STUDIES IN APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCTS

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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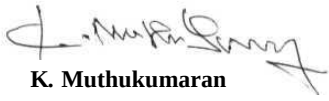
STATEMENT

1 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 **Professor 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

Hyderabad

August, 1999



K. Muthukumaran

CERTIFICATE

Certified that the work embodied in this thesis entitled "Studies in Applications of the Baylis-Hillman Adducts" has been carried out by **Mr. K. Muthukumaran,** under my supervision and the same has not been submitted elsewhere for a degree.

Aug. 2017

Professor D. Basavaiah
(Thesis Supervisor)

Dean 2018

School of Chemistry
University of Hyderabad

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K. Muthukumaran

ABBREVIATIONS

Ac	acetyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
i-Bu	isobutyl
n-Bu or Bu^n	n-butyl
t-Bu or Bu^t	*tert*-butyl
cat.	catalyst
CSA	camphorsulfonic acid
cy	cyclo
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
de	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DMAC	N,N-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMS	dimethyl sulfide
dppe	1,2-bis(diphenylphosphino)ethane
ee	enantiomeric excess
Et	ethyl

evk	ethyl vinyl ketone
EWG	electron withdrawing group
n-Hex	n-hexyl
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
Me	methyl
MPM	(*p*-methoxyphenyl)methyl
Ms	mesityl
mvk	methyl vinyl ketone
NBS	N-bromosuccinimide
NOESY	nuclear Overhauser enhancement spectroscopy
Ph	phenyl
PMP	1,2,2,6,6-pentamethylpiperidine
i-Pr or Pr^i	isopropyl
PTC	phase transfer catalyst
py	pyridine
TBAF	tetrabutylammonium fluoride
TBDMS	t-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMSOTf	trimethylsilyl trifluoromethanesulfonate
p-TsOH	*p*-toluenesulfonic acid

ABSTRACT

Organic synthesis has been and continues to be one of the most important and successful scientific disciplines having enormous practical utility. The development of synthetic organic chemistry mostly depends on the building block chemistry which essentially involves the formation of new carbon-carbon bonds and various organic transformations. Literature records a number of C-C bond forming reactions such as Grignard reaction, Diels-Alder reaction, Heck reaction, Reformatsky reaction, aldol reaction *etc.* which have indeed made organic synthesis an useful scientific discipline In recent years, there has been much emphasis on yet another important C-C bond forming reaction *i.e.* the Baylis-Hillman reaction During the last 10-15 years there has been an exponential growth of this reaction as evidenced by three major reviews and a number of publications and in fact, this reaction is now recognized as one of the important and useful reactions in synthetic organic chemistry.

This thesis deals with applications of the Baylis-Hillman chemistry with a view to develop new synthetic methods and consists of three chapters *i.e.*, 1) Introduction, 2) Objectives, Results and Discussion and 3) Experimental. The first chapter, introduction describes briefly the literature reports on recent developments and applications of the Baylis-Hillman reaction.

The second chapter deals with the objectives, results, and discussion. The Baylis-Hillman reaction is an emerging C-C bond forming reaction, producing a very useful

class of molecules possessing a minimum of three functional groups in close proximity. These Baylis-Hillman adducts have been successfully used in a variety of organic transformations with high stereoselectivities. With a view to further expand the scope of the Baylis-Hillman reaction in organic synthesis, we have undertaken this research program with the following objectives:

1). Isomerization of the Baylis-Hillman adducts *i.e.* methyl 3-aryl-3-hydroxy-2-methylenepropanoates, obtained from an activated alkene methyl acrylate, under the catalytic influence of $RuCl_2(PPh_3)_3$ to provide methyl 3-aryl-2-methyl-3-oxopropanoates.

2). Synthesis of methyl 2-arylmethyl-3-oxoaIkanoates *via* the arylation of the Baylis-Hillman adducts *i.e.* methyl 3-hydroxy-2-methylenealkanoates with aryl bromides under the catalytic influence of Pd $(OAc)_2$ (Heck conditions).

3). Stereoselective synthesis of methyl (2*E*)-2-cyanomethylalk-2-enoates and (3Z)-3-cyanoalk-3-enenitriles *via* the nucleophilic addition of cyanide ion to acetates of the Baylis-Hillman adducts *i.e.* methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles respectively.

4). Transformation of acetates of the Baylis-Hillman adducts *i.e.* methyl 3-acetoxy-3-aryl-2-methylenepropanoates and 3-acetoxy-3-aryl-2-methylenepropanenitriles into methyl (2*E*)-2-acetoxymethyl-3-arylprop-2-enoates and (2*E*)-2-acetoxymethyl-3-aryl-prop-2-enenitriles respectively *via* the trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed isomerization.

Objectives of the thesis also include: 5). Synthesis of ethyl 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates *via* the chalcogeno-Baylis-Hillman reaction of alkyl vinyl ketones (methyl vinyl ketone and ethyl vinyl ketone) with a-keto esters. 6) Development of an asymmetric version of the Baylis-Hillman reaction using chiral a-keto esters as electrophiles for coupling with alkyl acrylates and acrylonitrile.

Isomerization of the Baylis-Hillman adducts

Transition metal catalyzed isomerization of ally] alcohols to saturated carbonyl molecules is an important and useful operation in synthetic organic chemistry There are many reports in the literature describing isomerization of various allyl alcohols into saturated carbonyl molecules. However, the Baylis-Hillman adducts possessing allylic alcohol moiety have not been employed as substrates for transition metal catalyzed isomerization to obtain the corresponding saturated carbonyl molecules. We have therefore planned to investigate the possible isomerization of the Baylis-Hillman adducts *i.e.* methyl 3-hydroxy-2-methyIenealkanoates (26a-f) under the catalytic influence of $RuCl_2(PPh_3)_3$ with a view to provide a simple synthesis of methyl 2-methyl-3-oxoalkanoates **(27a-f)** Thus, treatment of methyl 3-aryl-3-hydroxy-2-methylenepropanoates **(26a-f)** with a catalytic amount of $RuCl_2(PPh_3)_3$ in the presence of K2CO3 in toluene at reflux temperature provided the desired methyl 3-aryl-2-methyl-3-oxopropanoates **(27a-f)** in good yields (equations 38 & 39).

Arylation of the Baylis-Hillman adducts

A variety of substituted and functionalized alkenes have been successfully arylated or alkenylated *via* the Heck reaction to produce synthetically useful molecules. The Heck reaction *i.e.* arylation of allylic alcohols has been well studied to provide arylated saturated carbonyl compounds or arylated allyl alcohols by changing reaction conditions. Also, the Heck reaction of a,P-unsaturated esters has been well documented to produce the arylated a,p-unsaturated esters. However, the Heck reaction *i.e.* arylation of alkenes possessing both allylic alcohol and a,P-unsaturated ester moieties in which carbon- carbon double bond is an integral part of both allyl alcohol and a,P-unsaturated ester moieties has not been studied. Therefore, we have carried out the Heck reaction *i.e.* arylation of Baylis-Hillman adducts, methyl 3-hydroxy-2-methylenealkanoates **(26a-d, 26g-i)** (in which double bond is an integral part of both allyl alcohol and a,P-unsaturated ester moieties) with various bromoarenes under the catalytic influence of $Pd(OAc)_2$. The resulting methyl 2-arylmethyl-3-oxoalkanoates **(30-42)** were obtained in high yields (equations 42 & 43, Scheme 33).

Nucleophilic addition of cyanide ion to acetates of the Baylis-Hillman adducts

Baylis-Hillman adducts have been successfully transformed into various trisubstituted alkenes with high stereoselectivity *via* the addition of various nucleophiles to the

corresponding **acetates** However, in these addition reactions, application **of** sterically less hindered cyanide ion as a nucleophile has not been studied. Therefore, we have undertaken the study of nucleophilic addition of cyanide ion to acetates of the Baylis-Hillman adducts. Thus, treatment of methyl 3-acetoxy-2-**methylenealkanoates (43-48)** with NaCN in acetonitrile at room temperature provided methyl 2-cyanomethylalk-2-enoates **(49-54)** in good yields with high **(*E*)-**stereoselectivity **(*E*/*Z*** ratio = **82-98/18-2)** (equations 47 & **48)**

With a view to provide a general synthesis of 3-cyanoalk-3-enenitriles (57a-f) and to examine the stereochemical directive effect of nitrile group with respect to ester group in these reactions, we have also carried out the reaction of 3-acetoxy-2-**methylenealkanenitriles (56a-f)** with NaCN in acetonitrile. The resulting **3-cyanoalk-3-enenitriles (57a-f)** were obtained in moderate to good yields with high (Z)-selectivity **(*Z*/*E*** ratio = 72-95/28-5) (equations 49 & 50).

Stereoselective synthesis of methyl (2*E*)-2-acetoxymethyl-3-arylprop-2-enoates and (2*E*)-2-acetoxymethyl-3-arylprop-2-enenitriles

We have developed a simple synthesis of methyl 2-acetoxymethyl-3-arylprop-2-enoates **(60-65)** (primary acetates) with exclusive **(*E*)-stereoselectivity** *via* the rearrangement of methyl 3-acetoxy-3-aryl-2-methylenepropanoates **(43-46, 58, 59)**

(secondary acetates) under the catalytic influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (equations 53 & 55).

Similar rearrangement of 3-acetoxy-3-aryl-2-methylenepropanenitriles **(56a, 56b, 66-**69) in the presence of TMSOTf provided 2-acetoxymethyl-3-arylprop-2-enenitriles (70-75) with exclusive **(*E*)-stereochemistry** (equations 57 & 58).

The chalcogeno-Baylis-Hillman reaction of alkyl vinyl ketones with a-keto esters

We have developed a simple and convenient synthesis of ethyl 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates **(82a-e, 83, 84)** *via* the **Baylis-Hillman** reaction between ethyl arylglyoxylates **(81a-e,** a-keto esters) and a,P-unsaturated ketones (methyl vinyl ketone and ethyl vinyl ketone) under the catalytic influence of dimethyl sulfide in the presence of titanium tetrachloride in **dichloromethane** (equations 61, 63 & 64). This reaction gains importance in the sense that similar coupling reaction with DABCO as catalyst is **ineffective**

Chiral a-keto esters as substrates in asymmetric Baylis-Hillman reaction

Considerable efforts have been made to achieve high asymmetric induction in the Baylis-Hillman reaction using chiral acrylates, chiral catalysts, chiral aldehydes. However, application of chiral a-keto esters, derived from chiral auxiliaries, have not

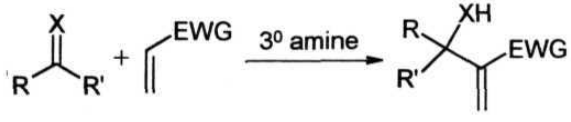
been studied for asymmetric Baylis-Hillman reaction. Therefore, we have investigated the Baylis-Hillman coupling of the chiral a-keto esters (86, 91, 94) derived from menthol and (1R,2S)-2-phenylcyclohexan-1-ol as chiral auxiliaries with alkyl acrylates and acrylonitrile in the presence of DABCO (equations 66, 67, 69 & 70, Schemes 42 & 44). The resulting Baylis-Hillman adducts (87, 88, 92, 93, 95, 96) were obtained in 10-80% diastereoselectivities.

The third chapter deals with the experimental procedures in detail, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, microanalyses and physical constants (bp, mp, and optical rotations).

INTRODUCTION

Organic synthesis has been and continues to be one of the most important and successful scientific disciplines having enormous practical utility.[1-4] The development of synthetic organic chemistry mostly depends on the building block chemistry which essentially involves the formation of new carbon-carbon bonds Literature records a number of important C-C bond forming reactions such as Grignard reaction,[1-4, 5] Diels-Alder reaction,[1-4, 6, 7] Heck reaction,[1-4, 8] Reformatsky reaction,[1-4, 9] aldol reaction,[1-4, 10, 11] *etc.* which indeed made organic synthesis an useful scientific discipline. In recent years, there has been much emphasis on yet another important C-C bond forming reaction *i.e.* the Baylis-Hillman reaction.[12] During the last 10-15 years there has been an exponential growth of this reaction as evidenced by three major reviews[13-15] and a number of publications and in fact this reaction is now recognized as one of the important and useful reactions in synthetic organic chemistry.

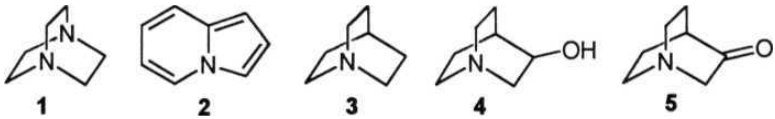
The Baylis-Hillman reaction is a novel carbon-carbon bond forming reaction which originates from a German patent.[12] This reaction involves basically three components *i.e.* an activated alkene, a carbon electrophile and a tertiary amine (catalyst) leading to the coupling of α-position of activated alkene with carbon



(eq. 1)

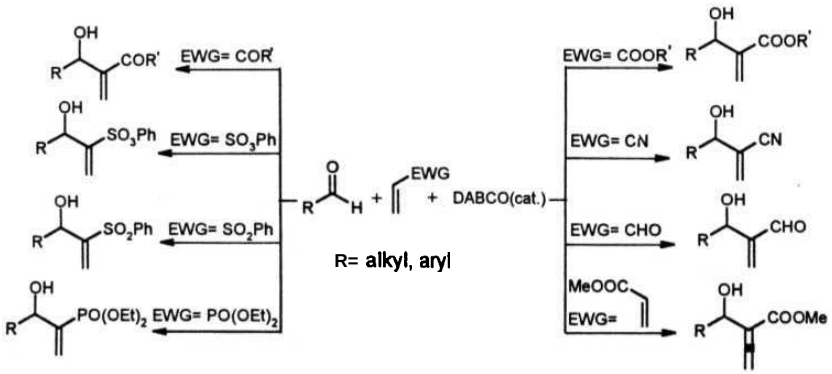
X= O, NR^2 ; EWG= electron withdrawing group

electrophile producing a novel class of multifunctional molecules (eq. 1). During the last decade this reaction has seen considerable success and progress with respect to all the three components. Thus, several bicyclic tertiary amines such as DABCO (1), pyrrocoline (2), quinuclidine (3), 3-hydroxyquinuclidine (4), and 3-quinuclidone (5) have been employed as catalysts in this reaction.[12-]

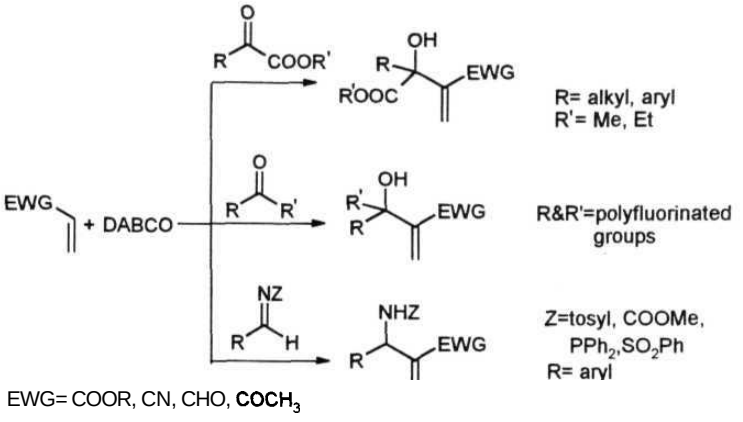


Various a, p-unsaturated esters,[16, 17] nitriles,[18, 19] ketones,[19,21] sulfones,[22] sulfonates,[23] phosphonates,[24] allenic esters[25, 26] and acrolein[27-29] have been used as activated alkenes in this reaction (Scheme 1). Several electrophiles such as aldehydes,[16-29] α-keto esters,[30-32] fluorinated ketones,[33] and aldimine derivatives[34-36] have been successfully employed in this reaction (Scheme 2).

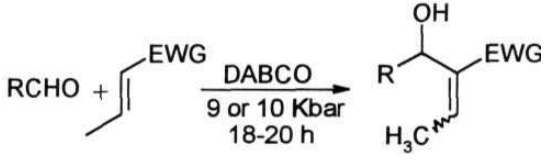
Scheme 1



Scheme 2



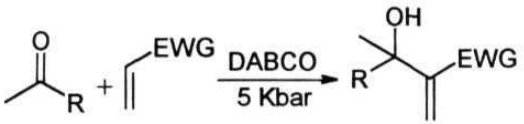
The β-substituted activated alkenes such as methyl crotonate,[37] crotononitrile[37] and phenyl prop-1-enyl sulfoxide[38] do not undergo this reaction under ordinary conditions. However they react with aldehydes at elevated pressure to provide the Baylis-Hillman adducts (eq. 2). Similarly, the Baylis-Hillman reaction of



(eq. 2)

EWG= COOMe, CN, SOPh

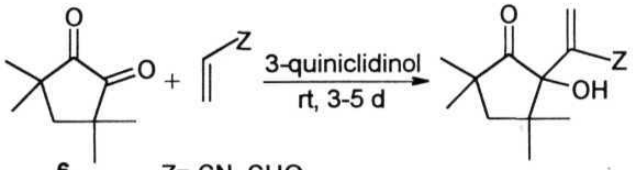
unactivated ketones also requires high pressure (eq. 3).[27, 37] However, the cyclic



(eq. 3)

R= Me, Et; EWG= COOMe, CN

non-enolizable 1,2-diketones such as 6 undergo this reaction with acrylonitrile and acrolein in the presence of catalytic amount of 3-quiniclidinol at atmospheric pressure (eq. 4).[28]

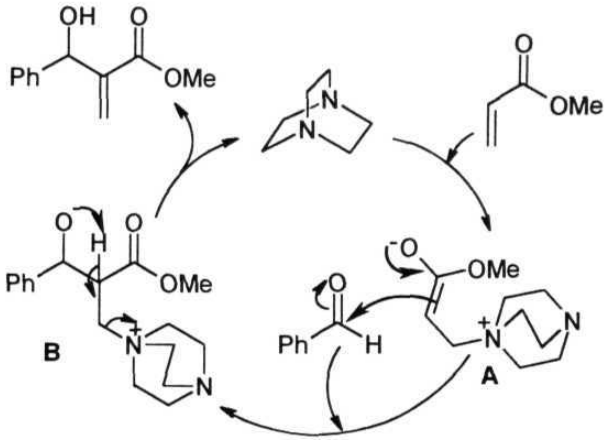


6 Z= CN, CHO

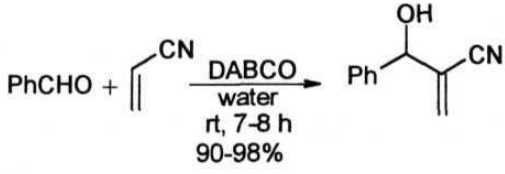
(eq. 4)

The mechanism of the Baylis-Hillman reaction is believed to proceed through Michael initiated addition-elimination sequence.[39-41] This is illustrated in Scheme 3 using a representative example of reaction between methyl acrylate and benzaldehyde under the influence of DABCO as a model case. First step involves the Michael type addition of tertiary amine (DABCO) to activated alkene (methyl acrylate) generating a zwitter ion enolate A, which makes a nucleophilic attack on the electrophile (benzaldehyde) to give zwitter ion B. Subsequent internal proton transfer followed by elimination of tertiary amine provides the desired multifunctional product (Scheme 3).

Scheme 3

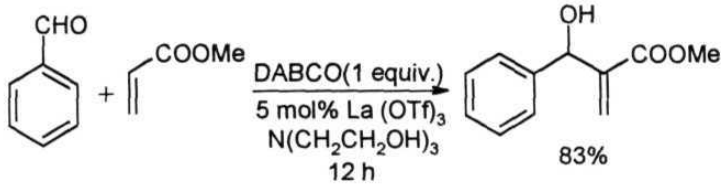


The usual DABCO catalyzed Baylis-Hillman reaction is slow reaction requiring few hours to few days for completion depending upon the activated alkene and electrophile.[12-5] To overcome this problem, new catalysts/catalytic systems and different reaction conditions have been investigated. Auge *et al.*[42] described that the DABCO catalyzed coupling of benzaldehyde with acrylonitrile was greatly accelerated in water (eq. 5). They have also observed that the reaction was even more accelerated by adding lithium or sodium iodide in aqueous medium.

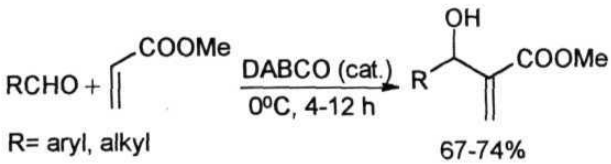


(eq. 5)

Aggarwal and coworkers[43, 44] have demonstrated the utility of lanthanide catalysts, particularly lanthanum triflates, in the rate enhancement of the Baylis-Hillman reaction (eq. 6). Rafel and Leahy[45] have described that the Baylis-Hillman reaction is very rapid at 0°C (eq. 7).

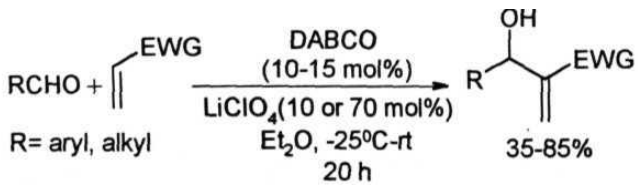


(eq. 6)



(eq. 7)

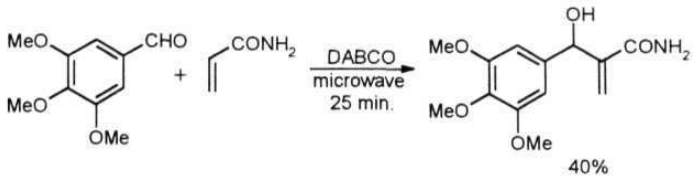
Lithium perchlorate accelerated Baylis-Hillman reaction between various α,β-unsaturated carbonyl compounds and a variety of aldehydes has been recently reported by Kobayashi and Kawamura (eq. 8).[29]



(eq. 8)

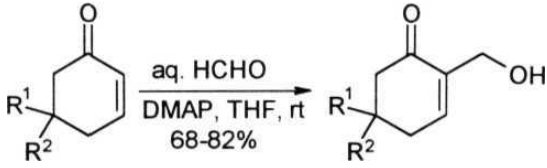
EWG= COOEt, CO_2Bn, CO_2Bu^t, CHO, COMe, CN

Bhat and coworkers[46] have demonstrated the application of microwave irradiation in accelerating the Baylis-Hillman reaction. It is interesting to mention that acrylamide reacts with 3,4,5-trimethoxybenzaldehyde under microwave conditions (eq. 9) (which is otherwise unreactive)



(eq. 9)

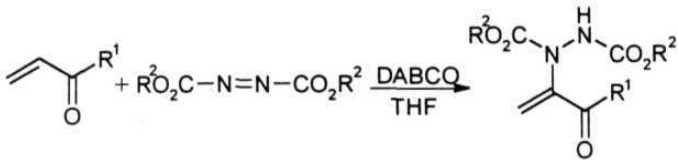
Recently, Rezgui and El Gaied[47] have used 4-dimethylaminopyridine (4-DMAP) as catalyst for the Baylis-Hillman coupling of various substituted cyclohex-2-enones with aqueous formaldehyde to provide the corresponding a-hydroxymethylated cyclohex-2-enones (eq. 10).



(eq. 10)

R^1= H, Me; R^2= H, Me, Ph

Dialkyl azodicarboxylates have been successfully employed as electrophiles for the Baylis-Hillman reaction with alkyl vinyl ketones in the presence of catalytic amount of DABCO leading to the formation of α-(N,N'-bisalkoxycarbonyl)-hydrazino-a, P-unsaturated ketones (eq 11).[48]



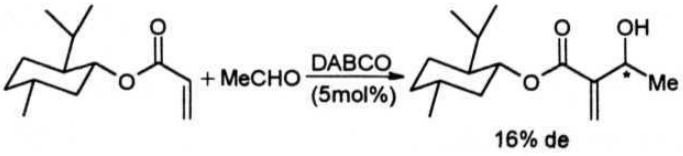
R^1= Me, Et, n-hexyl, n-heptyl, cinnamyl; R^2= Et, *t*-Bu

Asymmetric Baylis-Hillman Reaction

Asymmetric Baylis-Hillman reaction in principle, can be achieved with the help of suitable chiral source in any of the three essential components of the reaction In fact, several efforts have been made in this direction *i.e.* by employing i) Chiral activated alkene ii) Chiral catalyst and iii) Chiral electrophile to achieve the asymmetric induction in the Baylis-Hillman reaction. Some of the important and recent endeavors on these aspects have been discussed below

i) Chiral activated alkenes

Though various activated alkenes have been used in Baylis-Hillman reaction (Scheme 1), so far only chiral acrylates have been used for asymmetric Baylis-Hillman reaction. This may be due to the easy accessibility of chiral acrylates and easy removal of chiral auxiliaries from the products (in comparison with other chiral activated alkenes). Brown and coworkers[49] have reported 16% diastereo-selectivity in the Baylis-Hillman coupling between menthyl acrylate and

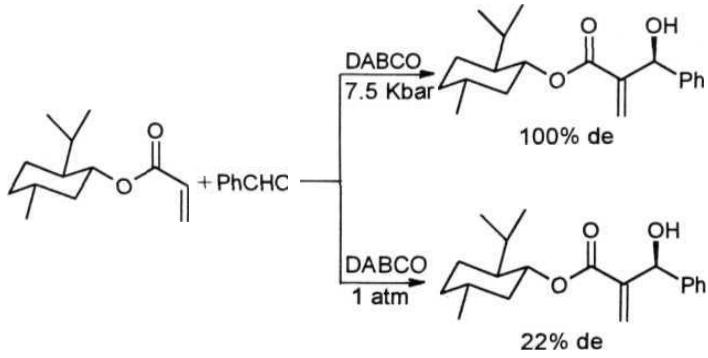


(eq. 12)

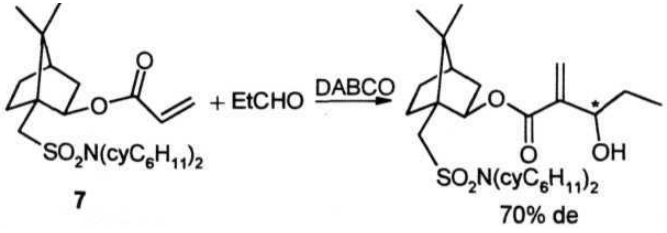
acetaldehyde in the presence of DABCO (eq. 12).

Isaacs and coworkers[50] have demonstrated the application of high pressure in achieving high diastereoselection in the chiral auxiliary mediated asymmetric Baylis-Hillman reaction. Thus menthyl acrylate reacts with benzaldehyde at 7.5 Kbar pressure in the presence of DABCO to provide the desired adduct in 100% diastereoselection while the same reaction when carried out at atmospheric pressure results in 22% diastereoselectivity (Scheme 4).

Scheme 4



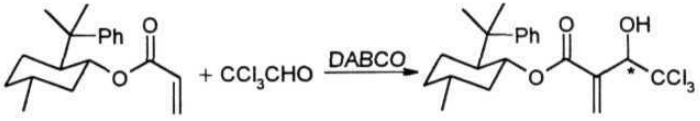
In our laboratory, we have systematically studied asymmetric Baylis-Hillman reaction using various chiral acrylates derived from variety of chiral auxiliaries.[51]



(eq. 13)

The best diastereoselectivity of 70% was obtained in the coupling of propionaldehyde with the chiral acrylate (7), derived from the Oppolzer's chiral auxiliary, in the presence of DABCO as a catalyst (eq. 13).[52]

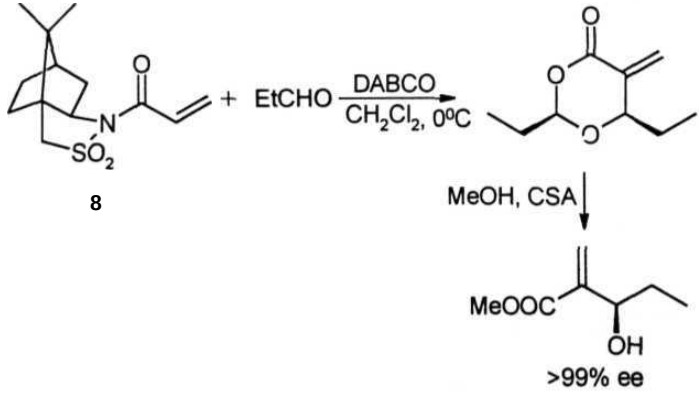
Drewes and coworkers[53] have reported 70% diastereoselectivity in the Baylis-Hillman reaction of chloral with chiral acrylate derived from 8-phenylmenthol (eq 14).



(eq. 14)

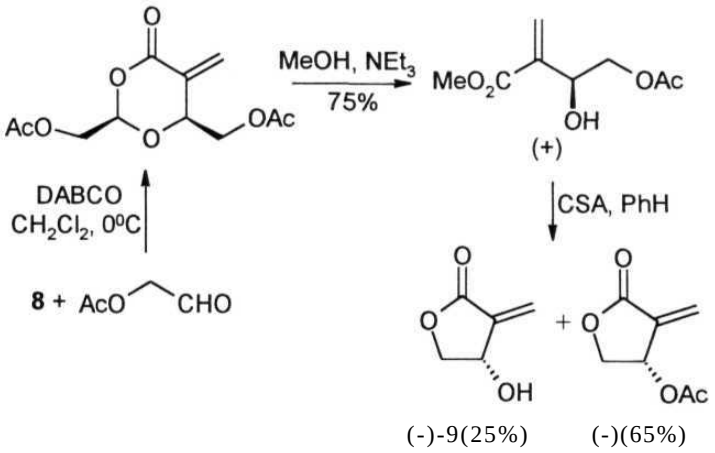
Recently, Leahy and coworkers[54, 55] have efficiently used chiral acrylamide (8), derived from Oppolzer's sultam, as an activated alkene for the coupling with various aldehydes in presence of DABCO to obtain the desired adducts in very high diastereoselectivities (Scheme 5). In fact this methodology has been

Scheme 5



applied for enantioselective synthesis of tulipalin B (9), the contact dermatitic agent in tulip bulbs (Scheme 6).[54]

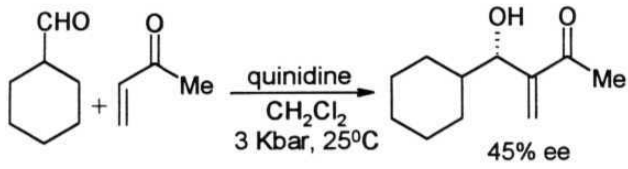
Scheme 6



ii) Chiral Catalysts

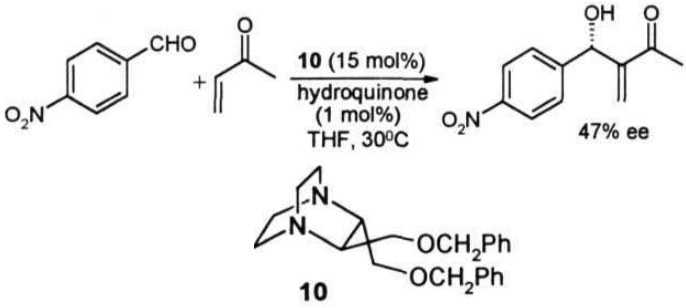
Organic chemists have also made some sincere efforts to achieve chiral induction in the Baylis-Hillman reaction with the help of chiral tertiary amine catalysts Quinidine has been the first catalyst used for this purpose. Thus, coupling of methyl vinyl ketone with acetaldehyde using quinidine as catalyst provided the resulting adduct (4-hydroxy-3-methylenepentan-2-one) in low enantioselectivity (12% ee).[13] Also, coupling of acrylonitrile with propionaldehyde in the presence of quinidine as catalyst provided the desired adduct (3-hydroxy-2-methylenepentanenitrile) in 20% enantiomeric excess.[51a] Marko and coworkers have reported that coupling of methyl vinyl ketone with cyclohexanecarboxaldehyde using

quinidine as catalyst under high pressure provided the required adduct in 45% enantiomeric excess (eq. 15).



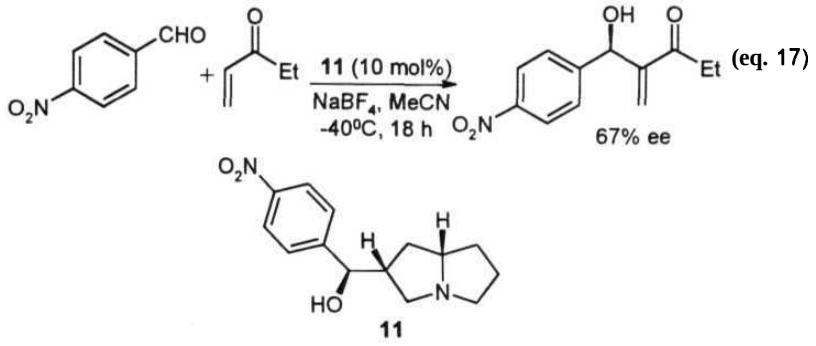
(eq. 15)

Hirama and coworkers[57] have synthesized chiral 2,3-bis(benzyloxymethyl)-l,4-diazabicyclo[2.2.2]octane (10) and used this molecule as chiral catalyst for asymmetric Baylis-Hillman reaction They observed in their studies that the reaction between 4-nitrobenzaldehyde and methyl vinyl ketone in the presence of this catalyst (10) provides the highest enantioselectivity of 47% (eq. 16).



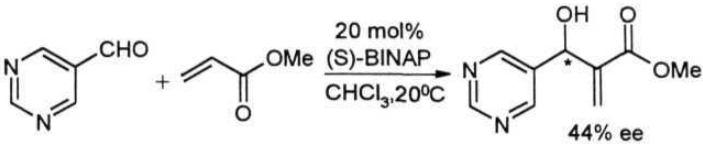
(eq. 16)

Recently, Barrett *et al.*[58] have synthesized a new chiral pyrrolizidine catalyst (11) for asymmetric Baylis-Hillman reaction. Coupling of ethyl vinyl ketone with 4-nitrobenzaldehyde using this molecule (11) as catalyst provides the required Baylis-Hillman adduct in 67% enantioselectivity (eq. 17).



(eq. 17)

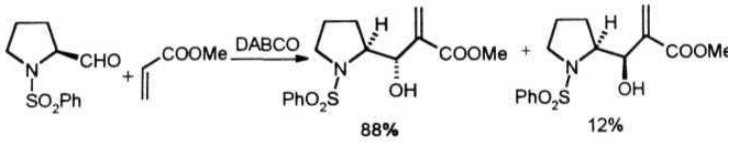
Soai and coworkers[59] have described an interesting (S)-BINAP catalyzed Baylis-Hillman coupling of pyrimidine-5-carboxaldehyde with methyl acrylate leading to the formation of the desired product in 44% ee (eq 18).



(eq. 18)

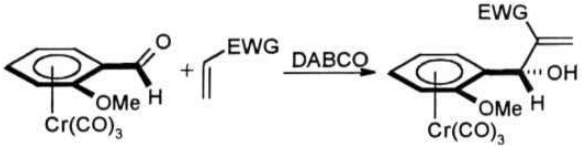
iii) Chiral Electrophiles

Considerable efforts have been made for achieving asymmetric Baylis-Hillman reaction using chiral electrophiles. Various chiral aldehydes, such as (S)-O-protected lactaldehyde,[60] (3S)-O-benzylated 3-hydroxybutyraldehyde[61] and N-protected α-aminoaldehydes[62, 63] have been used as electrophiles in the Baylis-Hillman reaction. The highest diastereoselectivity of 76% was reported in the Baylis-Hillman coupling of N-phenylsulfonyl-L-prolinal with methyl acrylate in the presence of DABCO (eq. 19). [62]



(eq. 19)

Kundig *et al.*[64,65] have successfully employed non-racemic ortho substituted benzaldehydetricarbonylchromium complexes as electrophiles for the Baylis-Hillman reaction with methyl acrylate and acrylonitrile in the presence of DABCO to provide the required adducts with high diastereoselectivity of >95% (eq. 20).

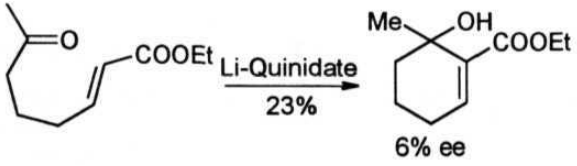


(eq. 20)

EWG= COOMe, CN

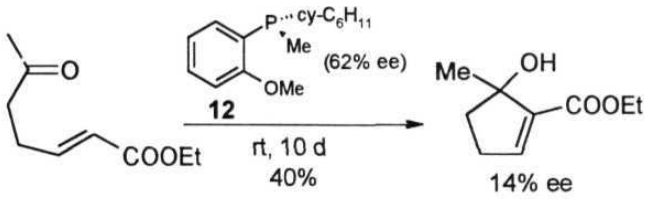
Intramolecular Baylis-Hillman Reaction

Though there is a possibility of intramolecular Baylis-Hillman reaction in cases where electrophiles and activated alkenes are suitably oriented, there are not many efforts made in this direction. Roth and coworkers[66] have reported an intramolecular Baylis-Hillman reaction of ethyl (2*E*)-7-oxooct-2-enoate catalyzed by lithium salt of quinidine to provide the cyclic molecule with 6% enantioselectivity in 23 % yield (eq. 21). They have also used the chiral phosphine



(eq. 21)

(12) to catalyze enantioselective intramolecular **Baylis-Hillman** reaction of ethyl **(2*E*)-6-oxohept-2-enoate** (eq. 22). However, enantioselectivity in this reaction was found to be poor.[66]



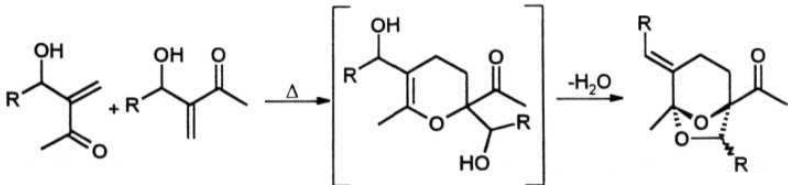
(eq. 22)

Applications of the Baylis-Hillman adducts

Functional groups play an important role in bringing latitude to organic **synthesis** The Baylis-Hillman adducts possessing a minimum of three such functional groups in close proximity should in principle be useful in various stereoselective **transformations In** fact, literature reveals a number of applications of the Baylis-Hillman adducts in a variety of stereoselective transformations. Some of the important and recent applications are described in this section.

Hoffmann and **coworkers**[67] have successfully transformed the Baylis-Hillman adducts derived from methyl vinyl **ketone** into 6,8-dioxobicyclo[3 2.1]octanes, an

Scheme 7

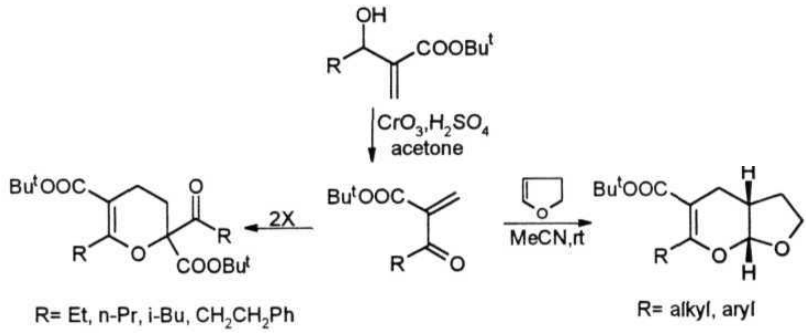


R= **H,** Me, Et, **$PhCH_2CH_2$, Me_2CHCH_2**

useful class of molecules *via* Diels-Alder type dimerization (Scheme 7).

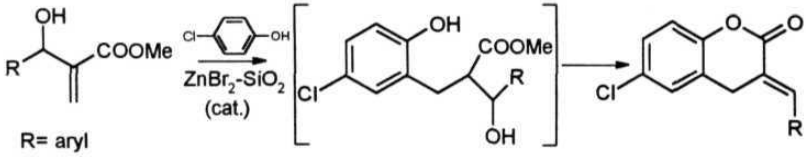
Hoffmann *et al*.[68] have also synthesized a variety of oxygen heterocycles *via* the cycloaddition reaction of α-methylene-β-keto esters, which were prepared from corresponding Baylis-Hillman adducts *via* modified Jones oxidation (Scheme 8).

Scheme 8



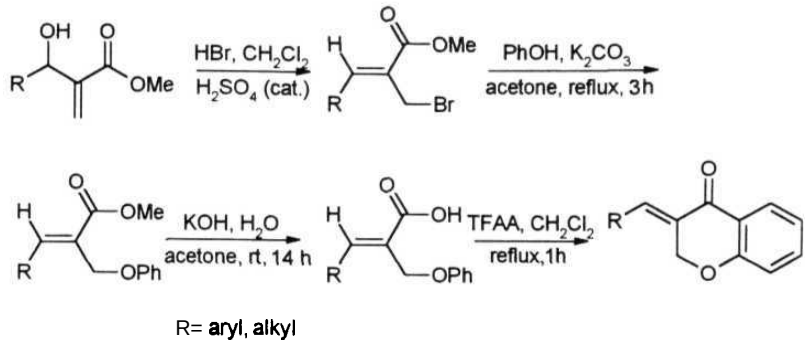
Foucaud and Brine[69] have successfully employed the Baylis-Hillman adducts for the synthesis of dihydrocoumarins according to the Scheme 9.

Scheme 9



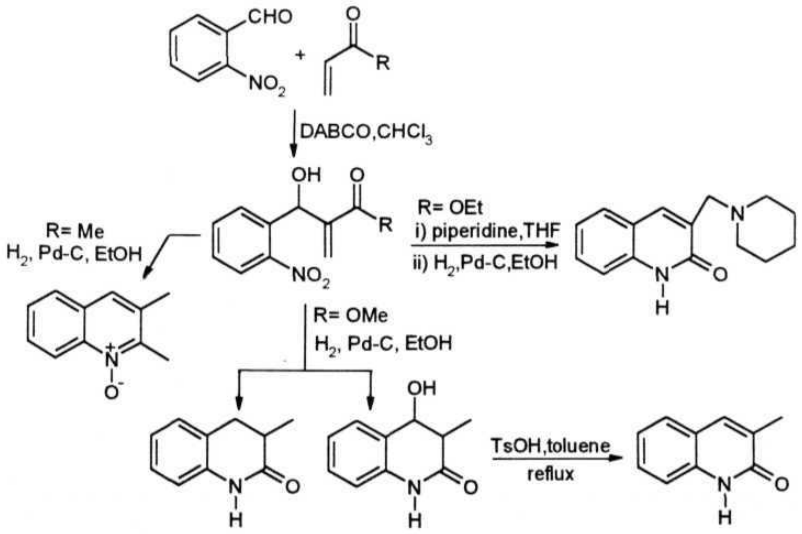
A new protocol for the synthesis of (*E*)-3-arylidene(or alkylidene)chroman-4-one moiety, an important key structural unit present in several natural products has been described by our research group (Scheme 10).[70]

Scheme 10



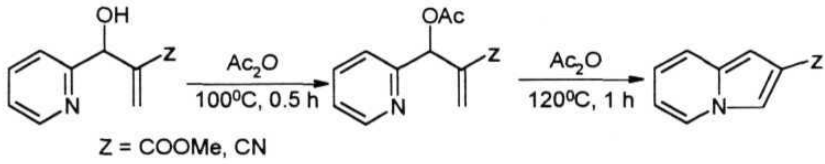
Recently, Kaye and coworkers[71] have developed a novel synthesis of quinoline derivatives using Baylis-Hillman adducts derived from o-nitrobenzaldehyde according to Scheme 11.

Scheme 11



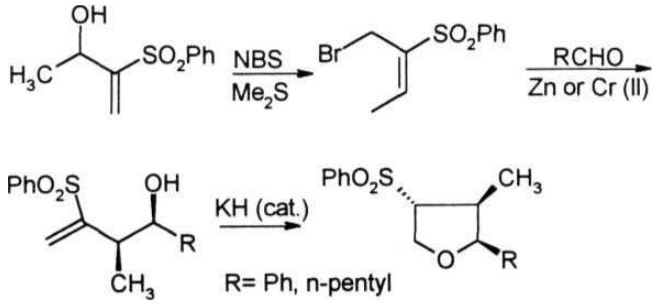
Bode and Kaye[72,73] have successfully transformed the Baylis-Hillman adducts derived from 2-pyridinecarboxaldehyde into indolizines according to Scheme 12.

Scheme 12



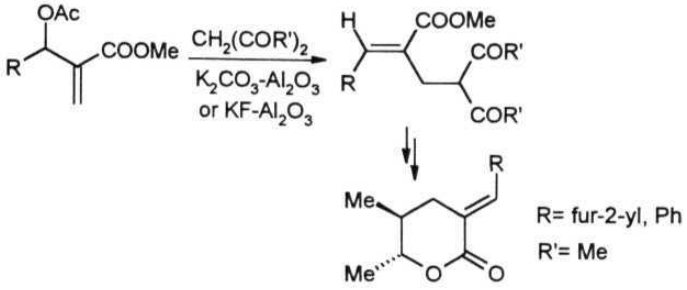
Normant and coworkers[74,75] have developed an interesting stereoselective synthesis of tetrahydrofUran derivatives using the Baylis-Hillman adducts *i.e.* 3-hydroxy-2-(phenylsulfonyl)but-l-ene, derived from phenyl vinyl sulfone (Scheme 13).

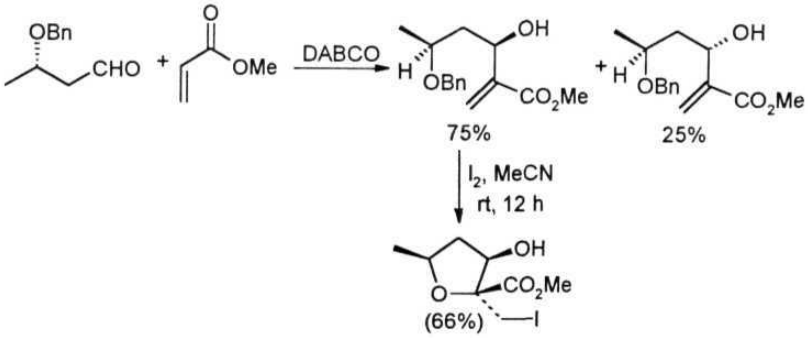
Scheme 13

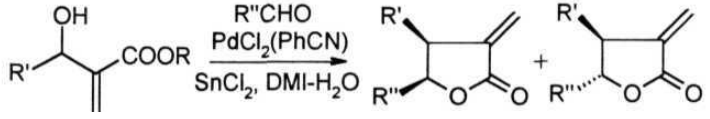


Bauchat and coworkers[76] have carried out the nucleophilic addition of carbanions generated from 1,3-diketone to acetates of the Baylis-Hillman adducts to provide trisubstituted alkenes, with (*E*)-selectivity, which were subsequently transformed to δ-lactones (Scheme 14).

Scheme 14







(eq. 23)

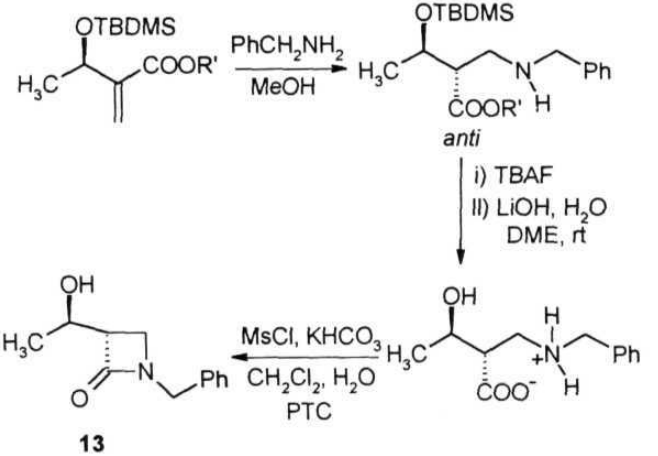
R'= n-Bu, cyclohexyl, 4-(COOMe)C_6H_4

R= Me, Et; R"= Me, n-Bu, Ph

aldehydes in the presence of $PdCl_2(PhCN)$ as catalyst (eq. 23).

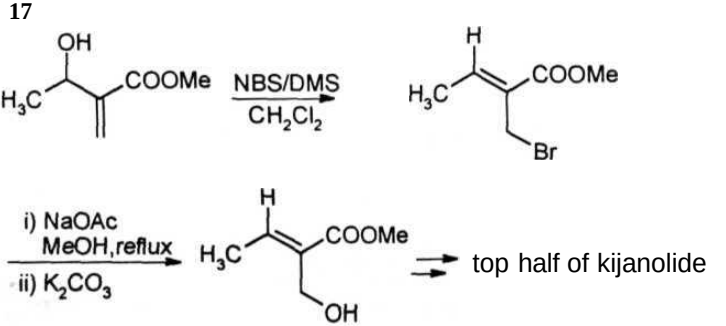
Perlmutter and Tabone[78,79] have reported an elegant synthesis of β-lactam (13) *via* the highly diastereoselective Michael addition of benzylamine to the O-protected Baylis-Hillman adducts (Scheme 16).

Scheme 16



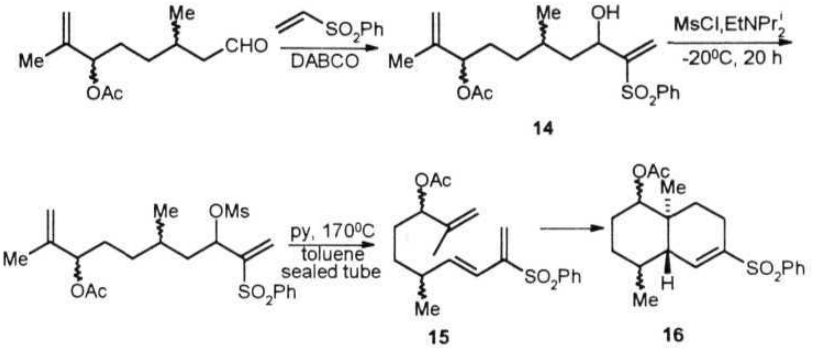
Roush and Brown[80] demonstrated the utility of the Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate in synthesis of the top half of the kijanolide (kijanolide, an aglycon of the spirotetronate antibiotic kijanimicin) (Scheme 17).

Scheme 17



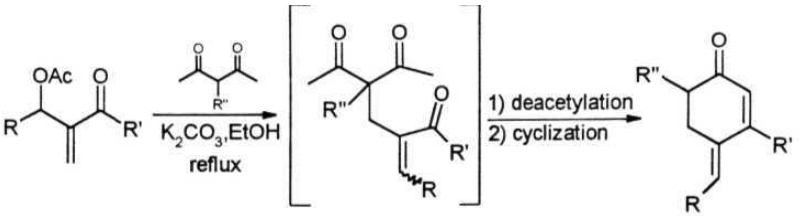
Weichert and Hoffmann[81] have reported an elegant synthesis of the eudesmane precursor (16) *via* intramolecular [4+2] cycloaddition reaction of the triene 15 generated *in situ* from mesylate of the Baylis-Hillman adduct 14 (Scheme 18)

Scheme 18



Chamakh and Amri[82] have successfully transformed acetates of the Baylis-Hillman adducts, derived from alkyl vinyl ketones into (*E*)-4-alkylidene-2-cyclohexen-1-ones according to Scheme 19.

Scheme 19

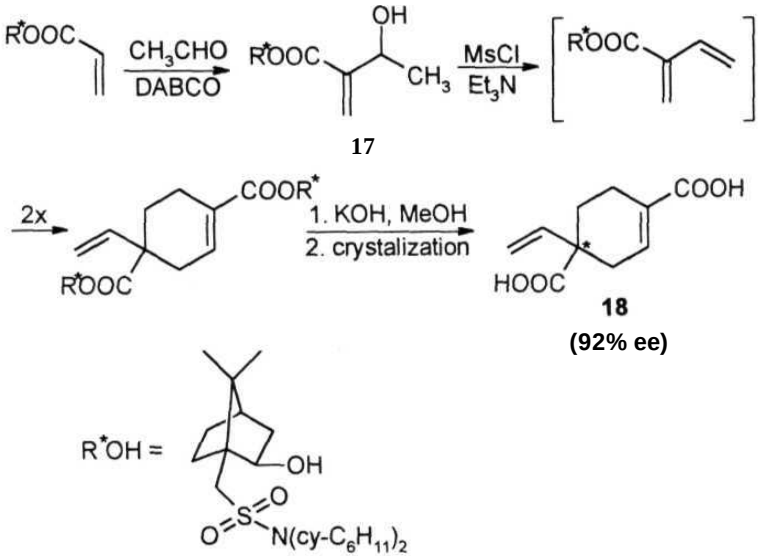


R= alkyl, aryl; R'= Me, Et; R"= H, Me

First asymmetric synthesis of mikanecic acid (18), an interesting terpene dicarboxylic acid possessing chiral quaternary vinyl centre has been reported from our laboratory *via* Diels-Alder type self dimerization of the diene derived from the

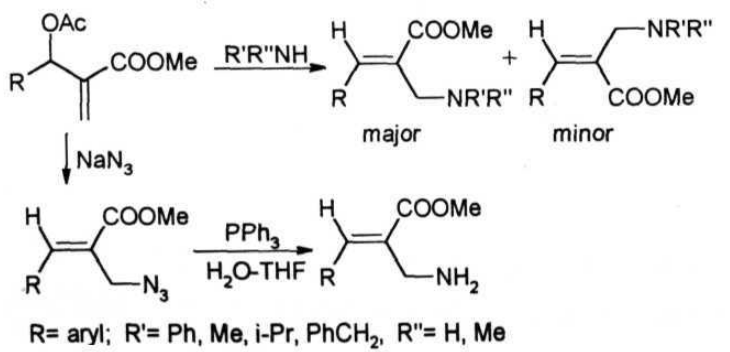
Baylis-Hillman adduct (17) (Scheme 20):

Scheme 20



Foucaud and El Guemmout[84] have described stereoselective synthesis of trisubstituted (*E*)-allyl amines by nucleophilic addition of primary or secondary amines to acetates of the Baylis-Hillman adducts. They also prepared primary

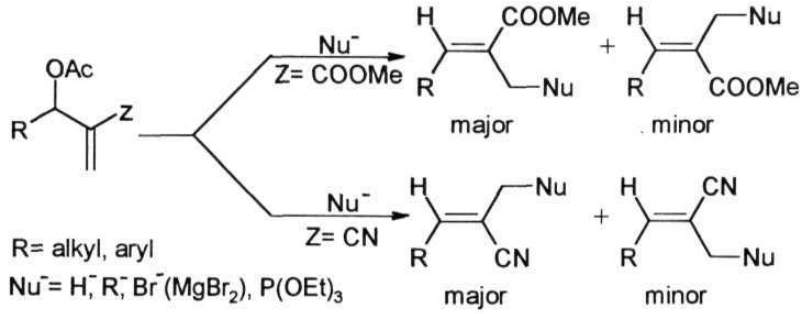
Scheme 21



allyl amines by treating the acetates of the Baylis-Hillman adducts with sodium azide followed by reduction with triphenylphosphine and water (Scheme 21).

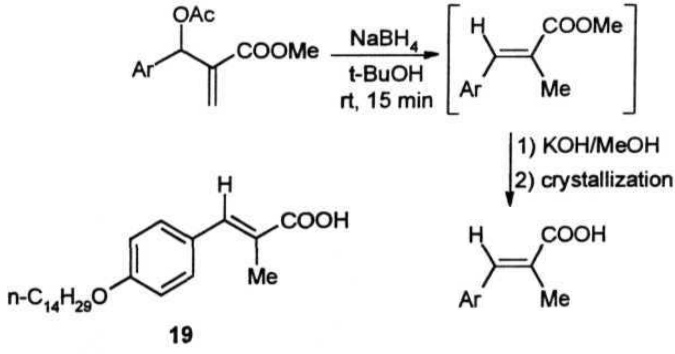
In our laboratory, acetates of the Baylis-Hillman adducts have been successfully transformed into various trisubstituted alkenes with high stereoselectivity. Our research group has noticed a remarkable reversal of stereoselectivity from ester to nitrile groups in these nucleophilic addition reactions (Scheme 22).[85-88]

Scheme 22



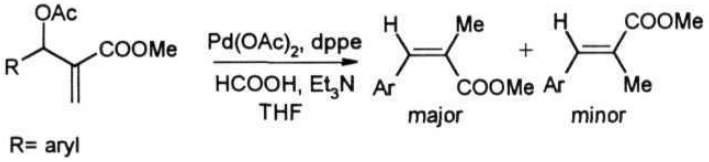
Our research group has recently reported an efficient synthesis of (*E*)-α-methyl-cinnamic acids using the acetates of the Baylis-Hillman adducts (Scheme 23).[89]

Scheme 23



The efficacy of this methodology has been demonstrated by synthesis of (*E*)-2-methyl-3-(4-myristyloxyphenyl)prop-2-enoic acid (19), a good hypolipidemic agent.

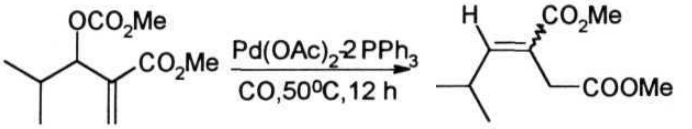
Recently Pachamuthu and Vankar[90] have reported a simple synthesis of (Z)-a-methylcinnamic esters *via* the reduction of acetates of the Baylis-Hillman adducts with HCOOH in the presence of $Pd(OAc)_2$, Et_3N (eq. 24).



R= aryl

(eq. 24)

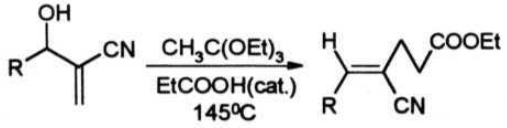
Yamamoto and coworkers[91] have described the palladium catalyzed stereoselective carbonylation of carbonates of the Baylis-Hillman adducts to provide trisubstituted alkenes with high (*E*)-stereoselectivity (eq. 25).



E:Z = 14:1

(eq. 25)

Our research group has successfully transformed 3-hydroxy-2-methylene-alkanenitriles, the Baylis-Hillman adducts derived from acrylonitrile, into (Z)-4-



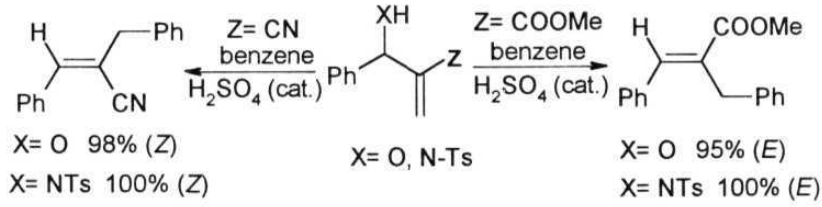
(eq. 26)

R = alkyl, aryl

cyanoalk-4-enoates *via* the Johnson-Claisen rearrangement (eq. 26).[92]

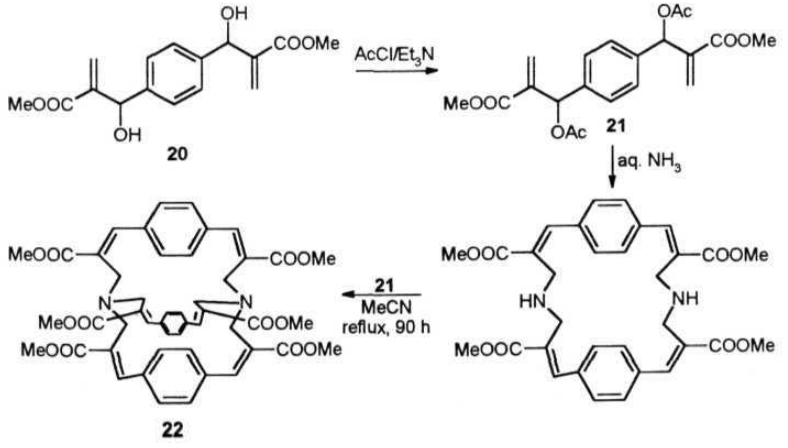
The Baylis-Hillman adducts, methyl 3-hydroxy-2-methylene-3-phenylpropanoate, 3-hydroxy-2-methylene-3-phenylpropanenitrile, methyl 2-methylene-3-phenyl-3-tosylaminopropanoate and 2-methylene-3-phenyl-3-tosylaminopropanenitrile have been used as β-electrophiles for the Friedel-Crafts reaction to provide trisubstituted alkenes with high stereoselectivities (Scheme 24).[93, 94]

Scheme 24

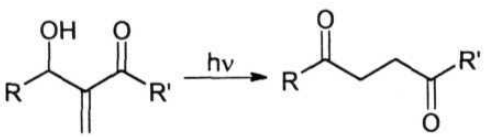


The diacetate 21 of bis-Baylis-Hillman adduct 20, derived from terphthaldehyde and methyl acrylate, has been elegantly transformed into diazamacrobicycle 22 by Bauchat and Foucaud following the reaction sequence delineated in Scheme 25 "

Scheme 25



Recently, Mikami and coworkers[96] have described an interesting photochemical reaction of Baylis-Hillman adducts derived from vinyl ketones leading to synthesis of 1,4-dicarbonyl compounds (eq. 27).

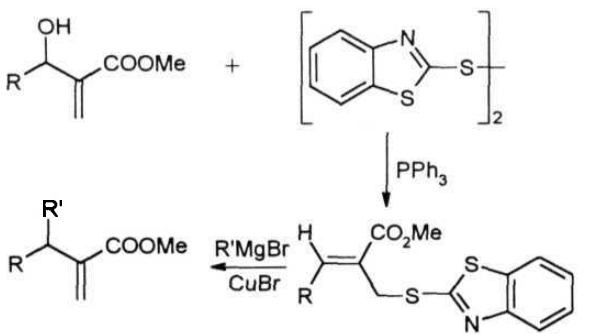


(eq. 27)

R = aryl, alkyl
R'= Me, phenyl

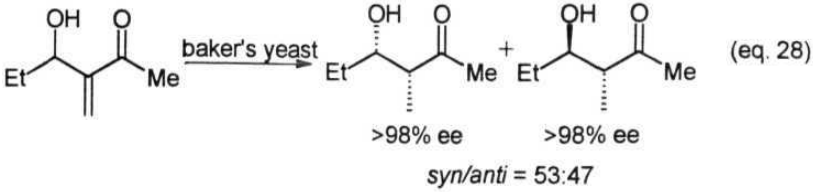
Calo and coworkers[97] have reported the synthesis of β,β-disubstituted-α-methylenealkanoates from the Baylis-Hillman adducts according to Scheme 26.

Scheme 26



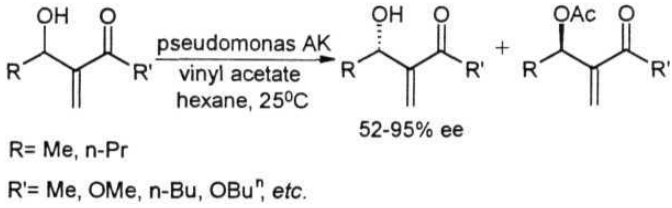
R= Me, Me_2CH, n-C_8H_{17}; R'= n-C_4H_9, n-C_8H_{17}, Me_3SiCH_2

Utaka *et al*[98] reported an interesting baker's yeast mediated asymmetric reduction of the Baylis-Hillman adducts leading to the formation of aldol type products in high enantioselectivities (eq. 28).



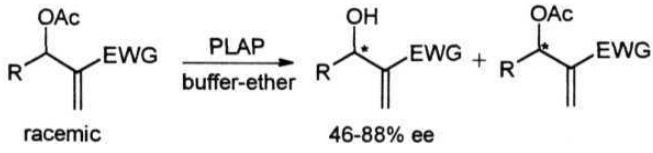
(eq. 28)

Burgess and Jennings have described the biocatalytic kinetic resolution of Baylis-Hillman adducts using pseudomonas AK (eq. 29)."



(eq. 29)

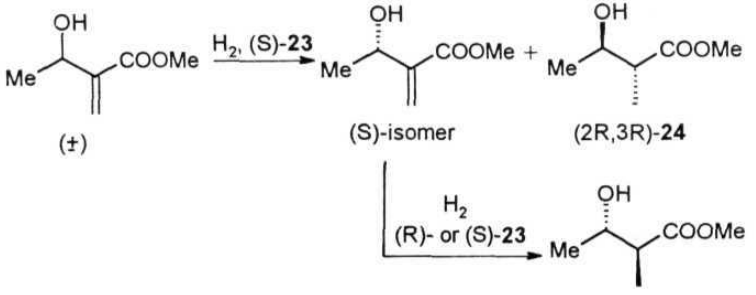
Our research group has reported the pig liver acetone powder (PLAP) mediated enantioselective hydrolysis of racemic 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles to provide the optically active Baylis-Hillman adducts *i.e.* 3-hydroxy-2-methylenealkanoates and 3-hydroxy-2-methylenealkane-nitriles in 46-88% enantiomeric excess (eq. 30).[100]

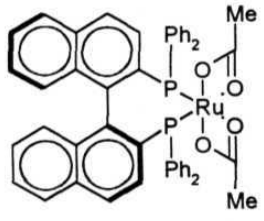


(eq. 30)

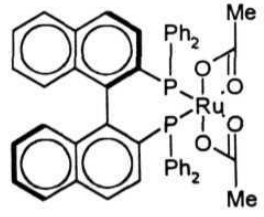
Noyori and coworkers[101] have reported the asymmetric hydrogenation of the Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate using the chiral catalyst (S)-BINAP-Ru (II) diacetate complex {(S)-23} to provide the kinetically resolved Baylis-Hillman adduct methyl (S)-3-hydroxy-2-methylenebutanoate in >99% enantiomeric excess along with *anti* aldol type molecule **(2R,3R)-24** in 37% enantiomeric purity. Interestingly this molecule *i.e.* methyl (S)-3-hydroxy-2-methylenebutanoate on asymmetric hydrogenation with either (R) or (S) BINAP-Ru (II) diacetate complex {(S)- or (R)-23} as catalyst provides the **(2S,3S)-24** *anti* isomer (Scheme 27).

Scheme 27





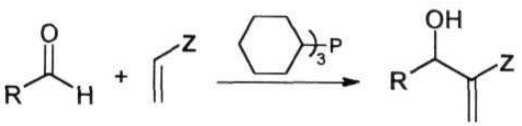
(S)-23



(R)-23

Baylis-Hillman Type reactions

In fact, in 1968 Morita *et al.*[102] have reported tricyclohexylphosphine induced coupling of methyl acrylate and acrylonitrile with aldehydes to produce the corresponding a-substituted methyl acrylates and acrylonitriles (eq. 31).

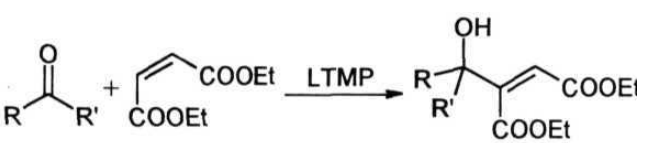


(eq. 31)

R= alkyl, aryl; Z= COOMe, CN

Organic chemists have also directed their efforts to synthesize the Baylis-Hillman adducts using other catalysts or catalytic systems with a view to expand the scope of this reaction. For example, trialkyl phosphines,[103-104] ruthenium (II) complex $\{RuH_2(PPh_3)_4\}$[105, 106] or rhodium (I) complex $\{RhH(PPh_3)_4\}$[106, 107] have been used as catalysts for coupling of a-position of activated alkenes with aldehydes Also literature records some important strategies to obtain the Baylis-Hillman adducts Some of the relevant and recent reports have been described in this section.

Diethyl maleate was coupled with aldehydes and ketones under the influence of LTMP to provide α-hydroxyalkylated maleates (eq. 32).[108]

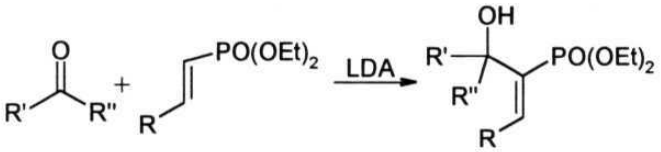


(eq. 32)

R' = H, aryl, alkyl, CD_3, *etc.*

R= aryl, CD_3, *etc.*

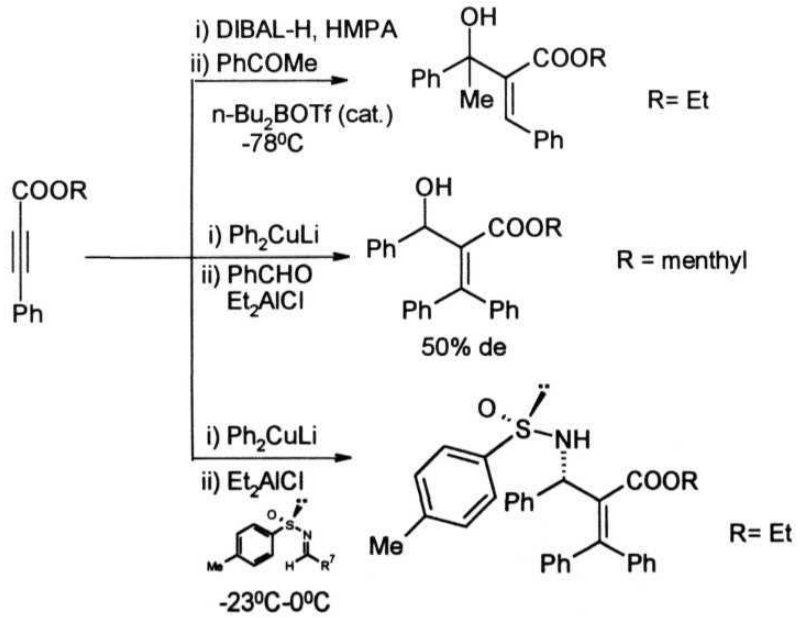
Recently, Nagaoka and Tomioka[109] reported an interesting Baylis-Hillman type coupling of vinyl phosphonates with aldehydes in the presence of LDA thus providing a-hydroxyalkylated vinyl phosphonates in 50-90% yields (eq. 33).



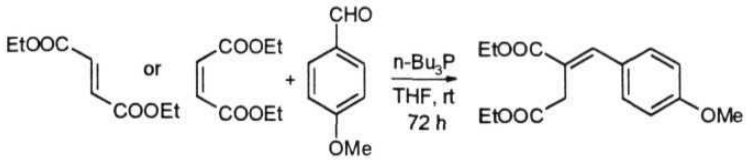
R= H, Me, Ph; R'= *t*-Bu, Et, Ph, *etc.*; R"= H, Me

Recently, Li and coworkers[110-112] have used acetylenic esters for coupling with various aldehydes, ketones and *p*-toluenesulfinimines to generate the Baylis-Hillman type adducts (Scheme 28).

Scheme 28



McCombie and Luchaco reported tri n-butylphosphine catalyzed coupling of diethyl maleate or diethyl fumarate with aldehydes to furnish Stobbe type condensed products (eq. 34).[113]



(eq. 34)

Objectives, Results and Discussion

Objectives

From the preceding chapter, it is evident that Baylis-Hillman reaction is one of the important and emerging C-C bond forming reactions, producing a very useful class of molecules possessing a minimum of three functional groups in close proximity. These Baylis-Hillman adducts have been successfully used in a variety of organic transformations with high stereoselectivities.[13-15] With a view to further expand the scope of the Baylis-Hillman reaction and to develop this reaction as a source of stereoselective processes we have undertaken a long range research program on this fascinating reaction. This thesis deals with studies in the Baylis-Hillman Chemistry with the following objectives.

1). Isomerization of the Baylis-Hillman adducts *i.e.* methyl 3-aryl-3-hydroxy-2-methylenepropanoates, obtained from an activated alkene methyl acrylate, under the catalytic influence of $RuCl_2(PPh_3)_3$ to provide methyl 3-aryl-2-methyl-3-oxopropanoates.

2). Synthesis of methyl 2-arylmethyl-3-oxoalkanoates *via* the arylation of the Baylis-Hillman adducts *i.e.* methyl 3-hydroxy-2-methylenealkanoates with aryl bromides under the catalytic influence of $Pd(OAc)_2$ (Heck conditions).

3). Stereoselective synthesis of methyl (2*E*)-2-cyanomethylalk-2-enoates and (3Z)-3-cyanoalk-3-enenitriles *via* the nucleophilic addition of cyanide ion to acetates of the Baylis-Hillman adducts *i.e.* methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles respectively

4) Transformation of acetates of the Baylis-Hillman adducts *i.e.* methyl 3-acetoxy-3-aryl-2-methylenepropanoates and 3-acetoxy-3-aryl-2-methylenepropanenitriles into methyl (2*E*)-2-acetoxymethyl-3-arylprop-2-enoates and (2E)-2-acetoxymethyl-3-aryl-prop-2-enenitriles respectively *via* the trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed isomerization

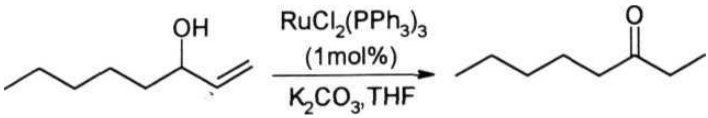
Objectives of the thesis also include: 5). Synthesis of ethyl 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates *via* the chalcogeno-Baylis-Hillman reaction of alkyl vinyl ketones (methyl vinyl ketone and ethyl vinyl ketone) with a-keto esters. 6) Development of an asymmetric version of the Baylis-Hillman reaction using chiral α-keto esters as electrophiles for coupling with alkyl acrylates and acrylonitrile.

Results and Discussions

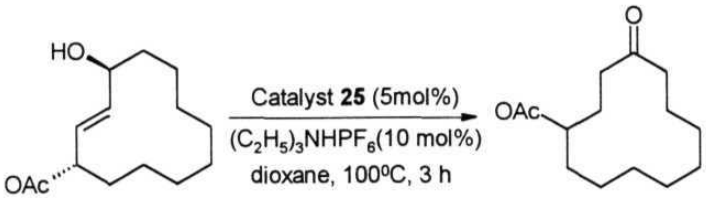
Isomerization of the Baylis-Hillman adducts

Transition metal catalyzed isomerization of allyl alcohols to saturated carbonyl molecules is an important and useful operation in synthetic organic chemistry. There are many reports in the literature describing isomerization of various allyl alcohols

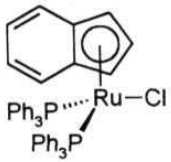
into saturated carbonyl molecules[114] [7] and two such important examples are described in the equations 35[114] and 36.[115] However, the Baylis-Hillman adducts



(eq. 35)



(eq. 36)



25

possessing allylic alcohol moiety have not been employed as substrates for transition metal catalyzed isomerization to obtain the corresponding saturated carbonyl molecules. We have therefore undertaken the possible isomerization of methyl 3-hydroxy-2-methylenealkanoates **(26a-f),** the Baylis-Hillman adducts obtained *via* the coupling of activated alkene, methyl acrylate with representative aldehydes (eq. 37),

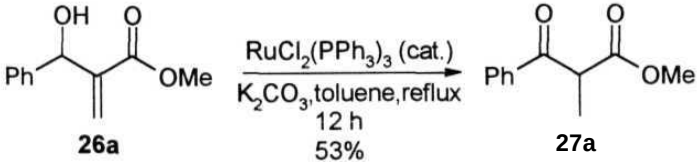
under the catalytic influence of $RuCl_2(PPh_3)_3$ with a view to provide a simple synthesis of methyl 2-methyl-3-oxoalkanoates

(eq. 37)

26a-f

R= phenyl, 4-methylphenyl, 4-isopropylphenyl, 2-methoxyphenyl, 4-ethylphenyl, 4-methoxyphenyl

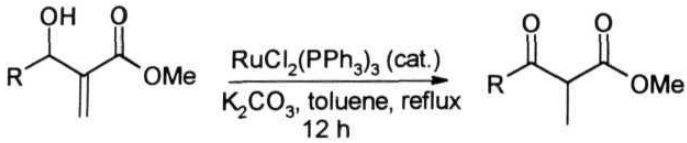
First, we have selected methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(26a)** as a substrate Isomerization was carried out at various conditions. The best result was obtained when this molecule *i.e.* methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(26a)** (1 mmol) was treated with a catalytic amount of $RuCl_2(PPh_3)_3$ (4 mol%) and K_2CO_3 (1 mmol) in toluene (2 mL) at reflux temperature for 12 h, thus providing the desired methyl 2-methyl-3-oxo-3-phenylpropanoate **(27a)** in 53% yield (eq. 38). The structure of this molecule was confirmed by IR, ^1H NMR, ^{13}C NMR (Fig. 1), mass spectral data and elemental analysis



(eq. 38)

Encouraged by this result, we have subjected a representative class of Baylis-Hillman adducts **(26b-f)** to $RuCl_2(PPh_3)_3$ catalyzed isomerization, which provided the desired

methyl 3-aryl-2-methyl-3-oxopropanoates **(27b-f)** in good yields (eq. 39, Table 1).



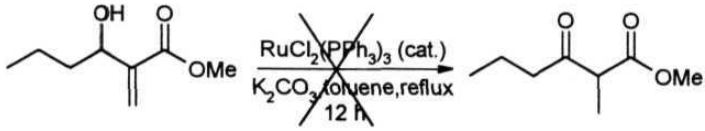
(eq. 39)

26b-f 42-61% 27b-f

R= 4-methylphenyl, 4-isopropylphenyl, 2-methoxyphenyl
4-ethylphenyl, 4-methoxyphenyl

Thus, this methodology describes the $RuCl_2(PPh_3)_3$ catalyzed isomerization of the Baylis-Hillman adducts *i.e.* methyl 3-aryl-3-hydroxy-2-methylenepropanoates **(26a-f)** to provide α-methyl-β-keto esters *i.e.* methyl 3-aryl-2-methyl-3-oxopropanoates (27a-f).

However, the Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenehexanoate (obtained from coupling of n-butyraldehyde with methyl acrylate under the influence of DABCO) did not undergo isomerization reaction under similar conditions (eq 40)



(eq. 40)

Also, attempted $RuCl_2(PPh_3)_3$ catalyzed isomerization of 3-hydroxy-2-methylene-3-phenylpropanenitrile, the Baylis-Hillman adduct obtained *via* the coupling of acrylonitrile with benzaldehyde, under various conditions was unsuccessful.

Table 1: Isomerization of the Baylis-Hillman adducts[a,b]

Substrate	R	Product	Yield[c] (%)
26a	phenyl	**27a**	53
26b	4-methylphenyl	**27b**	51
26c	4-isopropylphenyl	27c	57
26d	2-methoxyphenyl	**27d**	50
26e	4-ethylphenyl	**27e**	42
26f	4-methoxyphenyl	**27f**	61

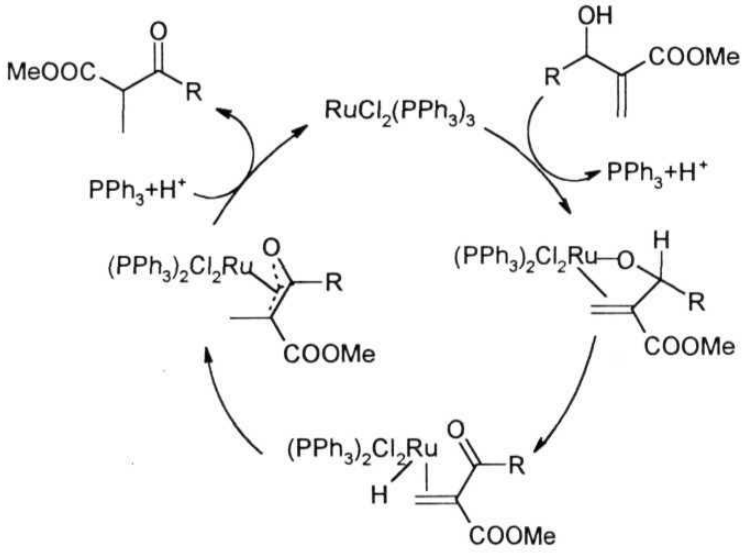
a) All reactions were carried out on lmmol scale of allyl alcohol with $RuCl_2(PPh_3)_3$ (4 mol%) in toluene at reflux temperature for 12 h.

b) All products were obtained as colorless liquids and gave satisfactory IR, ^1H NMR, ^{13}C NMR, mass spectral and elemental analyses.

c) Yields of the products after column chromatography (5% EtOAc in hexanes, silica gel).

This isomerization of methyl 3-aryl-3-hydroxy-2-methylenepropanoates into methyl 3-aryl-2-methy l-3-oxopropanoates can be possibly explained on the basis of similar mechanism reported in the literature (Scheme 29).[113-115]

Scheme 29

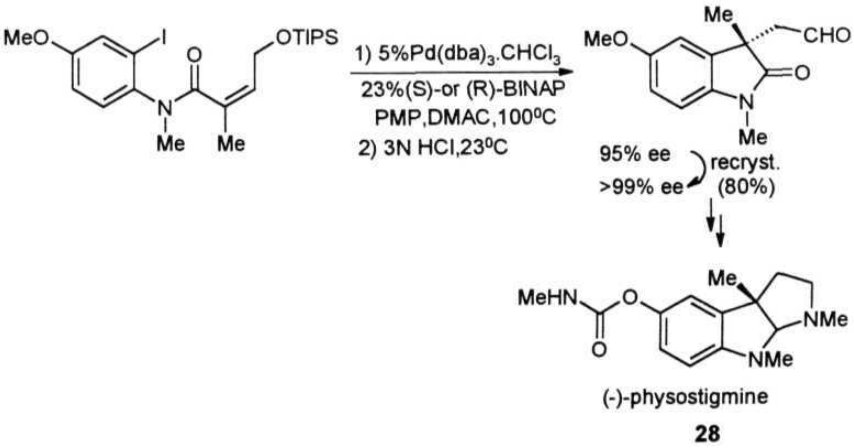


With an objective of providing general synthesis of a-substituted P-keto esters using the Baylis-Hillman adducts, we have undertaken the arylation of the Baylis-Hillman adducts under Heck conditions.[8]

Arylation of the Baylis-Hillman adducts

In recent years there has been much emphasis on the Heck reaction for the construction of carbon-carbon bond at the vinylic position involving palladium catalyzed coupling of haloarenes and haloalkenes with alkenes.[8, 23] A variety of substituted and fiinctionalized alkenes have been successfully arylated or alkenylated *via* the Heck reaction to produce synthetically useful molecules.[8, 118-123] In fact, some important natural and biologically active molecules such as 28 and 29 have been synthesized using the Heck reaction as the key step (Schemes 30[120] and 31[121]).

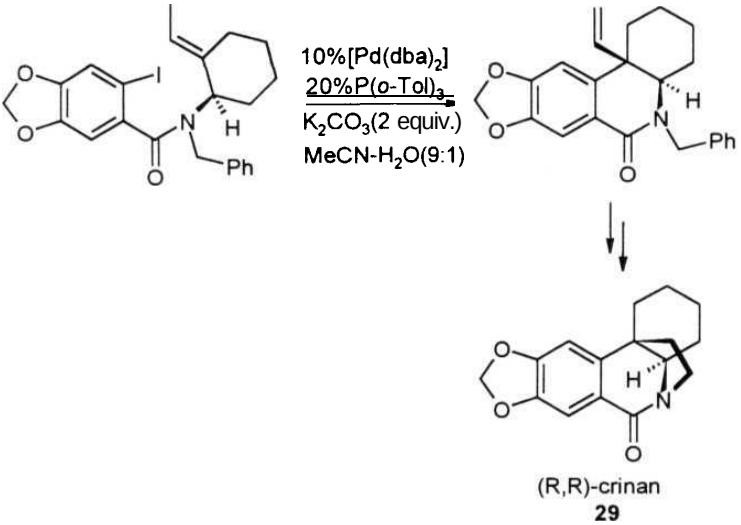
Scheme 30



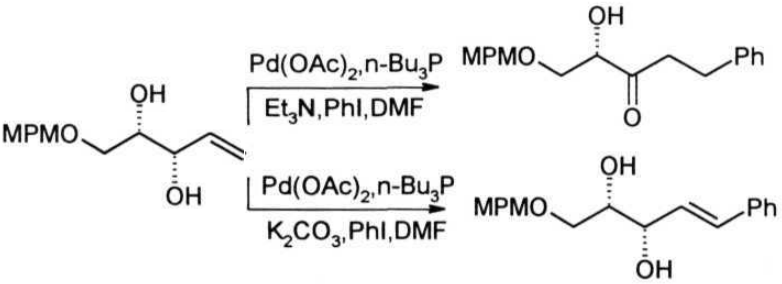
The Heck reaction *i.e.* arylation of allylic alcohols has been well studied to provide arylated saturated carbonyl compounds or arylated allyl alcohols by changing

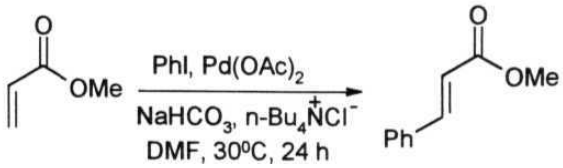
reaction conditions (Scheme 32).[122] Also the Heck reaction of a,3-unsaturated esters has been well documented to produce the arylated α,β-unsaturated esters (eq. 41).[123]

Scheme 31



Scheme 32



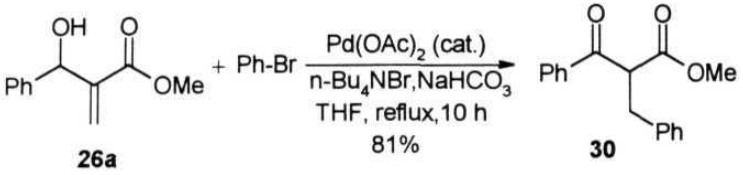


(eq. 41)

However, the Heck reaction *i.e.* arylation of alkenes possessing both allylic alcohol and a,P-unsaturated ester moieties in which carbon-carbon double bond is an integral part of both allyl alcohol and a,P-unsaturated ester moieties has not been studied The Baylis-Hillman reaction provides an easy access for such interesting class of alkenes having both allyl alcohol and a,(3-unsaturated ester moieties Therefore, we have decided to study the Heck reaction *i.e.* arylation of Baylis-Hillman adducts *i.e.* methyl 3-hydroxy-2-methylenealkanoates with various bromoarenes under the catalytic influence of $Pd(OAC)_2$

Accordingly, we have first carried out the reaction of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (26a) with bromobenzene in the presence of $Pd(OAC)_2$ under various conditions The best result was obtained when a solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (26a) (1 mmol) and bromobenzene (2 mmol) in THF (3 mL) was refluxed for 10 h in the presence of $Pd(OAC)_2$ (2 mol%), $NaHCO_3$ (2.5 mmol) and $n\text{-}Bu_4N^+Br^-$ (1 mmol), providing methyl 2-benzyl-3-oxo-3-phenylpropanoate (30) in 81% yield (eq. 42). This molecule contains ≈5% impurity and was further purified by preparative HPLC (Shim-pack PREP-ODS column,

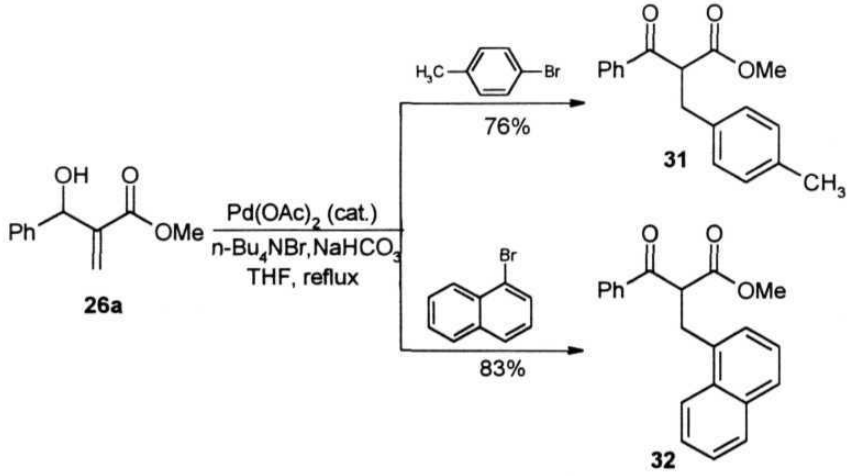
methanol). Structure of 30 was confirmed by IR, ^{1}H NMR and ^{13}C NMR (Fig. 2), mass spectral data and elemental analysis.



26a 30 **(eq. 42)**

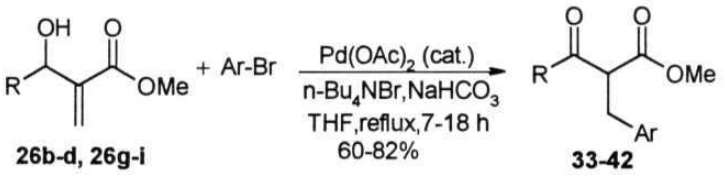
We have also successfully used 4-bromotoluene and α-bromonaphthalene as substrates for the Heck reaction with methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(26a),** thus providing the required a-substituted P-keto esters (31 & 32) (Scheme 33, Table 2).

Scheme 33



26a 31 32

Encouraged by this result, we have subjected a variety of the Baylis-Hillman adducts **(26b-d, 26g-i)** to arylation using various bromoarenes which produced the desired methyl 2-arylmethyl-3-oxoalkanoates **(33-42)** (eq. 43, Table 2). The molecules **33-38** contain ≈5% impurity and were further purified by preparative HPLC (Shim-pack PREP-ODS column, methanol). The molecules **39-42** contain ≈5-8% impurity and further attempts to purify by preparative HPLC (Shim-pack PREP-ODS column, methanol) were unsuccessful.



26b-d, 26g-i **33-42** **(eq. 43)**

R = 4-methylphenyl, 4-isopropylphenyl, 2-methoxyphenyl, 4-chlorophenyl, isopropyl, n-pentyl.
Ar= phenyl, 4-methylphenyl, naphth-1-yl

A possible mechanism for this arylation of the Baylis-Hillman adducts *i.e.* methyl 3-hydroxy-2-methylenealkanoates is described in the Scheme 34 on the basis of similar pathway proposed in the literature. [118, 119]

Thus, this methodology describes a simple procedure for the arylation of the Baylis-Hillman adducts, methyl 3-hydroxy-2-methylenealkanoates **(26a-d, 26g-i)** providing an easy access to methyl 2-arylmethyl-3-oxoalkanoates **(30-42),** an important class of organic synthons.

Table 2: Arylation of Baylis-Hillman adducts*

Substrate	R	Ar	Time	Product	Yield[b] (%)
26a	phenyl	phenyl	10	**30**[c]	81
26a	phenyl	p-methylphenyl	10	31	76
26a	phenyl	naphth-1-yl	7	**32**	83
26b	4-methylphenyl	phenyl	12	**33**[c]	80
26c	4-isopropylphenyl	phenyl	10	**34**	**75**
26c	4-isopropylphenyl	4-methylphenyl	10	35	76
26c	4-isopropylphenyl	naphth-1-yl	**8**	**36**	82
26d	2-methoxyphenyl	phenyl	18	37	67
26g	4-chlorophenyl	phenyl	8	38	60
26h	isopropyl	phenyl	10	**39**[d]	61
26h	isopropyl	4-methylphenyl	7	**40**[d]	76
26i	n-pentyl	phenyl	9	**41**[d]	64
26i	n-pentyl	naphth-1-yl	7	**42**[d]	79

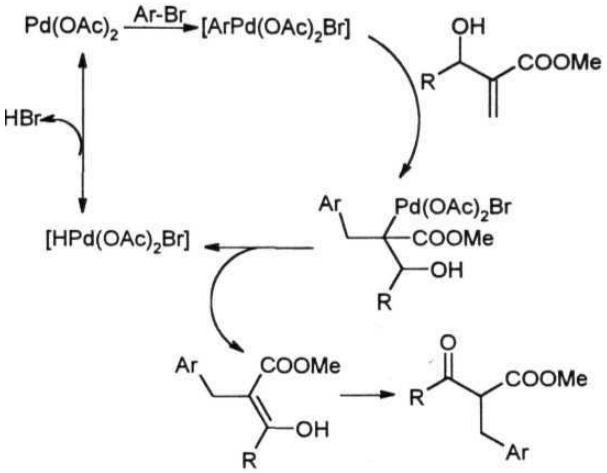
a) All reactions were carried out on 1 mmol scale of allyl alcohol with aryl bromides (2 mmol) in the presence of Pd $(OAc)_2$ (2 mol%) in THF at reflux temperature.

b) Yields of the products obtained after column chromatography (5% EtOAc in hexanes, silica gel). The molecules **30, 31, 33-42** were obtained as colorless liquids and the molecule 32 was obtained as a colorless solid.

c) The molecules **30, 33-38** contain ≈5% impurity and were further purified by preparative HPLC (Shim-pack PREP-ODS column, methanol). All these compounds **30-38** gave satisfactory IR, ^1H NMR, ^{13}C NMR, mass spectral and elemental analyses.

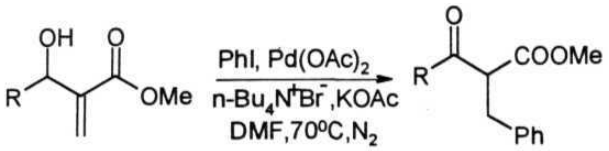
d) ^1H NMR and ^{13}C NMR spectra show that these molecules **39-42** contain ≈5-8% impurity.

Scheme 34



However, similar $Pd(OAc)_2$ catalyzed arylation of 3-hydroxy-2-methylene-3-phenyl-propanenitrile, the Baylis-Hillman adduct obtained *via* the coupling of acrylonitrile with benzaldehyde, under various reaction conditions was unsuccessful.

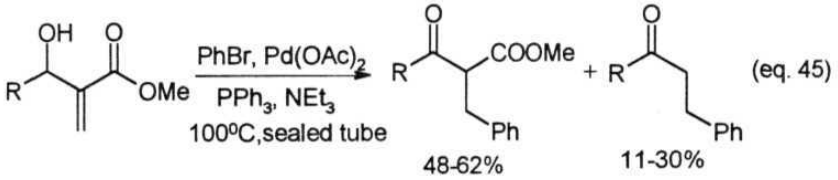
It is worth mentioning here that after the publication of our work, two interesting papers describing similar type of Heck reactions on the Baylis-Hillman adducts have appeared. Kumareswaran and Vankar have reported the Heck reaction of methyl 3-hydroxy-2-methylenealkanoates with iodobenzene in the presence of $Pd(OAc)_2$, tetrabutylammonium bromide and potassium acetate in DMF at 70°C to provide α-benzyl-β-keto esters (eq. 44).[124]



(eq. 44)

R= Ph, Et, n-Pr, i-Pr, fur-2-yl

Also, Sundar and Bhat have reported the $Pd(OAc)_2$ catalyzed arylation of the Baylis-Hillman adducts with bromobenzene in the presence of PPh_3 and NEt_3 at 100°C in sealed tube to furnish the corresponding α-benzyl-β-keto esters along with minor amounts of decarboxylated molecules (eq. 45).[125]



(eq. 45)

R= aryl, alkyl

Stereoselective synthesis of trisubstituted alkenes

Baylis-Hillman adducts have been successfully transformed into various trisubstituted alkenes with high stereoselectivity *via* the addition of various nucleophiles to the corresponding acetates (see Scheme 14,[76] Schemes 21-23,[84-89] Scheme 25[95] and eq 24[90] in Introduction chapter). In fact, stereoselective synthesis of trisubstituted olefins has been one of the major applications of the Baylis-Hillman adducts.[13-15]

During the studies on the chemistry of acetates of the Baylis-Hillman adducts, our re-

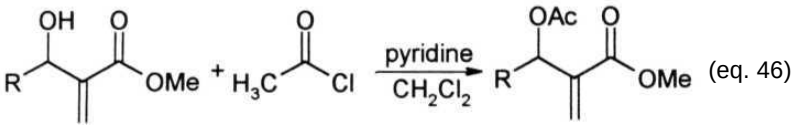
search group has observed that methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles always provided products with opposite stereoselectivities in various nucleophilic reactions, thus indicating that there is a reversal of stereochemical directive effect from ester group to nitrile group (see Scheme 22 in Introduction chapter).[85-88]

Stereoselective synthesis of methyl (2*E*)-2-cyanomethylalk-2-enoates

Though various nucleophiles have been used for addition reactions to acetates of the Baylis-Hillman adducts, sterically less hindered cyanide ion has not been used as a nucleophile Therefore, we have undertaken the study of nucleophilic addition of cyanide ion to acetates of the Baylis-Hillman adducts *i.e.* methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles with a view to provide a general synthesis of 2-cyanomethylalk-2-enoates and 3-cyanoalk-3-enenitriles respectively and also to examine the stereochemical directive effects of ester and nitrile groups in these reactions

Accordingly, we have prepared representative class of acetates of the Baylis-Hillman adducts methyl 3-acetoxy-2-methylenealkanoates **(43-48)*** (eq. 46) and studied the

For easy understanding and continuity, the allyl acetates synthesized from the Baylis-Hillman adducts *i.e.* methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(26a),** methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate **(26b)**, methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate (26c), methyl 3-(4-chIorophenyl)-3-hydroxy-2-methylenepropanoate **(26g),** methyl 3-hydroxy-4-methyl-2-methylenepentanoate **(26h)** and methyl 3-hydroxy-2-methyleneoctanoate **(26i)** respectively were numbered as **43-48.**

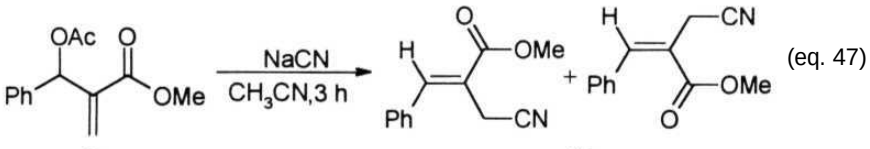


(eq. 46)

26a-c, 26g-i **43-48**

R= phenyl, 4-methylphenyl, 4-isopropylphenyl, 4-chlorophenyl, isopropyl, n-pentyl

nucleophilic addition of cyanide ion to these molecules. Thus, we have first treated methyl 3-acetoxy-2-methylene-3-phenylpropanoate (43) with NaCN under various conditions. The best result was obtained when methyl 3-acetoxy-2-methylene-3-phenylpropanoate (43) (2 mmol) was treated with NaCN (2.5 mmol) in acetonitrile at room temperature for 3 h to provide methyl 2-cyanomethyl-3-phenylprop-2-enoate (49) in ≈98% (*E*)-selectivity and 83% yield (eq. 47). Structure of this molecule was



(eq. 47)

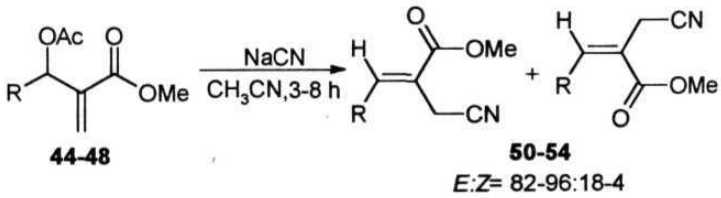
43 **49**

E:*Z*= ≈98:2

established by IR, ^{1}H NMR (Fig. 3), ^{13}C NMR (Fig. 4) spectral data and elemental analysis. The (*E*)-stereochemistry was confirmed by the ^{1}H NMR spectral analysis. It has been well documented in the literature that the (*E*)- and (Z)-isomers of 2-alkyl-3-arylalk-2-enoates (trisubstituted alkenes) 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].[126, 9] In the case of molecule 49, the olefinic proton appears at 6 7.97, therefore, we have assigned (*E*)-stereochemistry to the molecule 49. However, ^{13}C NMR spectrum shows a peak with very low intensity at 8 23.06 along with a peak at δ 16.68 (allylic carbon of [*E*]-isomer) thus indicating the presence of approximately 2% [*Z*]-isomer[Φ]. Further, the ^{1}H NMR spectrum of this molecule shows a peak at 8 3.68 (in addition to peak at 3.90 due to COOCH3 protons) with very low intensity (≈2%) presumably arising due to $COOC\underline{H}_3$ group of minor (Z)-isomer.

Encouraged by this result, we have carried out nucleophilic addition of cyanide ion (NaCN) to representative acetates of the Baylis-Hillman adducts *i.e.* methyl 3-acetoxy-2-methylenealkanoates (44-48) to provide methyl 2-cyanomethylalk-2-enoates (50-54) (Fig. 5 & 6, ^{1}H NMR and ^{13}C NMR spectra of molecule 53) in good yields



(eq. 48)

44-48 **50-54**

E:*Z*= 82-96:18-4

R= 4-methylphenyl, 4-isopropylphenyl, 4-chlorophenyl isopropyl, n-pentyl

Φ In ^{13}C NMR spectra of trisubstituted alkenes, allylic carbon *cis* to aryl group appears upfield while the same carbon *trans* to aryl group appears downfield.[87]

Table 3: Synthesis of methyl (2*E*)-2-cyanomethylalk-2-enoates (49-54)[a.h]:

Acetate	R	Time	Product	Yield[c] (%)	E:Z
43	phenyl	3	49	83	≈98:2[d]
44	4-methylphenyl	3	50	85	94:6[e]
45	4-isopropylphenyl	3	51	86	82:18[e]
46	4-chlorophenyl	3	52	80	96:4[e]
47	isopropyl	8	53	75	82:18[e]
48	n-pentyl	6	54	79	88:12'

a) All reactions were carried out \n *1* mmol sca\e of acetate and 2.5 mmol of NaCN in acetonitrile at room temperature.

b) All compounds have characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.

c) Isolated yields of the products after column chromatography (2% EtOAc in hexanes, silica gel).

d) ^{13}C NMR indicates the presence of approximately 2% [Z]-isomer

e) The stereochemical assignments and isomer ratios were assigned on the basis of chemical shift values and integration ratios of the isomeric olefinic proton signals respectively in the ^{1}HNMR spectra.[@]

@ In 'H NMR spectra of trisubstituted alkenes, P-vinylic proton *cis* to the ester group [(*E*)-isomer] appears at ≈ 8 6.8 while p-vinylic proton *trans* to the ester group [(*Z*)-isomer] appears at * δ 5.7 when R is alkyl. Similarly, the P-vinylic proton of (*E*)-isomer appears at ≈ δ 7.5 while that (Z)-isomer appears at ≈ 6 6.4 when **R** is aryl.[126-129]

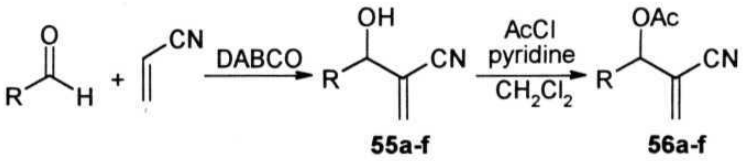
with high (*E*)-selectivities (eq. 48, Table 3). The (*E*)-stereochemistry for the molecules **50-54** were assigned on the basis of chemical shift values of olefinic protons/'''

Stereoselective synthesis of (*Z*)-3-cyanoalk-3-enenitriles

After obtaining reasonable success in the stereoselective synthesis of methyl 2-cyanomethylalk-2-enoates **(49-54),** we have next directed our studies towards the nucleophilic addition of cyanide ion to acetates of the Baylis-Hillman adducts derived from acrylonitrile *i.e.* 3-acetoxy-2-methylenealkanenitriIes with a view to examine the stereochemical outcome of the reaction.

Accordingly, we have prepared the required allyl acetates **56a-f** from the Baylis-Hillman adducts *i.e.* 3-hydroxy-2-methylenealkanenitriles **(55a-f),** obtained *via* the coupling of acrylonitrile with aldehydes (Scheme 35). We have then carried out the

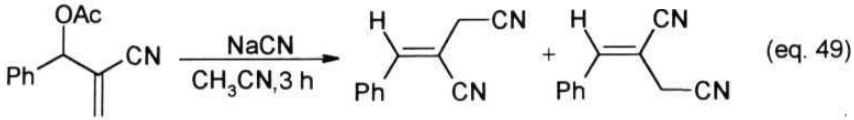
Scheme 35



55a-f **56a-f**

R= phenyl, 4-methylphenyl, 2-methoxyphenyl, n-propyl, isopropyl, n-pentyl

nucleophilic addition of cyanide ion (NaCN) to 3-acetoxy-2-methylene-3-phenylpropanenitrile **(56a)** in acetonitrile for 3 h at room temperature. The resulting 3-cyano-4-phenylbut-3-enenitrile **(57a)** was obtained in 95% [Z]-selectivity and in 48% chemical yield (eq. 49). The structure of this molecule was established by IR, ^{1}H NMR, ^{13}C NMR (Fig. 7) spectral data and elemental analyses. (*Z*)-Stereochemistry



56a **57a** (eq. 49)

Z:E = 95:5

of the major isomer was assigned by a 2D NOESY (Fig. 8) experiment which shows correlation between allylic methylene proton of the major isomer *(i.e.* 5 3.52) and the olefinic proton *(i.e.* 8 7.32). ^{1}H NMR spectrum of the molecule shows that two singlets for allylic methylene protons at 8 3.49 and δ 3.52 in the ratio of 5:95 arising from minor (*E*)- and major (Z)-isomers respectively. (*Z*)-Stereochemistry of major isomer was also confirmed by comparing the ^{13}C NMR chemical shift value of allylic methylene carbon (δ 23.91) with that of (*Z*)–isomer of 49 (8 23.06, downfield).[Φ] Similarly, the peak at 8 19.31 was assigned to the allylic carbon of the minor (*E*)-isomer in analogy with that of(*E*)-isomer of 49 (8 16.68, upfield).[Φ]

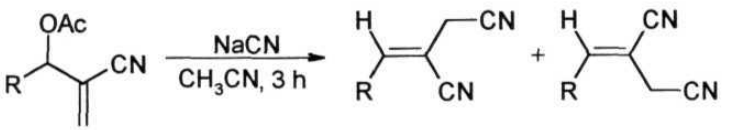
Φ In ^{13}C NMR spectra of trisubstituted alkenes, allylic carbon *cis* to aryl group appears upfield while the same carbon *trans* to aryl group appears downfield.[87, 130, 191]

Table 4: Synthesis of (3Z)-3-cyanoalk-3-enenitriles (57a-57f)[a]

Acetate	R	Product	Yield (%)	Z:E
56a	phenyl	57a	48[c]	95:5[d, e]
56b	4-methylphenyl	57b	67[c]	≈90:10[f, g]
56c	2-methoxyphenyl	57c	56[c]	72:28[e, g]
56d	n-propyl	57d	68[h]	90:10[i]
56e	isopropyl	57e	65[h]	90:10[j]
56f	n-pentyl	57f	81[c]	95:5[k]

a) All reactions were carried out on 2 mmol scale of acetate with NaCN (2.5 mmol) in acetonitrile at room temperature for 3 h.
b) All compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses.
c) Isolated yields of the products (isomeric mixture) after column chromatography (5% EtOAc in hexanes, silica gel).
d) (Z)-stereochemistry for the major isomer was assigned on the basis of a 2D NOESY experiment.
e) Isomeric ratio was determined on the basis of integration ratio of isomeric allylic methylene proton signals in ^{1}H NMR spectrum.
f) Isomeric ratio was determined on the basis of the ^{13}C NMR analysis (peak with low intensity (≈10%) at 8 19.26 was assigned to allylic methylene carbon of minor (*E*)-isomer).
g) [Z]-stereochemistry of the major isomer was assigned on the basis of ^{13}C NMR chemical shift value of the allylic methylene carbons in comparison with that of the molecule **57a.**
h) Isolated yields of the pure (Z)- isomers after column chromatography (5% EtOAc in hexanes, silica gel).
i) Isomeric ratio was determined on the basis of integration ratio of isomeric α-allylic methylene proton signals in ^{1}H NMR spectrum of crude concentrated product. (Z)-Stereochemistry for major isomer was assigned on the basis of a 2D NOESY experiment.
j) Isomeric ratio was determined on the basis of integration ratio of the isomeric β-allylic methyne proton signals in ^{1}H NMR spectrum of crude concentrated product. [*Z*]-Stereochemistry for the major isomer was assigned on the basis of ^{13}C NMR chemical shift value of allylic methylene carbon in comparison with that of corresponding methyl ester (53) and also in analogy with 57d.
k) The isomeric ratio was determined by ^{1}H NMR spectral analysis (on the basis of integration ratio of the isomeric allylic methylene proton signals). The [Z]-stereochemistry was assigned in analogy with 57d and 57e.

Encouraged by this result, we have subjected a variety of 3-acetoxy-2-methylenealkanenitriles **(56b-f)** to the nucleophilic addition of cyanide ion which provided 3-cyanoalk-3-enenitriles **(57b-f)** (Fig. 9, ^{13}C NMR spectrum of molecule 57e) in moderate to good yields with high (Z)- stereoselectivities (eq. 50, Table 4).

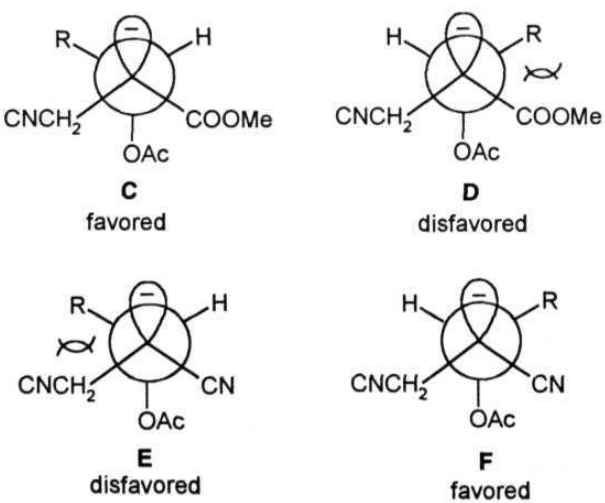


56b-f **57b-f** (eq. 50)

Z:E = 72-95:28-5

R= 4-methylphenyl, 2-methoxyphenyl, n-propyl, isopropyl, n-pentyl

Thus, the stereochemical outcome in the addition of cyanide ion to acetates **(56a-f)** of the Baylis-Hillman adducts is consistent with our earlier results.[85-88] The reversal in



stereochemical directive effects of nitrile group with respect to ester group can possibly be explained from the transition state models C & D and E & F. In the case of methyl 3-acetoxy-2-methylenealkanoates, the ester group has a larger steric effect than the cyanomethyl group and therefore the transition state model C is favored. In the case of 3-acetoxy-2-methylenealkanenitriles, the transition state model F is favored due to nitrile group having a smaller steric effect than the cyanomethyl group.

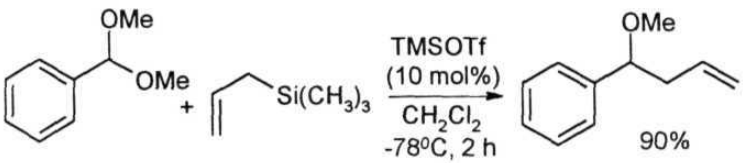
Thus, we have transformed acetates of the Baylis-Hillman adducts, methyl 3-acetoxy-2-methylenealkanoates **(43-48)** and 3-acetoxy-2-methyIenealkanenitriles **(56a-f)** respectively into methyl (2*E*)-2-cyanomethylalk-2-enoates **(49-54)** and (3Z)-3-cyanoalk-3-enenitriles (57a-f) *via* the nucleophilic addition of cyanide ion, with high stereoselectivities.

Next, we have directed our efforts to transform methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles (secondary acetates) into methyl 2-acetoxymethylaIk-2-enoates and 2-acetoxymethylalk-2-enenitriles (primary acetates) respectively with an objective of examining the stereochemical outcome in these transformations.

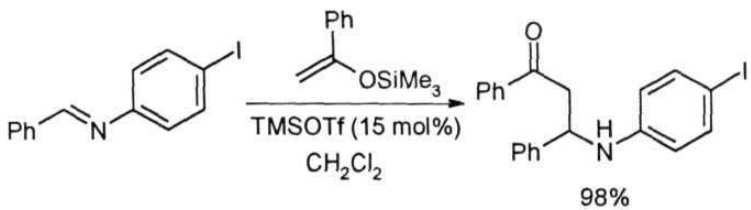
Synthesis of methyl (2*E*)-2-acetoxymethyl-3-arylprop-2-enoates

Synthetic applications of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in a variety of stereoselective reactions and transformations have been well documented in the literature and in fact TMSOTf has become a reagent of choice to the organic

chemists in recent years for conducting various interesting organic reactions.[132-138] Two such important and representative examples have been described in the equations 51[132] and 52[133]. Therfore it occurred to us that trimethylsilyl trifluoromethanesulfonate might be a suitable reagent to transform methyl 3-acetoxy-2-methylenealkanoates (secondary acetates) into methyl 2-acetoxymethylalk-2-enoates (primary acetates) with high stereoselectivities.



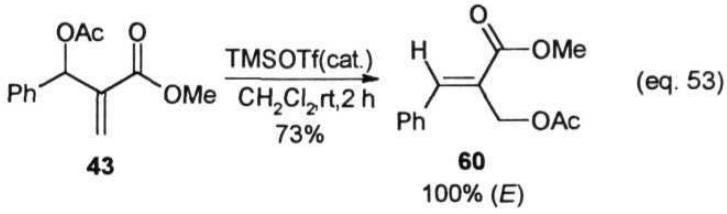
(eq. 51)



(eq. 52)

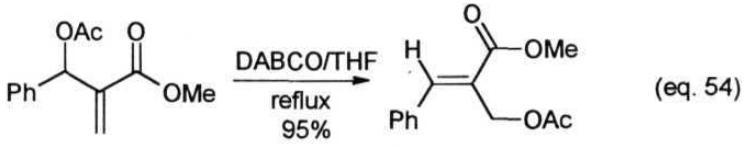
Accordingly, first we have examined the reaction of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (43) with TMSOTf under various conditions. The best results were obtained when this molecule (43) (1 mmol) was treated with TMSOTf (11 mol%) in dichloromethane at room temperature for 2 h, thus providing the required

methyl 2-acetoxymethyl-3-phenylprop-2-enoate **(60)**[Π] in 73% yield with **(*E*)-stereo**-selectivity (eq. 53). The structure of this molecule was confirmed by **IR**, ^{1}**H**



43 **60** 100% (*E*) (eq. 53)

NMR (Fig. 10), ^{13}**C** NMR (Fig. **11)** spectral data and elemental analysis. The **(*E*)-**stereochemistry for this molecule was assigned on the basis of ^{1}**H** and ^{13}**C** NMR spectral data in comparison with that of the literature data. This molecule was earlier prepared by treating methyl 3-acetoxy-2-methylene-3-phenylpropanoate with DABCO in THF at reflux temperature (eq. 54) in 95% yield with ***E*/*Z*** ratio of 93:7.[139]

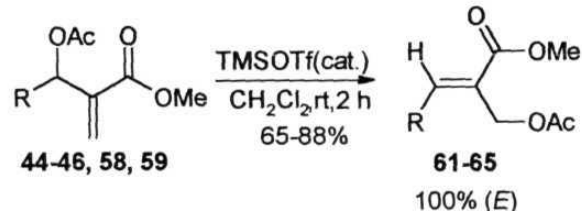


E:Z= 97:3 (eq. 54)

Encouraged by this result, we have carried out the **isomerization** of acetates of the

Π For easy understanding and continuity, the **allyl** acetates obtained from the Baylis-Hillman adducts *i.e.* methyl **3-hydroxy-3-(4-ethylphenyl)-2-methylenepropanoate (26e)** and methyl 3-**hydroxy-2-methylene-3-(2-methylphenyl)propanoate (26j)** (obtained via the coupling of 2-methylbenzaldehyde with methyl **acry late)** respectively were numbered as 58 and 59. Hence, the number 60 was given to the molecule methyl **2-acetoxymethyl-3-phenylprop-2-enoate**

Baylis-Hillman adducts, methyl 3-acetoxy-3-aryl-2-methylenepropanoates (44-46, 58, 59) into desired methyl 2-acetoxymethyl-3-arylprop-2-enoates (61-65) in high yields with exclusive (*E*)-stereochemistry (eq. 55, Table 5).



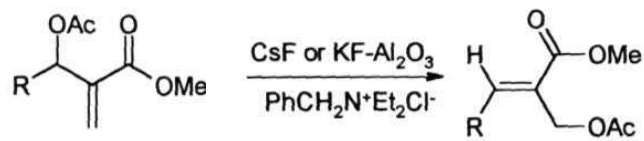
44-46, 58, 59 **61-65**

100% (*E*)

(eq. 55)

R= 4-methylphenyl, 4-isopropylphenyl, 4-chlorophenyl, 4-ethylphenyl, 2-methylphenyl

It is worth mentioning here the work of Foucaud and El Guemmout who have carried out the rearrangement of acetates of the Baylis-Hillman adducts (derived *via* the coupling of methyl acrylate with aldehydes) in the presence of metal salts and a catalytic amount of benzyltrimethylammonium chloride to provide the rearranged allyl acetates in good yields (eq. 56).[84]



(eq. 56)

R=aryl

Table 5: Synthesis of methyl **(2*E*)-2-acetoxymethyl-3-arylprop-2-enoates** (60-65)*"

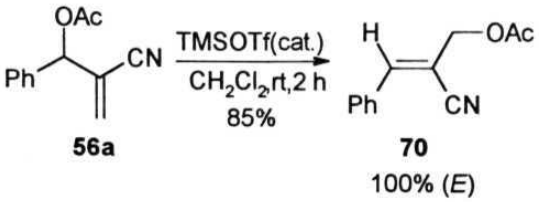
Substrate	Ar	Product	Yield[e]
43	phenyl	**60**[f]	73
44	4-methylphenyl	**61**[g]	65
45	4-isopropylphenyl	**62**[g]	83
46	4-chlorophenyl	**63**[g]	80
58	4-ethylphenyl	**64**[g]	88
59	2-methylphenyl	**65**[g, h]	77[i]

a) All reactions were carried out on 1 mmol scale of acetates of the Baylis-Hillman adducts with TMSOTf (11 mol%) in dichloromethane at room temperature for 2 h.
b) All compounds were obtained as colorless liquids and characterized by IR, ^{1}H NMR, ^{1}C NMR spectral data and microanalysis.
c) ^{1}H and ^{13}C NMR indicate the absence of any (Z)-isomer.
d) (*E*)-Stereochemistry was assigned on the basis of ^{1}H NMR chemical shift values of the p-vinylic protons.@
e) Isolated yields of the products after column chromatography (3% EtOAc in hexanes).
f) This molecule is known in the literature. ^{1}H NMR and ^{13}C NMR spectral data are in agreement with that of literature data.
g) (*E*)-Stereochemistry was confirmed on the basis of the ^{13}C NMR chemical shift values of allylic methylene carbons in analogy with 60.
h) This compound contains ≈10% impurity and was further purified by preparative HPLC (Shim-Pack PREP-ODS column, methanol).
i) Isolated yield after purification by preparative HPLC

@ In ^{1}H NMR spectra of trisubstituted alkenes, p-vinylic proton *cis* to the ester group [(*E*)-isomer] appears at ≈ 8 6.8 while p-vinylic proton *trans* to the ester group [(Z)-isomer] appears at ≈ δ 5.7 when R is alkyl. Similarly, the p-vinylic proton of (*E*)-isomer appears at ≈ 8 7.5 while that (Z)-isomer appears at ≈ 8 6.4 when R is aryl.[126-129]

Synthesis of (2*E*)-2-acetoxymethylalk-3-enenitriles

After developing a simple methodology for successful interconversion of methyl 3-acetoxy-3-aryl-2-methylenepropanoates **(43-46, 58, 59)** into methyl **(2*E*)-2-acetoxy-**methyl-3-arylprop-2-enoates **(60-65)** under the catalytic influence of TMSOTf, our efforts have been directed towards TMSOTf catalyzed isomerization of 3-acetoxy-2-**methylenealkanenitriles (56a, 56b, 66-69)** into the corresponding primary **ally!** acetates with a view to study the stereochemical course of this reaction. During our studies in this direction, we have first treated 3-acetoxy-2-methylene-3-phenylpropanenitrile **(56a)** with TMSOTf. The best result was obtained when 3-acetoxy-2-**methylene-3-phenylpropanenitrile (56a)** (1 **mmol)** is treated with catalytic influence of TMSOTf **(11** mol%) in **dichloromethane** for two hours, thus providing a simple synthesis of 2-acetoxymethyl-3-phenylprop-2-enenitriIe **(70)**[□] with exclusive **(*E*)-**stereoselectivity (eq. 57) in 85% yield. The structure of this molecule was confirmed

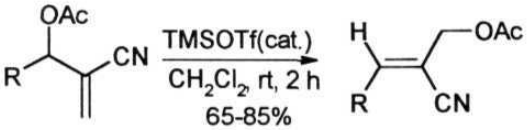


56a **70** 100% (*E*) **(eq. 57)**

D For easy understanding and continuity, the **allyl** acetates synthesized from the Baylis-**Hillman** adducts *i.e.* **3-hydroxy-3-(4-ethylphenyl)-2-methylenepropanenitrile** (55g), 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanenitrile **(55h), 3-hydroxy-3 -(4-chlorophenyl)-2-methylenepropanenitrile** (55i), **3-hydroxy-3-(2-methylphenyl)-2-methylenepropanenitrile (55j)** respectively were numbered as 66, 67, 68 and 69. Hence we have given number 70 to the product **2-acetoxymethyl-3-phenylprop-2-enenitrile**.

by IR, ^1H NMR, ^{13}C NMR (Fig 12) spectral data and elemental analysis. The (*E*)-stereochemistry was assigned on the basis of a 2D NOESY (Fig. 13) experiment.[θ] The ^{13}C NMR spectrum shows absence of any (Z)- isomer.[Φ]

This reaction clearly demonstrates that there is a reversal in stereochemical directive effect of nitrile group with respect to ester group. We have then carried out the isomerization of representative 3-acetoxy-3-aryl-2-methylenepropanenitriles (56b, 66-69) under the catalytic influence of TMSOTf which provided 2-acetoxymethyl-3-arylprop-2-enenitriles (71-75) (eq. 58, Table 6) in high yields with exclusive (*E*) stereoselectivity. The (*E*)-stereochemistry for the molecules 71-75 were assigned on the basis of the comparison of the ^{13}C NMR chemical shift values of allylic methylene carbon with that of the molecule **70**.[Φ]



56b, 66-69 **71-75** (eq. 58)

100% (*E*)

R= 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-chlorophenyl, 2-methylphenyl

However, our attempts to isomerize acetates of the Baylis-Hillman adducts, methyl 3-acetoxy-2-methyleneoctanoate and 3-acetoxy-2-methyleneoctanenitrile under the cat-

9 2D NOESY experiment shows correlation between allylic methylene protons (8 4.82) and olefinic proton (8 7.23).

Φ In ^{13}C NMR spectra of trisubstituted alkenes, allylic carbon *cis* to aryl group appears upfield while the same carbon *trans* to aryl group appears downfield. [130]

Table 6: Synthesis of (2*E*)-2-acetoxymethyl-3-arylprop-2-enenitriles (70-75)[a,b,c]

Substrate	Ar	Product	Yield[d]
56a	phenyl	**70**[e]	**85**
56b	4-methylphenyl	**71**[f]	68
66	4-ethylphenyl	**72**[f]	78
67	4-isopropylphenyl	**73**[f]	74
68	4-chlorophenyl	**74**[f]	65
69	2-methylphenyl	**75**[f]	84

a) All reactions were carried out on 1 mmol scale of acetates of the Baylis-Hillman adducts with TMSOTf (11 mol%) in dichloromethane at room temperature for 2 h.

b) All compounds were obtained as colorless liquids and characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and microanalysis.

c) ^{1}H and ^{13}C NMR indicate the absence of any (Z)-isomer.

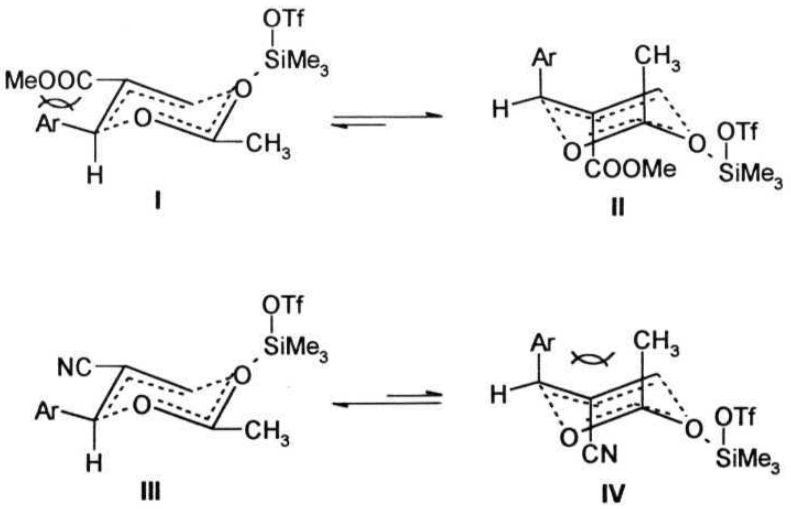
d) Isolated yields of the products after column chromatography (3% EtOAc in hexanes).

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

f) (*E*)-Stereochemistry was assigned on the basis of the ^{13}C NMR chemical shift values of the allylic methylene carbons in comparison with that of 70.

alytic influence of TMSOTf were unsuccessful.

The reversal of stereochemical directive effect of nitrile group with respect to ester group is consistent with our earlier results[85,88] and can be possibly explained through the Claisen type rearrangement (transition state models I, II, III, and IV). In the case of molecules 43-46, 58, 59, the unusual 1,2 interaction may be more predominant than the classical 1,3 interaction (transition state models I and II) leading to (*E*)-selectivity while in the case of molecules 56a, 56b, 66-69, the classical 1,3 interaction may be more predominant than unusual 1,2 interaction (transition state models ID and IV) resulting to (*E*)- molecules. It is worth mentioning here, our recent work on the Johnson-Claisen rearrangement of methyl 3-hydroxy-2-



methylenealkanoates with triethyl orthoacetate wherein we invoked 1,2-unsual interaction in the transition state to explain the unprecedented stereochemical reversal from alkyl to aryl substituents.[140]

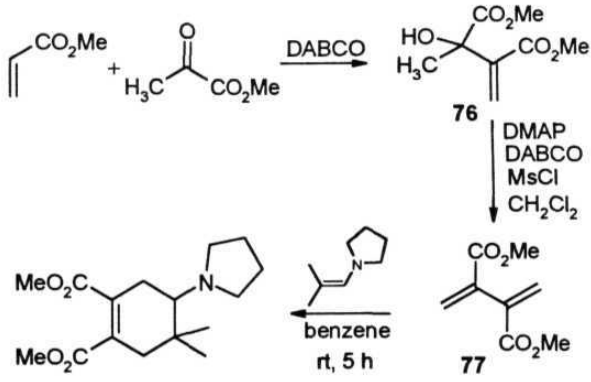
Another possible explanation for the reversal of stereochemical directive effect of nitrile group with respect to ester group is that the products are those of thermodynamic control in all these cases *i.e.* more sterically demanding ester group requires **a** particular conformation for optimal conjugation compared to the slim cyano group with local cylindrical symmetry.

We have thus, stereoselectively transformed acetates of the Baylis-Hillman adducts *i.e.* methyl 3-acetoxy-3-aryl-2-methylenepropanoates **(43-46, 58, 59)** and 3-acetoxy-3-aryl-2-methylenepropanenitriles **(56a, 56b, 66-69)** under the catalytic influence of trimethylsilyl trifluoromethanesulfonate into methyl (2*E*)-2-acetoxymethyl-3-arylprop-2-enoates **(60-65)** and (2*E*)-2-acetoxymethyl-3-arylprop-2-enenitriles (70-75) respectively. This study clearly demonstrates the synthetic applications of trimethylsilyl trifluoromethanesulfonate and also the importance of the Baylis-Hillman adducts in stereoselective synthesis of trisubstituted alkenes.

Synthesis of ethyl 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates

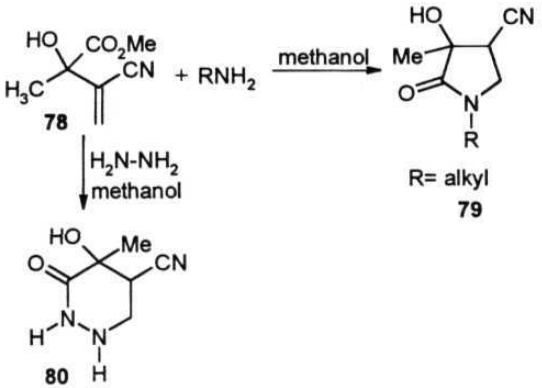
The Baylis-Hillman reaction of α-keto esters with activated alkenes such as acrylates and acrylonitrile providing densely functionalized products with a quaternary carbon centre and the applications of these molecules in organic synthesis have been well documented in the literature.[30-33] For example, Hoffmann has utilized methyl 2-hydroxy-2-carbomethoxy-3-methylenebutanoate (76), the Baylis-Hillman adduct obtained *via* the coupling of methyl pyruvate with methyl acrylate, for the synthesis of 77, an important diene for Diels-Alder reaction (Scheme 38).[32]

Scheme 38

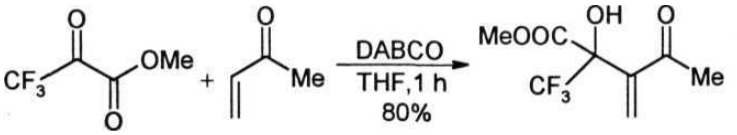


Amri *et al.* have successfully applied 2-hydroxy-2-carbomethoxy-3-methylene-butanenitrile (78), obtained *via* the coupling of methyl pyruvate with acrylonitrile, for the synthesis of important heterocyclic molecules l,3,4-substituted-2-pyrrolidone 79 and perhydro-l,2-pyridazin-3-one 80 (Scheme 39).[141]

Scheme 39



During our work on the ongoing research program on the Baylis-Hillman reaction, we required 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates. Literature survey reveals that Golubev and coworkers reported the DABCO catalyzed coupling of methyl vinyl ketone (mvk) with methyl trifluoropyruvate to provide methyl 2-hydroxy-3-methylene-4-oxo-2-trifluoromethylpentanoate in high yield (eq. 59).[33] On

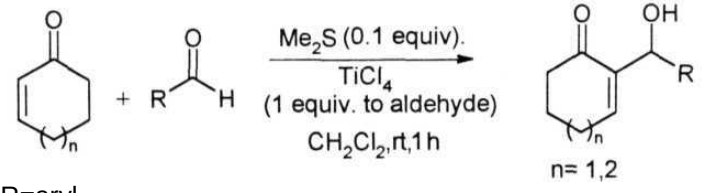


(eq. 59)

similar lines, we attempted the synthesis of 2-hydroxy-3-methylene-2-phenyl-4-oxopentanoate **(82a)** *via* the coupling of methyl vinyl ketone with ethyl phenylgly-

oxylate (81a) under the influence of DABCO in different conditions *i.e.* neat, 2M THF solution, 2M methanol solution. Unfortunately in all these cases, the reaction was not clean by TLC examination and also the desired product was formed in low yield (<10%) (the ^{1}H NMR spectrum of the crude concentrated product after the usual workup in each case indicated the presence of at least 60% of the unreacted keto ester, formation of the desired product 82a in low yield (<10%), formation of the dimer of mvk *i.e.* 3-methylene-2,6-heptanedione as a major product, and some other side products). This failure led us to look for an alternative method for synthesizing this molecule (82a).

Recently Kataoka *et al.*[142-144] reported an interesting Baylis-Hillman coupling of aldehydes with different a, β-unsaturated ketones in the presence of Lewis acid under the catalytic influence of dimethyl sulfide to provide the desired α-hydroxyalkylated enones (eq. 60)[142] in moderate to good yields.

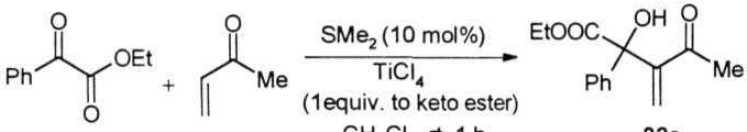


(eq. 60)

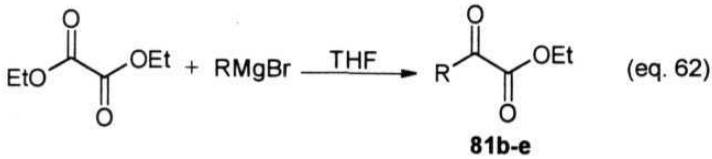
R=aryl

With a view to providing a convenient synthesis of 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates and also with a view to expanding the scope of chalcogeno-Baylis-Hillman reaction we have examined the possibility of coupling a, P-unsaturated

ketones with a-keto esters under the catalytic influence of dimethyl sulfide in the presence of Lewis acid. During our studies in this direction, we have first carried out the reaction of ethyl phenylglyoxylate (81a) with methyl vinyl ketone (mvk) under various conditions. The best result was obtained when ethyl phenylglyoxylate (81a) was treated with methyl vinyl ketone and a catalytic amount of dimethyl sulfide in the presence of titanium tetrachloride in dichloromethane at room temperature for one hour, thus providing the desired ethyl 2-hydroxy-2-phenyl-3-methylene-4-oxopentanoate (82a) in 73% yield (eq. 61). The structure of this molecule was confirmed by IR, ^{1}H NMR (Fig 14), ^{13}C NMR (Fig. 15) spectral data and elemental analysis.

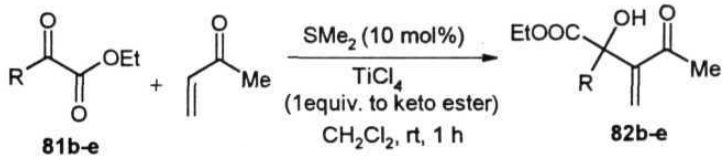


This success led us to apply this methodology for the coupling of other a-keto esters (81b-e) {the required a-keto esters have been prepared *via* the reaction of diethyl oxalate with corresponding Grignard reagents (eq. 62)} with methyl vinyl ketone



R= 4-methylphenyl, 4-bromophenyl, 4-methoxyphenyl, naphth-1-yl

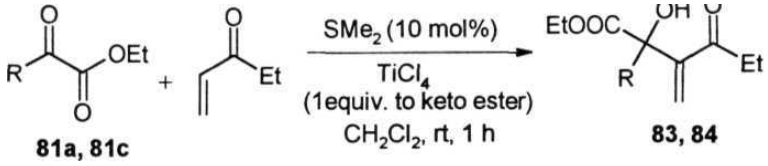
under similar conditions thus providing a simple synthesis of 2-aryl-2-hydroxy-3-methylene-4-oxopentanoates **(82b-e)** (eq. 63, Table 7).



(eq. 63)

R = 4-methylphenyl, 4-bromophenyl, 4-methoxyphenyl, naphth-1-yl

With a view to understand the generality of this reaction we have also used ethyl vinyl ketone (evk) as an activated alkene for coupling with a-keto esters (81a, 81c) to provide the desired products (83, 84) in reasonable yields (eq 64, Table 7) This reaction is believed to proceed through transition state model G, similar to that described by Kataoka *et al*.[142]



(eq. 64)

R = phenyl, 4-bromophenyl

However, our attempts to use ethyl pyruvate as an electrophile for coupling reaction with methyl vinyl ketone under similar conditions were unsuccessful. This failure might be due to enolization ofethyl pyruvate in the presence of $TiCl_4$ which might be causing problem in the course of the reaction.

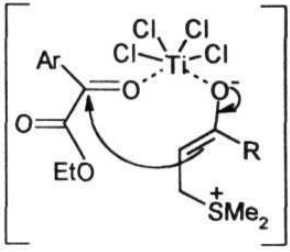
Table 7: Synthesis of 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates (82a-e, 83, 84)[a,b].

Keto ester	Ar	Enone	Product	Yield (%)[c]
81a	phenyl	**mvk**	**82a**	73
81b	**4-methylphenyl**	**mvk**	**82b**	51
81c	**4-bromophenyl**	mvk	**82c**	62
81d	**4-methoxyphenyl**	mvk	**82d**	64
81c	***naphth-1-yl***	mvk	82e	43
81a	phenyl	evk	83	40
81c	4-bromophenyl	evk	84	42

a) All reactions were carried out on 1 mmol scale of a-keto ester with enone (3 mmol), dimethyl sulfide (10 mol%) and TiCU (1 mmol) in dichloromethane at room temperature for **1** h.

b) All products **(82a-e, 83, 84)** were obtained as solids and characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses.

c) Yields of the products after purification by column chromatography (silica gel, 5% EtOAc in hexanes) followed by crystallization.



G

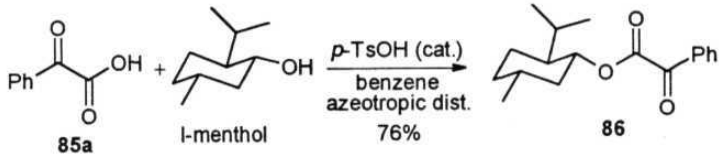
Thus, this methodology describes the Baylis-Hillman reaction between a-keto esters and a,p-unsaturated ketones under the catalytic influence of dimethyl sulfide in the presence of titanium tetrachloride in dichloromethane, thus leading to the synthesis of 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates (82a-e, 83, 84). This methodology also gains importance in the sense that similar coupling reaction with DABCO as catalyst is ineffective.

Asymmetric Baylis-Hillman reaction

Considerable efforts have been made to achieve high asymmetric induction in the Baylis-Hillman reaction using chiral acrylates, chiral catalysts, chiral aldehydes (refer page No. 8 in Introduction).[13-15] However, application of chiral a-keto esters (as electrophiles), derived from chiral auxiliaries, have not been studied for asymmetric Baylis-Hillman reaction. Therefore, we have planned to investigate the Baylis-Hillman coupling of the chiral a-keto esters with alkyl acrylates and

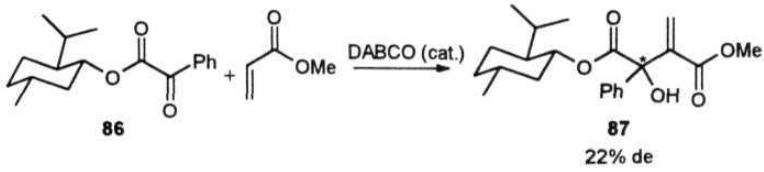
acrylonitrile in the presence of DABCO with an aim of providing a simple methodology for obtaining multifunctional molecules possessing quaternary chiral centers.

We have therefore decided first to study reaction of menthyl phenylglyoxylate (86) with methyl acrylate in the presence of DABCO with an idea of investigating the level of diastereoselectivity that menthyl group can offer as chiral directing source. The desired menthyl phenylglyoxylate (86) was prepared *via* the reaction of benzoylformic acid (85a) with (1R,2S,5R)-menthol according to equation 65.



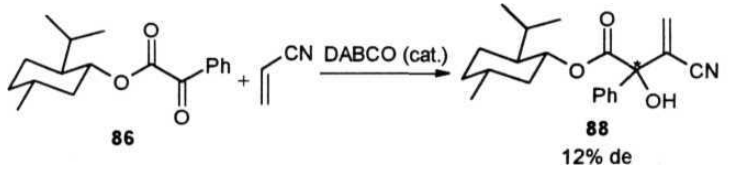
(eq. 65)

Then, we have carried out the Baylis-Hillman reaction of menthyl phenylglyoxylate (86) (1 mmol) with methyl acrylate (2 mmol) in the presence of DABCO (15 mol%) for 8 days at room temperature. The resulting product, menthyl 2-hydroxy-3-(methoxycarbonyl)-2-phenylbut-3-enoate (87), was obtained with 22% diastereoselectivity (eq. 66). The structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis. The diastereomeric excess was determined by ^{1}H NMR analysis. The olefinic proton *trans* to ester group shows two distinct singlets (due to diastereomers) in ^{1}H NMR (Fig. 16) spectrum in the ratio of 39:61, thus indicating 22% diastereoselectivity in this reaction.



86 87 22% de (eq.66)

With a view to compare the diastereoselective directive effect of COOMe group with that of CN group, we have performed the reaction between menthyl phenylglyoxylate (86) with acrylonitrile in the presence of DABCO. The resulting adduct *i.e.* menthyl 3-cyano-2-hydroxy-2-phenylbut-3-enoate (88) (eq. 67) was obtained in 12% de and 83% yield. Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis. ^{1}H NMR spectrum shows two distinct singlets (due to diastereomers) each for both olefinic protons in the ratio of 56:44 which indicates that the reaction is 12% diastereoselective. This clearly shows that COOMe group offers better diastereoselectivity than the cyano group.

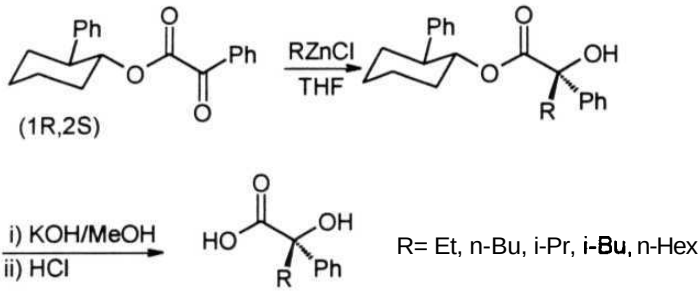


86 88 12% de (eq. 67)

Though diastereoselectivity in these reactions is not high, this result is encouraging in the sense that the selection of appropriate chiral auxiliary might offer better diastereoselectivities. In our laboratory, we have demonstrated the application of (1R,2S)-2-phenylcyclohexan-1-ol {(-)-89} as a chiral auxiliary for synthesis of a-

hydroxy acids in high diastereoselectivities (Scheme 40).[145]

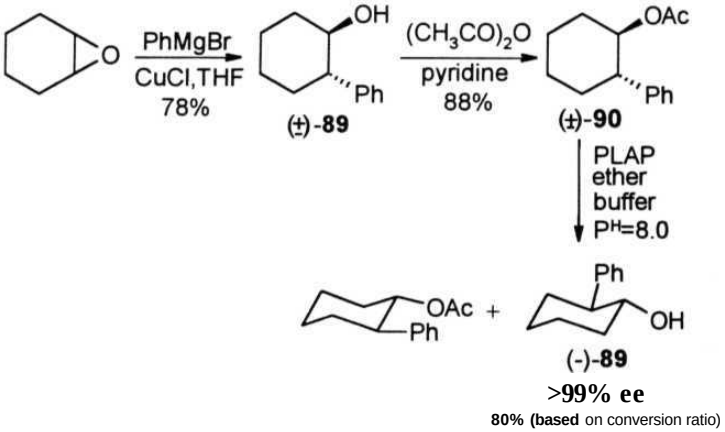
Scheme 40



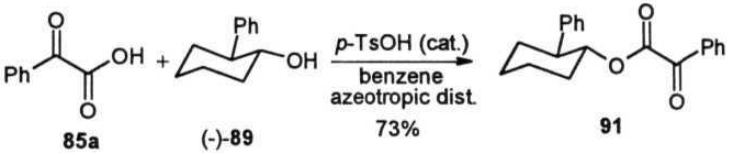
84-93% ee

On this basis, we thought that chiral α-keto esters, derived from (lR,2S)-2-phenylcyclohexanol {(-)-89}, would possibly offer better diastereoselectivities in the Baylis-Hillman reaction with activated alkenes. We have therefore prepared the required chiral auxiliary (1R,2S)-2-phenylcyclohexanol {(-)-89} via the resolution of

Scheme 41



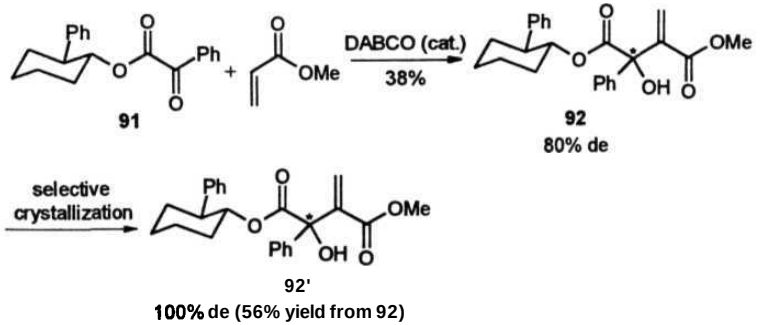
racemic fra/w-l-acetoxy-2-phenylcyclohexane {(±)-90} with pig liver acetone powder (PLAP) according to the procedure developed by Whitesell (Scheme 41).[14c] Then the desired {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate (91) was prepared *via* the treatment of (1R,2S)-2-phenylcyclohexanol {(-)-89)} with benzoylformic acid in the presence of catalytic amount of *p*-toluenesulfonic acid (eq. 68).



85a (-)-89 91 (eq. 68)

Subsequently, {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate (91) was subjected to Baylis-Hillman reaction with methyl acrylate under the catalytic influence of DABCO. As expected the desired adduct *i.e.* {(1R,2S)-2-phenylcyclohexyl} 2-hydroxy-3-(methoxycarbonyl)-2-phenylbut-3-enoate (92) was obtained in high diastereomeric excess (80%) in 38% yield (Scheme 42). The structure of this molecule was

Scheme 42



91 92 80% de

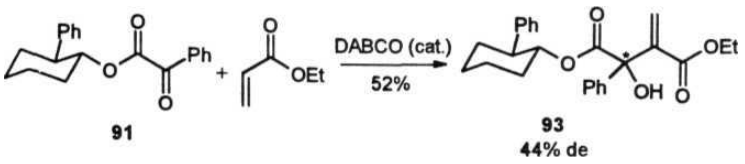
92'

100% de (56% yield from 92)

established by IR, ^{1}H NMR (Fig. 17), ^{13}C NMR spectral data and elemental analysis. The diastereomeric excess was determined by ^{1}H NMR spectral analysis. In the ^{1}H NMR spectrum, olefinic proton *cis* to the COOMe group shows two distinct singlets (due to diastereomers) in the ratio of 90:10 thus indicating 80% diastereoselectivity in this reaction. Careful selective crystallization of the molecule 92 (from 10% EtOAc in hexanes) produced {(1R,2S)-2-phenylcyclohexyl} 2-hydroxy-3-(methoxycarbonyl)-2-phenylbut-3-enoate (92*) in 100% diastereomeric excess as evidenced by ^{1}H NMR (Fig. 18) and ^{13}C NMR$^{\psi}$ (Fig. 19) spectral analysis. Thus, in the ^{1}H NMR spectrum of 92*, olefinic proton *cis* to the COOMe group (which showed two distinct singlets before crystallization) shows only one singlet.

In order to examine the influence of alkyl group on ester grouping in the diastereoselectivity, we have also carried out the reaction of {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate (91) with ethyl acrylate under the Baylis-Hillman conditions. The required product 93 was obtained with 44% diastereomeric excess in 52 % yield (eq. 69, Table 8). In ^{1}H NMR spectrum, the olefinic proton *cis* to the COOEt group clearly shows two distinct singlets (due to diastereomers) in the ratio of 72:28 thus indicating that this reaction is 44% diastereoselective.

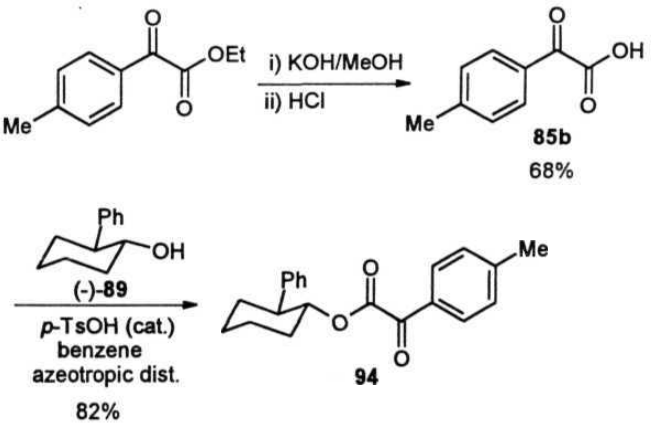
ψ ^{13}C NMR spectrum of 92 shows additional signals due to the presence of other diastereomer. These additional signals have now disappeared in ^{13}C NMR (Fig. 19) spectrum of 92" which indicates that 92" is a single diastereomer.



(eq. 69)

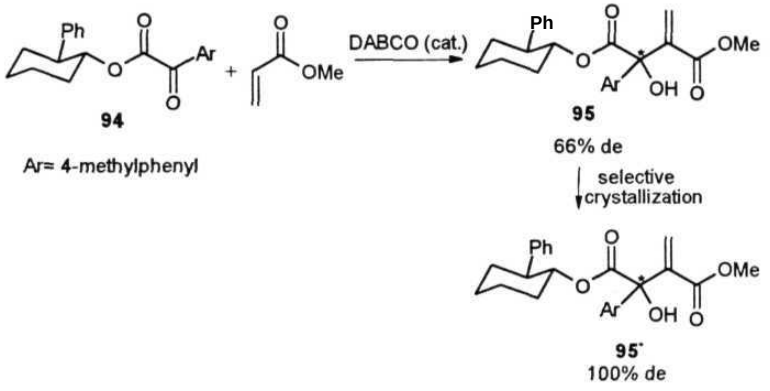
Since methyl acrylate has offered better selectivity than ethyl acrylate in the Baylis-Hillman reaction with {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate, we have planned to investigate the Baylis-Hillman coupling of {(lR,2S)-2-phenylcyclohexyl} (4-methylphenyl)glyoxylate (94) with methyl acrylate. The required chiral a-keto ester was prepared *via* the reaction of the corresponding a-keto acid (85b) (which in turn was prepared by the hydrolysis of the corresponding ethyl ester) with (1R,2S)-2-phenylcyclohexan-1-ol {(-)-89} in similar manner to that of 91 (Scheme 43).

Scheme 43



We have then examined the Baylis-Hillman reaction of 94 with methyl acrylate which provided the desired {(1R,2S)-2-phenylcyclohexyl} 2-hydroxy-3-(methoxy-carbonyl)-2-(4-methylphenyl)but-3-enoate (95) in 66% diastereomeric excess[η] (Scheme 44, Table 8) in 25% yield. Careful selective crystallization of the molecule

Scheme 44



95 (from 10% EtOAc in hexanes) produced {(1R,2S)-2-phenylcyclohexyl} 2-hydro-xy-3-(methoxycarbonyl)-2-(4-methylphenyl)but-3-enoate (95*) in 100% diastereo-meric excess[φ] in 37% yield.

η In ^{1}H NMR spectrum, the olefinic proton *cis* to the COOMe group shows two clear singlets (due to diastereomers) in the ratio of 83:17.

φ This was evidenced by the presence of one singlet for the olefinic proton *cis* to COOMe group in ^{1}H NMR spectrum. ^{13}C NMR spectrum of 95* clearly indicates that this is a single diastereomer.

Table 8: Baylis-Hillman coupling of chiral a-keto esters with activated alkenes[a,b]

a-Keto ester	Activated alkene	Time (days)	Product	Yield[c] (%)	de[d] (%)
86	methyl acrylate	8	87	48[e]	22
86	acrylonitrile	7	88	82	12
91	methyl acrylate	14	92	44'	80[f]
91	ethyl acrylate	14	93	47[e]	44
94	methyl acrylate	14	95	25'	66[f]
91	acrylonitrile	7	96	84	10

a) All reactions were carried out on 1 mmol scale of chiral a-keto esters with 2 mmol of activated alkene in the presence of DABCO (15 mol%).

b) All products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.

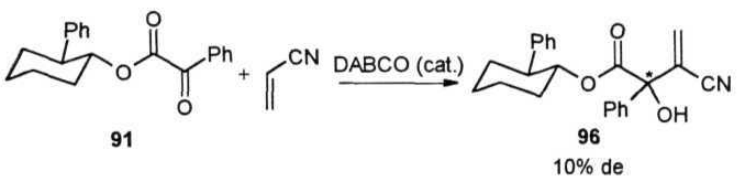
c) Isolated actual yields of the products after column chromatography (5% EtOAc in hexanes, silica gel).

d) The diastereomeric excess were determined from ^{1}H NMR spectral data

e) In these reactions substantial amounts (40-65%) of starting materials (unreacted) were recovered.

f) These were selectively crystallized to provide single diastereomer whose structure were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.

With a view to study the diastereoselective directive effect of cyano group in the Baylis-Hillman reaction, we have carried out the coupling of {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate (91) with acrylonitrile under the catalytic influence of DABCO. The required product *i.e.* {(1R,2S)-2-phenylcyclohexyl} 3-cyano-2-hydroxy-2-phenylbut-3-enoate (96) was obtained in 10% de and 84% yield (eq. 70, Table 8). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis. The diastereomeric excess was determined by the ^{1}H NMR spectral analysis. In ^{1}H NMR spectrum, one of the olefmic proton (presumably *cis* to the CN group) shows two distinct singlets (due to diastereomers) in the ratio of 55:45, thus indicating that this reaction is 10% diastereoselective.



91 **96** 10% de **(eq. 70)**

Thus we have been to some extent successful in achieving the asymmetric Baylis-Hillman reaction using chiral a-keto esters having 2-phenylcyclohexyl group as a chiral directing group thus providing a simple procedure for obtaining multifunctional molecules possessing chiral quaternary centres. These studies clearly demonstrates that methyl acrylate offers better selectivities than ethyl acrylate

and acrylonitrile in the Baylis-Hillman reaction with chiral a-keto esters as electrophiles.

CONCLUSIONS

We have made considerable progress in achieving our objective in demonstrating the applications of the Baylis-Hillman adducts in organic synthesis We have successfully isomerized methyl 3-hydroxy-3-aryl-2-methylenepropanoates, the Baylis-Hillman adducts derived from methyl acrylate, into methyl 3-aryl-2-methyl-3-oxopropanoates under the catalytic influence of $RuCl_2(PPh_3)_3$. We have synthesized methyl 2-arylmethyl-3-oxoalkanoates *via* the arylation of the Baylis-Hillman adducts, methyl 3-hydroxy-2-methylenealkanoates with aryl bromides under the catalytic influence of $Pd(OAc)_2$ We have used sterically less hindered cyanide ion (NaCN) as a nucleophile for the nucleophilic addition to methyl 3-acetoxy-2-methyl-enealkanoates and 3-acetoxy-2-methylene-alkanenitriles (acetates of the Baylis-Hillman adducts), to provide trisubstituted alkenes, methyl (2*E*)-2-cyanomethylalk-2-enoates and (3Z)-3-cyanoalk-3-enenitriles with high stereoselectivities. We have stereoselectively carried out the interconversion of methyl 3-acetoxy-3-aryl-2-methylenepropanoates and 3-acetoxy-3-aryl-2-methylenepropanenitriles respectively (acetates of the Baylis-Hillman adducts, secondary acetates) into methyl (2*E*)-2-

acetoxymethyl-3-arylprop-2-enoates and (2*E*)-2-acetoxymethyl-3-arylprop-2-enenitriles (primary acetates) with exclusive (*E*)-stereoselectivities. We have provided a simple and convenient methodology for the synthesis of ethyl 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates *via* the chalcogeno-Baylis-Hillman reaction of alkyl vinyl ketones with α-keto esters. We have also demonstrated the application of chiral a-keto esters as electrophiles in asymmetric Baylis-Hillman reaction thus providing a simple synthesis of multifunctional molecules having chiral quaternary centre

EXPERIMENTAL

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

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

Elemental Analysis: Elemental analyses were performed on a Perkin-Elmer 240c-CHN analyzer.

Infrared Spectra: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers or solution spectra in CH_2Cl_2 and liquid samples as thin film between NaCl plates.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on BRUKER-AC-200 spectrometer. ^{1}H NMR (200 MHz) spectra for all the samples were measured in chloroform-d with TMS (5 = 0 ppm) as internal standard. ^{13}C NMR (50 MHz) spectra for all the samples were measured in chloroform-d with its middle peak of the triplet (δ = 77.10 ppm) as internal standard. Spectral assignments are as follows: (1) Chemical shifts on the δ scale, (2) Standard abbreviation for multiplicity, *i.e.* s - singlet, d = doublet, t = triplet, q = quartet, 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.

Mass Spectral Analysis: Mass spectra were recorded on Hewlett Packard (model HP 5989A) or Finnigon MAT (1020C) mass spectrometer.

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 sulfate 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.

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.

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (26a):

A mixture of benzaldehyde (50 mmol, 5.306 g), methyl acrylate (75 mmol, 6.456 g) and DABCO (7.5 mmol, 0.841 g) was kept at room temperature for 7 days. The reaction mixture was diluted with ether (50 mL) and washed successively with 2N HC1 solution, water and aqueous $NaHCO_3$ solution. Organic layer was dried over anhydrous Na_2SO_4, solvent was evaporated and residue thus obtained was distilled under reduced pressure to afford the alcohol **26a** as a colorless liquid in 84% (8.075 g) yield.

bp : 120-121°C/2.5 mm

IR (neat) : 3449, 1720, 1630 cm^{-1}

^1H NMR :8 3.12(br, 1H), 3.70 (s,3H), 5.55 (s, 1H), 5.83 (s, lH),6.32(s, 1H), 7.34 (m, 5H)

^{13}C NMR : 8 51.68, 72.71, 125.56, 126.59, 127.61, 128.23, 141.40, 142.20, 166.58

Methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (26b):

This compound was prepared from 4-tolualdehyde, methyl acrylate and DABCO (cat.) following a similar procedure described for the molecule **26a,** as a colorless liquid.

Reaction time : 8 days

Yield : 80%

bp : 140°C/5 mm

IR(neat) : 3341, 1716, 1631 cm^{-1}

^1H NMR : 8 2.33 (s, 3H), 2.71 (br, 1H), 3.71 (s, 3H), 5.53 (s, 1H), 5.84 (s, 1H), 6.32 (s, 1H), 7.14 (d, 2H, J= 7.8 Hz), 7.26 (d, 2H, J= 8.0 Hz)

^{13}C NMR : δ 20.91, 51.63, 72.51, 125.28, 126.50, 128.89, 137.21, 138.40, 142.20, 166.57

Methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methyIenepropanoate (26c):

This compound was obtained as a colorless liquid *via* the reaction between 4-isopropylbenzaldehyde and methyl acrylate in the presence of catalytic amount of DABCO following a similar procedure described for the molecule **26a.**

Reaction time : 6 days

Yield . 84%

bp : 160-161°C/3.8 mm

IR (neat) : 3466, 1722, 1630 cm^{-1}

^1H NMR : δ 1.22 (d, 6H, J = 6.8 Hz), 2.88 (m, 1H), 3.00 (br, 1H), 3.70 (s, 3H), 5.53 (s, 1H), 5.84 (s, 1H), 6.32 (s, 1H), 7.19 (d, 2H, J= 7.6 Hz), 7 28 (d, 2H, J= 7.6 Hz)

^{13}C NMR : δ 23.87, 33.72, 51 73, 72.73, 125.46, 126.37, 126.61, 138.81, 142.29, 148.31, 166.69

Methyl 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanoate (26d):

This compound was obtained as a colorless **liquid** *via* coupling of 2-methoxybenzaldehyde with methyl acrylate in the presence of catalytic amount of DABCO following a similar procedure described for the molecule **26a.**

Reaction time : 9 days

Yield : 73%

bp : 156-157^{0}C/3 mm

IR (neat) : 3499, 1722, 1631 cm^{-1}

^{1}H NMR : 8 3.03 (br, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 5.72 (s, 1H), 5.87 (s, 1H) 6.30 (s, 1H), 6.84-7.01 (m, 2H), 7.21-7.39 (m, 2H)

^{13}C NMR : 8 51.48, 55.07, 67.37, 110.38, 120.35, 125.20, 127.28, 128.57, 129.20, 141.54, 156.37, 166.75

Methyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (26e):

This compound was prepared from 4-ethylbenzaldehyde, methyl acrylate and DABCO (cat.) following a similar procedure described for the molecule **26a,** as a colorless liquid.

Reaction time : **7 days**

Yield : **82%**

bp : **153-154^{0}C/5 mm**

IR (neat) : **3445, 1722,** 1630 **cm^{-1}**

^{1}H NMR ; 8 1.23 (t, 3H, J= 7.0 Hz), 2.64 (q, 2H, J= 7.0 Hz), 2.98 (br, 1H), 3.73 (s, 3H), 5.55 (s, 1H), 5.86 (s, 1H), 6.34 (s, 1H), 7.18 (d, 2H, J= 8.4 Hz), 7 29 (d, 2H, J= 8.0 Hz)

^{13}C NMR : 5 15.28, 28.34, 51.63, 72.55, 125.31, 126.55,127.69, 138.61, 142.19, 143.57, 166.58

Methyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate (26f):

This compound was obtained as a crystalline solid *via* the reaction between 4-methoxybenzaldehyde and methyl acrylate in the presence of DABCO (cat.) following a similar procedure described for the molecule **26a** {after column chromatography (silica gel, 10% EtOAc in hexanes)}.

Reaction time : 10 days

Yield : 68%

mp : 59-60°C

IR (KBr) : 3348, 1714, 1628 cm^{-1}

^{1}H NMR : 8 2.87 (br, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 5.53 (s, 1H), 5.84 (s, 1H), 6.31 (s, 1H), 6.87 (d, 2H, J= 8.6 Hz), 7.28 (d, 2H, J= 8.6 Hz)

^{13}C NMR : 51.74,55.15,72.42, 113.77, 125.18, 127.92, 133.64, 142.43, 159.17, 166.70

Methyl 2-methyl-3-oxo-3-phenylpropanoate (27a):

To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(26a)** (1

mmol, 0.192 g) in toluene (2 mL), was added $RuCl_2(PPh_3)_3$ (4 mol%, 0 04 mmol, 0.038 g) followed by K_2CO_3 (1 mmol, 0.138 g) at room temperature and this suspension was refluxed for 12 h. Solvent was evaporated under reduced pressure The residue obtained was purified by column chromatography (5% EtOAc in hexane. silica gel) under N_2 pressure to obtain the pure product 27a in 53% (0.101 g) yield as a colorless liquid

IR(neat) :1687,1743 cm^{-1}

^1H NMR 8 1.50 (d, 3H, J= 6.8 Hz), 3.68 (s, 3H), 4 40 (q, 1H, J= 6.8 Hz), 7.40-7.67 (m, 3H), 7.98 (d, 2H, J= 7.2 Hz)

^{13}C NMR :8 13.81, 48.09, 52.38, 128.59, 128.76, 133.47, 135.88, 171.26, 195.79

MS (m/z) : 192 (M^+)

Analysis calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29

Found : C, 68.80; H, 6.32

Methyl 2-methyl-3-(4-methylphenyl)-3-oxopropanoate (27b):

This was obtained *via* isomerization of methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate **(26b)** in the presence of catalytic amount of $RuCl_2(PPh_3)_3$ following a similar procedure described for the molecule 27a, as a colorless liquid

Yield : 51%

IR(neat) : 1682, 1743 cm^{-1}

^{1}H NMR : 6 1 49 (d, 3H, J= 7.0 Hz), 2.42 (s, 3H), 3.68 (s, 3H), 4.38 (q, 1H, J= 7 0 Hz), 7.27 (d, 2H, J= 8.2 Hz), 7.88 (d, 2H, J= 8.2 Hz)

^{13}C NMR 8 13 69, 21.38, 47.76, 52.11, 128.58, 129.30, 133.25, 144.23, 171.19, 195.23

MS (m/z) : 206 (M^{+})

Analysis calcd. for $C_{12}H_{14}O_3$: C, 69 88; H, 6.84

Found :C, 70.11; H, 6.83

Methyl 3-(4-isopropylphenyl)-2-methyl-3-oxopropanoate (27c):

This was obtained by treatment of methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methyleneпropanoate (26c) with catalytic amount of $RuCl_2(PPh_3)_3$ following a similar procedure described for the molecule **27a,** as a colorless liquid.

Yield : 57%

IR (neat) : 1684, 1743 cm^{-1}

^{1}H NMR : 5 1.27 (d, 6H, J= 7.2 Hz), 1.48 (d, 3H, J= 7.0 Hz), 2 95 (q, 1H, J= 7.2 Hz), 3.69 (s,3H), 4.39 (q, 1H, J= 7.0 Hz), 7.32 (d, 2H, J= 8.0 Hz), 7.93 (d, 2H, J= 8.0 Hz)

^{13}C *NMR* : δ 13.80, 23.49, 34.16, 47.84, 52.23, 126.78, 128.83, 133.60, 155.00, 171.30, 195 30

MS (m/z) : 234 (M^{+})

Analysis calcd. for $C_{14}H_{18}O_3$:C, 71.77; H, 7.74

Found :C, 71.80; H, 7.76

Methyl 3-(2-methoxyphenyl)-2-methyl-3-oxopropanoate (27d):

This was obtained as a colorless liquid *via* $RuCl_2(PPh_3)_3$ catalyzed isomerization of methyl 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanoate **(26d)** following a similar procedure described for the molecule **27a.**

Yield : 50%

IR(neat) : 1678, 1741 cm^{-1}

^1H NMR : 5 1.43 (d, 3H, J= 6.8 Hz), 3.66 (s, 3H), 3.87 (s, 3H), 4.33 (q, 1H, J= 6.8 Hz), 7.00 (m, 2H), 7.48 (m, 1H), 7.79 (d, 1H, J= 7.8 Hz)

^{13}C NMR :5 13.41, 51.94, 52.54, 55.26, 111.54, 120.88, 126.69, 131.07, 134.10, 158.47, 171.97, 197.08

MS (m/z) : 222 (M^+)

Analysis calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.34

Found :C, 65.00; H, 6.31

Methyl 3-(4-ethylphenyl)-2-methyl-3-oxopropanoate (27e):

This was obtained *via* isomerization of methyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate **(26e)** in the presence of catalytic amount of $RuCl_2(PPh_3)_3$ following a similar procedure described for the molecule **27a,** as a colorless liquid.

Yield : 42%

ER (neat) : 1684, 1745 cm"[1]

^{1}H NMR : 5 1.26 (t, 3H, J= 7.6 Hz), 1.48 (d, 3H, J= 6.8 Hz), 2.72 (q, 2H, J= 7.6 Hz), 3.68 (s,3H), 4.39 (q, 1H, J= 6.8 Hz), 7.30 (d, 2H, J= 8.4 Hz), 7.90 (d, 2H, J= 8.4 Hz)

^{13}C NMR : 5 13.86, 15.00, 28.91, 47.97, 52.33, 128.25, 128.84, 133.56, 150.53, 171.38, 195.38

MS (m/z) : 220 (M^+)

Analysis calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32

Found : C, 70.57; H, 7.35

Methyl 3-(4-methoxyphenyl)-2-methyl-3-oxopropanoate (27f):

This was obtained as a colorless liquid *via* the treatment of methyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate **(26f)** with catalytic amount of $RuCl_2(PPh_3)_3$ following a similar procedure described for the molecule 27a.

Yield : 61%

IR(neat) : 1678, 1743 cm^{-1}

^{1}H NMR : 5 1.48 (d, 3H, J= 7.0 Hz), 3.68 (s, 3H), 3.87 (s, 3H), 4.35 (q, 1H, J= 7.0 Hz), 6.95 (d, 2H, J= 8.8 Hz), 7.96 (d, 2H, J= 8.8 Hz)

^{13}C NMR 6 13.78, 47.59, 52 16, 55 35, 113.86, 128.66, 130 83, 163 79, **171.33,** 194.16

MS (m/z) : 222 (M^+)

Analysis calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6 34

Found : C, 64 62; H, 6.32

Methyl 3-(4-ehlorophenyl)-3-hydroxy-2-methylenepropanoate (26g):

This compound was obtained as a colorless liquid *via* the reaction between 4-chlorobenzaldehyde and methyl acrylate in the presence of DABCO (cat.) following a similar procedure described for the molecule **26a**

Reaction time : 6 days

Yield : 85%

bp : 115-116^{0}C/0.4 mm

IR(neat) : 3476, 1716, 1631 cm^{-1}

^{1}H NMR : 5 3.11 (br, 1H), 3.72 (s, 3H), 5.52 (s, 1H), 5.83 (s, 1H), 6.33 (s, 1H), 7.30 (m, 4H)

^{13}C NMR : 5 51.88, 72.13, 125.94, 128.03, 128.43, 133.41, 139.93, 141.79, 166.48

Methyl 3-hydroxy-4-methyl-2-methylenepentanoate (26h):

This compound was obtained as a colorless liquid *via* the coupling of isobutyralde-

hyde with methyl acrylate in the presence catalytic amount of DABCO following a similar procedure described for the molecule 26a.

Reaction time : 8 days

Yield : 77%

bp : 93-95°C/3.4 mm

IR (neat) : 3491, 1720, 1630 cm^{-1}

^1H NMR : 5 0.88 (d, 3H, J= 6.8 Hz), 0.96 (d, 3H, J= 6.8 Hz), 1.94 (m, 1H), 2.55 (br, 1H), 3.77 (s, 3H), 4.08 (d, 1H, J= 6.0 Hz), 5.75 (s, 1H), 6.25 (s, 1H)

^{13}C NMR :8 17.22, 19.45, 32.52, 51.71, 76.89, 125.82, 141.59, 167 10

Methyl 3-hydroxy-2-methyleneoctanoate (26i):

This compound was obtained as a colorless liquid *via* the reaction between n-hexanaldehyde and methyl acrylate in the presence of DABCO (cat.) following a similar procedure described for the molecule 26a.

Reaction time : 7 days

Yield : 81%

bp : 87-88°C/1.3 mm

IR (neat) : 3449, 1720, 1630 cm^{-1}

^1H NMR δ 0.91 (t, 3H, J= 6.2 Hz), 1.16-1 82 (m, 8H), 2.57 (br, 1H), 3.78 (s,

3H), 4.38 (m, 1H), 5.79 (s, 1H), 6.22 (s, 1H)

^{13}C NMR :5 13.92, 22.51, 25.39, 31.56, 36.23, 51.72, 71.23, 124.65, 142.80, 167.01

Methyl 2-benzyl-3-oxo-3-phenylpropanoate (30):

A solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(26a)** (1 mmol, 0.192 g) and bromobenzene (2 mmol, 0.314 g) in THF (3 mL) was refluxed for 10 h in the presence of $Pd(OAc)_2$ (2 mol%, 0.02 mmol, 0.0045 g), $NaHCO_3$ (2.5 mmol, 0 210 g) and $n\text{-}Bu_4NBr$ (1 mmol, 0.322 g). Then the reaction mixture was cooled to room temperature, diluted with water (5 mL) and extracted with ether (3x10 mL) The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated The crude product obtained, was purified by column chromatography (5% EtOAc in hexanes, silica gel). This product contained 5% impurity and was further purified by preparative HPLC (Shim-pack PREP-ODS column) using methanol as eluent to provide pure molecule 30, as a colorless liquid.

Yield : 81% (0.217 g)

IR(neat) : 1685, 1741 cm^{-1}

^1HNMR : 5 3.33 (d, 2H, J= 7.0 Hz), 3.63 (s, 3H), 4.64 (t, 1H, J= 7.0 Hz), 7.11-7.62 (m, 8H), 7.89-8.05 (m, 2H)

^{13}C NMR 5 34.83, 52.40, 55.82, 126.61, 128.50, 128.59, 128.68, 128.82, 133.51, 136 13, 138.32, 169.66, 194.39

MS (m/z) : 268 (M^+)

Analysis calcd. for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01

Found : C, 76.15; H, 6.03

Methyl **2-(4-methylphenyl)methyl-3-oxo-3-phenylpropanoate** (31):

This was prepared by the reaction of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (26a) with 4-bromotoluene in the presence of catalytic amount of Pd(OAc)2 following a similar procedure described for the molecule 30, as a colorless liquid

Time: : 10 h

Yield : 76%

IR(neat) : 1687, 1741 cm^{-1}

^{1}H NMR : 5 2.27 (s, 3H), 3 28 (d, 2H, J= 7.0 Hz), 3.62 (s, 3H), 4 61 (t, 1H, J= 7.0 Hz), 7 01-7.63 (m, 7H), 7.94 (d, 2H, J= 7.2 Hz)

^{13}C NMR : 5 20.97, 34.46, 52.43, 56.04, 128.72, 129.23, 133.52, 135.28, 136.15, 169.77, 194.47

MS (m/z) : 282 (M^+)

Analysis calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.42

Found : C, 76.36; H, 6.45

Methyl 2-(naphth-1-ylmethyl)-3-oxo-3-phenylpropanoate (32):

This was prepared *via* the treatment of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (26a) with 1-bromonaphthalene in the presence of catalytic amount of $Pd(OAc)_2$ following a similar procedure described for the molecule 30, as a colorless solid

Time: : 7 h

Yield : 83%

mp : 68-70°C

IR (CH_2Cl_2) : 1676, 1738 cm^{-1}

^1H NMR : 5 3.63 (s, 3H), 3.82 (d, 2H, J= 6.8 Hz), 4.83 (t, 1H, J= 6.8 Hz), 7.17-8.19 (m, 12 H)

^{13}C NMR :8 31.81, 52.50, 54.59, 123.16, 125.41, 125.59, 126.27, 127.25, 127.53, 128.53, 128.61, 129.00, 131.63, 133.47, 133.93, 134.14, 136.26, 169.88, 194.54

MS (m/z) : 318 (M^+)

Analysis calcd. for $C_{21}H_{18}O_3$: C, 79.22; H, 5.69

Found : C, 79.26; H, 5.67

Methyl 2-benzyl-3-(4-methylphenyl)-3-oxopropanoate (33):

This was prepared *via* the $Pd(OAc)_2$ catalyzed Heck coupling of methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (26b) with bromobenzene following a

similar procedure described for the molecule 30. This product contained ≈5% impurity and was further purified by preparative HPLC (Shim-pack PREP-ODS column, methanol) to provide pure 33 as a colorless liquid.

Time: : 12 h

Yield : 80%

IR(neat) : 1682, 1741 cm^{-1}

^1H NMR : 5 2.39 (s, 3H), 3.31 (m, 2H), 3.62 (s, 3H), 4.62 (t, 1H, J= 7.2 Hz), 7.15-7.30 (m, 7H), 7.85 (d, 2H, J= 8.0 Hz)

^{13}C NMR : 21.60, 34.89, 52.41, 55.80, 126.61, 128.52, 128.82, 128.85, 129.43, 133.72, 138.51, 144.52, 169.83, 193.95

MS (m/z) : 282 (M^+)

Analysis calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.42

Found : C, 76.65; H, 6.39

Methyl 2-benzyl-3-(4-isopropylphenyl)-3-oxopropanoate (34):

This was prepared by the reaction of methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate **(26c)** with bromobenzene in the presence of catalytic amount of $Pd(OAc)_2$ following a similar procedure described for the molecule 30. This product contained ≈5% impurity. Further purification by preparative HPLC (Shim-pack PREP-ODS column, methanol) provided the pure compound 34, as a colorless liquid.

Time: : 10 h

Yield : 75%

IR(neat) : 1682, 1741 cm^{-1}

^1H NMR : 8 1.24 (d, 6H, J= 6.8 Hz), 2.92 (sept, 1H, J= 6 8 Hz), 3.32 (m, 2H), 3.63 (s, 3H), 4.63 (t, 1H, J= 7.2 Hz), 7.12-7.35 (m, 7H), 7.89 (d, 2H, J= 8 4 Hz)

^{13}C NMR : 6 23.61, 34.31, 34.95, 52.50, 55.93, 126.66, 126.91, 128.58, 128.94, 129.02, 134.07, 138.62, 155.26, 169.91, 193.93

MS (m/z) : 310 (M^+)

Analysis calcd. for $C_{20}H_{22}O_3$: C, 77.39, H, 7.14

Found C, 77.45; H, 7.18

Methyl 3-(4-isopropylphenyl)-2-(4-methylphenyl)methyl-3-oxopropanoate (35): This was prepared by treatment of methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate (26c) with 4-bromotoluene in the presence of catalytic amount of $Pd(OAc)_2$ following a similar procedure described for the molecule 30. This product contained ≈5% impurity and was further purified by preparative HPLC (Shim-pack PREP-ODS column, methanol) to provide pure 35, as a colorless liquid.

Time: : 10 h

Yield : 76%

IR(neat) : 1682, 1741 cm^{-1}

^1H NMR : 5 1 25 (d, 6H, J= 6.8 Hz), 2.28 (s, 3H), 2.93 (sept, 1H, J= 6 8 Hz), 3.28 (m, 2H), 3.64 (s, 3H), 4.60 (t, 1H, J= 7.0 Hz), 7.01-7.39 (m, 6H), 7.89 (d, 2H, J= 8.0 Hz)

^{13}C NMR : 8 21.03, 23.62, 34.31, 34.54, 52.48, 56.09, 126.90, 128.79, 129.03, 129.27, 134.08, 135.53, 136.16, 155.23, 169.98, 194.00

MS (m/z) . 324 (M^+)

Analysis calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.45

Found : C, 77.65; H, 7.42

Methyl 3-(4-isopropylphenyl)-2-(naphth-1-ylmethyl)-3-oxopropanoate (36):

This was prepared *via* the $Pd(OAc)_2$ catalyzed Heck coupling of methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate **(26c)** with 1-bromonaphthalene following a similar procedure described for the molecule 30. This product contained ≈5% impurity. Further purification by preparative HPLC (Shim-pack PREP-ODS column, methanol) provided pure molecule 36, as a colorless liquid.

Time: : 8 h

Yield : 82%

IR (neat) : 1682, 1739 cm^{-1}

^1H NMR : δ 1.22 (d, 6H, J= 7.0 Hz), 2.91 (m, 1H), 3.63 (s, 3H), 3.80 (d, 2H, J=

7.2 Hz), 4.81 (t, 1H, J= 7.2 Hz), 7.15-8.08 (m, 11H)

^{13}C NMR : 8 23.57, 31.90, 34.28, 52.51, 54.71, 123.33, 125.51, 125.63, 126.29, 126.82, 127.33, 127.55, 128.95, 129.05, 131.81, 134.08, 134.30, 134.44, 155.18, 170.10, 194.09

MS (m/z) : 360 (M^+)

Analysis calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71

Found :C, 80.21; H, 6.68

Methyl **2-benzyl-3-(2-methoxyphenyl)-3-oxopropanoate** (37):

This was prepared by the reaction of methyl 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanoate (26d) with bromobenzene in the presence of catalytic amount of $Pd(OAc)_2$ following a similar procedure described for the molecule 30. This product contained ≈5% impurity and was further purified by preparative HPLC (Shim-pack PREP-ODS column, methanol) to provide pure compound 37, as a colorless liquid.

Time: : 18 h

Yield : 67%

IR(neat) :1672,1739 cm^1

^1H NMR : 8 3.27 (m, 2H), 3.64 (s, 3H), 3.85 (s, 3H), 4.67 (t, 1H, J= 6.8 Hz), 6.85-7.70 (m, 9H)

^{13}C NMR : 8 34.61, 52.02, 55.24, 60.10, 111.49, 120.86, 126.32, 126.90, 128.28, 128.88, 131.04, **134.17,** 138.99, 158.31, 170.41, 19603

MS (m/z) : 298 (M^+)

Analysis calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08

Found :C, 72.24; H, 6.10

Methyl 2-benzyl-3-(4-chlorophenyl)-3-oxopropanoate (38):

This was prepared by treatment of methyl 3-(4-chlorophenyl)-3-hydroxy-2-methyl-enepropanoate **(26g)** with bromobenzene in the presence of catalytic amount of $Pd(OAc)_2$ following a similar procedure described for the molecule 30. This product contained ≈5% impurity. Further purification by preparative HPLC (Shim-pack PREP-ODS column, methanol) provided pure molecule 38, as a colorless liquid

Time: : 8 h

Yield : 60%

IR (neat) : 1687, **1741** cm^{-1}

^1H NMR : 8 3.32 **(d, 2H, J=** 7.2 **Hz),** 3.64 (s, **3H), 4.58 (t, 1H, J=** 7.6 **Hz),** 7.16-**7.47 (m, 7H), 7.86 (m, 2H)**

^{13}C NMR :8 34.80, 52.53, 55.88, 126.73, 128.57, 128.83, 129.02, 130.02, **134.56, 138.15, 140.07, 169.41, 193.24**

MS (m/z) **:** 302 (M^+)

Analysis calcd. for $C_{17}H_{15}O_3Cl$: C, 67.44; H, 4.99

Found ;C, 67.31; H, 5.01

Methyl 2-benzyl-4-methyl-3-oxopentanoate (39):

This was prepared *via* the $Pd(OAc)_2$ catalyzed Heck coupling of methyl 3-hydroxy-4-methyl-2-methylenepentanoate (26h) with bromobenzene following a similar procedure described for the molecule 30, as a colorless liquid. This product contained ≈5-8% impurity as indicated by ^1H NMR and ^{13}C NMR spectral analysis. Attempts to further purification by preparative HPLC were not successful.

Time: : 10 h

Yield : 61%

IR(neat) : 1714, 1743 cm^{-1}

^1H NMR : 5 0.86 (d, 3H, J= 6.8 Hz), 1.04 (d, 3H, J= 6.8 Hz), 2.60 (m, 1H), 3.15 (d, 2H, J= 7.4 Hz), 3.68 (s, 3H), 3.95 (t, 1H, J= 7.4 Hz), 7.05-7.36 (m, 5H)

^{13}C NMR : 6 17.67, 17.76, 34.51, 41.33, 52.34, 58.54, 126.67, 128.55, 128.92, 138.42, 169.54, 208.29

Methyl 2-(4-methylphenyl)methyl-4-methyl-3-oxopentanoate (40):

This was prepared by the reaction of methyl 3-hydroxy-4-methyl-2-methylenepentanoate (26h) with 4-bromotoluene in the presence of catalytic amount

of $Pd(OAc)_2$ following a similar procedure described for the molecule 30, as a colorless liquid ^1H NMR and ^{13}C NMR spectral analysis of this product showed ≈5-8% impurity. Attempts to further purification by preparative HPLC were not successful.

Time: : 7 h

Yield : 76%

IR(neat) :1714,1745 cm^{-1}

^1H NMR : 5 0.89 (d, 3H, J= 6.8 Hz), 1.05 (d, 3H, J= 6.8 Hz), 2 29 (s, 3H), 2.60 (m, 1H), 3.11 (d, 2H, J= 7 2Hz), 3.68 (s, 3H), 3.93 (t, 1H, J= 7.2 Hz), 7.05 (m, 4H)

^{13}C NMR : 5 17.65, 17.73, 20 94, 34.06, 41.25, 52.25, 58.57, 128.70, 129.16, 135.21, 136.09, 169.55,208.37

Methyl 2-benzyl-3-oxooctanoate (41):

This was obtained by treatment of methyl 3-hydroxy-2-methyleneoctanoate (26i) with bromobenzene in the presence of catalytic amount of $Pd(OAc)_2$ following a similar procedure described for the molecule 30, as a colorless liquid. This product contained ≈5-8% impurity as indicated by ^1H NMR and ^{13}C NMR spectral analysis. Attempts to further purification by preparative HPLC were not successful.

Time: : 9 h

Yield : 64%

IR(neat) : 1716, 1743 cm^{-1}

^1H NMR : δ 0.83 (t, 3H, J= 6 8 HZ), 1.05-1.62 (m, 6H), 2.18-2.61 (m, 2H), 3.15 (d, 2H, J=7 6 Hz), 3.68 (s,3H), 3.80 (t, 1H, J= 7.6 Hz), 7.05-7 36 (m, 5H)

^{13}C NMR : 8 13.74, 22.26, 22.89, 30.99, 34.10, 42.75, 52.21, 60.30, 126.57, 128.48, 128.72, 138.22, 169.51,204.54

Methyl 2-(naphth-l-ylmethyl)-3-oxooctanoate (42):

This was obtained *via* the $Pd(OAc)_2$ catalyzed Heck coupling of methyl 3-hydroxy-2-methyleneoctanoate (26i) with 1-bromonaphthalene following a similar procedure described for the molecule **30,** as a colorless liquid. ^1H NMR and ^{13}C NMR spectral analysis of this product showed ≈5-8% impurity. Attempts to further purification by preparative HPLC were not successful.

Time: : 7 h

Yield : 79%

IR(neat) 1716, 1745 cm^{-1}

^1H NMR : 8 0.82 (t, 3H, J= 6.6 Hz), 1.00-1.55 (m, 6H), 2.10-2.58 (m, 2H), 3.67 (m, 5H), 4.00 (t, 1H, J= 7.6 Hz), 7.25-8.05 (m, 7H)

^{13}C NMR : 8 13.78, 22.29, 22.90, 30.99, 31.20, 43.02, 52.37, 59.06, 123.16,

125.44, 125.64, 126.27, 127.26, 127.56, 129.01, 131.50, 133.96, 134.10, 169.79,204.83

Methyl **3-acetoxy-2-methylene-3-phenylpropanoate** (43):

To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (26a) (25 mmol, 4.80 g) and pyridine (50 mmol, 3.955 g) in dry dichloromethane (25 mL), acetyl chloride (50 mmol, 3.925 g) was added slowly at 0°C. After stirring for 2 h at room temperature, the reaction mixture was taken up in ether (40 mL) and washed successively with 2N HC1 solution, water and aqueous $NaHCO_3$ solution. Organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was distilled under reduced pressure to provide pure acetate 43 in 89% (5.20 g) yield, as a colorless liquid.

bp : 122-124°C/2.3 mm

IR (neat) : 1743, 1729, 1633 cm^{-1}

^1H NMR : 5 2.09 (s, 3H), 3.70 (s, 3H), 5.85 (s, 1H), 6.39 (s, 1H), 6.68 (s, 1H), 7.33 (m, 5H)

^{13}C NMR : 5 20.87, 51.82, 73.09, 125.63, 127.64, 128.35, 128.44, 137.93, 139.84, 165.31, 169.20

Methyl **3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate** (44):

This was obtained *via* the reaction of methyl 3-hydroxy-2-methylene-3-(4-methyl-

phenyOpropanoate **(26b)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **43,** as a colorless liquid.

Yield : 92%

bp : 142-144°C/4.3 mm

IR (neat) : 1745, 1732, 1633 cm^{-1}

^1H NMR : 6 2.08 (s, 3H), 2.32 (s, 3H), 3.70 (s, 3H), 5.85 (s, 1H), 6.37 (s, 1H), 6.64 (s, 1H), 7.20 (d, 2H, J=8.2 Hz), 7.27 (d, 2H, J= 8.2 Hz)

^{13}C NMR : 5 21.06, 51.82, 73.03, 125.33, 127.60, 129.11, 134.90, 138.12, 139.90, 165.41, 169.28

Methyl 3-acetoxy-3-(4-isopropylphenyl)-2-methylenepropanoate (45):

This was prepared *via* the treatment of methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate **(26c)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **43,** as a colorless liquid

Yield : 87%

bp : 163-164°C/3.3 mm

IR (neat) : 1747, 1730, 1633 cm^{-1}

^1H NMR : 8 1.23 (d, 6H, J= 7.0 Hz), 2.10 (s, 3H), 2.89 (sept, 1H, J= 7.0 Hz), 3.71 (s, 3H), 5.86 (s, 1H), 6.39 (s, 1H), 6.67 (s, 1H), 7.19 (d, 2H, J= 8.0 Hz), 7.30 (d, 2H, J= 8.0 Hz)

^{13}C NMR : 5 21.04, 23.85, 33.80, 51.88, 73.02, 125.40, 126.51, 127.65, 135.12, 139.92, 149.02, 165.45, 169.36

Methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (46):

This was prepared *via* the reaction of methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (26g) with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **43,** as a colorless liquid.

Yield : 93%

bp : 143-144^{0}C/3.5 mm

IR(neat) : 1745, 1731, 1634 cm^{-1}

'H NMR : 6 2.09 (s, 3H), 3.70 (s, 3H), 5.87 (s, 1H), 6.39 (s, 1H), 6.62 (s, 1H), 7.30 (s, 4H)

^{13}C NMR : 5 20.92, 51.95, 72.50, 125.80, 128.67, 129.07, 134.29, 136.57, 139.49, 165.22, 169.19

Methyl 3-acetoxy-4-methyl-2-methylenepentanoate (47):

This was obtained *via* the acetylation of methyl 3-hydroxy-4-methyl-2-methylenepentanoate **(26h)** (with acetyl chloride) in the presence of pyridine following a similar procedure described for the molecule **43,** as a colorless liquid.

Yield : 79%

bp : 73-74°C/4.8 mm

IR (neat) : 1741, 1728, 1631 cm^{-1}

^1H NMR : 8 0.90 (m, 6H), 2.08 (m, 4H), 3 77 (s, 3H), 5.46 (d, 1H, J= 6.0 Hz), 5.71 (s, 1H), 6 31 (s, 1H)

^{13}C NMR :6 16.83, 18.85, 20.76, 31.23, 51.75, 76.01, 125.64, 139.39, 165.81, 16981

Methyl 3-acetoxy-2-methyleneoctanoate (48):

This was obtained *via* the treatment of methyl 3-hydroxy-2-methyleneoctanoate (26i) with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule 43, as a colorless liquid.

Yield : 77%

bp : 138-139^{0}C/2.3 mm

IR (neat) : 1745, 1726, 1633 cm^{-1}

^1H NMR : δ 0.87 (t, 3H, J= 6.6 Hz), 1.28 (m, 6H), 1.68 (m, 2H), 2.08 (s, 3H), 3.77 (s, 3H), 5.61 (m, 1H), 5.75 (s, 1H), 6.27 (s, 1H)

^{13}C NMR : δ 13.89, 20.97, 22.42, 24.94, 31.39, 34.24, 51.83, 71.88, 124.88, 140.41, 165.76, 169.85

Methyl (2*E*) 2-cyanomethyl-3-phenylprop-2-enoate (49):

To a stirred solution of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (43) (2 mmol, 0.468 g) in acetonitrile at room temperature was added NaCN (2.5 mmol,

0.122 g). After 3 h, the reaction mixture was diluted with water (10 mL) and extracted with ether (3x10 mL). The combined ether layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (2% EtOAc in hexanes) to afford 49 in 83% (0.334 g) yield, as a colorless liquid.

E:Z : ≈98:2

IR (neat) : 2251, 1712, 1633 cm^{-1}

^{1}HNMR : δ 3.53 (s, 2H), 3.90 (s, 3H), 7.30-7.55 (m, 5H), 7.97 (s, 1H)

In addition, a peak at 3.68 with very low intensity appeared due to the presence of minor (Z)-isomer.

^{13}C NMR : δ 16.68, 52.44, 117.10, 121.84, 128.23, 128.82,128.97,129.59, 133.59, 143.67, 165.96.

In addition, a peak at 23.06 with very low intensity appeared due to the presence of minor (Z)-isomer.

Analysis calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96

Found :C, 71.75; H, 5.49; N, 6.93

Methyl **(2*E*)-2-cyanomethyl-3-(4-methylphenyl)prop-2-enoate** (SO):

This molecule was prepared by the reaction of methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (44) with NaCN following a similar procedure described

for the molecule 49, as a colorless solid.

Reaction time : 3 h

E:Z : 94:6

Yield : 85%

m.p. : 39-40°C

IR (KBr) : 2251, 1711, 1637 cm^{-1}

^1H NMR : 8 2.40 (s, 3H), 3.55, 3.70 (2s, 2H), 3.89 (s, 3H), 7.29 (m, 4H), 7.18 & 7.94 (2s, 1H)

^{13}C NMR : δ 16.90, 21.34, 22.54, 52.57, 117.34, 120.96, 128.81, 129.31, 129.72, 130.90, 140.26, 143.97, 166.34.

The underlined chemical shift values are due to minor (Z)-isomer.

MS (m/z) : 215 (M^+)

Analysis calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51

Found : C, 72.45; H, 6.06; N, 6.54

Methyl (2*E*)-2-cyanomethyl-3-(4-isopropylphenyl)prop-2-enoate (51):

This molecule was obtained as a colorless liquid *via* the treatment of methyl 3-acetoxy-3-(4-isopropylphenyl)-2-methylenepropanoate (45) with NaCN following a similar procedure described for the molecule 49.

Reaction time : 3 h

E:Z : 82:18

Yield : 86%

IR (neat) : 2251, 1714, 1635 cm^{-1}

^1H NMR : 5 1.25 (m, 6H), 2.97 (m, 1H), 3.51& 3.56 (2s, 2H), 3.72 & 3.90 (2s, 3H), 7.15-7.35 (m, 4H), 7.19& 7.94 (2s, 1H)..

^{13}C NMR : 8 17.02, 23.40. 23.76, 34.08, 52.08. 52 66, 116.76. 117.44, 121.03, 126.27. 127.19, 129.08. 129.52, 131.33. 140.92. 144.06, 150.13. 151.18, 166.43.

The underlined chemical shift values arise from the minor (*Z*)-isomer

Analysis calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76

Found : C, 73.88, H, 7.07; N, 5.79

Methyl **(2*E*)-3-(4-chlorophenyl)-2-cyanomethylprop-2-enoate** (52):

This molecule was prepared as a colorless solid *via* the reaction between methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (46) and NaCN following a similar procedure described for the molecule 49.

Reaction time : 3 h

E:Z : 96:4

Yield : 80%

m.p. : 74-76^{0}C

IR (KBr) : 2253, 1716, 1641 cm^{-1}

^1H NMR : δ 3.50 (s, 2H), 3.68 & 3.90 (2s, 3H), 7.31-7.48 (m, 4H), 7.18 & 7.91 (2s, 1H)

^{13}C NMR : δ 16.79, 23.13, 52.71, 116.93, 122.52, 128.28, 129.27, 130.05, 130.44, 132.13, 135.88. 139.47, 142.48, 165.86

The underlined chemical shift values are due to minor (Z)-isomer.

Analysis calcd. for $C_{12}H_{10}NO_2Cl$: C, 61.15; H, 4.27; N, 5.94

Found : C, 61.30; H, 4.29; N, 5.97

Methyl (2*E*)-2-cyanomethyl-4-methylpent-2-enoate (53):

This molecule was prepared by the reaction of methyl 3-acetoxy-4-methyl-2-methylenepentanoate (47) with NaCN following a similar procedure described for the molecule 49, as a colorless liquid.

Reaction time : 8 h

E:Z : 82:18

Yield : 75%

IR (neat) : 2251, 1716, 1651 cm^{-1}

^1H NMR : δ 0.98 & 1.05 (2d, 6H, J= 6.8 Hz), 2.62 (m, 1H), 128 & 3.34 (2s, 2H), 174 & 3.75 (2s, 3H), 6.14 & 6.80 (2d, 1H, J= 10.5 Hz)

^{13}C NMR : δ 14.95, 21.48, 22.05, 22.55, 28.34, 28.62. 51.77, 52.22, 117.17, 118.80. 119.75, 153.92, 154.75, 165.93

The underlined chemical shift values arise from the minor (Z)-isomer.

Analysis calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38

Found : C, 64.81; H, 7.81; N, 8.34

Methyl (2*E*)-2-cyanomethyloct-2-enoate (54):

This molecule was obtained as a colorless liquid *via* the treatment of methyl 3-acetoxy-2-methyleneoctanoate (48) with NaCN following a similar procedure described for the molecule **49.**

Reaction time : 6 h

E:Z : **88:12**

Yield : 79%

IR(neat) : 2251, 1716, 1651 cm^{-1}

^{1}HNMR : 8 0.91 (t, 3H, J= 6.4 Hz), 1.22-1.62 (m, 6H), 2.28 & 2.60 (2q, 2H, J= 7.4 Hz), 136 & 3.38 (2s, 2H), 180, 3.81 (2s, 3H), 6.45 & 7.06 (2t, 1H, J= 7.6 Hz)

^{13}C NMR : δ 13.61, 14.88, 22.14, 22.37. 27.62, 28.37, 28.85, 29.39. 31.19, 51.58. 52.04, 116.81, 117.13. 120.71. 121.84, 147.93, 148.70. 165.58

The underlined chemical shift values **are** due to minor (Z)-isomer.

Analysis calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17

Found : C, 67.44; H, 8.82; N, 7.15

3-Hydroxy-2-methylene-3-phenylpropanenitrile (55a):

A mixture of benzaldehyde (50 mmol, 5.306 g), acrylonitrile (75 mmol, 3.979 g) and DABCO (7.5 mmol, 0.841 g) was kept at room temperature for 2 days. The reaction mixture was diluted with ether (50 mL) and washed successively with 2N HC1 solution, water and aqueous $NaHCO_3$ solution. Ethereal layer was dried over Na_2SO_4 and concentrated. The residue thus obtained was distilled under reduced pressure to afford the alcohol 55a as a colorless liquid in 83% (6.598 g) yield.

bp : 115-117^{0}C/0.9 mm

IR (neat) : 3466, 2227, 1624 cm^{-1}

^{1}H NMR : δ 2.51 (br, 1H), 5.27 (s, 1H), 6.01 (s, lH), 6.09(s, 1H), 7.38 (s, 5H)

^{13}C NMR : δ 73.90, 116.95, 126.27, 126.46, 128.75, 129.91, 139.23

3-Hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (55b):

This compound was prepared from 4-tolualdehyde, acrylonitrile and DABCO (cat.) following a similar procedure described for the molecule 55a, as a colorless liquid.

Reaction time : 2 days

Yield : 80%

bp : 130-131^{0}C/1.4 mm

IR (neat) : 3450, 2229, 1616 cm^{-1}

^{1}H NMR : δ 2.30(br, 1H), 2.36 (s, 3H), 5.25 (s, 1H), 6.02 (s, 1H), 6.10 (s,lH),

7.21 (d, 2H, J= 7.2 Hz), 7.27 (d, 2H, J= 7.2 Hz)

^{13}C NMR : 8 21.03, 73.68, 117.01, 126.40, 129.39, 129.62, 136.26, 138.51

3-Hydroxy-3-(2-methoxyphenyl)-2-methylenepropanenitrile (55c):

This compound was obtained as a colorless liquid *via* the reaction between 2-anisaldehyde and acrylonitrile in the presence of catalytic amount of DABCO following a similar procedure described for the molecule **55a.**

Reaction time : 2 days

Yield : 76%

bp : 136-138^{0}C/0.6 mm

IR (neat) : 3445, 2227, 1621 cm^{-1}

^{1}H NMR . δ 3.22 (d, 1H, J= 6.8 Hz), 3 86 (s, 3H), 5 49 (d, 1H, J= 6.8 Hz), 6.01 (s, 2H), 6.85-7.08 (m, 2H), 7.25-7.42 (m, 2H)

^{13}C NMR : δ 55.09, 68.97, 110.57, 117.08, 120.66, 125.48, 127.09, 129.47, 129.83, 156.15

3-Hydroxy-2-methylenehexanenitrile (55d):

This compound was obtained as a colorless liquid *via* the coupling of n-butyraldehyde with acrylonitrile in the presence of DABCO (cat.) following a similar procedure described for the molecule **55a.**

Reaction time : 5 days

Yield : 75%

bp : 65-67°C/2.2 mm

IR (neat) : 3441, 2227, 1624 cm^{1}

^{1}H NMR : 5 0.94 (t, 3H, J= 7.0 Hz), 1.25-1.85 (m, 4H), 2.35 (d, 1H, J= 5.0 Hz), 4.23 (m, 1H), 5.97 (s, 1H), 5.99 (s, 1H)

^{13}C NMR :6 13.54, 18.22, 37.50, 71.75, 117.07, 126.90, 129.88

3-Hydroxy-4-methyl-2-methylenepentanenitrile (55e):

This compound was obtained as a colorless liquid *via* the DABCO catalyzed coupling of isobutyraldehyde with acrylonitrile following a similar procedure described for the molecule **55a,** as a colorless liquid.

Reaction time : 5 days

Yield : 78%

bp : 103-104°C/12.2 mm

IR (neat) : 3445, 2227, 1624 cm^{-1}

^{1}H NMR : 8 0.97 (m, 6H), 1.73 (m, 1H), 1.99 (s, 1H), 4.19 (t, 1H, J= 6.2 Hz), 6.00 (s, 2H)

^{13}C NMR : δ 9.19, 28.50, 73.31, **117.07, 126.60,** 130.17

3-Hydroxy-2-methyleneoctanenitrile (55f):

This compound was prepared from n-hexanaldehyde, acrylonitrile and DABCO (cat.)

following a similar procedure described for the molecule 55a, as a colorless liquid.

Reaction time : 6 days

Yield : 80%

bp : 119-120^{0}C/3.9 mm

IR (neat) : 3443, 2227, 1622 cm^{-1}

^{1}H NMR : 5 0.90 (t, 3H, J= 6.8 Hz), 1.15-1.45 (m, 6H), 1.60-1.82 (m, 2H), 2.33 (d, 1H, J= 5.0 Hz), 4.25 (m, 1H), 5.98 (s, 1H), 5.99 (s, 1H)

^{13}C NMR : 5 13.84, 22 38, 24.65, 31.33, 35.44, 72.10, 117.08, 126.91, 129.94

3-Acetoxy-2-methylene-3-phenylpropanenitrile (56a):

To a solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (55a) (25 mmol, 3.975 g) and pyridine (50 mmol, 3.955 g) in dry dichloromethane (25 mL), acetyl chloride (50 mmol, 3.925 g) was added slowly at 0°C. After stirring for 2 h at room temperature, the reaction mixture was diluted with ether (30 mL) and washed successively with 2N HCl solution, water and aqueous $NaHCO_3$ solution. Organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was distilled under reduced pressure to furnish pure acetate 56a in 80% (4.02 g) yield, as a colorless liquid.

bp : 114-116^{0}C/1.4 mm

IR (neat) : 2229, 1749, 1624 cm^{-1}

^{1}H NMR : 5 2.18 (s, 3H), 6.01 (s, 1H), 6.08 (s, 1H), 6.33 (s, 1H), 7.40 (s, 5H)

^{13}C NMR : 6 20.80, 74.31, 116.11, 123.26, 126.92, 128.89, 129.18, 131.87, 135.68, 169.15

3-Acetoxy-2-methylene-3-(4-methylphenyl)propanenitrile (56b):

This was prepared as a colorless liquid by the treatment of 3-hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile **(55b)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a.**

Yield : 83%

bp : 134-135^{0}C/2.5 mm

IR (neat) : 2227, 1745, 1616 cm^{-1}

^{1}H NMR : δ 2.16 (s, 3H), 2.36 (S, 3H), 5.99 (s, 1H), 6.06 (S, 1H), 6.31 (S, 1H), 7.21 (d, 2H, J= 8.0 Hz), 7.29 (d, 2H, J= 8.0 Hz)

^{13}C NMR : 520.80, 21.09, 74.21, **116.18, 123.38,** 126.90, 129.54, 131.57, 132.74,139.12, 169.16

3-Acetoxy-3-(2-methoxyphenyl)-2-methylenepropanenitrile (56c):

This was obtained as a colorless liquid *via* the reaction of 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanenitri!e **(55c)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a.**

Yield : **82%**

bp : 125-127°C/0.9 mm

IR (neat) : 2227, 1751, 1620 cm^{1}

^{1}H NMR : 8 2.18 (s, 3H), 3.85 (s, 3H), 5.98 (s, 1H), 6.01 (s, 1H), 6.73 (s, 1H), 6.86-7.09 (m, 2H), 7.27-7.52 (m, 2H)

^{13}C NMR : 8 20.71, 55.37, 68.86, 110.70, 116.27, 120.77, 122.50, 124.16, 126.80, 130.06, 131.79, 156.19, 169.02

3-Acetoxy-2-methylenehexanenitrile (56d):

This was prepared by the reaction between 3-hydroxy-2-methylenehexanenitrile (55d) and acetyl chloride in the presence of pyridine following a similar procedure described for the molecule 56a, as a colorless liquid.

Yield : 76%

bp : 102-103^{0}C/14 mm

IR (neat) : 2227, 1747, 1626 cm^{-1}

^{1}H NMR : δ 0.95 (t, 3H, J= 7.0 Hz), 1.36 (m, 2H), 1.76 (m, 2H), 2.10 (s, 3H), 5.28 (t, 1H, J= 6.6 Hz), 5.98 (s, 1H), 6.03 (s, 1H)

^{13}C NMR : δ 13.39, 18.03, 20.73, 34.76, 72.85, 116.06, 122.80, 132.36, 169.71

3-Acetoxy-4-methyl-2-methylenepentanenitrile (56e):

This was prepared by the treatment of 3-hydroxy-4-methyl-2-methylenepentanenitrile (55e) with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a,** as a colorless liquid.

Yield : 80%

bp : 76-77°C/5 mm

IR (neat) : 2227, 1749, 1625 cm^{-1}

^1H NMR : 8 0.96 (m, 6H), 1.98-2.21 (m, 4H), 4.99 (d, 1H, J= 8.0 Hz), 5.95 (s, 1H), 6.07 (s, 1H)

^{13}C NMR : 8 17.18, 17.85,20.21,30.48,77.49, **115.93, 121.70, 132.71,** 169 **24**

3-Acetoxy-2-methyleneoctanenitrile (56f):

This was obtained as a colorless liquid *via* the reaction of 3-hydroxy-2-methyleneoctanenitrile **(55f)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a.**

Yield : 78%

bp : 98-99^{0}C/1.2 mm

IR (neat) : 2227, 1749, 1620 cm^{-1}

^1H NMR : 8 0.89 (t, 3H, J= 6.6 Hz), 1.26 (m, 6H), 1.75 (m, 2H), 2.10 (s, 3H), 5.27 (t, 1H, J= 7.0 Hz), 5.97 (s, 1H), 6.03 (s, 1H)

^{13}C NMR : 8 13.81, 20.82, 22.32, 24.43,31.15, 32.74,73.19, 116.12, 122.92, 132.42, 169.76

(3*Z*)-3-Cyano-4-phenylbut-3-enenitrile (57a):

To a stirred solution of 3-acetoxy-2-methylene-3-phenylpropanenitrile(56a) (2 mmol,

0.402 g) in acetonitrile at room temperature was added NaCN (2.5 mmol, 0.122 g). After 3 h, the reaction mixture was diluted with water (10 mL) and extracted with ether (3x10 mL). The combined ether layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (2% EtOAc in hexanes to afFord the pure product 57a in 48% (0 162 g) yield, as a colorless solid.

Z:E : 95:5

mp : 47-48°C

IR (KBr) : 2250, 2216, 1624 cm^{-1}

^1H NMR : δ 3.49(s) & 3.52 (d, 2H, J= 1.8 Hz), 7.32 (s, 1H), 7.46 (m, 3H), 7.76 (m, 2H)

^{13}C NMR :5 19.31, 23.91, 99.74, 114.74, 116.71, 129.03, 129.07, 12931, 130.73, 131.39, 132.10, 147.04. 149.06

The underlined chemical shift values are due to minor (*E*)-isomer.

Analysis calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.65

Found : C, 78.45; H, 4.77; N, 16.70

(3*Z*)-3-Cyano-4-(4-methylphenyl)but-3-enenitrile (57b):

This molecule was obtained as a colorless solid *via* the reaction between 3-acetoxy-2-methylene-3-(4-methylphenyl)propanenitrile (56b) and NaCN following a similar procedure described for the molecule 57a.

Z:*E* : ≈90:10

Yield : 67%

mp : 57-58°C

IR (KBr) : 2254, 2214, 1623 cm^{-1}

^1H NMR : δ 2.45 (s, 3H), 3.54 (s, 2H), 7.20-7.38 (m, 3H), 7.72 (d, 2H, J= 8.0 Hz).

In addition, a peak at δ 7.51 with very low intensity appears for olefinic proton of the minor (*E*)-isomer.

^{13}C NMR : δ 19.26. 21.43. 23.80. 98.33. 102.59. 114.90, 116.92, 129.00. 129.42. 129.70, 129.92. 141.36. 142.03, 146.96, 148.90

MS (m/z) : 182 (M^+)

The underlined chemical shift values arise from the minor (*E*)-isomer.

Analysis calcd. for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37

Found : C, 79.47; H, 5.51; N, 15.30

(3*Z*)-3-Cyano-4-(2-methoxyphenyl)but-3-enenitrile (57c):

This molecule was prepared by the treatment of 3-acetoxy-3-(2-methoxyphenyl)-2-methylenepropanenitrile (56c) with NaCN following a similar procedure described for the molecule 57a, as a colorless liquid.

Z.*E* : 72:28

Yield : 56%

IR (neat) : 2254, 2216, 1621 cm^{-1}

^{1}H NMR : δ 3.35 & 3.48 (2s, 2H), 1.84, 3.85 (2s, 3H), 6.82-8.01 (m, 5H)

^{13}C NMR : δ 19.71, 23.94, 55.59, 99.56, 103.90, 110.93, 111.37, 114.96, 115.19, 116.87, 118.10, 120.74, 120.95, 121.32, 128.24, 129.62, 132.36, 132.77, 142.52, 145.38, 157.05, 157.60

The underlined chemical shift values are due to minor (*E*)-isomer.

Analysis calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13

Found :C, 72.50; H, 5.10; N, 14.15

(3Z)-3-Cyanohept-3-enenitri]e (57d):

This molecule was obtained *via* the reaction of 3-acetoxy-2-methylenehexanenitrile **(56d)** with NaCN following a similar procedure described for the molecule **57a,** as a colorless liquid.

Z:*E* : 90:10 (In ^{1}H NMR spectrum of the crude concentrated product, the allylic methylene protons of [*E*]- and [Z]-isomers separate. However, column chromatography (2% EtOAc in hexanes) has provided the pure (Z)-isomer in 68% yield).

IR (neat) : 2256, 2222, 1641 cm^{-1}

^{1}H NMR : δ 0.98 (t, 3H, J= 7.2 Hz), 1.42-1.64 (m, 2H), 2.42 (m, 2H), 3.32 (s, 2H), 6.63 (t, 1H, J= 8.0 Hz)

^{13}C NMR : 8 13.49, 21.49, 22.37, 33.59, 104.23, 114.72, 115.32, 152.31

Analysis calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88

Found :C, 71.42; H, 7.48; N, 20.81

(3*Z*)-3-Cyano-5-methylhex-3-enenitrile (57e):

This molecule was obtained as a colorless liquid *via* the reaction between 3-acetoxy-4-methyl-2-methylenepentanenitrile (56e) and NaCN following a similar procedure described for the molecule 57a.

Z.E : ≈90:10 (In ^{1}H NMR spectrum of the crude concentrated product, the allylic methylene protons of *[E]*- and [Z]-isomers separate. However, column chromatography (2% EtOAc in hexanes) has provided the pure (Z)-isomer in 65% yield)

IR (neat) : 2256, 2224, 1643 cm^{1}

^{1}H NMR : 6 1.07 (d, 6H, J= 6.8 Hz), 2.85 (m, 1H), 3.28 (d, 2H, J= 1.2 Hz), 6.41 (d, 1H, J= 8.0 Hz)

^{13}C NMR : 8 21.43, 22.17, 31.49, 101.83, 114.78, 115.09, 158.41

Analysts calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88

Found : C, 71.91; H, 7.54; N, 20.78

(3*Z*)-3-Cyanonon-3-enenitrile (57f):

This molecule was prepared by the treatment of 3-acetoxy-2-methyleneoctanenitrile (56f) with NaCN following a similar procedure described for the molecule 57a, as a colorless liquid.

Z:E :95:5

Yield : 81%

IR (neat) : 2256, 2222, 1641 cm^{-1}

^1H NMR : 8 0.91 (t, 3H, J= 6.6 Hz), 1.19-1.61 (m, 6H), 129 & 2.43 (2q, 2H, *J*-7.4 Hz), 129 & 3.32 (2s, 2H), 6.62 (t, 1H, J= 6.0 Hz)

^{13}C NMR : δ 13.78, 17.62. 22.22, 22.31, 27 44, 27.73, 29.07. 31.08, 31.63, 103.93, 114.74, 115.28, 152.57. 153 84

The underlined chemical shift values arise from the minor (*E*)-isomer.

Analysis calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27

Found : C, 73.86; H, 8.74; N, 17.30

Methyl **3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate** (26j):

This compound was obtained via the coupling of 2-methylbenzaldehyde with methyl acrylate in the presence of DABCO following a similar procedure described for the molecule (26a), as a colorless liquid.

Reaction time : 8 days

Yield : 82%

bp : 130-131°C/3 mm

IR (neat) : 3427, 1720, 1631 cm^{-1}

^1H NMR : δ 2.31 (s, 3H), 2.90 (br, 1H), 3.75 (s, 3H), 5.59 (s, 1H), 5.79 (s, 1H),

6.31 (s, 1H), 7.05-7.25 (m, 3H), 7.35-7.51 (m, 1H)

^{13}C NMR : 8 18.83, 51.70, 68.81, 125.66, 125.92, 126.22, 127.55, 130.24, 135.56, 138.90, 141.89, 166.83

Methyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate (58):

This was prepared by the reaction of methyl 3-(4-ethylphenyl)-3-hydroxy-2-methy I enepropanoate (26e) with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule 43, as a colorless liquid.

Yield : 90%

bp : 145-147°C/3.1 mm

IR (neat) : 1745, 1720, 1633 cm^{-1}

^{1}H NMR : 8 1.22 (t, 3H, J= 7.2 Hz), 2.09 (s, 3H), 2.63 (q, 2H, J= 7.2 Hz), 3.71 (s, 3H), 5.87 (s, 1H), 6.39 (s, 1H), 6.66 (s, 1H), 7.17 (d, 2H, J= 9.4 Hz), 7.28 (d, 2H, J= 9.4 Hz)

^{13}C NMR :5 15.34, 21.11, 28.60, 51.95, 73.15, 125.47, 127.75, 128.01, 135.16, 140.01, 144.53, 165.56, 169.44

Methyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (59):

This was prepared by the treatment of methyl 3-hydroxy-2-methylene-3-(2-methyl-phenyl)propanoate **(26j)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule 43, as a colorless liquid.

Yield : 84%

bp : 122-123°C/2.4 mm

IR (neat) : 1746, 1732, 1633 cm^{-1}

^1H NMR : 8 2.10 (s, 3H), 2.42 (s, 3H), 3.73 (s, 3H), 5.71 (s, 1H), 6.42 (s, 1H), 6.89 (s, 1H), 7.15-7.40 (m, 4H)

^{13}C NMR : 8 19.06, 20.87, 51.92, 70.08, 126.00, 126.45, 127.07, 128.30, 130.58, 135.74, 136.55, 139.30, 165.57, 169.35

Methyl (2*E*)-2-acetoxymethyl-3-phenylprop-2-enoate (60):

To a stirred solution of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (43) (1 mmol, 0.234 g) in 2 mL of dichloromethane, was added TMSOTf (11 mol%, 0.02 mL (0.0245 g)) at room temperature. After 2 h, the reaction mixture was diluted with water (3 mL) and extracted with ether (3x10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained was purified by column chromatography (3% EtOAc in hexanes, silica gel) to provide pure product 60 in 73% (0.17 g) yield, as a colorless liquid.

IR (neat) : 1741, 1720, 163 5 cm^{-1}

^1H NMR : 8 2.10 (s, 3H), 3.84 (s, 3H), 4.95 (s, 2H), 7.39 (s, 5H), 7.98 (s, 1H)

^{13}C NMR : 8 20.78, 52.14, 59.26, 126.77, 128.64, 129.37, 129.47, 134.19, 145.25, 167.19, 170.49

Analysis calculated for $C_{13}H_{14}O_4$: C, 66 65, H, 6.02

Found : C, 66 89, H, 6.05

Methyl (2*E*)-2-acetoxymethyl-3-(4-methylphenyl)prop-2-enoate (61)

This was obtained as a colorless liquid *via* TMSOTf mediated isomerization of methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (44) following a similar procedure described for the molecule 60.

Yield : 65%

IR (neat) : 1740, 1718, 1633 cm^{-1}

^1H NMR 5 2 11 (s, 3H), 2.39 (s, 3H), 3.85 (s, 3H), 4.98 (s, 2H), 7.22 (d, 2H, J= 8.0 Hz), 7.30 (d, 2H, J= 8.0 Hz), 7.96 (s, 1H)

^{13}C NMR : δ 20.75, 21.22, 52.03, 59.34, 125.74, 129.37, 129.50, 131.33, 139.87, 145.37, 167.31, 170.49

Analysis calculated for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50

Found : C, 67.86; H, 6.49

Methyl (2*E*)-2-acetoxymethyl-3-(4-isopropylphenyl)prop-2-enoate (62)

This was prepared by the treatment of methyl 3-acetoxy-3-(4-isopropylphenyl)-2-methylenepropanoate (45) with catalytic amount of TMSOTf following a similar procedure described for the molecule 60, as a colorless liquid.

Yield : 83%

IR(neat) : 1741, 1718, 1631 cm^{-1}

^1H NMR 5 1.26 (d, 6H, J= 6.8 Hz), 2.10 (s, 3H), 2.94 (m, 1H), 3.84 (s, 3H), 4.97 (s, 2H), 7.20 -7.45 (m, 4H), 7.96 (s, 1H)

^{13}C NMR : 5 20.82, 23.66, 33.95, 52.07, 59.44, 125.74, 126.80, 129.68, 131.71, 145.44, 150.77, 167.36, 170.58

Analysis calculated for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30

Found : C, 69.30; H, 7 28.

Methyl **(2*E*)-2-acetoxymethyl-3-(4-chlorophenyl)prop-2-enoate** (63):

This was obtained *via* isomerization of methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (46) in the presence of catalytic amount of TMSOTf following a similar procedure described for the molecule 60, as a colorless liquid

Yield : 80%

IR(neat) : 1740, 1720, 1637 cm^{-1}

^1H NMR : 5 2.10 (s, 3H), 3.85 (s, 3H), 4.92 (s, 2H), 7.25-7.46 (m, 4H), 7.91 (s, 1H)

^{13}C NMR : 8 20.82, 52.31, 59.05, 127.32, 129.00, 130.73, 132.62, 135.71, 143.89, 167.02, 170.51

Analysis calculated for $C_{13}H_{13}O_4Cl$: C, 58.11; H, 4.88

Found : C, 58.38; H, 4.86.

Methyl (2*E*)-2-acetoxymethyl-3-(4-ethylphenyl)prop-2-enoate (64):

This was obtained *via* TMSOTf induced isomerization of methyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate (58) following a similar procedure described for the molecule 60, as a colorless liquid

Yield : 88%

IR(neat) : 1741, 1718, 1633 cm^{-1}

^1H NMR : **5 1.25 (t, 3H, J=** 7.6 **Hz), 2.11 (s, 3H),** 2.68 **(q, 2H, J=** 7.6 **Hz), 3.85 (s, 3H),** 4.97 **(s, 2H),** 7.24 **(d, 2H, J= 8 0 Hz),** 7.32 **(d, 2H, J= 8.0 Hz),** 7.97 **(s, 1H)**

^{13}C NMR : **6 15.12,** 20 76,28.60,52.03,59.36,125.66,128.16,129.60, 131.52, 145.43, 146.13, 167.31, 170.53

Analysis calculated for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92

Found : C, 68.54, H, 6 96.

Methyl (2*E*)-2-acetoxymethyl-3-(2-methylphenyl)prop-2-enoate (65):

This was obtained *via* TMSOTf mediated isomerization of methyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (59) following the similar procedure described for the molecule 60, as a colorless liquid

Yield : 77%

IR (neat) : 1740, 1722, 1637 cm^{-1}

^{1}H NMR : 5 2.07 (s, 3H), 2 31 (s, 3H), 3.86 (s, 3H), 4.83 (s, 2H), 7.16-7.37 (m, 4H), 8.06 (s, 1H)

^{13}C NMR : 5 19.81, 20.75, 52.12, 59.36, 125.84, 127.43, 128.54, 129.24, 130.11, 133.46, 136.91, 144.53, 166.95, 170.44

Analysis calculated for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50

Found : C, 67 83; H, 6.55.

3-Hydroxy-3-(4-ethylphenyl)-2-methylenepropanenitrile (55g):

This compound was prepared from 4-ethylbenzaldehyde, acrylonitrile and DABCO following a similar procedure described for the molecule 55a, as a colorless liquid

Reaction time : 40 h

Yield : 79%

bp : 144-146^{0}C/1.9 mm

IR (neat) : 3447, 2229, 1616 cm^{-1}

^{1}H NMR :5 1.24 (t, 3H, J= 7.8 Hz), 2.16(br, 1H), 2.66 (q, 2H, J= 7.8 Hz), 5.27 (s, 1H), 6.03 (s, 1H), 6.11 (s, 1H), 7.26 (m, 4H)

^{13}C NMR 5 15.19, 28.29, 73.50, 116.95, 126.15, 126.35, 128 04, 129.67, 136.34, 144.61

3-Hydroxy-3-(4-isopropylphenyl)-2-methylenepropanenitrile (55h):

This compound was obtained *via* the reaction of 4-isopropylbenzaldehyde with acry-

Jonitrile in the presence of DABCO following a similar procedure described for the molecule 55a, as a colorless liquid.

Reaction time : 48 h

Yield : 82%

bp : 141-143°C/0.8 mm

IR (neat) : 3443, 2229, 1616 cm^{-1}

'H NMR : 8 1.26 (t, 6H, J= 6.8 Hz), 2.38 (br, 1H), 2.93 (sept., 1H, J= 6 8 Hz), 5.26 (s, 1H), 6.02 (s, 1H), 6.11 (s, 1H), 7.28 (m, 4H)

^{13}C NMR : δ 23.83, 33.77, 73.79, 117.08, 126.32, 126.52, 126.85, 129.73, 136.58, 149.53

3-Hydroxy-3-(4-chlorophenyl)-2-methylenepropanenitrile (55i):

This compound was obtained as colorless liquid *via* the coupling of 4-chlorobenzaldehyde with acrylonitrile in the presence of DABCO following a similar procedure described for the molecule **55a.**

Reaction time : 30 h

Yield : 86%

bp : 143-145°C/1 mm

IR (neat) : 3443, 2231, 1616 cm^{-1}

^{1}H NMR : 8 2.68 (s, 1H), 5.29 (s, 1H), 6.04 (s, 1H), 6.11 (s, 1H), 7.34 (m, 4H)

^{13}C NMR : S 73.25, 116.75, 125.87, 127.86, 128.95, 130.44, 134.55, 137.67

3-Hydroxy-2-methylene-3-(2-methylphenyl)propanenitrile (55j):

This compound was prepared from 2-tolualdehyde, acrylonitrile and DABCO following a similar procedure described for the molecule **55a,** as a colorless liquid.

Reaction time : 2 days

Yield : 79%

bp : 136-137°C/2.4 mm

IR (neat) : 3429, 2229, 1622 cm^{-1}

^{1}H NMR : 5 2 33 (s, 3H), 2.75 (br, 1H), 5.48 (s, 1H), 5.98 (s, 1H), 6.02 (s, 1H), 7.20 (m, 3H), 7.38 (m, 1H)

^{13}C NMR : δ 18.80, 70.20, 117.02, 125.15, 126.15, 126.29, 128 38, 130.35, 130.54, 135.39, 136.79

3-Acetoxy-3-(4-ethylphenyl)-2-methylenepropanenitrile (66):

This was prepared by the reaction of 3-hydroxy-3-(4-ethyIphenyI)-2-methylenepropanenitrile (55g) with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a,** as **a** colorless liquid.

Yield : 87%

bp : 138-139°C/1 mm

IR (neat) : 2229, 1749, 1616 cm^{-1}

^1H NMR 5 1.24 (t, 3H, J= 7.6 Hz), 2.17 (s, 3H), 2.66 (q, 2H, J= 7 6 Hz), 5 99 (s, 1H), 6 07 (s, 1H), 6.31 (s, 1H), 7 14-7.39 (m, 4H)

^{13}C NMR : 6 15.34, 20.88, 28.61, 74.37, 116.32, 123.58, 127.12, 128.47, 131 65, 133.12, 145.52, 169.25

3-Acetoxy-3-(4-isopropylphenyl)-2-methylenepropanenitrile (67):

This was obtained as a colorless liquid ***via*** the reaction between 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanenitrile **(55h)** and acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a**

Yield : 81%

bp : 124-126°C/0.3 mm

IR (neat) : 2229, 1747, 1624 cm^{-1}

^1H NMR :6 1.25 (d, 6H, J= 6.8 Hz), 2.17 (s,3H), 2.90 (sept., 1H, J= 6.8 Hz), 5.99 (s, 1H), 6.06 (s, 1H), 6.31 (s, 1H), 7.25 (d, 2H, J= 8 4 Hz), 7 32 (d, 2H, J= 8 4 Hz)

^{13}C NMR : 6 20.86, 23.81,33.86, 74.28, 116.27, 123.46, 127.01, 131.60, 133.04, 150.05, 169.23

3-Acetoxy-3-(4-chlorophenyl)-2-methylenepropanenitrile(68):

This was obtained as a colorless liquid *via* the treatment of 3-hydroxy-3-(4-chloro-

phenyl)-2-methylenepropanenitrile **(55i)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a.**

Yield : 85%

bp : 118-119^{0}C/0.6 mm

IR (neat) :2229, 1751, 1620 cm^{-1}

^{1}H NMR 52 17(s, 3H), 601 (s, 1H), 6.09 (s, 1H), 6 29 (s, **1H),** 7.31-7.46 (m, 4H)

^{13}C NMR : 5 20.76, 73.65, 115.90, 122.89, 128.35, 129.15, 132.11, 134.27, 135.20. 169.01

3-Acetoxy-2-methylene-3-(2-methylphenyl)propanenitrile (69):

This was prepared by the reaction of 3-hydroxy-2-methylene-3-(2-methylphenyl)-propanenitrile **(55j)** with acetyl chloride in the presence of pyridine following a similar procedure described for the molecule **56a,** as a colorless liquid

Yield : 78%

bp : 111-113^{0}C/0.8 mm

IR (neat) : 2229, **1749, 1624 cm^{-1}**

^{1}H NMR : 5 **2.18** (s, 3H), 2.38 (s, 3H), **5.88** (s, **1H),** 6.08 (s, **1H),** 6.54 (s, 1H), 7.10-7 51 **(m,4H)**

^{13}C NMR : 5 1908, 20.75, **71.17,** 116.26, 122.50, 126.56, 126 82, 129 04,

130.76, 131.97, 133.72, 135.75, 169.16

(2*E*)-2-Acetoxymethyl-3-phenylprop-2-enenitrile (70):

To a stirred solution of 3-acetoxy-2-methylene-3-phenylpropanenitrile (56a) (1 mmol, 0.201 g) in dichloromethane (2 mL), was added TMSOTf (11 mol%, 0 02 mL (0 0245 g)) at room temperature After 2 h, the reaction mixture was diluted with water (3 mL) and extracted with ether (3x10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained was purified by column chromatography (3% EtOAc in hexanes, silica gel) to provide pure product 70 in 85% (0.171g) yield, as a colorless liquid.

IR (neat) : 2216, 1747, 1626 cm^{-1}

^1H NMR : 8 2.16 (s, 3H), 4.82 (s, 2H), 7.23 (s, 1H), 7.45 (m, 3H), 7.79 (m, 2H)

^{13}C NMR : δ 20.51, 65.02, 105.88, 117.04, 128.81, 129.02, 130.94, 132.52, 147.05, 169.99

Analysis calculated for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96

Found :C, 71.31; H, 5.53; N, 6.93.

(2*E*)-2-Acetoxymethyl-3-(4-methylphenyl)prop-2-enenitrile (71)

This was obtained *via* TMSOTf catalyzed isomerization of 3-acetoxy-2-methylene-3-(4-methylphenyl)propanenitrile (56b) following a similar procedure described for the molecule 70, as a colorless liquid.

Yield : 68%

IR (neat) : 2214, 1745, 1625 cm^{-1}

^1H NMR 5 2 14 (s, 3H), 2.39 (s, 3H), 4.80 (s, 2H), 7 18 (s, 1H), 7.24 (d, 2H, J= 8.2 Hz), 7 69 (d, 2H, J=8.2 Hz)

^{13}C NMR : δ 20.68, 21.48, 65.36, 104.56, 117.43, 129.22, 129.64, 129.92, 141.76, 147.35, 170.20

Analysis calculated for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51

Found : C, 72.74; H, 6.07; N, 6.55.

(2*E*)-2-Acetoxymethyl-3-(4-ethylphenyl)prop-2-enenitrile (72):

This was obtained as a colorless liquid *via* TMSOTf induced interconversion of 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanenitrile (66) following a similar procedure described for the molecule 70.

Yield : 78%

IR (neat) : 2214, 1747, 1625 cm^{-1}

^1H NMR : 5 1.25 (t, 3H, J= 8.0 Hz), 2.15 (s, 3H), 2.69 (q, 2H, J= 8.0 Hz), 4.81 (s, 2H), 7.20 (s, 1H), 7.28 (d, 2H, J= 8.0 Hz), 7.73 (d, 2H, J= 8.0 Hz)

^{13}C NMR δ 14.97, 20 52, 28.66, 65.21, 104.44, 117.34, 128.30, 129.19, 130.02, 147.22, 147.82, 170.03

Analysis calculated for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11

Found : C, 73.52; H, 6.54; N, 6. 09.

(2*E*)-2-Acetoxymethyl-3-(4-isopropylphenyl)prop-2-enenitrile (73):

This was obtained *via* the isomerization of 3-acetoxy-3-(4-isopropylphenyl)-2-methylenepropanenitrile (67) under the influence of catalytic amount of TMSOTf following a similar procedure described for the molecule 70, as a colorless liquid.

Yield : 74%

IR (neat) : 2214, 1747, 1626 cm^{-1}

^1H NMR : 6 1.27 (d, 6H, J= 8.0 Hz), 2.15 (s, 3H), 2.95 (m, 1H), 4.81 (s, 2H), 7.20 (s, 1H), 7.30 (d, 2H, J= 8.2 Hz), 7.74 (d, 2H, J= 8.2 Hz)

^{13}C NMR : 620.66, 23.61, 34.11, 65.35, 104.67, 117.44, 127.04, 129.37, 130.29, 147.33,152.58, 170.17

Analysis calculated for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76

Found : C, 73.74; H, 7.07; N, 5.73.

(2*E*)-2-Acetoxymethyl-3-(4-chlorophenyl)prop-2-enenitrile (74):

This was obtained *via* the interconversion of 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanenitrile (68) in the presence of TMSOTf (cat.) following a similar procedure described for the molecule 70, as a colorless liquid.

Yield : 65%

IR (neat) : 2212, 1743, 1624 cm^{-1}

^{1}H NMR : 8 2.15 (s, 3H), 4.80 (s, 2H), 7.17 (s, 1H), 7.42 (d, 2H, J= 8.8 Hz), 7.72 (d, 2H, J= 8.8 Hz)

^{13}C NMR : δ 20.71, 65.04, 106.75, 116.93, 129.34, 130.45, 131.10, 137.23, 145.72, 170.20

Analysis calculated for $C_{12}H_{10}NO_2Cl$: C, 61.16; H, 4.28; N, 5.94

Found : C, 61.02; H, 4.27; N, 5.99.

(2*E*)-2-Acetoxymethyl-3-(2-methylphenyl)prop-2-enenitrile (75):

This was obtained as a colorless liquid *via* TMSOTf catalyzed isomerization of 3-acetoxy-2-methylene-3-(2-methylphenyl)propanenitrile (69) following a similar procedure described for the molecule 70.

Yield : 84 %

IR (neat) 2218, 1747, 1624 cm^{-1}

^{1}H NMR : δ 2.16 (s, 3H), 2.35 (s, 3H), 4.83 (s, 2H), 7.09-7.50 (m, 4H), 7.83 (m, 1H)

^{13}C NMR : δ 19.58, 20.65, 64.89, 107.95, 116.87, 126.32, 127.79, 130.46, 130.59, 131.83, 137.26, 146.13, 170.15

Analysis calculated for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51

Found : C, 72.87; H, 6.12; N, 6.49.

Ethyl (4-methylphenyl)glyoxylate (81b):

This compound was prepared according to the literature method

To a solution of diethyl oxalate (150 mmol, 21.921 g) in THF (200 mL), was added a solution of (4-methylphenyl)magnesium bromide (50 mmol) [prepared from 4-bromotoluene (50 mmol, 8.552 g) and magnesium turnings (50 mmol, 1.215 g)] in THF slowly at -10°C over a period of 1 h The reaction mixture was quenched immediately with 2N HCl solution to a pH of 4 0 and extracted with dichloromethane (3x50 mL). Combined organic layers were dried over anhydrous Na_2SO_4. Removal of solvent followed by distillation of the residue afforded the pure product **81b** in 63% (6 04 g) yield as colorless liquid.

bp : 97-98°C/0.6 mm

IR(neat) :1738,1682 cm^{-1}

^1H NMR : 5 1.42 (t, 3H, J= 6 8 Hz), 2.44 (s, 3H), 4.45 (q, 2H, J= 6 8 Hz), 7.31 (d, 2H, J= 7.8 Hz), 7.91 (d, 2H, J= 8.6 Hz),

^{13}C NMR :8 14.06,21.82,62.19, 129.59, 130.10, 146.23, 164.04, 186.11

Ethyl (4-bromophenyl)glyoxylate (81c):

This compound was prepared by treatment of (4-bromophenyl)magnesium bromide with diethyl oxalate following a similar procedure described for the molecule **81b,** as a colorless liquid.

Yield : 43%

bp : 116-117^{0}C/0.2 mm

IR(neat) : 1736, 1693 cm^{-1}

'H NMR : 5 1.42 (t, 3H, J= 7.0 Hz), 4.44 (q, 2H, J= 7.0 Hz), 7.66 (d, 2H, J= 8.6 Hz), 7.90 (d, 2H, J= 8.6 Hz)

^{13}C NMR : 8 14.06, 62.46, 128.86, 130.40, 131.39, 132.28, 163.17, 185.04

Ethyl (4-methoxyphenyl)glyoxylate (81d):

This compound was prepared as a colorless liquid by the reaction of (4-methoxyphenyl)magnesium bromide with diethyl oxalate following the similar procedure described for the molecule **81b**

Yield : 58%

bp : 114-115^{0}C/0.3 mm

IR(neat) :1736,1676 cm^{-1}

^{1}H NMR : 5 1.42 (t, 3H, J= 7.0 Hz), 3.89 (s, 3H), 4 43 (q, 2H, J= 7 0 Hz), 6 97 (d, 2H, J= 8.8 Hz), 8.01 (d, 2H, J= 8.8 Hz)

^{13}C NMR : 5 14.06, 55.58, 62.06, 114 24, 125 57, 132.48, 164.18, 165.03, 184.86

Ethyl (naphth-1-yl)glyoxylate (81e):

This compound was prepared by the reaction between α-naphthylmagnesium bromi-

de and diethyl oxalate following a similar procedure described for the molecule **81b,** as a colorless liquid

Yield : 40%

bp : 128-130^{0}C/0.07 mm

IR(neat) : 1736, 1678 cm^{-1}

^{1}H NMR : 5 1.43 (t, 3H, J= 6 8 Hz), 4.47 (q, 2H, J= 6.8 Hz), 7.41-8.12 (m, 6H), 9.04 (m, 1H)

^{13}C NMR : 8 14.08, 62.37,124.25, 125.53, 126.98, 127.88, 128.13, 128.73, 129.21, 130.91, 133.93, 135.80, 164.64, 188.88

Ethyl 2-hydroxy-3-methylene-4-oxo-2-phenylpentanoate (82a):

To a stirred solution of ethyl phenylglyoxylate **(81a)** (1 mmol, 0.178 g) and methyl vinyl ketone (mvk) (3 mmol, 0.210 g) in dichloromethane (2 mL), was added dimethyl sulfide (10mol%, 0.1 mL of 0.1 M solution in CH_2Cl_2) followed by $TiCl_4$ (1 mmol, 1 mL of 0.1 M solution in CH_2Cl_2) at room temperature After stirring for 1 h, the reaction mixture was diluted with water (5 mL) and extracted with ether (3x10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (5% EtOAc in hexanes, silica gel) followed by crystallization from 10% EtOAc in hexanes to furnish the pure molecule **82a** in 73% (0.181 g) yield, as a colorless solid.

mp : 85°C

IR (KBr) : 3481, 1722, 1668 cm^{-1}

^1H NMR 5 1.26 (t, 3H, J=7.0 Hz), 2.42 (s, 3H), 4.23 (q, 2H, J=7.0 Hz), 4.34 (s, 1H), 5.53 (s, 1H), 6.21 (s, 1H), 7.31-7.48 (m, 3H); 7 56-7.69 (m, 2H)

^{13}C NMR 6 13.90,26.31,62.19,78.67, 126.68, 128.13, 129.13, 137.96, 151.15, 173.35, 200.11

Analysis Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50

Found :C, 67.55; H, 6 51.

Ethyl 2-hydroxy-3-methylene-2-(4-methylphenyl)-4-oxopentanoate (82b):

This was prepared by the reaction of ethyl (4-methylphenyl)glyoxylate **(81b)** with methyl vinyl ketone (mvk) in the presence of TiCU under the influence of catalytic amount of dimethyl sulfide following a similar procedure described for the molecule **82a,** as a colorless solid

Yield : 51%

mp : 121-123°C

IR (KBr) : 3456, 1724, 1668 cm^{-1}

^1H NMR 5 1.25 (t, 3H, J= 7.4 Hz), 2.35 (s, 3H), 2.40 (s, 3H), 4.23 (q, 2H, J= 7.4 Hz), 4.30 (s, 1H), 5.56 (s, 1H), 6.19 (s, 1H), 7.18 (d, 2H, J= 8.0 Hz), 7.47 (d, 2H, J= 8.0 Hz)

^{13}C NMR : 8 13.97, 21.02, 26.38, 62.18, 78.74, 126.69, 128.91, 135.16, 137 97,

151.43, 173.52, 200 19

Analysis calcd for $C_{15}H_{18}O_4$: C, 68 69; H, 6 92

Found : C, 68 44; H, 6.91

Ethyl **2-(4-bromophenyl)-2-hydroxy-3-methylene-4-oxopentanoate** (82c):

This was obtained *via* the dimethyl sulfide catalyzed coupling of ethyl (4-bromophenyl)glyoxylate (81c) with methyl vinyl ketone (mvk) in the presence of $TiCl_4$ following a similar procedure described for the molecule 82a, as a colorless solid

Yield : 62%

mp : 82-83°C

IR (KBr) : 3450, 1730, 1670 cm^{-1}

^1H NMR : 5 1.26 (t, 3H, J= 7.0 Hz), 2.42 (s, 3H), 4.23 (q, 2H, J= 7.0 Hz), 4.34 (s, 1H), 5.55 (s, 1H), 6.23 (s, 1H), 7.51 (s, 4H)

^{13}C NMR : 8 13.89, 26.25, 62.37, 78.39, 122.48, 128.64, 128.88, 131.26, 137.31, 150.88, 172.89, 199.78

Analysis calcd. for $C_{14}H_{15}O_4Br$: C, 51.40; H, 4 62

Found :C, 51.65; H, 4.64

Ethyl **2-hydroxy-2-(4-methoxyphenyl)-3-methylene-4-oxopentanoate (82d):**

This was prepared by the reaction between ethyl (4-methoxyphenyl)glyoxylate (81d)

and methyl vinyl ketone (mvk) under the catalytic influence of dimethyl sulfide in the presence of TiCU following a similar procedure described for the molecule **82a,** as a colorless solid.

Yield : 64%

mp : 68-69°C

IR (KBr) : 3462, 1724, 1670 cm^{-1}

^{1}H NMR 8 1.25 (t, 3H, J= 6.8 Hz), 2.40 (s, 3H), 3.81 (s, 3H), 4 25 (q, 2H, J= 6.8 Hz), 4.29 (s, 1H), 5.57 (s, 1H), 6.19 (s, 1H), 6.89 (d, 2H, J= 9.4 Hz), 7.50 (d, 2H, J= 9.4 Hz)

^{13}C NMR :5 13.82,26 23,55.10,61.98,78.29, 113.44, 127.87, 128.87, 129.92, 151.30, 159.41, 173.41,200.07

Analysis calcd. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52

Found : C, 64.82; H, 6.52

Ethyl 2-hydroxy-3-methylene-2-(naphth-l-yl)-4-oxopentanoate (82e):

This was obtained as a colorless solid *via* the coupling of ethyl (naphth-1-yl)glyoxylate **(81e)** with methyl vinyl ketone (mvk) in the presence of $TiCl_4$, under the influence of catalytic amount of dimethyl sulfide following a similar procedure described for the molecule **82a.**

Yield : 43%

mp ; 64-66°C

IR (KBr) : 3474, 1747, 1674 cm^{1}

^{1}H NMR : 8 1.24 (t, 3H, J= 7.4 Hz), 2.51 (s, 3H), 4.30 (q, 2H, J= 7.4 Hz), 5.07 (s, 1H), 5.41 (s, 1H), 6.18 (s, 1H), 7.37- 7.65 (m, 4H), 7.83 (m, 2H), 8.21 (m, 1H)

^{13}C NMR : 8 13.93, 27.05, 62.40, 81.95, 124.85, 125.50, 127.63, 128.81, 129.52, 129.85, 131.21, 134.41, 134.72, 148.77, 173.37,201.68

Analysis calcd. for $C_{18}H_{18}O_4$: C, 72 47; H, 6.08

Found :C, 72.81; H, 6.11

Ethyl 2-hydroxy-3-methylene-4-oxo-2-phenylhexanoate (83):

This was obtained *via* the dimethyl sulfide catalyzed coupling of ethyl phenylglyoxylate **(81a)** with ethyl vinyl ketone (evk) in the presence of $TiCl_4$, following a similar procedure described for the molecule **82a,** as a colorless solid.

Yield : 40%

mp : 71-72^{0}C

IR (KBr) : 3477, 1718, 1670 cm^{-1}

^{1}H NMR : 8 1.14 (t, 3H, J= 6.8 Hz), 1.25 (t, 3H, J= 6.8 Hz), 2.78 (q, 2H, J= 6.8 Hz), 4.24 (q, 2H, J= 6.8 Hz), 4.38 (s, 1H), 5.48 (s, 1H), 6.19 (s, 1H), 7.30-7.67 (m, 5H)

^{13}C NMR : 5 **8.11,** 13.95, 31.53, 62.23, 78.99,126.75,127.86,128.16,138.00,

150.74, 173.48,203.09

Analysis calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92

Found : C, 68.42; H, 6.89

Ethyl 2-(4-bromophenyl)-2-hydroxy-3-methylene-4-oxohexanoate (84):

This was obtained as a colorless solid *via* the coupling of ethyl (4-bromophenyl)glyoxylate **(81c)** with ethyl vinyl ketone (evk) under the catalytic influence of dimethyl sulfide in the presence of TiCU, following a similar procedure described for the molecule **82a.**

Yield : 42%

mp : 87°C

IR (KBr) : 3487, 1722, 1674 cm^{-1}

^1H NMR 5 1.13 (t, 3H, J= 7.0 Hz), 1 25 (t, 3H, J= 7.4 Hz), 2 78 (q, 2H, J= 7 4 Hz), 4.24 (q, 2H, J= 7.0 Hz), 4.37 (s, 1H), 5.49 (s, 1H), 6.20 (s, 1H), 7.50 (s,4H)

^{13}C NMR : 5 8.13, 13.99, 31.55, 62.49, 78.72, 122.58, 127.76, 128.70, 131.35, 137.21, 150.46, **173 11, 202** 89

Analysis calcd. for $C_{15}H_{17}O_4Br$: C, 52.80; H, 5.02

Found :C, 52.61; H, 5.04

(-)-Menthyl phenylglyoxylate (86):

This molecule was prepared according to the literature procedure.[148]

A solution of (-)-(1R,2S,5R)-menthol (20 mmol, 3.125 g), benzoyl formic acid (85a) (22 mmol, 3.302 g) and p-toluenesulfonic acid (0.190 g) in dry benzene (50 mL) was heated under reflux with azeotropic removal of water for 3 h. The reaction mixture was cooled, diluted with ether (30 mL) and washed with saturated K2CO3 solution and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated The crude product thus obtained was purified by column chromatography (silica gel, 5% EtOAc in hexanes) followed by crystallization from hexanes to provide the pure molecule 86 in 76% (4.358 g) yield, as a crystalline solid.

$[\alpha]_D^{25}$: -46.26 (c 1.3, ethanol) {Lit.[148] $[\alpha]_D^{25}$ -46.2 (c 0.66, ethanol)}

mp : 70-71^{0}C [Lit.[148] 71-72^{0}C]

IR(KBr) :1734,1685 cm^{-1}

^{1}H NMR : 5 0.72-2.2.7 (m, 18H), 4.99 (m, 1H), 7.41-7.65 (m, 3H), 7.90-8.01 (m, 2H)

^{13}C NMR : δ 16 18, 20.62, 21.92, 23.40, 26.20, 31.52, 34.06, 40.64, 46.85, 76.88, 128.88, 129.83, 132.58, 134.75, 163.88, 186.73

Menthyl 2-hydroxy-3-(methoxycarbonyl)-2-phenylbut-3-enoate (87):

A mixture of menthyl phenylglyoxylate (86) (1 mmol, 0.288 g) and methyl acrylate (2 mmol, 0.172 g) and DABCO (0.3 mmol, 0.033 g) was kept at room temperature

for 8 days. The reaction mixture was diluted with ether (10 mL) and washed successively with dil. HC1, water and saturated aqueous $NaHCO_3$ solution. Organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 5% EtOAc/hexanes) to provide the desired product 87 in 48% (0.181 g) yield {0.130 g (45%) of starting material 86 (unreacted) was recovered}, as a colorless oil.

de : 22%

$[\alpha]_D^{25}$: -31.6 (c 0.64, $CHCl_3$)

IR (neat) : 3493, 1732, 1631 cm^{-1}

^1H NMR : 5 0.57-2.06 (m, 18H), 3.79 (s,3H), 4.36 & 4 41 (2s, 1H), 4.70 (m, 1H), 5.38 & 5 44 (2s, 1H), 6.38 & 6.39 (2s, 1H), 7.35 (m, 3H), 7.62 (m, 2H)

^{13}C NMR : 6 15.54, 15.88, 20.63, 20.77, 21.91, 22.89, 23.19. 25.60, 31.35, 34.11, 34.20. 40.14, 47.07, 51.94, 76.87, 76.99. 78.87. 78.96, 126.90. 126.96, 127.85, 128.14, 128.69, 137.90. 138.13, 142.93. 143.00, 166.73. 172.58. 172.83

The underlined chemical shift values are due to the minor diastereomer.

Analysis calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07

Found : C, 70.37; H, 8.11

Menthyl 3-cyano-2-hydroxy-2-phenylbut-3-enoate (88):

This was obtained *via* the coupling of menthyl phenylglyoxylate (86) with acrylonitrile in the presence of DABCO following a similar procedure described for the molecule 87, as a colorless oil.

Reaction time : 7 **d**

de : ≈10%

Yield : 82%

$[\alpha]_D^{25}$ -63.1 (c 0 58, $CHCl_3$)

IR (neat) : 3474, 2229, 1728, 1620 cm^{-1}

^1H NMR (mixture of diastereomers) : 8 0.59-2.25 (m, 18H), 4.20 & 4.27 (2s, 1H), 4.90 (m, 1H), 6.15 & 6.18 (2s, 1H), 6.23 & 6.24 (2s, 1H), 7.28-7.65 (m, 5H)

^{13}C NMR (mixture of diastereomers) : 8 15.63, 15.83, 20.61, 20.69, 21.87, 22.98, 23.08, 25.73, 25.98, 31.50, 33.99, 40.26, 46.92, 78.56, 78.69, 78.97, 79.09, 116.91, 125.45, 125.59, 126.33, 126.54, 128.45, 128.57, 128.99, 129.88, 132.40, 132.75, 137.86, 171.26, 171.38.

Analysis calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10

Found : C, 74.20; H, 7.95; N, 4.12

(±)-*trans*-2-Phenylcyclohexan-1-ol (±89):

This molecule was prepared according to the procedure reported by Whitesell *et al.*[146]

To a solution of phenylmagnesium bromide (150 mmol) [prepared from bromoben-

zene (150 mmol, 23.553 g) and magnesium turnings (150 mmol, 3.646 g)] in dry THF (150 mL) at -20^0C, copper (I) chloride (7 mmol, 0.692 g) was added with stirring. After 10 minutes, a solution of cyclohexene oxide (125 mmol, 12.268 g) in dry THF (10 mL) was added slowly at the same temperature. The reaction was allowed to warm to 0°C. After stirring for 2 h at 0°C, the reaction mixture was quenched with saturated $(NH_4)_2SO_4$ solution (50 mL). Layers were separated and the organic layer was washed with saturated $(NH_4)_2SO_4$ solution until the aqueous layer was no longer blue. The combined aqueous layer was extracted with ether (3x20 mL) The organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrated The solid obtained was crystallized from pentane to furnish the racemic alcohol (±)-89 as a crystalline solid in 78% (17.12 g) yield.

mp : 56-57^{0}C [Lit.[146] mp 56-57°C]

IR (KBr) :3306 cm^{-1}

^{1}H NMR : 6 1.22-2.20 (m, 9H), 2.42 (m, 1H), 3.67 (m, 1H), 7.29 (m, 5H)

^{13}C NMR : 6 25.01, 25.99, 33.30, 34.42, 53.09, 74.18, 126.61, 127.85, 128.56, 143.39

(±)-*trans*-1-Acetoxy-2-phenylcyclohexane (±90):

To a stirred solution of (±)-*trans*-2-phenylcyclohexan-1-ol (±89) (75 mmol, 13.20 g), pyridine (150 mmol, 11.865 g) and 4-dimethylaminopyridine (3 mmol, 0.366 g) in

dichloromethane (75 mL) at 0°C was added acetic anhydride (150 mmol, 15.313 g) slowly at the same temperature. After stirring for 2 h at room temperature, the reaction mixture was poured into ice cold solution of 6N HCl (50 mL) and extracted with ether (3x20 mL). The combined organic layer was washed with 2N HCl solution, saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4 Solvent was evaporated and residue obtained was purified by column chromatography (10% EtOAc in hexanes) to provide pure racemic acetate (±)-90 as a colorless liquid in 88% (14.36 g) yield.

IR(neat) :1736 cm^{-1}

^1H NMR 6 1.23-2.18 (m, 11H), 2.64 (m, 1H),4.91 (m, 1H), 7.23 (m, 5H)

^{13}C NMR : 5 20.85, 24.74, 25.81, 32.31, 33.77, 49.71, 75.83, 126.34, 127.45, 128.18, 143.07, 170.21

Preparation of pig liver acetone powder (PLAP):

This was prepared according to the procedure reported by Ohno *et al.*[145]

Fresh pig liver (500 g) was homogenized in 2 L of chilled acetone using kitchen juicer. The homogenized brown mass obtained after filtration was further washed with chilled acetone (2 L) and air dried at room temperature. The dried mass was then powdered using juicer. Fibrous material was removed by sieving to furnish about 100

g of PLAP as a fine powder. This powder can be stored for 2-3 months in refrigerator without any significant loss of activity.

Enzymatic **hydrolysis of (±)-*trans*-1-acetoxy-2-phenylcyclohexane (±90):**

(−)-(1R,2S)-2-Phenylcyclohexan-1-ol (−89):

To a stirred solution of **(±)-*trans*-1-acetoxy-2-phenylcyclohexane** (±90) (50 mmol, 10.900 g) in ether (50 mL), was added 400 mL of 0.5 M, pH 8.0 KH_2PO_4/K_2HPO_4 aqueous buffer at room temperature. After 10 minutes, pig liver acetone powder (PLAP) (8 g) was added and the stirring was continued for 10 days (35:65 conversion ratio by HPLC). The reaction was quenched by adding 2N HC1 to pH 4.0. Then NaCl solid (5 g) and dichloromethane (100 mL) were added and the mixture was stirred for 30 minutes. The PLAP residue was removed by filtration with suction and the layers were separated. The aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product obtained was purified by column chromatography (10% EtOAc in hexanes) to furnish 6.33 g of acetate and 2.47 g of (-)-alcohol. The (-)-alcohol {(-)-**89**} obtained was crystallized from pentane as a crystalline solid in >99% ee.

Yield : 80% (based on conversion ratio)

$[\alpha]_D^{25}$: -58.3 (c 0.98, MeOH) {Lit.[146] $[\alpha]_D^{20}$ -58.4 (c 10, MeOH) ee 100%}

mp :63-64°C [Lit.[146] mp 64-65°C]

IR, ^{1}H NMR and ^{13}C NMR spectra are identical with that of the racemic alcohol **89**

{(lR,2S)-2-Phenylcyclohexyl} phenylglyoxylate (91):

This was obtained as a crystalline solid *via* the reaction between **(1R,2S)-2-phenylcyclohexan-1-ol** (-89) and benzoyl formic acid in the presence of catalytic amount of **p-toluenesulfonic** acid following a similar procedure described for the molecule **86**

Yield : 73%

$[\alpha]_D^{25}$: **-14.54 (c** 0.70, ethanol) [Lit.[150] $[\alpha]_D^{25}$ -14.68 (c 1.97, ethanol)]

mp 69^0C [Lit.[150] mp 66-68°C]

IR(KBr) : 1736, 1687 cm^{-1}

^{1}H NMR 5 **1.30-2.35** (m, 8H), 2.76 (m, 1H), 5.42 (m, 1H), 7.17-7.59 (m, 10H)

^{13}C NMR : 5 24 75, **25.59,** 32 17, 34.08, 49.85, 78.36, 126.79, 127.82, 128.66, 129 68, 132.11, 134.39, 142.69, 163.81, 187.06

{(1R,2S)-2-Phenylcyclohexyl} 2-hydroxy-3-(methoxycarbonyl)-2-phenylbut-3-enoate (92):

This was obtained *via* the Baylis-Hillman coupling of {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate (91) with methyl acrylate in the presence of DABCO following a similar procedure described for the molecule 87, as a colorless solid.

Reaction time : 14 d

de : 80%

Yield : 44% {43% of starting material 91 (unreacted) was recovered}

r 1 ^{25} : +9.73 (c 0.60, $CHCl_3$)

mp : 103-105^{0}C

IR (KBr) : 3499, 1728, 1631 cm^{-1}

^{1}H NMR : 8 1.15-2.05 (m, 7H), 2.38 (m, 1H), 2.75 (m, 1H), 150, 3.78 (2s, 3H), 4.11. 4.24 (2s. 1H), 5.07(s, 1H), 5 13 (m, 1H), 6JL2, 6 26 (2s, 1H), 6.86-7.45 (m, 10H)

^{13}C NMR : δ 24.55, 25.72, 31.48, 31.70. 33 99. 34.81, 49 28. 49.50, 51.95, 78.63. 78.85. 79.13. 126.41, 126.67, 127.41, 127.60, 127.85. 128.20. 128.32. 128.62, 128.80, 13769, 142.50. 142 58. 142 88, 143.08, 166.19. 166.46. 172.07. 172.82

The underlined chemical shift values are due to the minor diastereomer

Selective Crystallization of 92:

Selective crystallization of the molecule 92 (0.25 mmol, 0.099 g) was carried out from 10% EtOAc in hexanes to provide the single diastereomer (92*) (0.055 g, 56% yield) as evidenced by one singlet for the olefinic proton ***cis*** to ester group in ^{1}H NMR spectrum.

de : 100%

$[\alpha]^{25}$: +46.03 (c 0.20, $CHCl_3$)

mp : 151-152°C

IR (KBr) : 3493, 1730, 1631 cm^{-1}

^1H NMR : 5 1.15-2.11 (m, 7H), 2.38 (m, 1H), 2.75 (m, 1H), 3.77 (s, 3H), 4.10 (s, 1H,), 5 03-5.21 (m, 2H), 6.25 (s, 1H), 6.85-7.40 (m, 10H)

^{13}C NMR : 6 24.70, 25.87, 31.64, 34.96, 49.67, 52.09, 78.79, 79.30, 126.57, 126.81, 127.57, 127.75, 127.99, 128.76, 128.99, 137.84, 143.00, 143.22, 166.62, 172.98

Analysis calcd for $C_{24}H_{26}O_5$: C, 73.08; H, 6.64

Found : C, 73 29; H, 6.66

{(1R,2S)-2-PhenylcyclohexyI} 2-hydroxy-3-(ethoxycarbonyl)-2-phenylbut-3-enoate (93):

This was obtained *via* the reaction of {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate (91) with ethyl acrylate in the presence of catalytic influence of DABCO following a similar procedure described for the molecule 87, as a colorless semisolid

Reaction time : 14 d

de : 44%

Yield : 47% {40% of starting material 91 (unreacted) was recovered}

$[\alpha]_D^{25}$: +4.26 (c 1.26, $CHCl_3$)

IR (CH_2Cl_2) : 3499, 1728, 1631 cm^{-1}

^{1}H NMR : 5 1.14-2.50 (m, 11H), 2.35 (m, 1H), 2.75 (m, 1H), 195 & 4.27 (2m, 2H), 4.92-5.25 (m, 2H), 6.16& 6 25 (2s, 1H), 6.86-7.46 (m, 10H)

^{13}C NMR :5 13.78. 14.07, 24.47,25.67, 31.43, 31.63. 33.86. 34.74. 49.17. 49.47, 60.87. 61.01, 78.63, 78.69. 78.99, 126.23. 126.37, 126.58, 127.35, 127.49, 127.76. 127.91. 128.10, 128.25. 128.53, 137.69, 137.78. 142.50. 142.70. 143.01, 143.12, 165.80. 166.00, 172.03. 172.76

The underlined chemical shift values arise from the minor diastereomer

Analysis calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91

Found : C, 73.38; H, 6.88

(4-Methylbenzoyl)formic acid (85b):

To a stirred solution of KOH (1.122 g) in methanol (5 mL), was added ethyl (4-methylbenzoyl)formate (10 mmol, 1.920 g) at room temperature. After 2 h, methanol was distilled off and the residue was acidified with dil. HC1 and extracted with ethyl acetate (4x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product obtained was crystallized in 20% EtOAc in hexanes to give the desired acid **85b** in 68 % (1.123 g) yield, as a colorless solid.

m.p. : 90-91°C [Lit.[151] mp 91-93°C]

IR (KBr) : 3450, 1700, 1643 cm^{-1}

^{1}H NMR : 5 2.47 (s, 3H), 6.07 (br, 1H), 7.34 (d, 2H, J= 8.2 Hz), 8.31 (d, 2H, J=

8.2 Hz)

^{13}C NMR : 8 21.94, 129.34, 129 74, 131 12, 147.18, 164 09, 184.58

{(1R,2S)-2-Phenylcyclohexyl} (4-methylphenyl)glyoxylate (94):

This was prepared by the reaction of (lR,2S)-2-phenylcyclohexan-l-ol (-89) with (4-methylbenzoyl)formic acid in the presence of p-toluenesulfonic acid following a similar procedure described for the molecule 86, as a crystalline solid

Yield : 82%

$[\alpha]_D^{25}$: -18.45 (c 0 76, $CHCl_3$)

mp : 67^{0}C

IR (KBr) : 1730, 1674 cm^{-1}

^{1}H NMR : 8 1.22-2.33 (m, 8H), 2.37 (s, 3H), 2.72 (m, 1H), 5.41 (m, 1H). 7.04 (d, 2H, J= 8.4 Hz), 7 13 (d, 2H, J= 8.4 Hz), 7.22-7.44 (m, 5H)

^{13}C NMR : 8 21.79, 24.75, 25 59, 32.16, 34.11, 49.83,78.16, 126.76, 127.81, 128 65, 129.37, 129.83, 142.72, 145.65, 164.00, 186.72

{(1R,2S)-2-Phenylcyclohexyl} 2-hydroxy-3-(methoxycarbonyl)-2-(4-methylphenyl)-but-3-enoate (95):

This was obtained *via* the coupling of {(1R,2S)-2-phenylcyclohexyl} (4-methylphenyl)glyoxylate (91) with methyl acrylate in the presence of DABCO following a similar procedure described for the molecule 87, as a colorless solid.

Reaction time : 14 d

de : 66%

Yield : 25% {65% of starting material 94 (unreacted) was recovered}

IR (KBr) : 3510, 1740, 1625 cm^{-1}

^1H NMR : 5 1.20-2.51 (m, 11H), 2.75 (m,1H), 3.40& 3.77 (2s, 3H), 4.07 & 4.19 (2s, 1H), 5.16 (m, 2H), 6.15 &6.25 (2s, 1H), 6.70-7 41 (m, 9H)

The underlined chemical shift values are due to the minor diastereomer.

Since this molecule contains ≈5-8% unseparable impurities (^1H NMR), it was selectively crystallized to obtain the pure single diastereomer.

Selective Crystallization of **95**

Crystallization of the molecule 95 (0.2 mmol, 0.082 g) from 10% EtOAc in hexanes provided the single diastereomer (95*) (0.030 g, 37% yield) as evidenced by ^1H NMR and ^{13}C NMR spectral data.

$[\alpha]_D^{25}$: +28.36 (c 0.28, $CHCl_3$)

mp : 142-143^{0}C

IR (KBr) : 3516, 1743, 1630 cm^{-1}

^1H NMR : 5 1.21-2.02 (m, 7H), 2.23 (s, 3H), 2.30 (m, 1H), 2.70 (m, 1H), 3.76 (s, 3H), 4.06 (s, 1H), 5.11 (m, 2H), 6.24 (s, 1H), 6.70 (m, 4H), 7.11-7.39 (m, 5H)

^{13}C NMR : 5 21.06, 24.70, 25.88, 31.64, 34.97, 49.65, 52.06, 78.71, 79.13, 126.46, 126.69, 127.55, 128.70, 128.95, 134.90, 137.37, 143.04, 143.23, 166.66, 173.08

Analysis calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91

Found : C, 73 75; **H,** 6.89

{(1R,2S)-2-Phenylcyclohexyl} 3-cyano-2-hydroxy-2-phenylbut-3-enoate (96):

This was prepared by the reaction of {(1R,2S)-2-phenylcyclohexyl} phenylglyoxylate (91) with acrylonitrile in the presence of DABCO following a similar procedure described for the molecule 87, as a colorless oil.

Reaction time : 7 d

de : ≈10%

Yield : 84%

$[\alpha]_D^{25}$:+6 70 (c 0.63, $CHCl_3$)

IR (neat) : 3472, 2230, 1730, 1602 cm^{-1}

^1H NMR : 5 1.15-2.41 (m, 8H), 2.81 (m, 1H), 3.94 (s. 1H), 5.21 (m, 1H), 5 54 (mixture of & 5.70 (2s, 1H), 5.92 & 6.09 (2s, 1H), 6.75-7.47 (m, 10H) diastereomers)

^{13}C NMR : 8 24.61, 25.56, 31.79, 34.04, 34.39, 49 45,49.69,78.24,78 75, 80.58, 80.98, 116.79, 116.92, 124.96, 125.57, 126.15, 126.22, 126.84, 127.59, 127.66, 128.45, 128.52, 128.59, 128.72, 128 85. 131.63, 132.57, 137.20, 137.98, 142.34, 142 66, 170.94, 171.32

(mixture of diastereomers)

Analysis calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6 41; N, 3.88

Found . C, 76.71; H, 6.40; N, 3.90

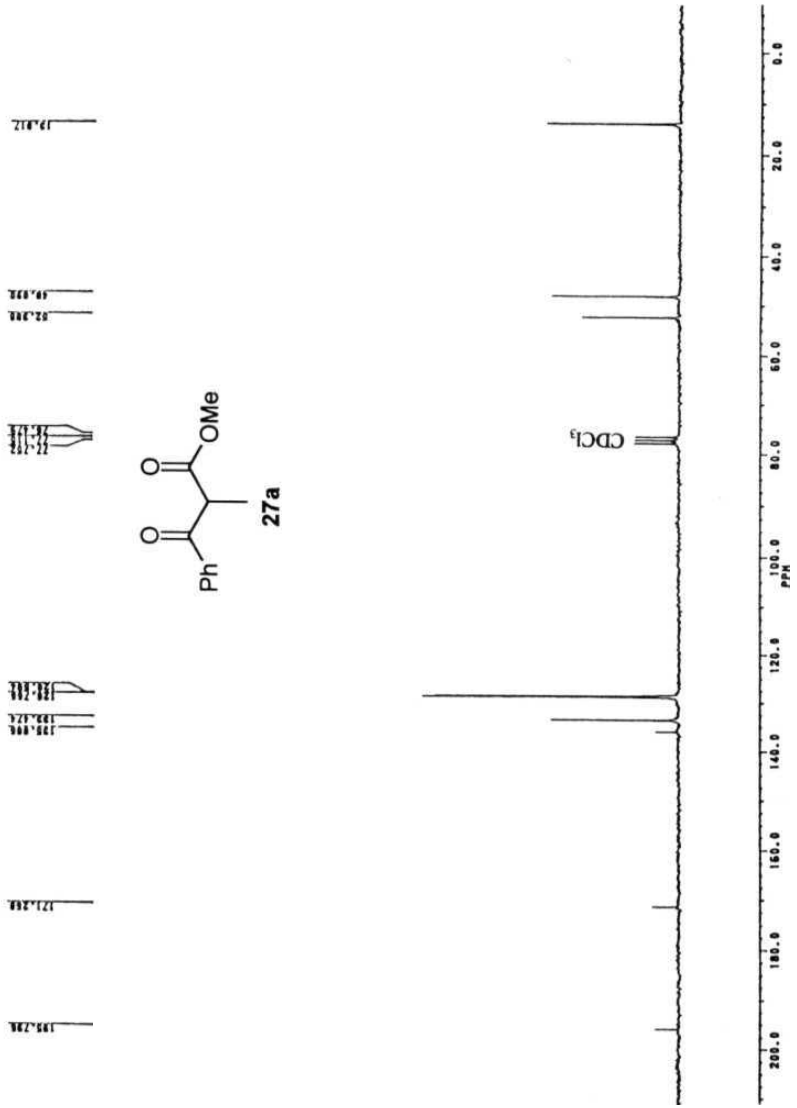


Fig. 1: ^{13}C NMR spectrum of **27a**

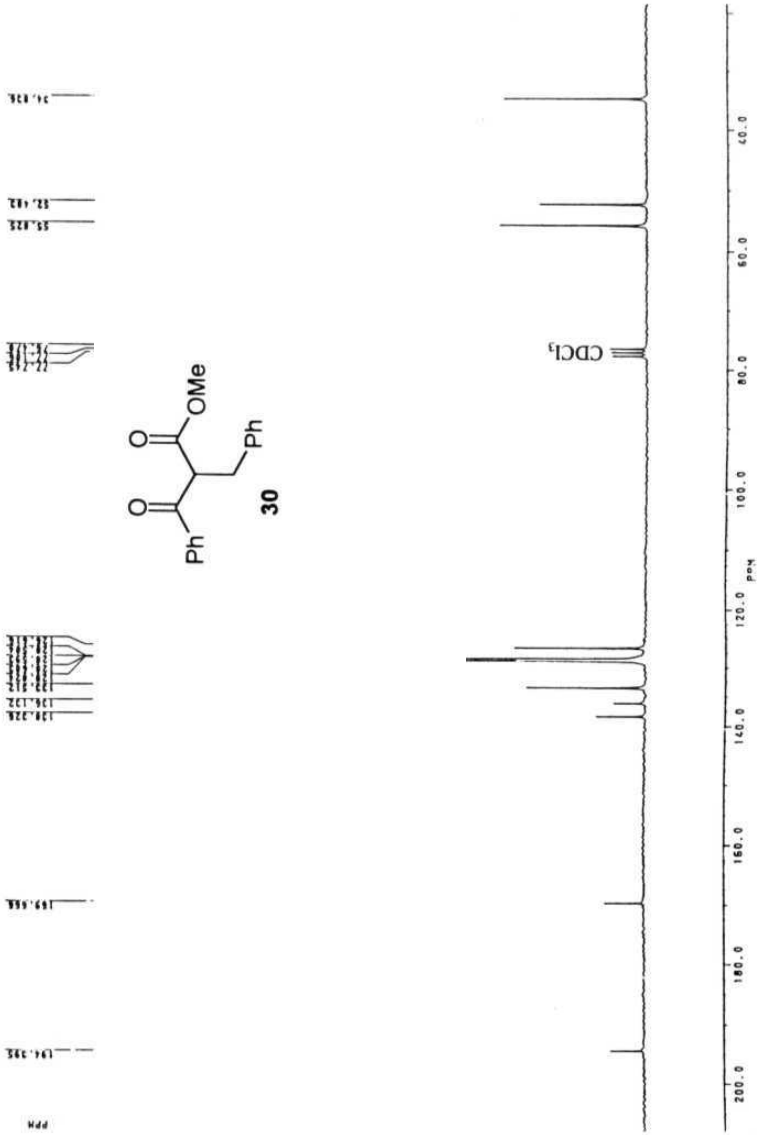


Fig. 2: ^{13}C NMR spectrum of **30**

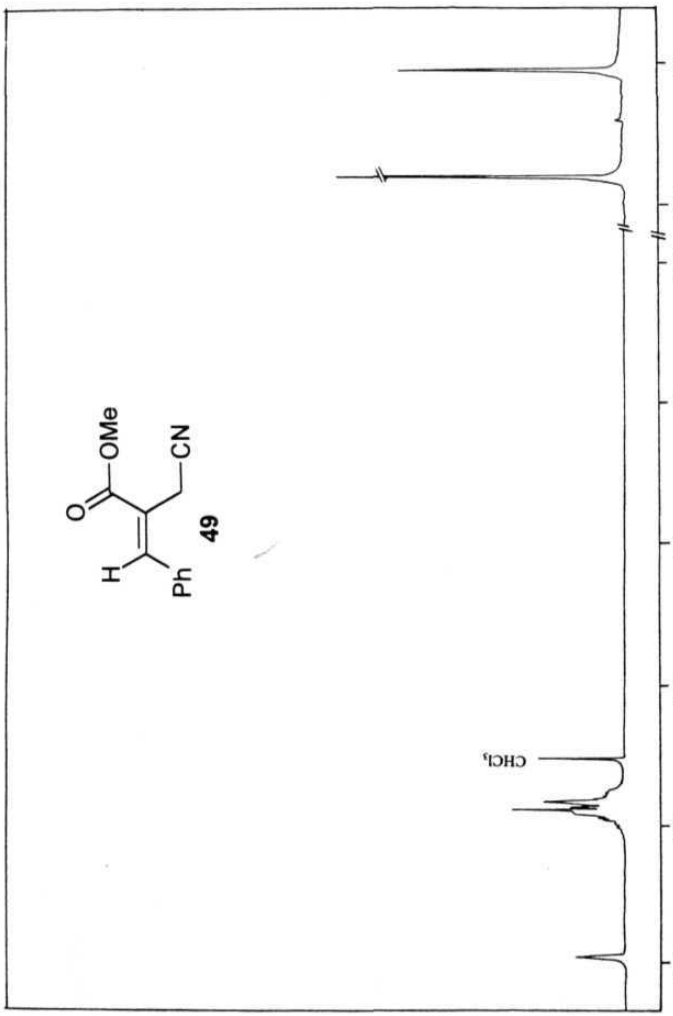


Fig. 3: ^{1}H NMR spectrum of **49**

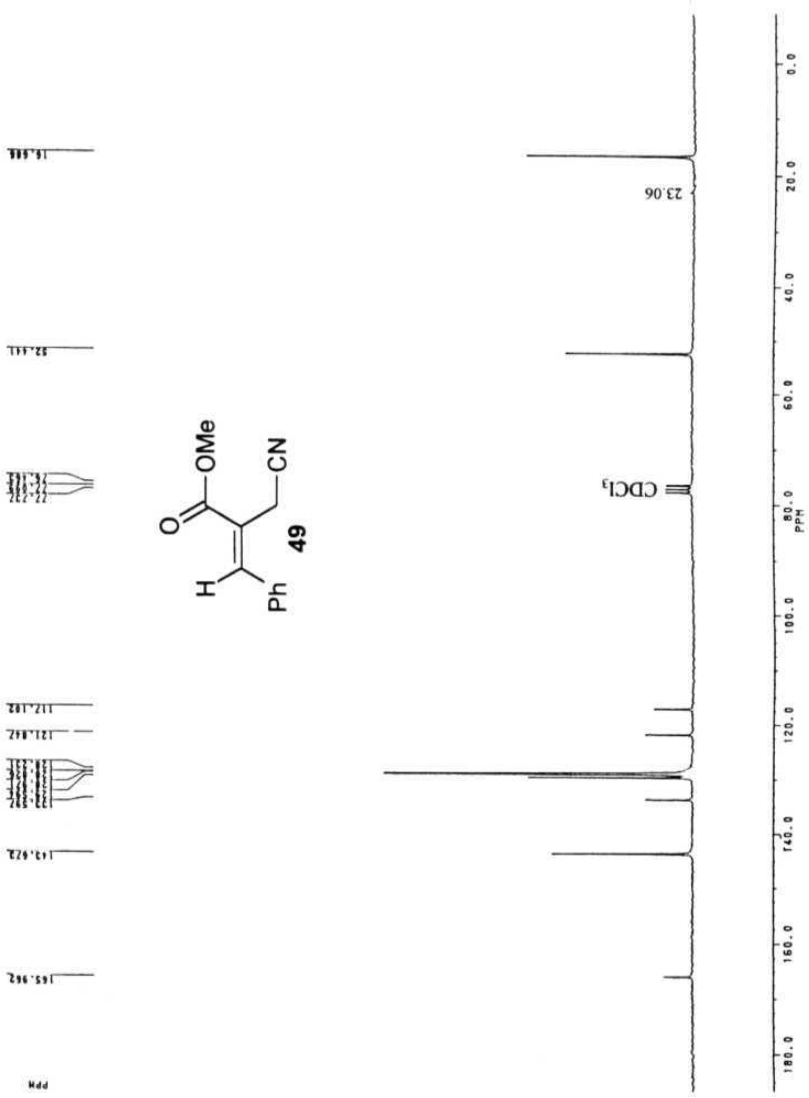


Fig. 4: ^{13}C NMR spectrum of **49**

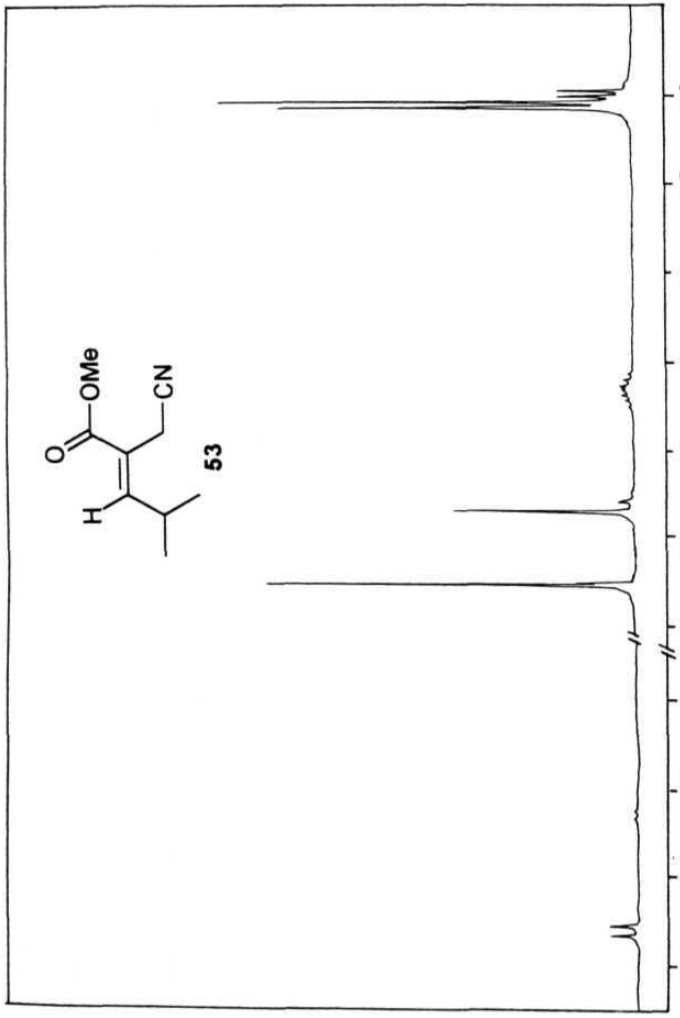


Fig. 5: ^{1}H NMR spectrum of **53**

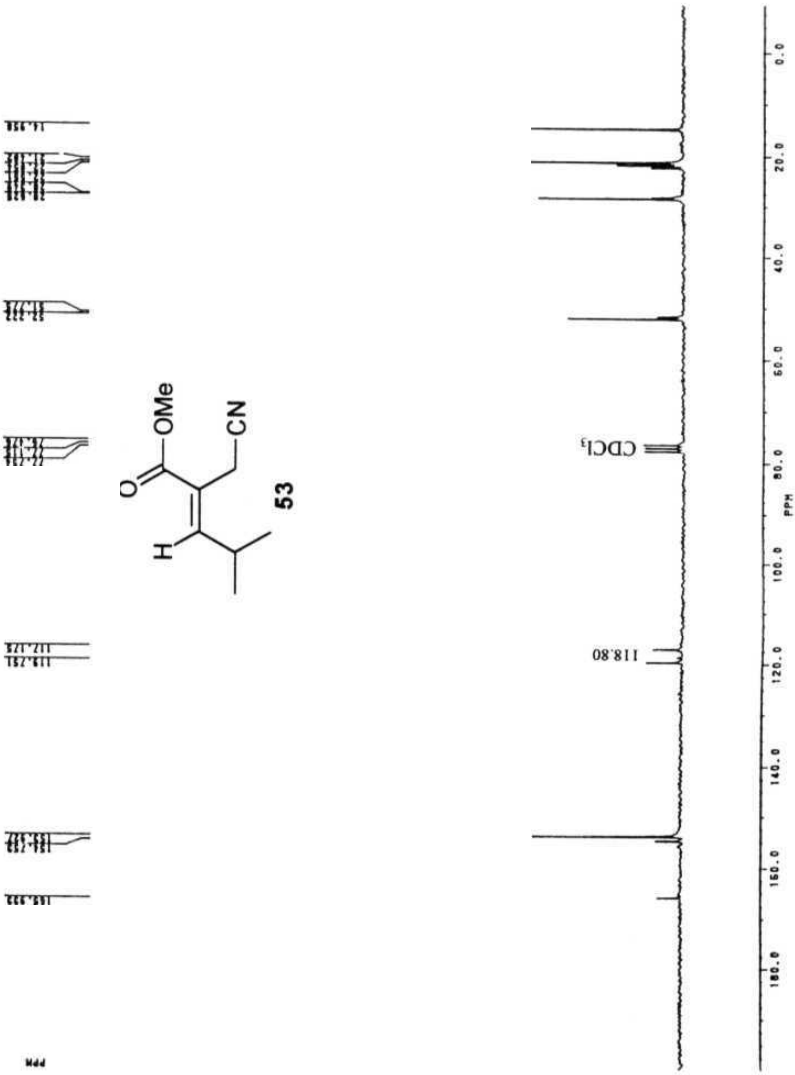


Fig. 6: ^{13}C NMR spectrum of **53**

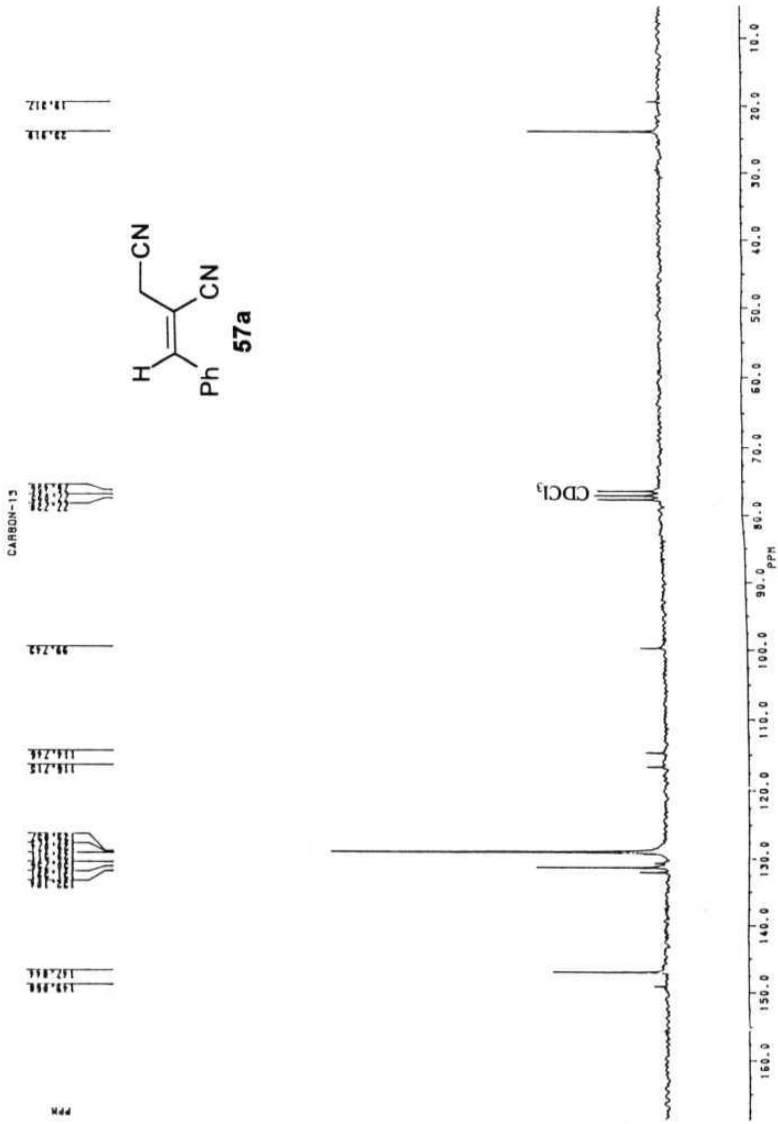


Fig. 7. ^{13}C NMR spectrum of **57a**

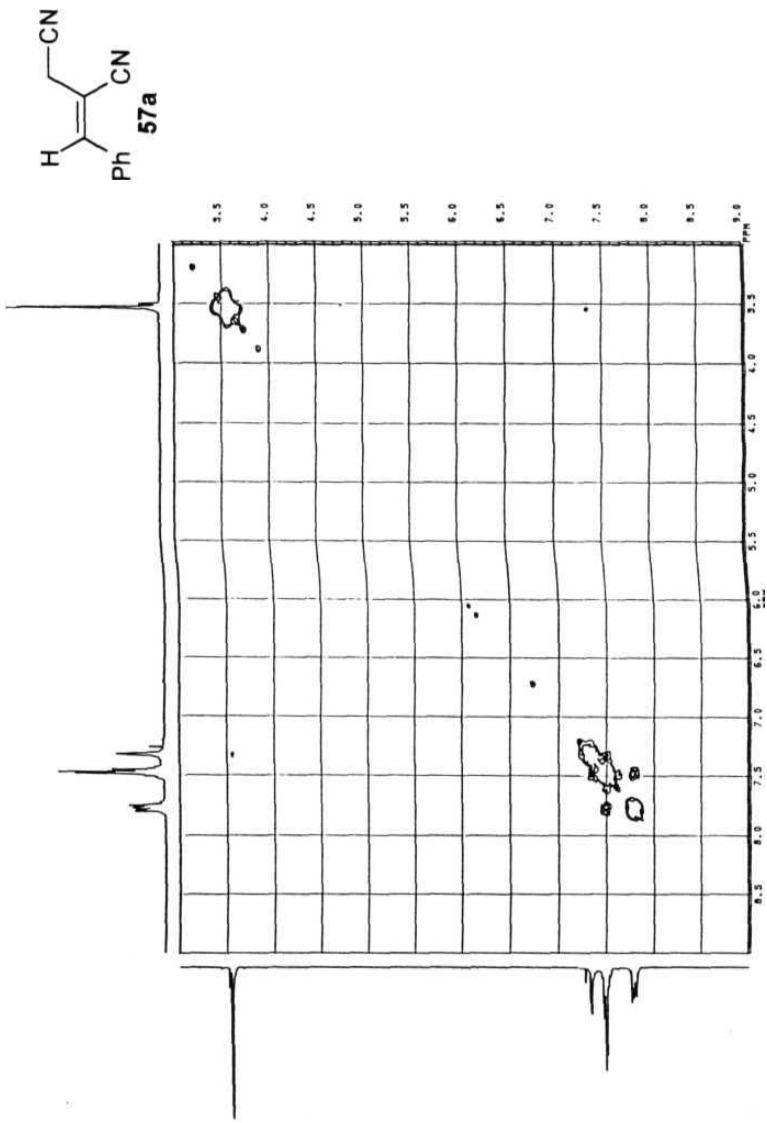


Fig. 8: 2D NOESY of **57a**

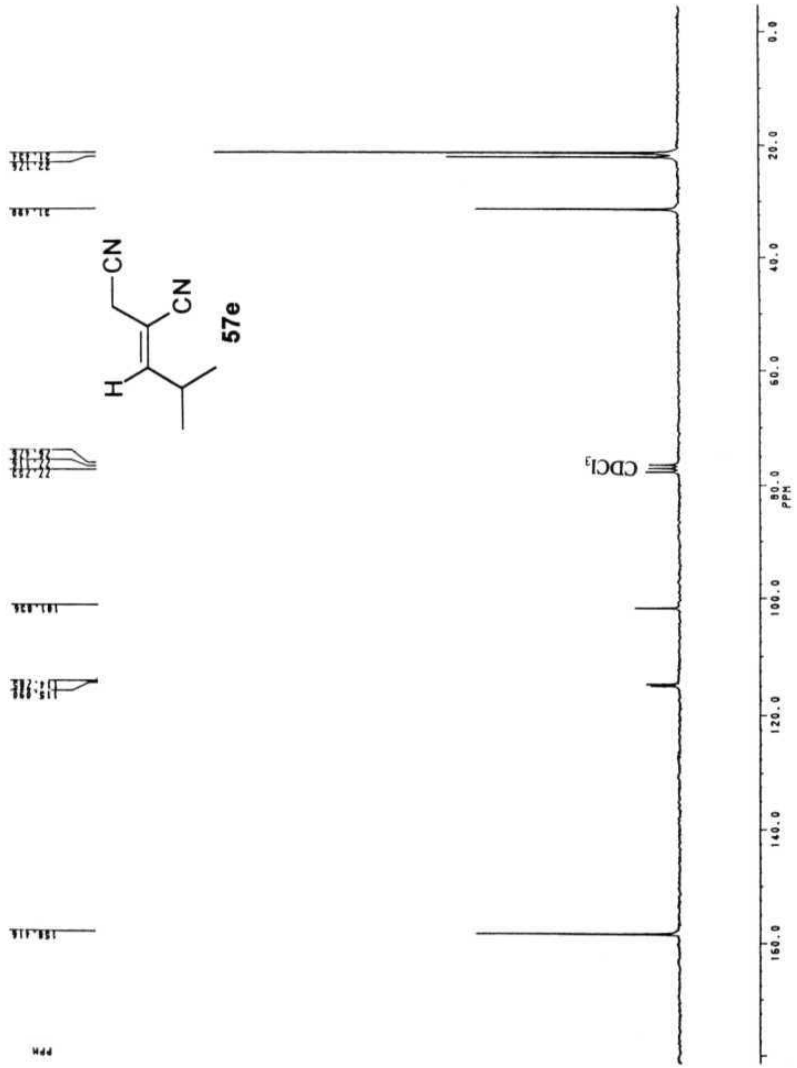


Fig. 9: ^{13}C NMR spectrum of **57e**

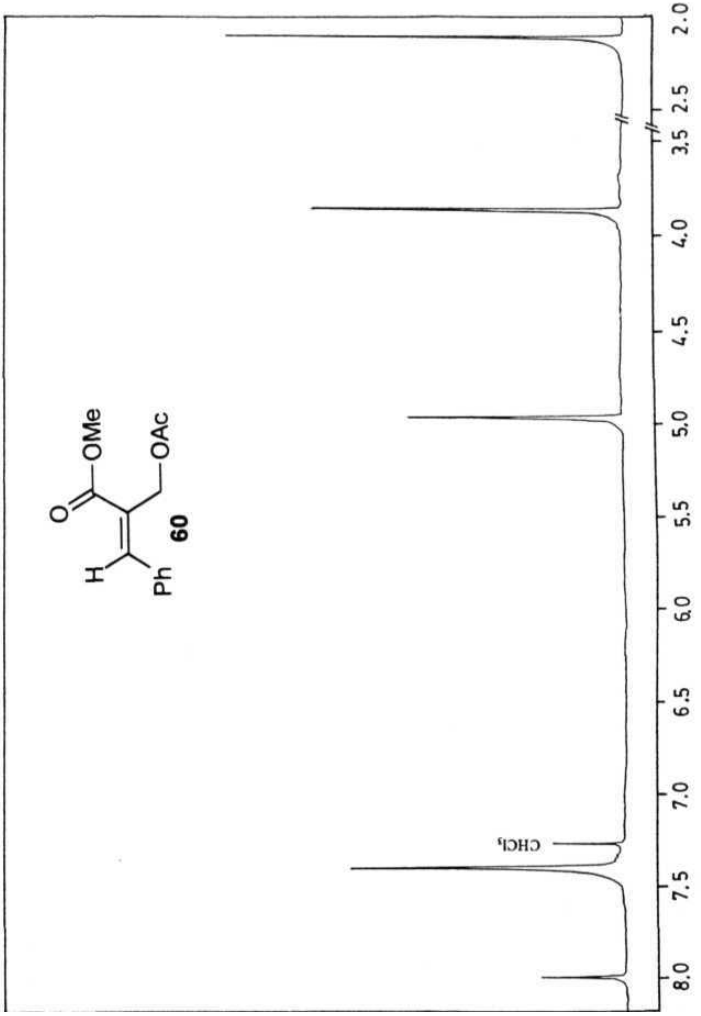


Fig. 10: ^{1}H NMR spectrum of **60**

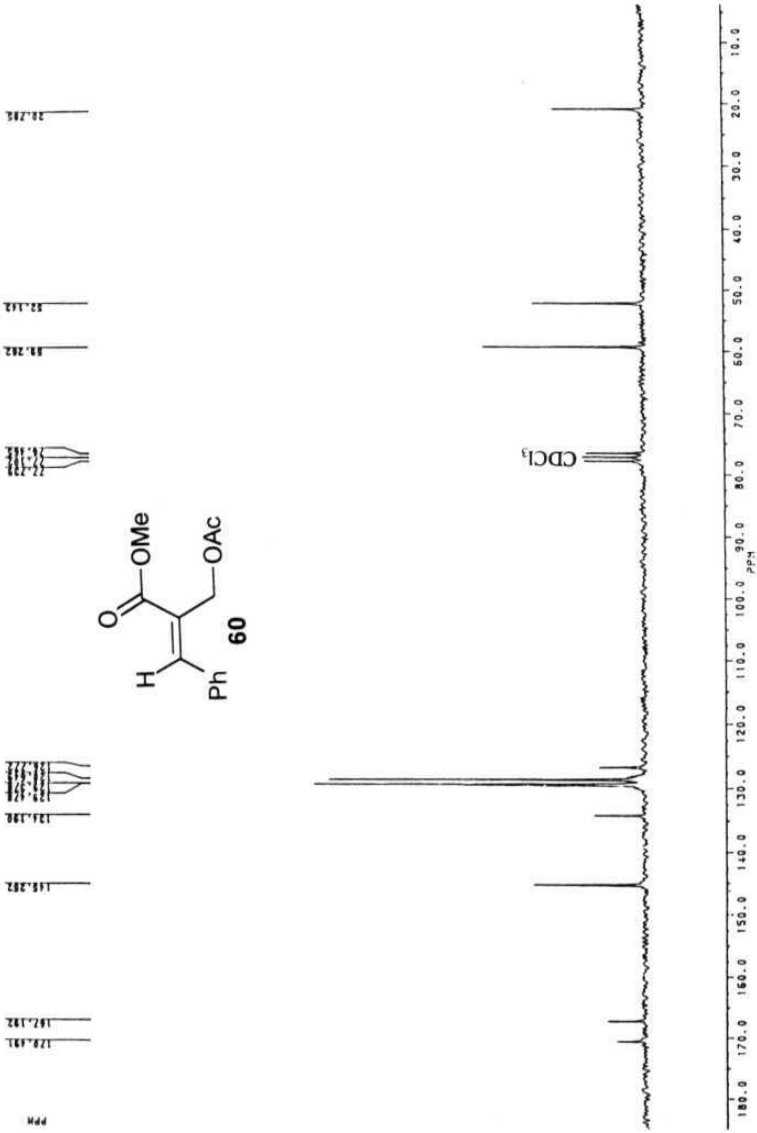


Fig. 11: ^{13}C NMR spectrum of **60**

Fig. 12: ^{13}C NMR spectrum of **70**

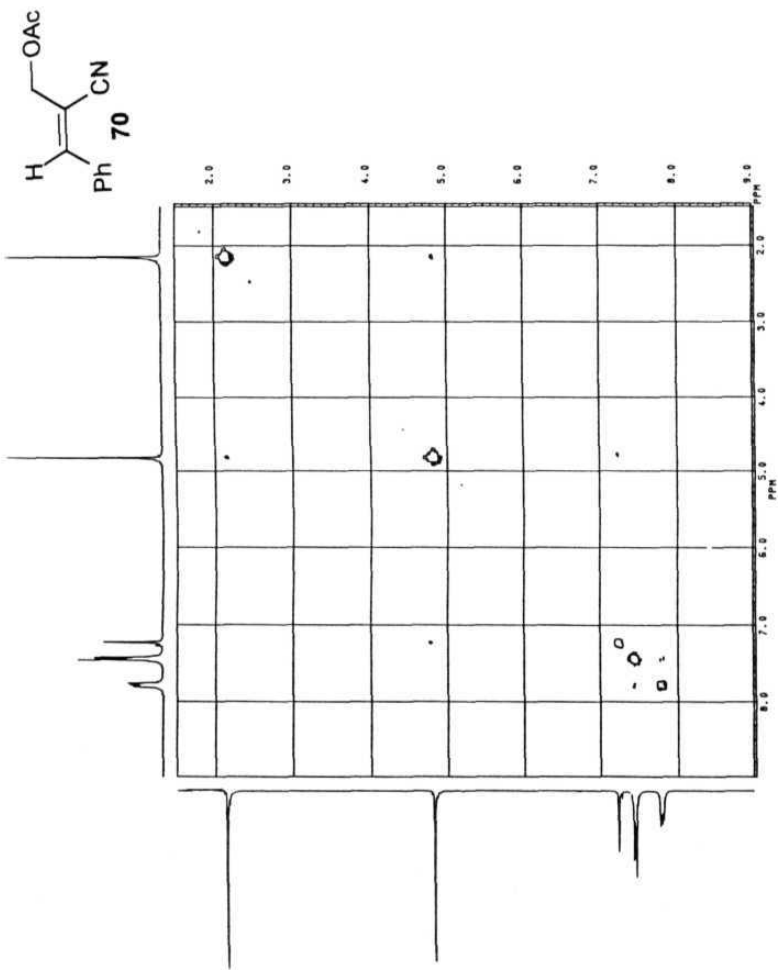


Fig. 13: 2D NOESY of **70**

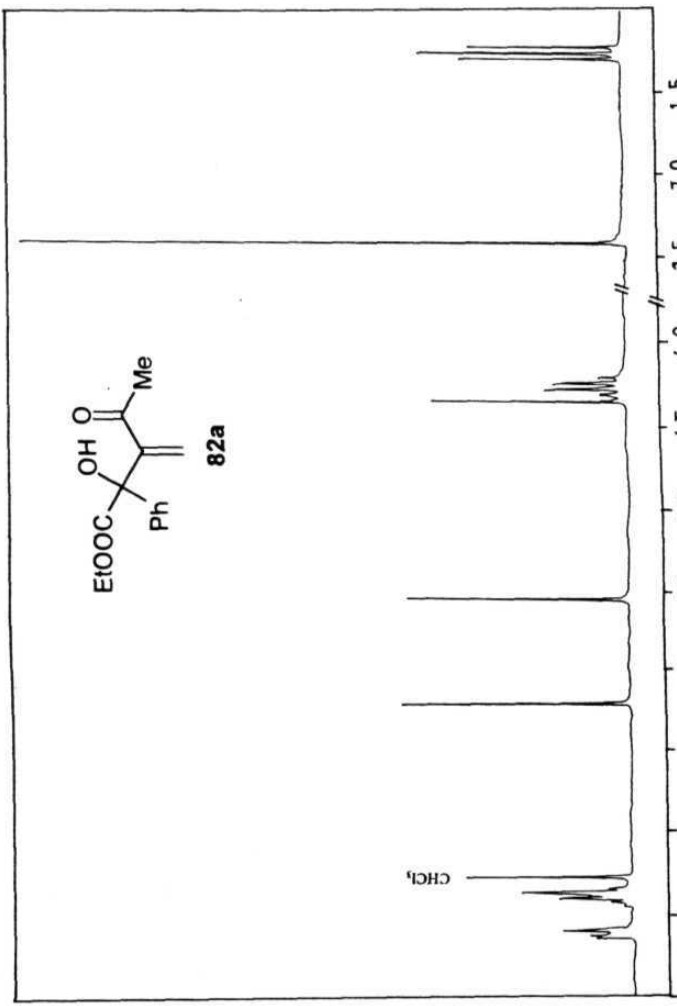


Fig. 14: ^{1}H NMR spectrum of **82a**

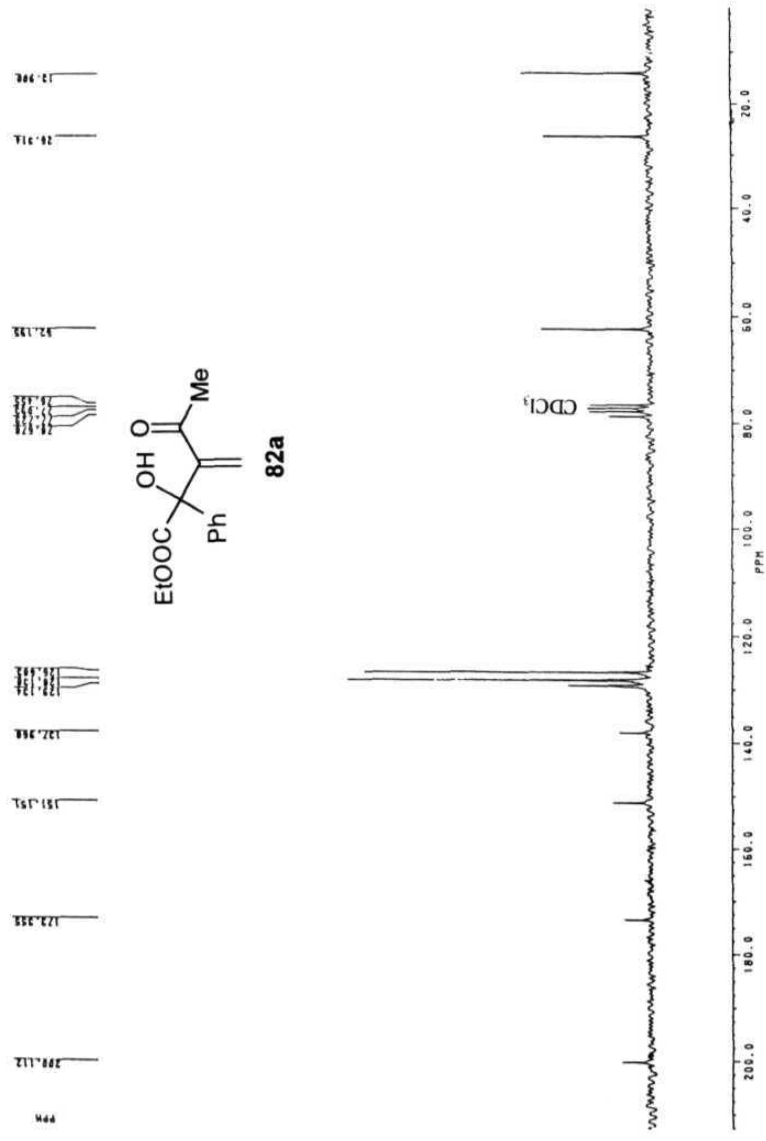


Fig. 15: ^{13}C NMR spectrum of **82a**

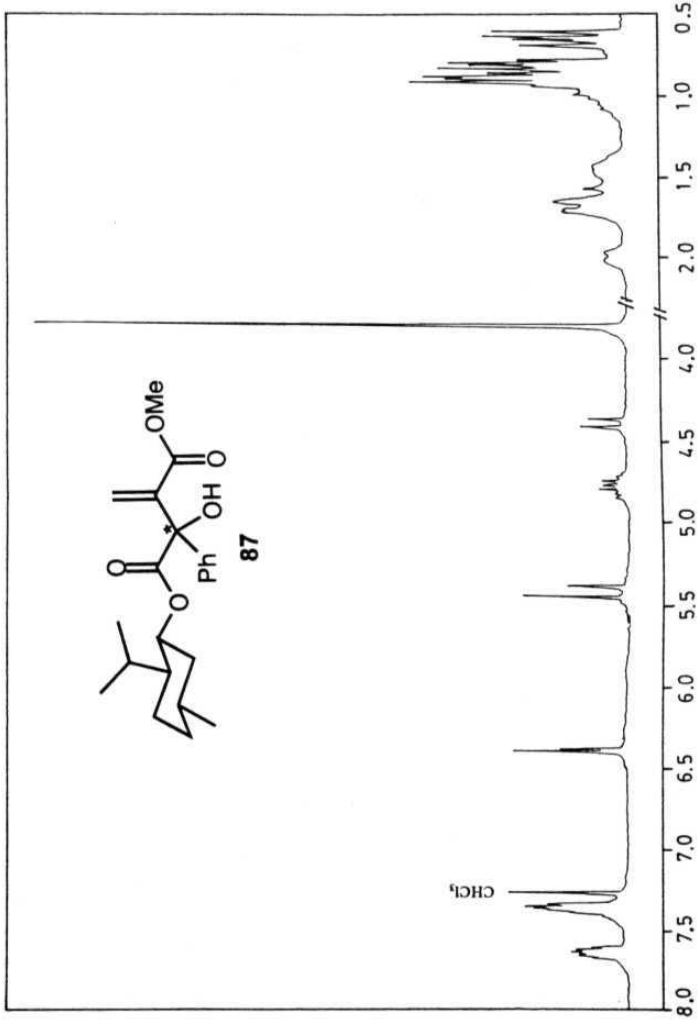


Fig. 16: ^{1}H NMR spectrum of **87**

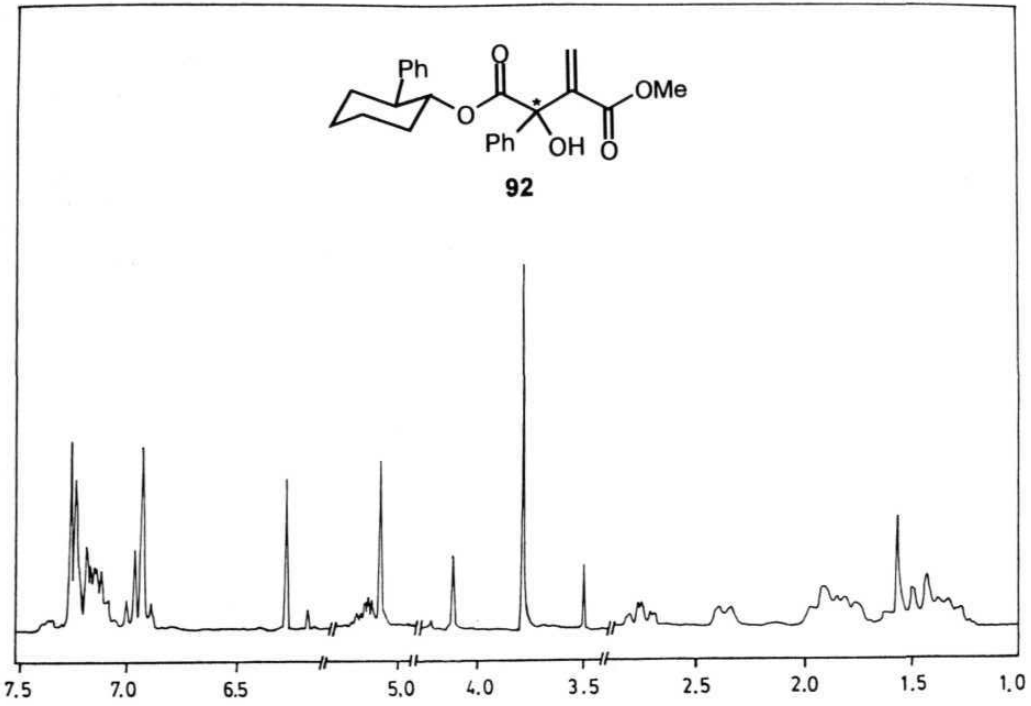


Fig. 17: ^{1}H NMR spectrum of **92**

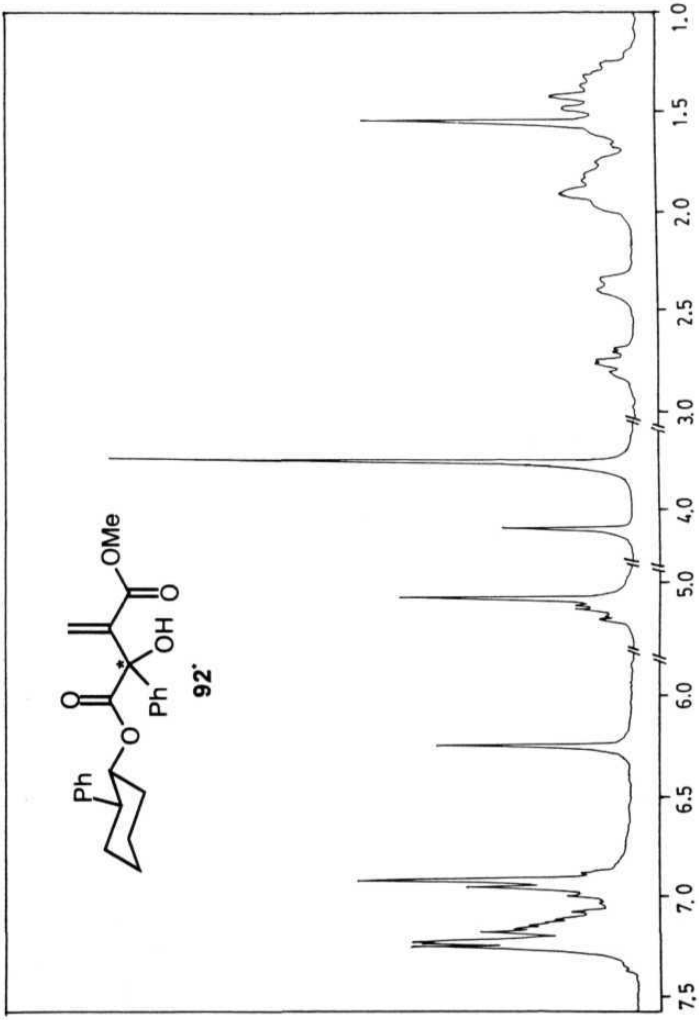


Fig. 18: ^{1}H NMR spectrum of **92***

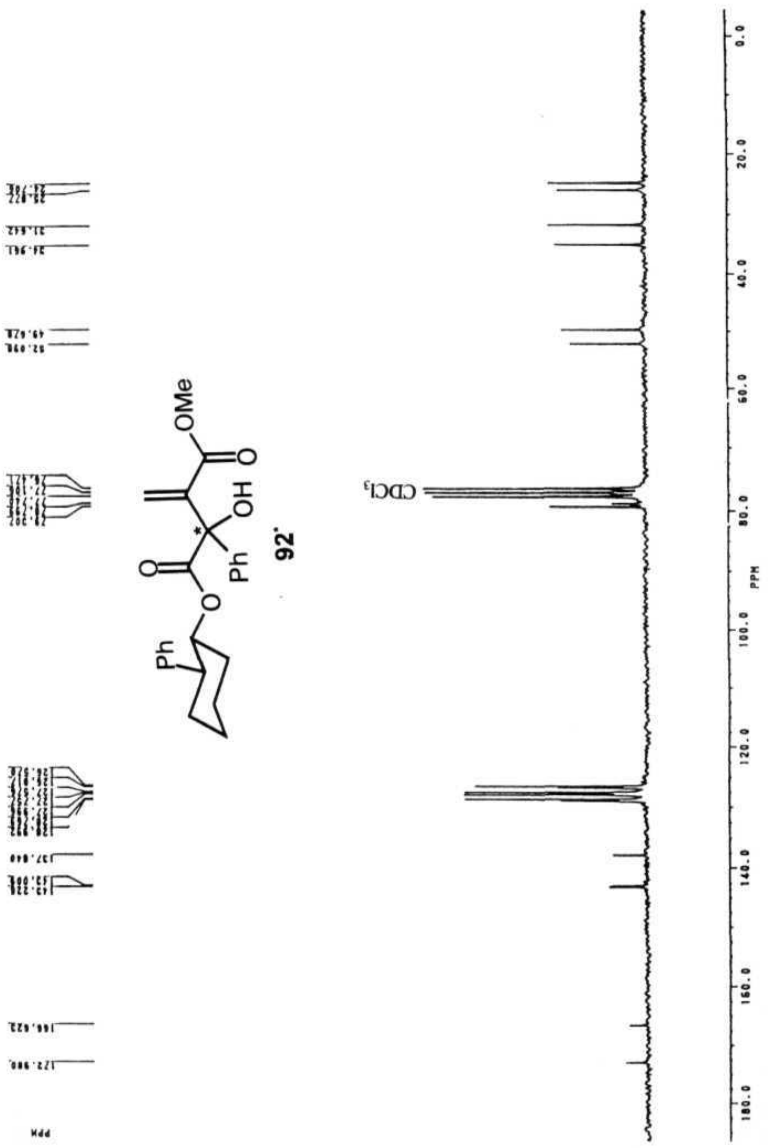


Fig. 19: ^{13}C NMR spectrum of **92'**

REFERENCES

1 Carey, F. A.; Sundberg, R J. *Advanced Organic chemistry, Part A & B,* 3 edition, Plenum Press, New York, 1990

2 March, J. *Advanced Organic Chemistry*, 4th edition, John Wiley & Sons, New York, USA, 1992

3. Carruthers, W. *Some Modern Methods of Organic Synthesis,* 3rd edition, Cambridge University Press, Cambridge, 1986

4 Hassner, A.; Stumer, C. *Organic Syntheses Based on Name Reactions and Unnamed Reactions,* Tetrahedron Organic Chemistry Series, Baldwin, J. E.; Magnus, P. D. (Editors), Pergamon Press, 1998, *Vol. 11*

5 Kumada, M *Pure and Appl. Chem.,* 1980, *52,* 669.

6 Oppolzer, W. *Angew. Chem. Int. Ed Engl.*, 1984, *23,* 876.

7. Helmchen, G ; Karge, R.; Weetman, J. *Modern Synthetic Methods,* Scheffold, R. (Editor), Springer-Verlag, Berlin, 1986, *4,* 261.

8. Meijere, A. de; Meyer, F. *Angew. Chem. Int. Ed. Engl.*, 1994, *33,* 2379.

9. Furstner, A. *Synthesis,* 1989, 571.

10. Mahrwald, R. *Chem. Rev.,* 1999, *99,* 1095.

11 Heathcock, C. H.; *Comprehensive Organic Synthesis,* Trost, B M. (Editor), Pergamon: Oxford, 1993, *Vol. 2,* Chapter 1.5.

12. Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972, *Chem. Abst.,* 1972, *77,* 34174q.

13. Drewes, S E.; Roos, G. H. P. *Tetrahedron,* 1988, *44*, 4653

14. Basavaiah, D., Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron,* **1996,** *52,* 8001.

15. Ciganek, E. *Organic Reactions,* Paquette, L.A., Ed.; John Wiley & Sons, New York, **1997;** *Vol 51,* pp 201.

16. Drewes, S. E.; Emslie, N D. *J. Chem. Soc. Perkin Trans. I,* **1982,** 2079.

17 Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed Engl.,* **1983,** *22,* 795.

18 Basavaiah, D ; Gowriswari, V. V. L. *Synth. Commun.,* **1987,** *17,* 587.

19. Amri, H.; Villieras, J. *Tetrahedron Lett.,* **1986,** *27,* 4307.

20. Basavaiah, D ; Gowriswari, V V. L. *Tetrahedron Lett.,* **1986,** *27,* 2031.

21. Basavaiah, D ; Bharathi, T. K.; Gowriswari, V. V. L. *Synth. Commun.,* 1987, *17,* 1893.

22. Auvray, P.; Knochel, P.; Normant, J F *Tetrahedron Lett.,* **1986,** *27,* 5095

23. Wang, S.-Z.; Yamamoto, K.; Yamada, H ; Takahashi, T. *Tetrahedron,* **1992,** *48,* 2333.

24. Amri, H; El Gaied, M. M ; Villieras, J. *Synth. Commun.,* **1990,** *20,* 659.

25. Tsuboi, S.; Takatsuka, S.; Utaka, M. *Chem. Lett.,* **1988,** 2003.

26. Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem.,* **1993,** *58,* 5952.

27. Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.,* **1986,** *27,* 5007.

28. Strunz, G. M.; Bethell, R.; Sampson, G.; White, P. *Can. J. Chem.,* **1995,** *73,* 1666.

29. Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.,* **1999,** *40,* 1539.

30 Basavaiah, D.; Bharathi, T. K.; Gowriswari, V. V. L. *Tetrahedron Lett.*, 1987, *28*, 4351.

31 Basavaiah, D ; Gowriswari, V. V. L. *Synth. Commun.,* 1989, *19,* 2461.

32. Grundke, C ; Hoffmann, H. M. R *Chem. Ber.*, 1987,*120,* 1461.

33 Golubev, A. S.; Galakhov, M V ; Kolomiets, A. F ; Fokin, A V. *Bull. Rus. Acad.Sci.,* 1992,47,2193.

34 Perlmutter, P.; Teo, C C *Tetrahedron Lett.*, 1984, *25,* 5951

35 Yamamoto, K ; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn.,* 1988, *61,* 319.

36. Takagi, M.; Yamamoto, K. *Tetrahedron,* 1991, *47,* 8869.

37 Hill, J. S ; Isaacs, N. S. *J. Chem. Res. (S)*, 1988, 330.

38 Ando, D.; Bevan, C; Brown, J M.; Price, D W. *J. Chem. Soc., Chem. Commun.,* 1992, 592.

39. Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.,* 1990, *3,* 285.

40. Fort, Y.; Berthe, M. C; Caubere, P. *Tetrahedron,* 1992, *48,* 6371.

41 Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.,* 1991, *32,* 5611.

42 Auge, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.,* 1994, 35, 7947.

43. Aggarwal, V. K.; Tarver, G. J.; McCague, R. *Chem. Commun.,* 1996, 2713.

44 Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.*, 1998, *63,* 7183.

45 Rafel, S.; Leahy, J. W. *J. Org. Chem.,* 1997, *62,* 1521.

46. Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S V *Synlett,* 1994, 444.

47. Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.,* **1998,** *39,* 5965.

48. Kamimura, A.; Gunjigake, Y ; Mitsudera, H ; Yokoyama, S. *Tetrahedron Lett.,* **1998,** *39,* 7323.

49. Brown, J. M; Cutting, I., Evans, P. L ; Maddox, P. J. *Tetrahedron Lett.*, **1986,** *27,* 3307.

50. Gilbert, A.; Heritage, T W ; Isaacs, N. S. *Tetrahedron: Asymmetry,* **1991,** *2,* 969.

51. a) Gowriswari, V V. L. *Ph. D. thesis*, University of Hyderabad, **1989**

b) Sarma, P. K. S. *Ph. D. thesis*, University of Hyderabad, **1993**

c) Pandiaraju, S. *Ph. D. thesis*, University of Hyderabad, **1995.**

52. Basavaiah, D; Gowriswari, V. V. L ; Sarma, P K. S.; Dharma Rao, P *Tetrahedron Lett.,* **1990,** *31,* 1621.

53 Drewes, S. E.;Emslie, N D ; Khan, A. A. *Synth. Commun.,* **1993,** *23,* 1215

54. Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc,* **1997,** *119*, 4317

55. Piber, M; Leahy, J. W. *Tetrahedron Lett.*, **1998,** *39,* 2043.

56. Marko, I. E.; Giles, P. R., Hindley, N. J. *Tetrahedron,* **1997,** 53, 1015.

57. Oishi, T.; Oguri, H.; Hirama, M *Tetrahedron: Asymmetry,* **1995,** *6, MAX.*

58. Barrett, A. G. M.; Cook, A. S., Kamimura, A. *Chem. Commun.,* **1998,** 2533.

59. Hayase, T.; Shibata, T ; Soai, K ; Wakatsuki, Y *Chem. Commun.*, **1998,** 1271.

60. Drewes, S E.; Manickum, T ; Roos, G H. P *Synth. Commun,* **1988,** *18*, 1065.

61. Drewes, S. E.; Njamela, O. L ; Roos, G. H. P. *Chem. Ber.,* **1990,** *123,* 2455.

62 Manickum, T.; Roos, G. H P. *Synth. Commun.,* **1991,** *21,* 2269.

63. Drewes, S. E.; Khan, A. A ; Rowland, K. *Synth. Commun.*, **1993,** *23,* 183.

64. Kundig, E P.; Xu, L. H.; Romanens, P.; Bernardinelli, G *Tetrahedron Lett.*, **1993,** *34,* 7049.

65 Kundig, E. P.; Xu, L. H.; Schnell, B. *Synlett,* **1994,** 413.

66 Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.,* **1992,** *33,* 1045.

67 Daude, N.; Eggert, U.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.*, **1988,** 206.

68 Hoffmann, H. M. R.; Gassner, A ; Eggert, U. *Chem. Ber.,* **1991,** *124,* 2475.

69. Foucaud, A.; Brine, N. *Synth. Commun.,* **1994,** *24,* 2851.

70. Basavaiah, D.; Bakthadoss, M; Pandiaraju, S. *Chem. Commun.,* **1998,** 1639.

71 Familoni, O. B.; Kaye, P T.; Klaas, P. J. *Chem. Commun.,* **1998,** 2563.

72. Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. I,* **1990,** 2612.

73. Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. I,* **1993,** 1809

74 Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.,* **1986,** *27,* 5091

75. Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron,* **1988,** *44,* 6095.

76. Bauchat, P.; Le Rouille, E.; Foucaud, A. *Bull. Soc. Chim. Fr.,* **1991,** 267; *Chem. Abstr.,* **1991**, *115*, 91980b.

77. Masuyama, Y.; Nimura, Y.; Kurusu, Y. *Tetrahedron Lett.,* **1991,** 52, 225.

78. Perlmutter, P.; Tabone, M. *Tetrahedron Lett.,* **1988,** *29,* 949.

79. Perlmutter, P.; Tabone, M. *J. Org. Chem.,* **1995,** *60,* 6515.

80. Roush, W. R.; Brown, B. B. *J. Org. Chem.,* **1993,** *58,* 2151.

81. Weichert, A.; Hoffmann, H. M. R. *J. Chem. Soc, Perkin Trans. I,* **1990,** 2154.

82. Chamakh, A.; Amri, H. *Tetrahedron Lett.,* **1998,** *39,* 375.

83. Basavaiah, D.; Pandiaraju, S.; Sarma, P K. S. *Tetrahedron Lett.,* **1994,** 35, 4227.

84. Foucaud, A.; El Guemmout, F *Bull. Soc. Chim. Fr.,* **1989,** 403.

85. Basavaiah, D ; Sarma, P. K. S. *J. Chem. Soc, Chem. Commun.,* **1992,** 955.

86. Basavaiah, D ; Sarma, P. K. S.; Bhavani, A. K. D. *J. Chem. Soc, Chem. Commun.,* **1994,** 1091.

87. Basavaiah, D.; Bhavani, A. K. D.; Pandiaraju, S.; Sarma, P. K. S. *Synlett,* **1995,** 243.

88. Basavaiah, D ; Pandiaraju, S. *Tetrahedron,* **1996,** *52,* 2261.

89. Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R., Sarma, P K S.; Kumaragurubaran, N. *J. Org. Chem.,* **1999,** *64,* 1197.

90. Pachamuthu, K.; Vankar, Y. D. *Tetrahedron Lett.,* **1998,** *39,* 5439.

91. Yamamoto, K; Deguchi, R.; Tsuji, J. *Bull. Chem. Soc. Jpn,* **1985,** *58,* 3397

92. Basavaiah, D.; Pandiaraju, S. *Tetrahedron Lett.,* **1995,** *36,* 757.

93. Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Pandiaraju, S. *Tetrahedron Lett.,* **1997,** *38,* 2141.

94 Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett,* **1998,** *39,* 6223

95. Bauchat, P.; Foucaud, A. *Tetrahedron Lett.,* **1989,** *30,* 6337.

96 Matsumoto, S ; Okubo, Y.; Mikami, K *J. Am. Chem. Soc.,* **1998,***120,* 4015.

97 Calo, V.; Lopez, L.; Pesce, G *J. Organomel. Chem.,* **1988,** *353,* 405.

98. Utaka, M.; Onoue, S.; Takeda, A *Chem. Lett.,* **1987,** 971.

99 Burgess, K ; Jennings, L D. *J. Org. Chem* , **1990,** *55,* 1138

100 Basavaiah, D ; Dharma Rao, P. *Synth. Commun.,* **1994,** *24,* 917

101. Kitamura, M; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.,* **1988**, *53*, 708

102. Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.,* **1968,** *41,* 2815.

103. Imagawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, M *Synth. Commun.,* **1984,** *14,* 1267.

104 Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.,* **1989,** *30*, 2731.

105. Matsuda, I.; Shibata, M.; Sato, S. *J. Organomet. Chem.,* **1988,** *340,* C_5-C_7

106 Sato, S.; Matsuda, I.; Shibata, M. *J. Organomet. Chem,* **1989,** *377,* 347

107. Sato, S.; Matsuda, L; Izumi, Y. *Chem. Lett.,* **1985,** 1875.

108. Harrowven, D C; Poon, H. S. *Tetrahedron,* **1996,** *52,* 1389

109. Nagaoka, Y.; Tomioka, K. *J. Org. Chem,* **1998,** *63,* 6428.

110. Li, G.; Wei, H.- X.; Willis, S. *Tetrahedron Lett.,* **1998,** *39,* 4607.

111. Wei, H -X ; Willis, S ; Li, G. *Tetrahedron Lett.,* **1998,** *39,* 8203

112 Li, G.; Wei, H.-X.; Whittlesey, B. R.; Batrice, N. N. *J. Org. Chem.,* **1999,** *64,* 1061.

113. McCombie, S. W.; Luchaco, C. A. *Tetrahedron Lett.,* **1997,** *38,* 5775.

114. Backvall, J.-E.; Andreasson, U. *Tetrahedron Lett.*, **1993,** *34,* 5459.

115. Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc,* **1993**, *115*, 2027.

116. McGrath, D. V.; Grubbs, R. H. *Organometallics*, **1994,** *13,* 224.

117. Alper, H.; Hachem, K. *J. Org. Chem.*, **1980,** *45,* 2269.

118. Melpolder, J. B ; Heck, R. F. *J. Org. Chem.,* **1976,** *41,* 265.

119 Chalk, A. J.; Magennis, S. A. *J. Org. Chem.,* **1976,** *41,* 273

120. Ashimori, A.; Matsuura, T.; Overman, L.E.; Poon, D. J. *J. Org. Chem.,* **1993,** 55, 6949.

121. Grigg, R.; Santhakumar, V.; Sridharan, V ; Thornton-Pett, M; Bridge, A. W *Tetrahedron,* **1993,** *49,* 5177

122. Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoong, E.-Y.; Kim, T.-H *Tetrahedron Lett.,* **1995,** *36,* 6287.

123. Jeffery, T. *J. Chem. Soc, Chem. Commun.*, **1984,** 1287.

124. Kumareswaran, R.; Vankar, Y D. *Synth. Commun.,* **1998,** *28,* 2291

125. Sundar, N.; Bhat, S. V. *Synth. Commun.,* **1998,** *28,* 2311.

126. Larson, G. L.; de Kaifer, C. F.; Seda, R.; Torres, L. E.; Ramirez, J. R. *J. Org. Chem.,* **1984,** *49,* 3385.

127 Baraldi, P. G.; Guarneri, M.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *J. Chem. Soc., Perkin Trans. I,* **1984,** 2501.

128. Tanaka, K.; Yamagishi, N.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn.,* **1979,** *52,* 3619.

129. Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd edition, Pergamon Press*, **1969,** *vol. 5*

130. Gruiec, A.; Foucaud, A *New. J. Chem.*, **1991,** *15,* 943.

131. Funabiki, T.; Hosomi, H ; Yoshida, S.; Tarama, K. *J. Am. Chem. Soc,* **1982,** *104,* 1560.

132. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.,* **1980,** *21,* 71.

133. Pilli, R. A.; Russowsky, D. *J. Chem. Soc, Chem. Commun.,* **1987,** 1053.

134. Wuts, P. G. M.;Jung, Y.-W. *J. Org. Chem.,* **1988,** ***53***, 1957.

135. Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G G. A. *Chem. Commun.,* 1996,2625.

136. Fujii, N.; Otaka, A.; Ikemura, O.; Akaji, K.; Funakoshi, S.; Hayashi, Y.; Kuroda, Y.; Yajima, H *J. Chem. Soc, Chem. Commun.,* **1987,** 274

137. Hunter, R.; Michael, J. P.; Tomlinson, G. D. *Tetrahedron,* **1994,** 50, 871.

138. Kobayashi, M; Masumoto, K.; Nakai, E.; Nakai, T. *Tetrahedron Lett.*, **1996,** *37,* 3005.

139. Mason, P. H.; Emslie, N. D. *Tetrahedron,* **1994,** 50, 12001.

140. Basavaiah, D.; Pandiaraju, S.; Krishnamacharyulu, M. *Synlett,* **1996,** 747

141. Amri, H.; El Gaied, M. M.; Ayed, T. B.; Villieras, J. *Tetrahedron Lett.,* **1992,** *33,* 7345.

142. Kataoka, T.; Iwama, T.; Tsujiyama, S. *Chem. Commun.,* **1998,** 197.

143. Kataoka, T.; Iwama, T; Tsujiyama, S.; Iwamura, T.; Watanabe, S *Tetrahedron,* **1998,** *54,* 11813.

144 Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsujiyama, S.; Tsurukami, Y.; Iwamura, T.; Watanabe, S. *Synlett,* **1999,** 197.

145 Basavaiah, D ; Bharathi, T. K. *Tetrahedron Lett.*, **1991,** *32,* 3417.

146. Whitesell, J. K.; Lawrence, R. M *Chimia,* **1986,** *40,* 318.

147 Weinstock, L M.; Currie, R. B.; Lovell A. V. *Synth. Commun.*, **1981,** *11,* 943.

148.Matsumoto, K.; Harada, K. *J. Org. Chem.,* **1966,** *31,* 1956.

149. Adachi, K.; Kobayashi, S.; Ohno, M. *Chimia,* **1986,** *40,* 311.

150. Bharathi, T. K. *Ph. D. thesis*, University of Hyderabad, **1991.**

151.Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.,* **1981, *46,*** 211.

LIST OF PUBLICATIONS

1 Enantioselective Synthesis of (1R,2R)- and (lS,2S)-2-Nitroxycyclohexan-l-ols

D Basavaiah, S. Pandiaraju, **K. Muthukumaran**, *Tetrahedron: Asymmetry*, **1996,** 7, 13

2 (1R,2R)-2-Nitroxycyclohexan-1-ol: First Example of a Cyclohexyl Based Chiral Auxiliary with Nitroxy Function as Diastereoface Discriminating Group

D Basavaiah, S Pandiaraju, M Bakthadoss, **K. Muthukumaran,** *Tetrahedron: Asymmetry,* **1996,** 7, 997.

3. Arylation of the Baylis-Hillman Adducts

D Basavaiah, **K. Muthukumaran,** *Tetrahedron,* **1998,** ***54,*** 4943

4. $RuCl_2(PPh_3)_3$ Catalyzed Isomerization of the Baylis-Hillman Adducts

D Basavaiah, **K. Muthukumaran,** *Synth. Commun*, **1999,** *29,* 713.

5. a-Keto Esters as Electrophiles for the Chalcogeno-Baylis-Hillman Reaction

D Basavaiah, **K. Muthukumaran,** B Sreenivasulu, *Synlett,* **1999,** 1249.