STUDIES TOWARDS NOVEL APPLICATIONS OF THE BAYLIS-HILLMAN CHEMISTRY

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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To
Almighty
&
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.

8.12.03

HYDERABAD

NOVEMBER, 2003

D. S. SHARADA

CERTIFICATE

Certified that the work embodied in this thesis entitled **"Studies towards novel applications of the Baylis-Hillman chemistry"** has been carried out by **Ms.** D. S. **SHARADA**, under my supervision and the same has not been submitted elsewhere for a degree.

D Basavaiah

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D. *S. Sharada*

ABBREVIATIONS

Ac	acetyl
aq.	aqueous
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
t-Boc	*t*-butoxycarbonyl
Bp	boiling point
Bu	butyl
/-Bu	*iso*butyl
s-Bu	*secondary-butyl*
t-Bu or Bu^1	*tert*-butyl
BINOL	1,1′-bi-2-naphthol
Bz	benzoyl
cat.	catalyst
mCPBA	*meta*-chloroperbenzoic acid
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBP	dibutyl phthalate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
(DHQD)$_2$PHAL	hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	diisobutylaluminium hydride
DIPAMP	1,2-bis(anisylphenyl)phosphinoethane
DMAP	4-(dimethylamino)pyridine

DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
EWG	electron withdrawing group
eq.	equivalents
Hept	heptyl
Hex	hexyl
c-Hex	cyclohexyl
HMPA	hexamethylphosphoramide
3-HQD	3-hydroxyquinuclidine
Eu(fod)3	Europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)
Eu(hfc)3	Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]
KDP	ketodicyclopentadiene
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
Me	methyl
MEM	(2-methoxyethoxy)methyl
Mp	melting point
Ms	mesyl
MS	molecular sieves
MVK	methyl vinyl ketone
MW	microwave
NMO	4-methylmorpholine *N*-oxide

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pent	pentyl
Ph	phenyl
PLAP	pig liver acetone powder
PMP	1,2,2,6,6-pentamethylpiperidine
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr or Pr'	*iso*-propyl
PTC	phase transfer catalyst
Py	pyridine
RCM	ring closing metathesis
rt	room temperature
TBAF	tetrabutylammonium flouride
TBSC1	ter/-butyldimethylsilyl chloride
tert.	tertiary
TEA	triethylamine
THF	tetrahydrofuran
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMG	1,1,3,3-tetramethylguanidine
TMS	tetramethylsilane
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Trt	trityl
Ts	tosyl

ABSTRACT

Construction of carbon-carbon bond is one of the most fundamental reactions in organic chemistry and hence the development of new methodologies and strategies for formation of carbon-carbon bonds has been and continues to be one of the most challenging and fascinating endeavors in organic chemistry. Recent developments in organic chemistry demand the concepts of atom economy, selectivity and generation of chemospecific functional groups, for developing any efficient synthetic reaction, particularly C-C bond forming reaction. The Baylis-Hillman carbon-carbon bond forming reaction is one such reaction, well equipped with the concepts of atom economy and generation of densely functionalized molecules. The Baylis-Hillman reaction is basically a three-component reaction involving an activated alkene, an electrophile and a catalyst (usually a tertiary amine) leading to the coupling of α-position of activated alkene with an electrophile providing an interesting class of highly, synthetically useful multifunctional molecules.

This thesis deals with the studies in the applications of Baylis–Hillman chemistry and consists of three chapters, that is, 1. Introduction 2. Objectives, Results & Discussion and 3. Experimental. The first chapter, that is, Introduction presents a brief literature

survey on recent developments in the Baylis–Hillman reaction and applications of the Baylis–Hillman adducts in the organic synthesis.

The second chapter deals with the objectives, results and discussion. With a view to study the applications of Baylis-Hillman chemistry in organic synthesis, we have undertaken a research program with the following objectives.

1). To employ alkyl 2-(bromomethyl)prop-2-enoates, derived from Baylis-Hillman adducts, as valuable electrophiles in the Baylis-Hillman coupling reaction with various activated alkenes with a view to develop a one-pot convenient methodology for synthesis of 2,4-functionalized 1,4-pentadienes.

2). To employ the Baylis-Hillman adducts as valuable substrates for tandem construction of C-O and C-C bonds involving Prins type and Friedel-Crafts type reactions with an aim of developing one-pot facile methodology for synthesis of 2-benzoxepine derivatives.

3). To develop highly diastereoselective methodology for transformation of alkyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates, obtained from the Baylis-Hillman adducts, derived from chiral acrylates and aldehydes into propargylic and phenolic ethers of Baylis-Hillman adducts.

4). To describe the first organobase mediated Cannizzaro reaction of reactive aldehydes.

Applications of alkyl 2-(bromomethyl)prop-2-enoates as valuable electrophiles in the Baylis-Hillman reaction: a one-pot facile synthesis of 2,4-functionalized 1,4-pentadienes

We have successfully employed alkyl 2-(bromomethyl)prop-2-enoates (**101a-c**) as useful electrophiles for Baylis-Hillman coupling with various activated alkenes such as acyclic & cyclic enones, acrylonitrile and alkyl acrylates, in the presence of tertiary amines such as DABCO (or DBU), thus leading to the development of a one-pot convenient methodology for synthesis of 2,4-functionalized 1,4-pentadienes **(102-114)** in 77-85% isolated yields (eqs 22-28 and Table 1).

Tandem construction of C-O and C-C bonds: a one-pot facile transformation of the Baylis-Hillman adducts into 2-benzoxepine derivatives

2-Benzoxepine moiety is an important structural unit present in many natural products and biologically important molecules which are found to be antiinflamatory, spasmolytic, analgesic, antipyretic, neuroleptic, antinaphylactic, hypotensive, antiulcer agents and are also found useful for treatment of depression and schizophrenia. Hence, development of simple and convenient methodologies for the synthesis of 2-

benzoxepine derivatives represents an attractive and interesting area of research in synthetic organic chemistry and medicinal chemistry. We have successfully developed one-pot facile methodology for synthesis of 2-benzoxepine derivatives **(133a-e, 134a,b)** *via* the tandem construction of C-0 and C-C bonds involving the Prins type and Friedel-Crafts type reactions of Baylis-Hillman adducts **(131a-e, 132a,b)** (derived form various aromatic aldehydes and alkyl acrylates) with HCHO in the presence of conc. H_2SO_4 in 44-61% isolated yields (eqs 30, 32 & Table 2). We have also successfully transformed the rearranged alcohol **(135a)** into the desired 2-benzoxepine derivative (133a) in 59% isolated yield (eq 34).

Chiral auxiliary mediated diastereoselective synthesis of propargylic and phenol ethers of Baylis-Hillman adducts from the alkyl (2*Z*)-3-aryl-2-(bromomethyl)prop- 2-enoates

With a view to examine the chiral auxiliary mediated diastereoselective S_N2' addition of oxygen nucleophiles on to the allyl bromides derived from Baylis-Hillman adducts, which in turn would be obtained from chiral acrylates **(14** & 18) and aldehydes, we have selected two auxiliaries (-)-menthol **(151)** and (1*S*,2*R*,4*R*)-1-(diisopropyl-aminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol **(162).** We have prepared representative allyl bromides **(154a,b, 155 & 169-174)** according to the Schemes 76 & 82. Then we have examined nucleophilic (SN2') addition of propargyl alcohol and phenol on to the bromides **(154a,b 155)** in the presence of triethylamine at room temperature, which provided the required (–)-menthyl 3-aryl-2-methylene-3-(prop-2-yn-l-yloxy)propanoates **(156a,b, 157)** and (-)-menthyl 3-aryl-2-methylene-3-phenoxypropanoates **(158a,b 159)** in 4-23% and 26-35% diastereoselectivities respectively (Schemes 77-80 and Table 5). Similar S_N2' addition of propargyl alcohol and phenol on to the allyl bromides **(169-174)** provided the desired (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-(prop-2-yn-l-yloxy)propanoates (175-180) and (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-phenoxypropanoates **(181-186)** in 51-88% and 54-82% diastereoselectivities respectively (Scheme 83, eqs 38,40,41 and Tables 7 and 9).

First example of organo base induced Cannizzaro reaction

During our attempts to perform the Baylis–Hillman reaction between phenyl vinyl sulfoxide **(188)** and pyridine-4-carboxaldehyde **(130j)** under the influence of TMG (1,1,3,3-tetramethylguanidine) **(187)** in aqueous/dioxane medium, we have observed that there was no Baylis-Hillman reaction and in fact, we have isolated 4-pyridinemethanol **(189)** as a major product, which was produced due to the Cannizzaro reaction (Scheme 86). We have confirmed this TMG-induced Cannizzaro reaction by treating pyridine-4-carboxaldehyde **(130j)** with TMG in H_2O, which provided 4-

pyridinemethanol in 42% isolated yield (eq 44). However, our attempts to isolate **pyridine-4-carboxylic** acid in pure form were not successful. We have then **successfully** employed TMG for promoting Cannizzaro reaction of reactive aromatic aldehydes **(130k-n)** (eq 45-47 and Table 10) (however, our attempts to isolate corresponding acids in case of pyridine-3-carboxaldehyde **(130k)** and **pyridine-2-carboxaldehyde (1301)** met with failure). In case of **4-nitrobenzaldehyde (130m)** and **3-nitrobenzaldehyde (130n),** we have also successfully isolated acids **(194** and **196)** (oxidized product) respectively. We have also performed TMG-promoted cross-Cannizzaro reaction of these aldehydes **(130j-n),** with HCHO to provide the corresponding alcohols **(189,191-193,195)** in good yields (eq 48, Scheme 88 and Table 12). Thus we have for the first time described the TMG (organobase) mediated Cannizzaro reaction of reactive aromatic aldehydes.

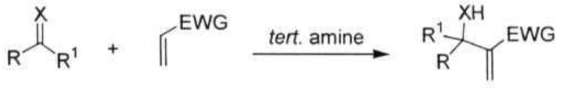
The third chapter deals with the detailed experimental procedures, 1R, ^{1}H NMR, ^{13}C NMR, mass spectral data, microanalyses, physical constants (bp, mp) and optical rotations.

INTRODUCTION

Construction of carbon-carbon bond is one of the most fundamental reactions in organic chemistry and hence the development of new methodologies and strategies for formation of carbon-carbon bonds has been and continues to be one of the most challenging and fascinating endeavors in organic chemistry.[1-7] Several carbon-carbon bond forming reactions such as aldol reaction,[8,10] Diels-Alder reaction,[11,12] Grignard reaction,[13,14] Friedel-Crafts reaction,[1516] Reformatsky reaction,[17] Wittig reaction,[18] Heck reaction,[19] Claisen rearrangements,[20] Suzuki coupling,[21] Grubb's ring closing metathesis[22,23] *etc.*, have been developed and their applications in organic synthesis have been well documented.

Recent developments in organic chemistry demand the concepts of atom economy, selectivity and generation of chemospecific functional groups, for developing any efficient synthetic reaction, particularly C-C bond forming reaction. The Baylis-Hillman carbon-carbon bond forming reaction, originating from a German patent,[24] is one such reaction, well equipped with the concepts of atom economy and generation of densely functionalized molecules and in fact, this reaction has recently enjoyed the distinction of becoming a "text-book" reaction.

The Baylis-Hillman reaction is basically a three-component reaction involving an activated alkene, an electrophile and a catalyst (usually a tertiary amine) leading to the coupling of a-position of activated alkene with an electrophile providing an interesting class of highly, synthetically useful multifunctional molecules (eq 1).[24-29]



eq 1

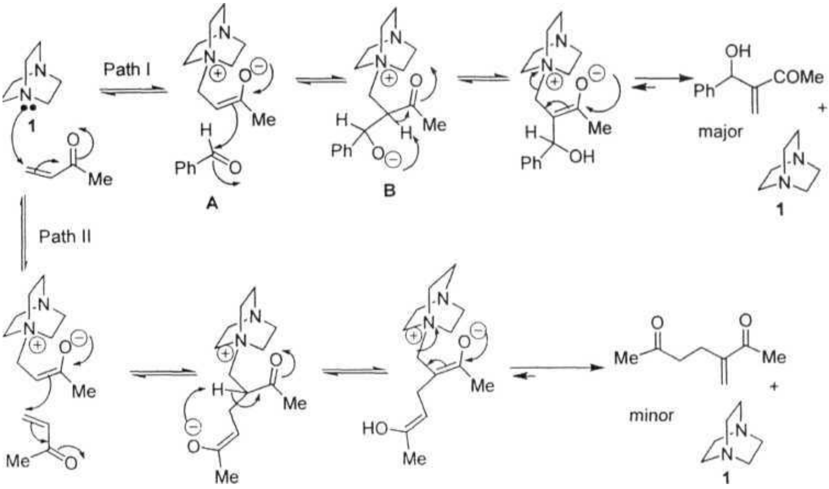
R = aryl, alkyl, aralkyl, heteroaryl

R^1 = H, alkyl, COOR X = O, NCOOR, NTs, NSO_2Ph

EWG = COR, CHO, CN, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh

The most generally accepted mechanism[25-32] of the Baylis-Hillman reaction is illustrated in the Scheme 1 (Path I) taking the reaction between benzaldehyde (as an electrophile) and methyl vinyl ketone (as an activated olefin) under the catalytic influence of DABCO (1), as a model case. The mechanism of the reaction is believed to proceed through the Michael initiated addition-elimination sequence. The first step involves the Michael type nucleophilic addition of the tertiary amine catalyst (DABCO) to the activated alkene (methyl vinyl ketone), leading to the formation of zwitterionic enolate A, which adds on to the electrophile (benzaldehyde) in an aldol fashion, to generate the zwitterionic species B. This zwitterion B undergoes proton migration and subsequently, releases the catalyst to provide the desired multifunctional molecule. In the case of reactive activated alkenes such as alkyl vinyl ketones, Michael type dimers are formed as side products because they themselves act as electrophiles (Scheme 1; Path II).

Scheme 1

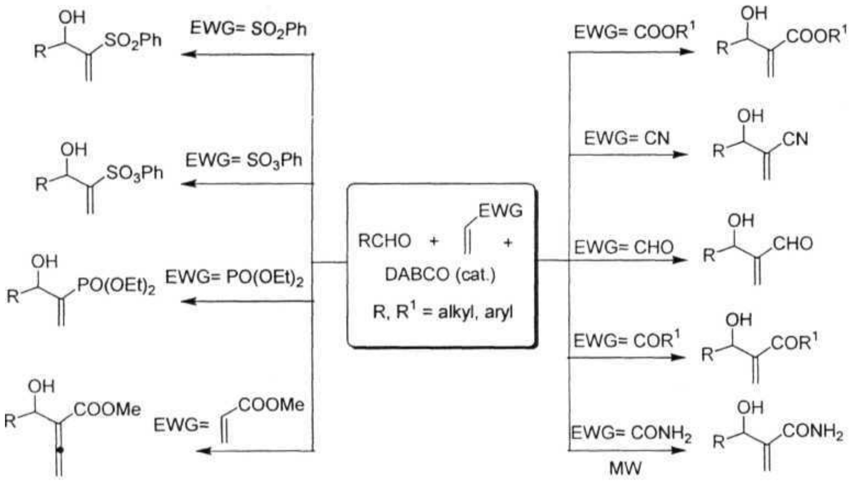


The Baylis-Hillman reaction has experienced a very rapid growth in terms of all the three essential components and also the Baylis-Hillman adducts have been extensively used as a source for developing various new synthetic transformation methodologies during the last two decades.[25-29] Some of the very important and recent developments of this reaction with respect to all the three essential components and applications of Baylis-Hillman adducts in organic synthesis have been described in this section.

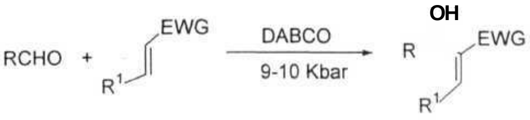
ACTIVATED ALKENES

Various activated alkenes such as alkyl (aryl) acrylates,[32-34] acrylonitrile,[35 36] acrolien,[37-39] alkyl vinyl ketones,[35,40,41] vinyl sulfones,[42] vinyl sulfonates,[43] vinyl phosphonates[44] and allenic esters[45,46] have been successfully employed for Baylis-Hillman coupling with a number of carbon electrophiles (Scheme 2). However, less reactive acrylamide[47] was brought into scope of the reaction under microwave conditions (Scheme 2).

Scheme 2



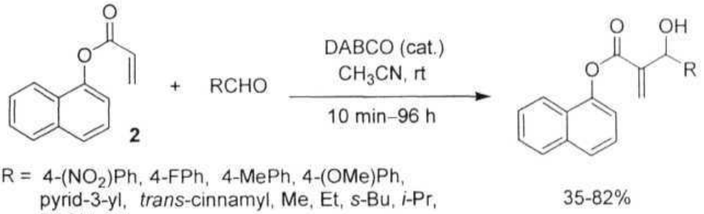
The p-substituted activated alkenes such as crotononitrile,[48,49] crotonic acid esters[48] and less reactive alkenes such as phenyl vinyl sulfoxide,[50] which do not participate in this reaction under normal conditions have been successfully employed for coupling with aldehydes under high pressures (eq 2).



eq 2

R = R^1= Me; EWG = CN, COOMe
R = Ph, Me; R^1 = H; EWG = SOPh

α-Naphthyl acrylate (2) was found to be a fast reactive activated alkene in the Baylis-Hillman reaction for coupling with various aldehydes (eq 3).[51]

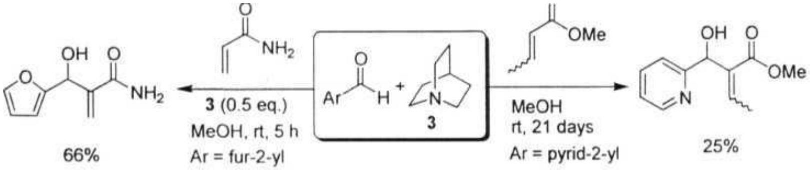


eq 3

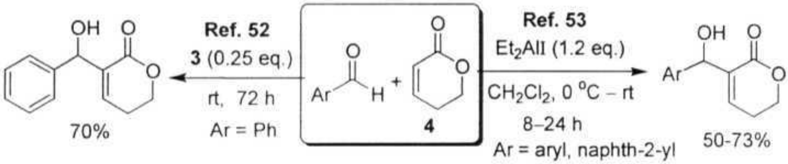
R = 4-(NO$_2$)Ph, 4-FPh, 4-MePh, 4-(OMe)Ph, pyrid-3-yl, *trans*-cinnamyl, Me, Et, *s*-Bu, *i*-Pr, PhCH$_2$CH$_2$

Very recently, Aggarwal and co-workers[52] have found that the less reactive activated olefins such as acrylamides and methyl crotonate undergo Baylis-Hillman coupling with various aldehydes under the influence of combination of quinuclidine (3) and methanol (Scheme 3). They have also used 5,6-dihydro-2*H*-pyran-2-one (4) as an activated alkene in the Baylis-Hillman coupling with aldehydes under the influence of quinuclidine (3) and methanol[52] (Scheme 4). Subsequently, Li and co-workers[53] reported a similar coupling of 5,6-dihydro-2*H*-pyran-2-one (4) with aldehydes under the influence of diethylaluminum iodide (Scheme 4).

Scheme 3



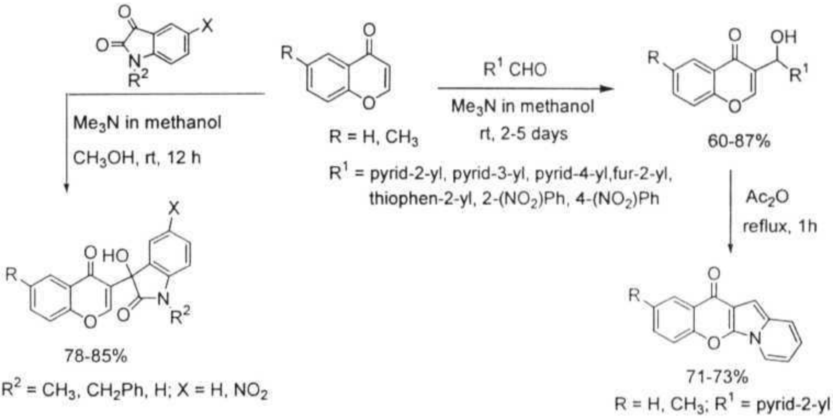
Scheme 4



Very recently, our research group[54] has successfully employed 1-benzopyran-4(4*H*)-one derivatives, for the first time, as activated alkenes in the Baylis-Hillman coupling with heteroaromatic-aldehydes, nitrobezaldehydes and isatin derivatives under the influence of methanolic trimethylamine (Scheme 5). The resulting Baylis-Hillman adducts, obtained from chromone derivatives and pyridine-2-carboxaldehyde, were

successfully transformed into a novel tetracyclic indolizine fused chromone systems (Scheme 5).

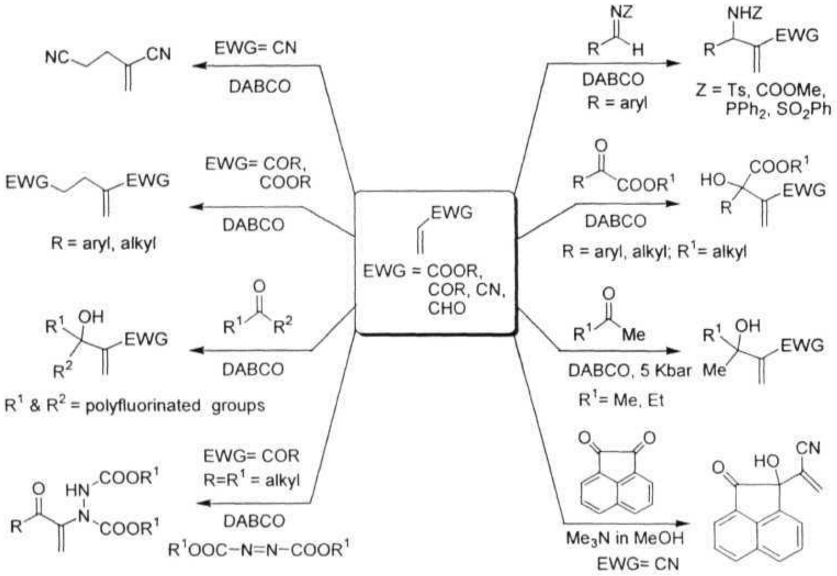
Scheme 5



ELECTROPHILES

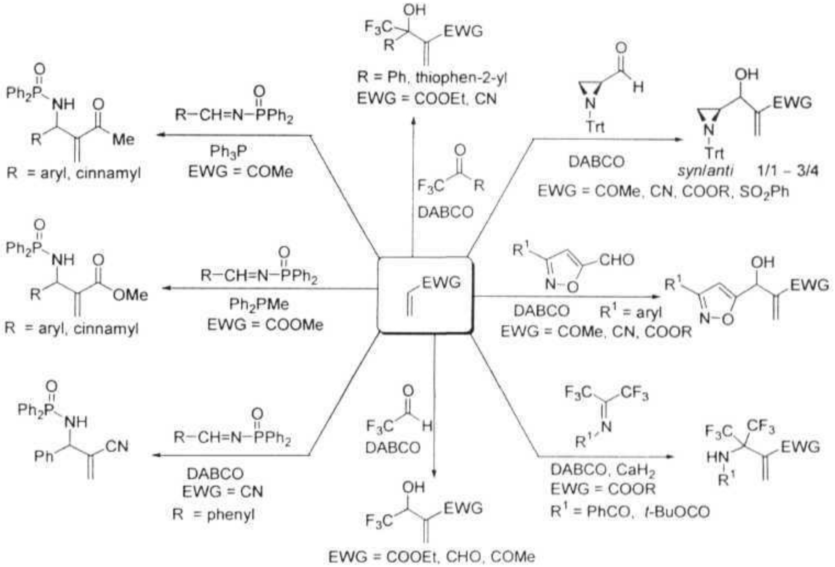
Although aldehydes are the most widely used electrophiles, various other carbon electrophiles such as aldimine derivatives,[55-57] α-keto esters,[58-60] non-enolizable 1,2-diketones,[38,39] activated alkenes[61-64] and fluoro-ketones[65] have been utilized successively in this reaction (Scheme 6). Less reactive electrophiles (simple ketones) such as propan-2-one and butan-2-one,[37,48] which do not undergo Baylis-Hillman reaction under normal conditions, were brought into scope of the reaction **under high** pressure (Scheme 6). Recently, azodicarboxylates have also been successfully employed as novel (non-carbon) electrophiles in the Baylis-Hillman reaction with various alkyl vinyl ketones in the presence of DABCO as a catalyst, to provide 2-(*N,N'*-bisalkoxycarbonyl)hydrazinoalk-l-en-3-ones (Scheme 6).[66]

Scheme 6



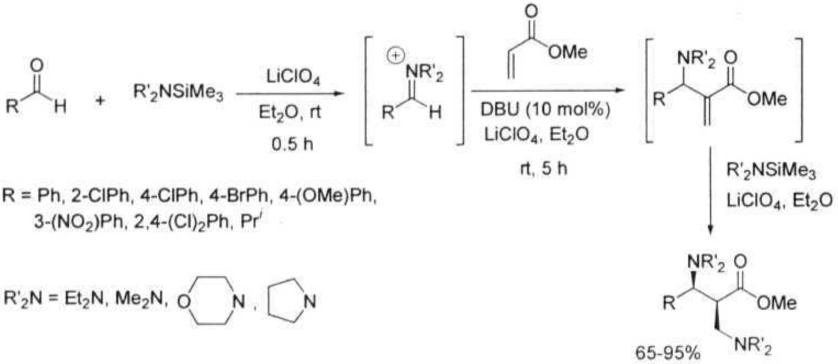
Very recently, interesting electrophiles such as *N*-tritylaziridine-2-(*S*)-carboxaldehyde,[67] 5-isoxazolecarboxaldehydes,[68] fluorinated aldehydes,[69] fluorinated ketones,[70] fluorinated imines[71] and *N*-arylidenediphenylphosphinamides[72] have been successfully employed in Baylis-Hillman reaction (Scheme 7).

Scheme 7



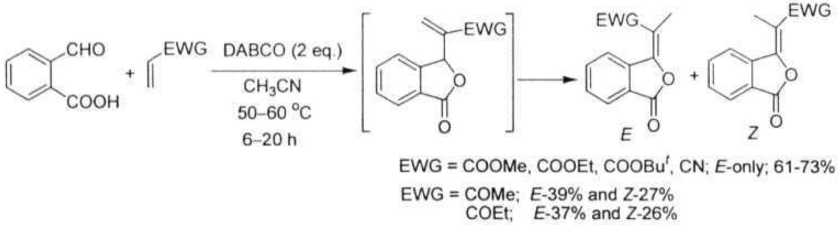
Azizi and Saidi have employed *in situ* generated iminium salts [obtained by the treatment of (trimethylsilyl)dialkylamines with aldehydes] as electrophiles in the Baylis-Hillman coupling with methyl acrylate in the presence of DBU. The corresponding adducts, thus obtained, undergo Michael addition with (trimethylsilyl)dialkylamines to give the diamines (Scheme 8).[73]

Scheme 8



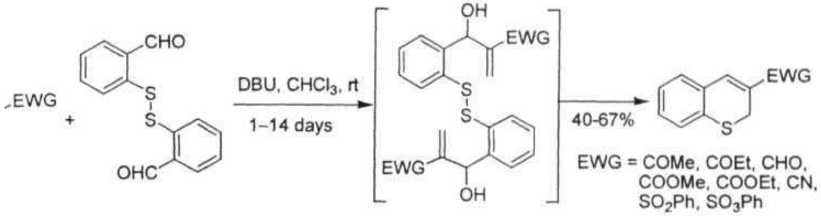
Very recently, Kim and co-workers [4] have reported the Baylis–Hillman coupling of 2-carboxybenzaldehyde with various activated alkenes, leading to the formation of enol lactone derivatives (Scheme 9).

Scheme 9



2,2′-Dithiobenzaldehyde has been used as an electrophile for Baylis-Hillman coupling **with various activated olefins in the presence of DBU, to provide a convenient one-pot** synthesis **of** benzothiopyran **derivatives (Scheme 10).**[75]

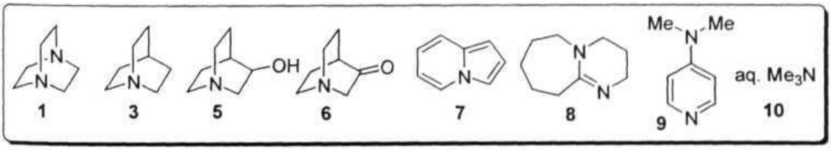
Scheme 10



CATALYSTS/CATALYTIC SYSTEMS

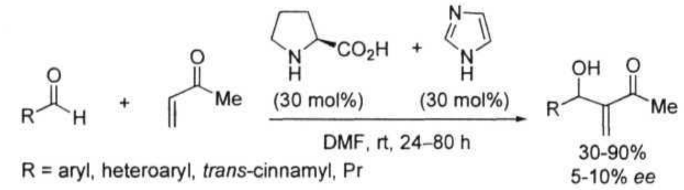
Although DABCO (1) has been the most frequently used catalyst in this reaction, various other tertiary amine catalysts such as quinuclidine (3), 3-hydroxyquinuclidine (3-HQD) (5), 3-quinuclidone (6), indolizine **(7),** DBU **(8), DMAP (9) and aqueous** trimethylamine (10) (Figure 1) have been successfully employed in certain Baylis-Hillman reactions.[24-29,76,79]

Figure 1



Shi and co-workers[80] have reported proline catalyzed Baylis-Hillman reaction between various aldehydes and MVK in the presence of a weak base such as imidazole.

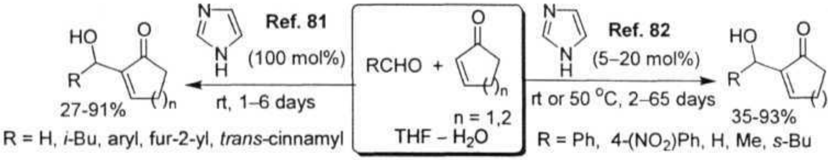
However, the enantioselectivities obtained in these reactions were found to be very low (eq 4).



eq 4

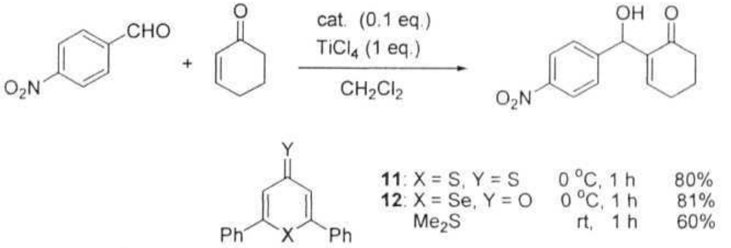
Later on, Cheng and co-workers[81] & Gatri and El Gaied[82] have independently used imidazole as a catalytic source for Baylis-Hillman coupling of cycloalkenones with aldehydes (Scheme 11).

Scheme 11



NON-AMINE CATALYSTS

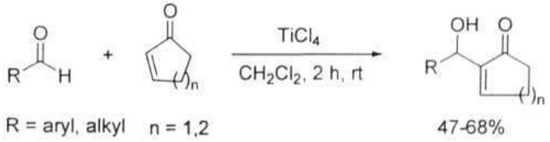
Several non-amine catalysts such as trialkyl phosphines,[83-85] triaryl phosphines[86] and metal complexes like $RhH(PPh_3)_4$,[87,88] $RuH_2(PPh_3)_4$,[88,89] have been successfully used in the coupling of activated alkenes with aldehydes. Kataoka et al.[90-92] demonstrated the application of sulfides or selenides (chalcogenides) as catalysts for the Baylis-Hillman coupling of vinyl ketones with various aldehydes in the presence of $TiCl_4$. They also found 2,6-diphenyl-4*H*-chalcogenopyran-4-ones 11 and 12, to be more efficient catalysts than Me_2S, for the Baylis-Hillman reaction. One representative example is presented in the equation 5.[91,92]



eq 5

11: X = S, Y = S	0 °C, 1 h	80%
12: X = Se, Y = O	0 °C, 1 h	81%
Me_2S	rt, 1 h	60%

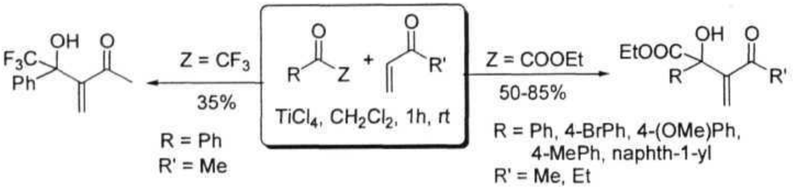
Li and co-workers[93] have reported the $TiCl_4$-mediated Baylis-Hillman reaction of cyclic enones with various aldehydes in the absence of any Lewis base (eq 6).



eq 6

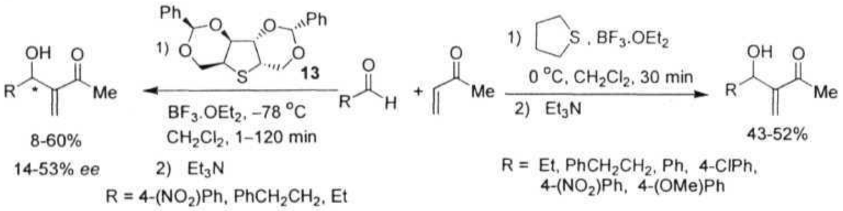
In our laboratory, a-keto esters and trifluoromethyl phenyl ketone have been utilized as electrophiles in the Baylis-Hillman coupling with alkyl vinyl ketones under the influence of $TiCl_4$, to provide the desired adducts (Scheme 12).[94]

Scheme 12



Goodman and co-workers[95] have reported Baylis-Hillman reaction between aldehydes and MVK using tetrahydrothiophene-BF3.OEt2 as a catalytic system. Subsequently, they have used enantiopure sulfide (13) for asymmetric Baylis-Hillman reaction, which provided desired adducts up to 53% enantiomeric excess (Scheme 13).

Scheme 13



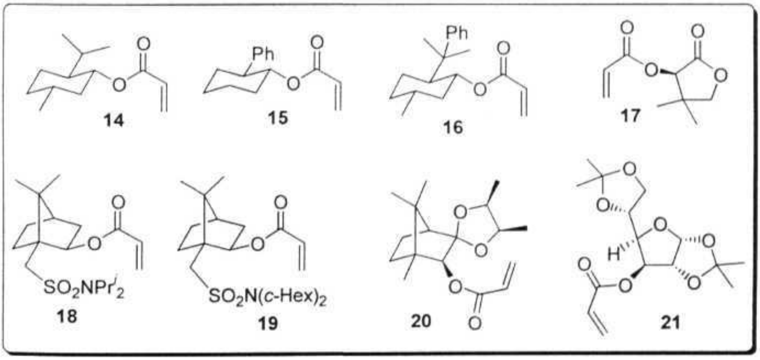
ASYMMETRIC BAYLIS-HILLMAN REACTION

Since the Baylis-Hillman reaction creates a new stereogenic center, there are opportunities and challenges to perform the asymmetric version of this reaction by selecting appropriate chiral sources in any one of the (or two or three) essential components *i.e.*, activated alkene, electrophile and catalyst. Already efforts have been made in this direction [illegible] and some relevant and recent developments in this direction have been described in the following.

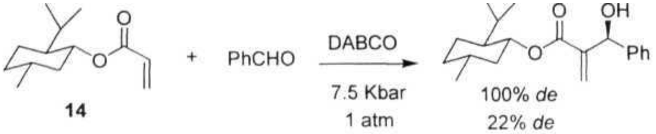
i) Chiral activated alkenes:

Considerable progress has been achieved in the asymmetric version of this reaction using chiral activated alkenes[25-29] such as chiral acrylates[96-107] and chiral acrylamide derivatives.[108-110] A variety of chiral acrylates **(14-21)** (Figure 2) derived from various chiral auxiliaries have been employed in the Baylis-Hillman reaction, to provide the resulting adducts in low to high diastereoselectivities.[24-29,96-110]

Figure 2



Gilbert et al.[105] reported the influence of high pressure on the diastereoselectivities of chiral auxiliary mediated coupling of activated alkenes with aldehydes. Thus, the reaction of (-)-menthyl acrylate (14) with benzaldehyde under the catalytic influence of DABCO at higher pressure provided the corresponding Baylis-Hillman adduct with 100% diastereoselectivity, whereas the similar reaction at atmospheric pressure gave the required adduct with 22% diastereoselectivity (eq 7).

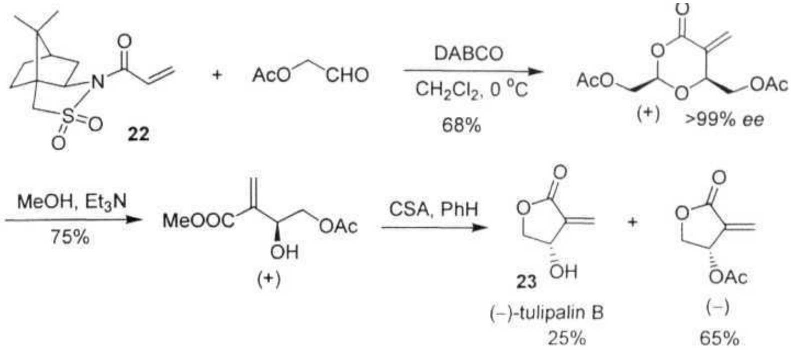


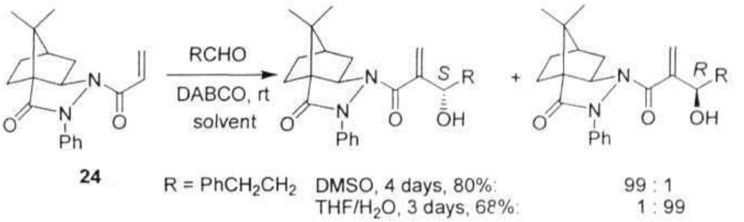
eq 7

Leahy and co-workers[108,109] have employed chiral acrylamide (22) derived from Oppolzer's camphor sultam, as an activated alkene in the Baylis-Hillman reaction to provide the desired adducts in high enantioselectivities. This methodology has been successfully employed for the synthesis of biologically important natural product (-)-tulipalin B (23) (Scheme 14).[108]

Enantiopure acryloylhydrazide (24) has been used as a chiral activated alkene in the Baylis-Hillman coupling with aldehydes by Yang and Chen, to afford desired adducts in high diastereoselectivities. They have also observed reversal of diastereoselectivity by changing the solvent from DMSO to THF/H2O. One representative example is presented in the equation 8.[110]

Scheme 14



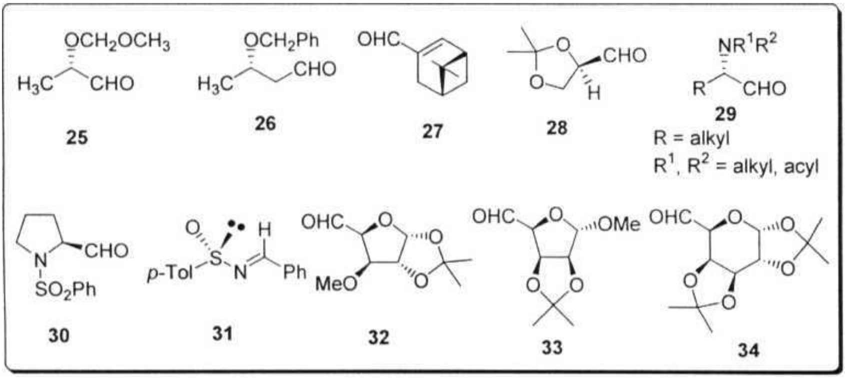


eq 8

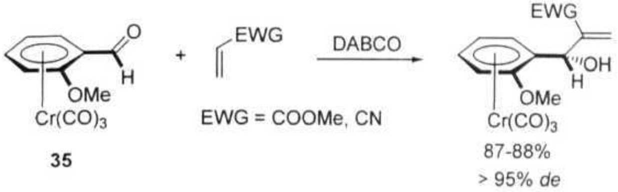
ii) Chiral electrophiles:

Significant efforts have also been made towards the asymmetric Baylis-Hillman reaction using chiral electrophiles. Thus, various chiral electrophiles such as (*S*)-*O*-(methoxymethyl)lactaldehyde (**25**),[111] (*S*)-3-benzyloxybutyraldehyde (**26**),[112] (*R*)-myrtenal (**27**),[105] isopropylidene (*R*)-glyceraldehyde (**28**),[105] α-dialkylamino and α-(*N*-acylamino)aldehydes (**29**),[113,114] *N*-phenylsulfonyl-*L*-prolinal (30),[114] *N*-sulfinimines (**31**),[115] sugar derived aldehydes (**32-34**)[116] *etc.*, (Figure 3), have been employed in this fascinating reaction, to afford the resulting adducts with poor to high diastereoselectivities.

Figure 3

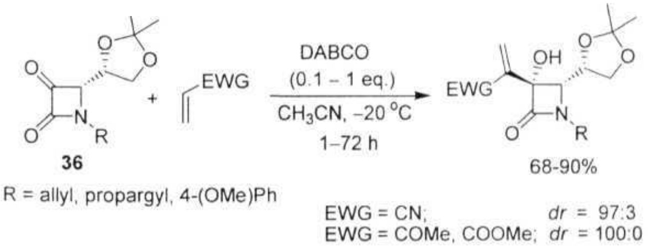


Kundig et al.[117,118] employed ortho substituted benzaldehyde tricarbonylchromium complex (35) as an electrophile in the Baylis-Hillman reaction with various activated olefins catalyzed by DABCO to afford the desired Baylis-Hillman adducts in >95% *de*. One representative example is presented in eq 9.



eq 9

Alcaide and co-workers[119] have reported a highly diastereoselective Baylis-Hillman reaction, using enantiopure 3-oxo-2-azetidinones (36) as chiral electrophiles, leading to the formation of interesting 3-substituted-3-hydroxy-p-lactam derivatives (eq 10).

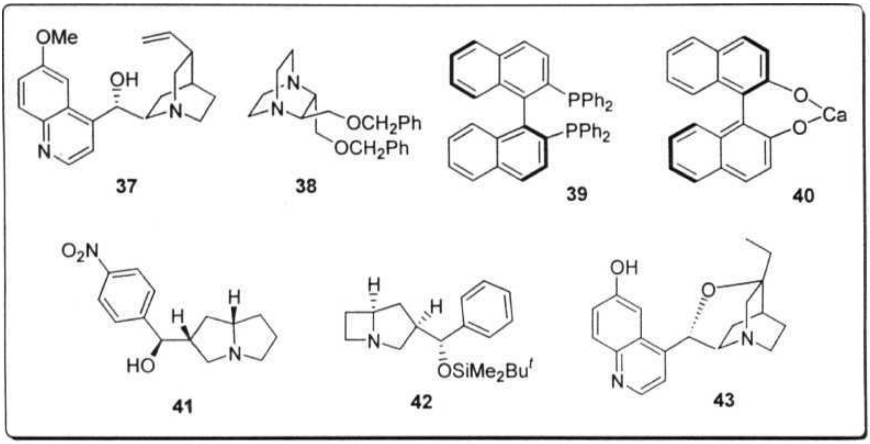


eq 10

ii) Chiral catalysts:

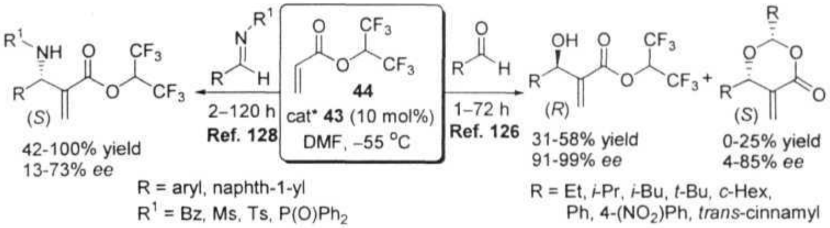
Efforts have been directed towards developing asymmetric version of Baylis-Hillman reaction using various chiral catalysts.[25-29] Thus, quinidine (**37**),[25,97] chiral DABCO (**38**) [120,121] (*S*)-BINAP (**39**),[122] calcium salt of (*R*)-BINOL (**40**),[123] enantiopure pyrrolizidine (41),[124] chiral bicyclic azetidine (42),[125] *β*-isocupreidine (**43**)[126-130] (Figure 4) have been used as chiral catalysts in this reaction with moderate to good success (up to 99% *ee*).

Figure 4



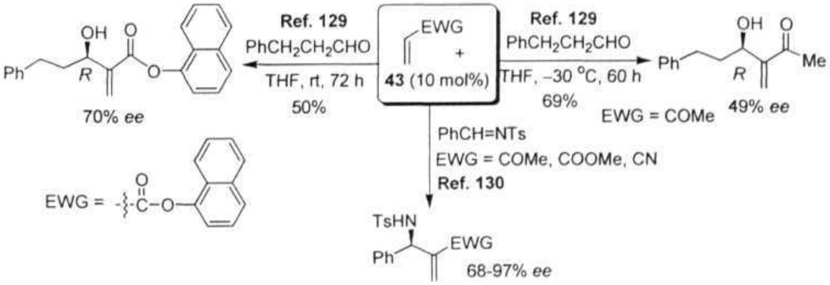
Hatakeyama and co-workers[126,127] have described an elegant asymmetric Baylis-Hillman reaction using β-isocupreidine (43), derived from quinidine (37), as a catalyst for the coupling between various aldehydes and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (44) (as activated alkene), thus, providing the desired adducts up to 99% enantiomeric purity (Scheme 15). Very recently, they have also successfully employed β-isocupreidine (43) as a catalyst for Baylis-Hillman reaction of aromatic imines with acrylate (44). It is interesting to note that the resulting compounds were formed with (*S*)-selectivity, in contrast to the aldehydes which afforded adducts with (*R*)-selectivity (Scheme 15).[128]

Scheme 15

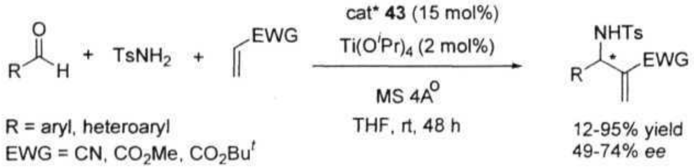


Later on, Shi and co-workers have utilized this catalyst (43) for the asymmetric Baylis-Hillman coupling of methyl vinyl ketone (MVK) and a-naphthyl acrylate with various aldehydes, to provide the desired adducts in poor to good enantioselectivities. One representative example is presented in Scheme 16.[129] Subsequently, they have also studied the application of this catalyst for coupling of aldimines with various activated alkenes to provide the desired adducts in high enantioselectivities (Scheme 16).[130]

Scheme 16

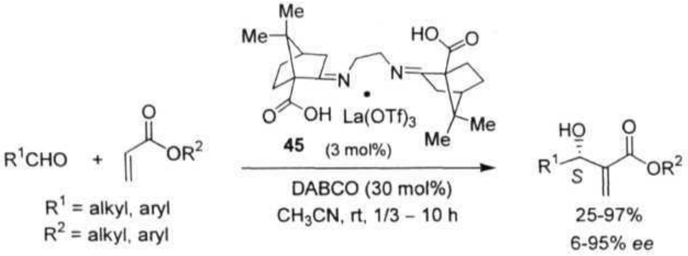


Recently, Adolfson and Balan, have also used *β*-isocupreidine (43) for the Baylis-Hillman coupling of arylaldehydes and tosylamide with activated alkenes (eq 11).[131]



eq 11

Chen and co-workers[132] have elegantly employed a novel bidendate ligand (45) derived from camphor, in the presence of Lewis acid, $La(OTf)_3$ for performing the asymmetric version of the Baylis-Hillman reaction between various aldehydes and acrylates, under the influence of DABCO, to provide the corresponding adducts in 6-95% enantioselectivities (eq 12).

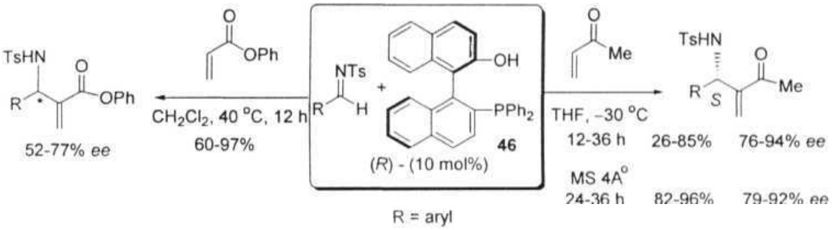


eq 12

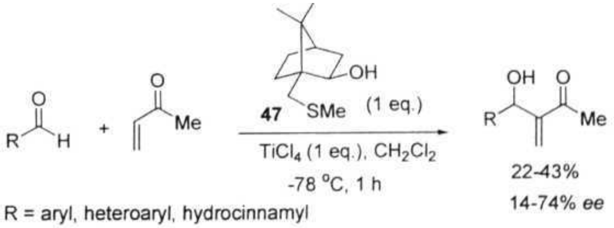
Very recently, Shi and Chen[133] have described an interesting asymmetric version of Baylis-Hillman reaction, employing (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-

2-ol (46) as a chiral phosphine catalyst, in the coupling of *N*-sulfonated imines with methyl vinyl ketone and phenyl acrylate to provide the corresponding adducts in high enantioselectivities (Scheme 17).

Scheme 17



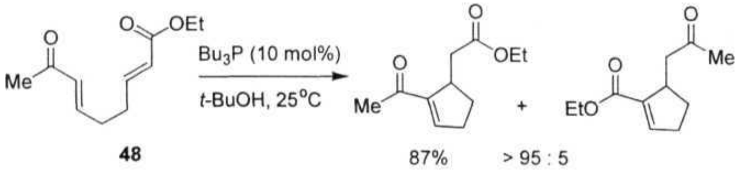
Katoaka and co-workers have reported asymmetric chalcogeno Baylis-Hillman reaction using various enantiopure hydroxy chalcogenides.[134,135] The catalyst 10-methyl-thioisoborneol (47) offered best results in the reaction between MVK and various aldehydes, thus providing the desired adducts up to 74% enantiomeric excess (eq 13).[134]



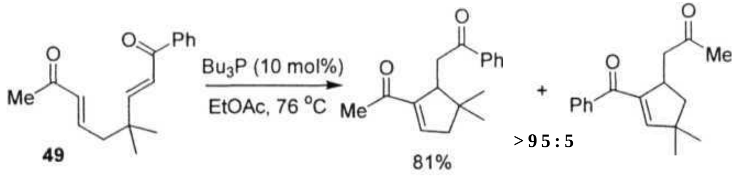
eq 13

INTRAMOLECULAR BAYLIS-HILLMAN REACTION

In spite of rapid advances in the Baylis-Hillman chemistry, the aspect of intramolecular Baylis-Hillman reaction has not been systematically investigated. Some of the very recent developments are presented in this section. Krische and co-workers[136] have described an interesting Bu_3P catalyzed cycloisomerization of bis(enones) (48 & 49). They have examined the effect of electronic (eq 14) and steric factors (eq 15) on cyclization.

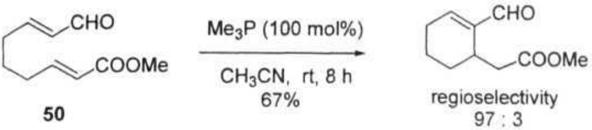


eq 14



eq 15

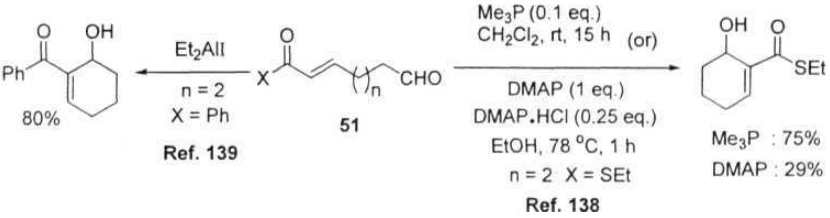
Intramolecular Baylis-Hillman reaction of diactivated dienes (50) to provide a convenient synthesis of functionalized cycloalkene derivatives has been reported by Roush and co-workers[137] (eq 16).



eq 16

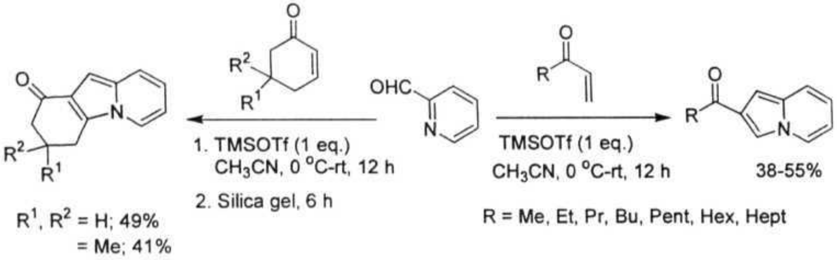
Intramolecular Baylis-Hillman reaction of a,p-unsaturated systems (51) containing enolizable aldehyde group, has been recently reported by Keck & Welch[138] (using Me_3P or DMAP, DMAP.HC1) and later on by Oshima and co-workers[139] (using Et_2AlI) (Scheme 18).

Scheme 18



Recently, our research group described the first example of an electrophile induced intramolecular Baylis-Hillman reaction *via* the treatment of activated alkenes with pyridine-2-carboxldehyde, under the influence of trimethylsilyl trifluoromethane-sulfonate (TMSOTf), leading to a novel synthesis of indolizine derivatives in one-pot operation (Scheme 19).

Scheme 19

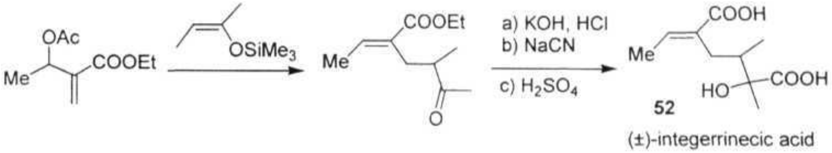


APPLICATIONS OF THE BAYLIS–HILLMAN ADDUCTS

The proximity of three chemospecific functional groups such as hydroxy group (or amino), olefin and electron withdrawing groups in the Baylis-Hillman adducts, have attracted the attention of organic chemists and in fact, these molecules have been employed in various stereoselective transformations methodologies, by appropriate tuning of the functional groups.[25-29] These adducts have also been successfully used as valuable synthons for the synthesis of various trisubstituted olefins, heterocycles, carbocycles, biologically active molecules and natural products.[25-29] Some of the important and recent developments on applications of **Baylis-Hillman adducts** have been presented in this section.

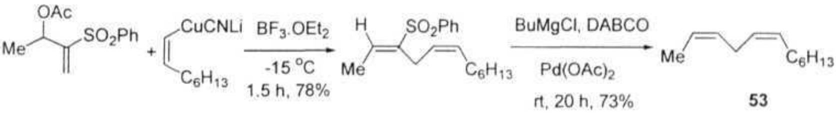
Drewes et al.[33] reported the synthesis of racemic integerrinecic acid (52) starting from ethyl 3-acetoxy-2-methylenebutanoate, acetate of the Baylis–Hillman adduct (Scheme 20).

Scheme 20



Knochel and co-workers[42,141] have described the stereoselective synthesis of skipped (*Z,Z*)-dienes (53) *via* the regioselective nucleophilic addition of lithium cyanocuprates to the acetate of Baylis-Hillman adduct, obtained from phenyl vinyl sulfone and acetaldehyde, following the reaction sequence as shown in Scheme 21.

Scheme 21



Our research group[142] developed a simple stereoselective synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2Z)-2-methylalk-2-enenitriles *via* the nucleophilic addition of hydride ion from lithium aluminum hydride [LAHrEtOH (1:1)] to methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles (derived from the corresponding Baylis-Hillman adducts) respectively (Scheme 22). This methodology has been successfully utilized for the synthesis of (*E*)-nuciferol (54), a biologically active terpenoid and the precursor of (Z)-nuciferol (55) (Figure 5).

Scheme 22

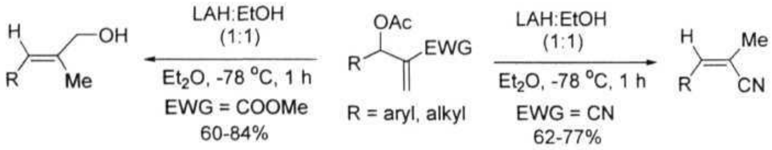
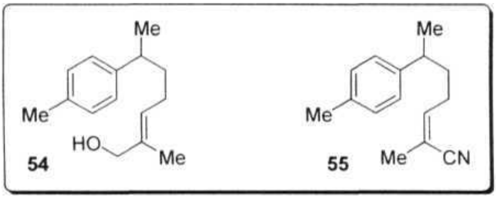
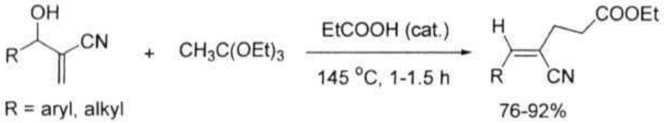


Figure 5



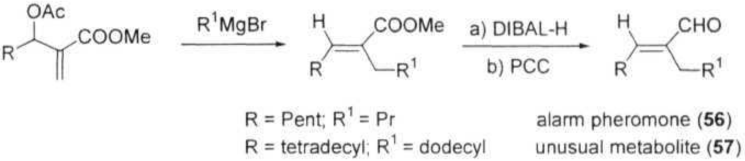
Simple stereoselective synthesis of trisubstituted alkenes *via* Johnson-Claisen rearrangenent of 3-hydroxy-2-methylenealkanenitriles, the Baylis-Hillman adducts derived from acrylonitrile, has been reported by our research group (eq 17).[143]



eq 17

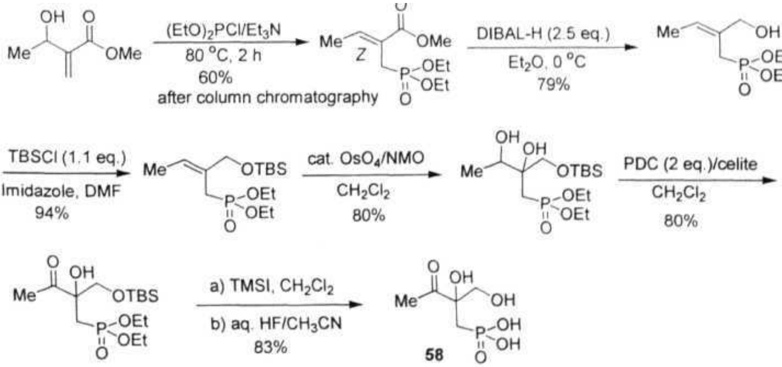
Our research group[144] developed a simple stereoselective synthesis of (2*E*)-2-substituted alk-2-enoates and (2Z)-2-substituted alk-2-enenitriles *via* the treatment of 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles respectively, with Grignard reagents. The efficacy of this methodology has been demonstrated by the synthesis of (2*E*)-2-butyloct-2-enal (56), an alarm pheromone component of the African weaver ant, *Oecophylla longinoda* and (2*E*)-2-tridecylheptadec-2-enal (57) an unusual metabolite from the red alga, *Laurencia* species (Scheme 23).[145]

Scheme 23



Fields described an efficient and convenient synthesis of phosphonothrixin (58), an important natural product starting from the Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate, following the reaction sequence as shown in Scheme 24.[146]

Scheme 24



In our laboratory, we have developed a simple and convenient synthesis for (*E*)-α-methylcinnamic acids *via* the nucleophilic addition of hydride ion from $NaBH_4$ to the acetates of the Baylis-Hillman adducts, followed by hydrolysis and crystallization (Scheme 25).[147] This methodology has been successfully employed for the synthesis of **(*E*)-*p*-(myristyloxy)-α-methylcinnamic** acid (59), a hypolipidemic active agent, which is also a precursor for another active hypolipidemic agent LK-903 (60) and [*E*]-*p*-(carbomethoxy)-a-methylcinnamic acid (61), a valuable synthon for an orally active serine protease inhibitor (62) (Figure 6).[147]

Scheme 25

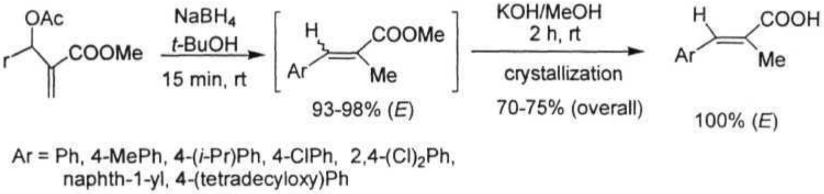
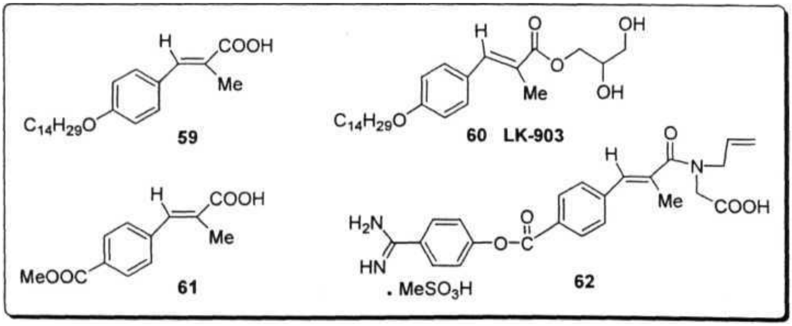
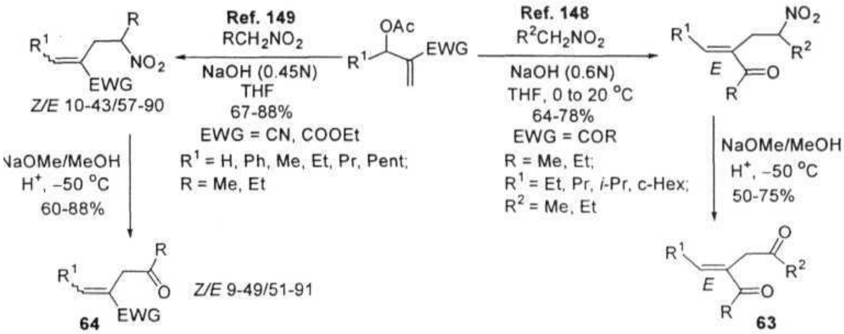


Figure 6



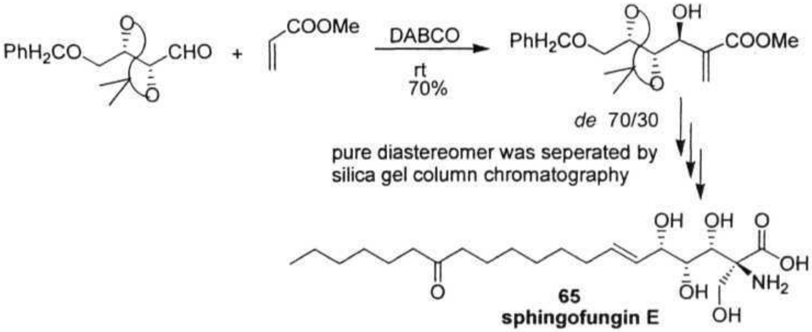
Amri and co-workers[148,149] have developed an interesting synthesis of 1,4-diketones (63) and keto alkene derivatives (64) *via* nucleophilic addition of nitroalkanes to the acetates of the Baylis–Hillman adducts, followed by Nef reaction (Scheme 26).

Scheme 26



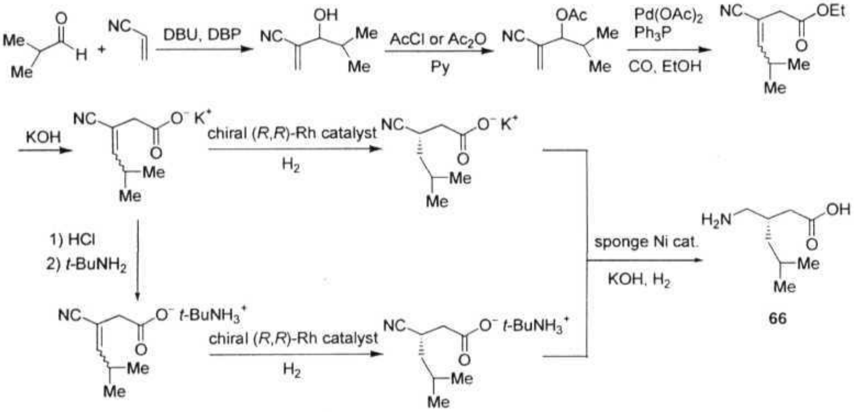
Lin and co-workers[150] successfully utilized the Baylis-Hillman methodology as the key step in the total synthesis of sphingofungin E (65) (Scheme 27).

Scheme 27



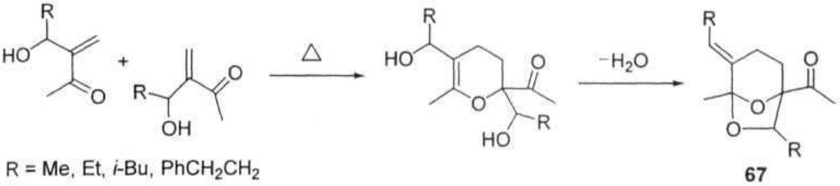
Recently, the Pfizer (pharmaceutical industry)[151] reported an interesting asymmetric synthesis of pregabalin (66), a future drug for the treatment of neuropathic pain, epilepsy, a variety of anxiety disorders and chronic pain conditions, using Baylis-Hillman reaction as the key step (Scheme 28).

Scheme 28



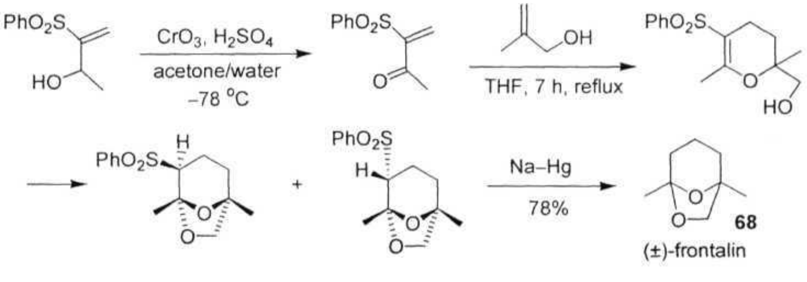
Hoffmann and co-workers[152] reported an intermolecular dehydrative double cyclization of the Baylis-Hillman adducts, obtained from methyl vinyl ketone, to provide bicyclic molecules containing functionalized 6,8-dioxabicyclo[3.2.1]octane moiety (67), an important basic framework present in a number of pheromones and other biologically active molecules (Scheme 29).

Scheme 29



Weichert and Hoffman developed an elegant synthesis of racemic frontalin (68), an interesting biologically active molecule, starting from 3-oxo-2-(phenylsulphonyl)but-l-ene, obtained *via* the Jones oxidation of corresponding Baylis-Hillman adduct, according to Scheme 30.[153]

Scheme 30



Our research group[154] has developed a convenient synthesis of 3-arylidene(alkylidene)-chroman-4-ones, from the Baylis-Hillman adducts, following the reaction sequence described in Scheme 31 and has subsequently utilized this methodology for **the** synthesis of bonducellin methyl ether (69), an important natural product and 3-(4-methoxybenzylidene)-6-methoxychroman-4-one, an antifungal agent **(70)** (Figure 7).

Scheme 31

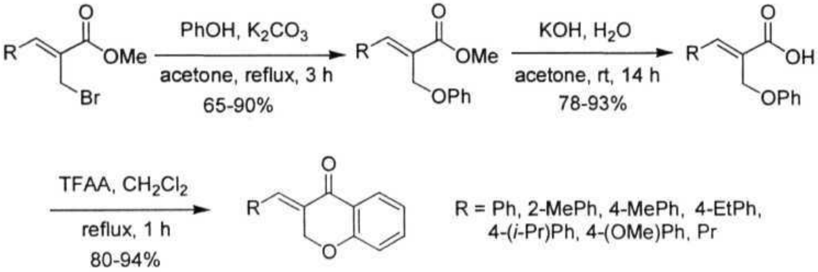
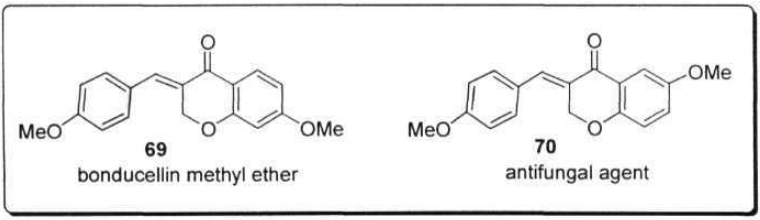


Figure 7

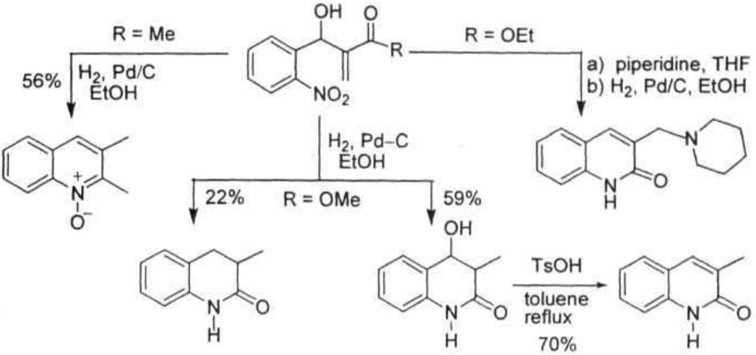


69
bonducellin methyl ether

70
antifungal agent

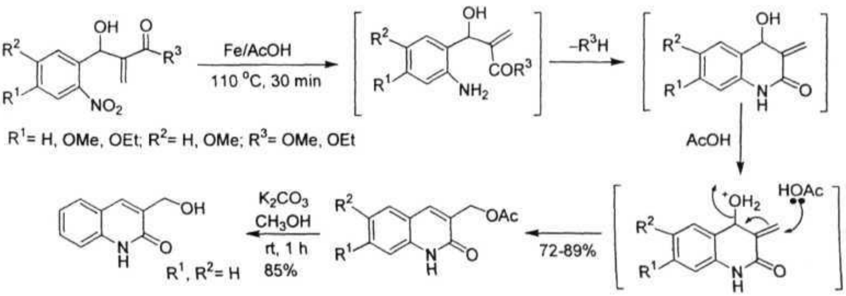
Kaye and co-workers have reported an interesting methodology for an efficient transformation of the Baylis-Hillman adducts, derived from *ortho*-nitrobenzaldehyde and **alkyl** vinyl ketones/acrylates, into quinoline derivatives *via* the catalytic hydrogenation using Pd/C (Scheme 32).[155]

Scheme 32



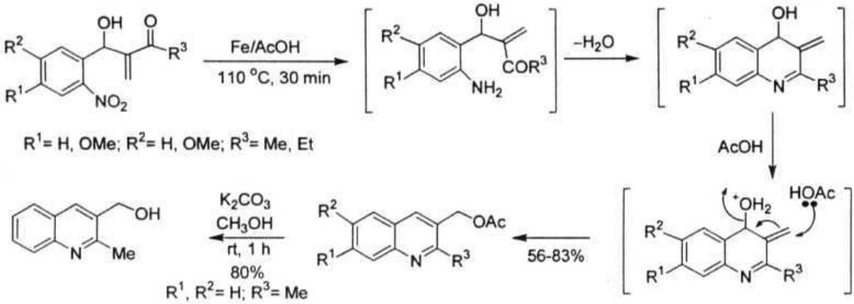
Later on, our research group has conveniently transformed the Baylis-Hillman alcohols derived from *o*-nitrobenzaldehydes and alkyl acrylates into functionalized (1*H*)-quinol-2-ones *via* the treatment with Fe/AcOH (Scheme 33).[156] Similarly, the Baylis-Hillman adducts obtained from *o*-nitrobenzaldehydes and alkyl vinyl ketones have been successfully transformed into quinolines, in one-pot operation (Scheme 34).[156]

Scheme 33



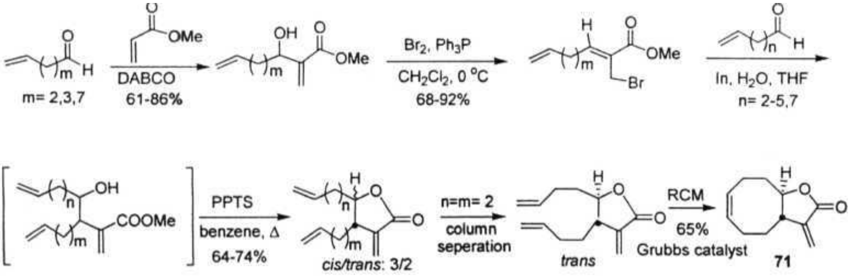
R^1= H, OMe, OEt; R^2= H, OMe; R^3= OMe, OEt

Scheme 34



Paquette and Mendez-Andino have described an interesting synthesis of bicyclic lactones 71 from the Baylis-Hillman adducts. One representative example is shown in the Scheme 35.[157]

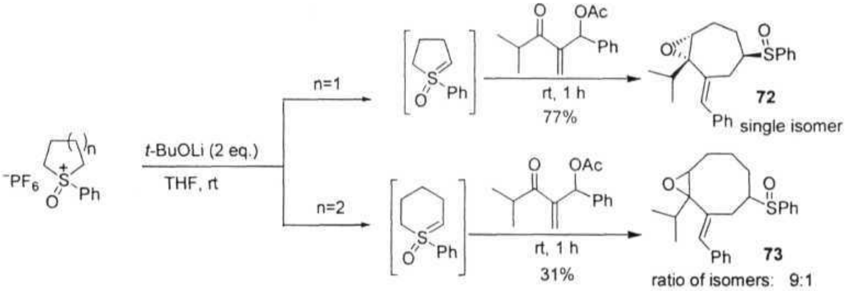
Scheme 35



Fujimoto and co-workers[158159] have described an interesting stereoselective synthesis of cycloheptene oxide derivatives 72 *via* a tandem Michael-intramolecular Corey-

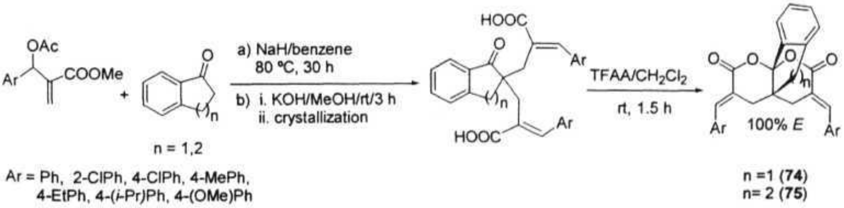
Chaykovsky reaction of the five membered cyclic oxosulfonium ylide with acetates of the Baylis-Hillman adducts. However, in the case of six membered oxosulfonium ylide, the resulting cyclooctene oxide derivatives 73 were obtained as mixture of stereoisomers in moderate yields. Representative examples are described in Scheme 36.

Scheme 36



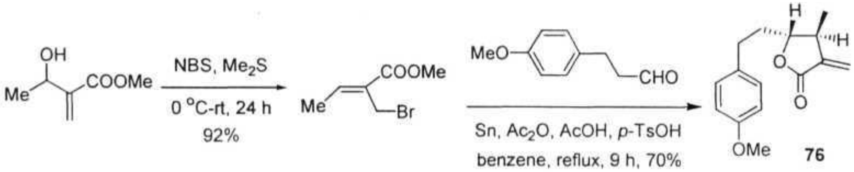
A simple and convenient three-step synthesis of functionalized [4.4.3] and [4.4.4]propellano-bislactones (74) & (75) from acetates of Baylis-Hillman adducts, has been developed by our research group (Scheme 37).[160]

Scheme 37



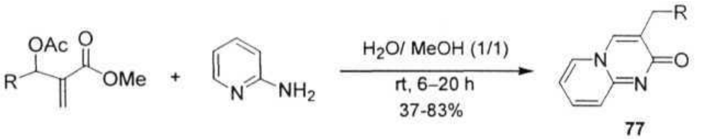
Bermojo et **al.**[161] have reported the synthesis of an interesting compound 76, from Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate (Scheme 38). This molecule is found to possess extremely interesting properties with regard to its apoptosis-inducing ability in HL-60 cells.

Scheme 38



76

An interesting facile, one-pot synthetic transformation of the acetates of the Baylis-Hillman adducts into fused pyrimidones (77) *via* the reaction with 2-aminopyridine in environment-friendly aqueous media, has been developed by our research group (eq 18).[162]



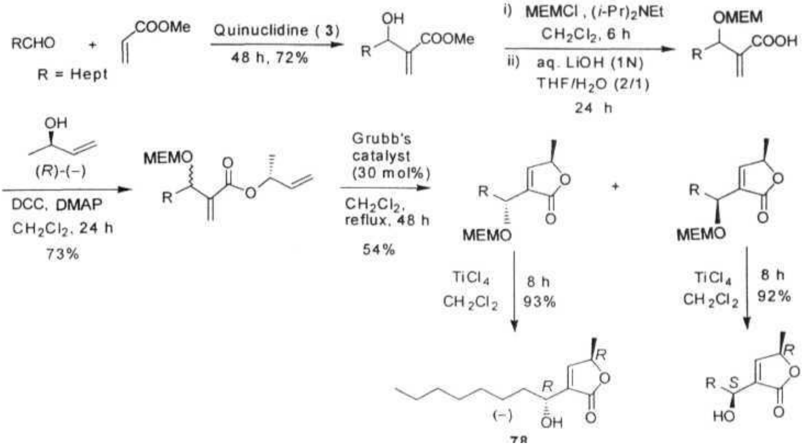
77

eq 18

R = Ph, 2-ClPh, 4-ClPh, 4-MePh, 4-EtPh, 4-(*i*-Pr)Ph, 3-(OMe)Ph, 4-(OMe)Ph, Pent

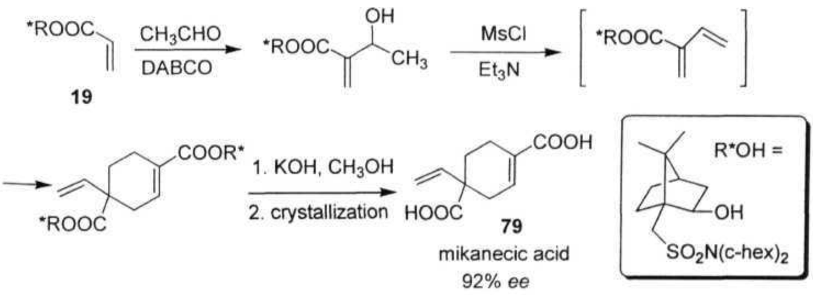
Very recently, Singh and co-workers[163] have reported a stereoselective synthesis of (-)-acaterin (78), a biologically important natural product from the Baylis–Hillman adduct, obtained from octanal and methyl acrylate according to Scheme 39.

Scheme 39



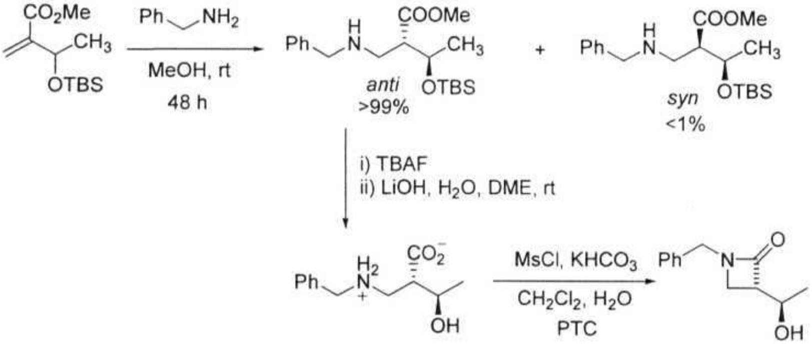
Our research group[164] described a simple enantioselective synthesis of mikanecic acid (79), an interesting terpene dicarboxylic acid, containing **quaternary vinylic chiral** center, from the Baylis-Hillman adduct derived from acetaldehyde and chiral acrylate (19) (Scheme 40).

Scheme 40



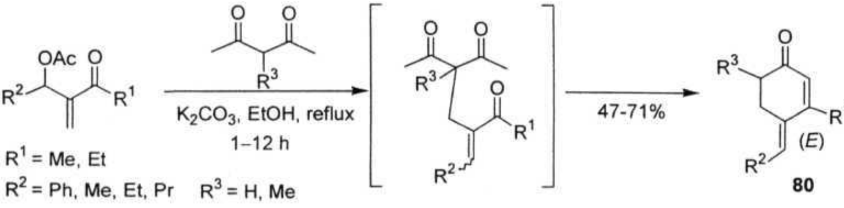
Perlmutter and Tabone have described a simple synthesis of azetidinone moiety of carbapenems *via* a highly *anti* diastereoselective Michael addition of benzylamine to *O*-protected Baylis-Hillman adducts. One representative example is presented in Scheme 41.[165,166]

Scheme 41



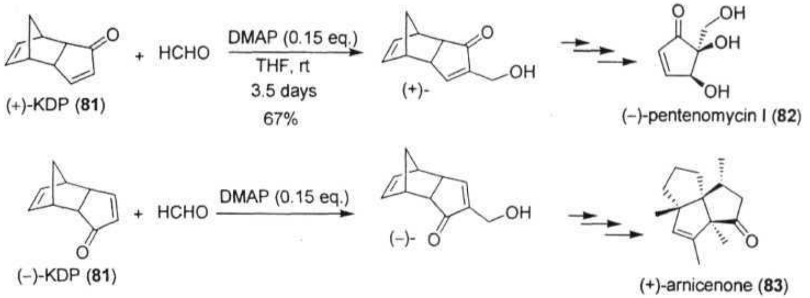
Chamakh and Amri transformed the acetates of the Baylis-Hillman adducts into alkylidene-2-cyclohexenones (80) *via* the treatment with aliphatic 1,3-diketones in the presence of K_2CO_3 in ethanol at reflux temperature (Scheme 42).[167]

Scheme 42



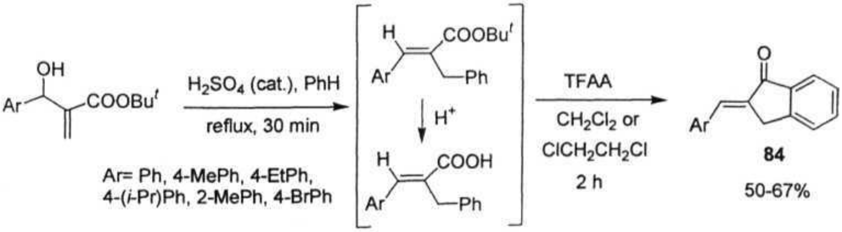
Ogasawara and co-workers[168,169] have successfully employed the Baylis-Hillman adducts derived from chiral bicyclic enones (+)- & (−)-**81** and formalin, in the synthesis of cyclopentanoid antibiotic (-)-pentenomycin I (82) and angular triquinane sesquiterpene (+)-arnicenone (83) respectively according to the Scheme 43.

Scheme 43



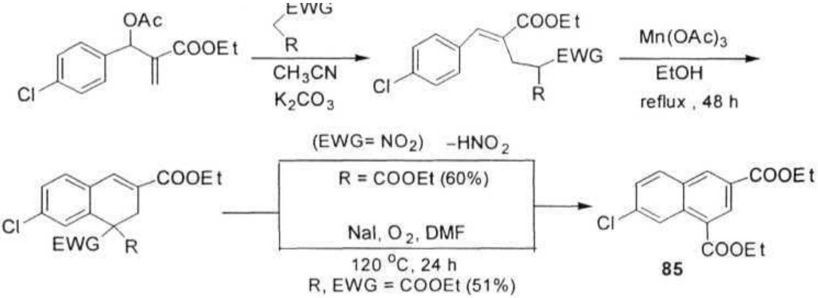
Our research group[170] developed a simple one-pot methodology for stereoselective transformation of Baylis-Hillman adducts, obtained from aromatic aldehydes and *tert.*-butyl acrylate, into (*E*)-2-arylideneindan-1-ones (84), involving one inter- and intramolecular Friedel-Crafts reactions according to Scheme 44.

Scheme 44



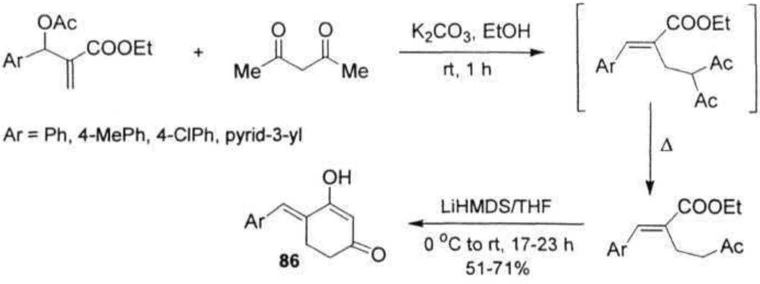
An elegant synthesis of 1,3-disubstituted naphthalenes (85) has been developed by Kim and co-workers[171] *via* manganese(III) acetate assisted radical cyclization and aromatization of the acetates of the Baylis–Hillman adducts. Representative examples are presented in Scheme 45. Very recently, they have also described an interesting methodology for the synthesis of 4-arylidenecyclohexane-l,3-diones (86), from the Baylis-Hillman acetates, following the reaction sequence as shown in Scheme 46.[172]

Scheme 45



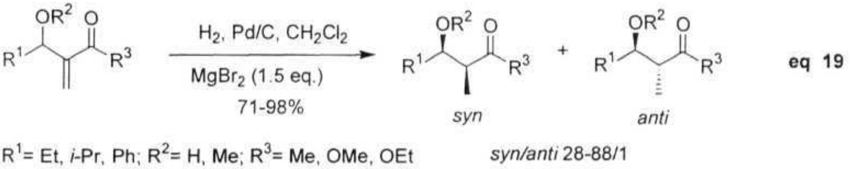
85

Scheme 46

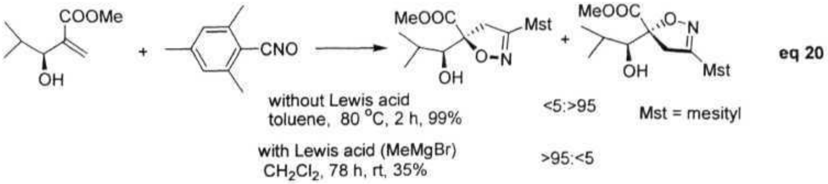


86

Diastereoselective catalytic hydrogenation (including its asymmetric version) of the Baylis-Hillman adducts has been well studied by Brown,[173,177] Yamamoto,[56,57] Noyori,[178] Sato[88] and Coelho.[179,180] Recently, Bouzide reported a highly *syn*-diastereoslelective heterogeneous hydrogenation of Baylis-Hillman adducts with palladium on carbon combined with $MgBr_2$, to afford the corresponding *syn*-aldol derivatives (eq 19).[181]

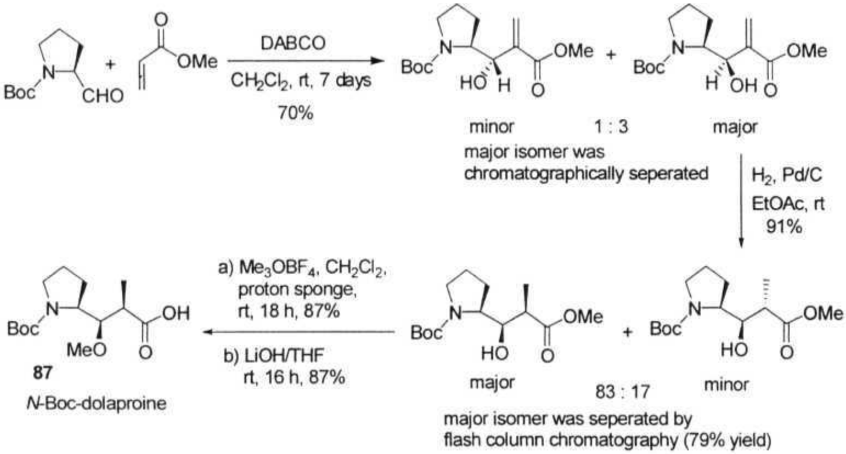


Fisera and co-workers[182,183] have reported highly diastereoselective 1,3-dipolar cycloaddition reactions of Baylis-Hillman adducts with mesitonitrile oxide. They have observed reversal of diastereoselectivity on addition of Grignard reagent. One representative example is shown in eq 20.



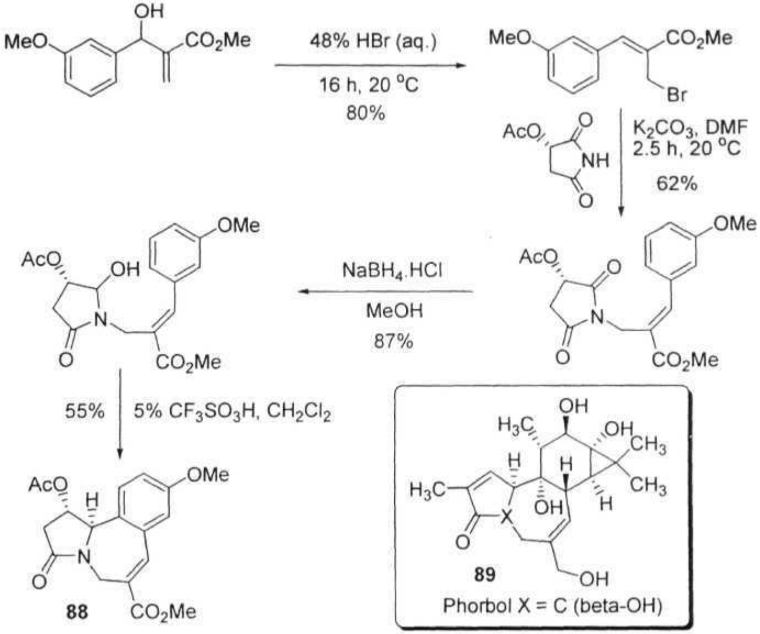
Very recently, Almeida and Coelho have described an elegant synthesis of *N*-Boc-dolaproine (87), an amino acid residue of the antineoplastic pentapeptide Dolastatin 10 using the Baylis–Hillman reaction as the key step (Scheme 47).[184]

Scheme 47



Marson and co-workers[185] have reported a convergent stereo-controlled construction of 5-6-7 tricylic aza analogue (88) of phorbol (89) (a representative diterpene of tigliane skeleton), from the Baylis-Hillman adduct according to Scheme 48.

Scheme 48


OH
MeO
CO2Me
48% HBr (aq.)
16 h, 20 °C
80%
MeO
CO2Me
Br
AcO
O
NH
O
K2CO3, DMF
2.5 h, 20 °C
62%
OMe
AcO
O
N
O
CO2Me
NaBH4.HCl
MeOH
87%
OMe
AcO
OH
N
O
CO2Me
55%
5% CF3SO3H, CH2Cl2
AcO
H
OMe
N
O
88
CO2Me
OH
H3C
OH
CH3
H
H
CH3
H3C
OH
H
X
O
89
OH
Phorbol X = C (beta-OH)

Objectives, Results and Discussion

From the previous section it is quite clear that the Baylis-Hillman reaction has been and continues to be one of the most powerful and important carbon-carbon bond forming reactions, providing a unique class of densely functionalized molecules whose applications in a variety of organic transformations have been well documented.[25-29] Our research group has been actively working on various aspects of this reaction for the last nineteen years with the main objective of developing this reaction into a valuable source for stereoselective processes and has in fact contributed significantly in this direction.[25,29] This thesis deals with some aspects of the Baylis-Hillman reaction and applications with the following objectives.

Objectives

1). To employ alkyl 2-(bromomethyl)prop-2-enoates, derived from Baylis-Hillman adducts, as valuable electrophiles in the Baylis-Hillman coupling reaction with various activated alkenes with a view to develop a one-pot convenient methodology for synthesis of 2,4-functionalized 1,4-pentadienes.

2). To employ the Baylis-Hillman adducts as valuable substrates for tandem construction of C-0 and C-C bonds involving Prins type and Friedel-Crafts type reactions with an aim of developing one-pot facile methodology for synthesis of 2-benzoxepine derivatives.

3). To develop highly diastereoselective methodology for transformation of alkyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates, obtained from the Baylis-Hillman adducts, derived from chiral acrylates and aldehydes, into propargylic and phenolic ethers of Baylis-Hillman adducts.

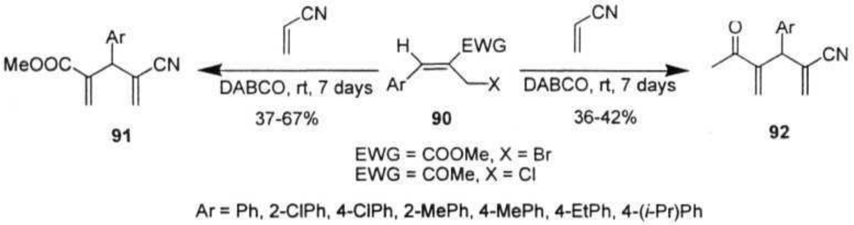
4). To describe the first organobase mediated Cannizzaro reaction of reactive aldehydes.

Results and Discussion

Applications of alkyl 2-(bromomethyl)prop-2-enoates as valuable electrophiles in the Baylis-Hillman reaction: a one-pot facile synthesis of 2,4-functionalized 1,4-pentadienes

Although a variety of electrophiles have been extensively used in this fascinating reaction,[25-29] the applications of allyl halides, yet another highly important class of carbon electrophiles, in the Baylis-Hillman reaction have not been well explored. We have recently described, for the first time, the application of methyl (2Z)-2-(bromomethyl)alk-2-enoates (90, EWG = COOMe, X = Br) and (3Z)-4-aryl-3-(chloromethyl)but-3-en-2-ones (90, EWG = COMe, X = Cl), the allyl halides, obtained from the corresponding Baylis-Hillman adducts, as suitable electrophiles in the Baylis-Hillman coupling reaction with acrylonitrile, in the presence of DABCO, thus providing a simple and novel synthesis of (3-substituted 2,4-functionalized 1,4-pentadienes) 3-aryl-4-cyano-2-methoxycarbonylpenta-1,4-dienes (91) and 2-acetyl-3-aryl-4-cyanopenta-1,4-dienes (92) respectively (Scheme 49).[186]

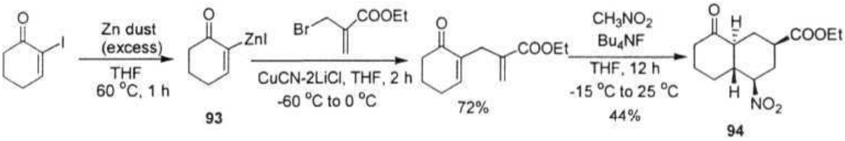
Scheme 49



Literature survey reveals that 1,4-diene framework constitutes an important structural assembly owing to the presence of this structural unit in various molecules of biological importance[187-189] and in fact, 1,4-pentadiene skeleton occupies a special place in 1,4-diene framework due to the high degree of applicability of this moiety in various aspects of organic synthesis.[190-193] Hence, the development of new, simple and efficient methodologies for the synthesis of 1,4-pentadiene framework represents an important and attractive endeavor in the area of synthetic organic chemistry.[194-197] Relevant representative examples highlighting the syntheses of 1,4-pentadienes and their applications are described in this section.

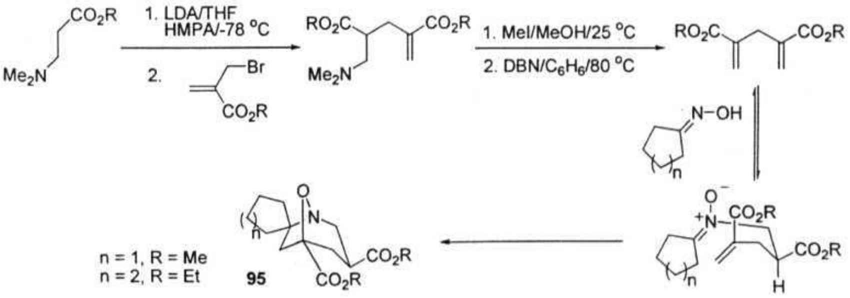
Prasad and Knochel have developed a simple methodology for the synthesis of cyclohexane based 1,4-pentadienes, *via* the reaction of 2-zincated cyclohexenone (93) with ethyl 2-(bromomethyl)prop-2-enoate and have successfully transformed into polyfunctionalized decalin (94) diastereoselectively (Scheme 50).

Scheme 50

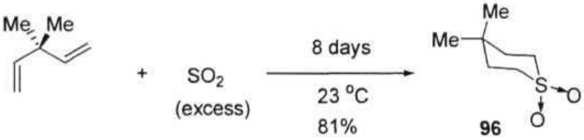


Grigg et al.[191] have described a facile synthesis of 1,4-pentadiene diesters and subsequently utilized them as bifunctional Michael acceptors/dipolarophile components in a tandem Michael addition-1,3-dipolar cycloaddtition reactions with ketoximes to provide spirohetero-bicyclic adducts (95) (Scheme 51).

Scheme 51



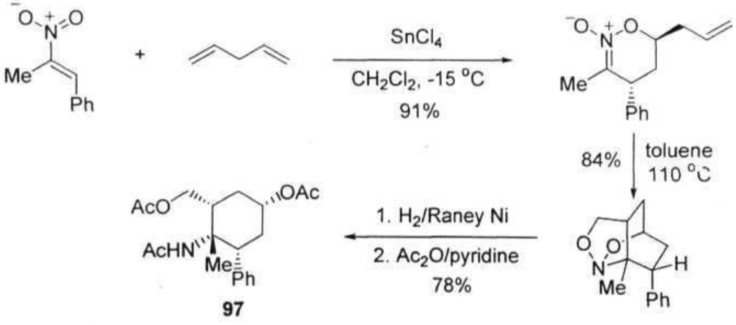
Vogel and co-workers[192] have described the synthesis of sulfolane (96) *via* the treatment of 3,3-dimethylpenta-1,4-diene with SO_2 (eq 21).



96

Denmark et al.[193] have reported $SnCl_4$-promoted tandem inter [4+2] / intra [3+2] cycloaddition of nitroalkene to the 1,4-penatadiene, leading to the stereoselective formation of functionalized cyclohexane derivative (97) according to Scheme 52.

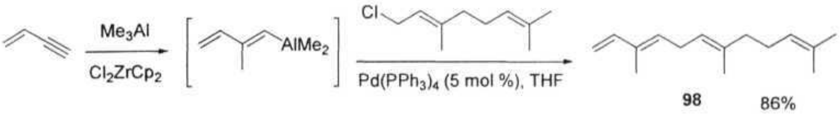
Scheme 52



97

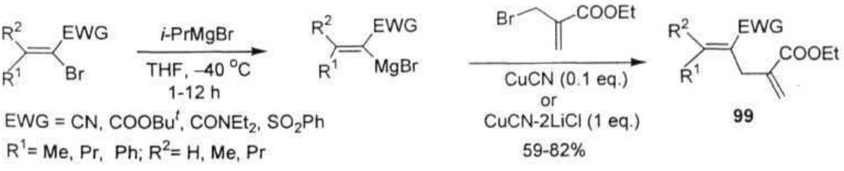
Negishi and Matsushita have developed a simple selective synthesis of 1,4-dienes *via* Pd-catalyzed stereo- and regiospecific coupling of allylic derivatives with alkenyl and arylmetals, and successfully applied this strategy for the one-step synthesis of a-farnesene (98), a terpenoid molecule (Scheme 53).[194]

Scheme 53



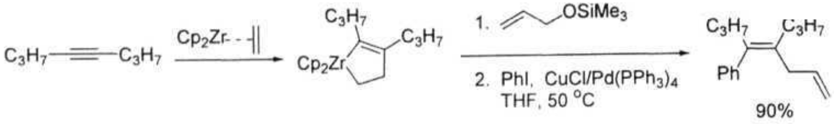
Knochel and co-workers[195] have developed an important synthesis of functionalized 1,4-pentadienes (99) *via* the reaction of ethyl 2-(bromomethyl)prop-2-enoate with alkenylmagnesium derivatives obtained *via* halide-magnesium exchange with *i*-PrMgBr (Scheme 54).

Scheme 54

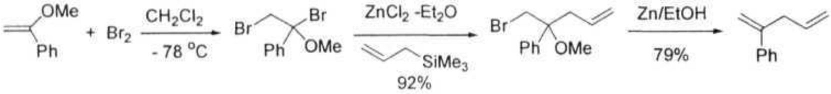


Takahashi and co-workers[196] have described an interesting synthesis of 1,4-pentadienes *via* the coupling of alkenylzirconocenes with aryl iodides in the presence of $CuCl/Pd(PPh_3)_4$ as catalytic system. One representative example is presented in Scheme 55.

Scheme 55



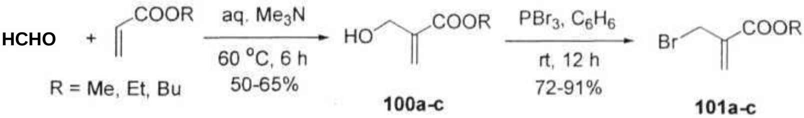
Mayr and co-workers[197] have developed a versatile synthesis of 1,4-pentadienes starting from vinyl ethers following the reaction sequence as described in the Scheme 56 (One representative example is presented).



Since we have already developed a simple methodology for synthesis of 3-substituted 2,4-functionalized 1,4-pentadienes[186] using the Baylis-Hillman chemistry (Scheme 49), it occurred to us that if we can also utilize the Baylis-Hillman chemistry for generating simple procedures for synthesis of 2,4-functionalized 1,4-pentadienes without any substitution at the 3-position, this methodology will not only compliment our earlier procedure but also demonstrate the importance of Baylis-Hillman chemistry in organic synthesis.

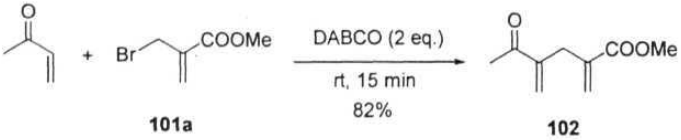
In this direction, it appeared to us that the Baylis-Hillman reaction between alkyl 2-(bromomethyl)prop-2-enoates and the activated alkenes would provide the desired 1,4-pentadiene framework with appropriate functionalities at 2- and 4-positions. Accordingly, we have first selected methyl 2-(bromomethyl)prop-2-enoate **(101a)** as a carbon electrophile and methyl vinyl ketone (MVK) as an activated alkene for performing the Baylis-Hillman reaction. The desired allyl bromide **(101a)** was synthesized *via* the treatment of methyl 2-(hydroxymethyl)prop-2-enoate **(100a)** with PBr_3 according to the literature procedure.[198] The required Baylis-Hillman adduct (100a) was obtained *via* the coupling of paraformaldehyde with methyl acrylate, mediated by aqueous trimethylamine, according to the procedure developed in our laboratory (Scheme 57).[79]

Scheme 57



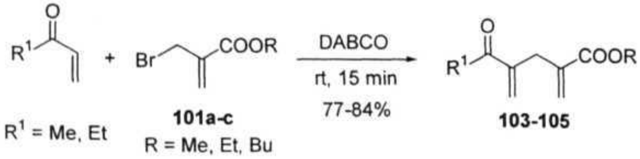
Next we examined the Baylis-Hillman coupling between MVK, which is a reactive activated alkene and methyl 2-(bromomethyl)prop-2-enoate **(101a)**. The best results in this direction were achieved when methyl 2-(bromomethyl)prop-2-enoate **(101a)** (1 mmol) was treated with MVK (1 mL) in the presence of DABCO (2 mmol) at room temperature for 15min, thus providing 4-acetyl-2-methoxycarbonylpenta-l,4-diene

(102) in 82% yield, after usual work-up followed by column chromatography (silica gel, 4% EtOAc in hexanes) (eq 22). Structure of this molecule, was established by IR, ^{1}H NMR (Spectrum 1), ^{13}C NMR (Spectrum 2), mass spectral data and elemental analysis.



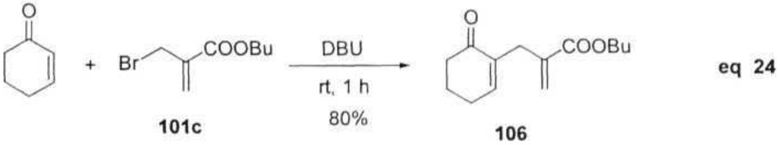
eq 22

With a view to understand the generality of the reaction, we have prepared representative alkyl 2-(bromomethyl)prop-2-enoates (**101b,c**) from the corresponding Baylis-Hillman adducts **(100b,c)** (Scheme 57) and successfully employed these allyl bromides **(lOla-c)** in the Baylis-Hillman coupling with alkyl vinyl ketones (methyl vinyl ketone/ethyl vinyl ketone), in the presence of DABCO, to provide 4-alkanoyl-2-alkoxycarbonylpenta-l,4-dienes (103-105) in 77-84% yields (eq 23 & Table 1). All these molecules were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses.



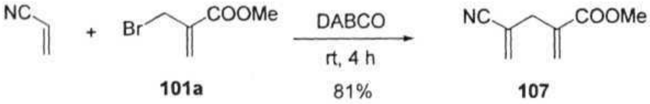
eq 23

After having successfully employed these allyl bromides **(101a-c)** in the Baylis-Hillman coupling with alkyl vinyl ketones (acyclic enones), we directed our studies to examine the applicability of cyclic enones in this reaction sequence. In this direction, we have employed cyclohex-2-enone for coupling with butyl 2-(bromomethyl)prop-2-enoate **(101c)** in the presence of DABCO under various conditions. But the reaction was not clean. However, the best result was obtained when we have performed the reaction between cyclohex-2-enone (1 mL) and butyl 2-(bromomethyl)prop-2-enoate **(101c)** (1 mmol) in the presence of DBU (2 mmol), at room temperature for 1 h, to provide 2-[2-(butoxycarbonyl)prop-2-en-1-yl]cyclohex-2-en-1-one **(106),** in 80% yield, after usual work-up followed by column chromatography (silica gel, 4% EtOAc in hexanes) (eq 24). Structure of this molecule was established by IR, ^{1}H NMR (Spectrum 3), ^{13}C NMR (Spectrum 4), mass spectral data and elemental analysis.



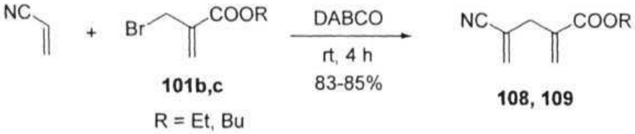
eq 24

With a view to expanding the scope of this methodology, we have next examined the reaction of acrylonitrile as an activated alkene in the Baylis-Hillman reaction with methyl 2-(bromomethyl)prop-2-enoate **(101a).** The best results were obtained when methyl 2-(bromomethyl)prop-2-enoate **(101a)** (1 mmol) was treated with acrylonitrile (1 mL) in the presence of DABCO (2 mmol) at room temperature for 4 h, to provide methyl 2-methylidene-4-cyanopent-4-enoate **(107)**, in 81% yield, after usual work-up followed by column chromatography (silica gel, 4% EtOAc in hexanes) (eq 25). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 5), ^{13}C NMR (Spectrum 6), mass spectral data and elemental analysis.



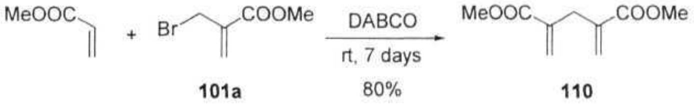
eq 25

Encouraged by this result, we have then synthesized representative class of 4-cyano-2-alkoxycarbonylpenta-1,4-dienes **(108, 109)** *via* the reaction between allyl bromides (**101b,c**) and acrylonitrile under the influence of DABCO (eq 26 & Table 1). All these molecules were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses.



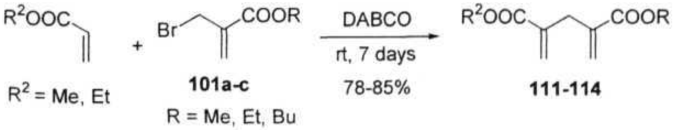
eq 26

Thus, we have successfully employed alkyl vinyl ketones, cyclohex-2-enone and acrylonitrile as activated alkenes in the Baylis-Hillman coupling with alkyl 2-(bromomethyl)prop-2-enoates (**101a-c**), thus leading to the development of a simple methodology for synthesis of functionalized 1,4-pentadienes containing ester and keto functionalities at 1 & 4- positions and ester & nitrile functionalities at 1,4-positions. With an objective of developing a general synthesis of 1,4-pentadiene containing ester functionalities at both 1- and 4-positions, we have examined the coupling of methyl acrylate with allyl bromide, methyl 2-(bromomethyl)prop-2-enoate **(101a).** The best results were obtained when methyl 2-(bromomethyl)prop-2-enoate **(101a)** (1 mmol) was treated with methyl acrylate (1 mL) in the presence of DABCO (2 mmol) at room temperature for 7 days, to provide 2,4-di(methoxycarbonyl)penta-l,4-diene (**110**), in 80% yield, after usual work-up followed by column chromatography (silica gel, 4% EtOAc in hexanes) (eq 27 & Table 1). Structure of this molecule was confirmed by IR, ^{1}H NMR, C NMR, mass spectral data and elemental analysis



eq 27

We have next performed the coupling reaction of representative alkyl 2-(bromomethyl)prop-2-enoates (**101a-c**) with alkyl acrylates (methyl acrylate and ethyl acrylate) in the presence of DABCO (for 7 days), to afford 2,4-dialkoxycarbonylpenta-1,4-dienes (**111-114**) in 78-85% yields (eq 28 & Table 1). All these molecules were characterized by IR, ^{1}H NMR (See: Spectra 7 & 9 for molecules **111** & **114** respectively), ^{13}C NMR (See: Spectra 8 & 10 for molecules **111** & **114** respectively) spectral data and elemental analyses.



eq 28

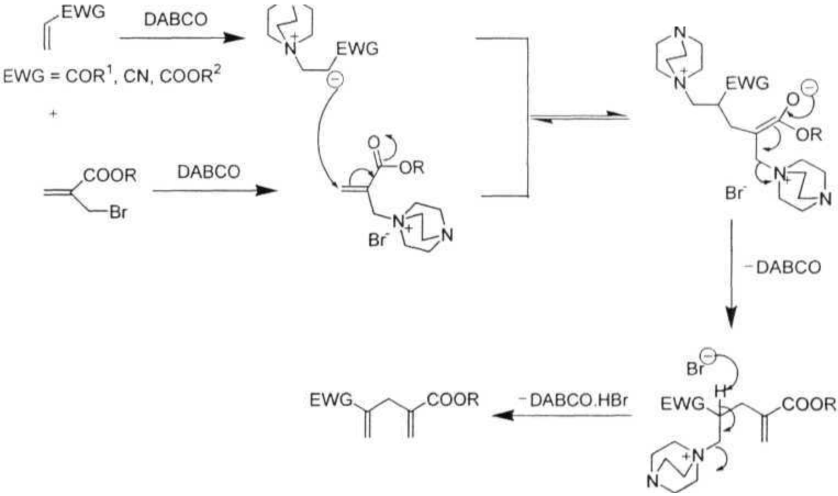
Table 1. Synthesis of functionalized 1,4-pentadienes[a,b,c,d]

S.No	Allyl bromide	Activated alkene	Product[e]	Yield (%)[f]
1	**101a**	**Methyl vinyl ketone**	**102**[a,g]	**82**
2	**101b**	**Methyl vinyl ketone**	**103**[a]	**78**
3	**101c**	**Methyl vinyl ketone**	**104**[a]	**84**
4	**101a**	**Ethyl vinyl ketone**	**105**[a]	77
5	**101c**	Cyclohex-2-enone	**106**[b,g]	80
6	**101a**	Acrylonitrile	**107**[c]	**81**
7	**101b**	**Acrylonitrile**	**108**[c]	83
8	**101c**	Acrylonitrile	**109**[c,g]	85
9	**101a**	Methyl acrylate	**110**[d,h]	**80**
10	**101b**	Methyl acrylate	**111**[d]	**84**
11	**101c**	Methyl acrylate	**112**[d,g]	**85**
12	**101a**	Ethyl acrylate	**111**[d]	**81**
13	**101b**	Ethyl **acrylate**	**113**[d,h]	82
14	**101c**	Ethyl acrylate	**114**[d]	78

a) All the reactions were carried out on 1 mmol scale of allyl bromides (101a-c) with alkyl vinyl ketone (1 mL) in the presence of DABCO (2 mmol) at room temperature for 15 min. b) The reaction was carried out on 1 mmol scale of allyl bromide (101c) with cyclohex-2-enone (1 mL) in the presence of DBU (2 mmol) at room temperature for 1 h. c) All the reactions were carried out on 1 mmol scale of allyl bromides (**101a-c**) with acrylonitrile (1 mL) in the presence of DABCO (2 mmol) at room temperature for 4 h. d) All the reactions were carried out on 1 mmol scale of allyl bromides (**101a-c**) with alkyl acrylate (1 mL) in the presence of DABCO (2 mmol) at room temperature for 7 days. e) All the products were obtained as colorless liquids and gave satisfactory IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses. f) Isolated yields of the pure products (based on allyl bromides) after column chromatography (silica gel, 4% EtOAc in hexanes). g) These products were also characterized by mass spectral analyses. h) These molecules are known in the literature.[191] ^{1}H NMR spectral data of molecule **113** is reported[191] and our data is in agreement with that of the literature.

A plausible mechanism for the formation of 1,4-pentadienes in the reaction between alkyl 2-(bromomethyl)prop-2-enoates and various activated alkenes in the presence of DABCO, is described in the Scheme 58. We have earlier proposed a similar mechanism for synthesis of 3-substituted 2,4-functionalized 1,4-pentadienes.[186]

Scheme 58

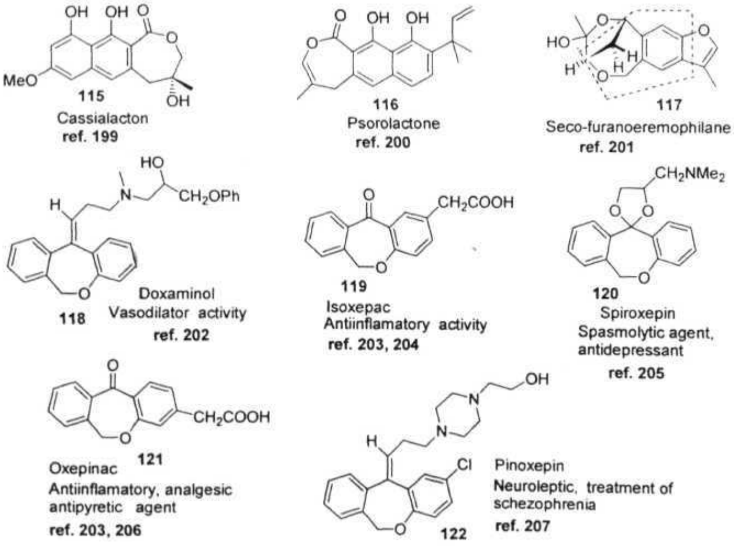


In conclusion, we have successfully employed alkyl 2-(bromomethyl)prop-2-enoates as useful electrophiles for Baylis-Hillman coupling with various activated alkenes thus leading to the development of a one-pot convenient methodology for synthesis of 2,4-functionalized 1,4-pentadienes.

Tandem construction of C-O and C-C bonds: a one-pot facile transformation of the Baylis-Hillman adducts into 2-benzoxepine derivatives

2-Benzoxepine moiety is an important structural unit present in many natural products and biologically important molecules which are found to be antiinflamatory, spasmolytic, analgesic, antipyretic, neuroleptic, antinaphylactic, hypotensive, antiulcer agents and are also found useful for treatment of depression and schizophrenia.[199-210] Some of the important and representative examples **(115-122)** are shown below (Figure 8).

Figure 8



115
Cassialacton
ref. 199

116
Psorolactone
ref. 200

117
Seco-furanoeremophilane
ref. 201

118 Doxaminol
Vasodilator activity
ref. 202

119
Isoxepac
Antiinflamatory activity
ref. 203, 204

120
Spiroxepin
Spasmolytic agent, antidepressant
ref. 205

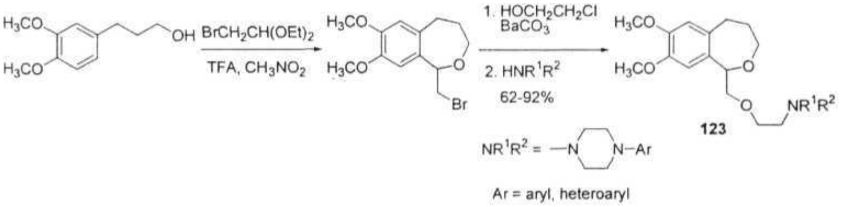
121
Oxepinac
Antiinflamatory, analgesic antipyretic agent
ref. 203, 206

122
Pinoxepin
Neuroleptic, treatment of schezophrenia
ref. 207

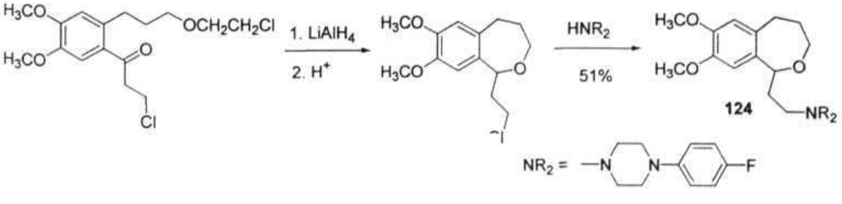
Due to their interesting and important biological properties, development of simple and convenient methodologies for the synthesis of 2-benzoxepine derivatives represents an attractive and interesting endeavor in synthetic organic chemistry and medicinal chemistry and in fact, a number of methodologies/strategies are reported in the literature for the synthesis of these molecules (Schemes 59-65).[203, 208-213]

TenBrink and co-workers[208] have developed a simple methodology for the synthesis of 2-benzoxepines **(123),** which are active antinaphylactic agents (Scheme 59). Subsequently, they have also reported an alternative route to the 2-benzoxepine derivative (**124**), which showed hypotensive activity (Scheme 60).[209]

Scheme 59

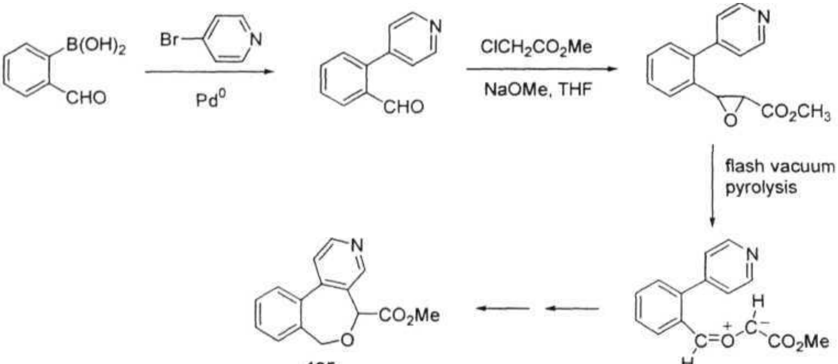


Scheme 60



Sharp and O'Shea have elegantly synthesized hetero-fused dihydrobenzoxepines **(125)** *via* 1,7-electrocyclisation of carbonyl ylides. One representative example is presented in Scheme 61.[210]

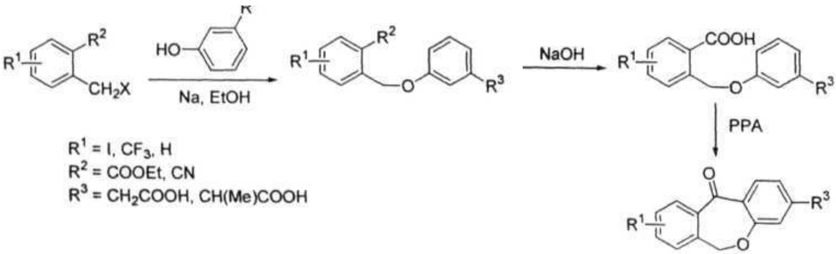
Scheme 61



125

Ueno and co-workers[203] have described an interesting synthesis of various dibenzoxepine derivatives **(126),** following a general route outlined in the Scheme 62. These compounds were found to possess good anti inflammatory activity.

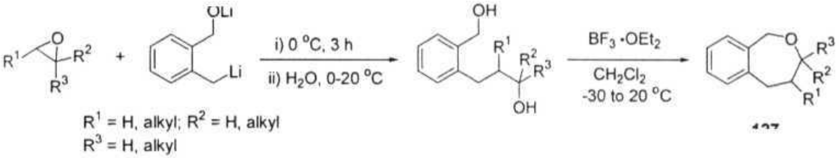
Scheme 62



126

Yus and co-workers[211] have reported a simple methodology for the synthesis of tetrahydrobenzoxepines (127) *via* the reaction of functionalized organolithium compounds with substituted oxiranes, followed by dehydration of the 1,6-diols (Scheme 63).

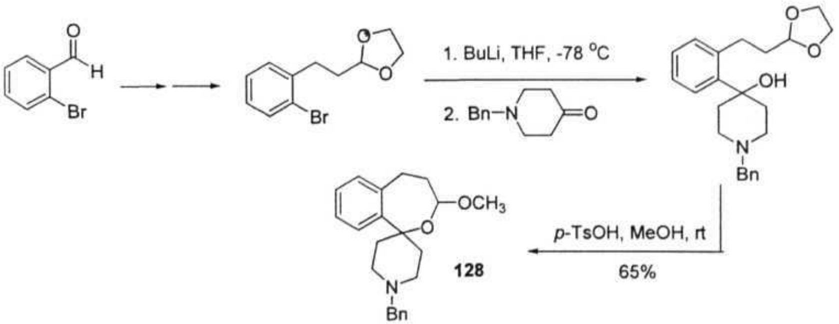
Scheme 63



127

Very recently, Maier and Wunsch have described an elegant synthesis of biologically active spiro-2-benzoxepine derivatives (128), starting from 2-bromobenzaldehyde as shown in the Scheme 64 (One representative example is presented).[212]

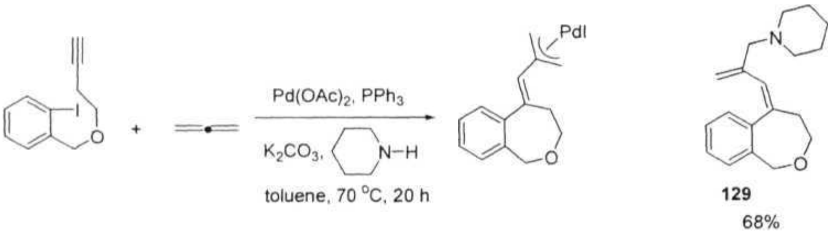
Scheme 64



128

Grigg and co-workers[213] developed an interesting methodology for the synthesis of 2-benzoxepine derivatives (129) *via* palladium catalyzed cyclization, following the reaction sequence as described in Scheme 65 (One representative example is presented).

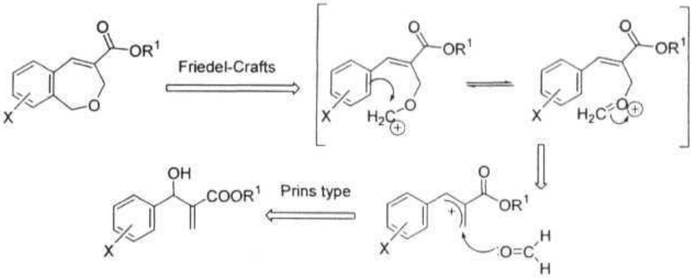
Scheme 65



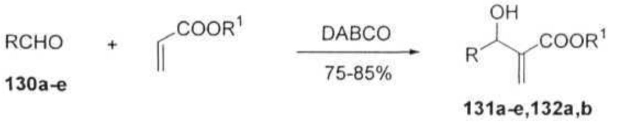
129

During our ongoing research program on heterocyclic chemistry[140,154,156,160,162,214] we required various 2-benzoxepine derivatives. We have envisioned that Baylis-Hillman adducts could be directly transformed to 2-benzoxepine derivatives *via* the construction of C-0 bond followed by simultaneous construction of C-C bond. We have also envisaged that the C-0 bond could be constructed through the Prins type reaction on the Baylis-Hillman adducts and the C-C bond could be simultaneously constructed through the Friedel-Crafts reaction as there would be a carbocation (oxonium ion) (according to the retrosynthetic pathway as described in Scheme 66).

Scheme 66



Accordingly, we have first selected methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(Ola),** as a substrate for performing the Prins type and Friedel-Crafts reactions with HCHO, in the presence of conc. H2SO4 under various conditions. The required Baylis-Hillman adduct **(131a)** was obtained *via* the reaction between methyl acrylate and benzaldehyde, in the presence of catalytic amount of DABCO (eq 29).[*]



eq 29

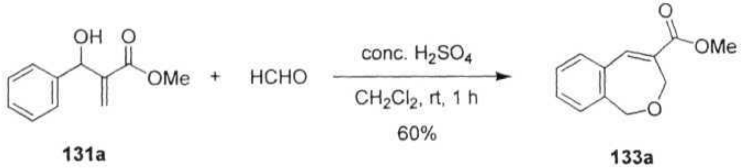
R = Ph, 4-MePh, 4-EtPh, 2-MePh, 4-(*i*-Pr)Ph
R^1 = Me, Et

The best results, in this direction, were obtained when the Baylis-Hillman **adduct** (**131a**) (2 mmol) was treated with HCHO (2 mmol) in CH_2Cl_2 (4 mL) in **the presence of** conc. H_2SO_4 (2 mmol) at room temperature for 1 h, thus providing the desired **4-meth-**

---

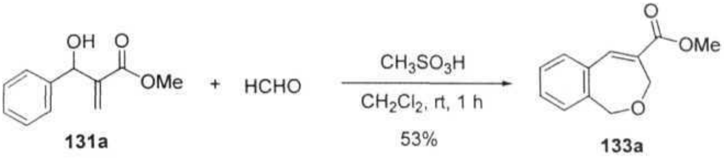
[*] For continuity and better understanding, we have numbered the Baylis-Hillman alcohol obtained from benzaldehyde and ethyl acrylate and that obtained from 4-methylbenzaldehyde and ethyl acrylate as 132a and **132b** respectively (eq 29 & Table 2).

oxycarbonyl-1,3-dihydro-2-benzoxepine (133a) in 60% yield after usual work-up followed by column chromatography (eq 30 & Table 2). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 11), ^{13}CNMR (Spectrum 12), mass spectral data and elemental analysis.



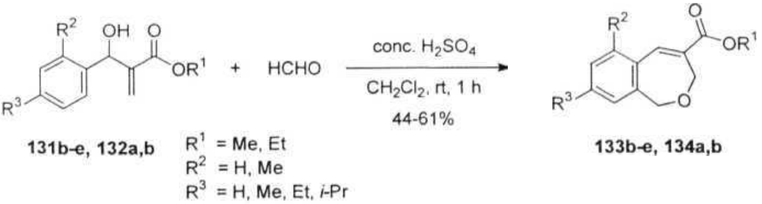
eq 30

With a view to understand the reaction better and also to increase the yield of the product, we have examined the application of methanesulfonic acid in the place of H_2SO_4. The best results were obtained, when **Ola** (2 mmol) was treated with HCHO (2 mmol) in CH_2Cl_2 (4 mL) in the presence of methanesulfonic acid (6 mmol) at room temperature for 1 h, thus providing the desired 4-methoxycarbonyl-1,3-dihydro-2-benzoxepine **(133a)** in 53% yield after usual work-up followed by column chromatography (eq 31 & Table 2). Structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. In fact, this spectral data is in complete agreement **with that** of the molecule prepared from methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(Ola)** *via* **the treatment with HCHO in** the presence of conc. H_2SO_4.



eq 31

Since sulfuric acid provided slightly better result than methanesulfonic acid, we have extended this strategy to representative Baylis-Hillman adducts [obtained from aldehydes (**130a-e**) and alkyl acrylates (eq 29)] to provide the desired 2-benzoxepine derivatives **(133b-e, 134a,b)**[Σ] in moderate to good yields (eq 32 & Table 2). Structures of these molecules were confirmed by IR, ^{1}H NMR (See: Spectra 13 & 15 for molecules **133e & 134b** respectively), ^{13}C NMR (See: Spectra 14 & 16 for molecules 133e & **134b** respectively) spectral data and elemental analyses.

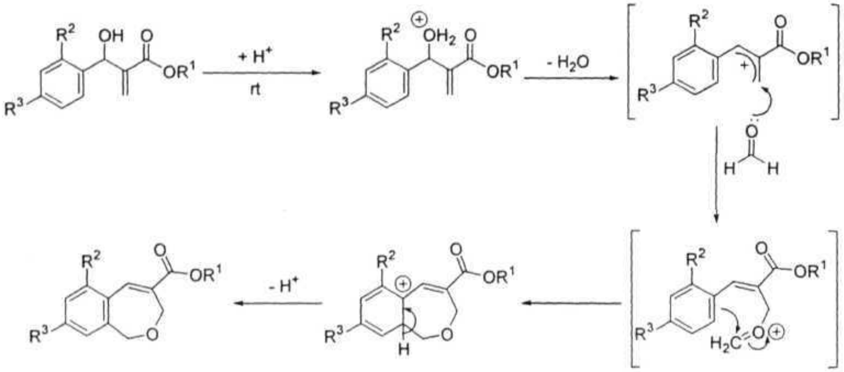


eq 32

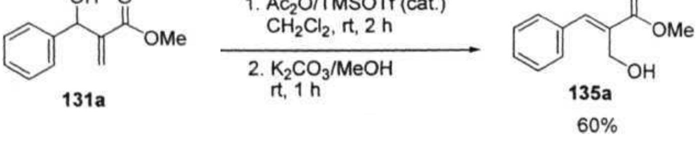
A plausible mechanism for the formation of 2-benzoxepines is described in **the Scheme** 67.

[Σ] We have numbered 4-ethoxycarbonyl-l,3-dihydro-2-benzoxepine and 4-ethoxycarbonyl-8-methyl-1,3-dihydro-2-benzoxepine as **134a** and **134b** respectively, for continuity and better understanding.

Scheme 67

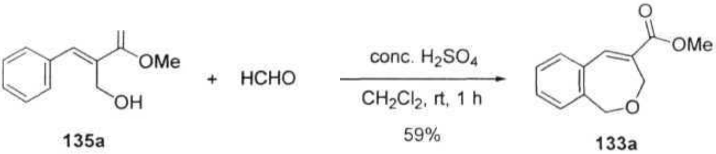


With a view to understand the reaction mechanism and to increase the yield of 2-benzoxepine derivative, we have planned to extend this strategy to the rearranged alcohol, methyl (2*E*)-2-(hydroxymethyl)-3-phenylprop-2-enoate (135a). The desired rearranged alcohol (135a) was obtained from methyl 3-hydroxy-2-methylene-3-phenylpropanoate (131a), following the known procedure[215] developed in our laboratory (eq 33).



eq 33

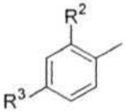
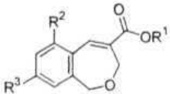
In fact, we have successfully transformed the rearranged alcohol **(135a)** into the desired 2-benzoxepine derivative **(133a).** Thus the reaction of **135a** (2 mmol) with HCHO (2 mmol) in CH_2Cl_2 (4 mL) in the presence of conc. H_2SO_4 (2 mmol) at room temperature for 1 h, provided **4-methoxycarbonyl-1,3-dihydro-2-benzoxepine (133a)** in 59% yield (eq 34 & Table 2). Structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. This spectral data is in complete agreement with that of the molecule prepared from methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(131a)** *via* the treatment with HCHO in the presence of conc. H2SO4. This reaction probably provides an evidence for the mechanistic pathway.



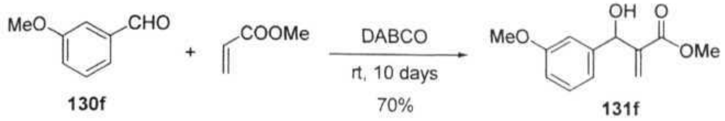
eq 34

With a view to extend this methodology to methyl 3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanoate **(131f),** the Baylis-Hillman adduct obtained from *m*-anisaldehyde **(130f)** and methyl acrylate (eq 35), we have performed the reaction between methyl 3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanoate **(131**f) and HCHO in the presence of conc. H_2SO_4 under various conditions (eq 36). We noticed that the reaction was not clean. Also, our attempts to use *p*-TsOH and methanesulfonic acid under various conditions for the conversion of Baylis-Hillman adduct **(131** f) into the corresponding 2-benzoxepine derivative were not successful.

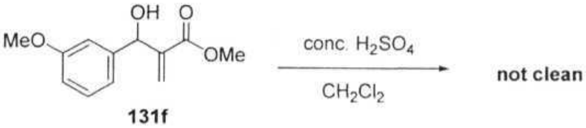
Table 2. Synthesis of 2-benzoxepine derivatives from the Baylis-Hillman adducts[a]

Alcohol		R^1	 Product[b,c]	Yield(%)[d]	Mp (°C)
131a	Phenyl	Me	**133a[e]**	60	46-48
131a	Phenyl	Me	**133a[f]**	53	46-48
131b	4-Methylphenyl	Me	**133b[e]**	51	58-60
131c	4-Ethylphenyl	Me	**133c**	56	–
131d	2-Methylphenyl	Me	**133d[e]**	48	59-60
131e	4-Isopropylphenyl	Me	**133c**	44	57-59
132a	Phenyl	Et	**134a**	61	36-39
132b	4-Methylphenyl	Et	**134b**	56	–
135a	Phenyl	Me	**133a**	59	46-48

a) All reactions were carried out on 2 mmol scale of Baylis-Hillman alcohols **(131a-e, 132a,b)** or rearranged alcohol **(135a)** with 2 mmol of HCHO in 4 mL of CH_2Cl_2 in the presence of conc. H_2SO_4 (2 mmol) at room temperature for 1 h. b) The compounds **133a,b,d,e & 134a** were obtained as colorless solids and the compounds **133c & 134b** were obtained as colorless viscous liquids. c) All the products gave satisfactory IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) and elemental analyses. d) Yields of the pure products obtained after column chromatography (silica gel, 4% EtOAc in hexanes). e) These compounds were also characterized by mass spectral analyses. f) This reaction was carried out on 2 mmol scale of Baylis-Hillman alcohol **(131a)** with 2 mmol of HCHO in 4 mL of CH_2Cl_2 in the presence of methanesulfonic acid (6 mmol) at room temperature for 1 h.



eq 35



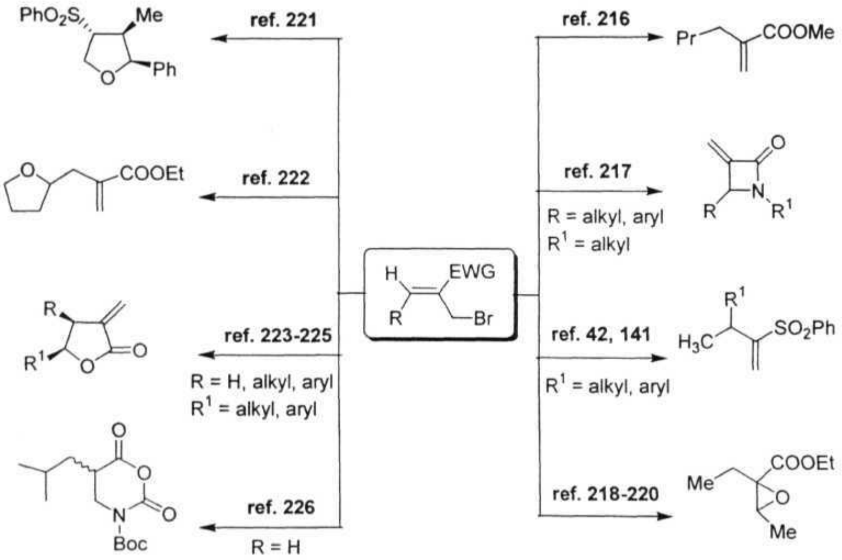
eq 36

In conclusion, we have successfully developed one-pot simple methodology for synthesis of 2-benzoxepine derivatives involving tandem construction of C-0 and C-C bonds through Prins type and Friedel-Crafts type reactions *via* the treatment of Baylis-Hillman adducts with HCHO under the influence of H_2SO_4.

Chiral auxiliary mediated diastereoselective synthesis of propargylic and phenolic ethers of Baylis-Hillman adducts from alkyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates

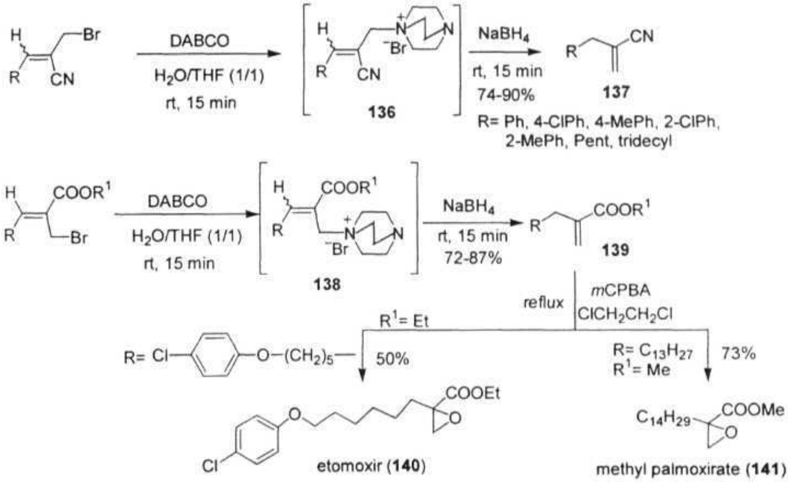
Allyl bromides derived from Baylis-Hillman adducts have been successfully employed in various organic transformation methodologies. Relevant examples are represented pictorially in Scheme 68.[42,141,216-226]

Scheme 68



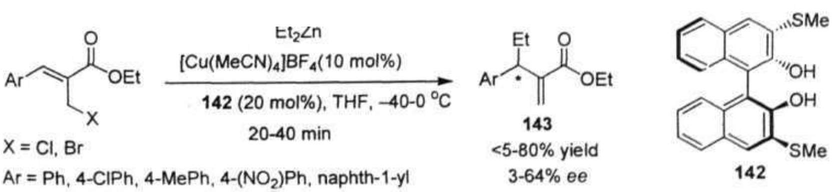
Recently, our research group[227] has developed a simple and general synthesis of 2-methylene alkanenitriles **(137)** and alkanoates **(139)** *via* the nuleophilic S_N2' addition of hydride **ion from** $NaBH_4$ to **the** *in situ* generated DABCO-allyl bromide salts **(136** *&* **138)** in **an** environment-friendly aqueous media. This methodology was successfully **applied for the** synthesis of **two** hypoglycemic agents etomoxir **(140) and** methyl palmoxirate **(141)** (Scheme 69).

Scheme 69



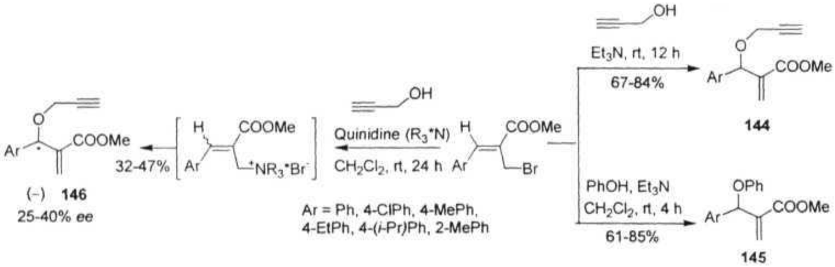
An asymmetric copper-catalyzed chemo- and regiospecific S_N2' addition of organozinc reagents to (Z)-allyl halides, derived from the Baylis-Hillman adducts, in the presence of chiral ligand **142** to provide the corresponding products **143** upto 64% *ee*, was reported by Woodward et al.[228] (Scheme 70).

Scheme 70



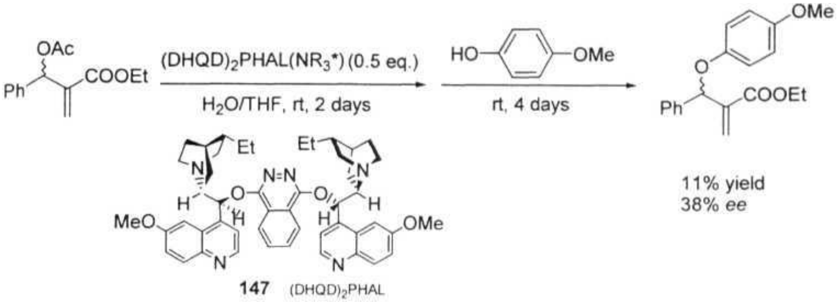
Our research group[229] has described the nucleophilic additions of propargyl alcohol and phenol to the Baylis-Hillman bromides in the presence of Et_3N to provide the corresponding methyl 3-aryl-2-methylene-3-(prop-2-yn-l-yloxy)propanoates (144) and methyl 3-aryl-2-methylene-3-phenoxypropanoates (145) respectively. We have also developed a simple enantioselective synthesis of propargylic ether (146) of the Baylis-Hillman adducts *via* the deracemization process, under the influence of chiral leaving group (quinidine) in 25-40% enantiomeric purities as shown in the Scheme 71.

Scheme 71



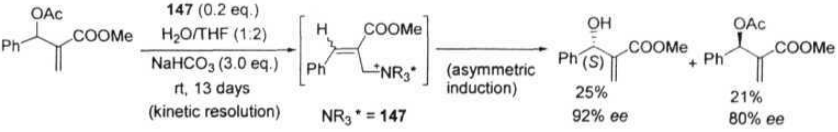
More recently, Kim and co-workers[230] have reported deracemization type process by the addition of *p*-methoxyphenol as nucleophile, on to the Baylis-Hillman acetate in the presence of chiral amine (147) in aq. THF, however, with low chemical yields and enantioselectivities. Representative example which provided the best *ee* of 38% is presented in Scheme 72.

Scheme 72



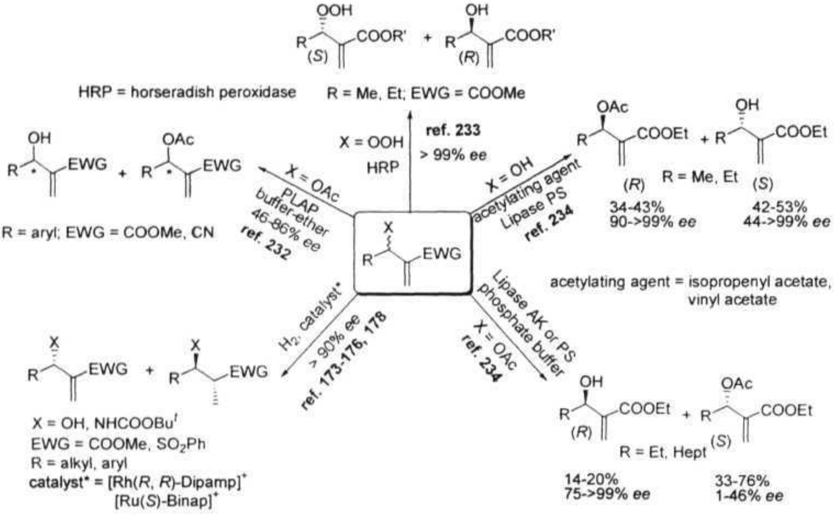
They have also successfully synthesized enantiomerically enriched Baylis-Hillman adducts with optical purities of 54-92% from their racemic acetates using the combined concept of kinetic resolution during salt formation with $(DHQD)_2PHAL$ and the asymmetric induction during the (S_N2') type reaction with sodium bicarbonate as a water surrogate. One representative example is presented in the Scheme 73.[230]

Scheme 73



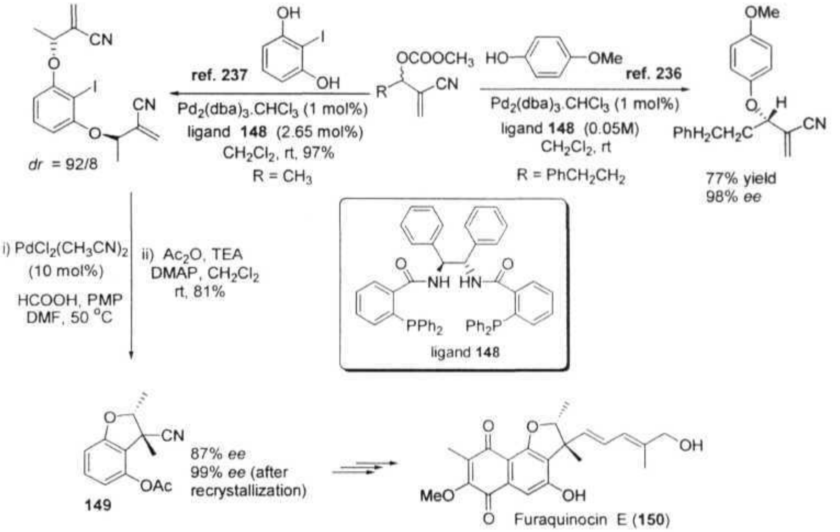
The enantiomerically pure Baylis-Hillman adducts can also be obtained *via* 1) kinetic resolution of alcohols using asymmetric hydrogenation methodology,[56,57,173-176,178] 2) kinetic resolution of alcohols and their derivatives *via* chemoenzymatic methodology[231-234,39] and epoxidation.[235] Representative examples are presented in Scheme 74.

Scheme 74

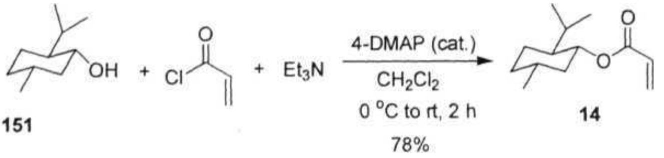


Trost et al. have developed an efficient procedure for deracemization of Baylis-Hillman carbonates *via* the reaction with phenols in the presence of palladium catalyst, **following DYKAT *(dynamic kinetic asymmetric transformation)* process using chiral** phosphine ligand (148) leading to the formation of aryl ethers of Baylis-Hillman adducts in high enantiomeric purities (Scheme 75). Subsequently, they have successfully applied this methodology for the preparation of enantiomerically pure dihydrobenzofuran derivative 149, which was further transformed into Furaquinocin E (150) (Scheme 75).[237]

Scheme 75



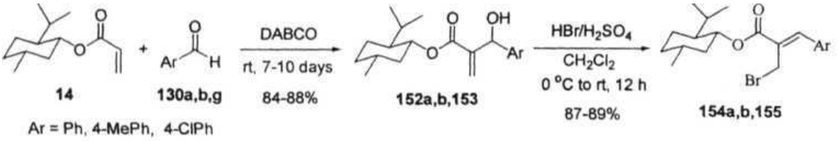
Chiral auxiliaries play important role in asymmetric organic synthesis.[238-241] Also, allyl propargylic ethers are versatile synthons for the synthesis of various interesting molecules.[242-246] In continuation of our interest on deracemization process of the Baylis-Hillman adducts[229] with various nucleophiles, we directed our studies to examine the diastereoselectivities on addition of oxygen nucleophiles such as propargylic alcohol and phenol on to the Baylis-Hillman bromides under the influence of chiral auxiliaries. **In this direction,** we have first selected (-)-menthol as chiral auxiliary. The desired (-)-menthyl acrylate (14) was prepared *via* the reaction of (-)-menthol **(151)** with acryloyl chloride in the presence of triethylamine, following the known procedure (eq 37).[247]



eq 37

The Baylis-Hillman adduct **(152a)** was obtained in 88% yield *via* the coupling of (-)-menthyl acrylate (14) with benzaldehyde in the presence of DABCO, following the procedure developed in our laboratory (Scheme 76).[96,©] The structure of the molecule was established by IR, ^{1}H NMR, and ^{13}C NMR spectral data. The required allyl bromide, (-)-menthyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate **(154a)** was obtained in 88% yield *via* the treatment of (-)-menthyl 3-hydroxy-2-methylene-3-phenylpropanoate **(152a)** with HBr/H_2SO_4 (Scheme 76). Structure of this molecule was established by IR, ^{1}H NMR, and ^{13}C NMR spectral data.

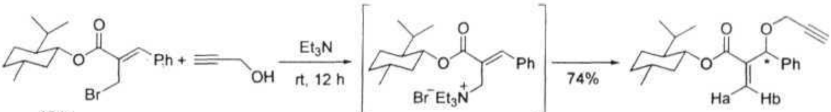
Scheme 76



[©] **For continuity and better understanding, we have numbered 4-chlorobenzaldehyde as 130g (Scheme 76). We have also numbered the Baylis-Hillman adduct obtained from 4-chlorobenzaldehyde (130g) and menthyl acrylate as 153 and corresponding allyl bromide (-)-menthyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate as 155 (Scheme 76).**

We have first selected propargyl alcohol as nucleophile for our study. The best result was accomplished when the molecule **154a** (1 mmol) was treated with propargyl alcohol (5 mmol) in the presence of Et_3N (1 mL) at room temperature for 12 h, thus providing (-)-menthyl 2-methylene-3-(prop-2-yn-l-yloxy)-3-phenylpropanoate **(156a)** as a colorless viscous liquid in 74% yield and 18% diastereomeric excess, after usual work-up followed by column chromatography (silica gel, 2% EtOAc in hexanes) (Scheme 77). The molecule was well characterized by IR, ^{1}H NMR (Spectrum 17), ^{13}C NMR (Spectrum 18) spectral data and elemental analysis.

Scheme 77



154a

156a 18% *de*

154a

156a **18% *de***

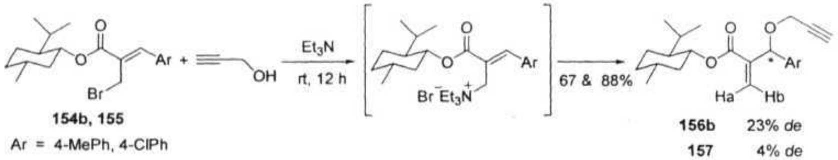
Determination of **the** diastereomeric **purity** of (156a):

The diastereomeric purity of this molecule **(156a)** was determined by the ^{1}H NMR spectral analysis. The two singlets at 8 6.31 & 6.41 are attributed to β-vinylic protons (Ha) (*cis*- to the ester group) of the minor and major diastereomers respectively. The integration of these two singlets is in the ratio of 41:59 indicating that the reaction is 18% diastereoselective[κ] [Spectrum 17: (A)].

[κ] We have also recorded the ^{1}H NMR spectrum of the crude product, which also shows the diastereoselectivitity of 18%, as evidenced by the integration of diastereomeric β-olefinic (Ha) proton (*cis*-to the ester group) singlets.

With a view to understand the diastereoselectivity trend, we extended the same strategy to a representative (-)-menthyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates (154b, 155),[Ψ] the allyl bromides obtained from the corresponding Baylis-Hillman adducts (152b, 153)[Ψ] (Scheme 76). The resulting products (-)-menthyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (156b, 157)[Ψ] were obtained in 67 & 88% yields and with 23 and 4% diastereoselectivities respectively (Scheme 78 & Table 5). These two molecules were well characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses, The diastereomeric purity of these molecules were determined by the ^{1}H NMR spectral analysis, by the integration of the singlets arising from the olefinic (Ha) protons *(cis-* to the ester group) of both the diastereomers [Π](Table 3).

Scheme 78



[Ψ] For continuity and better understanding, we have numbered the Baylis-Hillman adduct, obtained from 4-chlorobenzaldehyde (130g) and menthyl acrylate, as 153 (Scheme 76), the corresponding allyl bromide (-)-menthyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate as 155 (Scheme 76) and the propargylic ether (-)-menthyl 3-(4-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate as 157 (Scheme 78).

[Π] ^{1}H NMR spectra of the crude products (156b, 157) also show the diastereomeric purities of these molecules as 23 and 4% respectively, as indicated by the integration of the diastereomeric singlets arising from the olefinic (Ha) protons *(cis-* to the ester group).

Table 3. Determination of diastereomeric purities of menthyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (156a,b & 157): Analysis of key protons in ^{1}H NMR spectra

Compound	Key protons	Chemical shifts of diastereomeric proton singlets (integration ratio)	D.e (%)
156a	β-olefinic proton (Ha)	5 6.31 & 6.41 (41:59)	18
156b	β-olefinic proton (Ha)	6 6.29 & 6.39 (38.5:61.5)	23
157	p-olefinic proton (Ha)	δ 6.31 &6.41 (52:48)	4

With a view of examining deracemization process of Baylis-Hillman adducts, we next selected phenol as a nucleophile for addition on to the Baylis-Hillman bromides **(154a,b & 155).** Accordingly, we first examined the reaction of (-)-menthyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate **(154a)** (1 mmol) with phenol (1 mmol) in the presence of Et_3N (1 mL) in CH_2Cl_2 (2 mL) at room temperature for 4 h, to provide (-)-menthyl 2-methylene-3-phenoxy-3-phenylpropanoate **(158a)** in 72% yield and 35% *de* (Scheme 79). The molecule was well characterized by IR, ^{1}H NMR (Spectrum 19), ^{13}C NMR (Spectrum 20) spectral data and elemental analysis. The diastereomeric excess of this molecule was determined by the H **NMR** spectral analysis. The integration of two singlets at δ 5.83 & 5.93 arising due to the benzylic (H3) protons of the minor and major diastereomers respectively, is in the ratio of 32.5:67.5, indicating that the reaction is 35% diastereoselective[0] [Spectrum 19: (A)].

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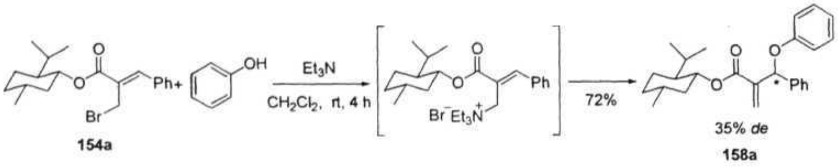
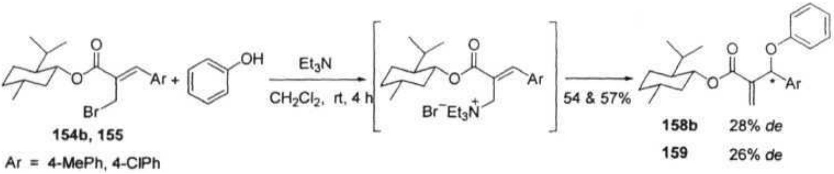
[0] **We** have also recorded the ^{1}H NMR spectrum of the crude product, which also shows **the** diastereoselectivitity of 35%, as evidenced by the integration of diastereomeric benzylic (H3) proton singlets.

Scheme 79



We have then examined the nucleophilic addition of phenols to representative allyl bromides **(154b, 155).** The resulting (-)-menthyl 3-aryl-2-methylene-3-phenoxypropanoates 158b, **159**[a] were obtained with 28 & 26% diastereoselectivities and in 54 & 57% yields respectively (Scheme 80 & Table 5). Structures of these two molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses. Diastereomeric purities of these molecules were determined by the ^{1}H NMR spectral analysis, *i. e.*, *via* the integration of the singlets arising due to the benzylic (H3) protons of both the diastereomers (Table 4).[b]

Scheme 80



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[a] For continuity and better understanding, the phenolic ether, (-)-menthyl **3-(4-chlorophenyl)-2-methylene-3-phenoxypropanoate** was numbered as **159.**

[b] ^{1}H NMR spectra of the crude products **(158b, 159)** also show the diastereomeric purities of these molecules as 28 and 26% respectively, as indicated by the integration of the diastereomeric benzylic (H3) proton singlets.

Table 4. Determination of diastereomeric purities of menthyl 3-aryl-2-methylene-3-phenoxypropanoates (158a,b & 159): Analysis of key protons in ^{1}H NMR spectra

Compound	Key protons	Chemical shifts of diastereomeric proton singlets (integration ratio)	D.e (%)
158a	benzylic (H3) proton	(two singlets) δ 5.83 & 5.93 (32.5:67.5)	35
158b	benzylic (H3) proton	(two singlets) δ 5.73 & 5.84 (36:64)	28
159	benzylic (H3) proton	(two singlets) δ 5.86 & 5.96 (37:63)	26

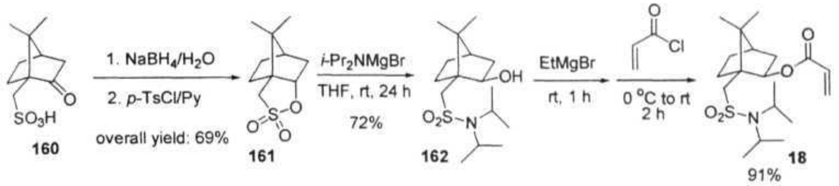
Though the diastereoselectivities observed in the above reactions using (-)-menthyl group as a chiral source, are not high, these results are encouraging in the sense that the selection of appropriate chiral auxiliary might offer better diastereoselectivities. In our laboratory, we have demonstrated the application of Oppolzer's chiral auxiliaries **(18** & 19) for synthesis of mikanecic acid in high enantioselectivity *via* asymmetric Diels-Alder reaction (Scheme 40, Introduction, page no. 39). We have therefore planned to examine the application of **18** as chiral auxiliary for diastereoselective addition of oxygen nucleophiles to the (*Z*)-allyl bromides. The required chiral auxiliary (18) was prepared following the reaction sequence described in the Scheme 81, starting from commercially available (+)-10-camphorsulfonic acid **(160).** Reduction of **160** with $NaBH_4$ followed by intramolecular cyclodehydration with *p*-TsCl in dry pyridine, provided isobornyl sultone **(161)** in 69% yield (Scheme 81). Nucleophilic opening of isobornyl sultone **(161)** with bromomagnesium diisopropylamide afforded the alcohol **(162),** in 72% yield (Scheme 81). Structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Table 5. Diastereoselective synthesis of (–)-menthyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates and (–)-menthyl 3-aryl-2-methylene-3-phenoxypropanoates [a,b]

Allyl bromide	Ar	Product[c]	Yield(%)[d]	$[\alpha]_D^{25}$ (c, $CHCl_3$)	D.e (%)[e,f]
154a	Phenyl	**156a**[a]	74	-60.31 (4.15)	18
154b	4-Methylphenyl	**156b**[a]	67	-60.40 (3.00)	23
155	4-Chlorophenyl	**157**[a]	88	-36.45 (3.36)	4
154a	Phenyl	**158a**[b]	72	-76.16(5.00)	35
154b	4-Methylphenyl	**158b**[b]	54	-71.56(2.11)	28
155	4-Chlorophenyl	**159**[b]	57	-69.81 (3.71)	26

a) All the reactions were carried out on 1 mmol scale of allyl bromides **(154a,b & 155)** with propargyl alcohol (5 mmol) in the presence of Et_3N (1 mL) at room temperature for 12 h. b) All the reactions were carried out on 1 mmol scale of allyl bromides **(154a,b & 155)** with phenol (1 mmol) in the presence of Et_3N (1 mL) in 2 mL of CH_2Cl_2 at room tempereture for 4 h. c) All the products were obtained as colorless viscous liquids and were characterized by IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectral data and elemental analyses. d) Isolated yields of the pure products after column chromatography (silica gel, 2% EtOAc in hexanes). e) Diastereomeric purities of these molecules were determined by ^1H NMR (200 MHz) spectral analysis (in fact the ^1H NMR spectra of the crude products showed same diastereoselectivities as that of the purified). f) Our attempts to determine the diastereoselectivities of these molecules using HPLC were unsuccessful.

Scheme 81



The required acrylate (1*S*,2*R*,4*R*)-1-(diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)hept-2-yl acrylate (18) was obtained in 91% yield, by the treatment of magnesium salt of alcohol **(162)** with acryloyl chloride (Scheme 81). Structure of this molecule was in full agreement with IR, ^{1}H NMR, and ^{13}C NMR spectral data.

The Baylis-Hillman coupling reaction of the acrylate (18) with benzaldehyde in the presence of DABCO, following the procedure developed in our laboratory, provided the desired adduct (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-hydroxy-2-methylene-3-phenylpropanoate (**163**),[∞] in 92% yield and 14% diastereomeric excess (Scheme 82). Structure of this molecule was confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectral data. Diastereomeric excess was determined by the ^{1}H NMR spectral analysis. The two singlets at 8 6.15 and 6.20 are attributed to the β-vinylic protons (Ha) (*cis*- to ester group) of minor and major diaster-

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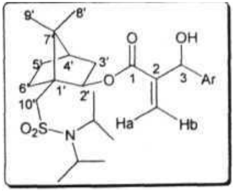
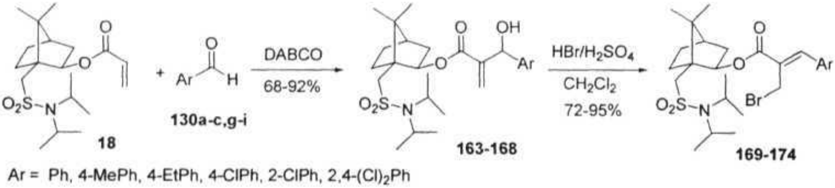
[∞] For better understanding, we have adopted the following numbering for molecules **163-168.**



eomers respectively. The integration ratio of these two singlets shows that the reaction is 14% diastereoselective. The required allyl bromide **(1'*S*,2'*R*,4'*R*)-1'-diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (169)**,[σ] was prepared in 88% yield, *via* the treatment of alcohol (163) with HBr/H_2SO_4 (Scheme 82).[ω] Structure of the molecule was confirmed by IR, ^1H NMR, and ^{13}C NMR spectral data.

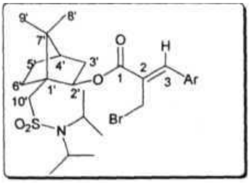
Scheme 82



We have examined the reaction of allyl bromide (169) with propargyl alcohol in the presence of triethylamine. Encouraging results were obtained when we have treated **169** (0.5 mmol) with propargyl alcohol (2.5 mmol) in the presence of Et_3N (1 mL) at room temperature for 12 h, thus providing the desired propargylic ether, (1'*S*,2'*R*,4'*R*)-

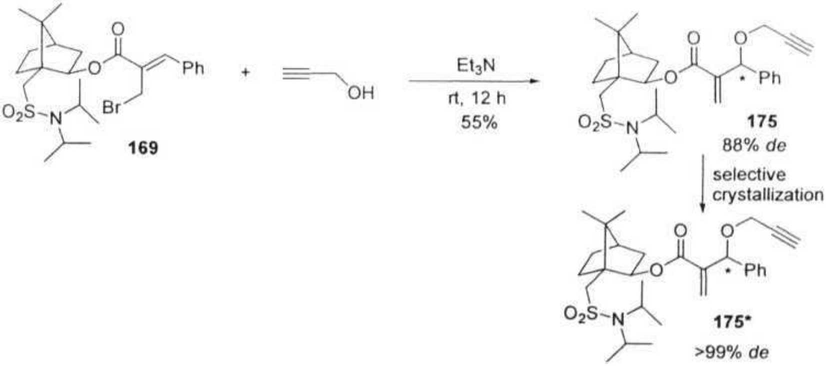
[ω] For continuity and better understanding, we have numbered the aromatic aldehydes that is 4-chlorobenzaldehyde, 2-chlorobenzaldehyde and 2,4-dichlorobenzaldehyde as **130g**, **130h** and **130i** respectively.

[σ] For better understanding, we have adopted the following numbering for molecules **169-174.**



1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 2-methylene-3-(prop-2-yn-1-yloxy)-3-phenylpropanoate (175) in 88% diastereoselectivity and in 55% yield, after usual work-up, followed by column chromatography (silica gel, 4% EtOAc in hexanes) (Scheme 83). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 21), ^{13}C NMR (Spectrum 23) spectral data and elemental analysis. Diastereomeric excess was determined by the ^{1}H NMR spectral analysis. The two singlets at δ 5.92 & 6.03 are attributed to the olefinic (Hb) protons, {*trans*- to the ester group) of major and minor diastereomers respectively. The integration of these two singlets is in the ratio of 94:6, indicating that the reaction is 88% diastereoselective[φ] [Spectrum 21: (A)].

Scheme 83



[φ] We have also recorded the ^{1}H NMR spectrum of the crude product, which also shows the diastereoselectivitity of 88%, as evidenced by the integration of diastereomeric olefinic (Hb) proton {*trans*- to the ester group) singlets.

Careful selective crystallization of the molecule (175) from 10% EtOAc in hexanes, provided the single diastereomer (175*) in >99% *de* (Scheme 83), as evidenced by ^{1}H NMR (Spectrum 22) and ^{13}C NMR (Spectrum 24) spectral data. Thus, in ^{1}H NMR spectrum of 175*, olefinic (Hb) proton, *trans*- to the ester group (which showed two distinct singlets before crystallization) shows only one singlet at 5 5.91 [Spectrum 22: (A)] (Table 6).

This is indeed an encouraging result. We have therefore planned to extend this strategy to a variety of allyl bromides with a view to understand the generality of this reaction. The required (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates (170-174) were synthesized from the corresponding Baylis-Hillman adducts (164-168), which in turn were prepared *via* the reaction between the chiral acrylate (18) and aryl aldehydes (**130b,c,g-i**)[∇] (Scheme 82).

These (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates (170-174) were subjected to the reaction with propargyl alcohol under similar conditions as mentioned in the case of 175 in the presence of Et$_3$N. The resulting (1'*S*,2'*R*,4 '*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (176 -180) were obtained with 51-87% diastereoselectivities and in 63-83% yields (eq 38 & Table 7). Structure of these molecules were confirmed by IR, ^{1}H NMR (See: Spectrum 25 for the molecule 176), ^{13}C NMR (See: Spectrum 27 for the

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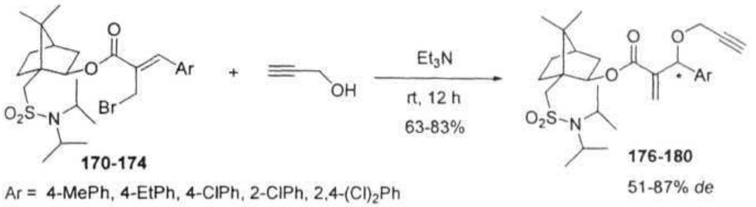
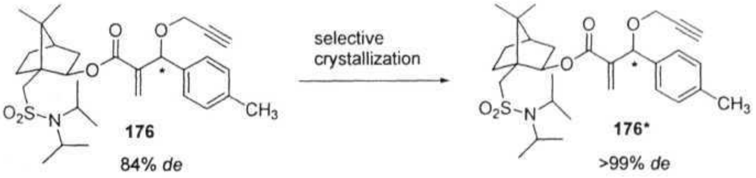
[∇] For continuity and better understanding, we have numbered the aromatic aldehydes that is 4-chlorobenzaldehyde, 2-chlorobenzaldehyde and 2,4-dichlorobenzaldehyde as 130g, 130h and 130i respectively.

molecule **176)** spectral data and elemental analyses, Diastereomeric purity of these molecules were determined by the ^{1}H NMR spectral analysis[*,∂](Table 6).



eq 38

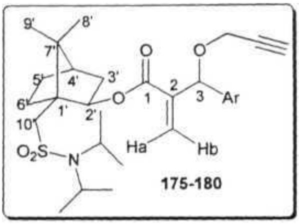
We have also performed careful selective crystallization of (1'*S*,2'*R*,4'*R*)-1'-(di-isopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 2-methylene-3-(4-methylphenyl)-3-(prop-2-yn-l-yloxy)propanoate (176) from 10% EtOAc in hexanes, which provided single diastereomer (176*), in >99% *de*, as evidenced by ^{1}H NMR (Spectrum 26) and ^{13}C NMR (Spectrum 28) spectral data (eq 39).



eq 39

*In the case of **176-178,** the diastereomeric olefinic protons (Hb) separate and the diastereoselectivity is determined by their integration ratio [See: Spectrum 25: (A) for the molecule 176]. In the case of **179** & **180** the diastereomeric excess is determined by the integration of diastereomeric olefinic proton (Ha) signals.

[∂]The ^{1}H NMR spectra of the crude products of **176-180** also show the diastereoselective purities of 51-87% respectively, as indicated by the integration of diastereomeric olefinic proton (Hb) singlets in the case of **176-178** and diastereomeric olefinic proton (Ha) singlets in the case of **179** & **180.**



175-180

Table 6. Determination of diastereomeric purities of (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-(prop-2-yn-l-yloxy)propanoates: Analysis of key protons in ^{1}H NMR spectra

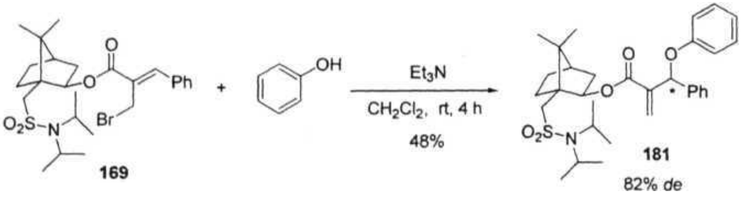
Compound	Key protons	Chemical shifts of diastereomeric proton singlets (integration ratio)	D.e (%)
175	β-olefinic proton (Hb)	5 5.92 & 6.03 (94:6)	88
175* (after crysallization)	β-olefinic proton (Hb)	one singlet at δ 5.91	>99% (pure)
176	β-olefinic proton (Hb)	5 5.91 &6.01 (92:8)	84
176* (after crystallization)	p-olefinic proton (Hb)	one singlet at 8 5.90	>99% (pure)
177	p-olefinic proton (Hb)	8 5.91 &6.02 (93.5:6.5)	87
178	p-olefinic proton (Hb)	δ 5.94 & 6.02 (89:11)	78
179	P-olefinic proton (Ha)	δ 6.10 & 6.32 (88.5:11.5)	77
180	β-olefinic proton (Ha)	δ 6.18 & 6.37 (75.5:24.5)	51

Table 7. Diastereoselective synthesis of (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates [a,b]

Allyl bromide	Ar	Product[c]	Yield(%)[d]	$[\alpha]_D^{25}$ (c, $CHCl_3$)	D.e (%)[e,f]
169	Phenyl	**175**[g]	55	-104.14(3.50)	**88**[g,h]
170	4-Methylphenyl	**176**[g]	68	-106.65(3.50)	**84**[g,h]
171	4-Ethylphenyl	177	72	-101.88(2.92)	87
172	4-Chlorophenyl	**178**	83	-107.66(2.68)	78
173	2-Chlorophenyl	**179**	63	-54.28(1.09)	77
174	2,4-Dichlorophenyl	**180**	69	-51.14(3.15)	51

a) All the reactions were carried out on 0.5 mmol scale of allyl bromides **(169-174)** with propargyl alcohol (2.5 mmol) in the presence of Et_3N (1 mL) at room temperature for 12 h. b) All the products were characterized by IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectral data and elemental analyses. c) Products **175-179** were obtained as colorless solids and the product **180** was obtained as a colorless viscous liquid. d) Isolated yields of the pure products after column chromatography (silica gel, 4% EtOAc in hexanes). e) Diastereomeric purities of these molecules were determined by ^1H NMR (200 MHz) spectral analysis (Table 6) (in fact, the ^1H NMR spectra of the crude products showed same diastereoselectivities as that of the purified). f) Our attempts to determine the diastereoselectivities of these molecules using HPLC were unsuccessful. g) Selective crystallization of these compounds provided the single diastereomer in >99% *de*, as evidenced by the ^1H NMR and ^{13}C NMR spectral data. h) These compounds were also characterized by mass spectral analyses.

After having obtained success in the deracemization process of Baylis-Hillman adducts *via* diastereoselective addition of propargyl alcohol to the allyl bromides, using the Oppolzer's chiral auxiliary (162) as a chiral source, our next objective was focused on to the examination of deracemization process of Baylis-Hillman adducts by addition of phenol on to the Baylis-Hillman bromides, using the concept of chiral auxiliary induced asymmetric synthesis. Accordingly, we first examined the reaction of (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate (169) with phenol in the presence of triethylamine. We have indeed obtained encouraging results, when allyl bromide (169) (0.5 mmol) was treated with phenol (0.5 mmol) in the presence of Et_3N (1 mL) in CH_2Cl_2 (1 mL), at room temperature for 4 h, thus providing the desired phenolic ether (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 2-methylene-3-phenoxy-3-phenylpropanoate (**181**) in 82% diastereoselectivity and in 48% yield, after usual work-up, followed by column chromatography (silica gel, 4% EtOAc in hexanes) (eq 40). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 29), ^{13}C NMR (Spectrum 32) spectral data and elemental analysis.



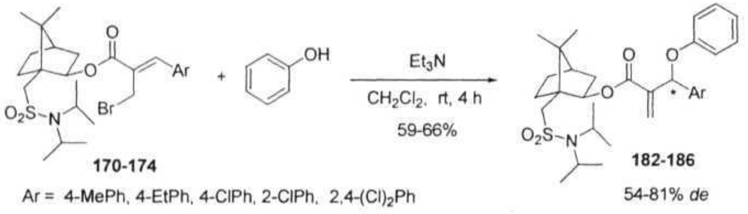
eq 40

Diastereomeric excess of the molecule 181 was determined by the ^{1}H NMR spectral analysis. The two singlets at 6 5.78 & 6.02 are attributed to the benzylic (H3) proton of major and minor diastereomers respectively. The integration of these two singlets is in the ratio of 91:9, indicating that the reaction is 82% diastereoselective [Spectrum 29: (A)].[ρ, Φ]

[ρ] ^{1}H NMR spectrum of the crude product also indicates that the reaction is 82% diastereoselective as evidenced by the integration of diastereomeric benzylic (H3) proton singlets.

[Φ] ^{1}H NMR spectrum showed five singlets at 8 5.78. 6.02, 6.18, 6.21 and 6.26 (the underlined peaks are attributed to the minor diastereomer) due to the benzylic (H3) and olefinic (Hb and Ha) protons of both the diastereomers. The singlets at δ 5.78 & 6.02 can be attributed to the benzylic (H3) protons of the major and minor diastereomers respectively and are in the ratio of 91:9, indicating that the reaction is 82% diastereoselective. To further confirm our assignment, we have recorded ^{1}H NMR spectrum (Spectrum 30) in the presence of chiral shift reagent Eu(hfc)3, which clearly showed that the minor peaks originally at 8 6.26 and 6.02 are in the ratio of 2:1, thus indicating that the peak originally at δ 6.26 arises due to Hb and Ha protons of minor diastereomer. With a view to have further understanding, we have also recorded ^{1}H NMR spectrum (Spectrum 31) in the presence of shift reagent Eu(fod)$_3$, the multiplet originally at 8 5.05-5.24 due to the H2' proton nicely splits into two multiplets at 8 5.44-5.52 and 8 5.53-5.65 in the ratio of 9:91 indicating that the molecule 181 is 82% diastereomerically pure.

With a view to examine the generality of the reaction, we have extended the same strategy to representative class of allyl bromides **(170-174).** The resulting (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-phenoxypropanoates **(182-186)** were obtained with 54-81% diastereoselectivities and in 59-66% yields (eq 41 & Table 9). Structure of these molecules were confirmed by IR, ^1H NMR (See: Spectra 33 & 35 for molecules **182** & **183** respectively), ^{13}C NMR (See: Spectrum 36 for the molecule **185)** spectral data and elemental analyses. Diastereomeric purities of these molecules were determined by the ^1H NMR spectral analysis (Table 8).[#,◊]



eq 41

[#] In the case of **182-186,** the diastereomeric benzylic (H3) protons separate and the diastereoselectivity is determined by their integration ratio [See: Spectrum 33: (A) & (B) for the molecule **182** and Spectrum 35: (A) for the molecule **183].** In the case of **182,** it is further established by the diastereomeric H2' proton signal which nicely separates into two multiplets in the presence of $Eu(fod)_3$, in the ratio of 12:88 (Spectrum 34).

[◊] The ^1H NMR spectra of the crude products of **182-186** also showed the diastereoselective purities of 54-81% respectively as indicated by the integration of diastereomeric benzylic (H3) protons.

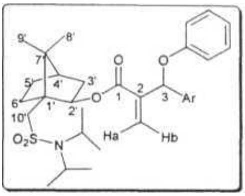


Table 8. Determination of diastereomeric purities of (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene -3-phenoxypropanoates: Analysis of key protons in ^{1}H NMR spectra

Compound	Key protons	Chemical shifts of diastereomeric proton (integration ratio)	D.e (%)
181	benzylic (H3) proton	δ 5.78 & 6.02 (91:9)	82[a]
182	benzylic (H3) proton	δ 5.78 & 6.00 (88:12)	76[b]
183	benzylic (H3) proton	δ 5.78 & 6.01 (89:11)	78[c]
184	benzylic (H3) proton	δ 5.77 & 5.95 (90.5:9.5)	81[d]
185	benzylic (H3) proton	δ 5.31 & 5.77 (83.5:16.5)	67[e]
186	benzylic (H3) proton	δ 5.48 & 5.86 (77:23)	54[f]

a) This is further confirmed by the integration of the two multiplets at 6 5.44-5.52 and 8 5.53-5.65 due to the H2' proton (originally at 8 5.05-5.24) of the minor and major diastereomers respectively, in the presence of $Eu(fod)_3$ (Spectrum 31). b) The diastereomeric H2' protons separate as two distinct multiplets in the presence of Eu(fod)3, in the ratio of 12:88 indicating that the reaction is 76% diastereoselective (Spectrum 34). This is further confirmed by the integration of two singlets at 8 2.30 & 2.33 of the diastereomeric methyl protons on the aromatic ring (Spectrum 33). c) Diastereoselectivity is further established by the integration of the two doublets at 8 3.21 & 3.25 arising from the H10' proton (second part of d of ABq) of the minor and major diastereomers respectively. d) The two doublets at 8 2.60 & 2.63 are due to the H10' proton (first part of d of ABq) of the minor and major diastereomers respectively and are in the ratio of 9.5:90.5, also indicating 81% diastereoselectivity. e) This is further confirmed by the integration of two multiplets at 8 4.92-5.02 & 5.05-5.18 arising from the diastereomeric H2' proton. f) Diastereoselectivity is further established by the integration of two multiplets at 8 5.01-5.11 & 5.13-5.23 (23:77) arising from the H2' protons of the minor and major diastereomers respectively.

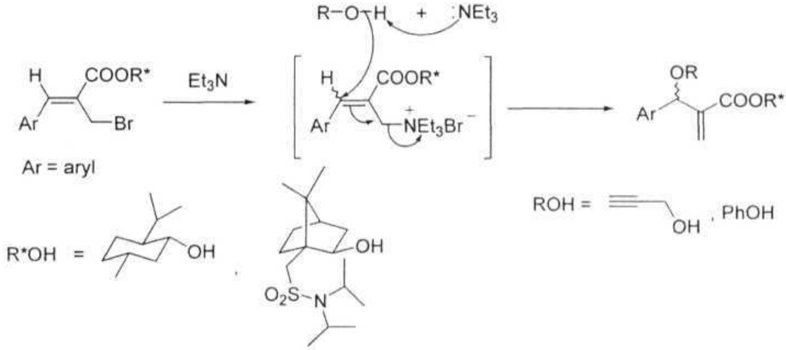
Table 9. Diastereoselective synthesis of (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-phenoxypro- panoates [a,b]

Allyl bromide	Ar	Product[c]	Yield(%)[d]	$[\alpha]_D^{25}$ (c, $CHCl_3$)	D.e (%)[e,f]
169	Phenyl	**181**	48	-55.56(1.78)	82
170	4-Methylphenyl	**182**	61	-61.66(1.26)	76
171	4-Ethylphenyl	**183**	66	-59.26(1.44)	78
172	4-Chlorophenyl	**184**[g]	63	-75.80 (2.50)	81
173	2-Chlorophenyl	**185**	64	2.22(1.88)	67
174	2,4-Dichlorophenyl	186	59	-8.96 (2.55)	54

a) All the reactions were carried out on 0.5 mmol scale of allyl bromides **(169-174)** with phenol (0.5 mmol) in the presence of Et_3N (1 mL) in 1 mL of CH_2Cl_2 at room temperature for 4 h. b) All the products were characterized by IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectral data and elemental analyses. c) Products **181-183** & **185** were obtained as colorless viscous liquids, while the products **184** and **186** were obtained as colorless solids. d) Isolated yields of the pure products after column chromatography (silica gel, 4% EtOAc in hexanes). e) Diastereomeric purities of these molecules were determined by ^1H NMR (200 MHz) spectral analysis (Table 8) (in fact the ^1H NMR spectra of the crude products showed same diastereoselectivities as that of the purified). f) Our attempts to determine the diastereoselectivities of these molecules using HPLC were unsuccessful. g) This product was also characterized by mass spectral analysis.

A plausible mechanism for addition of oxygen nucleophiles (from propargyl alcohol and phenol) onto alkyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates is described in the Scheme 84.

Scheme 84



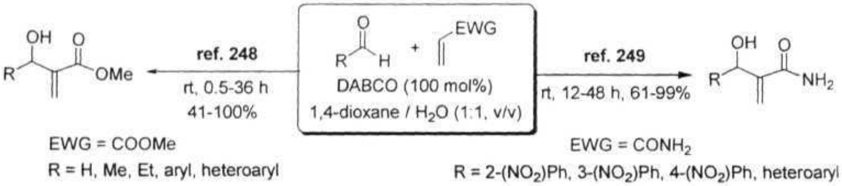
In conclusion, we have developed a simple methodology for diastereoselective synthesis of phenolic and propargylic ethers of Baylis-Hillman adducts, using Oppolzer's chiral auxiliary as a chiral source in the deracemization of Baylis-Hillman adducts.

First example of organo base induced Cannizzaro reaction

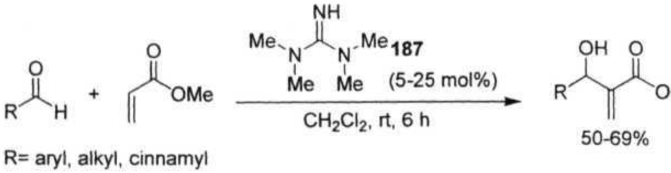
Although a large variety of activated alkenes have been successfully employed in the Baylis-Hillman reaction (Scheme 2, introduction, pages 3 and 4), application of phenyl vinyl sulfoxide as activated alkene has not been studied systematically, probably due to its less reactivity.[50]

Hu and co-workers[248] have reported an interesting rate acceleration in the Baylis-Hillman coupling of various aldehydes with methyl acrylate, using stoichiometric amount of DABCO in a 1:1 (v/v) mixture of 1,4-dioxane and water as a medium (Scheme 85). Later on, they have successfully employed less reactive activated alkene, acrylamide, in the Baylis-Hillman coupling with various reactive aromatic and hetero-aromatic aldehydes under these conditions (Scheme 85). [49]

Scheme 85



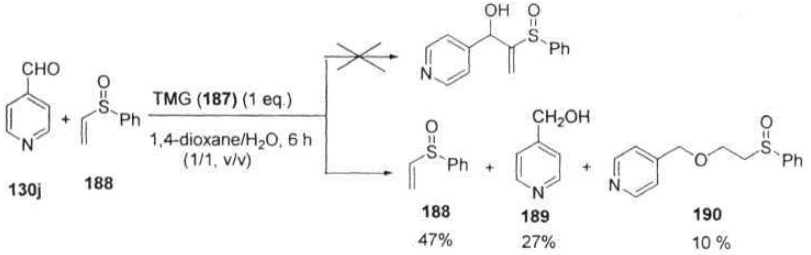
Leadbeater and co-workers[250251] elegantly demonstrated the application of 1,1,3,3-tetramethylguanidine (187) for the first time, as a catalyst for performing Baylis-Hillman reaction between various aldehydes and methyl acrylate at faster reaction rates (eq 42).

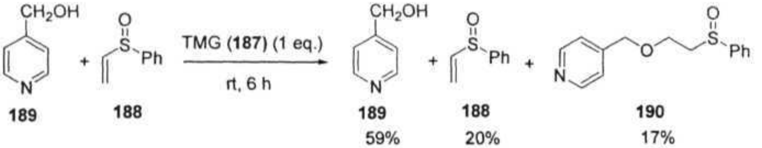


eq 42

Therefore, it occurred to us that application of TMG as a catalyst and application of aqueous medium might facilitate the less reactive activated alkene, phenyl vinyl sulfoxide to participate in Baylis-Hillman reaction with aldehydes. Accordingly, we have planned to examine the application of TMG for coupling of phenyl vinyl sulfoxide **(188)** with representative electrophiles in aqueous medium. We have first selected pyridine-4-carboxaldehyde (130j) as an electrophile because it is a very reactive aldehyde. Thus, we have carried out the reaction of pyridine-4-carboxaldehyde (**130j**) (2 mmol) with phenyl vinyl sulfoxide **(188)** (2 mmol) in the presence of 1,1,3,3-tetramethylguanidine **(187)** (2 mmol) in dioxane-water solvent system. It was interesting to note that there was no Baylis-Hillman reaction. To our pleasant surprise, 4-pyridinemethanol **(189)** was obtained in low yield (27%). The structure of this molecule was confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectral data. We were able to recover activated alkene, phenyl vinyl sulfoxide **(188)** in 47% yield. We have also noticed the formation of 1-phenylsulfinyl-2-(4-pyridylmethoxy)ethane **(190),** in 10% yield (contaminated with ~5-10% impurities) (Scheme 86). The structure of this molecule was established by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. This molecule might be formed *via* the Michael addition of 4-pyridinemethanol **(189)** (which was generated *in situ)* to phenyl vinyl sulfoxide. In fact, we have carried the reaction between 4-pyridinemethanol **(189)** (1 mmol) and phenyl vinyl sulfoxide (1 mmol) in the presence of 1,1,3,3-tetramethylguanidine (187) (1 mmol) (eq 43), with a view to confirm the structure of this product **(190).** As expected 1-phenylsulfinyl-2-(4-pyridylmethoxy)ethane **(190)** was isolated in 17% yield. This molecule is chemically pure and the structure is established by IR, ^{1}H NMR (Spectrum 37) and ^{13}C NMR (Spectrum 38) spectral data. In fact, the spectral data is in agreement with that of the molecule **190** (baring ≈5-10% impurities) formed in the attempted Baylis-Hillman reaction between pyridine-4-carboxaldehyde **(130j)** and phenyl vinyl sulfoxide **(188).** We have also recovered 4-pyridinemethanol **(189)** in 59% yield and phenyl vinyl sulfoxide **(188)** in 20% yield.

Scheme 86





eq 43

With a view to understanding the reaction, we have also performed the reaction between pyridine-4-carboxaldehyde **(130j)**[η] and phenyl vinyl sulfoxide **(188)** in the

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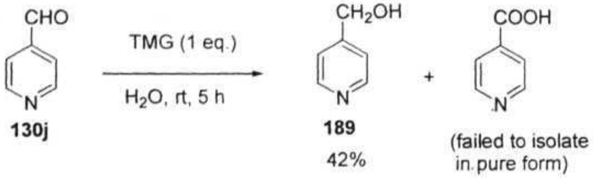
[η] For continuity and better understanding, we have numbered pyridine-4-carboxaldehyde, pyridine-3-carboxaldehyde (eq 45) and pyridine-2-carboxaldehyde (eq 45), as 130j, 130k and 130l, respectively.

presence of TMG in THF/water solvent system. In this case also, there was no Baylis-Hillman reaction and we have isolated 4-pyridinemethanol **(189)** in 23% yield and recovered phenyl vinyl sulfoxide **(188)** (46%). We also noticed the formation of 1-phenylsulfinyl-2-(4-pyridylmethoxy)ethane **(190)** in 11% yield. These results clearly suggest that phenyl vinyl sulfoxide is not undergoing the Baylis-Hillman coupling with aldehyde. In fact, it looks that the aldehyde is undergoing Cannizzaro reaction in the presence of TMG in water. To understand this aspect, we have carried out the reaction of pyridine-4-carboxaldehyde **(130j)** in water with TMG. The best result was obtained when pyridine-4-carboxaldehyde **(130j)** (2 mmol) was treated with 1,1,3,3-tetramethylguanidine **(187)** (2 mmol) in 0.5 mL of water at room temperature for 5h, thus providing 4-pyridinemethanol **(189)** in 42% yield after usual work-up followed by column chromatography (silica gel, 100% EtOAc) (eq 44 & Table 10). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 39), and ^{13}C NMR (Spectrum 40), spectral data. This result clearly indicates that the formation of alcohol **(189)** is due to the Cannizzaro reaction *i.e.*, pyridine-4-carboxaldehyde **(130j)** underwent Cannizzaro reaction in H_2O in the presence of TMG. However, our attempts to isolate pyridine-4-carboxylic acid in pure form were not successful.

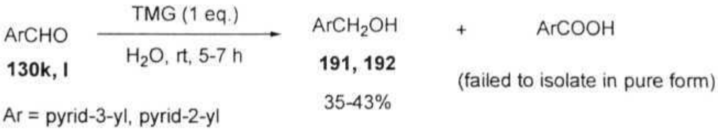


eq 44

This is an encouraging result in the sense that this is a first example of organo base (TMG) induced Cannizzaro reaction. As is well known, Cannizzaro reaction is a base induced disproportionation of an aldehyde devoid of α-hydrogens, to the corresponding primary alcohol and carboxylic acid, thus essentially involving both oxidation and reduction reactions.[1,3,252,253] In fact, prior to the discovery of metal hydrides as synthetic reagents, this reaction was considered to be one of the most fundamental reactions in synthetic organic chemistry. Several mechanistic studies[254-257] have been made on this reaction, which is usually carried out using strong alkali in aqueous or alcoholic solution, alkali amides in liquid ammonia, alkali alkoxides in alcohol solution, and alkoxides of metals such as aluminium and magnesium in alcoholic solution or in suspension in inert solvents.[253] Also, intramolecular,[258-260] asymmetric,[261] Lewis acid catalyzed,[262] metal catalyzed,[263-266] solid state[267,268] and microwave-induced Cannizzaro reactions [69-72] are known in the literature. However, to the best of our knowledge, there is no report in the literature on the organo base-induced Cannizzaro reaction. Thus, this TMG promoted Cannizzaro reaction has fascinated us. With a view to examine whether the bases such as DABCO, DBU and 3-hydroxyquinuclidine would perform Cannizzaro reaction, we have treated pyridine-4-carboxaldehyde with DABCO (1), 3-

hydroxyquinuclidine (3-HQD) (5) and DBU (8) independently in aqueous medium and noticed that there was no Cannizzaro reaction. The failure of DABCO/3-HQD/DBU to mediate Cannizzaro reaction might be attributed to the low basicity (with pKa values of 8.5, 9.9 and 12 respectively in water) while the success of TMG to perform Cannizzaro reaction might be due to its high basicity (pKa 13.6 in water).

With a view to examine the generality of TMG-promoted Cannizzaro reaction, we have selected two more aldehydes i.e., pyridine-3-carboxaldehyde **(130k)** & pyridine-2-carboxaldehyde **(130l)** for reaction with TMG in water. As expected we have isolated the corresponding alcohols **(191 & 192)** in 43 & 35% yields respectively (eq 45 & Table 10). All the molecules gave satisfactory IR, ^{1}H NMR and ^{13}C NMR spectral data. However, our attempts to isolate the corresponding acids in pure form met with failure.

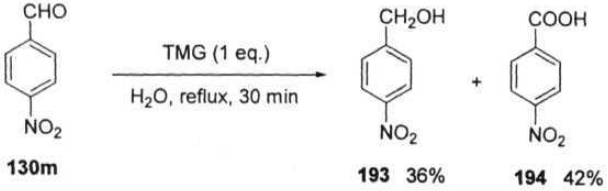


$$\underset{\textbf{130k, l}}{ArCHO} \xrightarrow[H_2O,\ rt,\ 5\text{-}7\ h]{TMG\ (1\ eq.)} \underset{\substack{\textbf{191, 192}\\ 35\text{-}43\%}}{ArCH_2OH} + \underset{\text{(failed to isolate in pure form)}}{ArCOOH} \qquad \textbf{eq 45}$$

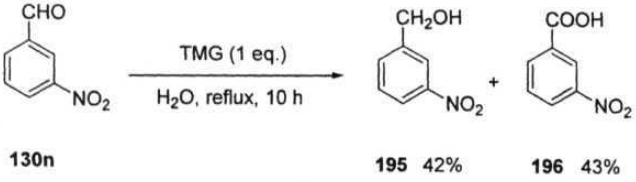
Ar = pyrid-3-yl, pyrid-2-yl

To further examine the scope of this methodology and also with a view to isolate the oxidized product (corresponding acid), we next employed **4-nitrobenzaldehyde (130m)** as a substrate in TMG promoted Cannizzaro reaction. The best result was obtained when 4-nitrobenzaldehyde **(130m)** (2 mmol) was treated with 1,1,3,3-tetramethyl-guanidine (2 mmol) in 0.5 mL of water at reflux for 30 min, thus providing 4-nitrobenzyl alcohol (193) in 36% yield, after usual work-up followed by column chromatography (silica gel, 20% EtOAc in hexanes). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 41) and ^{13}CNMR (Spectrum 42) spectral data. In this case, we have successfully isolated the corresponding oxidized product, *i.e.,* 4-nitrobenzoic acid (194) in 42% yield, after usual work-up (from the aqueous layer), followed by crystallization from EtOAc: hexanes (1:4) (eq 46 & Table 10). Structure of this molecule was confirmed by IR, ^{1}H NMR and ^{13}C NMR (Spectrum 43) spectral data.

Next, we have extended the same methodology to 3-nitrobenzaldehyde (130n). The resulting primary alcohol 195 was obtained in 42% yield. We have also successfully isolated the corresponding oxidized product 3-nitrobenzoic acid (196) in 43% yield (eq 47 & Table 10). Structures of these molecules were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.



eq 46



eq 47

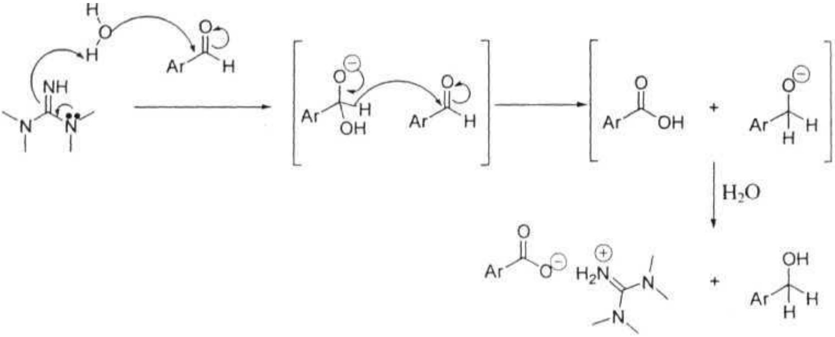
Table 10. TMG promoted Cannizzaro reaction of reactive aldehydes[a]

S.No.	Substrate	Ar	Time (hours)	Products[b-d]			
				Alcohol	Yield (%)[c]	Acid	Yield (%)[c]
1	**130j**	pyrid-4-yl	5	**189**	42	failed to isolate in pure form	
2	**130k**	pyrid-3-yl	7	**191**	43	-do-	
3	**130l**	pyrid-2-yl	5	**192**	35	-do-	
4	**130m**	4-(NO_2)Ph	0.5	**193**	36	**194**	42
5	**130n**	3-(NO_2)Ph	10	**195**	42	**196**	43

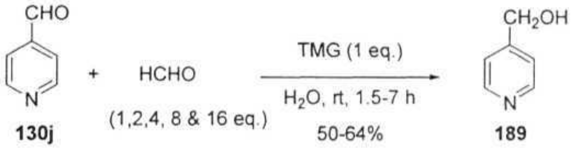
a) Cannizzaro reaction of aldehydes **130j-l**, were carried out on 2 mmol scale using 1,1,3,3-tetramethylguanidine (2 mmol) in 0.5 mL water, at room temperature while that of aldehydes **(130m,n)** were carried on 2 mmol scale using 1,1,3,3-tetramethylguanidine (2 mmol) in 0.5 mL water at reflux temperature. b) The products **189, 193, 194, 196** were obtained as crystalline solids, while **191, 192, 195** as liquids. c) All the products gave satisfactory IR, ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectral data. d) These molecules are known in the literature and even Aldrich **sells these** molecules.[273-276] The IR and ^{1}H NMR spectra of these molecules are in agreement with that of the reported. e) Isolated yields of the pure products [for **189, 191, 192** after column chromatography (silica gel, 100% EtOAc), for **193, 195** after column chromatography (silica gel, 20% EtOAc in hexanes) and for **194, 196** after crystallization from EtOAc: hexanes (1:4)].

Based on the above observations, we have proposed the following plausible mechanism for the TMG induced Cannizzaro reaction (Scheme 87).

Scheme 87



As is well known, Cannizzaro reaction provides the reduced product (alcohol) and the oxidized product (acid) in maximum of 50% yield from the corresponding aldehyde. HCHO has been successfully employed as **sacrificing** aldehyde in cross-Cannizzaro reaction where the expensive aldehyde has the opportunity to be converted into the corresponding alcohol in high yields.[269,272] With a view to examine this aspect, we have carried out the reaction between **pyridine-4-carboxaldehyde** (130j) and HCHO in the presence of TMG in water. The best results were obtained when **pyridine-4-**carboxaldehyde (130j) (2 **mmol**) was treated with formalin (37% w/v) (2 **mmol**) in 0.5 **mL** of water in the presence of **1,1,3,3-tetramethylguanidine** (187) (2 mmol) at room temperature for 4 h, thus providing the desired alcohol (189) in 50% yield. Structure of this molecule was confirmed by **IR**, ^{1}H NMR and ^{13}C NMR spectral data. In order to optimize the reaction conditions, we have carried out the cross-Cannizzaro reaction of pyridine-4-carboxaldehyde **(130j)** (2 mmol, 0.214 g) with various amounts of HCHO (2, 4, 8 and 16 equivalents) in the presence of TMG in water and found that the maximum yield (64%) of desired alcohol (189), was obtained with 16 eq. of formalin (eq 48 & Table 11).



eq 48

Table 11. TMG promoted Cannizzaro reaction of pyridine-4-carboxaldehyde (130j) with varying amounts of **HCHO**[a]

S.No.	No. of equivalents of HCHO	Time (hours)	4-Pyridinemethanol Yield (%)[d]
1	1	4	50
2	2	1.5	57
3	4	1.5	59
4	8	4	60
5	16	7	64

a) All the reactions were carried out on 2 mmol scale of aldehyde **(130j)** using 1,1,3,3-tetramethylguanidine (2 mmol) in 0.5 **mL** water at room temperature.

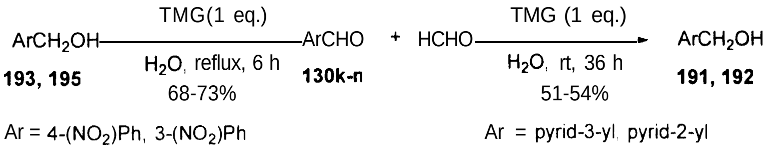
Table 12. TMG promoted cross-Cannizzaro reaction of aldehydes with 16 eq. of HCHO[a]

S.No	Substrate	Ar	Time (hours)	Product[b-d] ($ArCH_2OH$)	Yield (%)[c]
1	**130j**	pyrid-4-yl	7	**189**	64
2	**130k**	pyrid-3-yl	36	191	54
3	**130l**	pyrid-2-yl	36	192	51
4	**130m**	4-(NO_2)Ph	6	193	73
5	**130n**	3-(NO_2)Ph	6	195	68

a) Cross-Cannizzaro reaction of aldehydes **130j-l**, were carried out on 2 mmol scale with 16 eq. of HCHO (37% w/v) in the presence of 1,1,3,3-tetramethylguanidine (2 mmol) in 0.5 mL water at room temperature, while that of the aldehydes **130m,n** were carried on 2 mmol scale with 16 eq. of HCHO using 1,1,3,3-tetramethylguanidine (2 mmol) in 0.5 mL water at reflux temperature. b) The products **189** & **193** were obtained as crystalline solids, while the products **191, 192** & **195** as liquids. c) All the products gave satisfactory IR, ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectral data. d) These molecules are known in the literature and even Aldrich sells these molecules.[273-275] The IR and ^{1}H NMR spectra of these molecules are in agreement with that of the reported. e) Isolated yields of the pure products [for **189, 191** & **192** after column chromatography (silica gel, 100% EtOAc), and for **193** & **195** after column chromatography (silica gel, 20% EtOAc in hexanes).

With a view to understand the generality of cross-Cannizzaro reaction, we have employed representative aldehydes **(130k,l)** for reaction with HCHO (16 eq.) in the presence of TMG, thus providing the desired alcohols **(191** & **192)** in 54 & 51% yields respectively. Pyridine carboxaldehydes undergo cross-Cannizzaro reaction at room temperature while nitrobenzaldehydes **(130m,n)** required high temperatures to undergo cross-Cannizzaro reaction, to provide the desired alcohols **(193** & **195)** in 73 & 68% yields respectively (Scheme 88 & Table 12). Structures of these molecules, were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Scheme 88



However, our attempts to use less reactive aldehyde, benzaldehyde for TMG promoted Cannizzaro/cross-Cannizzaro reaction (with HCHO) were unsuccessful.

In conclusion, though we were not successful in employing phenyl vinyl sulfoxide as an activated alkene in Baylis-Hillman coupling using TMG, we have for the first time described an organo base (TMG) promoted Cannizzaro reaction. Although this reaction is applicable to only very reactive aldehydes, this work provides new perspectives for Cannizzaro reaction.

CONCLUSIONS

We have achieved considerable success in our objectives on the applications of Baylis-Hillman chemistry as mentioned in the beginning of this section. We have successfully employed alkyl 2-(bromomethyl)prop-2-enoates derived from Baylis-Hillman adducts, as valuable electrophiles in the Baylis-Hillman coupling reaction with various activated alkenes such as acyclic & cyclic enones, acrylonitrile and alkyl acrylates in the presence of tertiary amines such as DABCO (or DBU), thus leading to the development of a one-pot convenient methodology for synthesis of 2,4-functionalized 1,4-pentadienes. We have successfully developed a one-pot facile methodology for synthesis of 2-benzoxepine derivatives *via* the tandem construction of C-0 and C-C bonds involving the Prins type and Friedel-Crafts type reactions of Baylis-Hillman adducts (derived form various aromatic aldehydes and alkyl acrylates) with HCHO in the presence of conc. H2SO4. We have examined the diastereoselective addition of oxygen nucleophiles such as propargyl alcohol and phenol on to the Baylis-Hillman bromides, under the influence of chiral auxiliaries. (-)-Menthol as a chiral auxiliary provides the resulting (-)-menthyl 3-aryl-2-methylene-3-(prop-2-yn-l-yloxy)propanoates and (-)-menthyl 3-aryl-2-methylene-3-phenoxypropanoates in 4-23% and 26-35% diastereoselectivities respectively, while the Oppolzer's chiral auxiliary [(1*S*,2*R*,4*R*)-1-(diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol] provides the resulting (1 '*S*,2'*R*,4'*R*)-1 '-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo-

(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates and (1'*S*,2'*R*,4'*R*)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-phenoxypropanoates in 51-88% and 54-82% diastereoselectivities respectively. Finally, though we were not successful in employing phenyl vinyl sulfoxide as an activated alkene in Baylis-Hillman coupling with reactive aldehydes using 1,1,3,3-tetramethylguanidine (TMG), we have for the first time described an organo base (TMG) promoted Cannizzaro reaction of reactive aldehydes.

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 Analyses: 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. ^{1}H NMR (200 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, with TMS (5 = 0 ppm) as internal standard. ^{13}C NMR (50 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, with its middle peak of the triplet (8 = **77.10** ppm) as **internal** standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity, that is, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ABq = AB quartet, d of ABq = doublet of AB quartet, b = broad, (3) number of hydrogens integrated for the signal, (4) coupling constant J in Hertz.

Mass **Spectral Analyses:** Mass spectra were recorded cither on VG7070H mass spectrometer using EI technique or on Auto spec mass spectrometer using LSIMS technique (FAB).

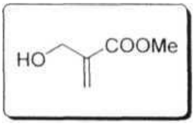
Optical Rotations: Optical rotations were measured on JASCO DIP 370 digital polarimeter at the wavelength of the sodium D-line (589 nm) at ambient temperature.

Chromatography: Analytical Thin Layer Chromatography (TLC) was performed on glass plates (7 × 2 cm) coated with Acme's silica gel GF 254 (254 mμ) containing 13% calcium **sulfate** as a 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-lOA UV-VIS detector using HPLC grade solvents.

General: All the solvents 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 using Thin Layer Chromatography (TLC).

Methyl 2-(hydroxymethyl)prop-2-enoate (100a):

This molecule was prepared according to the procedure developed in our laboratory.[79] A mixture of paraformaldehyde (200 mmol, 6.006 g), aqueous trimethylamine (30%, w/v) (240 mmol, 47.28 mL) and methyl acrylate (400 mmol, 34.4 g) was heated at 60 °C for 6 h. The reaction mixture was then cooled to room temperature. Organic layer was separated and the aqueous layer was extracted with ether (2x25 mL). The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4). Solvent was evaporated and the crude product thus obtained, was distilled under reduced pressure to afford the desired product **100a,** as colorless oil, in 50% (11.5 g) yield.



Bp.: 84-85 °C/4 mm (lit.[79] 71-72 °C/2 mm)

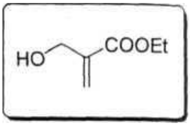
IR (Neat): v 3431, 1720, 1637 cm^{-1}

^{1}H NMR: δ 2.28 (b, 1H), 3.79 (s, 3H), 4.33 (s, 2H), 5.84 (s, 1H), 6.26 (s, 1H)

^{13}C NMR: 5 51.65,61.55, 125.22, 139.46, 166.65

Ethyl 2-(hydroxymethyl)prop-2-enoate (100b):

This was obtained *via* the treatment of paraformaldeyde with ethyl acrylate in the presence of aqueous trimethylamine (30%, w/v), following a similar procedure described for the molecule **100a,** as a colorless liquid.



Yield: 62%

Bp.: 84-87 °C/2.5 mm (lit.[198] 65-70 °C/1 mm)

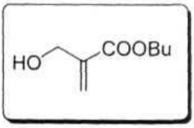
IR (Neat): ν 3410, 1712, 1639 cm^{-1}

^{1}H NMR: 6 1.32 (t, 3H, *J* = 6.8 Hz), 2.24 (b, 1H), 4.25 (q, 2H, *J* = 6.8 Hz), 4.33 (s, 2H), 5.82 (s, 1H), 6.25 (s, 1H)

^{13}C NMR: δ 13.95, 60.69, 61.67, 124.97, 139.75, 166.27

Butyl 2-(hydroxymethyl)prop-2-enoate (100c):

This was prepared *via* the reaction of paraformaldeyde with butyl acrylate under the influence of aqueous trimethylamine (30%, w/v), following a similar procedure described for the molecule **100a**, as a colorless liquid.



Yield: 65%

Bp.: 69-71 °C/0.2 mm (lit.[79] 80 °C/0.5 mm)

IR (Neat): ν 3420, 1712, 1637 cm"^{1}

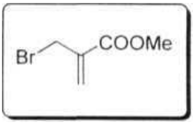
^{1}H NMR: δ 0.94 (t, 3H, *J* = 7.4 Hz), 1.30-1.52 (m, 2H), 1.57-1.78 (m, 2H), 2.32 (b, 1H), 4.18 (t, 2H, *J* = 6.8 Hz), 4.32 (s, 2H), 5.81 (s, 1H), 6.24 (s, 1H)

^{13}C NMR: δ 13.51, 19.05, 30.49, 61.79, 64.57, 124.92, 139.76, 166.30

Methyl 2-(bromomethyl)prop-2-enoate (101a):

This molecule was prepared according to the literature procedure.[198]

To a stirred solution of methyl 2-(hydroxymethyl)prop-2-enoate **(100a)** (30 mmol, 3.48 g) in benzene (25 mL) was added PBr_3 (75 mmol, 20.3 g) drop wise at room temperature. 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, saturated aqueous $NaHCO_3$ solution and water successively and was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained, was purified by column chromatography (silica gel, 2% EtOAc in hexanes) followed by distillation under reduced pressure to provide the desired product **101a,** as a colorless liquid, in 85% (4.55 g) yield.



Bp.: 47-48 °C/3.7 mm (lit.[277] 35-37 °C/1.3 mm)

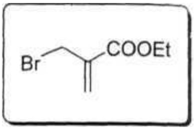
IR(Neat): v 1728, 1631 cm^{-1}

^1H NMR: 8 3.82 (s, 3H), 4.18 (s, 2H), 5.96 (s, 1H), 6.34 (s, 1H)

^{13}C NMR: 8 29.16, 52.16, 129.06, 137.33, 165.20

Ethyl 2-(bromomethyl)prop-2-enoate (101b):

The treatment of ethyl 2-(hydroxymethyl)prop-2-enoate **(100b)** with PBr_3, following a similar procedure described for the molecule **101a,** afforded the desired **compound 101b,** as a colorless liquid.



Yield: 72%

Bp.: 56-57 °C/3.0 mm (lit.[198] 44-45 °C/1.7 mm)

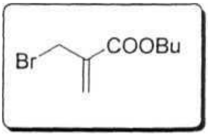
IR (Neat): v 1724, 1630 cm^{-1}

H NMR: δ 1.33 (t, 3H,./ = 6.8 Hz), 4.18 (s, 2H), 4.27 (q, 2H, J = 6.8 Hz), 5.94 (s, 1H), 6.33(s, 1H)

^{13}C NMR: 6 14.08,29.30,61.21, 128.76, 137.60, 164.73

Butyl 2-(bromomethyl)prop-2-enoate (101c):

This was prepared *via* the reaction of butyl 2-(hydroxymethyl)prop-2-enoate **(100c)** with PBr_3, following a similar procedure described for the molecule **101a,** as a colorless liquid.



Yield: 91%

Bp.: 67-68 °C/0.6 mm

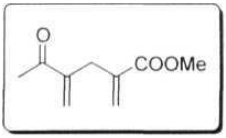
IR (Neat): v 1724, 1631 cm^{-1}

H NMR: 5 0.95 (t, 3H, J= 7.4 Hz), 1.32-1.57 (m, 2H), 1.59-1.81 (m, 2H), **4.18** (s, 2H), 4.22 (t, 2H, J= 6.4 Hz), 5.94 (s, 1H), 6.33 (s, 1H)

^{13}C NMR: 6 13.62, 19.12, 29.28, 30.55, 65.07, 128.77, 137.62, 164.81

Methyl 2,4-dimethylidene-5-oxohexanoate (102):

A solution of methyl 2-(bromomethyl)prop-2-enoate **(101a)** (1 mmol, 0.179 g) and DABCO (2 mmol, 0.224 g) in methyl vinyl ketone (1 mL) was kept at room temperature for 15 minutes. 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, 4% EtOAc in hexanes) to provide pure methyl 2,4-dimethylidene-5-oxohexanoate (102), as a colorless liquid.

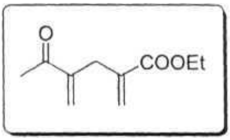


Yield:	82% (0.138 g)
IR(Neat):	v 1722, 1680, 1631cm^{-1}
^{1}H NMR:	5 2.35 (s, 3H), 3.29 (s, 2H), 3.74 (s, 3H), 5.57 (s, 1H), 5.81 (s, 1H), 6.10(s, 1H), 6.24(s, 1H)
^{13}C NMR:	5 25.49, 32.35, 51.56, 126.28, 126.62, 137.91, 146.15, 166.84, 198.34
MS (*m/z*):	168 (M$^+$)

Analysis calcd. for $C_9H_{12}O_3$:	C, 64.27; H, 7.19
Found:	C, 64.42; H, 7.21

Ethyl 2,4-dimethylidene-5-oxohexanoate (103):

The treatment of ethyl 2-(bromomethyl)prop-2-enoate **(101b)** with methyl vinyl ketone, under the influence of DABCO, following a similar procedure described for the molecule **102,** provided the desired product **103,** as a colorless liquid.



Yield: 78%

IR(Neat): v 1718, 1680,1631 cm^{-1}

^{1}H NMR: δ 1.28 (t, 3H, J = 7.0 Hz), 2.35 (s, 3H), 3.29 (s, 2H), 4.19 (q, 2H, J = 7.0 Hz), 5.55 (d, 1H, J = 1.4 Hz), 5.81 (s, 1H), 6.10 (s, 1H), 6.24 (s, 1H)

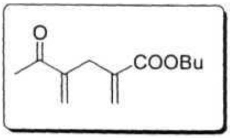
^{13}C NMR: δ 13.96, 25.55, 32.37, 60.51, 126.25, 126.41, 138.25, 146.30, 166.43, 198.41

Analysis calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74

Found: C, 65.69; H, 7.70

Butyl 2,4-dimethylidene-5-oxohexanoate (104):

This product was isolated as a colorless liquid *via* the reaction of butyl 2-(bromomethyl)prop-2-enoate **(101c)** with methyl vinyl ketone, in the presence of DABCO, following a similar procedure described for the molecule **102.**



Yield: 84%

IR (Neat): v 1718, 1680, 1631 cm^{-1}

^{1}H NMR: 6 0.93 (t, 3H, *J* = 7.1 Hz), 1.24-1.50 (m, 2H), 1.53-1.73 (m, 2H), 2.34 (s, 3H), 3.29 (s, 2H), 4.13 (t, 2H, *J* = 6.8 Hz), 5.55 (d, 1H, *J* = 2.0 Hz), 5.80 (d, 1H, *J* = 1.6 Hz), 6.10 (s, 1H), 6.24 (s, 1H)

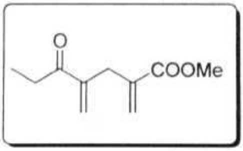
^{13}C NMR: 5 13.47, 19.04, 25.55, 30.55, 32.45, 64.45, 126.06, 126.41, 138.34, 146.44, 166.53, 198.35

Analysis calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63

Found: C, 68.29; H, 8.68

Methyl 2,4-dimethylidene-5-oxoheptanoate (105):

This was prepared *via* the treatment of methyl 2-(bromomethyl)prop-2-enoate (**101a**) with ethyl vinyl ketone, **under** the influence of DABCO, following a similar **procedure** described for the molecule **102**, as a colorless liquid.



Yield: 77%

IR (Neat): v 1724, 1680, 1631 cm^{-1}

^{1}H NMR: 8 1.10 (t, 3H, *J* = 7.2 Hz), 2.72 (q, 2H, *J* = 7.2 Hz), 3.31 (s, 2H), 3.74 (s, 3H), 5.57 (d, 1H, *J* = 1.2 Hz), 5.75 (d, 1H, *J*= 1.2 Hz), 6.09 (s, 1H),6.23(s, 1H)

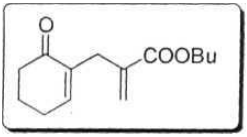
^{13}C NMR: δ 8.14, 30.69, 32.75, 51.64, 125.02, 126.70, 137.98, 145.67, 166.93,201.17

Analysis calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74

Found: C, 66.22; H, 7.71

2-[2-(Butoxycarbonyl)prop-2-en-1-yl]cyclohex-2-en-1-one (106):

A solution of butyl 2-(bromomethyl)prop-2-enoate **(101c)** (1 mmol, 0.221 g) and DBU (2 mmol, 0.304 g) in cyclohex-2-enone (1 mL) was kept at room temperature for 1h. The reaction mixture was diluted with ether (15 mL) and washed successively with 2N HC1 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, 4% EtOAc in hexanes) to provide the pure 2-[2-(butoxycarbonyl)prop-2-en-l-yl]cyclohex-2-en-l-one **(106),** as colorless liquid.



Yield: 80% (0.189 g)

IR (Neat): ν 1718, 1676, 1631 cm^{-1}

^{1}H NMR: δ 0.93 (t, 3H, J = 7.2 Hz). 1.24-1.52 (m, 2H), 1.54-1.75 (m, 2H), 1.90-2.10 (m, 2H), 2.28-2.51 (m, 4H), 3.22 (s, 2H), 4.13 (t, 2H, J = 6.5 Hz), 5.55 (s, 1H), 6.21 (s, 1H), 6.75 (t, 1H, J = 4.2 Hz)

^{13}C NMR: δ 13.48, 19.01, 22.88, 25.93, 30.50, 31.15, 38.25, 64.31, 126.20, 136.95, 138.38, 146.46, 166.68, 198.12

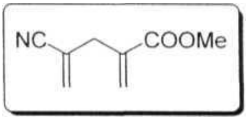
MS (*m/z*): 236 (M^+)

Analysis calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53

Found: C, 71.30; H, 8.50

Methyl 2-methylidene-4-cyanopent-4-enoate (107):

A solution of methyl 2-(bromomethyl)prop-2-enoate **(101a)** (1 mmol, 0.179 g) and DABCO (2 mmol, 0.224 g) in acrylonitrile (1 mL) was kept at room temperature for 4 h. 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, 4% EtOAc in hexanes) to provide the pure methyl 2-methylidene-4-cyanopent-4-enoate (**107**), as colorless liquid.



Yield: 81% (0.122 g)

IR (Neat): v 2226, 1722, 1635 cm"^{1}

^{1}H NMR: δ 3.25 (s, 2H), 3.77 (s, 3H), 5.77 (s, 1H), 5.83 (s, 1H), 5.96 (s, 1H), 6.39 (s, 1H)

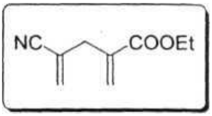
^{13}C NMR: 8 36.47,51.85, 117.84, 120.31, 128.21, 132.07, 135.28, 165.97

Analysis calcd. for $C_8H_9NO_2$: C, 63.57; H, 6.00; N,9.27

Found: C, 63.78; H, 6.05; N, 9.31

Ethyl 2-methylidene-4-cyanopent-4-enoate (108):

The treatment of ethyl 2-(bromomethyl)prop-2-enoate **(101b)** with acrylonitrile, under the influence of DABCO, following a similar procedure described for the molecule 107, afforded the desired compound **108,** as a colorless liquid.



Yield: **83%**

IR (Neat): ν 2226, 1718, 1633 cm^{-1}

H NMR: 8 1.31 **(t,** 3H,./= 7.3 Hz), 3.25 (s, **2H),** 4.22 **(q,** 2H, *J*= 7.3 Hz), 5.75 (s, **1H),** 5.83 (s, 1H), 5.96 (s, 1H), 6.38 (s, 1H)

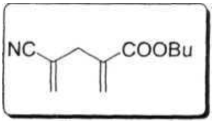
^{13}C NMR: δ 13.92, 36.49, 60.92, 117.92, 120.38, 128.02, 132.08, 135.51, 165.51

Analysis calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48

Found: C, 65.17; H, 6.67; N, 8.53

Butyl 2-methylidene-4-cyanopent-4-enoate (109):

This was obtained as a colorless liquid *via* the reaction of butyl 2-(bromomethyl)prop-2-enoate **(101c)** with acrylonitrile, in the presence of DABCO, following a similar procedure described for the molecule **107.**



Yield: 85%

IR (Neat): ν **2226, 1718,** 1633 cm^{-1}

HNMR: δ **0.94 (t,** 3H, 7.3 Hz), 1.24-1.52 (m, 2H), **1.54-1.77** (m, 2H), 3.25 (s, 2H), **4.17 (t, 2H,** *J* =6.9 Hz), 5.75 **(s, 1H),** 5.83 (s, **1H),** **5.96** (s, 1H),6.38(s, **1H)**

^{13}C NMR: 8 13.47, 19.04, 30.50, 36.57, 64.85, 117.91, 120.54, 127.98, 131.93, 135.62, 165.61

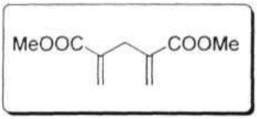
MS (*m/z*): 193 (M^+)

Analysis calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25

Found: C, 68.13; H, 7.86; N, 7.19

2,4-Di(methoxycarbonyl)penta-1,4-diene (110):

A solution of methyl 2-(bromomethyl)prop-2-enoate **(101a)** (1 mmol, 0.179 g) and DABCO (2 mmol, 0.224 g) in methyl acrylate (1 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 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, 4% EtOAc in hexanes) to provide pure 2,4-di(methoxycarbonyl)penta-1,4-diene (**110**), as colorless liquid.



Yield: 80% (0.147 g)

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

^{1}H NMR: 8 3.33 (s, 2H), 3.74 (s, 6H), 5.60 (s, 2H), 6.25 (s, 2H)

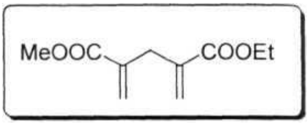
^{13}C NMR: 8 33.65, 51.69, 126.61, 137.69, 166.85

Analysis calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57

Found: C, 58.88; H, 6.50

2-Ethoxycarbonyl-4-methoxycarbonylpenta-1,4-diene (111):

This was prepared *via* the treatment of ethyl 2-(bromomethyl)prop-2-enoate **(101b)** with methyl acrylate, under the influence of DABCO, following a similar procedure described for the molecule **110**, as a colorless liquid.



Yield: 84%

IR(Neat): ν 1722, 1631 cm^{-1}

^1H NMR: δ 1.28 (t, 3H, J = 7.3 Hz), 3.33 (s, 2H), 3.75 (s, 3H), 4.20 (q, 2H, J = 7.3 Hz), 5.56-5.66 (m, 2H), 6.25 (s, 2H)

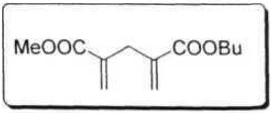
^{13}C NMR: δ 14.03, 33.68, 51.73, 60.64, 126.38, 126.62, 137.83, 138.04, 166.42, 166.94

Analysis calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12

Found: C, 60.42; H, 7.15

2-(Butoxycarbonyl)-4-methoxycarbonylpenta-1,4-diene (112):

This compound was isolated as a colorless liquid *via* the reaction of butyl 2-(bromomethyl)prop-2-enoate **(101c)** with methyl acrylate, in the presence of DABCO, following a similar procedure described for the molecule **110**.



Yield: 85%

IR(Neat): ν 1722, 1631 cm^{-1}

^{1}H NMR: 8 0.94 (t, 3H, *J* = 7.0 Hz), 1.24-1.52 (m, 2H), 1.54-1.75 (m, 2H), 3.33 (s, 2H), 3.75 (s, 3H), 4.15 (t, 2H, *J* = 6.4 Hz), 5.59 (m, 2H), 6.26 (s, 2H)

^{13}C NMR: 8 13.51, 19.06, 30.55, 33.66, 51.67, 64.50, 126.32, 126.49, 137.84, 138.06, 166.45, 166.88

MS (*m/z*): 226 (M^{+})

Analysis calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02

Found: C, 63.62; H, 8.04

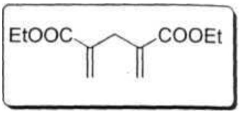
2-Ethoxycarbonyl-4-methoxycarbonylpenta-1,4-diene (111):

The treatment of methyl 2-(bromomethyl)prop-2-enoate **(101a)** with ethyl acrylate, under the influence of DABCO, following a similar procedure described for the molecule **110**, provided the desired compound **111**, as a colorless liquid, in 81% yield.

Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are identical with that of the molecule prepared from ethyl 2-(bromomethyl)prop-2-enoate (**101b**) and methyl acrylate.

2,4-Di(ethoxycarbonyl)penta-1,4-diene (113):

This was obtained as a colorless liquid *via* the treatment of ethyl 2-(bromomethyl)prop-2-enoate **(101b)** with ethyl acrylate, under the influence of DABCO, following a similar procedure described for the molecule **110.**



Yield: 82%

IR(Neat): v 1720, 1631 cm^{-1}

^{1}H NMR: 8 1.28 (t, 6H, *J* = 7.2 Hz), 3.33 (s, 2H), 4.20 (q, 4H, *J*= *12* Hz), 5.57 (s, 2H), 6.24 (s, 2H)

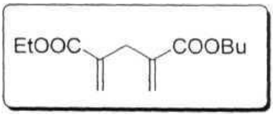
^{13}C NMR: 8 14.02, 33.64, 60.60, 126.29, 138.13, 166.44

Analysis calcd. for $C_{11}H_{16}O_4$: C, 62.25; 11, 7.60

Found: C, 62.48; H, 7.56

2-(Butoxycarbonyl)-4-ethoxycarbonylpenta-1,4-diene (114):

This was prepared *via* the treatment of butyl 2-(bromomethyl)prop-2-enoate (101c) with ethyl acrylate, in the presence of DABCO, following a similar procedure described for the molecule **110**, as a colorless liquid.



Yield: 78%

IR (Neat): v 1720, 1633 cm^{-1}

^{1}H NMR: 8 0.93 (t, 3H, *J* = 7.3 Hz), 1.20-1.52 (m, 5H), 1.54-1.76 (m, 2H), 3.33 (s, 2H), 4.09-4.29 (m, 4H), 5.58 (s, 2H), 6.25 (s, 2H)

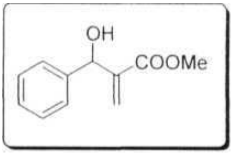
^{13}C NMR: 8 13.56, 14.06, 19.11, 30.60, 33.69, 60.63, 64.54, 126.31, 138.18, 166.47,166.53

Analysis calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39

Found: C, 65.14; H, 8.35

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (131a):

A mixture of benzaldehyde **(130a)** (50 mmol, 5.306 g), methyl acrylate (75 mmol, 6.456 g) and DABCO (15 mol%, 7.5 mmol, 0.841 g) was kept at room temperature for 7 days. The reaction mixture was diluted with ether (50 mL) and washed successively with 2N HC1 solution, water and saturated $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained, was distilled under reduced pressure, to afford the desired product **131a**, as a colorless liquid.



Yield: 85% (8.112 g)

Bp.: 121-122 ^{0}C/2.4 mm

IR(Neat): v 3470, 1716, 1630 cm^{-1}

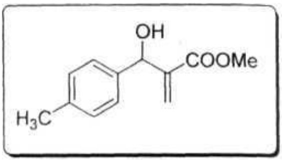
^{1}H NMR: δ 3.02 (d, 1H, J = 5.2 Hz), 3.73 (s, 3H), 5.57 (d, 1H, J = 5.2 Hz), 5.83 (s, 1H), 6.34 (s, 1H), 7.21-7.53 (m, 5H)

^{13}C NMR: 5 51.86, 72.90, 125.78, 126.72, 127.78, 128.39, 141.50, 142.27, 166.74

Methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (131b):

It was obtained as a colorless liquid *via* the reaction of 4-methylbenzaldehyde **(130b)** with methyl acrylate in the presence of a catalytic amount of DABCO, following the similar procedure described for the molecule **Ola.**

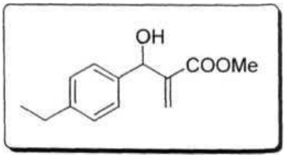
Reaction time:	8 days
Yield:	85%
Bp.:	135-136 °C/2.3 mm
IR (Neat):	v 3439, 1722, 1630 cm^{-1}
^1H NMR:	6 2.34 (s, 3H), 2.89 (d, 1H, *J* = 5.0 Hz), 3.72 (s, 3H), 5.54 (d, 1H, *J* = 5.0 Hz), 5.85 (s, 1H), 6.32 (s, 1H), 7.15 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz)
^{13}C NMR:	6 21.11, 51.77, 72.68, 125.41, 126.09, 126.72, 137.39, 138.66, 142.44, 166.75



Methyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (131c):

This compound was prepared *via* the coupling of 4-ethylbenzaldehyde **(130c)** with methyl acrylate in the presence of DABCO (cat.), following a similar procedure **described** for **the molecule 131a, as a colorless viscous liquid.**

Reaction time:	7 **days**
Yield:	**77%**
Bp.:	152-154 °C/4.8 **mm**
IR (Neat):	**ν 3462, 1722, 1630 cm^{-1}**

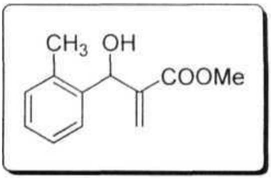


^{1}H NMR: δ 1.23 (t, 3H, *J*= 7.6 Hz), 2.64 (q, 2H, *J* = 7.6 Hz), 2.89 (d, 1H, *J* = 5.4 Hz), 3.72 (s, 3H), 5.54 (d, 1H, *J* = 5.4 Hz), 5.85 (d, 1H, *J* = 1.8 Hz), 6.33 (s, 1H), 7.17 (d, 2H, *J*= 7.8 Hz),), 7.29 (d, 2H, *J*= 7.8 Hz)

^{13}C NMR: 8 15.45, 28.53, 51.81, 72.79, 125.51, 126.72, 127.88, 138.80, 142.39, 143.77, 166.77

Methyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate (131d):

The reaction of 2-methylbenzaldehyde **(130d)** with methyl acrylate in the presence of DABCO (cat.), following a similar procedure described for the molecule **Ola,** provided the desired compound **131** d, as a colorless liquid.



Reaction time: 8 days

Yield: 78%

Bp.: 137-139 °C/4 mm

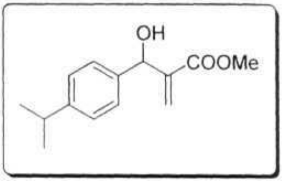
IR (Neat): v 3433, 1722, 1630 cm^{-1}

^{1}H NMR: 8 2.33 (s, 3H), 2.82 (b, 1H), 3.77 (s, 3H), 5.61 (s, 1H), 5.82 (s, 1H), 6.32 (s, 1H), 7.09-7.30 (m, 3H), 7.37-7.49 (m, 1H)

^{13}C NMR: δ 19.04, 51.93, 69.08, 125.95, 126.13, 126.38, 127.76, 130.43, 135.72, 138.99, 141.97, 167.05

Methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate (131 e):

This compound was isolated as a colorless viscous liquid *via* the reaction of 4-isopropylbenzaldehyde (130e) with methyl acrylate in the presence of DABCO (cat.), following a similar procedure described for the molecule **131a.**



Reaction time: 7 days

Yield: 75%

Bp.: 160-161 ^{0}C/3 mm

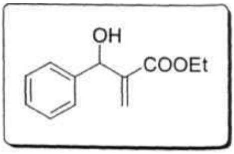
IR (Neat): v 3466, 1722, 1630 cm^{-1}

^{1}H NMR: 8 1.24 (d, 6H, *J* = 7.0 Hz), 2.81-3.02 (m, 1H), 3.10 (b, 1H), 3.73 (s, 3H), 5.55 (d, 1H, *J*= 5.2 Hz), 5.85 (s, 1H), 6.33 (s, 1H), 7.20 (d, 2H, *J* = 8.6 Hz), 7.30 (d, 2H, *J* = 8.6 Hz)

^{13}C NMR: 5 23.97, 33.82, 51.81, 72.77, 125.51, 126.43, 126.72, 138.90, 142.39, 148.36, 166.65

Ethyl 3-hydroxy-2-methylene-3-phenylpropanoate (132a):

This product was prepared by the reaction between benzaldehyde **(130a)** and ethyl acrylate in the presence of catalytic amount of DABCO, following the similar procedure described for the molecule **131a,** as colorless liquid.



Reaction time: 7 days

Yield: 80%

Bp.: 120-122 °C/1.2 mm

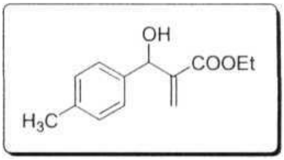
IR (Neat): v 3462, 1714, 1630 cm^{-1}

^{1}H NMR: 8 1.24 (t, 3H, *J*= 7.0 Hz), 3.03 (d. 1H, *J* = 5.8 Hz), 4.18 (q, 2H, *J* = 7.0 Hz), 5.57 (d, 1H. *J* = 5.8 Hz), 5.81 (d, 1H, *J* = 2.0 Hz)), 6.34 (s, 1H), 7.20-7.45 (m,5H)

^{13}C NMR: 8 13.98, 60.85, 72.97, 125.29. 126.72, 127.70, 128.33, 141.58, 142.53, 166.31

Ethyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (132b):

The treatment of 4-methylbenzaldehyde **(130b)** with ethyl acrylate in the presence of a catalytic amount of DABCO, following the similar procedure described for **the** molecule **Ola,** afforded the desired compound **132b,** as a colorless liquid.



Reaction time: 8 days

Yield: 75%

Bp.: 130-133 °C/0.9 mm

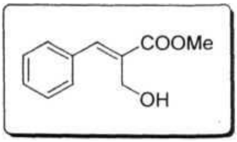
IR (Neat): v 3466, 1716, 1630 cm^{-1}

^{1}H NMR: 8 1.25 (t, 3H, *J* = 7.6 Hz), 2.34 (s, 3H), 2.94 (d, 1H, *J* = 5.8 Hz), 4.17 (q, 2H, *J* =7.6 Hz), 5.55 (d, 1H. *J* =5.8 Hz), 5.82 (d, 1H, J = 2.0 Hz), 6.32 (s, 1H), 7.15 (d, 2H, *J*= 7.8 Hz), 7.27 (d, 2H, *J*= 7.8 Hz)

^{13}C NMR: 6 14.01, 21.07, 60.79, 72.78, 125.15, 126.70, 129.02, 137.31, 138.71, 142.69, 166.33

Methyl (2*E*)-2-(hydroxymethyl)-3-phenylprop-2-enoate (135a):

This molecule was prepared according to **the procedure developed in** our laboratory.[215] To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(Ola)** (20 mmol, 3.84 g) and acetic anhydride (24 mmol, 2.45 g,) in CH_2Cl_2 (20 mL), was added TMSOTf (11 mol%, 2.2 mmol, 0.489 g) at room temperature. The reaction mixture was stirred for 2 h, at room temperature. Then CH_2Cl_2 was removed under reduced pressure and MeOH (40 mL) and K_2CO_3 (60 mmol, 8.29 g) were added and the reaction mixture **was** stirred for 1 h at room temperature. **Then the solvent MeOH** was removed under reduced pressure and the residue was diluted with water (20 mL) and extracted with ether (3x20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product thus obtained, was **purified** by **column** chromatography (silica gel, 8% EtOAc in hexanes) to provide the **desired product 135a, as** a **colorless crystalline solid.**



Yield: **60%** (2.314 g)

Mp.: **56-58** °C (lit.[215] 57-58 °C)

IR (KBr): **v 3468, 1693, 1630 cm^{-1}**

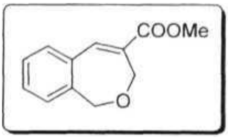
^{1}H NMR: **8** 2,55 **(t,** 1H, ***J*** **=6.8 Hz), 3.87 (s,** 3H), **4.49 (d, 2H, *J* = 6.8 Hz),** 7.31-7.54 (m, 5H), 7.84 (s,1H)

^{13}C NMR: 8 52.10, 57.64, 128.56, 129.20, 129.63, 131.04, 134.58, 142.68, 168.43

4-Methoxycarbonyl-1,3-dihydro-2-benzoxepine (133a):

[from methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**131a**)]

To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (131a) (2 mmol, 0.384 g) and paraformaldehyde (2 mmol, 0.06 g) in CH_2Cl_2 (4 mL), was added drop wise conc. H_2SO_4 (2 mmol, 0.196 g) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was diluted with water (4 mL) and extracted with ether (3×10 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 4% EtOAc in hexanes) to furnish the title molecule 133a, as a colorless solid.



Yield: 60% (0.243 g)

Mp.: 46-48 °C

IR (KBr): v 1714, 1633 cm"^{1}

^{1}H NMR: δ 3.81 (s, 3H), 4.69 (s, 2H), 4.80 (d, 2H, *J*= 1.4 Hz), 7.11-7.48 (m, 4H, aromatic), 7.72 (t, 1H, *J*= 1.4 Hz)

^{13}C NMR: 5 51.82, 72.85, 73.88, 127.17, 127.88, 129.10, 132.45, 133.06, 133.35, 138.68, 141.13, 166.72

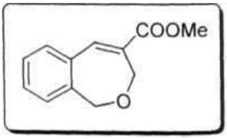
MS (*m/z*): 204 (M^+)

Analysis calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92

Found: C, 70.45; H, 5.94

4-Methoxycarbonyl-1,3-dihydro-2-benzoxepine (133a):
[from methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(Ola)** using methanesulfonic acid]

To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (Ola) (2 mmol, 0.384 g) and paraformaldehyde (2 mmol, 0.06 g) in CH_2Cl_2 (4 mL) was added methanesulfonic acid (6 mmol, 0.576 g) at room temperature. After stirring 1 h, at room temperature, the reaction mixture was diluted with water (4 mL), and extracted with ether (3×10 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 4% EtOAc in hexanes) to provide the desired compound **133a,** as a colorless solid.



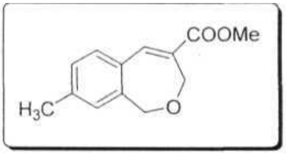
Yield: 53% (0.218 g)

Mp.: 46-48 °C

Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are identical with that of the molecule prepared from methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(131a)** and paraformaldehyde, under the influence of conc. H2SO4.

4-Methoxycarbonyl-8-methyl-1,3-dihydro-2-benzoxepine (133b):

This product was obtained by the reaction between methyl 3-hydroxy-2-methylene-3-**(4-methylphenyl)propanoate (131b) and paraformaldehyde in** CH_2Cl_2 **in the presence of** conc. H_2SO_4, following the similar procedure **described for the molecule 133a,** as **a** colorless solid.



Yield: 51%

Mp.: 58-60 °C

IR(KBr): v 1730, 1635 cm^{-1}

^{1}H NMR: δ 2.34 (s, 3H), 3.80 (s, 3H), 4.66 (s, 2H), 4.78 (s, 2H), 6.97 (s, 1H), 7.11 (d, 1H, J = 7.6 Hz), 7.31 (d, 1H, J = 7.6 Hz), 7.69 (s, 1H)

^{13}C NMR: 5 21.06, 51.72, 72.85, 74.01, 128.01, 128.44, 130.29, 131.24, 133.49, 138.67, 139.49, 141.08, 166.84

MS *(m/z):* 218 (M$^+$)

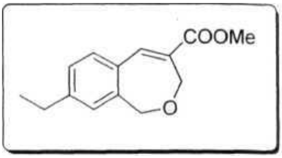
Analysis calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47

Found: C, 71.75; H, 6.51

8-Ethyl-4-methoxycarbonyl-1,3-dihydro-2-benzoxepine (133c):

This molecule was prepared *via* the treatment of methyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate **(131c) with paraformaldehyde in** CH_2Cl_2, **under the influence**

of conc. H_2SO_4, as a colorless viscous liquid, following the similar procedure as described for the molecule **133a.**



Yield: 56%

IR (Neat): v 1703, 1633 cm^{-1}

^{1}H NMR: 6 1.22 (t, 3H,./ = 7.8 Hz), 2.64 (q, 2H, *J* = 7.8 Hz), 3.80 (s, 3H), 4.67 (s, 2H), 4.78 (d, 2H,./= 1.4 Hz)), 6.98 (s, 1H), 7.16 (d, 1H, ./= 7.8 Hz), 7.33 (d, 1H, *J* = 7.8 Hz). 7.69 (t, 1H, *J* = 1.4 Hz)

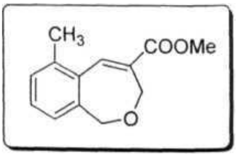
^{13}C NMR: δ 15.04, 28.53, 51.71, 72.85, 74.16, 126.90, 127.27, 130.70, 131.45, 133.62, 138.76, 141.28, 145.87, 166.92

Analysis calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94

Found: C, 72.16; H, 6.91

4-Methoxycarbonyl-6-methyl-1,3-dihydro-2-benzoxepine (133d):

This compound was isolated as a colorless solid *via* the reaction between methyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate **(Old)** and paraformaldehyde in CH_2Cl_2 in the presence of conc. H2SO4, following the similar procedure described for the molecule **133a.**



Yield: **48%**

Mp.: 59-60 °C

IR (**KBr**): v 1707, 1635 cm^{-1}

^{1}H NMR: δ 2.46 (s, 3H), 3.83 (s, 3H), 4.55 (s, 2H), 4.68 (s, 2H), 7.02-7.25 (m, 3H), 8.06 (s, 1H)

^{13}C NMR: δ 20.17, 51.94, 70.62, 72.20, 125.90, 129.19, 130.29, 131.99, 132.39, 136.59, 138.94, 140.86, 166.94

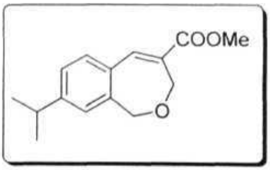
MS (*m/z*): 218 (M^+)

Analysis calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47

Found: C, 71.62; H, 6.42

8-Isopropyl-4-methoxycarbonyl-1,3-dihydro-2-benzoxepine (133e):

The reaction of methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate **(131e)** with paraformaldehyde in CH_2Cl_2 in the presence of conc. H_2SO_4, following the similar procedure described for the molecule **133a,** afforded the desired product **133e,** as a colorless solid.



Yield: 44%

Mp.: 57-59 °C

IR (KBr): ν 1693, 1630 cm^{-1}

^{1}H NMR: δ 1.23 (d, 6H, *J* = 6.8 Hz), 2.90 (sept, 1H, *J* = 6.8 Hz), 3.80 (s, 3H), 4.68 (s, 2H), 4.79 (s, 2H), 7.01 (d, 1H, *J* = 1.2 Hz), 7.16 (dd, 1H, *J* = 1.2 & 7.8 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 7.70 (s, 1H)

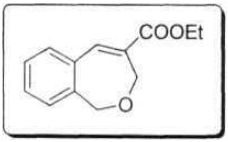
^{13}C NMR: 6 23.59, 33.83, 51.74, 72.89, 74.20, 125.51, 125.84, 130.71, 131.34, 133.63, 138.69, 141.16, 150.43, 166.89

Analysis calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37

Found: C, 72.90; H, 7.42

4-Ethoxycarbonyl-1,3-dihydro-2-benzoxepine (134a):

This compound was obtained as a colorless solid *via* the reaction between ethyl 3-hydroxy-2-methylene-3-phenylpropanoate **(132a)** and paraformaldehyde in CH_2Cl_2 in the presence of conc. H2SO4, following the similar procedure described for the molecule **133a.**



Yield: 61%

Mp: 36-39 ^{0}C

IR (KBr): v 1707, 1631 cm"^{1}

^{1}H NMR: δ 1.34 (t, 3H, *J* = 6.8 Hz), 4.26 (q, 2H, *J* = 6.8 Hz), 4.69 (s, 2H), 4.80 (d, 2H, *J*= 1.4 Hz), 7.09-7.48 (m, 4H), 7.71 (d, 1H, *J* = 1.4 Hz)

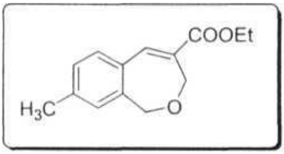
^{13}C NMR: 8 14.16, 60.77, 72.90, 73.87, 127.16, 127.86, 129.02, 132.74, 133.12, 133.30, 138.38, 141.10, 166.27

Analysis calcd. **for** $C_{13}H_{14}O_3$: C, 71.54; H, 6.47

Found: C, 71.40; H, 6.50

4-Ethoxycarbonyl-8-methyl-1,3-dihydro-2-benzoxepine (134b):

This product was prepared by the reaction between ethyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate **(132b)** and paraformaldehyde in CH_2Cl_2 in the presence of conc. H_2SO_4, following the similar procedure described for the molecule **133a,** as a colorless viscous liquid.



Yield: 56%

Ik (Neat): v 1699, 1633 cm''^{1}

^{1}H NMR: o 1.33 (t, 3H,./ = 7.0 Hz), 2.34 (s, 3H), 4.26 (q, 2H,./ = 7.0 Hz), 4.66 (s, 2H), 4.78 (s, 2H), 6.97 (s, 1H), 7.15 (d, 1H, *J* = 7.6 Hz), 7.32 (d, 1H, *J* = 7.6 Hz), 7.68 (s, 1H)

^{13}C NMR: o 14.18, 21.07, 60.66, 72.89, 74.01, 128.01, 128.44, 130.38, 131.56, 133.46, 138.40, 139.40, 141.06, 166.41

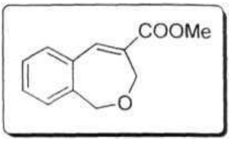
Analysis calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94

Found: C, 72.70; H, 6.86

4-Methoxycarbonyl-1,3-dihydro-2-benzoxepine (133a):

[from methyl (2*E*)-2-(hydroxymethyl)-3-phenylprop-2-enoate **(135a)]**

This compound was obtained as a colorless solid *via* the reaction between methyl (2*E*)-2-(hydroxymethyl)-3-phenylprop-2-enoate **(135a)** and paraformaldehyde in CH_2Cl_2 in the presence of conc. H2SO4, **following the similar procedure described for preparation** of the molecule **133a,** from methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(131a)** and paraformaldehyde, under the influence of conc. H2SO4.



Reaction time: 1 h

Yield: 59% (0.24 g)

Mp.: 46-48 °C

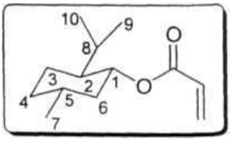
Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are in complete agreement with that of the molecule prepared from methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(131a)** and paraformaldehyde, under the influence of conc. H2SO4.

(-)-Menthyl acrylate (14):

This molecule was prepared according to the literature procedure. [4]

To a stirred solution of (-)-menthol **(151)** (100 mmol, 15.627 g), acryloyl chloride (150 mmol, 13.576 g) and 4-dimethylaminopyridine (15 mmol, 1.832 g) in anhydrous CH_2Cl_2 (100 mL), was added triethylarnine (150 mmol, 15.167 g) drop wise at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was diluted with ether (100 mL) and washed successively with 2N HC1 solution, water, saturated aqueous $NaHCO_3$ solution and water. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and **the** crude product thus obtained, was distilled under reduced pressure to afford **14** as a colorless liquid.

Yield: **78% (16.42 g)**



Bp.: 62-64 °C/1 mm (lit.[247] 78-80 °C/5 mm)

Optical rotation: $[\alpha]_D^{25}$ -86.9 (*c* **8,** dioxane) [lit.[247] -80.2 (c 10, **dioxane)]**

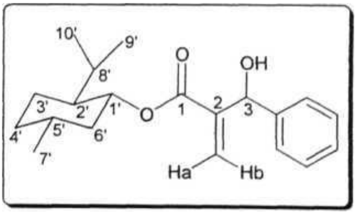
IR (Neat): v 1722, 1633 cm"^{1}

^{1}H NMR: 5 0.69-2.12 (m, 18H), 4.77 (dt, 1H, *J*= 10.8 & 4.8 Hz), 5.79 (dd, 1H, *J* = 10.6 & 1.8 Hz), 6.10 (dd, 1H, *J* = 16.6 & 10.6 Hz), 6.39 (dd, 1H,./= 16.6 & 1.8 Hz)

^{13}C NMR: 5 16.40, 20.62, 21.93, 23.63, 26.34, 31.34, 34.25, 40.85, 47.11, 74.28, 129.05, 129.97, 165.68

(-)-Menthyl 3-hydroxy-2-methylene-3-phenylpropanoate (152a):

A mixture of benzaldehyde **(130a)** (150 mmol, 15.9 g), (-)-menthyl acrylate **(14) (50** mmol, 10.516 g) and DABCO (50 mmol, 5.609 g) was kept at room temperature for 8 days. The reaction mixture was diluted with ether (100 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 purified by **column chromatography** (silica gel, 10% **EtOAc in hexanes)** to **afford 152a, as a colorless solid.**



Yield: **88%** (13.924 g)

Mp.: 105-108 °C

Optical rotation: $[\alpha]_D^{25}$ −117.46 (*c* 3.24, $CHCl_3$)

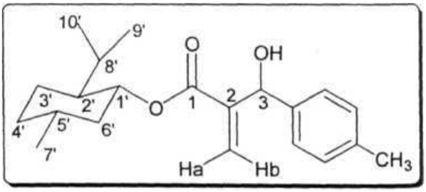
IR (KBr): ν 3312, 1712, 1639 cm^{-1}

^{1}H NMR: 5 0.55-2.01 (m, 18H, H2'-H10'), 3.01 (d, 1H, *J* = 6.0 Hz, OH), 4.71 (dt, 1H, *J* = 10.0 Hz, 4.2 Hz, H1'), 5.54 (d, 1H, *J* = 6.0 Hz, H3), 5.81 & 5.82 (2s, 1H, diastereomeric Hb), 6.33 (s, 1H, Ha), 7.25-7.46 (m, 5H, aromatic)

^{3}C NMR: 8 16.07, 20.78, 21.96, 23.31, 26.00, 31.38, 34.20, 40.76, 47.09, 73.32, 74.87, 125.32, 126.69, 127.73, 128.37, 141.56, 142.57, 165.95

(−)-Menthyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (152b):

This product was prepared from 4-methylbenzaldehyde **(130b),** (-)-menthyl acrylate (14) and DABCO following the similar procedure described for the molecule **152a,** as a colorless solid.



Reaction time: 10 days

Yield: 84%

Mp.: 120-123 °C

Optical rotation: $[\alpha]_D^{25}$ −127.80 (*c* 1.64, $CHCl_3$)

IR (KBr): ν 3325, 1711,1637 cm^{-1}

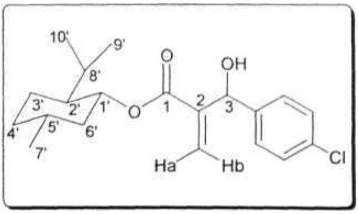
^{1}H NMR: 6 0.55-2.03 (m, 18H, H2'-H10'), 2.34 (s, 3H, CH_3), 2.89 (d, 1H, *J* = 5.2 Hz, OH), 4.71 (dt, 1H, *J* = 10.2 Hz, 4.4 Hz, H1'), 5.51 (d, 1H, ./= 5.2 Hz, H3), 5.83 (s, 1H, Hb), 6.33 (s, 1H, Ha), 7.14 (d, 2H, *J* = 8.0 Hz), 7.24 (d, 2H, ./ = 8.0 Hz)

^{3}C NMR: δ 15.97, 20.75, 21.07, 21.95, 23.14, 25.80, 31.33, 34.13, 40.71, 46.99, 73.00, 74.68, 125.08, 126.64, 129.02, 137.32, 138.58, 142.54,165.90

(–)-Menthyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (153):

This compound was isolated as a colorless solid *via* the reaction of 4-chlorobenzaldehyde **(130g)** with (-)-menthyl acrylate (14) in the presence of DABCO, following the similar procedure described for the molecule **152a.**

Reaction time: 7 days



Yield: 87%

Mp.: 52-54 °C

Optical rotation: $[\alpha]_D^{25}$ –56.13 (*c* 2.72, $CHCl_3$)

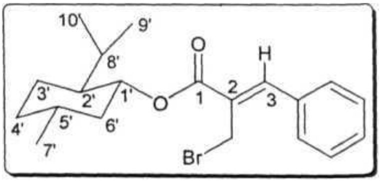
IR (KBr): ν 3314, 1712, 1639 cm"^{1}

^{1}H NMR: 5 0.56-2.08 (m, 18H, H2'-H10'), 3.03-3.23 (m, 1H, OH), 4.61-4.86 (m, 1H, H1'), 5.50 (d, 1H, *J* =6.0 Hz, H3), 5.77 & 5.81 (2s, 1H, diastereomeric Hb), 6.33 (s, 1H, Ha), 7.21-7.51 (m, 4H, aromatic)

^{13}C NMR: (mixture of diastereomers) 5 16.06, 16.22, 20.71, 21.96, 23.23, 23.37, 26.03, 26.21, 31.36, 34.13, 40.65, 40.71, 47.06, 72.70, 72.85, 75.03, 75.15, 125.65, 127.90, 128.10, 128.49, 133.45, 133.54, 140.09, 142.15, 165.78

(–)-Menthyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (154a):

To a stirred solution of (-)-menthyl 3-hydroxy-2-methylene-3-phenylpropanoate **(152a)** (10 mmol, 3.163 g) in CH_2Cl_2 (20 mL) was added drop wise HBr (48%, 25 mmol, 4.21 ml) followed by conc. H_2SO_4 (10 mmol, 0.98 g) at 0 ^{o}C. After stirring for 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 and dried over anhydrous sodium sulfate (Na_2SO_4). Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 2% EtOAc ate in hexanes) to afford the desired compound **154a,** as colorless viscous liquid.



Yield: 88% (3.353 g)

Optical rotation: $[\alpha]_D^{25}$ –80.34 (*c* 3.17, $CHCl_3$)

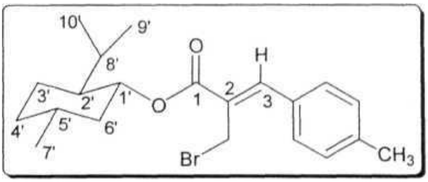
IR (Neat): ν 1709, 1626 cm^{-1}

^{1}H NMR: 8 0.81 (d, J = 7.0 Hz) & 0.89-2.19 (m) (18H, H2'-H10'), **4.40** (s, 2H, CH$_2$Br), 4.89 (dt, 1H, J = 10.0 Hz, 4.4 Hz, H1'), 7.29-7.64 (m, 5H, aromatic), 7.80 (s, 1H, H3)

^{13}C NMR: δ 16.40, 20.85, 22.06, 23.53, 26.37, 26.85, 31.49, 34.33, 40.90, 47.25, 75.49, 128.85, 129.45, 129.58, 134.48, 142.35, 165.63

(–)-Menthyl (2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (154b):

This compound was prepared by the reaction of (-)-menthyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate **(152b)** with HBr (48%) in the presence of conc. H$_2$SO$_4$, following the similar **procedure** described for the molecule **154a,** as colorless viscous liquid.



Yield: 89%

Optical rotation: $[\alpha]_D^{25}$ –71.96 (*c* 2.64, CHCl$_3$)

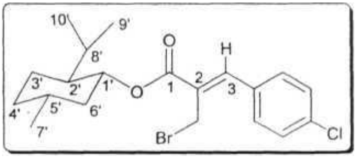
IR (Neat): ν 1716, 1624 cm"^{1}

^{1}H NMR: 8 0.80 (d, J= 7.0 Hz) & 0.88-2.21 (m) (18H, H2'-H10'), 2.39 (s, 3H, CH$_3$), 4.40 (s, 2H, CH$_2$Br), 4.87 (dt, 1H, J= 10.8 Hz, 4.6 Hz, H1'), 7.26 (d, 2H, J= 8.0 Hz, aromatic), 7.48 (d, 2H, J= 8.0 Hz, aromatic), 7.76 (s, 1H,H3)

^{3}C NMR: 8 16.38, 20.86, 21.47, 22.07, 23.50, 26.34, 27.24, 31.50, 34.34, 40.92, 47.24, 75.40, 128.51, 129.62, 129.82, 131.65, 139.87, 142.60, 165.82

(–)-Menthyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (155):

The treatment of (-)-menthyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate **(153)** with HBr (48%) and conc. H2SO4, following the similar procedure described for the molecule **154a,** afforded the desired compound **155,** as a colorless viscous liquid.



Yield: 87%

Optical rotation: $[\alpha]_D^{25}$ –81.30 (*c* 2.30, $CHCl_3$)

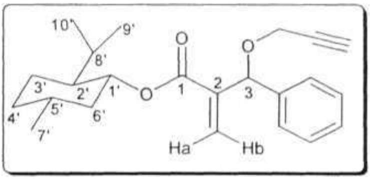
IR (Neat): ν 1703, 1626 cm^{-1}

^{1}H NMR: 8 0.81 (d, *J* = 7.0 Hz) & 0.87-2.22 (m) (18H, H2'-H10'), 4.35 (s, 2H, CH_2Br), 4.89 (dt, 1H, *J* = 10.6 Hz, 4.4 Hz, H1'), 7.37-7.62 (m, 4H, aromatic), 7.73 (s, 1H, H3)

^{3}C NMR: 8 16.34, 20.85, 22.05, 23.47, 26.35, 26.43, 31.48, 34.29, 40.87, 47.21, 75.67, 129.16, 130.03, 130.90, 132.88, 135.58, 140.94, **165.40**

(–)-Menthyl 2-methylene-3-(prop-2-yn-1-yloxy)-3-phenylpropanoate (156a):

To a stirred solution of (-)-menthyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (154a) (1 mmol, 0.379 g) and 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), 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% EtOAc in hexanes) to provide pure (-)-menthyl 2-methylene-3-(prop-2-yn-1-yloxy)-3-phenylpropanoate **(156a),** as colorless viscous liquid.



Yield:	74% (0.261 g)
de:	18%
Optical rotation:	$[\alpha]_D^{25}$ –60.31 (*c* 4.15, $CHCl_3$)
IR(Neat):	ν 3308, 2130, 1712, 1631 cm^{-1}
^1H NMR:	5 0.55-2.01 (m, 18H, H2'-H10'), 2.40-2.51 (m, 1H, HC≡C), 3.95-4.25 (m, 2H, $CH_2C{\equiv}C$), 4.58-4.79 (m, 1H, H1'), 5.46 & 5.50 (2s, 1H, diastereomeric H3), 5.91 & 6.00 (2d, 1H, *J* = 2.0 Hz, Hb), 6.31 & 6.41 (2s, 1H, Ha), 7.21-7.44 (m, 5H, aromatic)

The underlined peaks are due to the minor diastereomer.

The two singlets at 6 6.31 & 6.41 are due to the p-vinylic protons (Ha) *(cis-* to the ester group) of the minor and major diastereomers respectively. The diastereomeric excess was determined by the integration (41:59) of these two singlets and was found to be 18%.

^{13}C NMR: (mixture of diastereomers) 8 15.92, 16.33, 20.66, 20.90, 21.96, 23.09, 23.51, 25.67, 26.26, 31.34, 34.19, 40.54, 40.78, 47.04, 55.78, 74.55, 74.66, 77.73, 77.84, 79.50, 124.33, 124.99, 127.89, 127.98, 128.11, 128.33, 138.55, 140.83, 141.29, 165.11, 165.26

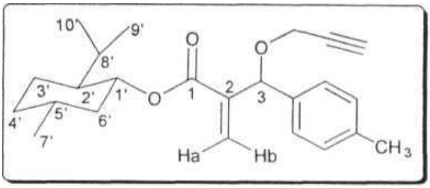
The peaks at δ 165.11 and 165.26 are attributed to the carbonyl carbon of the major and minor diastereomers respectively.

Analysis calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53

Found: C, 78.23; H, 8.44

(–)-Menthyl 2-methylene-3-(4-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate (156b):

It was **prepared** *via* **the reaction of (-)-menthyl (2Z)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (154b)** with propargyl alcohol in the presence of **triethylamine, following the similar procedure described for the molecule 156a, as a colorless viscous liquid.**



Reaction time: 12h

Yield: 67%

de: 23%

Optical rotation: $[\alpha]_D^{25}$ –60.4 (*c* 3.00, $CHCl_3$)

IR (Neat): ν 3312, 2131, 1714, 1635 cm^{-1}

^1H NMR: 5 0.55-1.99 (m, 18H, H2'-H10'), 2.33 (s, 3H, CH_3), 2.41-2.49 (m, 1H, HC≡C), 3.94-4.24 (m, 2H, $CH_2C≡C$), 4.59-4.79 (m, 1H, H1'), 5.42 & 546 (2s, 1H, H3), 5.90 & 6.00 (2d, 1H, ./= 2.0 Hz, Hb), *629* & 6.39 (2s, 1H, Ha), 7.13 (d, 2H, ./ = 7.8 Hz, aromatic), 7.23 (d, 2H, *J* = 7.8 Hz, aromatic)

The underlined peaks arise due to the minor diastereomer.

The two singlets at 5 6.29 & 6.39 are arising from the olefinic (Ha) protons (*cis*- to the ester functionality) of the minor and major diastereomers respectively and are in the ratio of 38.5:61.5, indicating 23% diastereoselectivity in the reaction.

^{13}C NMR: (mixture of diastereomers) 6 15.91, 16.34, 20.68, 20.86, 21.14, 21.98, 23.07, 23.51, 25.62, 26.23, 31.36, 34.21, 40.55, 40.81, 47.04, 55.61, 55.68, 74.48, 74.57, 77.64, 79.62, 124.06, 124.74, 127.85, 127.98, 129.03, 135.50, 137.80, 140.96, 141.49, 165.15, 165.35

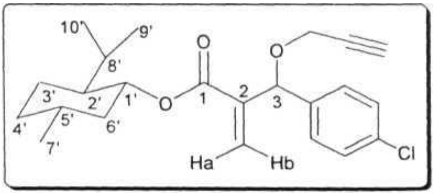
The peaks at 6 165.15 and 165.35 are attributed to the carbonyl carbon of ester group of both major and minor diastereomers respectively.

Analysis calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75

Found: C, 78.00; H, 8.83

(–)-Menthyl 3-(4-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (157):

This product was isolated as a colorless viscous liquid *via* the reaction of (-)-menthyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (155) with propargyl alcohol in the presence of triethylamine, following the similar procedure described for the molecule 156a.



Reaction time: 12 h

Yield: 88%

de: 4%

Optical rotation: $[\alpha]_D^{25}$ –36.45 (*c* 3.36, $CHCl_3$)

IR (Neat): ν 3308, 2110, 1716, 1635 cm^{-1}

^1H NMR: 8 0.54-2.00 (m, 18H, ffi'-HIO^1), 2.41-2.52 (m, 1H, HC≡C), 3.94-4.27 (m, 2H, $CH_2C≡C$), 4.56-4.81 (m, 1H, H1'), 5.43 & 5.47 (2s, 1H, diastereomeric H3), 5.94 & 6.02 (2s, 1H, diastereomeric Hb), 6.31 & 6.41 (2s, 1H, diastereomeric Ha), 7.30 (s, 4H, aromatic)

The diastereomeric excess was determined by the integration of the two singlets at 8 6.31 & 6.41 (from two diastereomers) arising from the β-vinylic proton (Ha), *cis*- to the ester functionality and was found to be 4%.

^{13}C NMR: (mixture of diastereomers) δ 15.97, 16.37, 20.65, 20.83, 21.98, 23.13, 23.56, 25.81, 26.34, 31.38, 34.20, 40.62, 40.82, 47.12, 55.88, 74.75, 74.87, 74.95, 77.10, 77.18, 79.27, 79.29, 124.57, 125.27, 128.50, 128.55, 129.25, 129.39, 133.89, 133.98, 137.36, 140.48, 140.96, 164.91, 165.10

The peaks at δ 164.91 and 165.10 are due to the carbonyl carbon of the major and minor diastereomers respectively.

Analysis calcd. for $C_{23}H_{29}O_3Cl$: C, 71.03; H, 7.52

Found: C, 70.75; H, 7.40

(–)-Menthyl 2-methylene-3-phenoxy-3-phenylpropanoate (158a):

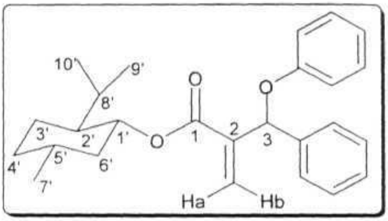
A solution of (-)-menthyl (2Z)-2-(bromomethyl)-3-phenylprop-2-enoate **(154a)** (1 mmol, 0.379 g), phenol (1 mmol, 0.094 g) and Et_3N (1 mL) in CH_2Cl_2 (2 mL), was stirred at room temperature for 4 hours. Then 2N HC1 (5 mL) was added and the reaction mixture was extracted with ether (2×10 mL). The combined layer was washed with aqueous $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, *2%* EtOAc in hexanes) to provide pure (-)-menthyl 2-methylene-3-phenoxy-3-phenylpropanoate (158a), as colorless viscous liquid.

Yield: 72% (0.283 g)

de: 35% ,

Optical rotation: $[\alpha]_D^{25}$ -76.16 (*c* 5.00, $CHCl_3$)

1R (Neat): v 1711, 1635 cm^{-1}



^{1}H NMR: δ 0.56-2.15 (m, 18H, H2'-H10'), 4.64-4.92 (m, 1H, H1'), 5.83 & 5.93 (2s, 1H, H3), 6.13 & 6.15 (2s, 1H, diastereomeric Hb), 632 & 6.40 (2s, 1H, Ha), 6.89-7.10 (m, 3H, aromatic), 7.18-7.61 (m, 7H, aromatic)

The underlined peaks are attributed to the minor diastereomer.

The two singlets at 5 5.83 & 5.93 are attributed to the benzylic (H3) protons of the minor and major diastereomers respectively. The diastereomeric excess was determined by the integration (32.5:67.5) of these two singlets and was found to be 35%.

^{13}C NMR: (mixture of diastereomers) 8 16.09, 16.25, 20.68, 20.88, 22.02, 23.23, 23.45, 25.94, 26.25, 31.42, 34.22, 40.71, 40.85, 47.13, 74.92, 77.34, 77.53, 115.86, 115.93, 121.17, 125.45, 126.00, 127.40, 127.52, 128.12, 128.49, 129.38, 138.97, 140.64, 141.16, 157.74, 165.24, 165.42

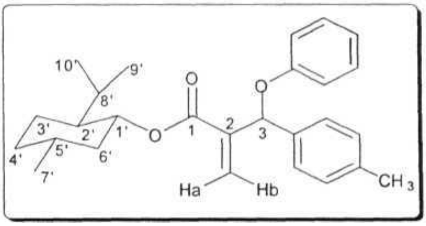
The peaks at 5 165.24 and 165.42 are **attributed to carbonyl carbon of ester group of** the major and minor diastereomers respectively.

Analysis calcd. for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22

Found: C, 79.76; H, 8.13

(–)-Menthyl 2-methylene-3-(4-methylphenyl)-3-phenoxypropanoate (158b):

This was prepared *via* the reaction of (-)-menthyl (2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate **(154b)** with phenol in the presence of triethylamine, following the similar procedure described for the molecule **158a,** as a colorless viscous liquid.



Reaction time: 4h

Yield: 54%

de: 28%

Optical rotation: $[\alpha]_D^{25}$ –71.56 (*c* 2.11, $CHCl_3$)

IR (Neat): **v 1711,** 1633 cm"^{1}

^{1}H NMR: 8 0.56-2.02 (m, 18H, H2'-H10'), **2.25 (s, 3H), 4.54-4.85** (m, **1H,** H1'), 5.73 **& 5.84 (2s, 1H, H3), 6.01 & 6.04 (2s, 1H, diastereomeric Hb),** 6.22 **&** 6.31 **(2s, 1H, Ha), 6.82-7.03** (m, **3H, aromatic), 7.05-7.48 (m, 6H, aromatic)**

The underlined peaks arise due to the minor diastereomer.

The two singlets at δ 5.73 & 5.84 arise from benzylic methine protons (H3) of the minor and major diastereomers respectively. They are in the ratio of 36:64, indicating that the reaction is 28% diastereoselective.

^{13}C NMR: (mixture of diastereomers) δ 16.08, 16.26, 20.70, 20.84, 21.18, 22.02, 23.24, 23.45, 25.91, 26.27, 31.43, 34.23, 40.72, 40.89, 47.15, 74.87, 77.23, 77.43, 115.94, 121.09, 125.24, 125.80, 127.36, 127.51, 129.19, 129.35, 135.89, 136.00, 137.76, 137.85, 140.72, 141.32, 157.82, 165.30, 165.52.

The peaks at 8 165.30 and 165.52 are attributed to carbonyl carbon of ester group of the major and minor diastereomers respectively.

Analysis calcd. for $C_{27}H_{34}O_3$: C, 79.77; H, 8.43

Found: C, 79.98; H, 8.54

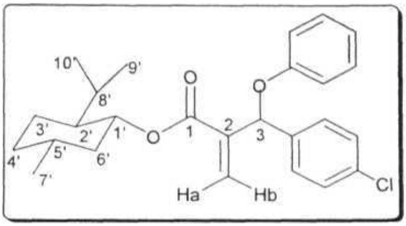
(–)-Menthyl 3-(4-chlorophenyl)-2-methylene-3-phenoxypropanoate (159):

This product was obtained as a colorless viscous liquid *via* the reaction of (–)-menthyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (155) with phenol in the presence of triethylamine, following the similar procedure described for the molecule 158a.

Reaction time: 4h

Yield: 57%

de: 26%



Optical rotation: $[\alpha]_D^{25}$ –69.81 (*c* 3.71, CHCl$_3$)

IR(Neat): v 1714, 1638 cm"^{1}

^{1}H NMR: o 0.60-2.10 (m, 18H, H2'-H10'), 4.64-4.88 (m, 1H, H1'), 5.86 & 5.96 (2s, 1H, H3), 6.08 & 6.11 (2s, 1H, Mb), 632 & 6.41 (2s, 1H, Ha), 6.88-7.09 (m, 3H, aromatic), 7.18-7.50 (m, 6H, aromatic)

The underlined chemical shifts values are attributed to the minor diastereomer.

The two singlets at δ 5.86 & 5.96 are arising from the benzylic methine proton (H3) of the minor and major diastereomers respectively and are in the ratio of 37:63, indicating 26% diastereoselectivity in the reaction.

^{13}C NMR: (mixture of diastereomers) 6 16.16, 16.32, 20.69, 20.86, 22.05, 23.30, 23.52, 26.08, 26.36, 31.46, 34.25, 40.78, 40.91, 47.20, 75.08, 76.80, 76.96, 115.93, 116.01, 121.48, 125.48, 126.12, 128.73, 128.81, 128.96, 129.49, 134.02, 137.64, 137.73, 140.38, 140.92, 157.51, 165.03, 165.24

The peaks at 8 165.03 and 165.24 are attributed to carbonyl carbon of ester group of the major and minor diastereomers respectively.

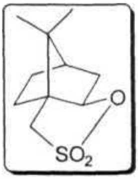
Analysis calcd. for $C_{26}H_{31}O_3Cl$: C, 73.14; H, 7.32

Found: C, 73.40; H, 7.26

Isobornyl sultone (161):

This was prepared according to the literature method.[278]

A solution of (+)-10-camphorsulfonic acid **(160)** (120 mmol, 27.876 g) in 60 mL of water was added carefully to solid sodium borohydride (225 mmol, 8.511 g). Water was removed under reduced pressure and the reaction mixture was heated for 4 hours at 120 °C. Absolute ethanol (900 mL) was added and refluxed for 2 hours. Salts were removed by filtration. Ethanol (300 mL) was added to salts, refluxed and again filtered. This process was repeated 3-4 times. Then all the ethanolic solutions were combined and ethanol was removed by distillation. Crude solid thus obtained, was dried at 120 °C for 2 hours. This solid was dissolved in pyridine (48 mL) and freshly crystallized *p*-toluenesulfonyl chloride (27 g) was added with stirring. After 5 hours at room temperature, the reaction mixture was poured into ice-cold water (120 mL) and refrigerated (-20 °C) overnight. Solid isobornyl sultone **(161)** was **filtered and** dried.

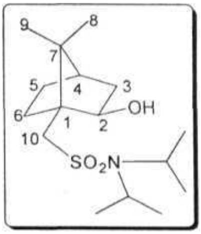


Yield: 17.958 g (69%)

Mp.: 114-116 °C (lit.[279] 116-118 °C)

(1*S*,2*R*,4*R*)-1-(Diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (162):

To a stirred solution of ethylmagnesium bromide (480 mmol) in THF, *N*,*N*-diisopropylamine (480 mmol, 48.571 g) was added slowly over an hour at room temperature under nitrogen. After the evolution of ethane gas was completely seized, sultone **161** (60 mmol, 12.978 g) in 100 mL of THF was added. After stirring for 24 hours at room temperature, the reaction mixture was poured into 250 mL of cold 2N HC1 and extracted with ether (3x80 mL). The combined ethereal solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crystallization of the resulting crude product from hexane (two times) **provided pure** 162, **as a colorless crystalline solid.**



Yield: 72% (13.748 g)

Mp.: 100-103 °C (lit.[279] 102-103 °C)

Optical rotation: $[\alpha]_D^{25}$ -34.68 (*c* 10, EtOH) **[lit.[280]** -34.4 (*c* 4.74, EtOH)]

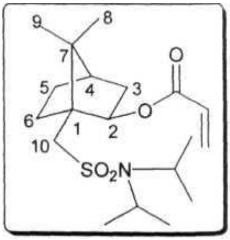
IR (KBr): **v** 3508 **cm"^{1}**

^{1}H NMR: o **0.81** (s, **3H,** CH_3**, H9), 1.06 (s, 3H,** CH_3**, H8), 1.33 (d,** 12H, ***J*** = 6.8 Hz, $2\times CH(\underline{CH}_3)_2$), **1.56-1.89** (m, **7H,** H3, H4, **H5, H6), 2.67 & 3.27 (ABq, 2H, *J* =** 13.4 **Hz,** H10), **3.47 (d,** 1H, ***J* = 4.0 Hz, OH) 3.67-3.86** (m, 2H, $2\times \underline{CH}(CH_3)_2$), 4.04-4.17 **(m, 1H, H2)**

^{13}C NMR: 6 19.90, 20.55, 22.17, 22.50, 27.34, 30.93, 38.83, **44.46,** 48.49, 50.74, 54.27, 76.49

(1*S*,2*R*,4*R*)-1-(Diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)hept-2-yl acrylate (18):

To a stirred solution of the alcohol **162** (30 mmol, 9.524 g) in 75 mL of dry ether was added slowly ethylmagnesium bromide (30 mmol) in ether (60 mL) at room temperature. After stirring at room temperature for 1 hour, the reaction mixture was cooled to 0 °C. Acryloyl chloride (75 mmol, 6.788 g) in ether (75 mL) was added and stirred at room temperature for 2 h. The reaction mixture was diluted with ether (100 mL) and washed with water (100 mL). The organic layer was dried over anhydrous Na_2SO_4, **concentrated** and the solid thus obtained, was crystallized from hexane to give **acrylate 18,** as a colorless crystalline solid.



Yield: 91% (10.189 g)

Mp.: 116-118 °C (lit.[279] 117-118 °C)

Optical rotation: $[\alpha]_D^{25}$ -50.44 (*c* 2.50, acetone)

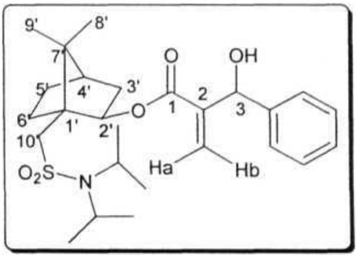
IR(KBr): v **1728,** 1637 cm"^{1}

^{1}H NMR: 8 0.89 (s, **3H,** CH_3, **H9),** 1.01 (s, 3H, CH_3, **H8), 1.27** & **1.28** (2d, **12H,** ***J*** **= 6.0 Hz,** diastereomeric 2×CH($\underline{CH_3}$)$_2$), **1.59-2.14** (m, **7H, H3, H4, H5, H6), 2.72 & 3.28 (ABq, 2H, *J* = 13.0 Hz, H10),** 3.58-3.82 (m, 2H, $2\times\underline{CH}(CH_3)_2$), 5.03-5.16 (m, 1H, H2), 5.78 (dd, 1H, *J* = 2.0 & 9.6 Hz), 6.07 (dd, 1H, *J* = 9.6 & 17.4 Hz), 6.33 (dd, 1H, *J* = 2.0& 17.4 Hz)

^{13}C NMR: δ 19.90, 20.31, 22.21, 22.31, 26.95, 29.82, 39.37, 44.49, 48.11, 49.01, 49.42, 52.92, 78.31, 129.09, 129.61, 164.39

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-hydroxy-2-methylene-3-phenylpropanoate (163):

A mixture of acrylate (18) (5 mmol, 1.857 g), benzaldehyde (130a) (25 mmol, 2.65 g) and DABCO (5 mmol, 0.56 g) was allowed to react at room temperature for 10 days. The reaction mixture was diluted with ether (10 mL) and washed successively with 2N HCl solution, water and saturated aqueous $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and the crude product thus obtained, was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to afford **163,** as a colorless solid.



Yield: 92% (2.211 g)

de: **14%**

Mp.: 130-132°C

Optical rotation: $[\alpha]_D^{25}$ -33.55 (*c* 3.07, acetone) [lit.[96] -36.6 (*c* 0.3, acetone), for *\5%de]*

IR (KBr): v 3489, 1718, 1620 cm^{-1}

^1H NMR: 5 0.88 (s, 3H, CH_3, H9'), 0.96 & 0.97 (2s, 3H, CH_3, H8'), 1.21-1.38 (m, 12H, $2\times CH(\underline{CH_3})_2$), 1.59-2.07 (m, 7H, H3', H4', H5', H6'), 2.65-2.78 (m, 1H, H10'), 3.18-3.47 (m, 2H, H10', OH), 3.57-3.78 (m, 2H, $2\times \underline{CH}(CH_3)_2$), 5.06-5.18 (m, 1H, H2'), 5.56-5.71 (m, 2H, Hb & H3), $\underline{6.15}$ & 6.20 (2s, 1H, Ha), 7.27-7.41 (m, 5H, aromatic)

The underlined peaks are attributed to minor diastereomer.

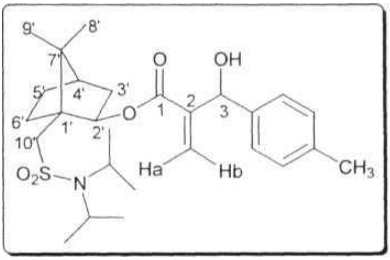
The two singlets at 5 6.15 and 6.20 are attributed to the β-vinylic protons (Ha) *(cis-* to ester group) of the minor and major diastereomers respectively and are in the ratio of 57:43, indicating that the reaction is 14% diastereoselective.

^{13}C NMR: (mixture of diastereomers) 6 19.89, 20.29, 22.09, 22.48, 22.59, 26.95, 30.01, 39.28, 44.39, 48.16, 49.03, 49.53, 53.05, 72.54, 73.34, 78.84, 124.83, 125.14, 126.45, 126.61, 127.57, 127.67, 128.30, 141.15, 141.25, 143.20, 143.42, 164.88, 165.05

The peaks at 6 72.54 & 73.34 and at 5 164.88 & 165.05 are attributed to benzylic carbon and carbonyl group of major and minor diastereomers respectively.

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (164):

This product was prepared from 4-methylbenzaldehyde **(130b),** acrylate (18) and DABCO, following the similar procedure described for the molecule **163,** as a colorless viscous liquid.



Reaction time:	30 days
Yield:	92%
de:	10%
Optical rotation:	$[\alpha]_D^{25}$ −31.21 (*c* 0.66, acetone)
IR (Neat):	v 3504, 1714, 1628 cm''^{1}
^{1}H NMR:	8 0.88 (s, 3H, CH_3, H9'), 0.96 (s, 3H, CH_3, H8'), 1.21-1.37 (m, 12H, 2×$CH(CH_3)_2$), 1.57-2.07 (m, 7H, H3', H4', H5', H6'), 2.32 (s, 3H), 2.70 & 3.24 and 2.72 & 3.26 (2ABq, 2H, *J* = 13.2 Hz, diastereomeric H10'), 3.04 & 3.31 (2d, 1H, diastereomeric CHOH, *J* = 5.0 Hz, D_2O washable), 3.55-3.77 (m, 2H, 2×$CH(CH_3)_2$), 5.03-5.17 (m, 1H, H2'), 5.52-5.72 (m, 2H, H3, Hb), 6.12 & 6.18 (2s, 1H, Ha), 7.11-7.28 (m, 4H, aromatic)

The underlined peak is due to minor diastereomer.

The singlets at 5 6.12 and 6.18 are due to β-vinylic (Ha) protons *(cis-* to ester group) of major and minor diastereomers respectively and are in the ratio of 55:45, indicating that there is 10% diastereoselectivity in the reaction.

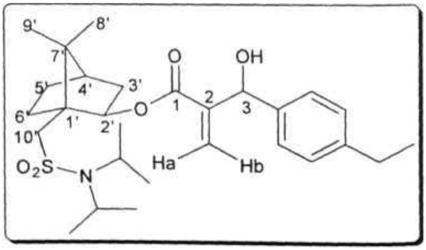
^{13}C NMR: (mixture of diastereomers)	5 19.88, 20.28, 20.99, 22.05, 22.49, 22.58, 26.96, 30.02, 39.32, 44.50, 48.18, 48.99, 49.60, 53.13, 72.42, 73.20, 78.84, 124.38, 124.66, 126.40, 126.56, 128.95, 137.08, 137.20, 138.38, 138.46, 143.54, 143.71, 164.86, 165.03

The peaks at 6 72.42 & 73.20 and 8 164.86 & 165.03 are due to benzylic carbon and carbonyl group of major and minor diastereomers respectively.

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (165):

This compound was obtained as a colorless viscous liquid *via* the reaction of 4-ethyl benzaldehyde (130c) with acrylate (18) in the presence of DABCO, following the similar procedure described for the molecule **163.**

Reaction time:	40 days
Yield:	82%
de:	10%



Optical rotation: $[\alpha]_D^{25}$ -40.63 (*c* 1.77, acetone)

IR (Neat): v 3497, 1716, 1628 cm^{-1}

^{1}H NMR: 6 0.79 (s, 3H, CH_3, H9'), 0.88 (s, 3H, CH_3, H8'), 1.12-1.46 (m, 15H, 2×CH(CH_3)$_2$, CH_3), 1.62-2.07 (m, 7H, H3', H4', H5', H6'), 2.57-2.76 (m, 3H, CH2CH3, H10'), 3.03 & 3.31 (2d, 1H, diastereomeric CHOH, *J* = 4 Hz, D_2O washable), 3.18-3.32 (m, 1H, H10'), 3.55-3.78 (m, 2H, 2×CH(CH_3)$_2$), 5.01-5.17 (m, 1H, H2'), 5.52-5.60 (m, 1H, H3), 5.61 & 5.69 (2s, 1H, Hb), 6.13 & 6.19 (2s, 1H, Ha), 7.10-7.37 (m, 4H, aromatic)

The underlined chemical shift values are due to minor diastereomer.

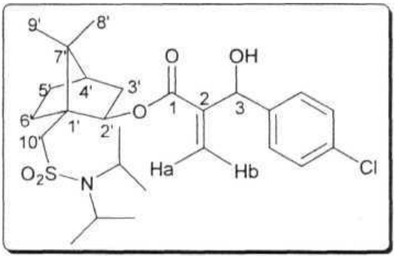
The peaks at δ 6.13 and 6.19 are attributed to the β-vinylic (Ha) protons *(cis-* to ester group) of the major and minor diastereomers respectively and are in the ratio of 55:45, indicating that the reaction is 10% diastereoselective.

^{13}C NMR: (mixture of diastereomers) 5 15.37, 19.89, 20.29, 22.07, 22.51, 22.61, 26.97, 28.44, 30.04, 39.33, 44.51, 48.20, 49.00, 49.61, 53.14, 72.44, 73.25, 78.86, 124.46, 124.71, 126.47, 126.64, 127.76, 138.61, 138.69, 143.51, 143.61, 164.88, 165.06

The peaks at δ 72.44 & 73.25 **and δ 164.88** & **165.06 arise from the benzylic and ester carbonyl carbons respectively of both the diastereomers.**

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (166):

This product was prepared from 4-chlorobenzaldehyde (**130g**), acrylate (18) and DABCO in 4 mL of THF, following the similar procedure described for the molecule **163,** as a colorless solid.



Reaction time: 10 days

Yield: 91%

dc: 12%

Mp.: 80-82 ^{o}C

Optical rotation: $[\alpha]_D^{25}$ -32.45 (*c* 2.16, acetone)

IR(KBr): ν 3501, 1714, 1628 cm"^{1}

^{1}H NMR: 6 0.89 (s, 3H, CH$_3$, H9^1), 0.96 & 1.00 (2s, 3H, CH$_3$, H8'), 1.18-1.39 (m, 12H, 2×CH(CH$_3$)$_2$), 1.58-2.10 (m, 7H, H3', H4', H5', H6'), 2.69 & 3.21 and 2.70 & 3.23 (2ABq, 2H, *J* = 13.0 Hz, H10'), *3.25 & 3.54 (2d, 1H, *J* = 5.0 Hz, diastereomeric OH, D$_2$O washable), 3.57-3.75 (m, 2H, 2×CH(CH$_3$)$_2$), 5.06-5.17 (m, 1H, H2'), 5.52-5.65 (m, **2H, H3, Hb),** 6.15 & **6.18** (2s, **1H,** Ha), 7.32 (s, **4H, aromatic)**

***The doublet at 8 3.25 merges with ABq.**

The underlined values arise due to minor diastereomer.

The diastereomeric excess was determined by **the integration** of **the peaks at** δ **6.15 and** 6.18 **arising from the** β-vinylic (Ha) protons (*cis*- to **ester group) of** minor **and major** diastereomers **respectively** and was found to be 12%.

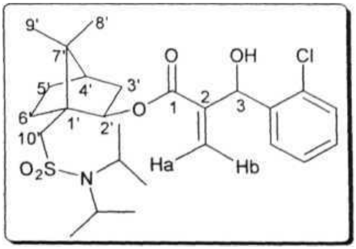
^{13}C NMR: (mixture of diastereomers)	5 19.87, 20.23, 22.09, 22.35, 22.49, 26.92, 30.06, 39.26, 44.39, 48.16, 49.01, 49.53, 53.08, 71.68, 72.69, 78.88, 78.91, 124.61, 125.12, 127.96, 128.36, 133.22, 140.06, 142.90, 143.33, 164.62, 164.86

The peaks at 5 71.68 & 72.69 and 164.62 & 164.86 are attributed to the benzylic and ester carbonyl carbon of major and minor diastereomers respectively.

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate (167):

This compound was obtained as a colorless viscous liquid *via* the reaction of 2-chlorobenzaldehyde **(130h)** with acrylate (18) in the presence of DABCO, **following** the similar procedure described for the molecule **163.**

Reaction time:	10 days
Yield:	90%
de:	62%



Optical rotation: $[\alpha]_D^{25}$ **-18.66** (*c* 1.50, acetone)

IR(Neat): ν 3491, 1716, 1630 cm^{-1}

^{1}H NMR: δ 0.81-1.50 (m, 18H, H9', H8', 2×CH(CH_3)$_2$), 1.58-2.13 (m, 7H, H3', H4^1, H5', H6'), 2.71 & 3.25 and 2.73 & 3.32 (2ABq, 2H, *J* = 13.4 Hz, H10'), 3.54-3.86 (m, 3H, 2×CH(CH_3)$_2$ & CHOH, 1H D_2O washable), 5.05-5.14 & 5.14-5.29 (2m, 1H, H2'), 538 & 5.45 (2s, 1H, H3), 5.94-6.05 (m, 1H, Hb), 6.07 & 6.26 (2s, 1H, Ha), 7.18-7.46 (m, 3H, aromatic), 7.55-7.68 (m, 1H, aromatic)

The underlined peaks are attributed to the minor diastereomer.

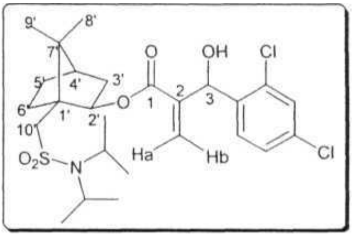
The peaks at δ 5.38 and 5.45 arise due to the benzylic proton (H3) of minor and major diastereomers respectively and are in the ratio of 19:81, indicating 62% diastereoselectivity in the reaction.

^{13}C NMR: **8 19.69,** 19.95, 20.26, 22.02, 22.59, 26.95, 29.90, 30.30, **39.16, 39.35, 44.38,** 48.24, 49.05, 49.55, 52.94, 53.35, 68.88, 69.74, 78.82, 79.04, 125.09, 126.05, 127.01, 128.12, 128.81, 128.97, 129.30, 132.49, 132.83, 138.30, 141.68, 164.92, 165.31

The underlined peaks arise due to the minor diastereomer.

pt-2'-yl 3-(2,4-dichlorophenyl)-3-hydroxy-2-methylenepropanoate (168):

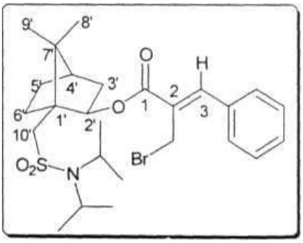
The reaction of 2,4-dichlorobenzaldehyde (130i) with acrylate (18) in the presence of DABCO in 4 mL of THF, following the similar procedure described for the molecule 163, afforded the desired compound 168, as a colorless solid.



Reaction time:	10 days
Yield:	68%
Mp.:	130-132 °C
Optical rotation:	$[\alpha]_D^{25}$ 4.06 (*c* 0.64, acetone)
IR (KBr):	ν 3479, 1714, 1628 cm"^{1}
^{1}H NMR:	5 0.89 (s, 3H, CH_3, H9'), 0.97 (s, 3H, CH_3, H8'), 1.28 (d, 12H, *J* = 6.0 Hz, 2×CH($\underline{CH_3}$)$_2$), 1.65-2.11 (m, 7H, H3', H4', H5', H6^1), 2.73 & 3.31 (ABq, 2H, *J* = 13.2 Hz, H10'), 3.55-3.88 (m, 3H, 2×$\underline{CH}$(CH_3)$_2$ & CHOH, 1H D_2O washable), 5.06-5.21 (m, 1H, H2'), 5.40 (s, 1H, H3), 5.92 (s, 1H, Hb), 6.23 (s, 1H, Ha), 7.26-7.43 (m, 2H, aromatic), 7.56 (d, 1H, *J* = 8.2 Hz, aromatic)
^{3}C NMR:	6 19.73, 20.21, 22.02, 22.52, 26.93, 30.35, 39.37, 44.38, 48.23, 49.04, 49.58, 53.40, 68.47, 79.12, 125.94, 127.23, 129.01, 129.21, 133.42, 133.93, 137.19, 141.55, 164.68

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (169):

To a stirred solution of alcohol 163 (5 mmol, 2.387 g) in CH_2Cl_2 (20 mL) was added drop wise HBr (48%, 12.5 mmol, 2.10 mL) followed by conc. H_2SO_4 (5 mmol, 0.49 g) at 0 °C. After 12 h of stirring at room temperature, the reaction mixture was carefully poured into ice-cold water and extracted with ether (2x20 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained, was purified by column chromatography (silica gel, 4% EtOAc in hexanes) to afford 169, as a colorless solid.

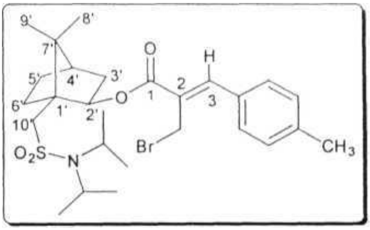


Yield:	88% (2.385 g)
Mp.:	106-108 °C
Optical rotation:	$[\alpha]_D$ +75.03 (*c* 4.27, $CHCl_3$)
IR (KBr):	ν 1722, 1630 cm^{-1}
H NMR:	6 0.92 (s, 3H, CH_3, H9'), 1.13 (s, 3H, CH_3, H8'), 1.25 (d, 12H, *J* = 6.6 Hz, $2\times CH(\underline{CH}_3)_2$), 1.61-2.18 (m, 7H, H3', H4', H5', H6'), 2.75 & 3.36 (ABq, 2H, *J* = 13.6 Hz, H10'), 3.57-3.82 (m, 2H, $2\times\underline{CH}(CH_3)_2$), 4.32 & 4.42 (ABq, 2H, *J* =9.8 Hz, CH_2Br), 5.19-5.28 (m, 1H, H2'), 7.39-7.65 (m, 5H, aromatic), 7.76 (s, 1H, H3)

^{3}C NMR: 8 20.27, 20.42, 22.15, 22.69, 26.67, 27.06, 30.20, 39.51, 44.59, 48.24, 49.19, 49.78, 53.24, 79.31, 128.91, 129.52, 134.32, 142.33, 164.69

pt-2'-yl (2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (170):

This compound was prepared by the reaction of alcohol **164** with HBr (48%) in the presence of conc. H2SO4, following the similar procedure described for the molecule 169, as a colorless solid.



Yield: 95%

Mp.: 134-136 °C

Optical rotation: $[\alpha]_D^{25}$ +87.04 (*c* 5.00, $CHCl_3$)

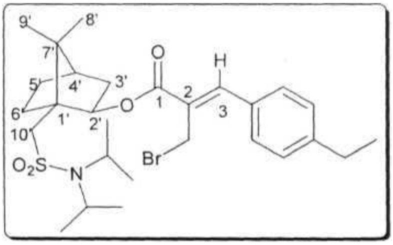
IR (KBr): v 1714, 1624 cm"^{1}

^{1}H NMR: δ 0.93 (s, 3H, CH_3, H9'), 1.14 (s, 3H, CH_3, H8'), 1.25 (d, 12H,./ = 6.6 Hz, 2×CH($\underline{CH_3}$)$_2$), 1.60-2.17 (m, 7H, H3', H4', H5', H6'), 2.40 (s, 3H, CH_3), 2.75 & 3.37 (ABq, 2H, *J* = 13.4 Hz, H10'), 3.59-3.82 (m, 2H, 2×$\underline{CH}$(CH_3)$_2$), 4.33 & 4.44 (ABq, 2H, *J* = 10.0 Hz, CH_2Br), 5.17-5.32 (m, 1H, H2'), 7.27 (d, 2H, *J* = 8.0 Hz, aromatic), 7.47 (d, 2H, *J* = 8.0 Hz, aromatic), 7.73 (s, 1H, H3)

^{13}C NMR: 5 20.27, 20.42, 21.38, 22.13, 22.69, 26.91, 27.07, 30.19, 39.54, 44.66, 48.24, 49.16, 49.82, 53.29, 79.26, 128.66, 129.67, 131.53, 139.99, 142.43, 164.79

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl (2*Z*)-2-(bromomethyl)-3-(4-ethylphenyl)prop-2-enoate (171):

This compound was isolated as a colorless solid *via* the reaction of alcohol **165** with HBr (48%) in the presence of conc. H2SO4, following the similar procedure described for the molecule **169.**



Yield: 72%

Mp: 94-96 °C

Optical rotation: $[\alpha]_D^{25}$ +85.5 (*c* 2.60, $CHCl_3$)

IR (KBr): v 1712, 1628 cm^{-1}

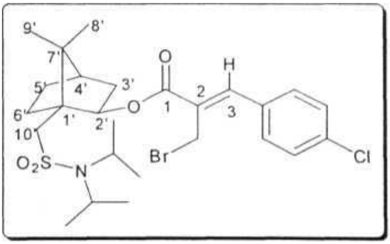
^{1}H NMR: 6 0.94 (s, 3H, CH_3, H9'), 1.15 (s, 3H, CH_3, H8'), 1.17-1.37 (m, 15H, $2\times CH(\underline{CH_3})_2$ & CH2CH3), 1.50-2.17 (m, 7H, H3', H4', H5', H6'), 2.65-2.81 (m, 3H, CH2CH3 & H10'), 3.37 (d, 1H, *J* =13.6 Hz, H10'), 3.56-3.81 (m, 2H, $2\times \underline{CH}(CH_3)_2$), 4.36 & 4.46 (ABq, 2H, *J* =9.8 Hz, CH_2Br), 5.17-5.32 (m, 1H, H2'), 7.30 (d, 2H, *J* =

7.8 Hz, aromatic), 7.51 (d, 2H, *J* = 7.8 Hz, aromatic), 7.75 (s, 1H,H3)

^{13}C NMR:	8 15.19, 20.24, 20.40, 22.11, 22.67, 27.03, 28.72, 30.14, 39.50, 44.57,48.20,49.14,49.74,53.20,79.17, 128.43, 129.81, 131.68, 142.48, 146.23, 164.78

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yI (2Z)-2-(bromomethyI)-3-(4-chlorophenyl)prop-2-enoate (172):

The reaction of alcohol 166 with HBr (48%) in the presence of conc. H_2SO_4, following the similar procedure described for the molecule 169, provided the desired compound 172, as a colorless solid.



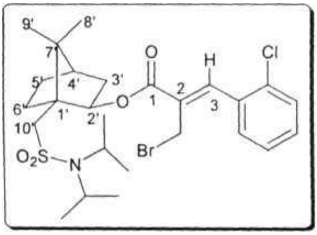
Yield:	93%
Mp.:	152-154°C
Optical rotation:	$[\alpha]_D^{25}$ +89.44 (*c* 5.00, $CHCl_3$)
IR (KBr):	v 1720, 1630 cm$'^{1}$
^{1}H NMR:	8 0.93 (s, 3H, CH_3, H9'), 1.14 (s, 3H, CH_3, H8'), 1.25 (d, 12H, *J* = 6.8 Hz, 2×CH($\underline{CH_3}$)$_2$), 1.62-2.18 (m, 7H, H3', H4', H5', H6'), 2.75 & 3.35 (ABq, 2H, *J* = 13.2 Hz, H10'), 3.57-3.82 (m, 2H, 2×$\underline{CH}$(CH_3)$_2$), 4.26 & 4.39 (ABq, 2H, *J* = 10.0 Hz, CH_2Br),

5.17-5.33 (m, 1H, H2'), 7.37-7.58 (m, 4H, aromatic), 7.70 (s, 1H, H3)

X NMR: 5 20.26, 20.39, 22.17, 22.64, 26.12, 27.05, 30.30, 39.52, 44.65, 48.26, 49.17, 49.86, 53.38, 79.52, 129.19, 130.20, 130.79, 132.80, 135.65, 140.83, 164.42

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl (2*Z*)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate (173):

This compound was obtained as a colorless solid *via* the treatment of alcohol **167** with HBr (48%) and conc. H2SO4, following the similar procedure described for the molecule **169.**



Yield: 81%

Mp.: 122-124°C

Optical rotation: $[\alpha]_D^{25}$ +96.96 (*c* 5.00, $CHCl_3$)

IR (KBr): ν 1720, 1631 cm^{-1}

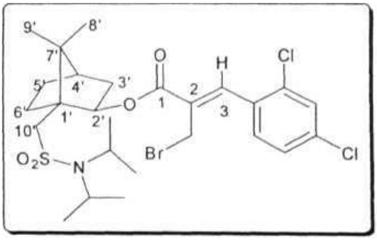
^{1}H NMR: 8 0.93 (s, 3H, CH_3, H9'), 1.14 (s, 3H, CH_3, H8'), 1.24 (d, 12H, J = 6.6 Hz, 2×CH($\underline{CH_3}$)$_2$), 1.58-2.19 (m, 7H, H3', H4', H5', H6'), 2.74 & 3.34 (ABq, 2H, *J* = 13.0 Hz, H10'), 3.60-3.82 (m, 2H, 2×$\underline{CH}$(CH_3)$_2$), 4.17 & 4.35 (ABq, 2H, *J* = 9.8 Hz, CH_2Br), 5.25-

5.40 (m, 1H, H2'), 7.32-7.58 (m, 3H, aromatic), 7.71-7.86 (m, 1H, aromatic), 7.88 (s, 1H, H3)

^{3}C NMR: 6 20.20, 20.41, 22.13, 22.64, 26.02, 27.05, 30.04, 39.40, 44.53, 48.23, 49.18, 49.74, 53.12, 79.30, 127.12, 129.51, 129.92, 130.65, 131.23, 132.77, 134.58, 138.48, 164.04

pt-2'-yl (2*Z*)-2-(bromomethyl)-3-(2,4-dichlorophenyl)prop-2-enoate (174):

The treatment of alcohol **168** with HBr (48%) and conc. H_2SO_4, following the **similar** procedure described for the molecule **169,** afforded the desired product **174**, as a colorless solid.



Yield: **93%**

Mp.: 142-144 °C

Optical rotation: $[\alpha]_D^{25}$ +111.9 (c 5.00, $CHCl_3$)

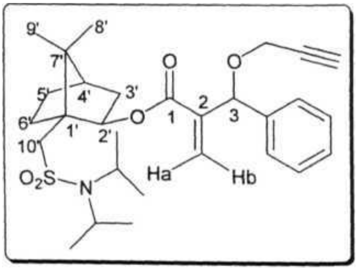
IR(KBr): v **1718,** 1635 cm^{-1}

^{1}H **NMR:** 6 0.92 (s, 3H, CH_3, H9'), 1.13 (s, 3H, CH_3, H8'), 1.24 (d, **12H,** *J* = 6.8 Hz, 2×CH($\underline{CH_3}$)$_2$), **1.62-2.16** (m, 7H, H3', **H4',** H5', H6'), 2.75 & 3.33 **(ABq, 2H,** ***J*** = **13.6** Hz, H10'), 3.56-3.78 (m, **2H,** 2×$\underline{CH}$(CH_3)$_2$), 4.13 **& 4.32 (ABq, 2H,** ***J*** **=9.6 Hz,** CH_2Br), **5.22-**

	5.33 (m, 1H, H2'), 7.34-7.52 (m, 2H, aromatic), 7.68 (d, 1H, *J* = 8.2 Hz, aromatic), 7.80 (s, 1H, H3)
^{13}C NMR:	20.20, 20.38, 22.17, 22.60, 25.53, 27.04, 30.16, 39.44, 44.63, 48.26, 49.17, 49.83, 53.27, 79.54, 127.51, 129.85, 130.29, 131.41, 131.96, 135.37, 135.95, 137.20, 163.78

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 2-methylene-3-(prop-2-yn-1-yloxy)-3-phenylpropanoate (175):

To a stirred solution of allyl bromide 169 (0.5 mmol, 0.27 g) in Et_3N (1 mL) was added propargyl alcohol (2.5 mmol, 0.14 g). After stirring for 12 h at room temperature, the reaction mixture was diluted with ether (10 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, 4% EtOAc in hexanes) to provide pure propargylic ether 175, as a colorless solid.



Yield:	55% (0.142 g)
de:	88%
Mp.:	90-92 °C
Optical rotation:	$[\alpha]_D^{25}$ -104.14 (*c* 3.50, $CHCl_3$)

IR (KBr): v 3240, 2115, 1716, 1620 cm^{-1}

^1H NMR: 5 0.85-1.39 (m,18H, H9', H8', $2\times CH(\underline{CH_3})_2$), 1.56-2.10 (m, 7H, H3', H4', H5', H6'), 2.42 (t, 1H, J = 2.6 Hz, HC≡C), 2.62-2.71 (m, 1H, H10'), 3.18-3.36 (m, 1H, H10'), 3.54-3.82 (m, 2H, $2\times \underline{CH}(CH_3)_2$), 4.02 & 4.15 (d of ABq, 2H,./ = 2.6 & 15.6 Hz, $CH_2C{\equiv}C$), 5.07-5.17 (m, 1H, H2'), 5.52 & $\underline{5.56}$ (2s, 1H, H3), 5.92 & 6.03(2s, 1H, Hb), 6.18 & 6.23 (2s, 1H, Ha), 7.20-7.44 (m, 5H, aromatic)

The underlined peaks arise due to minor diastereomer.

The two singlets at 8 5.92 & 6.03 arise from the olefinic (Hb) proton, *(trans*- to the ester functionality) of major and minor diastereomers respectively. The diastereomeric excess was determined by the integration (94:6) of these two singlets and found to be 88%

^{13}C NMR: δ 19.97, 20.31, 22.01, 22.35, 22.67, 26.96, 29.89, 39.28, 44.43, 48.14, 48.96, 49.57, 52.99, 55.99, 74.62, 77.45, 77.73, 78.48, $\underline{78.73}$, 79.45, 123.72, 127.57, 127.93, 128.26, $\underline{138.61}$, 138.93, $\underline{141.64}$,142.01, 164.03

The underlined signals are attributed to the minor diastereomer.

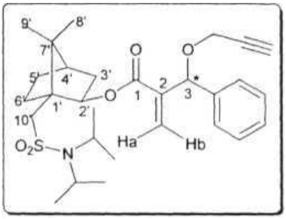
MS (*m/z*): 516 (M^+)

Analysis calcd. for $C_{29}H_{41}NO_5S$: C, 67.54; H, 8.01; N, 2.72

Found: C, 67.38; H, 8.11; N, 2.73

Selective crystallization:

Crystallization of the molecule 175 (0.2 mmol, 0.103 g) from 10% EtOAc in hexanes provided the single diastereomer (175*) (0.071 g, 69% yield) as evidenced by ^{1}H NMR and ^{13}C NMR spectral data.



de: >99%

Mp.: 90-92 °C

Optical rotation: $[\alpha]_D^{25}$ −109.65 (c 2.31, CHCl$_3$)

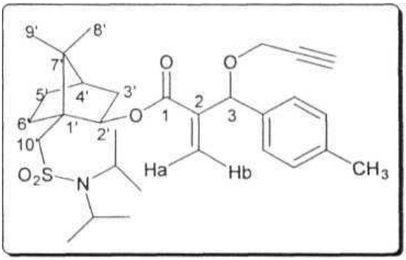
IR (KBr): v 3238,2121, 1716, 1624 cm^{-1}

^{1}H NMR: δ 0.88 (s, 3H, CH$_3$, H9'), 0.98 (s, 3H, CH$_3$, H8'), 1.29 (d, 12H, J = 6.8 Hz, $2\times CH(\underline{CH}_3)_2$), 1.55-2.12 (m, 7H, H3', H4', H5', H6'), 2.41 (t, 1H, J = 2.2 Hz, HC≡C), 2.70 & 3.26 (ABq, 2H, J = 13.6 Hz, H10'), 3.58-3.80 (m, 2H, $2\times \underline{CH}(CH_3)_2$), 4.02 & 4.15 (d of ABq, 2H, J= 2.0 & 15.6 Hz, CH$_2$C≡C), 5.10 (dd, 1H, J =3.2 & 7.8 Hz, H2'), 5.51 (s, 1H, H3), 5.91 (s, 1H, Hb), 6.17 (s, 1H, Ha), 7.21-7.46 (m, 5H, aromatic)

^{13}C NMR: 8 20.09, 20.44, 22.13, 22.79, 27.07, 30.00, 39.40, 44.57, 48.27, 49.08, 49.70, 53.13, 56.13, 74.66, 77.87, 78.63, 79.58, 123.76, 127.70, 128.04, 128.38, 139.07, 142.18, 164.15

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 2-methylene-3-(4-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate (176):

This compound was isolated as a colorless solid *via* the reaction of allyl **bromide 170** with propargyl alcohol in the presence of triethylamine, following the similar **procedure** described for the molecule **175**.



Reaction time: 12 h

Yield: 68%

de: 84%

Mp.: 104-106 ^{o}C

Optical rotation: $[\alpha]_{D}^{25}$ -106.65 (*c* 3.50, $CHCl_3$)

IR (KBr): ν 3240, 2117, 1716, 1622 cm"^{1}

^{1}H NMR: 5 0.88-1.45 (m, 18H, H9', H8', 2×CH(CH_3)$_2$), 1.56-2.11 (m, 7H, H3', H4', H5', H6'), 230 & 2.33 (2s, 3H, CH_3), 2.42 (t, 1H, *J* = 1.8 Hz, HC≡C), * 2.67 & 2.70 (2d, 1H, ./ = 13.4 Hz, H10'),* 3.21 & 3.26 (2d, 1H, *J* = 13.4 Hz, H10'),* 3.56-3.80 (m, 2H, 2×CH(CH_3)$_2$), 3.96-4.26 (m, 2H, CH_2C≡C), 4.95-5.03 & 5.06-5.17 (2m, 1H, H2'), 5.47 & 5.52 (2s, 1H, H3), 5.91 (d, 1H, *J* = 1.4 Hz) & 6.01 (s) (lH,Hb), 6.16 & 6.21 (2s, 1H, Ha), 7.09-7.38 (m, 4H, aromatic)

The underlined peaks are due to the minor diastereomer.

•These doublets are part of the two AB quartets of $\underline{CH_2}$ group at C-10' of major and minor diastereomers.

The two singlets at δ 5.91 & 6.01 arise from the β-olefinic (Hb) proton {*trans*- to the ester functionality) of the major and minor diastereomers respectively and are in the ratio of 92:8, indicating that the reaction is 84% diastereoselective.

^{13}C NMR: 5 20.04, 20.38, 21.11, 22.07, 22.42, 22.73, 27.03, $\underline{29.64}$, 29.95, 39.37, 44.56, 48.21, 49.01, 49.68, 53.10, 55.94, 74.50, 7734, 77.45, 77.72, 78.54, 78.81, 79.64, 123.52, 127.59, 129.01, 135.99, 137.62, $\underline{141.91}$, 142.30, 164.13

The underlined peaks are attributed to the minor diastereomer.

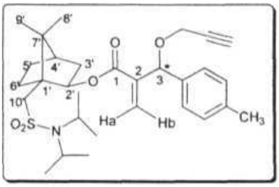
MS (*m/z*): 530 (M^+)

Analysis calcd. for $C_{30}H_{43}NO_5S$: C, 68.02; H, 8.18; N, 2.64

Found: C, 68.15; H, 8.16; N, 2.68

Selective crystallization:

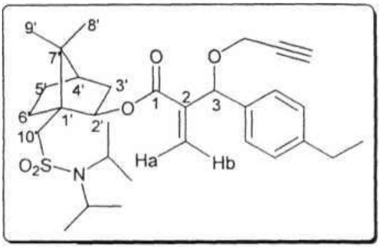
Crystallization of the molecule **176** (0.21 mmol, 0.111 g) from 10% EtOAc in hexanes provided the single diastereomer **(176*)** (0.064 g, 58% yield) as evidenced by the ^1H NMR and ^{13}C NMR spectral data.



Mp.:	104-106 °C
Optical rotation:	$[\alpha]_D^{25}$ −116.26 (*c* 2.09, $CHCl_3$)
IR (KBr):	ν 3240, 2123, 1716, 1622 cm^{-1}
^{1}H NMR:	δ 0.88 (s, 3H, CH_3, H9'), 0.98 (s, 3H, CH_3, H8'), 1.28 (d, 12H, *J* = 6.8 Hz, 2×CH($\underline{CH_3}$)$_2$), 1.56-2.11 (m, 7H, H3', H4', H5', H6'), 2.32 (s, 3H, CH_3), 2.40 (t, 1H, *J* = 2.0 Hz, HC≡C), 2.69 & 3.26 (ABq, 2H, *J* = 13.4 Hz, H10'), 3.63-3.79 (m, 2H, 2×$\underline{CH}$(CH_3)$_2$), 3.99 & 4.12 (d of ABq, 2H, *J* = 2.0 & 15.8 Hz, CH_2C≡C), 5.09 (dd, 1H, *J*= 3.2 & 7.8 Hz, H2'), 5.46 (s, 1H, H3), 5.90 (s, 1H, Hb), 6.15 (s, 1H, Ha), 7.12 (d, 2H, *J* = 7.8 Hz, aromatic), 7.27 (d, 2H, *J*= 7.8 Hz, aromatic)
^{13}C NMR:	δ 20.13, 20.47, 21.22, 22.15, 22.81, 27.10, 29.99, 39.43, 44.61, 48.29, 49.10, 49.73, 53.15, 56.00, 74.57, 77.74, 78.60, 79.71, 123.58, 127.70, 129.12, 136.03, 137.77, 142.30, 164.18

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(4-ethylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (177):

This compound was prepared *via* the treatment of allyl bromide **171** with propargyl alcohol under the influence of triethylamine, as a colorless solid, following the similar procedure described for the molecule 175.



Reaction time: 12 h

Yield: 72%

de: 87%

Mp.: 74-76 °C

Optical rotation: $[\alpha]_D^{25}$ -101.88 (*c* 2.92, $CHCl_3$)

IR(KBr): v 3238, 2120, 1718, 1622 cm"^{1}

^{1}H NMR: δ 0.78-1.41 (m, 21H, H9', H8', $2\times CH(\underline{CH_3})_2$, $-CH_2\underline{CH_3}$), 1.56-2.15 (m, 7H, H3', H4', H5', H6'), 2.40 (t, 1H, *J* = 2.8 Hz, HC≡C), 2.57-2.78 (m, 3H, -CH2CH3, H10'), 3.16-3.33 (m, 1H, H10'), 3.54-3.81 (m, 2H, $2\times\underline{CH}(CH_3)_2$), 3.95-4.21 (m, 2H, $CH_2C{\equiv}C$), 5.04-5.15 (m, 1H, H2'), 5.48 & 5.52 (2s, 1H, H3), 5.91 & $\underline{6.02}$ (2s, 1H, Hb), 6.16 & 622 (2s, 1H, Ha), 7.08-7.35 (m, 4H, aromatic)

The underlined chemical shift values are due to minor diastereomer.

The two singlets at 5 5.91 & 6.02 are attributed the **β-olefinic** (Hb) proton *(trans-* to the ester functionality) of the major and minor diastereomers respectively. The diastereomeric excess was determined by the integration (93.5:6.5) of these two singlets and was found to be 87%.

^{13}C NMR: δ 14.08, 15.40, 20.05, 20.38, 22.07, 22.43, 22.74, 27.03, 28.54, 29.32, 29.94, 31.90, 39.35, 44.53, 48.20, 49.02, 49.66, 53.06, 55.95, 74.54, 77.41, 77.70, 78.51, 78.76, 79.64, 123.56, 127.63, 127.82, 135.84, 136.18, 141.82, 142.22, 143.97, 164.16

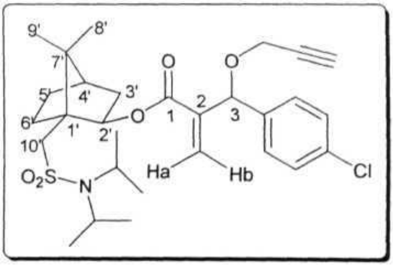
The underlined peaks are attributed to the minor diastereomer.

Analysis calcd. for $C_{31}H_{45}NO_5S$: C, 68.47; H, 8.34; N, 2.58

Found: C, 68.35; H, 8.30; N, 2.52

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(4-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (178):

The treatment of allyl bromide 172 with propargyl alcohol in the presence of triethylamine, following the similar procedure described for the molecule **175,** furnished the desired compound **178,** as a colorless solid.



Reaction time:	12 h
Yield:	83%
de:	78%
Mp.:	88-91 °
Optical rotation:	$[\alpha]_D^{25}$ −107.66 (*c* 2.68, $CHCl_3$)
IR (KBr):	ν 3231, 2115, 1716, 1626 cm^{-1}

^1H NMR: 8 0.86-1.45 (m, 18H, H9', H8', $2\times CH(\underline{CH_3})_2$), 1.56-2.09 (m, 7H, H3', H4', H5', H6'), 2.42 (t, 1H, *J* =2.8 Hz, HC≡C), $\underline{2.67\ \&\ 3.18}$ and 2.70 & 3.25 (2ABq, 2H, *J* = 13.4 Hz, H10'), 3.52-3.78 (m, 2H, $2\times \underline{CH}(CH_3)_2$), 3.95-4.22 (m, 2H, CH_2C≡C), 5.04-5.16 (m, 1H, H2'), 5.49 & $\underline{5.55}$ (2s, 1H, H3), 5.94 & 6.02 (2S, 1H, Hb), 6.18 & $\underline{6.21}$ (2s, 1H, Ha), 7.26-7.35 (m, 4H, aromatic)

The underlined chemical shift values arise from the minor diastereomer.

The diastereomeric excess was determined by the integration (89:11) of the two singlets at δ 5.94 & 6.02 arising from the olefinic (Hb) protons {*trans*- to the ester functionality) of major and minor diastereomers respectively and was found to be 78%.

^{13}C NMR: δ 19.96, 20.30, 22.04, $\underline{22.21}$, 22.64, 26.96, 29.99, 39.32, 44.50, 48.18, 48.99, 49.66, 53.09, 53.37, 56.09, 74.83, $\underline{76.81}$, 77.10, 78.62, $\underline{78.84}$, 79.23, 123.78, 128.43, $\underline{128.77}$, 128.97, 133.71, $\underline{137.64}$, 137.82, $\underline{141.52}$, 141.77, 163.86

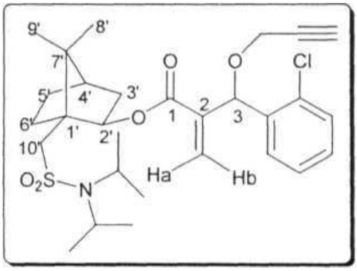
The underlined peaks are attributed to the minor diastereomer.

Analysis calcd. for $C_{29}H_{40}NO_5SCl$: C, 63.31; H, 7.33; N, 2.55

Found: C, 63.52; H, 7.38; N, 2.58

pt-2'-yl 3-(2-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (179):

This compound was isolated as a colorless solid *via* the reaction of the allyl bromide 173 with propargyl alcohol in the presence of triethylamine, following the similar procedure described for the molecule **175**.



Reaction time: 12 h

Yield: 63%

de: 77%

Mp.: 116-118 °C

Optical rotation: $[\alpha]_D^{25}$ -54.28 (*c* 1.09, $CHCl_3$)

IR (KBr): ν 3244, 2130, 1711, 1624 cm^{-1}

^1H NMR: 6 0.75 & 0.83 (2s, 3H, CH_3, H9'), 0/78 & 0.95 (2s, 3H, CH_3, H8'), 1.08-1.41 (m, 12H, $2\times CH(\underline{CH_3})_2$), 1.56-2.07 (m, 7H, H3', H4', H5', H6'), 2.27-2.41 (m, 1H, HC≡C), 2.61 & 2.64 (2d, 1H, *J* = 13.6 Hz, H10'), 3.20 (d, 1H, *J* = 13.6 Hz, H10'), 3.52-3.76 (m, 2H, $2\times \underline{CH}(CH_3)_2$), 4.09-4.23 (m, 2H, $CH_2C\equiv C$), 4.91-5.01 & 5.04-5.17 (2m, 1H, H2'), 5.50 & 5.75 (2s, 1H, H3), 5.80 & 5.98 (2s, 1H, Hb), 6.10 & 6.32 (2s, 1H, Ha), 7.12-7.48 (m, 4H, aromatic)

The underlined peaks are due to minor diastereomer.

The two singlets at 8 6.10 & 6.32 are from the olefinic (Ha) protons (*cis*- to the ester functionality) of major and minor diastereomers respectively. The diastereomeric excess was determined by the integration (88.5:11.5) of these two singlets and was found to be 77%.

^{13}C NMR: 8 19.69, 20.09, 20.40, 22.07, 22.76, 27.02, 29.86, 30.21, 39.37, 44.54, 48.19, 49.05, 49.63, 53.06, 57.28, 57.42, 74.65, 75.26, 75.55, 78.77, 79.05, 79.49, 125.32, 126.41, 126.79, 128.59, 129.14, 129.39, 129.61, 133.78, 134.26, 136.70, 139.97, 141.11, 163.81, 164.14

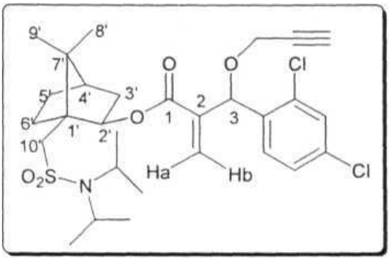
The underlined chemical shift values arise due to the minor diastereomer.

Analysis calcd. for $C_{29}H_{40}NO_5SCl$: C, 63.31; H, 7.33; N, 2.55

Found: C, 63.18; H, 7.30; N, 2.60

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(2,4-dichlorophenyl)-2-methylene-3-(prop-2-yn-l-yloxy)propanoate (180):

This compound was obtained *via* the reaction of allyl bromide **174** with propargyl alcohol under the influence of triethylamine, as a colorless viscous liquid, following the similar procedure described for the molecule **175.**



Reaction time: 12 h

Yield: 69%

de: 51%

Optical rotation: $[\alpha]_D^{25}$ −51.14 (*c* 3.15, $CHCl_3$)

1R (Neat): ν 3304, 2250, 1716, 1589 cm^{-1}

^1H NMR: 6 0.86-1.41 (m, 18H, H9', $H8^1$, $2\times CH(\underline{CH_3})_2$), 1.56-2.12 (m, 7H, H3', H4', H5', H6'), 2.36-2.46 (m, 1H, HC≡C), $\underline{2.69}$ & 2.71 (2d, 1H, *J* = 13.4 Hz, H10'), 3.26 (d, 1H, *J* = 13.4 Hz, H10'), 3.58-3.79 (m, 2H, $2\times \underline{CH}(CH_3)_2$), 4.19-4.26 (m, 2H, $CH_2C{\equiv}C$), $\underline{4.97\text{-}5.07}$ & 5.10-5.19 (2m, 1H, H2'), 5.62 & 578 (2s, 1H, H3), 5.82 & $\underline{5.87}$ (2s, 1H, Hb), 6.18 & 6.37 (2s, 1H, Ha), 7.17-7.48 (m, 3H, aromatic)

The underlined peaks are attributed to the minor diastereomer.

The diastereomeric excess was determined by the integration (75.5:24.5) of the two singlets at 8 6.18 & 6.37 arising from the β-olefinic (Ha) proton, (*cis*~ to the ester functionality) of major and minor diastereomers respectively and was found to be 51%.

^{13}C NMR: δ $\underline{19.73}$, 20.04, 20.31, 22.06, $\underline{22.15}$, $\underline{22.57}$, 22.67, 26.98, 29.90, 30.24, 39.34, 44.50, 48.16, 49.01, 49.51, 49.62, 53.06, 57.26, 74.87, 75.03, 78.77, 79.06, 79.23, 125.34, 126.27, 127.10, 129.33, 129.66, 134.22, 134.40, 134.82, 135.39, 135.61, 139.75, 140.71, 163.58, 163.85

The underlined peaks arise due to minor diastereomer.

Analysis calcd. for $C_{29}H_{39}NO_5SCl_2$: C, 59.58; H, 6.72; N, 2.40

Found: C, 59.38; H, 6.79; N, 2.35

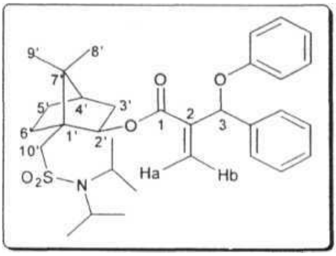
(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 2-methylene-3-phenoxy-3-phenylpropanoate (181):

A solution of the allyl bromide **169** (0.5 mmol, 0.27 g), phenol (0.5 mmol, 0.047 g) and Et_3N (1 mL) in CH_2Cl_2 (1 mL), was stirred at room temperature for 4 hours. Then 2N HCl (5 mL) was added slowly and the reaction mixture was extracted with ether (2×10 mL). The combined organic layer was washed with aqueous $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 4% EtOAc in hexanes) to provide **181,** as colorless viscous liquid.

Yield: 48% (0.132 g)

de: 82%

Optical rotation: $[\alpha]_D^{25}$ -55.56 (*c* 1.78, CHCl$_3$)



IR (Neat): ν 1716, 1631 cm^{-1}

^{1}H NMR: 6 0.76-2.11 (m, 25H, H9', H8', 2×CH($\underline{CH_3}$)$_2$, H3', H4', H5', H6'), 2.61-2.81 (m, 1H, H10'),* 3.16, 3.22 & 3.28 (3s, 1H, H10'),* 3.54-3.81 (m, 2H, 2×$\underline{CH}$(CH$_3$)$_2$), 5.05-5.24 (m, 1H, H2'), 5.78 & $\underline{6.02}$, 6.18, 6.21 & $\underline{6.26}$ (5s, 3H, H3, Hb, Ha), 6.82-7.02 (m, 3H, aromatic), 7.13-7.54 (m, 7H, aromatic)

The underlined peaks are attributed to the minor diastereomer.

*These actually belong to doublet of AB quartet (H10'). Due to merging of peaks of major and minor diastereomers, first part of ABq appears as multiplet at 5 2.61-2.81. Similarly due to merging of one of the peaks of doublet of minor diastereomer with one of the peaks of the major diastereomer, three singlets were obsereved at δ 3.16, 3.22 & 3.28 for second part of ABq (of both major and minor diastereomers).

The singlets at δ 5.78 & $\underline{6.02}$ can be attributed to the benzylic (H3) protons of the major and minor diastereomers respectively and are in the ratio of 91:9, indicating that the reaction is 82% diastereoselective. To further confirm our assignment, we have recorded ^{1}H NMR in the presence of chiral shift reagent Eu(hfc)3, which clearly showed, that the minor peaks originally at 8 6.26 and 8 6.02 are in the ratio of 2:1, thus indicating that the peak originally at 5 6.26 arises due to Hb and Ha protons of minor diastereomer. For further understanding, we have also recorded ^{1}H NMR spectrum in the presence of shift reagent Eu(fod)$_3$, the multiplet originally at 8 5.05-5.24 due to the H2' proton nicely splits into two multiplets at 8 5.44-5.52 and 8 5.53-5.65 in the ratio of 9:91, indicating that the molecule **181** is 82% diastereomerically pure.

^{13}C NMR: 8 19.90, 20.35, 22.12, 22.42, 22.70, 27.03, 29.70, 30.07, 39.40, 44.50, 48.20, 49.06, 49.62, 53.18, 77.09, 78.85, 79.15, 115.40, 115.89, 120.24, 121.07, 125.00, 126.99, 127.16, 128.00, 128.52, 129.39, 139.17, 141.23, 141.90, 157.54, 157.80, 163.55, 164.22.

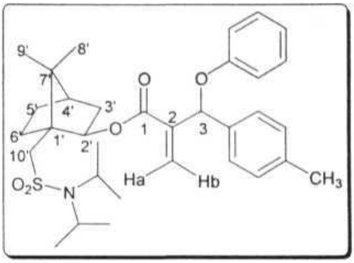
The underlined peaks are due to the minor diastereomer.

Analysis calcd. for $C_{32}H_{43}NO_5S$: C, 69.41; H, 7.83; N, 2.53

Found: C, 69.25; H, 7.70; N, 2.55

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 2-methylene-3-(4-methylphenyl)-3-phenoxypropanoate (182):

It was obtained as a colorless viscous liquid *via* the reaction of allyl bromide **170** with phenol in the presence of triethylamine, following the similar procedure described for the molecule **181.**



Reaction time: 4h

Yield: 61%

de: 76%

Optical rotation: $[\alpha]_D^{25}$ -61.66 (*c* 1.26, $CHCl_3$)

IR(Neat): ν 1716, 1631 cm^{-1}

^{1}H NMR: δ 0.79-2.10 (m, 25H, H9', H8', 2×CH(CH_3)$_2$, H3', H4', H5', H6'), 2.30 & 2.33 (2s, 3H, CH_3), 2.68 & 3.21 and 2.70 & 3.26 (2ABq, 2H, *J* = 13.4 Hz, H10'), 3.53-3.78 (m, 2H, 2×CH(CH_3)$_2$), 5.02-5.22 (m, 1H, H2'), 5.78 & 6.00 (2s, 1H, H3), 6.10-6.28 (m, 2H, Hb, Ha), 6.83-6.98 (m, 3H, aromatic), 7.07-7.41 (m, 6H, aromatic)

The underlined chemical shift values are due to the minor diastereomer.

The singlets at δ 5.78 and 6.00 in the ratio of 88:12 are attributed to the benzylic (H3) protons of major and minor diastereomers respectively, indicating that the reaction is 76% diastereoselective. This is further confirmed by the integration of singlets at δ 2.30 and 2.33 arising from the CH3 protons on the aromatic ring of the minor and major diastereomers respectively. We have also recorded the ^{1}H NMR in the presence of shift reagent [sample: Eu(fod)$_3$ = 1:1], the **multiplet** originally at δ 5.02-5.22 (due to **H2'** proton) nicely splits into two multiplets at 6 5.34-5.44 and 5.46-5.57 in the ratio of 12:88, also indicating 76% diastereoselectivity in the reaction.

^{13}C NMR: 8 19.92, 20.35, 21.15, 22.12, 22.42, 22.71, 27.05, 30.08, 39.44, 44.56, 48.22, 49.05, 49.66, 53.22, 76.65, 77.07, 78.84, 79.13, 115.93, 121.00, 124.80, 127.13, 129.22, 129.34, 136.21, 137.69, 141.42, 142.05, 157.92, 164.27

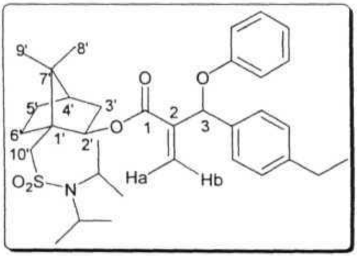
The underlined peaks are attributed to the minor diastereomer.

Analysis calcd. for $C_{33}H_{45}NO_5S$: C, 69.81; H, 7.99; N, 2.47

Found: C, 70.00; H, 7.93; N, 2.51

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(4-ethylphenyl)-2-methylene-3-phenoxypropanoate (183):

This product was prepared *via* the treatment of allyl bromide **171** with phenol in the presence of triethylamine, following the similar procedure described for the molecule **181,** as a colorless viscous liquid.



Reaction time:	**4 h**
Yield:	**66%**
de:	**78%**
Optical rotation:	$[\alpha]_D^{25}$ −59.26 (*c* 1.44, $CHCl_3$)
IR (Neat):	ν 1718, 1615 cm^{-1}

^{1}H NMR: δ 0.72-2.11 (m, 28H, H9', H8', 2×CH($\underline{CH_3}$)$_2$, -CH2$\underline{CH}$3, H3', H4', H5', H6'), 2.52-2.77 (m, 3H, CH2CH3 & H10'), $\underline{3.21}$ & 3.25 (2d, 1H, *J* = 13.4 Hz, H10'), 3.49-3.81 (m, 2H, 2×$\underline{CH}$(CH$_3$)$_2$), 5.06-5.20 (m, 1H, H2^1), 5.78 & $\underline{6.01}$ (2s, 1H, H3), 6.15, 6.19, 6.21 & 6.27 (4s, 2H, Hb, Ha), 6.80-7.01 (m, 3H, aromatic), 7.07-7.42 (m, 6H, aromatic)

The underlined peaks arise due to minor diastereomer.

The two singlets at δ 5.78 & 6.01 integrating in the ratio of 89:11 arise from the benzylic (H3) protons of major and minor diastereomers respectively, indicating that there is 78% distereoselectivity in the reaction. This is further confirmed by the integration of two doublets at 8 3.21 and 3.25 (second part of d of ABq) arising from the H10' proton of the minor and major diastereomers respectively.

^{13}C NMR: 8 15.41, 19.94, 20.38, 22.15, $\underline{22.50}$, 22.74, 27.09, 28.57, 30.14, 39.47, 44.57, 48.25, 49.07, 49.69, 53.24, 77.11, 78.85, $\underline{79.18}$, $\underline{115.52}$, 115.93, 120.00, 121.01, 124.85, 127.18, 128.03, 129.39, 136.42, $\underline{141.28}$, 142.08, 144.00, $\underline{157.72}$, 157.97, 164.32

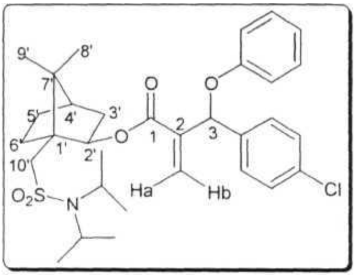
The underlined chemical shift values are attributed to the minor diastereomer.

Analysis calcd. for $C_{34}H_{47}NO_5S$: C, 70.19; H, 8.14; N, 2.41

Found: C, 69.92; H, 8.24; N, 2.38

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(4-chlorophenyl)-2-methylene-3-phenoxypropanoate (184):

The treatment of allyl bromide **172** with phenol under the influence of triethylamine, following the similar procedure described for the molecule **181,** afforded the desired compound **184**, as a colorless solid.



Reaction time:	4 h
Yield:	63%
de:	81%
Mp.:	46-48 °C
Optical rotation:	$[\alpha]_D^{25}$ -75.8 (*c* 2.50, $CHCl_3$)
IR (KBr):	v 1716, 1620 cm^{-1}
^1H NMR:	5 0.74-1.39 (m, 18H, H9', H8', 2×CH(CH_3)$_2$), 1.46-2.08 (m, 7H, H3', H4', H5', H6'), 160 & 2.63 (2d, 1H, *J* = 13.4 Hz, H10'),* 3.06, 3.13 & 3.19 (3s, 1H, H10'),** 3.44-3.72 (m, 2H, 2×CH(CH_3)$_2$), 4.99-5.12 (m, 1H, H2'), 5.77 & 5.95 (2s, 1H, H3), 6.04-6.21 (m, 2H, Hb, Ha), 6.74-6.92 (m, 3H, aromatic), 7.07-**7.42 (m, 6H, aromatic)**

The underlined peaks arise due to minor diastereomer.

This is actually first part of doublet of the AB quartet. **This is the second part of doublet of AB quartet in which one of the peaks of doublet of minor diastereomer merges with one of the peaks of the major diastereomer, thus appearing as three singlets.

The two singlets at 5 5.77 & 5.95 in the ratio of 90.5:9.5 arise from the benzylic (H3) protons of major and minor diastereomers respectively, indicating that the reaction is 81% diastereoselective. This is further confirmed by the integration of the doublets at 5 2.60 and 2.63 (first part of d of ABq) arising from the H10' proton of the minor and major diastereomers respectively.

^{13}C NMR: 5 19.86, 20.27, 22.08, 22.60, 26.99, 30.11, 39.37, 44.47, 48.16, 49.01, 49.63, 53.20, 75.84, 76.45, 78.87, 79.11, 115.42, 115.85, 121.29, 124.86, 128.20, 128.55, 128.63, 129.41, 133.73, 137.91, 141.14, 141.52, 157.48, 163.94

The underlined peaks are due to the minor diastereomer.

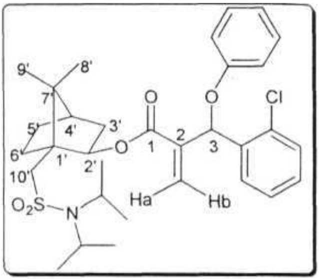
MS (*m/z*): 588 (M^+)

Analysis calcd. for $C_{32}H_{42}NO_5SCl$: C, 65.34; H, 7.20; N, 2.38

Found: C, 65.56; H, 7.27; N, 2.35

(1'*S*,2'*R*,4'*R*)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(2-chlorophenyl)-2-methylene-3-phenoxypropanoate (185):

This product was isolated as a colorless viscous liquid *via* the reaction of allyl bromide **173** with phenol in the presence of triethylamine, following the similar procedure described for the molecule **181**.



Reaction time: 4h

Yield: 64%

de: 67%

Optical rotation: $[\alpha]_D^{25}$ 2.22 (*c* 1.88, $CHCl_3$)

IR (Neat): v 1720, 1635 cm''^{1}

'H NMR: 5 0.56, 0.78, 0.75 & 0.80 (4s, 6H, H9', H8'), 1.05-2.02 (m, 19H, 2×$CH(CH_3)_2$, H3', H4', H5', H6'), 2.59 & 3.23 and 2.62 & 3.19 (2ABq, 2H,./ = 13.2 Hz, H10'), 3.56-3.74 (m, 2H, 2×$CH(CH_3)_2$), 4.92-5.02 & 5.05-5.18 (2m, 1H, H2'), 5.31 & 5/77 (2s, 1H, H3), 6.15, 6.42, 6.45 (3s, 2H, Hb, Ha), 6.72-6.95 (m, 3H, aromatic), 7.06-7.45 (m, 6H, aromatic)

The underlined chemical shifts arise due to the minor diastereomer.

The two singlets at 6 5.31 & 5.77 arise from the benzylic (H3) protons of the major and minor diastereomers respectively. The diastereomeric excess was determined by the integration (83.5:16.5) of these two singlets and was found to be 67%. The diastereoselectivity is further confirmed by the integration of two multiplets at 8 4.92-5.02 & δ 5.05-5.18 which are in the ratio of 16.5:83.5 arising due to H2' proton of minor and major diastereomers respectively.

^{13}C NMR: 5 $\underline{19.38}$, 19.91, 20.36, 22.16, 22.81, 27.03, 29.99, $\underline{30.66}$, 39.41, $\underline{39.58}$, 44.53, 48.25, 49.04, 49.59, 53.09, $\underline{53.44}$, $\underline{74.21}$, 74.61, 79.00, $\underline{79.33}$, 115.41, 115.78, 120.30, 121.31, 126.13, 127.16, $\underline{128.13}$, 128.70, 129.41, 129.77, 133.35, $\underline{134.34}$, 136.12, $\underline{136.45}$, $\underline{138.80}$, 140.57, $\underline{156.06}$, 157.93, 163.89, 164.28

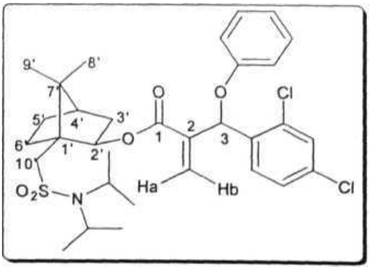
The underlined peaks are attributed to the minor diastereomer.

Analysis calcd. for $C_{32}H_{42}NO_5SCl$: C, 65.34; H, 7.20; N, 2.38

Found: C, 65.58; H, 7.14; N, 2.40

(1'*S*,2'*R*,4'*R*)-1-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-(2,4-dichlorophenyl)-2-methylene-3-phenoxypropanoate (186):

The reaction of allyl bromide 174 with phenol in the presence of triethylamine, following the similar procedure described for the molecule **181**, furnished the desired product 186, as a colorless solid.



Reaction time: 4 h

Yield: 59%

de: 54%

Mp.: 50-52 °C

Optical rotation: $[\alpha]_D^{25}$ -8.96 (*c* 2.55, $CHCl_3$)

IR (KBr): v 1720, 1635cm^{1}

^{1}H NMR: 8 0.69-1.02 (m, 6H, H9', H8'), 1.11-1.47 (m, 12H, 2×CH($\underline{CH_3}$)$_2$), 1.54-2.12 (m, 7H, H3', H4', H5', H6'), 2.62-2.83 (m, 1H, H10'), 3.19-3.34 (m, 1H, H10'), 3.59-3.83 (m, 2H, 2×$\underline{CH}$(CH$_3$)$_2$), $\underline{5.01-}$5.11 & 5.13-5.23 (2m, 1H, H2'), 5.48 & 5.86(2s, 1H, H3), {6.25 (s) & 6.42-6.55 (m), 2H, Hb, Ha}, 6.81-7.04 (m, 3H, aromatic), 7.14-7.48 (m, 5H, aromatic)

The underlined peaks are due to minor diastereomer.

The two singlets at 8 5.48 & 5.86 in the ratio of 77:23 arise from the benzylic (H3) protons of major and minor diastereomers respectively, indicating 54% diastereoselectivity in this reaction. Diastereoselectivity was further confirmed by the integration of the multiplets at 8 5.01-5.11 & 5.13-5.23 arising from the methine protons at C2' of minor and major diastereomers respectively.

^{13}C NMR: 8 $\underline{19.44}$, 19.90, 20.29, 22.13, 22.71, 26.99, 30.04, $\underline{30.64}$, 39.40, $\underline{39.56}$, 44.49, 48.20, 49.01, 49.59, 53.11, 53.42, 73.78, 74.19, 79.00, $\underline{79.33}$, 115.74, 121.51, 126.09, $\underline{127.31}$, 127.46, $\underline{127.84}$, 129.43, 129.63, 134.14, 134.62, $\underline{134.80}$, 134.97, $\underline{135.24}$, $\underline{138.67}$, 140.13, 157.65, $\underline{163.60}$, 163.88

The underlined peaks arise due to the minor diastereomer.

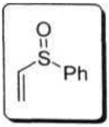
Analysis calcd. for $C_{32}H_{41}NO_5SCl_2$: C, 61.73; H, 6.64; N, 2.25

Found: C, 61.55; H, 6.66; N, 2.19

Reaction of pyridine-4-carboxaldehyde (130j) and phenyl vinyl sulfoxide (188) with TMG (187) in dioxane-water:

A mixture of pyridine-4-carboxaldehyde **(130j)** (2 mmol, 0.214 g), 1,1,3,3-tetramethylguanidine (187) (2 mmol, 0.23 g) and phenyl vinyl sulfoxide **(188)** (2 mmol, 0.304 g) in 1 mL of dioxane/water (1:1) was kept at room temperature for 6 h. The reaction mixture was extracted with $CHCl_3$ (4x40 mL) and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4). Solvent was evaporated and the crude product thus obtained, was subjected to column chromatography (silica gel) which provided phenyl vinyl sulfoxide **(188),** as colorless liquid, in 47% (0.144 g) (recovered) yield (with 12% EtOAc in hexanes), 4-pyridinemethanol **(189)** as colorless solid, in 27% (0.060 g) yield (with 100% EtOAc) and 1-phenylsulfinyl-2-(4-pyridylmethoxy)ethane **(190),** as a colorless liquid, in 10% (0.051 g) yield (with 1% MeOH in EtOAc).

Phenyl vinyl sulfoxide (188):

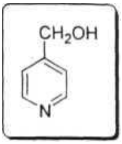


IR(Neat): v 3479, 1047 cm^{-1}

^{1}H NMR: 6 5.89 (d, 1H, *J* = 9.4 Hz), 6.19 (d, 1H, *J* = 16.6 Hz), 6.60 (dd, 1H, *J* = 16.6 & 9.4 Hz), 7.46-7.69 (m, 5H)

^{13}C NMR: δ 120.26, 124.27, 129.12, 130.90, 142.69, 142.98

4-Pyridinemethanol (189):



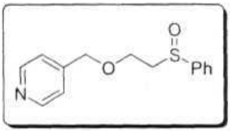
Mp.: 55-57 °C (lit.[273] 57-59 °C)

IR (KBr): ν 3375 cm^{-1}

^{1}H NMR: 6 2.62 (b, 1H), 4.74 (s, 2H), 7.29 (d, 2H, *J* = 6.0 Hz), 8.53 (d, 2H, *J* = 6.0 Hz)

^{13}C NMR: 6 62.54, 121.34, 148.84, 151.95

1-Phenylsulfinyl-2-(4-pyridylmethoxy)ethane (190):



IR (Neat): ν 3435, 1111,1041 cm^{-}

H NMR: 6 2.85-3.23 (m, 2H), 3.62-4.15 (m, 2H), 4.51 & 4.60 (ABq, 2H, *J* = 12.0 Hz), 7.23 (d, 2H, *J*= 5.0 Hz), 7.36-7.74 (m, 5H), 8.56 (d, 2H, *J* = 5.0 Hz)

^{13}C NMR: 6 57.85, 63.60, 71.54, 121.72, 123.88, 129.32, 131.09, 143.97, 146.83, 149.72

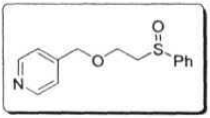
MS (*m/z*): 262 (M$^+$+1)

However, ^{1}H NMR and ^{13}C NMR spectral data indicate that this molecule is contaminated with ~5-10% impurities. This spectral data (except the impurities) is in complete agreement with that of the pure product **190** obtained *via* the Michael addition of **189** to **188** in the presence of TMG **(187)** (page no. 201).

Reaction of 4-pyridinemethanol (189) with phenyl vinyl sulfoxide (188) in the presence of TMG (187):

The treatment of a mixture of 4-pyridinemethanol **(189)** (1 mmol, 0.109 g) and phenyl vinyl sulfoxide **(188)** (1 mmol, 0.152 g) with 1,1,3,3-tetramethylguanidine **(187)** (1 mmol, 0.115 g) for 6 h at room temperature (following the similar work-up procedure described for the reaction of pyridine-4-carboxaldehyde (**130j**) and phenyl vinyl sulfoxide **(188)** with TMG **(187)** in dioxane-water) afforded 1-phenylsulfinyl-2-(4-pyridylmeth-oxy)ethane **(190),** as a colorless liquid, in 17% (0.045 g) yield along with recovered 4-pyridinemethanol **(189)** (59%) and phenyl vinyl sulfoxide **(188)** (20%).

1-Phenylsulfinyl-2-(4-pyridylmethoxy)ethane (190)



IR (Neat): ν 3445, 1043, 1113 cm^{-1}

^{1}H NMR: δ 2.86-3.20 (m, 2H), 3.67-4.09 (m, 2H), 4.47 & 4.56 (**ABq,** 2H, *J* = 12.0 Hz), 7.19 (d, 2H, *J* =5.0 Hz), 7.38-7.75 (m, 5H), 8.52 (d, 2H, *J* = 5.0 Hz)

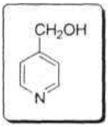
^{13}C NMR: δ 57.88, 63.60, 71.56, 121.72, 123.86, 129.34, 131.09, 143.94, 146.81, 149.77

Reaction of pyridine-4-carboxaldehyde (130j) and phenyl vinyl sulfoxide (188) with TMG (187), in THF-water:

The treatment of a mixture of pyridine-4-carboxaldehyde **(130j)** (2 mmol, 0.214 g) **and** phenyl vinyl sulfoxide **(188)** (2 mmol, 0.304 g) in 1 mL of THF/water (1:1) with

1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g), following the similar procedure described for the reaction of pyridine-4-carboxaldehyde **(130j)** and phenyl vinyl sulfoxide **(188)** with TMG **(187)** in dioxane-water, afforded **4-pyridinemethanol (189)** as colorless solid, in 23% (0.051 g) yield and **1-phenylsulfinyl-2-(4-pyridylmethoxy)ethane (190),** as a colorless liquid, in 11% (0.059 g) yield. Phenyl vinyl sulfoxide **(188)** was recovered as colorless liquid, in 46% (0.141 g) yield.

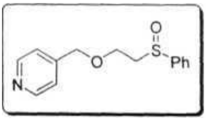
4-Pyridinemethanol (189):



Mp.: 55-57 °C (lit.[273] 57-59 °C)

Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are in agreement with that of the molecule obtained on reaction of pyridine-4-carboxaldehyde **(130j)** and phenyl vinyl sulfoxide **(188)** with TMG (187) in dioxane-water.

1-Phenylsulfinyl-2-(4-pyridylmethoxy)ethane (190):



Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are identical with that of the molecule obtained by the reaction of pyridine-4-carboxaldehyde **(130j)** and phenyl vinyl sulfoxide **(188)** with TMG **(187)** in dioxane-water. ^{1}H NMR and ^{13}C NMR spectral data also indicate the presence of ~5-10% impurities.

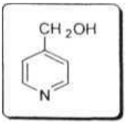
Cannizzaro reaction

Reaction between pyridine-4-carboxaldehyde (130j) and 1,1,3,3-tetramethylguanidine (187) in water:

4-Pyridinemethanol (189):

A mixture of pyridine-4-carboxaldehyde **(130j)** (2 mmol, 0.214 g) and 1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g) in 0.5 mL of water was kept at room temperature for 5 h. The reaction mixture was extracted with $CHCl_3$ (4x40 mL) and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4). Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 100% EtOAc) to afford the pure molecule **189,** as a colorless solid, in 42% (0.092 g) yield {expected yield, 50% (0.109 g)}. Our attempts to isolate the corresponding acid in pure form were not successful.

Mp.: 56-59 °C (lit.[273] 57-59 °C)



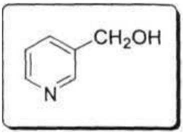
Spectral data (IR, ^1H and ^{13}C NMR) of this molecule are in complete agreement with that of the molecule obtained on reaction of pyridine-4-carboxaldehyde **(130j)** and phenyl vinyl sulfoxide **(188)** with TMG (187) in dioxane-water.

Reaction between pyridine-3-carboxaldehyde (130k) and 1,1,3,3-tetramethylguanidine (187) in water:

3-Pyridinemethanol (191):

Treatment of pyridine-3-carboxaldehyde **(130k)** with 1,1,3,3-tetramethylguanidine **(187),** following the similar procedure described for the molecule **189** (from pyridine-4-

carboxaldehyde and TMG), provided **3-pyridinemethanol** (191), as a colorless liquid, in 43% (0.093 g) yield {expected yield, 50% (0.109 g)}.



Reaction time: 7 h

IR (Neat): v 3308 cm'^{1}

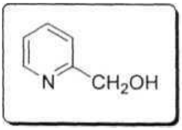
H NMR: δ 1.92 (b, 1H), 4.74 (s, 2H), 7.23-7.38 (m, 1H), 7.73 (d, 1H, J= 7.8 Hz), 8:52 (d, 1H, J = 4.6 Hz), 8.58 (s, 1H)

^{13}C NMR: 5 61.61, 123.57, 135.16, 137.44, 147.68

Reaction between pyridine-2-carboxaldehyde (1301) and **1,1,3,3-tetramethylguanidine** (187) in water:

2-Pyridinemethanol (192):

The treatment of pyridine-2-carboxaldehyde (1301) with 1,1,3,3-tetramethylguanidine (187) in water, following the similar procedure described for 189 (from pyridine-4-carboxaldehyde and TMG), afforded the desired molecule **192**, as a colorless liquid.



Reaction time: 5 h

Yield: 35% (0.077 g) {expected yield, 50% (0.109 g)}

IR (Neat): v 3356 cm*^{1}

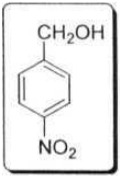
^{1}H NMR: 5 2.80 (s, 1H), 4.76 (s, 2H), 7.15-7.39 (m, 2H), 7.61-7.78 (m, 1H),8.57(d, 1H, J = 4.8 Hz)

^{13}C NMR: S 64.43, 120.71, 122.11, 136.81, 148.36, 160.20

Reaction between 4-nitrobenzaldehyde (130m) and 1,1,3,3-tetramethylguanidine (187) **in** water:

4-Nitrobenzyl alcohol (193):

A mixture of 4-nitrobenzaldehyde **(130m)** (2 mmol, 0.302 g) and 1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g) in 0.5 mL of water was refluxed for 30 minutes. The reaction mixture was then cooled to room temperature and extracted with $CHCl_3$ (3x20 mL), The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford 4-nitrobenzyl alcohol **(193),** as a yellow colored crystalline solid, in 36% (0.110 g) yield {expected yield, 50% (0.153 g)}.



Mp.: 91-93 °C (lit.^{275} 92-94 °C)

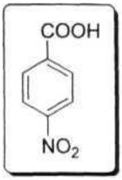
IR(KBr): ν 3514 cm'^{1}

^{1}H NMR: 5 1.92 (t, 1H, *J* = 6.0 Hz), 4.83 (d, 2H, *J* =6.0 Hz), 7.53 (d, 2H, *J* = 8.6 Hz), 8.22 (d, 2H, ./= 8.6 Hz)

^{13}C NMR: δ 63.93, 123.67, 127.04, 147.29, 148.39

4-Nitrobenzoic acid (194):

The aqueous layer in the above-mentioned experiment was acidified with conc. HC1, extracted with ethyl acetate (2x20 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was crystallized from EtOAc: hexanes (1:4) to provide 4-nitrobenzoic acid **(194),** as colorless crystalline solid, in 42% (0.141 g) yield {expected yield, 50% (0.167 g)}.

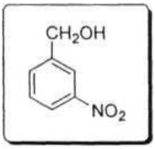


Mp.:	240-243 °C (lit.[276] 239-245 °C)
IR (KBr):	3150-2300, 1689, 1606 cm^{-1}
^1H NMR: (DMSO-d_6)	δ 8.17 (d, 2H, *J* = 8.6 Hz), 8.32 (d, 2H, *J* = 8.6 Hz)
^{13}C NMR: (DMSO-d_6)	δ 123.75, 130.81, 136.60, 150.19, 165.92

Reaction between 3-nitrobenzaldehyde (130n) and 1,1,3,3-tetramethylguanidine (187) in water :

3-Nitrobenzyl alcohol (195):

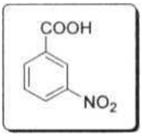
The reaction of 3-nitrobenzaldehyde **(130n)** with 1,1,3,3-tetramethylguanidine **(187)** in water (0.5 mL), following the similar procedure as in the case of 4-nitrobenzaldehyde, provided 3-nitrobenzyl alcohol **(195),** as a yellow colored viscous liquid and 3-nitrobenzoic acid (**196**), as a light yellow colored crystalline solid.



Reaction time:	10 h
Yield:	42% (0.128 g){expected yield, 50% (0.153 g)}
IR (Neat):	ν 3385 cm^{-1}
^1H NMR:	δ 1.91 (t, 1H, *J* = 5.8 Hz), 4.82 (d, 2H, *J* = 5.8 Hz), 7.47-7.62 (m, 1H), 7.70 (d, 1H, *J* = 7.6 Hz), 8.14 (d, 1H, *J* = 8.2 Hz), 8.25 (s, 1H)

^{13}C NMR: 6 63.50, 121.23, 122.16, 129.28, 132.64, 143.00, **148.14**

3-Nitrobenzoic acid (196):



Yield: 43% (0.144 g) {expected yield, 50% (0.167 g)}

Mp.: 141-143 °C (lit.[276] 140-142 °C)

IR (KBr): v 3200-2400, 1703, 1618 cm^{1}

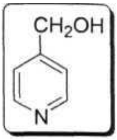
^{1}H NMR: δ 5.70 (b, 1H), 7.65-7.87 (m, 1H), 8.39-8.65 (m, 2H), 8.91-9.08 (m, 1H)

^{13}C NMR: δ 125.28, 128.37, 129.96, 131.09, 135.80, 148.58, 170.14

4-Pyridinemethanol (189):

[*via* TMG-mediated cross-Cannizzaro reaction between pyridine-4-carboxaldehyde **(130j)** and formalin in the ratio of 1:1]

To a mixture of pyridine-4-carboxaldehyde **(130j)** (2 mmol, 0.214 g) and formalin (37% w/v) (2 mmol, 0.162 mL) in 0.5 mL of water, was added 1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g) drop-wise and kept at **room temperature** for 4 h. The reaction mixture was extracted with $CHCl_3$ (3x40 mL) and the **combined** organic layer was washed with brine and dried over anhydrous sodium sulfate (Na_2SO_4). Solvent was evaporated and the crude **product thus obtained,** was **purified by** column chromatography (silica gel, 100%EtOAc) to afford **the desired product 189,** as a colorless solid, in 50% **(0.109** g) **yield** {expected yield, 100% (0.218 g)}.



Mp.: 56-59 °C (lit.[273] 57-59 °C)

Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are identical with that of the molecule obtained on reaction of pyridine-4-carboxaldehyde **(130j)** and phenyl vinyl sulfoxide **(188)** with TMG **(187)** in dioxane-water (page no. 200).

*The TMG promoted cross-Cannizzaro reaction of pyridine-4-carboxaldehyde **(J30j)** (2 mmol 0.214 g) with 2, 4, 8 and 16 equivalents of formalin (37% w/v) in the presence of 1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g) for 1.5, 1.5, 4 and 7 hours respectively, following the similar procedure described for the preparation of **189** [from pyridine-4-carboxaldehyde **(130j)** and formalin in the ratio of 1:1], provided 4-pyridinemathanol as colorless solid, in 57, 59, 60 and 64% yields respectively.*

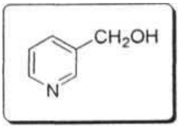
*Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are identical with that of the molecule obtained on reaction of pyridine-4-carboxaldehyde **(130j)** and phenyl vinyl sulfoxide **(188)** with TMG **(187)** in dioxane-water (page no. 200).*

3-Pyridinemethanol (191):

[*via* TMG-mediated cross-Cannizzaro reaction between pyridine-3-carboxaldehyde **(130k)** and formalin in the ratio of 1:16]

The treatment of a mixture of pyridine-3-carboxaldehyde **(130k)** (2 mmol, 0.214 g) and formalin (37% w/v) (32 mmol, 2.59 mL) with 1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g), following the similar procedure described for the preparation of **189**

[from pyridine-4-carboxaldehyde **(130j)** and formalin in the ratio of 1:1], provided the desired compound **191,** as a colorless liquid.



Reaction time: 1 ½ days

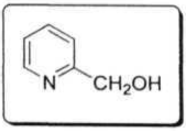
Yield: 54% (0.118 g) {expected yield, 100% (0.218 g)}

Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are in agreement with that of the molecule prepared from pyridine-3-carboxaldehyde **(130k)** and 1,1,3,3-tetramethylguanidine (page no. 204).

2-Pyridinemethanol (192):

[via TMG-mediated cross-Cannizzaro reaction between pyridine-2-carboxaldehyde (**130l**) and formalin in the ratio of 1:16]

This molecule is prepared *via* the reaction of a mixture of pyridine-2-carboxaldehyde **(1301)** (2 mmol, 0.214 g) and formalin (37% w/v) (32 mmol, 2.59 mL), with 1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g), following the similar procedure described for the preparation of **189** [from **pyridine-4-carboxaldehyde (130j)** and formalin in the ratio of 1:1], as colorless liquid.



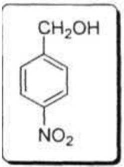
Reaction time: 1½ days

Yield: 51% (0.111 g) {expected yield, 100% (0.218 g)}

Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are in full agreement with that of the molecule prepared from pyridine-2-carboxaldehyde (**130l**) and 1,1,3,3-tetramethylguanidine (page no. 204).

4-Nitrobenzyl alcohol (193):
[*via* TMG-mediated cross-Cannizzaro reaction between 4-nitrobenzaldehyde **(130m)** and formalin in the ratio of 1:16]

A mixture of 4-nitrobenzaldehyde **(130m)** (2 mmol, 0.302 g), formalin (37% w/v) (32 mmol, 2.59 mL) and 1,1,3,3-tetramethylguanidine **(187)** (2 mmol, 0.23 g) in 0.5 mL of water was refluxed for 6 h. The reaction mixture was then cooled to room temperature, extracted with $CHCl_3$ (20 mL) and washed with water. The organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford 4-nitrobenzyl alcohol **(193),** as a yellow colored crystalline solid, in 73% (0.224 g) yield {expected yield, 100% (0.306 g)}.



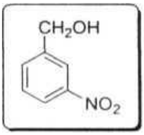
Mp: **92-94** °C (lit.[275] 92-94 °C)

Spectral data (IR, ^{1}H and ^{13}C NMR) of this molecule are identical with that of the molecule prepared from 4-nitrobenzaldehyde **(130m)** and 1,1,3,3-tetramethylguanidine (page no. 205).

3-Nitrobenzyl alcohol (195):

[via TMG-mediated cross-Cannizzaro reaction between **3-nitrobenzaldehyde (130n)** and formalin in the ratio of 1:16]

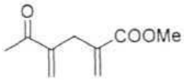
This compound was isolated as yellow colored viscous liquid *via* the treatment of **a** mixture of 3-nitrobenzaldehyde **(130n)** and formalin, with **1,1,3,3-tetramethylguanidine (187),** following the similar procedure described for the preparation of **193** [from the 4-nitrobenzaldehyde **(130m)** and formalin in the ratio of 1:16].



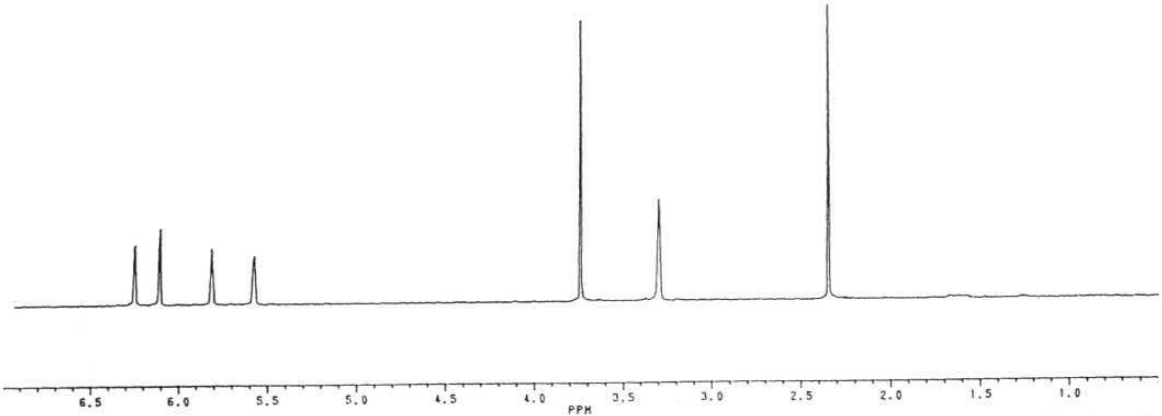
Reaction time: 6 h

Yield: 68% (0.209 g) {expected yield, 100% (0.306 g)}.

Spectral data (1R, ^{1}H and ^{13}C NMR) of this molecule are in complete agreement with that of the molecule prepared from **3-nitrobenzaldehyde (130n)** and 1,1,3,3-tetramethylguanidine (page no. 206).

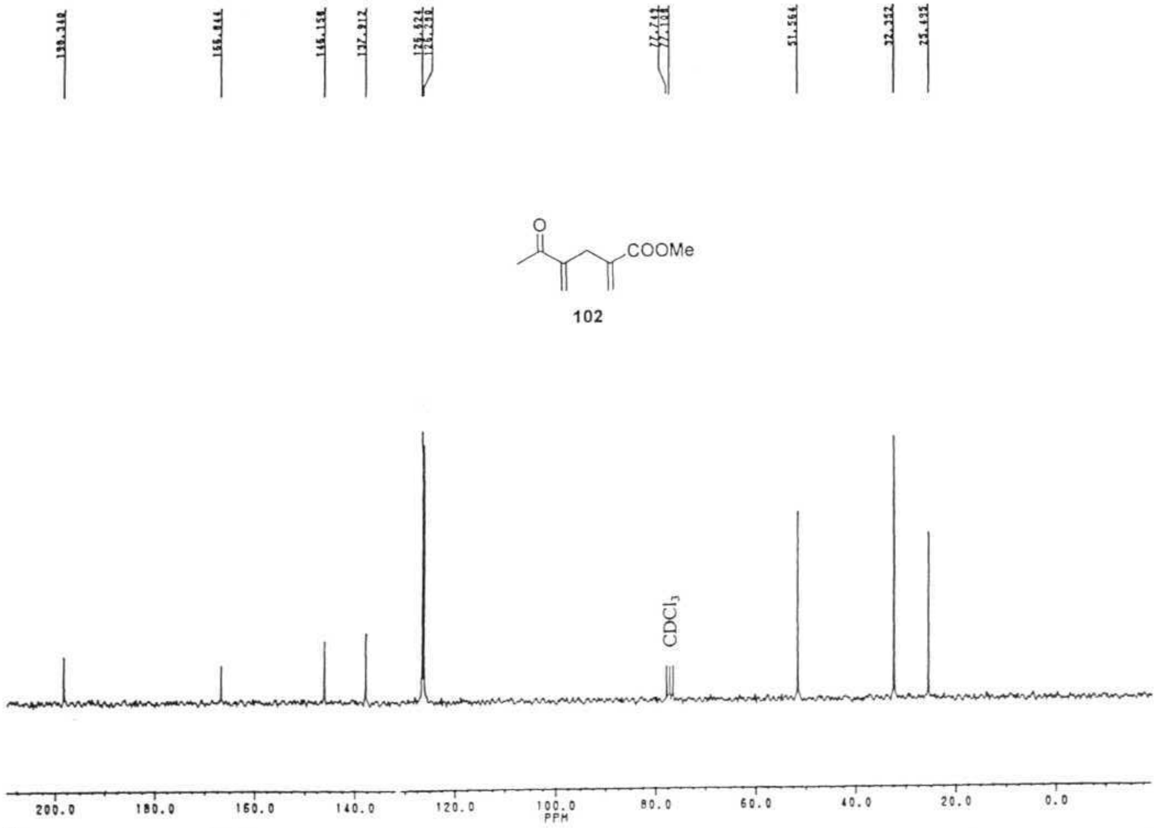


102



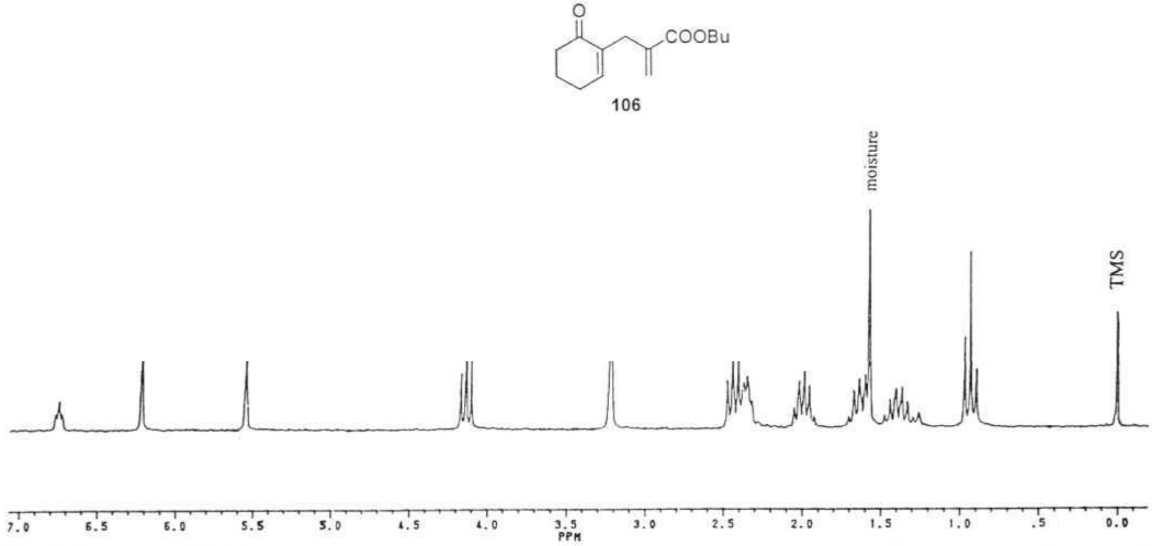
^{1}H NMR spectrum of **102**

Spectrum 1



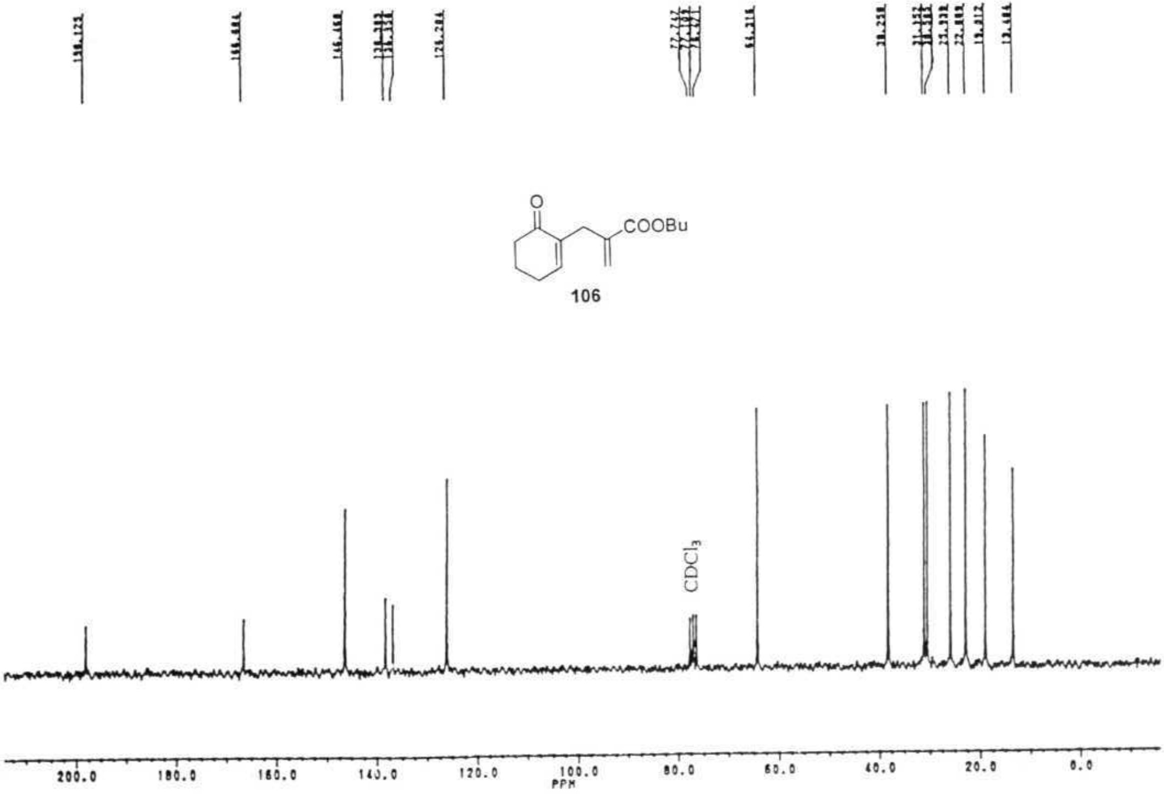
^{13}C NMR spectrum of **102**

Spectrum 2



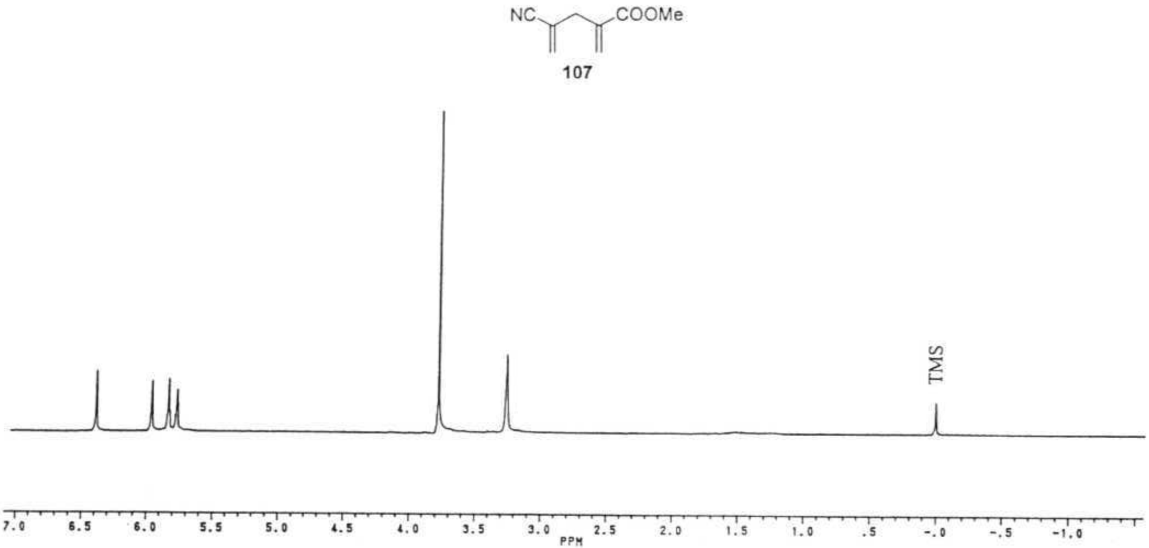
^{1}H NMR spectrum of **106**

Spectrum 3



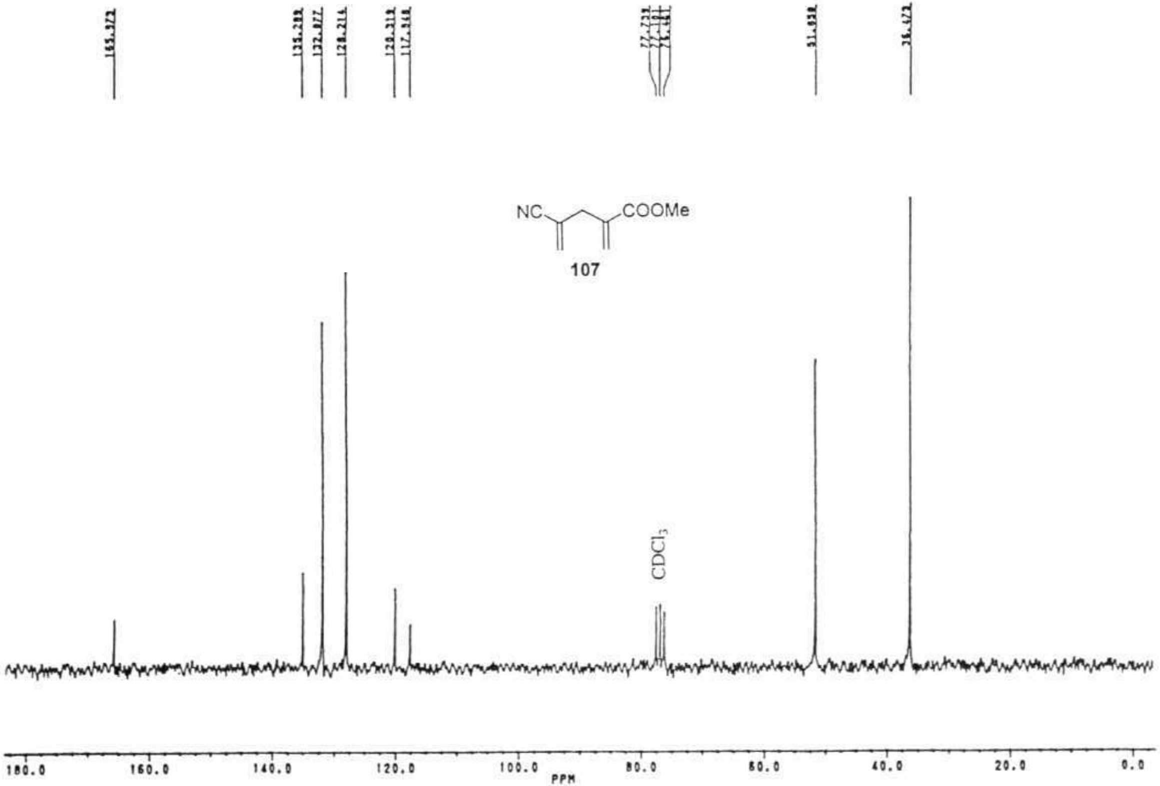
^{13}C NMR spectrum of **106**

Spectrum 4



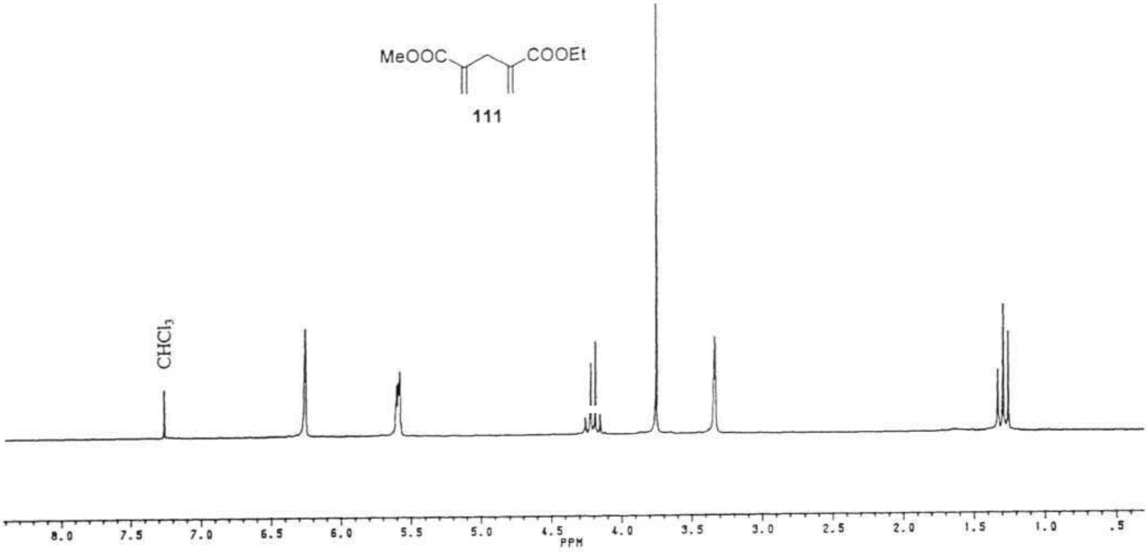
^{1}H NMR spectrum of **107**

Spectrum 5



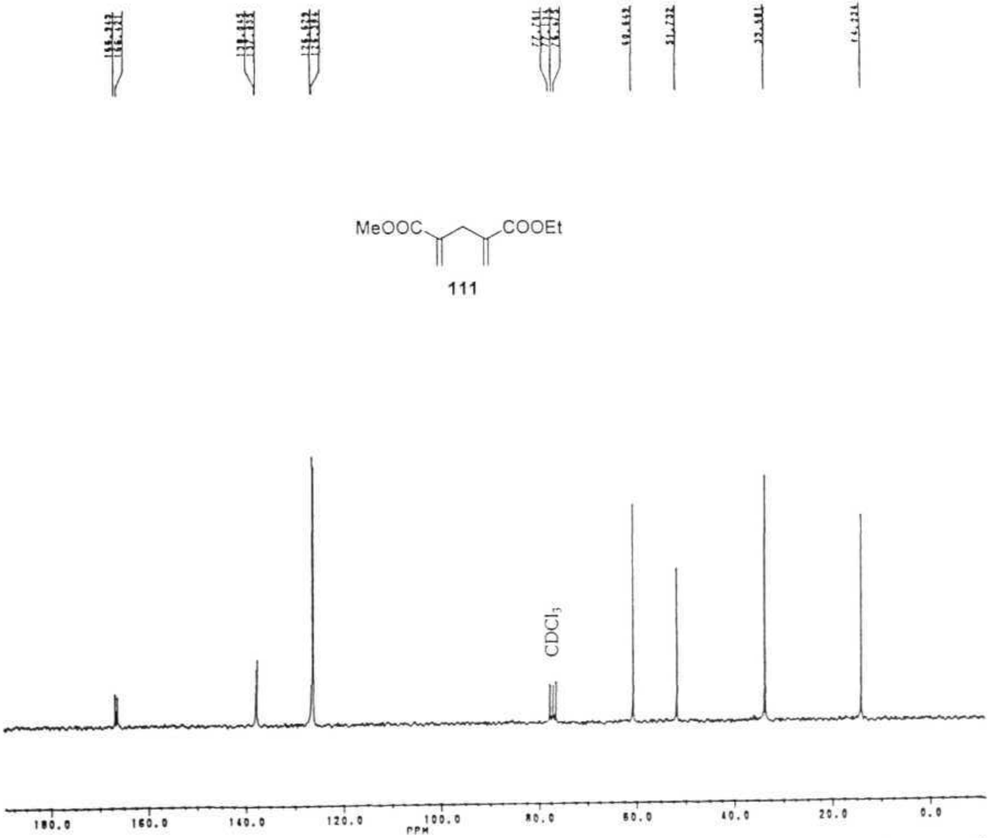
^{13}C NMR spectrum of **107**

Spectrum 6



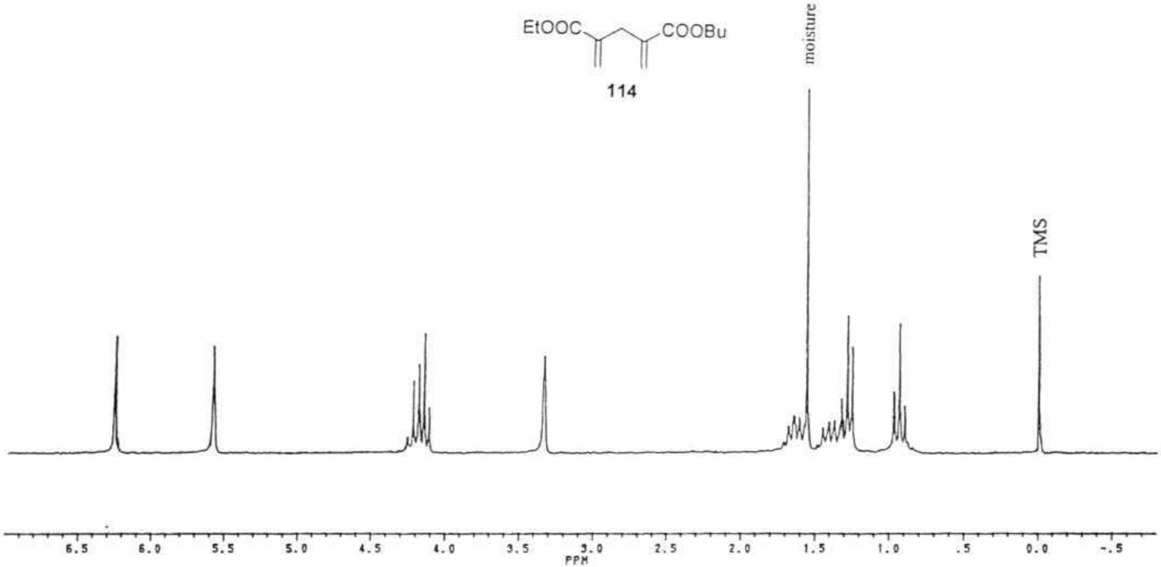
^{1}H NMR spectrum of **111**

Spectrum 7



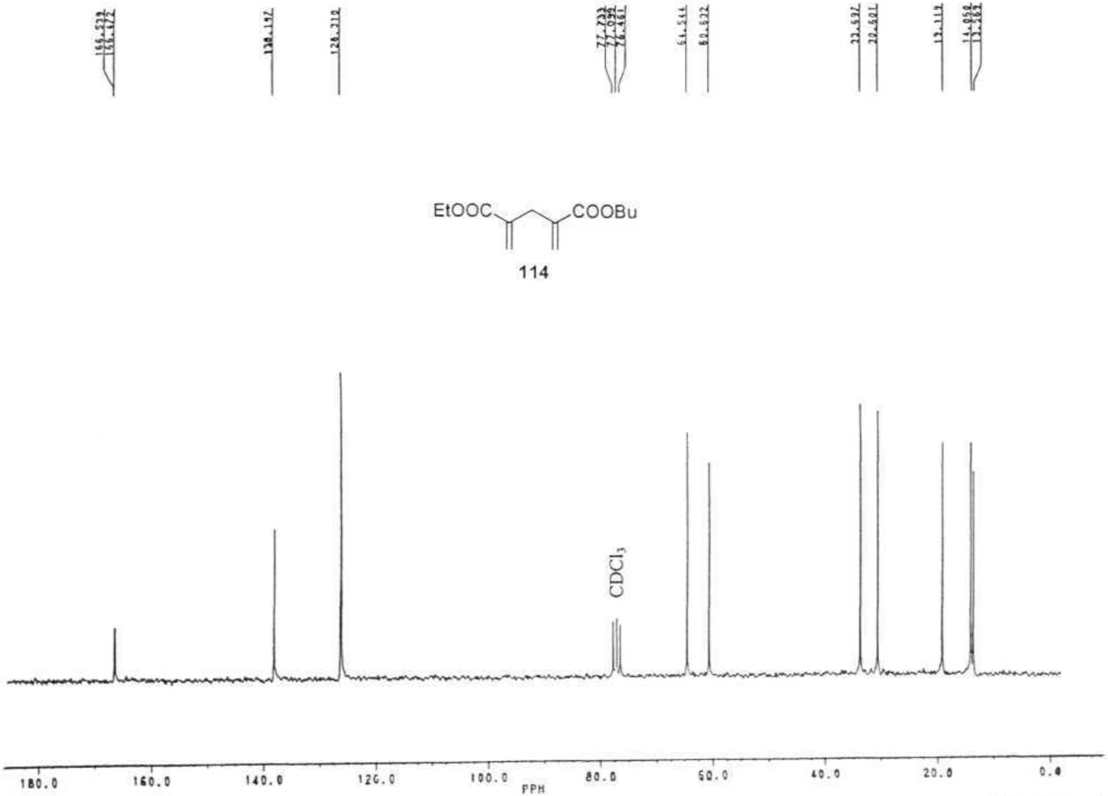
^{13}C NMR spectrum of **111**

Spectrum 8



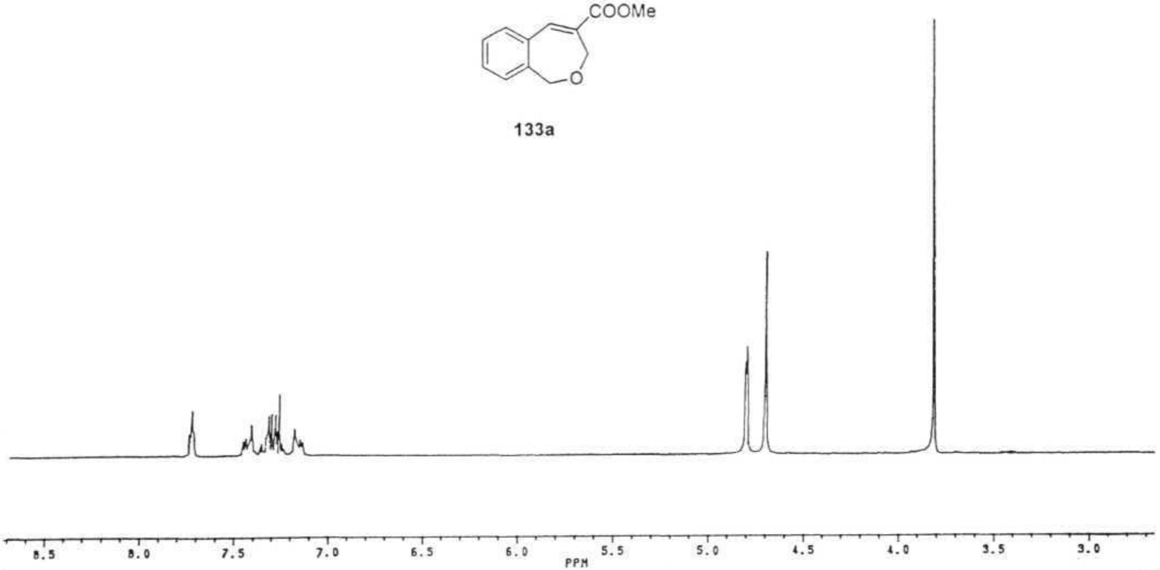
^{1}H NMR spectrum of **114**

Spectrum 9



^{13}C NMR spectrum of **114**

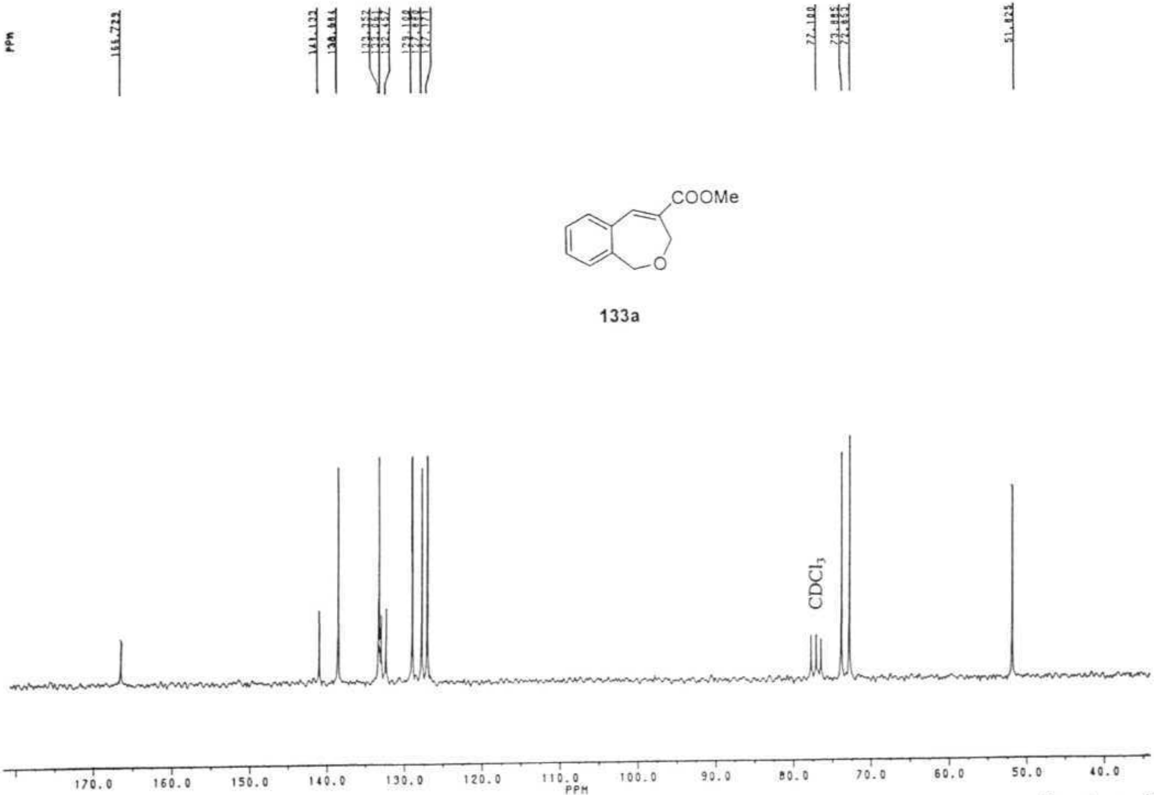
Spectrum 10



133a

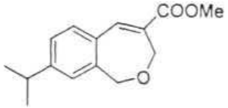
^{1}H NMR spectrum of **133a**

Spectrum 11

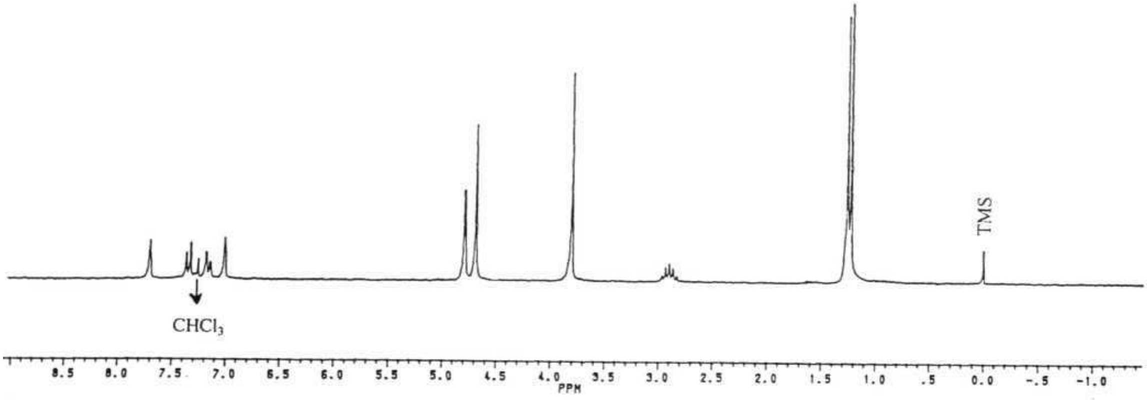


^{13}C NMR spectrum of **133a**

Spectrum 12

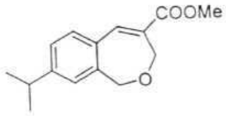


133e

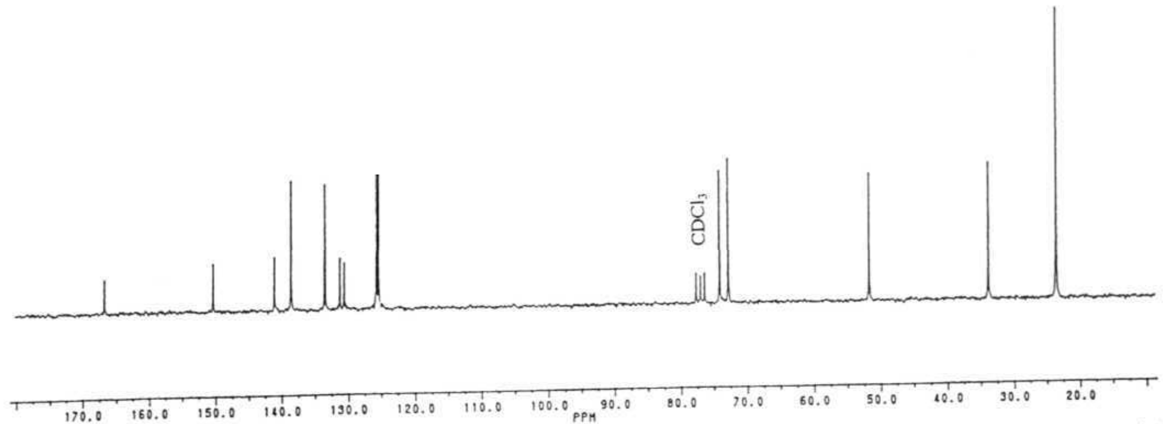


^{1}H NMR spectrum of **133e**

Spectrum 13

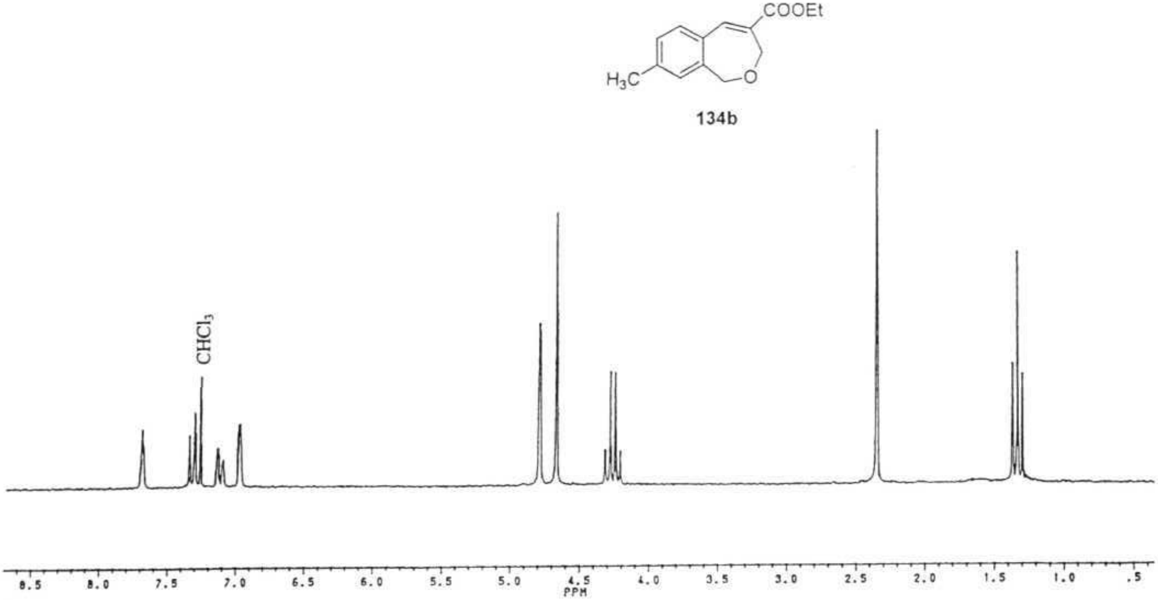


133e



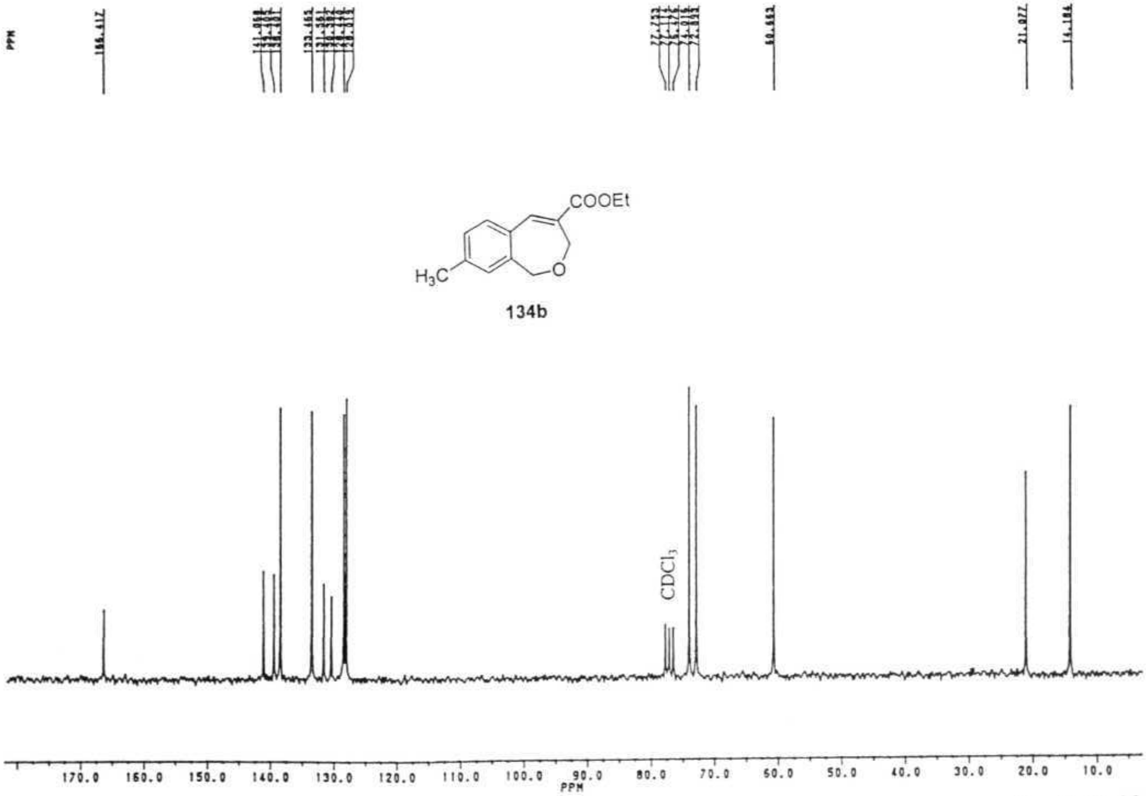
^{13}C NMR spectrum of **133e**

Spectrum 14



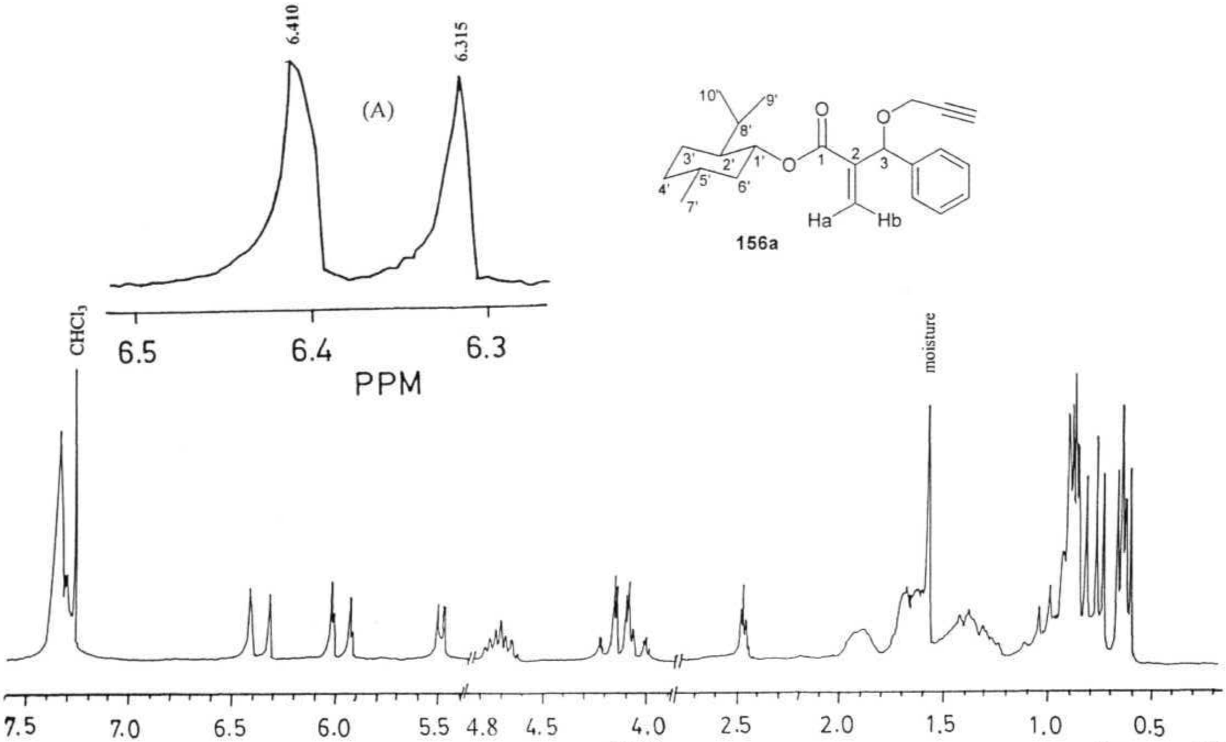
^{1}H NMR spectrum of **134b**

Spectrum 15



^{13}C NMR spectrum of **134b**

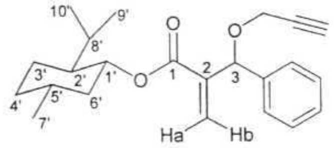
Spectrum 16



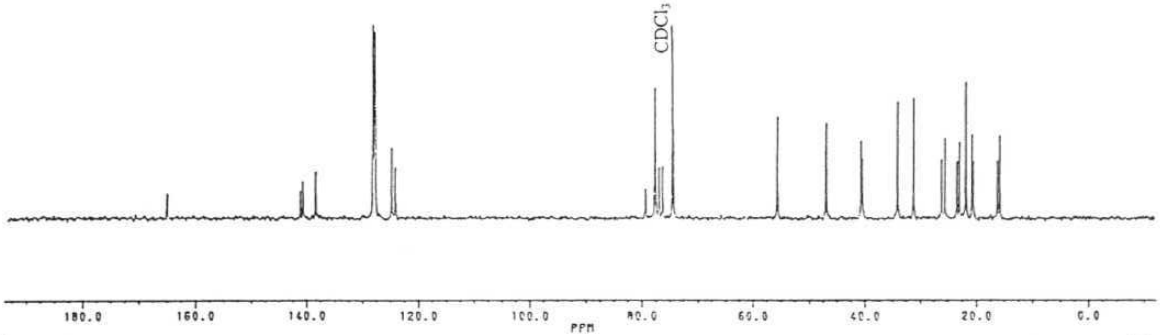
^{1}H NMR spectrum of **156a**

Spectrum 17

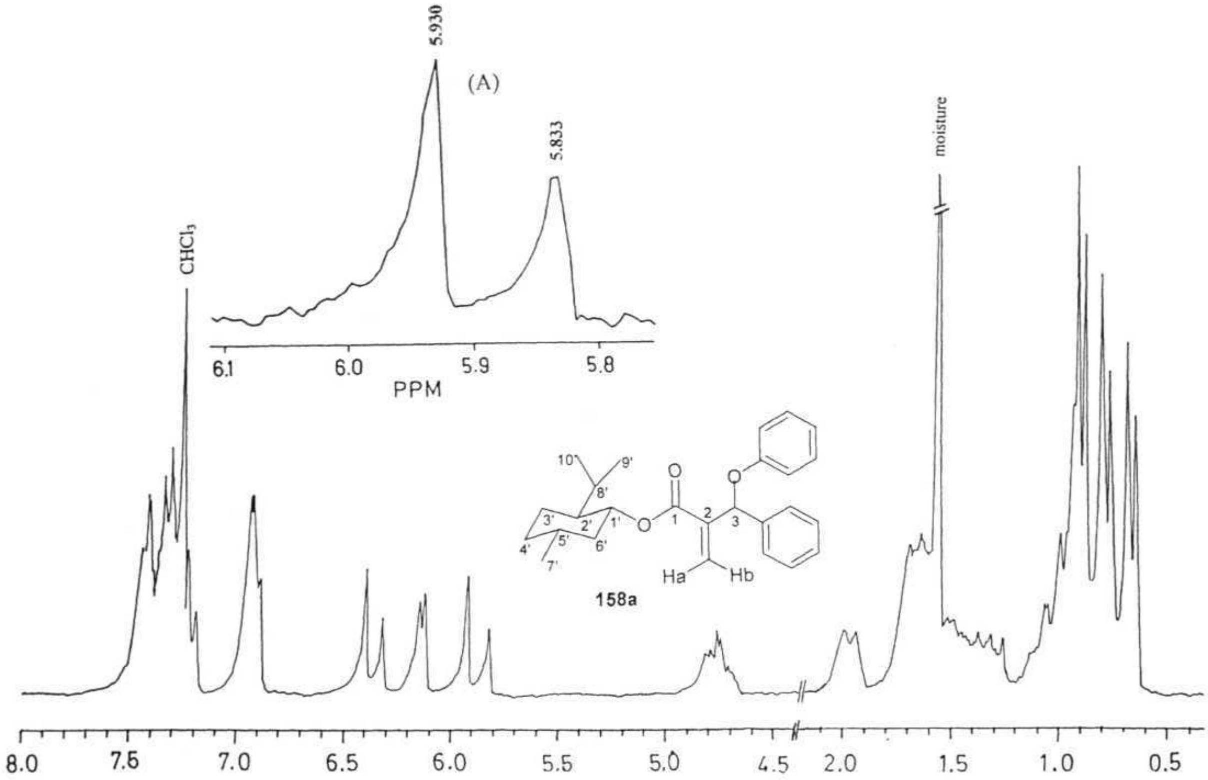
(A) Expansion of the diastereomeric β-vinylic (Ha) protons (*cis*- to ester group), 18% *de*



156a



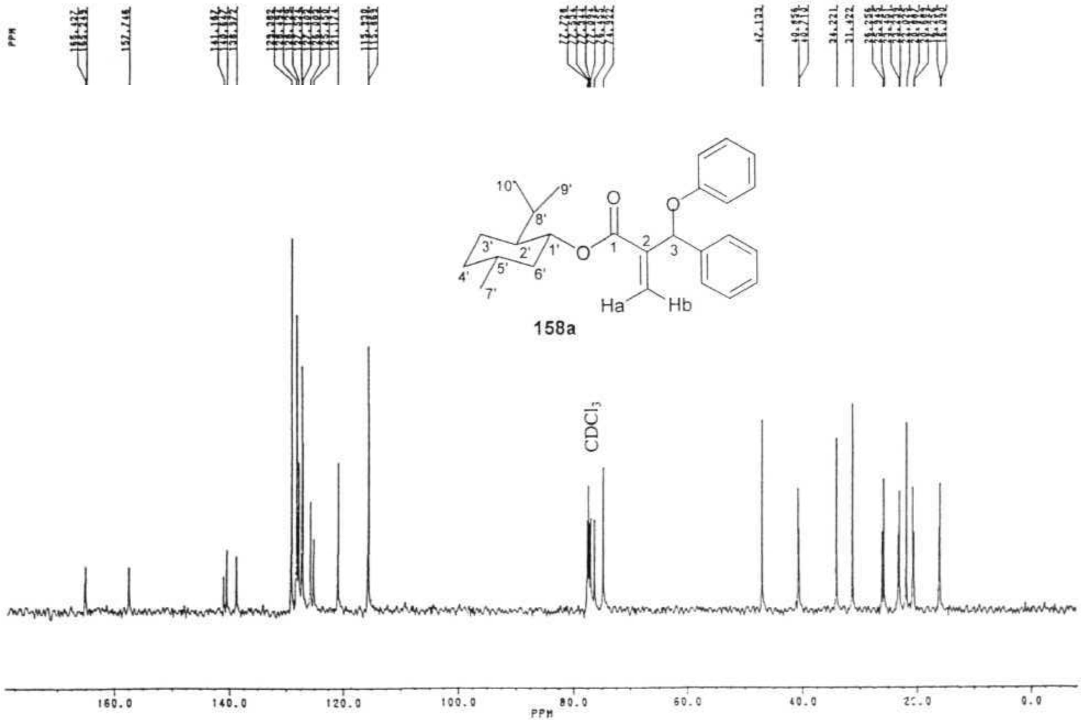
^{13}C NMR spectrum of **156a** *Spectrum 18*



^{1}H NMR spectrum of **158a**

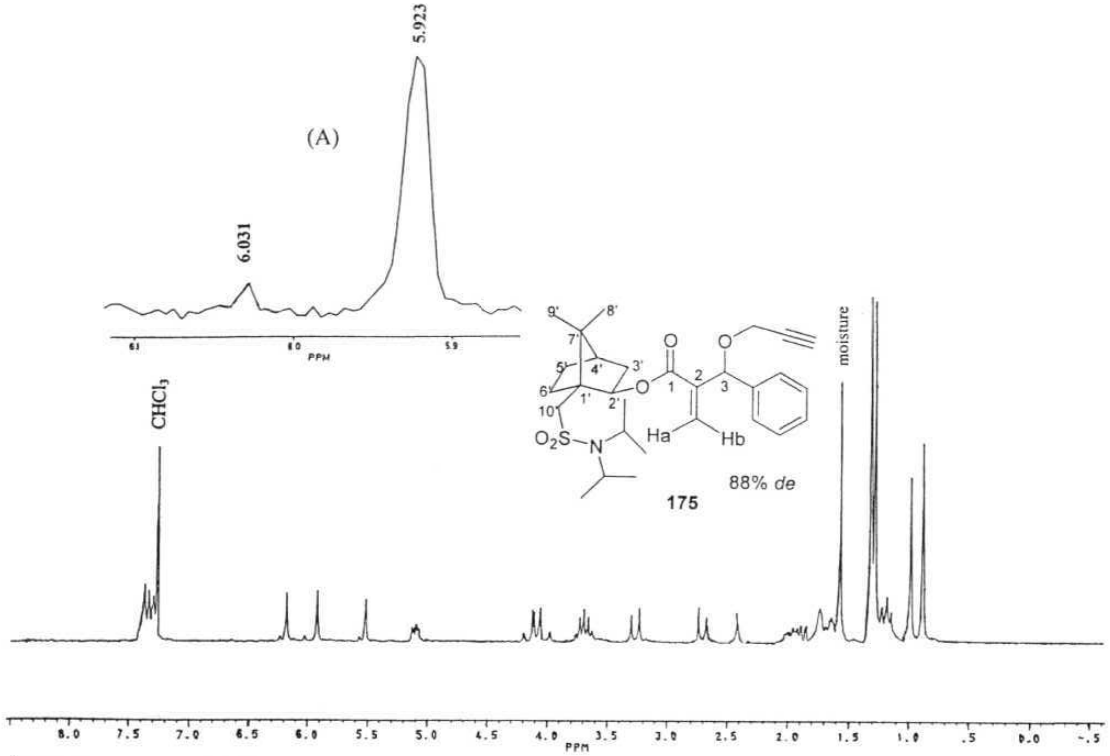
Spectrum 19

(A) Expansion of the diastereomeric benzylic (H3) protons, 35% *de*



^{13}C NMR spectrum of **158a**

Spectrum 20

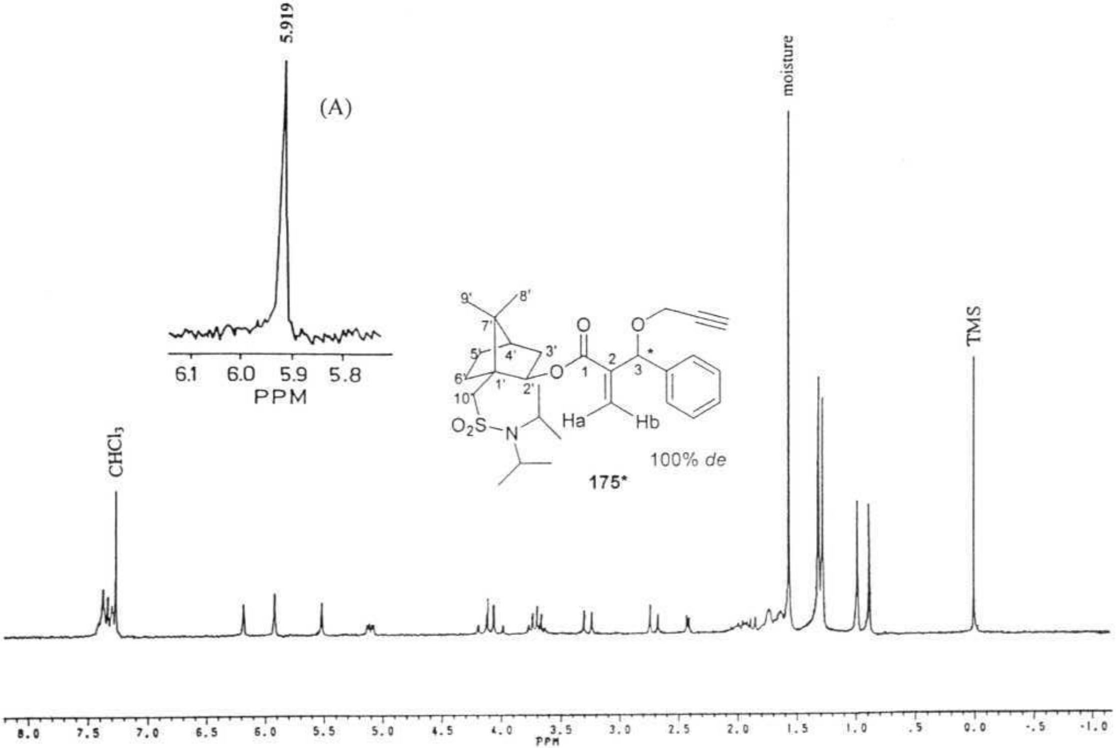


175

^{1}H NMR spectrum of **175**

Spectrum 21

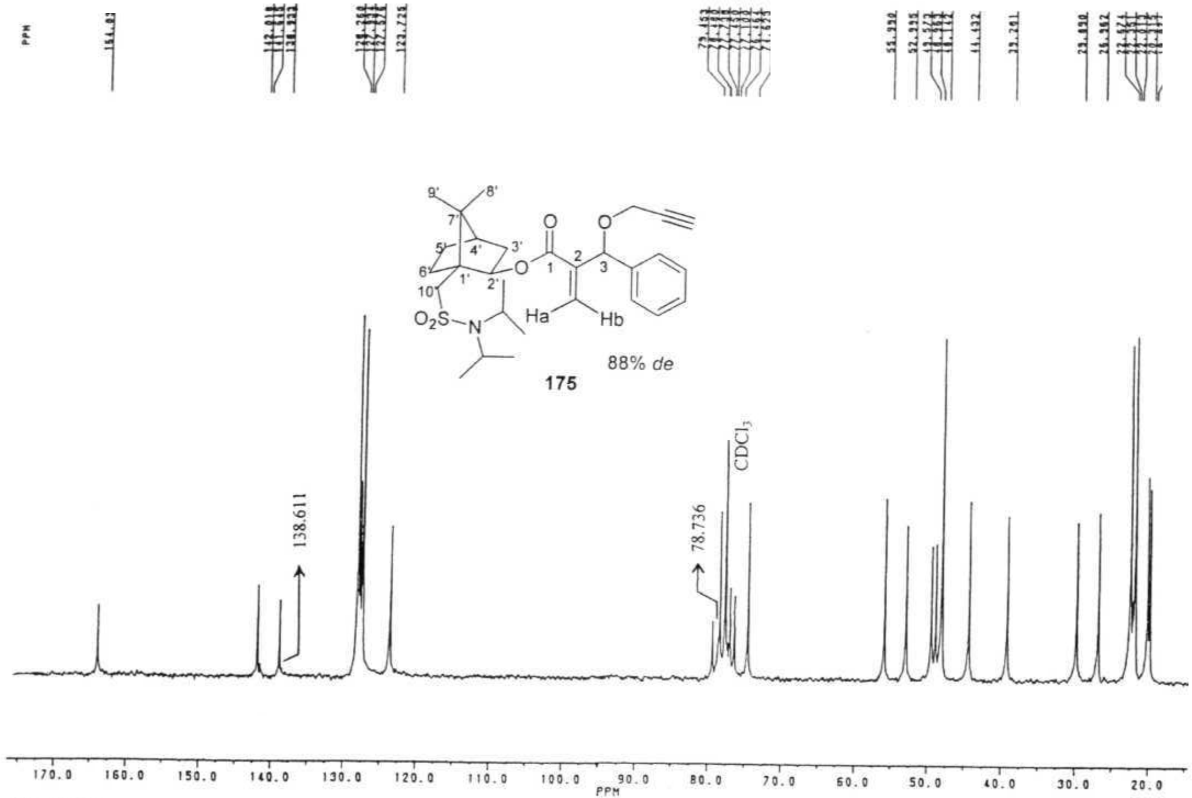
(A) Expansion of the diastereomeric β-vinylic (Hb) protons (*trans-* to ester group), 88% *de*



^{1}H NMR spectrum of **175***

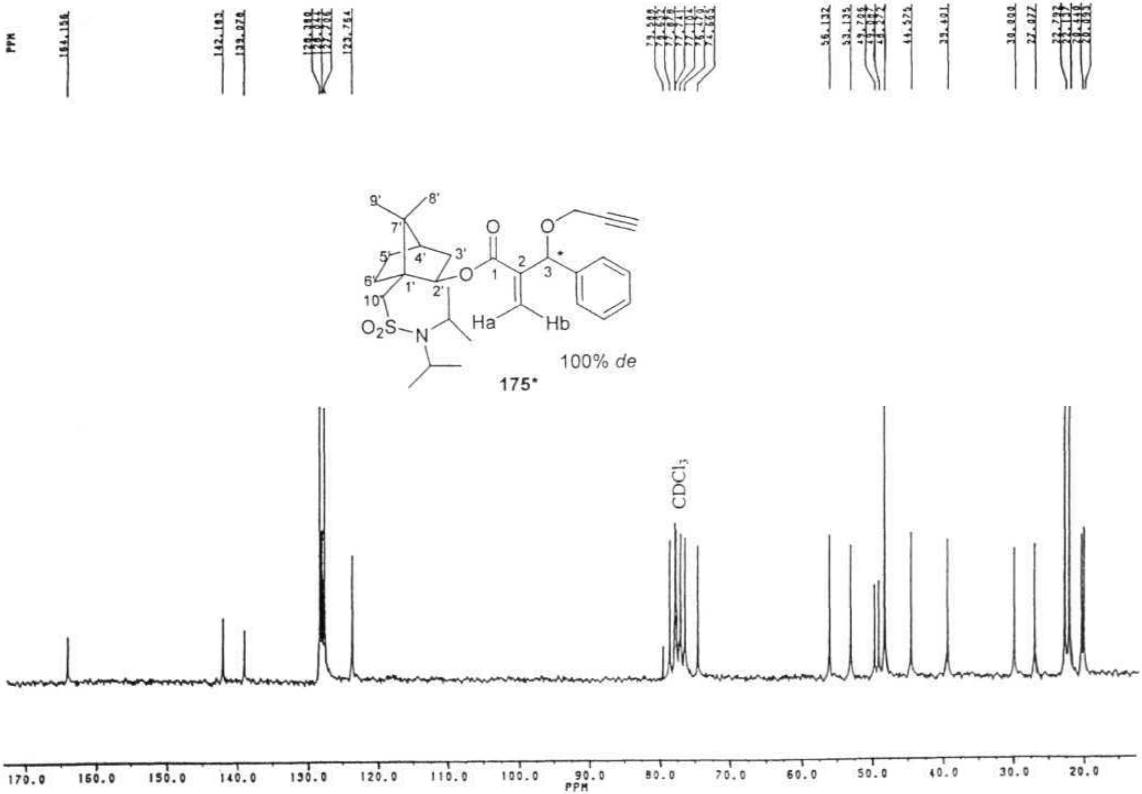
Spectrum 22

(A) Expansion of the β-vinylic (Hb) proton (*trans*- to ester group), 100% *de*



^{13}C NMR spectrum of **175**

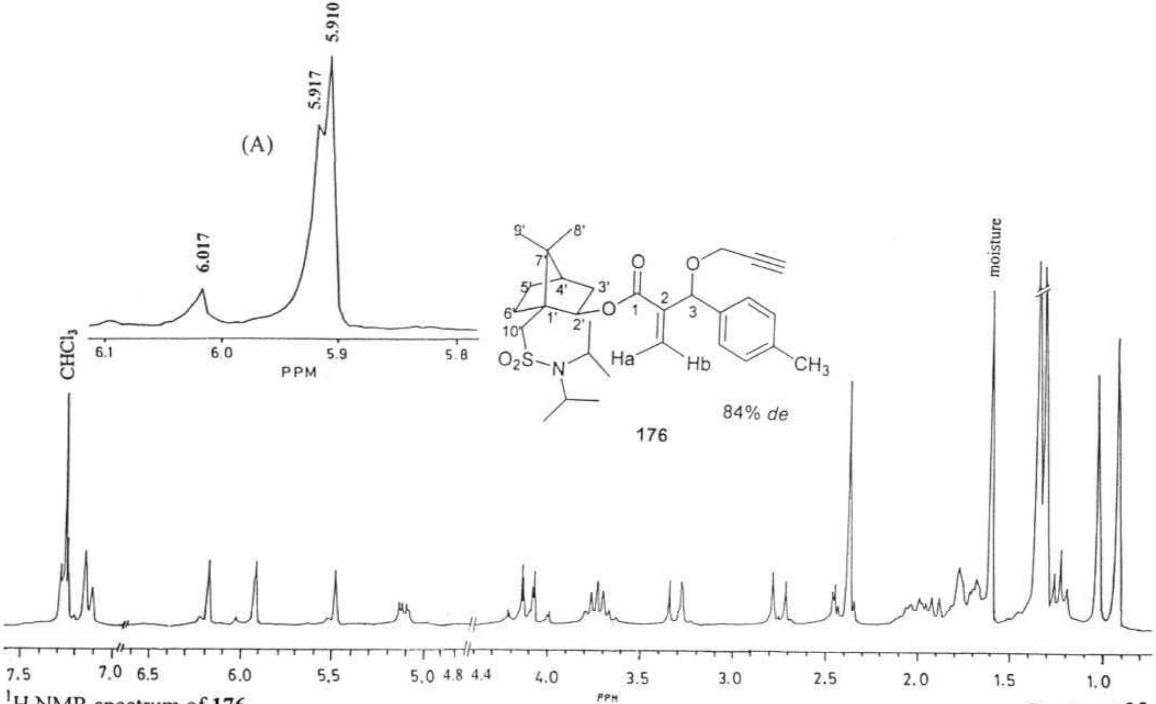
Spectrum 23



175*

^{13}C NMR spectrum of **175***

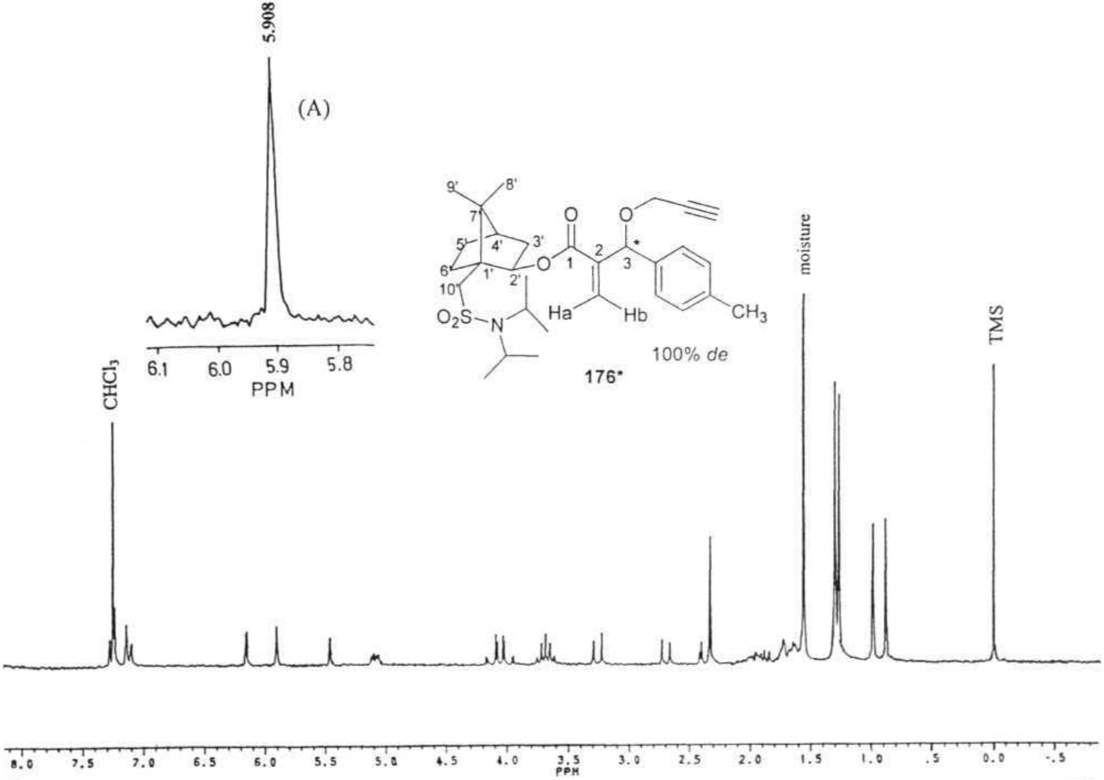
Spectrum 24



^{1}H NMR spectrum of **176**

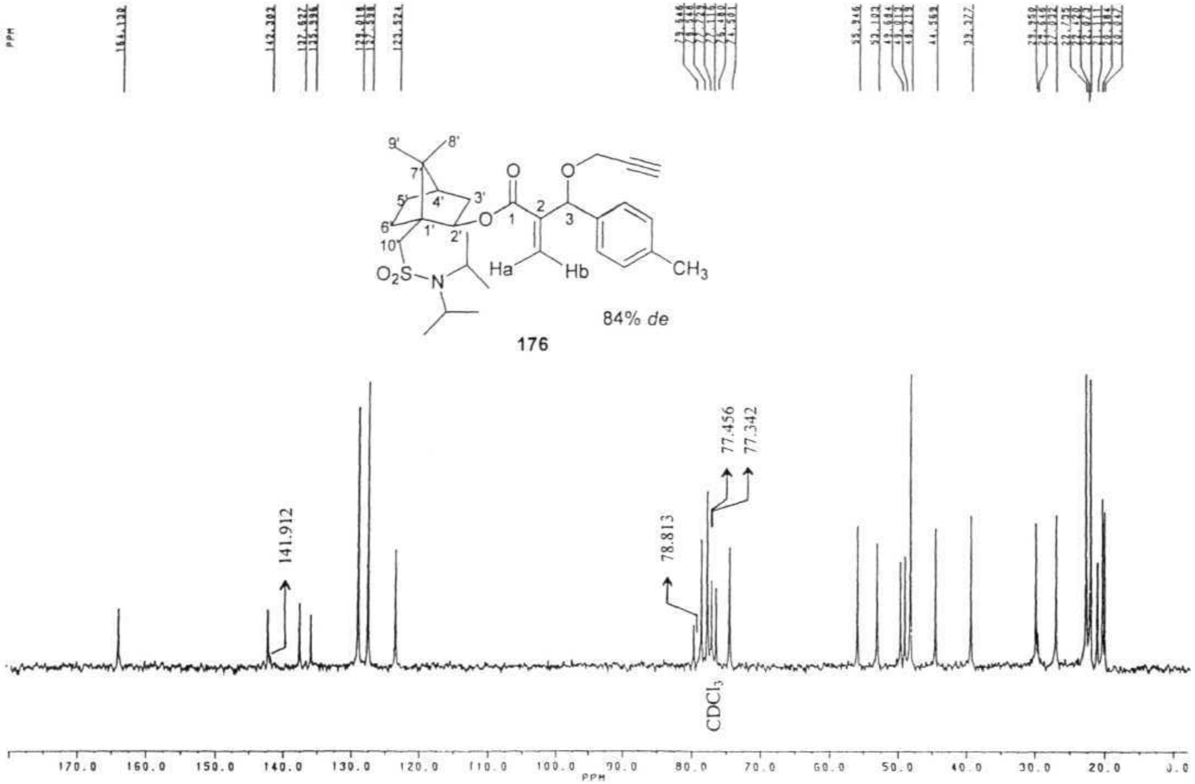
Spectrum 25

(A) Expansion of the diastereomeric β-vinylic (Hb) protons (*trans*- to ester group), 84% *de*



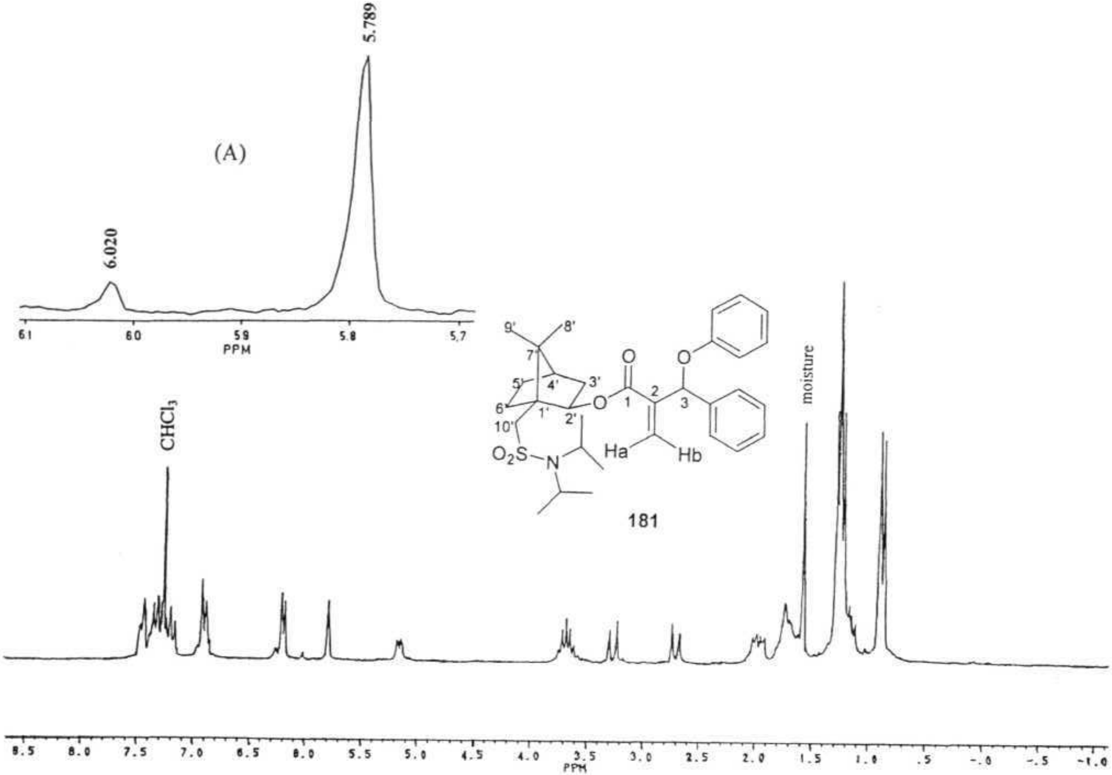
^{1}H NMR spectrum of **176*** ***Spectrum 26***

(A) Expansion of the β-vinylic (Hb) proton (*trans*- to ester group), 100% *de*



^{13}C NMR spectrum of **176**

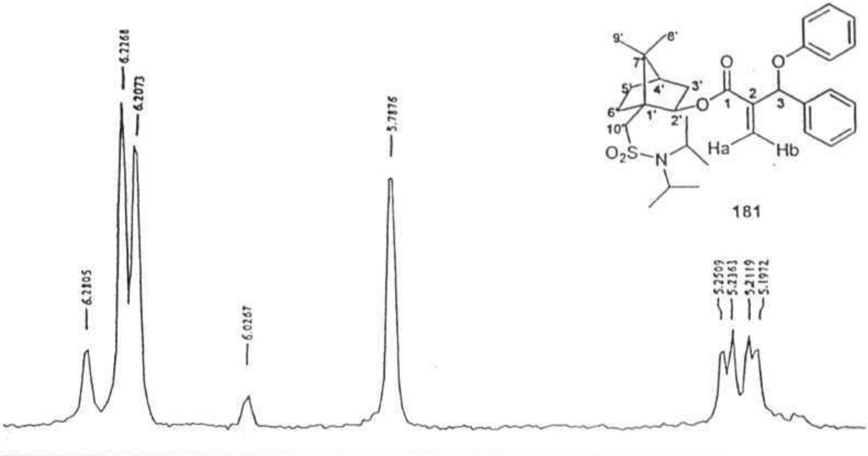
Spectrum 27



^{1}H NMR spectrum of **181**

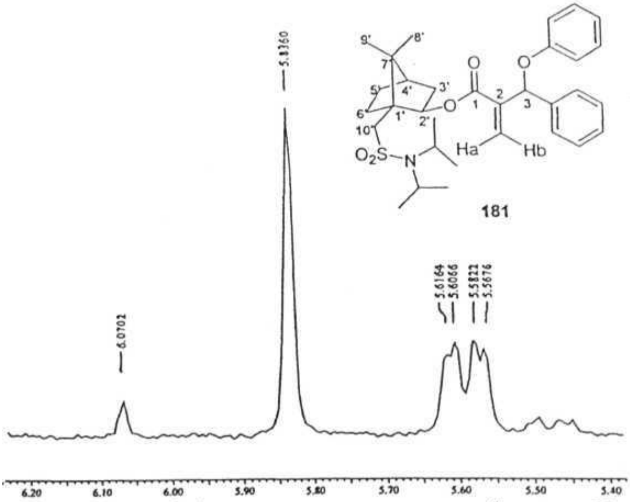
Spectrum 29

(A) Expansion of the diastereomeric benzylic (H3) protons, 82% *de*



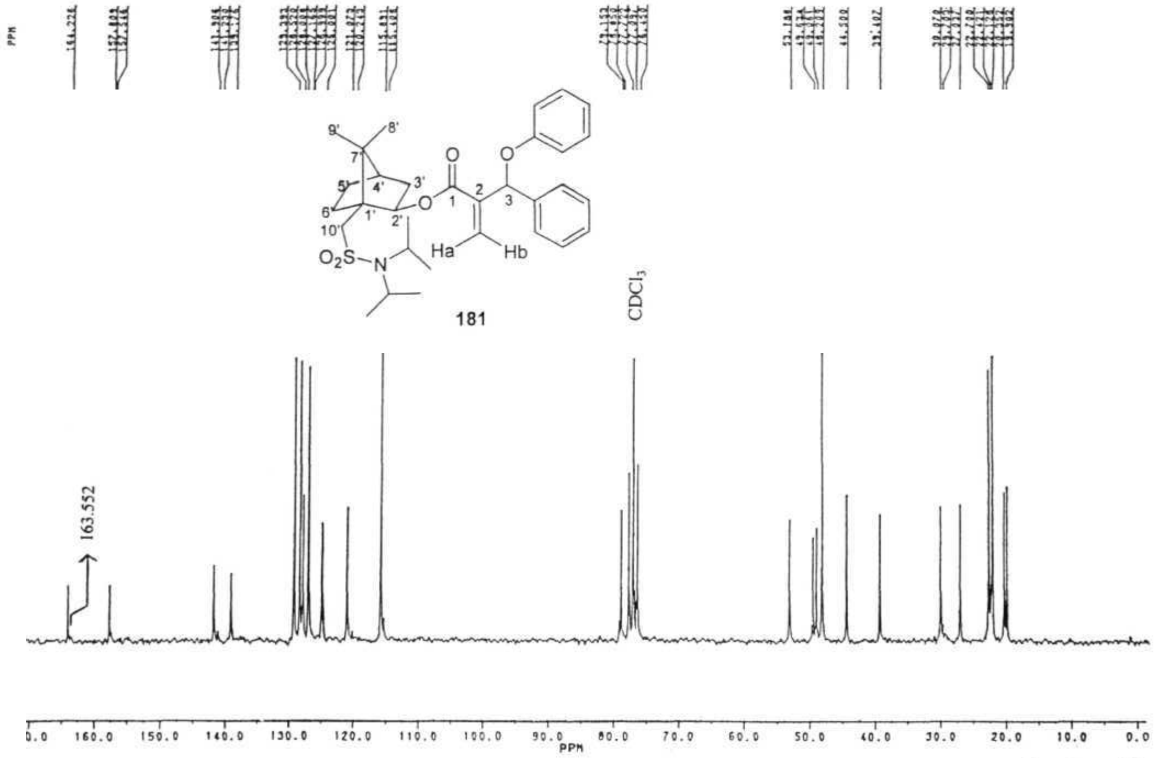
Spectrum 30

Splitting pattern of H3, Hb and Ha protons of the molecule **181** in the presence of Eu(hfc)$_3$, 82% *de*



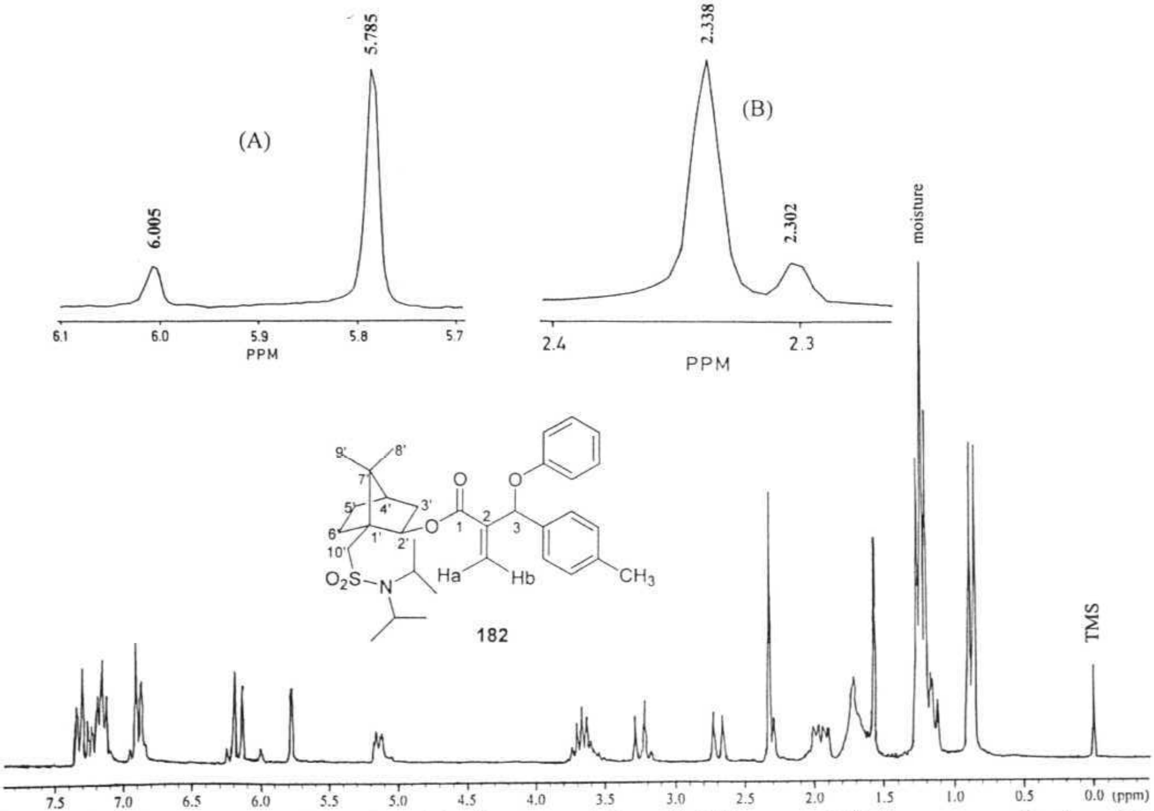
Spectrum 31

Splitting pattern of H3 and Hb protons of the molecule **181** in the presence of Eu(fod)$_3$, 82% *de*



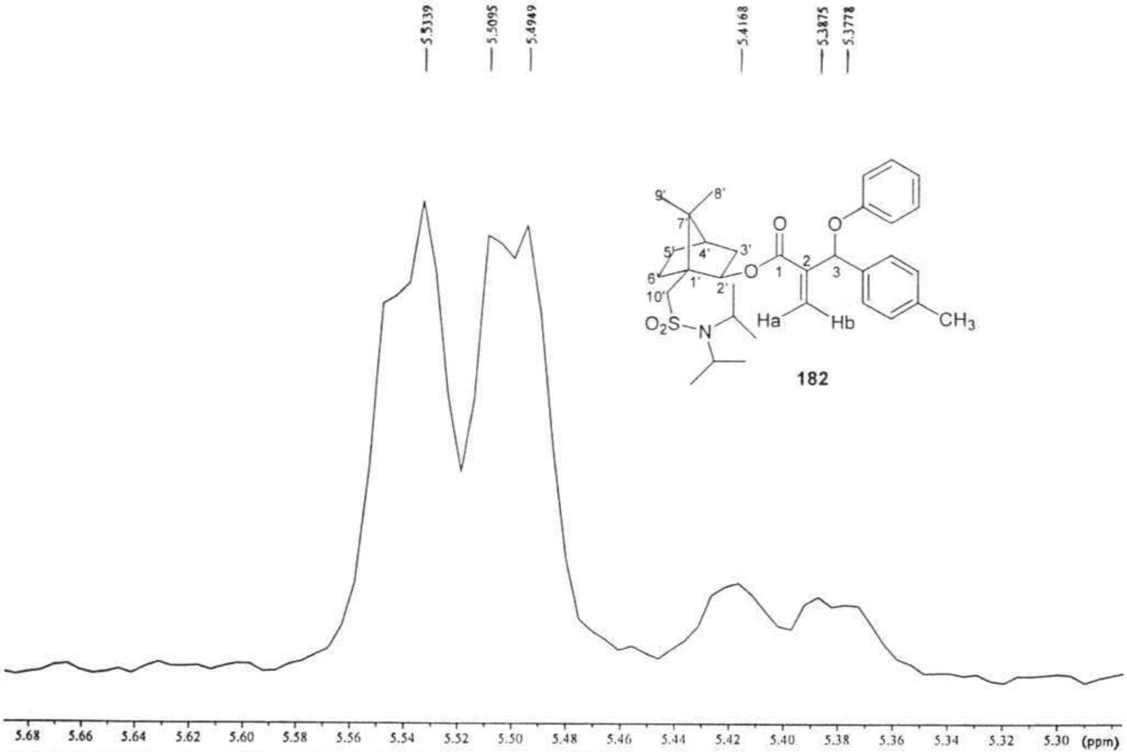
C NMR spectrum of **181**

Spectrum 32



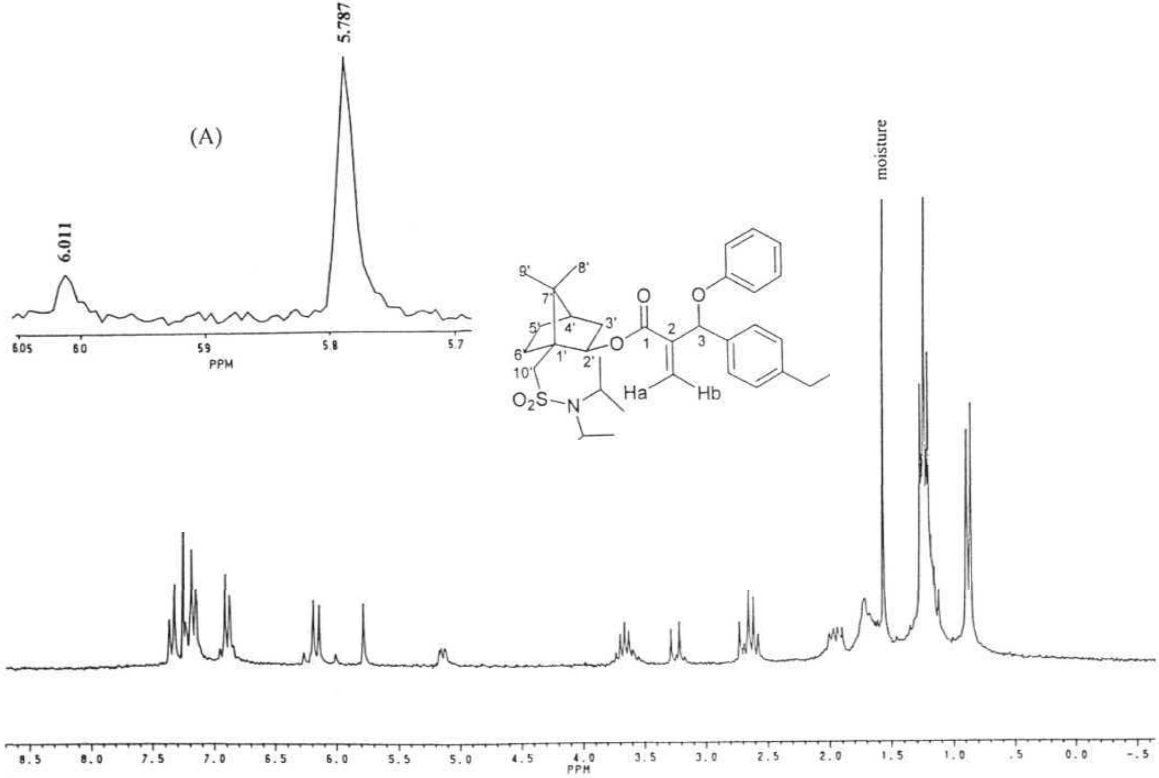
^{1}H NMR spectrum of **182** (A) Expansion of the diastereomeric benzylic (H3) protons, 76% *de* ***Spectrum 33***

(B) Expansion of the diastereomeric methyl protons on the aromatic ring, 76% *de*



Splitting of H2' proton of the molecule **182** in the presence of Eu(fod)$_3$, 76% *de*

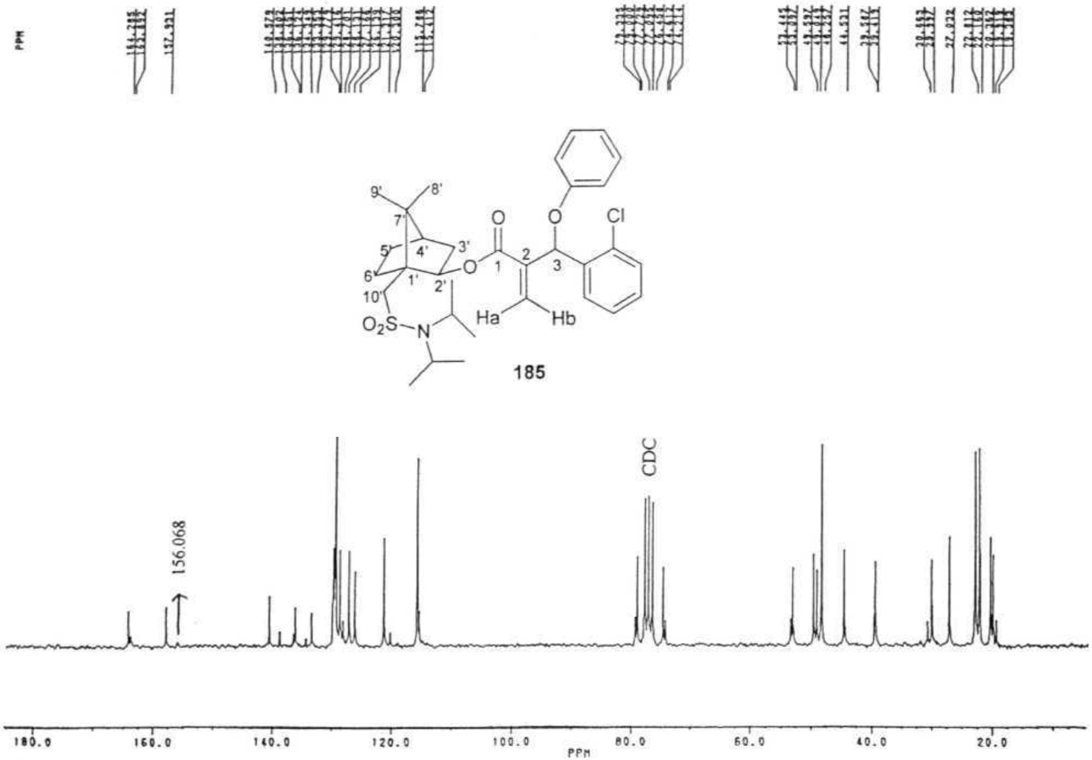
Spectrum 34



^{1}H NMR spectrum of **183**

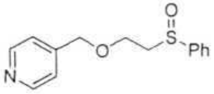
Spectrum 35

(A) Expansion of the diastereomeric benzylic (H3) protons, 78% *de*

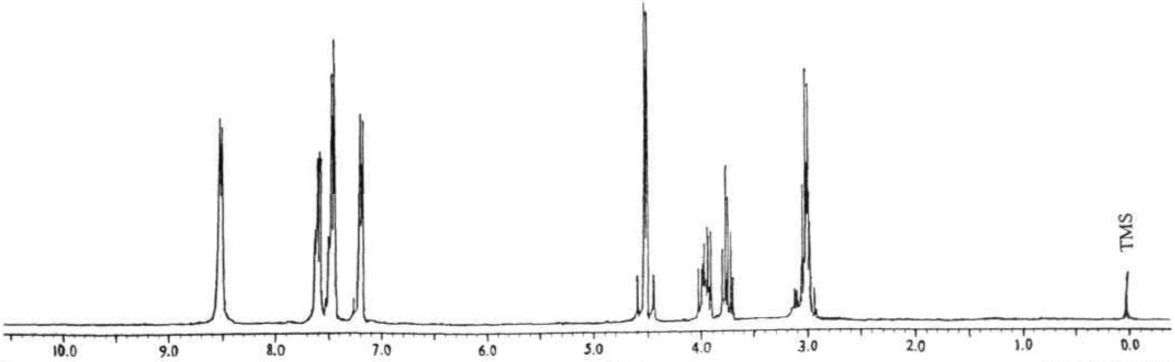


^{13}C NMR spectrum of **185**

Spectrum 36

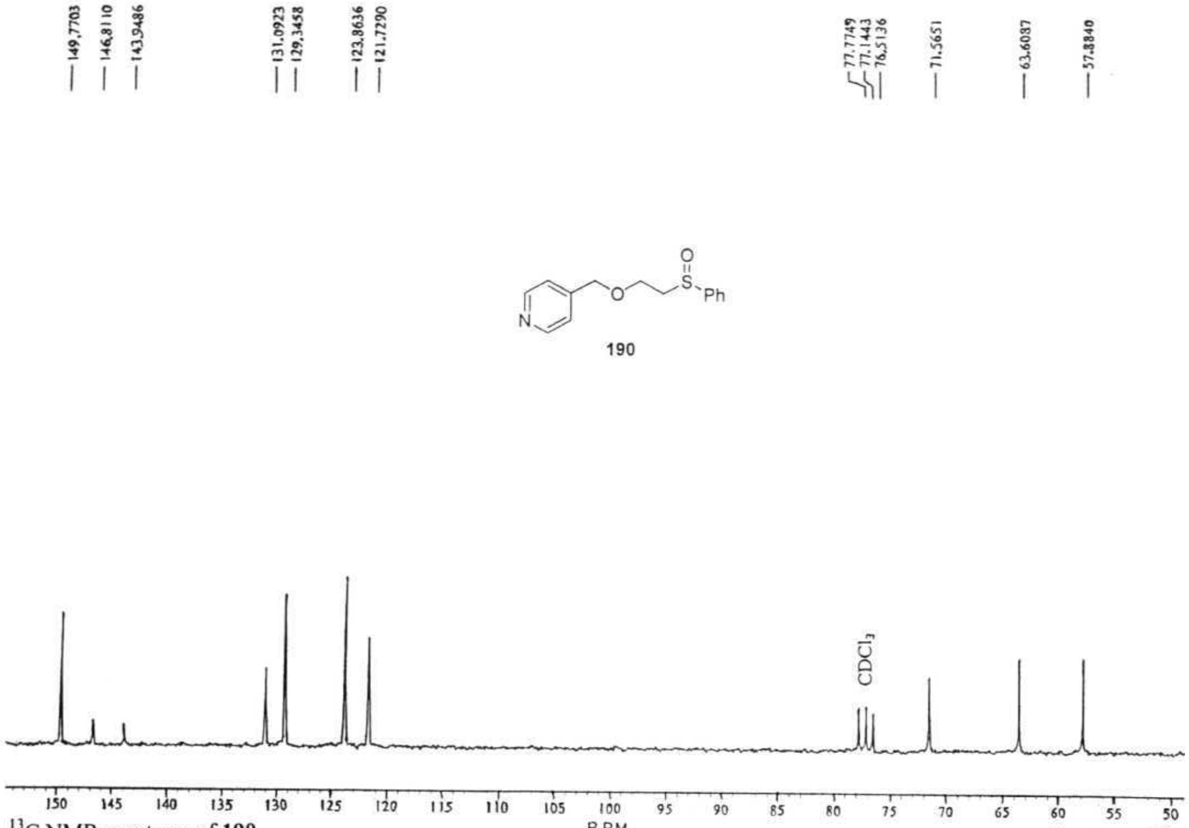


190



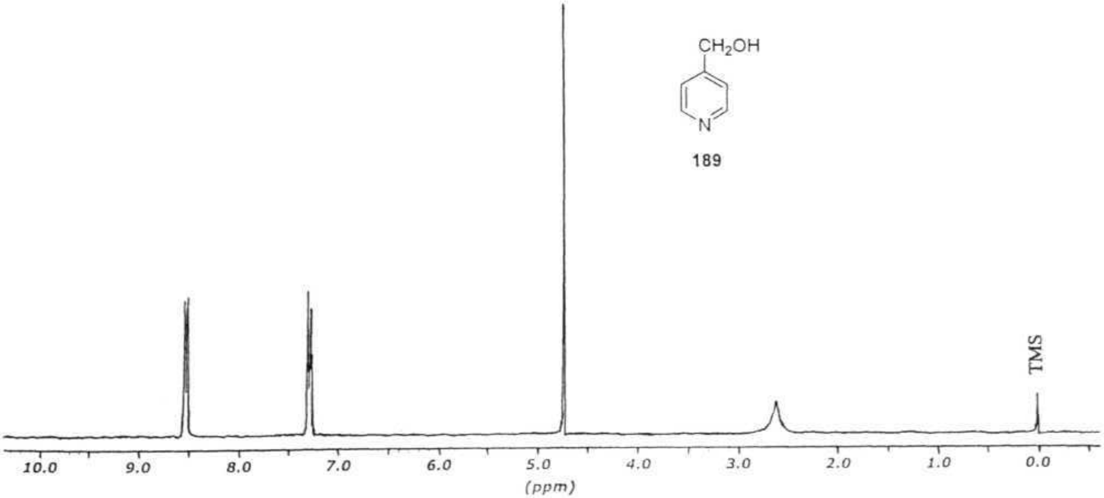
^{1}H NMR spectrum of **190**

Spectrum 37



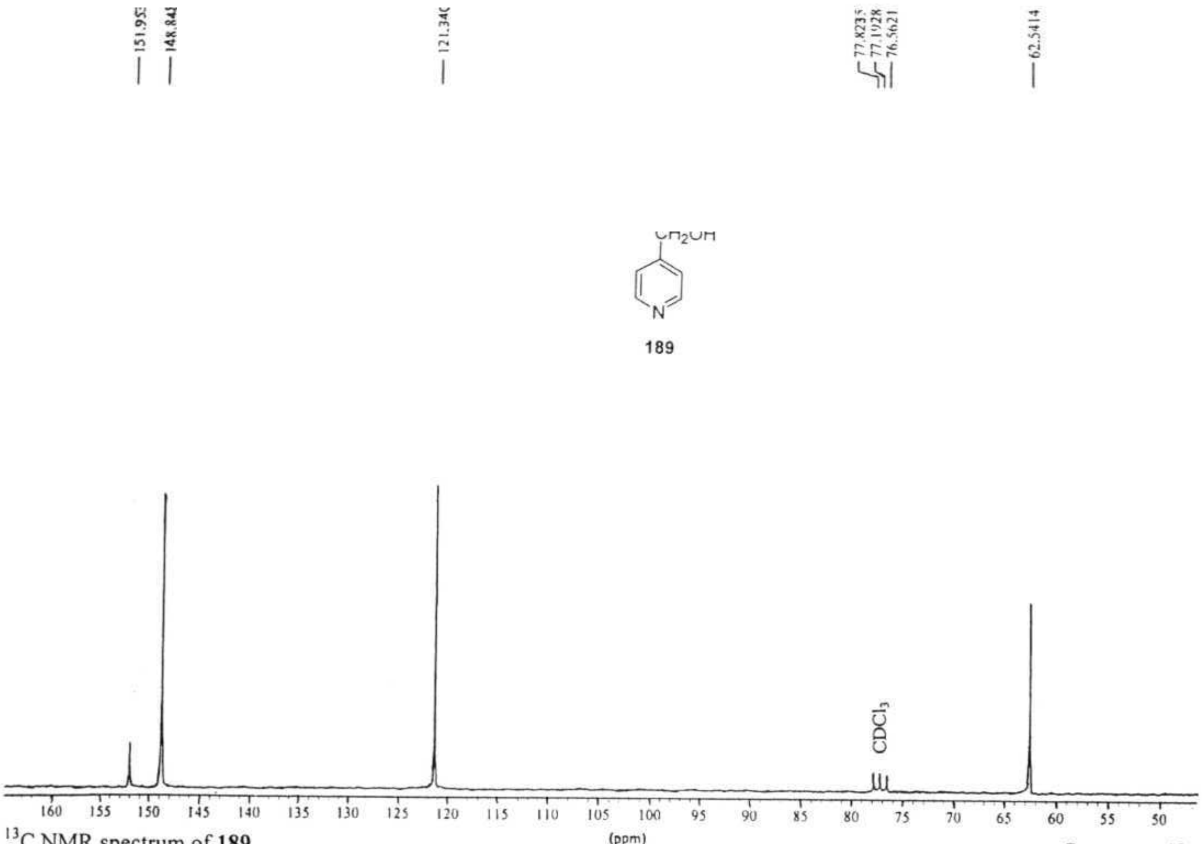
^{13}C NMR spectrum of **190**

Spectrum 38



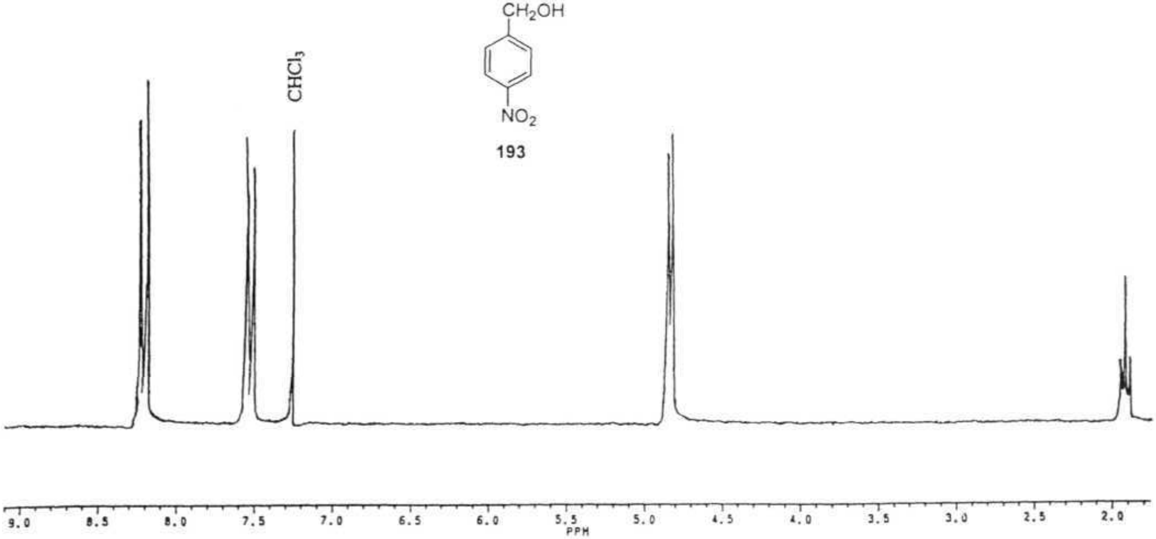
^{1}H NMR spectrum of **189**

Spectrum 39



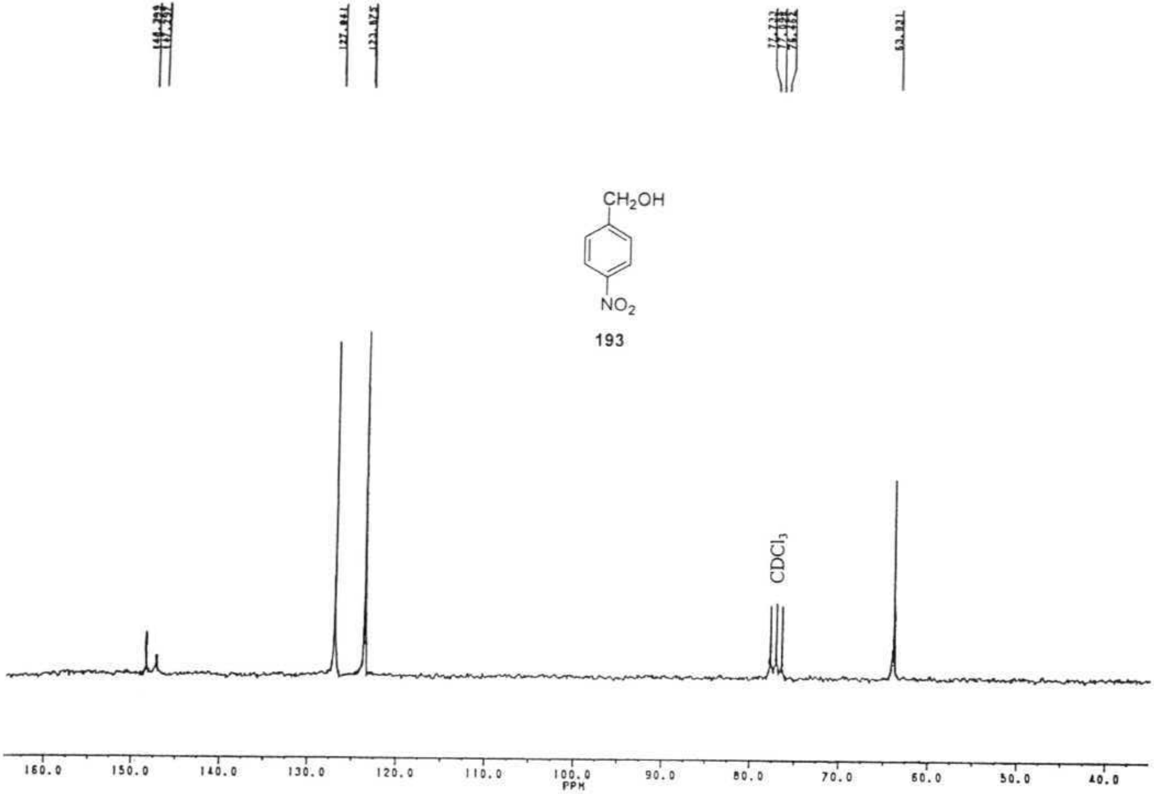
^{13}C NMR spectrum of **189**

Spectrum 40



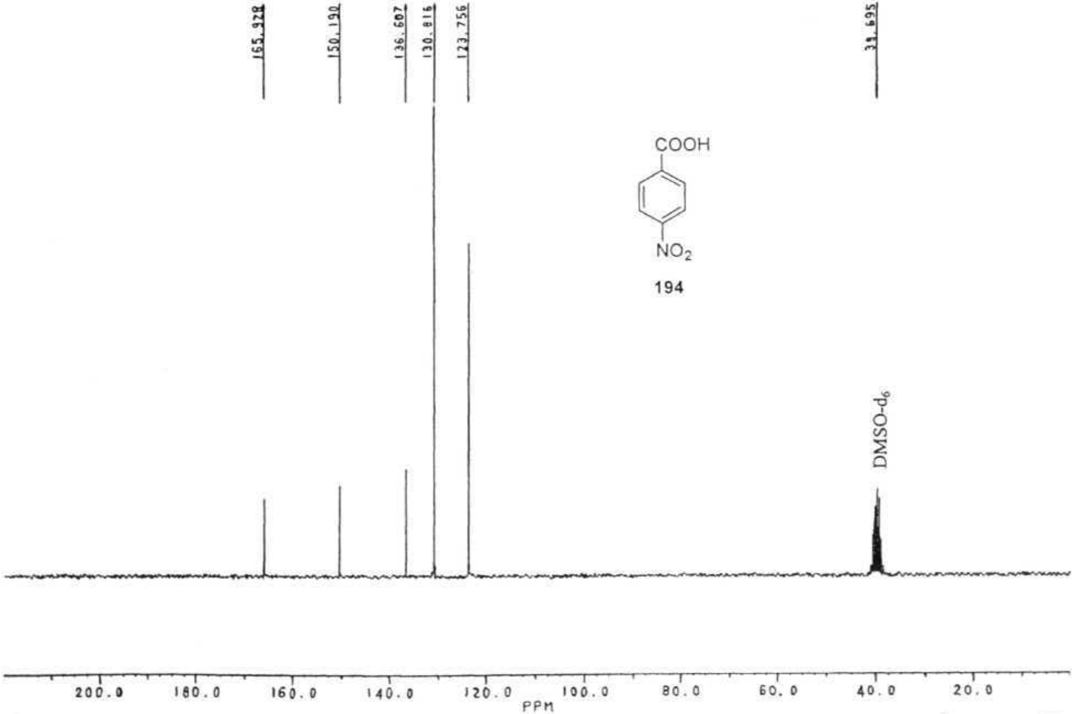
^{1}H NMR spectrum of **193**

Spectrum 41



^{13}C NMR spectrum of **193**

Spectrum 42



^{13}C NMR spectrum of **194**

Spectrum 43

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LIST OF PUBLICATIONS

(1). The Baylis-Hillman Reaction: One-Pot Facile Synthesis of 2,4-Functionalized 1,4-Pentadienes

D. Basavaiah, **Duddu.** S. Sharada, N. Kumragurubaran and R. Mallikarjuna Reddy,J. *Org. Chem* 2002, 7135-7137.

(2). Applications of Baylis-Hillman chemistry: one-pot convenient synthesis of functionlized (lH)-quinol-2-ones and quinolines

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(3). Baylis-Hillman chemistry: a novel synthesis of functionalized 1,4-pentadienes

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(5). Tandem construction of C-O and C-C bonds: a one-pot facile transformation of the Baylis-Hillman adducts into 2-benzoxepines

D. Basavaiah, **Duddu.** S. **Sharada** and A. Veerendhar, to be communicated.

(6). Applications of Baylis-Hillman chemistry: Diastereoselective transformation of alkyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates, into propargylic and phenol ethers of Baylis-Hillman adducts, using chiral auxiliaries.

D. Basavaiah, and **Duddu. S. Sharada,** manuscript under preparation.

(7). First Example of Organic base induced Cannizzaro reaction

D. Basavaiah, **Duddu. S. Sharada** and A. Veerendhar, to be communicated.