STEREOSELECTIVE SYNTHESES USING BAYLIS-HILLMAN ADDUCTS

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

BY
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To

my brothers Selvam, Ravichandran
and
sister Valarmathi

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STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Dr. D. Basavaiah.**

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

SPRaju

Hyderabad **S. Pandiaraju**

March 1995

CERTIFICATE

Certified that the work embodied in this thesis entitled **"Stereoselective Syntheses Using Baylis-Hillman Adducts"** has been carried out by **Mr. S. Pandiaraju,** under my supervision and the same has not been submitted elsewhere for a degree.

D Basavaiah
March 10, 1995

Dr. D. BASAVAIAH
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

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SPRaja

S. PANDIARAJU

ABBREVIATIONS

Ac	acetyl
Bu	butyl
Bn	benzyl
CAN	ammonium cerium(IV) nitrate
cod	cyclooctadiene
NOESY	nuclear Overhauser enhancement spectroscopy
DABCO	1,4-diazabicyclo(2.2.2)octane
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
4-DMAP	4-dimethylaminopyridine
DIBAL-H	diisobutylaluminium hydride
dppe	diphenylphosphinoethane
ee	enantiomeric excess
Et	ethyl
Fur	furyl
HCA	hexachloroacetone
Hex	hexyl
Hept	heptyl
LAH	lithium aluminium hydride
Mes	mesityl
MsCl	methanesulfonyl chloride
Me	methyl

NBS	N-bromosuccinimide
Np	naphthyl
Oct	octyl
Pr	propyl
Pent	pentyl
Ph	phenyl
Py	pyridine
PLAP	pig liver acetone powder
R_f	retention flow
R_t	retention time
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
p-TsCl	p-toluenesulfonyl chloride

ABSTRACT

Development of stereoselective processes has been and continues to be a challenging task in organic chemistry. Synthetic organic chemists have enthusiastically embraced this challenge and developed innumerable number of reagents reactions and methodologies to achieve chemo-, regio- and stereoselective syntheses. Baylis-Hillman reaction is one such reaction which has attracted the attention of organic chemists in recent years.

Baylis-Hillman reaction is a novel C-C bond forming reaction. It involves the coupling of α-position of activated vinylic system with electrophile containing sp^2 carbon atom under the catalytic influence of tertiary amines, particularly, 1,4-diazabicyclo(2.2.2)octane (DABCO), producing the molecules containing chemospecific functional groups, *i.e.*, hydroxyl, alkene and electron withdrawing group in close proximity. This thesis deals with the development of simple and convenient stereoselective processes using Baylis-Hillman adducts.

This thesis consists of three chapters 1) Introduction, 2) Objectives, Results and Discussion and 3) Experimental. The first chapter, introduction, describes briefly the literature, dealing with the utility of Baylis-Hillman adducts in various stereoselective processes.

The second chapter deals with the objectives, results and

discussion. We have envisioned that the Baylis-Hillman adducts, with chemospecific functional groups in close proximity will have tremendous synthetic potential in a variety of stereoselective processes. We have therefore undertaken this research project with the main objective of utilizing the Baylis-Hillman adducts for:

1) enantioselective synthesis of mikanecic acid *via* Diels-Alder cycloaddition mediated construction of chiral vinylic quaternary center,

2) stereoselective synthesis of a) [E]- and [Z]-alk-4-enoates *via* the Johnson-Claisen rearrangement, b) [E]- and [Z]-allyl bromides using magnesium bromide and c) [E]- and [Z]-allylphosphonates *via* thermal Arbuzov rearrangement.

Our objective also includes the utilization of these adducts as stereodefined β-electrophiles in the Friedel-Crafts reaction.

Mikanecic acid (**59**), a terpene dicarboxylic acid, has attracted our attention owing to its special feature of having a vinylic quaternary carbon center in a functionalized six membered cyclic system. To our knowledge, there is no report in the literature on optically active mikanecic acid. We have carried out enantioselective synthesis of mikanecic acid using the Baylis-Hillman adducts, obtained by the DABCO catalyzed coupling of acetaldehyde and chiral acrylates. The key step in this transformation involves the Diels-Alder cycloaddition of *in situ* generated novel, chiral 1,3-butadiene-2-carboxylate ($\mathbf{A_1}$-$\mathbf{A_5}$) which

acts both as diene and dienophile, to produce the desired chiral vinylic quaternary center.

We have used chiral acrylates **67a-67e** derived from various chiral auxiliaries **66a-66e** for the enantioselective synthesis of mikanecic acid. The enantiomeric purities of mikanecic acid (**59a-59e**) obtained by using chiral acrylates **67a-67e** were found to be 25%, 11%, 8%, 69% and 74% respectively. However, single crystallization of the Diels-Alder dimer **69e** afforded, after hydrolysis, the mikanecic acid (**59e'**) in 92% ee. We have determined the enantiomeric purity of mikanecic acid, in all the cases, by HPLC analysis of the corresponding dimethyl ester (**60a-60e** and **60e'**) using chiral column (CHIRALCEL OD).

During our studies on enantioselective synthesis of mikanecic acid, we have developed a convenient methodology for the synthesis of, hitherto unknown, (1R,2R)- and (1S,2S)-2-nitroxy-cyclohexan-1-ols [**66b** and **78**] in homochiral form *via* enantio-selective hydrolysis of corresponding racemic acetate **79** using pig liver acetone powder (PLAP) as biocatalyst. We have also established the absolute stereochemistry of these molecules.

We have next examined the potentiality of methyl 3-hydroxy-2-methylenealkanoates (**90**) for stereoselective synthesis of functionalized trisubstituted alkenes **91** *via* the Johnson-Claisen rearrangement. Thus treatment of **90**, **92** and **93** with triethyl orthoacetate in the presence of catalytic amount of propionic

acid afforded the desired alk-4-enoates **91a-91g** as a mixture of (E)- and (Z)-isomers. We have observed an interesting substrate dependant stereoselectivity in these reactions, thus (E)-alk-4-enoates were obtained predominantly (E/Z = 70-80/30-20) when R is aryl (C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 1-Np) and (Z)-alk-4-enoates were obtained predominantly (Z/E = 74-80/26-20) when R is alkyl (i-C_3H_7, n-C_3H_7, n-C_4H_9).

Interestingly, the Johnson-Claisen rearrangement of 3-hydroxy-2-methylenealkanenitriles (**96**) afforded stereomerically pure (4Z)-4-cyanoalk-4-enoates **97** in excellent yields.

(2Z)-2-(Bromomethyl)alk-2-enoates (**99**) are versatile building blocks for the stereoselective synthesis of a variety of natural products. We have developed a simple methodology for the synthesis of these molecules **99** ***via*** treatment of methyl 3-acetoxy-2-methylenealkanoates (**98**) with freshly prepared magnesium bromide.

Similar reaction of 3-acetoxy-2-methylenealkanenitriles (**100 103**) with magnesium bromide provided 2-(bromomethyl)alk-2-enenitriles (**101**) in high (E)-stereoselectivity (E/Z = 88-95/12-5).

With a view to provide a simple and convenient stereoselective synthesis of allylphosphonates ***via*** thermal Arbuzov rearrangement we have treated **98**, **106** with triethyl phosphite to afford methyl 2-(diethoxyphosphorylmethyl)alk-2-enoates (**104**) in high (Z)-stereoselectivity (Z/E = 65-93/35-7) and in excellent yields.

Similar reaction of **100, 109** with triethyl phosphite affor-

ded 2-(diethoxyphosphorylmethyl)alk-2-enenitriles (**107**) in high (E)-stereoselectivity (E/Z = 75-93/25-7) and in excellent yields.

Our interest, in understanding and exploring the utility of the acetate of Baylis-Hillman adducts has led us to examine the hitherto unknown application of **98** and **100** as stereodefined β-electrophiles in the Friedel-Crafts reaction. Thus, the Friedel-Crafts reaction of benzene with **98**, **106** in the presence of anhydrous $AlCl_3$ provided methyl 2-benzylalk-2-enoates (**110**) in high (E)- stereoselectivity (E/Z = 80->96/20-<4).

Similar reaction of benzene with **100** in the presence of anhydrous $AlCl_3$ afforded stereomerically pure (2Z)-2-benzylalk-2-enenitriles **111** in high yields.

With a view to synthesize indene-2-carboxylate derivatives *via* intramolecular Friedal-Crafts reaction we have treated **98**, **116**, **117** with anhydrous $AlCl_3$ in dichloromethane. This has not provided the expected indene-2-carboxylates, instead stereomerically pure methyl (2Z)-2-(chloromethyl)-3-arylprop-2-enoates (**112**) were obtained.

Similar reaction of 3-acetoxy-2-methylene-3-phenylpropanenitrile (**100a**) with anhydrous $AlCl_3$ in dichloromethane has also not provided 2-cyanoindene, instead 2-chloromethyl-3-phenylprop-2-enenitrile (**118**) with high (E)-stereoselectivity (E/Z = 90/10) and stereochemically pure (2E)-2-acetoxymethyl-3-phenylprop-2-ene nitrile (**119**) were obtained.

Possible explanation for the stereochemical observations in the formation of functionalized trisubstituted alkenes has been provided.

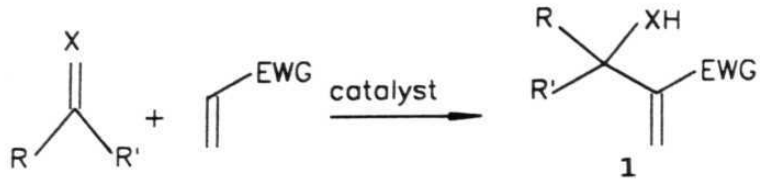
The third chapter provides experimental procedures in detail along with the (IR, ^{1}H NMR, ^{13}C NMR and ^{31}P NMR) spectral data, microanalyses and physical constants (m.p., b.p. and optical rotations). Determination of enantiomeric purities of the products by HPLC analyses using chiral column (CHIRALCEL OD) is also described in detail.

INTRODUCTION

Success in organic synthesis, in a broad sense, depends on the efficiency of the process called selectivity. The term 'selectivity' in organic chemistry can be categorized according to chemical reactivity (chemoselectivity), orientation (regioselectivity) and spatial arrangement (stereoselectivity).

In fact, development of truly economical and practical synthetic processes with high selectivity has been and continues to be a challenging task in organic chemistry. Synthetic organic chemists have enthusiastically embraced this challenge and developed innumerable number of reagents, reactions and methodologies to achieve chemo-, regio- and stereoselective processes.[1,2] Baylis-Hillman reaction[3,4] is one such reaction which has attracted the attention of organic chemists in recent years.

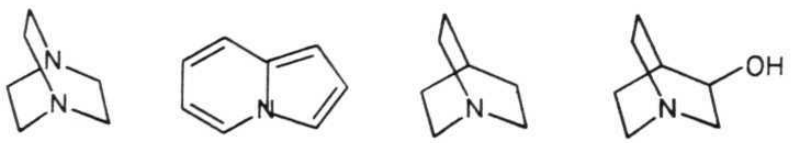
The Baylis-Hillman reaction is an emerging carbon-carbon bond forming reaction producing synthetically useful multifunctional molecules (**1**). It involves the coupling of α-position of activated alkenes with electrophiles containing sp^2 carbon atom under the catalytic influence of tertiary amines particularly 1,4-diazabicyclo(2.2.2)octane (DABCO) (**2**) (eq.1). Several activated alkenes such as acrylic esters,[5,6] acrylonitrile,[7,8] vinyl ketones,[8-10] phenyl vinyl sulfones,[11,12] phenyl vinylsulfonates,[13]



(1)

R = aryl, alkyl
R' = H, alkyl, COOR
X = O, NCOOR', NTs
EWG = COOR, COR, CN, SO_2Ph, etc.,
catalyst = tertiary amine

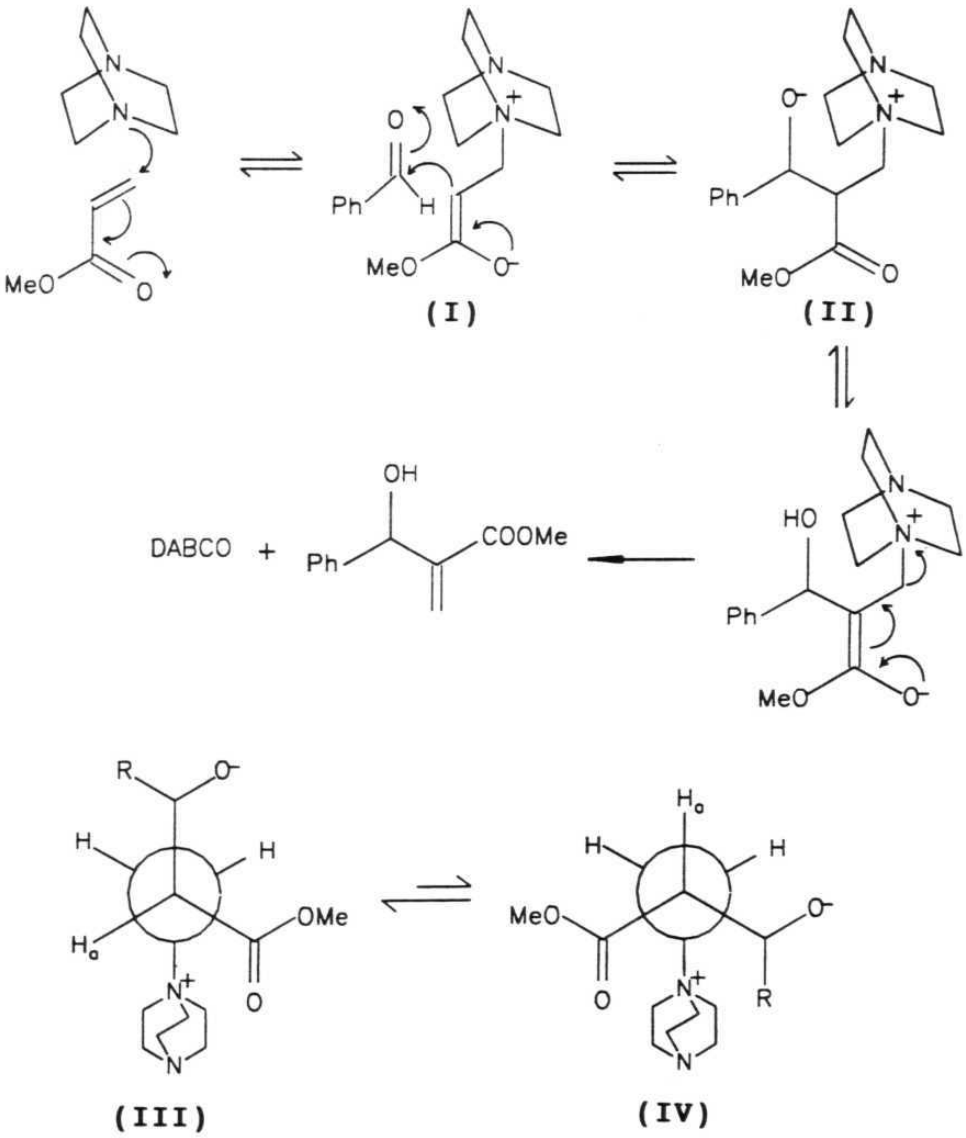
vinyl phosphonate,[14] allenic acid esters,[15,16] acrolein[17] and crotonic acid derivatives[18,19] have been employed in this reaction. Aldehydes are the most commonly used electrophiles.[3,4] In addition to aldehydes a variety of other electrophiles such as α-keto esters,[20-22] aldimines,[23] α,β-unsaturated aldehydes,[24] α,β-unsaturated ketones,[25] acrylonitrile,[25] acrylic acid esters[26] and ketones[17,18] have been employed as electrophiles. The most commonly used catalyst is DABCO, though other catalysts such as pyrrocoline[3] (**3**), quinuclidine[3] (**4**), 3-hydroxyquinuclidine[27] (**5**), triethylamine,[17] quinidine[4,28] etc., have been used in special cases.



2 **3** **4** **5**

Though the exact mechanism of this reaction has not yet been established the existing evidence[19,29-32] points to the following course for the reaction (Scheme 1). Initial step in the catalytic cycle involves the Michael type addition of tertiary amine (DABCO) to activated vinylic system (methyl acrylate) to result in a transient zwitterionic enolate (**I**) which subsequently

Scheme 1



attacks the electrophile (aldehyde) to produce the zwitterionic adduct (**II**). The dipolar adduct (**II**) provides the final product after suffering a proton migration followed by elimination of the catalyst. Hoffmann and Rabe[6] even proposed conformations **III** and **IV** for the zwitterionic adduct (**II**).

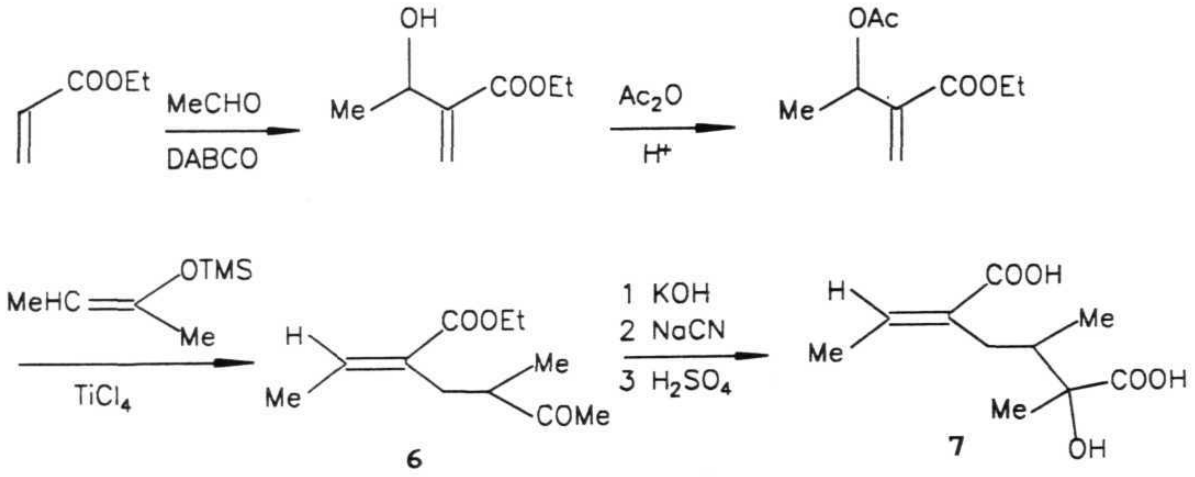
The Baylis-Hillman adducts (**1**) (obtained using aldehydes or ketones as electrophiles) contain three chemospecific functional groups namely hydroxyl, alkene and an electron withdrawing group in close proximity. Through proper tuning of these functional groups organic chemists have demonstrated the potentiality of these adducts in a variety of chemo-, regio- and stereoselective transformations and thus a number of research papers have appeared in the literature describing the various aspects of this reaction. Since this thesis deals with the development of stereoselective syntheses using Baylis-Hillman adducts, many elegant reports describing developmental aspects such as asymmetric version[33-35] and other important applications[36,37] have not been discussed, emphasis has been made only on the work describing the utility of these adducts in stereoselective transformations.

Stereoselective syntheses using Baylis-Hillman adducts can be mainly classified into two categories 1) synthesis of stereodefined functionalized trisubstituted alkenes and 2) diastereoselective and enantioselective processes.

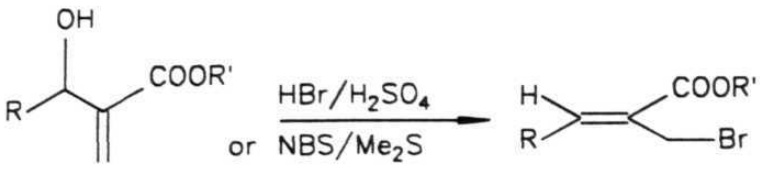
1) Synthesis of stereodefined functionalized trisubstituted alkenes:

The first reference to Baylis-Hillman reaction was made by Drewes and Emslie[5] in 1982. This report describes a synthesis of ethyl 3-hydroxy-2-methylenebutanoate and its subsequent conversion to (5E)-5-ethoxycarbonyl-3-methylhept-5-en-2-one (**6**), a precursor for integerrinecic acid (**7**), ***via*** stereoselective addition of 2-trimethylsilyloxybut-2-ene in the presence of $TiCl_4$ (Scheme 2).

Scheme 2



Drewes and coworkers[4,5,38] have successfully converted alkyl 3-hydroxy-2-methylenealkanoates into alkyl (2Z)-2-(bromomethyl)-alk-2-enoates, a key synthon for a wide range of naturally occurring necic acids, by treatment with either HBr/H_2SO_4 or NBS/Me_2S (eq.2).

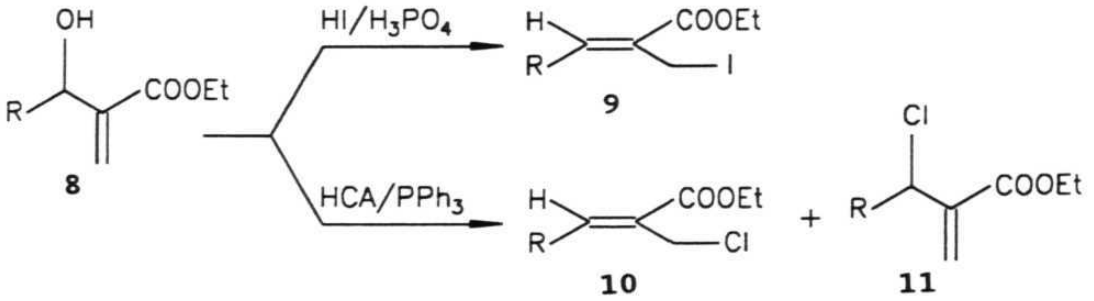


(2)

R = Ph, Me, n-Pr; R' = Me, Et, n-Pr, t-Bu

Subsequent report from Drewes[39] laboratory described that treatment of ethyl 3-hydroxy-2-methylenealkanoates (**8**) with conc. HI/H_3PO_4 produced exclusively ethyl (2Z)-2-(iodomethyl)alk-2-enoates (**9**) while the same molecules on treatment with hexachloroacetone-triphenylphosphine (HCA-PPh_3) complex produced a mixture of ethyl (2Z)-2-(chloromethyl)alk-2-enoates (**10**) and ethyl 3-chloro-2-methylenealkanoates (**11**) (Scheme 3).

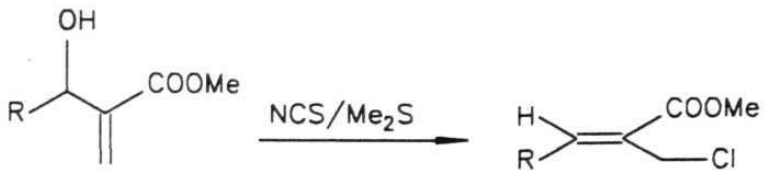
Scheme 3



(100% when R = Ph)

R = Ph, Me, n-Pr

Hoffmann and Rabe[40] employed N-chlorosuccinimide (NCS) for stereoselective transformation of methyl 3-hydroxy-2-methylenealkanoates into methyl (2Z)-2-(chloromethyl)alk-2-enoates (eq.3).

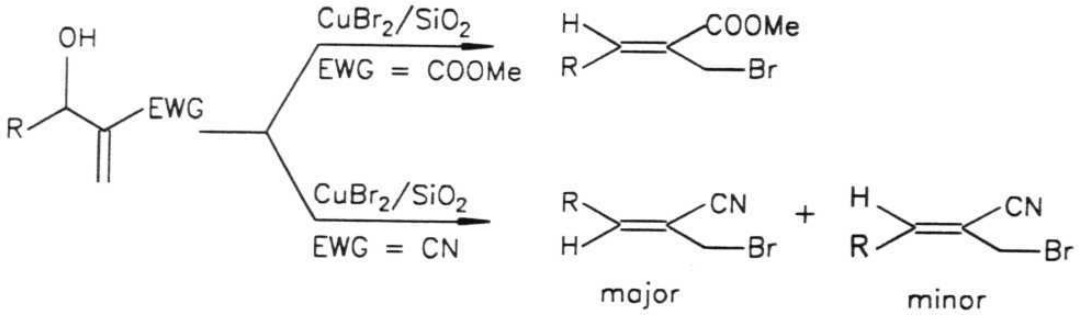


(3)

R = Mes-$CO_2(CH_2)_3$, Cl-$(CH_2)_3$, THP-O-$(CH_2)_3$

Grueic and Foucaud[41] reported stereoselective synthesis of methyl (2Z)-3-aryl-2-bromomethylprop-2-enoates and (2E)-3-aryl-2-bromomethylprop-2-enenitriles *via* bromination of methyl 3-aryl-3-hydroxy-2-methylenepropanoates and 3-aryl-3-hydroxy-2-methylenepropanenitriles respectively with $CuBr_2$ supported on silica gel under microwave irradiation (Scheme 4).

Scheme 4



(R = Ph, 4-ClC_6H_4)

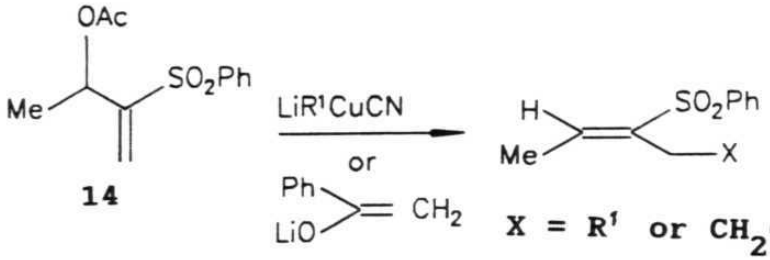
R = Ph, 4-ClC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 1-Np, 2-Furyl

Auvray and coworkers[11,42] employed NBS-Me_2S complex for the stereoselective transformation of 2-(benzenesulfonyl)alk-1-en-3-ols (**12**) into (E)-1-(benzenesulfonyl)-1-(bromomethyl)alk-1-enes (**13**) (eq.4). They have also reported stereoselective addition of

lithium organocuprates to 3-acetoxy-2-(benzenesulfonyl)alk-1-enes (**14**) (eq.5) and this methodology has been utilized for stereoselective synthesis of (2Z,5Z)-dodecadiene (**15**) (eq.6).

12 **13** **(4)**

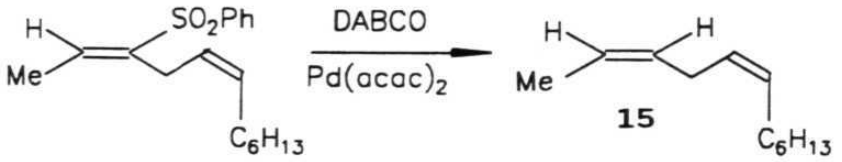
R = Me, n-Pr, n-Bu, i-Bu



14 **(5)**

X = R^1 or CH_2COPh

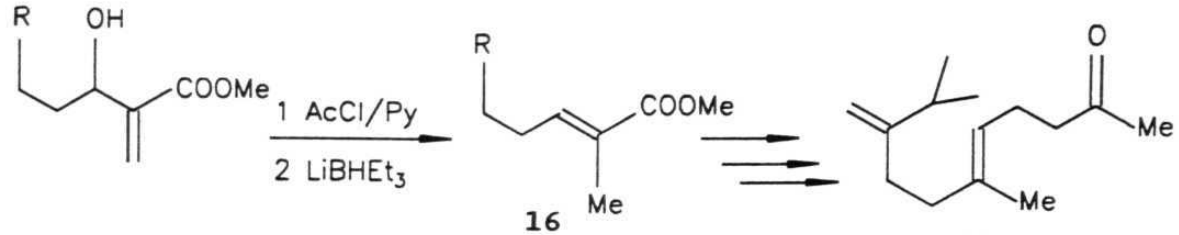
R^1 = Ph, n-Bu, (Z)-$C_6H_{13}CH{=}CH$, cy-C_6H_{11}, t-Bu

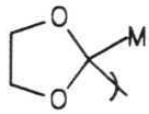


15 **(6)**

Rabe and Hoffmann[40,43] reported an interesting chemo- and stereoselective reaction of lithium triethylborohydride with methyl 3-acetoxy-2-methylenealkanoates producing methyl (E)-2-methylalk-2-enoates (**16**) (Scheme 5). The molecule **16b** is an important precursor for the stereoselective synthesis of novel terpenoid C_{14} ketone **17**.

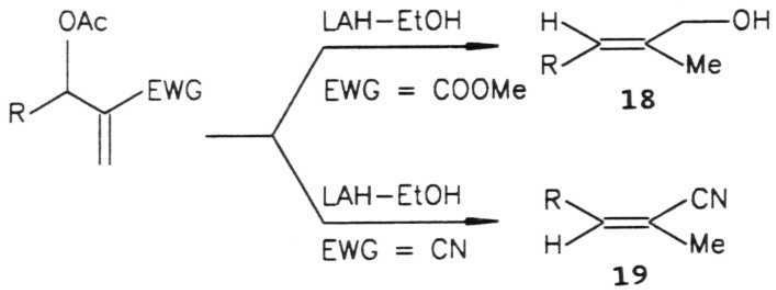
Scheme 5

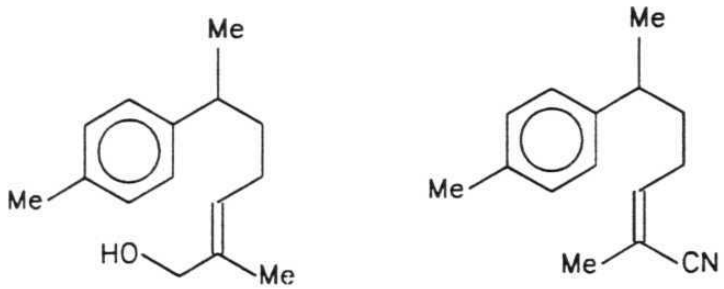


R = Me (16a),  **(16b)**

Our research group[44] has successfully carried out stereo-selective nucleophilic addition of hydride ion from lithium aluminium hydride [LAH :EtOH (1:1)] to alkyl 3-acetoxy-2-methyle-

Scheme 6



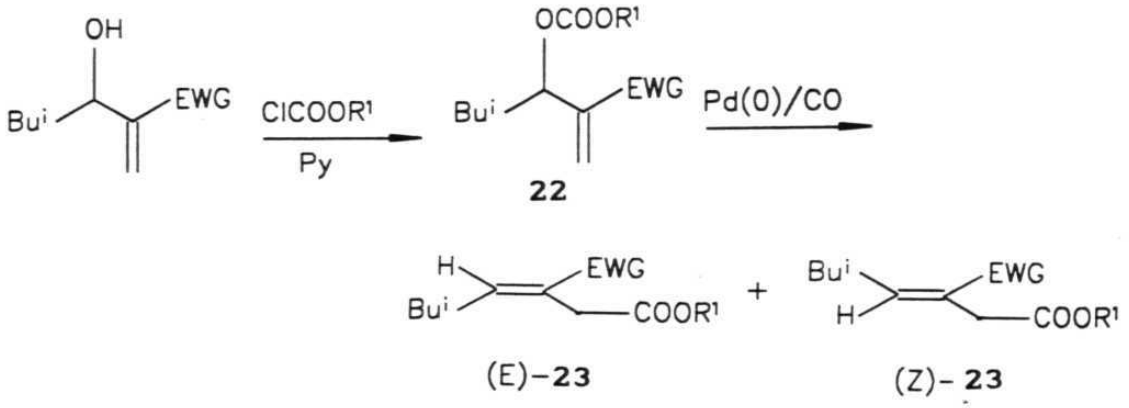


R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, n-Bu, n-Pent, n-Hex

nealkanoates and 3-acetoxy-2-methylenealkanenitriles thus proving a general synthesis of (2E)-2-methylalk-2-en-1-ols (**18**) and (2Z)-2-methylalk-2-enenitriles (**19**) respectively (Scheme 6). The efficacy of this methodology has been demonstrated by short and simple stereoselective synthesis of (E)-nuciferol (**20**), a biologically important terpenoid, and **21**, precursor for (Z)-nuciferol.

Yamamoto *et al*[13,45] have studied stereoselective palladium catalyzed carbonylation of carbonates **22** of various Baylis-Hillman adducts thus providing a simple synthesis of alkylidene succinates and analogs **23** (Scheme 7). This methodology represents an attractive alternative to Stobbe condensation.

Scheme 7



R^1 = Me or Et

EWG = COOMe E/Z = 92 : 8

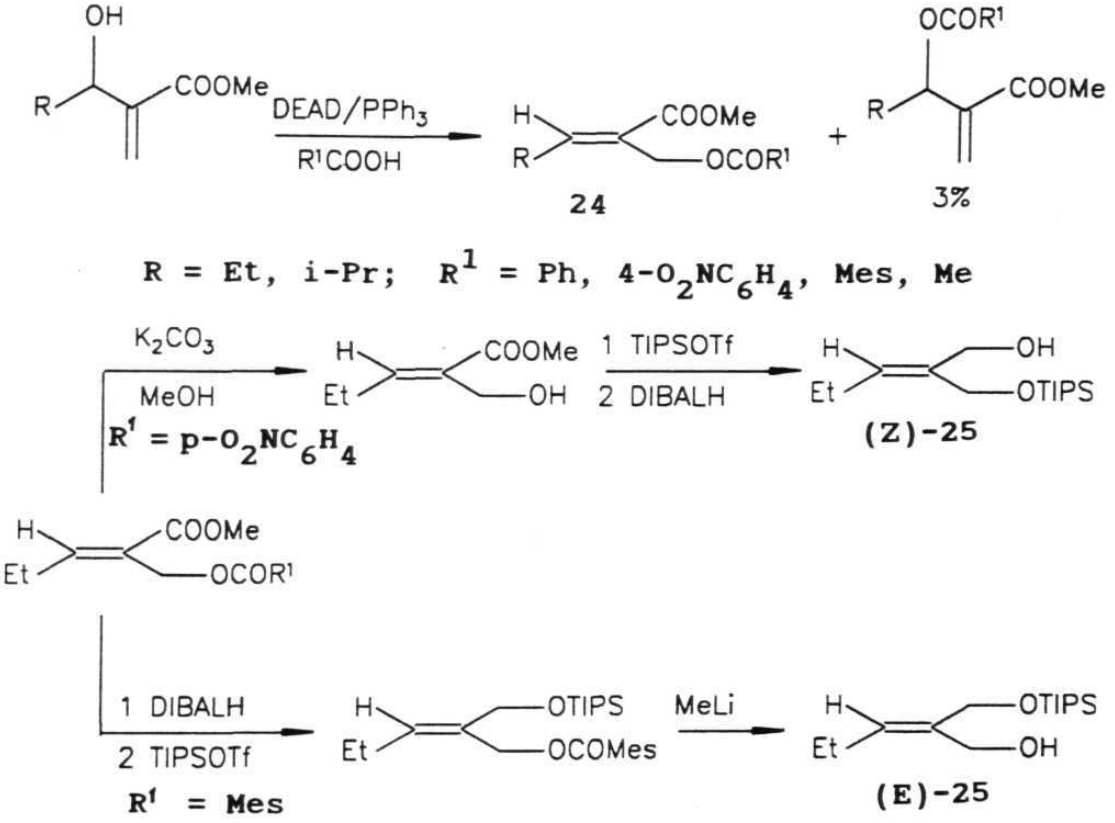
EWG = CN E/Z = 16 : 84

EWG = SO_3Ph E/Z = 100 : 0

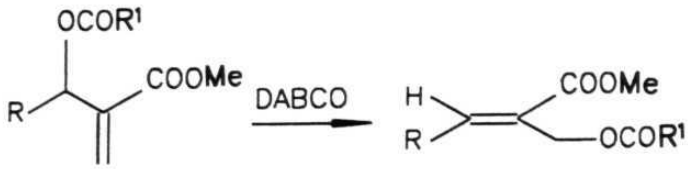
EWG = $CONMe_2$ E/Z = 30 : 70

Charette and Cote[46] converted methyl 3-hydroxy-2-methylene-alkanoates into methyl (2E)-2-(carbonyloxymethyl)alk-2-enoates (**24**) ***via*** unusual regio-, stereoselective S_N2' Mitsunobu reaction (Scheme 8). The resultant (E)-esters (**24**) were successfully transformed into both monoprotected (E)- and (Z)-alkylidene-1,3-propanediols (**25**).

Scheme 8



Mason and Emslie[47] reported DABCO catalyzed stereoselective allylic transposition of methyl 3-acyloxy-3-aryl-2-methyleneprop-anoates in refluxing THF leading to the formation of methyl (2E)-2-acyloxymethyl-3-arylprop-2-enoates (eq.7).

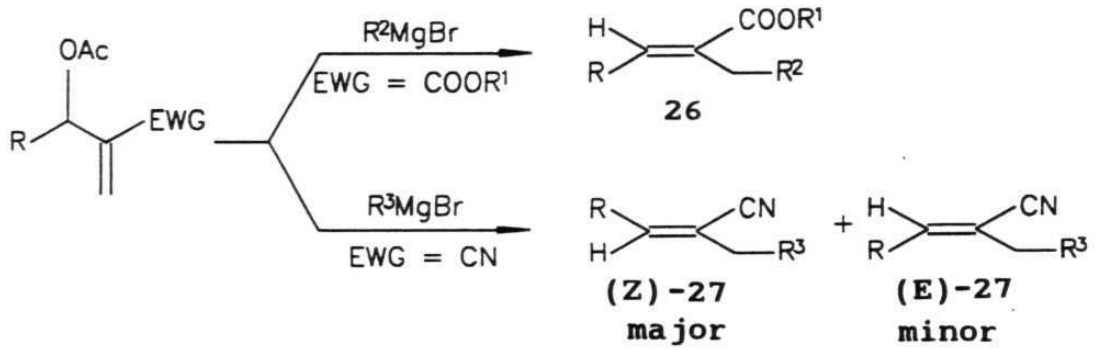


(7)

R = Ph, 2-$NO_2C_6H_4$, 2-Fur, 2-Py; R^1 = Me, Et, $CH=CH_2$, H_2C-COOEt

Our research group[48] has recently developed a simple stereoselective synthesis of trisubstituted alkenes, (2E)-alk-2-enoates (**26**) and (2Z)-alk-2-enenitriles (**27**) *via* uncatalyzed conjugate addition of Grignard reagents to alkyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles respectively (Scheme 9). The simplicity and high stereoselectivity of this reaction render it a useful and attractive alternative to the classical Horner-Wadsworth-Emmons reaction, particularly for esters.

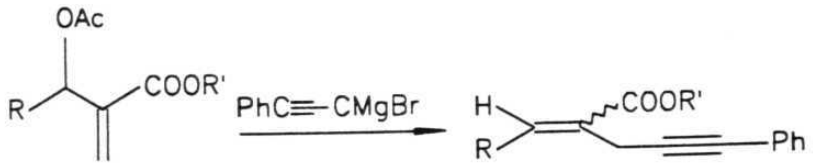
Scheme 9



R = Ph, Me, n-Pr, n-Bu, n-Hex; R^1 = Me, Et;

R^2 = Ph, Me, n-Bu, n-Hept; R^3 = Ph, 4-MeC_6H_4, Me, n-Pr, n-Bu

Drewes and Slater-Kinghorn[49] described a stereoselective synthesis of substituted pent-1-ene-4-ynes *via* nucleophilic addition of bromomagnesium phenylacetylide to alkyl 3-acetoxy-2-methylene-3-arylpropanoates (eq.8).



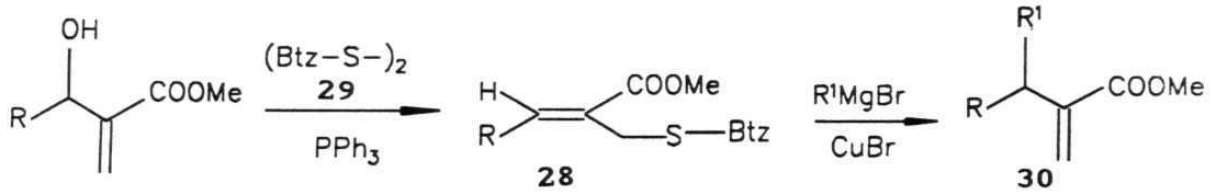
(8)

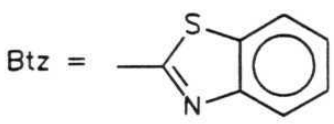
E/Z = 3/1

R = Ph, 2-ClC$_6$H$_4$; R' = Me, Et

Calo *et al*[50] reported stereoselective synthesis of methyl (Z)-2-(benzothiazole-2-thiomethyl)alk-2-enoates (**28**) by treating methyl 3-hydroxy-2-methylenealkanoates with benzothiazole disulfide (**29**) in the presence of triphenylphosphine (Scheme 10). These derivatives have been converted into β,β-disubstituted acrylates (**30**).

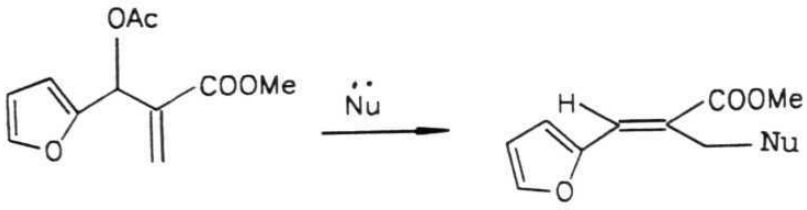
Scheme 10





R = Me, i-Pr, n-Oct; R^1 = n-Bu, n-Oct, TMSCH$_2$

Bauchat *et al*[51] described stereoselective nucleophilic addition of stabilized carbanions (generated from β-diones, methyl cyanoacetate and nitroalkane) to methyl 3-acetoxy-2-methylene-3-furylpropanoates (eq.9). The resultant alk-2-enoates were, subsequently, converted into corresponding γ- or δ-lactones.

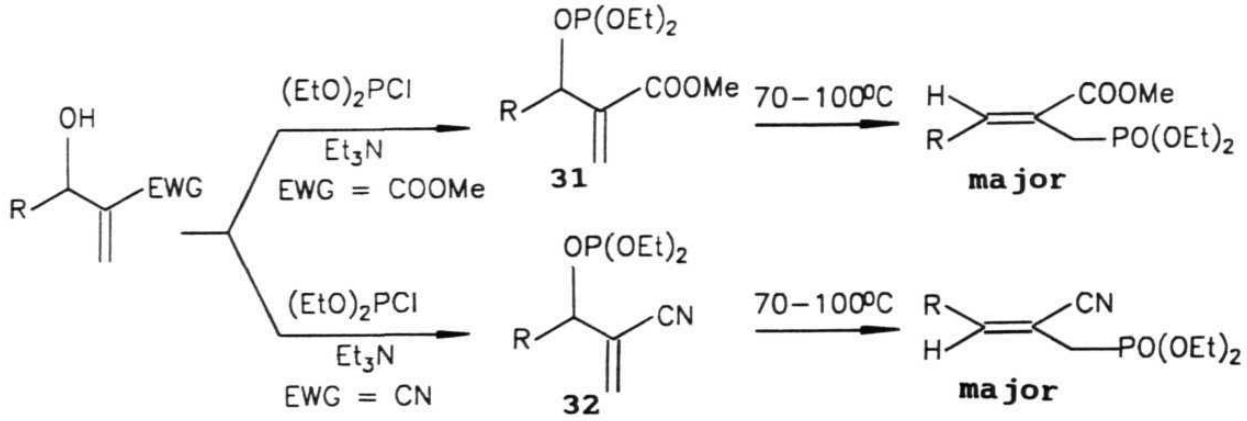


(9)

Nu = stabilized carbanions

Recently Janecki and Bodalski[52] described stereoselective synthesis of methyl (2Z)-2-(diethoxyphosphorylmethyl)alk-2-enoates (Z/E = 95/5) and (2E)-2-(diethoxyphosphorylmethyl)alk-2-ene-

Scheme 11

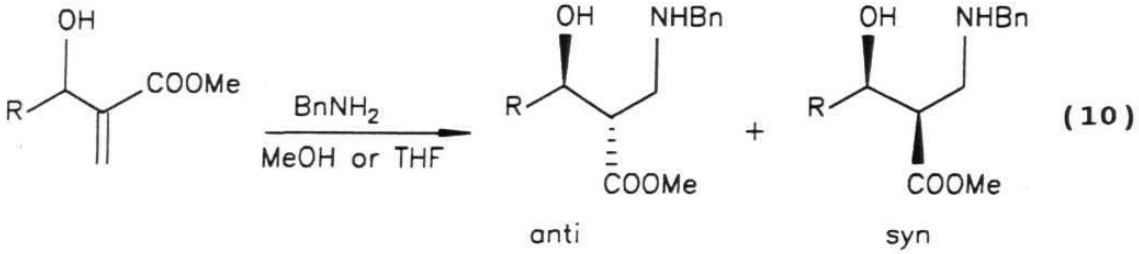


R = Ph, 3-Py, Me, Et, i-Pr, Geranyl

nitriles (E/Z = 60-75/40-25) *via* thermal Arbuzov rearrangement of allyl phosphites **31** and **32** (Scheme 11). These allyl phosphites were derived from Baylis-Hillman adducts.

2. Diastereo- and enantioselective processes:

Perlmutter and Tabone[53] reported that nucleophilic conjugate addition of benzylamine to methyl 3-hydroxy-2-methylenealkanoates proceeds in modest diastereoselectivity. The stereoselectivity is solvent dependent and thus stereochemical reversal is observed from THF to MeOH (eq.10). They also found that addition of benzylamine to silyl ether **33** results in exclusive formation of *anti* isomer (*anti/syn* = >20/1) (Scheme 12).

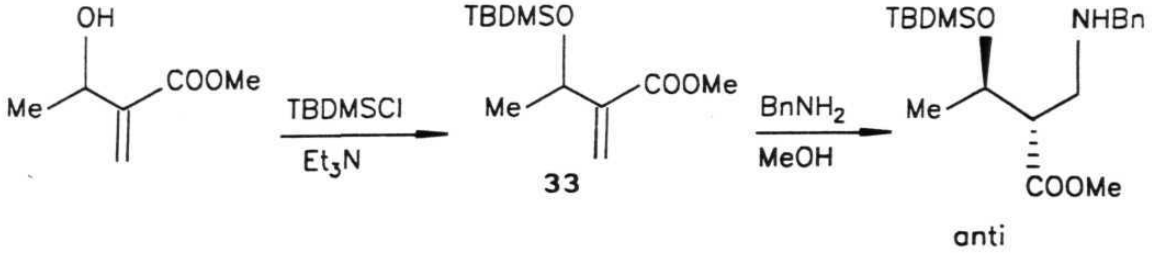


(10)

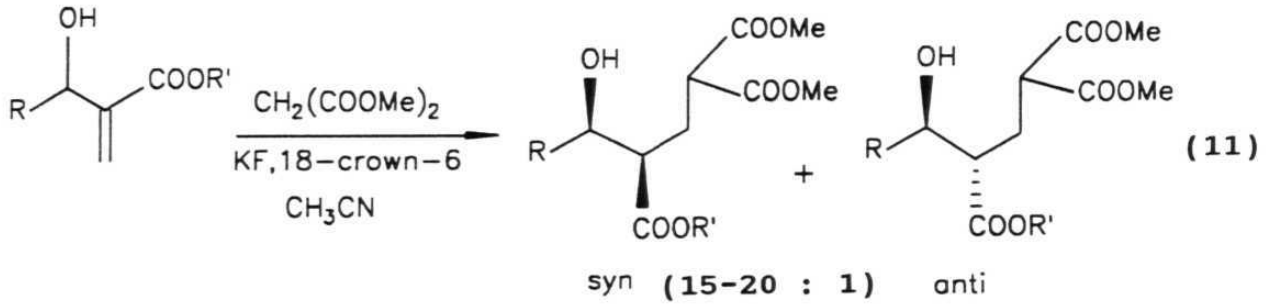
R = Ph, 2-Py, Me

In THF	**major**	**minor**
MeOH	**minor**	**major**

Scheme 12

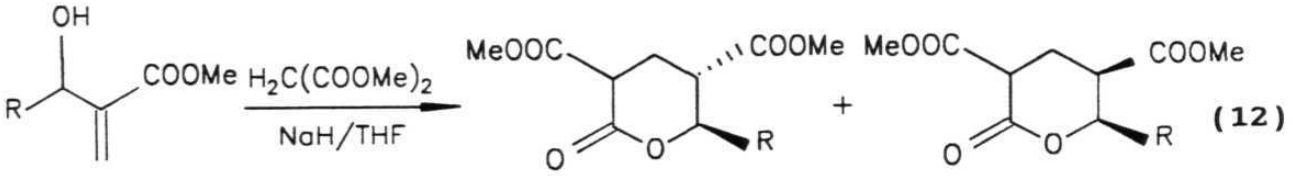


Lawrence and Perlmutter[54] reported stereocontrolled Michael reaction of dimethyl malonate with alkyl 3-hydroxy-2-methylene-alkanoates in acetonitrile under the influence of phase transfer catalyst, KF/18-crown-6 (eq.11). The high *syn* selectivity in this reaction was found to be under thermodynamic control. It was also observed that the same reaction when carried out in THF in the presence of sodium hydride, lactones were obtained as the major products (eq.12).



(11)

R = Ph, 3-Py, 2-Fur, 1-Np, 4-$O_2NC_6H_4$; R' = Me, Bn



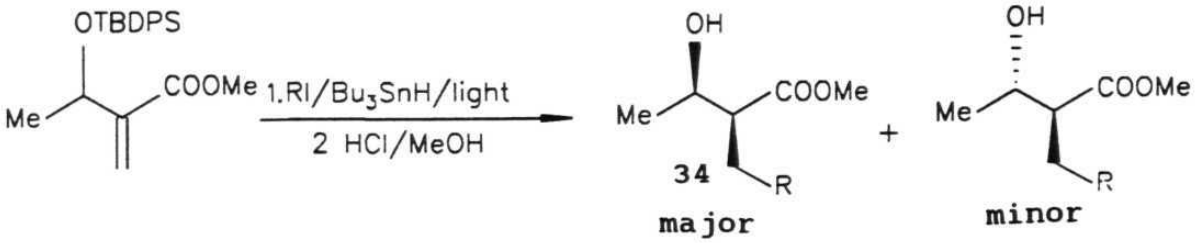
(12)

R = Ph, 3-Py, 2-Fur, Me

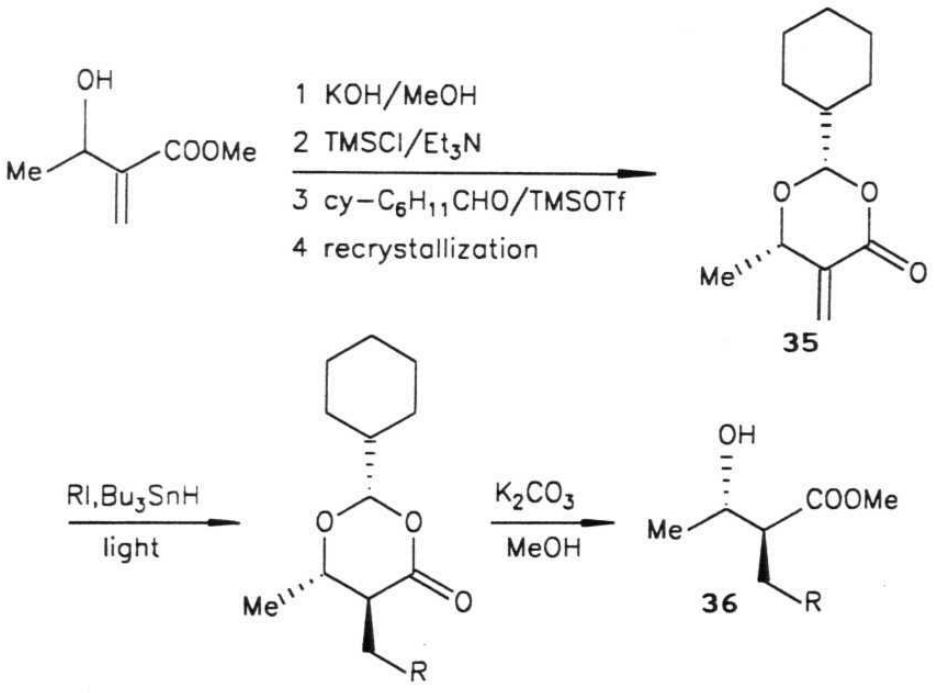
Giese and coworkers[55,56] have observed that conjugate addition of radicals to methyl 3-[(*tert*-butyl)diphenylsilyloxy]-2-methylenebutanoate provided predominantly *erythro* isomer **34** whereas the similar addition of radicals to 2-cyclohexyl-5-methy-

lene-6-methyl-1,3-dioxan-4-one (**35**) results in the formation of (exclusively) *threo* isomer **36** (Scheme 13). They explained that the observed stereochemical reversibility is due to the difference in the conformations of the reactive intermediates.

Scheme 13

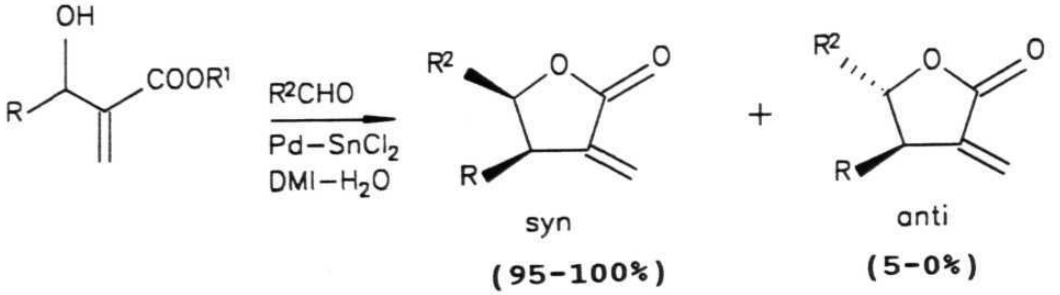


R = t-Bu, cy-Hex, n-Oct



R = t-Bu, cy-Hex, n-Oct

Masuyama *et al*[57] have employed methyl 3-hydroxy-2-methylene-alkanoates for the ethoxycarbonylallylation of aldehydes using $PdCl_2/(PhCN)_2/SnCl_2$ system thus providing stereoselective synthesis of α-methylene-γ-butyrolactones (eq.13).



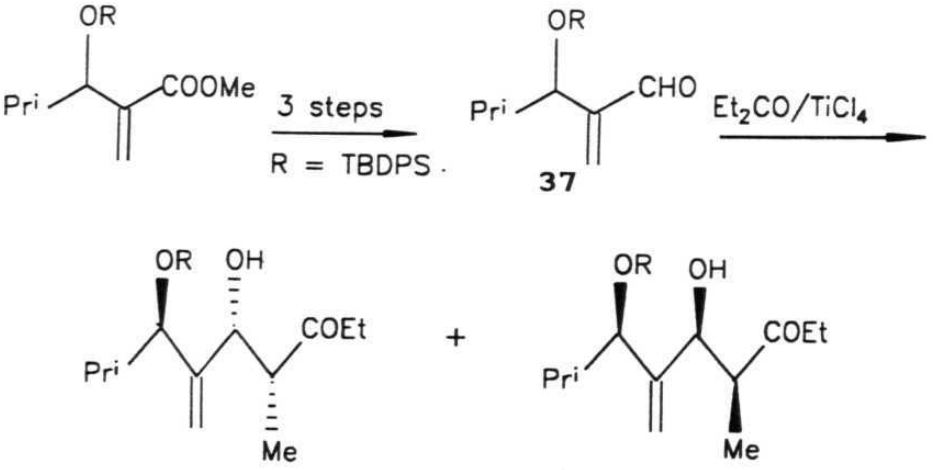
(13)

R = Ph, Me, n-Bu; R^1 = Me, Et

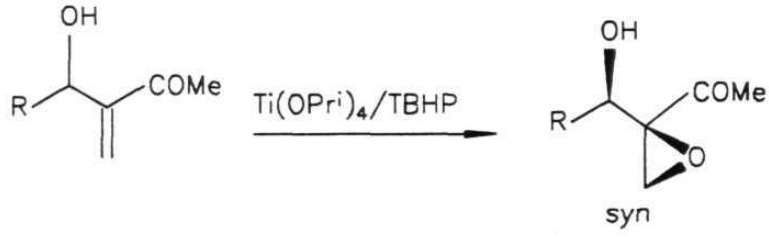
R^2 = 4-$MeO_2CC_6H_4$, n-Bu, cy-Hex

Paterson *et al*[58] reported highly *syn* selective aldol reaction of 3-*tert*-butyldiphenylsilyloxy-2-methylene-4-methylpentanal (**37**) obtained *via* the Baylis-Hillman reaction with titanium (Z)-enolate (Scheme 14).

Scheme 14

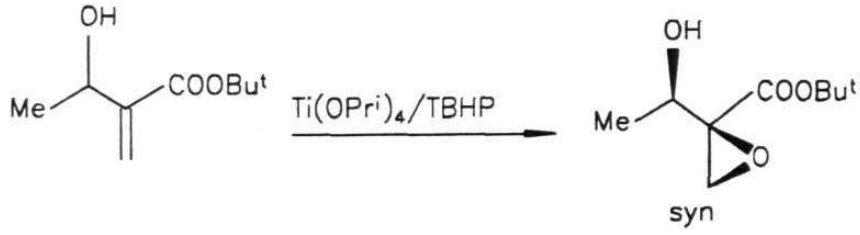


Bailey and coworkers reported that the Sharpless epoxidation of 4-hydroxy-3-methylenealkan-2-ones[59] (eq.14) and *tert*-butyl 3-hydroxy-2-methylenebutanoates[60] (eq.15) produced exclusively *syn* epoxides. However, asymmetric Sharpless epoxidation of 4-cyclohexyl-4-hydroxy-3-methylenebutan-2-one[61] results in very poor enantioselectivity (eq.16). They have also observed that the classical epoxidation of these substrates with mCPBA failed to provide epoxides.

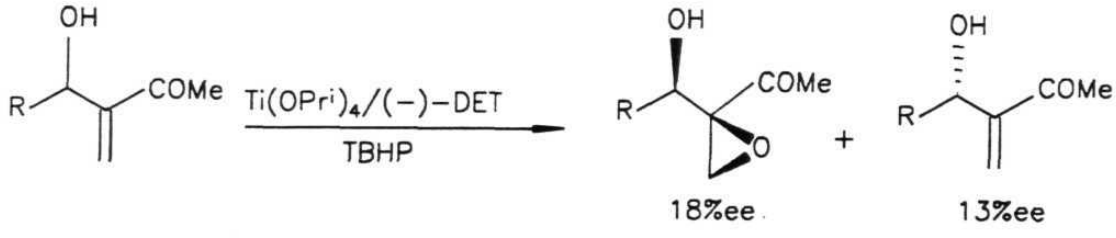


(14)

R = Me, Et, i-Pr, cy-Hex



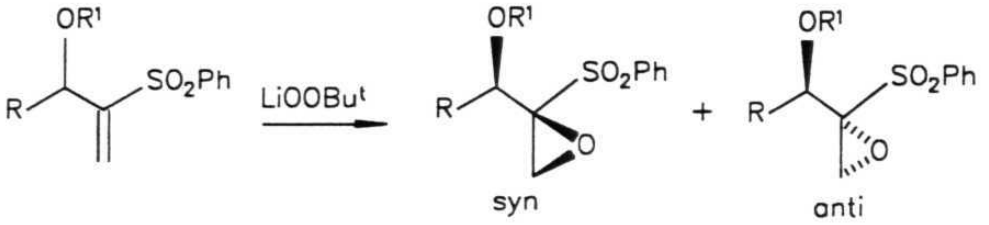
(15)



(16)

R = cy-Hex

Jackson *et al*[62] have used lithium *tert*-butyl peroxide for nucleophilic epoxidation of 2-(benzenesulfonyl)alk-2-en-1-ols to provide *syn* products as major isomers (eq.17). Similar reaction with 2-(benzenesulfonyl)-3-(triisopropylsilyloxy)alk-1-ene results in the formation of *anti* epoxides as major isomer.



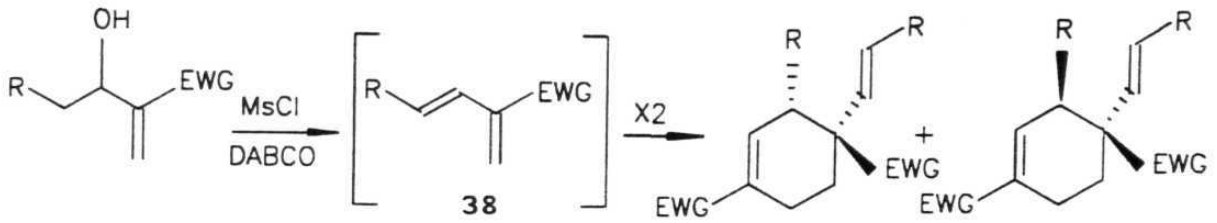
(17)

R = Me, n-Pr, i-Pr

If R = H	**25**	**:**	**1**
If R = TIPS	**1**	**:**	**4-25**

Hoffmann and coworkers have elegantly utilized the Baylis-Hillman adducts in a number of cycloaddition reactions. Thus, treatment of methyl 3-hydroxy-2-methylenealkanoates,[63] 4-hydroxy-3-methylenealkan-2-ones[64] and 2-(benzenesulfonyl)-alk-1-ene-3-ols,[65] with MsCl/DABCO produced analogous functionalized cyclohexenes through spontaneous dimerization of corresponding *in situ* generated (E)-2-(substituted)alka-1,3-dienes (**38**) (Scheme 15). They have also found that the dimerization is *para* selective and the stereochemistry at the C-3 carbon of functionalized cyclohexenes (major isomer) is *trans* with reference to electron withdrawing group and alkyl group.

Scheme 15



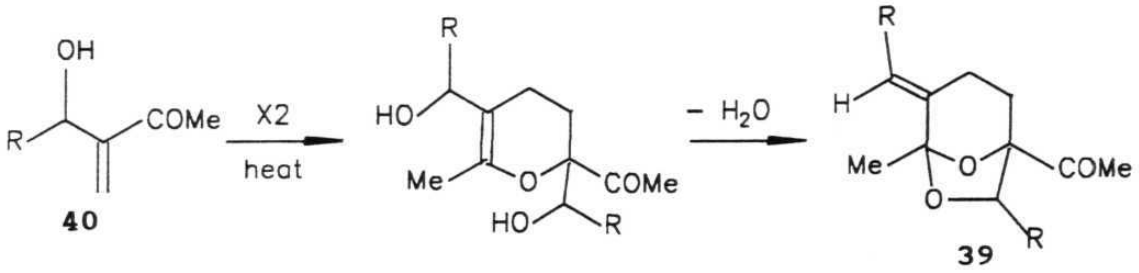
major **minor**

(100% when R = SO_2Ph)

R = aryl, alkyl; EWG = COOMe, COMe, SO_2Ph

Hoffmann *et al*[66] described a simple synthetic route to functionalized 6,8-dioxabicyclo(3.2.1)octanes **39**, a basic framework of a number of pheromones such as frontalin, *exo*- and *endo*-brevicomins and α-multistriatin through thermal dimerization of 4-hydroxy-3-methylenealkan-2-ones **40** (Scheme 16).

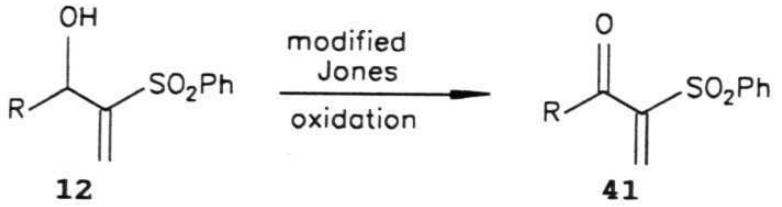
Scheme 16



R = $PhCH_2CH_2$, H, Me, Et, i-Bu

Weichert and Hoffmann[12] oxidized 2-(benzenesulfonyl)-alk-1-en-3-ols to 2-(benzenesulfonyl)-alk-1-en-3-ones (**41**) ***via*** modified Jones oxidation followed by non-nucleophilic workup (eq.18). They have successfully utilized 3-(benzenesulfonyl)-3-buten-2-one (**41**

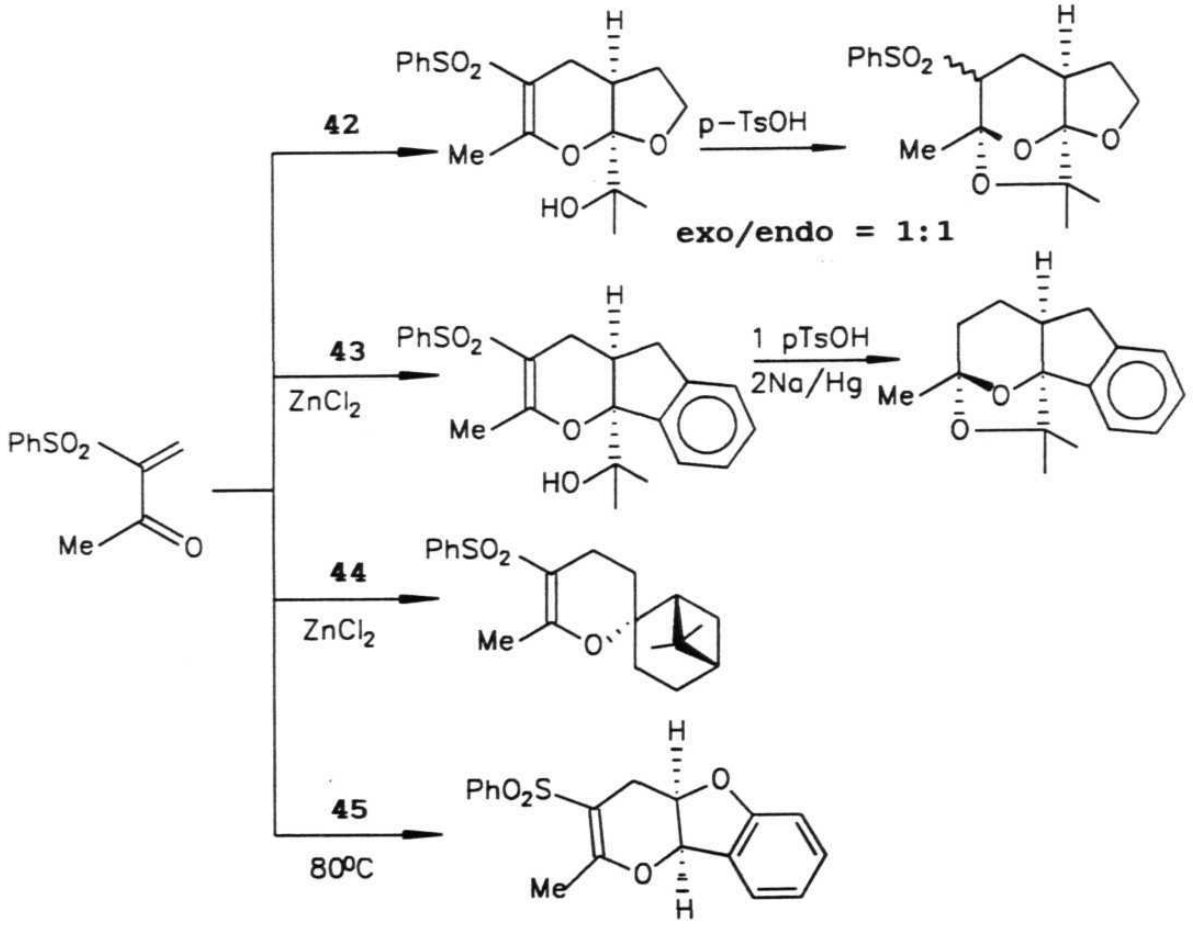
R = Me) as a 1-oxa-1,3-butadiene unit in an inverse electron demand hetero-Diels-Alder reaction with a wide range of alkenes of graded nucleophilicity **42-45** thus providing the resulting adducts in high stereoselectivity (Scheme 17).

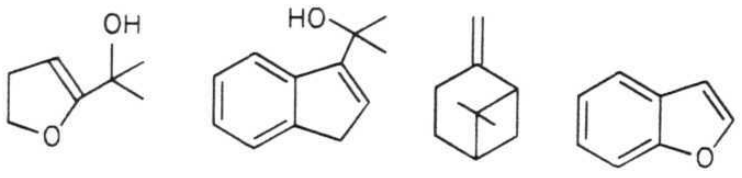


12 **41** **(18)**

R = $Ph(CH_2)_2$, $Ph(CH_2)_3$, Me, Et, n-Pr, i-Bu

Scheme 17

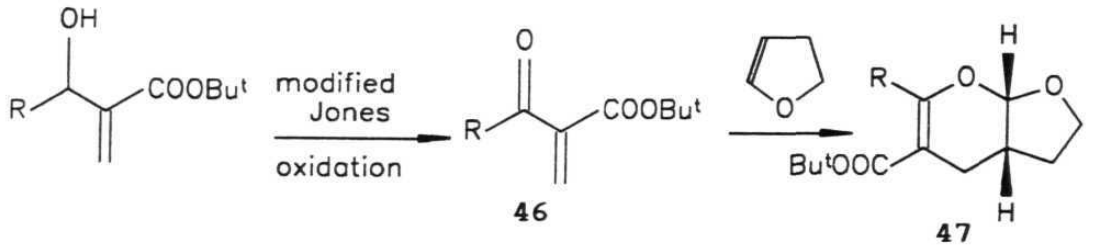




42 **43** **44** **45**

Similar oxidation of *tert*-butyl 3-hydroxy-2-methylenealkanoates produced *tert*-butyl 2-methylene-3-oxoalkanoates (**46**). These molecules participate in an inverse electron demand hetero-Diels-Alder reaction with 1,3-dihydropyran to produce the dioxabicyclic molecules **47** with high stereoselectivity[67] (Scheme 18).

Scheme 18

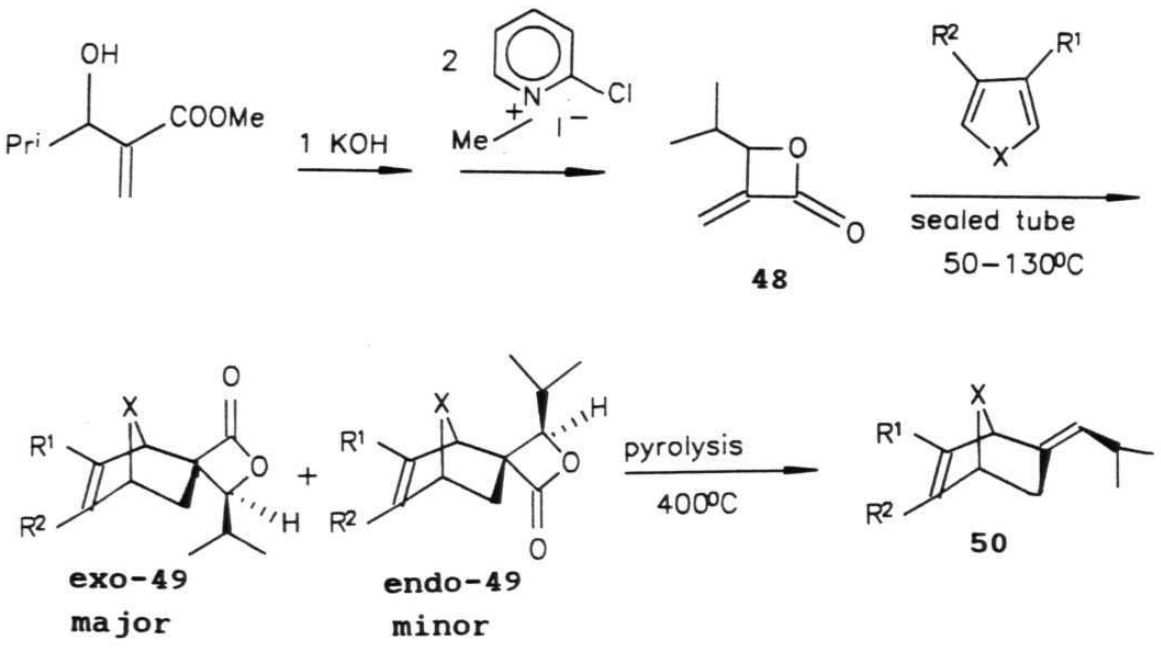


R = Ph, 4-Br-C_6H_4, $C_6H_5CH_2CH_2$, Et, n-Pr, i-Bu, cy-Hex

Adam *et al*[68] successfully utilized β-isopropyl-α-methylene-β-lactone (**48**), which was obtained from the corresponding Baylis-Hillman adduct (methyl 3-hydroxy-2-methylene-4-methylpentanoate), for stereoselective synthesis of α,β-*trans*-spiro-β-lactones (**49**) *via* Diels-Alder cycloaddition. Flash pyrolysis of the resulting

spiro-β-lactones **49** yielded (E)-isopropylidenealkenes (**50**) through decarboxylation (Scheme 19).

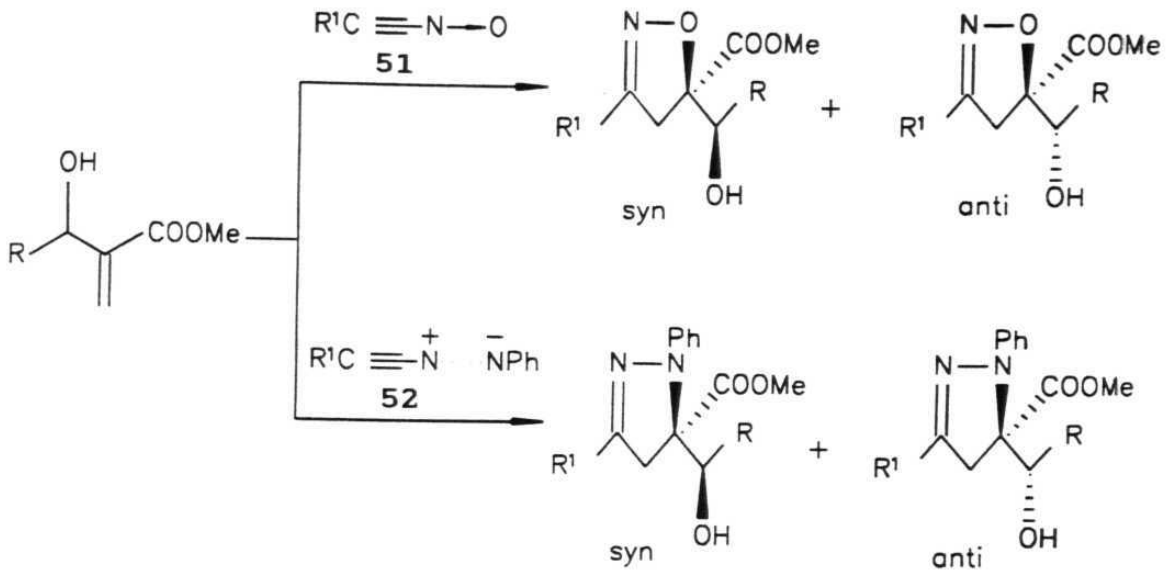
Scheme 19



Dienes: Butadiene, Isoprene, Cyclopentadiene, Furan, 1,3-Cyclohexadiene, Anthracene

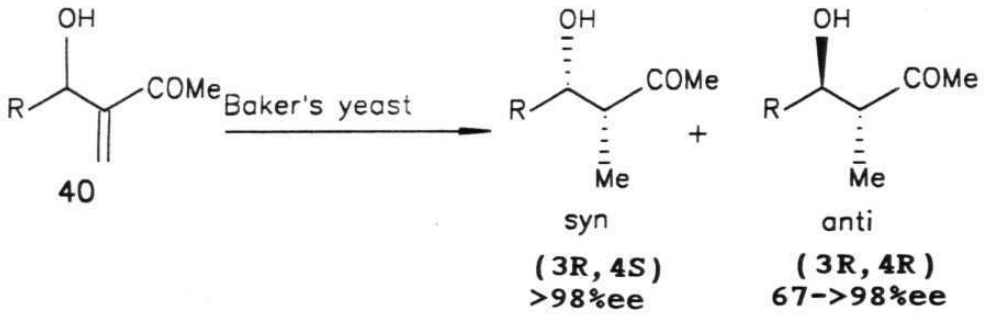
Kanemasa and Kobayasi[69] made an interesting observation of stereochemical reversibility due to the presence and absence of Lewis acid during stereoselective 1,3-dipolar cycloaddition reaction of methyl 3-hydroxy-2-methylenealkanoates with nitrile oxides **51** and nitrile imines **52** (Scheme 20). The Lewis acid coordinated dipoles provide *syn* molecule as major product, while free dipoles provide *anti* molecule as the major product.

Scheme 20



R = Me, Et; R^1 = Ph, 4-MeOC_6H_4, t-Bu

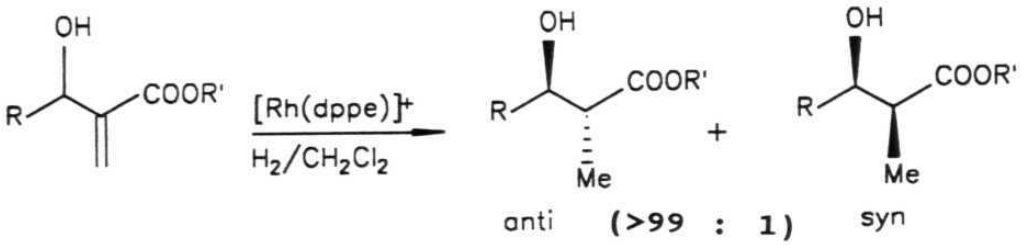
Utaka *et al*[70] reported high enantioselective synthesis of both (3R,4S)- and (3R,4R)-4-hydroxy-3-methylalkan-2-ones (*syn* : *anti* = 1 : 1-2) *via* biocatalytic (fermented baker's yeast) reduction of 4-hydroxy-3-methylenealkan-2-ones (**40**) (eq.19).



(19)

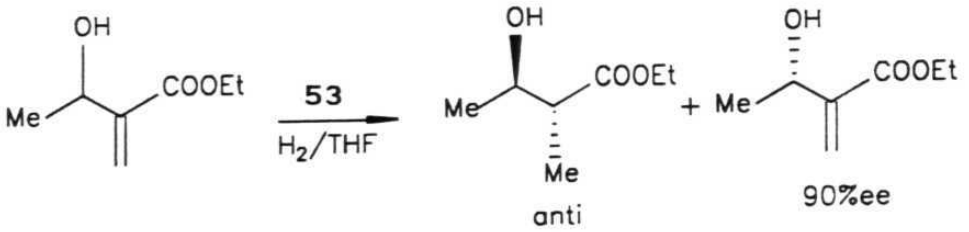
R = Et, n-Pr, n-Bu, n-Pent

Brown and Cutting reported highly diastereoselective hydrogenation of alkyl 3-hydroxy-2-methylenealkanoates with $[Rh(dppe)]^+$ as catalyst to produce *anti* product[71] (eq.20). They have also studied kinetic resolution of alkyl 3-hydroxy-2-methylenealkanoates (eq.21) and 2-(benzenesulfonyl)but-1-en-2-ols (eq.22) using **53** as chiral catalyst.[71-73] This methodology provides an efficient and easy access to *anti* aldol derivatives in comparison to conventional aldol addition reaction.



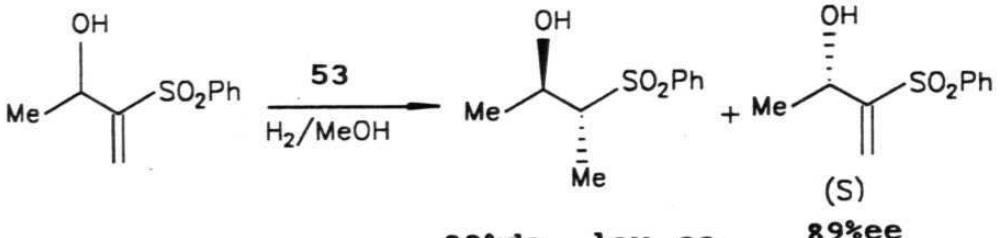
(20)

R = Me, Ph, 2-Fur; R' = Me, Et



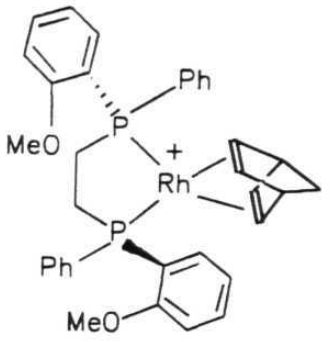
(2R,3R)
95%ee

(21)



99%de, low ee **89%ee**

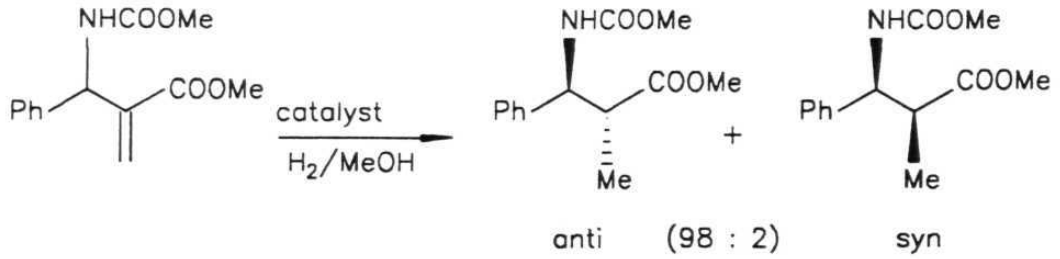
(22)



53

(R,R)-DIPAMP-Rh(I)

Later, Yamamoto *et al*[74] have reported similar *anti* selectivity in the hydrogenation of methyl 3-(methoxycarbonylamino)-2-methylene-3-phenylpropanoate with Ru(II) or Rh(I) catalyst (eq 23).



anti (98 : 2) syn **(23)**

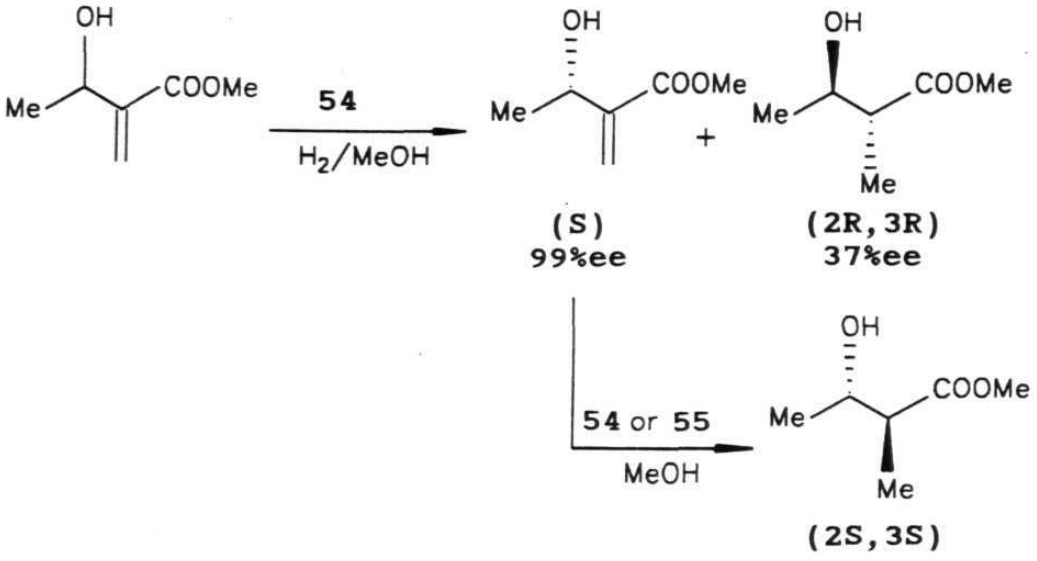
R = Me, Ph; R' = Me, Et

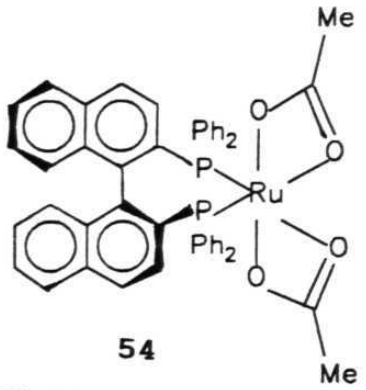
catalyst : $Ru(OCOCF_3)_2(PPh_3)_2$ or $Rh[(cod)(dppe)]ClO_4$

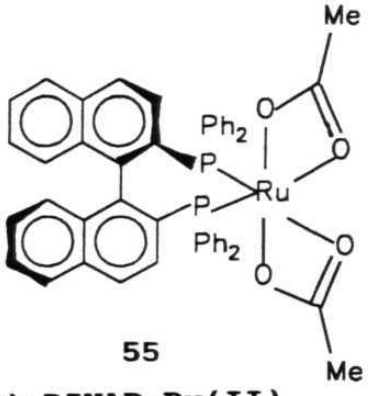
Noyori *et al*[75] studied the kinetic resolution of racemic methyl 3-hydroxy-2-methylenebutanoate *via* hydrogenation with **54** as catalyst to produce (S)-methyl 3-hydroxy-2-methylenebutanoate in >99% ee (Scheme 21). They have also observed an overwhelming substrate control in asymmetric hydrogenation of (S)-methyl

3-hydroxy-2-methylenebutanoate. Thus the hydrogenation with either catalyst **54** or **55** leads to the formation of (2S,3S)-molecule.

Scheme 21

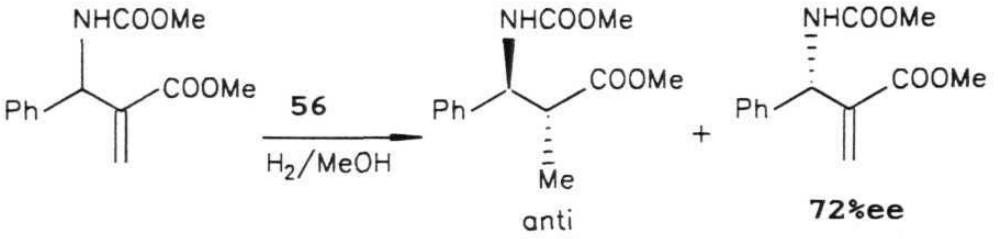




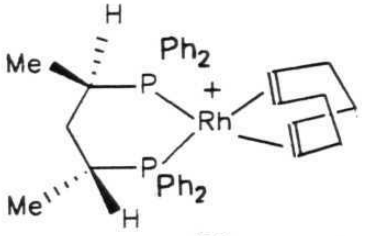


Takagi and Yamamoto[76] have studied the kinetic resolution of methyl 3-(methoxycarbonylamino)-2-methylene-3-phenylpropanoate

with various chiral Rh(I)-diphosphine catalysts (eq.24). They have enantioselectively hydrogenated methyl 2-(methoxycarbonyl-aminomethyl)propenoate (**57**) using Rh-(S)-BINAP (**54**) as catalyst to produce the resulting product **58** in 85% ee (Scheme 22).



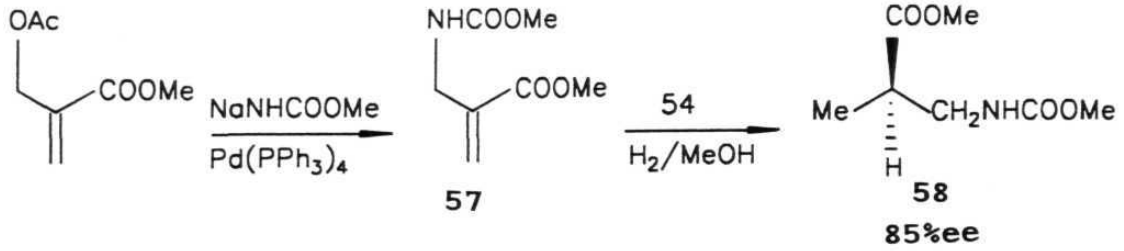
anti:syn = 93:7 **(24)**



56

(S,S)-SKEWPHOS-Rh(I)

Scheme 22



OBJECTIVES, RESULTS AND DISCUSSION

From the preceding chapter it is quite evident that the Baylis-Hillman adducts (**1**), with the unique glamour of possessing three functional groups in close proximity have been successfully employed in a number of stereoselective transformations. The proximity of these functional groups plays a key role in these stereoselective processes. Some of these stereoselective processes are considered to be attractive alternatives or complementary approaches to the well known reactions such as Wittig reaction,[48] aldol[71-73,75] and Stobbe condensation[13,45] *etc*. During the last few years our research group has been actively involved in various aspects of this fascinating reaction.[9,20,25]

OBJECTIVES

We have envisioned that the Baylis-Hillman reaction would be a novel source for various stereoselective processes. We have, therefore, undertaken this project, "**STEREOSELECTIVE SYNTHESES USING BAYLIS-HILLMAN ADDUCTS**" with the main objective of utilizing these adducts for

1) enantioselective synthesis of mikanecic acid ***via*** Diels-Alder cycloaddition mediated construction of chiral vinylic quaternary center,

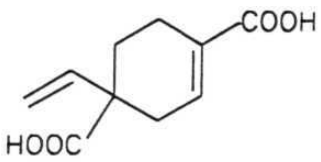
2) stereoselective synthesis of a) (E)- and (Z)-alk-4-enoates *via* Johnson-Claisen rearrangement, b) (E)- and (Z)-allyl bromides using magnesium bromide and c) (E)- and (Z)-allylphosphonates *via* thermal Arbuzov rearrangement.

Our objective also includes the utilization of these adducts as stereodefined β-electrophiles in the Friedel-Crafts reaction.

RESULTS AND DISCUSSION

Enantioselective synthesis of mikanecic acid:

Mikanecic acid (**59**), a terpene dicarboxylic acid was isolated in 1936 by Manske[77] from the products of alkaline hydrolysis of the alkaloid mikanoidine (and hence the name) obtained from *Senecio mikanioides* Otto. This molecule has an interesting history[78-81] and the correct structure of mikanecic acid was established by Culvenor and Geissman, in 1959 as 4-vinylcyclohex-1-ene-1,4-dicarboxylic acid (**59**).[82]

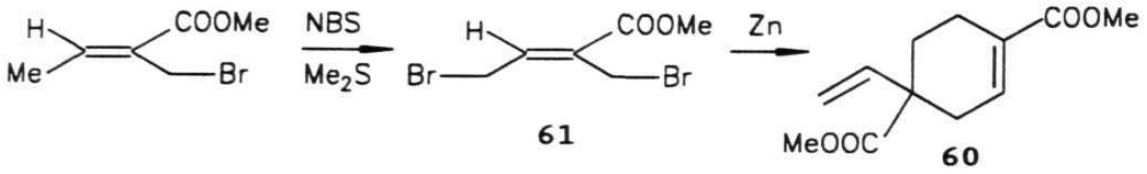


59

In 1975, Sydnes *et al*[81] described the synthesis of dimethyl ester **60** of racemic mikanecic acid by treating methyl (2Z)-4-bromo-2-bromomethyl-but-2-enoate (**61**) with zinc (Scheme 23). This reaction involves reductive debromination, presumably,

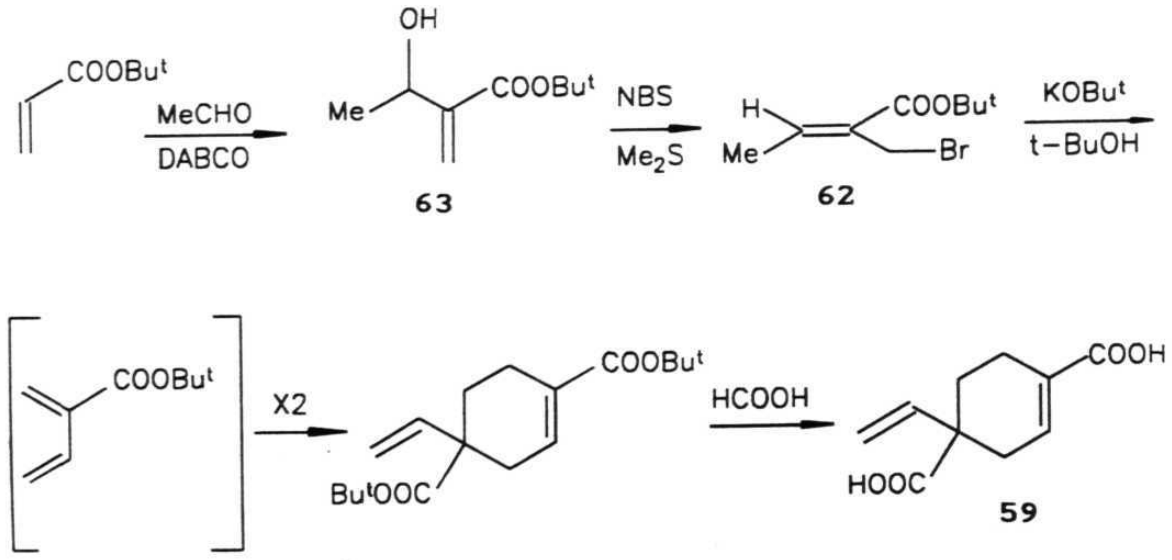
leading to the *in situ* formation of 1,3-butadiene-2-carboxylate which dimerizes to provide **60**.

Scheme 23



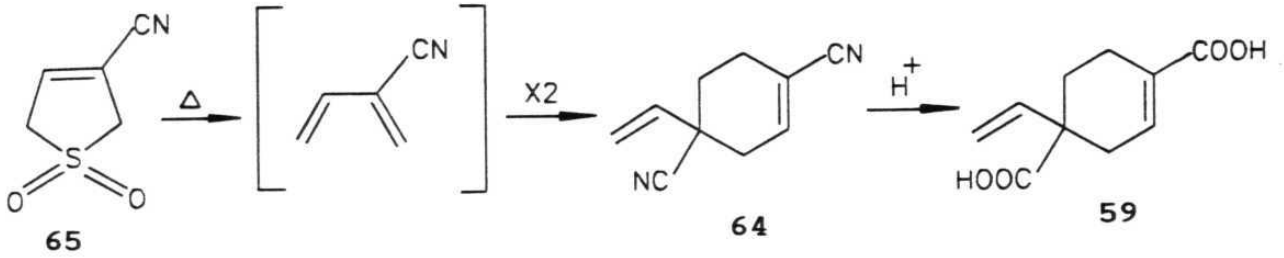
In 1983, Hoffmann and Rabe[83] reported a simple synthetic route to the synthesis of racemic mikanecic acid (**59**) from the allyl bromide **62** which in turn was obtained from the Baylis-Hillman adduct, *tert*-butyl 3-hydroxy-2-methylenebutanoate (**63**) (Scheme 24).

Scheme 24



In 1988, Baraldi *et al*[84] described the synthesis of racemic mikanecic acid (**59**) *via* hydrolysis of dicyano compound **64** which was obtained by heating 3-cyano-2,5-dihydrothiophen-1,1-dioxide (**65**) in refluxing toluene (Scheme 25).

Scheme 25

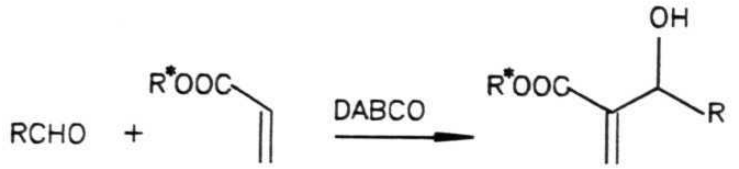


65 **64** **59**

Mikanecic acid (**59**) has attracted our attention owing to its special feature of having a chiral vinylic quaternary center in a functionalized six membered cyclic system. To the best of our knowledge there has been no report in the literature on optically active mikanecic acid. In fact, construction of chiral quaternary carbon center(s) has been one of the challenging and attractive areas in synthetic organic chemistry because a number of biologically active natural products contain such structural units.[85-88] Although, the Diels-Alder reaction is undoubtedly one of the corner-stones of organic chemistry, very few examples have been documented for the construction of chiral quaternary carbon centers and these demonstrate a number of practical difficulties[89,90]

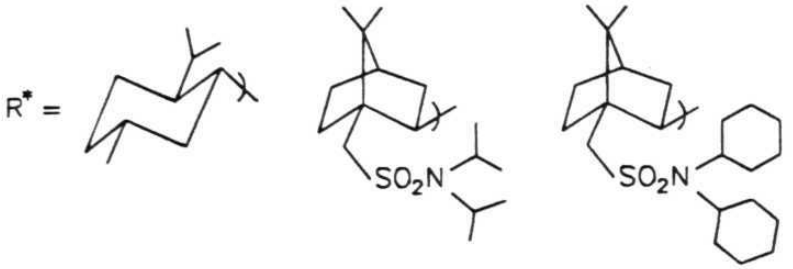
Recently, our research group[91] has used a variety of chiral acrylates for diastereoselective formation of Baylis-Hillman

adducts, alkyl 3-hydroxy-2-methylenealkanoates (eq.25).



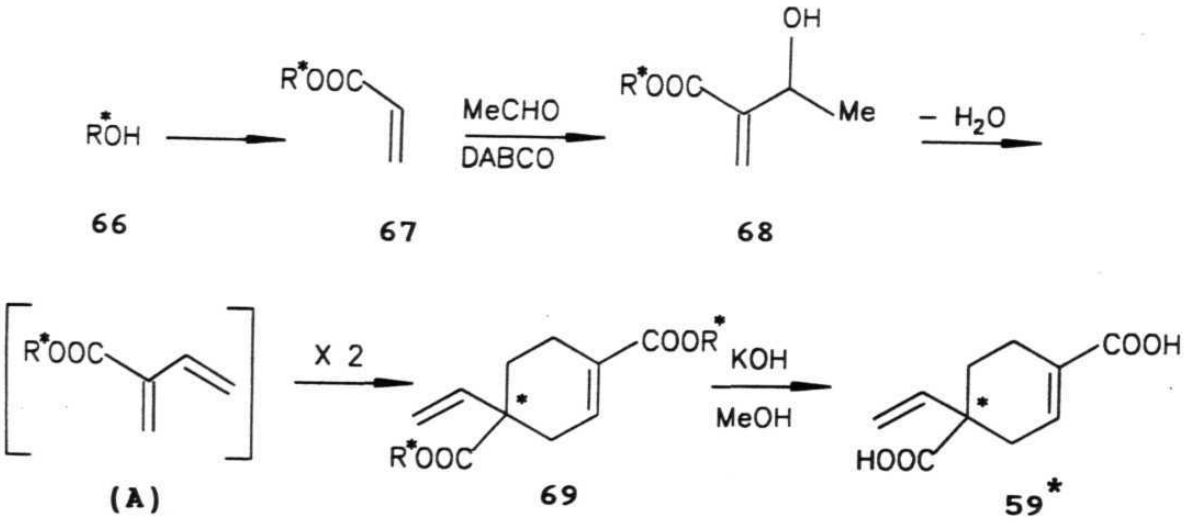
(25)

R = alkyl or aryl



These studies led us to consider the possibility of utilizing the Baylis-Hillman adduct, obtained by the coupling of suitable chiral acrylate and acetaldehyde, as an appropriate starting material for the *in situ* generation of novel chiral 1,3-butadiene-2-carboxylate (**A**) (Scheme 26). This would be expected to undergo spontaneous double stereodifferentiating asymmetric

Scheme 26



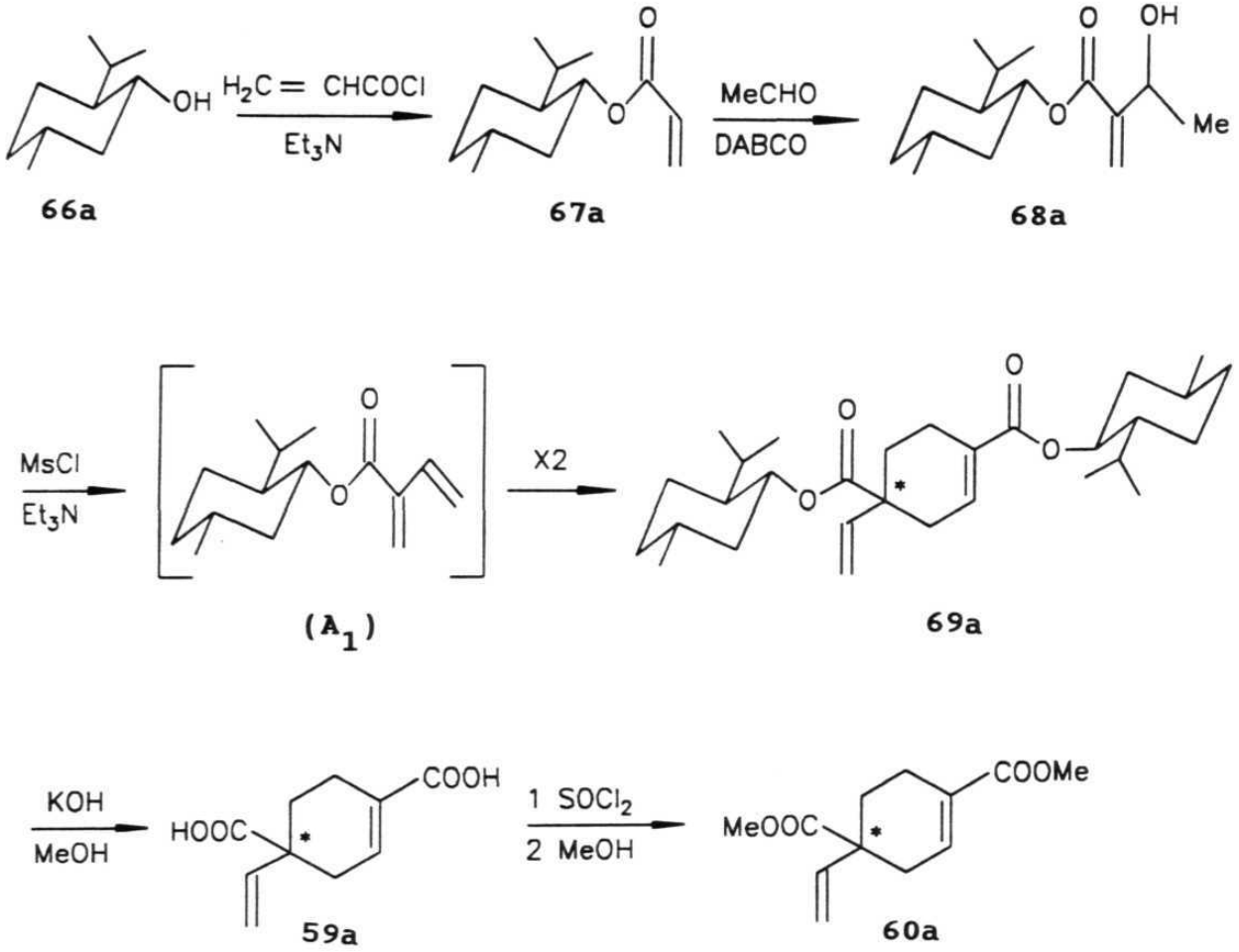
Diels-Alder reaction[92] to provide, after hydrolysis, the desired optically active mikanecic acid (**59***).

We have first selected (l)-menthol (**66a**)# as a chiral auxiliary. The desired (l)-menthyl acrylate (**67a**) was obtained in 67% yield by the treatment of **66a** with acryloyl chloride in the presence of Et_3N according to the literature procedure[93] (Scheme 27). The Baylis-Hillman coupling reaction of **67a** with acetaldehyde in the presence of DABCO was carried out according to the method developed in our laboratory.[28] The Baylis-Hillman adduct, menthyl 3-hydroxy-2-methylenebutanoate (**68a**), was obtained as colorless liquid $[\alpha]_D^{22}$ -73.4° (c 1.58, MeOH) in 89% yield. Treatment of the Baylis-Hillman adduct **68a** with MsCl in the presence of Et_3N in CH_2Cl_2 at 0°C afforded the desired dimenthyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (**69a**) ($[\alpha]_D^{22}$ -83.3° (c 2.98,

---

For convenience and easy understanding, Chiral auxiliaries (l)-menthol, (1S,2S)-2-phenoxycyclohexan-1-ol, (1R,2R)-2-nitroxycyclohexan-1-ol, (1S,2R,4R)-1-[(diisopropylamino sulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)heptan-2-ol&(1S,2R,4R) 1-[(dicyclohexylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)-heptan-2-ol were numbered as **66a-66e** *and the corresponding chiral acrylates, Baylis-Hillman adducts and Diels-Alder adducts were numbered as* **67a-67e, 68a-68e** *and* **69a-69e** *respectively.*
Mikanecic acid (derived from all these chiral auxiliaries) and the corresponding dimethyl esters were numbered as **59a-59e** *and* **60a-60e** *respectively.*
Different Schemes were used to represent the reaction course for different chiral auxiliaries.

Scheme 27



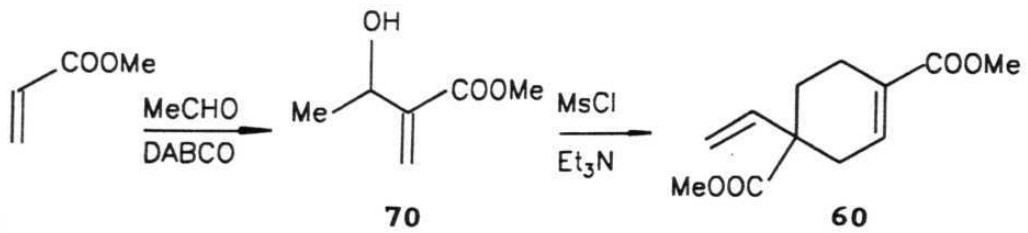
EtOH)), as viscous liquid in 85% yield through Diels-Alder reaction (dimerization) of the *in situ* generated (l)-menthyl 1,3-butadiene-2-carboxylate ($\mathbf{A_1}$). The structure of the Diels-Alder adduct **69a** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. Subsequent hydrolysis with KOH/MeOH furnished optically active mikanecic acid **59a** m.p. 236-238^{o}C (lit[84] m.p. of racemic sample 239-240^{o}C), $[\alpha]_D^{22}$ -3.30^{o} (c 1.74, acetone) in 68% yield.

Determination of enantiomeric purity of **59a:**

First we attempted to determine the diastereoselectivity in the formation of **69a**. Thus, we have examined the HPLC analysis of **69a** on silica column as well as on chiral column (CHIRALCEL OD) under a variety of conditions. There was no indication of separation of diastereomers. This failure has led us to examine the HPLC analysis of dimethyl ester **60a** of mikanecic acid (**59a**) with reference to the racemic dimethyl ester **60** for the determination of enantiomeric purity of **59a**.

Accordingly, the dimethyl ester of racemic mikanecic acid was prepared according to Scheme 28. Thus, Baylis-Hillman coupling reaction of acetaldehyde with methyl acrylate in the presence of catalytic amount of DABCO afforded methyl 3-hydroxy-2-methylene-butanoate (**70**). Subsequent treatment with $MsCl/Et_3N$ afforded the desired racemic dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (**60**) in 85% yield. The structure of this molecule **60** was confirmed by IR, ^1H NMR (Fig.1) and ^{13}C NMR (Fig.2) spectral data. ^1H

Scheme 28



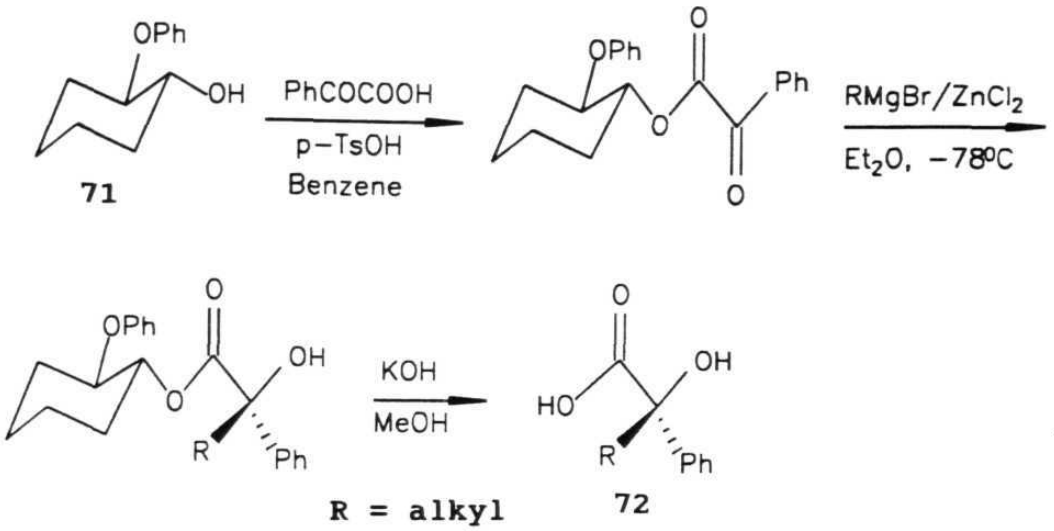
NMR and ^{13}C NMR spectra of this molecule did not indicate the presence of any regioisomer.

HPLC analysis (column : CHIRALCEL OD, eluent : 2% isopropyl alcohol in hexane) of **60** showed two well resolved peaks (Fig.3a) in approximately equal ratio indicating that they arise from (R)- and (S)-enantiomers. It is worth mentioning that the HPLC analysis showed the presence of two small peaks (~ 3%) with equal integration in addition to the above mentioned peaks. These small peaks may be attributed to the presence of regioisomeric (R)- and (S)-enantiomers.

Then, the optically active mikanecic acid **59a** was converted into corresponding dimethyl ester **60a** by the treatment with $SOCl_2$ followed by MeOH (Scheme 27). HPLC analysis (column : CHIRALCEL OD, eluent : 2% isopropyl alcohol in hexane) of **60a** showed two peaks in the ratio of 37.72 and 62.27 indicating that the enantiomeric purity of mikanecic acid **59a** is 25%. HPLC analysis did not show the presence of regioisomer.

During the research work on novel chiral auxiliary mediated asymmetric synthesis, our research group[94] has recently demonstrated the potential of (1R,2R)-2-phenoxycyclohexan-1-ol (**71**) as a chiral auxiliary for the enantioselective synthesis of α-hydroxy acids **72** (Scheme 29).

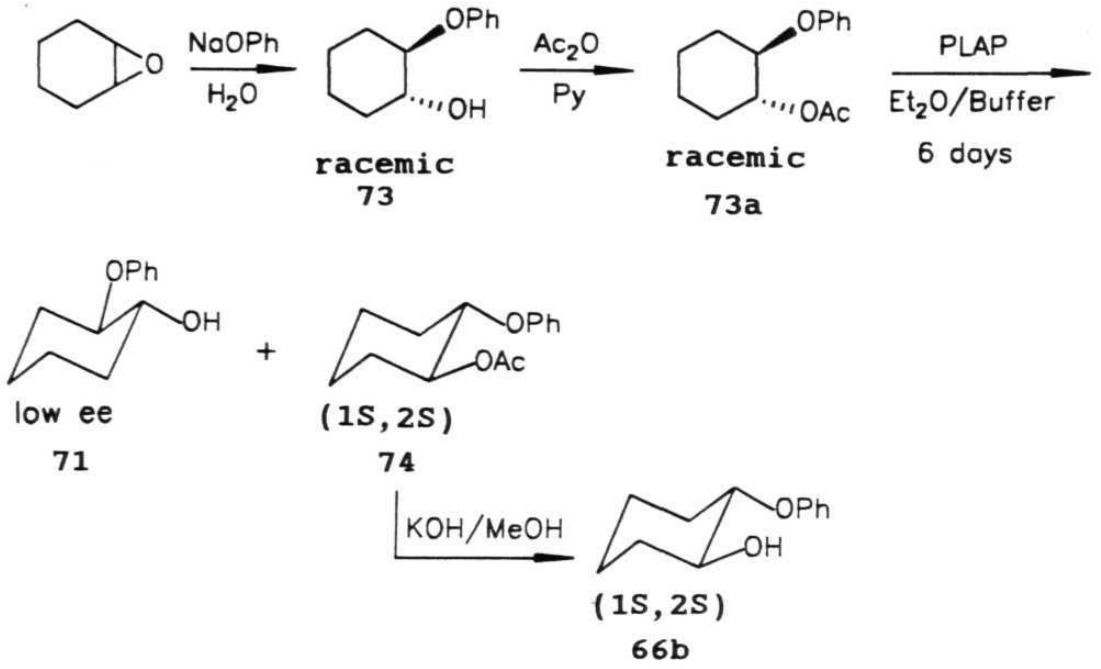
Scheme 29



Encouraged by this report, we planned to examine the potentiality of (1S,2S)-2-phenoxycyclohexan-1-ol (**66b**) as chiral auxiliary for the enantioselective synthesis of mikanecic acid. The required enantiopure (1S,2S)-2-phenoxycyclohexan-1-ol (**66b**) was obtained according to the procedure developed in our laboratory[95] (Scheme 30).

Thus, the nucleophilic opening of cyclohexene oxide with aq. sodium phenoxide furnished racemic *trans*-2-phenoxycyclohexan-1-ol (**73**) as crystalline solid m.p. 81-82°C (lit.[96] m.p. 82°C) in 78% yield. Acetylation of **73** with Ac_2O in the presence of pyridine afforded racemic *trans*-1-acetoxy-2-phenoxycyclohexane (**73a**) as colorless liquid in 94% yield. Biocatalytic hydrolysis of **73a** was carried out with pig liver acetone powder (PLAP) in biphasic media (Et_2O/phosphate buffer) for 6 days (conversion ratio 56:44) to afford (1R,2R)-2-phenoxycyclohexan-1-ol (**71**) and (1S,2S)-1-

Scheme 30

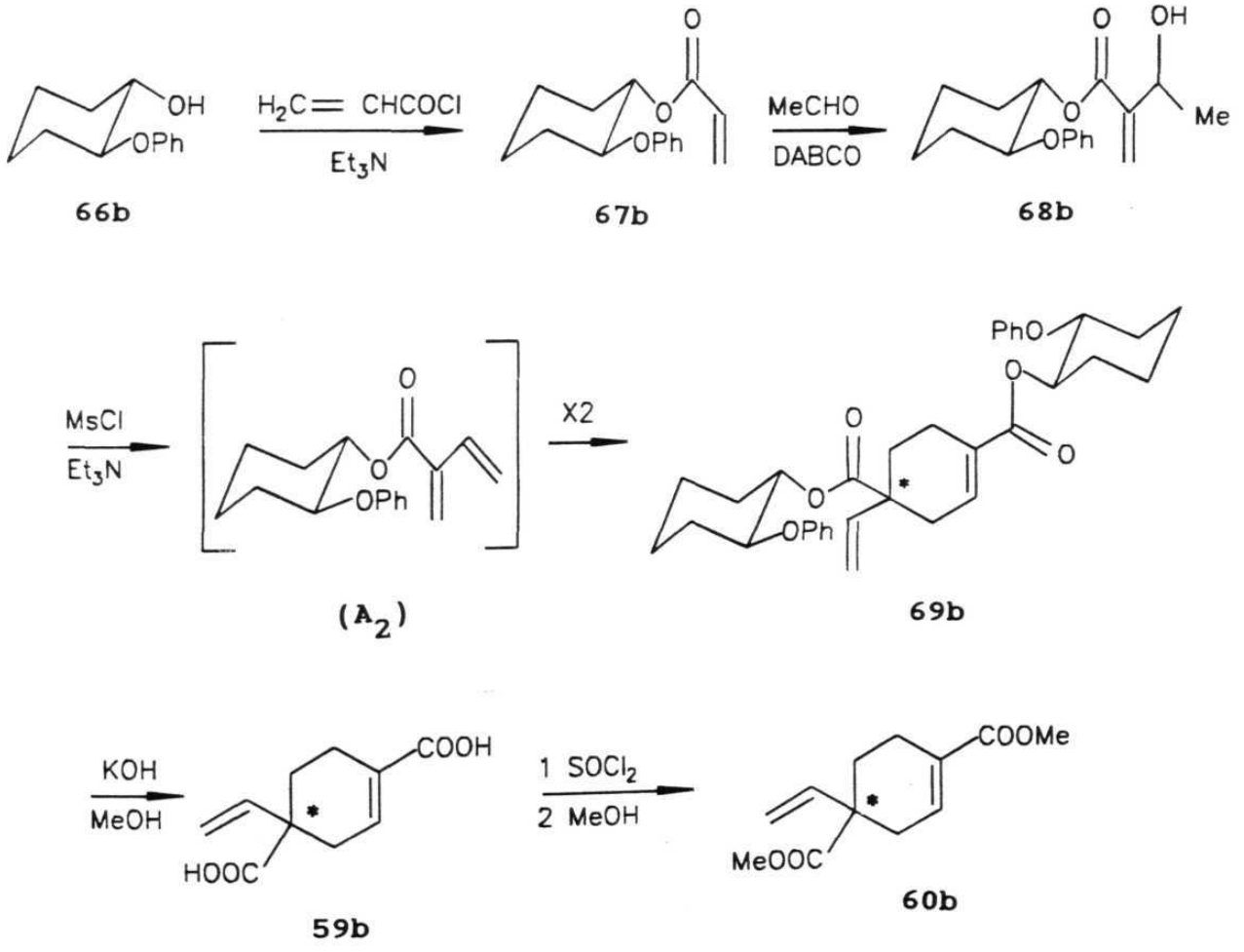


acetoxy-2-phenoxycyclohexane (**74**). Saponification of **74** with KOH/MeOH afforded the desired **66b** $[\alpha]_D^{22}$ +80.4° (c 1.43, methanol) [lit.[95] $[\alpha]_D^{20}$ -79.1° (c 0.86, MeOH), 98% ee, conf. (1R,2R)] in >99% enantiomeric purity. This was further confirmed by HPLC analysis of **66b** using chiral column (CHIRALCEL OD) with reference to the racemic analog (**73**).

Having the desired homochiral (1S,2S)-2-phenoxycyclohexan-1-ol (**66b**) in hand we have carried out the enantioselective synthesis of mikanecic acid according to Scheme 31. The Baylis-Hillman coupling reaction of (1S,2S)-2-phenoxycyclohex-1-yl acrylate (**67b**), obtained by treating **66b** with acryloyl chloride in

presence of Et_3N, with acetaldehyde in the presence of DABCO afforded the desired adduct **68b** ($[\alpha]_D^{22}$ +50.6° (c 0.99, CH_2Cl_2)) as viscous liquid in 72% yield. The structure of the molecule **68b** was confirmed by IR, ^1H NMR and ^{13}C NMR spectral analysis. This molecule **68b** on treatment with MsCl in the presence of Et_3N afforded the Diels-Alder adduct **69b** ($[\alpha]_D^{22}$ +34.7° [c 1.93, acetone]) as colorless liquid in 92% yield. The structure of the

Scheme 31



66b **67b** **68b**

(A_2) **69b**

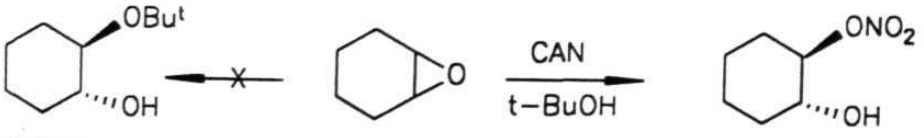
59b **60b**

molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. Subsequent saponification with KOH/MeOH afforded mikanecic acid (**59b**) (m.p. 236-238^{o}C) which was converted into the dimethyl ester **60b** by treatment with $SOCl_2$ followed by MeOH.

HPLC analysis (column : CHIRALCEL OD, 2% isopropyl alcohol in hexane) of dimethyl ester **60b** showed two peaks in the ratio of 44.76 and 55.28, thus indicating that the enantiomeric purity of mikanecic acid (**59b**) is 11%. Also HPLC analysis indicated the absence of regioisomer.

In order to compare the chiral induction efficiency of enantiomerically pure *trans*-2-*tert*-butyloxycyclohexan-1-ol (**75**) as chiral auxiliary with (1S,2S)-2-phenoxycyclohexan-1-ol (**66b**) in enantioselective synthesis of mikanecic acid, we planned to synthesize **75** in enantiomerically pure form *via* enzymatic hydrolysis of the corresponding racemic acetate.

Attempted preparation of racemic *trans*-2-*tert*-butyloxycyclohexan-1-ol (**75**) according to the literature procedure[97] (by Iranpoor *et al*) *i.e.* ceric ammonium nitrate (CAN) catalyzed opening of cyclohexene oxide in t-BuOH, did not provide the desired



(ANTICIPATED)

75

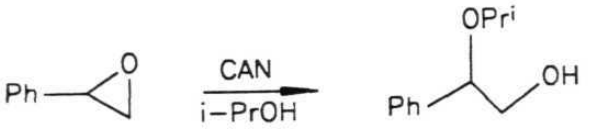
(OBTAINED)

76

(26)

molecule **75** (eq.26). Instead, racemic *trans*-2-nitroxycyclohexan-1-ol (**76**) b.p. 110-111°C/7mm (lit[98] b.p. 100°C/3mm) was obtained as colorless liquid in 67% yield. The structure of the molecule was confirmed by IR, ^{1}H NMR (Fig.4) and ^{13}C NMR (Fig.5) spectral data and microanalysis. The *trans* stereochemistry of the molecule **76** was confirmed by **2D NOESY** experiment (Fig.6).

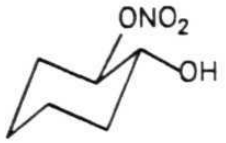
The reproducibility of this result was confirmed by repeating this experiment several times in both small scale (10 mM) and large scale (200 mM). We have also confirmed the quality of CAN by the synthesis of 2-isopropyloxy-2-phenylethanol (**77**) by the action of styrene oxide with CAN in i-PrOH according to the literature report[97] (eq.27).



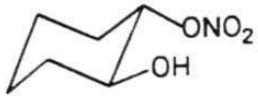
77 **(27)**

In early 1995, the same author reported the synthesis of **76** *via* ceric ammonium nitrate (CAN) catalyzed opening of cyclohexene oxide in acetonitrile.[99] Literature survey (an European patent[100]) revealed that the molecule **76** is known to be a drug for heart and vascular diseases. Our curiosity in *trans*-2-nitroxycyclohexan-1-ol **76** has increased enormously owing to its unexpected formation and its medicinal value. It is desirable to have both (R,R)- and (S,S)-enantiomers of *trans*-2-nitroxycyclohexan-1-ols [**66c** and **78**]

for the better understanding of enantiomer recognition in biological activities. Therefore, we have turned our attention towards the synthesis of both **66c** and **78**, hitherto unknown molecules,



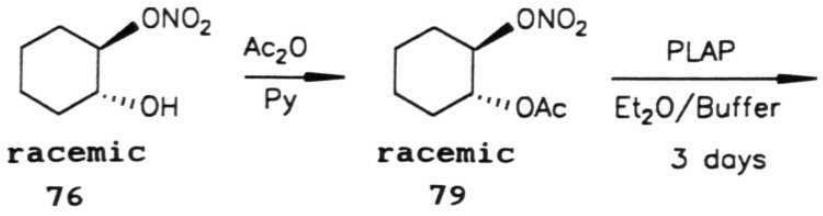
66c



78

in enantiomerically pure form *via* biocatalyst (PLAP) mediated enantioselective hydrolysis of the corresponding (±)-acetate **79** (Scheme 32). The desired racemic acetate **79** was prepared by treating the racemic alcohol **76** with Ac_2O in the presence of pyridine. PLAP mediated biocatalytic hydrolysis of racemic acetate **79** in biphasic media (Et_2O/phosphate buffer) [conversion ratio 39 : 61] afforded, after usual workup followed by column

Scheme 32



racemic 76

racemic 79

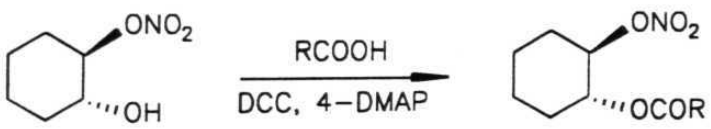
66c **80, low ee**

chromatography (2% EtOAc in hexane), the required (-)-alcohol **66c** as colorless solid and the recovered (+)-acetate **80** as colorless oily liquid. Single recrystallization of the (-)-alcohol from hexane at $0^{o}C$ afforded pure **66c** m.p. 55-56 ^{o}C, $[\alpha]_D^{22}$ -71.5 ^{o} (c 1.17, CH_2Cl_2] as colorless crystals.

Determination of enantiomeric purity of **66c:**

Our research group[101] has successfully determined the enantiomeric purity of secondary alcohols by HPLC analysis of the corresponding 2-methoxybenzoate derivatives on chiral column (CHIRALCEL OD).

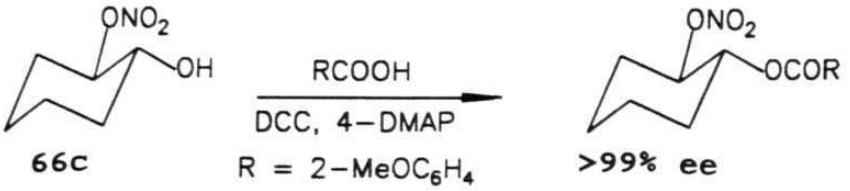
With a view to determine the enantiomeric purity of **66c**, we have prepared racemic *trans*-1-(2-methoxyphenylcarbonyloxy)-2-nitroxycyclohexane (**81**) by treating **76** with 2-methoxybenzoic acid in the presence of DCC in CH_2Cl_2 (eq.28). HPLC analysis (column : CHIRALCEL OD, eluent : 5% i-PrOH in hexane) of this molecule **81** showed two peaks (Fig.7a) in approximately equal ratio indicating that they arise from (R,R) and (S,S)- enantiomers.



racemic **76** **racemic** **81** **(28)**

Then we have converted (-)-alcohol **66c** into the corresponding 2-methoxybenzoate **82** (eq.29) and subjected to similar HPLC

analysis on chiral column which showed only one peak (Fig.7b) indicating that the enantiomeric purity of (-)-alcohol **66c** is >99%.



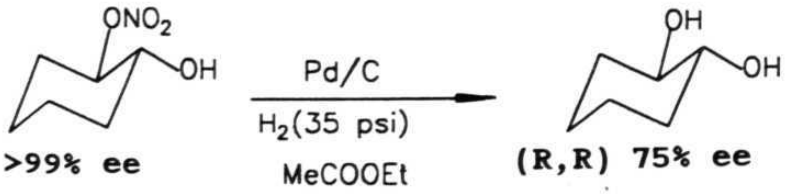
66c **>99% ee** **82** **(29)**

Assignment of absolute configuration of **66c**:

The absolute configuration of enantiomerically pure **66c** was unequivocally assigned by using the following methodologies.

(a) *Hydrogenolysis*

Hydrogenolysis of enantiomerically pure (-)-*trans*-2-nitroxy-cyclohexan-1-ol (**66c**) with Pd/C as catalyst in ethyl acetate afforded (R,R)-cyclohexane-1,2-diol (**83**) m.p. 111-112°C, $[\alpha]_D^{22}$ -30.1° (c 0.94, $CHCl_3$) [lit[102] m.p. 113-114°C, $[\alpha]_D^{20}$ -40° (c 0.32 $CHCl_3$), 100% ee conf. (R,R)] in 75% ee (eq.30). We have therefore assigned (R,R)-stereochemistry to **83**. The fall in the enantiomeric purity of (R,R)-cyclohexane-1,2-diol (**83**) is attributed to racemization during hydrogenolysis.



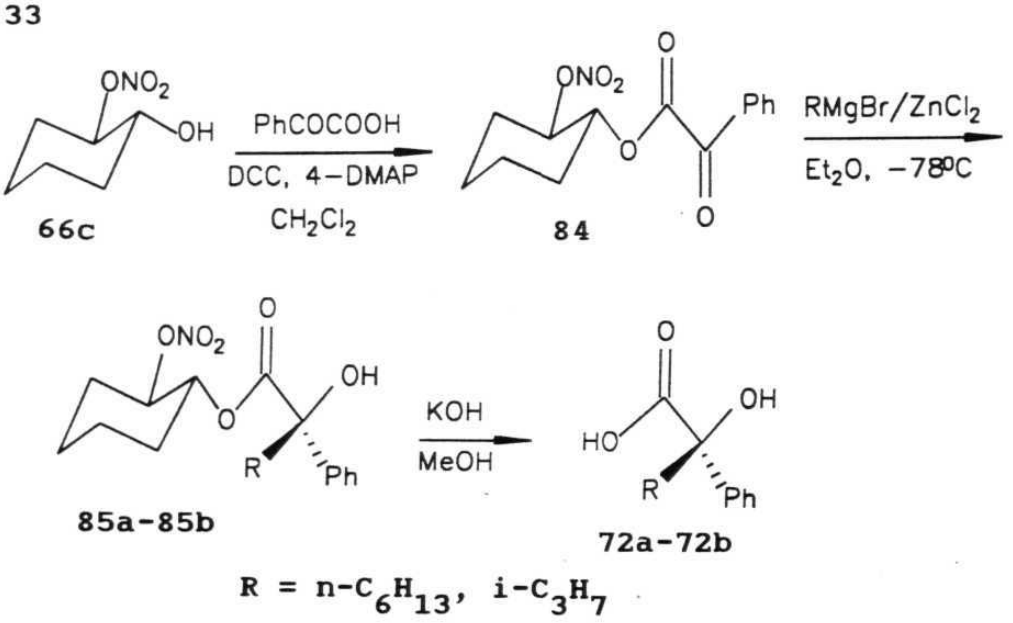
>99% ee **(R,R) 75% ee** **(30)**

66c **83**

b) Product correlation methodology

It has been well documented in the literature[103] that absolute configurational assignments of chiral auxiliaries were made by establishing the sense of asymmetric induction of the chiral auxiliaries. Our research group has recently used (1R,2R)-2-phenoxycyclohexan-1-ol (**71**) as a chiral auxiliary for the enantioselective synthesis of α-hydroxy acids **72** (Scheme 29). In order to further confirm the absolute stereochemistry of **66c** and also to understand its potential as chiral auxiliary we have planned the enantioselective synthesis of α-hydroxy acids **72** according to Scheme 33.

Scheme 33



66c **84** **85a-85b** **72a-72b**

R = n-C_6H_{13}, i-C_3H_7

The desired (-)-*trans*-2-nitroxycyclohex-1-yl phenylglyoxylate **84** was obtained as colorless crystalline solid m.p. 61-62°C, $[\alpha]_D^{22}$ -21.7° (c 0.56, CH_2Cl_2) by the action of benzoylformic acid

on **66c** in presence of DCC. The structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and microanalysis.

Treatment of **84** with n-$C_6H_{13}ZnCl$ (obtained by the action of n-$C_6H_{13}MgBr$ on anhyd. $ZnCl_2$) at -78°C afforded **85a** as colorless liquid $[\alpha]_D^{22}$ -85.9° (c 0.73, CH_2Cl_2) in 85% yield. The structure of the molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. Saponification of **85a** with KOH in methanol afforded (R)-2-hydroxy-2-phenyloctanoic acid **72a** as amorphous solid m.p. 98-99°C, $[\alpha]_D^{22}$ -16.3° (c 0.95, EtOH) [lit.[104] $[\alpha]_D^{22}$ -17° (c 2.2, EtOH), 88% ee, conf. (R)] in 85% ee.

Similar reaction of **84** with i-C_3H_7ZnCl (obtained by the action of i-C_3H_7MgBr on $ZnCl_2$) at -78°C followed by saponification afforded (R)-2-hydroxy-3-methyl-2-phenylbutanoic acid **72b** m.p. 104°C, $[\alpha]_D^{22}$ -25.9° (c 0.85, EtOH) [lit.[105] m.p. 103-105°C, $[\alpha]_D^{25}$ +32.5° (c 2, EtOH), >99% ee, conf. (S)] in 80% ee.

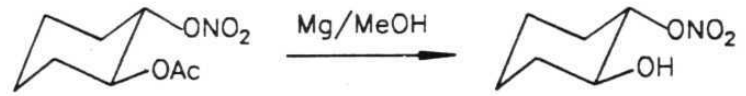
Comparison of the sense of asymmetric induction of (-)-*trans*-2-nitroxycyclohexan-1-ol (**66c**) as chiral auxiliary with that of **71** (Scheme 30), further confirms the absolute stereochemistry of **66c** as (1R,2R).

In order to obtain (1S,2S)-2-nitroxycyclohexan-1-ol (**78**) also in enantiomerically pure form we have subjected racemic acetate **79** to PLAP mediated biocatalytic hydrolysis in biphasic media (Et_2O\phosphate buffer) for more time (6 days) (eq.31). Usual workup followed by column chromatography (2% ethyl acetate

in hexane) provided enantiopure (+)-acetate **80** $[\alpha]_D^{22}$ +23.5° (c 0.77, acetone) and (-)-alcohol (64% ee).

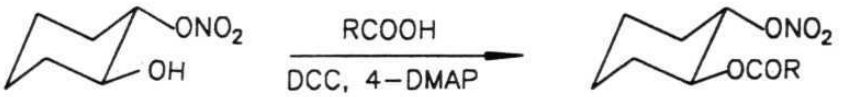
79 **64% ee** **80** **>99% ee** **(31)**

The conversion of this (+)-acetate **80** into the corresponding (+)-alcohol **78** demands a chemoselective cleavage of acetoxy function in the presence of nitroxy function. In fact, we have achieved this transformation using magnesium in MeOH as a chemoselective reagent (eq.32).[106] Thus the enantiopure **78** was obtained as colorless crystals m.p. 58-59°C, $[\alpha]_D^{22}$ +71.5° (c 0.43, CH_2Cl_2) in >99% ee.



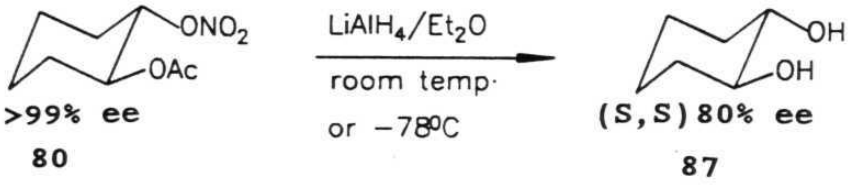
>99% ee **80** **>99% ee** **78** **(32)**

The enantiomeric purity was further confirmed by HPLC analysis of its 2-methoxybenzoate derivative **86** (eq.33) (Fig.7c) using chiral column (CHIRALCEL OD).



78 **>99% ee** **86** **(33)**

With a view to obtain enantiomerically pure cyclohexane-1,2-diol, we have carried out the reaction of enantiopure (1S,2S)-1-acetoxy-2-nitroxycyclohexane **80** with $LiAlH_4$ in ether at room temperature. The required (S,S)-diol **87** was obtained as colorless solid m.p 110-112°C, $[\alpha]_D^{22}$ +32.3° (c 0.98, $CHCl_3$) in 80% ee (eq.34). The loss in enantiomeric purity of **87** may be attributed to racemization during reduction. Attempted reduction with $LiAlH_4$ in ether at low temperature (-78°C) did not show any improvement in the enantiomeric purity of **87**.

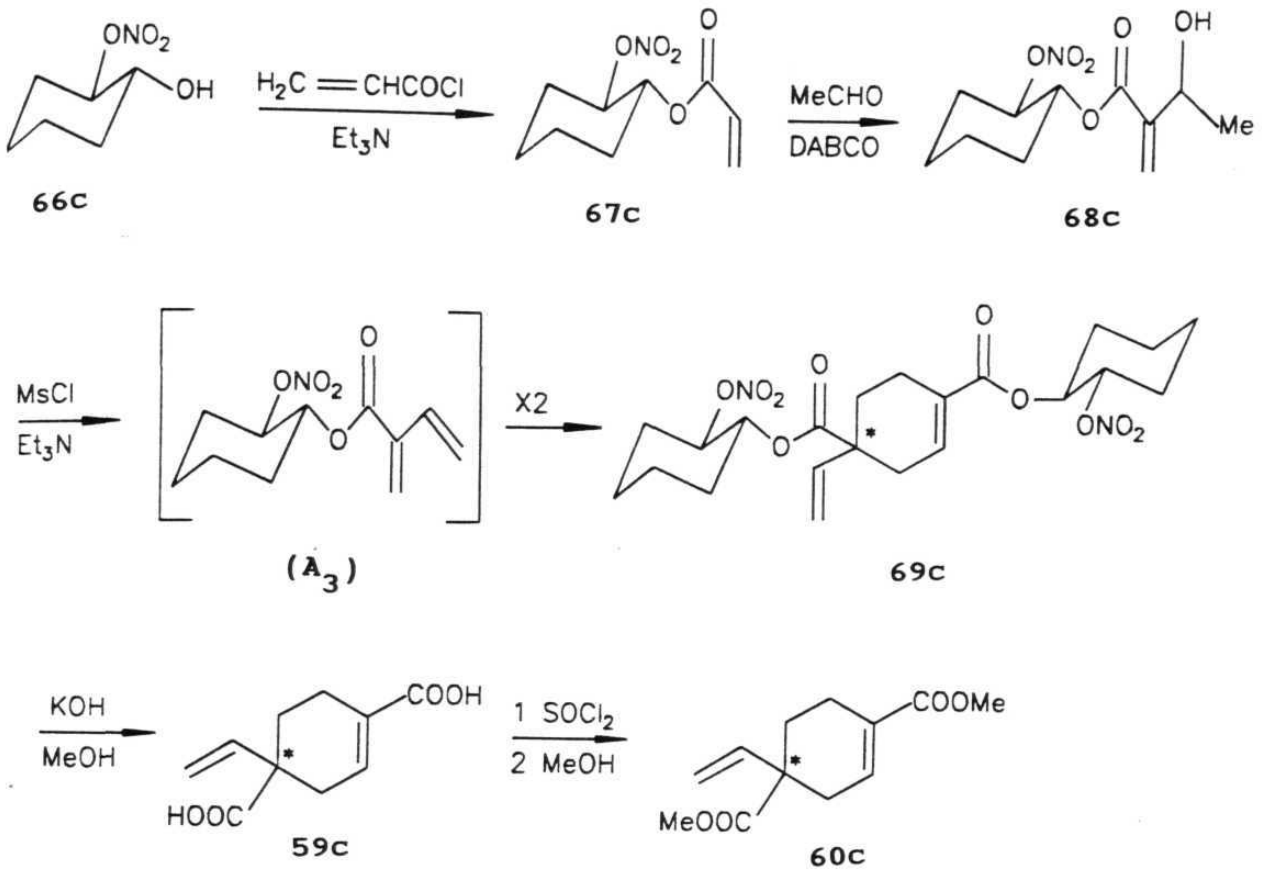


>99% ee **(S,S) 80% ee** **(34)**

80 **87**

Having secured both (1R,2R)- and (1S,2S)-2-nitroxycyclohexan-1-ol (**66c** and **78**) in enantiomerically pure form we proceeded further to study the potentiality of **66c** as a chiral auxiliary in enantioselective synthesis of mikanecic acid according to Scheme 34. Treatment of **66c** with acryloyl chloride in the presence of Et_3N afforded the desired acrylate **67c** as colorless liquid $[\alpha]_D^{22}$ -32.5° (c 0.19, acetone)] in 90% yield. This acrylate **67c** on subsequent reaction with acetaldehyde in the presence of DABCO provided the adduct **68c** as colorless liquid $[\alpha]_D^{22}$ -45.1° (c 0.92 acetone) in 83% yield. The structure of this

Scheme 34



66c **67c** **68c**

(A_3) **69c**

59c **60c**

molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. Subsequent treatment with MsCl in the presence of Et_3N afforded, after usual workup followed by column chromatography (5% ethyl acetate in hexane), diester **69c** as colorless viscous liquid $[\alpha]_D^{22}$ -63.03^o (c 1.26, acetone) in 78% yield. Saponification of **69c** with KOH/MeOH, produced mikanecic acid (**59c**) as solid m.p. 238-240^{o}C. The HPLC analysis (CHIRALCEL OD column, 2% i-PrOH in hexane) of dimethyl ester **60c** of mikanecic acid (**59c**) showed two

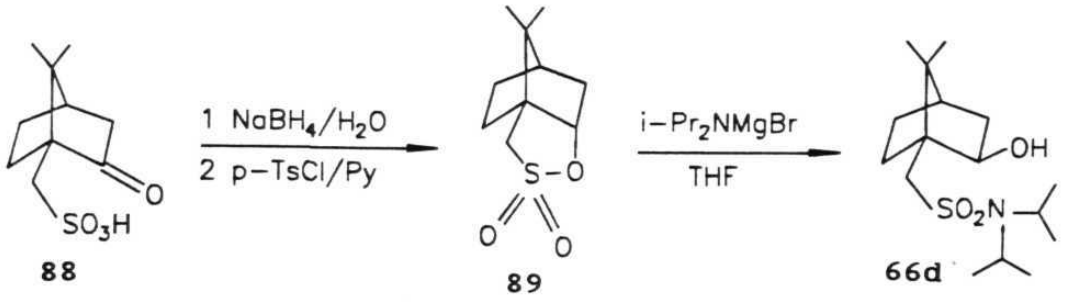
peaks in the ratio of 46.13 and 53.86 indicating that the enantiomeric purity of mikanecic acid (**59c**) is 8%.

Our limited success in enantioselective synthesis of mikanecic acid mediated by chiral auxiliaries **66a-66c**, based on cyclohexyl framework, prompted us to consider (+)-10-camphorsulfonic acid derived chiral auxiliaries[107] such as (1S,2R,4R)-1-[(diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (**66d**) and (1S,2R,4R)-1-[(dicyclohexylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (**66e**) (familiarly known as Oppolzer's chiral auxiliaries) for this purpose. In fact, **66d** and **66e** were proven to be powerful chiral auxiliaries in a variety of rapidly expanding stereoselective reactions[91,108] such as Diels-Alder reaction, Michael reaction and Baylis-Hillman reaction *etc*.

The required chiral auxiliary **66d** was prepared following the sequence described in the Scheme 35 starting from commercially available (1S,2R,4R)-10-camphorsulfonic acid (**88**). Reduction of **88** with $NaBH_4$ followed by intramolecular cyclodehydration with p-TsCl in dry pyridine furnished isobornyl sultone (**89**) m.p. 116-118^{o}C (lit.[109] m.p. 116-118^{o}C) as white solid. Nucleophilic opening of isobornyl sultone (**89**) with bromomagnesium diisopropylamide, obtained by the action EtMgBr with diisopropylamine, afforded **66d** m.p. 101-103^{o}C, $[\alpha]_D^{22}$ -34.6^{o} (c 1.07, EtOH) [lit[107,109] m.p. 102-103^{o}C, $[\alpha]_D^{22}$ -34.4^{o} (c 4.74, EtOH)] in 60%

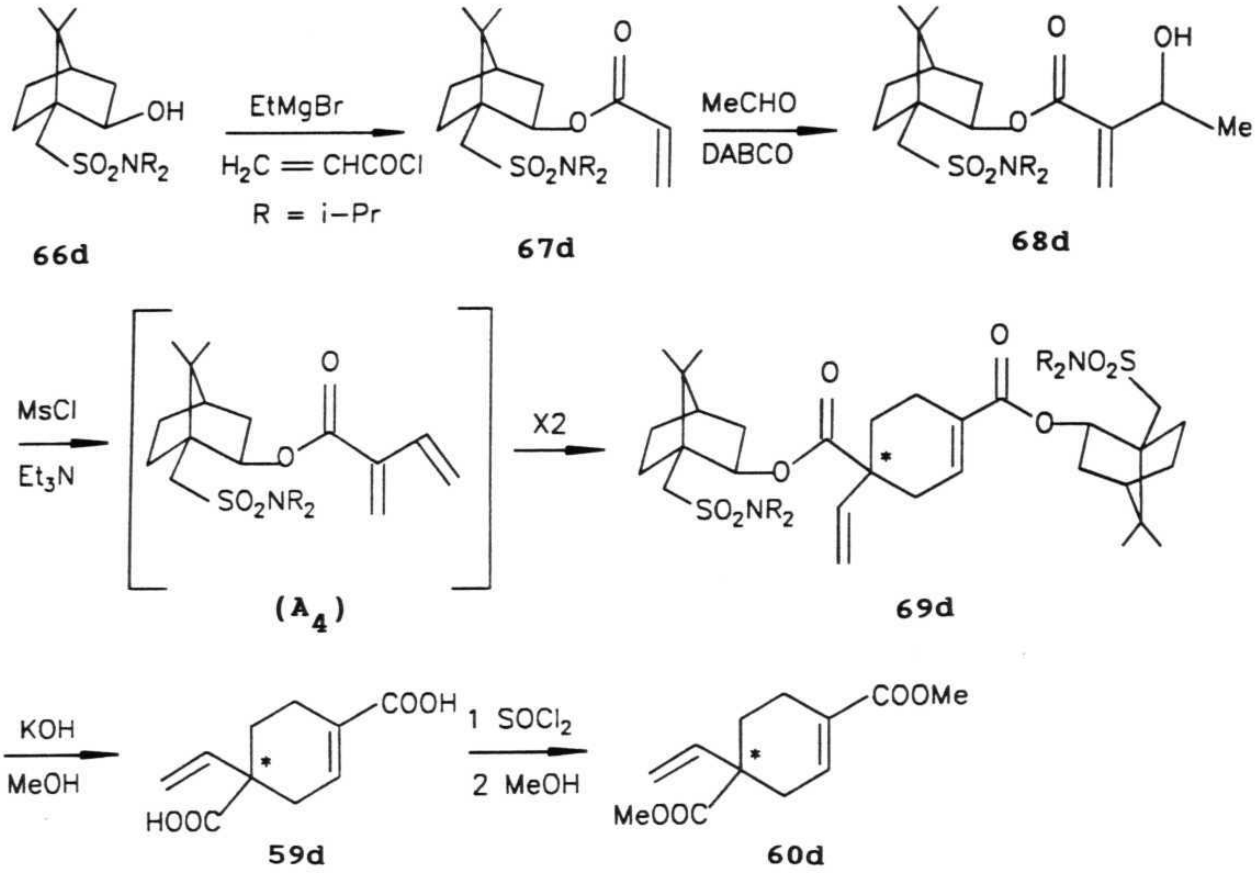
yield. The structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Scheme 35



The required acrylate **67d** m.p. 118-119^{o}C (lit.[109] m.p. 117-118^{o}C), $[\alpha]_D^{22}$ -64.7^{o} (c 0.55, acetone) was obtained as colorless crystals in 61% yield by treating magnesium salt of **66d** with acryloyl chloride (Scheme 36). Baylis-Hillman reaction of the acrylate **67d** with acetaldehyde in the presence of DABCO produced the corresponding adduct **68d** m.p 111-113^{o}C, $[\alpha]_D^{22}$ -55.3^{o} (c 0.65, acetone) in 90% yield. The structure of the molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. Treatment of Baylis-Hillman adduct **68d** with MsCl in the presence of Et_3N in CH_2Cl_2 furnished diester **69d** m.p. 88-92^{o}C, $[\alpha]_D^{22}$ -64.37^{o} (c 1.13, acetone) as colorless solid, after column chromatography (5% ethyl acetate in hexane) in 70% yield. Saponification of **69d** with KOH/MeOH afforded (+)-mikanecic acid **59d** as colorless solid m.p. 234-236^{o}C, $[\alpha]_D^{22}$ +8.62^{o} (c 0.96, acetone) in 64% yield. HPLC analysis of the corresponding dimethyl ester **60d** of (+)-mikanecic

Scheme 36



66d **67d** **68d**

(A_4) **69d**

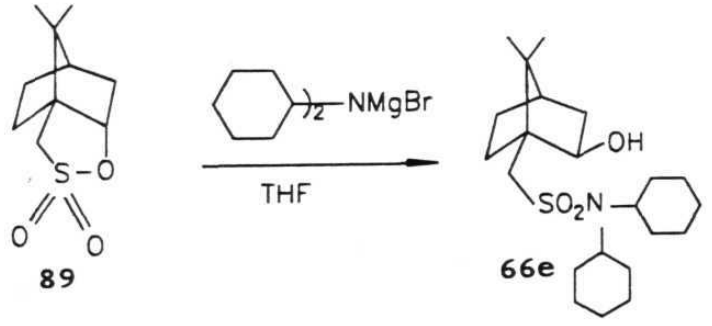
59d **60d**

acid (**59d**) showed two peaks in the ratio of 84.44 and 15.56 indicating that the enantiomeric purity of mikanecic acid (**59d**) is 69%. HPLC analysis did not indicate the presence of any regio-isomer.

Our attempts to obtain single diasteromer by selective crystallization of **69d** under a variety of conditions did not result in any significant improvement in the enantiomeric purity of (+)-mikanecic acid (**59d**) as determined by HPLC analysis of the corresponding dimethyl ester.

With a view to obtain better enantioselectivity, we planned to examine the potential of **66e** as a chiral auxiliary for the enantioselective synthesis of mikanecic acid.

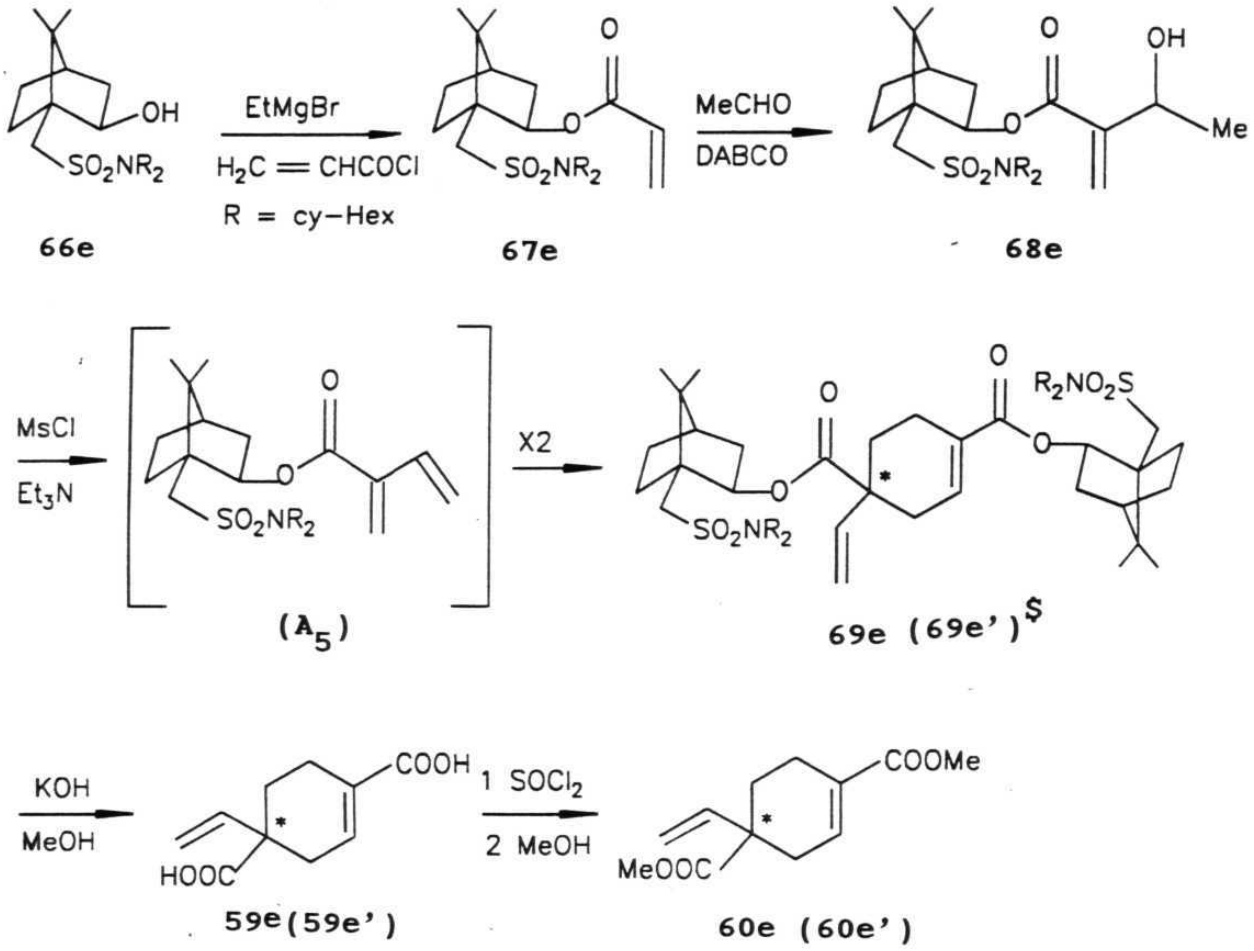
The desired chiral auxiliary **66e** was synthesized according to the eq 35. Nucleophilic opening of isobornyl sultone (**89**) with bromomagnesium dicyclohexylamide (obtained by the action EtMgBr with dicyclohexylamine) at 60°C afforded the desired chiral auxiliary **66e** m.p. 158-159°C, $[\alpha]_D^{22}$ -25.4° (c 1.39, EtOH) [lit.[107] m.p. 163-164°C, $[\alpha]_D^{22}$ -25.7° (c 0.76, EtOH)] in 40% yield. The structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.



(35)

This alcohol **66e** was converted into acrylate **67e** m.p. 193-194°C, $[\alpha]_D^{22}$ -33.2° (c 0.78, acetone) in 95% yield by treating its magnesium salt with acryloyl chloride (Scheme 37). Subsequent coupling reaction with acetaldehyde in the presence of DABCO produced the corresponding adduct **68e** m.p. 147-148°C, $[\alpha]_D^{22}$ -39.6° (c 0.98, acetone)] in 76% yield. The structure of the molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data. The

Scheme 37



66e **67e** **68e**

(A_5) **69e (69e')$**

59e(59e') **60e (60e')**

diastereoselectivity of the reaction was found to be 49% (the olefinic proton signals separate). Treatment of Baylis-Hillman adduct **68e** with MsCl in the presence of Et_3N in CH_2Cl_2 furnished **69e** m.p. 202-204°C, $[\alpha]_D^{22}$ -59.8° (c 0.72, acetone)] as colorless solid, after column chromatography (5% ethyl acetate in hexane)

$ *For better understanding, the crystallized diester was numbered as* **69e'**. *The corresponding mikanecic acid and its dimethyl ester were numbered as* **59e'** *and* **60e'** *respectively.*

in 75% yield (Scheme 37). Saponification of **69e** with KOH/MeOH afforded (+)-mikanecic acid **59e** as colorless solid (m.p. 236-238^{o} $[\alpha]_D^{22}$ +9.17^{o} (c 0.43, acetone)] in 69% yield. HPLC analysis of the corresponding dimethyl ester **60e** showed two peaks in the ratio of 86.72 and 13.24 indicating that the enantiomeric purity of mikanecic acid **59e** is 74% (Fig.3b). Also HPLC analysis did not show the presence of any regioisomer.

Single crystallization of **69e** from 25% benzene in hexane afforded crystalline diester **69e'** m.p. 202-204^{o}C, $[\alpha]_D^{22}$ -61.8^{o} (c 0.87, acetone). Saponification of **69e'** with KOH/MeOH furnished (+)-mikanecic acid **59e'** m.p. 233-235^{o}C, $[\alpha]_D^{22}$ +11.21^{o} (c 0.33, acetone). HPLC analysis (CHIRALCEL OD column, 2% i-PrOH in hexane) of the corresponding dimethyl ester **60e'** showed two peaks (Fig.3c) in the ratio of 96.06 and 3.93 indicating that the enantiomeric excess of (+)-mikanecic acid **59e'** is 92%. Repeated diastereoselective crystallization of **69e'** did not show any further improvement in the enantiomeric purity of (+)-mikanecic acid **59e'**.

Our endeavours in chiral auxiliary mediated enantioselective synthesis of mikanecic acid has been summarized in Table 1.

It is evident from Table 1 that cyclohexyl based chiral auxiliaries such as **66a**, **66b** and **66c** afforded optically active mikanecic acid **59a-59c** in low enantiomeric purities (upto 25% ee), whereas camphor based chiral auxiliaries such as **66d** and **66e**

Table 1: Enantioselective synthesis of mikanecic acid.[a]

	Mikanecic acid			
Chiral acrylate	Product	Overall yield (%)[b]	$[\alpha]_D^{22}$ (c, acetone)	ee (%)[c]
67a	**59a**	51	-3.30° (1.74)	25
67b	**59b**	46	-	11
67c	**59c**	52	-	8
67d	**59d**	40	+8.62° (0.96)	69
67e	**59e**	39	+9.17° (0.43)	74[d]

a) Satisfactory spectral data (IR, ^{1}H NMR and ^{13}C NMR) were obtained for all the molecules involved in the sequence from chiral acrylates **67a-67e** to mikanecic acid **59a-59e**.

b) Overall yield based on the corresponding chiral acrylate.

c) Unequivocally determined by the HPLC analysis using chiral column (CHIRALCEL OD) of dimethyl ester of mikanecic acid **60a-60e** in comparison with that of racemic analog **60**.

d) A single recrystallization of the molecule **69e** from 25% benzene in hexane afforded, after hydrolysis, mikanecic acid **59e'** [m.p. 233-235^{0}C, $[\alpha]_D^{22}$ = +11.21° (C 0.33, acetone)] in 92% ee.

afforded optically active mikanecic acid (**59d-59e**) in 69% ee and 74% ee respectively. The key step in this reaction sequence can be visualized as double stereodifferentiating asymmetric Diels-Alder reaction because the *in situ* generated novel, chiral 1,3-butadiene-2-carboxylate acts as both the chiral diene and chiral dienophile. Our attempts to trap chiral 1,3-butadiene-2-carboxylate with large excess of ethyl vinyl ether or methyl acrylate met with failure and dimer is the only product obtained.

The high instability of the chiral 1,3-butadiene-2-carboxylates (due to spontaneous dimerization) did not allow us to have an insight of the reaction so as to understand whether the chiral diene and chiral dienophile are matched pair or mismatched pair.

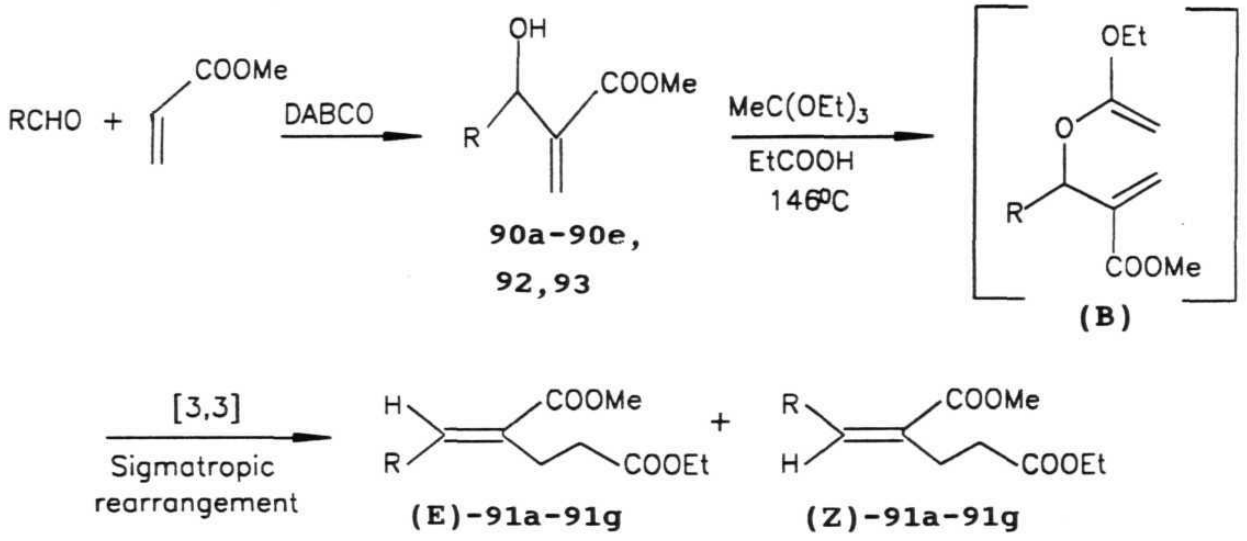
Having achieved reasonable success in the enantioselective synthesis of mikanecic acid using Baylis-Hillman adducts, we have directed our studies towards stereoselective synthesis of functionalized trisubstituted alkenes using these adducts.

Stereoselective synthesis of (E)- and [Z]-alk-4-enoates:

The Johnson-Claisen rearrangement[110] of allyl alcohols is an important and useful synthetic transformations involving C-C bond construction and has been successfully employed for stereoselective synthesis of γ,δ-unsaturated esters.[111-113] It occurred to us that Baylis-Hillman adducts (**1**) (the functionalized allylic alcohols) would, in principle, serve as valuable substrates for

Claisen orthoester rearrangement to produce functionalized trisubstituted alkenes, possibly, with defined stereochemistry. Therefore, first we have studied the Claisen orthoester rearrangement of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (R = Ph, **90a**) in accordance with the Scheme 38.

Scheme 38



R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, n-Pr, i-Pr, 1-Np, n-Bu

The required **90a** was obtained by the Baylis-Hillman coupling reaction of methyl acrylate with benzaldehyde in the presence of DABCO. Treatment of **90a** with triethyl orthoacetate in presence catalytic amount of propionic acid afforded, after usual workup followed by column chromatography (2% ethyl acetate in hexane), ethyl 4-methoxycarbonyl-5-phenylpent-4-enoate (**91a**) in high (E)-

stereoselectivity (E/Z = 80 : 20) *via* [3.3] sigmatropic rearrangement of *in situ* generated allyl vinyl ether (**B**). The structure of the molecule **91a** was established by IR, ^{1}H NMR, ^{13}C NMR spectral data and microanalysis.

In ^{1}H NMR spectrum of **91a**, the isomeric olefinic proton of minor isomer appeared as singlet at δ 6.76 (upfield) and that of major isomer appeared at δ 7.74 (downfield). It has been well documented[114] that the (E)- and (Z)-isomers of 1-alkyl-2-arylalk-2-enoates were distinguished by their appreciable difference in chemical shift values of isomeric olefinic protons [δ 6.4 (upfield) for olefinic proton *trans* to ester group and δ 7.5 (downfield) for olefinic proton *cis* to ester group]. Accordingly we have assigned (E)-stereochemistry to the major isomer and (Z)-stereochemistry to the minor isomer. Integration of the isomeric olefinic proton signals indicated that E/Z ratio is 80:20

In order to understand the generality of this stereochemical observation, we have studied the Johnson-Claisen rearrangement of a variety of Baylis-Hillman adducts **90b-90e, 92**[@] and **93**[@] (obtained by the coupling of various aldehydes with methyl acrylate in presence of DABCO) with triethyl orthoacetate in the presence of propionic acid (3-4 drops) at 146°C. The resulting ethyl 4-methoxycarbonyl-5-arylpent-4-enoates **91b**, **91c** and **91f** were formed in

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@ *To have a continuous numbering we have numbered the Baylis-Hillman adducts obtained from 1-naphthaldehyde and n-valeraldehyde as* **92** *and* **93** *respectively.*

Table 2: Synthesis of ethyl [4E]-5-aryl-4-(methoxycarbonyl)pent-4-enoates and ethyl [4Z]-4-(methoxycarbonyl)alk-4-enoates.[a-c]

Baylis-Hillman adduct	R	Product	Yield[d] (%)	(E) : (Z) ratio[e]
90a	Ph	**91a**	78	80 : 20
90b	4-MeC_6H_4	**91b**	87	75 : 25
90c	4-ClC_6H_4	**91c**	85	70 : 30
90d	n-Pr	**91d**	70	26 : 74
90e	i-Pr	**91e**	85	20 : 80
92	1-Np	**91f**	82	74 : 26
93	n-Bu	**91g**	84	25 : 75

a) All reactions were carried out in 2 mM scale of Baylis-Hillman adducts with triethyl orthoacetate (10 mM) in presence of propionic acid (3-4 drops) at 146°C for 1.5-2.5 h.

b) Satisfactory spectral (IR, ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz)) data were obtained for all products **91a-91g**.

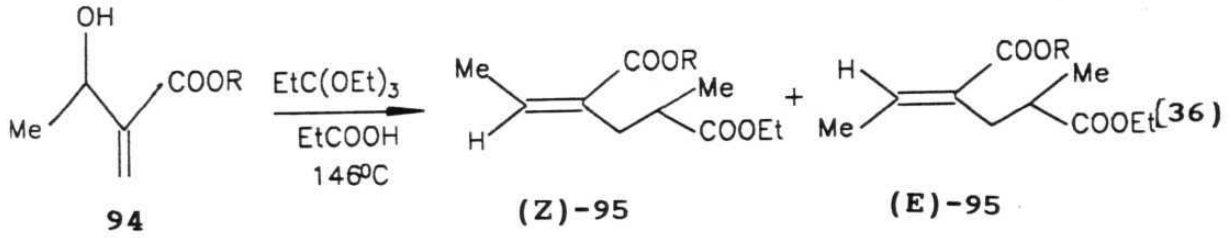
c) Stereochemical assignments were made on the basis of ^{1}H NMR spectra.

d) Isolated yield of the products after column chromatography (2% ethyl acetate in hexane).

e) Determined by the integration ratio of (E)- and (Z)-olefinic protons in ^{1}H NMR spectra.

high (E)-stereoselectivity (E/Z = 74-80/26-20) and in 82-87% yield, whereas ethyl 4-methoxycarbonyl-alk-4-enoates **91d, 91e** and **91g** were formed in high (Z)-stereoselectivity (Z\E = 74-80/26-20) and in 70-85% yield (Table 2). The structure of these molecules **91b-91g** were confirmed by IR, ^{1}H NMR (Fig.8 ^{1}H NMR spectrum of **91e** R = i-Pr) and ^{13}C NMR spectral data.

It is worth mentioning here about the work of Drewes and co-workers[115] who reported the Claisen rearrangement of various alkyl 3-hydroxy-2-methylenebutanoates (**94**) with triethyl ortho-propionate in presence of propionic acid producing isomeric mixture of ethyl 4-alkoxycarbonyl-2-methylhex-4-enoates (**95**) with (Z)-isomer predominating (eq.36). However this report did not provide any information about Z/E ratio of **95**.



94 **(Z)-95** **(E)-95**

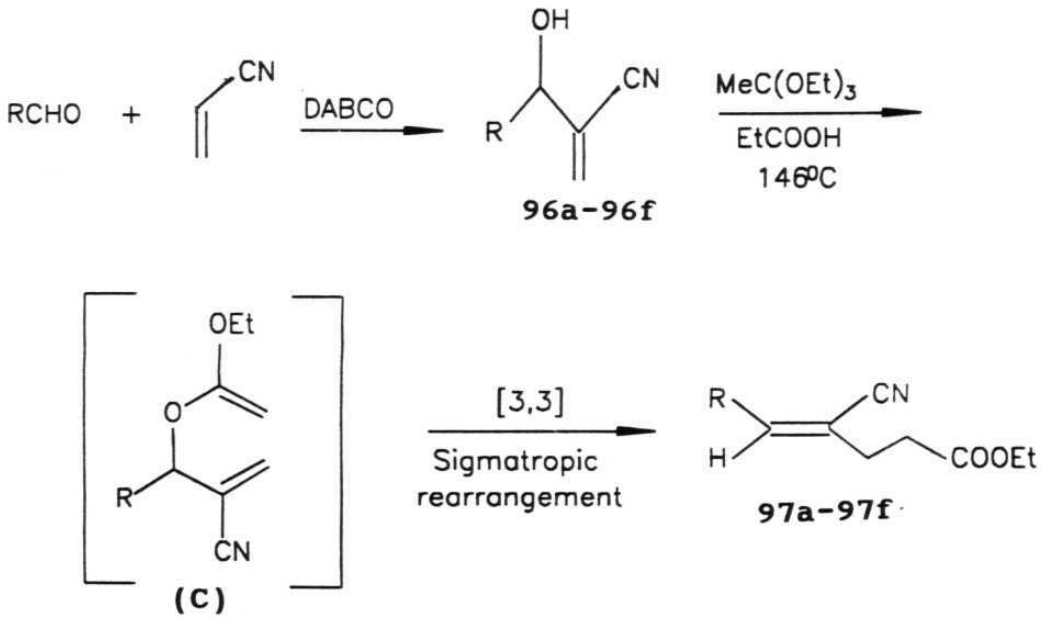
R = alkyl

With a view to understand the substituent effect on the stereochemistry and to provide a convenient synthesis of function alized trisubstituted alkenes, our efforts were directed to study the Johnson-Claisen rearrangement of 3-hydroxy-2-methylenealkane-

nitriles (**96**). To the best of our knowledge, there is no report in the literature either on the Johnson-Claisen rearrangement of these molecules **96** or on the stereoselective synthesis of 4-cyanoalk-4-enoates (**97**).

We have first selected 3-hydroxy-2-methylene-3-phenylpropanenitrile (**96a** R = Ph) as a substrate for our study (Scheme 39). This was obtained by the coupling reaction of acrylonitrile with benzaldehyde in presence of DABCO. Treatment of **96a** with triethyl orthoacetate in presence of propionic acid at 146°C afforded, after usual workup followed by column chromatography (2% ethyl acetate in hexane), stereomerically pure ethyl (2Z)-4-

Scheme 39



R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, n-Pr, n-Hex, i-Pr

cyano-5-phenylpent-4-enoates **97a** in 92% yield. The structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data and microanalysis.

The (Z)-stereochemistry was assigned by comparing the ^{13}C NMR chemical shift value of allylic methylene carbon of **97a** (δ 31.36) with that of (E)- and (Z)-isomers of 2-ethyl-3-phenylprop-2-ene-nitrile[116] (δ 22.92 (upfield) for (E)-isomer and δ 29.52 (down-field) for (Z)-isomer). This was also confirmed by comparing the ^{13}C NMR chemical shift value of the isomeric allylic carbon of **97a** with that of ethyl (E)- and (Z)-isomers of 4-methoxycarbonyl-5-phenylpent-4-enoate **91a** (δ 22.92 (upfield) for (E)-isomer and δ 30.47 (downfield) for (Z)-isomer).

Encouraged by this study, we have prepared a variety of 3-hydroxy-2-methylenealkanenitriles (**96b-96f**) ***via*** the Baylis-Hillman coupling reaction of the corresponding aldehydes with acrylonitrile in presence of DABCO. Then, **96b-96f** were subjected to the Johnson-Claisen rearrangement with triethyl orthoacetate in presence of propionic acid (3-4 drops). Usual workup followed by column chromatography (2% ethyl acetate in hexane) afforded stereochemically pure ethyl (4Z)-4-cyanoalk-4-enoates **97b-97f** in good yields ***via*** [3.3] sigmatropic rearrangement of allyl vinyl ether intermediate (**C**) (Table 3). The structure of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR (Fig.9 ^{13}C NMR spectrum of **97d** R = n-Pr) spectral data and microanalyses.

Table 3: Synthesis of ethyl [4Z]-4-(cyano)alk-4-enoates.[a,b]

Baylis-Hillman adduct	R	Reaction time (h)	Product	Yield[c] (%)
96a	Ph	1	**97a**[d]	92
96b	4-MeC_6H_4	1	**97b**[e]	87
96c	4-ClC_6H_4	1	**97c**[d]	76
96d	n-Pr	1.5	**97d**[f]	79
96e	n-Hex	1.5	**97e**[f]	90
96f	i-Pr	1.5	**97f**[e]	83

a) All reactions were carried out in 2 mM scale of Baylis-Hillman adducts with triethyl orthoacetate (10 mM) in presence of propionic acid (3-4 drops) at 146°C.

b) Satisfactory spectral [IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz] data and microanalyses were obtained for all products **97a-97f**. ^1H NMR and ^{13}C NMR spectra indicate the absence of any (E)-isomer.

c) Isolated yield of the products after column chromatography (2% ethyl acetate in hexane).

d) (Z)-Stereochemistry was assigned on the basis of ^{13}C NMR chemical shift (δ) value of allylic methylene carbon in comparison with that of **97b**.

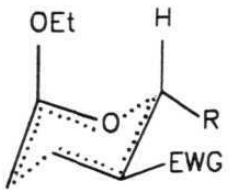
e) (Z)-Stereochemistry was assigned by **2D NOESY** experiment.

f) (Z)-Stereochemistry was assigned in anology with **97f**.

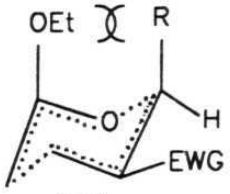
2D NOESY experiment of **97b** (Fig.10 R = 4-MeC_6H_4) (a representative for R is aryl) and of **97f** (Fig.11 R = i-Pr) (a representative for R is alkyl) also indicate that these molecules possess (Z)-stereochemistry. Therefore we have assigned the (Z)-stereochemistry for all 4-cyanoalk-4-enoates **97a-97f**.

It is clear that the Johnson-Claisen rearrangement of methyl 3-hydroxy-2-methylenealkanoates afforded functionalized trisubstituted alkenes with high (E)-stereoselectivity when R is aryl and with high (Z)-stereoselectivity when R is alkyl (Table 2). It is also quite clear that Johnson-Claisen rearrangement of 3-hydroxy-2-methylenealkanenitriles afforded exclusively (Z)-4-cyanoalk-4-enoates irrespective of the nature of R substituent, *i.e.*, when R is aryl or alkyl (Table 3).

Ample theoretical considerations[117,118] and experimental evidence[119-122] on various [3.3] sigmatropic rearrangements indicate quite clearly that, in the absence of any unusual steric constraints, the rearrangement proceeds through a chair-like transition state. Based on this fact, we have proposed transition states (**D**) and (**E**) in order to explain our results.



(D)



(E)

An examination of non-bonded interaction readily indicates that the transition state (**D**) is more favoured than (**E**) and thus should lead, in principle, to the formation of (Z)-alk-4-enoates. This transition state (**D**) supports our experimental result, *i.e.*, the predominant formation of **91d, 91e, 91g** and exclusive formation of **97a-97f**. However, it is not possible to explain the predominant formation of (E)-alk-4-enoates **91a-91c** and **91f** respectively from the Baylis-Hillman adducts **90a-90c** and **92** (aryl substituted) based on the transition state (**D**). We, therefore, believe that this observation requires an alternate explanation.

Stereoselective synthesis of [E]- and [Z]-allyl bromides:

(2Z)-2-(Bromomethyl)alk-2-enoates are versatile building blocks for stereoselective synthesis of a variety of natural products such as α-methylene-γ-butyrolactones,[123] necic acids[5] and α-alkylidene-β-lactams.[124] As it is evident from the introduction chapter that several synthetic methodologies (eq. 2, Scheme 4 and eq.4) have been developed for the synthesis of (2Z)-2-(bromomethyl)alk-2-enoates using Baylis-Hillman adducts.

Our research group has used acetates of Baylis-Hillman adducts for stereoselective synthesis of trisubstituted alkenes.[44,48] During these studies our research group has observed a remarkable reversal of stereochemistry from esters to nitriles in the products formed in the reaction of either hydride nucleophile

(LAH : EtOH) (Scheme 6) or carbon nucleophile (Grignard reagent) (Scheme 9) with methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles. This interesting observation has led us to examine the stereochemical directive effects of ester and nitrile in the nucleophilic substitution of other nucleophiles, particularly, bromide ion from magnesium bromide on the acetates of Baylis-Hillman adducts with a view to provide simple stereoselective synthesis of (E)- and (Z)-allyl bromides.

Magnesium bromide, a very mild Lewis acid, has been used in a variety of synthetic transformations such as selective cleavage of ethers,[125] nucleophilic bromination of mesylates and tosylates,[126] bromination of olefins,[127] and as a catalyst in the stereoselective allylation[128,129] etc. However, there is not much information available in the literature on the stereoselective transfer of bromide from magnesium bromide for the synthesis of (E) and (Z)-allyl bromides

We have first planned to study the reaction of magnesium bromide with methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**98a** R = Ph). Thus the required **98a** was obtained by treating Baylis-Hillman adduct **90a** with AcCl in presence of pyridine. We have treated this molecule **98a** with freshly prepared magnesium bromide in refluxing THF for 2 h. Usual workup followed by column chromatography (1% EtOAc in hexane) afforded the desired stereomerically pure methyl (2Z)-2-bromomethyl-3-phenylprop-2-enoate

Table 4: Synthesis of methyl [2Z]-2-(bromomethyl)alk-2-enoates[a,b]

Acetate of Baylis-Hillman adduct	R	Reaction time (h)	Product	Yield[c] (%)	Conf.
98a	Ph	1.5	**99a**	84	(Z)-isomer[d]
98b	4-MeC_6H_4	2	**99b**	80	(Z)-isomer[d]
98c	4-ClC_6H_4	1.5	**99c**	83	(Z)-isomer[d]
98d	n-Pr	3	**99d**	64	(Z)-(>96%)[e]
98e	i-Pr	3	**99e**	67	(Z)-(>96%)[e]
98f	n-Hex	3	**99f**	78	(Z)-(>96%)[e]

a) All reactions were carried out in 5 mM scale of acetate with magnesium bromide (12 mM) in THF at reflux temperature.

b) Satisfactory spectral [IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz)] data were obtained for all products **99a-99f**.

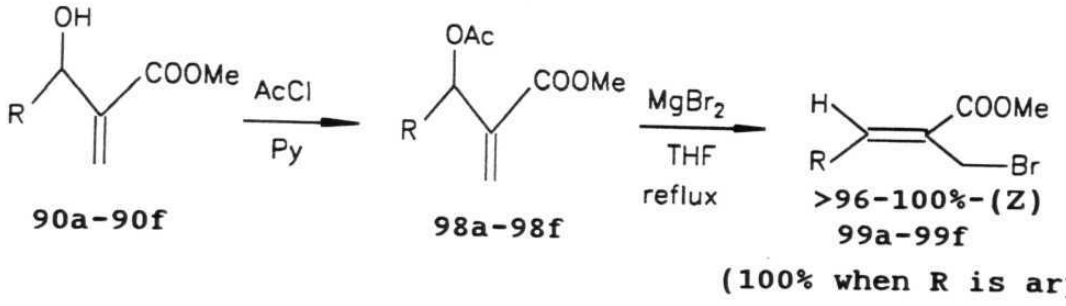
c) Isolated yield of the products after column chromatography (1% ethyl acetate in hexane).

d) ^1H NMR and ^{13}C NMR spectra indicate the absence of any (E)-isomer

e) ^1H NMR spectrum indicates at least >96% (Z)-isomeric purity.

(**99a**) in 84% yield (Scheme 40). The structure of this molecule was established by IR, ^{1}H and ^{13}C NMR (Fig.12) spectral data. The (Z)-stereochemistry was assigned on the basis of chemical shift value (δ 7.84) of olefinic proton in its ^{1}H NMR spectrum.

Scheme 40



90a-90f **98a-98f** **>96-100%-(Z) 99a-99f**

(100% when R is aryl)

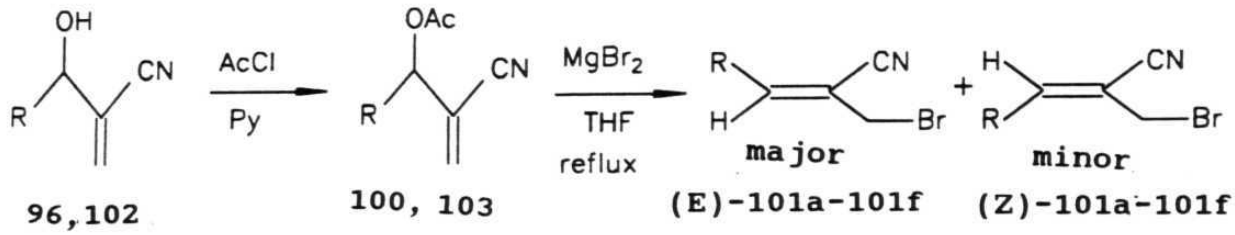
R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, n-Pr, i-Pr, n-Hex

To generalize this result we have prepared a representative class of methyl 3-acetoxy-2-methylenealkanoates **98b-98f** and subjected to the reaction with $MgBr_2$ in THF. The resulting methyl (2Z)-2-(bromomethyl)alk-2-enoates **99b-99f** were obtained in high (Z)-stereoselectivity (>96-100%) and in high yields (Scheme 40) (Table 4). The structure of these molecules **99b-99f** were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Encouraged by this result, we have carried out the reaction of 3-acetoxy-2-methylene-3-phenylpropanenitrile (**100a**, R = Ph), (obtained by the action of AcCl on **96a** in the presence of pyridine) with magnesium bromide in THF at reflux temperature

(Scheme 41). The resulting 2-(bromomethyl)-3-phenylprop-2-ene-nitrile (**101a**) was obtained in high (E)-stereoselectivity (E/Z is 91/9) and in 90% yield. The structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Scheme 41



96,102 **100, 103** **(E)-101a-101f** **(Z)-101a-101f**

R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, n-Pr, n-Hex, n-Pent

The stereochemistry was assigned on the basis of ^{1}H NMR spectral analysis. ^{1}H NMR spectrum of this molecule (**101a**) showed two singlets at δ 7.22 and δ 7.34 for olefinic proton due to major and minor isomer respectively. Therefore, major isomer was assigned as (E)-stereochemistry. It was further confirmed by ^{13}C NMR spectral analysis. In ^{13}C NMR spectrum of this molecule (**101a**) isomeric allylic methylene carbons appear at δ 26.64 and δ 32.70 due to minor (Z)- and major (E)-isomers respectively. In fact, ^{1}H NMR, and ^{13}C NMR spectral data of (E)- and (Z)-isomers of **101a** were reported in the literature.[41] Our stereochemical assignment was consistent with reported spectral values.

Then a representative class of acetates of Baylis-Hillman adducts **100b-100e, 103** were prepared and were treated with $MgBr_2$

in THF at reflux temperature to afford, after usual workup followed by column chromatography (1% ethyl acetate in hexane), (2E)-2-(bromomethyl)alk-2-enenitriles **101b-101f** in high (E)-stereoselectivity (Z/E = 95-88/5-12) and in high yields (Table 5). The structure of these molecules **101b-101f** were confirmed by IR, ^{1}H NMR (Fig.13 ^{1}H NMR spectrum of **101e** R = n-C_6H_{13}) and ^{13}C NMR spectral data. The (E)-stereochemistry of **101b** and **101c** was based on the ^{13}C NMR chemical shift values of isomeric allylic carbon.

Stereochemical assignment of molecules **101d-101f** were based on ^{1}H NMR spectral analysis. It has been well established in the literature[130] that in the ^{1}H NMR spectra of alk-2-enenitriles, β-allylic methylene protons *cis* to nitrile appear at δ 2.42 (downfield) while the same protons *trans* to nitrile appear at δ 2.26 (upfield). In the ^{1}H NMR spectra of **101d-101f**, β-allylic methylene protons appear at ~ δ 2.40 (downfield) for major isomer whereas the same protons appear at ~ δ 2.27 (upfield) for minor isomer. In the case of **101e** and **101f**, the vinylic proton appears as triplet at ~ δ 6.55 (downfield) for minor isomer and at ~ δ 6.53 (upfield) for major isomer. We have, therefore, assigned (E)- stereochemistry for major isomers and (Z)-stereochemistry for minor isomers.

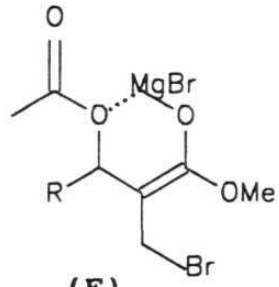
It is quite evident from Table 4 and Table 5 that esters **98a-98f** and nitriles **101a-101e, 103** provide allyl bromides (**99**

Table 5: Synthesis of [2E]-2-(bromomethyl)alk-2-enenitriles[a,b]

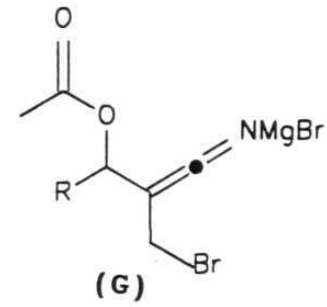
Acetate of Baylis-Hillman adduct	R	Reaction time (h)	Product	Yield[c] (%)	(E) : (Z) ratio
100a	Ph	3	**101a**	90	91 : 09[d]
100b	4-MeC_6H_4	2	**101b**	85	90 : 10[e]
100c	4-ClC_6H_4	2	**101c**	77	95 : 05[d]
100d	n-Pr	10	**101d**	70	91 : 09[f]
100e	n-Hex	10	**101e**	78	91 : 09[f]
103	n-Pent	10	**101f**	84	88 : 12[f]

a) All reactions were carried out in 5 mM scale of acetate with magnesium bromide (12 mM) in THF at reflux temperature. b) Satisfactory spectral [IR, ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz)] data were obtained for all products **101a-101f**. c) Isolated yield of the products after column chromatography (1% ethyl acetate in hexane). d) Assignment of (E)-configuration and establishment of isomeric ratio were based on difference in chemical shift value of isomeric α-allylic carbon in ^{13}C NMR spectra and integration ratio of isomeric olefinic proton in ^{1}H NMR spectra respectively. e) ^{13}C NMR spectra indicates the presence of ~ 10% of (Z)-isomer. f) (E)-Configuration and isomeric ratio were based on difference in chemical shifts and integration ratios of isomeric β-allylic methylene proton in ^{1}H NMR spectrum.

and **101**) with opposite stereochemistry. This observation is consistent with our earlier results and may be explained by considering difference in steric demands of ester and nitrile groups. Alternatively our results may be explained by considering the possible six membered chelated transition state (**F**) in the case of esters **98** resulting in (Z)-allyl bromides **99** and the non-chelated transition state (**G**) in the case of nitriles **100, 103** leading to (E)-allyl bromides **101**.



(F)



(G)

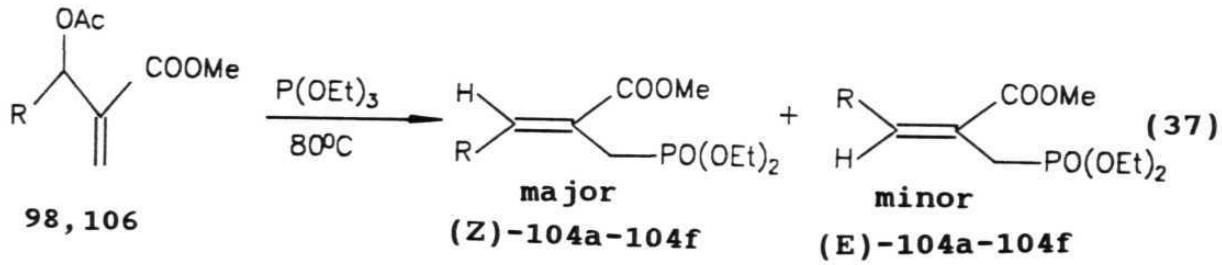
Stereoselective synthesis of [E]- and [Z]-allylphosphonates:

The stereochemical reversal in directive effects from ester to nitrile in the nucleophilic addition of $MgBr_2$ (a metallated nucleophile) to the acetates of Baylis-Hillman adducts as well as our earlier reports (Scheme 6 and 9) led us to examine the stereochemical outcome in the addition of non-metallic nucleophile to the acetates of Baylis-Hillman adducts.

To our knowledge, there is no such systematic study on the reaction of acetates of Baylis-Hillman adducts with non-metallic

nucleophile in the literature. We have, therefore, selected triethyl phosphite as a suitable non-metallic nucleophile to understand the stereochemical outcome and also with the main aim of providing a simple stereoselective synthesis of allylphosphonates, which are precursors for the synthesis of synthetically attractive 1,3-butadiene derivatives.[131]

Accordingly, we have treated methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**98a** R = Ph) with triethylphosphite at 80°C for 30 min to afford, after fractional distillation under reduced pressure, methyl 2-(diethoxyphosphorylmethyl)-3-phenylprop-2-enoate (**104a** R = Ph) in high (Z)-stereoselectivity (Z/E = 91/9) and in 87% yield (eq.37). The structure of the molecule was established by IR, ^{1}H NMR (Fig.14), ^{13}C NMR, ^{31}P NMR spectral data and microanalysis.



R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, n-Pr, 2-MeOC$_6$H$_4$, n-Hex

^{1}H NMR spectrum (Fig.14) of **104a** shows two doublets at δ 6.90 and at δ 7.78 (J = 5.6 Hz) in the ratio 91 : 9 for olefinic proton of major isomer and minor isomer respectively. Therefore,

we have assigned (Z)-stereochemistry for major isomer and (E)-stereochemistry for minor isomer. Further in ^{1}H NMR spectrum, allylic methylene protons appeared as two doublets at δ 2.98 and at δ 3.21 (J = 22 Hz) arising respectively from minor and major isomers which clearly indicate the coupling due to phosphorus. ^{31}P NMR spectrum shows two peaks at δ 24.31 and δ 24.89 arising from (E)- and (Z)-isomer respectively. This molecule is known in the literature.[52] ^{1}H NMR and ^{31}P NMR spectral data are identical with reported values.

^{13}C NMR spectrum of **104a** clearly indicates short and long range coupling of some of the carbon atoms with phosphorus. Thus, allylic carbon of (Z)-isomer appeared as doublet at δ 26.05 (J = 139.5 Hz) and that of (E)-isomer as doublet at δ 32.32 (J = 139.5 Hz). The α-olefinic, β-olefinic carbons and phenyl carbon α- to olefinic group of (Z)-isomer appear as doublets at δ 123.75 (J = 11.6 Hz)], δ 141.34 (J = 11 Hz) and δ 134.72 (J = 3.2 Hz) and that of (E)-isomer as doublets at δ 123.98 (11.6 Hz), δ 139.08 (J = 11 Hz) and δ 136.52 (J = 3.2 Hz) respectively. The methyl and methylene carbons of ethoxy group appear as doublets at δ 16.17 (J = 6.1 Hz) and at δ 61.94 (J = 6.4 Hz) respectively.

To generalize this observation, we have subjected a variety of acetates of Baylis-Hillman adducts **98b-98d, 98f** and **106** [obtained from acylation of methyl 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanoate (**105**)] to similar reaction with triethyl phosphite

Table 6: Synthesis of methyl [2Z]-2-(diethoxyphosphorylmethyl)-alk-2-enoates[a-c]

Acetate of Baylis-Hillman adduct	R	Product	b.p.(^{o}C)/ mm Hg	Yield[d] (%)	(Z) : (E) ratio[e]
98a	Ph	**104a**	168-170/1.6	87	91 : 09
98b	4-MeC_6H_4	**104b**	193-195/2.1	90	90 : 10
98c	4-ClC_6H_4	**104c**	204-207/2.3	90	88 : 12
98d	n-Pr	**104d**	144-146/2.9	95	65 : 35
106	2-MeOC_6H_4	**104e**	185-186/1.5	95	93 : 07
98f	n-Hex	**104f**	149-151/1.5	90	65 : 35

a) All reactions were carried out in 5 mM scale of acetate with triethyl phosphite (7 mM) at 95^{o}C for 30 min.

b) Satisfactory spectral [IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) and ^{31}P NMR (81 MHz)] data and microanalyses were obtained for all products **104a-104f**.

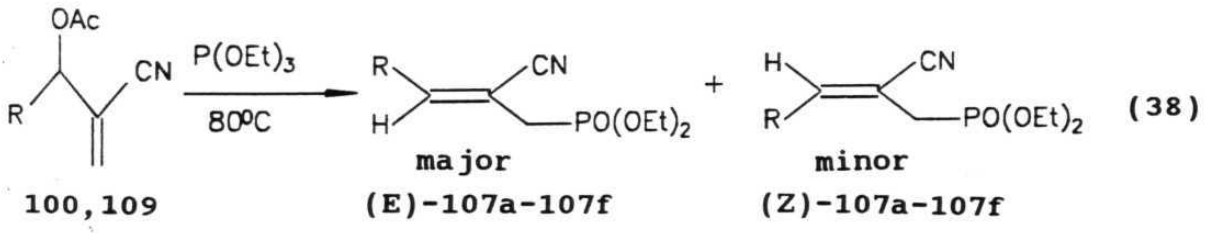
c) (Z)-Stereochemistry was assigned to all major isomers of **104a-104f** on the basis of ^{1}H NMR spectra.

d) Isolated yield of the products after distillation under reduced pressure.

e) Determined by ^{1}H NMR spectral analysis.

at 80°C to afford, methyl 2-(diethoxyphosphorylmethyl)alk-2-enoates **104b-104f** in high (Z)-stereoselectivity (Z/E = 93-65 : 7-35) and in excellent yields (Table 6). We have established the structure of the molecules by IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectral data and microanalyses. The stereochemical assignments of all these molecules **104b-104f** were made on the basis of ^{1}H NMR spectral data. ^{13}C NMR spectra of all these molecules clearly indicate coupling of some carbon with phosphorus.

Then, we have studied the reaction of 3-acetoxy-2-methylene-3-phenylpropanenitrile (**100a** R = Ph) with triethyl phosphite at 80°C. The resultant 2-(diethoxyphosphorylmethyl)-3-phenylprop-2-enenitrile **107a** was obtained in high (E)-stereoselectivity (E/Z = 75/25) (eq.38). The structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR (Fig. 15) and ^{31}P NMR spectral data and microanalysis. The stereochemistry was assigned on the basis of ^{1}H NMR and ^{13}C NMR spectral data.



100,109 **major (E)-107a-107f** **minor (Z)-107a-107f** **(38)**

R = Ph, 4-MeC$_6$H$_4$, Me, n-Pr, n-Hex, i-Pr

Table 7: Synthesis of [2E]-2-(diethoxyphosphorylmethyl)alk-2-ene-nitriles[a-c]

Acetate of Baylis-Hillman adduct	R	Product	b.p. (^{o}C)/ mm Hg	Yield[d] (%)	(E) : (Z) ratio[e]
100a	Ph	**107a**	190-192/2.8	94	75 : 25
100b	4-MeC_6H_4	**107b**	182-184/1.8	90	80 : 20
109	Me	**107c**	92-94/1.7	85	91 : 09
100d	n-Pr	**107d**	146-148/1.6	91	93 : 07
100e	n-Hex	**107e**	172-174/2.4	88	93 : 07
100f	i-Pr	**107f**	119-121/1.6	92	91 : 09

a) All reactions were carried out in 5 mM scale of acetate with triethyl phosphite (10 mM) at 95^{o}C for 30 min.

b) Satisfactory spectral [IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) and ^{31}P NMR (81 MHz)] data and microanalyses were obtained for all products **107a-107f**.

c) (E)-Stereochemistry was assigned to all major isomers of **107a-107f** on the basis of ^{1}H NMR spectra.

d) Isolated yield of the products after distillation under reduced pressure.

e) Determined by ^{1}H NMR spectral analysis.

^{1}H NMR spectrum of **107a** shows two doublets at δ 2.90 (J = 20.9 Hz) and δ 2.98 (J = 20.9 Hz) in the ratio 75 : 25 for allylic methylene protons due to major and minor isomers which clearly indicates the coupling due to phosphorus. Therefore, we have assigned (E)-stereochemistry for major isomer and (Z)-stereochemistry for minor isomer. ^{31}P NMR spectrum shows two peaks at δ 21.65 and δ 21.97 arising from (Z)- and (E)-isomer respectively. This molecule is known in the literature[52] (Scheme 11), ^{1}H NMR and ^{31}P NMR spectral data are identical with reported values.

^{13}C NMR spectrum (Fig.15) of **107a** clearly indicates short and long range coupling of some of the carbon atoms with phosphorus. Thus, allylic carbon of (Z)-isomer appeared as doublet at δ 27.92 (J = 140.5 Hz) and that of (E)-isomer as doublet at δ 32.77 (J = 140.5 Hz). The α-olefinic, β-olefinic carbons, phenyl carbon α- to olefinic group and nitrile carbon of (E)-isomer appear as doublets at δ 100.91 (J = 12.1 Hz), δ 147.11 (J = 10.5 Hz), δ 132.93 (J = 3 Hz) and δ 117.82 (J = 4.8 Hz) respectively. The α-olefinic, β-olefinic carbons and nitrile carbon of (Z)-isomer appear as doublets at δ 105.57 (J = 12.1 Hz) δ 147.27 (J = 10.5 Hz) and δ 119.37 (J = 4.8 Hz) respectively. The methyl and methylene carbons of ethoxy group of (E)-isomer appear as doublets at δ 16.02 (J = 5.4 Hz) and at δ 62.26 (J = 6.5 Hz) respectively. The methyl and methylene carbons of ethoxy

group appear as douplets at δ 15.65 (J = 5.4 Hz) and at δ 62.26 (J = 6.5 Hz) respectively.

We have then studied the reaction of a variety of acetates of Baylis-Hillman adducts **100a-100b, 100d-100f** and **109** (obtained by treating the Baylis-Hillman adduct, 3-hydroxy-2-methylenebutanenitrile (**108**), with acetyl chloride in the presence of pyridine) with triethyl phosphite at 80°C. The (2E)-2-(diethoxyphosphorylmethyl)alk-2-enenitriles **107b-107f** were obtained in high (E)-stereoselectivity (E/Z = 93-80/7-20) and in excellent yields (eq.38) (Table 7). The structure of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectral data and microanalyses. The stereochemical assignment of these molecules was based on the chemical shift value of isomeric allylic methylene protons in ^{1}H NMR spectra.

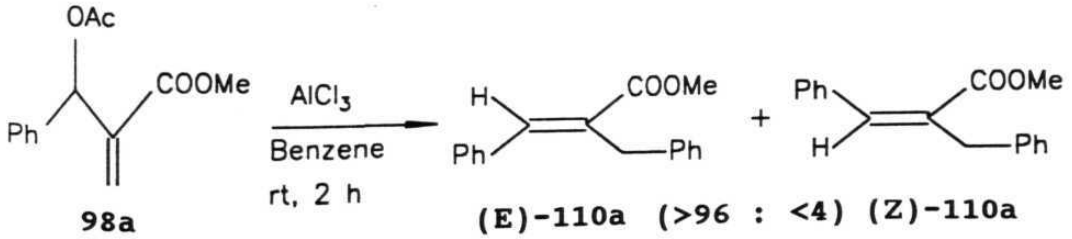
It is evident from Table 6 and Table 7 that the reaction of triethyl phosphite with acetate of Baylis-Hillman adducts depends significantly on the nature of alkyl or aryl substituent. Thus, (Z)-allylphosphonates were formed in high stereoselectivity [Z/E is >90/<10] from methyl 3-acetoxy-2-methylenealkanoates when R is aryl (Table 6), while 3-acetoxy-2-methylenealkanenitriles afforded (E)-allylphosphonates in high stereoselectivity [E/Z is >90/<10] when R is alkyl (Table 7). It is worth mentioning here that the work of Janecki and Bodalski[52] which describes the substituent independent stereoselective synthesis of (E)- and

(Z)-allylphosphonates (Scheme 11). The stereochemical reversal from ester to nitrile group in the formation of allylphosphonates can be attributed to difference in spatial requirements of the methoxycarbonyl group and nitrile group.

Acetates of Baylis-Hillman adducts as stereodefined β-electrophiles

Our interest, in understanding and exploring the utility of the acetates of Baylis-Hillman adducts, has led us to investigate the hitherto unknown application of these adducts **98** and **100** as stereodefined β-electrophiles in the Friedel-Crafts reaction.[132,133]

Accordingly we have first examined the reaction of **98a** with benzene in presence of anhydrous $AlCl_3$ at room temperature. Usual workup followed by column chromatography (1% ethyl acetate in hexane) afforded methyl 2-(benzyl)-3-phenylprop-2-enoate (**110a**) in high (Z)-stereoselectivity (Z/E = 96/4) and in 75% yield (eq.39). The structure of the molecule **110a** was established by IR, ^1H NMR and ^{13}C NMR spectral data. The stereochemistry was established by examining the ^1H NMR spectrum.



98a **(E)-110a (>96 : <4) (Z)-110a** **(39)**

Table 8: The Friedel-Crafts reaction of benzene with acetates of Baylis-Hillman adducts as stereodefined β-electrophiles.[a-c]

Acetate of Baylis-Hillman adduct	R	Product	Yield[d] (%)	(E) : (Z) ratio[e]
98a	Ph	**110a**	75	>96 : <4
106	2-$MeOC_6H_4$	**110b**	40	>96 : <4
98c	4-ClC_6H_4	**110c**	85	>96 : <4
98f	n-Hex	**110d**	65	80 : 20

a) All reactions were carried out in 5 mM scale of acetate with benzene (10 mL) in presence of anhydrous $AlCl_3$ (8 mM) at room temperature (except the case of **98f**, which requires reflux temperature for 10 h) for 1.5-2 h.

b) Satisfactory spectral [IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz)] data were obtained for all products **110a-110d**. ^1H NMR and ^{13}C NMR spectra of all products, except **110a**, indicate the presence of ~ 10% of unidentified impurities.

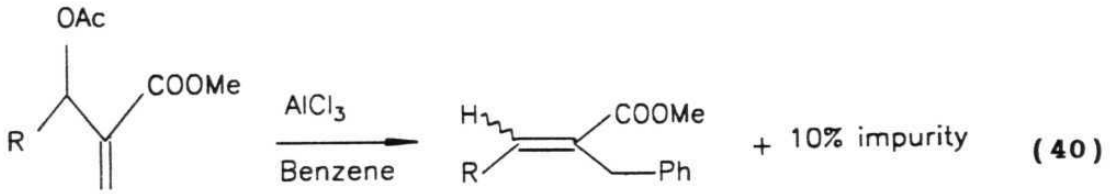
c) Stereochemical assignments were based on ^1H NMR spectra.

d) Isolated yield of the products after column chromatography (1% ethyl acetate in hexane).

e) Determined by ^1H NMR spectral analysis.

The singlets at δ 7.94 and δ 6.64 (in the ratio >96 : <4) are due to olefinic protons of (E)- and (Z)-isomers respectively.

In order to generalize this reaction, we have used a variety of acetates of Baylis-Hillman adducts **106, 98c, 98f** as β-electrophiles in the Friedel-Crafts reaction with benzene in presence of anhydrous $AlCl_3$ (eq.40). The resultant products **110b-110d** were



106, 98 **E/Z = 80->96/20-<4** **110b-110d** **(40)**

R = 2-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, n-C$_6$H$_{13}$

obtained in 75-84% yield and in high (E)-stereoselectivity (E/Z = 80->96/20-<4) (Table 8) The stereochemistry of all these products was assigned on the basis of ^{1}H NMR spectral analysis. Unfortunately, all these products were contaminated with ~ 10% of unknown impurity as indicated by ^{1}H NMR and ^{13}C NMR spectra. Our attempts to purify these molecules either by column chromatography or by distillation under reduced pressure resulted in failure.

With a view to examine the potential of 3-acetoxy-2-methylenealkanenitriles (**100**) as a stereodefined β-electrophile we have examined the reaction of 3-acetoxy-2-methylene-3-phenylpropanenitrile (**100a**, R = Ph) with benzene in the presence of anhydrous

Table 9: The Friedel-Crafts reaction of benzene with acetate of Baylis-Hillman adducts as stereodefined β-electrophile.[a-c]

Acetate of Baylis-Hillman adduct	R	Product	Yield[d] (%)	(Z) : (E) ratio
100a	Ph	**111a**	75	98 : 2[e]
100b	4-MeC_6H_4	**111b**	74	100 : 00
100c	4-ClC_6H_4	**111c**	85	100 : 00
100d	n-Pr	**111d**	46	>96 : <4

a) All reactions were carried out in 5 mM scale of acetate with benzene (10 mL) in presence of anhydrous $AlCl_3$ (8 mM) at room temperature (except the case of **100d** which requires reflux temperature for 40 h) for 1.5-2 h.

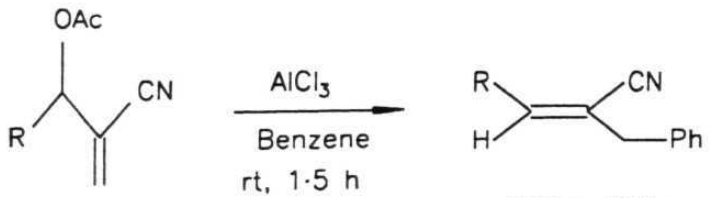
b) Satisfactory spectral [IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz)] data were obtained for all products **111a-111d**.

c) Stereochemical assignments were based on ^{13}C NMR spectra.

d) Isolated yield of the products after column chromatography (1% ethyl acetate in hexane).

e) ^{13}C NMR indicate the presence of ~ 2% of (E)-isomer.

$AlCl_3$. The desired product, 2-benzyl-3-phenylprop-2-enenitrile (**111a**), was obtained in 75% yield and in ›98% (Z)-stereoselectivity (eq.41). The structure of this molecule was confirmed by IR, ^1H NMR and ^{13}C NMR spectral analyses. The (Z)-stereochemistry was assigned on the basis of ^{13}C NMR spectral analysis. The peak at δ 42.26 (downfield) is attributed to the allylic carbon of (Z)-isomer and very low intensity peak at δ 35.42 is due to allylic carbon of (E)-isomer.

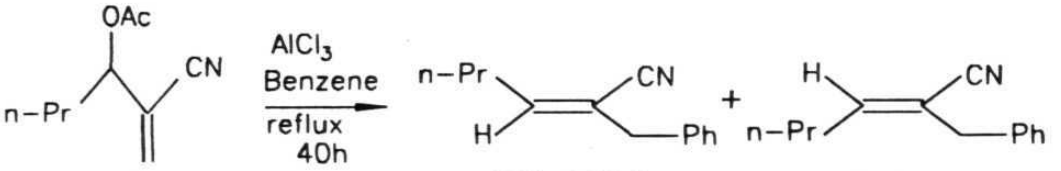


100a-100c **111a-111c** **(41)**

R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$

Encouraged by this reaction, we have subjected **100b, 100c** to Friedel-Crafts reaction with benzene in presence of anhydrous $AlCl_3$. The resulting products **111b, 111c** were found to be stereochemically pure [(Z)-stereochemistry] and in high yields (Table 9). The structure of these molecules were confirmed by IR, ^1H NMR and ^{13}C NMR spectral data. The stereochemistry was assigned on the basis of chemical shift values of allylic carbon in ^{13}C NMR spectra.

When the similar reaction was extended to 3-acetoxy-2-methylenehexanenitrile (**100d**), we have found that the reaction requires longer duration (40 h) and high temperature (refluxing benzene) (eq.42). The resultant product, 2-benzylhex-2-enenitrile (**111d**), was obtained in poor yield (40%) but in high (Z)-stereoselectivity (Z/E = 96/4) as indicated by ^{1}H NMR and ^{13}C NMR spectral analyses.

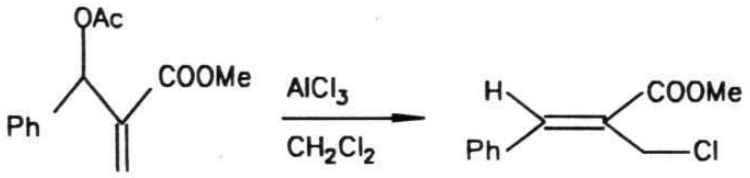


100d **(Z)-111d** **(E)-111d**

(>96 : <4) **(42)**

It occurred to us that in the absence of aromatic molecule the acetates of Baylis-Hillman adducts containing aryl moiety, in principle, would undergo intramolecular Friedel-Crafts reaction and thus provide indene-2-carboxylate molecules.

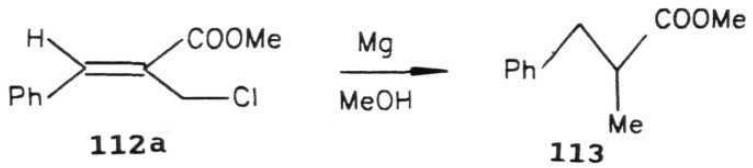
Accordingly, we have treated methyl 3-acetoxy-2-methylene-3-phenylpropanoate **98a** with anhydrous $AlCl_3$ in dry CH_2Cl_2 (eq.43). The reaction is very clean and afforded the product in



98a **112a** **(43)**

excellent yield. Spectral (^{1}H NMR) analysis of this molecule however indicates the absence of expected indene derivative. Instead, stereomerically pure methyl (2Z)-2-(chloromethyl)-3-phenylprop-2-enoate (**112a**) was formed in high yield. The structure of this molecule was established by IR, ^{1}H NMR, ^{13}C NMR spectral analyses and elemental analysis. The stereochemistry was established by ^{1}H NMR spectral analysis.

The structure of the molecule **112a** was confirmed further by converting it in to the corresponding methyl 2-methyl-3-phenylpropanoate (**113**) ***via*** reductive dechlorination by magnesium in absolute methanol (eq.44).



112a **113** **(44)**

To understand the generality of this reaction, a variety of acetates of Baylis-Hillman adducts **98b, 98c, 116, 117** (**116** and **117** were obtained by treating methyl 3-(2,4-dichlorophenyl)-3-hydroxy-2-methylenepropanoate (**114**) and methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (**115**), with acetyl chloride in the presence of pyridine respectively) were treated with anhydrous $AlCl_3$ in dry CH_2Cl_2 (eq.45). The resulting methyl (2Z)-2-chloromethyl-3-**arylprop-2-enoates 112b-112e** were found to be stereo-

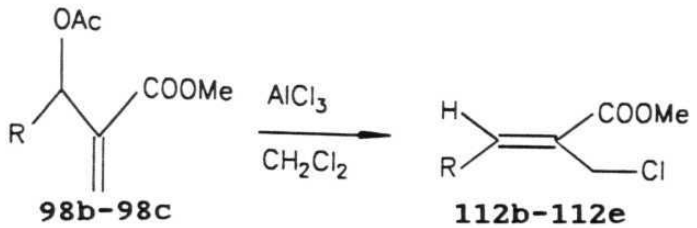
Table 10: Synthesis of methyl [2Z]-2-(chloromethyl)alk-2-enoates[a,b]

Acetate of Baylis-Hillman adduct	R	Product	Yield[c] (%)
98a	Ph	**112a**	72
98b	4-MeC_6H_4	**112b**	56
98c	4-ClC_6H_4	**112c**	78
116	2,4-$Cl_2C_6H_4$	**112d**	70
117	2-$NO_2C_6H_4$	**112e**	66

a) All reactions were carried out in 5 mM scale of acetate with anhydrous $AlCl_3$ (8 mM) in CH_2Cl_2 at room temperature for 1.5-2 h

b) Satisfactory spectral [IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz)] data and elemental analyses were obtained for all products **112a-112e**. ^1H NMR and ^{13}C NMR spectra indicate the absence any (E)-isomer.

d) Isolated yield of the products after column chromatography (1% ethyl acetate in hexane).



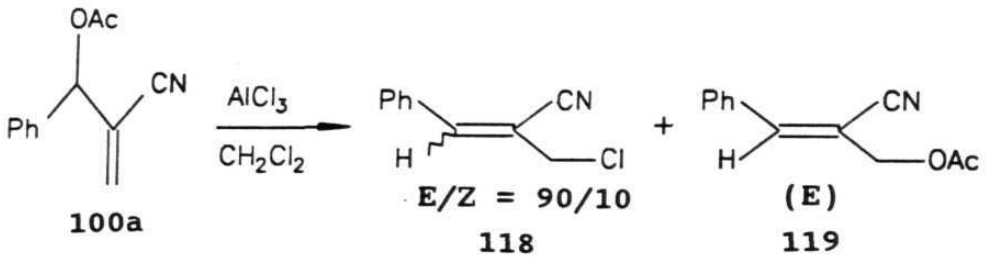
98b-98c **112b-112e** **(45)**

116,117

R = 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_4$, 2-O$_2$NC$_6$H$_4$

chemically pure and were obtained in excellent yields (Table 10). The structures of these molecules were confirmed by IR, ^{1}H NMR (Fig.16 ^{1}H NMR spectrum of **112b**), ^{13}C NMR spectral data and elemental analyses. The (Z)-stereochemistry was assigned to all these molecules on the basis of ^{1}H NMR spectra.

With a view to examine the possibility of intramolecular Friedel-Crafts reaction of acetates of Baylis-Hillman adducts **100** (aryl substituted), we have treated 3-acetoxy-2-methylene-3-phenylpropanenitrile **100a** with anhydrous $AlCl_3$ in dry CH_2Cl_2 (eq.46). This reaction also does not provide indene derivative instead isomeric mixture of (2E)-2-(chloromethyl)3-phenylprop-2-2-enenitrile **118** (E/Z = 90/10) and (2E)-2-acetoxymethyl-3-phenyl-propanenitrile **119** were obtained in 30% and 38% yield respectively. The structure of these molecules was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral analyses. The stereochemistry was assigned on the basis of ^{13}C NMR chemical shift values of allylic carbon.



100a **E/Z = 90/10** **118** **(E)** **119** **(46)**

The failure of intramolecular Friedal-Crafts reaction of these substrates can be attributed to the presence of electron withdrawing groups (CN, COOMe) which destabilizes carbonium ion system leading to the formation of indene derivatives.

We believe this investigation *i. e.*, utility of acetates of Baylis-Hillman adducts as stereodefined β-electrophiles for Friedal-Crafts reaction is just a beginning and it requires further investigation to understand the pathway which is, currently, under progress in our laboratory.

Conclusion

We have studied, systematically, the chiral induction efficiency of various chiral auxiliaries **66a-66e** to achieve our first objective "enantioselective synthesis of mikanecic acid" and thus optically active mikanecic acid was obtained in 92% ee (after single crystallization of the Diels-Alder adduct **69e**). We have developed a simple and convenient methodology for the synthesis of both the enantiomers of [(R,R)- and (S,S)-]

trans-2-nitroxycyclohexan-1-ol, hitherto unknown molecules. A new class of functionalized trisubstituted alkenes (**97**) with defined stereochemistry was developed ***via*** the Johnson-Claisen rearrangement of the Baylis-Hillman adducts **90** and **96**. We have developed a mild and efficient methodology for the synthesis of methyl (2Z)-2-bromomethylalk-2-enoates (**99**) and 2-bromomethylalk-2-enenitriles (**101**) using acetates of Baylis-Hillman adducts and $MgBr_2$ We have also developed a simple and convenient methodology for the stereoselective synthesis allylphosphonates, which are attractive precursors for the synthesis of synthetically useful substituted-1,3-butadiene derivatives using acetates of Baylis-Hillman adducts. We have demonstrated the utility of the acetates of Baylis-Hillman adducts as stereodefined β-electrophiles in the Friedel-Crafts reaction. We believe that "THE BAYLIS-HILLMAN ADDUCTS" will prove to be novel source for stereoselective processes in the years to come.

EXPERIMENTAL

Melting points: All melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected.

Boiling points: Boiling points refer to the temperatures measured using short path distillation units and are uncorrected.

Elemental analysis: Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyzer.

Infrared spectra: Infrared spectra were recorded on Perkin-Elmer model 1310 or 297 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 $cm.^{-1}$ Solid samples were recorded as KBr wafers and liquid samples as film between NaCl plates.

Nuclear magnetic resonance spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on either on BRUKER-AC-200 spectrometer or JEOL-FX-100 spectrometer. Wherever we have made specification, *i.e.*, ^{1}H NMR (100 MHz) and ^{13}C NMR (25 MHz), those spectra were recorded on JEOL-FX-100 spectrometer while other spectra were recorded on BRUKER-AC-200 spectrometer. Phosphorus-31 spectra were recorded on BRUKER-AC-

200 spectrometer. ^{1}H NMR Spectra for all the samples [except **59a-59e** and **59e'** which were measured in dimethyl sulfoxide-d_6 (DMSO-d_6) were measured in chloroform-d with TMS (δ = 0 ppm) as internal standard. ^{13}C NMR Spectra for all the samples [except **59a-59e** and **59e'** which were measured in dimethyl sulfoxide-d_6 (DMSO- d_6)] were measured in chloroform-d with its middle peak of the triplet (δ = 77.10 ppm) as internal standard. ^{31}P NMR Spectra for all the samples were measured in chloroform-d with 85% H_3PO_4 (δ = 0) as external standard. Spectral assignments are as follows: (1) Chemical shifts are expressed on δ scale downfield from the signal for internal standard, (2) Standard abbreviation for multiplicity, i.e. s = singlet, d = doublet, t = triplet, q = quartet, quint = quint, sext = sextet, sept = septet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, br = broad, (3) Number of hydrogens integrated for the signal, (4) Coupling constant J in Hertz.

Optical rotations: Optical rotations were measured on Jasco DIP 370 digital polarimeter at the wavelength of the sodium D-line (589 nm) and at ambient temperatures.

Chromatography: Analytical thin layer chromatography (TLC) was performed on glass plates (7x2 cm) coated with Acme's silica gel G or GF 254 (250 mμ) containing 13% calcium sulphate as binder.

The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using Acme's silica gel (100-200 mesh). High pressure liquid chromatography (HPLC) analysis was carried out on Shimadzu LC-10AD Chromatopac equipped with SPD-10A UV-VIS detector using HPLC grade solvents. Enantiomeric purities were determined using chiral column, CHIRALCEL OD (25 cm), supplied by Daicel, Jpn.

General: All the solvents used were dried and distilled using suitable drying agents before use. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. All reactions were monitored by TLC.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohex-1-yl acrylate (67a):

[(l)-Menthyl acrylate]:

This was prepared according to the literature procedure.[93]

To a stirred solution of (l)-menthol (**66a**) (4.68 g, 30 mM), acryloyl chloride (3.7 mL, 45 mM), 4-DMAP (10 mg) in dry dichloromethane (30 mL) at $0^{o}C$, triethylamine (6.3 mL, 45 mM) was added slowly. After stirring one hour at room temperature, the reaction mixture was diluted with ether (50 mL) and washed, successively, with 2N HCl solution, water and saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and the residue was distilled under reduced pressure to give **67a** as colorless liquid.

Yield : 4.22 g (67%)

b.p. : 72-73^{o}C/4 mm (lit.[134] b.p. 78-80^{o}C/5 mm)

$[\alpha]_D^{22}$: -79.8^{o} (c 9.0, dioxane)

: [lit.[134] $[\alpha]_D^{20}$ -80.2^{o} (c 10, dioxane)]

IR (neat) : 1634, 1724 cm^{-1}

^1H NMR : δ 0.72-2.14 (m, 18H), 4.76 (dt, 1H, J = 10.6 Hz and 4.5 Hz), 5.82 (dd, 1H, J = 9.2 Hz and 1.6 Hz), 6.12 (dd, 1H, J = 15.6 Hz and 9.2 Hz), 6.41 (dd, 1H, J = 15.6 Hz and 1.6 Hz).

^{13}C NMR : δ 16.53 20.69, 22.01, 23.77, 26.49, 31.47, 34.40, 41.00, 47.23, 74.28, 129.20, 129.87, 165.60.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohex-1-yl 3-hydroxy-2-methylenebutanoate (68a):

A mixture of (l)-menthyl acrylate (**67a**) (5.25 g, 25 mM) acetaldehyde (5 mL) and DABCO (1.12 g, 10 mM) was allowed to react at room temperature for 6 days. Excess acetaldehyde was removed under reduced pressure and the resulting crude material was purified by column chromatography (10% ethyl acetate in hexane) to provide **68a** as viscous liquid.

Yield : 5.65 g (89%)

$[\alpha]_D^{22}$: -73.4^o (c 1.58, MeOH)

IR (neat) : 1620, 1710, 3350 cm^{-1}

^1H NMR : δ 0.76-2.12 (m, 21H), 2.77 (t, 1H, J = 6 Hz, OH), 4.62 (m, 1H), 4.80 (dt, 1H, J = 10 Hz, and 4.2 Hz), 5.77 (s, 1H), 6.17 (s, 1H).

^{13}C NMR (25 MHz) : δ 16.29, 20.64, 21.94, 22.06, 23.47, 26.41, 31.35, 34.17, 40.76, 47.12, 67.01, 74.88, 123.42, 144.36, 166.42.

Di[(1R,2S,5R)-2-isopropyl-5-methylcyclohex-1-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (69a):

To a solution of (1R,2S,5R)-2-isopropyl-5-methylcyclohex-1-yl 3-hydroxy-2-methylenebutanoate (**68a**) (3.81 g, 15 mM) in dichloromethane (10 mL) at 0^oC was added a solution of mesyl chloride (1.2 mL, 15 mM) in dichloromethane (2 mL) followed by dropwise

addition of a solution of triethylamine (8.4 mL, 60 mM) in dichloromethane (5 mL). After stirring 1 h at $0^{o}C$ and 4 h at room temperature the reaction mixture was diluted with ether and washed successively with 2N HCl solution, water, saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and the crude product was purified by column chromatography (2% ethyl acetate in hexane) to afford **69a** as colorless viscous liquid.

Yield : 3 g (85%)

$[\alpha]_D^{22}$: -83.3^{o} (c 2.98, EtOH)

IR (neat) : 1640, 1698 cm^{-1}

^1H NMR : δ 0.65-2.98 (m, 42H), 4.68 (dt, 2H, J = 10 Hz and 4.2 Hz), 5.04-5.22 (m, 2H), 5.76-5.98 (m, 1H), 6.92 (m, 1H).

^{13}C NMR : δ 15.79, 15.93, 16.52, 20.76, 21.99, 23.12, 23.62, 25.95, 26.06, 26.41, 29.62, 31.36, 32.26, 32.52, 34.29, 40.51, 40.99, 47.05, 47.17, 47.35, 47.44, 74.03, 74.70, 114.74, 114.94, 129.99, 136.44, 136.56, 139.81, 140.27, 166.37, 173.61, 173.87.

^{13}C NMR shows that it is a mixture of diastereomers.

(-)-4-Vinylcyclohex-1-ene-1,4-dicarboxylic acid (59a):

[(-)-Mikanecic acid]:

To a solution of 85% KOH (0.57 g, 10 mM) in methanol (4 mL)

di[(1R,2S,5R)-2-isopropyl-5-methylcyclohex-1-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (**69a**) (0.944 g, 2 mM) was added and stirred at room temperature for 12h. Methanol was removed under reduced pressure, and the reaction mixture was diluted with water (10 mL) and washed thoroughly with ether (3 x 10 mL) to remove the chiral auxiliary completely. The aqueous phase was acidified with 2N HCl solution, extracted with ether (3 x 10 mL) and the ethereal extract was dried over anhydrous Na_2SO_4. Evaporation of ether followed by decolorization of the crude solid with animal charcoal afforded **59a** as colorless solid.

Yield : 0.27 g (68%)

m.p. : 236-238^{o}C (m.p. of racemic acid is 239-240^{o}C)[84]

$[\alpha]_D^{22}$: -3.30^{o} (c 1.74, acetone)

IR (KBr) : 1640, 1690, 2600-3300 cm^{-1}

^{1}H NMR (DMSO-d_6) : δ 1.67-2.82 (m, 6H), 5.02-5.28 (m, 2H), 5.76-6.02 (m, 1H), 6.85 (m, 1H), 12.42 (br s, 2H).

^{13}C NMR (DMSO-d_6) : δ 21.58, 29.06, 31.71, 46.53, 114.55, 129.31, 136.78, 140.29, 167.66, 175.21.

Determination of Enantiomeric Purity of 59a:

Methyl 3-hydroxy-2-methylenebutanoate (70):

A mixture of methyl acrylate (4.5 mL, 50 mM), acetaldehyde (5 mL) and DABCO (0.84 g, 7.5 mM) was kept (no stirring is required) at room temperature for 5 days. The reaction mixture was diluted

with ether (125 mL) and was washed sucessively with 2N HCl solution, water and saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and the residue was distilled under reduced pressure to give **70** as colorless liquid.

Yield : 4.94 g (76%)

b.p. : 80-82°C/14 mm

IR (neat) : 1631, 1716, 3424 cm^{-1}

^1H NMR : δ 1.36 (d, 3H, J = 6.6 Hz), 2.72 (br, 1H, OH) 3.77 (s, 3H), 4.62 (q, 1H, J = 6.6 Hz), 5.82 (s, 1H), 6.20 (d, 1H J = 0.6 Hz).

(±)-Dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (60):

To an ice-cooled solution of methyl 3-hydroxy-2-methylene-butanoate (**70**) (2.6 g, 20 mM) and mesyl chloride (MsCl) (1.6 mL, 20 mM) in dichloromethane (15 mL) was added a solution of tri-ethylamine (11.2 mL, 80 mM) in dichloromethane (10 mL) dropwise. After stirring 3 h at room temperature, the reaction mixture was taken up in ether, washed successively with 2N HCl solution, water, and $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and the residue was distilled under reduced pressure to give **60** as yellow oil.

Yield : 3.80 g (85%)

b.p. : 150°C/5mm

IR (neat) : 1640, 1710 cm^{-1}

^1H NMR : δ 1.72-1.92 (m, 1H), 2.04-2.18 (m, 1H) 2.28-2.44 (m 3H), 2.72-2.92 (m, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 5.02-5.20 (m, 2H), 5.78-5.98 (m, 1H), 6.97 (m, 1H).

^{13}C NMR : δ 21.71, 29.46, 32.17, 47.21, 51.47, 52.16, 115.10, 129.37, 136.90, 139.41, 167.20, 174.68.

Dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (60a): [Dimethyl ester of (-)-mikanecic acid]:

A solution of (-)-mikanecic acid (**59a**) (0.196 g, 1 mM) in thionyl chloride (3 mL) was stirred for 4 h at room temperature. Excess thionyl chloride was removed under reduced pressure and absolute methanol (2 mL) was added to the resultant crude diacid chloride. After stirring 15 min the reaction mixture was concentrated and the crude product thus obtained was purified by column chromatography (2% ethyl acetate in hexane) to give dimethyl ester **60a** of (-)-mikanecic acid (**59a**) in 75% yield (0.17 g).

IR, ^1H NMR and ^{13}C NMR spectra of this molecule were identical to that of corresponding racemic analog **60**.

HPLC analysis (column: CHIRALCEL OD; eluent : 2% isopropyl alcohol in hexane; flow rate (R_f) = 0.5 mL/min, UV detection limit λ_{max} = 240 nm) of dimethyl ester **60** of (±)-mikanecic acid (**59**) showed two well resolved peaks arising from both enantiomers (retention time (R_t) = 17.35 min and 22.06 min) in approximately

equal integration. In addition to these two peaks, there appeared two small peaks (~ 3%) with equal integration (retention time (R_t) ~ 18.05 min and 20.15 min). These small peaks may be attributed to the presence of regiomeric (R)- and (S)-enantiomers.

Similar HPLC analysis of the above diester **60a** showed two peaks (retention time (R_t) = 18.40 min. and 23.49 min.) in the integration ratio of 37.72 and 62.27 indicating that the enantiomeric purity of **59a** is 25%.

(±)-*trans*-2-Phenoxycyclohexan-1-ol (73):

This was prepared according to the literature procedure described for *trans*-2-(2-naphthyloxy)cyclohexan-1-ol.[135]

To a stirred solution of sodium phenoxide (300 mM) in water (50 mL) [prepared from NaOH (12 g, 300 mM) and phenol (26.4 mL, 300 mM] cyclohexene oxide (10.1 mL, 100 mM) was added slowly at reflux temperature. After 2h, the reaction mixture was allowed to cool to room temperature. The solid obtained was filtered, washed thoroughly with 2N NaOH solution, water and was recrystallized from hexane to give **73** as white crystalline solid.

Yield : 15 g (78%)

m.p. : 81-82^{o}C (lit.[96] m.p. 82^{o}C)

IR (KBr) : 3450 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.21-2.24 (m, 8H), 2.53 (s, 1H, OH), 3.74 (m, 1H) 3.96 (m, 1H), 6.92-7.32 (m, 5H).

^{13}C NMR (25 MHz) : δ 23.94, 29.18, 32.06, 73.41, 82.24, 116.47, 121.36, 129.65, 158.00.

Analysis for calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39

Found: C, 74.94; H, 8.40.

(±)-*trans*-1-Acetoxy-2-phenoxycyclohexane (73a):

To a stirred solution of (±)-*trans*-2-phenoxycyclohexan-1-ol (**73**) (19.2 g, 100 mM), pyridine (16.2 mL, 200 mM) and 4-DMAP (15 mg) in dichloromethane was added acetic anhydride (18.9 mL, 200 mM) dropwise at room temperature. After 2h, the reaction mixture was poured into ice-cold 2N HCl solution and extracted with ether (2 x 100 mL). The combined ethereal extract was washed with aqueous $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by distillation of the residue under reduced pressure afforded **73a** as colorless oil.

Yield : 22 g (94%)

b.p. : 126-128°C/1.4 mm

IR (neat) : 1617, 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.20-2.22 (m, 11H), 4.22 (m, 1H), 4.96 (m, 1H), 6.84-7.41 (m, 5H).

^{13}C NMR (25 MHz) : δ 21.06, 23.01, 29.70, 74.24, 77.70, 116.41, 121.12, 129.53, 158.47, 170.51.

Biocatalytic (PLAP) resolution of (±)-*trans*-1-acetoxy-2-phenoxy-cyclohexane (73a):

(1S,2S)-2-Phenoxycyclohexan-1-ol (66b)

Enzymatic hydrolysis was carried out according to the procedure developed in our laboratory.[95]

To a stirred K_2HPO_4-KH_2PO_4 buffer solution (500 mL, 0.5 M, pH 8.0), an ethereal (100 mL) solution of *trans*-1-acetoxy-2-phenoxy-cyclohexane (**73**) (23.4 g, 100 mM) and pig liver acetone powder (PLAP) (20g) were added. After stirring for 6 days (conversion ratio 56 : 44) at room temperature, the reaction was quenched by acidification (p^H 4.0) with 2N HCl solution. To this NaCl and ether (200 mL) were added and the mixture was stirred for 30 min. The PLAP residue was removed by filtration with suction and the layers were separated and the aqueous phase was extracted with ether (2 x 100 mL). The combined ethereal extract was dried over anhydrous Na_2SO_4, concentrated and the crude material, thus obtained, was purified by column chromatography (5% ethyl acetate in hexane) to afford unhydrolyzed (+)-acetate **74** as yellow oil in 93% (9.6 g) yield and (-)-alcohol **71** as colorless solid in 82% (8.81 g) yield.

The unhydrolyzed (+)-acetate **74** (8.81 g, 41 mM) was stirred with 85% KOH in methanol (50 mL) at room temperature for 2h. Methanol was distilled off and reaction mixture was acidified with 2N HCl solution and extracted with ether (3 x 50mL). The

ethereal extract was dried over anhydrous Na_2SO_4, and concentrated. The crude solid thus obtained was recrystallized from hexane to give **66b** as colorless crystals.

Yield : 6.69 g (85%)

$[\alpha]_D^{22}$: $+80.4^o$ (c 1.43, MeOH), >99% ee, [conf.1S,2S]

[lit.[95] -79.16^o (c 0.86, MeOH) ee 98%, conf.(1R,2R)]

Analytical data (m.p. IR, ^1H NMR and ^{13}C NMR spectra) of this molecule were identical with that of **73**.

HPLC analysis of racemic alcohol **73** showed two peaks in 1:1 ratio (column : CHIRALCEL OD, eluent : 5% isopropyl alcohol in hexane, flow rate (R_f) : 0.5 mL/min; retention time (R_t) : 18.72 and 21.64 min) due to (R,R) and (S,S) enantiomers. Similar analysis of (-)-alcohol **66b** showed only one peak (R_t : 22.35 min) indicating that its enantiomeric purity is >99%.

(1S,2S)-2-Phenoxycyclohex-1-yl acrylate (67b):

It was obtained, as a colourless liquid, by the action of acryloyl chloride on (1S,2S)-2-phenoxycyclohexan-1-ol (**66a**) in the presence of triethylamine following the similar procedure described for compound **67a**.

Yield : 95%

$[\alpha]_D^{22}$: +99.86 (c 1.48, dichloromethane)

IR (neat) : 1590, 1710 cm^{-1}

^1H NMR : δ 1.24-2.22 (m, 8H), 4.28 (dt, 1H, J = 9 Hz and 4

Hz), 5.05 (m, 1H), 5.72 (dd, 1H, J = 10.2 Hz and 1.8 Hz), 6.04 (dd, 1H, J = 17.4 Hz and 10.2 Hz), 6.31 (dd, 1H, J = 17.4 Hz and 1.8 Hz), 6.88-7.02 (m, 3H), 7.18-7.30 (m, 2H).

^{13}C NMR : δ 22.80, 22.94, 29.40, 29.57, 74.06, 77.95, 116.41, 121.11, 128.69, 129.43, 130.47, 158.33, 165.46.

(1S,2S)-2-Phenoxycyclohex-1-yl 3-hydroxy-2-methylenebutanoate (68b):

It was obtained, as colorless viscous liquid, by the DABCO catalyzed coupling of (1S,2S)-2-phenoxycyclohex-1-yl acrylate (**67b**) with acetaldehyde following the similar procedure described for compound **68a**.

Time : 5 days

Yield : 72%

$[\alpha]_D^{22}$: +50.6^o (c 0.99, dichloromethane)

IR (neat) : 1585, 1705, 3370 cm^{-1}

^{1}H NMR : δ 1.08-2.22 (m, 11H), 2.71 (dist. t, 1H, OH), 4.29 (m, 1H), 4.48-4.62 (m, 1H), 4.98-5.12 (m, 1H), 5.71 (s, 1H), 6.04 (s, 1H), 6.84-6.98 (m, 3H), 7.14-7.30 (m, 2H).

^{13}C NMR (25 MHz) : δ 21.82, 22.06, 22.59, 22.76, 29.17, 29.41, 66.42, 66.74, 74.42, 75.71, 116.24, 121.06, 123.71, 129.42, 144.01, 158.06, 165.95.

Di[(1S,2S)-2-phenoxycyclohex-1-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (69b):

It was obtained, as pale yellow viscous liquid, by the treatment of (1S,2S)-2-phenoxy-cyclohex-1-yl 3-hydroxy-2-methylenebutanoate (**68b**) with mesyl chloride in the presence of triethylamine following similar procedure described for the molecule **69a**.

Yield : 92%

$[\alpha]_D^{22}$: +34.7° (c 1.93, acetone)

IR (neat) : 1590, 1698 cm^{-1}

^1H NMR : δ 1.16-2.78 (m, 22H), 4.14-4.24 (m, 2H), 4.84-5.08 (m, 4H), 5.60-5.84 (m, 1H), 6.68 and 6.78 (2m, 1H), 6.85-6.98 (m, 6H), 7.14-7.32 (m, 4H).

^{13}C NMR : δ 21.53, 21.62, 22.84, 29.21, 29.49, 32.23, 47.30, 73.66, 73.84, 74.24, 74.47, 115.03, 115.12, 116.01, 116.46, 120.99, 129.42, 129.63, 137.05, 139.37, 139.56, 157.98, 158.39, 166.18, 173.69.

^{13}C NMR indicates that it is a mixture of diastereomers.

4-Vinylcyclohex-1-ene-1,4-dicarboxylic acid (59b): [Mikanecic acid]:

It was obtained by the hydrolysis of di[(1S,2S)-2-phenoxy-cyclohex-1-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (**69b**) with methanolic KOH in 69% yield following similar procedure described for the molecule **59a**.

This molecule has identical spectral data (IR, ^{1}H NMR, and ^{13}C NMR) as that of (-)-mikanecic acid **59a**.

Determination of enantiomeric purity of 59b:

Dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (60b):

[Dimethyl ester of mikanecic acid]:

This was prepared by treating the mikanecic acid **59b** with $SOCl_2$ followed by methanol according to the procedure described for analogous dimethyl ester **60a** of (-)-mikanecic acid (**59a**).

HPLC analysis of the above diester **60b** showed two peaks (retention time (R_t) = 18.63 min and 23.38 min) in the integration ratio of 44.76 and 55.28 indicating that enantiomeric purity of mikanecic acid **59b** is 11%.

(±)-*trans*-2-Nitroxycyclohexan-1-ol (76):

A mixture of cyclohexene oxide (10.1 mL, 100 mM) in *tert*-butanol (100 mL) was stirred in the presence of anhydrous ammonium cerium (IV) nitrate (CAN) (13.70 g, 25 mM) at room temperature. After 3h, the *tert*-butanol was removed under reduced pressure and the residue was diluted with water and extracted with ether (3 x 75 mL). The combined ethereal extract was dried over anhydrous Na_2SO_4, concentrated and the resulant crude liquid was distilled under reduced pressure to give **76** as a pale yellow oil.

Yield : 10.78 g (67%)

b.p. : 110-111^{o}C/7 mm (lit.[98] 100^{o}C/3mm)

IR (neat) : 1628, 3381 cm^{-1}

^{1}H NMR : δ 1.18-1.56 (m, 4H), 1.64-1.92 (m, 2H), 2.02-2.32 (m, 2H), 2.51 (br s, 1H, -OH) 3.56-3.78 (m, 1H) 4.72-4.92 (m, 1H).

^{13}C NMR : δ 23.54, 23.83, 28.81, 33.19, 70.50, 87.33.

Analysis calculated for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69

Found : C, 44.68; H, 6.86; N, 8.66.

2-Isopropyloxy-2-phenylethan-1-ol (77):

This was prepared by the action of CAN on cyclohexene oxide in isopropyl alcohol following the similar procedure described for the molecule **76**.

Yield : 68%

IR (neat) : 1635, 3420 cm^{-1}

^{1}H NMR : 1.14 (d, 3H, J = 6.6 Hz), 1.20 (d, 3H, J = 6.6 Hz), 3.24 (s 1H, OH), 3.48-3.92 (m, 3H), 4.54 (m, 1H), 7.22-7.54 (m, 5H).

(±)-*trans*-1-Acetoxy-2-nitroxycyclohexane (79):

It was obtained, as colorless liquid, by the action of acetic anhydride and pyridine on racemic *trans*-2-nitroxycyclohexan-1-ol (**76**) in presence of catalytic amount of 4-DMAP following similar procedure described for the molecule **73a**.

Yield : 87%

b.p. : 82°C/3 mm

IR (neat) : 1630, 1735 cm^{-1}

^1H NMR : δ 1.18-2.18 (m, 8H), 1.99 (s, 3H), 4.68-4.84 (m, 1H), 4.88-5.08 (m, 1H).

^{13}C NMR : δ 20.49, 22.68, 23.03, 28.45, 29.97, 71.53, 82.30, 169.54.

Biocatalytic (PLAP) hydrolysis of (±)-*trans*-1-acetoxy-2-nitroxy-cyclohexane (79):

Biocatalytic hydrolysis of (±)-*trans*-1-acetoxy-2-nitroxycyclohexane (**79**) (20.3 g, 100 mM) with PLAP (20 g) was carried out in biphasic media (ether/ phosphate buffer) according to the similar procedure described for the molecule **73a**. Usual work up followed by column chromatography (4% ethyl acetate in hexane) of the crude material afforded (-)-alcohol **66c** and (+)-acetate **80** as colorless liquids.

Reaction time : 72 h

Conversion ratio : 39 : 61 (based on isolated yields)

(a) (-)-Alcohol 66c :

The (-)-alcohol, thus obtained, was crystallized from hexane at 0°C to afford the pure (-)-alcohol as colorless crystals.

Yield : 5.65 g (90%)

m.p. : 55-56°C

$[\alpha]_D^{22}$: -71.5^{o} (c 1.17, CH_2Cl_2)

This molecule has identical spectral data (IR, ^1H NMR, and ^{13}C NMR) as that of racemic *trans*-2-nitroxycyclohexan-1-ol (**76**).

(b) (+)-Acetate 80 :

Yield : 10.52 g (85%)

b.p. : $84^{o}C$/2.5 mm

$[\alpha]_D^{22}$: $+16.8^{o}$ (c 1.70, acetone)

Determination of enantiomeric purity of 66c:

(±)-*trans*-1-(2-methoxyphenyl)carbonyloxy-2-nitroxycyclohexane (81):

To a solution of racemic *trans*-2-nitroxycyclohexan-1-ol (**76**) (0.161 g, 1 mM), 2-methoxybenzoic acid (0.152 g, 1 mM) and 4-DMAP (2 mg) in dry dichloromethane, a solution of dicyclohexylcarbodiimide (DCC) (0.23 g, 1.1 mM) in dichloromethane (2 mL) was added dropwise at $0^{o}C$ with stirring. After the addition the stirring was continued at room temperature for 1.5 h. Then the precipitated dicyclohexyl urea was filtered out. The filtrate was diluted with ether, washed successively with aqueous oxalic acid solution, aqueous $NaHCO_3$ solution and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (1% ethyl acetate in hexane) to afford **81** as viscous liquid.

Yield : 0.171 g (58%)

IR (neat) : 1630, 1720 cm^{-1}

^{1}H NMR : δ 1.40-1.94 (m, 6H), 2.16-2.48 (m, 2H), 3.87 (s 3H) 5.02-5.30 (m, 2H), 6.92-7.04 (m, 2H), 7.40-7.52 (m, 1H), 7.68-7.78 (m, 1H).

^{13}C NMR : δ 22.83, 23.26, 28.71, 30.11, 55.77, 72.16, 82.28, 112.01, 119.83, 120.07, 131.44, 133.62, 159.15, 165.36.

HPLC analysis (column: CHIRALCEL OD; eluent : 5% isopropyl alcohol in hexane; flow rate (R_t) : 0.5 mL/min, UV detection limit λ_{max} = 254 nm) of racemic **81** showed two well resolved peaks, (retention time (R_t) = 20.15 and 22.29 min.) arising from two enantiomers, in approximately equal integration.

(-)-*trans*-1-(2-methoxyphenyl)carbonyloxy-2-nitroxycyclohexane (82):

This was obtained by the treatment of (-)-*trans*-2-nitroxy-cyclohexan-1-ol (**66c**) with 2-methoxybenzoic acid and DCC in the presence of 4-DMAP following similar procedure described for its racemic analog **81**.

IR, ^{1}H NMR and ^{13}C NMR spectra of **82** were identical with that of racemic **81**.

HPLC analysis (column: CHIRALCEL OD; eluent : 5% isopropyl alcohol in hexane; flow rate (R_f) : 0.5 mL/min, UV detection limit λ_{max} = 254 nm) of this molecule **82** showed only one peak (retention time (R_t) = 21.58) indicating that the enantiomeric purity of **66c** is >99%

Assignment of absolute configuration of 66c:

Synthesis of (-)-(R,R)-cyclohexan-1,2-diol (83):

A solution of (-)-*trans*-2-nitroxycyclohexan-1-ol (**66c**) (0.161 g, 1 mM) in ethyl acetate was shaken with 10% Pd/C (10 mg) under hydrogen atmosphere (35 psi) at room temperature in a Parr hydrogenator for 5h. The catalyst was removed by filtration. The filtrate was concentrated and the solid, thus obtained, was recrystallized from hexane to afford **83** as colorless crystalline solid.

Yield : 0.095 g (82%)

m.p. : 111-112^{o}C (lit.[102] m.p. 113-114^{0}C)

$[\alpha]_D^{22}$: -30.1^{o} (c 0.94, $CHCl_3$), 75% ee, [conf. (R,R)]

: [lit[102] -40^{o} (c 0.32, $CHCl_3$), 100% ee, conf (R,R)]

IR (neat) : 3381 cm^{-1}

^{1}H NMR : δ 1.12-1.44 (m, 4H), 1.54-1.71 (m, 2H), 1.80-2.01 (m, 2H), 2.35 (br, 2H, OH), 3.24-3.50 (m, 2H).

^{13}C NMR : δ 24.35, 32.90, 75.77.

(-)-*trans*-2-Nitroxycyclohex-1-yl phenylglyoxylate (84):

To a solution of (-)-*trans*-2-nitroxycyclohexan-1-ol (**66c**) (4.025 g, 25 mM), benzoylformic acid (4.053 g, 27 mM), and 4-DMAP (5 mg) in dichloromethane (45 mL) was added a dilute solution of dicyclohexyl carbodiimide (DCC) (5.57 g, 27mM) in dichloromethane dropwise at 0^{o}C with stirring. After the addition the reaction

mixture was stirred at room temperature for 3 h. The precipitate, dicyclohexyl urea, was removed by filtration. The filtrate was concentrated and the crude material was purified by column chromatography (3% ethyl acetate in hexane) to provide **84** as white crystalline solid.

Yield : 3.36 g (46%)

m.p. : 61-62^{o}C

$[\alpha]_D^{22}$: -21.7^{o} (c 0.56, CH_2Cl_2)

IR (KBr) : 1597, 1635, 1693, 1739 cm^{-1}

^1H NMR : δ 1.18-1.42 (m, 6H), 2.11-2.42 (m, 2H), 4.96-5.18 (m, 1H), 5.28-5.48 (m, 1H), 6.98-8.12 (m, 5H).

^{13}C NMR : δ 23.06, 23.20, 29.04, 30.24, 73.42, 82.35, 129.04, 129.90, 135.09, 163.14, 185.95.

Analysis calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.15; N, 4.77

Found : C, 57.25; H, 5.17; N, 4.75.

(-)-*trans*-2-Nitroxycyclohex-1-yl 2-hydroxy-2-phenyloctanoate (85a):

Anhydrous zinc chloride (1.02 g, 7.5 mM) was added to a stirred solution of n-hexylmagnesium bromide (freshly prepared by the action of n-hexyl bromide (1.1 mL, 7.5 mM) on magnesium turnings (0.182 g, 7.5 mM) in dry ether) in dry ether (15 mL) at 0^{o}C under N_2 atmosphere with stirring. After 3h, the reaction mixture was cooled to -78^{o}C and a solution of (-)-*trans*-2-nitroxycyclohex-1-yl phenylglyoxylate (**84**) (0.73 g, 2.5 mM) in dry

ether (5 mL) was added dropwise. After stirring for 3 h at -78°C, the reaction mixture was brought to room temperature and a saturated solution of aqueous NH_4Cl (10 mL) was added. The ethereal phase was separated, dried over anhydrous Na_2SO_4 and concentrated. The residue, obtained, was purified by column chromatography (5% ethyl acetate in hexane) to provide **85a** as colorless viscous liquid.

Yield : 0.80 g (85%)

$[\alpha]_D^{22}$: -85.9° (c 0.73, CH_2Cl_2)

IR (neat) : 1637, 1732, 3524 cm^{-1}

^1H NMR : δ 0.87 (dist. t, 3H), 1.08-2.32 (m, 18H), 3.73 (s, 1H, OH), 4.74-5.08 (m, 2H), 7.18-7.34 (m, 3H), 7.42-7.62 (m, 2H)

^{13}C NMR : δ 14,00, 22.54, 22.94, 23.23, 23.55, 28.96, 29.35, 30.20, 31.64, 39.12, 73.41, 78.37, 82.00, 125.19, 127.80, 128.25, 141.58, 174.73. These values are due to major diastereomer only.

(R)-2-Hydroxy-2-phenyloctanoic acid (72a):

(1R,2R)-2-Nitroxycyclohex-1-yl 2-hydroxy-2-phenyloctanoate (**85a**) (0.55 g, 1.45 mM) was stirred with 85% KOH in methanol (5 mL) at room temperature for 2h. The reaction mixture was concentrated under reduced pressure, acidifed with ice cold 2N HCl solution and extracted with ether (2 x 10 mL). The ethereal extract was dried over anhydrous Na_2SO_4, concentrated, and the

crude solid was crystallized from ether : hexane (1:3) to provide **72a** as white solid.

Yield : 0.297 g (87%)

m.p. : 98-99^{o}C

$[\alpha]_D^{22}$: -16.3^{o} (c 0.95, EtOH), 85% ee, [conf. R]

: (lit[104] $[\alpha]_D^{22}$ -17^{o} (c 2.2, EtOH), 88% ee, [conf. R])

IR (KBr) : 1724, 2530-3180, 3427 cm^{-1}

^{1}H NMR : δ 0.86 (dist. t, 3H), 1.08-1.54 (m, 8H), 1.92-2.38 (m, 2H), 4.00-5.00 (br, 2H, OH) 7.22-7.46 (m, 3H), 7.52-7.72 (m, 2H).

^{13}C NMR : δ 14.07, 22.62, 23.59, 29.35, 31.66, 39.74, 78.53, 125.56, 128.02, 128.41, 141.11, 180.51.

(-)-*trans*-2-Nitroxycyclohex-1-yl 2-hydroxy-3-methyl-2-phenylbutanoate (85b):

This was obtained, as colorless viscous liquid, by the action of isopropylzinc chloride on (-)-*trans*-2-nitroxycyclohex-1-yl phenylglyoxylate (**84**) following the similar procedure described for the molecule **85a**.

Yield : 90%

$[\alpha]_D^{22}$: -117.1^{o} (c 1.08, dichloromethane)

IR (neat) : 1635, 1728, 3522 cm^{-1}

^{1}H NMR : δ 0.69 & 0.71 (2d, 3H, J = 6.8 Hz), 0.97 & 0.95 (2d, 3H, J = 6.6 Hz), 1.22-2.38 (m, 8H), 2.64 (m,

1H), 3.63 & 3.65 (2s, 1H, OH), 4.84 (m, 1H), 5.04 & 5.12 (2m, 1H), 7.18-7.38 (m, 3H), 7.52-7.68 (m, 2H).

^{13}C NMR : δ 15.77, 16.95, 22.93, 23.22, 29.00, 29.74, 30.16, 35.22, 35.47, 73.41, 74.33, 80.88, 81.99, 125.62, 125.93, 127.64, 128.12, 140.70, 175.00.

The underlined chemical shift (δ) values in ^{1}H NMR and ^{13}C NMR spectra are due to minor diastereomer.

(R)-2-Hydroxy-3-methyl-2-phenylbutanoic acid (72b):

Saponification of (-)-*trans*-2-nitroxycyclohex-1-yl 2-hydroxy-3-methyl-2-phenylbutanoate (**85b**) with methanolic KOH was carried out according to similar procedure described for the molecule **72a** to provide **72b** as white solid.

Yield : 75%

m.p. : 104°C (lit.[105] m.p. 103-105°C)

$[\alpha]_D^{22}$: -25.9° (c 0.85, EtOH), 80% ee, [conf. R]

: (lit.[105] $[\alpha]_D^{25}$ +32.5° (c 2, EtOH) ee >99%, [conf.S])

IR (KBr) : 1720, 2600-3300, 3475 cm^{-1}

^{1}H NMR : δ 0.71 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.0 Hz), 2.66 (sept, 1H, J = 6.0 Hz), 3.28-5.26 (br, 2H, 2 OH), 7.22-7.46 (m, 3H), 7.62-7.76 (m, 2H).

^{13}C NMR : δ 15.77, 17.27, 35.92, 81.10, 125.98, 127.86, 128.30, 140.41, 180.58.

(1S,2S)-1-Acetoxy-2-nitroxycyclohexane (80):

The (±)-acetate **79** (20.3 g, 100 mM) was subjected to bio-catalytic hydrolysis with PLAP following the similar procedure described for the molecule **73** to provide (-)-alcohol and (+)-acetate (**80**).

Reaction time : 6 days

Conversion ratio : 58 : 42 (based on isolated yields)

Recovered (+)-acetate (**80**)

Yield : 7.41 g (87%)

$[\alpha]_D^{22}$: $+23.5^o$ (c 0.77, acetone), >99% ee, conf. (1S,2S)

(-)-Alcohol

Yield : 8.87 g (95%)

$[\alpha]_D^{22}$: -45.4^o (c 1.22, acetone), 64% ee

(1S,2S)-2-Nitroxycyclohexan-1-ol (78):

To a stirred solution of (1S,2S)-1-acetoxy-2-nitroxycyclohexane (**80b**) (1.015 g, 5 mM) in dry methanol (10 mL) was added magnesium powder (0.486 g, 20 mM) at room temperature. After 48h, the reaction mixture was concentrated under reduced pressure, acidified with 2N HCl solution and extracted with ether (2 x 10 mL). The ethereal extract was dried over anhydrous Na_2SO_4, concentrated and the crude material, thus obtained, was recrystallized from hexane at 0^oC to give (+)-alcohol **78** as colorless crystals.

Yield : 0.442 g (55%)

m.p. : 58-59^{o}C

$[\alpha]_D^{22}$: +71.5^{o} (c 0.43, CH_2Cl_2) >99% ee, conf.(1S,2S)

IR, ^{1}H NMR and ^{13}C NMR spectra of this molecule is identical with that of (1R,2R)-2-nitroxycyclohexan-1-ol.

Determination of enantiomeric purity of 78:

(1S,2S)-1-(2-Methoxyphenyl)carbonyloxy-2-nitroxycyclohexane (86):

This was prepared by the reaction of (1S,2S)-2-nitroxycyclohexan-1-ol (**78**) with 2-methoxybenzoic acid and DCC in the presence of catalytic amount of 4-DMAP according to the similar procedure described for the racemic analog **81**.

HPLC analysis (column CHIRALCEL OD; eluent : 5% isopropyl alcohol in hexane; flow rate (R_f) : 0.5 mL/min; UV detection limit λ_{max} = 254 nm) of this molecule showed one peak (retention time (R_t) = 18.89 min.) indicating that **86** is enantiomerically pure.

(S,S)-Cyclohexane-1,2-diol (87):

To a stirred suspension of lithium aluminium hydride (LAH) (0.456 g, 12 mM) in dry ether (7 mL), a solution of enantiomerically pure (1S,2S)-1-acetoxy-2-nitroxycyclohexane (**80b**) (1.015 g, 5 mM) in ether (2 mL) was added slowly at room temperature. After 1 h, saturated aqueous Na_2SO_4 solution was added slowly and

stirred 15 min. The reaction mixture was diluted with ether (10 mL) and the aluminium salts were filtered. The ethereal layer was separated, dried over anhydrous Na_2SO_4 and concentrated. The crude solid, thus obtained, was recrystallized from hexane to afford **87** as white solid.

Yield : 0.35 g (60%)

m.p. : 110-112^{o}C

$[\alpha]_D^{22}$: +32.3^{o} (c 0.98, $CHCl_3$), 80% ee, conf.(S,S)

: [lit.[102] $[\alpha]_D^{20}$ -40^{o} (c 0.32, $CHCl_3$), conf. (R,R)]

IR, ^{1}H NMR and ^{13}C NMR spectra of this molecule were identical with that of (R,R)-cyclohexane-1,2-diol (**83**).

(1R,2R)-2-Nitroxycyclohex-1-yl acrylate (67c):

It was obtained, as colorless liquid, by the action of acryloyl chloride on (1R,2R)-2-nitroxycyclohexan-1-ol (**66c**) following the similar procedure described for the molecule **67a**.

Yield : 90%

IR (neat) : 1628, 1720 cm^{-1}

$[\alpha]_D^{22}$: -32.5^{o} (c 0.19, acetone)

^{1}H NMR : δ 1.18-1.91 (m, 6H), 2.11-2.28 (m, 2H), 4.78-4.94 (m, 1H), 5.00-5.18 (m, 1H), 5.78-5.90 (m, 1H), 5.98-6.18 (m, 1H), 6.30-6.48 (m, 1H).

^{13}C NMR : δ 22.91, 23.31, 28.72, 30.19, 72.14, 82.34, 128.11, 131.24, 165.01.

(1R,2R)-2-Nitroxycyclohex-1-yl 3-hydroxy-2-methylenebutanoate (68c):

It was obtained as colorless, viscous liquid by the coupling reaction of (1R,2R)-2-nitroxycyclohex-1-yl acrylate (**67c**) with acetaldehyde in presence of catalytic amount of DABCO according to the similar procedure described for the molecule **68a**.

Time : 28h.

Yield : 83%

$[\alpha]_D^{22}$: -45.1^o (c 0.92, acetone)

IR (neat) : 1615, 1705, 3350 cm^{-1}

^1H NMR : δ 1.22-2.42 (m, 11H), 2.58 (br s, 1H, OH), 4.52-4.70 (m, 1H), 4.74-5.02 (m, 1H), 5.08-5.22 (m 1H), 5.85 (s, 1H), 6.16 (s, 1H).

^{13}C NMR : δ 22.09, <u>22.22</u>, 22.85, 23.26, <u>23.68</u>, 28.65, 30.06, <u>33.09</u>, 66.53, <u>66.73</u>, <u>70.26</u>, 72.61, 82.25, <u>87.11</u>, 124.37, 143.59, 165.48.

Underlined chemical shift (δ) values in ^{13}C NMR spectra are due to minor diastereomer.

Di[(1R,2R)-2-nitroxycyclohex-1-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (69c):

It was obtained, as viscous liquid, by the treatment of (1R,2R)-2-nitroxycyclohex-1-yl 3-hydroxy-2-methylenebutanoate (**68c**) with mesyl chloride in the presence of triethylamine following

similar procedure described for the molecule **69a**.

Yield : 2.65 g (78%)

$[\alpha]_D^{22}$: -63.03° (c 1.26, acetone)

IR (neat) : 1630, 1710, 1730 cm^{-1}

^1H NMR : δ 1.24-2.94 (m, 22H), 4.72-4.94 (m, 2H), 4.98-5.25 (m, 4H), 5.70-5.94 (m, 1H), 6.84-6.94 (m, 1H).

^{13}C NMR : δ 21.52, 21.63, 22.94, 23.41, 28.68, 28.89, 29.36, 30.03, 30.15, 32.28, 32.47, 47.26, 47.36, 72.30, 72.36, 72.76, 72.79, 82.36, 115.38, 115.50, 129.14, 129.26, 137.53, 137.65, 139.08, 139.26, 165.61, 173.10, 173.22.

The chemical shift (δ) values in ^{13}C NMR spectra indicates that it is a mixture of diastereomers.

(+)-4-Vinylcyclohex-1-ene-1,4-dicarboxylic acid (59c):

[Mikanecic acid]:

It was obtained in 80% yield by the saponification of di[(1R, 2R)-2-nitroxycyclohex-1-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (**69c**) with methanolic KOH following similar procedure described for the molecule **59a**.

Analytical data (m.p., IR, ^1H NMR, ^{13}C NMR) of this molecule were identical to that of (-)-mikanecic acid (**59a**).

Determination of enantiomeric purity of 59c:

Dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (60c):

[Dimethyl ester of mikanecic acid]:

This was prepared by the treatment of mikanecic acid **59c** with $SOCl_2$ followed by methanol according to the procedure described for dimethyl ester (**60c**) of (-)-mikanecic acid (**59c**).

HPLC analysis of the above diester (**60c**) showed two peaks (retention time (R_t) = 17.42 min. and 21.94 min.) in the ratio of 46.13 and 53.86 indicating that enantiomeric purity of the mikanecic acid **59c** is 8%.

Isobornyl sultone (89):

This was prepared according to the literature procedure.[109]

(+)-10-Camphorsulfonic acid (**88**) (18.57 g, 80 mM) in water (40 mL) was added slowly to $NaBH_4$ (6.08 g, 160 mM). Then water was removed under reduced pressure and the resulting reaction mixture was dried at 120°C for 4h. The crude solid obtained was extracted (3-4 times) with absolute ethanol (400 mL) under reflux condition for 30 min. The combined ethanol extracts was concentrated to provide isobornyl alcohol. It was dried at 120°C for 2h and was dissolved in dry pyridine (32 mL). Then p-toluenesulfonyl chloride (p-TsCl) (19.1 g, 100 mM) (freshly recrystallized from hexane) was added with stirring at room temperature. After 5h, the reaction mixture was poured into ice (60 g) and

refrigerated (-20°C) for overnight. Precipitated isobornyl sultone (**89**) was filtered and dried under vacuum.

Yield : 8.29 g (48%)

m.p. : 116-118°C (lit.[109] m.p. 116-118°C)

(1S,2R,4R)-1-[(Diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (66d):

To a stirred solution of bromomagnesium diisopropylamide (240 mM) in THF (prepared by treating ethylmagnesium bromide (240 mM) in THF with a solution of diisopropylamine (31.5 mL, 240 mM) in THF (50 mL)], was added a solution of isobornyl sultone (**89**) (6.48 g, 30 mM) in THF under N_2 atmosphere at room temperature. After stirring 24 h, the reaction mixture was poured into ice-cold 2N HCl (50 mL) solution and solid NaCl (25 g) was added. The reaction mixture was extracted with ether (3x150 mL) and the combined ether extract was dried over anhydrous Na_2SO_4 and concentrated. The resultant crude material was crystallized from hexane at room temperature to give pure alcohol **66d** as pale yellow crystals.

Yield : 5.75 g (60%)

m.p. : 101-103°C (lit.[109] m.p. 102-103°C)

$[\alpha]_D^{22}$: -34.6° (c 1.07, ethanol)

: [lit.[107] $[\alpha]_D^{22}$ -34.4° (c 4.74, ethanol)]

IR (KBr) : 3458 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.82 (s, 3H), 1.04 (s, 3H), 1.32 (d, 12H, J = 7 Hz), 1.64 (m, 7H), 2.64 and 3.24 (AB quartet, 2H, J = 14 Hz), 3.44 (d, 1H, OH), 3.72 (m, 2H), 4.04 (m, 1H).

^{13}C NMR (25 MHz) : δ 19.88, 20.53, 22.17, 22.53, 27.35, 30.94, 38.82, 44.53, 48.53, 50.80, 54.35, 76.59.

(1R,2R,4R)-1-[(Diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl acrylate (67d):

A solution of (1S,2R,4R)-1-[(diisopropylaminosulfonyl)methyl] 7,7-dimethylbicyclo(2.2.1)heptan-2-ol (**66d**) (9.51 g, 30 mM) in dry ether (40 mL) was added to an ethereal solution of ethylmagnesium bromide (30 mM) at 0°C. After 30 min, acryloyl chloride (6.1 mL, 75 mM) in ether (15 mL) was added slowly and stirred for 2h at room temperature. Reaction mixture was filtered and the filtrate was concentrated to provide acrylate **67d**, after crystallization from hexane, as colorless crystalline solid.

Yield : 6.78 g (61%)

m.p. : 118-119°C (lit.[109] m.p. 117-118°C)

$[\alpha]_D^{22}$: -64.7° (c 0.55, acetone)

IR (KBr) : 1628, 1725 cm^{-1}

^{1}H NMR : δ 0.89 (s, 3H), 1.01 (s, 3H), 1.29 (d, 12H, J = 6.8 Hz), 1.10-2.12 (m, 7H), 2.79 and 3.24 (AB quartet, 2H, J = 14 Hz), 3.74 (sept, 2H, J = 6.8 Hz),

5.02-5.12 (m, 1H), 5.72-5.82 (m, 1H), 5.99-6.18 (m, 1H), 6.28-6.42 (m, 1H).

^{13}C NMR (25 MHz) : δ 19.82, 20.23, 22.77, 26.88, 29.76, 39.21, 44.41, 48.06, 49.00, 49.35, 52.82, 78.29, 129.12, 129.77, 164.53.

(1S,2R,4R)-1-[(Diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl 3-hydroxy-2-methylenebutanoate (68d):

It was obtained, as white crystalline solid, by the coupling of (1R,2R,4R)-1-[(diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl acrylate (**67d**) with acetaldehyde in the presence of DABCO following the similar procedure described for the molecule **68a**.

Time : 52 h

Yield : 90%

m.p. : 111-113^{o}C

$[\alpha]_D^{22}$: -55.3^{o} (c 0.65, acetone)

IR (KBr) : 1620, 1705, 3450 cm^{-1}

^{1}H NMR : δ 0.91 (s, 3H), 1.05 (s, 3H), 1.27 (d, 12H, J = 6.8 Hz), 1.36 (d, 3H, J = 6.4 Hz), 1.56-2.16 (m, 8H, 1 OH), 2.72 and 3.28 (AB quartet, 2H, J = 12 Hz), 3.68 (sept, 2H, J = 6.4 Hz), 4.54-4.78 (m, 1H), 5.08-5.24 (m, 1H), 5.74 & 5.82 (2s, 1H), 6.02 & 6.10 (2s, 1H).

^{13}C NMR (25 MHz) : δ 19.92, 20.23, 22.00, 22.47, 26.94, 30.00, 39.23, 44.41, 48.12, 49.06, 49.53, 53.00, 66.41 <u>67.53</u>, 78.53, 122.01, <u>122.65</u>, <u>144.53</u>, 145.24, 165.30.

The underlined chemical shift (δ) values are due to minor diastereomer.

Di[(1S,2R,4R)-1-[(diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (69d):

It was obtained as white solid, after column chromatography (3% ethyl acetate in hexane), by the treatment of (1S,2R,4R)-1-[(diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl 3-hydroxy-2-methylenebutanoate (**68d**) with mesyl chloride in the presence of triethylamine following similar procedure described for the molecule **69a**.

Yield : 70%

m.p. : 88-92^{o}C

$[\alpha]_D^{22}$: -64.37^{o} (c 1.13, acetone)

IR (neat) : 1635, 1645, 1720 cm^{-1}

^{1}H NMR : δ 0.86 (s, 3H), 0.88 (s, 3H), 0.98 (s, 3H), 1.04 (s, 3H), 1.18-2.52 (m, 44H), 2.70 and 3.20 (AB quartet, 2H, J = 12 Hz), 2.76 and 3.26 (AB quartet, 2H, J = 12 Hz), 4.68 (sept, 4H, J = 6.4 Hz), 4.87-4.96 (m, 1H), 5.00-5.12 (m, 3H), 5.72-5.82 (m,

1H), 6.92-6.98 (m, 1H).

^{13}C NMR : δ 20.09, 20.17, 20.45, <u>21.13</u>, 21.59, 21.78, 22.17, 22.63, 23.09, 27.05, <u>29.16</u>, 29.68, 29.95, 30.31, 31.78, <u>32.03</u>, 39.58, 44.40, 44.55, <u>46.77</u>, 47.00, 48.22, 49.14, 49.42, 49.55, 52.91, 53.00, 78.22, <u>79.04</u>, 79.26, <u>115.18</u>, 115.43, 130.15, <u>135.82</u>, 136.01, 138.59, 165.17, 172.94.

The underlined chemical shift (δ) values are due to minor diastereomer.

4-Vinylcyclohex-1-ene-1,4-dicarboxylic acid (59d):

[(+)-Mikanecic acid]:

It was obtained as white solid by the saponification of di-[(1S,2R,4R)-1-[(diisopropylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (**69d**) with methanolic KOH following similar procedure described for the preparation of (-)-mikanecic acid(**59a**).

Time : 12 h

Yield : 64%

m.p. : 234-236^{o}C (m.p. of racemic acid is 239-240^{o}C)[84]

$[\alpha]_D^{22}$: +8.62^{o} (c 0.96, acetone)

This molecule has identical spectral data (IR, ^{1}H NMR, and ^{13}C NMR) as that of (-)-mikanecic acid(**59a**).

Determination of enantiomeric purity 59d:

Dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (60d):

[Dimethyl ester of mikanecic acid]:

This was prepared by treating mikanecic acid (**59d**) with $SOCl_2$ followed by methanol according to the procedure described for dimethyl ester **60a** of (-)-mikanecic acid (**59a**).

HPLC analysis (column : CHIRALCEL OD; eluent : 2% isopropyl alcohol in hexane; flow rate:0.5 mL\min; UV detection limit λ_{max}: 240 nm) of the above diester **60d** showed two peaks (retention time (R_t) = 17.82 min. and 22.81 min.) in the ratio of 84.44 and 15.56 indicating that enantiomeric purity of mikanecic acid **59d** is 69%.

Attempts to improve the enantiomeric purity of (+)-mikanecic acid **59d** through diastereoselective crystallization of **69d** were not successful.

(1S,2R,4R)-1-[(Dicyclohexylaminosulfonyl)methyl]-7,7-dimethyl-bicyclo(2.2.1)heptan-2-ol (66e):

To a solution of bromomagnesium dicyclohexylamide (160 mM) [prepared by treating ethylmagnesium bromide (160 mM) in THF (150 mL) with dicyclohexylamine (31.88 mL, 160 mM) in THF (50 mL) at room temperature for 10 h] in THF, was added isobornyl sultone **89** (4.32 g, 20 mM) slowly at room temperature. After the addition, the reaction mixture was stirred at 60°C for 20 h. Then the reaction mixture was poured into ice-cold 2N HCl solution (100

mL) and filtered under suction to remove insoluble salts. The filtrate was saturated with NaCl and extracted with dichloromethane (3 x 75 mL). The salts also were extracted with dichloromethane (3 x 100 mL). Organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrated. The crude product, thus obtained, was crystallized from hexane (3 times) to provide alcohol **66e** as pale yellow crystals.

Yield : 3.17 g (40%)

m.p. : 158-159°C (lit.[107] m.p. 163-164°C)

$[\alpha]_D^{22}$: -25.4° (c 1.39, ethanol)

: [lit.[107] $[\alpha]_D^{20}$ -25.7° (c 0.76, ethanol)]

IR (neat) : 3470 cm^{-1}

^1H NMR : δ 0.79 (s, 3H), 1.04 (s, 3H), 1.06-1.92 (m, 27H), 2.65 and 3.25 (AB quartet, 2H J = 12 Hz), 3.18-3.38 (m, 2H), 3.52 (br s, 1H, OH), 4.04-4.26 (m, 1H).

^{13}C NMR : δ 20.03, 20.68, 25.24, 26.52, 27.43, 31.08, 32.82, 33.02, 38.93, 44.62, 48.52, 50.99, 55.37, 57.91, 76.63.

(1R,2R,4R)-1-[(Dicyclohexylaminosulfonyl)methyl]-7,7-dimethyl-bicyclo(2.2.1)hept-2-yl acrylate (67e):

It was obtained as colorless crystals by the action of acryloyl chloride on the magnesium salt of (1S,2R,4R)-1-[(dicyclohexylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)heptan-2-ol **66e**

following similar procedure described for the preparation of **67d**.

Yield : 95%

m.p. : 193-194^{o}C (lit.[107] m.p. 198-199^{o}C)

$[\alpha]_D^{22}$: -33.2^{o} (c 0.78, acetone)

IR (KBr) : 1620, 1715 cm^{-1}

^{1}H NMR : δ 0.90 (s, 3H), 1.01 (s, 3H), 1.06-2.14 (m, 27H), 2.68 and 3.28 (AB quartet, 2H, J = 16 Hz), 3.12-3.38 (m, 2H), 5.02-5.14 (m, 1H), 5.74 (dd, 1H, J = 10 Hz and 1.6 Hz), 6.12 (dd, 1H, J = 16 Hz and 10 Hz), 6.37 (dd, 1H, J = 16 Hz and 1.6 Hz).

^{13}C NMR : δ 20.03, 20.47, 25.20, 26.50, 27.06, 29.98, 32.86, 39.47, 44.65, 49.12, 49.60, 53.75, 57.53, 78.48, 129.28, 129.64, 164.46.

(1S,2R,4R)-1-[(Dicyclohexylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl 3-hydroxy-2-methylenebutanoate (68e):

It was obtained as white solid, after column chromatography (5% ethyl acetate in hexane) by the DABCO induced coupling of (1S,2R,4R)-1-[(dicyclohexylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl acrylate (**67e**) with acetaldehyde following similar procedure described for the preparation of the molecule **68a**.

Yield : 76%

m.p. : 147-148^{o}C

$[\alpha]_D^{22}$: -39.6^o (c 0.98, acetone), de is 49%

IR (KBr) : 1630, 1695, 3480 cm^{-1}

^1H NMR : δ 0.90 (s, 3H), 1.04 (s, 3H), 1.06-2.18 (m, 30H), 2.48 and 3.24 (AB quartet, 2H, J = 16 Hz), 2.85 & 2.91 (2 br, 1H, OH), 3.12-3.36 (m, 2H), 4.52-4.78 (m, 1H), 5.08-5.20 (m, 1H), 5.74 & 5.82 (2s, 1H), 6.06 & 6.10 (2s, 1H).

^{13}C NMR : δ 20.04, 20.42, 21.94, 25.16, 26.44, 27.05, 30.25, 32.67, 33.01, 39.42, 44.54, 49.15, 49.65, 53.81, 57.49, 66.54, 67.53, 78.66, 122.06, 122.53, 144.50, 144.91, 165.16.

The underlined chemical shift (δ) values are due to minor diastereomer.

Di[(1S,2R,4R)-1-[(dicyclohexylaminosulfonyl)methyl]-7,7-dimethyl-bicyclo(2.2.1)hept-2-yl] 4-vinylcyclohex-1-ene-1,4-dicarboxylate (69e):

It was obtained as white solid,after column chromatography (3% ethyl acetate in hexane), by treating (1S,2R,4R)-1-[(dicyclohexylaminosulfonyl)methyl]-7,7-dimethylbicyclo(2.2.1)hept-2-yl 3-hydroxy-2-methylenebutanoate (**68e**) with mesyl chloride in the presence of triethylamine following similar procedure described for the molecule **69a**.

Yield : 75%

m.p. : 202-204^{o}C

$[\alpha]_D^{22}$: -59.8^{o} (c 0.72, acetone)

IR (KBr) : 1635, 1705 cm^{-1}

^{1}H NMR : δ 0.82-3.41 (m, 80H), 4.82-5.26 (m, 4H), 5.72-5.98 (m, 1H), 6.88 (m, 1H).

^{13}C NMR : δ 20.09, 20.19, 20.52, 21.70, 25.20, 26.52, 27.07, 30.09, 30.18, 30.67, 31.86, 32.33, 32.68, 33.03, 33.38, 39.76, 44.38, 44.51, 47.11, 49.16, 49.46, 49.52, 53.72, 53.85, 57.50, 57.54, 78.29, 79.35, 115.72, 130.13, 136.21, 138.45, 165.16, 173.10.

4-Vinylcyclohex-1-ene-1,4-dicarboxylic acid (59e):

[(+)-Mikanecic acid]:

It was obtained as white solid by the saponification of **69e** with methanolic KOH following similar procedure described for the preparation of (-)-mikanecic acid **59a**.

Time : 12 h

Yield : 69%

m.p. : 236-238^{o}C

$[\alpha]_D^{22}$: +9.17^{o} (c 0.43, acetone)

This molecule has identical spectral data (IR, ^{1}H NMR, and ^{13}C NMR) as that of (-)-mikanecic acid **59a**.

Determination of enantiomeric purity 59e:

Dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (60e):

[Dimethyl ester of mikanecic acid]:

This was prepared by treating mikanecic acid (**59e**) with $SOCl_2$ followed by methanol according to the procedure described for dimethyl ester **60a** of (-)-mikanecic acid (**59a**).

HPLC analysis of the above diester **60e** showed two peaks (retention time (R_t) = 17.77 min and 22.82 min) in the ratio of 86.72 and 13.24 indicating that enantiomeric purity of mikanecic acid **59e** is 74%.

Selective crystallization of 69e.

Single recrystallization of **69e** (0.79 g) from 25% benzene in hexane at -20^{0}C afforded crystalline solid **69e'** (0.56 g).

m.p. : 202-204^{o}C

$[\alpha]_D^{22}$: -61.8^{o} (c 0.87, acetone)

4-Vinylcyclohex-1-ene-1,4-dicarboxylic acid (59e'):

[(+)-Mikanecic acid]:

It was obtained by the saponification of **69e'** with methanolic KOH following similar procedure described for the preparation of (-)-mikanecic acid **59a**.

Time : 12 h

Yield : 69%

m.p. : 233-235^{o}C

$[\alpha]_{D}^{22}$: +11.21^{o} (c 0.33, acetone)

This molecule has identical spectral data (IR, ^{1}H NMR, and ^{13}C NMR) as that of (-)-mikanecic acid **59a**.

Determination of enantiomeric purity:

Dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (60e'):

[Dimethyl ester of mikanecic acid]:

The molecule **59e'** was converted into the corresponding dimethyl ester **60e'** following the similar procedure described for dimethyl ester (**60a**) of (-)-mikanecic acid (**59a**)

HPLC analysis (column : CHIRALCEL OD; eluent : 2% isopropyl alcohol in hexane; flow rate : 0.5 mL\min ; UV detection limit λ_{max} : 240 nm) of the above diester **60e'** showed two peaks (retention time (R_t) = 16.96 min. and 20.47 min.) in the ratio of 96.06 and 3.93 indicating that enantiomeric purity of mikanecic acid **59e'** is 92%.

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (90a):

A mixture of benzaldehyde (10.2 mL, 100 mM), methyl acrylate (13.5 mL, 150 mM) and DABCO (1.68 g, 15 mM) was allowed to react at room temperature for 7 days. The reaction mixture was diluted with ether (200 mL) and washed, successively, with 2N HCl solution, water and saturated aqueous $NaHCO_3$ solution. The

ethereal extract was dried over anhydrous Na_2SO_4, concentrated and the crude product, thus obtained, was distilled under reduced pressure to afford **90a** as colorless viscous liquid.

Yield : 16.32 g (85%)

b.p. : 128°C/4 mm

IR (neat) : 1630, 1720, 3464 cm^{-1}

^1H NMR : δ 3.08 (d, 1H, OH, J = 4 Hz), 3.73 (s, 3H), 5.58 (d, 1H, J = 4 Hz), 5.86 (s, 1H), 6.38 (s, 1H), 7.24-7.48 (m, 5H)

Methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (90b):

It was obtained as colorless viscous liquid by the reaction of 4-methylbenzaldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 8 days

Yield : 75%

b.p. : 132°C/3 mm

IR (neat) : 1630, 1722, 3464 cm^{-1}

^1H NMR : δ 2.34 (s, 3H), 3.09 (br s, 1H, OH), 3.71 (s, 3H), 5.53 (s, 1H), 5.86 (s, 1H), 6.33 (s, 1H), 7.19 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8 Hz)

Methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (90c):

It was prepared as colorless viscous liquid by the reaction of 4-chlorobenzaldehyde with methyl acrylate in the presence of

DABCO following similar procedure described for compound **90a**.

Time : 6 days

Yield : 78%

b.p. : 126°C/1 mm

IR (neat) : 1710, 3425 cm^{-1}

^1H NMR : δ 3.06 (d, 1H, OH, J = 6 Hz), 3.72 (s, 3H), 5.50 (d, 1H, J = 6 Hz), 5.80 (s, 1H), 6.32 (s, 1H), 7.30 (s, 4H).

Methyl 3-hydroxy-2-methylenehexanoate (90d):

It was obtained as colorless viscous liquid by the reaction of n-butyraldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 5 days

Yield : 70%

b.p. : 95-97°C/5 mm

IR (neat) : 1628, 1714, 3480 cm^{-1}

^1H NMR (100 MHz) : δ 0.92 (dist. t, 3H), 1.12-1.76 (m, 4H), 2.62 (br s, 1H, OH), 3.76 (s, 3H), 4.42 (t, 1H, J = 6 Hz), 5.78 (s, 1H), 6.19 (s, 1H).

Methyl 3-hydroxy-2-methylene-4-methylpentanoate (90e):

It was obtained as colorless viscous liquid by the reaction of isobutyraldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 5 days

Yield : 68%

b.p. : 104-106^{o}C/7 mm

IR (neat) : 3489, 1716 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.96 (d, 3H, J = 8 Hz) 0.98 (d, 3H, J = 8 Hz), 1.72-2.16 (m, 1H), 2.45 (br, 1H, OH), 3.76 (s, 3H), 4.05 (d, 1H, J = 6 Hz), 5.77 (s, 1H), 6.25 (s, 1H).

Methyl 3-hydroxy-2-methylenenonanoate (90f):

It was obtained as colorless viscous liquid by the reaction of n-heptanaldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 8 days

Yield : 77%

b.p. : 108-110^{o}C/4 mm

IR (neat) : 1640, 1710, 3460 cm^{-1}

^{1}H NMR : δ 0.87 (dist. t, 3H), 1.12-1.92 (m, 10H), 2.44-2.78 (br, 1H, OH), 3.77 (s, 3H), 4.34-4.48 (m, 1H), 5.79 (s, 1H), 6.22 (s, 1H)

Methyl 3-hydroxy-2-methylene-3-(1-naphthyl)propanoate (92):

It was obtained as white solid by the reaction of 1-naphthaldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 7 days

Yield : 94%

m.p. : 108-110^{o}C

IR (KBr) : 1628, 1726, 3207 cm^{-1}

^{1}H NMR : δ 3.16 (d, 1H, J = 3.2 Hz), 3.79 (s, 3H), 5.59 (s, 1H), 6.36 (m, 2H), 7.46-8.12 (m, 7H)

Methyl 3-hydroxy-2-methyleneheptanoate (93):

It was obtained as colorless viscous liquid by the reaction of valeraldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 5 days

Yield : 76%

b.p. : 95^{o}C/3 mm

IR (neat) : 3478, 1716, 1637 cm^{-1}

^{1}H NMR : δ 0.88 (dist. t, 3H), 1.02-1.78 (m, 6H), 2.60 (br s, 1H, OH), 3.76 (s, 3H), 4.16-4.50 (m, 1H), 5.80 (s, 1H), 6.20 (s, 1H).

Methyl 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanoate (105):

It was obtained as colorless viscous liquid by the reaction of 2-methoxybenzaldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 8 days

Yield : 92%

b.p. : 154-156^{o}C/2.8 mm

IR (neat) : 1640, 1710, 3450

^{1}H NMR : δ 3.02 (br s, 1H, OH), 3.74 (s, 3H), 3.82 (s, 3H), 5.72 (s, 1H), 5.87 (s, 1H), 6.30 (s, 1H), 6.64-7.12 (m, 2H), 7.22-7.38 (m, 2H).

Methyl 3-(2,4-dichlorophenyl)-3-hydroxy-2-methylenepropanoate (114):

It was obtained as colorless solid by the reaction of 2,4-dichlorobenzaldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 5 days

Yield : 95%

m.p. : 79^{o}C

IR (KBr) : 1631, 1722, 3429 cm^{-1}

^{1}H NMR : δ 3.70 (d, 1H, J = 4.8 Hz, OH), 3.74 (s, 3H), 5.59 (s, 1H), 5.88 (d, 1H, J = 4.8 Hz), 6.32 (s, 1H), 7.22-7.52 (m, 3H)

Methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (115):

It was obtained as a colorless viscous liquid by the reaction of 2-nitrobenzaldehyde with methyl acrylate in the presence of DABCO following the similar procedure described for molecule **90a**.

Time : 3 days

Yield : 90%

b.p. : 165^{o}C/3 mm

IR (neat) : 1625, 1720, 3468 cm^{-1}

^{1}H NMR : δ 3.69 (s, 3H), 3.90 (br s, 1H, OH), 5.70 (s, 1H), 6.19 (s, 1H), 6.32 (s, 1H), 7.38-7.52 (m, 1H), 7.58-7.68 (m, 1H), 7.72-7.79 (m, 1H), 7.88-7.96 (m, 1H).

3-Hydroxy-2-methylene-3-phenylpropanenitrile (96a):

This was prepared following the procedure developed in our laboratory.[28]

A mixture of benzaldehyde (10.2 mL, 100 mM), acrylonitrile (9.87 mL, 150 mM) and DABCO (1.68 g, 15 mM) was allowed to react at room temperature for 40h. The reaction mixture was taken up in ether and washed, successively, with 2N HCl solution, water and aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and the crude product, thus obtained, was distilled under reduced pressure to afford **96a** as colorless liquid.

Yield : 12.7 g (80%)

b.p. : 120-124^{o}C/1.5 mm

IR (neat) : 1617, 2215, 3320 cm^{-1}

^{1}H NMR : δ 2.61 (br, 1H, OH), 5.29 (s, 1H), 6.03 (s, 1H), 6.11 (s, 1H), 7.39 (m, 5H)

3-Hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (96b):

It was prepared as colorless liquid by the reaction of 4-methylbenzaldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for molecule **96a**.

Yield : 78%

b.p. : 146-148^{o}C\1.7 mm

IR (neat) : 1645, 2229, 3449 cm^{-1}

^{1}H NMR : δ 2.38 (s, 3H), 2.62 (br, 1H, OH), 5.28 (s, 1H), 6.01 (s, 1H), 6.12 (s, 1H), 7.29 (q, 4H, J = 7 Hz).

3-(4-Chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (96c):

It was prepared as colorless liquid by the reaction of 4-chlorobenzaldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for molecule **96a**.

Yield : 83%

b.p. : 141-143^{o}C/1.5 mm

IR (neat) : 1595, 2118, 3365 cm^{-1}

^{1}H NMR : δ 2.82 (br s, 1H, OH), 5.27 (s, 1H), 6.03 (d, 1H, J = 1.1 Hz), 6.10 (d, 1H, J = 1.1 Hz), 7.26-7.48 (m, 4H)

3-Hydroxy-2-methylenehexanenitrile (96d):

It was prepared as colorless liquid by the reaction of n-butyraldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for molecule **96a**.

Yield : 68%

b.p. : 84-86^{o}C/8 mm

IR (neat) : 1620, 2224, 3327 cm^{-1}

^{1}H NMR : δ 0.98 (t, 3H, J = 6.4 Hz), 1.24-1.84 (m, 4H), 2.20 (br s, 1H, OH), 4.24 (dist. t, 1H), 5.92 (s, 1H), 5.96 (s, 1H).

3-Hydroxy-2-methylenenonanenitrile (96e):

It was prepared as colorless liquid by the reaction of n-heptanaldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for molecule **96a**.

Yield : 84%

b.p. : 154-157^{o}C/3.4 mm

IR (neat) : 1614, 2225, 3447 cm^{-1}

^{1}H NMR : δ 0.88 (dist. t, 3H), 1.18-1.88 (m, 10H), 2.14 (br s, 1H, OH), 4.26 (dist. t, 1H), 5.97 (s, 1H), 5.99 (s, 1H).

3-Hydroxy-2-methylene-4-methylpentanenitrile (96f):

It was prepared as colorless liquid by the reaction of isobutyraldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for molecule **96a**.

Yield : 74%

b.p. : 104-106^{o}C/14 mm

IR (neat) : 1611, 2227, 3429 cm^{-1}

^1H NMR (100 MHz) : δ 1.07 (d, 6H, J = 7.2 Hz), 1.78-2.18 (m, 2H, 1H D_2O washable) 3.98 (d, 1H, J = 5.4 Hz), 6.01 (s, 1H), 6.03 (s, 1H).

3-Hydroxy-2-methyleneoctanenitrile (102):

It was prepared as colorless liquid by the reaction of hexanaldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for molecule **96a**.

Yield : 81%

b.p. : 120-121°C/4 mm

IR (neat) : 1618, 2213, 3427 cm^{-1}

^1H NMR (100 MHz) : δ 0.89 (dist. t, 3H), 1.22-1.82 (m, 8H), 2.24 (br, 1H OH), 4.29 (dist t, 1H), 5.97 (s, 1H), 6.02 (s, 1H)

3-Hydroxy-2-methylenebutanenitrile (108):

It was prepared as colorless liquid by the reaction of acetaldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for molecule **96a**.

Yield : 68%

b.p. : 85-87°C/20 mm

IR (neat) : 1617, 2234, 3445 cm^{-1}

^1H NMR : δ 1.47 (d, 3H, J = 6.6 Hz), 2.24 (br, 1H, OH), 5.38 (q 1H, J = 6.6 Hz), 6.05 (s, 1H), 6.07 (s, 1H).

Ethyl 4-methoxycarbonyl-5-phenylpent-4-enoate (91a):

A solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**90a**) (0.384 g, 2 mM) in triethyl orthoacetate (1.8 mL, 10 mM) was heated at 146^{o}C in presence of propionic acid (3-4 drops) for 1.5 h. The reaction mixture was diluted with ether (15 mL) and washed successively with 4N HCl solution (2 x 5 mL), water and saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (2% ethyl acetate in hexane) to afford **91a** as colorless viscous liquid.

Yield : 0.41 g (78%)

E : Z : 80 : 20

IR (neat) : 1633, 1716, 1734 cm^{-1}

^{1}H NMR : δ 1.26 & 1.28 (2t, 3H, J = 7 Hz), 2.50 (m, 2H), 2.71 & 2.92 (2m, 2H), 3.68 & 3.82 (2s, 3H), 4.12 (q, 2H, J = 7 Hz), 6.76 & 7.74 (2s, 1H), 7.18-7.48 (m, 5H).

^{13}C NMR : δ 13.88, 22.92, 30.47, 33.14, 33.26, 51.16 51.61, 60.04, 127.35, 127.59, 127.85, 128.34, 128.89, 131.14, 132.31, 134.60, 135.07, 135.75, 139.99, 167.87, 169.08, 171.94, 172.19.

Analysis calculated for $C_{15}H_{18}O_4$: C, 68.68; H, 6.91

Found : C, 68.61; H, 6.92

The underlined chemical shift (δ) values are due to minor

(Z)-isomer.

Ethyl 4-methoxycarbonyl-5-(4-methylphenyl)pent-4-enoate (91b):

It was obtained as colorless viscous liquid by the treatment of methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (**90b**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **91a**.

Time : 2 h

Yield : 87%

E : Z : 75 : 25

IR (neat) : 1634, 1710, 1734 cm^{-1}

^{1}H NMR : δ 1.28 & 1.29 (2t, 3H, J = 7.2 Hz), 2.38 & 2.42 (2s, 3H), 2.58 (m, 2H), 2.76 & 2.92 (2m, 2H), 3.68 & 3.84 (2s, 3H), 4.14 (m, 2H), 6.72 & 7.70 (2s, 1H), 7.04-7.34 (m, 4H).

^{13}C NMR : δ 14.14, 21.23, 23.13, 30.75, 33.47, 51.51, 51.91, 60.35, 128.12, 128.81, 129.28, 130.29, 131.44, 132.33, 132.93, 135.03, 137.81, 138.79, 140.35, 168.37, 169.56, 172.40, 172.66.

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

Ethyl 5-(4-chlorophenyl)-4-methoxycarbonylpent-4-enoate (91c):

It was obtained as colorless viscous liquid by the treatment of methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**90c**)

with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **91a**.

Time : 1.5 h

Yield : 85%

E : Z : 70 : 30

IR (neat) : 1634, 1713, 1732 cm^{-1}

^{1}H NMR : δ 1.24 & 1.26 (2t, 3H, J = 7.2 Hz), 2.51 (m, 2H), 2.61 & 2.85 (2m, 2H), 3.66 & 3.83 (2s, 3H), 4.11 (m, 2H), 6.70 & 7.67 (2s, 1H), 7.08-7.42 (m, 4H).

^{13}C NMR : δ 14.18, 23.10, 30.67, 33.38, 51.70, 52.11, 60.51, 128.34, 128.89, 129.51, 130.48, 131.88, 133.13, 133.69, 134.01, 134.41, 134.64, 139.01, 168.03 169.05, 172.33, 172.52.

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

Ethyl 4-(methoxycarbonyl)oct-4-enoate (91d):

It was obtained as colorless viscous liquid by the treatment of methyl 3-hydroxy-2-methylenehexanoate (**90d**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **91a**.

Time : 2.0 h

Yield : 70%

Z : E : 74 : 26

IR (neat) : 1645, 1711, 1736 cm^{-1}

^1H NMR : δ 0.91 & 0.94 (2t, 3H, J = 7 Hz), 1.24 & 1.25 (2t, 3H, J = 7.2 Hz), 1.43 (m, 2H), 2.12-2.70 (m, 6H), 3.74 (s, 3H), 4.12 (q, 2H, J = 7.2 Hz), 6.00 & 6.81 (2t, 1H, J = 7.6 Hz).

^{13}C NMR : δ 13.50, 13.63, 14.02, 21.86, 22.17, 22.37, 29.88, 30.32, 31.40, 33.45, 33.93, 50.94, 51.38, 60.04, 129.86, 130.36, 143.95, 144.11, 167.59, 172.54, 172.71.

The underlined chemical shift (δ) values are due to minor (E)-isomer.

Ethyl 4-(methoxycarbonyl)-6-methylhept-4-enoate (91e):

It was obtained as colorless viscous liquid by the treatment of methyl 3-hydroxy-2-methylene-4-methylpentanoate (**90e**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **91a**.

Time : 2.0 h

Yield : 85%

Z : E : 80 : 20

IR (neat) : 1643, 1711, 1732 cm^{-1}

^1H NMR : δ 0.87 & 0.88 (2d, 6H, J = 6.6 Hz), 1.14 (t, 3H, J = 7 Hz), 2.20-2.64 (m, 4H), 3.08 (m, 1H), 3.62 (s, 3H), 4.01 (q, 2H, J = 7 Hz), 5.62 & 6.48 (d, 1H, J

= 7.2 Hz)

^{13}C NMR : δ 14.12, 22.15, 22.34, 22.47, 27.75, 28.29, 29.95, 33.92, 34.04, 51.10, 51.51, 60.14, 127.61, 128.04, 150.62, 167.75, 167.96, 172.62, 172.74.

The underlined chemical shift (δ) values are due to minor (E)-isomer.

Ethyl 4-methoxycarbonyl-5-(1-naphthyl)pent-4-enoate (91f):

It was obtained as colorless viscous liquid by the treatment of methyl 3-hydroxy-2-methylene-3-(1-naphthyl)propanoate (**92**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **91a**.

Time : 2.5 h

Yield : 82%

E : Z : 74 : 26

IR (neat) : 1591, 1637, 1710, 1732 cm^{-1}

^{1}H NMR : δ 1.11 & 1.27 (2t, 3H, J = 7.2 Hz), 2.47-2.91 (m, 4H), 3.40 & 3.87 (2s, 3H), 3.95 & 4.18 (2q, 2H, J = 7.1 Hz), 7.22-7.58 (m, 4H), 7.62-7.92 (m, 3H), 8.22 (s, 1H)

^{13}C NMR : δ 13.83, 14.06, 23.27, 30.08, 33.34, 33.53, 51.08, 51.80, 60.02, 60.26, 124.38, 124.93, 125.05, 125.37, 125.70, 126.00, 126.24, 127.93, 128.23, 128.33, 128.58, 131.05, 131.24, 132.55, 133.16,

133.32, 134.05, 134.42, 134.74, 167.58, 168.50, 172.20.

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

Ethyl 4-(methoxycarbonyl)non-4-enoate (91g):

It was obtained as colorless viscous liquid by the treatment of methyl 3-hydroxy-2-methyleneheptanoate (**93**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **91a**.

Time : 2.5 h

Yield : 84%

Z : E : 75 : 25

IR (neat) : 1736, 1718, 1643 cm^{-1}

^{1}H NMR : δ 0.82-0.98 (m, 3H), 1.18-1.52 (m, 7H), 2.15-2.68 (m, 6H), 3.74 (s, 3H), 4.12 (q, 2H, J = 7.2 Hz), 6.00 & 6.82 (2t, 1H, J = 7.4 Hz).

^{13}C NMR : δ 13.61, 13.99, 22.11, 22.23, 28.02, 29.09, 29.86 30.74, 31.30, 33.42, 33.89, 50.90 51.33, 60.00, 129.64, 130.15, 144.12, 144.33, 167.54, 172.49, 172.60.

The underlined chemical shift (δ) values are due to minor (E)-isomer.

Ethyl (4Z)-4-cyano-5-phenylpent-4-enoate (97a):

A solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**96a**) (0.318 g, 2 mM) in triethyl orthoacetate (1.8 mL 10 mM) was heated at 146°C in presence of propionic acid (3-4 drops) for 1h. The reaction mixture was diluted with ether (15 mL) and washed successively with 4N HCl (10 mL) solution, water and saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (2% ethyl acetate in hexane) to afford **97a** as colorless viscous liquid.

Yield : 0.42 g (92%)

IR (neat) : 1624, 1734, 2210 cm^{-1}

^1H NMR : δ 1.26 (t, 3H, J = 7 Hz), 2.62-2.86 (m, 4H), 4.16 (q, 2H, J = 7 Hz), 7.02 (s, 1H), 7.32-7.48 (m, 3H), 7.66-7.78 (m, 2H)

^{13}C NMR : δ 14.18, 31.36, 32.75, 60.72, 109.42, 118.21, 128.63, 128.79, 130.13, 133.53, 144.55, 171.58

Analysis calcd. for $C_{14}H_{15}NO_2$: C, 73.33; H, 6.59; N, 6.11

Found : C, 73.45; H, 6.61; N, 6.14.

Ethyl (4Z)-4-cyano-5-(4-methylphenyl)pent-4-enoate (97b):

It was obtained as colorless viscous liquid by the treatment of 3-hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (**96b**) with triethyl orthoacetate in the presence of propionic acid

following similar procedure described for the molecule **97a**.

Time : 1 h

Yield : 87%

IR (neat) : 1610, 1736, 2208 cm^{-1}

^1H NMR : δ 1.25 (t, 3H, J = 7 Hz), 2.36 (s, 3H), 2.61-2.82 (m, 4H), 4.15 (q, 2H, J = 7 Hz), 6.97 (s, 1H), 7.20 (d, 2H, J = 8 Hz), 7.62 (d, 2H, J = 8 Hz)

^{13}C NMR : δ 14.15, 21.35, 31.30, 32.79, 60.66, 107.99, 118.43 128.61, 129.46, 130.76, 140.53, 144.53, 171.63.

Analysis calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.75

Found : C, 73.95; H, 7.00; N, 5.78.

Ethyl (4Z)-5-(4-chlorophenyl)-4-cyanopent-4-enoate (97c):

It was obtained as colorless viscous liquid by the treatment of 3-hydroxy-3-(4-chlorophenyl)-2-methylenepropanenitrile (**96c**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **97a**.

Time : 1 h

Yield : 76%

IR (neat) : 1615, 1734, 2210 cm^{-1}

^1H NMR : δ 1.26 (t, 3H, J = 7.2 Hz), 2.62-2.82 (m, 4H), 4.16 (q, 2H, J = 7.2 Hz), 6.98 (s, 1H), 7.32-7.42 (m, 2H), 7.62-7.72 (m, 2H)

^{13}C NMR : δ 14.09, 31.18, 32.49, 60.68, 110.00, 117.86,

128.96, 129.79, 131.85, 135.92, 143.06, 171.43.

Analysis calcd for $C_{14}H_{14}NO_2Cl$: C, 63.76; H, 5.35; N, 5.31

Found : C, 63.78; H, 5.34; N, 5.29.

Ethyl (4Z)-4-cyanooct-4-enoate (97d):

It was obtained as colorless viscous liquid by the treatment of 3-hydroxy-2-methylenehexanenitrile (**96d**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **97a**.

Time : 1.5 h

Yield : 79%

IR (neat) : 1625, 1738, 2216 cm^{-1}

^1H NMR : δ 0.94 (t, 3H, J = 7.3 Hz), 1.26 (t, 3H, J = 7 Hz), 1.47 (sext, 2H, J = 7.4 Hz), 2.33 (q, 2H, J = 7.3 Hz), 2.54 (s, 4H), 4.15 (q, 2H, J = 7 Hz), 6.24 (t, 1H, J = 7.6 Hz)

^{13}C NMR : δ 13.34, 14.10, 21.71, 29.39, 32.68, 33.38, 60.56, 113.05, 117.04, 148.76, 171.59.

Analysis calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17

Found : C, 67.68; H, 8.74; N, 7.12.

Ethyl (4Z)-4-cyanoundec-4-enoate (97e):

It was obtained as colorless viscous liquid by the treatment of 3-hydroxy-2-methylenenonanenitrile (**96e**) with triethyl

orthoacetate in the presence of propionic acid following similar procedure described for the molecule **97a**.

Time : 1.5 h

Yield : 90%

IR (neat) : 1615, 1738, 2216 cm^{-1}

^1H NMR : δ 0.89 (dist. t, 3H), 1.18-1.52 (m, 11H), 2.35 (q, 2H, J = 7 Hz), 2.54 (s, 4H), 4.15 (q, 2H, J = 7.2 Hz), 6.24 (t, 1H, J = 7.6 Hz)

^{13}C NMR : δ 14.00, 14.20, 22.52, 28.49, 28.68, 29.46, 31.53, 31.57, 32.76, 60.69, 112.83, 117.16, 149.26, 171.74

Analysis calcd for $C_{14}H_{23}NO_2$: C, 70.84; H, 9.76; N, 5.90

Found : C, 70.75; H, 9.79; N, 5.88.

Ethyl (4Z)-4-cyano-6-methylhept-4-enoate (97f) :

It was obtained as colorless viscous liquid by the treatment of 3-hydroxy-2-methylene-4-methylpentanenitrile (**96f**) with triethyl orthoacetate in the presence of propionic acid following similar procedure described for the molecule **97a**.

Time : 1.5 h

Yield : 83%

IR (neat) : 1625, 1738, 2216 cm^{-1}

^1H NMR : δ 1.04 (d, 6H, J = 6.6 Hz), 1.26 (t, 3H, J = 7 Hz), 2.44-2.64 (m, 4H), 2.73-2.96 (m, 1H), 4.14 (q, 2H, J = 7.2 Hz), 6.04 (d, 1H, J = 10 Hz)

^{13}C NMR : δ 13.95, 21.71, 29.12, 31.08, 32.49, 60.34, 110.25, 116.71, 155.23, 171.34.

Analysis calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17

Found : C, 67.59; H, 8.78; N, 7.20.

Methyl 3-acetoxy-2-methylene-3-phenylpropanoate (98a):

To a solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**90a**) (19.2 g, 100 mM), pyridine (16.1 mL, 200 mM) in dry benzene (100 mL) at 0°C acetyl chloride (14.2 mL, 200 mM) was added slowly and was stirred at room temperature for 3h. Reaction mixture was taken up in ether (2 x 75 mL) and washed successively with 2N HCl solution, water and saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4. concentrated and distilled under reduced pressure to afford **98a** as viscous, pale yellow liquid.

Yield : 20.35 g (87%)

b.p. : 138°C/4 mm

IR (neat) : 1625, 1713 cm^{-1}

^1H NMR : δ 2.11 (s, 3H), 3.71 (s, 3H), 5.86 (s,1H), 6.41 (s, 1H), 6.69 (s, 1H), 7.30-7.48 (m, 5H).

Methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (98b):

It was obtained as pale yellow colored viscous liquid by the action of acetyl chloride on methyl 3-hydroxy-2-methylene-3-(4-

methylphenyl)propanoate (**90b**) in presence of pyridine following similar procedure described for the molecule **98a**.

Yield : 84%

b.p. : 136°C/3.7 mm

IR (neat) : 1644, 1711, 1738 cm^{-1}

^1H NMR : δ 2.09 (s, 3H), 2.33 (s, 3H), 3.69 (s, 3H), 5.86 (s, 1H), 6.38 (s, 1H), 6.68 (s, 1H), 7.22 (d, 2H, J = 7Hz), 7.25 (d, 2H, J = 7 Hz).

Methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (98c):

It was obtained as pale yellow colored viscous liquid by the action of acetyl chloride on methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**90c**) in presence of pyridine following similar procedure described for the molecule **98a**.

Yield : 91%

b.p. : 142°C/3.7 mm

IR (neat) : 1620, 1650, 1718 cm^{-1}

^1H NMR : δ 2.08 (s, 3H), 3.70 (s, 3H), 5.88 (s, 1H), 6.36 (s, 1H), 6.60 (s, 1H), 7.30 (m, 4H).

Methyl 3-acetoxy-2-methylenehexanoate (98d):

It was obtained as pale yellow colored viscous liquid by the action of acetyl chloride on methyl 3-hydroxy-2-methylenehexanoate (**90d**) in presence of pyridine following similar procedure

described for the molecule **98a**.

Yield : 78%

b.p. : 66°C/5 mm

IR (neat) : 1633, 1722, 1743 cm^{-1}

^1H NMR : δ 0.88 (dist t, 3H), 1.14-1.80 (m, 4H), 2.07 (s, 3H), 3.75 (s, 3H), 5.43-5.95 (m, 1H), 6.24 (s, 1H), 6.38 (s, 1H).

Methyl 3-acetoxy-2-methylene-4-methylpentanoate (98e):

It was obtained as pale yellow colored viscous liquid by the action of acetyl chloride on methyl 3-hydroxy-2-methylene-4-methylpentanoate (**90e**) in presence of pyridine following similar procedure described for the molecule **98a**.

Yield : 65%

b.p. : 74°C/5 mm

IR (neat) : 1628, 1724, 1737 cm^{-1}

^1H NMR (100 MHz) : δ 0.93 (d, 3H, J = 5 Hz), 0.98 (d, 3H, J = 5Hz), 2.14 (s, 3H), 3.76 (s, 3H), 5.48 (d, 1H, J = 6Hz), 5.72 (s, 1H), 6.36 (s, 1H).

Methyl 3-acetoxy-2-methylenenonanoate (98f):

It was obtained as pale yellow colored viscous liquid by the action of acetyl chloride on methyl 3-hydroxy-2-methylenenonanoate (**90f**) in presence of pyridine following similar procedure described for the molecule **98a**.

Yield : 87%

b.p. : 144°C/3 mm

IR (neat) : 1633, 1720, 1745 cm^{-1}

^1H NMR : δ 0.89 (dist. t, 3H), 1.14-1.88 (m, 10H), 2.08 (s, 3H), 3.77 (s, 3H), 5.52-5.64 (m, 1H), 5.75 (s, 1H), 6.27 (s, 1H).

Methyl 3-acetoxy-3-(2-methoxyphenyl)-2-methylenepropanoate (106):

It was obtained as pale yellow colored viscous liquid by the action of acetyl chloride on methyl 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanoate (**105**) in presence of pyridine following similar procedure described for the molecule **98a**.

Yield : 87%

b.p. : 147°C/2.8 mm

IR (neat) : 1639, 1716, 1743 cm^{-1}

^1H NMR : δ 2.08 (s, 3H), 3.72 (s, 3H), 3.82 (s, 3H), 5.61 (s, 1H), 6.36 (s, 1H), 6.76-7.08 (m, 3H), 7.12-7.40 (m, 2H).

Methyl 3-acetoxy-3-(2,4-dichlorophenyl)-2-methylenepropanoate (116):

It was obtained as colorless solid by the action of acetyl chloride on methyl 3-(2,4-dichlorophenyl)-3-hydroxy-2-methylene-propanoate (**114**) in presence of pyridine following similar

procedure described for the molecule **98a.**

Yield : 95%

m.p. : 58-60^{o}C

IR (neat) : 1645, 1711, 1745 cm^{-1}

^{1}H NMR : δ 2.12 (s, 3H), 3.74 (s, 3H), 5.69 (s, 1H), 6.48 (s, 1H), 6.97 (s, 1H), 7.28-7.48 (m, 3H)

Methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (117):

It was obtained as pale colorless solid by the action of acetyl chloride on methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)-propanoate (**115**) in presence of pyridine following similar procedure described for the molecule **98a**.

Yield : 95%

m.p. : 64^{o}C

IR (neat) : 1639, 1709, 1747 cm^{-1}

^{1}H NMR : δ 2.12 (s, 3H), 3.75 (s, 3H), 5.58 (s, 1H), 6.48 (s, 1H), 7.31 (s, 1H), 7.42-7.76 (m, 3H), 8.04 (d, 1H, J = 4 Hz).

3-Acetoxy-2-methylene-3-phenylpropanenitrile (100a):

To a solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**96a**) (15.9 g, 100 mM), pyridine (16 mL, 200 mM) in dry benzene (100 mL) at 0^{o}C acetyl chloride (14.2 mL 200 mM) was added slowly and was stirred at room temperature for 3h. Reaction mixture was

taken up in ether and washed successively with 2N HCl solution, water and saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and distilled under reduced pressure to afford **100a** as viscous, pale yellow liquid.

Yield : 17 g (85%)

b.p. : 115°C/1.5 mm

IR (neat) : 1611, 1749, 2229 cm^{-1}

^1H NMR : δ 2.18 (s, 3H), 6.01 (s, 1H), 6.08 (s, 1H), 6.34 (s, 1H), 7.40 (s, 5H).

3-Acetoxy-2-methylene-3-(4-methylphenyl)propanenitrile (100b):

It was obtained as colorless viscous liquid by the action of acetyl chloride on 3-hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (**96b**) in presence of pyridine following similar procedure described for the molecule **100a**.

Yield : 80%

b.p. : 132°C/2.5 mm

IR (neat) : 1614, 1747, 2231 cm^{-1}

^1H NMR : δ 2.14 (s, 3H), 2.36 (s, 3H), 5.96 (d, 1H, J = 2 Hz), 6.06 (d, 1H, J = 2 Hz), 6.26 (s, 1H), 7.12-7.36 (m, 4H).

3-Acetoxy-3-(4-chlorophenyl)-2-methylenepropanenitrile (100c):

It was obtained as colorless viscous liquid by the action of

acetyl chloride on 3-hydroxy-3-(4-chlorophenyl)-2-methylenepropanenitrile (**96c**) in presence of pyridine following similar procedure described for the molecule **100a**.

Yield : 83%

b.p. : 158°C/3.1 mm

IR (neat) : 1595, 1728, 2120 cm^{-1}

^1H NMR : δ 2.17 (s, 3H), 6.03 (s, 1H) 6.09 (s, 1H), 6.29 (s, 1H), 7.28-7.42 (m, 4H).

3-Acetoxy-2-methylenehexanenitrile (100d):

It was obtained as colorless viscous liquid by the action of acetyl chloride on 3-hydroxy-2-methylenehexanenitrile (**96d**) in presence of pyridine following similar procedure described for the molecule **100a**.

Yield : 81%

b.p. : 94°C/8 mm

IR (neat) : 1655, 1749, 2196 cm^{-1}

^1H NMR : δ 0.95 (t, 3H, J = 7.2 Hz), 1.36 (sext, 2H, J = 7 Hz), 1.68-1.92 (m, 2H), 2.11 (s, 3H), 5.28 (t, 1H), 5.99 (s, 1H), 6.04 (s, 1H)

3-Acetoxy-2-methylenenonanenitrile (100e):

It was obtained as colorless viscous liquid by the action of acetyl chloride on 3-hydroxy-2-methylenenonanenitrile (**96e**) in

presence of pyridine following similar procedure described for the molecule **100a**.

Yield : 84%

b.p. : 130°C/4 mm

IR (neat) : 1611, 1734, 2211 cm^{-1}

^1H NMR : δ 0.88 (dist. t, 3H), 1.18-1.42 (m, 8H), 1.62-1.92 (m, 2H), 2.11 (s, 3H), 5.28 (t, 1H, J = 6 Hz), 5.98 (s, 1H), 6.04 (s, 1H)

3-Acetoxy-2-methylene-4-methylpentanenitrile (100f):

It was obtained as colorless viscous liquid by the action of acetyl chloride on 3-hydroxy-2-methylene-4-methylpentanenitrile (**96f**) in presence of pyridine following similar procedure described for the molecule **100a**.

Yield : 78%

b.p. : 88°C/10 mm

IR (neat) : 1635, 1747, 2226 cm^{-1}

^1H NMR : δ 0.95 (m, 6H), 2.10 (s, 3H), 2.00-2.22 (m, 1H), 4.98 (d, 1H, J = 7.8 Hz), 5.94 (s, 1H), 6.06 (s, 1H).

3-Acetoxy-2-methyleneoctanenitrile (103):

It was obtained as colorless viscous liquid by the action of acetyl chloride on 3-hydroxy-2-methyleneoctanenitrile (**102**) in

presence of pyridine following similar procedure described for the molecule **100a**.

Yield : 87%

b.p. : 107°C/1.9 mm

IR (neat) : 1624, 2217 cm^{-1}

^1H NMR : δ 0.87 (dist. t, 3H), 1.21-1.42 (m, 6H), 1.62-1.88 (m, 2H), 2.08 (s, 3H), 5.24 (t, 1H, J = 6.4 Hz), 5.96 (s, 1H), 6.01 (s, 1H)

3-Acetoxy-2-methylenebutanenitrile (109):

It was obtained as colorless viscous liquid by the action of acetyl chloride on 3-hydroxy-2-methylenebutanenitrile (**108**) in presence of pyridine following similar procedure described for the molecule **100a**.

Yield : 74%

b.p. : 65°C/10 mm

IR (neat) : 1632, 2209 cm^{-1}

^1H NMR : δ 1.45 (d, 3H, J = 6 Hz), 2.09 (s, 3H), 5.42 (q, 1H, J = 6.6 Hz), 6.01 (s, 1H), 6.03 (s, 1H)

Methyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate (99a):

To a mixture of magnesium bromide (12 mM) (freshly prepared by treating 1,2-dibromoethane (0.86 mL, 10 mM) with magnesium turnings (0.243 g, 10 mM) in THF (20 mL) at room temperature) in

THF, a solution of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**98a**) (1.17 g, 5 mM) in THF (5 mL) was added at room temperature under N_2 atmosphere. The reaction mixture was refluxed for 1.5 h. Then THF was distilled off and 2N HCl (10 mL) solution was added to the residue and was extracted with ether (2 x 15 mL). The ethereal extract was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (1% ethyl acetate in hexane) to furnish **99a** as colorless liquid.

Yield : 1.067 g (84%)

IR (neat) : 1620, 1705 cm^{-1}

^1H NMR : δ 3.85 (s, 3H), 4.37 (s, 2H), 7.32-7.58 (m, 5H), 7.84 (s, 1H).

^{13}C NMR : δ 26.69, 52.35, 128.65, 128.82, 129.56, 134.17, 142.84, 166.48.

Methyl (2Z)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (99b)

It was prepared, as colorless liquid, by treating methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (**98b**) with $MgBr_2$ following similar procedure described for the molecule **99a**.

Time : 2 h

Yield : 80%

IR (neat) : 1615, 1710 cm^{-1}

^1H NMR : δ 2.38 (s, 3H), 3.86 (s, 3H), 4.41 (s, 2H), 7.25 (d, 2H, J = 7.8 Hz), 7.47 (d, 2H, J = 7.8 Hz), 7.79

(s, 1H)

^{13}C NMR : δ 21.33, 26.96, 52.23, 127.65, 129.55, 129.77, 131.33, 139.97, 142.96, 166.59.

Methyl (2Z)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (99c)

It was prepared as colorless liquid by treating methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (**98c**) with $MgBr_2$ following similar procedure described for the molecule **99a**.

Time : 1.5 h

Yield : 83%

IR (neat) : 1625, 1715 cm^{-1}

^{1}H NMR : δ 3.88 (s, 3H), 4.35 (s, 2H), 7.42 (d, 2H, J = 7 Hz), 7.52 (d, 2H, J = 7 Hz), 7.76 (s, 1H)

^{13}C NMR : δ 26.25, 52.53, 129.21, 130.94, 132.67, 135.77, 141.47, 166.34.

Methyl (2Z)-2-(bromomethyl)hex-2-enoate (99d):

It was prepared, as colorless liquid, by treating methyl 3-acetoxy-2-methylenehexanoate (**98d**) with $MgBr_2$ following similar procedure described for the molecule **99a**.

Time : 3 h

Yield : 64%

Z : E : >96 : <4

IR (neat) : 1625, 1710 cm^{-1}

^{1}H NMR : δ 0.98 (t, 3H, J = 7.4 Hz), 1.55 (sext, 2H, J = 7.4 Hz), 2.26 & 2.54 (2q, 2H, J = 7.4 Hz), 3.80 & 3.81 (2s, 3H), 4.21 & 4.23 (2s, 2H), 6.35 & 6.98 (2t, 1H, J = 7.6 Hz)

^{13}C NMR : δ 13.82, 21.42, 24.20, 30.77, 52.01, 129.36, 148.21, 166.00.

In ^{1}H NMR spectrum, the underlined chemical shift (δ) values are due to minor (E)-isomer.

Methyl (2Z)-2-(bromomethyl)-4-methylpent-2-enoate (99e):

It was prepared as colorless liquid by treating methyl 3-acetoxy-2-methylene-4-methylpentanoate (**98e**) with magnesium bromide following similar procedure described for the molecule **99a**.

Time : 3h

Yield : 67%

Z : E : >96 : <4

IR (neat) : 1635, 1705 cm^{-1}

^{1}H NMR : δ 1.12 (d, 6H, J = 6.6 Hz), 2.68-2.98 (m, 1H), 3.80 (s, 3H), 4.24 (s, 2H), 6.09 & 6.80 (2d, 1H, J = 10.4 Hz).

^{13}C NMR : δ 21.78, 24.37, 28.66, 52.28, 127.26, 154.53, 166.53.

In ^{1}H NMR spectrum, the underlined chemical shift (δ) values are due to minor (E)-isomer.

Methyl (2Z)-2-(bromomethyl)non-2-enoate (99f):

It was prepared, as colorless liquid, by treating methyl 3-acetoxy-2-methylenenonanoate (**98f**) with magnesium bromide following similar procedure described for the molecule **99a**.

Time : 3 h

Yield : 78%

Z : E : >96 : <4

IR (neat) : 1624, 1707 cm^{-1}

^{1}H NMR : δ 0.89 (dist. t, 3H), 1.22-1.68 (m, 8H), 2.29 & 2.54 (2q, 2H, J = 7.4 Hz), 3.72 & 3.80 (2s, 3H), 4.23 (s, 2H), 6.36 & 6.98 (2t, 1H J = 7.6 Hz)

^{13}C NMR : δ 13.88, 22.40, 24.11, 28.02, 28.77, 28.93, 31.46, 51.89, 129.10, 148.35, 165.86.

In ^{1}H NMR spectrum, underlined chemical shift (δ) values are due to minor (E)-isomer.

2-(Bromomethyl)-3-phenylprop-2-enenitrile (101a):

A mixture of 3-acetoxy-2-methylene-3-phenylpropanenitrile (**100a**) (1.0 g, 5 mM) and magnesium bromide (freshly prepared by the action of 1,2-dibromoethane (1.0 mL, 12 mM) on magnesium turnings (12 mM) in THF (20 mL) at room temperature) in THF (5 mL) was refluxed under N_2 atmosphere for 3h. THF was distilled off and the reaction mixture was diluted with 2N HCl solution (10 mL), and was extracted with ether (2 x 15 mL). The combined

ethereal extract was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (1% ethyl acetate in hexane) to afford **101a** as white solid.

Yield : 0.99 g (90%)

m.p. : 51-52^{o}C

E : Z : 91 : 9

IR (KBr) : 1610, 2120 cm^{-1}

^{1}H NMR : δ 4.19 (s) & 4.21 (d, 2H, J = 0.8 Hz), 7.22 & 7.34 (2s, 1H), 7.38-7.52 (m, 3H), 7.71-7.84 (m, 2H)

^{13}C NMR : δ 26.64, 32.70, 108.04, 117.04, 129.02, 129.21 130.41, 131.35, 132.40, 146.49, 147.17

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Bromomethyl)-3-(4-methylphenyl)prop-2-enenitrile (101b):

It was prepared, as colorless liquid, by treating 3-acetoxy-2-methylene-3-(4-methylphenyl)propanenitrile (**100b**) with magnesium bromide following similar procedure described for the molecule **101a**.

Time : 2 h

Yield : 85%

m.p. : 52-54^{o}C

E : Z : 90 : 10

IR (KBr) : 1590, 2200 cm^{-1}

^{1}H NMR : δ 2.40 (s, 3H), 4.21 (d, 2H, J = 0.6 Hz), 7.17 (s, 1H), 7.24 (m, 2H), 7.69 (d, 2H, J = 8.2 Hz)

^{13}C NMR : δ 21.59 & <u>26.93</u>, 33.02, 106.71, 117.30, 129.31, 129.77, <u>141.21</u>, 142.15, 146.57 & <u>147.32</u>

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Bromomethyl)-3-(4-chlorophenyl)prop-2-enenitrile (101c):

It was prepared, as colorless liquid, by treating 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanenitrile (**100c**) with magnesium bromide following similar procedure described for the molecule **101a**.

Time : 2 h

Yield : 77%

m.p. : 55-57^{o}C

E : Z : 95 : 5

IR (KBr) : 1595, 1615, 2224 cm^{-1}

^{1}H NMR : δ <u>4.18</u> & 4.21 (2d, 2H, J = 0.8 Hz), 7.18 & <u>7.30</u> (2s, 1H), 7.38-7.52 (m, 2H), 7.68-7.78 (m, 2H).

^{13}C NMR : δ 32.45, 108.86, 116.89, 129.46, 130.54, 131.00, 137.51, 145.07.

In ^{1}H NMR spectrum, the underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Bromomethyl)hex-2-enenitrile (101d):

It was prepared, as colorless liquid, by treating 3-acetoxy-2-methylenehexanenitrile (**100d**) with magnesium bromide following similar procedure described for the molecule **101a**.

Time : 10 h

Yield : 70%

E : Z : 91 : 9

IR (neat) : 1630, 2234 cm^{-1}

^{1}H NMR : δ 0.95 (t, 3H, J = 7.4 Hz), 1.50 (m, 2H), 2.26 & 2.37 (2q, 2H, J = 7 Hz), 3.99 (s, 3H), 6.50 (t, 1H, J = 7 Hz).

^{13}C NMR : δ 13.56, 13.73, 21.58, 24.45, 30.56, 33.58, 112.69, 113.07, 115.76, 151.94, 152.41.

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Bromomethyl)non-2-enenitrile (101e):

It was prepared, as colorless liquid, by treating 3-acetoxy-2-methylenenonanenitrile (**100e**) with magnesium bromide following similar procedure described for the molecule **101a**.

Time : 10 h

Yield : 78%

E : Z : 91 : 9

IR (neat) : 1628, 2225 cm^{-1}

^{1}H NMR : δ 0.88 (dist. t, 3H), 1.18-1.58 (m, 8H), 2.28 & 2.41 (2q, 2H, J = 7.2 Hz), 4.00 (s, 2H), 6.51 & 6.52 (2t, 1H, J = 7 Hz)

^{13}C NMR : δ 14.02, 22.50, 24.32, 27.96, 28.13, 28.71 28.87, 30.48, 31.47, 31.68, 112.39, 112.73,115.71, 152.21, 152.67.

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Bromomethyl)oct-2-enenitrile (101f):

It was prepared, as colorless liquid, by treating 3-acetoxy-2-methyleneoctanenitrile (**103**) with magnesium bromide following similar procedure described for the molecule **101a**.

Time : 10 h

Yield : 84%

E : Z : 88 : 12

IR (neat) : 1630, 2225 cm^{-1}

^{1}H NMR : δ 0.90 (dist. t, 3H), 1.22-1.64 (m, 6H), 2.29 & 2.36 (2q, 2H, J = 7.4 Hz), 4.03 (s, 2H), 6.53 & 6.55 (2t, 1H, J = 7.8 Hz)

^{13}C NMR : δ 13.62, 22.05, 24.32, 27.37, 27.50, 28.41, 30.44, 30.87, 31.02, 31.32, 112.07, 112.44, 115.44, 151.95 152.39

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

Methyl 2-(diethoxyphosphorylmethyl)-3-phenylprop-2-enoate (104a):

A solution of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**98a**) (1.17 g, 5 mM) and triethyl phosphite (1.2 mL, 7 mM) was stirred at 90°C for 30 min. Fractional distillation of reaction mixture under reduced pressure afforded **104a** as viscous liquid.

Yield : 1.35 g (87%)

b.p. : 168-170°C/1.6 mm

Z : E : 91 : 9

IR (neat) : 1615, 1710 cm^{-1}

^{1}H NMR : δ 1.22 & 1.28 (2t, 6H, J = 7 Hz), 2.98 & 3.21 (2d, 2H, J = 22 Hz), 3.62 & 3.80 (2s, 3H), 4.04 & 4.06 (2quint, 4H, J = 7 Hz), 6.90 & 7.78 (2d, 1H, J = 5.6 Hz), 7.28-7.62 (m, 5H).

^{13}C NMR : δ 16.17 (d, J ≈ 6.1 Hz), 26.05 & 32.32 (2d, J = 139.5 Hz), 51.60, 52.18, 61.94 (d, J = 6.4 Hz), 123.75 & 123.98 (2d, J = 11.6 Hz), 127.94, 128.08, 128.24, 128.47, 128.86, 129.29, 134.72 & 136.52 (2d, J = 3.2 Hz), 139.08 & 141.34 (2d, J = 11 Hz), 167.87.

^{31}P NMR : δ 24.31, 24.89

Analysis calculated for $C_{15}H_{21}O_5P$: C, 57.68; H, 6.77

Found : C, 57.72; H, 6.80

The underlined chemical shift (δ) values are due to minor (E)-isomer.

Methyl 2-(diethoxyphosphorylmethyl)-3-(4-methylphenyl)prop-2-enoate (104b):

This was obtained, as yellow colored viscous liquid, by the action of triethyl phosphite on methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (**98b**) following similar procedure described for the molecule **104a**.

Yield : 90%

b.p. : 193-195^{o}C/2.1 mm

Z : E : 90 : 10

IR (neat) : 1610, 1705 cm^{-1}

^{1}H NMR : δ 1.24 & 1.34 (2t, 6H, J = 7 Hz), 2.32 & 2.34 (2s, 3H), 2.98 & 3.22 (2d, 2H, J = 22 Hz), 3.66 & 3.81 (2s, 3H), 4.06 (quint, 4H, J = 7 Hz), 6.88 & 7.74 (2d, 1H, J = 5.6 Hz), 7.14 & 7.18 (2d, 2H, J = 8 Hz), 7.48 (d, 2H, J = 8 Hz).

^{13}C NMR : δ 16.07 (d, J = 6.1 Hz), 21.08, 26.03 & 32.31 (2d, J = 139.7 Hz), 51.43, 51.98, 61.85 (d, J = 6.6 Hz), 122.64 (d, J = 11.6 Hz), 128.20, 128.55, 129.07, 129.34, 131.75 & 132.52 (2d, J = 3.1 Hz), 138.00, 138.98, 141.29 (d, J = 10.9 Hz), 167.88.

^{31}P NMR : δ 24.39, 24.99.

Analysis calculated for $C_{16}H_{23}O_5P$: C, 58.88; H, 7.10

Found : C, 58.95; H, 7.14

The underlined chemical shift (δ) values are due to minor

(E)-isomer.

Methyl 3-(4-chlorophenyl)-2-(diethoxyphosphorylmethyl)prop-2-enoate (104c):

It was obtained as yellow colored viscous liquid by the action of triethyl phosphite on methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (**98c**) following similar procedure described for the molecule **104a**.

Yield : 90%

b.p. : 204-207^{o}C/2.3 mm

Z : E : 88 : 12

IR (neat) : 1615, 1645, 1708 cm^{-1}

^{1}H NMR : δ 1.26 & 1.31 (2t, 6H, J = 6.9 Hz), 3.01 & 3.18 (2d, 2H, J = 22.6 Hz), 3.64 & 3.83 (2s, 3H), 4.08 (quint, 4H, J = 7 Hz), 6.88 & 7.72 (2d, 1H, J = 7.4 Hz), 7.18 & 7.35 (2d, 2H, J = 8 Hz), 7.56 (d, 2H, J = 8 Hz).

^{13}C NMR : δ 16.15 (d, J = 6 Hz), 26.15 & 32.32 (2d, J = 139.5 Hz), 51.65, 52.19, 62.00 (d, J = 6.7 Hz), 124.35 & 124.89 (2d, J = 11.7 Hz), 128.11, 128.67, 129.60, 130.67, 133.10 & 133.95 (2d, J = 3 Hz), 134.88, 137.85 & 139.95 (2d, J = 11.1 Hz), 167.59.

^{31}P NMR : δ 24.01, 24.47

Analysis calculated for $C_{15}H_{20}O_5PCl$: C, 51.95; H, 5.81

Found : C, 51.85; H, 5.81

The underlined chemical shift (δ) values are due to minor (E)-isomer.

Methyl 2-(diethoxyphosphorylmethyl)hex-2-enoate (104d):

It was obtained, as colorless liquid, by the action of triethyl phosphite on methyl 3-acetoxy-2-methylenehexanoate (**98d**) following similar procedure described for the molecule **104a**.

Yield : 95%

b.p. : 144-146^{o}C/2.9 mm

Z : E : 65 : 35

IR (neat) : 1645, 1716 cm^{-1}

^{1}H NMR : δ 0.90 & 0.93 (2t, 3H, J = 6 Hz), 1.28 & 1.34 (2t, 6H, J = 7 Hz), 1.50 (m, 2H), 2.28 & 2.50 (2m, 2H), 2.84 & 2.98 (2d, 2H, J = 24 Hz) 3.76 (s, 3H), 4.08 (quint, 4H, J = 7 Hz), 6.14 & 6.91 (q, 1H, J = 6 Hz).

^{13}C NMR : δ 12.89, 13.06, 15.54 (d, J = 5.9 Hz), 20.95 & 21.63 (2d, J = 1.7 Hz), 24.19 & 30.43 (2d, J = 139.7 Hz), 30.43, 30.47, 31.00, 50.61, 51.07, 61.07 & 62.72 (2d, J = 6.4 Hz), 121.77 & 122.33 (2d, J = 11.3 Hz), 145.06 & 146.26 (2d, J = 10.2 Hz), 166.09 & 166.28.

^{31}P NMR : δ 25.04, 25.24.

Analysis calculated for $C_{12}H_{23}O_5P$: C, 51.79; H, 8.32

Found : C, 51.74; H, 8.31

The underlined chemical shift (δ) values are due to minor (E)-isomer.

Methyl 2-(diethoxyphosphorylmethyl)-3-(2-methoxyphenyl)prop-2-enoate (104e):

This was obtained as yellow colored viscous liquid by the action of triethyl phosphite on methyl 3-acetoxy-2-methylene-3-(2-methoxyphenyl)propanoate (**106**) following similar procedure described for the molecule **104a**.

Yield : 95%

b.p. : 185-186^{O}C/1.5 mm

Z : E : 93 : 7

IR (neat) : 1633, 1716 cm^{-1}

^{1}H NMR : δ 1.26 & <u>1.28</u> (2t, 6H, J = 7 Hz), <u>3.08</u> & 3.18 (2d, 2H, J = 22 Hz), <u>3.61</u> & 3.84 (2s, 6H), 4.06 (quint, 4H, J = 7 Hz), 6.82-7.06 (m, 2H), 7.32-7.38 (m, 1H), 7.73 (d, 1H, J = 6Hz), 7.94 (d, 1H, J = 6Hz).

^{13}C NMR : 16.03 (d, J = 6.1 Hz), 26.08 & <u>32.08</u> (2d, J = 139.5 Hz), <u>51.31</u>, 51.92, 55.20, 61.73 & 62.03 (2d, J = 6.3 Hz), 110.25, <u>119.81</u>, 120.22, 123.43, 123.65, <u>129.44</u>, 129.77, 130.27, <u>135.50</u> & 137.32 (2d, J = 11.1 Hz), <u>156.46</u>, 157.26, 167.77.

^{31}P NMR : δ <u>24.39</u>, 25.19.

Analysis calculated for $C_{16}H_{23}O_6P$: C, 56.13; H, 6.77

Found : C, 56.08; H, 6.73

The underlined chemical shift (δ) values are due to minor (E)-isomer.

Methyl 2-(diethoxyphosphorylmethyl)non-2-enoate (104f):

It was obtained as colorless viscous liquid by the action of triethyl phosphite on methyl 3-acetoxy-2-methylenenonanoate (**98f**) following similar procedure described for the molecule **104a**.

Yield : 90%

b.p. : 149-151^{o}C/1.5 mm

Z : E : 65 : 35

IR (neat) : 1645, 1718 cm^{-1}

^{1}H NMR : δ 0.87 (dist. t, 3H), 1.12-1.58 (m, 14H), 2.24 & 2.52 (2m, 2H), 2.85 & 2.95 (2d, 2H, J = 24 Hz), 3.72 (s, 3H), 4.08 (quint, 4H, J = 7 Hz), 6.14 & 6.91 (2q, 1H, J = 5.8 Hz).

^{13}C NMR : δ 13.55, 15.89 (d, J = 5.9 Hz), 22.11, 24.53 & 30.77 (2d, J = 139.8 Hz), 27.98, 28.47, 28.65, 28.86, 29.38, 31.21, 50.97, 51.44, 61.42 & 63.07 (2d, J = 6.5 Hz), 121.79 & 122.42 (2d, J = 11.3 Hz), 145.79 & 147.02 (2d, J = 10.1 Hz), 166.51, 166.68.

^{31}P NMR : δ 25.30, 25.46

Analysis calculated for $C_{15}H_{29}O_5P$: C, 56.23; H, 9.12

Found : C, 56.25; H, 9.13

The underlined chemical shift (δ) values are due to minor (E)-isomer.

2-(Diethoxyphosphorylmethyl)-3-phenylprop-2-enenitrile (107a):

A solution of 3-acetoxy-2-methylene-3-phenylpropanenitrile (**100a**) (1.05 g, 5 mM) and triethyl phosphite (1.2 mL, 7 mM) was heated at 90°C for 30 min. Fractional distillation of reaction mixture under reduced pressure afforded **107a** as colorless liquid.

Yield : 1.31 g (94%)

b.p. : 190-192°C/2.8 mm

E : Z : 75 : 25

IR (neat) : 1620, 2216 cm^{-1}

^1H NMR : δ 1.33 & 1.36 (t, 6H, J = 7.4 Hz), 2.90 & 2.98 (2d, 2H, J = 20.9 Hz), 4.02-4.34 (m, 4H), 7.02 (d, 1H, J = 4 Hz), 7.34-7.84 (m, 5H).

^{13}C NMR : δ 15.65, 16.02 (2d, J = 5.4Hz), 27.92 & 32.77 (2d, J = 140.5 Hz), 62.26 & 63.28 (2d, J = 6.5 Hz), 100.91 & 105.57 (2d, J = 12.1 Hz), 117.82 & 119.37 (2d, J = 4.8 Hz), 128.44, 128.66, 129.46, 130.11, 132.93 (d, J = 3 Hz), 147.11 & 147.27 (2d, J = 10.5 Hz).

^{31}P NMR : δ 21.65, 21.97.

Analysis calculated for $C_{14}H_{18}NO_3P$: C, 60.21; H, 6.49; N, 5.01

Found : C, 60.19; H, 6.46; N, 5.02

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Diethoxyphosphorylmethyl)-3-(4-methylphenyl)prop-2-enenitrile (107b):

This was obtained as yellow colored viscous liquid by the action of triethyl phosphite on 3-acetoxy-2-methylene-3-(4-methylphenyl)propanenitrile (**100b**) following similar procedure described for the molecule **107a**.

Yield : 90%

b.p. : 182-184^{o}C/1.8 mm

E : Z : 80 : 20

IR (neat) : 1608, 2214 cm^{-1}

^{1}H NMR : δ 1.36 (t, 6H, J = 7 Hz), 2.38 (s, 3H), 2.88 & <u>3.02</u> (2d, 2H, J = 20.8 Hz), 4.08-4.32 (m, 4H), 7.08 (d, 1H, J = 6.2 Hz) 7.16-7.72 (m, 4H).

^{13}C NMR : δ 16.28 (d, J = 5.15 Hz), 21.34, <u>28.24</u> & 33.02 (2d, J = 140.8 Hz), 62.55 & 63.61 (2d, J = 6.5 Hz), 99.61 & <u>104.40</u> (2d, J = 12.1 Hz), 118.34 & <u>119.84</u> (2d, J = 4.7 Hz), 128.72, <u>129.03</u>, 129.43, 130.49 (d, J = 3.3 Hz), <u>140.19</u>, 140.93, 147.41 & <u>147.61</u> (2d, J = 10.3 Hz).

^{31}P NMR : δ <u>21.81</u>, 22.18.

Analysis calculated for $C_{15}H_{20}NO_3P$: C, 61.43; H, 6.87; N, 4.77

Found : C, 61.37; H, 6.84; N, 4.76

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Diethoxyphosphorylmethyl)but-2-enenitrile (107c):

This was obtained, as yellow colored viscous liquid, by the action of triethyl phosphite on 3-acetoxy-2-methylenebutane-nitrile (**109**) following the similar procedure described for the the molecule **107a**.

Yield : 85%

b.p. : 92-94^{o}C/1.7 mm

E : Z : 91 : 9

IR (neat) : 1635, 2215 cm^{-1}

^{1}H NMR : δ 1.30 (t, 3H, J = 7.2 Hz), <u>1.88</u> & 1.99 (2t, 3H, J = 6.6 Hz), 2.65 & <u>2.70</u> (2d, 2H, J = 20.6 Hz), 4.10 (m, 4H), 6.41 & <u>6.59</u> (2m, 1H)

^{13}C NMR : δ <u>14.78</u>, <u>15.89</u> & 16.22 (2d, J = 5.7 Hz), 17.39, <u>26.99</u> & 31.19 (2d, J = 141.8 Hz), 62.40 & <u>63.45</u> (2d, J = 6.7 Hz), 105.91 (2d, J = 11.5 Hz), 116.49, <u>147.11</u> & 147.44 (2d, J = 10.6 Hz).

^{31}P NMR : δ <u>22.14</u>, 22.29.

Analysis calculated for $C_9H_{16}NO_3P$: C, 49.76; H, 7.42; N, 6.44

Found : C, 49.65; H, 7.45; N, 6.40

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

2-(Diethoxyphosphorylmethyl)hex-2-enenitrile (107d):

It was obtained, as colorless viscous liquid, by the action of triethyl phosphite on 3-acetoxy-2-methylenehexanenitrile (**100d**) following the similar procedure described for the molecule **107a**.

Yield : 91%

b.p. : 146-148^{o}C/1.6 mm

E : Z : 93 : 7

IR (neat) : 1640, 2220 cm^{-1}

^{1}H NMR : δ 0.96 (t, 3H, J = 7.4 Hz), 1.35 (t, 6H, J = 6.6 Hz), 1.51 (sext, 2H, 7.4 Hz), 2.26 & 2.39 (2m, 2H), 2.71 & 2.75 (2d, 2H, J = 20.5 Hz), 4.16 (m, 4H), 6.39 & 6.52 (2m, 1H).

^{13}C NMR : δ 13.16, 13.40, 15.77 & 16.09 (2d, J = 5.7 Hz), 21.13 & 21.40 (2d, J = 2.6 Hz), 26.87 & 31.05 (2d, J = 141.4 Hz), 30.67, 33.45, 62.22 & 63.30 (2d, J = 6.4 Hz), 104.85 (d, J = 11.4 Hz), 116.56, 119.01, 151.86 & 152.32 (2d, J = 10.4 Hz).

^{31}P NMR : δ 21.91, 22.24.

Analysis calculated for $C_{11}H_{20}NO_3P$: C, 53.87; H, 8.22; N, 5.71

Found : C, 53.92; H, 8.20; N, 5.69

The underlined chemical shift (δ) values are due to minor

(Z)-isomer.

2-(Diethoxyphosphorylmethyl)non-2-enenitrile (107e):

It was obtained as yellow colored viscous liquid by the action of triethyl phosphite on 3-acetoxy-2-methylenenonanenitrile (**100e**) following similar procedure described for the molecule **107a**.

Yield : 88%

b.p. : 172-174^{O}C/2.4 mm

E : Z : 93 : 7

IR (neat) : 1620, 2220 cm^{-1}

^{1}H NMR : δ 0.88 (dist. t, 3H), 1.18-1.56 (m, 14H), 2.26 & 2.41 (2m, 2H), 2.69 & 2.73 (2d, 2H, J = 21.4 Hz), 4.15 (m, 4H), 6.39 & 6.52 (2m, 1H)

^{13}C NMR : δ 13.72, 15.85 & 16.10 (2d, J = 5.7 Hz), 22.24, 27.83, 28.03, 28.08, 28.36, 28.56, 28.65, 27.13 & 31.08 (2d, J = 141.4 Hz), 31.22, 31.60, 62.25 & 62.32, (2d, J = 6.7 Hz), 104.67 (d, J = 11.5 Hz), 116.62 & 119.04 (2d, J = 4.2 Hz), 152.10 & 152.60 (2d, J = 10.5 Hz).

^{31}P NMR : δ 21.92, 22.24

Analysis calculated for $C_{14}H_{26}NO_3P$: C, 58.52; H, 9.12; N, 4.87

Found : C, 58.45; H, 9.15; N, 4.86

The underlined chemical shift (δ) values are due to minor

(Z)-isomer.

2-(Diethoxyphosphorylmethyl)-4-methylpent-2-enenitrile (107f):

This was obtained, as yellow colored viscous liquid, by the action of triethyl phosphite on 3-acetoxy-2-methylene-4-methyl-pentanenitrile (**100f**) following the similar procedure described for the the molecule **107a**.

Yield : 92%

b.p. : 119-121^{o}C/1.6 mm

E : Z : 91 : 9

IR (neat) : 1620, 2210 cm^{-1}

^{1}H NMR : δ <u>1.03</u> & 1.05 (2d, 6H, J = 6.6 Hz), 1.33 & <u>1.34</u> (2t, 6H, J = 7 Hz), 2.64 & <u>2.72</u> (2d, 2H, J = 20.6 Hz), 2.80-2.98 (m, 1H), 4.13 (m, 4H), 6.16 & <u>6.31</u> (2m, 1H)

^{13}C NMR : δ <u>15.77</u> & 16.07 (2d, J = 5.7 Hz), <u>21.20</u>, 21.50, 21.54, <u>26.99</u> & 30.95 (2d, J = 142 Hz), 31.39, 62.22 & 63.31 (2d, J = 6.5 Hz), 102.41 (d, J = 11.3 Hz), 116.41, <u>157.86</u> & 158.72 (2d, J = 10.5 Hz).

^{31}P NMR : δ <u>21.94</u>, 22.13

Analysis calculated for $C_{11}H_{20}NO_3P$: C, 53.87; H, 8.22; N, 5.71

Found : C, 53.95; H, 8.25; N, 5.70

The underlined chemical shift (δ) values are due to minor (Z)-isomer.

Methyl (2E)-2-benzyl-3-phenylprop-2-enoate (110a):

To a stirred solution of methyl 3-acetoxy-2-methylenepropanoate (**98a**) (1.17 g, 5 mM) in dry benzene, anhydrous $AlCl_3$ (1.07 g, 8 mM) was added at room temperature under N_2 atmosphere. After 2h, the reaction mixture was cooled to 0^oC and diluted with ether (25 mL) and 2N HCl solution (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2 x 25 mL). The combined organic extract was dried over anhydrous Na_2SO_4 concentrated and the resultant crude product was purified by column chromatogaphy (1% ethyl acetate in hexane) to afford **110a** as colorless liquid.

Yield : 0.94 g (75%)

E : Z : >96 : <4

IR (neat) : 1630, 1716 cm^{-1}

^1H NMR : δ 3.57 & 3.76 (2s, 3H), 3.96 (s, 2H), 6.64 & 7.94 (2s, 1H), 7.08-7.44 (m, 10H)

^{13}C NMR : δ 33.13, 41.24, 51.41, 51.96, 126.07, 126.53, 127.87, 128.50, 128.69, 129.13, 130.76, 134.95, 135.32, 139.36, 140.85, 168.50.

The underlined chemical shift (δ) values in ^{13}C NMR spectra are due to minor (Z)-isomer.

Methyl (2E)-2-benzyl-3-(2-methoxyphenyl)prop-2-enoate (110b):

It was prepared as colorless liquid by the $AlCl_3$ catalyzed

reaction of methyl 3-acetoxy-3-(2-methoxyphenyl)-2-methylenepropanoate (**106**) with benzene following similar procedure described for the molecule **110a**.

Time : 1 h

Yield : 40%

E : Z : >96 : <4

IR (neat) : 1630, 1713 cm^{-1}

^1H NMR : δ <u>3.51</u> & 3.74 (2s, 3H), 3.85 (s, 3H), 3.88 (s, 2H), 6.78-7.64 (m, 9H), 8.06 (s, 1H).

The underlined chemical shift (δ) value in ^1H NMR spectra are due to minor (Z)-isomer. ^1H NMR spectrum indicates the presence of $\tilde{}$ 10% unidentifiable impurity.

Methyl (2E)-2-benzyl-3-(4-chlorophenyl)prop-2-enoate (110c):

It was prepared as colorless liquid by the $AlCl_3$ catalyzed reaction of methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (**98c**) with benzene following similar procedure described for the molecule **110a**.

Time : 1.5 h

Yield : 85%

E : Z : >96 : <4

IR (neat) : 1624, 1709 cm^{-1}

^1H NMR : δ <u>3.57</u> & 3.74 (2s, 3H), 3.92 (s, 2H), <u>6.58</u>, & 7.86 (2s, 1H), 7.08-7.44 (m, 9H).

The underlined chemical shift (δ) value in ^{1}H NMR spectra are due to minor (Z)-isomer. ^{1}H NMR spectrum indicates the presence of $\tilde{}$ 10% unidentifiable impurity.

Methyl 2-benzylnon-2-enoate (110d):

It was prepared as colorless liquid by the $AlCl_3$ catalyzed reaction of methyl 3-acetoxy-2-methylenenonanoate (**98f**) with benzene following similar procedure described for the molecule **110a**.

Time : 10 h reflux

Yield : 65%

E : Z : 80 : 20

IR (neat) : 1602, 1645, 1716 cm^{-1}

^{1}H NMR : δ 0.84 (dist. t, 3H), 1.12-1.52 (m, 8H), 2.18 and 2.27 (q, 2H, J = 5.8 Hz), 3.52-3.68 (m, 5H), 5.90 and 6.91 (t, 1H, J = 7.4 Hz), 7.04-7.32 (m, 5H)

^{13}C NMR : δ 13.95, 22.48, 28.58, 28.87, 28.99, 29.28, 29.54, 31.55, 32.24, 40.37, 50.97, 51.51, 125.83, 126.02, 128.08, 128.20, 128.58, 130.68, 130.85, 139.53, 139.70, 144.27, 167.79, 167.96.

The underlined chemical shift (δ) values in ^{13}C NMR spectra are due to minor (E)-isomer.

Methyl (2Z)-2-benzyl-3-phenylprop-2-enenitrile (111a):

To a stirred solution of 3-acetoxy-2-methylene-3-phenylprop-

anenitrile (**100a**) (1.005 g, 5 mM) in dry benzene, anhydrous $AlCl_3$ (1.07 g, 8 mM) was added at room temperature under N_2 atmosphere. After 1h, the reaction mixture was cooled to 0^oC and diluted with ether (10 mL) and 2N HCl solution (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic extract was dried over anhydrous Na_2SO_4, concentrated and the resultant crude product was purified by column chromatogaphy (1% ethyl acetate in hexane) to afford **111a** as colorless liquid.

Yield : 0.82 g (75%)

Z : E : 98 : 2

IR (neat) : 1590, 2200 cm^{-1}

^1H NMR : δ 3.71 (s, 2H), 6.96 (s, 1H), 7.22-7.48 (m, 8H), 7.68-7.78 (m, 2H)

^{13}C NMR : δ <u>35.42</u>, 42.06, 110.69, 118.61, 127.26, 128.60, 128.72, 128.81, 130.03, 133.51, 136.44, 143.97.

The underlined chemical shift value in ^{13}C NMR is due to minor ($\sim$ 2%) (E)-isomer.

(2Z)-2-benzyl-3-(4-methylphenyl)prop-2-enenitrile (111b):

It was prepared as colorless liquid by the $AlCl_3$ catalyzed reaction of 3-acetoxy-2-methylene-3-(4-methylphenyl)propanenitrile (**100b**) with benzene following similar procedure described for the molecule **111a**.

Time : 1.5 h

Yield : 74%

IR (neat) : 1608, 2210 cm^{-1}

^{1}H NMR : δ 2.31 (s, 3H), 3.61 (s, 2H), 6.88 (s, 1H), 7.14 (d, 2H, J = 8 Hz), 7.20-7.38 (m, 5H), 7.60 (d, 2H, J = 8 Hz).

^{13}C NMR : δ 21.31, 42.00, 109.31, 118.82, 127.15, 128.58, 128.75, 129.39, 130.77, 136.60, 140.38, 143.94.

Methyl (2Z)-2-benzyl-3-(4-chlorophenyl)prop-2-enenitrile (111c):

It was prepared as colorless liquid by the $AlCl_3$ catalyzed reaction of 3-acetoxy-2-methylene-3-(4-chlorophenyl)propane nitrile (**100c**) with benzene following similar procedure described for the molecule **111a**.

Time : 1 h

Yield : 85%

IR (neat) : 1593, 1614, 2212 cm^{-1}

^{1}H NMR : δ 3.60 (s, 2H), 6.83 (s, 1H), 7.12-7.36 (m, 7H), 7.57 (d, 2H, J = 8.2 Hz)

^{13}C NMR : δ 41.97, 111.44, 118.31, 127.34, 128.83, 128.92, 129.83, 131.93, 135.83, 136.13, 142.45.

(2Z)-2-benzylhex-2-enenitrile (111d):

It was prepared as colorless liquid by the $AlCl_3$ catalyzed

reaction of 3-acetoxy-2-methylenehexanenitrile (**100d**) with benzene at reflux temperature for 40 h followed by usual workup as described for the molecule **111a**.

Yield : 46%

Z : E : >96 : <4

IR (neat) : 1602, 1633, 2216 cm^{-1}

^1H NMR : δ 0.93 (t, 3H, J = 7.4 Hz), 1.47 (m, 2H), 2.35 (q, 2H, J = 7.2 Hz), 3.50 & 4.12 (2s, 3H), 6.18 & 6.38 (2t, 1H, J = 7.6 Hz), 7.14-7.42 (m, 5H).

^{13}C NMR : δ 13.52, 21.47, 21.84, 33.42, 40.32, 43.96, 114.39, 117.53, 127.09, 128.73, 136.72, 148.48, 151.86.

Methyl (2Z)-2-(chloromethyl)-3-phenylprop-2-enoate (112a):

A solution of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**98a**) (1.17 g, 5 mM) in dry dichloromethane (10 mL) was stirred at room temperature in the presence of anhydrous $AlCl_3$ (1.07 g, 8 mM) for 2 h. Then the reaction mixture was diluted with ether (10 mL) and 2N HCl solution (10 mL) was added at 0°C. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic extract was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (1% ethyl acetate in hexane) to afford **112a** as colorless liquid.

Yield : 0.76 g (72%)

b.p. : 142-144^{o}C/5 mm

IR (neat) : 1718, 1630 cm^{-1}

^{1}H NMR : δ 3.87 (s, 3H), 4.47 (d, 2H, J = 1.4 Hz), 7.32-7.52 (m, 5H), 7.87 (s, 1H)

^{13}C NMR : δ 38.98, 52.22, 128.32, 128.73, 129.48, 129.57, 134.01, 143.54, 166.47.

Analysis caculated for $C_{11}H_{11}O_2Cl$: C, 62.71; H, 5.26

Found : C, 62.67; H, 5.25

Methyl 2-methyl-3-phenylpropanoate (113):

To a stirred suspension of magnesium powder (0.14 g, 6 mM) in absolute methanol (10 mL) at 0^{o}C was added methyl (2Z)-2-(chloromethyl)-3-phenylprop-2-enoate (**112a**) (0.42 g, 2 mM) dropwise under N_2 atmosphere. After 1h, methanol was removed under reduced pressure and the reaction mixture was acidified with 2N HCl solution (5 mL) and extracted with ether (2 x 10 mL). The ethereal extract was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography to afford **113** as colorless liquid.

Yield : 0.227 g (64%)

IR (neat) : 1604, 1738 cm^{-1}

^{1}H NMR : δ 1.15 (d, 3H, 6.8 Hz), 2.71 (m, 2H), 3.02 (m, 1H), 3.64 (s, 3H), 7.12-7.38 (m, 5H)

^{13}C NMR : δ 16.76, 39.75, 41.44, 51.57, 126.34, 128.38, 128.98, 139.38, 176.55.

Methyl (2Z)-2-(chloromethyl)-3-(4-methylphenyl)prop-2-enoate (112b):

It was prepared as colorless liquid by the treatment of methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (**98b**) with anhydrous $AlCl_3$ in dichloromethane following similar procedure described for the molecule **112a**.

Time : 2 h

Yield : 56%

b.p. : 128-129^{o}C/3 mm

IR (neat) : 1610, 1630, 1716 cm^{-1}

^{1}H NMR : δ 2.39 (s, 3H), 3.87 (s, 3H), 4.49 (s, 2H), 7.25 (d, 2H, J = 8 Hz), 7.46 (d, 2H, J = 8 Hz), 7.85 (s, 1H)

^{13}C NMR : δ 21.36, 39.28, 52.29, 127.39, 129.58, 129.76, 131.27, 140.14, 143.85, 166.80.

Analysis caculated for $C_{12}H_{13}O_2Cl$: C, 64.14; H, 5.83

Found : C, 64.17; H, 5.81

Methyl (2Z)-2-(chloromethyl)-3-(4-chlorophenyl)prop-2-enoate (112c):

It was prepared as colorless liquid by the treatment of methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (**98c**) with anhydrous $AlCl_3$ in dichloromethane following similar procedure described for the molecule **112a**.

Time : 2 h

Yield : 78%

b.p. : 148-149^{o}C/4 mm

IR (neat) : 1631, 1718 cm^{-1}

^{1}H NMR : δ 3.88 (s, 3H), 4.43 (s, 2H), 7.38-7.54 (m, 4H), 7.81 (s, 1H)

^{13}C NMR : δ 38.78, 52.49, 128.98, 129.18, 130.92, 132.56, 135.88, 142.29, 166.40.

Analysis caculated for $C_{11}H_{10}O_2Cl_2$: C, 53.90; H, 4.11

Found : C, 53.90; H, 4.14

Methyl (2Z)-2-(chloromethyl)-3-(2,4-dichlorophenyl)prop-2-enoate (112d):

It was prepared as colorless solid by the treatment of methyl 3-acetoxy-3-(2,4-dichlorophenyl)-2-methylenepropanoate (**116**) with anhydrous $AlCl_3$ following similar procedure described for the molecule **112a**.

Time : 1.5 h

Yield : 70%

m.p. : 72-74^{o}C

IR (KBr) : 1630, 1714 cm^{-1}

^{1}H NMR : δ 3.89 (s, 3H), 4.32 (s, 2H), 7.42-7.62 (m, 3H), 7.88 (s, 1H)

^{13}C NMR : δ 38.66, 52.64, 127.51, 129.78, 130.84, 131.29, 135.27, 136.14, 139.10, 165.88

Analysis caculated for $C_{11}H_9O_2Cl_3$: C, 47.26; H, 3.24

Found : C, 47.38; H, 3.20

Methyl (2Z)-2-(chloromethyl)-3-(2-nitrophenyl)prop-2-enoate (112e):

It was prepared as pale yellow crystals by the treatment of methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**117**) with anhydrous $AlCl_3$ in dichloromethane following similar procedure described for the molecule **112a**.

Time : 1.5 h

Yield : 66%

m.p. : 87-89^{o}C

IR (KBr) : 1604, 1643, 1718 cm^{-1}

^{1}H NMR : δ 3.91 (s, 3H), 4.24 (s, 2H), 7.54-7.82 (m, 3H), 8.11 (s, 1H), 8.22 (d, 1H, J = 6 Hz)

^{13}C NMR : δ 38.57, 52.62, 125.18, 129.88, 130.16, 130.66, 134.04, 140.37, 147.39, 165.69.

Analysis caculated for $C_{11}H_{10}NO_4Cl$: C, 51.67; H, 3.94; N, 5.47

Found : C, 51.82; H, 3.96; N, 5.43

Reaction of 100a with $AlCl_3$ in Dichloromethane

To a stirred solution of 3-acetoxy-2-methylene-3-phenylpropanenitrile (**100a**) (1.05 g, 5 mM) in dry dichloromethane (10 mL) was added anhydrous $AlCl_3$ (1.07 g, 8 mM) at room temperature

under N_2 atmosphere. After 2h, the reaction mixture was diluted with ether (15 mL) and was acidified with 2N HCl solution (10 mL) at 0°C. The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined ethereal extract was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (1% ethyl acetate in hexane) to afford **118** as colorless solid and **119** as colorless liquid.

(2E)-2-(Chloromethyl)-3-phenylprop-2-enenitrile (118):

Yield : 0.38 g (43%)

m.p. : 55-57°C

IR (KBr) : 1615, 2195 cm^{-1}

^1H NMR : δ 4.31 (d, 2H, J = 0.96 Hz), 7.22 (s, 1H), 7.32-7.58 (m, 3H), 7.68-7.92 (m, 2H)

^{13}C NMR : δ 39.93 and 45.97, 107.51, 116.93, 128.93, 129.12, 130.44, 131.24, 132.25, 146.64, 147.83.

Analysis caculated for $C_{10}H_8NCl$: C, 67.61; H, 4.53; N, 7.88

Found : C, 67.63; H, 4.52; N, 7.88

The underlined chemical shift (δ) values in ^{13}C NMR are due to minor (Z)-isomer (approximately 5-10%). However, ^1H NMR does not indicate the presence of any (Z)-isomer.

(2E)-2-(Acetoxymethyl)-3-phenylprop-2-enenitrile (119):

Yield : 0.41 g (40%)

IR (neat) : 1626, 1747, 2216 cm^{-1}

^1H NMR : δ 2.15 (s, 3H), 4.81 (d, 2H, J = 1 Hz), 7.22 (s,

1H), 7.42-7.54 (m, 3H), 7.72-7.84 (m, 2H)

^{13}C NMR : δ 20.68, 65.18, 105.82, 117.18, 128.92, 129.13, 131.08, 132.54, 147.28, 170.20.

Analysis caculated for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96

Found : C, 71.62; H, 5.53; N, 6.95

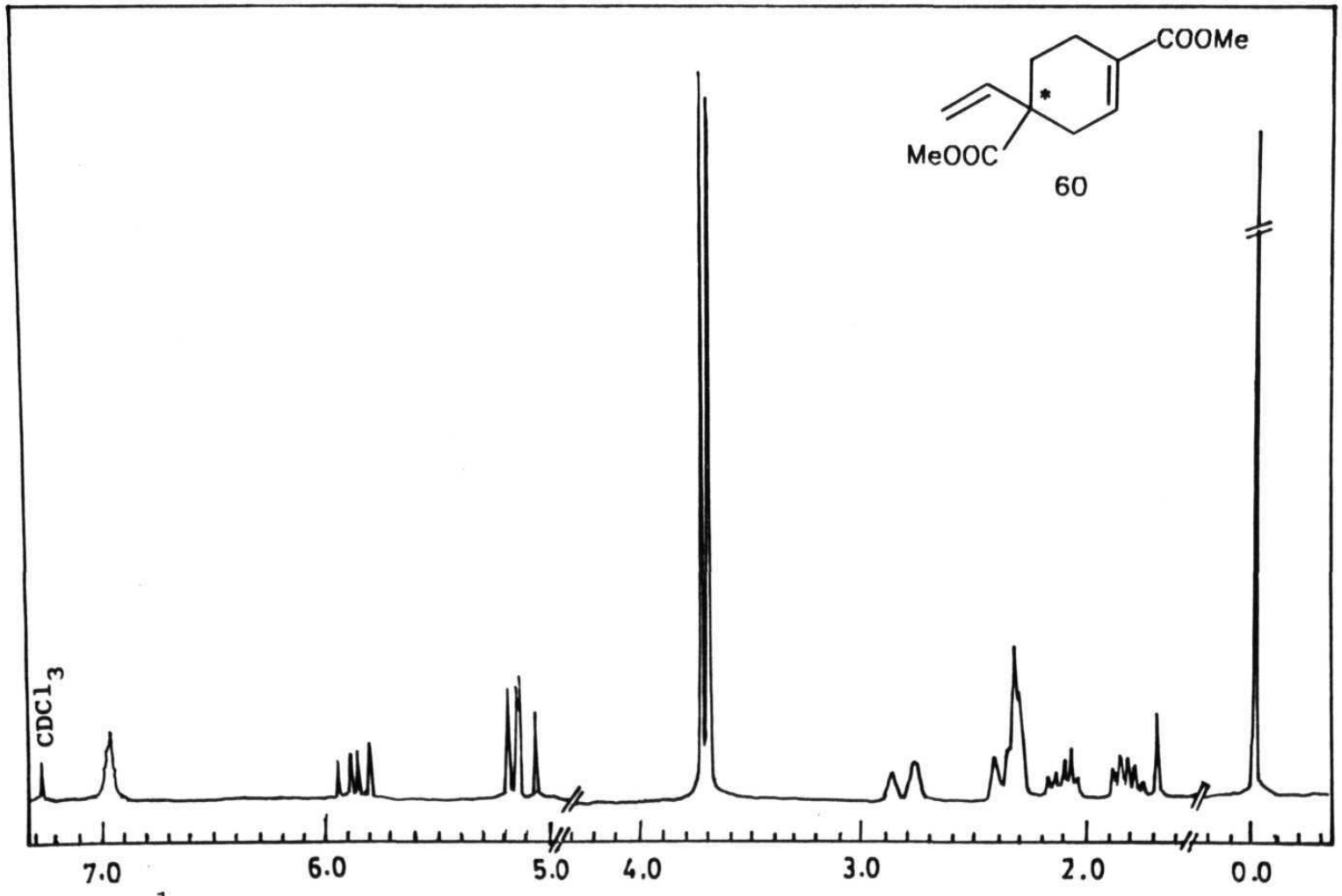


Fig.1: ^{1}H NMR Spectrum of **60**

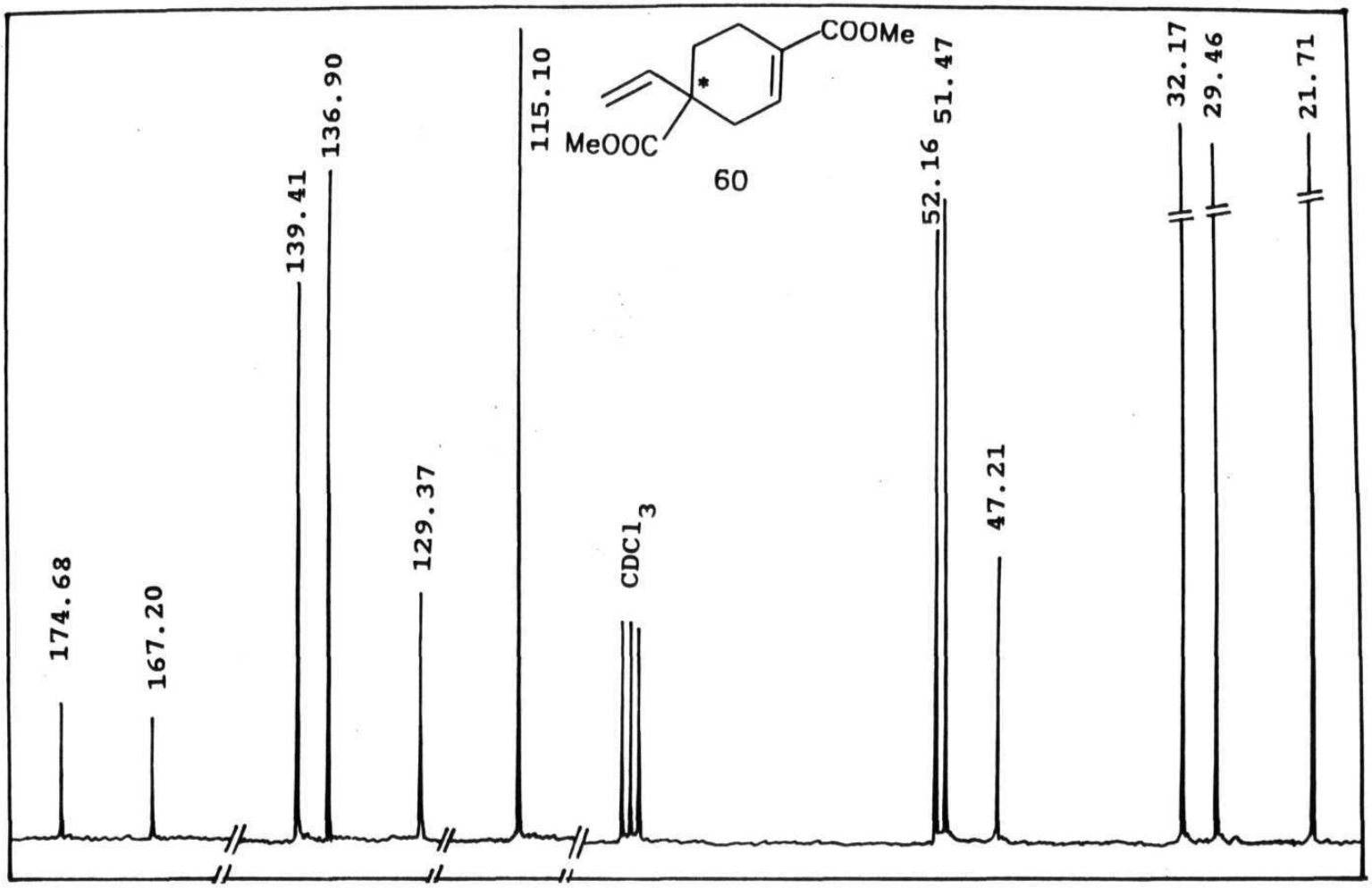


Fig.2: ^{13}C NMR Spectrum of **60**

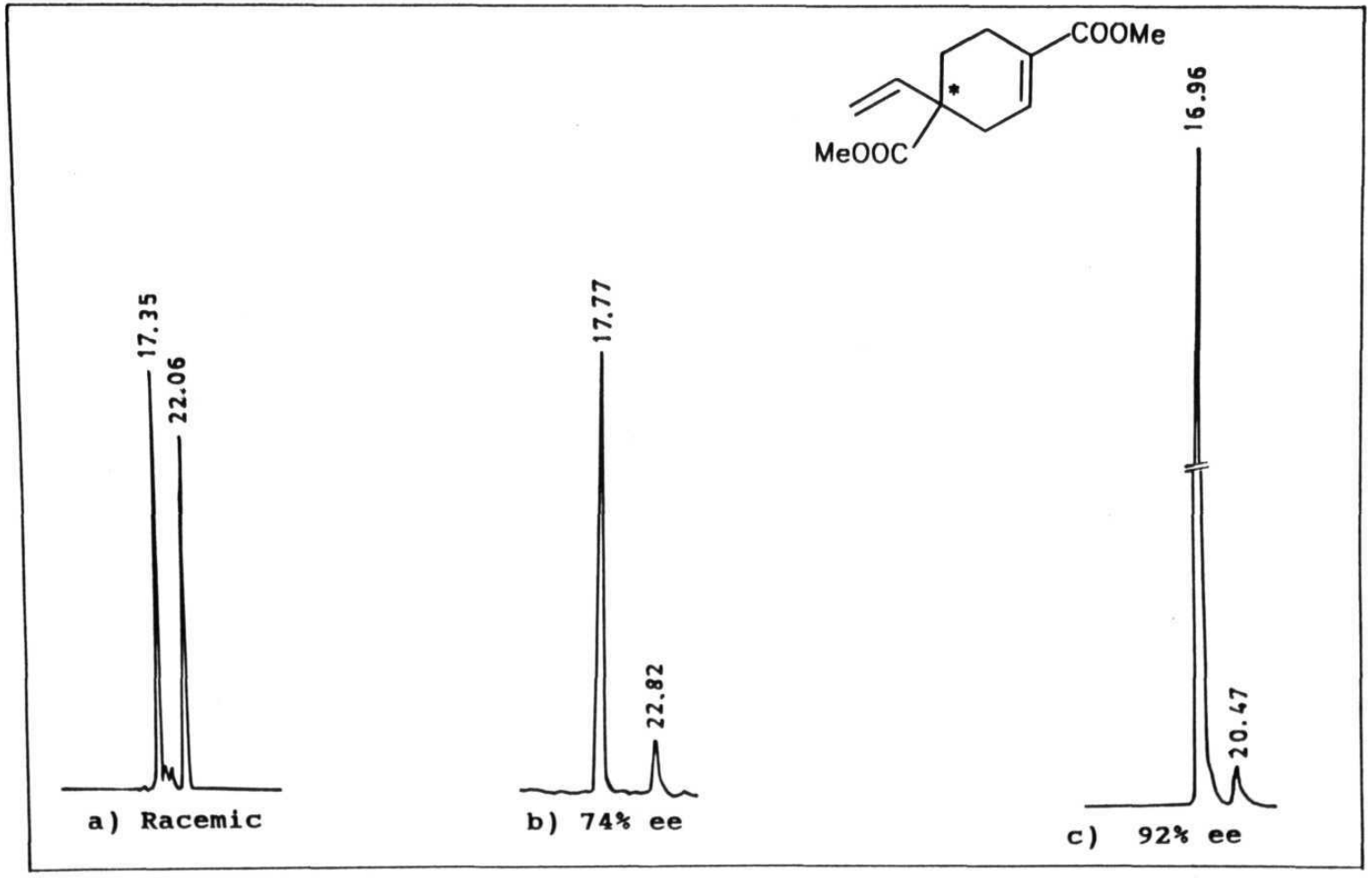


Fig.3: HPLC analysis of **60, 60e** and **60e'** on CHIRALCEL OD column
a) Chromatogram of **60**, b) Chromatogram of **60e** (74% ee) and
c) Chromatogram of **60e'** (92% ee)

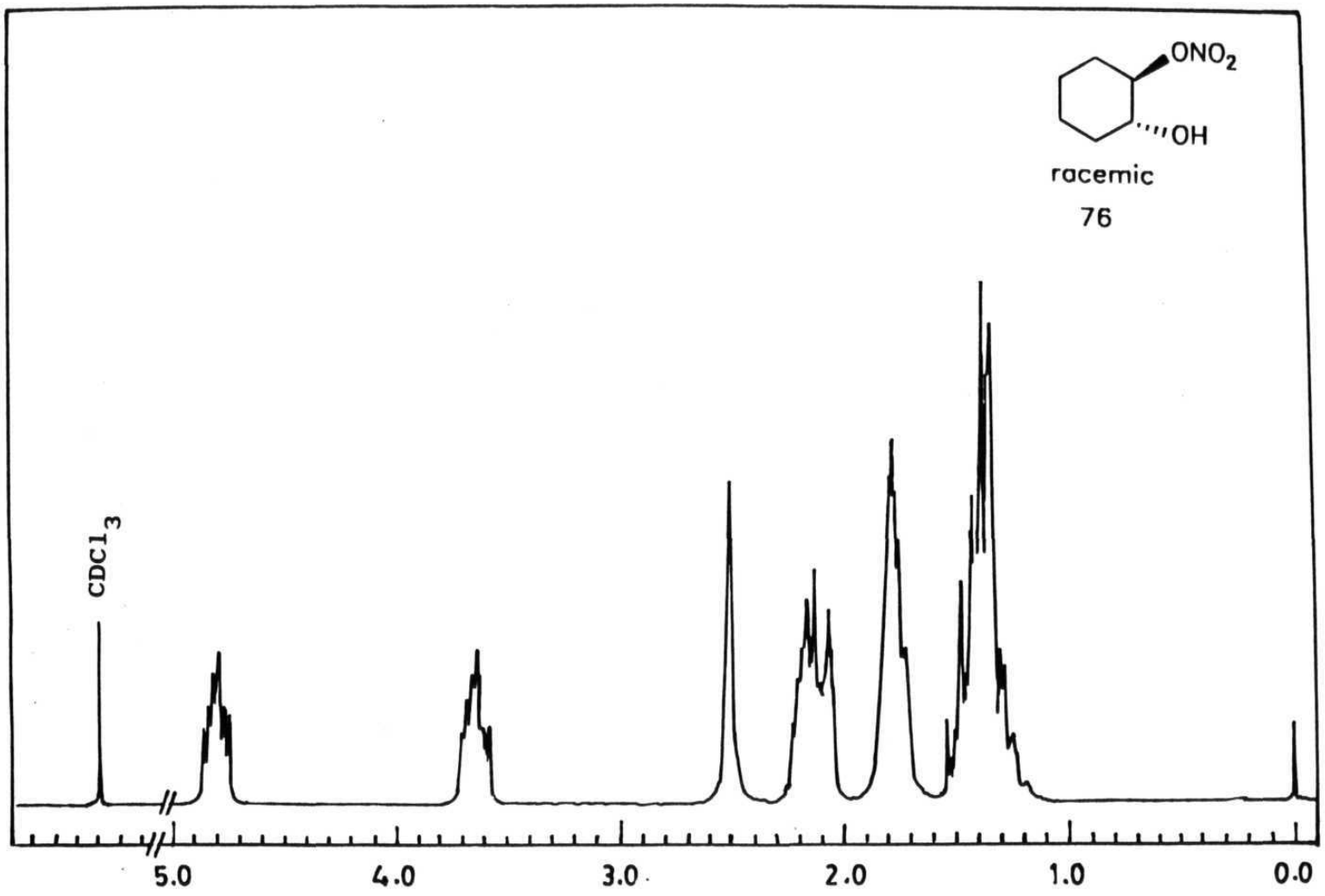


Fig.4: ^{1}H NMR Spectrum of **76**

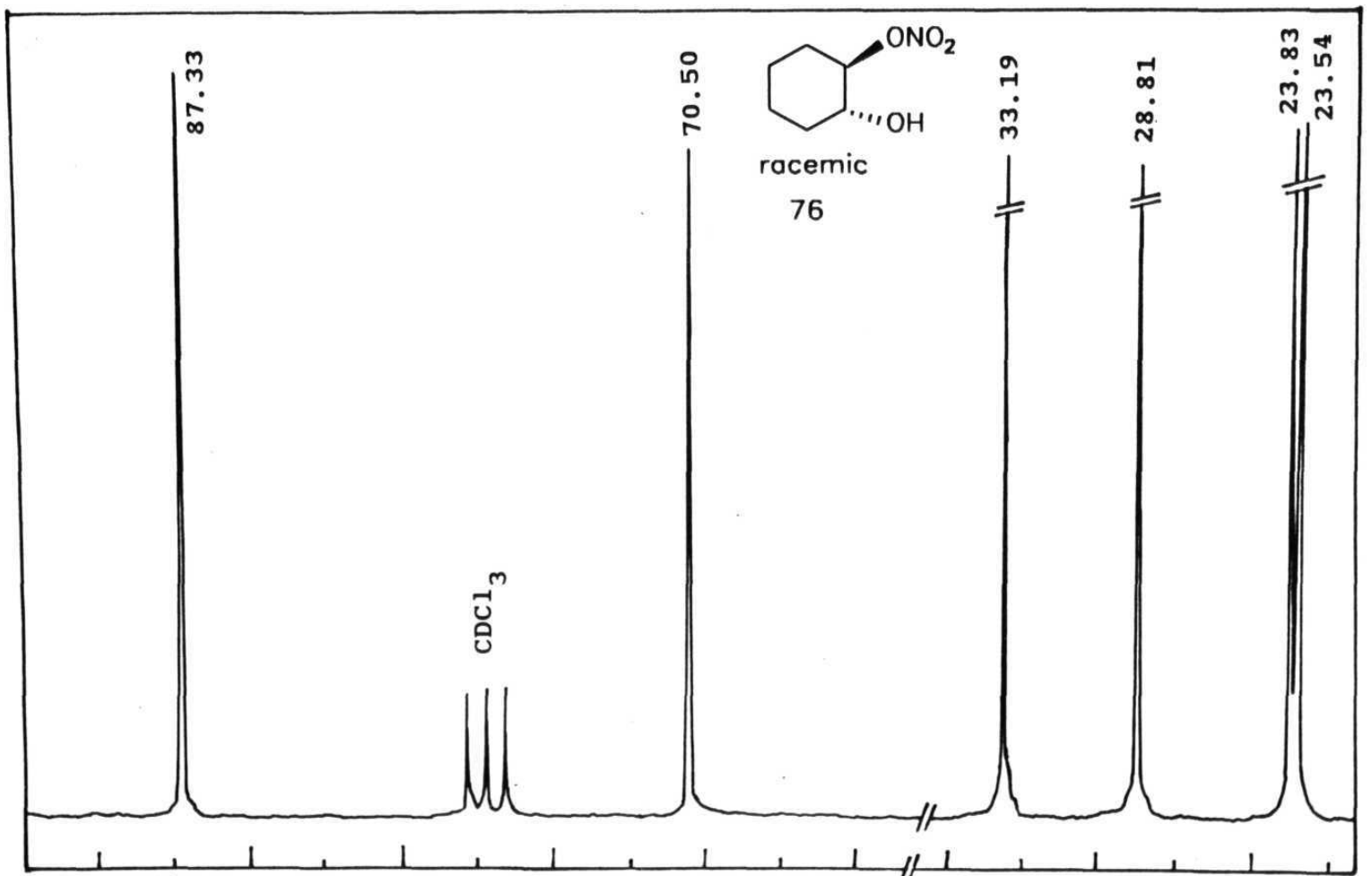


Fig.5: ^{13}C NMR Spectrum of **76**

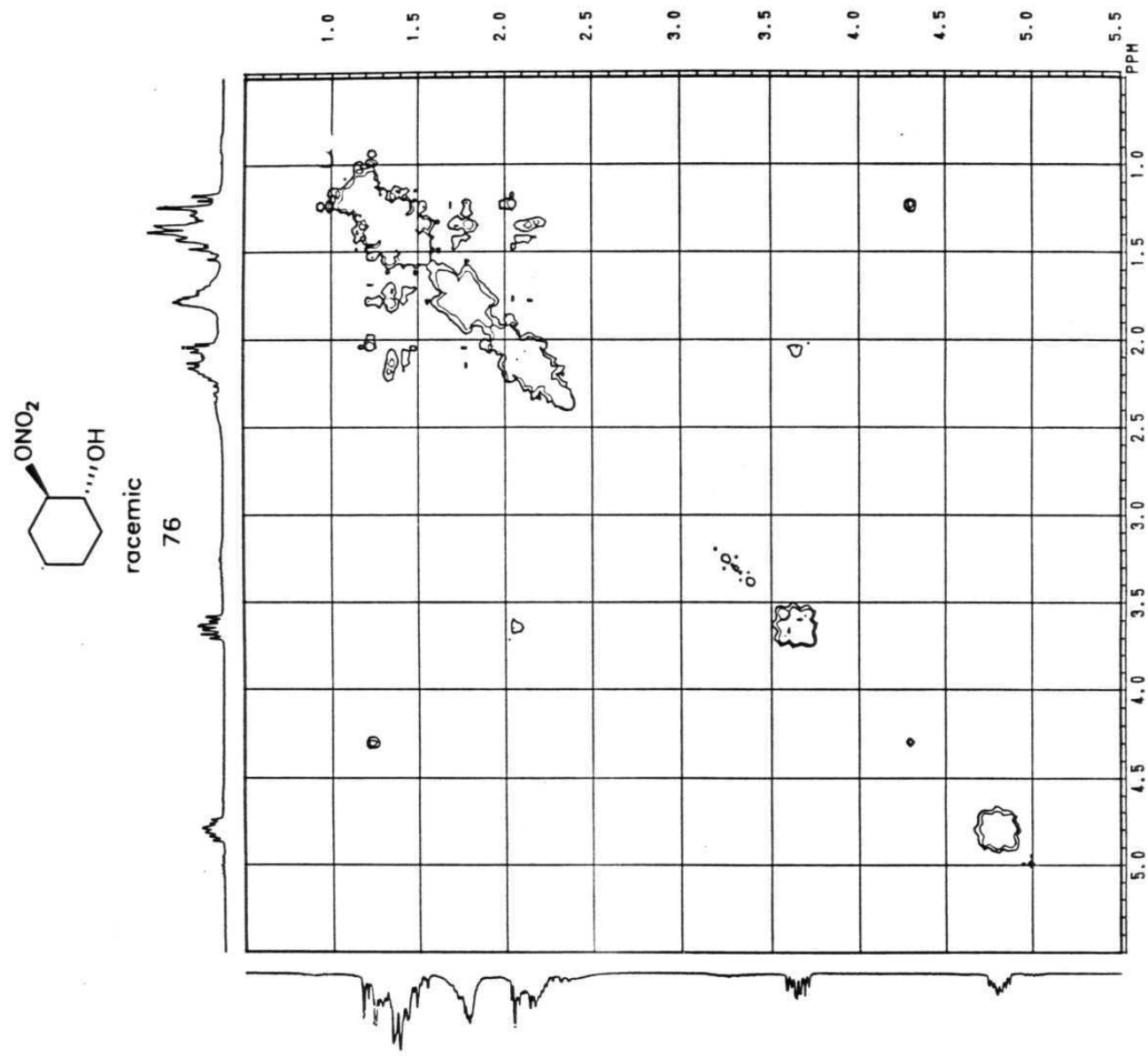


Fig.6: 2D NOESY of 76

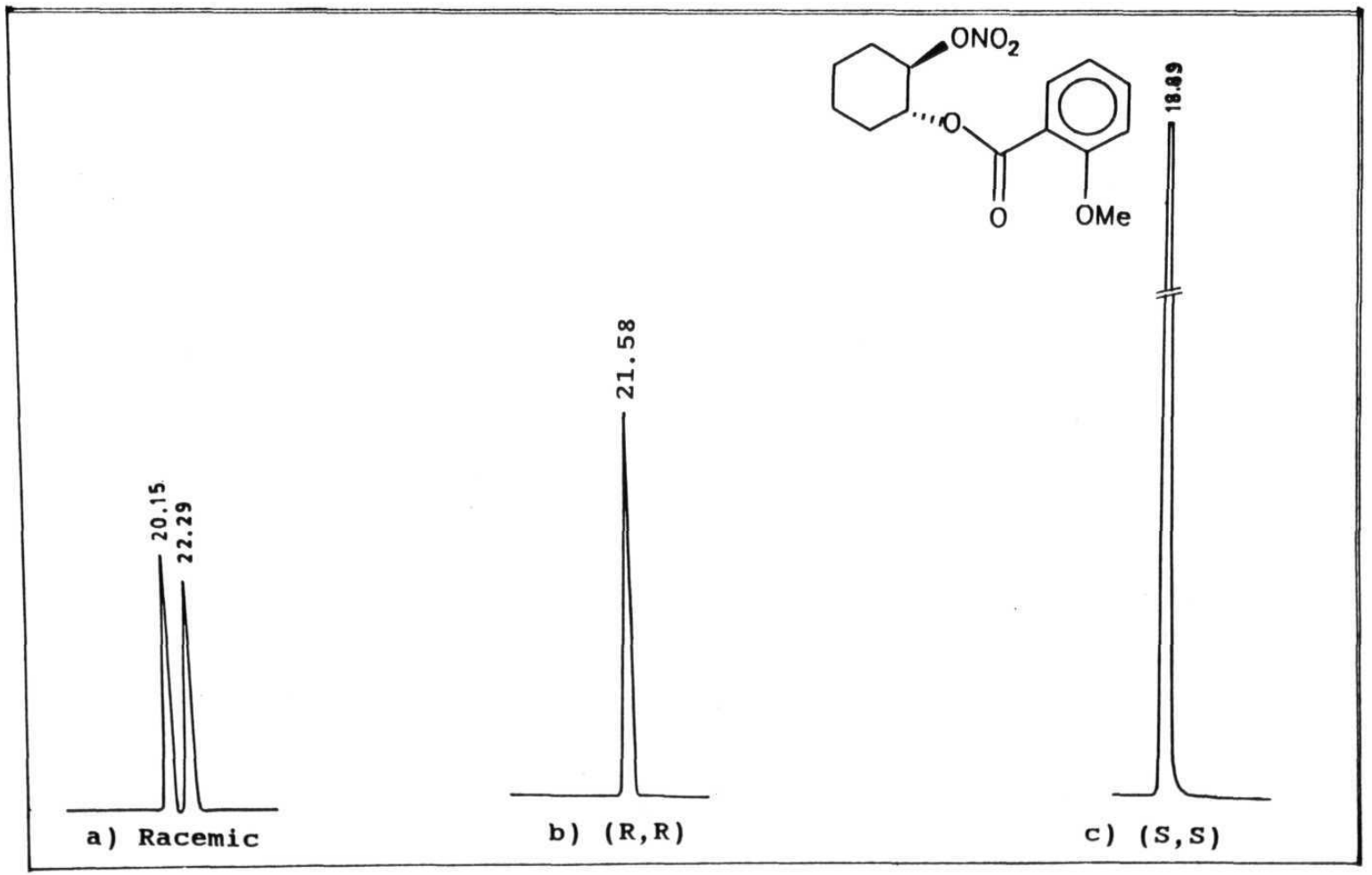


Fig.7: HPLC analysis of **81, 82** and **86** on CHIRALCEL OD column
a) Chromatogram of **81**, b) Chromatogram of **82** (>99% ee) and
c) Chromatogram of **86** (>99% ee)

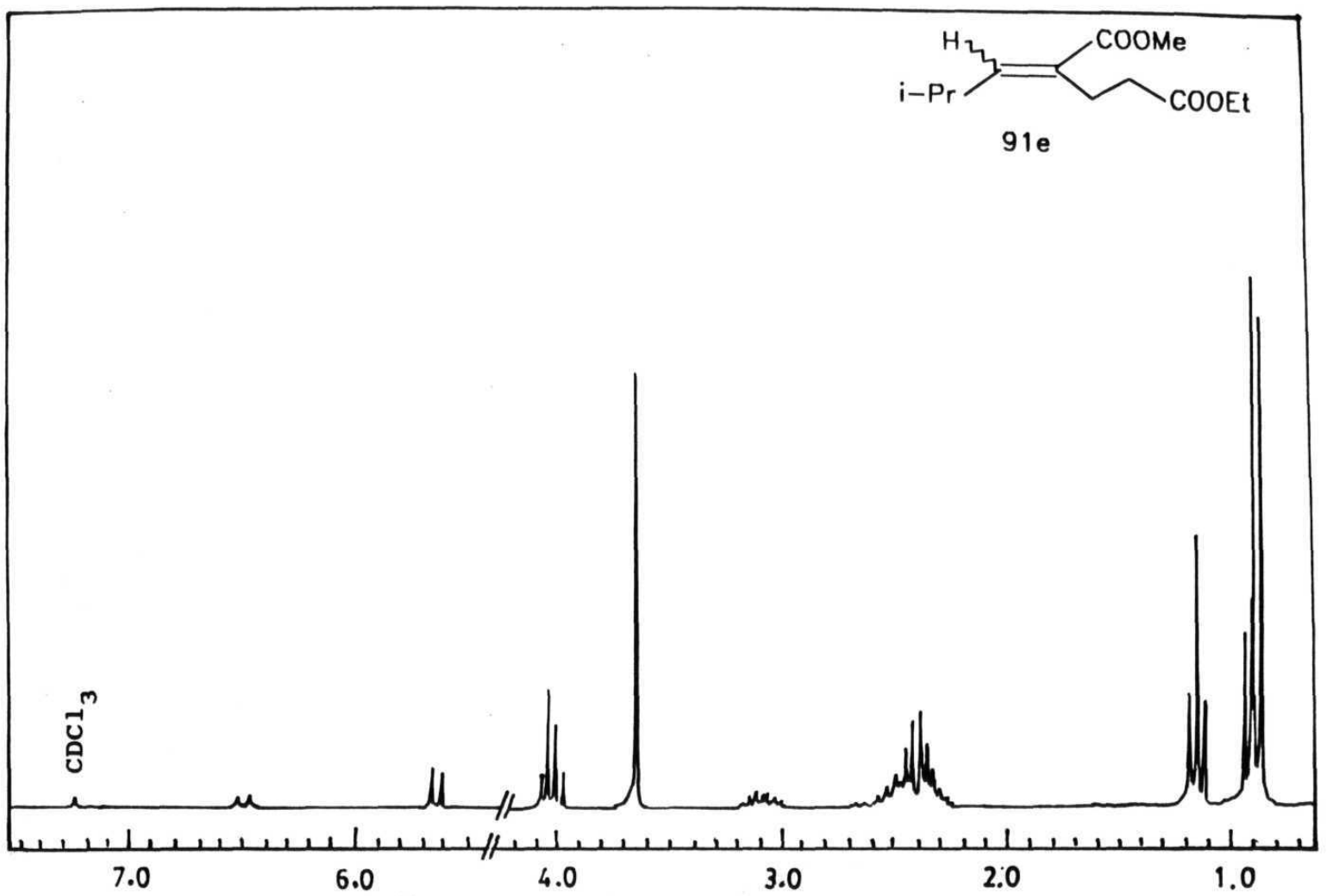


Fig.8: ^{1}H NMR spectrum of **91e** (E/Z = 20/80)

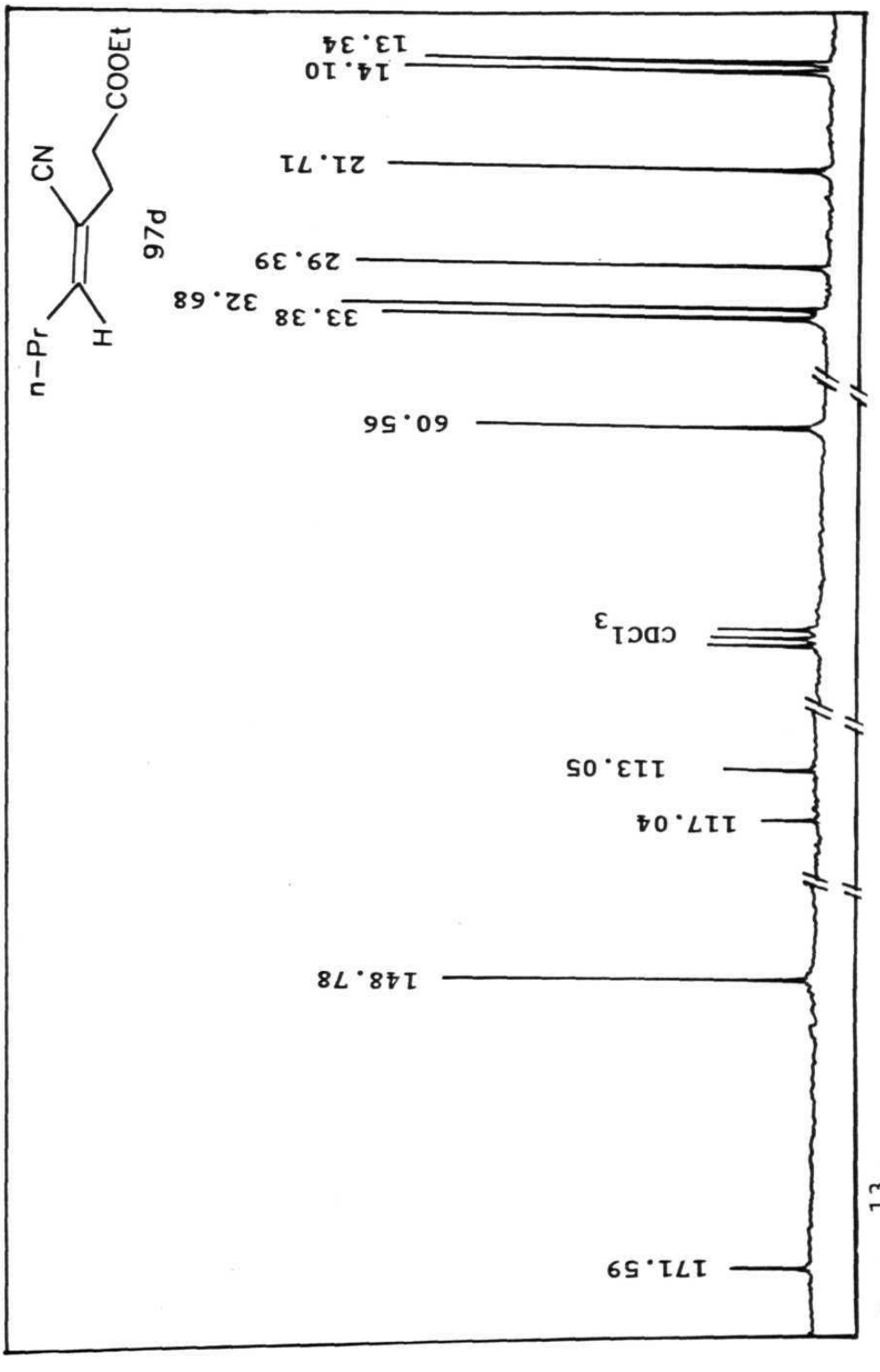


Fig.9: ^{13}C NMR Spectrum of **97d**

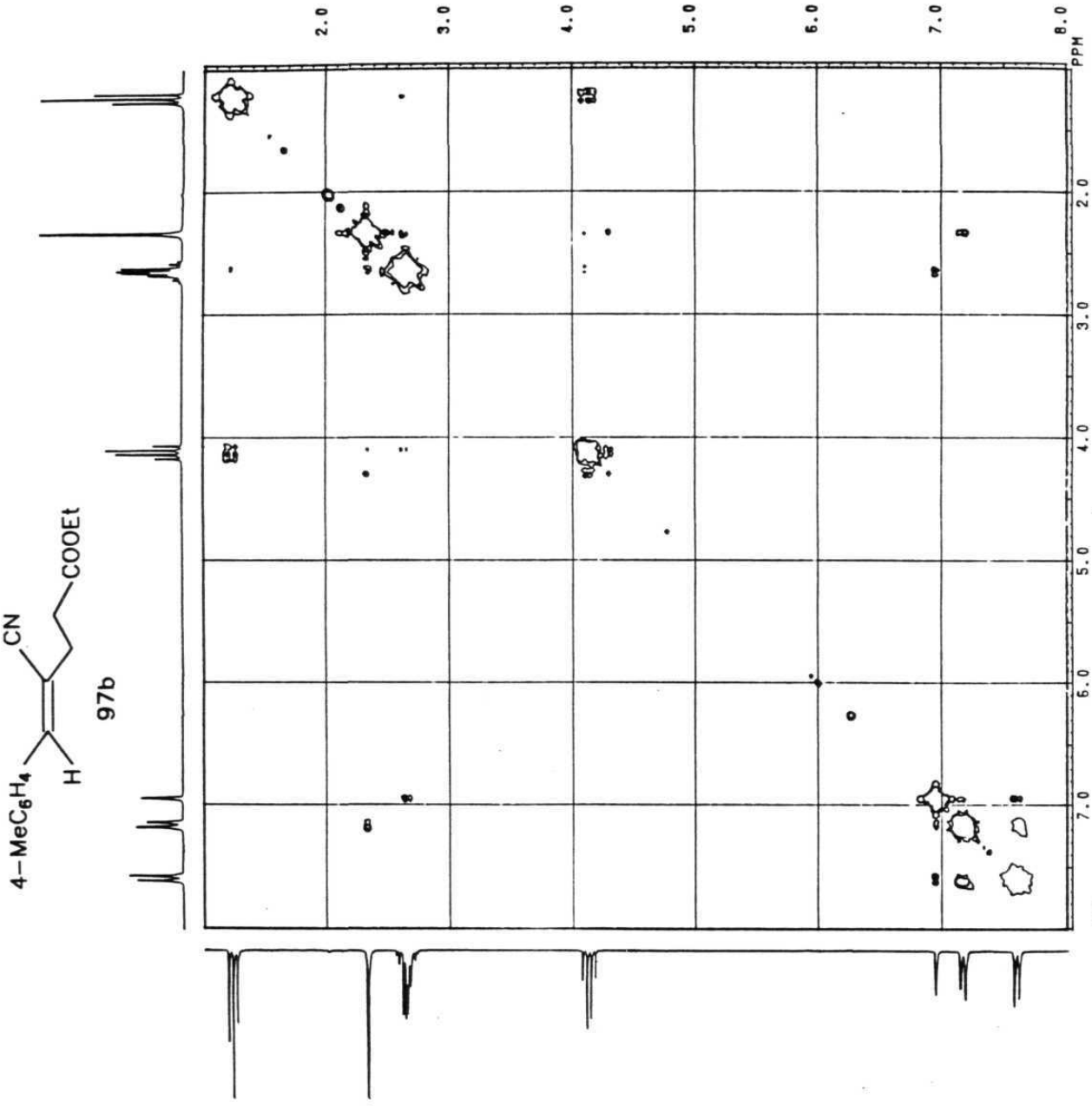


Fig.10: 2D NOESY of **97b**

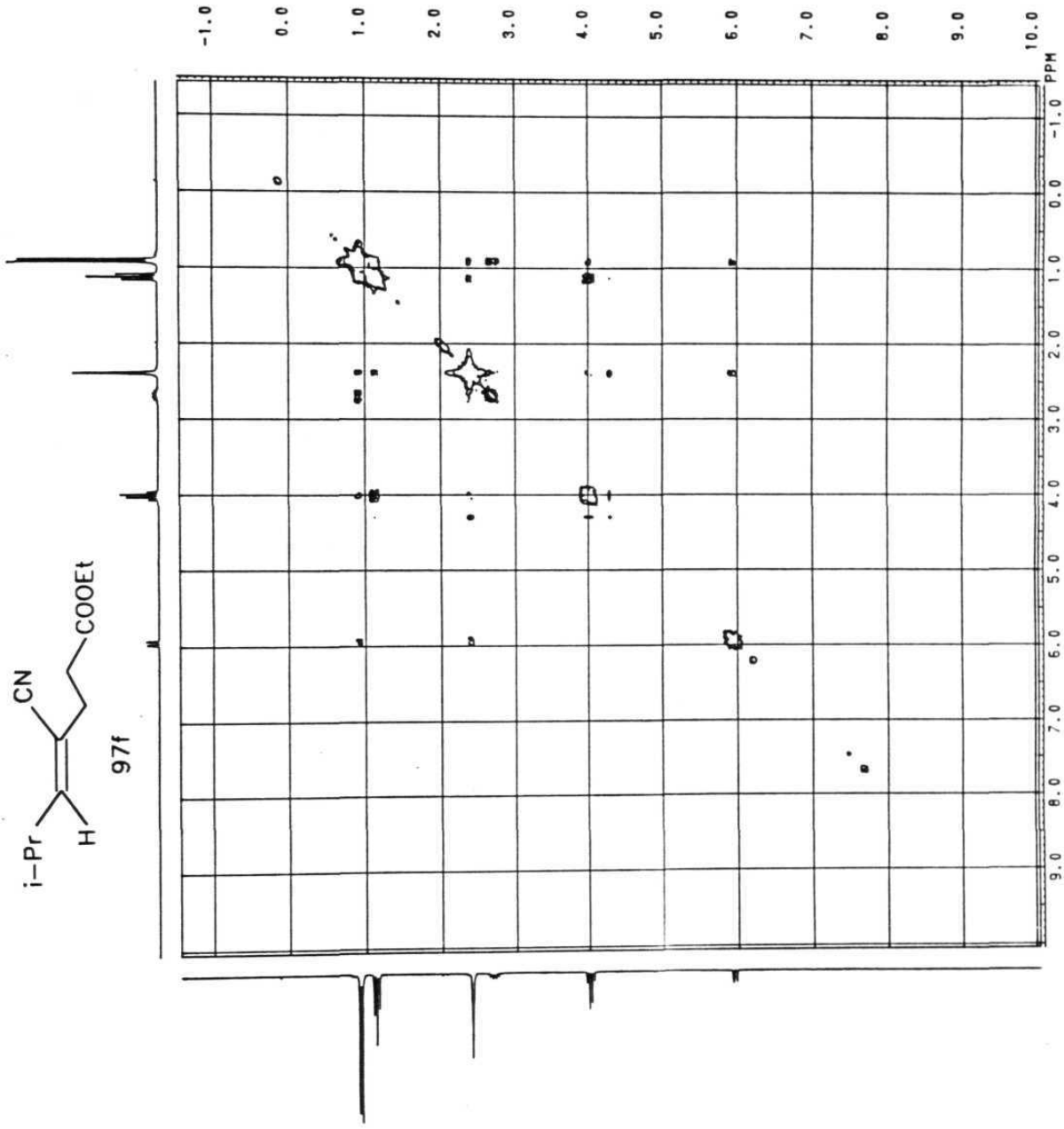


Fig.11: 2D NOESY of **97f**

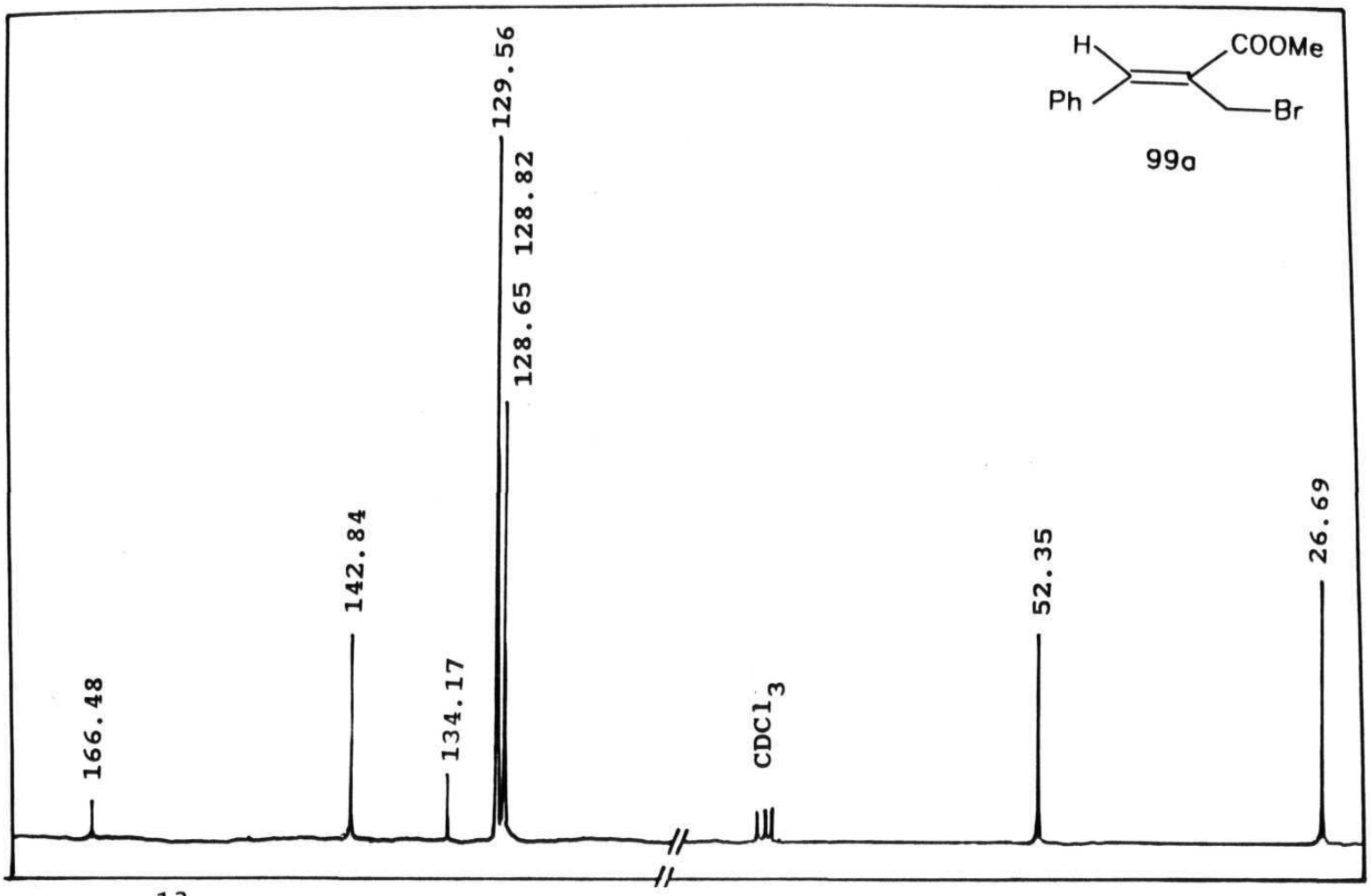


Fig.12: ^{13}C NMR Spectrum of **99a**

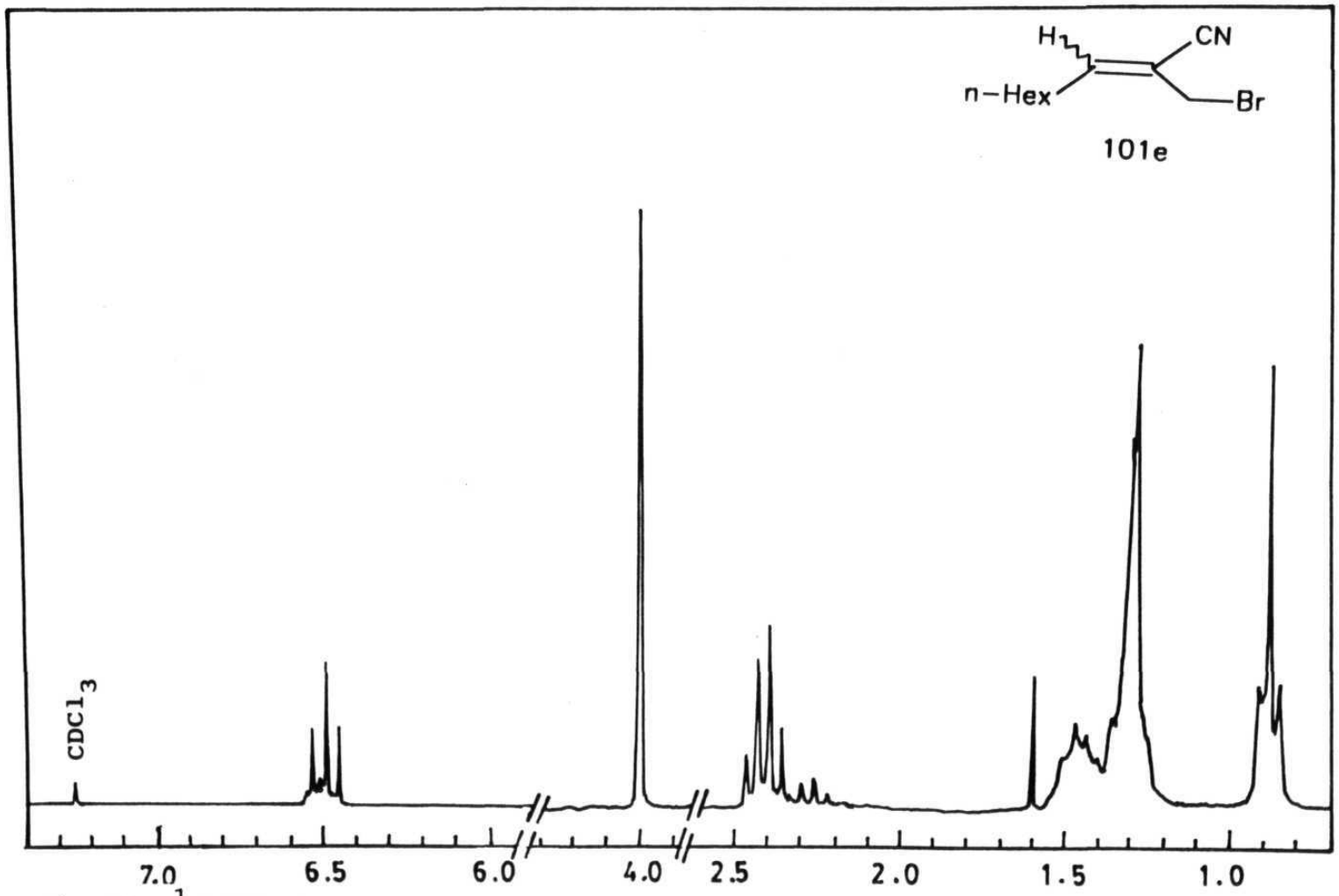


Fig.13: ^{1}H NMR Spectrum of **101e** (E/Z = 91/9)

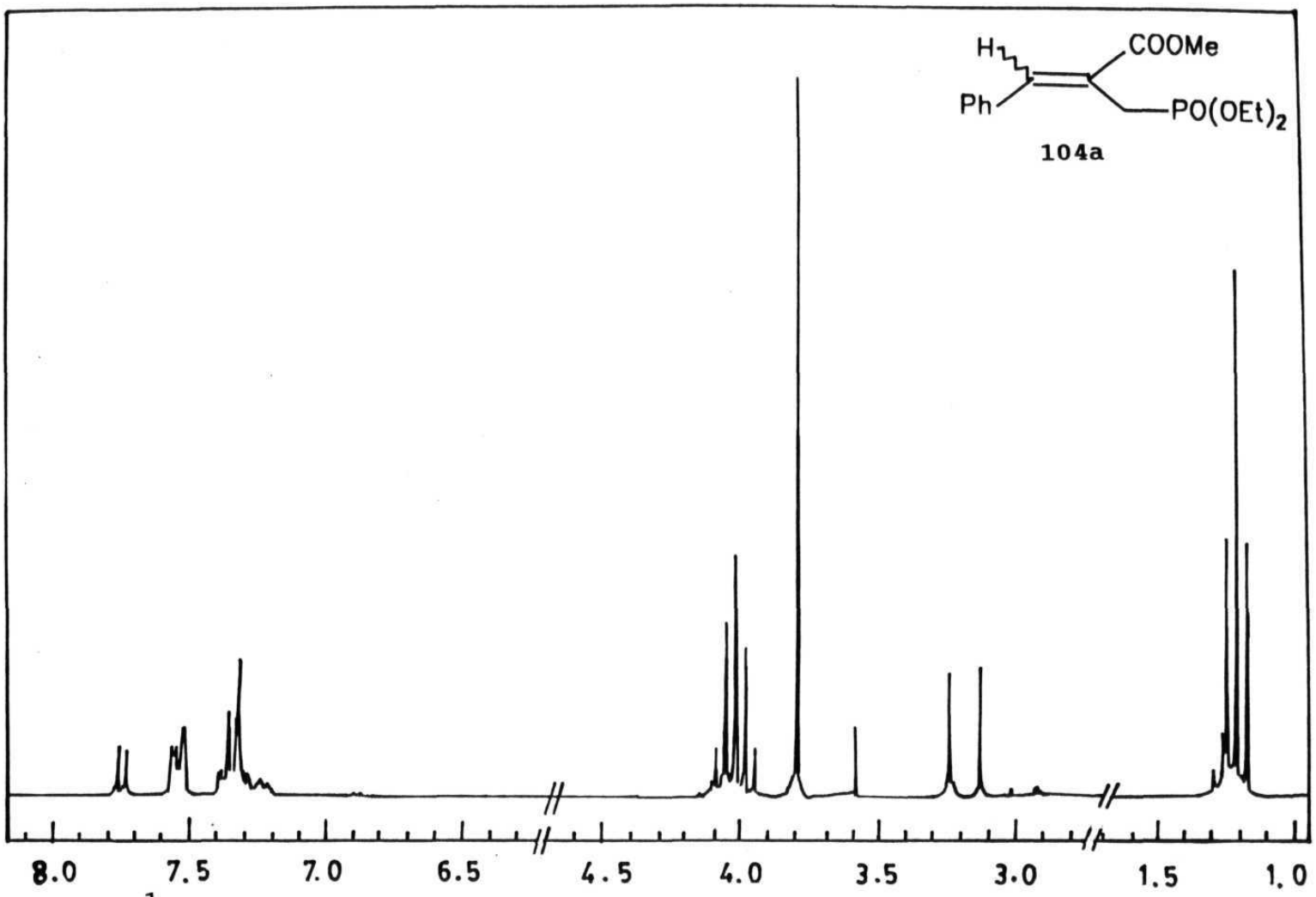


Fig.14: ^{1}H NMR Spectrum of **104a** (Z/E = 91/9)

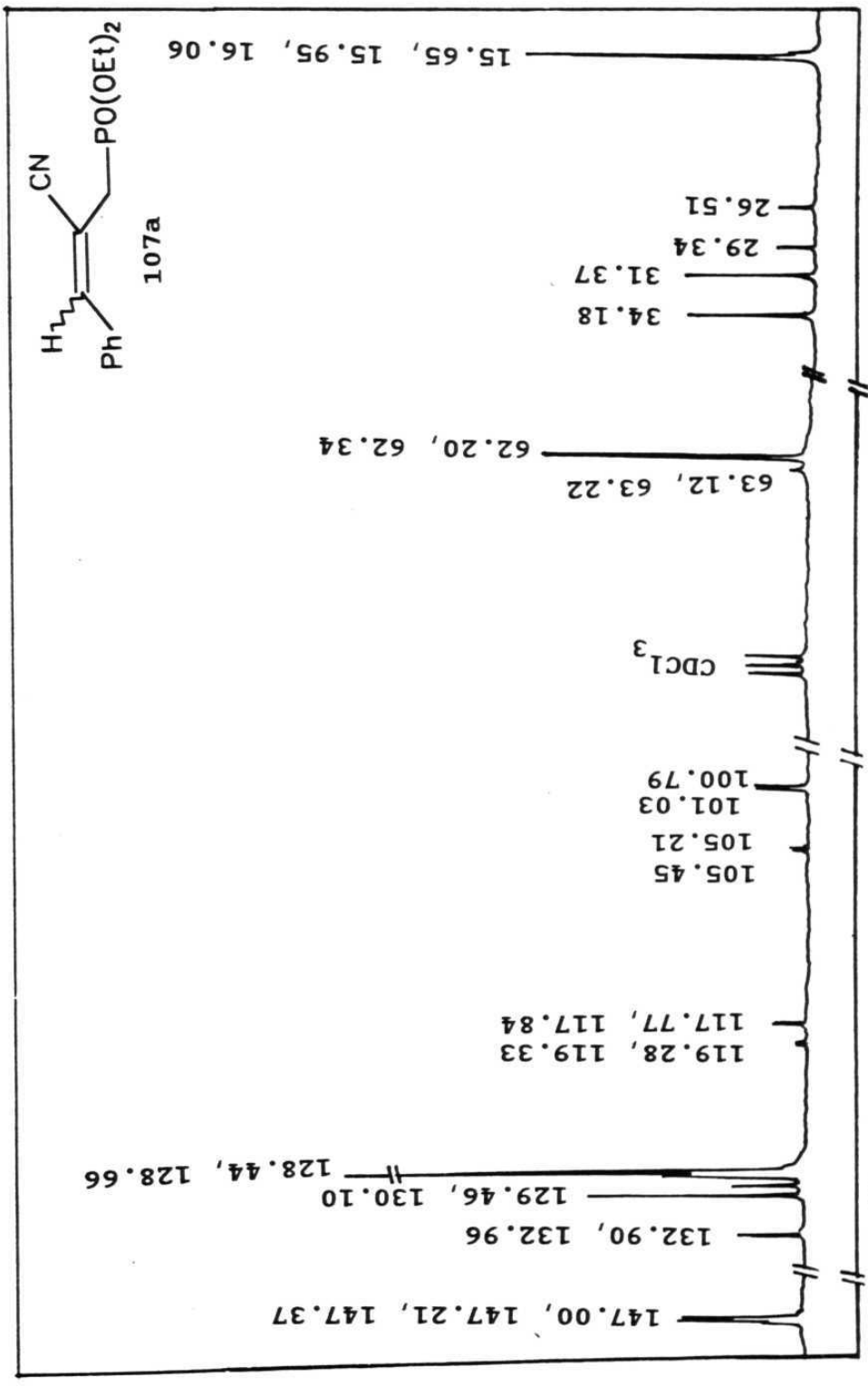


Fig.15: ^{13}C NMR Spectrum of **107a** (E/Z = 75/25)

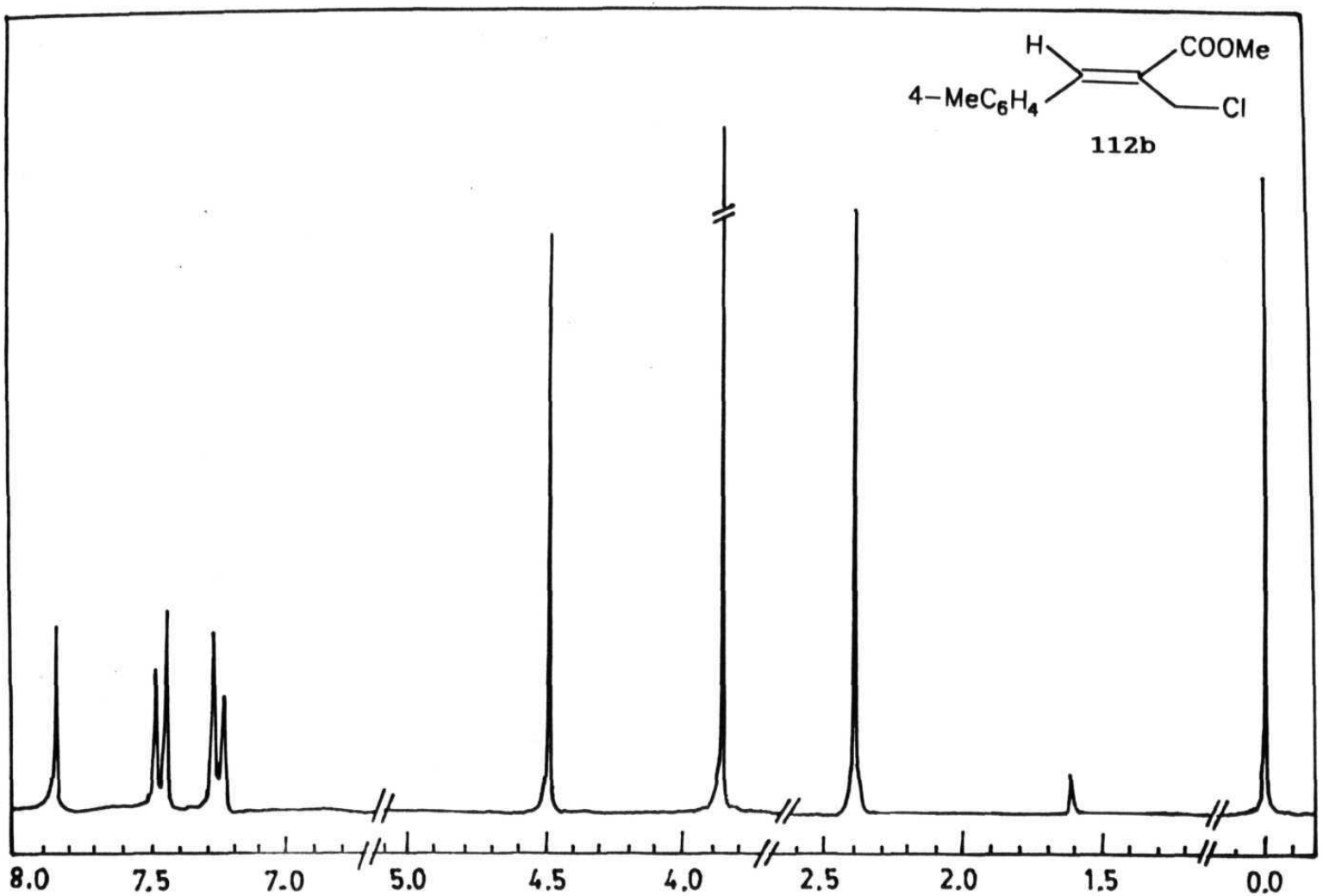


Fig.16: ^{1}H NMR Spectrum of **112b**

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List of publications:

1. First Enantioselective Synthesis of Mikanecic Acid *via* Diels-Alder Cycloaddition Mediated Construction of Chiral Vinylic Quaternary Center: D.Basavaiah, S.Pandiaraju and P.K.S.Sarma, *Tetrahedron Lett.*, **1994**, 35, 4227.
2. The Johnson-Claisen Rearrangement of 3-Hydroxy-2-methylene-alkanenitriles: Stereoselective Synthesis of Functionalized Trisubstituted Alkenes: D.Basavaiah and S.Pandiaraju, *Tetrahedron Lett.*, **1995,** 36, 757.
3. Baylis-Hillman Reaction: Magnesium Bromide as a Stereoselective Reagent for the Synthesis of [E]- and [Z]-Allyl Bromides: D.Basavaiah, A.K.D.Bhavani, S.Pandiaraju and P.K.S.Sarma, ***SYNLETT,*** **1995**, 243.