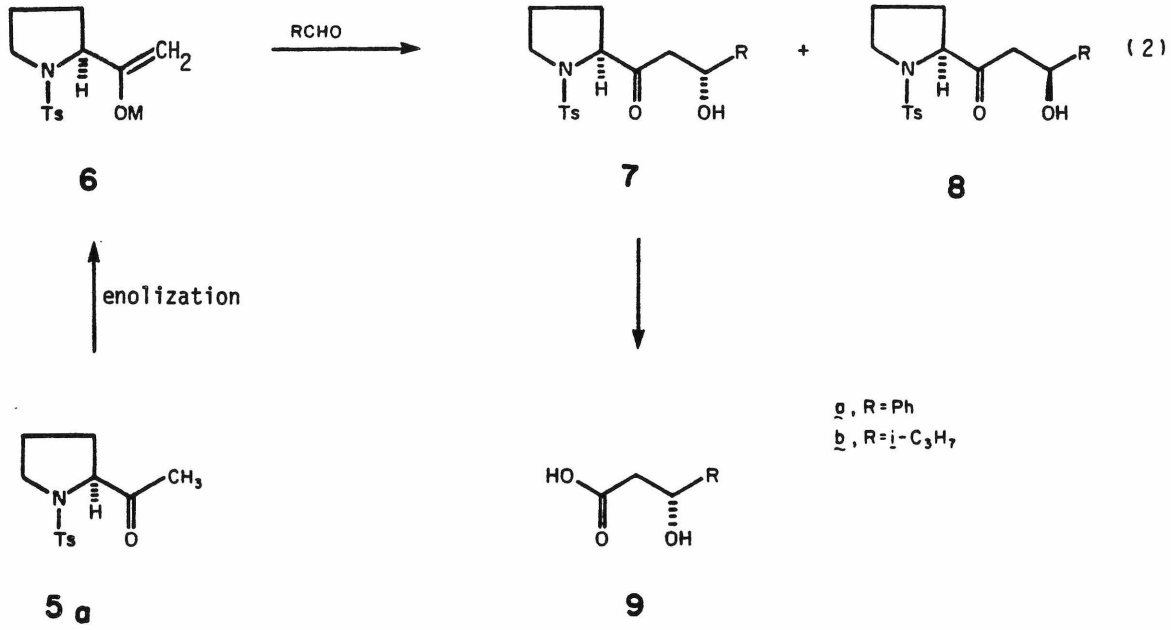
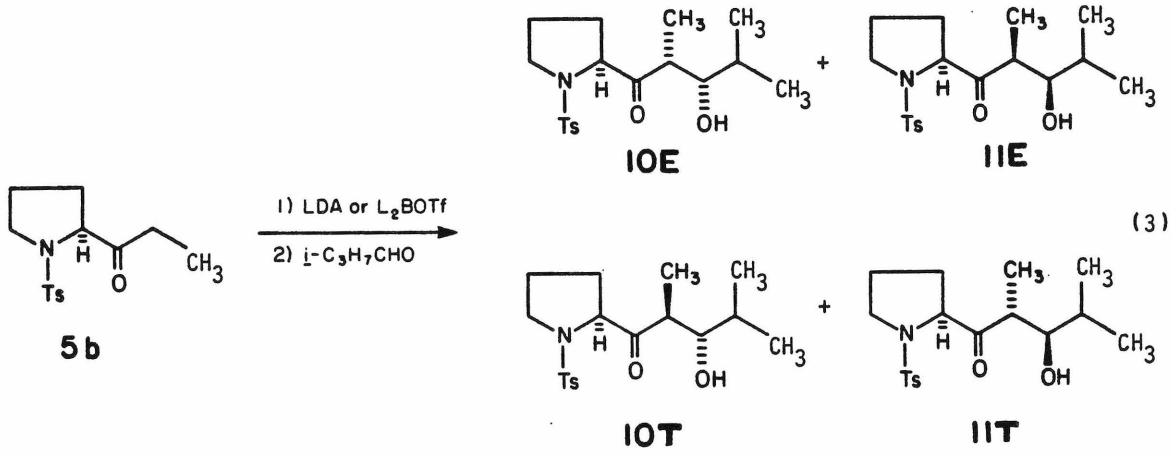


Table I. Metal-Dependent Condensation of Enolate 6 With Representative Aldehydes (Eq. 2).

Entry	Metal (M)	Solvent	RCHO	Condensation[a] T°C	Ratio[b,c] 7:8
A	Li	ether	PhCHO	-78	45:55
B	Li	ether	i-C_3H_7CHO	-78	54:46
C	(n-C_4H_9)$_2$B	CH_2Cl_2	PhCHO	-78	83:17
D	(n-C_4H_9)$_2$B	ether	PhCHO	-78	74:26
E	(c-C_5H_9)$_2$B	ether	PhCHO	0	69:31
F	(n-C_4H_9)$_2$B	CH_2Cl_2	i-C_3H_7CHO	-78	74:26
G	(n-C_4H_9)$_2$B	ether	i-C_3H_7CHO	-78	72:28

a) Reaction times were as follows: A,B, 5 sec; C,D,F,G, 30 min, 1.0 h at 0°C; E, 90 min. b) Ratios determined by analytical HPLC. c) Yields for Entries D,G = 77% (isolated); other yields 77 ± 14% (unpurified).

With information in hand on the chirality transfer via boron enolates derived from methyl ketones, the analogous aldol condensations of ketone 5b were studied to determine the influence of methyl substitution at the reacting center. These condensations could produce four diastereoisomers (2 erythro: 10E + 11E; 2 threo: 10T + 11T) with the threo-diastereoisomer 10T necessary for A-23187. The results of the condensation of 5b with isobutyraldehyde are summarized in Table II. The erythro,threo ratios (10E + 11E:10T + 11T) were determined by ^{13}C NMR[8] and the ratios of erythro diastereoisomers (10E:11E) were determined by both ^{13}C NMR and analytical HPLC. The lithium aldol condensation gave predominantly the erythro diastereoisomer (erythro:threo, 78:22) with fair diastereoselection (10E:11E, 70:30). However, analysis of the unpurified boron aldol condensations (entries B-D) revealed the presence of a single erythro-diastereoisomer (10E) along with approximately 10% of the threo-products (10T and 11T). Recrystallization of the reaction mixture afforded a 57% yield of the stereochemically homogeneous erythro-aldol adduct 10E, $[\alpha]_D$ = -92.5° ($CHCl_3$, C = 0.0294 g/mL). The absolute configuration of 10E was proven by non-regioselective Baeyer-Villiger oxidation (CH_3CO_3H, Na_2HPO_4, CH_2Cl_2, 45°C, 72 h) to the β-hydroxyacid 12, $[\alpha]_D$ =



(3)

Table II. Aldol Condensation of 5b With Isobutyraldehyde (Eq. 3).

Entry	Metal (M)[a]	Solvent	Condensation[b] T°C	Ratio[c] E:T	Ratio[d] 10E:11E
A	Li	THF	-78	78:22	70:30
B	$(n\text{-}C_4H_9)_2B$	CH_2Cl_2	-78	91:9	97:3
C	$(c\text{-}C_5H_9)_2B$	ether-CH_2Cl_2	-78	87:13	97:3
D	$(n\text{-}C_4H_9)_2B$	ether-CH_2Cl_2	-78	90:10	97:3

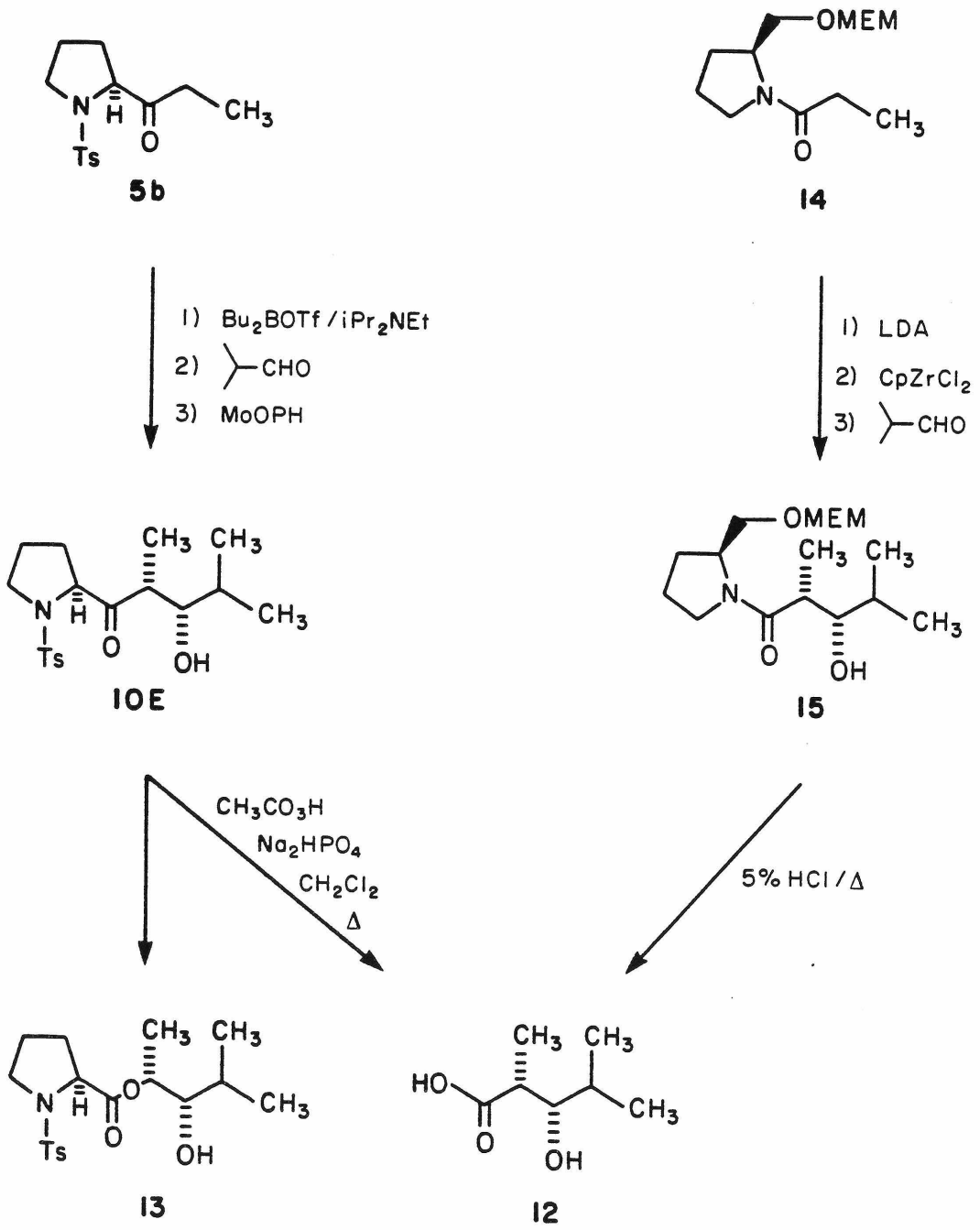
a) For Entry A, LDA employed for enolate formation; for Entry B enolate formed from DPEA at 45°C; for Entries C and D, enolate formed at 25°C. b) Reaction times as follows: A, 5 sec; B,C, and D, 30 min, 1 h at 0°C. c) Erythro-threo ratios determined by ^{13}C NMR, Ref. 37. d) Erythro diastereoisomer ratios determined by ^{13}C NMR and HPLC.

+10.5° ($CHCl_3$, C = 0.0921 g/mL) whose absolute configuration was determined as outlined in Scheme III. Hydrolysis of aldol adduct 15, prepared in 96% optical purity *via* a zirconium-mediated aldol process of known chirality transfer,[9] also gave hydroxyacid 12, $[\alpha]_D$ = +10.0° ($CHCl_3$, C = 0.1167 g/mL). The same sense of rotation confirmed the absolute configuration of 10E as 2(R),3(S).

The ratios of the *threo*-products 10T and 11T (even though obtained in minor amounts) are interesting to note. Since the absolute configurations of the *threo*-products were not determined, it is not known which threo diastereoisomer is the major product (10T or 11T). Nevertheless, the same major threo diastereoisomer is obtained from both the lithium and boron aldols. The ratio of threo diastereoisomers ranges from 1:1 (entry B, M = Bu_2B) to 3:1 (entries A, D; M = Li, Bu_2B) to 10:1 (entry C, M = Cp_2B).

Although the desired *threo*-diastereoisomer was not obtained, the development of an effective asymmetric aldol was realized. The level of chirality transfer from the cis-enolate was nearly complete (>97:3). We surmise that the enhanced chirality observed here *via* methyl substitution (*cf.* ketones 5a and 5b) in the cis-configuration will prove to be general, and we have already made parallel observations with other chiral ketones in

Scheme III


OMEM
N
CH3
O
5b
14
1) Bu2BOTf / iPr2NEt
2) CHO
3) MoOPH
1) LDA
2) CpZrCl2
3) CHO
CH3 CH3
N H
Ts
O
OH
CH3
10E
15
CH3CO3H
Na2HPO4
CH2Cl2
Δ
5% HCl / Δ
HO
13
12

unrelated systems.[9] Since efforts to prepare the requisite trans-enolate from 5b failed, we were unable to study the chirality transfer (and to generate the desired threo-adduct) from a trans-enolate.

In order to more fully explore boron enolates in asymmetric aldol reactions and to develop appropriate transition state models, vide supra, we reexamined the aldol condensation reported by Seebach between the enolate derived from (±)-3-methyl-2-pentanone (16) and propanal (eq. 4).[1,10] Condensation of the lithium enolate 17 (M = Li) with freshly distilled propanal under the reported conditions (-100°C, 15 min) afforded an authentic mixture of diastereoisomers 18 and 19 (Table III, entry B) in a ratio (55:45) which was in excellent agreement to that reported by Seebach (18:19, 57:43 ± 2%, entry A). The corresponding boron enolate 17 (M = Bu_2B) was prepared in the solvents indicated and condensed with propanal (Table III). In line with previously reported solvent effects on the boron aldol condensation,[11] the highest diastereoselection was observed in pentane (64:36), while the diastereoselection in ether was comparable to that observed with the lithium enolate.

Several trends were evident from the results of the aldol condensations of enolates 6a, 6b, and 17. First, for all three ketone enolate systems studied, the boron enolates

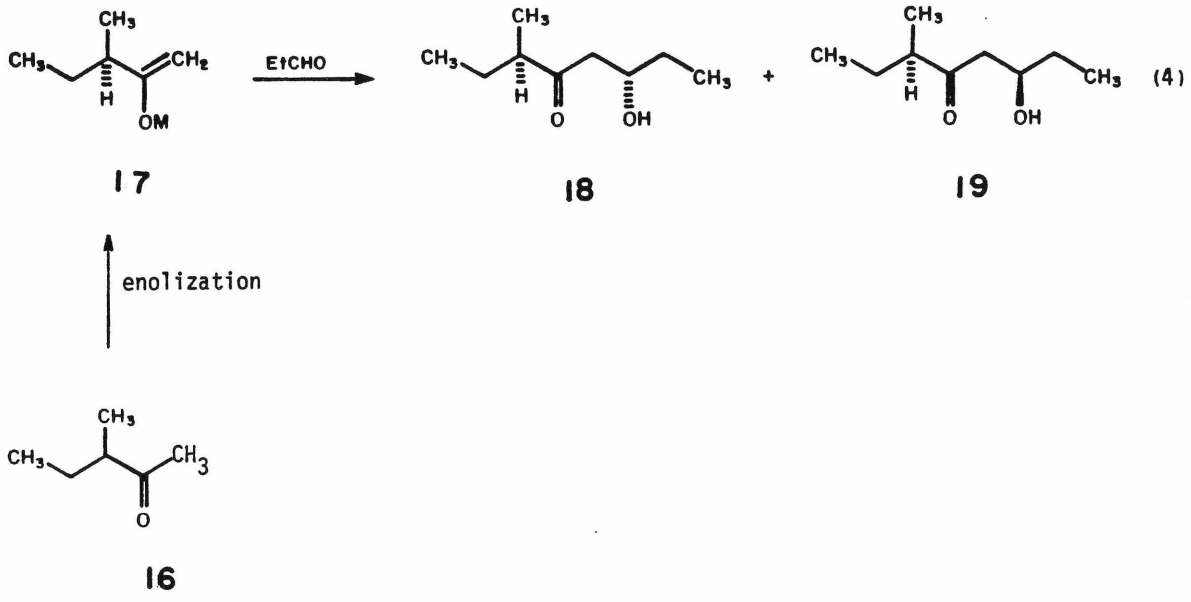


Table III. Metal-Dependent Aldol Condensations of Enolate 17 With Propanal (Eq. 4).

Entry	Metal (M)	Solvent	Condensation[a] T°C	Ratio[b,c] 18:19
A	Li	THF-C_7H_8	-100	57:43[d]
B	Li	THF-C_7H_8	-100	55:45
C	Li	THF-C_7H_8	-78	53:47
D	$(n\text{-}C_4H_9)_2B$	pentane	-78	64:36
E	$(n\text{-}C_4H_9)_2B$	CH_2Cl_2	-78	63:37
F	$(n\text{-}C_4H_9)_2B$	ether	-78	57:43

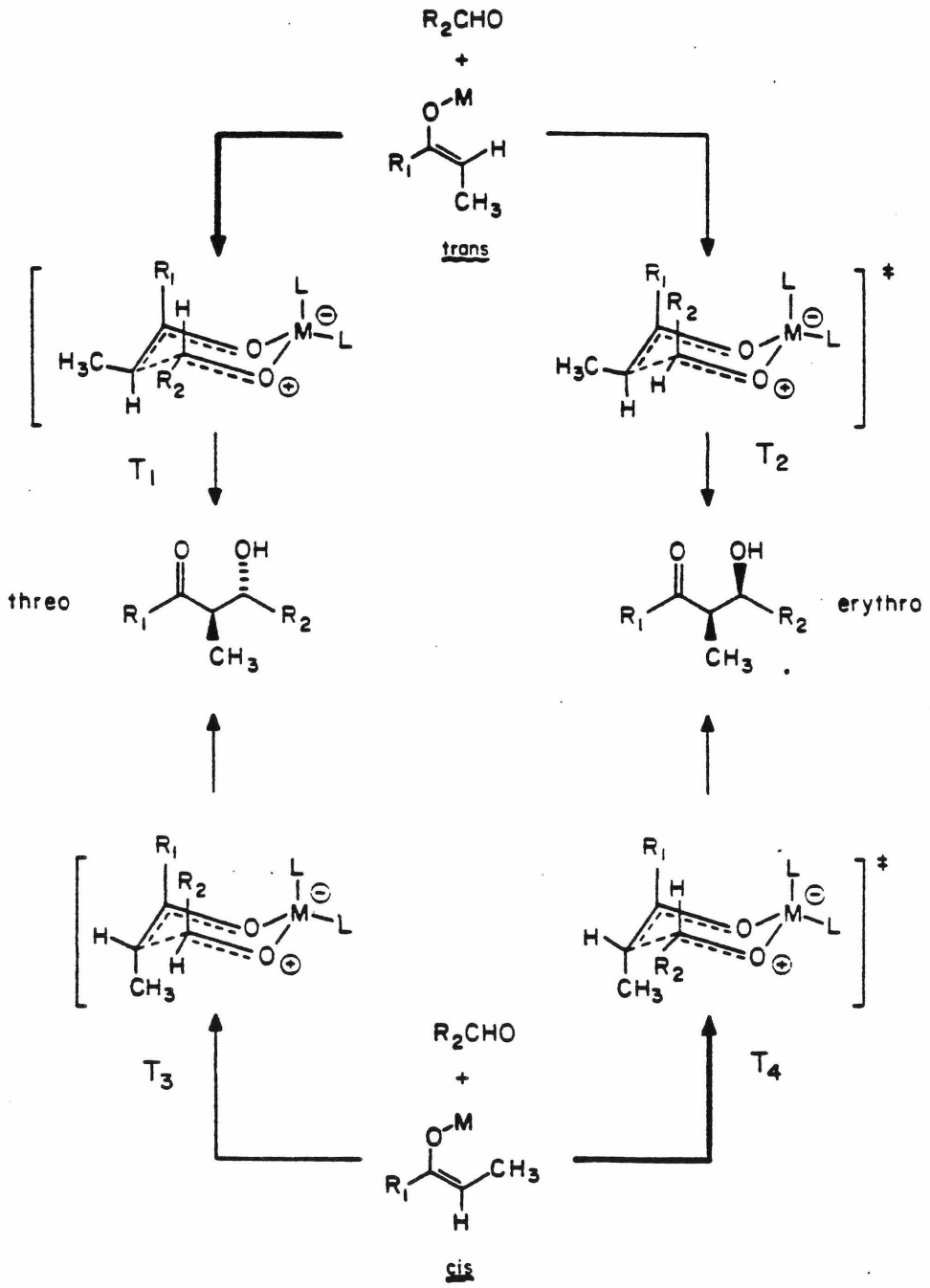
a) Reaction times were as follows: A, B, 15 min; C, 5 sec; D-F, 30 min, 1 h at 0°C. b) Ratios were determined by analytical HPLC. c) Yields for Entries A - B = 65% (distilled); C-F = 81 ± 2% (unpurified). d) Ratio determined by Seebach (±2%), Ref. 32.

displayed greater diastereoselection than the corresponding lithium enolates. Secondly, the sense of chirality transfer observed for 6a,b (R_S = CH_2, R_L = TsN) and 17 (R_S = CH_3, R_L = C_2H_5) was identical. Finally, selectivity was somewhat enhanced in pentane and dichloromethane (a good, general choice of solvent for these reactions). In order to correlate these results, the following steric model is proposed.

Given the reasonable postulate that the aldol condensation proceeds *via* a pericyclic process,[12] there are two key factors to consider in order to achieve high levels of asymmetric induction. One must control the orientation of the aldehyde (pseudo-axial R_2 *vs* pseudo-equatorial R_2, Scheme IV) and the net direction of approach (T_5 *vs* T_6, Scheme V; T_7 *vs* T_8, Scheme VI) of the aldehyde in the transition state for a given enolate geometry. Lower diastereoselectivity can result from lack of control of either factor. Since relatively high levels of diastereoselection (>97:3) were observed with boron enolates, the model must explain the steric interactions responsible for controlling the orientation and approach of the aldehyde.

It has recently been shown that the pseudo-1,3-diaxial $R_2 \leftrightarrow L$ interactions (Scheme IV) are maximized with boron enolates in comparison to other commonly used metal

Scheme IV

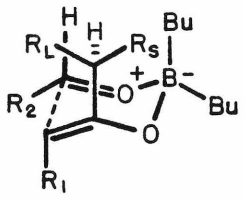


enolates (M = Li, MgL, ZnL, AlX_2).[11,13] This 1,3 diaxial interaction has been instrumental in providing excellent (>97:3) erythro,threo diastereoselection in the boron aldol process by insuring the pseudo-equatorial configuration for R_2 in the transition state. This same effect is operative in the boron aldol condensations of the ketones 5a, 5b, and 16 and provides the orientation control of R_2 in these systems. With the lithium enolates of 5a, 5b, and 16 the metal-oxygen and metal-ligand bond lengths are longer, and such orientation control of the aldehyde in the transition state is only possible for very sterically demanding R_1 groups (i.e. t-Bu, Scheme IV, $R_2 \leftrightarrow R_1$ is the dominant steric interactions).[14] The lack of a sterically demanding R_1 group in the ketones 5a, 5b, and 16 probably accounts somewhat for the lower diastereoselection observed with the lithium enolates 6a,b and 17, vide supra.

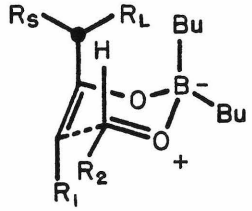
To rationalize the control of the aldehyde approach, two reasonable diastereoisomeric transition states, T_5 and T_6, which accommodate minimal nonbonded interactions with the aldehyde, vide supra, are illustrated in Scheme V for methyl ketone and cis enolates (R_1 = H, Me). Substituents R_S and R_L are respectively designated as "small" and "large". In those transition states involving boron, where both chelation (with R_S or R_L) and aggregation

phenomena are absent, one might expect transition state T_5 to be preferred over T_6 as a consequence of the influence of metal-center steric parameters ($R_S \leftrightarrow Bu \prec R_L \leftrightarrow Bu$). All of the cases examined in this study can be interpreted to proceed preferentially through the illustrated T_5-transition state.

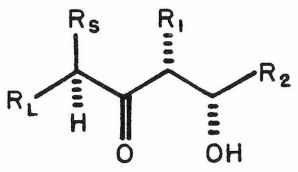
Scheme V



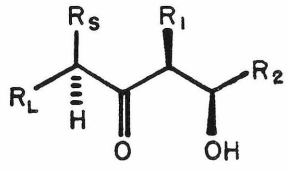
T_5



T_6



20

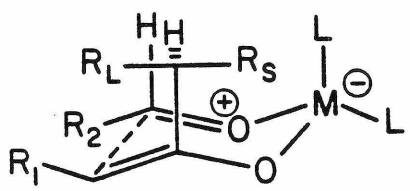


21

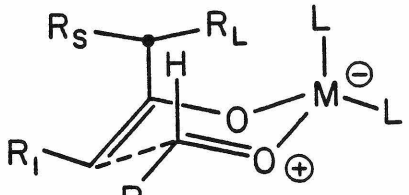
Additionally, the increase in the size of R_L relative to R_S from C_2H_5 (3-methyl-2-pentanone) to NTs (5a,5b) should improve the diastereoselection; indeed, increased selectivity was observed with enolates derived from ketones 5a and 5b. However, the origin of the nearly complete chirality transfer (>97:3) with the cis-boron enolate of ketone 5b is not apparent from the transition state model. Whether the enolate system (R_1 = CH_3) introduces some new steric parameter (not apparent) to account for its high stereoselectivity or the enolate system (R_1 = H) allows a new reaction pathway (boat transition state?) to account for its decreased selectivity is not fully understood.

The real test of any model is whether or not it can reliably predict the outcome of further experimentation. Thus, some experiments to test this model are outlined. In order to enhance diastereoselection, the model indicates that one might "lock" the chiral center into one position instead of relying upon a freely rotating chiral center. The Heathcock aldol condensation[2] mentioned earlier (R_1 = CH_3, R_S = $OSiMe_3$, R_L = t-Bu, eq. 1) has the potential for such "locking" via internal chelation of the lithium counterion and the $OSiMe_3$ ligand. The diastereoselectivity for this system was substantially higher than any other lithium enolate system studied, and the postulated product is the diastereoisomer 20 predicted by the preferred

Scheme VI



T_7



T_8

transition state T_5. Finally, based on the transition state model, interactions between R_1 and R_S, R_L, R_2 might be important for trans-enolates (Scheme VI, $R_1 = CH_3$). Heathcock and co-workers have already observed such an effect between $R_2 \leftrightarrow R_1$ in trans-enolates[14] while studying erythro,threo stereoselectivity. However, no data are available on the pertinent steric parameters involved in chirality transfer with chiral trans-enolates in the aldol condensation. Additional experimentation will be needed to address this issue.

Summary

Asymmetric induction in the aldol reaction was studied with boron and lithium enolates. Boron enolates were found to be superior to lithium enolates in all cases. The sense of chirality transfer was determined and a transition state model proposed to outline the critical steric parameters involved in the condensation.

Experimental Section

General. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz), integration, and interpretation. ^{13}C magnetic resonance spectra were recorded on a JEOL-FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Multiplicities are reported using the format given above. Mass spectra were recorded on a Dupont 21-492B spectrometer by the California Institute of Technology Microanalytical Laboratory. Combustion analyses were performed by California Institute of Technology Microanalytical Laboratory, Spang Microanalytical Laboratory (Eagle Harbor, Michigan), and Galbraith Laboratories (Knoxville, Tennessee).

Analytical gas-liquid chromatography was carried out on a Hewlett-Packard Model gas chromatograph, equipped with a flame ionization detector, using a 25 m by 0.25 mm

Hewlett-Packard capillary column with Carbowax 20 M support. Medium pressure liquid chromatography was performed using EM Laboratories LoBar silica gel 60 prepacked columns on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP Lab Pump. Analytical HPLC was performed on a Water's Associates Model ALC 202/401 high pressure liquid chromatograph equipped with a Model 6000 pump and ultraviolet and refractive index detectors. Preparative HPLC was performed on a Water's Associates "Prep 500" equipped with a refractive index detector.

Optical rotations were recorded on a Perkin Elmer 141 or Jasco DIP-181 polarimeter at the sodium D line.

When necessary, solvents and reagents were dried prior to use. Diethyl ether and tetrahydrofuran were distilled from benzophenone ketyl. Pentane was distilled from sodium and filtered through activity I alumina before use. Methylene chloride, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride. Benzaldehyde and isobutyraldehyde were distilled and stored at 0°C. The method of Vedejs[18] and co-workers was used for the preparation of MoO_5·pyridine·HMPT (MoOPH).

All commercial alkyllithium reagents were titrated by the procedure of Watson and Eastham.[19]

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

Preparation of Dialkylboryl trifluoromethanesulfonates. General Considerations on Handling and Storage. The dialkylboryl triflates are extremely air and moisture sensitive reagents which must be transferred and stored under a scrupulously maintained argon atmosphere. With proper handling the reagents can be stored for several months without any significant decomposition. Although the dialkylboryl triflates often become yellow or orange upon storage, this discoloration had no significant effect on the yields of subsequent reactions. The trifluoromethanesulfonic acid[15] used in the procedures below was obtained from a freshly opened bottle and was not purified before use; partially used bottles which have been opened more than a few weeks should be avoided.

Di-n-butylboryl trifluoromethanesulfonate. The reagent was prepared by the procedure of Mukaiyama[16] and co-workers and was stored at room temperature.

Dicyclopentylboryl trifluoromethanesulfonate. To 14.9 g (68 mmol) of tricyclopentylboron[17] at room temperature under argon was added 10.2 g (68 mmol) of trifluoromethanesulfonic acid dropwise with intermittent cooling to maintain the reaction temperature at approximately room temperature. The deep orange solution was stirred for 30 min at room temperature and was then distilled (70-72°C, 1 mm) to yield 18.3 g (90%) of the air-sensitive

boryl triflate as a colorless liquid. Dicyclopentylboryl triflate was stored at 0°C.

General Procedures for the Formation of Boron Enolates.

Kinetic Generation of Boron Enolates. To a stirred solution of amine (1.1-1.2 equiv) and dialkylboryl triflate (1.1 equiv) in the indicated solvents (2-3 mL/mmol substrate) at the indicated temperatures (≤25°C) under an argon atmosphere was added the substrate (1.0 equiv) dropwise. For reactions in ether and pentane, the progress of the reaction could be monitored by the formation of a white precipitate of ammonium triflate. After the indicated time period the dialkylboron enolate was ready for subsequent reactions.

General Procedures for the Aldol Condensation of Dialkylboron Enolates.

To a solution of the dialkylboron enolate at -78°C under an argon atmosphere was added the aldehyde (non-enolizable: 1.0 equiv, neat; enolizable: 1.2-1.5 equiv, solution in 2-3 mL solvent/mmol aldehyde). The mixture was then stirred for 30 min at -78°C and 1 h at 0°C.

MoOPH Workup. The dialkylboron alkoxides were oxidized by the addition of MoOPH (1.5 equiv) and the yellow slurry was stirred initially at 0°C (30 min) then at room temperature (45 min). The mixture was added to 1 N aqueous sodium hydroxide and extracted with

ether. The ether solution was washed with dilute brine and brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude aldol adducts.

Condensations of 3-methyl-2-pentanone (16). Lithium Aldols. The lithium enolate of 16 (1.00 g, 10 mmol) was prepared and condensed with freshly distilled propionaldehyde (0.58 g, 10 mmol) according to the literature procedure.[1] The product was purified by distillation[1] to give 1.04 g (65%) of a colorless oil: IR (Film) 3460, 2970, 2940, 2880, 1700, 1410, 1380 cm^{-1}; ^1H NMR (CCl_4) δ 3.80 (m, J = 6 Hz, 1 H, $-CH_2\underline{C}'\underline{H}OH$), 3.10 (broad s, 1 H, $-O\underline{H}$), 2.60-2.20 (m, 3 H, $-OC\underline{C}H_2$, $-CH_2\underline{C}'\underline{H}CO-$), 1.88-1.15 (m, 4H, $CH_3\underline{C}H_2$, $CH_3\underline{C}H_2$), 1.10-0.70 (m, 9 H, three-$C\underline{H}_3$'s); ^{13}C NMR (CH_2Cl_2) δ 69.1, 48.5, 47.6, 29.9, 25.9, 15.5, 11.5, 9.9. These spectral data are identical with those reported in the literature for 18 and 19.[1]

Anal. calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.96; H, 11.78.

Boron Aldols. Kinetic enolization of 0.20 g (2 mmol) of 3-methyl-2-pentanone (16) with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-n-butylboryl triflate in dichloromethane at -78°C for 30 min (pentane: 60 min at 0°C; ether: 30 min at -78°C) was

followed by aldol condensation and MoOPH workup with 0.13 g (2.2 mmol) of freshly distilled propionaldehyde to give 263 mg (83%) of a light yellow oil. A portion of the mixture was purified by distillation to give a colorless oil: IR (Film) 3460, 2960, 2940, 2880, 1700, 1455, 1410, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (m, J = 6 Hz, 1 H, $-CH_2\dot{C}\underline{H}OH$), 3.20 (broad s, 1 H, $-O\underline{H}$), 2.60-2.30 (m, 3 H, $-O\dot{C}\underline{CH}_2-$, $-CH_2\dot{C}\underline{H}CO$), 1.88-1.23 (m, 4 H, $CH_3\underline{CH}_2$, $CH_3\underline{CH}_2$), 1.20-0.80 (m, 9 H, three-$\underline{CH}_3$'s); ^{13}C NMR (CH_2Cl_2) δ 69.2, 48.5, 47.6, 29.8, 25.9, 15.5, 11.5, 9.8. These spectra are identical with the spectra above and those reported in the literature.[1]

It is an interesting sidelight that the mixture of diastereoisomers does not display any difference in the ^{13}C NMR spectrum. Thus, the diastereoisomeric ratios were determined by analytical HPLC (DuPont Zorbax Sil, 4.6 mm x 25 cm, 15% ether-hexane): k_A (major, 18) = 6.08; k_B (minor, 19) = 6.70. The ratio was obtained by integration of the corresponding peaks after one recycle to obtain complete separation. In this manner, the purified lithium aldol adduct was shown to be a 55:45 mixture of 18:19. The unpurified boron aldol adducts were determined to be a mixture of 18:19 as indicated: pentane (64:36), dichloromethane (63:37), and ether (57:43). Finally, the lithium aldol condensation was repeated

under "kinetic" conditions[14] at -78°C and the ratio of 24:25 was found to be 53:47 (Table V).

S-(-)-N-4-toluenesulfonylproline (4). The title compound was prepared from L-(-)-proline (20.0 g, 0.17 mol) and p-toluenesulfonyl chloride (39.0 g, 0.20 mol) according to the published procedure.[4] The oily, white solid was purified by a modification of the reported recrystallization from benzene[4] to ensure complete removal of water. The solid was over-layered with benzene and the suspension refluxed for 3 h with removal of water via a Dean-Stark trap. The hot suspension was filtered and the filtrate cooled to room temperature to precipitate 35.0 g (66%) of 4 (as a benzene solvate) as a white crystalline solid: mp 92-96°C; lit.[4] mp 95-98°C; IR (CH_2Cl_2) 3540-2400 (broad), 1760, 1720, 1595, 1475, 1345, 1195, 1160, 1090, 1010, 810, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.87 (s, 1 H, $-CO_2\underline{H}$), 7.78 (d, J = 8 Hz, 2 H, aromatic H's), 7.35 (benzene solvate, 13.2% by integration), 7.32 (d, J = 8 Hz, 2 H, aromatic H), 4.40-4.20 (d of d, J = 4.5 Hz, 7 Hz, 1 H, $-\overset{|}{\underset{|}{N}}\underline{C}HCO_2H$), 3.65-3.10 (m, 2 H, $-\underline{CH_2}\overset{|}{\underset{|}{N}}-$), 2.45 (s, 3 H, $-\underline{CH_3}$), 2.22-1.53 (m, 4 H, $-\underline{CH_2}\underline{CH_2}CH_2\overset{|}{\underset{|}{N}}-$). The properties of this compound are identical with those reported in the literature.[4]

S-(-)-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-

ethanone (5a). To a solution of the benzene solvate of 4 (3.3 g of the benzene solvate, 13.2% benzene; 10.7 mmol of 4) in ether (100 mL) cooled to 0°C was added a solution of methyllithium in ether (12.2 mL, 1.80 M, 22.0 mmol) dropwise over 30 min. After the addition was complete, the white suspension was warmed to room temperature and stirred for 5 h. The reaction mixture was quenched by the slow addition of 30 mL aliquots to ice-cold 20% HCl solution. The aliquots were combined and the ether layer washed with 20% sodium carbonate and brine solutions. The ether layer was dried (Na_2SO_4) and the solvent removed in vacuo to give 1.9 g (66%) of a colorless oil containing ketone 5a (TLC, silica gel, 50% EtOAc-hexane, R_f = 0.23). Purification by MPLC (Merck Lobar size B, 50% EtOAc-hexane) gave 1.4 g (50%) of a colorless oil which crystallized upon standing to give 5a as a white solid: mp 59-60.5°C; IR ($CHCl_3$) 3020, 2980, 2890, 1715, 1600, 1365, 1350, 1310, 1225, 1190, 1165, 1095, 1065, 1015, 1010, 915, 820, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (d, J = 9 Hz, 2 H, aromatic H's), 7.31 (d, J = 9 Hz, 2 H, aromatic H's), 3.96 (d of d, J = 7 Hz, 1 H, TsN'CH'COCH$_3$), 3.68-3.07 (m, 2 H, -CH_2CH_2N'Ts), 2.40 (s, 3 H, tosyl -CH_3), 2.31 (s, 3 H, -$COCH_3$), 2.03-1.40 (m, 4 H, TsN'$CH_2CH_2CH_2$-); ^{13}C NMR ($CDCl_3$) δ 208.1, 143.9, 133.5, 129.7, 127.5, 67.5,

49.2, 29.6, 26.1, 24.7, 21.6; $[\alpha]_D = -155.6°$ (C = 0.0447 g/mL, $CHCl_3$).

Anal. calcd. for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.05; H, 6.17; N, 4.85.

Optical purity of ketone (5a). The optical purity was determined by ^1H NMR analysis employing the chiral shift reagent Tris-[3-(heptafluropropylhydroxymethylene)-d-camphorato], europium (III). A sample of racemic ketone 5a was prepared from racemic proline according to the above procedures. In the proton spectrum of the racemic ketone containing 1.5 mg of the chiral shift reagent, the ketone methyl protons appeared at 2.80 and 2.87 ppm (s) and the methine resonances appeared at 4.78 ppm (m). With 1.5 mg of the chiral shift reagent added to the sample of the optically active ketone, the methyl protons appeared only at 2.93 ppm (s) and the methine proton appeared at 4.92 ppm (d of d). With additional chiral shift reagent these distinctive differences became even more pronounced (Table IV). Considering the limits of NMR detection, the optical purity of ketone 5a was determined to be $\geq$95%.

S-(-)-1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-1-propanone (5b). To a solution of the benzene solvate of 4 (12.4 g of the benzene solvate, 13.2% benzene; 40.0 mmol of 4) in THF (360 mL) cooled to -35°C was added

Table IV.

Shift Reagent (mg)	Racemic Ketone 5a		Opt. Active Ketone 5a	
	$-CH_3$	Methine H	$-CH_3$	Methine H
0	2.31, s	3.96, d of d	2.30, s	3.96, d of d
1.5	2.80, s; 2.87, s (1:1 ratio)	4.78, m	2.93, s	4.92, d of d
3.0	3.73, s; 3.90, s (1:1 ratio)	6.50-6.06, m	3.78, s	6.21, d of d

triethylamine (5.56 mL, 40.0 mmol) and trimethylacetyl chloride (5.00 mL, 40.0 mmol).[5] After 25 min the mixture was cooled to -78°C and a solution of ethylmagnesium bromide in ether (19.9 mL, 2.01 M, 40.0 mmol) was added over 10 min. After an additional 10 min the reaction was quenched with 10% ammonium chloride solution (100 mL) and warmed to room temperature. The mixture was partitioned between ether and 10% aqueous ammonium chloride. The ether layer was washed with 5% sodium bicarbonate and brine solutions, dried (Na_2SO_4), and filtered. Removal of solvent in vacuo gave 7.61 g (68%) of a white solid containing ketone 5b (TLC, silica gel, 50% EtOAc-hexane, R_f = 0.46) accompanied by minor impurities. Purification by MPLC (Merck Lobar size C, 50% EtOAc-hexane) gave 5.9 g (53%) of ketone 5b as a white solid: mp 73-74.5°C; IR (CH_2Cl_2) 3060, 2980, 2940, 2880, 1715, 1600, 1460, 1350, 1305, 1205, 1185, 1170, 1160, 1095, 1010, 990, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 9 Hz, 2 H, aromatic H's), 7.32 (d, J = 9 Hz, 2 H, aromatic H's), 4.05 (d of d, J = 7 Hz, 1 H, -CHCOCH$_2$CH$_3$), 3.68-2.50 (m, 4 H, -CH$_2$NTs, -COCH$_2$CH$_3$), 2.43 (s, 3 H, tosyl-CH$_3$), 2.07-1.37 (m, 4 H, TsNCH$_2$CH$_2$CH$_2$-), 1.09 (t, J = 7.5 Hz, 3 H, -COCH$_2$CH$_3$); ^{13}C NMR ($CDCl_3$) δ 210.8, 143.9, 134.0, 129.8, 127.6, 67.1, 49.3, 31.8,

29.8, 24.8, 21.6, 7.5; $[\alpha]_D = -157.8°$ (C = 0.0203 g/mL, $CHCl_3$).

Anal. calcd. for $C_{14}H_{19}NSO_3$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.96; H, 6.67; N, 5.05.

1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-3-hydroxy-3-phenyl-1-propanone (Table I, Entry D). Kinetic enolization of 1.38 g (5.62 mmol) of ketone 5a with 0.836 g (6.47 mmol) of diisopropylethylamine and 1.69 g (6.18 mmol) of di-n-butylboryl triflate in 20 mL ether at -78°C for 60 min was followed by aldol condensation and MoOPH workup with 0.596 g (5.62 mmol) of benzaldehyde to yield 1.59 g (80%) of a yellow solid. Analysis of the unpurified aldol adduct by HPLC (μ-porasil, 3.9 mm x 30 cm, 25% EtOAc-hexane) showed both diastereoisomers in a 3:1 ratio: k_A (major) = 8.83; k_B (minor) = 6.92. Purification on a Waters' Prep 500 (silica gel, 2 x 325 g, 2 columns, 15% EtOAc-hexane) gave 1.13 g (57%) of aldol diastereoisomer 7a as a white solid and 0.38 g (19%) of aldol diastereoisomer 8a as a white solid. 7a: mp 162-163°C; IR ($CHCl_3$) 3580, 3020, 1710, 1600, 1495, 1455, 1405, 1380, 1350, 1310, 1215, 1165, 1095, 1055, 820, 700, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.50-7.20 (m, 7 H, aromatic H's), 5.18 (d of d, J = 4 Hz, 9 Hz, 1 H, $-\overset{'}{C}H_2\overset{'}{C}\underline{H}OH$), 3.96 (d of d,

J = 7 Hz, 1 H, TsNCHCO-), 3.68-2.80 (m, 5 H, CH_2NTs, $-COCH_2CHOH$, -OH), 2.41 (s, 3 H, tosyl-CH_3), 1.98-1.16 (m, 4 H, $TsNCH_2CH_2CH_2$-); ^{13}C NMR ($CDCl_3$) δ 210.2, 144.0, 129.8, 128.4, 127.6, 127.5, 125.6, 69.7, 67.6, 49.3, 47.0, 29.3, 24.6, 21.5; $[\alpha]_D$ = -90.9° (C = 0.0444 g/mL, $CHCl_3$).

Anal. calcd. for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.58; H, 6.08; N, 3.78.

8a: mp 117-118.5°C; IR (CH_2Cl_2) 3580, 3060, 3000-2900, 1710, 1600, 1490, 1350, 1160, 1090, 815, 750-700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.48-7.12 (m, 7 H, aromatic H's), 5.16 (d of d, J = 4 Hz, 9 Hz, 1 H, $-CH_2CHOH$), 4.07 (m, 1 H, TsNCHCO-), 3.60-2.78 (m, 5 H, $-CH_2NTs$, $-COCH_2CHOH$), 2.41 (s, 3 H, tosyl-CH_3), 1.97-1.32 (m, 4 H, $TsNCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 209.4, 144.0, 129.9, 128.4, 127.7, 125.8, 70.0, 67.2, 49.2, 47.7, 29.1, 24.6, 21.5; $[\alpha]_D$ = -133° (C = 0.0272 g/mL, $CHCl_3$).

Anal. calcd. for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75; S, 8.59. Found: C, 64.28; H, 6.21; N, 3.75; S, 8.67.

Proof of absolute configuration of carbinol stereocenters of (7a) and (8a). To a solution of aldol diastereoisomer 7a (0.125 g, 0.34 mmol) in dichloromethane cooled to 0°C was added disodium hydrogen phos-

phate (0.280 g) and 13% peracetic acid in acetic acid (0.26 mL, 0.51 mmol). After 5 min the ice bath was removed and the mixture stirred for 5 h. The reaction mixture was partitioned between dichloromethane and 20% sodium carbonate solution. The carbonate solution was acidified to Congo Red test paper with dilute HCl, saturated with salt, and extracted with EtOAc (3 x 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 20 mg of optically active 3-hydroxy-3-phenylpropanoic acid: IR (CH_2Cl_2) 3460, 3400-2400 (broad), 3070, 1715, 1415, 1210, 1170, 1060, 1030, 1010 cm^{-1}; ^1H NMR ($CDCl_3$ + d_6-DMSO) δ 7.32 (m, 5 H, aromatic H's), 6.50 (broad s, 2 H, -O<u>H</u>, -CO_2<u>H</u>), 5.07 (d of d, J = 7 Hz, 1 H, -CH_2<u>C'H</u>OH), 2.65 (d, 2 H, -OC<u>C'H$_2$</u>); $[\alpha]_D$ = +21.0° (C = 0.0148 g/mL, EtOH). The literature value for R-(+)-3-hydroxy-3-phenylpropanoic acid is +21.1° (1.9% solution, EtOH).[6] This confirmed the absolute configuration at the carbinol stereocenter in 7a as R. In a similar manner the carbinol stereocenter in 8a was confirmed as S.

1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-3-hydroxy-4-methyl-1-pentanone (Table I, Entry G).

Kinetic enolization of 0.980 g (3.67 mmol) of ketone 5a with 0.57 g (4.4 mmol) of diisopropylethylamine and 1.10 g (4.0 mmol) of di-<u>n</u>-butylboryl triflate in 6 mL ether at

-78°C for 60 min was followed by aldol condensation and MoOPH workup with 0.32 g (4.4 mmol) of isobutyraldehyde to yield 1.28 g (100%) of a yellow oil. Analysis of the unpurified aldol adduct by HPLC (μ-porasil, 3.9 mm x 30 cm, 25% EtOAc-hexane) showed both diastereoisomers in a 3:1 ratio: k_A (major) = 7.65; k_B (minor) = 5.80. Purification on a Waters' Prep 500 (silica gel, 2 x 325 g, 2 columns, 30% EtOAc-hexane) gave 0.700 g (56%) of aldol diastereoisomer 7b as a colorless oil and 0.260 g (21%) of aldol diastereoisomer 8b as a colorless oil.

7b: IR (Film) 3530, 2960, 2880, 1715, 1600, 1345, 1150, 1095, 1000, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$-CCl_4) δ 7.68 (d, J = 9 Hz, 2 H, aromatic H's), 7.30 (d, J = 9 Hz, 2 H, aromatic H's), 4.10-3.63 (m, 2 H, -CH_2C<u>H</u>OH, TsNC<u>H</u>CO-), 3.63-2.96 (m, 2 H, -C<u>H</u>$_2$NTs), 2.96-2.57 (m, 3 H, -OCC<u>H</u>$_2$-, -O<u>H</u>), 2.43 (s, 3 H, tosyl-C<u>H</u>$_3$), 2.10-1.32 (m, 5 H, CH_3C<u>H</u>CH_3, -C<u>H</u>$_2$C<u>H</u>$_2$$CH_2$NTs), 0.96 (d, J = 6 Hz, 6 H, C<u>H</u>$_3$CHC<u>H</u>$_3$); $[\alpha]_D$ = -115.3° (C = 0.0075 g/mL, $CHCl_3$).

Anal. calcd. for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42. Found: C, 60.18; H, 7.58.

8b: IR (Film) 3540, 2960, 2880, 1715, 1600, 1340, 1160, 1095, 1000, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$-CCl_4) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.23 (d, J = 9 Hz, 2 H, aromatic H's), 4.23-3.96 (m, 1 H, TsNC<u>H</u>CO-), 3.96-

3.56 (m, 1 H, $-CH_2\underline{C}\underline{H}OH$), 3.50-3.00 (m, 2 H, $-C\underline{H}_2\underline{N}Ts$), 2.93-2.57 (m, 3 H, $-OCC\underline{H}_2-$, $-O\underline{H}$), 2.42 (s, 3 H, tosyl-$C\underline{H}_3$), 2.07-1.36 (m, 5 H, $CH_3\underline{C}\underline{H}CH_3$, $TsNCH_2C\underline{H}_2C\underline{H}_2-$), 0.94 (d, J = 6 Hz, 6 H, $C\underline{H}_3CHC\underline{H}_3$).

Anal. calcd. for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42. Found: C, 60.06; H, 7.64.

Proof of absolute configurations of carbinol stereocenters of (7b) and (8b). Aldol diastereoisomer 7b (0.200 g, 0.59 mmol) was oxidized with peracetic acid as outlined above to give 57 mg of a colorless oil. This oil was purified by bulb-to-bulb distillation to give optically active 3-hydroxy-4-methylpentanoic acid: IR ($CHCl_3$) 3600-2400 (broad), 1705, 1410, 1225, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48 (broad s, 2 H, $-CO_2\underline{H}$, $-O\underline{H}$), 3.80 (m, 1 H, $-CH_2\underline{C}\underline{H}OH$), 2.48 (m, 2 H, $HOOCC\underline{H}_2-$), 1.70 (m, 1 H, $CH_3\underline{C}\underline{H}CH_3$), 0.93 (two d, J = 6 Hz, 6 H, $C\underline{H}_3CHC\underline{H}_3$); $[\alpha]_D$ = +40.5° (C = 0.0063 g/mL, $CHCl_3$). The literature value is +26.4° (C = 0.021 g/mL, $CHCl_3$).[7] Independent synthesis of S-(-)-3-hydroxy-4-methylpentanoic acid in our laboratories gave $[\alpha]_D$ = -40.0° (C = 0.0464 g/mL, $CHCl_3$).[7] Nevertheless, the rotation confirmed the absolute configuration of the carbinol stereocenter of 7b as R. In a similar manner the carbinol stereocenter in 8b was confirmed as S.

Erythro-[1-(4-toluenesulfonyl)-1-azacyclopentan-2-yl]-

2,4-dimethyl-3-hydroxy-1-pentanone (Table II, Entry B). Enolization of 0.500 g (1.78 mmol) of ketone 5b with 0.275 g (2.12 mmol) of diisopropylethylamine and 0.535 g (1.96 mmol) of di-n-butylboryl triflate in refluxing dichloromethane for 2 h was followed by aldol condensation and MoOPH workup with 0.159 g (2.21 mmol) of isobutyraldehyde to yield 705 mg (>100%) of an oily, light yellow solid. The enolization conditions are not known to fully equilibrate the two possible enolates. Analysis of the unpurified aldol adduct by ^{13}C NMR and analytical HPLC (Waters' Radial Pak, 8 mm x 10 cm, silica gel, 15% EtOAc-hexane) indicated only one erythro-diastereoisomer accompanied by approximately 10% of the two threo diastereoisomers. The mixture was purified by recrystallization from EtOAc-hexane to afford 10E (57%) as fine white needles: mp 155.5-156.5°C; IR (CH_2Cl_2) 3520, 3060, 2960, 2935, 2880, 1710, 1595, 1450, 1340, 1200, 1160, 1095, 985, 815, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.29 (d, J = 9 Hz, 2 H, aromatic H's), 4.57 (m, 1 H, TsNCHCO-), 3.70-3.03 (m, 4 H, $-CH_2NTs$, $-CH_2CHOH$, $OCCHCH_3$), 2.77 (d, J = 3 Hz, 1 H, -OH), 2.41 (s, 3 H, tosyl-CH_3), 2.00-1.37 (m, 5 H, $TsNCH_2CH_2CH_2-$, CH_3CHCH_3), 1.13 (d, J = 7 Hz, 3 H, $-OCCHCH_3$), 1.00 (d, J = 7 Hz, 3 H, CH_3CHCH_3), 0.88 (d, J = 7 Hz, 3 H, CH_3CHCH_3);

^{13}C NMR (CH_2Cl_2) δ 213.9, 144.2, 135.0, 130.0, 127.6, 76.5, 66.0, 49.2, 44.6, 30.9, 29.7, 24.8, 21.4, 19.0, 9.5; $[\alpha]_D$ = -92.5° (C = 0.0294 g/mL, $CHCl_3$).

Anal. calcd. for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.70; N, 3.96. Found: C, 61.13; H, 7.36; N, 3.76.

Erythro-1-[1-(4-toluenesulfonyl)-1-azacyclopentan-2-yl]-2,4-dimethyl-3-hydroxy-1-pentanone (Table II, Entry C).

Kinetic enolization of 0.562 g (2.00 mmol) of ketone 5b with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of dicyclopentylboryl triflate in 3 mL ether-2 mL dichloromethane (dichloromethane was used to add ketone 5b) at room temperature for 45 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of isobutyraldehyde to afford 540 mg (77%) of an off-white solid. Again, as above, analysis of the unpurified aldol adduct by ^{13}C NMR and analytical HPLC indicated mainly erythro-diastereoisomer 10E. A portion of the mixture was purified by analytical HPLC (Altex Li Chromosorb Si 60 5μ, 10 mm x 25 mm, 25% EtOAc-hexane) to give diastereoisomer 10E as a white crystalline solid. Additionally, the mixture could be purified by recrystallization to give pure 10E, vide supra. 10E: mp 155-156°C; IR (CH_2Cl_2) 3520, 3060, 2960, 2935, 2880, 1710, 1595, 1450, 1340, 1200, 1160, 1095, 985, 815, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.29

(d, J = 9 Hz, 2 H, aromatic H's), 4.57 (m, 1 H, TsNCHCO-), 3.70-3.03 (m, 4 H, -CH_2NTs, -CH_2CHOH, OCCHCH$_3$), 2.77 (d, J = 3 Hz, 1 H, -OH), 2.41 (s, 3 H, tosyl-CH_3), 2.00-1.37 (m, 5 H, TsNCH$_2$$CH_2$$CH_2$-, CH_3CHCH$_3$), 1.13 (d, J = 7 Hz, 3 H, -OCCHCH_3), 1.00 (d, J = 7 Hz, 3 H, CH_3CHCH$_3$), 0.88 (d, J = 7 Hz, 3 H, CH_3CHCH_3); ^{13}C NMR (CH_2Cl_2) δ 213.8, 144.1, 134.9, 129.9, 127.6, 76.4, 65.9, 49.2, 44.6, 30.9, 29.6, 24.8, 21.4, 19.0, 9.5. These spectra are identical with the spectra reported for Entry B in Table II.

The aldol condensation of the lithium enolate of 5b (LDA, -78°C, 60 min) and isobutyraldehyde was performed under "kinetic" conditions according to the published procedure.[14] The unpurified aldol adduct was then analyzed by ^{13}C NMR and HPLC as outlined above. All four possible diastereoisomers were detected and this served as an authentic mixture. The differences in the two possible erythro-diastereoisomers which allowed their distinction are outlined in Table V below.

Table V.

	^{13}C NMR (CH_2Cl_2) δ		HPLC[a]
	Carbinol Carbon	Methyl Carbon α to Ketone	k
10E	76.5	9.5	16.7
11E	76.2	9.0	14.4

a) Waters' Radial Pak, 8 mm x 10 cm, silica gel, 15% EtOAc-hexane, flow rate = 8.0 mL/min.

(2R,3S)-2,4-Dimethyl-3-hydroxypentanoic acid (12), via boron aldol. To a solution of aldol diastereoisomer 10E (0.900 g, 2.55 mmol) in dichloromethane (25 mL) cooled to 0°C was added disodium hydrogen phosphate (4.0 g) and 13% peracetic acid in acetic acid (2.60 mL, 5.1 mmol). After 5 min the ice bath was removed and the mixture heated to the reflux temperature of dichloromethane. Additional peracid (1.30 mL, 2.55 mmol) was added 48 h later. After 72 h the reaction mixture was partitioned between dichloromethane and 5% sodium bicarbonate solution (caution, CO_2 evolved vigorously). The carbonate solution was adjusted to pH 4 with concentrated hydrochloric acid, saturated with salt, and extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 200 mg of a colorless oil. The oil was purified by bulb-to-bulb distillation to afford 130 mg (35%) of acid 12 as a colorless oil: IR (film) 3440, 3700-2200 (broad), 2980, 1715, 1470, 1460, 1390, 1220, 1000, 980, 950, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (broad s, 2H, -O<u>H</u>, -CO_2<u>H</u>), 3.62 (d of d, J = 4 Hz, 8 Hz, 1 H, -C<u>H</u>OH), 2.68 (d of q, J = 4 Hz, 7 Hz, 1 H, -C<u>H</u>(CH_3)CHOH), 1.67 (m, 1 H, CH_3C<u>H</u>CH_3), 1.20 (d, J = 7 Hz, 3 H, -CCH<u>H</u>$_3$), 1.00 (d, J = 6 Hz, 3 H, -CH<u>H</u>$_3$), 0.89 (d, J = 6 Hz, 3 H, -CH<u>H</u>$_3$), $[\alpha]_D$ = +10.5° ($CHCl_3$, C = 0.0921 g/mL).

Anal. calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.36; H, 9.69.

The sense of rotation and spectral data for the unpurified acid 12 were identical to pure acid 12.

(2R,3S)-2,4-Dimethyl-3-hydroxypentanoic acid (12, via zirconium aldol). To a solution of diisopropylamine (0.487 g, 4.81 mmol) in THF (26 mL) cooled to 0°C was added a hexane solution of n-butyllithium (2.80 mL, 1.70 M, 4.76 mmol) dropwise. After 10 min the solution was cooled to -78°C and the amide 14 (0.972 g, 3.96 mmol) was added via syringe. The solution was warmed to room temperature over 15 min and then cooled to -78°C again. A solution of dicyclopentadienyl zirconium dichloride (1.27 g, 4.36 mmol) in THF (26 mL) was added rapidly via cannulation. The solution turned orange and was warmed to 0°C over 15 min. After cooling to -78°C, isobutyraldehyde (0.373 g, 5.18 mmol) was quickly added. After 2 min the orange color had dissipated and the cold bath was removed. The solution was warmed to room temperature over 15 min. The reaction was quenched with saturated ammonium chloride solution and vigorously stirred for 3 h at 25°C. The resulting suspension was filtered through Celite and the filtrate partitioned between dichloromethane and H_2O. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 900 mg of aldol adduct 15 as a light yellow oil: IR (film) 3440, 2970, 2950, 2880, 1635, 1470, 1460, 1430, 1380, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (s, 2 H, -OC$\underline{H}_2$O-), 4.22 (m, 1 H,

-NCHCH$_2$-), 3.90-3.20 (m, 9, CH$_2$N-, -CH$_2$OCH$_2$OCH$_2$CH$_2$OCH$_3$, -CHOH), 3.37 (s, 3 H, -OCH$_3$), 2.70 (m, 1 H, -CCHCH$_3$), 2.00-1.50 (m, 5 H, -CH$_2$CH$_2$CH$_2$N-; CH$_3$CHCH$_3$), 1.10 (d, J = 6 Hz, -CCHCH$_3$), 1.00 (d, J = 6 Hz, CH$_3$CHCH$_3$), 0.86 (d, J = 6 Hz, CH$_3$CHCH$_3$). Analysis of the unpurified aldol adduct 15 by GLC (25 m by 0.25 mm capillary column coated with Carbowax 20M, col = 200°C, det = 325°C) showed a 99:1 mixture of the two possible erythro diastereoisomers and 3% of racemic threo diastereoisomers. Thus, 15 is 96% optically pure (starting material was also present, approximately 40%).

The unpurified aldol adduct (0.850 g, 2.69 mmol) was suspended in 5% hydrochloric acid solution (25 mL) and heated to 100°C. The reaction mixture was refluxed for 2 h. The brown solution was adjusted to pH 8 with saturated sodium bicarbonate and extracted with dichloromethane. The aqueous layer was then acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 x 50 mL). The organic extracts (after acidification) were combined, dried (Na_2SO_4) and concentrated in vacuo to afford 170 mg of a colorless oil. The oil was purified by bulb-to-bulb distillation to give 140 mg (60%) of acid 12 as a colorless oil: IR (film) 3440, 3700-2300 (broad), 2980, 1715, 1470, 1460, 1390, 1210, 1000, 980, 970, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (broad s, 2 H, -OH, -CO_2H), 3.62 (d of d, J = 4 Hz, 8 Hz, 1 H, -CHOH), 2.68 (d of q, J = 4 Hz, 7 Hz, 1 H,

-C<u>H</u>(CH$_3$)CHOH), 1.68 (m, 1 H, CH$_3$C<u>H</u>CH$_3$), 1.18 (d, J = 7 Hz, 3 H, -CCHC<u>H</u>$_3$), 1.00 (d, J = 6 Hz, 3 H, C<u>H</u>$_3$CHCH$_3$), 0.88 (d, J = 6 Hz, 3 H, CH$_3$CHC<u>H</u>$_3$); $[\alpha]_D$ = +10.0° ($CHCl_3$, C = 0.1167 g/mL).

Anal. calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.33; H, 9.77.

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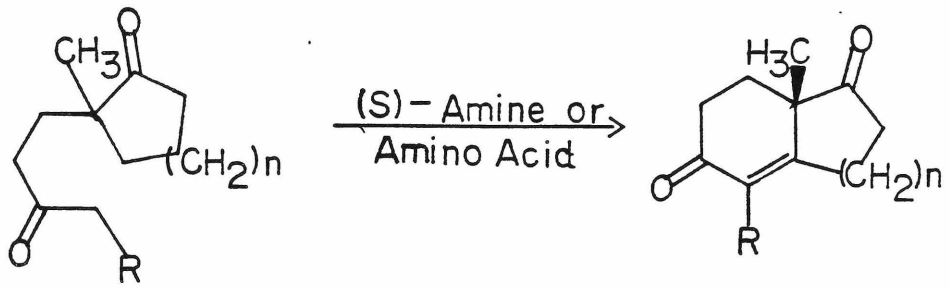
APPENDIX I

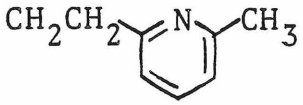
A Brief Review of Enantioselective Aldol Condensations

The following compendium of asymmetric aldol condensations is divided into major subgroups according to the source of chirality transfer. Within each subgroup a listing of pertinent reactions, key references, % ee, and chemical yields is given. The references cited extensively cover from 1971 to the present. Earlier work is occasionally referenced, but the reader is referred to Morrison and Mosher's excellent review[1] if further information is desired.

I. Chirality Transfer Via Chiral Bases.[2-5]



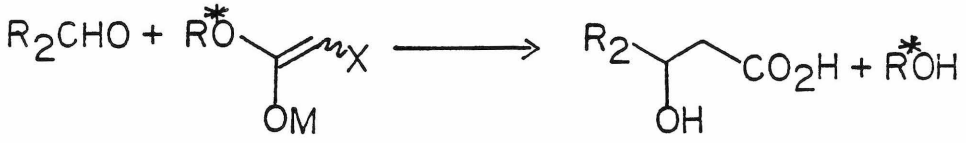
R = H, CH_3, $CH_2CH_2C_6H_4OCH_3$(m), $CH_2CH_2CO_2CH_3$,



For n = 1: generally 60-85% ee, 70-90% yield.
n = 2: generally 50-70% ee, 70-90% yield.

II. Chirality Transfer Utilizing Chiral Ester and Amide Enolates.

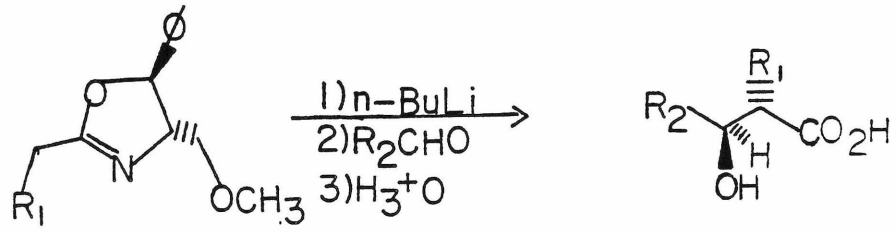
A)



X = H, M = Li[1] and X = Br, M = ZnL[1]

Three cases 60-93% ee, others: 20-35% ee, 60-70% yield.

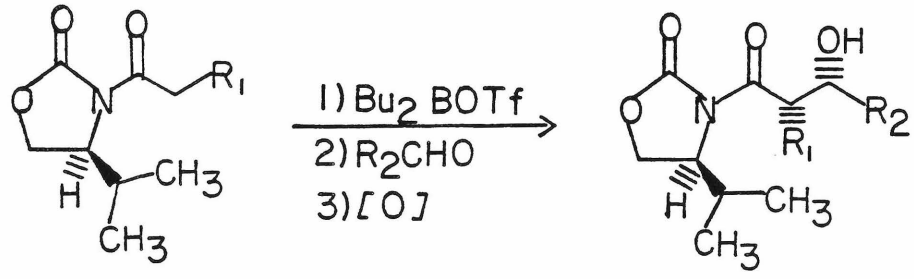
B)



R_1 = H 20% ee, 80-90% yield.[6a]

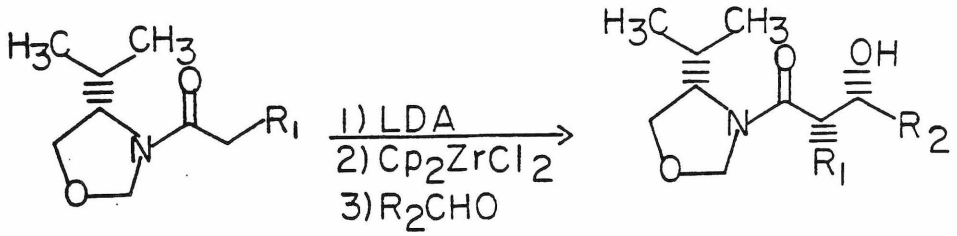
R_1 = CH_3 90% ee, 75-80% yield[6b] (threo).

C)



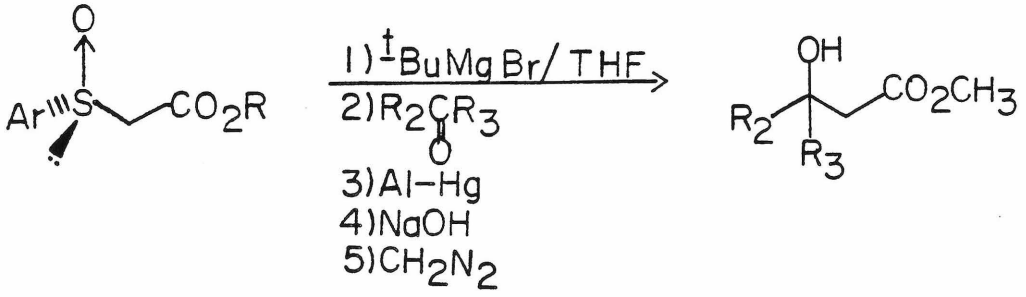
R_1 = H 0-10% ee, 90-95% yield.[7]
R_1 = CH_3 >98% ee, 60-80% yield[8] (erythro).
R_1 = SMe 98% ee, 70-90% yield.[7]

D)



R_1 = H 20% ee, 70-90% yield.[9]
R_1 = CH_3 >95% ee, 70-90% yield[9] (erythro).

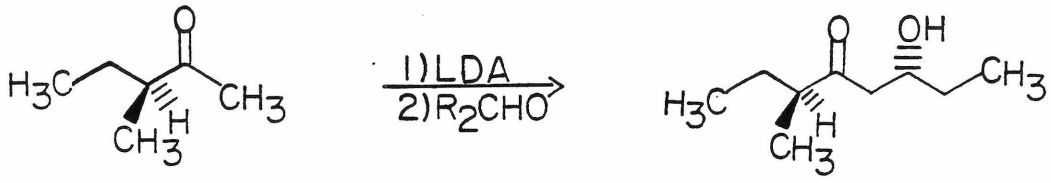
E)



70-95% ee, 70-90% yield.[10,11]

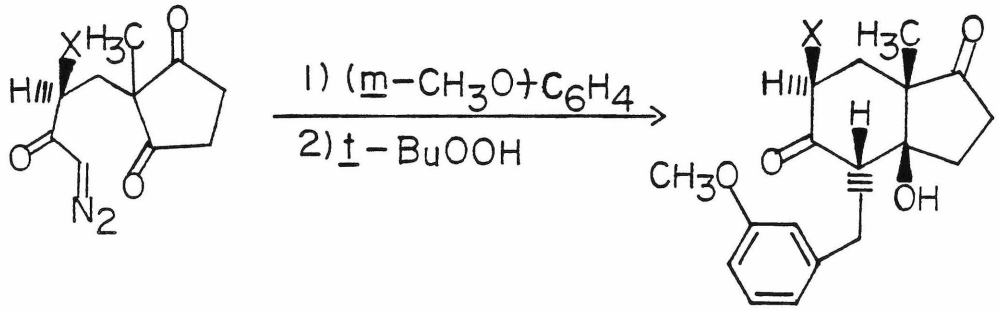
III. Chirality Transfer Via Chiral Ketone Enolates.

A)



12-18% ee, 60-70% yield.[12]

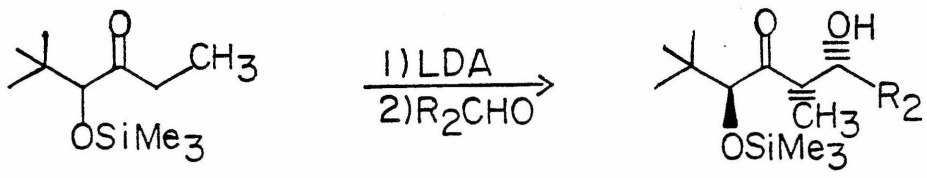
B)



X = OAc, Cl

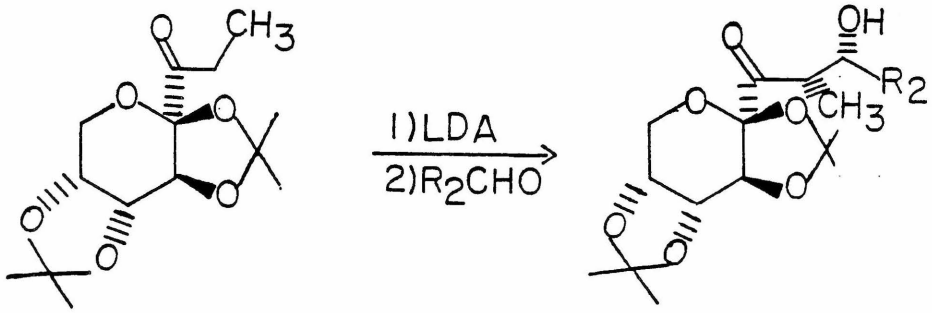
95-100% ee, no yield given.[13]

C)



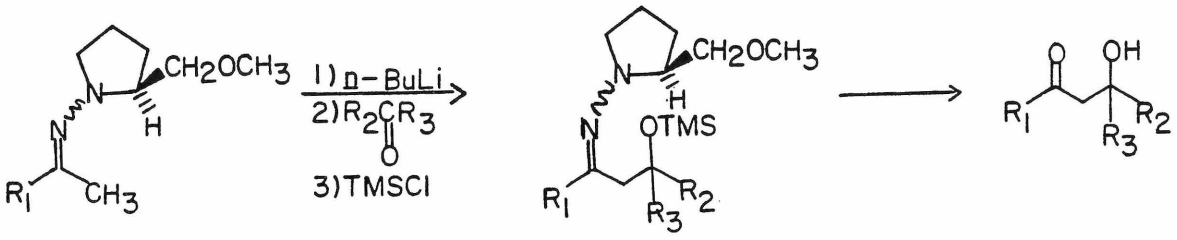
50-90% ee, 50-90% yield[14]
(erythro).

D)



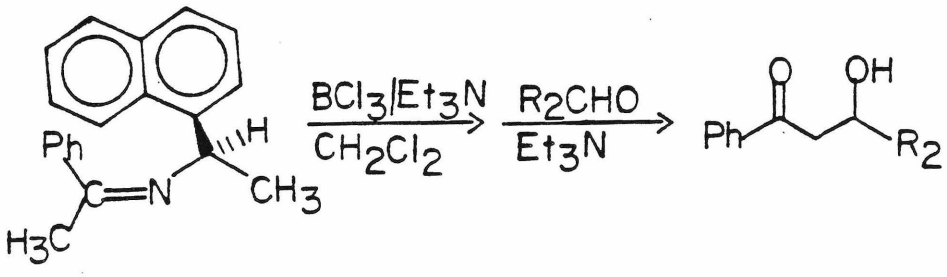
40-95% ee, 85-94% yield[15] (erythro).

E)



17-62% ee, 42-77% yield.[16]

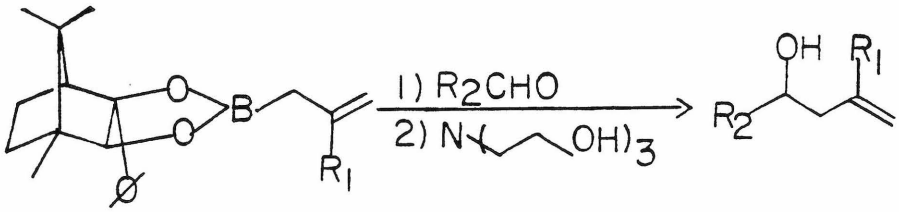
F)



2-40% ee, 6-40% yield.[17]

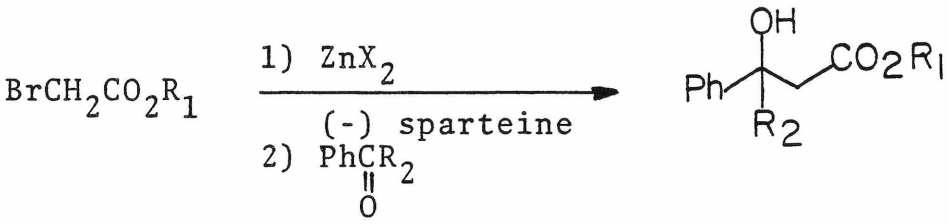
IV. Chirality Transfer Utilizing Chiral Ligands on the Metal Center.

A)



45-77% ee, 82-93% yield.[18]

B)

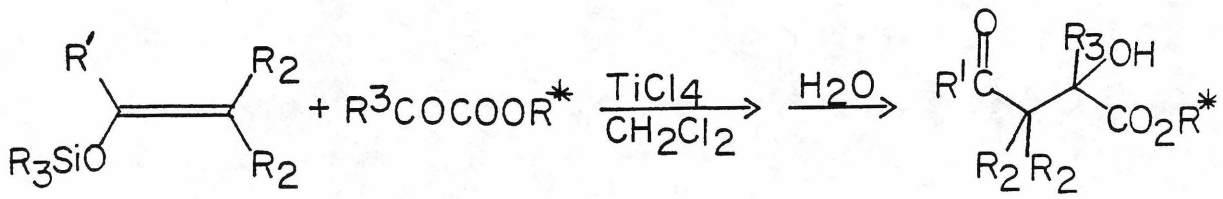


R_2 = H 60-95% ee, 20-60% yield.[19]

R_2 = alkyl 7-40% ee, 15-45% yield.[19]

V. Miscellaneous.

A) Chiral aldehyde equivalent



R' = alkyl, aryl	18-60% ee, 75-100% yield.[20]
R' = oalkyl	25-68% ee, 83-88% yield.[20]

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APPENDIX II

IR and ^{1}H NMR Spectral Catalog for Chapters I and II

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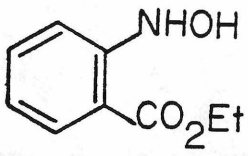

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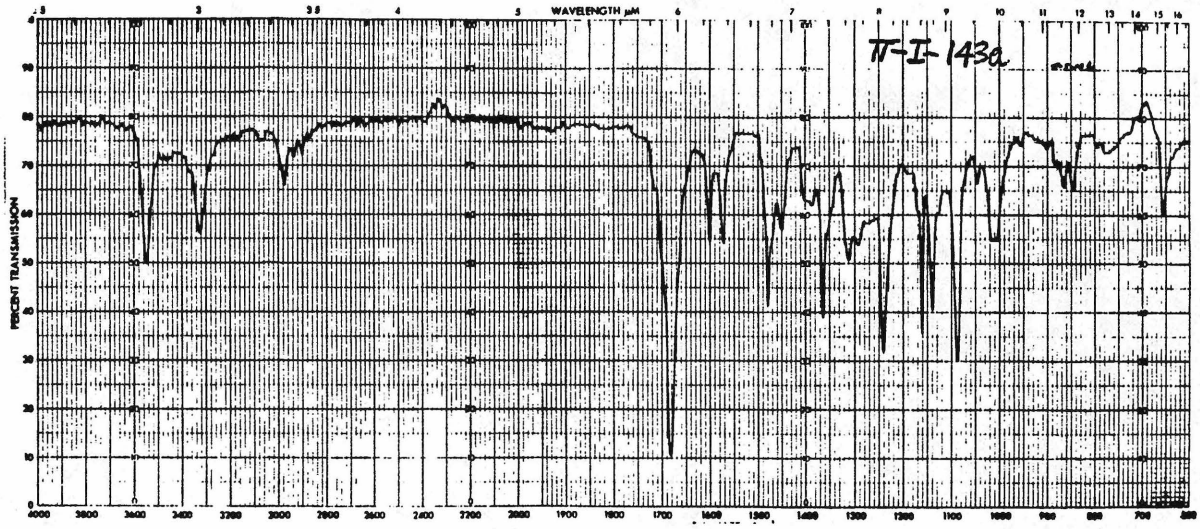

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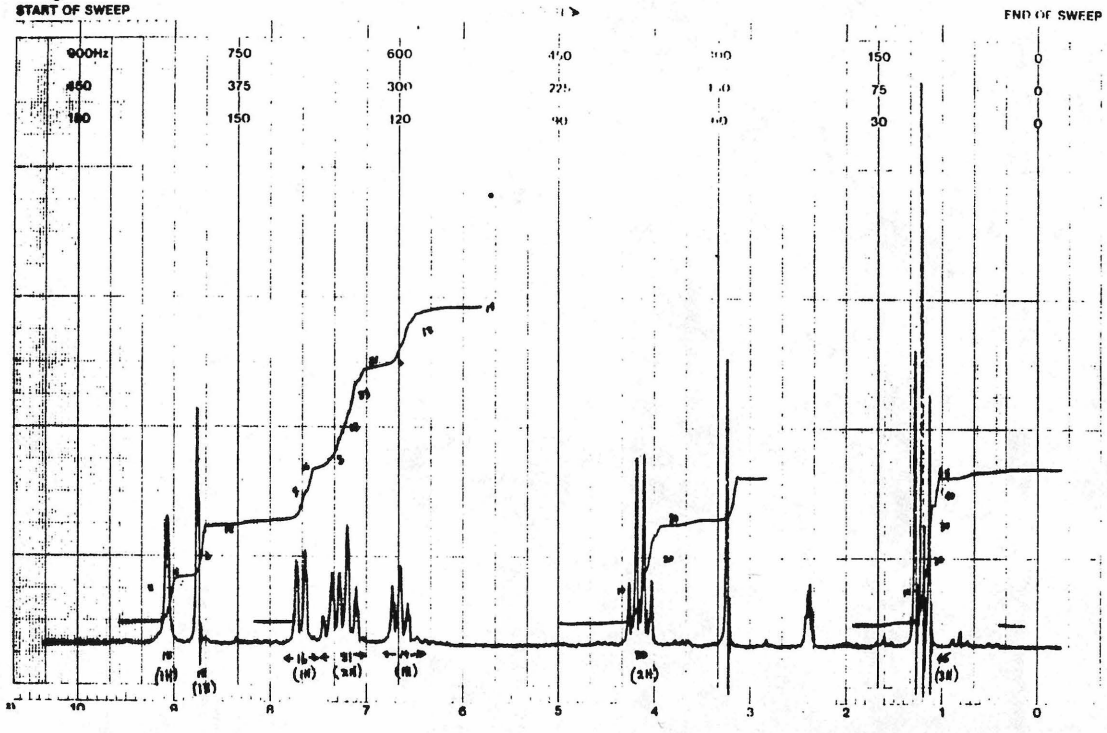

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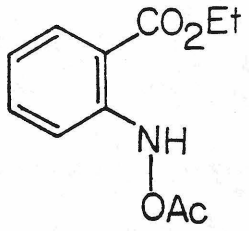

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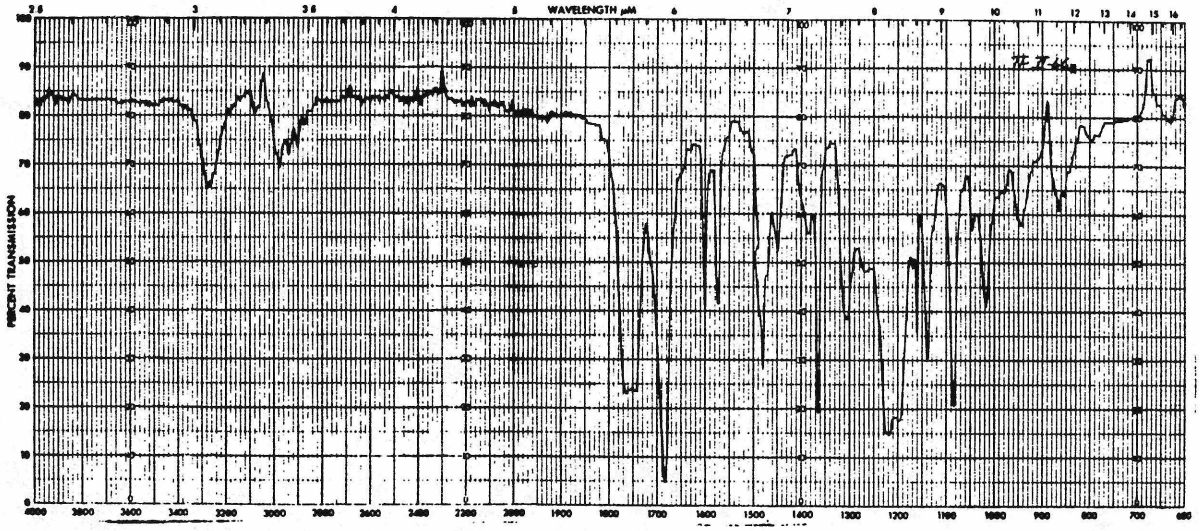

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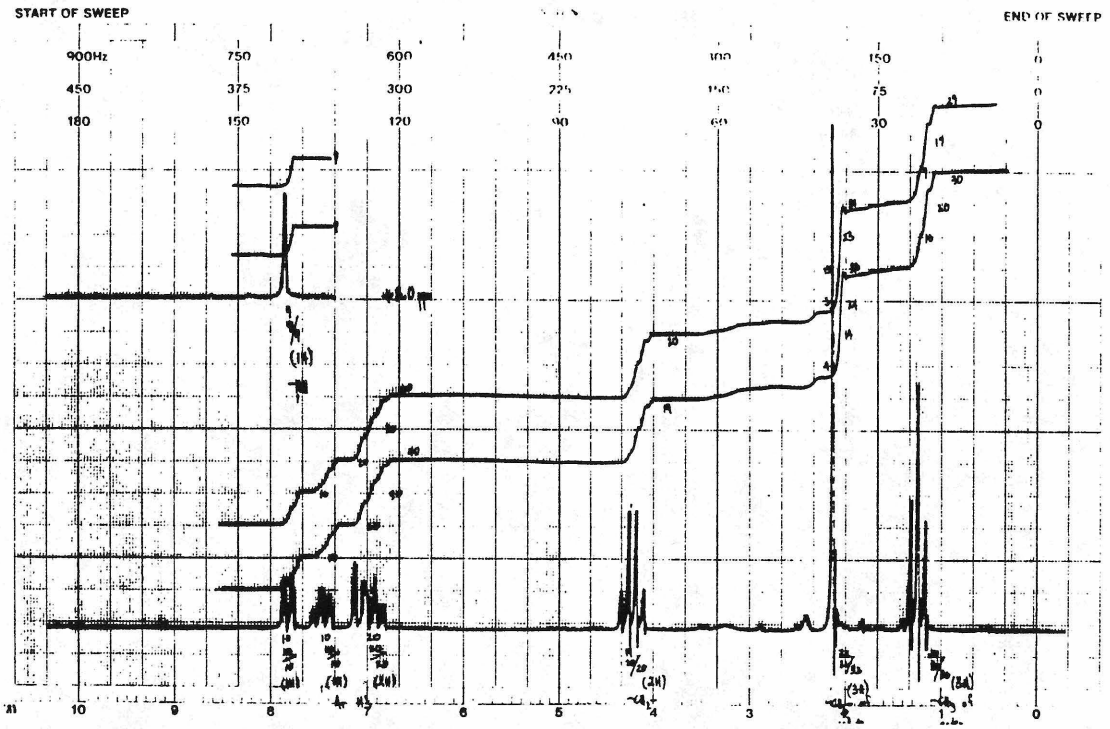

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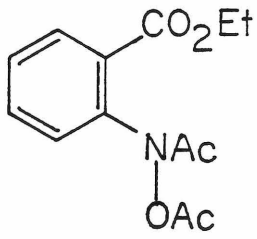

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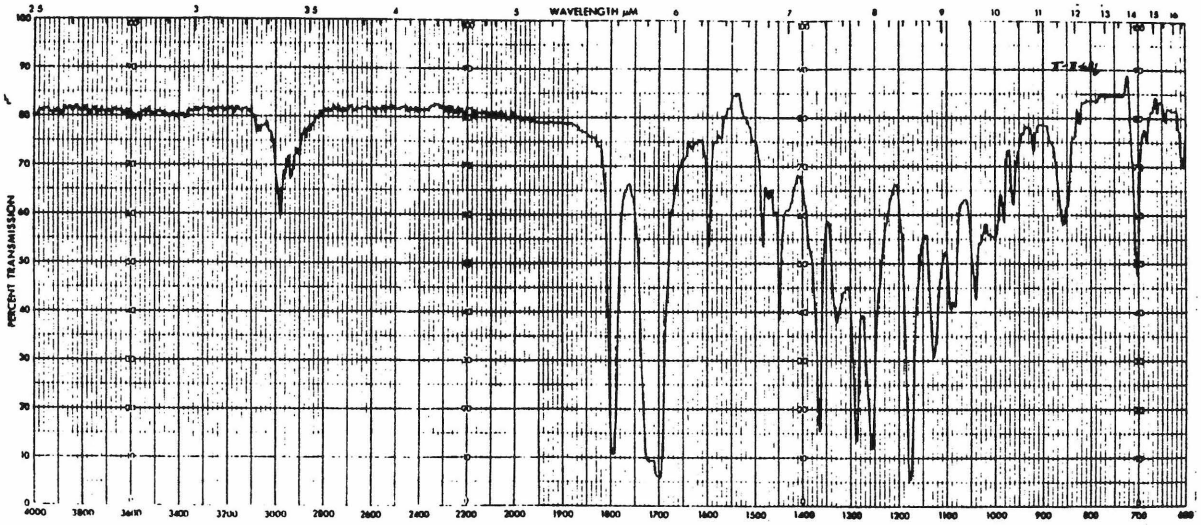

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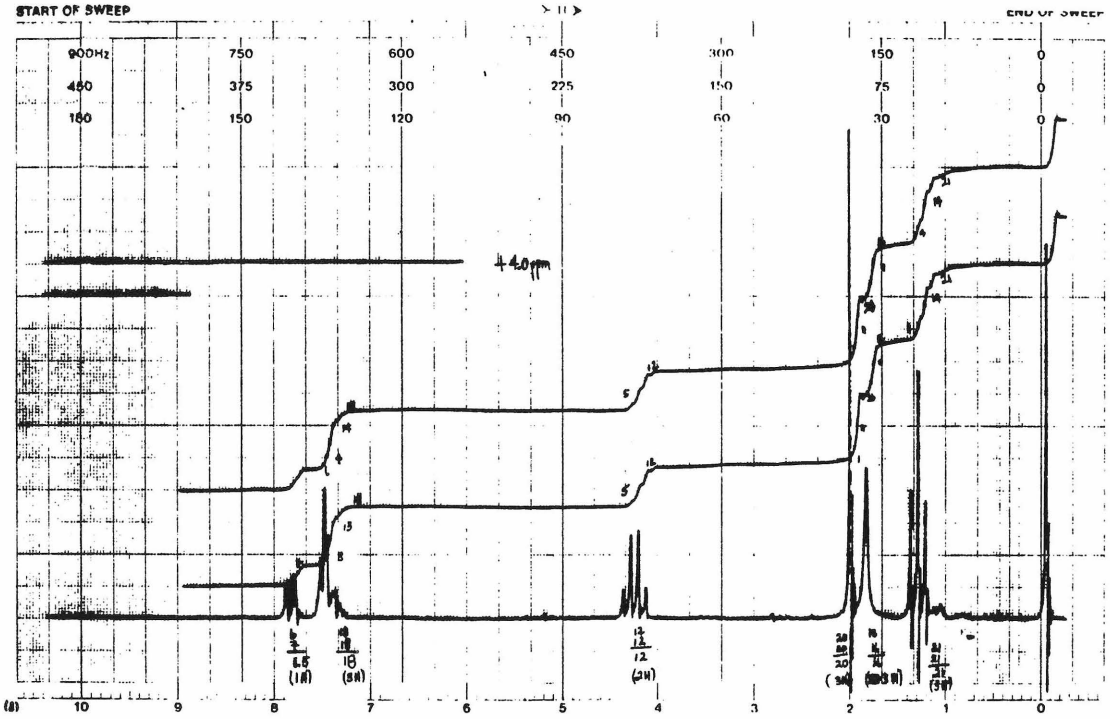

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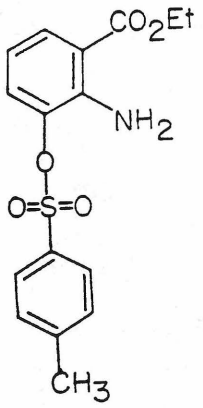

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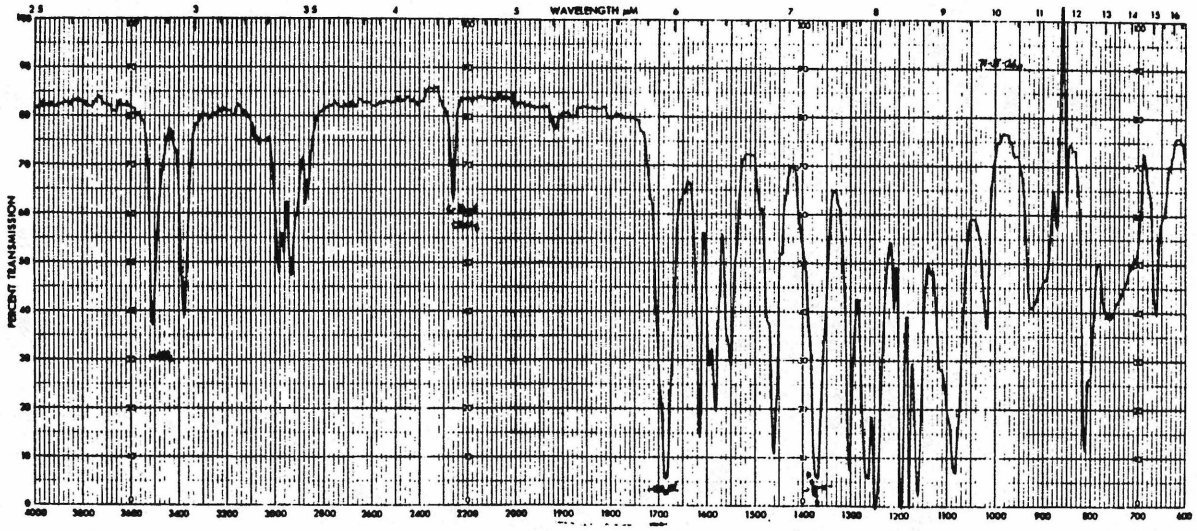

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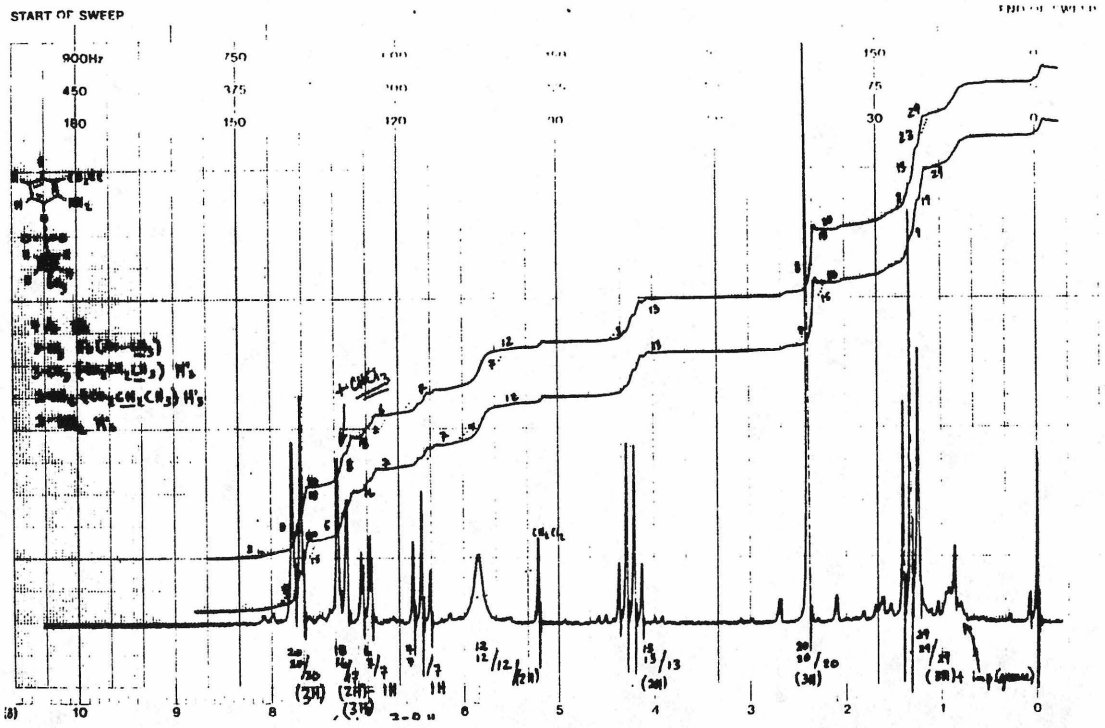

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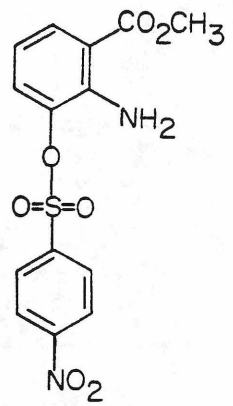

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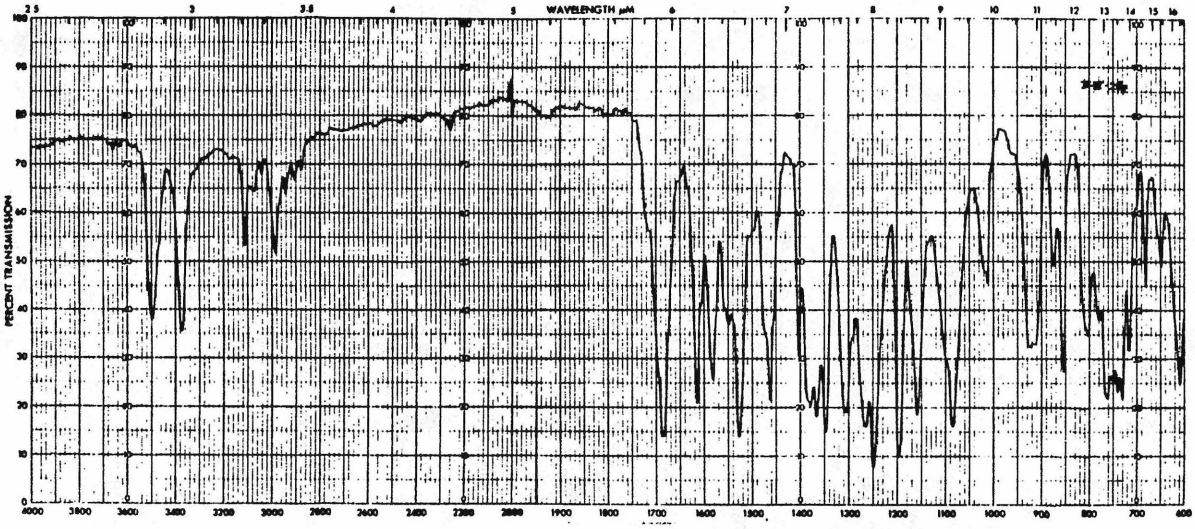

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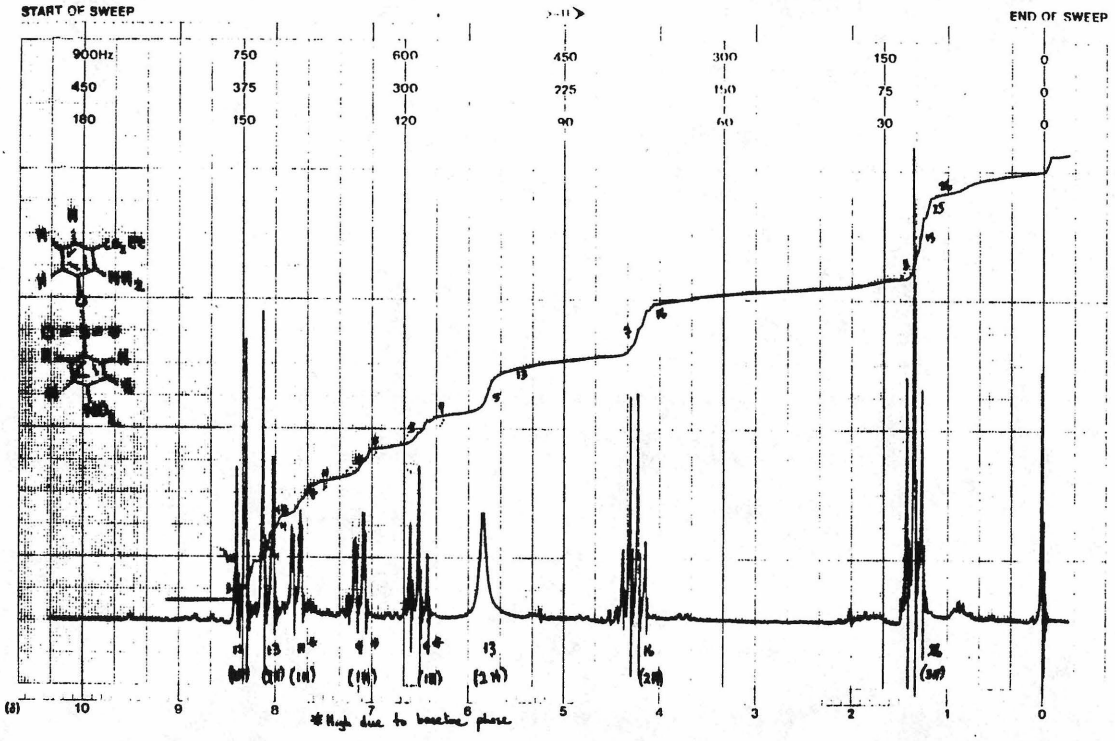

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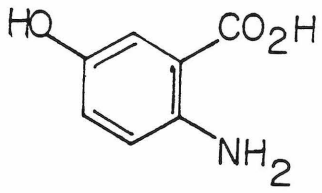

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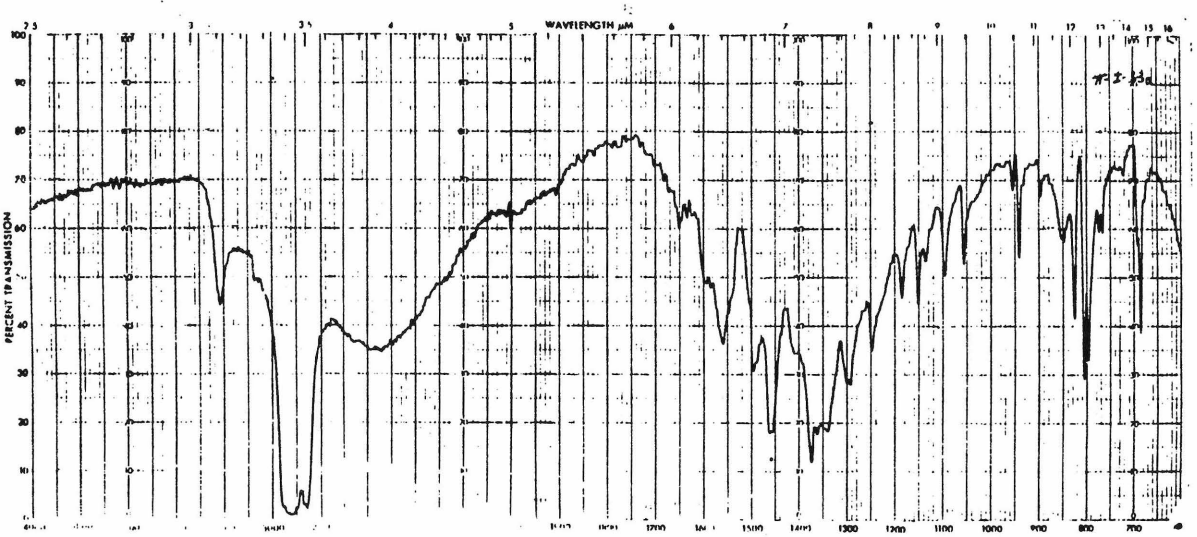
Nujol



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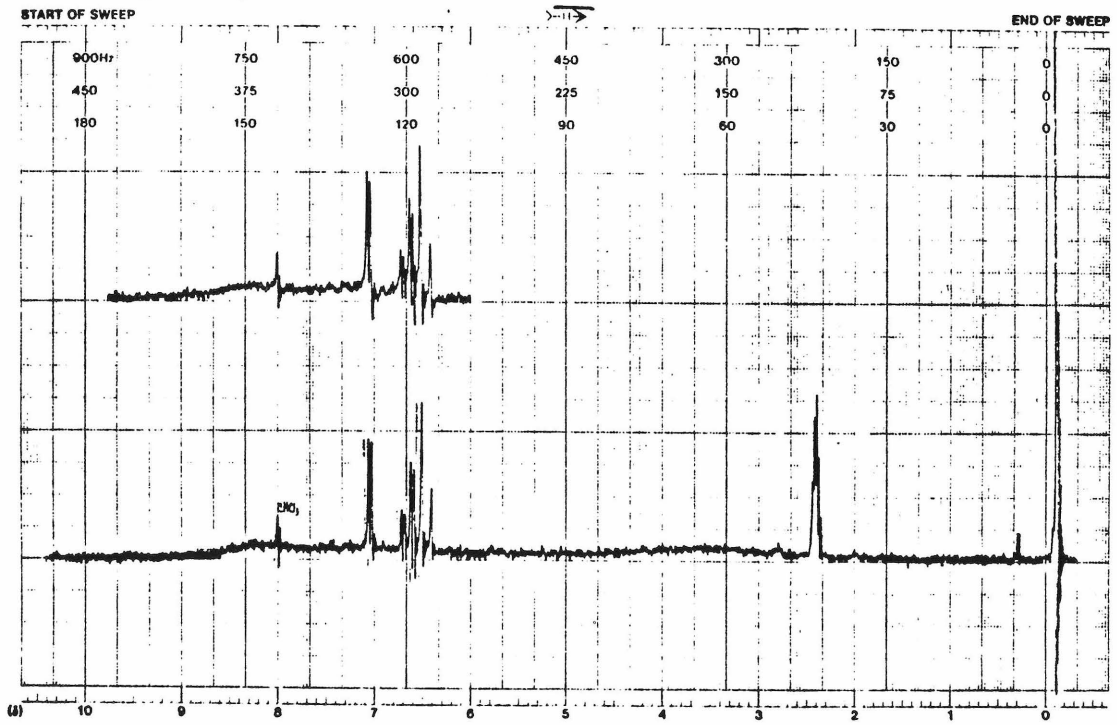

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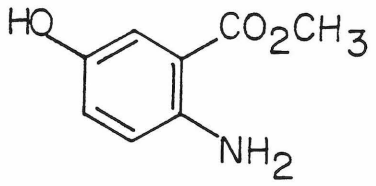

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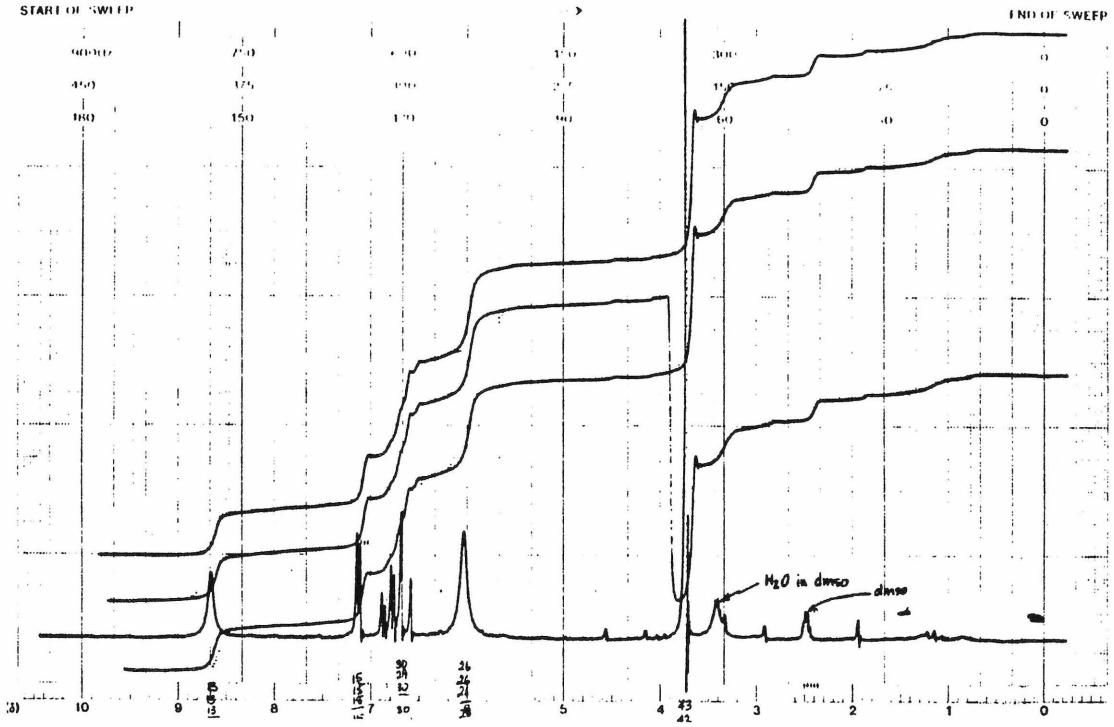

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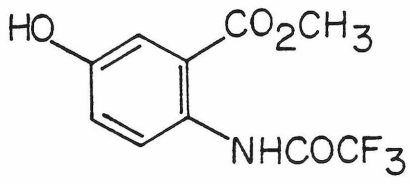

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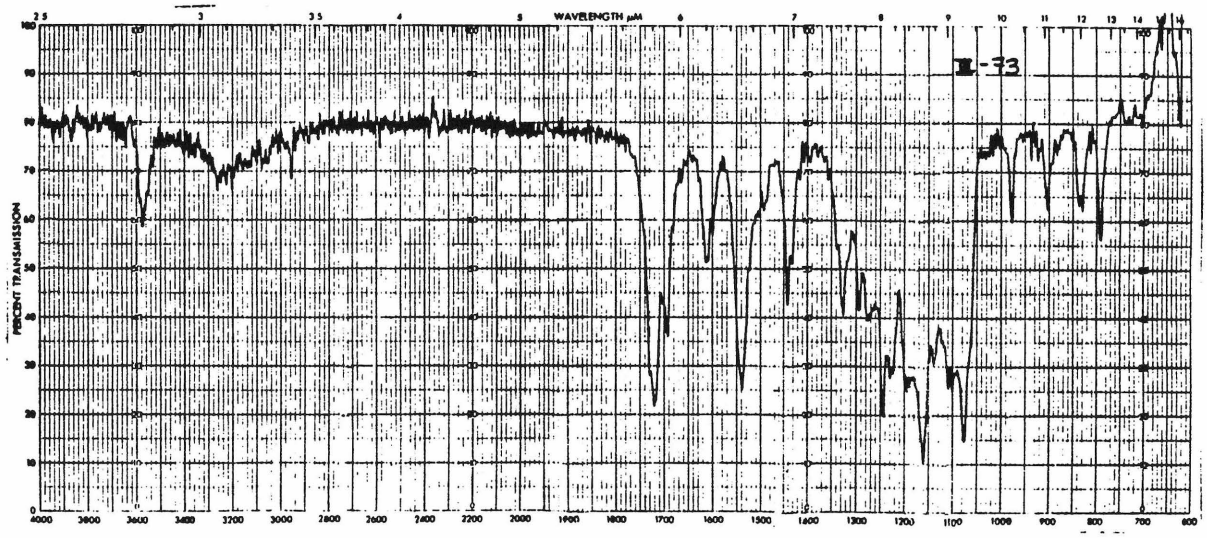

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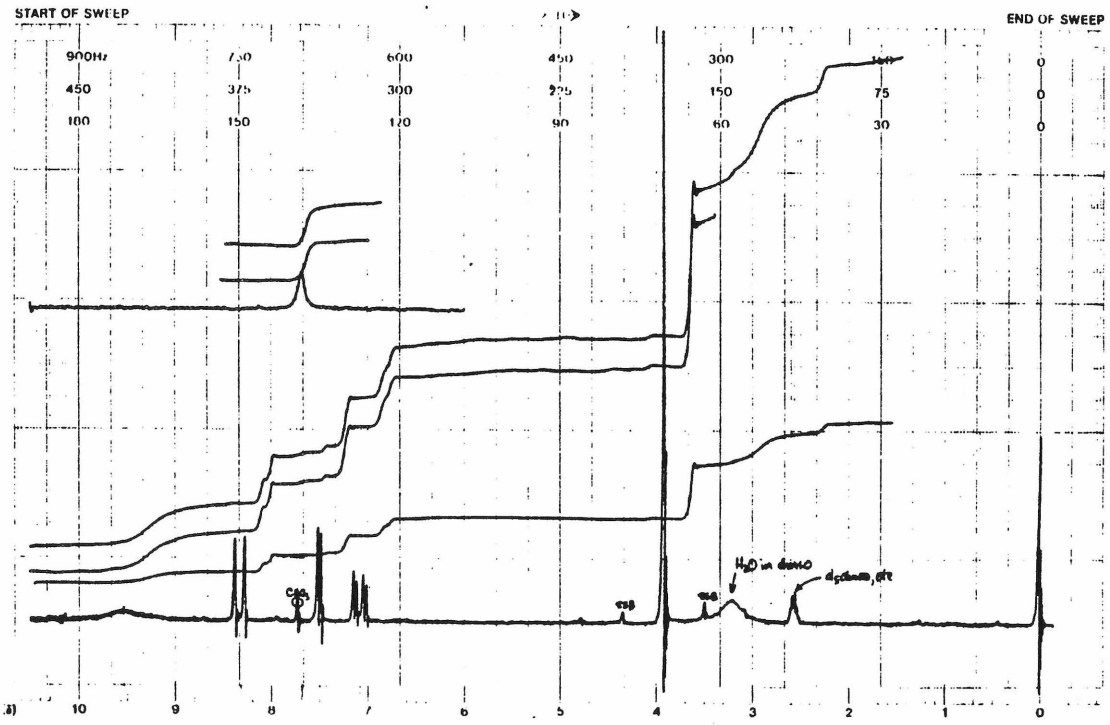

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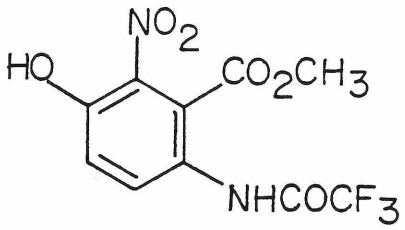

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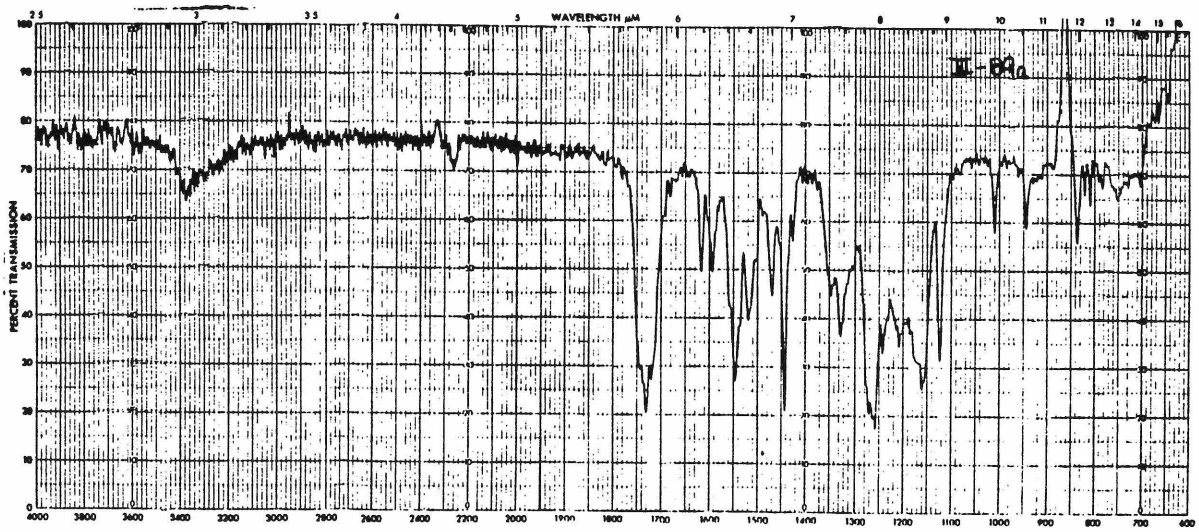

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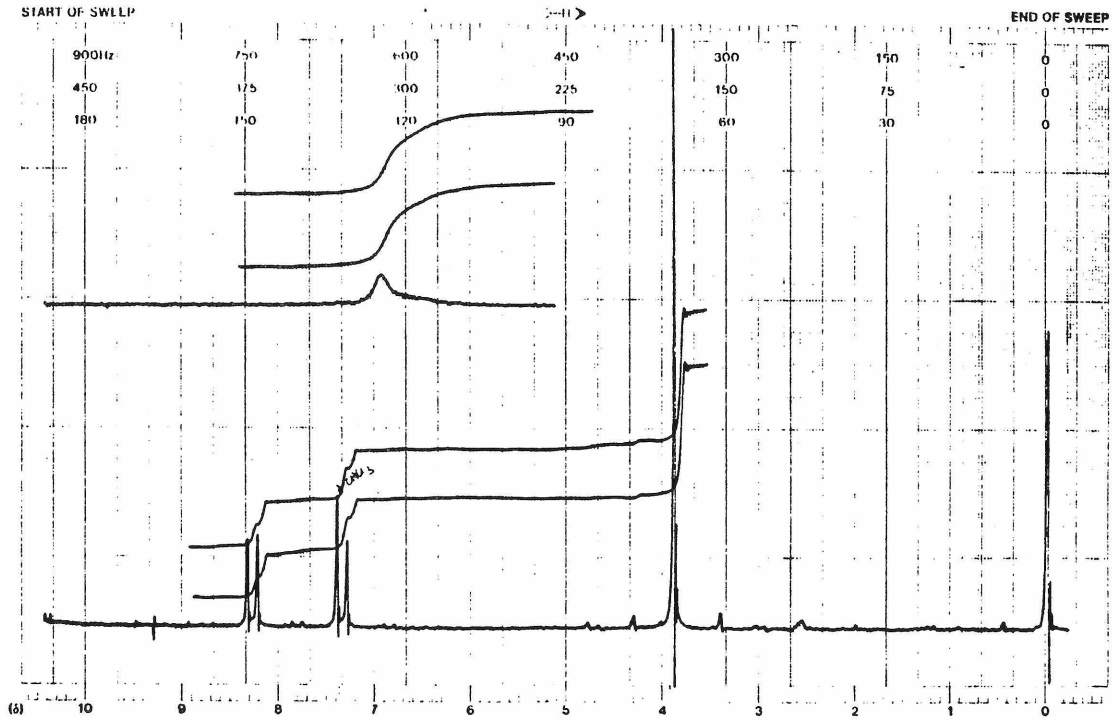

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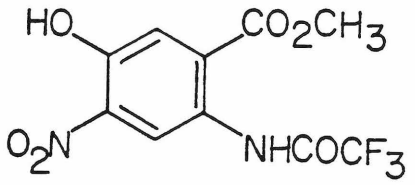

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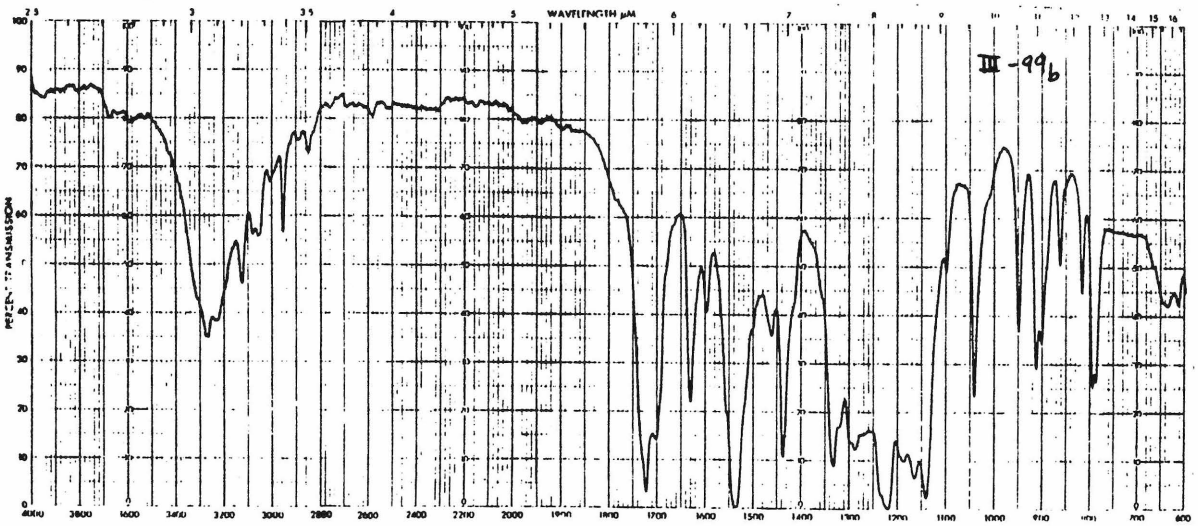

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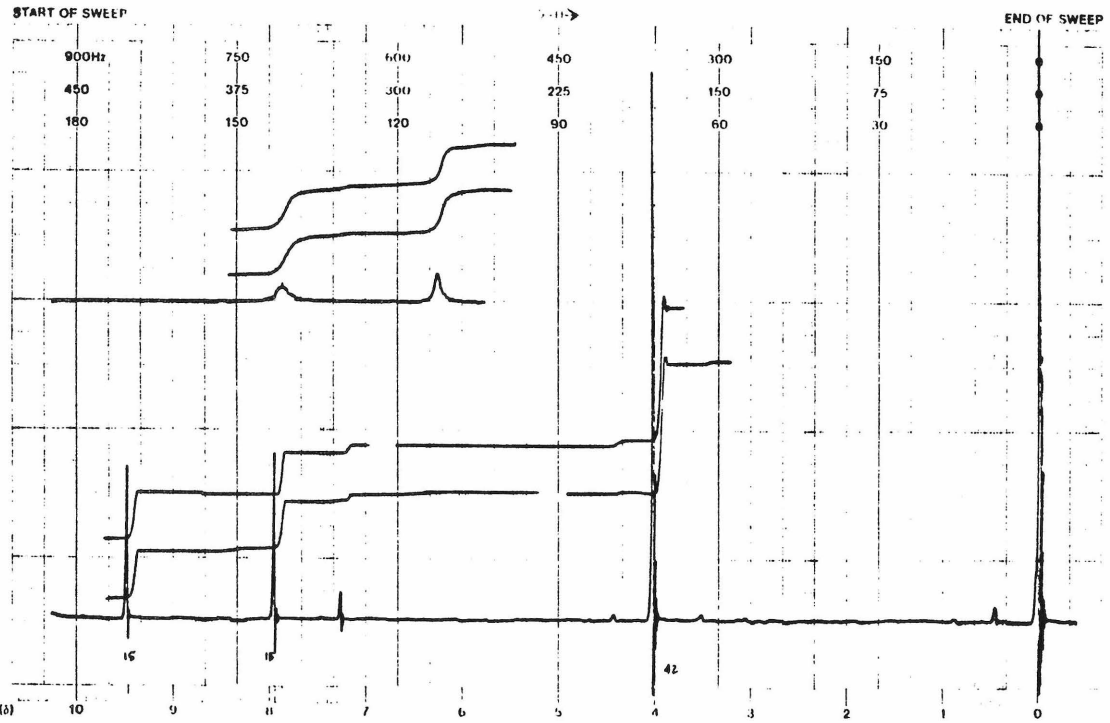

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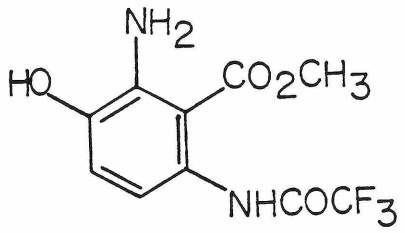

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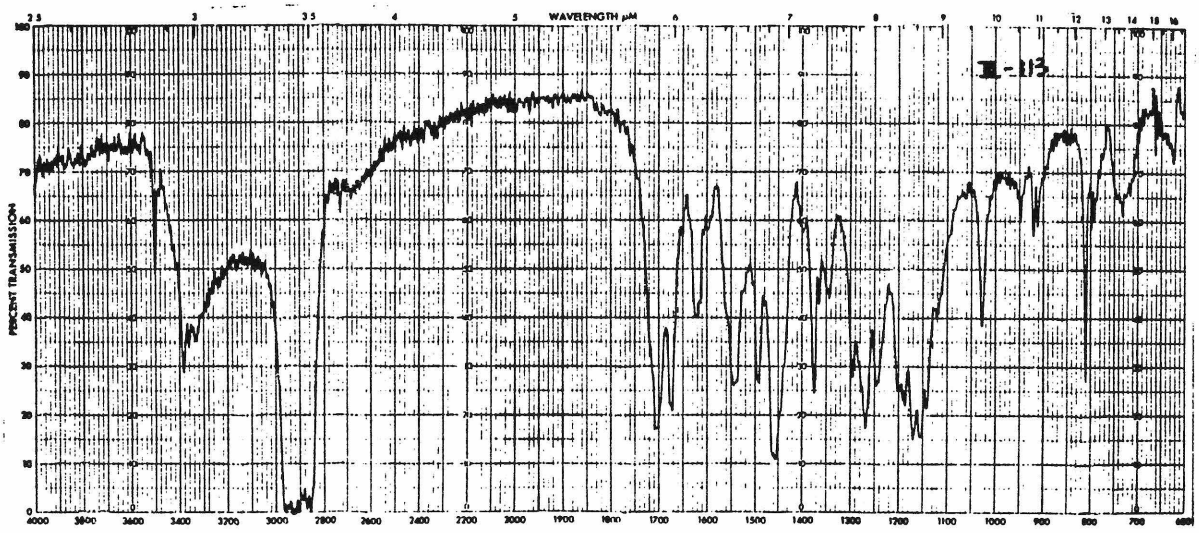

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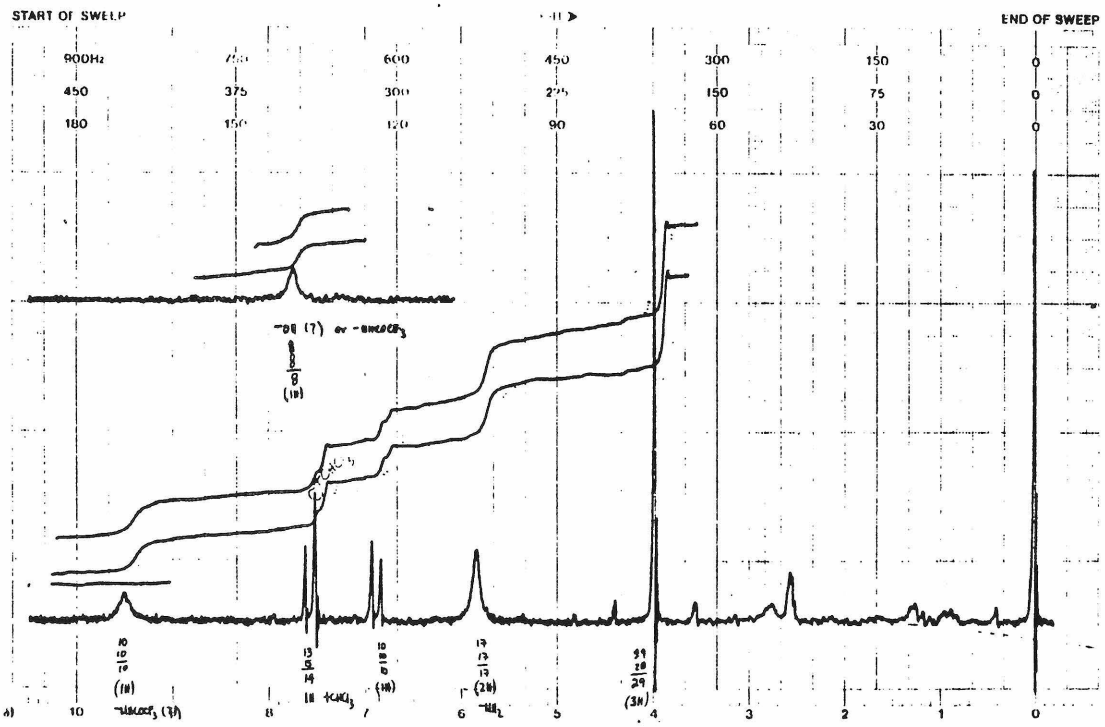

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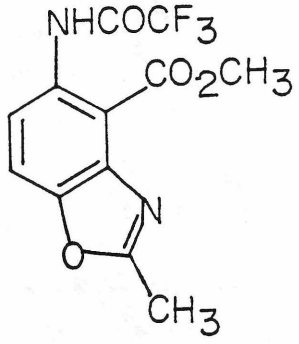

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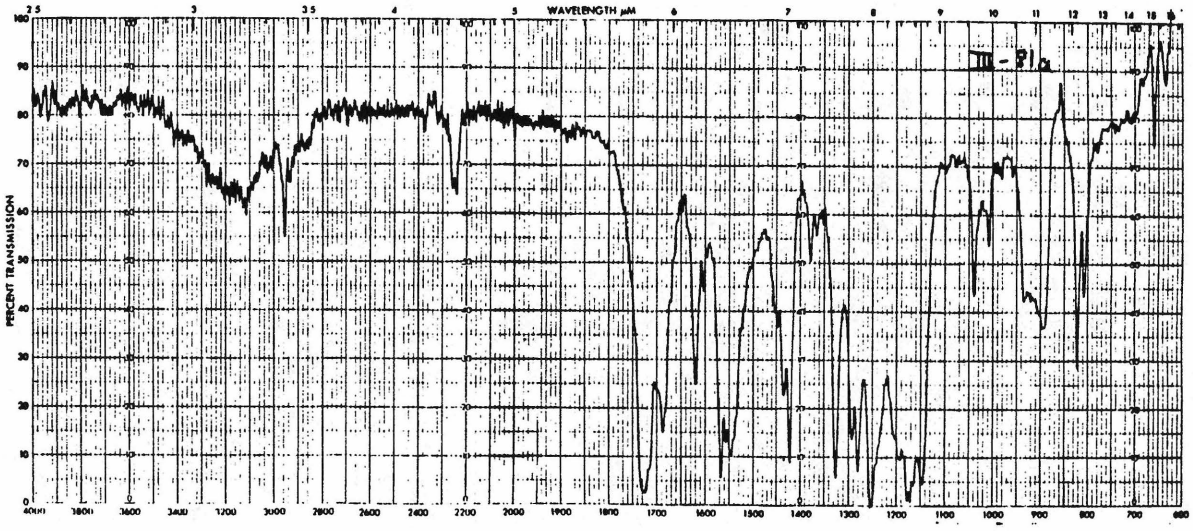

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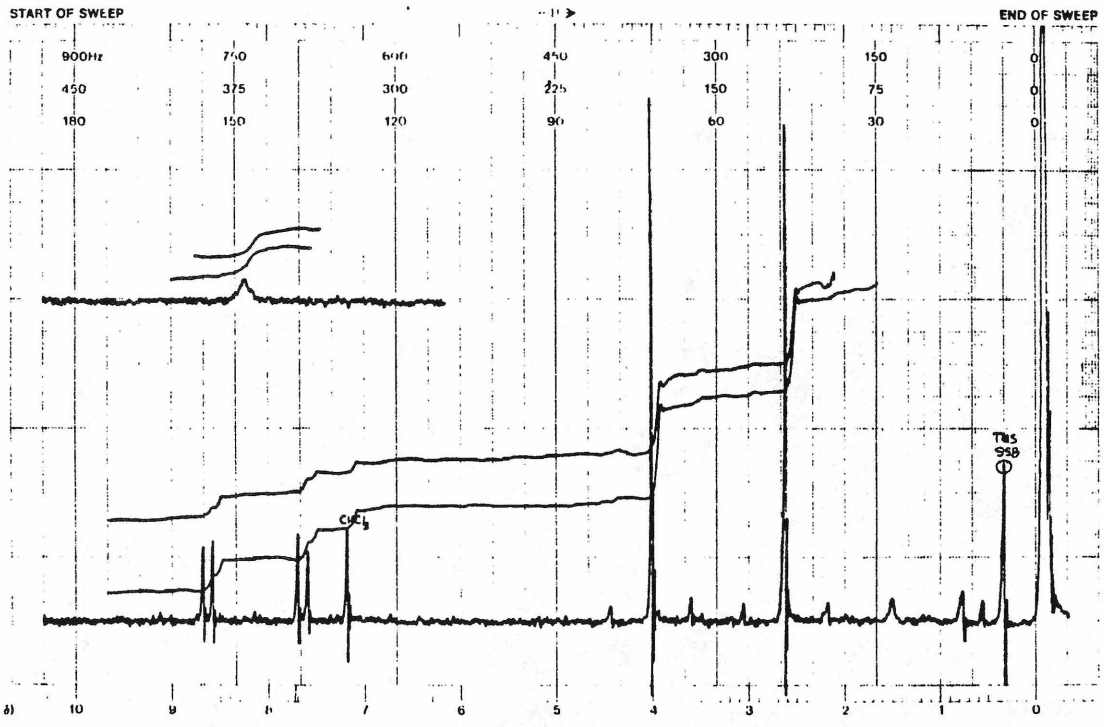

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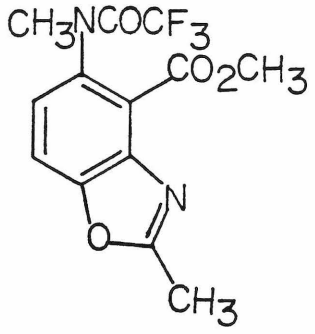

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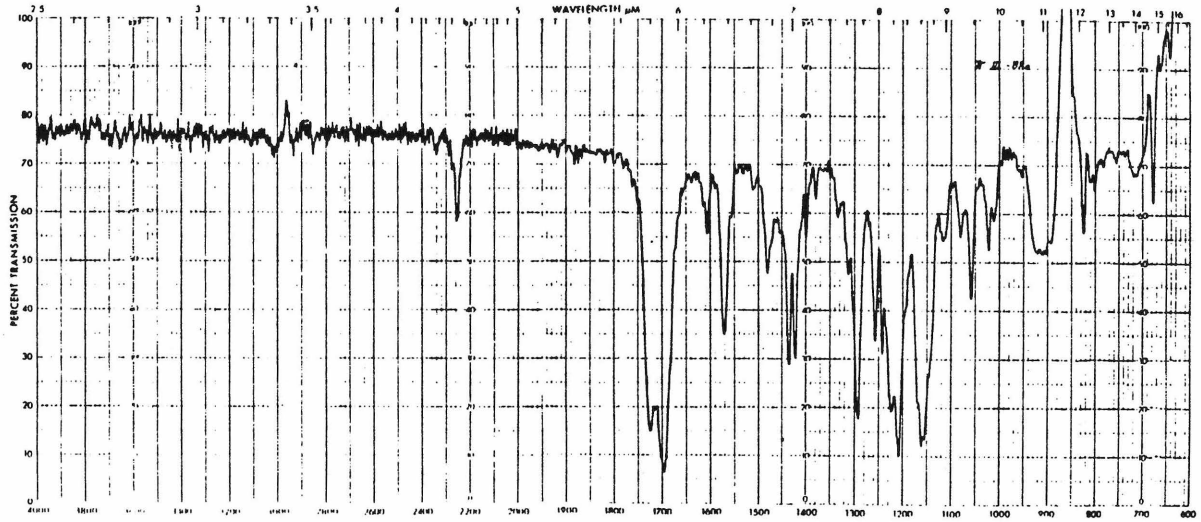

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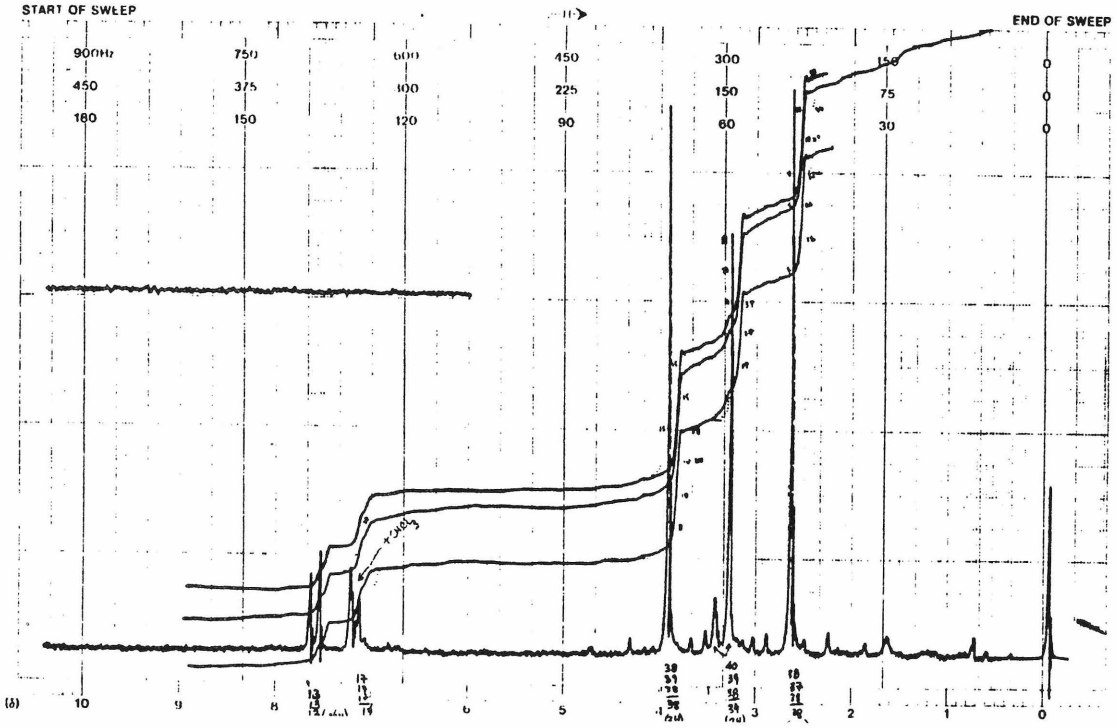

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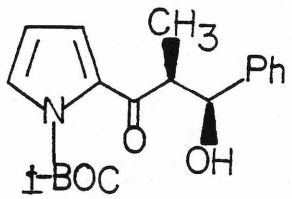

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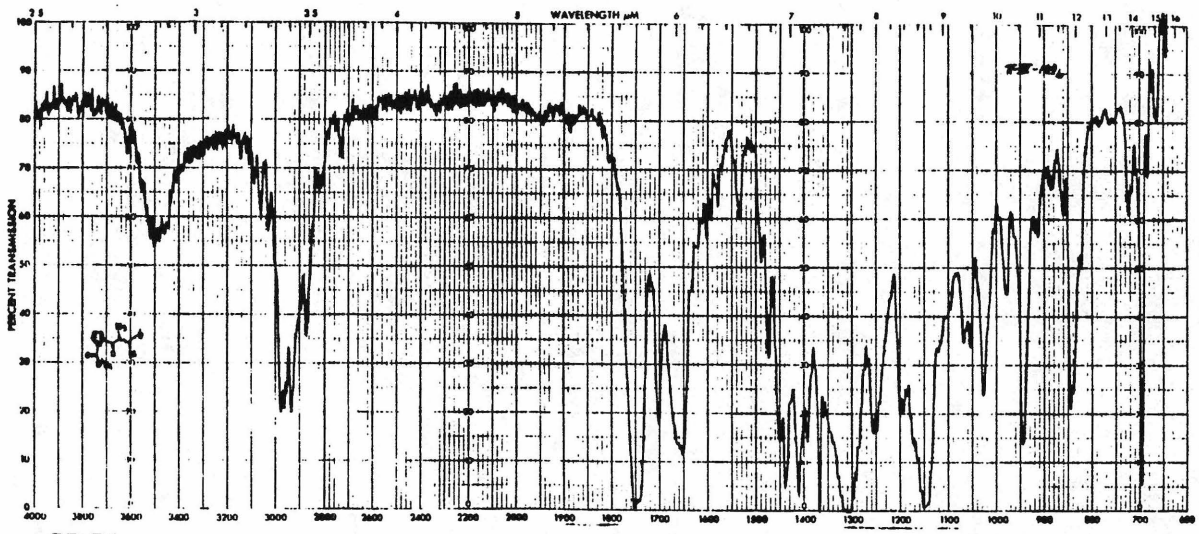

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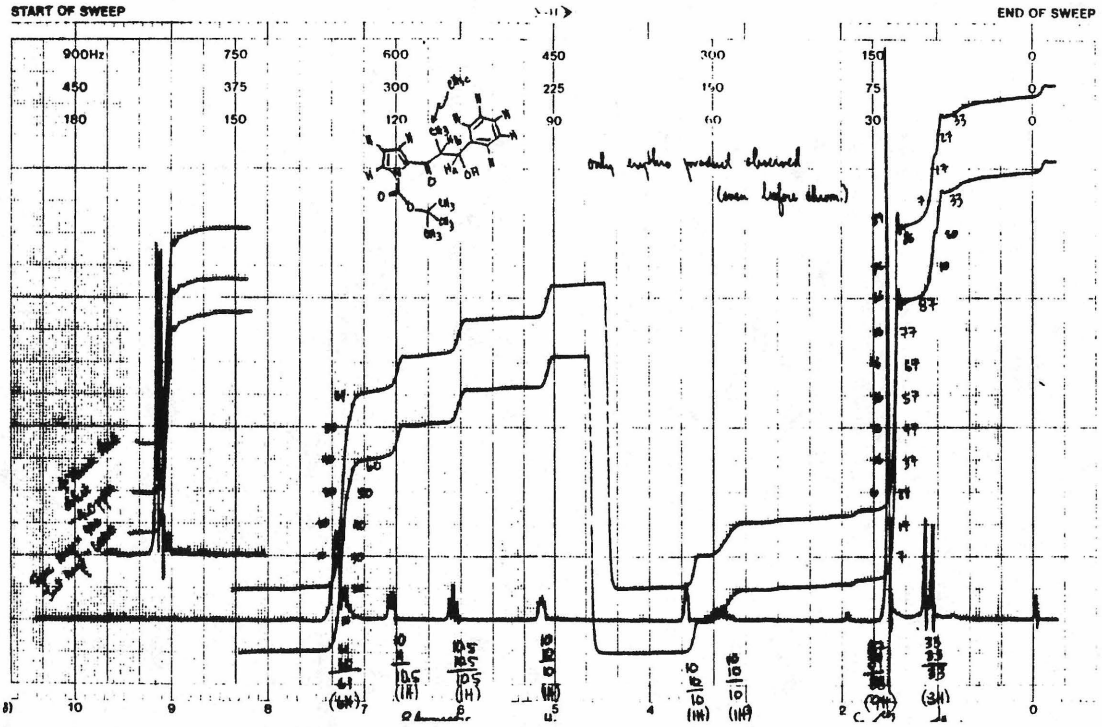

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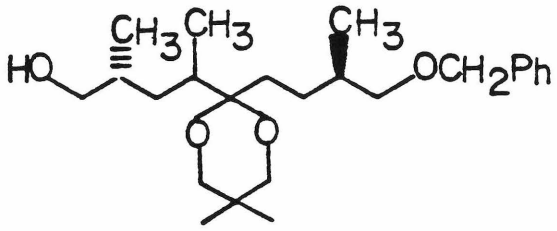

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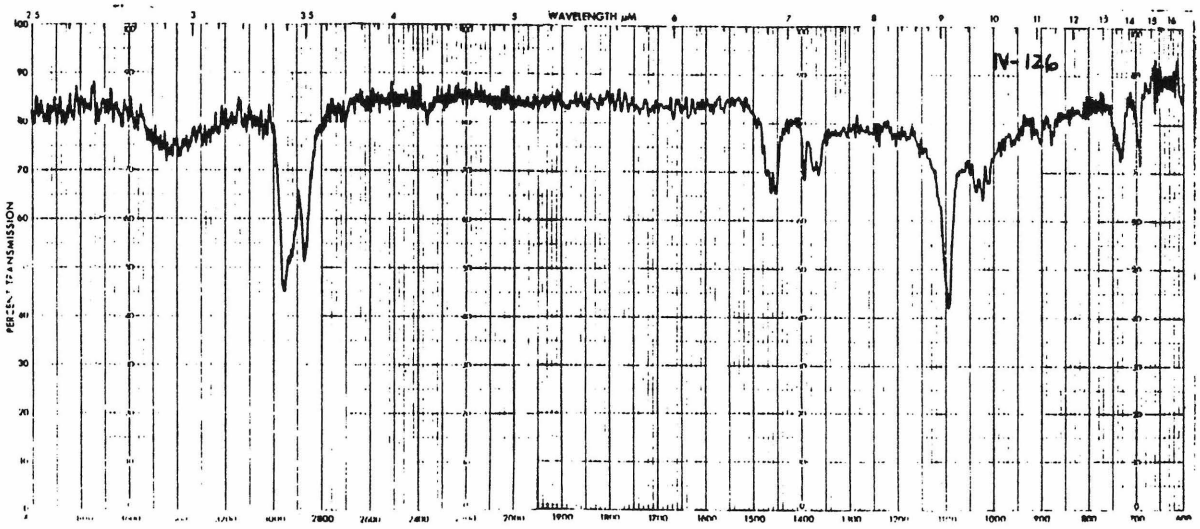

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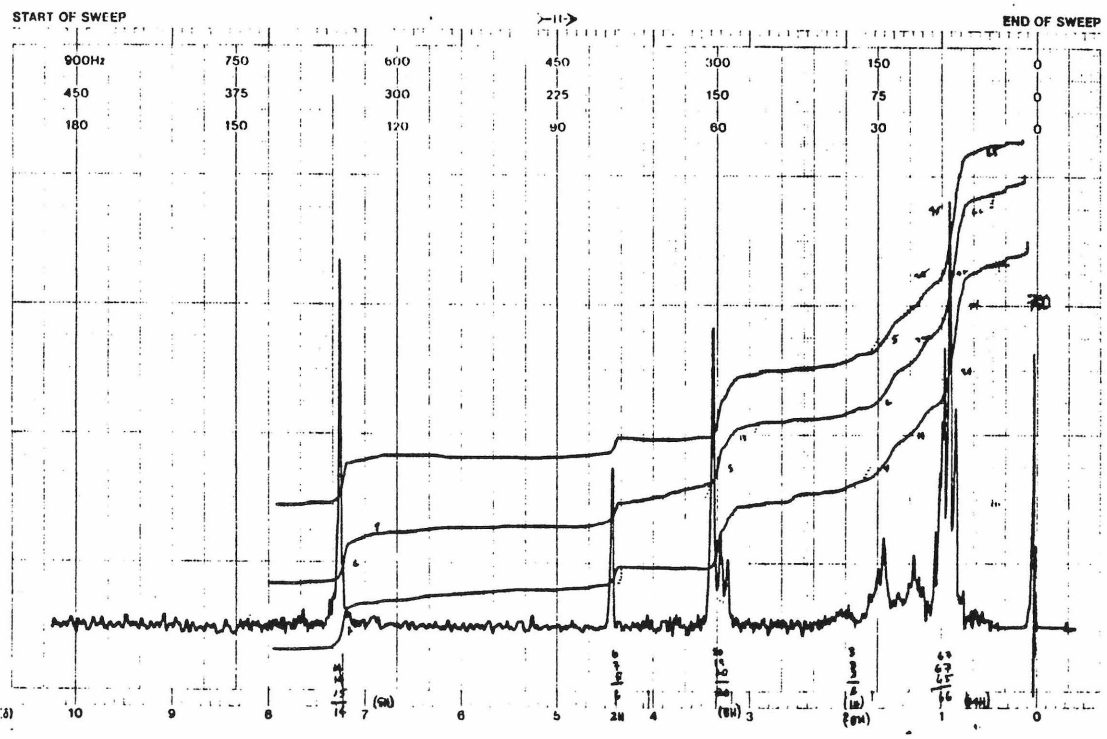

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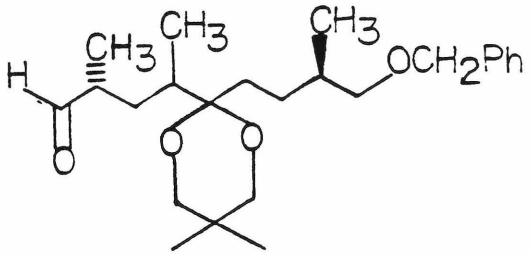

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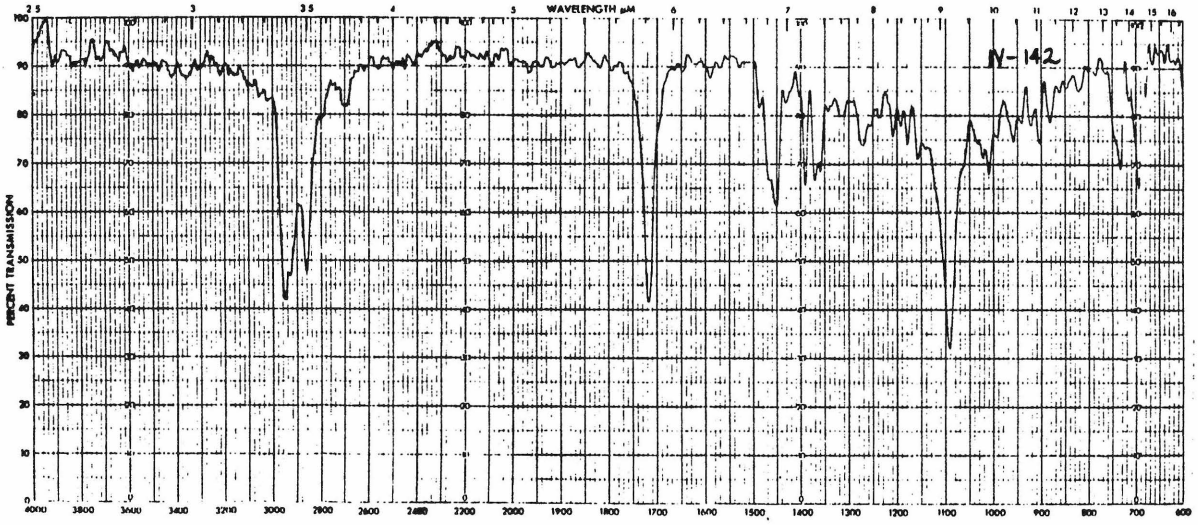

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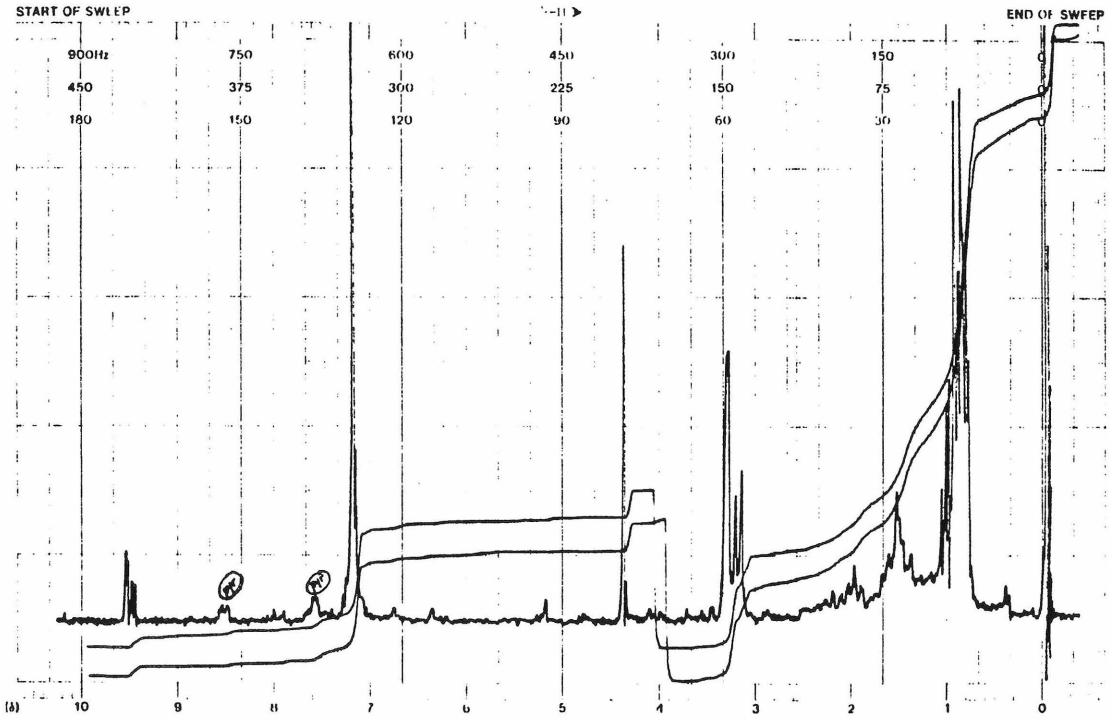

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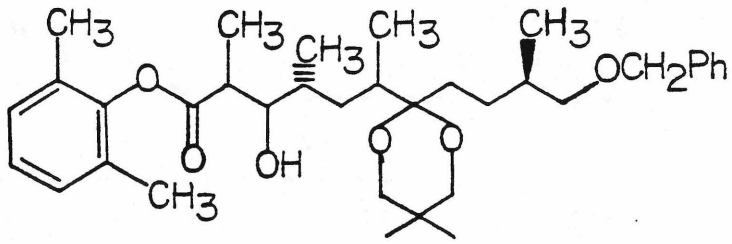

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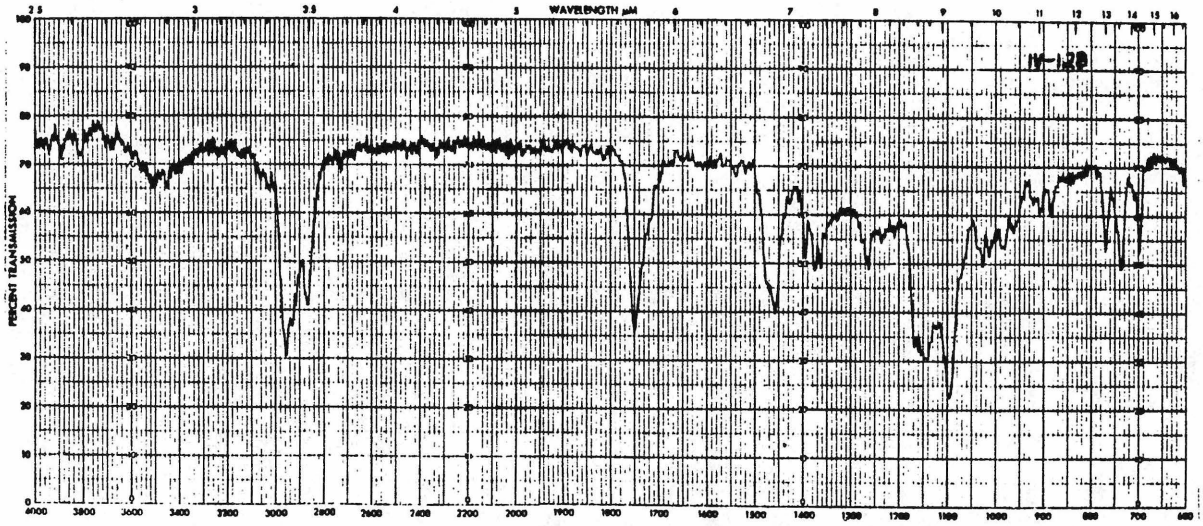

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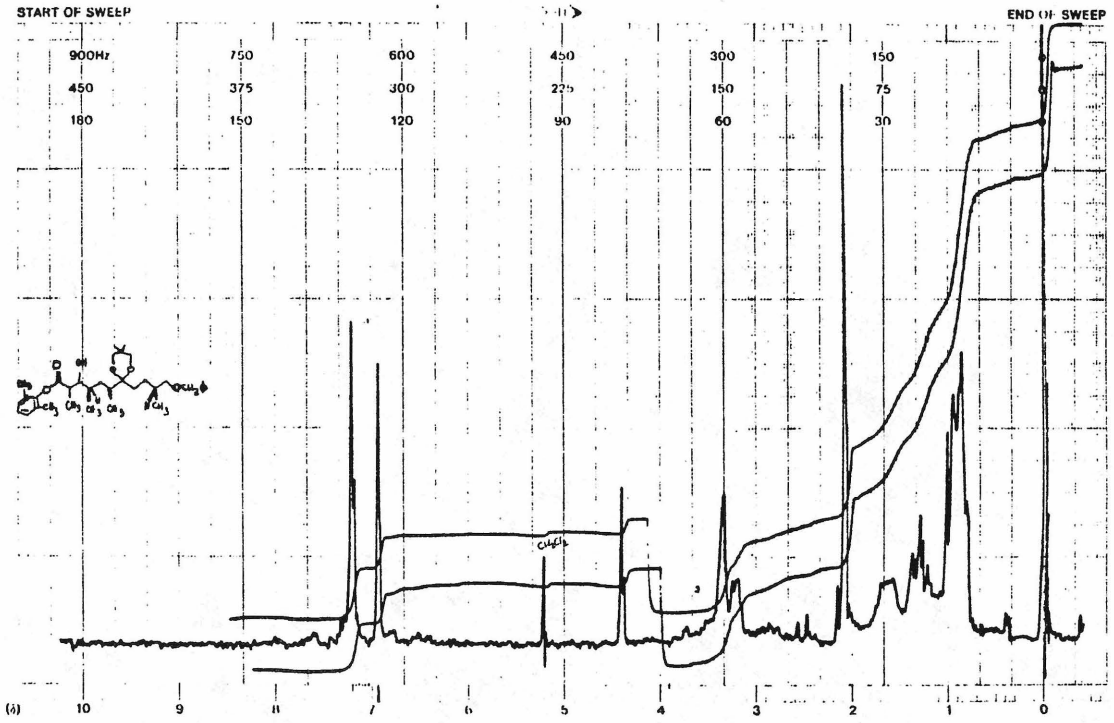

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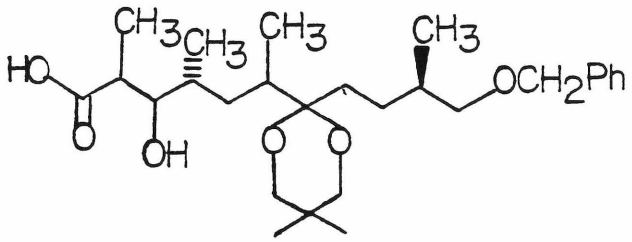

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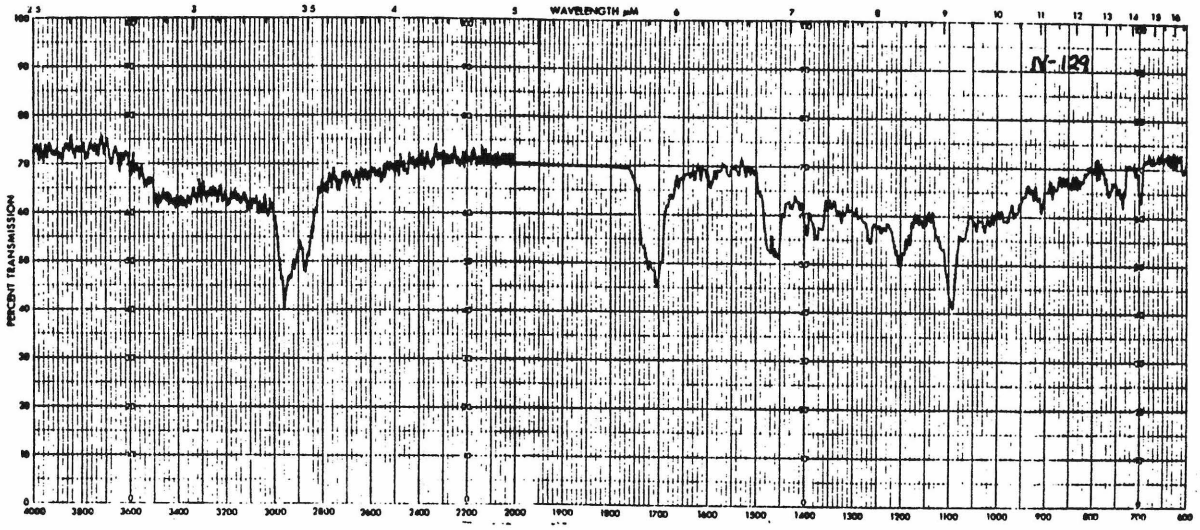

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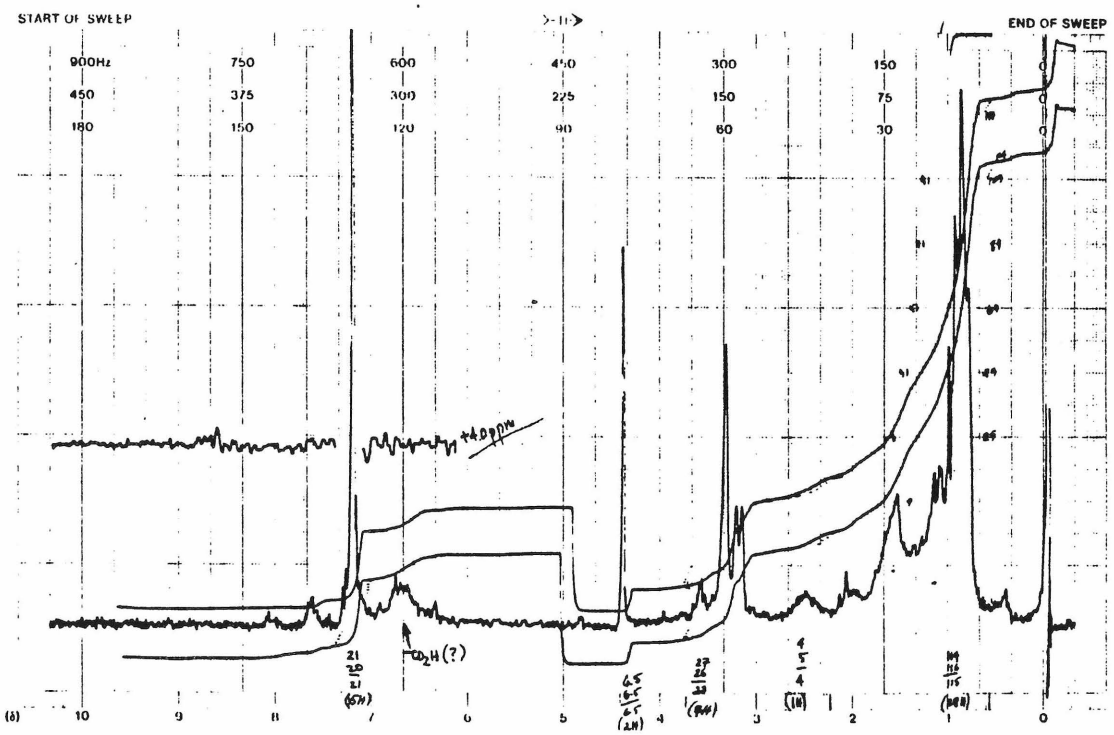

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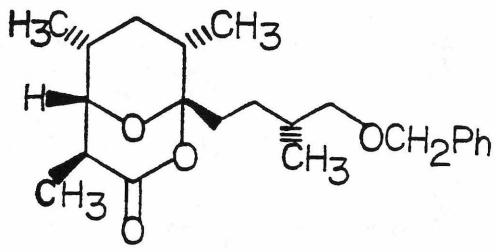

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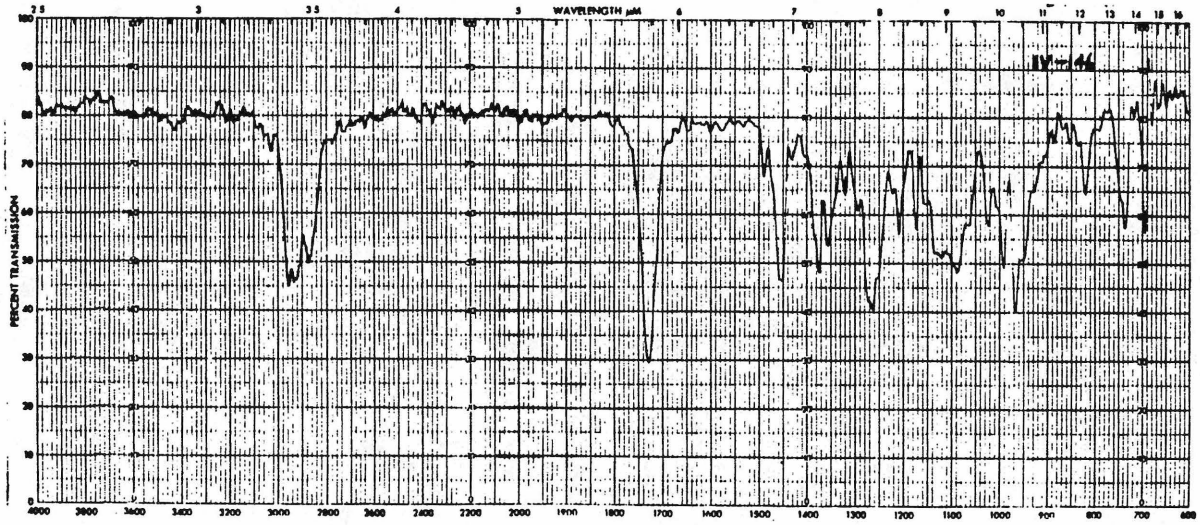
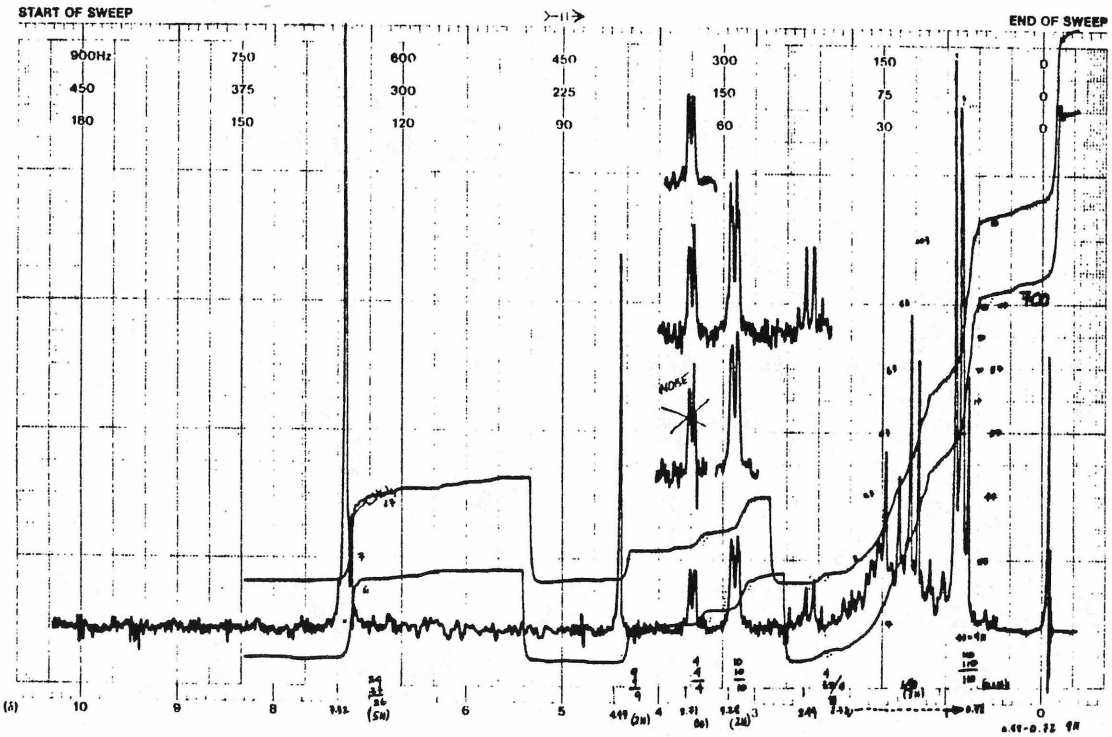


$CDCl_3$



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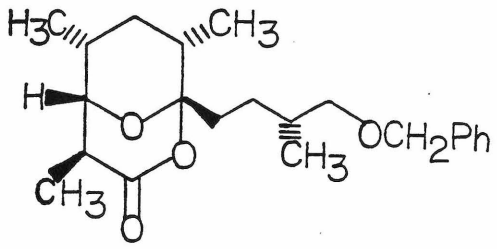
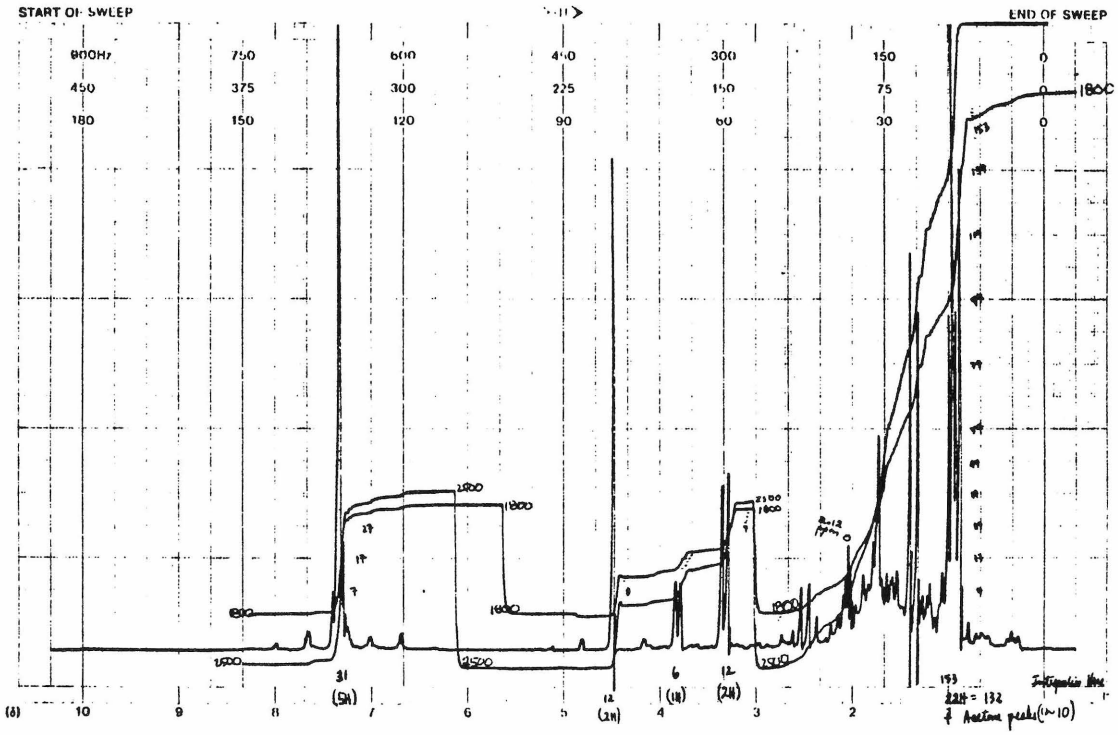


60a

d_6-acetone



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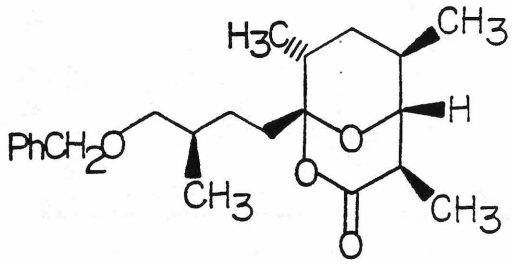
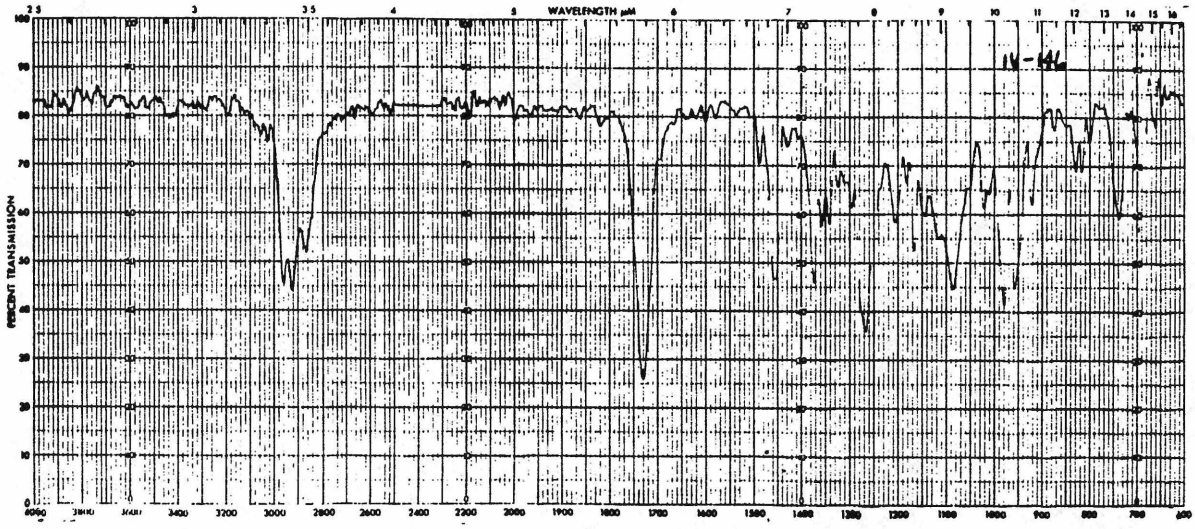


60b

neat



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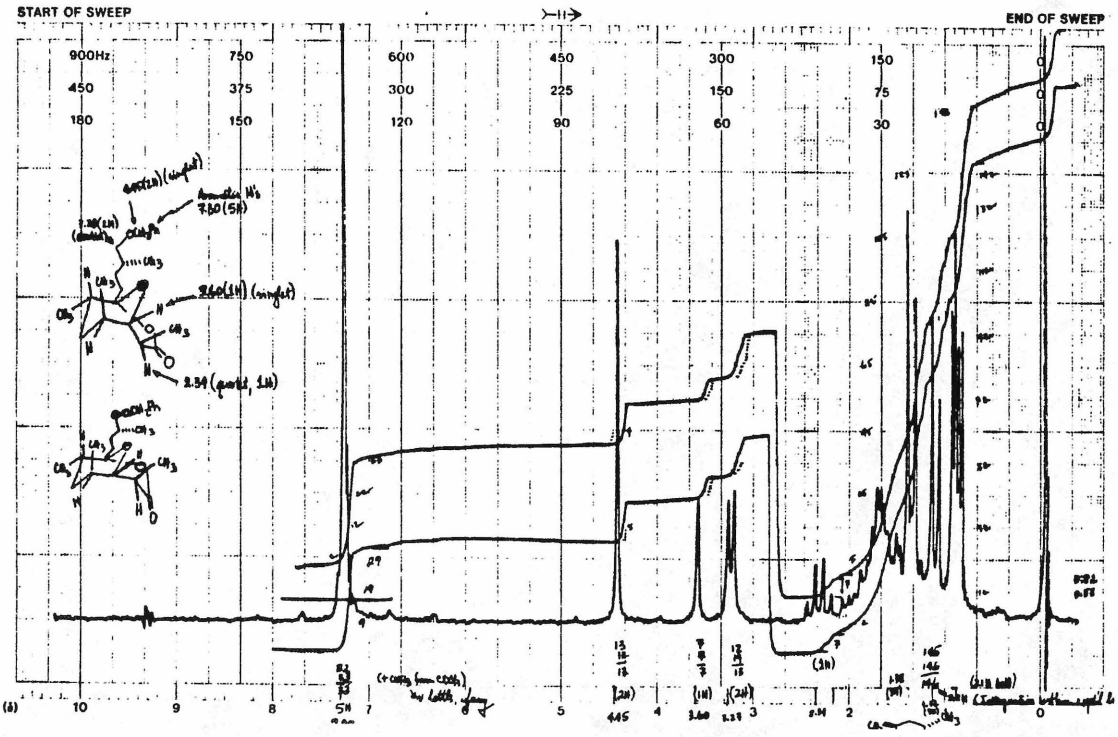

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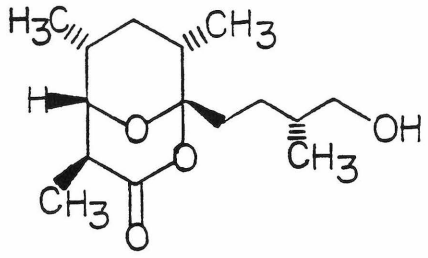
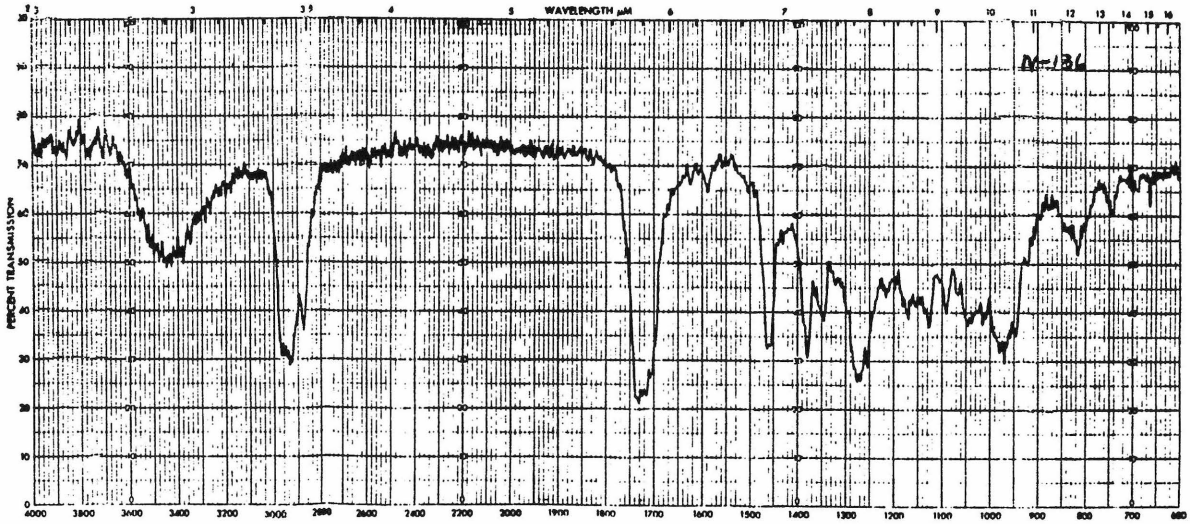
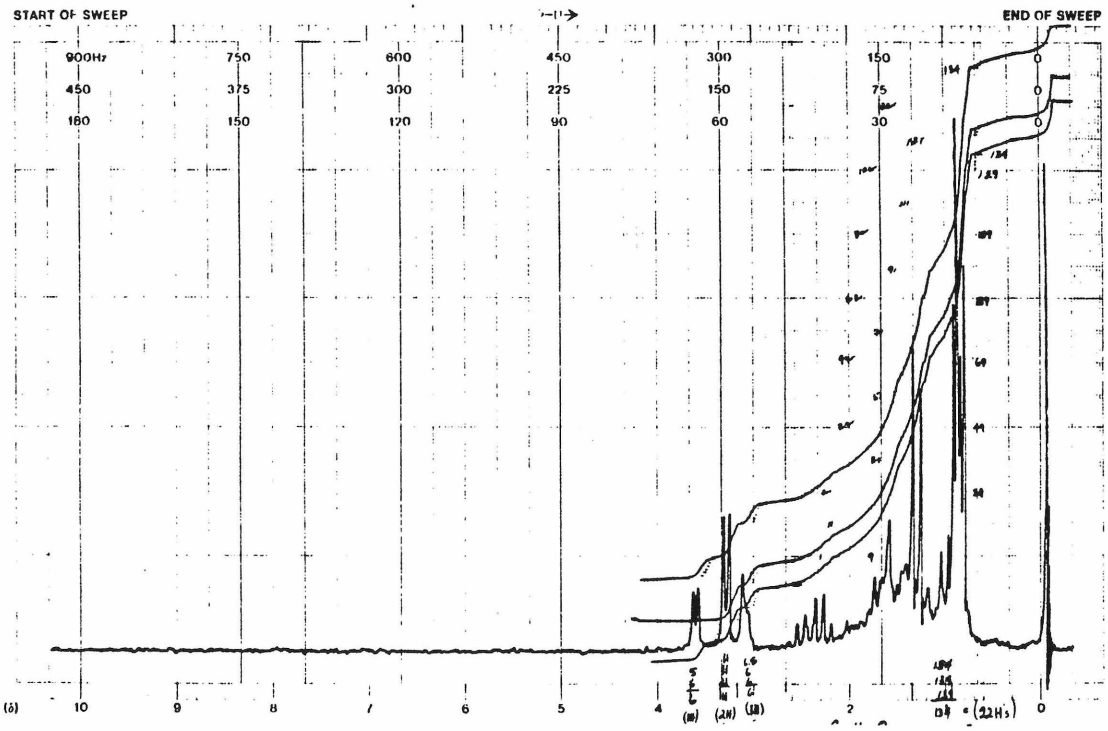


61a

neat



CCl_4



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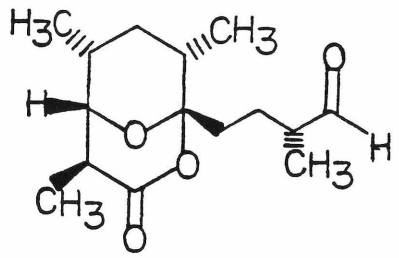
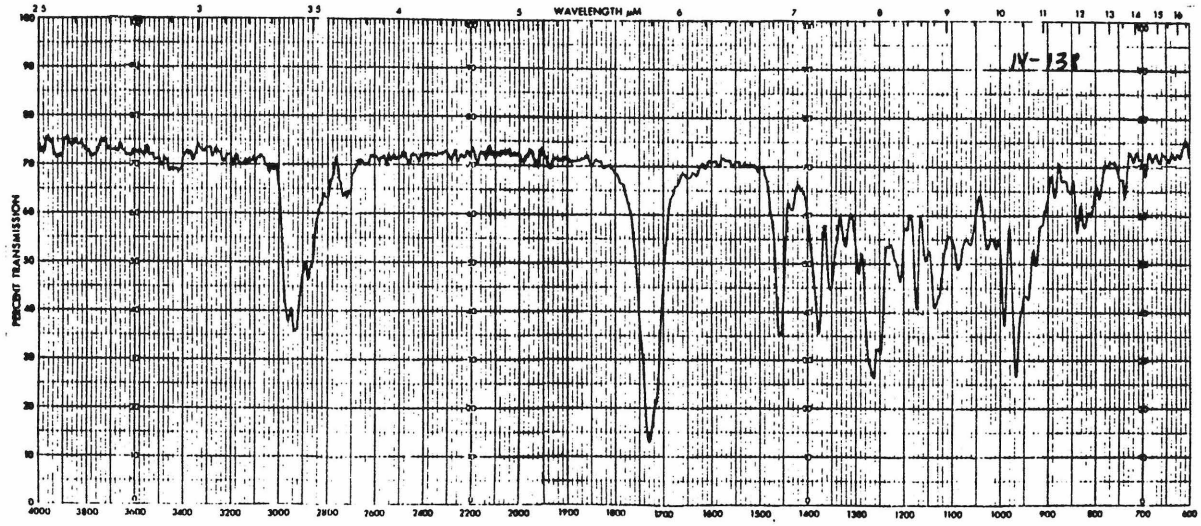


61b

neat



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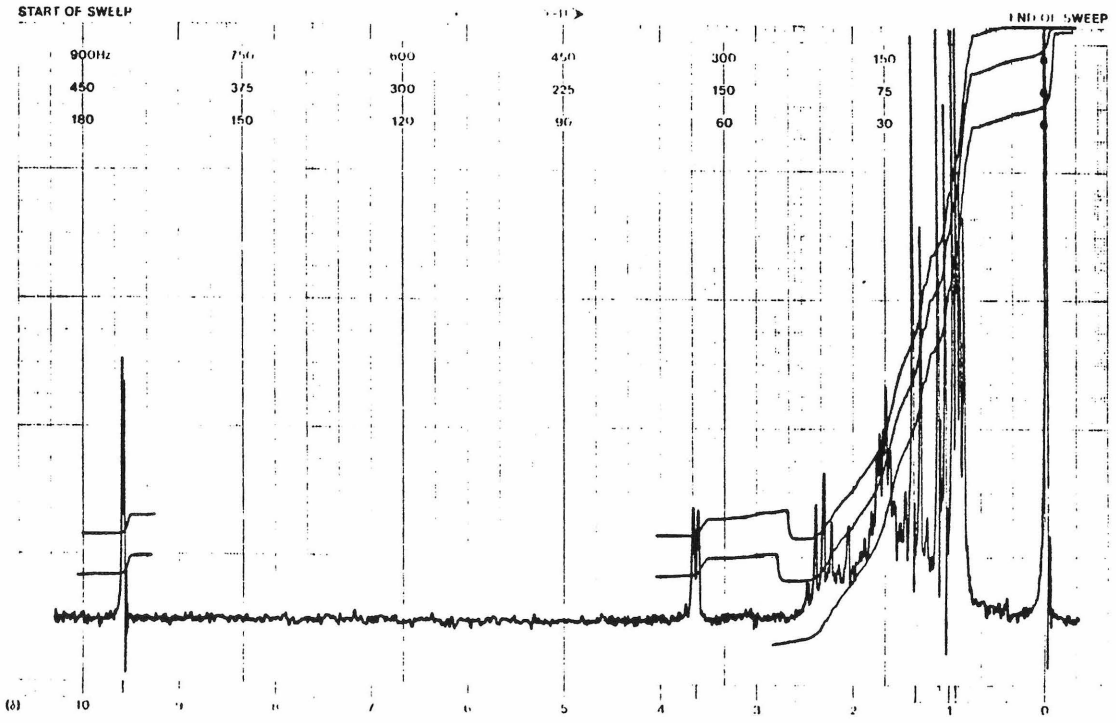

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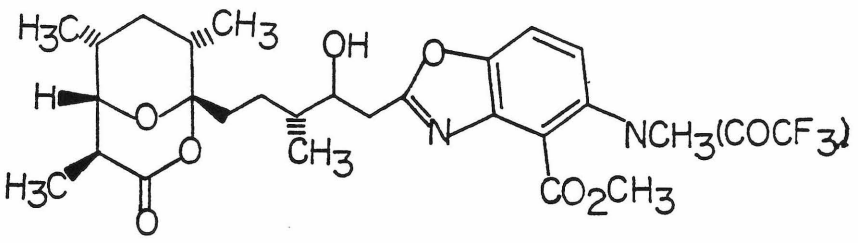
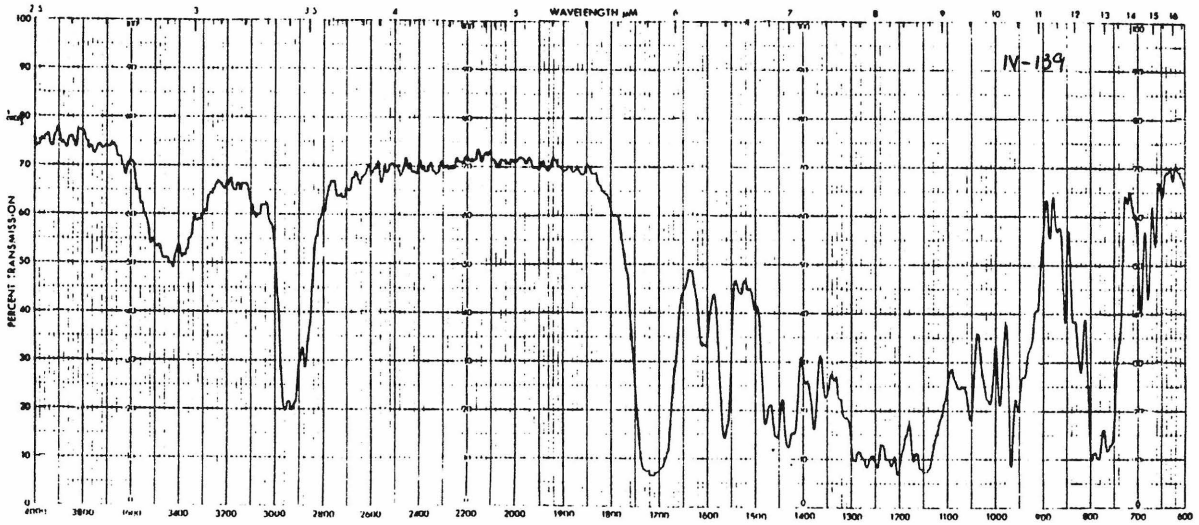


62a,b

neat



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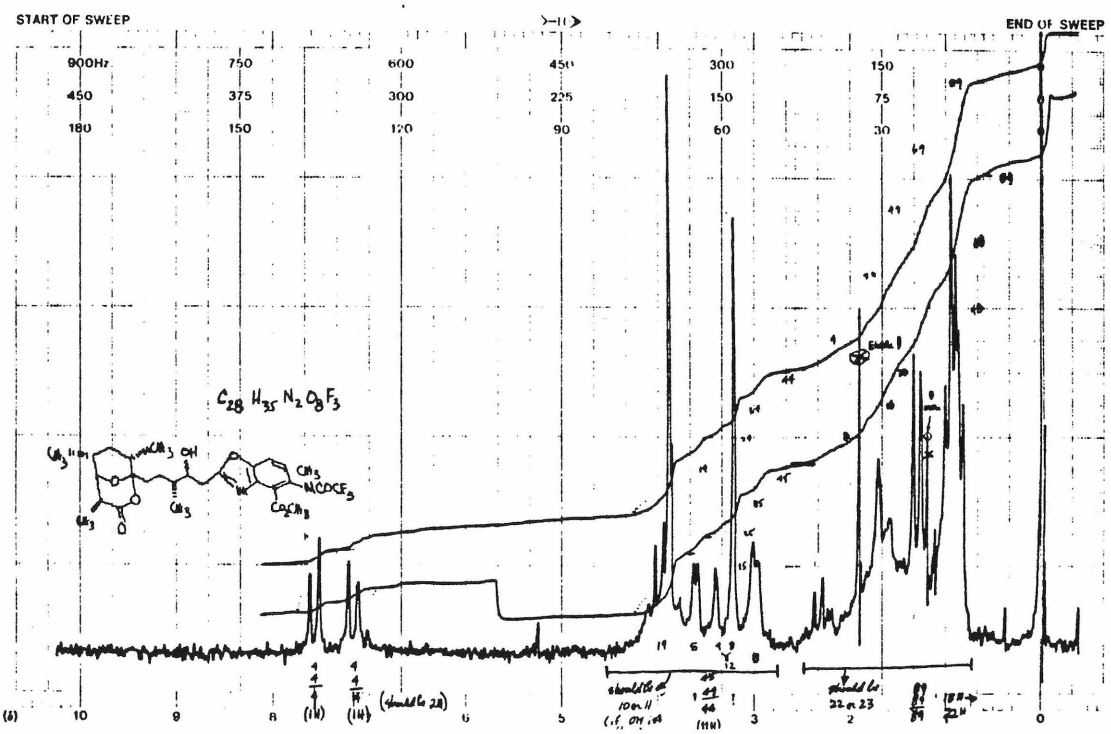

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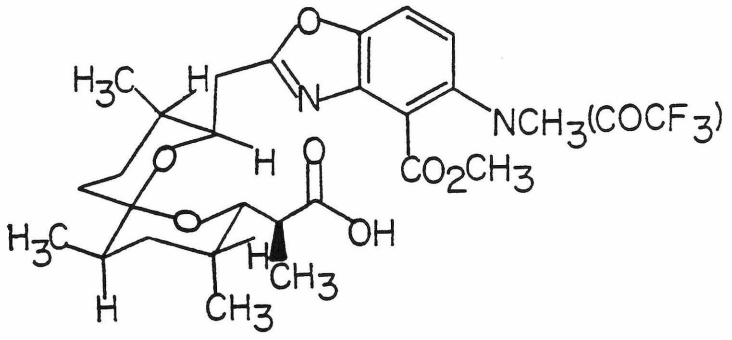
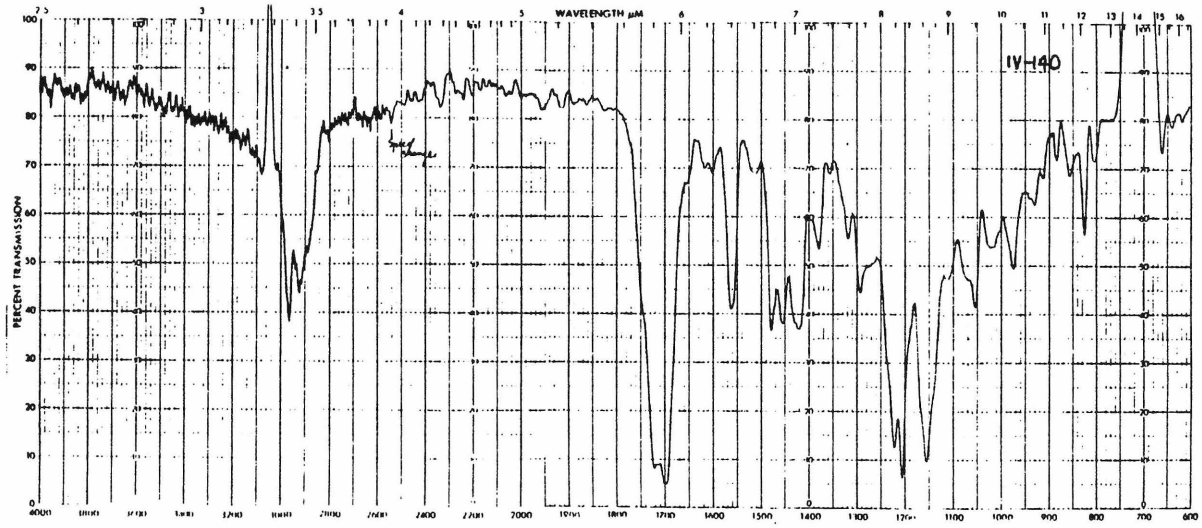
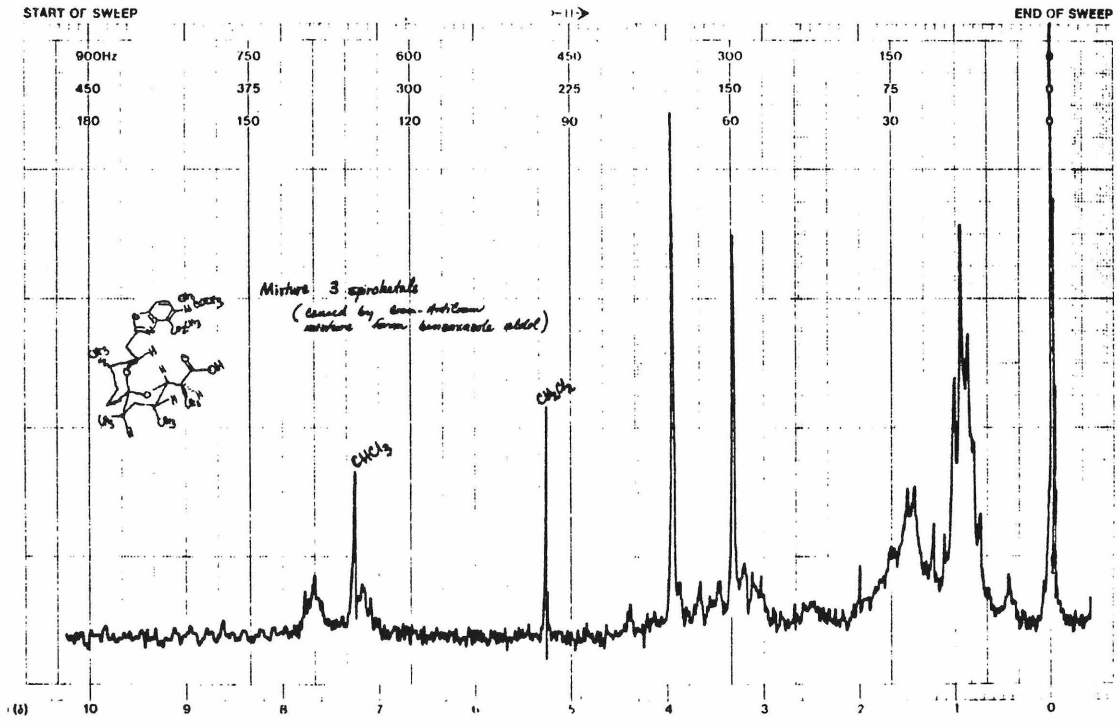


63a,b,c

CH_2Cl_2



$CDCl_3$



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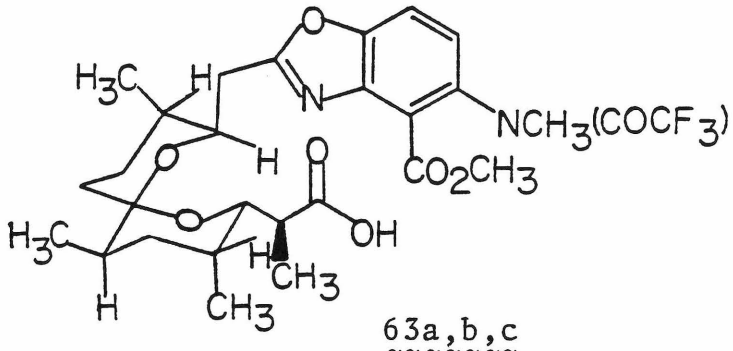

63a,b,c

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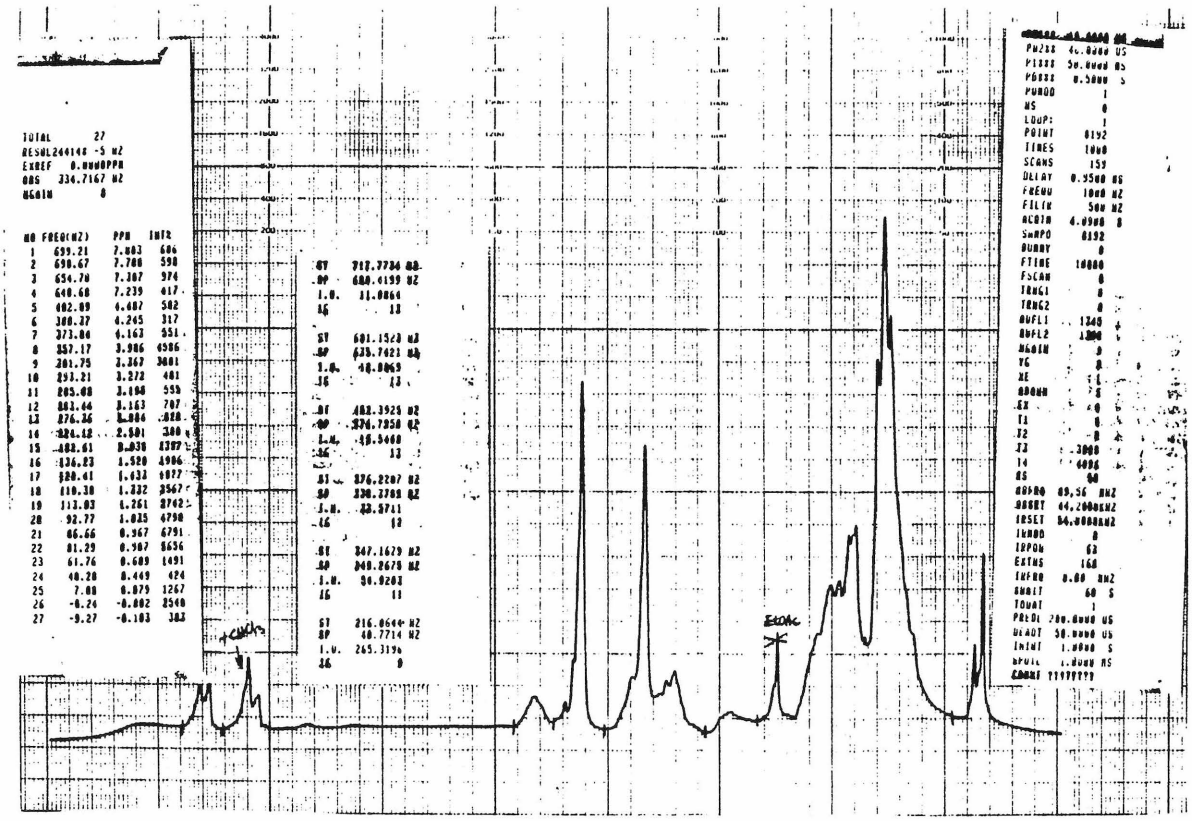

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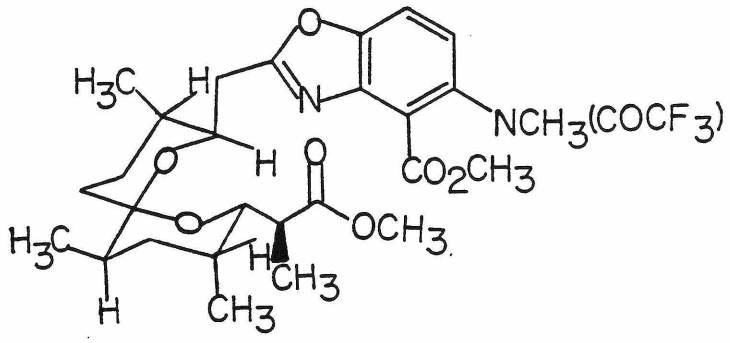
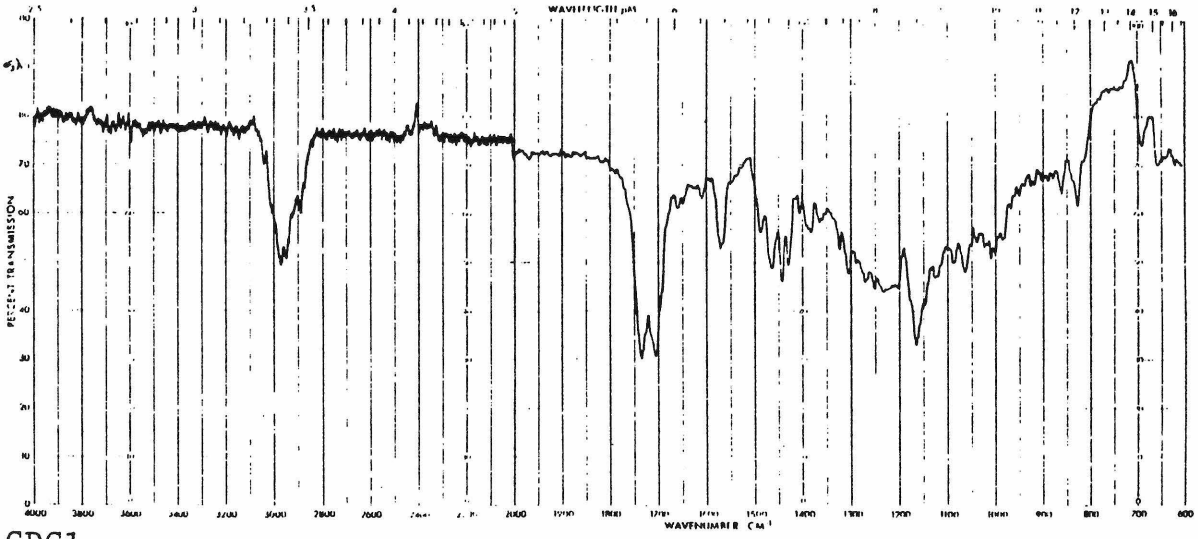


73a,b,c

$CHCl_3$



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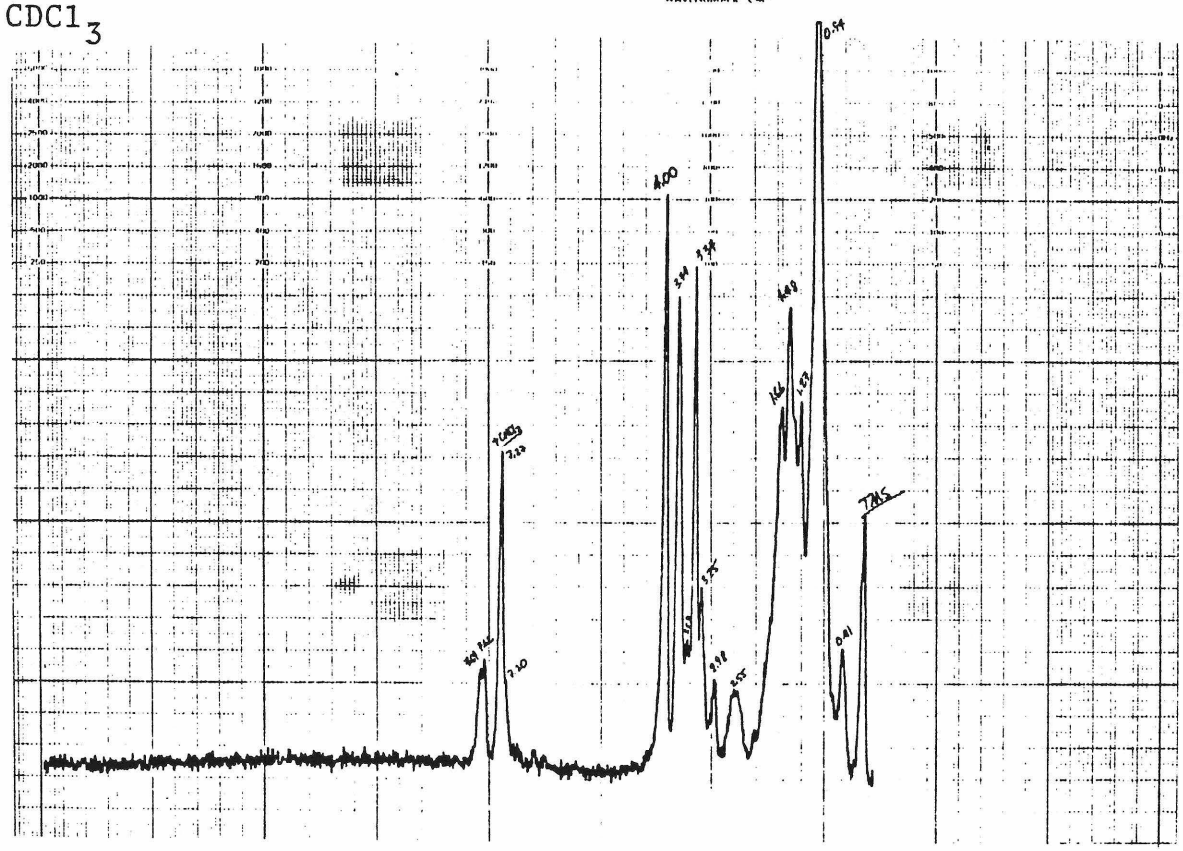
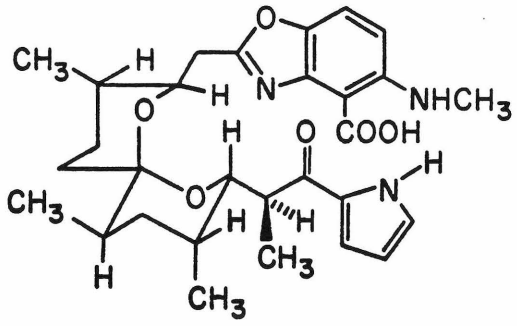
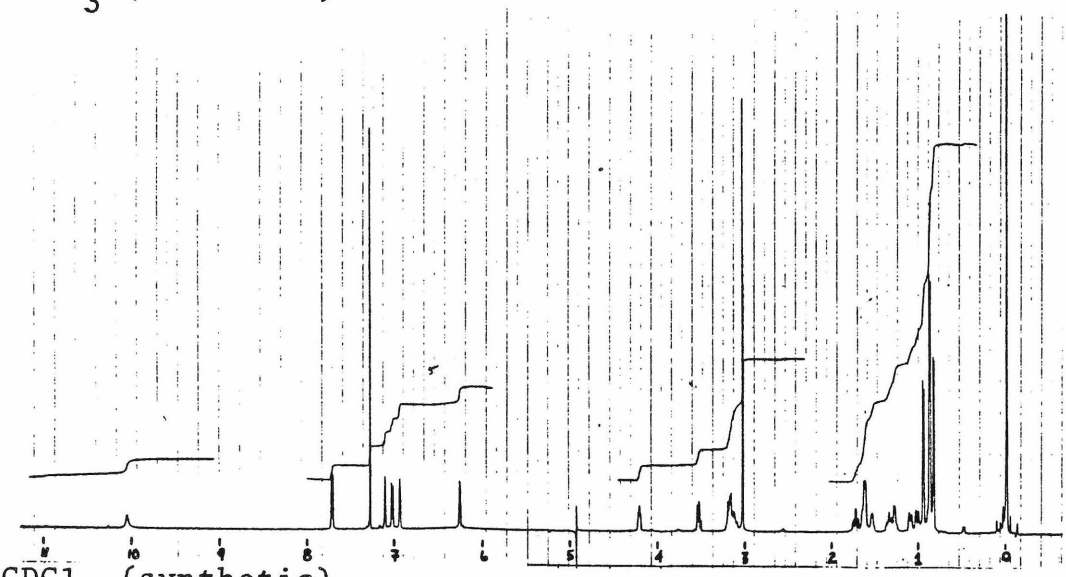


500 MHz ^1H NMR



$CDCl_3$ (authentic)

A-23187



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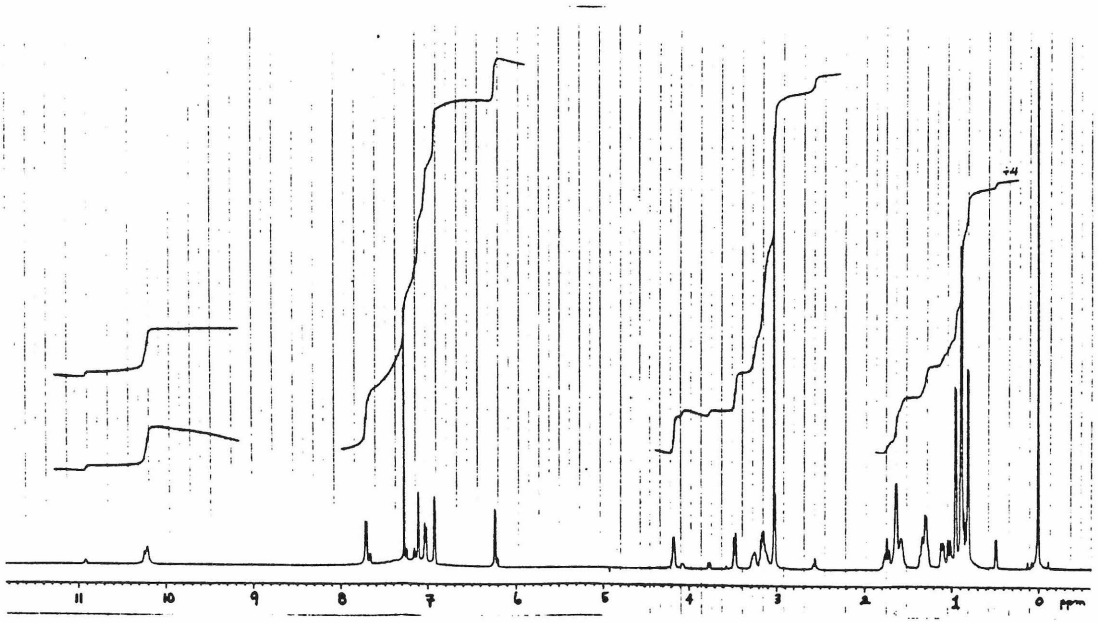

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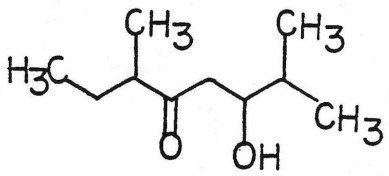
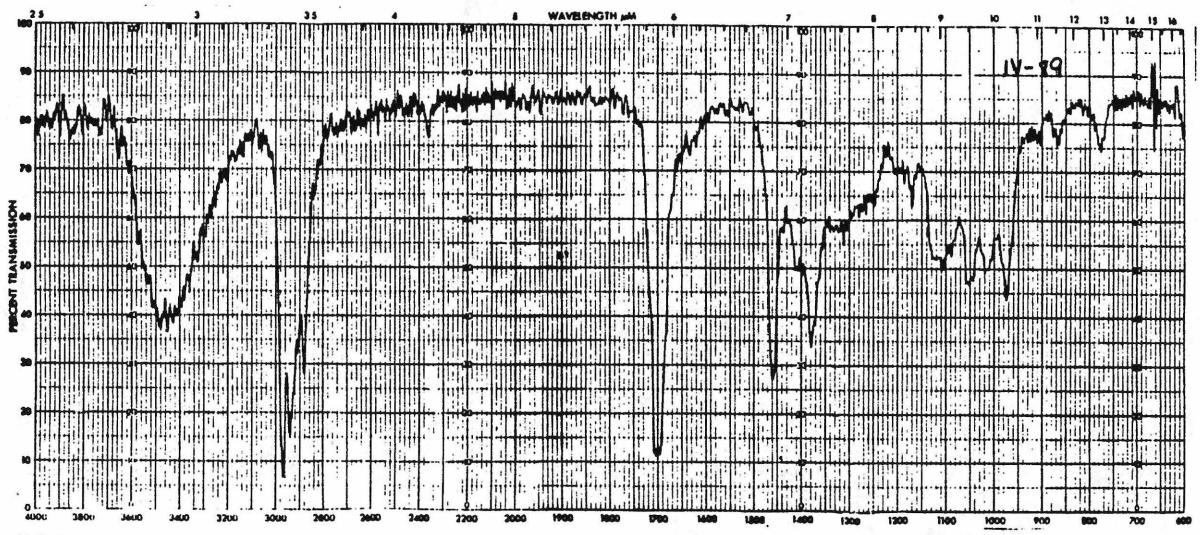
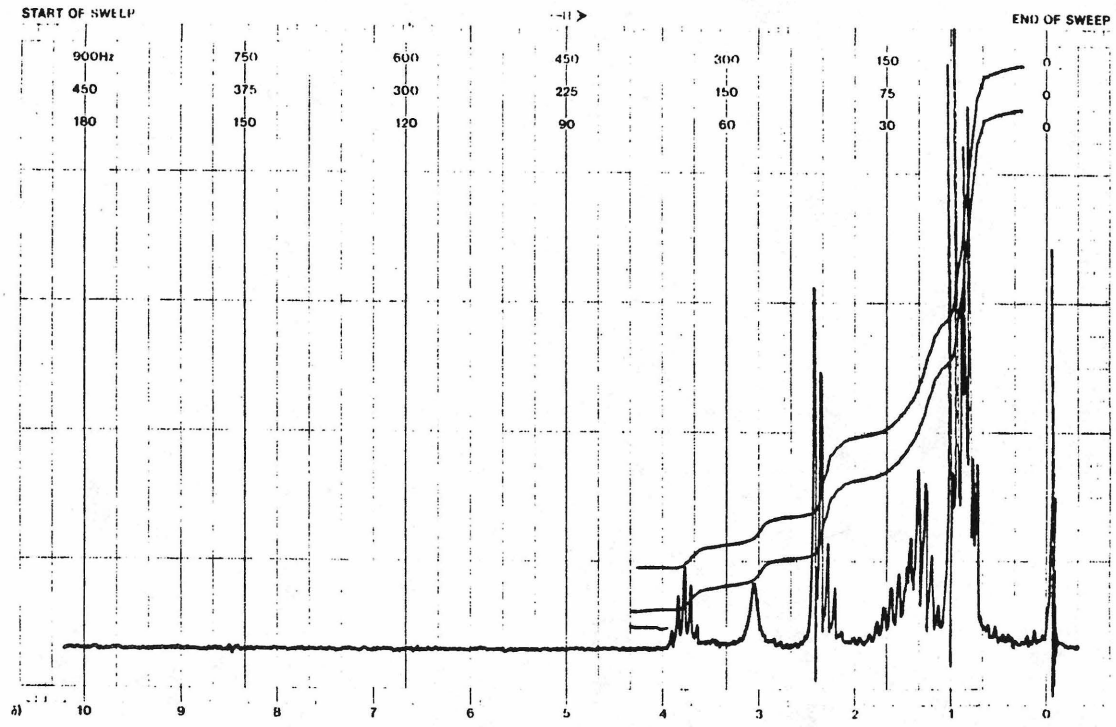


neat



CCl_4



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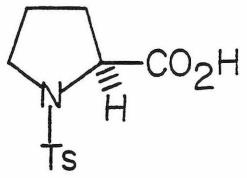
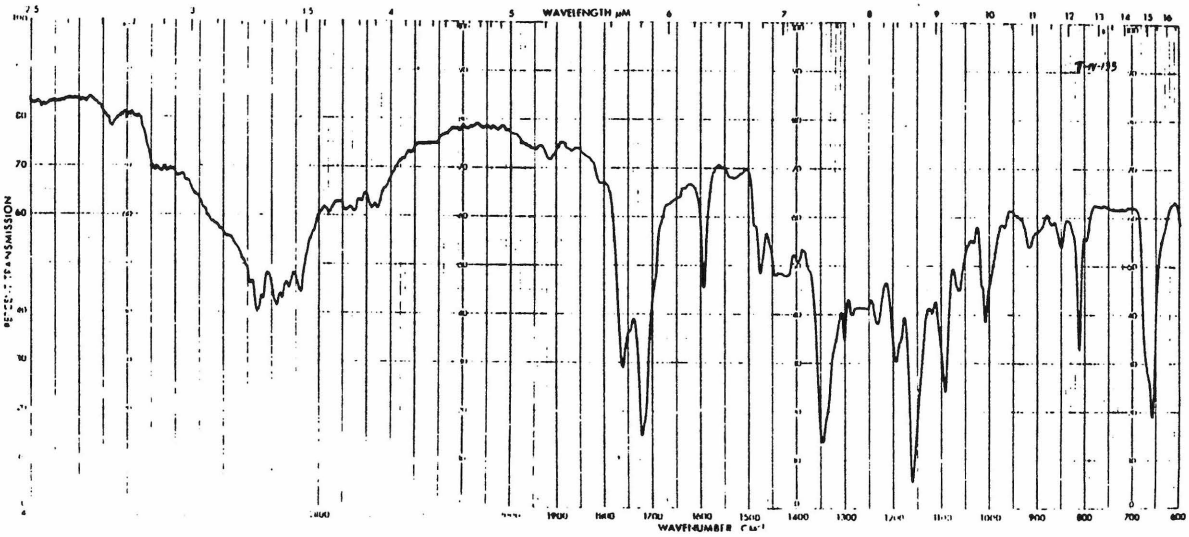
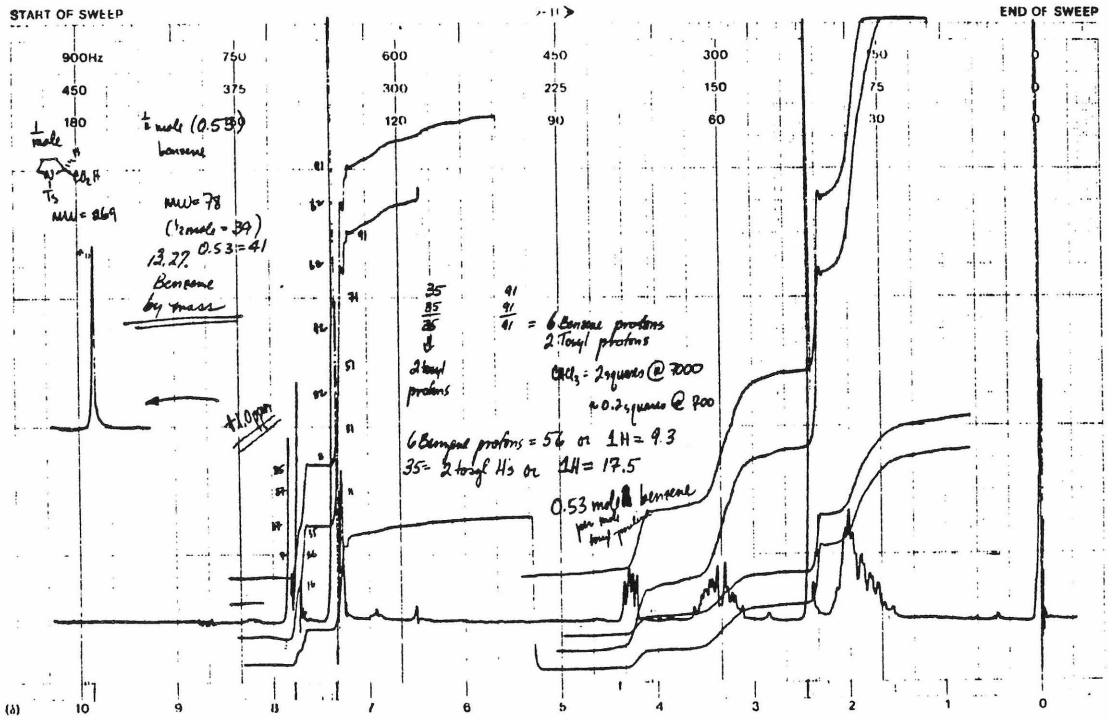


4

CH_2Cl_2



$CDCl_3$



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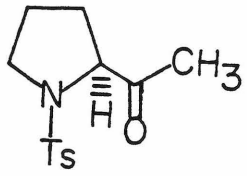
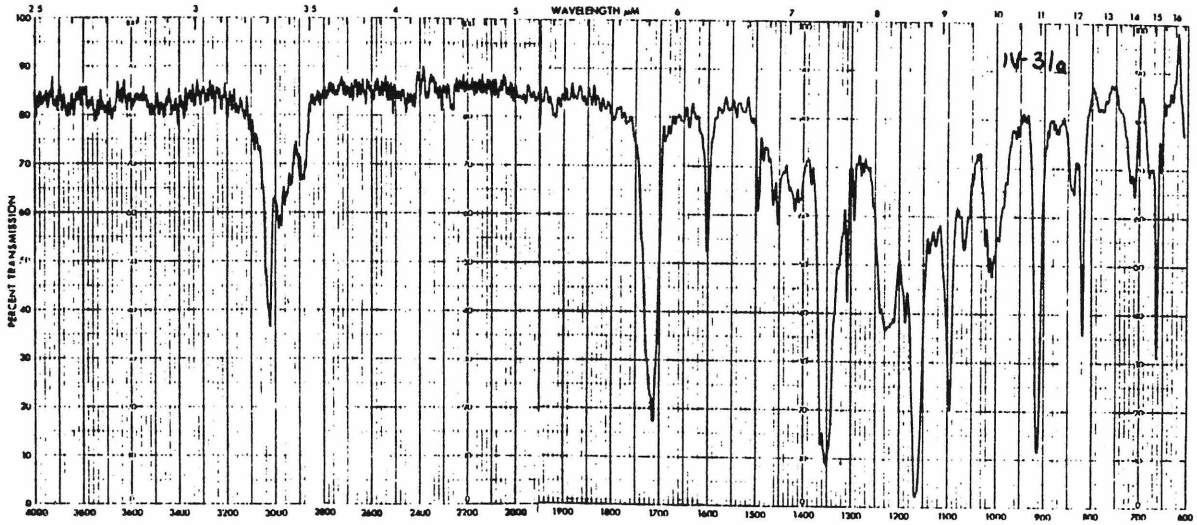


5a

$CHCl_3$



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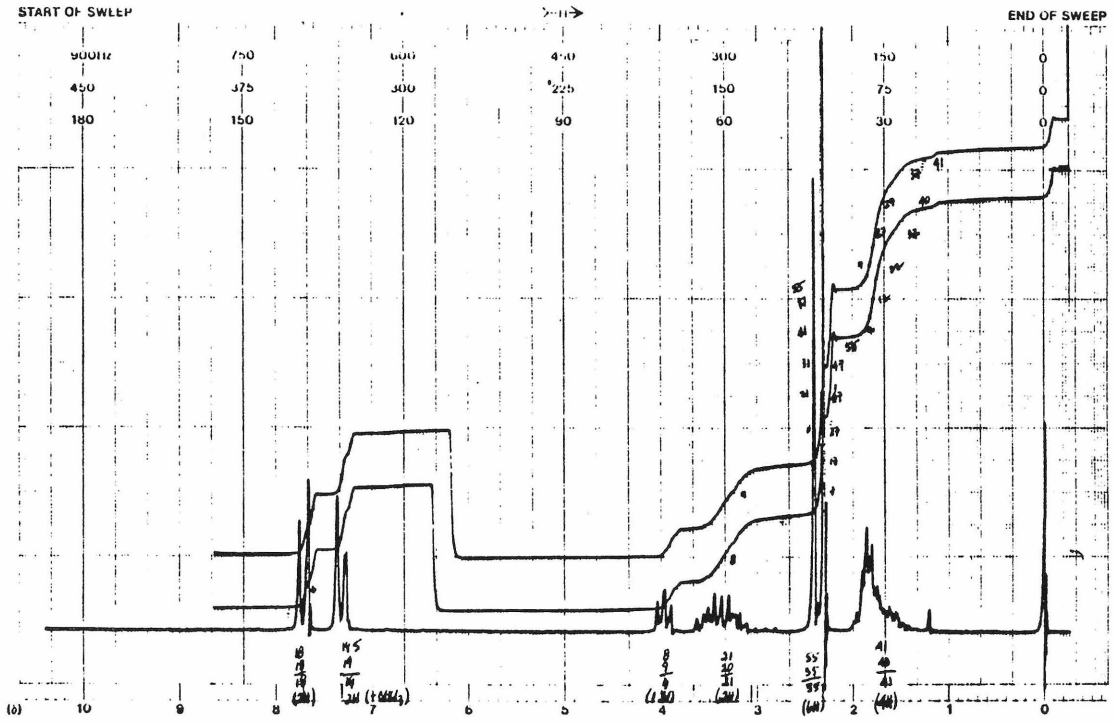

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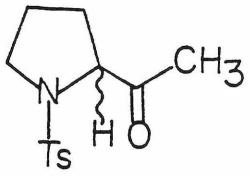
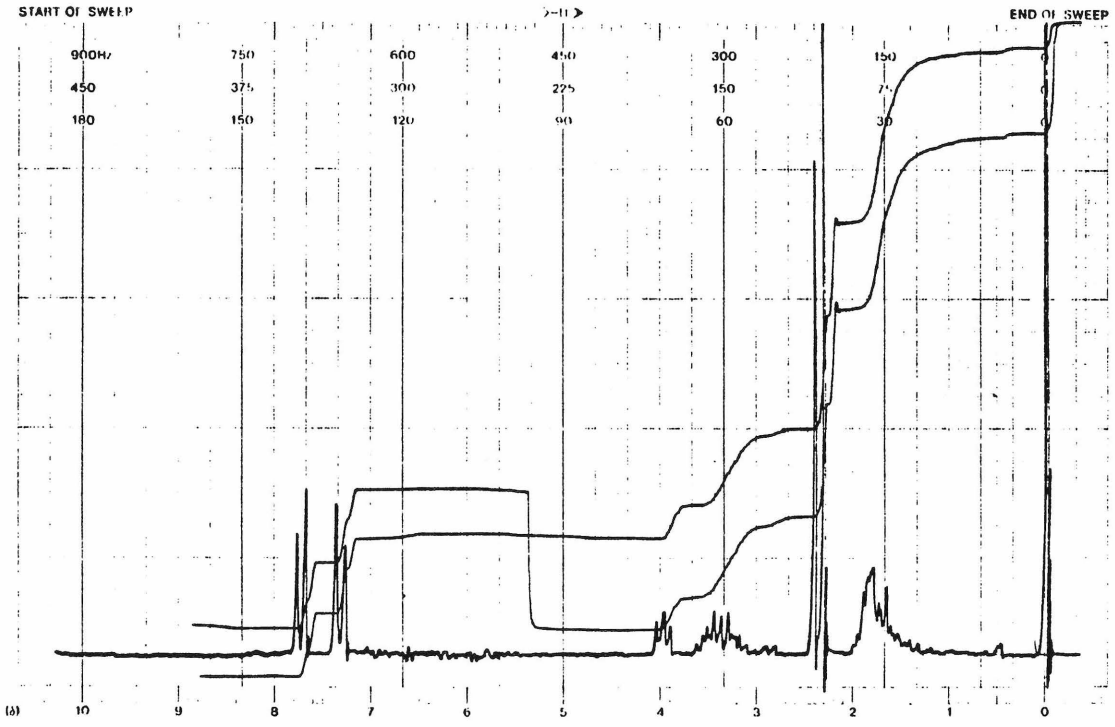


5a (racemic)

$CDCl_3$



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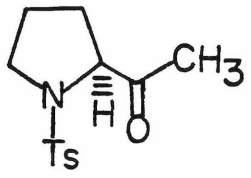
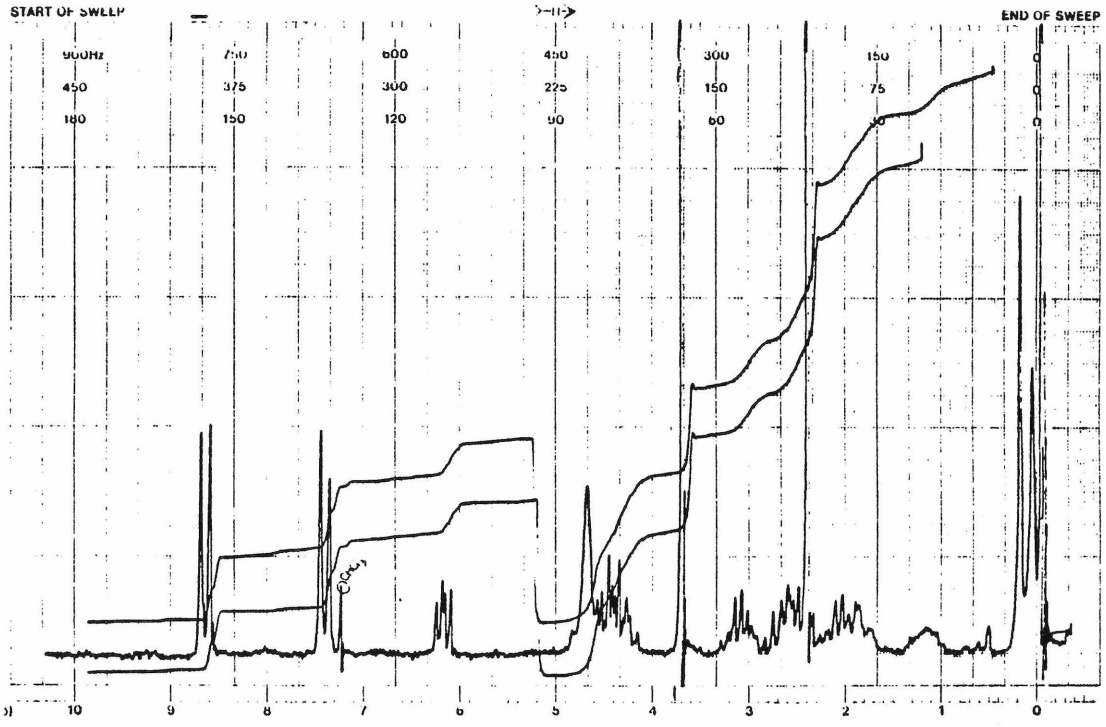


5a

$CDCl_3$ + Eu(III)



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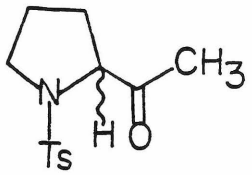
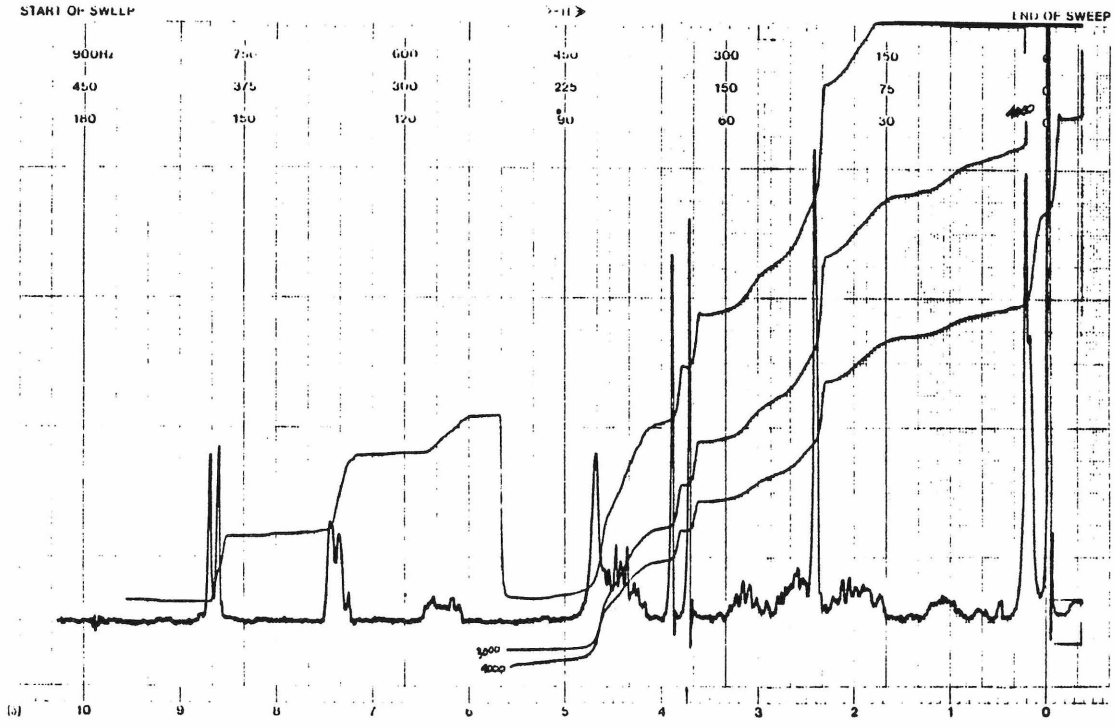


5a (racemic)

$CDCl_3$ + EU(III)



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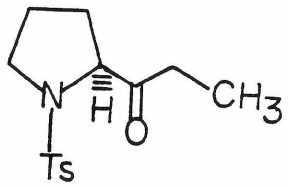
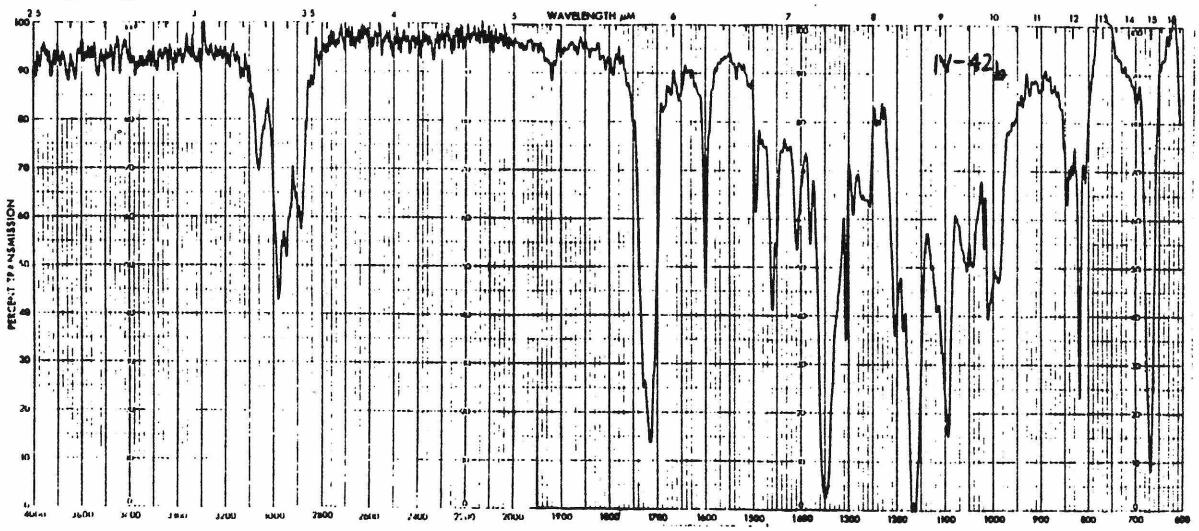
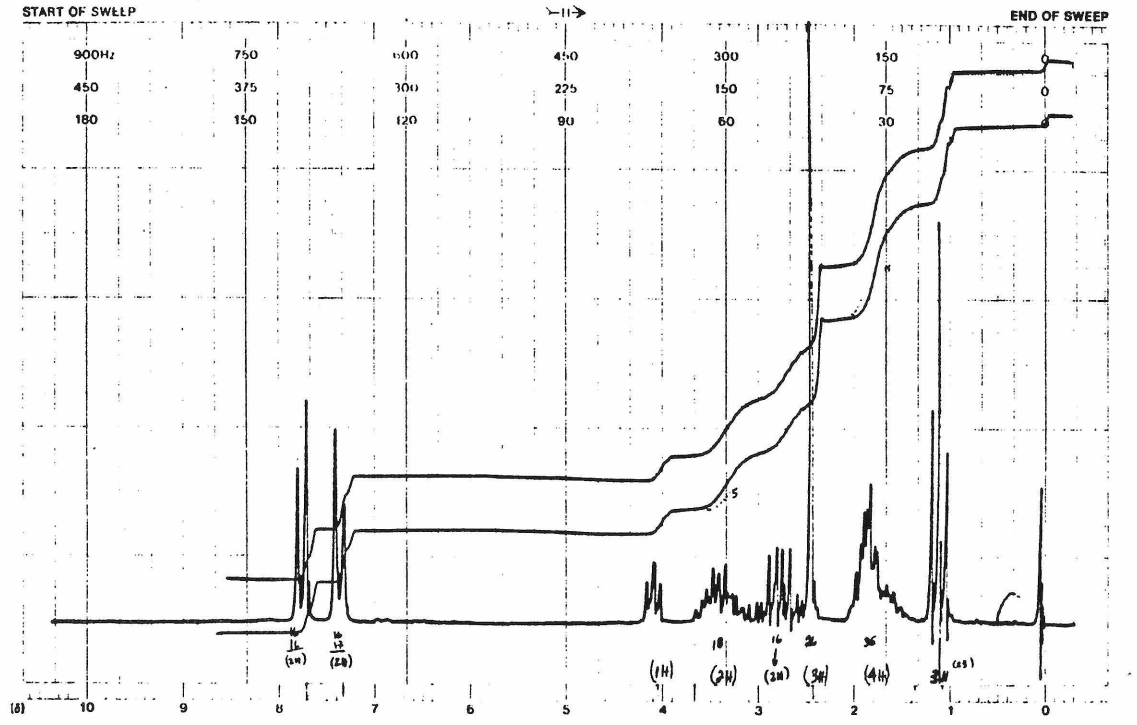


5b

CH_2Cl_2



$CDCl_3$



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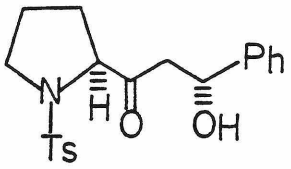
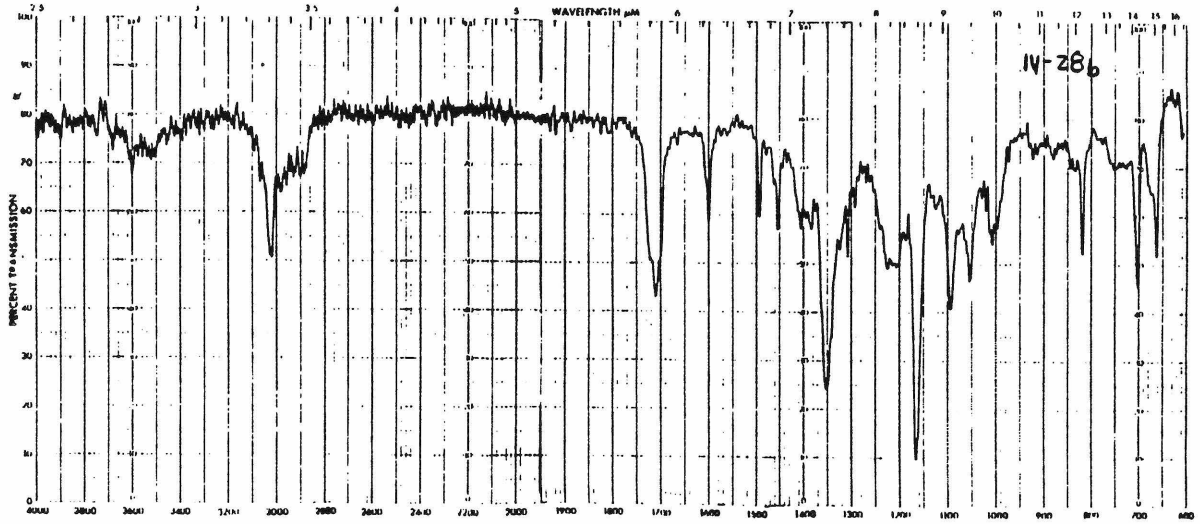


7a

$CHCl_3$



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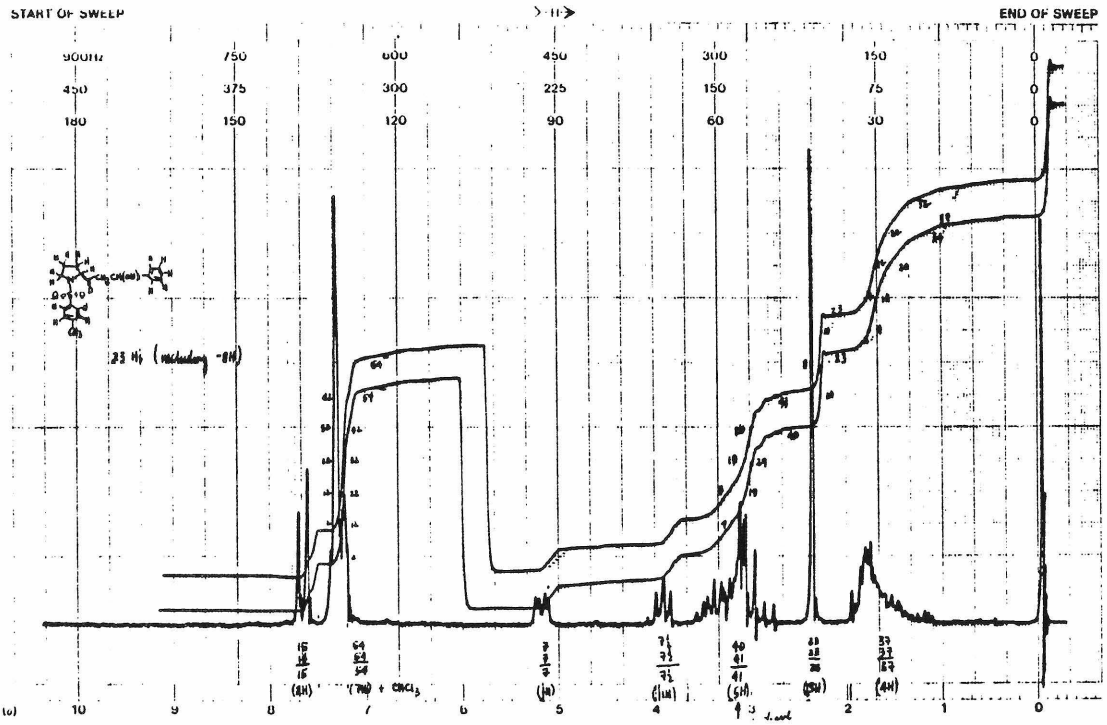

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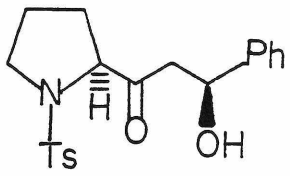
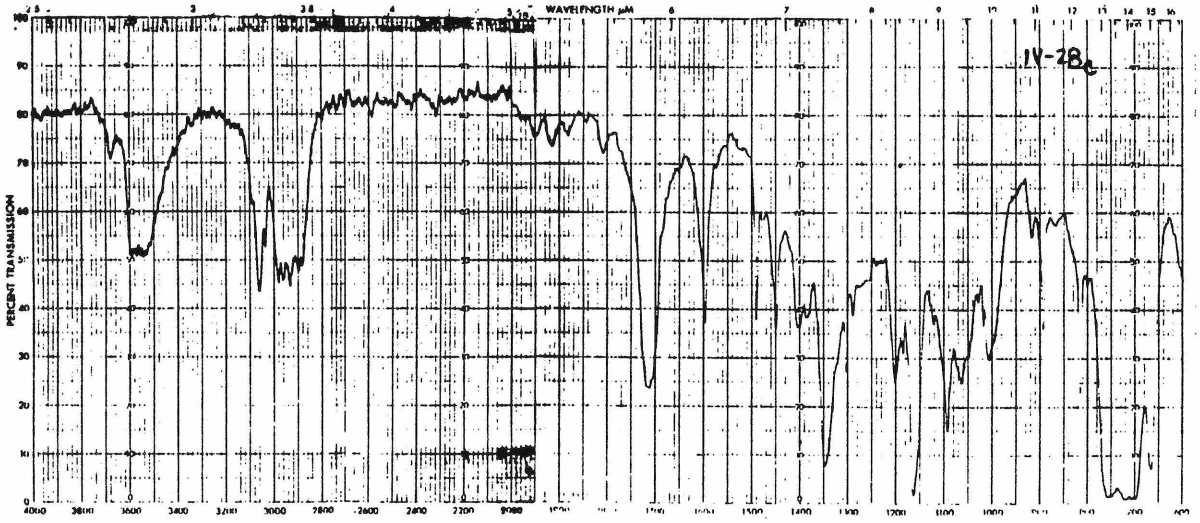


8a

CH_2Cl_2



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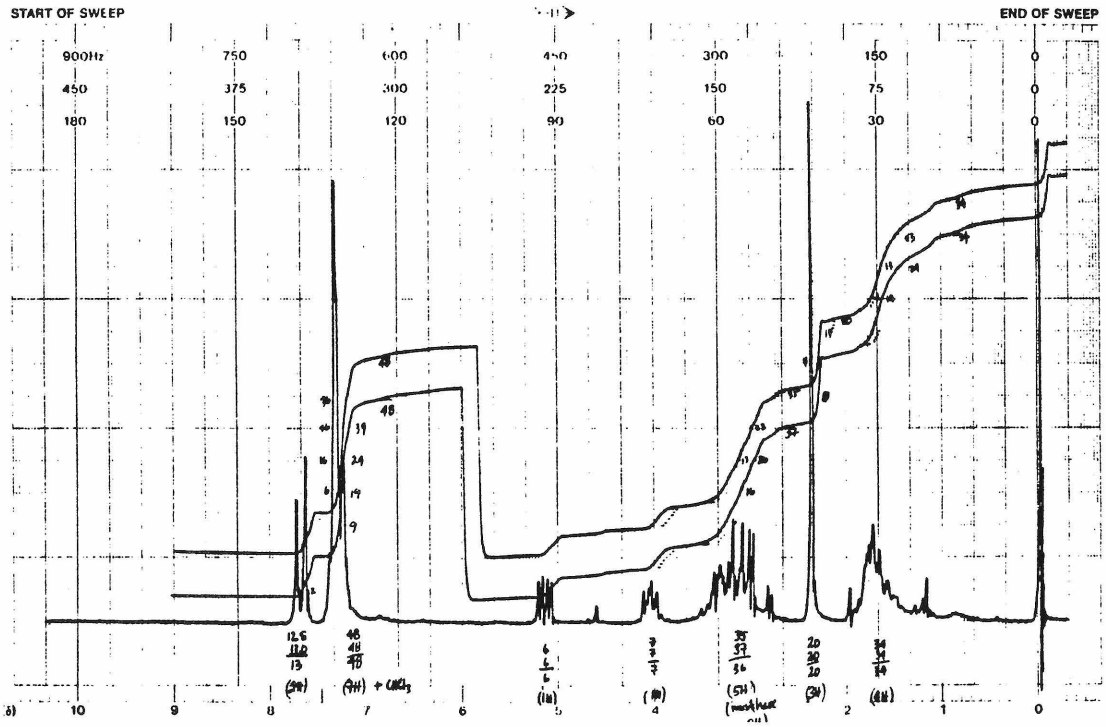

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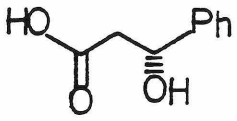
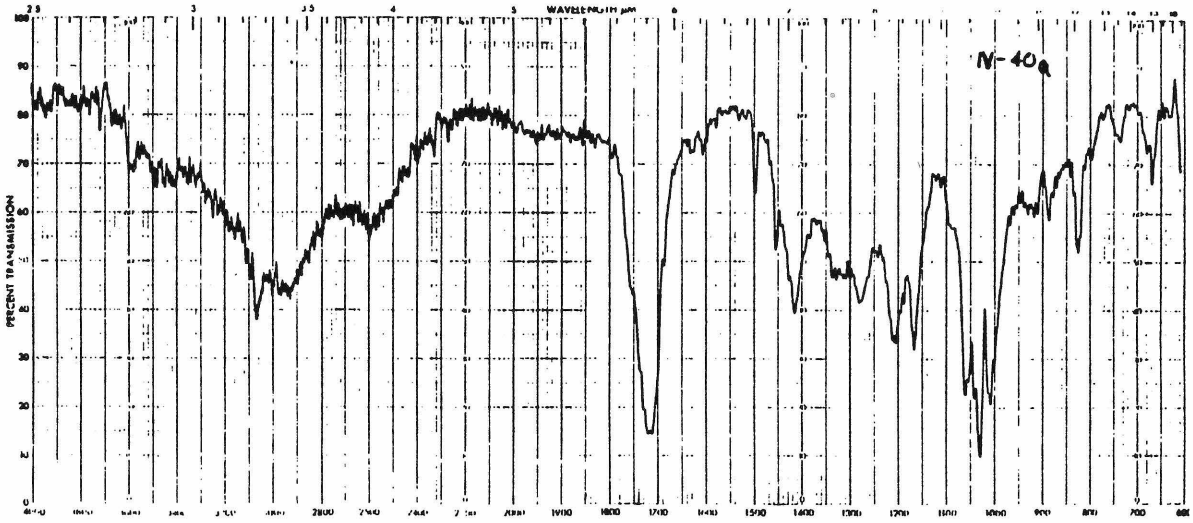
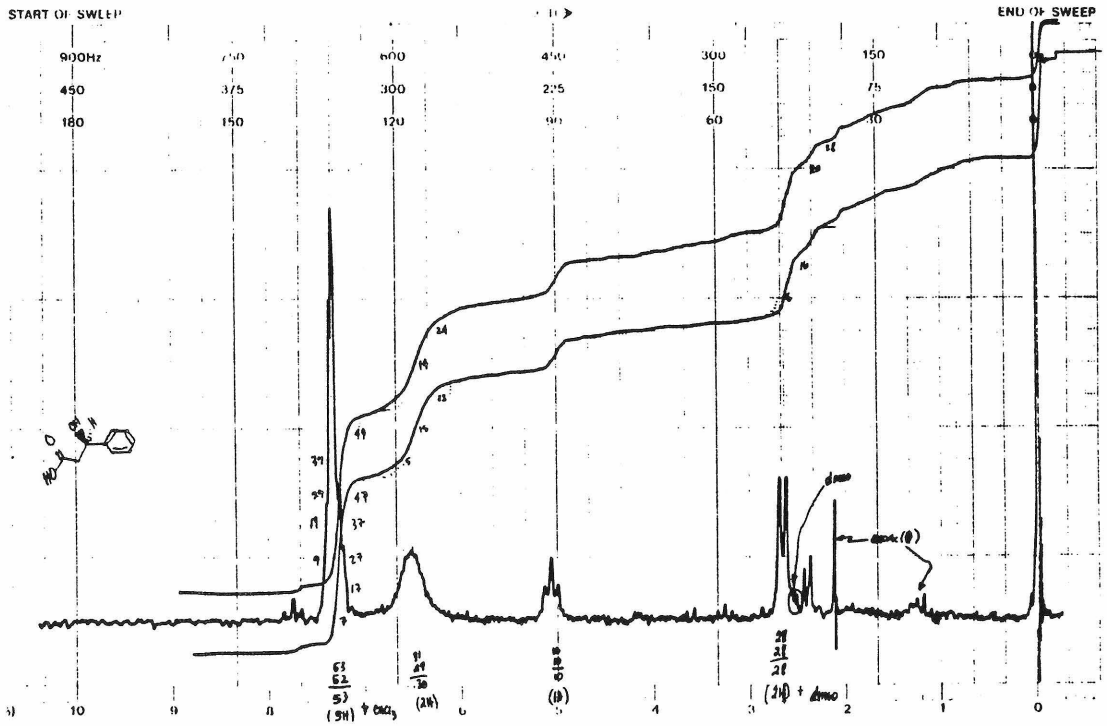


CH_2Cl_2



$CDCl_3$; d_6-DMSO



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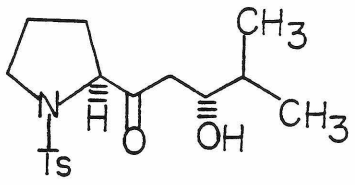
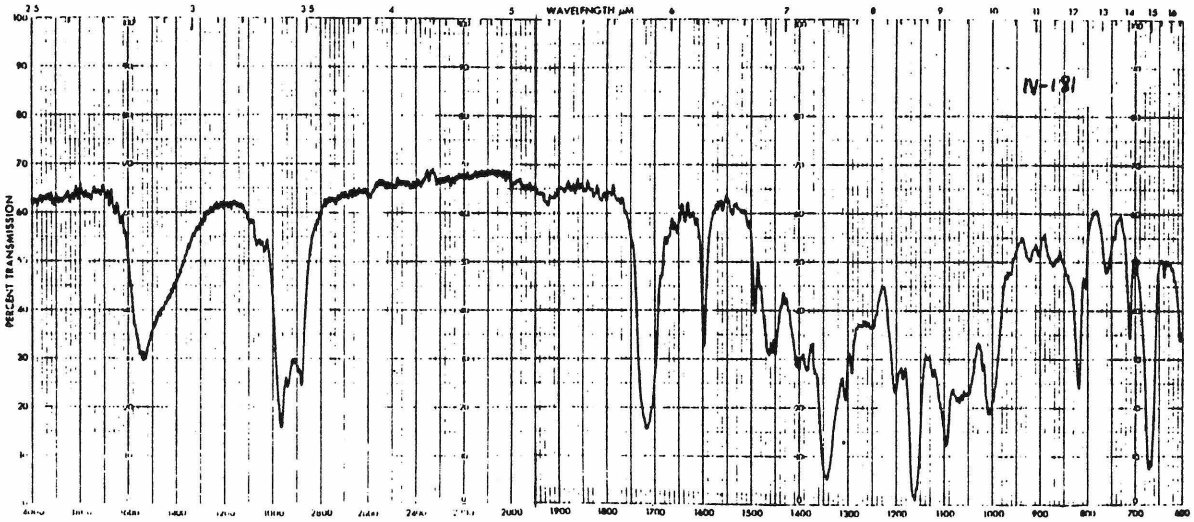
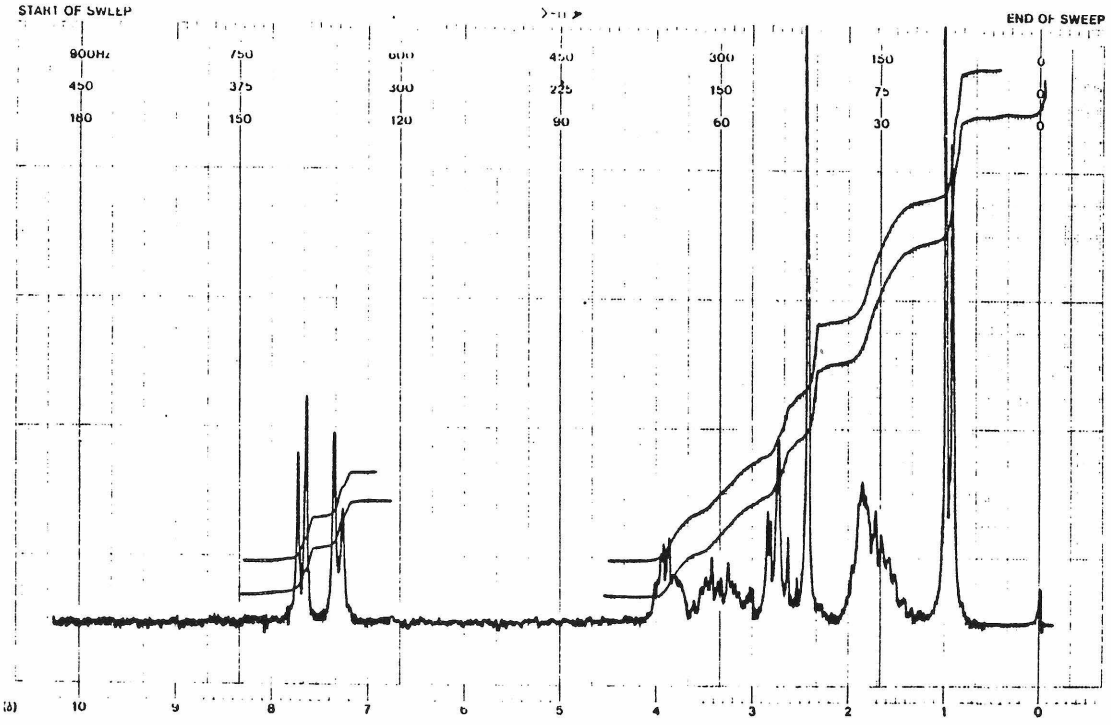


7b

neat



$CDCl_3$-CCl_4



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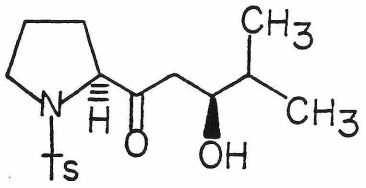
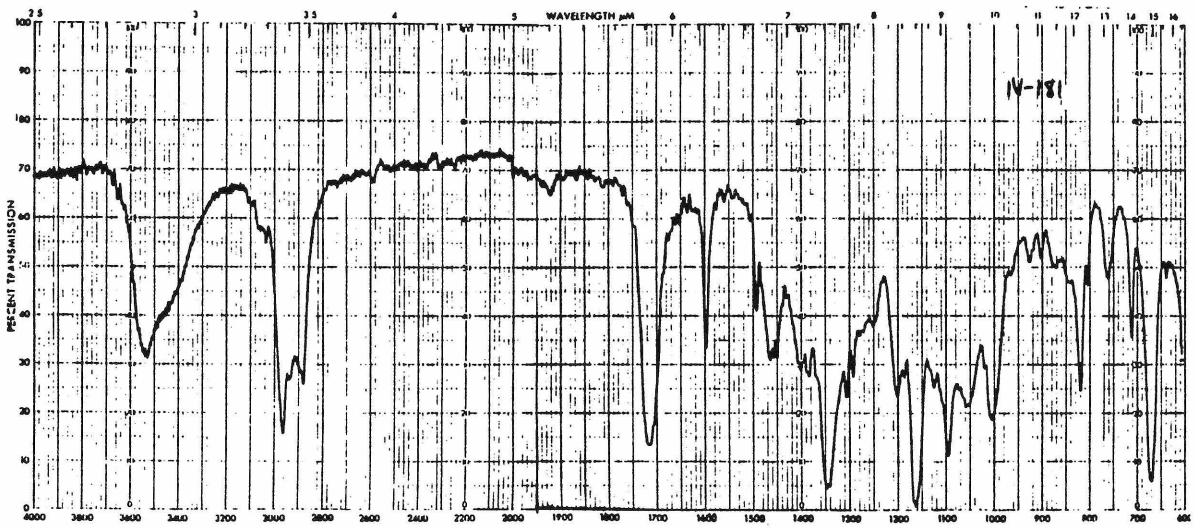
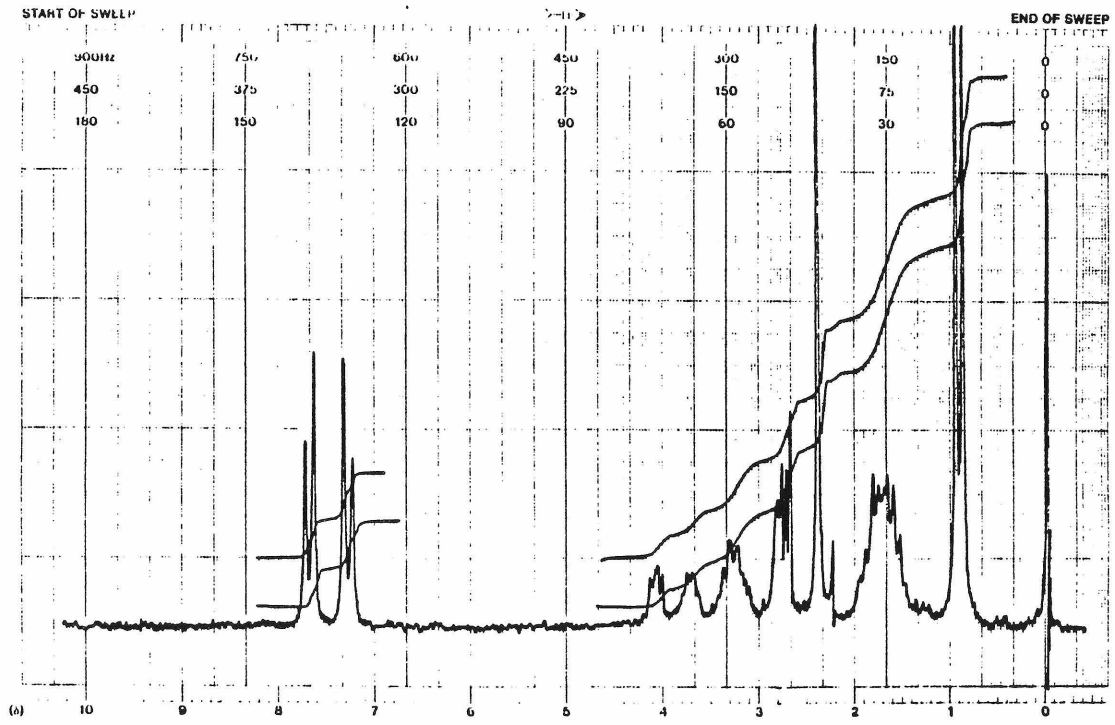


8b

neat



$CDCl_3$-CCl_4



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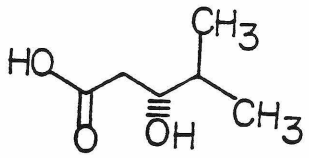
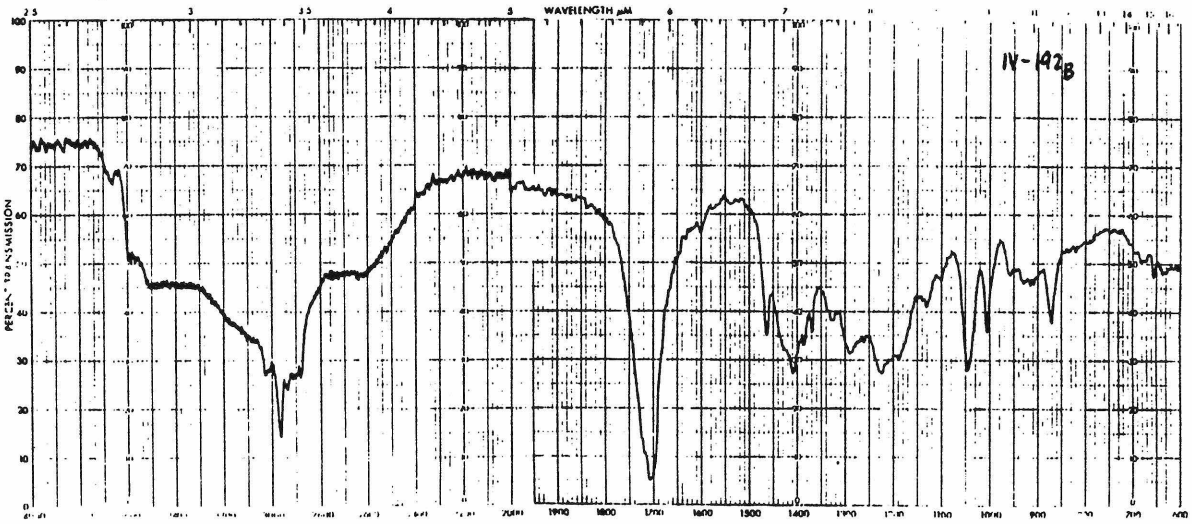


$CHCl_3$



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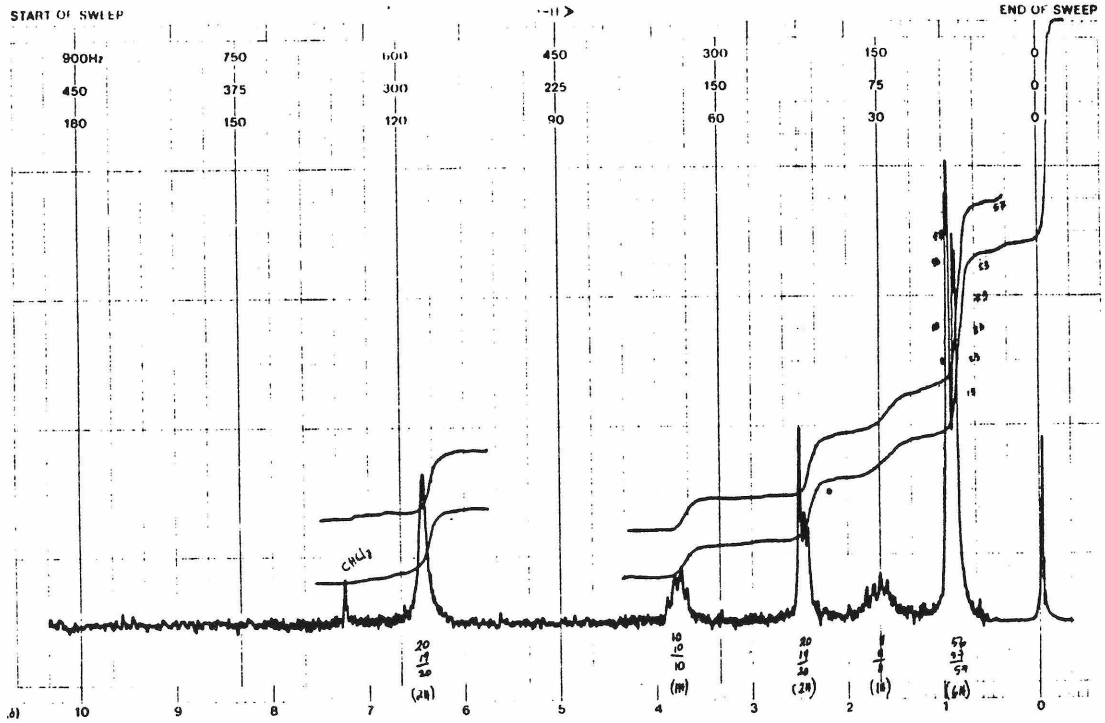

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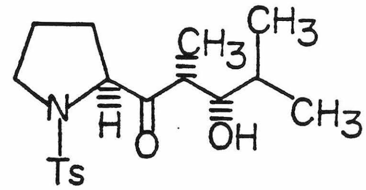
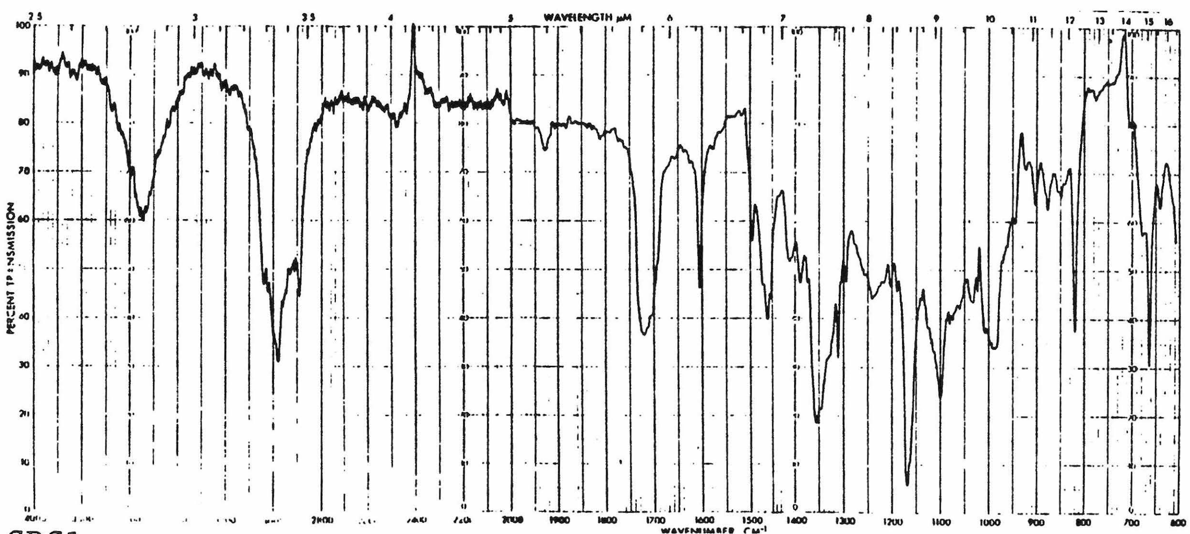


10E

CH_2Cl_2



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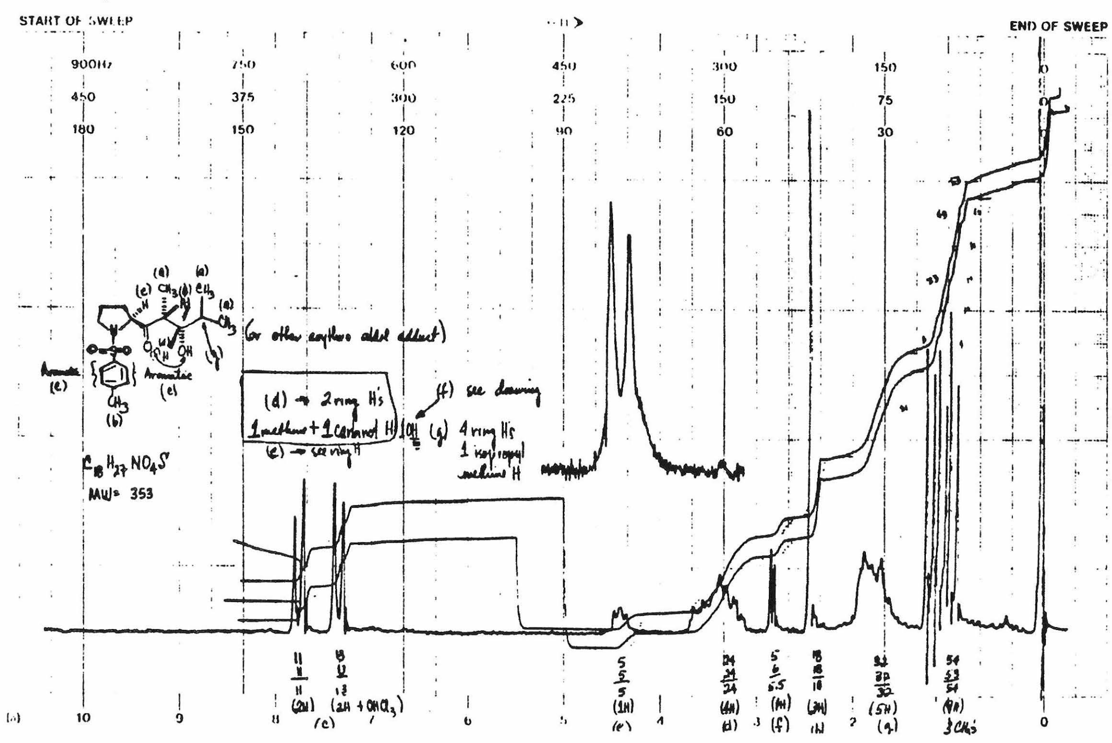

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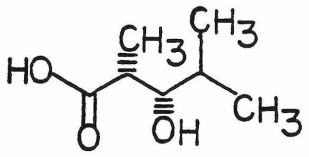
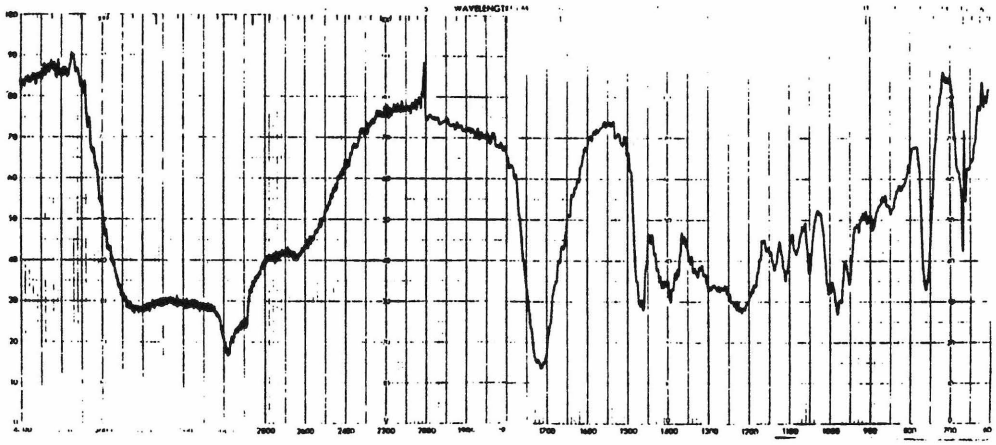


12 (boron aldol)

neat



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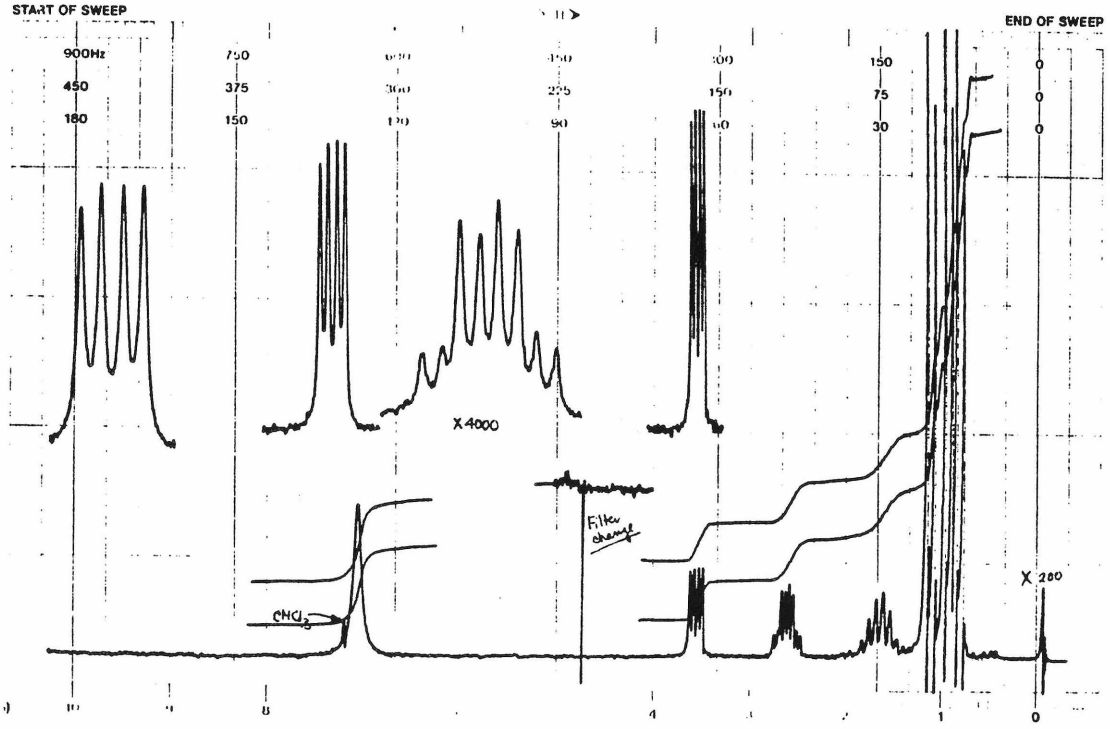

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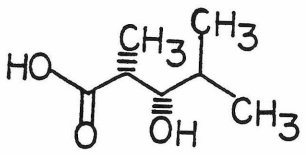
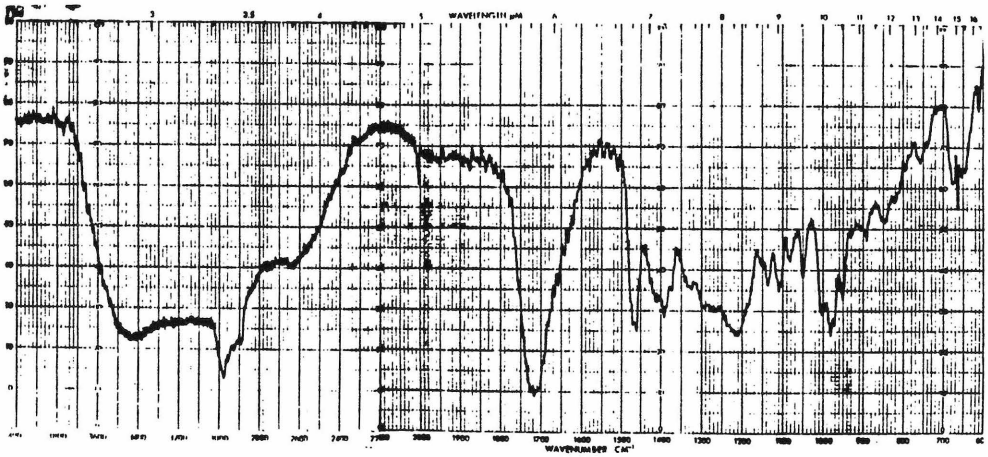


12 (Zr aldol)

neat



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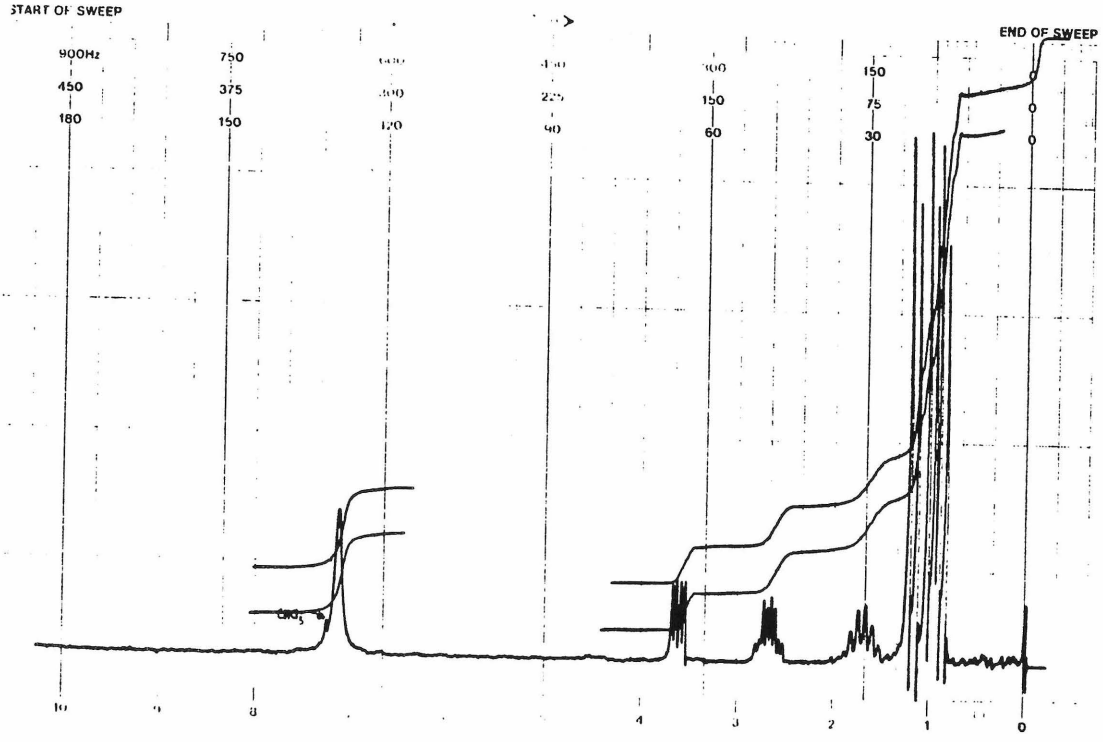

APPENDIX III

^{13}C NMR Spectral Catalog for Chapters I and II

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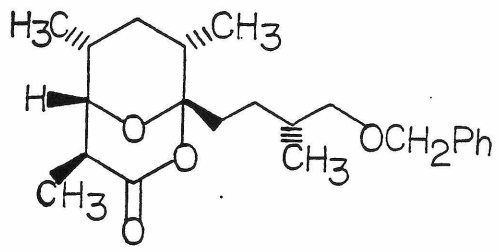

60a

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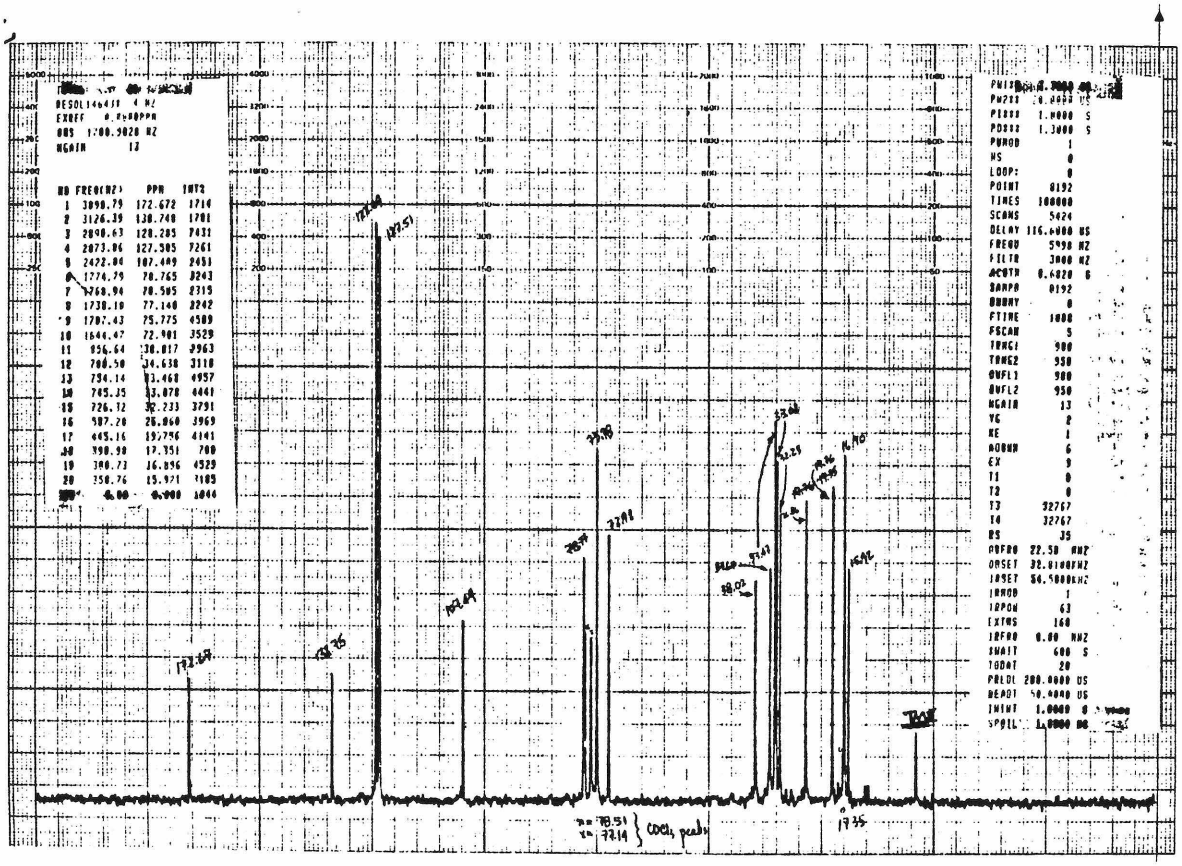

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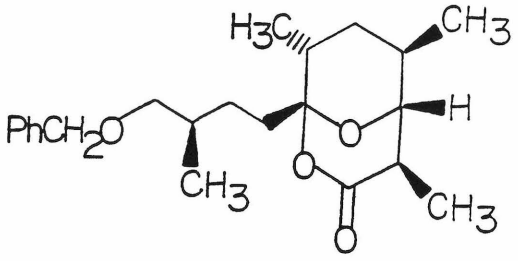

60b

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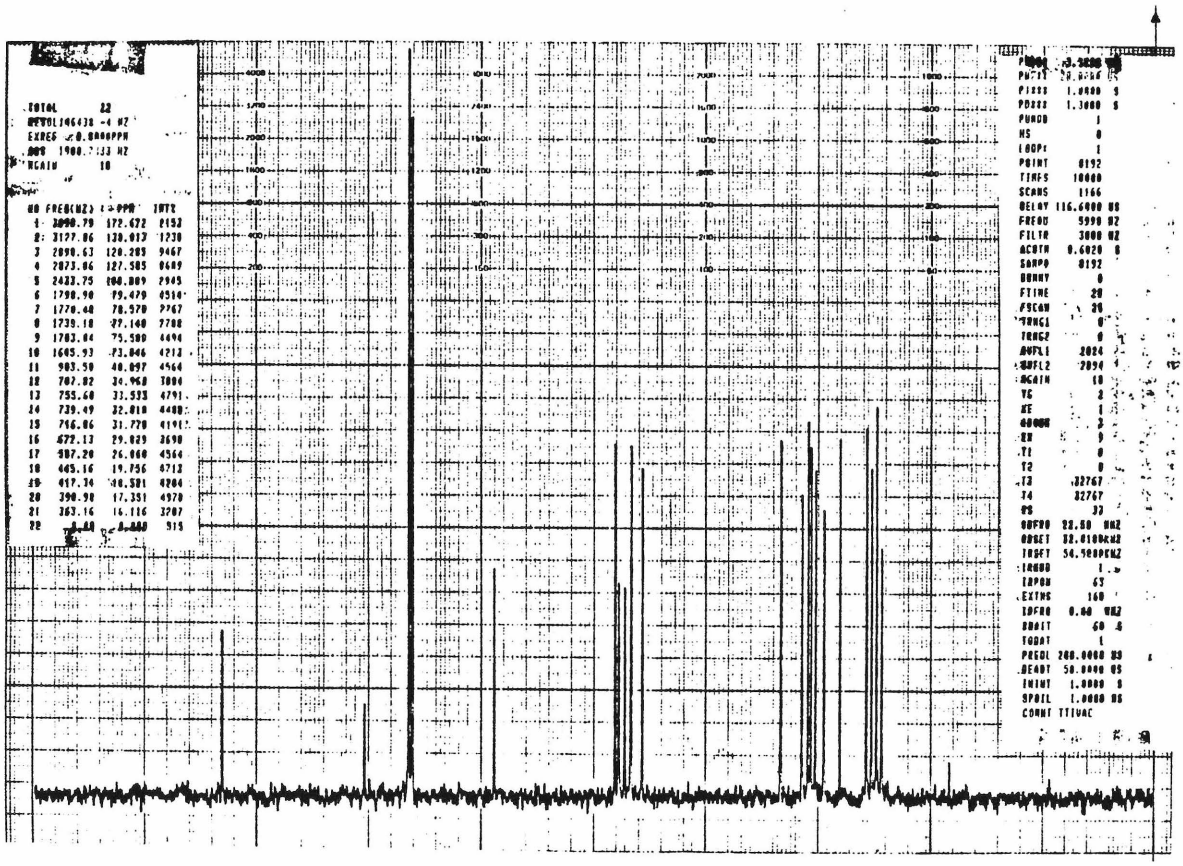

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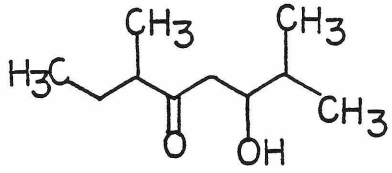
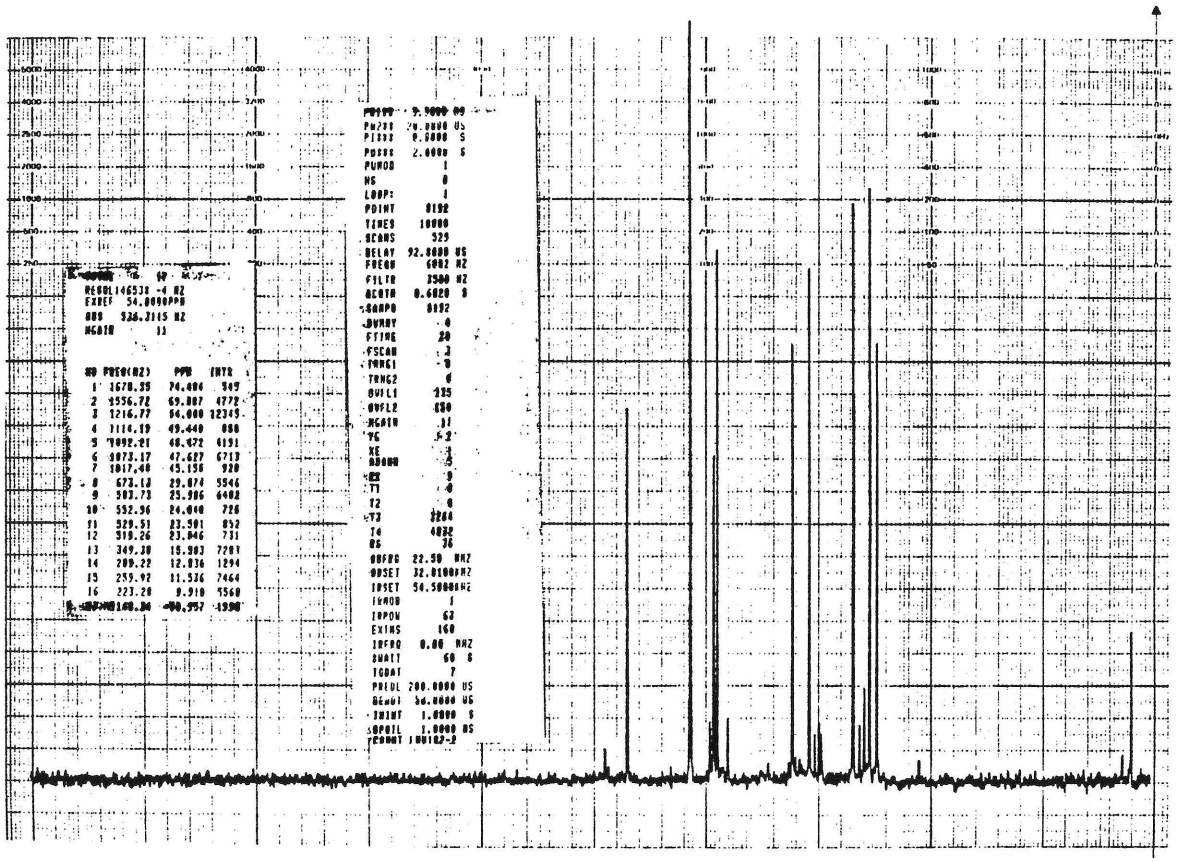


18, 19 (lithium)

CH_2Cl_2



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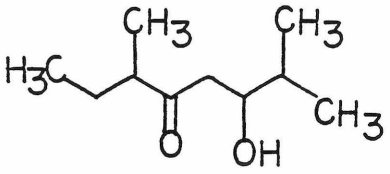

18, 19 (boron)

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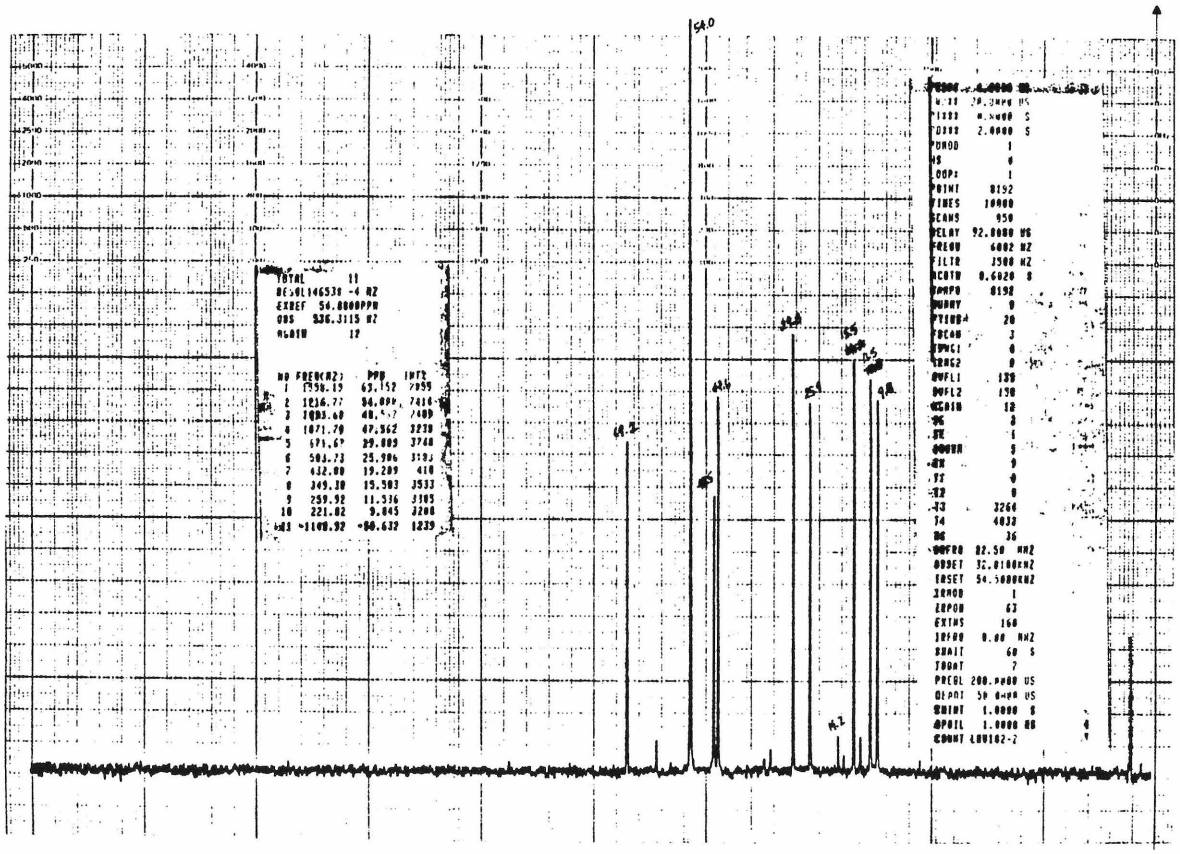

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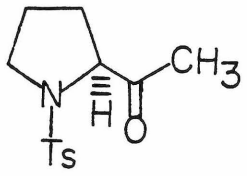
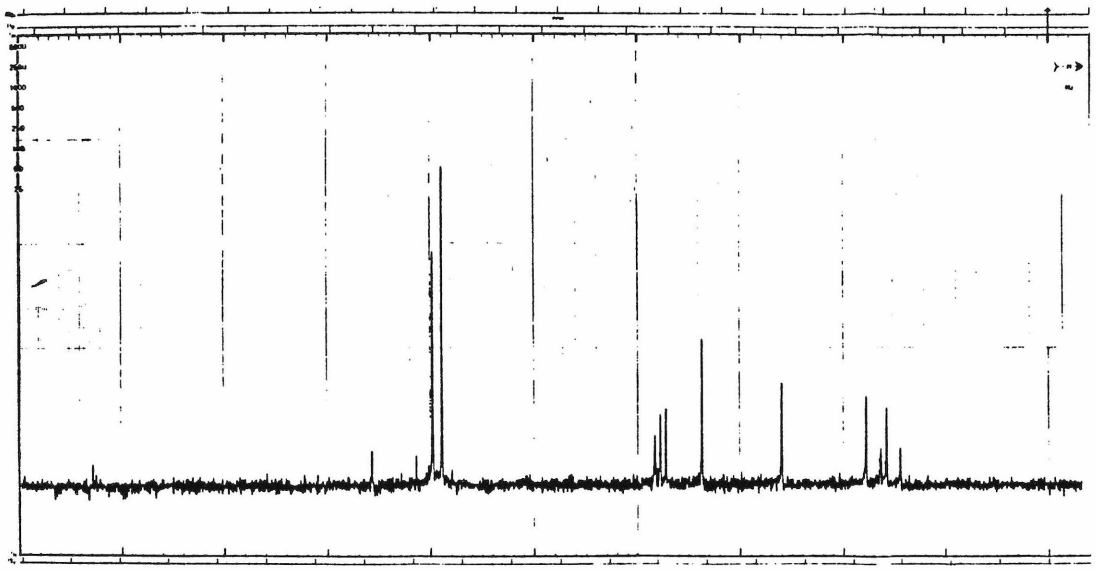


5a

$CDCl_3$



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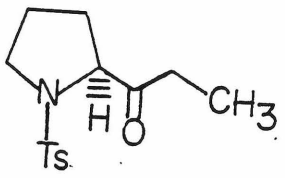

5b

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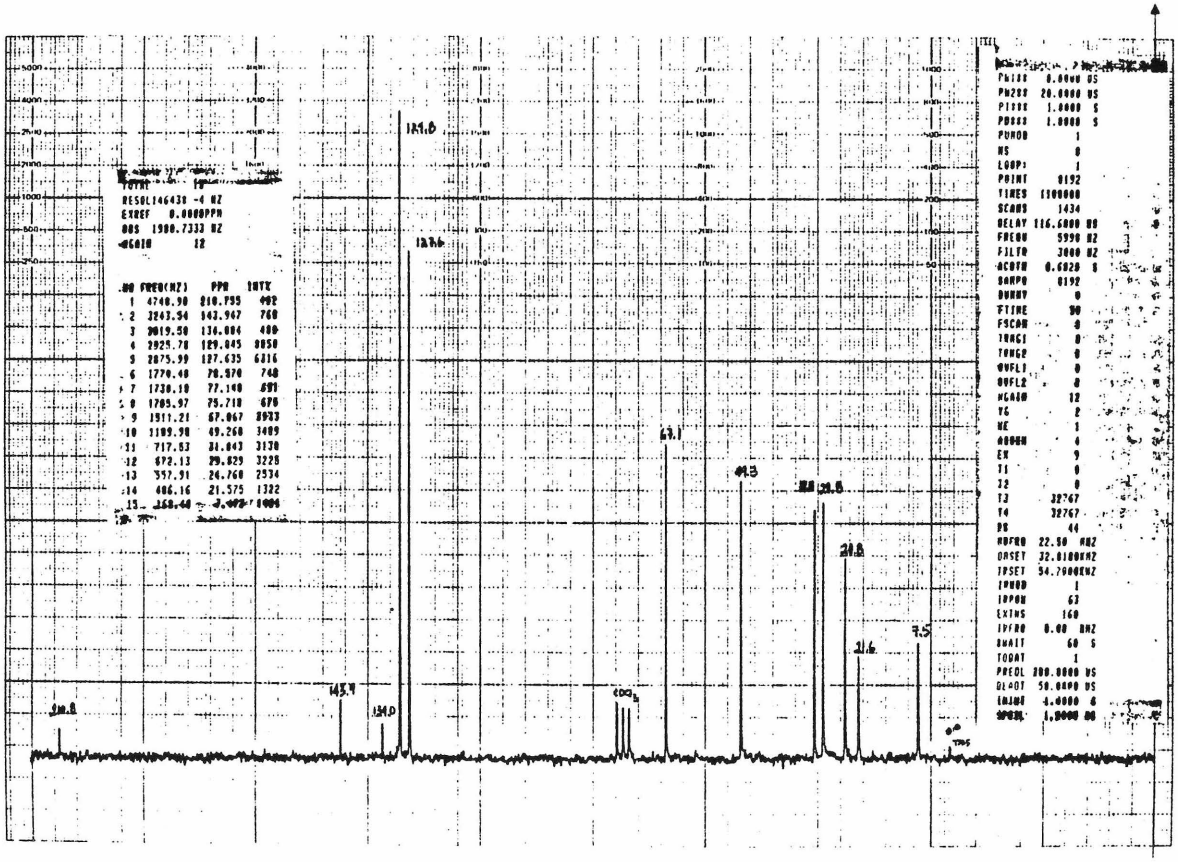

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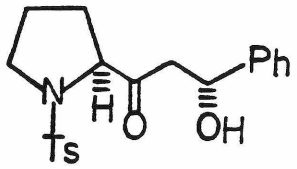
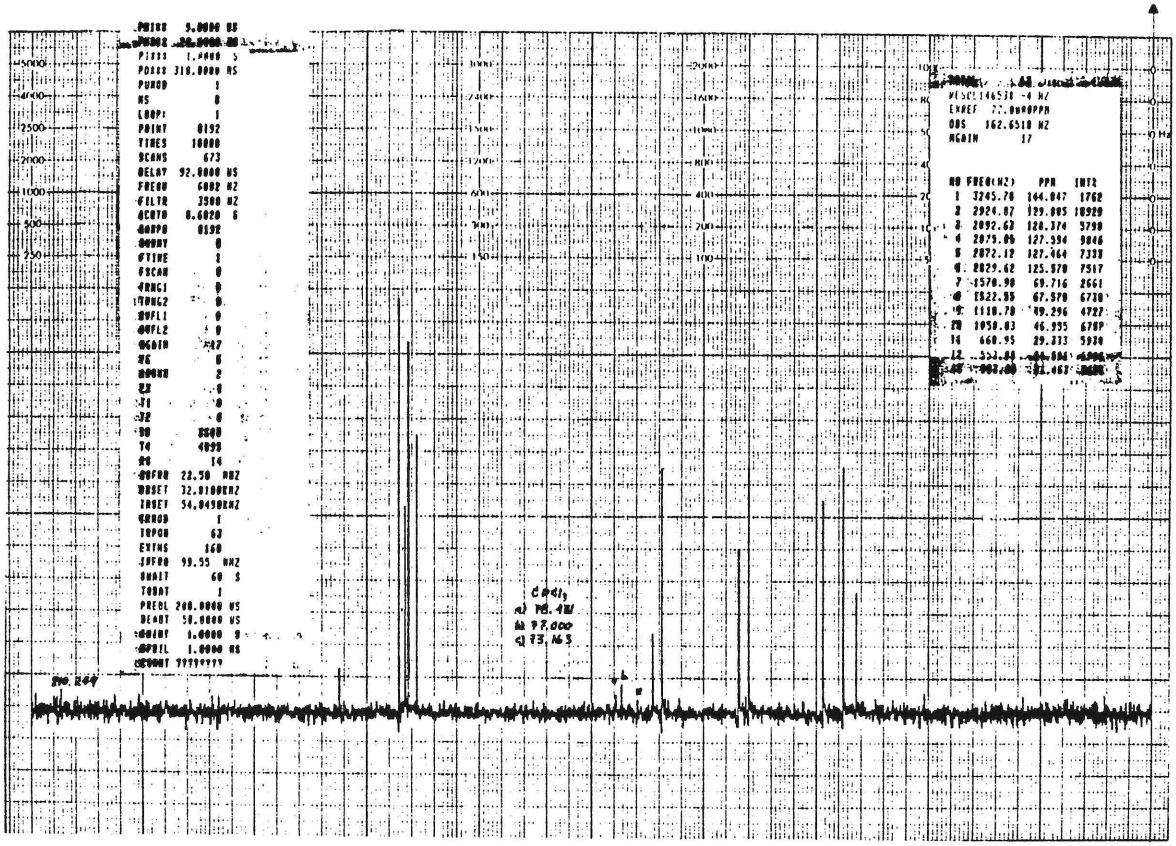


7a

$CDCl_3$



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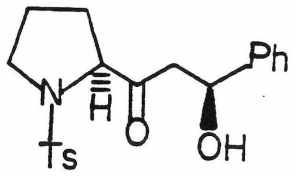
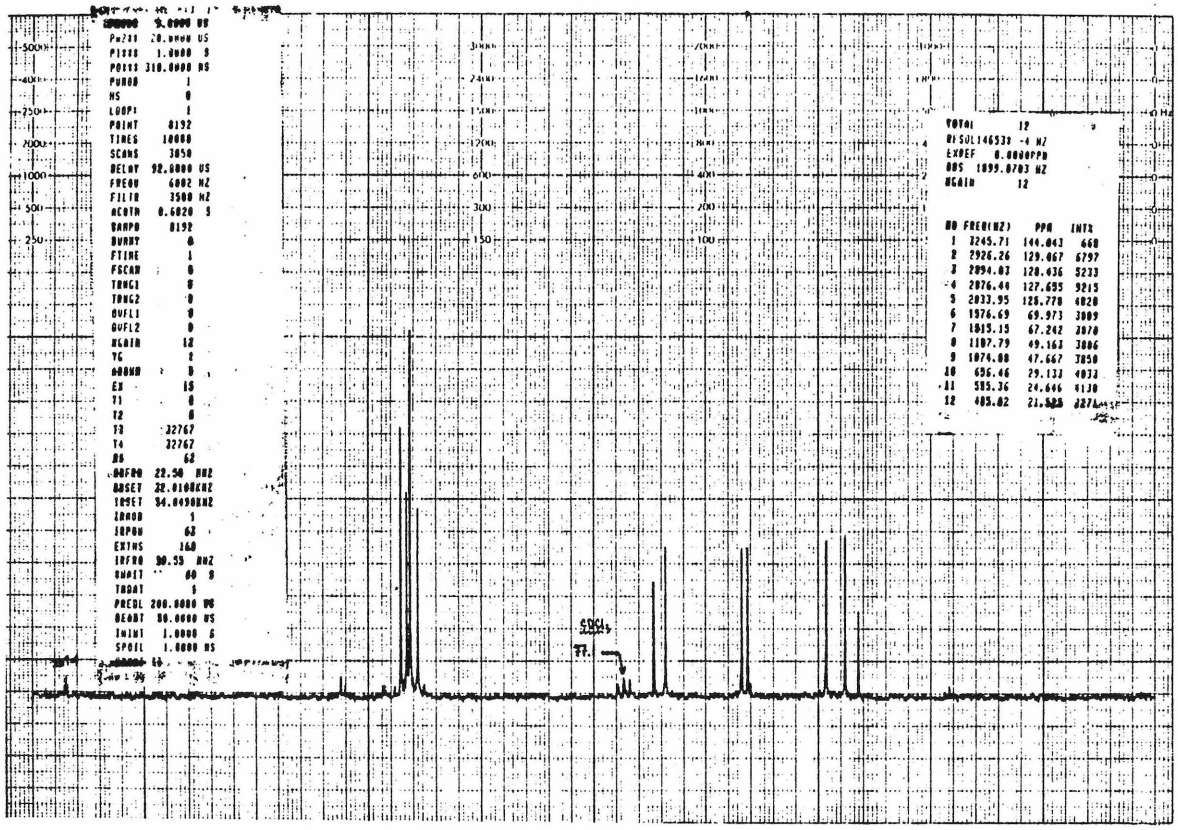


8a

$CDCl_3$



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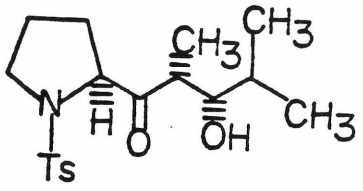
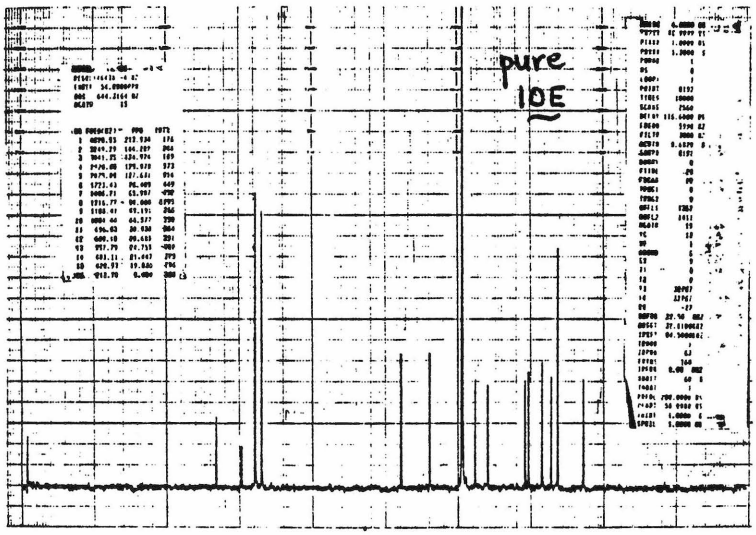
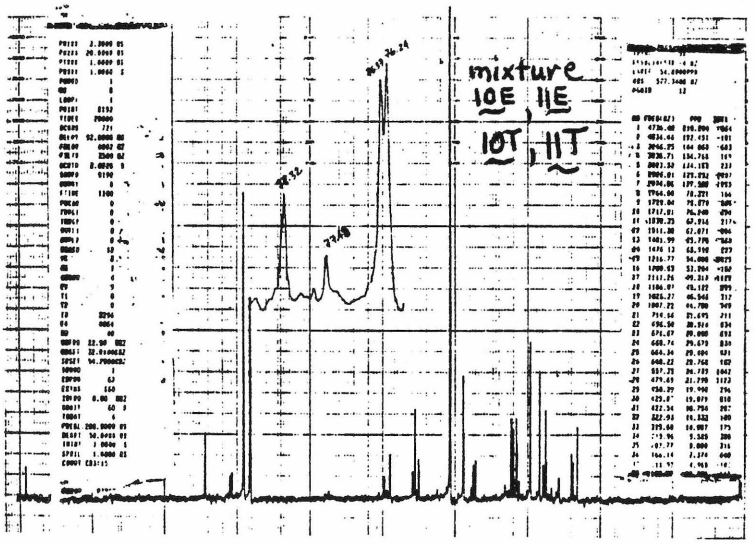


10E

CH_2Cl_2





PROPOSITIONS

ABSTRACTS

PROPOSITION I: Synthesis of the pumiliotoxin 251-D, utilizing an intramolecular S_N2' closure, is proposed.

PROPOSITION II: Enantioselective synthesis of chiral allylic alcohols and α-hydroxycarbonyl compounds via an internally-chelated Grignard reagent is proposed.

PROPOSITION III: The total synthesis of the antibiotic versiol is proposed.

PROPOSITION IV: The use of chiral ligands to induce chirality in the S_N2' reaction is proposed.

PROPOSITION V: A series of experiments are suggested to probe mechanistic aspects of the aldolase enzymes.

PROPOSITION I

Synthesis of the pumiliotoxin 251-D, utilizing an intramolecular S_N2' closure, is proposed.

* * * * * * *

A wide variety of structurally unique alkaloids have been isolated from neotropical frogs of the genera Dendrobates.[1,2] These bases, which are localized in the frog's defensive skin secretions, characteristically possess high pharmacological activity on nerve and muscle functions.[3] This physiological activity, the relatively small quantities of alkaloids available (750-1000 frogs for 20-80 mg alkaloids), and the diverse structural features have combined to attract widespread interest in these alkaloids as synthetic targets.

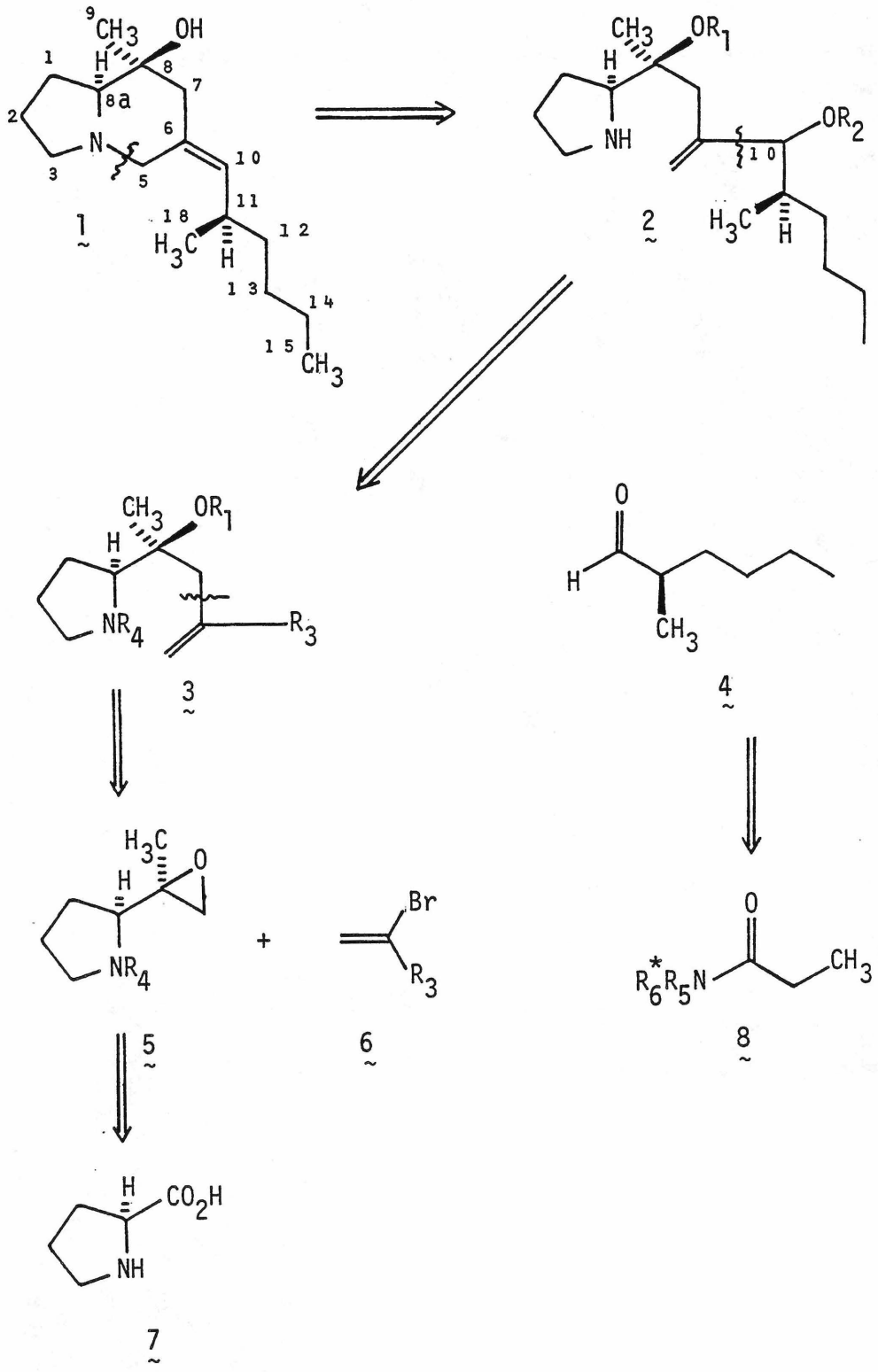
Recently, a new class of indolizidine alkaloids was isolated from these tropical frogs.[4] The structure of one of its members was elucidated utilizing X-ray and other spectroscopic techniques. The cardiac-active indolizidine alkaloid, 1 (251-D), represents the first structurally defined member of the pumiliotoxin A class of dendrobatid alkaloids. An enantioselective total synthesis of 251-D (1), employing an intramolecular S_N2' reaction to form the

indolizidine skeleton, is proposed in this report.

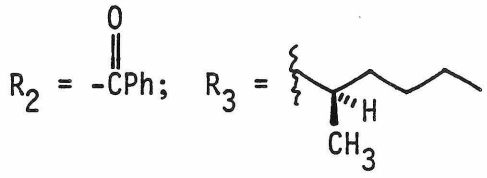
In an enantioselective synthesis of 251-D,[5] the key issues to be addressed are establishing the correct absolute configurations at the three chiral centers (C-8a, C-8, C-11) and controlling the olefin geometry. In a retrosynthetic analysis of 1, the bonds N-C_5, C_7-C_8, and C_6-C_{10} were disconnected to give the subunits 4, 5, 6 (Scheme I). In this manner, the stereocenters C-8a and C-8 could be generated from (S)-proline. The correct configuration of stereocenter C-11 should be accessible from amide 8 by using any of the chiral alkylation procedures now available.[6,7] The olefin geometry is established in the intramolecular S_N2' reaction and warrants a more detailed discussion.

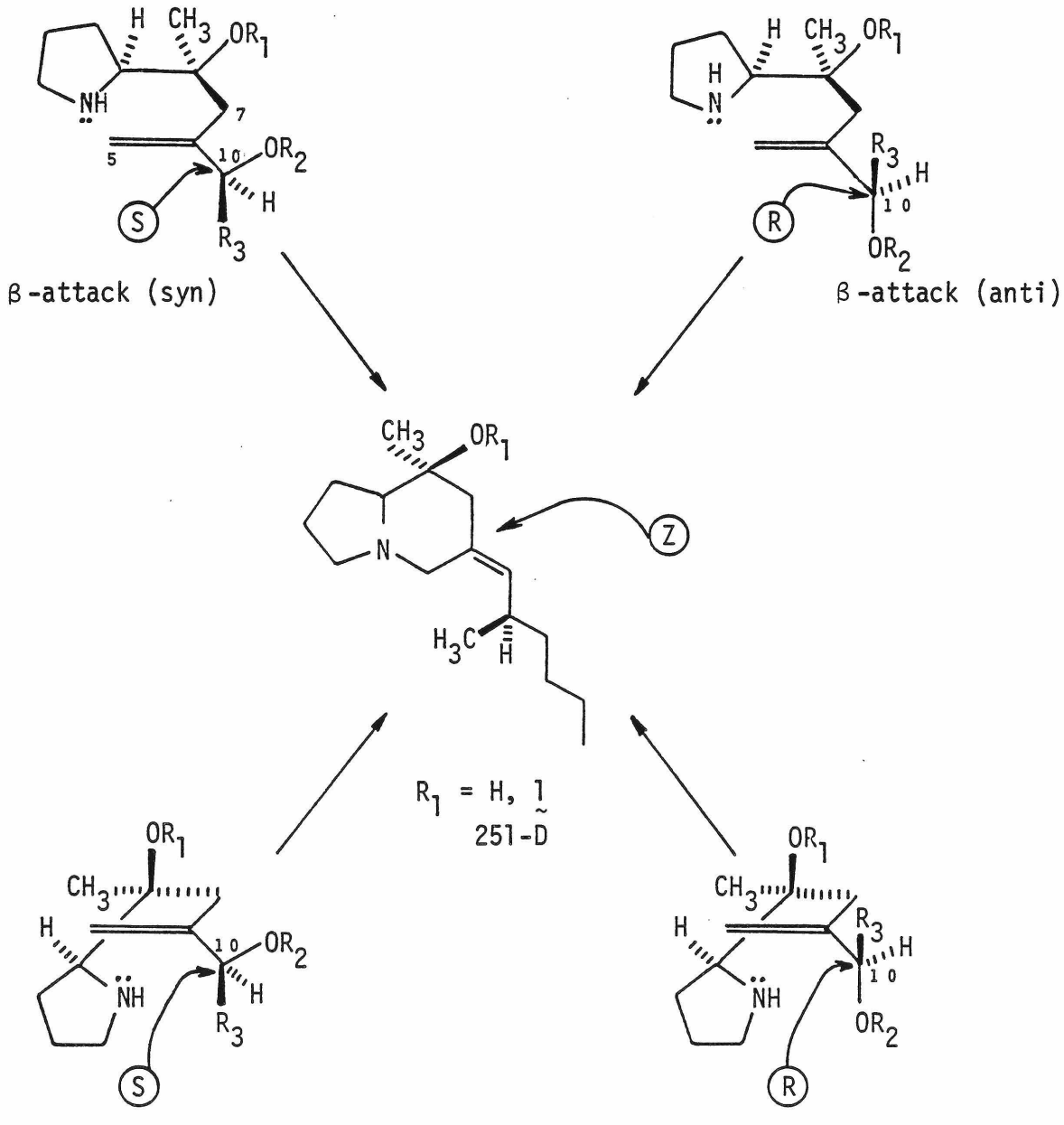
To control the olefin geometry, there are three major issues to consider in the proposed S_N2' ring closure. They are attack of the amine nucleophile on the α *vs* β face of the allylic system, syn (nucleophile and leaving group on the same side of the allylic system) *vs* anti stereoselectivity, and the absolute configuration of stereocenter C-10 in the penultimate intermediate 2 (Scheme II). These factors are interrelated, since the correct olefin geometry can be obtained in several fashions (see Scheme II). With the syn stereoselectivity of amine nucleophiles in the S_N2' reaction well-documented,[11] the correct olefin

Scheme I

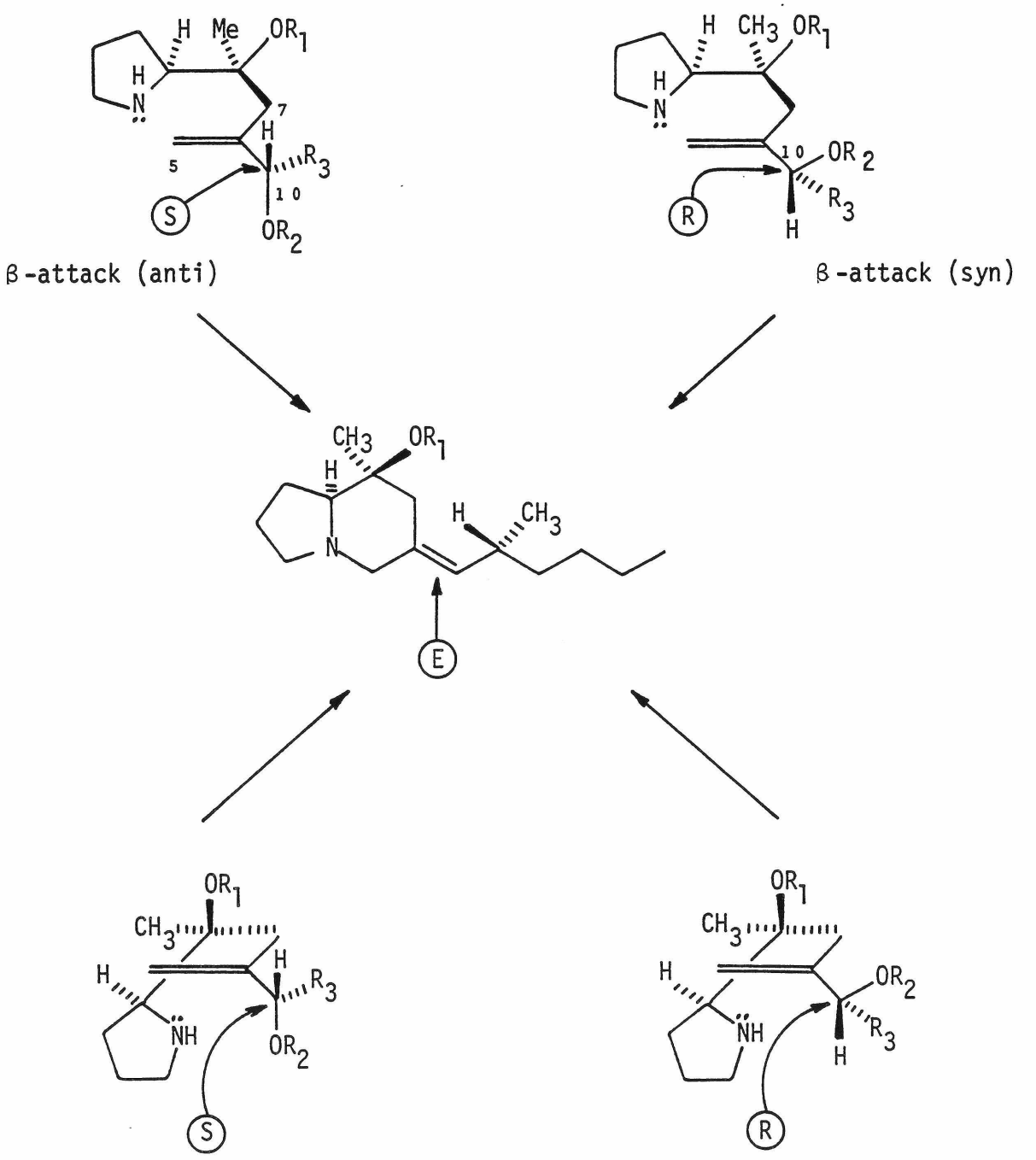


Scheme II


R2 = -CPh;
R3 =
H
CH3


β-attack (syn)
β-attack (anti)
R1 = H, 1
251-D
α-attack (anti)
α-attack (syn)

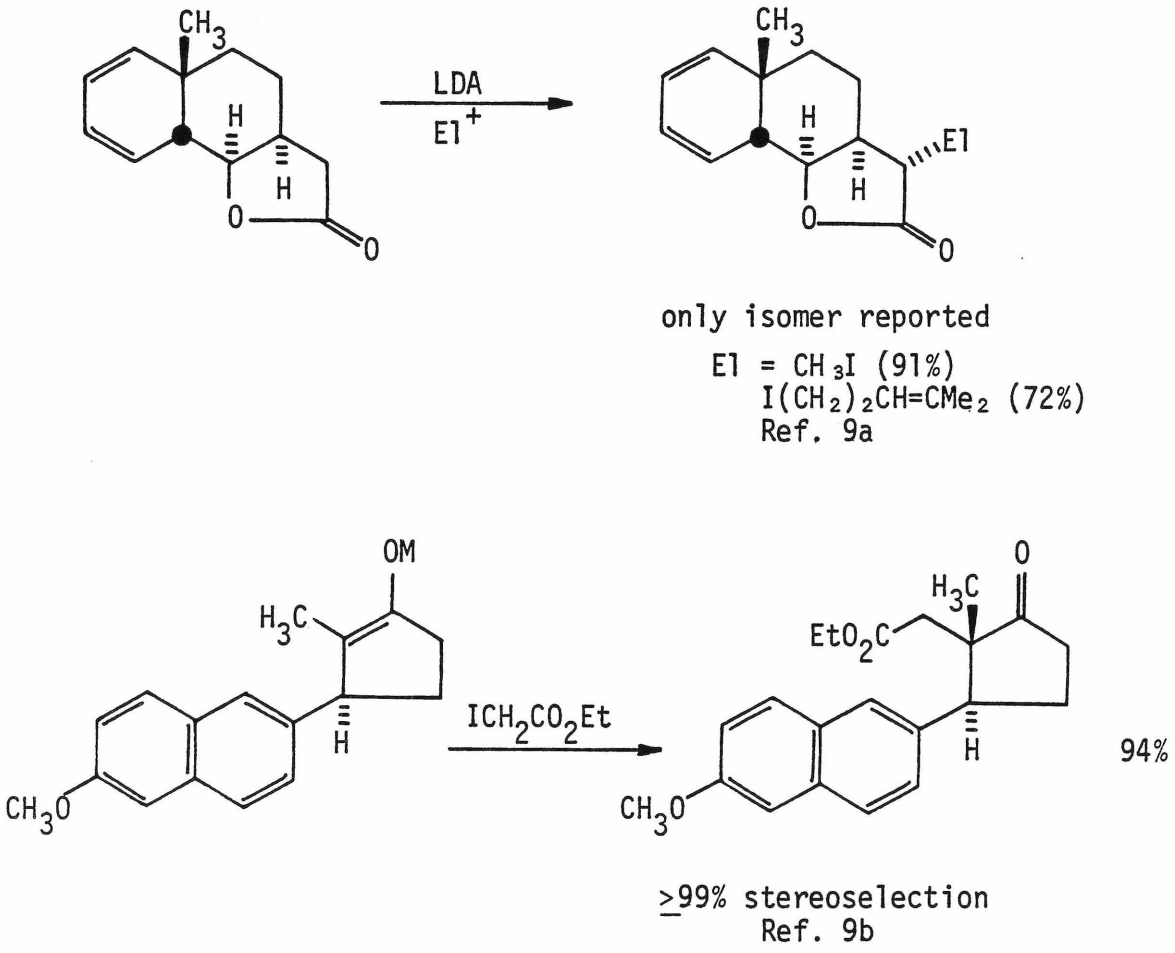
Scheme II (con'd)



geometry for 1 can be obtained by either preferential α (R-configuration at C-10) or β (S-configuration at C-10) attack. Based on the conformational bias of the indolizidine ring system (trans ring fusion favored over cis by 2.4 kcal),[8] attack of the amine on the β-face should be favored in a late transition state (product-like, the conformational bias would be strongly felt). In a kinetically controlled reaction (early transition state), β-attack may also be favored based upon the stereochemical results in alkylations of 5-membered ring enolates containing a chiral center (Scheme III). In numerous examples, the alkylation displayed high trans selectivity (new alkyl group trans to the larger ligand of the chiral centers).[9,10] In the S_N2' reaction at hand, such trans selectivity would translate to the amine nucleophile attacking the β-face of the olefin (Scheme II). It is possible that this kinetic bias may not be as strong in the intramolecular example (2) as it is in the intermolecular reactions in Scheme III. If the experimental results confirm this, then there are viable synthetic options to pursue, vide infra.

With syn stereoselectivity and β-attack, the absolute configuration required at C-10 (in 2) to obtain the correct olefin geometry is (S). This stereocenter is established in the addition of 3 (as the vinyl anion, R_3 = Li, Scheme I) to the chiral aldehyde 4. In accordance with Cram's

Scheme III



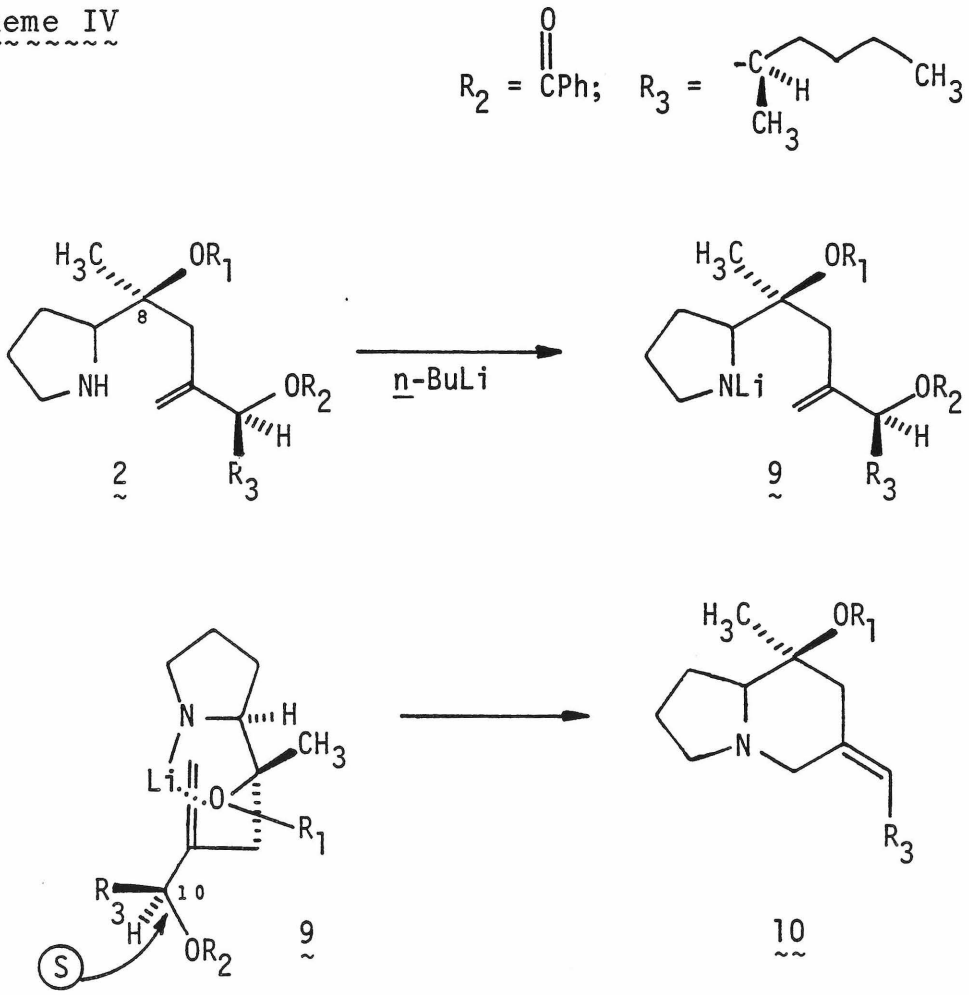
Rule,[12,13] the expected product would contain the desired (S)-configuration at C-10 (in 2, Scheme I).

Finally, one might also consider the difference in allylic strain between R_3-C_5 and R_3-C_7 in the transition state of the S_N2' closure (Scheme II). If large enough, this allylic interaction could override other steric interactions and influence the stereochemical outcome of the reaction. However, previously conducted S_N2' reactions

producing trisubstituted olefins[14] indicated this difference to be small (< 0.5 kcal) and it should have very little influence on the arguments outlined above.

If preferential β-attack of the amine is not observed (as outlined above), the proposed S_N2' reaction provides options which are of synthetic and theoretical value. By forming the anion of the secondary amine, internal chelation is possible to the suitably disposed C-8 oxygen (Scheme IV).

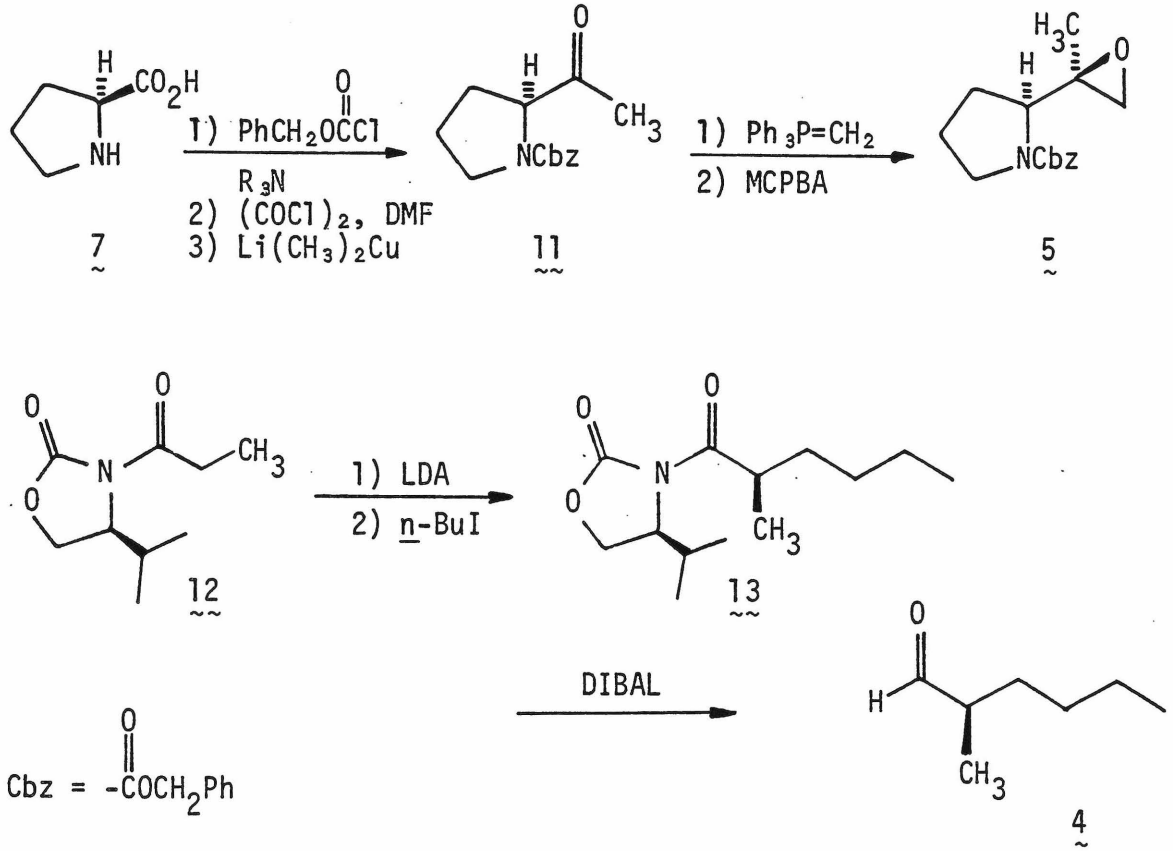
Scheme IV



This forms a pseudo-bicyclo[3.3.0]octane, a ring system which is known to be only cis-fused.[15] With this conformational constraint and the configuration of stereocenter C-8, nucleophilic attack of the anion can only occur from the β-face of the olefin (Scheme IV). If the charged nitrogen nucleophile displays the same syn stereoselectivity as the neutral amine nucleophiles, then with the (S)-configuration at C-10 (in 9, Scheme IV) the correct olefin geometry will be formed. However, charged carbon, sulfur, and oxygen nucleophiles in S_N2' reactions have demonstrated anti selectivity in some cases and syn selectivity in others.[16] Thus, this reaction provides the opportunity to study the syn vs anti selectivity of a charged nitrogen nucleophile in the S_N2' process. After these experiments are conducted, the absolute configuration at C-10 (in 9, Scheme IV) can be adjusted in accordance with the results [(S) for syn; (R) for anti] to obtain the requisite olefin geometry for 251-D.

With these stereochemical arguments in hand, the syntheses of the requisite subunits 4 and 5 are outlined in Scheme V. After protection of the amine as a carbamate ($PhCH_2O\overset{O}{\overset{\|}{C}}Cl$, R_3N), the carboxylic acid can be converted into the acid chloride with oxalyl chloride in DMF.[17] Treatment of the acid chloride with lithium dimethyl cuprate[18] should give the ketone 11. After olefination ($Ph_3P = CH_2$),

Scheme V

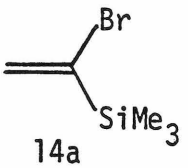


the epoxide 5 can be formed by epoxidation. Examination of Dreiding models reveals some preference for the formation of the desired epoxide. Conceivably, if the wrong epoxide is formed (predicted to be minor), then it could be removed chromatographically. This early in the synthesis (coupled with the overall convergency of the approach), such a mixture would not be a critical loss.[19]

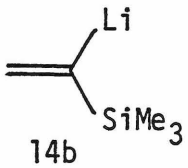
Preparation of the aldehyde subunit 4 is relatively straightforward. Alkylation of the lithium enolate (LDA) of oxazolidinone 12 with n-butyl iodide should provide

the alkylated product 13 in >90% ee.[20] Subsequent reduction of 13 with DIBAL would afford the desired aldehyde 4.[20,21]

To assemble the subunits, 4 and 5 requires a 1,1-vinyl dianion equivalent (Scheme VI). The known compound, 1-bromo-1-trimethylsilylethene 14a,[22] should provide such a reactivity pattern. Treatment of epoxide 5 with the



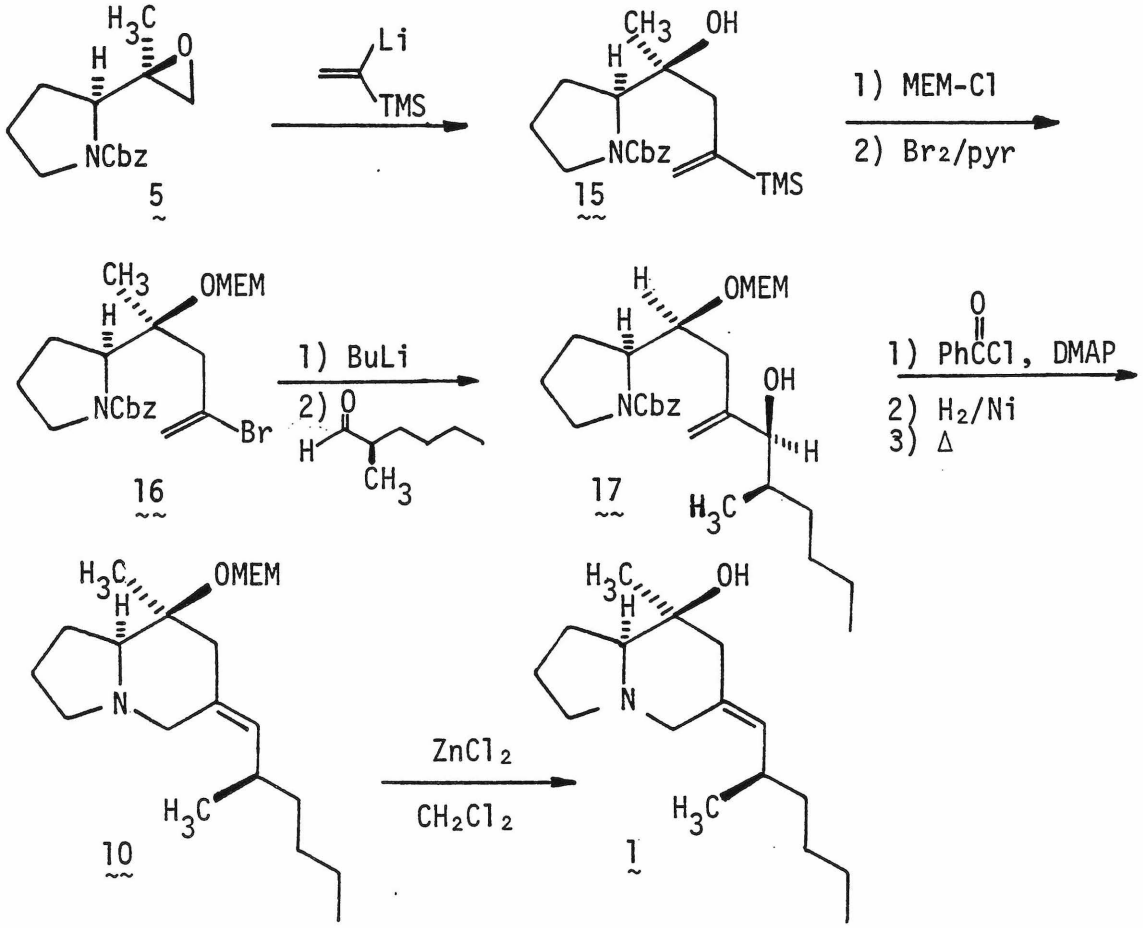
14a



14b

lithium anion 14b, formed by metal-halogen exchange of 14a with n-butyllithium, would open the epoxide to afford alcohol 15. Protection of the alcohol as the MEM ether (MEM-Cl, iPr_2NEt)[23] followed by bromination of the olefin and debromosilylation[24] would give vinyl bromide 16. Metal-halogen exchange (n-butyllithium, -100°C) to provide the vinyl anion and quenching with aldehyde 4 should afford the desired allylic alcohol 17 (only the predicted Cram product is pictured). After protection of the alcohol as a benzoate ester (PhCOCl, DMAP), the carbobenzoxy group could be removed by catalytic hydrogenolysis (H_2, Pd or Ni catalyst) to provide the free amine 2. Heating this substrate may be necessary to promote the S_N2' closure to afford indolizidine 10. Removal of the MEM

Scheme VI



protecting group ($ZnBr_2$, CH_2Cl_2)[23] would provide 251-D, 1.

In closing, an enantioselective synthesis of a recently isolated pumiliotoxin, 251-D (1), is proposed. The stereocenters C-8, C-8a, and C-11 would be generated through the use of chiral starting materials (proline) or chiral alkylation procedures. The double bond geometry would be controlled by an intramolecular S_N2' reaction.

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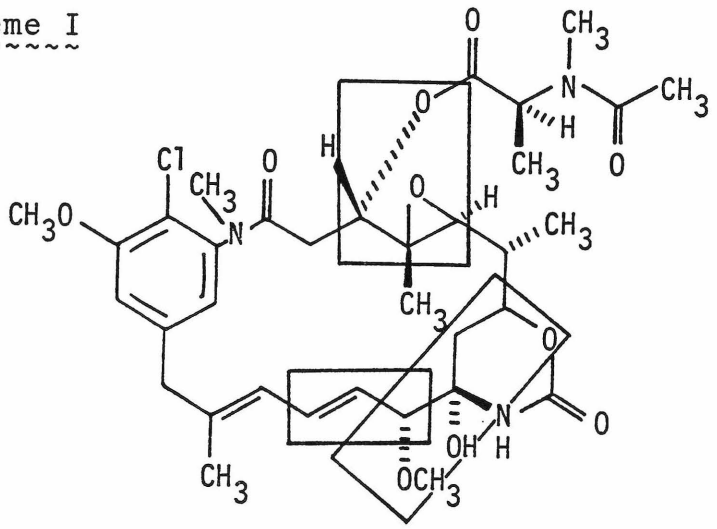
PROPOSITION II

Enantioselective synthesis of chiral allylic alcohols and α-hydroxycarbonyl compounds via an internally-chelated Grignard reagent is proposed.

* * * * * * * *

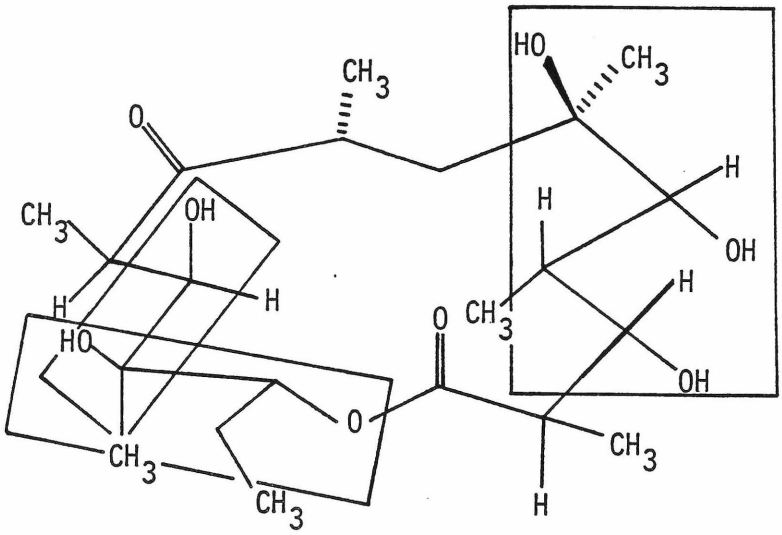
Recently, the natural product classes of macrolides,[1] polyether antibiotics,[2] and ansamycins,[3] have received considerable attention as potential synthetic targets due to their wide range of biological activity and their complex and unique structures. These compounds characteristically contain several asymmetric stereocenters and are highly-oxygenated. In the few existing syntheses of representative members of these classes of natural products,[4,5] a major stereochemical issue involved the stereoselective generation of hydroxyl-bearing stereocenters in 1,2-, 1,3-, and 1,4-relationships (Scheme I). In several approaches, chiral allylic alcohol and α-hydroxycarbonyl subunits were utilized to establish the appropriate stereorelationships, but the preparation of these chiral building blocks usually required a resolution. Allylic alcohols (1) and α-hydroxycarbonyl compounds (2) may be

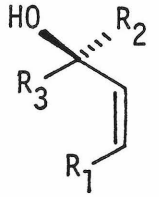
Scheme I



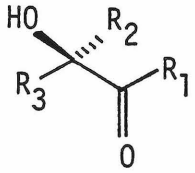
Maytansine

Erythronolide B





1

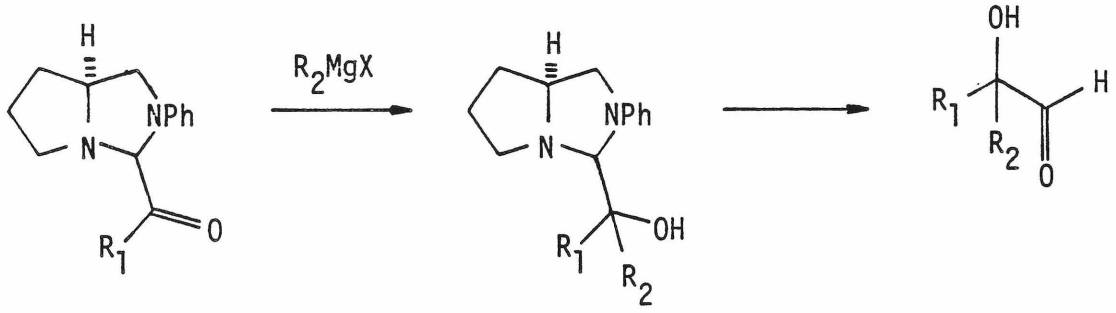


2

useful in other natural product syntheses as well (i.e., insect sex pheremones), if they could be easily attained in optically active forms.

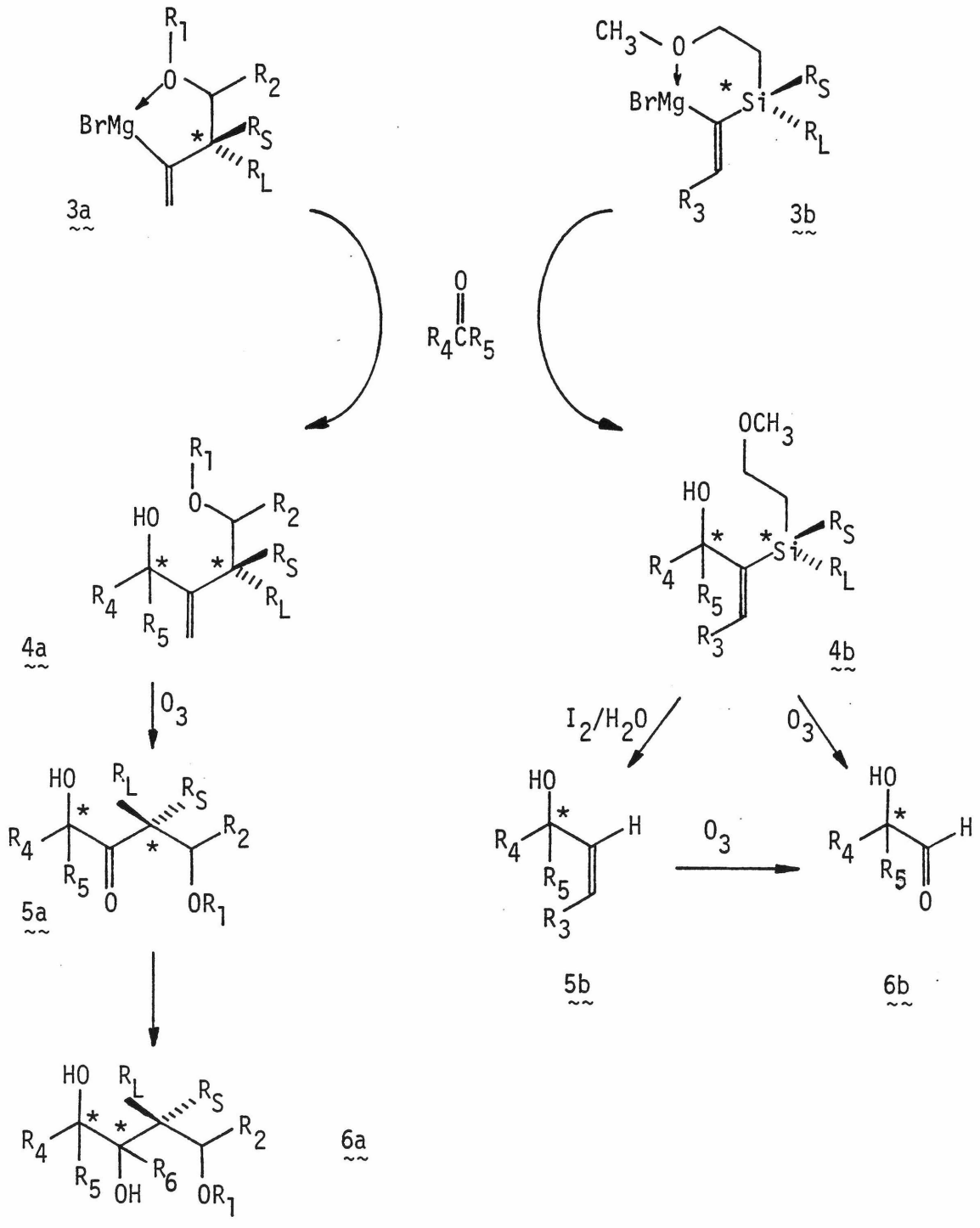
Mukaiyama has recently developed a procedure for the preparation of chiral α-hydroxyaldehydes (Scheme II).[6] The optical yield is excellent for R_1 or R_2 = Ph, but the optical purity declines when R_1,R_2 = alkyl. Sharpless has also prepared optically active vicinal-diols but the optical yields are generally less than 60%.[7,24] It is envisaged that this general class of chiral substrates (1 and 2) can be stereoselectively generated from the addition of optically active Grignard reagents (3a, 3b) to aldehydes and ketones (Scheme III).

Scheme II



Scheme III

R_S = small ligand; R_L = large ligand



The Grignard reagents 3a and 3b provide a highly ordered environment via an internal chelation of Mg by oxygen. The asymmetry of this environment is provided by the α-chiral center. The two sides of the reagent can be easily differentiated by appropriate R_S (small) and R_L (large) groups (Scheme III). Additionally, location of the chiral center α to the reaction site should provide maximum interaction with the carbonyl substrate and afford high levels of asymmetric induction, vide infra.

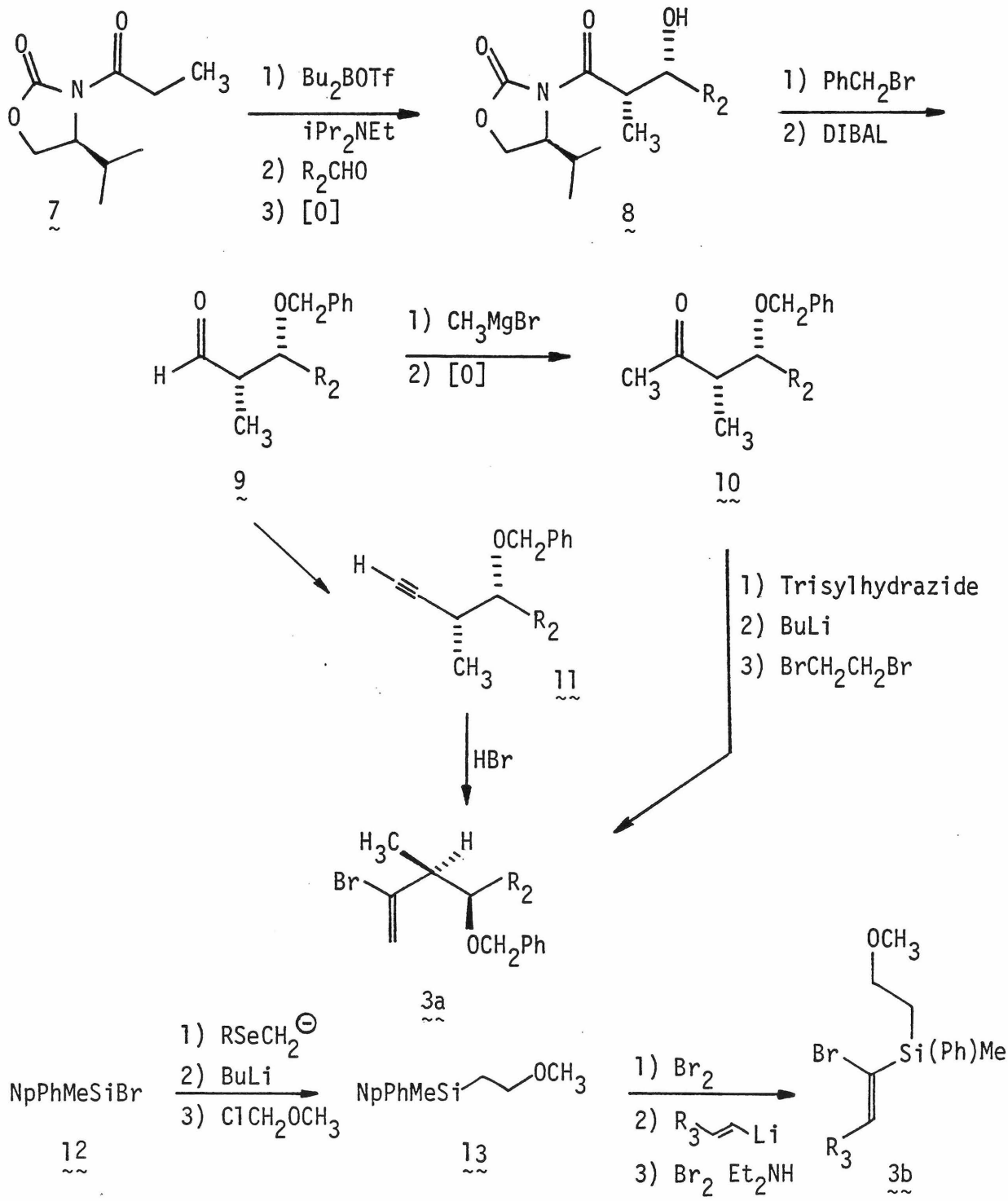
The two types of Grignard reagents (carbon and silicon at the chiral centers) were selected to provide access to several types of chiral compounds. Addition of 3a to aldehydes or ketones would give allylic alcohols of general structure 4a, which, after hydroxyl protection, could easily be converted to ketones 5a (Scheme III). A method recently developed by Still et al.[8] would provide for the transformation of ketones 5a into triols 6a in high stereoselection. By employing a chiral silicon α to the Grignard reagent, the various reactions of vinylsilanes[9] would be available to the addition product 4b (Scheme III). For example, the silicon could be replaced with a proton to afford allylic alcohol 5b. Optically active α-hydroxyaldehydes (6b) could be obtained by ozonolysis of 5b or 4b after appropriate protection.

The syntheses of the requisite vinyl bromides 3a and

3b are relatively straightforward and an example of each class (carbon and silicon chiral centers) is outlined in Scheme IV. Aldol condensation of the aldehyde R_2-CHO (R_2 = alkyl, aromatic) with optically active oxazolidone 7 (Bu_2BOTf, iPr_2NEt, -78°C) would afford aldol adduct 8 in excellent diastereoselection (≥98% ee).[10] Protection of the hydroxy group followed by reduction with DIBAL should give aldehyde 9[11] which could be converted to acetylene 11 by standard methods (CBr_4, Ph_3P, Zn, CH_2Cl_2).[12,13] Addition of HBr to acetylene 11 should afford vinyl bromide 3a (R_1 = CH_2Ph, R_S = H, R_L = CH_3, Scheme IV).[23] Synthesis of vinyl bromide 3b would start with the known, optically active silicon halide 12[14] (Scheme IV). Formation of the α-lithiated silane from 12 by literature procedure[15] and subsequent treatment with chloromethyl methyl ether would afford ether 13.[16,17] Removal of the naphthyl (Np) group by bromination,[18] displacement of the resulting silicon bromide with vinyllithium reagents (R_3 = alkyl, H) and treatment of the subsequent vinylsilane with bromine followed by an amine base would give the desired, optically active vinyl bromide 3b (R_S = CH_3, R_L = Ph, Scheme IV).[19,20] A route to vinyl bromide 3b with larger steric differentiation between R_S and R_L is outlined in Scheme V.

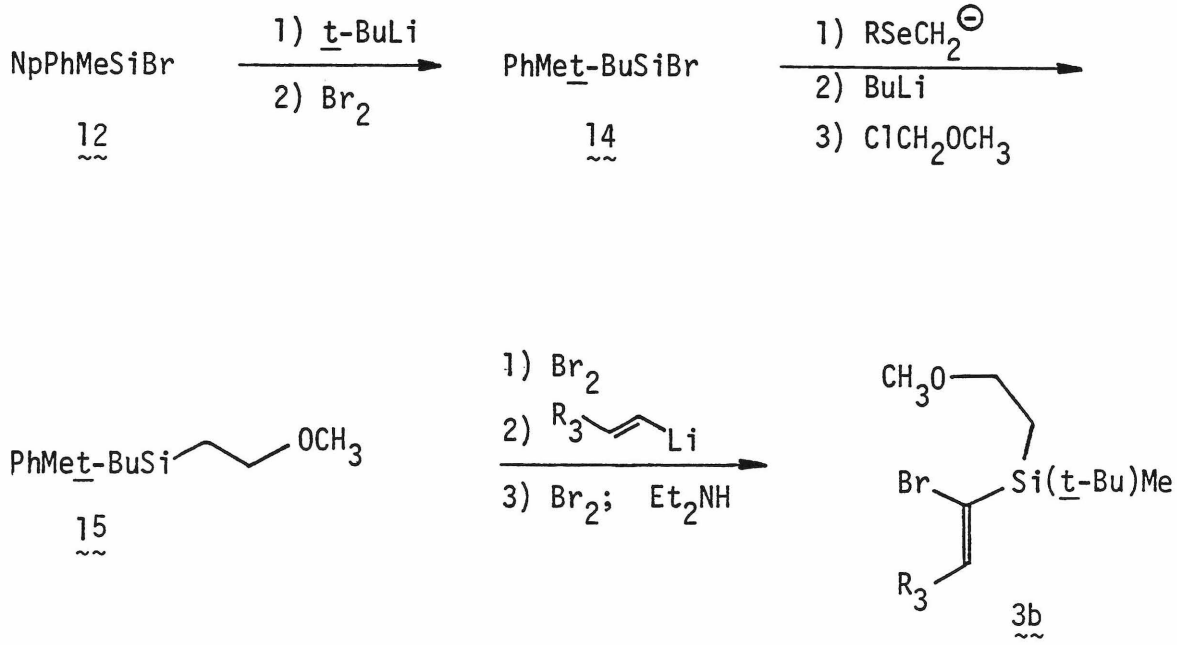
In order to predict the magnitude and direction of asymmetric induction expected with Grignard reagents 3a and

Scheme IV



(Np = naphthyl)

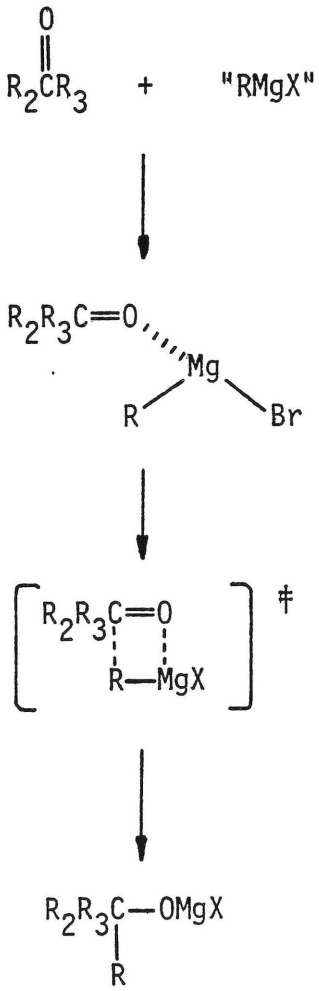
Scheme V



3b, one must develop a transition state model based on the mechanism of the addition of Grignard reagents to carbonyl substrates. Although the exact mechanism of the Grignard reaction may not be known, Ashby[21] has presented good evidence on several facets of the mechanism: 1) the reaction is first order in organomagnesium compound; 2) under the right experimental conditions (< 0.1 M RMgX in ether, X = Br) the reacting species is monomeric RMgX and R_2Mg; and 3) a polar, 4-centered transition state (with prior complexation of carbonyl oxygen to Mg of the reacting species, (Scheme VI) is proposed for addition of vinyl Grignard reagents to

non-aromatic ketones and aldehydes (no single electron transfer occurs or if the radical does form, it couples so quickly to carbonyl carbon as to be undetectable. For vinyl Grignards the coupling reaction would have to occur with a rate constant of about 10^{10}-10^{11} sec^{-1} -- nearly indistinguishable from a polar process).

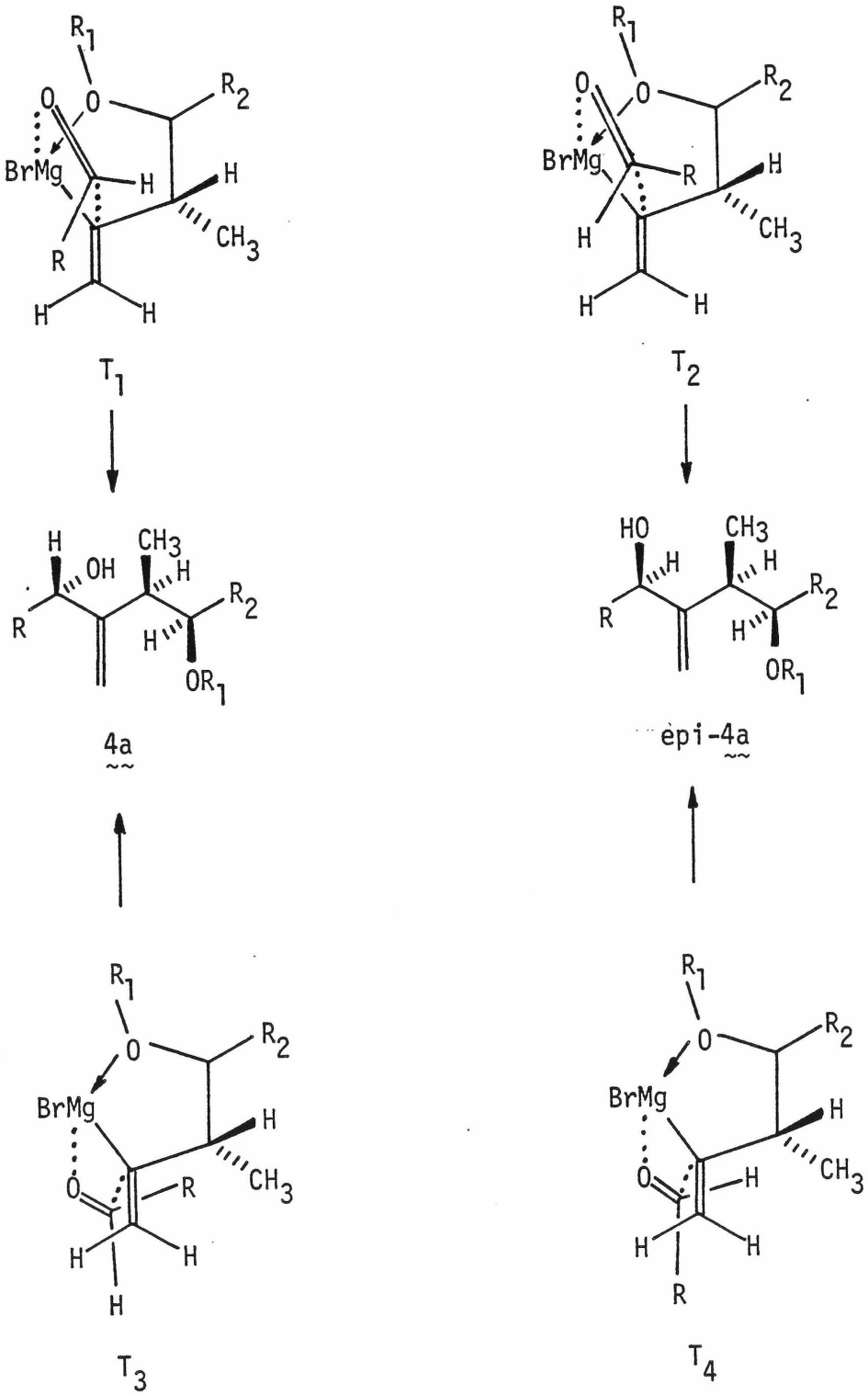
Scheme VI



With these mechanistic points in mind, there are four possible diastereoisomeric transition states to consider in the addition of vinyl Grignards 3a or 3b to carbonyl substrates (Scheme VII).[22] The aldehyde (or ketone) should approach and complex from the least sterically-hindered face of the Grignard complex (T_1, T_2 favored over T_3, T_4; Me *vs* H). Reaction from that approach would be expected to occur from T_1 since the steric interactions between the aldehyde and chiral center would be minimized [H ↔ H < H ↔ R (alkyl)]. The predicted product from favored transition state T_1 would be alcohol 4a. The exact magnitude of the asymmetric induction is difficult to predict, but placement of the chiral center α to the site of reaction allows for maximum interaction of the chiral center and the incoming substrate (see $T_1 \rightarrow T_4$, Scheme VII). In addition, the success of Mukaiyama's procedure to synthesize optically active α-hydroxyaldehydes (Scheme II) depends upon prior complexation of Mg to both the carbonyl oxygen *and* the pyrrolidine nitrogen.[6] In cases where R_1 or R_2 = Ph, this system works well (≥ 95% ee).

The proposed study of internally-chelated anions (3a, 3b) could easily be extended to study the effects of metals other than magnesium (i.e., Cu, Li) on the course of the reaction. The experimental results with these metals,

Scheme VII


R1
O
O
R2
BrMg
H
H
CH3
R
H
H
T1
R1
O
O
R2
BrMg
R
H
H
CH3
H
H
T2
H
OH
CH3
H
R
R2
H
OR1
4a
HO
CH3
H
H
R
R2
H
OR1
epi-4a
R1
O
R2
BrMg
H
O
R
CH3
H
H
H
T3
R1
O
R2
BrMg
H
O
H
CH3
H
H
R
T4

successful or unsuccessful, might provide valuable information on the mechanism of 1,2-addition of organometallics to carbonyl substrates. Nevertheless, study of the Grignard reagents, 3a and 3b should prove useful for organic synthesis. If the asymmetric induction is highly successful with these reagents, then these reactions would provide a general procedure for the synthesis of optically active allylic alcohols and α-hydroxyaldehydes and ketones.

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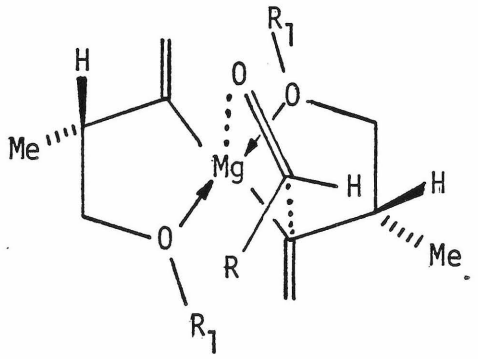
(18) Sommer, L. H.; Michael, K. W.; Korte, W. D. J. Am. Chem. Soc. 1967, 89, 868-875.

(19) Ottolenghi, A.; Fridkin, M.; Zilkha, A. Can. J. Chem. 1963, 41, 2977-2982.

(20) Although several displacements on the optically active silicon center are proposed, these reactions have been demonstrated to occur with excellent stereoselectivity (inversion or retention depending upon the nucleophile), see Refs. 14, 18, 16.

(21) Ashby, E. C. Pure & Appl. Chem. 1980, 52, 545-569, and references cited therein.

(22) For convenience the transition states are drawn with RMgX as the reacting species. If R_2Mg is the reactive species, then the arguments presented above should still be sound, but the transition state may look like the following:



If necessary, reaction via R_2Mg could be suppressed by the addition of excess MgX_2 -- see Ref. 21.

(23) Alternatively, 3a could be prepared via the trisylhydrazone of ketone 10 as outlined in Scheme IV.

(24) Sharpless has recently published an asymmetric epoxidation procedure with high enantioselectivity. This allows the facile introduction of one hydroxyl-bearing stereocenter, but the procedure is limited to allylic alcohol substrates. Katsuki, T.; Sharpless, K. B. J. Am. Chem. Soc. 1980, 102, 5974-5976.

PROPOSITION III

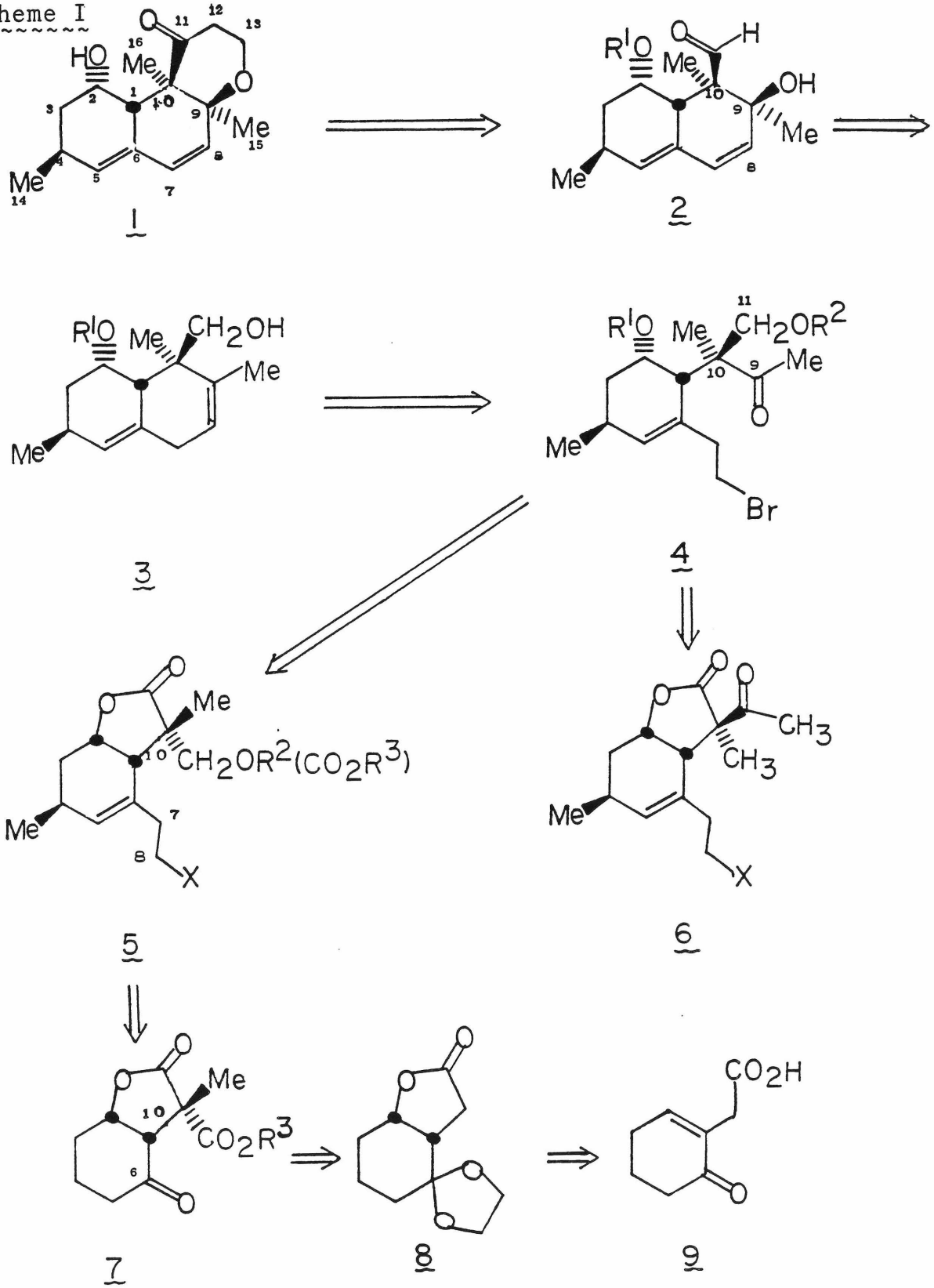
The total synthesis of the antibiotic versiol is proposed.

* * * * * * * *

McGahren and coworkers have recently isolated several antifungal agents from Sporormia affinis.[1] One of the more interesting molecules is versiol (1, Scheme I), which displays activity against a number of pathogenic fungi.[2] Interestingly enough, versiol was also isolated as a metabolite of the mold Aspergillus versicolor by Fukuyama et al.[3] The structure and absolute configuration of versiol were conclusively determined by X-ray techniques in 1978.[3] Among the unique structural features of versiol are the C-9 and C-10 quaternary centers. Such centers are rare in polyketide derived antibiotics.[1] This proposition suggests a synthesis of versiol which employs an intramolecular Wittig reaction to aid in establishing the two quaternary centers.

In an analysis of (1) there are three key stereochemical issues to consider (see 1, Scheme I); namely, establishing the A-ring stereocenters (C-1, C-2, C-4) relative to each other, relating the two quaternary stereo-

Scheme I


HO
Me
16
11
12
13
1
2
3
4
5
6
7
8
9
10
Me
15
Me
14
1
R¹O
Me
H
O
OH
10
9
Me
Me
8
2
R¹O
Me
CH2OH
Me
Me
3
R¹O
Me
11
CH2OR2
10
9
Me
Me
O
Br
4
Me
10
CH2OR2(CO2R3)
Me
7
8
X
5
R¹O
Me
CH3
CH3
Me
X
6
Me
10
CO2R3
6
7
8
CO2H
9

centers to the stereocenters in the A-ring, and constructing the stereochemistry of the B,C ring juncture. Another consideration might involve the formation of the C-ring (pyranone) rather late in the synthesis due to possible acid sensitivity. In this regard, chemical studies on versiol have demonstrated the cleavage of the pyranone ring under acidic conditions, but the dienylic alcohol at C-9 could be retained.[1]

This report suggests to deal with the above issues by constructing the three stereocenters in the A-ring early in the synthesis and then relating the C-10 quaternary center to the A-ring via a bicyclic lactone (see 5 or 6, Scheme I). The C-10 stereocenter will then be used to establish the B,C ring juncture (cis). This allows for late formation of the pyranone and should construct all the stereocenters in the proper relative configuration.

With this synthetic approach in mind, a retrosynthetic plan for the synthesis of 1 is outlined in Scheme I. The pyranone could be formed via an intramolecular Michael addition of the C-9 oxygen to an α,β-unsaturated system; thus, a suitable precursor for 1 would be hydroxyaldehyde 2. The allylic alcohol in this intermediate (2) would be readily available from an epoxide across C-8 and C-9. Further, the aldehyde at C-10 could be reduced to an alcohol to direct the epoxidation across C-8 and C-9 and

thereby establish the correct relative stereochemistry between C-9 and C-10. Of course, an olefin between C-8 and C-9 would be the precursor for the epoxide (see 3). This suggests an intramolecular Witting reaction to form this olefin during the closure of ring B. An appropriate precursor for this reaction would be ketone 4.

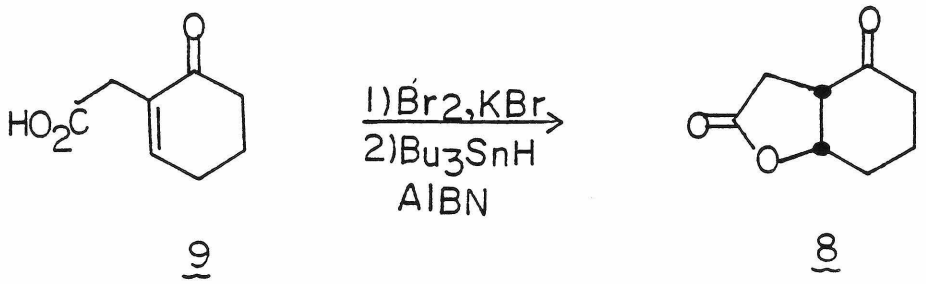
For ketone 4, one can visualize two bicyclic lactones as suitable precursors by using either the ketone side chain (C-9) or the hydroxy side chain (C-11) as the ultimate carbonyl in the lactone (see 5 and 6, Scheme I) This raises an important point in that the requisite stereochemistry at C-10, relative to the A-ring can be established regardless of the stereochemistry of the quaternary center (C-10) in the bicyclic lactones 5 and 6 (this assumes that 5 or 6 is only one isomer with respect to C-10 and not a mixture). Depending on the isomer, 5 or 6, appropriate distinction between the lactone carbonyl and the side chain carbonyl will ensure the proper relative stereochemistry between C-10 and the A-ring stereo-centers (see 4, 5, and 6; Scheme I).

Based on previous studies on enolate alkylation stereoselection,[4] *vide infra*, the stereochemistry of C-10 in lactone 5 would be easily prepared. Therefore we will concentrate on lactone 5 only. Lactone 5 should be accessible from the keto-lactone 7. The carbonyl at C-6

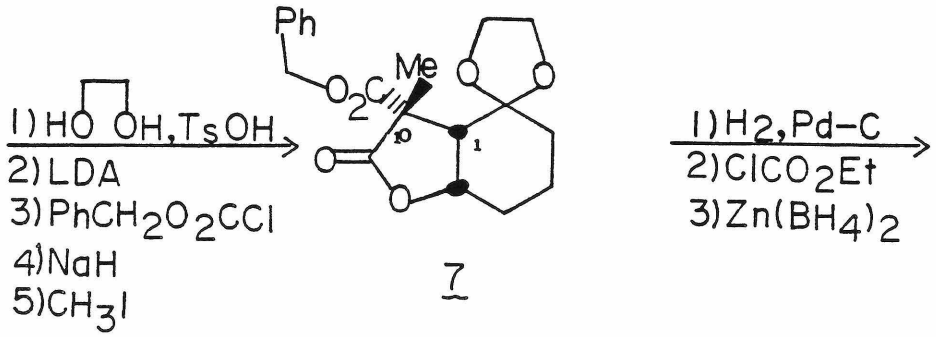
would serve to introduce the alkyl side chain (C-7 → C-8 in 5) with formation of the C-5 → C-6 double bond *via* Shapiro-type chemistry.[5] The C-6 carbonyl could also serve for the introduction of the C-4 methyl by cuprate addition to an enone. The desired trans relation between the C-4 methyl and the C-2 hydroxyl should be established in such a cuprate addition. Since the C-10 methyl and ester substituents in 7 could be introduced *via* enolate technology, lactone 7 should be readily attained from lactone 8. This *cis*-lactone could be prepared from the keto-acid 9 by halolactonization.[6] This synthetic plan has the advantage of allowing for various synthetic options throughout its course. During the discussion of the synthesis below, areas where other pathways might be taken will be noted.

The first key intermediate in the synthesis of 1 is the protected keto-lactone 11 (Scheme II). Starting from the known keto-acid 9,[7] bromolactonization of the potassium salt of 9 (Br_2, KBr; followed by removal of the bromide with Bu_3SnH, AIBN) should provide keto-lactone 8 (Scheme II). Corey *et al.* have carried out similar bromolactonizations on enone systems in high yield.[8] After ketalization, the lactone can be acylated ($PhCH_2O_2CCl$, LDA) and then alkylated with methyl iodide to afford lactone 7. Several studies[4] have shown that in alkylation

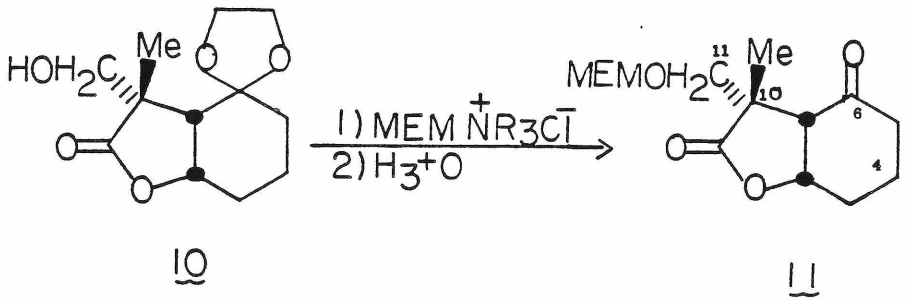
Scheme II



9 8



7



10 11

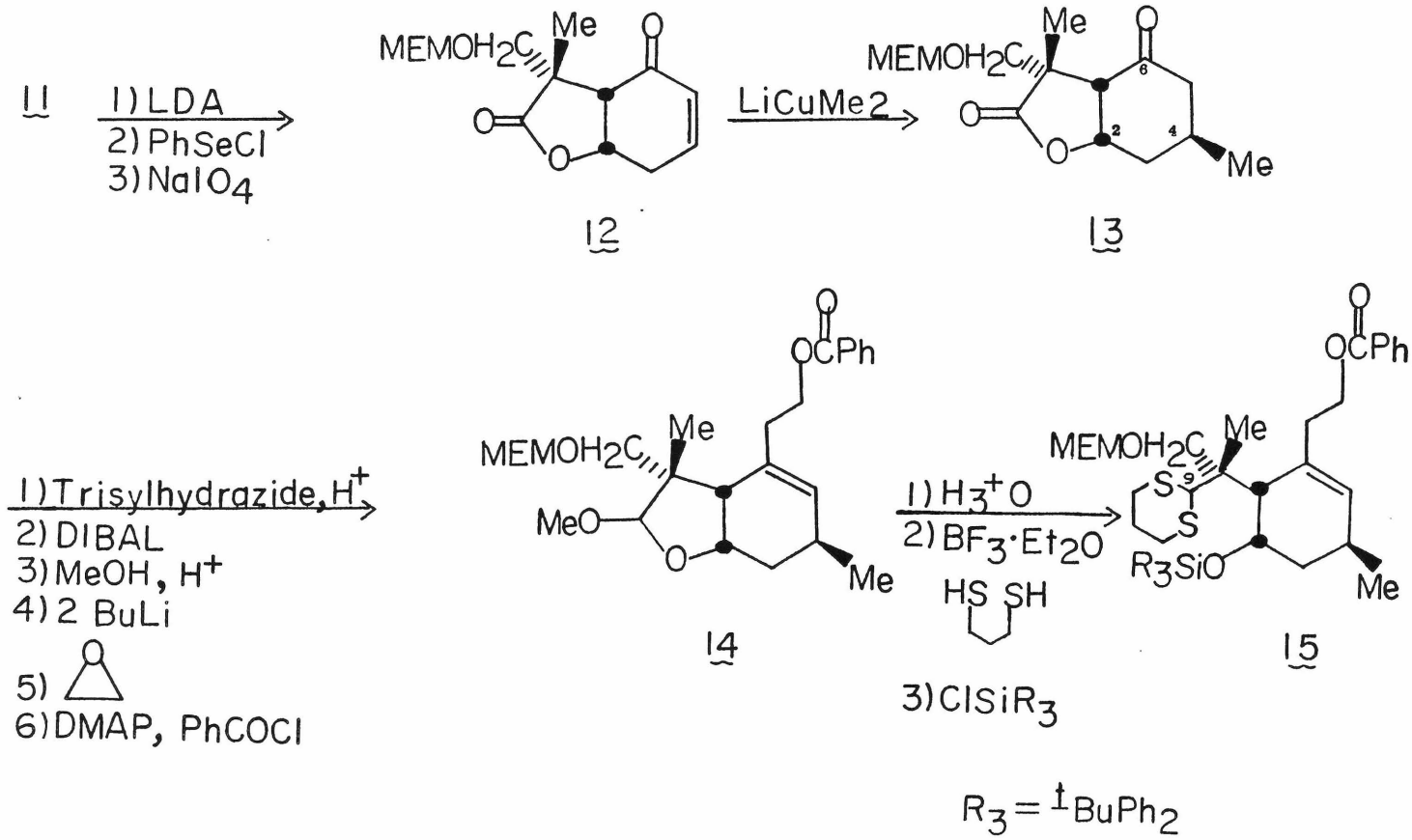
of endocyclic 5-membered ring enolates the electrophile entered cis to the smallest group at adjacent centers of asymmetry. Thus, the C-10 methyl and C-1 hydrogen should be cis in the lactone 7.

As previously mentioned, control of stereocenter C-10 will be based on distinguishing the lactone and the ester carbonyls in 7. One method for this distinction is outlined in Schemes II and III, although several other possibilities to accomplish this distinction exist. After hydrogenolysis of the benzyl ester in 7, the acid can be converted into a mixed anhydride and reduced to the primary alcohol with $Zn(BH_4)_2$. Protection of the alcohol as the MEM ether can be achieved under neutral conditions ($MEM\text{-}\overset{+}{N}R_3Cl^-$)[9] and subsequent ketal hydrolysis would afford ketone 11. This successfully distinguishes the C-11 and C-9 carbonyls.

The C-6 carbonyl could now be used to introduce the C-4 methyl and alkyl side chain (see 4, Scheme I). After formation of enone 12 by standard conditions,[10] addition of dimethyl cuprate should provide 13 with the requisite relative stereochemistry between C-4 and C-2.[11]

The side chain introduced at C-6 will be the precursor for the Wittig reagent, thus a potential halide must be present in this alkyl chain. One possible masking of the halide would be as an alcohol. Accordingly, the ketone at C-6 will be converted into a vinyl anion

Scheme III

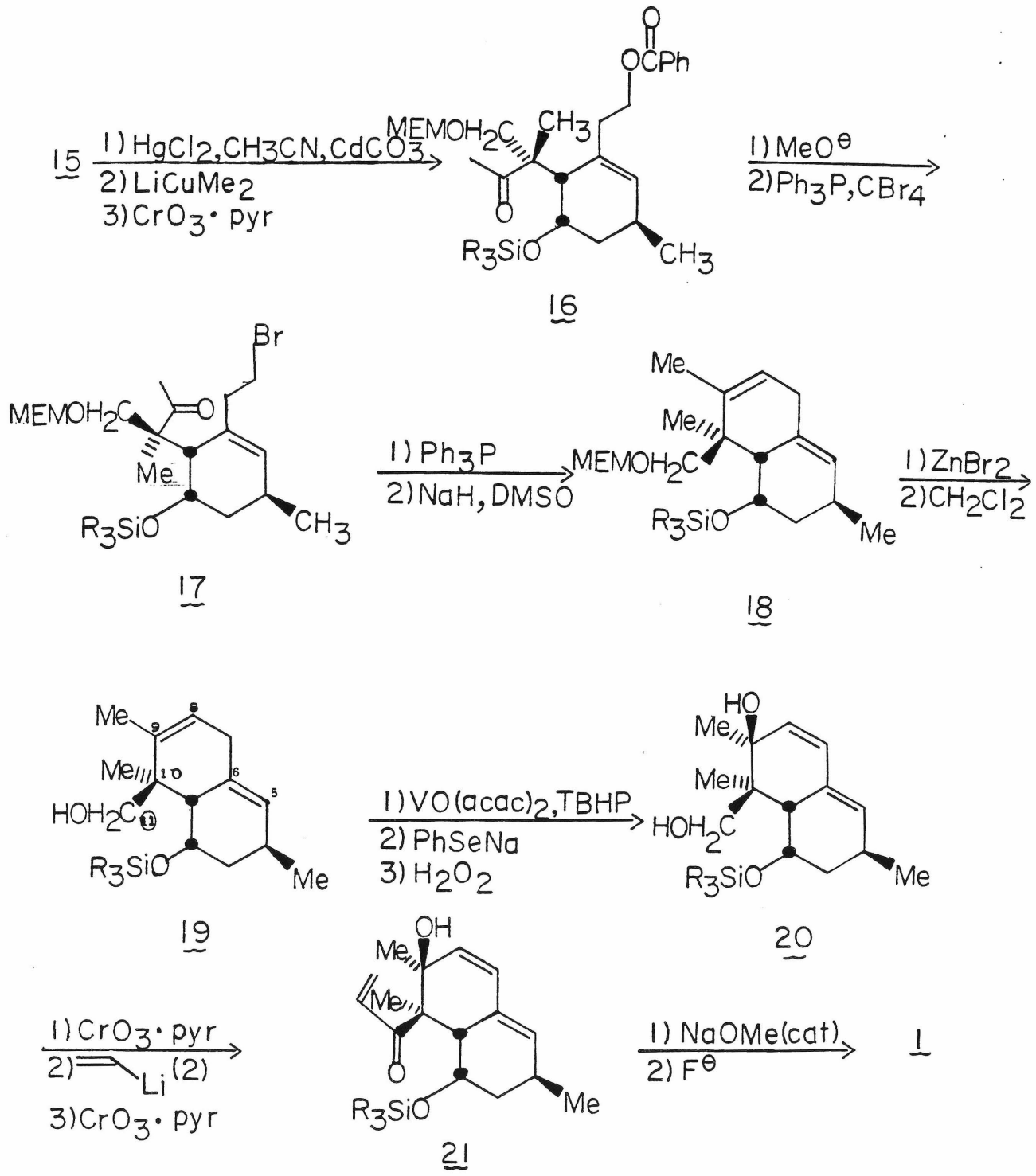

11
1) LDA
2) PhSeCl
3) NaIO4
MEMOH2C
Me
O
LiCuMe2
12
13
1) Trisylhydrazide, H+
2) DIBAL
3) MeOH, H+
4) 2 BuLi
5)
6) DMAP, PhCOCl
OCPh
MeO
14
1) H3+O
2) BF3·Et2O
HS SH
3) ClSiR3
R3SiO
15
R3 = tBuPh2

and trapped with ethylene oxide. To this end, the carbonyl in 13 can be converted to the trisylhydrazone.[12] However, before generation of the vinyl anion, the lactone carbonyl must be protected. Reduction to the lactol and protection as the mixed acetal should serve the purpose. Subsequent deprotonation of the trisylhydrazone with butyllithium to form the vinyl anion, trapping with ethylene oxide, and protection of the resultant alcohol as the benzoate should provide 14. It should be noted that with the reported conditions,[12] trisylhydrazones will exclusively form the less substituted vinyllithium reagent. Although no problems are anticipated in this sequence, the order of reactions could be changed, if necessary. Hydrolysis of the mixed acetal and trapping of the aldehyde as the thioacetal[13] would complete the distinction between the oxidation states of C-11 and C-9. Additionally, the alcohol at C-2 (from lactol) could be protected as the silyl ether to complete the transformation of 14 → 15.

The intramolecular Wittig to form ring B and the completion of the synthesis of 1 is outlined in Scheme IV. For the Wittig reaction the C-9 aldehyde (thioacetal) must be converted into a methyl ketone and the C-8 alcohol must be transformed into a halide. Hydrolysis of the thioacetal (Hg^{+2}),[14] addition of dimethyl cuprate to the

aldehyde, and oxidation of the resultant alcohol should give ketone 16. Removal of the benzoate protecting group to give a primary alcohol would allow for conversion to the halide 17 under mild conditions.[15] Formation of the Wittig reagent should proceed smoothly, if NaH in DMSO is used as the base,[16] and subsequent intramolecular closure would provide decalin 18. Removal of the MEM protecting group can be carried out under neutral conditions to provide alcohol 19. By employing Sharpless' vanadium catalyzed epoxidation conditions,[17] the C-11 hydroxyl should enhance the rate of epoxidation of the C-8 → C-9 olefin relative to the C-5 → C-6 olefin. Just as important, the C-11 hydroxyl should direct epoxidation from the β-face. This ensures the correct relative stereochemistry between C-9 and C-10. Alternatively, the same result could be achieved by using the "phosphate extension" method devised by Bartlett for the stereoselective functionalization of homoallylic alcohols.[18] In either case, the resultant epoxide can be opened with sodium phenylselenide and subsequent elimination would afford the allylic alcohol 20.[19] The phenylselenide should open the epoxide at the least hindered site (C-8), as required. Additionally, an examination of Drieding models reveals that in the favored conformation of 19-epoxide, attack at C-8 would be a trans-diaxial opening.

Scheme IV


15
1) HgCl2, CH3CN, CdCO3
2) LiCuMe2
3) CrO3 · pyr
MEMOH2C
CH3
OCPh
O
R3SiO
CH3
16
1) MeO⊖
2) Ph3P, CBr4
Br
MEMOH2C
Me
R3SiO
CH3
17
1) Ph3P
2) NaH, DMSO
Me
Me
MEMOH2C
R3SiO
Me
18
1) ZnBr2
2) CH2Cl2
Me
Me
HOH2C
R3SiO
Me
19
1) VO(acac)2, TBHP
2) PhSeNa
3) H2O2
HO
Me
Me
HOH2C
R3SiO
Me
20
OH
Me
Me
O
R3SiO
Me
21
1) CrO3 · pyr
2) Li (2)
3) CrO3 · pyr
1) NaOMe(cat)
2) F⊖
1

(Note: although no problems are anticipated with the above sequence, if the C-5 → C-6 olefin does cause side products and reactions, then it could be suitably protected and regenerated at the end of the synthesis.)

The final series of reactions involve the formation of ring C -- the pyranone. Oxidation of the primary alcohol in 20 to an aldehyde, addition of vinyllithium (2 equiv), and oxidation again should give the enone 21. With a catalytic amount of base, closure to a pyranone should readily occur. In fact, such a procedure has been used to generate simple pyranones.[20] Removal of the silicon protecting group should complete the synthesis of 1.

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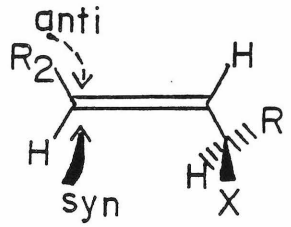
PROPOSITION IV

The use of chiral ligands to induce chirality in the S_N2' reaction is proposed.

* * * * * * * *

Much attention has recently been devoted to the theoretical and synthetic aspects of the S_N2' reaction.[1,2] Some of the critical issues involved the following: (a) possible stereoelectronic control [syn (incoming nucleophile and leaving group on the same face of the allylic system) vs anti selectivity, Scheme I]; (b) S_N2' vs S_N2 reactivity; (c) the role of the nucleophile, and to some extent (d) chirality transfer. Although the theoretical debate con-

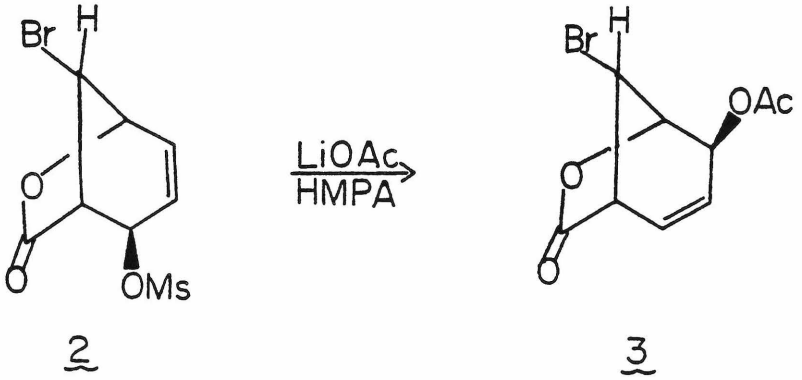
Scheme I



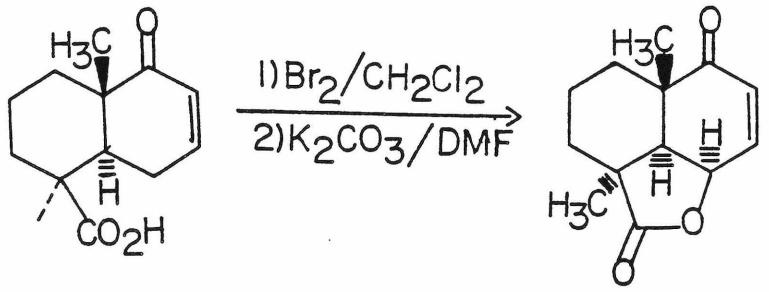
I

cerning the S_N2' reaction is unsettled, a limited number of applications of the S_N2' reaction in total syntheses has proven the synthetic viability of this process (Scheme II).[3,4] Additional applications of the S_N2'

Scheme II



2 3



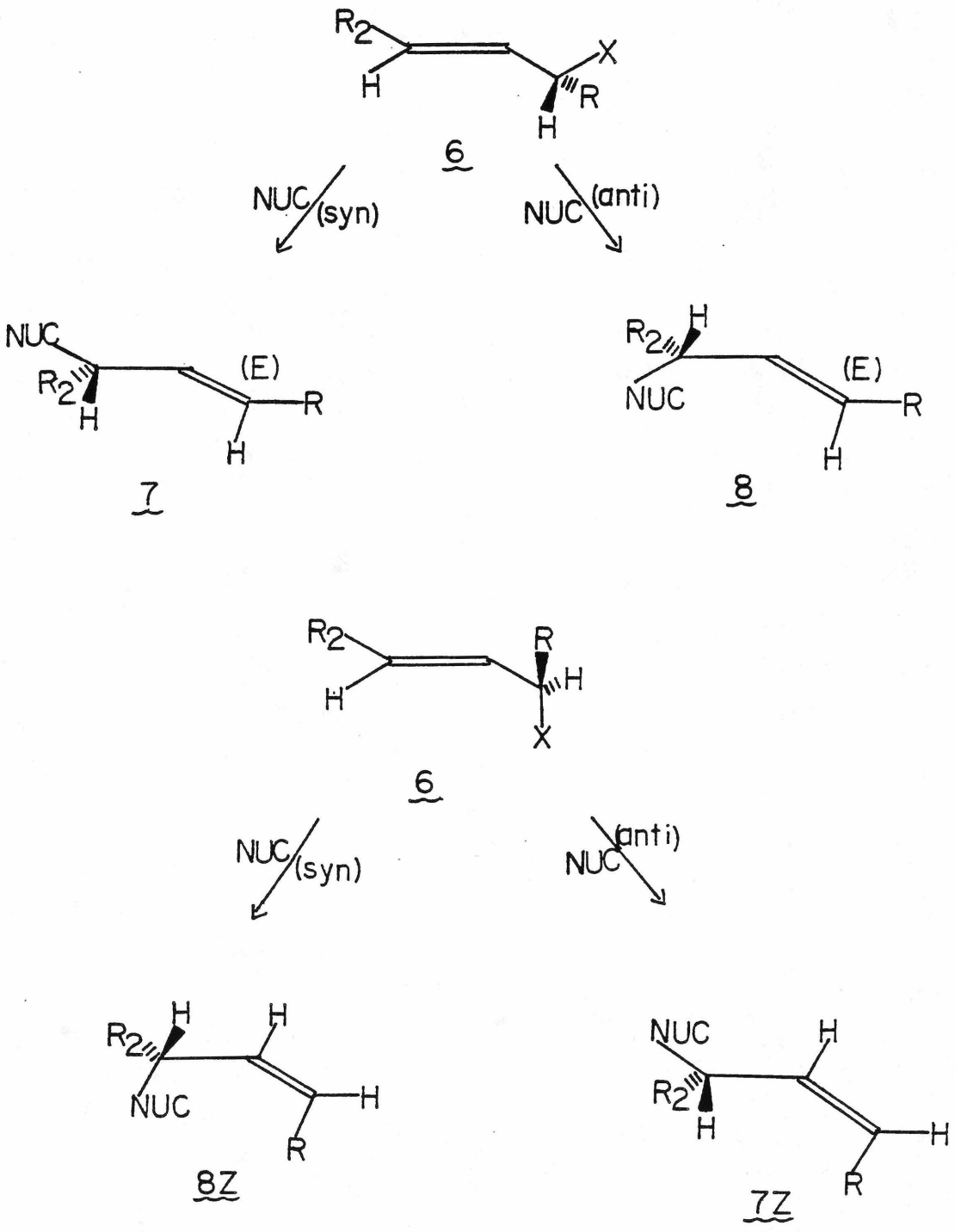
4 5

reaction to the synthesis of natural products will be forthcoming since methods have been developed to provide nearly exclusive syn stereoselectivity or anti stereo-

tereoselectivity.[5,6] However, an important aspect of the S_N2' process has been neglected, namely, the area of chirality transfer.

Chiral induction in the S_N2' reaction has been examined only within the context of syn vs anti stereoselectivity.[2a,6a] With the leaving group on a chiral center and reaction occurring from a given rotomer, syn attack of the nucleophile would afford one enantiomer (7) while anti attack would give the other (8, Scheme III) [generally the difference in allylic strain between the terminal H ↔ R and the terminal H ↔ H influenced the course of the reaction so that formation of the (E)-olefin was greatly favored over the (Z)-olefin, Scheme III]. Although the levels of asymmetric induction were generally high, this approach to chirality transfer in the S_N2' reaction has two major drawbacks. First, the transfer of chirality is dependent upon the synthesis of an optically active allylic substrate. To obtain the appropriate substrate optically pure may involve more work and loss of synthetic material than a resolution of a final racemic mixture. In fact, the substrates for the approach above (Scheme III) were usually 70-85% optically pure. Secondly, even if the substrate had been 100% optically pure and the transfer of chirality excellent, one chiral center was destroyed in order to establish only one additional center of

Scheme III

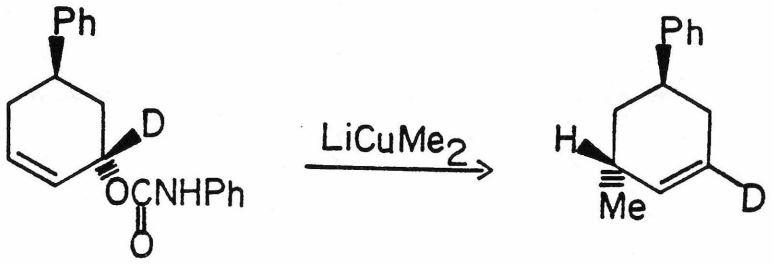

R2
H
X
R
H
6
NUC (syn)
NUC (anti)
NUC
R2
H
(E)
R
H
7
H
R2
NUC
(E)
R
H
8
R2
H
R
H
X
6
NUC (syn)
NUC (anti)
H
R2
NUC
H
H
R
8Z
NUC
H
R2
H
H
R
7Z

asymmetry. A more efficient method of inducing chirality would be to employ an asymmetric center which is easily prepared optically pure and which could be recovered for future use. This proposal suggests the use of chiral ligands on the incoming nucleophile to generate new centers of asymmetry in optically active form.

To maximize asymmetric induction in the S_N2' process, one needs a system which ensures exclusive syn or anti attack of the incoming nucleophile, vide supra. Gallina and coworkers have demonstrated complete syn stereoselectivity with two equivalents of a cuprate reagent and the allylic carbamate 9 (Scheme IV).[7] Presumably, this selectivity arises from the formation of the mixed cuprate 11, since no displacement was observed with one equivalent of cuprate and other carbamates and esters without acidic protons displayed anti selectivity with no preference for S_N2' vs S_N2 reactivity (Table I, this premise could easily be tested by preforming the cuprate reagent 11, Scheme V).

The carbamate system devised by Gallina provides an excellent opportunity for asymmetric induction. By introducing a chiral ligand on the carbamate which would complex the cuprate reagent, one could form a highly ordered and asymmetric reagent (Scheme VI). One possible ligand would be the pyrrolidine 12.[8] Conversion of allylic alcohol 13 to the carbamate 14 by standard procedures,[9] followed by deprotonation and

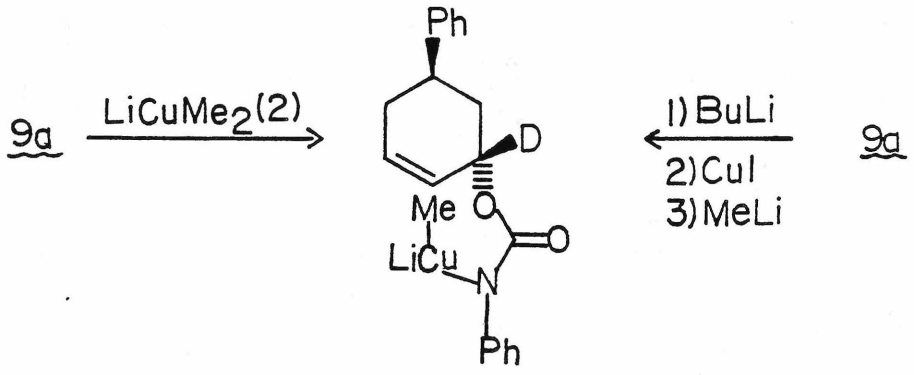
Scheme IV



9a 9b

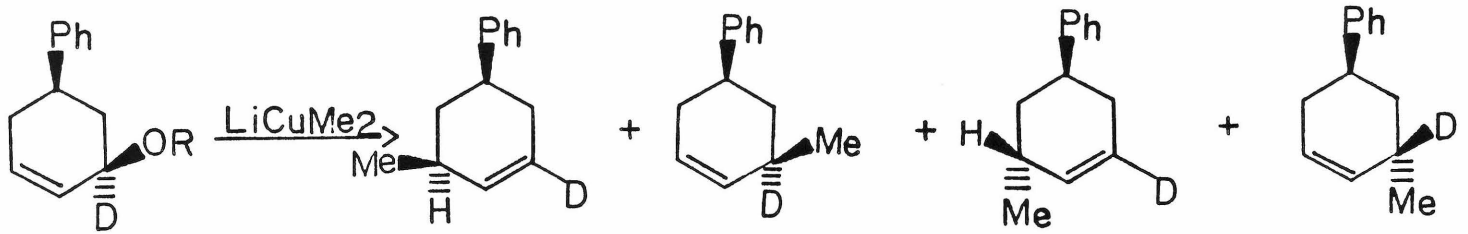
(only one enantiomer shown)

Scheme V



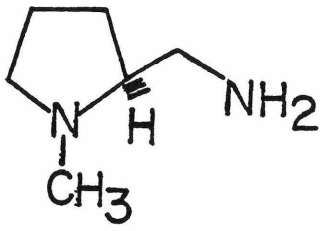
11

Table I



10a 10b 10c 10d 10e

Entry	R	10b:10c	10d:10e
A	CONHPh	>98:2	--
B	HCO	--	58:42
C	MeCO	--	51:49
D	PhCO	--	50:50
E	EtOCO	--	53:47
F	Me(Ph)NCO	--	54:46

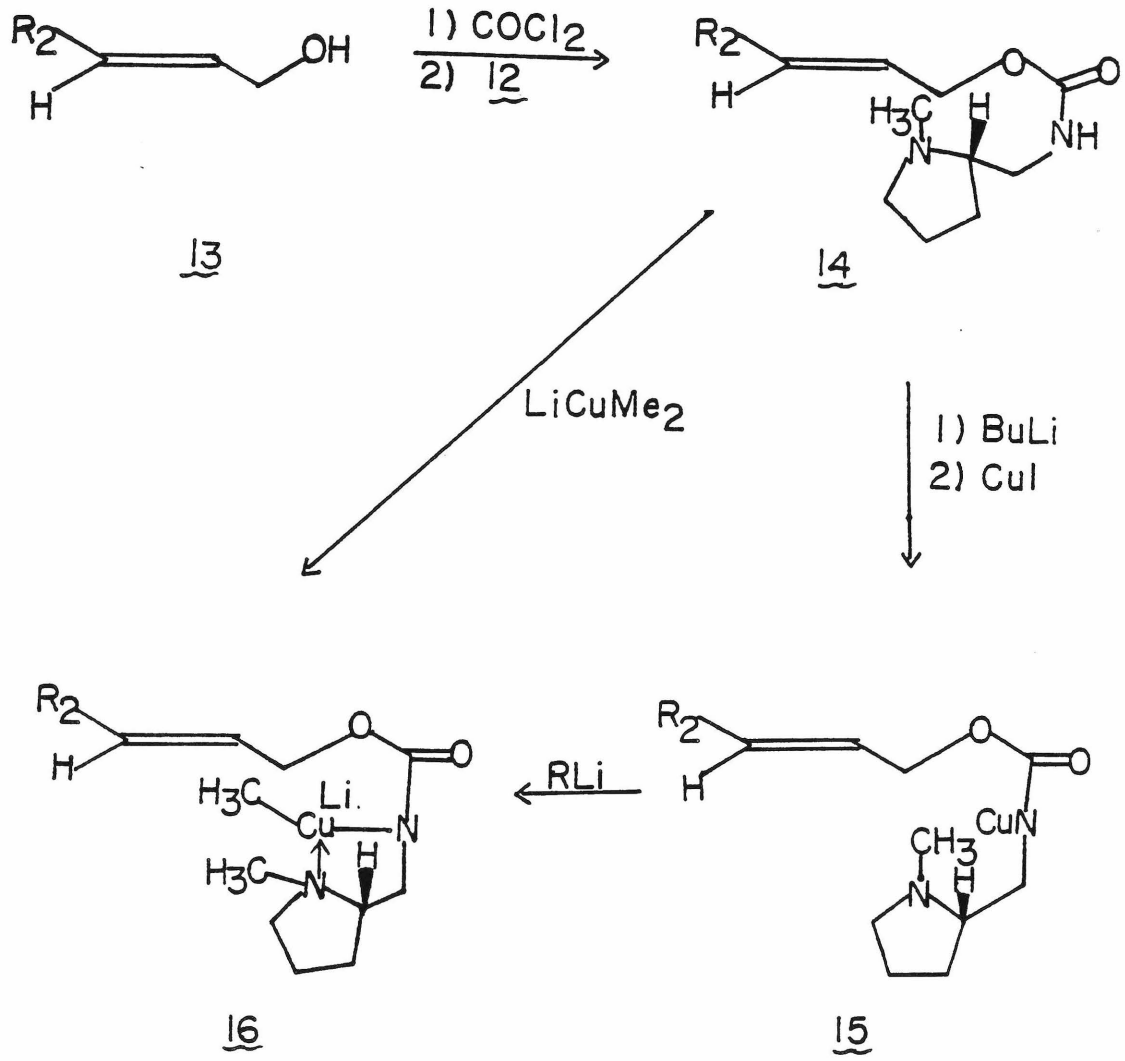


12

quenching with cuprous iodide[10] would afford the copper reagent 15. Addition of an organometallic would then give the desired mixed cuprate reagent 16. Presumably, carbamate 14 could also be treated with two equivalents of a cuprate reagent (Gallina procedure) to afford the mixed cuprate reagent 16. Subsequent reaction of this complex (16) *via* S_N2' (syn attack) could give enantiomer 17 or 18 (Scheme VII). The direction and magnitude of the asymmetric induction would be dependent upon the energy differences in the diastereoisomeric transition states leading to 17 and 18, *vide infra*.

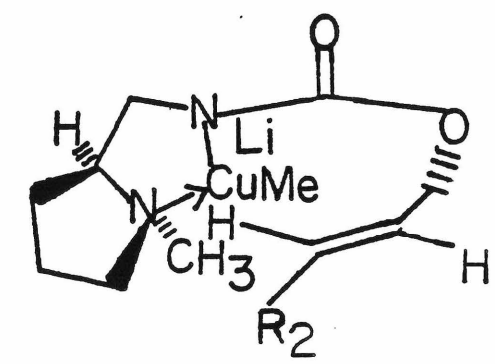
Since the exact mechanism of the S_N2' reaction with cuprate reagents is not known, detailed transition states cannot be examined. However, the proposed reagent 16 contains several properties which would lead one to expect good asymmetric induction. Namely, the copper center (which is probably intimately involved in the transition state) is in a highly ordered (*cis*-fused, pseudo-bicyclo-

Scheme VI

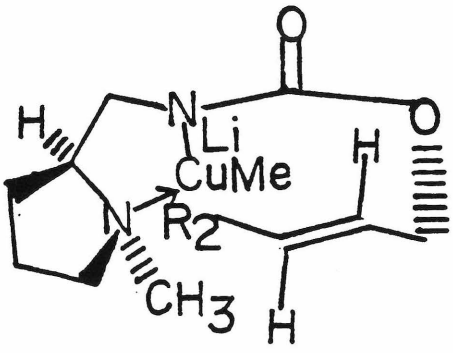


[3.3.0]octane ring system), asymmetric environment (Scheme VI). This should provide a good basis for distinguishing between the two diastereoisomeric transition states. Additionally, the cuprate reagent must approach the allylic system syn to the leaving group, vide supra. By examining the two possible approaches, A and B (leading to opposite

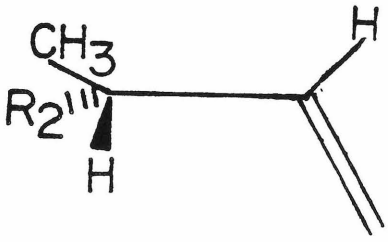
Scheme VII



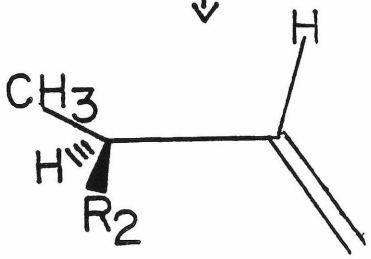
A



B



17



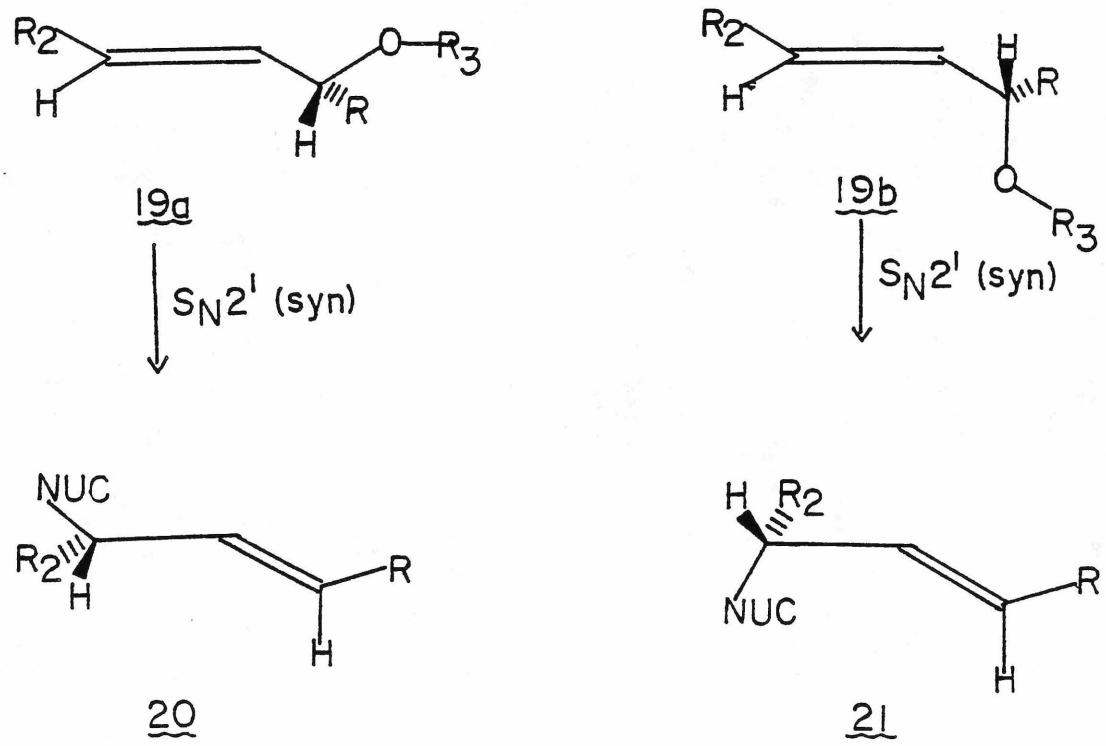
18

enantiomers, Scheme VII), one can envisage a difference in steric interactions between A and B. In A a proton would be interacting with the bicyclic ring system, while in B the alkyl group (R_2) would be interacting with the bicyclic system. On this basis A (and, subsequently, enantiomer 17) would be favored. Based on the fairly good levels of asymmetric induction obtained in the S_N2' reaction of cuprates with chiral acetylenes,[11] the transition state must be somewhat ordered. Thus, the steric interactions and differences discussed above should be present in the transition state of the proposed S_N2' reaction. This should lead to good diastereoselectivity.

With this particular system, one limitation would be that allylic alcohols of substitution pattern 19 (asymmetric center at the hydroxyl-bearing carbon) could not be used as substrates. As mentioned previously, with these substrates the formation of the (E)-olefin is favored over formation of the (Z)-olefin. With a racemic alcohol (such as 19), this factor would probably mean low diastereoselectivity (Scheme VIII) since reaction of each enantiomer of 19 with a nucleophile in the S_N2' sense to form the (E)-olefin affords opposite enantiomers (20,21).

In closing, a system is proposed to study for asymmetric induction in the S_N2' reaction. If successful, its advantages would include easy preparation of the

Scheme VIII



chiral subunit and the potential to recover the chiral subunit after the reaction.

References and Notes

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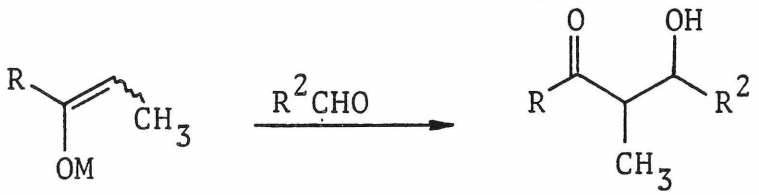
PROPOSITION V

A series of experiments are suggested to probe mechanistic aspects of the aldolase enzymes.

* * * * * * *

The aldol condensation (eq. 1) is prominent among the enzyme-catalyzed reactions that lead to carbon-carbon bond formation (in the biosynthetic direction) or to carbon-carbon bond cleavage (in the degradative direction).[1] In line with this observation is the fact that the enzymes



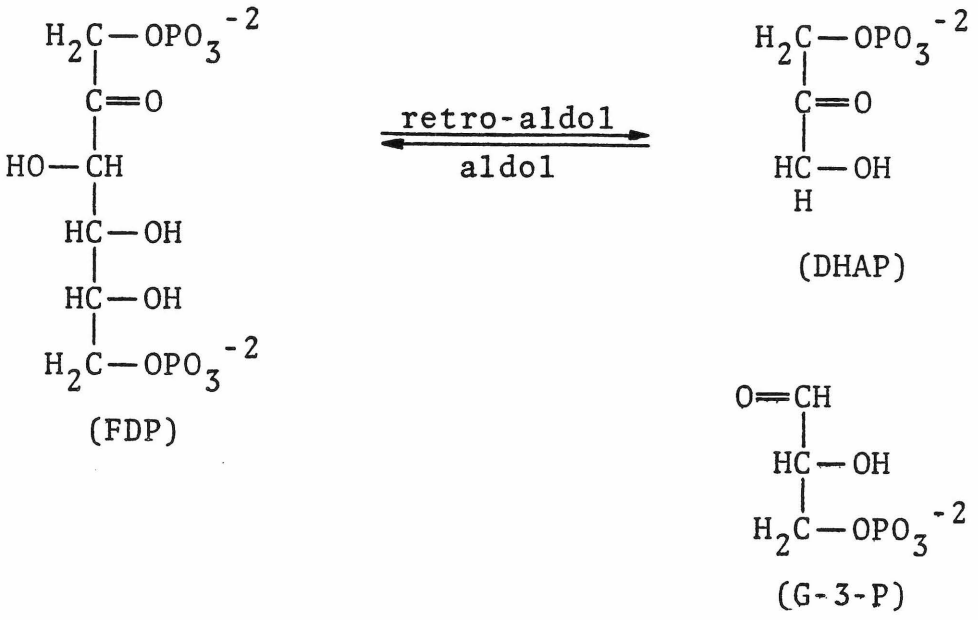
1 2 (1)

which catalyze the aldol condensation (aldolases) have been shown to be highly ubiquitous in nature. Aldolases have been found in all plant and animal tissue examined and in most microorganisms. The importance of aldolases has further been underscored by the intense research effort which has been (and still is) conducted to understand the mechanism(s) of these enzymes.

In enzymatic aldol reactions which have been characterized, the requisite enolate (1, eq. 1) forms by two general mechanisms: (1) the substrate carbonyl forms an imine linkage with an E-amino group of a lysine residue at the active site as prelude to enamine formation (Class I)[2] and (2) the enzyme active site contains a divalent cation that coordinates to the substrate carbonyl oxygen (in a Lewis acid sense) and facilitates enolization by carbonyl polarization (Class II).[3] This proposal will be directly concerned with a Class I and a Class II aldolase which catalyzes the reversible cleavage of fructose-1,6-diphosphate (FDP) into dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate (G-3-P) (Scheme I, these enzymes will hereafter be referred to simply as aldolase I and aldolase II).

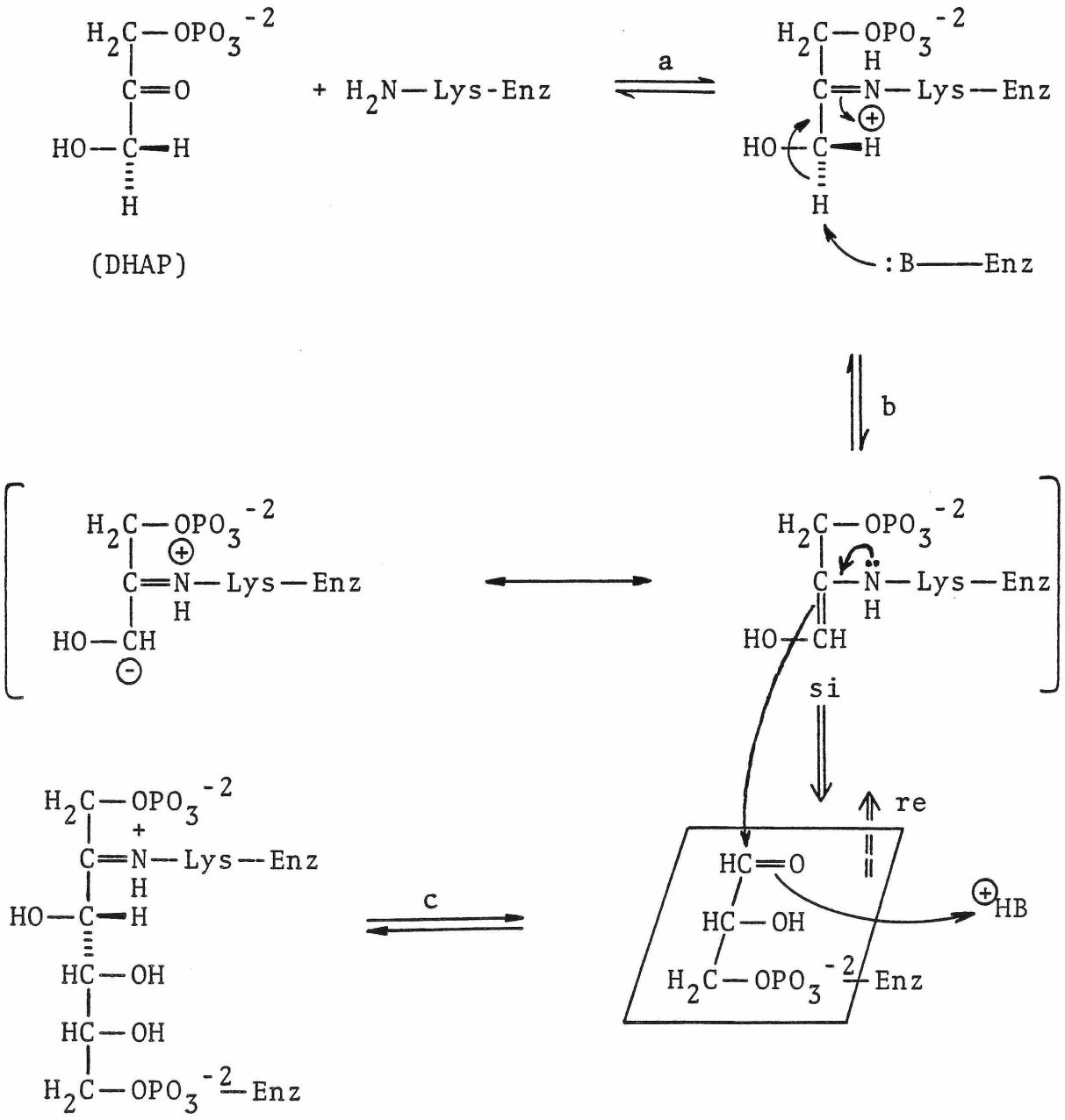
Based on years of experimental work,[4] a general mechanism has been presented for aldolase I (Scheme II, the mechanism for aldolase II is thought to be similar except for carbonyl activation by metal ion instead of imine formation[4]). After formation of an iminium ion with DHAP (step a), the pro-S proton is abstracted (step b). The proton abstraction occurs prior to the binding of G-3-P, which precedes formation of the iminium ion of F-1,6-P_2 (step c). This iminium ion is subsequently hydrolyzed to generate F-1,6-P_2.

Scheme I

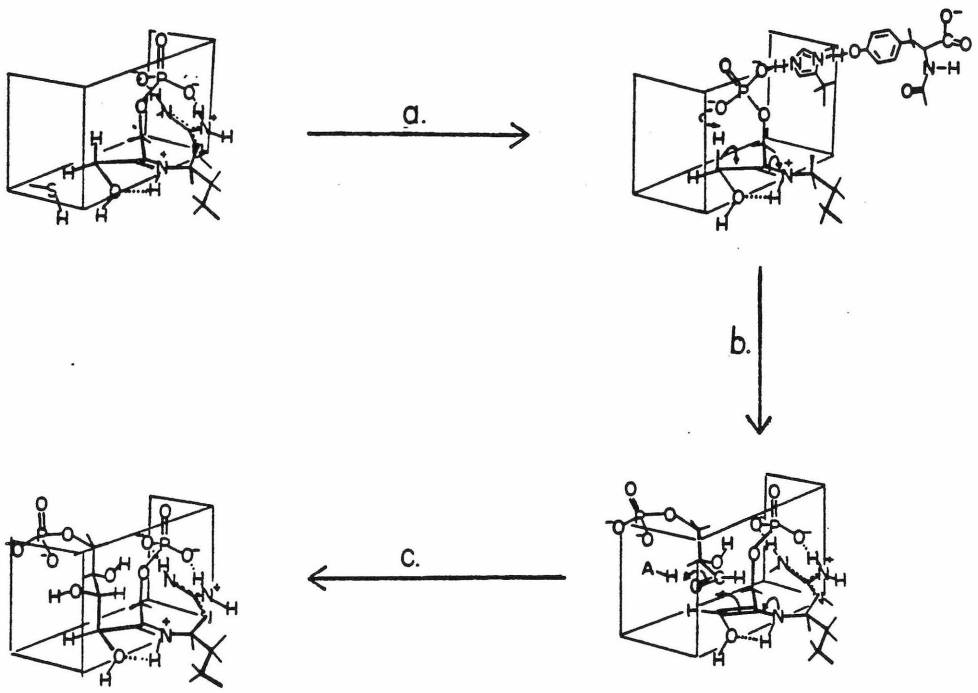


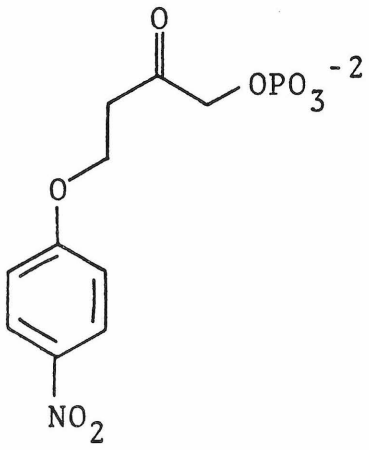
Recently, Hupe et al. have proposed that enolization (step b) occurs via an intramolecular proton transfer utilizing the phosphate group on the substrate as the base (Scheme III).[5] This proposal is based on the fact that dihydroxyacetone sulfate (DHAS) binds to aldolase I and forms an iminium ion, but does not undergo aldol condensation with G-3-P or deuterium exchange with solvent.[6] Further, pH-rate profiles for the elimination of p-nitrophenol from 3 and 4 indicate intramolecular proton abstraction was possible for the phosphate 3 but not the sulfate 4. This is consistent with phosphate being a stronger base than sulfate [pK_a ($ROPO_3^-H$) = 6.8 vs

Scheme II

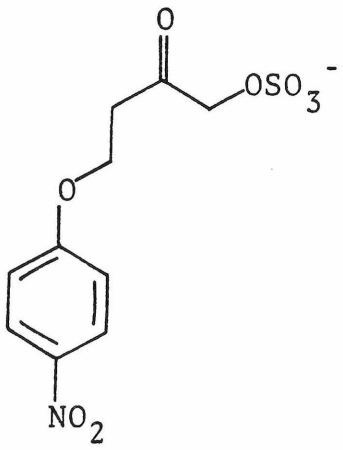


Scheme III





3



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pK_a ($ROSO_3H$ < 1).[7] Additionally, removal of Tyr-361 decreases the rate of proton transfer.[8] Hupe contends Tyr-361 is necessary for repositioning the phosphate from its original orientation (bound to an arginine residue) to a conformation where proton abstraction can occur (Scheme III). Without Tyr-361 this repositioning is slow to occur (phosphate remains bound to arginine) or else the phosphate group is freely rotating with no residue to hold it into place for proton abstraction to occur. The data are consistent with Hupe's mechanism, but not definitive. Electronic or conformational differences caused by the sulfate group could also be reponsible for its failure to undergo aldol condensation. Nevertheless, Hupe's supposition of the substrate providing the catalyst for proton abstraction is intriguing and experiments to test its validity seem to be in order. This proposal suggests the use of ^{31}P NMR and substrates related to DHAP to probe the mechanistic differences between intramolecular and intermolecular proton transfer in aldolase.

A necessity for intramolecular proton transfer, but not intermolecular, is conformational mobility of the phosphate group within the active site. It must move into position for deprotonation (step a, Scheme III) and then swing out of the way for addition to the aldehyde (step b, Scheme III; it is known that the proton is

removed and replaced with the aldehyde on the same face).[9] Several ^{31}P NMR techniques are appropriate to study the conformational mobility of the phosphate group in the enzyme-substrate complex of aldolase I (rabbit muscle aldolase), modified aldolase I (proton abstraction rate greatly decreased), and aldolase II (yeast aldolase). The results with aldolase II should provide valuable data, since previous studies using paramagnetic metal-induced relaxation data[10] suggest the phosphate group is tightly bound in the active site of aldolase II.[11]

In general, the overall molecular motion of a molecule in solution (tumbling) can be related to spin relaxation phenomena of the atom being observed by resonance techniques. Moreover, internal motion of certain atoms or segmental motion of a group of atoms relative to tumbling are reflected in relaxation data and can give valuable conformational information. Relaxation studies involving ^{13}C, ^{1}H, and ^{31}P have been utilized to obtain such information in many examples.[12]

One possible probe for the phosphate group in question would be NOE studies (Nuclear Overhauser Effect). This effect is related to the dipolar relaxation of the phosphorus by atoms with a magnetic spin (in most cases these atoms are hydrogens). NOE studies could provide motional

models and molecular conformations for the phosphorus with respect to the atoms which are involved in its relaxation.[13] This technique has been successfully applied to study the motion of phosphate groups in phospholipid bilayers[14] and conformational effects in ATP (intramolecular folding).[15]

Spin-lattice relaxation data (interactions between ^{31}P nuclei and the lattice) for the phosphorus atom in each aldolase enzyme complex could be applied in two ways to also provide valuable conformational information. First, the relaxation time for phosphorus has been used to show immobilization of a phosphate group in a kinase enzyme-substrate complex.[16] This was achieved by comparison of the correlation time (reorientation time) for the phosphate and for the entire enzyme-substrate complex. Any internal motion of the phosphate would have been reflected in a difference of these two correlation times; however, they were found to be the same. Secondly, spin-lattice relaxation data is useful if dipole-dipole relaxation is a major component of the relaxation mechanism (T_1^{DD}). This has been the case in several similar enzyme studies.[12b] Quantitative relationships based on T_1^{DD} (internuclear distances, etc.) ate still in the infant stages, but qualitative differences in conformation can still be determined.[12b]

Other studies are proposed which utilize modified DHAP substrates. As mentioned previously, the phosphate group in aldolase II may be tightly bound at the active site. If so, it is probable that proton abstraction is intermolecular (enzyme residue acts as base). Therefore DHAS should undergo aldol condensation if its basicity is the reason for no observable reaction in aldolase I. On the other hand, if the sulfate group disturbs the active site in some electronic or conformational manner, aldol condensation will not occur.

Finally, in an intramolecular mechanism, there should be a dependence on the base strength of the substrate (phosphate vs sulfate). Thiophosphates of general structures 5 and 6 would be interesting subsrates to study, since conformational disturbances of the system would be minimized and the base strengths should be less than phosphate (based on the analogy of thiolates vs alcoholates). Thiophosphates of this substitution pattern are well known compounds and their syntheses should be relatively straightforward.[17]

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In conclusion, several experiments which are designed to test the validity of an intramolecular proton abstraction in the catalytic mechanism of aldolases are proposed.

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