BAYLIS-HILLMAN CHEMISTRY: NOVEL ORGANIC TRANSFORMATIONS AND APPLICATIONS

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

BY

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“தாயிற்சிறந்த கோயிலுமில்லை

தந்தைசொல்மிக்க மந்திரம் இல்லை

ஆயிரம் உறவில் பெருமைகள் இல்லை

அன்னை தந்தையே அன்பின் எல்லை”

- Dedicated to my Beloved Parents

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STATEMENT

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

DECEMBER, 2000

N. KUMARAGURUBARAN

CERTIFICATE

Certified that the work embodied in this thesis entitled **"Baylis-Hillman Chemistry: Novel Organic Transformations and Applications"** has been carried out by **Mr. N. KUMARAGURUBARAN,** under my supervision and the same has not been submitted elsewhere for a degree.

December 15, 2000

Professor D. BASAVAIAH

(THESIS SUPERVISOR)

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N. Kumaragurubaran

ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
BIN AP	2,2'-bis(diphen ylphosphino)-1,1 '-binaphthy 1
Bn	benzyl
bp	boiling point
n-Bu	n-butyl
t-Bu or Bu'	*tert*-butyl
n-Bu_2BOTf	n-dibutylboron triflate
cat.	catalyst
m-CPBA	*meta*-chloroperbenzoic acid
cy	cyclo
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicylo[5.4.0]undec-7-ene
de	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
ee	enantiomeric excess
Et	ethyl
EWG	electron withdrawing group

HMPA	hexamethylphosphoramide
3-HQ	3-hydroxyquinuclidine
HRP	horseradish peroxidase
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
Me	methyl
mp	melting point
Ms	mesyl
NBS	N-bromosuccinimide
NOESY	nuclear Overhauser enhancement spectroscopy
PCC	pyridinium chlorochromate
PPTS	pyridinium *p*-toluenesulfonate
Ph	phenyl
PLAP	pig liver acetone powder
/-Pr or Pr'	isopropyl
PTC	phase transfer catalyst
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran
Trt	trityl
TFAA	trifluoroacetic anhydride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TEAF	triethylammonium formate

ABSTRACT

Synthetic organic chemistry is one of the most rapidly developing, expanding and successful branches of science. Construction of carbon-carbon bonds and carbon-hetero atom bonds is one of the most fundamental reactions in synthetic organic chemistry and hence represents a forefront of research in organic chemistry. More recently, the concepts of atom economy, selective (both stereo- and regio-) transformations and catalytic processes have become primary requirements for the development of synthetic organic chemistry to be one of the leading scientific disciplines. During the last fifteen years, synthetic organic chemistry has seen enormous growth, not only in terms of development of new methodologies for construction of carbon-carbon and carbon-hetero atom bonds but also in terms of development of new reagents, catalysts, strategies, transformations and technologies often involving the concepts of atom economy and selectivity. Though the arsenal of synthetic organic chemistry is now very rich in the sense that there are methods available to synthesize any molecule which was once thought to be difficult to prepare, the continuing sophistication in and ever changing scenario of synthetic organic chemistry requires and even demands the continuous evolution of synthetic methods that meet the requirements of atom

economy and very high levels of selectivity. The Baylis-Hillman reaction is one such atom economy reaction, which has been nowadays recognized, as an useful and emerging reaction having enormous synthetic potential as a source for various stereoselective processes.

This thesis deals with our efforts to expand the scope of the Baylis-Hillman reaction as an attractive source for organic transformations 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 a catalytic process, essentially involving three components, leading to the construction of carbon-carbon bond between the a-position of activated alkene and carbon electrophile under the catalytic influence of a tertiary amine particularly DABCO, thus producing synthetically useful multifunctional molecules. During the last fifteen years, our research group has been actively involved in the development of this fascinating reaction as an useful synthetic tool in organic chemistry and has in fact contributed significantly in this direction. With a view to further expand the scope of Baylis-Hillman chemistry in organic

synthesis, we have undertaken this research program with the following objectives.

1. Development of simple and convenient methodology for stereoselective synthesis of (*E*)-α-cyanocinnamyl alcohols and (*E*)-α-cyanocinnamic aldehydes from 3-aryl-3-hydroxy-2-methylenepropanenitriles, the Baylis-Hillman adducts derived from acrylonitrile, in aqueous media.
2. Development of simple methodology for synthesis of 2-methylenealkanoates and alkanenitriles *via* the regioselective nucleophilic (SN2') addition of hydride ion from $NaBH_4$ to (2Z)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)-alk-2-ene-nitriles, the allyl halides derived from Baylis-Hillman adducts, respectively in the presence of DABCO in environment friendly aqueous media.
3. Application of this methodology (objective 2) for the synthesis of methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir), the important hypoglycemic agents.
4. Application of methyl (2Z)-2-(bromomethyl)alk-2-enoates and (3Z)-3-(chloromethyl)alk-3-en-2-ones as electrophiles in the Baylis-Hillman reaction with

acrylonitrile in the presence of DABCO leading to synthesis of functionalized 1,4-pentadienes.

5. Synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates and methyl 3-aryl-2-methylene-3-phenoxypropanoates *via* the nucleophilic addition (SN2') of prop-2-yn-1-ol (propargyl alcohol) and phenol respectively to methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates in the presence of triethylamine.
6. Enantioselective synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates *via* chiral leaving group strategy.

Stereoselective synthesis of (*E*)-α-cyanocinnamyl alcohols and (*E*)-α-cyanocinnamic aldehydes

Development of simple and convenient methodology for stereoselective synthesis of (*E*)-α-cyanocinnamyl alcohols and (*E*)-α-cyanocinnamic aldehydes has been an important endeavor in synthetic organic chemistry because these molecules constitute an important class of synthons for synthesis of various biologically active and heterocyclic molecules. In continuation of our studies on the development of the Baylis-Hillman reaction as a novel source for stereoselective processes, we have developed an aqueous sulfuric acid (20%) mediated

isomerization of the Baylis-Hillman adducts, *i.e.* 3-aryl-3-hydroxy-2-methylene-propanenitriles **(48a-g)** derived from an activated alkene, acrylonitrile, thus providing simple and efficient methodology for synthesis of (*E*)-α-cyanocinnamyl alcohols **(49a-g)** in good yields (eq. 29 & 30). Subsequent oxidation of these (*E*)-α-cyanocinnamyl alcohols **(49a-g)** with pyridinium chlorochromate (PCC) provided the desired stereochemically pure (*E*)-α-cyanocinnamic aldehydes **(50a-g)** (eq. 33 & 34). This methodology represents an efficient alternative route to Knoevenagel condensation reaction.

Simple synthesis of **2-methylenealkanoates and** alkanenitriles

Development of simple and convenient methodology for the synthesis of 2-methylenealkanoates and alkanenitriles is an interesting problem in organic synthesis because of their versatile applications as synthons in the synthesis of various biologically active molecules and liquid crystalline polymers. For example, methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (51) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52) have been found to be potent inhibitors of the fatty acid oxidation and oral hypoglycemic agents in mammals including human beings. In connection with our ongoing research program in environment friendly chemistry and sodium borohydride chemistry, we have planned to develop a general and convenient

methodology for the synthesis **of pure 2-methylenealkanoates (55a-g)** *via* the regioselective nucleophilic **(S_N2')** addition of hydride ion from sodium borohydride to methyl **(2*Z*)-2-(bromomethyl)alk-2-enoates (54a-g),** the **allyl** bromides obtained from the corresponding Baylis-Hillman adducts *i.e.* methyl 3-**hydroxy-2-methylenealkanoates (53a-g),** in environment friendly aqueous media. Thus, treatment of methyl (2Z)-2-(bromomethyl)alk-2-enoates **(54a-g)** with DABCO in the presence of H_2O/THF at room temperature followed by the treatment with $NaBH_4$ at room temperature provided the desired pure 2-**methylenealkanoates (55a-g)** in high yields (Schemes 42 & 43).

With a view to understanding the generality of this methodology, we have also transformed 2-(bromomethyl)alk-2-enenitriles **(57a-c, 58-61),** the allyl bromides obtained from the corresponding Baylis-Hillman adducts **(48a-c, e, h-j),** into 2-**methylenealkanenitriles (63a-g)** in high yields (Schemes **44** & 45).

Synthesis of hypoglycemic agents

To prove the efficacy of this methodology we have undertaken the synthesis of two representative hypoglycemic agents methyl 2-tetradecyloxirane-2-carboxylate (methyl **palmoxirate)** (51) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52).

Synthesis of methyl **2-tetradecyloxirane-2-carboxylate** (methyl palmoxirate)

We have synthesized methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (51) *via* the reaction of methyl 2-methylenehexadecanoate (55g) with *m*-CPBA in 1,2-dichloroethane at reflux temperature (eq. 40).

Synthesis of ethyl 2-|6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir)

We have next synthesized ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52) starting from 4-chlorophenol *via* the Baylis-Hillman methodology according to equations 41 & 42 and Schemes 46 & 47.

Application of (2Z)-2-(bromomethyl)alk-2-enoates and **(3*Z*)-3-(chloromethyl)alk-3-en-2-ones** as electrophiles in the Baylis-Hillman reaction: A novel synthesis of functionalized **1,4-pentadienes**

Though various electrophiles such as aldehydes, aldimines, α-keto esters, fluorinated ketones, non-enolizable 1,2-diketones, acrylonitrile, alkyl vinyl ketones have been successfully employed in the Baylis-Hillman reaction, application of allyl halides as electrophiles has not been studied so far in the literature. We have therefore undertaken this research program of examining the possible application of allyl halides as electrophiles in the Baylis-Hillman reaction. During our efforts in this study, we directed our attention towards the

application of methyl **(2*Z*)-2-(bromomethyl)alk-2-enoates (54a-e, 73, 74)** as electrophiles in the Baylis-Hillman reaction. Accordingly, we have developed a simple methodology for the coupling of acrylonitrile with methyl (2Z)-3-aryl-2-**(bromomethyl)prop-2-enoates (54a-e, 73, 74)** in the presence of DABCO at room temperature for 7 days, thus leading to the formation of **functionalized** 1,4-pentadienes **(72a-g)** (eq. 43 & **44).**

With a view to understanding the generality of this reaction, we have also **carried** out the coupling of acrylonitrile with **(3*Z*)-4-aryl-3-(chloromethyl)but-3-en-2-ones** (75a-c) in the presence of DABCO at room temperature to provide the desired 2-**acetyl-3-aryl-4-cyanopenta-1,4-dienes (76a-c)** (eq. 46 & 47).

Synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates and methyl 3-aryl-2-methylene-3-phenoxypropanoates

With a view to expand the scope of the **allyl** bromides, methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates **(54a-e,** 73, **74)** in organic synthesis, we have used propargyl alcohol as a nucleophile for addition onto these allyl bromides in S_N2' fashion under the influence of **triethylamine** thus providing a simple methodology for the synthesis of **3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (79a-g)** in high yields (eq. 53 & 54).

We have next used phenol as a nucleophile for the addition (S_N2') onto methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates **(54a-e, 73, 74)** in the presence of triethylamine to provide the desired methyl 3-aryl-2-methylene-3-phenoxy-propanoates **(80a-g)** in good yields (eq. 55 & 56).

Enantioselective synthesis **of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates** *via* **chiral leaving group strategy**

On the basis of above successful results, we envisioned that if we use a chiral tertiary amine in place of triethylamine, which subsequently becomes a chiral leaving group, there might be chiral induction. We have therefore directed our studies towards the enantioselective synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (79) *via* chiral leaving group strategy. We have thus developed a simple method for enantioselective synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates {(-)-79a-g} in 25-40% enantiomeric excess *via* the nucleophilic addition (S_N2') of prop-2-yn-l-ol to a representative class of methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates **(54a-e, 73, 74)** in the presence of quinidine (Schemes 59 & 60).

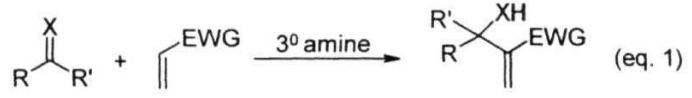
The third chapter deals with the experimental procedures in detail, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, elemental analyses and physical constants (bp, mp and optical rotations).

INTRODUCTION

Synthetic organic chemistry is one of the most rapidly developing, expanding and successful branches of science. Construction of carbon-carbon bonds and carbon-hetero atom bonds is one of the most fundamental reactions in synthetic organic chemistry and hence represents a forefront of research in organic chemistry.[1-6] More recently, the concepts of atom economy, selective (both stereo- and regio-) transformations and catalytic processes have become primary requirements for the development of synthetic organic chemistry to be one of the leading scientific disciplines.[1]* During the last fifteen years, synthetic organic chemistry has seen enormous growth, not only in terms of development of new methodologies for construction of carbon-carbon bonds and carbon-hetero atom bonds but also in terms of development of new reagents, catalysts, strategies, transformations and technologies often involving the concepts of atom economy and selectivity. Though the arsenal of synthetic organic chemistry is now very rich in the sense that there are methods available to synthesize any molecule which was once thought to be difficult to prepare, the continuing sophistication in and ever changing scenario of synthetic organic chemistry requires and even demands the continuous evolution of synthetic methods that meet the requirements of atom

economy and very high levels of selectivity. The Baylis-Hillman reaction[9] is one such atom economy reaction, which has been nowadays recognized, as an useful and emerging reaction having enormous synthetic potential as a source for various stereoselective processes.[10,,12]

The Baylis-Hillman reaction originates from a German patent.[9] It is a catalytic process, essentially involving three components, leading to the construction of a carbon-carbon bond between the a-position of activated alkene and carbon electrophile under the catalytic influence of a tertiary amine, particularly DABCO (1), thus producing synthetically useful multifunctional molecules (eq. 1).[10-12]

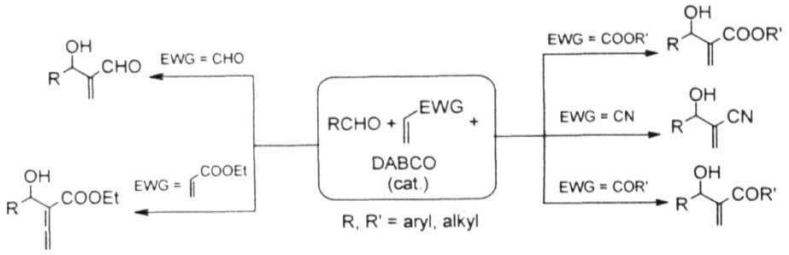


(eq. 1)

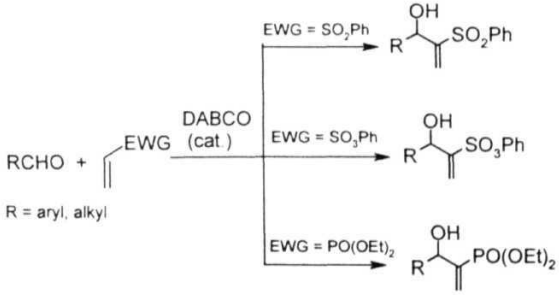
X = O, NR^2 EWG = electron withdrawing group

A variety of activated alkenes such as acrylic acid esters,[13,14] acrylonitrile,[15,16] vinyl ketones,[16-18] acrolein,[19-21] allenic esters,[2223] vinyl sulfones,[24] vinyl sulfonates[25] and vinyl phosphonates[26] have been extensively employed in this reaction (Scheme 1 & 2).

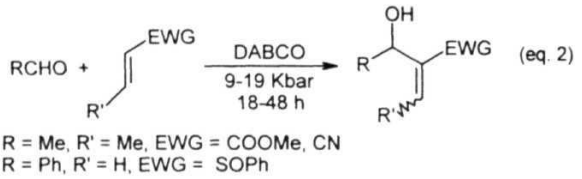
Scheme 1



Scheme 2

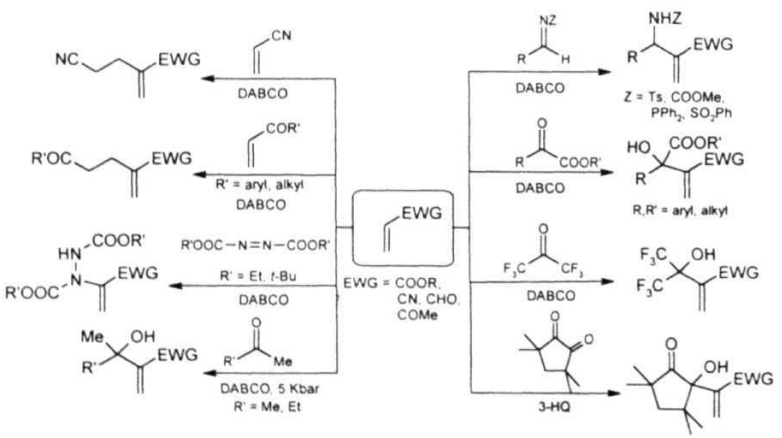


The p-substituted activated alkenes such as methyl crotonate,[27] crotononitrile[27] and the less reactive activated alkene, phenylprop-1-enyl sulfoxide[28] do not react with aldehydes at normal conditions. They require high pressure (9 to 19 Kbar) to undergo the Baylis-Hillman coupling with aldehydes (eq. 2).



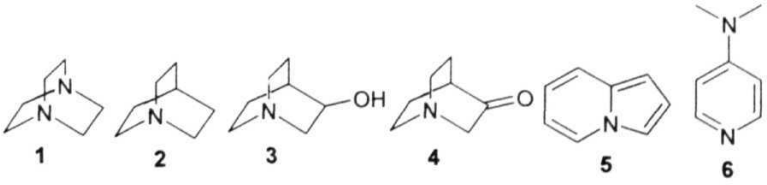
Though aldehydes are the most commonly used electrophiles, a number of other carbon electrophiles such as aldimines,[29-31] α-keto esters,[32-34] fluorinated ketones,[35] non-enolizable 1,2-diketones,[20] acrylonitrile,[36,37] alkyl and aryl vinyl ketones[36,37] have been utilized in the Baylis-Hillman reaction (Scheme 3).

Scheme 3



The non-carbon electrophiles like **dialkyl azodicarboxylates**[38] have also been employed successfully in the Baylis-Hillman coupling with activated alkenes (Scheme 3). The less reactive ketones such as propan-2-one, butan-2-one do not undergo Baylis-Hillman reaction with activated olefins at atmospheric pressure. However, they were brought into the scope of this reaction at high pressure (Scheme 3).[19,27]

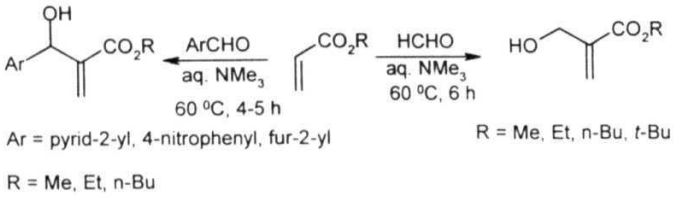
Though DABCO (1) is the most commonly used catalyst, a variety of other tertiary amine catalysts such as quinuclidine (2), 3-hydroxyquinuclidine **(3-HQ)** (3). quinuclidinone (4), pyrrocoline (5) and 4-DMAP (6) have been employed in this reaction.[9,11,12,39]



Very recently, our research group has demonstrated an interesting aqueous trimethylamine mediated Baylis-Hillman coupling of **alkyl acrylates with reactive**

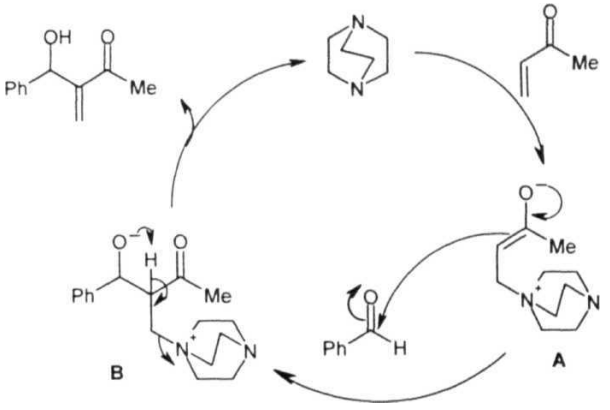
aldehydes and formaldehyde to provide the desired multifunctional molecules (Scheme 4).[40]

Scheme 4



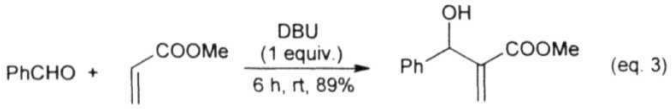
The most accepted mechanism of the Baylis-Hillman reaction[11,41-43] is shown in Scheme 5, considering the reaction between benzaldehyde and methyl vinyl ketone under the catalytic influence of DABCO as a model case. The first step is believed to involve Michael type nucleophilic addition of the tertiary amine (DABCO) to the activated alkene (methyl vinyl ketone) to produce the zwitterionic enolate (A), which makes the nucleophilic attack on the electrophile (benzaldehyde) to afford the zwitterionic species (B). Subsequent proton migration followed by the elimination of the tertiary amine results in the formation of multifunctional molecule (Scheme 5).

Scheme 5



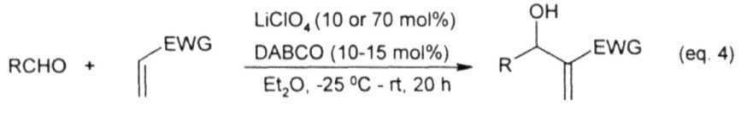
The normal DABCO catalyzed Baylis-Hillman transformation of activated alkenes and electrophiles into the corresponding adducts is a very slow process and requires few days to few weeks for completion depending upon the substrates. Therefore, to surmount this problem of slow reaction rate, effect of several factors like hydrogen bonding,[44-46] high pressure,[19,27] ultrasound,[47] microwave irradiation,[48] low temperature (at 0 °C),[49] utilizing aqueous medium (also using additives such as NaI and LiI in aqueous medium)[50] and using lanthanum triflates[51,52] have been examined with moderate to remarkable success. **Recently, Aggarwal and**

Mereu have demonstrated that bicyclic tertiary amine, DBU, accelerates the Baylis-Hillman reaction much faster than the DABCO and 3-hydroxyquinuclidine (eq. 3).[53]



(eq. 3)

Kawamura and Kobayashi reported the application of lithium perchlorate ($LiClO_4$) in ether as an additive (along with a catalytic amount of DABCO) in accelerating the Baylis-Hillman reaction (eq. 4).[21]



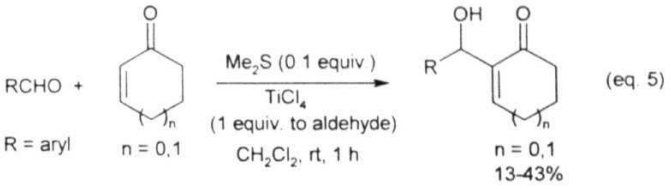
(eq. 4)

R = aryl, alkyl, EWG = COOR', COMe, CHO, CN *etc.* 35-85%

Non-tertiary amine catalyzed Baylis-Hillman reaction

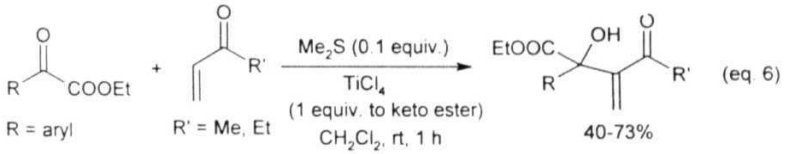
Several non-tertiary amine catalysts or catalytic systems, for example, trialkylphosphines,[54-56] $RhH(PPh_3)_4$,[57,58] $RuH_2(PPh_3)_4$,[58,59] have been used as catalysts for coupling of various activated alkenes with aldehydes to obtain the desired multifunctional molecules. Recently, Kataoka *et al.* demonstrated the

applications of sulfides or sclenides (chalcogenides) as catalysts in presence of $TiCl_4$, in the Baylis-Hillman reaction (eq. 5).[60-63]



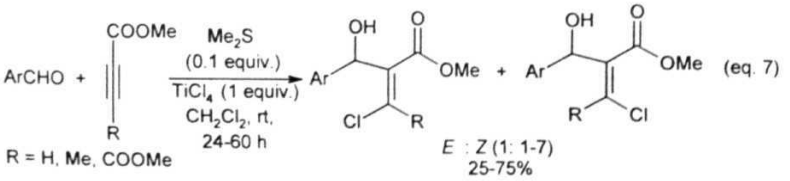
(eq. 5)

Our research group has successfully demonstrated the application of α-keto esters as electrophiles in the chalcogeno-Baylis-Hillman reaction (eq. 6).[64]



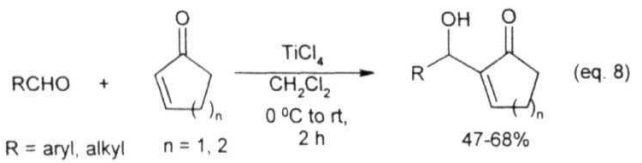
(eq. 6)

Kataoka *et al.*[65] described an interesting chalcogeno-Baylis-Hillman reaction of activated **alkynes** with aldehydes, thus providing a simple method for the preparation of p-halo-a-(hydoxybenzyl)acrylates (eq. 7).

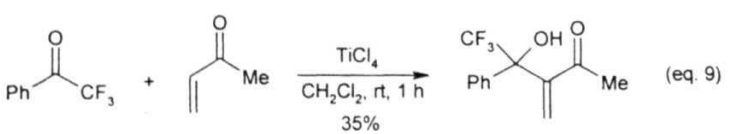


(eq. 7)

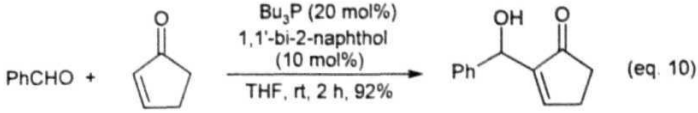
$TiCl_4$ mediated Baylis-Hillman reaction of various aldehydes with α,β-unsaturated ketones has been recently reported by Li and coworkers (eq. 8).[66]



Very recently, in our laboratory, trifluoromethyl phenyl ketone has been utilized as an electrophile in the Baylis-Hillman reaction with methyl vinyl ketone under the influence of TiCU, leading to the formation of 1,1,1-trifluoro-2-hydroxy-2-phenyl-3-methylenepentan-4-one (eq. 9).[67]

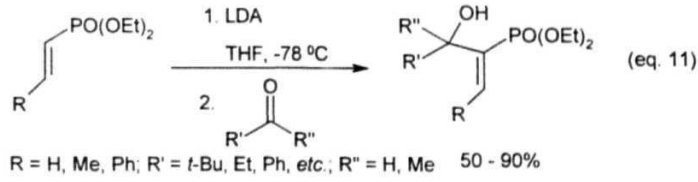


Yamada and Ikegami have found that Bu_3P catalyzes the Baylis-Hillman reaction more efficiently in the presence of (±)-1,1'-bi-2-naphthol to give the desired products (eq. 10).[68]



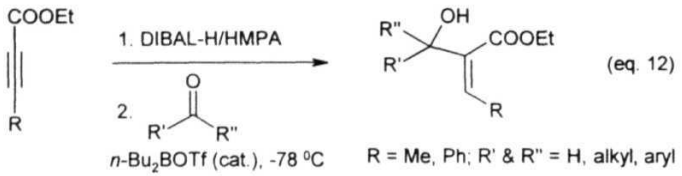
(eq. 10)

Nagaoka and Tomioka have described the Baylis-Hillman type carbon-carbon bond formation between the a-position of alkenylphosphonates with carbonyl compounds under the influence of LDA leading to the synthesis of α-hydroxyalkylated vinyl phosphonates (eq. 11).[69]



(eq. 11)

Li *et al.*[70] have reported the stereospecific synthesis of (*Z*)-β-branched Baylis-Hillman coupling products with high selectivity *via* the reaction between acetylenic esters and carbonyl compounds under the influence of DIBAL-H/HMPA in the presence of catalytic amount of Lewis acid, n-Bu_2BOTf (eq. 12).

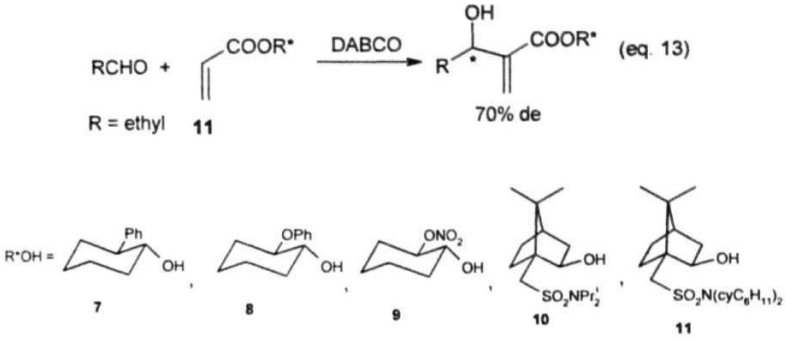


Asymmetric Baylis-Hillman Reaction

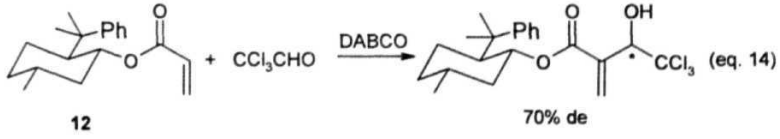
The asymmetric version of the Baylis-Hillman reaction has attracted much attention in recent years. The asymmetric induction can be achieved in this reaction by employing chiral source in any one of the three components *i.e* activated alkene, electrophile or tertiary amine. Recent developments in this direction have been described in the following.

i) Chiral activated alkenes:

So far only chiral acrylate/acrylamide derivatives have been employed as chiral activated alkenes in the Baylis-Hillman reaction probably because of the easy availability of these derivatives and easy removal of the chiral auxiliaries from the products. In our laboratory, the asymmetric Baylis-Hillman reaction has been studied using a variety of chiral acrylates **(7-11)** (eq. 13).[71-74] The maximum diastereoselectivity achieved in these studies is 70% in the reaction of 11, derived from Oppolzer's chiral auxiliary, with propionaldehyde in the presence of DABCO (eq. 13).[72]



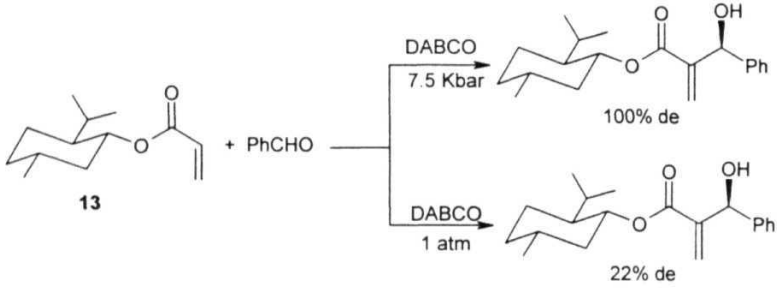
Drewes and coworkers[75] employed 8-phenylmenthyl acrylate (12) as chiral activated alkene in the Baylis-Hillman reaction with a variety of aldehydes under the catalytic influence of DABCO. The best asymmetric induction (70% de) was obtained when the chiral acrylate 12 was treated with chloral (eq. 14).



Gilbert *et al.* reported the influence of high pressure in the asymmetric Baylis-Hillman reaction. Thus, the reaction of menthyl acrylate (13) with benzaldehyde

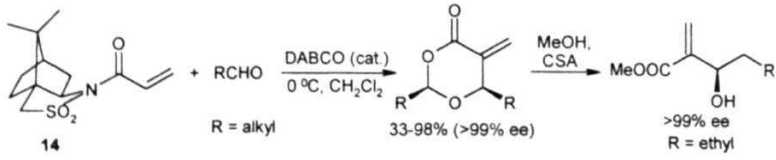
in the presence of DABCO at high pressure (7.5 Kbar) provides the product with 100% de while the same reaction at atmospheric pressure provides the desired Baylis-Hillman adduct in only 22% diastereoselectivity (Scheme 6).[76]

Scheme 6

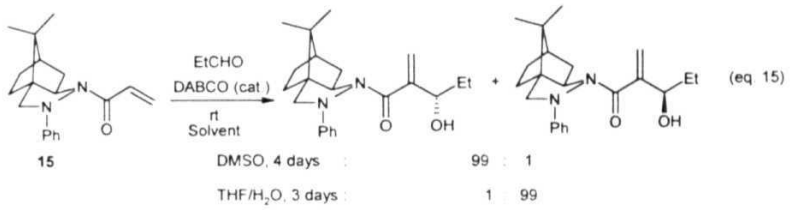


Chiral acrylamide 14 derived from camphorsulfonic acid has been successfully used as an activated alkene for asymmetric Baylis-Hillman reaction with various aldehydes to provide the desired adducts in high enantioselectivities (Scheme 7).[77]

Scheme 7



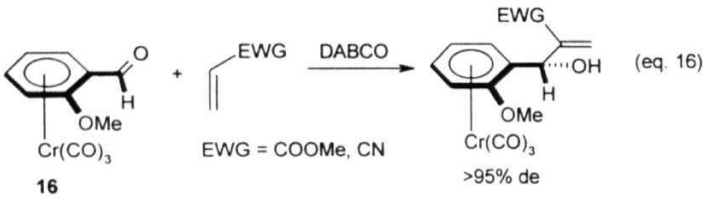
Very recently, Yang and Chen have reported the applications of chiral acryloylhydrazide (15) as a novel chiral activated alkene in the Baylis-Hillman reaction with aldehydes to provide the desired β-hydroxy-α-methylene carbonyl derivatives in high diastereoselectivities (eq. 15).



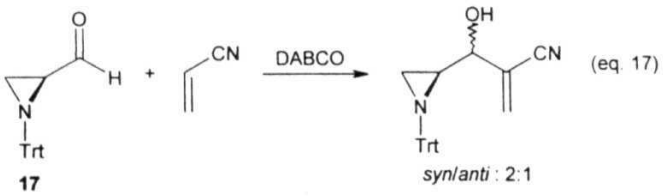
ii) Chiral electrophiles:

Attempts have been made to employ several non-racemic electrophiles for coupling with various activated alkenes **to achieve high levels of disatereoselectivity in the Baylis-Hillman reaction. Thus various chiral aldehydes such as** (S)-O-(methoxymethyl)lactaldehyde,[79] (S)-3-benzyloxybutyraldehyde,[80] α-dialkylamino **and** α-(N-acylamino)aldehydes[81,82] **have been utilized as chiral electrophiles in this fascinating reaction with moderate diastereoselectivities.** Kundig *et al.*[83,84] **employed ortho susbstituted benzaldehyde tricarbonylchromium complex (16) as an electrophile in the Baylis-Hillman reaction with methyl**

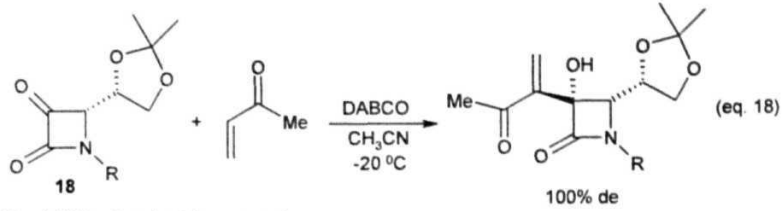
acrylate and acrylonitrile catalyzed by DABCO to afford the desired Baylis-Hillman adducts in >95% de (eq. 16).



Zwanenburg and coworkers[85] have used N-trityl aziridine-2-(S)-carboxaldehyde (17) as a chiral electrophile for the Baylis-Hillman reaction with activated alkenes in the presence of a catalytic amount of DABCO (eq. 17).

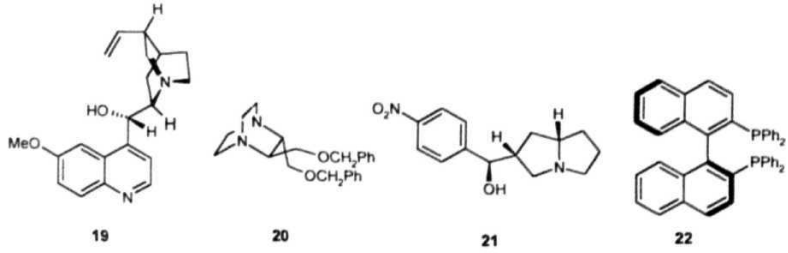


Very recently, Alcaide *et al*. reported an interesting reaction of enantiomerically pure 3-oxo-2-azetidinones (18) with methyl vinyl ketone in the presence of DABCO to provide functional ized 3-substituted-3-hydroxy-β-lactams in diastereomerically pure form (eq. 18).[86]



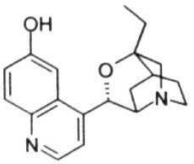
iii) Chiral catalysts:

Efforts have been made to expand the scope of the asymmetric Baylis-Hillman reaction using various chiral tertiary amines / other catalysts. For example, quinidine **(19)**,[10,71,87] chiraJ DABCO **(20)**,[88] pyrrolizidine **(21)**,[89] (S)-BINAP **(22)**[90] have been used as chiral catalysts in this reaction with moderate success (up to 67% ee).

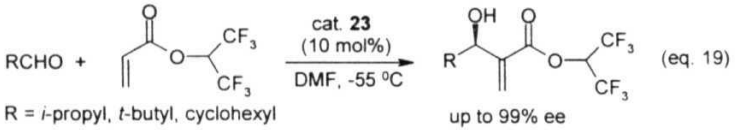


Recently, Hatakayama and **coworkers**[91] have successfully employed new chiral catalyst **(3R,8R,9S)-10,11-dihydro-3,9-epoxy-6'-hydroxycinchonane** (23) for

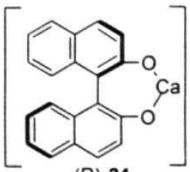
achieving high levels of asymmetric induction in the Baylis-Hillman reaction of 1,1,1,3,3,3-hexafluoroisopropyl acrylate with various aldehydes (eq. 19).



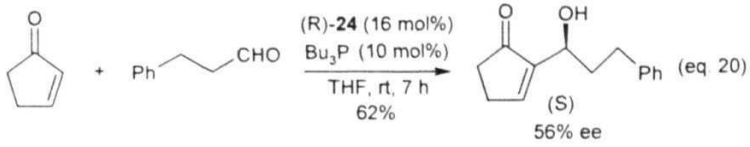
23



Yamada and Ikegami have demonstrated the application of the chiral molecule 24 in catalytic amount in combination with Bu_3P (catalyst) in the Baylis-Hillman reaction of cyclopent-2-en-1-one with 3-phenylpropanal to provide the desired Baylis-Hillman adduct with 56% ee (eq. 20).[68]

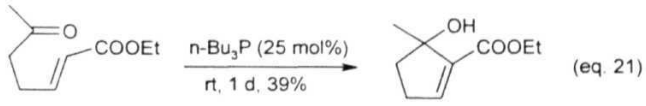


(R)-**24**

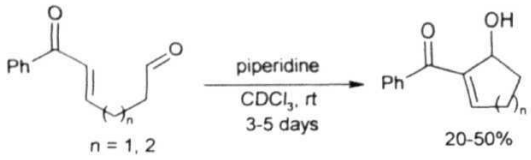


Intramolecular Baylis-Hillman reaction

In spite of the rapid developments and advances made in the Baylis-Hillman chemistry, limited success has been reported in the aspect of intramolecular Baylis-Hillman reaction. Roth *et al*. reported an intramolecular Baylis-Hillman reaction of (2*E*)-6-oxohept-2-enoate under the influence of n-Bu_3P (eq. 21).[92]



Recently Murphy and coworkers[93,94] described the secondary amine mediated intramolecular Baylis-Hillman reaction of (4*E*)-6-phenyl-6-oxohex-4-enal and (5*E*)-7-phenyl-7-oxohept-5-enal to obtain the substituted cyclopentenols and cyclohexenols (eq. 22).



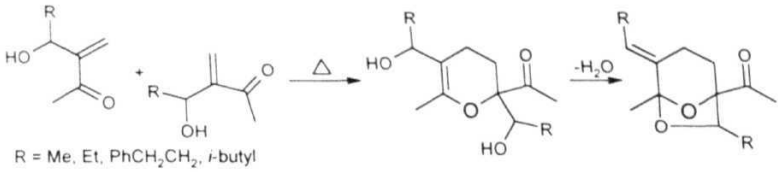
(eq. 22)

Applications of the Baylis-Hillman adducts

The Baylis-Hillman reaction provides a simple and efficient atom economic synthesis of an interesting class of molecules having chemospecific functional groups.[10,11,12] The proximity of these chemospecific functional groups have made these molecules as valuable substrates for a variety of stereoselective transformations.[10-12] A large number of publications have appeared in recent years describing various applications of Baylis-Hillman adducts in a number of stereoselective transformations. This section describes some of the important and most recent transformations and their applications in organic synthesis.

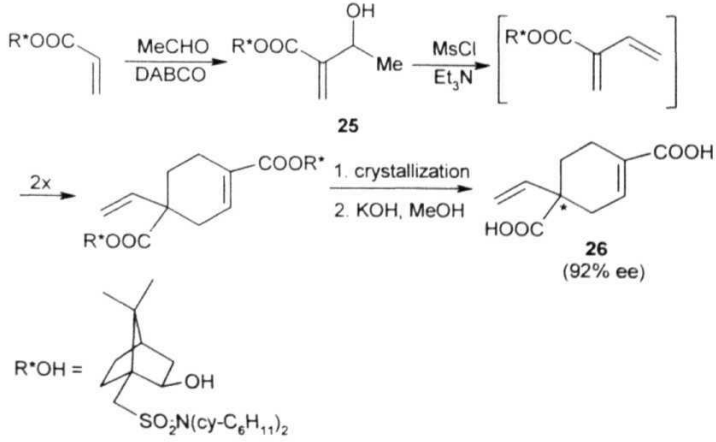
Hoffmann and coworkers reported a convenient synthesis of fiinctionalized 6,8-dioxabicyclo[3.2.1]octane moiety, an important basic framework present in a number of pheromones, *via* intermolecular dehydrative double cyclization of the Baylis-Hillman adducts, obtained from methyl vinyl ketone (Scheme 8).[95]

Scheme 8



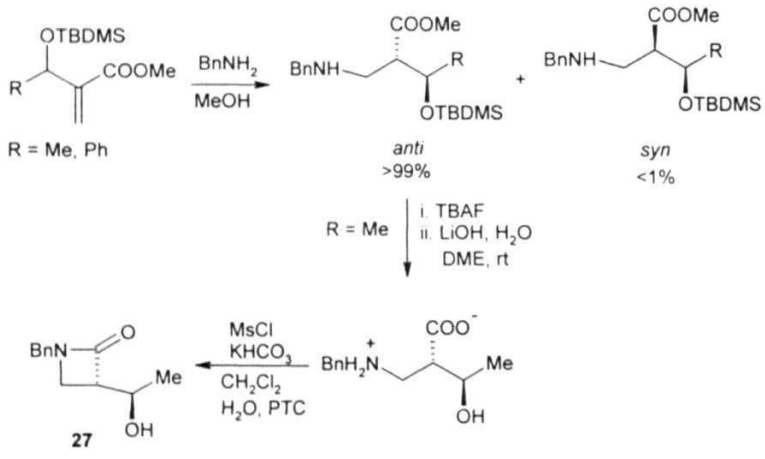
Our research group has reported, the first enantioselective synthesis of mikanecic acid (26) a terpene dicarboxylic acid possessing chiral quarternary vinylic center *via* Diels-Alder type self dimerization of diene carboxylate obtained from the Baylis-Hillman adduct (25) (Scheme 9).[96]

Scheme 9



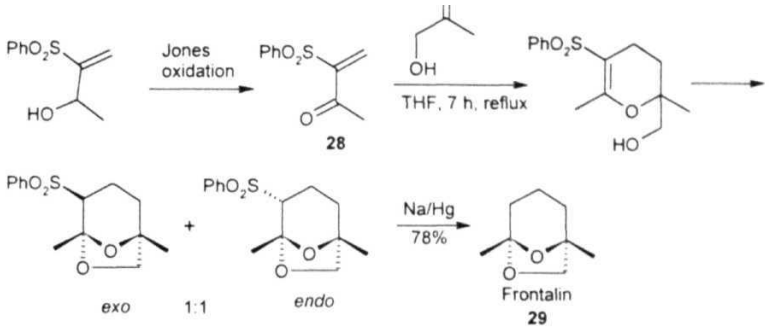
Perlmutter and Tabone[97,98] have reported a simple synthesis of β-lactam (27) *via* stereoselective conjugate addition of benzylamine to the O-protected Baylis-Hiilman adducts according to Scheme 10.

Scheme 10

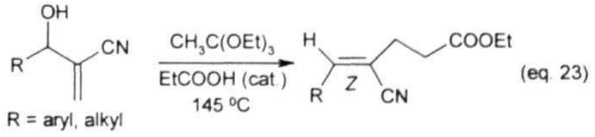


Weichert and Hoffmann have successfully converted a-methylene-p-keto sulfone **(28)**, obtained from oxidation of the corresponding Baylis-Hillman adduct, into frontalin (29) according to Scheme 11.

Scheme 11



The Johnson-Claisen rearrangement of 3-hydroxy-2-methylenealkanenitriles, the Baylis-Hillman adducts obtained from acrylonitrile, has been described from our laboratory thus providing simple stereoselective synthesis of trisubstituted alkenes (eq. 23).[100]

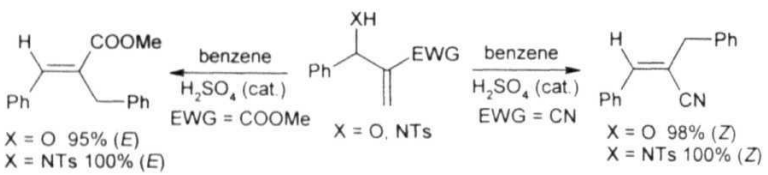


(eq. 23)

The Baylis-Hillman adducts, methyl 3-hydroxy-2-methylene-3-phenylpropanoate, 3-hydroxy-2-methylene-3-phenylpropanenitrile, methyl 2-methylene-3-phenyl-3-

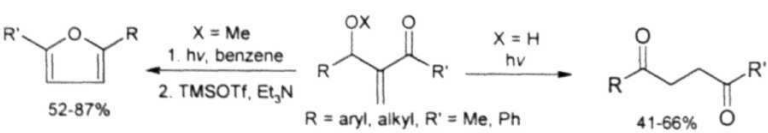
tosylaminopropanoate and 2-methylene-3-phenyl-3-tosylaminopropanenitrile were successfully used as β-electrophiles for the Friedel-Crafts reaction with benzene to provide the trisubstituted alkenes with high stereoselectivities (Scheme 12).[101,102]

Scheme 12



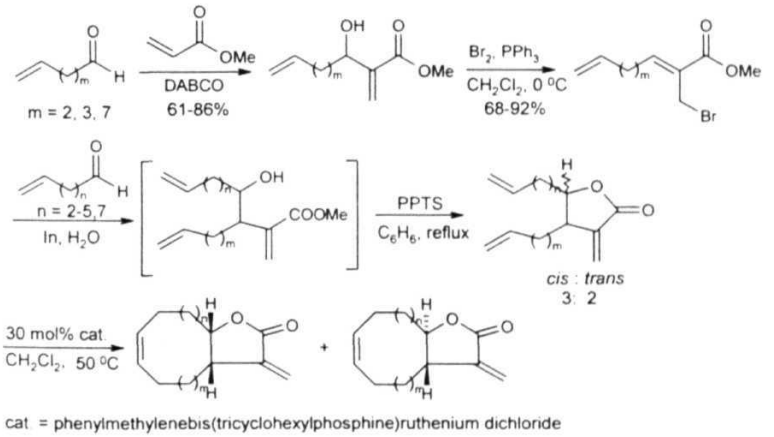
Mikami and coworkers[103,104] have transformed the Baylis-Hillman adducts and their derivatives into an interesting 1,4-diketones and substituted furan derivatives under photochemical conditions as described in Scheme 13.

Scheme 13



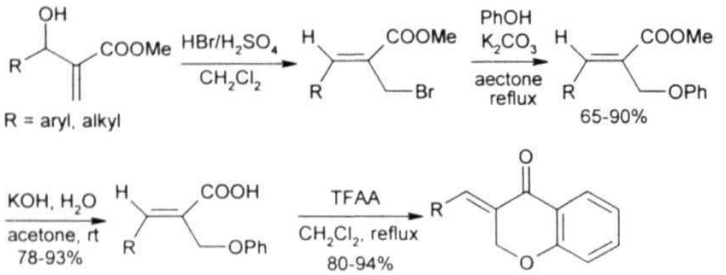
Paquette *et al.*[105] have described a general procedure for the synthesis of α-methylene-γ-lactones *cis*- or *trans*-fused to medium or large rings *via* Baylis-Hillman adducts following the sequence of reactions as described in Scheme 14.

Scheme 14



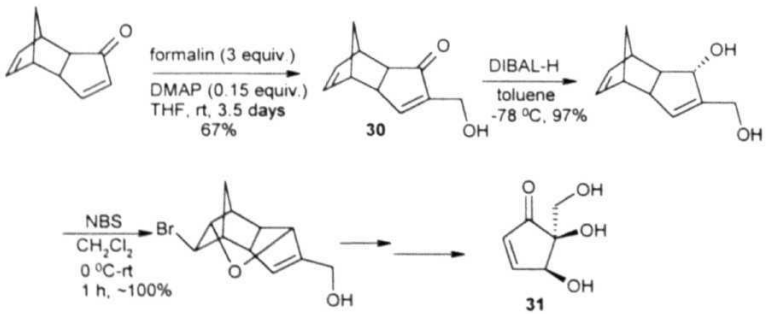
A new protocol for the synthesis of (*E*)-3-benzylidenechroman-4-one moiety, an important structural unit present in various biologically active molecules and natural products has been developed in our laboratory starting from the Baylis-Hillman adducts (Scheme 15).[106]

Scheme 15



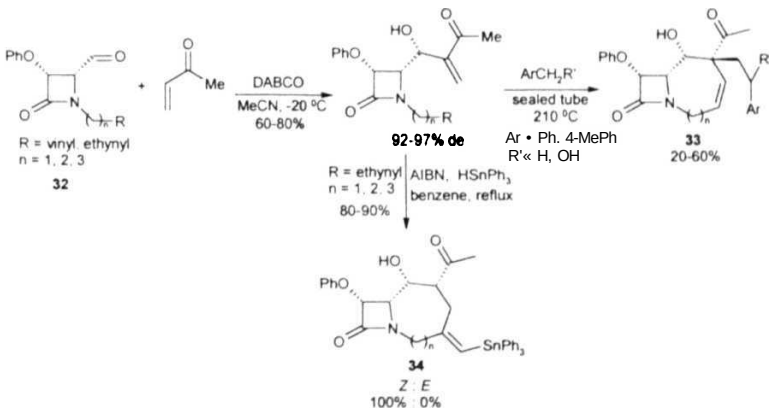
Sugahara and Ogasawara have developed a convenient synthesis of cyclopentanoid antibiotic (-)-pentenomycin 1 (31) using the Baylis-Hillman adduct 30 according to Scheme 16.[107]

Scheme 16

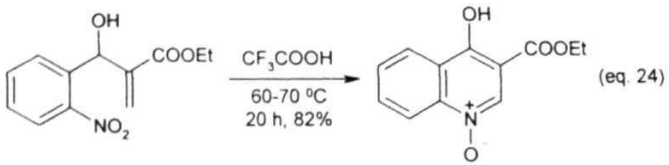


Recently, Alcaide *et al.*[108] have reported the stereoselective and divergent synthesis of highly functionalized bicyclic P-lactams (33 & 34) fused to medium rings through novel, chemocontrolled tandem radical addition-cyclization sequence using the Baylis-Hillman adducts derived from enantiopure 1-alkenyl- or alkynyl-4-oxoazetidine-2-carbaldehydes (32) (Scheme 17).

Scheme 17



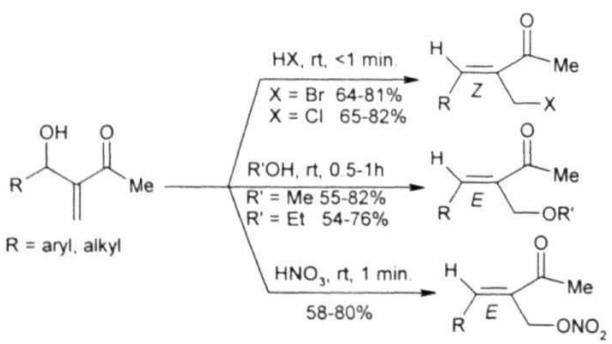
Kim *et al.* have successfully transformed the Baylis-Hillman adducts derived from substituted 2-nitrobenzaldehyde into an interesting class of 3-ethoxycarbonyl-4-hydroxyquinoline N-oxide (eq. 24).[109]



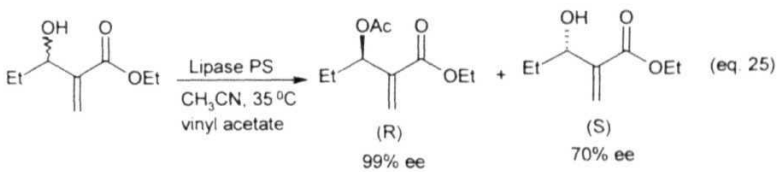
(eq. 24)

In our laboratory, 4-hvdroxy-3-methylenealkane-2-ones, the Baylis-Hillman adducts obtained from a reactive activated alkene, methyl vinyl ketone, have been successfully transformed into (Z)-keto allyl halides,[110] (*E*)-allyl ethers[111] and (*E*)-allyl nitrates[112] (Scheme 18).

Scheme 18

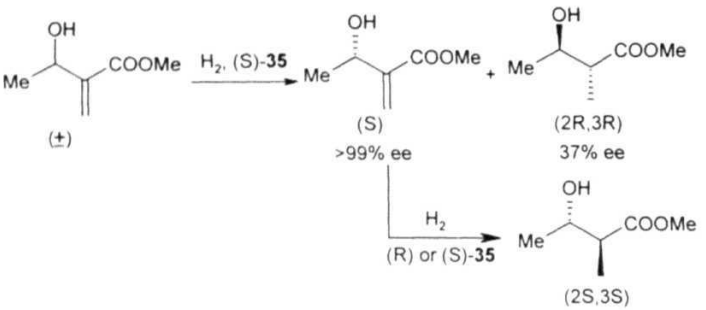


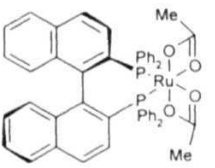
Enantiomerically pure/enriched Baylis-Hillman adducts were successfully prepared *via* the enzymatic resolution of racemic molecules using various biocatalysts such as *Pseudomonas* AK lipase,[113] pig liver acetone powder (PLAP)[114] and horseradish peroxidase (HRP).[115] Most recently lipase PS has been successfully used as a biocatalyst for the resolution of the Baylis-Hillman adducts by Hayashi *et al* (eq. 25)."[6]



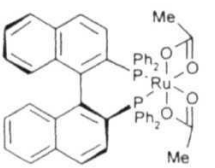
Asymmetric hydrogenation of racemic methyl 3-hydroxy-2-methylenebutanoate was reported by Noyori and coworkers[117] using (S)-BINAP-Ru(OAc)$_2$ {(S)-35} as catalyst, leading to the production of kinetically resolved Baylis-Hillman adduct, (S)-methyl 3-hydroxy-2-methylenebutanoate in >99% enantiomeric purity and the hydrogenated product with 37% enantiomeric purity. It is interesting to note that hydrogenation of (S)-methyl 3-hydroxy-2-methylenebutanoate with the catalytic influence of (S)- or (R)-BINAP-Ru(OAc)$_2$ {(S)- or (R)- 35} provided the same *anti*-isomer (Scheme 19).[117]

Scheme 19



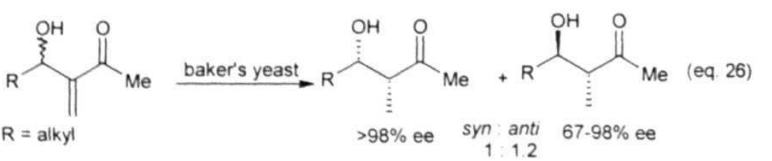


(R)-**35**



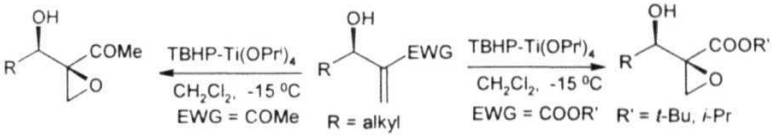
(S)-35

Utaka and covvorkers reported baker's yeast mediated reduction of the Baylis-Hillman adducts derived from methyl vinyl ketone, which proceeded with high enantioselection (eq. 26).[118]

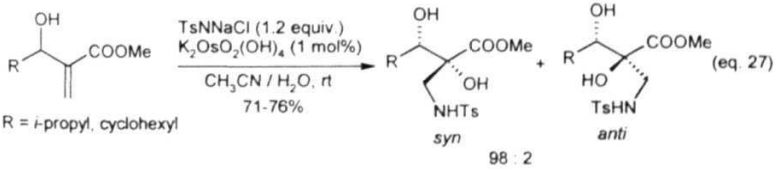


The Baylis-Hillman adducts were conveniently transformed into ***syn*** epoxides under Sharpless conditions (Scheme 20).[119,120]

Scheme 20

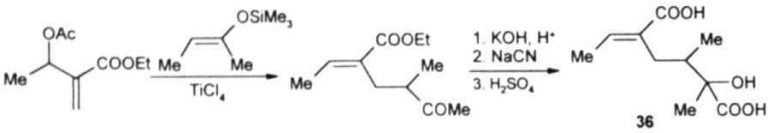


Elegant osmium catalyzed aminohydroxylation of the Baylis-Hillman adducts with high diastereoselectivity has been recently reported by **Pringle** and Sharpless (eq. 27).[121]



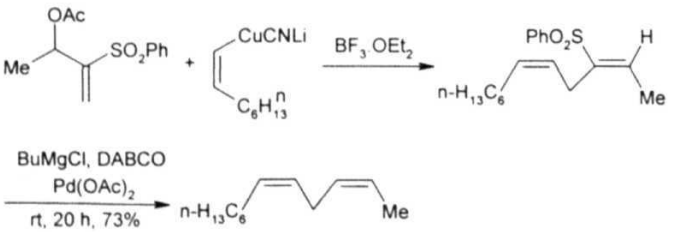
Drewes *et* ***al.***[13] have successfully transformed ethyl **3-acetoxy-2-methylene-butanoate,** the acetate of the Baylis-Hillman adduct into integerrinecic acid (36) (Scheme 21).

Scheme 21



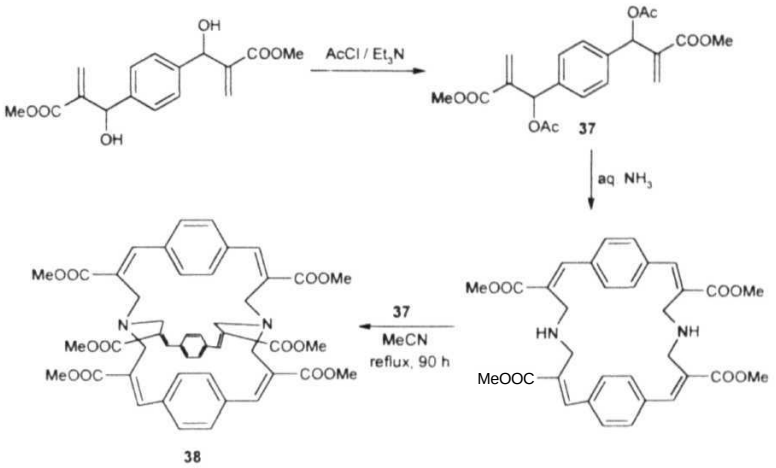
Knochel and coworkers[24,122] have described the stereoselective synthesis of skipped (Z.Z)-dienes *via* the regioselective nucleophilic addition of lithium cyanocuprates to the acetates of the Baylis-Hillman adducts obtained from phenyl vinyl sulfone following the synthetic pathway as described in Scheme 22.

Scheme 22



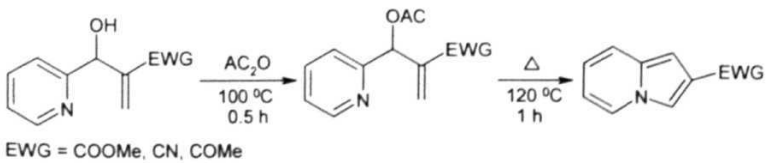
Bauchat and Foucaud have successfully transformed the diacetate (37) of the bis-Baylis-Hillman adduct, obtained from methyl acrylate and terephthaldehyde into diazamacrocycle (38) according to the Scheme 23.[123]

Scheme 23



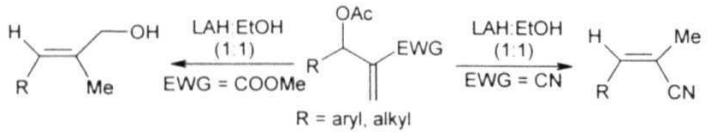
Bode and Kaye[124,125] have transformed the Bayiis-Hillman adducts obtained from 2-pyridinecarboxaldehyde into indolizines (Scheme 24).

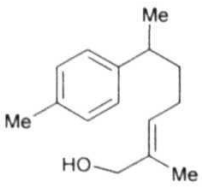
Scheme 24



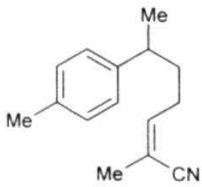
Our research group has developed a very simple method for stereoselective nucleophilic addition of hydride ion from lithium aluminium hydride (LAH)/ EtOH (1:1) to methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methy~ lenealkanenitriles thus providing general synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles respectively (Scheme 25).[126] The efficacy of this methodology has been demonstrated by the synthesis of (*E*)-nuciferol (**39**), a biologically active terpenoid and the precursor for (Z)-nuciferol (40).

Scheme 25





39

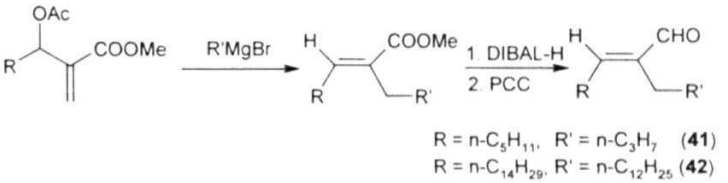


40

Stereoselective synthesis of (2*E*)-2-substituted alk-2-enoates and (2Z)-2-substituted alk-2-enenitriles *via* the treatment of the corresponding acetates of Baylis-Hillman adducts with Grignard reagents have been reported from our

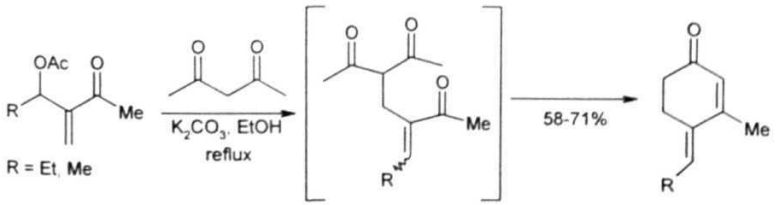
laboratory.[127] The efficacy of this methodology has been demonstrated by the synthesis of (2*E*)-2-butyloct-2-enal (41) an alarm pheromone component of the African weaver ant and (2*E*)-2-tridecylheptadec-2-enal (42) an unusual metabolite from the red alga *Laurenciaspecies* (Scheme 26).[128]

Scheme 26



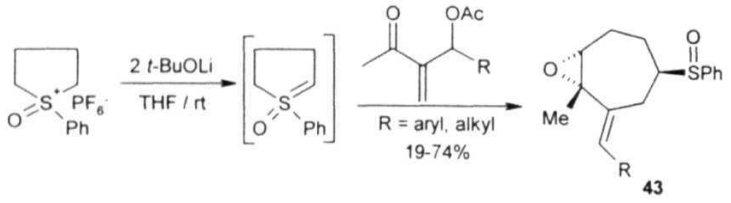
Chamakh and Amri transformed the acetates of the Baylis-Hillman adducts into (*E*)-4-alkylidene-2-cyclohexen-1-ones according to Scheme 27.[129]

Scheme 27



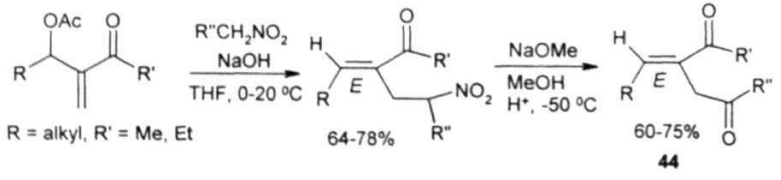
Fujimoto and his research group reported an interesting novel tandem Michael-intramolecular Corey-Chaykovsky reaction of cyclic oxosulfonium ylide with acetates of the Baylis-Hillman adducts thus providing a stereoselective synthesis of cycloheptene oxide derivatives (43) (Scheme 28).[130]

Scheme 28



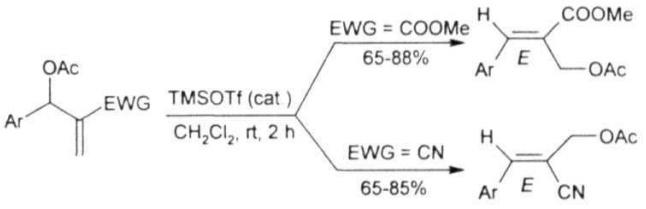
Very recently Amri and coworkers reported a simple route to (*E*)-2-alkylidene-1,4-diketones (44) *via* conjugate addition of nitroalkanes to acetates of the Baylis-Hillman adducts derived from methyl vinyl ketone, followed by Nef reaction (conversion of the nitro group into carbonyl group) (Scheme 29).

Scheme 29



Our research group reported the TMSOTf catalyzed stereoselective isomerization of acetates of the Baylis-Hillman adducts, *i.e.* methyl 3-acetoxy-3-aryl-2-methylenepropanoates and 3-acetoxy-3-aryl-2-methylenepropanenitriles thus providing a simple procedure for the preparation of methyl (2*E*)-2-(acetoxymethyl)-3-arylprop-2-enoates and (2*E*)-2-(acetoxymethyl)-3-arylprop-2-enenitriles respectively (Scheme 30).[132]

Scheme 30



OBJECTIVES, RESULTS AND DISCUSSION

It is quite clear from the preceding chapter that the Baylis-Hillman reaction occupies a special place in the area of synthetic organic chemistry due to its versatility and importance as a source for stereoselective processes. During the last fifteen years, our research group has been actively involved in the development *of* this fascinating reaction as an useful synthetic tool in organic chemistry and has in fact contributed significantly in this direction. With a view to further expand the scope of Baylis-Hillman chemistry in organic synthesis, we have undertaken this research program with the following objectives.

Objectives

1. Development of simple and convenient methodology for stereoselective synthesis of (*E*)-α-cyanocinnamyl alcohols and (*E*)-α-cyanocinnamic aldehydes from 3-aryl-3-hydroxy-2-methylenepropanenitriles, the Baylis-Hillman adducts derived from acrylonitrile, in aqueous media.
2. Development of simple methodology for synthesis of 2-methylenealkanoates and alkanenitriles *via* the regioselective nucleophilic (S_N2') addition of hydride ion from $NaBH_4$ to (2*Z*)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)-

alk-2-enenitriles, the allyl halides derived from Baylis-Hillman adducts, respectively in the presence of DABCO in environment friendly aqueous media.

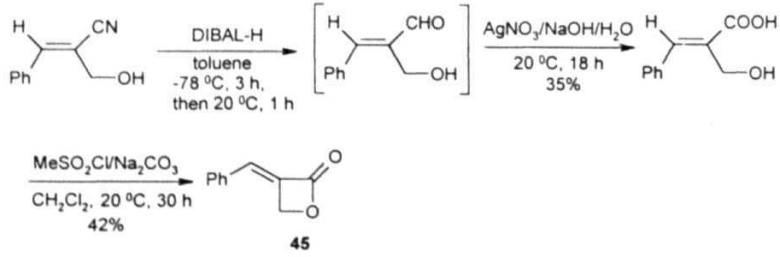
3. Application of this methodology (objective 2) for the synthesis of methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir), the important hypoglycemic agents.
4. Application of methyl (2Z)-2-(bromomethyl)alk-2-enoates and (3Z)-3-(chloromethyl)alk-3-en-2-ones as electrophiles in the Baylis-Hillman reaction with acrylonitrile in the presence of DABCO leading to synthesis of functionalized 1,4-pentadienes.
5. Synthesis of methyl 3-aryl-2-mcthylene-3-(prop-2-yn-l-yloxy)propanoates and methyl 3-aryl-2-methylene-3-phenoxypropanoates *via* the nucleophilic (S_N2') addition of prop-2-yn-1-ol (propargyl alcohol) and phenol respectively to methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates in the presence of triethylamine.
6. Enantioselective synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates *via* chiral leaving group strategy.

Results and Discussion

Stereoselective synthesis of (*E*)-α-cyanocinnamyl alcohols and (*E*)-a-cyanocinnamic aldehydes

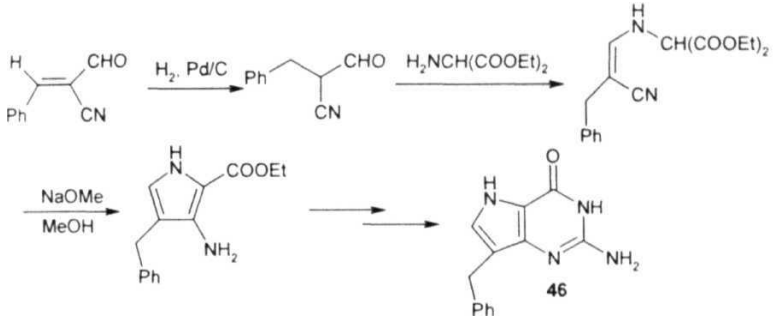
Development of simple and convenient methodology for stereoselective synthesis of (*E*)-α-cyanocinnamyl alcohols and (*E*)-α-cyanocinnamic aldehydes has been an important endeavor in synthetic organic chemistry because these molecules constitute an important class of synthons for synthesis of various biologically active and heterocyclic molecules.[133-140] Applications of these molecules for synthesis of representative important heterocyclic molecules such as **45-47** have been presented in Schemes 31-33.[136,137,139]

Scheme 31

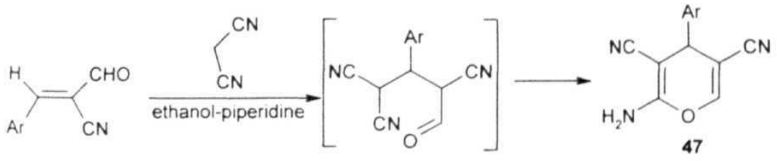


45

Scheme 32



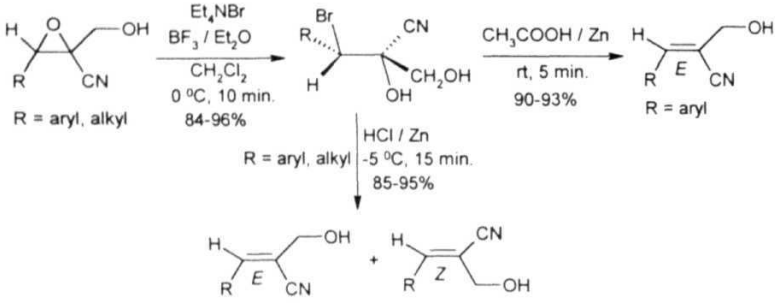
Scheme 33



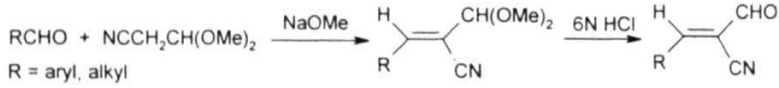
However, careful literature survey reveals that a very few methods are available for the synthesis of α-cyanocinnamyl alcohols[133-135] and α-cyanocinnamic aldehydes.[137,139,140] Some of the important methods are described in Schemes 34-

[133,137,139,140]

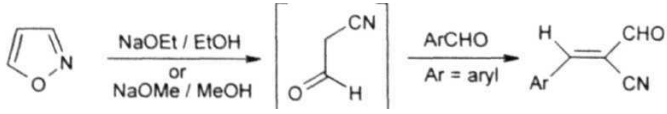
Scheme 34



Scheme 35



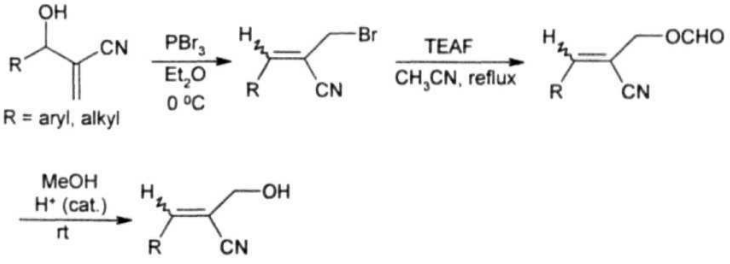
Scheme 36



Stereoselective synthesis of **(*E*)-α-cyanocinnamyl** alcohols

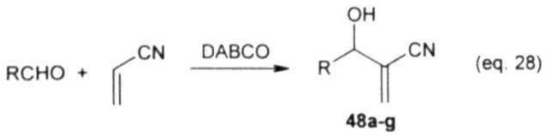
Recently, **Amri** and coworkers reported an interesting three step reaction sequence **"bromination-formylation-hydrolysis"** for conversion of 3-hydroxy-2-methylene-alkanenitriles, the **Baylis-Hillman** adducts obtained from **acrylonitrile**, into 3-substituted 2-cyano allylic alcohols in good (60-100%) **(*E*)-stereoselectivity (Scheme 37).**[134,135]

Scheme 37



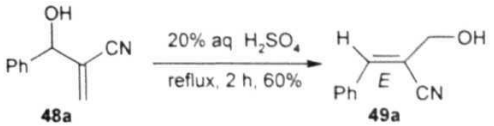
In **view** of the importance of 3-substituted 2-cyano allylic alcohols, we felt that it will be highly useful if the Baylis-Hillman adducts, 3-hydroxy-2-methylene-**alkanenitriles** can be transformed directly into 3-substituted 2-cyano allylic alcohols in one step with 100% **(*E*)-stereoselectivity**. Therefore, we have undertaken this research program of examining the possible isomerization of 3-**hydroxy-2-methylenealkanenitriles (48),** the Baylis-Hillman adducts, obtained

from acrylonitrile and representative aldehydes (eq. 28), with a view to provide a simple and convenient methodology for obtaining stereochemically pure (*E*)-3-substituted 2-cyano allylic alcohols.



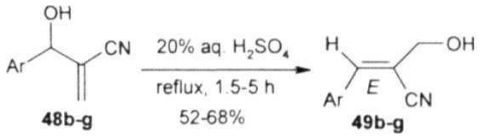
R = phenyl, 4-chlorophenyl, 4-methylphenyl, 4-isopropylphenyl, 2-methylphenyl, 2-methoxyphenyl, naphth-1-yl

During our studies in this direction, we have first examined the possible isomerization of 3-hydroxy-2-methylene-3-phenylpropanenitrile **(48a)** with aqueous sulfuric acid under variety of conditions. The best results were obtained when this molecule **48a** (5 mmol) was treated with aqueous sulfuric acid (20%, 10 mL) at reflux temperature for 2 hours, thus providing after usual work up followed by column chromatography (silica gel, 5% ethyl acetate in hexanes), stereochemically pure **(2*E*)-2-cyano-3-phenylprop-2-en-1-ol (49a)** in 60% yield (eq. 29). Structure of this molecule was confirmed by IR, ^{1}H NMR (Fig 1), ^{13}C NMR (Fig 2) spectral data and elemental analysis. Both **(*E*)-** and **(*Z*)-isomers** of **49a** are known in the literature and the spectral data is reported.[133-135] The **(*E*)-** stereochemistry of this molecule was confirmed by comparing the ^{13}C NMR spectral data with literature values.[9]



48a 49a (eq. 29)

Encouraged by this result, we have transformed the representative 3-aryl-3-hydroxy-2-methylenepropanenitriles **(48b-g)** into stereochemically pure (*E*)-α-cyanocinnamyl alcohols (**49b-g**) in good yields (eq. 30, Table 1). The (*E*)-**stereochemistry** of these molecules was assigned on the basis of C NMR chemical shift value of the allylic methylene carbon with that of **49a.**



48b-g **49b-g** (eq. 30)

R = 4-chlorophenyl, 4-methylphenyl, 4-isopropylphenyl, 2-methylphenyl, 2-methoxyphenyl, naphth-1-yl

However, our attempts to transform 3-hydroxy-2-mcthylenehexancnitrile and 3-hydroxy-2-methyleneoctanenitrile (obtained from the reaction of n-butyraldehyde and hexanal respectively with acrylonitnle in the presence of a catalytic amount of

[a] ^{13}C NMR spectral data for (*E*)- and (*Z*)-isomers of 49a are reported.[133-135] The allylic methylene carbon of the (*E*)-isomer appears at 6 * 64.00 while that of (*Z*)-isomer appears at δ ≈ 57.00.[133-135] In the case of our molecule, the allylic methylene carbon appears at δ 64.00. We have therefore assigned the (*E*)-stereochemistry to **49a**

Table 1: Synthesis of (*E*)-α-cyanocinnamyl alcohols (49a-g)[a]

Substrate	Ar	Reaction time (h)	Product	Yield[e] (%)
48a	phenyl	2	49a[f]	60
48b	4-chlorophenyl	5	49b[f]	62
48c	4-methylphenyl	15	49c[f]	68
48d	4-isopropylphenyl	2	49d[g]	65
48e	2-methylphenyl	2	49e[g]	67
48f	2-methoxyphenyl	2	49f[g]	52
	naphth-1-yl	:	49g[g]	58

a) All reactions were carried out on a 5 mmol scale of the allyl alcohol (48a-g) with 10 mL of aq. sulfuric acid (20%) at reflux temperature.

b) Products 49a, 49d and 49e were isolated as colorless liquids and 49b, 49c, 49f and 49g were isolated as solids after silica gel column chromatography (5% ethyl acetate in hexanes). All these molecules (49a-g) were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses.

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

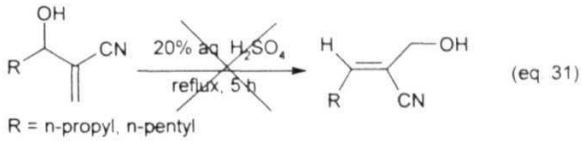
d) In all the cases, the ^{1}H NMR spectrum of the crude product shows the presence of* 5-20% unreacted starting material.

e) Isolated yields of the pure products either after column chromatography or after column chromatography followed by crystallization from ethyl acetate in hexanes.

0 These molecules (49a-c) are known in the literature. Spectral data of 49a-c is in agreement with literature data.[133-135]

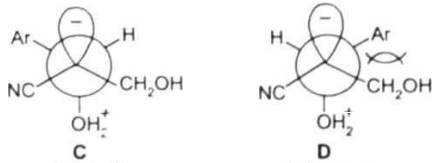
g) The (*E*)-stereochemistry of the molecules 49d-g was assigned by comparing the ^{13}C NMR chemical shift value of allylic methylene carbon with that of 49a.

DABCO) into the corresponding 3-substituted 2-cyano allylic alcohols were unsuccessful (eq. 31).

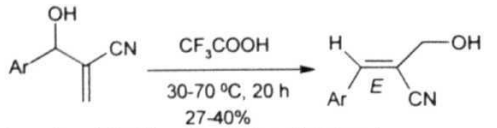


(eq. 31)

The (*E*)-selectivity in the sulfuric acid mediated transformation of the Baylis-Hillman adducts, *i.e,* 3-aryl-3-hydroxy-2-methylenepropanenitriles **(48a-g)** into (*E*)-α-cyanocinnamyl alcohols **(49a-g)** can be possibly explained through the transition state models C and D. The transition state C is more favored than I) due to the CN group having smaller steric effect than the CH_2OH group.



It is worth mentioning here that after our publication, Kim and coworkers have reported the similar transformation using trifluoroacetic acid at 30-70 °C to provide the corresponding (*E*)-α-cyanocinnamyl alcohols in 27-40% yields (eq. 32).[141]



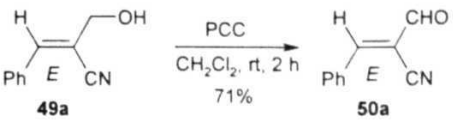
(eq. 32)

Ar = phenyl, 2-chlorophenyl, 4-methylphenyl

Stereoselective synthesis of (*E*)-α-cyanocinnamic aldehydes

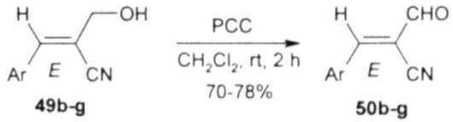
After the successful transformation of 3-aryl-3-hydroxy-2-methylenepropanenitriles **(48a-g)** into stereochemically pure (*E*)-α-cyanocinnamyl alcohols **(49a-g)** in good yields, we planned to oxidize these alcohols **49a-g** using pyridinium chlorochromate (PCC) to provide an efficient and alternative route to Knoevenagel condensation reaction to obtain stereochemically pure (*E*)-α-cyanocinnamic aldehydes. Accordingly, we have first treated **(2*E*)-2-cyano-3-phenylprop-2-en-1-ol (49a)** (2 mmol) with PCC (3 mmol) at room temperature for 2 hours in CH_2Cl_2, thus providing the desired **(2*E*)-2-cyano-3-phenylprop-2-enal (50a)** in 71% yield (eq. 33). Structure of this molecule was established by IR, ^1H NMR, ^{13}C NMR (Fig 3) spectral data and elemental analysis. Though this molecule **50a** was already known in the literature,[137,139,140] the stereochemical assignment was not reported. Therefore, we have established the **(*E*)-stereochemistry** of this molecule by a 2D NOESY experiment (Fig 4).[*]

[*] 2D NOESY spectrum clearly shows that there is correlation between β-vinylic proton (6 and aldehydic proton (5 9 60).



(eq 33)

With a view to understand the generality of this reaction, we have successfully transformed the representative (*E*)-α-cyanocinnamyl alcohols (**49b-g**) ***via*** the treatment with PCC, into (*E*)-α-cyanocinnamic aldehydes **(50b-g)** in good yields (eq. 34. Table 2).



(eq 34)

Ar = 4-chlorophenyl, 4-methylphenyl, 4-isopropylphenyl, 2-methylphenyl, 2-methoxyphenyl, naphth-1-yl

Thus, this methodology describes a facile aqueous sulfuric acid mediated one-step conversion of the Baylis-Hillman adducts *i.e.* 3-aryl-3-hydroxy-2-methylenepropanenitriles into (*E*)-α-cyanocinnamyl alcohols and subsequent oxidation with PCC leading to the formation of (*E*)-α-cyanocinnamic aldehydes. Thus, this methodology represents an efficient alternative route to Knoevenagel condensation reaction for obtaining stereochemically pure (*E*)-α-cyanocinnamic aldehydes.

Table 2: Synthesis of (*E*)-α-cyanocinnamic aldehydes (50a-g)[a-c]

Substrate	Ar	Product	Yield[d] (%)
49a	phenyl	**50a**[e]	71
49b	4-chlorophenyl	**50b**[f]	70
49c	4-methylphenyl	**50c**[f]	74
494	4-isopropylphenyl	**50d**[f]	71
49e	2-methylphenyl	**50e**[f]	77
49f	2-methoxyphenyl	**50f**[f]	75
49g	naphth-1-yl	**50g**[f]	78

a) All reactions were carried out on a 2 mmol scale of (*E*)-α-cyanocinnamyl alcohols (49a-g) with PCC (3 mmol) at room temperature for 2 hours in dichloromethane.

b) Products **50a-c**, **50e-g** were isolated as solids and the compound **50d** was isolated as colorless liquid. All these products gave satisfactory IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses. Molecules, **50a-d** and **50f-g** were known in the literature but their stereochemical assignment has not been reported.

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

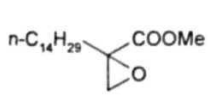
d) Isolated yields of the pure products obtained either after crystallization (**50a-c**, **50e-g**) from ethyl acetate and hexanes (1:2) or after silica gel column chromatography (**50d**) (2% ethyl acetate in hexanes).

c) The (*E*)-stereochemistry was assigned by a 2D NOESY experiment.

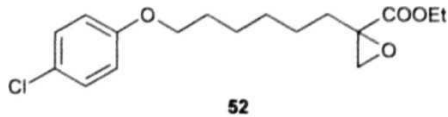
0 The (*E*)-stereochemistry was assigned in analogy with **50a.**

Simple synthesis of 2-methylenealkanoates and alkanenitriles *via* regioselective nucleophilic (S_N2') addition of hydride ion to allyl bromides derived from the Baylis-Hillman adducts in environment friendly aqueous media

Development of simple and convenient methodology for the synthesis of 2-methylenealkanoates and alkanenitriles is an interesting problem in organic synthesis because of their versatile applications as synthons in the synthesis of various biologically active molecules[142-147] and liquid crystalline polymers.[148] For example, methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (51) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52) have been found to be potent inhibitors of the fatty acid oxidation and oral hypoglycemic agents in mammals including human beings.[142-147]



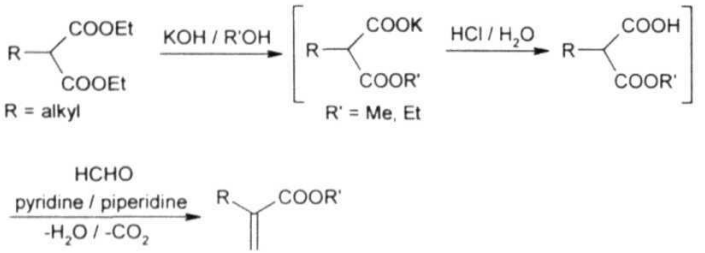
51



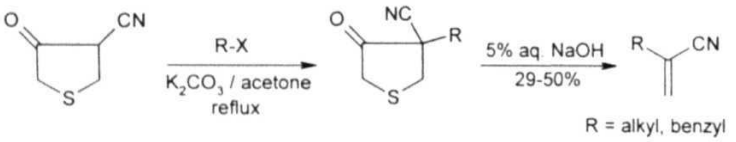
52

Number of synthetic methods have been developed for the synthesis of 2-methylenealkanoates and 2-methylenealkanenitriles[149-154] and two representative literature methods are described in Schemes 38 & 39.[149-152]

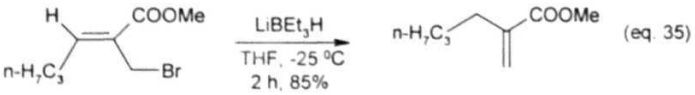
Scheme 38



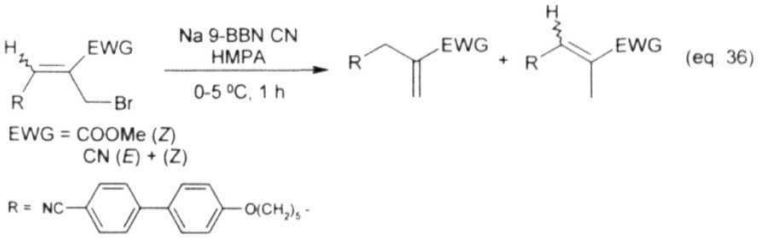
Scheme 39



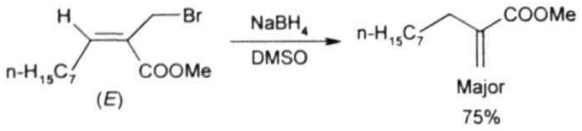
HotTmann and Rabe used **superhydride ($LiBEt_3H$)** for the conversion of methyl (2Z)-2-(bromomethyl)hex-2-enoate, the **allyl** bromide obtained from the **Baylis-**Hillman **adduct,** into methyl **2-methylenehexanoate (S_N2'** product) (eq. **35).**[155]



Hall and coworkers described sodium 9-cyano-9-hydrido-9-borabicyclo-[3.3.1]nonane (Na 9-BBN CN) as a hydride source for nucleophilic addition to 2-bromomethyl-8-[4-(4-cyanophenyl)phenoxy]oct-2-enenitrile and methyl 2-bromo-meth\l-8-[4-(4-cyanophenyl)phenoxy]oct-2-enoate in the presence of HMPA leading to the formation of 2-methylene-8-[4-(4-cyanophenyl)phenoxy)octane-nitrile and methyl 2-methylene-8-[4-(4-cyanophenyl)phcnoxy]octanoate (S_N2' products) respectively along with the trisubstituted olefins (S_N2 products) (eq. 36).[148]



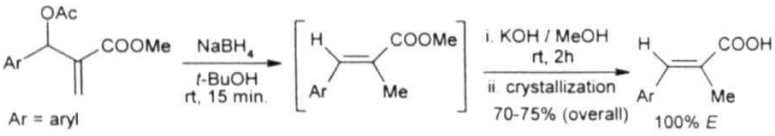
Corey, during his elegant synthesis of α-santalol, described an interesting reaction of methyl (2*E*)-2-(bromomethyl)dec-2-enoate with sodium borohydride in DMSO as solvent leading to the formation of methyl 2-methylenedecanoate as a major product (S_N2' product) (≈ 75% yield) along with two other compounds in minor amounts (≈ 10% and ≈ 15% yields) (eq. 37).[156]



(eq. 37)

It is worth mentioning here our recent report on the utility of $NaBH_4$ as a source for hydride nucleophile for the stereoselective nucleophilic addition (SN2') to methyl 3-acetoxy-3-aryl-2-methylenepropanoates leading to the synthesis of (*E*)-α-methylcinnamic acids after hydrolysis (Scheme 40).[157]

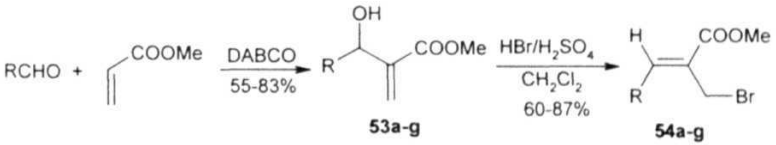
Scheme 40



In connection with our ongoing research program in environment friendly chemistry[158] and sodium borohydride chemistry,[157] we felt that if we can develop a general and convenient methodology for the synthesis of pure methyl 2-methylenealkanoates *via* the reduction of methyl (2Z)-2-(bromomethyl)alk-2-enoates with sodium borohydride in high yields under appropriate conditions in aqueous media, this methodology will be of high synthetic importance.

Accordingly, we have first selected methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate **(54a)** as a substrate for our study. The required allyl bromide **(54a)** was synthesized *via* the treatment of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(53a)** (the Baylis-Hillman adduct obtained *via* the coupling of benzaldehyde with methyl acrylate, in the presence of catalytic amount of DABCO) with HBr/H_2SO_4 according to the literature procedure (Scheme 41).[159] Spectral data and assignment of (*Z*)-stereochemistry of this molecule **(54a)** are in complete agreement with the literature data.[159] *

Scheme 41



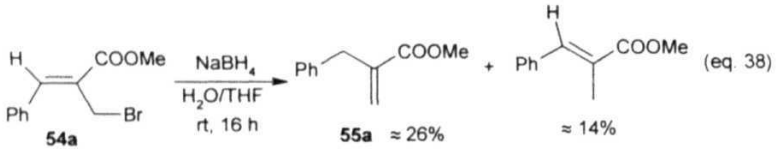
53a-g 54a-g

R = phenyl, 4-chlorophenyl, 4-methylphenyl, 2-chlorophenyl, 2-methylphenyl, n-pentyl, n-tridecyl

We have examined the reaction of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate **(54a)** with sodium borohydride in water/THF medium. This reaction was very slow *i.e.* even after 16 hours time at room temperature about 60% of the

* It is well documented in the literature that in the ^1H NMR spectrum of trisubstituted alkenes, β-vinylic proton *cis* to the ester group appears downfield in companson with that of the β-vinylic proton *trans* to the ester group. The (*Z*)-stereochemistry of the allyl bromides (**54**) was assigned on the basis of the chemical shift value of the β-vinylic protons *i.e* δ 7.76-7.92 (when R = aryl) and 6 6.97 (R = alkyl).

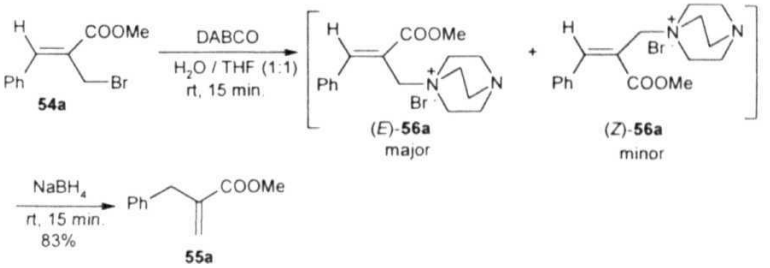
starting material remained intact, thus providing the desired product methyl 2-methylene-3-phenylpropanoate (55a) in about 26% yield only along with methyl α-methylcinnamate (≈ 14% yield) as evidenced by the ^1H NMR spectrum of the crude concentrated product (eq. 38).



At this juncture, we felt that conversion of this (allyl) bromide group into another facile leaving group might help in faster reaction rate and also in obtaining the desired product in pure form without any side products. In this direction, we have examined the possible conversion of this allyl bromide 54a into the corresponding amine salt (56a) *in situ via* the treatment with DABCO and subsequent treatment of this salt with $NaBH_4$ under various conditions to obtain the desired product methyl 2-methylene-3-phenylpropanoate (55a). The best results were obtained when this molecule *i.e.* methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) (2 mmol) was treated with DABCO (2 mmol) in the presence of H_2O/THF (1:1) at room temperature for 15 minutes followed by the treatment with $NaBH_4$ (2 mmol) for 15 minutes at room temperature, thus providing methyl 2-methylene-3-phenylpropanoate (55a) after usual work up followed by column

chromatography (silica gel, 2% ethyl acetate in hexanes) in 83% yield (Scheme 42). Structure of this molecule was established by IR. ^{1}H NMR (Fig 5), ^{13}C NMR (Fig 6), mass spectral data and elemental analysis. This is indeed a very encouraging result.

Scheme 42



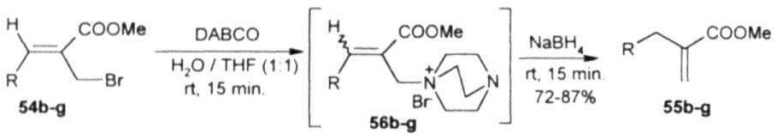
In order to understand the actual structure of the amine salt (56a) we have isolated the salt. Spectral data (IR, ^{1}H and ^{13}C NMR) of this salt clearly confirms the proposed structure (56a) (as indicated in Scheme 42). However, the ^{1}H and ^{13}C NMR spectral analysis indicates that this salt is a mixture of *E* and *Z* isomers (56a£& 56aZ) in the ratio of* 82:18 [#] [$] [o]

[$] In the ^{1}H NMR spectrum of 56a, the β-vinylic proton *as* to the ester group (£-isomer) appears at 6 8 40 (≈ 82%) where as the β-vinylic proton *tram* to the ester group (Z-isomcr) appears at o 7.98 (≈ 18%)

[o] In ^{13}C NMR spectra of trisubstituted alkenes, the allylic carbon *cut* to the aryl group appears upfield while the same carbon *trans* to the aryl group appears downfield.[165-167] In the ^{13}C NMR spectrum of 56a, the allylic methylene carbon of the major (*E*)-isomer appears at 6 57.81 whereas the minor (Z)-isomer appears at δ 67.53.

We have then synthesized a variety of methyl (2*Z*)-2-(bromomethyl)alk-2-enoates (**54b-g**)[a] from the corresponding Baylis-Hillman adducts (Scheme 41) and successfully transformed these allyl bromides (**54b-g**) into 2-methylenealkanoates (**55b-g**) in high yields *via* the treatment with $NaBH_4$ in the presence of DABCO in H_2O/THF medium (Scheme 43, Table 3).

Scheme 43



R = 4-chlorophenyl, 4-methylphenyl, 2-chlorophenyl, 2-methylphenyl, n-pentyl, n-tridecyl

Synthesis of **2-methylenealkanenitriles**

Successful transformation of (2*Z*)-2-(bromomethyl)alk-2-enoates into 2-methylenealkanoates in high yields led us to direct our studies towards the transformation of 2-(bromomethyl)alk-2-enenitriles into 2-methylenealkanenitriles with a view to understand the generality of this methodology. Therefore, we have first prepared 2-(bromomethyl)-3-phenylprop-2-enenitrile (57a) *via* the treatment of 3-hydroxy-

[a] It is well documented in the literature that in the ^{1}H NMR spectrum of trisubstituted alkenes, β-vinylic proton *cis* to the ester group appears down field in comparison with that of the β-vinylic proton *trans* to the ester group.[11] [164] The (ZVstercochemistry of the allyl bromides (54) was assigned on the basis of the chemical shift value of the β-vinylic protons *i e* δ 7.76-7.92 (when R = aryl) and 6 6 97 (R = alkyl)

Table 3: Synthesis **of 2-methylenealkanoates (55a-g)**[a,b]

Substrate	R	Product	Yield[c] (%)
54a	phenyl	**55a**[d,e]	83
54b	4-chlorophenyl	**55b**[d]	87
54c	4-methylphenyl	**55c**[d]	80
54d	2-chlorophenyl	**55d**[d]	82
54c	2-methylphenyl	**55e**[d]	84
54f	n-pentyl	**55f**[d,e]	72
54g	n-tridecyl	**55g**	76

(a) All reactions were carried out on a 2 mmol scale of the allyl bromides **(54a-g)** with 2 mmol of DABCO in H_2O/THF (1:1) at room temperature for 15 minutes followed by the treatment with $NaBH_4$ (2 mmol) at room temperature for 15 minutes.

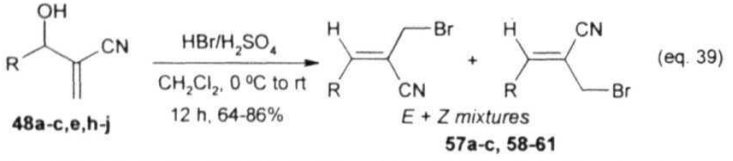
(b) All the products **(55a-g)** were obtained as colorless liquids and were characterized by IR, ^1H NMR, ^{13}C NMR spectral data and elemental analyses.

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

(d) Structures of these molecules were further confirmed by mass spectral analysis.

(e) These molecules **(55a,f)** are known in the **literarture**.[149,150] ^1H NMR spectral data of **55a** is **reported**.[150] Our ^1H NMR spectral data of **55a** is in **agreement** with the literature data.

2-methylene-3-phenylpropanenitrile (48a) with HBr/H_2SO_4 according to the literature procedure (eq. 39).[159] This molecule was obtained as a mixture of (*E*)- and (Z)-isomers (≈ 85:15) as evidence by ^1H and ^{13}C NMR spectral data.[0] •



R = phenyl, 4-chlorophenyl, 4-methylphenyl, 2-methylphenyl, 2-chlorophenyl, n-pentyl, n-tridecyl

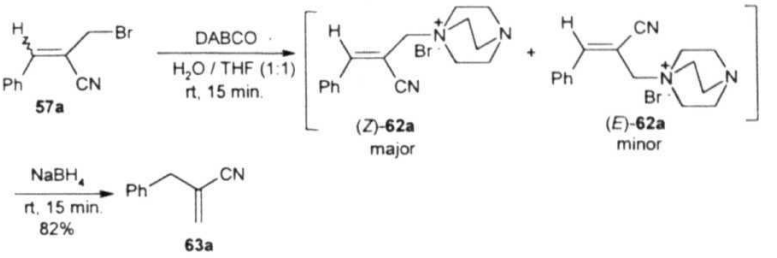
However, this (*E*)- and (Z)-mixture (57a) was used, as such, for further reaction. Thus, treatment of 57a (2 mmol) with DABCO (2 mmol) in the presence of H_2O/THF (1:1) at room temperature for 15 minutes generates the amine salt (62a) *in situ* and subsequent reaction with $NaBH_4$ (2 mmol) for 15 minutes at room temperature provided the desired 2-methylene-3-phenylpropanenitrile (63a) after usual work up followed by column chromatography (silica gel, 2% ethyl acetate in hexanes) in 82% yield (Scheme 44).

◊ In ^{13}C NMR spectra of trisubstituted alkenes, the allylic carbon *cis* to the aryl group appears upheld while the same carbon *trans* to the aryl group appears down field.[*5*167] In the case of 57t. the allylic methylene carbon of the major (*E*)-isomer appears at 6 32.78 whereas the minor (*Z*)-isomer appears at 5 26 66.

• In ^1H NMR spectrum of 57a, the β-vinylic proton *cis* to the CN group (*Z*-isomer) appears at 6 7 25 (≈15%) while that of the β-vinylic proton *trans* to the CN group (*E*-isomer) appears at 5 7 21 (•85%).

Structure of this molecule was confirmed by IR. ^{1}H NMR (Fig 7), ^{13}C NMR (Fig 8), mass spectral data and elemental analysis.

Scheme 44

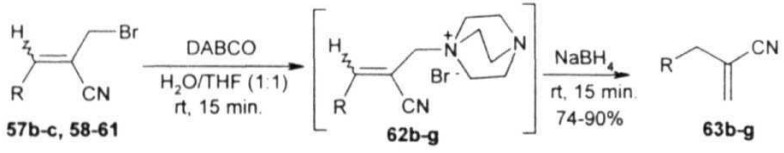


We have also isolated the amine salt **62a** in order to understand its actual structure (Scheme 44). Spectral data (IR, ^{1}H and ^{13}C NMR) of this salt clearly confirms the proposed structure **(62a).** However, the ^{1}H and ^{13}C NMR^ spectral analysis indicates that this salt is a mixture of £ and Z isomers (62a£ & 62aZ). ^{1}H NMR spectnim of this molecule **(62a)** shows two singlets for allylic methylene protons at 6 4.11 and 8 4.41 in the ratio of 22:78 arising from minor **(*E*)-** and major (Z)-isomers respectively.

In ^{13}C NMR spectra of trisubstituted alkenes, the allylic carbon *cis* to the aryl group appears upfield while the same carbon *trans* to the aryl group appears downfield.[165-167] In the case of 62a, the allylic methylene carbon of the minor **(*E*)-**isomer appears at 6 50.59 whereas the major **(*Z*)-**isomer appears at 6 65 13

Encouraged by this result, we have prepared a variety of 2-(bromomethyl)alk-2-enenitriles **(57b-c, 58-61)**[r] as mixtures of *(E)*- and *(Z)*-isomers *via* the reaction of 3-hydroxy-2-methylenealkanenitriles **(48b-c,e,h-j)**[r] with HBr/H_2SO_4. These allyl bromides {*(E)* & (Z)-mixtures} as such were successfully transformed into 2-methylenealkanenitriles **(63b-g)**[0] under the similar reaction conditions as described for **63a** (Scheme 45, Table 4).

Scheme 45



R = 4-chlorophenyl, 4-methylphenyl, 2-methylphenyl, 2-chlorophenyl, n-pentyl, n-tridecyl

Thus, we have successfully developed a convenient and general synthesis of 2-methylenealkanoates and alkanenitriles *via* the regioselective nucleophilic addition **(S_N2')** of hydride ion from the easily available and inexpensive reagent $NaBH_4$

For **easy** understanding and continuity the Baylis-Hiliman **adducts** *t e* 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile, 3-hydroxy-2-methyleneoctanenitrile and 3-hydroxy-2-methylenehexadecanenitrile obtained *via* the coupling of 2-chlorobenzaldehyde, hexanal and tetradecanal with acry lon itrile in the presence of catalytic amount of DABCO, were numbered respectively as **48h**, **48i** and **48j**. For continuity; the allyl bromides derived from the Baylis-Hillman adducts, **48e**, 48h-j respectively were numbered as **58-61**.

[r] For continuity, the allyl bromide-DABCO salts and 2-methylenealkanenitriles obtained from the allyl bromides, **57a-c**, **58-61**, were respectively numbered as **62a-g** and **63a-g**.

Table 4: Synthesis of 2-methylenealkanenitriles (63a-g)[a,b]

Substrate	R	Product	Yield[c] (%)
57a	phenyl	63a[d,e]	82
57b	4-chlorophenyl	63b[d]	90
57c	4-methylphenyl	63c[d]	81
58	2-methylphenyl	63d[d]	87
59	2-chlorophenyl	63e[d]	85
60	n-pentyl	63f[e]	74
61	n-tridecyl	63g[f]	82

(a) All reactions were carried out on a 2 mmol scale of the allyl bromides (57a-c, 58-61) with 2 mmol of DABCO in H_2O/THF (1:1) at room temperature for 15 min followed by the treatment with $NaBH_4$ (2 mmol) at room temperature for 15 min.

(b) All the products were obtained as colorless liquids and were characterized by IR, ^1H NMR ^{13}C NMR spectra] data and elemental analyses.

(c) Isolated yields of the pure products after column chromatography (silica gel, 2% ethyl acetate in hcxanes).

(d) Structures of these molecules were further confirmed by mass spectral analysis.

(e) These molecules (63a,f) are known in the literature and ^1H NMR spectral data is reported.[152] Our ^1H NMR spectral data of these molecules (63a,f) are in agreement with the literature data.

(0 This reaction was carried out on a 1 mmol scale of the allyl bromide.

to allyl bromides derived from the Baylis-Hillman adducts in presence of DABCO in environment friendly aqueous media.

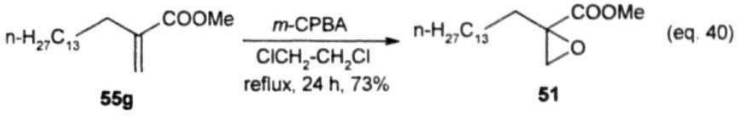
Synthesis of hypoglycemic agents

To prove the efficacy of this methodology we have undertaken the synthesis of two representative hypoglycemic agents methyl **2-tetradecyloxirane-2-carboxylate** (methyl **palmoxirate)** (51) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) **(52).**

Synthesis of methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate)

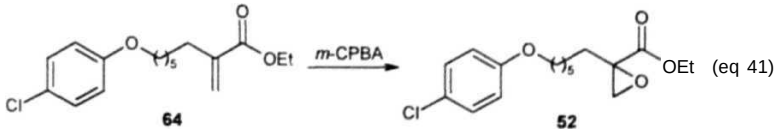
We have first planned the synthesis of methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) **(51)** *via* epoxidation of the methyl **2-methylenehexadecanoate (55g)** using ***m*-CPBA** under various conditions. The best results were obtained when this molecule methyl **2-methylenehexadecanoate** (55g) (1 **mmol)** was treated with ***m*-CPBA** (3 mmol) in **1,2-dichloroethane** as a solvent at reflux temperature for 24 hours thus providing the desired methyl **2-tetradecyloxirane-2-**carboxylate (methyl palmoxirate) (51) in 73% yield **(eq**. 40). The structure of this molecule was established by **IR, ^{1}H** and **^{13}C** NMR (Fig 9) spectral data. This molecule is known in the literature and the physical & **^{1}H** NMR spectral data were

reported.[142] The physical and ^1H NMR spectral data of this molecule are in agreement with literature data.



Synthesis of ethyl **2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate** (Etomoxir)

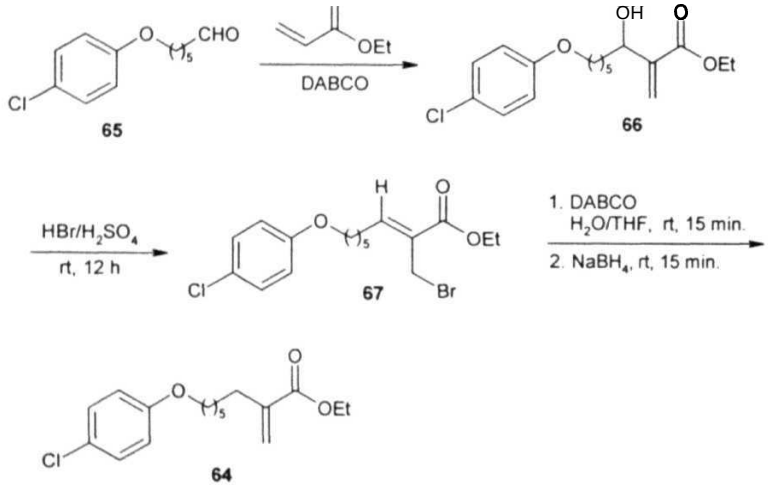
We have next aimed at the synthesis of ethyl **2-[6-(4-chlorophenoxy)hexyl]-oxirane-2-carboxylate** (Etomoxir) (52) *via* the epoxidation of ethyl **2-methylene-8-(4-chlorophenoxy)octanoate** (64) according to the equation **41**.



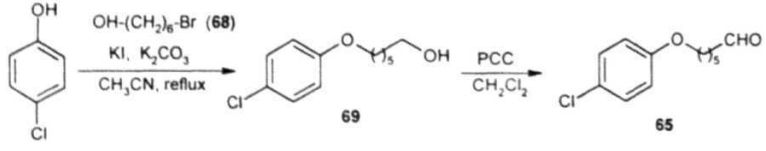
We have designed the synthesis of required ethyl **2-methylene-8-(4-chlorophenoxy)octanoate** (64) from **6-(4-chlorophenoxy)hexanal** (65) *via* the Baylis-Hillman methodology (Scheme 46). Synthesis of the required **6-(4-chlorophenoxy)hexanal** (65) for the **Bayis-Hillman** coupling with ethyl acrylate in the

presence of DABCO was planned from **4-chlorophenol** according to the Scheme 47

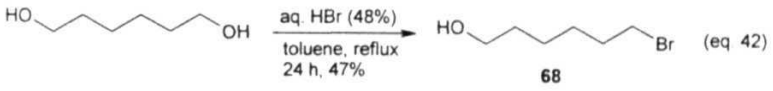
Scheme 46



Scheme 47



The desired **6-bromohexan-1-ol** (68) was prepared *via* the reaction of 1,6-hexanediol with aq. HBr according to the literature procedure with some modifications (eq. 42).[168] Treatment of this bromide (68) with **4-chlorophenol** in the presence of KI/K_2CO_3 in **acetonitrile** at reflux temperature for 4 hours provided **6-(4-chlorophenoxy)hexan-1-ol** (69) in 70% yield. Oxidation of this alcohol by **pyridinium chlorochromate** (PCC) afforded the desired 6-(4-chlorophenoxy)hexanal (65) in 71% yield (Scheme 47).



(eq 42)

The **Baylis-Hillman** coupling of this aldehyde 65 with ethyl **acrylate** in the presence of catalytic amount of DABCO (30 mol%) for 10 days at room temperature **furnished** the required **Baylis-Hillman adduct** *i.e.* ethyl 3-hydroxy-2-**methylene-8-(4-chlorophenoxy)octanoate** (66) in 49% yield. This was transformed into the corresponding **allyl** bromide *i.e.* ethyl **2-(bromomethyl)-8-(4-**chlorophenoxy)octanoate (67) in 66% yield *via* the treatment with HBr/H_2SO_4. ^1H NMR **and** ^{13}C NMR spectral data indicate that 67 is a mixture of (Z)- and ***(E)***-isomers in the ratio of ≈ 90:10. However, subsequent **treatment** of this **allyl**

bromide 67 as such, with DABCO in H_2O/THF at room temperature for 15 minutes, followed by the treatment with $NaBH_4$ provided ethyl 2-methylene-8-(4-chlorophenoxy)octanoate (64) in 73% yield. Structure of this product was confirmed by IR, ^1H and ^{13}C NMR spectral data and elemental analysis (Scheme 46). Epoxidation of this molecule 64 (1 mmol) with *m*-CPBA (3 mmol) in the presence of 1,2-dichloroethane under reflux temperature provided the desired ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52) in 50% yield (eq. 41). Structure of this molecule was established by IR, ^1H and ^{13}C NMR (Fig 10) spectral data. This molecule is known in the literature and the ^1H NMR spectrum was reported.[144] The ^1H NMR spectral data of this molecule is in agreement with literature data.

Thus our methodology has been successfully utilized for the synthesis of two representative hypoglycemic agents methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (51) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52) thus demonstrating the synthetic potential of Baylis-Hillman adducts.

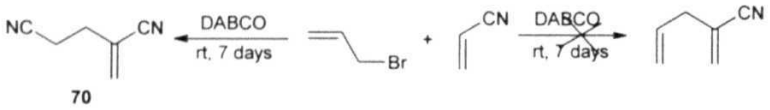
Application of (2*Z*)-2-(bromomethyl)alk-2-enoates and (3Z)-3-(chloromethyl)alk-3-en-2-ones as electrophiles in the Baylis-Hillman reaction: A novel synthesis of functionalized 1,4-pentadienes

The Baylis-Hillman reaction is basically a three component reaction involving an activated alkene, a carbon electrophile and a tertiary amine catalyst (particularly DABCO) leading to the formation of carbon-carbon bond between the α-position of the activated alkene and the carbon electrophile (eq. 1). Though various electrophiles such as aldehydes,[10-12] aldimines,[29-31] α-keto esters,[32-34] fluorinated ketones,[35] non enolizable 1,2-diketones,[20] acrylonitrile,[36,37] alkyl and aryl vinyl ketones[36,37] have been successfully employed in this fascinating reaction (Scheme 3), application of allyl halides as electrophiles has not been studied so far in the literature. We have therefore undertaken this research program of examining the possible application of allyl halides as electrophiles in the Baylis-Hillman reaction.

During our efforts in this study, we have first selected 3-bromoprop-1-ene (allyl bromide) as a possible electrophile in the Baylis-Hillman reaction. Accordingly, we have first examined the coupling of acrylonitrile with 3-bromoprop-l-ene in the presence of DABCO with a view to obtain 2-cyanopenta-1,4-diene. However,

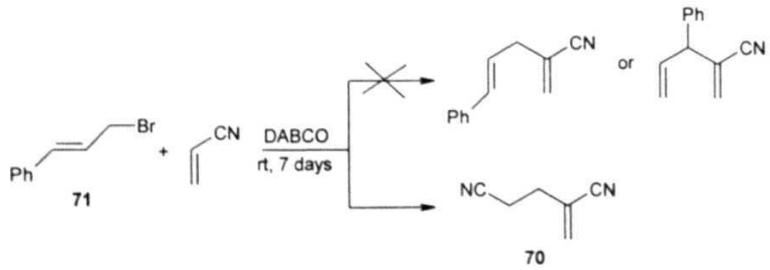
our attempts in this direction did not result in the formation of the desired product *i.e.* **2-cyanopenta-1,4-diene,** instead we have obtained **2,4-dicyanobut-1-ene** (70) (Scheme 48). It is well documented in the literature that acrylonitrile undergoes Michael type **dimerization** in the presence of DABCO to provide **70**.[36]

Scheme 48

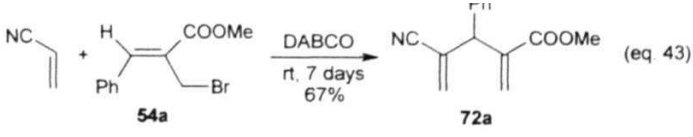


We have **also** examined the application of cinnamyl bromide (71) as a possible electrophile in the **Baylis-Hillman** coupling with acrylonitrile in the presence of DABCO. We did not obtain any desired product, instead **2,4-dicyanobut-1-ene** (70) was obtained (Scheme 49).

Scheme 49

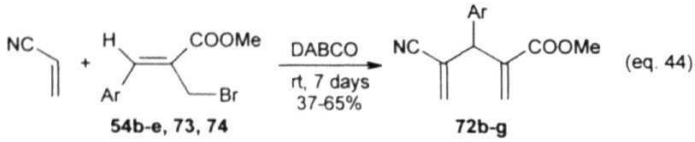


On the basis of our previous results (Schemes 42-45), on the regioselective nucleophilic addition (S_N2') of hydride ion from $NaBH_4$ to allyl bromides derived from the Baylis-Hillman adducts in the presence of DABCO, we envisaged that these allyl bromides might act as suitable electrophiles in the Baylis-Hillman coupling with acrylonitrile in the presence of DABCO. During our efforts in this direction, we have first examined the coupling of acrylonitrile with methyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) in the presence of DABCO. A fascinating result was obtained when we treated methyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate (**54a**)[4] (2 mmol), with acrylonitrile (2 mL) in the presence of DABCO (4 mmol) at room temperature for 7 days, thus leading to the formation of 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**72a**)[4] in 67% yield after usual work up followed by column chromatography (silica gel, 4% ethyl acetate in hexanes) (eq. 43). The structure of this product was confirmed by IR, ^1H NMR (Fig 11), ^{13}C NMR (Fig 12), mass spectral data and elemental analysis.



Encouraged by this interesting result, we extended the reaction to a representative class of allyl bromides (**54b-e,** 73 & **74**),[m] derived from methyl 3-aryl-3-hydroxy-

2-methylenepropanoates (53b-e, h-i),[m] to produce the functionalized 1,4-pentadienes (72b-g)[k] (eq. 44, Table 5).

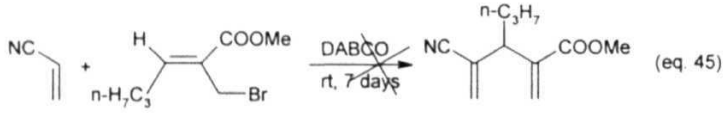


(eq. 44)

54b-e, 73, 74 72b-g

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

However, our attempts to use methyl (2Z)-2-(bromomethyl)hex-2-enoate (obtained from the corresponding Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenehexanoate), as an electrophile for coupling with acrylonitrile in the presence of DABCO were unsuccessful (eq. 45).



(eq. 45)

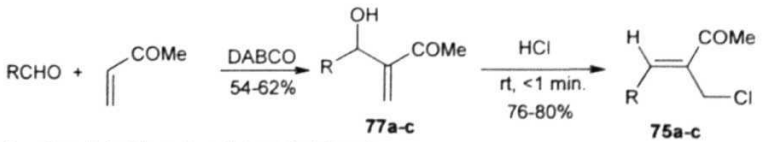
[m] For easy understanding and continuity the Baylis-Hillman adducts *i.e* methyl 3-hydroxy-2-methylene-3-(4-ethylphenyl)propanoate and methyl 3-hydroxy-2-methylene-3-(4-isopropylphenyl)propanoate obtained *via* the coupling of 4-ethylbenzaldehyde and 4-isopropylbenzaldehyde with methyl acrylate in the presence of DABCO were numbered as 53h and 53i. For continuity the corresponding allyl bromides *t e* methyl (2Z)-2-bromomethyl-3-(4-ethylphenyl)prop-2-enoate and methyl (2Z)-2-bromomethyl-3-(4-isopropylphenyl)prop-2-enoate derived from 53h and 53i were numbered as 73 and 74.

[k] For continuity and easy understanding the functional ized 1,4-pentadienes obtained by the treatment of the allyl bromides 54a-e, 73 & 74 with acrylonitrile in the presence of DABCO were numbered as 72a-g

After the successful utility of methyl **(2*Z*)-2-(bromomethyl)prop-2-enoates (54a-g,** 73 & **74)** as electrophiles in the Baylis-Hillman reaction thus providing **functionalized 1,4-pentadienes (72a-g)** in moderate to good yields, we have directed our studies towards the application of **(3*Z*)-4-aryl-3-(chloromethyl)but-3-en-2-ones** (75) as possible electrophiles in the Baylis-Hillman reaction with acrylonitrile under the influence of DABCO for the synthesis of **2-acetyl-3-aryl-4-cyanopenta-1,4-dienes** (76) with a view to understanding the generality of this reaction.

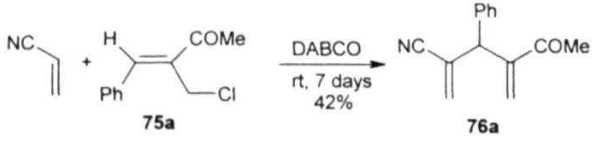
We have first prepared **(3*Z*)-3-(chloromethyl)-4-phenylbut-3-en-2-ones (75a)** from **4-hydroxy-3-methylene-4-phenylbutan-2-one (77a)** (the Baylis-Hillman adduct obtained from the reactive activated alkene, methyl vinyl ketone and benzaldehyde in the presence of catalytic amount of DABCO) by the treatment with **conc**. HCl, according to the known procedure developed in our laboratory (Scheme 50).[110]

Scheme 50



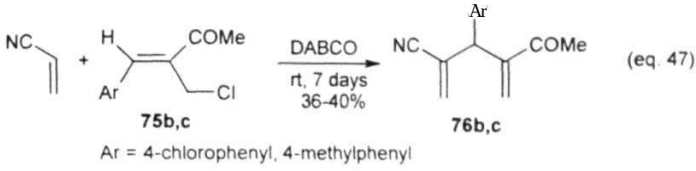
R = phenyl, 4-chlorophenyl, 4-methylphenyl

The coupling of **(3*Z*)-3-(chloromethyl)-4-phenylbut-3-en-2-one (75a)** with acrylonitrile in the presence of DABCO was best accomplished when **75a** (2 mmol) was treated with **acrylonitrile** (2 **mL**) in the presence of DABCO (4 mmol) at room temperature for 7 days, thus providing **2-acetyl-4-cyano-3-phenylpenta-1,4-diene (76a)** in 42% yield after usual work up followed by column chromatography (silica gel, 4% ethyl acetate in hexanes) (eq. 46). Structure of this molecule was confirmed by IR, ^{1}H NMR (Fig 13), ^{13}C NMR (Fig 14), mass spectral data and elemental analysis.



(eq. 46)

With a view to understand the generality of this reaction, we have then prepared **(3*Z*)-3-(chloromethyl)-4-(4-chlorophenyl)but-3-en-2-one** (75b) and **(3*Z*)-3-(chloromethyl)-4-(4-methylphenyl)but-3-en-2-one** (75c) from the corresponding **Baylis-Hillman adducts (77b-c)** and subjected them to the reaction with acrylonitrile in the presence of DABCO for 7 days to afford **2-acetyl-3-(4-chlorophenyl)-4-cyanopenta-1,4-diene** (76b) and **2-acetyl-4-cyano-3-(4-methylphenyl)-penta-1,4-diene** (76c) **respectively** (eq. 47, **Table** 5).



A plausible mechanism for the formation of functional ized 1,4-pentadienes in the reaction between allyl halides (derived from the Baylis-Hillman adducts) and acrylonitrile in the presence of DABCO is described in the Scheme 51.

Scheme 51

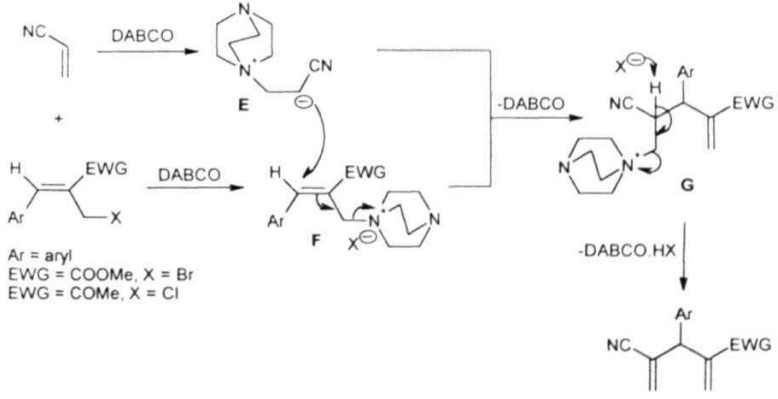


Table 5: Synthesis of functionalizcd 1,4-pentadienes (72a-g & 76a-c)[ab]

Substrate	Ar	Product	Yield[c] (%)
54a	**phenyl**	**72a[d]**	67
54b	**4-chlorophenyl**	**72b**	63
54c	4-methylphenyl	**72c**	65
54<!	**2-chlorophenyl**	**72d**	60
54e	**2-methylphenyl**	72e	37
73	**4-ethylphenyl**	**72f**	55
74	**4-isopropylphenyl**	**72g**	59
75a	phenyl	**76a[d]**	42
75b	**4-chlorophenyl**	**76b**	36
75c	4-methylphenyl	**76c**	40

a) All reactions were carried out using 2 mmol of the **allyl halides (54a-e, 73, 74 & 75a-c)** with **acrylonitrile** (2 **mL**) in the presence of DABCO (4 mmol) at room temperature for 7 days.

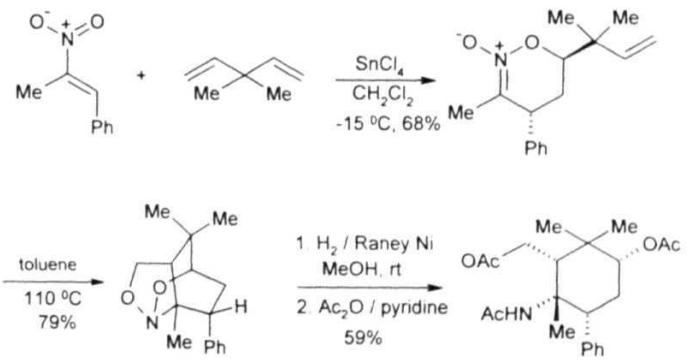
b) All products were obtained as colorless viscous liquids and gave satisfactory **IR, ^{1}H NMR, ^{13}C NMR** spectral data and elemental analyses.

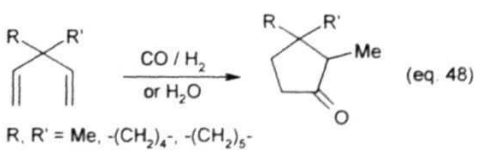
c) Isolated yields of the pure products after column chromatography (silica gel, 4% ethyl acetate in hexanes).

d) **These** products were also **characterized** by mass spectral analysis.

It is interesting to note that the 1,4-diene moiety is an important structural unit present in several biologically active molecules[169,170] and in particular, substituted 1,4-pentadienes are versatile synthons for the synthesis of various interesting molecules.[171,172] Representative applications have been described in Scheme 52 and equation 48.[171,172]

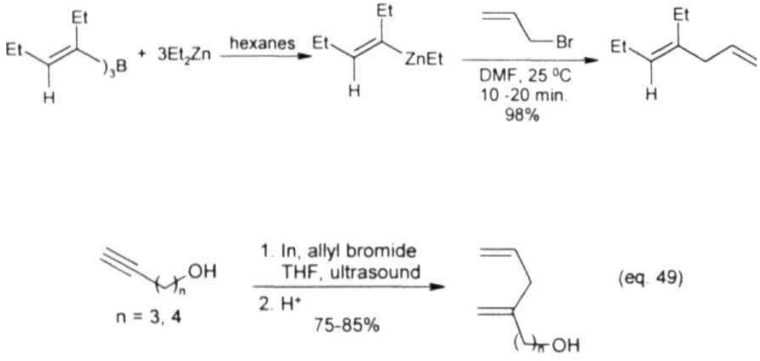
Scheme 52





It is worth mentioning here that literature survey reveals that several methods are known for the synthesis of 1,4-dienes,[173-178] two representative methods are described in Schemes 53 and equation 49.

Scheme 53

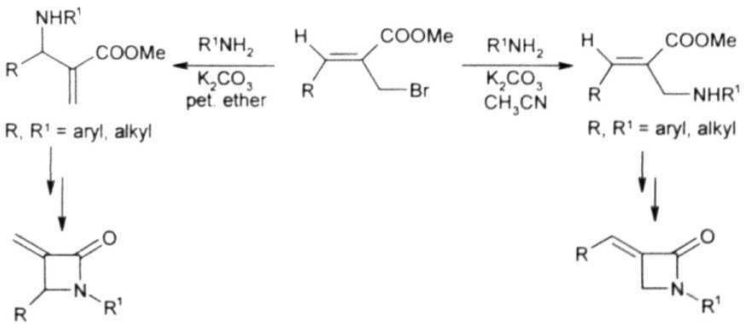


Our methodology, describes the application of allyl halides, derived from the Baylis-Hillman adducts, as electrophiles in the Baylis-Hillman reaction, for the first time thus providing a novel synthesis of functional ized 1,4-pentadienes, an important class of molecules.

Synthesis of methyl **3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)-**propanoates and methyl **3-aryl-2-methylene-3-phenoxypropano-**ates *via* **nucleophilic** (S_N2') addition of propargyl alcohol and phenol to methyl **(2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates**

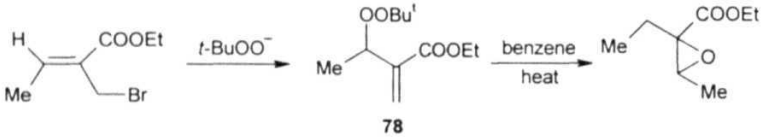
Literature survey reveals that there are few reports known on nucleophilic addition reactions onto the allyl bromides, obtained from the Baylis-Hillman adducts, in S_N2' fashion. Hoffmann and Buchholz reported that the reaction of methyl (2Z)-2-(bromomethyl)alk-2-enoates with amine in petroleum ether as a solvent proceeds in S_N2' manner while the same reaction proceeds S_N2 path way if CH3CN is used as solvent. Both these products (S_N2' & S_N2) were transformed into the corresponding β-lactams (Scheme 54).[159]

Scheme **54**

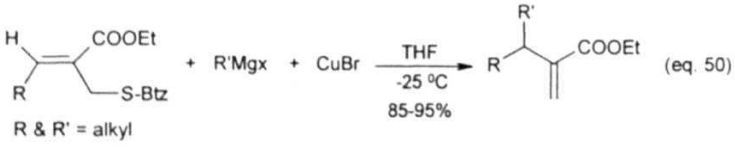


Mailard and coworkers described the nucleophilic addition of /-butylperoxylate anion to ethyl 2-(bromomethyl)but-2-enoate in S_N2' fashion to provide the allyl /-butyl peroxide (78) in the presence of polyethyleneoxide 400 which was subsequently converted into the corresponding glycedic ester (Scheme 55).[179-181]

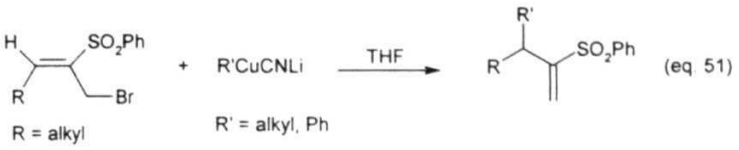
Scheme 55



An interesting synthesis of p,p-disubstituted acrylates *via* the reaction of allylic sulfides of benzothiazole, obtained from the Baylis-Hillman adducts, with organo copper reagents has been reported by Calo *etal*. (eq. 50).[182]



Auvray *et ai* have successfully used lithium cyanocuprates as nucleophiles for addition to (*E*)-1-bromo-2-phenylsulfonyl-2-alkenes in S_N2' fashion leading to the synthesis of 2-substituted phenyl vinyl sulfones (eq. 51).[24 122]

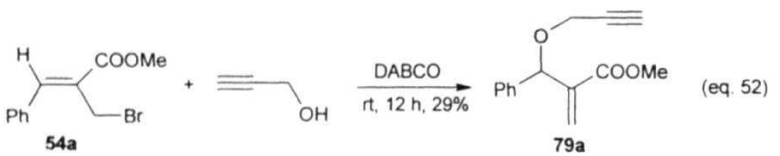


Synthesis of methyl **3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates**

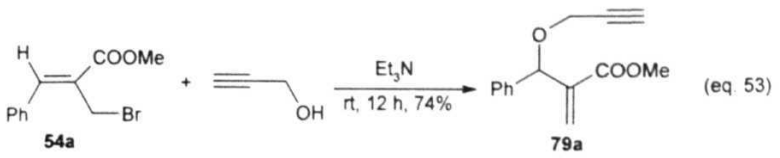
Though various nucleophiles have been successfully employed in the regioselective (S_N2') nucleophilic addition onto the allyl bromides obtained from Baylis-Hillman adducts, addition of oxygen nucleophiles from alcohols has not been well studied. During our efforts in this direction, we have planned to study the addition of oxygen nucleophile from prop-2-yn-1-ol (propargyl alcohol) to methyl (2*Z*)-2-(bromomethyl)alk-2-enoates in S_N2' fashion with a view to expand the scope of application of these allyl bromides as electrophiles in organic synthesis.

On the basis of our earlier observations (Scheme 42 & eq. 43), we felt that prop-2-yn-1-ol might add to methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) in S_N2' fashion under the influence of DABCO. Accordingly we have carried out the reaction of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) with prop-2-yn-1-ol in the presence of DABCO under various conditions. The best result was accomplished when this molecule 54a (1 mmol) was treated with prop-

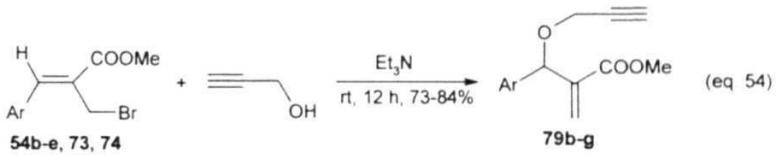
2-yn-1-ol (5 mmol) in the presence of DABCO (2 mmol) in CH_2Cl_2 at room temperature for 12 hours thus providing the required methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate (79a) in 29% yield (eq. 52).



Though the desired product is obtained in pure form, the yield is not encouraging. At this stage, we envisioned that the yield can be possibly improved if we use appropriate tertiary amines in place of DABCO. During our efforts in this direction, we have obtained encouraging result, when methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a)[9] (1 mmol) was treated with prop-2-yn-1-ol (5 mmol) in the presence of triethylamine (1 mL) at room temperature for 12 hours (without any solvent), thus providing the desired methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate (79a)[9] in 74% yield after usual work up followed by column chromatography (silica gel, 2% ethyl acetate in hexanes) (eq. 53). Structure of this molecule was established by ^1H NMR (Fig 15), ^{13}C NMR (Fig 16), mass spectral data and elemental analysis.



This reaction is indeed encouraging as triethylamine is inexpensive and also easily available. We have then extended the same strategy to a representative class of methyl (2Z)-3-aryl-2-(bromomethyl)lprop-2-enoates **(54b-e, 73 & 74)**[φ]to provide the desired methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates **(79b-g)**[φ]in high yields (eq. 54, Table 6).



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

Synthesis of 3 aryl-2-methylene-3-phenoxypropanoates

After successfully employing prop-2-yn-1-ol as oxygen nucleophile, for addition (SN2') onto methyl **(2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates (54a-e, 73 & 74)**

• **For continuity and easy understanding the methyl 3-aryl-2-methylene-3-(prop-2-yn-1-y loxy)propanoates obtained in the reaction** of **the** corresponding **ally 1** bromides **54a-e,** 73 **&** 74 **with propargyl** alcohol in **the presence** of **triethylamine were numbered as 79a-g respectively**

Table 6: Synthesis of methyl **3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (79a-g)**[a,b]

Substrate	Ar	Product	Yield[c] (%)
54a	phenyl	**79a**[d]	74
54b	4-chlorophenyl	**79b**	84
54c	4-methylphenyl	79c	76
54d	2-chlorophenyl	79d	73
54e	2-methylphenyl	79e	76
73	4-ethylphenyl	79f	67
74	4-isopropylphenyl	79g	77

a) All reactions were carried out on a 1 mmol scale of allyl bromides (**54a-e,** 73, 74) with prop-2-yn-1-ol (propargyl alcohol) (5 mmol) in the presence of Et_3N (1 mL) at room temperature for 12 hours.

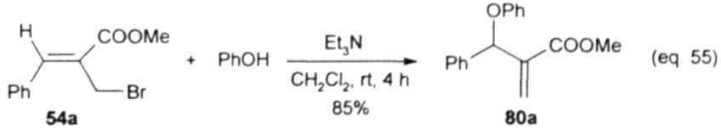
b) Products **79a-c,f,g** were obtained as colorless viscous liquids and products **79d,e** were obtained as colorless solids and all the products gave satisfactory IR, ^1H NMR, ^{13}C NMR spectral data and elemental analyses.

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

d) This product was also characterized by mass spectral analysis.

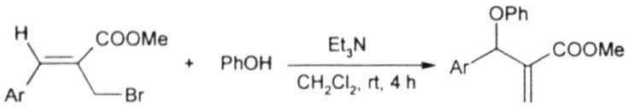
in the presence of triethylamine leading to the synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (79a-g), we have next directed our studies towards the application of phenol as a possible nucleophile, with a view to further understand and expand the scope of this methodology.

Accordingly, we have first selected methyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) for reaction with phenol. We have obtained a promising result when methyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoatc (54a)[n] (1 mmol) was treated with phenol (1 mmol) in the presence of triethylamine (1 mL) in dichloromethane (2 mL) at room temperature for 4 hours thus providing methyl 2-methylene-3-phenyl-3-phenoxypropanoate (80a)[n] in 85% yield, after usual work up followed by column chromatography (silica gel, 2% ethyl acetate in hexanes) (eq. 55). Structure of this molecule was established by ^{1}H NMR (Fig 17), ^{13}C NMR (Fig 18), mass spectral data and elemental analysis.



We have then extended the same reaction to a representative class of methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates (54b-e, 73 & 74)° thus providing a

general synthesis of 3-aryl-2-methylene-3-phenoxypropanoates **(80b-g)**[σ] in good yields **(eq. 56,** Table 7).

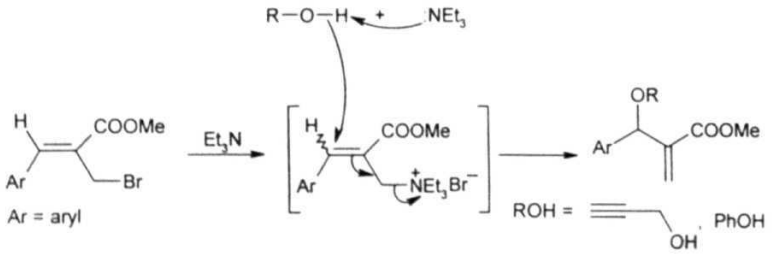


54b-e, 73, 74 **80b-g**

Ar • **4-chlorophenyl, 4-methylphenyl, 2-chlorophenyl, 2-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl**

A plausible mechanism for addition of oxygen nucleophiles (from **prop-2-yn-1-ol** and phenol) onto methyl **(2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates** is described in the Scheme 56.

Scheme 56



[σ] For easy understanding and continuity the methyl **3-aryl-2-methylene-3-phenoxypropanoates obtained** *via* the reaction of the corresponding **allyl** bromides **54a-e,** 73 **&** 74 with phenol under the influence of **triethylamine** were respectively numbered as **80a-g**

Table 7: Synthesis of methyl 3-aryl-2-methylene-3-phenoxypropanoates (80a-

Substrate	Ar	Product	Yield[c] (%)
54a	phcnyl	**80a**[d]	85
54b	4-chlorophenyl	**80b**	76
54c	4-methylphenyl	**80c**	69
54d	2-chlorophenyl	**80d**	66
54e	2-methylphenyl	**80c**	63
73	4-ethylphenyl	**80f**	64
74	4-isopropylphenyl	**80g**	61

a) All reactions were carried out on a 1 mmol scale of allyl bromides **(54a-e,** 73 & **74)** with phenol (1 mmol) and Et_3N (1 mL) in dichloromethane (2 mL) at room temperature for 4 hours.

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

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

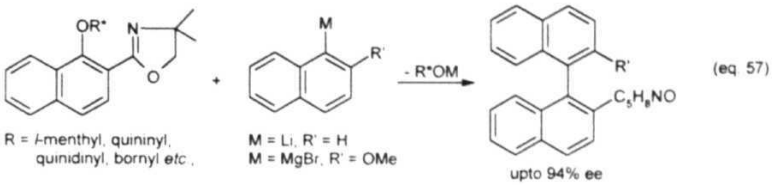
d) This product was also characterized by mass spectral analysis.

Thus, we have developed a simple methodology for regioselective synthesis of methyl **3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates** and **3-aryl-2-methylene-3-phenoxypropanoates** *via* the addition of propargyl alcohol and phenol respectively onto methyl *(2Z)*-3-aryl-2-(bromomethyl)lprop-2-enoates in the presence **of** triethylamine.

Enantioselective synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates *via* chiral leaving group strategy

The above successful results led us to envision that if we use appropriate chiral tertiary amine, in place of triethylamine, which subsequently becomes leaving group, there might be chiral induction. We have therefore directed our studies towards enantioselective synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-l-yloxy)propanoates *via* chiral leaving group strategy.

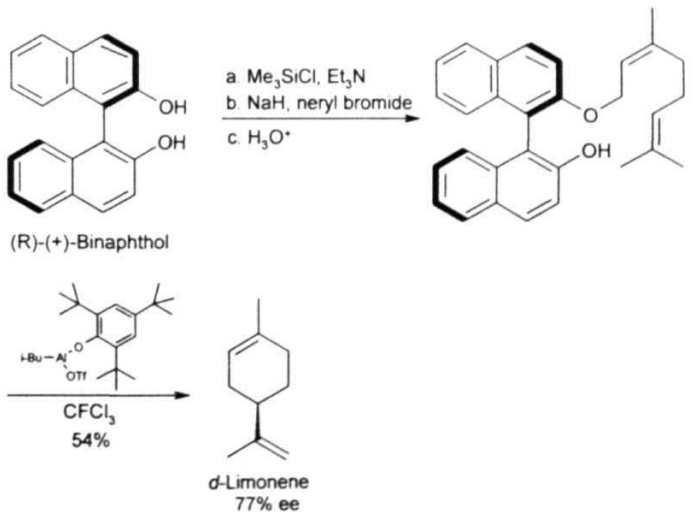
Literature survey reveals that a number of asymmetric reactions have been reported under the influence of chiral leaving group.[183-191] Some of important and relevant methods have been presented in the following. Wilson and Cram reported an interesting synthesis of substituted binaphthyl compounds in moderate to high enantioseiectivity *via* the transfer of asymmetry from a leaving group in the nucleophilic, aromatic substitution reactions (eq. 57).[131]



(eq. 57)

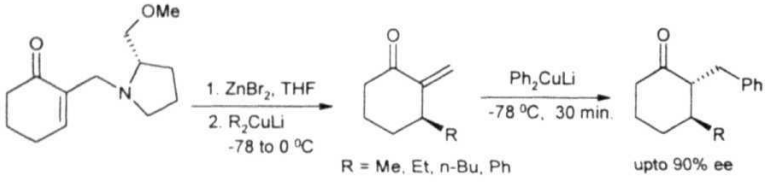
Enantioselective synthesis of ***d*-limonene *via*** chiral leaving group strategy has been reported by Yamamoto and coworkers according to the strategy described in **Scheme 57**.[185,186]

Scheme 57

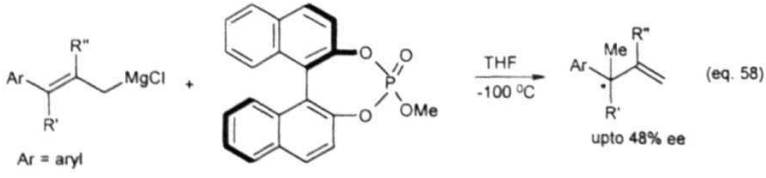


Tamura *et al*. described an efficient enantioselecive synthesis of 3-substituted 2-*exo*-methylenealkanones *via* the chiral leaving group (proline based) strategy (Scheme 58).[187, 188]

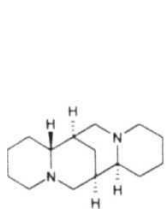
Scheme 58



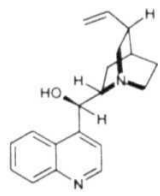
Yamamoto and coworkers described an interesting asymmetric γ-methylation of allyl Grignard reagents using chiral leaving group strategy in which optically active methyl 1,1'-binapthyl-2,2'-diylphosphate acts as methylating agent (eq. 58)."*



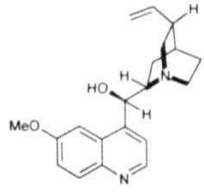
With an objective of providing a simple synthesis of enantiomerically pure/ enriched methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates *via* the chiral leaving group strategy, we have planned to use various chiral tertiary amines such as sparteine (81) cinchonidine (82), quinine (83) and quinidine (19) which are naturally occurring and easily accessible, in our study on chiral leaving group induced asymmetric synthesis.



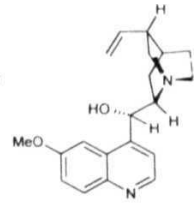
( )-Sparteine (81)



Cinchonidine (82)



Quinine (83)

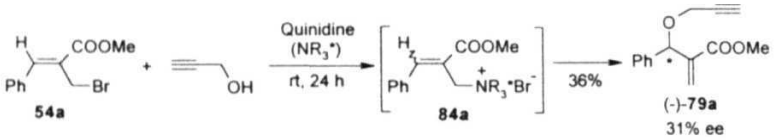


Quinidine (19)

We have first examined the reaction of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) with prop-2-yn-1-ol under the influence of chiral tertiary amines (81-83 & 19). Encouraging result was obtained when methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a)[p] (1 mmol) was treated with prop-2-yn-1-ol (5 mmol) in the presence of quinidine (19) (2 mmol) in dichloromethane (4 mL) at room temperature for 24 hours thus providing (-)-

methyl 2-methylene-3-(prop-2-yn-1-yloxy)-3-phenylpropanoate {(-)-79a}[ρ] in 31% enantioselectivity and in 36% yield (Scheme 59). Structure of this molecule was confirmed by IR and ^{1}H NMR and ^{13}C NMR spectral data, which are identical with that of the corresponding racemic molecule. However, other chiral tertiary amines **81-83** provided inferior results (4-12% enantioselectivity).

Scheme 59

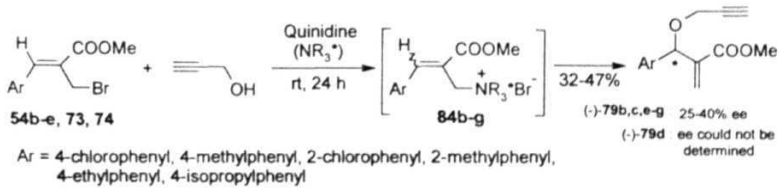


Determination of cnantiomeric purity of (-)-(79a):

The enantiomeric purity of this molecule {(-)-79a} was determined by the HPLC analysis by using chiral column, CHIRALCEL OD, and 5% *i*-PrOH in hexane as eluent (0.5 mL / min) with reference to its racemic (79a) molecule. The racemic molecule **79*** showed two peaks (retention times: 12.33 & 13.85 minutes) with equal intensity (Fig 19a) arising from both the enantiomers whereas the optically active molecule (-)-79a showed two peaks (retention times: 12.38 & 14.02 minutes) in the ratio of 65.5:34.5 indicating that the optical purity of this compound is 31% (Fig 19b).

We have then extended the same strategy to representative allyl bromides, *i.e,* methyl (*2Z*)-3-aryl-2-(bromomethyl)lprop-2-enoates (**54b-e,** 73 & **74**),[p] thus providing simple synthesis of (-)-methyl **3-aryl-2-methylene-3-(prop-2-yn-1-yl-**oxy)propanoates {(-)-(**79b-c, e-g**)}[p] in 25-40% enantiomeric purities and in 32-47% yields (Scheme 60, Table 8). The **enantiomeric** purities of these molecules were determined by the HPLC analysis using chiral column (CHIRALCEL OD) with reference to the corresponding racemic molecules. However, our attempts to determine the enantiomeric purity of **(-)-79d** either through HPLC analysis on chiral column (CHIRALCEL OD) or through ^1H NMR analysis by using chiral shift reagents. Eu(hfc)$_3$ or Eu(tfc)$_3$ were unsuccessful.

Scheme 60



For easy understanding and continuity the allyl **bromide-quinidine** salts and optically active *(-)*-methyl **3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates** obtained from the corresponding allyl bromides **54a-e,** 73 & 74 were numbered respectively as **84a-g** and **(-)-79a-g**.

Table 8: **Enantioselective** synthesis of **(-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates {(-)-79a-g}**[a-b]

Substrate	Ar	Product	Yield (%)[c]	Optical rotation $[\alpha]_D^{20}$ (c, $CHCl_3$)	ee[d]
54a	phenyl	(-)-79a	36	-70.24(1.24)	31
54b	**4-chlorophenyl**	(-)-79b	47	-83.24(1.074)	39
54c	**4-methylphenyl**	**(-)-79c**	37	-64.19(0.592)	25
54d	**2-chlorophenyl**	**(-)-79d**	33	-51.60(0.56)	-
54e	**2-methylphenyl**	(-)-79e	35	-58.06(0.632)	32
73	**4-ethylphenyl**	(-)-79f	32	-74.91 (0.606)	35
74	**4-isopropylphenyl**	**(-)-79g**	36	-81.59(0.516)	40

(a) All reactions were **carried** out on a 1 mmol scale of **allyl** bromides (**54a-e,** 73 & 74) with propargyl alcohol (5 mmol) in the presence of quinidine (2 mmol) in **dichloromethane** (4 **mL**) at room temperature for 24 hours.

(b) Products **(-)-79a-d,** f-g were obtained as colorless viscous liquids and product **(-)-79e** was obtained as colorless solid. All the products gave satisfactory **IR,** ^{1}**H** and ^{13}**C** NMR spectral **data,** which are identical with that of the corresponding racemic molecules.

(c) **Isolated** yields of the pure products after column chromatography (silica gel, 2% ethyl acetate in **hexanes**).

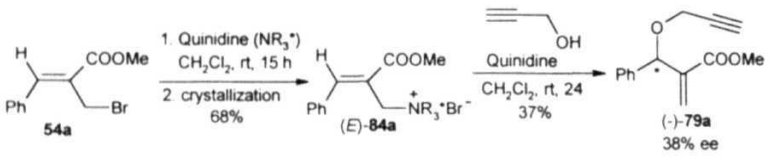
(d) **Enantiomeric** puritiy **of (-)-79a-c, e-g** was determined by using HPLC analysis using chiral column CHIRALCEL OD (5% *i*-**PrOH** in **hexane,** 0.5 **mL/min)** with reference to the corresponding racemic molecules. In the case of molecule (-)-79d determination of enantiomeric purity either by HPLC analysis using chiral column CHIRALCEL OD or ^{1}**H** NMR analysis using chiral shift reagents, **Eu(hfc)$_3$** or **Eu(tfc)$_3$** were unsuccessful.

In order to understand the structure of the allyl bromide-quinidine salt, we have isolated methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-quinidine salt (84a) *via* the treatment of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) (1 mmol) with quinidine (1 mmol) in dichloromethane at room temperature for 15 hours as a crude salt. ^{1}H NMR and ^{13}C NMR spectra of this crude salt indicate that the major compound is (*E*)-isomer (≈ 85%).[θ] Spectral analysis also indicates the presence of ≈ 15% impurities in which presumably (Z)-isomer is the major component. Careful and selective crystallization of this crude salt (84a) from chloroform in hexanes (1:1) provided (*E*)-84a (as evidenced by ^{1}H NMR and ^{13}C NMR (Fig 20) spectral data) as a crystalline solid in 68% yield.[θ] This crystalline solid (*E*)-84a (0.5 mmol) on treatment with prop-2-yn-1-ol (2.5 mmol) in the presence of quinidine (0.5 mmol) in dichloromethane for 24 hours at room temperature provided the desired product (-)-methyl 2-methylene-3-(prop-2-yn-l-yloxy)-3-phenylpropanoate (-)-(79a) in 38% enantiomeric purity and in 37% yield (Scheme 61).

The (*E*)-stereochemistry of this molecule (84a) was established in comparison of chemical shift value of the P-vinylic proton in ^{1}H NMR spectrum with that of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-DABCO salt (56a) In the case of 56a, the P-vinylic proton *cis* to the ester group appears at 6 8 40 (£-isomer) whereas the P-vinylic proton *trans* to the ester group appears at δ 7 98 (*Z*-isomer) In the case of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-quinidine salt (84a), the p-vinylic proton appears at δ 8 47 Therefore we have assigned (*E*)-stereochemistry to the major isomer 84a

The enantiomeric purity of this molecule was determined by HPLC analysis by using chiral column CHIRALCEL OD with reference to the corresponding racemic molecule **(79a).** This indicates that the less enantiomeric excess obtained, from the quinidine salt without crystallization, is presumably due to the presence of (Z)-isomcr.

Scheme 61

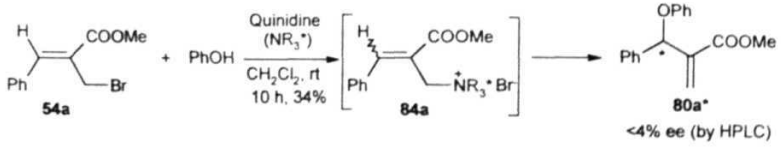


Since the enantiomeric purities are not that high, we did not proceed further for obtaining the pure ***(E)*-isomers *via*** crystallization in the case of other **allyl bromides-quinidine** salts **(84b-f)**

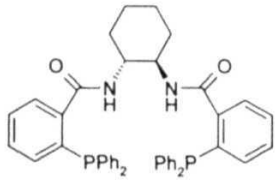
Thus, we have developed a simple methodology for enantioselective synthesis of (-)-methyl **3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates** under the influence of chiral leaving group.

Next our objective was focused towards the synthesis of methyl 2-methylene-3-phenyl-3-phenoxypropanoate (80a) in enantiomerically enriched form following the chiral leaving group strategy. Accordingly, we have treated methyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) (1 mmol) with phenol (1 mmol) in the presence of quinidine (2 mmol) in dichloromethane at room temperature for 10 hours to provide the desired product methyl 2-methylene-3-phenyl-3-phenoxypropanoate (80a) in 34% yield (Scheme 62). The enantioselectivity of the resulting product was determined by HPLC analysis by using chiral column, CHIRALCEL OD (5% *i*-PrOH in hexane, 0.5 mL/min), with reference to its corresponding racemic molecule (80a). The enantioselectivity is not satisfactory (4% ee). Since the enantiomeric purity of this molecule is not encouraging, we did not proceed further in this direction.

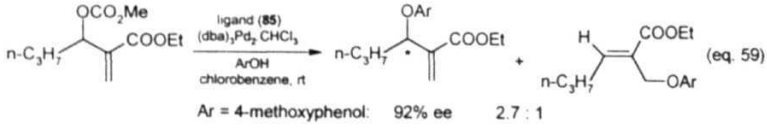
Scheme 62



It is worth mentioning here that during the course of our study, Trost *et al.* have reported enantioselectivc synthesis of aryl ethers of Baylis-Hillman adducts *via* the reaction of carbonates of the Baylis-Hillman adducts with various phenols in the presence of a chiral catalyst derived from the Pd(0) complex at ambient temperature (eq. 59).[192]

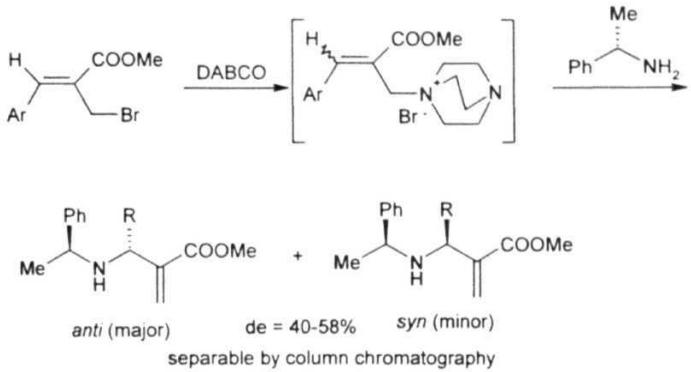


85



Very recently our research group has developed a simple methodology for the diastereoselective synthesis of chiral allyl amines via the reaction of (S)-l-phcnylethylamine with methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates in the presence of DABCO (Scheme 63).[193]

Scheme 63



CONCLUSIONS

We have successfully transformed 3-aryl-3-hydroxy-2-methylenepropanenitriles, the Baylis-Hillman adducts derived from acrylonitrile into (*E*)-α-cyanocinnamyl alcohols *via* aqueous sulfuric acid mediated isomerization. Subsequent oxidation with PCC provides of (*E*)-α-cyanocinnamic aldehydes thus describing an alternative route to Knoevenagel condensation reaction. We have developed a simple methodology for synthesis of 2-methylenealkanoates and alkanenitriiles *via* the regioselective nucleophilic (S_N2') addition of hydride ion from $NaBH_4$ to (2Z)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)alk-2-enenitriles, the allyl

halides derived from Baylis-Hillman adducts, respectively in the presence of DABCO in environment friendly aqueous media. We have successfully used this methodology for the synthesis of methyl 2-tetradecyloxiranecarboxylate (methyl palmoxirate) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) the important hypoglycemic agents. We have successfully employed methyl (2*Z*)-2-(bromomethyl)alk-2-enoates and (3*Z*)-3-(chloromethyl)alk-3-en-2-ones as electrophiles in the Baylis-Hillman reaction with acrylonitrile in the presence of DABCO, thus providing a simple and convenient synthesis of functionalized 1,4-pentadienes. We have utilized propargyl alcohol and phenol as oxygen nucleophiles for addition (SN2') onto methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates in the presence of triethylamine, leading to the synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates and methyl 3-aryl-2-methylene-3-phenoxypropanoates respectively. We have also developed a simple methodology for synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yl-oxy)propanoates in 25-40% enantiomeric purities *via* chiral leaving group strategy using quinidine as a chiral leaving group. We have, thus achieved considerable success in our objectives mentioned in the beginning of the chapter, thus demonstrating the potential of the Baylis-Hillman reaction as an attractive source for various important organic transformations.

EXPERIMENTAL

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

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

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

Infrared Spectra: Infrared spectra were recorded on 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 and liquid samples as thin film between NaCl plates or solution spectra in CH_2Cl_2.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a BRUKER-AC-200 spectrometer. ^1H NMR (200 MHz) spectra for all the samples were measured in chloroform-d with TMS (8 = 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 8 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, b = broad, (3) Number of hydrogens integrated for the signal, (4) coupling constant J in Hertz.

Mass Spectral Analysis: Mass spectra were recorded on a Micromass VG 7070H instrument.

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

Chromatography. *Analytical Thin Layer Chromatography (TLC) was performed on glass plates (7x2 cm) coated with Acme's silica gel G or GF 254 (254 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. Enantiomeric purities were determined using chiral column, CHIRALCEL OD (24 cm) supplied by Daicel, Japan.*

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.

3-Hydroxy-2-methylene-3-phenylpropanenitrile (48a):

A mixture of benzaldehyde (50 mmol, 5.306 g), acrylonitrile (75 mmol, 3.979 g) and DABCO (15 mol%, 7.5 mmol, 0.841 g) was allowed to react at room temperature for 2 days. The reaction mixture was taken up in ether (50 mL) and washed successively with 2N HCl solution, water and aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was distilled under reduced pressure to afford **48a**, as a colorless liquid.

Yield : 78% (6.201 g)

bp : 125-126 °C/2.4 mm {lit.[55] 110 °C/0.95 mm}

IR(neat) : 3447, 2229, 1622 cm^{-1}

^1H NMR : δ 2.38 (d, 1H, J = 4.0 Hz), 5.32 (s, 1H), 6.05 (d, 1H, J = 1.2 Hz), 6.12 (s, 1H), 7.40 (s, 5H).

^{13}C NMR : δ 73.77, 116.95, 126.12, 126.41, 128.69, 130.05, 139.15.

3-(4-Chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (48b):

This compound was obtained as a colorless liquid *via* the reaction of 4-chlorobenzaldehyde with acrylonitrile in the presence of DABCO (cat.) following the similar procedure described for the molecule **48a**.

Reaction time : 40 h

Yield : 82%

bp : 139-141 °C/0.9 mm

IR(neat) : 3443,2231,1625 cm^{-1}

^1H NMR : 8 2.68 (d, 1H, J = 4.0 Hz), 5.29 (s, 1H), 6.04 (s, 1H), 6.10 (d, 1H, J = 1.4 Hz), 7.20-7.49 (m, 4H).

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

3-Hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (48c):

This product was prepared *via* the treatment of 4-methylbenzaldehyde with acrylonitrile in the presence of catalytic amount of DABCO following the similar procedure described for the molecule 48a,as a colorless liquid.

Reaction time : 2 days

Yield : 77%

bp : 122-124 °C/0.8 mm

IR(neat) :3452,2229,1616 cm^{-1}

^1H NMR : 8 2.35 (s, 3H), 2.48 (d, 1H, J = 4.0 Hz), 5.26 (d, 1H, J = 4.0 Hz), 6.01 (s, 1H), 6.09 (d, 1H, J = 1.4 Hz), 7.20 (d, 2H, J = 7.8 Hz), 7.27 (d, 2H, J = 7.8 Hz).

^{13}C NMR : 8 21.06, 73.73, 117.03, 126.29, 126.41, 129.44, 129.68, 136.24,

138.58.

3-Hydroxy-3-(4-isopropylphenyl)-2-methylenepropanenitrile (48d):

It was obtained as a colorless liquid *via* the DABCO catalyzed coupling of 4-isopropylbenzaldehyde with acrylonitrile following the similar procedure described for the molecule 48a.

Reaction time : 2 days

Yield : 80%

bp : 146-147 °C/2.4 mm

IR(neat) : 3435, 2229, 1614 cm^{-1}

^1H NMR : δ 1.24 (d, 6H, J = 6.8 Hz), 2.10 (b, 1H), 2.91 (sept. 1H, J = 6.8 Hz), 5.26 (s, 1H), 6.01 (d, 1H, J =1.2 Hz), 6.10 (s, 1H), 7.18-7.36 (m, 4H).

^{13}C NMR : 6 23.83, 33.78, 73.83, 117.07,126.34, 126.51, 126.87, 129.69, 136.60, 149.57.

3-Hydroxy-2-methylene-3-(2-methylphenyl)propanenitrile (48e):

This molecule was prepared by the reaction of 2-methylbenzaldehyde with acrylonitrile in the presence of catalytic amount of DABCO following the similar

procedure described for the molecule 48a,as a colorless liquid.

Reaction time : 2 days

Yield : 75%

bp : 130-132 °C/1.3 mm

IR (neat) : 3452, 2229. 1616 cm^{-1}

^{1}H NMR : δ2.34(S, 3H). 2.81, (b, 1H), 5.47 (s. 1H), 5.98 (s, lH),6.02(s, 1H), 7.12-7.32 (m, 3H), 7.35-7.44 (m, 1H).

^{13}C NMR : δ 18.80, 70.20, 117.02, 125.15, 126.15, P.6.29, 128.38, 130.35, 130.54, 135.39, 136.79.

3-Hydroxy-3-(2-methoxyphenyl)-2-methylenepropanenitrile (48f)'.

This product was prepared as a colorless liquid *via* the reaction between 2-methoxybenzaldehyde and acrylonitrile under the catalytic influence of DABCO following the similar procedure described for the molecule 48a.

Reaction time : 2 days

Yield : 76%

bp : 147-149 °C/1.5 mm

IR (neat) : 3449, 2227, 1620 cm^{1}

^{1}H NMR : 5 3.18 (b, 1H), 3.86 (s, 3H), 5.50 (s, 1H), 6.01 (m, 2H), 6.87-7.05

(m,2H), 7.23-7.40 (m, 2H).

^{13}C NMR : δ 55.35, 69.97, 110.90, 117.24, 121.03, 125.88, 127.27, 127.59, 129.80, 156.54

3-Hydroxy-2-methylene-3-(naphth-1-yl)propanenitrile (48g):

It was obtained as a colorless viscous liquid by the reaction of 1-naphthaldehyde with acrylonitrile in the presence of DABCO (cat.) following the similar procedure described for the molecule **48a.**

Reaction time : 2 days

Yield : 72%

IR (neat) : 3437, 2227, 1620 cm^{-1}

^{1}H NMR : δ 2.75 (d, 1H, J = 4.0 Hz), 5.97 (d, 1H, J = 4.0 Hz), 6.05 (s, 1H), 6.08 (s, 1H), 7.32-7.68 (m, 4H), 7.76-8.10 (m, 3H).

^{13}C NMR : 5 71.38, 117.22, 123.16, 125.19, 125.44, 125.65, 126.07, 126.72, 129.12, 129.81, 130.54, 131.05, 134.06, 134.42.

(2*E*)-2-Cyano-3-phenylprop-2-en-1-ol (49a):

To 3-hydroxy-2-methylene-3-phenylpropanenitrile (48a) (5 mmol, 0.795 g), aqueous sulfuric acid (20%, 10 mL) was added with stirring at room temperature

and the reaction mixture was refluxed for 2 hours. Then the reaction mixture was cooled to room temperature and diluted with ether (25 mL) and washed successively with aqueous saturated potassium carbonate solution and water. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained, was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide stereochemically pure (2*E*)-2-cyano-3-phenylprop-2-en-1-ol (**49a**), as a colorless liquid.

Yield : 60% (0.477 g)

IR(neat) : 3410, 2216, 1626 cm^{-1}

^1H NMR : 5 2.76 (t, 1H, J = 6.0 Hz, D_2O washable), 4.40 (d, 2H, J = 6.0 Hz), 7.20 (s, 1H), 7.35-7.50 (m, 3H), 7.70-7.82 (m, 2H).

^{13}C NMR .864.00, 110.52, 117.79, 128.74, 130.40, 132.93, 143.90.

Analysis calculated for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80

Found : **C, 75.31; H, 5.72; N, 8.87**

(2*E*)-3-(4-Chlorophenyl)-2-cyanoprop-2-enol (49b):

It was prepared as a colorless solid by the treatment of 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile **(48b)** with aqueous sulfuric acid following the similar procedure described for the molecule **49a.**

Reaction time : 5 h

Yield : 62%

mp : 65-66 °C {lit.[133] mp 65 °C}

IR (KBr) :3412,2216,1626 cm^{-1}

^1H NMR : δ 2.31 (t, 1H, J = 5.8 Hz), 4.42 (d, 2H, J = 5.8 Hz), 7.17 (s, 1H), 7.40 (d, 2H, J = 8.6 Hz), 7.70 (d, 2H, J = 8.6 Hz).

^{13}C NMR : 564.01, 111.17, 117.53, 129.08, 130.05, 131.39, 136.43, 142.40.

Analysis calculated for $C_{10}H_8NOCl$: C, 62.03; H, 4.16; N, 7.23

Found : C, 62.20; H, 4.17; N, 7.20

(2*E*)-2-Cyano-3-(4-methylphenyl)prop-2-en-1-ol (49c):

This product was obtained as a colorless solid *via* the treatment of 3-hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile **(48c)** with aqueous sulfuric acid following the similar procedure described for the molecule **49a**.

Reaction time : 1.5 h

Yield : 68%

mp : 60°C {lit.[133] mp 60 °C}

1R (KBr) : 3412, 2214, 1625 cm^{-1}

^1H NMR : δ 2.37 (s, 3H), 2.58 (b, 1H), 4.37 (d, 2H, J = 5.7 Hz), 7.14 (s, 1H),

7.20 (d, 2H, *J* = 8.0 Hz), 7.64 (d, 2H, *J* - 8.0 Hz).

^{13}C NMR : 8 21.33, 64.19, 109.29, 118.08, 128.86, 129.47, 130.31, 140.95, **143.99.**

Analysis calculated for $C_{11}H_{11}NO$: C, 76.28; H. 6.40; N, 8.09

Found : C, 76.28; H, 6.37; N, 8.05

(2*E*)-2-Cyano-3-(4-isopropylphenyl)prop-2-en-1-ol (49d):

It was prepared *via* the reaction of 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanenitrile **(48d)** with aqueous sulfuric acid following the similar procedure described for the molecule **49a,as** a colorless liquid.

Reaction time : 2 h

Yield : 65%

IR (neat) : 3422, 2214, 1626 cm^{-1}

^{1}H NMR : δ 1.26 (d, 6H, *J* = 6.8 Hz), 2.34 (t, 1H, *J*= 5.8 Hz), 2.94 (sept. 1H, *J* = 6.8 Hz), 4.40 (d, 2H, *J* = 5.8 Hz), 7.17 (s, 1H), 7.28 (d, 2H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR : 23.61, 33.99, **64.24,** 109.35, 118.14, 126.92, **129.04, 130.68, 144.00,** 151.83.

Analysis calculated **for $C_{13}H_{15}NO$** : C, **77.58;** H, **7.51;** N, **6.96**

Found : C, 77.39; H, 7.43; N, 6.98

(2*E*)-2-Cyano-3-(2-methylphenyl)prop-2-en-1-ol (49e):

It was obtained as a colorless liquid by the reaction of 3-hydroxy-2-methylene-3-(2-methylphenyl)propanenitrile (48e) with aqueous sulfuric acid following the similar procedure described for the molecule **49a**.

Reaction time : 2 h

Yield : 67%

IR(ncat) : 3416,2218, 1626 cm^{-1}

^1H NMR : 8 2.33 (s, 3H), 2.65 (t, 1H, J = 6.4 Hz), 4.42 (d, 2H../ = 6.4 Hz), 7.18-7.41 (m, 3H), 7.44 (s, 1H), 7.82 (d, 1H, J = 6.5 Hz).

^{13}C NMR :5 19.50,63.79, 112.92, 117.54, 126.16, 127.69, 130.03, 130.34, 132.38, 137.01, 142.70.

Analysis calculated for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09

Found : C, 76.00; H, 6.43; N, 8.17

(2*E*)-2-Cyano-3-(2-methoxyphenyl)prop-2-en-1-ol (49f):

This product was obtained as a colorless solid ***via*** the reaction between 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanenitrile (48f) and aqueous sulfuric

acid following the similar procedure described for the molecule **49a.**

Reaction time : 2 h

Yield : 52%

mp : 70-72 °C

IR (KBr) :3435,2214,1624 cm^{1}

^{1}H NMR : 6 2.35 (t, 1H, J =5.8 Hz), 3.84 (s, 3H), 4.40 (d, 2H, J =5.8 Hz), 6.90 (d, 1H, J = 8.2 Hz), 7.01 (t, 1H, J = 7.4 Hz), 7.38 (m, 1H), 7.58 (s, 1H), 7.99 (dd, 1H, J = 1.2 & 7.8 Hz)

^{13}C NMR : 8 55.48, 64.30, 110.84, 117.94, 120.61, 122.28, 128.28, 131.79, 139.05, 157.47.

Analysis calculated for $C_{11}H_{11}NO_2$: C 69.83; H, 5.86; N, 7.40

Found : **C, 70.03;** H, 5.84; N, 7.38

(2*E*)-2-Cyano-3-(naphth-1-yl)prop-2-en-1-ol (49g):

This compound was prepared as a colorless solid *via* the treatment of **3-hydroxy-2-methylene-3-(naphth-1-yl)propanenitrile (48g)** with aqueous sulfuric acid following the similar procedure described for the molecule **49a.**

Reaction time : 2 h

Yield : 58%

mp : 94-95 °C

IR (KBr) : 3474, 2218, 1626 cm $^{-1}$

^{1}H NMR : δ 2.40 (t, 1H, J = 6.0 Hz), 4.51 (d, 2H, J= 6.0 Hz), 7.41-7.70 (m, 3H), 7.79-8.13 (m, 5H).

^{13}C NMR : δ 63.82, 114.57, 117.52, 123.25, 125.34, 126.31, 126.60, 126.86, 128.76, 130.39, 130.56, 131.14, 133.44, 142.01.

Analysis calculated for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69

Found : C, 80.21; H, 5.30; N, 6.66

(2*E*)-2-Cyano-3-phenylprop-2-enal (50a):

To a stirred solution of (2*E*)-2-cyano-3-phenylprop-2-en-1-ol (49a) (2 mmol, 0.318 g) in dichloromethane was added pyridinium chlorochromate (PCC) (3 mmol, 0.646 g) at room temperature. After 2 h, the reaction mixture was passed through a silica gel pad. Solvent was evaporated and the crude solid obtained was crystallized from ethyl acetate and hexanes (1:2) to afford stereochemically pure (2*E*)-2-cyano-3-phenylprop-2-enal (50a) as a colorless crystalline solid in 71% (0.223 g) yield.

mp : 94-96 °C {lit.[137] mp 96-97 °C}

IR (KBr) : 2222, 1691, 1593 cm^{-1}

^{1}H NMR : δ 7.48-7.70 (m, 3H), 7.92 (s, 1H), 8.02-8.15 (m, 2H), 9.60 (s, 1H).

^{13}C NMR : 5 112.40, 114.06, 129.49, 131.30, 134.28, 159.37, 187.05.

Analysis calculated for $C_{10}H_7NO$: C, 76.42; H, 4.49; N, 8.91

Found : C, 76.22; H, 4.48; N, 8.93

(2*E*)-3-(4-Chlorophenyl)-2-cyanoprop-2-enal (50b):

This product was obtained as a colorless solid *via* the oxidation of (2*E*)-3-(4-chlorophenyl)-2-cyanoprop-2-en-1-ol **(49b)** with PCC following the similar procedure described for the molecule **50a.**

Yield : 70%

mp : 106-108 °C

IR (KBr) : 2216, 1695, 1608 cm^{-1}

^{1}H NMR : δ 7.54 (d. 2H, *J* = 8.4 Hz), 7.86 (s, 1H), 7.99 (d, 2H, *J* = 8.4 Hz), 9.59 (s, 1H).

^{13}C NMR : 6 112.78, 114.01, 129.76, 130.03, 132.50, 140.79, 157.19, 186.50.

Analysis calculated for $C_{10}H_6NOCl$: C, 62.68; H, 3.16; N, 7.30

Found : C, 62.41; H, 3.16; N, 7.33

(2*E*)-2-Cyano-3-(4-methylphenyl)prop-2-enal (50c):

This compound was prepared as a colorless solid *via* the treatment of (2*E*)-2-cyano-3-(4-methylphenyl)prop-2-en-1-ol **(49c)** with PCC following the similar procedure described for the molecule 50a.

Yield : 74%

mp : 118-1 19 °C

IR (KBr) : 2224, 1693, 1593 cm^{-1}

^1H NMR : δ 2.46 (s, 3H), 7.35 (d, 2H, *J* = 8.0 Hz), 7.87 (s, 1H), 7.95 (d, 2H, *J* = 8.0 Hz), 9.57 (s, 1H).

^{13}C NMR : δ 21.93, 111.18, 114.34, 128.73, 130.30, 131.55, 146.01, 159.27, 187.19.

Analysis calculated for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18

Found : C, 77.31; H, 5.33; N, 8.17

(2*E*)-2-Cyano-3-(4-isopropylphenyl)prop-2-enal (50d):

This product was obtained *via* the reaction between (2*E*)-2-cyano-3-(4-isopropylphenyl)prop-2-en-1-ol (49d) and PCC following the similar procedure described for the molecule 50a as a colorless liquid.

Yield .71%

IR (neat) : 2227, 1695, 1599 cm^{-1}

^1H NMR : 8 1.28 (d, 6H, J = 7.0 Hz), 3.00 (sept. 1H, J = 7.0 Hz), 7.40 (d, 2H, J = 8.0 Hz), 7.88 (s, 1H), 7.98 (d, 2H, J =8.0 Hz), 9.57 (s, 1H).

^{13}C NMR : δ 23.32, 34.37, 111.35, 114.32, 127.65, 129.13, 131.67, 156.49, 159.07, 187.03.

Analysis calculated for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03

Found : C, 78.65; H, 6.51; N, 7.06

(2*E*)-2-Cyano-3-(2-methylphenyl)prop-2-enal (50e):

This compound was obtained ***via*** the oxidation of (2*E*)-2-cyano-3-(2-methylphenyl)prop-2-en-1-ol **(49e)** with PCC following the similar procedure described for the molecule **50a** as a colorless solid.

Yield : 77%

mp : 76-78 °C

IR (KBr) :2227, 1685, 1583 cm^{-1}

^1H NMR : δ 2.51 (s, 3H), 7.28-7.56 (m, 3H), 8.25 (m, 2H), 9.63 (s, 1H).

^{13}C NMR .8 19.65, 113.44, 114.03, 126.78, 128.64, 130.12, 131.28, 133.74, 140.24, 156.96, 187.12.

Analysis calculated for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18

Found : C, 76.93; H, 5.27; N, 8.12

(2*E*)-2-Cyano-3-(2-methoxyphenyl)prop-2-enal (50f):

This compound was obtained as a colorless solid by the treatment of (2*E*)-2-cyano-3-(2-methoxyphenyl)prop-2-en-1-ol **(49f)** with PCC following the similar procedure described for the molecule **50a.**

Yield : 75%

mp : 98-99 °C

IR (KBr) :2222, 1689, 1595 cm^{-1}

^1H NMR : δ 3.95 (s, 3H), 6.97-7.18 (m, 2H), **7.52-7.67 (m, 1H),** 8.38 (d, 1H, ***J* = 7.4 Hz),** 8.47 (s, 1H), 9.59 (s, **1H).**

^{13}C NMR : δ 55.89, 111.54, 114.29, 120.33, 121.03, 129.37, 136.24, 153.49, 159.32, 187.44.

Analysis calculated for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48

Found : C, 70.79; H, 4.83; N, 7.46

(2*E*)-2-Cyano-3-(naphth-1-yl)prop-2-enal (50g):

This product was obtained as a colorless solid *via* the reaction between **(2*E*)-2-**

cyano-3-(naphth-1-yl)prop-2-en-1-ol (49g) and PCC following the similar procedure described for the molecule 50a.

Yield : 78%

mp : 174-175 °C {lit.[137] mp 172-174 °C}

IR (KBr) :2220, 1691, 1597 cm^{-1}

^1H NMR : δ 7.53-7.80 (m, 3H), 7.90-8.22 (m, 3H), 8.49 (d, 1H, *J*= 7.4 Hz), 8.83 (s, 1H), 9.76 (s, 1H).

^{13}C NMR : δ 114.38, 114.63, 122.35, 125.62, 127.15, 127.87, 128.41, 129.03, 129.56, 131.73, 133.76, 134.80, 155.43, 186.49.

Analysis calculated for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76

Found : C, 80.98; H, 4.40; N, 6.77

Methyl **3-hydroxy-2-methylene-3-phenylpropanoate** (53a):

A mixture of benzaldehyde (50 mmol, 5.306 g), methyl acrylate (75 mmol, 6.456 g) and DABCO (15 mol%, 7.5 mM, 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 saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and the crude product thus obtained was distilled under reduced pressure to afford **53a**

as a colorless liquid in 82% (7.871 g) yield.

bp : 117-119 °C/2.1 mm

IR(neat) : 3448, 1720, 1631 cm^{-1}

^1H NMR : 3.04 (d, 1H, J =5.2 Hz), 3.71 (s, 3H), 5.56 (d, 1H, J = 5.2 Hz), 5.82 (d, 1H, J = 2.4 Hz), 6.33 (s, 1H), 7.22-7.AS (m, 5H).

^{13}C NMR .51.67,72.66, 125.56, 126.55, 127.58, 128.20, 141.32, 142.10, 166.56.

Methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (53b):

It was obtained as a colorless liquid *via* the reaction of 4-chlorobenzaldehyde with methyl acrylate in the presence of a catalytic amount of DABCO following the similar procedure described for the molecule **53a.**

Reaction time : 7 days

Yield : 80%

bp : 126-128 °C/0.9 mm

IR (neat) : 3475, 1716, 1630 cm^{-1}

^1H NMR : 6 3.06 (b, 1H), 3.72 (s, 3H), 5.52 (s, 1H), 5.84 (s, 1H), 6.34 (s, 1H), 7.30 (s, 4H).

^{13}C NMR : δ 51.88, 72.14, 125.94, 128.04, 128.43, 133.42, 139.94, 141.79,

166.48.

Methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (53c):

This product was prepared from 4-methylbenzaldehyde, methyl acrylate and DABCO (cat.) following the similar procedure described for the molecule 53a, as a colorless liquid.

Reaction time : 8 days

Yield : 78%

bp : 131-133 °C/2.8 mm

IR (neat) : 3451, 1720, 1630 cm^{-1}

^1H NMR : δ 1.65 (b, 1H), 2.34 (s, 3H), 3.72 (s, 3H), 5.54 (s, 1H), 5.85 (s, 1H), 6.33 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz).

^{13}C NMR : δ 21.10, 51.87, 73.00, 125.70, 126.58, 129.13, 137.50, 138.47, 142.25, 166.80.

Methyl **3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate** (53d):

This compound was obtained as a colorless liquid *via* the reaction of **2-chloro-**benzaldehyde with methyl acrylate in the presence of catalytic amount of DABCO

following the similar procedure described for the molecule 53a.

Reaction time : 6 days

Yield : 79%

bp : 106-107 °C/0.2 mm

IR(neat) : 3433, 1724, 1631 cm^{-1}

^1H NMR : δ 3.17 (b, 1H), 3.78 (s, 311), 5.58 (s, 1H), 5.98 (s, 1H), 6.33 (s, 1H), 7.20-7.45 (m, 3H), 7.51-7.65 (m, 1H).

^{13}C NMR : 5 52.07, 69.16, 126.88, 126.99, 128.16, 128.98, 129.44, 132.82, 138.40, 140.75, 166.96.

Methyl **3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate** (53e):

This product was prepared from 2-methylbenzaldehyde, methyl acrylate and DABCO (cat.) following the similar procedure described for the molecule 53a, as a colorless liquid.

Reaction time : 8 days

Yield : 83%

bp : 142-143 °C/5 mm

IR (neat) :3433,1722,1630 cm^{-1}

^1H NMR : δ 2.33 (s, 3H), 2.82 (s, 1H), 3.76 (s, 3H), 5.61 (s, 1H), 5.82 (s,

1H), 6.32 (s, 1H), 7.11-7.32 (m, 3H), 7.37-7.52 (m, 1H).

^{13}C NMR : 6 18.99, 51.88, 69.15, 125.90, 126.10, 126.35, 127.74, 130.41, 135.68, 138.96, 141.98, 167.04.

Methyl 3-hydroxy-2-methyleneoctanoate (53f):

This compound was obtained as a colorless liquid *via* the DABCO catalyzed coupling of hexanal with methyl acrylate following the similar procedure described for the molecule 53a.

Reaction time : 8 days

Yield : 73%

bp : 80-82 °C/0.7 mm {lit.[128] 102-104 °C74 mm}

IR (neat) : 3445. 1718, 1630 cm^{-1}

^{1}H NMR : o 0.88 (t, 3H, J = 6.0 Hz), 1.18-1.75 (m, 8H), 2.66 (d, 1H, J = 6.4 Hz), 3.77 (s, 3H), 4.38 (m, 1H), 5.79(s, 1H), 6.21 (s, 1H).

^{13}C NMR : 8 13.74, 22.37, 25.22, 31.45, 36.20, 51.52, 70.80, 124.32, 143.00, 166.89.

Methyl 3-hydroxy-2-methylenehexadecanoate (53g):

This compound was prepared *via* the coupling of tetradecanal with methyl acry-

late under the catalytic influence of DABCO (30 mol%) following the similar procedure described for the molecule **53a** as a colorless solid.

Reaction time : 10 days

Yield : 55%

mp : 39-41 °C

IR (KBr) :3445, 1720, 1630 cm^{-1}

^1H NMR : δ 0.88 (t, 3H, *J*= 6.8 Hz), 1.10-1.42 (m,22H), 1.55-1.72 (m, 2H), 2.54 (d, 1H, *J* = 6.8 Hz), 3.77 (s, 3H), 4.37 (m, 1H), 5.79 (s, 1H), 6.21 (s, 1H).

^{13}C NMR : 6 14.05, 22.66, 25.79, 29.34, 29.44, 29.65, 31.91, 36.32, 51.72, 71.44, 124.64, 142.81, 167.00.

Methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a):

This molecule was prepared according to the literature procedure.[159]

To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(53a)** (10 mmol, 1.92 g) in CH_2Cl_2 (20 mL) was added drop wise conc. HBr (48%, 25 mmol, 2.023 g) followed by conc. H_2SO_4 (10 mmol, 0.98 g) at 0 °C. After 12 h at room temperature, the reaction mixture was carefully poured into ice cold water and extracted with ether (3x20 mL). The combined organic layer was washed

with water, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes) to afford **54a** as a colorless liquid in 87% (2.218 g) yield.

IR (neat) : 1716, 1626 cm^{-1}

^1H NMR : δ 3.89 (s, 3H), 4.40 (s, 2H), 7.28-7.64 (m, 5H), 7.83 (s, 1H).

^{13}C NMR : 8 26.67, 52.36, 128.69, 128.83, 129.56, 134.18, 142.85, 166.51.

Methyl **(2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (54b):**

It was obtained as a colorless liquid *via* the treatment of methyl 3-(4-chlorophcnyl)-3-hydroxy-2-methylenepropanoate (53b) with HBr (48%) and conc. H_2SO_4 following the similar procedure described for the molecule **54a.**

Yield : 85%

IR(neat) : 1718, 1626 cm^{-1}

^1H NMR : δ 3.88 (s, 3H), 4.35 (s, 2H), 7.43 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz), 7.76 (s, 1H).

^{13}C NMR : δ 26.25, 52.53, 129.22, 130.94, 132.68, 135.77, 141.47, 166.34.

Methyl (2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (54c):

This compound was prepared by the reaction of methyl 3-hydroxy-2-methylene-

3-(4-methylphenyl)propanoate (53c) with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **54a** as a colorless liquid.

Yield : 83%

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

^1H NMR : δ 2.39 (s, 3H), 3.87 (s, 3H), 4.42 (s, 2H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.49 (d, 2H, *J* = 8.0 Hz), 7.80 (s, 1H).

^{13}C NMR : 5 21.49, 27.11, 52.44, 127.79, 129.70, 129.91, 131.48, 140.16, 143.19,166.85.

Methyl (2*Z*)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate (54d):

This product was obtained as a colorless viscous liquid *via* the reaction between methyl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate (53d) and HBr (48%) in the presence of conc. H2SO4 following the similar procedure described for the molecule **54a**.

Yield : 80%

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

^1H NMR : 6 3.90 (s, 3H), 4.27 (s, 2H), 7.21-7.53 (m, 3H), 7.65-7.77 (m, 1H), 7.92 (s, 1H).

^{13}C NMR : **5 26.23, 52.60,** 127.05, 129.61, 129.88, 130.61, 132.91, **134.54,** 139.56, 166.10.

Methyl (2*Z*)-2-(bromomethyl)-3-(2-methylphenyl)prop-2-enoate (54e):

It was obtained as a colorless liquid by treatment of methyl **3-hydroxy-2-**methylene-3-(2-methylphenyl)propanoate (53e) with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **54a.**

Yield : 86%

IR (neat) : 1724. 1632 cm*[1]

^{1}H NMR : δ 2.29 (s. 3H), 3.88 (s, 3H). 4.27 (s, **2H), 7.17-7.32** (m, 3H). **7.46-**7.58 (m. 1H). 7.90 (s. 1H).

^{13}C NMR : 8 19.73, 26.43, 52.23, 125.98, 127.84, 129.25, 129.52, 130.25, 133.48, 137.15, 141.96, 166.27.

Methyl (2Z)-2-(bromomethyl)oct-2-enoate (54f):

This product was obtained as a colorless liquid *via* the reaction of methyl 3-hydroxy-2-methyleneoctanoate **(53f)** with HBr (48%) and conc. H_2SO_4 following the similar procedure described for the molecule **54a.**

Yield :60%

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

^1H NMR : 6 0.90 (t, 3H, J = 7.6 Hz), 1.20-1.74 (m, 6H), 2.28 (m, 2H), 3.80 (s, 3H), 4 22 (s, 2H), 6.98 (t, 1H, J = 7.6 Hz).

^{13}C NMR : 8 13.85, 22.39, 24.21, 27.81, 28.82, 31.50, 52.02, 129.22, 148.51, 166.05.

Methyl (2*Z*)-2-(bromomethyl)hexadec-2-enoate (54g):

It was prepared as a colorless liquid by the reaction of methyl 3-hydroxy-2-methylenehexadecanoate (53g) with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **54a.**

Yield : 65%

IR(neat) : 1724, 1641 cm^{-1}

^1H NMR : **δ 0.87 (t, 3H, J - 6.6 Hz),** 1.18-1.62 (m, 22H), 2.28 (m, **2H),** 3.79 **(s, 3H), 4.22 (s, 2H), 6.97 (t, 1H, J = 7.8 Hz).**

^{13}C NMR : *8* **14.07, 22.68, 24.17, 28.19, 28.90, 29.39, 29.50, 29.65, 31.93, 52.01, 129.28, 148.48, 166.04.**

Methyl **2-methylene-3-phenylpropanoate** (55a):

To a stirred mixture of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a) (2 mmol, 0.510 g) in H_2O (2 mL)/THF (2 mL), was added DABCO (2 mmol, 0.224 g) at room temperature. After 15 minutes, $NaBH_4$ (2 mmol, 0.076 g) was added and stirring was continued for further 15 minutes. Reaction mixture was diluted with water (10 mL) and extracted with ether (2 × 10 mL). Combined organic layer was washed successively with 2N HC1 solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product obtained was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes) to afford 55a in 83 % (0.292 g) yield as a colorless liquid.

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

^1H NMR : 6 3.63 (s, 2H), 3.72 (s, 3H), 5.46 (s, 1H), 6.23 (s, 1H), 7.12-7.35 (m, 5H).

^{13}C NMR .8 38.02,51.72, 126.06, 126.29, 128.37, 128.96, 138.67, 140.15, 167.23.

MS(nVz) : 176 (M^+)

Analysis calculated for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86

Found : C, 74.72; H, 6.89

Methyl 3-(4-chlorophenyl)-2-methylenepropanoate (55b):

This molecule was prepared by the reaction of methyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (54b) with $NaBH_4$ in the presence of DABCO in H_2O/THF, following the similar procedure described for the molecule **55a** as a colorless liquid.

Yield : 87%

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

^1H NMR : δ 3.60 (s, 2H), 3.73 (s, 3H), 5.48 (s, 1H), 6.24 (s, 1H), 7.13 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR : 6 37.44, 51.78, 126.31, 128.47, 130.27, 132.13, 137.21, 139.68, 166.97.

MS (m/z) : 210 (M^+), 212 $(M+2)^+$

Analysis calculated for $C_{11}H_{11}O_2Cl$: C, 62.71; h, 5.26

Found : C, 62.49; H, 5.23

Methyl 2-methylene-3-(4-methylphenyl)propanoate (55c):

This compound was prepared as a colorless liquid *via* the reaction between methyl (2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (54c) and $NaBH_4$ in the

presence of DABCO in H_2O/THF, following the similar procedure described for the molecule **55a.**

Yield : 80%

IR(neat) : 1724, 1631 cm^{-1}

^1H NMR : δ 2.31 (s, 3H), **3.58** (s, 2H), **3.72** (s, 3H), **5.45** (d, 1H, *J* = 1.4 Hz), 6.21 (s, 1H), 7.09 (s,4H).

^{13}C NMR : δ 20.95, 37.61,51.74, 125.93, 128.87, 129.08. 135.58, 135.74, 140.33,167.32.

MS(m/z) : 190 (M^+)

Analysis calculated for $C_{12}H_{14}O_2$: C, 75.56; H, 7.42

Found : C, 75.80; H, 7.40

Methyl 3-(2-chlorophenyl)-2-methylenepropanoate (55d):

It was prepared as a colorless liquid by the treatment of methyl (2Z)-2-(bromo-methyl)-3-(2-chlorophenyl)prop-2-enoate **(54d)** with $NaBH_4$ in the presence of DABCO in H_2O / THF following the similar procedure described for the molecule **55a.**

Yield : 82%

IR (neat) : 1722, 1633 cm^{-1}

^1H NMR : 6 3.76 (s, 5H), 5.33 (s, 1H), 6.26 (s, 1H), 7.10-7.29 (m, 3H), 7.30-7.42 (m, 1H).

^{13}C NMR : δ 35.37, 51.86, 126.46, 126.82, 127.96, 129.58, 131.13, 134.47, 136.36, 138.17, 167.15.

MS (m/z) : 210 (M^+), 212 $(M+2)^+$

Analysis calculated for $C_{11}H_{11}O_2Cl$: C, 62.71; H, 5.26

Found :C, 62.41; H, 5.22

Methyl 2-methylene-3-(2-methylphenyl)propanoate (55e):

This product was prepared as a colorless liquid *via* the reaction of methyl (2Z)-2-(bromomethyl)-3-(2-methylphenyl)prop-2-enoate (54e) with $NaBH_4$ in the presence of DABCO in H_2O / THF following the similar procedure described for the molecule 55a.

Yield : 84%

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

^1H NMR : 5 2.23 (s, 3H), 3.61 (s, 2H), 3.76 (s, 3H), 5.16 (d, 1H, J = 1.8 Hz),

6.20 (s, 1H), 7.04-7.24 (m, 4H).

^{13}C NMR : 8 19.15, 35.24, 51.75, 125.60, 126.01, 126.65, 129.86, 130.24, 136.57, 139.28, 167.40.

MS (m/z) : 190 (M^+)

Analysis calculated for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42

Found : C, 76.02; H, 7.46

Methyl **2-methyleneoctanoate** (55f):

This compound was prepared as a colorless liquid *via* the treatment of methyl (2*Z*)-2-(bromomethyl)oct-2-enoate **(54f)** with $NaBH_4$ in the presence of DABCO in H2O/THF, following the similar procedure described for the molecule **55a.**

Yield : 72%

IR(neat) : 1722, 1633 cm^{-1}

^{1}H NMR : 8 0.87 (t, 3H, *J* = 5.8 Hz), 1.20-1.58 (m, 8H), 2.29 (t, 2H, *J* = 6.6 Hz), 3.74 (s,3H), 5.51 (s, 1H), 6.11 (s, 1H).

^{13}C NMR : 8 13.85, 22.48, 28.31, 28.79, 31.54, 31.81, **51.41,** 124.08, 140.84, 167.54.

MS (m/z) : 170 (M^+)

Analysis calculated for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66

Found : C, 70.76; H, 10.60

Methyl 2-methylenehexadecanoate (55g):

It was prepared as a colorless liquid by the reaction of methyl (2*Z*)-2-(bromomethyl)hexadec-2-enoate (**54g**) with $NaBH_4$ in the presence of DABCO in H_2O/THF following the similar procedure described for the molecule 55a.

Yield : 76%

IR(neat) : 1726, 1631 cm^{-1}

^1H NMR : δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.18-1.56 (m, 24H), 2.29 (t, 2H, *J* = 7.6 Hz), 3.74 (s, 3H), 5.51 (s, 1H), 6.11 (s, 1H).

^{13}C NMR : δ 14.14, 22.76, 28.50, 29.30, 29.43, 29.50, 29.75, 31.99, 51.72, 124.36, 141.02, 167.91.

Analysis calculated for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13

Found ;C, 76.41; H, 12.20

Methyl **(2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate DABCO salt (56a):**

To a stirred mixture of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**54a**) (1 mmol, 0.255 g) in H_2O (1 mL)/THF (1 mL) was added DABCO (1 mmol, 0.112 g) at room temperature. After 30 minutes, THF was evaporated and

the water was removed under reduced pressure to afford the amine salt (methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-DABCO salt) **56a** as a colorless solid.

E:*Z* : 82:18

IR (KBr) : 1711, 1630 cm^{-1}

^1H NMR : δ 3.13 & 1.25 (2t, 6H, *J* = 7.0 Hz), 3.41-3.98 (m, 9H), 4.91 (s, 2H), 7.36-7.78 (m, 5H), 7.98 & 8.40 (2s, 1H).

^{13}C NMR : δ 45.14, 52.03, 52.38, 53.01, 57.81, 67.53, 119.09, 119.82, 127.95, 128.72, 129.43, 130.39, 132.65, 133.59, 150.18, 152.03, 166.81, 167.69.

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

3-(2-Chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (48h):

This compound was obtained as a colorless viscous liquid by the reaction of 2-chlorobenzaldehyde with acrylonitrile in the presence of DABCO following the similar procedure described for the molecule **48a.**

Reaction time : 40 h

Yield : 80%

IR(neat) : 3447, 2231, 1622 cm^{-1}

^{1}H NMR : 8 2.96 (d, 1H, J = 4.2 Hz), 5.74 (d, 1H, J = 4.2 Hz), 6.04 (s, 2H), 7.23-7.44 (m, 3H), 7.57-7.70 (m, 1H).

^{13}C NMR : 8 70.21, 116.66, 124.55, 127.42, 127.89, 129.59, 129.83, 131.43, 132.45,136.50.

3-Hydroxy-2-methyleneoctanenitrile (48i):

This compound was obtained as a colorless liquid *via* the DABCO catalyzed coupling of hexanal with acrylonitrile following the similar procedure described for the molecule 48a.

Reaction time : 2 days

Yield : 74%

bp : 110-111 °C/2.2 mm {lit.[15] 88-90 °C/1.0 mm}

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

^{1}H NMR : 8 0.90 (t, 3H, J =6.8 Hz), 1.20-1.53 (m, 6H), 1.57-1.88 (m, 2H), 2.32 (d, 1H, J = 5.0 Hz), 4.25 (m, 1H), 5.98 (s, 1H), 5.99 (s, 1H).

^{13}C NMR : 8 13.84, 22.38, 24.65, 31.33, 35.44, 72.10, 117.08, 126.91, 129.94.

3-Hydroxy-2-methylenehexadecanenitrile (48j):

This compound was prepared *via* the Baylis-Hillman coupling of tetradecanal with acrylonitrile under the catalytic influence of DABCO (30 mol%) following the similar procedure described for the molecule 48a as a colorless viscous liquid.

Reaction time : 12 days

Yield : 72%

IR (neat) : 3423, 2227, 1624 cm^{-1}

^{1}HNMR : δ 0.87 (t, 3H, J = 6.6 Hz), 1.11 -1.43 (m, 22H), 1.58-1.77 (m, 2H), 1.93 (d, 1H, J =5.2 Hz), 4.23 (m,1H), 5.96 (s, 1H), 5.98 (s, 1H).

^{13}CNMR : δ 14.02, 22.63, 25.07, 29.30, 29.62, 31.89, 35.70, 72.27, 117.07, 127.18, 129.65.

2-(Bromomethyl)-3-phenylprop-2-enenitrile (57a):

This molecule was prepared according to the literature procedure.[159]

To a stirred solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (48a) (10 mmol, 1.59 g) in CH_2Cl_2 (20 mL) was added drop wise conc. HBr (48%, 25 mmol, 2.023 g) followed by conc. H_2SO_4 (10 mmol, 0.98 g) at 0 °C. After stirring 12 h at room temperature, the reaction mixture was carefully poured into ice cold water and extracted with ether (3x20 mL). The combined organic layer was

washed with water, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, 2% ethyl acetate in hcxanes) to afford 57a as a colorless solid in 83% (1.842 g) yield, as *E.Z* mixtures in the ratio of * 85:15.

mp: : 49-51 °C

IR (KBr) : 2220, 1616 cm^{-1}

^1H NMR : 5 4.19 & 4.22 (2s, 2H), 7.21 & 7.25 (2s, 1H), 7.39-7.86 (m, 5H).

^{13}C NMR : δ 26.66, 32.78, 107.81, 111.71, 116.98, 118.57, 128.88, 129.06, 130.33, 131.21, 132.23, 132.46, 146.39, 147.08.

The underlined chemical shift values are due to minor (Z)-isomer (≈ 15%).

2-(Bromomethyl)-3-(4-chlorophenyl)prop-2-enenitrile (57b):

It was prepared as a colorless solid by the treatment of 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (48b) with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule 57a.

Yield : 74%

E.Z : 84:16

mp : 48-50 °C

IR (KBr) .2222, 1616 cm^{1}

^{1}H NMR : δ 4.16 & 4.21 (2s, 2H), 7.17 & *129* (2s, 1H), 7.42 (m, 2H), 7.73 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR : 8 26.31, 32.42, 108.56, 112.37, 116.73, 118.34, 129.20, 129.39, 130.32, 130.75, 136.55, 137.21, 144.87, 145.67.

The underlined chemical shift values are due to minor (Z)-isomer (≈ 16%).

2-(Bromomethyl)-3-(4-methylphenyl)prop-2-enenitrile (57c):

This compound was prepared by the reaction of 3-hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile **(48c)** with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **57a** as a colorless solid.

Yield : 86%

E.Z : ≈ 95:5

mp : 58-61 °C

IR (KBr) : 2212, 1606 cm^{-1}

^{1}H NMR : δ 2.40 (s, 3H), 4.21 (s, 2H), 7.17 (s, 1H), 7.25 (d, 2H, *J* = 7.6 Hz), 7.70 (d, 2H, *J* = 7.6 Hz).

^{13}C NMR : 5 21.50, 26.93, 33.06, **106.61, 117.24,** 129.20, 129.66, 142.03, **146.49**, 147.25.

The underlined chemical shift values are due to minor (Z)-isomer (≈ 5%).

2-(Bromomethyl)-3-(2-methylphenyl)prop-2-enenitrile (58):

It was obtained as a colorless solid ***via*** the reaction between 3-hydroxy-2-methylene-3-(2-methylphenyl)propanenitrile **(48e)** and HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule 57a.

Yield : 73%

E:*Z* : ≈77:23

mp : 66-69 °C

IR (KBr) : 2218, 1610 cm^{-1}

^{1}H NMR : δ *230* & 2.36 (2s, 3H), 4.10 & **4.24** (2s, 2H), 7.18-7.90 (m, 5H).

^{13}C NMR : δ 19.67, 26.42, 32.21, 110.14, 112.82, 116.79, 118.36, 126.24, **126.39**, 127.85. 130.24, 130.55, 130.82, 131.63, 137.19, 137.40, 145.19, 146.45.

The underlined chemical shift values are due to minor (Z)-isomer **(≈ 23%)**.

2-(Bromomethyl)-3-(2-chlorophenyl)prop-2-enenitrile (59):

This product was obtained as a colorless solid ***via*** the treatment of **3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (48h)** with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **57a.**

Yield : 72%

Z:£ : ≈ 81:19

mp : 52-54 °C

IR (KBr) :2222, 1618 cm^{-1}

^1H NMR : δ 4.09 & 4.24 (2s, 2H), 7.23-8.10 (m, 5H).

^{13}C NMR : δ 26.17, 31.86, 111.26, 113.86, 116.32, 117.90, 127.19, 129.16, 129.39, 129.89, 130.16, 130.68, 130.94, 131.48, 131.98, 134.18, 134.51, 142.59, 143.82.

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

2-(Bromomethyl)oct-2-enenitrile (60):

It was prepared by the reaction of 3-hydroxy-2-methyleneoctanenitrile **(48i)** with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **57a** as a colorless liquid.

Yield : 64%

E.Z : ≈ 62:38

IR (neat) : 2220, 1628 cm^{-1}

^1H NMR : δ 0.92 (t, 3H, *J* = 6.4 Hz), 1.25-1.61 (m, 6H), 2.29 & 2.43 (2q, 2H, *J* - 7.2 Hz), 4.02 (s, 2H), 6.45-6.60 (m, 1H).

^{13}C NMR : δ 13.86, 22.34, 24.25, 27.66, 27.83, 28.71, 30.40, 31.18, 31.34, 31.61, 112.43, 112.78, 115.66, 11814, 15214, 152.61.

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

2-(Bromomethyl)hexadec-2-enenitrile (61):

It was obtained as a colorless liquid by the reaction of 3-hydroxy-2-methylenehexadecanenitrile **(48j)** with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **57a.**

Yield : 80%

I.E : ≈ 72:28

IR (neat) : 2224, 1633 cm^{-1}

^1HNMR : δ 0.87 (t, 3H *J* = 6.6 Hz), 1.20-1.60 (m, 22H), 2.27 & 2.40 (2q, 2H, *J* - 7.2 Hz), 3.99 (d, 2H, *J* = 2.0 Hz), 6.49 (m, 1H).

^{13}C NMR : *b* 14.09, 22.69, 24.25, 27.99. 28.17, 28.73. 29.04, 29.29, 29.35,

29.46, 29.65, 30.39, 31.65, 31.93, 112.42, 112.75, 115.64, 118.10, 152.09, 152.54.

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

2-(Bromomethyl)-3-phenylprop-2-enenitrile-DABCO salt (62a):

To a stirred solution of 2-(bromomethyl)-3-phenylprop-2-enenitrile **(57a)** (1 mmol, 0.222 g) in H_2O (1 mL)/THF (1 ml) was added **DABCO** (1 mmol, 0.112 g) at room temperature. After 30 minutes, **THF** was evaporated and the water was removed under reduced pressure to afford the amine salt **(2-(bromomethyl)-3-phenylprop-2-enenitrile-DABCO salt) 62a** as a colorless solid.

Z:*E* : ≈ 78:22

mp : 215-218 °C (dec.)

IR (KBr) :2210,1618 cm^{-1}

^{1}H NMR (DMSO) : *b* 3.07 (t, 6H,./ = 7.4 Hz), 3.47 (t, 6H, *J* = 7.4 Hz), 4.11 & 4.41 (2s, 2H), 7.50-7.74 (m, 3H), 7.82-8.02 (m, 3H).

^{13}C NMR (DMSO) : 5 44.88, 50.59, 51.71, 65.13, 97.23, 98.01, 118.24, 118.58, 129.21, 129.73, 132.22, 132.50, 156.90, 157.73.

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

2-Methylene-3-phenylpropanenitrile (63a):

To a stirred solution of 2-(bromomethyl)-3-phenylprop-2-enenitrile **(57a)** (2 mmol, 0.444 g) in H_2O (2 mL)/THF (2 mL), was added DABCO (2 mmol, 0.224 g) at room temperature. After 15 minutes, $NaBH_4$ (2 mmol, 0.076 g) was added and stirring was continued for further 15 minutes. Then the reaction mixture was diluted with water (10 mL) and extracted with ether (2 × 10 mL). Combined organic layer was washed successively with 2N HC1 solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product obtained was purified by column chromatography (silica gel. 2% ethyl acetate in hexanes) to afford **63a** in 82% (0.234 g) yield as a colorless liquid.

IR(neat) : 2224, 1622 cm^{-1}

^1H NMR : δ 3.56 (s, 2H), 5.70 (S, 1H), 5.91 (s, 1H), 7.13-7.42 (m, 5H).

^{13}C NMR .6 40.55, 118.33, 122.51, 127.23, 128.74, 130.87, 135.54.

MS (m/z) : 143 (M^+)

Analysis calculated for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78

Found : C, 83.60; H, 6.34; N, 9.83

3-(4-Chlorophenyl)-2-methylenepropanenitrile (63b):

This molecule was prepared by the reaction of 2-(bromomethyl)-3-(4-chlorophe-

nyl)prop-2-enenitrile **(57b)** with $NaBH_4$ in the presence of DABCO in H_2O/THF following the similar procedure described for the molecule **63a** as a colorless liquid.

Yield : 90%

IR (neat) : 2224, 1622 cm^{1}

^{1}H NMR : 6 3.49 (s, 2H), 5.70 (s, 1H), 5.89 (s, **1H),** 7.13 **(d,** 2H, J = 8.6 Hz), 7.29 (d, 2H, J = 8.6 Hz).

^{13}C NMR : δ **39.84,** 118.04, 122.00, 128.83, 130.10, 131.15, 133.10, 134.08.

MS (m/z) : 177 (M^{+})

Analysis calculated for $C_{10}H_8NCl$: C, 67.61; H, 4.54; N, 7.88

Found : C, 67.46; H, 4.56; N, 7.86

2-Methylene-3-(4-methylphenyl)propanenitrile (63c):

This compound was prepared as a colorless liquid *via* the treatment of 2-(bromomethyl)-3-(4-methylphenyl)prop-2-enenitrile (57c) with $NaBH_4$ in the presence of DABCO in H_2O/THF following the similar procedure described for the molecule **63a**

Yield : 81%

IR(neat) : 2224, 1622 cm^{-1}

^{1}H NMR : 6 2.32 (s, 3H), 3.50 (s, 2H), 5.67 (s, 1H), 5.88 (s, 1H), 7.05-7.25 (m, 4H).

^{13}C NMR : 6 20.92, 40.23, 118.43, 122.88, 128.68, 129.45, 130.58, 132.50, 136.87.

MS(nVz) : 157 (M^+)

Analysis calculated for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91

Found : C, 84.41; H, 7.08; N, 8.87

2-Methylene-3-(2-methylphenyl)propanenitrile (63d):

This product was prepared as a colorless liquid ***via*** the treatment of 2-(bromomethyl)-3-(2-methylphenyl)prop-2-enenitrile (58) with $NaBH_4$ in the presence of DABCO in H_2O/THF following the similar procedure described for the molecule **63a**

Yield : 87%

IR (neat) : 2224, 1622 cm^{-1}

^{1}H NMR : 5 2.27 (s, 3H), 3.53 (d, 2H, J = 1.6 Hz), 5.50 (s, 1H), 5.89 (s, 1H), 7.10-7.24 (m, 4H).

^{13}C NMR : 5 19.08, 37.93, 118.53. 121.77, 126.38, 127.59, 129.86, 130.56, 130.67, 133.57, 136.51.

MS (m/z) : 157 (M^+)

Analysis calculated for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91

Found : C, 84.36; H, 7.01; N, 8.96

3-(2-Chlorophenyl)-2-methylenepropanenitrile (63e):

It was prepared as a colorless liquid by the reaction of 2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enenitrile (59) with $NaBH_4$ in the presence of DABCO in H_2O/THF following the similar procedure described for the molecule **63a.**

Yield : 85%

IR(neat) : 2224, 1622 cm^1

^1H NMR : 6 3.69 (s, 2H). 5.67 (d, 1H. J = 1.6 Hz), **5.96** (s, 1H), 7.20-7.32 (m, 3H), 7.35-7.45 (m, 1H).

^{13}C NMR : 6 37.89, 118.18, 120.57, 127.21, 128.94, 129.80, 131.01, **131.61,** 133.32, 134.31.

MS(m/z) : 177 (M^+)

Analysis calculated for $C_{10}H_8NCl$: C, 67.61; H, 4.54; N, 7.88

Found : C, **67.51; H,** 4.57; N, 7.85

2 Methyleneoctanenitrile (63f):

It was prepared *via* the reaction of 2-(bromomethyl)oct-2-enenitrile (60) with $NaBH_4$ in the presence of DABCO in H_2O/THF following the similar procedure described for the molecule **63a** as a colorless liquid.

Yield : 74%

IR(neat) 2224, 1622 cm^{-1}

^1H NMR : 5 0.88 (t, 3H, J = 5.6 Hz), 1.15-1.70 (m, 8H), 2.24 (t, 2H, J = 7.6 Hz), 5.68 (s, 1H), 5.81 (s, 1H).

^{13}C NMR : δ 13.85, 22.39, 27.46, 28.17, 31.32, 34.55, 118.56, 123.45, 129.77.

Analysis calculated for $C_9H_{15}N$: C, 78.78; H, 11.02; N, 10.21

Found : C, 78.95; H, 10.94; N, 10.30

2-Methylenehexadecanenitrile (63g):

It was prepared as a colorless liquid by the reaction of 2-(bromomethyl)hexadec-2-enenitrile (61) with $NaBH_4$ in the presence of DABCO in H_2O/THF following the similar procedure described for the molecule **63a.**

Yield : 82%

IR (neat) : 2224, 1622 cm^{-1}

^{1}H NMR : δ 0.87 (t, 3H, J = 6.4 Hz), 1.21-1.65 (m, 24H), 2.24 (t, 2H, J = 7.8 Hz), 5.69 (s, 1H), 5.82 (s, 1H).

^{13}C NMR : 6 14.12, 22.71, 27.59, 28.64, 29.25, 29.39, 29.51, 29.69, 31.96, 34.67, 118.73, 123.53, 129.92.

Analysis calculated for $C_{17}H_{31}N$: C, 81.86; H, 12.53; N, 5.62

Found : C, 81.65; H, 12.47; N, 5.66

Methyl **2-tetradecyloxirane-2-carboxylate** (methyl palmoxirate) (51)

To a stirred solution of methyl 2-methylenehexadecanoate (55g) (1 mmol, 0.282 g) in 1,2-dichloroethane, was added *m*-CPBA (3 mmol, 0.517 g) and the reaction mixture was heated under reflux temperature for 24 hours. The reaction mixture was allowed to come to room temperature and diluted with ether (10 ml.) and washed successively with aq. $NaHCO_3$ solution, 10% aq. sodium sulfite solution and water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue was purified by column chromatography (silica gel, 3% ethyl acetate in hexanes) to provide the pure methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (51) in 73% (0.217 g) yield as a white solid.

mp : 42-44 °C {lit.[142] mp 44-46 °C}

IR (KBr) : 1747 cm^{-1}

^{1}H NMR : 6 0.87 (t, 3H, J = 7.2 Hz), 1.24 (s, 24H), 1.57-2.15 (m, 2H), 2.77 (d, 1H, J =6.0 Hz), 3.02 (d, 1H, J =6.0 Hz), 3.75 (s, 3H).

^{13}C NMR : 6 14.02, 22.64, 24.72, 29.38, 29.63, 31.23, 31.90, 51.67, 52.32, 56.98, 170.86.

6-Bromohexan-1-ol (68):

This molecule was prepared according to the literature procedure with some modifications.[168]

A mixture of 1,6-hexanediol (30 mmol, 3.545 g) and aq. HBr (48%) (104 mmol, 8.424 g) in toluene (25 mL) was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature. The toluene layer was separated and washed with water and dried over anhydrous Na_2SO_4. Removal of the solvent and distillation of the residue under reduced pressure provided the pure 6-bromohexan-1-ol (68) in 47% (2.552 g) yield as a colorless liquid.

bp : 85 °C/3.5 mm {lit.[194] 105-106 °C/5 mm }

IR (neat) : 3352 cm^{-1}

^{1}H NMR : o 1.31-2.00(m,9H), 3.42 (t, 2H, J =6.8 HZ), 3.64 (t, 2H, J = 6.8 Hz).

^{13}C NMR : o 24.85, 27.84, 32.33, 32.63, 33.72, 62.37.

6-(4-Chlorophenoxy)hexan-1-ol (69):

To a stirred mixture of 4-chlorophenol (10 mmol, 1.285 g) and anhydrous K_2CO_3 (25 mmol, 3.45 g) in acetonitrile (15 mL), 6-bromohexan-1 -ol (68) (10 mmol, 1.81 g) and KI (10 mmol. 1.66 g) were added and the reaction mixture was heated at reflux temperature for 4 hours. The reaction mixture was allowed to cool to room temperature and diluted with water (20 mL) and extracted with ether (2 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the pure 6-(4-chlorophenoxy)hexan-1-ol (69) as a colorless viscous liquid in 70% yield (1.599 g).

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

^1H NMR : δ 1.28-1.95 (m, 9H), 3.65 (t, 2H, J = 6.2 Hz), 3.91 (t, 2H, J = 6.2 Hz), 6.80 (d, 2H, J = 8.6 Hz), 7.20 (d, 2H, J = 8.6 Hz).

^{13}C NMR : δ 25.48, 25.78, 29.10, 32.53, 62.53, 68.17, 115.76, 125.27, 129.17, 157.67.

6-(4-Chlorophenoxy)hexanal (65):

To a stirred solution of 6-(4-chlorophenoxy)hexan-l-ol (69) (10 mmol, 2.285 g) in dichloromethane was added PCC (15 mmol, 3.233 g) at room temperature. After

2 hours, the reaction mixture was passed through silica gel pad. Solvent was evaporated and the residue was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to afford 6-(4-chlorophenoxy)hexanal (65) as a colorless viscous liquid in 71% yield (1.608 g).

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

^1H NMR : 6 1.34-1.98 (m, 6H), 2.49 (t, 2H, J = 6.8 Hz), 3.92 (t, 2H, J= 6.6 Hz), 6.78 (d, 2H, J = 8.6 Hz), 7.20 (d, 2H, J = 8.6 Hz), 9.77 (s, 1H).

^{13}C NMR : δ 21.68, 25.55, 28.87, 43.62, 67.82, 115.71, 125.26, 129.15, 157.59,202.07.

Ethyl 3-hydroxy-2-methylene-8-(4-chlorophenoxy)octanoate (66):

This product was obtained as a colorless viscous liquid *via* the reaction between 6-(4-chlorophenoxy)hexanal (65) (5 mmol, 1.132 g) and ethyl acrylate (10 mmol, 1.001 g) under the catalytic influence of DABCO (30 mol%) according to the similar procedure described for the molecule 53a.

Reaction time : 10 days

Yield : 49%

IR (neat) : 3447, 1711, 1628 cm^{-1}

^{1}H NMR : δ 1.31 (t, 3H, *J* = 7.0 Hz), 1.39-1.97 (m, 8H), 2.61 (d, 1H, *J* = 6.6 Hz), 3.91 (t, 2H, *J* = 6.6 Hz), 4.23 (q, 2H, *J* = 7.0 Hz). 4.40 (m, 1H), 5.77 (s, 1H), 6.22 (s, 1H), 6.80 (d, 2H, *J* = 8.6 Hz), 7.20 (d, 2H, *J* = 8.6 Hz).

^{13}C NMR : δ 14.05, 25.44, 25.73, 29.03, 36.15, 60.70, 68.14, 71.25, 115.77, 124.33, 125.25, 129.15, 143.00, 157.68, 166.49.

Ethyl (2*Z*)-2-(bromomethyl)-8-(4-chlorophenoxy)oct-2-enoate (67):

It was obtained as a colorless viscous liquid by the reaction of ethyl 3-hydroxy-2-methylene-8-(4-chlorophenoxy)octanoate (66) with HBr (48%) in the presence of conc. H_2SO_4 following the similar procedure described for the molecule **54a.**

Yield : 66%

Z:*E* : ≈ 90:10

IR(neat) : 1714, 1641 cm^{-1}

^{1}H NMR : δ 1.34 (t, 3H, *J* = 7.2 Hz), 1.40-1.94 (m, 6H), 2.34 & 1.62 (2m, 2H), 3.94 (m, 2H), 4.17-4.35 (m, 4H), 6.82 (d, 2H, *J* = 8.8 Hz), 6.35 & 6.98 (2t, 1H, *J* = 7.6 Hz), 7.24 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR : δ 14.20, 24.31, 25.83, 27.86, 28.73, 28.92, 29.53, 33.63, 60.76, 61.02, 67.94, 115.74, 125.33, 129.22, 129.67, 147.59, 157.62,

166.12.

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

Ethyl 2-methylene-8-(4-chlorophenoxy)octanoate (64):

It was prepared as a colorless liquid by the reaction of ethyl (2Z)-2-(bromomethyl)-8-(4-chlorophenoxy)oct-2-enoate (67) (1 mmol, 0.389 g) with $NaBH_4$ (1 mmol, 0.038 g) in the presence of DABCO (1 mmol, 0.112 g) in H_2O/THF following the similar procedure described for the molecule 55a.

Yield : 73%

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

^1H NMR : 6 1.29 (t, 3H, *J* = 6.8 Hz), 1.30-1.60 (m, 6H), 1.65-1.90 (m, 2H), 2.31 (t, 2H, *J* = 7.4 Hz), 3.91 (t, 3H, *J* = 6.6 Hz), 4.20 (q, 2H, *J* = 6.8 Hz), 5.50 (s, 1H), 6.12 (s, 1H), 6.80 (d, 2H, *J* = 8.8 Hz), 7.21 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR : 8 14.21, 25.81, 28.37, 28.91, 29.13, 31.81, 60.51, 68.27, 115.83, 124.15, 125.35, 129.25, 141 09, 157.80, 167.28.

Analysis calculated for $C_{17}H_{23}O_3Cl$: C, 65.69; H, 7.45

Found : C, 65.47; H, 7.50

Ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (52):

This compound was prepared as a colorless liquid ***via*** the reaction of ethyl 2-methylene-8-(4-chlorophenoxy)octanoate (64) with ***m*-CPBA** in dichloroethane according to the similar procedure described for the molecule 51.

Reaction time : 48 h

Yield : 50%

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

^1H NMR : 6 1.28 (t, 3H, J = 6.8 Hz), 1.38-1.95 (m, 8H), 2.02-2.23 (m, 2H), 2.76 (d, 1H, J = 5.8 Hz), 3.02 (d, 1H, J = 5.8 Hz), 3.90 (t, 2H, J = 6.6 Hz), 4.12-4.35 (m, 2H), 6.80 (d, 2H, J = 8.8 Hz), 7.20 (d, 2H, J = 8.8 Hz).

^{13}C NMR : δ 14.14, 24.72, 25.84, 29.07, 29.24, 31.20, 51.78, 57.01, 61.55, 68.25, 115.86, 125.39, 129.28, 157.80, 170.40.

Methyl **3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate** (53h):

This compound was obtained as a colorless viscous liquid *via* the coupling of 4-ethylbenzaldehyde with methyl acrylate in the presence of a catalytic amount of DABCO following the similar procedure described for the molecule **53a.**

Reaction time : 7 days

Yield : 81%

bp : 127-128 °C/1.2 mm

IR (neat) :3439, 1722, 1630 cm^{-1}

^1H NMR δ 1 22 (t, 3H, *J* = 7.4 Hz), 2.63 (q, 2H, *J* - 7.4 Hz), 3.02 (b, 1H), 3 71 (s, 3H), 5.54 (s, 1H), 5.85 (s, 1H), 6.32 (s, 1H), 7.17 (d, 2H, ./ - 8.4 Hz), 7.28 (d, 2H, *J* - 8.4 Hz).

'C NMR :5 15.46,28.49,51.85,72.90, 125.68, 126.62, 127.89, 138.63, 142.15, 143.80, 166.78.

Methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate (53i):

This product was prepared as a colorless liquid *via* the treatment of 4-isopropylbenzaldehyde with methyl acrylate under the catalytic influence of DABCO following the similar procedure described for the molecule **53a.**

Reaction time : 7 days

Yield : 85%

bp : 152-153 °C/2.0 mm

IR (neat) : 3455, 1724, 1631 cm^{-1}

^1H NMR : 5 1.24 (d, 6H, *J* = 7.2 Hz), 2.90 (sept. 1H, *J* = 7.0 Hz), 3.00 (b, 1H), 3.73 (s, 3H), 5.55 (s, 1H), 5.86 (s, 1H), 6.33 (s, 1H), 7.20 (d,

2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR : 6 23.90, 33.75, 51.80, 72.81, 125.60, 126.42, 126.61, 138.76, 142.19, 148.37, 166 74.

Methyl (2*Z*)-2-(bromomethyl)-3-(4-ethylphenyl)prop-2-enoate (73):

It was obtained as a colorless liquid *via* the reaction of methyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate **(53h)** with HBr (48%) and conc. H_2SO_4 following the similar procedure described for the molecule **54a.**

Yield : 86%

IR(neat) : 1718, 1624 cm^{-1}

^{1}H NMR : δ 1.26 (t. 3H, *J* = 7.8 Hz), 2.69 (q, 2H, *J* = 7.8 Hz), 3.87 (s, 3H), 4.42 (s, 2H), 7.29 (d, 2H, *J* 8.0 Hz), 7.52 (d, 2H, *J* = 8.0 Hz), 7.81 (s, 1H).

^{13}C NMR : δ 15.26, 27.12,28.77, 52.37, 127.69, 128.45, 129.98, 131.63, 143.12, 146.35, 166.77.

Methyl (2*Z*)-2-(bromomethyl)-3-(4-isopropylphenyl)prop-2-enoate (74):

It was prepared ***via*** the treatment of methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate **(53i)** with HBr (48%) and conc. H_2SO_4 following the simi-

lar procedure described for the molecule **54a** as a colorless liquid.

Yield : 84%

IR(neat) : 1716, 1623 cm^{-1}

^1H NMR : 6 1.27 (d, 6H, J = 7.0 Hz), 2.95 (sept. 1H, J = 7.0 Hz), 3.90 (s, 3H), 4.44 (s, 2H), 7.33 (d, 2H, J = 8.2 Hz), 7.54 (d, 2H, J = 8.4 Hz), 7 81 (s, 1H).

^{13}C NMR : δ 23.77, 27.14, 34.09, 52.40, 127.07, 127.77, 130.06, 131.82, 143.13, 150.98, 166.82.

1 (\ı no *1* • nu**thoxycarbonyl-3-phenylpenta-1,4-diene** (72a):

A solution of methyl **(2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a)** (2 mmol, 0.510 g) and DABCO (4 mmol 0.448 g) in acrylonitrile (2 mL) was kept at room temperature for 7 days. The reaction mixture was taken up in ether (15 mL) and washed successively with 2N HC1 solution, water and aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained, was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to afford **72a** as a colorless viscous liquid in 67 % (0.304 g) yield.

IR(neat) : 2224, 1724, 1631 cm^{-1}

^{1}H NMR : 6 3.73 (s, 3H), 4.94 (s, 1H), 5.60 (s, 1H), 5.63 (s, 1H), 6.08 (s, 1H), 6.56 (s, 1H), 7.14-7.45 (m, 5H).

^{13}C NMR : 8 50.64, 52.24, 118.18, 124.62, 127.91, 128.56, 128.73, 128.93, 132.54, 136.88, 139.45, 166.18.

MS (m/z) : 227 (M^+)

Analysis calculated for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16

Found : C, 74.05; H, 5.73; N, 6.19

3-(4-Chlorophenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (72b):

This product was obtained *via* the treatment of methyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (54b) with acrylonitrile under the influence of DABCO following the similar procedure described for the molecule 72a as a colorless viscous liquid.

Reaction time : 7 days

Yield : 63%

IR(neat) .2226, 1722, 1631 cm^{-1}

^{1}H NMR : δ 3.74 (s, 3H), 4.91 (S, 1H), 5.61 (s, 1H), 5.65 (s, 1H), 6.10 (s, 1H), 6.57 (s, 1H), 7.13 (d, 2H, *J* = 8.6 Hz), 7.34 (d, 2H, *J* = 8.6 Hz).

^{13}C NMR : 5 49.81, 52.27, 117.87, 123.88, 128.69, 129.03, 129.97, 132.89, 133.75, 135.26, 138.82, 165.83.

Analysis calculated for $C_{14}H_{12}NO_2Cl$: C, 64.25; H, 4.62; N, 5.35

Found : C, 64.02; H, 4.65; N, 5.38

4-Cyano-2-methoxycarbonyl-3-(4-methylphenyl)penta-1,4-diene (72c):

This product was obtained as a colorless viscous liquid by the reaction of methyl (2Z)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (54c) with acrylonitrile in the presence of DABCO following the similar procedure described for the molecule 72a.

Reaction time : 7 days

Yield : 65%

IR (neat) : 2224, 1724, 1631 cm^{-1}

^1H NMR : δ 2.33 (s, 3H), 3.72 (s, 3H), 4.91 (s, 1H), 5.59 (d, 1H, J= 1.6 Hz), 5.64 (s, 1H), 6.06 (s, 1H), 6.54 (s, 1H), 7.08 (d, 2H, J =8.0 Hz), 716(d, 2H, J = 8.0 Hz).

^{13}C NMR : 5 20.95, 50.10, 52.16, 118.21, 124.53, 128.33, 128.50, 129.53, 132.41, 133.58, 137.52, 139.33, 166.11.

Analysis calculated for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80

Found : C, 74.58; H, 6.31; N, 5.78

3-(2-Chlorophenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (72d):

This product was obtained ***via*** the treatment of methyl (2*Z*)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate **(54d)** with acrylonitrile under the influence of DABCO following the similar procedure described for the molecule **72a** as a colorless viscous liquid.

Reaction time : 7 days

Yield : 60%

IR(neat) : 2226, 1724, 1633 cm^{-1}

^1H NMR : δ **3.74 (s, 3H),** 5.37 (s, 1H), 5.61 (s, 1H), 5.62 (s, 1H), **6.13 (s, 1H),** 6.59 (s, 1H), 7.12-7.30 (m, 3H), 7.36-7.48 (m, 1H).

^{13}C NMR : δ 47.33, 52.33, 117.95, 122.73, 127.10, 128.82, 129.03, 129.24, 130.27, 133.24, 134.46, 134.84, 138.31, 165.80.

Analysis calculated for $C_{14}H_{12}NO_2Cl$: C, 64.25; H, 4.62; N, 5.35

Found : C, 64.52; H, 4.59; N, 5.31

4-Cyano-2-methoxycarbonyl-3-(2-methylphenyl)penta-1,4-diene (72e):

This product was obtained as a colorless viscous liquid by the **treatment** of meth-

yl (2*Z*)-2-(bromomethyl)-3-(2-methylphenyl)prop-2-enoate (**54e**) with acrylonitrile in the presence of DABCO following the similar procedure described for the molecule **72a**.

Reaction Time: 7 days

Yield : 37%

IR(neat) : 2224, 1724, 1631 cm^{-1}

^1H NMR : δ 2.31 (s, 3H), 3.73 (s, 3H), 5.10 (s, 1H), 5.52 (s, 1H), 5.57 (s, 1H), 6.09 (s, 1H), 6.55 (s, 1H), 7.05-7.24 (m, 4H).

^{13}C NMR .6 19.08,46.77,52.06, 118.16, 123.58, 126.11, 127.36, 127.72, 128.13, 130.92, 132.50, 134.90, 136.44, 138.94, 165.95.

Analysis calculated for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80

Found : C, 74.88; H, 6.31; N, 5.83

4-Cyano-3-(4-ethylphenyl)-2-methoxycarbonylpenta-1,4-diene (72f):

It was obtained as a colorless viscous liquid via treatment of methyl (2*Z*)-2-(bromomethyl)-3-(4-ethylphenyl)prop-2-enoate (73) with acrylonitrile under the influence of DABCO following the similar procedure described for the molecule **72a.**

Reaction time : 7 days

Yield : 55%

IR(neat) : 2224, 1724, 1631 cm^{-1}

^1H NMR : 5 1.23 (t, 3H, J = 7.6 Hz). 2.64 (q, 2H, J = 7.6 Hz), 3.74 (s, 3H). 4.92 (s, 1H), 5.60 (d, 1H, J= 1.4 Hz), 5.64 (s, 1H), 6.07 (s, 1H), 6.55 (s, 1H), 7.10 (d, 2H, J = 8.4 Hz), 7.19 (d, 2H, J = 8.4 Hz).

^{13}C NMR : δ 15.21, 28.29, 50.08, 52.10, 118.17, 124.52, 128.26, 128.52, 132.35, 133.77, 139.35, 143.74, 166.07.

Analysis calculated for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49

Found : C, 75.02; H, 6.69; N, 5.52

4-Cyano-3-(4-isopropylphenyl)-2-methoxycarbonylpenta-1,4-diene

This compound was obtained *via* the reaction between methyl (2Z)-2~(bromomethyl)-3-(4-isopropylphenyl)prop-2-enoate (74) and acrylonitrile in the presence of DABCO following the similar procedure described for the molecule 72a as a colorless viscous liquid.

Reaction time : 7 days

Yield : 59%

IR(neat) : 2224, 1724, 1631 cm^1

^1H NMR : 6 1.23 (d, 6H, J = 6.8 Hz), 2.89 (sept. 1H, J = 6.8 Hz), 3.73 (s,

3H), 4.91 (s, 1H), 5.62 (d, 1H, J = 1.2 Hz), 5.63 (s, 1H), 6.07 (s, 1H), 6.54 (s, 1H), 7.09 (d, 2H, J = 8.0 Hz), 7.20 (d, 2H, J =8.0 Hz).

^{13}C NMR : δ 23.82, 33.63, 50.11, 52.17, 118.24, 124.59, 126.88, 128.43, 128.55, 132.41, 133.89, 139.40, 148.40, 166.15.

Analysis calculated for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20

Found : C, 75.68; H, 7.15; N, 5.16

4-Hydroxy-3-methylene-4-phenylbutan-2-one (77a):

This was prepared according to the literature procedure developed in our laboratory.[17]

A solution of benzaldehyde (20 mmol, 2.122 g), methyl vinyl ketone (20 mmol, 1.401 g) and DABCO (3 mmol, 0.336 g) in THF (5 mL) was allowed to react at room temperature for 9 days. Then the reaction mixture was diluted with ether (20 mL) and washed successively with 2N HC1, water and aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to afford the pure **77a** as a colorless liquid in 54% (1.90 g) yield.

IR(neat) : 3433, 1674, 1620 cm^{-1}

^1H NMR : δ 2.32 (s, 3H), 3.20 (d, 1H, *J* = 5.0 Hz), 5.62 (d, 1H, *J* = 5.0 Hz), 5.97 (s, 1H), 6.19 (s, 1H), 7.22-7.46 (m, 5H).

^{13}C NMR : 6 26.27, 72.04, 126.17, 126.47, 127.45, 128.18, 141.65, 150.04, 200.02.

4-(4-Chlorophenyl)-4-hydroxy-3-methylenebutan-2-one (77b):

This compound was prepared as a colorless liquid by the reaction of 4-chlorobenzaldehyde with methyl vinyl ketone in the presence of DABCO (cat.) following the similar procedure described for the molecule **77a**

Reaction time : 8 days

Yield : 62%

IR (neat) : 3431, 1674, 1620 cm^1

^1H NMR : o 2.32 (s, 3H), 3.18 (d, 1H, *J* = 5.0 Hz), 5.58 (d, 1H *J* = 5.0 Hz), 5.97 (s, 1H), 6.19 (s, 1H), 7.29 (s, 4H).

^{13}C NMR : 6 26.14, 71.15, 126.29, 127.89, 128.21, 133.01,140.32, 149.76, **199.81.**

4-Hydroxy-4-(4-methylphenyl)-3-methylenebutan-2-one (77c):

This compound was prepared *via* the reaction between 4-methylbenzaldehyde and methyl vinyl ketone in the presence of catalytic amount of DABCO following the similar procedure described for the molecule 77a as a colorless liquid.

Reaction time : 9 days

Yield : 55%

IR (neat) : 3442, 1676, 1620 cm^{-1}

^1H NMR : 6 2.32 (s, 6H), 3.05 (d, 1H, J= 4.8 Hz), 5.55 (d, 1H, J= 4.8 Hz), 5.99 (s, 1H), 6.17 (s, 1H), 7.13 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.0 Hz).

^{13}C NMR : δ 20.95, 26.31, 72.00, 125.83, 126.43, 128.89, 137.07, 138.76, 150.23, 199.94.

3-(Chloromethyl)-4-phenylbut-3-en-2-one (75a):

This product was prepared according to the literature procedure reported in our laboratory.[110]

Conc. HCl (36%) (5 mL) was added to 4-hydroxy-3-methylene-4-phenylbutan-2-one (77a) (5 mmol, 0.88 g), at room temperature and swirled thoroughly for one minute (monitored by TLC). The reaction mixture was immediately diluted with

water (10 mL) and extracted with ether (2 x 20 mL). Combined organic layer was washed with aqueous K_2CO_3 solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes) to afford the pure **75a** as a colorless oil in 80% (0.778 g) yield.

IR(neat) : 1672, 1624 cm^1

^1H NMR : 8 2.49 (s, 3H), 4.44 (s, 2H), 7.39-7.65 (m, 5H), 7.68 (s, 1H).

^{13}C NMR : **6 25.75,** 37.53, 128.83, 129.53, 129.75, 134.08, 136.99, 143.47, 197.12.

(3*Z*)-3-(Chloromethyl)-4-(4-chloropl enyl)but-3-en-2-one (75b):

This compound was prepared as a colorless solid *via* the treatment of 4-(4-chloro-phenyl)-4-hydroxy-3-methylenebutan-2-one (77b) with conc. HC1 following the similar procedure described for the molecule **75a.**

Reaction time : 1 min.

Yield : 76%

mp : 76-78 °C

IR (KBr) : 1670, 1624 cm^{-1}

^1H NMR : δ 2.49 (s, 3H), **4.40 (s,** 2H), **7.44 (d, 2H *J* =** 8.6 **Hz),** 7.53 (d, 2H,

J= 8.6 Hz), 7.62 (s, 1H).

^{13}C NMR : δ 25.79, 37.28, 129.15, 130.89, 132.55, 135.92, 137.42, 142.00, 196.87.

(3*Z*)-3-(Chloromethyl)-4-(4-methylphenyl)but-3-en-2-one (75c):

This product was prepared by treating 4-hydroxy-3-methylene-4-(4-methylphenyl)but-3-en-2-one (77c) with conc. HC1 following the similar procedure described for the molecule 75a as a colorless liquid.

Reaction time : 1 min.

Yield : 79%

IR (neat) : 1660, 1616 cm^{-1}

^{1}H NMR : 8 2.40 (s, 3H), 2.48 (s, 3H), 4.46 (s, 2H), 7.27 (d, 2H J = 8.0 Hz), 7.49 (d, 2H, J = 8.0 Hz), 7.66 (s, 1H).

^{13}C NMR : δ 21.32, 25.71, 37.70, 129.62, 129.78, 131.25, 136.18, 140.31, 143.76, 197.27.

2-Acetyl-4-cyano-3-phenylpenta-1,4-diene(76a):

A solution of (3*Z*)-3-(chloromethyl)-4-phenylbut-3-en-2-one (75a) (2 mmol, 0.389 g) and DABCO (4 mmol 0.448 g) in acrylonitnle (2 mL) was kept at room

temperature for 7 days. The reaction mixture was diluted with ether (15 mL) and washed successively with 2N HC1 solution, water and aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 4% ethyl acetate in hexanes) to afford **76a** as a colorless viscous liquid in 42 % (0.177 g) yield.

IR (neat) : 2224, 1680, 1630 cm^{-1}

^1H NMR : δ 2.38 (s, 3H), 5.06 (s, 1H), 5.58 (s, 1H), 5.88 (s, 1H), 6.06 (s, 1H), 6.43 (s, 1H), 7.13-7.46 (m, 5H).

^{13}C NMR : δ 25.87, 48.89, 118.22, 124.78, 127.70, 128.46, 128.63, 128.85, 132.61,137.35,147.63, 197.36.

MS (m/z) : 211 (M^+)

Analysis calculated for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63

Found : C, 79.83; H, 6.22; N, 6.60

2-Acetyl-3-(4-chlorophenyl)-4-cyanopenta-1,4-diene (76b):

This compound was obtained as a colorless viscous **liquid by treating (3Z)-3-(chloromethyl)-4-(4-chlorolphenyl)but-3-en-2-one (75b) with acrylonitrile in the**

presence of DABCO following the similar procedure described for the molecule **76a**.

Reaction time : 7 days

Yield : 36%

IR (neat) : 2224, 1682, 1630 cm^{-1}

^1H NMR : 6 2.38 (s, 3H), 5.03 (s, 1H), 5.58 (s, 1H), 5.89 (s, 1H), 6.08 (s, 1H), 6.44 (s, 1H), 7.11 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 2H, *J* - 8.6 Hz).

^{13}C NMR .6 25.79,48.15, 117.94, 124.17, 128.72, 128.96, 129.92, 132.87, 133.54, 135.80, 147.06, 197.17.

Analysis calculated for $C_{14}H_{12}NOCl$: C, 68.43; H, 4.92; N, 5.70

Found : C, 68.65; H, 4.91; N, 5.74

2-Acetyl-4-cyano-3-(4-methylphenyl)penta-1,4-diene (76c):

This product was obtained as a colorless viscous liquid *via* the reaction of **(3*Z*)-3-(chloromethyl)-4-(4-methylphenyl)but-3-en-2-one** (75c) with acrylonitrile under the influence of DABCO following the similar procedure described for the molecule **76a.**

Reaction time : 7 days

Yield : 40%

1R (neat) : 2224, 1680, 1630 cm^{-1}

^1H NMR : δ 2.32 (s, 3H), 2.37 (s, 3H), 5.02 (s. 1H), 5.57 (s, 1H), 5.87 (s, 1H), 6.04 (s, 1H), 6.40 (s, 1H), 7.05 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.0 Hz).

^{13}C NMR : 6 20.84, 25.78,48.42, 118.19, 124.78, 128.21, 128.39, 129.41, 132.27, 134.12, 137.23, 147.54, 197.29.

Analysis calculated for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22

Found : C, 79.65; H, 6.66; N, 6.23

Methyl 2-methylene-3-(prop-2-yn-1-yloxy)-3-phenylpropanoate (79a):

To a stirred solution of methyl **(2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a)** (1 mmol, 0.255 g) in Et_3N (1 mL) was added propargyl alcohol (5 mmol, 0.28 g). After stirring for 12 h at room temperature, the reaction mixture was diluted with ether (15 mL) and washed successively with 2N HCl 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, 2% ethyl acetate in hexanes) to provide pure methyl 2-methylene-3-(prop-2-

yn-1-yloxy)-3-phenylpropanoate (79a) as a colorless viscous liquid in 74% yield **(0.17 g)**.

IR (neat) : 3288, **2118, 1722, 1631 cm^{-1}**

^{1}**H NMR** :52.45(t, **1H, *J*= 2.4 Hz),** 3.70(s, 3H),4.01 (dd, **1H, *J*=** 15.6 & **2.4 Hz), 4.18** (dd, **1H, *J* =15.6** & 2.4 Hz), 5.51 (s, lH),6.00(d, **1H, *J* =** 1.2 Hz), 6.37 (s, **1H),** 7.28-7.42 **(m,** 5H).

^{13}**C NMR** : 8 51.74, 55.93, 74.75, 77.79, 79.50, 125.24, 127.86, 128.17, 128.40, 138.65, 140.72, 166.01.

MS **(m/z)** : 230 **(M^{+})**

Analysis calculated for **$C_{14}H_{14}O_3$** : C, 73.03; H, 6.13

Found : **C, 73.40; H, 6.17**

Methyl 3-(4-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (79b):

This product was obtained as a colorless viscous liquid *via* the reaction of methyl **(2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (54b)** with propargyl alcohol in the presence of triethylamine following the similar procedure described for the molecule **79a.**

Yield : 84%

IR (neat) : 3298, 2118, 1722, 1631 cm^{-1}

^1H NMR : 6 2.44 (t, 1H, J = 2.6 Hz), 3.69 (s, 3H), 4.00 (dd, 1H, J = 15.6 & 2.6 Hz), 4.16 (dd, 1H, J = 15.6 & 2.6 Hz), 5.47 (s, lH),6.01(s, lH),6.37(s, 1H), 7.31 (s, 4H).

^{13}C NMR : δ 51.19, 55.33,74.36, 76.41,78.56, 124.82, 127.95, 128.58, 133.33, 136.67, 139.63, 165.15.

Analysis calculated for $C_{14}H_{13}O_3Cl$: C, 63.52; H, 4.95

Found :C, 63.38; H, 4.97

Methyl **2-methylene-3-(4-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate** (79c):

It was prepared as a colorless viscous liquid *via* the treatment of methyl (2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (54c) with propargyl alcohol in the presence of triethylamine following the similar procedure described for the molecule 79a.

Yield : 76%

IR(neat) : 3286, 2124,1719, 1631 cm^{-1}

^1H NMR : 6 2.33 (s, 3H), 2.44 (t, 1H, J = 1.8 Hz), 3.68 (s, 3H), 3.99 (dd, 1H, J = 15.6 & 1.8 Hz), 4.14 (dd, 1H, J = 15.6 & 1.8 Hz), 5.47 (s,

1H), 6.00 (d, 1H, J= 1.8 Hz), 6.35 (s, 1H), 7.14 (d, 2H, J = 7.8 Hz), 7.27 (d, 2H, J = 7.8 Hz).

^{13}C NMR : δ 21.12, 51.72, 55.73, 74.62, 77.53, 79.55, 124.96, 127.83, 129.09, 135.50, 137.89, 140.75, 166.03.

Analysis calculated for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60

Found :C, 73.98; H, 6.55

Methyl **3-(2-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate** (79d):

It was obtained as a colorless solid *via* the reaction of methyl (2Z)-2-(bromomethyl)-3-(2-chIorophenyl)prop-2-enoate (54d) with propargyl alcohol in the presence of triethylamine following the similar procedure described for the molecule 79a.

Yield : 73%

mp : 53-54 °C

IR (KBr) : 3267, 2118, 1720, 1632 cm^{-1}

^{1}H NMR : o 2.43 (m, 1H), 3.75 (s, 3H), 4.07-4.30 (m, 2H), 5.74 (s, 1H), 5.90 (s, 1H), 6.40 (s, 1H), 7.18-7.52 (m, 4H).

^{13}C NMR : 6 51.91, 56.99, 74.72, 74.97, 79.38, 126.95, 127.10, 128.76,

129.29, 129.62, 134.04, 136.34, 139.62, 165.99.

Analysis calculated for $C_{14}H_{13}O_3Cl$: C, 63.52; H, 4.95

Found : C, 63.28; H, 4.93

Methyl **2-methylene-3-(2-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate** (79e):

This product was prepared as a colorless solid by the treatment of methyl (2Z)-2-(bromomethyl)-3-(2-methylphenyl)prop-2-enoate (54e) with propargyl alcohol under the influence of triethylamine following the similar procedure described for the molecule 79a.

Yield : 76%

mp : 76-78 °C

IR (KBr) : 3263, 2114, 1714, 1630 cm^{-1}

^1H NMR : 8 2.40-2.48 (m, 4H), 3.72 (s, 3H), 4.04 (dd, 1H, J = 15.6 & 1.8 Hz), 4.19 (dd, 1H, J = 15.6 & 1.8 Hz), 5.76 (s, 1H), 5.81 (s, 1H), 6.39 (s, 1H), 7.15-7.40 (m,4H).

^{13}C NMR : 8 19.13, 51.80, 56.07, 74.54, 74.59, 79.70, 126.04, 127.29, 128.01, 130.52, 136.25, 136.97, 140.17, 166.25.

Analysis calculated for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60

Found : C, 73.67; H, 6.65

Methyl **3-(4-ethylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (79f):**

This product was prepared *via* the reaction between methyl (2Z)-2-(bromomethyl)-3-(4-ethylphenyl)prop-2-enoate (73) and propargyl alcohol under the influence of triethylamine as a colorless viscous liquid following the similar procedure described for the molecule 79a.

Yield : 67%

IR (neat) : 3288, 2118, 1724, 1631 cm^{-1}

^{1}HNMR : δ 1.21 (t, 3H, *J* = 7.8 Hz), 2.42 (t, 1H, *J* = 2.2 Hz), 2.63 (q, 2H, *J* = 7.8 Hz), 3.68 (s, 3H), 4.00 (dd, 1H, *J* = 15.6 & 2.2 Hz), 4.14 (dd, 1H, *J* = 15.6 & 2.2 Hz), 5.47 (s, 1H), 5.98(s, 1H), 6.34 (s, 1H), 7.15 (d, 2H, *J* = 7.8 Hz), 7.27 (d, 2H, *J* = 7.8 Hz).

^{13}C NMR : δ 15.33, 28.49, 51.66, 55.73, 74.58, 77.53, 79.54, 124.92, 127.83, 135.72, 140.75, 144.14, 166.00.

Analysis calculated for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02

Found : C, 74.25; H, 7.05

Methyl 3-(4-isopropylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (79g):

This compound was obtained as a colorless viscous liquid *via* the treatment of methyl **(2*Z*)-2-(bromomethyl)-3-(4-isopropylphenyl)prop-2-enoate** (74) with propargyl alcohol in the **presence of triethylamine** following the similar procedure described for the molecule **79a.**

Yield : 77%

IR (neat) : 3289, **2118, 1724, 1632 cm^{-1}**

^{1}**H NMR** : δ **1.23** (d, 6H, *J* = 6.8 Hz), 2.43 (t, **1H, *J*** = 2.4 Hz), 2.88 (sept. **1H,** *J* = 6.8 Hz), 3.69 (s, 3H), 4.01 **(dd, 1H, *J* = 15.6** & 2.4 Hz), **4.14** (dd, **1H, *J* = 15.6 & 2.4 Hz), 5.48 (s, 1H), 5.99** (d, **1H, *J*** = 2.4 Hz), 6.35 (s, 1H), **7.18** (d, 2H, ***J*** = 8.0 Hz), 7.28 (d, **2H, *J*** = 8.0 Hz).

^{13}**C NMR** : δ 23.93, 33.84, 51.79, **55.85,** 74.61, 77.58, **79.62,** 125.10, 126.50, 127.82, 135.85, 140.72, 148.83, 166.13.

Analysis calculated for **$C_{17}H_{20}O_3$** : C, 74.97; H, 7.40

Found : C, 75.23; H, 7.36

Methyl 2-methylene-3-phenoxy-3-phenylpropanoate (80a):

A solution of methyl **(2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a)** (1 **mmol,** 0.255 g), phenol (1 **mmol,** 0.094 g) and Et_3N (1 mL) in CH_2Cl_2 (2 mL), was stirred at room temperature for 4 hours. Then 2N HC1 (5 **mL)** was added and the reaction mixture was extracted with ether **(2x10 mL).** The combined layer was washed with aqueous $NaHCO_3$ **solution,** water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product was purified by column **chromatography** (silica gel, 2% ethyl acetate in hexanes) to provide the pure methyl 2-methylene-3-phenoxy-3-phenylpropanoate **(80a)** in 85% (0.228 g) yield as a colorless viscous liquid.

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

^1H NMR : 5 3.73 **(s,** 3H), 5.95 (s, **1H),** 6.14 (s, 1H), 6.37 (s, **1H), 6.87-6.98 (m, 3H), 7.15-7.50 (m,** 7H).

^{13}C NMR : 5 **51.90, 77.38, 116.01, 121.26, 126.15, 127.41, 128.12, 128.50, 129.39, 138.99, 140.41, 157.67,** 166.03.

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

Analysis calculated for $C_{17}H_{16}O_3$: C, **76.10;** H, 6.01

Found **: C, 75.91; H,** 6.04

Methyl 3-(4-chlorophenyl)-2-methylene-3-phenoxypropanoate (80b):

This compound was prepared as a colorless viscous liquid by the reaction of methyl **(2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (54b)** with phenol in the presence of triethylamine following the similar procedure described for the molecule **80a.**

Yield : 76%

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

^{1}H NMR : 5 3.74 (s, 3H), 5.99 (s, 1H), 6.11 (s, 1H), 6.38 <s, 1H), 6.87-7.01 (m,3H), 7.16-7.47 (m, 6H).

^{13}C NMR : 8 52.02, 76.81, 116.08, 121.56, 126.28, 128.77, 128.84, 129.51, 134.04, 137.69, 140.13, 157.46, 165.89.

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

Found :C,67 71; H, 4.96

Methyl 2-methylene-3-(4-methylphenyl)-3-phenoxypropanoate (80c):

This product was prepared *via* the reaction between methyl **(2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (54c)** and phenol in the presence of triethylamine as a colorless viscous liquid following the similar procedure described for the molecule **80a.**

Yield : 69%

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

^1H NMR : 8 2.32 (s, 3H), 3.73 (s, 3H), 5.96 (s, 1H), 6.11 (s, 1H), 6.36 (s, 1H), 6.84-6.98 (m, 3H), 7.10-7.37 (m, 6H).

^{13}C NMR : δ 21.15, 51.91, 77.31, 116.06, 121.20, 125.94, 127.43, 129.25, 129.39, 136.02, 137.90, 140.53, 157.79, 166.14.

Analysis calculated for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43

Found : C, 76.39; H, 6.39

Methyl **3-(2 chlorophenyl)-2-methylene-3-phenoxypropanoate (80d):**

This compound was obtained *via* the reaction of methyl (2Z)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate (54d) with phenol under the influence of triethylamine following the similar procedure described for the molecule 80a as a colorless viscous liquid.

Yield : 66%

IR (neat) : 1726,1635 cm^{-1}

^1H NMR : δ 3.76 (s, 3H), 5.66 (s, 1H), 6.45 (s, 1H), 6.55 (s, 1H), 6.83-6.98 (m, 3H), 7.14-7.56 (m, 6H).

^{13}C NMR : δ 51.99, 74.23, 115.78, 121.42, 127.04, 127.95, 128.79, 129.41,

129.70, 133.46, 136.10, 139.09, 157.72, 165.87.

Analysis calculated for $C_{16}H_{15}O_3Cl$: C, 67.44; H, 4.99

Found : C, 67.31; H, 5.02

Methyl **2-methylene-3-(2-methylphenyl)-3-phenoxypropanoate** (80c):

It was obtained as a colorless viscous liquid *via* the treatment of methyl (2Z)-2-(bromomethyl)-3-(2-methylphenyl)prop-2-enoate (54e) with phenol in the presence of **triethylamine** as a colorless viscous liquid following the similar procedure described for the molecule 80a.

Yield : 63%

IR(neat) : 1724, 1633 cm^{-1}

^1H NMR : 5 2.35 (s, 3H), 3.74 (s, 3H), 5.73 (s, 1H), 6.32 (s, 1H), 6.42 (s, 1H), 6.82-6.96 (m, 3H), 7.15-7.45 (m, 6H).

^{13}C NMR : 6 19.19, 52.01, 74.78, 115.81, 121.25, 126.20, 127.26, 127.39, 128.23, 129.43, 130.70, 136.32, 136.42, 139.46, 158.09, 166.30.

Analysis calculated for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43

Found : C, 76.79; H, 6.47

Methyl 3-(4-ethylphenyl)-2-methylene-3-phenoxypropanoate (80f):

It was obtained as a colorless viscous liquid *via* the reaction between methyl (2Z)-2-(bromomethyl)-3-(4-ethylphenyl)prop-2-enoate (73) and phenol in the presence of triethylamine following the similar procedure described for the molecule **80a.**

Yield : 64%

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

^1H NMR : 5 1.23 (t, 3H, *J* = 7.8 Hz), 2.64 (q, 2H, J = 7.8 Hz), 3.75 (s, 3H), 5.97 (s, 1H), 6.13 (s, 1H), 6.38 (s, 1H), 6.87-7.05 (m, 3H), 7.13-7.47 (m, 6H).

^{13}C NMR : 5 15.34, 28.56, 51.93, 77.26, 116.00, 121.17, 125.98, 127.45, 128.03, 129.39, 136.19, 140.46, 144.19, 157.78, 166.15.

Analysis calculated for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80

Found : C, 77.19; H, 6.78

Methyl 3-(4-isopropylphenyl)-2-methylene-3-phenoxypropanoate (80g):

This product was prepared as a colorless viscous liquid *via* the treatment of methyl (2*Z*)-2-(bromomethyl)-3-(4-isopropylphenyl)prop-2-enoate (74) with phenol in the presence of triethylamine following the similar procedure described for the molecule **80a.**

Yield : 61%

IR(neat) : 1722, 1632 cm^{-1}

^1H NMR : 8 1.24 (d, 6H, J = 7.2 Hz). 2.89 (sept. 1H, J = 7.2 Hz). 3.76 (s, 3H). 5.98 (s, 1H). 6.14 (s, 1H). 6.38 (s, 1H). 6.87-6.99 (m, 3H), 7.15-7.47 (m,6H).

^{13}C NMR : δ 23.83, 33.75, 51.83, 77.10, 115.86, 121.06, 125.88, 126.53, 127.34, 129.30, 136.19, 140.34, 148.70, 157.78, 166.05.

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

Found : C, 77.06; H, 7.20

(-)-Methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate {(-)-79a}:

To a stirred solution of methyl **(2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (54a)** (1 mmol, 0.255 g) in dichloromethane, quinidine (2 mmol, 0.648 g) and propargyl alcohol (5 mmol, 0.28 g) were added. After stirring for 24 hours at room temperature, the reaction mixture was diluted with ether (15 ml) and washed successive!) with 2N HC1 solution and water. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes) to provide the pure (-)-79a as a colorless viscous liquid in 36% yield (0.083 g).

The IR, ^1H and ^{13}C NMR spectral data of (-)-79a were identical with that of the corresponding racemic molecule.

Enantiomeric purity : 31%

Optical rotation : $[\alpha]_D^{20}$ -70.24 (c 1.24, $CHCl_3$)

Determination of **enantiomeric purity:**

HPLC analysis was carried out using chiral column (CHIRALCEL OD, eluent: 5% i-PrOH in hexane, flow rate: 0.5 mL/min)

Racemic molecule **79a** showed two peaks of equal intensity (retention times: 12.33 & 13.85 minutes). In the case of chiral compound (-)-79a two peaks are observed in the ratio of 65.5: 34.5 (retention times: 12.38 & 14.02 minutes) indicating that its enantiomeric purity is 31%.

(-)-Methyl 3-(4-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate {(-)-79b}:

This product was obtained as a colorless viscous liquid *via* the treatment of methyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (54b) with propargyl alcohol in the presence of quinidine following the similar procedure described for the molecule (-)-79a.

The IR, ^{1}H and ^{13}C NMR spectral data of (-)-79b were identical with that of the corresponding racemic molecule.

Yield : 47%

Enantiomeric purity : 39%

Optical rotation : $[\alpha]_D^{20}$ -83.24 (c 1.074, $CHCl_3$)

Determination of enantiomeric purity:

HPLC analysis was carried out using chiral column (CH1RALCEL OD, eluent 5% i-PrOH in hexane, flow rate: 0.5 mlJmin)

In the case of racemic molecule 79b. two peaks of equal intensity are observed (retention times: 10.37 & 12.28 minutes). Chiral molecule (-)-79b, showed two peaks in the ratio of 69.5:30.5 (retention times: 10.34 & 12.24 minutes) indicating that the enantiomeric purity is 39%.

(-)-Methyl2-methylene-3-(4-methylphenyl)-3-(prop-2-yn-1-yloxy)propanate {(-)-79c}:

It was prepared as a colorless viscous liquid by the treatment of methyl **(2*Z*)-2-**(bromomethyl)-3-(4-methylphenyl)prop-2-enoate **(54c)** with propargyl alcohol under the influence of quinidine following the similar procedure described for the molecule (-)-79a.

The IR, ^1H and ^{13}C NMR spectral data of (-)-79c were identical with that of the corresponding racemic molecule.

Yield : 37%

Enantiomeric purity : 25%

Optical rotation : $[\alpha]_D^{20}$ -64.19(c 0.592, $CHCl_3$)

Determination of **enantiomeric** purity:

HPLC analysis was carried out using chiral column (CHIRALCEL OD. eluent: 5% i-PrOH in hexane. flow rate: 0.5 mL/min)

Racemic molecule **79c** showed two peaks of equal intensity (retention times: 11.87 & 13.65 minutes). In the case of chiral molecule (-)-79c, two peaks are observed in the ratio of 62.5:37.5 (retention times: 11.68 & 13.29 minutes) indicating that its **enantiomeric** purity is 25%.

(-)-Methyl 3-(2-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate {(-)-79d}:

This product was obtained as a colorless viscous liquid *via* the treatment of methyl **(2*Z*)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate (54d)** with propargyl alcohol in the presence of quinidine following the similar procedure **described** for the molecule (-)-79a.

The IR, ^1H and ^{13}C NMR spectral data of (-)-79d were identical with that of the corresponding racemic molecule.

Yield : 33%

Optical rotation : $[\alpha]_D^{20}$ -51.60 (c 0.56, $CHCl_3$)

Attempts to determine the enantiomeric purity of this molecule (-)-79d either by HPLC analysis (chiral column, CH1RALCEL OD) or by ^1H NMR analysis in the presence of chiral shift reagents, $Eu(hfc)_3$ or $Eu(tfc)_3$ were unsuccessful.

(-)-Methyl 2-methylene-3-(2-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate {(-)-79e}:

This product was prepared as a colorless solid *via* the reaction of methyl (2Z)-2-(bromomethyl)-3-(2-methylphenyl)prop-2-enoate (54e) with propargyl alcohol in the presence of quinidine following the similar procedure described for the molecule (-)-79a.

The IR, ^1H and ^{13}C NMR spectral data of (-)-79e were identical with that of the corresponding racemic molecule.

mp : 72-73 °C

Yield : 35%

Enantiomeric purity : 32%

Optical rotation : $[\alpha]_D^{20}$ -58.06 (c 0.632, $CHCl_3$)

Determination of enantiomeric purity:

HPLC analysis was carried out using chiral column (CHIRALCEL OD, eluent 5% i-PrOH in hexane, flow rate 0.5 mL/min)

Racemic molecule **79e** showed two peaks of equal intensity (retention times: 10.98 & 12.98 minutes). The chiral molecule **(-)-79e**, showed two peaks in the ratio of 66.0:34.0 (retention times: 10.87 & 12.90 minutes) indicating that the enantiomeric purity is 32%.

(-)-Methyl V(4 ethylphenyl)-2-methylene-3-(prop-2 yn-1-yloxy)propanoate {(-)-79f}:

This product was prepared by the reaction of methyl (2Z)-2-(bromomethyl)-3-(4-ethylphenyl)prop-2-enoate (73) with propargyl alcohol in the presence of quinidine as a colorless viscous liquid following the similar procedure described for the molecule **(-)-79a**.

The IR, ^1H and ^{13}C NMR spectral data of (-)-79f were identical with that of the corresponding racemic molecule.

Yield : 32%

Enantiomeric purity : 35%

Optical rotation : $[\alpha]_D^{20}$ -74.91 (c 0.606, $CHCl_3$)

Determination of enantiomeric purit>:

HPLC analysis was carried out using chiral column (CHIRALCEL OD, eluent 5% i-PrOH in hexane, flow rate: 0.5 mL/min)

Racemic compound 79f showed two peaks of equal intensity (retention times: 9.47 & 11.18 minutes). In the case of chiral molecule (-)-79f, two peaks arc observed in the ratio of 67.5:32.5 (retention times: 9.47 & 11.19 minutes) indicating that the enantiomeric purity is 35%.

(-)-Methyl 3-(4-isopropylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate {(-)-79g}:

This compound was obtained as a colorless viscous liquid *via* the treatment of methyl **(2*Z*)-2-(bromomethyl)-3-(4-isopropylphenyl)prop-2-enoate** (74) with propargyl alcohol in the presence of quinidine following the similar procedure described for the molecule (-)-79a.

The IR, ^1H and ^{13}C NMR spectral data of (-)-79g were identical with that of the corresponding racemic molecule.

Yield : 36%

Enantiomeric purity : 40%

Optical rotation : $[\alpha]_D^{20}$ -81.59 (c 0.516, $CHCl_3$)

Determination of enantiomeric purity:

HPLC analysis was carried out using chiral column (CHIRALCEL OD, eluent: 5% i-PrOH in hexane, flow rate: 0.5 mL/min)

In the case of racemic molecule 79g, two peaks of equal intensity (retention times: 9.13 & 11.07 minutes) are observed. The chiral molecule (-)-79g showed two peaks in the ratio of 70:30 (retention times: 9.11 & 11.04 minutes) indicating that its enantiomeric purity is 40%.

Methyl **(2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-Quinidine** salt (84a):

To a stirred solution of methyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate **(54a)** (1 mmol, 0.255 g) in dichloromethane (4 mL), quinidine (1 mmol, 0.324 g) was added and stirred at room temperature for 15 hours. The solvent was removed under reduced pressure to afford the crude salt **(84a)** as a yellow solid. Careful and selective crystallization of this crude salt **(84a)** from chloroform in hexanes (1:1) provided the stereochemically pure salt **(*E*)-84a** as a colorless crystalline solid.

Yield : 68%

mp : 146-148 °C (dec.)

Optical rotation : $[\alpha]_D^{20}$ +84.76 (c 1.05, $CHCl_3$)

IR (KBr) : 1697,1622 cm^{-1}

^1H NMR : 6 0.8-1.04 (m, 1H), 1.60-3.80 (m, 10H), 3.93 (s, 3H), 4.07 (s, 3H), 4.73-5.20 (m, 3H), 5.58-6.03 (m, 2H), 6.61 (d, 1H, J = 5.4 Hz), 6.92 (s, 1H), 7.15-8.17 (m, 9H), 8.47 (s, 1H), 8.73 (d, 1H, J = 4.2 Hz).

^{13}C NMR : δ 21.38, 23.87, 26.12, 37.33, 53.39, 53.83, 55.85, 64.78, 68.97, 100.31, 117.55, 119.69, 120.13, 121.75, 125.44, 129.76, 129.83, 130.62, 131.99, 132.96, 135.22, 143.01, 144.07, 147.54, 152.50, 158.28,167.67.

We have also recorded the ^1H and ^{13}C NMR spectra before cyrstallization (crude salt). This spectral data indicates ≈ 15% impurities in which presumably (/)• isomer is the major component. In ^1H NMR spectrum, we have also observed singlets at 8 3.80 and 3.87 (probably arising due to $COO\underline{CH_3}$ and aromatic-OCH_3 protons of minor (Z)-isomer) with very low intensities in addition to the above mentioned data of crystallized product.

In ^{13}C NMR spectrum, we have also observed peaks at 5 23.04, 24.15, 27.28, 37.83, 52.49, 53.13, 57.38, 59.98, 66.27, 100.51, 118.66, 122.14, 128.03, 128.38, 128.64, 129.42, 131.09, 136.13, 144.19, 146.85, 158.20, 169.91 with very low intensities (≈ 15%) in addition to the above mentioned spectral data of crystallized product. In analogy with the ^{13}C NMR spectrum of methyl (2Z)-(2-bromomethyl)-3-phenylprop-2-enoate-DABCO salt (56a), the minor peak at 5 169.91 may be assigned to the ester carbonyl carbon of the (*Z*)-isomer.

(-)-Methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate {(-)-79a} from (*E*)-84a:

This product was obtained as a colorless viscous liquid *via* the treatment of methyl (2*E*)-2-(bromomethyl)-3-phenylprop-2-enoate-quinidine salt (*E*)-84a (0.5 mmol, 0.289 g) with propargyl alcohol (2.5 mmol, 0.14 g) in the presence of quinidine (0.5 mmol, 0.162 g) in dichloromethane following the similar procedure described for the molecule (-)-79a (page no. 183).

The IR, ^{1}H and ^{13}C NMR spectral data of (-)-79a from (*E*)-84a is identical with that of the corresponding racemic and optically active molecule (obtained with out isolating the quinidine salt).

Yield : 37% (0.043 g)

Enantiomeric purity : 38%

Optical rotation : $[\alpha]_D^{20}$ **-84.15** (c 0.284, $CHCl_3$)

Determination of enantiomeric purity:

HPLC analysis was carried out using chiral column (CHIRALCEL OD. eluent 5% i-PrOH in hexane. flow rate: 0 5 mL/min)

The racemic molecule **79a** showed two peaks of equal intensity (retention times: **11.36** & 12.64 minutes). **In** the case of chiral molecule (-)-79a (from **(E)-84a**), two peaks are observed in the ratio of **69.0:31.0** (retention times: **11.26** & 12.58 minutes) indicating that its enantiomeric purity is 38%.

Attempted enantioselective synthesis of methyl **2-methylene-3-phenyl-3-phenoxypropanoate (80a*):**

To a stirred solution of methyl **(2Z)-2-(bromomethyl)-3-phenylprop-2-enoate (54a)** (1 **mmol,** 0.255 g) in dichloromethane, **quinidine** (2 mmol, 0.648 g) and phenol (1 mmol. 0.094 g) were added. After stirring for 10 hours at room temperature, the reaction mixture was diluted with ether **(15 ml**) and washed successively with 2N HC1 solution, water and aqueous K_2CO_3 solution. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product, thus obtained was purified by column chromatography (silica gel, 2%

ethyl acetate in hexanes) to provide the pure **80a*** as a colorless viscous liquid in 34% yield (0.093 g).

The IR, ^{1}H and ^{13}C NMR spectral data of optically active **80a*** were identical with that of the corresponding racemic molecule.

Enantiomeric purity : 4%

Determination of **enantiomeric** purity:

HPLC analysis was carried out using chiral column (CHIRALCEL OD, eluent: 5% i-PrOH in hexane. flow rate: 0.5 mL/min)

In the case of racemic molecule **80a,** two peaks of equal intensity (retention times: 11.13 & 13.18 minutes) are observed. The chiral molecule (**80a***) showed two peaks in the ratio of 52.0:48.0 (retention times: 11.22 & 13.35 minutes) indicating that its **enantiomeric** purity is 4%.

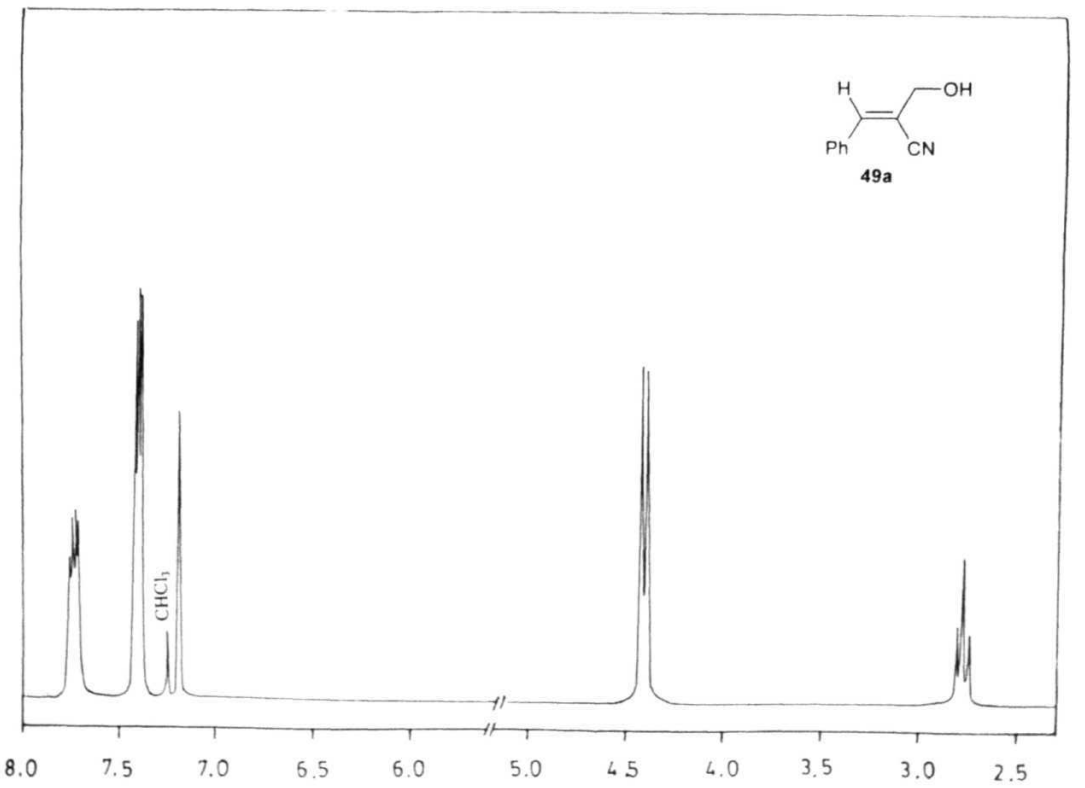


Fig. 1: ^{1}H NMR spectrum of **49a**

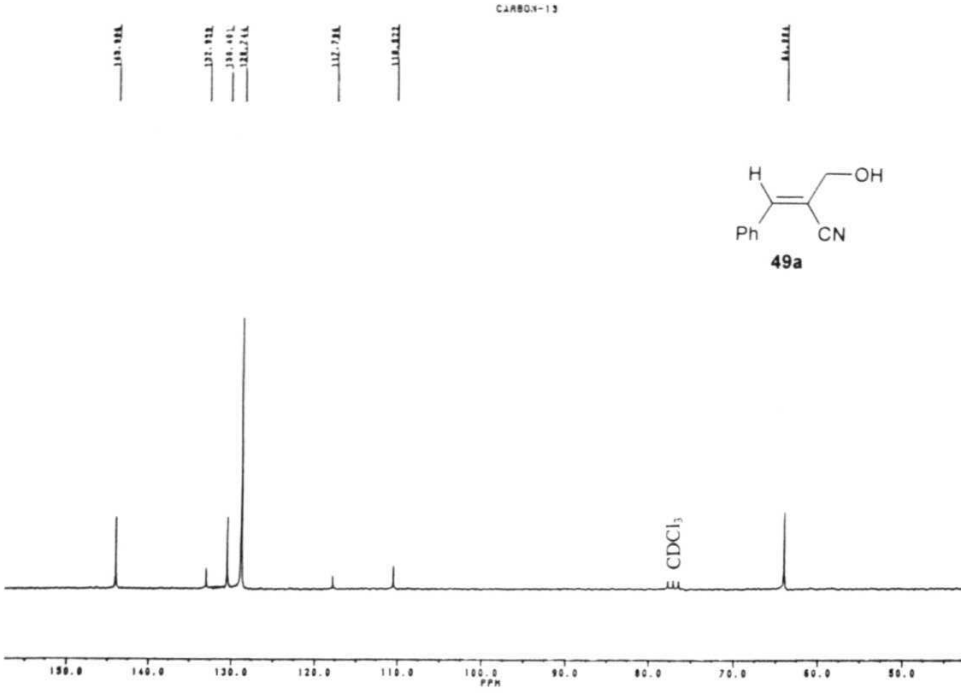


Fig. 2: ^{13}C NMR spectrum of **49a**

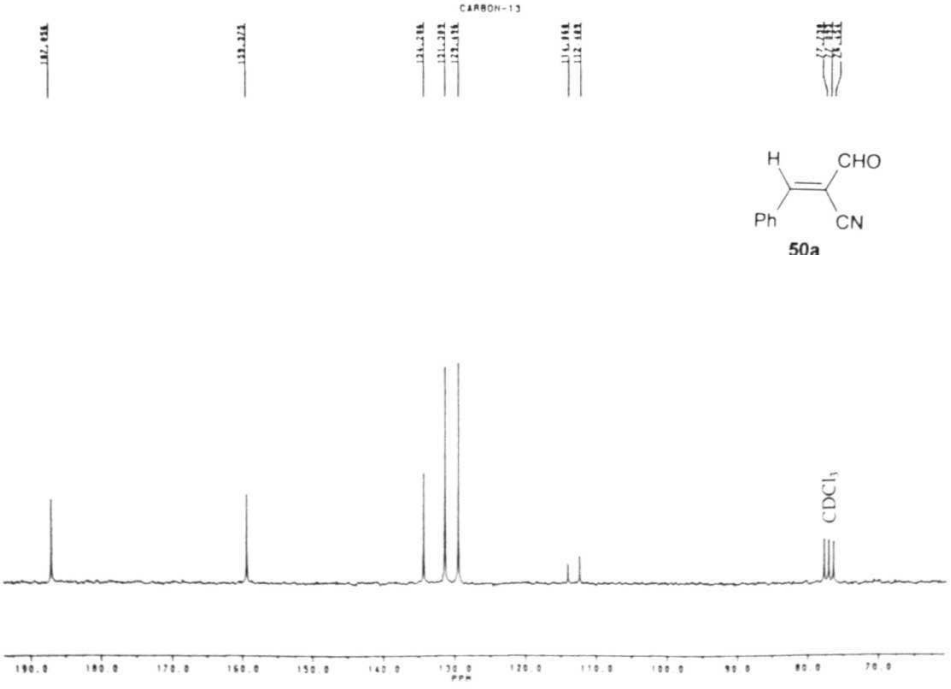


Fig. 3: ^{13}C NMR spectrum of **50a**

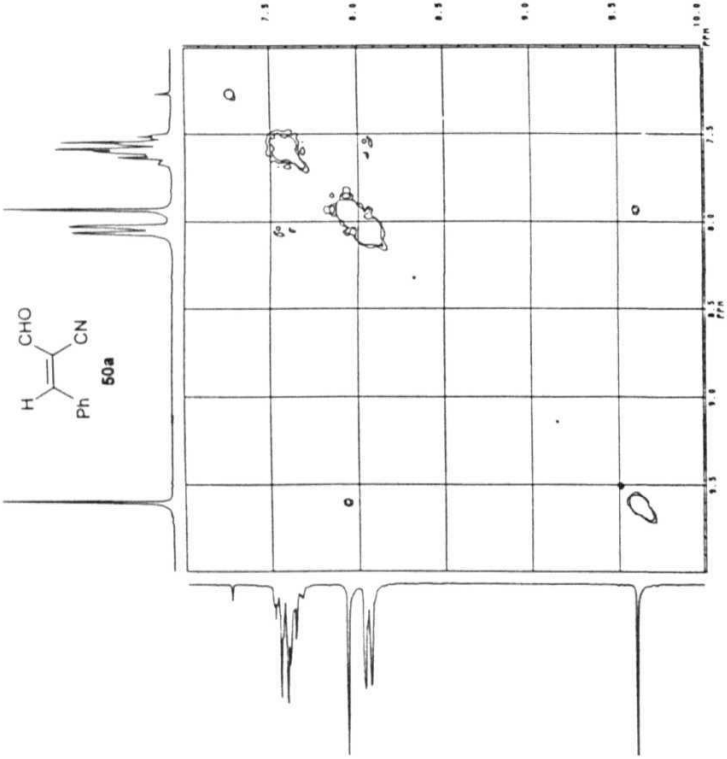


Fig. 4: 2D NOESY of **50a**

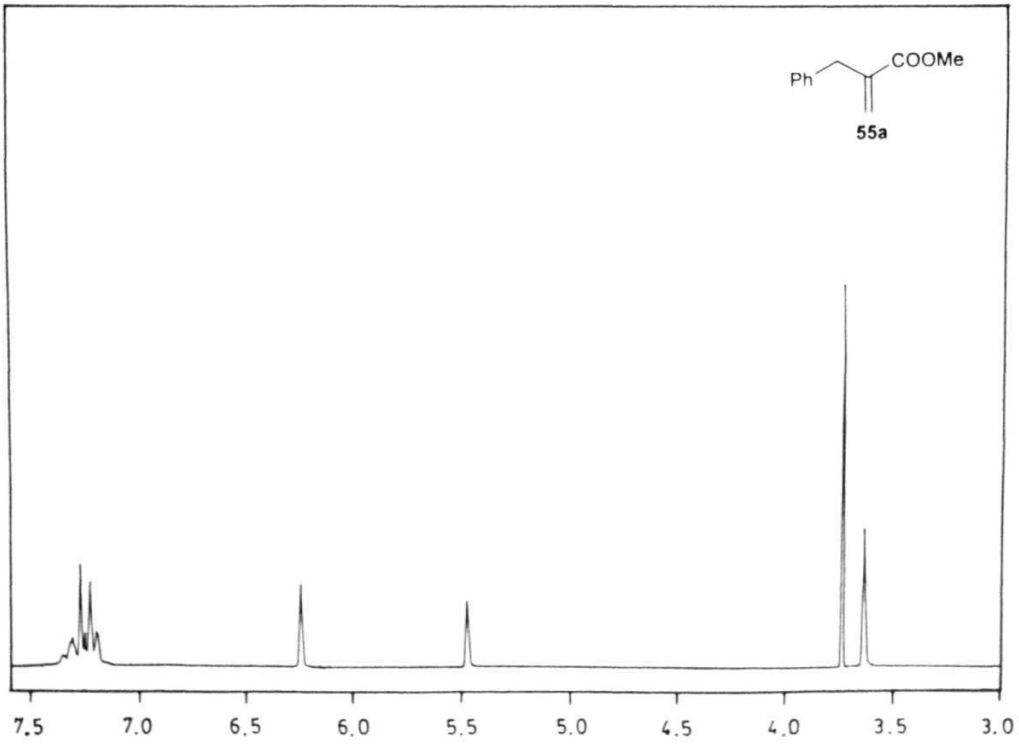


Fig. 5: ^{1}H NMR spectrum of **55a**

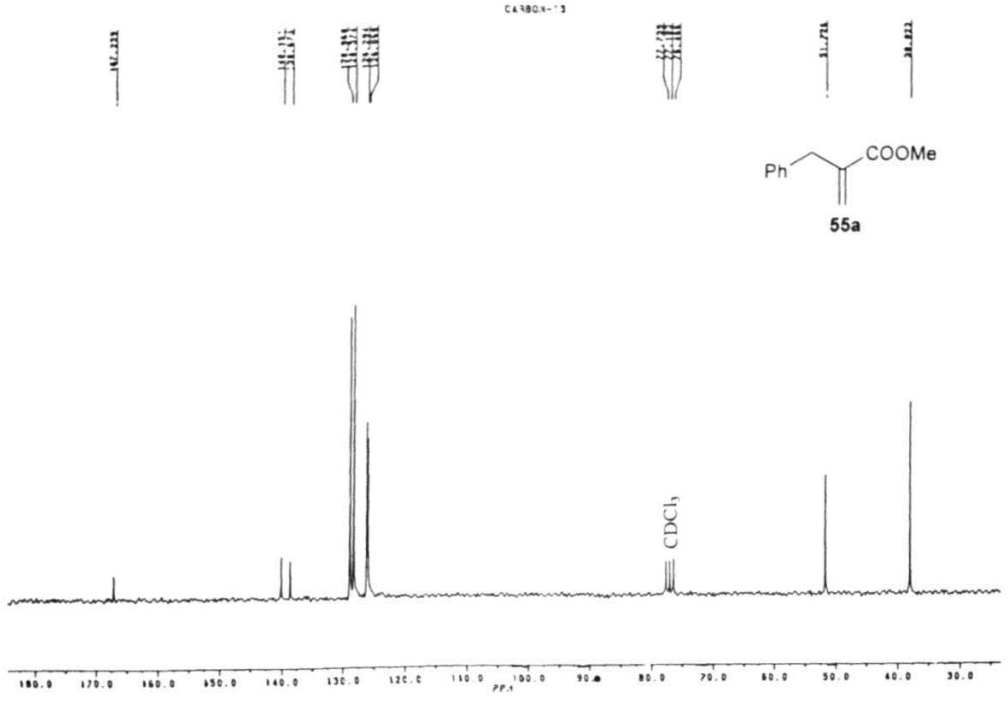


Fig. 6: ^{13}C NMR spectrum of **55a**

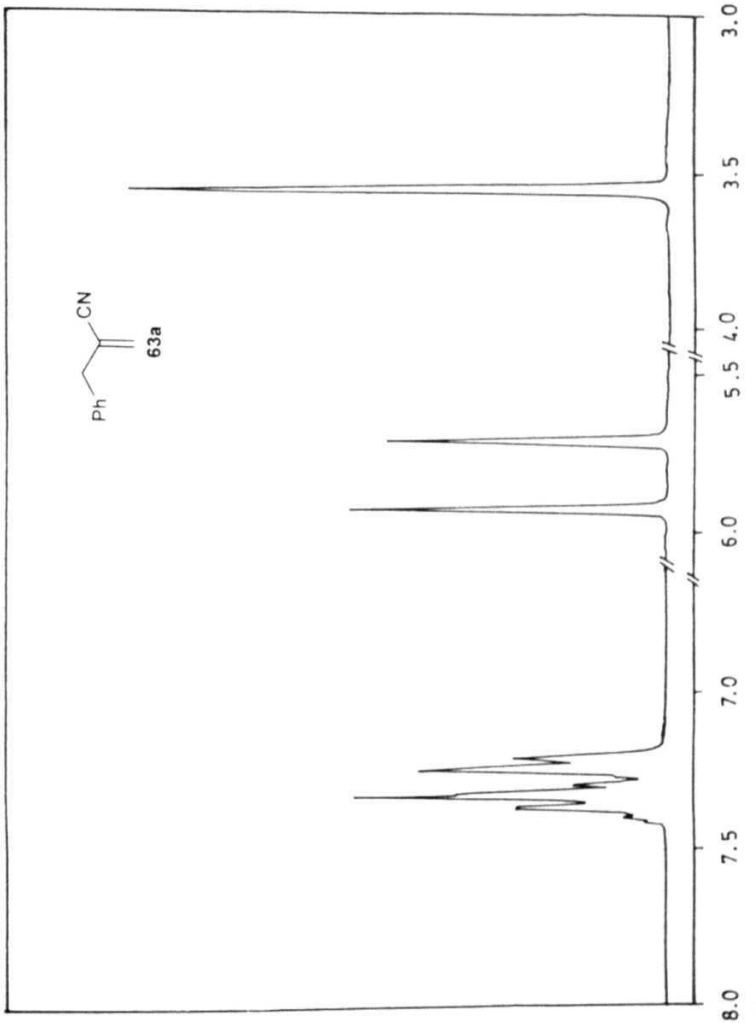


Fig. 7: ^{1}H NMR spectrum of **63a**

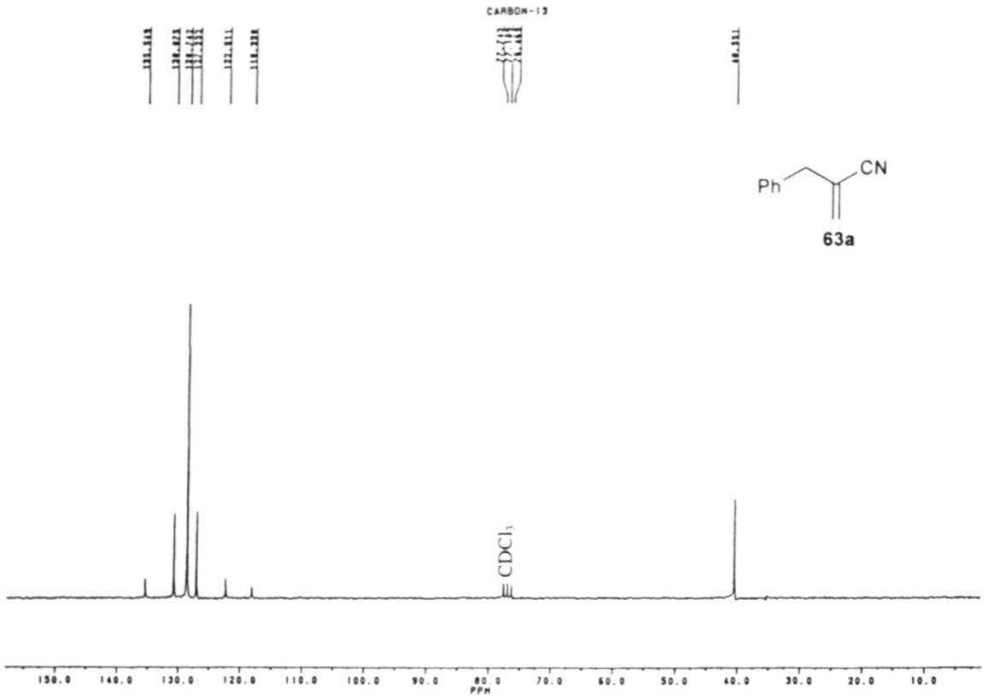


Fig. 8: ^{13}C NMR spectrum of **63a**

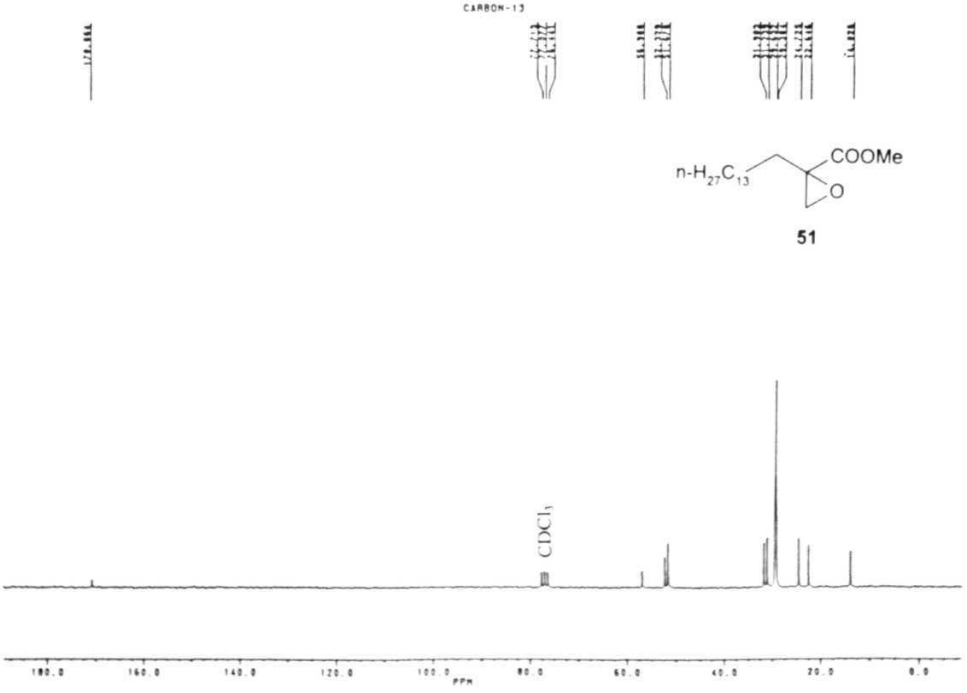


Fig. 9: ^{13}C NMR spectrum of **51**

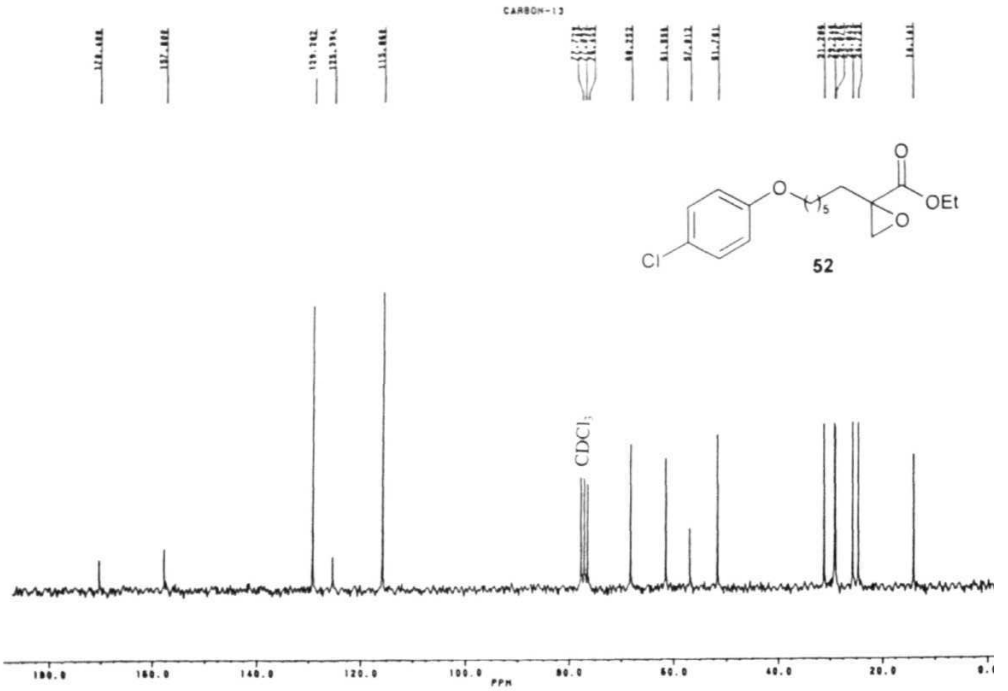


Fig. 10: ^{13}C NMR spectrum of **52**

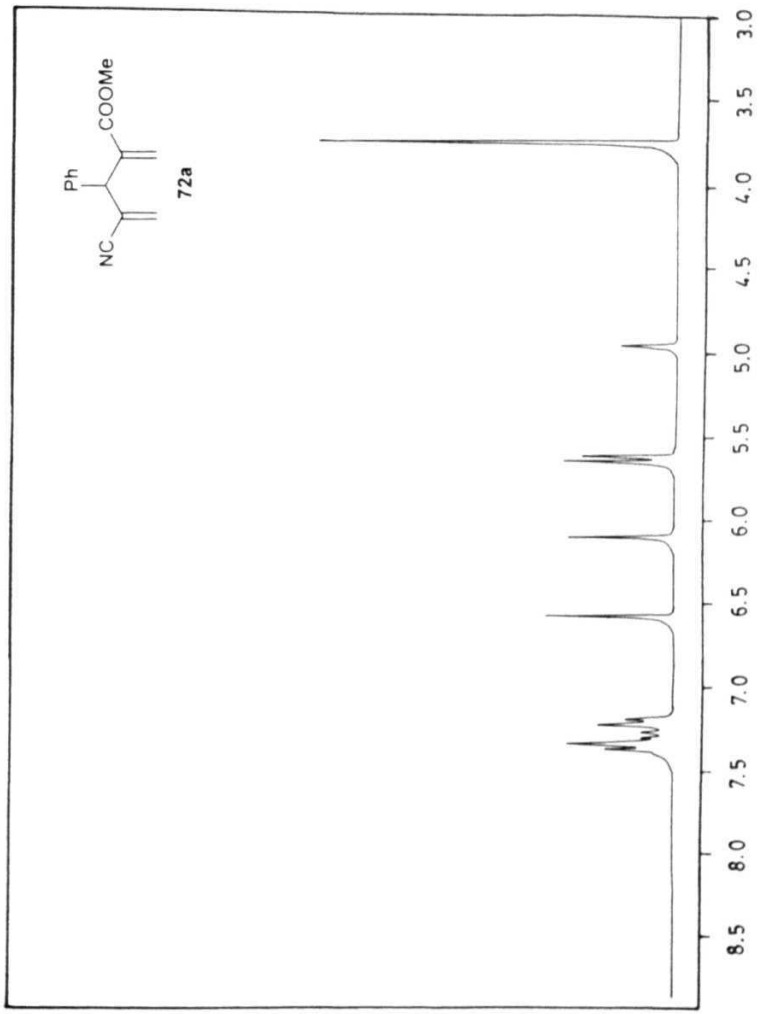


Fig. 11: ^{1}H NMR spectrum of **72a**

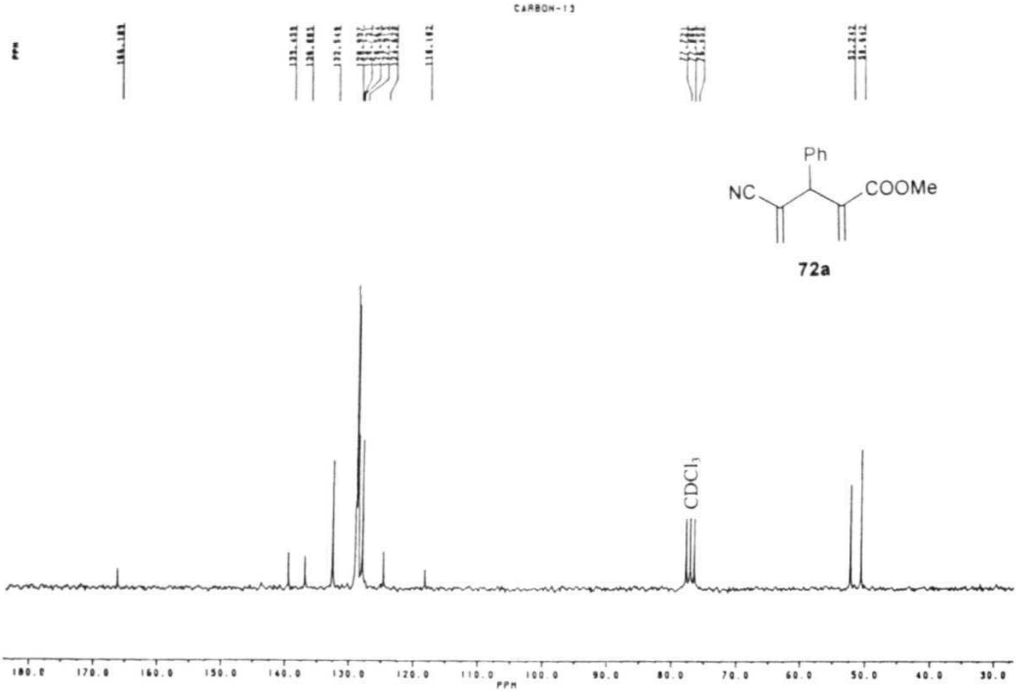


Fig. 12: ^{13}C NMR spectrum of **72a**

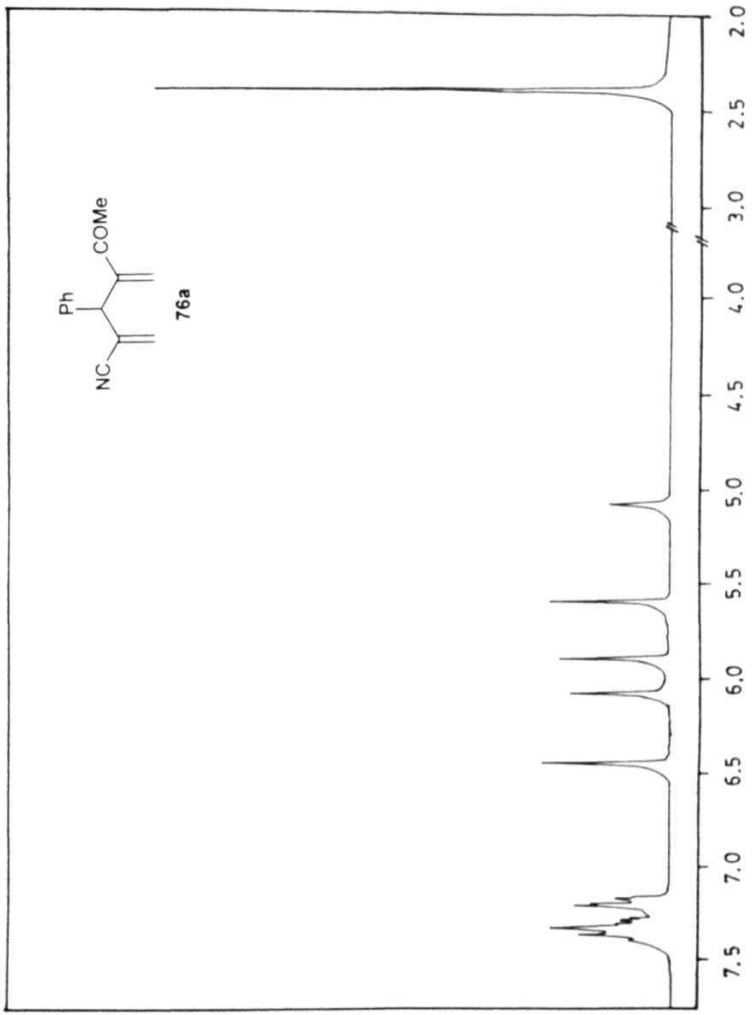


Fig. 13: ^{1}H NMR spectrum of **76a**

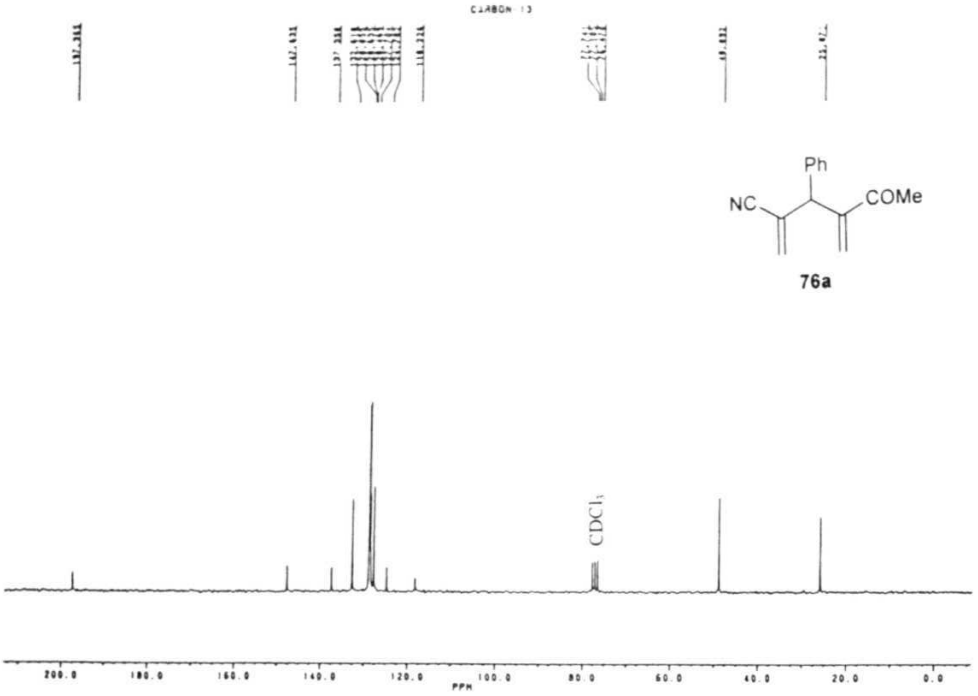


Fig. 14: ^{13}C NMR spectrum of **76a**

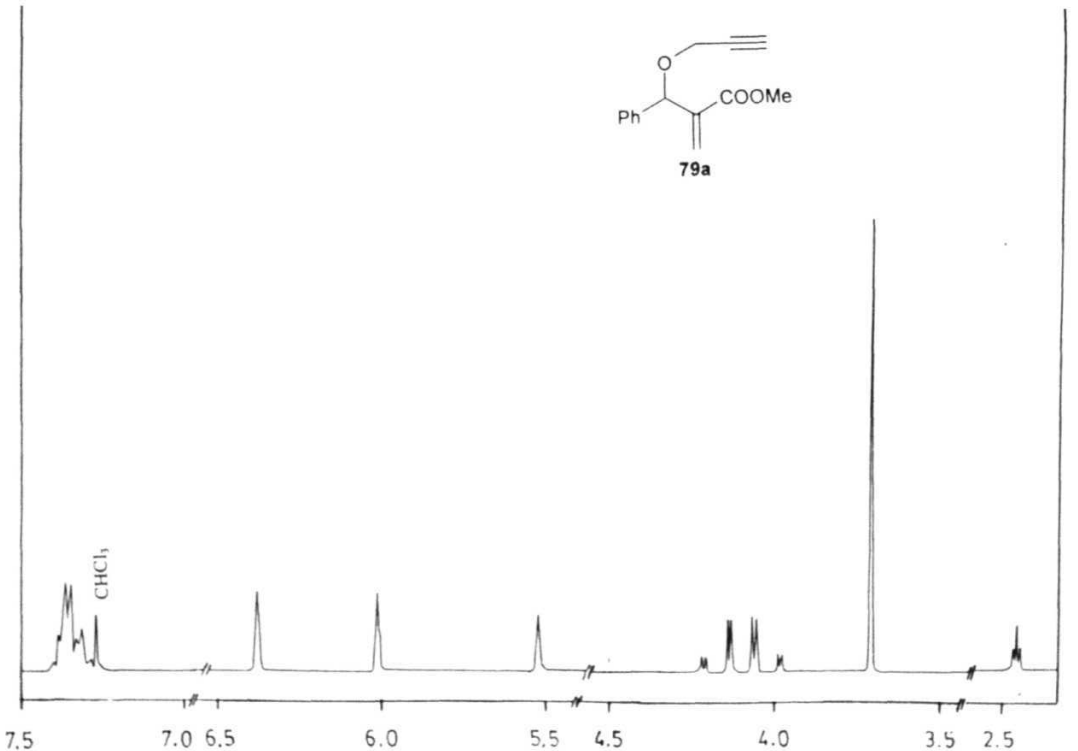


Fig. 15: ^{1}H NMR spectrum of **79a**

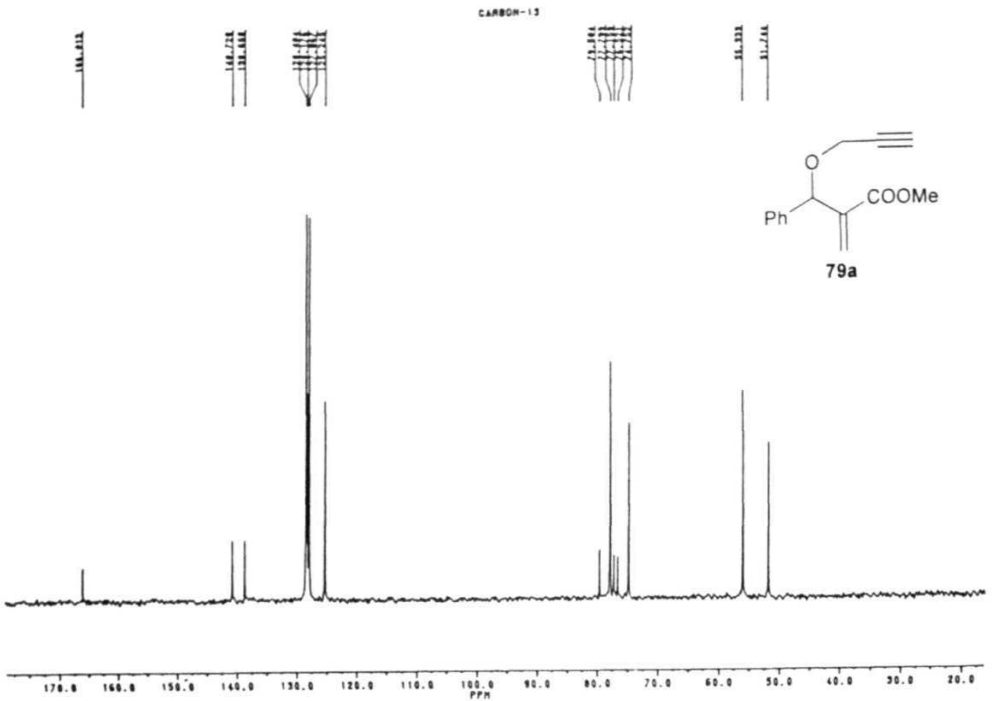


Fig. 16: ^{13}C NMR spectrum of **79a**

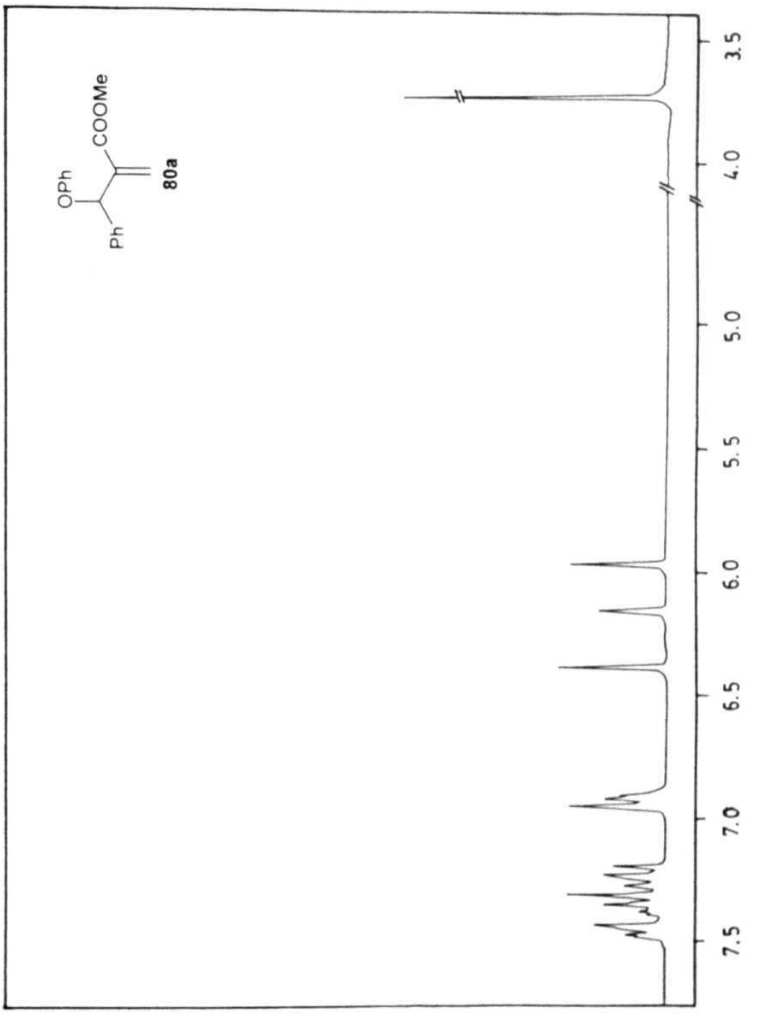


Fig. 17: ^{1}H NMR spectrum of **80a**

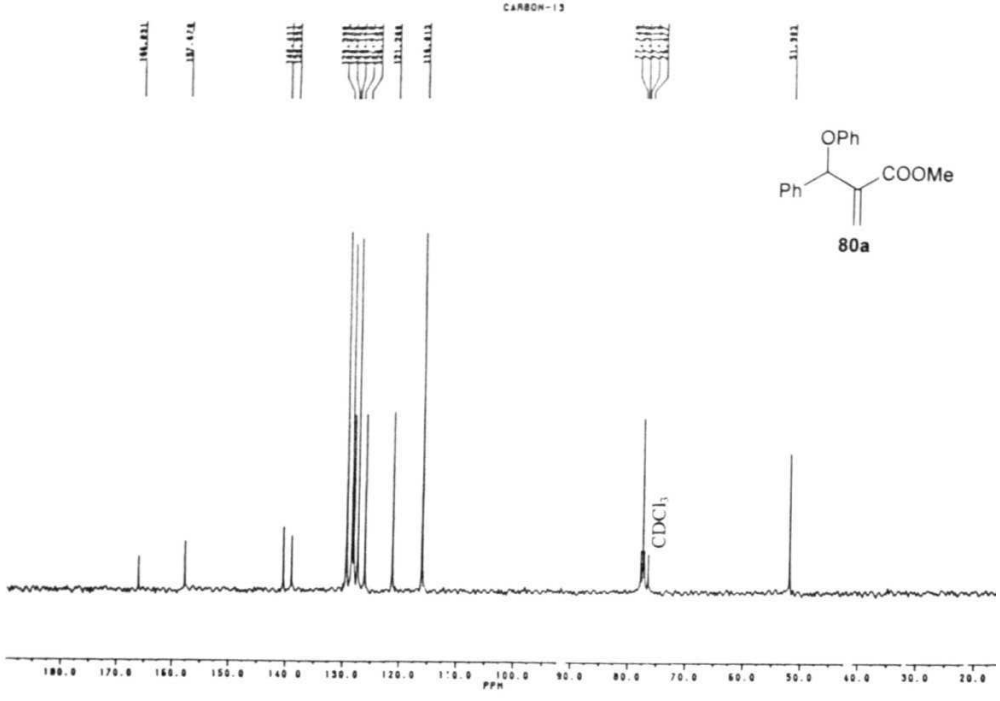


Fig. 18: ^{13}C NMR spectrum of **80a**

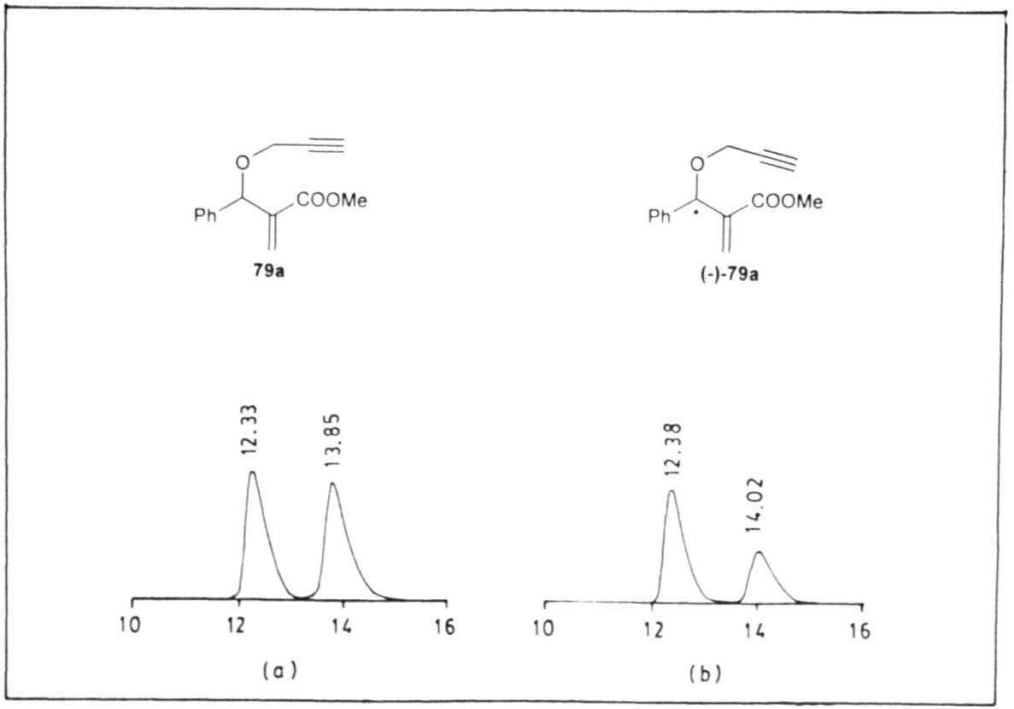


Fig. 19: HPLC analysis of **79a** on chiral column, CHIRALCEL OD

(a) chromatogram of (±)-**79a** (b) chromatogram of (-)-**79a**, ee 31%

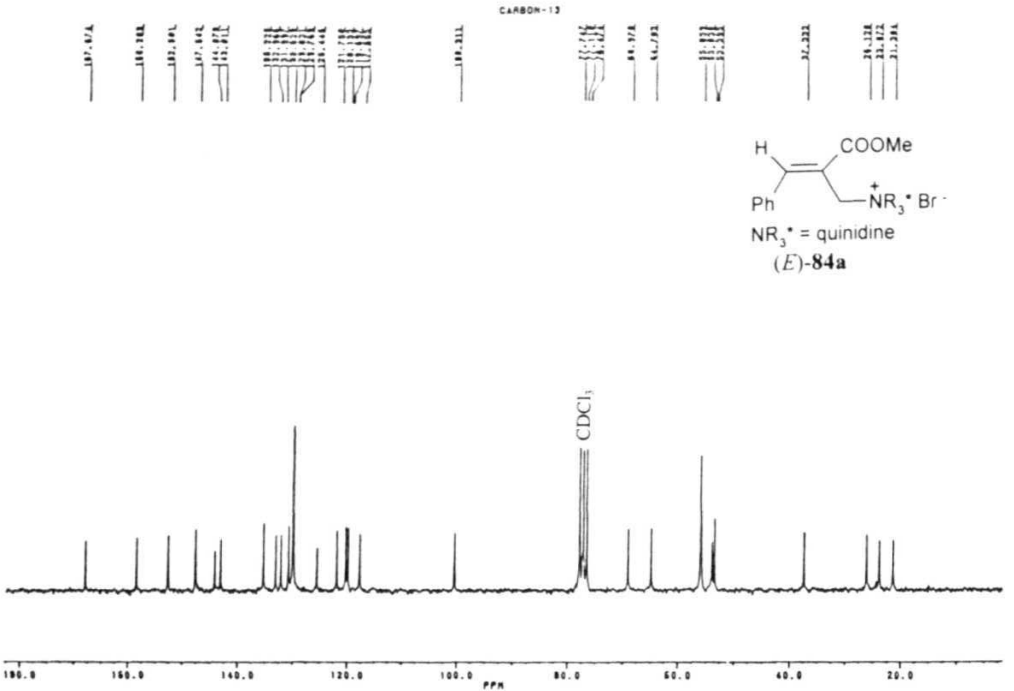


Fig. 20: ^{13}C NMR spectrum of (*E*)-**84a**

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List of **Publications:**

1. A Facile one-pot conversion of acetates of the Baylis-Hillman adducts to (*E*)-tt-methylcinnamic Acids
   D. Basavaiah, M. Krishnamacharyulu, R. Suguna Hyma, P. K. S. Sarma and N. Kumaragurubaran, *J Org Chem.* 1999, *64,* 1197
2. Applications of the Baylis-Hillman adducts in organic synthesis: A facile synthesis of (*E*)-α-cyanocinnamyl alcohols and (*E*)-α-cyanocinnamic aldehydes
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7. Asymmetric Baylis-Hillman chemistry: Enantioselective synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-l-yloxy)propanoates *via* chiral leaving group strategy
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