ASYMMETRIC SYNTHESIS WITH AN EPHEDRINE BASED CHIRAL AUXILIARY

by

DEAN GRAHAM SHANE MALISSAR, M. Sc., Natal

A thesis submitted in partial fulfilment of the
requirements for the degree of Doctor of Philosophy,
University of Natal.

Department of Chemistry
University of Natal
Pietermaritzburg
November, 1992.

DECLARATION

I hereby certify that this research is the result of my own investigation which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed: DG Malissar

D.G.S. MALISSAR

I hereby certify that this statement is correct.

Signed: S.E. Drewes.

PROFESSOR S.E. DREWES

SUPERVISOR

Department of Chemistry
University of Natal
Pietermaritzburg
November, 1992.

To NOELENE, KURT, DAD and the memory of my dear MOTHER

"We are all each other's intellectual feeders, reluctantly interdependent, learning still, yet rebelling for our identities and our place in the system."

Stephen Hanessian.

CONTENTS

ACKNOWLEDGEMENTS

I would like to thank my supervisor Prof. S.E. Drewes and my co-supervisor Dr. G.H.P. Roos for their interest, guidance and encouragement throughout this project.

I thank Dr. N.D. Emslie and my colleagues for helpful suggestions with respect to my research and the preparation of this thesis.

Thanks are also due to the following people:

Mr. M. Watson and Mrs. Z. Hall for NMR and mass spectra;
Mr. M. Somaru and Mr. H. Desai for elemental analyses;
Mr. P. Forder for glassblowing;
Mr. D. Crawley and Mr. C. Morewood and their staff for technical assistance.

I thank my wife Noelene for her love, understanding and patience throughout this project and for the many hours spent typing and proof-reading this thesis.

I would especially like to extend my thanks to my parents for their love, encouragement and understanding.

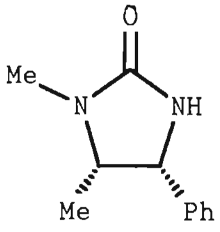
I gratefully acknowledge the FRD and the University of Natal for financial assistance.

ABBREVIATIONS

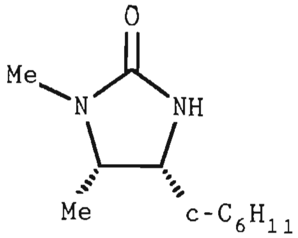
Ar - aryl
Bn - benzyl
Bu - butyl
Cy - cyclohexyl
DCC - dicyclohexylcarbodiimide
de - diastereomeric excess
E^+ - electrophile
ee - enantiomeric excess
Et - ethyl
GC - gas chromatography
HOMO - highest occupied molecular orbital
HPLC - high pressure liquid chromatography
IR - infra red
LAH - lithium aluminium hydride
LDA - lithium diisopropylamide
LUMO - lowest unoccupied molecular orbital
Me - methyl
MS - mass spectrometry
NCS - *N*-chlorosuccinimide
NMR - nuclear magnetic resonance
NOE - nuclear Overhauser effect
Ph - phenyl
Pr - propyl
RT - room temperature
TAI - trichloroacetyl isocyanate
TBDMS - *tert*-butyldimethylsilyl
TFA - trifluoroacetic acid
TfO - trifluoromethanesulphonate (triflate)
TMS - trimethylsilyl
TS - transition state

SUMMARY

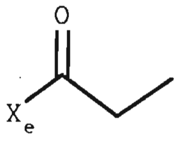
The use of chiral auxiliaries is a well established strategy for the synthesis of homochiral compounds. The utility of the ephedrine derived imidazolidin-2-one auxiliary (I) and the novel analogue (II) in asymmetric synthesis was the focus of this investigation. The aldol reaction of the boron enolate of the *N*-propionyl derivative (III) with aromatic aldehydes proceeded in a diastereoselective (*syn*) manner, while the analogous reactions with aliphatic aldehydes exhibited poor diastereoselectivity. The control element is of an electronic nature. The boron enolates of the *N*-acyl derivatives (IV) and (V) also underwent diastereoselective aldol reactions with both aromatic and aliphatic aldehydes. The lithium enolates of the *N*-acyl derivatives (IV) and (VI) were diastereoselectively alkylated and acylated. The control element for the reactions involving X_{cy} is a steric one.



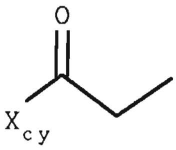
(I) = X_e



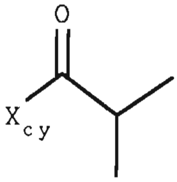
(II) = X_{cy}



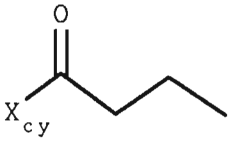
(III)



(IV)



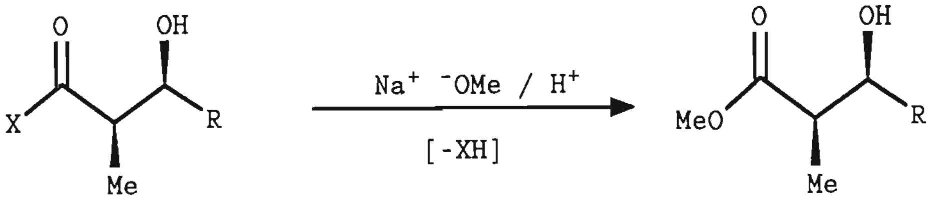
(V)



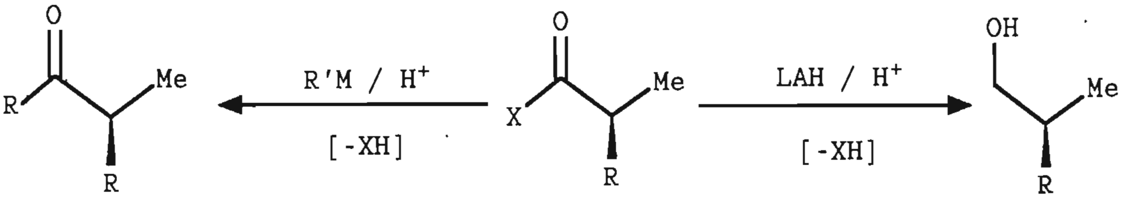
(VI)

The products of the aldol, alkylation and acylation reactions were readily purified by recrystallisation or column chromatography. The chiral auxiliaries were easily cleaved from the aldol products

in undiminished optical purity by treatment with an alkoxide to afford homochiral β-hydroxy esters (eqn. 1). The chiral auxiliaries were cleaved from the alkylation products to afford either homochiral primary alcohols by hydride addition or a ketone by reaction with a bulky carbon nucleophile (eqn. 2).



Eqn. 1



Eqn. 2

The diastereoselectivity ratios of the initial aldol products were determined by observing the diastereomeric downfield carbamate ^{1}H NMR resonance of the products of reaction between the hydroxyl group and trichloroacetyl isocyanate. For a particular aldol substrate a relationship between the shift of the carbamate resonance and the relative stereochemistry was found *viz.* δ_{NH}*syn* > δ_{NH}*anti*.

1. INTRODUCTION

The total synthesis of natural products continues to provide the organic chemist with synthetic challenges. As a result of the rapid evolution of synthetic organic chemistry, the complexity of the target molecules has increased. The total synthesis of daunting target compounds such as cortisone,[1,2] terramycin,[3] monensin[4] and erythromycin A[5] to name but a few, has resulted in the recognition of new and more complex natural products as viable targets for total synthesis.

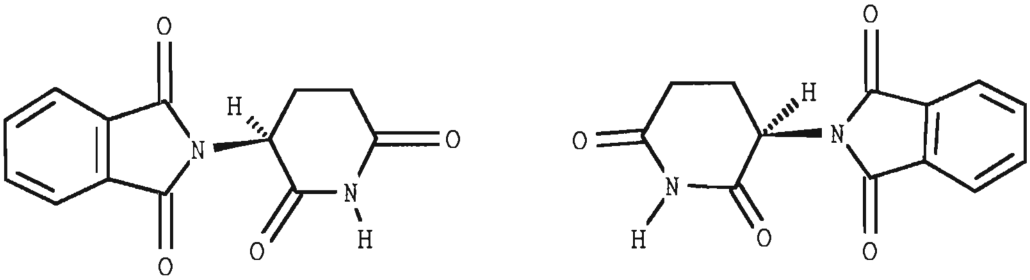
These targets include type A streptogramin[6] and ionophore antibiotics[7] and the polyketides,[8] all of which have a plethora of asymmetric centres. Absolute stereochemical control in total syntheses which involve the creation of new chiral centres is an ongoing problem, especially if the new centres are not part of a rigid framework. The importance of stereochemical control in the synthesis of a compound with an asymmetric centre is clear when the different pharmacological properties[9] of the two enantiomers of the compound are considered (Figure 1).

Chloropropanediol

(R)-Toxic

(S)-Antifertility activity; non-toxic

Thalidomide



(S)

(R)

FIGURE 1

The (R)-enantiomer of thalidomide shows a sedative effect on humans while the the racemate caused in expectant mothers a teratogenic effect on the foetus, in the main due to the (S)-enantiomer. Unfortunately the beneficial effects of thalidomide may never be fully utilised, since recent evidence indicates that homochiral (R)-thalidomide racemises under physiological conditions.[10]

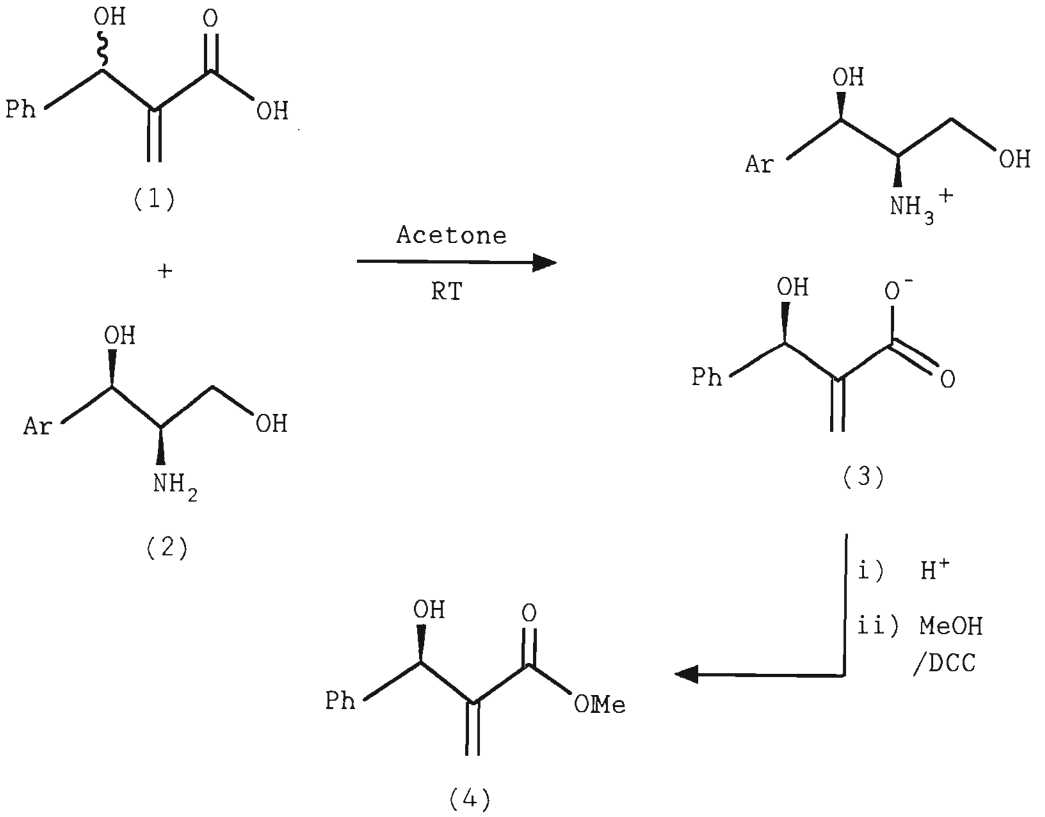
The relationship between absolute configuration and biological action is not restricted to pharmaceutical compounds. It also applies to environmentally sensitive compounds with herbicidal activity and to compounds which stimulate the senses (e.g. of taste and smell).

1.1 STRATEGIES FOR THE SYNTHESIS OF HOMOCHIRAL COMPOUNDS.

In a recent review Davies *et al.*[10] have outlined strategies for the synthesis of homochiral compounds. These are resolution, the 'chiron' approach, enzyme catalysis, asymmetric synthesis and enantioselective catalysis. Whilst this introduction will focus primarily on the asymmetric synthesis approach, the other strategies merit a brief mention.

1.1.1 RESOLUTION.

Resolution normally involves the use of a naturally occurring homochiral compound to convert a racemic mixture into a mixture of diastereomers which are then separated ideally by fractional crystallisation. The resolution of racemates constitutes the main method for the industrial synthesis of pure enantiomers. Resolution in the laboratory still has its place, especially with respect to the determination of the relationship between absolute configuration and specific rotation of a compound. Drewes *et al.*[11] recently published a report on the resolution and assignment of the absolute configuration of 2-(α-hydroxy)-aryl acrylic esters (4) (Scheme 1).



SCHEME 1

The racemic acid (1) was resolved by the addition of the homochiral amino diol (2) followed by fractional crystallisation of one diastereomer (3). Usual work up and esterification afforded the homochiral acrylate ester (4). The configuration at C3 in (4) was confirmed by X-ray analysis of the salt (3). Thus the authors were able to assign the (R) configuration to the laevorotatory enantiomer.

1.1.2 THE USE OF HOMOCHIRAL REACTANTS.

The synthesis of enantiomerically pure compounds may be achieved by using readily available homochiral natural products (from the chiral pool)[12] as one of the reactants. The sugars provide a wide variety of homochiral precursors although amino acids, hydroxy acids and terpenes have also found broad use.

Hanessian[12] has suggested the term 'chiron' to describe a homochiral reactant from the chiral pool. The chiron approach in organic synthesis involves disconnections of strategic bonds in a target compound with minimum perturbation of chiral centres. Ideally the chiron and the target (or substructure thereof) should have a maximum stereochemical and functional group overlap.

In 1990, Hanessian and co-workers[13] reported the total synthesis of (+)-ionomycin, a dibasic acid ionophore, via the chiron approach. The C_1-C_{22} portion of ionomycin was constructed from substructures derived in optically pure form from L-glutamic acid (Figure 2).

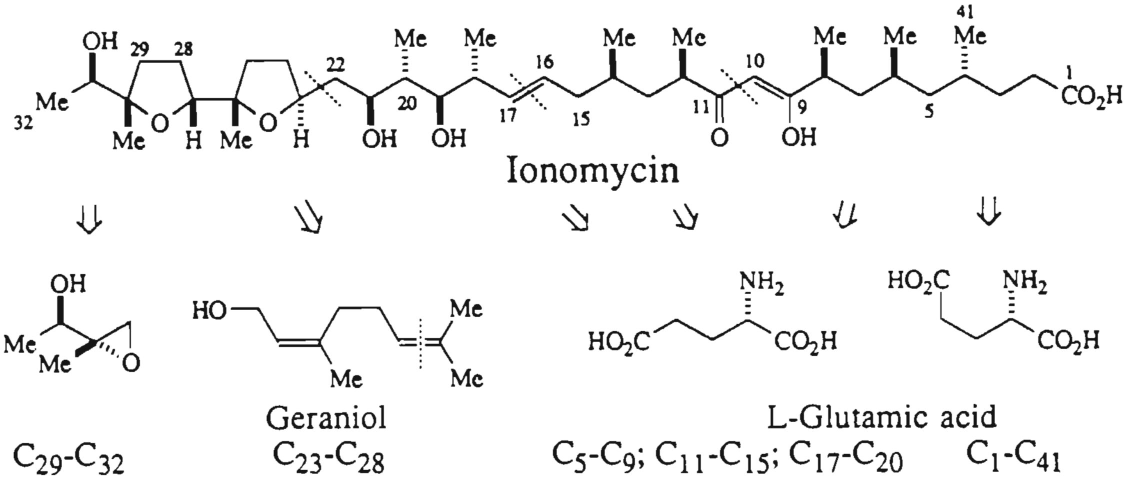
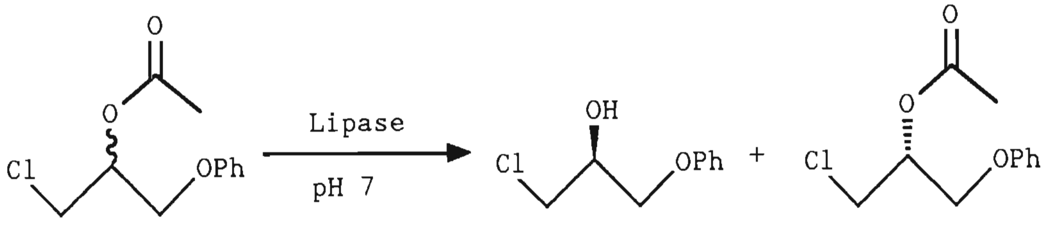


FIGURE 2

The successful syntheses of (+)-ionomycin and of deoxymannojirimycin (a glycosidase inhibitor from diacetoneglucose)[14] are excellent examples of the value of the chiron approach to total synthesis.

1.1.3 ENZYME CATALYSIS.

Enzyme catalysed reactions generally occur under very mild conditions and in most cases with high stereochemical control. Enzymes exhibit a high degree of substrate specificity and protecting groups on the substrate are seldom necessary. The many diverse chemical transformations that may be carried out using enzymes have been reviewed.[15,16] Schneider[17] has recently reported on the enzyme assisted enantioselective synthesis of the precursors to β-adrenergic blockers. The racemic ester (5) was hydrolysed by lipase from *Pseudomonas sp.* (Scheme 2).



(±) - (5)

(S) - (6)

(R) - (5)

SCHEME 2

It is expected that in future an alliance between molecular biology and enzyme catalysis will afford a powerful tool for enantioselective chemical transformations.

1.1.4 ASYMMETRIC SYNTHESIS.

Asymmetric synthesis currently remains the leading strategy (if not the only one in some cases) available to the synthetic organic chemist in the quest for homochiral compounds. Morrison and Mosher[18] have defined an asymmetric synthesis as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products (enantiomeric or diastereomeric) are formed in unequal amounts. This is to say an asymmetric synthesis is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result". The term 'reactant' refers to a chemical reagent, the solvent, a catalyst or a physical force.

1.1.4.1 REQUIREMENTS FOR A VIABLE ASYMMETRIC SYNTHESIS.

Eliel[19] has suggested that an efficient asymmetric synthesis should fulfil the following criteria:-

1. The synthesis should lead to the desired enantiomer with high stereoselectivity and high chemical yield;
2. The chiral product must be readily separable from the chiral reagent that is needed in the synthesis;
3. Unless the chiral reagent is very much cheaper than the desired product, the reagent must be recoverable in good yield and undiminished enantiomeric purity.

1.1.4.2 THE TERMINOLOGY OF ASYMMETRIC SYNTHESIS.

The terminology of asymmetric synthesis used in this thesis follows the generally accepted usage as defined in the literature.[18,20,21] The terms *syn* and *anti*, proposed by Masamune *et al.*[22] (Figure 3), will be used to describe diastereomeric pairs in preference to the *erythro/threo* terminology used by Heathcock.[23]

syn

anti

FIGURE 3

1.1.4.3 STEREO-DIFFERENTIATION.

It is possible to divide asymmetric reactions into six categories according to Izumi and Tai.[24] When the chirality imparted in the course of a reaction arises from :-

a) the reagent, catalyst or reaction medium, the reaction is enantiomer differentiating and yields enantiomers as products;

b) the substrate, the reaction is diastereomer differentiating and yields diastereomers as products. When the differentiation occurs at a sp^2 prochiral, a sp^3 prochiral or chiral centre, the reaction is face-differentiating, topos-differentiating or isomer-differentiating respectively. In the case of diastereo-differentiating reactions these three modes of differentiation may arise with respect to both configurational and conformational diastereo-zeroplanes.

If a chiral reagent in a reaction yields only one enantiomer as the product, the reagent and reaction are described as enantiospecific. If however it yields predominantly one enantiomer, the reagent and reaction are described as enantioselective. In the same way a reagent or reaction may be described as diastereospecific or diastereoselective. Some chemists choose to refer to degrees of enantio-specificity or diastereospecificity.

1.1.4.4 THE SYNTHON APPROACH TO SYNTHESIS.

In 1967, E.J. Corey[25] proposed the use of synthons in synthesis. Synthons are defined as units which can be joined to afford organic molecules by known or conceivable synthetic operations.

In the synthon approach[26] to total synthesis disconnections are generally made at logical sites[27] which facilitate bond formation in the forward sense. The presence of functional groups and chemical feasibility dictate the choice of strategy. Thus the presence of a β-hydroxy ester subunit in the target molecule would suggest the use of the aldol reaction. This would require the generation of an aldehyde and an enolate equivalent as synthons. Although these synthons may yield in the forward sense, a product with the correct relative stereochemistry, the ability to simultaneously control the absolute stereochemistry may be essential. The remainder of this introduction will concentrate on the use of chiral auxiliaries with respect to absolute stereochemical control in asymmetric synthesis.

1.2 CHIRAL AUXILIARIES IN ASYMMETRIC SYNTHESIS.

Chiral auxiliaries are generally obtained from homochiral natural products or by synthesis / resolution routines. The chiral reagent referred to in Eliel's second requirement for a viable asymmetric synthesis may be regarded as a chiral auxiliary. A useful chiral auxiliary should meet the following criteria:-

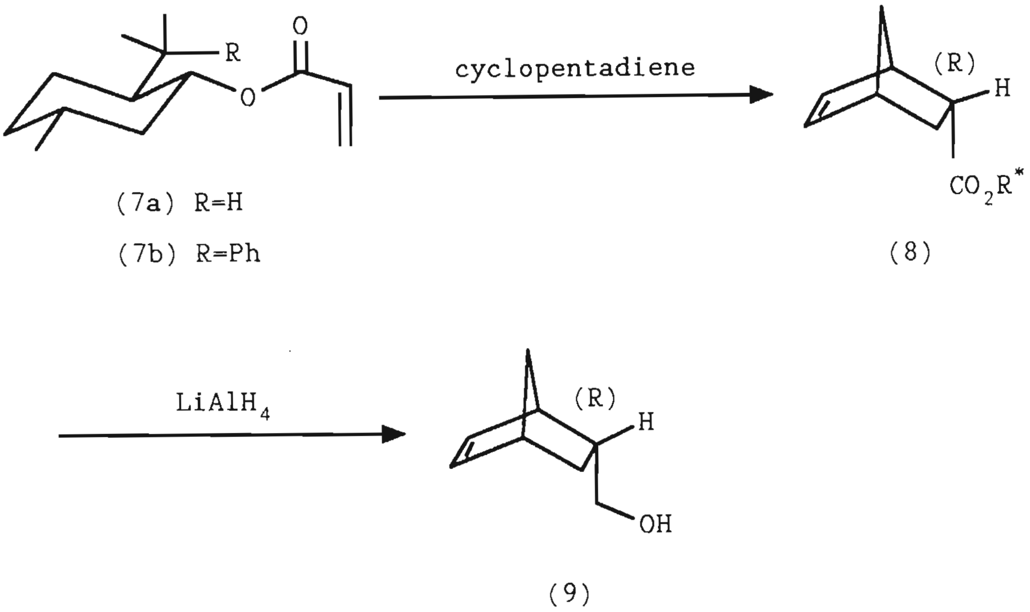
1) Both enantiomers should be readily available;
2) It should impose crystallinity on intermediates and products so as to facilitate purification to 100% de by recrystallisation;
3) It should be easily removed with complete retention of the induced configuration and itself be of undiminished optical purity.

1.2.1 ALCOHOLS AS CHIRAL AUXILIARIES.

As early as 1906 McKenzie[28] found evidence for face differentiation in the reactions of Grignard reagents with menthyl and bornyl esters. It was not until 1955 that a rationale for asymmetric inductions was provided by Prelog.[29,30] He invoked concepts such as preferred conformations and steric repulsions in the transition state to explain the observed inductions. The evolution of chiral auxiliaries with respect to asymmetric induction is best illustrated by the development of chiral esters for use as dienophiles in the Diels-Alder reaction.

1.2.1.1 DIELS-ALDER REACTIONS OF MENTHOL AND BORNEOL DERIVED ACRYLATES WITH CYCLOPENTADIENE.

Early studies carried out by Farmer and Hamer[31] on the Lewis acid catalysed addition reaction of (-)-menthyl acrylate (7a) and cyclopentadiene (Scheme 3), afforded the Diels-Alder adduct (8) with a de of 41%.



SCHEME 3

In 1975, Corey reported on the reaction of the 8-phenylmenthol derived acrylate (7b) with cyclopentadiene.[32] The reaction was catalysed by $TiCl_4$ and the adduct (8) was formed with a de of 90%. The topological bias exhibited by the 8-phenylmenthyl group has been explained by postulating a conformationally rigid cyclohexane ring with an acrylate conformation where the ester carbonyl group is anti-planar with the olefinic C,C-bond and syn-planar with the alkoxy-C,H_a-bond (Figure 4).

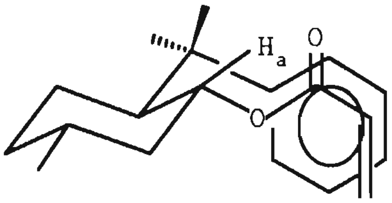
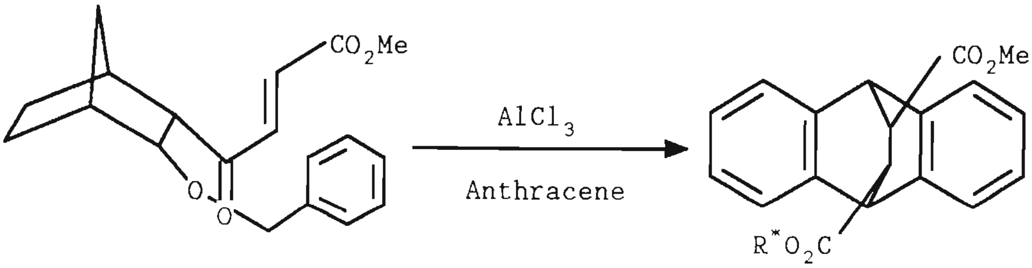


FIGURE 4

The enhanced diastereoselection has been explained as the consequence of a combination of steric effects (afforded by the α-*trans*-methyl-1-phenylethyl group) and electronic effects due to aryl-acrylate π-stacking.[33]

Helmchen[34] later exploited the concept of π-stacking as shown in Scheme 4. The fumarate (10) was added efficiently to anthracene. The shielding of one of the fumarate π-faces by the benzyloxy group led to the adduct (11) with a de of 99%.

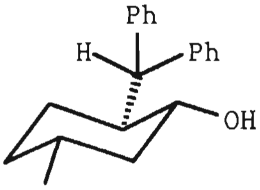


(10)

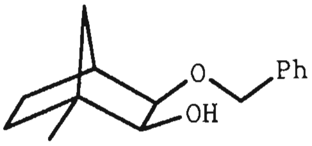
(11)

SCHEME 4

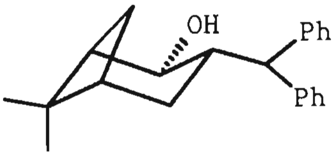
Oppolzer and co-workers[35-38] have investigated the $TiCl_4$ mediated addition of the acrylate esters, derived from compounds (12)-(18), to cyclopentadiene. The (5R)-2-norbornene adducts (8) were obtained with the % des shown.



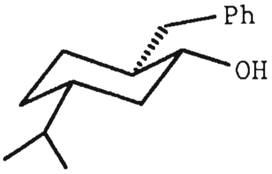
(12) 88%(R)



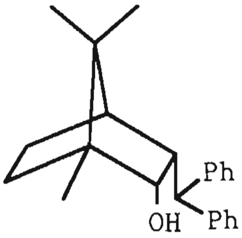
(13) 88%(R)



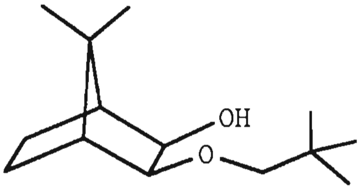
(14) 85%(R)



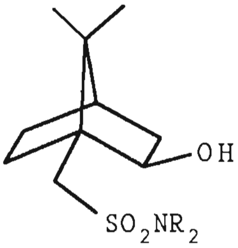
(15) 63%(R)



(16) 81.5%(R)



(17) 99.3%(R)



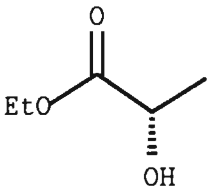
(18a) R = $CH(CH_3)_2$ 88%(R)

(18b) R = cyclohexyl 93%(R)

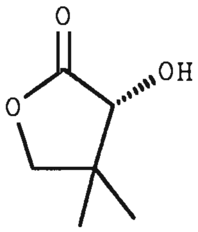
The higher levels of induction observed for the acrylates of (17) and (18b) are a result of steric effects rather than secondary electronic effects.

1.2.1.2 DIELS-ALDER REACTIONS OF ETHYL LACTATE AND PANTOLACTONE DERIVED ACRYLATES WITH CYCLOPENTADIENE.

Helmchen *et al.*[39,40] have reported the use of the acrylates of (S)-ethyl lactate (19) and (R)-pantolactone (20) in Lewis acid catalysed additions to cyclopentadiene. These reactions afforded the norbornene adducts (8) with de's of 86% and 94% respectively.



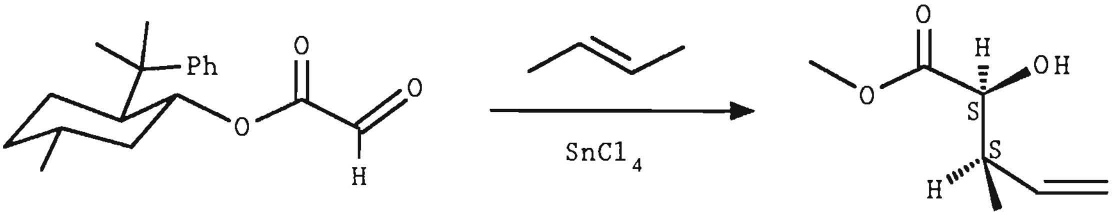
(19)



(20)

1.2.1.3 THE ENE-TYPE ADDITION TO GLYOXALATE DERIVATIVES.

Most chiral alcohols in use as chiral auxiliaries were developed for the Diels-Alder reaction from the concepts arising out of the explanation of the results obtained for 8-phenylmenthol derivatives. The 8-phenylmenthol auxiliary has also afforded good induction in the ene-type addition[41] of *trans*-2-butene to its glyoxalate derivative as shown in Scheme 5.



(21)

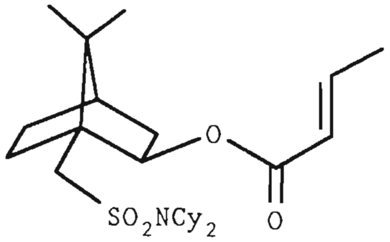
(22) S,S:S,R = 15:1

SCHEME 5

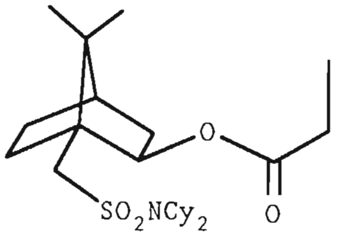
However major limitations of 8-phenylmenthol as an auxiliary include the difficulty of purification since it and products derived from it are oils; and the difficult accessibility of its (+)-enantiomer. Thus the development of chiral auxiliaries for asymmetric synthesis has hinged on the crystallinity of the auxiliaries themselves and of the products derived from them (eg. compounds (15)-(20)). The further requirement that an efficient chiral auxiliary should be available in both of its antipodes, resulted in the use of many camphor derived alcohols as asymmetric inducers.

1.2.1.4 MISCELLANEOUS REACTIONS OF CHIRAL ESTERS.

The reactions of the 10-sulphonamido-isobornyl derivatives (23) and (24) are illustrative of the wide applicability of chiral alcohols as asymmetric inducers. Diastereoselective 1,4-addition of RCu[42] to the *trans*-enoate (23) afforded a synthetic route to the southern corn rootworm pheromone.[43]



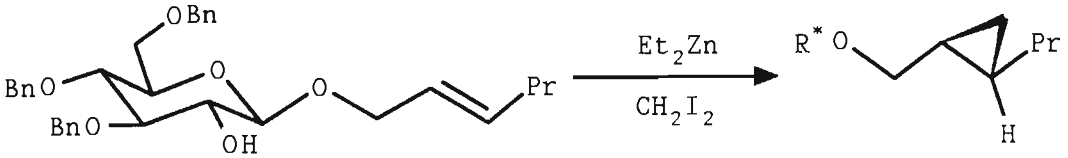
(23)



(24)

Kinetically controlled deprotonation of the propionate (24) followed by addition of alkyl bromides to the lithium enolates affords α-substituted esters with 78-89% diastereoface differentiation. Condensation of the enolate with aldimines yields *cis*-β-lactams in high enantiomeric purity.[44] The silyl enol ethers of (24) afford α-oxygenated compounds and α-halogenated compounds on treatment with $Pb(OAc)_4$ or NCS respectively.[45,46] Both reactions proceed with high π-face differentiation (>95% de).

Charette and co-workers[47] recently demonstrated the use of carbohydrates as chiral auxiliaries. They carried out diastereoselective cyclopropanation reactions of substituted allylic ethers as shown in Scheme 6.



(25)

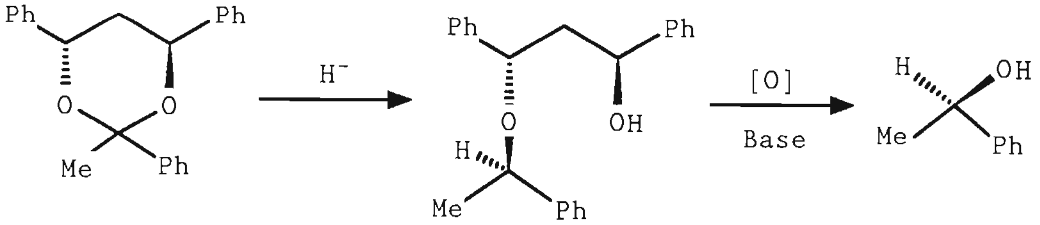
(26) >50:1

SCHEME 6

1.2.2 CHIRAL ACETALS IN ASYMMETRIC SYNTHESIS.

The growing number of papers dealing with chiral acetals demonstrates the usefulness of these auxiliaries in asymmetric synthesis. Two examples have been chosen to illustrate their chirality transfer ability.

Hydride cleavage of acetals is often used for the mono-deprotection of vicinal diols[48] in carbohydrate chemistry. In such cases the interest is in the diol part and not in the carbonyl part. With respect to the carbonyl part, Yamamoto and co-workers[49] have reported the reduction of the ketal (27) to afford the secondary alcohol (29) with an ee of 99% (Scheme 7).



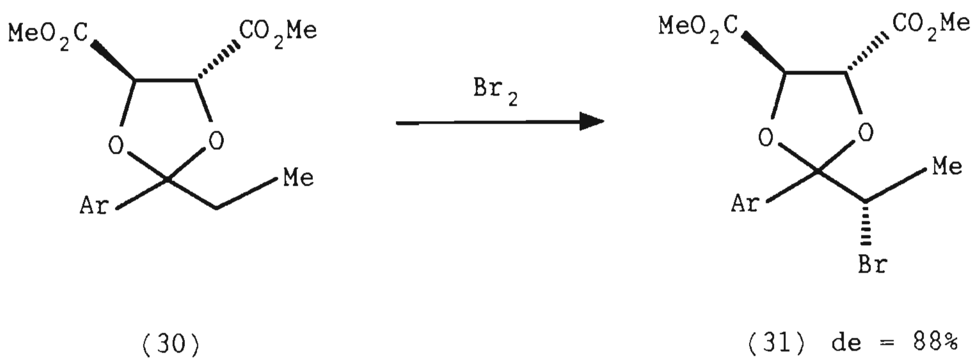
(27)

(28)

(29)

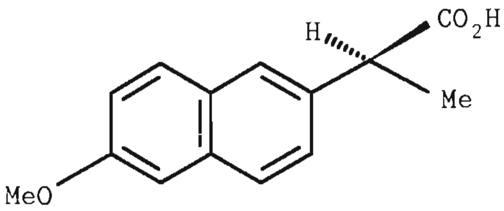
SCHEME 7

In this example chemical manipulation at the ketal yields a chiral product while manipulation α to the ketal is a strategy that has also been successful[50] (Scheme 8).



SCHEME 8

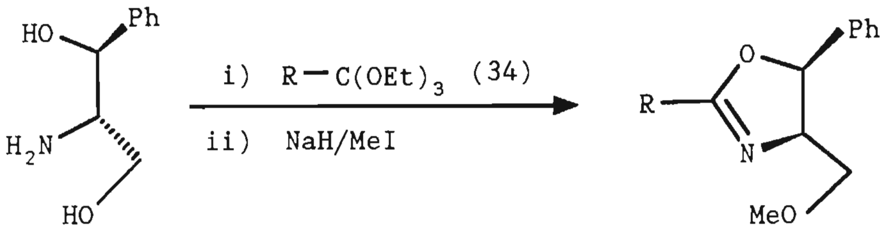
This methodology has been applied to the synthesis of the anti-inflammatory drug Naproxen (32).[51]



(32)

1.2.3 CHIRAL OXAZOLINES IN ASYMMETRIC SYNTHESIS.

During the seventies the Meyers group[52] investigated the use of chiral oxazolines for asymmetric induction. The chiral oxazolines (35) used by them were derived from the readily available (1S,2S)-1-phenyl-2-amino-1,3-propanediol (33) in two steps (Scheme 9).

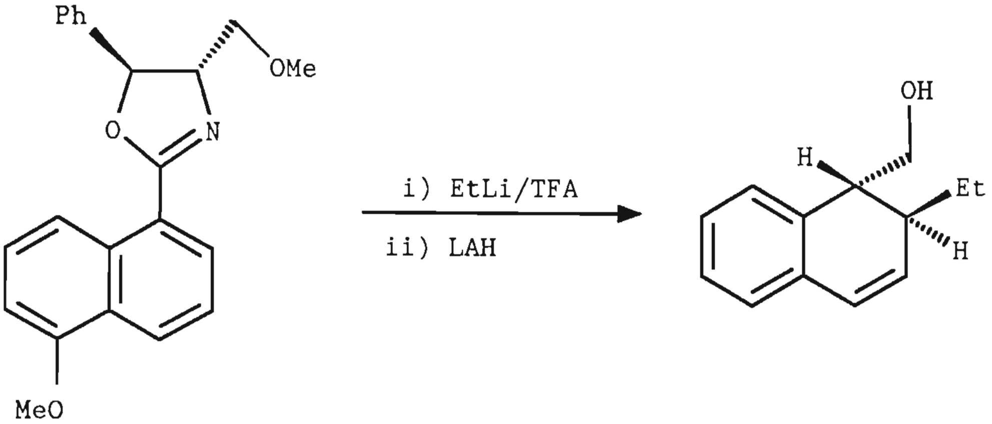


(33) (35)

SCHEME 9

Asymmetric synthesis using chiral oxazolines has been reviewed by Lutomski and Meyers.[53] The topics covered include among others the synthesis of dialkyl acids and lactones via asymmetric alkylations.[54,55]

Later Meyers published the results of the reaction between the boron azaenolates of chiral oxazolines and aldehydes.[56] The reactions exhibited high *syn* selectivity (97%) but the ee's were modest (40-70%). A further example of the utility of chiral oxazolines is the stereoselective protonation of azaenolates with TFA reported by Meyers.[57] Reduction of the intermediate product afforded 1,2-disubstituted-1,2-dihydronaphthalenes (37) in up to 94% ee (Scheme 10).

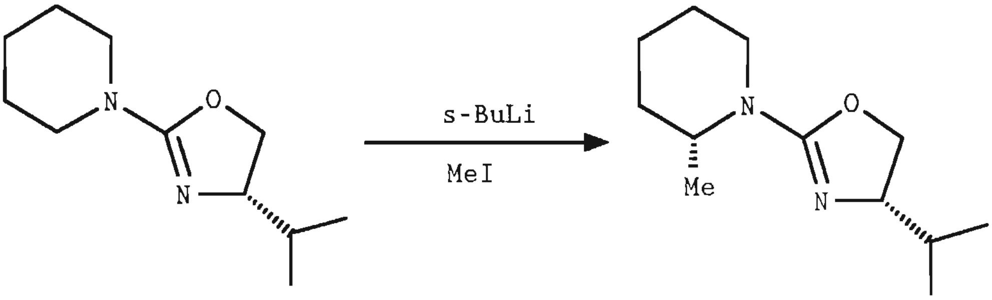


(36) (37)

SCHEME 10

Despite the high levels of stereochemical control that may be obtained with chiral oxazolines derived from (1S,2S)-1-phenyl-2-amino-1,3-propanediol (33), a major limitation is the inaccessibility of the antipode of (33).

A recent publication by Gawley *et al.*[58] describes the diastereospecific alkylation of the chiral oxazoline (38) derived from L-valinol (Scheme 11). Due to the availability of both antipodes of valinol, oxazolines derived from them are readily accessible.

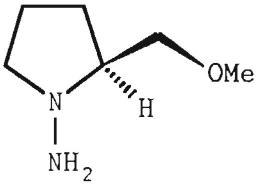


(38) (39)

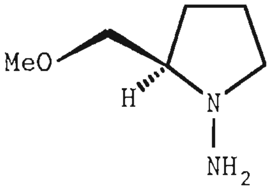
SCHEME 11

1.2.4 CHIRAL HYDRAZONES IN ASYMMETRIC SYNTHESIS.

Methods for stereoselective C,C-bond formation α to the carbonyl group are important in total synthesis. In an excellent review, Enders[59] discusses the enantioselective alkylation of hydrazones derived from the chiral auxiliaries (S)-and (R)-1-amino-2-methoxy pyrrolidine (40) and (41) (SAMP and RAMP).



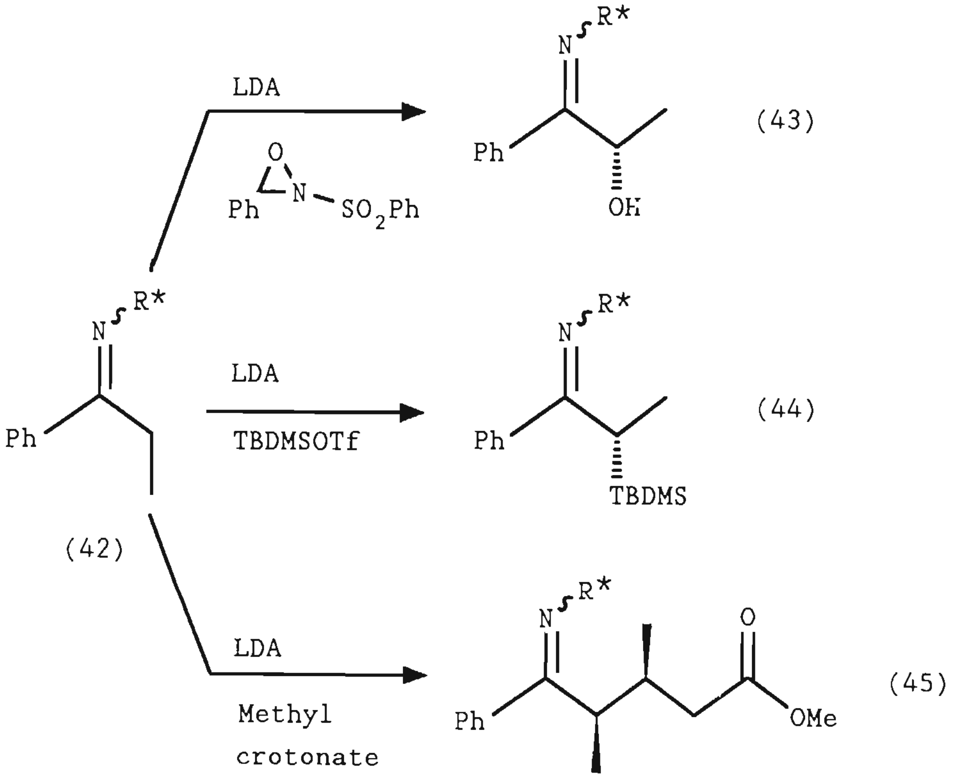
(40) SAMP



(41) RAMP

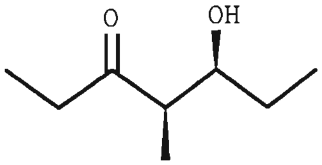
These auxiliaries have also been used for the enantioselective alkylation of the hydrazones of 2,2-dimethyl-1,3-dioxan-5-one.[60] In this way analogues of dihydroxyacetone phosphate were synthesized. Dihydroxyacetone phosphate is used to build 2-ketoses via enzyme catalysed aldols.

In recent years Enders has reported on the reaction of the azaenolate of chiral hydrazones with 2-(phenysulphonyl)-2-phenyloxaziridine,[61] triflates[62] and α,β-unsaturated compounds.[63] In all cases the products are formed with de's of >90% (Scheme 12).

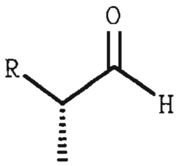


SCHEME 12

Many examples of the use of chiral hydrazone methodology in total synthesis have appeared in the literature. Kocienski has used this methodology in the synthesis of the C(1)-C(15) segment of the immunosuppressant FK506[64] and Enders has synthesised the aggregation pheromone sitophilure (46) and the artificial fragrances lilial (47) and methyl undecanal (48).[65,66]



(46)

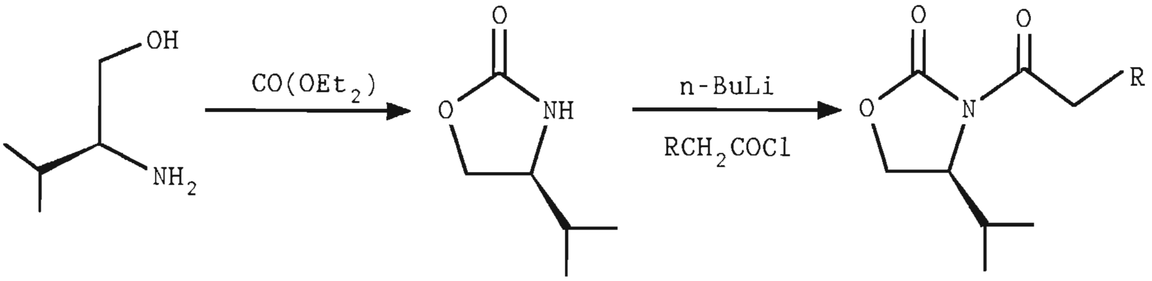


(47) R = 4-$^tBuC_6H_4CH_2$

(48) R = n-C_9H_{19}

1.2.5 AMINO ACIDS AS CHIRAL AUXILIARY PRECURSORS.

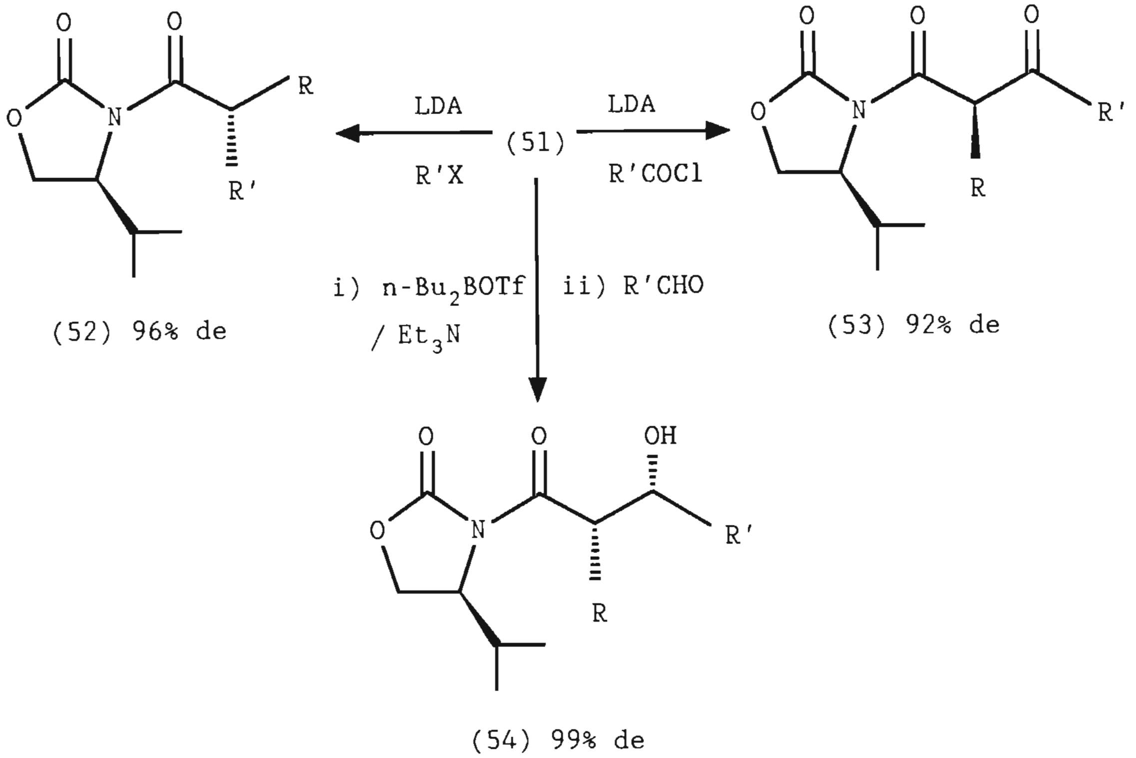
Amino acids as chiral auxiliary precursors appeal to the synthetic chemist because of their relatively low cost, commercial availability and high optical purity. A further advantage is the presence of readily elaborated functionalities. A major advance in amino acid based asymmetric synthesis is the development by Evans of N-acyl-oxazolidinones as chiral enolate synthons in C,C-bond forming reactions. Treatment of L-valinol (49) with diethyl carbonate affords the oxazolidinone (50) which is acylated to give the requisite N-acyloxazolidinone (51) as shown in Scheme 13.



(49) (50) (51)

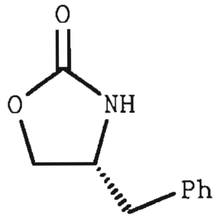
SCHEME 13

The chiral enolates of (51) exhibit a high degree of diastereoselection in aldol,[67] alkylation[68] and acylation[69] reactions (Scheme 14).

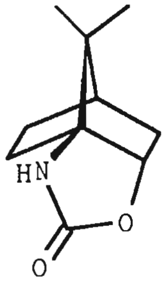


SCHEME 14

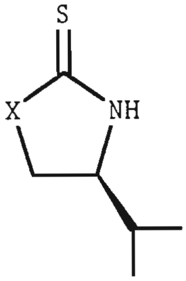
The adducts (52)-(54) are largely crystalline and are homochiral after one recrystallisation. The adducts may be cleaved via hydrolysis, transesterification or reduction to afford carboxylic acids, esters or alcohols with concomitant non-destructive removal of the chiral auxiliary. The oxazolidinones (55) and (56) derived from (S)-phenylalaninol[70] (Diels-Alder reaction) and ketopinic acid[71] (aldol reaction) respectively are excellent asymmetric inducers. Mention should also be made of the thio analogues (57) and (58) derived from valinol. Nagao[72] has shown that they also exhibit good diastereocontrol in the aldol reaction.



(55)



(56)

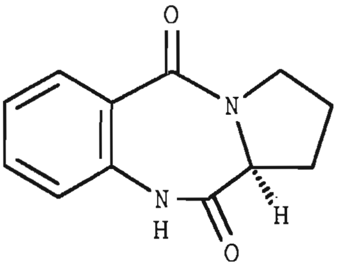


(57) X = O

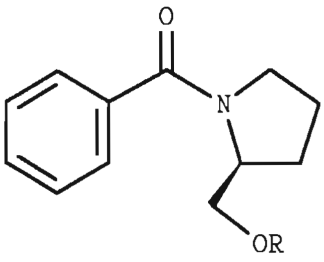
(58) X = S

The usefulness of chiral N-acyloxazolidinones is exemplified by the many elegant total syntheses that take advantage of their efficient chirality transfer ability and the ease of purification of adducts. These syntheses include those of the essential oil (+)-α-cuparenone,[73] a fragment of the streptogramin antibiotic madumycin II,[74] the antifungal lipopeptide Eschinocandin D[75] and (+)-ionomycin[7] (via the synthon approach).

The proline derived auxiliaries (59)-(61) have been utilised in the synthesis of chiral cyclohexanes in an enantioselective Birch-reduction/alkylation process.[76] Schultz[77] has used this methodology in the synthesis of (+)-perhydro-219A which is an unusual alkaloid isolated from the poisonous frogs of Colombia.



(59)



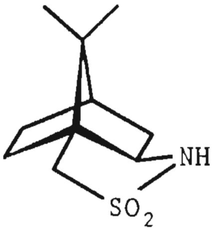
(60) R = H

(61) R = Me

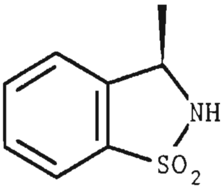
An important aspect of chiral auxiliaries derived from amino acids is the ready availability of both antipodes.

1.2.6 CHIRAL SULTAM AUXILIARIES.

The chiral sultam auxiliaries (62) and (63) developed by Oppolzer exhibit excellent chirality transfer in various chemical transformations.



(62)

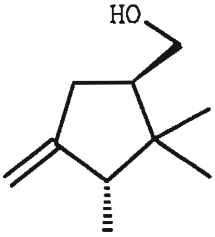


(63)

These include the Diels-Alder reaction, and alkylation, acylation and aldol reactions.[78,79] A major advantage of these auxiliaries is the crystallinity of the products. Thus, one recrystallisation affords in most cases homochiral products.

Other valuable transformations involving chiral sultams have been reported by Oppolzer. The N-enoyl derivatives of (62) undergo diastereoselective OsO_4-catalysed bis-hydroxylations[80] and 1,4-addition reactions of Grignard reagents[81] and hydrides.[82] Alkyl halides have been used to trap the enolates which result from 1,4-addition reactions. In this way the diastereoselective synthesis of compounds with two centres of asymmetry (at Cβ and Cα) has been achieved.

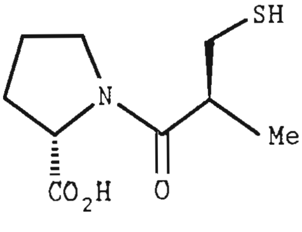
A total synthesis of β-necrodol (64), isolated from the defensive secretion of a carrion beetle has been reported by Oppolzer and co-workers.[83] The main step is the conjugate addition of methyl cuprate to a chiral N-enoyl sultam.



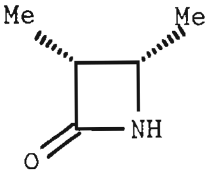
(64)

1.2.7 A METAL-CENTRED CHIRAL AUXILIARY.

The chiral auxiliary $[(C_5H_5)Fe(CO)(PPh_3)]$ exerts a high degree of stereochemical control over the reactions of the attached acyl ligands. Alkylation of enolates of saturated iron acyl complexes and tandem Michael addition/alkylation of α,β-unsaturated iron carbonyls, proceed with high diastereoselectivity. This stereochemical control has been harnessed in the synthesis of the antihypertensive drug (-)-captopril (65)[84] and β-lactams (66).[85]

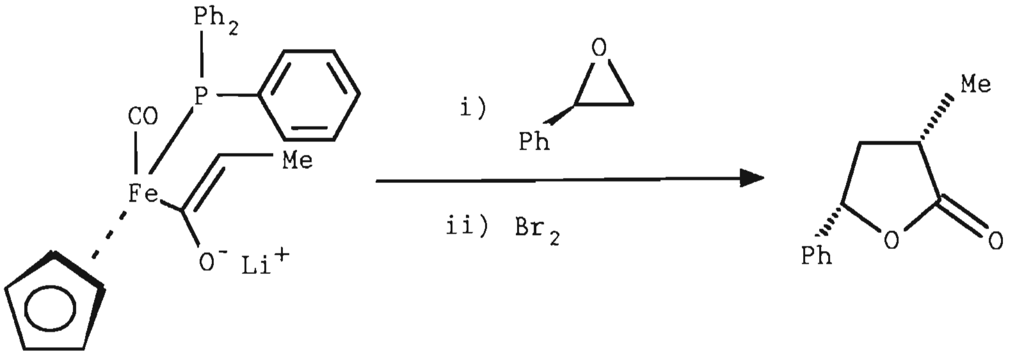


(65)



(66)

Davies has recently published[86] a method for the direct synthesis of homochiral sulphoxides via the oxidation of a sulphide bearing chiral iron complex. The utility of this chiral auxiliary is further demonstrated by the published method for the synthesis of homochiral lactones as shown in Scheme 15.[87] The reaction of the lithium enolate (67) with an epoxide followed by oxidative decomplexation afforded the lactone (68).



(67)

(68)

SCHEME 15

1.3 ENANTIOSELECTIVE CATALYSIS.

In recent years, research into the development of enantioselective catalysts for asymmetric synthesis has evolved at a rapid rate. This branch of chemistry is of special interest with respect to industrial applications. The enantioselective hydride addition reactions to C=O, C=C and C=N bonds are well known and have been reviewed.[88]

More recently Sharpless and co-workers[89] have reported on catalytic asymmetric dihydroxylations of alkenes. The catalysts AD-mix-β or AD-mix-α are prepared from potassium osmate, potassium carbonate, ferricyanide and a new class of phthalazine cinchona alkaloid based ligands. The ee's achieved are generally >90% (Figure 5).

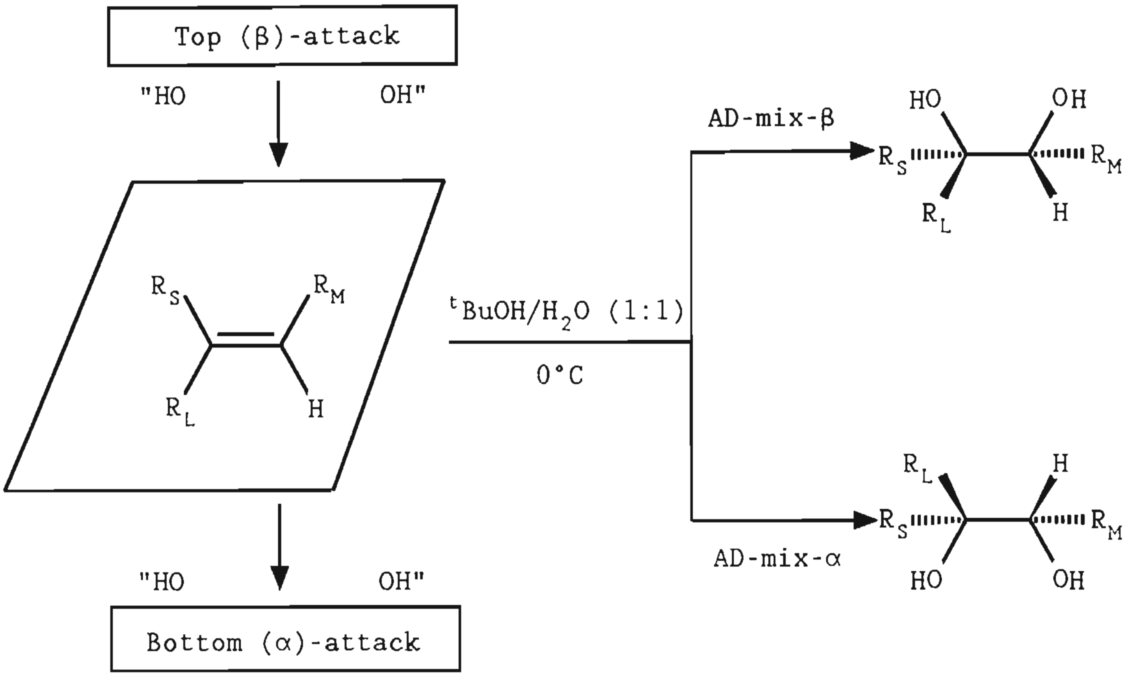
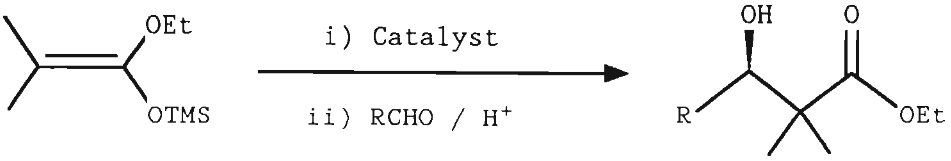


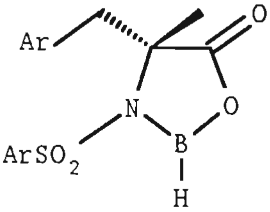
FIGURE 5

Attempts at carrying out enantioselective catalytic C,C-bond forming reactions have met with variable success. However, Masamune *et al.*[90] have recently reported on enantioselective catalytic aldol condensations which afford β-hydroxy esters with ee's of >90% (Scheme 17).



(69)

(70)

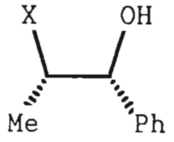


SCHEME 16

While it has not been the aim of this introduction to cover all of the variants of asymmetric synthesis via chiral auxiliaries, it is hoped that the development of this aspect has been placed somewhat in perspective.

2. DISCUSSION

Research groups around the world are actively engaged in developing new methods for the production of optically pure chiral compounds. A measure of the organic chemist's commitment to this end is the growing number of reviews and specialist conferences, and new journals dedicated to this topic. For many decades, the chiral pool has been the primary source of chiral auxiliaries. An often overlooked source of chirality for asymmetric synthesis is the alkaloid ephedrine (71), which constitutes 1% of the stems and leaves of *Ephedra equisetina* Bunge,[91] a plant indigenous to China and India. Ephedrine is readily available as its hydrochloride salt (72).



(71) X = NHMe

(72) X = NHMe.HCl

(73) X = $NHSO_2R$

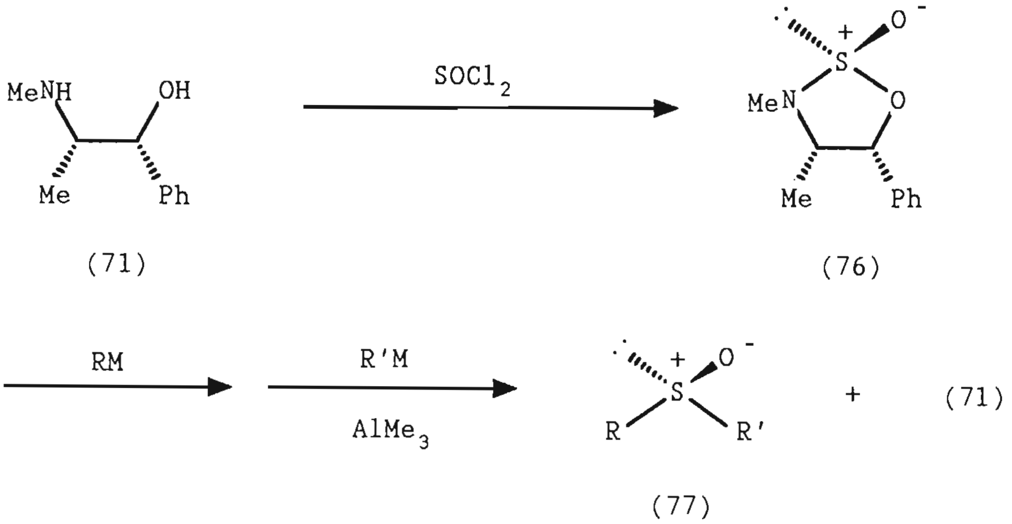
(74) X = NMe_2

(75) X = $MeN(CH_2)_2NMe_2$

Acyclic ephedrine derivatives (73)-(75), which are not covalently bound to one of the starting materials, have recently been used as chiral auxiliaries.

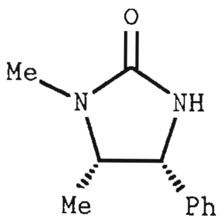
The chiral reagent (73) effects the addition of the methyl group to aldehydes[92] (~90% ee) while the chiral reagent (74) influences the hydride reduction of ketones[93] to yield 2° alcohols with ee's of up to 98%. The 1,4 addition of RCuM[94] to enones proceeds with an ee of up to 95% in the presence of (75).

In the case of cyclic ephedrine derivatives, the auxiliaries of greatest interest are those which are covalently bound to the starting material. A recently published report by Benson *et al.*[95] on the synthesis of chiral sulphoxides with ee's of >99%, demonstrates the chirality transfer ability of the ephedrine moiety (Scheme 17).

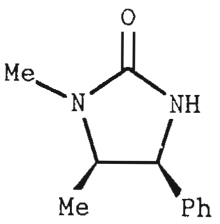


SCHEME 17

Additional examples that have recently found use in asymmetric synthesis are the imidazolidin-2-ones (78) and (79). They are derived from (-) and (+) -ephedrine hydrochloride respectively.[96]

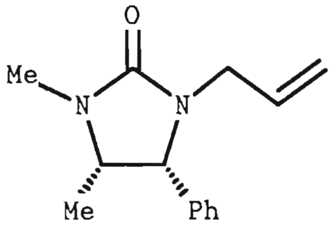


(78)

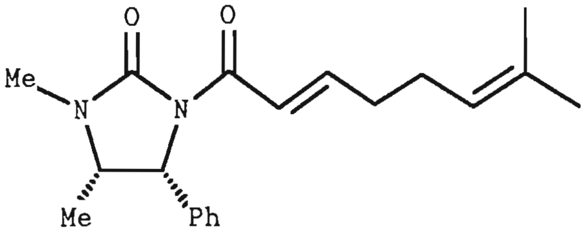


(79)

Helmchen and co-workers[97] found application for (78) in diastereoselective homoaldol additions of the carbanion of the *N*-allyl derivative (80) to aldehydes and ketones to afford homochiral γ-lactones. In recent years diastereoselective alkylations [98,99,100] of *N*-acylimidazolidin-2-ones have also been achieved. The short and efficient synthesis of (+)-citronellic acid described by Stephan *et al.*[101,102] has, as its crucial step, the diastereoselective conjugate addition of a methyl cuprate to the *N*-enoyl derivative (81).



(80)



(81)

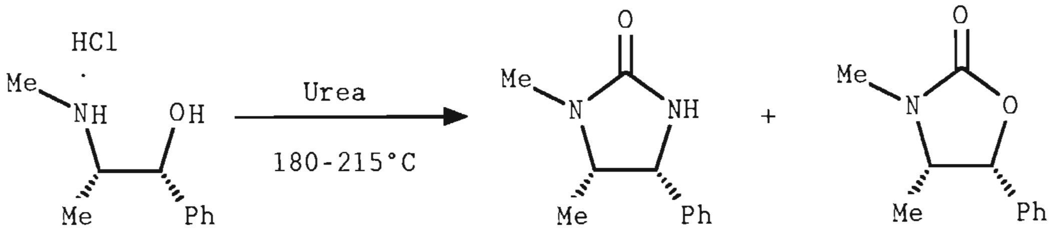
In each of the above examples, the imidazolidin-2-ones (78) and (79) exhibited excellent levels of asymmetric induction. With this background information in hand, the initial aims of this investigation were set out as follows:

1. To determine the diastereoselectivity of the aldol reactions of the *N*-propionyl derivative of (78) with various aldehydes.

2. To remove and recover the chiral auxiliary (78) *via* a non-destructive method.

2.1 THE SYNTHESIS OF (4R,5S)-1,5-DIMETHYL-4-PHENYL-IMIDAZOLIDIN-2-ONE (78).

The chiral imidazolidin-2-one (78) was synthesised according to the method published by Close[96] in which (-)-ephedrine hydrochloride is fused with urea as shown in Scheme 18.



(72) (78) (82)

SCHEME 18

However the yield of (78) reported by Close is relatively low, mainly due to the competing condensation process which affords the oxazolidin-2-one (82). Thus attempts were made to improve the yield of (78) as shown in Table 1. As one might expect, efficiency of stirring affected the yield.

TABLE 1: Optimisation of the yield of (78)

Entry	Conditions [a]	Yield (%)
1	A	47
2	B	60
3	C	58
4	D	30 [b]

a) Using the method described by Close with the following variations:

A = urea acts as both the solvent and the reagent at its melting point (without stirring);

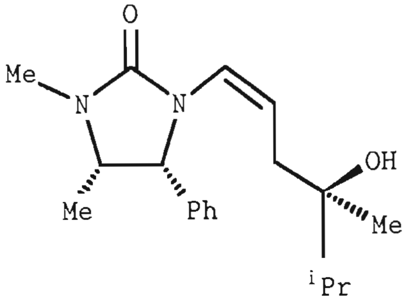
B = as for A but with magnetic stirring;

C = as for A with mechanical stirring for large scale preparations;

D = nitrobenzene as solvent with magnetic stirring.

b) Isolation of the product was difficult.

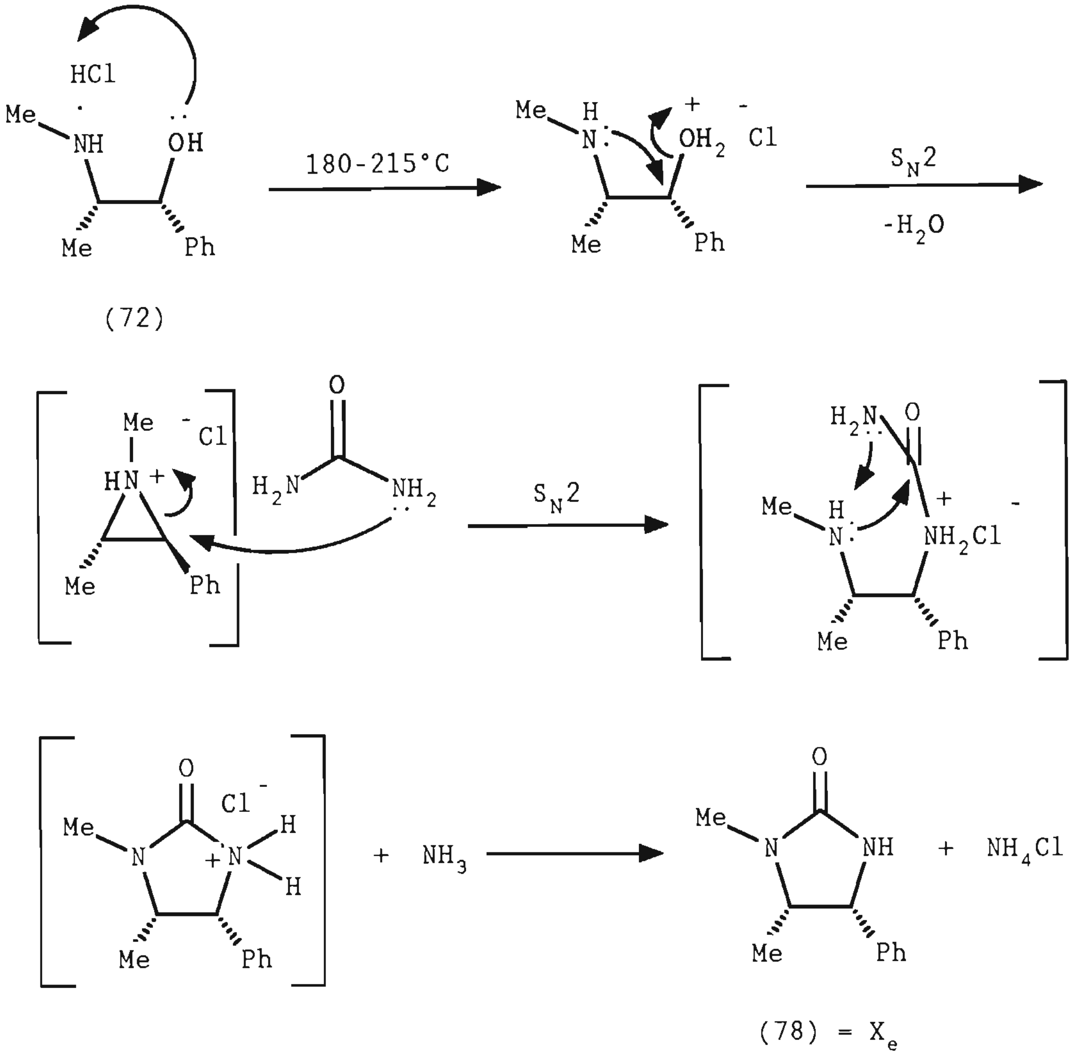
Close concluded that the product of the fusion reaction of (±)-ephedrine hydrochloride and urea is the imidazolidin-2-one with the 4,5-*trans*-configuration. However the *cis*-configuration was established from an X-ray crystal structure analysis of the homoaldol product (83) by Helmchen and co-workers.[97]



(83)

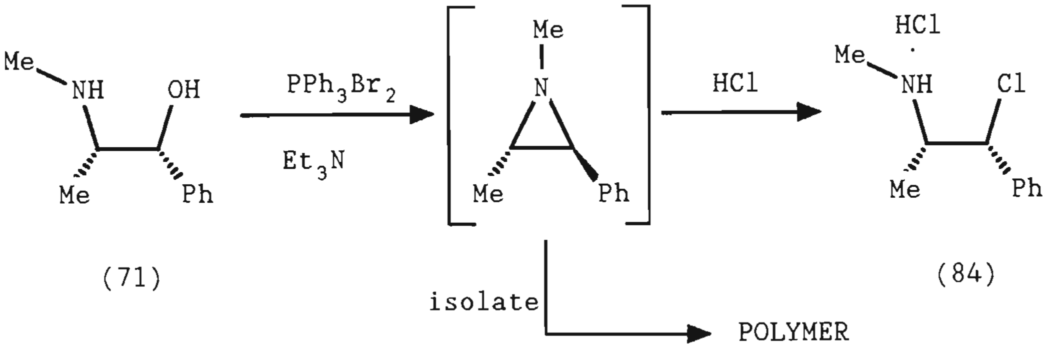
Whilst Helmchen and co-workers further refuted the possibility of the *trans*-configuration on the basis of 'mechanistic considerations', they did not offer an explanatory mechanism. It is thus proposed that the likely mechanism proceeds *via* a double inversion pathway (i.e. 2 x S_N2 steps, commonly referred to as the neighbouring group mechanism).[103,104a]

The first step of the proposed mechanism (Scheme 19) involves protonation of the hydroxyl group. This could occur *via* either an inter- or an intramolecular process. The latter is depicted in Scheme 19. The first S_N2 step involves the attack of the nitrogen lone pair (neighbouring group) at the benzylic carbon to form an intermediate aziridine salt.[105,106] This is followed by regioselective attack of the urea nitrogen lone pair at the more reactive benzylic carbon.



SCHEME 19

Several attempts were made to isolate the intermediate aziridine salt postulated in the mechanism. The attempts included melting (-)-ephedrine hydrochloride or refluxing a solution of (-)-ephedrine hydrochloride in nitrobenzene (in the absence of urea). Both of these attempts yielded a polymeric material. In fact Okada *et al.*[107] and Taguchi and Kojima[108] have independently reported polymeric materials as products of their attempts to synthesis the aziridine from (-) ephedrine (Scheme 20). Okada *et al.*[107] provided evidence for the existence of the aziridine by treatment of the reaction mixture with HCl as shown in Scheme 20 to afford the salt (84).

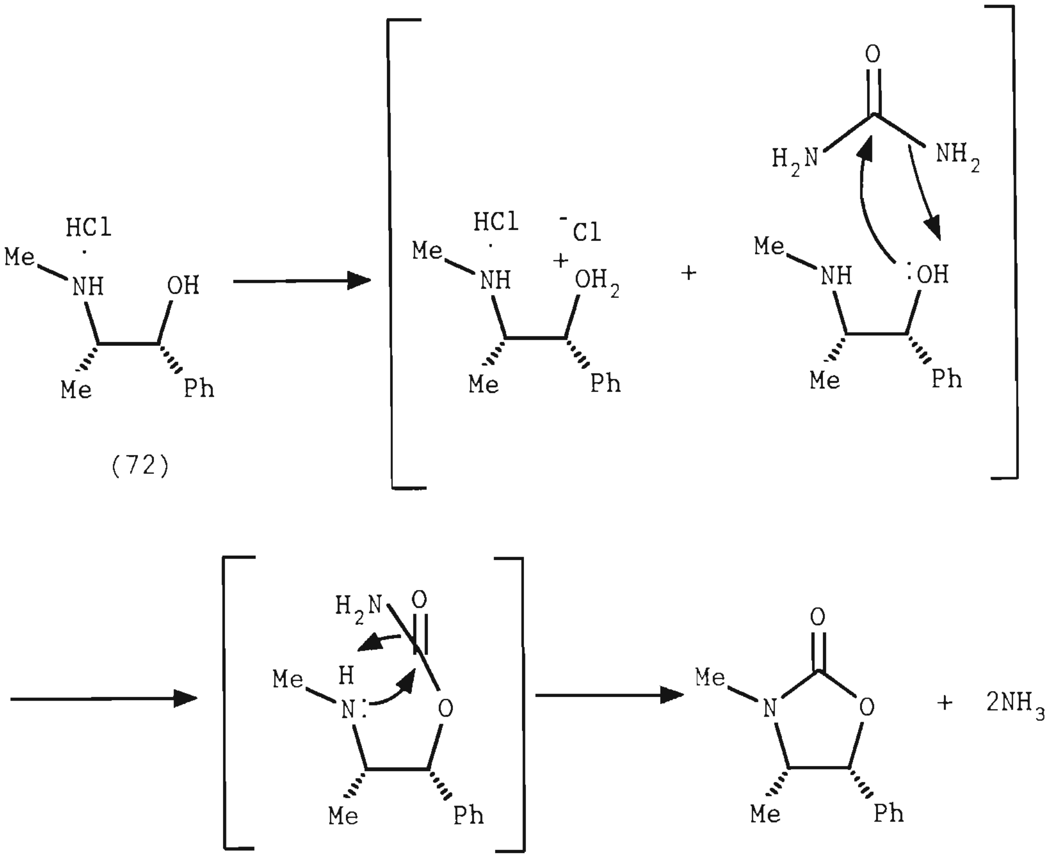


SCHEME 20

Under the conditions for the synthesis of (78) (i.e the formation of NH_4Cl), one would thus expect that the postulated aziridine salt would react with the NH_4Cl to form the hydrochloride salt (84). However during the reaction one observes NH_4Cl crystals on the condenser due to sublimation (i.e. it is removed from the melt). At the temperature of the attempted isolation, polymerisation would be expected to be a facile process since the polymerisation reported by Okada *et al.*[107] occurred at 0-25°C. Finally, instead of trying to isolate the postulated aziridine salt, urea (cf. HCl in Scheme 20) was added after 30 minutes. Again only a polymeric material was obtained.

In summary, the above observations strongly suggest that the formation of the imidazolidin-2-one (78) proceeds *via* a pathway with the aziridine salt as an intermediate.

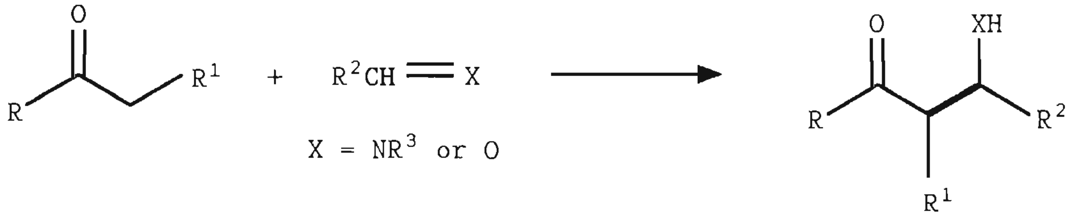
An explanation for the competing oxazolidin-2-one formation is illustrated in Scheme 21. In this mechanism, intermolecular protonation of the hydroxyl group is preferred over the intramolecular mode to afford ephedrine. Sequential nucleophilic attack by the ephedrine hydroxyl and amine lone pairs[104b] at the urea carbonyl lead to the undesired oxazolidin-2-one (82).



SCHEME 21

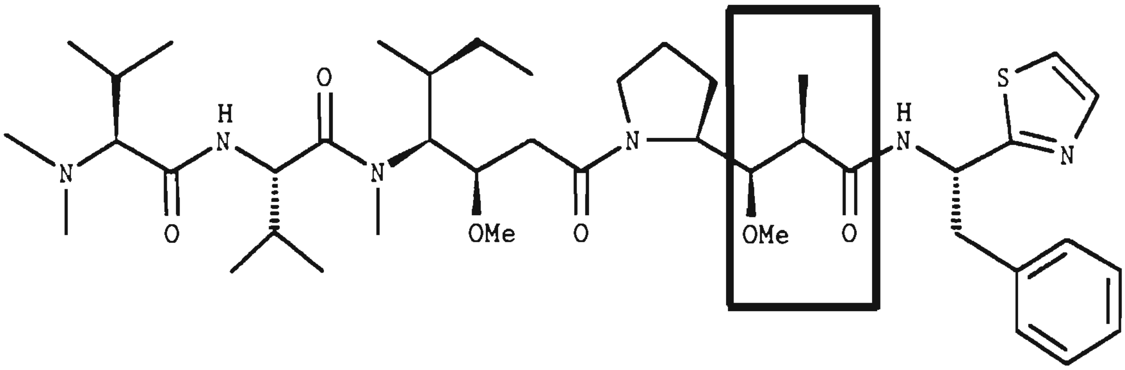
2.2 THE ALDOL REACTION.

The aldol reaction is one of the most important C-C bond forming and chain lengthening processes. This is especially so for the creation of 1,3 - O,O and 1,3 - N,O heteroatom relationships as shown in Scheme 22.

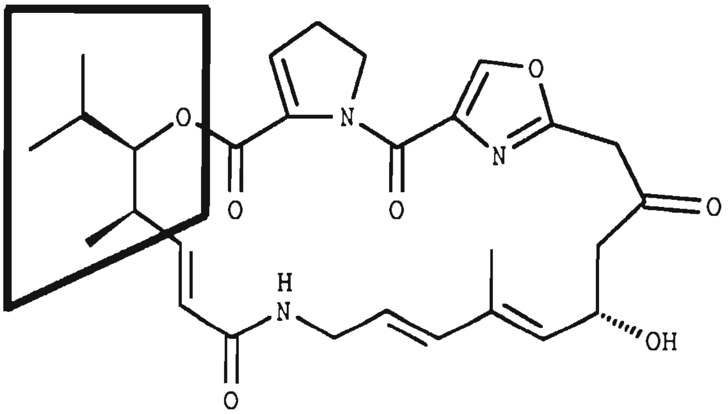


SCHEME 22

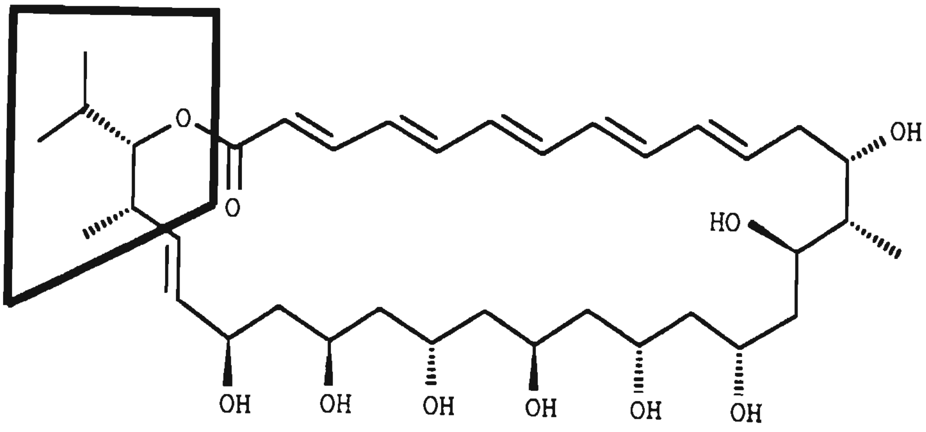
These heteroatomic relationships are an integral part of (and may lead to the synthesis of) numerous natural products. This is evident, for example from the structure of dolastatin 10[109] (an antineoplastic peptide from a sea hare) and the type A streptogramin antibiotics.[110]



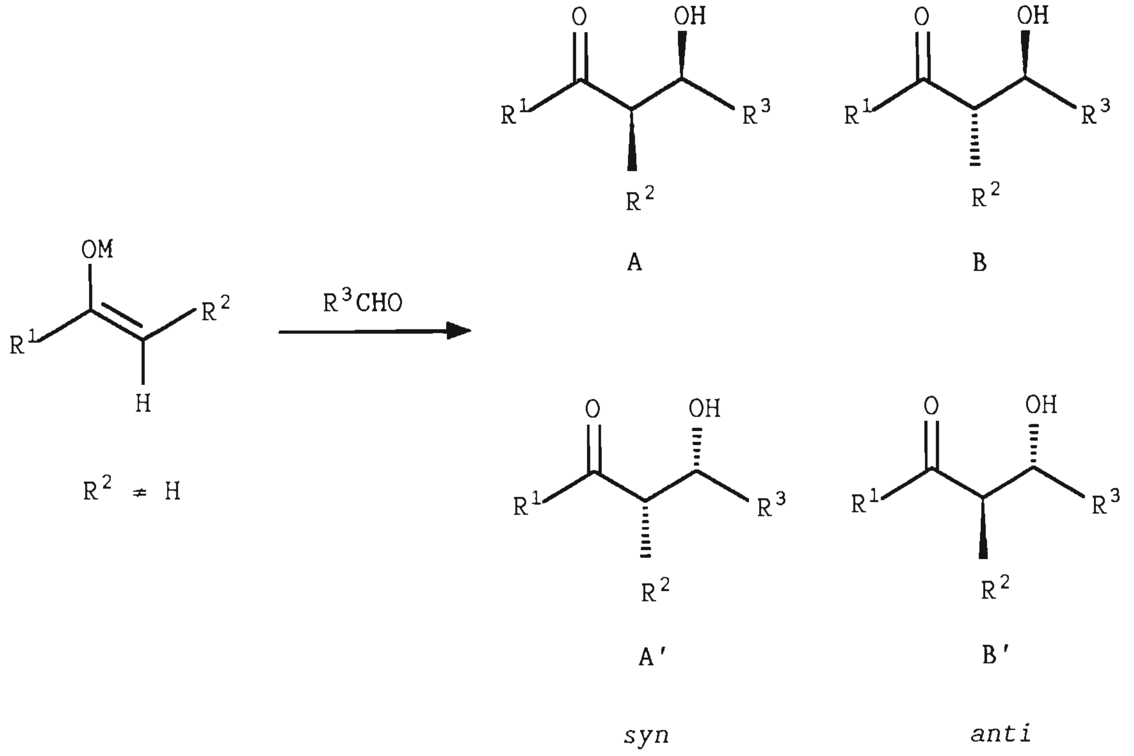
DOLASTATIN 10



STREPTOGRAMIN
ANTIBIOTICS



The general outcome of the aldol reaction when using prochiral preformed enolates, is the formation of four possible diastereomers (Scheme 23).



SCHEME 23

There are two stereochemical aspects which are evident. The first is diastereoselection [**A/A'** vs **B/B'**], and the second is enantioselection [**A** vs **A'**] or [**B** vs **B'**]. Diastereoselection to afford either the *syn* or the *anti* diastereomers is possible by the judicious choice of the metal counterion, the substituents R^1, R^2 and R^3 (steric effects) and optimised reaction conditions. However further differentiation to achieve enantioselection requires the incorporation of an asymmetric element, which for the purposes of this investigation means R^1 = asymmetric element = the chiral imidazolidin-2-one (78).

2.2.1 ENOLATE GEOMETRY *vs* DIASTEREOSELECTION.

The design of an efficient diastereoselective aldol reaction requires that all stereochemical aspects of the bond construction process be kinetically controlled. A major step forward has been the discovery that there exists a correlation between the enolate geometry and the stereochemical outcome of the reaction as shown in Figure 6.

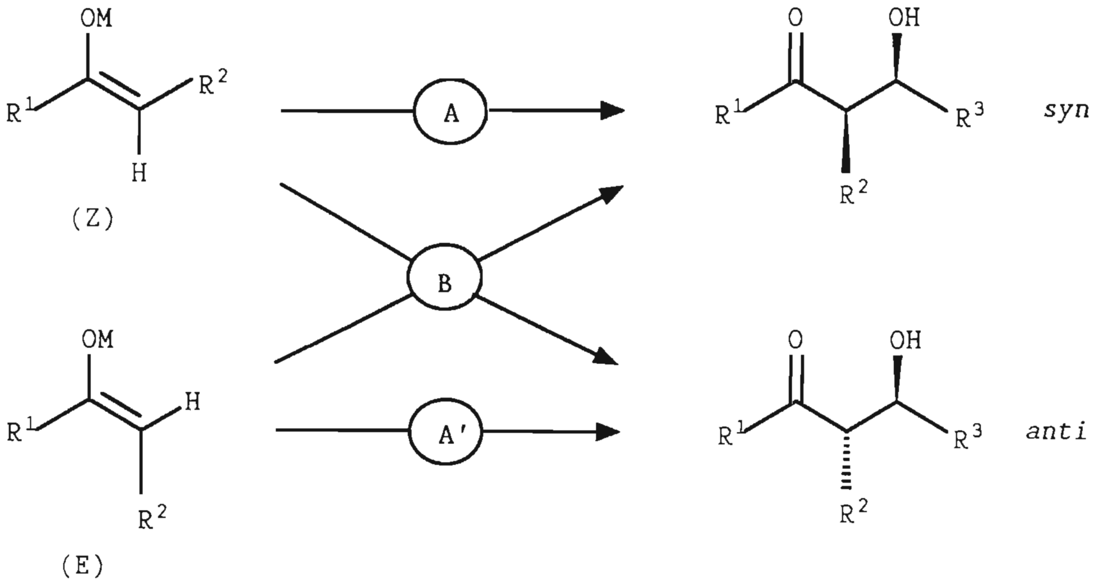
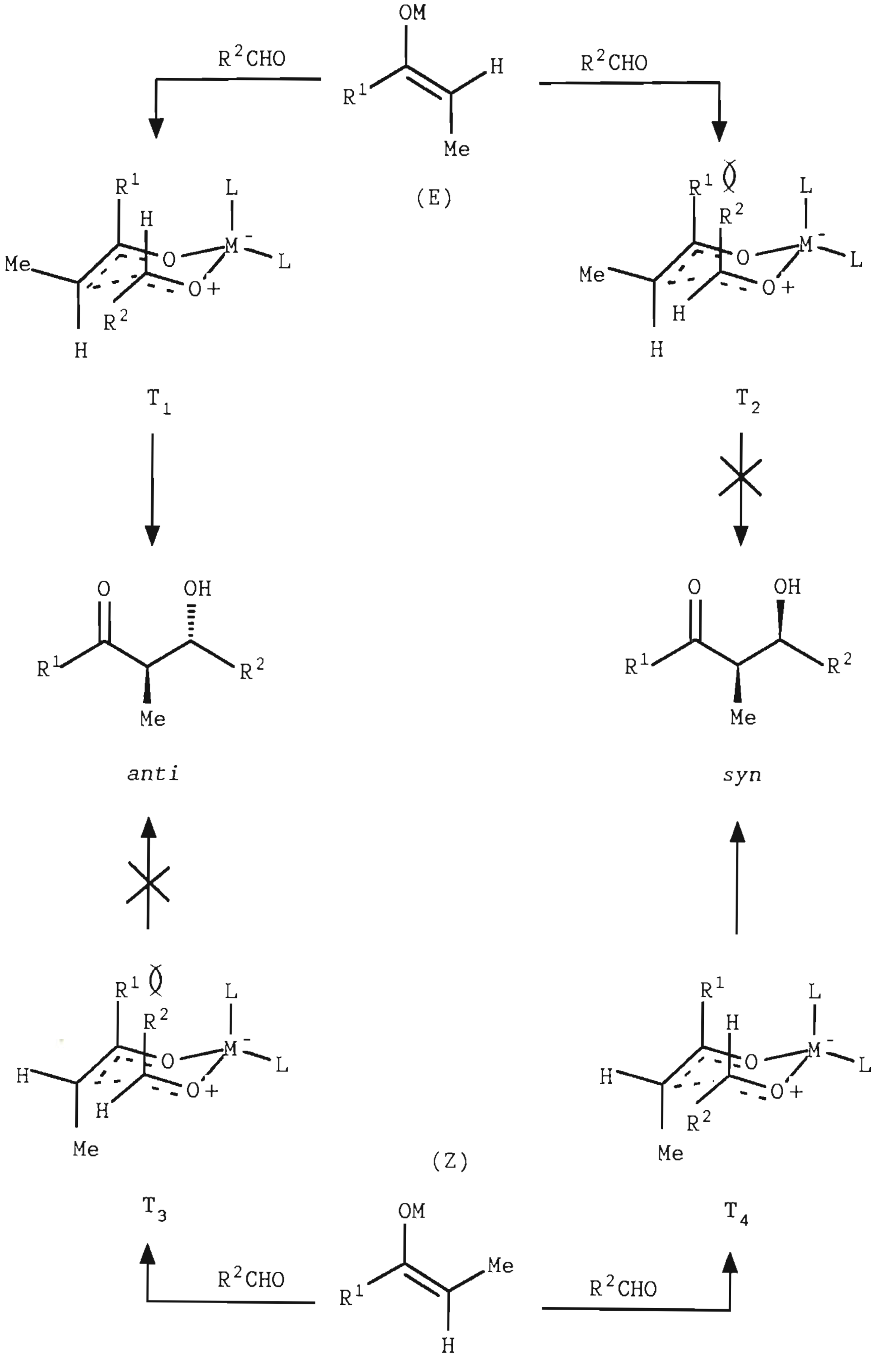


FIGURE 6

The correlation that generally applies when the metal counterion belongs to Group I, II or III is that Z-enolates tend to afford *syn* aldols and E-enolates tend to give *anti* aldols (pathways **A** and **A'** respectively).[111,112] This correlation is stronger for: (i) Z-enolates than for E-enolates; (ii) systems where R^3 is large; (iii) Z- or E-enolates where R^1 is sterically demanding. The correlation is reversed (pathway **B**) when R^2 is sterically demanding. The correlation between enolate geometry and aldol product stereochemistry has been accepted[113,114] as being the result of diastereomeric Zimmerman-Traxler[115] cyclic 6-membered chair transition states (Scheme 24).



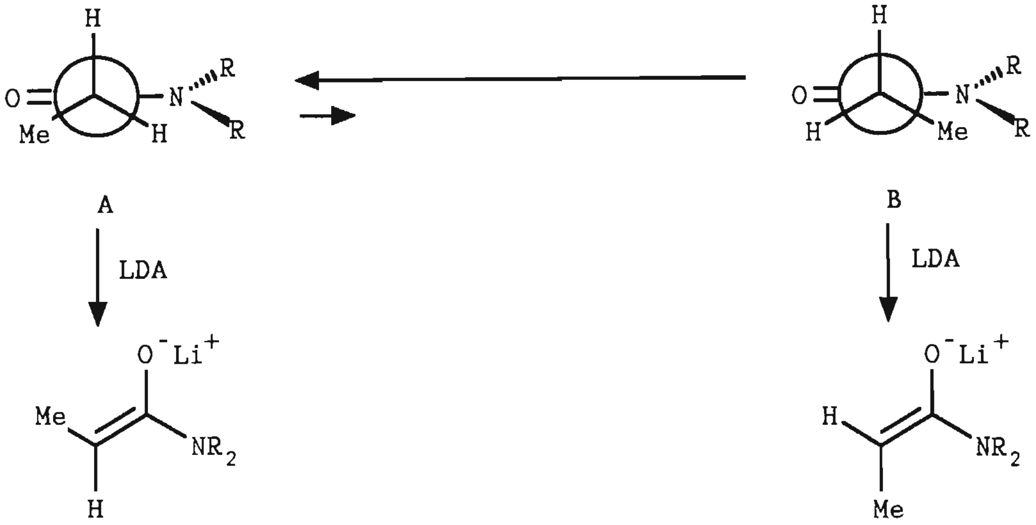
SCHEME 24

If the assumption that the aldol reaction using metal enolates proceeds *via* a pericyclic process[116] is followed, the influence of variable steric parameters may be analysed to determine their effect on the heats of formation of the diastereomeric transition states from an enolate of a particular geometry. In the case of the E-enolate the transition state $\mathbf{T_2}$ is expected to be destabilised by $R^1 \leftrightarrow R^2$ interactions and thus favour transition state $\mathbf{T_1}$. For the Z-enolate the same interactions would disfavour transition state $\mathbf{T_3}$ and thus favour transition state $\mathbf{T_4}$. These arguments, based on steric interactions, are in agreement with the Z → *syn* and the E → *anti* correlation described earlier.[111,112]

Heathcock has shown that for high levels of the above correlation to exist for Li enolates, R^1 must be a large group so as to maximise $R^1 \leftrightarrow R^2$ interactions (e.g. R^1 = ^{t}Bu or 1-adamantyl). However an increase in the size of the ligand at the metal centre would increase $L \leftrightarrow R^2$ interactions and thus irrespective of the size of R^1, $\mathbf{T_1}$ would again be favoured for the E-enolate and $\mathbf{T_4}$ for the Z-enolate. A combination of large R^1 and large L should enhance the probability of obtaining for example the *syn* product from the Z-lithium enolate.

2.2.2 LITHIUM AMIDE ENOLATES IN THE ALDOL REACTION.

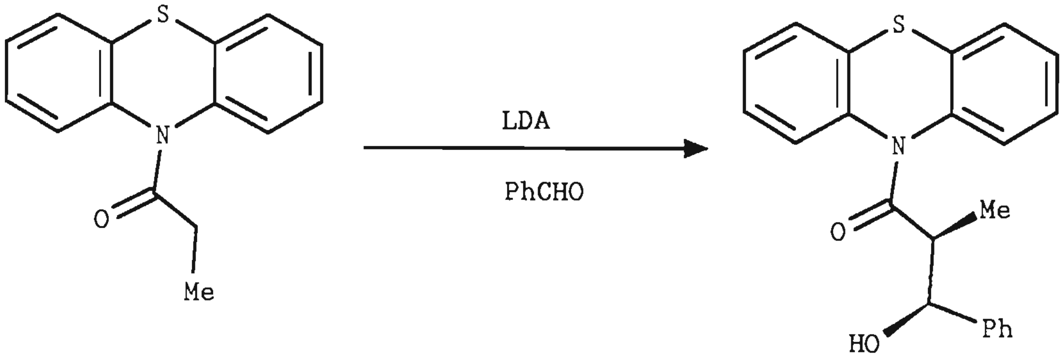
Studies carried out by Evans and co-workers[116,117] on the synthetic utility of lithium amide enolates have shown that dialkyl amides are stereoselectively enolised to afford the Z-isomer. They postulated that this high level of Z-diastereoselection is a result of ground state allylic strain interactions[118] between R and the methyl substituent (Scheme 25), which disfavours deprotonation *via* conformation **B** which leads to the E-enolate.



(Z)-enolate (E)-enolate

SCHEME 25

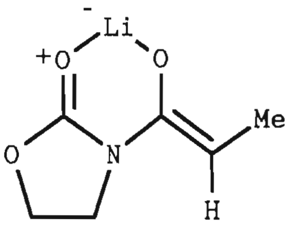
For simple propionamides (i.e. R = Me, ${}^{i}Pr$),[119,120] the reaction of the Z-enolate with benzaldehyde affords the aldol products in a *syn* : *anti* ratio of 60:40. This ratio is the same for *N*-propionylpyrrolidine which has been shown to give only the Z-enolate on treatment with LDA.[116] This low aldol selectivity appears to be a result of small $R^1 \leftrightarrow$ Ph steric interactions ($R^1 = NR_2$) for $\mathbf{T_3}$ in Scheme 24. Babudri *et al.*[121] have shown that an increase in the bulk of the nitrogen substituent (and as a result R^1 in Scheme 24) improves the diastereoselectivity of the aldol reaction (Scheme 26).



(85) (86)

SCHEME 26

Early work carried out by Evans *et al.*[122] has shown that the kinetic deprotonation of *N*-propionyloxazolidin-2-ones with LDA affords the Z-enolate exclusively (87).



(87)

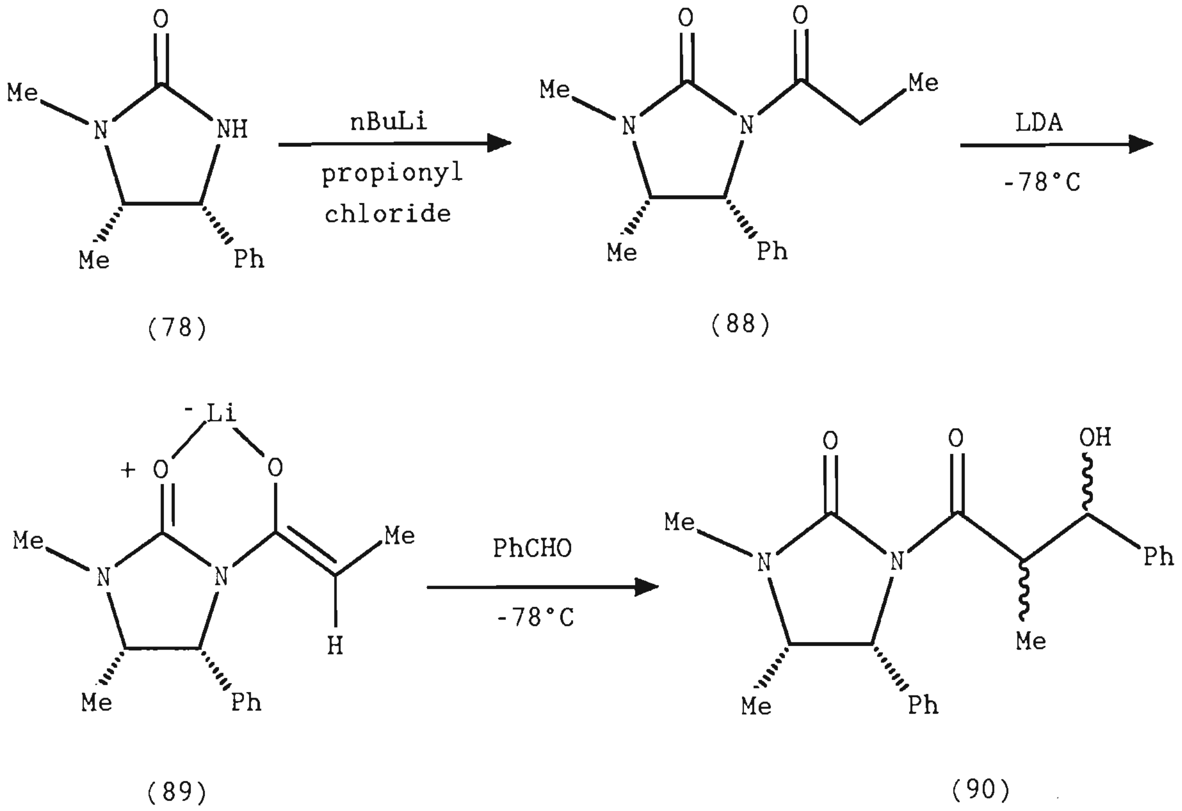
From this background information two points are clearly highlighted as being favourable for high levels of diastereoselectivity for the aldol reaction of the *N*-propionyl derivative of the imidazolidin-2-one (78):

(i) Kinetic deprotonation of this substrate with LDA should afford only the Z-enolates as is the case for *N*-propionyloxazolidin-2-ones;

(ii) When R^1 = imidazolidin-2-one moiety (78), R^1 may be regarded as a large group and thus the reaction of the Z-enolate should be *syn* selective (cf. Scheme 24).

2.2.3 THE ALDOL REACTION OF THE CHIRAL Li-ENOLATE (89) WITH BENZALDEHYDE.

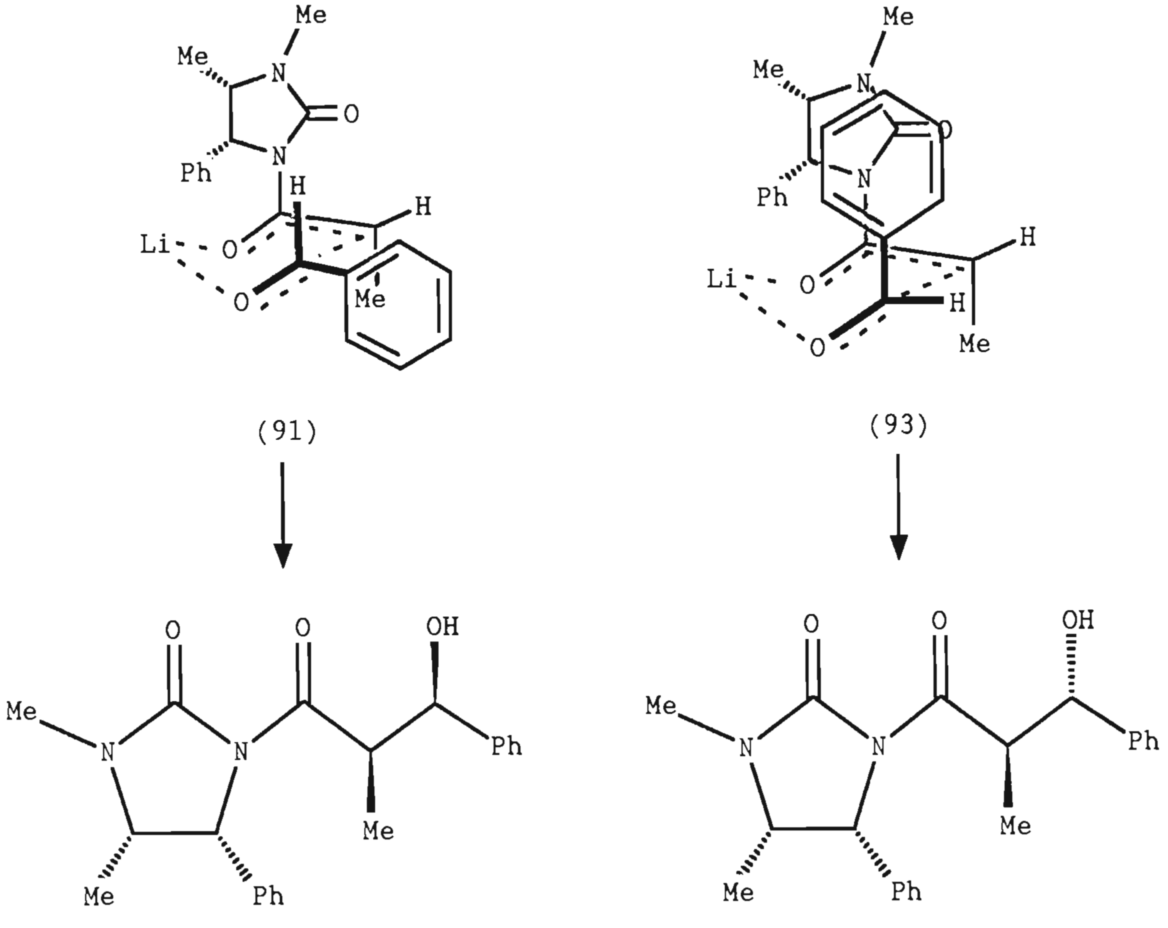
The chiral auxiliary (78) was smoothly acylated by the reaction of its lithium anion with either propanoyl chloride or propionic anhydride to afford (4R,5S)-1,5-dimethyl-4-phenyl-3-propanoylimidazolidin-2-one (88) (Scheme 27). Kinetic enolisation of (88) with LDA afforded the expected Z-enolate which upon reaction with benzaldehyde, yielded a mixture of aldol products (90).



SCHEME 27

^{1}H NMR analysis showed that the *syn* : *anti* ratio for this reaction was 40:60. This ratio was determined by measurement of the integral for the H-3$'$ doublet after D_2O treatment. The relative stereochemistry was determined from coupling constants (J_{AB} *syn* < J_{AB} *anti*). This result, although disappointing, corresponds well with that obtained by Evans *et al.*[122] for the reaction of lithium enolates of *N*-propionyloxazolidin-2-ones with benzaldehyde *viz.* *syn*:*anti* = 45:55 up to 40:60.

A possible explanation for this loss of Z-enolate → *syn* correlation may be due to both steric and electronic considerations in the transition state as shown in Figure 7.

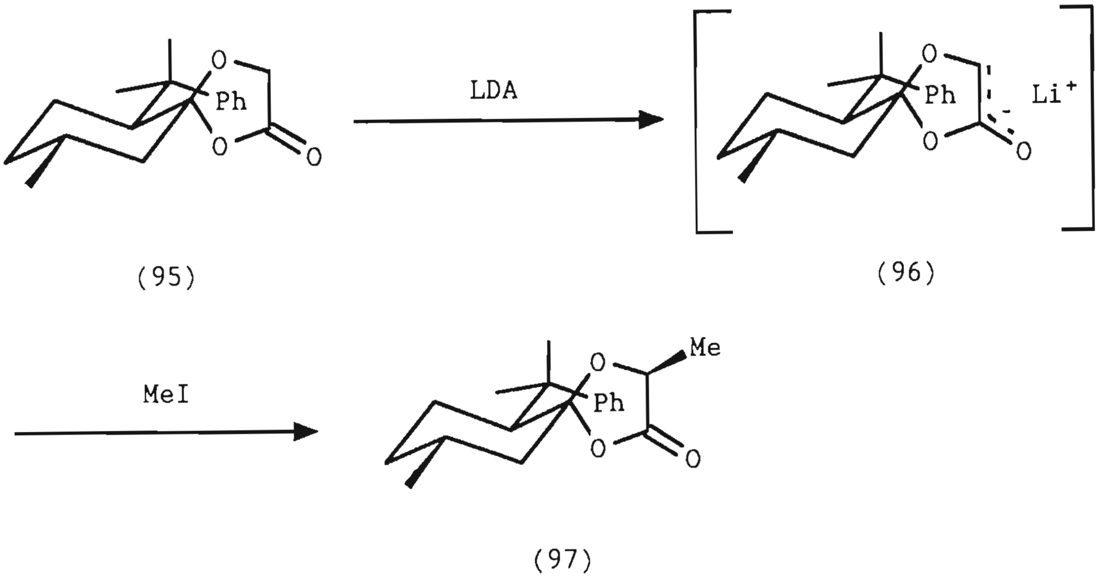


(91) (93) (92) (94)

FIGURE 7

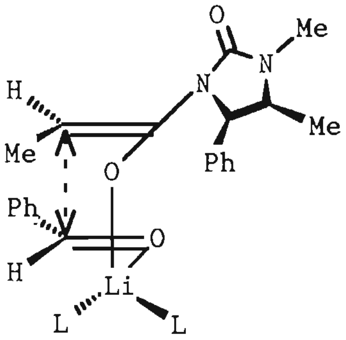
In transition state (91) the phenyl ring of the aldehyde assumes an equatorial orientation due to the pseudo-1,3-diaxial steric interaction Ph ↔ Xe. This transition state leads to the expected *syn* product (92). On the other hand the formation of the *anti* product (94) may arise from the transition state (93). The normally unfavourable axial orientation of the phenyl group is postulated on the basis of a net π-π attractive force between the phenyl ring and the N-CO-N system being favoured. The two π systems are parallel and offset from one another with an interplanar separation of ~3.10 Å (calculcated from molecular models). This fits with the model for π-π attractive interactions proposed by Hunter and Sanders[123] which suggests that the ideal interplanar distance is between 3 and 4 Å.

The concept of phenyl ring/heterocycle π-π attractive interaction may be invoked to rationalise the result obtained by Pearson and Cheng[124] for the diastereoselective alkylation of the dioxolanone derived from 8-phenylmenthone as illustrated in Scheme 28.



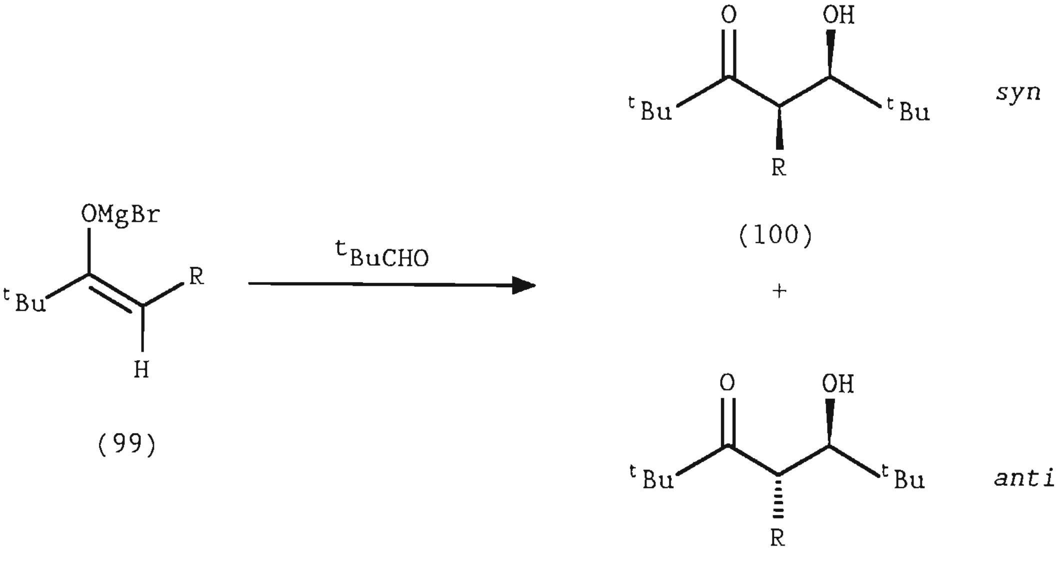
SCHEME 28

An alternative proposal for this decrease in the Z → *syn* correlation has been offered by Evans *et al.*[125] This involves the formation of a boat transition state (98). If one considers the methyl group of the enolate to be the large group (i.e. Ph ←→ Me gauche interactions are serious for the chair transition state (91)), the Evans postulate suggests that the heat of formation of the boat transition state (98) may be less than for the chair transition state (91). This implies that a 'crossover' from chair to boat might be favourable.



(98)

It should be noted that the validity of the boat transition state model requires that the enolate substituent be large. The results of an investigation by Dubois and Fellman[126] are of particular relevance here. They found that where for example, Xe and the aldehyde stay the same while the enolate ligand is varied, the methyl group may be regarded as a small ligand. They conclude that in such cases *syn* diastereoselection should result (Scheme 29; Table 2).



SCHEME 29

TABLE 2: Kinetic diastereoselection as a function of the enolate ligand R (Scheme 29).

R	*syn* : *anti*
CH_3	100 : 0
C_2H_5	100 : 0
n-C_3H_7	98 : 2
i-C_4H_9	97 : 3
i-C_3H_7	29 : 71
t-C_4H_9	0 : 100

Whilst the boat transition state proposal offered by Evans may suffice for simple amides it may be inappropriate for the π dispersed systems that are involved when dealing with imidazolidin-2-ones or oxazolidin-2-ones. In the light of the preceding arguments, the proposed π-stacked transition state (93) seems the more reasonable and the two proposals perhaps work in a co-operative manner against the normal correlation.

2.2.4 VARIATION OF THE METAL CENTRE.

As mentioned earlier, the presence of bulky ligands attached to the metal is expected to disfavour the chair transition state **C** leading to the *anti* product for the Z-enolate (Figure 8). This means that the combination of $R^1 \leftrightarrow R^2$, $R^1 \leftrightarrow L$ and $R^2 \leftrightarrow L$ steric interactions should reinforce the preference for R^2 to assume the equatorial position.

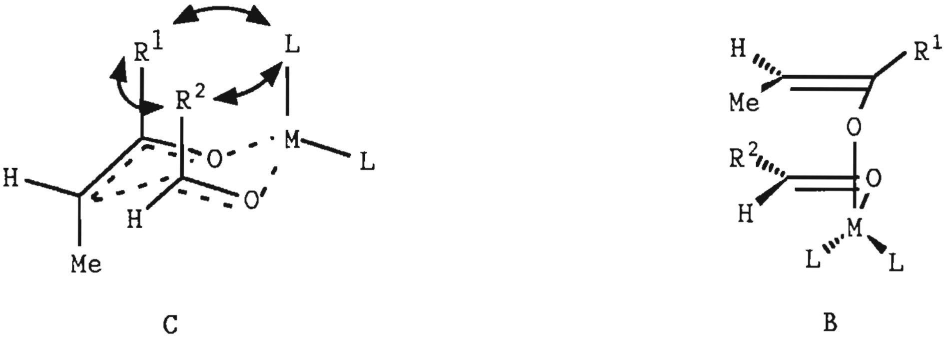


FIGURE 8

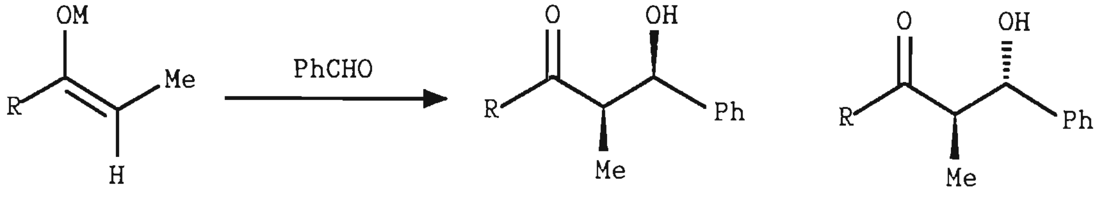
As a result the aldol reaction should be *syn* diastereoselective. However in the case of the boat transition state **B** for the Z-enolate (Figure 8), the $R^2 \leftrightarrow L$ steric interaction would serve to reinforce the formation of the *anti* aldol product.

Evans[127] has argued that the magnitude of the $R^2 \leftrightarrow L$ interaction may be inversely proportional to both metal-ligand and metal-oxygen bond lengths, as well as directly proportional to the bulk of the metal ligand. Thus greater stereochemical control in kineticlly controlled aldol reactions may be achieved by maximising the bulk of the ligand (L) and minimising the M-O and M-L bond lengths (Table 3).

TABLE 3: Metal-oxygen and metal-ligand bond lengths for various metals.[128]

Metal	M - O (Å)	L	M - L (Å)
Li	1.92-2.00	OR_2	1.92-2.00
Mg	2.01-2.00	Br	2.43
B	1.36-1.47	CR_3	1.51-1.58
Zr	2.15	C_5H_5	2.21

From the data in Table 3, dialkylboron triflates are ideal candidates for use in the aldol reaction since they possess both the steric features, and the short M-O and M-L bond lengths required to 'lock' the transition state in the chair conformation. The superior effectiveness of the dialkylboron centre with respect to *syn* diastereoselectivity (Scheme 30) is shown in Table 4.[129] In all cases, irrespective of the bulk of R, *syn* diastereoselection occurs.



(102) (103) (104)

SCHEME 30

TABLE 4: The effect of the metal centre on the diastereoselectivity of the aldol reaction.

R	Metal	*syn* : *anti*
^{t}Bu	Li	>98 : 2
	Bu_2B	>98 : 2
Ph	Li	80 : 20
	Bu_2B	>98 : 2
Et	Li	80 : 20
	Bu_2B	>98 : 2

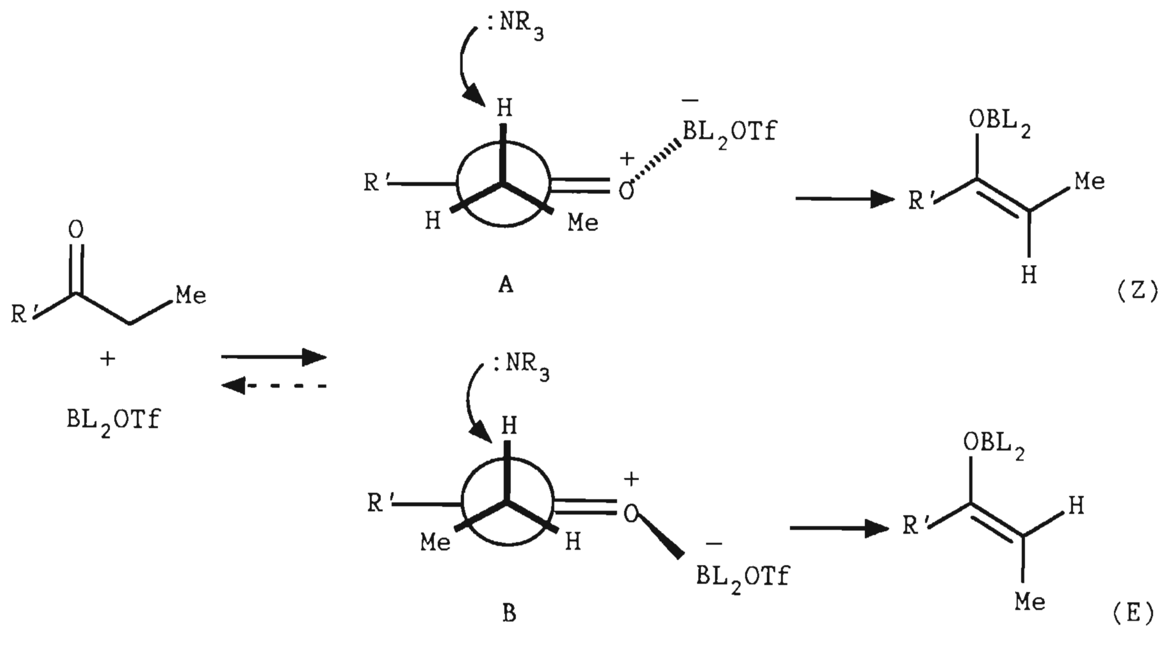
2.2.5 STEREOSELECTIVE KINETIC BORON ENOLATE FORMATION.

Studies carried by the Evans[113] and Masamune[130-133] groups have revealed that enolisations using boron reagents from -78°C to 0°C are completely kinetically controlled. Several factors have been shown to affect the kinetic enolisation of a carbonyl compound with a boryl triflate (Scheme 31).

(i) For a given base when the steric interaction between the boron moiety and R′ is small, the Z-enolate is formed *via* complex **A**;

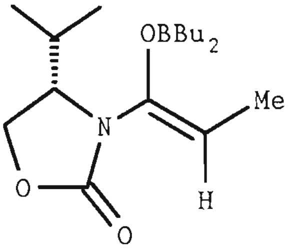
(ii) However in the case of severe R′ ↔ boron moiety interactions (i.e. large R′), the E-enolate is formed *via* complex **B**;

(iii) In the case where R′ is so large that R′ ↔ Me interactions are very severe (i.e. they override R′ ↔ BL_2OTf interactions), the boron reagent can only be complexed in a *syn* orientation to R′. This leads to a Z-enolate *via* complex **A**.

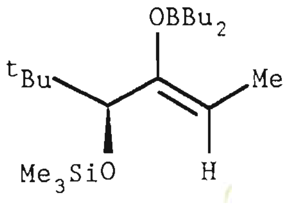


SCHEME 31

It has been shown that for R = very large group, as in (105) and (106), the Z-enolate is formed selectively.[67,134]



(105)



(106)

2.2.6 DIASTEREOFACIAL SELECTIVITY OF THE ALDOL REACTION OF AN IMIDAZOLIDIN-2-ONE DERIVED CHIRAL BORON ENOLATE.

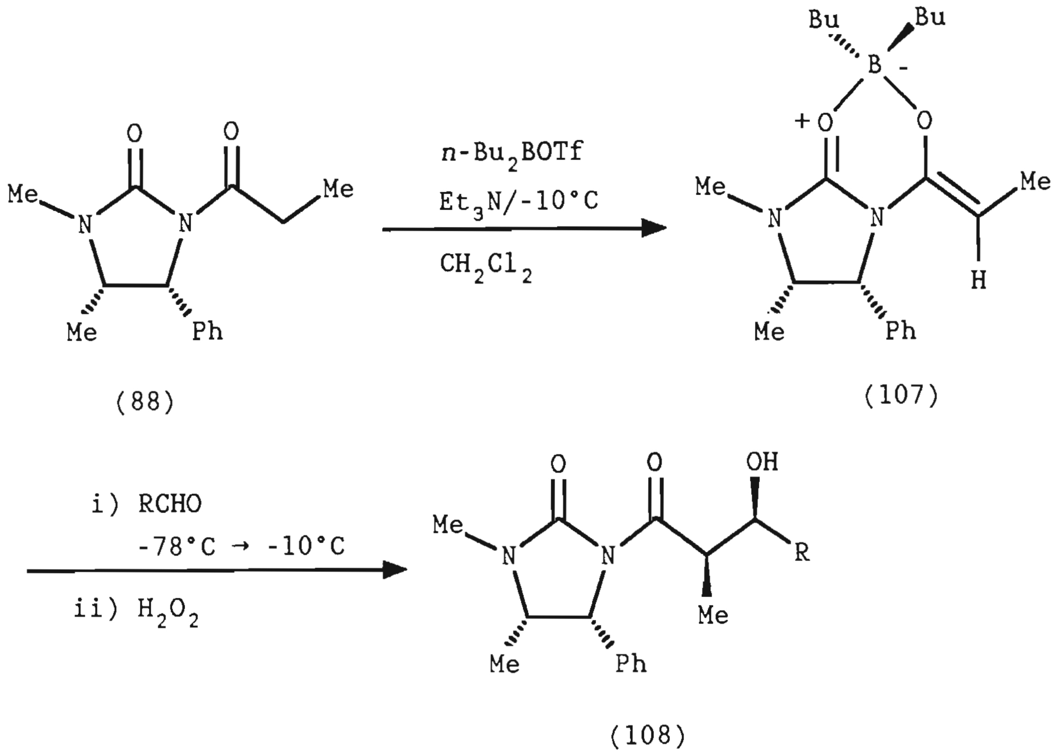
Since the aldol reaction of the lithium Z-enolate (89) of the *N*-propionylimidazolidin-2-one (88) failed to yield the expected *syn* aldol product diastereoselectively, the reaction of the corresponding boron enolate with various aldehydes was investigated. The foregoing discussion has shown that:

(i) Under conditions of kinetic control the boron Z-enolate will be formed selectively;

(ii) Boron will 'lock' the Zimmerman-Traxler cyclic chair transition state[115] such that chair-boat isomerism is not possible;

(iii) Alkyl ligands on the boron atom force the bulky group of the aldehyde to assume an equatorial orientation.

Thus standard Mukaiyama conditions[135] were used to generate the boron Z-enolate (107) of the *N*-propionylimidazolidin-2-one. This enolate was subsequently reacted with benzaldehyde as a test case (Scheme 32).



SCHEME 32

Experiments were carried out in which benzaldehyde was reacted with the boron enolate at various temperatures. The aim was to ascertain the effect of temperature on the diastereoselectivity of the reaction and on the chemical yield (Table 5).

TABLE 5: Optimisation of the aldol reaction conditions (Scheme 32).

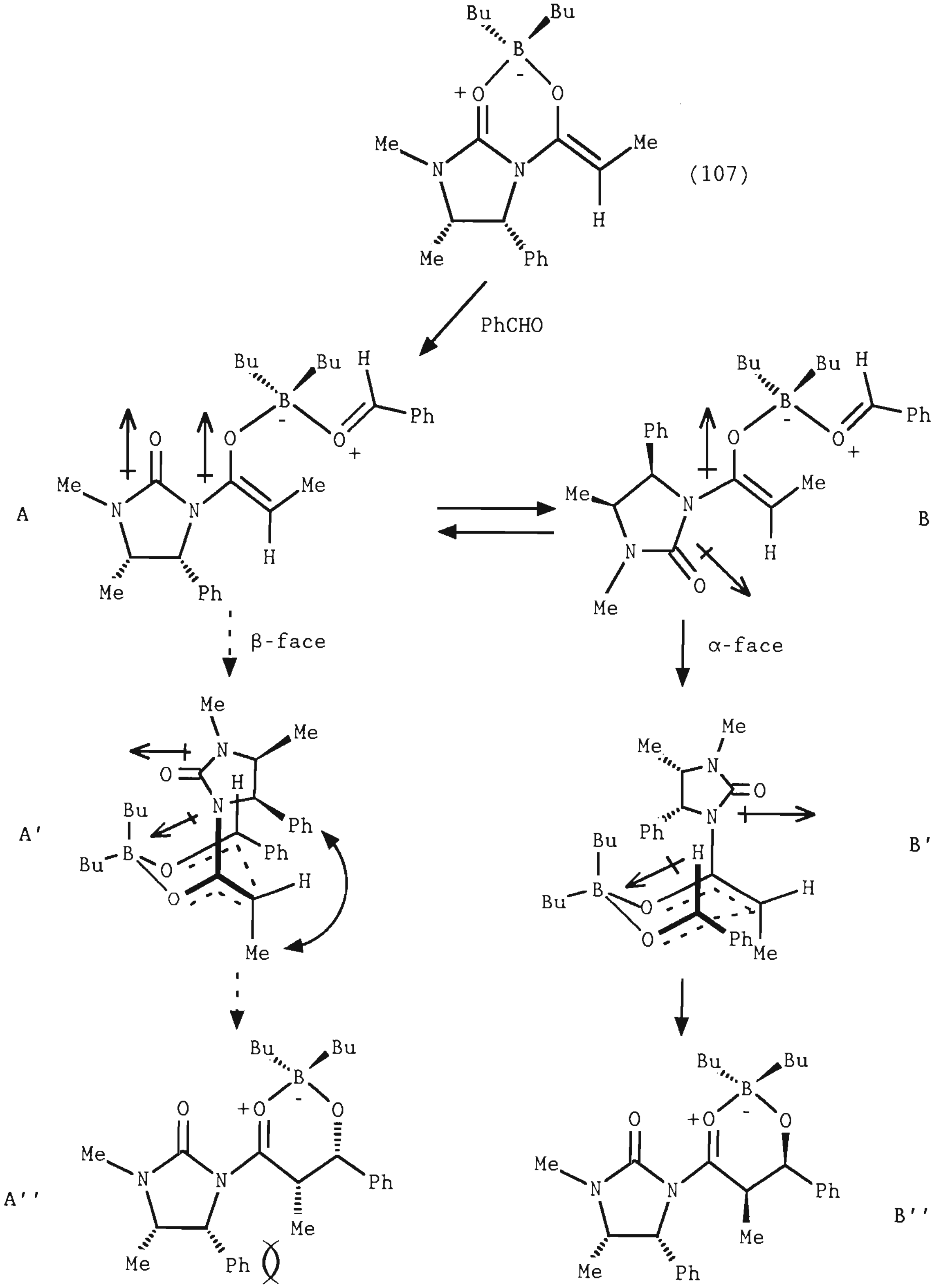
Entry	Temperature (°C)	Major aldol (108) : others
1	0 → RT	80 : 20
2	-10	98 : 2
3	-10	90 : 10 [a]
4	-78 → -30	98 : 2

a) Benzaldehyde was added as a CH_2Cl_2 solution.

The reaction of benzaldehyde with the boron enolate (107) afforded the aldol adducts in crude yields of >90% at all temperatures. However the diastereoselectivity of the reaction decreased as the temperature was increased. Dilution of the aldehyde also resulted in a decrease in selectivity (Entry 3). While the diastereoselectivity of the aldol reaction was the same when the reaction was carried out at -10°C and at -78°C, all further reactions were carried out at -78°C (30 min.) → -10°C (1 h) and in all cases the aldehydes were added neat.

2.2.6.1 RATIONALISATION OF THE STEREOCHEMICAL OUTCOME OF THE ALDOL REACTION (SCHEME 32).

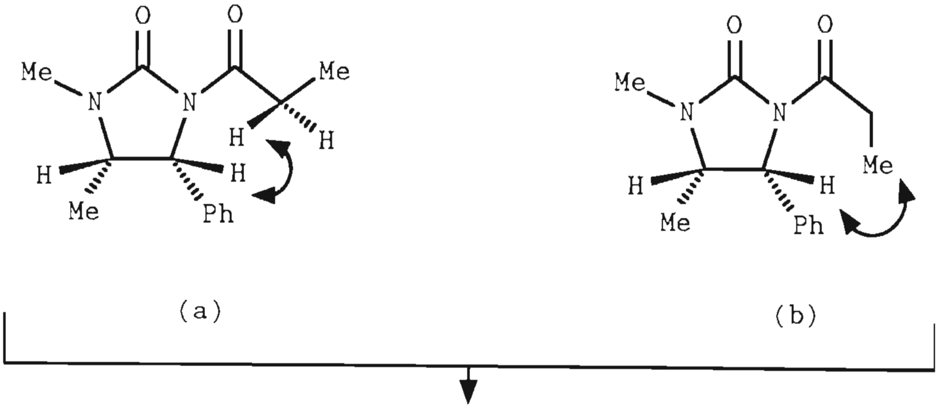
According to Evans,[129] a possible explanation of the source of the diastereoselectivity for the reaction of the chiral boron enolate (107) with benzaldehyde is as illustrated in Scheme 33. The more basic carbonyl group of the aldehyde interacts with the boron enolate to afford the intermediate complex **A** which equilibrates to conformer **B**. For the respective aldol transition states **A′** and **B′** which respectively lead to the *syn* diastereomeric chelates **A′′** and **B′′**, an assumption may be made that developing imide resonance will fix the chiral imidazolidin-2-one moiety in one of the in-plane conformations **A′′** and **B′′**. Evans has postulated that as a result, developing Me ↔ Ph allylic strain steric interaction disfavours the transition state **A′** leading to **A′′**. For the transition state **B′** leading to the observed *syn* aldol adduct *via* **B′′**, these steric considerations are negligible. The poor diastereoselectivity exhibited by the boron enolates of *N*-acetyloxazolidin-2-ones is regarded as corroborative evidence for this explanation.



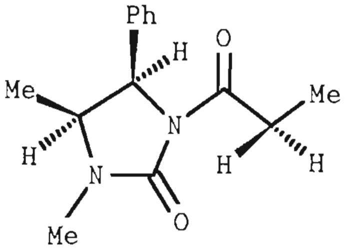
SCHEME 33

The favoured conformer **B** is expected to form due to a low barrier to rotation about the C-N bond as a result of carbonyl-carbonyl dipole effects. A report by Noe and Raban[136] shows that the preferred conformation for a *N*-acyl lactam is one in which the carbonyl groups are aligned in a preferred dipolar orientation (i.e. a E,Z conformation).

An NOE experiment was carried out on the *N*-propionyl derivative (88) in order to shed light on the preferred conformational geometry. Irradiation of the benzylic proton was expected to show enhancements for either the CH_2 resonance (conformer (a)) or the CH_3 resonance (conformer (b)) if the Z,Z-conformer was preferred (Figure 9). Since no enhancements were observed for these resonances, one may infer that the E,Z-conformer is indeed the preferred one.



(88) - Z,Z



(88) - E,Z

FIGURE 9

The high level of diastereoselectivity exhibited in the reaction of benzaldehyde with the boron enolate (107), prompted an investigation of the generality of the reaction by testing a range of aldehydes (Table 6).

TABLE 6: Details of the aldol reaction of the boron enolate (107) with RCHO

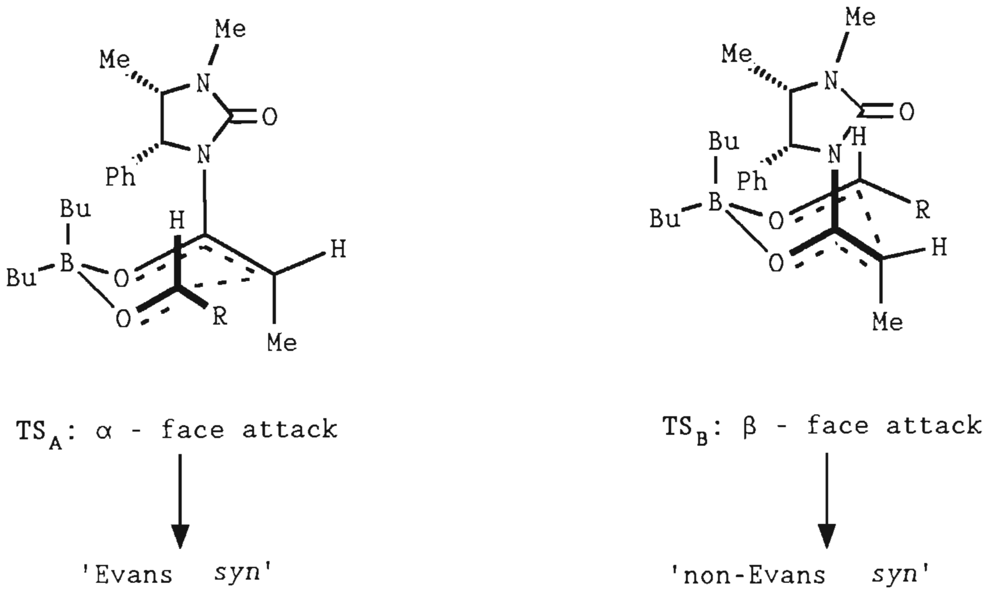
(108)	R	Major isomer (108) : Others	% de[a]	mp (°C)	Yield (%)[a]
a	Ph	98 : 2	>99[b]	135 - 136	88
b	4-NO$_2$-C$_6$H$_5$	96 : 4	>99	156 - 157	85
c	4-MeO-C$_6$H$_5$	96 : 4	>99	181 - 182	92
d	Me	55 : 45	–[c]	–	–
e	Et	74 : 26	–	–	–
f	$CH=CH_2$	82 : 18	–	–	–
g	*i*-Pr	80 : 20	–	–	–
h	*c*-C$_6$H$_{11}$	85 : 15	–	–	–

a) After recrystallisation;

b) The absolute configuration of (108a) is as shown since an excellent correlation between the $[\alpha]_D$ value of its methyl ester derivative with that of a lit. value was obtained;

c) The major aldol isomers (108d) - (108h) were not isolated.

An inspection of Table 5 reveals that for the aromatic aldehydes, the diastereoselectivity is high, while in the case of aliphatic aldehydes there is a marked decrease in diastereoselectivity. These results may be interpreted in terms of both electronic and steric factors. When one considers the Z-enolate with the carbonyl functionalities in the dipolar orientation, the phenyl ring is the steric control element (Figure 10).



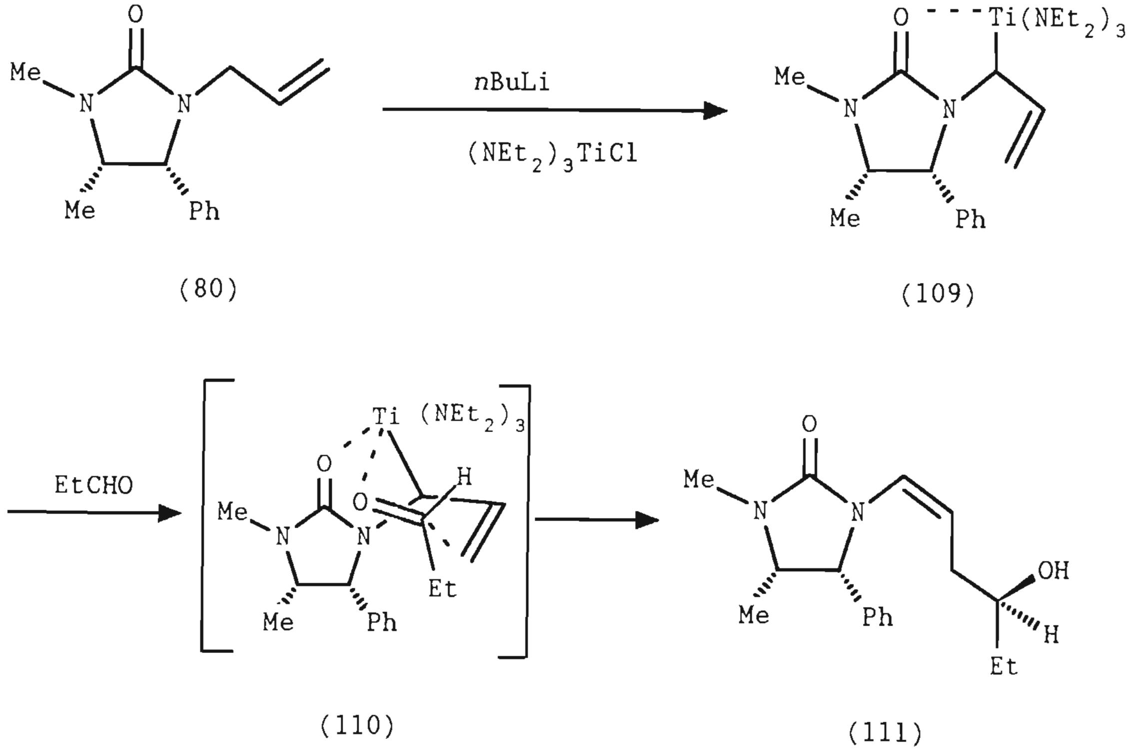
TS_A: α - face attack → 'Evans *syn*'

TS_B: β - face attack → 'non-Evans *syn*'

FIGURE 10

One would expect that attack on the β-face of the enolate double bond to be disfavoured since it is sterically hindered by the phenyl group as shown in $\mathbf{TS_A}$. This is the case for aromatic aldehydes. However the results for aliphatic aldehydes predict that attack on the β-face is in fact possible as shown by $\mathbf{TS_B}$. An inspection of coupling constants from ^1H NMR shows that the major isomer of the other three diastereomers has the *syn* configuration. This isomer is commonly referred to as the 'non-Evans'[137] *syn* aldol product. This result suggests that the phenyl ring is not an efficient steric control element. This is apparent from the trend seen in the table, i.e. the increase in the bulk of the aldehyde R group increases the diastereoselectivity of the reaction. Since this is the case the high diastereoselectivity exhibited when the R group is an aromatic one, should be under the dominant influence of an electronic rather than a steric control element. This means that for R = Ar, α-face attack occurs while β-face attack is precluded not only on steric grounds but also (or mainly) as a result of a <u>repulsive</u> interaction between the phenyl rings of the chiral auxiliary and the incoming aldehyde. It is this repulsive electronic interaction that must be regarded as a factor for the explanation of the increased diastereoselectivity exhibited by acrolein as compared with that obtained for propionaldehyde.

In the light of these findings, the high diastereoselectivity obtained by Helmchen and co-workers[97] for the homoaldol reaction shown in Scheme 34 warrants a brief analysis.



SCHEME 34

These researchers proposed that the reaction of the Ti carbanion (109) with propionaldehyde proceeds *via* the chair-like transition state (110) in which the large substituent of the carbonyl group assumes an equatorial orientation. The diastereoselectivity obtained is much higher than that obtained for the corresponding aldol reaction (cf. Table 6, Entry (108e)). This suggests that in this case an additional diastereocontrol element, in the form of attractive π-interactions, is operational. This idea is plausible since molecular models and molecular mechanics show that the double bond-phenyl ring interplanar distance is ~3.08Å and at this distance the π systems can assume a favourable offset geometry (Figure 11).[123]

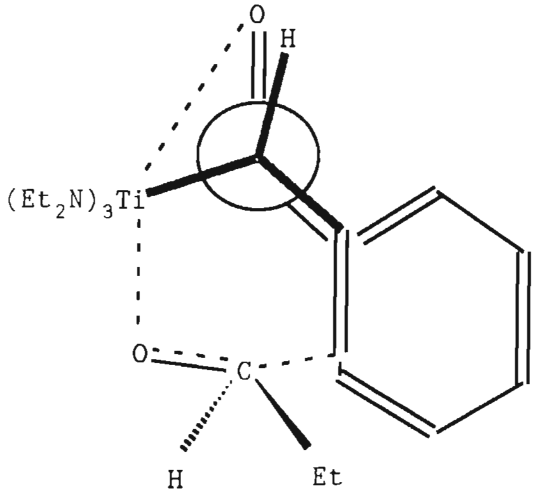


FIGURE 11

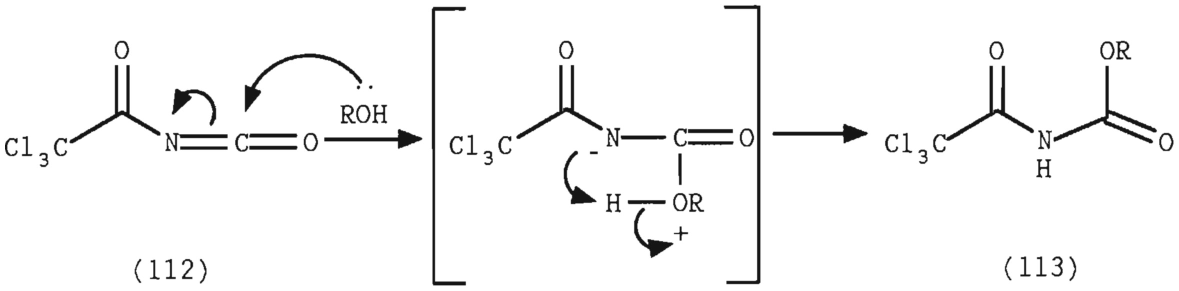
The above π-stacking model is possible if the carbanion maintains its sp^3 (tetrahedral) integrity (i.e. no delocalisation of the negative charge). In the case of the boron enolate (107), the sp^2 nature of the carbon α to the chiral auxiliary precludes any possibility of the enolate double bond aligning itself in a position relative to the phenyl ring that is favourable for π-stacking.

Notwithstanding the inefficiency of chirality transfer exhibited by the reaction of the boron enolate (107) with aliphatic aldehydes, this study has shown that the chiral auxiliary is able to confer a high level of diastereoselectivity to the reaction with aromatic aldehydes. An important additional feature of the aldol adducts (108a)-(108c) is that after one recrystallisation homochiral products are obtained.

2.3 THE DETERMINATION OF DIASTEREOSELECTIVITY RATIOS IN THE ALDOL REACTION.

The intrinsic diastereomeric ratio of a reaction, where the products contain hydroxyl groups, is often required to assess the efficiency of a chiral auxiliary for that particular reaction prior to purification. Many methods have been developed to achieve this goal. These include analysis of the silyl ether or trifluoroacetate derivatives of the reaction mixture *via* GC/MS or HPLC. However probably the most popular methods involve NMR spectroscopy.[138] This may take the form of direct analysis of the crude or of the analysis of derivatives. The commonly used derivatisation procedures are acetylation and benzoylation, dichloro-acetylation, formylation, trifluoroacetylation (^{19}F NMR), methylation and silyl ether formation (^{28}Si NMR).

All these derivatisation procedures require relatively large amounts of usually purified material. Ideally an *in situ* derivatisation/analysis method for small quantities is required. As far back as 1965 Goodlett[139] addressed this problem by *in situ* acylations of hydroxyl groups using t̲richloroa̲cetyl i̲socyanate (TAI) (112). TAI reacts quantitatively with 1°, 2° and 3° alcohols[140] as shown in Scheme 35 to afford the carbamate (113). The carbamate NH resonance appears normally at δ > 8 ppm with attendant spectral simplification of resonances belonging to groups close to the hydroxyl group.



SCHEME 35

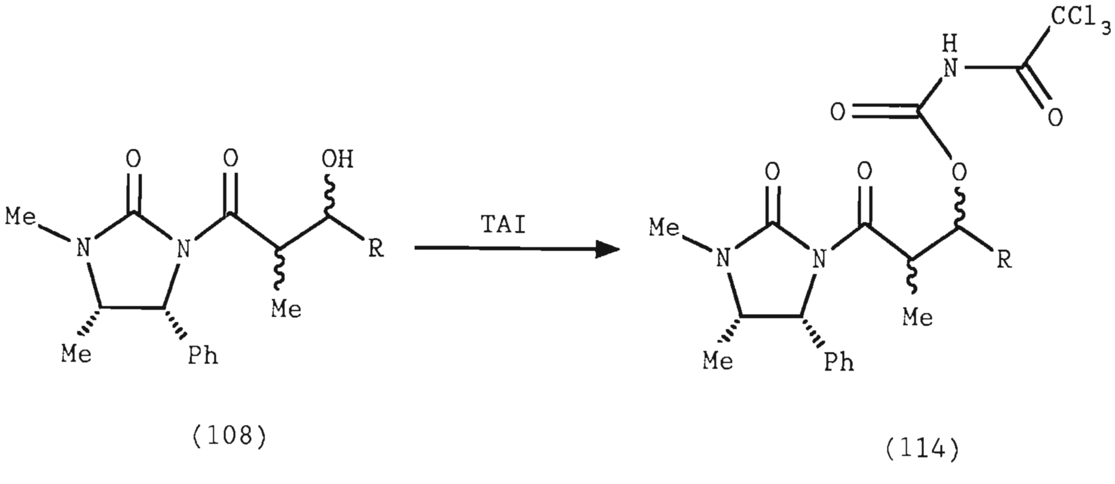
With respect to the aldol reaction the problem of diastereomeric ratio determination was initially addressed by the following methods:

(i) ^{1}H NMR - observation of the doublet of the benzylic proton of the chiral auxiliary or of the *N*-Me singlet;

(ii) GC/MS of the TMS ether;

(iii) ^{19}F NMR - observation of the singlet due to the trifluoroacetyl derivative.

However these methods are tedious. It was thus of interest to investigate whether a TAI-alcohol protocol could provide a means for facile de measurement (Scheme 36).



SCHEME 36

The diastereomeric carbamate NH resonances appeared as separate signals and as expected allowed for easy measurement of the de's of the crude aldol reaction mixtures. In test cases the results obtained from TAI derivatisation were in good agreement with those obtained by the more traditional methods (Table 7).

TABLE 7: Comparative diastereomeric ratios obtained by various analytical methods.

Entry	R in (108)	DIASTEREOMERIC RATIO (major : others)			
		^{1}H NMR	GC/MS	^{19}F NMR	TAI
1	C_6H_5	98 : 2	98 : 2	99 : 1	98 : 2
2	$4-NO_2-C_6H_4$	95 : 5	–	–	96 : 4
3	$4-MeO-C_6H_4$	96 : 4	–	–	96 : 4
4	C_2H_5	75 : 25	–	72 : 28	74 :26

The resulting spectrum after the addition of TAI generally exhibits signal shifts in much the same way as lanthanide contact shift reagents but without the corresponding loss of resolution normally associated with the latter. An example of these shift differences is seen in the spectra for (108a) before and after TAI addition (Figures 12a and 12b).

In this example one observes that the addition of TAI has three main outcomes: (i) The complete reaction of the alcohol (this is evidenced by the disappearance of the hydroxyl resonance at 3.65 ppm which results in the NH resonance at 8.48 ppm); (ii) The H-3′ doublet is resolved (cf. D_2O) and is shifted downfield (from 5.12 to 6.20 ppm); (iii) The H-2′ doublet of quartets is also shifted downfield (from 4.27 to 4.68 ppm).

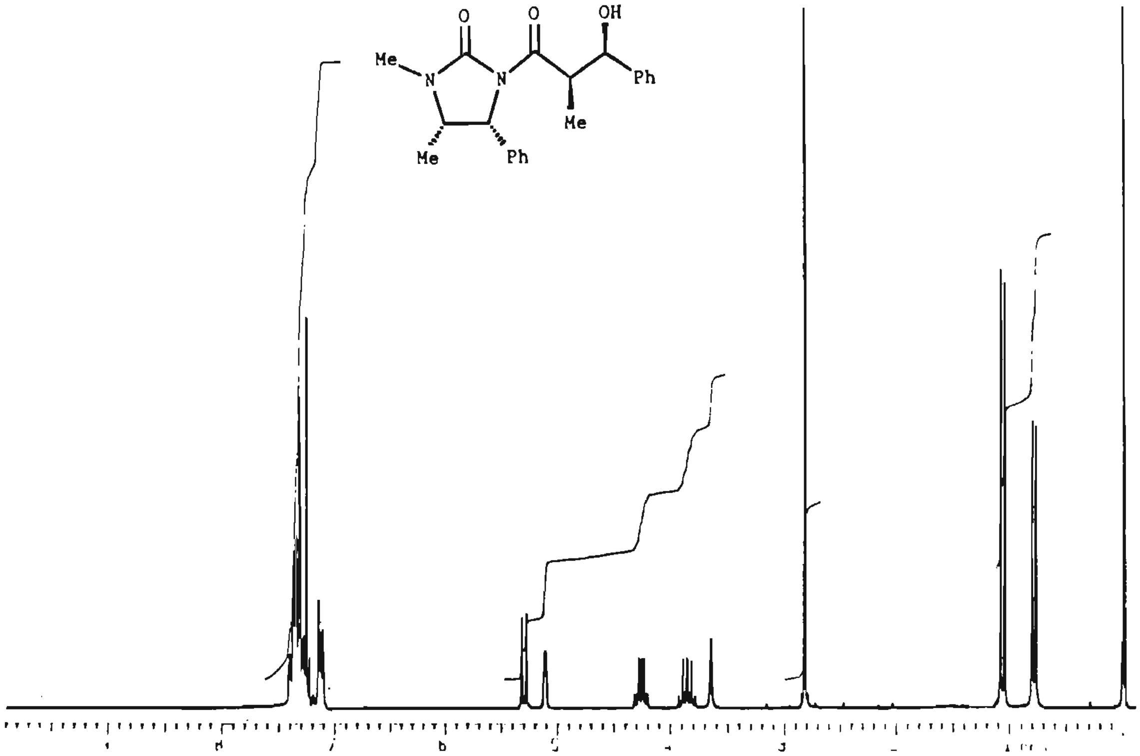


FIGURE 12a: ^{1}H NMR spectrum of (108a) before TAI addition.

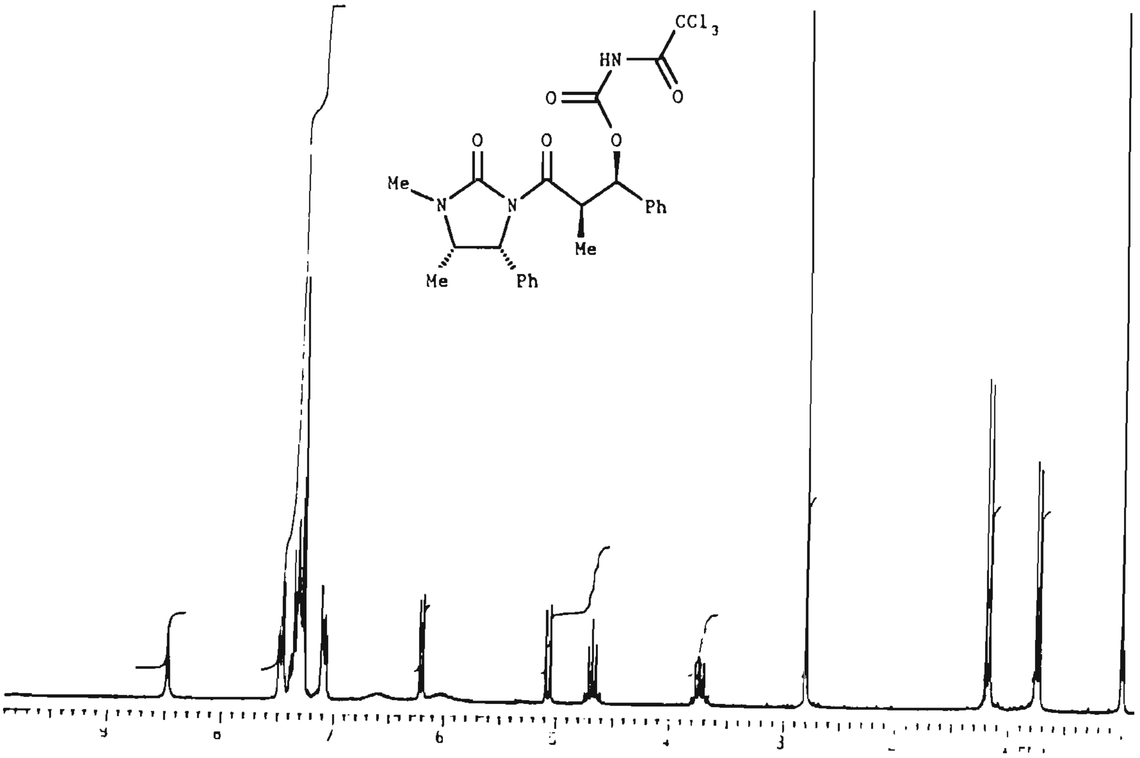
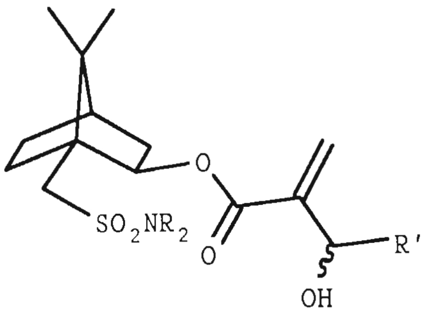
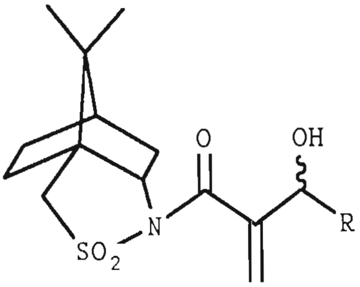


FIGURE 12b: ^{1}H NMR spectrum of (114a) (i.e. (108a) + TAI)

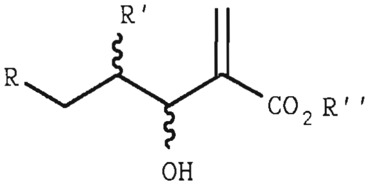
This TAI protocol has also been used in this laboratory to determine the de's of a variety of derivatives of compounds (115)-(117).[141]



(115)



(116)



(117)

2.4 RELATIVE STEREOSTRUCTURE ASSIGNMENT.

The relative configuration (*syn/anti*) of aldol products may be determined by the use of ^1H and ^{13}C NMR spectroscopy. In the cases where the aldol product possesses a proton at both the α and β positions and if both the aldols exist in a hydrogen bonded fashion, then J_{AB} = 2 - 6 Hz for the *syn* isomer (due to gauche relationships), and 7 - 10 Hz for the *anti* isomer (anti relationship) as illustrated in Figure 13. Heathcock[142] has shown that shielding of the α-methyl (*syn*) due to gauche interactions between the methyl and the C-O bond in **A** and between R and the C_α-C=O bonds in **B**, causes the ^{13}C resonance to appear upfield from that of the *anti* isomer.

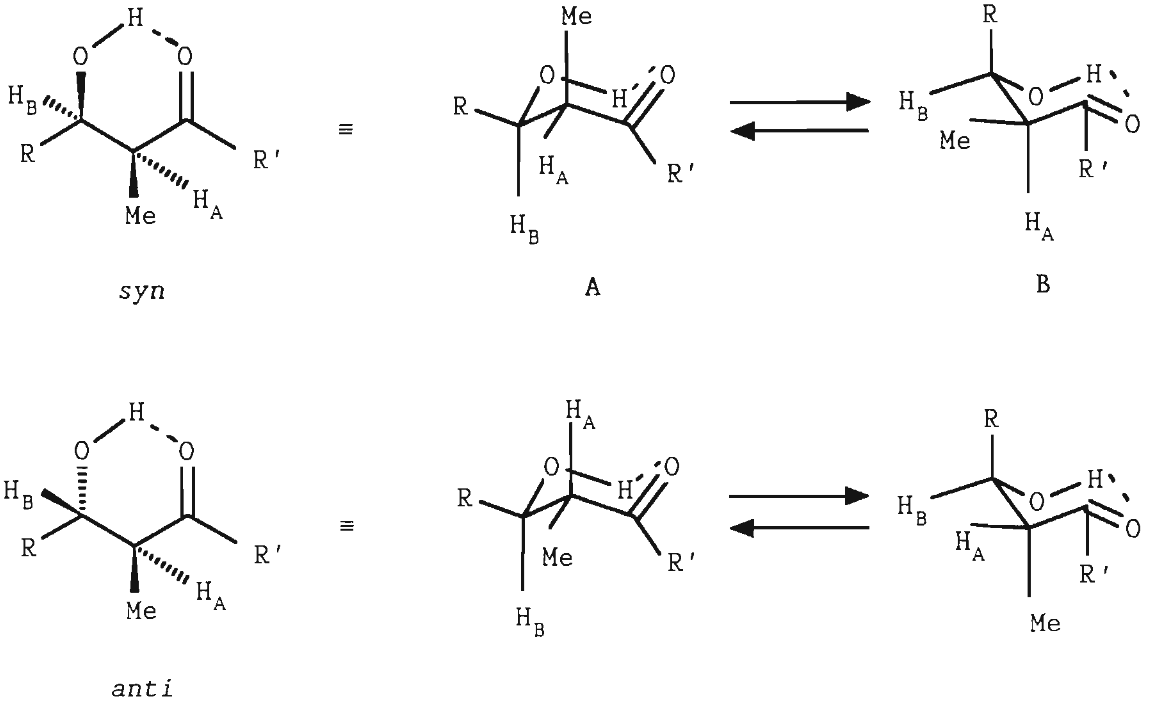


FIGURE 13

An analysis of the ^{1}H and ^{13}C NMR data for the aldol adducts (108a) - (108c) shows that they satisfy the criteria for the assignment of the *syn* configuration (Table 8).

TABLE 8: ^{1}H and ^{13}C NMR data for compounds (108a) - (108c).

108	J_{AB} (Hz)	δ - Me (ppm)
a	3.12 (8.00)	10.39 (13.54)
b	2.47	10.00
c	3.38	10.53

a) The values in parenthesis are for the TMS ether derivative (118) of (108a).

The above procedure is ideal for purified diastereomer mixtures, and not particularly suitable for the direct investigation of the relative configuration of crude reaction mixtures. This study has shown that the TAI-alcohol protocol may be readily applied to circumvent this problem. There is a significant shift difference between the NH resonances of the *syn* and the *anti* isomers.[143] For the reactions that afforded the aldol products (108 a-c) these shift differences are in the range 0.22 - 0.46 ppm. There is a downfield shift for δ NH *syn* relative to δ NH *anti*. This shift is clearly seen in Figure 14 where the spectra of a known *syn/anti* mixture of methyl 3-hydroxy-2-methyl-3-phenyl-propanoate are shown, before and after TAI addition.

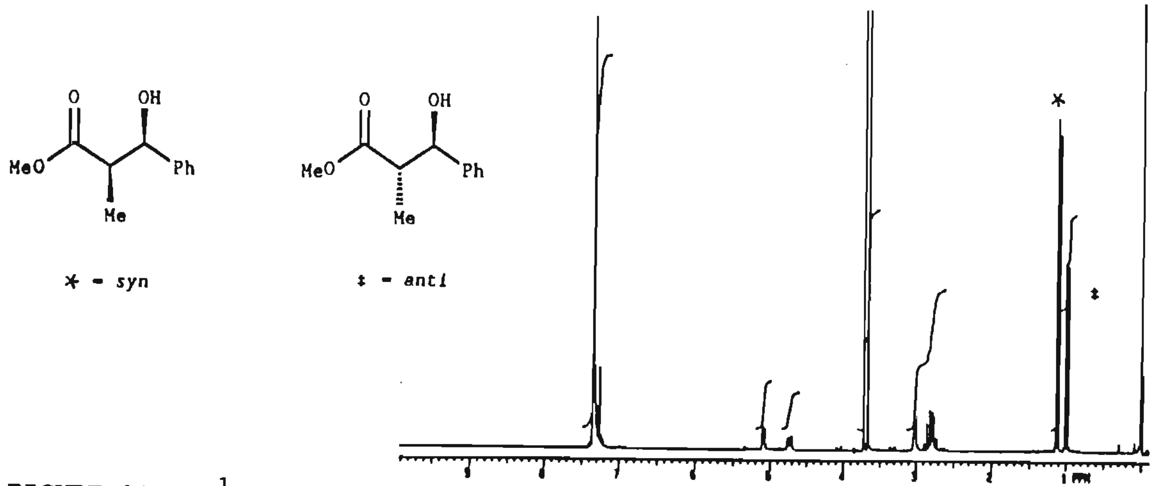


FIGURE 14a: ^{1}H NMR spectrum of a *syn/anti* mixture of methyl 3-hydroxy-2-methyl-3-phenylpropanoate.

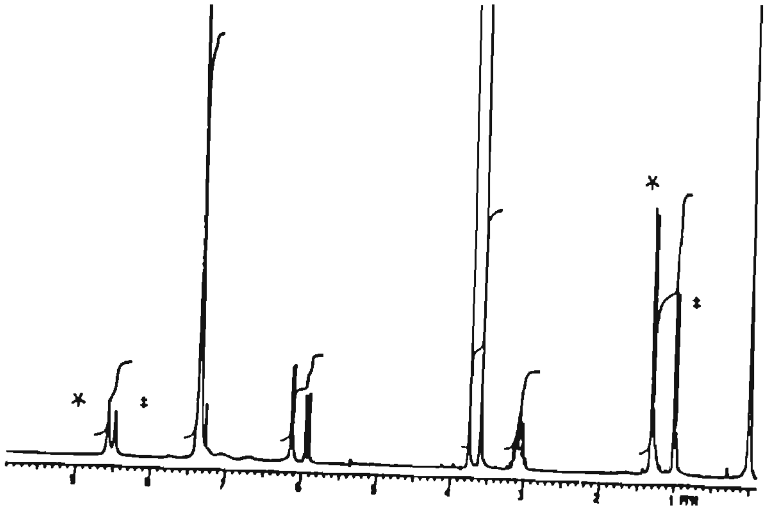


FIGURE 14b: ^{1}H NMR spectrum of the products of the reaction between TAI and a *syn/anti* mixture of methyl 3-hydroxy-2-methyl-3-phenylpropanoate.

2.4.1 ADVANTAGES OF TAI DERIVATISATION AS A ^{1}H NMR DIAGNOSTIC TOOL.

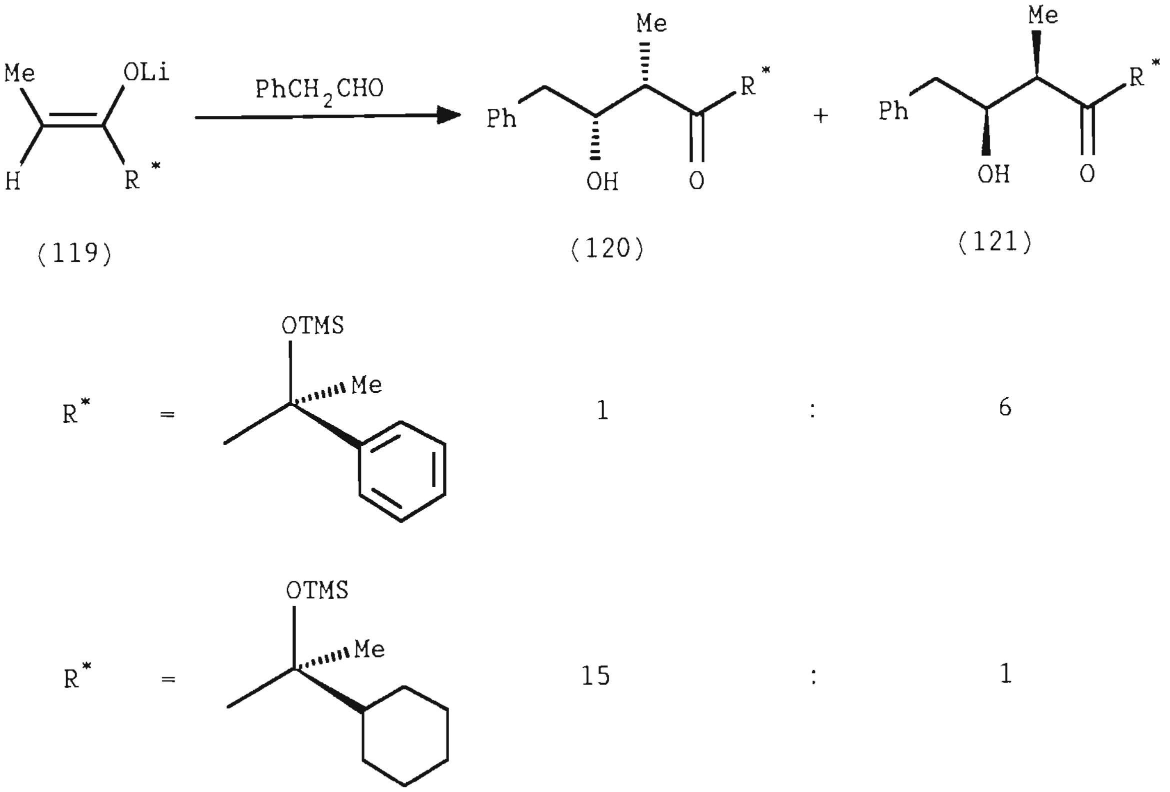
The many advantages of the TAI methodology are:

(i) TAI reacts rapidly and completely with hydroxyl groups;
(ii) reactions are carried out *in situ* which allows for ease of analysis of very small sample quantities;
(iii) the downfield shift of the carbamate NH singlets into the uncluttered region of the spectrum;
(iv) the lack of coupling between the carbamate NH and any of the substrate protons;
(v) the reagent can be used in excess since it itself has no protons to complicate a spectrum;
(vi) for an aldol diastereomeric mixture, the diastereomeric ratio and the relative configuration may be determined in one analysis.

2.5 A SOLUTION TO THE PROBLEM OF THE LIMITED CHIRALITY TRANSFER ABILITY OF THE PHENYL SUBSTITUTED IMIDAZOLIDIN-2-ONE (78) IN THE ALDOL REACTION.

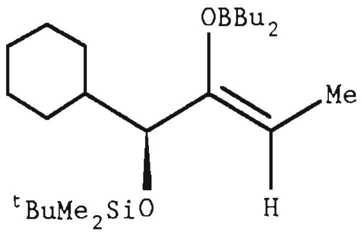
The inefficient diastereoselection imparted to the aldol reaction as regards aliphatic aldehydes by the imidazolidin-2-one (78), was in the main ascribed to the shortcomings of the phenyl substituent as a steric control element. Any successful solution to this problem required a chemical transformation that would afford a bulky substituent which would not participate in electronic interactions, neither attractive nor repulsive. For a phenyl ring, hydrogenation offers the solution. This strategy seems reasonable since in the aldol reaction of the boron enolate (107) with aliphatic aldehydes, the highest diastereoselectivity was obtained in the reaction with cyclohexanecarbaldehyde.

A survey of the literature revealed a precedent for this strategy. In 1980 Masamune *et al.*[22] described the diastereoselective aldol reaction of chiral lithium anolates (derived from atrolactic acid) with phenylacetaldehyde (Scheme 37).



SCHEME 37

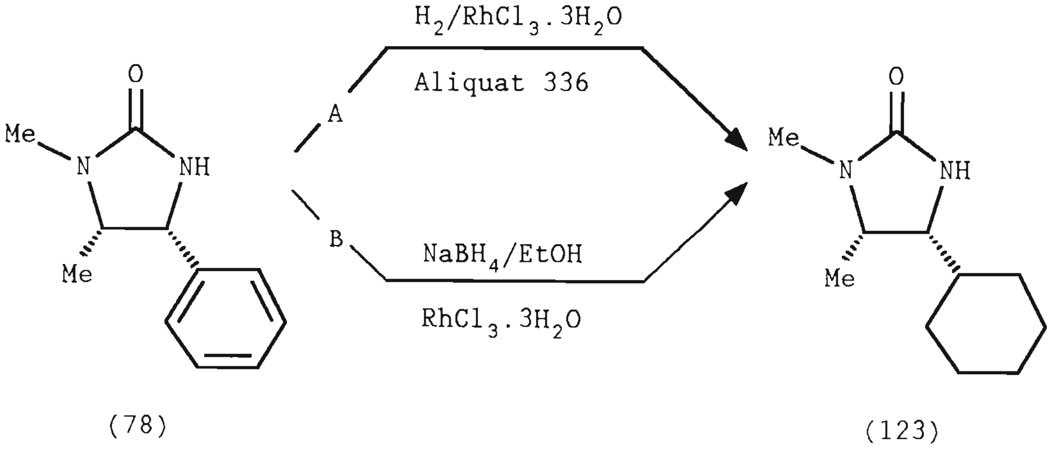
The chiral enolate containing the cyclohexyl substituent showed a >100% improvement in diastereoselection over the chiral enolate containing the phenyl ring. Soon thereafter Masamune *et al.*[144] reported high diastereoselectivities (>99:1) for the reaction of the chiral boron enolate (122) which is derived from mandelic acid. Although not reported, one can infer that diastereoselection with the unsaturated precursor was inferior.



(122)

2.5.1 THE SYNTHESIS OF (-)-(4R,5S)-4-CYCLOHEXYL-1,5-DIMETHYLIMIDAZOLIDIN-2-ONE (123).

Armed with these positive precedents, the decision to hydrogenate the phenyl ring of the chiral auxiliary (78) was taken with confidence. Two catalytic methods, reported by Blum *et al.*[145] and Satoh and co-workers,[146] for the hydrogenation of phenyl rings were compared as shown in Scheme 38.



SCHEME 38

The phase transfer catalytic method **A** afforded the hexahydro adduct (123) quantitatively while method **B** proceeded in 55% yield. Comparative studies with the *N*-propionyl imidazolidin-2-one (88) were also carried out. Application of the methods **A** and **B** on this substrate afforded the hexahydro *N*-propionyl derivative (124) in 60% and 0% yield respectively. The latter result was surprising since Satoh and co-workers[146] have claimed that amides, esters and carboxylic acids are unaffected by the reductive system. Method **A**, with an adaptation of high pressure conditions for large scale preparations, was thus the method of choice. Of practical importance is the fact that the hexahydro compounds (123) and (124) are crystalline which allows for easy purification.

A comparison of the ^{1}H Nmr spectra (Figure 15a and b) of the *N*-propionyl derivatives (88) and (124) shows that the C-2' protons of (88) appear as a quartet while for (124) they appear as a 16 line multiplet (1 x dq per proton).

FIGURE 15a: ^{1}H NMR spectrum of (88).

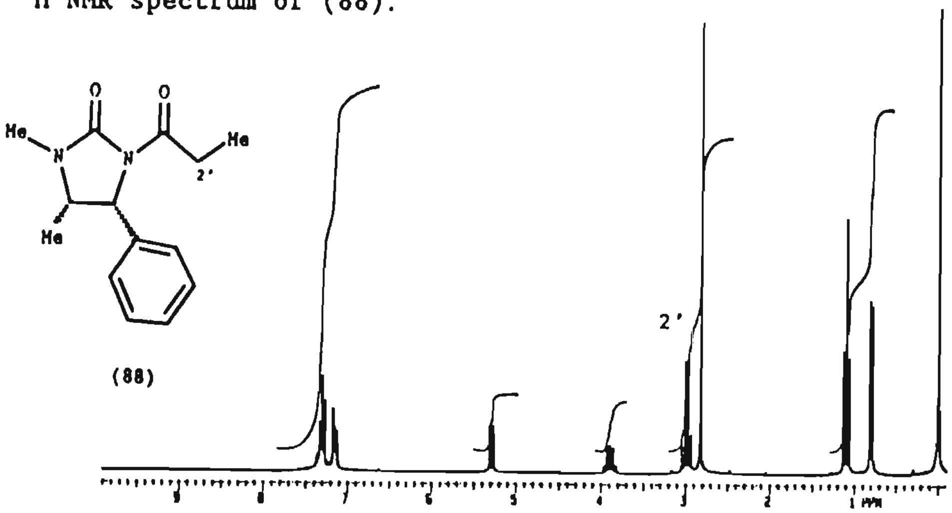
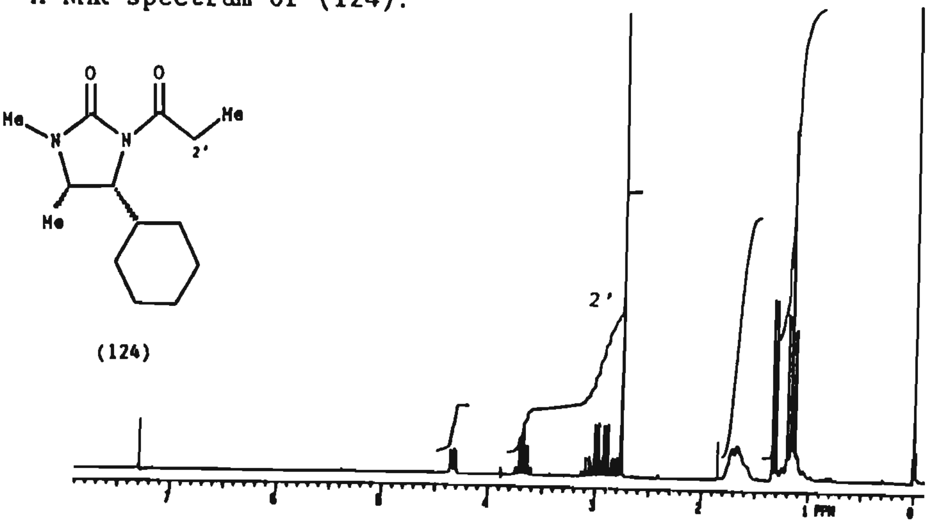
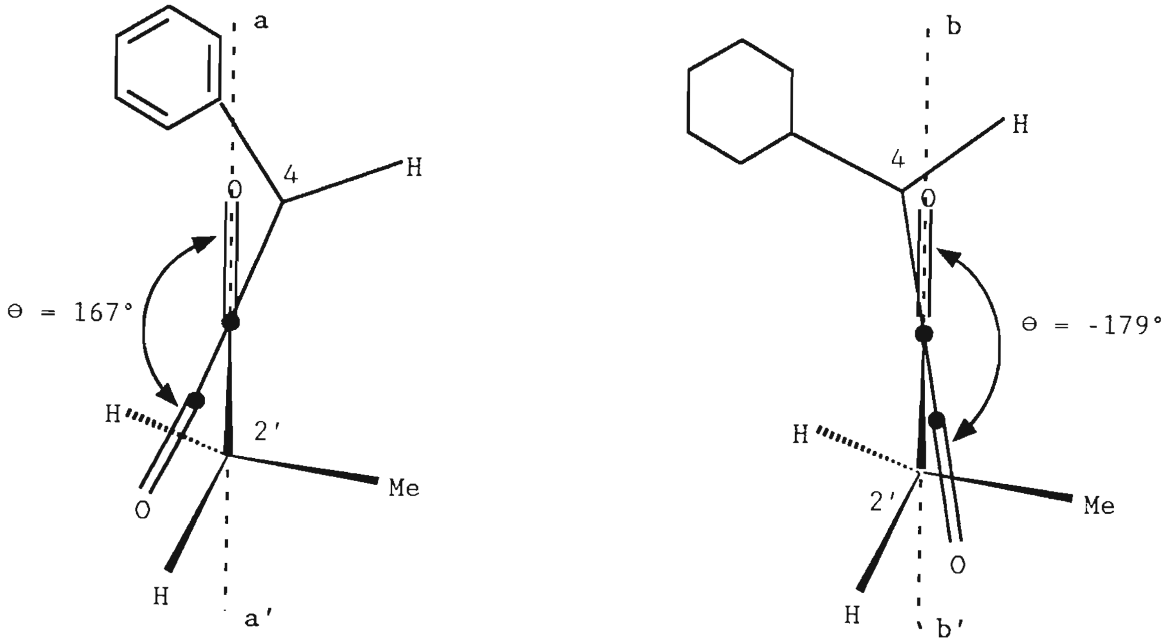


FIGURE 15b: ^{1}H NMR spectrum of (124).



These differences may be explained by an analysis of the relevant dihedral angles for the lowest energy conformations of the respective compounds. These lowest energy conformations were determined from MMX calculations using the PC MODEL (Ver. 3.0) program (Figure 16). When viewed edge on along the a - a′ axis, the lowest energy conformation for (88) has the chiral centre (C-4) *anti* to the C-2′ protons. For the lowest energy conformation of (124), a view along the b - b′ axis shows the chiral environment to be *syn* to the C-2′ protons. The difference in dihedral angles between the lowest energy confirmations are sufficient to reveal differences in levels of diastereotopicity. The dihedral angle differences arise probably because any synplanar Me ←→ Ph-C4 steric interactions in (88) would be better tolerated than any synplanar Me ←→ *c*-C_6H_{11}-C4 steric interactions in (124). As a result C-4 and Me are *anti* with respect to the b - b′ plane in (124).



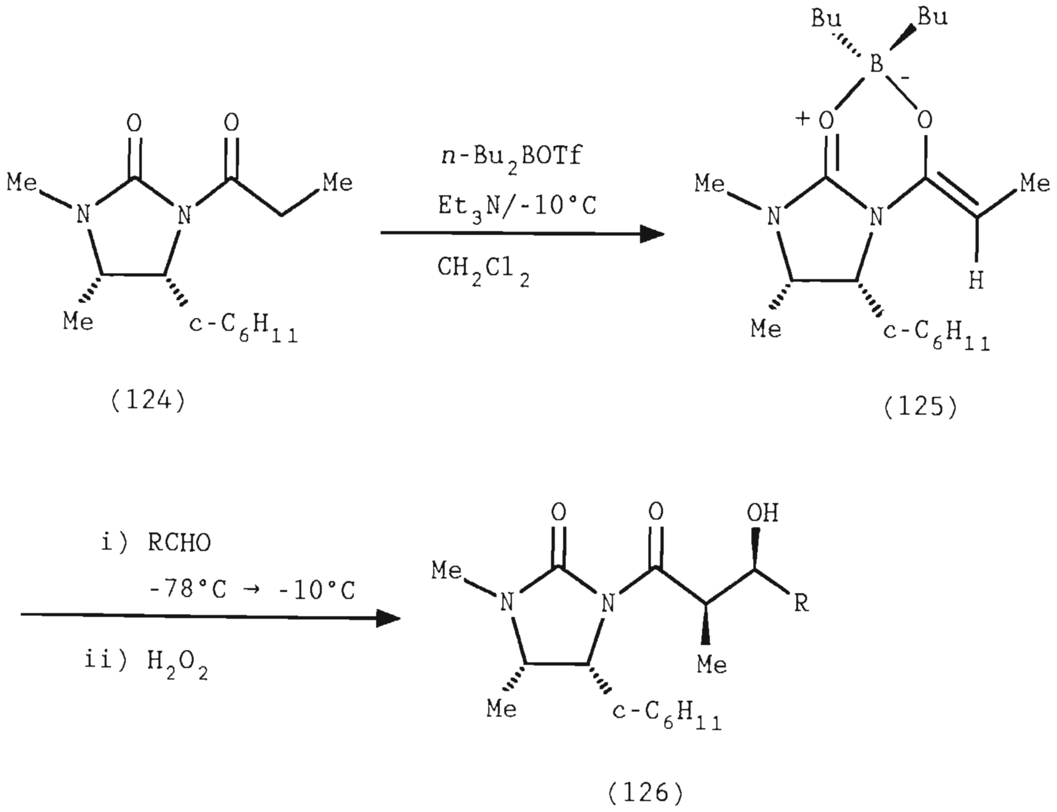
(88)

(124)

FIGURE 16

2.5.2 THE ALDOL REACTION OF THE *N*-PROPIONYL DERIVATIVE OF THE NOVEL CHIRAL AUXILIARY.

The lithium anion of the chiral auxiliary (123) is readily acylated with propionyl chloride to afford the aldol starting material (124) in 95% yield. The boron enolate (125), generated as described earlier, was allowed to react with various aldehydes as shown in Scheme 39.



SCHEME 39

The diastereoselectivity ratios obtained using the 4-cyclohexyl auxiliary (123) are a major improvement on those obtained with the 4-phenyl auxiliary (78) with respect to the reactions with aliphatic aldehydes (Table 9).

TABLE 9: Details of the aldol reaction (Scheme 39).

126	R	Major isomer (126) : others	Yield (%)
a	Me	97 : 3 [a,b]	80
b	*i*-Pr	>99 : 1	82
c	*c*-C_6H_{11}	>99 : 1	92
d	C_6H_5	98 : 2	75

a) The ratios of the crude reaction mixtures were obtained *via* the TAI-alcohol protocol;

b) The absolute stereochemistry was obtained by comparing the $[\alpha]_D$ values of the methyl esters derivatives with the literature values.

The only stereochemical control element is a steric one since, in the absence of a π system on the auxiliary, the aldol reaction with benzaldehyde is still diastereoselective (126d). From these results it is clear that the 4-cyclohexyl imidazolidin-2-one auxiliary is as efficient as the other auxiliaries currently in use for asymmetric aldol reactions. The proposed transition state for these reactions is shown in Figure 17 where the enolate and chiral auxiliary CO groups are aligned in the dipolar orientation.

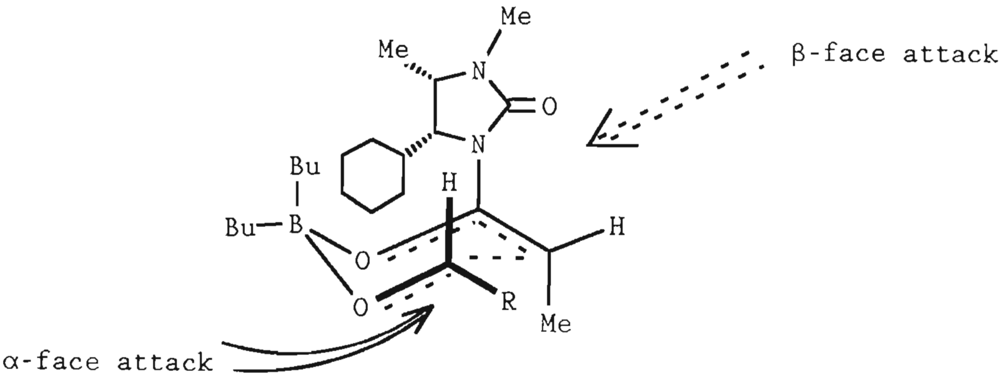


FIGURE 17

The aldehyde approach is from the least hindered and therefore more favourable α-face. The probability of approach of the aldehyde from the sterically hindered β-face is expected to be extremely small.

This increased diastereoselectivity proves that the substituent at C-4 of the imidazolidin-2-one ring imposes the diastereofacial bias on the enolate system while the nature of the C-5 substituent is of no consequence.

2.5.3 THE ASSIGNMENT OF RELATIVE STEREOCHEMISTRY TO THE ALDOL PRODUCTS.

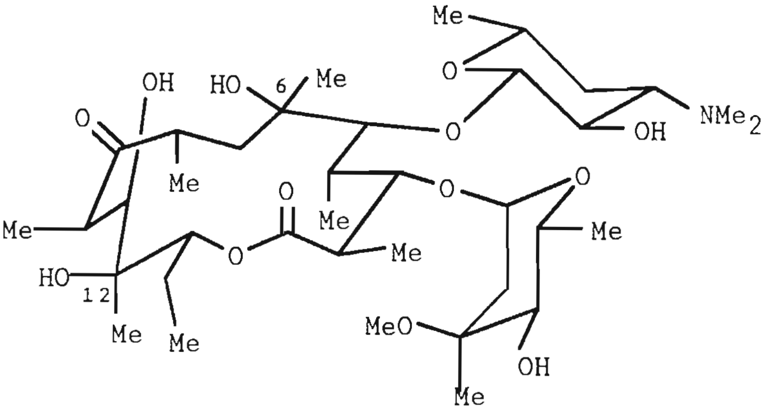
The theory on which the assignment of relative stereochemistry to α-substituted β-hydroxy carbonyl compounds is based (discussed in Section 2.4), was applied to the aldol products (126a-d). An analysis of the ^{1}H NMR and ^{13}C NMR data reveals that the relative stereochemistry of these compounds is again *syn* (Table 10).

TABLE 10: ^{1}H and ^{13}C NMR data for compounds (126a) - (126d).

126	J_{AB} (Hz)	δ - Me (ppm)
a	2.45	11.12
b	2.15	10.98
c	2.00	10.90
d	4.03	11.90

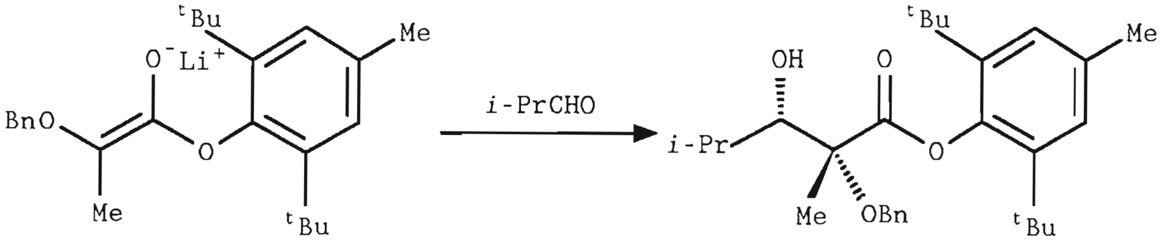
2.6 THE SYNTHESIS OF α,α-DISUBSTITUTED β-OH CARBONYL COMPOUNDS.

In a proposed synthesis of Erythromycin A (127), Heathcock *et al.*[147] encountered the problem of synthesizing the 3° alcohols at C-6 and C-12.



(127)

This problem was solved by the aldol reaction of the requisite aldehydes with the lithium enolate of the α,α-disubstituted ester (128) which is derived from lactic acid (Scheme 40).

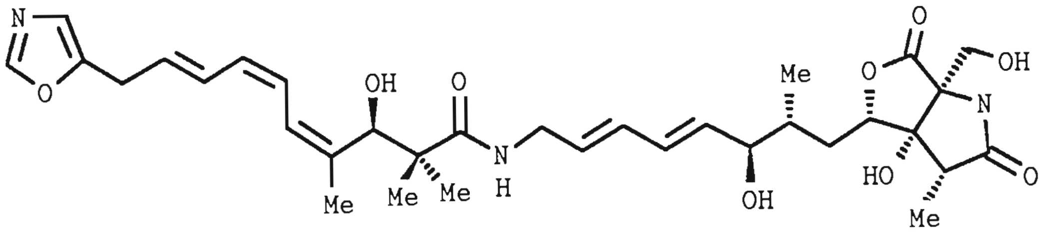


(128)

(129)

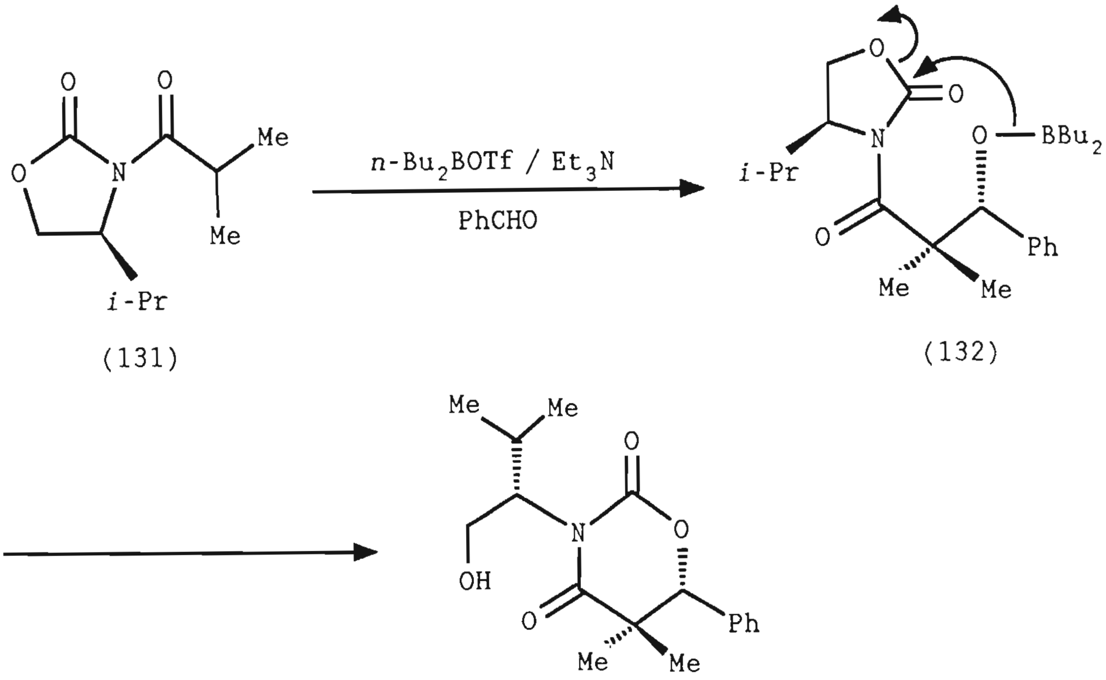
SCHEME 40

Kende *et al.*[148] were faced with a similar problem in their attempts to synthesize the novel polyene lactam-lactone antibiotic neooxazolomycin (130). They required a method to incorporate the α,α-dimethyl β-hydroxy carbonyl moiety *via* a diastereoselective aldol reaction.



(130)

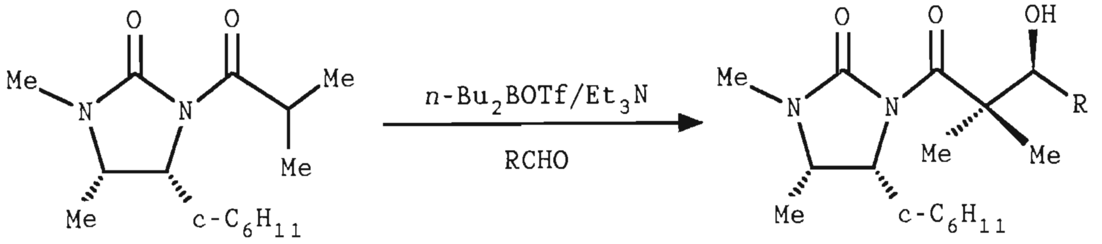
A test reaction between benzaldehyde and a chiral oxazolidin-2-one boron enolate did not afford the expected Evans product but rather the 1,3-oxazine-2,6-dione (133) as illustrated in Scheme 41.



(131) (132) (133)

SCHEME 41

The cyclic product is proposed to have formed *via* the boron complex (132). Although the hydrolysis of (133) afforded the required β-hydroxy carboxylic acid, an obvious drawback of this reaction is the ring opening of the oxazolidin-2-one moiety. It was thus of interest to ascertain the outcome of the analogous aldol reaction of the boron enolate of the *N*-isobutyryl imidazolidin-2-one (134) (Scheme 42).



(134) (135)

a) R = Ph; >99 : 1 (80%)

b) R = c-C_6H_{11}; >99 : 1 (40%)

SCHEME 42

On the basis of electronic factors (i.e. back donation of the nitrogen lone pairs which renders the C-2 carbonyl less susceptible to nucleophilic attack), the outcome of the reaction was as expected, not the reported ring opening process but rather the normal aldol products. The low yield for the reaction where R = c-C_6H_{11} must be due to serious Me ↔ c-C_6H_{11} gauche interactions as shown in Figure 18.

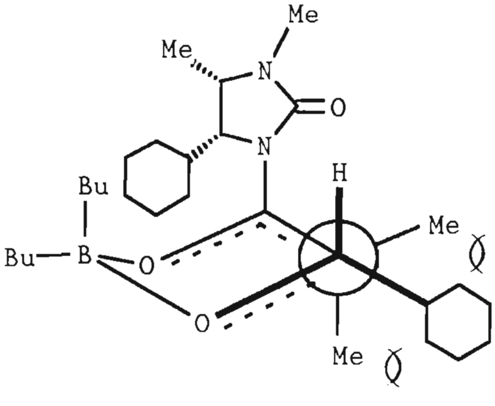
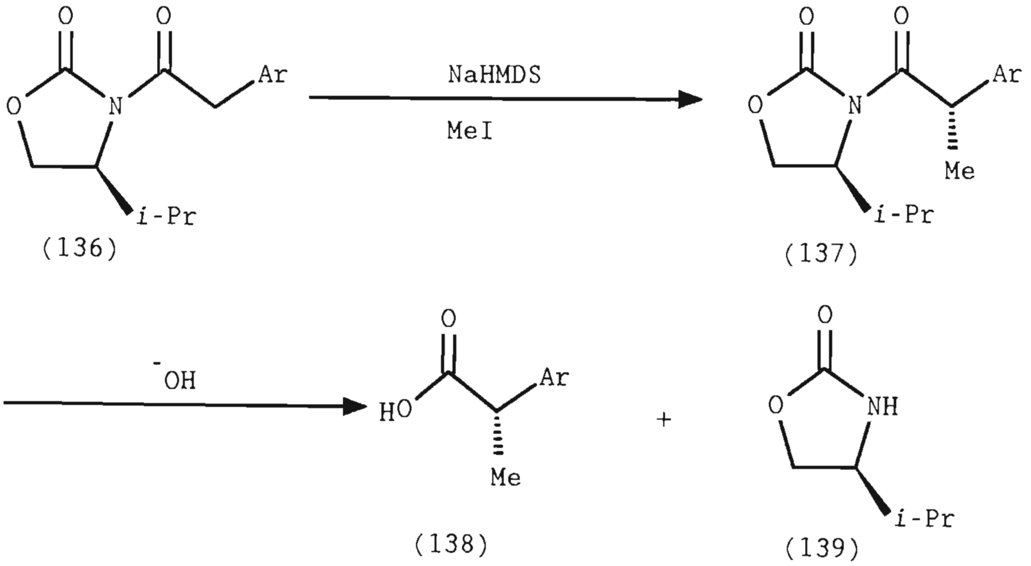


FIGURE 18

2.7 DIASTEREOSELECTIVE ALKYLATIONS AND ACYLATIONS.

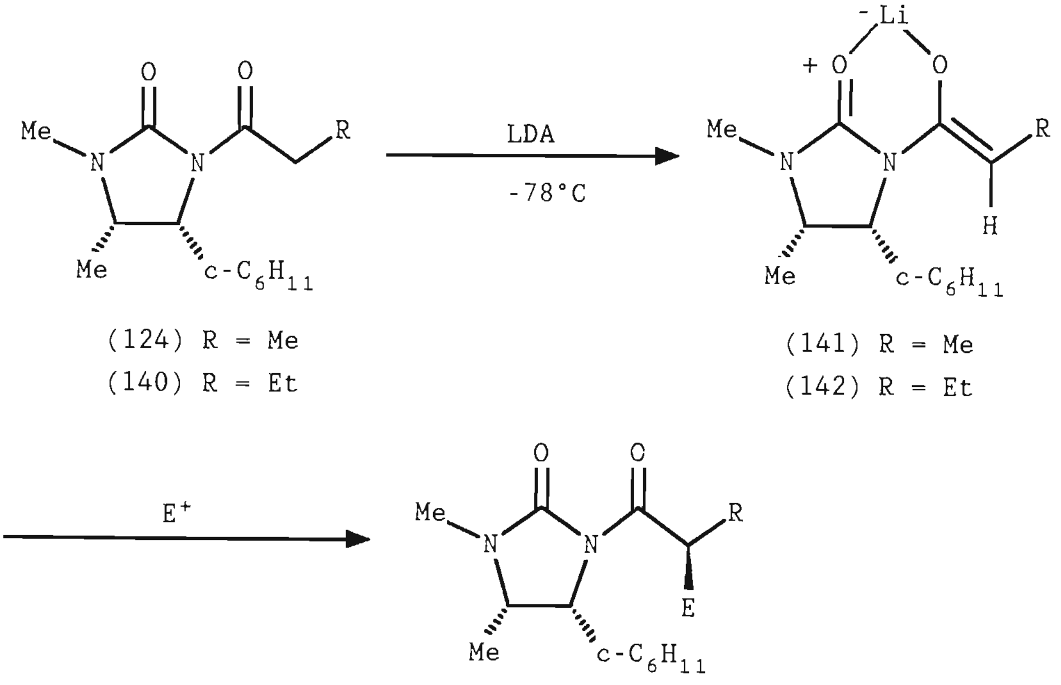
Alkylations and acylations are important chemical reactions for the synthesis of α-substituted carboxylic acids and 1,3-dicarbonyl compounds respectively. Existing evidence indicates that C-alkylations of metal enolates with electrophiles proceeds *via* an S_N2 mechanism where the HOMO of the enolate attacks the LUMO of the electrophile. The principle of stereoelectronic control[149,150] states that the electrophile approaches in a plane perpendicular to the enolate. Houk[151] has found from *ab initio* MO calculations that the developing enolate-electrophile bond angle is >90°. This supports the earlier crystallographic findings reported by the Dunitz group.[152] Of interest in this study was the diastereoselectivity of the non-perpendicular attack of the enolates derived from (123) on a range of electrophiles.

A recent report by Fadel[153] on the diastereoselective alkylation of arylpropionic acid derivatives is an excellent example of the usefulness of this reaction. Fadel's work led to the synthesis of a large range of non-steroidal anti-inflammatory agents (Scheme 43).



SCHEME 43

The chiral lithium enolate (89) derived from the 4-phenyl imidazolidin-2-one has been used by Cardillo *et al.*[98] in diastereoselective alkylations. Nonetheless the increased diastereoselectivities exhibited by the boron enolates of the 4-cyclohexyl auxiliary compared to those of the 4-phenyl auxiliary prompted a brief study to determine whether this trend was mirrored in the alkylation/acylation reactions (Scheme 44).



(124) R = Me
(140) R = Et

(141) R = Me
(142) R = Et

(143) R = Me
(144) R = Et

SCHEME 44

The lithium enolates (141) and (142) were kinetically generated, since as discussed earlier ground state allylic strain interaction favours the selective formation of the Z-enolate. The results of the alkylation/acylation reactions are detailed in Table 11.

TABLE 11: Details of the alkylation / acylation reactions.

Product	Electrophile	Major : Minor[a]	Yield (%)[b]
143 a	$PhCH_2Br$	>99 : 1 (96 : 4)[c]	85
b	n-$C_8H_{17}Br$	>99 : 1 (97 : 3)	83
c	$CH_2{=}CHCH_2Br$	>99 : 1	90
d	PhCOCl	>99 : 1	87
e	MeCOCl	98 : 2	80
f	EtCOCl	>99 : 1	85
144	PhSeCl	>99 : 1	66

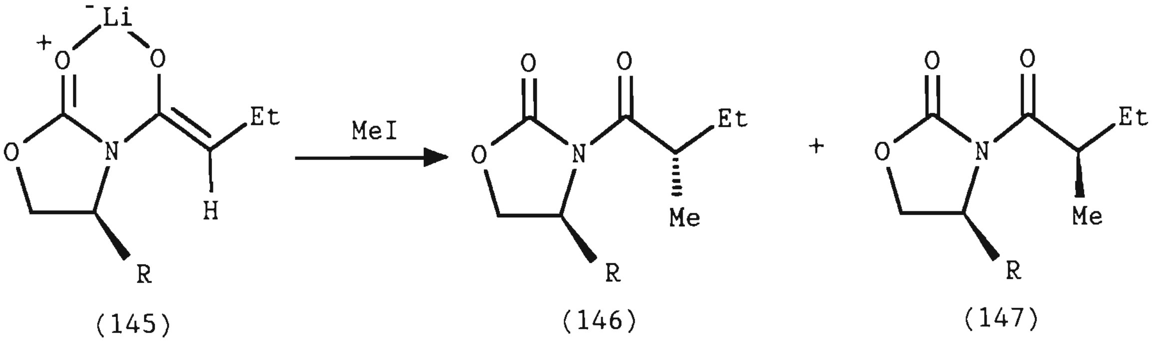
a) These ratios were determined by ^1H NMR and confirmed by GC/MS for (143 a), (143 e) and (143 f);

b) The products were purified by recrystallisation or in the case of (143 b), (143 c) and (144) by chromatography;

c) The ratios in parenthesis are those obtained by Cardillo *et al.*[98] with the 4 - phenyl auxiliary (78).

From an inspection of Table 11 it is evident that the 4-cyclohexyl auxiliary does indeed afford products with higher diastereoselectivity than does the 4-phenyl counterpart. The high diastereoselectivities obtained were gratifying since this obviated the need to change to the sodium enolate which Evans[154] has shown to be more selective than the lithium enolate. The diastereoselectivity of the reaction is simply explained as the attack of the chelated enolate on the electrophile which is positioned at the least hindered face of the enolate.

An interesting diastereoselectivity *vs* C-4 substituent study carried out by Evans[154] (Scheme 45, Table 12) confirms the phenyl ring as a relatively inefficient steric control element as compared to alkyl groups with respect to chiral auxiliaries of this type.



SCHEME 45

TABLE 12: Diastereoselectivity vs bulk of R (Scheme 45).

Entry	R	(146) : (147)
1	*i*-C_3H_7	90 : 10
2	C_6H_5	81 : 19
3	CH_3	86 : 14

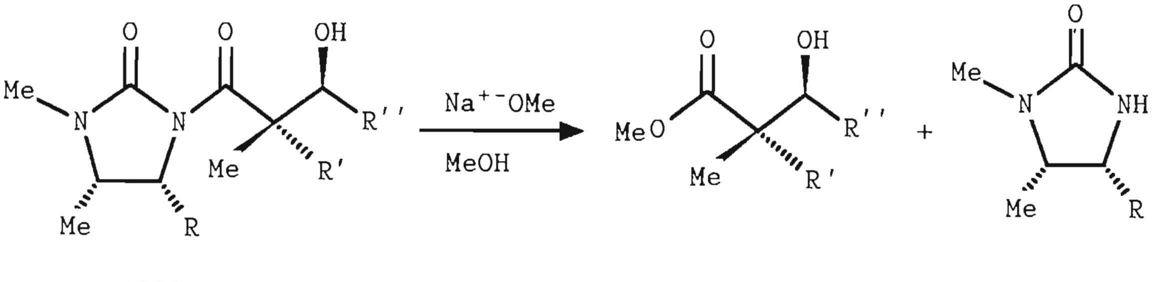
In the light of the excellent diastereoselectivities obtained for the alkylation/acylation reactions of the 4-cyclohexyl imidazolidin-2-one auxiliary it is surprising that the 4-cyclohexyl oxazolidin-2-one analogue (cf. Entry 2, Table 12) was not used in the above study. This analogue has however since been utilised as an efficient chiral auxiliary in intramolecular Diels-Alder reactions.[155]

2.8 THE NON-DESTRUCTIVE REMOVAL OF THE CHIRAL AUXILIARY.

A total synthesis that requires a chiral auxiliary for a particular diastereoselective step, will also require the removal of the chiral auxiliary at a convenient stage of the planned synthetic route. Ideally the removal should proceed efficiently and without loss of stereochemical integrity of both the chiral auxiliary and the newly created chiral centre.

2.8.1 CLEAVAGE OF THE AUXILIARY FROM THE INITIAL ALDOL PRODUCTS TO AFFORD HOMOCHIRAL β-HYDROXY ESTERS.

The synthesis of the required β-hydroxy esters was achieved by a transesterification process using sodium methoxide. Higher yields were obtained when the initial aldol product was added to a solution of *in situ* derived sodium methoxide, than if solid sodium methoxide was added to a methanolic solution of the aldol product (Scheme 46). An alternative route that is often used involves hydroxide induced saponification followed by esterification of the carboxylic acid with diazomethane.



(108 a-c)
(126 a-d)
(135 a-b)

(148 a-f)

(78) R = Ph
(123) R = c-C_6H_{11}

SCHEME 46

The synthesis of the β-hydroxy esters also served to conclusively assign the absolute configuration at C-2 and C-3 as depicted. This was done by comparison of the specific rotation of the adducts (148 a, d and e) with those of the known compounds (Table 13).

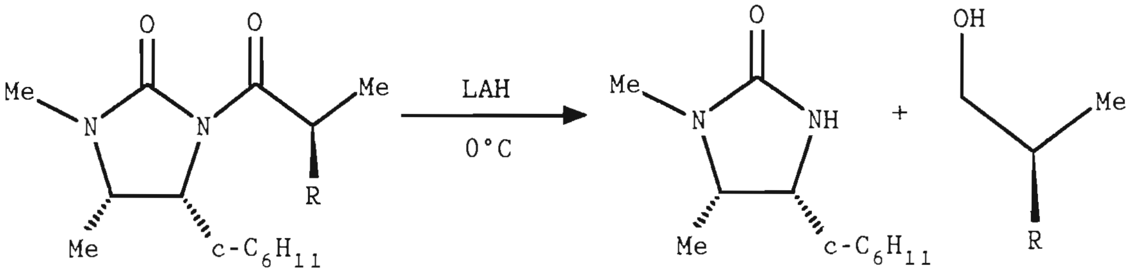
TABLE 13: Specific rotations of the β-OH methyl esters (148 a-f).

Ester	R'	R''	$[\alpha]_D$ °(c, solvent)	
			Experimental	Literature
148 a	H	Ph	+23.2 (1.50, $CHCl_3$)	+23.2 (3.2, $CHCl_3$)
b	H	$4\text{-}NO_2\text{-}C_6H_4$	+14.3 (1.30, $CHCl_3$)	—
c	H	$4\text{-MeO-}C_6H_4$	+16.9 (0.13, $CHCl_3$)	—
d	H	Me	-13.4 (0.51, MeOH)	-13.5 (0.87, MeOH)
e	H	*i*-Pr	+7.6 (1.21, $CHCl_3$)	+7.7 (5.40, $CHCl_3$)
f	H	*c*-C_6H_{11}	-6.17 (1.10, CH_2Cl_2)	—

The close correlation between the specific rotations of the experimentally determined and known values implies that the transesterification procedure is mild and non-destructive. The absolute configuration at C-2 and C-3 for esters (148 b, c and f) may thus be assigned as depicted by inference. Unfortunately the aldol products (135 a and b) undergo 'retroaldols' in the presence of base. This is thought to be due to the steric crowding at the α-position which precludes nucleophilic attack at the carbonyl.

2.8.2 CLEAVAGE OF THE CHIRAL AUXILIARY FROM THE ALKYLATION PRODUCTS.

The reductive cleavage of *N*-acylimidazolidin-2-ones with hydrides has been previously described by Cardillo *et al.* using LAH[98] or $NaBH_4$.[99] The method of choice for this study was the LAH reduction (Scheme 47).



(143) (123) (149)

SCHEME 47

Here again a comparison of specific rotations obtained experimentally with the literature values allowed for the assignment of the absolute configuration of the 1° alcohols (149a-b). Thus the absolute configuration of all the products of the alkylation/acylation study, (143 a-f) and (144), may be determined (Table 14).

TABLE 14: Specific rotations of the products of cleavage for compounds (143 a-c).

Prod.	R	$[\alpha]_D$ °(c, solvent)	
		Experimental	Literature
149 a	$PhCH_2$	-11.00 (2.75, C_6H_6)	-11.08 (4.60, C_6H_6)
149 b	n-C_8H_{17}	-9.94 (3.00, CH_2Cl_2)	-10.00 (4.20, CH_2Cl_2)
150	allyl	+0.94 (2.45, $CHCl_3$)[a]	——

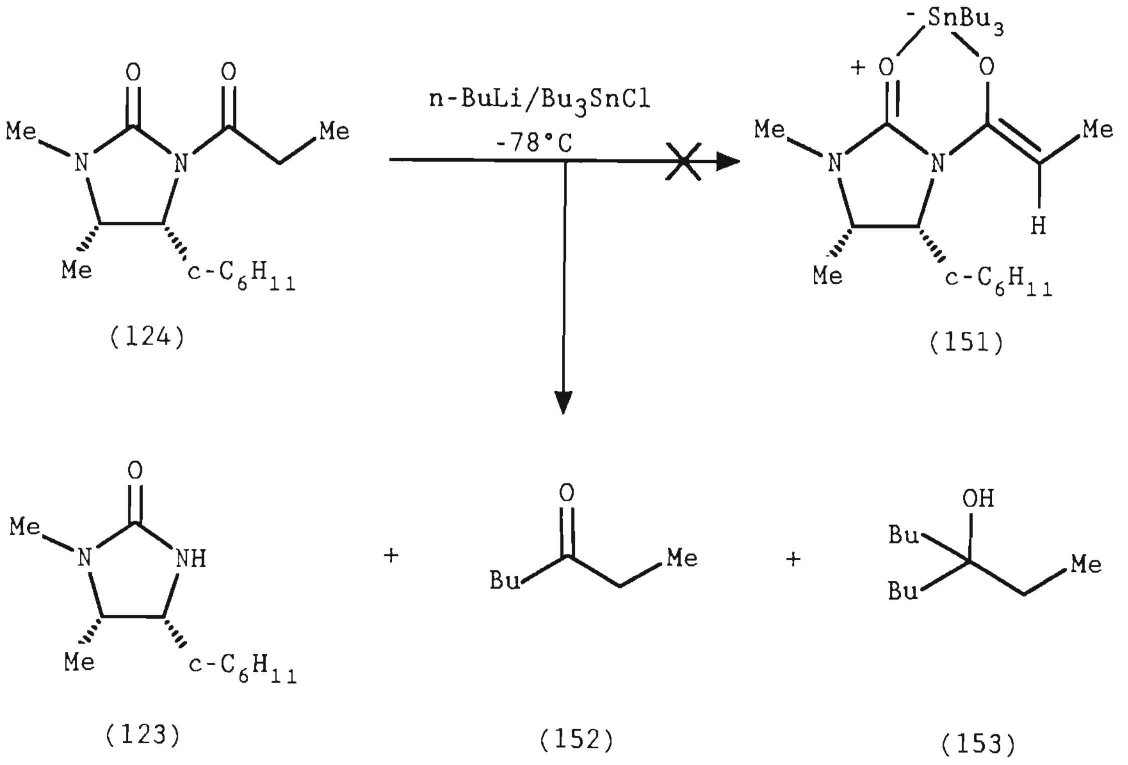
a) Isolated as the benzyl ester by cleavage of (143c) with BnO^-Li^+.

The 1° alcohol where R = allyl although difficult to isolate is a key intermediate in the synthesis of the masked lactol subunit of the antineoplastic macrolide antibiotic cytovaricin.[157] The homochiral alcohol (149) is a key intermediate for the synthesis of the pheromone of *Neodipirion sertifer*.[158]

From the high optical purities obtained for the β-hydroxy esters (148a) - (148f) and the 1° alcohols (149a) - (149b), and from the high diastereoselectivity ratios obtained for their precursors, the enolisation stereoselectivity in these systems can be inferred as being >97:3. In addition the stereochemical outcome of the aldol and alkylation/acylation reactions demands that both the boron and lithium enolates of the *N*-acylimidazolidin-2-ones have the Z geometry.

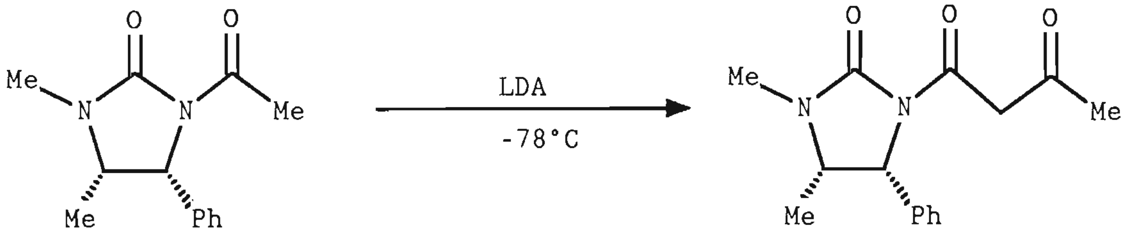
2.8.3 THE SYNTHESIS OF HOMOCHIRAL α-SUBSTITUTED KETONES.

As part of a study to obtain the 'non-Evans' *syn* aldol products from the tin enolate (151)[79] of the *N*-propionyl-imidazolidin-2-one (124), an interesting feature of these systems was revealed (Scheme 48).



SCHEME 48

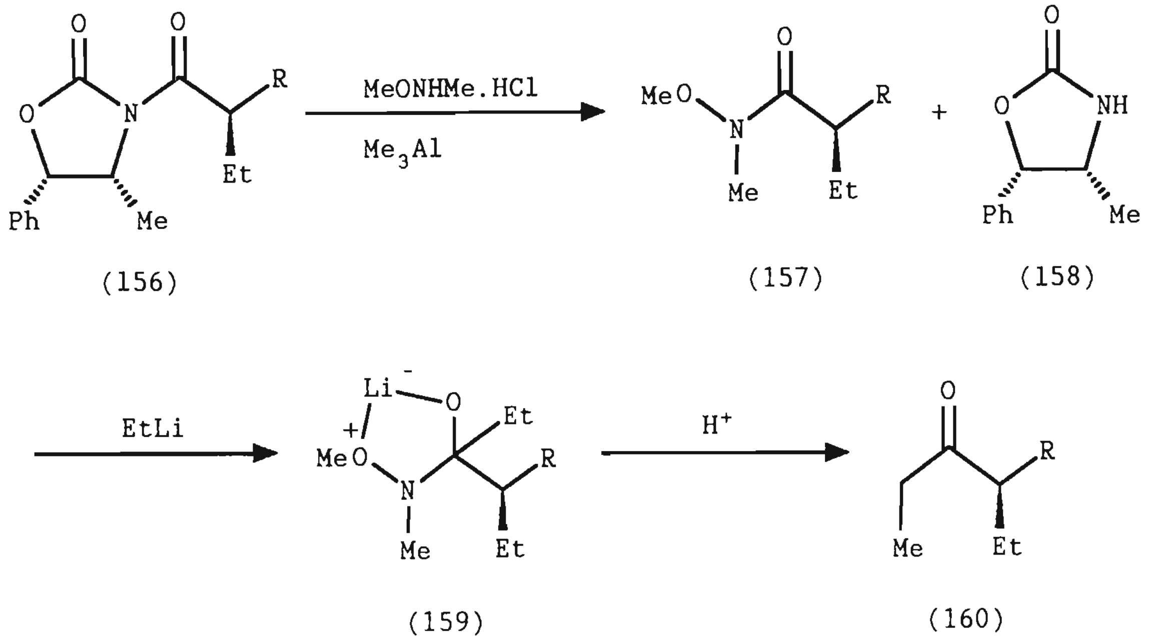
Instead of the expected deprotonation/transmetalation process to afford the enolate (151), the BuLi added to the C-1' position to afford a mixture of both the ketone (152) and the 3° alcohol (153). The presence of (152) and (153) was confirmed by ^{1}H NMR and GC/MS analysis of the crude reaction mixture. The ketone formation though surprising, has had an earlier precedent. Initial attempts to carry out the aldol reaction *via* the lithium enolate of the *N*-acetyl-imidazolidin-2-one (154) afforded the acylated product (155) *via* an intermolecular acyl transfer (Scheme 49).



SCHEME 49

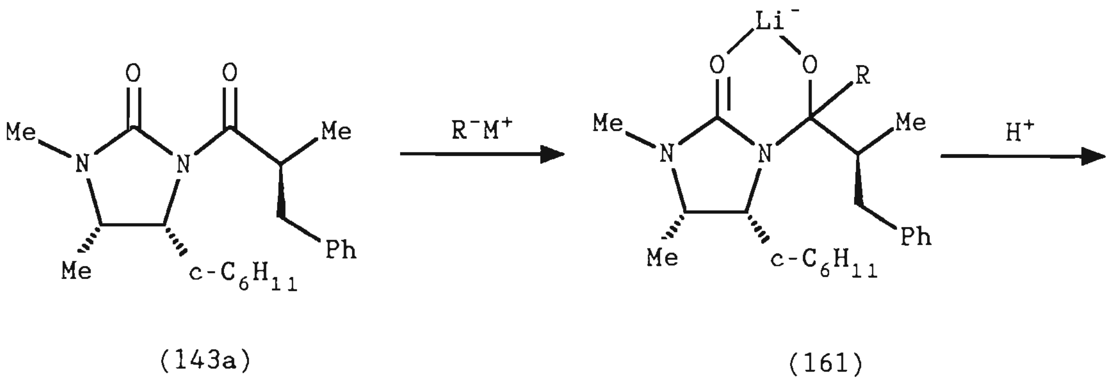
The outcome of these two reactions prompted an investigation into the synthesis of ketones derived from the initial aldol or alkylated adducts *via* nucleophilic displacement of the chiral auxiliary. The available methods for the synthesis of chiral α-substituted ketones in the main involve chemical manipulation of the chiral hydrazone derivatives.[59-63]

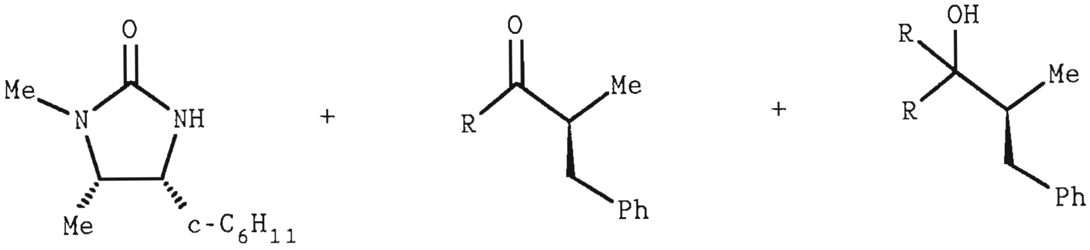
In their synthesis of the polyether antibiotic ferensimycin B, Evans *et al.*[159] required a process in which a chiral oxazolidin-2-one moiety could be cleaved such that a ketone was formed. This was necessary for operations to the left of the carbonyl (Scheme 50). The method chosen to achieve this goal was *via* the Weinreb amide.[160]



SCHEME 50

The Weinreb amide (157) has the advantage that the use of an excess of nucleophile does not result in the formation of the 3° alcohol. This is considered to be due to the formation of the stable five-membered chelate intermediate (159). However this process involves an additional step. It was hoped that the reaction of imidazolidin-2-one derivatives with nucleophiles could proceed directly *via* the chelated intermediate (161) to afford ketones in an analogous fashion (Scheme 51). The results of this investigation are shown in Table 15.

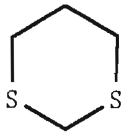




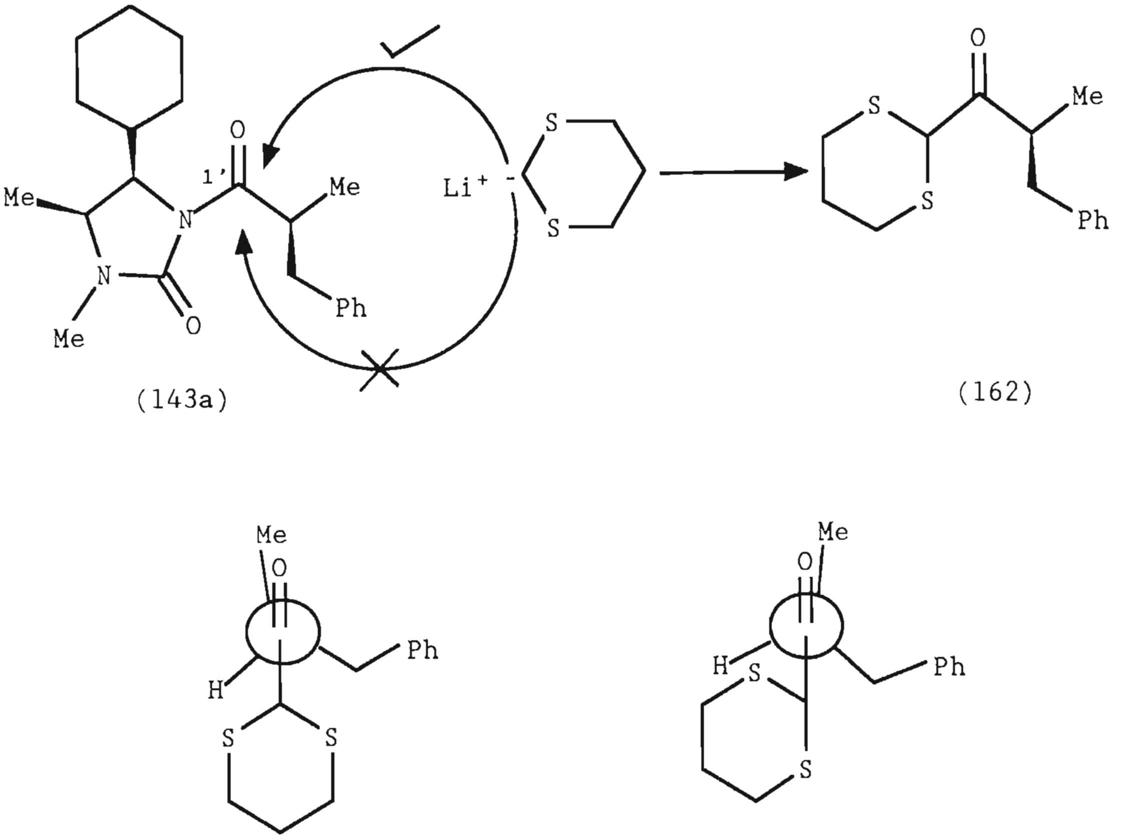
(123) (162) (163)

SCHEME 51

TABLE 15: Details of the attempted ketone synthesis with the *N*-acylimidazolidin-2-one (143a) as substrate.

Entry	R	M	Yield (%) of (162)	Yield (%) of (163)
1	Et	MgBr	—	—
2	PhC≡C	MgBr	—	—
3	PhC≡C	Li	—	42
4	*n*-Bu	Li	—	40
5		Li	64	—

From Table 15 it is apparent that the displacement does not occur with Grignard reagents but is facile with lithium nucleophiles. Even when the reactions (Entries 3 and 4) were carried out at low temperatures (-90°C) the formation of the 3° alcohols was not prevented. In the case of the dithiane anion, the required ketone was the sole product. This latter result is readily explained (Scheme 52) by considering that the addition of the nucleophile must occur from the least hindered face of the C-1′ carbonyl of the imide (143a) when the dipolar orientation is assumed.



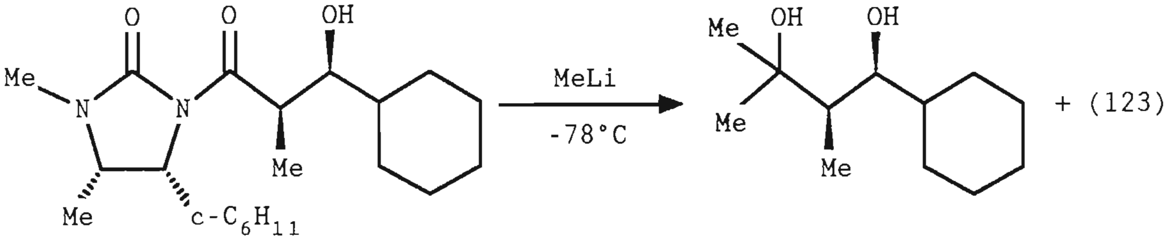
eclipsed
disfavoured

anticlinal
favoured

SCHEME 52

A Newman projection of (162) along the C2-C3 bond shows that the preferred conformation of the ketone has the dithiane moiety anticlinal to the 3-benzyl group. This conformation is forced on it by the severe steric interactions in the eclipsed conformation. In the preferred conformation both faces of the carbonyl are hindered, thus further reaction of the ketone with a nucleophile is precluded.

Finally, ketone formation from the aldol adduct (126c) was attempted by the reaction of 2.0 equivalents of methyl lithium. Unfortunately under the reaction conditions, the diol (164) was the only product (Scheme 53).



(126c)

(164)

SCHEME 53

Although the possibility of ketone formation is dependant on the steric bulk of the nucleophile, this potentially useful transformation is the subject of further investigations in these laboratories. The variation of the metal centre is regarded as the key to a possible solution.

2.9 CONCLUSION.

The preceding discussion[161] has shown that the 4-cyclohexyl imidazolidin-2-one (123) is an efficient chiral auxiliary. There are many advantages in its favour:

(i) It imparts crystallinity to most of its products;
(ii) It and its adducts are easily purified by either recrystallisation or flash chromatography;
(iii) It is prepared from readily available and relatively cheap starting materials;
(iv) It is removed by non-destructive methods and is recovered in yields of >85% with undiminished optical purity;
(v) It is not susceptible to ring opening on reaction with nucleophiles.

In recent years the oxazolidin-2-one chiral auxiliaries have been the focus of much research with respect to the synthesis of all four possible aldol products depending on the Lewis acid used in these reactions.[162] There is no reason why (-)-(4R,5S)-4-cyclohexyl-1,5-dimethylimidazolidin-2-one (123) and its antipode should not find similar and novel applications in the future.

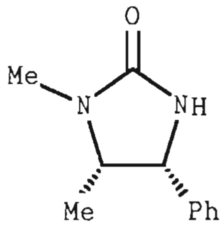
3. EXPERIMENTAL

3.1 INSTRUMENTATION AND CHEMICALS

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were determined using Perkin -Elmer 240B and 2400 elemental analysers. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 instrument. Unless specified to the contrary, $CDCl_3$ was used as the solvent. Tetramethylsilane was used as the internal standard. Mass spectra were recorded on a Hewlett-Packard gas chromatographic mass spectrometer (HP5988A) and a Varian high resolution mass spectrometer. Optical rotations were determined on a Perkin-Elmer 241 digital polarimeter. Infra-red spectra were obtained using Perkin-Elmer 1420 and Shimadzu FTIR-4300 spectrophotometers. Precoated Kieselgel 60 F_{254} Merck plastic sheets were used for thin layer chromatography. Preparative column chromatography was performed using the technique of Still *et al.* on Merck silica gel 60 (230-400 mesh). The imidazolidin-2-one derivatives were best visualised on the precoated Kieselgel plastic sheets by using the cobalt (II) thiocyanate dip reagent.[163] Solvents were dried using standard techniques and distilled prior to use. Low temperatures were maintained using dry ice/solvent baths according to the procedure of Phipps and Hume.[164]

3.2 PREPARATIONS

(4R,5S)-1,5-Dimethyl-4-phenylimidazolidin-2-one **(78)**

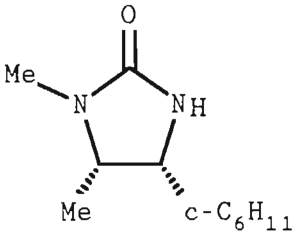


$C_{11}H_{14}N_2O$

MW = 190.24

(-)-Ephedrine hydrochloride (50.00 g) and urea (45.00 g) were heated for 30 min. at 170-175°C. The resultant melt was further heated at 200-210°C with magnetic stirring for 1 h. The mixture was cooled to 100°C, then treated with H_2O. The oily solid which formed was first washed with aq. HCl (5%) and then with H_2O. Recrystallization from ethanol afforded **(78)** (28.8 g, 60%), m.p. 177°C (lit.,[97] 177-179°C); (Found: C, 69.51; H, 7.48; N, 14.70. $C_{11}H_{14}N_2O$ requires C, 69.45; H, 7.42; N, 14.72%); $[\alpha]_D$ -44.3° (*c* 0.9, MeOH) (lit.,[97] $[\alpha]_D$ -44.5°(*c* 3.0, MeOH)); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3460 (NH) and 1704 (CO); δ_H (200 MHz) 0.73 (3H, d, *J* 6.5 Hz, 5-Me), 2.72 (3H, s, NMe), 3.86 (1H, dq, *J* 9 and 6.5 Hz, H-5), 4.77 (1H, d, *J* 9 Hz, H-4), 5.70 (1H, br s, NH), 7.24-7.38 (5H, m, Ph); δ_C (50 MHz) 14.30 (q, 5-Me), 28.22 (q, NMe), 57.74 (d, C-5), 58.25 (d, C-4), 127.55, 128.25 and 128.77 (d, Ph), 138.73 (s, Ph), 163.22 (s, C-2); *m/z* 190 (M^+, 62%), 175 (100) and 58 (43).

(4R,5S)-4-Cyclohexyl-1,5-dimethylimidazolidin-2-one **(123)**



$C_{11}H_{20}N_2O$

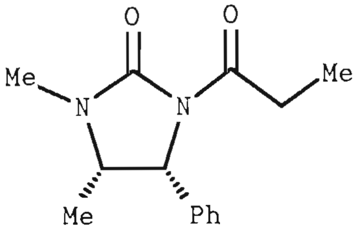
MW = 196.29

A teflon reaction vessel was charged with a mixture of $RhCl_3.3H_2O$ (263 mg, 1.26 mmol) in water (30 ml), Aliquat 336 (580 mg, 1.44 mmol) and **(78)** (5.00 g, 26.32 mmol) in 1,2-dichloroethane (30 ml). The reaction mixture was stirred at 30°C for 24 h under 5 atmospheres of H_2 pressure in an autoclave. The phases were separated and the organic phase was filtered through acidic alumina, treated with activated charcoal, filtered and concentrated. Recrystallization of the residue afforded **(123)** as off-white crystals (4.90 g, 95%), m.p. 162°C (from EtOAc);
(Found: C, 67.14; H, 10.15; N, 14.22. $C_{11}H_{20}N_2O$ requires C, 67.31; H, 10.27; N, 14.27%); $[\alpha]_D$ -1.0° (*c* 0.60, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 3220 (NH), 2952 (Me), and 1691 (CO);
δ_H (200 MHz) 0.82-1.82 (11H, m, cyclo-C_6H_{11}), 1.10 (3H, d, *J* 6 Hz, 5-Me), 2.75 (3H, s, NMe), 3.29 (1H, ddd, *J* 9, 7 and 2 Hz, H-4); 3.60 (1H, dq, *J* 7 Hz, H-5); 5.02 (1H, br s, NH);
δ_C (50 MHz) 10.65 (q, 5-Me); 25.56, 25.59 and 26.22 (t, 3 x CH_2), 27.91 (q, NMe), 29.65 and 29.92 (t, 2 x CH_2), 37.12 (d, ring-CH), 56.02 (d, C-4), 59.79 (d, C-5), 162.47 (s, C-2); *m/z* 196 (M^+, 9%) and 113 (100).

GENERAL PROCEDURE 1. Preparation 3-Acyl-imidazolidin-2-ones **(88)**, **(124)**, **(134)**, **(140)**, and **(154)**.

A stirred solution of the appropriate imidazolidin-2-one (1 equiv.) in dry THF (30 ml) was treated with an equimolar amount of *n*-BuLi at 0°C. After 30 min. at 0°C the appropriate acyl chloride or anhydride (1 equiv.) was added. The reaction mixture was stirred for 1 h at 0°C then quenched with saturated $NaHCO_3$. The THF was removed under reduced pressure and the residue was partitioned between H_2O and CH_2Cl_2. The organic phase was dried ($MgSO_4$), concentrated and purified.

(4R,5S)-1,5-Dimethyl-4-phenyl-3-propanoylimidazolidin-2-one **(88)**

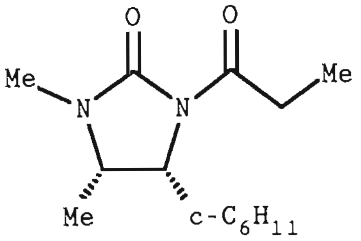


$C_{14}H_{18}N_2O_2$

MW = 246.31

Reaction of the lithium salt of **(78)** (5.00 g, 26.3 mmol) with propionyl chloride (2.29 ml, 26.30 mmol) according to General Procedure 1 afforded **(88)** as white crystals (6.15 g, 95%), m.p. 106°C (from $CHCl_3$) (lit.,[98] 90°C);
(Found: C, 68.38; H, 7.66; N, 11.28. $C_{14}H_{18}N_2O_2$ requires C, 68.27; H,7.37; N, 11.37%); $[\alpha]_D$ -54.1° (*c* 1.00, CH_2Cl_2) lit.,[98] $[\alpha]_D$ -54.7° (*c* 1.0, CH_2Cl_2)); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1728 (CO) and 1685 (CO); δ_H (200 MHz) 0.80 (3H, d, *J* 7 Hz, 5-Me), 1.10 (3H, t, *J* 7 Hz, H-3´), 2.82 (3H, s, NMe), 2.99 (2H, q, *J* 7 Hz, H-2´), 3.90 (1H, dq, *J* 9 and 7 Hz, H-5), 5.29 (1H, d, *J* 9 Hz, H-4), 7.12-7.34 (5H, m, Ph); δ_C (50 MHz) 8.62 (q, C-3'), 14.92 (q, 5-Me), 28.17 (t, C-2'), 29.34 (q, NMe), 54.10 (d, C-5), 59.38 (d, C-4), 127.27, 128.32 and 128.80 (d, Ph), 137.28 (s, Ph), 156.42 (s, C-2), 173.86 (s, C-1'); *m/z* 246 (M^+, 35%), 217 (0.7), 189 (47) and 132 (100).

(4R,5S)-4-Cyclohexyl-1,5-dimethyl-3-propanoylimidazolidin-2-one **(124)**

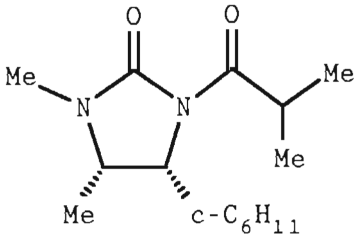


$C_{14}H_{24}N_2O_2$

MW = 252.35

Reaction of the lithium salt of **(123)** (5.0 g, 25.5 mmol) with propionyl chloride (2.22 ml, 25.50 mmol) according to General Proc. 1 afforded **(124)** as colourless crystals (6.10 g, 95%) m.p. 99-100°C (from hexane);
(Found: C, 66.39; H, 9.75; N, 11.04. $C_{14}H_{24}N_2O_4$ requires C, 66.63; H, 9.58; N, 11.10 %); $[\alpha]_D$ -14.2° (*c* 0.16, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2950 (Me), 1720 (CO) and 1681 (CO); δ_H (200 MHz) 0.82-1.36 and 1.52-1.82 (11 H, m, cyclo-C_6H_{11}), 1.17 (3H, t, *J* 7 Hz, H-3'), 1.32 (3H, d, *J* 7 Hz, 5-Me), 2.76 (3H, s, NMe), 2.86 (1H, dq, *J* 17 and 7 Hz, H-2'), 3.03 (1H, dq, *J* 17 and 7 Hz, H-2'), 3.67 (1H, dq, *J* 7 Hz, H-5), 4.33 (1H, dd, *J* 7 and 3 Hz, H-4); δ_C (50 MHz) 9.09 (q, 5-Me), 13.08 (q, C-3'), 26.19, 26.33 and 26.97 (t, 3 x CH_2), 27.75 (q, NMe), 27.75 and 29.29 (t, 2 x CH_2), 32.56 (t, C-2'), 39.19 (d, ring-CH), 54.84 (d, C-5), 59.07 (d, C-4), 156.60 (s, C-2), 174.29 (s, C-1'); *m/z* 252 (M^+, 12%), 223 (33), 195 (8) and 113 (100).

(4R,5S)-4-Cyclohexyl-1,5-dimethyl-3-(2'-methylpropanoyl)-imidazolidin-2-one **(134)**

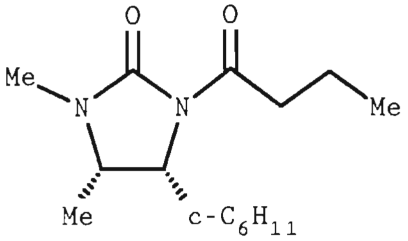


$C_{15}H_{26}N_2O_2$

MW = 266.20

Reaction of the lithium salt of **(123)** (5.0 g, 25.5 mmol) with *iso*-butyric anhydride (4.23 ml, 25.50 mmol) as in General Proc. 1 afforded **(134)** as a colourless oil (6.00 g, 88%); (Found: *M*$^+$, 266.1980. $C_{15}H_{26}N_2O_2$ requires *M*, 266.1994); $[\alpha]_D$ -8.22° (*c* 1.0, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 2960 (Me), 1736 (CO) and 1692 (CO); δ_H (200 MHz) 1.10 (3H, d, *J* 7 Hz, H-3'), 1.25 (3H, d, *J* 7 Hz, H-3´´), 1.33 (3H, d, *J* 7 Hz, 5-Me), 0.95-1.85 (11H, m, cyclo-C_6H_{11}), 2.77 (3H, s, NMe), 3.69 (1H, dq, *J* 7 Hz, H-5), 3.88 (1H, dq, *J* 7 Hz, H-2'), 4.36 (1H, dd, *J* 7 and 3 Hz, H-4); δ_C (50 MHz) 12.98 (q, 5-Me), 18.39 and 20.49 (q, C-3' and C-3''), 26.10, 26.26, 26.92, 27.59 (t, 4 x CH_2), 27.67 (q, NMe), 32.55 (t, CH_2), 32.65 (d, C-2'), 39.17 (d, ring-CH), 54.48 (d, C-5), 58.65 (d, C-4), 156.13 (s, C-2), 177.66 (s, C-1'); *m/z* 266 (M$^+$, 2%), 223 (8), 183 (9) and 113 (100).

(4R,5S)-3-Butanoyl-4-cyclohexyl-1,5-dimethylimidazolidin-2-one **(140)**

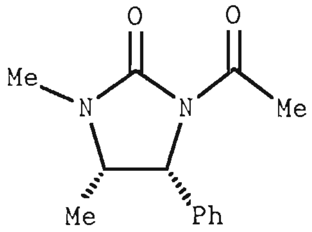


$C_{15}H_{26}N_2O_2$

MW = 266.20

Reaction of the lithium salt of **(123)** (5.0 g, 25.5 mmol) with *n*-butyric anhydride (4.17 ml, 25.50 mmol) according to General Proc. 1 afforded **(140)** as white crystals (6.20 g, 91%), m.p. 77°C (from $CHCl_3$);
(Found: C, 67.48; H, 10.02; N, 10.65. $C_{15}H_{26}N_2O_2$ requires C, 67.62; H, 9.84; N, 10.52%); $[\alpha]_D$ -14.93° (*c* 1.42, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 2960 (Me), 2860 (CH_2), 1724 (CO) and 1676 (CO); δ_H (200 MHz) 0.98 (3H, t, *J* 7 Hz, H-4'), 1.00-1.85 (13H, m, cyclo-C_6H_{11} and H-3'), 1.33 (3H, d, *J* 7 Hz, 5-Me), 2.76 (3H, s, NMe), 2.78 (1H, ddd, *J* 16, 8 and 7 Hz, H-2'), 3.04 (1H, ddd, *J* 16, 8 and 7 Hz, H-2'), 3.68 (1H, dq, *J* 7 Hz, H-5), 4.34 (1H, dd, *J* 7 and 4 Hz, H-4); δ_C (50 MHz) 13.08 (q, C-4'), 13.89 (q, 5-Me), 18.49, 26.10, 26.18, 26.89, 27.67, 32.49 and 37.61 (t, 5 x ring-CH_2, C-2' and C-3'), 27.67 (q, NMe), 39.06 (d, ring-CH), 54.62 (d, C-5), 58.80 (d, C-4), 156.53 (s, C-2), 173.34 (s, C-1'); *m/z* 266 (M^+, 3%), 223 (7) and 113 (100).

(4R,5S)-3-Acetyl-1,5-dimethyl-4-phenylimidazolidin-2-one **(154)**



$C_{13}H_{16}N_2O_2$

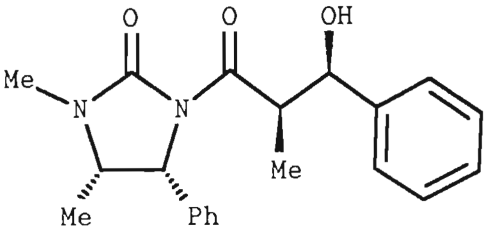
MW = 232.28

Reaction of the lithium salt of **(78)** (5.00 g, 26.3 mmol) with acetyl chloride (1.80 ml, 26.30 mmol) according to General Proc. 1 afforded **(154)** as pale yellow crystals (5.60 g, 92%), m.p. 130°C (from $CHCl_3$);
(Found: C, 66.90; H, 7.06; N, 12.01. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06%); $[\alpha]_D$ -44.9° (*c* 0.50, CH_2Cl_2)); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1730 (CO) and 1687 (CO); δ_H (200 MHz) 0.80 (3H, d, *J* 7 Hz, 5-Me), 2.53 (3H, s, H-2′), 2.83 (3H, s, NMe), 3.89 (1H, dq, *J* 9 and 7 Hz, H-5), 5.29 (1H, d, *J* 9 Hz, H-4), 7.12-7.38 (5H, m, Ph); δ_C (50 MHz) 14.94 (q, 5-Me), 24.10 (q, C-2′), 28.22 (q, NMe), 54.07 (d, C-5), 59.34 (d, C-4), 127.30, 128.43 and 128.86 (d, Ph), 136.98 (s, Ph), 156.48 (s, C-2), 170.22 (s, C-1′); *m/z* 232 (M^+, 11%), 189 (62), 175 (38) and 132 (100).

GENERAL PROCEDURE 2. Preparation of the aldol products **(108a-c)**, **(126a-d)** and **(135a-b)**

To a stirred, cold (-10°C) solution of the appropriate N-acylimidazolidin-2-one (1.00 equiv.) in dry CH_2Cl_2 (4 ml) was added dropwise over 1 min. di-*n*-butylboron triflate (1 M in CH_2Cl_2, 1.15 equiv.). After 5 min. Et_3N (1.30 equiv.) was added. The mixture was stirred at -10°C for 1 h, cooled to -78°C and the appropriate aldehyde (1.00 equiv.) was added. After 30 min. at -78°C the reaction temperature was allowed to rise to -10°C and maintained at this temperature for 1 h. The reaction mixture was then quenched by sequential addition of aq. pH 7 phosphate buffer (4.5 ml), MeOH (16.5 ml) and 30% H_2O_2 (4.5 ml) in MeOH (8.5 ml). After 1 h at 0°C the mixture was concentrated and the residue partitioned between Et_2O and H_2O. The organic phase was sequentially washed with cold HCl (5%), satd. aq. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated.

(4R,5S,2'R,3'R)-1,5-Dimethyl-4-phenyl-3-(3'-hydroxy-2'-methyl-3'-phenylpropanoyl)imidazolidin-2-one **(108a)**

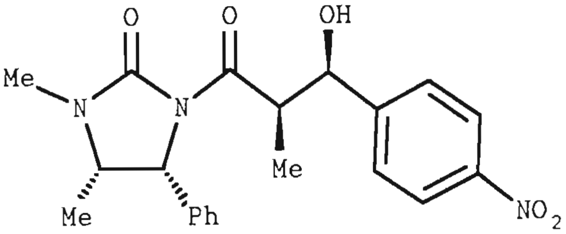


$C_{21}H_{24}N_2O_3$

MW = 352.18

The boron enolate of **(88)** (1.0 g, 4.1 mmol) was allowed to react with benzaldehyde (0.41 ml, 4.06 mmol) according to General Procedure 2 to afford **(108a)** as white crystals (1.26 g, 88%), m.p. 135-136°C (from C_6H_6); (Found: M^+, 352.1755. $C_{12}H_{24}N_2O_3$ requires M, 352.1786); $[\alpha]_D$ -35.3° (c 0.6, $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3500 (OH), 1730 (CO), 1660 (CO) and 1605 (Ph); δ_H (200 MHz) 0.76 (3H, d, J 7 Hz, 5-Me), 1.07 (3H, d, J 7 Hz, 2'-Me), 2.79 (3H, s, NMe), 3.75 (1H, d, OH, D_2O exch.), 3.81 (1H, dq, J 9 and 7 Hz, H-5), 4.28 (1H, dq, J 7 and 3 Hz, H-2'), 5.10 [1H, m, H-3'(D_2O exch., d, J 3 Hz)], 5.28 (1H, d, J 9 Hz, H-4), 7.10-7.43 (10H, m , 2 x Ph); δ_C (50 MHz) 10.39 (q, 2'-Me), 14.98 (q, 5-Me), 28.24 (q, NMe), 44.24 (d, C-2'), 53.80 (d, C-5), 59.29 (d, C-4), 73.49 (d, C-3'), 126.51, 127.02, 127.41, 128.38, 128.60 and 129.03 (d, Ph), 136.74 and 142.01 (s, Ph), 155.57 (s, C-2), 177.44 (s, C-1'); m/z 352 (M^+, 10%), 334 (2) and 246 (100).

(4R,5S,2'R,3'R)-1,5-Dimethyl-4-phenyl-3-[3'-hydroxy-2'-methyl-3'-(4-nitrophenyl)propanoyl]imidazolidin-2-one **(108b)**

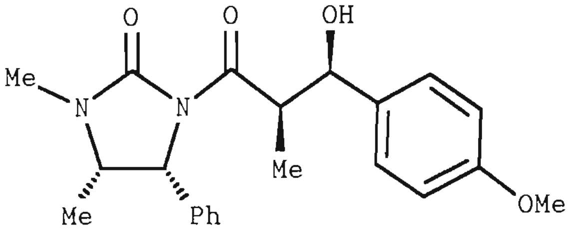


$C_{21}H_{23}N_3O_5$

MW = 397.16

The boron enolate of **(88)** (1.00 g, 4.06 mmol) was allowed to react with 4-nitrobenzaldehyde (0.16 g, 4.06 mmol) according to General Procedure 2 to afford **(108b)** as pale yellow crystals (1.37 g, 85%), m.p. 156-157°C (from C_6H_6); (Found: M^+, 397.1649. $C_{21}H_{23}N_3O_5$ requires *M*, 397.1637); $[\alpha]_D$ -28.0° (*c* 0.60, $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3500 (OH), 1732 (CO), 1658 (CO), 1603 (Ph), 1520 and 1348 ($C-NO_2$); δ_H (200 MHz) 0.82 (3H, d, *J* 7 Hz, 5-Me), 1.02 (3H, d, *J* 7 Hz, 2'-Me), 2.86 (3H, s, NMe), 3.96 (1H, dq, *J* 9 and 7 Hz, H-5), 4.06 (1H, d, OH, D_2O exch.), 4.29 (1H, dq, *J* 7 and 2.5 Hz, H-2'), 5.23 [1H, m, H-3'(D_2O exch., d, *J* 2.5 Hz)], 5.37 (1H, m, *J* 9 Hz, H-4), 7.28-7.40 (5H, m, Ph), 7.57-8.22 (4H, m, Ar); δ_C (50MHz) 10.00 (q, 2'-Me), 15.07 (q, 5-Me), 29.34 (q, NMe), 43.76 (d, C-2'), 53.92 (d, C-5), 59.29 (d, C-4), 72.55 (d, C-3'), 123.70, 126.99, 127.40, 128.78 and 129.15 (d, Ar and Ph), 136.51, 147.48 and 149.51 (s, Ar and Ph), 155.49 (s, C-2), 177.07 (s, C-1'); *m/z* 397 (M^+, 6%), 246 (100) and 189 (67).

(4R,5S,2'R,3'R)-1,5-Dimethyl-4-phenyl-3-[3'-hydroxy-2'-methyl-3'-(4-methoxyphenyl)propanoyl]imidazolidin-2-one **(108c)**

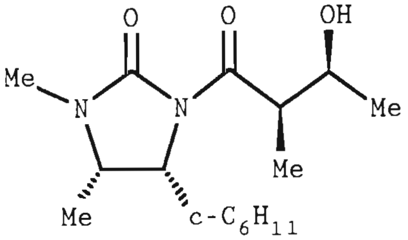


$C_{22}H_{26}N_2O_4$

MW = 382.19

The boron enolate of **(88)** (1.00 g, 4.06 mmol) was allowed to react with 4-methoxybenzaldehyde (0.55 g, 4.06 mmol) as in General Procedure 2 to afford **(108c)** as white crystals (1.43 g, 92%), m.p. 181-182°C (from $CHCl_3$); (Found: M^+, 382.1913. $C_{22}H_{26}N_2O_4$ requires *M*, 382.1892); $[\alpha]_D$ -40.0° (*c* 0.11, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 3482 (OH), 2987 (Me), 1732 (CO), 1674 (CO), 1606 and 1510 (Ph); δ_H (200 MHz) 0.77 (3H, d, *J* 7 Hz, 5-Me), 1.08 (3H, d, *J* 7 Hz, 2'-Me), 2.80 (3H, s, NMe), 3.65 (1H, m, OH, D_2O exch.), 3.78 (3H, s, OMe), 3.82 (1H, dq, *J* 9 and 7 Hz, H-5), 4.24 (1H, dq, *J* 7 and 3.4 Hz, H-2'), 5.05 [1H, m, H-3'(D_2O exch., d, *J* 3.4 Hz)], 5.27 (1H, d, *J* 9 Hz, H-4), 6.83-7.34 (9H, m, Ph and Ar); δ_C (50 MHz) 10.53 (q, 2'-Me), 14.96 (q, 5-Me), 28.18 (q, NMe), 44.22 (d, C-2'), 53.65 (d, C-5), 55.22 (q, OMe), 59.12 (d, C-4), 73.01 (d, C-3'), 113.37, 126.63, 127.54, 128.19 and 128.63 (d, Ar and Ph), 133.82, 136.36 and 155.15 (s, Ar and Ph), 158.61 (s, C-2), 176.87 (s, C-1'); *m/z* 382 (M^+, 3%), 364 (3), 246 (100) and 189 (55).

(4R,5S,2'R,3'S)-4-Cyclohexyl-1,5-dimethyl-3-(3'-hydroxy-2'-methylbutanoyl)imidazolidin-2-one **(126a)**

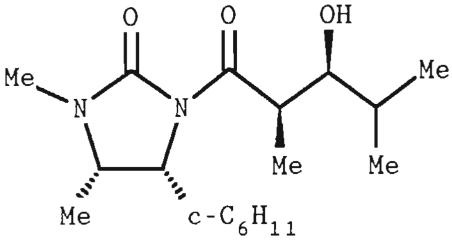


$C_{16}H_{28}N_2O_3$

MW = 296.21

The reaction between the boron enolate of **(124)** (1.00 g, 3.97 mmol) and acetaldehyde (0.22 ml, 3.97 mmol) according to General Procedure 2 yielded a residue which was chromatographed on silica gel with Et_2O/hexane (3:7) as the eluent to afford **(126a)** (0.94 g, 80%) as a colourless oil; (Found: M^+, 296.2056. $C_{16}H_{26}N_2O_3$ requires *M*, 296.2099); $[\alpha]_D$ -2.20° (*c* 1.064, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 3495 (OH), 2930 (CH_2), 1730 (CO) and 1678 (CO); δ_H (200 MHz) 0.95-1.85 (11H, m, cyclo-C_6H_{11}), 1.16 (3H, d, *J* 6.5 Hz, 2'-Me), 1.30 (3H, d, *J* 7 Hz, H-4'), 1.34 (3H, d, *J* 7 Hz, 5-Me), 2.78 (3H, s, NMe), 3.71 (1H, dq, *J* 7 Hz, H-5), 3.62-3.80 (1H, br s, OH), 3.80 (1H, dq, *J* 7 and 2.5 Hz, H-3'), 4.12 (1H, dq, *J* 6.5 and 2.5 Hz, H-2'), 4.39 (1H, dd, *J* 7 and 3 Hz, H-4); δ_C (50 MHz) 11.12 (q, 2'-Me), 12.92 (q, C-4'), 19.39 (q, 5-Me), 26.11, 26.26, 26.94 and 27.64 (t, 4 x CH_2), 27.76 (q, NMe), 32.65 (t, CH_2), 39.27 (d, ring-CH), 43.03 (d, C-2'), 54.57 (d, C-5), 58.71 (d, C-4), 67.53 (d, C-3'), 155.89 (s, C-2), 178.11 (s, C-1'); *m/z* 296 (M^+, 2%), 252 (2), 223 (12) and 113 (100).

(4R,5S,2'R,3'S)-4-Cyclohexyl-1,5-dimethyl-3-(2',4'-dimethyl-3'-hydroxypentanoyl)imidazolidin-2-one **(126b)**

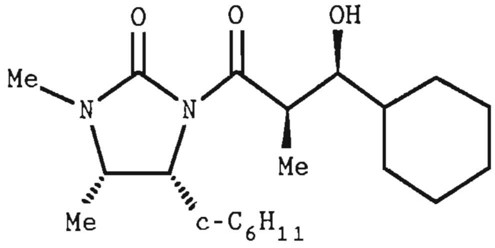


$C_{18}H_{32}N_2O_3$

MW = 324.24

The reaction between the boron enolate of **(124)** (1.00 g, 3.97 mmol) and *iso*-butyraldehyde (0.36 ml, 3.97 mmol) according to General Procedure 2 yielded a residue which was chromatographed on silica gel with Et_2O/hexane (1:1) as the eluent to afford **(126b)** as a colourless oil (1.05 g, 82%); (Found: M^+, 324.2390. $C_{18}H_{32}N_2O_3$ requires *M*, 324.2413); $[\alpha]_D$ +2.57° (*c* 0.62, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 3500 (OH), 2960 (Me), 1730 (CO) and 1670 (CO); δ_H (200 MHz) 0.88 (3H, d, *J* 7 Hz, 4'-Me), 1.03 (3H, d, J 7 Hz, H-5'), 0.92-1.32 and 1.52-1.82 (11H, m, cyclo-C_6H_{11}), 1.27 (3H, d, *J* 7 Hz, 2'-Me), 1.34 (3H, d, *J* 7 Hz, 5-Me), 1.72 (1H, 2 x dq, *J* 9 and 7 Hz, H-4'), 2.78 (3H, s, NMe), 3.45 (1H, ddd, *J* 9, 2 and 2 Hz, H-3'), 3.71 (1H, dq, *J* 7 Hz, H-5), 3.76 (1H, d, *J* 2 Hz, OH), 4.08 (1H, dq, *J* 7 and 2 Hz, H-2'), 4.39 (1H, dd, *J* 7 and 3 Hz, H-4); δ_C (50 MHz) 10.98 (q, 2'-Me), 12.96 (q, 5-Me), 18.92 (q, 4'-Me), 19.63 (q, C-5'), 26.06, 26.19, 26.87 and 27.58 (t, 4 x CH_2), 27.70 (q, NMe), 30.36 (d, C-4'), 32.49 (t, CH_2), 39.10 (d, ring-CH), 39.20 (d, C-2'), 54.34 (d, C-5), 58.42 (d, C-4), 76.60 (d, C-3'), 155.67 (s, C-2), 178.72 (s, C-1'); *m/z* 324 (M^+, 6%), 306 (7), 252 (51), 223 (70) and 113 (100).

(4R,5S,2'R,3'S)-4-Cyclohexyl-1,5-dimethyl-3-(3'-cyclohexyl-3'-hydroxy-2'-methylpropanoyl)imidazolidin-2-one **(126c)**

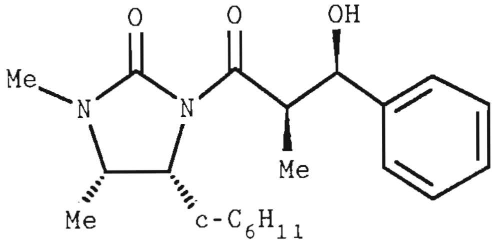


$C_{21}H_{36}N_2O_3$

MW = 364.27

The reaction between the boron enolate of **(124)** (1.00 g, 3.97 mmol) and cyclohexanecarbaldehyde (0.48 ml, 3.97 mmol) as in General Procedure 2 yielded **(126c)** as cream coloured crystals (1.33 g, 92%) m.p. 126-128°C (from hexane); (Found: M^+, 364.2738. $C_{21}H_{36}N_2O_3$ requires *M*, 364.2726); $[\alpha]_D$ -7.84° (*c* 1.12, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 3500 (OH), 2920 (CH_2), 1725 (CO) and 1650 (CO); δ_H (200 MHz) 0.80-1.82 (21H, m, 2 x cyclo-C_6H_{11}), 1.26 (3H, d, *J* 7 Hz, 2'-Me), 1.33 (3H, d, *J* 7 Hz, 5-Me), 2.08-2.22 (1H, m, ring-CH), 2.77 (3H, s, NMe), 3.52 (1H, ddd, *J* 9, 2 and 2 Hz, H-3') 3.71 (1H, dq, *J* 7 Hz, H-5), 3.76 (1H, d, *J* 2 Hz, OH), 4.06 (1H, dq, *J* 7 and 2 Hz, H-2'), 4.38 (1H, dd, *J* 7 and 3 Hz, H-4); δ_C (50 MHz) 10.90 (q, 2'-Me), 12.96 (q, 5-Me), 25.97, 26.06, 26.18, 26.46, 26.86, 27.57 (t, CH_2), 27.70 (q, NMe), 28.77, 29.93 and 32.49 (t, CH_2), 38.56 and 39.18 (d, 2 x ring-CH), 39.72 (d, C-2'), 54.34 (d, C-5), 58.40 (d, C-4), 75.33 (d, C-3), 155.68 (s, C-2), 178.82 (s, C-1); *m/z* 364 (M^+, 1%), 346 (3), 252 (18), 223 (27) and 113 (100).

(4R,5S,2'R,3'R)-4-Cyclohexyl-1,5-dimethyl-3-(3'-hydroxy-2'-methyl-3'-phenylpropanoyl)imidazolin-2-one **(126d)**

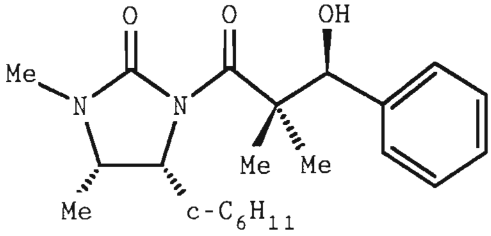


$C_{21}H_{30}N_2O_3$

MW = 358.23

The reaction between the boron enolate of **(124)** (1.00 g, 3.97 mmol) and benzaldehyde (0.40 ml, 3.97 mmol) according to General Procedure 2 yielded a residue which was chromatographed on silica gel with Et_2O/hexane (3:7) as the eluent to afford **(126d)** (1.07 g, 75%) as a colourless oil; (Found: M^+, 358.2255. $C_{21}H_{30}N_2O_3$ requires *M*, 358.2215); $[\alpha]_D$ -5.73° (*c* 1.00,$CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3500 (OH), 2930 (CH_2), 1730 (CO) and 1650 (CO); δ_H (200 MHz) 0.85-1.85 (11H, m, cyclo-C_6H_{11}), 1.22 (6H, 2 x d, *J* 7 Hz, 5-Me and 2'-Me), 2.66 (3H, s, NMe), 3.38 (1H, dq, *J* 7 Hz, H-5), 4.08 (1H, br s, OH, D_2O exch.), 4.22 (H, dd, *J* 7 and 3 Hz H-4), 4.23 (1H, dq, *J* 7 and 4 Hz, H-2'), 4.97 [1H, m, H-3'(D_2O exch., d, *J* 4 Hz)], 7.19-7.39 (5H, m, Ph); δ_C (50 MHz) 11.90 (q, 2'-Me), 12.75 (q, 5-Me), 25.98, 26.14 and 26.80 (t, 3 x CH_2), 27.49 (q, NMe), 27.49 and 32.46 (t, 2 x CH_2), 38.98 (d, ring-CH), 44.23 (d, C-2'), 54.14 (d, C-5), 58.70 (d, C-4), 73.84 (d, C-3'), 126.24, 126.95 and 127.87 (d, Ph), 141.92 (s, Ph), 155.55 (s, C-2), 177.16 (s, C-1'); *m/z* 358 (M^+, 4%), 340 (2), 252 (21), 223 (32) and 113 (100).

(4R,5S,3'R)-4-Cyclohexyl-1,5-dimethyl-3-(3'-hydroxy-2',2'-dimethyl-3'-phenylpropanoyl)imidazolidin-2-one **(135a)**

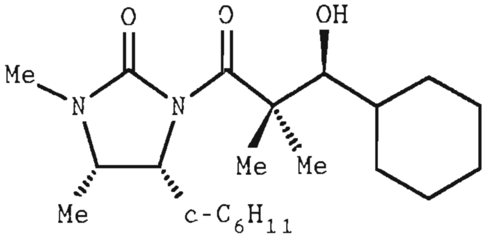


$C_{22}H_{32}N_2O_3$

MW = 372.24

The boron enolate of **(134)** (1.00 g, 3.76 mmol) was allowed to react with benzaldehyde (0.38 ml, 3.76 mmol) according to General Procedure 2 to afford a residue which was chromatographed on silica gel with Et_2O/hexane (3:7) as the eluent to yield **(135a)** as a colourless oil (1.16 g, 83%); (Found: *M*$^+$, 372.2426. $C_{22}H_{32}N_2O_3$ requires *M*, 372.2413); $[\alpha]_D$ +0.70° (*c* 5.79, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 3500 (OH), 2940 (CH_2), 1728 (CO) and 1672 (CO); δ_H (200 MHz) 1.00-1.80 (11H, m, cyclo-C_6H_{11}), 1.29 (3H, d, *J* 7 Hz, 5-Me), 1.32 and 1.35 (6H, 2 x s, 2 x 2'-Me), 2.75 (3H, s, NMe), 3.46 (1H, br s, OH), 3.67 (1H, dq, *J* 7 Hz, H-5), 4.49 (1H, dd, *J* 7 and 3 Hz, H-4), 5.46 (1H, br s, H-3'), 7.20-7.43 (5H, m, Ph); δ_C (50 MHz) 13.00 (q, 5-Me), 19.32 and 21.57 (q, 2 x 2'-Me), 26.20, 26.25, 26.90 and 27.68 (t, 4 x CH_2), 27.85 (q, NMe), 32,29 (t, CH_2), 39.18 (d, ring-CH), 50.79 (s, C-2'), 54.30 (d, C-5), 60.78 (d, C-4), 76.89 (d, C-3'), 127.22, 127.42 and 128.11 (d, Ph), 140.65 (s, Ph), 155.76 (s, C-2), 178.22 (s, C-1'); *m/z* 372 (M$^+$, 2%), 266 (3), 223 (13) and 113 (100).

(4R,5S,3'S)-4-Cyclohexyl-1,5-dimethyl-3-(3'-cyclohexyl-3' hydroxy-2',2'-dimethylpropanoyl)imidazolidin-2-one **(135b)**

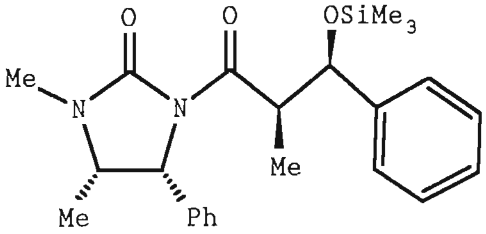


$C_{22}H_{38}N_2O_3$

MW = 378.29

The boron enolate of **(134)** (1.00 g, 3.76 mmol) was allowed to react with cyclohexanecarbaldehyde (0.46 ml, 3.76 mmol) according to General Procedure 2 to afford **(135b)** as white crystals (0.57 g, 40.0%) m.p. 141-142°C (from $CHCl_3$); (Found: C, 70.10; H, 10.29; N, 7.39. $C_{22}H_{38}N_2O_3$ requires C, 69.79; H, 10.12; N, 7.40%); $[\alpha]_D$ +0.75° (*c* 2.27, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 3520 (OH), 2960 (Me), 1732 (CO) and 1648 (CO); δ_H (200 MHz) 0.80-1.95 (22H, m, 2 x cyclo-C_6H_{11}), 1.31 (3H, d, *J* 7 Hz, 5-Me), 1.39 and 1.41 (6H, 2 x s, 2 x 2'-Me), 2.76 (3H, s, NMe), 3.29 (1H, br s, OH), 3.71 (1H, dq, *J* 7 Hz, H-5), 3.94 (1H, br s, H-3'), 4.48 (1H, dd, *J* 7 and 3 Hz, H-4); δ_C (50 MHz) 13.10 (q, 5-Me), 22.19 and 22.87 (q, 2 x 2'-Me), 26.20, 26.27, 26.37, 26.77 and 26.94 (t, 6 x CH_2), 27.77 (q, NMe), 27.84, 28.11, 32.06 and 32.93 (t, 4 x CH_2), 39.32 and 40.20 (d, 2 x ring-CH), 54.35 (d, C-5), 60.95 (d, C-4), 79.66 (d, C-3'), 156.02 (s, C-2), 178.46 (s, C-1); *m/z* 360 (M^+-18, 1%), 267 (5), 223 (24) and 113 (100).

(4R,5S,2'R,3'R)-1,5-Dimethyl-4-phenyl-3-[2'-methyl-3'-phenyl-3'-(trimethylsilyloxy)propanoyl]imidazolidin-2-one **(118)**



$C_{24}H_{32}N_2O_3Si$

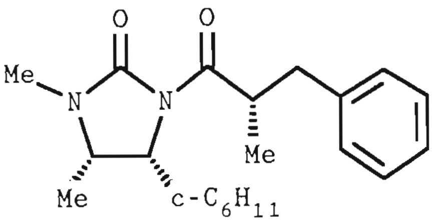
MW = 424.33

To a stirred solution of **(108a)** (0.434 g, 1.23 mmol) and TMSCl (0.31 ml, 2.00 equiv.) in dry CH_2Cl_2 (10 ml) was added Et_3N (0.34 ml, 2.00 equiv.) at 0°C. After 5 h, the mixture was concentrated and the resultant residue was partitioned between Et_2O and H_2O. The organic layer was dried ($MgSO_4$) and concentrated. Recrystallisation of the resultant residue afforded **(118)** as colourless crystals (0.44 g, 85%) m.p. 152-154°C (from $CHCl_3$);
(Found: C, 67.89; H, 7.59; N, 6.60. $C_{24}H_{32}N_2O_3Si$ requires C, 67.82; H,7.59; N, 6.59%); $[\alpha]_D$ -76.35° (*c* 2.03, $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2976 (Me), 1728 (CO), 1678 (CO) and 1232 (Si-C); δ_H (200 MHz) 0.02 (9H, s, $SiMe_3$), 0.67 (3H, d, *J* 7 Hz, 5-Me), 1.18 (3H, d, *J* 7 Hz, 2'-Me), 2.68 (3H, s, NMe), 3.34 (1H, dq, *J* 8 and 7 Hz, H-5), 4.39 (1H, dq, *J* 8 and 7 Hz, H-2'), 4.79 (1H, d, *J* 8 Hz, H-3'), 4.89 (1H, d, *J* 8 Hz, H-4), 7.04-7.43 (10H, m, 2 x Ph); δ_H (50 MHz) 0.01 (q, $SiMe_3$), 13.54 (q, 5-Me), 14.61 (q, 2'-Me), 27.95 (NMe), 46.61 (d, C-2'), 53.57 (d, C-5), 59.66 (d, C-4), 76.80 (d, C-3'), 127.09, 127.29, 127.89, 128.21 and 128.72 (d, 2 x Ph), 137.02 and 143.97 (s, C-2), 174.27 (s, C-1'); *m/z* 318 (M^+-106, 15%), 189 (6) and 73 (100).

GENERAL PROCEDURE 3. Diastereoselective Alkylations and Acylations of **(124)**.

To a stirred, cooled (0°C) solution of diisopropylamine (1.05 equiv.) in dry THF (10 ml) was added dropwise *n*-BuLi (1.00 equiv.). After 30 min. at 0°C the reaction mixture was cooled to -78°C and treated with **(124)** (1.00 equiv.). The reaction mixture was stirred for 30 min. then treated with the appropriate alkyl halide, acyl chloride or anhydride (1.00 equiv.) and kept at -78°C for a further 15 min., then allowed to warm to -20°C over 30 min. The reaction mixture was quenched with satd. aq. NH_4Cl and extracted with Et_2O. The combined extracts were dried ($MgSO_4$), concentrated and purified.

(4R,5S,2'S)-4-Cyclohexyl-1,5-dimethyl-3-(2'-methyl-3'-phenylpropanoyl)imidazolidin-2-one **(143a)**

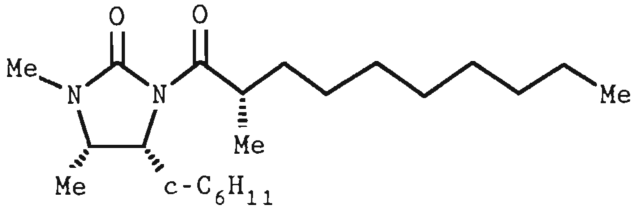


$C_{21}H_{30}N_2O_2$

MW = 342.23

The reaction between the lithium enolate of **(124)** (1.00 g, 3.97 mmol) and benzyl bromide (0.472 ml, 3.97 mmol) according to General Procedure 3 yielded **(143a)** as white crystals (1.15 g, 85%) m.p. 88°C (from Et_2O);
(Found: C, 73.97; H, 8.81; N, 8.29. $C_{21}H_{30}N_2O_2$ requires C, 73.63; H, 8.83; N, 8.18%); $[\alpha]_D$ +13.03° (*c* 1.45, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 2960 (Me), 1728 (CO), 1680 (CO) and 1495 (Ph); δ_H (200 MHz) 0.75-1.72 (1H, m, cyclo-C_6H_{11}), 1.10 (3H, d, *J* 7 Hz, 2'-Me), 1.30 (3H, d, *J* 7 Hz, 5-Me), 2.61 (1H, dd, *J* 13 and 8 Hz, H-3'), 2.78 (3H, s, NMe), 3.24 (1H, dd, *J* 13 and 7 Hz, H-3'), 3.65 (1H, dq, *J* 7 Hz, H-5), 4.31 (2H, m, H-2' and H-4), 7.12-7.39 (5H, m, Ph); δ_C (50 MHz) 12.96 (q, 5-Me), 16.45 (q, 2'-Me), 25.91, 25.98, 26.86 and 27.36 (t, 4 x CH_2), 27.57 (q, NMe), 32.25 (t, CH_2), 39.11 (d, C-2'), 39.33 (d, ring-CH), 40.57 (t, C-3'), 54.30 (d, C-5), 58.72 (d, C-4), 126.04, 128.14 and 129.28 (d, Ph), 139.88 (s, Ph), 156.19 (s, C-2), 176.45 (s, C-1'); *m/z* 342 (M^+, 2%), 195 (13), 113 (100) and 91 (45).

(4R,5S,2'S)-4-Cyclohexyl-1,5-dimethyl-3-(2'-methyldecanoyl)-imidazolidin-2-one **(143b)**

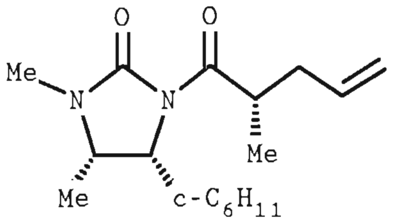


$C_{22}H_{40}N_2O_2$

MW = 364.31

The lithium enolate of **(124)** (1.00 g, 3.97 mmol) and octyl bromide (0.68 ml, 3.97 mmol) were allowed to react according to General Procedure 3. Purification via flash chromatography over silica gel with Et_2O/hexane (1:1) as eluent yielded **(143b)** as a yellow oil (1.20 g, 83%);
(Found: *M*$^+$, 364.3079. $C_{22}H_{40}N_2O_2$ requires *M*, 364.3089); $[\alpha]_D$ +0.35° (*c* 2.27, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 2940 (CH_2), 1736 (CO) and 1684 (CO); δ_H (200 MHz) 1.08 (3H, d, *J* 7 Hz, 2'-Me), 1.31 (3H, d, *J* 7 Hz, 5-Me), 0.82-1.95 (28H, m, cyclo-C_6H_{11} and H-3' to H-10'), 2.76 (3H, s, NMe), 3.67 (1H, dq, *J* 7 Hz, H-5), 3.89 (1H, m, H-2'), 4.38 (1H, dd, *J* 7 and 2.5 Hz, H-4); δ_C (50 MHz) 13.07 (q, 5-Me), 14.13 (q, C-10'), 16.60 (q, 2'-Me), 22.67, 26.13, 26.30, 27.00 and 27.22 (t, 5 x CH_2), 27.70 (q, NMe), 29.30, 29.67, 29.75, 29.84, 31.94, 32.52 and 34.83 (t, 7 x CH_2), 37.40 (d, C-2'), 39.29 (d, ring-CH), 54.40 (d, C-5), 58.82 (d, C-4), 156.28 (s, C-2), 177.50 (s, C-1'); *m/z* 364 (M$^+$, 1%), 223 (12), 195 (5) and 113 (100).

(4R,5S,2'S)-4-Cyclohexyl-1,5-dimethyl-3-(2'-methylpent-4'-enoyl)imidazolidin-2-one **(143c)**

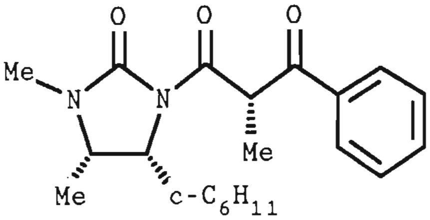


$C_{17}H_{28}N_2O_2$

MW = 292.22

The lithium enolate of **(124)** (1.00 g, 3.97 mmol) and allyl bromide (0.34 ml, 3.97 mmol) were allowed to react according to General Procedure 3. Purification via flash chromatography over silica gel with Et_2O/hexane (1:1) as eluent yielded **(143c)** as a colourless oil (1.04 g, 90%); (Found: C, 70.11; H, 9.78; N, 9.45. $C_{17}H_{28}N_2O_2$ requires C, 69.81; H, 9.66; N, 9.58%); $[\alpha]_D$ +5.66° (*c* 8.75, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 2960 (Me), 1736 (CO), 1684 (CO) and 920 (C=C); δ_H (200 MHz) 0.95-1.85 (11H, m, cyclo-C_6H_{11}), 1.09 (3H, d, *J* 7 Hz, 2'-Me), 1.32 (3H, d, *J* 7 Hz, 5-Me), 2.57 (1H, m, H-3'), 2.22 (1H, m, H-3'), 2.77 (3H, s, NMe), 3.68 (1H, dq, *J* 7 Hz, H-5), 3.99 (1H, m, H-2'), 4.37 (1H, dd, *J* 7 and 3 Hz, H-4), 5.08 (2H, m, H-5'), 5,87 (1H, m, H-4'); δ_C (50 MHz) 13.02 (q, 5-Me), 16.19 (q, 2'-Me), 26.00, 26.19, 26.96 and 27.60 (t, 4 x CH_2), 27.65 (q, NMe), 32.32 (t, CH_2), 37.15 (d, C-2'), 38.93 (t, C-3'), 39.27 (d, ring-CH), 54.40 (d, C-5), 58.94 (d, C-4), 116.65 (t, C-5'), 136.04 (d, C-4'), 156.25 (s, C-2), 176.67 (s, C-1'); *m/z* 292 (M^+, 1%), 195 (4) and 113 (100).

(4R,5S,2'S)-4-Cyclohexyl-1,5-dimethyl-3-(2'-methyl-3'-oxo-3'-phenylpropanoyl)imidazolidin-2-one **(143d)**

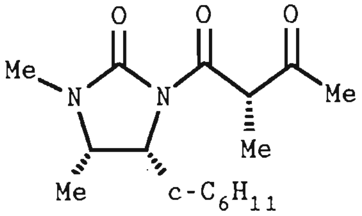


$C_{21}H_{28}N_2O_3$

MW = 356.21

The lithium enolate of **(124)** (1.00 g, 3.97 mmol) was allowed to react with benzoyl chloride (0.46 ml, 3.97 mmol) according to General Procedure 3 to yield **(143d)** as white crystals (1.23 g, 87%) m.p. 111°C (from $CHCl_3$/hexane); (Found: C, 71.11; H, 8.19; N, 7.58. $C_{21}H_{28}N_2O_3$ requires C, 70.74; H, 7.92; N, 7.86%) $[\alpha]_D$ +40.0° (*c* 1.35, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 2960 (Me), 1732 (CO), 1696 (CO) and 1676 (CO); δ_H (200 MHz) 1.00-1.90 (11H, m, cyclo-C_6H_{11}), 1.31 (3H, d, *J* 7 Hz, 5-Me), 1.41 (3H, d, *J* 7 Hz, 2'-Me), 2.72 (3H, s, NMe), 3.70 (1H, dq, *J* 7 Hz, H-5), 4.39 (1H, dd, *J* 7 and 2 Hz, H-4), 5.55 (1H, q, *J* 7 Hz, H-2'), 7.41-7.58 (3H, m, Ph), 8.00-8.07 (2H, m, Ph); δ_C (50 MHz) 12.84 (q, 5-Me), 13.68 (q, 2'-Me), 26.07, 26.12, 27.10, 27.27 and 32.16 (t, 5 x CH_2), 27.52 (q, NMe), 39.90 (d, ring-CH), 48.25 (d, C-2'), 54.58 (d, C-5), 59.23 (d, C-4), 128.64, 132.74 and 135.93 (d, Ph), 156.27 (s, C-2), 170.22 (s, C-1'), 197.91 (s, C-3'); *m/z* 356 (M$^+$, 4%), 251 (9), 223 (14), 195 (9) and 113 (100).

(4R,5S,2'S)-4-Cyclohexyl-1,5-dimethyl-3-(2'-methyl-3'-oxobutanoyl)imidazolidin-2-one **(143e)**

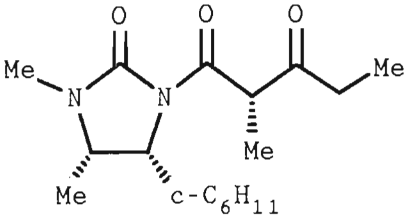


$C_{16}H_{26}N_2O_3$

MW = 294.19

The lithium enolate of **(124)** (1.00 g, 3.97 mmol) was allowed to react with acetyl chloride (0.28 ml, 3.97 mmol) according to General Procedure 3 to yield **(143e)** as colourless crystals (930 mg, 80%) m.p. 93°C (from $CHCl_3$/hexane);
(Found: C, 65.17; H, 9.24; N, 9.35. $C_{16}H_{26}N_2O_3$ requires C, 65.26; H, 8.91; N, 9.52%); $[\alpha]_D$ +54.0° (*c* 1.80, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 2940 (CH_2), 1728 (CO), 1716 (CO) and 1688 (CO); δ_H (200 MHz) 1.05-1.82 (11H, m, cyclo-C_6H_{11}), 1.34 (3H, d, *J* 6.5 Hz, 2'-Me), 1.35 (3H, d, *J* 7 Hz, 5-Me), 2.33 (3H, s, H-4'), 2.75 (3H, s, NMe), 3.72 (1H, dq, *J* 7 Hz, H-5), 4.36 (1H, dd, *J* 7 and 2 Hz, H-4), 4.56 (1H, q, *J* 6.5 Hz, H-2'); δ_C (50 MHz) 12.58 (q, 5-Me), 12.88 (q, 2'-Me), 26.15, 27.12 and 27.28 (t, 4 x CH_2), 27.45 (q, NMe), 28.37 (q, C-4'), 32.28 (t, CH_2), 39.86 (d, ring-CH), 53.04 (d, C-2'), 54.70 (d, C-5), 59.28 (d, C-4), 156.36 (s, C-2), 169.62 (s, C-1'), 205.75 (s, C-3'); *m/z* 294 (M^+, 0.8%), 252 (2), 223 (10) and 113 (100).

(4R,5S,2'S)-4-Cyclohexyl-1,5-dimethyl-3-(2'-methyl-3'-oxo-pentanoyl)imidazolidin-2-one **(143f)**

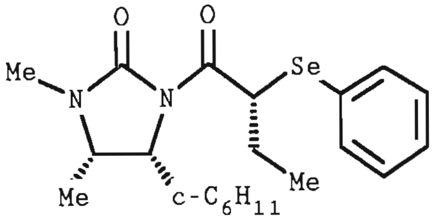


$C_{17}H_{28}N_2O_3$

MW = 308.21

The lithium enolate of **(124)** (0.50 g, 1.98 mmol) was allowed to react with propionic anhydride (0.26 ml, 1.98 mmol) according to General Procedure 3 to yield **(143f)** (518 mg, 85%) as white crystals m.p. 83°C (from $CHCl_3$/hexane); (Found: C, 66.66; H, 9.25; N, 9.13. $C_{17}H_{28}N_2O_3$ requires C, 66.67; H, 9.15; N, 9.15%); $[\alpha]_D$ +19.46° (*c* 2.23, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 2940 (CH_2), 1731 (CO), 1709 (CO) and 1690 (CO); δ_H (200 MHz) 1.10 (3H, t, *J* 7 Hz, H-5'), 1.33 (6H, 2 x d, *J* 7 Hz, 5-Me and 2'-Me), 1.00-1.80 (11H, m, cyclo-C_6H_{11}), 2.67 (2H, m, H-4'), 2.74 (3H, s, NMe), 3.70 (1H, dq, *J* 7 Hz, H-5), 4.35 (1H, dd, *J* 7 and 2.4 Hz, H-4), 4.58 (1H, q, *J* 7 Hz, H-2'); δ_C (50 MHz) 7.85 (q, C-5'), 12.93 (q, 5-Me), 12.99 (q, 2'-Me), 26.19, 27.11, 27.36, 32.34 and 33.96 (d, 5 x ring-CH_2 and C-4'), 27.52 (q, NMe), 39.78 (d, ring-CH), 52.37 (d, C-2'), 54.73 (d, C-5), 59.32 (d, C-4), 156.36 (s, C-2), 169.95 (s, C-1'), 208.18 (s, C-3'); *m/z* 308 (M^+, 0.7%) 223 (18), 195 (3) and 113 (100).

(4R,5S,2'R)-4-Cyclohexyl-1,5-dimethyl-3-[(2'-selenophenyl)-butanoyl]imidazolidin-2-one **(144)**



$C_{21}H_{30}N_2O_2Se$

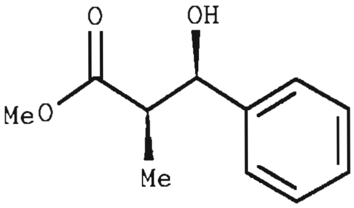
MW = 422.15

The lithium enolate of **(140)** (1.00 g, 3.76 mmol) and phenylselenenyl chloride (0.72 g, 3.76 mmol) were allowed to react according to General Procedure 3. Purification via flash chromatography over silica gel with Et_2O/hexane (3:7) as eluent yielded **(144)** as a yellow oil (1.05 g, 66%); (Found: M^+, 422.1480. $C_{21}H_{30}N_2O_2Se$ requires *M*, 422.1472); $[\alpha]_D$ -23.25° (*c* 7.44, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 2940 (CH_2), 1728 (CO) and 1680 (CO); δ_H (200 MHz) 0.92 (3H, t, *J* 7 Hz, H-4'), 1.05-1.95 (13H, m, cyclo-C_6H_{11} and H-3'), 1.33 (3H, d, *J* 7 Hz, 5-Me), 2.78 (3H, s, NMe), 3.69 (1H, dq, *J* 7 Hz, H-5), 4.39 (1H, dd, *J* 7 and 2.5 Hz, H-4), 5.11 (1H, t, *J* 7.5 Hz, H-2'), 7.22-7.32 (3H, m, Ph), 7.58-7.70 (2H, m, Ph); δ_C (50 MHz) 12.62 (q, C-4'), 13.11 (q, 5-Me), 24.19, 26.19, 27.08, 27.45 and 32.18 (t, 5 x ring-CH_2 and C-3'), 27.72 (q, NMe) 39.76 (d, ring-CH), 42.61 (d, C-2'), 54.53 (d, C-5), 58.93 (d, C-4), 128.03 and 128.75 (d, Ph), 135.73 (s, Ph), 156.22 (s, C-2), 172.54 (s, C-1'); *m/z* 422 (M^+, 2%), 265 (37) and 113 (100).

GENERAL PROCEDURE 4. Methanolysis of the initial aldol products.

Sodium metal (2.00 equiv.) was added to dry MeOH (4 ml) at 0°C and stirred for 30 min. at RT under N_2. The reaction mixture was cooled to 0°C then charged with a solution of the initial aldol (1.00 equiv.) in dry MeOH (2 ml), stirred at 0°C for 3 h and then quenched with satd. aq. NH_4Cl. After removal of MeOH, the aqueous phase was exhaustively extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated and purified by flash chromatography with Et_2O/hexane (1:1) as the eluent.

(2R,3R)-Methyl 3-Hydroxy-2-methyl-3-phenylpropanoate **(148a)**

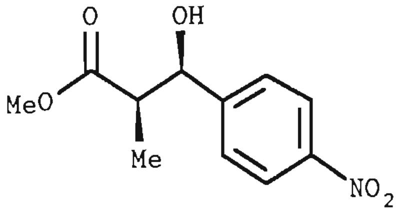


$C_{11}H_{14}O_3$

MW = 194.09

Methanolysis of **(108a)** or **(126d)** (0.50 g, 1.42 mmol) according to General Procedure 4 afforded **(148a)** as an oil (206 mg, 75%);
(Found: C, 68.32; H, 7.11. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.26%); $[\alpha]_D$ +23.3° (*c* 1.00, $CHCl_3$) (lit.,[67] $[\alpha]_D$ +23.2° (*c* 3.20, $CHCl_3$)); υ_{max} ($CHCl_3$)/cm^{-1} 3450 (OH) and 1734 (CO); δ_H (200 MHz) 1.24 (3H, d, *J* 7 Hz, 2-Me), 2.78 (1H, dq, *J* 4.3 and 7 Hz, H-2), 3.11 (1H, br s, OH, D_2O exch.), 3.64 (3H, s, OMe), 5.07 (1H, d, *J* 4.3 Hz, H-3), 7.24-7.35 (5H, m, Ph); δ_C (50 MHz) 10.78 (q, 2-Me), 46.45 (d, C-2), 51.87 (q, OMe), 73.66 (d, C-3), 125.95, 127.48 and 128.24 (d, Ph), 141.47 (s, Ph), 176.14 (s, C-1); *m/z* 194 (M^+, 49%), 107 (98) and 88 (100), 163 (8).

(2R,3R)-Methyl 3-Hydroxy-2-methyl-3-(4-nitrophenyl)propanoate **(148b)**



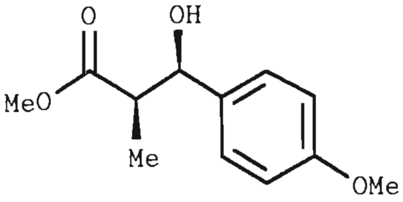
$C_{11}H_{13}NO_5$

MW = 239.08

Methanolysis of **(108b)** (0.50 g, 1.26 mmol) according to General Procedure 4 afforded **(148b)** as a yellow oil (240 mg, 80%);

(Found: C, 55.54; H, 5.48; N, 5.63. $C_{11}H_{13}NO_5$ requires C, 55.23; H, 5.48, N, 5.85%); $[\alpha]_D$ +14.30° (*c* 1.30, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 3500 (OH), 1730 (CO), 1605 (Ph) and 1350 (NO_2); δ_H (200 MHz) 1.09 (3H, d, *J* 7 Hz, 2-Me), 2.81 (1H, dq, *J* 7 and 4 Hz, H-2), 3.10-3.45 (1H, br s, OH, D_2O exch.), 3.72 (3H, s, OMe), 5.25 (1H, d, *J* 4 Hz, H-3), 7.51-8.22 (4H, m, Ar); δ_C (50 MHz) 10.34 (q, 2-Me), 45.94 (d, C-2), 52.22 (q, OMe), 72.59 (d, C-3), 123.50 and 126.90 (d, Ar), 147.24 and 148.92 (s, Ar), 175.87 (s, C-1); *m/z* 239 (M^+, 5%), 208 (5), 152 (33) and 88 (100).

(2R,3R)-Methyl 3-Hydroxy-2-methyl-3-(4-methoxyphenyl)propanoate **(148c)**

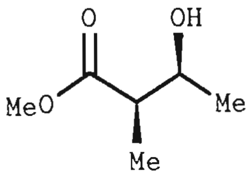


$C_{12}H_{16}O_4$

MW = 224.10

Methanolysis of **(108c)** (0.50 g, 1.30 mmol) according to General Procedure 4 afforded **(148c)** as a yellow oil (220 mg, 75%);
(Found: C, 63.99; H, 7.49. $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19%); $[\alpha]_D$ +16.90° (*c* 0.13, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 3500 (OH), 1732 (CO), 1612 and 1508 (Ph); δ_H (200 MHz) 1.14 (3H, d, *J* 7 Hz, 2-Me), 2.75 (1H, dq, *J* 7 and 5 Hz, H-2), 3.08 (1H, br s, OH, D_2O exch.), 3.63 (3H, s, 1-OMe), 3.78 (3H, s, Ar-OMe), 4.98 (1H, d, *J* 5 Hz, H-3), 6.83-6.88 and 7.21-7.27 (4H, m, Ar); δ_C (50 MHz) 11.22 (q, 2-Me), 46.70 (d, C-2), 51.82 (q, 1-OMe), 55.21 (q, Ar-OMe), 73.57 (d, C-3), 113.60 and 127.18 (d, Ar), 133.72 and 158.91 (s, Ar), 176.07 (s, C-1); *m/z* 224 (M^+, 11%), 193 (2), 137 (100).

(2R,3S)-Methyl 3-Hydroxy-2-methylbutanoate **(148d)**

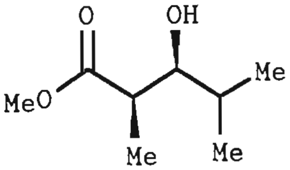


$C_6H_{12}O_3$

MW = 132.08

Methanolysis of **(126a)** (0.40 g, 1.35 mmol) according to General Procedure 4 afforded **(148d)** as a colourless oil (125 mg, 70%);
$[\alpha]_D$ -13.42° (*c* 0.514, MeOH) (lit.,[79] $[\alpha]_D$ -13.50° (*c* 0.867, MeOH)); υ_{max}(Neat)/cm^{-1} 3500 (OH), 2980 (Me) and 1760 (CO); δ_H (200 MHz) 1.18 (3H, d, *J* 6 Hz, H-4), 1.20 (3H, d, *J* 7 Hz, 2-Me), 2.53 (1H, dq, *J* 7 and 4 Hz, H-2), 2.73 (1H, br s, OH), 3.72 (3H, s, OMe), 4.08 (1H, dq, *J* 6 and 4 Hz, H-3);
δ_C (50 MHz) 11.13 (q, 2-Me), 19.88 (q, C-4), 45.62 (d, C-2), 51.96 (q, OMe), 68.22 (d, C-3), 176.40 (s, C-1); *m/z* 132 (M$^+$, 1%), 101 (15) and 88 (100).

(2R,3S)-Methyl 2,4-Dimethyl-3-hydroxypentanoate **(148e)**

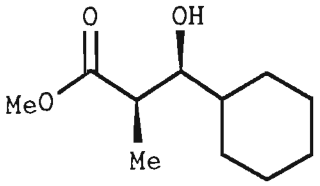


$C_8H_{16}O_3$

MW = 160.10

Methanolysis of **(126b)** (0.40 g, 1.23 mmol) according to General Procedure 4 yielded **(148e)** as a colourless oil (134 mg, 68%);
(Found: *M*$^+$, 160.1088. $C_8H_{16}O_3$ requires *M*, 160.1099);
$[\alpha]_D$ +7.63° (*c* 1.205, $CHCl_3$)(lit.,^{67} $[\alpha]_D$ +7.70°(*c* 5.40, $CHCl_3$)); υ_{max}(Neat)/cm^{-1} 3465 (OH), 2960 (Me) and 1760 (CO); δ_H (200 MHz) 0.88 (3H, d, *J* 7 Hz, 4-Me), 1.00 (3H, d, *J* 7 Hz, H-5), 1.18 (3H, d, *J* 7 Hz, 2-Me), 1.68 (1H, 2 x dq, *J* 8 and 7 Hz, H-4), 2.68 (1H, dq, *J* 7 and 4 Hz, H-2), 2.63-2.78 (1H, br s, OH), 3.57 (1H, dd, *J* 8 and 4 Hz, H-3), 3.71 (3H, s, OMe); δ_C (50 MHz) 10.29 (q, 2-Me), 18.63 (q, 4-Me), 19.18 (q, C-5), 30.77 (d, C-4), 41.99 (d, C-2), 51.99 (q, OMe), 77.07 (d, C-3), 176.98 (s, C-1); *m/z* 160 (M$^+$, 9%), 117 (62) and 88 (100).

(2R,3S)-Methyl 3-Cyclohexyl-3-hydroxy-2-methylpropanoate **(148f)**



$C_{11}H_{20}O_3$

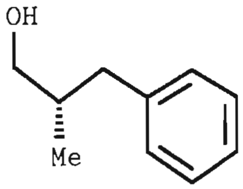
MW = 200.14

Methanolysis of **(126c)** (0.50 g, 1.37 mmol) according to General Procedure 4 yielded **(148f)** as a yellow oil (214 mg, 78%);
(Found: M^+, 200.1408. $C_{11}H_{20}O_3$ requires *M*, 200.1412); $[\alpha]_D$ -6.17° (*c* 1.103, CH_2Cl_2); υ_{max}(Neat)/cm^{-1} 3500 (OH), 2930 (CH_2) and 1760 (CO); δ_H (200 MHz) 0.85-1.85 (10H, m, cyclo-C_6H_{11}), 1.17 (3H, d, *J* 7 Hz, 2-Me), 2.00-2.15 (1H, m, ring-CH), 2.50-2.65 (1H br s, OH), 2.68 (1H, dq, *J* 7 and 3.3 Hz, H-2), 3.64 (1H, dd, *J* 8.5 and 3.3 Hz, H-3), 3.71 (3H, s, OMe); δ_C (50 MHz) 9.92 (q, 2-Me), 25.86, 26.07, 26.33, 28.99 and 29.13 (t, CH_2), 40.06 (d, ring-CH), 41.15 (d, C-2), 51.86 (q, OMe), 75.71 (d, C-3), 177.14 (s, C-1); *m/z* 200 (M^+, 1%), 182 (2), 117 (43) and 88 (100).

GENERAL PROCEDURE 5. Reductive cleavage of **(143a-b)**.

A solution of the appropriate alkylated product (1.00 equiv.) in dry THF (10 ml) was added to a stirred suspension of $LiAlH_4$ (2.50 equiv.) in THF (5 ml) at 0°C. After 3 h at 0°C the reaction mixture was quenched with satd. aq. NH_4Cl then extracted with Et_2O. The combined extracts were dried ($MgSO_4$), filtered, concentrated and purified.

(S)-2-Methyl-3-phenylpropan-1-ol **(149a)**

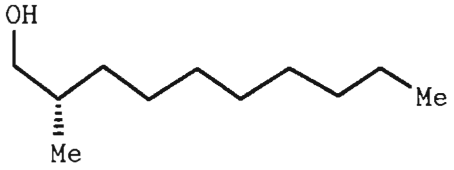


$C_{10}H_{14}O$

MW = 150.10

Applying General Procedure 5 to **(143a)** (0.40 g, 1.17 mmol) afforded the alcohol **(149a)** as a colourless oil after purification via flash chromatography over silica gel with Et_2O/hexane (3:7) as eluent (131 mg, 75%); (Found: M^+, 150.1044. $C_{10}H_{14}O$ requires *M*, 150.1045); $[\alpha]_D$ -11.02° (*c* 2.75, C_6H_6) (lit.,[156] $[\alpha]_D$ -11.08° (*c* 4.60, C_6H_6)); υ_{max}(Neat)/cm^{-1} 3380 (OH), 2940 (CH_2) and 1608 (Ph); δ_H (200 MHz) 0.86 (3H, d, *J* 7 Hz, 2-Me), 1.89 (1H, m, H-2), 2.34 (1H, dd, *J* 13 and 5 Hz, H-3), 2.74 (1H, dd, *J* 13 and 6 Hz, H-3), 2.98 (1H, br s, OH), 3.38 (1H, dd, *J* 11 and 6 Hz, H-1), 3.46 (1H, dd, *J* 11 and 6 Hz, H-1), 7.18-7.30 (5H, m, Ph); δ_C (50 MHz) 16.43 (q, 2-Me), 37.81 (d, C-2), 39.74 (t, C-3), 67.52 (t, C-1), 125.77, 128.17 and 129.11 (d, Ph), 140.66 (s, Ph); *m/z* 150 (M^+, 22%), 132 (16), 117 (57) and 91 (100).

(S)-2-Methyldecan-1-ol **(149b)**

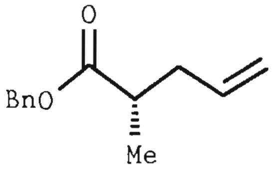


$C_{11}H_{24}O$

MW = 172.18

Applying General Procedure 5 to **(143b)** (0.50 g, 1.37 mmol) afforded the alcohol **(149b)** as a colourless oil after purification via flash chromatography over silica gel with Et_2O/hexane (1:1) as the eluent (170 mg, 72%);
(Found: M^+, 172.1824. $C_{11}H_{24}O$ requires M, 172.1827);
$[\alpha]_D$ -9.94° (*c* 3.00, CH_2Cl_2) (lit.,[68] $[\alpha]_D$ -10.00° (*c* 4.20, CH_2Cl_2)); υ_{max}(Neat)/cm^{-1} 3360 (OH) and 2940 (CH_2);
δ_C (200 MHz) 0.88 (3H, t, *J* 6.5 Hz, H-10), 0.91 (3H, d, *J* 7 Hz, 2-Me), 1.00-1.50 (14H, m, 7 x CH_2), 1.60 (1H, m, H-2), 2.28 (1H, br s, OH), 3.43 (1H, dd, *J* 11 and 6 Hz, H-1), 3.46 (1H, dd, *J* 11 and 6 Hz, H-1); δ_C (50 MHz) 14.18 (q, C-10), 16.67 (q, 2-Me), 22.79, 27.12, 29.48, 29.76, 30.11, 32.05 and 33.32 (t, 7 x CH_2), 35.88 (d, C-2), 68.53 (t, C-1);
m/z 154 (M^+-18, 4%), 69 (35), 57 (80) and 43 (100).

(S)-Benzyl 2-Methylpent-4-enoate **(150)**

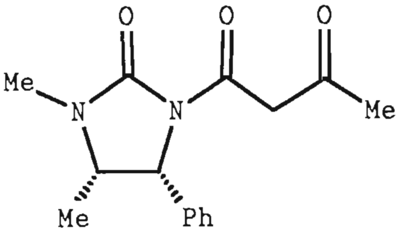


$C_{13}H_{16}O_2$

MW = 204.12

To a cold (-78°C) solution of benzyl alcohol (0.53 ml, 5.13 mmol) in dry THF (15 ml) was added *n*-BuLi (1.90 ml of a 1.80 M soln. in cyclohexane, 3.42 mmol). After 30 min. at this temperature, the reaction mixture was charged with a cooled (-78°C) solution of **(143c)** (0.50 g, 1.71 mmol) in THF (5 ml). The reaction mixture was stirred at -50°C for 3 h, then quenched with aq. pH 7 phosphate buffer. The resultant mixture was partitioned between H_2O and CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), concentrated and purified via flash chromatography over silica gel with Et_2O/ hexane (3:7) as the eluent to afford **(150)** as a colourless oil (314 mg, 90%);
(Found: M^+, 204:1161. $C_{13}H_{16}O_2$ requires M, 204.1150); $[\alpha]_D$ +0.94° (*c* 2.45, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 2980 (Me), 1740 (CO), 1648 (C=C) and 1452 (Ph); δ_H (200 MHz) 1.16 (3H, d, J 7 Hz, 2-Me), 2.17 (1H, m, H-3), 2.42 (1H, m, H-3), 2.56 (1H, tq, J 7 Hz, H-2), 5.02 (2H, m, H-5), 5.09 (2H, s, CH_2O), 5.70 (1H, m, H-4), 7.27-7.34 (5H, m, Ph); δ_C (50 MHz) 16.50 (q, 2-Me), 37.77 (t, C-3), 39.21 (d, C-2), 66.03 (t, CH_2O), 116.91 (t, C-5), 128.08, 128.48 and 135.33 (d, Ph), 136.18 (s, Ph), 175.67 (s, C-1); *m/z* 204 (M^+, 2%), 91 (100) and 41 (30).

(4R,5S)-1,5-Dimethyl-4-phenyl-3-(3'-oxo-butanoyl)imidazolidin-2-one **(155)**

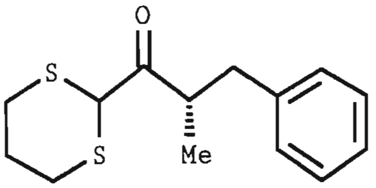


$C_{15}H_{18}N_2O_3$

MW = 274.13

To a stirred, cooled (0°C) solution of diisopropylamine (0.58 ml, 4.15 mmol) in dry THF (10 ml) was added *n*-BuLi dropwise (1.00 equiv.). After 30 min. the reaction mixture was cooled to -78°C and treated with **(154)** (1.00 g, 4.31 mmol). After 5 min. the reaction was quenched by the addition of satd. aq. NH_4Cl (10 ml) and extracted with Et_2O. The organic phase was dried ($MgSO_4$), filtered and concentrated to yield **(155)** as off-white crystals (0.47 g, 80%), m.p. 98°C (from $CHCl_3$); (Found: C, 65.53; H, 6.65; N, 10.11. $C_{15}H_{18}N_2O_3$ requires C, 65.68; H, 6.61; N, 10.21%); $[\alpha]_D$ -79.1° (*c* 0.11, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 2975 (Me), 1722 (CO), 1678 (CO) and 1420 (Ph); δ_H (200 MHz) 0.79 (3H, d, *J* 7 Hz, 5-Me), 2.27 (3H, s, H-4'), 2.79 (3H, s, NMe), 3.93 (1H, dq, *J* 7 and 9 Hz, H-5), 4.04 (2H, dd, *J* 4 Hz, H-2'), 5.33 (1H, d, *J* 9 Hz, H-4), 7.18-7.39 (5H, m, Ph); δ_C (50 MHz) 14.69 (q, 5-Me), 27.87 (q, C-4'), 29.93 (q, NMe), 51.62 (t, C-2'), 53.83 (d, C-5), 59.00 (d, C-4), 127.15, 128.19 and 128.52 (d, Ph), 136.10 (s, Ph), 155.76 (s, C-2), 165.80 (s, C-1'), 202.11 (s, C-3'); *m/z* 232 (M$^+$, 9%), 189 (50), 175 (33) and 132 (100).

(S)-1-(1,3-dithianyl)-3-methyl-4-phenylbutan-2-one **(162)**

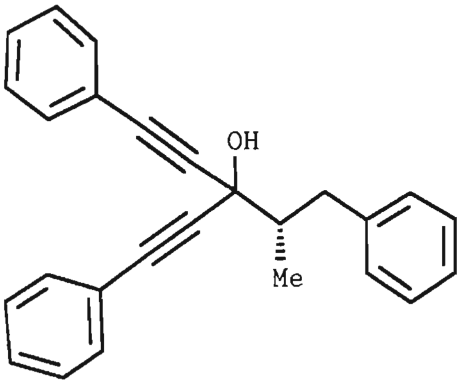


$C_{14}H_{18}OS_2$

MW = 266.08

To a cold (-30°C) stirred solution of 1,3-dithiane (0.30 g, 2.50 mmol) in dry THF (10 ml) was added *n*-BuLi (1.30 ml of a 1.80 M solution in cyclohexane, 2.34 mmol) dropwise under a nitrogen atmosphere. After 1.5 h the reaction mixture was added to a cooled (-30°C) solution of **(143a)** (0.80 g, 2.34 mmol) in THF (10 ml) via rapid cannulation. This reaction mixture was stirred for a further 30 min. at -30°C then allowed to warm to -5°C over 1 h. The reaction mixture was quenched with satd. aq. NH_4Cl (10 ml) and extracted with Et_2O (3 x 20 ml). The combined extracts were washed successively with aq. $Na_2S_2O_5$ (3%), aq. KOH (5%) and H_2O. The extracts were dried ($MgSO_4$) and concentrated. Flash chromatography over silica gel with Et_2O/hexane (1:9) as the eluent afforded **(162)** as a colourless oil (0.40 g, 64%);
(Found: M^+, 266.0792. $C_{14}H_{18}OS_2$ requires *M*, 266.0799); $[\alpha]_D$ +123.23° (*c* 3.28, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 2960 (CH_2), 1712 (CO) and 1456 (Ph); δ_H (200 MHz) 1.15 (3H, d, *J* 7 Hz, 3-Me), 1.95 (2H, m, CH_2), 2.45 (1H, m, H-3), 2.65 (1H, dd, *J* 13 and 7 Hz, H-4), 2.95 (1H, dd, *J* 13 and 7 Hz, H-4), 3.12 (4H, m, 2 x SCH_2), 3.92 (1H, s, H-1), 7.14-7.30 (5H, m, Ph); δ_C (50 MHz) 17.49 (q, 3-Me), 25.09 (t, CH_2), 25.74 and 25.86 (t, 2 x SCH_2), 40.01 (t, C-4), 46.05 and 46.45 (d, C-1 and C-3), 126.30, 128.33 and 128.92 (d, Ph), 139.18 (s, Ph), 204.89 (s, C-2); *m/z* 266 (M^+, 3%), 119 (100) and 91 (33).

(S)-1,5-Diphenyl-4-methyl-3-phenylethynyl-pent-1-yn-3-ol **(163a)**

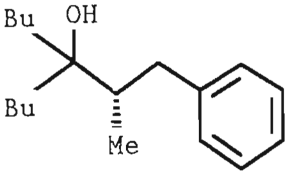


$C_{26}H_{22}O$

MW = 350.17

To a cold (-78°C) stirred solution of phenylacetylene (0.26 ml, 2.37 mmol) in dry THF (10 ml) was added *n*-BuLi (1.30 ml of a 1.80 M soln. in cyclohexane, 2.34 mmol) dropwise under a nitrogen atmosphere. After 30 min. the reaction mixture was added to a precooled (-78°C) solution of **(143a)** (0.80 g, 2.34 mmol) in THF (10 ml) via rapid cannulation. The reaction mixture was stirred for a further 30 min. at -78°C, then quenched with satd. aq. NH_4Cl (10 ml) and extracted with Et_2O (3 x 20 ml). The combined extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel with Et_2O/hexane (1:9) as the eluent afforded **(163a)** as a brown oil (344 mg, 42% based on **(143a)**); (Found: M^+, 350.1680. $C_{26}H_{22}O$ requires *M*, 350.1670); $[\alpha]_D$ -1.67° (*c* 8.32, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 3440 (OH), 3040 (Ph), 2240 (C≡C) and 1604 (Ph); δ_H (200 MHz) 1.18 (3H, d, *J* 6 Hz, 4-Me), 2.40 (1H, m, H-4), 2.57 (1H, dd, *J* 13 and 11 Hz, H-5), 3.16 (1H, s, OH), 3.53 (1H, dd, *J* 13 and 2 Hz, H-5), 7.12-7.52 (15H, m, 3 x Ph); δ_C (50 MHz) 14.25 (q, 4-Me), 38.10 (t, C-5), 47.27 (d, C-4), 68.32 (s, C-3), 84.48, 84.62, 88.55, and 88.65 (s, 2 x C≡C), 122.10 (s, Ph), 125.89, 128.24, 128.64, 129.28 and 131.81 (d, Ph), 140.71 (s, Ph); *m/z* (M^+-18, 1%), 129 (100) and 102 (74).

(S)-3-Butyl-2-methyl-1-phenylheptan-3-ol **(163b)**

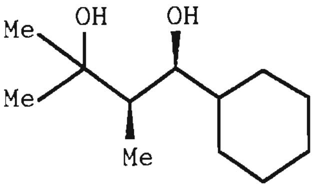


$C_{18}H_{30}O$

MW = 262.23

To a cold (-78°C) stirred solution of **(143a)** (0.40 g, 1.17 mmol) in dry THF (10 ml) was added dropwise under a nitrogen atmosphere *n*-BuLi (0.65 ml of a 1.80 M soln. in cyclohexane, 1.17 mmol). After 30 min. at -78°C the reaction was quenched with satd. aq. NH_4Cl (5 ml), extracted with Et_2O (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel with Et_2O/hexane (3:7) as the eluent afforded **(163b)** as a colourless oil (122 mg, 40% based on **(143a)**);
(Found: C, 82.45; H, 11.27. $C_{18}H_{30}O$ requires C, 82.37; H, 11.53%); $[\alpha]_D$ -8.13° (*c* 0.123, $CHCl_3$); υ_{max}(Neat)/cm^{-1} 3382 (OH), 2940 (CH_2) and 1498 (Ph); δ_H (200 MHz) 0.77 (3H, *J* 7 Hz, 2-Me), 0.80-1.70 (19H, m, 6 x CH_2, 2 x Me and OH), 1.86 (1H, m, H-2), 2.18 (1H, dd, *J* 13 and 11 Hz, H-1), 3.01 (1H, dd, *J* 13 and 2.6 Hz, H-1), 7.12-7.32 (5H, m, Ph); δ_C (50 MHz) 13.20 (q, 2-Me), 14.19 (q, C-4′ and C-7), 23.48, 23.52, 25.38, 25.52, 36.07, 36.28 and 37.19 (t, 7 x CH_2), 42.37 (d, C-2), 76.05 (s, C-3), 125.63, 128.19 and 129.17 (d, Ph), 142.15 (s, Ph); *m/z* 204 (M^+-57, 17%), 187 (4) and 91 (100).

(3R,1S)-1-Cyclohexyl-2,3-dimethyl-butan-1,3-diol **(164)**



$C_{12}H_{24}O_2$

MW = 200.18

To a stirred, cold (-78°C) soln. of **(126c)** (0.50 g, 1.37 mmol) in dry THF (10 ml) was added MeLi (5% soln. in Et_2O, 2.00 equiv.) dropwise under a nitrogen atmosphere at -78°C. The reaction was quenched with satd. aq. NH_4Cl (5 ml) then extracted with Et_2O (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel with Et_2O/hexane (1:1) as the eluent afforded **(164)** as cream coloured crystals (82 mg, 30% based on **(126c)**) m.p. 80-81°C (from hexane);
(Found: C, 72.25; H, 12.40. $C_{12}H_{24}O_2$ requires C, 71.94; H, 12.08%); $[\alpha]_D$ -3.58° (*c* 4.13, $CHCl_3$); υ_{max}(KBr)/cm^{-1} 3360 (OH), 2940 (CH_2) and 1452 (C-Me); δ_H (200 MHz) 0.95 (3H, d, *J* 7 Hz, 2-Me), 0.65-1.85 (12H, m, cyclo-C_6H_{11} and H-2), 1.21 (3H, s, H-4), 1.31 (3H, s, 3-Me), 2.10 (1H, br d, 1-OH), 3.70 (1H, m, H-1), 3.94 (1H, br s, 3-OH); δ_C (50 MHz) 6.64 (q, 2-Me), 25.87, 26.02, 26.45, 28.73 and 30.13 (t, 5 x CH_2), 28.91 (q, C-4), 29.14 (q, 3-Me), 40.86 (d, ring-CH), 41.27 (d, C-2), 73.75 (s, C-3), 76.58 (d, C-1); *m/z* 184 (M^+-16, 4%) and 112 (100).

4. REFERENCES

1. R.B. Woodward, F. Sondheimer, and D. Taub, *J. Am. Chem. Soc.*, 1951, **73**, 4057.

2. L.H. Sarrett, G.E. Arth, R.M. Lukes, R.E. Beyler, G.I. Poos, W.F. Johns, and J.M. Constantin, *J. Am. Chem. So* 1952, **74**, 4974.

3. H. Muxfeldt, G. Hardtmann, F. Kathawala, E. Vedejs, and J.B. Mooberry, *J. Am. Chem. Soc.*, 1968, **90**, 6534.

4.(a) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am Chem. Soc.*, 1979, **101**, 259.

(b) T. Fukuyama, C.-L.J. Wang, and Y. Kishi, *ibid.*, 1979, **1** 260.

(c) T. Fukuyama, K. Akasaka, D.S. Karanewsky, C.-L.J. Wang, G. Schmid, and Y, Kishi, *ibid.*, 1979, **101**, 262.

5.(a) R.B. Woodward *et al.*, *J. Am. Chem. Soc.*, 1981, **103**, 321

(b) R.B. Woodward *et al.*, *ibid.*, 1981, **103**, 3213.

(c) R.B. Woodward *et al.*, *ibid.*, 1981, **103**, 3215.

6.(a) D. Vazquez, *Antibiotics*, D. Gottlieb and P.D. Shaw (Eds Springer-Verlag, New York, 1967, **Vol.1**, pp. 387-403.

(b) C. Cocito and G. Chinali, *J. Antimicrob. Chemother.*, 19 **16** (Suppl. A), 35.

7. D.A. Evans, R.L. Dow, T.L. Shih, J.M. Takacs, and R. Zahler, *J. Am. Chem. Soc.*, 1990, **112**, 5290.

8. R.W. Hoffman, *Angew. Chem. Int. Ed. Engl.*, 1987, **26**, 48

9. D. Enders, *Chem. Tech.*, August 1981, 504.

10. J.M. Brown, G.W.J. Fleet, S.G. Davies, and A.J. Pratt, *Chem. Brit.*, 1989, 259.

11. S.E. Drewes, N.D. Emslie, J.S. Field, A.A. Khan, and N. Ramesar, *Tetrahedron Asymm.*, 1992, **3**, 255.

12. S. Hanessian, *The Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983.

13. S. Hanessian, N.G. Cooke, B. De Hoff, and Y. Sakito, *J. Am. Chem. Soc.*, 1990, **112**, 5276.

14. G.W.J. Fleet, N.G. Ramsden, and D.R. Witty, *Tetrahedro* 1989, **45**, *327.*
15. G.M. Whitesides and C-H. Wong, *Angew. Chem. Int. Ed. E* 1985, **24**, 617.
16. S.M. Roberts, *Chem. Ind.*, 1988, 384.
17. U. Ader and M.P. Schneider, *Tetrahedron Asymm.*, 1992, 205.
18. J.D. Morrison and H.S. Mosher, *Asymmetric Organic Reactions*, Prentice-Hall Englewood-Cliffs N.J., 1972.
19. E.L. Eliel, *Tetrahedron*, 1974, **30**, 1503.
20. K.R. Hanson, *J. Am. Chem. Soc.*, 1966, **88**, 2731.
21. R.S. Cahn, C.K. Ingold and, V. Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, **5**, 385.
22. S. Masamune, S.A. Ali, D.L. Snitman, and D.S. Garvey, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 557.
23. C.H. Heatcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung J.E. Sohn, and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066
24. Y. Izumi and A Tai, *Stereodifferentiating Reactions*, Academic Press, N.Y., 1977.
25. E.J. Corey, *Pure Appl. Chem.*, 1967, **14**, 19.
26. S. Warren, *Designing Organic Synthesis*; John Wiley and Sons: New York, 1977.
27. E.J. Corey and X-M. Cheng, *The Logic of Chemical Synthesis*; J. Wiley & Sons; New York, N.Y. 1989.
28. A. McKenzie, *J. Chem. Soc.*, 1906, 365.
29. V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 308.
30. V. Prelog, *Bull. Soc. Chim. Fr.*, 1956, 987.
31. R.F. Farmer and J. Hamer, *J. Org. Chem.*, 1966, **31**, 241
32. E.J. Corey and H.E. Ensley, *J. Am. Chem. Soc.*, 1975, **9** 6908.
33. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 87
34. G. Helmchen and R. Schmierer, *Angew. Chem. Int. Ed. En* 1981, **20**, 205.
35. W. Oppolzer, M Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt, and F. Moffat, *Helv. Chim. Acta.*, 1981, **64**, 2802.

36. W. Oppolzer, R. Pitteloud, G. Bernardinelli, and K. Baettig, *Tetrahedron Lett.*, 1983, **24**, 4975.

37. W. Oppolzer, C. Chapuis, and M. Kelly, *Helv. Chim. Act* 1983, **66**, 2358.

38. W. Oppolzer, C. Chapuis, and G. Bernardinelli, *Tetrahe Lett.*, 1984, **25**, 5885.

39. T. Poll, G. Helmchen, and B. Bauer, *Tetrahedron Lett.*, 1984, **25**, 2191.

40. T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, *Tetrahedron Lett.*, 1985, **26**, 3095.

41. J.K. Whitesell, A. Bhattacharya, D.A. Aguilar, and K. Henke, *J. Chem. Soc., Chem. Commun.*, 1982, 989.

42. W. Oppolzer, P. Dudfield, T. Stevenson, and T. Godel, *Helv. Chim. Acta*, 1985, **68**, 212.

43. S. Senda and K. Mori, *Agric. Biol. Chem.*, 1983, **47**, 79

44. D.J. Hart, C.-S. Lee, W.H. Pirkle, M.H. Hyon, and A. Tsipouras, *J. Am. Chem. Soc.*, 1986, **108**, 6054.

45. W. Oppolzer and P. Dudfield, *Helv. Chim. Acta*, 1985, **6** 216.

46. W. Oppolzer and P. Dudfield, *Tetrahedron Lett.*, 1985, 5037.

47. A.B. Charette, B.Côté, and J-F. Marcoux, *J. Am. Chem. Soc.*, 1991, **113**, 8166.

48. S. Takano, A. Kurotaki, Y. Sekigushi, S. Satoh, M. Hir and K. Ogasawara, *Synthesis*, 1986, 811.

49. K. Yamamoto, H. Ando, and H. Chikamatsu, *J. Chem. Soc. Chem. Commun.*, 1987, 334.

50. G. Castaldi, S. Cavicchioli, C. Giordano, and F. Ugger *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 259.

51. C. Giordano, G. Castaldi, S. Cavicchioli, and M. Villa, *Tetrahedron*, 1989, **45**, 4243.

52. A.I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc* 1974, **96**, 268.

53. K.A. Lutomski and A.I. Meyers, *Asymmetric Synthesis*, J.D. Morrison (ed), **Vol.3**, Part B. Academic Press, New York (1984), p. 213.

54. A.I. Meyers, G. Knaus, and M.E. Ford, *J. Am. Chem. Soc*
1976, **98**, 567.

55.(a) A.I. Meyers and E.D. Mihelich, *J. Org. Chem.*, 1975, **40**
1186.

(b) A.I. Meyers, Y. Yamamoto, E.D. Mihelich, and R.A. Bell
J. Org. Chem., 1980, **45**, 2792.

56. A.I. Meyers and Y. Yamamoto, *Tetrahedron*, 1984, **40**, 23

57. A.I. Meyers and B.A Barner, *J. Org. Chem.*, 1986, **51**, 1

58. R.E. Gawley, G.C. Hart, and L.J. Bartolotti, *J. Org. Chem.*, 1989, **54**, 175.

59. D. Enders, *Asymmetric Synthesis*, J.D. Morrison (ed),
Vol.3, Part B. Academic Press, New York (1984), p. 275

60. D. Enders and B. Bockstiegel, *Synthesis*, 1989, 493.

61. D. Enders and V. Bhushan, *Tetrahedron Lett.*, 1988, **29**,
2437.

62. D. Enders and B.B. Lohray, *Angew. Chem. Int. Ed. Engl.*
1987, **26**, 351.

63.(a) D. Enders and B.E.M. Rendenbach, *Tetrahedron*, 1986, **42**
2235.

(b) D. Enders and B.E.M. Rendenbach, *Chem. Ber.*, 1987, **120**
1223.

64. P. Kocienski, M. Stocks, D. Donald, M. Cooper, and
A. Manners, *Tetrahedron Lett.*, 1988, **29**, 4481.

65. D. Enders and B.B. Lohray, *Angew. Chem. Int. Ed. Engl.*
1988, **27**, 581.

66. D. Enders and H. Dyker, *Liebigs Ann. Chem.*, 1990, 1107

67. D.A. Evans, J. Bartroli, and T.L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.

68. D.A. Evans, M.D. Ennis, and D.J. Mathre, *J. Am. Chem.*, *Soc.*, 1982, **104**, 1737.

69. D.A. Evans, M.D. Ennis, T. Le, G. Mandel and N. Mandel
J. Am. Chem. Soc., 1984, **106**, 1154.

70. D.A. Evans, K.T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, 1984, **106**, 4261.

71. T-H. Yan, V-V. Chu, T-C. Lin, W-H. Tseng, and T-W. Che
Tetrahedron Lett., 1991, **32**, 5563.

72. Y. Nagao, Y. Hagiwara, T. Kumagi, M. Ochiai, T. Inoue, K. Hashimoto, and E. Fujita, *J. Org. Chem.*, 1986, **51**, 2393.

73. D.F. Faber, E.H. Petty, and K. Raman, *J. Am. Chem. Soc.* 1985, **107**, 196.

74. A.I. Meyers, R.F. Spohn, and R.J. Linderman, *J. Org. Chem.*, 1985, **50**, 3633.

75. D.A. Evans and A.E. Weber, *J. Am. Chem. Soc.*, 1987, **109** 7151.

76. A.G. Schultz, M. Macielag, P. Sundararaman, A.G. Tavera and M. Welch, *J. Am. Chem. Soc.*, 1988, **110**, 7828.

77. P.J. McCloskey and A.G. Schultz, *J. Org. Chem.*, 1988, **5** 1381.

78. (a) W. Oppolzer, R. Moretti, and S. Thomi, *Tetrahedron Lett* 1989, **30**, 5603.
    (b) W. Oppolzer, R. Moretti, and S. Thomi, *Tetrahedron Lett* 1989, **30**, 6009.
    (c) W. Oppolzer, I. Rodriguez, C. Starkemann and E. Walther *Tetrahedron Lett.*, 1990, **31**, 5019.

79. W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, 1990, **112**, 2767.

80. W. Oppolzer and J.-P. Barras, *Helv. Chim. Acta*, 1987, **7** 1666.

81. W. Oppolzer and G. Poli, *Tetrahedron Lett.*, 1986, **27**, 4717.

82. W. Oppolzer, G. Poli, G. Bernardinelli, A.J. Kingma, an C. Starkemann, *Helv. Chim. Acta*, 1987, **70**, 2201.

83. W. Oppolzer and P. Schneider, *Helv. Chim. Acta*, 1986, **6** 1817.

84. G. Bashiardes and S.G. Davies, *Tetrahedron Lett.*, 1987, **28**, 5563.

85. G. Bashiardes and S.G. Davies, *Tetrahedron Lett.*, 1988, **29**, 6509.

86. S.G. Davies and G.L. Gravatt, *J. Chem. Soc., Chem. Commun.*, 1988, 780.

87. S.G. Davies, R. Polywka, and P. Warner, *Tetrahedron*, 19

46, 4847.

88.(a) I. Ojima, N. Clos, and C. Bastos, *Tetrahedron*, 1989, **4**
6901.

(b) H-U. Blaser, *Tetrahedron Asymm.*, 1991, **2**, 843.

89. K.B. Sharpless, W. Amberg, Y.L. Bennani, G.A. Crispino
J. Hartung, K-S. Jeong, H-L. Kwong, K. Morikawa,
Z-M. Wang, D. Xu, and X-L. Zhang, *J. Org. Chem.*, 1992,
57, 2768.

90. E.R. Parmee, O. Tempkin, and S. Masamune, *J. Am. Chem.*
Soc., 1991, **113**, 9365.

91. *The Merck Index*, Eleventh Edition, 1989, Susan Budavar
(ed), Merck & Co., Inc., N.J., U.S.A.

92. R. Noyori and M Kitamura, *Angew. Chem. Int. Ed. Engl.*,
1991, **30**, 49.

93. H.C. Brown, W.S. Park, B.T. Cho, and P.V. Ramachandran
J. Org. Chem., 1987, **52**, 5406.

94. E.J. Corey, R. Naef, aand F.J. Hannon, *J. Am. Chem. Sc*
1986, **108**, 7114.

95. S.C. Benson and J.K. Snyder, *Tetrahedron Lett.*, 1991,
5885.

96. W.J. Close, *J. Org. Chem.*, 1950, **15**, 1131.

97. H. Roder, G. Helmchen, E-M. Peters, K. Peters, and H-G
Schnering, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 898.

98. G. Cardillo, A. D'Amico, M. Orena, and S. Sandri, *J. C*
Chem., 1988, **53**, 2354.

99. G. Cardillo, M Orena, M. Romero, and S. Sandri,
Tetrahedron, 1989, **45**, 1501.

100. M. Orena, G. Porzi, and S. Sandri, *Tetrahedron Lett.*,
1992, **33**, 3797.

101. E. Stephan, G. Pourcelot, and P. Cresson, *Chem. Ind.*,
1988, 562.

102. O. Melnyk, E. Stephan, G. Pourcelot, and P. Cresson,
Tetrahedron, 1992, **48**, 841.

103. *Advanced Organic Chemistry*, Jerry March, Third Editior
Wiley-Interscience, 1985.

104.(a) B. Capon, *Quart. Rev. Chem. Soc.*, 1964, **18**, 45.

(b) M.L. Bender, Y-L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, 1958, **80**, 5380.

105. P.L. Southwick and W.L. Walsh, *J. Am. Chem. Soc.*, 1955 **77**, 405.

106. K. Suzuki, K. Okano, K. Nakai, Y. Terao, and M. Sekiya *Synthesis*, 1983, 723.

107. I. Okada, K. Tchimura, and R. Sudo, *Bull. Chem. Soc., Jpn.*, 1970, **43**, 1185.

108. T. Taguchi and M. Kojima, *Chem. Pharm. Bull.* (Tokyo), 1959, **7**, 103.

109. Y. Hamada, K. Hayashi, and T. Shioiri, *Tetrahedron Let* 1991, **32**, 931.

110. F. Kazmierczak and P. Helquist, *J. Org. Chem.*, 1989, **5** 3988.

111. C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrun J.E. Sohn, and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066

112. J.E. Dubois and P. Fellman, *Tetrahedron Lett.*, 1975, 1

113. D.A. Evans, J.V. Nelson, E. Vogel and T.R. Taber, *J. A Chem. Soc.*, 1981, **103**, 3099.

114. J. Mulzer, J. Segner, and G. Brüntrup, *Tetrahedron Let* 1977, 4651.

115. H.E. Zimmerman and M.D. Traxler, *J. Am. Chem. Soc.*, 19 **79**, 1920.

116. D.A. Evans and L.R. McGee, *Tetrahedron Lett.*, 1980, 39

117. D.A. Evans and J.M. Takacs, *Tetrahedron Lett.*, 1980, 4

118. F.J. Johnson, *Chem. Rev.*, 1968, **68**, 375.

119. Y. Tamaru, T. Harada, S. Nishi, M. Mizutani, T. Hioki, Z. Yoshida, *J. Am. Chem. Soc.*, 1980, **102**, 7806.

120. (a) W.A. Kleschick, C.T. Buse and C.H. Heathcock, *J. Am. C Soc.*, 1977, **99**, 247.

(b) J.T. Welch and S. Eswarakrishnan, *J. Org. Chem.*, 1985, 5403.

121. F. Babudri, L. di Nunno and S. Florio, *Tetrahedron Let* 1983, **24**, 3883.

122. D.A. Evans, J.V. Nelson, and T.R. Taber, *Topics in Stereochem.*, 1982, **13**, 1.

123. C.A. Hunter and J.K.M. Sanders, *J. Am. Chem. Soc.*, 199 **112**, 5525.

124. W.H. Pearson and M.C. Cheng, *J. Org. Chem.*, 1986, **51**, 3746.

125. Ref. 122: page 18.

126. J.E. Dubois and P. Fellmann, *Tetrahedron*, 1978, **34**, 13

127. D.A. Evans, E. Vogel, and J.V. Nelson, *J. Am. Chem. So* 1979, **101**, 6120.

128. Ref. 122: page 38.

129. D.A. Evans, J.M. Takacs, L.R. McGee, M.D. Ennis, D.J. Mathre, and J. Bartroli, *Pure Appl. Chem.*, 1981, **53**, 1109.

130. M. Hirama, D.S. Garvey, L.D-L. Lu, and S. Masamune, *Tetrahedron Lett.*, 1979, 3937.

131. M. Hirama and S. Masamune, *Tetrahedron Lett.*, 1979, 22

132. D.E. Van Horn and S. Masamune, *Tetrahedron Lett.*, 1979 2229.

133. S. Masamune, S. Mori, D.E. Van Horn, and D.W. Brooks, *Tetrahedron Lett.*, 1979, 1665.

134. N.A. Van Draanen, S. Arseniyadis, M.T. Crimmins, and C.H. Heathcock, *J. Org. Chem.*, 1991, **56**, 2499.

135. T. Inoue and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1980 **53**, 174.

136. E.A. Noe and M. Raban, *J. Am. Chem. Soc.*, 1975, **97**, 58

137. C.H. Heathcock, *Aldrichimica Acta*, 1990, **23**, 99.

138. D. Parker, *Chem. Rev.*, 1991, **91**, 1441.

139. V.W. Goodlett, *Anal. Chem.*, 1965, **37**, 431.

140. Z. Savnek and M. Budesinsky, *Collect. Czech. Chem. Commun.*, 1979, **44**, 558; *idem, ibid.*, 1980, **50**, 2784.

141. G.H.P. Roos and M.C. Watson, *S. Afr. J. Chem.*, 1991, **4** 95.

142. C.H. Heathcock, M.C. Pirrung, and J.E. Sohn, *J. Org. Chem.*, 1979, **44**, 4294.

143. G.H.P. Roos, T. Manickum, and D.G.S. Malissar, *J. Chin Chem. Soc.*, 1992, **39**, 105.

144. S. Masamune, M. Hirama, S. Mori, S.A. Ali, and

D.S. Garvey, *J. Am. Chem. Soc.*, 1981, **103**, 1568.

145. J. Blum, I. Amer, A. Zoran, and Y. Sasson, *Tetrahedron Lett.*, 1983, **24**, 4139.

146. M. Nishiki, H. Miyataka, Y. Niino, N. Mitsuo, and T. Satoh, *Tetrahedron Lett.*, 1982, **23**, 193.

147. C.H. Heathcock, M.C. Pirrung, S.D. Young, J.P. Hagen, E.T. Jarvi, U. Badertscher, H-P. Märki, and S.H. Montgomery, *J. Am. Chem. Soc.*, 1984, **106**, 8161.

148. A.S. Kende, K. Kawamura, and M.J. Orwat, *Tetrahedron Lett.*, 1989, **30**, 5821.

149. E.J. Corey and R.A. Sneen, *J. Am. Chem. Soc.*, 1956, **78** 6269.

150. L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Int. Engl.*, 1965, **4**, 181.

151. K.N. Houk and M.N. Paddon-Row, *J. Am. Chem. Soc.*, 1986 **108**, 2659.

152. H.B. Burgi, J.D. Dunitz, J.M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563.

153. A. Fadel, *Synlett*, 1992, 48.

154. D.A. Evans, *Asymmetric Synthesis*, J.D. Morrison (ed), Academic Press, U.S.A., 1984, page 88.

155. D.A. Evans, K.T. Chapman, and J. Bisaha, *Tetrahedron Lett.*, 1984, **25**, 4071.

156. S. Terashima and S.-I. Yamada, *Chem. Pharm. Bull.*, 196 **16**, 1953.

157. D.A. Evans, S.W. Kaldor, T.K. Jones, J. Clardy, and T.J. Stout, *J. Am. Chem. Soc.*, 1990, **112**, 7001.

158. D.M. Jewett, F. Matsumura, and H.C. Coppel, *Science (Washington, D.C.)*, 1976, **51**, 192.

159. D.A. Evans, R.P. Polniaszek, K.M. De Vries, D.E. Guinn and D.J. Mathre, *J. Am. Chem. Soc.*, 1991, **113**, 7613.

160. S. Nahm and S.M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815.

161. Parts of this research have been published:

(a) S.E. Drewes, D.G.S. Malissar, and G.H.P. Roos, *Chem. B* 1991, **124**, 2913.

(b) S.E. Drewes, D.G.S. Malissar, and G.H.P. Roos, *Tetrahe* *Asymm.*, 1992, **3**, 515.

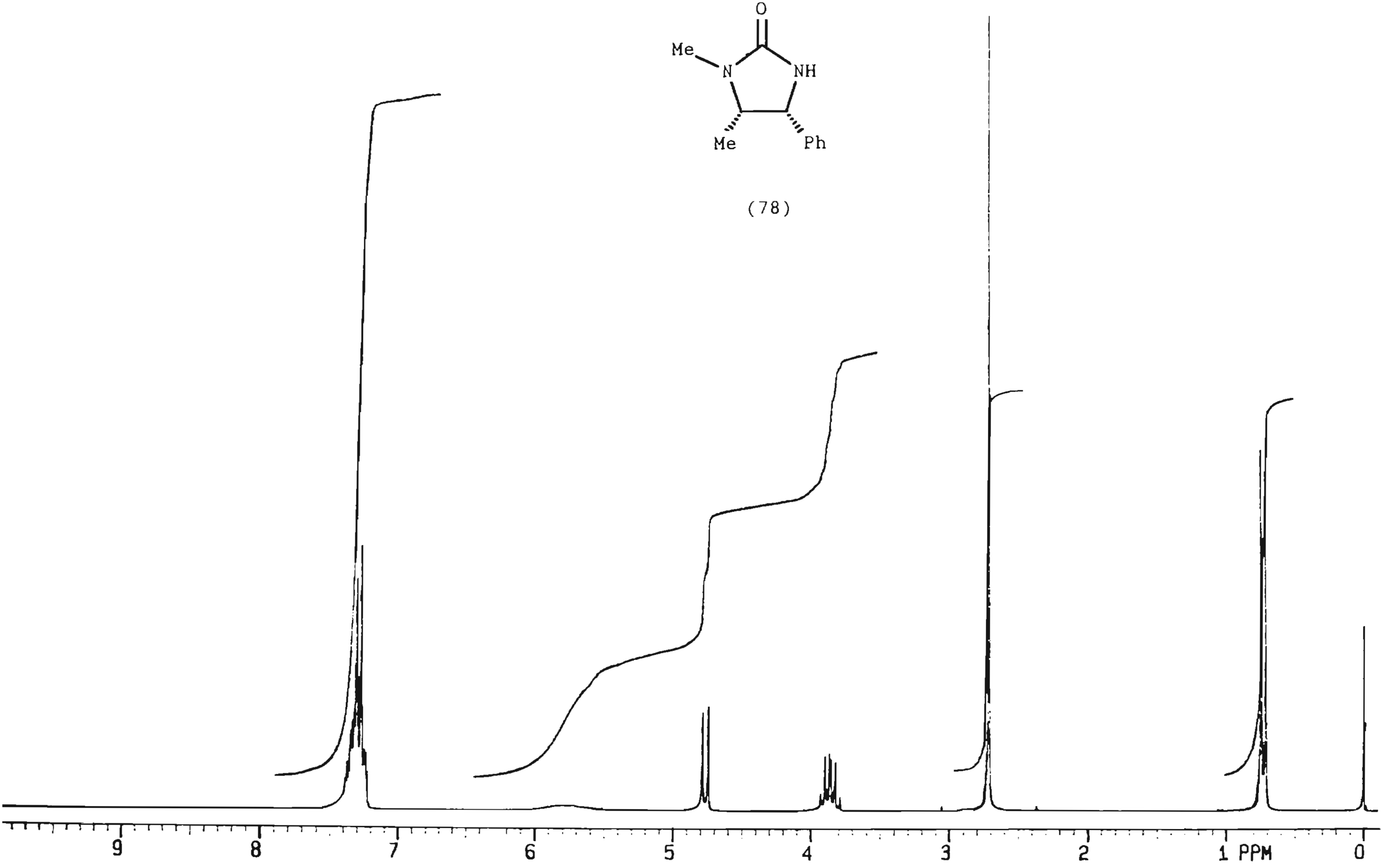
162. M.A. Walker and C.H. Heathcock, *J. Org. Chem.*, 1991, **5** 5747.

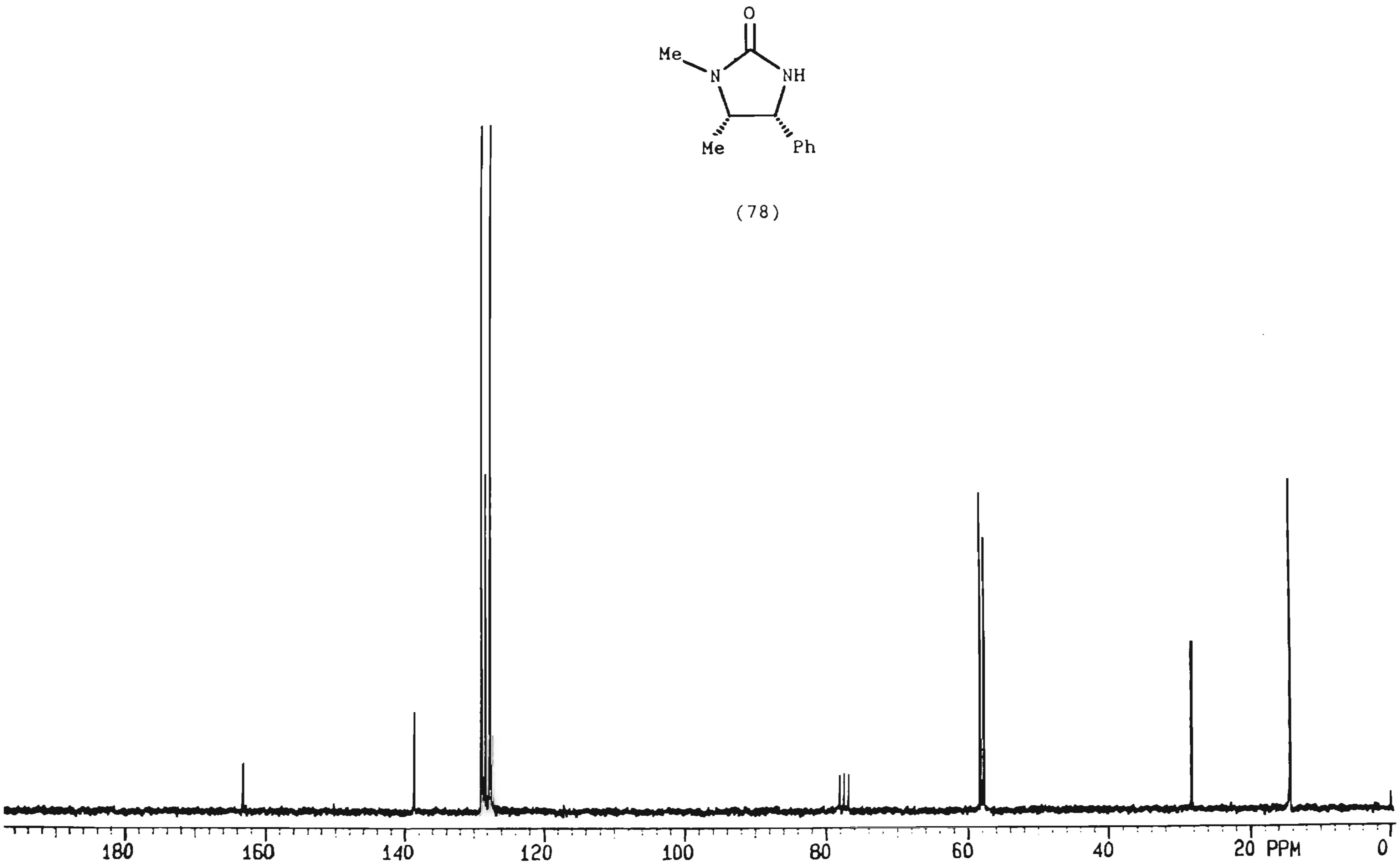
163. E.S. Lane, *J. Chromatog.*, 1965, **18**, 426.

164. A.M. Phipps and D.N. Hume, *J. Chem. Ed.*, 1968, **45**, 664

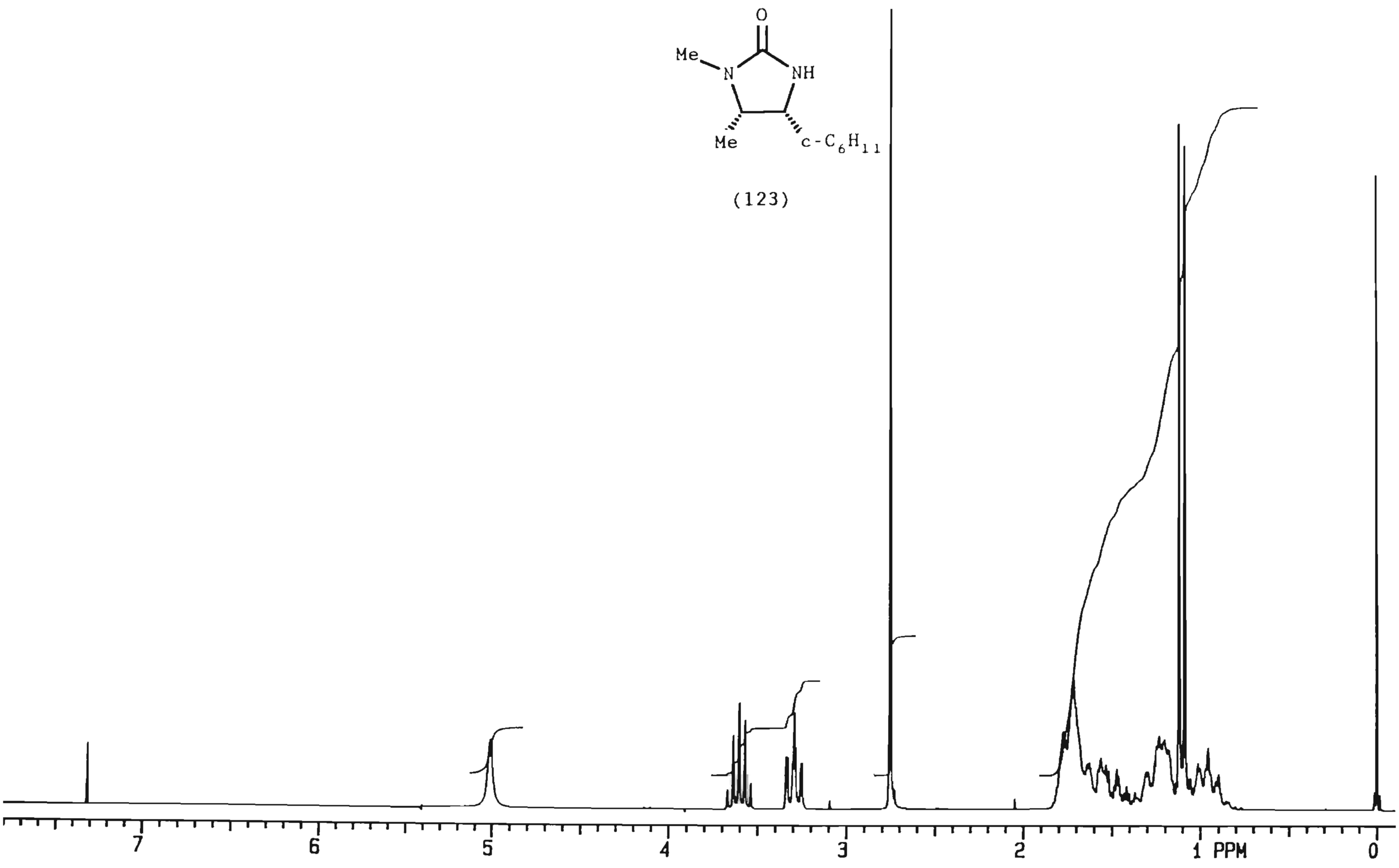
5. APPENDIX

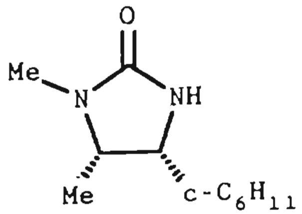
^{1}H and ^{13}C nuclear magnetic spectra.


(78)

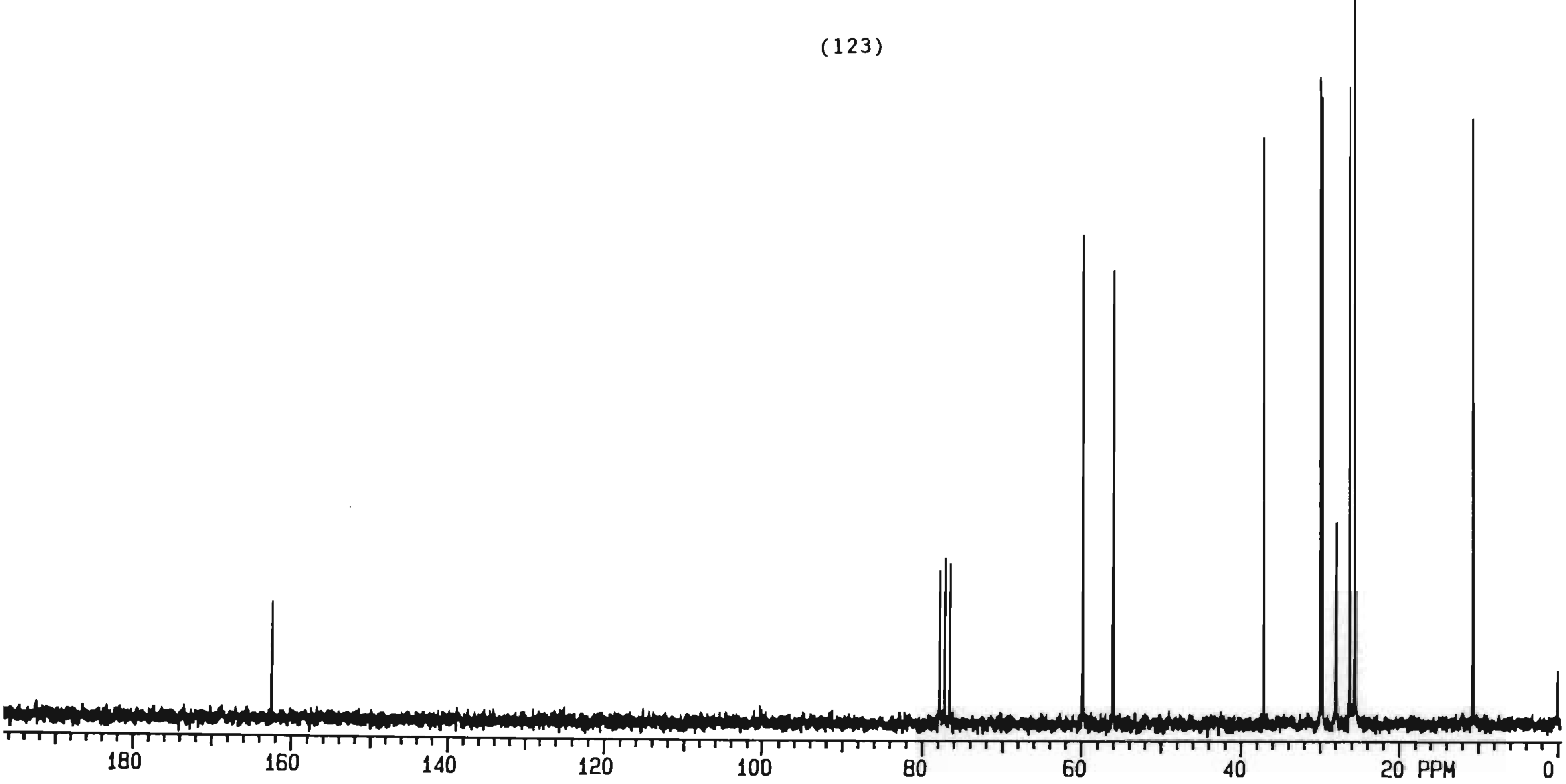


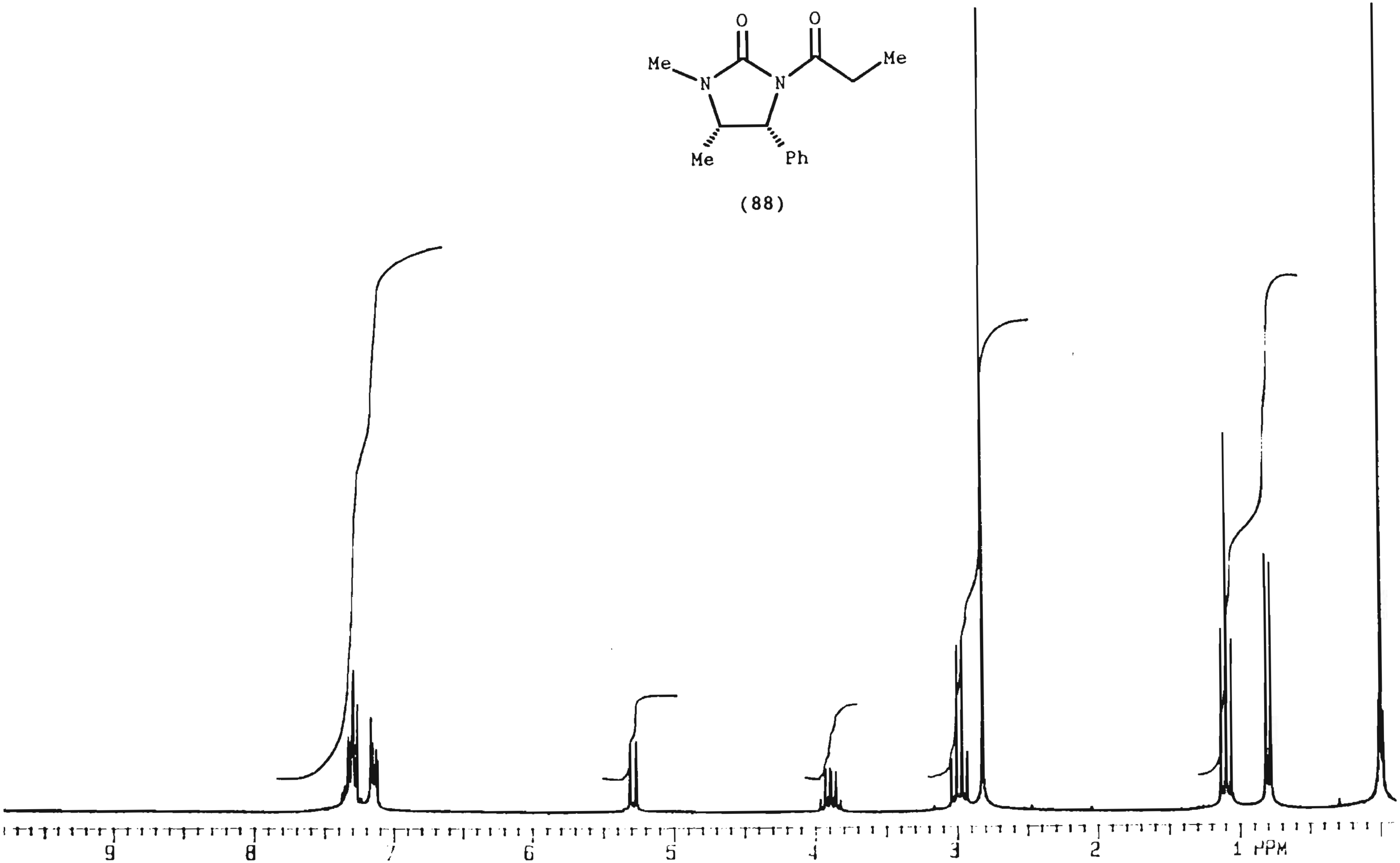
(78)


(123)

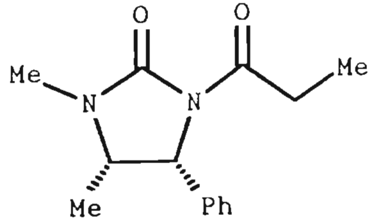


(123)

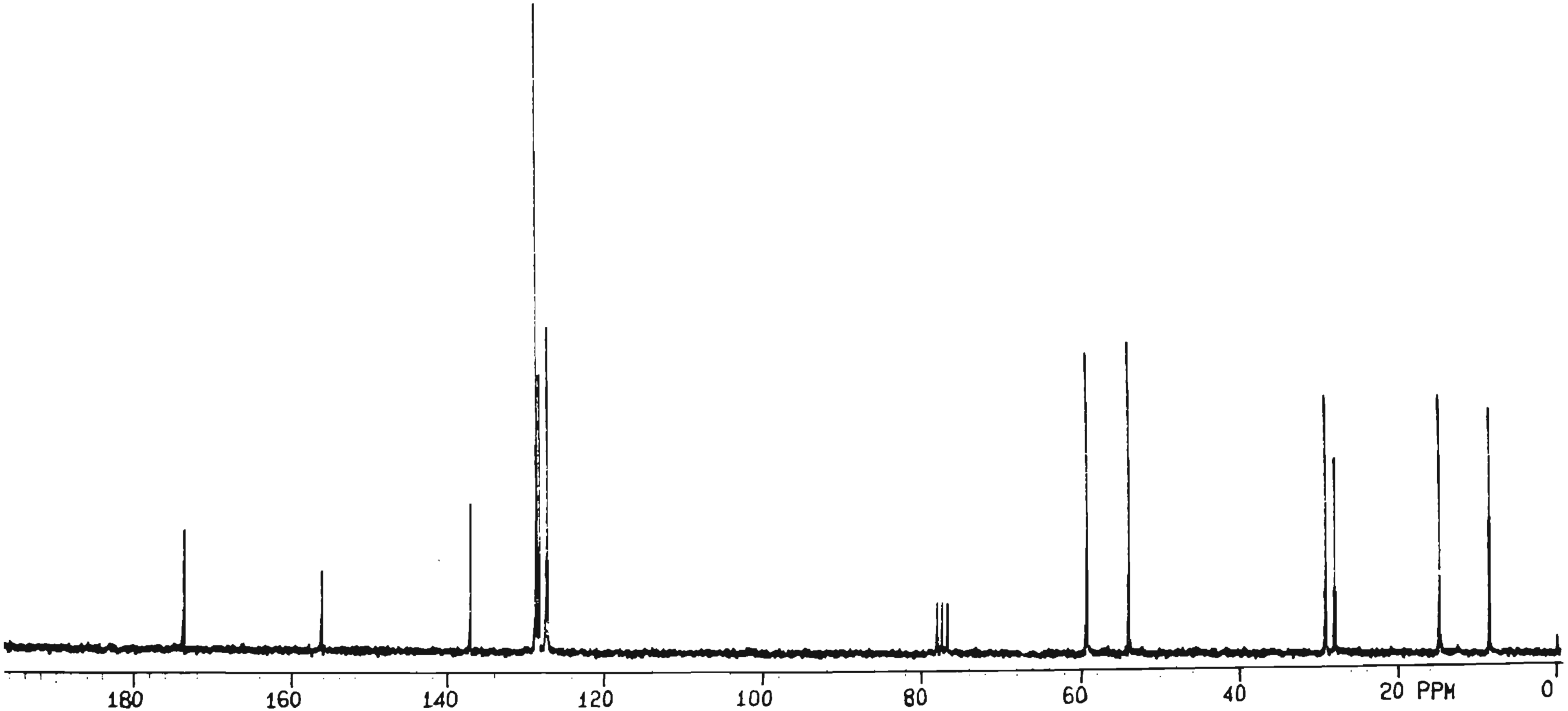


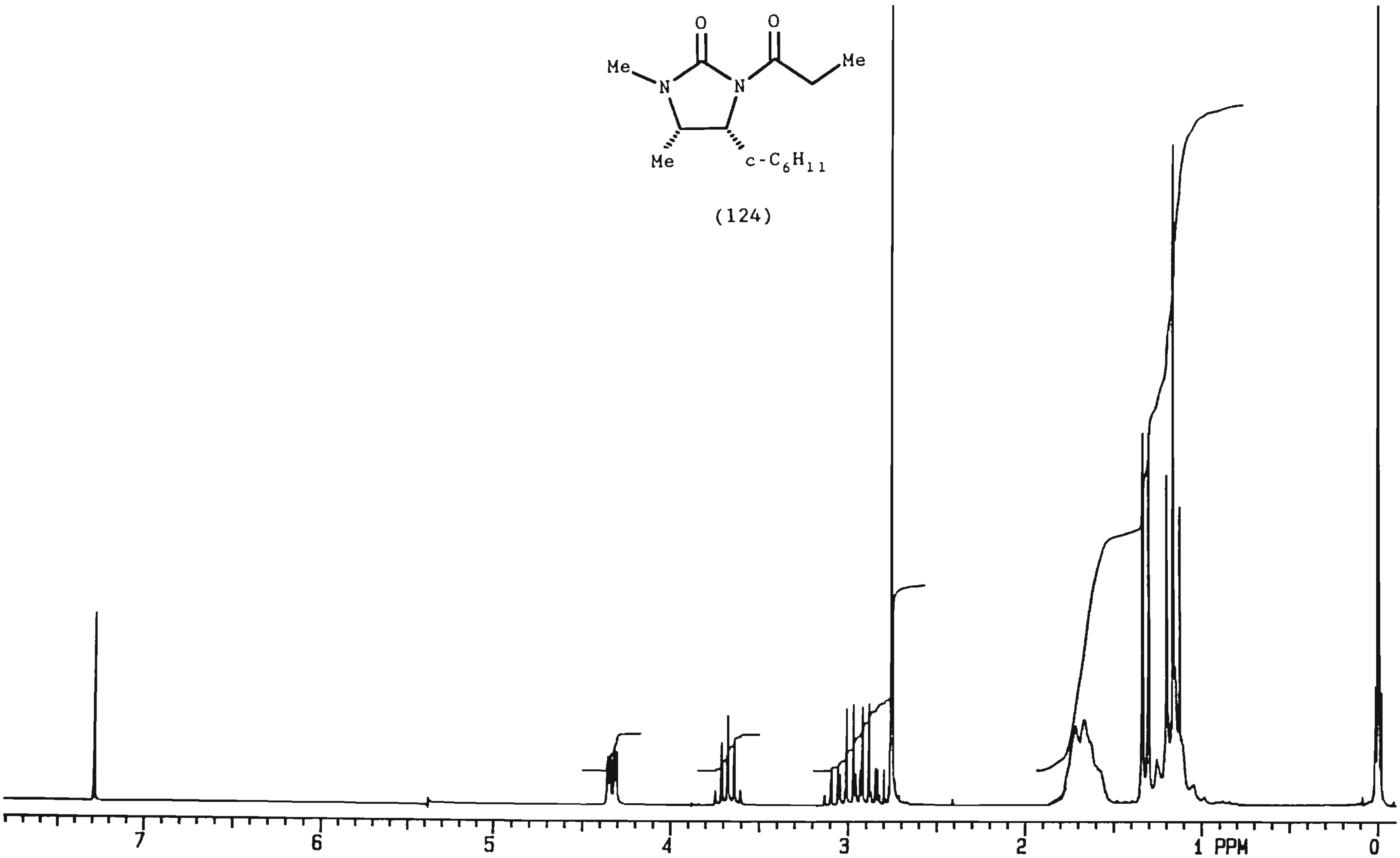


(88)

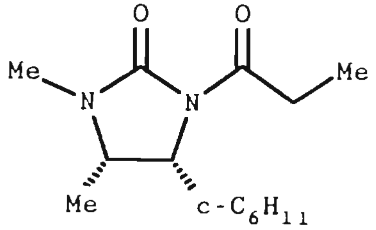


(88)

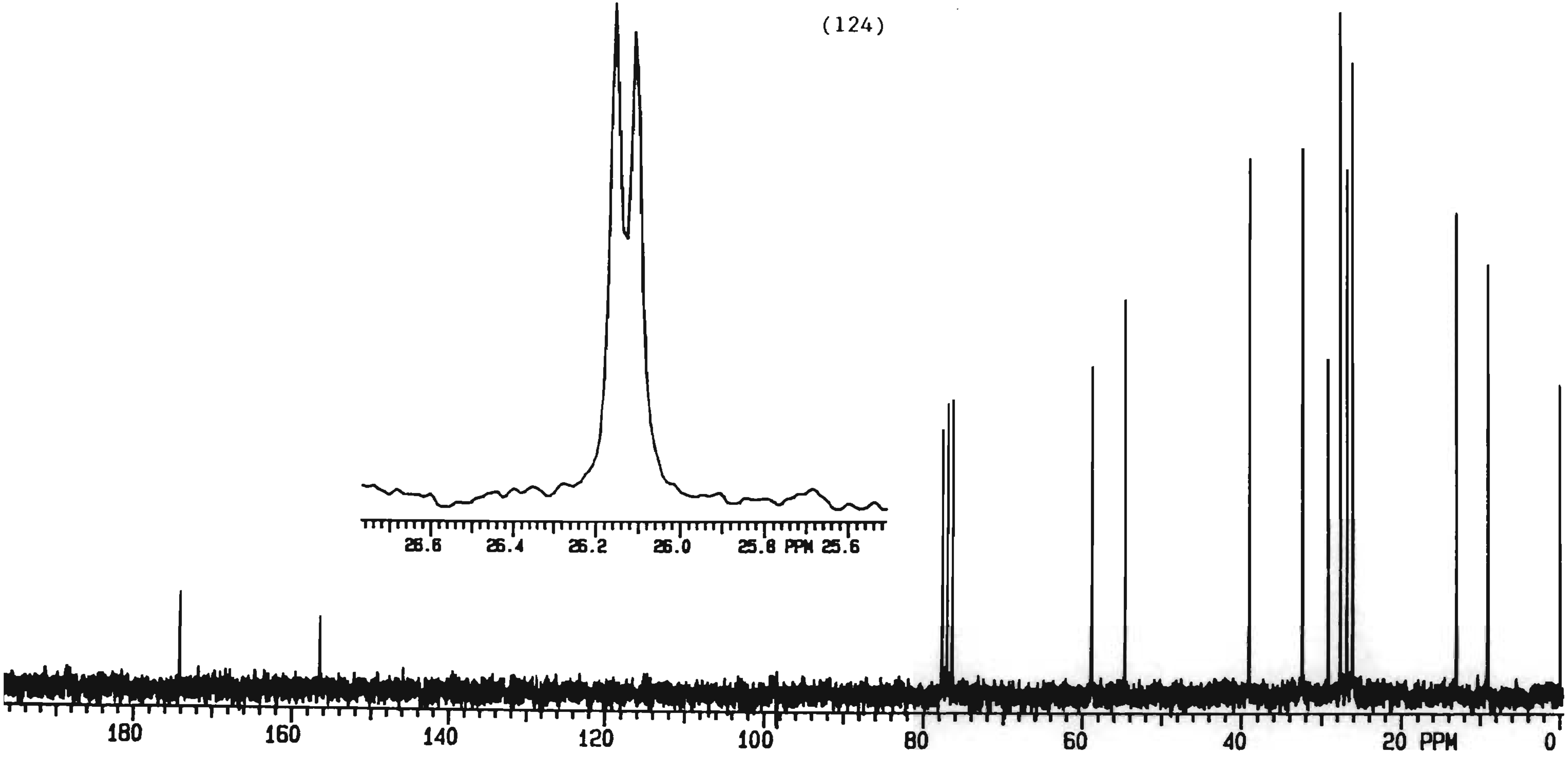


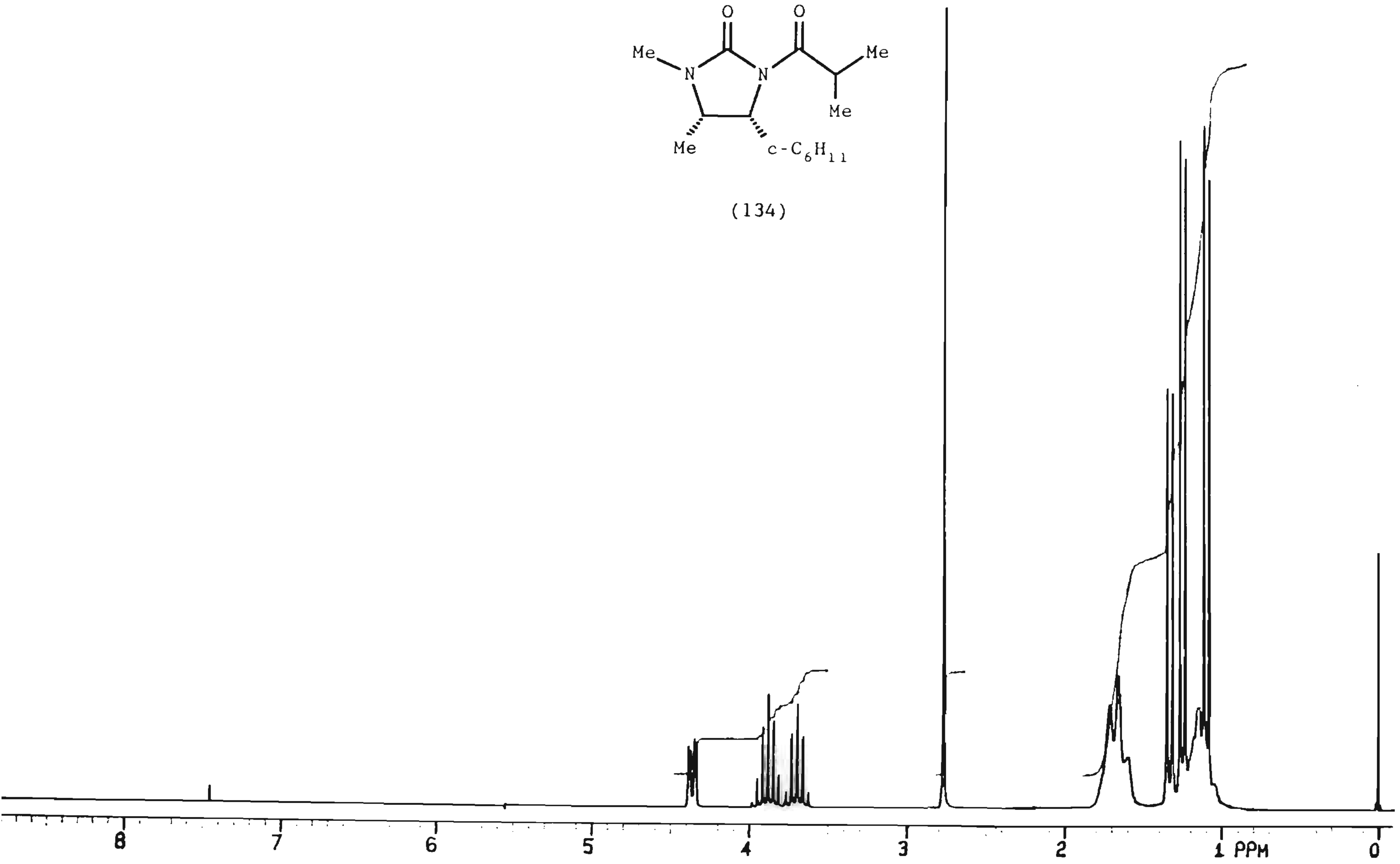


(124)

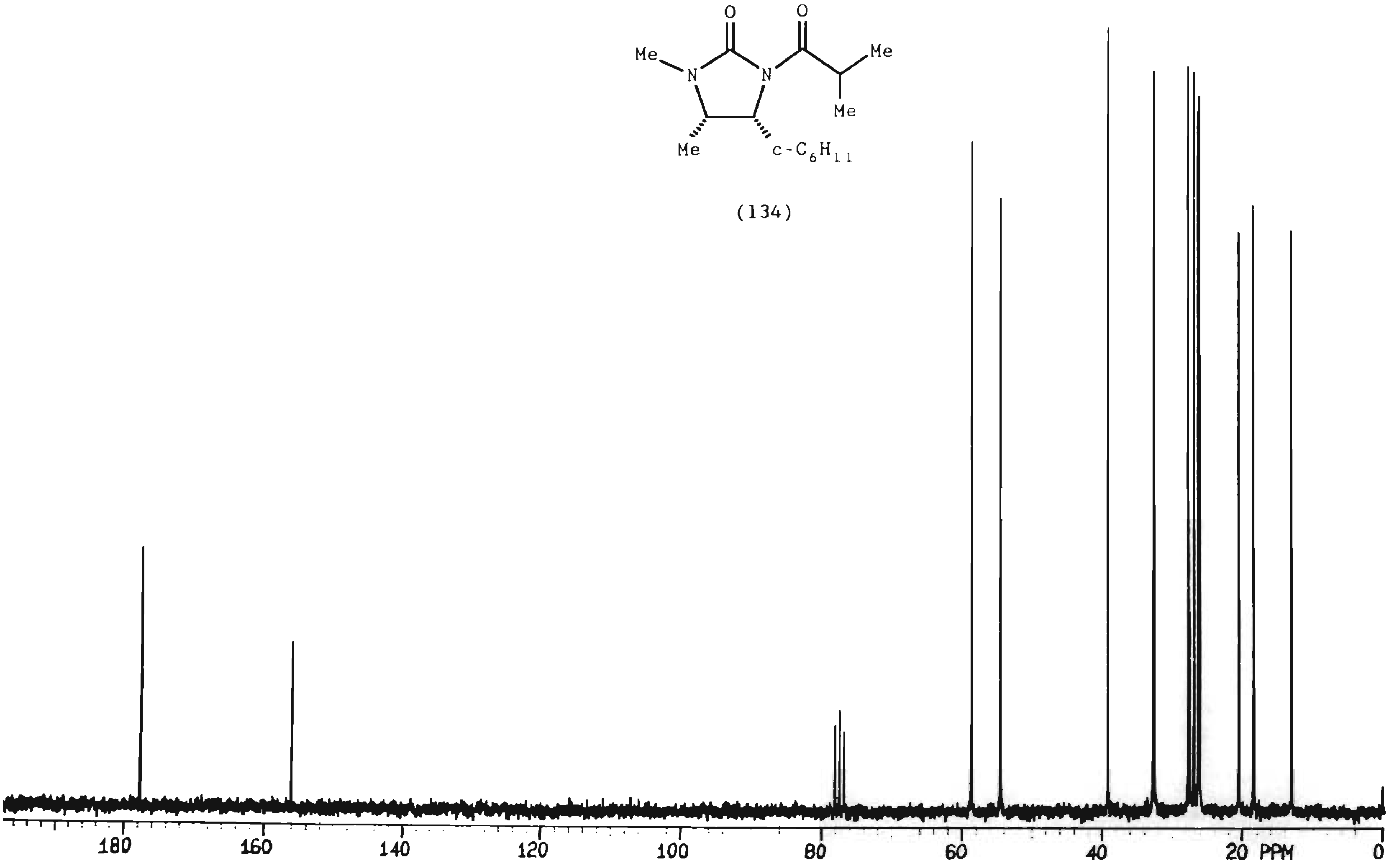

O
O
Me
N
N
Me
Me
c-C6H11

(124)

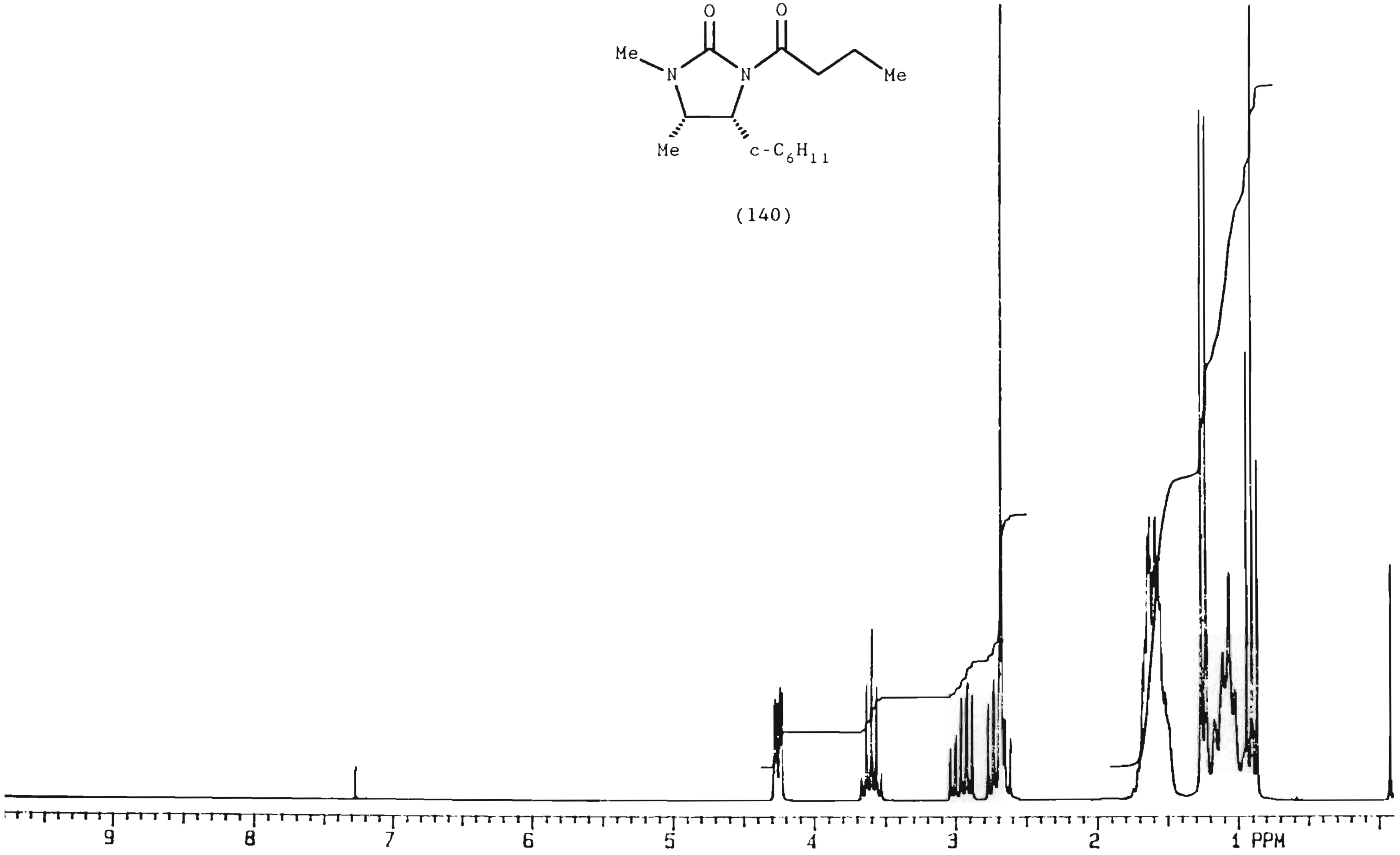

26.6
26.4
26.2
26.0
25.8 PPM 25.6
180
160
140
120
100
80
60
40
20 PPM
0



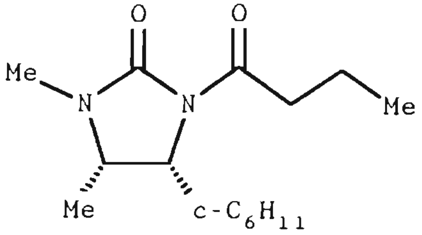
(134)



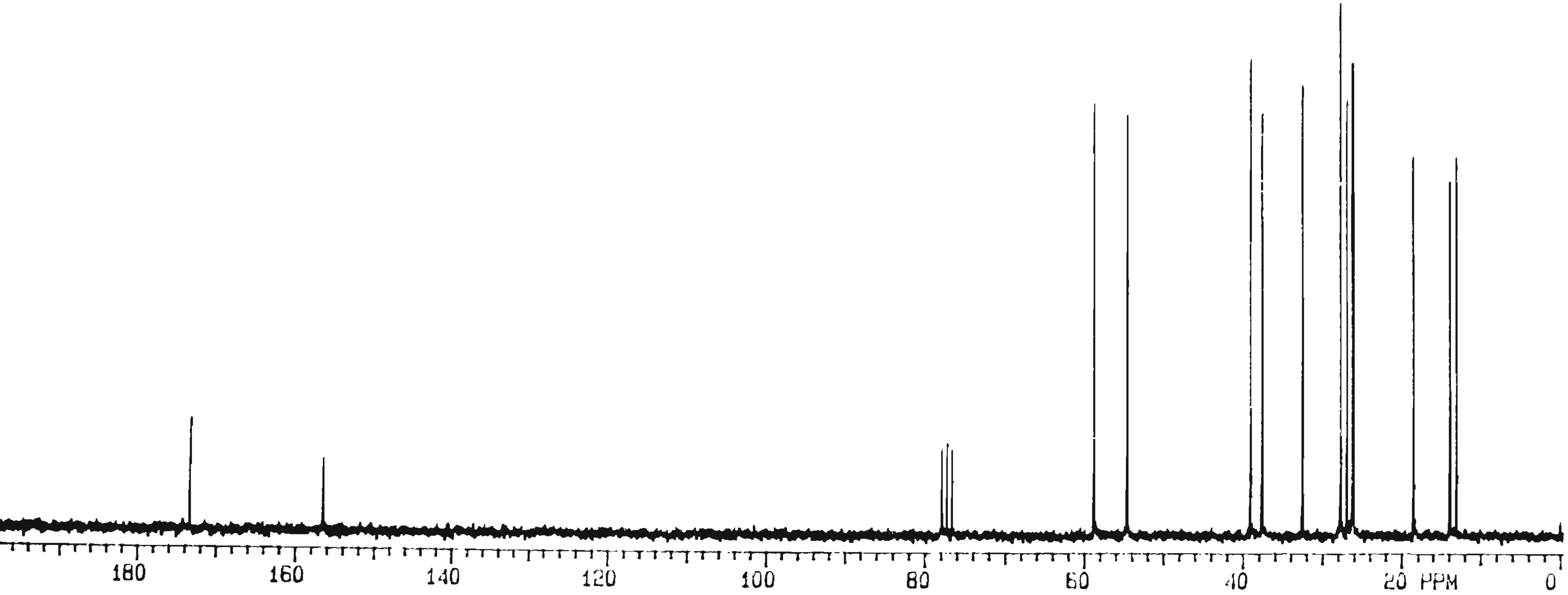
(134)

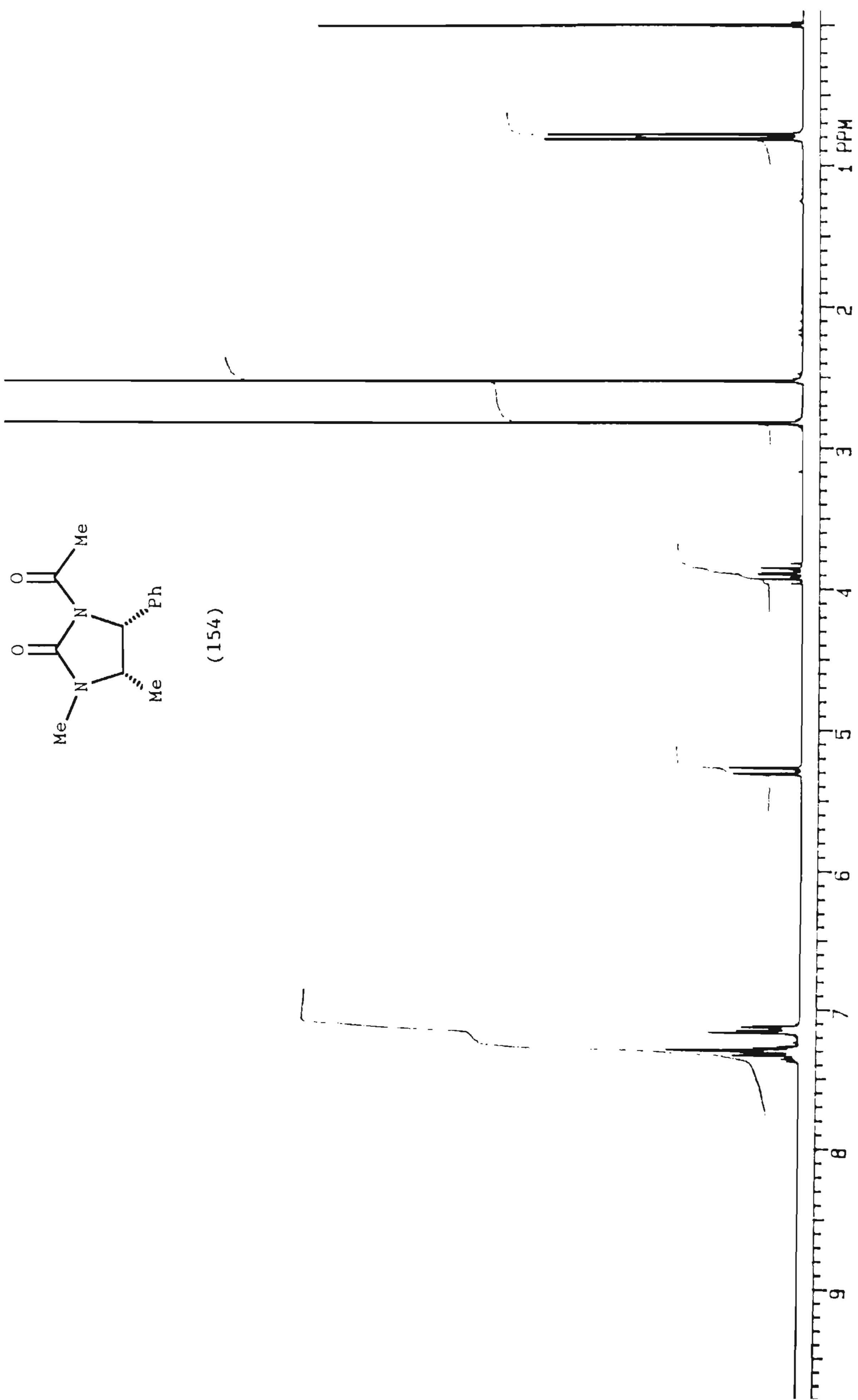


(140)

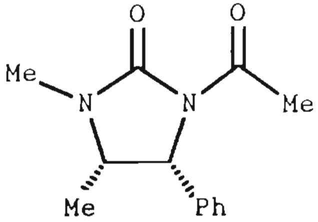


(140)

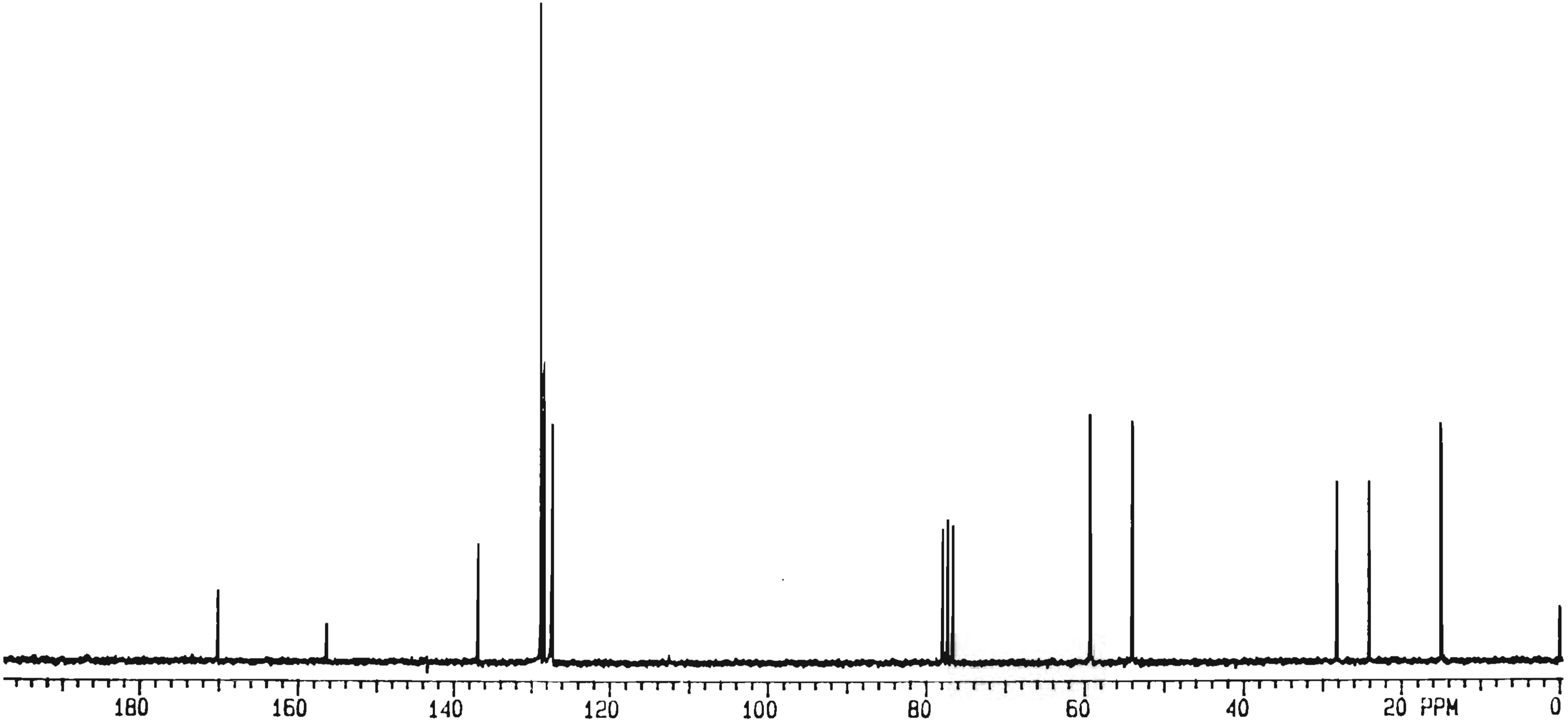


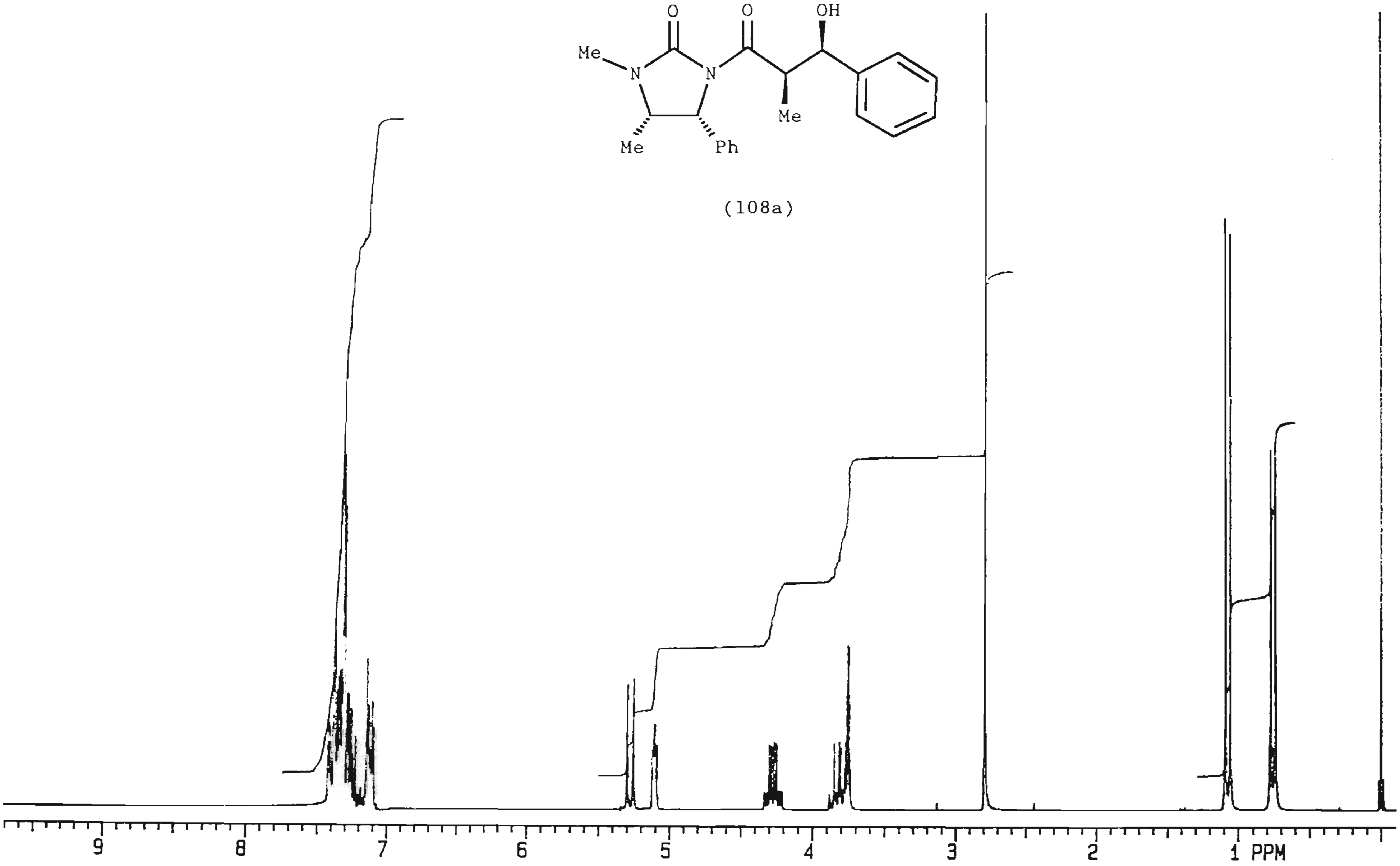


(154)

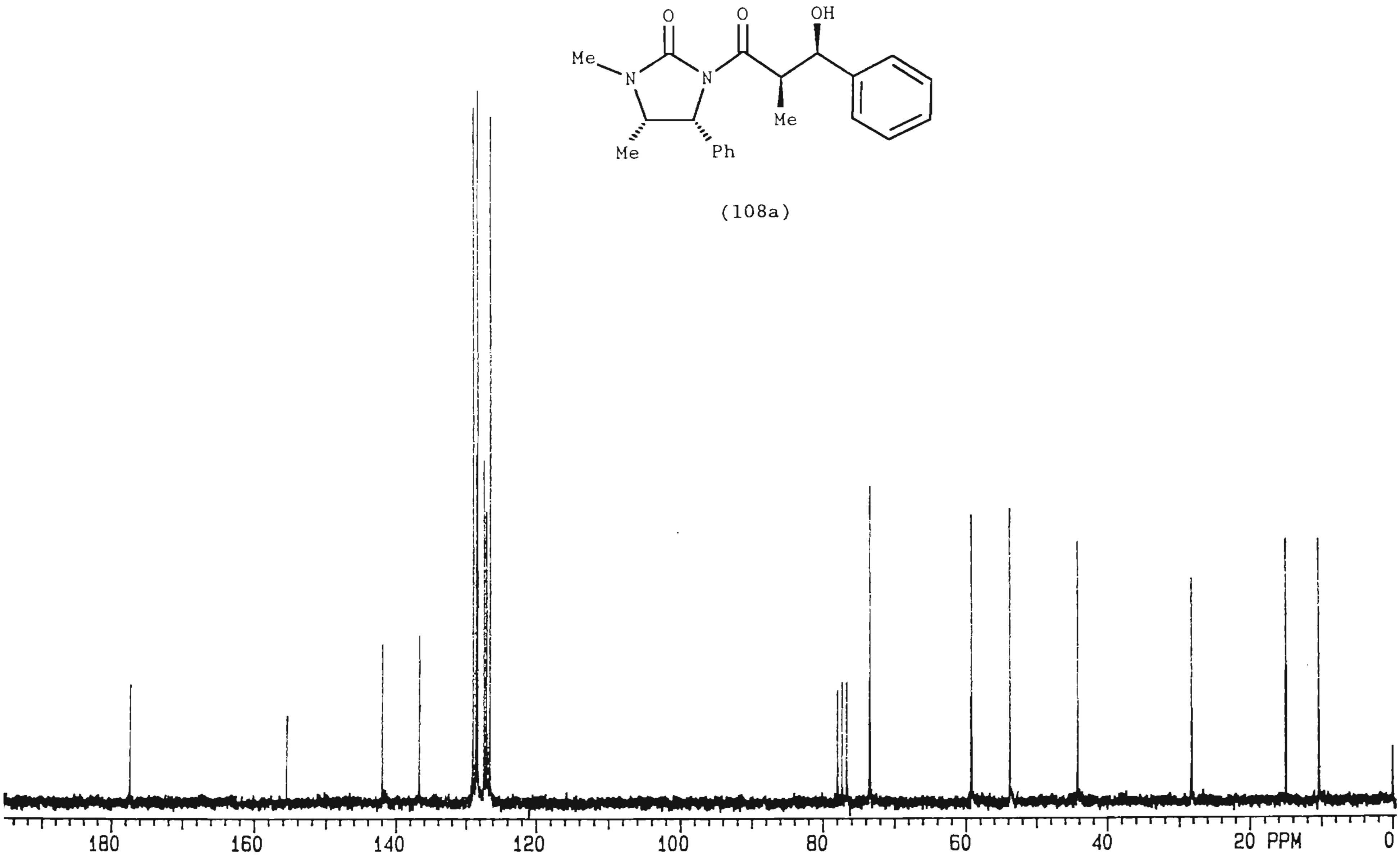


(154)

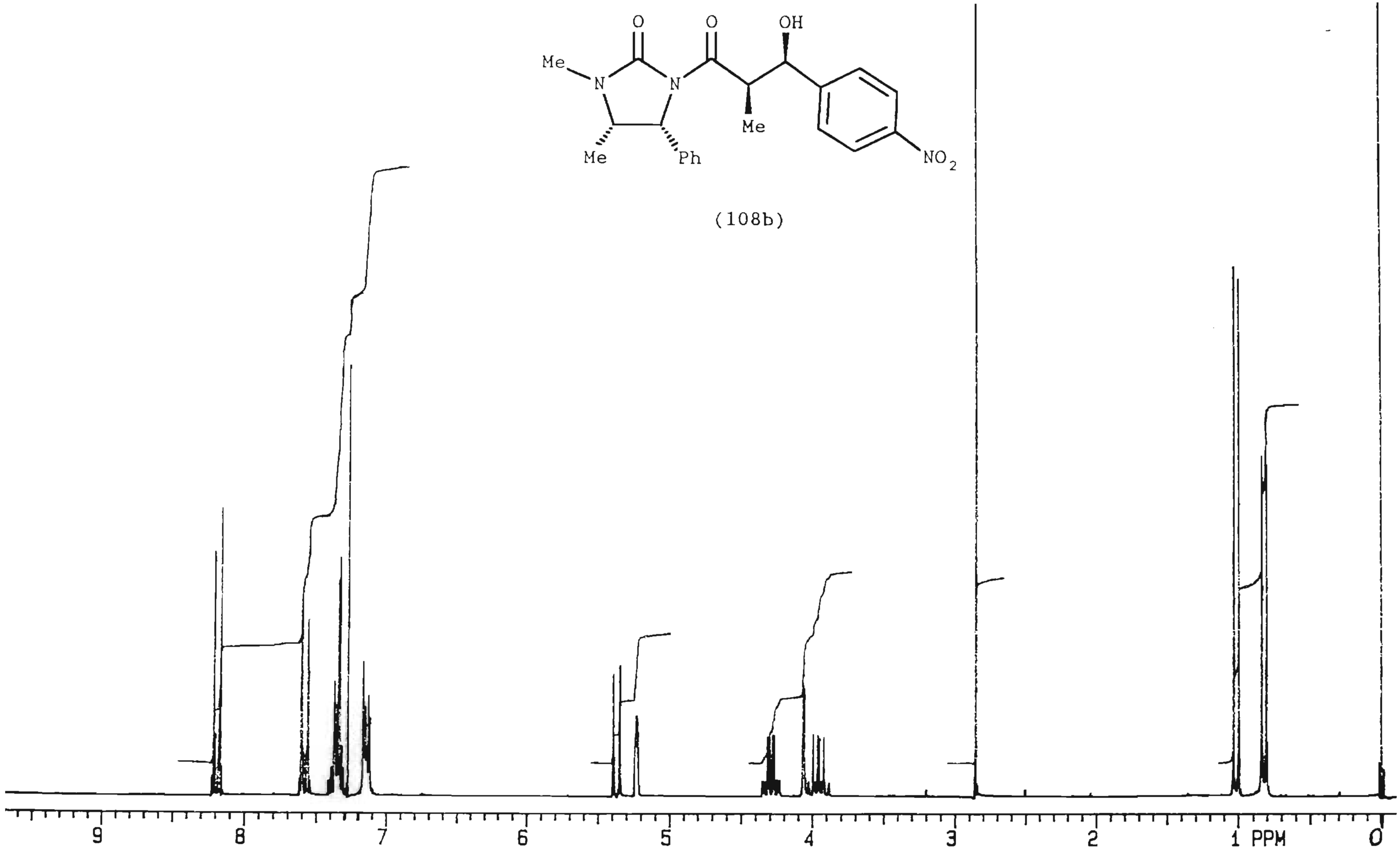


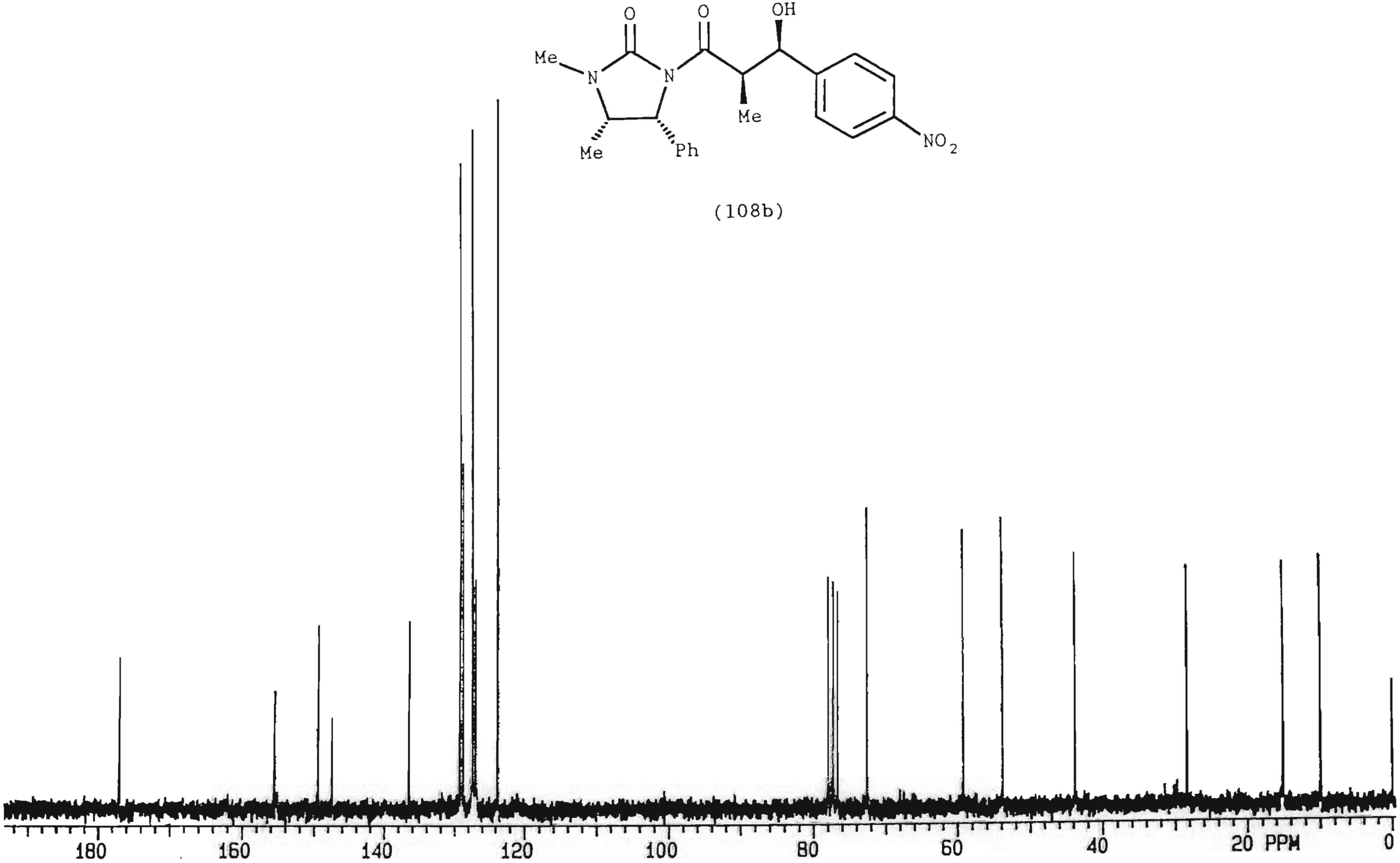


(108a)

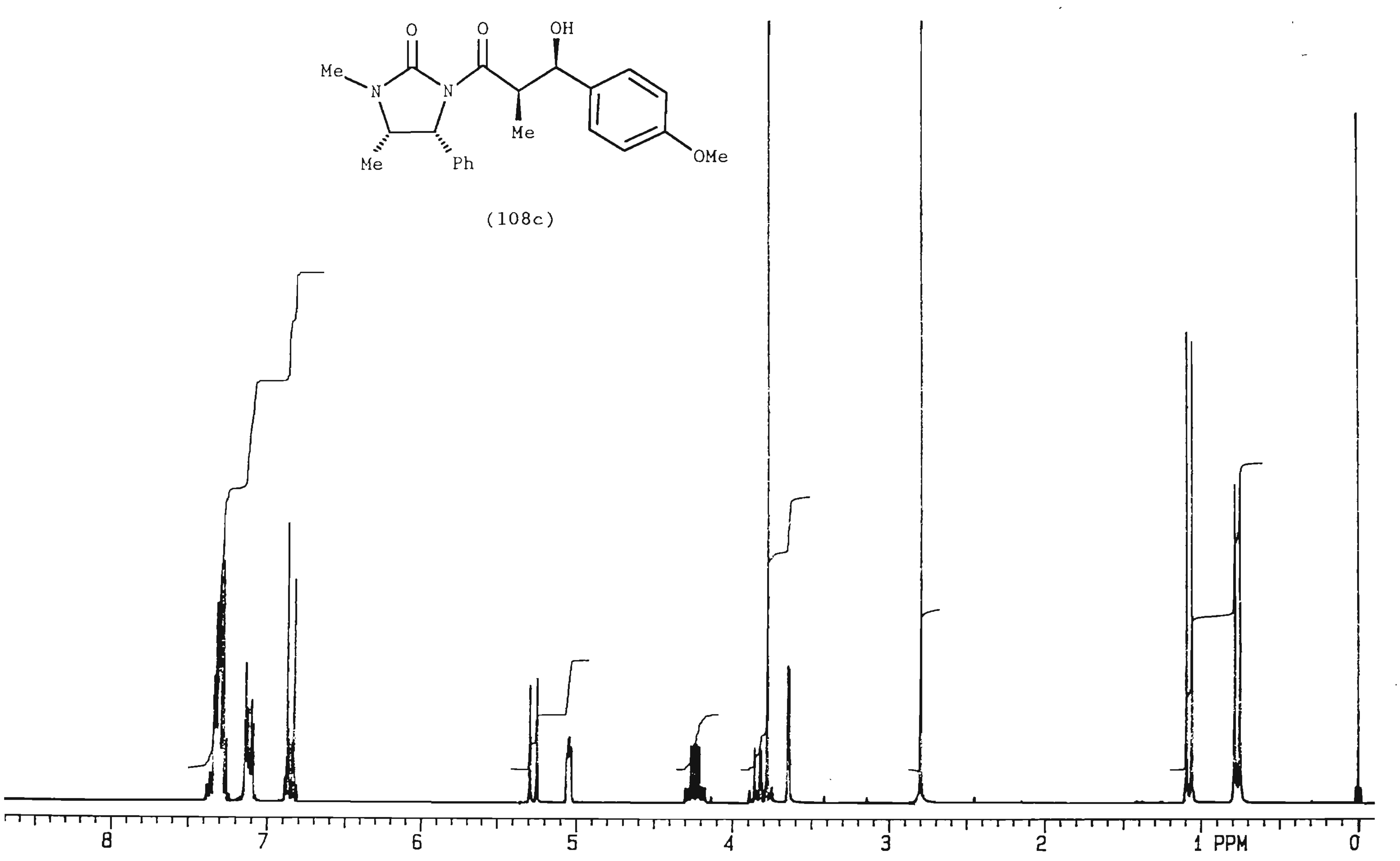


(108a)

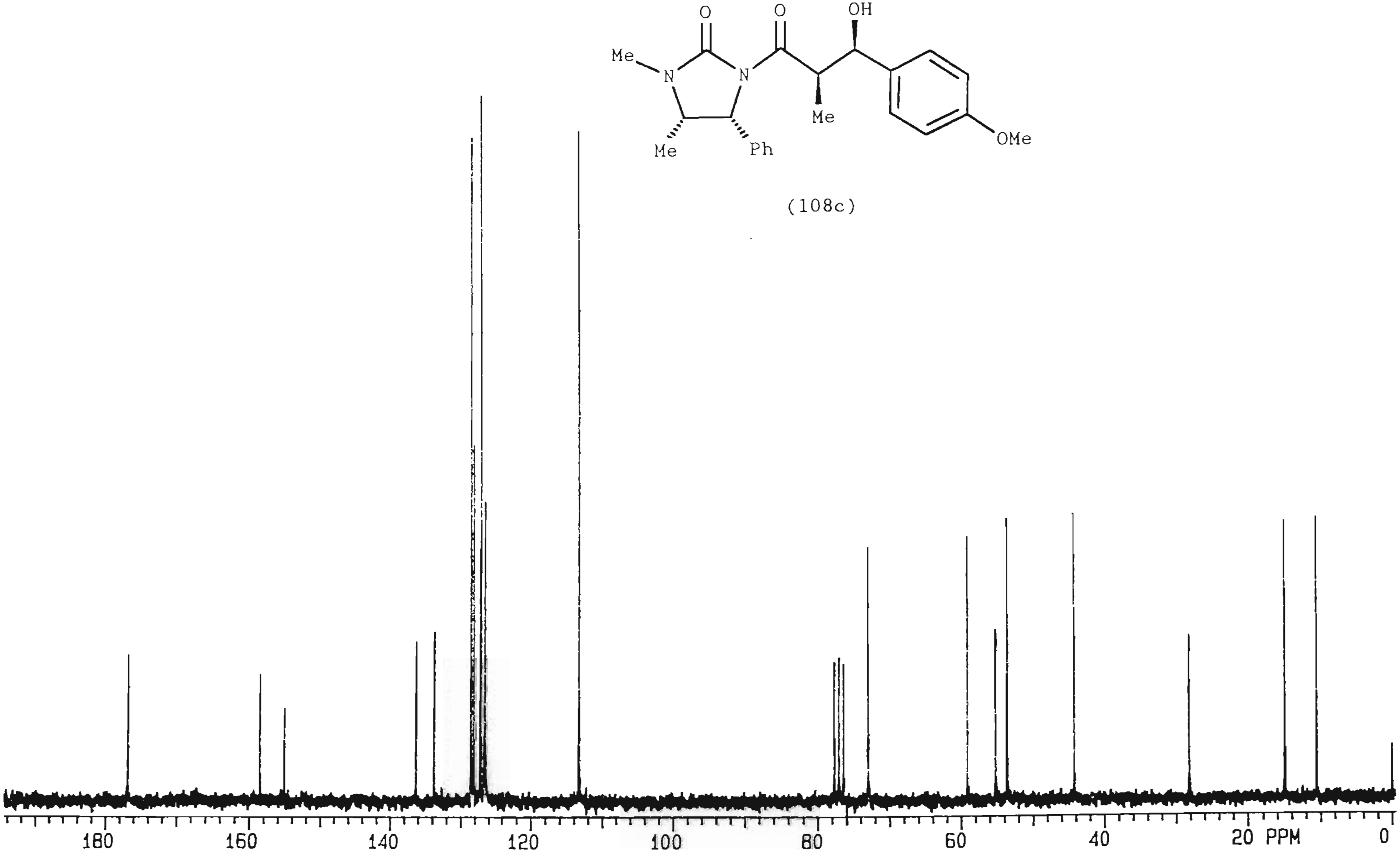

(108b)

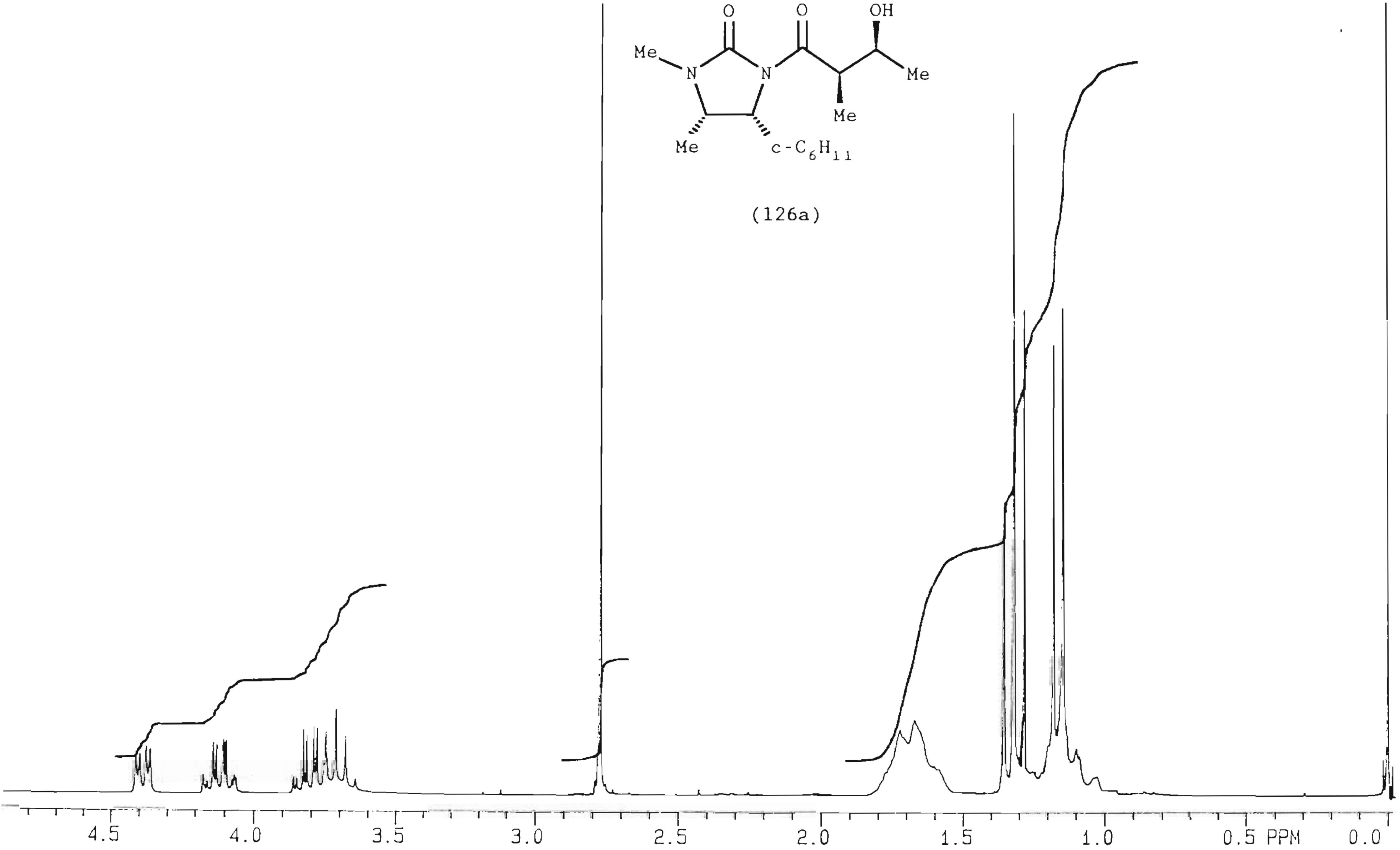


(108b)

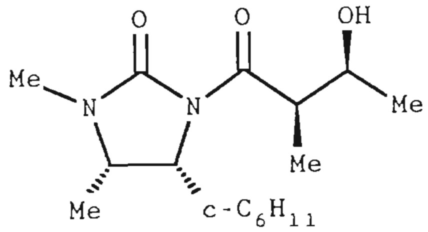


(108c)

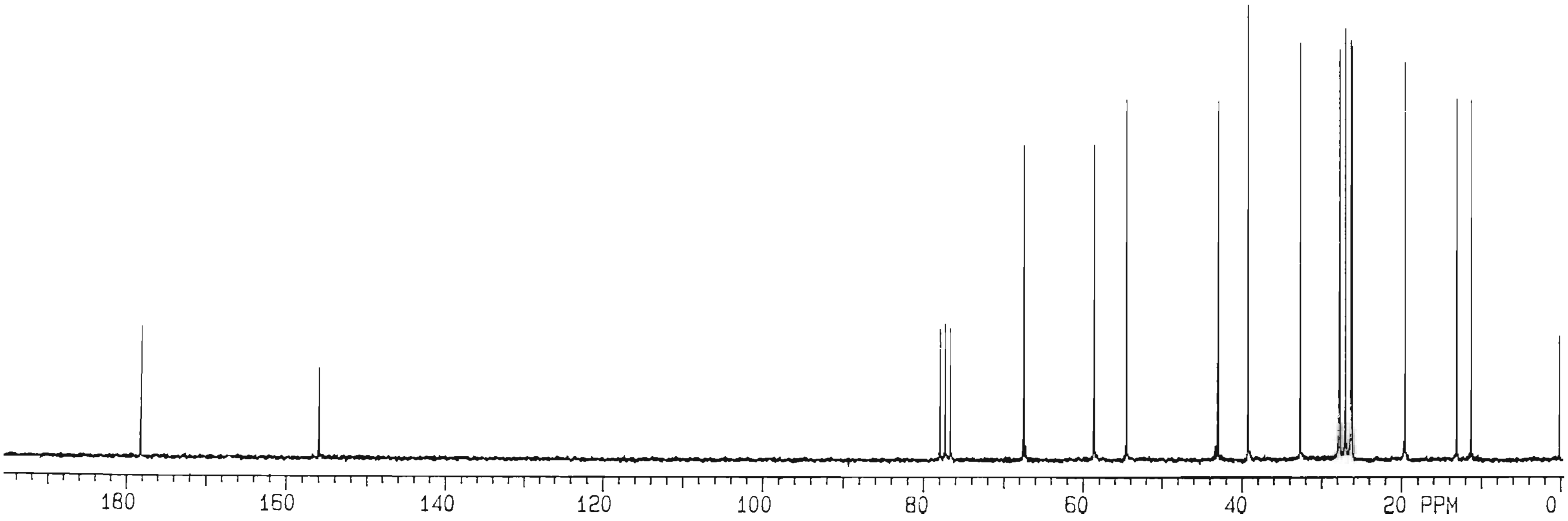

(108c)

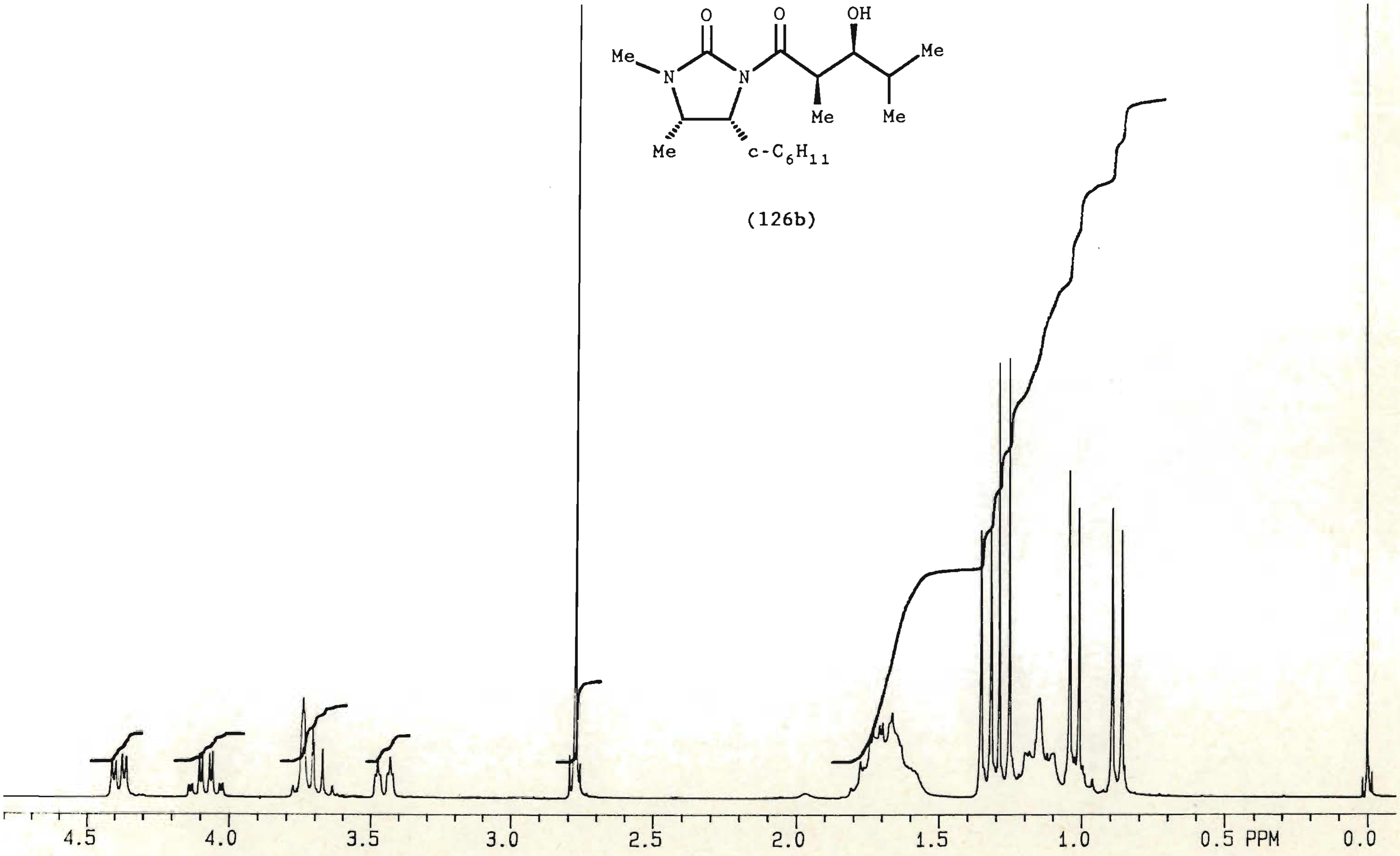


(126a)

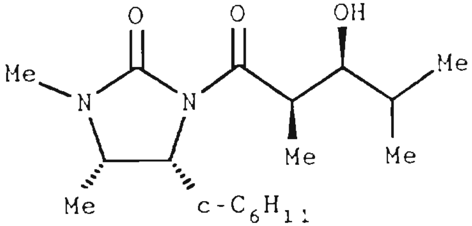


(126a)

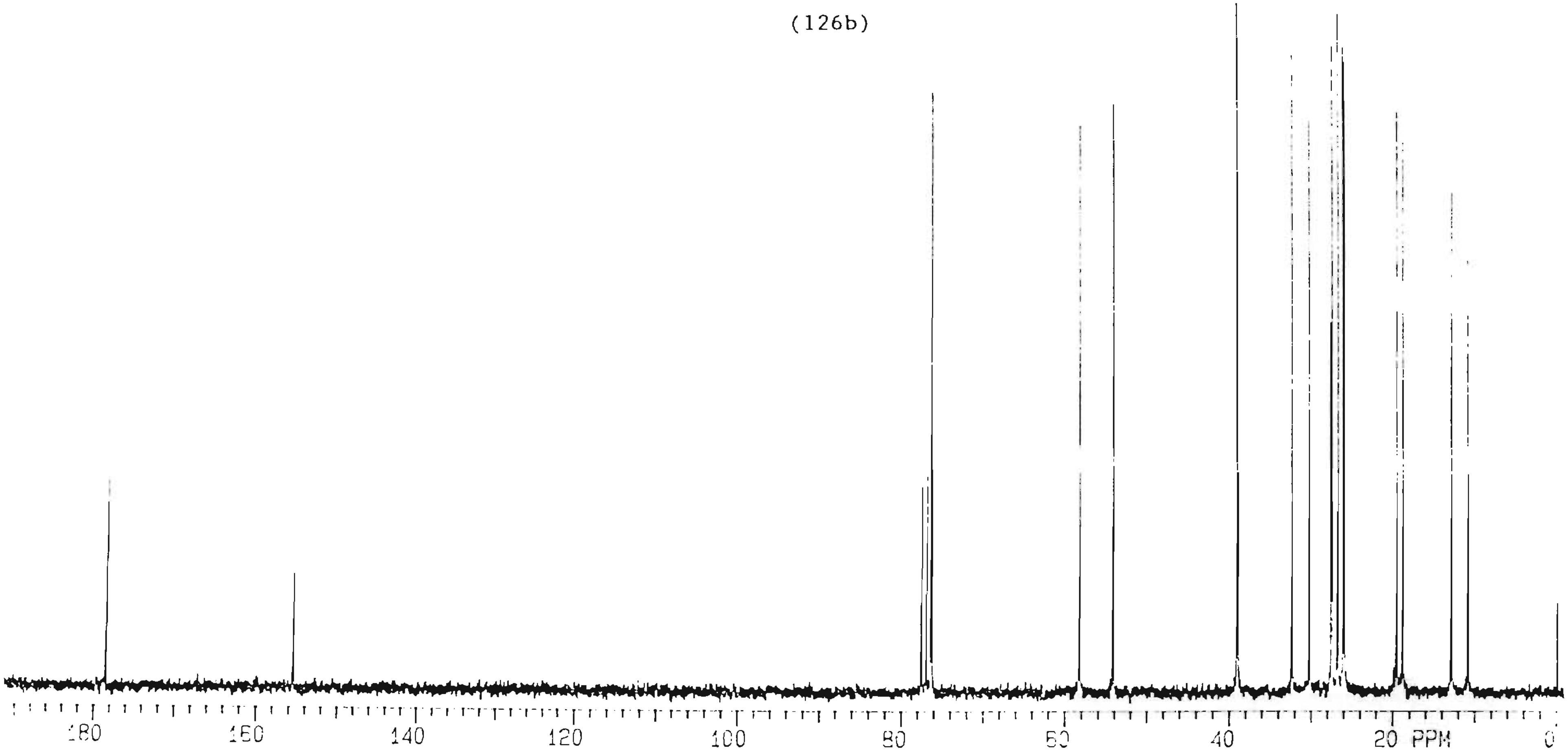


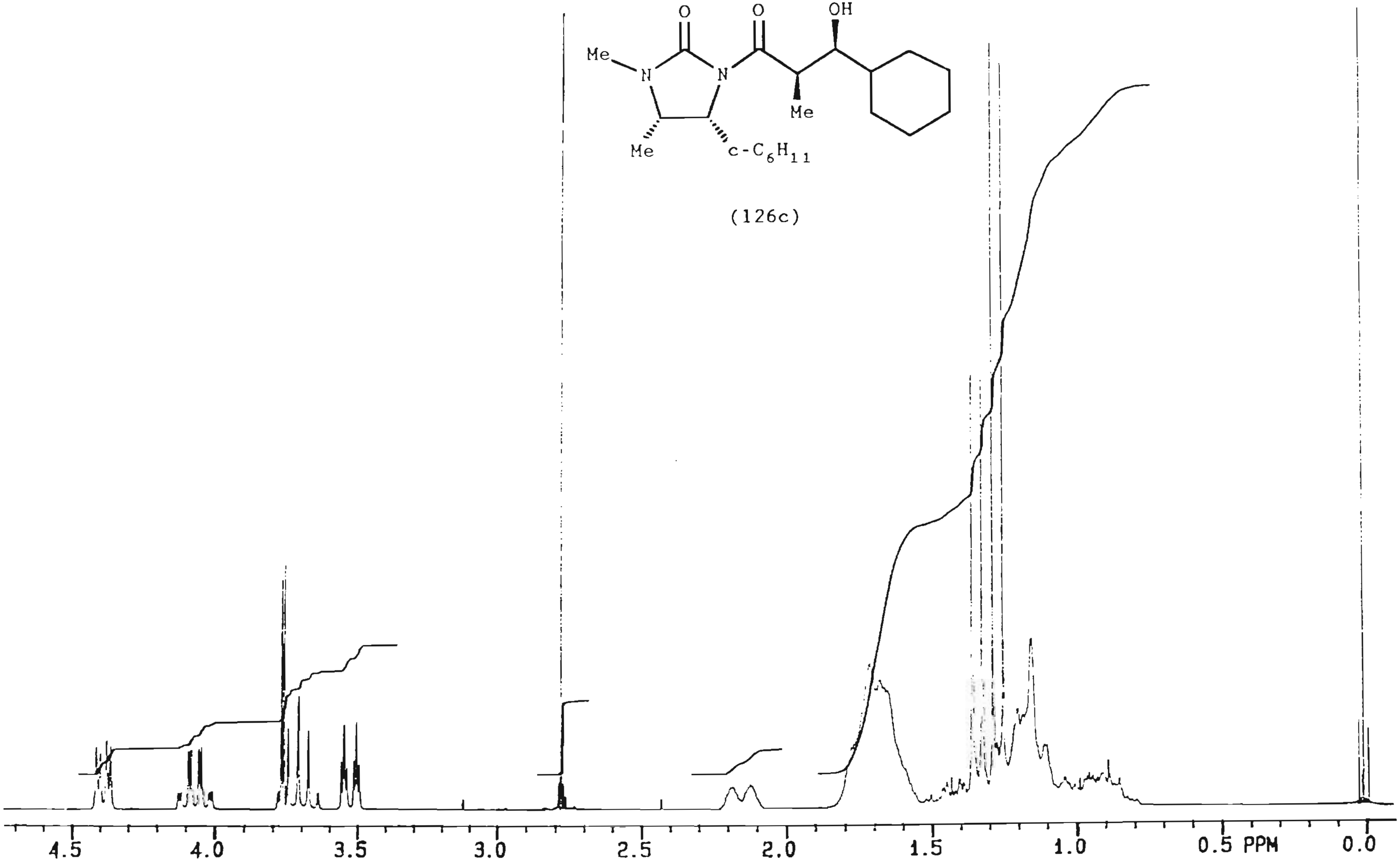


(126b)

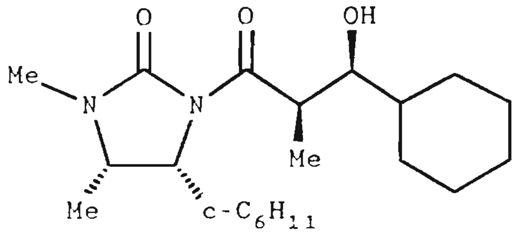


(126b)

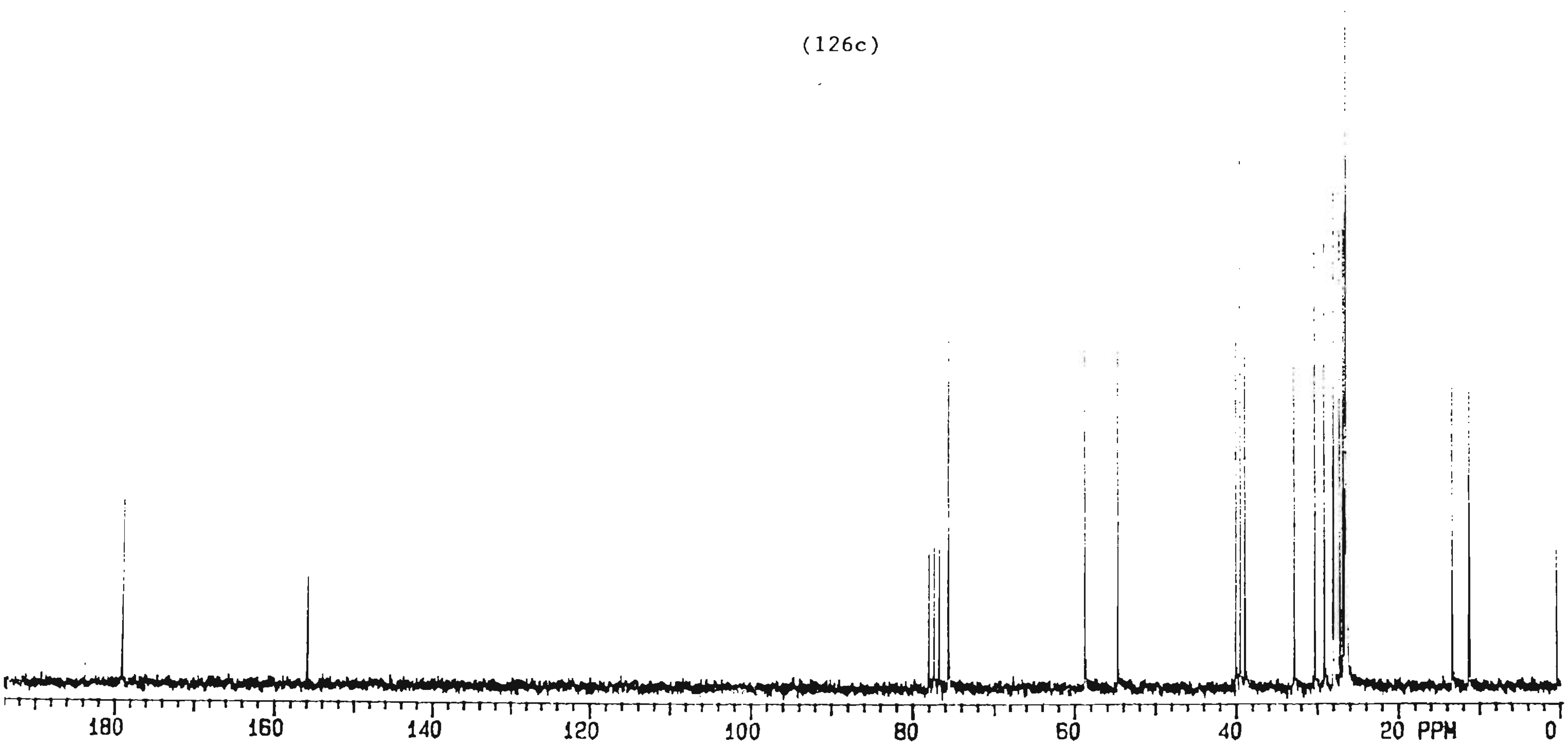


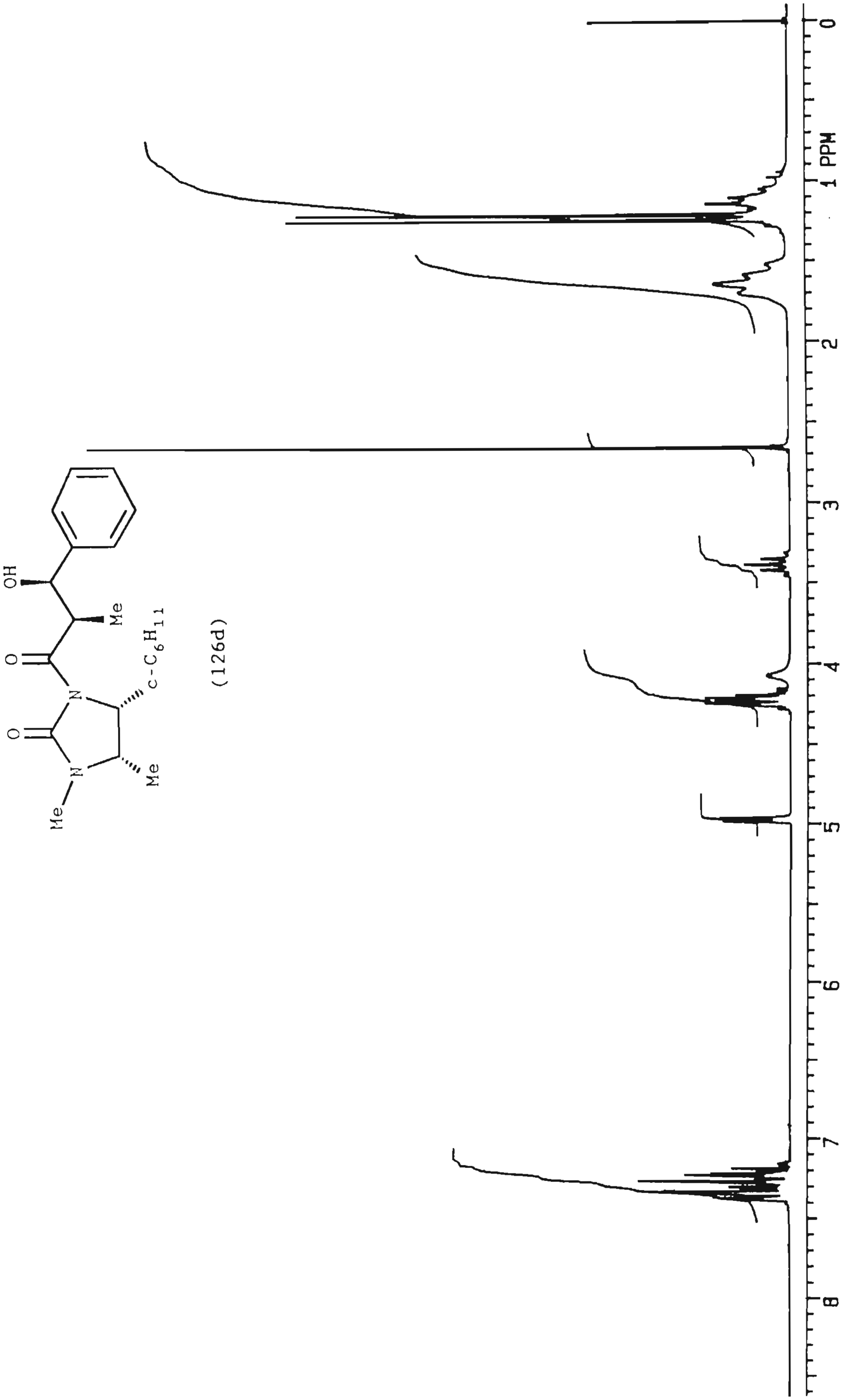


(126c)

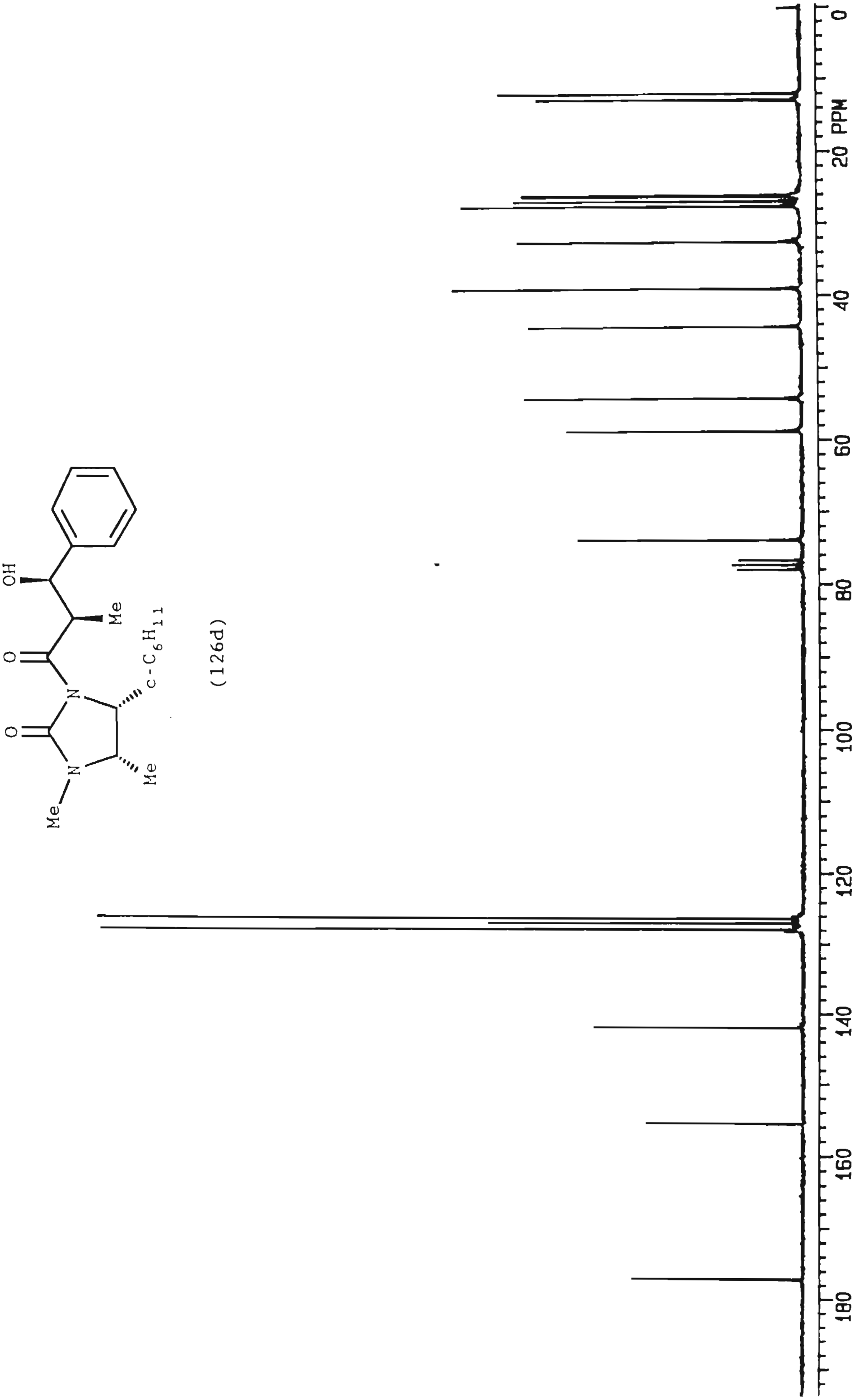


(126c)

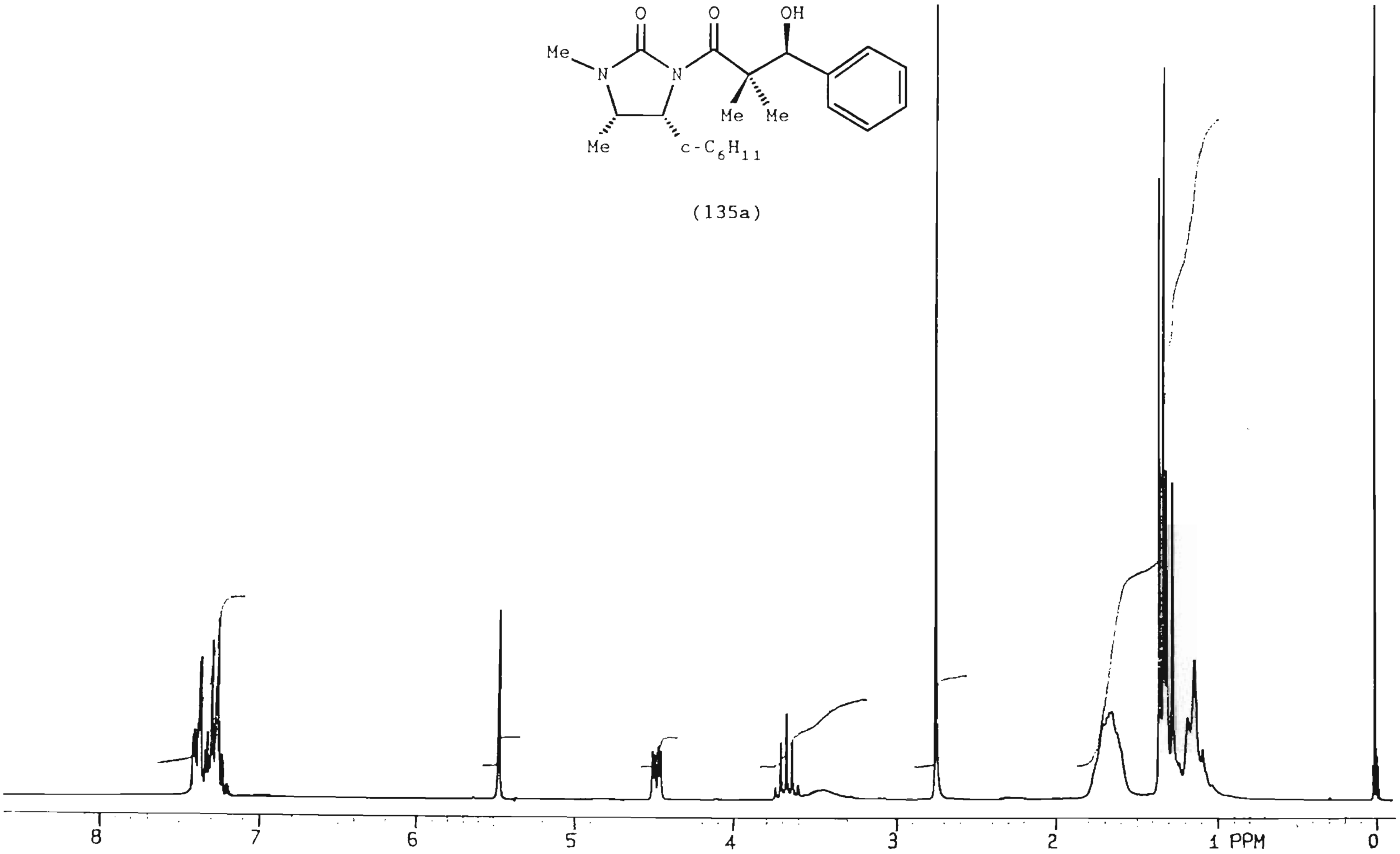




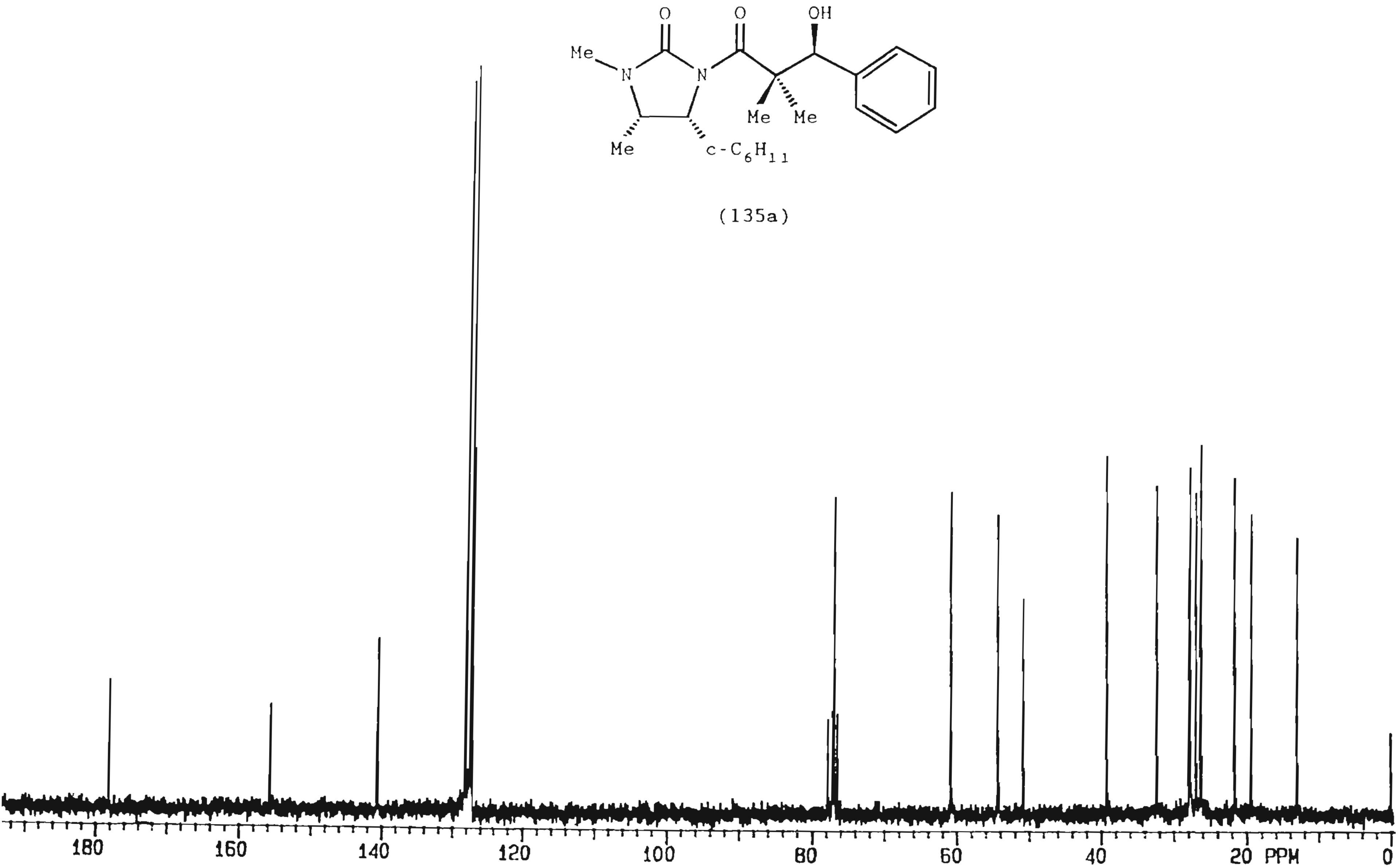
(126d)



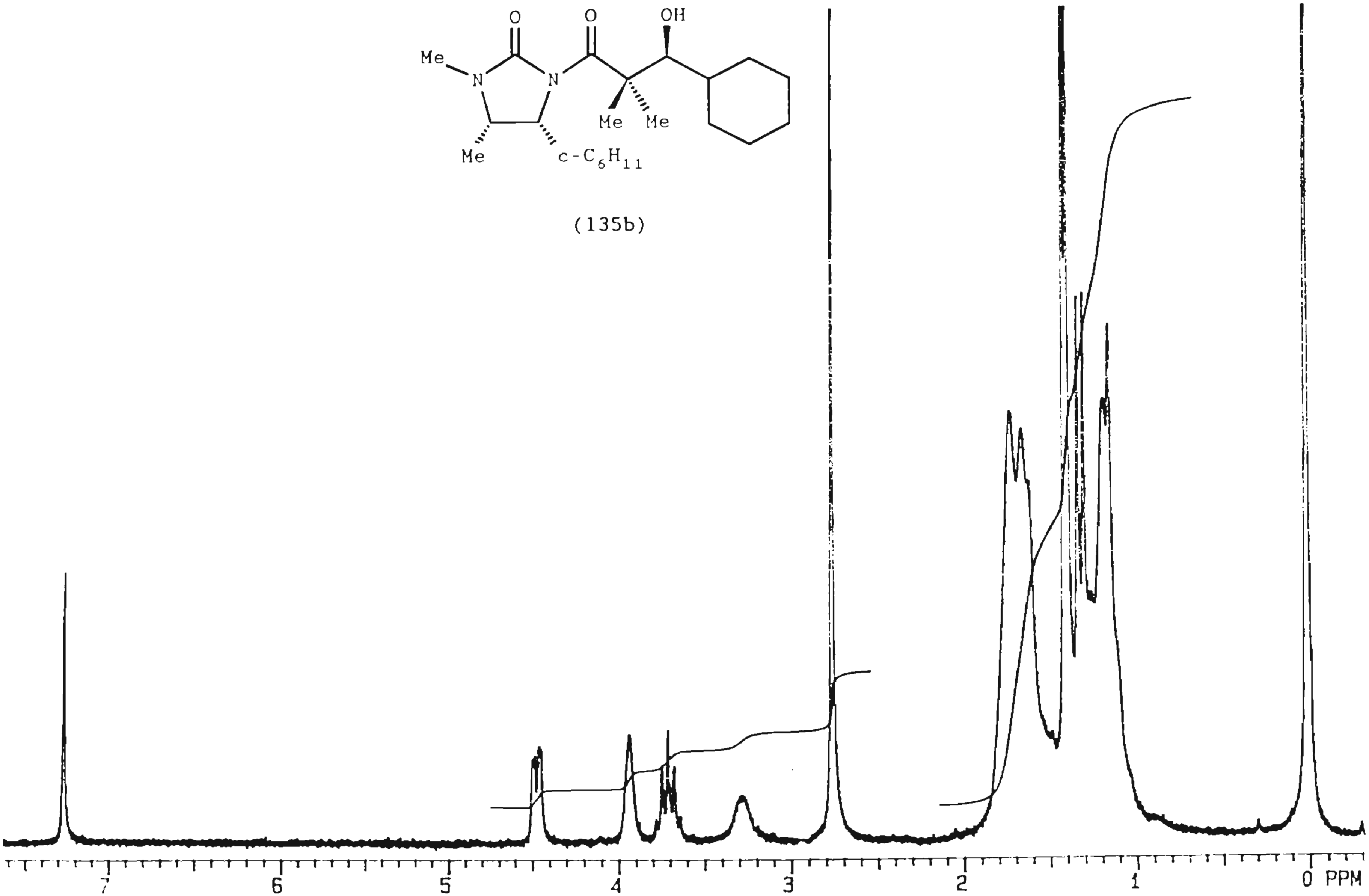
(126d)



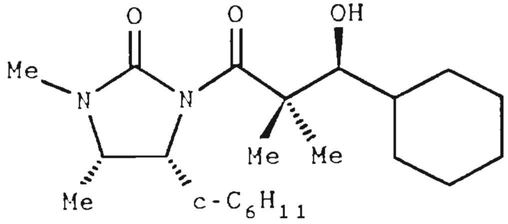
(135a)



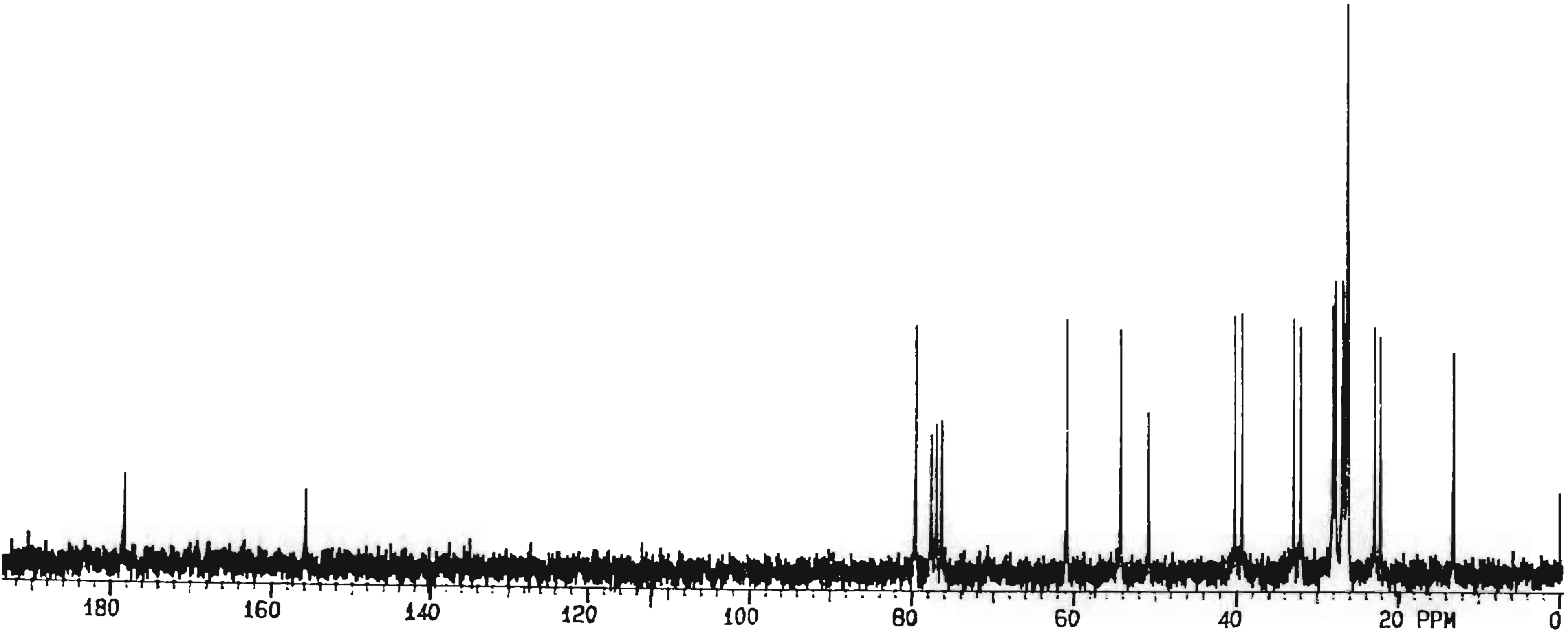
(135a)

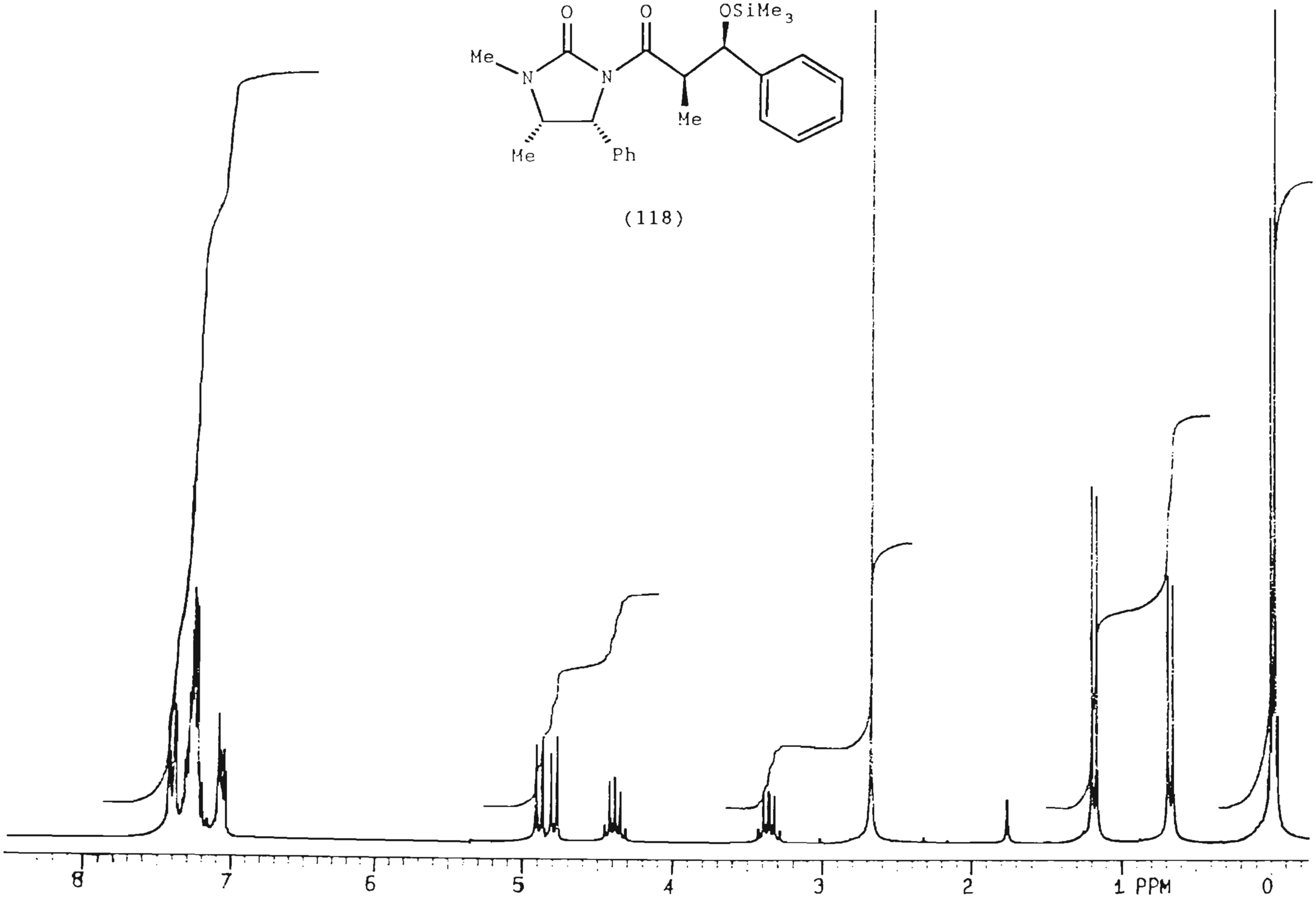


(135b)

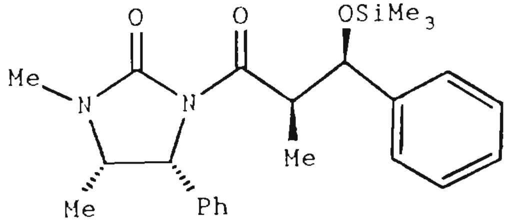


(135b)

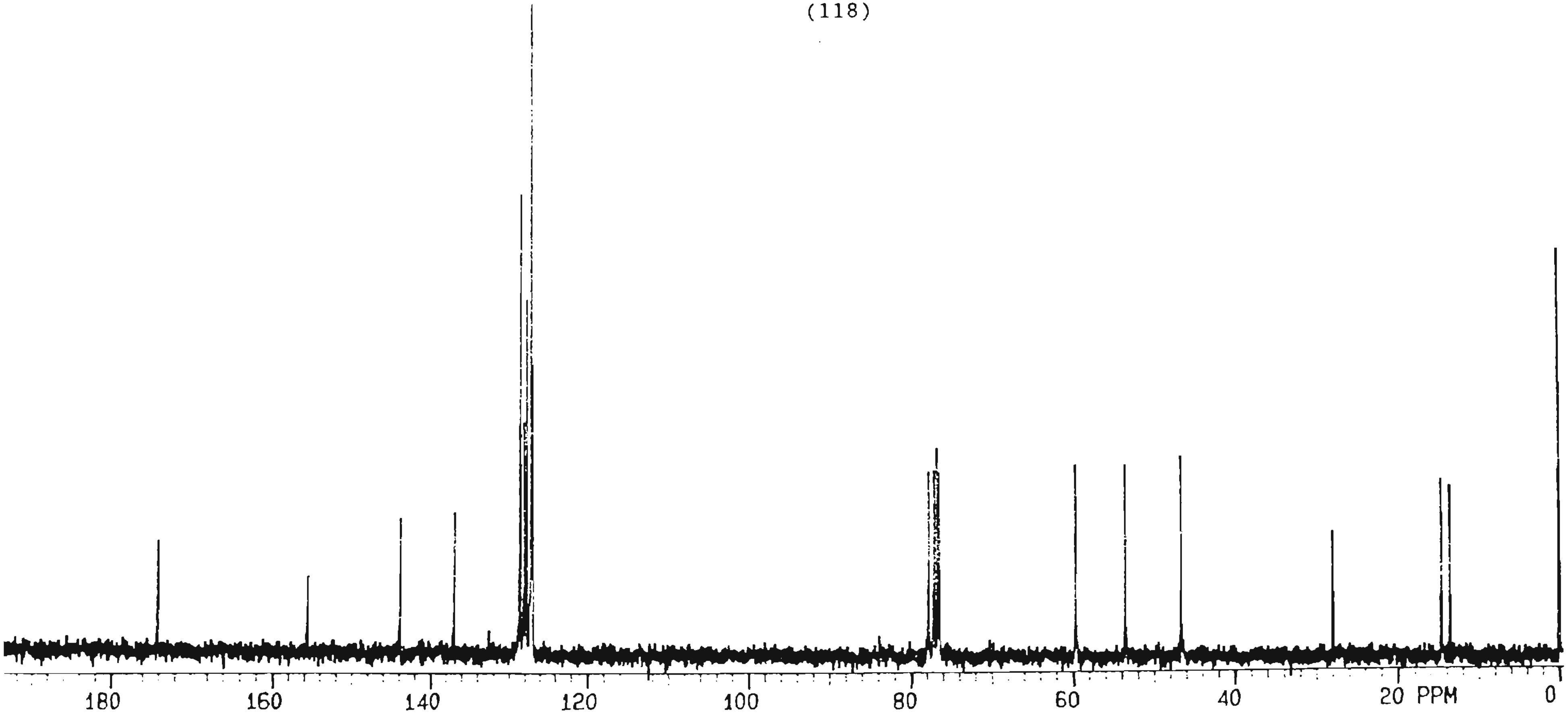


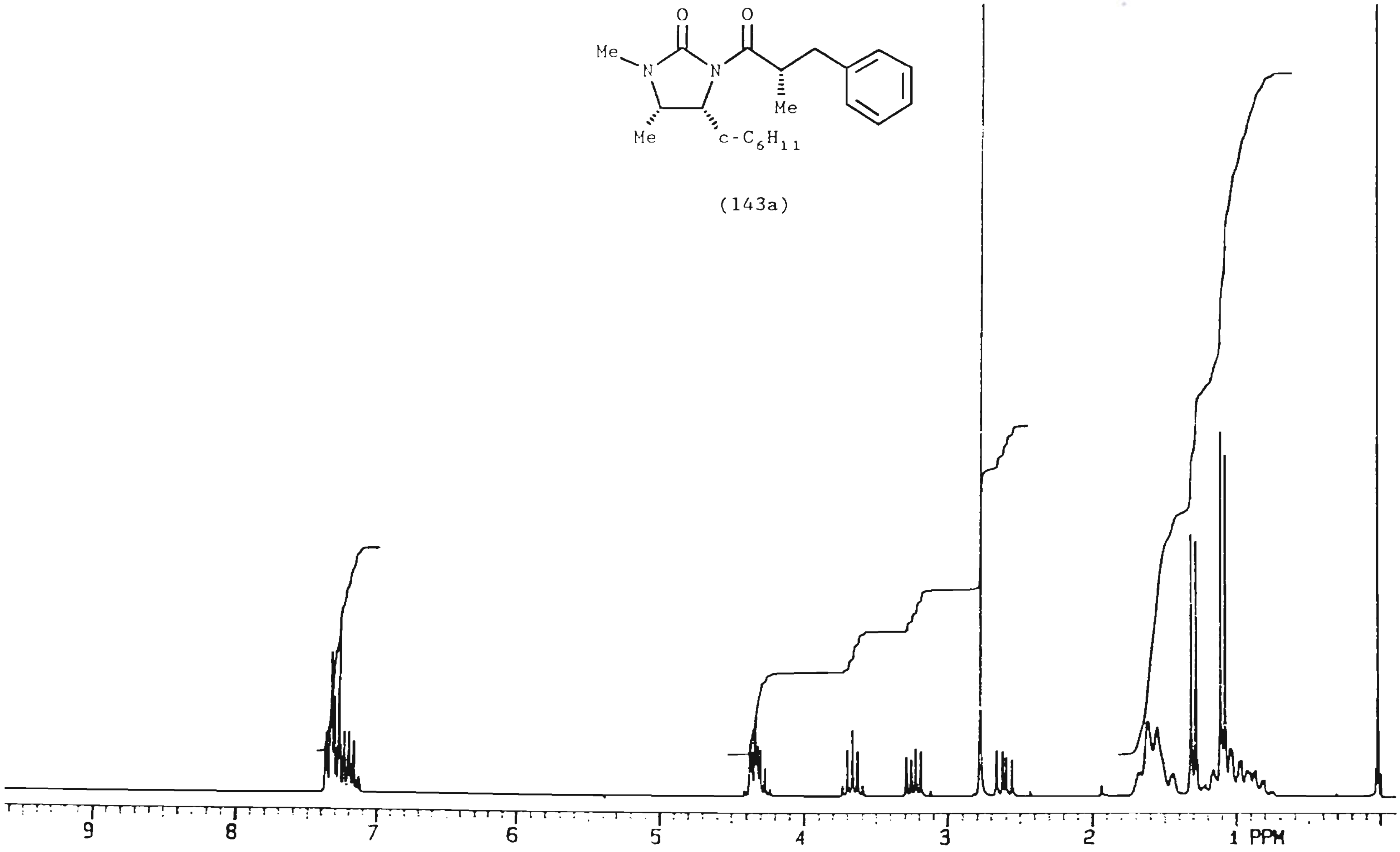


(118)

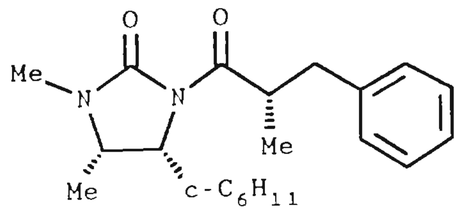


(118)

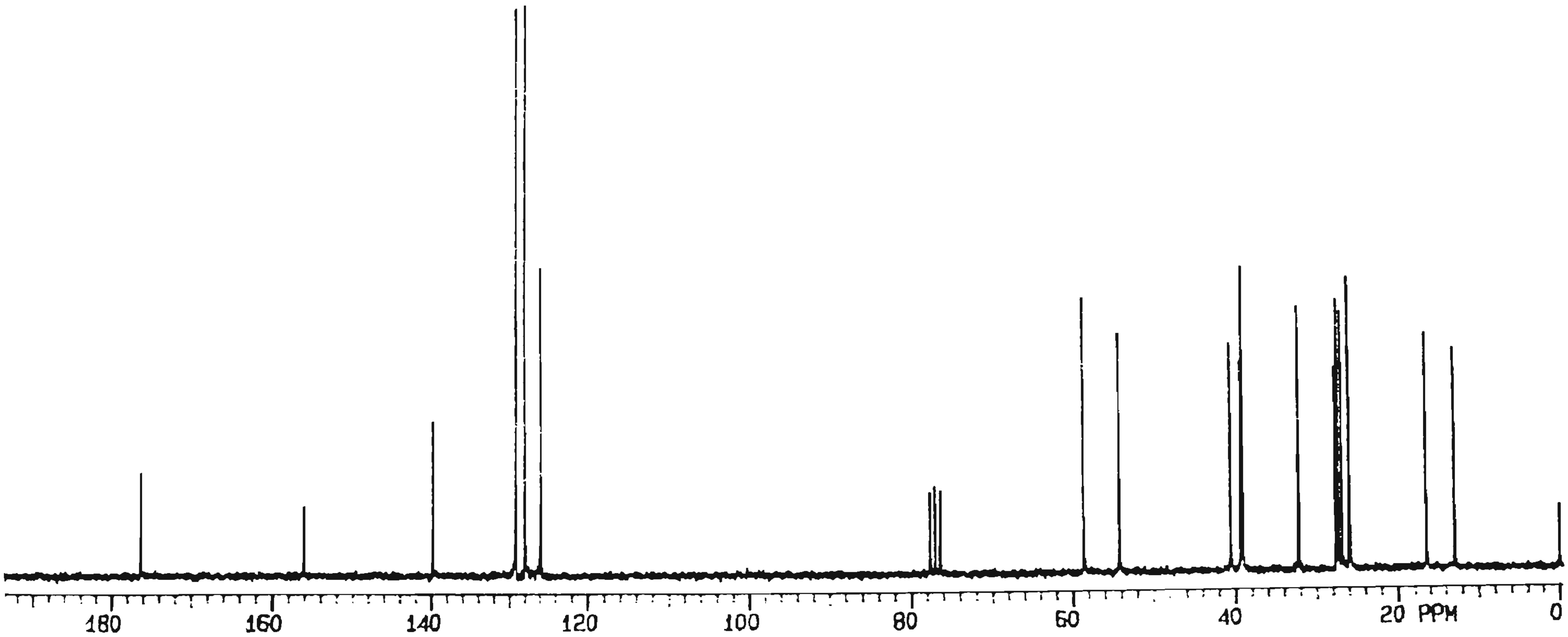


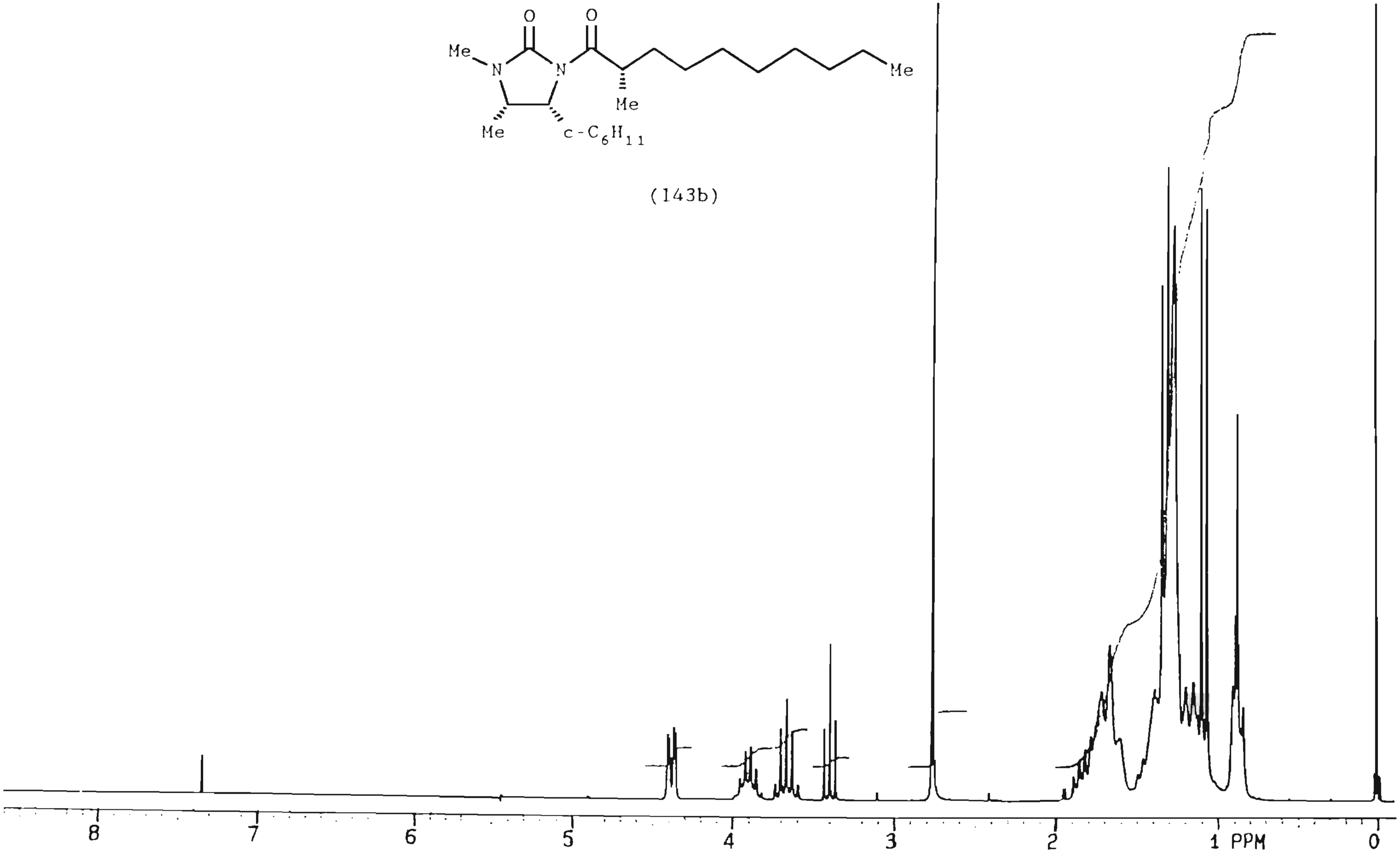


(143a)

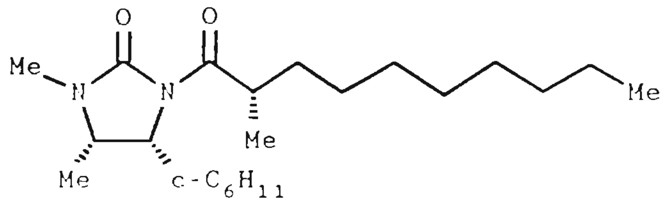


(143a)

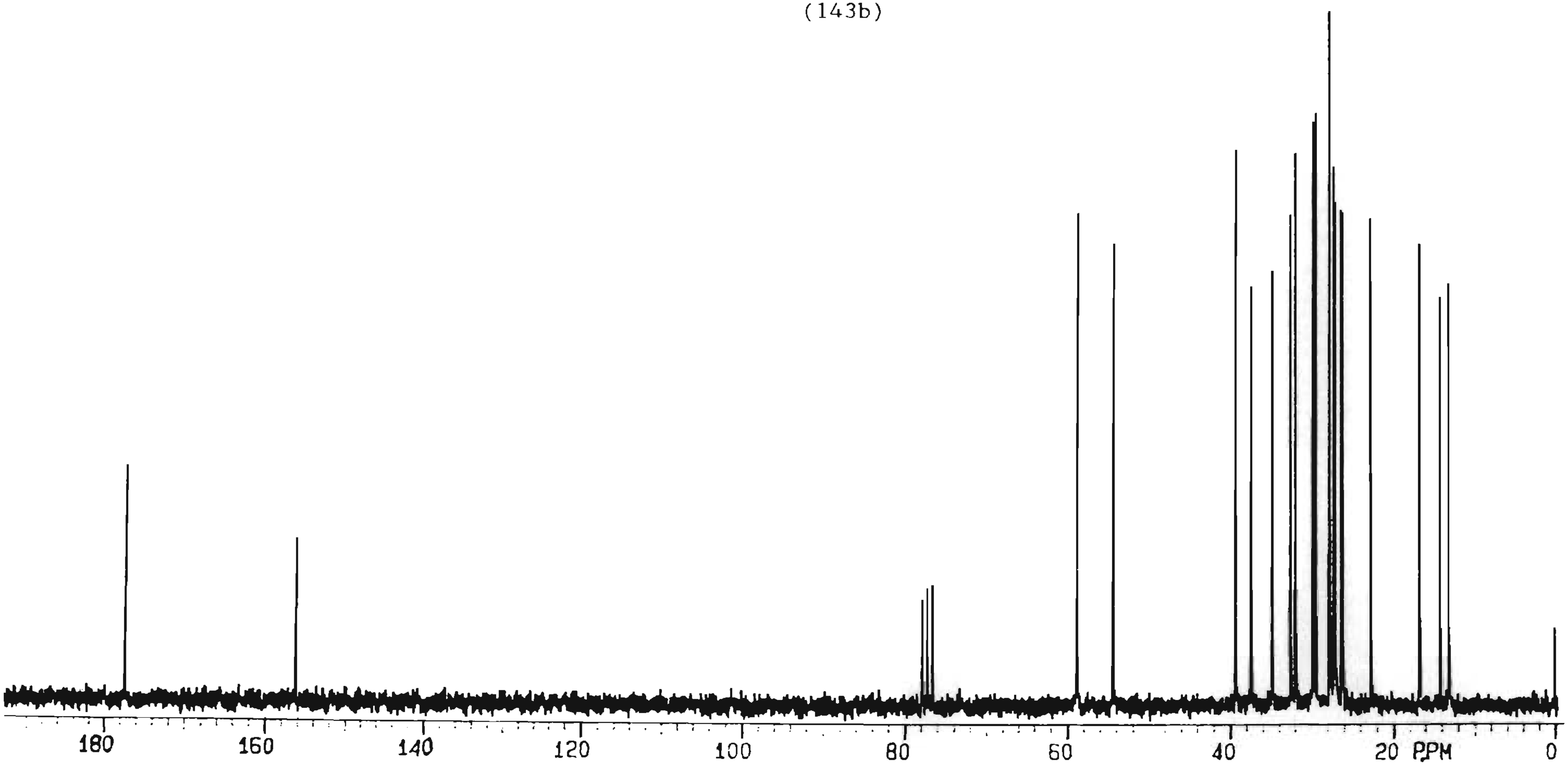


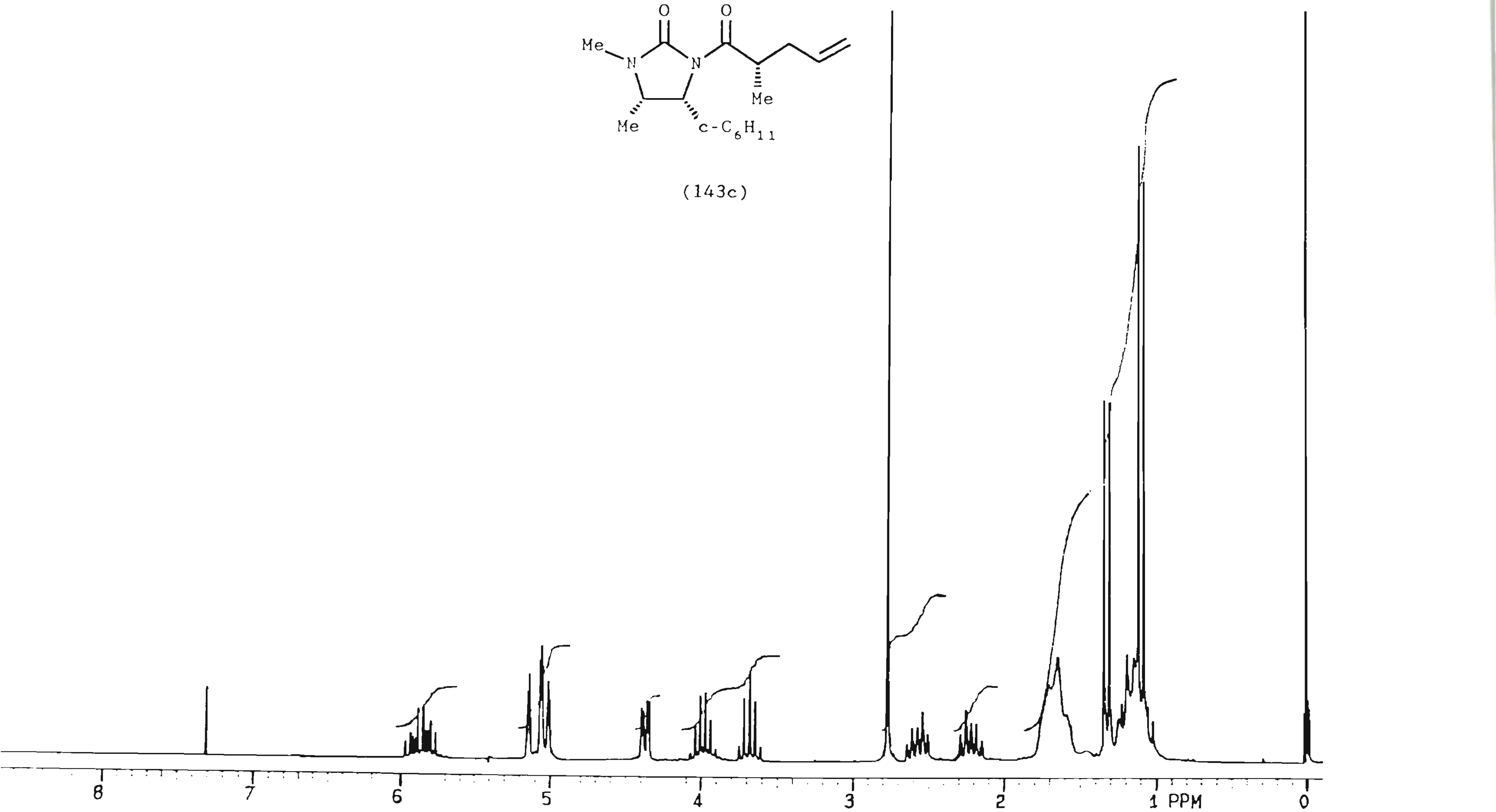


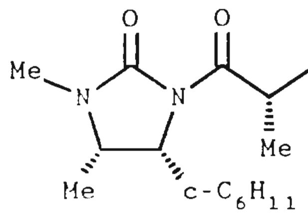
(143b)



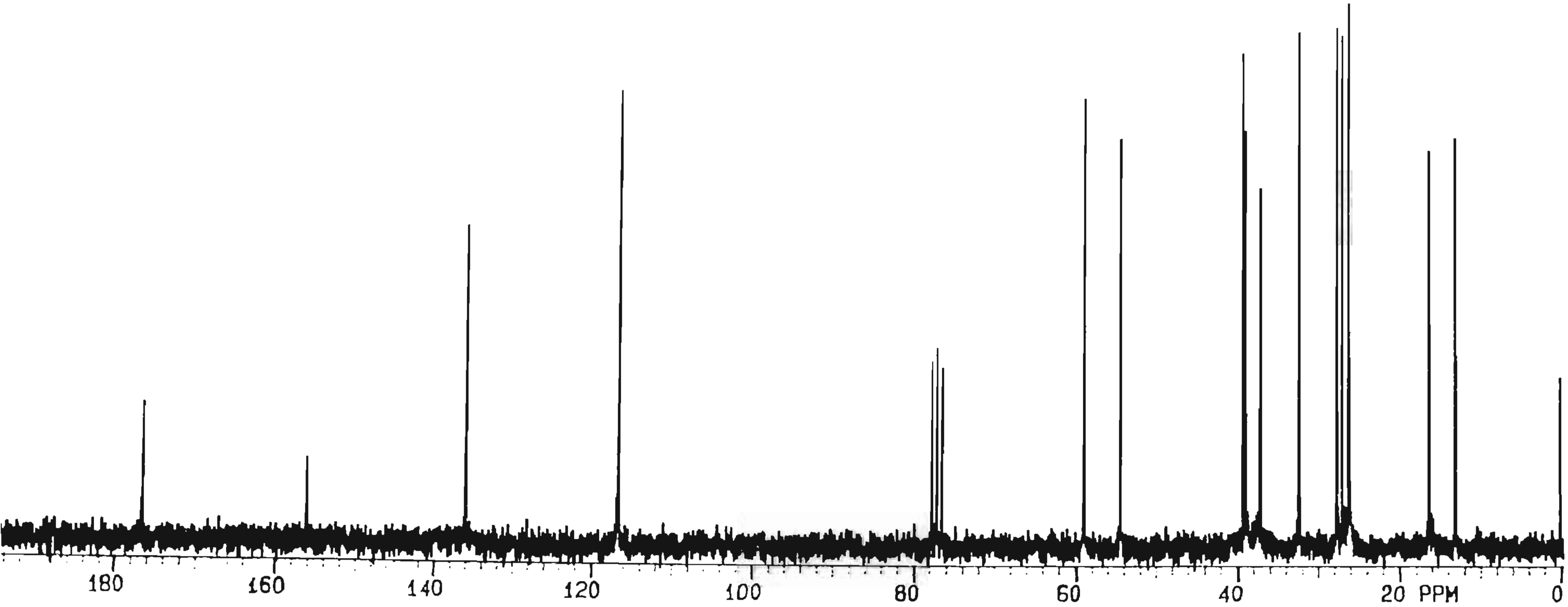
(143b)

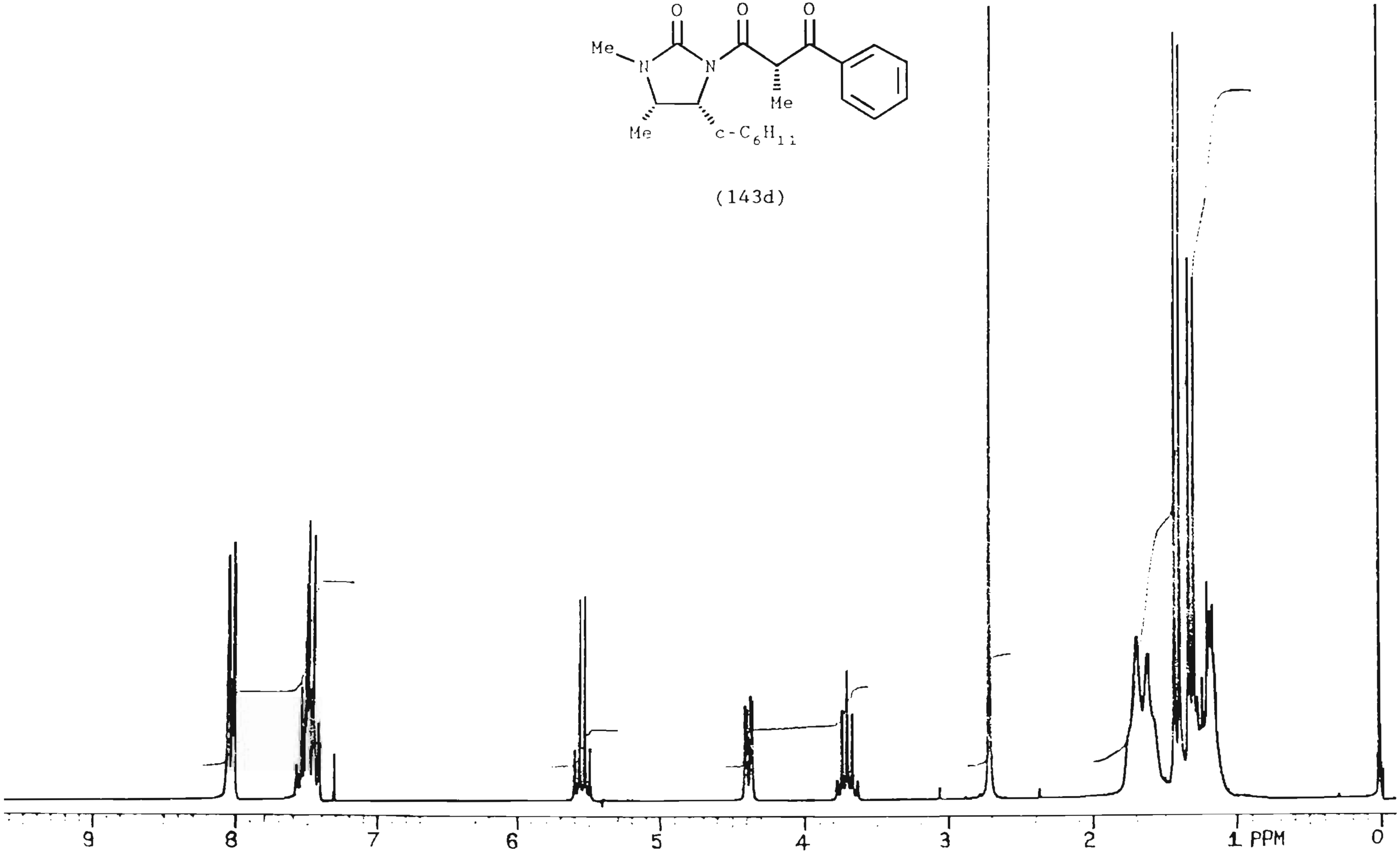



(143c)

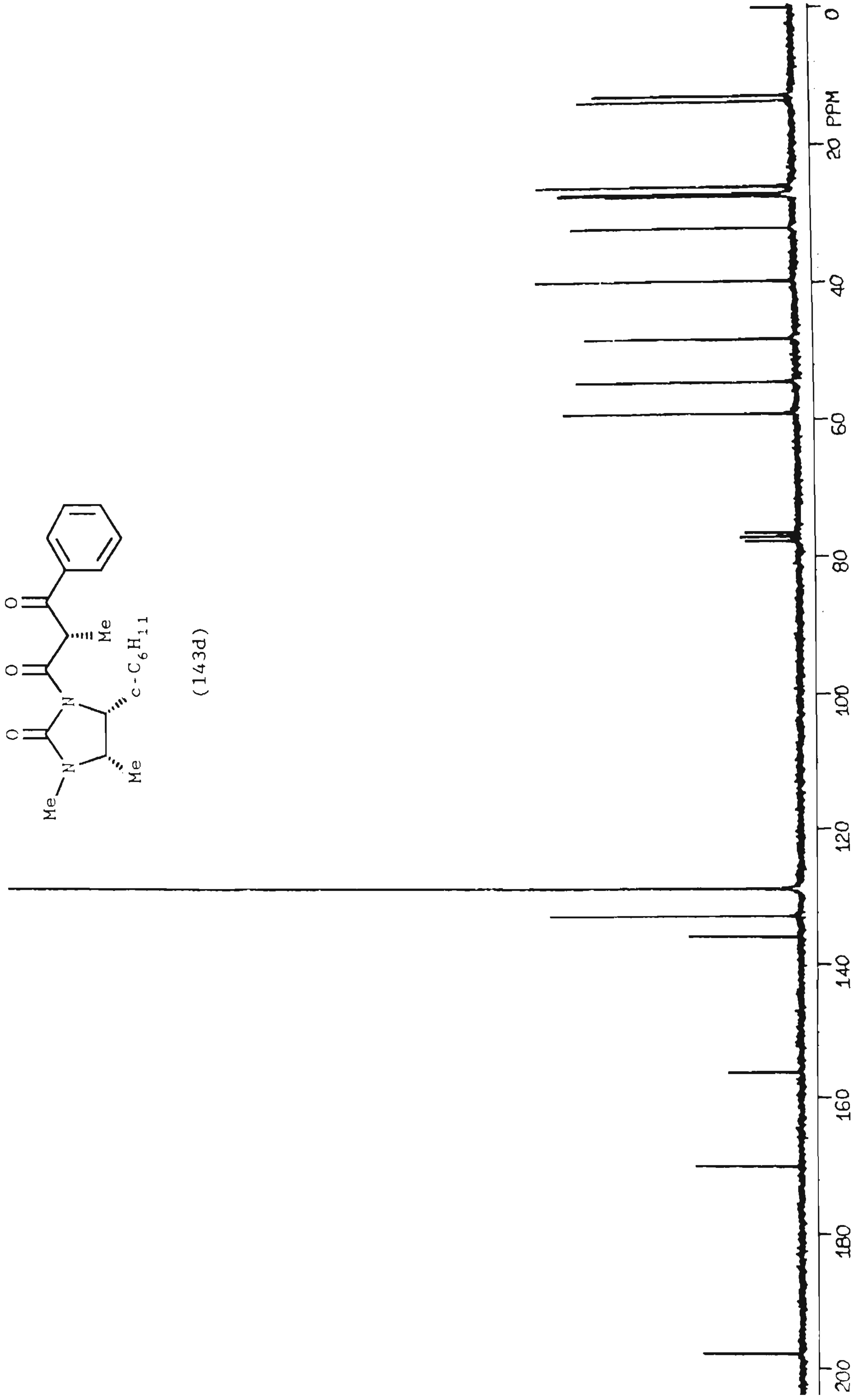


(143c)

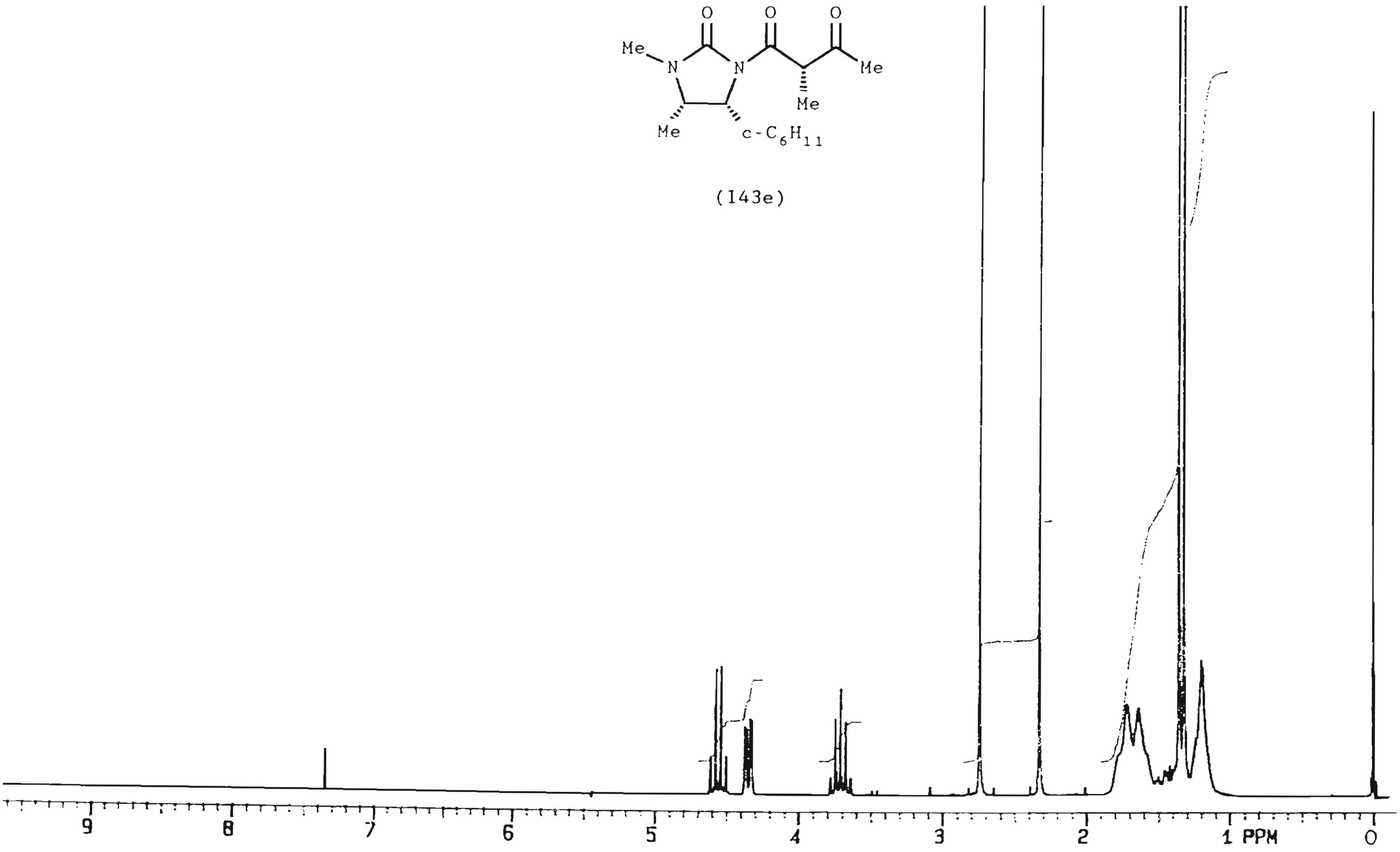




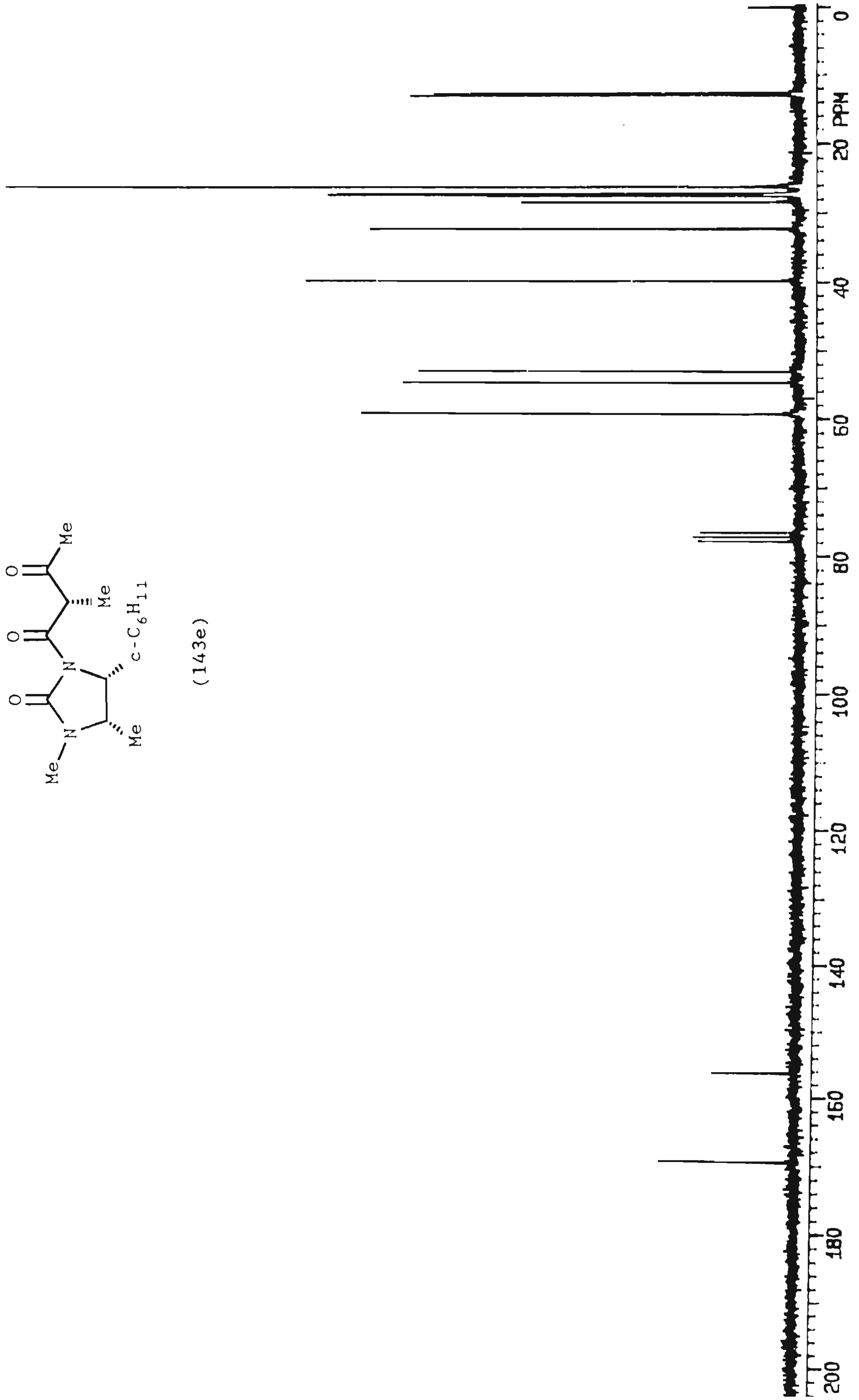
(143d)



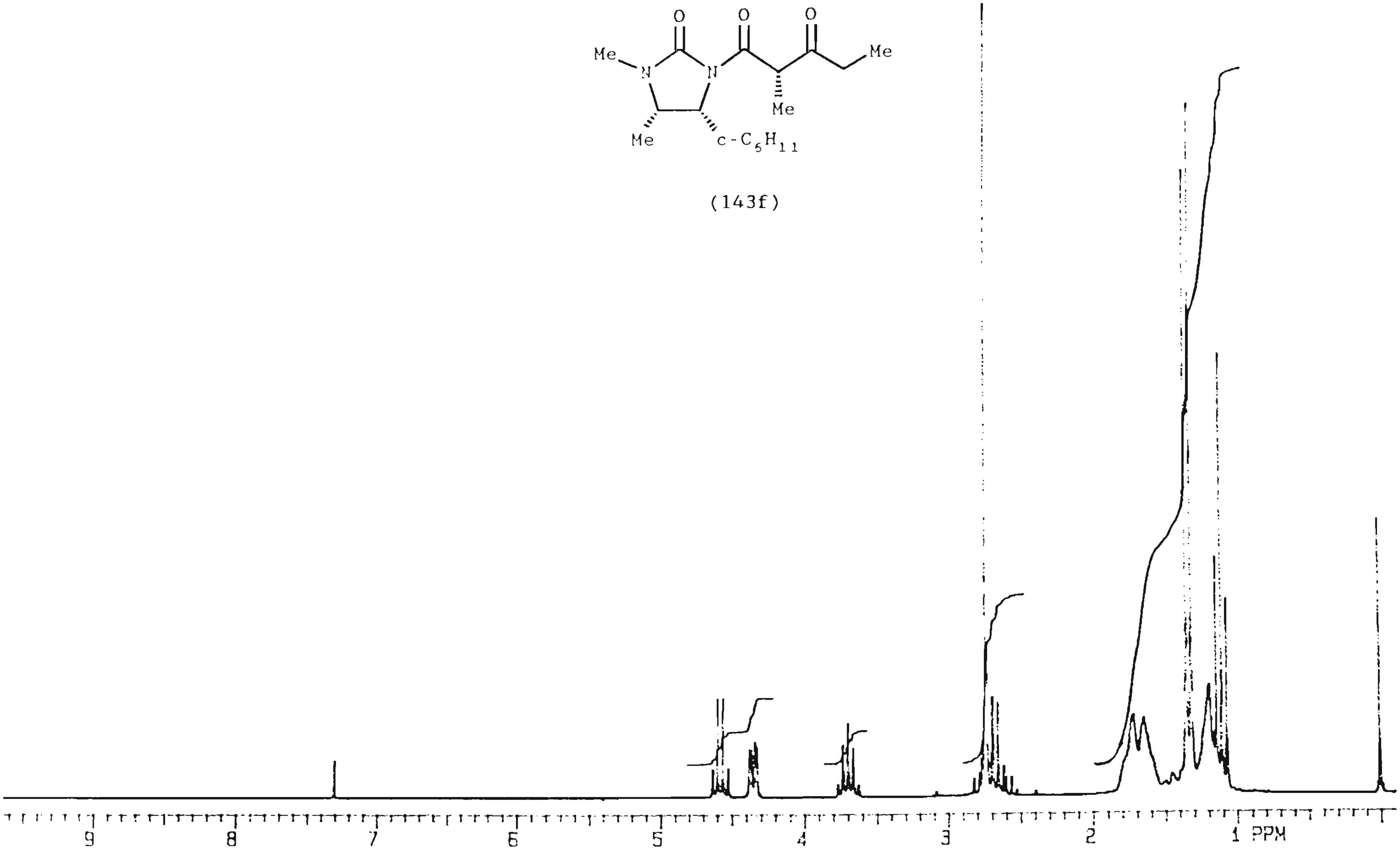
(143d)



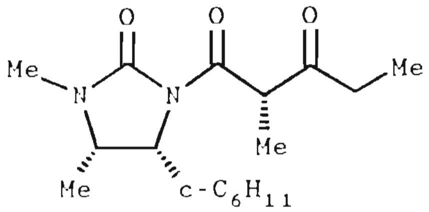
(143e)



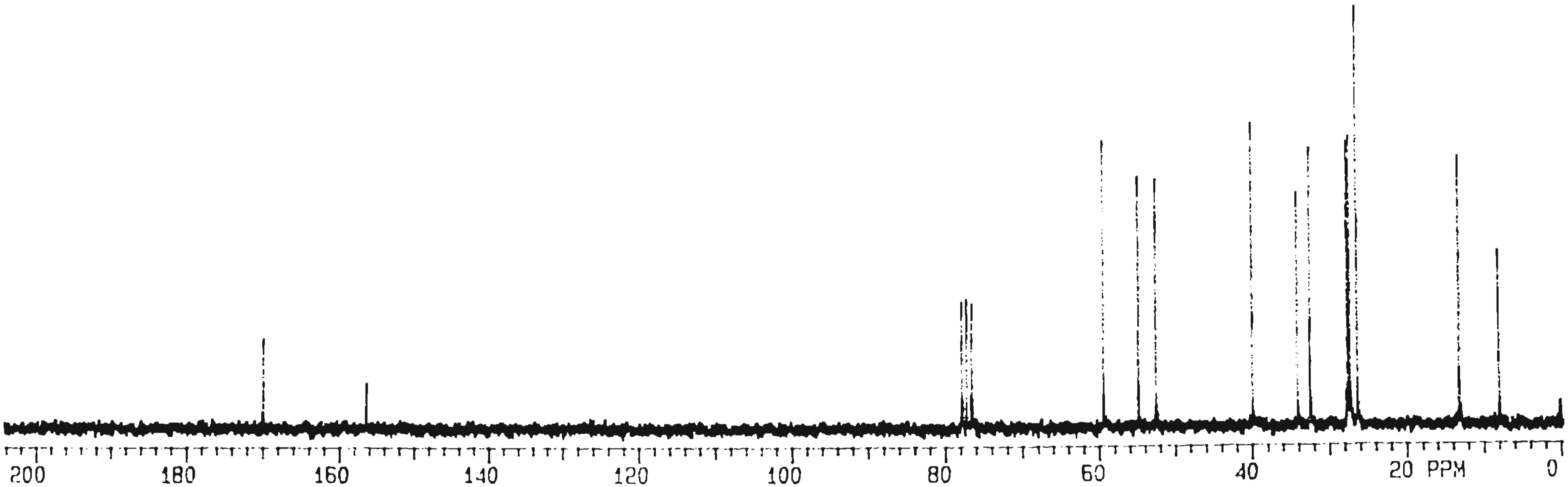
(143e)

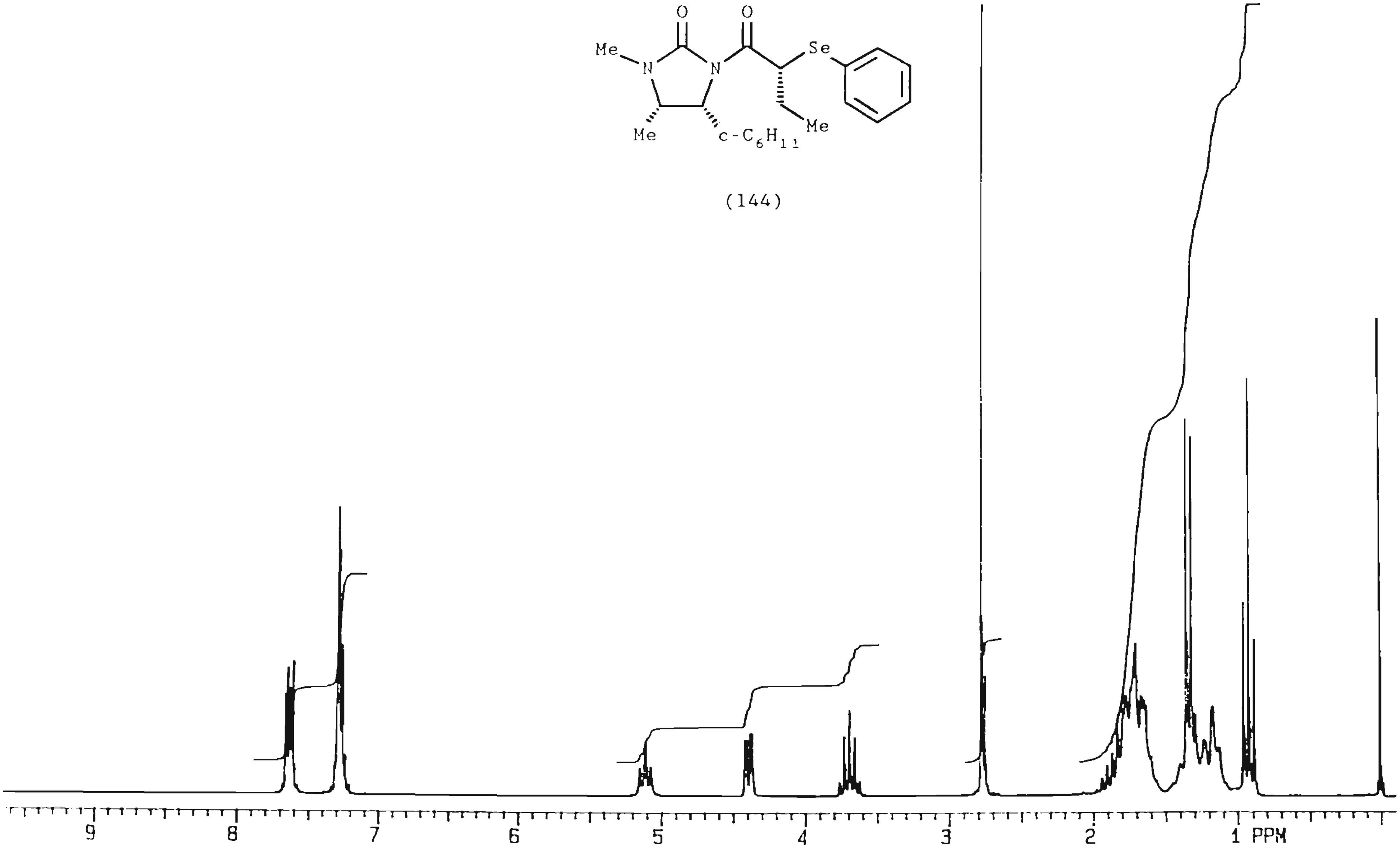


(143f)

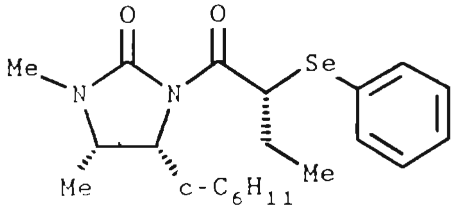


(143f)

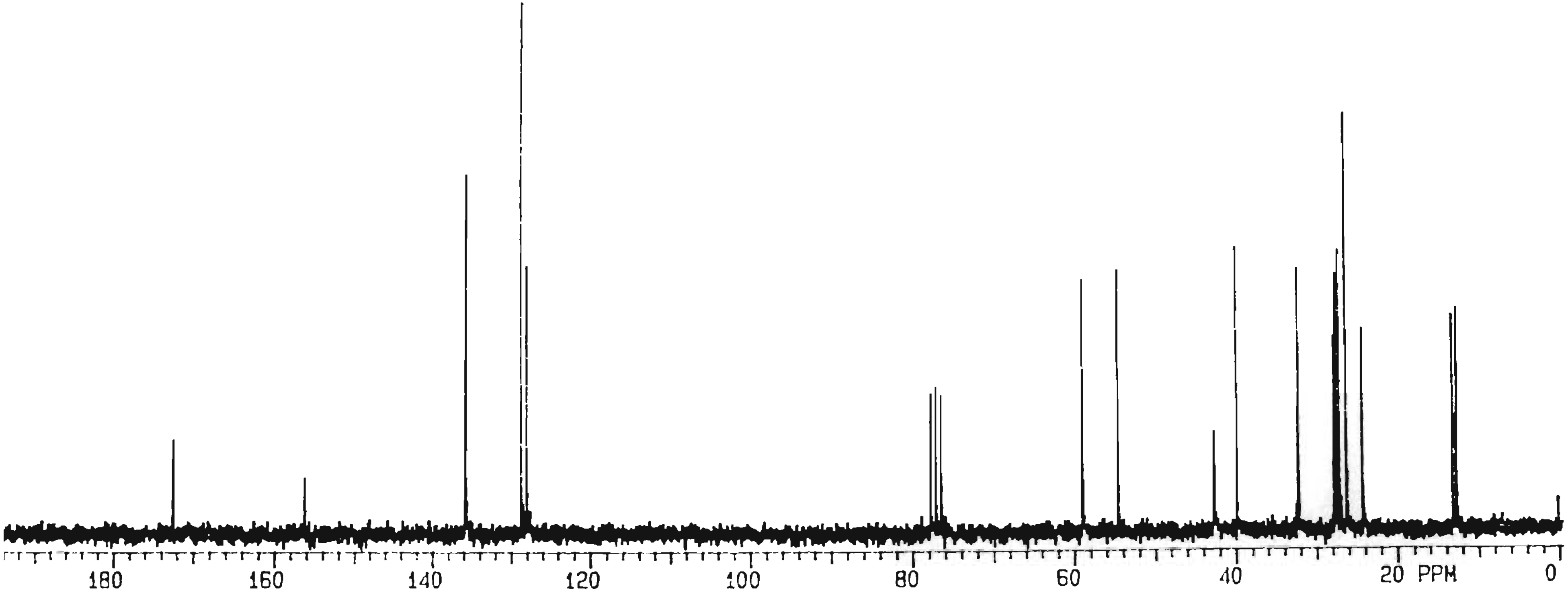


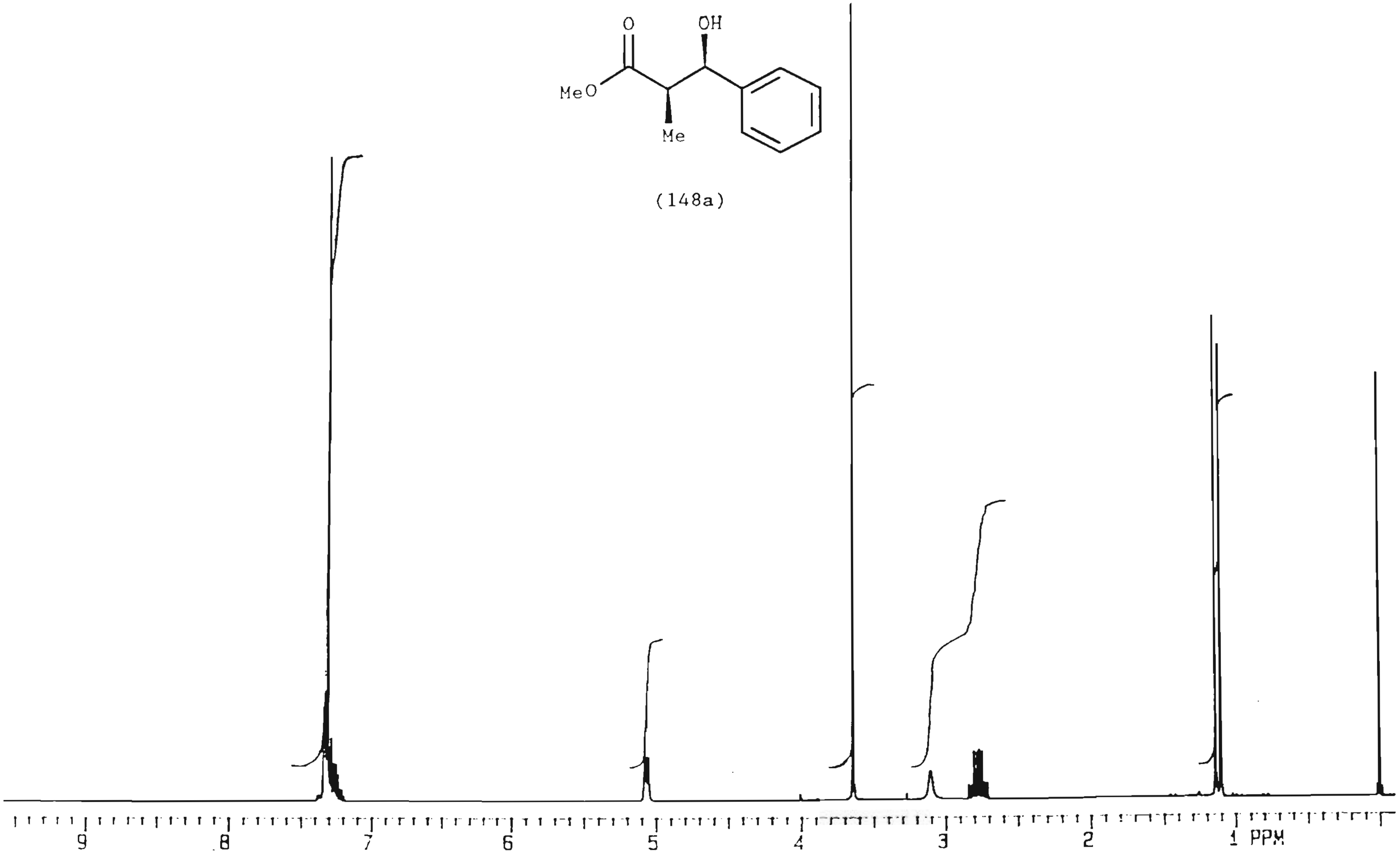


(144)

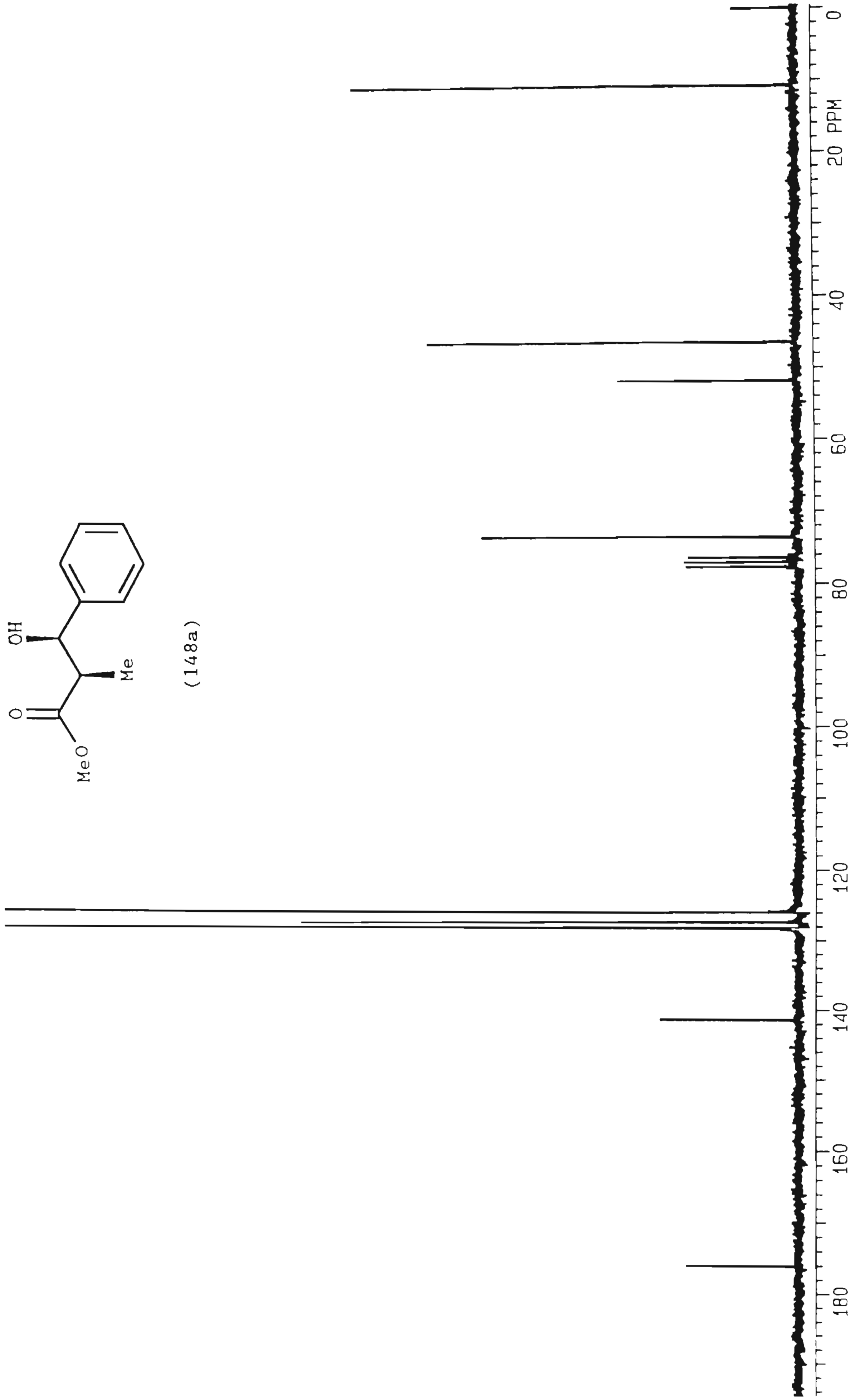


(144)

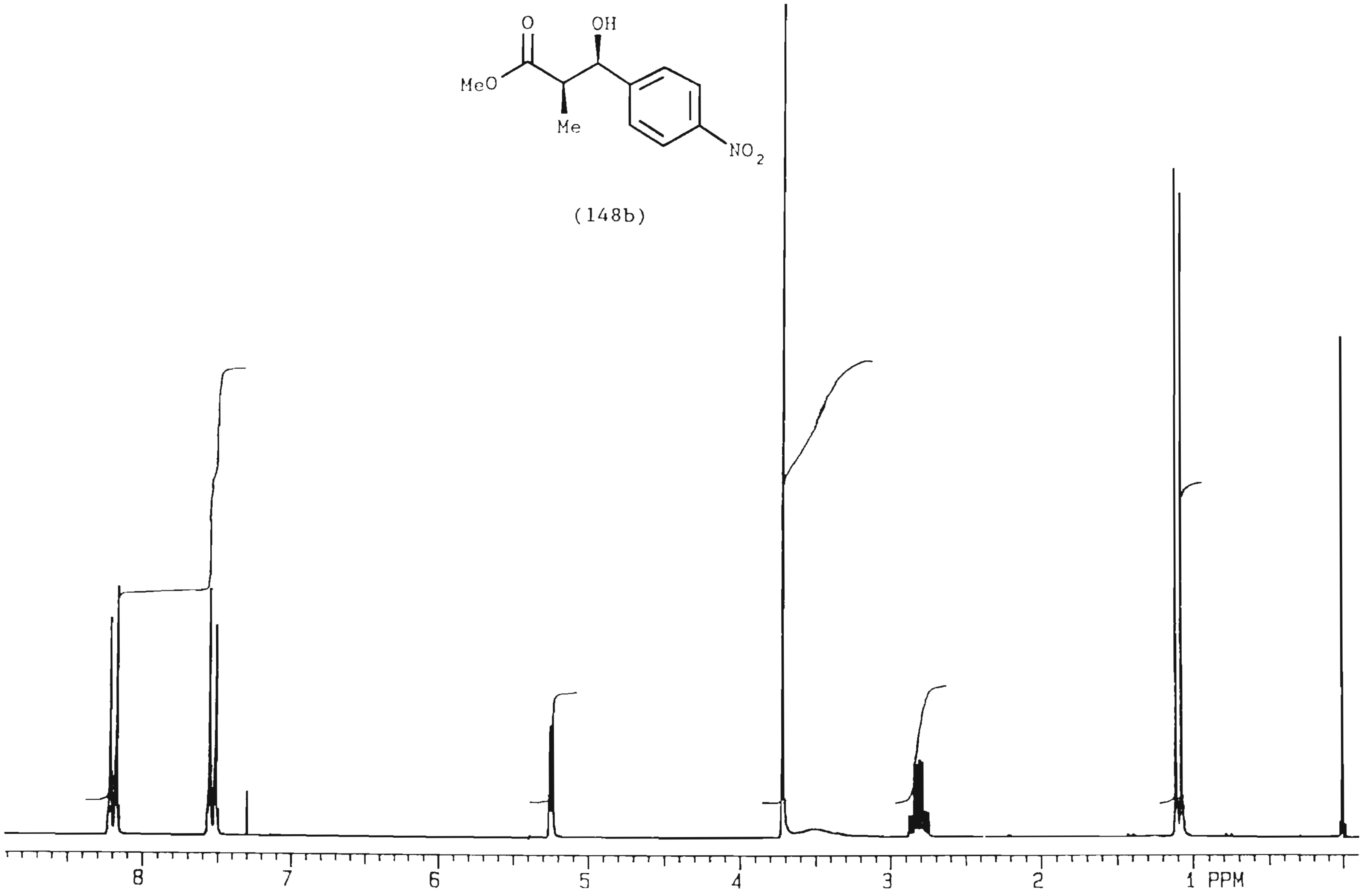




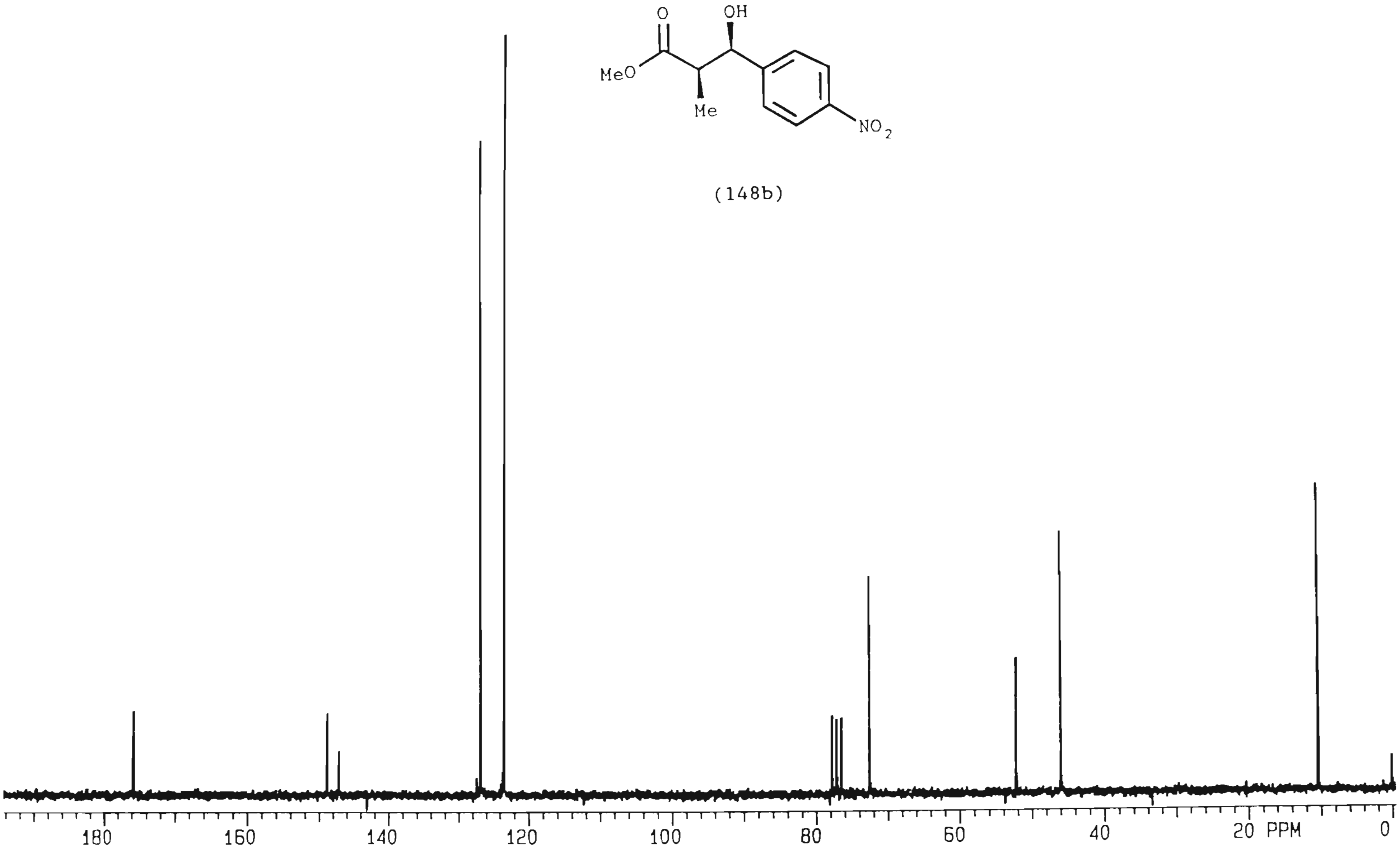
(148a)



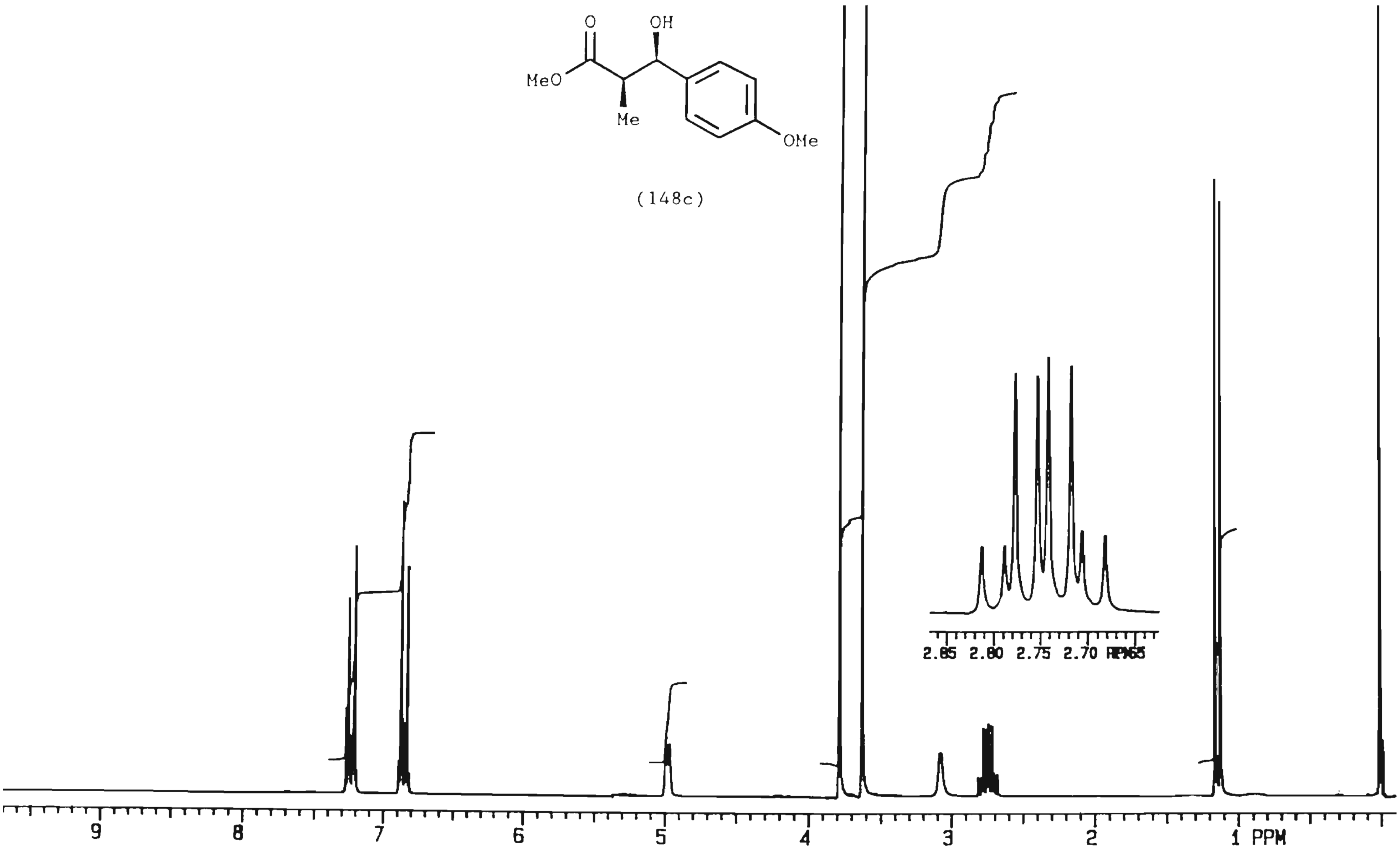
(148a)



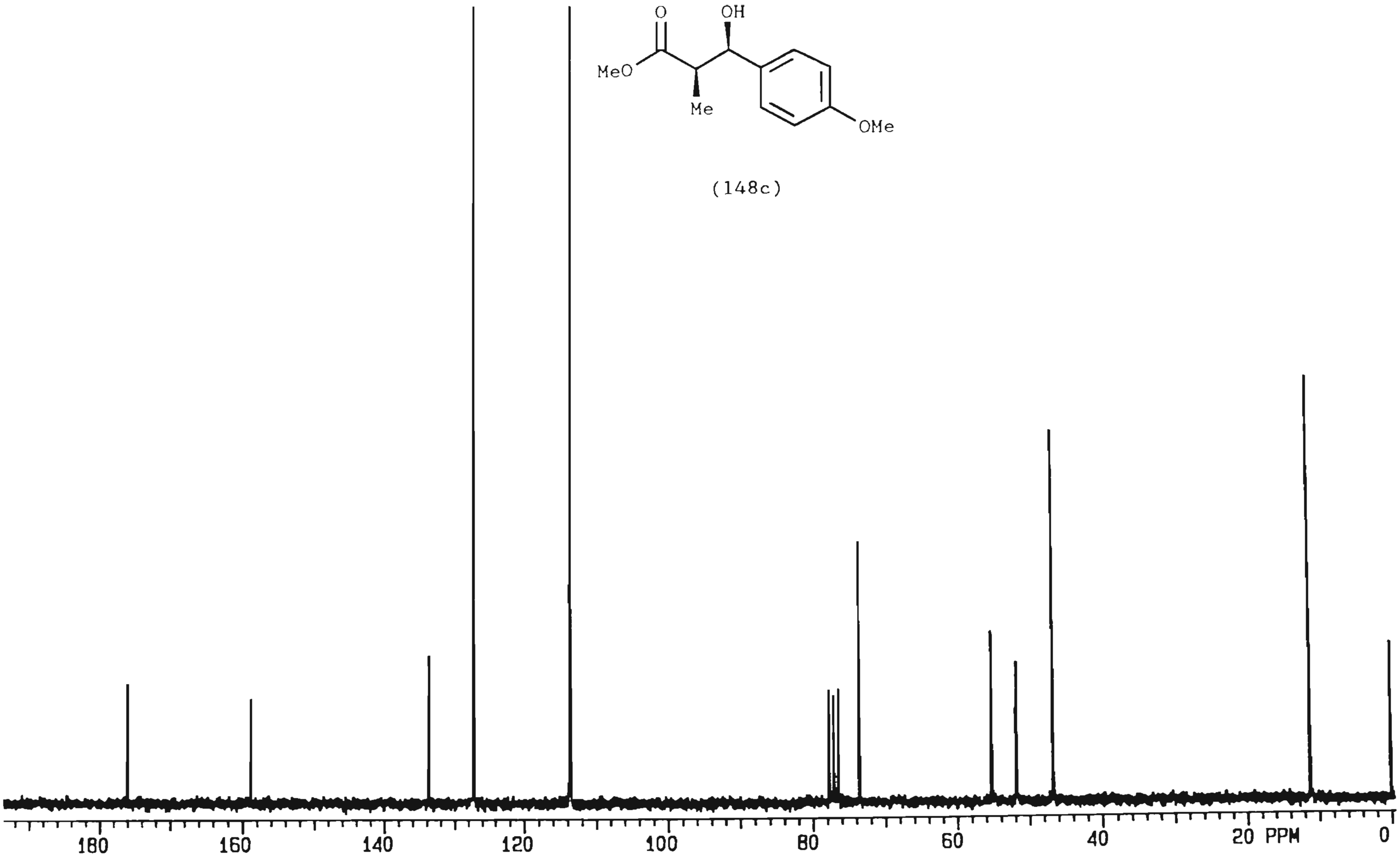
(148b)



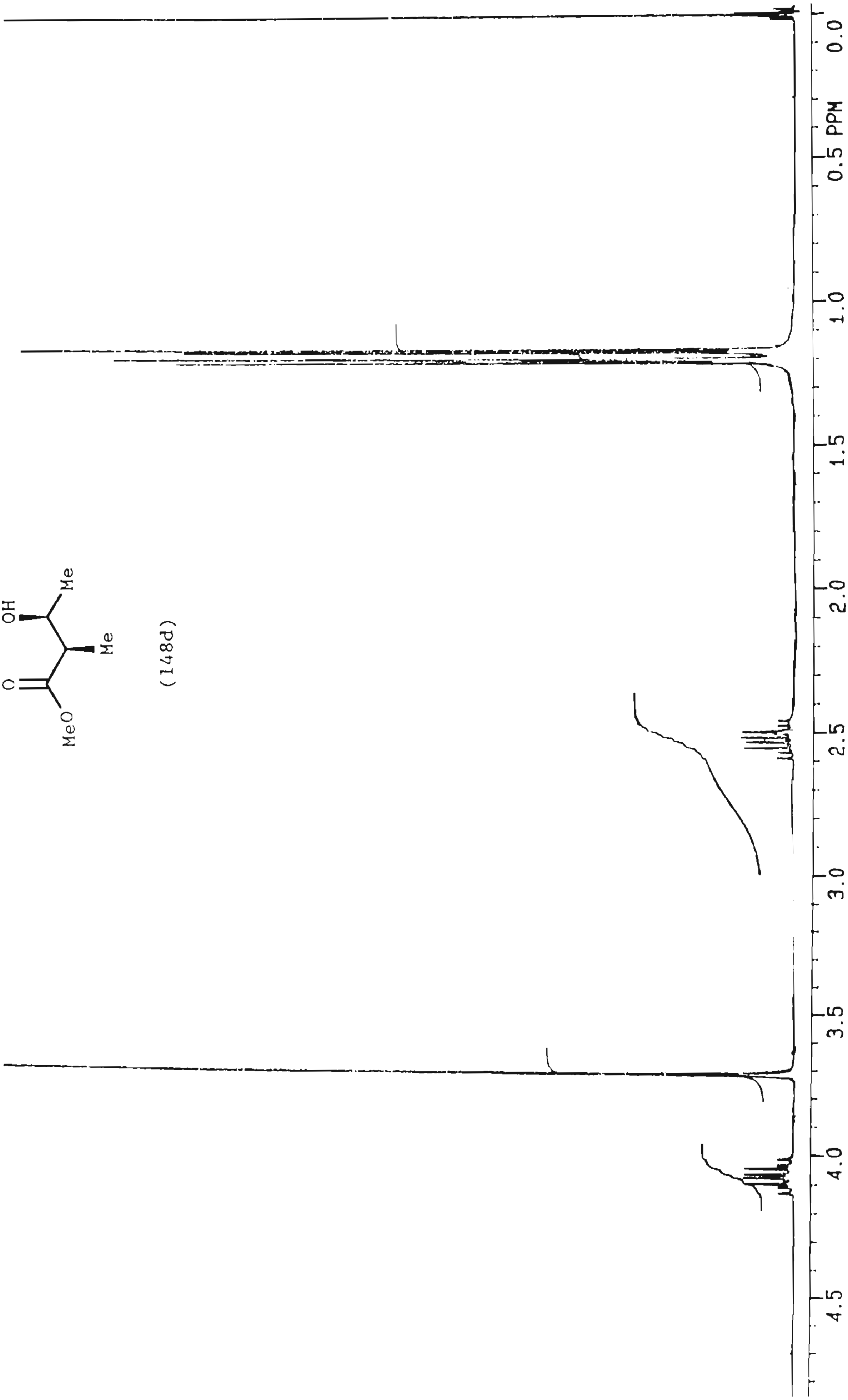
(148b)



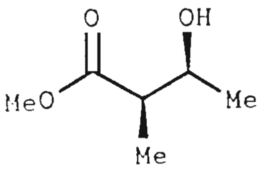
(148c)



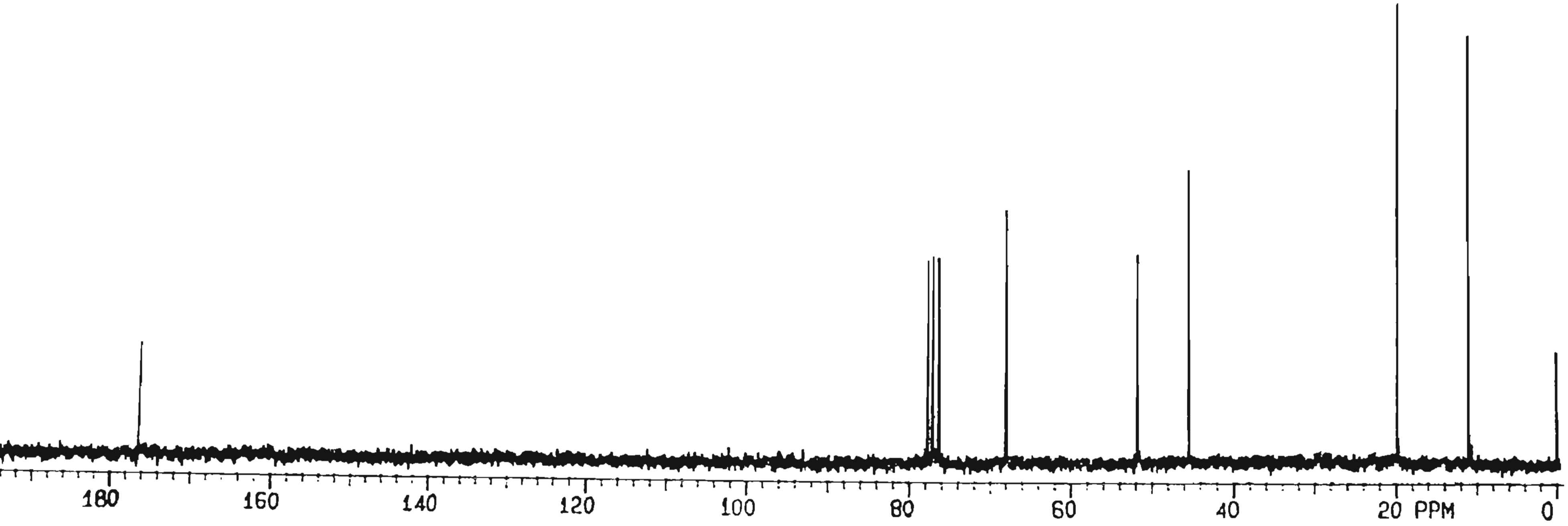
(148c)

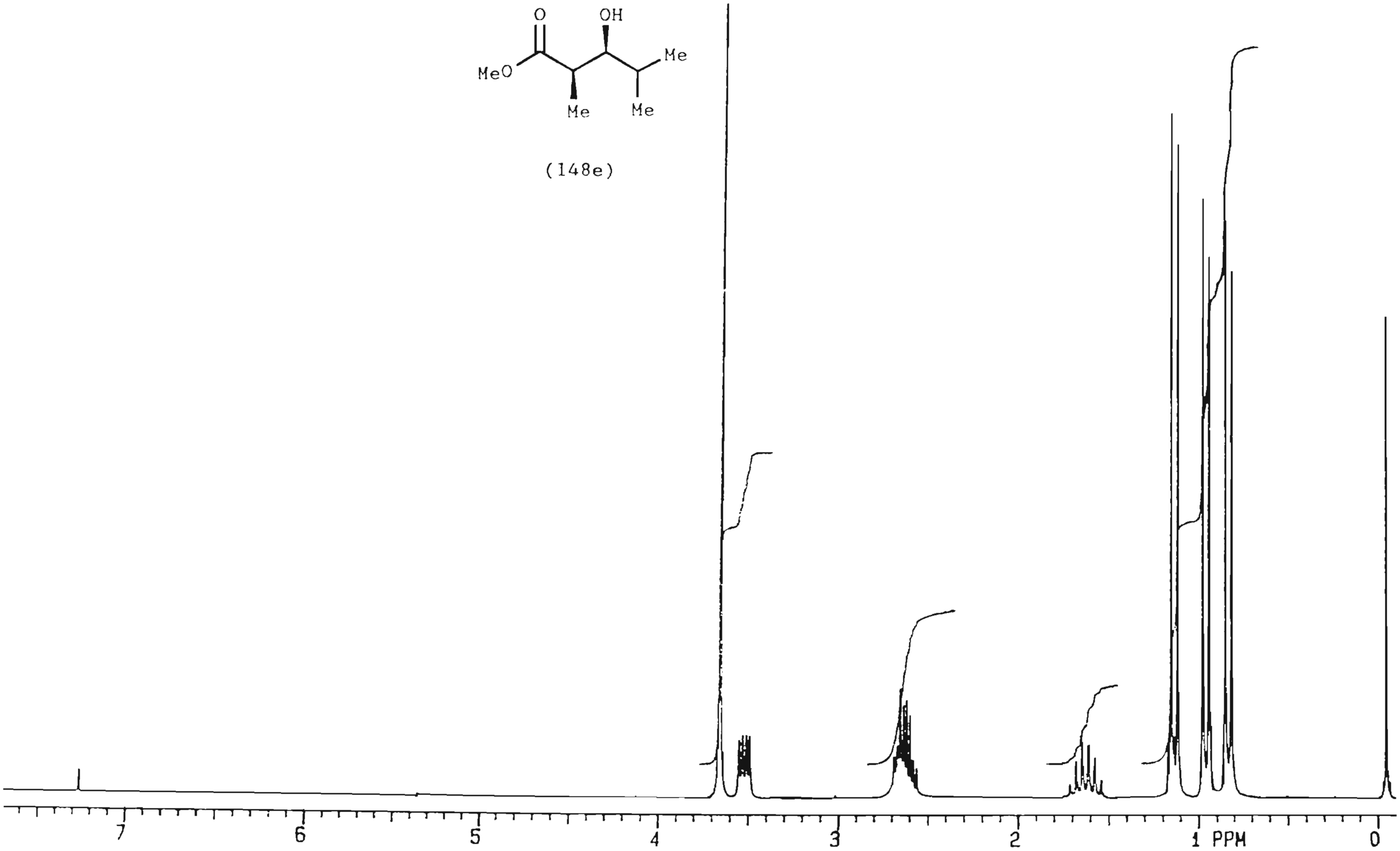


(148d)

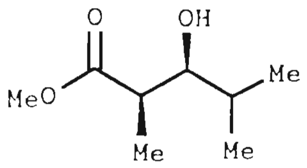


(148d)

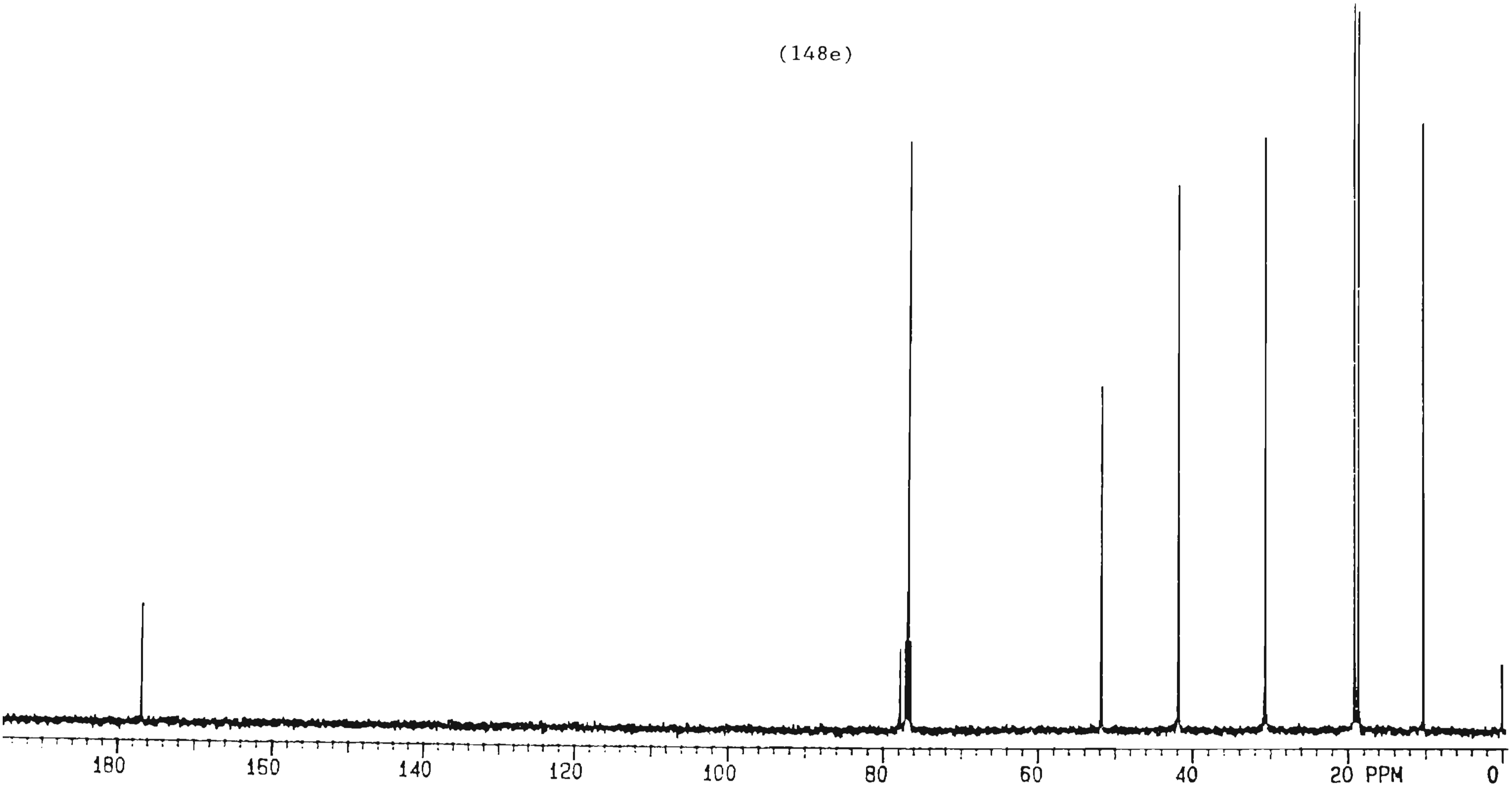


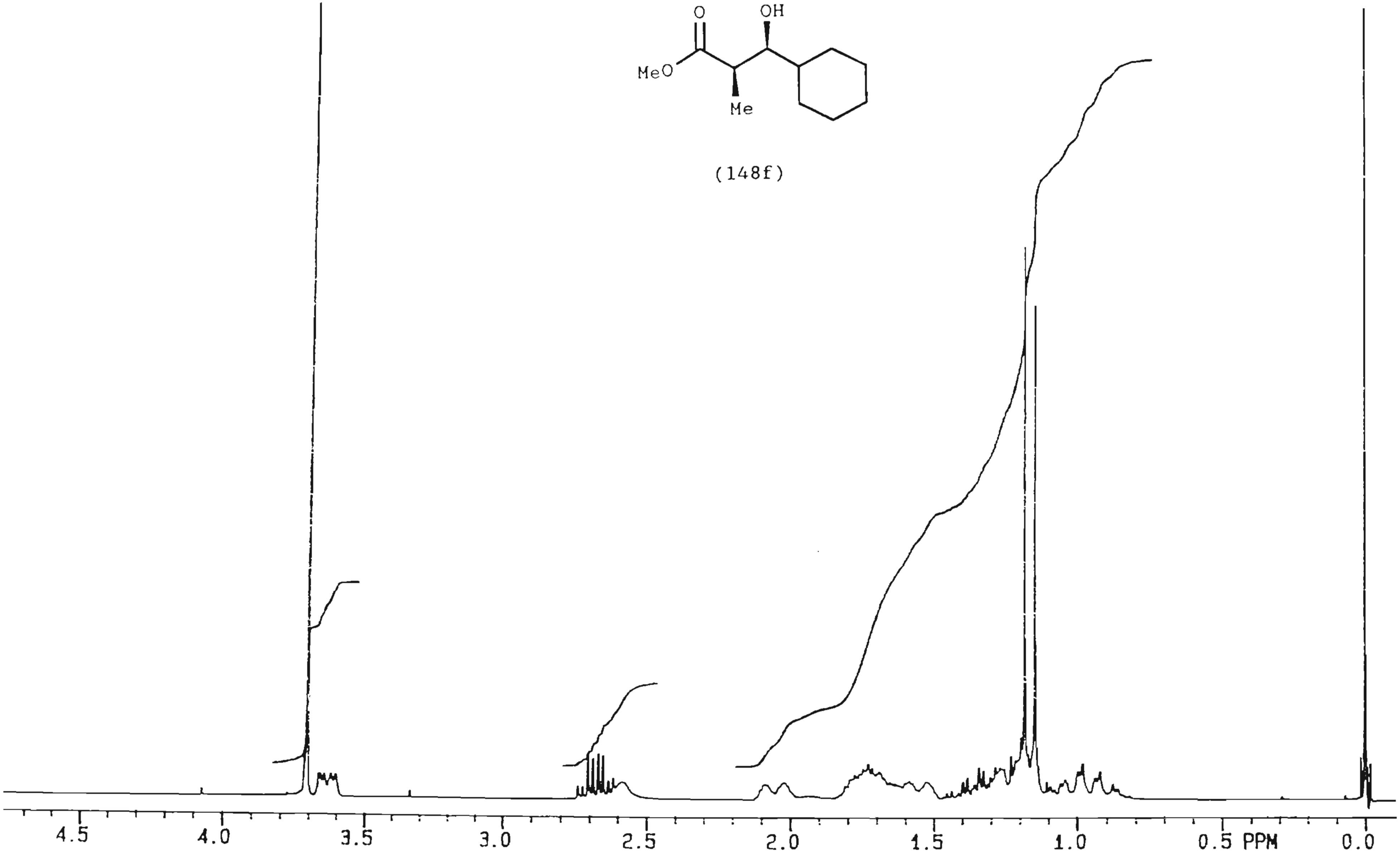


(148e)

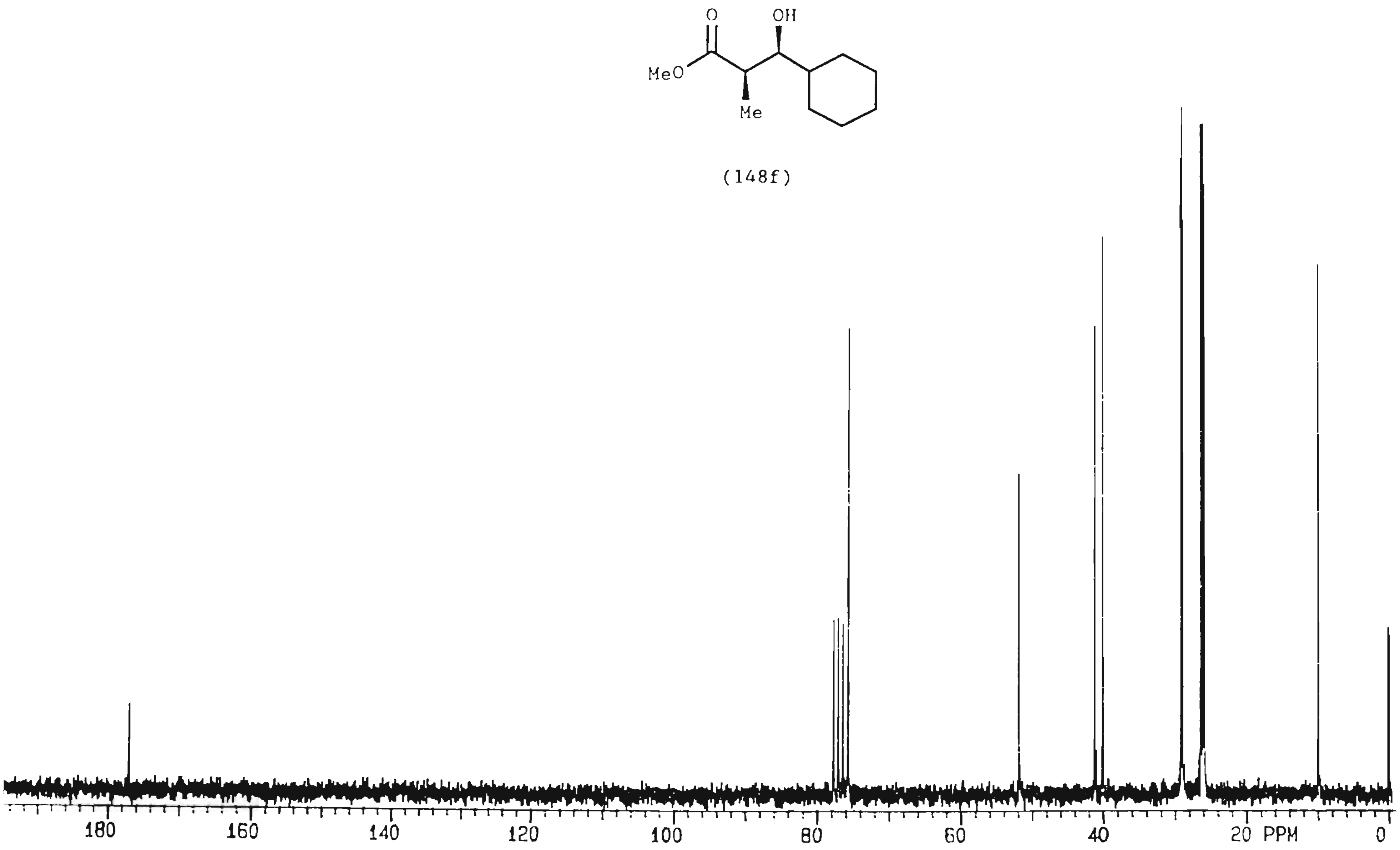


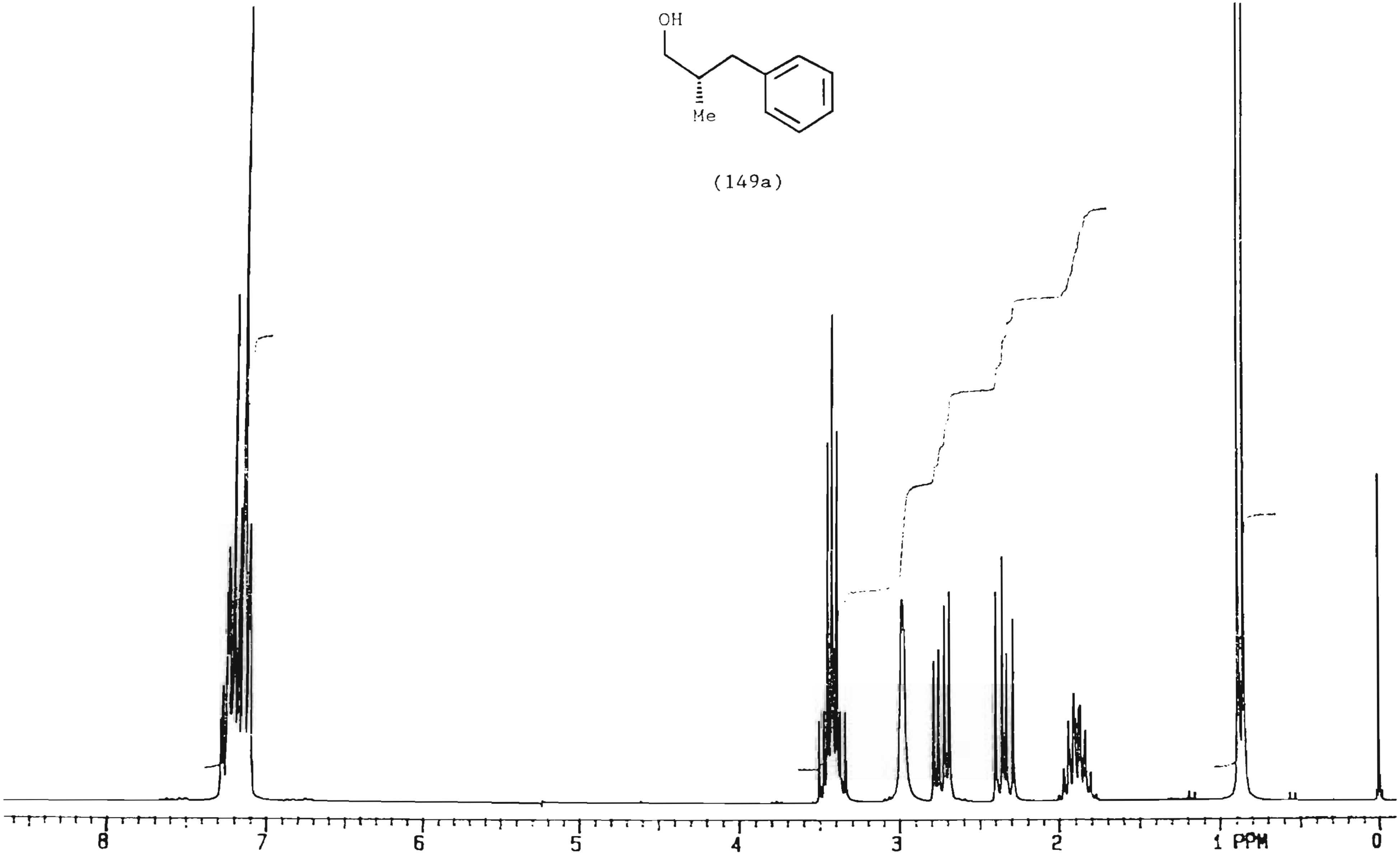
(148e)



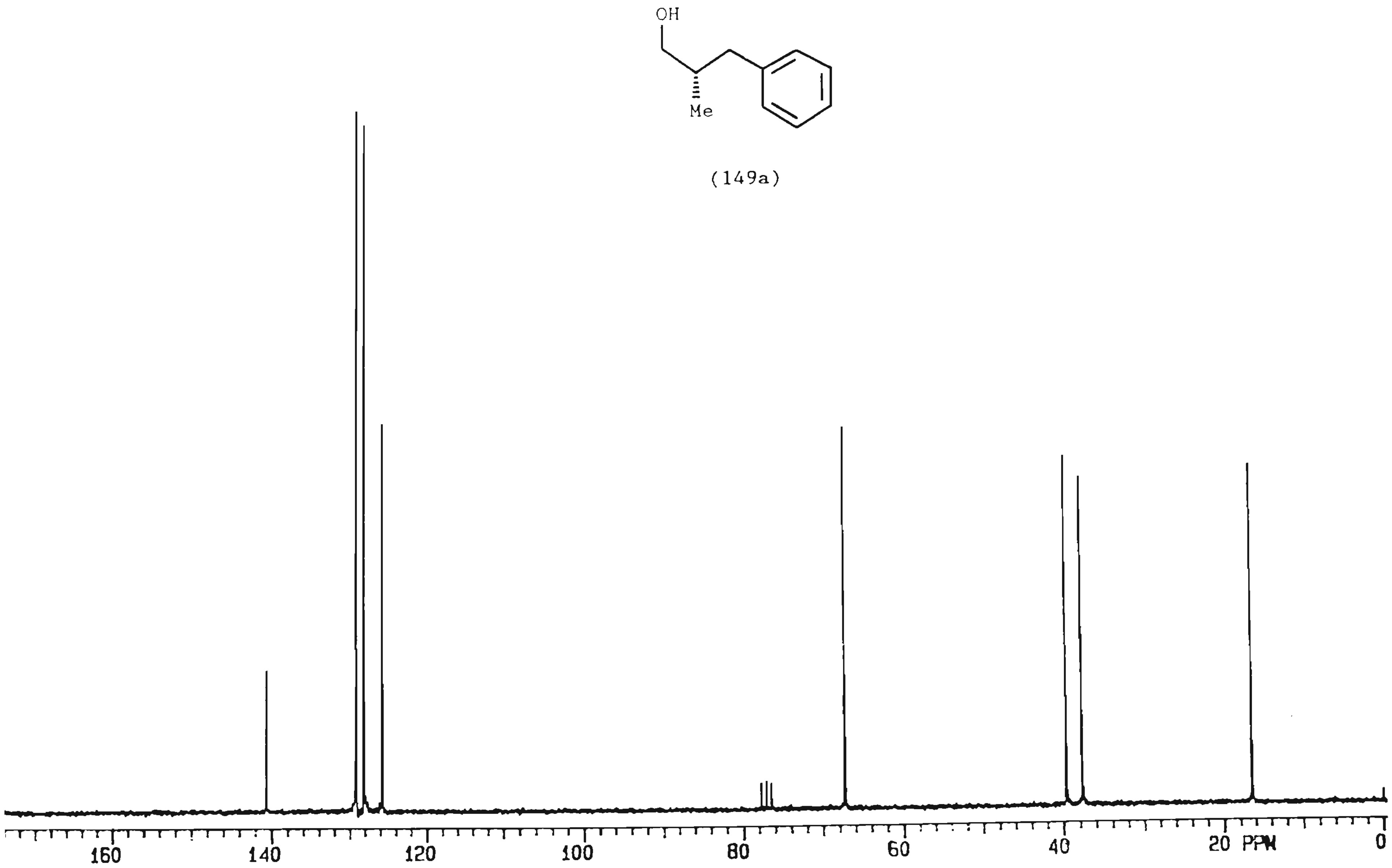


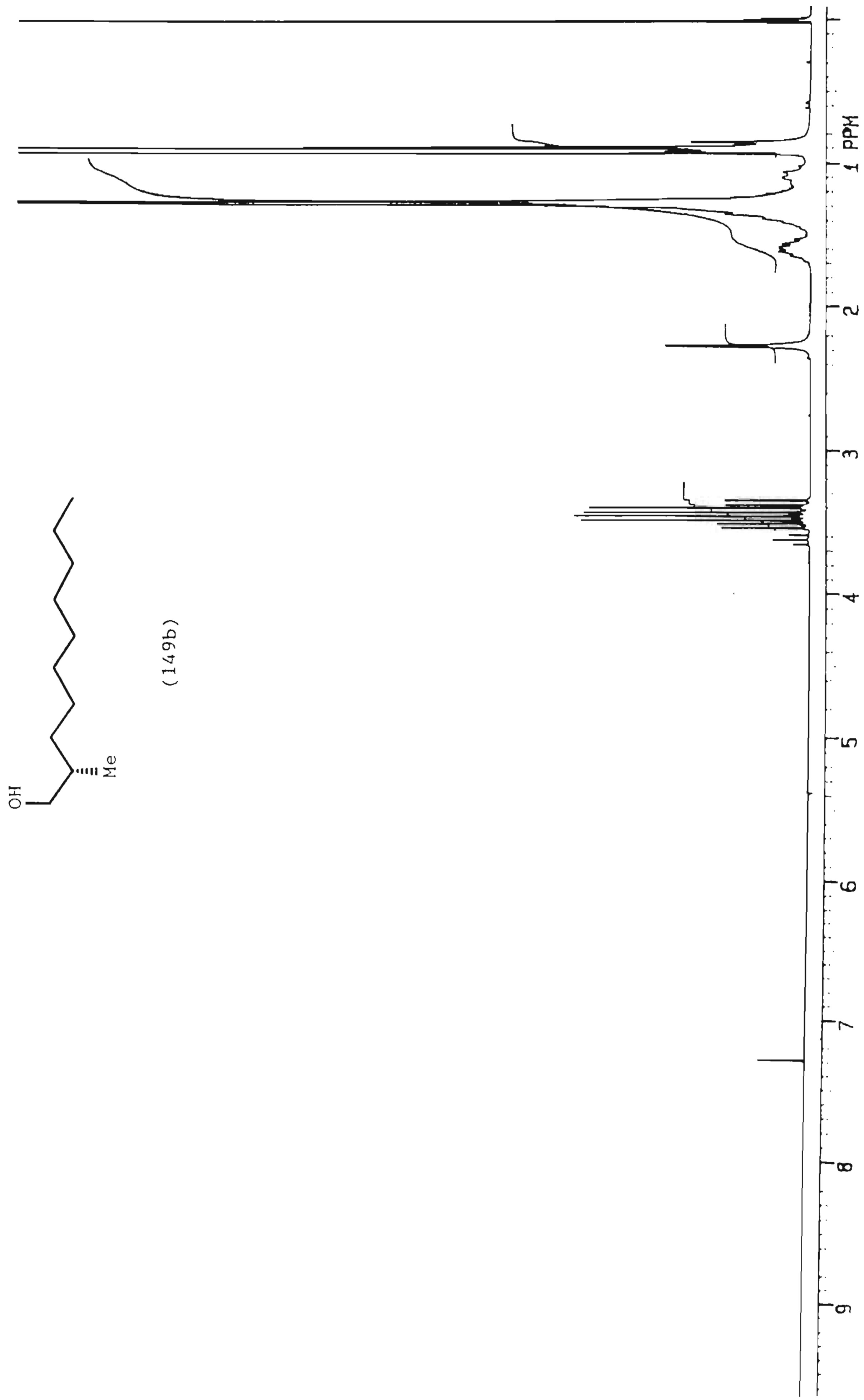
(148f)


O
OH
MeO
Me
(148f)
180
160
140
120
100
80
60
40
20 PPM
0

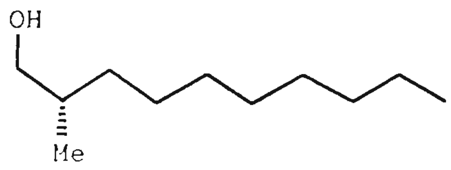


(149a)

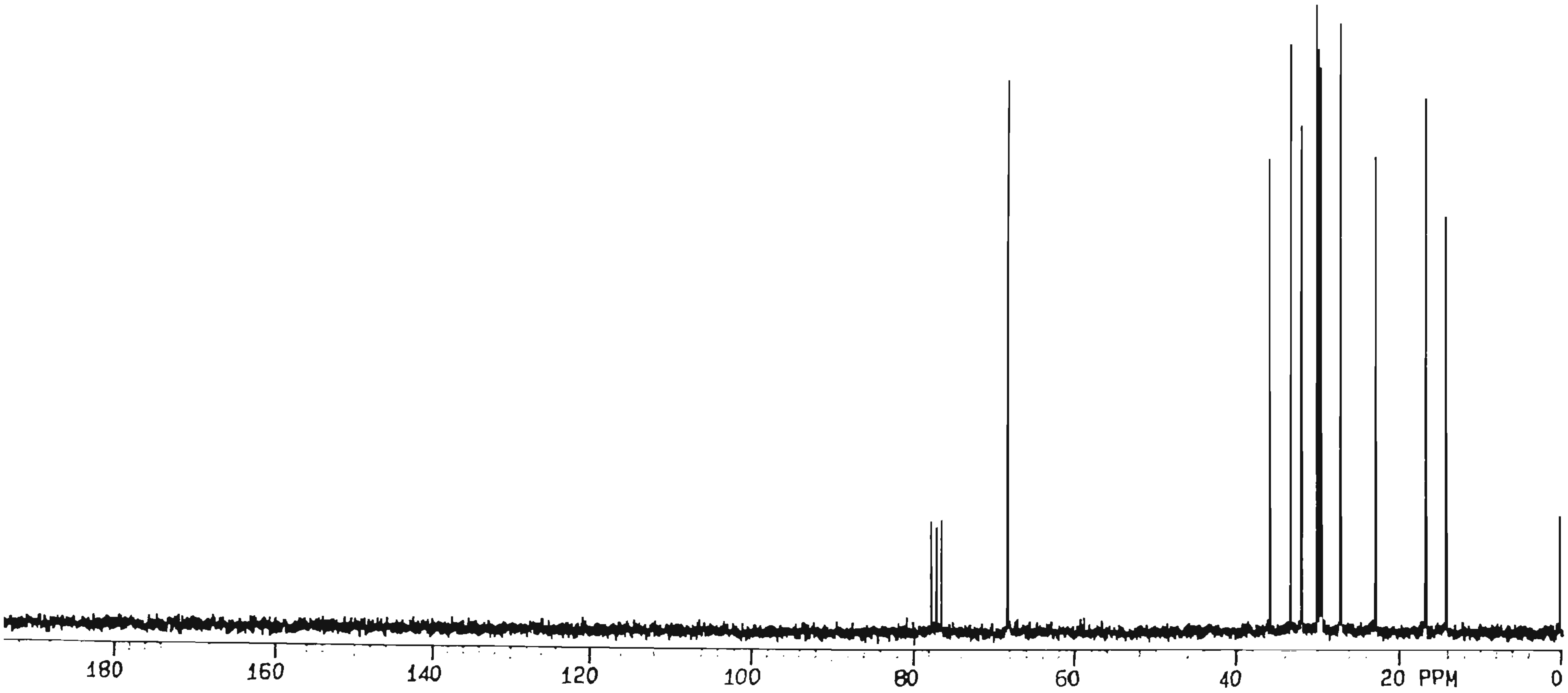

(149a)

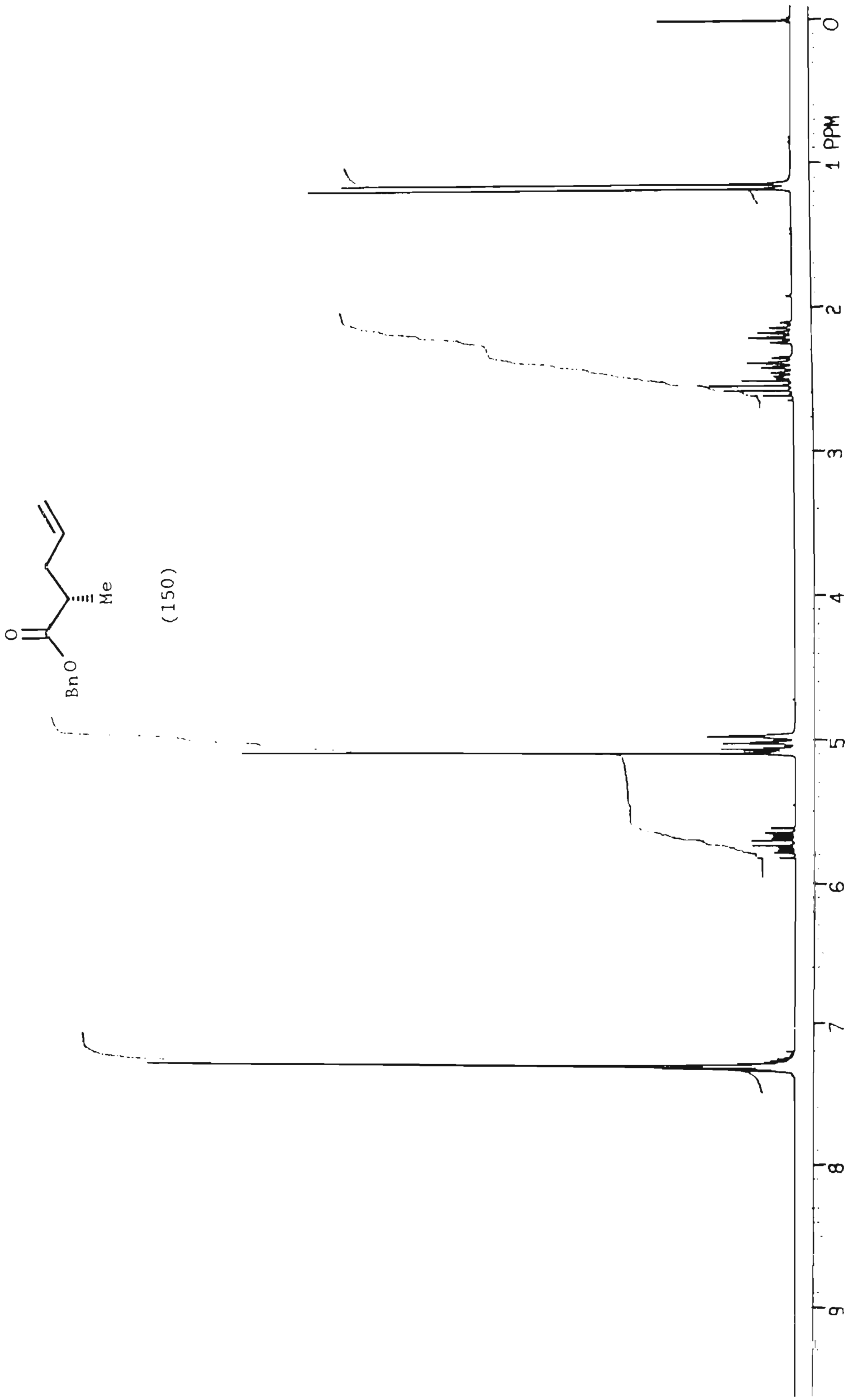


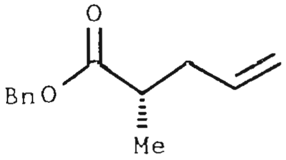
(149b)



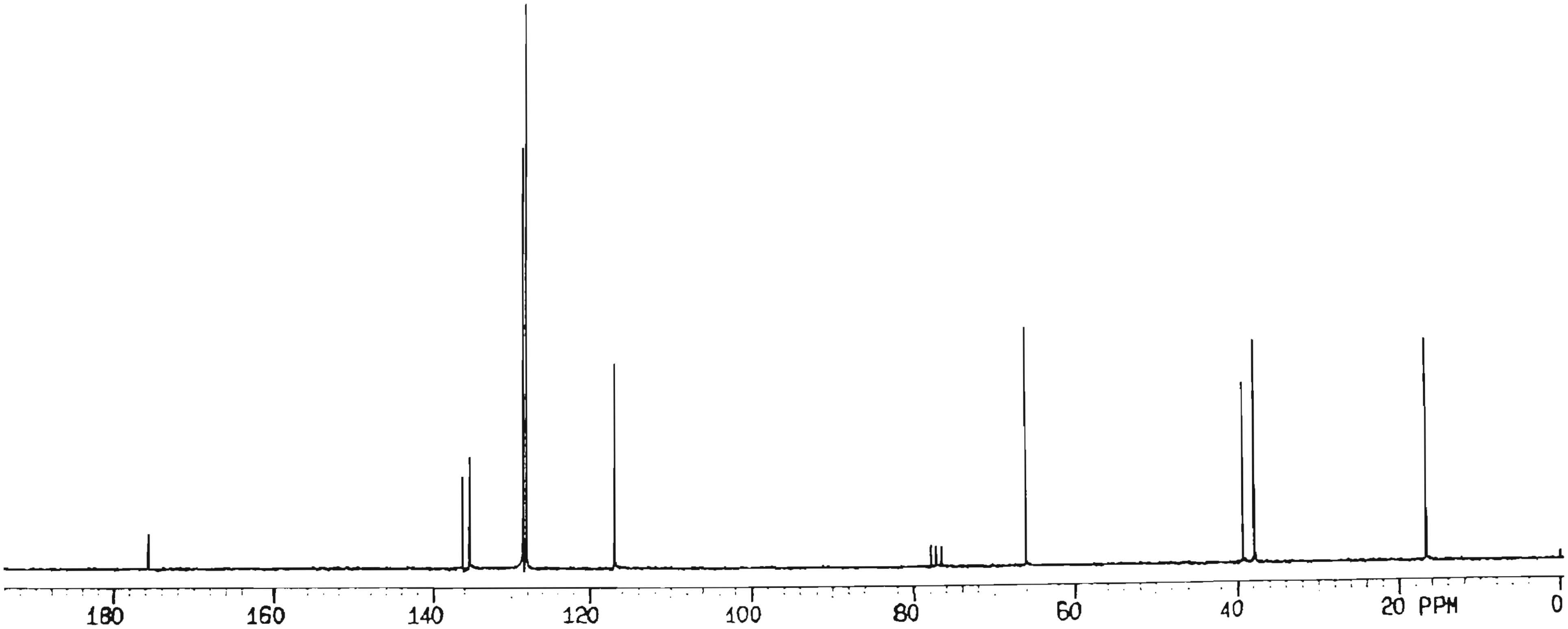
(149b)

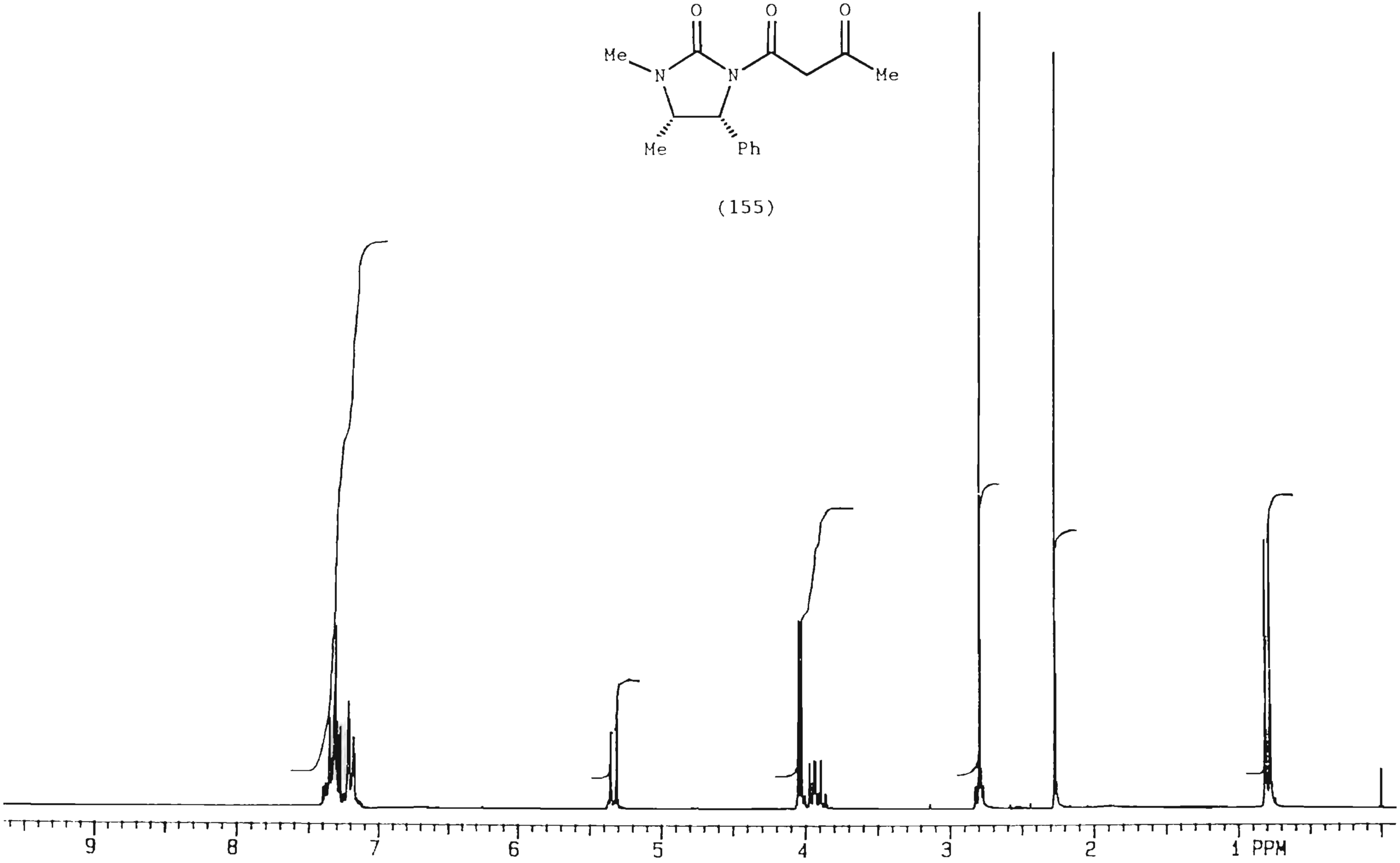



(150)

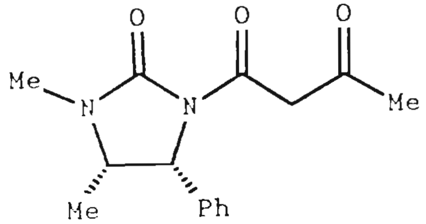


(150)

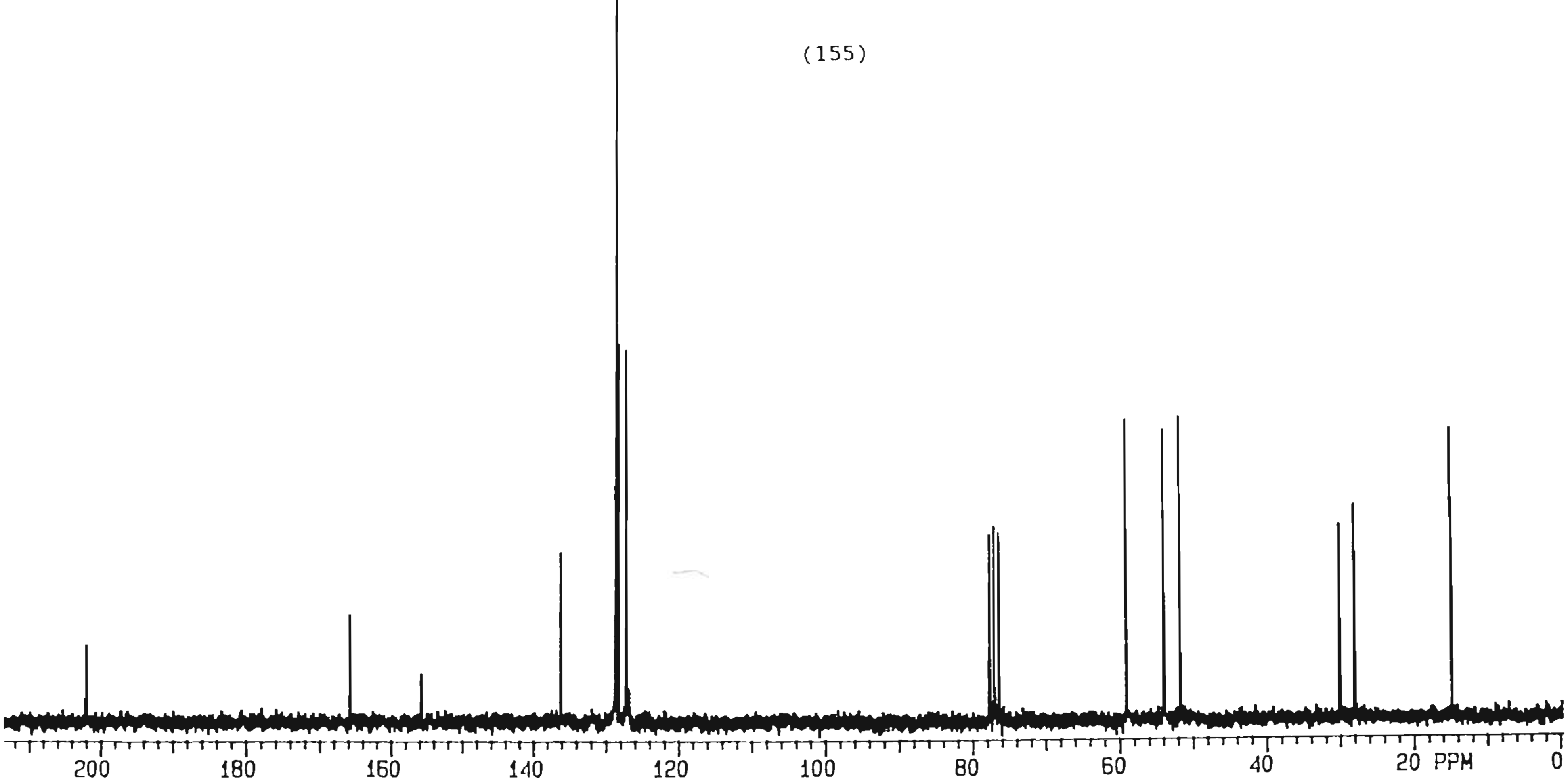


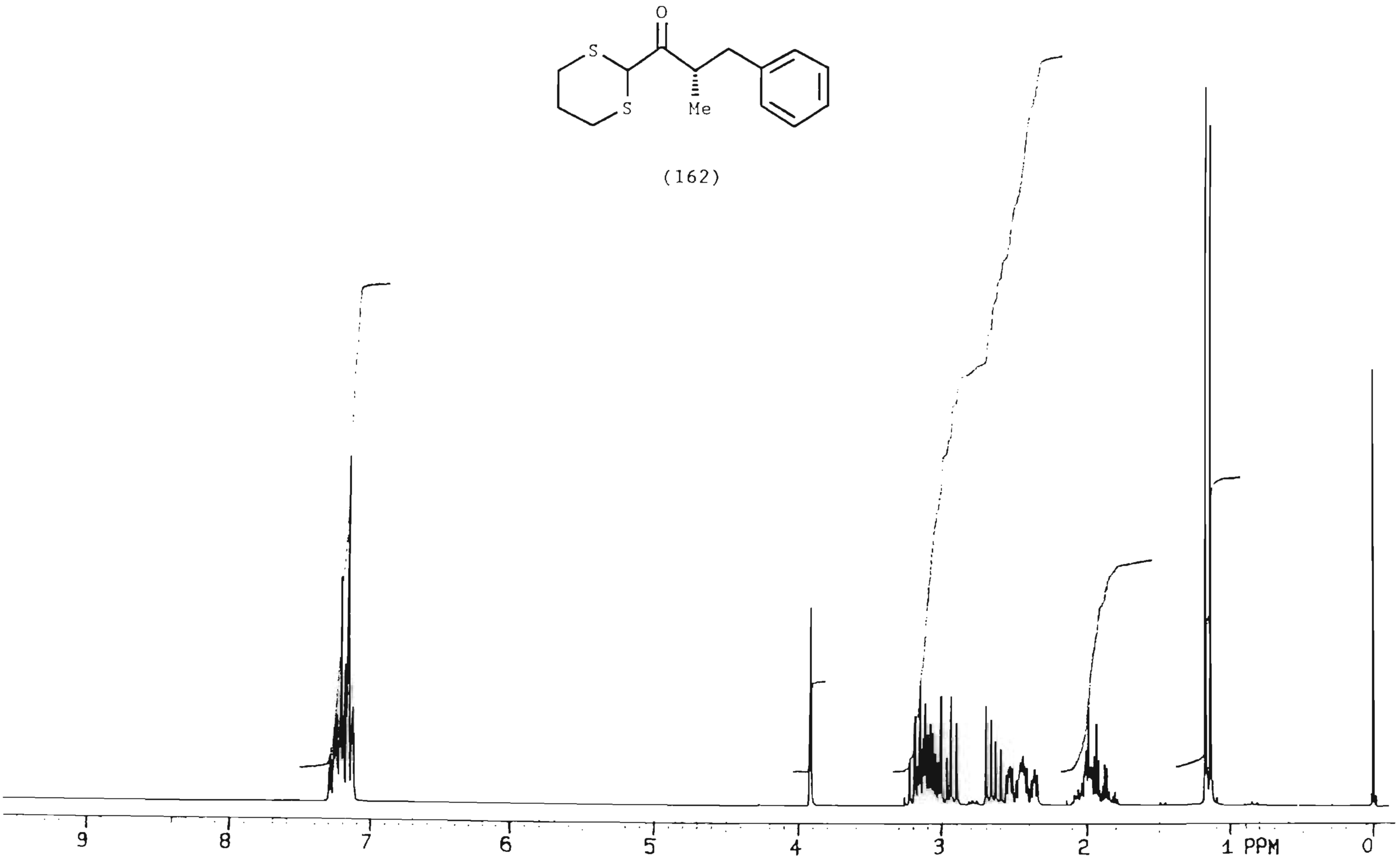


(155)

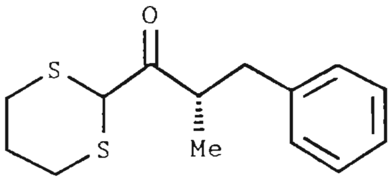


(155)

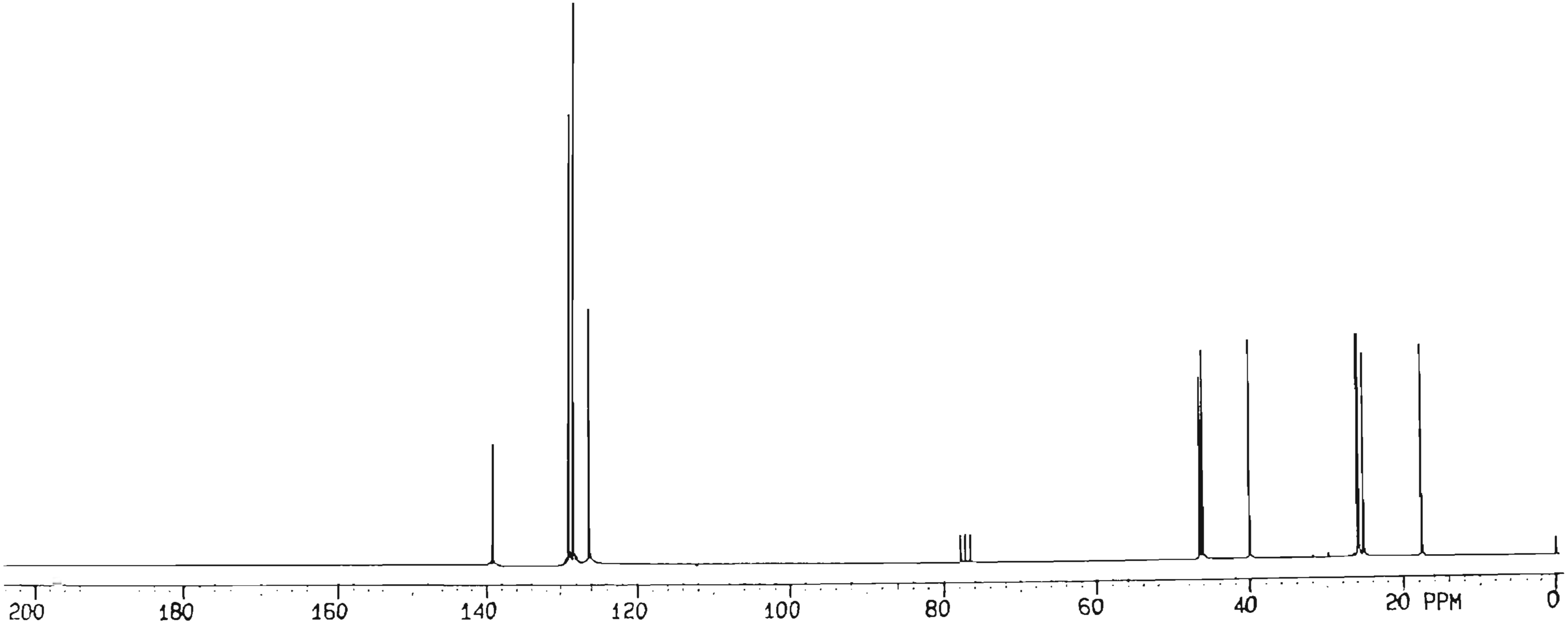


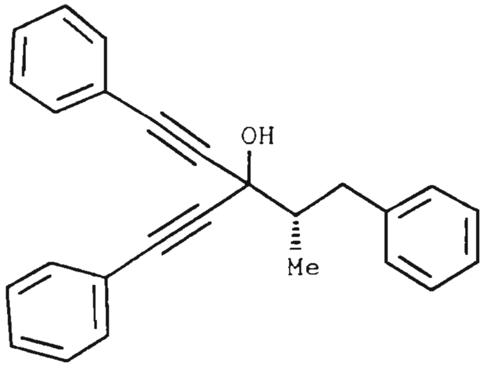


(162)

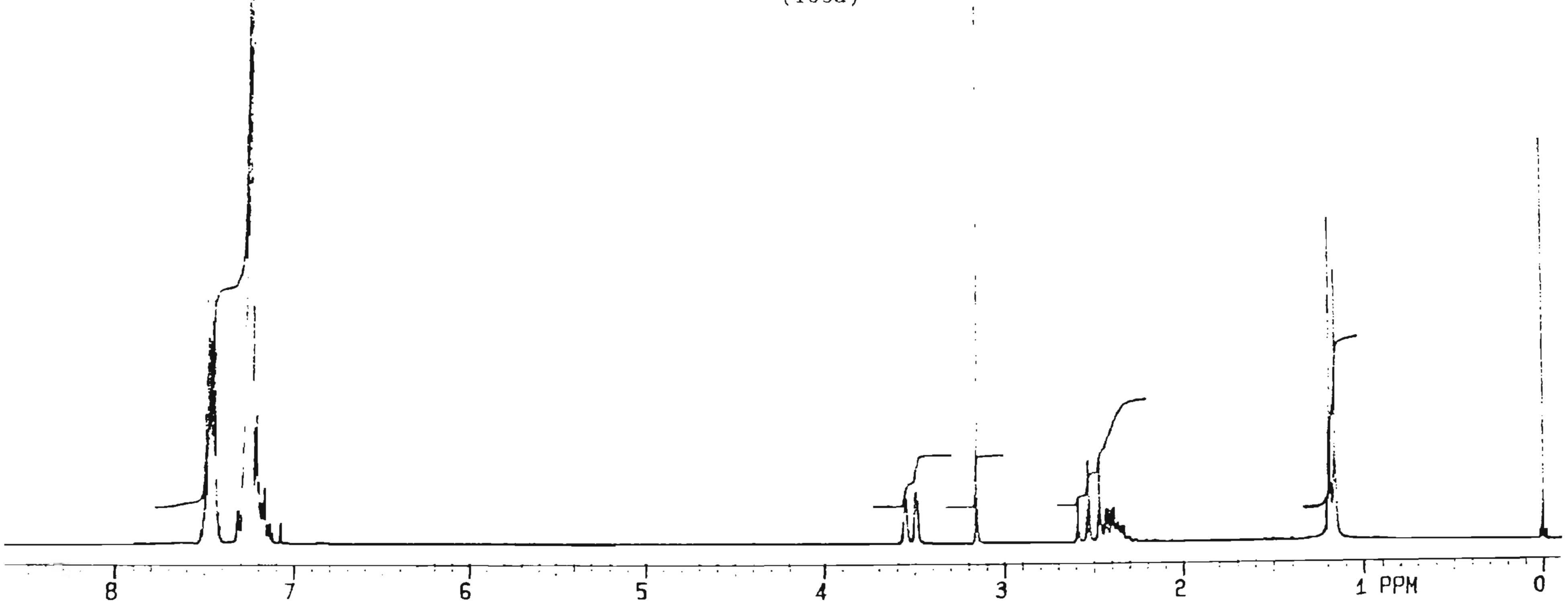


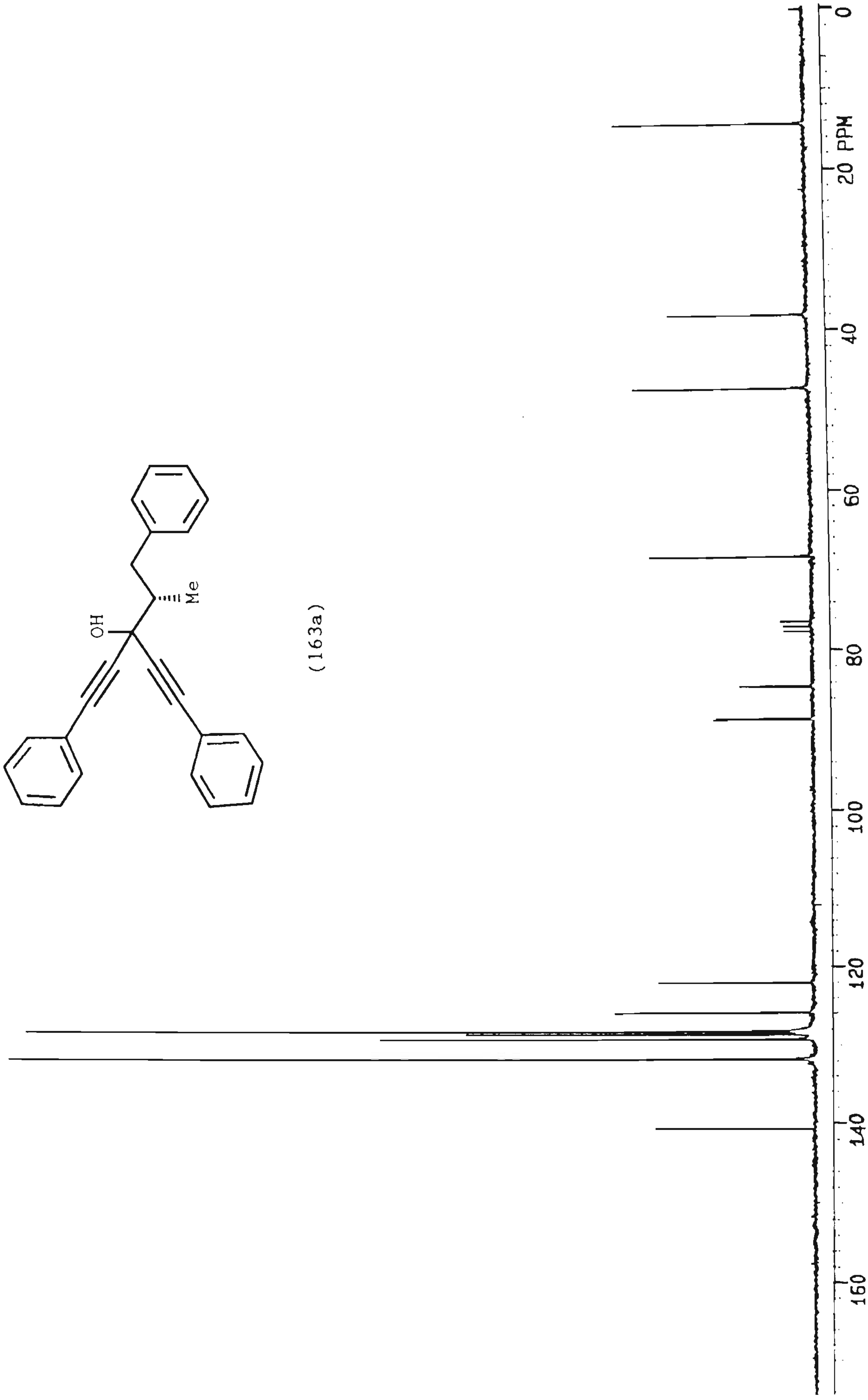
(162)



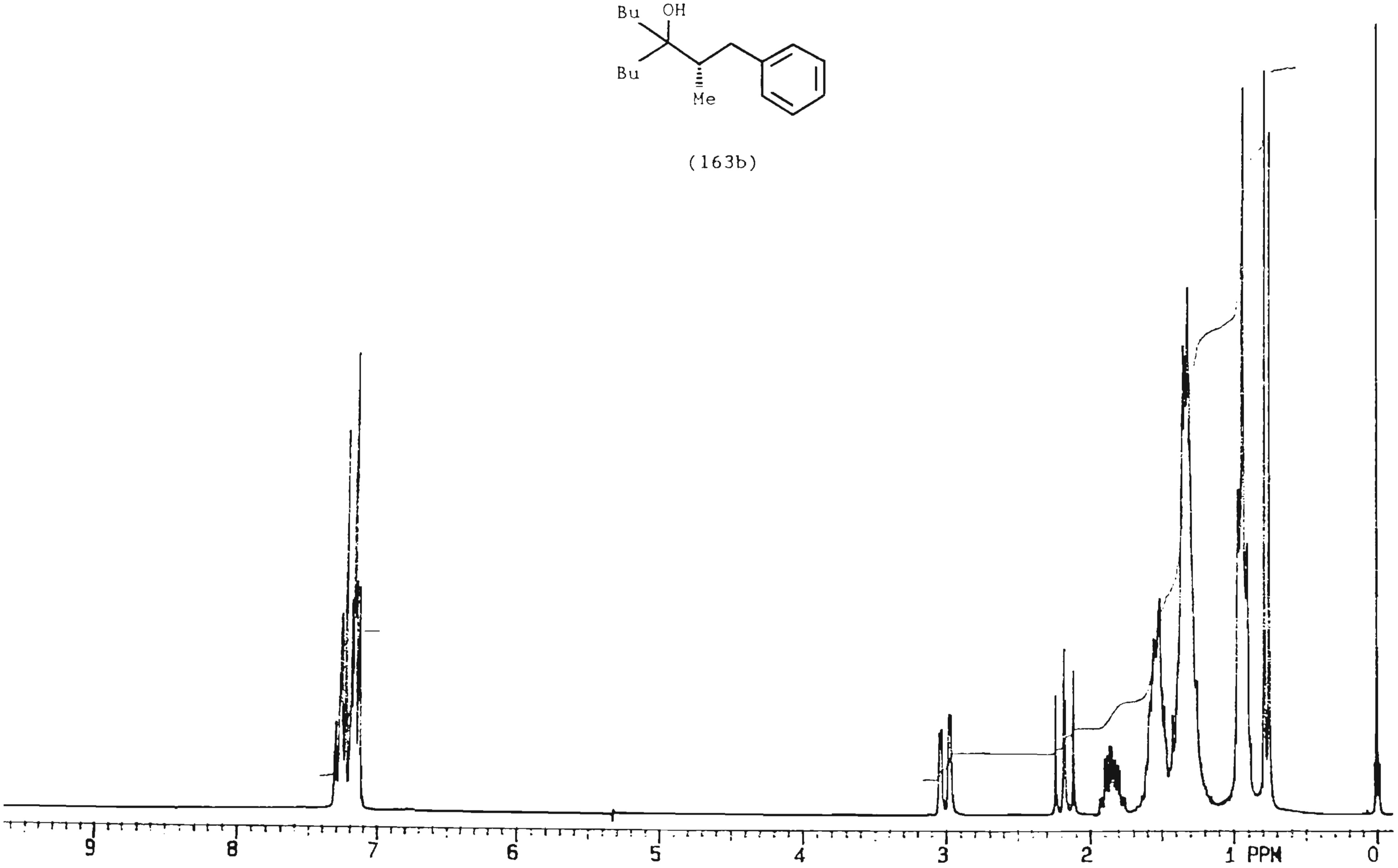


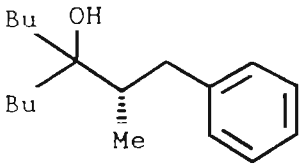
(163a)



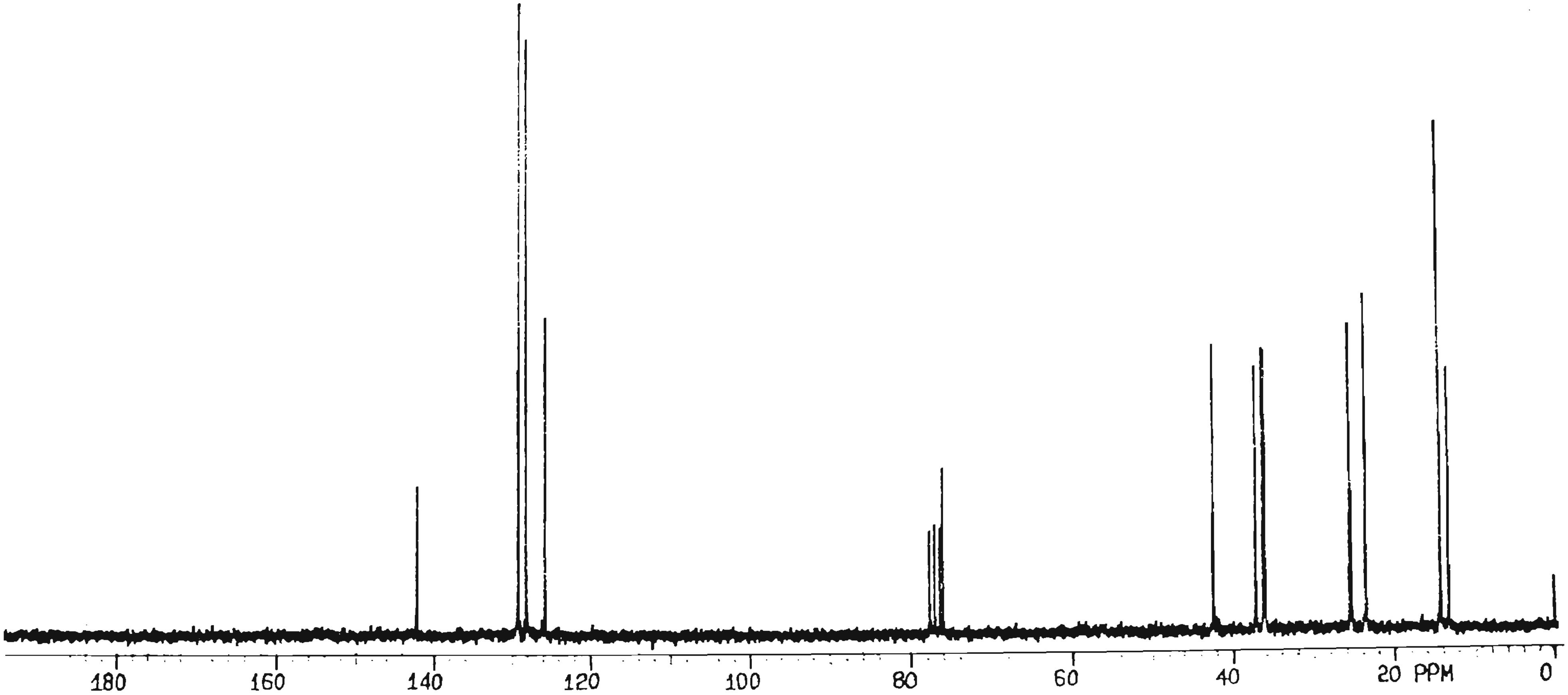


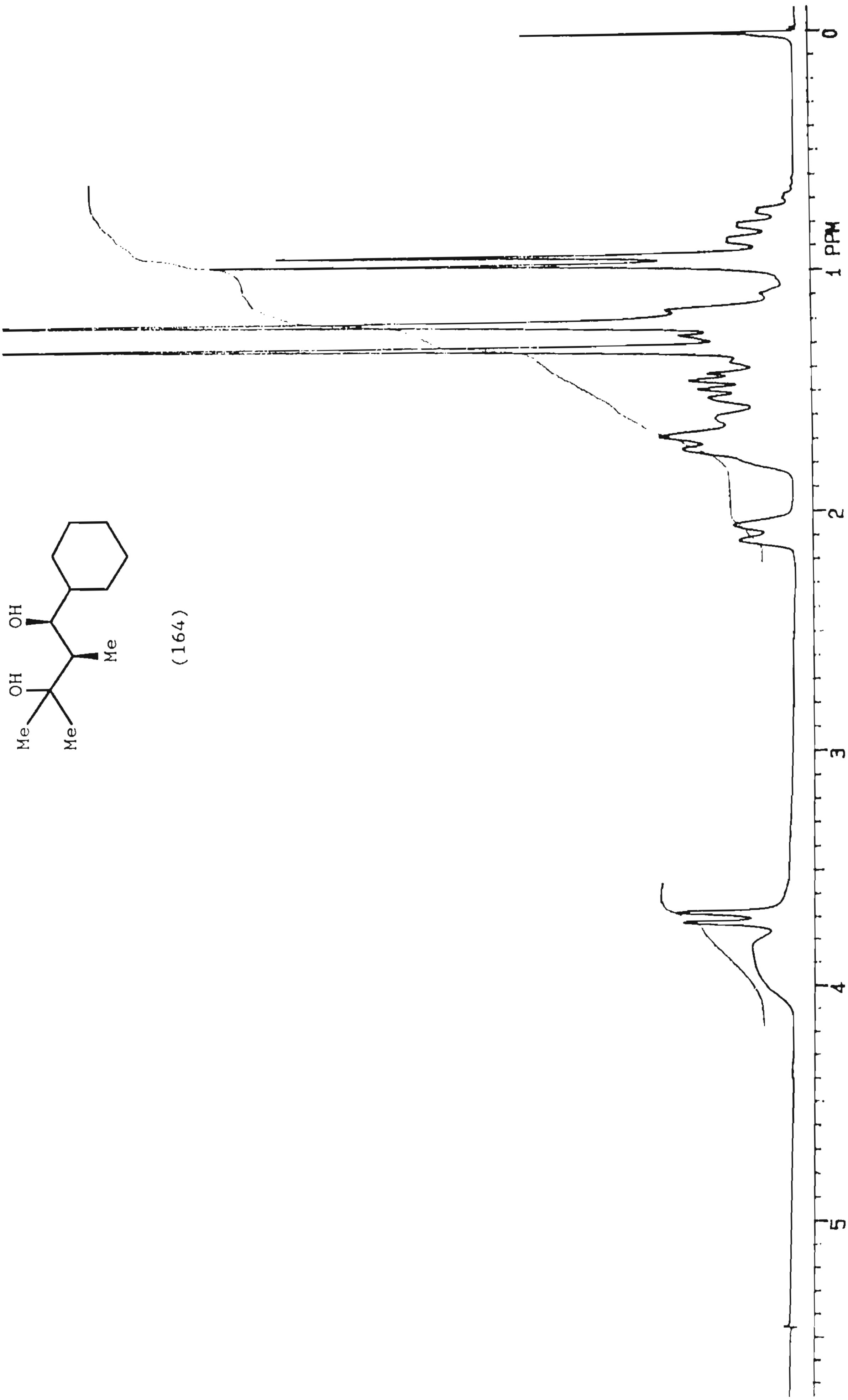
(163a)


(163b)

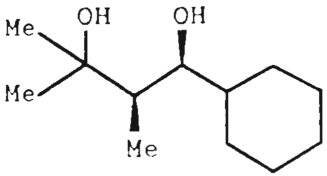


(163b)





(164)



(164)