THE SYNTHESIS OF OPTICALLY PURE 1,3-DIOLS

BY

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A thesis submitted in partial fulfilment of the requirements for the degree of Master of Science, University of Natal

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January, 1995

DECLARATION

I hereby certify that this research is a 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: _____

M J LONG

I hereby certify that this statement is correct.

SIGNED: _____

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SUPERVISOR

Department of Chemistry
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PIETERMARITZBURG

January, 1995

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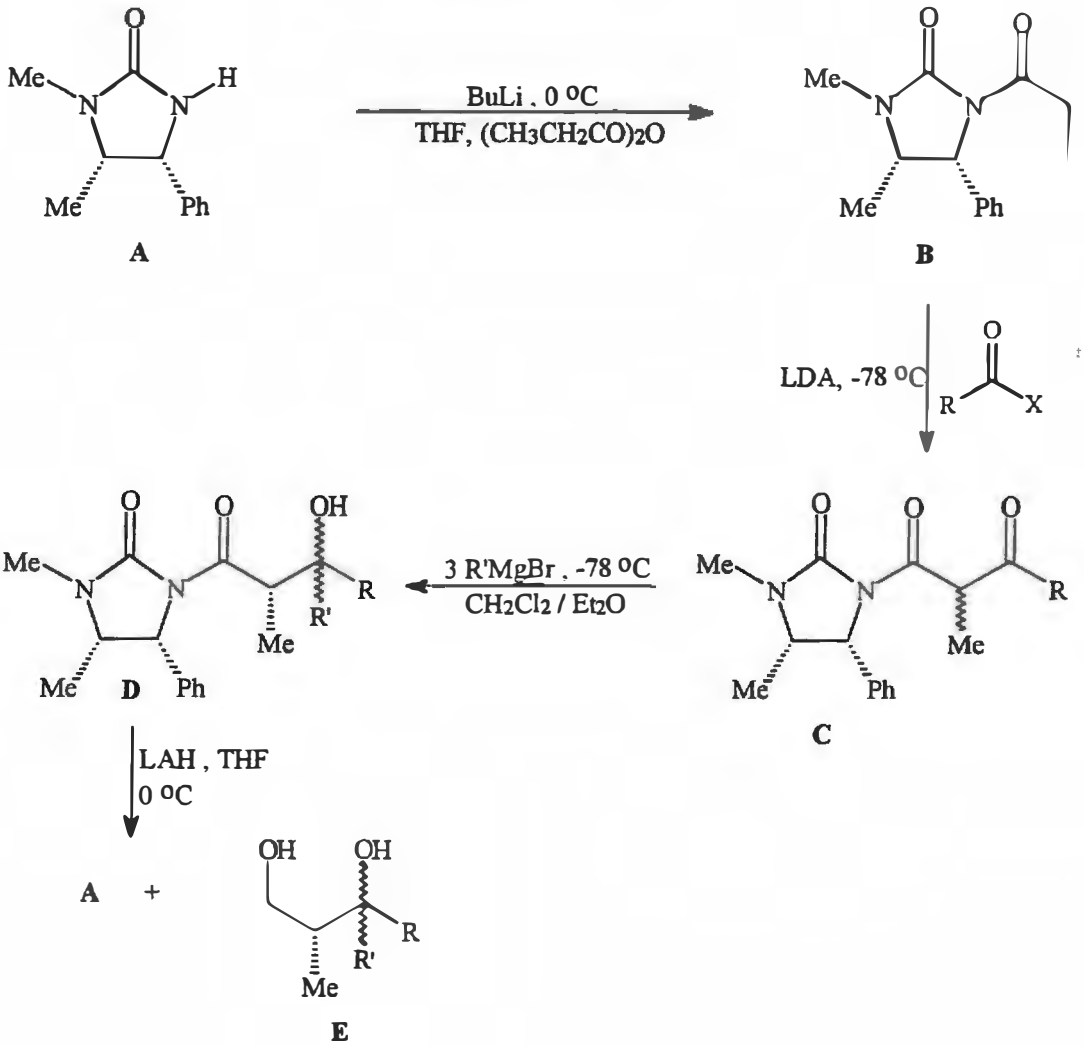
ABBREVIATIONS

AIBN	2,2'-Azobisisobutyronitrile
9-BBN	9-Borabicyclo[3,3,1]nonyl
BINAP	Bis(diphenylphosphino)-1,1'-binaphthyl
BuBOTf	Dibutylboron triflate
de	Diastereomeric excess
DET	Diethyl tartrate
DIBAL	Diisobutylaluminium hydride
ee	enantiomeric excess
GC/MS	Gas chromatography/mass spectroscpopy
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
MHz	Megahertz
NMR	Nuclear magnetic resonance
RedAL	Sodium bis(2-methoxyethoxy)aluminium hydride
TBHP	Tertiary butyl hydroperoxide
$ThexBH_2$	1,1,2-Trimethylpropylborane
THF	Tetrahydrofuran

SUMMARY

An investigation into the feasability of producing optically pure 1,3-diols by the method illustrated below was undertaken (Scheme I).



Scheme I

The reaction producing the β-dicarbonyl compounds (Scheme I, structure C) was successful with yields ranging from 53 to 20% and de's from 81 to greater than 95%.

The reaction sequence yielding the hydroxy carbonyl derivatives (Scheme I, structure D) was only moderately successful in this regard with yields ranging from 34 to 60%. The de's associated with the respective product mixtures was however much more successful and varied between 79% and 100%.

The reaction sequence producing the optically active 1,3-diols (Scheme I, structure E) was most disappointing with yields ranging between a minimum of 5% and a maximum of 18,5%. An explanation for this is not available at this time. Optical activity on the other hand was achieved with all chiral centers on the 1,3-diols being optically pure.

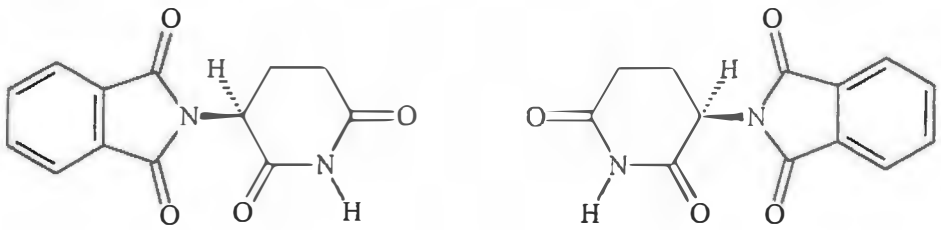
1. INTRODUCTION

"The spectacular advances in synthetic organic chemistry of the last decade, during which time the achievement of total synthesis of functionally and stereochemically complex structures has become almost routine, has placed an added requirement on the chemist, *i.e.* the synthesis of optically pure molecules."

J E Baldwin[1] FRS

Oxford 1983

Optically pure molecules, or more commonly, optically active molecules in various ratios are borne out of stereochemical control over the reactions which produce them. This aspect of stereochemical control assumes even greater significance when the different pharmacological properties of the two enantiomeric forms are considered. (Fig. 1.)

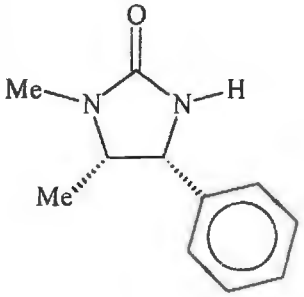


(S) (R)

Fig. 1. Thalidomide

The (*R*)-enantiomer of Thalidomide exhibits a sedative effect on humans whereas the racemate has a teratogenic effect on the foetus in expectant mothers[2].

This project will deal with the stereoselective synthesis of optically active 1,3-diols employing to this end the synthetic equivalent of an aldol reaction between an enolate and a ketone with the chiral transfer agent being (*4R*, *5S*)-1,5-Dimethyl-4-phenylimidazolidin-2-one. (1)

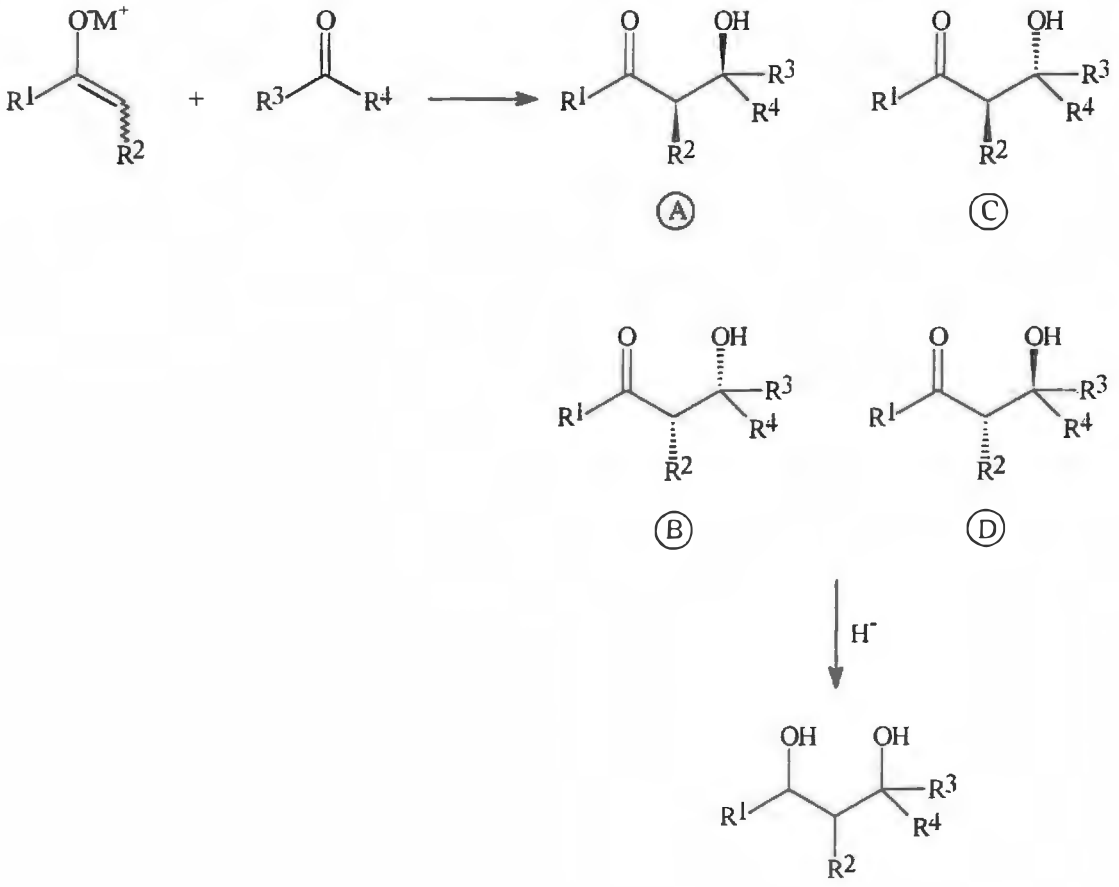


(1)

1.1 Strategies used for the synthesis of 1,3-diols

1.1.1 The Aldol Reaction

The aldol reaction which yields 1,3 difunctional products can be exploited in the synthesis of 1,3-diols.This is achieved by hydride reduction of these 1,3-difunctional products(Scheme 2).



Scheme 2.

As can be seen the reaction as written is of little use unless adequate steps can be taken to ensure stereocontrol. Diastereoselection to afford either the *syn*[3] ((A)/(B)) or *anti*[3] ((C)/(D)) diastereomeric pair can be achieved by careful choice of the metal counterion, the substituents R_1, R_2, R_3 and R_4 (steric constraints) as well as through optimization of the reaction conditions. Further differentiation is however needed to ensure enantioselection [((A) vs. (B)) and ((C) vs. (D))] and this requirement is met by use of the chiral auxiliary and various catalysts.

Perhaps the most popular auxiliaries used in this respect and others are the oxazolidin-2-ones developed by Evans.[4,5,6] (Fig. 2.)

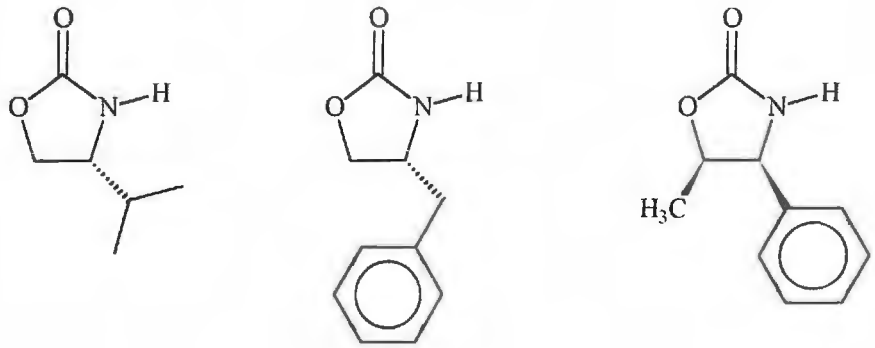
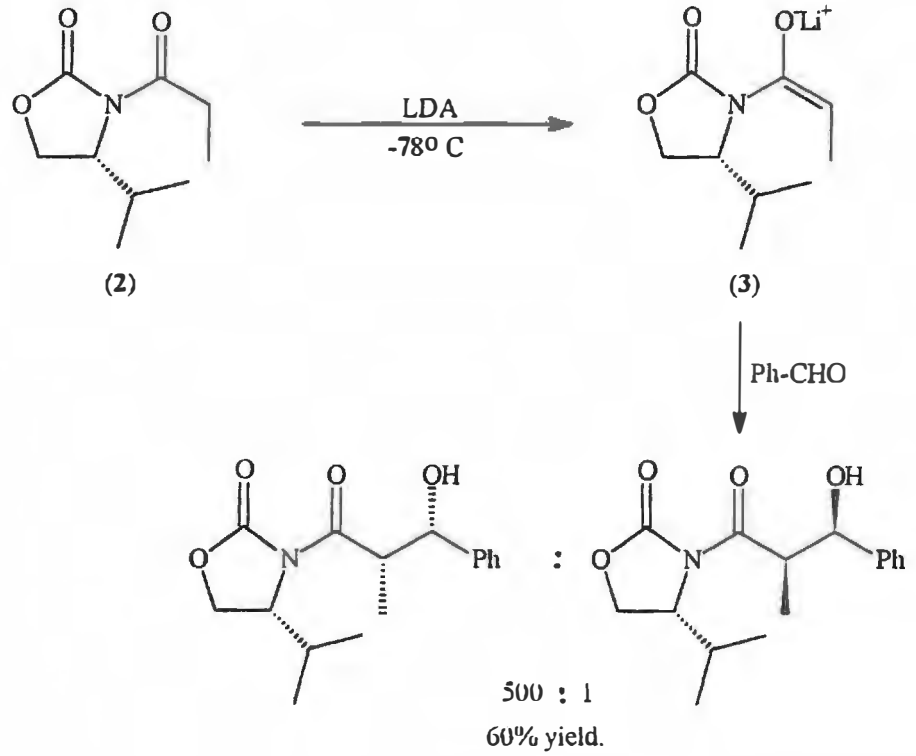


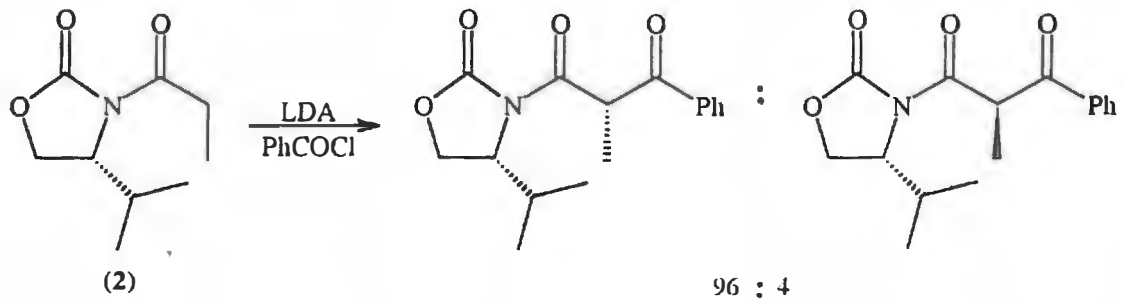
Fig. 2.

Kinetic deprotonation of the N-acyl derivatives (2) yield chiral enolates (3) which exhibit a high degree of stereoselection in the aldol reaction.[4] (Scheme 3.)



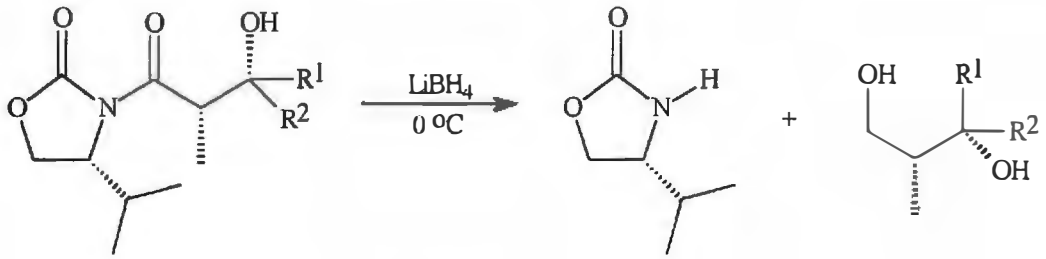
Scheme 3.

Acylation[5] of the N-acyloxazolidin-2-ones (2), also proceeds stereoselectively. (Scheme 4.)



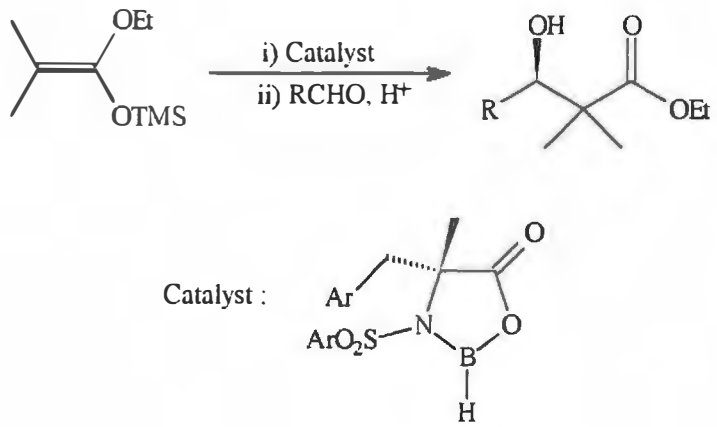
Scheme 4.

Reductive removal of the auxiliary gives the desired diols as well as the auxiliary itself in undiminished optical purity.[6] (Scheme 5.)



Scheme 5.

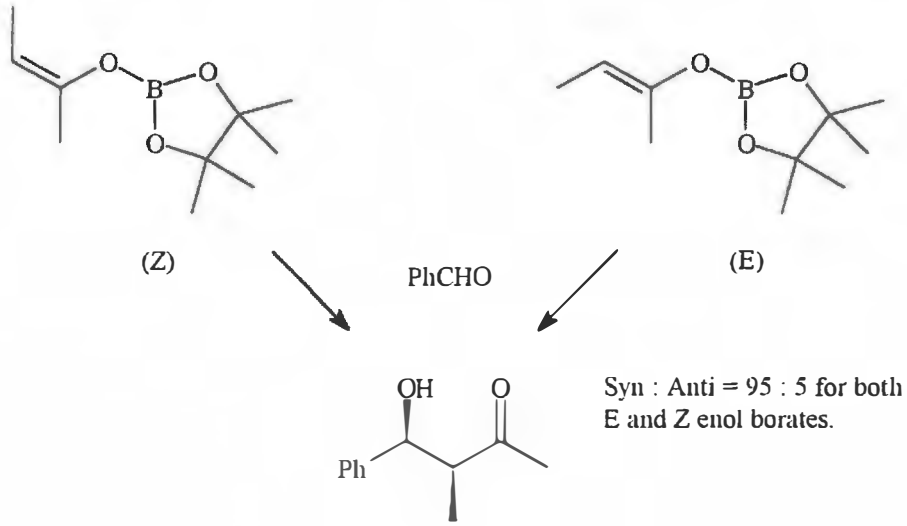
Catalysis on the other hand has not met with as much success as the auxiliary approach, although Masamune *et al.*[7] recently reported on a catalytic aldol reaction which formed β-hydroxy esters which are 1,3-diol precursors with ee's of greater than 90%.(Scheme 6)



Scheme 6.

Various enzymes,[8] the most readily available of which is Rabbit muscle aldolase, catalyse the aldol reaction between enolates and aldehydes with a high degree of stereoselection. An added bonus with this method is the disappearance of the need for protecting groups.

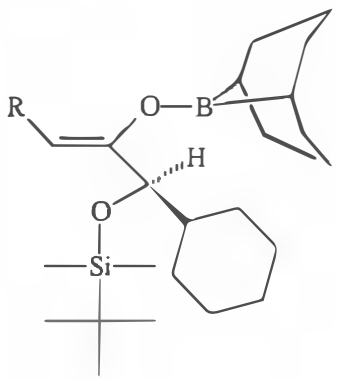
The classical aldol, as discussed up to now, has over the years spawned a number of variations, one of which is the addition of enol borates or Boron enolates to aldehydes. Reactions studied by Hoffman *et al.*[9] showed the excellent diastereoselectivities achievable with this reaction. It is also interesting to note that both *E* and *Z* enol borates yield *syn* products(3). (Scheme 7.)



Scheme 7.

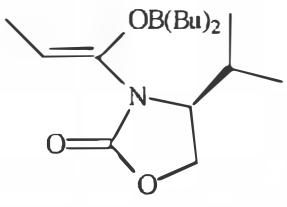
The ee's, as expected, showed the products to be racemic. This is not surprising if one considers that a chiral component was not included in the reaction.

Introduction of this chiral component i.e. a chiral centre by Masamune *et al.*[10] (4) as well as Evans *et al.*[4] (5) dramatically increased the degree of optical purity of the product mixture.The chiral boron enolates (4) and (5) are illustrated below.



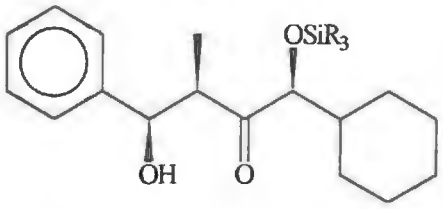
(4)

R = Me, H



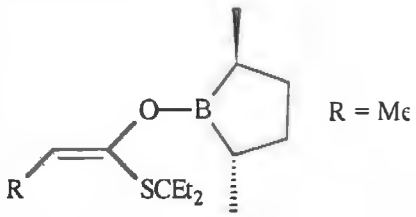
(5)

For the reaction between (4) and benzaldehyde the d.e. between products was 14:1 with the major product (6) illustrated below.



(6)

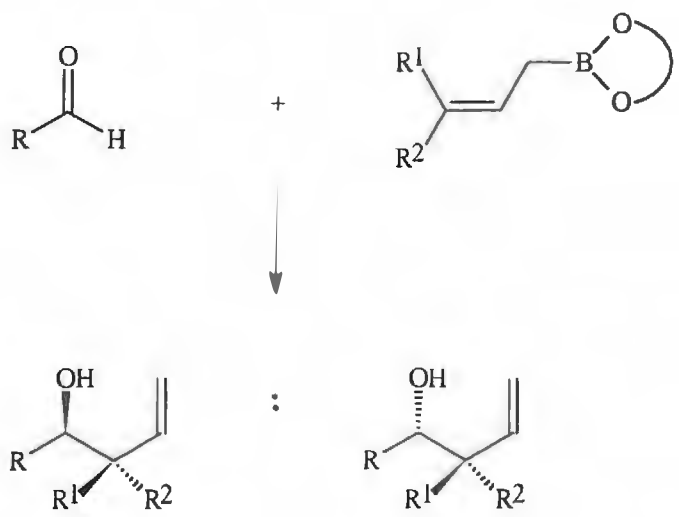
Anti diols can surprisingly enough also be accessed *via* this methodology by use of another optically active enol borate (7) development by Masamune *et al.*[11]



(7)

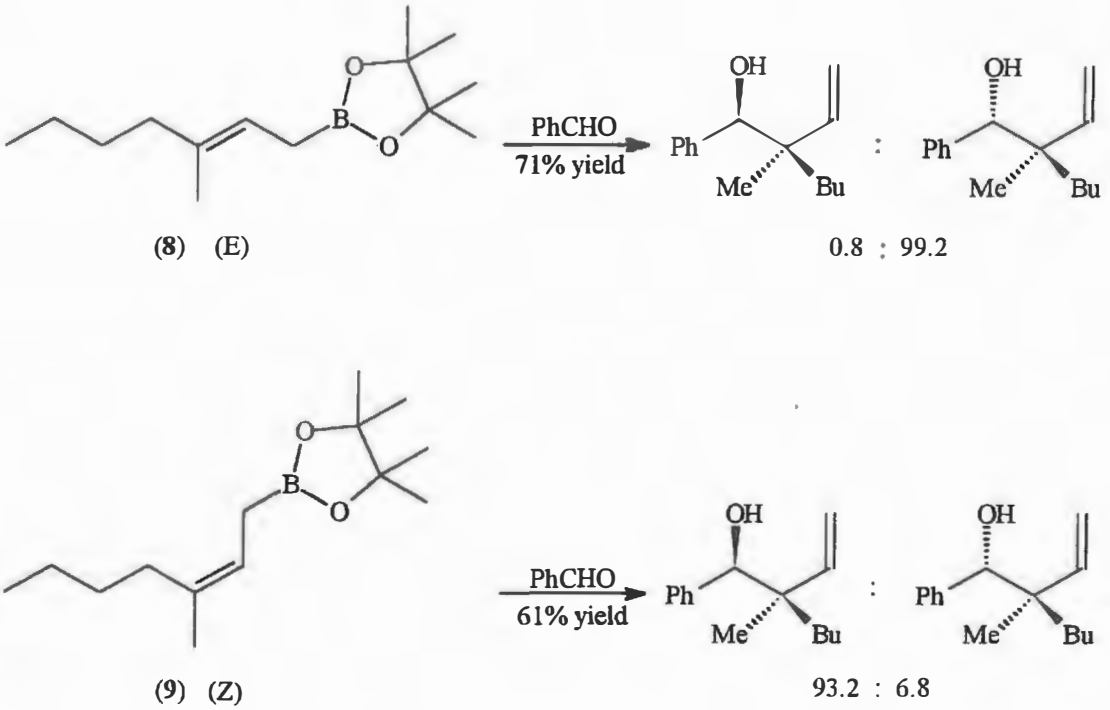
In reactions with typical aldehydes the *syn* : *anti* ratio did not fall below 1:30 , with correspondingly high ee's of at least 97:1.

A second variation of the classical aldol is the allylic boration reaction. (Scheme 8.)



Scheme 8.

This reaction may be compared with the addition of enol borates to aldehydes on the basis of the similarity between the 2 boron species; an oxygen atom has been replaced by a carbon atom; and one would therefore expect good diastereoselection but poor enantioselection. Despite the fact that the allylic borates are γ, γ-disubstituted, this was indeed the case as shown by Hoffman *et al.*[12] (Scheme 9.)



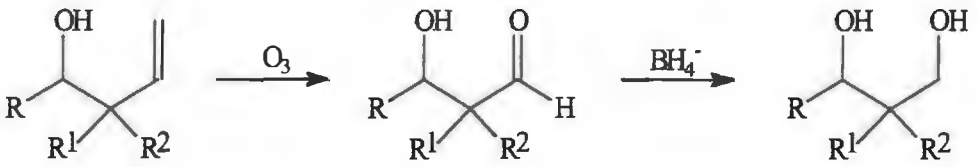
(8) (E) 0.8 : 99.2

(9) (Z) 93.2 : 6.8

Scheme 9.

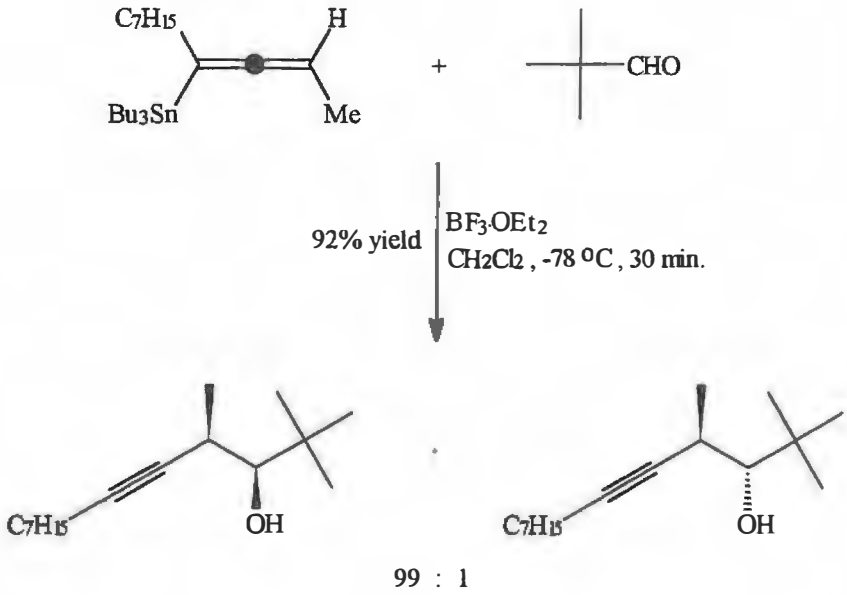
There is, as can be seen, a difference with this reaction, *i.e.* allylic boration when compared with the addition of boron enolates to aldehydes discussed previously (Scheme 7). The *E*-isomer (8) favours the *anti* diastereomeric pair whereas the *Z*-isomer (9) favours the *syn* pair.With the addition of boron enolates to aldehydes(Scheme 7) both *E* and *Z* enol borates favour the *syn* diastereomeric pair.

Ozonolysis followed by borohydride reduction yields the 1,3-diols from the allylic alcohol products of this reaction.[12] (Scheme 10.)



Scheme 10.

Also applicable here is the reaction between allenylstannates[13] and aldehydes, which for α-branched aldehydes proceeds diastereoselectively in the prescence of Lewis acids $BF_3.OEt_2$ or $MgBr_2.OEt_2$ (Scheme 11).

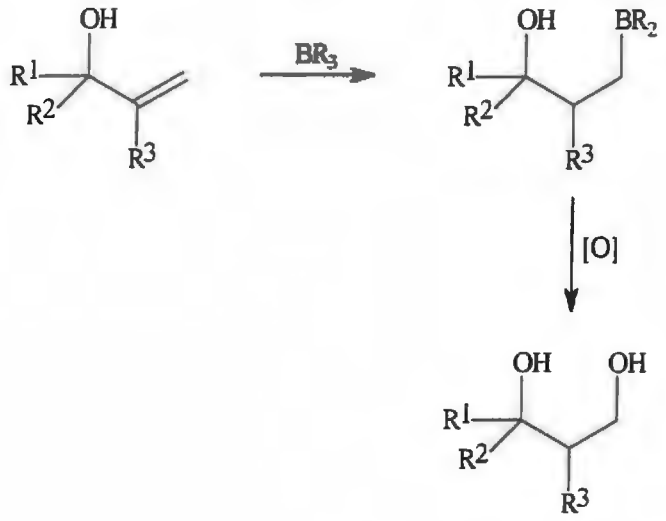


Scheme 11.

The diols are produced in three steps from the reaction products, hydrogenation of the triple bond to a double bond,followed by ozonolysis and borohydride reduction.

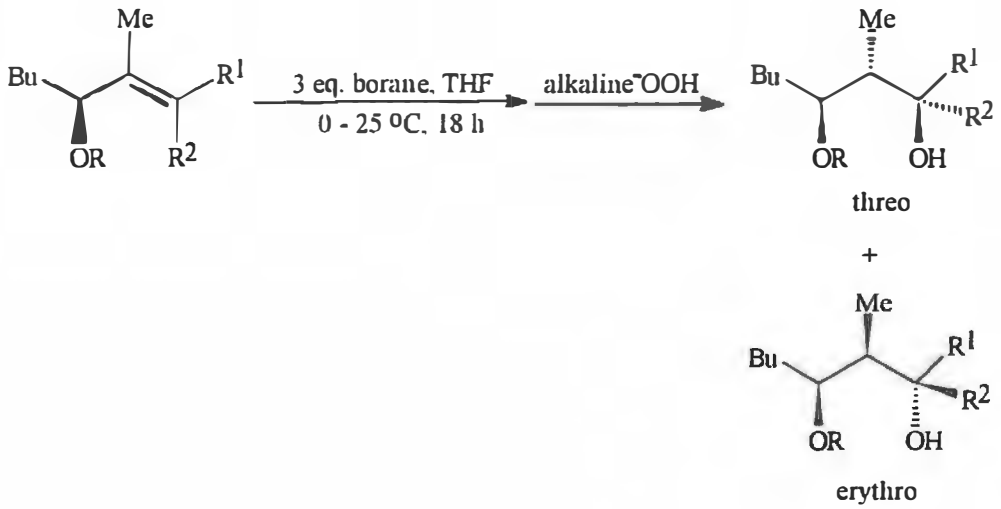
1.1.2. Olefin Hydroboration

Olefin hydroboration is another of the methods employed in the synthesis of 1,3-diols. (Scheme 12.)



Scheme 12.

Harnessing the reaction has ,however, evolved in two directions. The first of these involves boration by common hydroborating agents such as 9-BBN and $ThexBH_2$, amongst others. A representative example of this approach is taken from work carried out by Still and Barrish,[14] with the general reaction illustrated below. (Scheme 13.)



Scheme 13.

Variation in the substitution pattern of the starting allylic alcohol and the bulk of the hydroborating agent as well as other factors influence the stereochemical outcome of the reaction. The best results were achieved with sterically demanding boranes such as 9-BBN. (Table 1.)

Table 1.

R^1	R^2	R	Borating Agent	Yield	Threo: Erythro
H	H	H	9-BBN	80%	11 : 1
Bu	H	H	9-BBN	48%	9 : 1
H	Bu	H	9-BBN	31%	15 : 1
H	H	$SiMe_3$	9-BBN	57%	10.5 : 1
H	H	$COCF_3$	9-BBN	95%	14 : 1

The large degree of diastereoselection can be rationalized by the following model. (Fig. 3.)

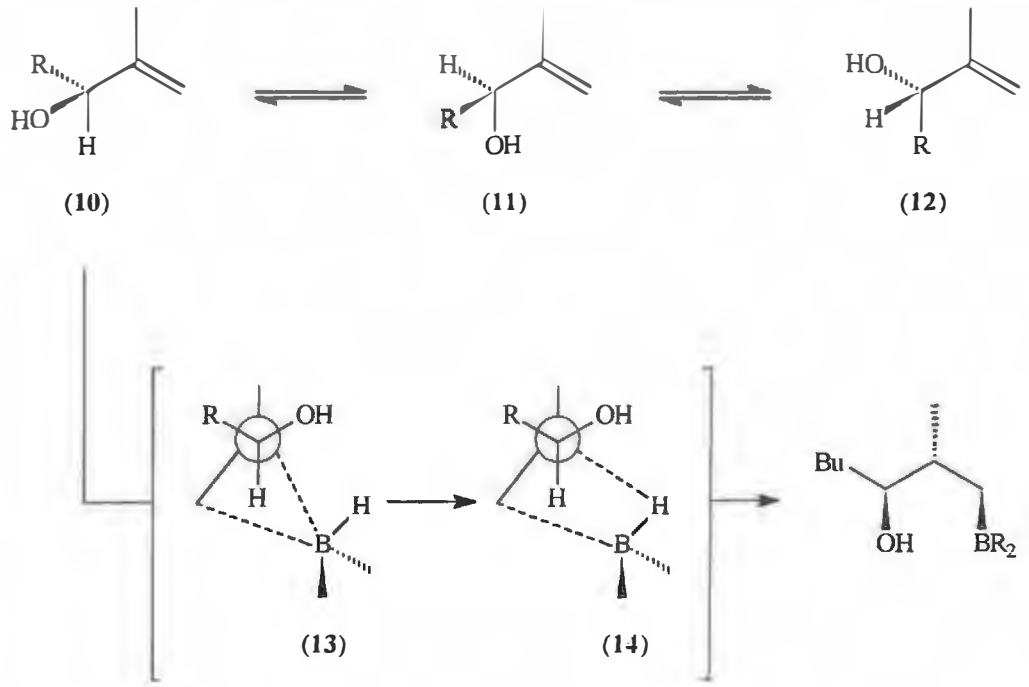
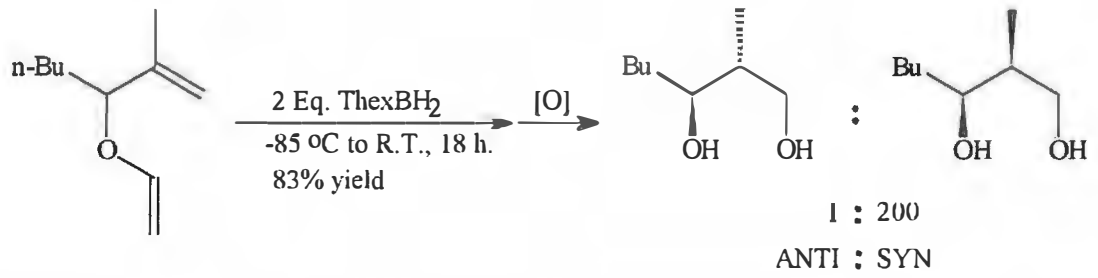


Fig. 3.

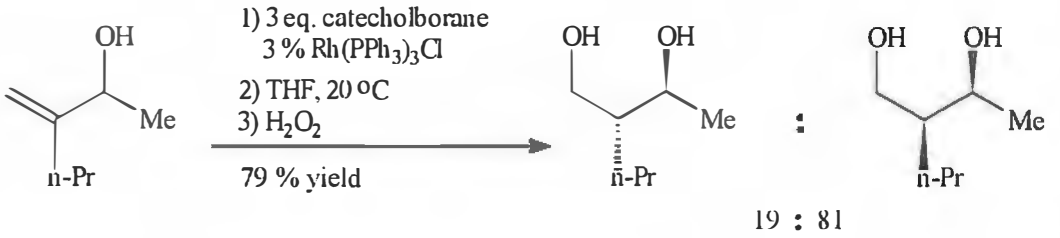
Attack of the borane on the least hindered side of olefinic π system (10) leads to the less sterically hindered transition state (13 or 14) and the *threo* product. The minor *erythro* isomer arises from attack of the borane on the least hindered side of another minimum energy conformer, in this case (11) and proceeds *via* transition states analogous to 13 and 14.

Uncatalysed intramolecular hydroboration of allyl vinyl ethers[15] leads to predominantly *syn* products(Scheme 14).The hydroboration agent employed in this case was $ThexBH_2$.This is contrary to the findings of Still and Barish[14](See Scheme 13 and Table 1)whose results showed that the *anti* product was favoured.



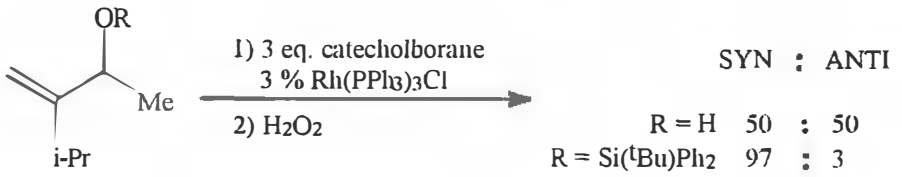
Scheme 14.

The second way of exploiting the hydroboration reaction involves the use of a catalyst such as Wilkinson's catalyst, $Rh(PPh_3)_3Cl$(Scheme 15).With this catalysed hydroboration reaction the products are predominantly *syn*. This fact and the selectivities shown by the reactions illustrated in schemes 13 and 14 can be reconciled if one considers that the mechanisms for each case.are. quite different and will therefore not show the same responce to the combination of electronic and steric factors influencing the reaction.



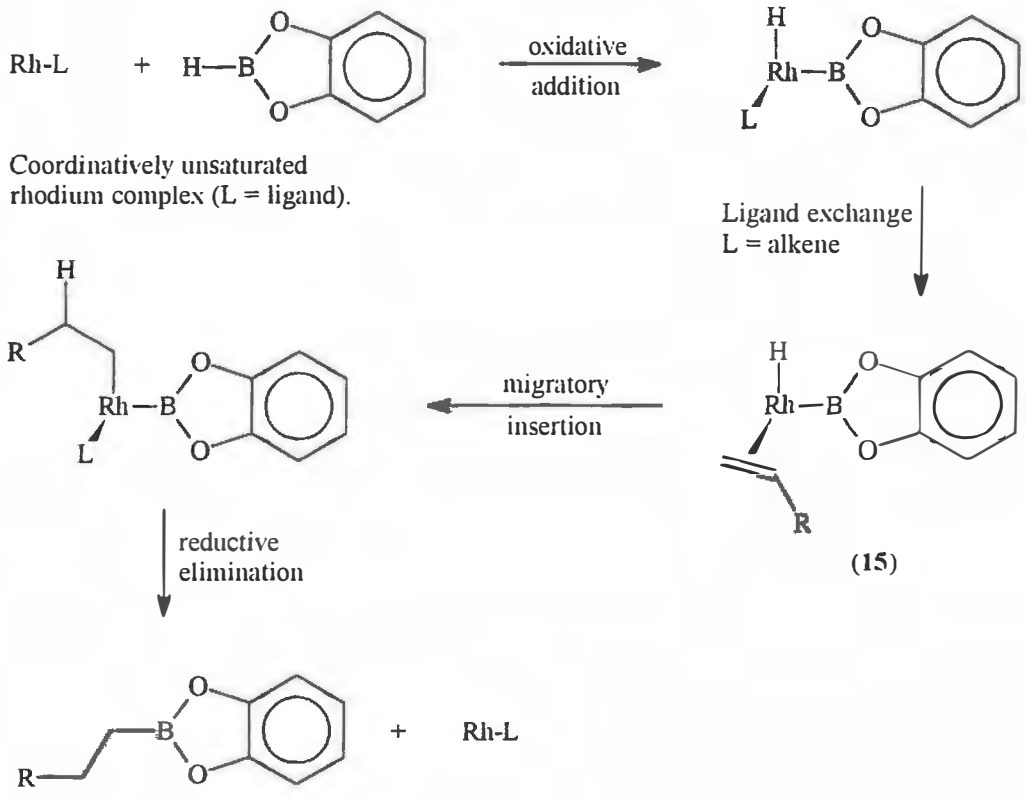
Scheme 15.

The catalysed version as shown by the above example[16] (Scheme 15.) is, when compared to its uncatalysed counterpart, (Scheme 13.) more susceptible to steric variation in the form of different substitution patterns on the substrates. (Scheme 16.)



Scheme 16.

The origin of the *syn* selectivity shown by catalysed hydroborations is an enigma in contemporary organic chemistry because the mechanism of the reaction is unknown. The following scheme,[17, 18] an attempt at explaining the mechanism, is reasonable when compared with Rhodium catalysed hydrogenations.[19, 20] (Scheme 17.)

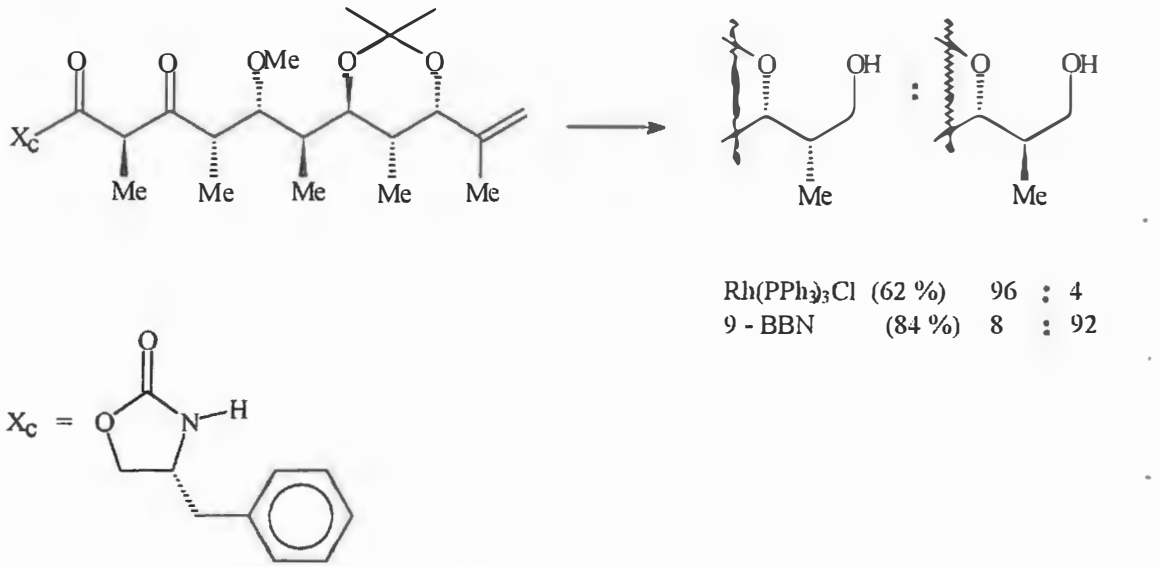


Scheme 17.

If the major diastereomer of type 15 forms irreversibly and/or reacts quickly to give the product, diastereoselection for catalysed hydroboration of certain allylic alcohol derivatives (various protected alcohols) will be determined *via* the diastereofacial selectivity of co-ordination to the alkene.

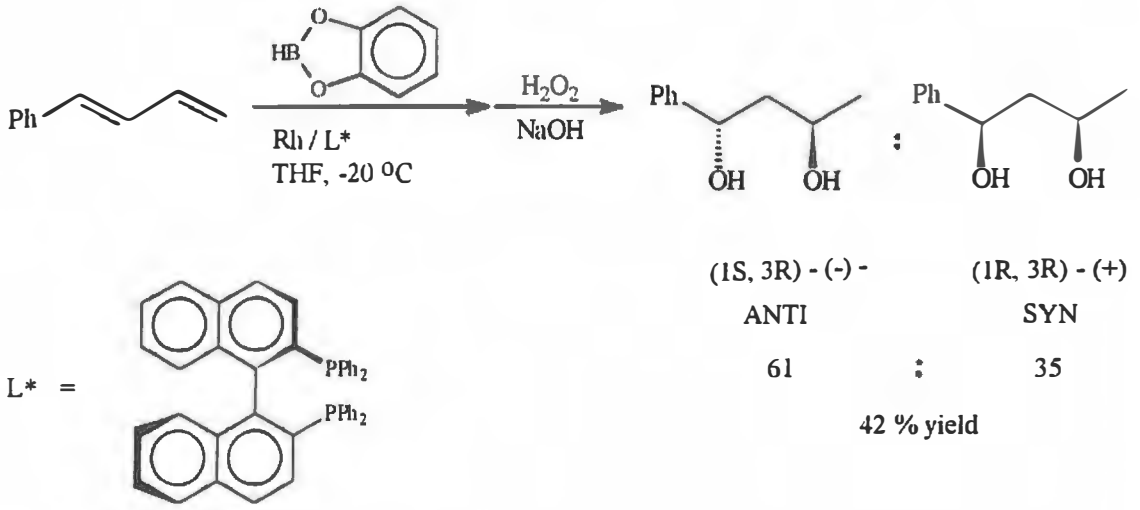
Stereochemical factors govern co-ordination of the alkene to rhodium and are thus directly responsible for the diastereoselection shown by the reaction, *i.e.* rhodium catalysed hydroboration of olefins.

Use of optically pure starting materials by Evans *et al.*[21] demonstrated the synthetic utility of this reaction as it was used in a synthesis of the C_1-C_{11} polypropionate portion of the polyether antibiotic, Lonomycin A. (Scheme 18.)



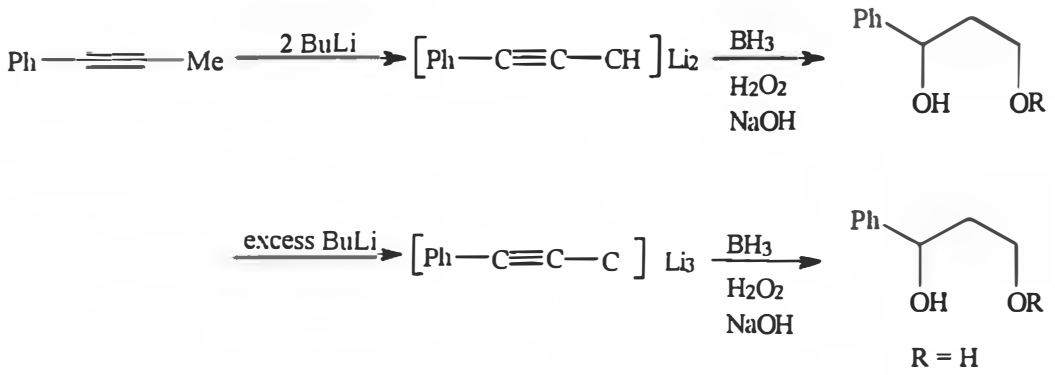
Scheme 18.

Asymmetric hydroboration of olefins as discussed up to now has one major flaw : it requires optically pure starting materials. A novel way of overcoming this and also the need for the allylic alcohol itself, is double asymmetric hydroboration[22] which converts a diene to an optically pure 1,3-diol with the requirement for enantioselection being met by a chiral catalyst. (Scheme 19.)



Scheme 19.

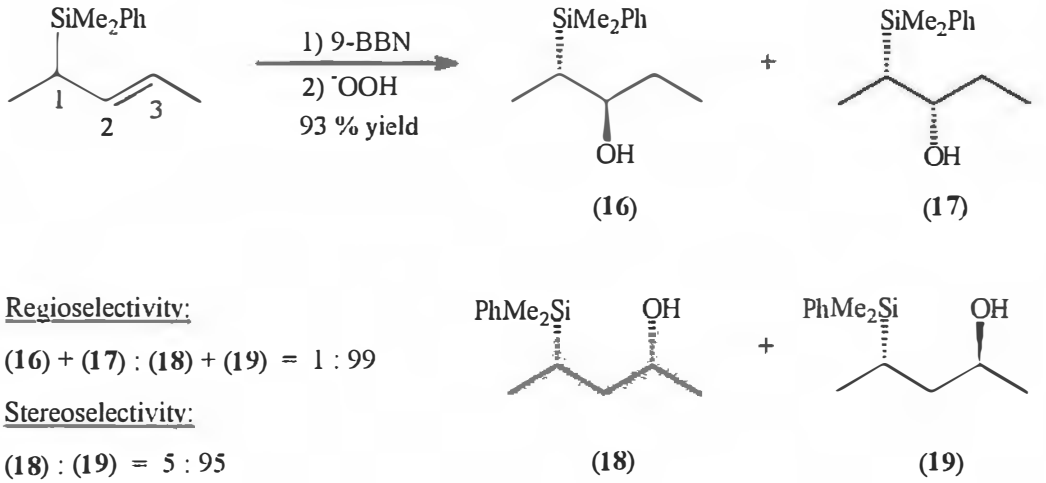
Another hydroboration reaction of interest here, even though the products are racemic, is hydroboration of metalated alkynes.[23] (Scheme 20.)



Scheme 20.

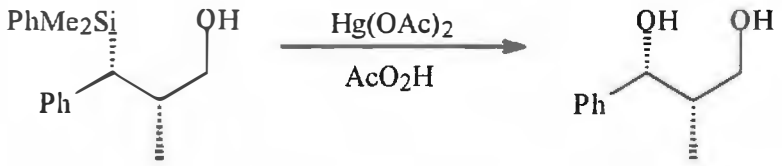
Replacement of the propargylic methyl group with an ethyl group yields a 1 : 2 mixture of threo and erythro 1,3 diol products.

Hydroboration of allylsilanes[24], as with normal alkenes and allylic alcohols, is found to be generally regioselective with attachment of the boron to C-3 of the allylsilane moiety. It is also stereoselective with attachment of the boron *anti* to the silyl moiety. As with the studies of Barrish and Still,[14] the best results are achieved with the bulky boranes such as 9-BBN although the substitution pattern of the allylsilane also plays a role in the reaction. (Scheme 21.)



Scheme 21.

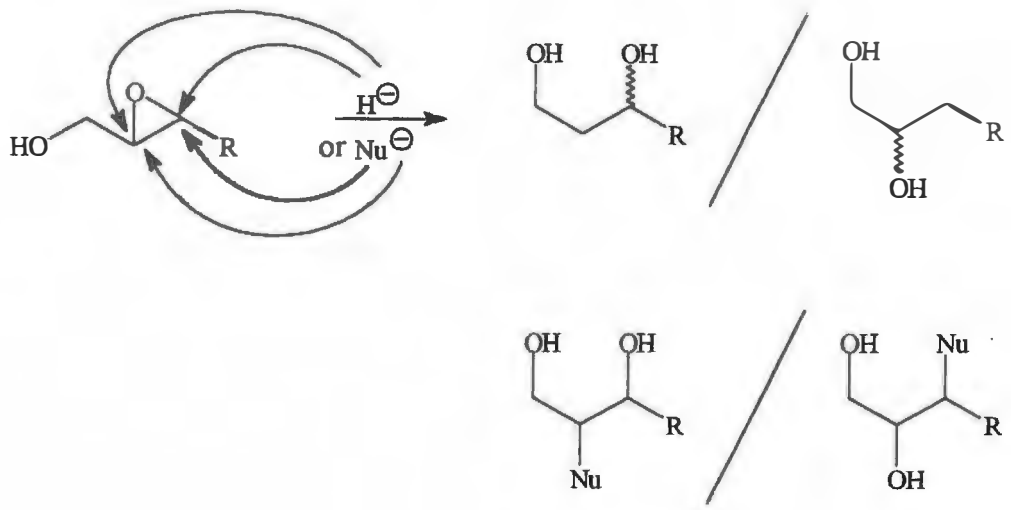
The desired 1,3-diols are easily formed by cleavage of the C-Si bond which occurs with retention of configuration.[24, 25] (Scheme 22.)



Scheme 22.

1.1.3. Epoxide/Oxirane ring opening

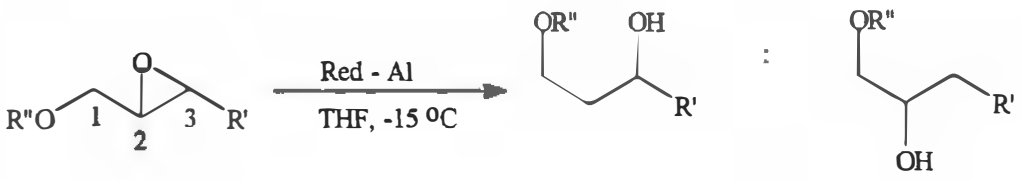
By far the most popular method for the synthesis of diols is ring opening of epoxy alcohols. This cleavage of the heterocycle can be achieved in two ways, either hydride reduction or nucleophilic attack. (Scheme 23.)



Scheme 23.

This immediately poses the problem of regioselectivity, *i.e.* how to direct attack such that one carbon of the heterocycle is favoured above the other.

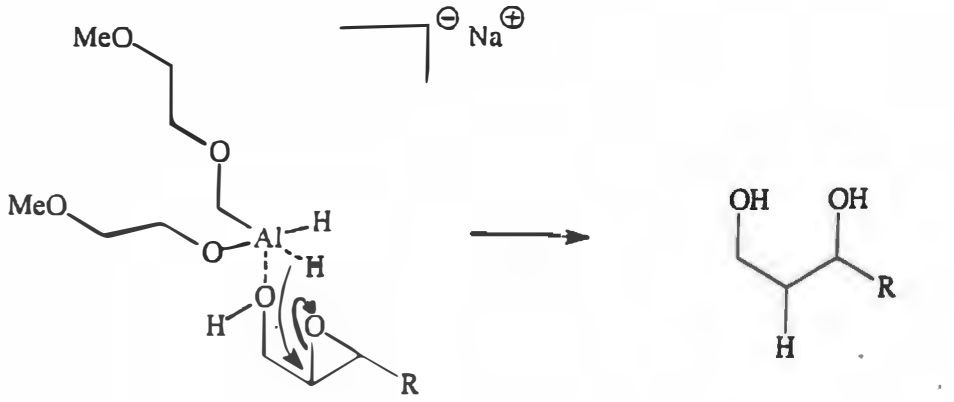
Vitti[26] reported on the regioselective reduction of racemic epoxy alcohols using Red-Al in THF at -15°C. (Scheme 24.)



R' = C_7H_{15} ; R" = H	90 % yield	~ 100 : 1
R' = C_7H_{15} ; R" = Bn	50 % yield	1 : 1.5

Scheme 24.

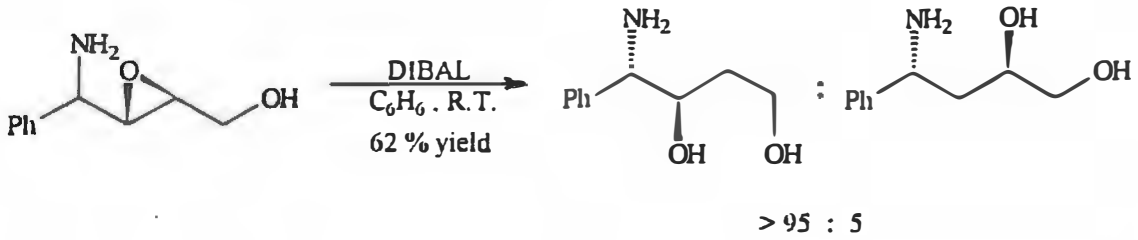
The large degree of regioselectivity was explained as follows: Co-ordination of the aluminium reagent to the hydroxyl group oxygen followed by intramolecular delivery of the hydride ion to C-2 gives the 1,3-diol product. Solvent choice also plays a role in the reaction. The reaction, given in Scheme 23 for the unprotected alcohol, was carried out in CH_2Cl_2 and gave a 1:1 mixture of products. (See Scheme 25.)



Scheme 25.

The explanation offered for the origin of regioselectivity and shown in scheme 25 is shown to be correct when the protected alcohol is allowed to react under the same conditions as it's free hydroxyl counterpart(Scheme 24 and 25).As can be seen from scheme 24 protection of the alcohol as the benzyl ether precludes the possibility for co-ordination between the aluminium atom and the unprotected alcohol moiety.This reduces the observed regioselectivity.

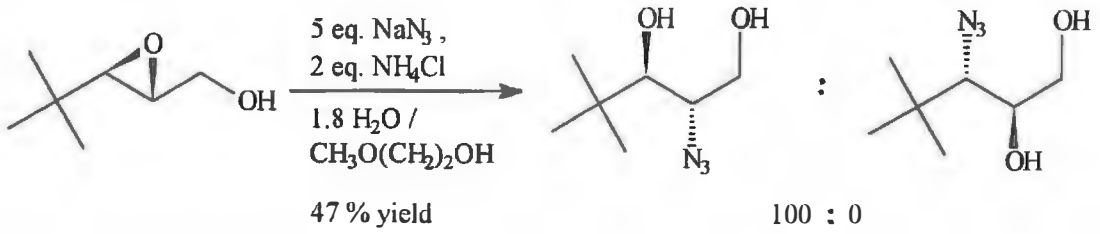
Reduction of optically pure epoxy alcohols with DIBAL[27] showed a product composition which mirrored the ratios obtained by Vitti [26] (Scheme 26.)



Scheme 26.

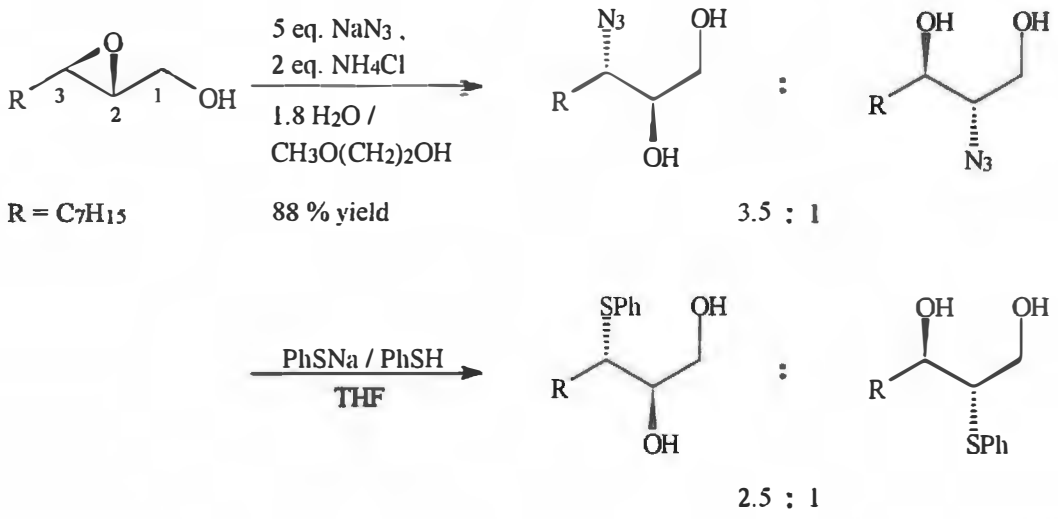
The hydroxyl moiety which plays an integral part in the origins of regioselectivity with respect to the reduction of epoxides by aluminium containing hydride reagents also influences bimolecular or nucleophilic ring openings. It now functions as the source of an electron withdrawing inductive effect which directs nucleophilic attack to C-3 and thus yields 1,2-diols. This observation was made by Behrens and Sharpless[28] who tested various 2,3-epoxy alcohols with NH_4N_3, PhSNa and PhSeNa.

Steric constraints are however the dominant influence which usually override the aforementioned directing ability of the hydroxyl group. (Scheme 27.)



Scheme 27.

In substrates where there is no significant steric bias between C-2 and C-3 the directing influence of the hydroxyl group leads to some regioselectivity, although it is interesting to note that the choice of nucleophile also plays a part. (Scheme 28.)



Scheme 28.

In conclusion therefore it can be said that two factors govern the regioselective ring openings of epoxides by nucleophiles. A major steric factor which dictates that nucleophilic attack will take place at the least hindered carbon and a secondary electronic factor, the electron withdrawing inductive effect of the hydroxyl group which favours nucleophilic attack at C-3. The combined effects of these two factors direct ring opening.

A specialized sub-branch of the general nucleophilic ring opening chemistry is nucleophilic oxymethylation of oxiranes[29]. (Scheme 29.)

Scheme 29.

This method is exceptionally useful because:-

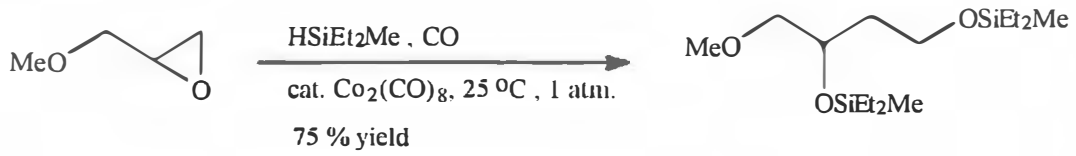
a) The large family of chiral oxiranes make it possible to synthesize a large family of chiral 1,3-diols.

b) No hydroxyl group is present in the substrate making 1,2- or 1,4-diol formation impossible.

c) The stereochemistry of two substituents of the 1,3-diol is fixed assuming normal S_N2 attack with inversion.

d) The possibility of exercising control over the stereochemistry of the entering centre relative to those already there.

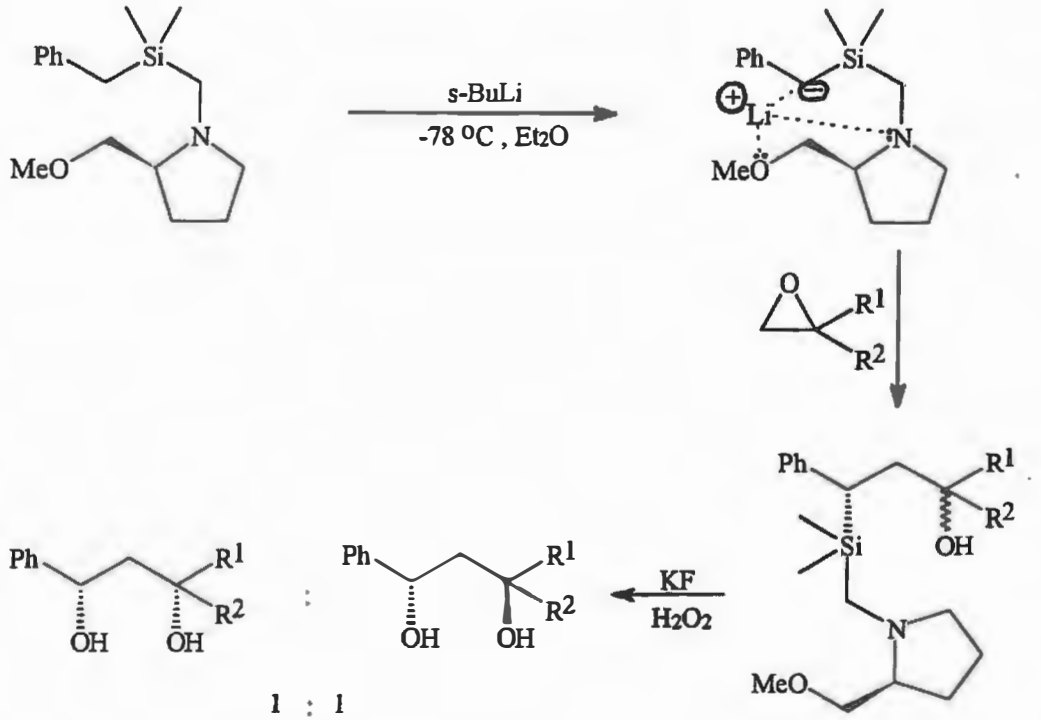
Murai *et al.*[29] showed that a combination of $Co_2(CO)_8$, $HSiEt_2Me$ and CO produces an oxymethylative equivalent which on reaction with an oxirane yields a masked 1,3-diol silyl ether product. (Scheme 30.)



Scheme 30.

The logical "next step" with this approach (oxymethylation) would be the use of optically active oxymethylative equivalents. A particularly elegant example of this is taken from work done by Chan and Nwe[30] who used an optically active organosilane

containing (S) - (+) - 2(methylmethoxy) pyrollidine as the chiral component. (Scheme 31.)

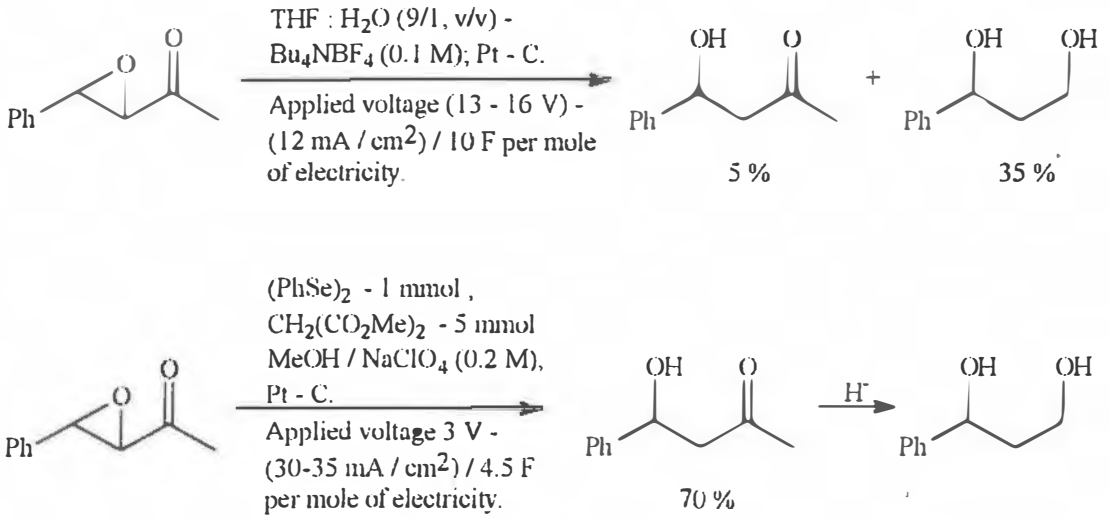


Scheme 31.

The organosilane gave practically complete stereocontrol over the formation of the benzylic chiral centre with ee's of greater than 99% being reported in all the examples studied.

Perhaps the most exotic of all ring opening procedures is the diphenyl diselenide or diphenyl ditelluride-mediated[31] electroreductive ring opening of α,β-epoxy compounds and their homologues.This reaction gives β-hydroxy ketones which are easily reduced to the 1,3-diol system(Scheme 32).

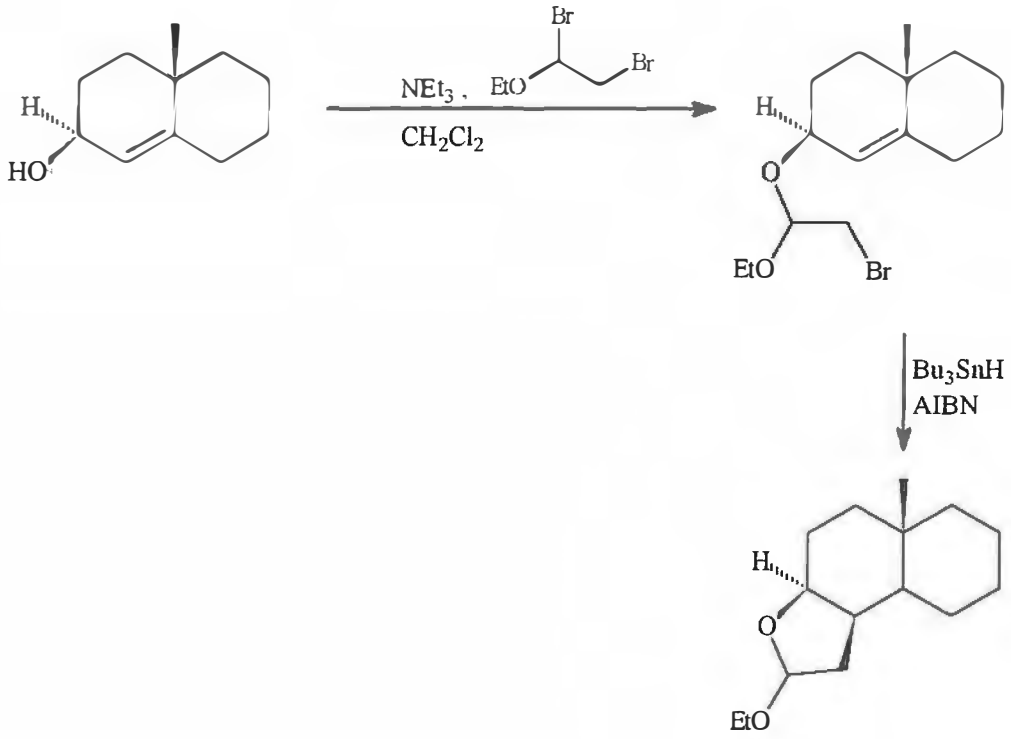
The "indirect" PhSe mediated method so called because cell conditions are strongly basic is when compared to the more traditional Birch type electroreduction more selective,gives better yields and uses less electricity.



Scheme 32.

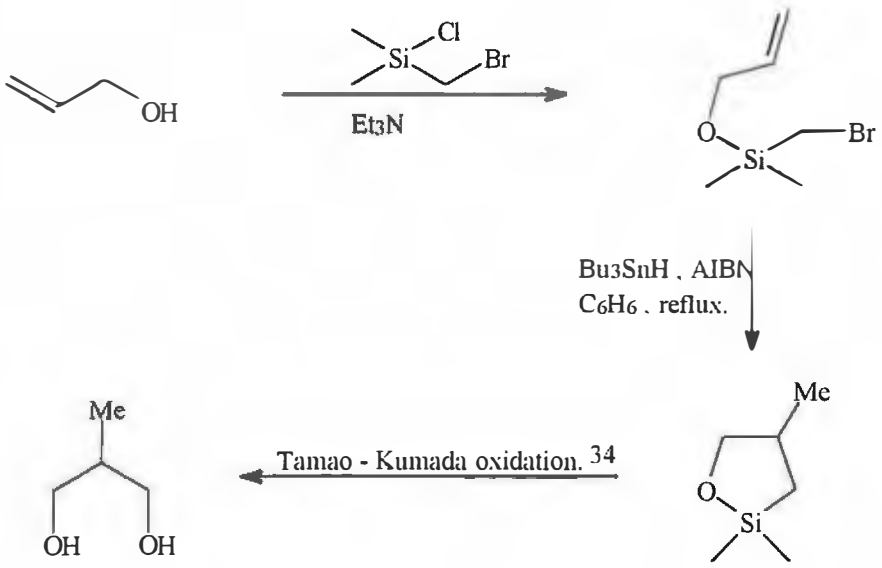
1.1.4. The use of radicals.

Free radical cyclization is currently looked upon as a potent methodology for ring construction via C-C bond forming reactions as can be seen by the following example taken from work done by Stork and Khan[32](Scheme 33).



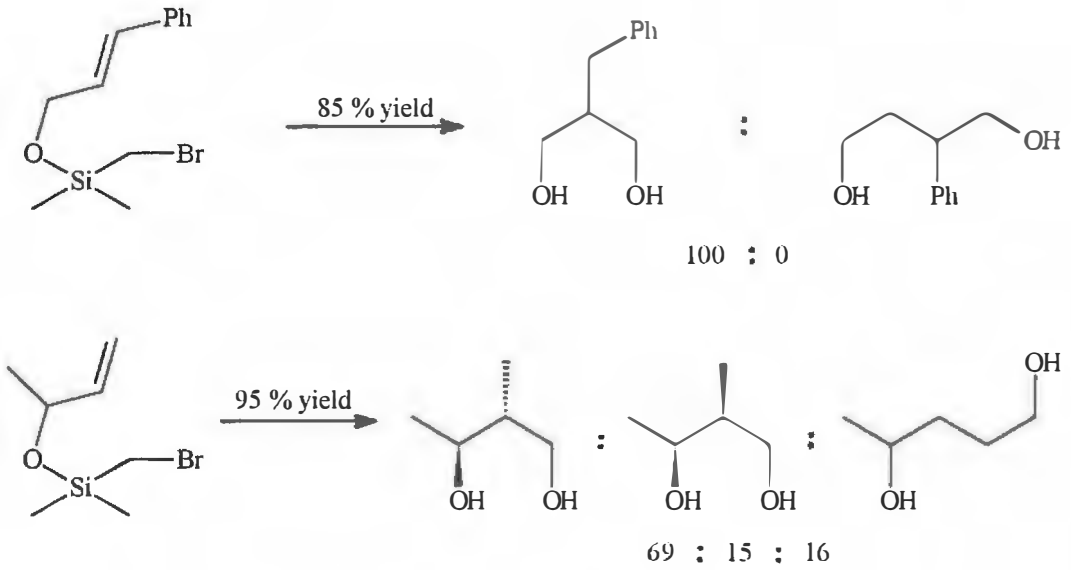
Scheme 33.

A specific aspect of this general methodology is the intramolecular reaction of a silyl methyl radical such as those derived from (bromomethyl) dimethylsilyl allyl ethers[33] and an intramolecular unsaturated chemical bond. This reaction yields silacycles and oxidative cleavage of these compounds produces 1,3-diol products[34]. (Scheme 34.)



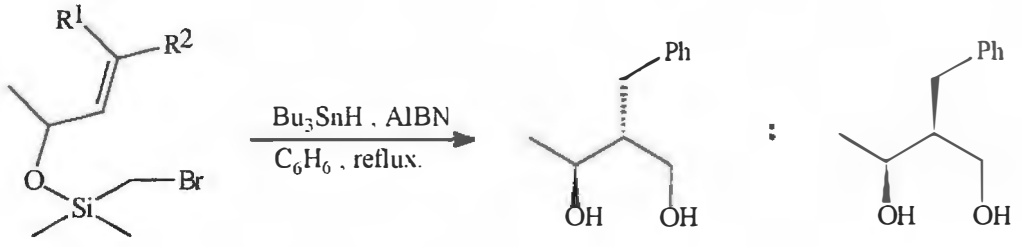
Scheme 34.

The 5-exo mode of cyclization predominates in all the cases studied, although some 6-endo cyclization leading to 1,4-diols was observed in substrates without terminal functionality. (Scheme 35.)



Scheme 35.

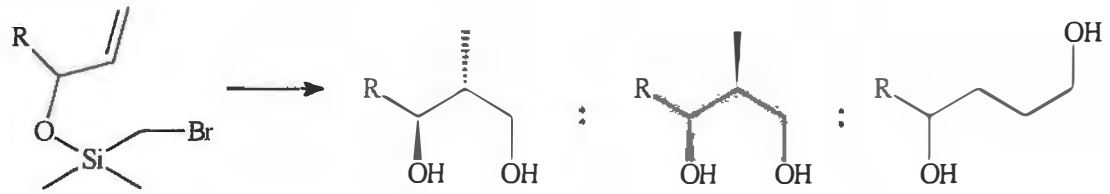
As can be seen from the above example (Scheme 35) and all the reactions studied, where the possibility for *syn* and *anti* exists, the *syn* or *threo*[35] isomer always exists as the major component. The rationale behind the observed selectivity, although speculative, is thought to depend largely on the steric bulk and orientation of the terminal substituents R^1 and R^2. (Scheme 36.)



R^1 = H ; R^2 = Ph (E) - 85 % yield :- 84 : 16
R^1 = Ph ; R^2 = H (Z) - 94 % yield :- 100 : 0

Scheme 36.

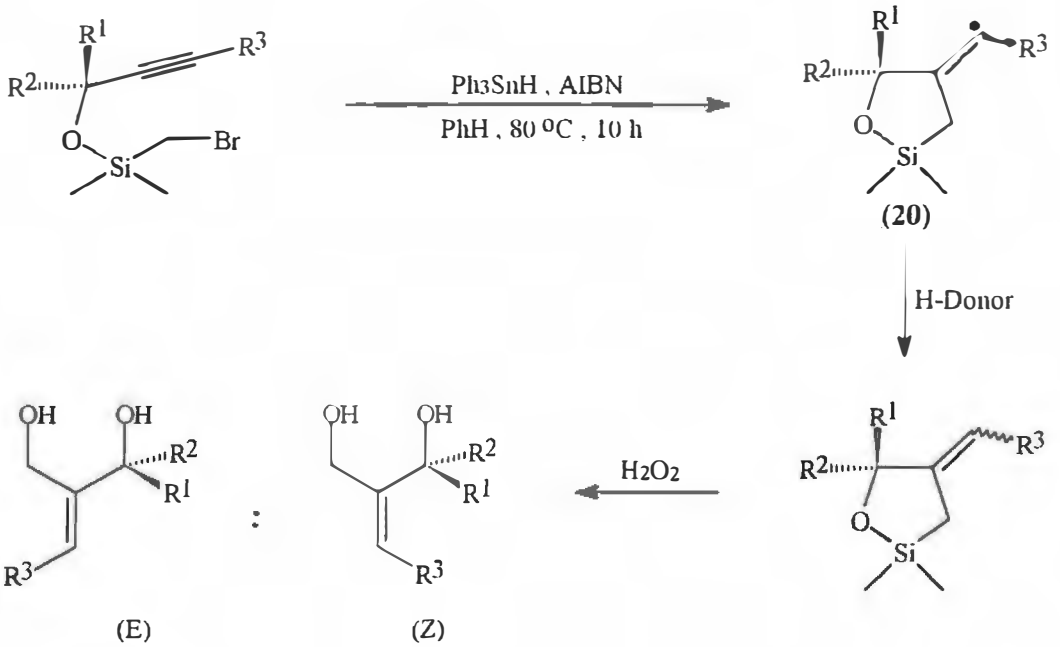
To a lesser degree the bulk of C-3 also plays a role as can be seen from the following example. (Scheme 37.)



R = Me 69 : 15 : 16
R = ^{i}Pr 82 : 0 : 18

Scheme 37.

This particular reaction was also extended to the propargylic equivalent and thus allowed entry to diallyl 1,3-diols.[36] (Scheme 38.)



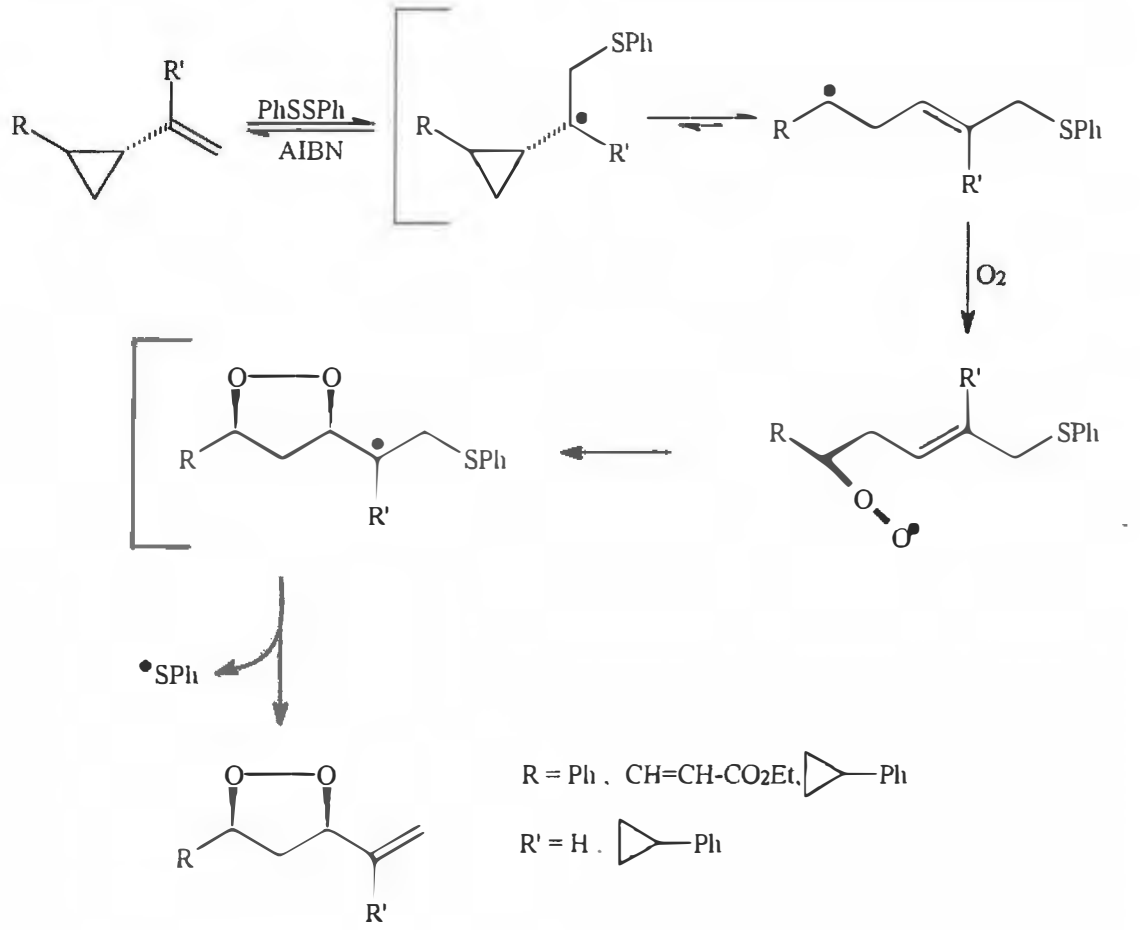
R^1 = H ; R^2 = n - C_4H_9 ; R^3 = n - C_4H_9 ; E : Z = 100 : 0

Scheme 38

It is important to note that the stereochemical integrity of the chiral centre was maintained during the course of this radical cyclization reaction.

The exocyclic vinyl radical (20) formed after cyclization has also been employed in the synthesis of trisubstituted double bonds, 5-membered unsaturated carbocycles and the diquinane system.

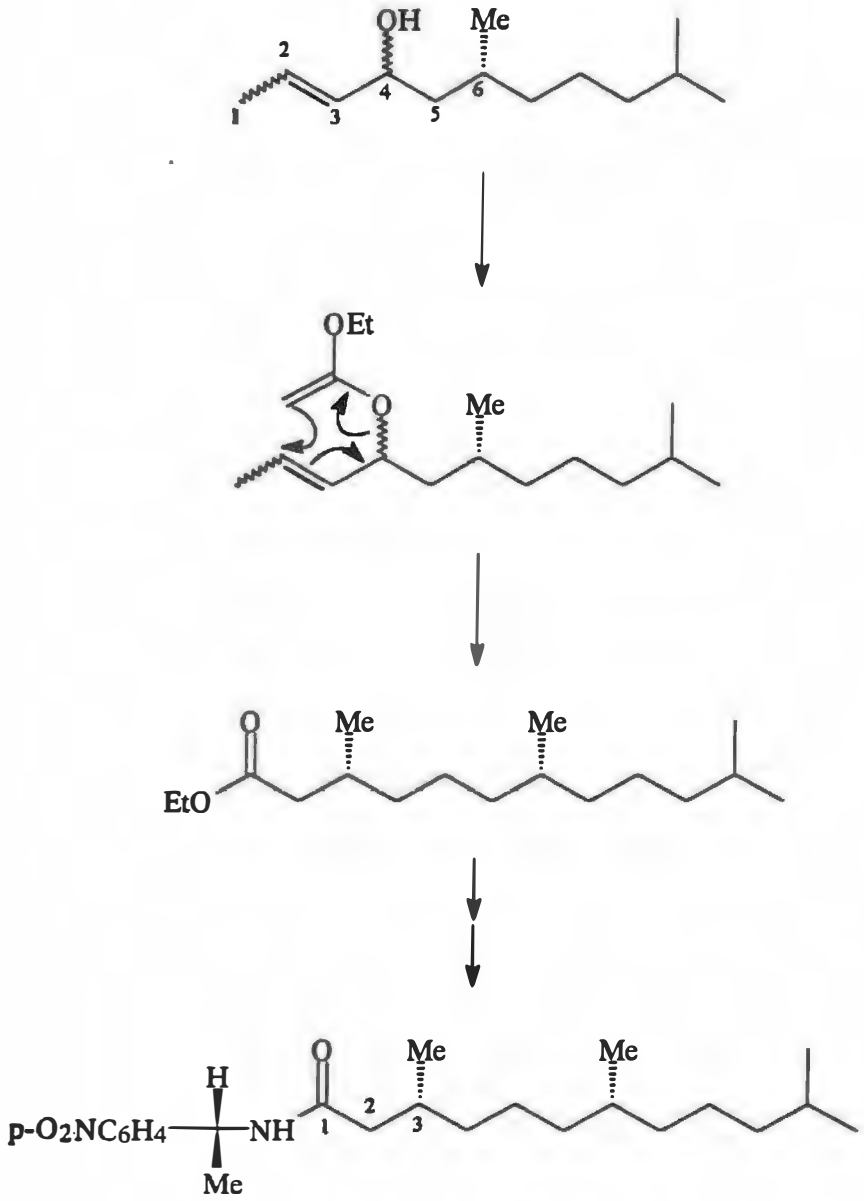
Other radical syntheses such as the chalcogen catalysed radical addition reaction of molecular oxygen and activated cyclopropane also produces 1,3-diols. These 1,3-diols are however masked as ring systems.[37] (Scheme 39.)



Scheme 39.

1.1.5. Rearrangement Reactions.

Claisen rearrangements, which are [3,3] sigmatropic reorganizations of allyl vinyl heterosystems, have been employed in numerous aspects of organic synthesis. The foundation for this utility lies in the stereo-differentiating ability of these concerted rearrangements as can be seen in the following example taken from work done by Chan *et al.*[38] (Scheme 40.)



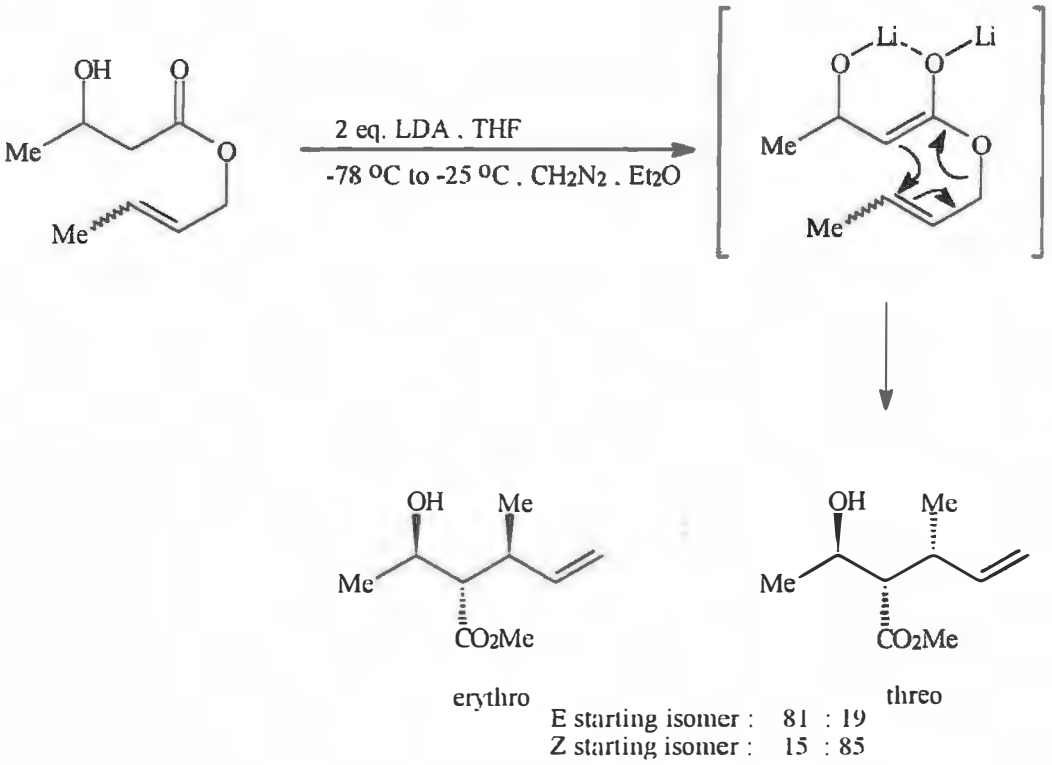
(21)

Scheme 40.

HPLC analysis of the amide (21) showed the enantiomeric composition at C_3 to be 99% pure. Thus can be seen the chiral transfer achievable with this reaction. [Both starting isomers *i.e.* *4R*, *6S*, *Z* and *4S*, *6S*, *E* gave the same product but proceed by different versions of the chair transition state.]

The Claisen rearrangement can also control the introduction of 2 chiral centres. Both relative and internal asymmetric induction is possible and this was ably demonstrated by Sucrow's[39] synthesis of steroid precursors which contain the 25-ethylated side chain.

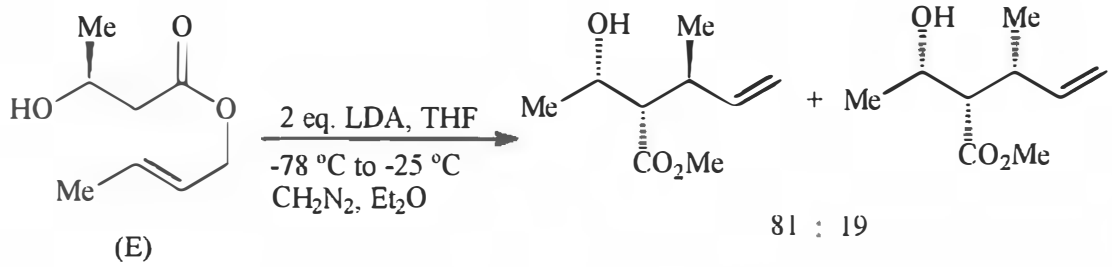
Armed with this precedent for acyclic stereocontrol, stereoselective synthesis of 1,3-diols by this method would be very attractive indeed. This was done by using a variant of the classical Claisen rearrangement, the dianionic Claisen rearrangement.[40] (Scheme 41.)



Scheme 41

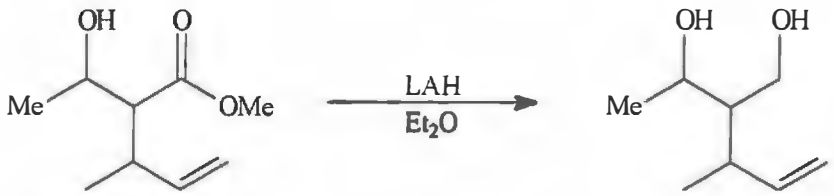
As can be seen the reaction offers excellent diastereocontrol. The products are however racemic due to exclusion of an optically pure chiral centre.

Inclusion of said chiral component, achievable in this case by resolution of the starting racemate, leads to optically pure products in good diastereomeric excess.[41] (Scheme 42.)



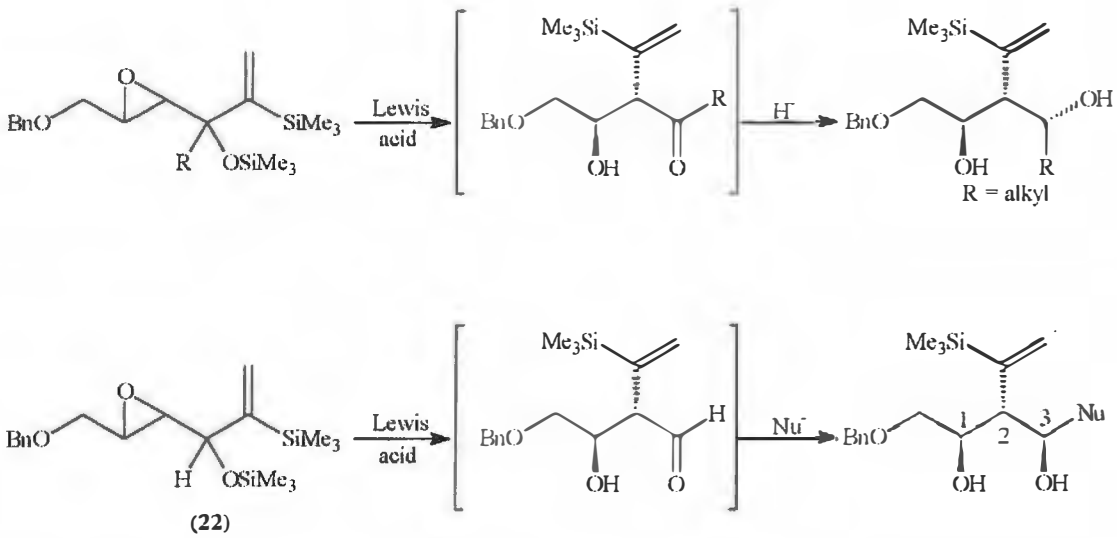
Scheme 42.

The β-hydroxy ester products are easily transformed to 1,3-diols by simple hydride reduction.[40(a)] (Scheme 43.)



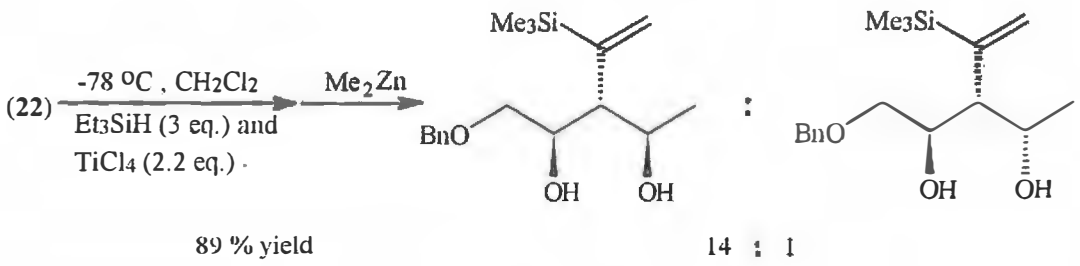
Scheme 43.

A second rearrangement allowing the synthesis of 1,3-diols was put forward by Shimazaki *et al.*[42] (Scheme 44.)



Scheme 44.

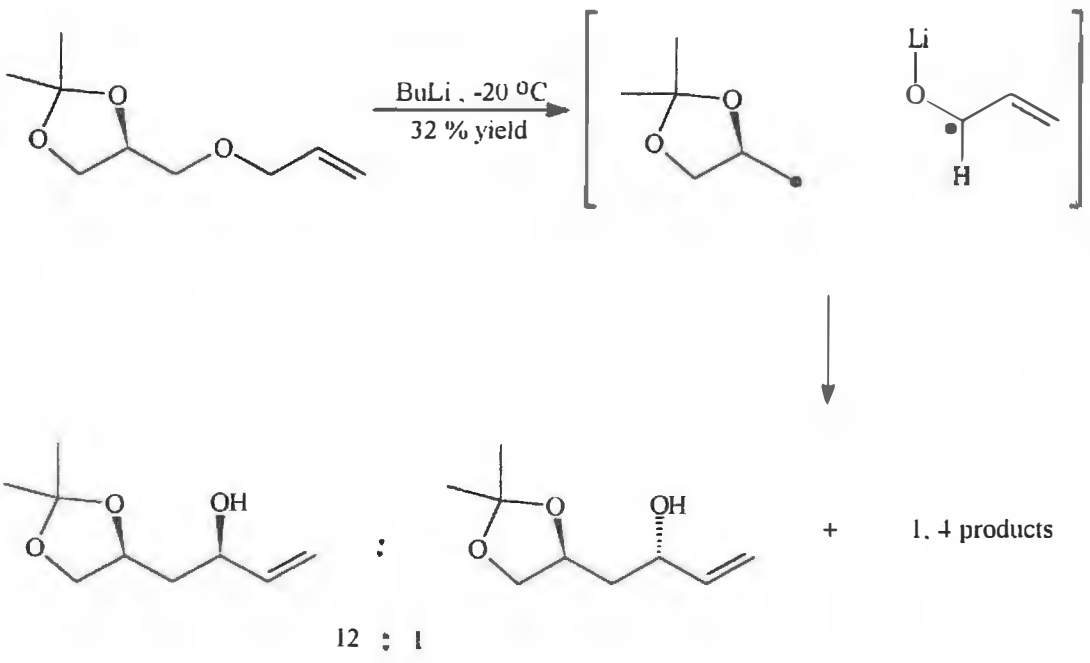
The reaction is remarkably diastereoselective and those using the epoxy TMS ether (22) as starting material display the *erythro* isomer as the major product. (Scheme 45.)



Scheme 45.

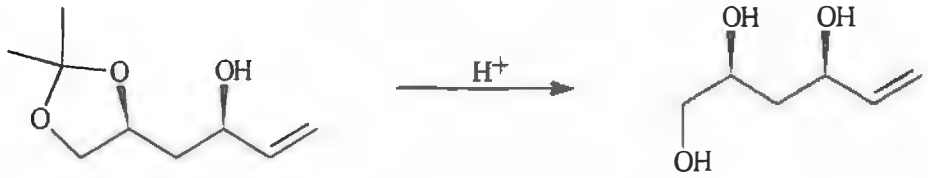
The reaction, although affording 1,3-diol products, also provides a route to establishing three and even four contiguous asymmetric centres in one step.

Another rearrangement yielding 1,3-diols is that undergone by β-hydroxy alkyl allyl ethers. On treatment with BuLi they undergo a [1,2] Wittig rearrangement to give *syn* 1,3-diols. The reaction proceeds *via* a radical intermediate and also yields the associated [1,4] Wittig products.[43] (Scheme 46.)



Scheme 46.

Simple acid catalysed deprotection will unmask the 1,3-diol products. (Scheme 47.)

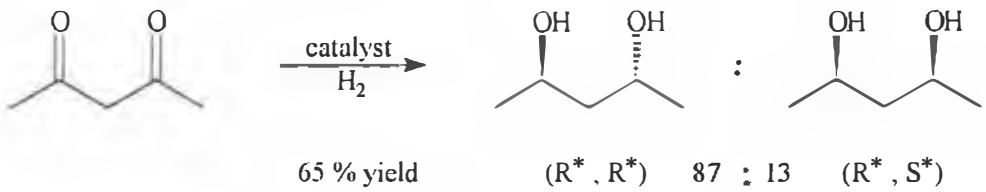


Scheme 47.

1 1.6. Hydrogenation.

All the synthetic strategies discussed up to now have a common shortcoming : they are not amenable to the large scale preparation of β-diols or, as they are more commonly known, 1,3-diols. Hydrogenation of suitable precursors is but one method capable of such large scale preparations.

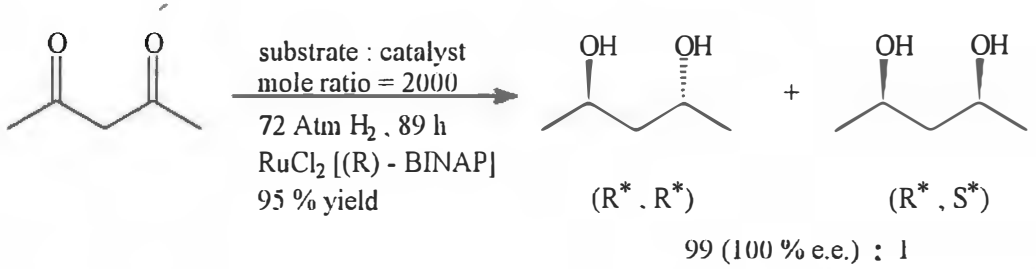
Hydrogenation of β-dicarbonyl skeletons over a Raney nickel catalyst modified with a mixture of tartaric acid and sodium bromide yields a mixture of optically active diols substantially richer in one component.[44] (Scheme 48.)



Scheme 48

In all the cases studied the major stereoisomer (R*, R*) was obtained optically pure after recrystallization. Selectivity however falls away slightly as the chain length of the substituents increase, *i.e.* replacing the methyl groups with ethyl groups for example. With ethyl groups the product ratio falls to 80:20 but still favours the (R*, R*) diastereomer.

Homogenous asymmetric hydrogenation of ketones with BINAP- Ru(II)[45] complexes is usually superior to the aforementioned heterogeneous version. (Scheme 49.)



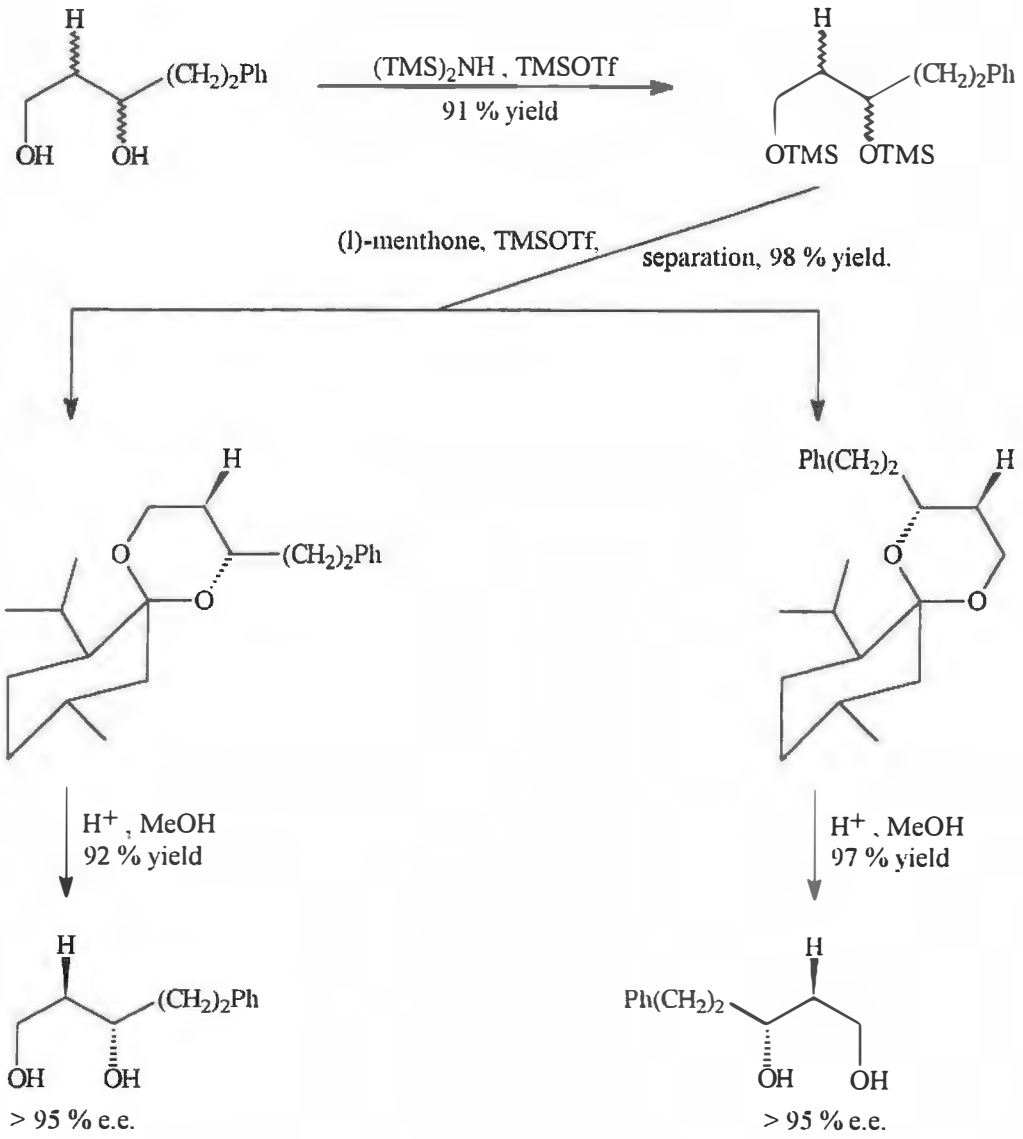
Scheme 49.

The overall stereochemical outcome of such homogeneous hydrogenations is determined by the efficiency of the catalyst/carbonyl chiral transfer(catalyst control) process and the stereochemistry of the structures adopted by the initially created hydroxy ketones. (Substrate control.) Thus the high degree of optical purity obtained for the major diastereomer (R*, R*) can be attributed to double stereoselection.[46] (stereodifferentiation.)

1.1.7 Resolution.

Another of the methods amenable to the large scale preperation of β-diols is resolution. Most resolutions involve derivatization of the diol and separation of the resulting derivatives, although a procedure put forward by Nakamura *et al.*[47] allowed enantiomeric separation without derivatization by use of a chiral polysiloxane GC column derived from (R, R)-tartramide.

Conversion of the enantiomeric 1,3-alkane diols into their diastereomeric acetals by reaction with a chiral ketone such as *l*-menthone[48] represents a typical resolution by derivatization procedure. (Scheme 50.)



Scheme 50.

Enzyme catalysed resolution of diols is also a viable method as shown by Mattson *et al.*[49] Their use of lipase from *Candida antarctica* (Component B) and the acyl donor, (*S*)-ethyl thiooctanate separated a mixture of all the stereoisomers of 2,5-hexanediol as well as other C_2-symmetrical diols by selective transesterification. (Table 2.)

Table 2:

Sub. Comp			Conver.	Remaining R-OH					Mono Ester					Diester				
SS	RS	RR		SS	SR	RR	ee	yield	SS	SR	RR	ee	yield	SS	SR	RR	ee	Yield
22	57	21	50%	98.7	1.3	0	99	86%	0.8	98.5	0.7	97	71%	0	0.1	98.9	99	78%

The transesterification reaction was rationalized as follows:

The enantiomer with two highly reactive hydroxyl moieties is transesterified to the diester, (R, R), that with one fast reacting and one slow reacting hydroxyl group to the

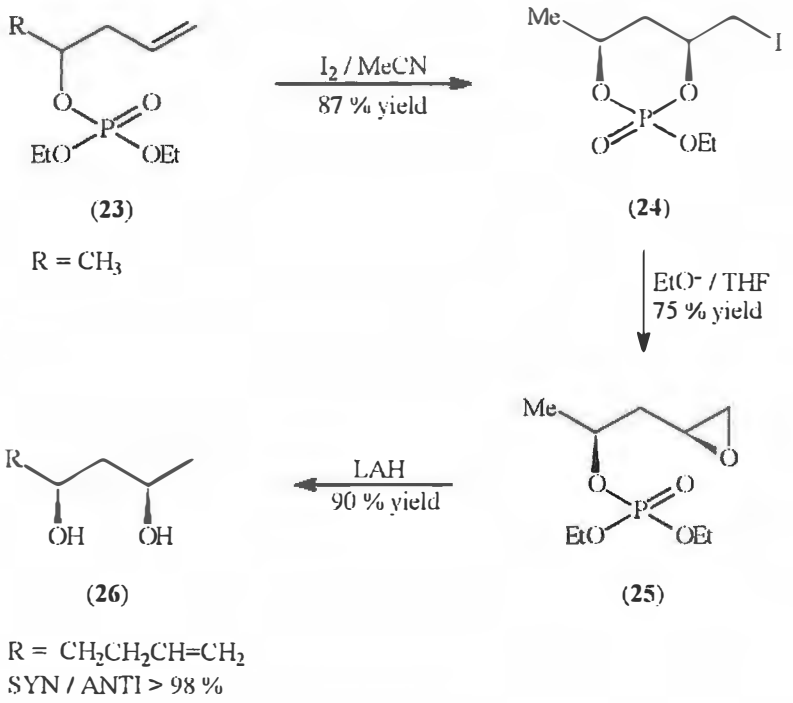
monoester, (R, S) and the isomer with 2 slow reacting hydroxyl groups (S,S) does not react at all.

1.2. Strategies employed in the synthesis of 1,3-polyols.

The 1,3-polyol, can to all intents and purposes, be looked upon as a polymer made up of discrete 1,3-diol units, the synthesis of which has been discussed up to now. This class of compound, the 1,3-polyol, forms the basis for another very useful class, the polyene macrolide antibiotics.[50]

The synthetic strategies employed in the synthesis of 1,3-polyols have recently been reviewed by Oishi and Nakata[51] and included amongst others the following examples.

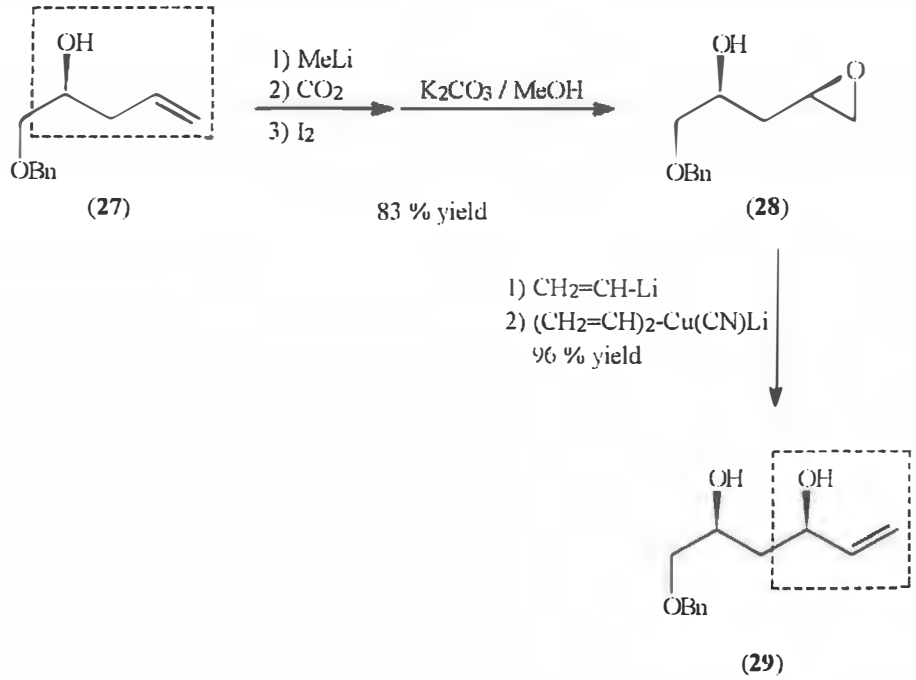
The diethylphosphate of 4-penten-2-ol (23) affords predominantly, after reaction with iodine, the corresponding *syn*-cyclic phosphate (24).[52] Ethoxide induced ring opening followed by LAH reduction produces syn 1,3-diols from (24). (Scheme 51.)



Scheme 51

Another example shows an elegant two step method for the preparation all 1,3-*syn*-1,3- polyol systems.[53] The first step involves preparation of (28) from (27) by a

modified Cardillo procedure and step two is a two carbon elongation step achieved by use of a higher order cuprate derived from vinyllithium and cuprous cyanide. (Scheme 52.)



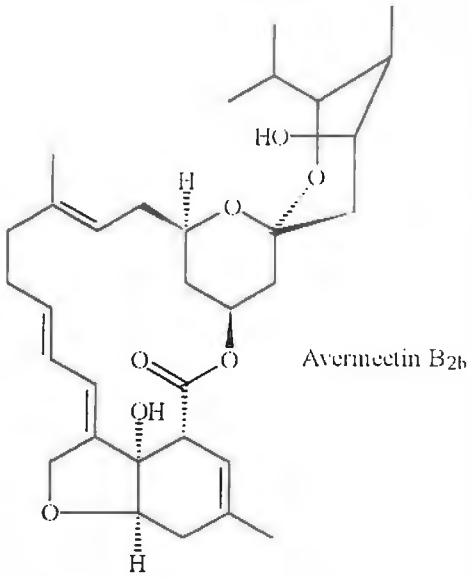
Scheme 52.

This method also lends itself to use in a repetitive strategy because the product (29) can now be used as the starting material for a second run with the aforementioned two step procedure.

1.3. Applications of 1.3-diols.

1.3.1 Precursors for the spiroacetyl moiety of Avermectins A_{1b}, B_{2b}(30), B_{1b}, B_{1a}, A_{1a}, A_{2a}, A_{2b} and B_{2a} as well as Milbemycins α_7 and α_8.

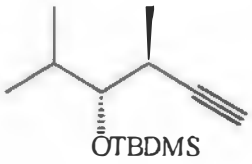
The avermectins are a family of macrocyclic lactones which exhibit exceptional pesticidal activity toward two major classes of parasite, the arthropods (insects, ticks, lice, and mites) and the nematodes (roundworm.) Surprisingly enough these macrocycles are devoid of the antibacterial activity shown by similar macrolide antibiotics[54]. These compounds act by interfering with invertebrate neurotransmission[54] and Invermectin, available in one step from the fermentation product of *Steptomyces avermitillis* has already been marked for veterinary use.[55]



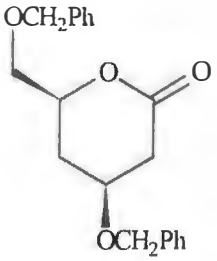
Avermectin B_{2b}

(30)

Retrosynthesis has shown that the spiroketal moiety can be synthesized from an optically active acetylene unit (31) and a six membered lactone (32).

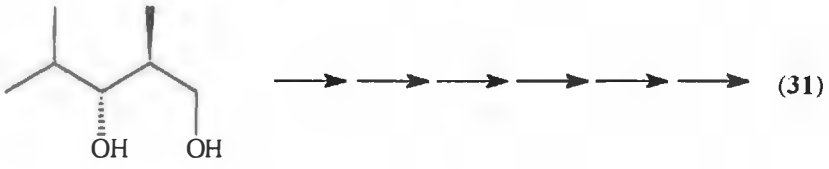


(31)



(32)

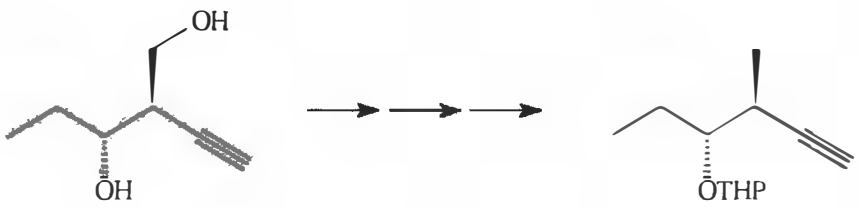
The acetylene unit (31) can be synthesized in 6 steps from an optically active 1,3-diol. (33). (Scheme 53.)



(33)

Scheme 53.

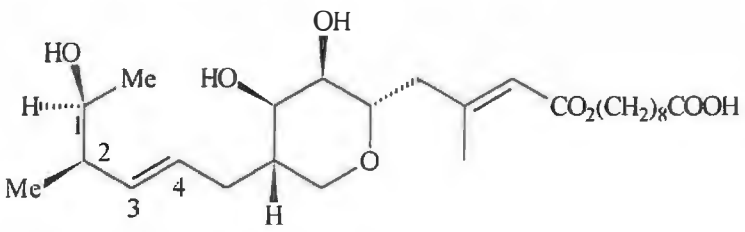
The milbemycin synthesis follows the same pattern except a different 1,3-diol (34) is used to afford the required acetylene unit (35). (Fig. 4.)



(34) (35)

(Fig. 4.)

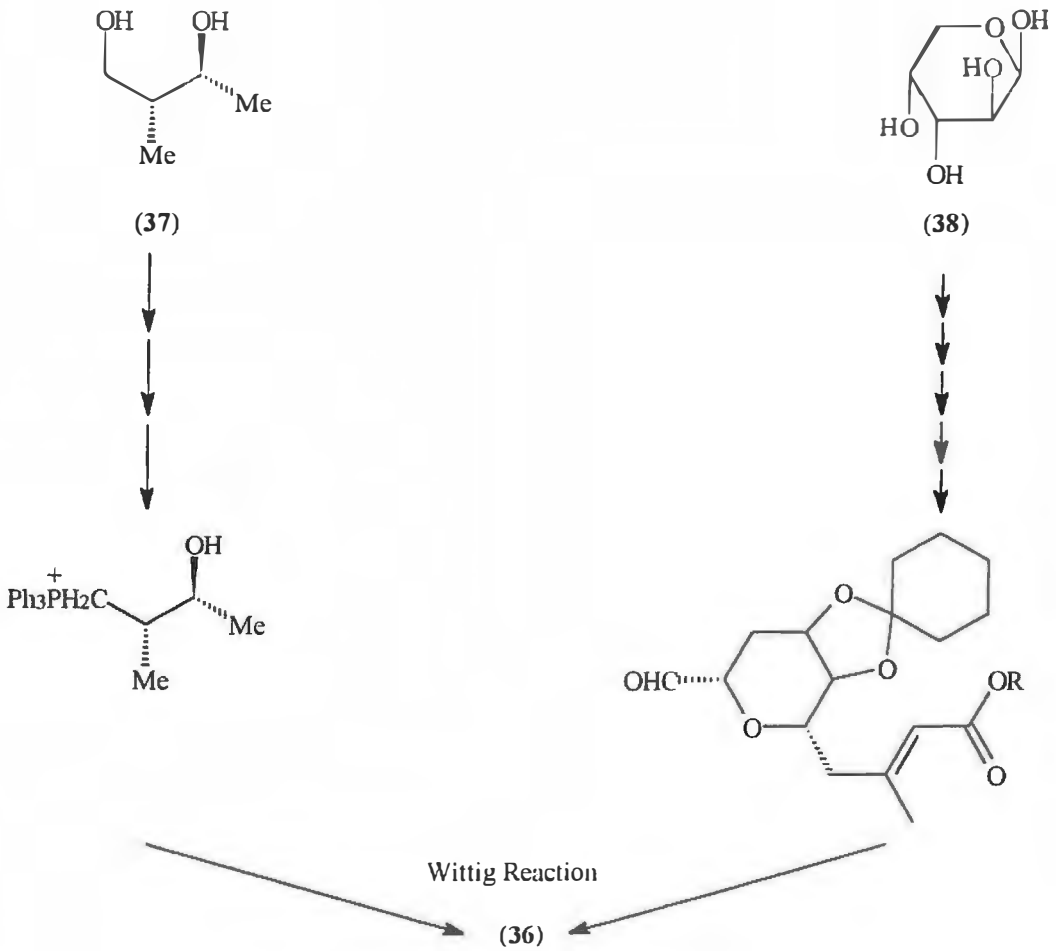
1.3.2 Precursors for Pseudomonic Acid C (36)



(36)

(Fig. 5.)

The strain *Pseudomonas flourescens* NCIB10586 produces 3 acids, Psuedomonic acids A, B and C [56, 57], all of which show antibacterial as well as antimycoplasmal abilities. Psuedomonic Acid C, by cleavage of the bond between C_3 and C_4 (Fig. 5.), can be synthesized from a derivative of *2R*-methylbutan-1,3-*S*-diol (37)[58] and an optically active derivative of D-arabinose (38)[56] (Fig. 6.).



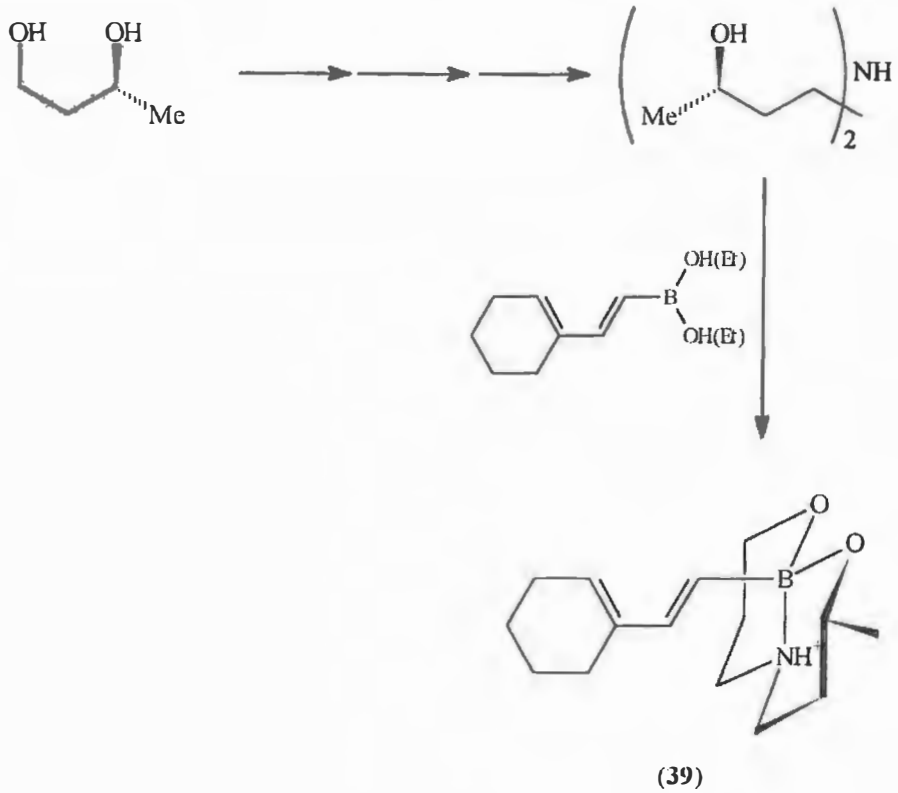
(Fig. 6.)

1.3.3 Precursors for the synthesis of chiral dienes to be used in the Diels Alder Reaction.

One of the most important molecule building tools known to the modern chemist is the Diels Alder reaction. (Fig. 7.)

(Fig. 7.)

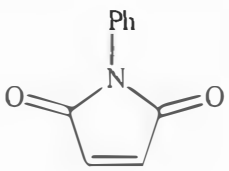
Chiral compounds which are usually biologically active can be synthesized with this reaction, but this necessitates the need for stereocontrol. This need for stereocontrol is satisfied in three ways, use of an optically pure diene or dienophile, or a chiral catalyst. The 1,3-diol has found a niche in this respect as it forms the basis of a chiral diene.[59] (39). (Fig. 8.)



(39)

(Fig. 8.)

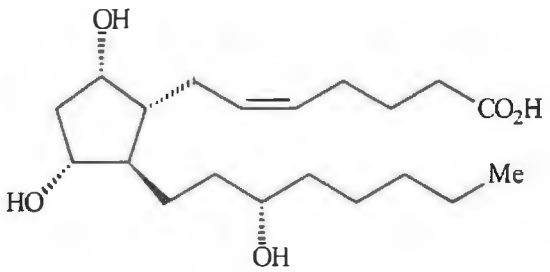
Reaction between diene (39) and N-phenylmaleimide (40) forms the endo adduct exclusively thus demonstrating the excellent stereocontrol achievable with the diol-derived chiral diene (39).



(40)

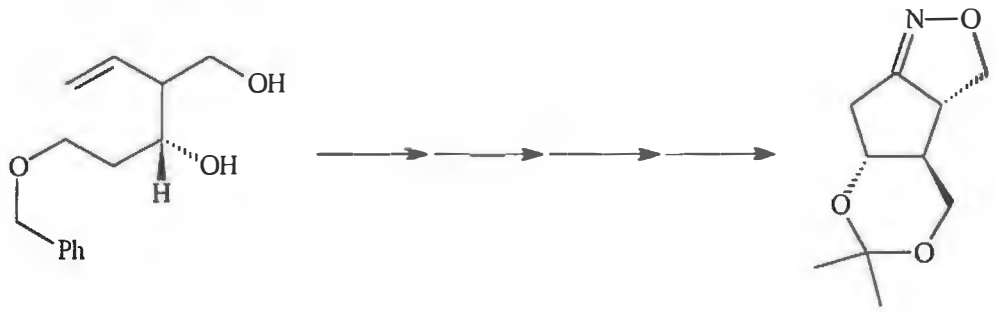
1.3.4 Precursors for prostoglandin $PGF_{2\alpha}$

Prostogladin $F_{2\alpha}$ (41), the most commonly occurring member of the prostoglandin family, shows potent biological activity. It is able to stop pregnancy in the second trimester[60] by inducing labour, has bronchoconstriction[61] properties as well as being able to inhibit platelet aggregation.[62] This makes it useful in the treatment and prevention of thrombosis.



(41)

The cyclopentane ring of $PGF_{2\alpha}$ can be synthesized from the appropriate 1,3-diol (42) by an intramolecular nitrile oxide cycloaddition reaction.[63] (Fig. 9.)



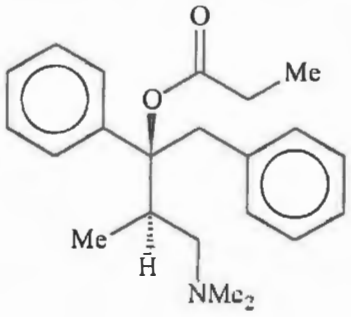
(42) (43)

Fig. 9.

The isoxazoline (43) is then used to synthesize $PGF_{2\alpha}$ by a number of chemical transformations.[63, 64]

1.3.5. Precursors for various pharmaceuticals.

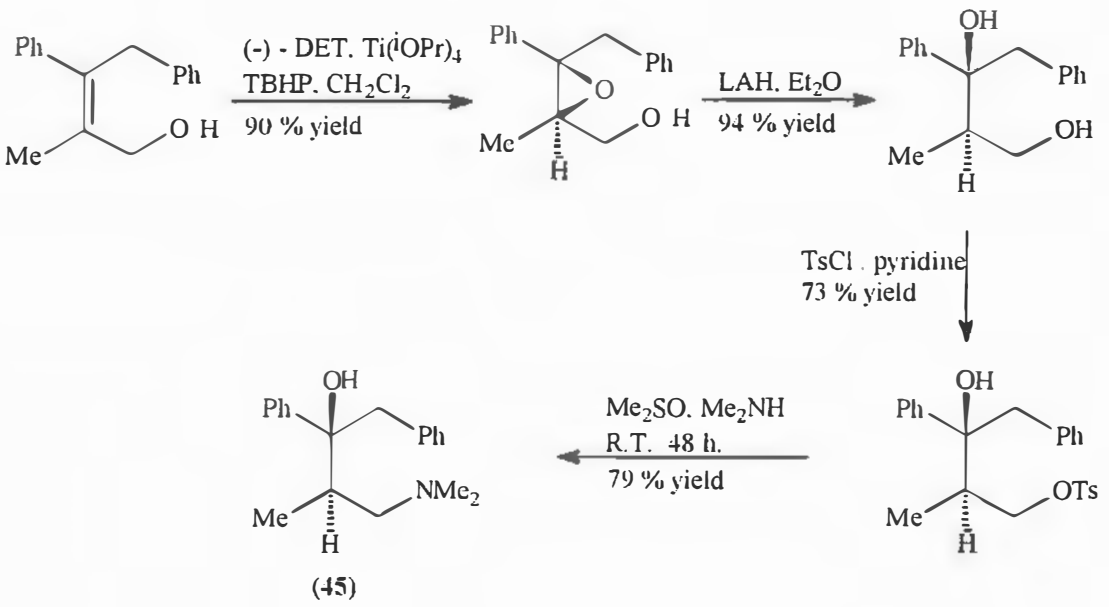
The *d*-isomer of 1-benzyl-3-dimethylamino-2-methyl-1-phenyl propylpropionate (44) [Tradenames: DARVON, PEPRONAL, DEVELIN][65] is an analgesic used for the relief of mild pain.



(44)

The *l*-isomer on the other hand is a cough suppressant (anti-tussive agent)

Both enantiomers are synthesized together with separation being achieved by resolution. The enantioselective synthesis of either enantiomer is thus extremely attractive because it alleviates the need for a resolution step. This was done for a key intermediate (45) in the synthesis of (44) by Erickson[66], who achieved this by harnessing the Sharpless asymmetric epoxidation reaction. (Scheme 54.)

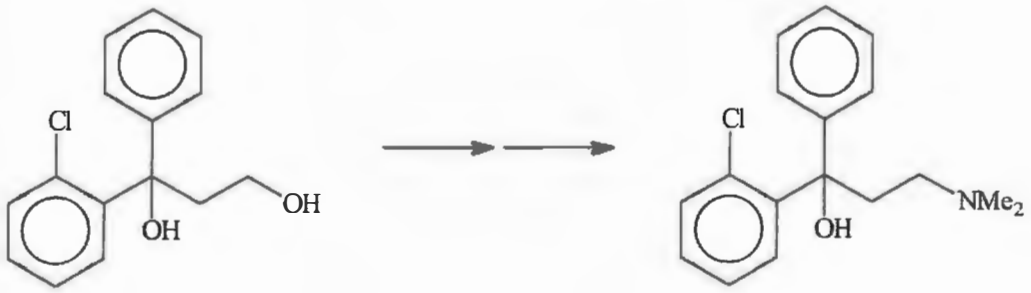


(45)

Scheme 54.

Simple esterification of the alcohol (45) will give the desired product (44).

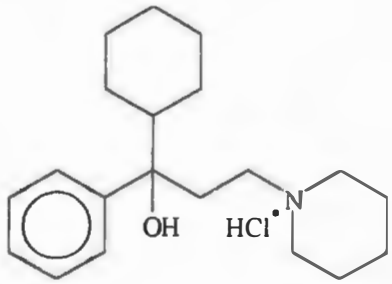
With the last two transformations in mind (Scheme 54), it is possible to synthesize chlophedianol, (46) [Tradenames: DETIGON, DECTOLITAN][67] a cough suppressant from the appropriate 1,3-diol (47). (Fig. 10.)



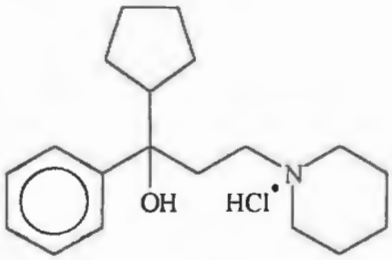
(47) (46)

(Fig. 10.)

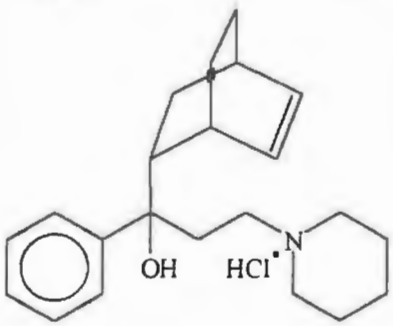
It is also interesting to note that substitution of one of the aromatic rings in (46) with an alicyclic ring gives a series of anti-cholinergic or anti-spasmodic drugs. (Fig. 11.)



Tradenames : ANTI-SPAS, APARKANE, BROFLEX.[68]
(HCl salt)



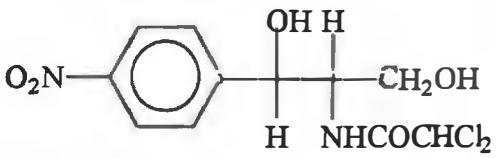
Tradenames : PAGITANE HCl[69]
(HCl salt)



Tradenames : AKINETON, AKINOPHYL[70]
(HCl salt)

(Fig. 11.)

Another 1,3-diol of pharmaceutical importance is 2,2-dichloro-N-[(αR, βR)-β-hydroxy-α-hydroxymethyl-4-nitrophenyl] acetamide (48), an antibiotic.



(48)

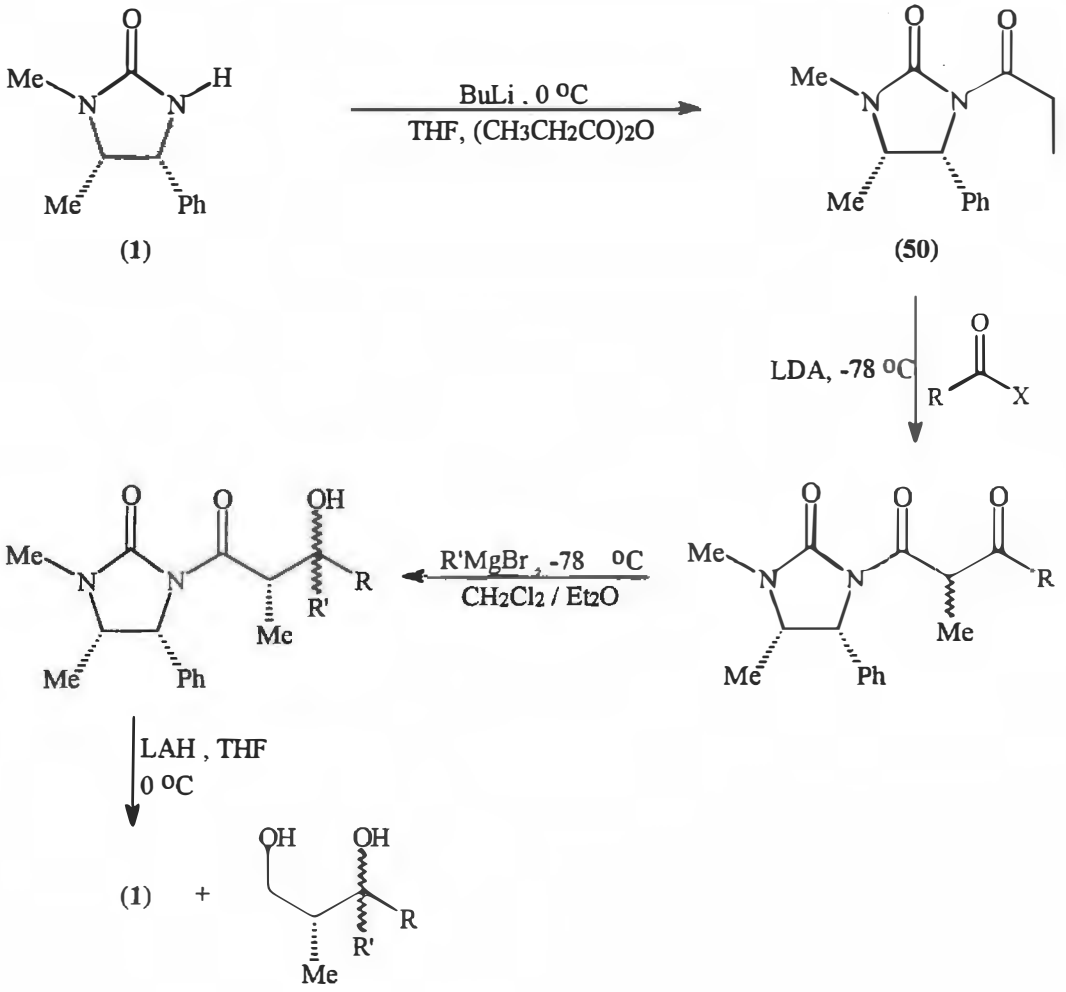
Tradename : CHLOROMYCETIN[71]

As can be seen from the preceding discussion the 1,3-diol synthon is exceptionally useful in the synthesis of various natural products, pharmaceuticals and other compounds.[72, 73]

2. DISCUSSION

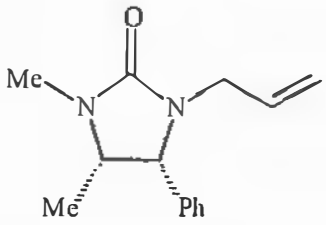
Chirality is a major phenomenon in nature and molecular asymmetry in particular plays a crucial role in science and technology. A variety of significant biological functions emerge through molecular recognition which requires strict matching of chirality. Accordingly enantioselective synthesis of chiral organic compounds is an important task allotted to the synthetic chemist. This concept is realized in a number of ways, an example of which is the chiral transfer agent or chiral auxiliary which allows stereoselective carbon-carbon bond forming reactions to occur.

As previously stated, this project will deal with the enantioselective synthesis of chiral 1,3-diols using a cyclic ephedrine derivative (1) as the chiral auxiliary. (Scheme 55.)



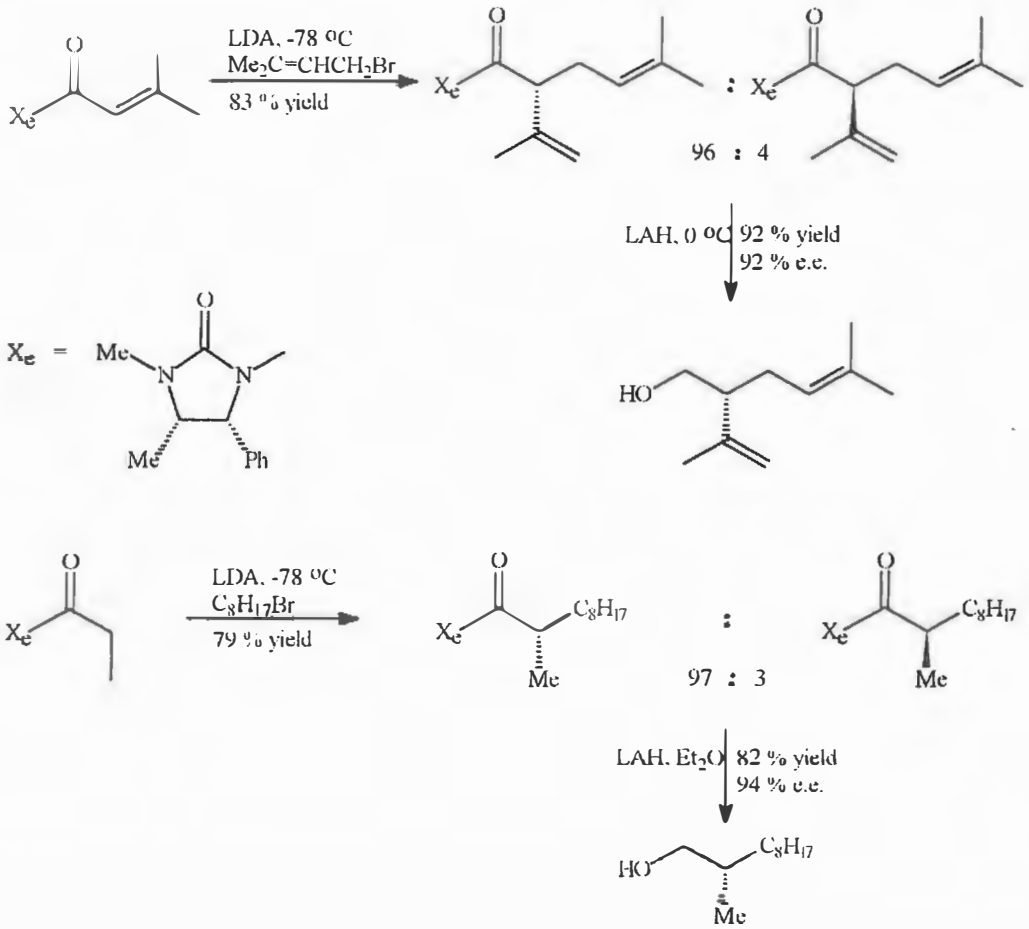
Scheme 55.

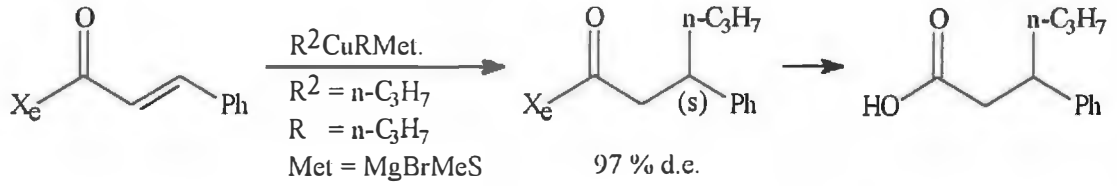
Imidazolidin-2-one (1), since its original synthesis by Close[74], has shown itself to be an extremely potent chiral auxiliary, as can be seen by a few of the more recent examples of its use. Helmchen and co-workers[75] used a carbanion derived from the N-allyl derivative (49) in diastereoselective homoaldol reactions with aldehydes and ketones to afford homochiral γ-lactones.



(49)

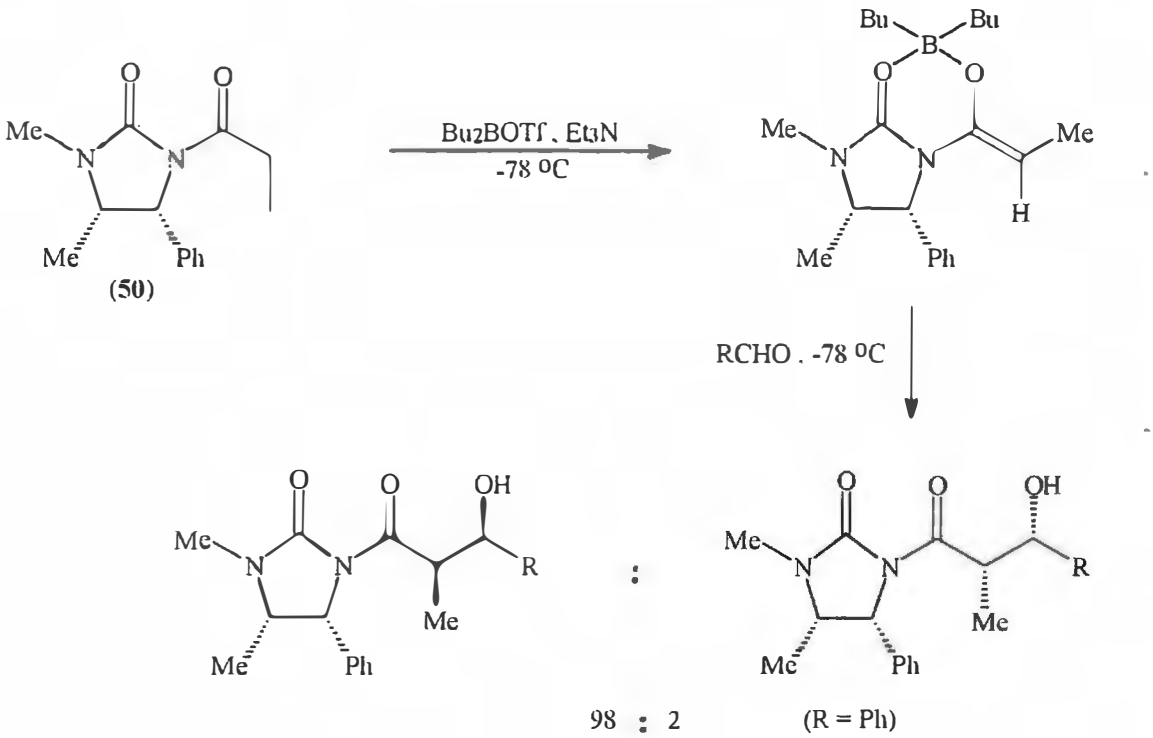
Alkylation of N-acylimidazolidin-2-ones[76, 77,78] as well as conjugate addition reactions with organocuprates[79, 80] all showed themselves to proceed diastereoselectively (Schemes 56)





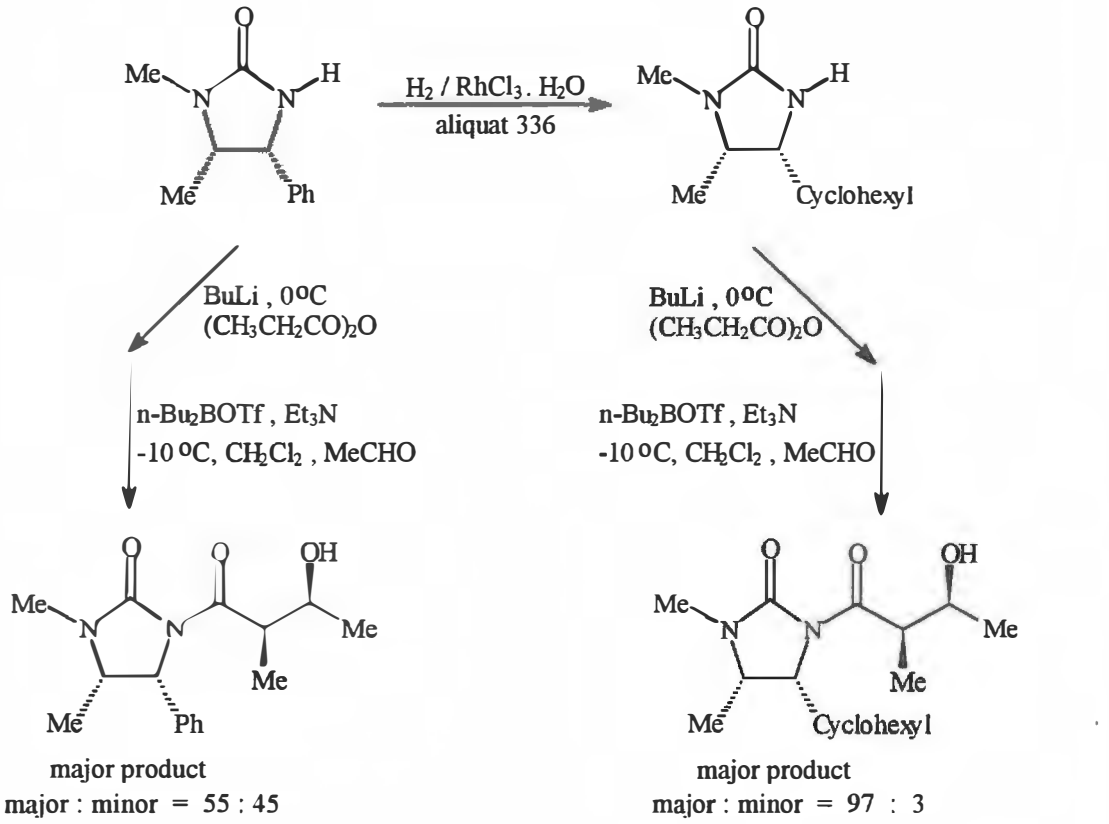
Scheme 56.

Malissar[81] has also recently shown that the aldol reactions between a carbanion derived from (50) and arylaldehydes proceeds stereoselectively. (Scheme 57.)



Scheme 57.

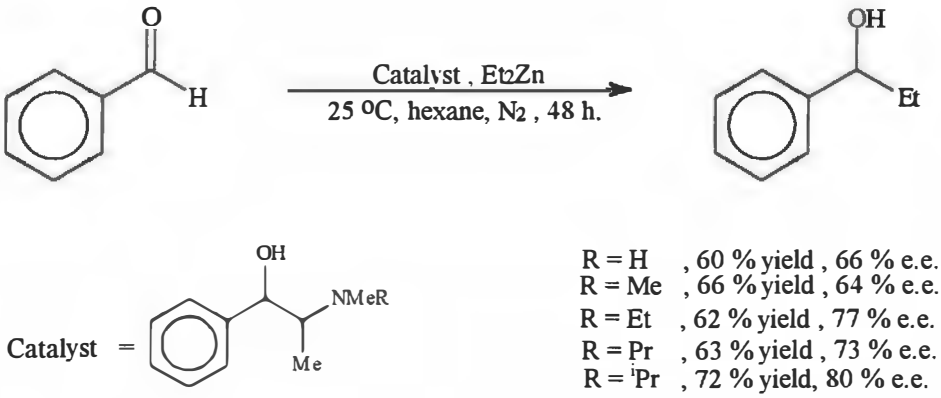
The equivalent reactions with aliphatic aldehydes was however not as selective. A novel modification to the auxiliary, hydrogenation of the phenyl ring to a cyclohexyl ring[82] increased the degree of stereoselection. Interestingly enough this increased stereoselection for aliphatic aldehydes was not accompanied by a loss of selectivity for arylaldehydes. (Scheme 58.)



Scheme 58.

Worth mentioning at this point is the fact that acyclic ephedrine derivatives are themselves potent chiral inducers.

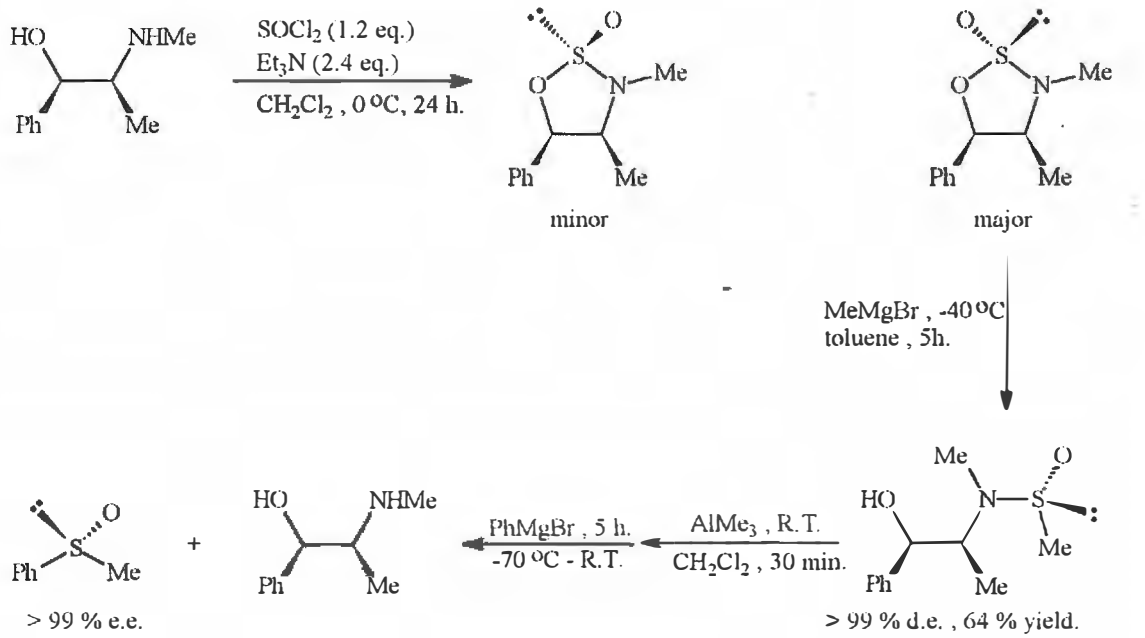
Chalconer *et al.*[83] used ephedrine as well as N-alkyl derivatives thereof to catalyse the enantioselective addition of diethylzinc to benzaldehyde and other arylaldehydes. This reaction, catalytic asymmetric alkylation of carbonyl compounds, is an important method for the synthesis of enantiomerically pure alcohols. (Scheme 59.)



Scheme 59.

Compared to other catalytic systems such as (*S*)-(+)-prolinol, quinine, chinchonidine, cinchonine and quinidine, (-)-N-methyl ephedrine gave better results for the ethylation of benzaldehyde.[84]

Benson and Snyder"s[85] synthesis of optically active sulphoxides, for potential use as chiral solvating agents in ^{1}H NMR spectroscopy also utilized ephedrine, although in this case the chiral auxiliary was covalently bonded to the starting material. (Scheme 60)

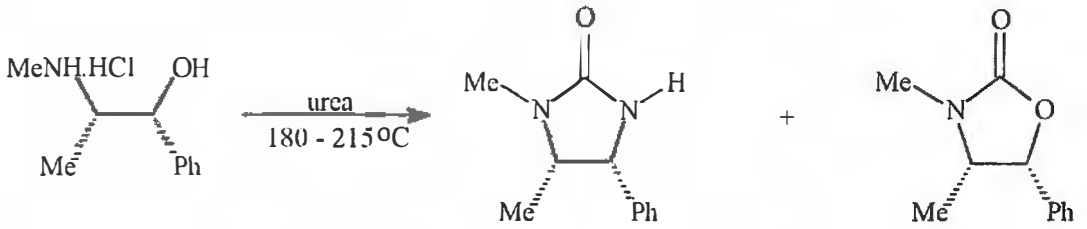


Scheme 60.

As can be seen from these precedents, ephedrine in both cyclic and acyclic forms is an impressive chiral inducer making the proposed synthesis of 1,3-diols (Scheme 55) using (1) extremely attractive.

2.1 The Synthesis of (*4R,5S*)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one.(1)

Imidazolidin-2-one (1) was prepared according to the method described by Close[74] involving the fusion of the hydrochloride salt of (-)-ephedrine and urea. The yields were however low due to a competing condensation reaction which afforded the oxazolidin-2-one (51) (Scheme 61.)



(1) (51)

Scheme 61.

Efforts by Malissar,[81] directed towards increasing the yield of (1), showed that magnetic or mechanical stirring optimized the yield of imidazolidin-2-one(1). (Table 3.)

Table 3:

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

(a) Using the method prescribed by Close with the following variations:

A. = Urea as both solvent and reactant without stirring.

B = as with A but magnetic stirring.

C = as with A but with mechanical stirring for large scale preparations.

D = nitrobenzene is solvent with magnetic stirring.

(b) isolation of product was difficult.

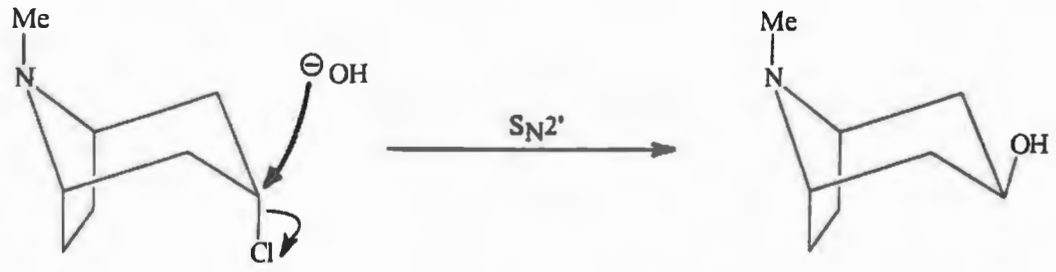
Based on this investigation by Malissar[81],(1) was prepared according to variation B (See table 3).

The proposed mechanism for the formation of (1) was a double inversion pathway more commonly referred to as the neighbouring group mechanism.[86, 87]

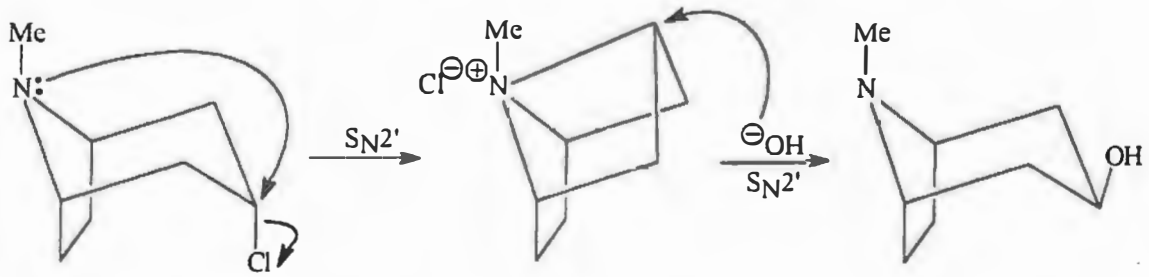
The neighbouring group concept as proposed by Capon[87] stated that molecular substituents may influence a reaction by stabilizing a transition state or intermediate. This stabilization is achieved by said substituents becoming fully or partially bonded to the reaction centre. It is also possible that as a direct result of the increased

stabilization, an increased reaction rate may result, in which case neighbouring group participation is now known as intramolecular catalysis. (Scheme 62.)

Without neighbouring group participation:

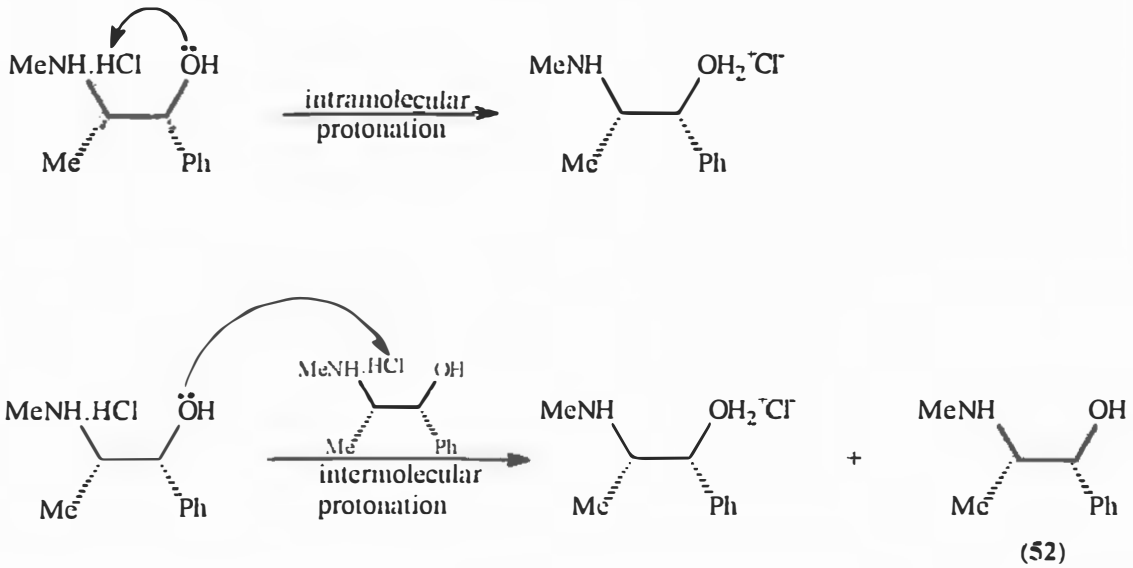


With neighbouring group participation:



Scheme 62.

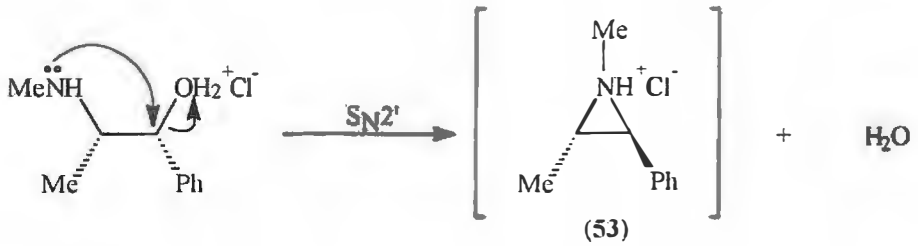
The first step in the proposed mechanism for the formation of (1), involves protonation of the hydroxyl group on the ephedrine moiety. This can occur either intramolecularly or intermolecularly. (Scheme 63)



(52)

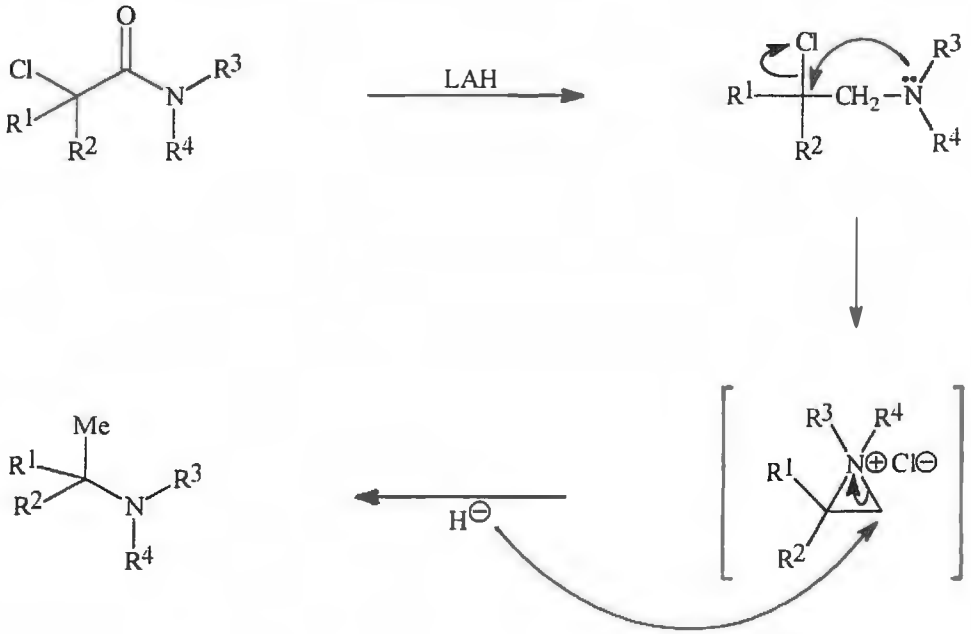
Scheme 63.

The second step in the proposed mechanism will follow two routes depending on the mode of protonation of the hydroxyl group. If protonation is intramolecular, then the next step of the reaction involves attack of the nitrogen lone pair (neighbouring group - Scheme 62.) on the benzylic carbon to form an intermediate aziridine salt (53) (Scheme 64.)

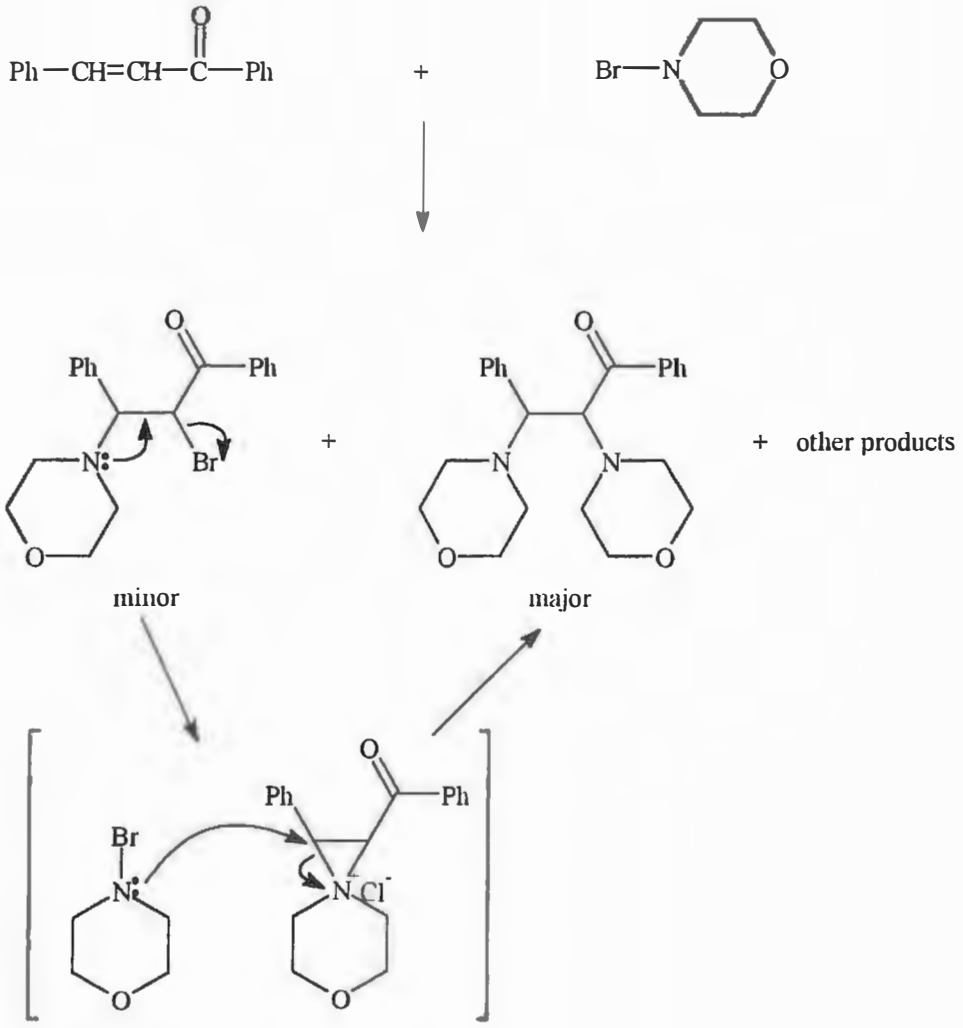


Scheme 64.

The existence of the this intermediate aziridine salt (53) is not unusual if one considers the following precedents.[88, 89] (Scheme 65 and 66.)

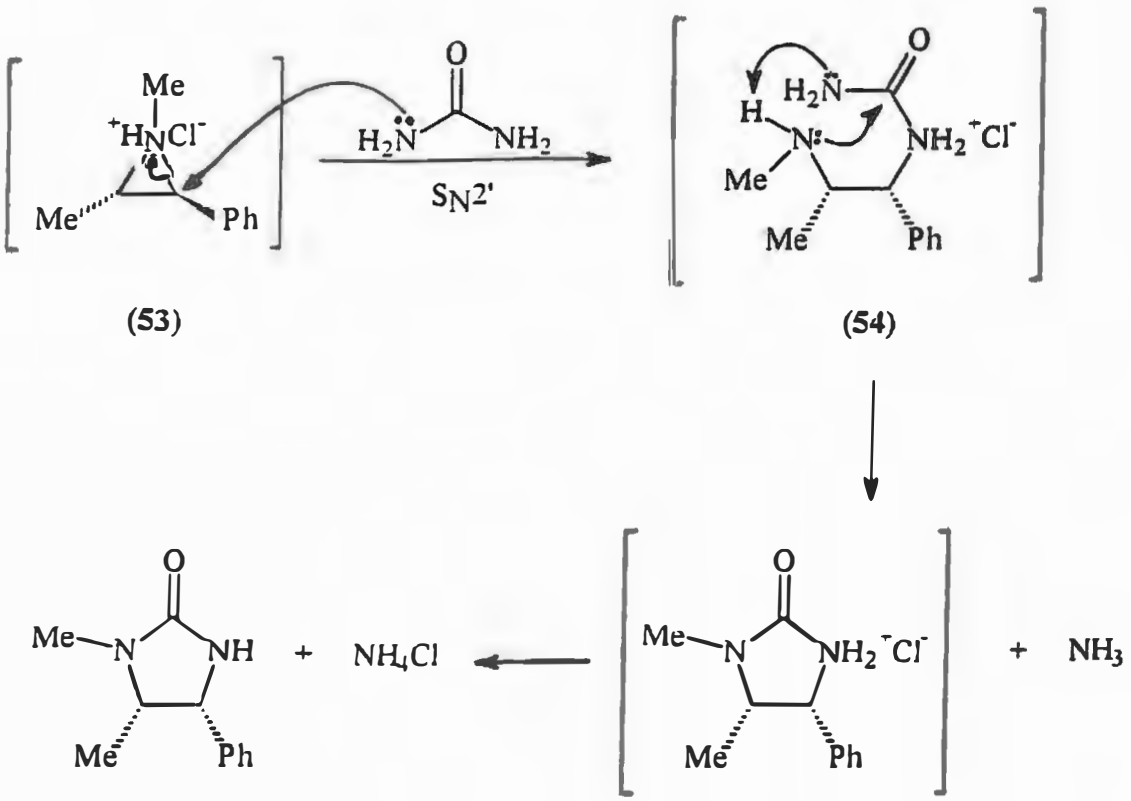


Scheme 65.[89]



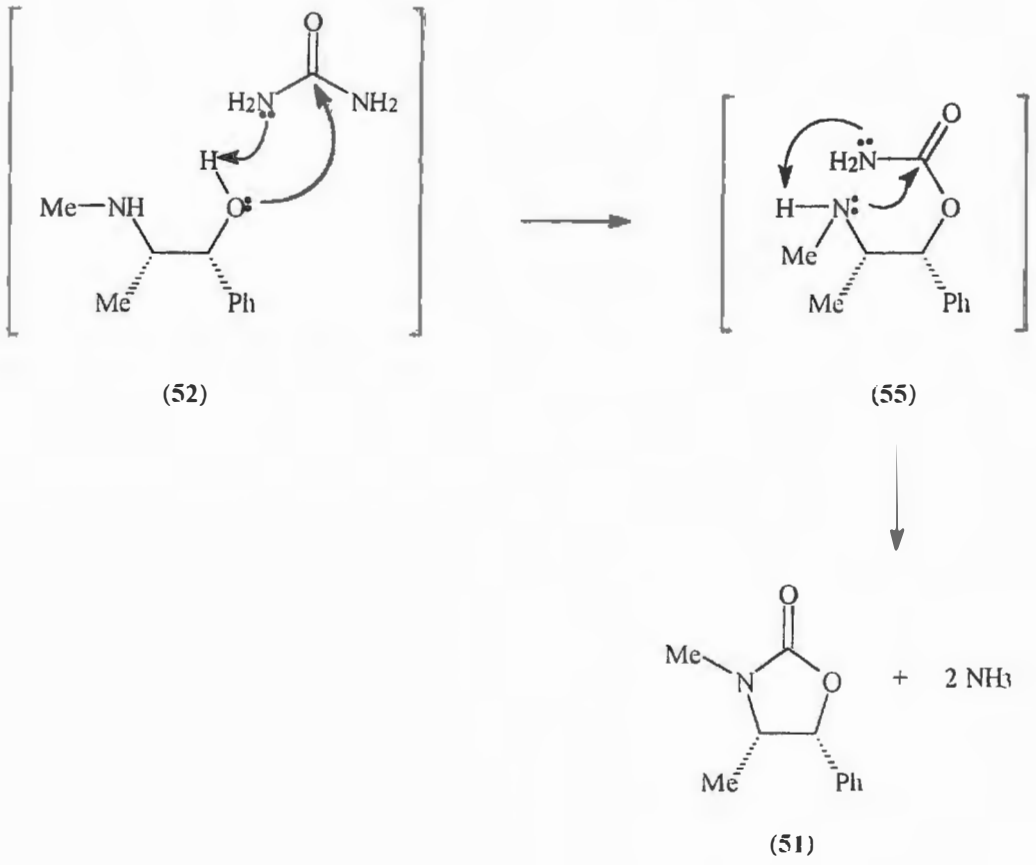
Scheme 66.[88]

This branch of the mechanism is completed by a second S_N2 displacement involving attack of one of the lone pairs on the urea nitrogen atoms at the benzylic position. It is followed by ring closure to give (1). (Scheme 67.)



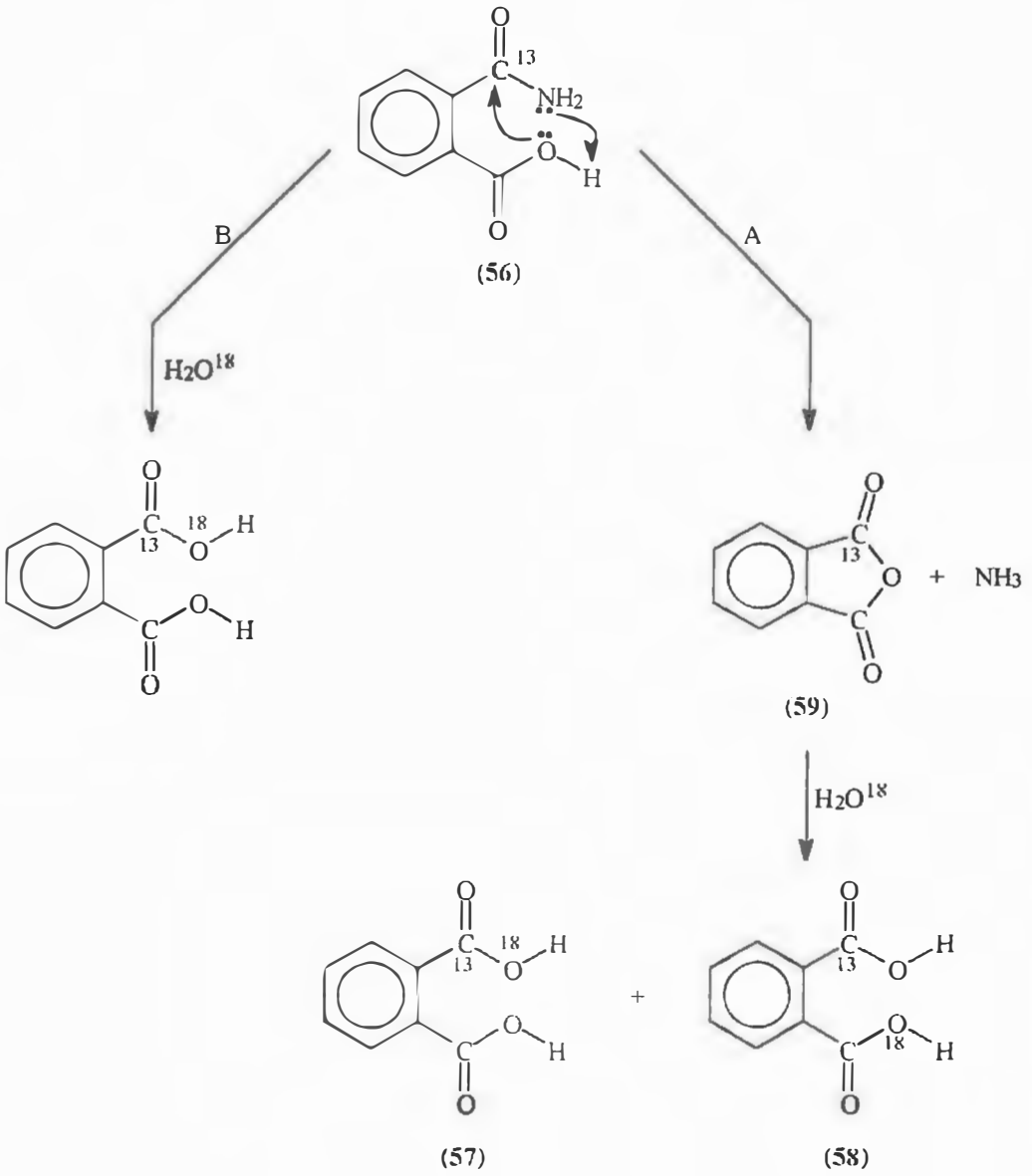
Scheme 67.

If protonation is intermolecular, the reaction is completed by attack of the hydroxyl lone pair (52) on the urea carbonyl accompanied by concomitant extraction of the hydroxyl proton by a lone pair on the urea moiety. This is followed by ring closure to give (51). (Scheme 68.)



Scheme 68.

The "electrophilic-nucleophilic" process central to both Schemes 67 and 68 (Intermediates 52, 53, 54 and 55) was shown to be feasible by Bender and co-workers.[90] (Scheme 69.)

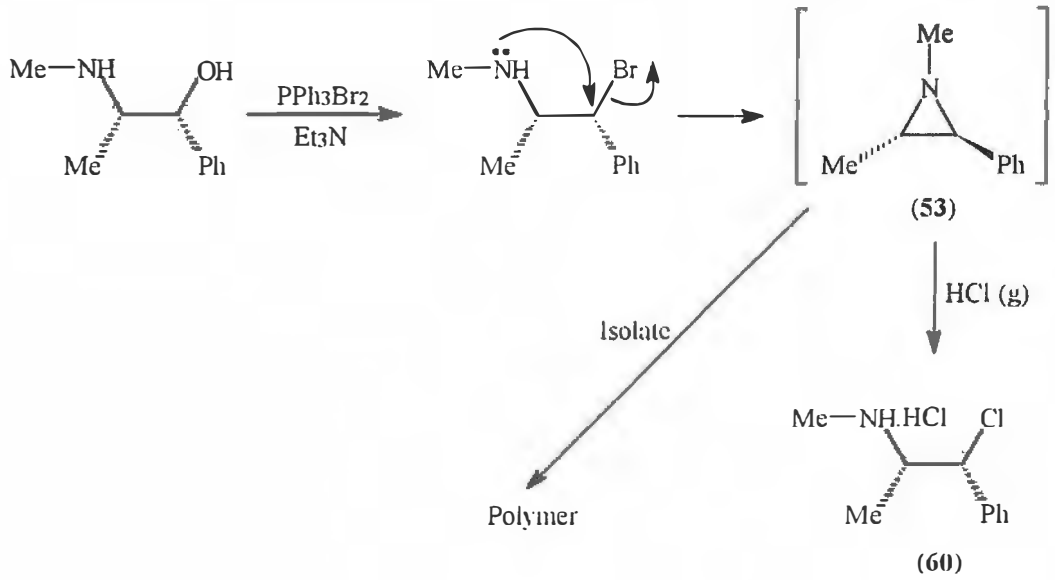


Scheme 69

If the hydrolysis of phthalamide (56) occurs *via* the anhydride (59) itself formed as a result of the aforementioned "electrophilic-nucleophilic" process then the resultant di-acid should exist as a mixture of labeled isomers (57) and (58). This was indeed found to be the case giving credence to the mechanism of formation of the anhydride and thereby supporting schemes 67 and 68.

Irrefutable proof for the mechanism of formation of (1) would be furnished if the intermediate aziridine salt (53) could be isolated. Attempts by Taguchi and Kojima[91]

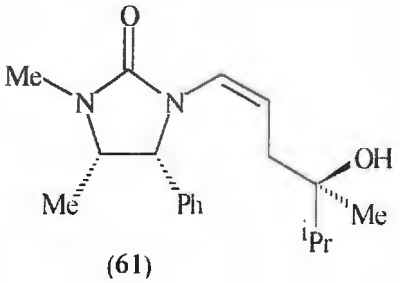
were unsuccessful yielding only polymeric material. Okada *et al.*[92] provided the required proof by showing that the salt (60) could only be formed if the required aziridine (53) was a reaction intermediate. (Scheme 70.)



Scheme 70.

Under the conditions of formation of (1), *i.e.* the production of NH_4Cl, one would expect the aziridine salt (53) to react with the NH_4Cl which is actually a reacting equivalent for HCl. This would lead to the formation of a salt similar to (60). This reaction does not occur as the NH_4Cl is removed from the melt by crystallizing out on the condenser.

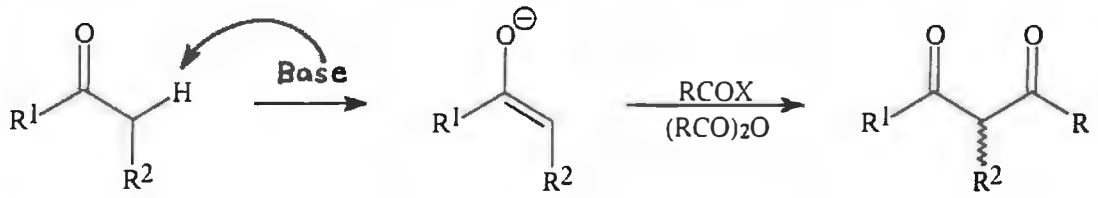
Last but not least, the 4,5-*Cis* configuration exhibited by (1) due to the mechanism, *i.e.* double inversion (2 x S_N2) was confirmed by Helmchen and co-workers[75] whose X-ray crystal structure of (61) showed the *Cis* relationship.



(61)

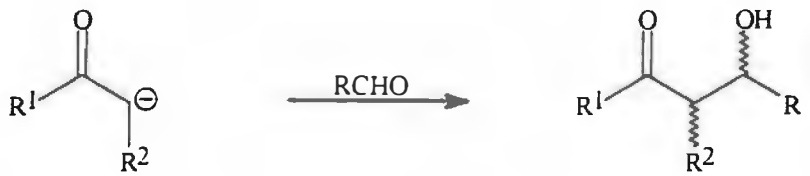
2.2. α-Acylation of Carbonyl Compounds - Synthesis of β-dicarbonyl skeletons.

α-Acylation of carbonyl compounds represents an important tool for the synthesis of β-dicarbonyl skeletons, *i.e.* compounds with a 1,3-heteroatom relationship. (Scheme 71.)



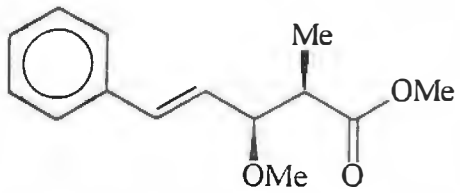
Scheme 71.

The reaction illustrated in Scheme 71 is not the only means of establishing a 1,3-heteroatom relationship, the aldol reaction is also capable of reproducing the aforementioned 1,3-functionality relationship. (Scheme 72.)



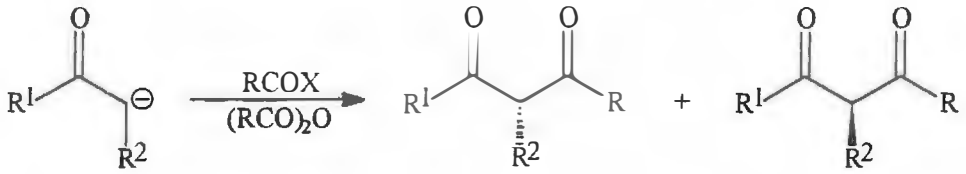
Scheme 72.

These heteroatom relationships are manifested in numerous compounds such a bleomysin A[93], an antitumour antibiotic, as well as in synthon (62) an important intermediate in the synthesis of oudemansin[94].



(62)

The general outcome of the acylation reaction in question (Scheme 71.) will be the formation of 2 enantiomers. (Scheme 73.)



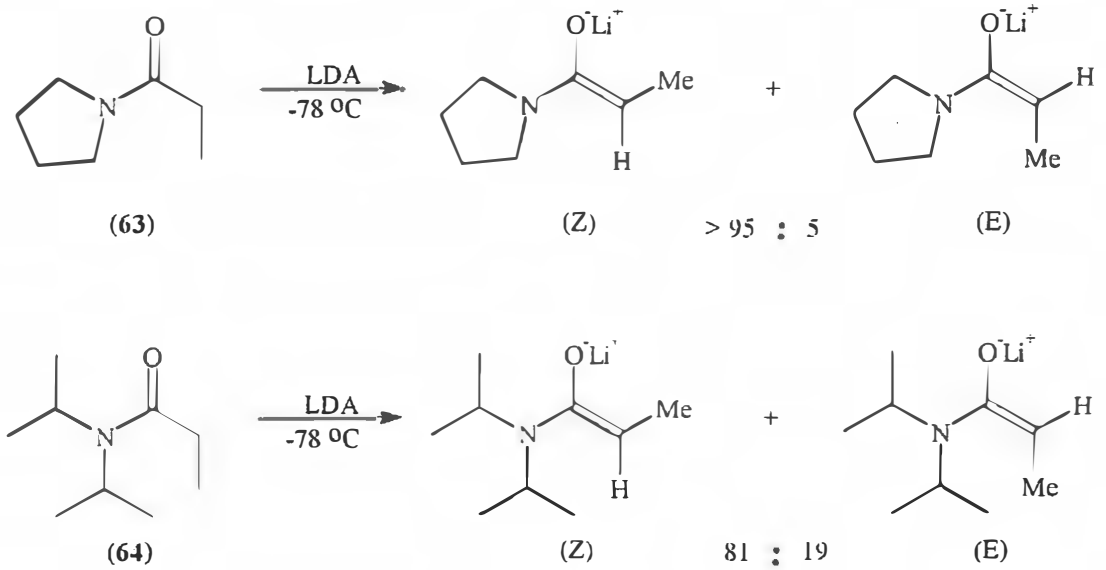
R^1 = Asymmetric unit.

Scheme 73.

Enantioselection leading to preferential formation of one enantiomer can only be brought about by incorporation of an asymmetric unit in this case imidazolidin-2-one.(1).

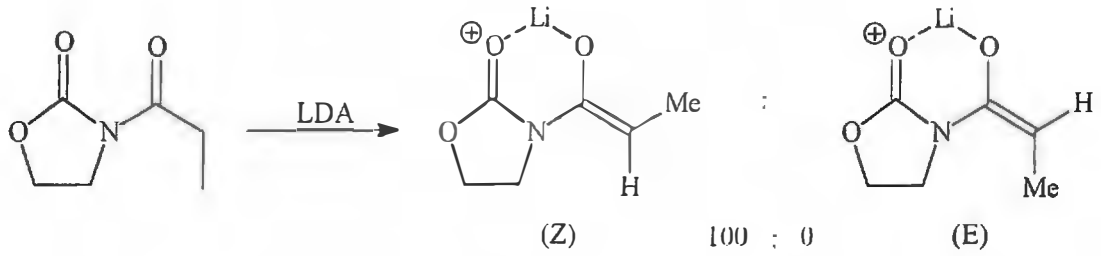
2.2.1. Lithium Amide Enolates.

The deprotonation of amides (63) and (64) with LDA has shown itself to proceed stereoselectivity.[95, 96] (Scheme 74.)



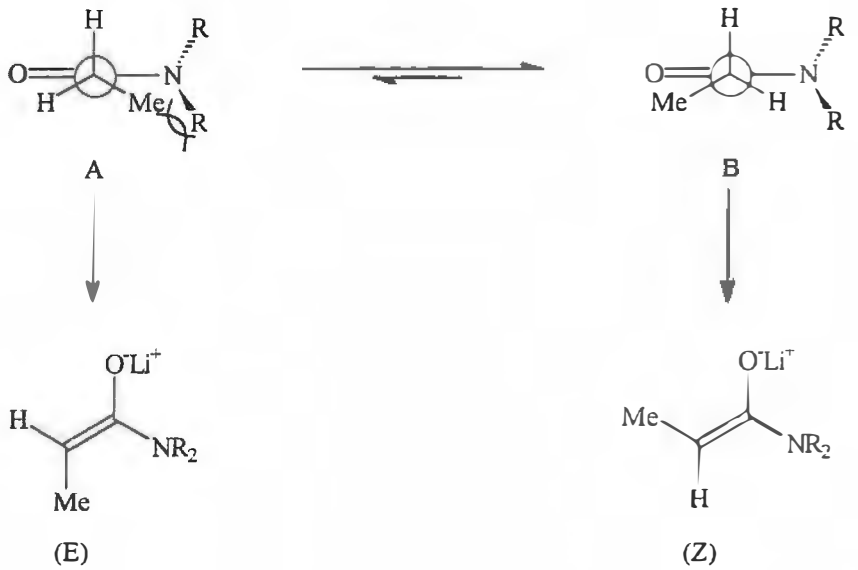
Scheme 74

Later work by Evans and co-workers[97] with N-propionyloxazolidin-2-ones echoed the aforementioned observation, with the resultant enolate mixture consisting exclusively of the *Z*-isomer. (Scheme 75.)



Scheme 75.

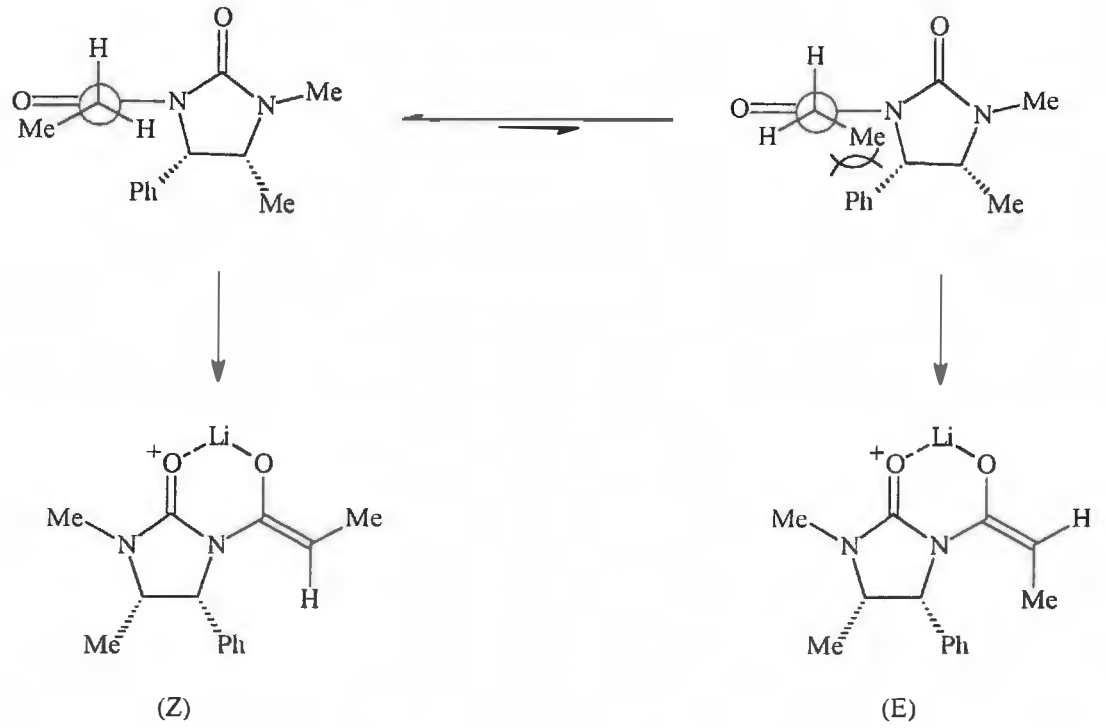
The rationalization for these observations is based on the preferred conformation of the starting amide. (Scheme 76.)



Scheme 76.

Allylic 1,3-strain[98] interactions between the methyl substituent and R destabilizes conformer A which leads to the *E*-enolate.

Armed with this precedent it seems likely that the deprotonation of N-propionylimidazolidin-2-one (50) with LDA will give only the *Z*-enolate. (Scheme 77.)



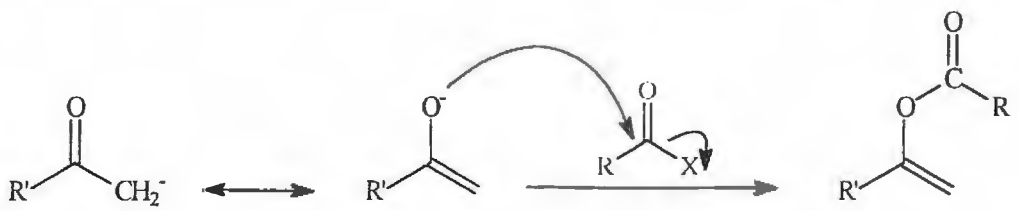
Scheme 77.

Conclusions drawn by Malissar[81] showed that the enolization stereoselectivity for (50) can be inferred as being >97:3 with the *Z*-isomer/enolate being favoured.

2.2.2. The chemistry of the acylation reaction affording a β-dicarbonyl skeleton from (50).

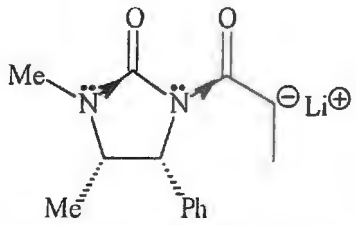
The acylation reaction depicted in Schemes 71 and 73 only shows the formation of the desired β-dicarbonyl compound. Other products formed due to side reactions are also possible.

The first of these possible side reactions is O-acylation. (Scheme 78.)



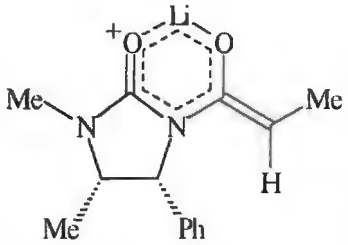
Scheme 78.

A possible explanation for the lack of O-acylation with the N-propionyl system (50) is as follows:



Back donation of electron density from the imide nitrogen atoms satisfies the electron demand of the two carbonyl moieties. With respect to the carbonyl moiety on the side chain this allows greater if not total concentration of electron density on the carbon atom leading to a greater proportion of C-acylation.

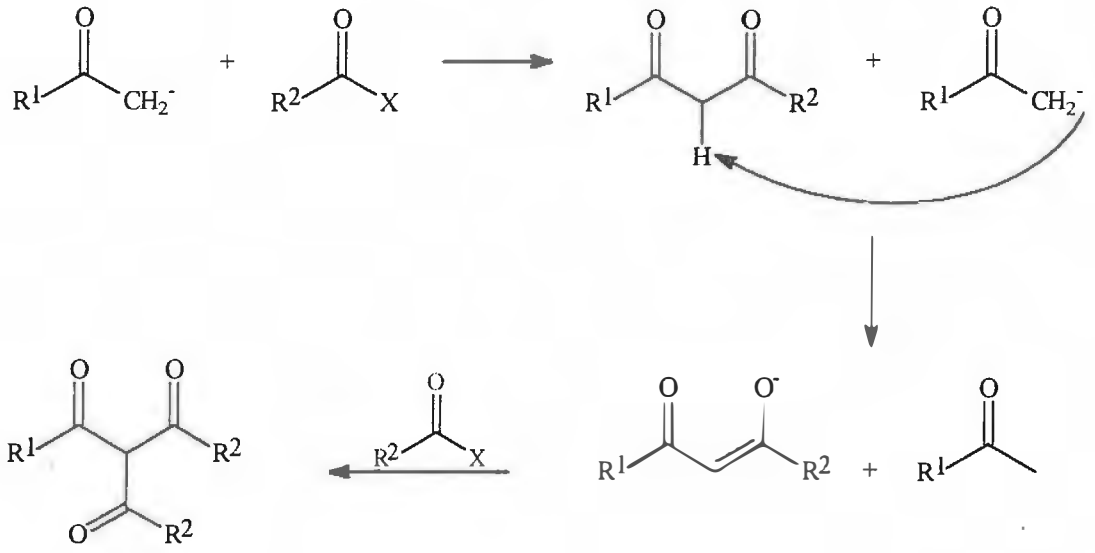
A second possible answer for the absence of O-acylation lies in the structure of the Li-co-ordinated enolate (65).



(65)

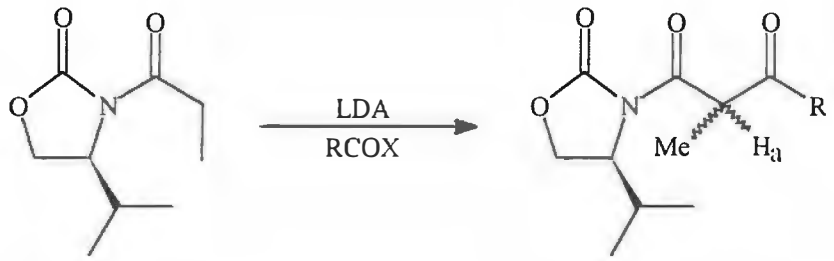
Co-ordination of the Li-cation forms a stable six membered enolate transition state and this may negate the possibility for O-acylation. This could be due to the actual co-ordination between Li and oxygen or the shape of the lithiated species (6 membered) or a combination of both. It is interesting to note that work by Jackman *et al.*[99, 100] showed that C-alkylation of metal enolates in solution is preferred due to co-ordination of the enolate oxygen and the metal cation which decreases the reactivity of the oxygen atom relative to the carbon atom.

A second possible side reaction involves proton exchange between the product and any unreacted enolate leading ultimately to disubstitution. (Scheme 79.)



Scheme 79.

This reaction is minimized or possibly stopped by the order of addition of reactants, *i.e.* the enolate is added slowly to the acid chloride or anhydride. Thus the product will never be in the presence of any unreacted enolate.[101] A second barrier to the said reaction (Scheme 79.) is applicable when N-propionyloxazolidin-2-ones and probably N-propionylimidazolidin-2-ones are α–acylated. (Scheme 80.)



(66)

Scheme 80.

The remaining proton H_a, is surprisingly enough, not very acidic even though conventional wisdom states that it should be so. Those conformations of the dicarbonyl (66)[5]that contribute to the acidity of H_a are destabilized by $A^{1,3}$ strain interactions.

Racemization studies carried out with (67) showed the followed results:

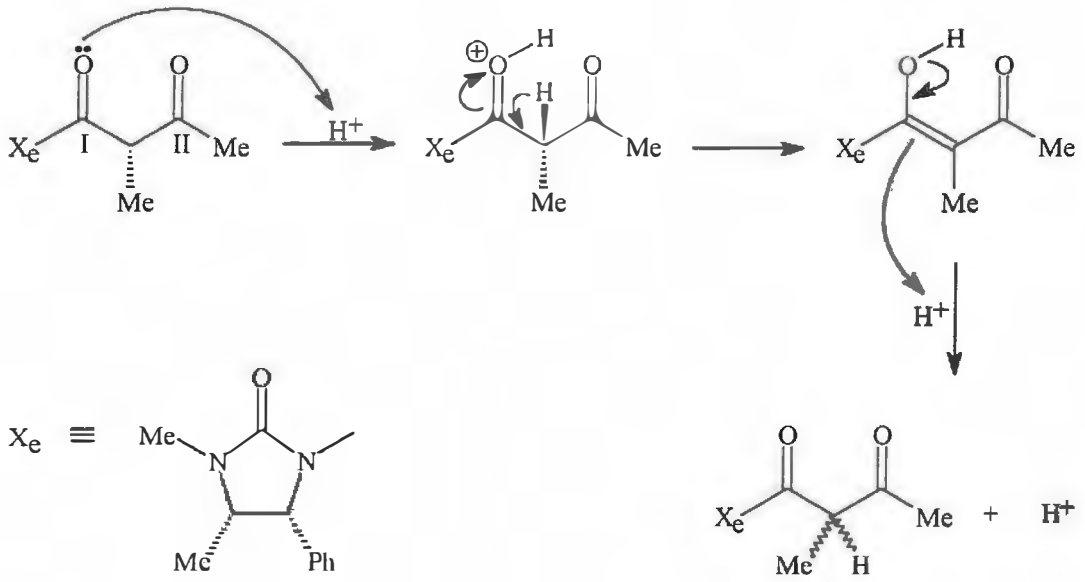
a) Under mildly basic conditions (Et_3N + (67), 25°C), the dicarbonyl skeleton (67) reached equilibrium with (68) over a 24h period.

(67) (68)

This compares well with (69) and (70) which equilibrate under mildly basic conditions (Et_3N) over an 18h period.[4]

(69) (70)

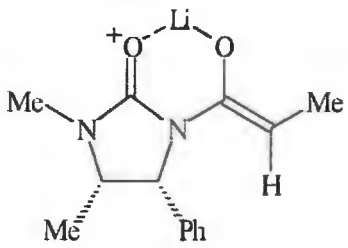
b) Under acidic conditions which include both silica and HCl, (67) reached equilibrium with (68) over 48 hours and 16 hours, respectively. Compound (69) on the other hand is resistant to HCl, $CHCl_3$ and silica.[4] A possible mechanistic explanation for this acid catalysed racemization is illustrated in Scheme 81.



Scheme 81.

Back donation from the imide nitrogen atom will probably mean that the lone pairs on carbonyl I will be more loosely bound and therefore more likely to take part in a chemical reaction as compared to the lone pairs on carbonyl II.

2.5. The acylation reaction between enolate (65) and various acylating agents.



(65)

The chiral auxiliary was smoothly acylated by reaction of its Li-anion with propionic anhydride or propionyl chloride yielding (*4R*, *5S*) - 1,5-dimethyl-4-phenyl-3-propanoylimidazolidin-2-one (50). Kinetic deprotonation of (50) yielded the expected *Z*-enolate (65) which upon reaction with various acylating agents gave a mixture of diastereomeric β-dicarbonyl compounds. (Scheme 82.)

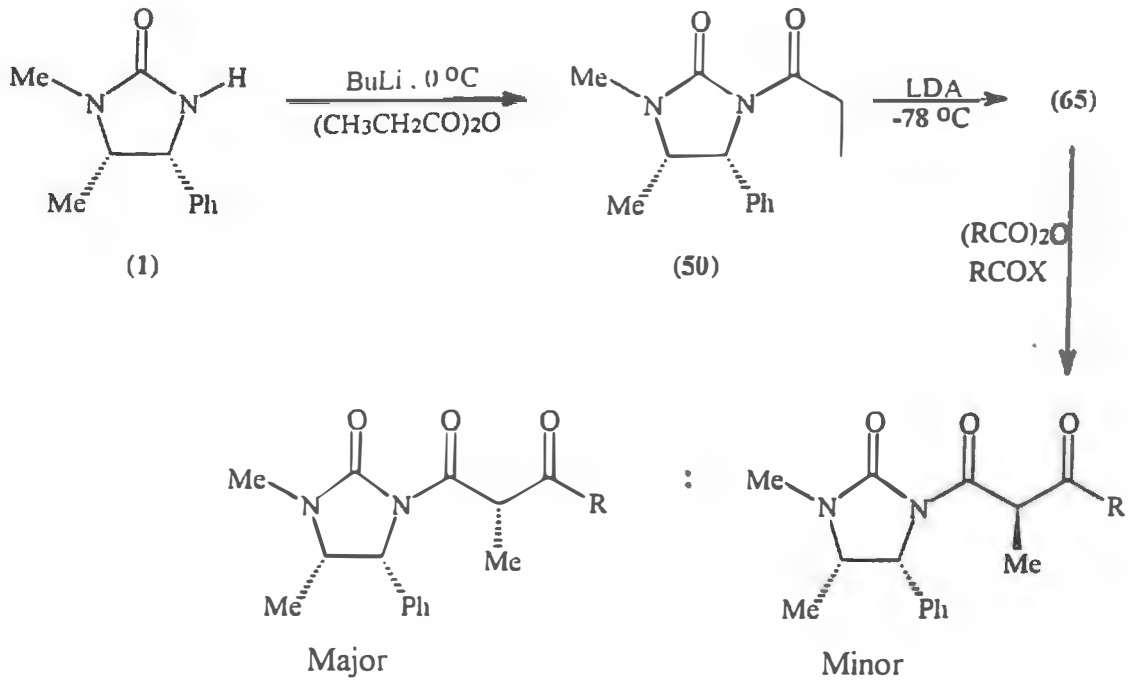


Table 4: d.e. for the acylation reactions

Entry	Major	R	Major:Minor	d.e.
1	67	Me	9.7 : 1	81.25%
2	73	Et	27 : 1	92.9%[a]
3	72	Ph	39 : 1	≥ 95%

[a] Product not isolated.

Scheme 82.

2.2.4. The determination of the diastereomeric ratio for the acylation reaction.

The d.e. for the acylation reaction (Scheme 82) can to all intents and purposes be interpreted as an indication of the asymmetric induction achievable with the imidazolidin-2-one moiety.

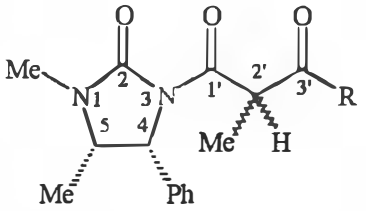
Physical determination of the d.e. can be achieved by ^{1}H NMR analysis of a number of peaks which include:-

a) the singlet due to the N-Me

b) the doublet due to H-4

c) The doublet due to the methyl attached to C-2′

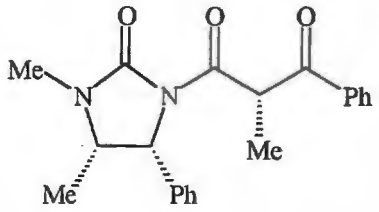
d) the quartet due to C-2′ itself. (See structure (71)).



(71)

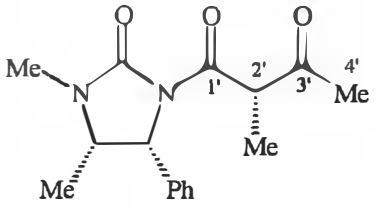
Cardillo and co-workers[76] used this method of ^{1}H NMR analysis choosing the doublet due to the protons on C-4 to determine the d.e. for alkylation reactions with N-acylimidazolidin-2-ones and stated that an asymmetric induction of ≥ 95% can be assumed if only one diastereomer is recognizable from ^{1}H NMR.

This was done for the reaction yielding (72) and the d.e. determined using possibility (b).



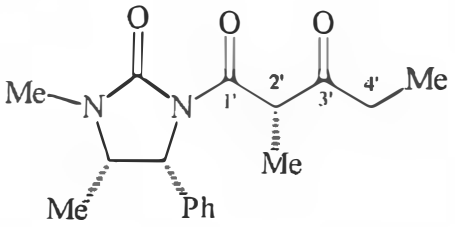
(72)

The d.e. determination for the reaction yielding (67) was carried out on the crude product mixture without removal/separation of precursor (50.) This was possible because the peak chosen for analysis, the singlet due to H-4′, is found in an uncluttered part of the spectrum and is not represented in precursor (50).



(67)

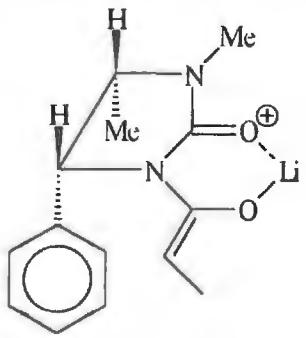
The d.e. determination for the reaction yielding (73) was achieved by H^1 NMR analysis of the quartet due to H-4'. The reasons governing this choice are akin to those which determined the choice for (67).



(73)

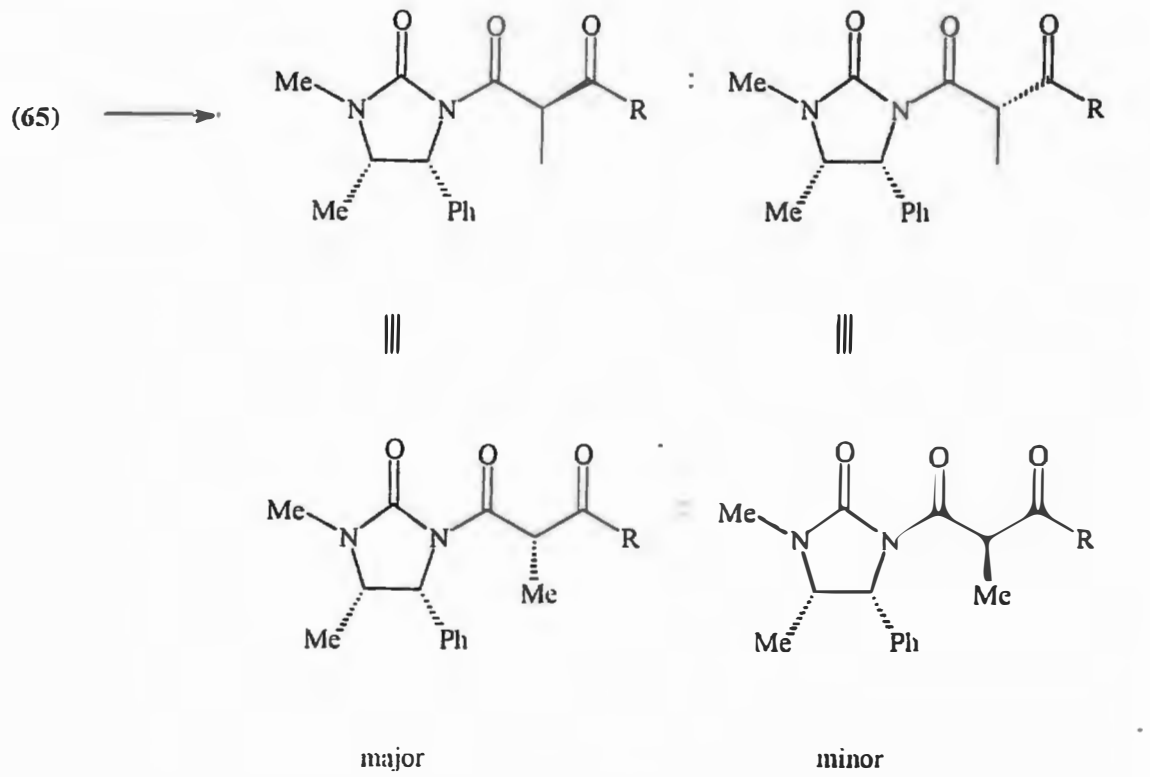
2.2.5. The origin of stereoselectivity in the acylation reaction.

The observed enantioselection can be explained by invoking the idea of a planar anion or enolate.[4, 76, 102] (65)



(65)

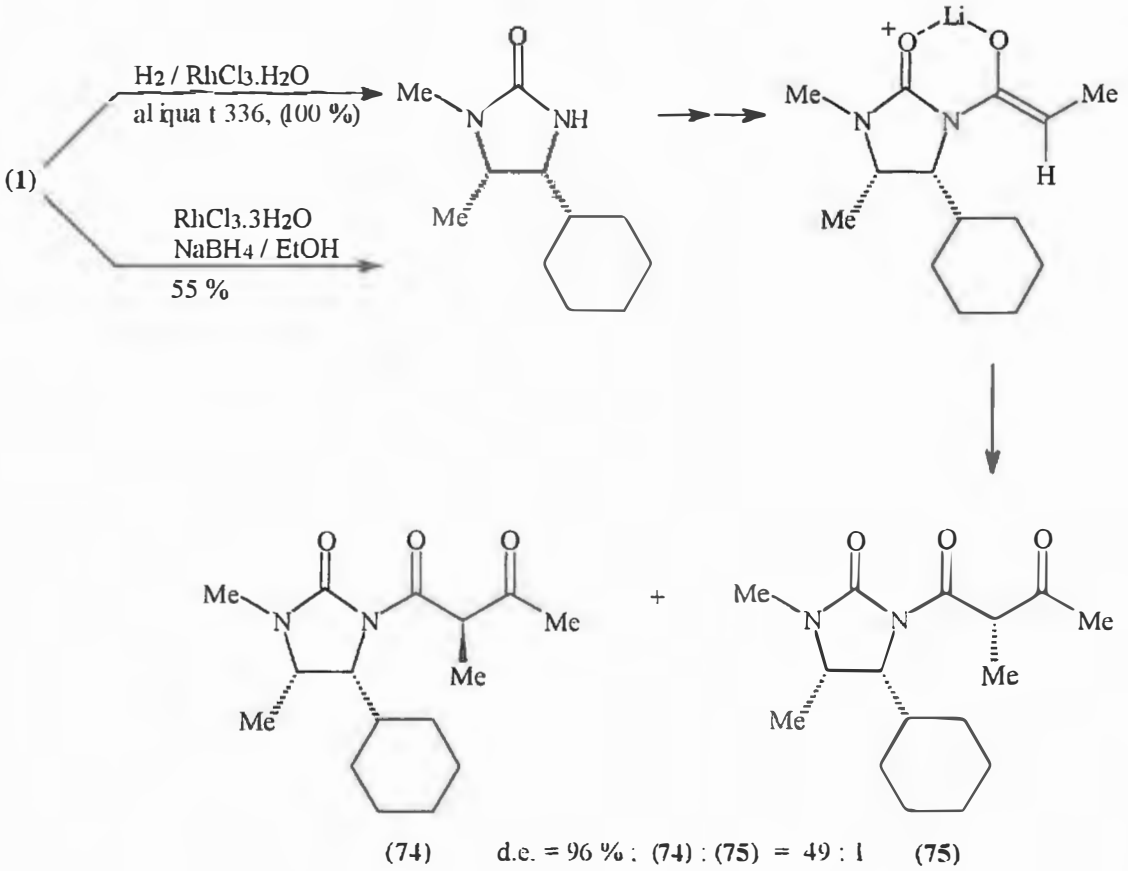
Enolate π-facial selection, *i.e.* whether attack comes from "above" or "below", is determined by the steric limitations imposed upon the transition state by the relevant substituents. With the enolate in question (65) the direction of approach of the acylating agent will be such that it nears the enolate from the least hindered side in accordance with Cram's Rule. Thus the acylating agent will approach the Enolate π-face opposite the phenyl ring which is the embodiment of the aforementioned steric constraints giving the following product mixture. (Scheme 83.)



Scheme 83.

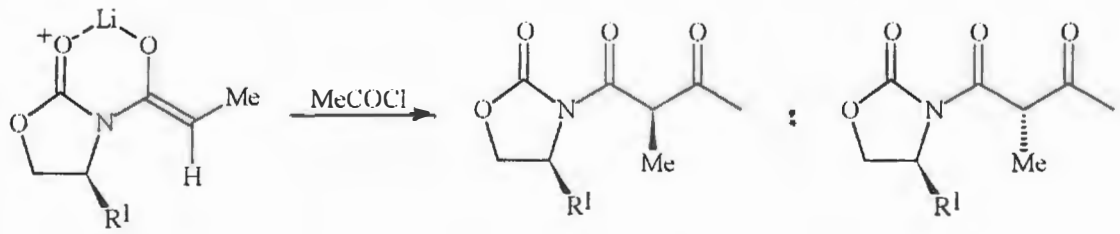
As previously stated the phenyl moiety is responsible for the directing influence which sees the major component being formed preferentially. It therefore stands to reason that if the steric bulk of this substituent could be increased, one would expect the product mixture to show an even greater proportion of the major component(See scheme 83).

This prediction was shown to be true by Drewes *et al*[82] who hydrogenated the phenyl moiety converting it to a cyclohexyl substituent. The d.e. for the acylation reaction using acetic anhydride or acetyl chloride then increased to 96%[81] as opposed to the 81.25% obtained by us. (Scheme 84)



Scheme 84.

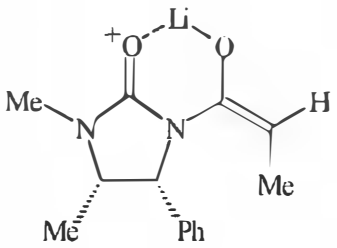
This mechanistic explanation for the observed stereoselection also holds true for alkylation and acylation of N-propionyloxazolidin-2-ones and shows a similar dependance on "steric bulk." (Scheme 85.)



Scheme 85.

From this one can see, if such an analogy is possible, that the cyclohexyl substituent is at worst as bulky as the isopropyl substituent.

It is also important to note that the minor diastereomer (See scheme 82 and83) in the context of the mechanism put forward is formed due to approach of the acylating agent from the more hindered side and not as a result of acylation of the *E*-Enolate. (76)

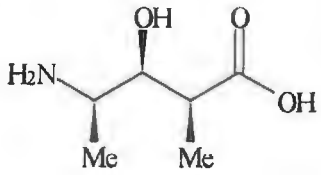


(76)

It would thus seem likely that enolate geometry whether *E* or *Z* is irrelevant to the stereochemical outcome of the reaction (because the enolate is planar.)

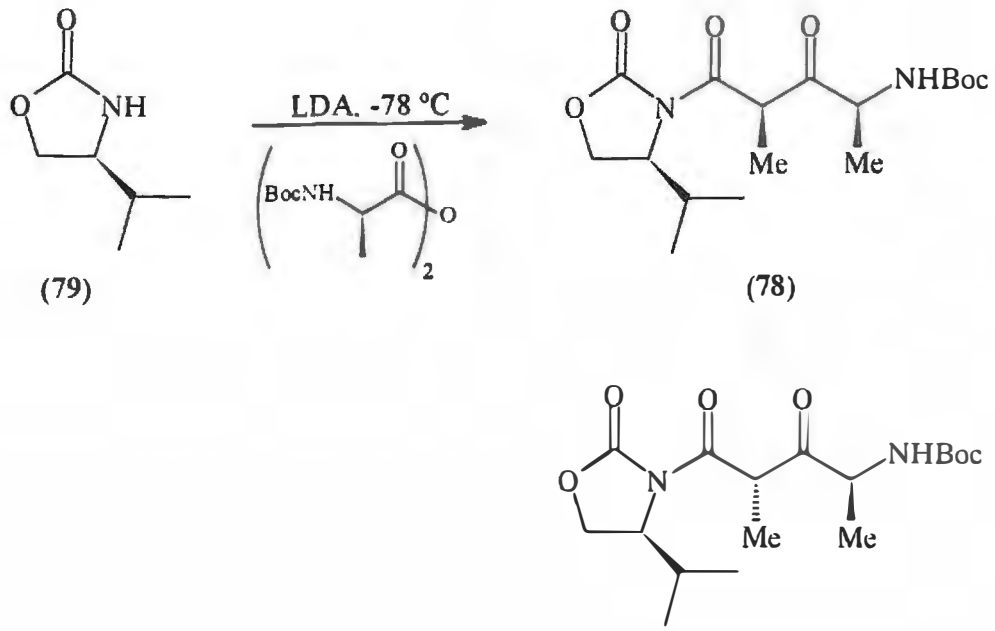
2.2.6. The importance of β-dicarbonyl compounds.

Retrosynthetic analysis of Bleomycin A_2[93], an antitumour antibiotic, has shown that (*2S*, *3S*, *4R*)-4-amino-3-hydroxy-2-methyl pentanoic acid (77) is a convenient starting point for its synthesis.



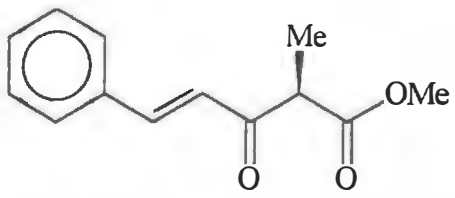
(77)

Synthon (77) is derived from a β-dicarbonyl precursor (78), itself formed interestingly enough by acylation of a N-propionyloxazolidin-2-one (79). (Scheme 86.)



Scheme 86.

Synthon (62), a key intermediate in the synthesis of oudemansin[94] (See Section 2.2), is also derived from a β-dicarbonyl precusor (80)



(80)

2.3 The Reductive alkylation of adduct (67) with various Grignard reagents.

Adduct (67) was allowed to react with 3 equivalents of the relevant Grignard reagent at -78°C to give the synthetic equivalent of the aldol products which would be produced by the reaction between ketones and N-propionylimidazolidin-2-one (50). (Scheme 87, Table 5)

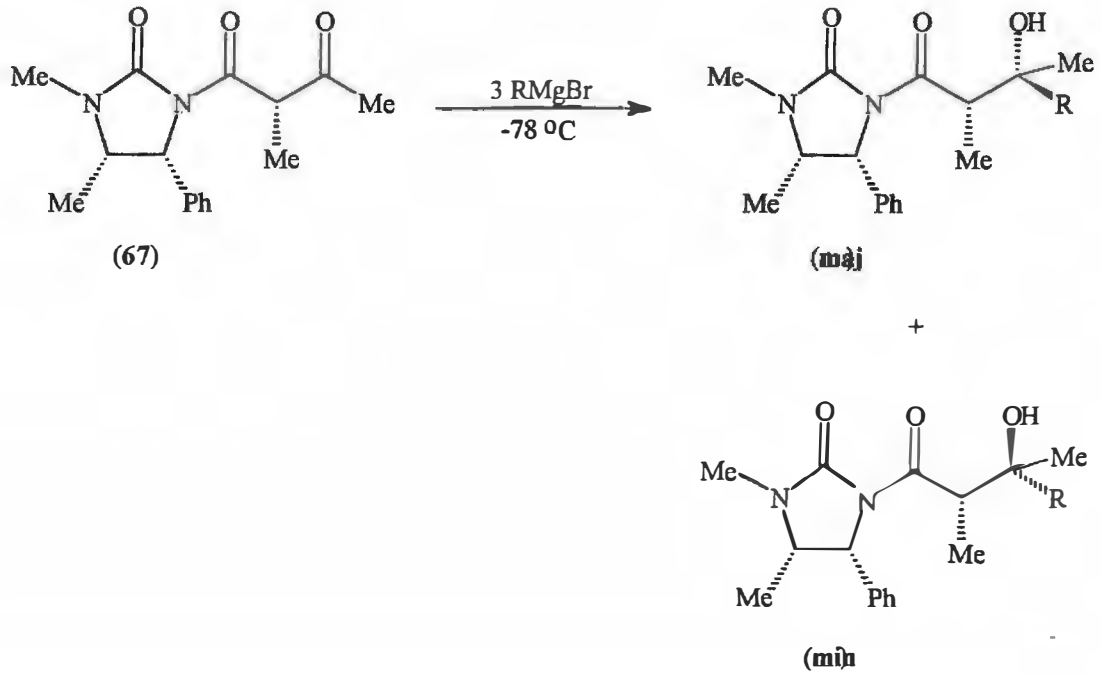


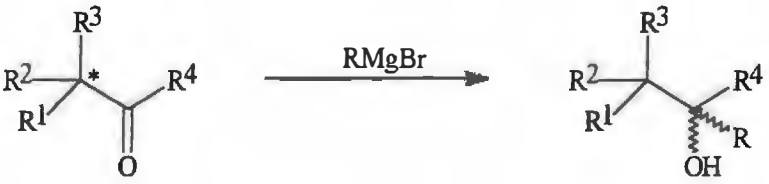
Table 5: d.e.'s for the various Grignard reactions.

major	R	major : minor	d.e.
1 (81)	Et	8,8 : 1	79,6%
2 (82)	Ph	16 : 1	88,3%
3 (83)	$CH_2 = CH$	10,5 : 1	82,7%
4 (84)	Benzyl	Only type (91) products.	100%

Scheme 87

2.3.1. The determination of the diastereomeric ratio in the Grignard reaction.

With the Grignard reaction in question (Scheme 87.) the d.e. is an indicator of the degree of asymmetric induction possible with an α-chiral centre. (Scheme 88.)



Scheme 88.

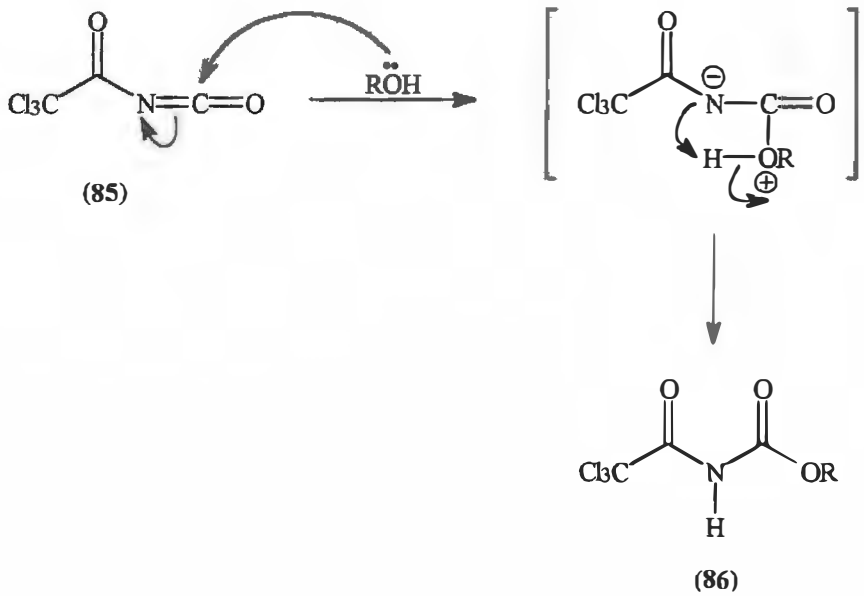
Various methods are used in the d.e. determination for reactions producing products containing a hydroxyl group. These include analysis of the silyl ether by GC/MS and

analysis of the trifluoroacetate derivatives by ^{19}F NMR spectroscopy. The most popular methods are however those which involve the use of NMR spectroscopy.

These may involve analysis of the crude product or derivatives thereof. Derivitization procedures are exceptionally diverse but the most popular ones are acetylation and benzoylation.

All the procedures discussed up to now are, however, subject to one major flaw : they require large amounts of pure material. The ideal derivitization/analysis method should allow *in situ* derivitization of small amounts of material.

Work by Malissar[81] and earlier by Goodlet[103] addressed this problem. They carried out *in situ* acylations of hydroxyl groups with trichloroacetyl isocyanate (TAI) (85). The resultant carbamate (86) is produced qualitatively irrespective of whether the alcohol moiety is 1°, 2° or 3°. (Scheme 89.)



Scheme 89.

The d.e.'s determined using the TAI protocol showed good agreement with the d.e.'s obtained using more traditional methods as can be seen from the following examples taken from work done by Malissar.[81] (Scheme 90, Table 6.)

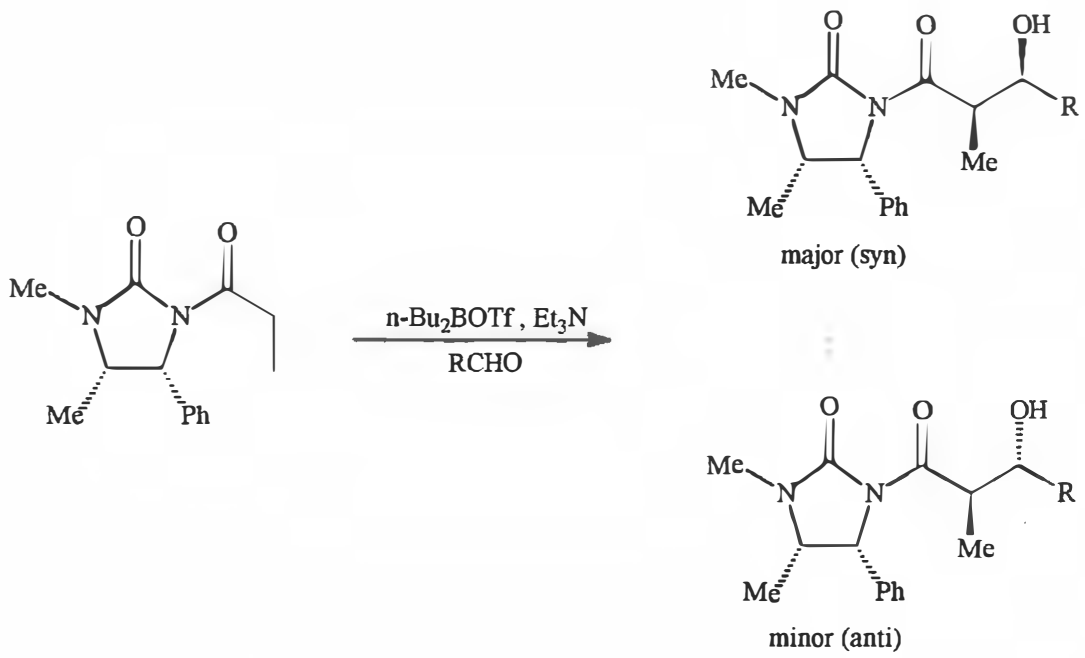


Table 6: Comparative d.e.'s obtained by various analytical methods.

Entry	R	d.e. (Major : minor)			
		^{1}H NMR[(a)]	GCIMS[(b)]	^{19}F NMR[(c)]	TAI
1	C_6H_5	98 : 2	98 : 2	99 : 1	98 : 2
2	$4NO_2$ - C_6H_5	95 : 5	-	-	96 : 4
3	4MeO - C_6H_5	96 : 4	-	-	96 : 4
4	C_2H_5	75 : 25	-	72 : 28	74 : 26

(a) ^{1}H NMR : analysis of the doublet due to C-4 or singlet due to N-Me.

(b) GC/MS analysis of the TMS ether.

(c) ^{19}F NMR analysis of the trifluoroacetyl derivative.

Scheme 90.

It was thus decided to employ the TAI protocol because not only are the d.e's accurate, but the method also has other advantages.

The carbamate N*H* resonance is shifted downfield with a value greater than 8 ppm. This means it is found in an uncluttered part of the spectrum and the N*H* resonance does not couple with any other substrate protons.

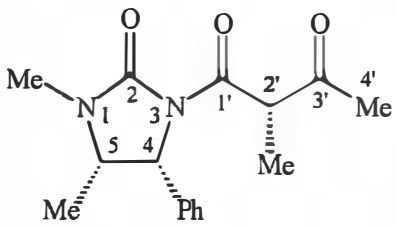
Attendant simplification of the spectrum is also possible as the hydroxyl signal disappears allowing better resolution of that part of the spectrum where it originally resided.

Last, but not least, the reagent can be used in excess as it does not contain any protons.

2.3.2. The chemistry of the Grignard reaction.

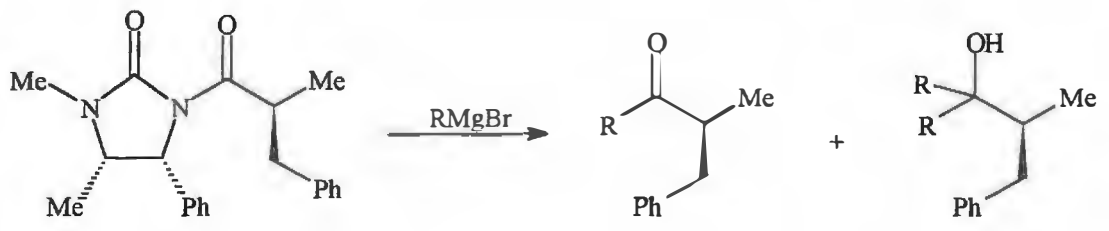
Perhaps the most striking feature of the Grignard reaction as illustrated in Scheme 87 is the selectivity of the reaction. Of the three potential reaction sites, *i.e.* three carbonyl moieties, only one takes part in the chemical reaction.

A possible explanation for this observation is based on electronic factors, *i.e.* back donation of the nitrogen lone pairs renders the C-2 carbonyl as well as C-1′ carbonyl less susceptible to nucleophilic attack. (Scheme 91.)



Scheme 91.

Attempts by Malissar[81] to synthesize ketones from (87) by displacing the auxiliary with Grignard reagents failed echoing the concept of diminished reactivity for carbonyls C-2 and C-1′ (Scheme 92.)



(87)

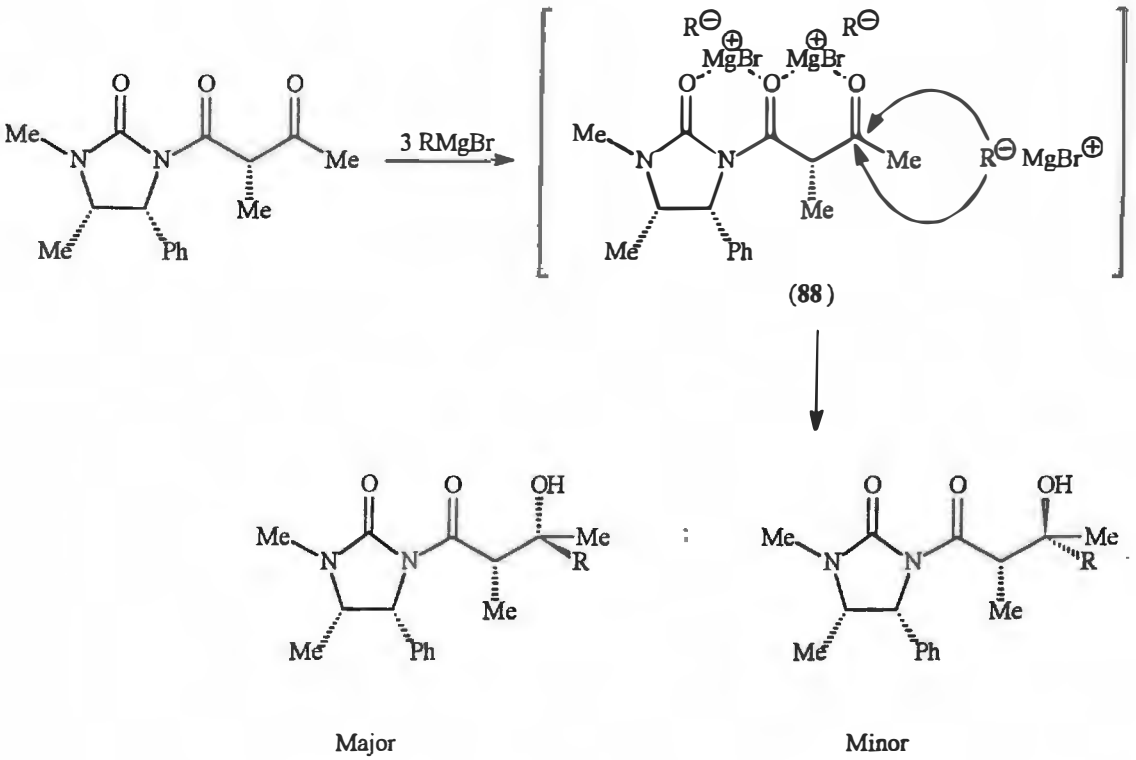
R = Et ; no reaction

R = PhC≡C ; no reaction

Scheme 92.

2.3.3. The origin of Stereoselectivity for the Grignard reaction.

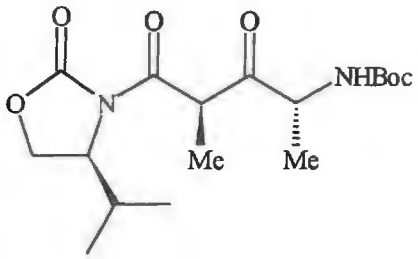
The stereochemical outcome of the reaction as illustrated in Scheme 87 is consistent with the proposed mechanism which postulates intermediate (88). (Scheme 93.)[93, 94, 4]



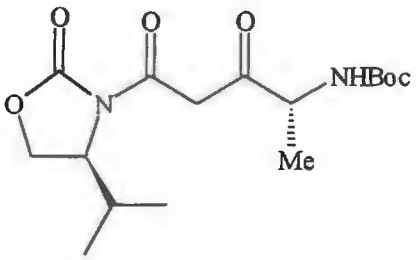
Scheme 93

As can be seen form Scheme 93 metal ion chelation plays a crucial role in diastereoselection with the observed 1,2 asymmetric induction solely due to the proximal methyl bearing carbon atom. Approach of the nucleophile from the less hindered side of the molecule or Si[104] face affords the major adduct, with the minor adduct being attributed to approach of the nucleophile from the more hindered side or Re face.[104]

That it was indeed the 2′ position and not the chiral centre on the auxiliary which predetermines the configuration of the 3′-hydroxyl group (Scheme 93) was demonstrated by Dipardo and Bock[93] who subjected ketones (89) and (90) to identical reduction procedures.

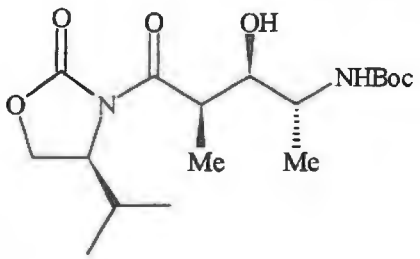


(89)

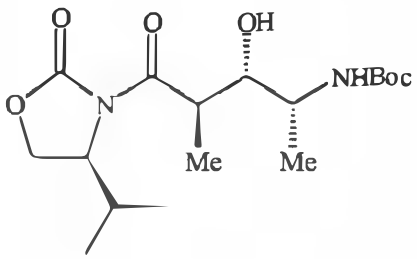


(90)

Reduction of (89) afforded alcohol (91) with less than 1% of the corresponding isomer (92) being formed.

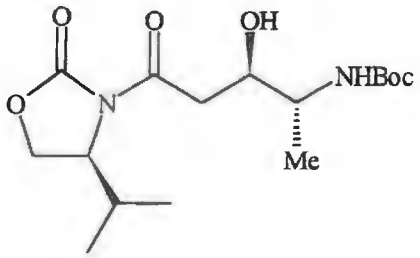


(91)

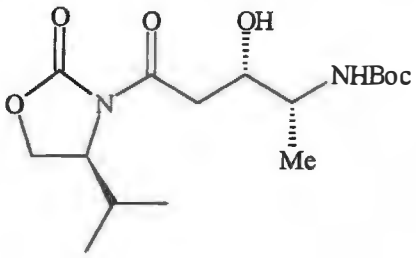


(92)

Reduction of (90) on the other hand afforded a 50/50 mixture of (93) and (94).



(93)

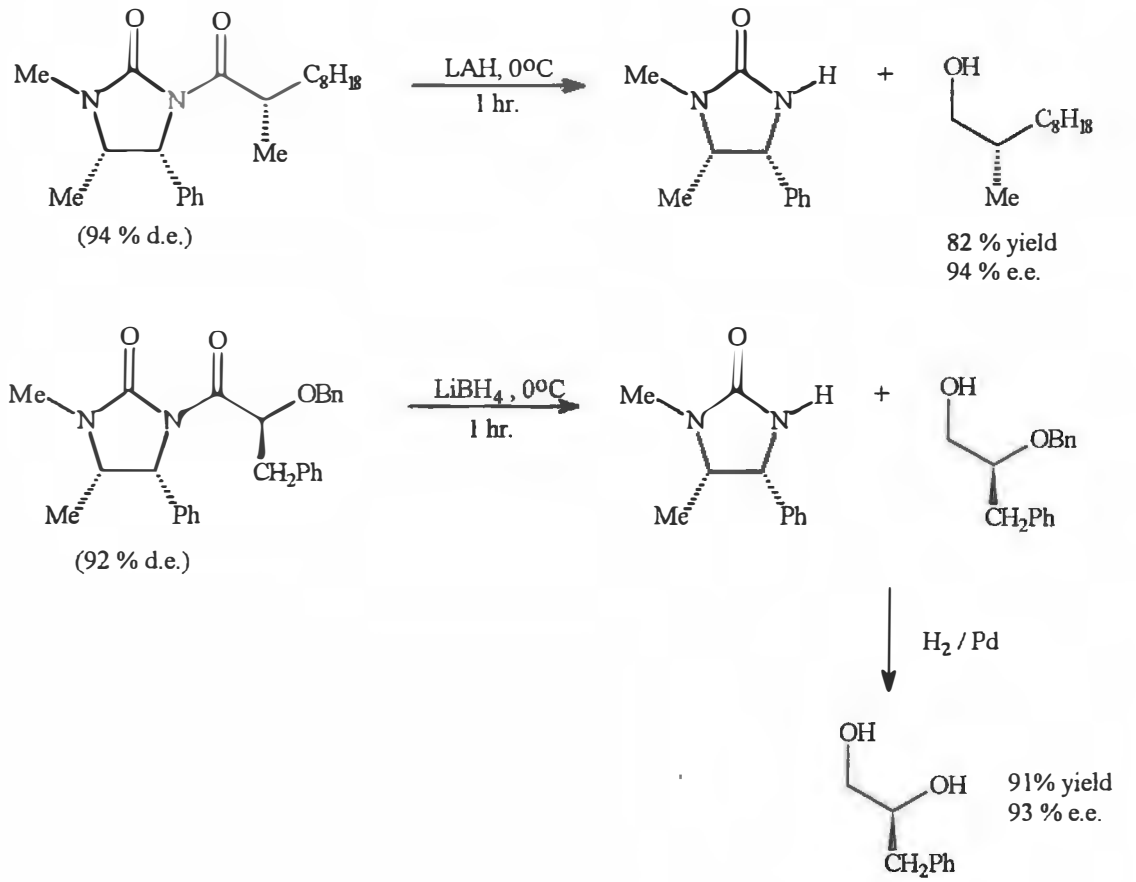


(94)

This observation showed that asymmetric induction was due to the 2′ chiral centre and not the chiral centre on the auxiliary itself.

2.4. Reductive Removal of the chiral auxiliary from the β-hydroxy carbonyl sidechain to afford the 1,3-diol.

Reductive cleavage of N-acylimidazolidin-2-ones with hydride reagents has previously been described by Cardillo and co-workers using both LAH[76] and $LiBH_4$.[76] (Scheme 94.)



Scheme 94.

As can be seen the reductive cleavage procedure affords the desired product in undiminished optical purity and also allows recovery of the auxiliary itself. The LAH protocol was therefore chosen to effect unmasking of the 1,3-diol. (Scheme 95.)

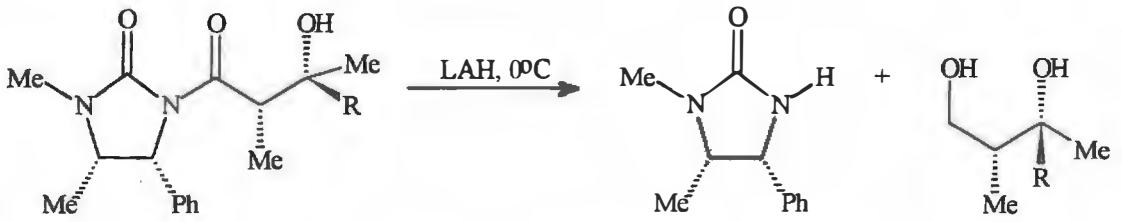


Table 7: Results of the cleavage reaction with LAH.

Entry	R	ee	Yield
1 (95)	Ph	100%	12.7%
2 (96)	CH_2Ph	-	-[(a)]
3 (97)	Et	100%	5.8%
4 (98)	$CH{=}CH_2$	100%	18,1%

(a) isolation of the diol was difficult and a pure sample was not obtained.

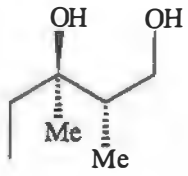
Scheme 95.

As can be seen the yields are exceptionally low, contrary to earlier expectations, and the reasons for this are unknown at this time.

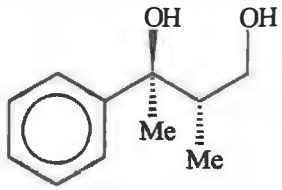
2.4.1. Evidence for the relative stereochemistry of the 1,3-diols.

The relative stereochemistry proposed by us due to mechanistic considerations for the 1,3-diols (and thus the Grignard adducts) was confirmed by comparison with data published by Hoffman and Sander.[105]

Their study of the allylboration reaction yielded two diols (99 and 100) whose relative stereochemistry was unambiguously determined.

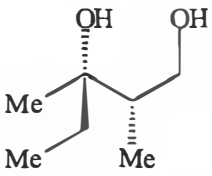


(99)

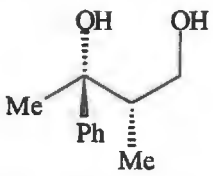


(100)

The NMR data, both ^{13}C and ^{1}H, published for (99) and (100), was identical to that obtained by us for (97) and (95), respectively. (Table 8 and 9)



(97)



(95)

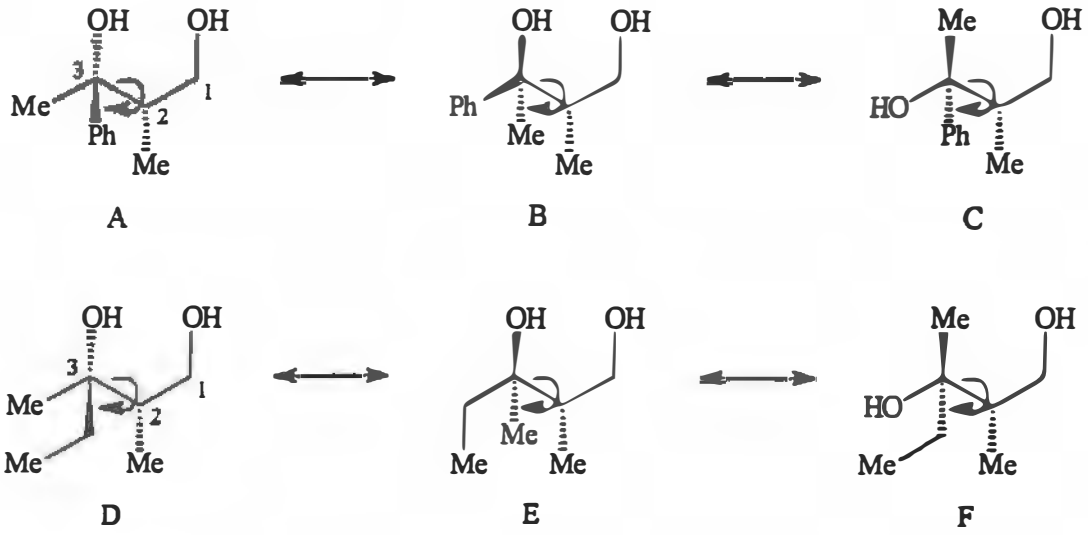
Table 8: Comparison of the NMR data for the pair (99)/(97)

^{1}H NMR		^{13}C NMR	
(99)	(97)	(99)	(97)
0,79	0,80	7,2	728
0,90	0,90	12,7	12,58
1,11	1,14	21,9	22,00
1,52	1,54	34,0	34,06
1,53		40,9	40,96
1,82 - 1,92	1,8 - 2,0	66,0	66,08
3,1 (2 x OH)	2,0 - 3,0 (2 x OH)	76,4	76,501
3,63	3,674 - 3,761		
3,73			

Table 9: Comparison of the NMR data for the pair (100)/(95).

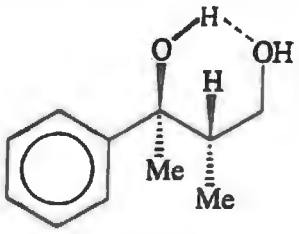
^{1}H NMR		^{13}C NMR	
(100)	(95)	(100)	(95)
0,91	0,95	12,3	12,31
1,48	1,518	25,7	25,48
1,94 - 2,05	1,988 - 2,07	44,0	43,86
2,71 (OH)	3,0 - 3,4 (OH)	66,2	66,12
3,35 (OH)	3,46 - 3,61	78,1	78,193
3,43 - 3,58	3,7 - 3,9 (OH)	125,0	125,03
7,19	7,195 - 7,46	126,7	126,63
		128,1	128,08
		148,3	148,26

As can be seen the diol structures proposed by us differ from those put forward by Hoffman *et al.*[106] All spectra were obtained using deuterochloroform as solvent. The relationship between (99) and (97) as well as (100) and (95) can be found in an examination of the fluctional behaviour associated with the diols. (Scheme 96.)



Scheme 96.

The various versions, *e.g.* (100) and (95) are in fact rotational conformers with the conformation adopted by the diol being that of lowest entropy. For the pair (100)/(95) the correct conformer will probably be (100) as the C_2-Me↔C_3-Me interactions associated with it will be smaller than the C_2-Me↔C_3-Ph interactions for (95). Hydrogen bonding which provides further stability is also possible with (100). (Scheme 97).



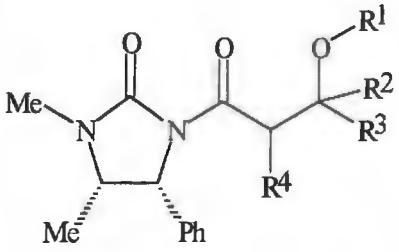
Scheme 97.

The same logic also applies to the (99)/(97) pair and will probably see (99) being the favoured conformer.

2.5. Further Research ideas.

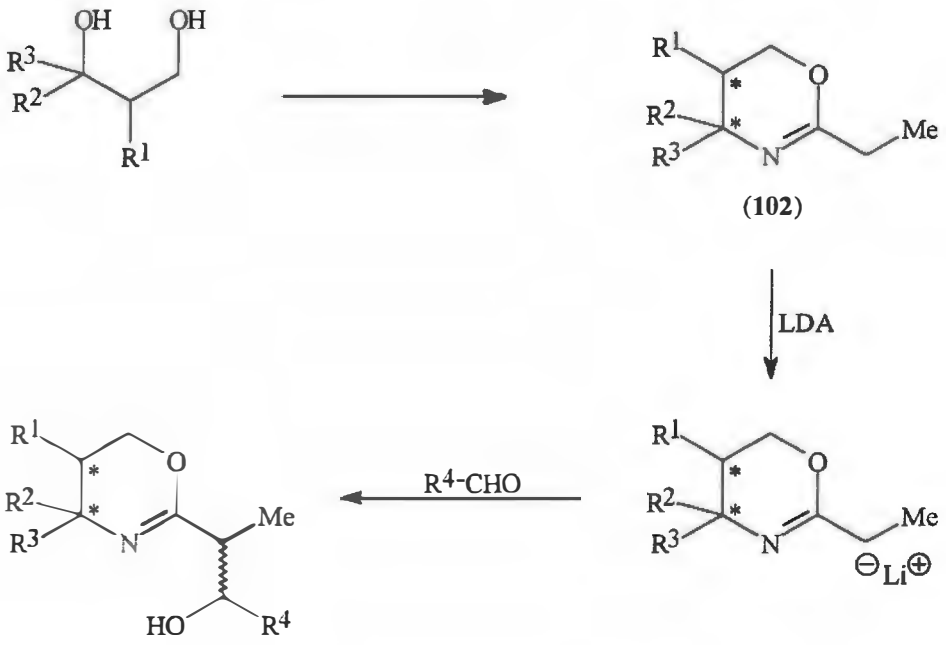
This scheme for preparation of 1,3-diols offers stereocontrol but the overall yields are low. Further research will be conducted in this area with particular interest being

focused on the reduction step (Scheme 95.). Different reducing agents will be tried as well as the reduction of a protected analogue (101) to see if it increases the yield.



(101)

New uses of the diols will also be explored. One possibility would be the synthesis of a chiral oxazine (102) which would serve as the basis of an investigation of the stereocontrol achievable with this moiety. (Scheme 98.)



Scheme 98.

3. EXPERIMENTAL.

3.1 Instrumentation and Chemicals.

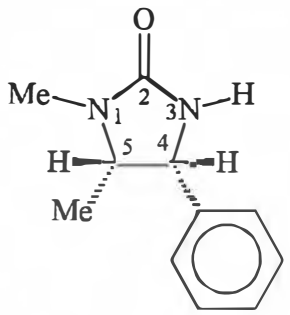
^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 Mhz instrument and, unless otherwise stated, $CDCl_3$ was used as the solvent with tetramethylsilane serving as internal standard. Mass Spectra were recorded on a Hewlett-Packard gas chromatographic mass spectrometer (HP 5988 A). Optical Rotations were determined using a Perkin-Elmer 241 digital polarimeter. Infra Red spectra were obtained using a Shimadzu FTIR - 4300 spectrophotometer. Elemental analyses were carried out using a Perkin Elmer 2400 CHN elemental analyser. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected.

Thin layer chromatography was carried out with precoated Kieselgel 60 F_{254} Merck plastic sheets and preparative column chromatography was performed according to the principles of Still *et al.*[106] on Merck silica gel 60(230 - 400 mesh). Solvents were dried using standard techniques and distilled prior to use. The imidazolidin-2-one derivatives were best visualized on precoated Kieselgel plastic sheets by using the cobalt (II) thiocyanate dip.[107] The 1,3-diols were visualized with the vanillin/H_2SO_4[108] stain which showed the diols as blue-green spots.

Low temperatures were maintained using dry ice/solvent slush baths according to the procedures of Phipps and Hume.[109] The alkyl halides utilized in the Grignard reactions were dried and purified according to the techniques catalogued by Perrin and co-workers.[110]

3.2. Preparations.

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

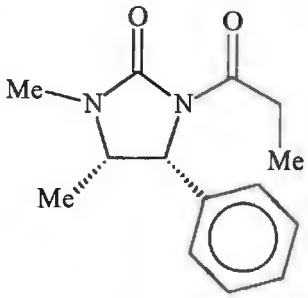


(1)

(-)- Ephedrine HCl (50,00g, 0,29 mol) and urea (45,00g 0,75 mol) were heated for 30 mins at 170-175°C. The resultant melt was further heated at 200-210°C for 60 min with magnetic stirring. Upon completion of said heating, the mixture was cooled to 100°C and treated with H_2O. The resulting solid was then washed with aq. HCl (5%) followed by H_2O. Decolourization with activated charcoal and recrystallzation from ethanol afforded (1) as white needles. (29,4g . 61,25%), m.p. 178°C (lit.[7], 177-179°C); (Found: C, 69,50; H, 7,40; N, 14,69. $C_{11}H_{14}N_2O$ requires C, 69.45; H, 7.42; N, 14.72%) $[\alpha]_D$ = -44,3° (c 0,9., MeOH); (Lit.[6] $[\alpha]_D$ = -44,5° (c 3,0 MeOH) ν_{max} ($CHCl_3$)cm^{-1} 3460 (NH) and 1704 (CO); δ_H (200 MHz)

0.73 (3H, d, *J* 6.5Hz, 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, bs, NH); 7,24 - 7,38 (5H, m, Ar-*H*); 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; 128,77 (5d, Ar-*C*H); 138,73 (s,Ar-*C*); 163,22 (s, C-2); m/z 190 (M^+, 62%); 175 (100%) and 58 (43%).

(*4R*, *5S*)-1,5-Dimethyl-4-phenyl-3-propanoylimidazolidin-2-one (50)



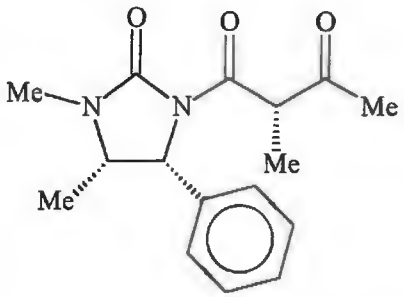
A stirred solution of (1) (5,00g, 26,28mmol) in dry THF (30 ml) was treated with an equimolar amount of n-BuLi at 0°C giving a yellow solution. After 30 min at 0°C propionic anhydride (3,39 ml; 26,28mmol) was added and the resultant mixture was stirred for a further 60 min at 0°C before being quenched with saturated $NaHCO_3$. The THF was removed under reduced pressure and the residue partitioned between H_2O and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and the solvent removed. Recrystallization of the residue from $CHCl_3$ afforded (50) as white crystals (5,7g, 88%) m.p. 103,5°C (Lit.[7], 90°C); (Found: C, 68,39; H, 7,62; N, 11,27. $C_{14}H_{18}N_2O_2$ requires C, 68,27; H, 7,37; N, 11,37%); $[\alpha]_D$ =54,1° (c 1,0 CH_2Cl_2) lit.[7], $[\alpha]_D$ = 54,7° (c 1,0 CH_2Cl_2); υ_{max} ($CHCl_3$)cm^{-1} 1728 (CO) and 1685 (CO); δ_H(200 MHz) 0.80(3H, d, *J* 6,7Hz, 5-Me), 1,10 (3H, t, *J* 7,4Hz, H-3′), 2,82 (3H, s, NMe), 3,00(2H,q, *J* 7,5 Hz, H-2′), 3,90(1H, dq, *J* 6,62 Hz, H-5); 5,30 (1H, d, *J* 8,58 Hz, H-4), 7,12 - 7,38 (5H, m, Ar-*H*); δ_c (50MH) 8,57 (q, C-3′), 14,93(q,5-Me); 28,17(q, NMe); 29,30 (t, C-2); 54,00 (d, C-5), 59,27(d, C-4), 126,91, 128,02, 128,48 (5d, Ar-*C*H); 136,7 (s, Ar-*C*), 156,00 (s, C-2), 173,86 (s, C-1′); m/z 246 (M^+,35%), 217(1%), 189(47%) and 132(100%).

General Procedure 1. Diastereoselective Acylations of (50)

n-BuLi (1.00eq) was added dropwise to a stirred, cooled (O°C) solution of DIPA (1.05eq) in dry THF (10ml). After 30 mins at 0°C the reaction mixture was cooled to

-78°C and treated with a solution of (50) (1,00eq) in THF (5 ml). The reaction mixture was then stirred for an additional 30 min before being treated with the appropriate acyl halide or anhydride (1,00 eq) and was kept at -78°C for a further 15 min. The resultant mixture was then removed from the cooling bath and allowed to warm up for 2 min before being quenched with saturated aq. NH_4Cl. The THF was then removed under reduced pressure and the residue partitioned between H_2O and CH_2Cl_2. The organic extract was then dried ($MgSO_4$), concentrated and purified.

(4R, 5S, 2'S) -1,5-Dimethyl-4-phenyl-3-(2'methyl-3-oxobutanoyl) imidazolidin-2-one, (67).

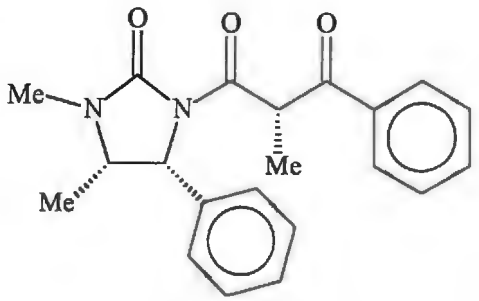


The lithum enolate of (50) (10,00g, 39,64 mmol) was allowed to reacted with acetic anhydride (3,75 ml, 39.64 mmol) according to general procedure 1. This reaction yielded (68) as white needles (6,06 g, 53,02%) m.p. 116°C (from EtOAc).

(found : C, 66,58; H, 7,05; N, 9,83%. $C_{16}H_{20}N_2O_3$ requires C, 66,65; H, 6,99; N,9,71%); $[\alpha]_D$ -14,125° (c 1,15, CH_2Cl_2); υ_{max} (KBr)cm^{-1} 1724(CO), 1720(CO) and 1691(CO); δ_H(200 MHz).

0,78 (3H, d, *J* 6,6Hz, 5-Me); 1,3 (3H, d, *J* 7,31 Hz, 2'-Me); 2,27 (3H, s, H-4'); 2,79 (3H,s, NMe); 3,90 (1H, dq, *J* 6,6 Hz, H-5); 4,60(1H, q, *J* 7,24 Hz, H-2'); 5,30 (1H, d, *J* 8,75 Hz, H-4); 7,19 - 7,36 (5H, m Ar-*H*); δ_c (50 MHz); 12,42 (q, 2'-Me); 15,00 (q, 5-Me); 28,04 (q, NMe); 28,41 (q, C-4'); 53,06 (d, C-2'); 54,07 (d, C-5); 59,45 (d, C-4); 127,13; 128,08; 128,37 (5d, Ar-*C*H); 135,88 (s, Ar-*C*); 155,70 (s, C-2); 169,22 (s, C-1'); 205,46 (s, C-3'), m/z 288 (M^+,2%); 246(55%); 217(1%); 188(56%); 175(44%); 58(100%).

(*4R,5S,2'S*)-1,5-Dimethyl-4-phenyl-3-(2'-methyl-3'-oxo-3'-phenylpropanoyl imidazolidin-2-one (72)



The lithium enolate of (50) (1,0g, 3,96 mmol) was allowed to react with benzoyl chloride (0,46 ml, 3,96 mmol) according to general procedure 1. This reaction yielded (75) as white crystals (0,97 g, 70,0%)m.p. 159-160°C. Purification was as follows:-

(a) Silca column using CH_2Cl_2 as eluent.

b) Gradient elution using a 2 mm chromatotron plate with

i) 70/30 Hex/EtOAc

ii) CH_2Cl_2

(Found : C, 71,85; H, 6,30; N, 7,82. $C_{21}H_{22}N_2O_3$ requires C, 71,98; H, 6,33;N, 7,99%); $[\alpha]_D^{=}$ + 73,506° (c. 1,0625, CH_2Cl_2); υ_{max} (KBr)cm^{-1} 1728(OH), 1696(CO) and 1683(CO); δ_H (200 MHz); 0,78 (3H, *d*, J 6,6 Hz, 5-Me); 1,40 (3H, d, *J* 7,3Hz, 2'-Me); 2,75 (3H, s, NMe); 3,80 - 4,00 (1H, dq *J* 6.6Hz, H-5); 5,30 - 5,40 (1H, d, *J* 8,8Hz, H-4);5,40 - 5,60 (1H, q, *J* 7.23Hz, H-2'), 7,22 - 8,02 (10H, m, Ar-*H*); δ_c (50 MHz); 13,53 (q, 2'-Me); 15,07 (q, 5-Me); 28,14 (q, NMe); 48,52 (d, C-2'); 54,10 (d, C-5); 59,50 (d, C-4); 127,11; 128,08; 128,34; 128, 36; 132, 78 (10d, Ar-*C*H); 135,80 (s, Ar-*C*); 155,65 (s, C-2); 197,96 (s, C-3'); m/z; 350 (M^+, 8%); 245 (15%); 190 (6%); 189 (25%); 175 (8%); 105(100%)

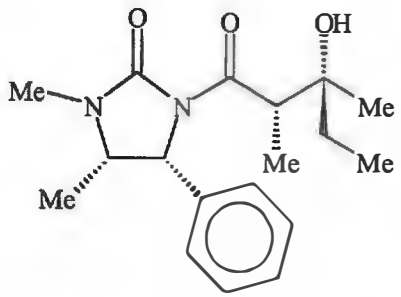
General Procedure 2: Diastereoselective Grignard reactions.

The appropriate alkyl halide (3,00 eq) was allowed to react with magnesium (3,00 eq) under strictly anhydrous conditions in dry Et_2O (25 ml). This solution of the freshly

formed Grignard reagent was then diluted with CH_2Cl_2, (25 ml) before being cooled to -78°C. This mixture was then transferred *via* a cannular to a solution of (68) (1,00 eq) in THF (10 ml) also at -78°C. The resultant reaction mixture was then stirred for an additional 3 hours at -78°C before being quenched with NH_4Cl. All operations to this point were carried out under N_2.

The mixture of organic solvents was removed under reduced pressure and the remaining residue partitioned beteween H_2O and CH_2Cl_2. The organic extracts were dried ($MgSO_4$), concentrated and purified.

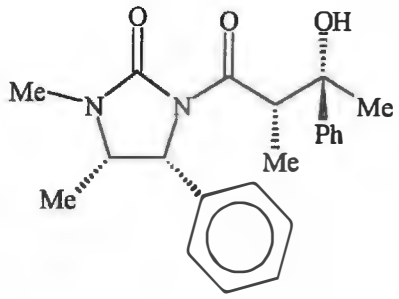
(*4R*, *5S*, *2'S*, *3'R*)-1,5-Dimethyl-4-Phenyl-3-(2',3'-dimethyl-3'-hydroxypentanoyl) imidazolidin-2-one. (81)



A solution of (67) (850 mg, 2,95 mmol) in THF (10 ml) was allowed to react with a solution of ethylmagnesium bromide (1,18 g, 8,84 mmol) according to general procedure 2. This reaction yielded (93) as white crystals. (562 mg, 59.8%) m.p. = 84°C (Purified by flash chromatography with Hex/EtOAc (80/20) as the eluent.)

(Found : C, 67,92; H, 8,19; N, 8,81. $C_{18}H_{26}N_2O_3$ requires C, 67,90; H, 8,23; N, 8,79%); $[\alpha]_D$ = -82,02° (c 0,7599 CH_2Cl_2); υ_{max} (KBr)cm^{-1} 3460(OH), 1710 (CO) and 1685 (CO); δ_H (200 MHz); 0,80 (3H, d, *J* 6,7 Hz, 5-Me); 0,92 (3H, t, *J* 7,4 Hz, H-5'); 1,01 (3H, *S*, 3'-Me); 1,17(3H, d, *J* 6,8 Hz, 2'-Me), 1,40 (2H, q, *J* 7,5 Hz, H-4'), 2,83 (3H, s, NMe); 3,90 (1H, dq, *J* 6,6 Hz, H-5); 3,99 (1H, bs, OH); 4,2 (1H, q, *J* 7 Hz, H-2'), 5,30 (1H, d, *J* 8,7 Hz, H-4); 7,16 - 7,37 (5H, m, Ar-*H*) ; δ_c (50 MHz); 8,04 (q, C-5'); 13,16 (q, 2'-Me); 14,93 (q, 5-Me); 22,00 (q, 3'-Me); 28,12 (q, NMe); 34,36 (t, C-4'), 43,57 (d, C-2'); 53,56 (d, C-5); 59,70 (d, C-4); 74,43 (s, C-3'); 126,92; 128,04; 128,40; (5d, Ar-*C*H); 136,39 (s, Ar-*C*); 156,05 (s, C-2); 176,64 (s, C-1'); m/z. 245 (6.%); 189 (20%); 132 (97%); 77 (42%); 58 (100%)

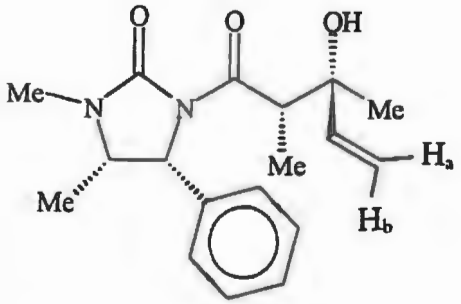
(*4R,5S,2'S,3'R*)-1,5-Dimethyl-4-phenyl-3-(3'-hydroxyl-2'-methyl-3'-phenylbutanoyl) imidazolidin-2-one. (82)



A solution of (67) (500 mg, 3,47 mmol) was allowed to react with a solution of PhMgBr (1,89 g, 10,40 mmol) according to general procedure 2 to afford (94) as white crystals. (426 mg, 34,6%) m.p. 140°C. (Purified by flash Chromotography with Hex/EtOAc (80/20) as eluent.)

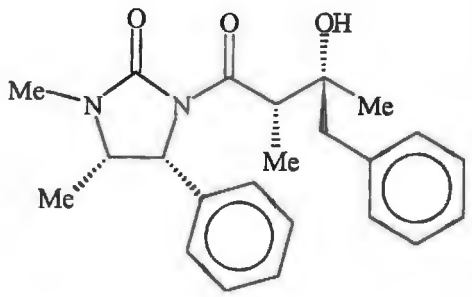
(Found : C, 70,91; H, 7,30; N, 7,78; $C_{12}H_{26}N_2O_3$ requires C, 71,16; H, 7,39; N, 7,90%); $[\alpha]_D$ = -145,67° (c 1,645, CH_2Cl_2); υ_{max} (KBr)cm^{-1} 3462 (OH); 1726 (CO) and 1656 (CO); δ_H (200 MHz); 0,65 (3H, d, *J* 6,6 Hz, 5-Me); 1,40 (3H, d, *J* 6,9 Hz, 2'-Me); 1,40 (3H, s, H-4'); 2,79 (3H, s, Nme), 3,80 (1H, dq, *J* 6,6 Hz, H-5); 4,86 (1H, bs, OH); 4,92 (1H, q, *J* 7,02 Hz, H-2'); 5,10 (1H, d, *J* 8,8 Hz, H-4); 6,44 - 7,45 (10H, m, Ar-*H*); δ_c (50 MHz); 13,11 (q, 2'-Me); 15,01 (q, 5-Me), 27,70 (q, C-4'); 28,26 (q, NMe); 44,42 (d, C-2'); 53,32 (d, C-5); 59,14 (d, C-4); 75,40 (s, C-3'); 124,81; 125,86; 126,31; 127,24; 128,08; 128,34 (10d, Ar-*C*H); 135,38; 148,37; (s, Ar-*C*); 154,91 (s, C-2); 177,75 (s, C-1'); m/z 245 (6%); 189 (24%); 132 (97%); 112 (28%); 77 (42%), 58 (100%).

(*4R*, *5S*, *2'S*, *3'S*)-1,5-Dimethyl-4-phenyl-3(2',3'-dimethyl-3'-hydroxy-4'-pentenoyl) imidazolidin-2-one. (83)



A solution of (67) (500 mg, 1.73 mmol)was allowed to react with a solution of vinyl magnesium bromide (682.8 mg, 5.2 mmol) according to general procedure 2 to afford (95) as white crystals. (309 mg, 56.5%) m.p. = 117°C. (Purified by flash chromatography with petroleum ether (60-80)/EtOAc (70/30) serving as the eluent.) (Found : C, 68,30; H, 7,70; N, 8,90. $C_{18}H_{24}N_2O_3$ requires C, 68,33; H, 7,65; N, 8,85%); $[\alpha]_D$ -119,93° (c 0,5253, CH_2Cl_2); υ_{max} (KBr)cm^{-1} 3456 (OH); 1768 (CO); 1658 (CO); and 985 - 1000 (R-CH=CH_2); δ_H (200 MHz); 0,80 (3H, d, *J* 6,61 Hz, 5-Me); 1,17 (3H, s, 3'-Me); 1,25 (3H, d, *J* 7,03 Hz, 2'-Me); 2,84 (3H, s, NMe); 3,90 (1H, dq, *J* 15.2 Hz, H-5); 4,15 (1H, bs, OH); 4,25 (1H, q, *J* 6,9 Hz, H-2'); 4,80 (1H, dd, *J* 11,9 Hz, H_a-5'); 5,08 (1H, dd, *J* 18,5 Hz, H_b-5'); 5,25 (1H, d, *J* 8,61 Hz, H-4), 5,80 - 6,00 (1H, dd, *J* 10,7 and 18,0 Hz, H-4'), 7,10 - 7,36 (5H, m, Ar-*H*); δ_c (50 MHz); 12,64 (q, 2'-Me); 14,93 (q, 6-Me), 24,06 (q, 3'-Me), 28,16 (q, NMe); 44,24 (d, C-2'); 53,59 (d, C-5); 59,67 (d, C-4); 112,56 (t, C-5'); 127,14; 128,08; 128,29 (5d, Ar-*C*H); 144,47 (d, C-4'); 155,69 (s, C-2); 176,79 (s, C-1'); 74,19 (s, C-3'), 135,95 (s, Ar-*C*); m/z. 245 (10%); 189 (25%); 175 (32%); 58 (100%)

(*4R,5S,2'S,3'R*)-1,5-Dimethyl-4-phenyl-3-(2',3'-dimethyl-3'-hydroxyl-4'-phenylbutanoyl)imidazolidin-2-one (84)



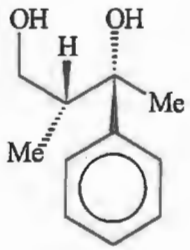
A solution of (67) (850 mg, 2,95 mmol) was allowed to react with a solution of Benzyl Magnesium Bromide (1,73 g, 8,84 mmol) according to general procedure 2 to afford (96) as white crystals (427 mg, 38,04%) m.p. = 168°C. (Purified by flash chromatography with petroleum ether. (60-80)/EtOAc (80/20) as eluent.)

(Found : C, 72,58; H, 7,38; N, 7,40. $C_{23}H_{28}N_2O_3$ requires C, 72,61; H, 7,42; N, 7,36%). $[\alpha]_D$ -42,89 (c 0,9023, CH_2Cl_2); υ_{max} (Kbr)cm^{-1} 3548 (OH); 1707 (CO) and 1652 (CO); δ_H (200 MHz); 0,80 (3H, d, *J* 6,6 Hz, 5-Me); 0,946 (3H, s, 3'-Me); 1,25 (3H, d *J* 6,96 Hz, 2'-Me); 2,706 (2H, s, H-4'); 2,812 (3H, s, NMe); 3,90 (1H, dq, *J* 6,6 Hz, H-5); 4,14 (1H, q, *J* 6,73 Hz, H-2'), 4,14 (1H, bs, OH), 5,30 (1H, d, *J* 8,6 Hz, H-4), 7,14 - 7,35 (10H, m, Ar-*H*); δ_c (50 MHz); 13,52 (q, 2'-Me); 14,90 (q, 5-Me); 22,15 (q, 3'-Me); 28.12 (q, NMe); 47,45 (t, C-4'); 45,17 (d, C-2'); 53,63 (d, C-5); 59,96 (d, C-4); 74,56 (5, C-3); 126,16; 126,90; 127,07; 128,50; 130,64; (d, Ar-*C*H); 136,23; 137,45 (s, Ar-*C*); 156,00 (s, C-2); 176 (5, C-1'); m/z 245 (4.2%); 189 (23%); 132 (98%); 112 (30%); 77 (42%); 58 (100%)

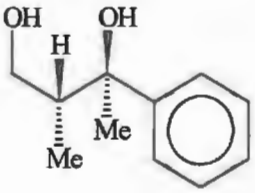
General Procedure 3: Reductive Cleavage of (95) - (98)

A solution of the appropriate product (1,00 eq) in dry THF (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (2,50 eq) in THF (5 ml) at 0°C. After 90 mins at 0°C the reaction mixture was quenched with saturated NH_4Cl. The THF was then removed under reduced pressure and minimal heat. The remaining residue was then partitioned between H_2O (saturated with NaCl) and CH_2Cl_2. The organic extracts were dried ($MgSO_4$) filtered, concentrated and purified. (Removal of CH_2Cl_2 under atmospheric pressure and minimal heat.)

(*2R, 3R*)-2-Methyl-3-phenyl-1,3-butanediol.



(95)



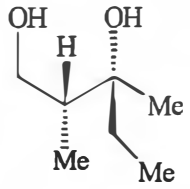
(100)

Applying general procedure 3 to (82) (477 mg, 1,35 mmol) afforded the diol (107) as white crystals which were purified *via* flash chromatography over silica gel with Hexane/EtOAc (80/20) as the eluent. (30,8 mg, 12,66%)

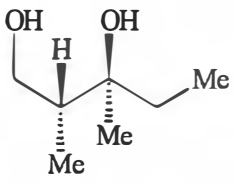
(Found : C, 73,00; H, 8,85; $C_{11}H_{16}O_2$ requires C, 73,28; H, 8,92%) $[\alpha]_D = {}^{+}35{,}065°$ (c, 0308, CH_2Cl_2); υ_{max} (CH_2Cl_2)cm^{-1} 3612 (OH) and 3496 (OH); δ_H (200 MHz); 0,95 (3H, d, *J* 7,13 Hz, 2-Me); 1,52 (3H, s, H-4); 1.99 - 2,07 (1H, m, H-2); 3,00 - 3,40 (1H, bs, OH); 3,46 - 3,62 (2H, m, H-1), 3,70 - 3,90 (1H, bs, OH); 7,20 - 7,46 (5H, m, Ar-*H*); δ_c (50 MHz); 12,31 (q, 2-Me), 25,48 (q, C-4); 43,86 (d, C-2), 66,12 (t, C-1), 78,193 (s, C-3); 125,03; 126,63; 128,08 (5d, Ar-*C*H); 148,26 (s, Ar-*C*); m/z 180 (M^+,1%); 162 (12%); 121 (100%); 105 (82%); 91 (14%).

(lit.[105] (2R, 3R)-2-Methyl-3-Phenyl-1,3-butanediol δ_H (300 MHz); 0,91 (d, J 7,1Hz, 3H); 1,48 (S, 3H), 1,94 - 2,05 (m, 1H); 2,71 (bs, 1H), 3,35 (bs, 1H); 3,43 - 3,58 (m, 2H), 7,19 - 7,41 (m, 5H); δ_c(75 MHz); 12,3; 25,7; 44,0; 66,2; 78,1; 125,0; 126,7; 128,1; 148,3.

(*2R, 3S*)-2,3-Dimethyl-1,3-pentanediol.



(97)

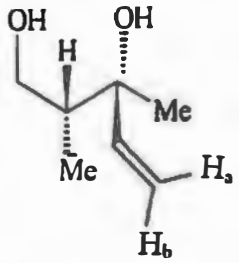


(99)

Applying general procedure 3 to (81) (562 mg, 1,77 mmol) yielded the diol (109) as a colourless oil which was purified *via* flash chromatography over silica gel with hexane/EtOAc (70/30) as the eluent. (13,6 mg, 5,8%). $[\alpha]_D$ -8,08° (c 0,136, CH_2Cl_2); δ_H (200 MHz); 0.80 (3H, d, *J* 7,14 Hz; 2-Me); 0,90 (3H, t, *J* 7,43 Hz, H-5), 1,14 (3H, s, 3-Me), 1,54 (2H, q, *J* 7,00 Hz, H-4); 1,80 - 2,00 (1H, m, H-2), 2,60 - 3,00 (bs, 2 x OH); 3,67 - 3,76 (2H, 2dd, H-1); δ_c (50 MHz); 7,28 (q, C-5), 12,58 (q, 2-Me),; 22,00 (q, 3-Me); 34,06 (t, C-4); 40,96 (d, C-2), 66,08 (t, C-1); 76,501 (s, C-3); υ_{max} (CH_2Cl_2)cm^{-1} 3496 (OH) and 3616 (OH); m/z 117 (5%); 103 (29 %); 85 (22%); 73 (100%); 57 (27%); 43 (50 %)

(lit.[105] (2R, 3S)-2,3-Dimethyl-1,3-pentanediol δ_H (300 MHz); 0,79 (d, J 7,1 Hz, 3H); 0,90 (t, J 7,5 Hz, 3H); 1,11 (S, 3H), 1,52 (q, J 7,4 Hz, 1H); 1,53 (q, J 7,6 Hz, 1H); 1,82 - 1,92 (m, 1H); 3,1 (bs, 2H); 3,63 (dd, J 10,9 Hz and 4,2 Hz, 1H); 3,73 (dd, J 10,9 and 42 Hz, 1H); δ_c (75 MHz); 7,2; 12,7; 21,9; 34,0; 40,9; 66,0; 76,4.

(*2S, 3R)*-2,3-Dimethyl-4-propene-1,3-diol (98)



Applying general procedure 3 to (83) (309 mg, 0,98 mmol) afforded the diol (98) as a viscous colourless oil which was purified *via* flash chromatography over silica gel with hexane/EtOAc (70/30) as the eluent. (23,4 mg, 18,1%) $[\alpha]_D$ = -4,32° (c 0,231, CH_2Cl_2); υ_{max} (CH_2Cl_2)cm^{-1} 3608 (OH); 3496 (OH) and 985 - 1000 (R-CH = CH_2); δ_H (200 MHz); 0,95 (3H, d, *J* 7,1 Hz, 2-Me); 1,25 (3H, s, 3-Me); 1,73 - 1,82 (1H, m, H-2); 2,60 - 3,10 (bs, 2 x OH); 3,62 - 3,80 (2H, m, H-1), 5,08 - 5,14 (1H, dd, *J* 12,02 Hz and 1,34 Hz, H_a-5); 5,24 - 5,34 (1H, dd, *J* 18,60 Hz and 1,325 Hz, H_b-5); 5,89 - 6,03 (1H, dd, *J* 10,705 and 28,02 Hz, H-4); δ_c (50 MHz); 12,14 (q, 2-Me); 23,48 (q, 3-Me); 29.70 (d,C-2), 42,54 (t, C-1); 66,00 (s, C-3); 112,30 (t, C-5), 145,11 (d, C-4); m/z 115 (5%); 97 (10 %); 83 (2 %); 71 (100%); 55 (16%); 43 (15 %)

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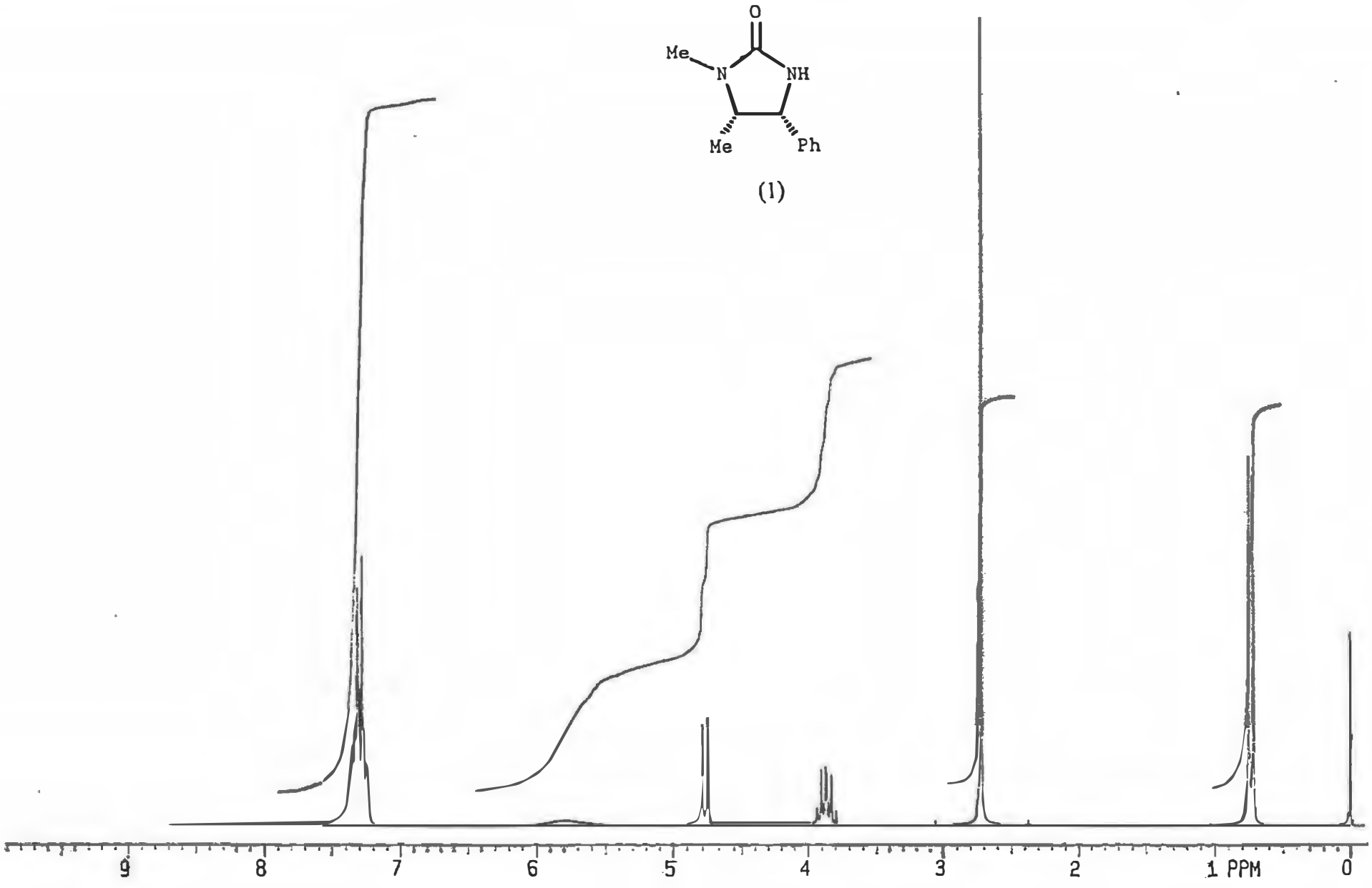
APPENDIX

^{1}H AND ^{13}C NUCLEAR MAGNETIC RESONANCE SPECTRA



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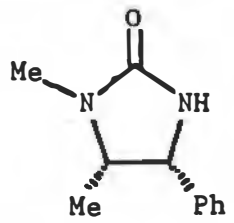

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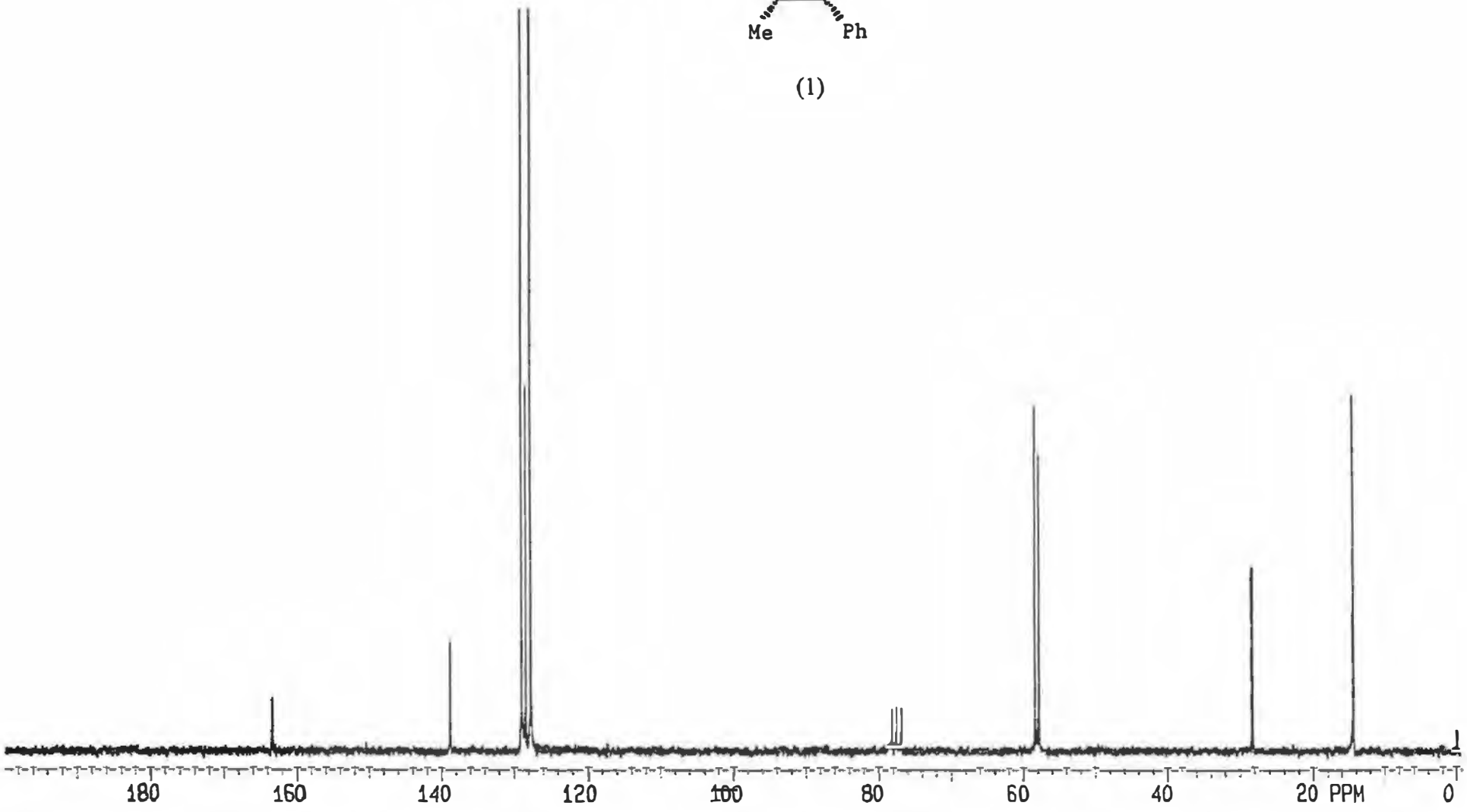

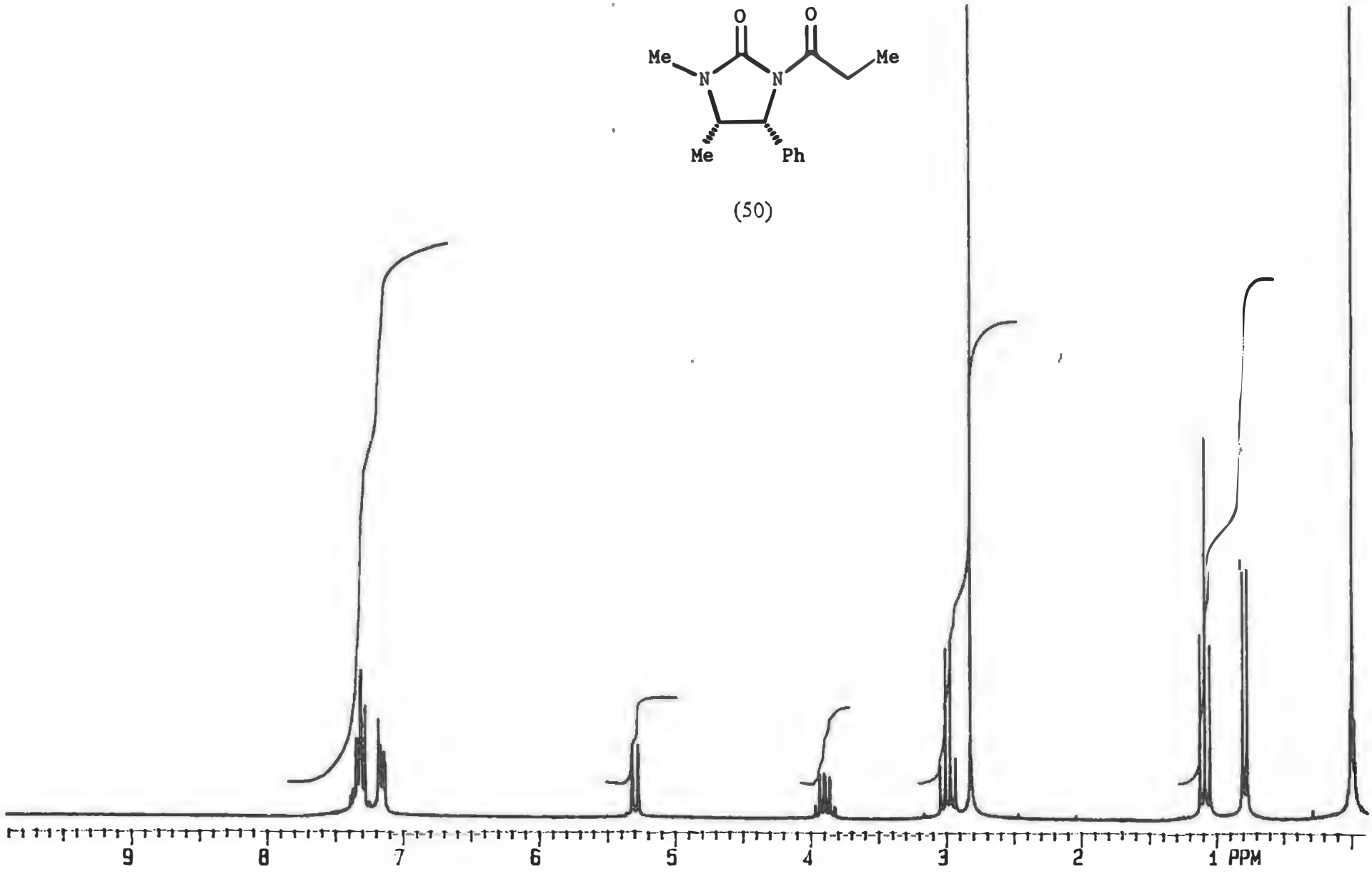

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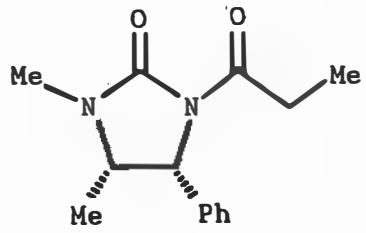

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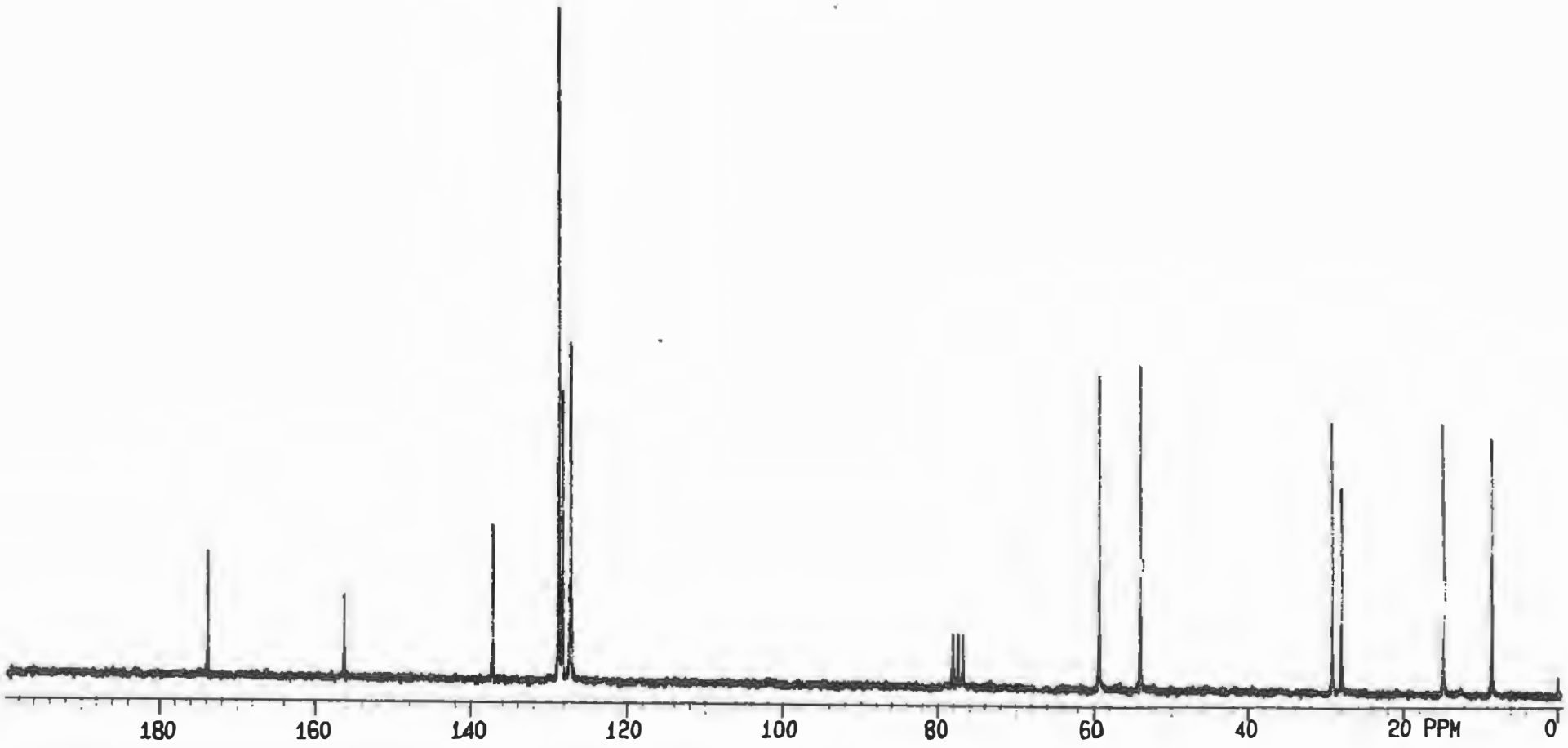

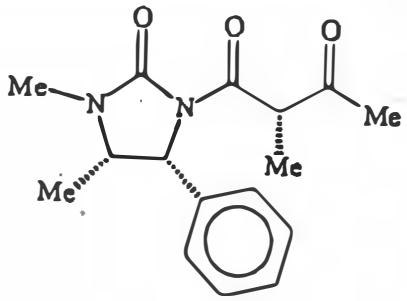

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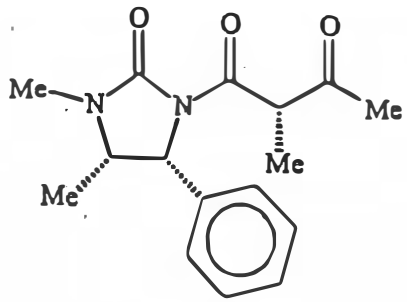

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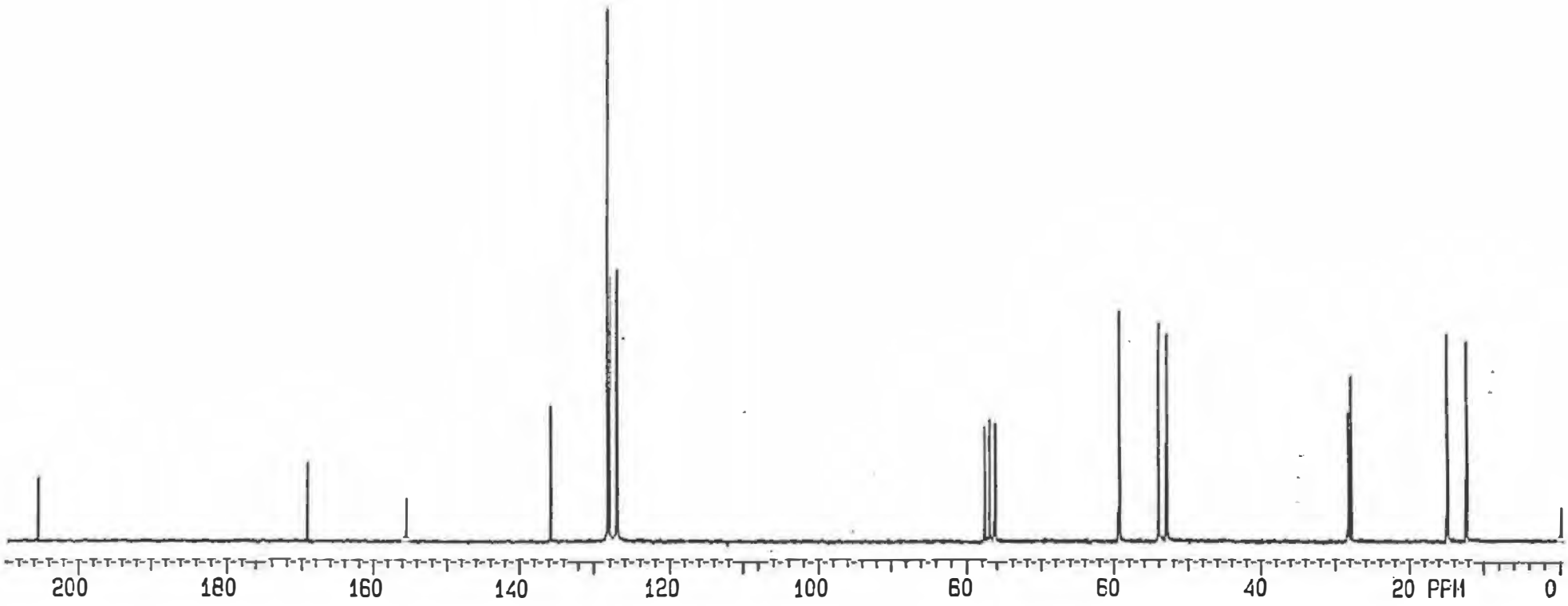

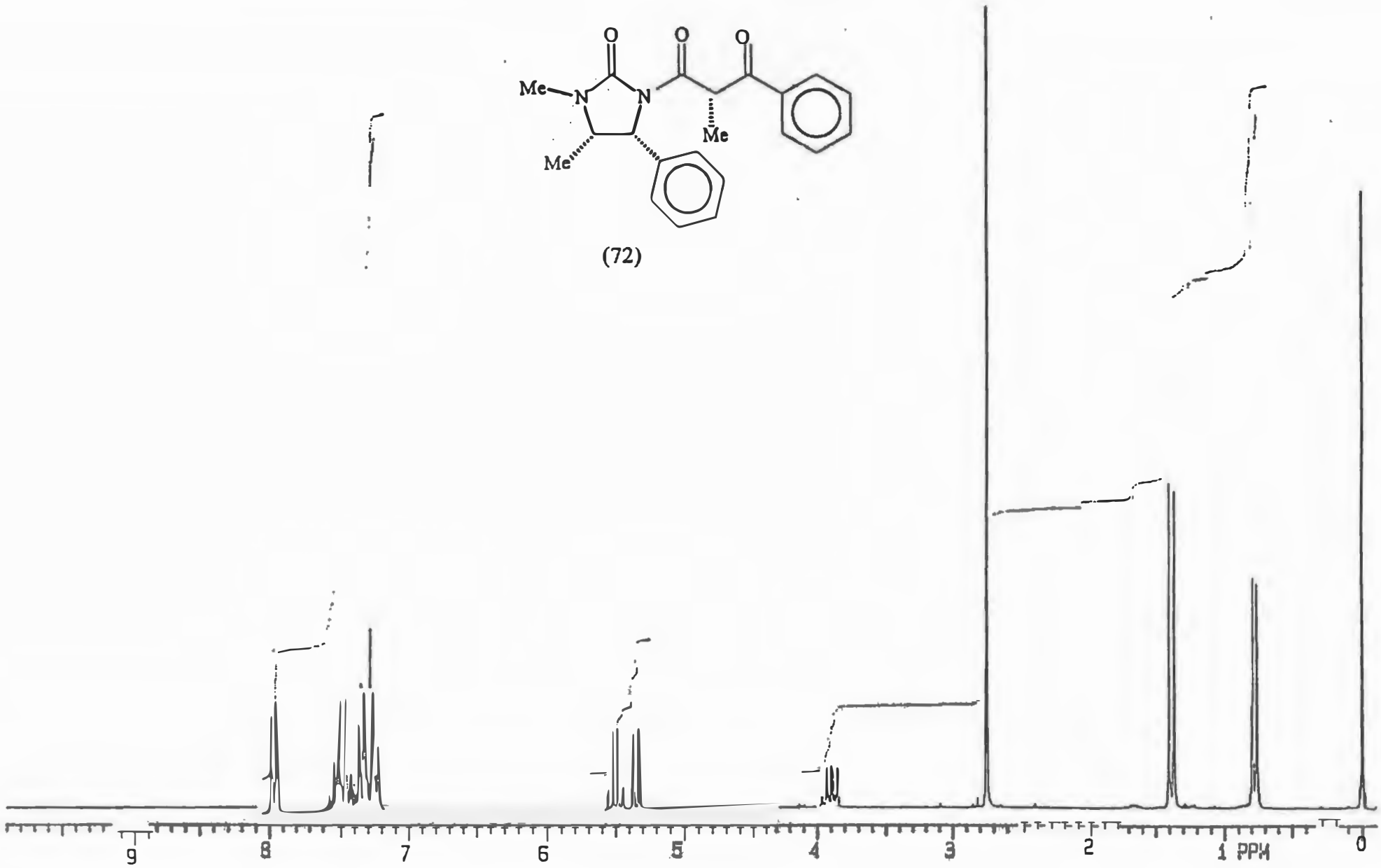

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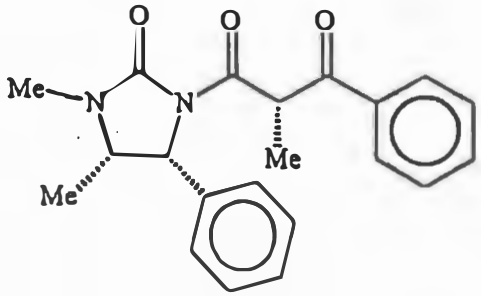

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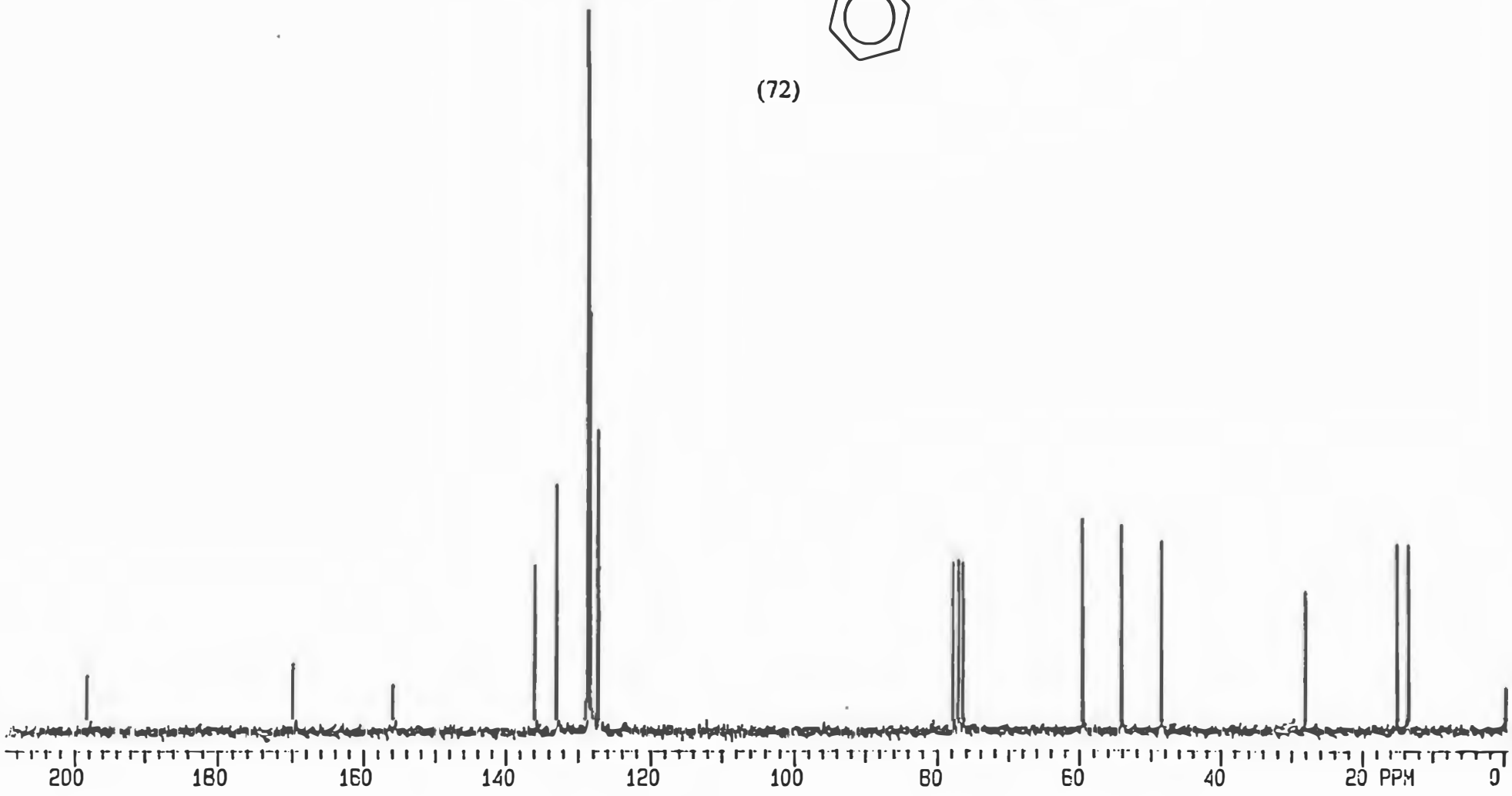

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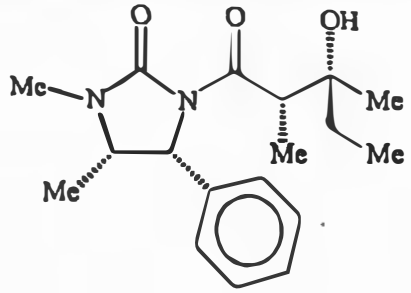

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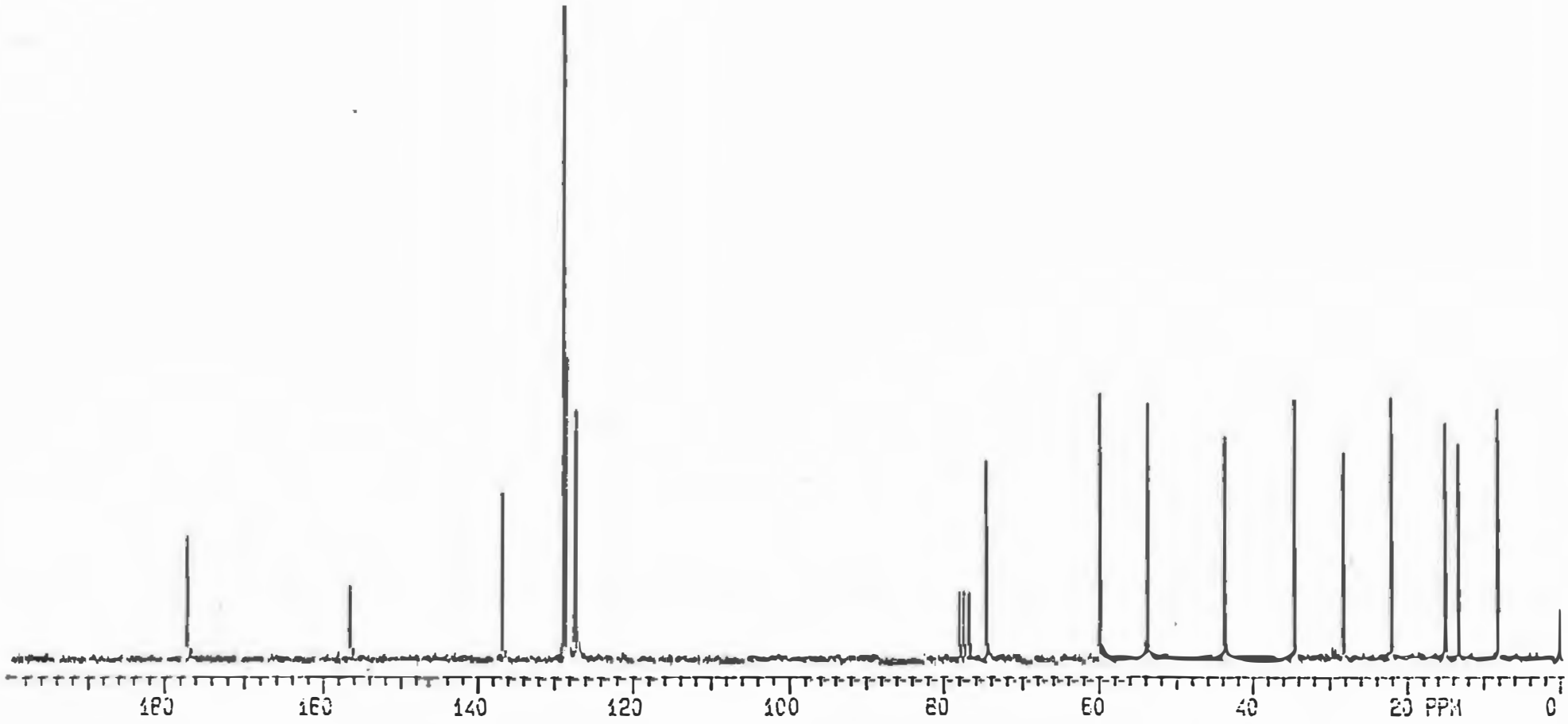

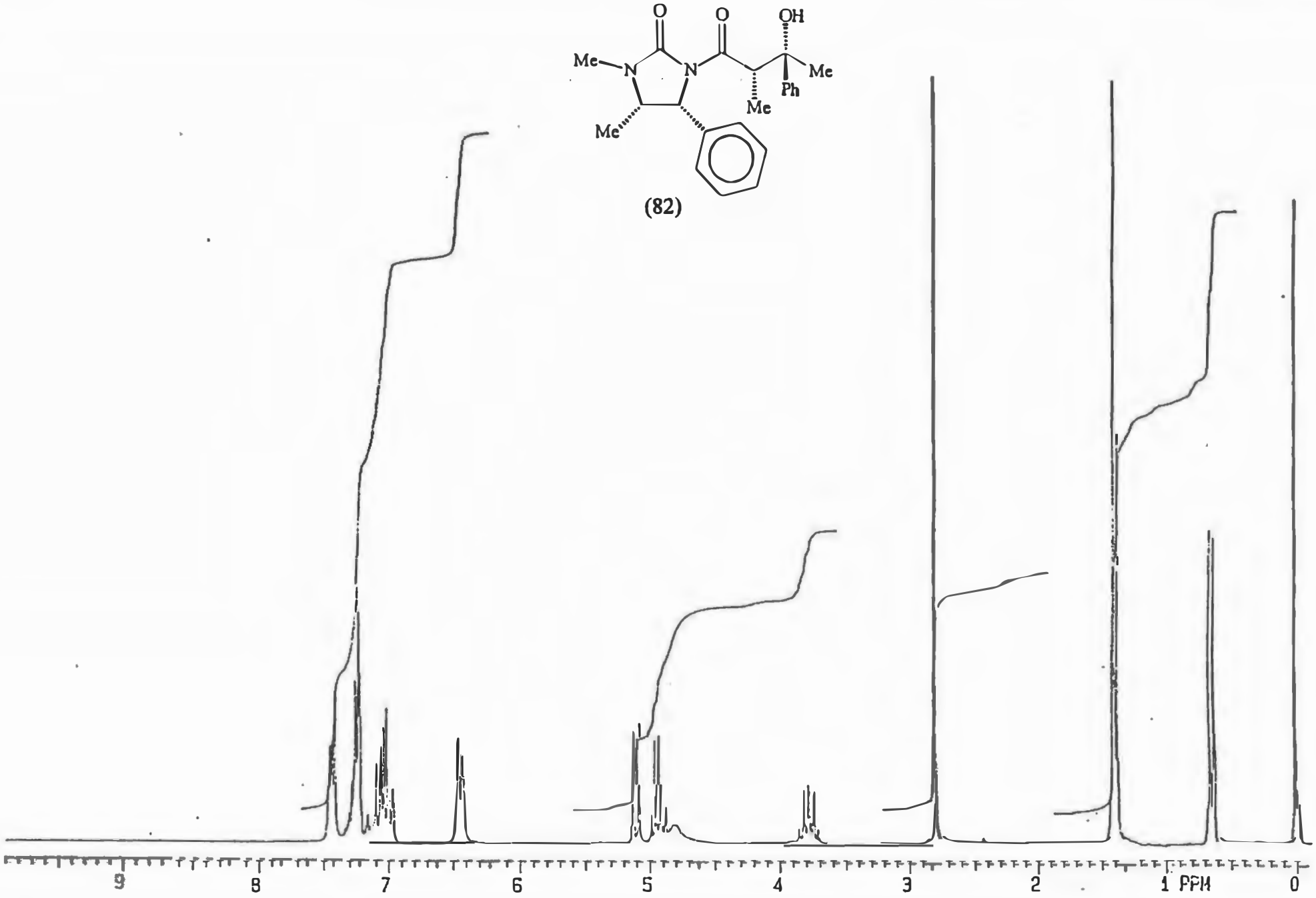

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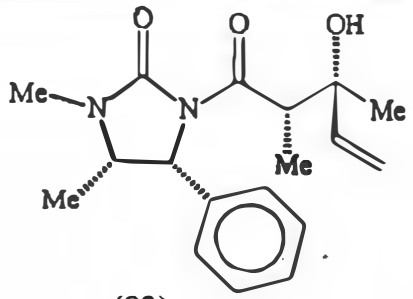

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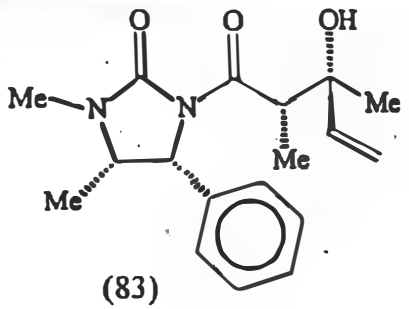

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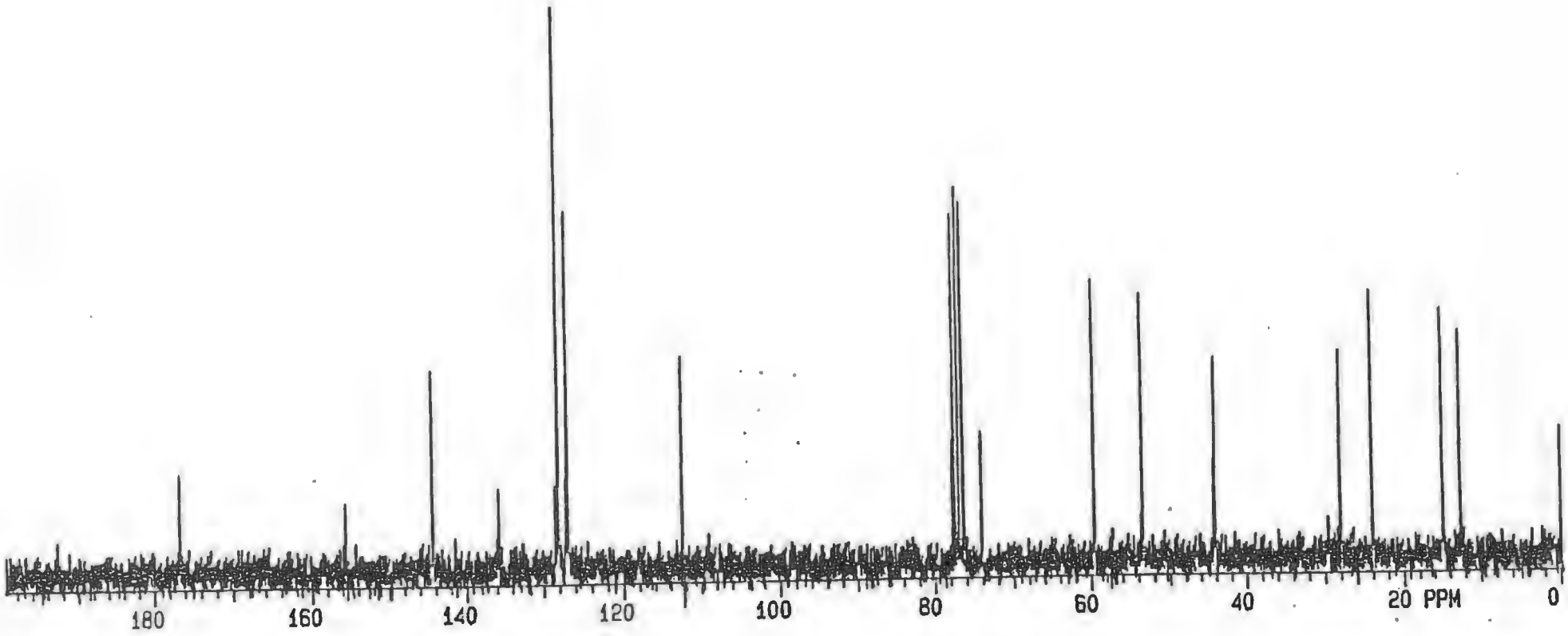

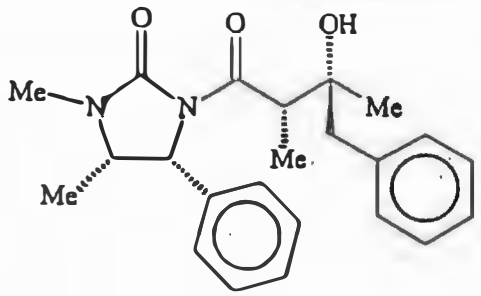

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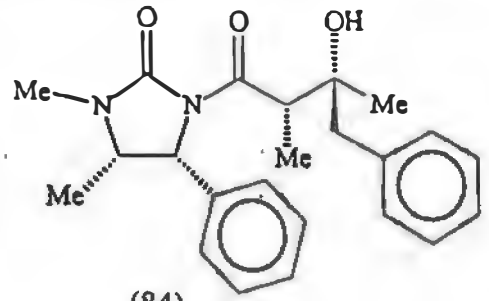

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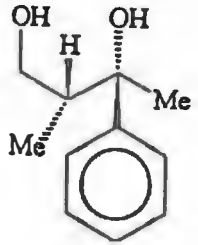

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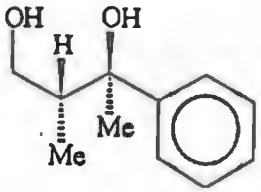

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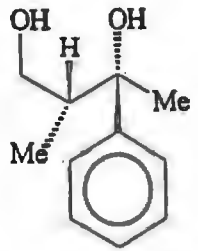

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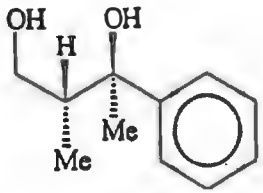

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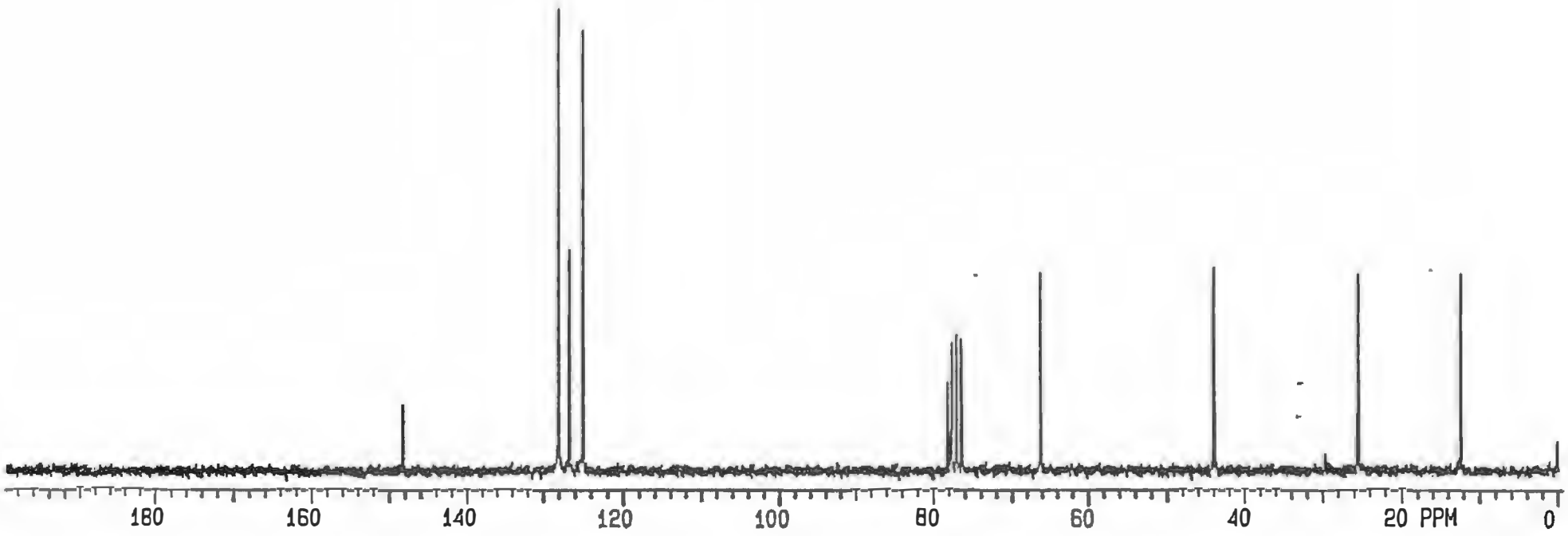

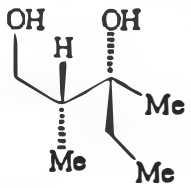

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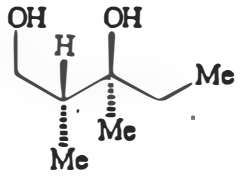

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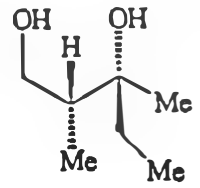

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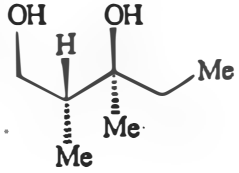

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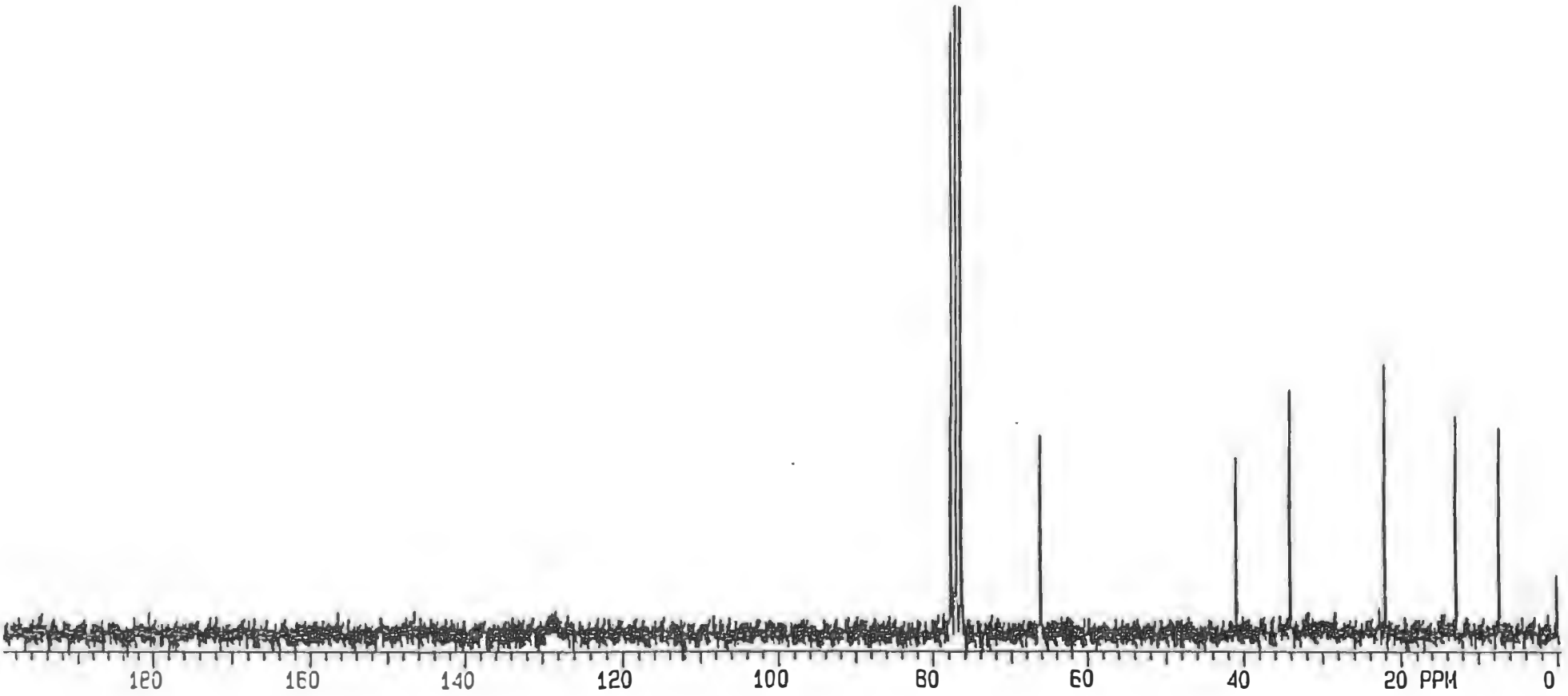

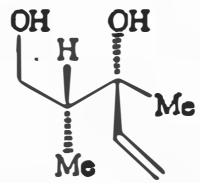

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