BAYLIS - HILLMAN REACTION
A NOVEL CARBON-CARBON BOND FORMING REACTION

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

BY
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HYDERABAD - 500 134

JULY 1989

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STATEMENT

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

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

Hyderabad

July, 1989

V. V. L. Gowriswari

V.V.L. GOWRISWARI

CERTIFICATE

Certified that the work contained in this thesis entitled **"Baylis-Hillman Reaction : A Novel Carbon-Carbon bond forming reaction"** has been carried out by Ms. V.V.L. Gowriswari, under my supervision and the same has not been submitted elsewhere for a degree.

D. BASAVAIAH
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

ACKNOWLEDGEMENTS

It is with great pleasure that I acknowledge my profound gratitude to my research supervisor, Dr. D. Basavaiah, for suggesting me this problem, for inspiring guidance and constant encouragement throughout the course of this work. All the faculty members of the School of Chemistry have been extremely helpful and I thank them all.

I appreciate the help rendered by my colleagues, Ms. T.K. Bharathi, Messrs P. Dharma Rao, P.K.S. Sharma, P. Rama Krishna and S. Bhaskara Raju.

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V.V.L. Gowriswari

V.V.L. GOWRISWARI

ABBREVIATIONS

Ac	acetyl
Bu	butyl
n-BuLi	n-butyl lithium
DABCO	1,4-diazabicyclo(2.2.2)octane
DBN	1,5-diazabicyclo(4.3.0)non-5-ene
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
de	diastereomeric excess
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
Et	ethyl
HMPT	hexamethylphosphoric triamide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
MCPBA	m-chloroperbenzoic acid
Me	methyl
MsCl	methanesulfonyl chloride
NBS	N-bromosuccinimide
Ph	phenyl
Ph_3P	triphenylphosphine
Py	pyridine
TBDMS	t-butyldimethylsilyl
THF	tetrahydrofuran
p-TsCl	p-toluenesulfonyl chloride

ABSTRACT

Carbon-carbon bond formation is one of the most fundamental reactions in organic chemistry. The development of an efficient and highly selective method for construction of C-C bond has been and continues to be a challenging and exciting endeavour in organic synthesis. Baylis-Hillman reaction refers to the construction of C-C bond at α-position of activated α,β-unsaturated vinylic systems (α,β-unsaturated ketones, esters, nitriles, etc.) via the coupling of activated alkenes with suitable electrophiles under the influence of tertiary amines. This thesis deals with the development of Baylis-Hillman reaction, i.e., the C-C bond forming reaction at α-position of activated alkenes providing multifunctional molecules.

The thesis consists of three chapters (i) Introduction, (ii) Objectives, Results and Discussion, (iii) Experimental. In the introduction chapter some important literature methods for construction of C-C bonds at α-position of α,β-unsaturated ketones and esters have been presented. The origin of Baylis-Hillman reaction and literature reports on this reaction have also been described in the introduction chapter.

The second chapter deals with our objectives, results and discussion. When we started this work in 1985 only few reports were available in literature on this reaction. With this little available information, we envisioned that Baylis-Hillman reaction will have tremendous synthetic potential. Accordingly, we have undertaken a long range research project with the following objectives:

(1) To study the generality of Baylis-Hillman reaction for various α,β-unsaturated ketones, nitriles, sulfones, esters and amides for carbon-carbon bond construction.

(2) To study the applicability of various electrophiles such as aldehydes, α-keto esters and other related molecules for Baylis-Hillman C-C bond formation.

(3) To study the applicability of various chiral tertiary amines as (chiral) catalysts in the place of DABCO to construct carbon-carbon bond wherein a chiral center is created.

(4) To investigate the applicability of various chiral acrylates for asymmetric C-C bond construction leading to multifunctional molecules and to design proper chiral (auxiliary) acrylate for high diastereoselective C-C bond formation.

(5) To develop Baylis-Hillman reaction as a powerful synthetic tool for construction of carbon-carbon bonds at α-position of activated olefins leading to the asymmetric synthesis of multifunctional molecules.

With the above objectives in mind, we have developed a simple methodology for the synthesis of α-methylene-β-hydroxyalkanones **75** via the reaction of commercially available methyl vinyl ketone with a variety of aldehydes catalyzed by DABCO (15 mole %) (eq. 17). We have successfully utilized acrylonitrile (eq.20) and phenyl vinyl sulfone (eq.22) for Baylis-Hillman C-C bond forming reaction. We have demonstrated the applicability of α-keto esters for coupling with acrylonitrile and methyl acrylate to produce the multifunctional molecules **87, 88** (eq.24,25). All these reactions described till now are generally slow reactions (2-7 days or even longer). During the course of our work we have found that diethyl ketomalonate reacts faster with activated olefins (eq.29).

DABCO also catalyzes the Michael type dimerization of α,β-unsaturated ketones (eq.31) and acrylonitrile (eq.32) to produce the multifunctional molecules **96** and **97**, respectively.

The development of carbon-carbon bond construction reaction, wherein chiral molecules are produced in high enantiomeric purity, has been a challenging as well as elusive endeavour. We have also directed our studies toward the asymmetric C-C bond formation using Baylis-Hillman reaction. We have followed two strategies for asymmetric C-C bond construction, (i) Application of chiral tertiary amines in the place of DABCO, (ii) Utility of chiral acrylates.

The chiral amines employed in the place of DABCO are (S)-N-benzylprolinol (**98**), (S)-1-aza-4-oxabicyclo(4.3.0)nonane (**99**) and quinidine (**100**). The reactions with **98** and **99** as chiral catalysts are not encouraging. Quinidine catalyzed reactions are encouraging and the products are obtained in 4-20% ee (Scheme 41 and eq. 36). Though quinidine did not offer high enantioselectivities, it certainly tells that the design of a proper chiral (DABCO) (**113-115**) amine would offer good enantioselectivities.

We have investigated the applicability of the three selected chiral acrylates **116-118** for synthesis of optically active 2-(1-hydroxyalkyl) acrylates. First, we have examined the coupling reaction of easily accessible (-)-menthyl acrylate with various aldehydes (Scheme 43). We have prepared a representative group of (-)-menthyl 2-(1-hydroxyalkyl)acrylates **119** and diastereoselectivities are found to be 7-20%. Next we have investigated the applicability of (S)-(N-benzylpyrrolidin-2-yl)methyl acrylate (**117**), prepared from N-benzylprolinol (**98**),(Scheme 45). The diastereoselectivities obtained are in the range of 4-16%.

Finally, we have selected the chiral acrylate **118** to achieve high diastereoselectivities in Baylis-Hillman reaction. This chiral acrylate is prepared by the action of (1S,2R,4R)-1-(diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (**126**), which was synthesized from (+)-10-camphorsulfonic acid, on acryloyl chloride. We have carried out the coupling reaction

(eq. 43, 44) with representative aldehydes and found that the diastereoselectivities are in the range of 15-42%. All the products are solids and fractional crystallization afforded the products with 100% diastereomeric excess.

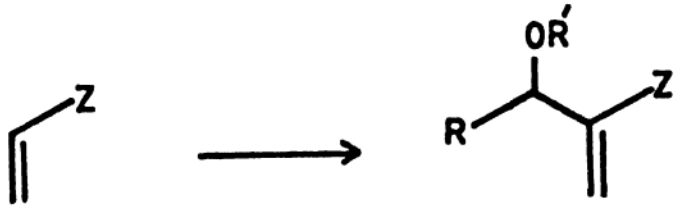
The third chapter describes all the experimental procedures in detail along with spectral data and physical constants (m.p., b.p. and optical rotations). Determination of ee and de of the products is also described in detail.

INTRODUCTION

Carbon-carbon bond formation is one of the most fundamental reactions in organic chemistry. Construction of carbon-carbon bond, in fact, is pivotal in bringing latitude to organic synthesis. Several important carbon-carbon bond forming reactions such as Diels-Alder reaction[1-3], aldol reactions[1,4,5], organometallic reactions[1,6,7], etc. have been well studied and their applications have been well documented.

One of the major objectives in organic synthesis has been the development of synthetic strategies for stereoselective carbon-carbon bond construction. Several synthetic methods for a variety of enantioselective carbon-carbon bond construction have been developed during the last ten years, thus adding asymmetric synthesis to the arsenal of tools available to the organic chemists for obtaining enantiomerically pure compounds.[8,9] Construction of carbon-carbon bonds, wherein multifunctional molecules are produced, has attracted the attention of synthetic organic chemists in recent years.

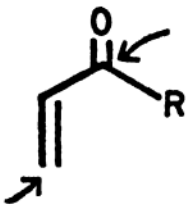
The α-alkoxyalkylation of α, β-unsaturated ketones, esters, nitriles, etc. represents a simple, useful and important organic reaction for the construction of carbon-carbon bonds, wherein multifunctional molecules are produced (eq.1).



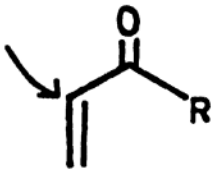
(1)

Z = COOR, COR, CN, etc.; R = alkyl or aryl; R' = H or alkyl

Applications of α,β-unsaturated ketones, esters, nitriles, etc. in organic synthesis have been well demonstrated. Literature survey reveals that most of the chemistry known for α,β-unsaturated ketones or esters is either at β-position or at carbonyl function. But there is not much literature available for reactions at α-position.



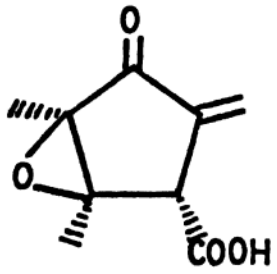
well known



not much known

R = alkyl, alkoxy

Construction of carbon-carbon bond at α-position of activated alkenes, i.e., α,β-unsaturated ketones, esters, nitriles, etc. represents a very useful and important synthetic reaction because several naturally occuring biologically active molecules possess these structural features. For example, methylenomycin A (1)[10], sarkomycin (2)[11], pentenomycin (3)[12] are well known biologically active molecules.



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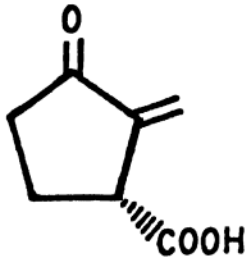

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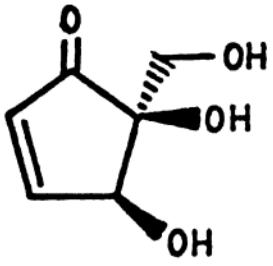
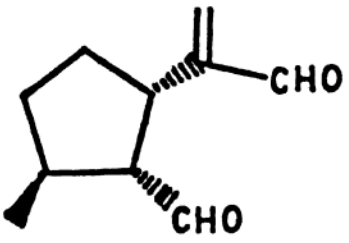


3

The recent review by Hoffmann[13] and the recent publication by Helquist[14] have highlighted the fact that acrylate unit features prominently in a number of naturally occuring molecules that possess biological activity.

Some of the important examples are the monoterpene dialdehyde 4 [15] (obtained from Teucrium marum), the tremetone derivative 5 [16] (from Ophryosporus angustifolius), conocandin (6)[17] (fungistatic antibiotic from Hormococcus conorum), and the fatty acid derivatives of β-alanine 7 [18] (isolated from Red Sea sponge Fasicospongia cavernosa).



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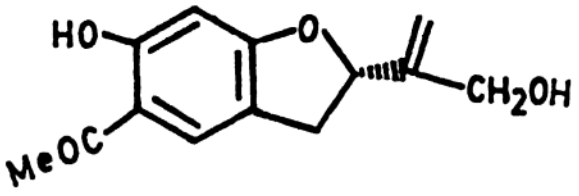

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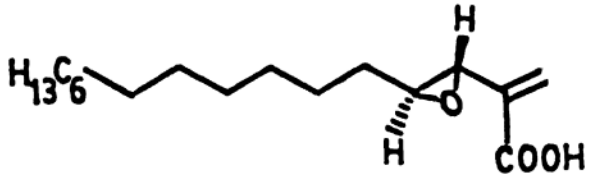

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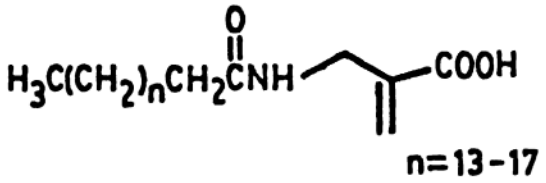
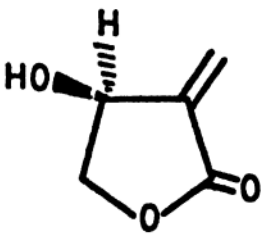


7

The best known acrylate unit often encountered as an integral building block of many natural products is α-methylene-γ-butyrolactone ring. Simplest among these lactones is tulipalin B (8)[19] (antibiotic isolated from compositae family plants). A number of sesquiterpene lactones such as vernolepin (9)[20], aromaticin (10)[21] (isolated from plant extracts) show tumor inhibiting activity. Parthenin (11)[21] (from Parthenium hysterophoros) is a primary allergin. In 1975 Grieco[22], Gammill et al.[23] and in 1986 Petragnani and co-workers[24] reviewed the synthesis of α-methylene-γ-butyrolactones.



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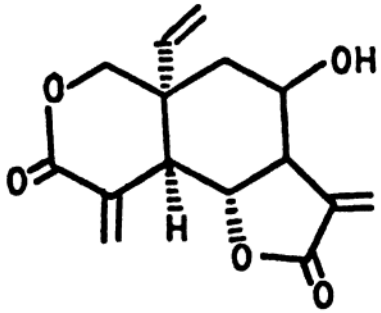

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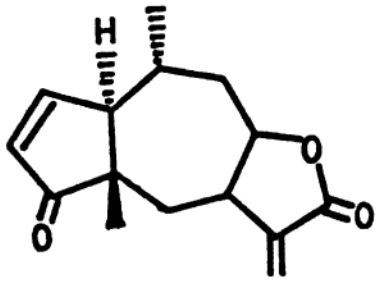

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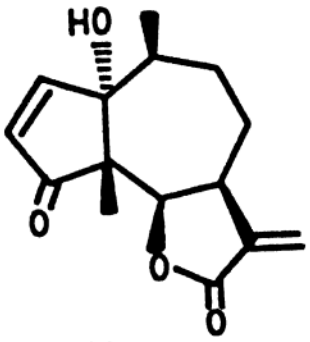

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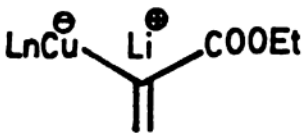
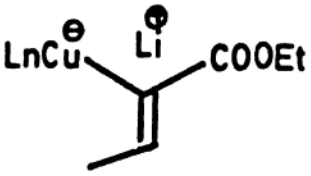
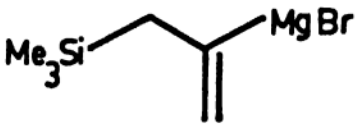
In response to synthetic challenges a number of methods have been developed to introduce acrylate units into the system using masked acrylates and precursors containing activating group that must be removed subsequently. Some important acrylic ester equivalents are listed below.



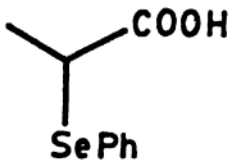
12^{25}



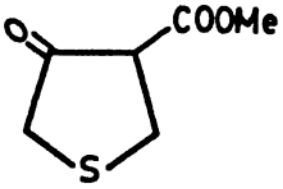
13^{25}



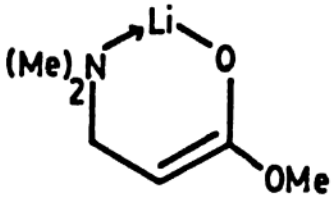
14^{26}



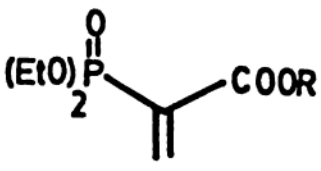
15^{27}



$16^{28,29}$



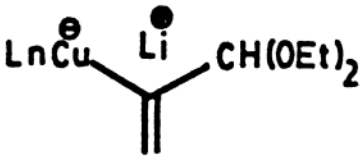
17^{14}



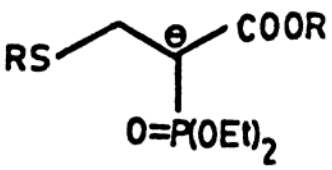
18^{30}

19^{31}

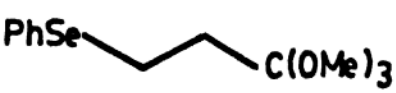
20^{32}



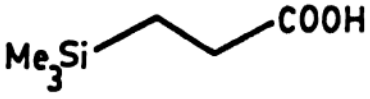
21[33]



22[34]



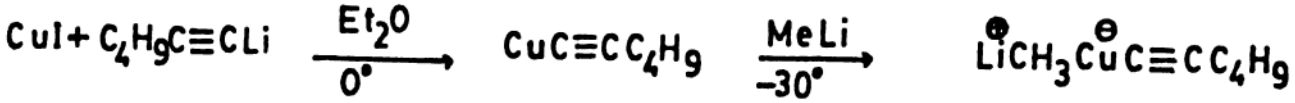
23[35]



24[36]

Marino and Floyd[37] reported the generation and alkylation reaction of the copper reagent 25 which serves as an efficient synthon for the acrylate anion (Scheme 1).

SCHEME 1:



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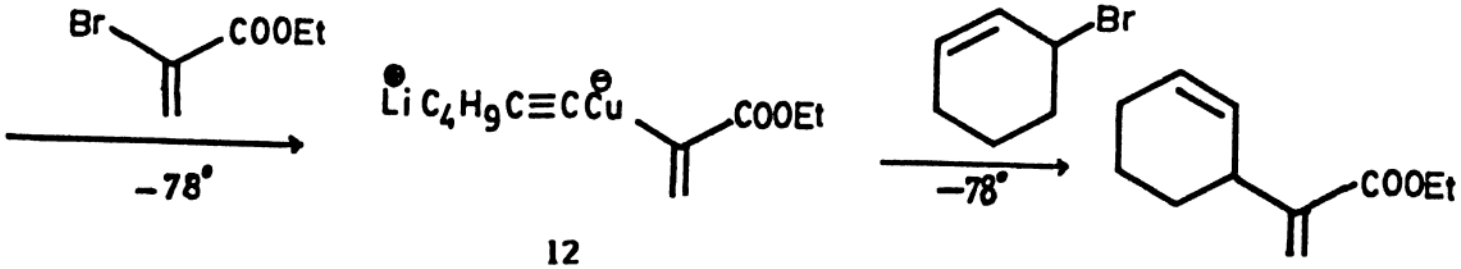
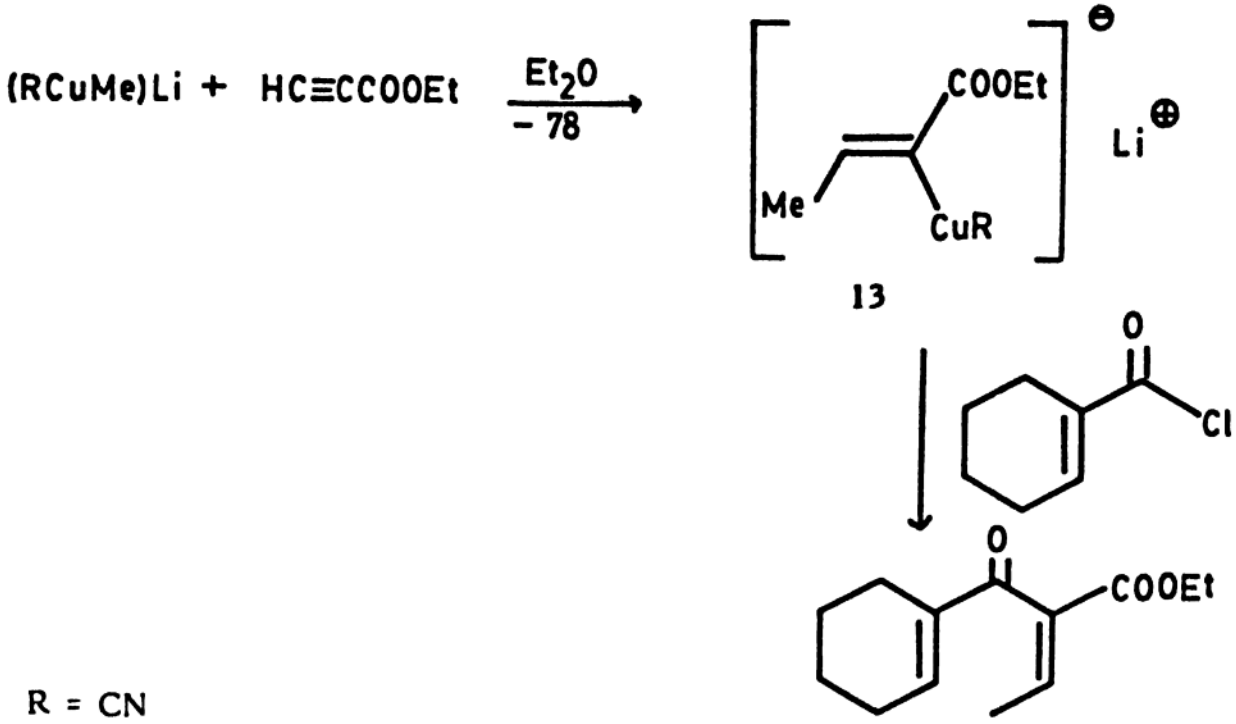


12

The vinylcuprate 13 was prepared by the conjugate addition of mixed alkyl cuprates to ethyl propiolate and subsequent reaction with acid chlorides of α, β-unsaturated acids led to the formation of α, α'-dienones[25] (Scheme 2), which were further utilized as precursors to annulated cyclopentenones via Nazarov type cyclization.

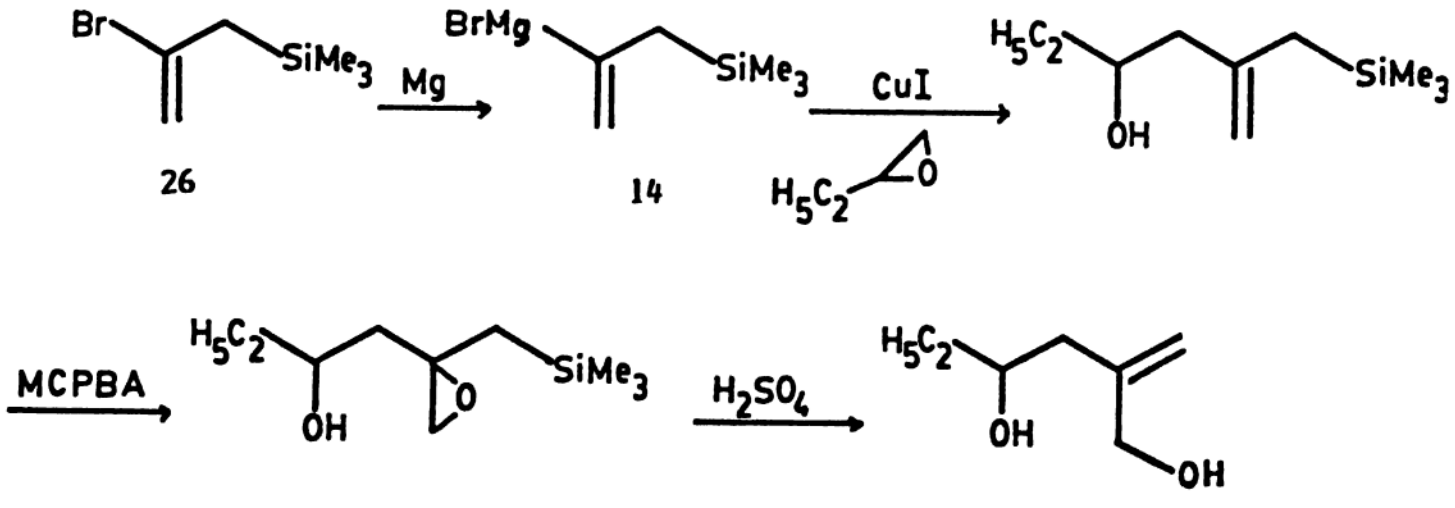
SCHEME 2:



R = CN

The synthetic utility of 2-bromoallyltrimethylsilane (26) as 1-hydroxy-methylvinyl anion equivalent has been reported by Itoh and co-workers[26] to produce the corresponding diols (Scheme 3), which are useful precursors to α-methylene-γ-lactones.

SCHEME 3:



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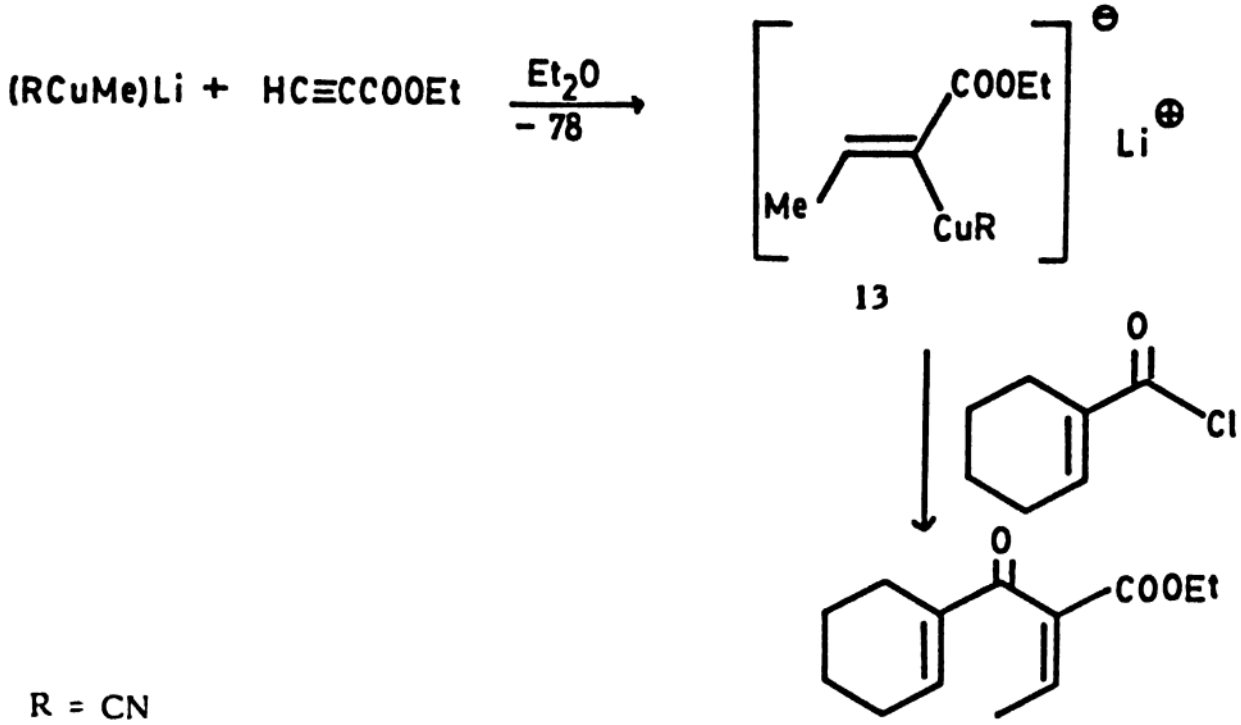

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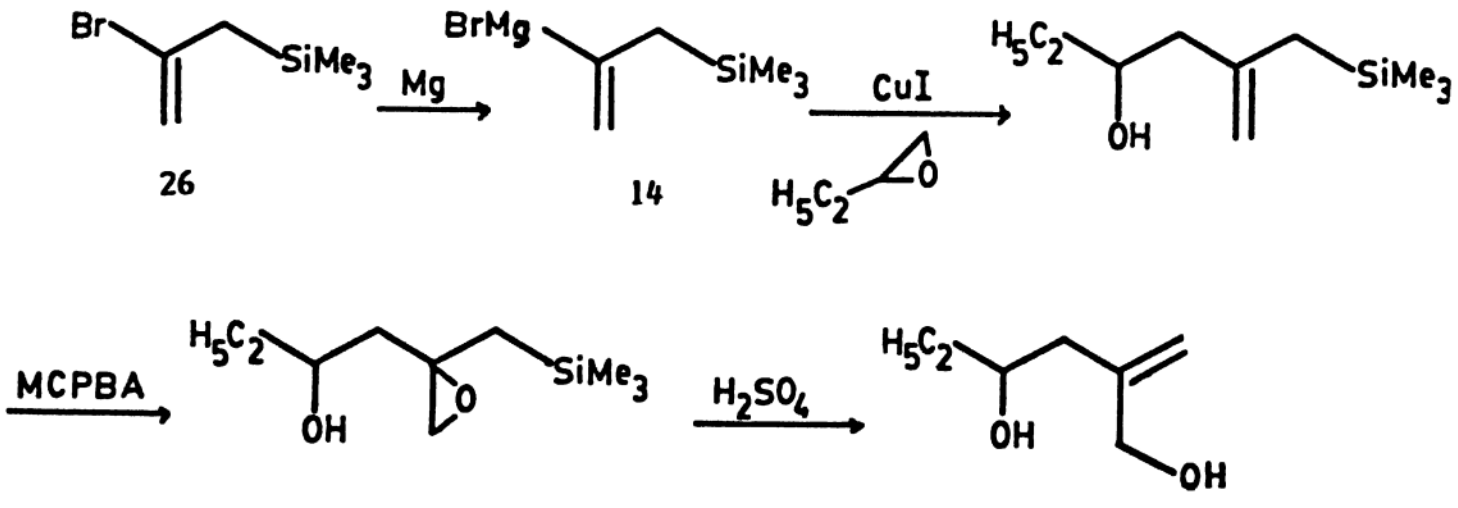
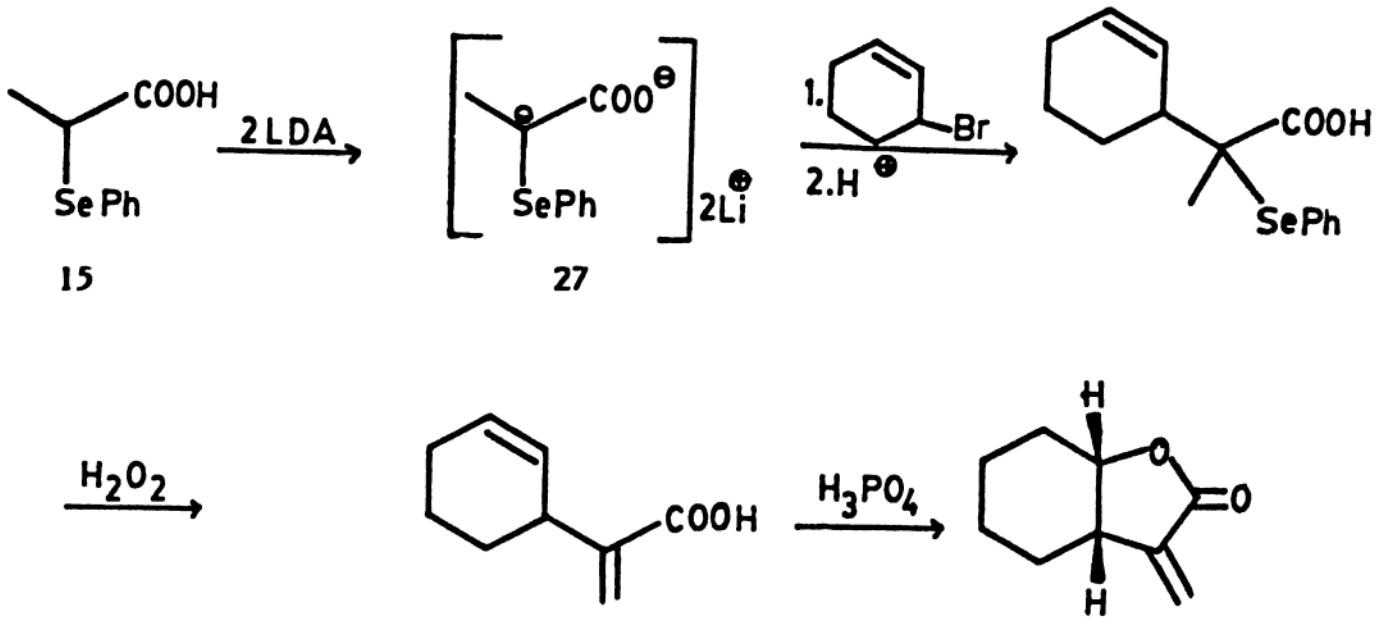


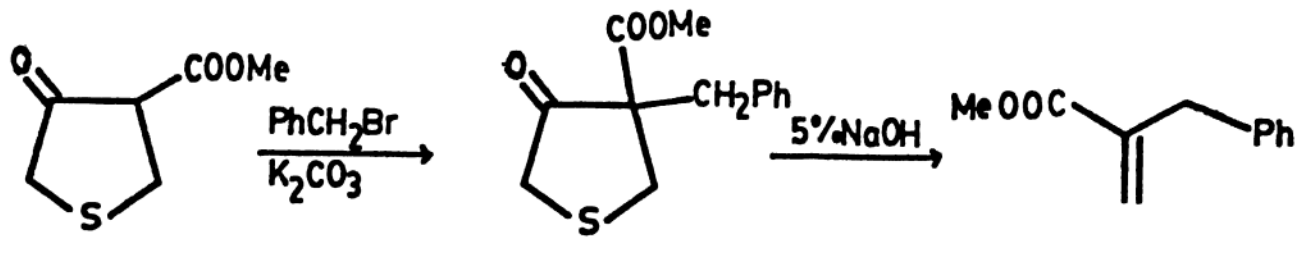
2-Phenylselenopropionic acid (15) has been used as a masked acrylate unit by Petragnani and Ferraz.[27] The dilithio derivative 27 obtained from 2-phenylselenopropionic acid (15) reacts with 3-bromocyclohexene giving the corresponding alkylated derivative which inturn is converted into α-substituted acrylic acid by selenoxide elimination (Scheme 4).

SCHEME 4:



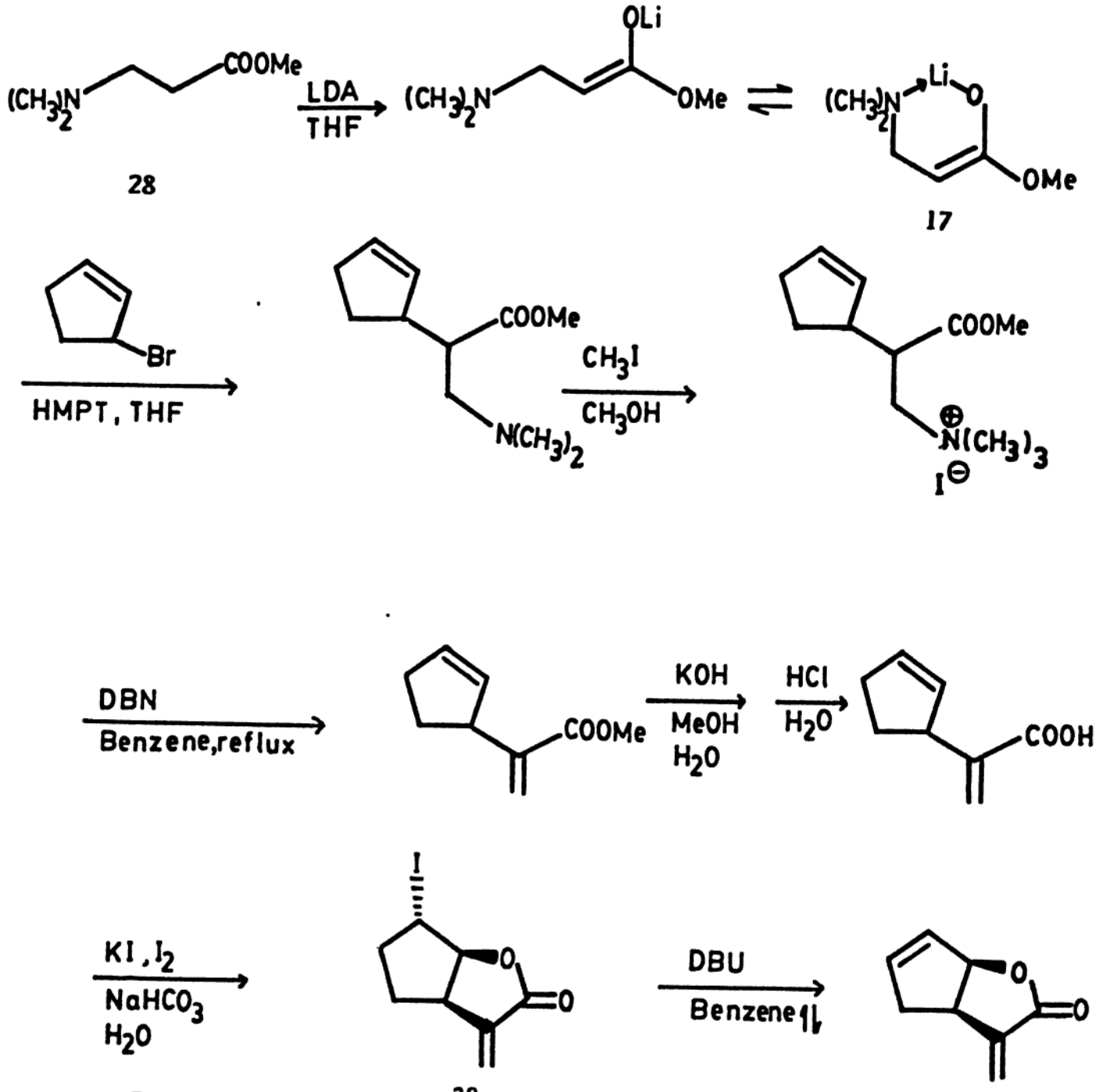
Methyl 4-oxothiolane-3-carboxylate (16) anion has been employed as synthetic equivalent of α-acrylate anion (Scheme 5) by Baraldi and co-workers.[29]

SCHEME 5:



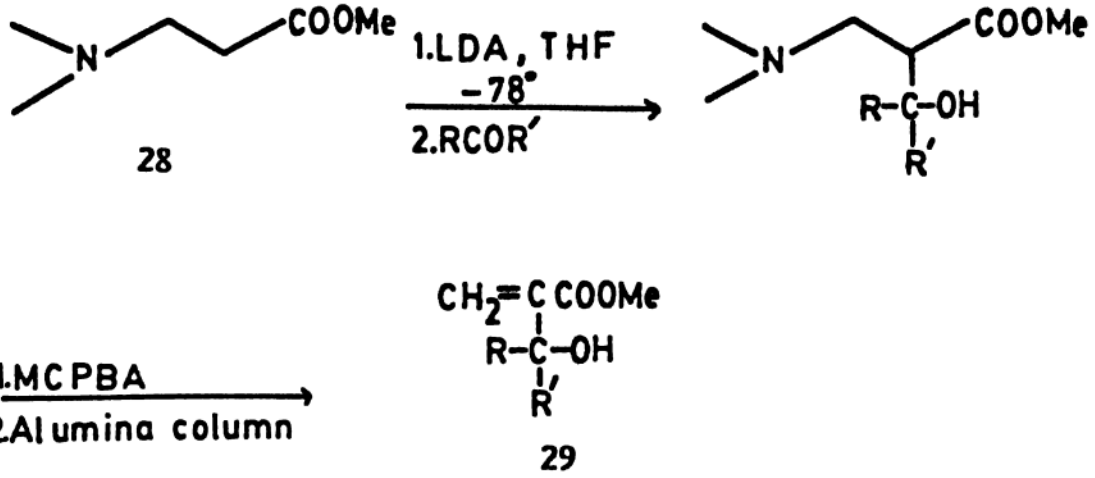
The lithium enolate 17 of methyl 3-(dimethylamino)propionate (28) has been shown to be a synthetic equivalent of the anion of acrylates (Scheme 6) and has been applied to the synthesis of α-methylene-γ-butyrolactones.[14]

SCHEME 6:



Drewes and co-workers[38] have obtained 2-substituted-2-propenoic acid esters 29 via a similar reaction of a masked acrylate ester with carbonyl compounds such as aldehydes, ketones, α,β-unsaturated aldehydes (Scheme 7).

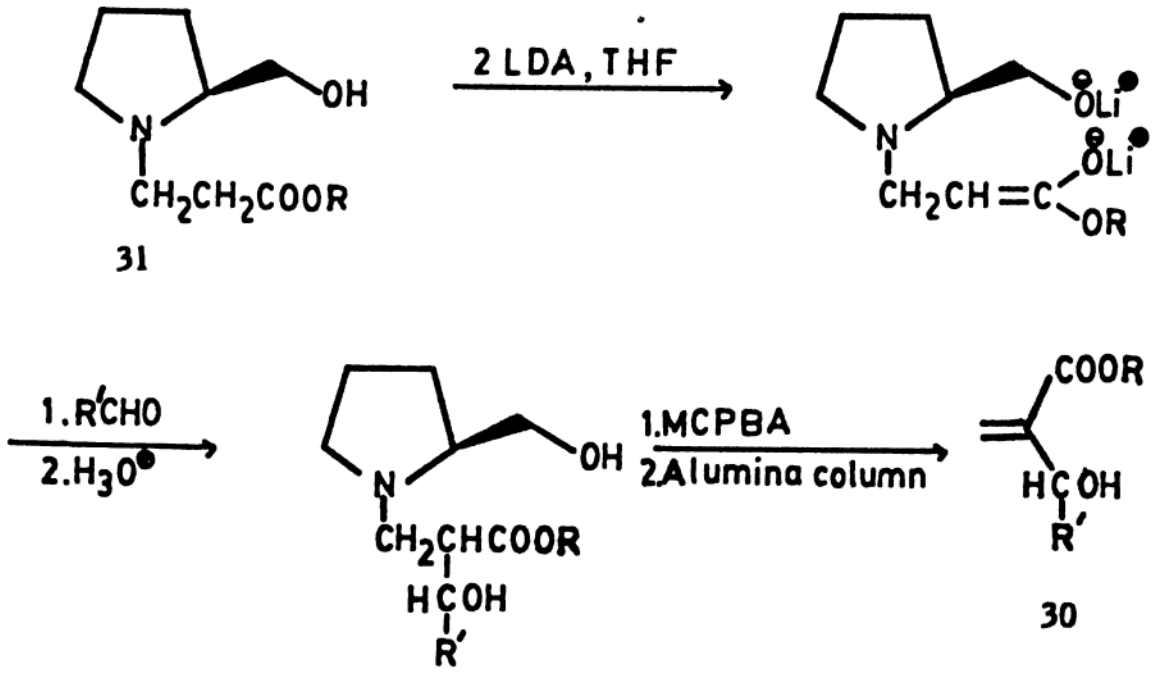
SCHEME 7:



R = Ph, $CH{=}CH_2$, $CH(CH_3)_2$; R' = H, CH_3

They also extended their study to the synthesis of chiral 2-substituted acrylic esters **30** by the reaction of aldehydes on masked acrylates, with an internal chiral auxiliary (Scheme 8).[39] The proline based derivative **31** has been used as a masked acrylate unit and the optical purities are in the range of 8-73%.

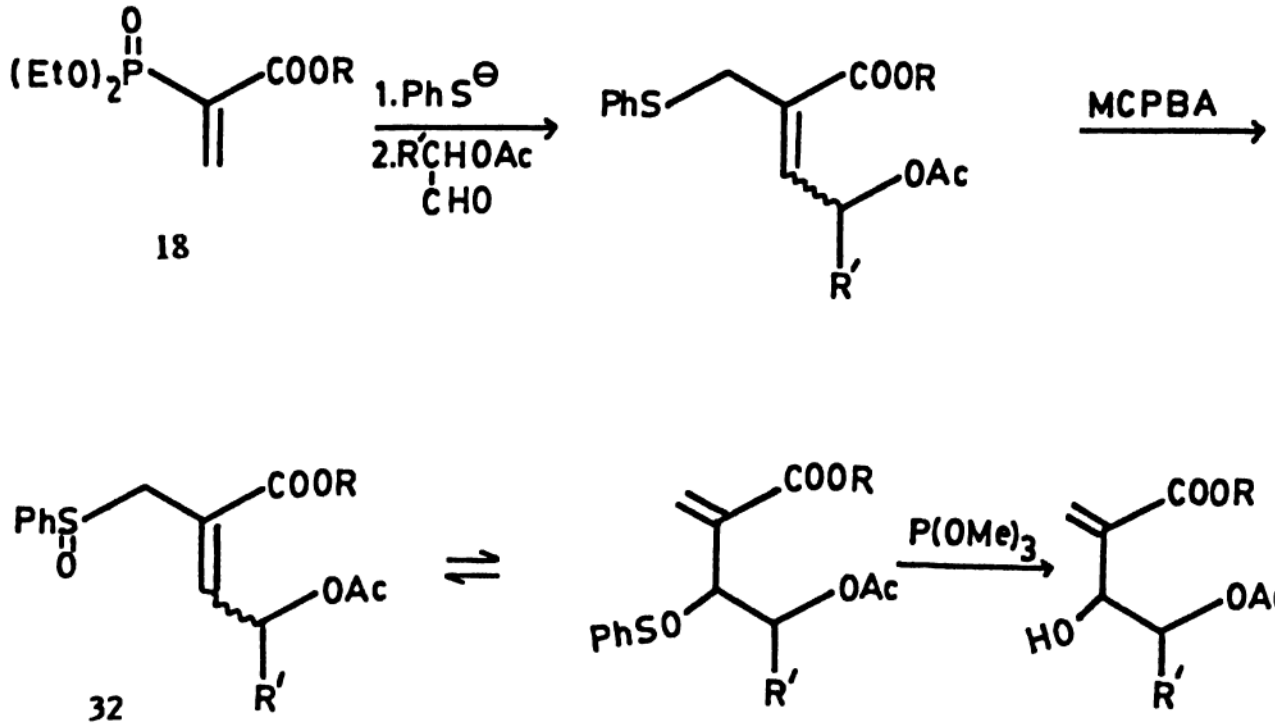
SCHEME 8:



R = CH_3, t-C_4H_9; R' = Ph, p-$OCH_3C_6H_4$, p-$NO_2C_6H_4$

The α-alkoxyalkylation method developed by Benezra et al.[30] involves the conjugate addition of the thiolate anion to the α-methylenephosphonate **18** followed by the addition of acetoxyaldehydes, giving the formal Wittig-Horner product. Subsequent oxidation to sulfoxide **32** followed by the addition of a thiophilic reagent yields the allylic alcohol via a Mislow-Evans rearrangement (Scheme 9).

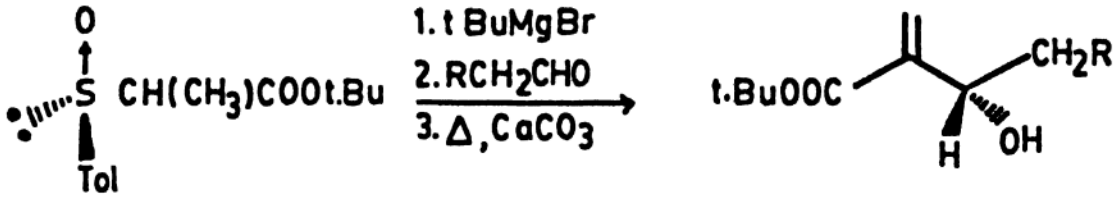
SCHEME 9:



R = CH_3, C_2H_5; R' = H, CH_3, C_2H_5, i-C_3H_7, C_5H_{11}

During the efforts to understand the molecular aspects of allergic control dermatitis, Benezra and Papageorgiou[40] synthesized the optically active sensitizers of the type α-(hydroxyalkyl)acrylates **33**. They prepared chiral α-(hydroxyalkyl)acrylates in 75% ee by the action of chiral p-tolyl sulfoxides **34** on aldehydes followed by thermal elimination of sulfoxides (Scheme 10).

SCHEME 10:

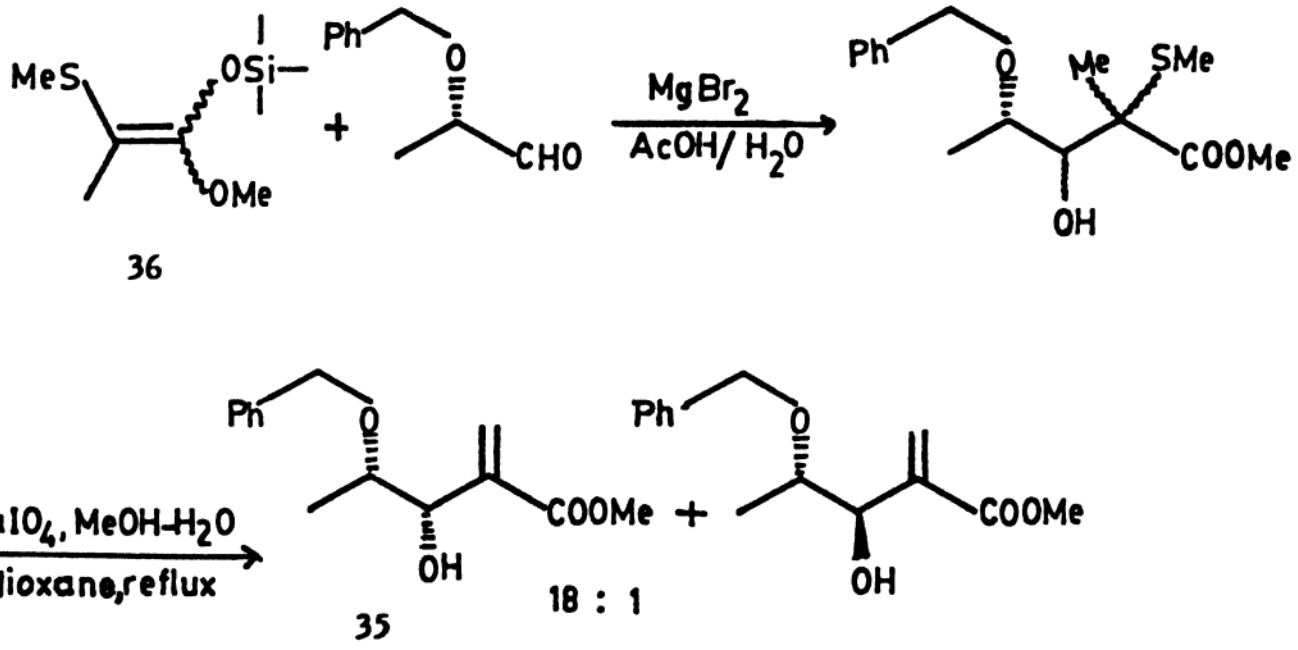


34 33

R = CH_3, n-C_4H_9, n-C_8H_{17}

Scolastico et al.[41] have used thiolactic acid derivative as an acrylate equivalent in the preparation of <u>syn</u> α-methylene-β-hydroxy-γ-alkoxy esters 35. Diastereoselective synthesis of <u>syn</u> α-methylene-β-hydroxy- γ -alkoxy esters was achieved by Lewis acid mediated addition of methyl α-methylthio propionate silylketene acetal (36) to α-alkoxyaldehydes (Scheme 11).

SCHEME 11:

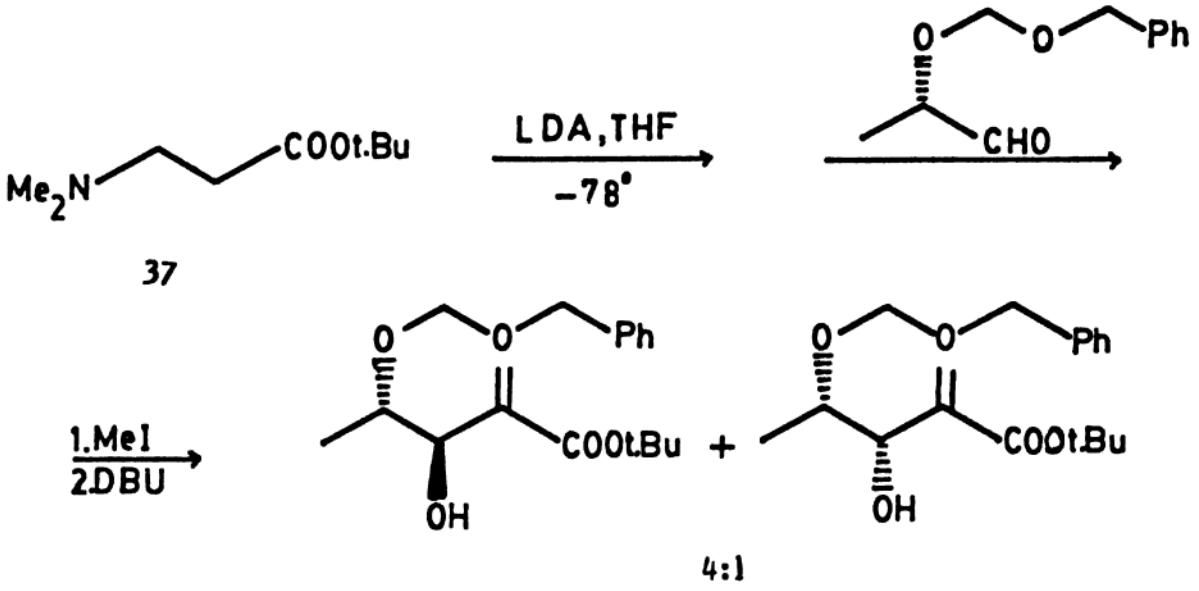


36

35

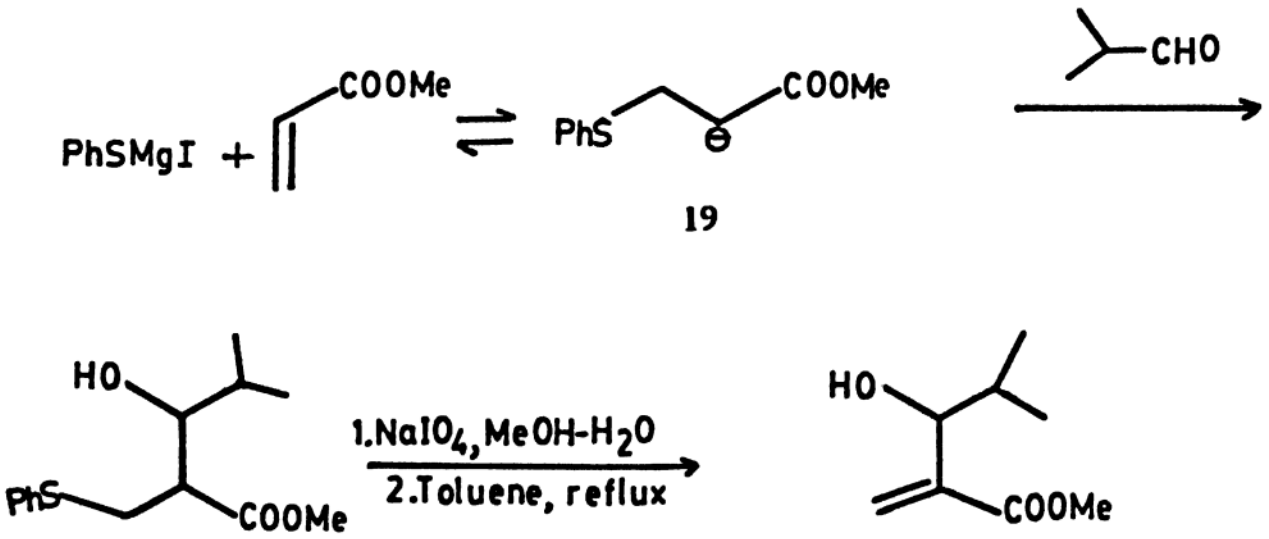
Thev have also reported[42] that t-butyl γ-(dimethylamino)propionate (37), a synthetic equivalent of t-butyl acrylate, readily reacts with α-alkoxyaldehydes to give <u>anti</u> α-methylene-β-hydroxy- γ -alkoxy esters with high selectivity (Scheme 12).

SCHEME 12:



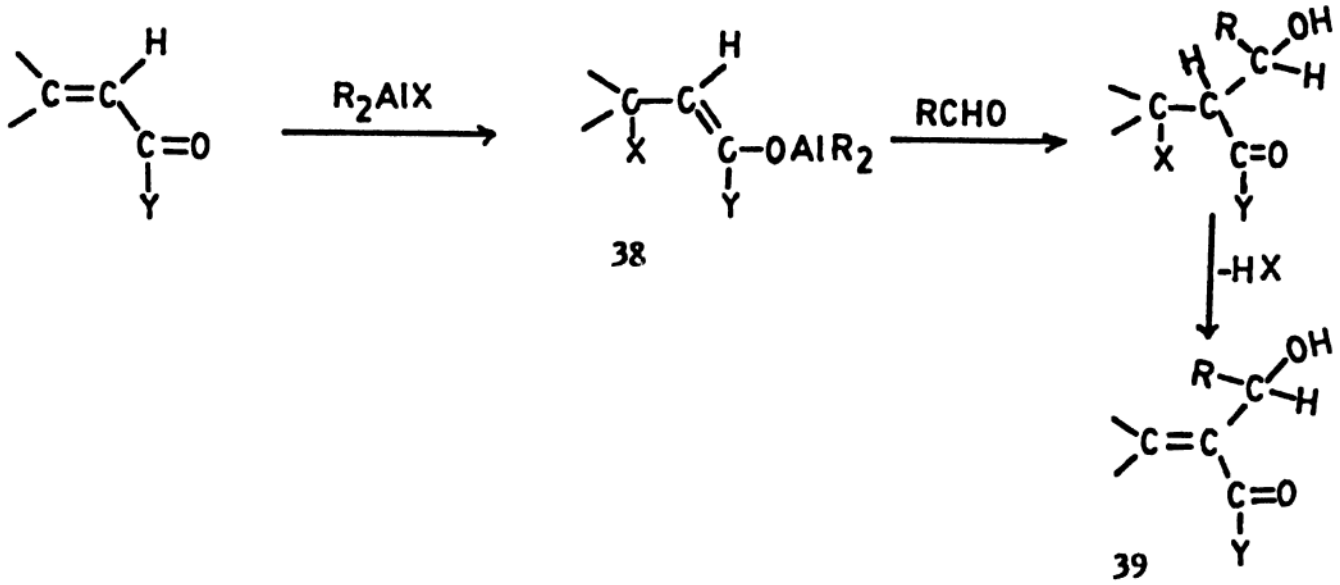
A possible α-hydroxyalkylation has been reported by Shono and coworkers[31] via a one step joining of thiolate anions, activated olefins and carbonyl compounds (Scheme 13).

SCHEME 13:



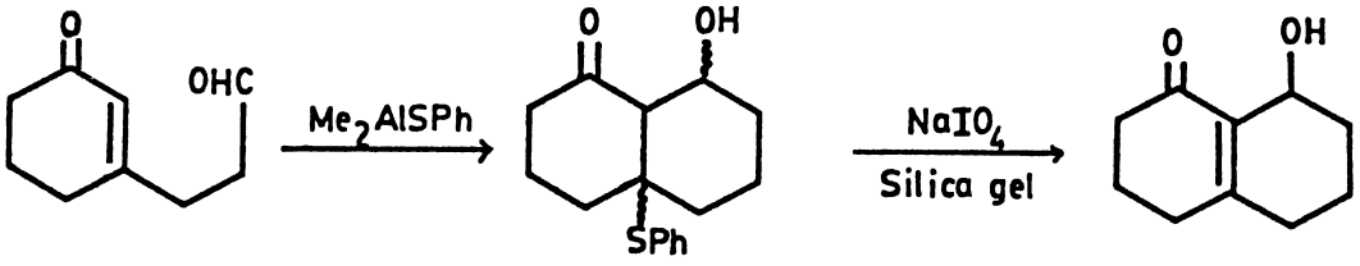
Oshima et al.[43] have also reported that 1,4-addition of R_2AlX to α,β-unsaturated carbonyl compounds gave the aluminium enolate **38**. subsequent aldol addition of the enolate with aldehydes followed by elimination of HX provides α-substituted α,β-unsaturated carbonyl compounds **39** (Scheme 14).

SCHEME 14:



R = H, CH_3, $CH_3(CH_2)_7$, Ph; X - SPh; Y - CH_3, OC_2H_5

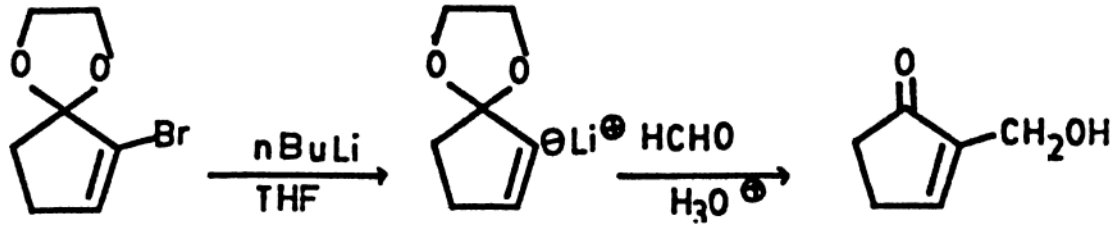
Intramolecular strategy:



During the synthesis of pentenomycin and dehydropentenomycins Branca and Smith[44] demonstrated that α-bromoketals hold considerable promise as latent α-keto vinyl anion equivalents. The vinyl anion **40**, generated by the addition of n-BuLi to bromoketal, reacts with a variety of electrophilic

reagents (Scheme 15) to yield the corresponding α-alkylated products.

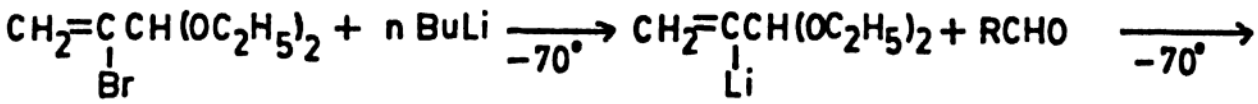
SCHEME 15:



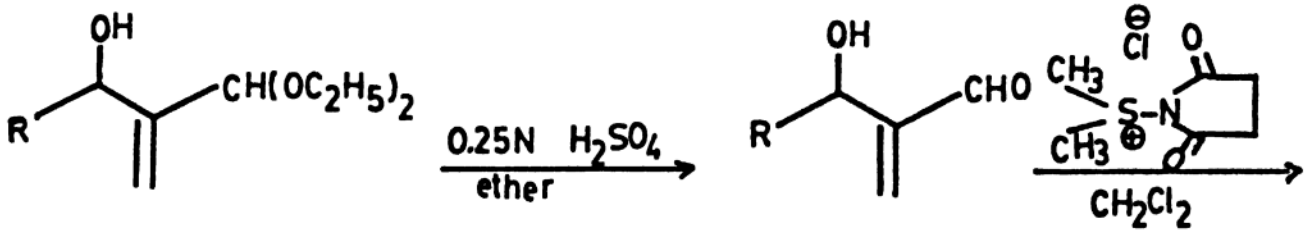
40

Depezay and Merrer[45] have also used protected α-bromoacrolein to prepare α-(hydroxyalkyl)acroleins **41**. The strategy involves the addition

SCHEME 16:



42



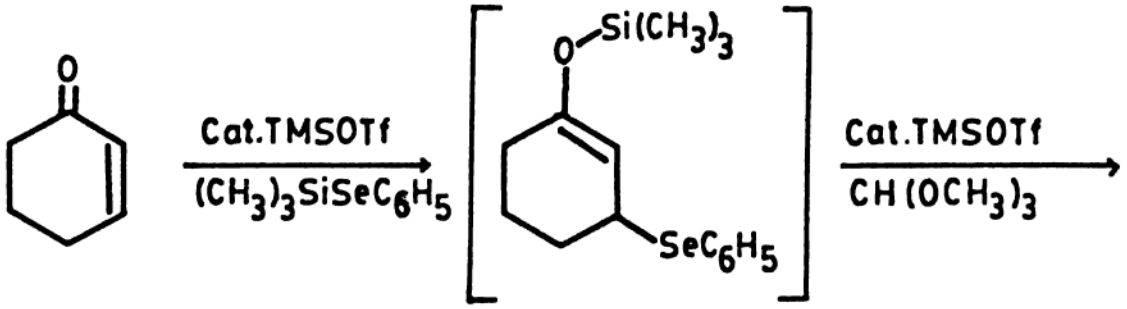
41

R = CH_3, C_2H_5, Ph, n-C_5H_{11}

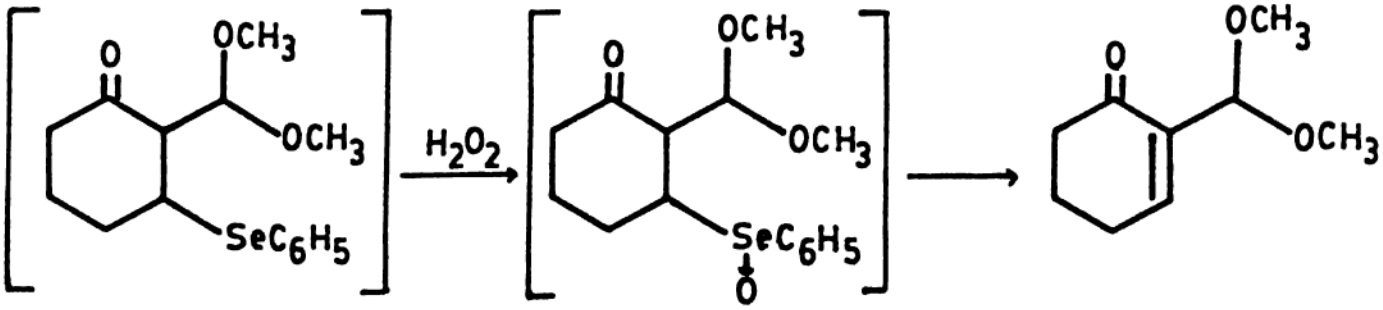
of n-BuLi to the 2-bromoacrolein diethylacetal to give the corresponding anion **42**, subsequent treatment with aldehyde followed by deprotection provides the 2-hydroxyalkylacrolein **41**. These acrolein derivatives had been successfully utilized for the stereoselective synthesis of <u>trans</u> olefins (Scheme 16).

Noyori et al.[46] have devised a procedure for α-alkoxyalkylation of α,β-unsaturated ketones (Scheme 17) via conjugate addition of phenyl silyl selenide to α,β-unsaturated ketones and the aldol type reaction of enol silyl ether **43** with acetals or orthoesters catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf), followed by the β-elimination.

SCHEME 17:

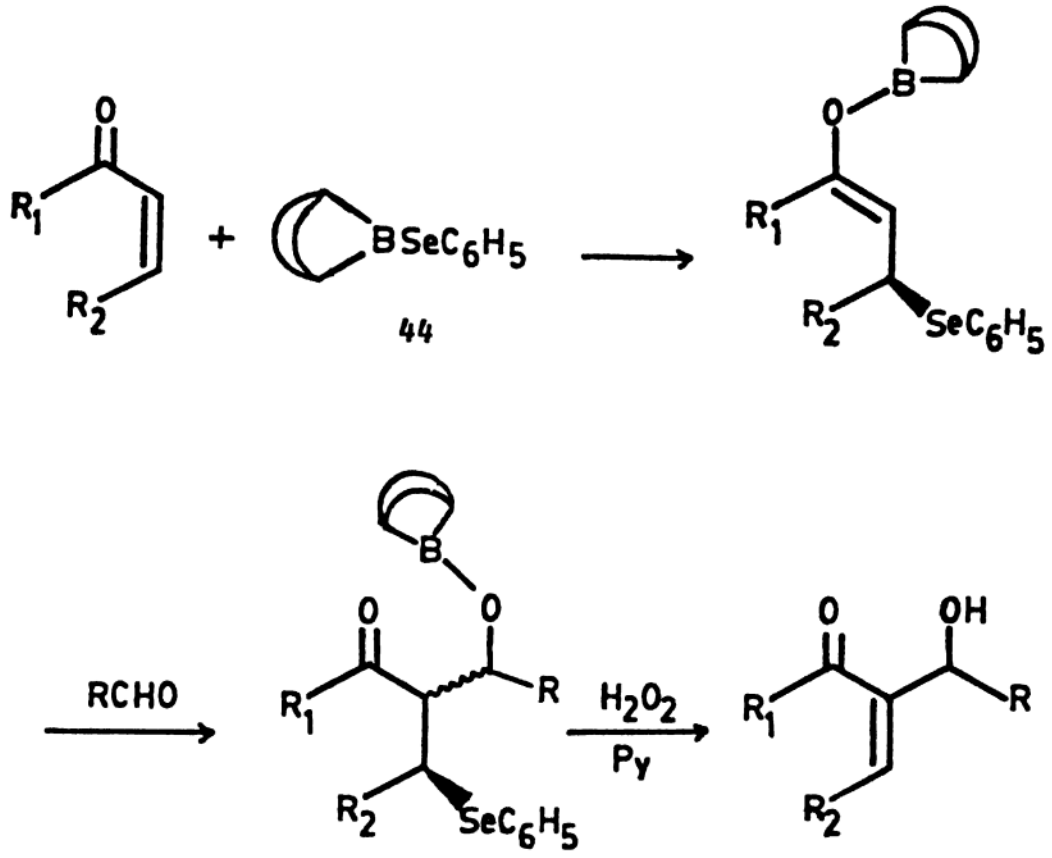


43



9-(Phenylseleno)-9-borabicyclononane (**44**) was employed by Leonard and Livinghouse[47] for the effective aldol type reaction at the α-carbon of α,β-unsaturated ketones (Scheme 18).

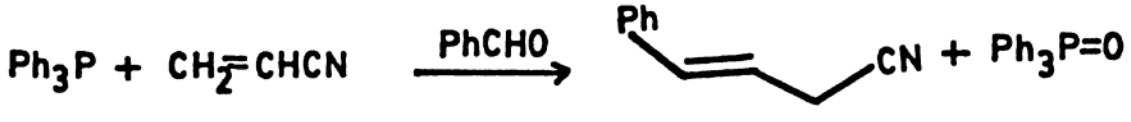
SCHEME 18:



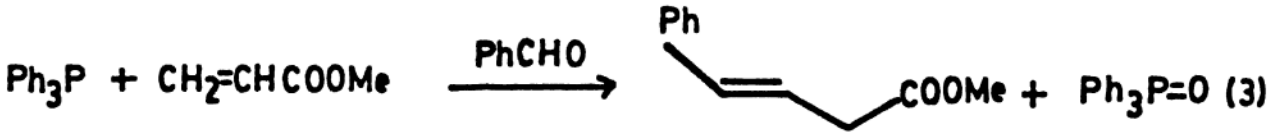
$R = C_6H_5$, i-C_3H_7; R_1 - CH_3, C_6H_5,etc.; R_2 = H, CH_3

New C-C bond forming reactions via trialkylphosphine catalyzed coupling of activated olefins with aldehydes:

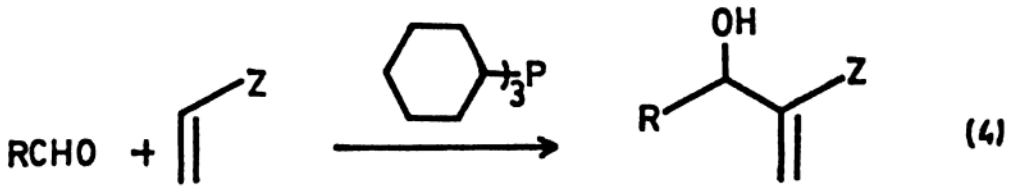
In 1964 Oda et al.[48] reported that the reaction of acrylonitrile with benzaldehyde in the presence of equimolar quantities of triphenylphosphine in alcoholic solvents at higher temperatures afforded the trans 4-phenyl-3-butenenitrile (in low yields) and triphenylphosphine oxide (eq.2). A similar reaction with methyl acrylate gave trans methyl 4-phenyl-3-butenoate (eq.3).



(2)



Later on in 1968 Morita et al.[49] carried out the reaction of methyl acrylate and acrylonitrile with various aldehydes in the presence of catalytic amount of tricyclohexylphosphine to give 2-substituted acrylates and acrylonitriles (eq.4).

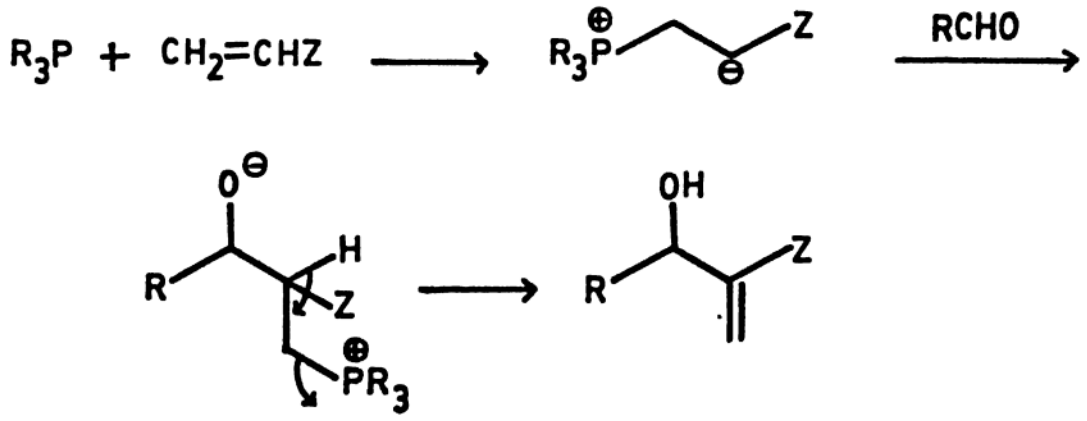


R = alkyl, aryl; Z = CN, COOMe

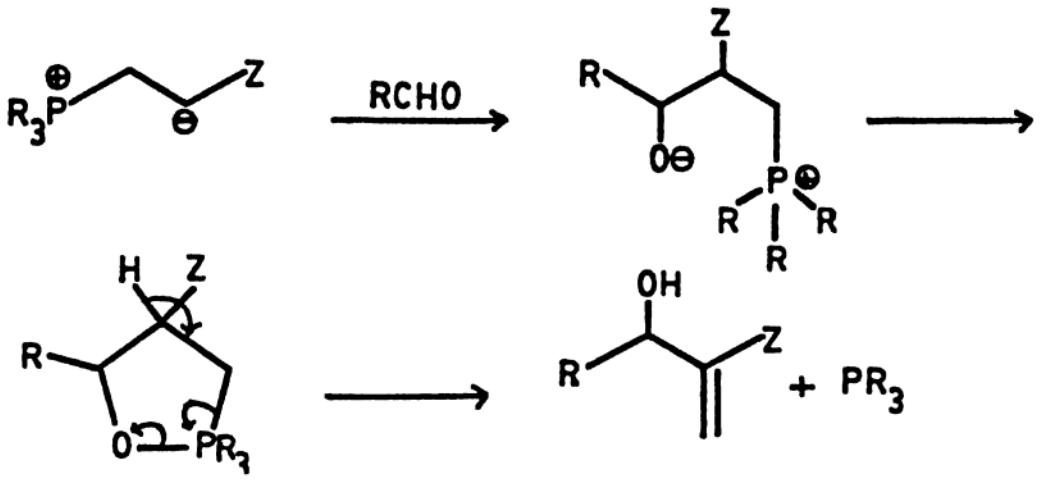
Two possible mechanisms have been proposed by Morita and co-workers for the above reaction (Scheme 19).

SCHEME 19:

Mechanism 1:



Mechanism 2:

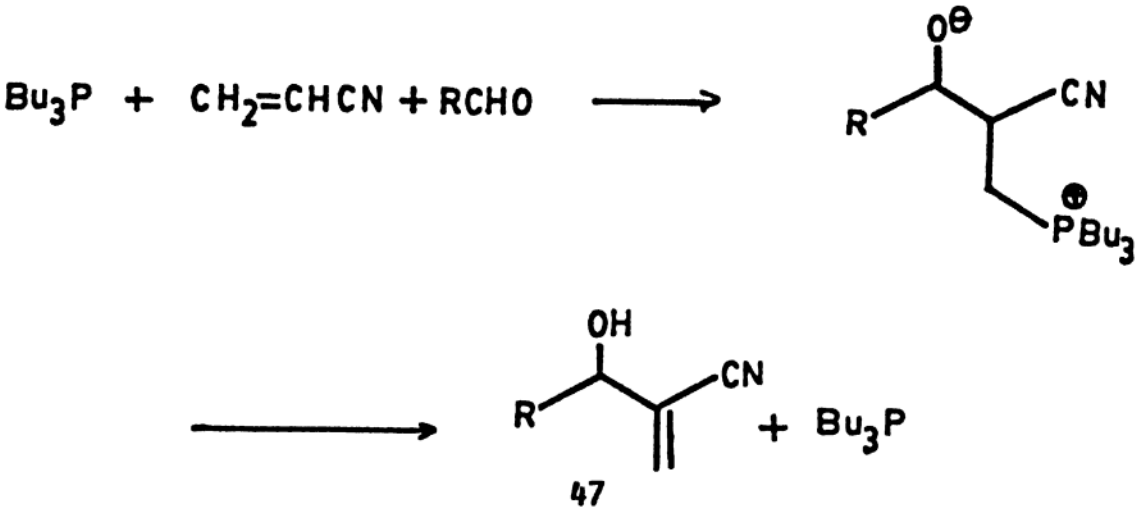


These workers have also suggested that if triphenylphosphine is used for the reaction, the Zwitterion **45** can isomerize to Ylide **46** by a proton transfer which then undergoes irriversible reaction with aldehydes to produce Wittig type product and triphenylphosphine oxide (eq.5). Actually, oligomers of acrylonitrile have been prepared by the reaction of acrylonitrile with catalytic amount of tertiary phosphines in the presence of proton donor.[50]

$$\underset{\textbf{45}}{Ph_3\overset{\oplus}{P}CH_2\overset{\ominus}{C}HCN} \rightleftharpoons \underset{\textbf{46}}{Ph_3\overset{\oplus\ominus}{P}CHCH_2CN} \xrightarrow{RCHO} RCH{=}CHCH_2CN \quad (5)$$

An interesting report[51] has appeared for the synthesis of 2-(1-hydroxyalkyl)acrylonitriles **47** from acrylonitrile and aliphatic aldehydes by cocatalysis of tributylphosphine and triethylaluminium (Scheme 20). Similar mechanism as in Scheme 19 has been suggested for this reaction also.

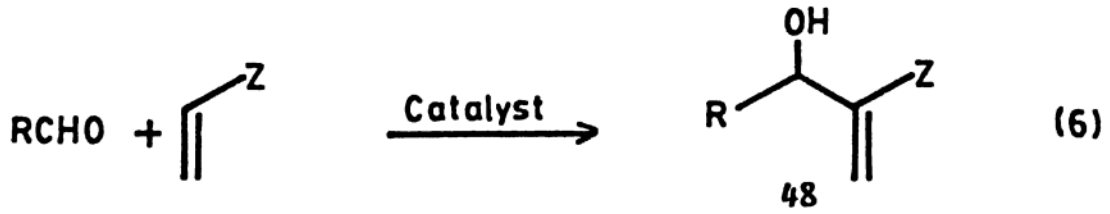
SCHEME 20:



R - n-C_4H_9, n-C_9H_{19}, c-C_6H_{11}, C_6H_5

Baylis-Hillman Reaction:

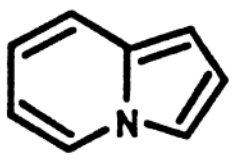
In 1972 Baylis and Hillman[52] in a German patent reported that activated alkenes such as α,β-unsaturated esters, nitriles, amides and ketones can be coupled to aldehydes catalyzed by bicyclic tertiary amines to produce the α-substituted activated alkenes **48** (eq. 6). This is entirely new type of reaction for the construction of carbon-carbon bond wherein multifunctional molecules are obtained. The amines, used by them, are 1,4-diazabicyclo(2.2.2) octane (DABCO) (**49**), pyrrocoline (**50**), quinuclidine (**51**).



(6)

Z = COR, COOR, CN, $CONR_2$

49



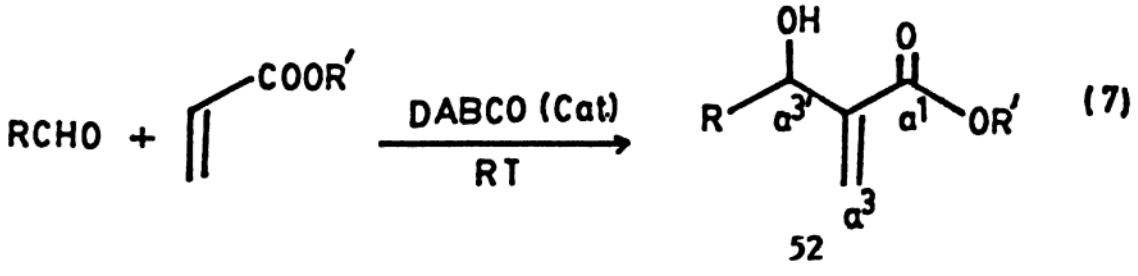
50

51

As the reaction conditions are very mild, carbanion generated in this reaction would be expected to react with aldehyde or related substrates to give the corresponding products without unwanted side reactions. However, very little or no attention was paid to this patented reaction for almost a decade.

In 1982 Drewes and Emslie used this reaction in connection with their work on synthesis of necic acid precursors.[53] Afterwards a number of publications appeared describing the synthetic potential of these tertiary amines catalyzed reaction and it is sure that this reaction will emerge as a powerful synthetic tool in organic synthesis. Since Baylis and Hillman are the originators or founders of this useful reaction, it is appropriate to name this reaction as Baylis-Hillman reaction.[54]

In 1983 Hoffmann and Rabe[55] reported that acrylic esters can be coupled with a variety of aldehydes under the influence of catalytic amount of DABCO at room temperature (eq.7) to produce the multifunctional molecules 52.



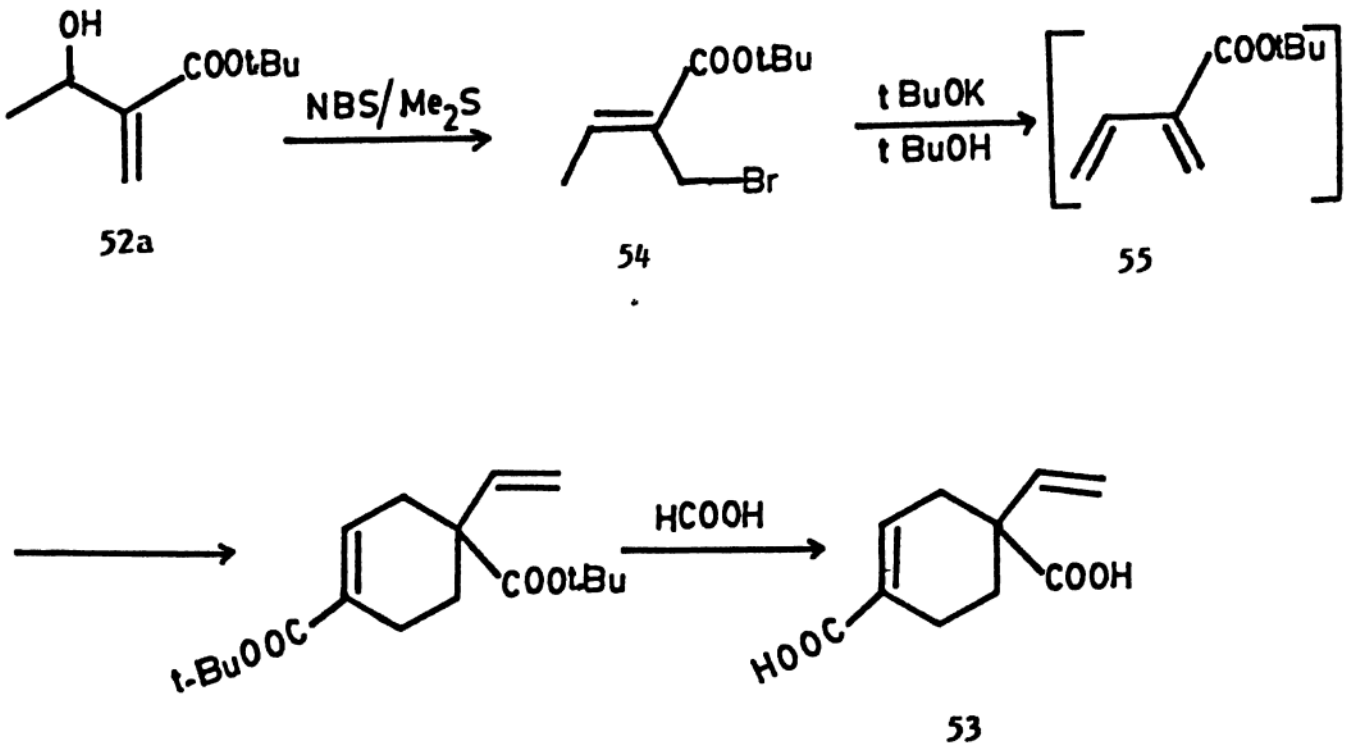
(7)

R = alkyl, aryl; R' = CH_3, C_2H_5, t-C_4H_9

They also noticed that furfural and 3-nicotinaldehyde react much faster. The reaction was reported to be remarkably clean. The resulting α-methylene-β-hydroxy esters *52* are highly versatile intermediates offering

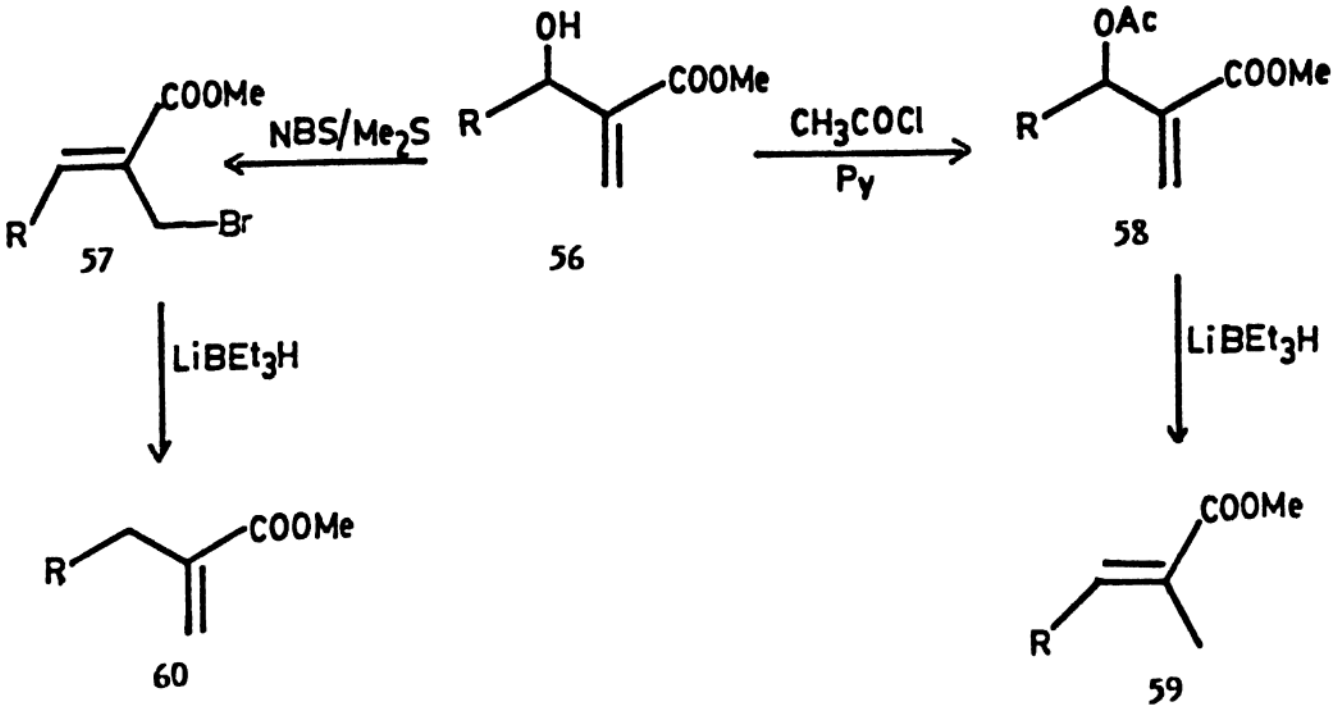
three electrophilic sites for further bond formation,[56] i.e., a^1, a^3, $a^{3'}$ components (using Seebach nomenclature).[57] Hoffmann and Rabe have demonstrated the applicability of these intermediates to a simple synthesis of mikanecic acid[58](53) utilizing t-butyl 2-(1-hydroxyethyl)acrylate (52a) (Scheme 21). The α-methylene-β-hydroxy ester 52a underwent allylic rearrangement when treated with N-bromosuccinimide (NBS)/dimethylsulfide[59] to cleanly afford the Z-alkene 54. Subsequent treatment with potassium t-butoxide in t-BuOH provided the t-butyl 2-methylene-3-butenoate (55) which dimerized insitu to the dit-butyl ester of mikanecic acid.

SCHEME 21:



The synthetic transformations of 2-(hydroxyalkyl)-2-propenoic esters 56 have been demonstrated in the following Scheme.[56,60] (Scheme 22).

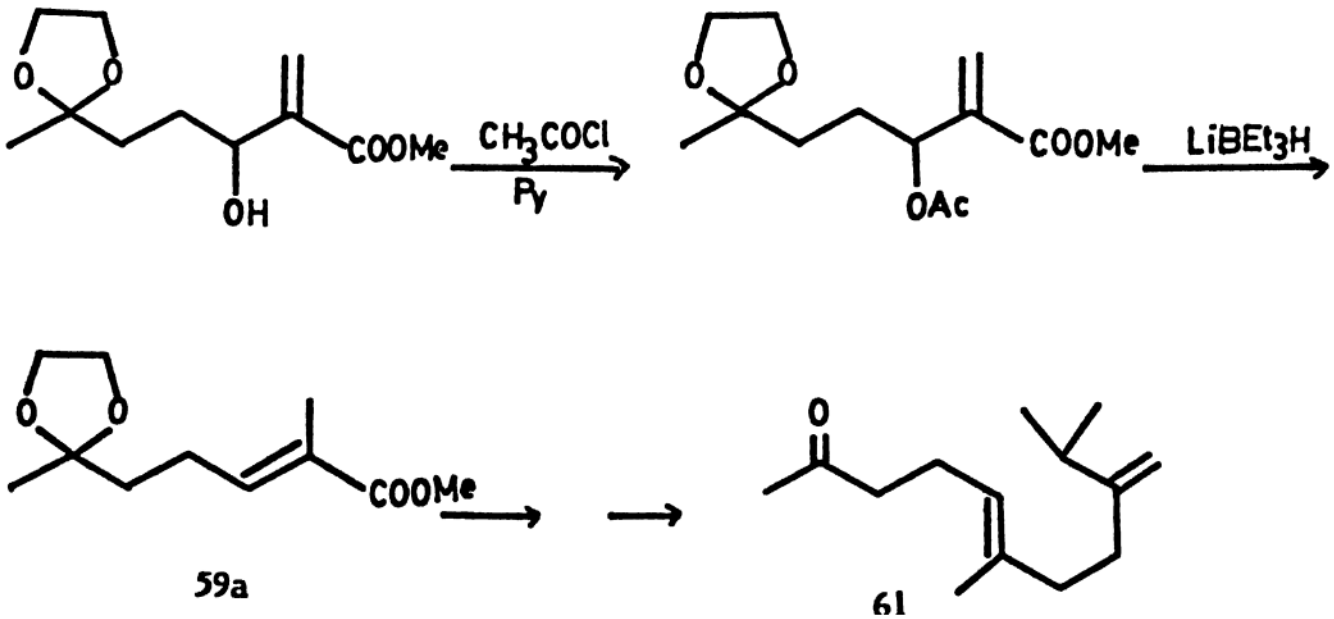
SCHEME 22:



R = alkyl

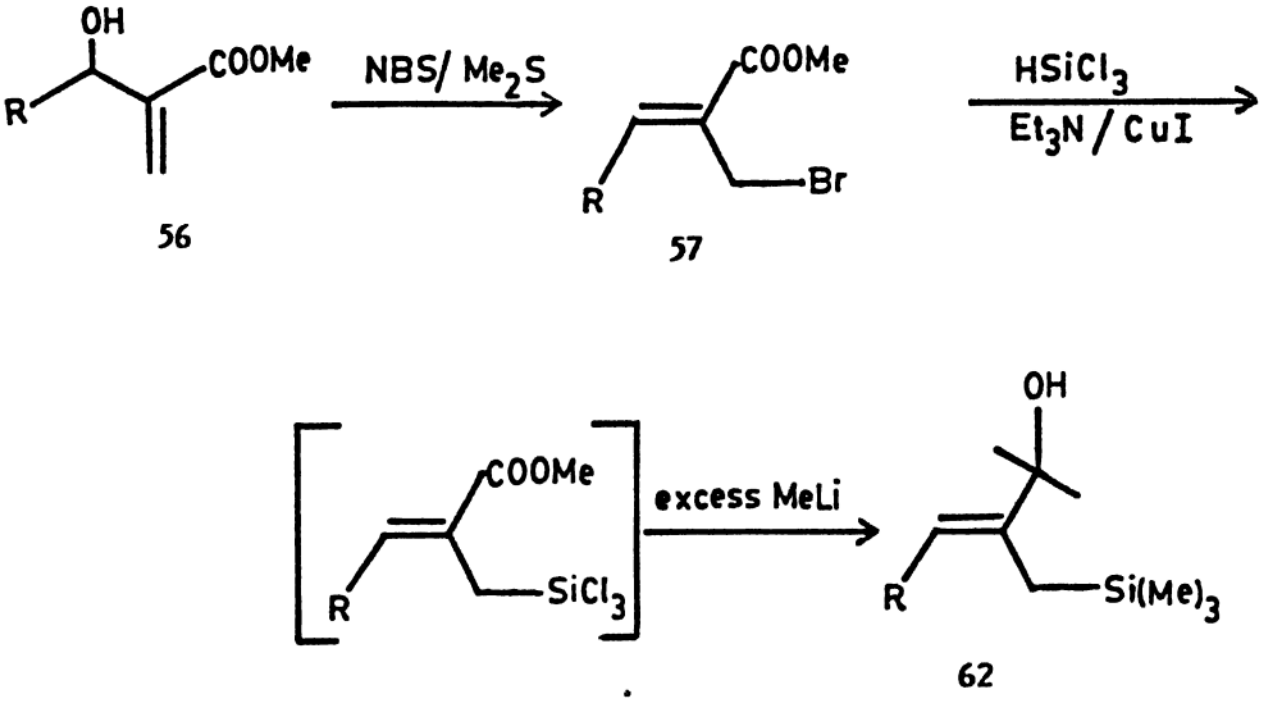
This scheme clearly demonstrates the convenient and stereocontrolled synthesis of trisubstituted alkenes, i.e., (E)-2-methyl-2-alkenoic esters **59** and a simple synthesis of 2-methylenealkanoic esters **60.** Trisubstituted olefin procedure was applied for the synthesis of **59a,** a key intermediate, for the terpene **61.** (Scheme 23).

SCHEME 23:



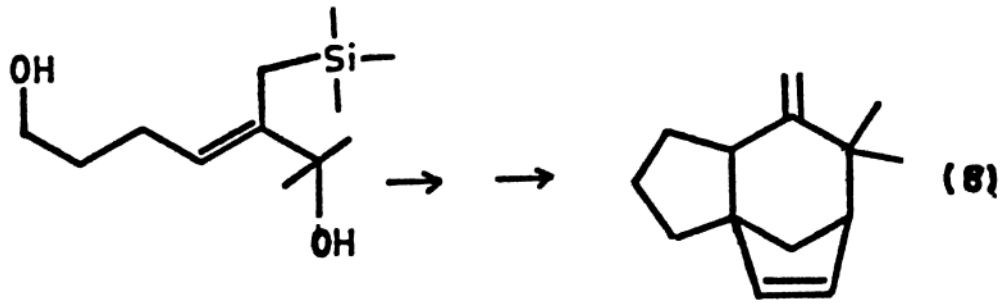
Another useful transformation of the α-bromoalkylacrylate **57** to allylsilane[56] has been described by Hoffmann. Treatment of the bromo-compound **57** with trichlorosilane and copper iodide produces the unstable trichlorosilyl intermediate which on quenching with excess MeLi, affords the desired allylsilane **62** (Scheme 24).

SCHEME 24:



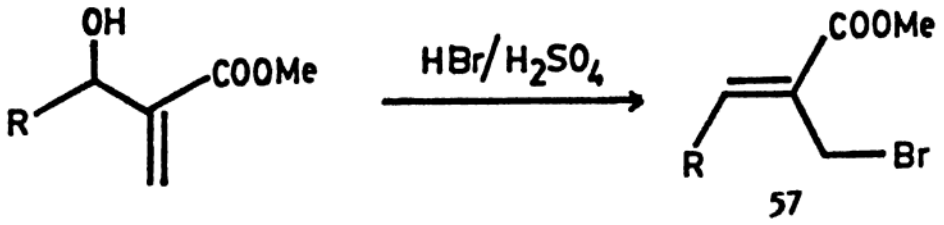
56 **57** **62**

These allylsilanes are useful intermediates. Hoffmann and co-workers prepared the allylsilane **62a**, a key precursor for the synthesis of dehydro-norzizaene[60] (**63**) (eq.8).



62a **63** (8)

Alternatively, α-hydroxyalkylacrylates 56 on treatment with HBr-H_2SO_4[61] undergoes brominative allylic rearrangement to afford the allyl bromide 57 (eq.9). The configuration of this intermediate is confirmed by X-ray crystallography.[62]

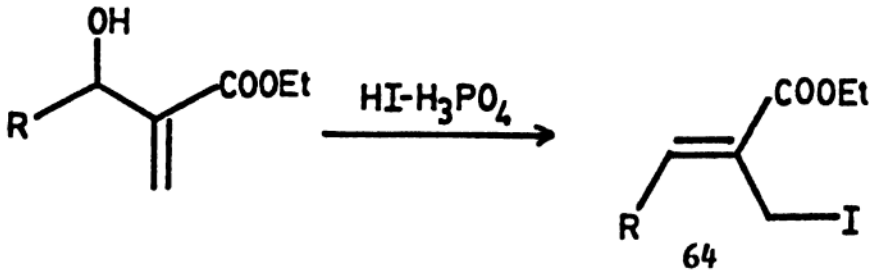


(9)

56 57

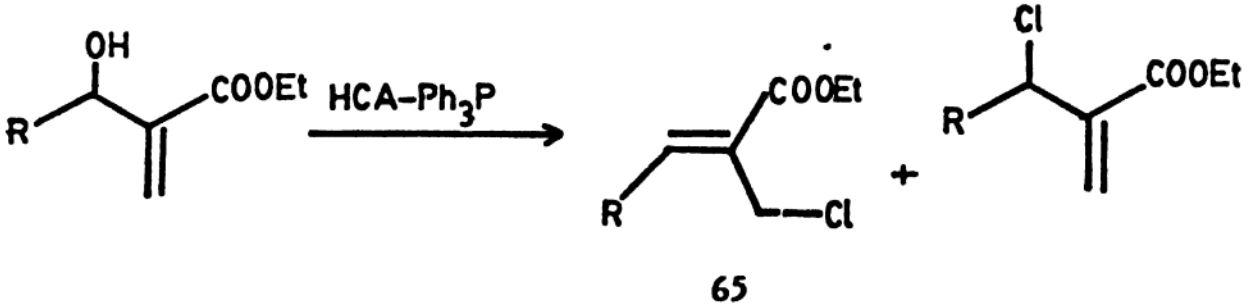
R = alkyl

α-Hydroxyalkylacrylate undergoes iodinative or chlorinative rearrangement stereoselectively.[63] With HI-conc. H_3PO_4 iodination takes place conveniently at the vinylic carbon (eq.10) where as with hexachloroacetone (HCA)-Ph_3P affords both normal and rearranged products in 1:1 ratio (eq.11).



(10)

64



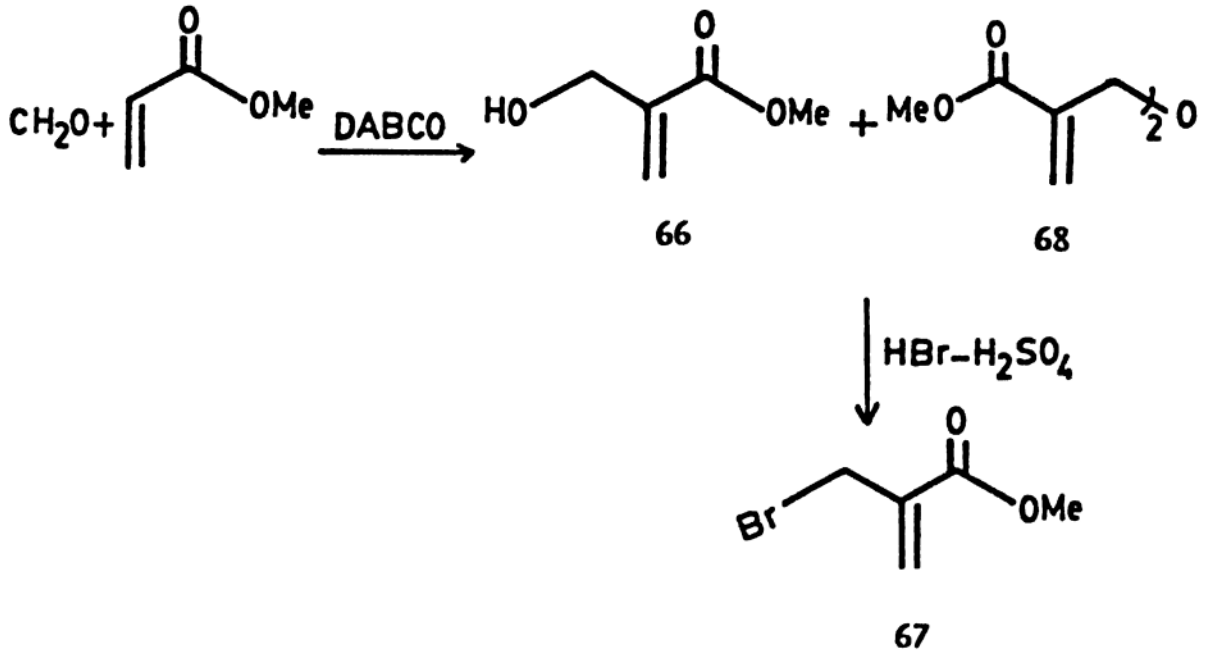
(11)

65

R = CH_3, Ph

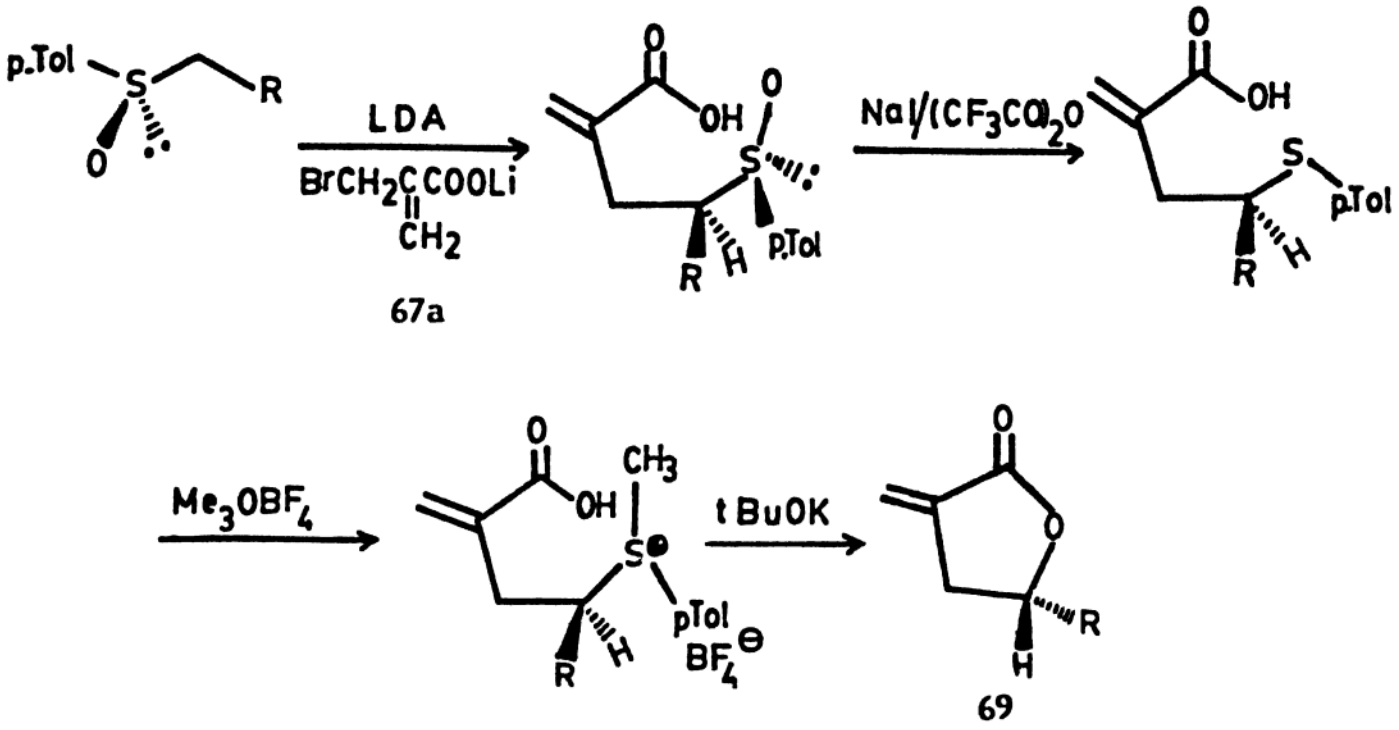
α-Hydroxymethylacrylates and the corresponding bromomethyl derivatives are known to be important synthetic intermediates[64] and their application in the synthesis of bicyclic[65] and spirocyclic[66] ring formation have been reported in literature. Several synthetic reports have appeared for the preparation of α-hydroxymethyl acrylate (66) and the corresponding bromomethyl derivative 67. Recently Drewes and co-workers[67] have demonstrated that formaldehyde can couple with methyl acrylate under the catalytic influence of DABCO to produce 66, contaminated with the ether 68. However, treatment of the mixture 66 and 68 with $HBr-H_2SO_4$ provides clean 67 in good yield (Scheme 25).

SCHEME 25:



The allyl bromide 67a has been employed for the synthesis of α- methylene-γ-butyrolactones. Bravo and co-workers[68] recently have employed this intermediate in the synthesis of chiral α-methylene-γ-butyrolactones 69 (Scheme 26).

SCHEME 26:



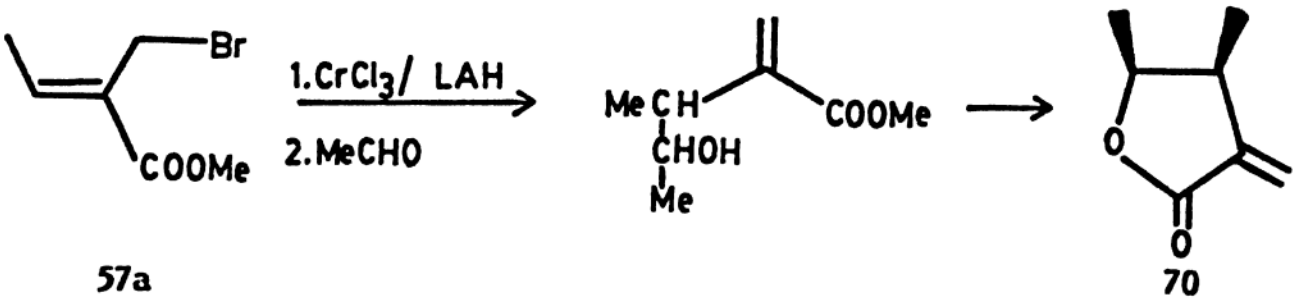
67a

69

R = H, CH_3, n-C_3H_7, i-C_4H_9, C_6H_5

The (Z)-2-bromomethyl-2-alkenoic esters have been well known useful synthetic intermediates for the preparation of α-methylene-γ-butyrolactones. Drewes et al.[69] have demonstrated the utility of the allyl bromide 57a for the preparation of cis-4,5-dihydro-4,5-dimethyl-3-methylene-2-(3H) furanone (70) (Scheme 27).

SCHEME 27:

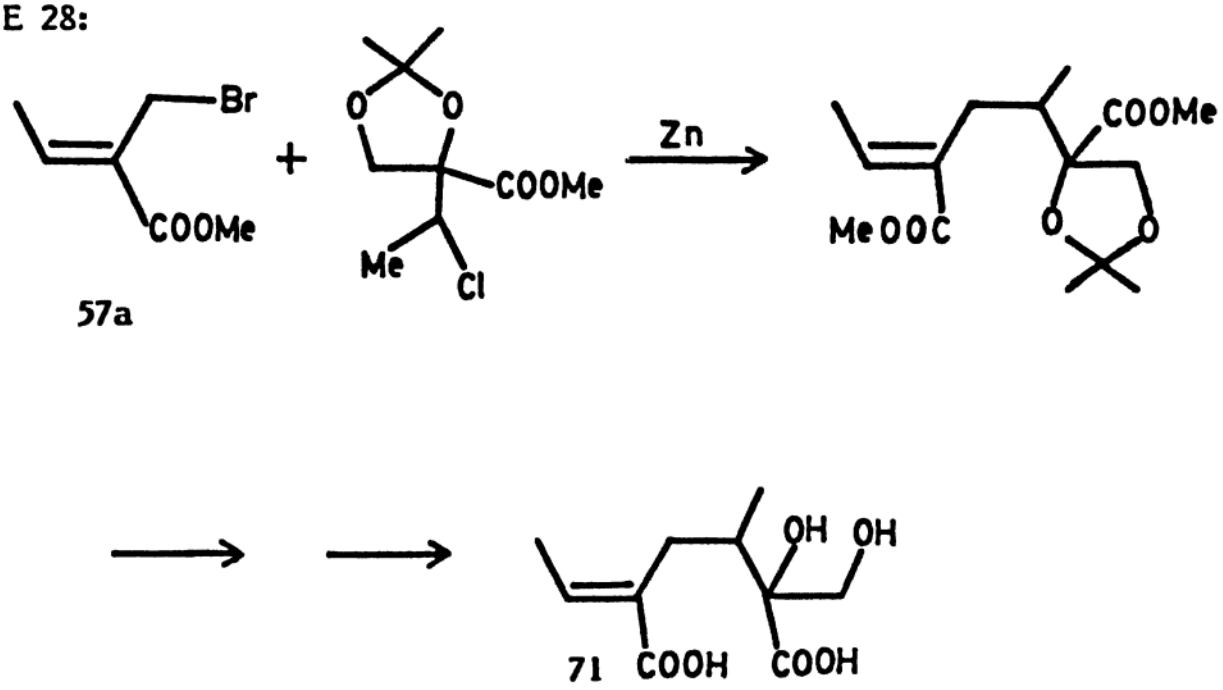


57a

70

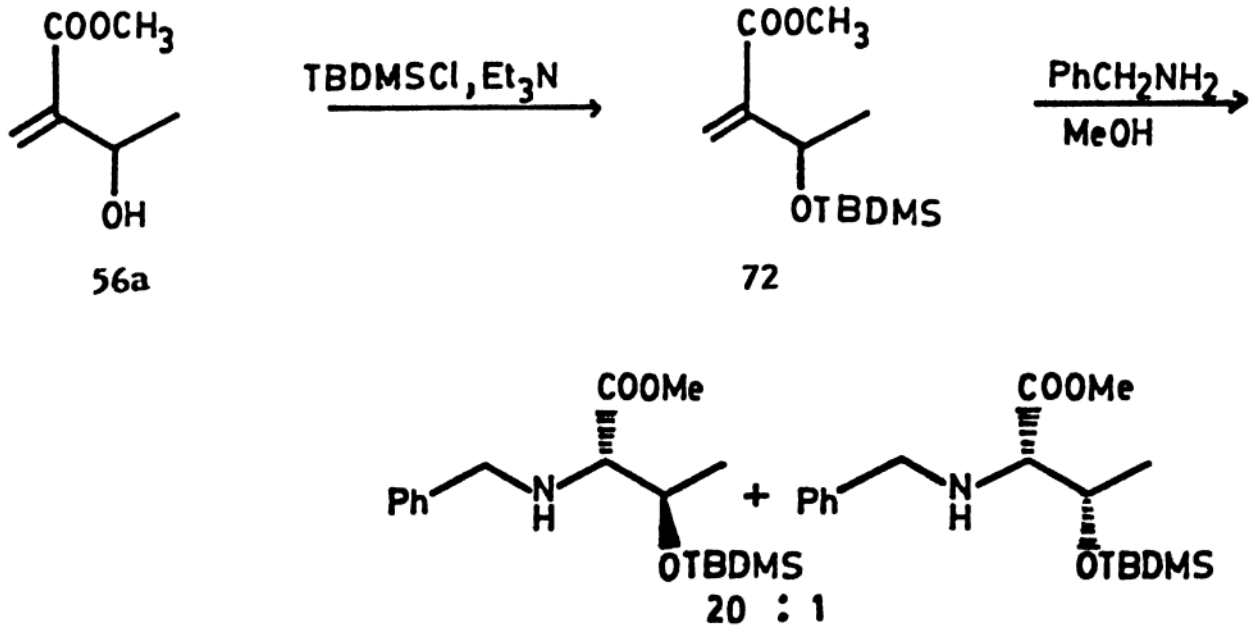
Drewes and co-workers[70] synthesized (Z)-retronecic acid (71) and related compounds via zinc mediated coupling of (Z)-2-bromomethyl-2-alkenoate esters (Scheme 28).

SCHEME 28:

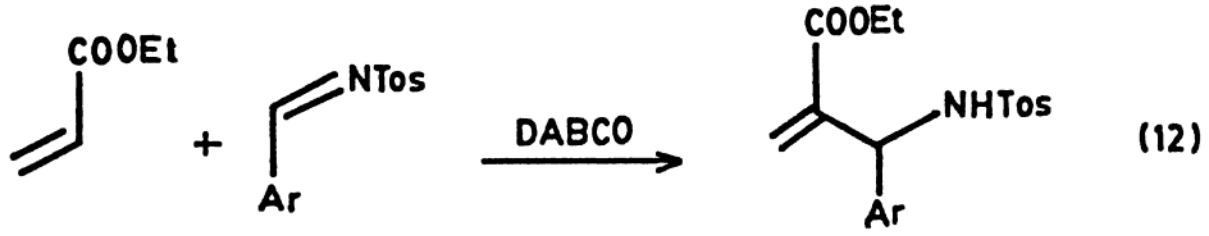


Nucleophilic diastereoselective addition of benzylamine to 2-substituted propenoates 56a was studied by Perlmutter and Tabone.[71] Highest diastereoselectivity (20:1) was observed when benzylamine was added to the corresponding silyl derivative 72 in methanol (Scheme 29).

SCHEME 29:

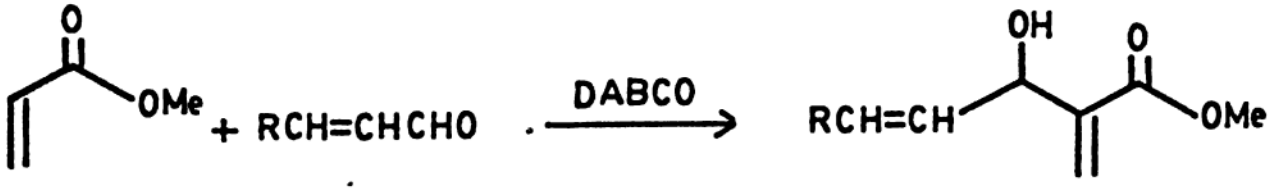


Perlmutter and Teo[72] have extended the same reaction of acrylates with imines in the presence of catalytic amount of DABCO. Tosylamines of aromatic aldehydes readily reacts with ethyl acrylate to produce the corresponding multifunctional molecules which are known to be precursors to β-lactams (eq.12).



(12)

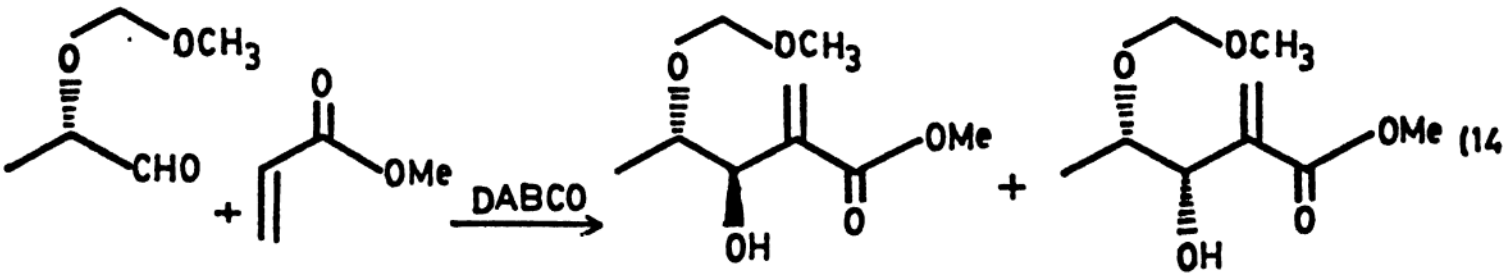
Drewes and Roos[54] have studied the reaction of acrylates with α, β-unsaturated aldehydes and noted that 1,2-addition takes place in all these cases (eq.13).



(13)

R = CH_3, Ph, 2-furyl

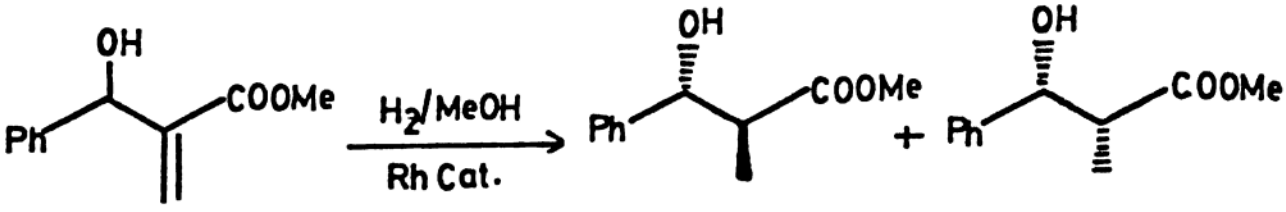
They have also extended the strategy to the chiral aldehydes[73] in order to study diastereoselectivities. Chiral α-alkoxyaldehydes have been employed for their study and reasonable diastereofacial selectivity (anti : syn = 70:30) was observed (eq.14).



(14)

70:30

Stereoselective formation of α-substituted-β-hydroxy esters has been a challenging synthetic effort because of their wide spread applicability in synthesis of natural products. Brown and Cutting[74] have studied the possible applications of 2-(1-hydroxyalkyl)acrylates obtained from Baylis-Hillman reaction, for stereoselective formation of α-substituted-β-hydroxyesters. All rhodium catalyzed hydrogenations of 2-(1-hydroxyalkyl)acrylates have been found to be highly antiselective (eq.15). This provides an equivalent to an anti-selective aldol condensation. Brown and Cutting have also studied the possible kinetic resolution in the asymmetric hydrogenation of 2-(1-hydroxyalkyl)acrylates with dipamp-Rh catalyst.

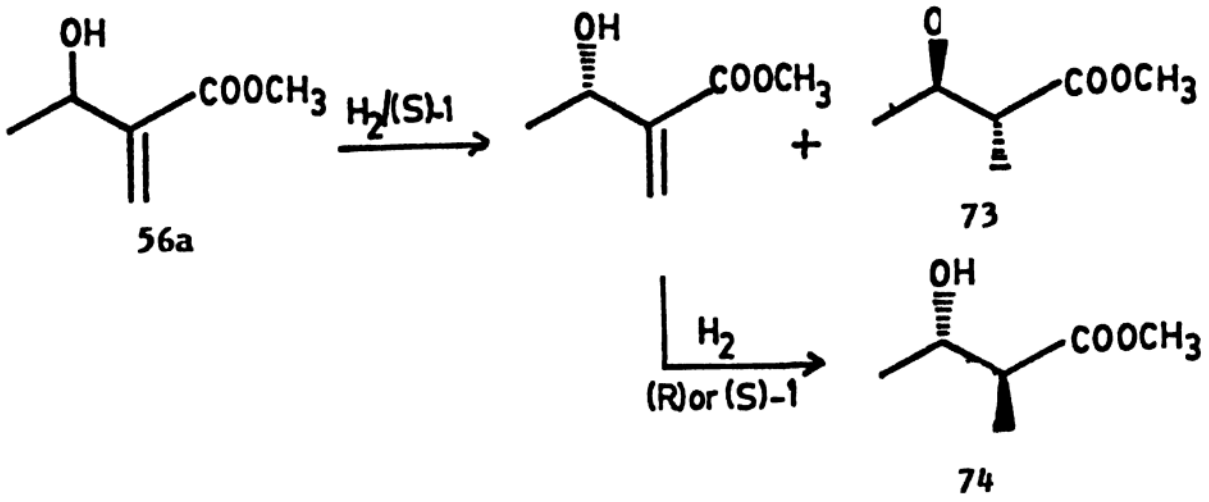


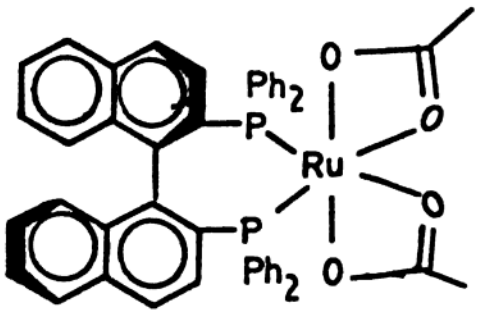
(15)

>99 <1

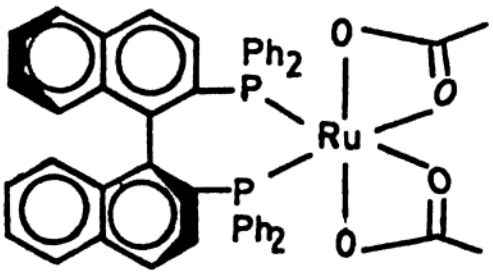
The 2-substituted propenoate **56a** has been successfully converted into optically active α-methyl-β-hydroxyalkanoates **73, 74** via asymmetric hydrogenation[75] (scheme.30)

SCHEME 30:



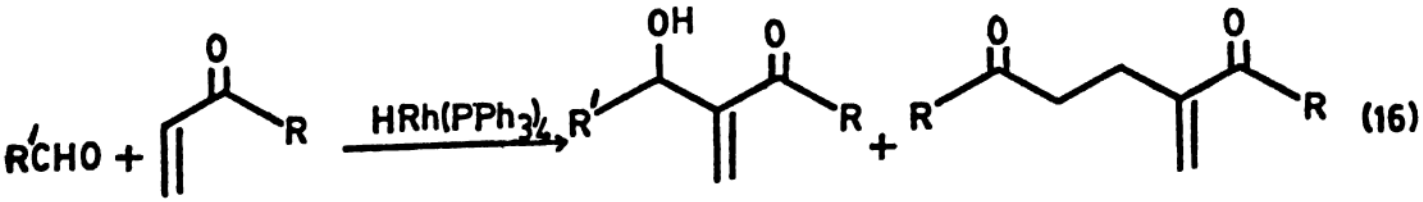


R-1



S-1

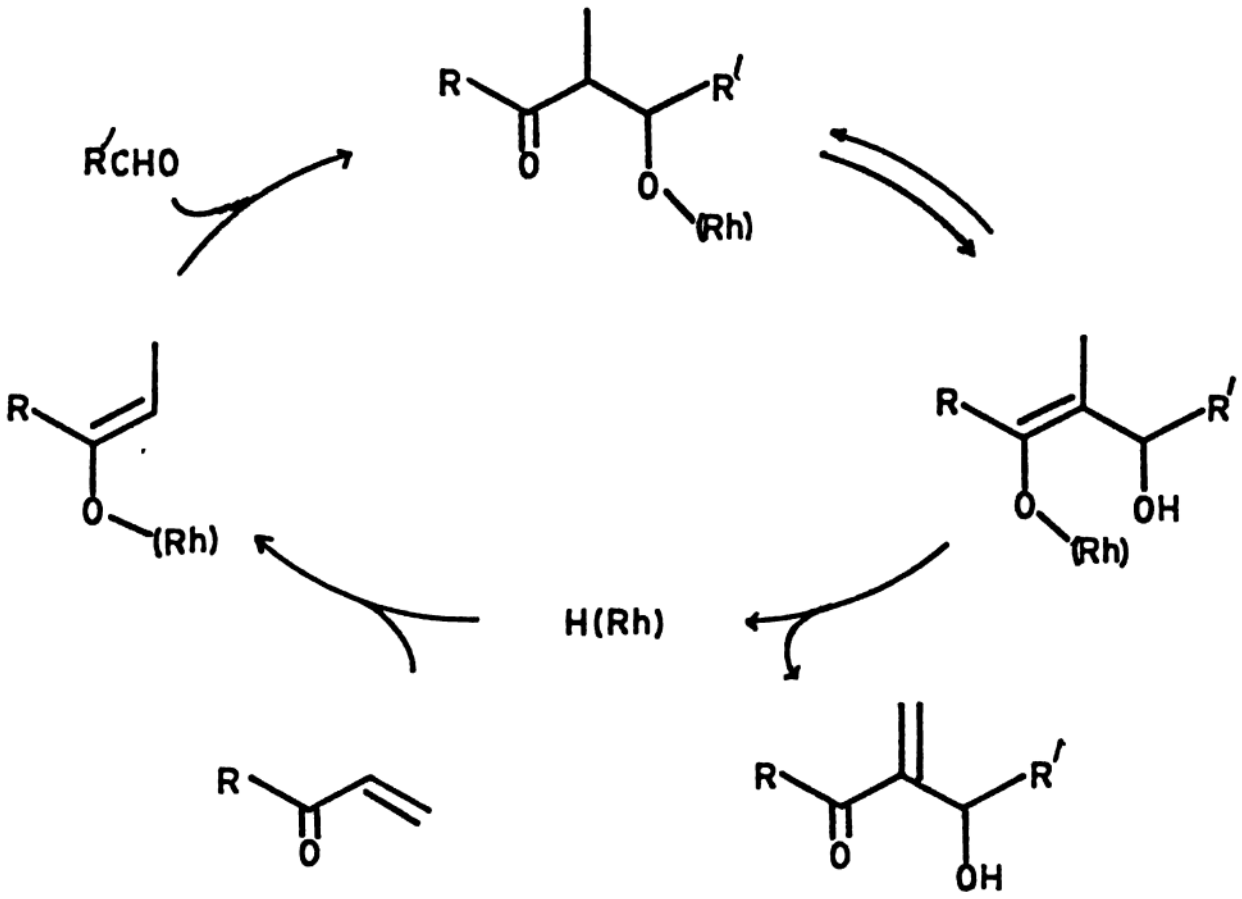
Recently an interesting report appeared from Matsuda's research group[76], for introduction of an electrophile to sp^2-hybridized α-position of α,β-unsaturated ketone catalyzed by Rh(I) hydride complex (eq.16).



(16)

They speculated that the mechanism involves the Michael type addition of catalyst to enone followed by aldol type C-C bond formation. (Scheme 31).

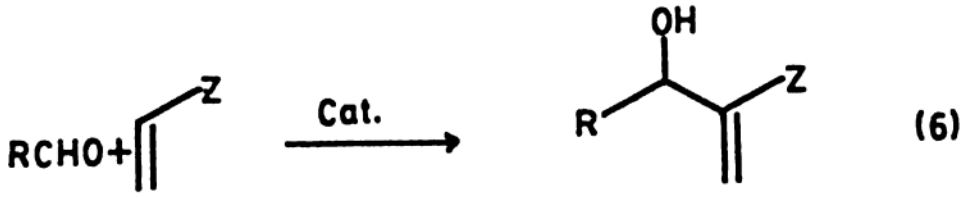
SCHEME 31:



OBJECTIVES, RESULTS AND DISCUSSION

Baylis-Hillman Reaction : Background

Baylis and Hillman, in 1972, in their German patent[52] reported that α, β-unsaturated ketones, esters, nitriles and amides can be coupled with aldehydes under the catalytic influence of tertiary amines to produce the multifunctional molecules (eq.6). Catalysts, used, are 1,4-diazabicyclo(2.2.2) octane (DABCO) (49), pyrrocoline (50) and quinuclidine (51).

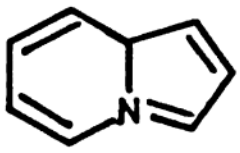


(6)

Z = COOR, COR, CN, $CONR_2$

Though this reaction has the obvious potential of creating carbon-carbon bonds at α-position of activated olefins, very little attention was paid for this reaction for almost ten years.

49



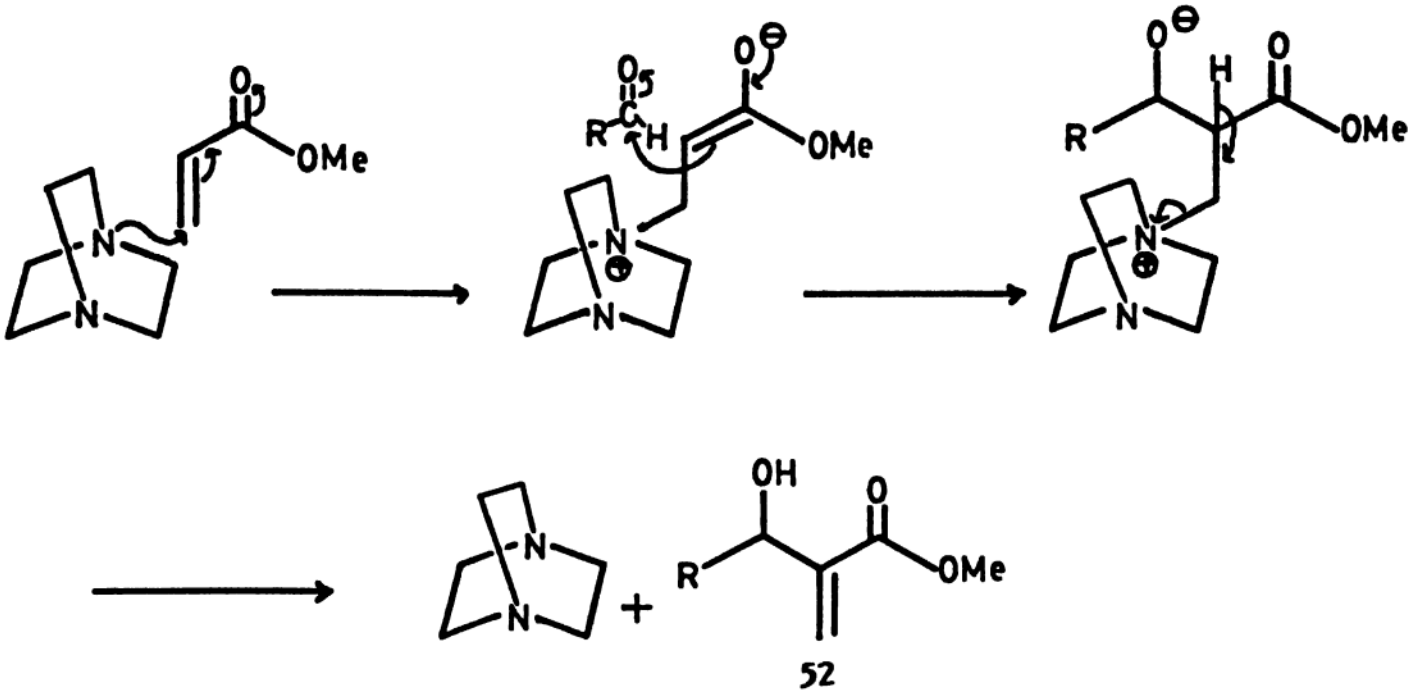
50

51

In 1983, Hoffmann and Rabe[55] reported the coupling of acrylic esters with a variety of aldehydes catalyzed by DABCO and the same reaction has been used for the synthesis of necic acids.[58] It is believed that this reaction

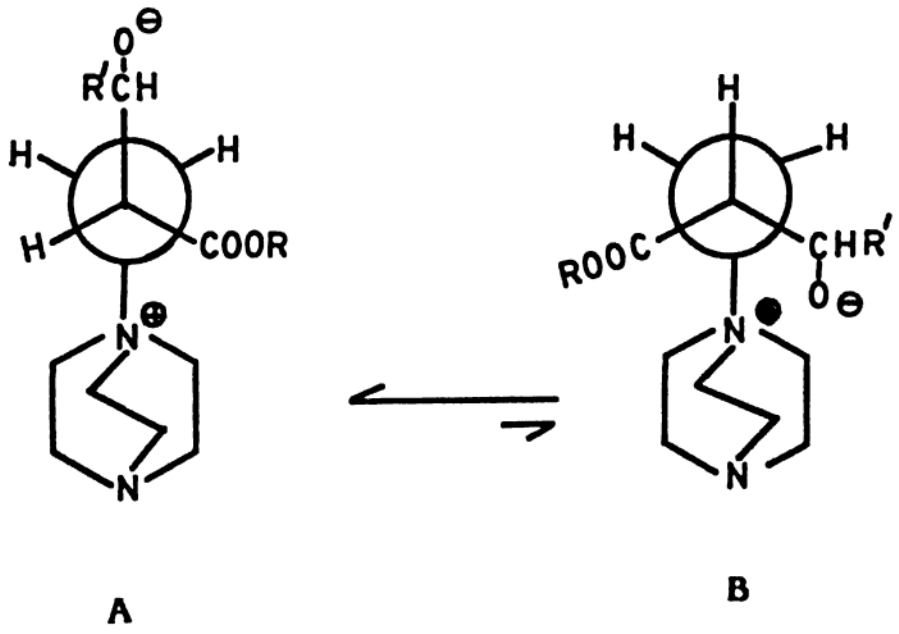
involves a Michael type addition of DABCO to α,β-unsaturated esters, followed by nucleophilic attack on aldehydes and subsequent elimination of DABCO to provide the corresponding 2-substituted acrylates **52** (Scheme 32).

SCHEME 32:



52

Hoffmann and Rabe have also speculated the two possible conformations **A** and **B** for Zwitterionic intermediate.



A **B**

The conformation **A** is favoured due to less unfavourable gauche interactions. However, there is no proof for these mechanistic speculations.

Objectives

With this available information, starting in 1985, we envisioned that Baylis-Hillman reaction will be a powerful synthetic tool for carbon-carbon bond forming reaction at α-position of the activated olefins such as α,β-unsaturated ketones, nitriles, esters, sulfones, etc., thus providing multifunctional molecules for possible use in the synthesis of natural products. Accordingly, we have undertaken a long range research programme with the following main objectives.

(1) To study the generality of Baylis-Hillman reaction for various α, β-unsaturated ketones, nitriles, sulfones, esters and amides for carbon-carbon bond construction.

(2) To study the applicability of various electrophiles such as aldehydes, α-keto esters and other related molecules for Baylis-Hillman C-C bond formation.

Applications to asymmetric synthesis

(3) To study the applicability of various chiral tertiary amines as (chiral) catalysts in the place of DABCO to construct carbon-carbon bond wherein a chiral center is created and to design a suitable catalyst for 100% enantioselective C-C bond formation.

(4) To investigate the applicability of various chiral acrylates for asymmetric C-C bond construction leading to multifunctional molecules and to design proper chiral (auxiliary) acrylate for high diastereoselective C-C bond formation.

(5) Finally, to develop Baylis-Hillman reaction as a useful synthetic tool for construction of C-C bonds at α-position of activated olefins leading to asymmetric synthesis of multifunctional molecules.

Results and Discussion

Coupling of methyl vinyl ketone with aldehydes

With the above mentioned objectives in mind, we first selected the easily and commercially available methyl vinyl ketone for Baylis-Hillman reaction. We have carried out the reaction of methyl vinyl ketone with decyl-aldehyde under neat conditions with 15 mole % of DABCO. We found that the reaction is not clean. The best results were obtained when the reaction was carried out in THF 2M solution (eq.17) though the reaction takes longer

(17)

75a-h

R = alkyl, aryl

time, i.e., 10 days. Thus, the desired product, i.e., 4-hydroxy-3-methylenetri-decan-2-one (**75a**) was obtained in 62% yield as a colorless liquid. The structure of this molecule was confirmed by IR, ^{1}H NMR (Fig.1), ^{13}C NMR (Fig.2) spectral data and elemental analysis.

Representative examples **75 a-h** of α-methylene-β-hydroxy alkanones were prepared from various aldehydes and methyl vinyl ketone (Table 1).

From our results, it appears that the rate of the reaction decreases as the number of carbon atoms increase in the alkyl chain of aliphatic aldehydes. It was also found that propionaldehyde and 2-furaldehyde did not give clean products under these conditions. We have also studied the applicability of various tertiary amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and diisopropylethylamine. DABCO proved to be the best catalyst for its remarkably

Table 1 : Preparation of α-methylene-β-hydroxyalkanones from methyl vinyl ketone and aldehydes catalyzed by DABCO in THF as solvent.[a,b]

R-CHO	Product	Reaction time	b.p. /mm	Yield (%)[c]
$^{n}C_9H_{19}CHO$	75a	10 days	117-120/0.5	62
$^{n}C_7H_{15}CHO$	75b	100 h	119-122/3	63
$^{n}C_6H_{13}CHO$	75c	80 h	80-85/0.5	73
$^{n}C_5H_{11}CHO$	75d	72 h	74-77/0.5	65
$^{i}C_4H_9CHO$	75e	72 h	76-79/1.5	51
C_6H_5CHO	75f	9 days	118-120/1	51
$C_6H_5CH_2CH_2CHO$[d]	75g	85 h	136-138/1.2	65
$^{n}C_{15}H_{31}CHO$[e]	75h	15 days	146-148/0.3	51[c]

a) All reactions were carried out on 20 mM scale in 2 M THF solution.

b) The products are identified spectroscopically by IR, ^{1}H NMR and ^{13}C NMR.

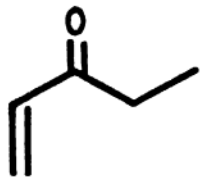
c) Yields of the pure products after purifying by column chromatography followed by distillation.

d) This reaction was carried out on 10 mM scale.

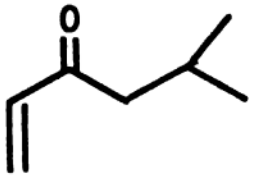
e) Only 70% reaction was complete. Percentage of yield was calculated accordingly.

clean reaction and for better yields of the products. This procedure represents a simple, one-pot synthesis of α-methylene-β-hydroxyalkanones **75.** In this reaction a carbon- carbon bond is constructed at α-position of methyl vinyl ketone thus providing multifunctional molecules.

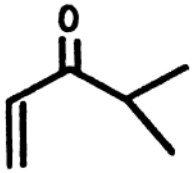
In our laboratory,[77] studies were also carried out towards the applicability of various α, β-unsaturated ketones for Baylis-Hillman reaction in order to generalize the reaction. Three α,β-unsaturated ketones of varying steric requirements, i.e., ethyl vinyl ketone (**76**), 5- methylhex-1-en-3-one (**77**) and 4-methylpent-1-en-3-one (**78**) were selected. The Baylis-Hillman coupling of



76

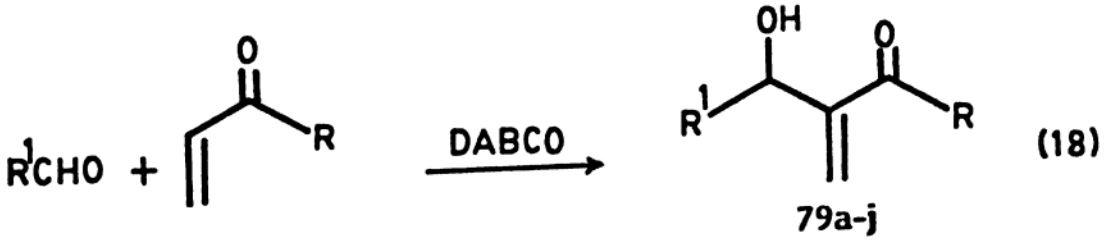


77



78

these alkenones **76-78** was carried out with variety of aldehydes (eq.18) to produce the multifunctional molecules **79a-j** in 20-60% yields.



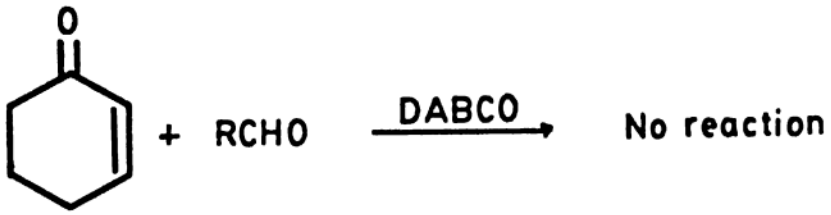
(18)

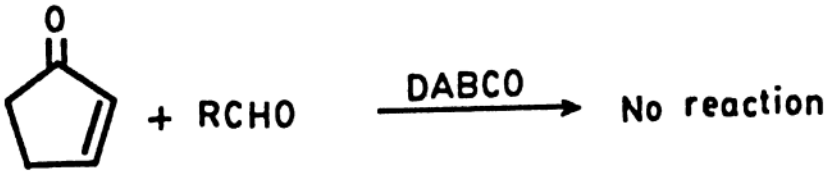
79a-j

R = C_2H_5	R' = C_2H_5	(79a)	R = i-C_4H_9	R' = n-C_3H_7	(79f)
R = C_2H_5	R' = n-C_3H_7	(79b)	R = i-C_4H_9	R' = i-C_3H_7	(79g)
R = C_2H_5	R' = i-C_3H_7	(79c)	R = i-C_3H_7	R' = C_2H_5	(79h)
R = C_2H_5	R' = C_6H_5	(79d)	R = i-C_3H_7	R' = n-C_3H_7	(79i)
R = i-C_4H_9	R' = C_2H_5	(79e)	R = i-C_3H_7	R' = i-C_3H_7	(79j)

The results from these studies indicate that the rate of reaction decreases as the steric bulk of alkyl vinyl ketone increases, also the yields of the products fall down considerably.

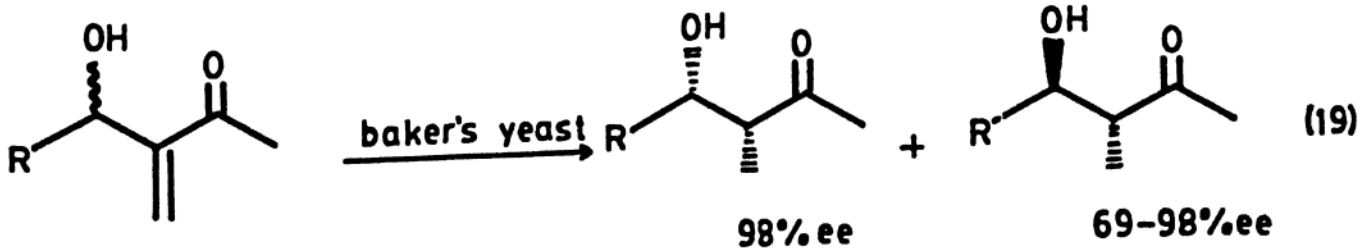
Attempted coupling reactions of cyclic enones such as 2-cyclohexen -1-one, 2-cyclopenten-1-one with various aldehydes (benzaldehyde, 2-furaldehyde, propionaldehyde) under variety of experimental conditions, even with excess of DABCO were unsuccessful.





Synthetic applications of α-methylene-β-hydroxyalkanones

The multifunctional molecules prepared by us as in (eq.17) have already found applications in synthetic organic chemistry. Utaka and co-workers[78] successfully prepared chiral 4-hydroxy-3-methylalkan-2- ones (syn : anti = 1:1-2) via asymmetric reduction of 4-hydroxy-3-methylene-2-alkanones (eq.19).

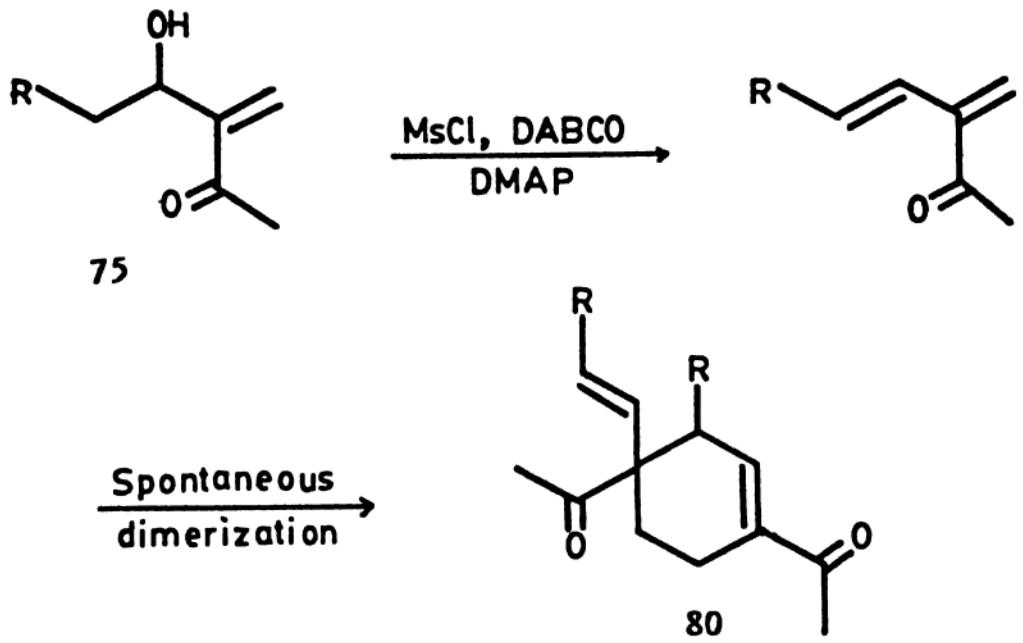


(19)

R = alkyl

Hoffmann et al.[79] have applied the 4-hydroxy-3-methylenealkan-2-ones *75* for the preparation of functionalized 1,4-diacetylcyclohexenes **80** (Scheme 33).

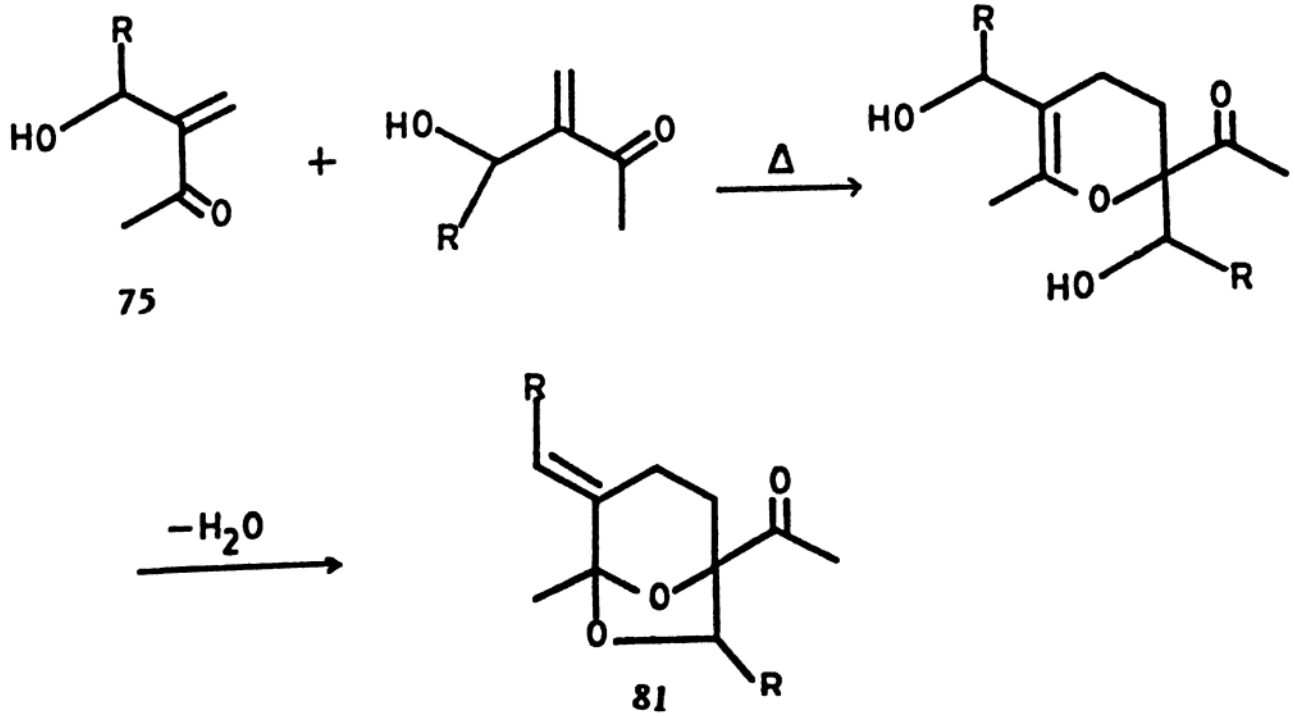
SCHEME 33:



R = alkyl

Hoffmann and co-workers[80] have also used 4-hydroxy-3-methylene-alkan-2-ones *75* for the preparation of functionalized 6,8-dioxabicyclo(3.2.1)

SCHEME 34:

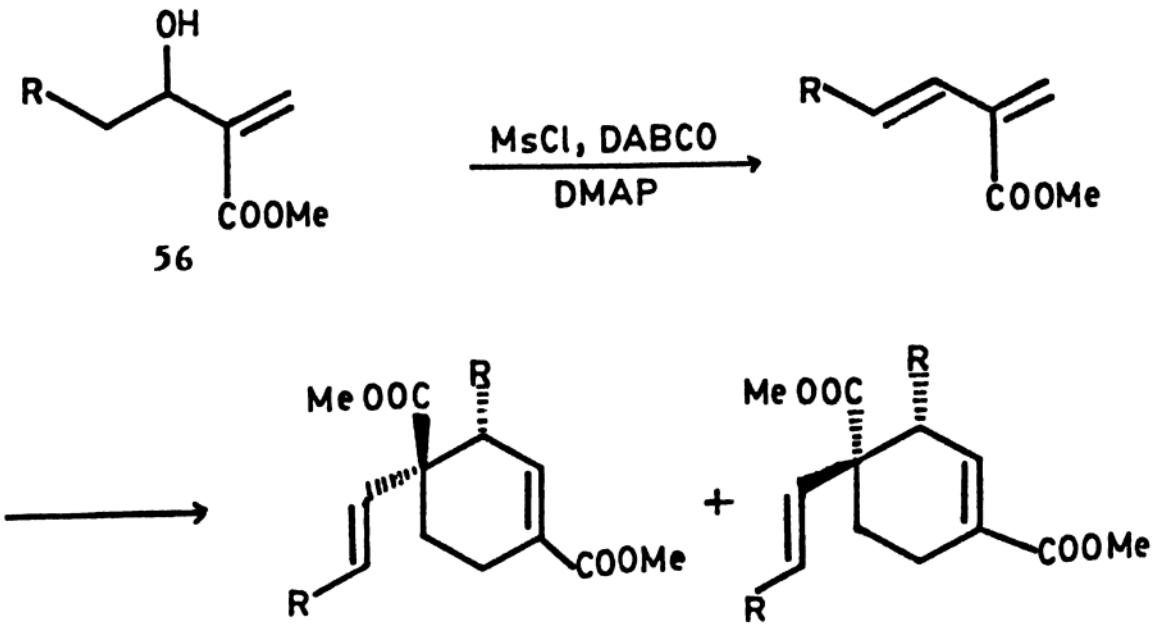


R = alkyl

octanes **81** (Scheme 34), which constitute the basic frame work of number of pheromones such as frontalin, brevicomin and α-multistriatin.

More recently Hoffmann and co-workers[81] described that the dehydration of 3-hydroxy-2-methylenealkanoic esters **56** generates (E)-2-methylene -3-alkenoic acid esters which dimerize spontaneously to give 4-[(E)-1-alkenyl] -3-alkyl-1-cyclohexene-1,4-dicarboxylic acid esters (Scheme 35).

SCHEME 35:

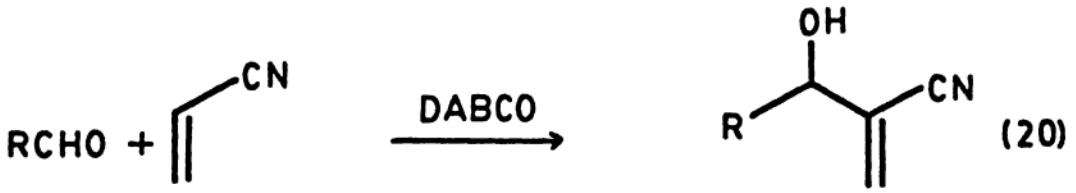


R = alkyl, phenyl

Synthesis of 2-(1-hydroxyalkyl)acrylonitriles

After achieving success in the utilization of α,β-unsaturated ketones for Baylis-Hillman carbon-carbon bond forming reaction, our attention was directed towards the utilization of acrylonitrile, abundantly available α,β-unsaturated nitrile, for Baylis-Hillman reaction. Accordingly, we examined the reaction of acrylonitrile with propionaldehyde under neat conditions using 15 mole % of DABCO. The reaction was clean and complete in 40h providing 2-cyano-pent-1-en-3-ol (**47a**) in 80% yield as a colorless liquid (eq.20). The structure

of this product was confirmed by IR, ^{1}H NMR (Fig.3), ^{13}C NMR (Fig.4) spectral data and elemental analysis. We also tried the applicability of other tertiary amine catalysts such as 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) and diisopropyl-ethylamine under various experimental conditions. It was found that DABCO offers much cleaner reaction than the other two amines and yields are also superior.



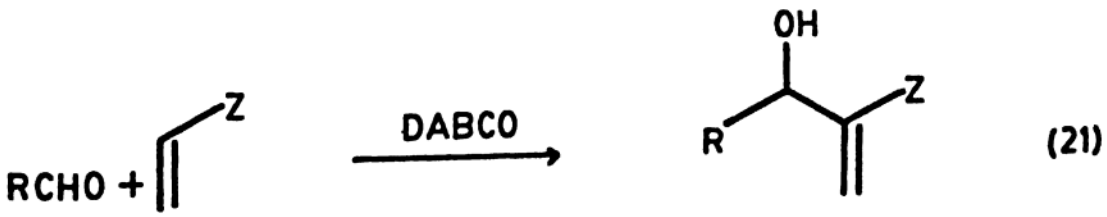
(20)

47a-g

R = alkyl, aryl

Representative examples of 2-(1-hydroxyalkyl)acrylonitriles 47a-g (eq.20) were prepared from various aldehydes and acrylonitrile catalyzed by DABCO (15 mole %) (Table 2).

Here also it was observed that the rate of the reaction decreases as the number of carbon atoms increase in the alkyl chain of aldehydes, consistent with our earlier observation in the case of methyl vinyl ketone. About the same time, Amri and Villieras[82] have also reported similar work on Baylis-Hillman coupling of methyl vinyl ketone, acrylonitrile and methyl acrylate with aldehydes (eq.21).



(21)

R = alkyl, aryl

Z = CN, COOMe, COMe

Table 2 : Preparation of 2-(1-hydroxyalkyl)acrylonitriles from acrylonitrile and aldehydes catalyzed by DABCO.[a,b]

RCHO	Product[c]	Time	b.p./mm[d]	Yield (%)[e]
CH_3CH_2CHO	**47a**	40 h	64-65/1	80[f]
$(CH_3)_2CHCHO$	**47b**	40 h	70-71/1	66[f]
$(CH_3)_2CHCH_2CHO$	**47c**	40 h	76/0.8	69[f]
$CH_3(CH_2)_4CHO$	**47d**	3 days	88-90/1	87[g]
$CH_3(CH_2)_8CHO$	**47e**	7 days	130-132/0.5 (120/0.15)[51]	84[g]
C_6H_5CHO	**47f**	40 h	120-124/2 (110/0.95)[51]	70[f]
$C_6H_5CH_2CH_2CHO$	**47g**	50 h	130/1	76[f]

a) All reactions were carried out on 10 mM scale.

b) All products were identified spectroscopically by IR, ^1H NMR and ^{13}C NMR.

c) The products **47a** and **47f** are 100% pure and the rest are 97% pure by GC analysis on a SE-30 column.

d) Literature values are given in parenthesis.

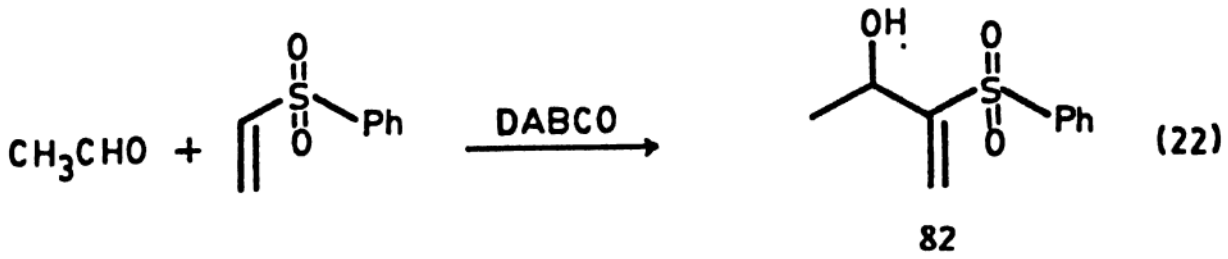
e) Yields of the pure distilled products.

f) Reaction was carried out with 15 mole per cent of DABCO.

g) Reaction was carried out with 30 mole per cent of DABCO.

Synthesis of 3-hydroxy-2-(phenylsulfonyl)-1-butene : Use of phenyl vinyl sulfone

We next examined the possible application of phenyl vinyl sulfone for Baylis-Hillman carbon-carbon bond forming reaction. First, we carried out the reaction of acetaldehyde with phenyl vinyl sulfone using 15 mole % of DABCO. The reaction is very slow taking 20 days for completion to provide the desired 3-hydroxy-2-(phenylsulfonyl)-1-butene (**82**) in 80% yield (eq.22). The structure of the compound **82** was in full agreement with spectral data IR, ^{1}H NMR (Fig.5) and ^{13}C NMR (Fig.6) and elemental analysis.

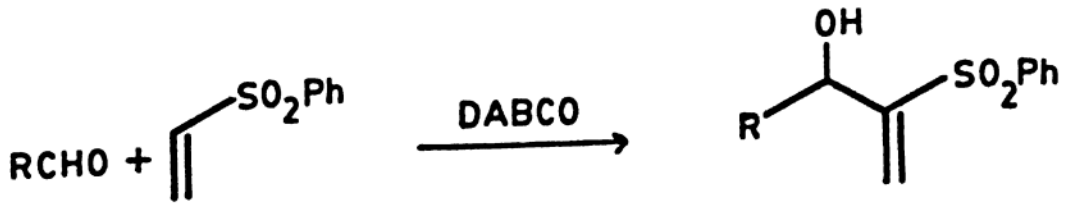


(22)

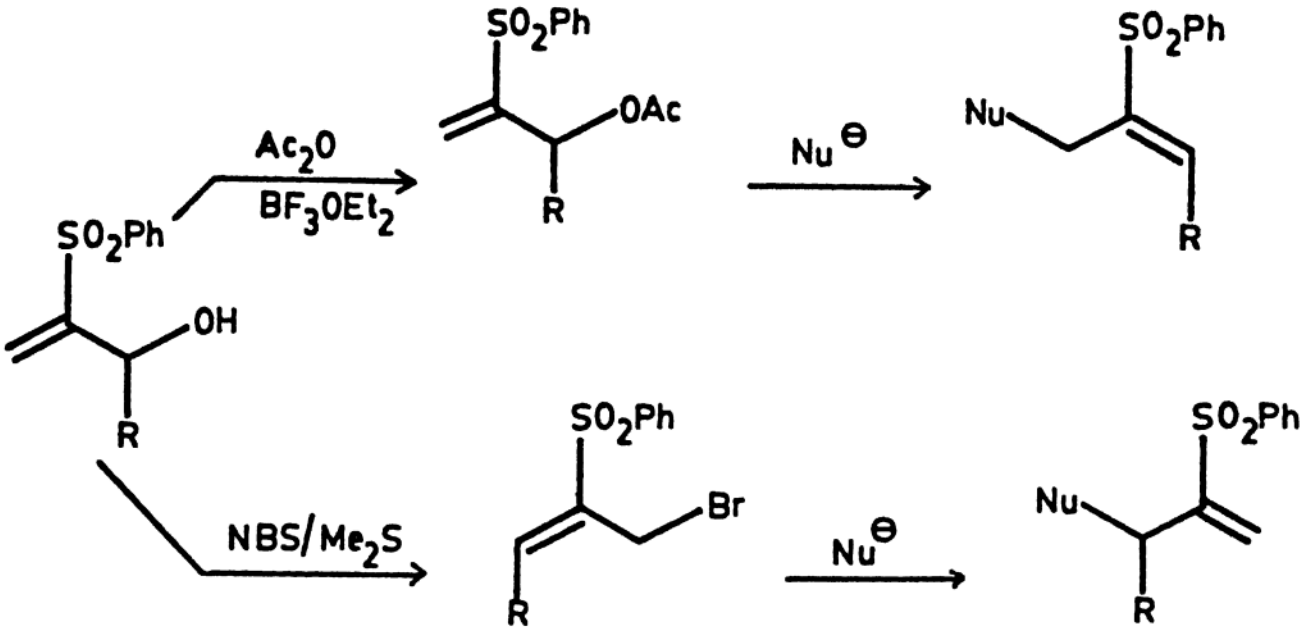
82

While our work on phenyl vinyl sulfone was in progress, two interesting papers from the research group of Normant[83] appeared, describing the preparation and application of 3-alkyl-3-hydroxy-2-(phenylsulfonyl)propenes (Scheme 36). Therefore, we did not proceed with our work further on phenyl vinyl sulfone.

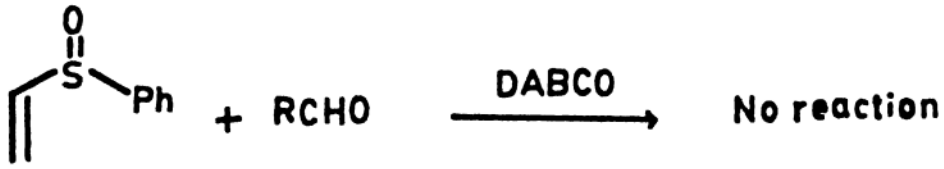
SCHEME 36:



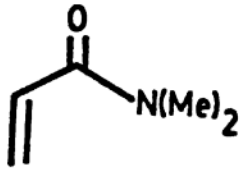
R = alkyl, phenyl



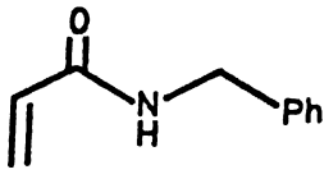
Our attempts in exploring the possibility of phenyl vinyl sulfoxide as a substrate for Baylis-Hillman reaction were unsuccessful.



We also tried the possibility of applying acrylamides **83, 84** for Baylis-Hillman carbon-carbon bond forming reaction. All our attempts at different conditions using different aldehydes met with failure.



83

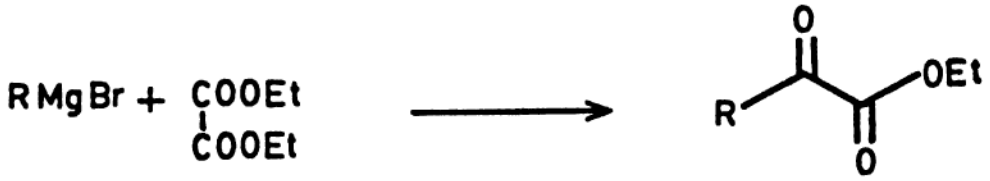


84

α-Keto esters in Baylis-Hillman Reaction

Till now we have only utilized aldehydes as possible substrates for Baylis-Hillman carbon-carbon bond forming reactions leading to multifunctional

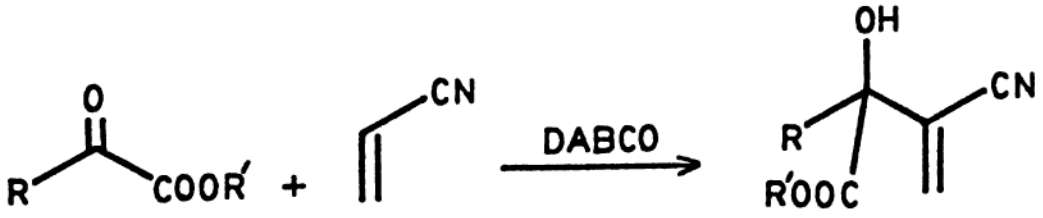
molecules. It occured to us that α-keto esters might also couple with activated olefins to provide the multifunctional molecules. Accordingly, we have selected four α-keto esters, i.e., ethyl phenylglyoxylate (85). ethyl p-tolylglyoxylate (86), ethyl pyruvate and methyl pyruvate. Ethyl phenylglyoxylate (85) and ethyl p-tolylglyoxylate (86) were prepared according to the literature method (eq.23).[84]



85,86 (23)

R = C_6H_5, p-Tolyl

The reaction of acrylonitrile and ethyl phenylglyoxylate (85) was carried out with DABCO as catalyst. The best results were obtained when the reaction was carried out under neat conditions using ethyl phenylglyoxylate and acrylonitrile in the ratio 1:2 with 30 mole % of DABCO at room temperature (eq. 24) providing ethyl 3-cyano-2-hydroxy-2-phenylbut-3-enoate (87a) in 65% yield as a colorless oil. The structure of the molecule was confirmed by spectral data IR, ^{1}H NMR (Fig.7), ^{13}C NMR (Fig.8) and elemental analysis.



87a-d (24)

R = CH_3, C_6H_5, p-Tolyl; R' = CH_3, C_2H_5

A representative group of multifunctional molecules 87a-d, 88a,b was prepared via the coupling of α-keto esters with acrylonitrile (eq.24) and methyl acrylate (eq.25) (Table 3).

Table 3 : Preparation of 2-[1-carboalkoxy-1-hydroxyalkyl]acrylonitriles (from α-keto esters and acrylonitrile) and 2-[1-carboalkoxy-1-hydroxyalkyl] acrylates (from α-keto esters and methyl acrylate).[a,b]

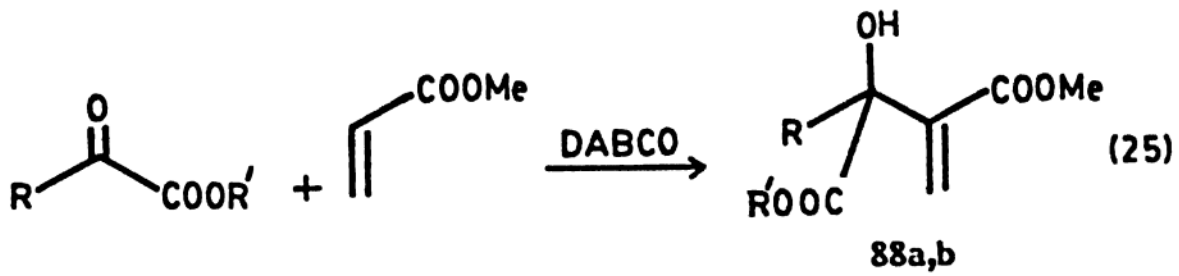
$R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}OR'$	R'' / $R'=$	Product	Reaction Time	b.p./mm or m.p.	Yield(%)[c]
$R' = -C_2H_5$					
R = -phenyl	CN	87a	5 days	164-166/4	65
R = -p-tolyl	CN	87b	7 days	162-164/1	74
$R = CH_3$					
$R' = -CH_3$	CN	87c[d]	24 h	98-100/5	38
$R' = -C_2H_5$	CN	87d[d]	24 h	84-86/2	41
$R' = -C_2H_5$					
R = -phenyl	$COOCH_3$	88a	7 days	154-155/1.5 (m.p. 54-56)	49
R = -p-tolyl	$COOCH_3$	88b	9 days	m.p. 87-89	41

a) All reactions were carried out on 10 mM scale (α-keto esters) using 30 mole % DABCO at room temperature.

b) All products were identified spectroscopically by IR, ^1H NMR and ^{13}C NMR.

c) Yields of the compounds purified by column chromatography followed by distillation or crystallization.

d) The reaction of acrylonitrile (20 mM) with these pyruvates (10 mM) is not clean. Therefore, pyruvates (10 mM) were added slowly to acrylonitrile (100 mM) containing DABCO (1.5 mM).



(25)

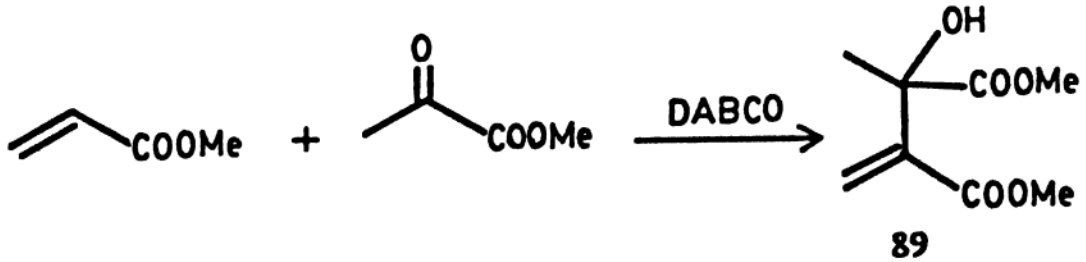
88a,b

R = C_6H_5, p-Tolyl; R' = C_2H_5

The reaction of acrylonitrile (20 mM) and methyl pyruvate (10 mM) with 30 mole % DABCO as catalyst did not give clean reaction. However, best results were obtained when pyruvate (10 mM) was added slowly to acrylonitrile (100 mM) containing DABCO (1.5 mM). The desired methyl 3-cyano-2-hydroxy-2-methylbut-3-enoate (**87c**) was obtained in 38% yield. A similar reaction of ethyl pyruvate provided **87d** in 41% yield. This methodology represents a simple synthesis of 2-(1-carboalkoxy-1-hydroxyalkyl)acrylonitriles and acrylates.

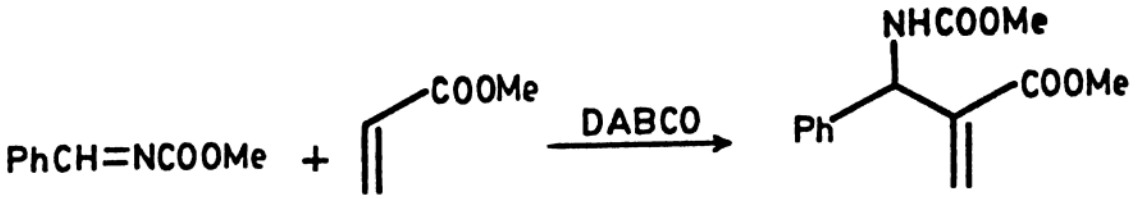
An interesting paper[85] appeared from Hoffmann's research group recently. They have reported that the reaction of methyl acrylate with methyl pyruvate under the catalytic influence of DABCO provides dimethyl 3-hydroxy-3-methyl-2-methylenesuccinate (**89**) which was further converted into dimethyl 2,3-dimethylenebutanedioate (**90**), an important diene for Diels-Alder reaction (Scheme 37).

SCHEME 37:



89

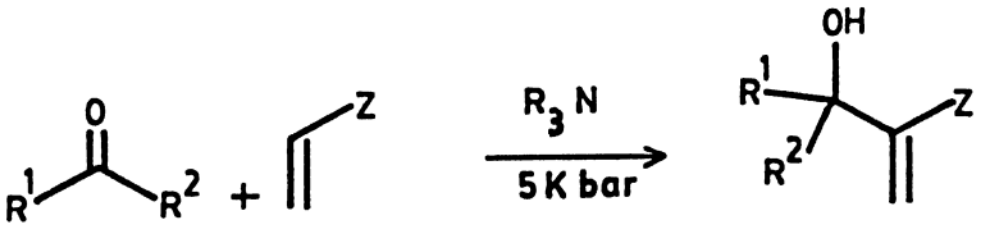
In 1988, Yamamoto and co-workers[86] have reported that DABCO also catalyzes the coupling of methyl acrylate with benzylidenecarbamates (eq.26). They also found that these reactions are much faster than that with common aldehydes. This reaction is complete overnight at room temperature. The resulting methyl 2-(α-methoxycarbonylamino)benzylacrylates are important synthons.



(26)

Diethyl ketomalonate: Fast reacting substrate for Baylis-Hillman Reaction

Now, it has been well documented that DABCO catalyzes the coupling of α,β-unsaturated esters, nitriles and ketones with aldehydes and α-keto esters to provide the corresponding multifunctional molecules. All these are generally slow reactions (4-7 days or even longer). Rate acceleration of these molecules at high pressure has been demonstrated by Hill and Isaacs[87,88] (eq.27). They



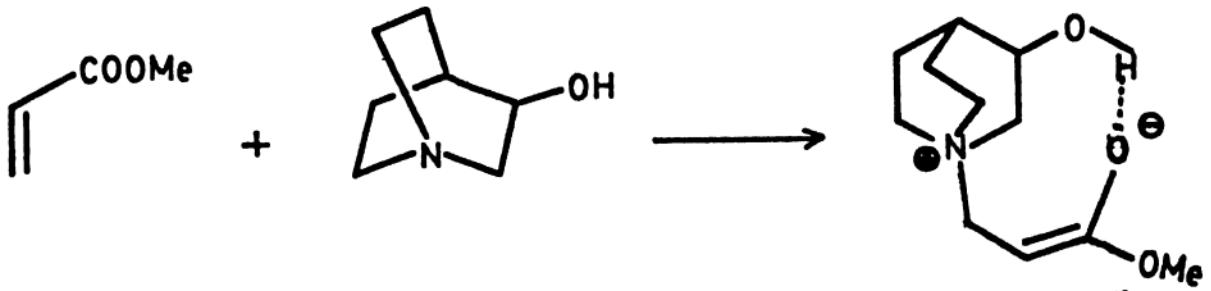
(27)

R^1 = H, CH_3, C_6H_5, etc.; R^2 = H, CH_3, C_2H_5

Z = CN, COOMe, COMe, $CONH_2$; R_3N = DABCO, $N(C_2H_5)_3$

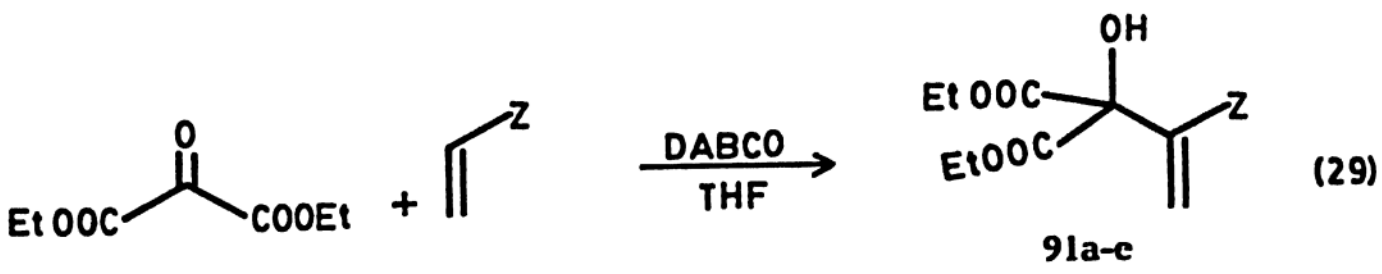
have also reported that ketones will also add to these activated olefins at high pressure to provide the corresponding 2-propen-1-ols. Even triethylamine catalyzes the coupling of acrolein with aldehydes at high pressure.

Drewes & co-workers[89] found that 3-hydroxyquinuclidine increases the rate via hydrogen bonding (eq.28). When they used 3-acetoxyquinuclidine the reaction takes longer time indicating the involvement of hydrogen bonding for faster reaction.



(28)

We are interested in finding a suitable substrate which can react faster with these activated α, β-unsaturated systems. We found that diethyl ketomalonate reacts faster with methyl acrylate (eq.29). The reaction is complete in 4h even in one molar THF solution with 10 mole % of DABCO to provide ethyl 2-carboethoxy-3-carbomethoxy-2-hydroxybut-3-enoate (91a) in 77% yield. The structure of this molecule was confirmed by elemental analysis and spectral data IR, ^{1}H NMR (Fig.9) and ^{13}C NMR (Fig.10). A similar reaction of methyl acrylate with aldehydes normally takes longer time (18h-7 days) under neat conditions. Diethyl ketomalonate reacts with methyl vinyl ketone in 30 minutes in one molar THF solution even with 5 mole % of DABCO at room temperature.



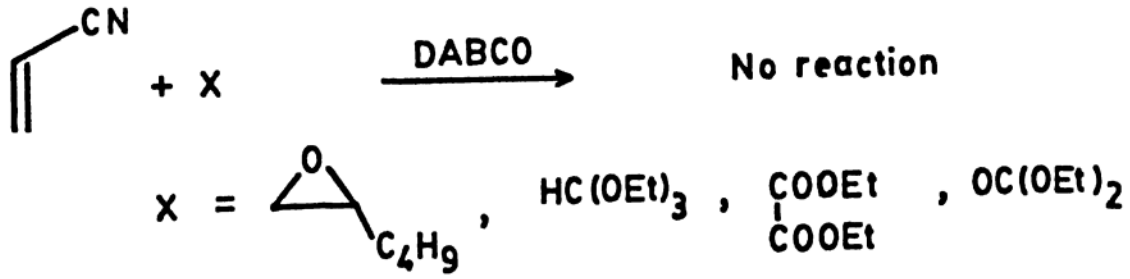
(29)

Z = COOMe, COOEt, COOt-Bu, CN, COMe

We have also carried out the reactions with acrylonitrile, ethyl acrylate, t-butyl acrylate and found that all these reactions are faster, providing the desired multifunctional molecules in high yields (Table 4).

Attempted Reactions : (i) with other Electrophiles

After successful utilization of aldehydes and α-keto esters for Baylis-Hillman reaction we tried the possibilities of applying other electrophiles such as triethyl formate, 1-hexene oxide, diethyl carbonate, diethyl oxalate at various experimental conditions. But all these reactions were unsuccessful.



ii) with substituted acrylates

All attempted coupling experiments of methyl crotonate and methyl methacrylate with various aldehydes failed.

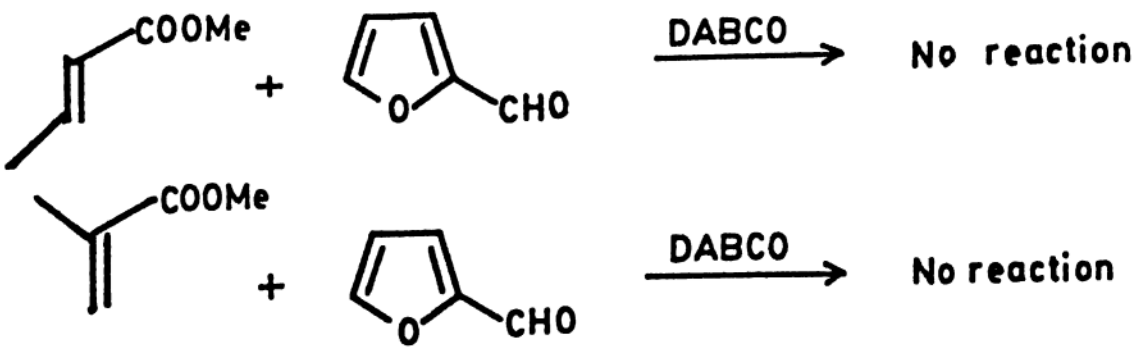
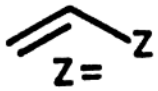


Table 4 : Reaction products of diethyl ketomalonate with activated Vinylic compounds.[a,b,c]

	Product	Time	Yield[d]
COOMe	**91a**	4 h	77[e]
COOEt	**91b**	6 h	73[e]
COOt.Bu	**91c**	36 h	67[e]
CN	**91d**	3 h	80[e]
COMe	**91e**	0.5 h	74[f]

a) All the reactions were carried out on 5 mM scale.

b) All products were identified spectroscopically by IR, ^{1}H NMR and ^{13}C NMR.

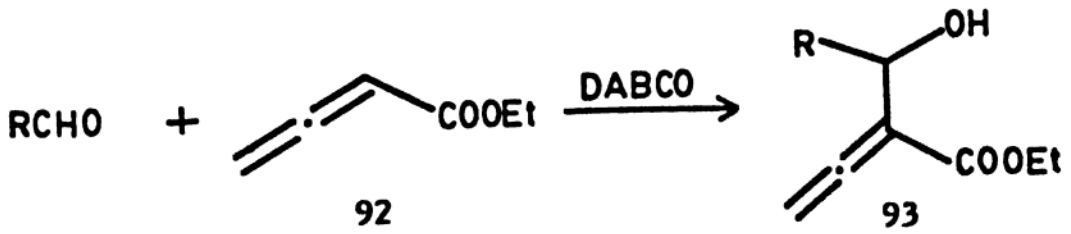
c) Reactions were carried out in 1M THF solution.

d) Yields of the column purified products. All these are obtained as colorless liquids.

e) Reaction was carried out with 10 mole % of DABCO.

f) Reaction was carried out with 5 mole % of DABCO.

More recently Tsuboi et al.[90] described that reaction of ethyl 2,3-butadienoate (92) with aldehydes in the presence of 14 mole % of DABCO gave 2-(1-hydroxyalkyl)-2,3-butadienoates 93 (eq.30) in 40-50% yield.



92 93 (30)

$R = C_2H_5, C_6H_{13}$

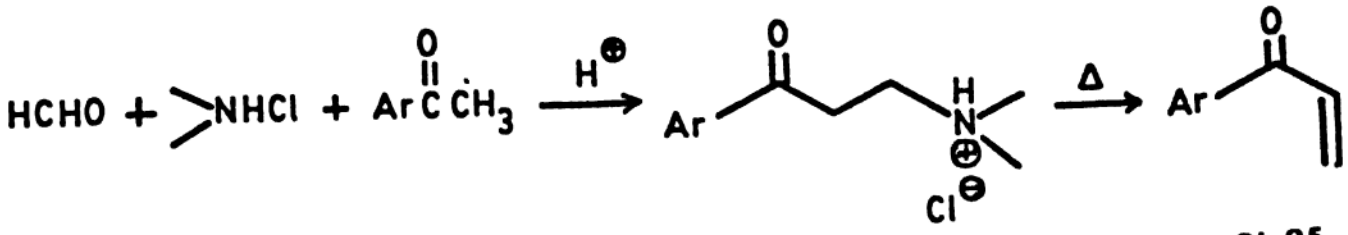
This success of allenic esters and the failure of methyl crotonate, methyl methacrylate, 2-cyclohexen-1-one, 2-cyclopenten-1-one for Baylis-Hillman carbon-carbon bond forming reactions with aldehydes, will certainly throw some light on the mechanism of the reaction as speculated by Hoffmann and Rabe (Scheme 32). However, more study is necessary to have a clear idea on the mechanism of this reaction.

Michael type DABCO catalyzed dimerization of α,β-unsaturated ketones and nitriles

We have so far described the coupling reaction of activated α,β-unsaturated systems with electrophiles such as aldehydes and α-keto esters under the catalytic influence of DABCO. The speculated mechanism of this reaction is believed to involve the conjugate addition of DABCO to α,β-unsaturated system followed by the coupling reaction with aldehydes, with subsequent elimination of DABCO thus providing multifunctional molecules (Scheme 32). It appeared to us that if the same reaction is carried out without aldehydes or α-keto esters, α,β-unsaturated ketones or nitriles would dimerize in the

presence of DABCO. Accordingly, the required phenyl vinyl ketone (94) and p-tolyl vinyl ketone (95) were prepared according to the known method[91] (Scheme 38).

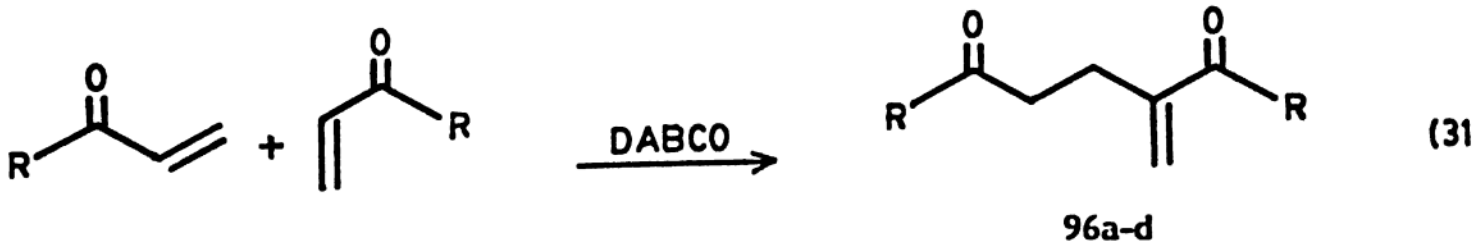
SCHEME 38:



94,95

Ar = C_6H_5, p-Tolyl

We first carried out the dimerization of p-tolyl vinyl ketone (95) in the presence of 15 mole % of DABCO. The dimerization is indeed complete at room temperature (35°C) in one hour (eq. 31) providing the Michael type product, 1,5-di(p-tolyl)-2-methylene-1,5-pentanedione (96a)as a crystalline solid with m.p. 89-90°C. The structure of this molecule has been confirmed by elemental analysis, mass spectrum (M/S m/e : 292 M^+) and spectral data IR, ^1H NMR (Fig.11) and ^{13}C NMR (Fig.12).



96a-d (31

R = p-Tolyl, C_6H_5, C_2H_5, CH_3

Representative examples 96a-d of dimeric products have been prepared (Table 5) from phenyl vinyl ketone, ethyl vinyl ketone, methyl vinyl ketone. We have also successfully carried out the dimerization of acrylonitrile with 50 mole % of DABCO providing 2,4-dicyanobut-1-ene (97) (eq.32) in 40%

Table 5 : Dimerization of α,β-unsaturated ketones and nitriles catalyzed by DABCO.[a,b]

α,β-unsaturated ketone/nitrile	Product	Time	b.p./mm or m.p.	Yield (%)[c]
p-tolyl vinyl ketone	**96a**	1 h	m.p. 89-90	49
phenyl vinyl ketone	**96b**	0.25 h	200/2	62[d]
ethyl vinyl ketone	**96c**	40 h	94-96/1	60
methyl vinyl ketone[e]	**96d**	4 days	98-100/6	59
acrylonitrile[f]	**97**	10 days	96-98/4	40

a) All reactions were carried on 15 mM scale using DABCO (15 mole %) at room temperature (35°C).

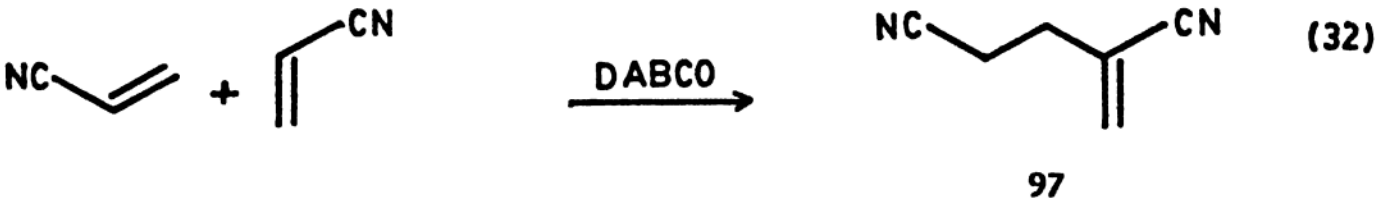
b) All products were identified spectroscopically by IR, ^{1}H NMR and ^{13}C NMR.

c) Yields of pure distilled or crystallized products.

d) Yield of the column purified compound. Distillation gives lower yields.

e) Reaction under neat conditions is not clean. Therefore, this reaction was carried out in 5 M THF solution.

f) This reaction was carried out with 50 mole % of DABCO.

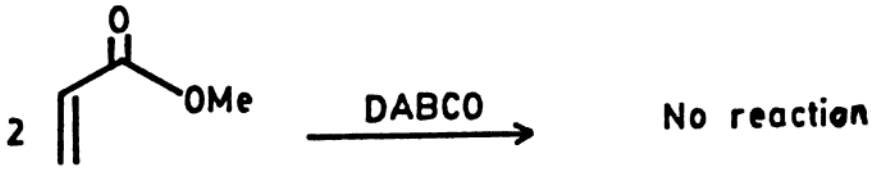


(32)

97

yield. The structure of this molecule **97** was in full agreement with spectral data, i.e.,IR, ^{1}H NMR (Fig.13), ^{13}C NMR (Fig.14) and elemental analysis.

Thus, this procedure represents a simple method for dimerization of α,β-unsaturated ketones and nitriles producing multifunctional molecules which otherwise would be difficult to make. Our attempts to dimerize methyl acrylate at various conditions were not successful.



We have till now discussed our work on the preparation of racemic Baylis-Hillman products. Our studies on asymmetric C-C bond formation are described in the following.

Asymmetric Baylis-Hillman Reaction

Before 1970, asymmetric synthesis was generally considered a rather esoteric subject. This is no longer the case. Today it is the primary focus of activity for most of the leading research laboratories in both academic and industrial communities. Development of synthetic strategies for carbon-carbon bond construction reactions, wherein new chiral centers are produced, represent a forefront of research in organic synthesis. We foresee that Baylis-Hillman coupling reaction will be a powerful synthetic tool for construction

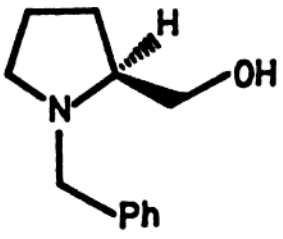
of asymmetric C-C bonds with multifunctionalities. We have planned two strategies for asymmetric Baylis-Hillman coupling reaction.

(i) To study the application of chiral tertiary amines in the place of DABCO and to design proper chiral amines for the best enantioselective carbon-carbon bond construction.

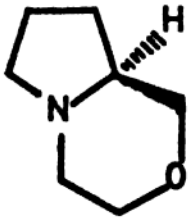
(ii) To study the application of chiral acrylate to provide the Baylis-Hillman products with diastereoselectivity, also to design a suitable chiral auxiliary for 100% diastereoselectivity.

Application of chiral amine-catalysis for Baylis-Hillman Reaction

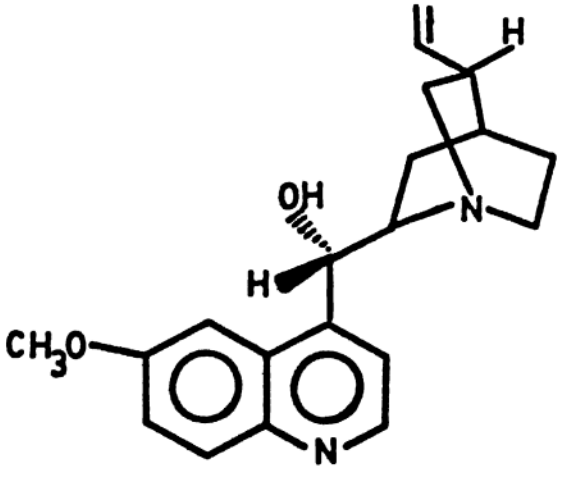
Though there is no proof, Baylis-Hillman reaction is believed to involve initial conjugate addition of DABCO to the α,β-unsaturated system followed by the nucleophilic attack on the aldehydes and subsequent elimination of DABCO thus providing multifunctional molecules. Application of chiral amine in the place of DABCO might not only provide asymmetric molecules, but also throw some light on the speculated mechanism. We have selected three representative chiral tertiary amines for our study (i) (S)-N-benzylprolinol (98), (ii) (S)-1-aza-4-oxabicyclo [4.3.0]nonane (99) and (iii) quinidine (100).



98

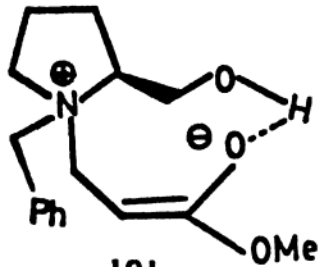


99



100

(S)-N-Benzylprolinol (98) was selected because of the possibility of hydrogen bonded stabilization of catalyst-acrylate adduct **101** as shown in the case of 3-hydroxyquinuclidine to provide asymmetric coupling product.

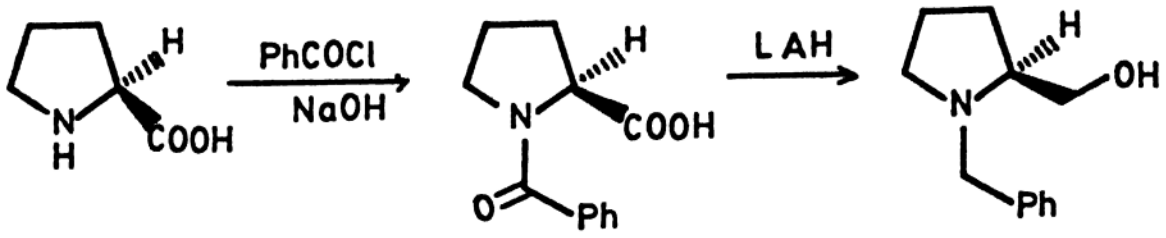


101

Hydrogen bonded stabilization

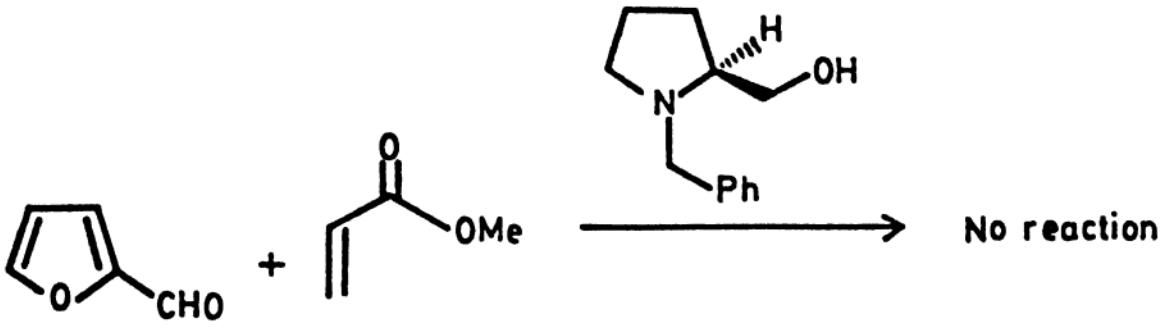
(S)-N-Benzylprolinol (98) was prepared according to the scheme 39. The commercially available (S)-proline was treated with benzoyl chloride in the presence of aqueous NaOH to provide the N-benzoylproline (102) in 80% yield. Subsequent reduction with lithium aluminium hydride provided the desired (S)-N-benzylprolinol (98) as a colorless oil in 79% yield. The structure of this molecule was confirmed by spectral data.

SCHEME 39:



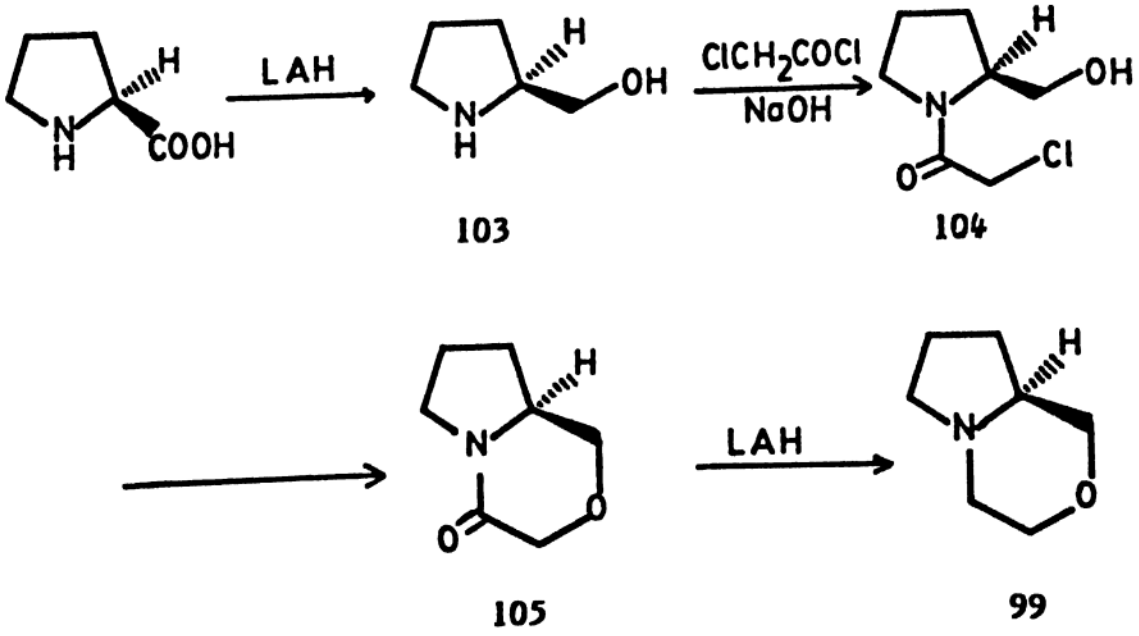
102 **98**

We carried out the reaction of methyl acrylate with 2-furaldehyde using (S)-N-benzylprolinol (98) as a catalyst. TLC examination of the reaction mixture indicated that no reaction occured in 2 months even with 100 mole% of (S)-N-benzylprolinol (98).

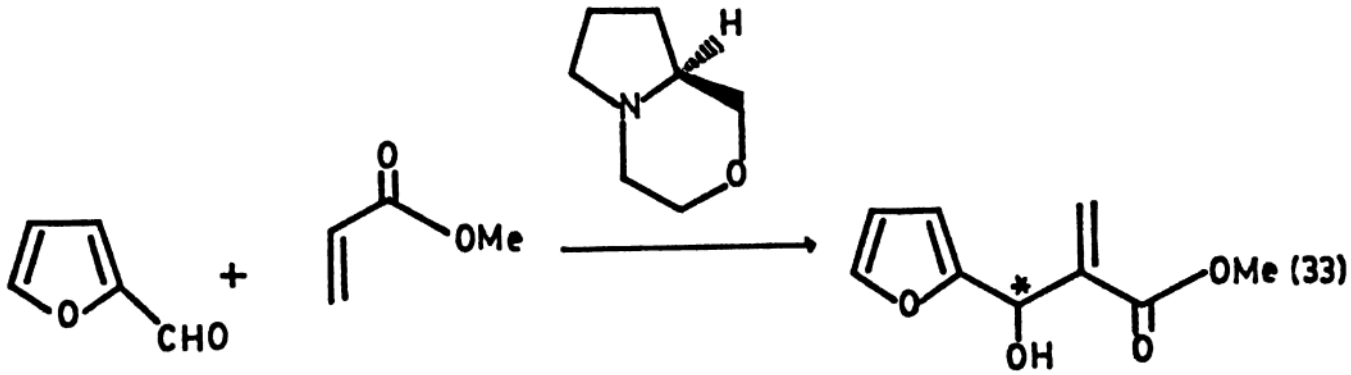


We therefore turned our attention toward the bicyclic amine **99** as a possible catalyst for Baylis-Hillman coupling reaction. The bicyclic tertiary amine **99** was synthesized according to the scheme 40. (S)-Proline was converted to (S)-prolinol (**103**) in 95% yield following the Ender's procedure.[92] Treatment of (S)-prolinol with chloroacetyl chloride in the presence of aqueous NaOH directly provides the bicyclic amide **105** in 38% yield, presumably through the intermediate **104**. Reduction of **105** with lithium aluminium hydride provides the desired (S)-1-aza-4-oxabicyclo(4.3.0)nonane (**99**) in 64% yield as a colorless oil. The structure of the molecule was confirmed by spectral data IR, ^{1}H NMR and ^{13}C NMR (Fig.15).

SCHEME 40:

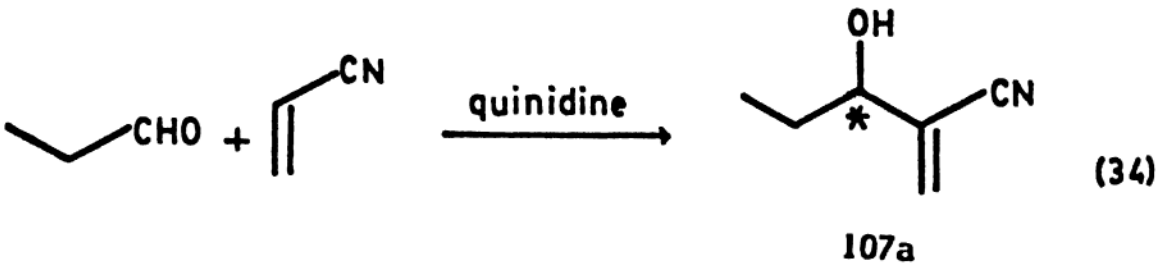


We carried out the reaction of 2-furaldehyde with methyl acrylate using (S)-1-aza-4-oxabicyclo(4.3.0)nonane (99) (50 mole %) (eq. 33). The reaction is very slow, providing the desired product 106 in 60% yield even after 120 days. This has the optical rotation $[\alpha]_D^{20}$ + 3.57° (C 2.8 ,methanol). This corresponds to 3-4% ee on the basis that the molecule 106' in eq.37 with 10% ee has $[\alpha]_D^{20}$ -13.2° (C 2.2, methanol).



106

Since the optical yield is not encouraging and the reaction is very slow, we did not proceed further with this bicyclic amine 99. We then selected quinidine (100), the commercially available alkaloid as a possible chiral catalyst for Baylis-Hillman coupling reaction. First, we carried out the coupling reaction of acrylonitrile with propionaldehyde using 30 mole % quinidine as catalyst. Excess acrylonitrile (2 mL for 10 mM reaction) was added to see that most of the quinidine was dissolved. The progress of the reaction was monitored by TLC. After 10 days, direct column chromatography of the reaction mixture [solvent system ethyl acetate and hexane (1:9)] afforded the pure 2-cyanopent -1-en-3-ol (107a) in 66% yield as a colorless liquid. $[\alpha]_D^{20}$ -2.7° (C 0.74, acetone) (eq.34).



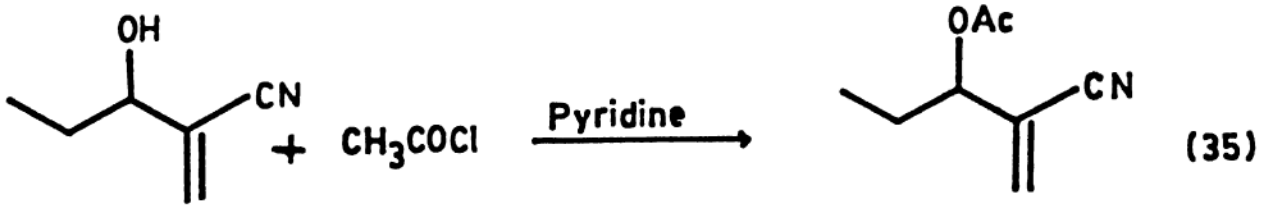
(34)

107a

The structure of the molecule was confirmed by spectral data. It has identical IR and ^{1}H NMR data as that of the molecule prepared by the action of acrylonitrile and propionaldehyde catalyzed by DABCO (eq.20).

Determination of optical purity

The racemic molecule 47a, obtained according to eq.20, was converted into the corresponding acetate 108a , by treatment with acetyl chloride in the presence of pyridine (eq.35). Examination of ^{1}H NMR spectrum shows a clean singlet for O=C$\underline{CH_3}$ protons at δ2.08 (Fig.16). The same singlet appeared as two singlets of equal intensities in ^{1}H NMR spectrum of 108a in the presence of Eu(hfc)$_3$ thus indicating that two singlets arise from two enantiomers.



(35)

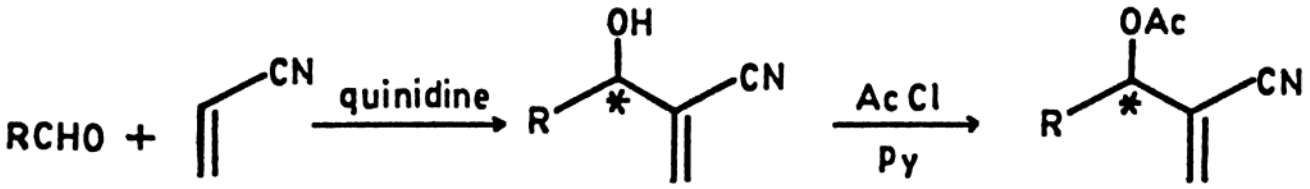
47a

108a

We have then converted the chiral alcohol into the corresponding acetate 109a following the same procedure as in 108a. ^{1}H NMR spectrum (Fig.16) of chiral acetate 109a in the presence of Eu(hfc)$_3$ provides two singlets

for acetyl methyl protons in the ratio 60:40 indicating that the product is 20% optically pure. This reaction is encouraging. We then selected two more aldehydes, i.e., benzaldehyde, p-tolualdehyde for our study using quinidine as chiral catalyst (30 mole %) (Scheme 41).

SCHEME 41:

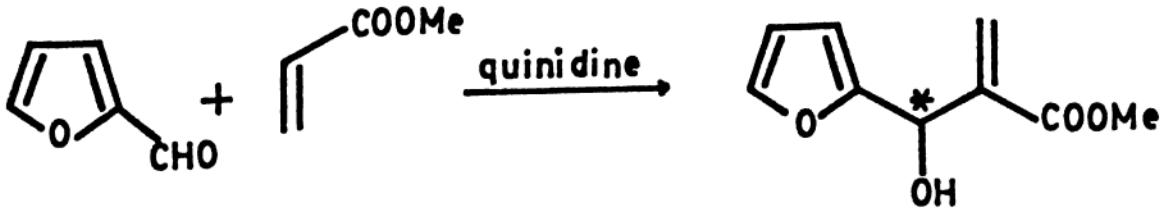


107a-c 109a-c

R = C_2H_5, C_6H_5, p-Tolyl

Benzaldehyde coupled product **107b** was obtained in 54% yield, whereas the coupling reaction with p-tolualdehyde is very slow and the coupled product **107c** was obtained in 58% yield even after one month. Optical purities are determined following the same strategy as in the case of propionaldehyde product. The optical yields are very low. The benzaldehyde coupled product **107b**, was obtained in 4% ee and the p-tolualdehyde product **107c** in 3-4% ee.

Finally, methyl acrylate was coupled with 2-furaldehyde using quinidine (30 mole %) as chiral catalyst (eq.36). The reaction is clean providing the methyl 3-hydroxy-3-(fur-2-yl)-2-methylenepropionate (**106'**) in 60% yield.

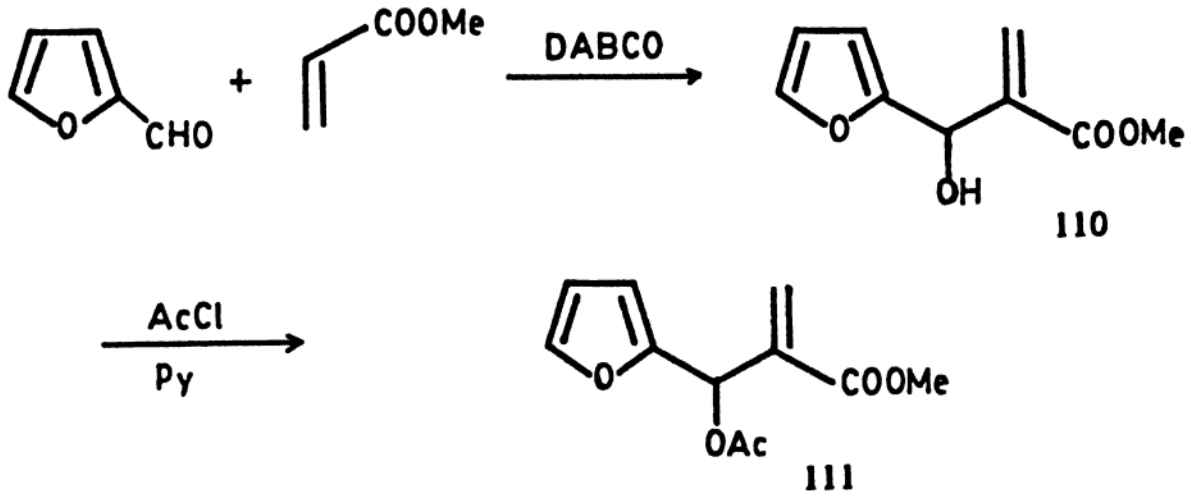


(36)

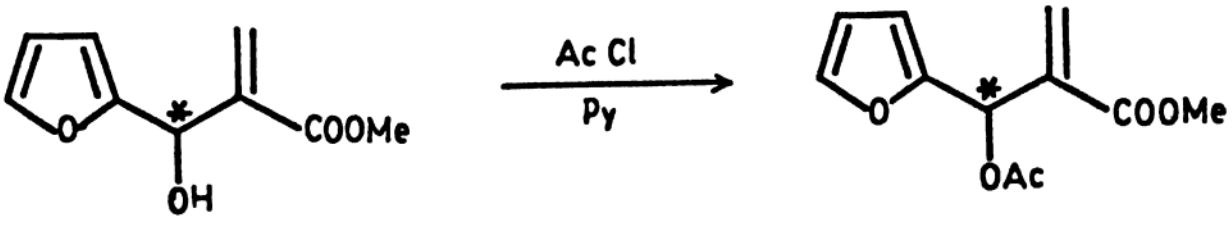
106'

Optical purity of 106' was determined as follows. First, racemic methyl 3-hydroxy-3(fur-2-yl)-2-methylenepropionate (110) was prepared by the action of methyl acrylate with 2-furaldehyde using 15 mole % of DABCO as catalyst (Scheme 42). This racemic alcohol was converted into the corresponding acetate 111. ^{1}H NMR spectrum of the acetate in the presence of

SCHEME 42:

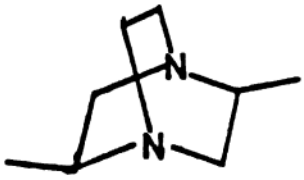


chiral shift reagent Eu(hfc)$_3$ provides two singlets for methoxy protons in equal intensities arising from both the enantiomers. We have then prepared the acetate (eq.37) of the chiral alcohol 106' and the ^{1}H NMR of the acetate 112 in the presence of Eu(hfc)$_3$ provides two singlets for methoxy protons in 55:45 ratio, indicating that the product is obtained in 10% enantiomeric excess.

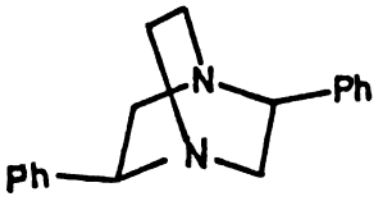


106' 112 (37)

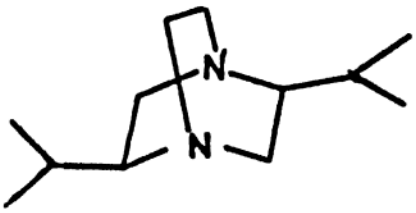
Though quinidine catalyzed reaction did not provide good enantioselectivities, this is still encouraging. We predict the chiral DABCOs 113-115 will offer promise in achieving high enantioselectivities in Baylis-Hillman reaction. This work is in progress in our laboratory.



113



114

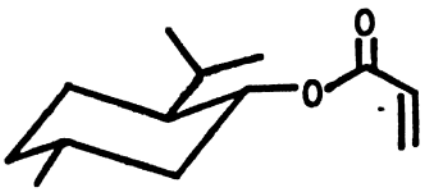


115

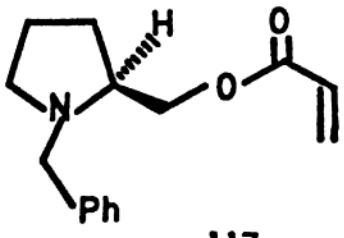
When our studies on chiral amine catalysis using chiral amines 98-100 were complete, there appeared a review by Drewes and Roos.[54] In this review they mentioned their work on chiral amine catalysts for Baylis-Hillman coupling reaction. They reported that optical yields are in the range of 0-12%.

Chiral acrylates for Baylis-Hillman coupling Reaction

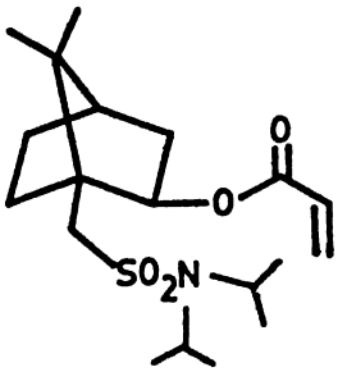
Our studies were also devoted towards the applicability of various chiral acrylates for diastereoselective Baylis-Hillman coupling with aldehydes. Three chiral acrylates (-)-menthyl acrylate (116), (S)-(N-benzylpyrrolidin-2-yl) methyl acrylate (117) and (1S, 2R, 4R)-1-(diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)hept-2-yl acrylate (118) were selected for our studies.



116

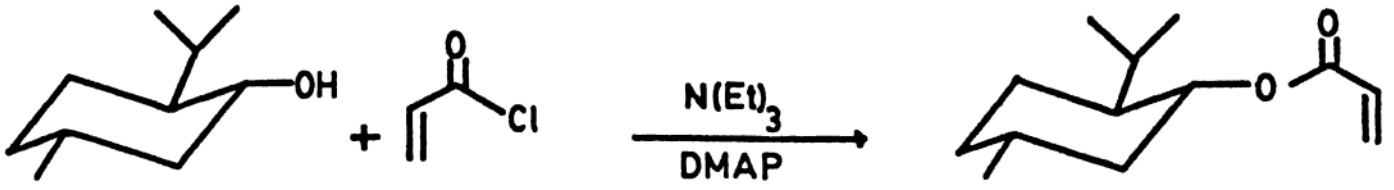


117



118

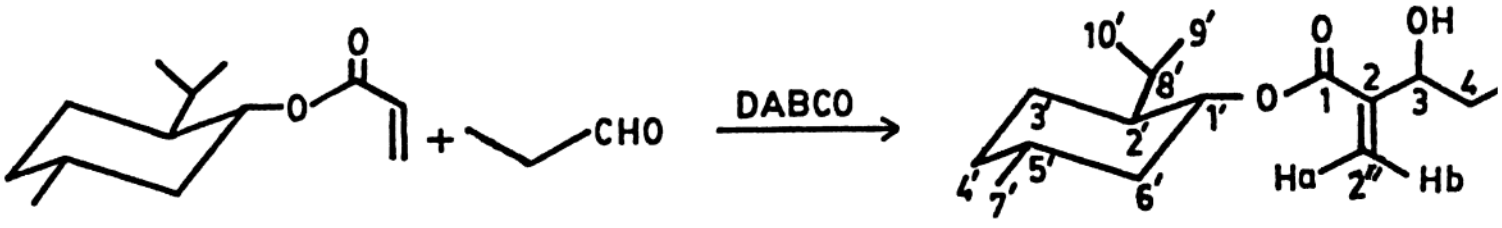
We have first investigated the applicability of easily accessible (-)-menthyl acrylate (^{13}C NMR, Fig.17)[93] which was easily obtained by the action of (-)-menthol on acryloyl chloride in the presence of triethylamine[94] (eq.38).



(3

116

Coupling reaction of (-)-menthyl acrylate with propionaldehyde under the catalytic influence of DABCO (15 mole %) was examined first. The reaction was found to be very slow. We have found that coupling is reasonably faster when the DABCO is used 100 mole %, i.e., in molar ratio and the (-)-menthyl 3-hydroxy-2-methylenepentanoate (119a) (chiral auxiliary group has been given numbering with primes, 1', 2', 3', etc.) was obtained in 86% yield after column chromatography as a pure, viscous liquid (eq.39). The structure of the compound was established by spectral data ,i.e., IR, ^1H NMR (Fig.18), ^{13}C NMR (Fig.19).



116

119a

Direct analysis of this molecule on capillary GC showed single peak thus not giving any indication on the diastereomeric ratio. Also ^1H NMR studies on this molecule using chiral shift reagent $Eu(hfc)_3$ are not much helpful in establishing the diastereomeric ratio. ^{13}C NMR analysis shows two resonances

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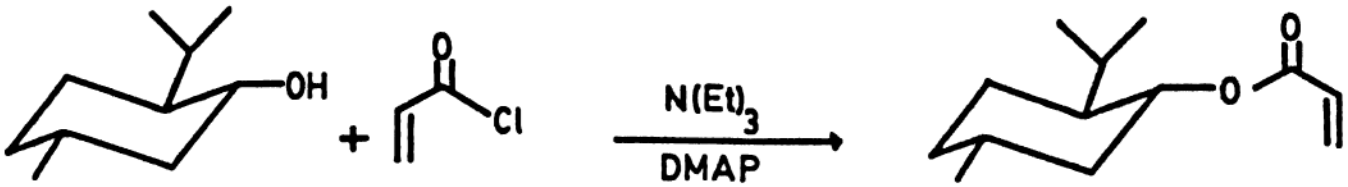

(38)

116

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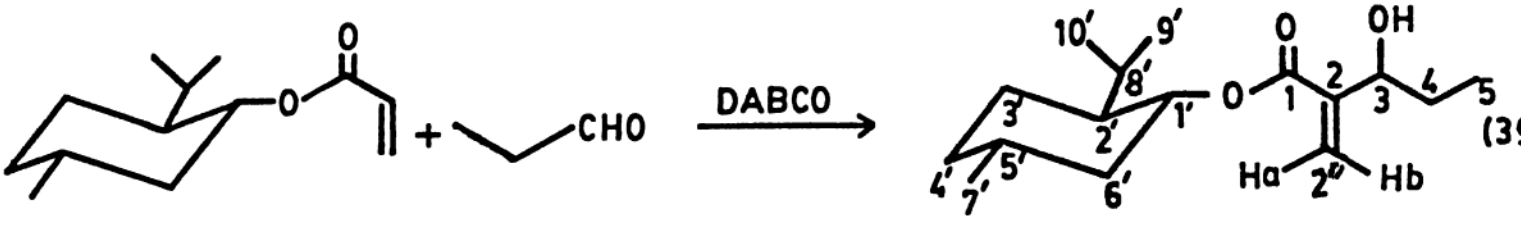
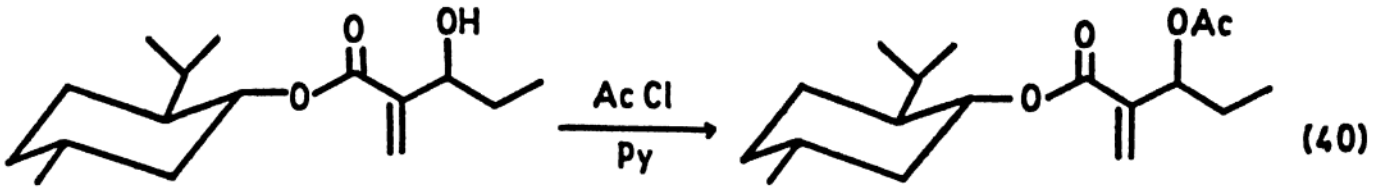


(39)

116 119a

Direct analysis of this molecule on capillary GC showed single peak thus not giving any indication on the diastereomeric ratio. Also ^1H NMR studies on this molecule using chiral shift reagent $Eu(hfc)_3$ are not much helpful in establishing the diastereomeric ratio. ^{13}C NMR analysis shows two resonances

(Fig.19) at δ72.24, 72.35 for C3 carbon probably arising from two diastereomers. No other carbon resonances separate. We converted the alcohol **119a** into its acetate **120a** by treatment with acetyl chloride in the presence of pyridine (eq.40). ^{1}H NMR spectrum (Fig.20) of this acetate in $CDCl_3$ also did not give



(40)

119a **120a**

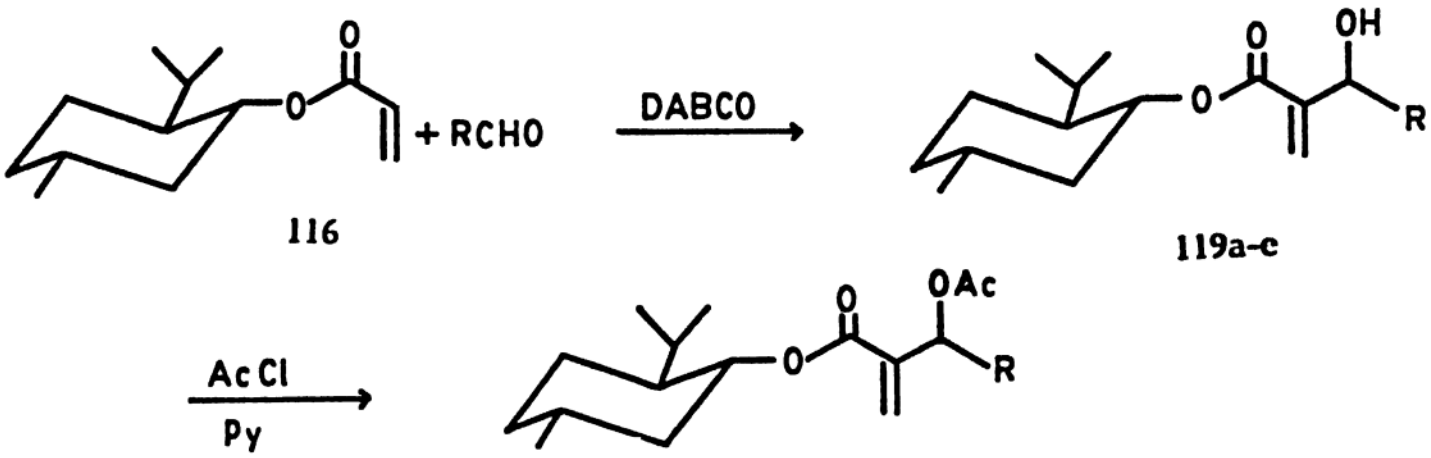
us any information regarding the diastereomeric ratio. ^{1}H NMR spectrum in the presence of chiral shift reagent Eu(hfc)$_3$ (fig. 20) (Sample/Eu(hfc)$_3$, : 1/3) provides two singlets in the ratio 42:58 for acetyl methyl protons(O=CCH_3) (originally singlet at δ2.04), each singlet arising from each diastereomer. This establishes that the diastereoselectivity in this reaction is 16%. Capillary GC analysis of this sample on methyl silicone showed two peaks (though not baseline separation) in the ratio 57.5:42.5, thus indicating that the diastereoselectivity is 15%. This further supports our ^{1}H NMR studies for the measurement of diastereoselectivity.

Acetaldehyde, isobutyraldehyde, 2-furaldehyde and benzaldehyde, were the other aldehydes selected for coupling reaction with (-)-menthyl acrytale (Scheme 43) (Table 6).

The ^{13}C NMR spectrum of (-)-menthyl 3-hydroxy-2-methylene-butanoate (**119b**) looks homogenous (thus not indicative of diastereomeric mixture). In order to establish diastereoselectivity (-)-menthyl 3-hydroxy-2-methylene-butanoate (**119b**) was converted into the corresponding acetate **120b**. GC analysis of acetate **120b** on capillary column (methyl silicone) shows two

peaks in the ratio 56:44 indicating that the diastereoselectivity is 12%. ^{1}H NMR spectrum analysis of the acetate **120b** in the presence of $Eu(hfc)_3$ reveals that the diastereoselectivity is 11% (by integration of separated acetyl methyl proton peaks). It is quiet appropriate to mention here the work of Brown and co-workers[95]. During the asymmetric hydrogenation studies Brown and co-workers have prepared the same compound **119b** in 16% de by the action of (-)-menthyl acrylate with acetaldehyde under the influence of DABCO. They determined the diastereoselectivity with the help of ^{13}C NMR (125.7 MHz) on the basis of C3 carbon resonances.

SCHEME 43:



116 **119a-c** **120a-c**

R = C_2H_5, CH_3, 2-Furyl, i-C_3H_7, C_6H_5

^{13}C NMR of (-)-menthyl 3-hydroxy-3-(fur-2-yl)-2-methylenepropionate (**119c**)[@] indicates that some carbon resonances separate. By comparison of ^{13}C NMR of (-)-menthyl acrylate, we can speculate that the resonances at δ66.34, 66.69 are due to the diastereomeric carbon C3. Similarly, we can also speculate the resonance pairs at δ 15.85 and 16.20, 23.36 and 23.51, 25.65 and 26.18, 125.34 and 125.52 correspond to diastereomeric C10', C3', C8' and C2'' respectively. This compound **119c** is obtained in 20% de as evidenced by ^{1}H NMR studies of the acetate **120c** (by integration of separated $O{=}CCH_3$ protons

Table 6 : Preparation of (-)-menthyl 2-(1-hydroxyalkyl)acrylates from (-)-menthyl acrylate and aldehydes.[a,b]

Aldehyde	Product	Time	Yield(%)[c]	$[\alpha]_D^{20}$	de(%)
CH_3CH_2CHO	**119a**	7 days	86	-75.4°(C 2.5, Acetone)	16[d,e]
CH_3CHO	**119b**	7 days	83	-73.4°(C 1.58, MeOH)	11[d,e]
2-Furaldehyde	**119c**	18 hours	85	-63.1°(C 1.47, Acetone)	20[d]
$(H_3C)_2CHCHO$	**119d**	14 days	85	-50°(C 1.2, Acetone)	7[d,e]
C_6H_5CHO	**119e**	7 days	40[f]	-142.4°(C 0.4, Acetone)[g]	100[d]

a) All reactions were carried out on 5 mM scale using 5 mM DABCO.

b) All the products were characterised by IR, ^1H NMR and ^{13}C NMR spectroscopy.

c) Yields of the column chromatography purified products. **119a-119d** are obtained as colorless liquids.

d) Determined by the integration of methyl ($COCH_3$) signals of corresponding acetates with $Eu(hfc)_3$.

e) Capillary GC analysis (methyl silicone column) of the corresponding acetate indicates that **119a, 119b, 119d** are obtained in 15%, 12%, 7% de respectively.

f) Overall yield after selective crystallization.

g) Optical rotation which did not increase on further crystallization from n-hexane.

$Eu(hfc)_3$ = Tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium (III) derivative.

peaks) with shift reagent. The isobutyraldehyde product **119d** was obtained in 7% de as established by GC analysis (capillary column methyl silicone) of its acetate **120d**. In the ^{1}H NMR spectrum of the acetate **120d** in the presence of $Eu(hfc)_3$, the olefinic protons Hb at δ 5.64 and Ha at δ6.24 split indicating the 7% diastereomeric excess. Examination of ^{13}C NMR of the alcohol **119d** shows two lines at δ 77.23, 77.53 for C3 and two reasonances at δ142.01, 142.12 for C2 carbon arising from two diastereomers.

In the case of benzaldehyde, the coupling product **119e** is a nice solid with m.p.104-112°C and $[\alpha]_D^{20}$: -51.70 (C 0.73, acetone). ^{1}H NMR spectrum of **119e**[@] shows that Hb proton appears as two singlets at δ5.76 and 5.8 indicating that they arise from diastereomers. In ^{1}H NMR of the acetate, the olefinic protons Hb and Ha also split due to diastereomeric mixture into two singlets each at δ5.7, 5.76 and 6.28, 6.34 respectively. However, diastereomeric excess was determined by ^{1}H NMR analysis of the corresponding acetate **120e** using $Eu(hfc)_3$ and found to be 15%. In ^{13}C NMR of the alcohol some carbon resonances of diastereomeric mixture separate. It can be speculated that the resonances at δ73.18, 73.29 correspond to diastereomeric C3 carbon. Resonance pairs at δ16.11 and 16.88, 23.11 and 23.29, 25.82 and 26.11, 40.53 and 40.65, 74.77 and 74.88, 125.18 and 125.36, 126.59 and 126.77, 142.59 and 142.71 arise

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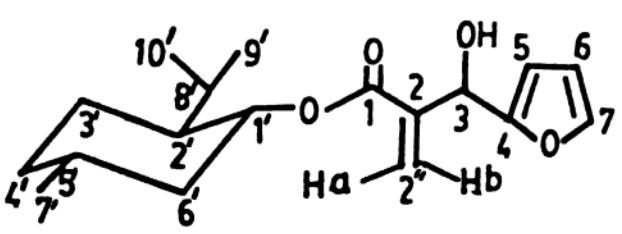
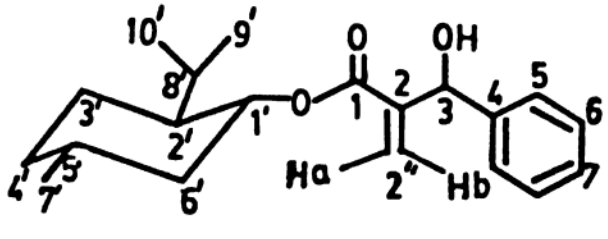
[@]For ^{1}H NMR and ^{13}C NMR assignments, we have adopted the following numbering for the molecules **119c** and **119e**.



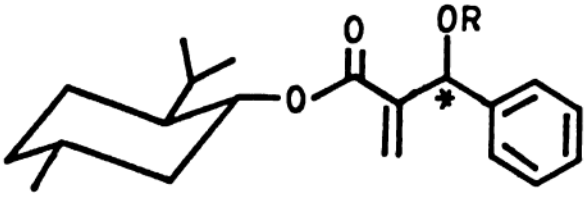
119c



119e

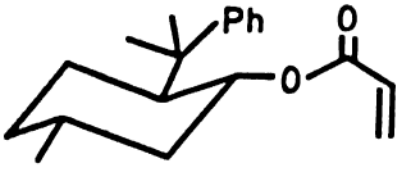
from C10', C3', C8', C6', C1', C2" (aromatic), aromatic (C2"), C2(C4) diastereomeric carbons respectively (Fig.21). Repeated fractional crystallizations of this alcohol from hexane afforded a good crystalline solid **119'e** with optical rotation $[\alpha]_D^{20}$ -142.4° (C 0.4, acetone), m.p.115-116°C. This is the maximum rotation observed. ^{1}H NMR spectrum of this sample has only one singlet for Hb at δ 5.8 indicating that it is a single diastereomer. ^{13}C NMR (Fig.22) shows only one resonance at δ73.53 for C3 carbon. The other carbons which show diastereomeric resonance pairs in the earlier spectrum (Fig.21) appear as single resonances at δ16.06, 23.29, 26.00, 40.76, 75.00, 125.65, 126.77, 142.65 for C10', C3', C8', C6', C1', C2" (aromatic), aromatic (C2"), C2(C4) thus confirming 100% de. ^{1}H NMR analysis of the acetate **120'e** shows only one singlet for Hb at δ 5.76 and a singlet for Ha at δ 6.36 thus confirming the 100% de. This is further confirmed by ^{1}H NMR analysis of the acetate in the presence of Eu(hfc)$_3$ which showed a clean singlet for acetyl CH_3.

Coupling reactions with (-)-menthyl acrylate are indeed encouraging though the optical yields are not that good. On the basis of these results we believe that (-)8-phenylmenthyl acrylate (121) and chiral <u>trans</u> 2-phenylcyclohexyl acrylate (122) will certainly provide high selectivities. The studies are underway in our laboratory.

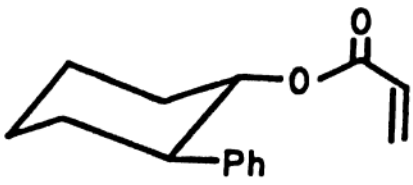


R = H, **119'e**

R = Ac, **120'e**



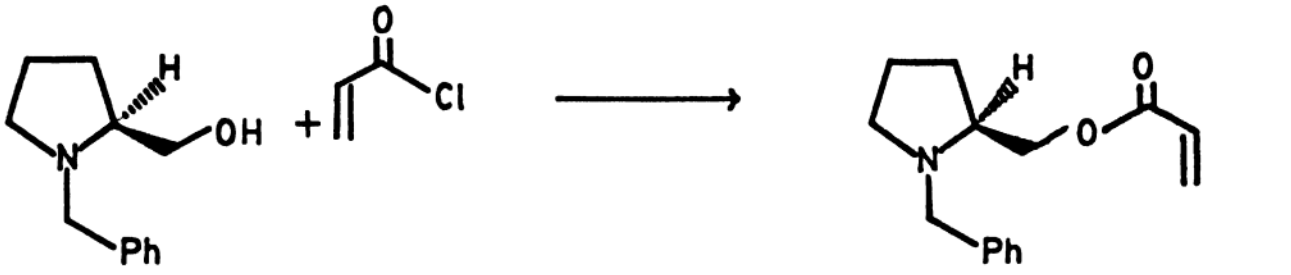
121



122

Application of (S)-(N-benzylpyrrolidin-2-yl)methyl acrylate (117)

Our attention was next drawn towards (S)-(N-benzylpyrrolidin-2-yl) methyl acrylate (117) for diastereoselective Baylis-Hillman C-C bond forming reaction. (S)-(N-benzylpyrrolidin-2-yl)methyl acrylate (117) was obtained in 70% yield by the action of the alcohol 98 on acryloyl chloride (eq.41).

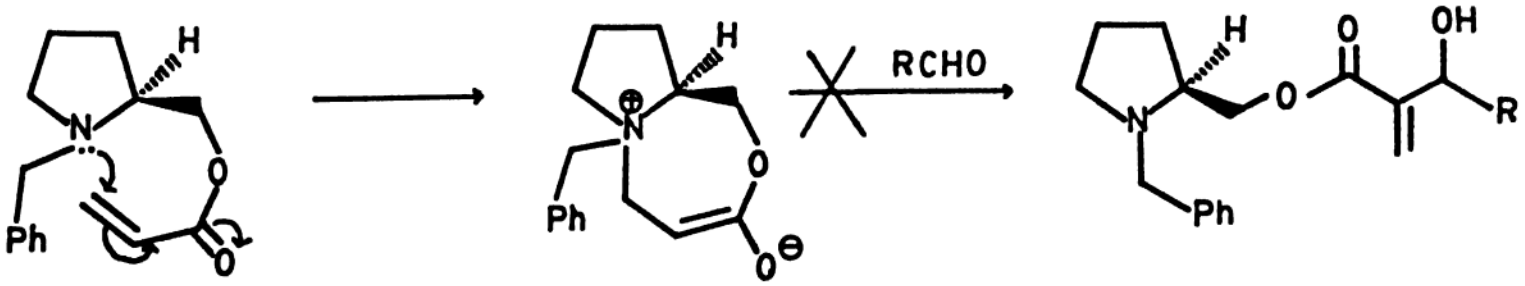


(41)

98 117

We have thought that acrylate can be coupled with the aldehydes directly without using DABCO as a catalyst because the nucleophilic ring nitrogen can possibly add to the acrylate in a intramolecular Michael fashion (Scheme 44). However, our expectation was found to be wrong. No reaction occured even when we used reactive aldehydes like 2-furaldehyde for coupling with this acrylate.

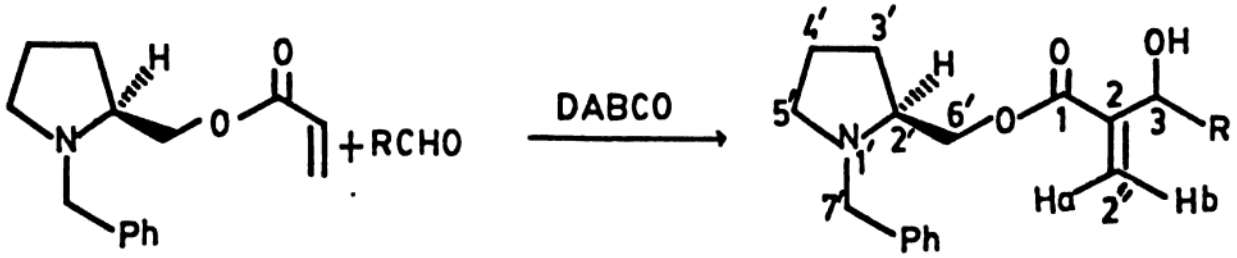
SCHEME 44:



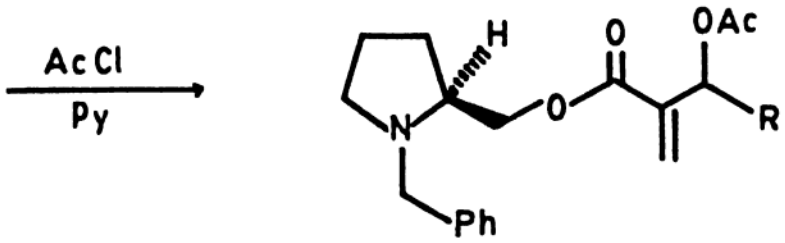
Then we examined the utility of this acrylate 117 for diastereo-selective Baylis-Hillman C-C bond construction using DABCO as a catalyst. Coupling reaction with acetaldehyde was tried first. It was realized that the

coupling is complete in two days when DABCO is used 100 mole % thus providing the desired (2'S)-(N-benzylpyrrolidin-2'-yl)methyl 3-hydroxy-2-methylenebutanoate (123a) (chiral auxiliary group has been given numbering with primes, 1', 2', 3', etc.) (Scheme 45) in 60% yield. The structure was confirmed by IR and ^{1}H NMR spectral data.

SCHEME 45:



117 123a-c



124a-c

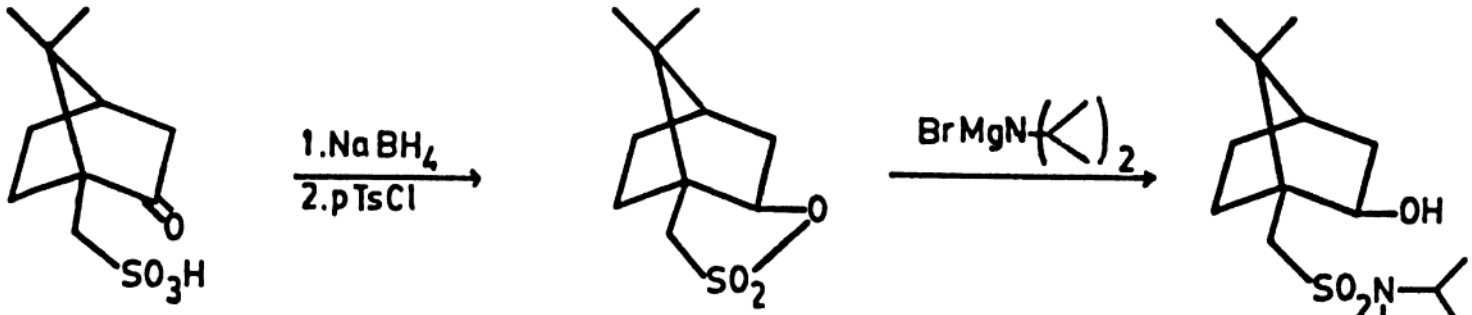
R = CH_3, C_2H_5, C_6H_5

The diastereomeric excess was determined by converting the alcohol **123a** into the corresponding acetate **124a** and inspecting the ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$. Two peaks are observed for O=CCH_3 protons in the ratio 58:42 indicating that there is 16% diastereoselectivity in this reaction. Propionaldehyde and benzaldehyde are the other two aldehydes selected. Propionaldehyde product **123b** was obtained in 7% de and the benzaldehyde product **123c** was in 4% de. These results are not encouraging.

Application of (1S,2R,4R)-1-(diisopropylaminosulfonyl)methyl-7,7-dimethyl bicyclo (2.2.1)hept-2-yl acrylate (118)

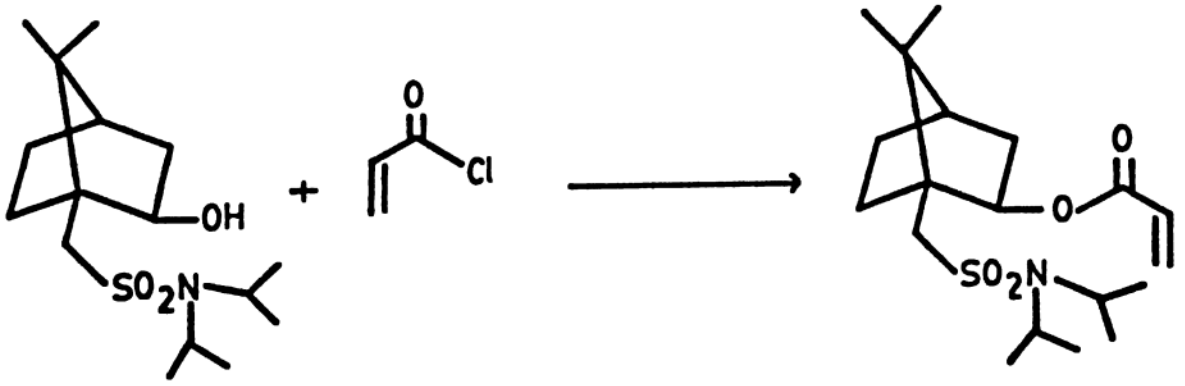
With a view to achieve high diastereoselectivities in Baylis-Hillman C-C bond forming reaction, the well known Oppolzer's chiral auxiliary (1S,2R,4R) -1-(diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (126) was finally selected. This chiral auxiliary was prepared acording to the scheme 46.[96]

SHEME 46:



125 126

The sultone 125 was prepared according to the reported procedure.[97] The opening of the sultone was reported[96] with Lithium diisopropylamide (6 mole equivalents) to provide the alcohol 126 m.p. 102-103°C, $[\alpha]_D^{20}$ -34.4° (C 4.74, EtOH).[98] We found that the opening of the sultone with bromomagnesium diisopropylamide (6 equivalents) also provides the desired alcohol 126

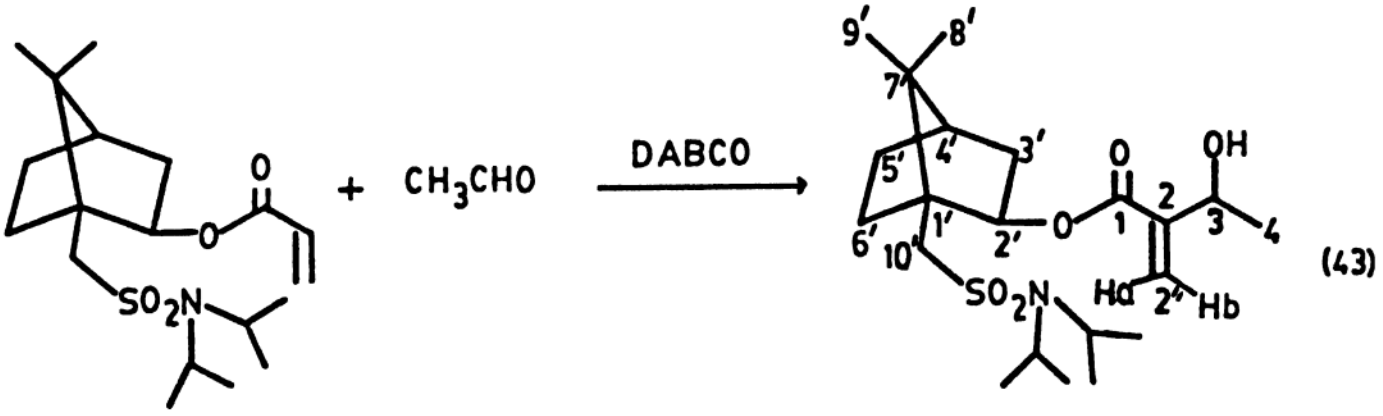


(42)

126 118

m.p. 101-103°C, $[\alpha]_D^{20}$: -34.3° (C 0.9, EtOH). The acrylate **118** was prepared by the action of alcohol **126** with acryloyl chloride (eq. 42), as a crystalline solid, m.p. 115-117°C, $[\alpha]_D^{20}$: -66.6° (C 0.18, acetone). The structure of this acrylate **118** was established by spectral data IR, ^{1}H NMR (Fig.23) and ^{13}C NMR (Fig.24) and elemental analysis.

Coupling reaction of the acrylate **118** with acetaldehyde using catalytic amount (15 mole %) of DABCO was tried. The reaction was very slow. The reaction was reasonably faster taking two days for completion when DABCO was used 100 mole %, thus providing the desired (1'S,2'R,4'R)-1'-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-hydroxy-2-methylenebutanoate (**127a**) (chiral auxiliary group has been given numbering with primes, 1', 2', 3', etc.) in 70% yield, m.p. 105-108°C, $[\alpha]_D^{20}$: -60° (C 0.8, acetone) (eq.43).

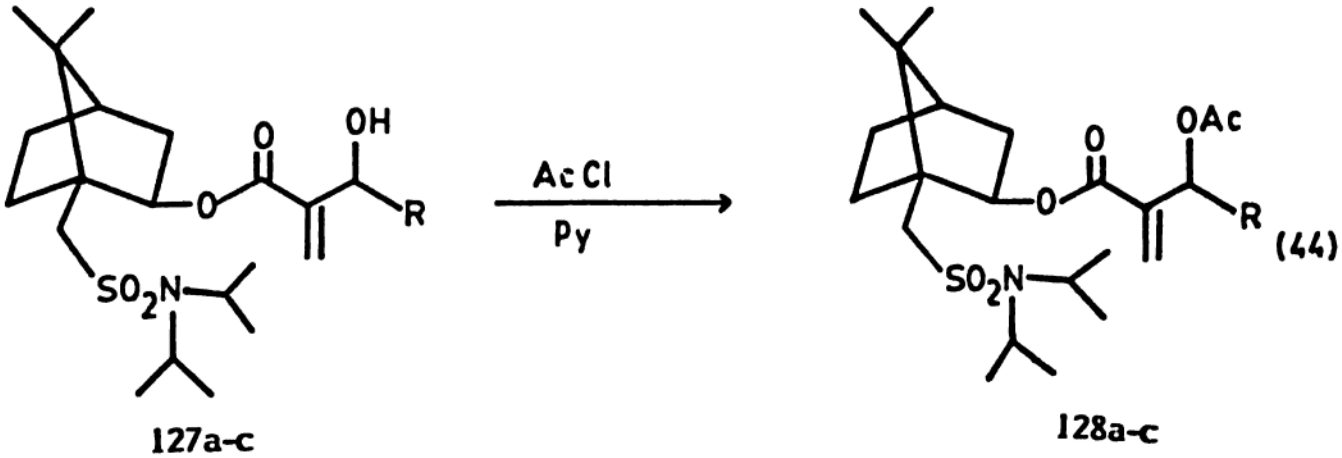


(43)

118 **127a**

Structure of this molecule was confirmed by elemental analysis, IR, ^{1}H NMR (Fig.25) and ^{13}C NMR (Fig.27) spectral data. Examination of ^{1}H NMR spectrum shows two singlets at δ6.0 and 6.04 in the ratio 66:34 for Ha proton, two singlets at δ5.72 and δ 5.79 in the same ratio for Hb proton indicating that two singlets will arise from two diastereomers. Two doublets appear for H4 protons at δ1.4, which arise from diastereomers. ^{13}C NMR is

also indicative of diastereomeric mixture. Carbon resonances at δ66.47 and δ 67.53 can be attributed to C3 carbon of diastereomers. Similarly resonances at δ 122.00, δ 122.65 and at δ 144.53, δ145.18 can arise from C2" and C2 carbons of diastereomers. However, diastereomeric excess was determined by ^{1}H NMR (Fig.29) spectrum analysis of the corresponding acetate **128a**(eq.44) using Eu(hfc)$_3$. ^{1}H NMR spectrum shows two singlets (not baseline separation) for O=CCH$_3$ protons at δ2.04 and 2.08. In the presence of Eu(hfc)$_3$ these signals appear as two distinct singlets, separated wide apart, in the ratio 65:35 indicating that diastereomeric excess is 30%. ^{1}H NMR spectrum of acetate (without shift reagent) also shows two singlets at δ 6.06 and 6.18 (Fig.29) for Ha proton indicating that these separate singlets arise from diastereomers. Two doublets appear for CH$_3$ (H4) protons at δ 1.4 arising from diastereomers. Also two singlets at δ 1.04 and 1.06 can be attributed to CH$_3$ protons (one of the gem dimethyl) of diastereomeric mixture.



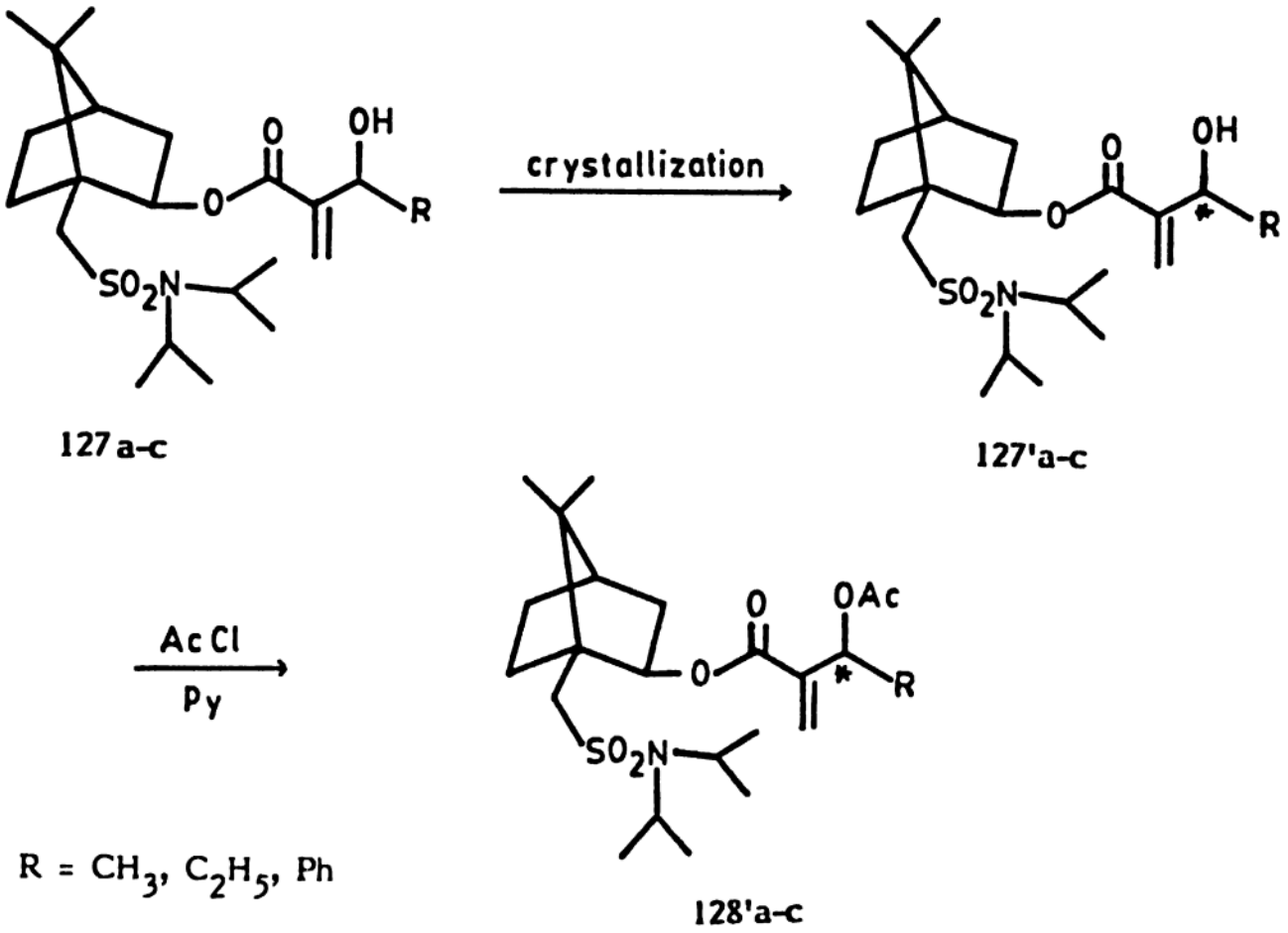
(44)

127a-c **128a-c**

Fractional crystallization from pet. ether & ether provides a pure single diastereomer **127'a** in 40% overall yield. [α]$_D^{20}$: -54.76° (C 0.82, acetone), m.p. 125-126°C. ^{1}H NMR spectrum (Fig.26) shows only one singlet at δ6.08 for Ha proton and only one singlet at δ5.80 for Hb proton indicating the presence of only one diastereomer. Similarly, ^{13}C NMR (Fig.28) gives only one resonance

at δ143.54 for C2, one line at δ120.36 for C2" and one resonance at δ64.88 for C3 carbon clearly demonstrating the 100% diastereomeric excess of the crystallized product (Scheme 47).

SCHEME 47:



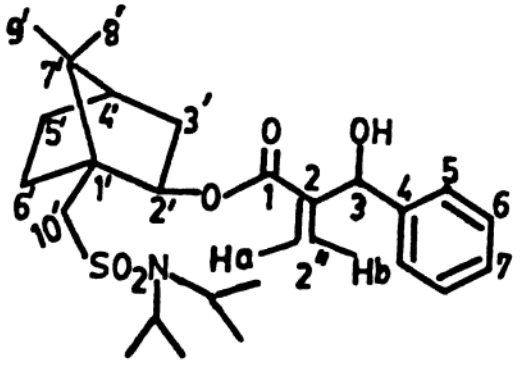
^1H NMR (Fig.30) analysis of the corresponding acetate **128'a** shows a singlet at δ2.07 for $O{=}CCH_3$ protons. This singlet does not split in the presence of $Eu(hfc)_3$ thus conforming 100% de. ^1H NMR of the acetate has only one doublet for CH_3 (H4) at δ1.4 indicating the absence of other diastereomer. Also the Ha proton which appeared as two singlets earlier due to diastereomeric mixture, now appeared as a singlet at δ6.06 thus confirming the 100% de. Studies to establish the absolute stereochemistry are now in progress in our laboratory. Propionaldehyde and benzaldehyde are the other two aldehydes selected for the coupling reaction.

Propionaldehyde coupled product **127b** was obtained in 78% yield, $[\alpha]_D^{20}$:-52.5° (C 0.4, acetone), m.p. 108-110°C. ^{13}C NMR examination reveals that two resonances appear at δ72.44 and 74.68 for C3 carbon arising from two diastereomers. Two resonances at δ10.33 and 10.45 can be attributed to C5 carbon from diastereomers. ^{1}H NMR spectrum was not of much help for determination of de. The product was converted into its acetate **128b**. ^{1}H NMR of the acetate shows two peaks at δ2.04 and 2.08 (not base line separation for $O{=}CCH_3$ protons arising from diastereomers). Diastereomeric excess was determined from integration of two singlets for $O{=}CCH_3$ protons in ^{1}H NMR spectrum of **128b** in the presence of $Eu(hfc)_3$ and found to be 42%. Here also Ha proton appears as two singlets at δ6.08 and 6.16 which arise due to diastereomeric mixture. Fractional crystallization (pet. ether and ether) provided clearly one diastereomer **127'b** with m.p.113-114°C, $[\alpha]_D^{20}$: -55.2° (C 0.8, acetone) in 45% overall yield. Examination of ^{13}C NMR indicates only one line at δ72.12 for C3 carbon and also only one resonance at δ10.06 for C5 carbon thus confirming 100% de. This is further confirmed by ^{1}H NMR analysis of the acetate **128'b**. The acetyl methyl protons appear as a singlet at δ2.08, also this singlet does not split in the presence of $Eu(hfc)_3$. Ha proton appears as a singlet at δ6.08 also confirming 100% de.

Benzaldehyde coupled product **127c** was obtained in 84% yield with m.p. 130-135°C, $[\alpha]_D^{20}$-36.6° (C 0.3, acetone). ^{1}H NMR spectrum@shows two singlets at δ6.12 and 6.16 for Ha proton which are due to diastereomeric mixture. ^{13}C NMR spectrum shows two resonances at δ73.94 and 74.71 for C3 carbon indicating that they are from two diastereomers. Similarly the resonance pairs at δ126.30 and 126.59 (C2" or aromatic), 127.89 and 128.01 (aromatic or C2"), 142.59 and 142.71 (C2 or C4), 144.65 and 144.81 (C4 or C2), 166.36 and 166.53 (C=O, C1) can be attributed to diastereomers. The product

was converted into the corresponding acetate **128c**. In ^{1}H NMR spectrum Hb proton appears as two singlets at δ5.42 and 5.84 in the ratio 57.5:42.5 which can come from diastereomers. The O-CCH_3 protons appear as two closed singlets at δ2.02 and 2.04 arising from diastereomers. In the presence of shift reagent Eu(hfc)$_3$, the two singlets separate nicely. Diastereomeric excess is determined by the integration of these peaks and found to be 15%. Fractional crystallization from a mixture of pet. ether and ether provides only one diastereomer **127'c** with m.p.165-167°C, $[\alpha]_D^{20}$ + 4.68° (C 0.62, acetone) in 35% overall yield. ^{1}H NMR shows only one singlet at δ6.2 for Ha indicating that this is one diastereomer. ^{13}C NMR of the crystallized sample shows one resonance at δ 72.82 for C3, one each at δ 125.18, 126.88 for C2" and aromatic C, 141.24 and 143.65 for C2 and C4, 165.18 or C1 confirming that this is a single diastereomer. It was further confirmed by ^{1}H NMR analysis of the acetate **128'c** which shows a single peak at δ 2.02 for O=CCH_3. This singlet at δ2.02 of acetyl methyl protons does not split in the presence of Eu(hfc)$_3$, thus confirming 100% de. Also the Hb proton appeared as a singlet at δ5.84 which is indication of 100% de.

@For ^{1}H NMR and ^{13}C NMR assignments, we have adopted the following numbering for the molecule **127c**.



127 c

Thus the chiral acrylate **118** offers diastereoselectivities in the range of 15-42%. These results are encouraging. Now our efforts are directed toward developing or modifying the chiral acrylate **118** to achieve 100% diastereoselectivity. The work is in progress in this direction in our laboratory.

Conclusion

We have made considerable progress in achieving the five objectives stated in the beginning of this chapter. We demonstrated that various α,β-unsaturated ketones, nitriles and sulfones are good substrates for Baylis-Hillman C-C bond forming reaction. We have also successfully utilized α-keto esters for Baylis-Hillman coupling with various activated alkenes. DABCO catalyzed Michael type dimerization of α, β-unsaturated ketones and nitriles provides important multifunctional molecules. Though quinidine catalyzed reactions do not provide good enantioselectivities in our studies, the results are encouraging. Suitable chiral catalysts such as **113**, **114** and **115** may provide good enantioselectivities. Our studies on the application of chiral acrylates for chiral C-C bond construction certainly throw light on the fabrication of suitable chiral acrylate for high diastereoselectivities. Our studies clearly demonstrate the potential of Baylis-Hillman reaction for C-C bond construction. This is the beginning. We predict that this reaction will be a powerful synthetic tool to organic chemists in the years to come.

EXPERIMENTAL

Melting points: Melting points were recorded on a Buchi 510 apparatus and are uncorrected.

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

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

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

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra (100 MHz) and carbon-13 magnetic resonance spectra (25 MHz) were recorded on JEOL-FX-100 spectrometer. Spectra for all the samples were measured in chloroform-d solution with tetramethylsilane (δ = 0 ppm) as internal standard. Spectral assignments are as follows: (1) Chemical shift on the δ scale. (2) Standard abbreviations for multiplicity. i.e., s = singlet, d - doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of a doublet, b = broad, (3) Number of hydrogens integrated for the signal. (4) Coupling constant J in Hertz. (5) Assignment of the signal (Cn - represents the carbon at numbering n, Hn - represents the proton(s) on Cn carbon). The chemical shifts of diastereomeric carbons are underlined.

Optical rotations: Optical rotations were measured on a Autopol II automatic polarimeter at the wavelength of the sodium D-line (589 nm) and at the temperature, 20°C.

Chromatography: Analytical thin layer chromatography (TLC) was performed on glass plates (7 x 2 cm) coated with Acme's silica gel G (250 mμ) containing 13% calcium sulphate as binder. Visualization of spots was achieved by exposure to iodine vapour. Column chromatography was carried out using Acme's silica gel (100-200 mesh). Gas chromatography analysis was carried out on a Packard Model-42 instrument equipped with a flame ionization detector on SE-30 column using nitrogen as carrier gas. Capillary gas chromatography analysis was carried out on Hewlett-Packard 5890A chromatograph using a 50 meter capillary column (0.25 mm ID) packed with methyl silicone.

General: All reactions were followed by TLC, using appropriate solvent system for development. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. All the solvents used were dried and distilled using suitable drying agents before use. Pet. ether refers to the fraction distilling between 60-80°C.

Preparation of 4-hydroxy-3-methylenetridecan-2-one (75a):

A solution of decyl aldehyde (3.12 g, 20 mM), methyl vinyl ketone (1.4 g, 20 mM) and DABCO (0.33 g, 3 mM) in 5 mL of THF was allowed to stand at room temperature for ten days. The reaction mixture was taken up in ether (25 mL) and washed with 2N hydrochloric acid, sodium bicarbonate solution and dried over anhydrous Na_2SO_4. After removal of the solvent the product was purified by column chromatography (5% ethyl acetate in hexane) and then distilled to obtain 75a in 62% (2.8g) yield.

b.p. : 117-120°C/0.5 mm

IR (neat) : 3450, 1665 cm^{-1}

^1H NMR : δ 0.87 (distorted t, 3H, $\underline{CH_3}$-CH_2-), 1.28 (m, 16H -$(CH_2)_8$), 2.35 (s, 3H, O-C-CH_3), 3.04 (b, 1H, D_2O washable CH$\underline{OH}$), 4.43 (m, 1H, $\underline{CH}$OH), 6.0 (s, 1H, C=CH), 6.08 (s, 1H, C-CH).

^{13}C NMR : δ 13.85, 22.48, 25.65, 26.18, 29.12, 29.41, 31.70, 36.40 (alkyl C), 70.10 (C-OH), 124.87, 150.88, (C C), 200.08 (C=O).

Analysis calcd. for $C_{14}H_{26}O_2$: C 74.283, H 11.578.

Found : C 74.50, H 11.576.

4-Hydroxy-3-methyleneundecan-2-one (75b):

This was prepared from octanal and methyl vinyl ketone using DABCO as catalyst.

Reaction time : 100h

Yield : 63%

b.p. : 119-122°C/3mm

IR (neat) : 3450, 1675 cm^{-1}

^1H NMR : δ 0.86 (distorted t, 3H), 1.26 (m, 12H), 2.32 (s, 3H), 3.84 (b, 1H), 4.44 (m, 1H), 6.02 (s, 1H), 6.08 (s, 1H).

^{13}C NMR : δ 13.85, 22.42, 25.65, 26.18, 29.06, 29.47, 31.64, 36.40 (alkyl C), 71.21 (C-OH), 124.98, 151.82 (C=C), 200.14 (C=O).

4-Hydroxy-3-methylenedecan-2-one (75c):

This was prepared from heptanal and methyl vinyl ketone using DABCO as catalyst.

Reaction time : 80h

yield : 73%

b.p. : 80-85°C/0.5 mm

IR (neat) : 3450, 1670 cm^{-1}

^1H NMR : δ 0.9 (distorted t, 3H), 1.26 (m, 10H), 2.36 (s, 3H), 3.04 (b, 1H), 4.4 (m, 1H), 6.0 (s, 1H), 6.08 (s, 1H).

^{13}C NMR : δ 14.00, 22.60, 25.80, 26.41, 29.12, 31.70, 36.45 (alkyl C), 70.80 (C-OH), 125.82, 150.70 (C=C), 200.48 (C-O).

4-Hydroxy-3-methylenenonan-2-one (75d):

This compound 75d was prepared from hexanal and methyl vinyl ketone using DABCO as catalyst.

Reaction time : 72h

yield : 65%

b.p. : 74-77°C/0.5 mm

IR (neat) : 3430, 1675 cm^{-1}

^1H NMR : δ 0.88 (distorted t, 3H), 1.3 (m, 8H), 2.34 (s, 3H), 3.08 (b, 1H), 4.4 (m, 1H), 6.0 (s, 1H), 6.08 (s, 1H).

^{13}C NMR : δ14.00, 22.60, 25.50, 26.47, 31.64, 36.45 (alkyl C), 70.68 (C-OH), 125.88, 150.88 (C=C), 200.55 (C=O).

Analysis calcd. for $C_{10}H_{18}O_2$: C 70.548, H 10.657.

Found : C 70.530, H 10.670.

4-Hydroxy-6-methyl-3-methyleneheptan-2-one (75e):

This was prepared from isovaleraldehyde and methyl vinyl ketone using DABCO as catalyst.

Reaction time : 72h

Yield : 51%

b.p. : 76-79°C/1.5 mm

IR (neat) : 3440, 1675 cm^{-1}

^{1}H NMR : δ 0.96 (two d, 6H, J = 6Hz), 1.44 (m, 2H), 1.76 (m, 1H), 2.36 (s, 3H), 3.14 (b, 1H), 4.54 (m, 1H), 6.04 (s, 1H), 6.1 (s, 1H).

^{13}C NMR : δ 21.60, 23.30, 24.65, 26.36, 45.61 (alkyl C), 68.63 (C-OH), 124.93, 151.29 (C=C), 200.37 (C=O).

4-Hydroxy-3-methylene-4-phenylbutan-2-one (75f):

This compound *75f* was prepared from benzaldehyde and methyl vinyl ketone employing DABCO as catalyst.

Reaction time : 9 days

Yield : 51%

b.p. : 118-120°C/1 mm

IR (neat) : 3420, 1665 cm^{-1}

^{1}H NMR : δ 2.26 (s, 3H), 3.56 (b, 1H), 5.52 (s, 1H), 5.90 (s, 1H), 6.04 (s, 1H), 7.26 (s, 5H).

^{13}C NMR : δ 26.41 ($-CH_3$), 72.15 (C-OH), 126.28, 126.51, 127.51, 128.22, 141.66, 150.06 (C=C and phenyl C), 200.01 (C=O).

Analysis Calcd. for $C_{11}H_{12}O_2$: C 74.977, H 6.864.

Found : C 75.031, H 6.842.

4-Hydroxy-3-methylene-6-phenylhexan-2-one (75g) :

The above compound 75g was prepared from dihydrocinnamaldehyde and methyl vinyl ketone using DABCO as catalyst.

Reaction time : 85h

Yield : 65%

b.p. : 136-138°C/1.2 mm

IR (neat) : 3450, 1670 cm^{-1}

^1H NMR : δ 1.9 (t, 2H J=6Hz), 2.26 (s, 3H), 2.66 (m, 2H), 3.16 (b, 1H), 4.44 (m, 1H), 6.0 (s, 1H), 6.04 (s, 1H), 7.18 (s, 5H).

^{13}C NMR : δ 26.30, 31.93, 37.80 (alkyl C), 69.92 (C-OH), 125.40, 125.64, 128.16, 128.28, 141.66, 152.35 (C=C and phenyl C), 200.37 (C=O).

Analysis Calcd. for $C_{13}H_{16}O_2$: C 76.44, H 7.895.

Found : C 76.20, H 7.90.

4-Hydroxy-3-methylenenonadecan-2-one (75h):

Compound 75h was prepared from cetylaldehyde and methyl vinyl ketone by using DABCO as catalyst. Reaction was stopped after 15 days at 70% completion.

Yield : 51%

b.p. : 146-148°C/0.3 mm

IR (neat) : 3450, 1675 cm^{-1}

^1H NMR : δ 0.8 (distorted t, 3H), 1.2 (m, 28H), 2.28 (s, 3H), 2.92 (b, 1H), 4.4 (m, 1H), 5.97 (s, 1H), 6.04 (s, 1H).

^{13}C NMR : δ 14.20, 22.77, 26.00, 26.53, 29.41, 29.76, 31.99, 36.45 (alkyl C), 71.33 (C-OH), 125.40, 150.65 (C C), 200.61 (C=O).

2-Cyanopent-1-en-3-ol (47a):

A mixture of propionaldehyde (0.72 mL, 10 mM) acrylonitrile (1 mL, 15 mM) and DABCO (0.168 g, 1.5 mM) was kept at room temperature for 40 hours. The reaction mixture was taken up in ether (25 mL) and washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution and dried over anhydrous sodium sulphate. Solvent was removed and the residue was distilled to afford 47a in 80% yield (0.9g).

b.p. : 64-65°C/1 mm

IR (neat) : 3460, 2200, 1620 cm^{-1}

^1H NMR : δ 0.91 (t, 3H, J = 7Hz, CH_3), 1.67 (m, 2H, CH_2), 3.4 (b, 1H, CHOH), 4.1 (t, 1H, J = 6Hz, CHOH), 5.95 (s, 2H, $C=CH_2$).

^{13}C NMR : δ 9.00, 27.17 (alkyl C), 73.06 (C-OH), 117.00 (C ≡N), 126.96, 130.30 (C=C).

Analysis Calcd. for C_6H_9NO : C 64.84, H 8.162, N 12.60.

Found : C 64.68, H 8.19, N 12.52.

2-Cyano-4-methylpent-1-en-3-ol (47b):

This was prepared from isobutyraldehyde, acrylonitrile and DABCO.

Reaction time : 40h

Yield : 66%

b.p. : 70-71°C/1 mm

IR (neat) : 3450, 2250, 1630 cm^{-1}

^1H NMR : δ 0.96 (d, 6H, J = 6Hz), 1.52 (m, 1H), 2.92 (b, 1H), 3.96 (d, 1H, J = 6Hz), 6.0 (s, 1H), 6.04 (s, 1H).

^{13}C NMR : δ 16.64, 18.58, 32.17 (alkyl C), 77.12 (C-OH), 117.30 (C≡N), 125.89, 131.00 (C=C).

2-Cyano-5-methylhex-1-en-3-ol (47c):

This was prepared from isovaleraldehyde, acrylonitrile and DABCO.

Reaction time : 40h

Yield : 69%

b.p. : 76°C/0.8 mm

IR (neat) : 3450, 2250, 1635 cm^{-1}

^1H NMR : δ 1.0 (d, 6H, J - 7Hz), 1.6 (m, 3H), 2.6 (b, 1H), 4.32 (t, 1H, J = 6Hz), 6.0 (s, 2H).

^{13}C NMR : δ 21.82, 22.94, 24.95, 44.70 (alkyl C), 70.71 (C-OH), 117.24 (C≡N), 127.53, 129.83 (C=C).

2-Cyanooct-1-en-3-ol (47d):

This was prepared from hexanal, acrylonitrile and DABCO.

Reaction time : 72h

Yield : 87%

b.p. : 88-90°C/1 mm

IR (neat) : 3450, 2250, 1630 cm^{-1}

^{1}H NMR : δ 0.88 (distorted t, 3H), 1.46 (m, 8H), 2.8 (b, 1H), 4.18 (t, 1H, J = 6Hz), 5.94 (s, 1H), 5.97 (s, 1H).

^{13}C NMR : δ 13.82, 22.41, 24.64, 31.35, 35.58 (alkyl C), 72.24 (C-OH), 117.18 (C≡N), 127.12, 130.01 (C=C).

2-Cyanododec-1-en-3-ol (47e):

This was prepared from decyl aldehyde, acrylonitrile and DABCO.

Reaction time : 7 days

Yield : 84%

b.p. : 130-132°C/0.5 mm (lit. b.p. 120°C/0.15 mm)[51]

IR (neat) : 3450, 2250, 1630 cm^{-1}

^{1}H NMR : δ 0.8 (distorted t, 3H), 1.2 (m, 16H), 2.04 (b, 1H), 4.12 (m, 1H), 5.88 (s, 2H).

^{13}C NMR : δ 14.05, 22.64, 25.06, 29.29, 29.47, 31.88, 35.70 (alkyl C), 72.47 (C-OH), 119.00 (C≡N), 127.18, 129.89 (C=C).

2-Cyano-1-phenylprop-2-en-1-ol (47f):

This was prepared from benzaldehyde, acrylonitrile and DABCO.

Reaction time : 40h

Yield : 70%

b.p. : 120-124°C/2 mm (lit. b.p.110°C/0.95 mm)[51]

IR (neat) : 3450, 2240, 1620 cm^{-1}

^{1}H NMR : δ3.5 (b, 1H), 5.08 (s, 1H), 5.85 (d, 1H, J = 2Hz), 5.95 (d, 1H, J = 2Hz), 7.23 (s, 5H).

^{13}C NMR : δ 73.71 (C-OH), 117.00 (C≡N), 126.06, 126.48, 128.77, 130.24, 139.12 (C=C and phenyl C).

Analysis Calcd. for $C_{10}H_9NO$: C 75.452, H 5.699, N 8.798.

Found : C 75.42, H 5.689, N 8.801.

2-Cyano-5-phenylpent-1-en-3-ol (47g):

This was prepared from dihydrocinnamaldehyde, acrylonitrile and DABCO.

Reaction time : 50h

Yield : 76%

b.p. : 130°C/1 mm

IR (neat) : 3450, 2250, 1620 cm^{-1}

^1H NMR : δ 2.08 (m, 2H), 2.18 (b, 1H), 2.78 (t, 2H, J 6Hz), 4.24 (t, 1H, J = 6Hz), 6.0 (s, 2H), 7.26 (s, 5H).

^{13}C NMR : δ 21.23, 27.06 (alkyl C), 71.47 (C-OH), 117.21, (C≡N), 126.06, 128.50, 128.74, 130.24, 140.88 (C=C and phenyl C).

3-Hydroxy-2-(phenylsulfonyl)-1-butene (82):

A mixture of phenyl vinyl sulfone (1.68 g, 10 mM), DABCO (0.168 g, 1.5 mM), acetaldehyde (5 mL) were allowed to react at room temperature for 20 days. Reaction mixture was charged on a column packed with silica gel and eluted with 20% ethyl acetate in hexane to obtain 82 in 80% yield (1.7g) as a viscous oil.

IR (neat) : 3500, 1600 cm^{-1}

^1H NMR : δ 1.26 (d, 3H, J = 6Hz, CH_3), 3.7 (b, 1H, CHOH), 4.5 (distorted q, 1H, CHOH), 6.12 (s, 1H, C-CH), 6.32 (s, 1H, C=CH), 7.52 (m, 3H, aromatic), 7.8 (m, 2H, aromatic).

^{13}C NMR : δ 23.00 (CH_3), 64.43 (C-OH), 124.48, 128.06, 129.42, 133.83, 139.30, 154.60 (C=C and phenyl C).

Analysis calcd. : C 56.585, H 5.698
for $C_{10}H_{12}O_3S$
Found : C 56.601, H 5.688.

Ethyl phenylglyoxylate (85):

This compound was prepared according to the literature method.[84]

Phenylmagnesium bromide (100 mM) in 100 mL of THF was added slowly to diethyl oxalate (43.8 g, 300 mM) in 200 mL of THF at -10°C over a period of one hour. The reaction was quenched immediately with 2N hydrochloric acid to a pH of 4.0 and the aqueous layer was extracted with methylene chloride (2x100 mL). Combined organic layers were dried over anhydrous $MgSO_4$. Removal of solvent followed by distillation afforded **85** in 50% (8.9 g) yield.

b.p. : 120-126°C/3 mm (lit. b.p.100-103°C/1 mm)[84]
IR (neat) : 1740, 1695, 1600 cm^{-1}
^1H NMR : δ 1.38 (t, 3H, J = 6Hz, CH_3), 4.4 (q, 2H, J - 6Hz, OCH_2), 7.7 (m, 3H, aromatic), 7.92 (m, 2H, aromatic).

Ethyl p-tolylglyoxylate (86):

This was prepared from p-tolylmagnesium bromide and diethyl oxalate following the same procedure as in the case of ethyl phenylglyoxylate, in 57% yield.

b.p. : 106-110°C/1 mm
IR (neat) : 1730, 1680, 1600 cm^{-1}
^1H NMR : δ 1.42 (t, 3H, J = 6Hz, CH_3), 2.42 (s, 3H, C_6H_4-$\underline{CH_3}$), 4.42 (q, 2H, J = 6Hz, -OCH_2), 7.26 (d, 2H, J = 8Hz, aromatic), 7.88 (d, 2H, J = 8Hz, aromatic).

Ethyl 3-cyano-2-hydroxy-2-phenylbut-3-enoate (87a):

A mixture of ethyl phenylglyoxylate (85) (1.78 g, 10 mM) acrylonitrile (1.3 mL, 20 mM) and DABCO (336 mg, 3 mM) was allowed to stand at room temperature for 5 days. The reaction mixture was taken up in dichloromethane (25 mL) and washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution and dried over anhydrous sodium sulphate. After the removal of the solvent, the product was purified by column chromatography (10% ethyl acetate in hexane) followed by distillation to give 87a in 65% (1.50 g) yield.

b.p. : 164-166°C/4 mm

IR (neat) : 3450, 2250, 1725, 1610 cm^{-1}

^1H NMR : δ 1.32 (t, 3H, J = 7Hz, CH_3), 4.32 (m, 3H, 1H D_2O washable, $-OCH_2$, C-OH), 6.08 (s, 1H, C-CH), 6.12 (s, 1H, C-CH), 7.40 (m, 5H, C_6H_5).

^{13}C NMR : δ 13.76 (CH_3). 63.76 (C-O), 78.59 (C-OH), 116.88 (C≡N), 125.30, 126.36, 128.65, 129.06, 133.95, 137.65, (C-C and phenyl C), 171.65 (C=O).

Analysis Calcd. for $C_{13}H_{13}NO_3$: C 67.521, H 5.666, N 6.056.

Found : C 67.459, H 5.680, N 6.070.

Ethyl 3-cyano-2-hydroxy-2-p.tolylbut-3-enoate (87b):

This was prepared from acrylonitrile, ethyl p-tolylglyoxylate (86) and DABCO.

Reaction time : 7 days

Yield : 74%

b.p. : 162-164°C/1 mm

IR (neat) : 3450, 2200, 1735, 1620 cm^{-1}

^1H NMR : δ 1.34 (t, 3H, J = 7Hz), 2.34 (s, 3H), 4.3 (m, 3H), 6.08 (s, 1H), 6.12 (s, 1H), 7.14 (d, 2H, J 8Hz), 7.36 (d, 2H, J = 8Hz).

^{13}C NMR : δ 13.64, 20.82 (alkyl C), 63.59 (C-O), 78.41 (C-OH), 116.88 (C ≡N), 125.36 126.18, 129.24, 132.71, 134.71, 138.48 (C-C and phenyl C), 171.71 (C=O).

Methyl 3-cyano-2-hydroxy-2-methylbut-3-enoate (87c):

Methyl pyruvate (1.02 g, 10 mM) was added to a mixture of acrylonitrile (5.3 g, 100 mM) and DABCO (168 mg, 1.5 mM) and allowed to react at room temperature for 24 h. Reaction mixture was taken up in methylene chloride (25 mL) washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate. Solvent was removed and the product was purified by column chromatography (10% ethyl acetate in hexane) followed by distillation to give the pure product **87c** in 38% yield (0.59 g).

b.p. : 98-100°C/5 mm

IR (neat) : 3450, 2250, 1740, 1625 cm^{-1}

^1H NMR : δ 1.64 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.0 (b, 1H, COH), 6.08 (s, 1H, C=CH), 6.24 (s, 1H, C-CH).

^{13}C NMR : δ 24.64 (CH_3), 53.76 (O-CH_3), 74.18 (C-OH), 116.82 (C ≡N), 125.53, 131.77 (C=C), 173.59 (C=O).

Ethyl 3-cyano-2-hydroxy-2-methylbut-3-enoate (87d):

This was prepared from acrylonitrile, ethyl pyruvate and DABCO following the same procedure as in **87c**.

Reaction time : 24h

Yield : 41%

b.p. : 84-86°C/2 mm

IR (neat) : 3450, 2250, 1730, 1620 cm^{-1}

^1H NMR : δ 1.34 (t, 3H, J - 6Hz), 1.66 (s, 3H), 4.1 (b, 1H), 4.3 (q, 2H, J = 6Hz), 6.08 (s, 1H), 6.26 (s, 1H).

^{13}C NMR : δ 13.82, 34.64 (alkyl C), 67.41 ($O-CH_2$), 71.00 (C-OH), 116.65 (C ≡N), 125.77, 131.59 (C=C), 173.24 (C=O).

Ethyl 3-carbomethoxy-2-hydroxy-2-phenylbut-3-enoate (88a):

A mixture of ethyl phenylglyoxylate (1.78 g, 10 mM) methyl acrylate (1.72 g, 20 mM) and DABCO (336 mg, 3 mM) was allowed to react at room temperature for seven days. Reaction mixture was taken up in methylene chloride (25 mL) washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution and dried over anhydrous sodium sulphate. Solvent was removed and the compound was purified by column chromatography (10% ethyl acetate in hexane) followed by distillation to afford 1.3 g (49%) of the compound 88a.

b.p. : 154-155°C/1.5 mm

m.p. : 54-56°C

IR (neat) : 3475, 1730, 1630 cm^{-1}

^1H NMR : δ 1.24 (t, 3H, J = 7Hz, CH_3), 3.74 (s, 3H, OCH_3), 4.24 (q, 2H, J = 7Hz, OCH_2), 4.4 (s, 1H, C-OH), 5.3 (s, 1H, C=CH), 6.3 (s, 1H, C=CH), 7.44 (m, 5H, C_6H_5).

^{13}C NMR : δ 13.17 (CH_3), 51.41 ($O-CH_3$), 61.71 ($O-CH_2$), 78.00 (C-OH), 126.24, 127.53, 127.71, 128.30, 137.42, 142.53 (C=C and phenyl C), 168.18, 172.71 (C=O).

Ethyl 3-carbomethoxy-2-hydroxy-2-p.tolylbut-3-enoate (88b):

This was prepared from methyl acrylate, ethyl p-tolylglyoxylate and DABCO following the same procedure as in **88a**.

Reaction time : 9 days

Yield : 41%

m.p. : 87-89°C

IR (neat) : 3450, 1720, 1625 cm^{-1}

^1H NMR : δ 1.26 (t, 3H, J = 6Hz), 2.34 (s, 3H), 3.78 (s, 3H), 4.26 (m, 3H), 5.38 (s, 1H), 6.34 (s, 1H), 7.14 (d, 2H, J - 8Hz), 7.48 (d, 2H, J - 8Hz).

^{13}C NMR : δ 13.76, 20.82 (alkyl C), 52.00(O-CH_3), 62.29(O-CH_2), 78.53 (C-OH), 126.65, 128.83, 129.06, 135.13, 138.06, 142.95 (C=C and phenyl C), 168.23 (C-O).

Analysis Calcd. for $C_{15}H_{18}O_5$: C 64.736, H 6.519.

Found : C 64.801, H 6.498.

Ethyl 2-carboethoxy-3-carbomethoxy-2-hydroxybut-3-enoate (91a):

A solution of diethyl ketomalonate (0.87 g, 5 mM), methyl acrylate (0.43 g, 5 mM) and DABCO (56 mg, 0.5 mM) in 3.7 mL of THF was allowed to stand at room temperature for 4h. The reaction mixture was taken up in methylene chloride (25 mL) and washed with dil.hydrochloric acid, sodium bicarbonate solution and dried over anhy. sodium sulphate. Removal of solvent followed by column chromatography (20% ethyl acetate in hexane) gave **91a** in 77% yield (1.0 g) as a colorless liquid.

IR (neat) : 3460, 1730, 1630 cm^{-1}

^{1}H NMR : δ 1.32 (t, 6H, J = 6Hz, $2CH_3$), 3.78 (s, 3H, OCH_3), 4.3 (q, 4H, J=6Hz, $2\times OCH_2$), 4.56 (b, 1H, C-OH), 6.02 (s, 1H, C=CH), 6.42 (s, 1H, C=CH).

^{13}C NMR : δ 13.35 (CH_3), 51.76 (O-CH_3), 62.41 (OCH_2), 78.71 (C-OH), 127.59, 137.36 (C=C), 162.59, 168.77 (C-O).

Analysis Calcd. for $C_{11}H_{16}O_7$: C 50.768, H 6.197.

Found : C 50.62, H 6.21.

Ethyl 2,3-dicarboethoxy-2-hydroxybut-3-enoate (91b):

This was prepared from diethyl ketomalonate, ethyl acrylate and DABCO following the same procedure as in **91a.**

Reaction time : 6h

Yield : 73%

IR (neat) : 3460, 1730, 1630 cm^{-1}

^{1}H NMR : δ 1.28 (t, 9H, J = 7Hz), 4.25 (m, 7H, 1H is D_2O washable), 5.98 (s, 1H), 6.44 (s, 1H).

^{13}C NMR : δ 13.11, 13.23 (alkyl C), 60.65, 62.18, 62.47 (O-CH_2), 78.41 (C-OH), 127.18, 137.12 (C=C), 164.41, 168.36 (C=O).

Analysis Calcd. for $C_{12}H_{18}O_7$: C 52.55, H 6.61.

Found : C 52.72, H 6.60.

Ethyl 2-carboethoxy-3-carbot.butoxy-2-hydroxybut-3-enoate (91c):

This was prepared from t-butyl acrylate, diethyl ketomalonate and DABCO following the same procedure as in **91a.**

Reaction time : 36h

Yield : 67%

IR (neat) : 3470, 1740, 1630 cm^{-1}

^1H NMR : δ 1.29 (t, 6H, J = 6Hz), 1.41 (s, 9H), 4.3 (m, 5H), 5.90 (s, 1H), 6.38 (s, 1H).

^{13}C NMR : δ 13.70 (alkyl C), 63.82 (O-CH_2 and C-O), 77.82 (C-OH), 119.71, 134.30 (C=C), 158.71, 167.36 (C-O).

Ethyl 2-carboethoxy-3-cyano-2-hydroxybut-3-enoate (91d):

This was prepared from acrylonitrile, diethyl ketomalonate and DABCO following the same procedure as in **91a.**

Reaction time : 3h

Yield : 80%

IR (neat) : 3450, 2200, 1730, 1620 cm^{-1}

^1H NMR : δ 1.34 (t, 6H, J = 6Hz), 4.34 (m, 5H, 1H is D_2O washable), 6.26 (s, 1H), 6.48 (s, 1H).

^{13}C NMR : δ 13.70 (CH_3), 63.88 (OCH_2), 77.77 (C-OH), 116.12 (C ≡N), 119.65, 134.30 (C=C), 167.36 (C-O).

Ethyl 2-carboethoxy-2-hydroxy-3-methylene-4-oxopentanoate (91e):

This was prepared by the coupling of methyl vinyl ketone with diethyl ketomalonate in 1M THF solution using DABCO (5 mole %) as catalyst.

Reaction time : 30 minutes

Yield : 74%

IR (neat) : 3460, 1730, 1680, 1620 cm^{-1}

^1H NMR : δ 1.28 (t, 6H, J = 6Hz), 2.4 (s, 3H), 4.26 (m, 5H), 6.16 (s, 1H), 6.32 (s, 1H).

^{13}C NMR : δ 13.05, 25.59 (alkyl C), 61.88 (OCH_2), 78.53 (C-OH), 127.36, 145.07 (C=C), 168.34, 197.59 (C=O).

Phenyl vinyl ketone (94):

This was prepared according to the known procedure.[91]

To a mixture of dimethylamine hydrochloride (26.1 g, 320 mM) paraformaldehyde (10 g), acetophenone (30 g, 250 mM), 95% ethanol (40 mL), 0.5 mL of conc. hydrochloric acid was added and the reaction mixture was refluxed for 2h. Reaction mixture became clear and homogeneous. It was transferred into a conical flask and 200 mL of acetone was added while it was still warm. Reaction mixture was cooled to room temperature and refrigerated overnight to yield crystals of dimethylaminopropiophenone hydrochloride.

m.p. : 154-156°C (lit. m.p.152-155°C)[91]

Yield : 35 g (65.4%)

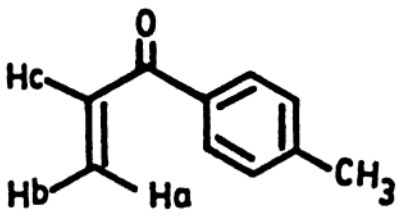
A mixture of dimethylaminopropiophenone hydrochloride (32.1 g, 150 mM) and hydroquinone (0.3 g) was heated to distil out phenyl vinyl ketone under reduced pressure. Compound was collected between 70 and 90°C/2 mm. Redistillation afforded the pure compound.

b.p. : 70-73°C/3 mm (lit. b.p.72-73°C/3 mm)[91]

Yield : 10.5 g (53%)

p-Tolyl vinyl ketone (95):

3-Dimethylamino-1-p-tolylpropan-2-one hydrochloride was prepared in 64% yield from p-tolyl methyl ketone, dimelthylamine hydrochloride and paraformaldehyde following the same procedure as in 94. Pyrolysis of this compound afforded p-tolyl vinyl ketone.



Yield : 50%

b.p. : 82-86°C/2 mm (lit. b.p.50°C/0.1 mm)[99]

IR (neat) : 1680, 1600, 1570 cm^{-1}

^1H NMR : δ 2.32 (s, 3H, CH_3), 5.8 (dd, 1H, J - 10Hz, 2Hz, Hb), 6.36 (dd, 1H, J - 16Hz, 2Hz, Ha), 7.14 (m, 3H, 2H from phenyl, Hc), 7.8 (d, 2H, J = 8Hz, 2H phenyl).

^{13}C NMR : δ 21.17 (CH_3), 128.24, 128.59, 129.06, 132.12, 134.54, 143.59 (C=C and phenyl C), 190.06 (C=O).

Dimerization of α,β -unsaturated ketones

1,5-Di(p-tolyl)-2-methylene-1,5-pentanedione (96a):

A mixture of p-tolyl vinyl ketone (2.19 g, 15 mM) and DABCO (0.25 g, 2.25 mM) was kept at room temperature (35°C) for one hour. The reaction mixture was taken up in ether (25 mL) washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution and dried over anhydrous sodium sulphate. After the removal of the solvent, the product was purified by column chromatography (10% ethyl acetate in hexane) and then crystallized from n-hexane to obtain 96a in 49% yield (1.07 g).

m.p. : 89-90°C

IR (KBr) : 1680, 1640, 1620, 1605 cm^{-1}

^1H NMR : δ 2.4 (s, 6H, $2CH_3$), 2.92 (m, 2H, CH_2), 3.17 (m, 2H, CH_2), 5.6 (s, 1H, C=CH), 5.88 (s, 1H, C=CH), 7.20 (d, 4H, J = 8Hz, aromatic), 7.64 (d, 2H, J = 8Hz, aromatic), 7.84 (d, 2H, J = 8Hz, aromatic).

^{13}C NMR : δ 21.35, 27.41, 36.88 (alkyl C), 125.89, 128.18, 128.89, 129.24, 129.71, 134.36, 135.00, 142.95, 143.77, 147.00 (C=C and phenyl C), 197.77, 198.83 (C=O).

MS m/e : 292 (M^+)

Analysis Calcd. : C 82.16, H 6.89.
for $C_{20}H_{20}O_2$
Found : C 81.81, H 6.91.

1,5-Diphenyl-2-methylene-1,5-pentanedione (96b):

This was prepared via dimerization of phenyl vinyl ketone (94) using DABCO as catalyst following the same procedure as in 96a.

Reaction time : 15 minutes

Yield : 62%

b.p. : 200°C/2 mm

IR (neat) : 1680, 1620, 1600 cm^{-1}

^1H NMR : δ 2.94 (m, 2H), 3.18 (m, 2H), 5.64 (s, 1H), 5.92 (s, 1H), 7.46 (m, 6H), 7.7 (m, 2H), 7.96 (m, 2H).

^{13}C NMR : δ 27.23, 37.12 (alkyl C), 127.24, 128.12, 128.24, 128.65, 129.52, 132.30, 133.12, 136.83, 146.83 (C=C and phenyl C), 199.18, 199.30 (C-O).

Analysis Calcd. : C 81.792, H 6.101.
for $C_{18}H_{16}O_2$
Found : C 81.900, H 6.089.

4-Methylene-3,7-nonanedione (96c):

A mixture of ethyl vinyl ketone (1.26 g, 15 mM) and DABCO (0.25 g, 2.25 mM) was allowed to react at room temperature for 40 h. Reaction mixture was taken up in ether (25 mL) washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution and dried over anhydrous sodium sulphate. Solvent was removed and distilled to afford 96c in 60% yield (0.75 g).

b.p. : 94-96°C/1 mm

IR (neat) : 1720, 1680, 1640 cm^{-1}

^1H NMR : δ 1.08 (m, 6H), 2.43 (q, 2H, J = 6Hz), 2.56 (s, 4H), 2.72 (q, 2H, J = 7Hz), 5.78 (s, 1H), 6.02 (s, 1H).

^{13}C NMR : δ 7.58, 8.23, 25.33, 30.70, 35.70, 41.00 (alkyl C), 124.77, 147.36 (C=C), 202.36 210.77 (C=O).

Analysis Calcd. for $C_{10}H_{16}O_2$: C 71.394, H 9.586.

Found : C 71.429, H 9.610.

3-Methylene-2,6-heptanedione (96d):

To a solution of methyl vinyl ketone (1.05 g, 15 mM) in 1.75 mL THF DABCO (0.25 g, 2.25 mM) was added at room temperature and kept at room temperature for four days. Reaction mixture was taken up in ether (25 mL) washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution and dried over anhydrous sodium sulphate. Solvent was removed and distilled to give pure **96d** in 59% yield (0.62 g).

b.p. : 98-100°C/6 mm

IR (neat) : 1710, 1670, 1620 cm^{-1}

^1H NMR : δ 2.12 (s, 3H), 2.32 (s, 3H), 2.54 (m, 4H), 5.82 (s, 1H), 6.04 (s, 1H).

^{13}C NMR : δ 24.70, 25.29, 29.23, 41.98 (alkyl C), 125.71, 147.42 (C=C), 199.07, 207.37 (C=O).

2,4-Dicyanobut-1-ene (97):

A mixture of acrylonitrile (0.8 g, 15 mM) and DABCO (0.84 g, 7.5 mM) was kept at room temperature for ten days. Reaction mixture was taken up in ether (25 mL) washed with 2N hydrochloric acid, aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate. Removal of

solvent followed by distillation afforded 0.32 g of (40%) the compound 97.

b.p. : 96-98°C/4 mm

IR (neat) : 2270, 2250, 1620 cm^{-1}

^1H NMR : δ 2.48[s, 4H, $(CH_2)_2$], 5.8 (s, 1H, C=CH), 5.9 (s, 1H, C=CH).

^{13}C NMR : δ 16.00, 30.17 (alkyl C), 117.42, 117.94 (C≡N), 119.24, 133.65 (C=C).

Analysis Calcd. for $C_6H_6N_2$: C 67.906, H 5.698, N 26.395.

Found : C 67.82, H 5.701, N 26.36.

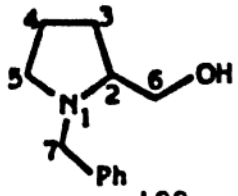
(S)-N-Benzoylproline (102):

(S)-Proline (11.5 g, 100 mM) was dissolved in 20 mL of sodium hydroxide solution (8 g, 200 mM). Benzoyl chloride (14 g, 100 mM) was added at 0°C to this. Stirring was continued for additional 1 h at 0°C. The reaction mixture was washed with chloroform to remove any excess benzoyl chloride. Aqueous layer was acidified with dil.HCl, extracted with methylene chloride (200 mL), dried over anhydrous Na_2SO_4. Removal of solvent followed by crystallization of the solid from hexane afforded 102 in 80% (17.52 g) yield.

m.p. : 125-130°C

(S)-N-Benzylprolinol (98):

(S)-N-Benzoylproline (102) (14.89 g, 68 mM) was added slowly to LAH (5.31 g, 140 mM) in 300 mL of THF over 30 minutes and the reaction mixture was refluxed for 1h. A solution of KOH (2.8 g), in 11.2 mL of water, was added slowly and refluxed for further 15 minutes. The salts were filtered through suction and the residue was again refluxed for 30 minutes with 150 mL of THF. The combined organic extracts were concentrated in vacuum and the distillation of the residue under reduced pressure afforded 10.3 g (79%) of (S)-N-benzylprolinol (98).



b.p. : 124-126°C/2 mm (lit. b.p.115-120°C/0.5 mm)[100]

IR (neat) : 3400, 1600 cm^{-1}

$[\alpha]_D^{20}$: -59.66° (C 2, $CHCl_3$) [(lit. $[\alpha]_D^{20}$: -59.9° (C 1, $CHCl_3$)][100]

^1H NMR : δ 1.3-1.96 (m, 4H, H3, H4), 2.0-3.0 (m, 3H, H2, H5), 3.26 and 3.94 (AB quartet, 2H, J = 14Hz, H7), 3.48 (m, 2H, H6), 3.78 (1H, OH, D_2O washable), 7.22 (s, 5H, aromatic).

^{13}C NMR : δ 22.76, 27.71, 54.00, 58.47, 62.18 (alkyl C), 64.18 ($\underline{CH_2}OH$), 126.65, 127.94, 128.53, 138.95 (aromatic C).

(S)-(+)-2-Hydroxymethylpyrrolidine (103):

This was prepared according to Ender's procedure[92] : Lithium aluminium hydride (10.1 g, 266 mM) was taken in 400 mL of dry THF and was heated to reflux. Then (S)-proline (19.1 g, 166 mM) was added in small portions so as to maintain reflux. After the addition, reaction mixture was refluxed for 1h. A solution of KOH (4.6 g) in 18.6 mL of water was added carefully. The resulting slurry was refluxed for additional 15 min. to complete the hydrolysis. The salts were removed by suction filtration and then the residue was again refluxed for 30 min. with 100 mL of THF in order to extract all of prolinol. The combined organic solutions were concentrated in vacuo and distilled.

b.p. : 90-93°C/8 mm (lit. b.p.79-82°C/3 mm)[92]

Yield : 13 g (78%)

$[\alpha]_D^{20}$: +31.5° (C 1,benzene) [lit. $[\alpha]_D^{20}$: +31.6°(C 1,benzene)][92]

IR (neat) : 3500-3000 cm^{-1}

(S)-1-Aza-4-oxabicyclo[4.3.0]nonan-2-one (105):

Chloroacetyl chloride (11 mL, 140 mM) was added dropwise with

stirring over 1h to a solution of 2-hydroxymethylpyrrolidine (11.6 g, 115 mM) in water (120 mL) at 0°C. After 30 minutes 30% (w/w) sodium hydroxide aqueous solution (30 mL) was added at 0°C. The reaction mixture was allowed to warm to room temperature. After 2h stirring at room temperature (30-35°C), conc. hydrochloric acid was added to adjust to p^H = 1 and the product was extracted with methylene chloride, dried over anhy. Na_2SO_4. Removal of the solvent afforded colorless crystals of 105 in 38% (6.2 g) yield.

m.p. : 64-66°C (lit. m.p.63.5-66°C)[101]

IR (KBr) : 1660 cm^{-1}

^1H NMR : δ1.4-2.2 (m, 4H), 3.1-4.32 (m, 7H).

^{13}C NMR : δ 21.76, 28.41, 44.35, 56.76, 66.47, 68.71 (alkyl C), 166.30 (C=O).

(S)-1-Aza-4-oxabicyclo[4.3.0]nonane (99):

(S)-1-Aza-4-oxa(4.3.0)nonan-2-one (105) (6.06 g, 43 mM) was slowly added to $LiAlH_4$ (2.43 g, 64mM)in 75 mL of THF and heated under reflux for 4h. Reaction mixture was cooled and 25 mL of 2.5N aq. sodium hydroxide solution was added cautiously. After 15 minutes, the salts were filtered and the salts were washed with THF (2x20 mL). The combined organic solutions were dried over anhy. Na_2SO_4. Removal of solvent under vacuum followed by distillation furnished 64% (3.5 g) of 99.

b.p. : 159-162°C

$[\alpha]_D^{20}$: -1.3° (C 6,acetone)

IR (neat) : No carbonyl absorption.

^1H NMR : δ1.2-2.4 and 2.6-4.04 (m, 13H).

^{13}C NMR : δ 20.53, 25.70, 52.59, 53.47, 62.18,65.88, 71.47 (alkyl C).

Coupling of methyl acrylate with 2-furaldehyde using (S)-1-aza-4-oxabicyclo [4.3.0]nonane as catalyst:

2-Furaldehyde (0.96 g, 10 mM), methyl acrylate (1.29 g, 15 mM) and the above catalyst **99** (0.5 g, 4 mM) were mixed together and allowed to react at room temperature. Only 75% of the reaction was complete even after 120 days. Direct column chromatography with 10% ethyl acetate in hexane gave **106** in 60% (1.1 g) yield.

$$[\alpha]_D^{20} = +3.57° \text{ (C 2.8, MeOH)}$$

This product has identical spectral data with the product obtained from furaldehyde and methyl acrylate catalyzed by DABCO.

Coupling of acrylonitrile with propionaldehyde using quinidine as catalyst:

To a mixture of acrylonitrile (0.66 mL, 10 mM) and propionaldehyde (2 mL), quinidine (0.97 g, 3 mM) was added. Quinidine did not dissolve in the reaction mixture initially. After 2-3 days the reaction mixture becomes homogeneous and was worked up after ten days by directly charging it on a column packed with silica gel using 10% ethyl acetate in hexane to afford chiral 2-cyanopent-1-en-3-ol (**107a**) in 66% (0.73 g) yield.

$$[\alpha]_D^{20} = -2.7° \text{ (C 0.74, acetone)}$$

$$\text{IR (neat)} = 3450, 2200, 1630 \text{ cm}^{-1}$$

Determination of ee

Preparation of (±) 3-acetoxy-2-cyanopent-1-ene (108a):

Racemic sample **47a** was converted to the corresponding acetate

108a in the following way. Acetyl chloride (0.8 g, 10 mM) was added dropwise at 0°C with stirring to the solution of pyridine (0.79 g, 10 mM) and the alcohol **47a** (0.56 g, 5 mM) in 20 mL of dry benzene and stirred overnight. The reaction mixture was taken up in ether (25 mL) washed with dil. hydrochloric acid followed by aq. sodium bicarbonate solution, dried over anhy. magnesium sulphate. Solvent was evaporated and distilled (bath temp. 100°C/1 mm) to afford the corresponding acetate **108a** in 81% (0.62 g) yield.

IR (neat) : 2250, 1740, 1630 cm^{-1}

^1H NMR : δ 0.92 (t, 3H, J = 6Hz), 1.78 (m, 2H), 2.08 (s, 3H), 5.16 (t, 1H, J = 7Hz), 5.94 (s, 1H), 6.0 (s, 1H).

^1H NMR analysis using chiral shift reagent Eu(hfc)$_3$:

^1H NMR spectrum of the acetate **108a** (20 mg) was recorded in the presence of Eu(hfc)$_3$ (60 mg). It was observed that the original singlet of O=CCH_3 (δ 2.08) appeared as two distinct singlets of almost equal intensity, each distinct singlet corresponding to the R and S enantiomers (Fig.16). At the same time the two olefinic proton signals at δ 5.94 and δ 6.0 also split.

Analysis of 107a : Acetate **109a** of the alcohol **107a** was prepared following the similar procedure as in **108a** and analyzed for enantiomeric excess using Eu(hfc)$_3$. The O=CCH_3 original singlet appeared as two distinct singlets (60:40) showing that the optical purity is 20% (20% ee).

Coupling of acrylonitrile with benzaldehyde using quinidine as catalyst:

Coupling reaction of acrylonitrile with benzaldehyde was carried out using quinidine as catalyst (30 mole %) in a similar procedure mentioned

as in 107a to provide chiral 2-cyano-3-phenylprop-1-en-3-ol (107b) as a colorless oil.

Reaction time : 10 days

Yield : 54%

$[\alpha]_D^{20}$: -0.69° (C 1.45, acetone)

IR (neat) : 3400, 2220, 1640, 1600 cm^{-1}

Determination of ee:

Racemic sample 47f, from DABCO catalyzed reaction, was converted to corresponding acetate 108b according to the procedure as in 108a.

IR neat : 2275, 1740, 1645 cm^{-1}

^1H NMR : δ 2.16 (s, 3H), 5.98 (d, 1H, J = 1.2 Hz), 6.04 (d, 1H, J = 1.2 Hz), 6.3 (s. 1H), 7.36 (s, 5H).

^1H NMR analysis using Eu(hfc)$_3$: Racemic acetate 108b (20 mg) spectrum was recorded in the presence of Eu(hfc)$_3$ (80 mg). It was observed that the original singlet at δ2.16 appeared as two distinct singlets of equal integration. The two olefinic protons also split. Similarly, acetate 109b, prepared from the chiral alcohol 107b, was analyzed for enantiomeric excess using Eu(hfc)$_3$. The O=CCH_3 original singlet appeared as two distinct singlets (3.8:3.5) showing that the optical purity is 4%.

Coupling of acrylonitrile with p-tolualdehyde using quinidine as catalyst:

Coupling of acrylonitrile with p-tolualdehyde using quinidine (30 mole %) was carried out to provide chiral 2-cyano-3-p-tolylprop-1-en-3-ol (107c), as a colorless oil, following the same procedure as in 107a.

Reaction time : 30 days

Yield : 58%

$[\alpha]_D^{20}$: -0.46° (C 2.16, acetone)

IR (neat) : 3350, 2225, 1610 cm^{-1}

^1H NMR : δ 2.3 (s, 3H), 3.3 (broad, 1H, D_2O washable), 5.1 (s, 1H), 5.88 (s, 1H), 5.96 (s, 1H), 7.15 (s, 4H)

^{13}C NMR : δ21.00 (CH_3), 73.71 (C-OH), 117.12 (C≡N) 126.53, 129.53, 129.77, 136.36, 138.65 (C-C and phenyl C).

Determination of ee:

Racemic 2-cyano-3-p-tolylprop-1-en-3-ol was first prepared via DABCO catalyzed coupling of acrylonitrile and p-tolualdehyde. This racemic sample was converted to the corresponding acetate according to the procedure as in **108a**.

IR (neat) : 2250, 1740, 1620 cm^{-1}

^1H NMR : δ 2.12 (s, 3H), 2.32 (s, 3H), 5.94 (s, 1H), 6.02 (s, 1H), 6.24 (s, 1H), 7.2 (m, 4H).

^1H NMR analysis using $Eu(hfc)_3$: Racemic acetate **108c** (20 mg) spectrum was recorded in the presence of shift reagent $Eu(hfc)_3$ (80 mg). The olefinic proton signals at δ5.94 and δ6.02 are splitting into two peaks each, of equal integration. Similarly, ^1H NMR spectrum of the acetate **109c** of the chiral alcohol **107c** was recorded in the presence of $Eu(hfc)_3$ and the original singlets for olefinic proton appeared as two distinct singlets corresponding to 3-4% ee.

Coupling of methyl acrylate with 2-furaldehyde using quinidine as catalyst:

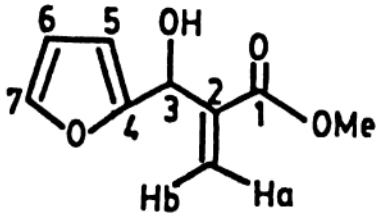
A mixture of 2-furaldehyde (0.48 g, 5 mM) methyl acrylate (1.5 mL) and quinidine (0.48 g, 1.5 mM) was allowed to stand at room temperature

for seven days. Pure product, chiral methyl 3-hydroxy-3-(fur-2-yl)-2-methylene-propionate (106') was obtained as colorless liquid by direct column chromatography of the reaction mixture using 10% ethyl acetate in hexane as eluent in 60% (0.55 g) yield.

$[\alpha]_D^{20}$: -13.3° (C 0.75, MeOH)

IR (neat) : 3450, 1720, 1640 cm^{-1}

^1H NMR : δ 3.6 (s, 3H $-OCH_3$), 3.79 (b, 1H, OH, D_2O washable), 5.48 (s, 1H, CHOH), 5.92 (d, 1H, J - 1.5 Hz, Hb or H6), 6.2 (m, 3H, H6 or Hb, Ha, H5), 7.04 (m, 1H, H7)



^{13}C NMR : δ 51.72 (OCH_3), 66.04 (C-OH), 106.90, 110.07, 126.10, 139.58, 142.01, 154.11 (C-C and furyl C), 166.14 (C=O).

Determination of ee:

Racemic alcohol **110**, prepared from DABCO catalyzed reaction, was converted to its corresponding acetate **111**.

IR (neat) : 1720, 1640 cm^{-1}

^1H NMR : δ 2.12 (s, 3H, $COCH_3$), 3.72 (s, 3H, OCH_3), 5.96 (s, 1H, Hb or H6), 6.3 (m, 2H, Ha, H6 or Hb), 6.44 (s, 1H, H3), 6.7 (b, 1H, H5), 7.36 (m, 1H, H7).

^1H NMR analysis using Eu(hfc)$_3$: ^1H NMR spectrum of the racemic acetate

111 was recorded in the presence of $Eu(hfc)_3$ and the $O{=}CCH_3$ singlet (δ 2.12) appeared as two distinct singlets in equal intensity. Similarly, the acetate **112** of the chiral alcohol **106'** was analyzed using $Eu(hfc)_3$. ^1H NMR spectrum has two distinct singlets for $O{=}CCH_3$ in 8.5:7 integration corresponding to 10% ee.

(-)-Menthyl acrylate (116):

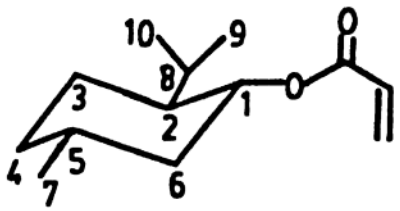
This was prepared according to Oppolzer's procedure.[94] To a solution of (-)Menthol (7.8g, 50 mM), acryloyl chloride (6.1 mL, 75 mM), 4-dimethylaminopyridine (0.9 g, 7.5 mM) in 50 mL of dry CH_2Cl_2, at 0°C, triethylamine (10.4 mL, 75 mM) was added dropwise and stirred for 1 h at room temperature. Reaction mixture was taken up in ether (50 mL), washed with aq. potassium bicarbonate solution and dried over anhydrous sodium sulphate. Solvent was removed and distilled to give pure (-)-menthyl acrylate (**116**) in 67% (7g) yield.

b.p. : 76-78°C/0.9 mm (lit. b.p. 78-80°C/5 mm)[102]

$[\alpha]_D^{20}$: -79.8° (C 9, dioxane)[lit.$[\alpha]_D^{20}$: -80.2° (C10, dioxane)][102]

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

^1H NMR : δ 0.68-2.1 (m, 18H, H2-H10), 4.72 (doublet of triplet, 1H, J = 10 Hz, 4Hz, H1), 5.6-6.5 (m, 3H, $HC{-}CH_2$).



^{13}C NMR : δ 16.17 (C10), 20.41 (C9), 21.76 (C7), 23.35 (C3), 26.11 (C8), 31.12 (C5), 34.06 (C4), 40.70 (C6), 46.88 (C2)

73.88 (C1), 129.00, 129.83 (C=C), 165.42 (C-O).

Analysis calcd. : C 74.24, H 10.54.
for $C_{13}H_{22}O_2$

Found : C 74.81, H 10.51.

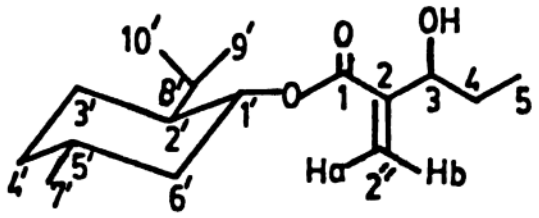
(-)-Menthyl 3-hydroxy-2-methylenepentanoate (119a):

(-)-Menthyl acrylate (116) (1.05 g, 5 mM), propionaldehyde (1.08 mL, 15 mM) and DABCO (0.5 g, 5 mM) were mixed together and allowed to react at room temperature for seven days. Direct column chromatography of the reaction mixture (10% ethyl acetate in hexane) provides 1.15 g (86%) of the product **119a** as a colorless oil.

$[\alpha]_D^{20}$: -75.4° (C 2.52, acetone)

IR (neat) : 3425, 1700, 1620 cm^{-1}

^1H NMR : δ 0.72-2.1 (m, 23H, H2'-H10', H4 and H5), 2.66 (broad, 1H, D_2O washable, OH), 4.28 (t, 1H, J 6Hz, H3), 4.74 (doublet of triplet, 1H, J - 10 Hz, 4Hz, H1'), 5.7 (s, 1H, Hb), 6.14 (s, 1H, Ha).



^{13}C NMR : δ 9.88, 16.23, 20.58, 21.94, 23.41, 26.35, 29.29, 31.35, 34.17, 40.76, 47.12 (alkyl C), 72.24, 72.35 (C3 diastereomeric), 74.59 (C1'), 124.00 (C2''), 143.47 (C2), 166.30 (C1).

Determination of de:

(-)-Menthyl 3-acetoxy-2-methylenepentanoate (120a):

Acetyl chloride (0.7 mL, 10 mM) was added slowly to a mixture of alcohol **119a** (1.07 g, 4 mM) and pyridine (0.8 mL, 10 mM) in 10 mL of dry benzene at 0°C and left overnight with stirring at room temperature. Reaction mixture was taken up in ether, washed with dil. hydrochloric acid, aq. $NaHCO_3$ solution and dried over anhydrous sodium sulphate. Solvent was removed to get the pure acetate **120a** in 84% (1.05 g) yield.

IR (neat) : 1720, 1640 cm^{-1}

^1H NMR : δ 0.6-1.96 (m, 23H, H2'-H10', H4 and H5). 2.04 (s, 3H, O-CCH_3), 4.74 (doublet of triplet, 1H, J = 10Hz, 4Hz, H1'), 5.54 (t, 1H, J = 6Hz, H3), 5.66 (s, 1H, Hb), 6.2 (s, 1H, Ha).

The singlet at δ2.04 for O=CCH_3 protons separated into two singlets in the presence of $Eu(hfc)_3$ (sample : shift reagent - 1:3)[@]. Diastereomeric excess was determined by the integration of these two singlets (58:42) and found to be 16%.

GC analysis on capillary column (methyl silicone, isothermal at 150°C) shows two peaks at retention times 57.60 and 57.99 minutes. The peaks are in the ratio 57.5 : 42.5 (no baseline separation) indicating that the de is 15%).

(-)-Menthyl 3-hydroxy-2-methylenebutanoate (119b):

This was prepared from (-)-menthyl acrylate (**116**), acetaldehyde and DABCO.

Reaction time : seven days

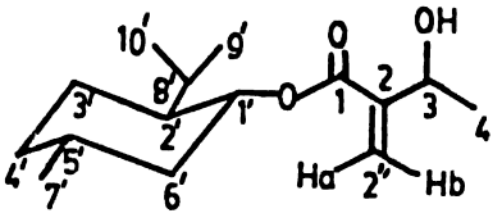
[@]In the chiral shift reagent studies the ratio of sample and shift reagent refers to the ratio of their weights.

Yield : 83%

$[\alpha]_D^{20}$: -73.4° (C 1.58, MeOH), [lit. $[\alpha]_D^{20}$: -75.3° (C 0.66, MeOH)][94]

IR (neat) : 3400, 1700, 1620 cm^{-1}

^1H NMR : δ 0.64-2.12 (m, 21 H, H2'-H10' and H4), 2.9 (broad, 1H, D_2O washable, OH), 4.5-4.92 (m, 2H, H1' and H3), 5.76 (s, 1H, Hb), 6.14 (s, 1H, Ha).



^{13}C NMR δ16.29, 20.64, 21.94, 22.06, 23.47, 26.41, 31.35, 34.17, 40.76, 47.12 (alkyl C), 67.00 (C3), 74.88 (C1'), 123.42 (C2''), 144.36 (C2), 166.42 (C1).

Determination of dc

(-)-Menthyl 3-acetoxy-2-methylenebutanoate (120b):

The above alcohol **119b** was converted to the corresponding acetate **120b** using acetyl chloride and pyridine, following the same procedure as in **120a**.

IR (neat) : 1740, 1630 cm^{-1}

^1H NMR : δ 0.72-1.8 (m, 21H, H2'-H10' and H4), 2.04 (s, 3H, $O{=}CCH_3$), 4.76 (m, 1H, H1'), 5.72 (m, 2H, H3 and Hb), 6.2 (s, 1H, Ha).

The singlet at δ2.04 for $O{=}CCH_3$ protons separated into two singlets in the presence of $Eu(hfc)_3$ (sample/shift reagent = 1/3). Diastereomeric

excess was determined by the integration of these two singlets (55.5 : 44.5) and found to be 11%.

GC analysis on capillary column (methyl silicone, Isothermal at 160°C) showed two peaks at retention times 30.29 and 30.65 minutes. The peak areas are in the ratio 56:44 indicating that diastereomeric excess is 12%.

(-)-Menthyl 3-hydroxy-3-(fur-2-yl)-2-methylenepropionate (119c) :

This was prepared from (-)-menthyl acrylate **(116)** , 2-furaldehyde and DABCO.

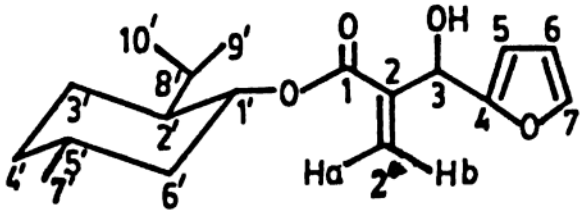
Reaction time : 18h

Yield : 85%

$[\alpha]_D^{20}$: -63.09° (C 1.47, acetone)

IR (neat) : 3450, 1700, 1640, 1580 cm^{-1}

^1H NMR : δ0.6-1.8 (m, 18H, H2'-H10'), 3.41 (broad, 1H, D_2O washable, OH), 4.74 (doublet of triplet, 1H, J - 10Hz, 4Hz, H1'), 5.6 (s, 1H, H3), 6.0 (m, 1H, Hb or H6), 6.3 (m, 3H, H6 or Hb, H5 and Ha), 7.34 (m, 1H, H7).



^{13}C NMR : δ<u>15.85</u> and <u>16.20</u> (diastereomeric C10'), 20.72, 21.84, <u>23.36</u> and <u>23.51</u> (diastereomeric C3'), <u>25.65</u> and <u>26.18</u> (diastereomeric C8'), 31.23, 34.05, 40.56, 46.85 (alkyl C), <u>66.34</u> and <u>66.69</u> (diastereomeric C3), 74.73 (C1'),

107.94, 110.14, 125.34 and 125.52 (diastereomeric C2"), 140.20, 141.96, 156.46, 165.38 (C=O).

Determination of de:

(-)-Menthyl 3-acetoxy-3-(fur-2-yl)-2-methylenepropionate (120c):

The above alcohol **119c** was converted to the acetate **120c** following the same procedure as in **120a**.

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

^1H NMR : δ 0.56-1.96 (m, 18H, H2'-H10'), 2.08 (s, 3H, O CCH_3), 4.66 (m, 1H, H1'), 5.88 (s, 1H, Hb or H6), 6.28 (s, 2H, Ha and H6 or Hb), 6.4 (m, 1H, H5), 6.7 (s, 1H, H3), 7.34 (s, 1H, H7).

The singlet at δ 2.08 for O-CCH_3 protons separated into two singlets in the presence of Eu(hfc)$_3$ (Sample/Eu(hfc)$_3$ = 1/4). Diastereomeric excess was determined by the integration of these two singlets (60:40) and found to be 20%.

(-)-Menthyl 3-hydroxy-4-methyl-2-methylenepentanoate (119d):

This was prepared from isobutyraldehyde, (-)-menthyl acrylate (**116**) and DABCO.

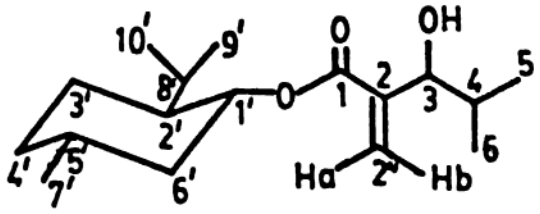
Reaction time : 14 days

Yield : 85%

$[\alpha]_D^{20}$: -50° (C 1.2, acetone)

IR (neat) : 3400, 1700, 1620 cm^{-1}

^1H NMR : δ 0.7-2.1 (m, 25H, H2'-H10', H4, H5 and H6), 3.04 (broad, 1H, D_2O washable, OH), 4.1 (m, 1H, H3), 4.72 (m, 1H, H1'), 5.7 (s, 1H, Hb), 6.16 (s, 1H, Ha).



^{13}C NMR : δ 16.11, 17.35, 19.23, 20.41, 21.76, 23.29, 26.23, 31.17, 32.70, 34.00, 40.53, 46.94 (alkyl C), 74.59 (C1'), 77.23 and 77.53 (C3, diastereomeric), 125.06 (C2"), 142.01 and 142.12 (C2, diastereomeric), 166.42 (C1).

Analysis calcd. for $C_{17}H_{30}O_3$: C 72.30, H 10.70.

Found : C 72.41, H 10.68.

Determination of de:

(-)-Menthyl 3-acetoxy-4-methyl-2-methylenepentanoate (120d):

The above alcohol **119d** was converted to the corresponding acetate **120d** following the same procedure as in **120a.**

IR (neat) : 1720, 1640 cm^{-1}

^1H NMR : δ 0.72-2.0 (m, 25H, H2'-H10', H4, H5, H6), 2.06 (s, 3H, $O{=}CCH_3$), 4.72 (m, 1H, H1'), 5.4 (distorted d, 1H, H3), 5.64 (s, 1H, Hb), 6.24 (s, 1H, Ha).

The singlet at δ5.64 for Hb proton and singlet at δ6.24 for Ha proton split into two singlets each in the presence of Eu(hfc)$_3$(sample/shift reagent : 1/3). Diastereomeric excess was determined by the integration of these separated singlets and found to be 7%.

GC analysis on capillary column (methyl silicone, isothermal at 160°C) shows two peaks at retention times 44.83 and 45.14 minutes. The peak areas are in the ratio 46.5:53.5 ,i.e.,de is 7%.

(-)-Menthyl 3-hydroxy-2-methylene-3-phenylpropionate (119c):

This was prepared from (-)-menthyl acrylate (**116**), benzaldehyde and DABCO.

Reaction time : 7 days

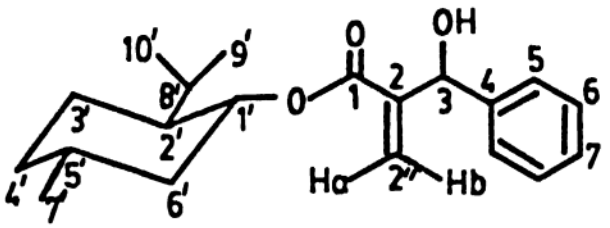
Yield : 89%

$[\alpha]_D^{20}$: -51.70° (C 0.73, acetone)

m.p. : 104-112°C

IR (KBr) : 3400, 1725, 1640 cm^{-1}

^1H NMR : δ 0.5-2.0 (m, 18H, H2'-H10'), 3.04 (broad, 1H, D_2O washable, OH), 4.7 (doublet of triplet, 1H, J = 10Hz, 4Hz, H1'), 5.72 (d, 1H, J - 6Hz, H3), 5.76 and 5.8 (2s, 1H, diastereomeric Hb), 6.3 (s, 1H, Ha), 7.3 (s, 5H, C_6H_5).



^{13}C NMR : δ <u>16.11</u> and <u>16.88</u> (diastereomeric C10'), 20.70, 21.88, <u>23.11</u> and <u>23.29</u> (diastereomeric C3'), <u>25.82</u> and <u>26.11</u> (diastereomeric C8'), 31.33, 34.66, <u>40.53</u> and <u>40.65</u> (diastereomeric C6'), 47.60, <u>73.18</u> and <u>73.29</u> (diastereomeric C3), <u>74.77</u> and <u>74.88</u> (diastereomeric C1'), <u>125.18</u> and

125.36 (diastereomeric C2" or aromatic C), 126.59 and 126.77 (diastereomeric aromatic C or C2"), 127.77, 128.36, 141.65, 142.59 and 142.71 (diastereomeric C2 or C4), 166.00 (C1).

Analysis Calcd. for $C_{20}H_{28}O_3$: C 75.91, H 8.92.

Found : C 75.79, H 8.90.

Determination of de

(-)-Menthyl 3-acetoxy-2-methylene-3-phenylpropionate (120e):

The above alcohol **119e** was converted to the corresponding acetate **120e** using acetyl chloride and pyridine following the procedure as in **120a**.

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

^1H NMR : δ 0.44-1.7(m, 18H, H2'-H10'), 2.04 (s, 3H, O-CCH_3), 4.42 (m, 1H, H1'), 5.7 and 5.76 (2s, 1H, diastereomeric Hb), 6.28 and 6.34 (2s, 1H, diastereomeric Ha), 6.6 (s, 1H, H3), 7.26 (s, 5H).

The singlet at δ 2.04 for O=CCH_3 protons separated into two singlets in the presence of Eu(hfc)$_3$ (sample/Eu(hfc)$_3$: 1/3). Diastereomeric excess was determined by the integration of these two singlets (57.5:42.5) and found to be 15%.

Selective Crystallization : Repeated crystallizations were performed on alcohol **119e** from n-hexane, till the sample **119'e** with maximum rotation is obtained.

Overall yield : 40%

$[\alpha]_D^{20}$: -142.4° (C 0.4, acetone)

m.p. : 115-116°C

^{1}H NMR : δ 0.4-2.04 (m, 18H, H2'-H10'), 2.66 (s, 1H, D_2O washable, OH), 4.7 (m, 1H, H1'), 5.5 (s, 1H, H3), 5.8 (s, 1H, Hb), 6.3 (s, 1H, Ha), 7.3 (s, 5H, C_6H_5).

^{13}C NMR : δ 16.06 (C10'), 20.76, 21.94, 23.29 (C3'), 26.00 (C8'), 31.41, 34.17, 40.76 (C6'), 47.14, 73.53 (C3), 75.00 (C1'), 125.65 (C2" or aromatic C), 126.77 (aromatic C or C2"), 127.94, 128.53, 141.59, 142.65 (C2 or C4), 166.18 (C1).

Determination of de:

The above alcohol **119'e** was converted to the corresponding acetate **120'e** following the same procedure as in **120'a**.

^{1}H NMR : δ 0.4-2.0 (m, 18H, H2'-H10'), 2.04 (s, 3H, O CCH_3), 4.04 (m, 1H, H1'), 5.76 (s, 1H, Hb), 6.36 (s, 1H, Ha), 6.36 (s, 1H, H3), 7.26 (s, 5H, C_6H_5).

The singlet at δ2.04 is intact in the presence of Eu(hfc)$_3$, thus indicating the 100% diastereomeric excess of the crystallized sample.

(S)-(N-Benzylpyrrolidin-2-yl)methyl acrylate (117):

(S)-N-Benzylprolinol (**98**) (9.55 g, 50 mM), acryloyl chloride (6.1 mL, 75 mM), 4-dimethylaminopyridine (0.9 g, 7.5 mM) were taken in 50 mL of anhydrous CH_2Cl_2, and cooled to 0°C. Triethylamine (10.4 mL, 75 mM) was added dropwise with stirring. After addition was complete, the reaction mixture was allowed to warm to room temperature. After one hour at r.t. reaction mixture was taken up in ether (100 mL) washed with aq. potassium bicarbonate solution and dried over anhydrous sodium sulphate. Solvent

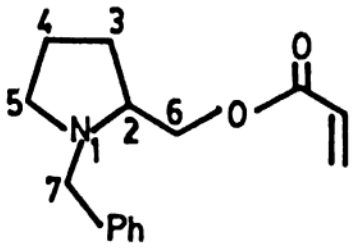
was removed and the residue was distilled to give pure **117** in 70% (8.58 g) yield as a colorless oil.

b.p. : 119-122°C/0.5 mm

$[\alpha]_D^{20}$: -49.23° (C 1.3, acetone)

IR (neat) : 1730, 1625 cm^{-1}

^1H NMR : δ 1.4-2.39 (m, 5H) and 2.61-3.0 (m, 2H) (H2-H5), 3.38 and 4.06 (AB quartet, 2H, J - 14Hz, H7), 4.12 (m, mixed with AB quartet, 2H, H6), 5.6-6.52 (m, 3H, $HC=CH_2$), 7.25 (s, 5H, aromatic).



^{13}C NMR : δ 22.88, 28.41, 54.35, 59.41, 61.82 (alkyl C), 67.18 (HC-O), 126.95, 128.24, 128.59, 128.89, 130.71, 139.59 (C=C and aromatic C), 166.24 (C=O).

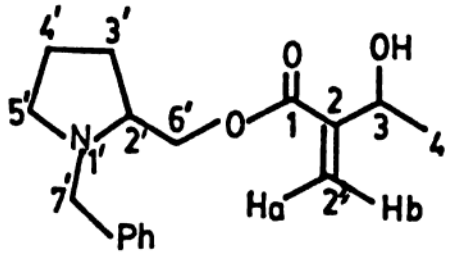
(2'S)-(N-Benzylpyrrolidin-2'-yl)methyl 3-hydroxy-2-methylenebutanoate (123a):

A mixture of (S)-(N-benzylpyrrolidin-2-yl)methyl acrylate **(117)** (1.23 g, 5 mM), acetaldehyde (0.22 g, 5 mM) and DABCO (0.56 g, 5 mM) was allowed to react at room temperature for four days. Direct column chromatography of the reaction mixture (10% ethyl acetate in hexane) afforded the compound **123a** in 60% (0.87 g) yield, as a colorless oil.

$[\alpha]_D^{20}$: -37.7° (C 0.86, acetone)

IR (neat) : 3425, 1720, 1640 cm^{-1}

^{1}H NMR : δ 1.32 (d, 3H, J = 6Hz, H4), 1.4-2.39 (m, 5H) and 2.61-3.0 (m, 2H), (H2'-H5'), 3.04 (s, 1H, OH, D_2O washable), 3.32 and 4.0 (AB quartet, 2H, J - 14Hz, H7'), 4.15 (d, mixed with AB quartet, 2H, J = 6Hz, H6'), 4.52 (m, 1H, H3), 5.72 (s, 1H, Hb), 6.12 (s, 1H, Ha), 7.2 (s, 5H, aromatic).



Determination of de

(2'S)-(N-Benzylpyrrolidin-2'-yl)methyl 3-acetoxy-2-methylenebutanoate (124a):

To a solution of the alcohol **123a** (0.29 g, 1 mM) in dry benzene (10 mL) at 0°C, pyridine (0.16 mL, 2 mM) was added. To this, with stirring, acetyl chloride (0.14 mL, 2 mM) was added dropwise and stirring was continued overnight at room temperature. Reaction mixture was taken up in ether, washed with dil. HCl, aq. $NaHCO_3$ solution, dried over anhydrous sodium sulphate. Removal of the solvent afforded the pure compound **124a** as a viscous oil in 60% (0.2 g) yield.

IR (neat) : 1720, 1640 cm^{-1}

^{1}H NMR : δ 1.4 (d, 3H, J = 6Hz, H4), 1.45-2.41 (m, 5H) and 2.6-2.96 (m, 2H), (H2'-H5'), 2.04 (s, 3H, $O{=}CCH_3$), 3.4 and 4.04 (AB quartet, 2H, J = 14Hz, H7'), 4.14 (d, mixed with AB quartet, 2H, J = 6Hz, H6'), 5.8 (m, 2H, Hb and H3), 6.24 (s, 1H, Ha), 7.24 (s, 5H, aromatic).

In the presence of $Eu(hfc)_3$ (Sample : $Eu(hfc)_3$ is 1:3) acetyl methyl protons signal at δ2.04 shifts and splits into two signals in the ratio 58:42 indicating that the diastereomeric excess is 16%.

(2'S)-(N-Benzylpyrrolidin-2'-yl)methyl 3-hydroxy-2-methylenepentanoate (123b):

This was prepared, from propionaldehyde, acrylate **117** and DABCO following the similar procedure as in **123a.**

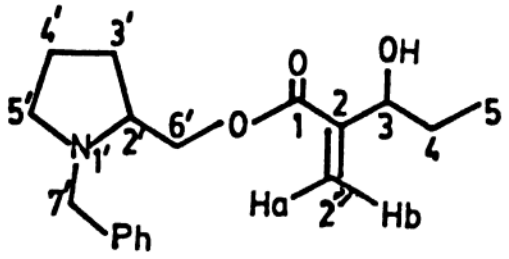
Reaction time : 10 days

Yield : 50%

$[\alpha]_D^{20}$: -43.2° (C .1, acetone)

IR (neat) : 3450, 1710, 1630 cm^{-1}

^1H NMR : δ0.88 (t, 3H, J = 6Hz, H5), 1.1-3.0 (m, 9H, H2'-H5' and H4), 3.34 and 4.0 (AB quartet, 2H, J - 14Hz, H7'), 4.2 (m, mixed with AB quartet, 3H, H6' and OH, one H is D_2O washable), 5.7 (s, 1H, Hb), 6.16 (s, 1H, Ha), 7.2 (s, 5H, aromatic).



Determination of de

(2'S)-(N-Benzylpyrrolidin-2'-yl)methyl 3-acetoxy-2-methylenepentanoate (124b):

This was prepared from the alcohol **123b** using the same procedure as in **124a.**

IR (neat) : 1730, 1640 cm^{-1}

^{1}H NMR : δ0.88 (t, 3H, J = 7Hz, H5), 1.4-3.0 (m, 9H, H2'-H5' and H4), 2.06 (s, 3H, O=CCH_3), 3.4 and 4.06 (AB quartet, 2H, J = 14Hz, H7'), 4.16 (d, comes along with AB quartet, 2H, J - 6Hz, H6'), 5.56 (distorted t, 1H, H3), 5.72 (s, 1H, Hb), 6.28 (s, 1H, Ha), 7.26 (s, 5H, aromatic).

In the presence of Eu(hfc)$_3$ (Sample : Eu(hfc)$_3$ 1:4) the acetyl methyl proton singlet at δ2.06 shifts and splits into two singlets in the ratio 53.5:46.5, indicating that the diastereomeric excess is 7%.

(2'S)-(N-Benzylpyrrolidin-2'-yl)methyl 3-hydroxy-2-methylene-3-phenylpropionate (123c):

This was prepared from the acrylate **117**, benzaldehyde and DABCO following the similar procedure as in **123a**.

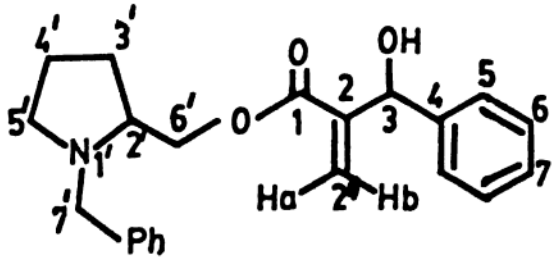
Reaction time: : 10 days

Yield : 50%

$[\alpha]_D^{20}$: -36.8° (C 0.82, acetone)

IR (neat) : 3450, 1720, 1625, 1600 cm^{-1}

^{1}H NMR : δ 1.4-3.0 (m, 8H, H2'-H5' and OH, 1H D_2O washable), 3.31 and 3.61 (AB quartet, 2H, J - 14Hz, H7'), 4.08 (m, mixed with AB quartet, 2H, H6'), 5.5 (s, 1H, H3), 5.66 and 5.76 (2s, 1H, Hb, diastereomeric), 6.24 (broad s, 1H, Ha), 7.22 (m, 10H, aromatic).



Determination of de

(2'S)-(N-Benzylpyrrolidin-2'-yl)methyl 3-acetoxy-2-methylene-3-phenylpropionate (124c):

This was prepared from the alcohol **123c** following the same procedure as in **124a**.

IR (neat) : 1730, 1640, 1620 cm^{-1}

^1H NMR : δ 1.4-2.91 (m, 7H, H2'-H5'), 2.08 (s, 3H, O-CCH_3), 3.32 and 3.96 (distorted AB quartet, 2H, H7'), 4.06 (m, mixed with AB quartet, 2H, H6'), 5.82 (s, 1H, Hb), 6.38 (s, 1H, Ha), 6.66 (s, 1H, H3), 7.3 (m, 10H, aromatic).

In the presence of $Eu(hfc)_3$ (Sample : $Eu(hfc)_3$ is 1:4) acetyl methyl proton singlet at δ 2.08 shifts and splits into two singlets in the ratio 52:48 indicating that de is 4%.

Isobornyl sultone (125):

This was prepared according to the literature method.[97] (+)-10-Camphorsulfonic acid (9.3 g, 40 mM) in 20 mL of water was added carefully to solid sodium borohydride (2.84 g, 75 mM). Water was removed under reduced pressure and the reaction mixture was heated for 4h at 120°C. Absolute ethanol (300 mL) was added and refluxed for 2h. Salts were removed by filtration. Ethanol (100 mL) was added to salts, refluxed and again filtered. This process is repeated 3-4 times. Then all the ethanolic solutions were mixed and ethanol was removed by distillation. Crude solid was dried at 120°C for 2h, dissolved in pyridine (16 mL). Freshly crystallized p-toluenesulfonyl chloride (9 g) was added with stirring. After 5h at room temperature, the reaction mixture was poured into cold water (40 mL) and refrigerated (-20°C) overnight. Isobornyl sultone (125) was filtered and dried.

Yield : 4.5 g (52%)

m.p. : 116-118°C (lit. m.p. 116-118°C)[96]

(1S,2R,4R)-1-(Diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (126):

To the ethylmagnesium bromide (280 mM), N,N-diisopropylamine (39.3 mL, 280 mM) was added slowly over an hour at room temperature under nitrogen. After the completion of evolution of ethane gas, sultone **125** (8.6 g, 40 mM) in 50 mL of THF was added and stirring was continued for 24h at room temperature. Reaction mixture was poured into cold dil. HCl and extracted with ether (3x40 mL). The combined ethereal solution was washed with aq. sodium bicarbonate solution, brine and dried over anhydrous Na_2SO_4. Solvent was removed and crystallization of the solid from hexane (two times) gave pure **126** in 50% yield (6.34 g).

m.p. : 101-103°C (lit. m.p.102-103°C)[96]

$[\alpha]_D^{20}$: -34.3° (C 0.9, EtOH) [lit. $[\alpha]_D^{20}$: -34.4° (C 4.74, EtOH)][98]

^{1}H NMR : δ 0.8 (s, 3H, CH_3, H9), 1.04 (s, 3H, CH_3, H8), 1.3 [d, 12H, J = 7Hz, 2x$CH(\underline{CH_3})_2$] 1.64 (m, 7H, H3, H4, H5, H6), 2.64 and 3.24 (AB quartet, 2H, J = 14Hz, H10), 3.44 (d, 1H, OH, D_2O washable), 3.72 [m, 2H, 2x$\underline{CH}(CH_3)_2$] 4.04 (m, 1H, H2).

^{13}C NMR : δ 19.88, 20.53, 22.17, 22.53, 27.35, 30.94, 38.82, 44.53, 48.53, 50.80, 54.35 (alkyl C), 76.59 (C2).

(1S,2R,4R)-1-(Diisopropylaminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)hept-2-yl acrylate (118):

Ethylmagnesium bromide (4 mM) was added slowly to the alcohol

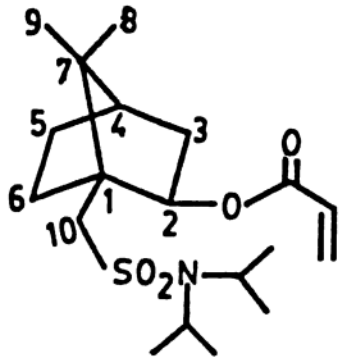
126 (1.26 g, 4 mM) in dry ether (10 mL) at room temperature with stirring. The reaction mixture was cooled to 0°C and acryloyl chloride (0.9 g, 10 mM) in ether (10 mL) was added. Stirring was continued for 2h at room temperature. Salts were filtered and the ethereal solution was dried over anhydrous Na_2SO_4. Solvent was removed and the solid obtained, was crystallized from hexane to give **118** in 62% (0.92 g) yield.

m.p. : 115-117°C (lit. m.p.117-118°C)[96]

$[\alpha]_D^{20}$: -66.6° (C 0.18, acetone)

IR (KBr) : 1725, 1640 cm^{-1}

^1H NMR : δ 0.9 (s, 3H, CH_3, H9), 1.02 (s, 3H, CH_3, H8), 1.3 [d, 12H, J = 7Hz, 2xCH($\underline{CH_3}$)$_2$], 1.76 (m, 7H, H3, H4, H5, H6), 2.7 and 3.3 (AB quartet, 2H, J 14Hz, H10), 3.66 [m, 2H, 2x$\underline{CH}$(CH_3)$_2$], 5.04 (m, 1H, H2), 5.68-6.4 (m, 3H, HC=CH_2).



^{13}C NMR : δ 19.47, 19.88, 21.26, 26.53, 29.34, 38.90, 44.00, 47.70, 48.59, 48.90, 52.47 (alkyl C), 77.94 ($\underline{C}$-O), 128.77, 129.47 (C=C), 164.00 (C· O).

Analysis Calcd. for $C_{19}H_{33}NO_4S$: C 61.42, H 8.95, N 3.77.

Found : C 61.48, H 8.98, N 3.74.

(1'S,2'R,4'R)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-hydroxy-2-methylenebutanoate (127a):

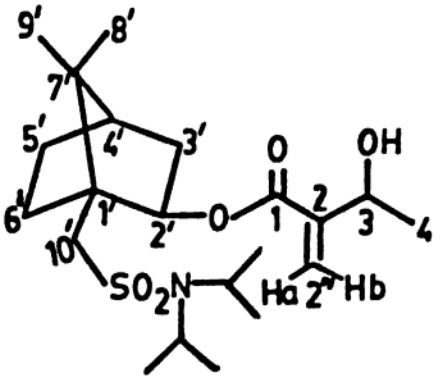
Acetaldehyde (1 mL), acrylate **118** (0.74 g, 2 mM) and DABCO (0.224 g, 2 mM) were mixed and allowed to react at room temperature. The reaction was monitored by TLC. Reaction is complete in 2 days. Direct column chromatography of the reaction mixture (10% ethyl acetate in hexane) provides 70% (0.58 g) of the pure compound **127a.**

m.p. : 105-108°C

$[\alpha]_D^{20}$: -60° (C 0.8, acetone)

IR (KBr) : 3450, 1700, 1625 cm^{-1}

^1H NMR : δ 0.88, (s, 3H, CH_3, H9'), 1.02 (s, 3H, CH_3, H8'), 1.26 [d, 12H, J = 6Hz, 2xCH($\underline{CH_3}$)$_2$], 1.4 (2d, 3H, J 6Hz, H4, diastereomeric), 1.8 (m, 7H, H3', H4', H5', H6'), 2.7 and 3.28 (AB quartet, 2H, J - 14Hz, H10'), 2.7 (1H, along with AB quartet, D_2O washable $\underline{OH}$), 3.66 [m, 2H, 2x$\underline{CH}$(CH_3)$_2$]. 4.6 (m, 1H, H3), 5.14 (m, 1H, H2'), 5.72 and 5.79 (2s, 1H, diastereomeric Hb), 6.00 and 6.04 (2s, 1H, diastereomeric Ha).



^{13}C NMR : δ 19.94, 20.23, 22.00, 22.47, 26.94, 30.00, 39.23, 44.41, 48.18, 49.06, 49.53, 51.00 (alkyl C), 66.47 and 67.53 (C3, diastereomeric), 78.53 (C2'), 122.00 and 122.65 (C2", diastereomeric), 144.53 and 145.18 (C2, diastereomeric), 165.18 (C1).

Analysis Calcd. for $C_{21}H_{37}NO_5S$: C 60.69, H 8.97, N 3.37.

Found : C 60.72, H 8.95, N 3.36.

Determination of de

Alcohol **127a** was converted into the acetate **128a** as follows. To the above alcohol (83 mg, 0.2 mM) in dry benzene (10 mL) at 0°C, pyridine (0.08 mL, 1 mM) was added. To the above stirred solution, acetyl chloride (0.07 mL, 1 mM) was added at the same temperature and stirring was continued overnight at room temperature. Reaction mixture was washed with dil. HCl, aq $NaHCO_3$ solution, dried over anhy. $MgSO_4$. Solvent was removed to get the pure acetate **128a** in 92% (84 mg) yield.

IR (KBr) : 1730, 1700, 1630 cm^{-1}

^1H NMR : δ 0.92 (s, 3H, CH_3, H9'), 1.04 and 1.06 (2s, 3H, CH_3, H8', diastereomeric), 1.3 [d, 12H, J - 6Hz, 2xCH($\underline{CH_3}$)$_2$], 1.4 (2d, 3H, J = 7Hz, H4, diastereomeric), 1.8 (m, 7H, H3', H4', H5', H6'), 2.04 and 2.08 (2s, 3H, diastereomeric O=CCH_3), 2.78 and 3.36 (AB quartet, 2H, J = 14Hz, H10'), 3.66 [m, 2H, 2x$\underline{CH}$(CH_3)$_2$], 5.1 (m, 1H, H2'), 5.74 (m, 2H, Hb and H3), 6.06 and 6.18 (2s, 1H, diastereomeric Ha).

The two closed singlets at δ 2.04 and 2.08 for $O{=}CCH_3$ protons separated wide apart in the presence of $Eu(hfc)_3$ (sample : $Eu(hfc)_3$ - 1:1). The de is determined by the integration of these two singlets and found to be 30%.

Selective Crystallization

The above alcohol **127a** was crystallized repeatedly from 1:1 mixture of ether & pet. ether till the sample **127'a** with rotation $[\alpha]_D^{20}$ = -54.76° (C 0.82, acetone) is obtained, on further crystallization, the rotation does not change.

Overall yield : 40%

m.p. : 125-126°C

^1H NMR : δ 0.88 (s, 3H, CH_3, H9'), 1.04 (s, 3H, CH_3, H8'), 1.26 [m, 15H, $2xCH(\underline{CH_3})_2$ and H4], 1.8 (m, 7H, H3', H4', H5', H6'), 2.5 (broad, 1H, D_2O washable, OH), 2.7 and and 3.2 (AB quartet, 2H, J = 14Hz, H10'), 3.64 [m, 2H, $2x\underline{CH}(CH_3)_2$]. 4.68 (m, 1H, H3), 5.14 (m, 1H, H2'), 5.8 (s, 1H, Hb), 6.08 (s, 1H, Ha).

^{13}C NMR ; δ 18.29, 18.64, 20.35, 20.82, 26.29, 28.35, 37.65, 42.82, 46.53, 47.41, 47.94, 51.45 (alkyl C), 64.88 (C3), 76.94 (C2'), 120.36 (C2''), 143.54 (C2), 163.54 (C1).

Determination of de

The above alcohol **127'a** was converted to the acetate **128'a** to confirm 100% de.

^1H NMR : δ 0.88 (s, 3H, CH_3, H9'), 1.04 (s, 3H, CH_3, H8'), 1.24 [d, 12H, J = 6Hz, $2xCH(\underline{CH_3})_2$], 1.40 (d, 3H, CH_3, H4), 1.68 (m, 7H, H3', H4', H5', H6'), 2.07 (s, 3H, $O{=}CCH_3$), 2.7 and 3.24 (AB quartet, 2H, J = 14Hz, H10'), 3.64 [m,

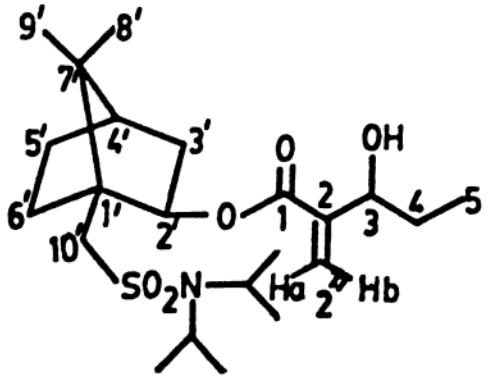
2H, 2x<u>CH</u>$(CH_3)_2$], 5.12 (m, 1H, H2'), 5.72 (m, 2H, Hb and H3), 6.06 (s, 1H, Ha).

The singlet at δ2.07 is intact in the presence of Eu(hfc)$_3$, thus indicating the 100% de of the crystallized sample.

(1'S,2'R,4'R)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1) hept-2'-yl 3-hydroxy-2-methylenepentanoate (127b):

This was prepared from propionaldehyde, acrylate **118** and DABCO following the same procedure as in **127a.**

Reaction time	:	7 days
Yield	:	78%
m.p.	:	108-110°C
$[\alpha]_D^{20}$	:	-52.5° (C 0.4, acetone)
IR (KBr)	:	3450, 1700, 1625 cm^{-1}
^{1}H NMR	:	δ 0.88 (m, 6H, 2CH$_3$, H9', H5), 1.04 (s, 3H, CH$_3$, H8'), 1.28 [d, 12H, 2xCH(<u>CH$_3$</u>)$_2$], 1.74 (m, 9H, H3', H4', H5', H6', H4), 2.68 and 3.24 (AB quartet, 2H, J - 14 Hz, H10'), 3.64 [m, 3H, 2x<u>CH</u>$(CH_3)_2$ and OH], 4.36 (m, 1H, H3), 5.08 (m, 1H, H2'), 5.72 (broad s, 1H, Hb), 6.04 (broad s, 1H, Ha).



^{13}C NMR : δ 10.33 and 10.45 (C5, diastereomeric), 20.13, 20.48, 22.19, 22.72, 27.12, 29.23, 30.17, 39.57, 44.61, 48.31, 49.25, 49.72, 53.19 (alkyl C), 72.44 and 74.68 (C3, diastereomeric), 78.72 (C2'), 122.82 (C2''), 143.89 (C2), 165.32 (C1).

Analysis calcd. for $C_{22}H_{39}NO_5S$: C 61.51, H 9.15, N 3.26.

Found : C 61.51, H 9.16, N 3.26.

Determination of de

Above alcohol **127b** was converted to the acetate **128b** following the same procedure as in **128a.**

IR (KBr) : 1730, 1710, 1620 cm^{-1}

^1H NMR : δ 0.88 (t + s, 6H, $2CH_3$, H9', H5), 1.04 (s, 3H, CH_3, H8'), 1.28 [d, 12H, J = 6Hz, $2xCH(\underline{CH_3})_2$], 1.76 (m, 9H, H3', H4', H5', H6', H4), 2.04 and 2.08 (2s, 3H, O-CCH_3, diastereomeric), 2.66 and 3.04 (AB quartet, 2H, J = 14Hz, H10'), 3.7 [m, 2H, $2x\underline{CH}(CH_3)_2$], 5.1 (m, 1H, H2'), 5.7 (m, 2H, Hb and H3), 6.08 and 6.16 (2s, 1H, diastereomeric, Ha).

The two singlets at δ2.04 and 2.08 for O=CCH_3 protons separate wide apart in the presence of Eu(hfc)$_3$ (Sample : Eu(hfc)$_3$ = 1:1). The de is determined by the integration of these two signals and found to be 42%.

Selective Crystallization

The above alcohol **127b** was crystallized from 1:1 mixture of ether and pet. ether till we obtained the sample **127'b** with maximum rotation.

Overall yield : 45%

m.p. : 113-114°C

$[\alpha]_D^{20}$: -55.2° (C 0.8, acetone)

^{1}H NMR : δ 0.9 (m, 6H, $2CH_3$, H9', H5), 1.04 (s, 3H, CH_3, H8'), 1.24 [d, 12H, J = 6Hz, $2xCH(\underline{CH_3})_2$], 1.74 (m, 9H, H3', H4', H5', H6', H4), 2.66 and 3.24 (AB quartet, 2H, J = 14Hz, H10'), 2.7 (1H, along with AB quartet, D_2O washable, OH), 3.64 [m, 2H, $2x\underline{CH}(CH_3)_2$], 4.38 (m, 1H, H3), 5.1 (m, 1H, H2'), 5.76 (s, 1H, Hb), 6.04 (s, 1H, Ha).

^{13}C NMR : δ 10.06 (C5), 19.88, 20.29, 21.94, 22.53, 26.94, 29.11, 30.00, 39.26, 44.41, 48.12, 49.06, 49.53, 53.00 (alkyl C), 72.12 (C3), 78.53 (C2'), 122.77 (C2''), 144.06 (C2), 165.06 (C1).

Determination of de

The above alcohol **127'b** was converted to the acetate **128'b** to confirm the 100% de.

^{1}H NMR : δ 0.9 (s + t, 6H, $2CH_3$, H9', H5), 1.04 (s, 3H, CH_3, H8'), 1.26 [d, 12H, J = 6Hz, $2xCH(\underline{CH_3})_2$], 1.8 (m, 9H, H3', H4', H5', H6' and H4), 2.08 (s, 3H, O-CCH_3), 2.66 and 3.24 (AB quartet, 2H, J = 14Hz, H10'), 3.64 [m, 2H, $2x\underline{CH}(CH_3)_2$], 5.1 (m, 1H, H2'), 5.66 (m, 2H, Hb and H3), 6.08 (s, 1H, Ha).

The singlet at δ 2.08 remains intact in the presence of $Eu(hfc)_3$, thus indicating the 100% de of the crystallized material.

(1'S,2'R,4'R)-1'-(Diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1) hept-2'-yl 3-hydroxy-2-methylene-3-phenylpropionate (127c):

This was prepared from benzaldehyde, acrylate **118** and DABCO following the same procedure as in **127a.**

Reaction time : 10 days

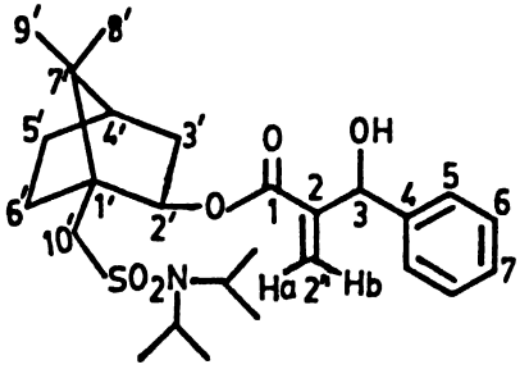
Yield : 84%

m.p. : 130-135°C

$[\alpha]_D^{20}$: -36.6° (C 0.3, acetone)

IR(KBr) : 3500, 1710, 1640 cm^{-1}

^1H NMR : δ 0.86 (s, 3H, CH_3, H9'), 0.94 (s, 3H, CH_3, H8'), 1.24 [d, 12H, J = 6Hz, 2x$CH(\underline{CH_3})_2$], 1.7 (m, 7H, H3', H4', H5', H6'), 2.66 and 3.04 (AB quartet, 2H, J = 14 Hz, H10'), 3.62 [m, 3H, 2x$\underline{CH}(CH_3)_2$ and $CH\underline{OH}$, 1H D_2O washable], 5.08 (m, 1H, H2'), 5.52 (m, 2H, Hb and H3), 6.12 and 6.16 (2s, 1H, diastereomeric, Ha), 7.28 (s, 5H, aromatic).



^{13}C NMR : δ 21.17, 21.58, 23.35, 23.76, 28.23, 31.29, 40.59, 45.70, 49.47, 50.35, 50.82, 54.35 (alkyl C), $\underline{73.94}$ and $\underline{74.71}$ (C3, diastereomeric), 80.24 (C2'), $\underline{126.30}$ and $\underline{126.59}$ (C2" or aromatic C, diastereomeric),

127.89 and 128.01 (aromatic C or C2', diastereomeric), 129.12, 129.71, 142.59 and 142.71 (C2 or C4 diastereomeric), 144.65 and 144.81 (C4 or C2 diastereomeric), 166.36 and 166.53 (C1 , diastereomeric).

Analysis Calcd. for $C_{26}H_{39}NO_5S$: C 65.38, H 8.23, N 2.93.

Found : C 65.12, H 8.24, N 2.91.

Determination of de

The above alcohol **127c** was converted to the corresponding acetate **128c** following the same procedure as in **128a**.

IR (KBr) : 1740, 1720, 1640, 1620 cm^{-1}

^1H NMR : δ 0.68-1.9 [m, 25H, H3'-H9', 2x$CH(CH_3)_2$], 2.02 and 2.04 (2s, 3H, O=CCH_3 diastereomeric), 2.62 and 3.16 (distorted AB quartet, 2H, H10'), 3.6 [m, 2H, 2x$CH(CH_3)_2$], 5.0 (m, 1H, H2'), 5.42 and 5.84 (2s, 1H, diastereomeric, Hb), 6.24 (broad, 1H, Ha), 6.68 (s, 1H, H3), 7.26 (s, 5H, C_6H_5).

The two singlets at δ 2.02 and δ 2.04 for O-CCH_3 protons separated wide apart in the presence of Eu(hfc)$_3$ (Sample : Eu(hfc)$_3$ = 1:1). The de is determined by the integration of these two signals and found to be 15%.

Selective Crystallization:

The above alcohol **127c** was crystallized repeatedly from 1:1 mixture of ether and pet. ether, till we obtained a sample **127'c** with rotation $[\alpha]_D^{20}$ = +4.68 (C 0.62, acetone). On further crystallization, the rotation does not change.

Overall yield : 35%

m.p. : 165-167°C

^{1}H NMR : δ 0.88 (s, 3H, CH_3, H9'), 0.97 (s, 3H, CH_3, H8'), 1.28 [d, 12H, J = 6Hz, 2xCH($\underline{CH_3}$)$_2$], 1.74 (m, 7H, H3', H4', H5', H6'), 2.7 and 3.26 (AB quartet, 2H, J - 14Hz, H10'), 3.24 (broad s, 1H, D_2O washable, mixes with AB quartet, OH), 3.64 [m, 2H, 2x$\underline{CH}$(CH_3)$_2$], 5.08 (m, 1H, H2'), 5.68 (m, 2H, Hb and H3), 6.2 (s, 1H, Ha), 7.32 (s, 5H, C_6H_5).

^{13}C NMR : δ 20.00, 20.35, 22.17, 22.59, 27.00, 30.12, 39.35, 44.53, 48.29, 49.18, 49.65, 53.29 (alkyl C), 72.82 (C3), 79.00 (C2'), 125.18 (C2" or aromatic C), 126.88 (aromatic C or C2"), 127.94, 128.59, 141.24 (C2 or C4), 143.65 (C4 or C2), 165.18 (C1).

Determination of de:

The above alcohol **127'c** was converted to the corresponding acetate **128'c** following the same procedure as in the case of **128a.**

^{1}H NMR : δ 0.76 (s, 6H, 2CH_3, H8', H9'), 1.2 [2d. 12H, J - 6Hz, 2xCH($\underline{CH_3}$)$_2$], 1.6 (m, 7H, H3', H4', H5', H6'), 2.02 (s, 3H, O=CCH_3), 2.64 and 3.22 (AB quartet, 2H, J 14Hz, H10'), 3.56 [m, 2H, 2x$\underline{CH}$(CH_3)$_2$], 4.96 (m, 1H, H2'), 5.84 (s, 1H, Hb), 6.2 (s, 1H, Ha), 6.64 (s, 1H, H3), 7.24 (s, 5H, C_6H_5).

The singlet at δ 2.02 remains intact in the presence of Eu(hfc)$_3$, thus indicating the 100% de of the crystallized material.

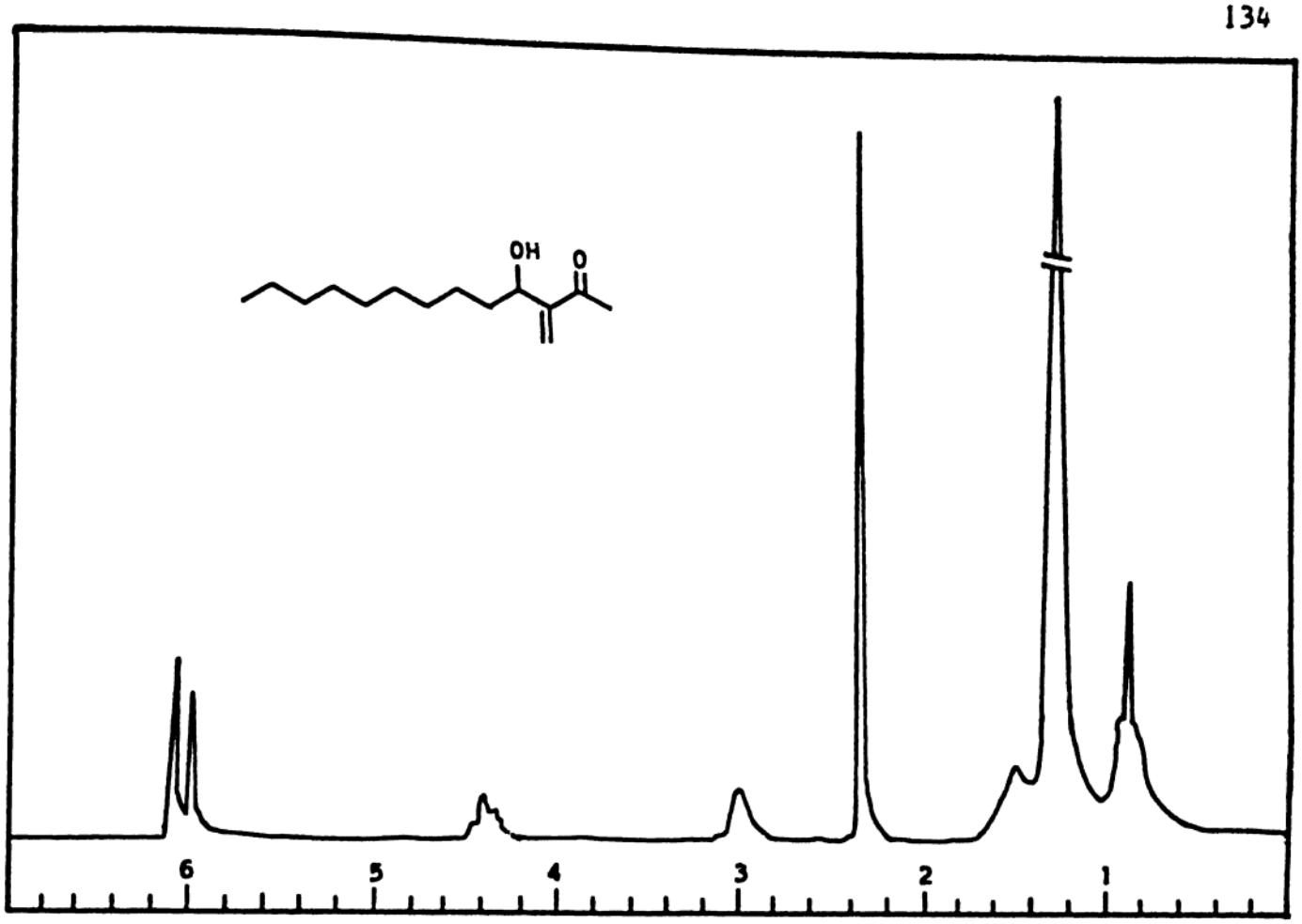
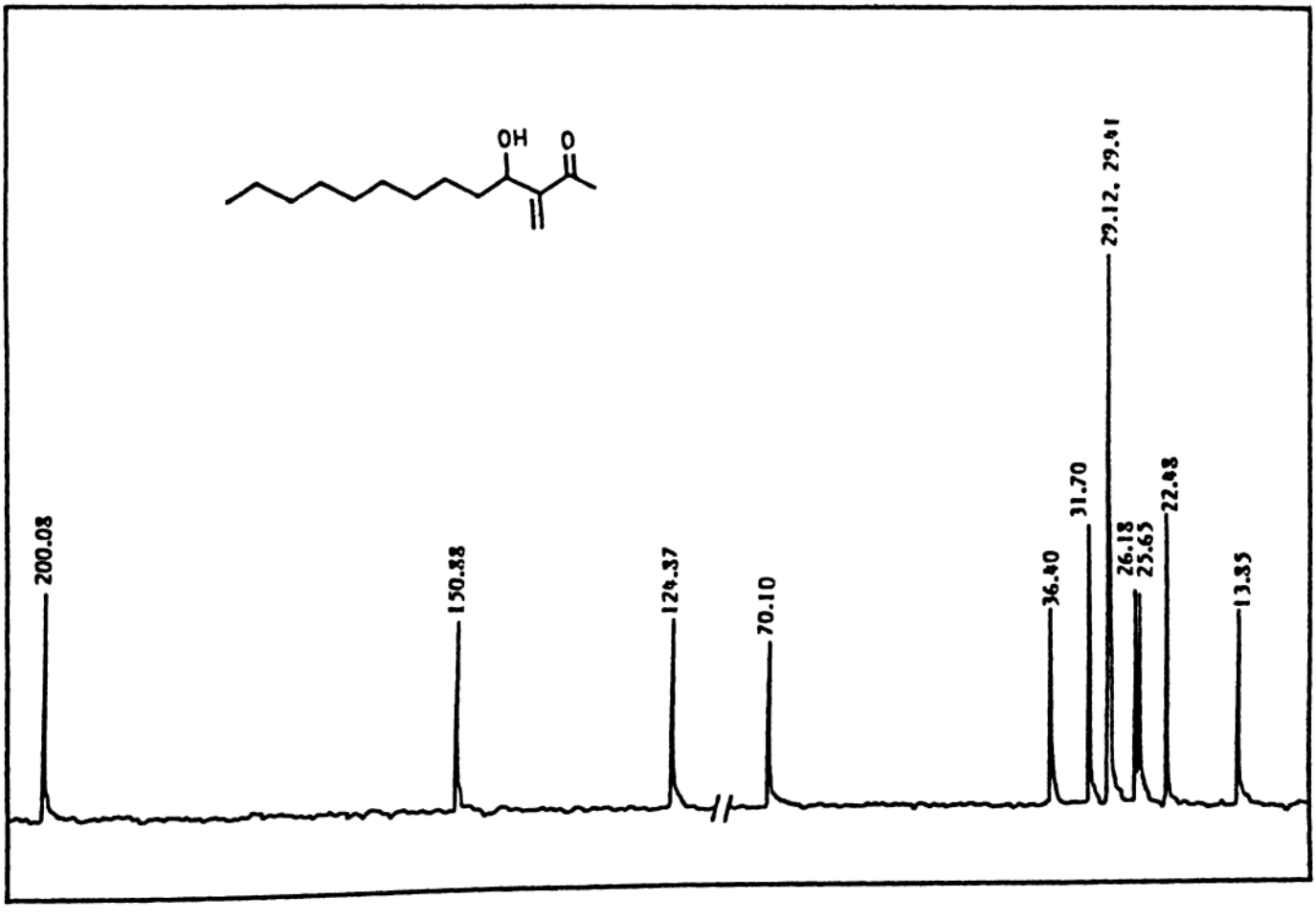


Fig. 1 : ^{1}H NMR spectrum of **75a**.



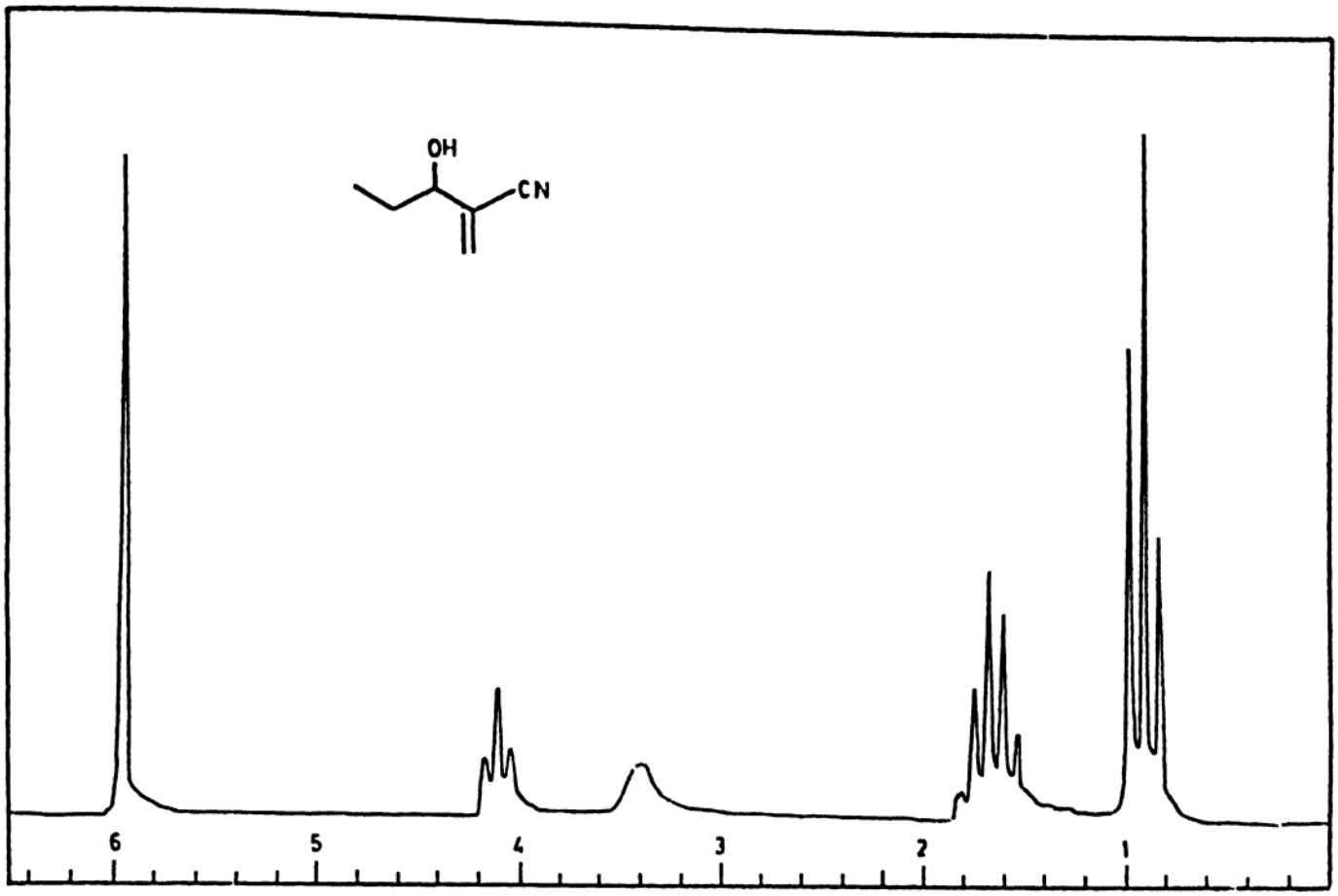


Fig. 3 : ^{1}H NMR spectrum of **47a**.

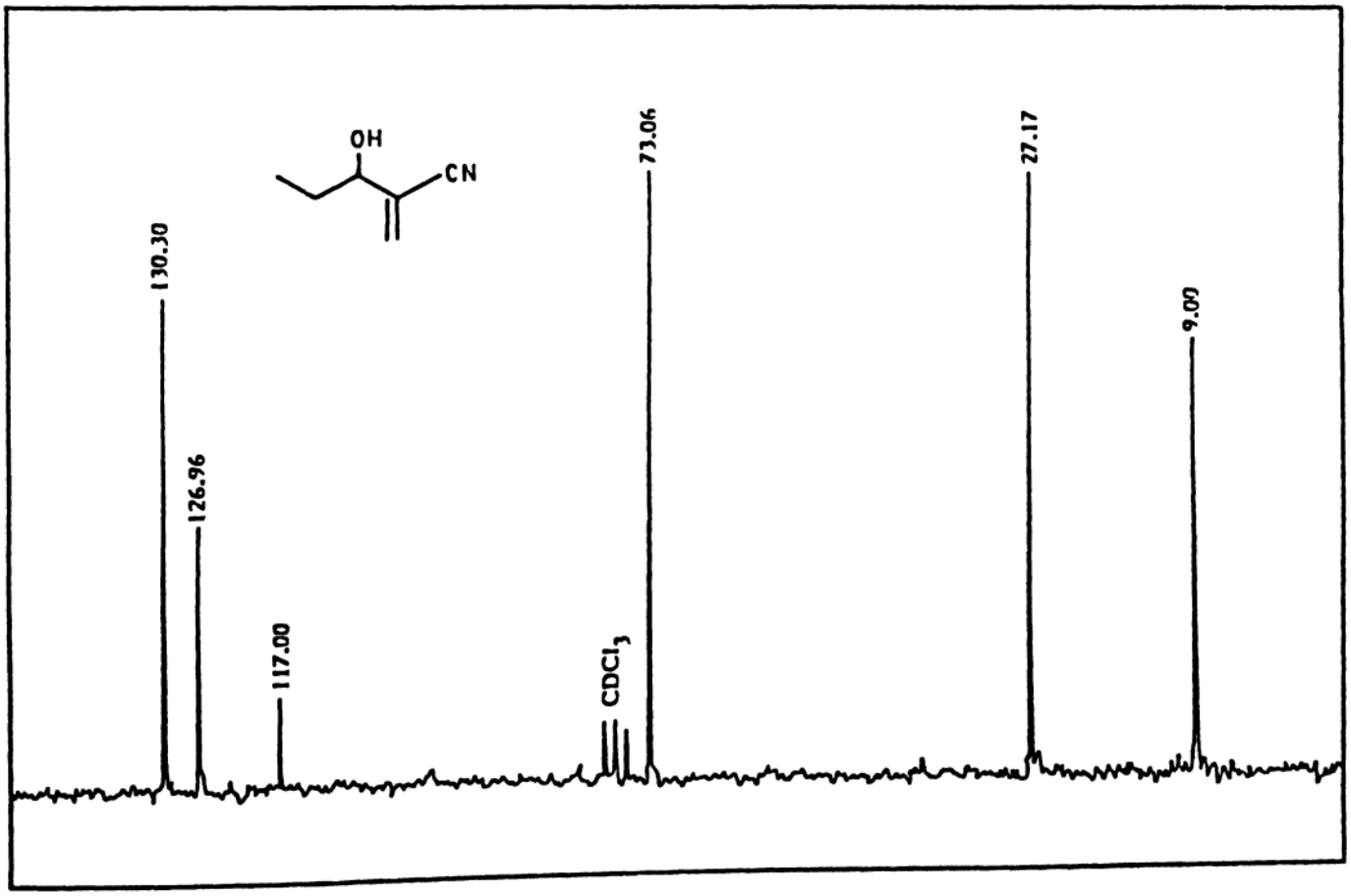


Fig. 4 : ^{13}C NMR spectrum of **47a**.

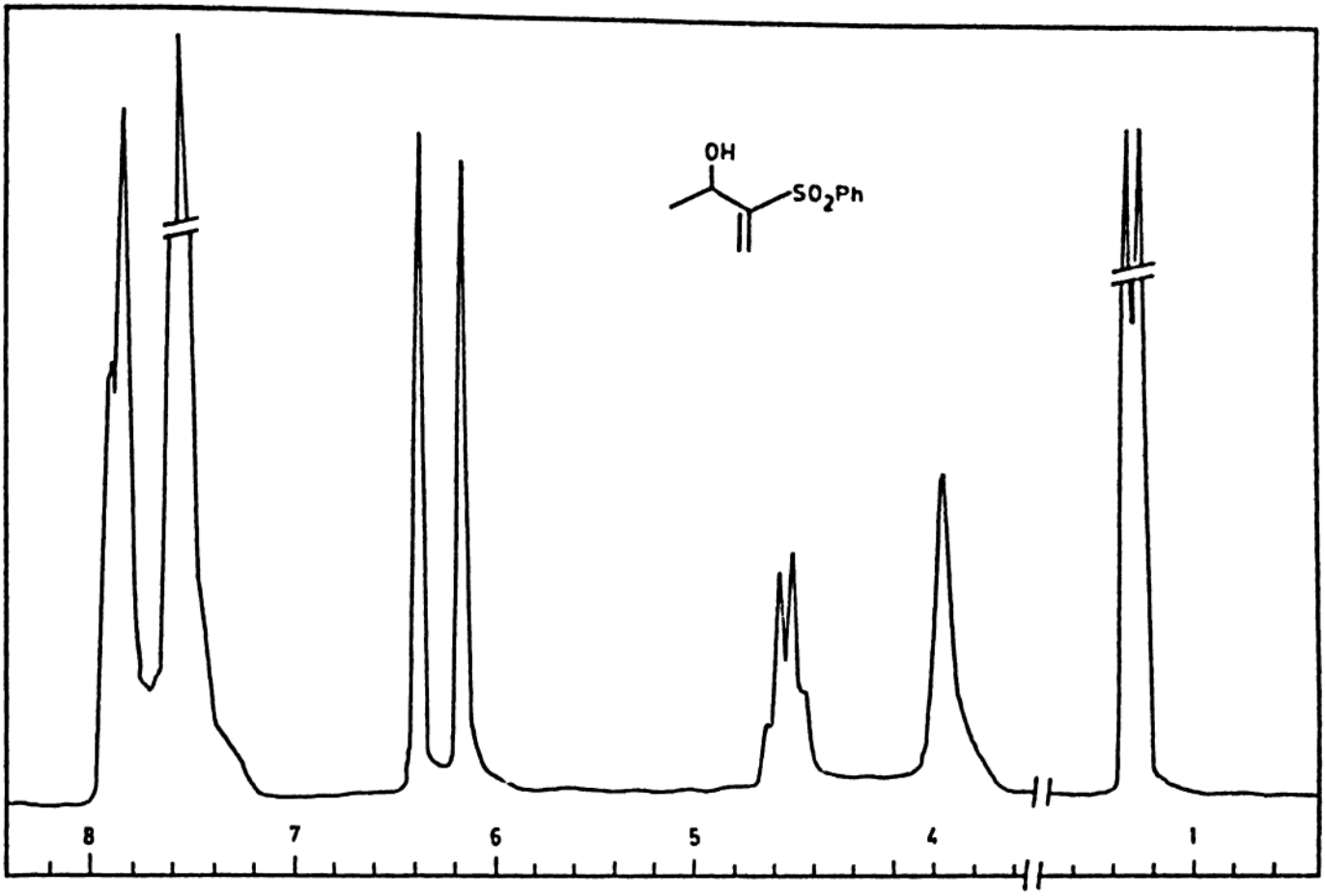


Fig. 5 : ^{1}H NMR spectrum of **82.**

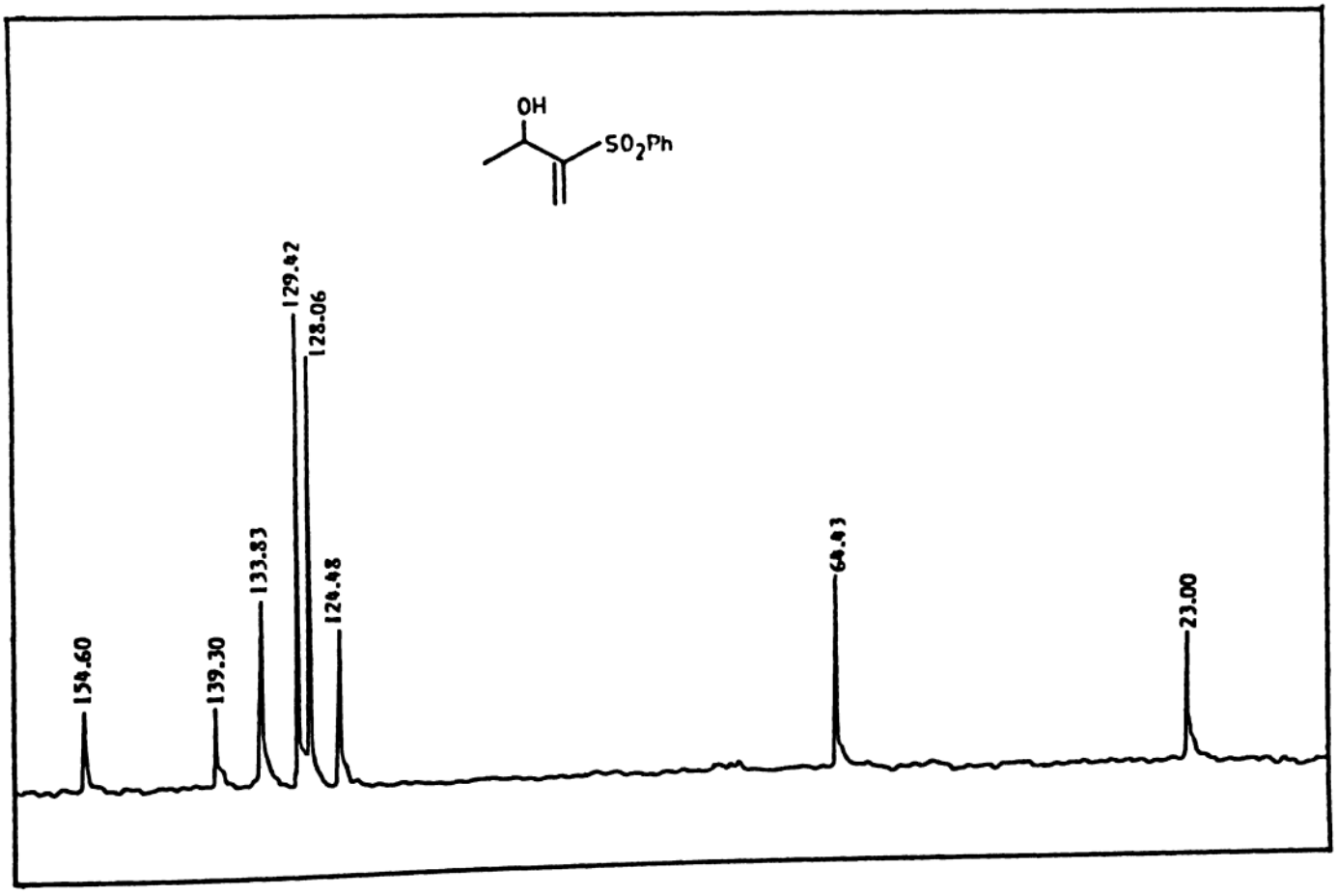


Fig. 6 : ^{13}C NMR spectrum of **82.**

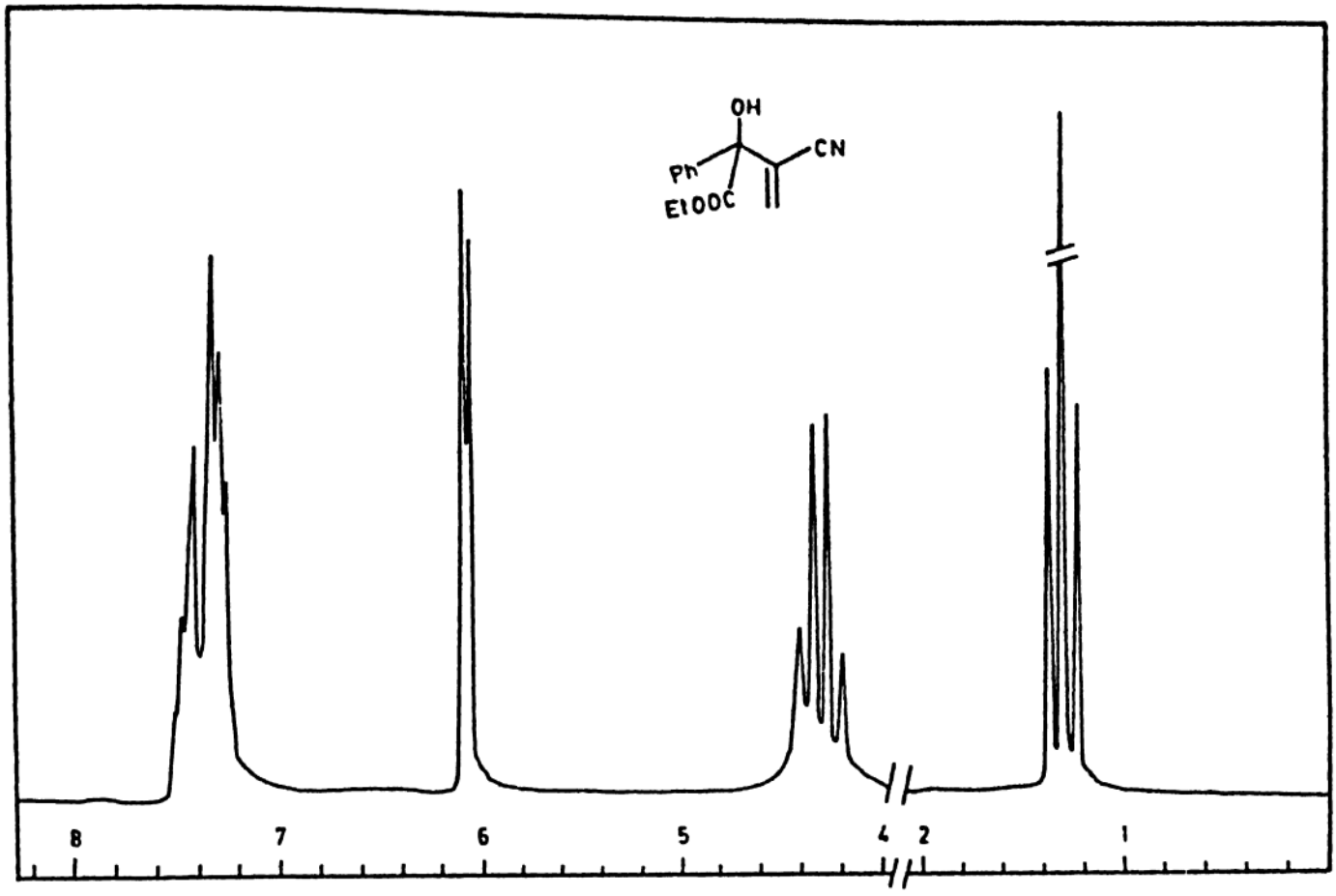


Fig. 7 : ^{1}H NMR spectrum of **87a**.

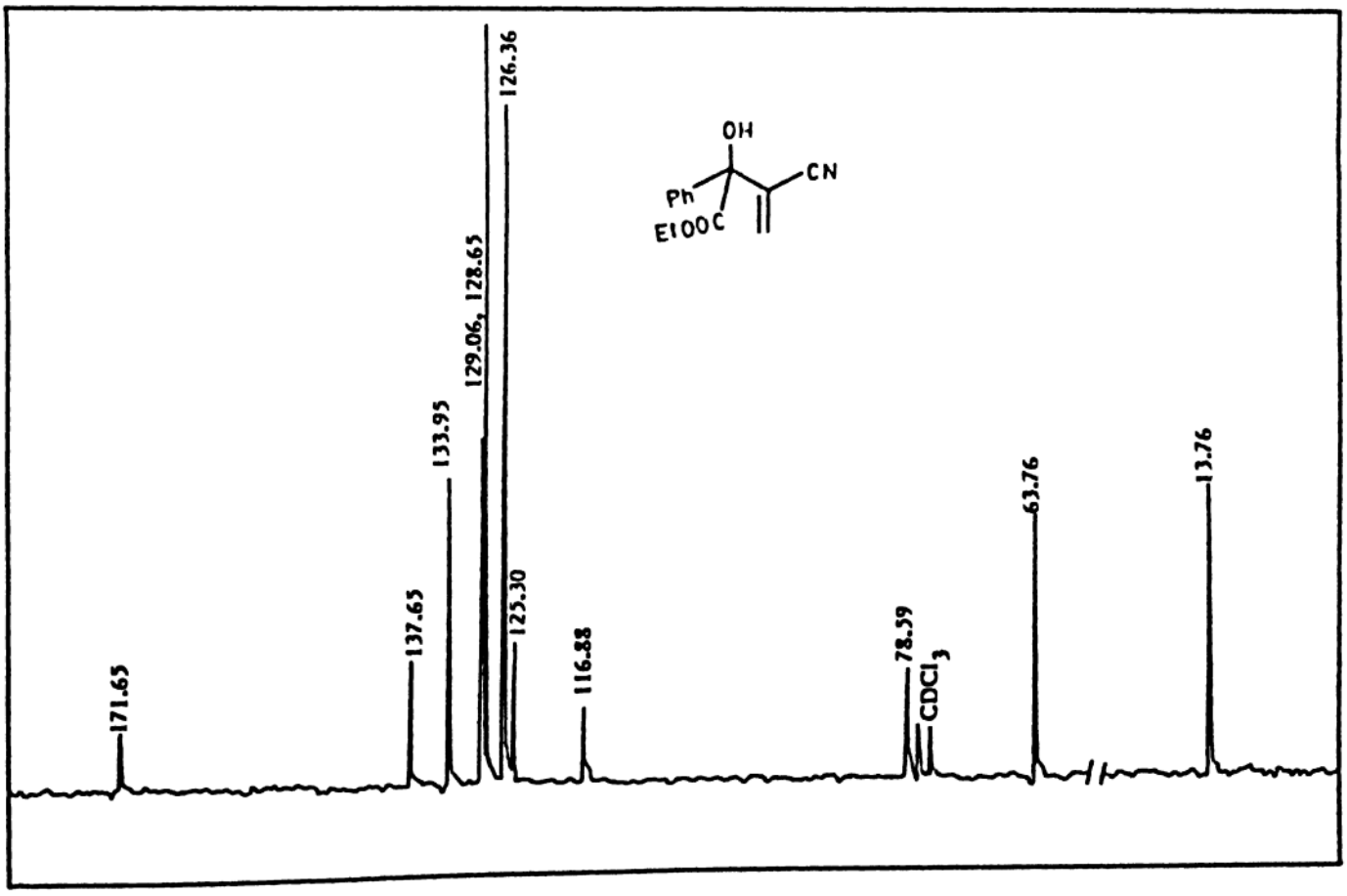


Fig. 8 : ^{13}C NMR spectrum of **87a**.

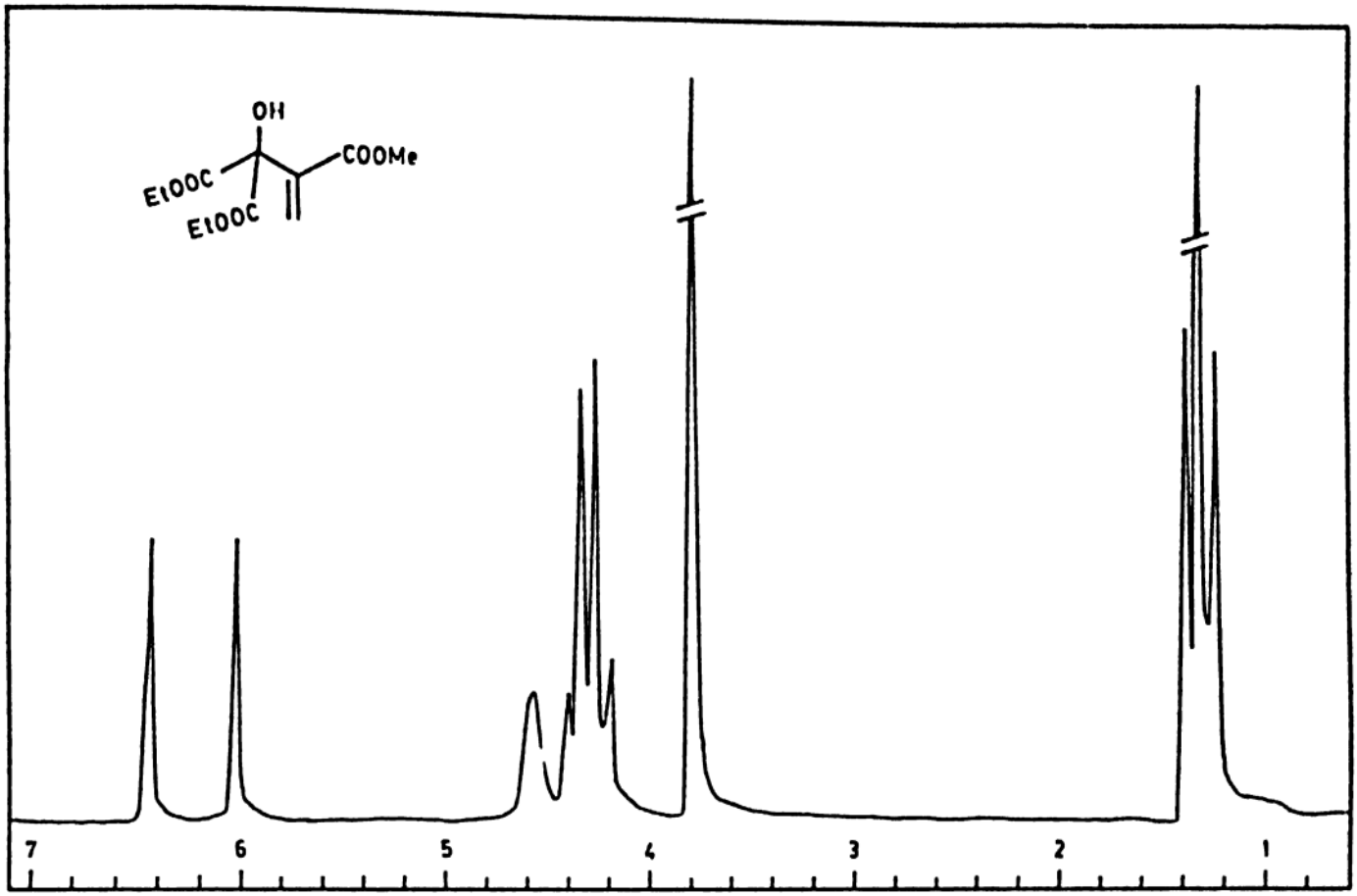


Fig. 9 : ^{1}H NMR spectrum of **91a.**

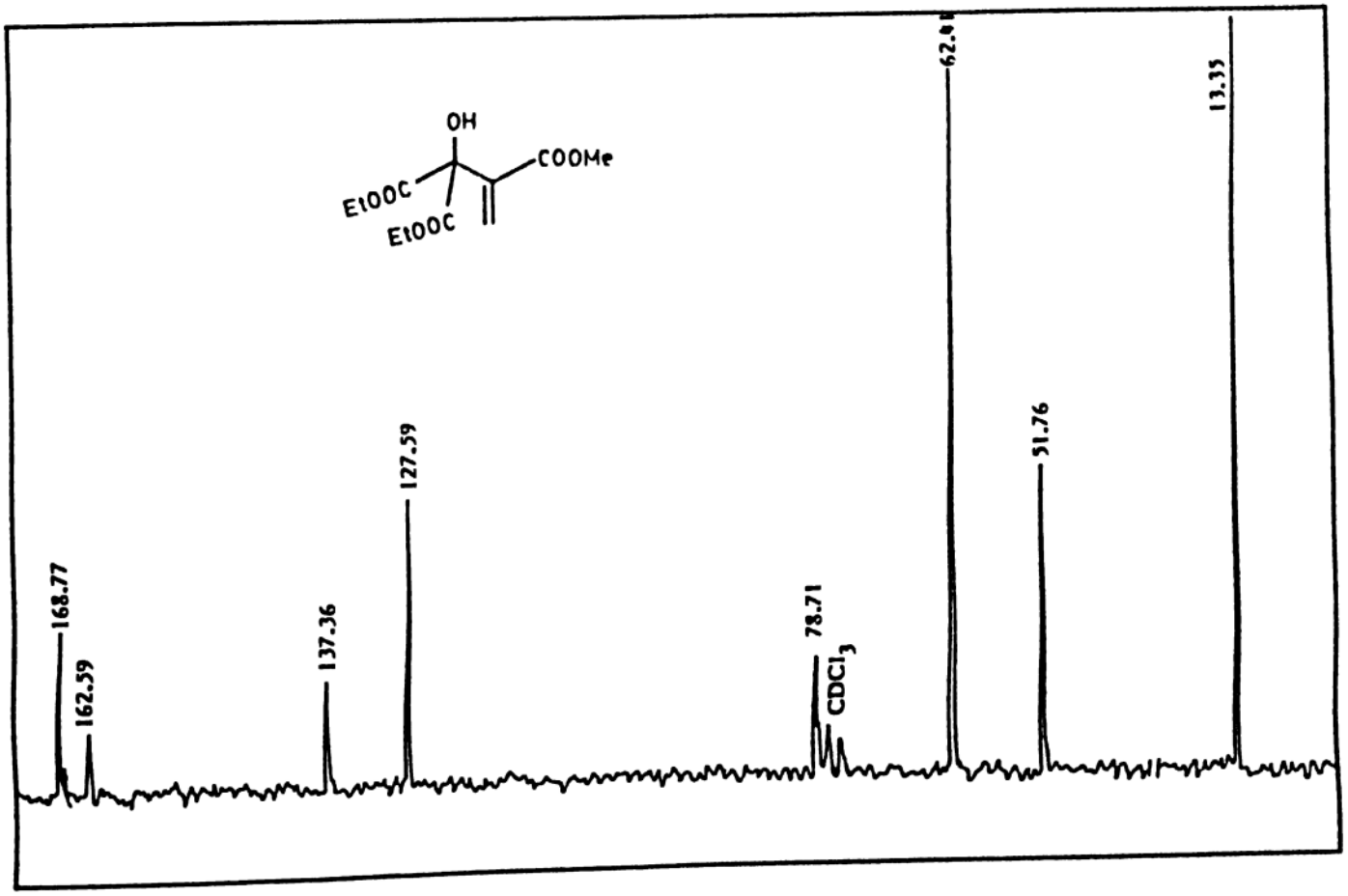


Fig. 10 : ^{13}C NMR spectrum of **91a.**

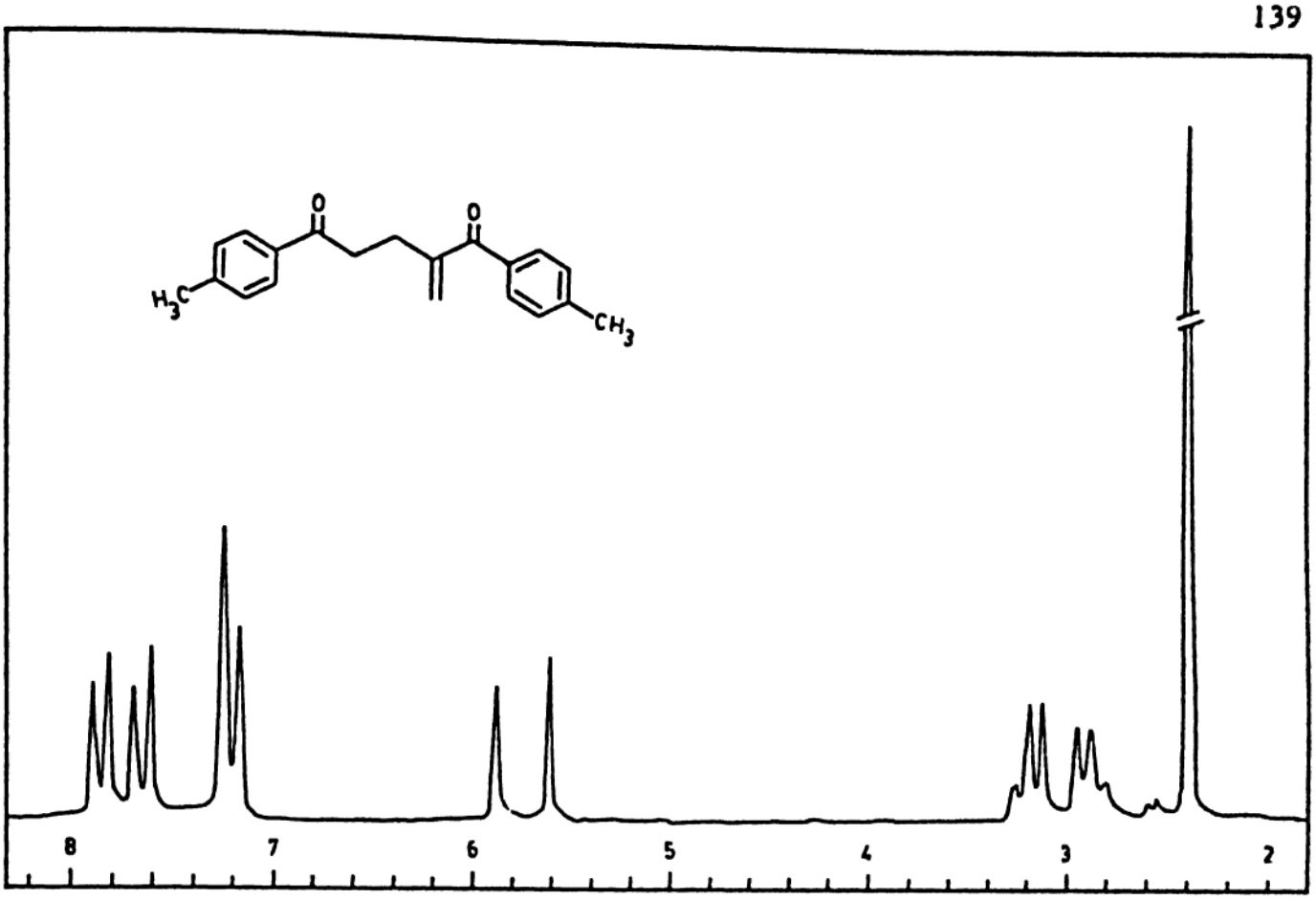


Fig. 11 : ^{1}H NMR spectrum of **96a**.

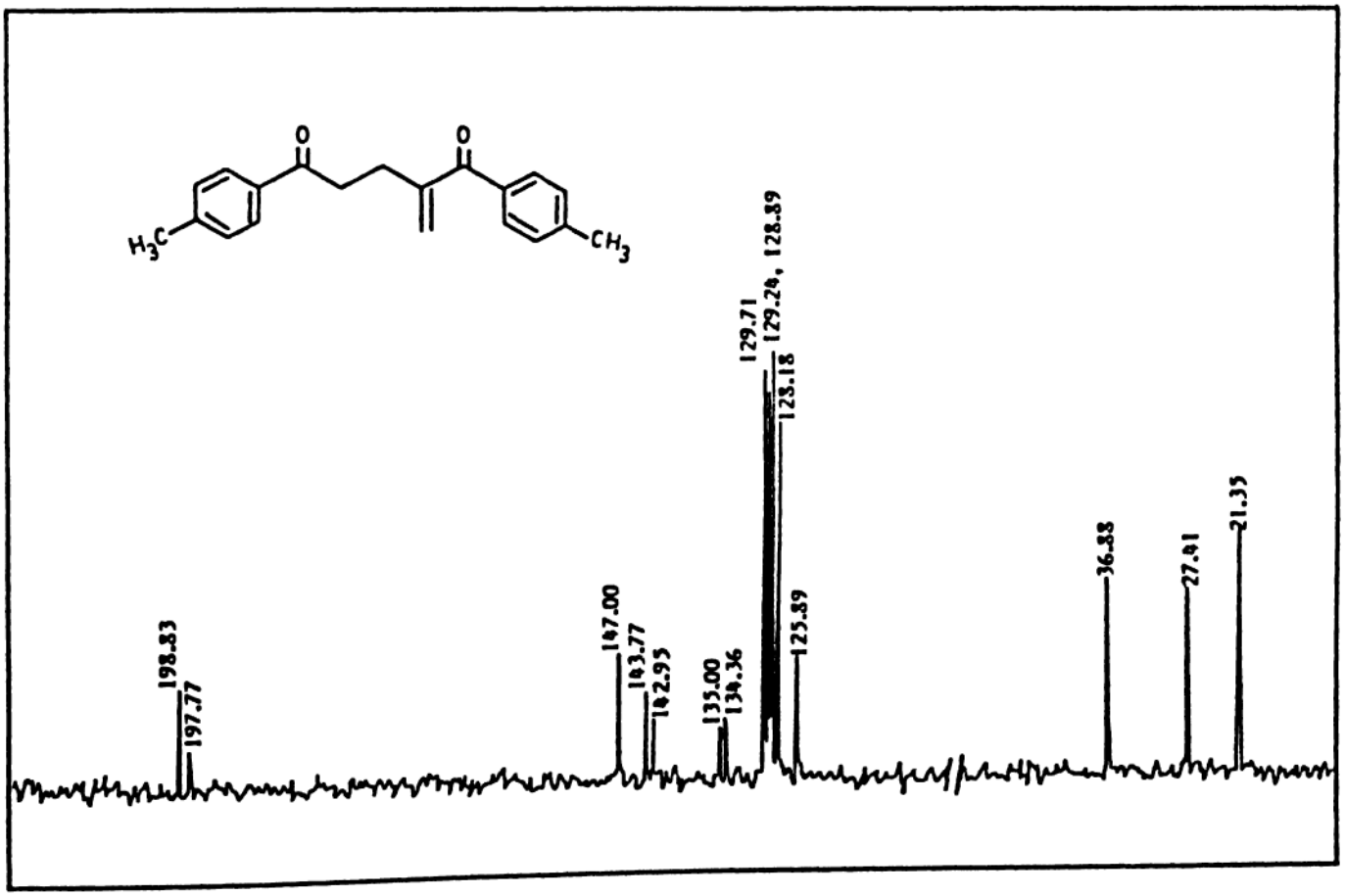


Fig. 12 : ^{13}C NMR spectrum of **96a**.

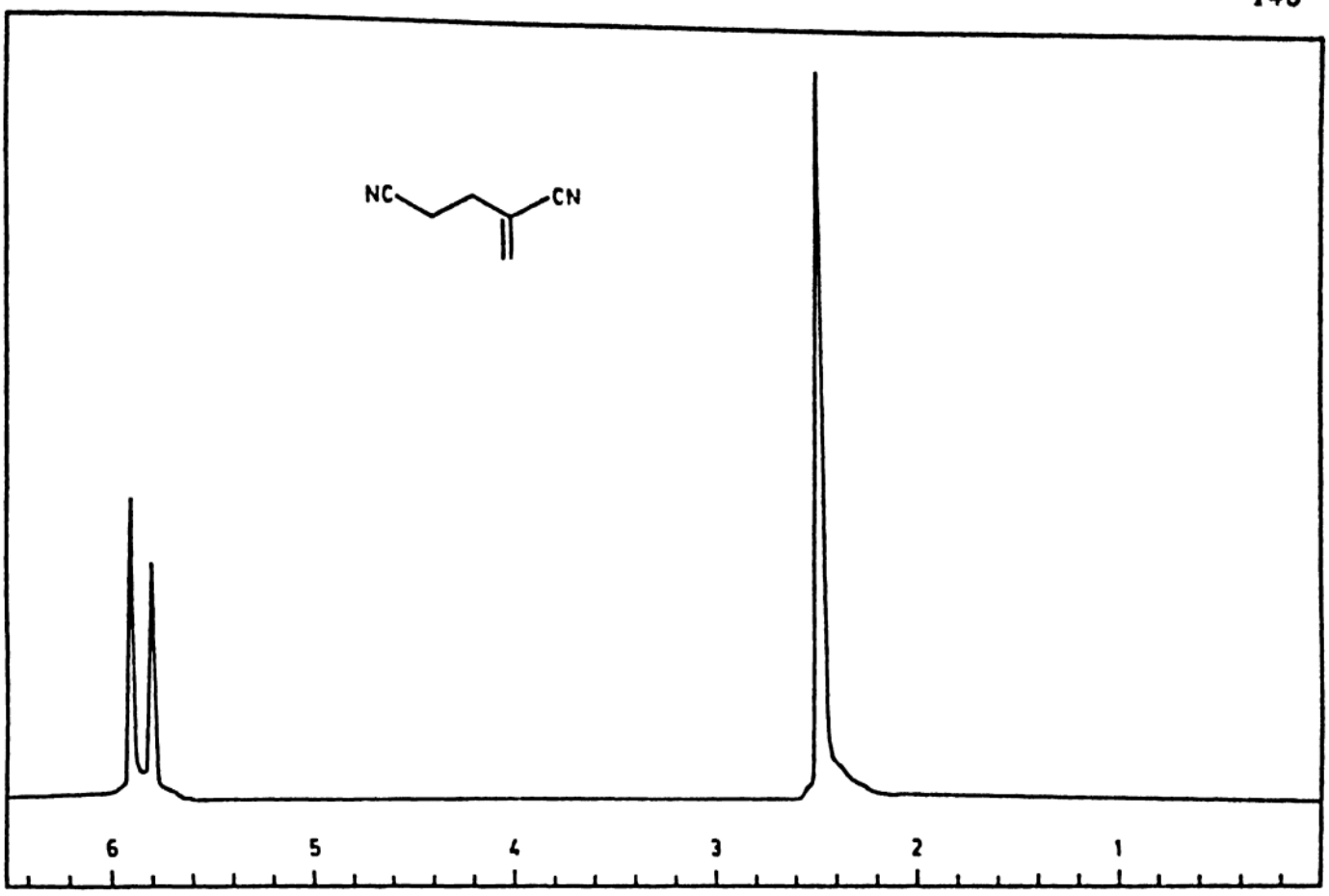


Fig. 13 : ^{1}H NMR spectrum of **97.**

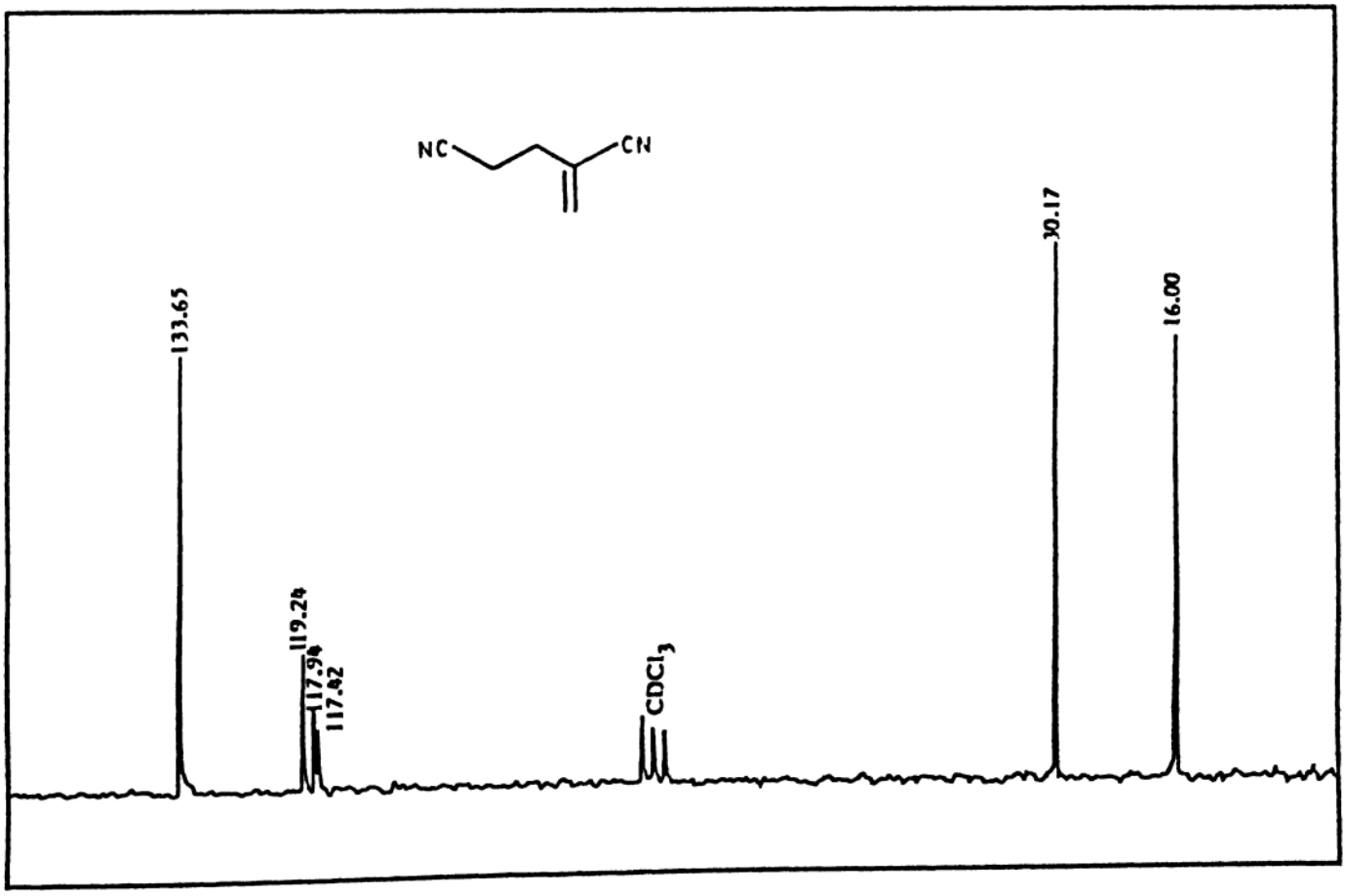


Fig. 14 : ^{13}C NMR spectrum of **97.**

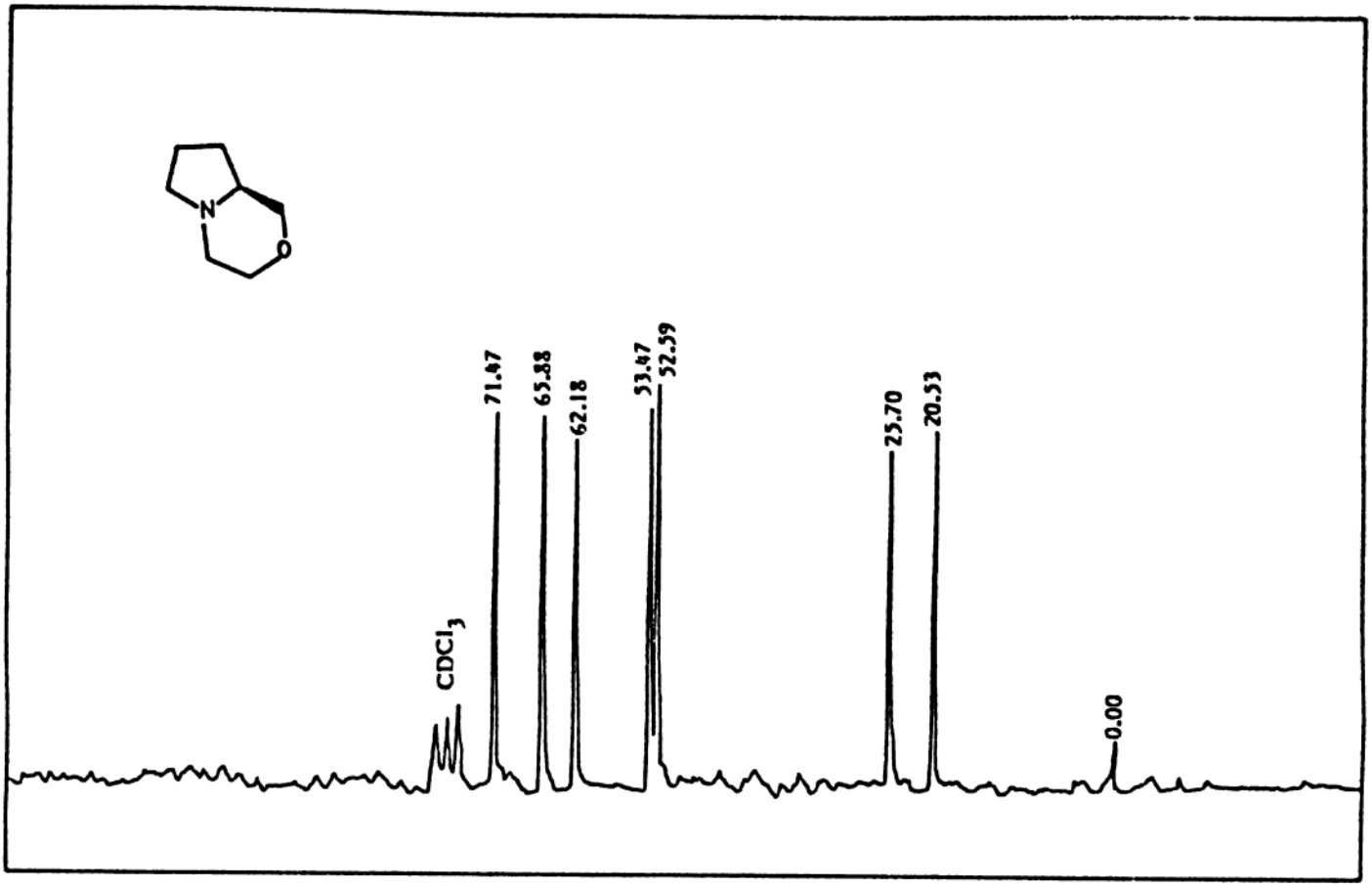


Fig. 15 : ^{13}C NMR spectrum of **99**.

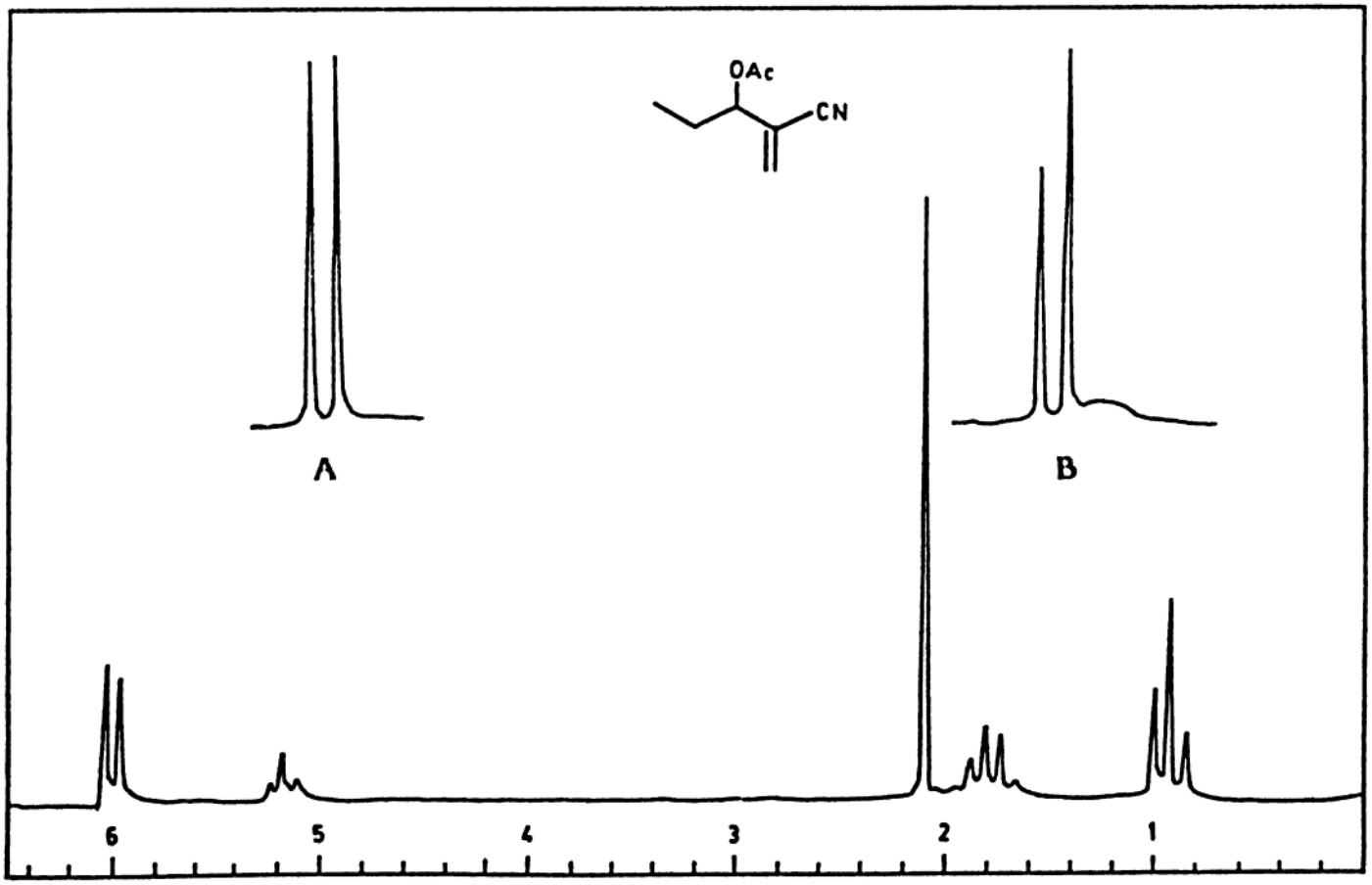


Fig. 16 : ^{1}H NMR spectrum of **108a**. **A.** splitting of $O=CCH_3$ signal of **108a** in the presence of $Eu(hfc)_3$. **B.** splitting of $O=CCH_3$ signal of **109a** in the presence of $Eu(hfc)_3$.

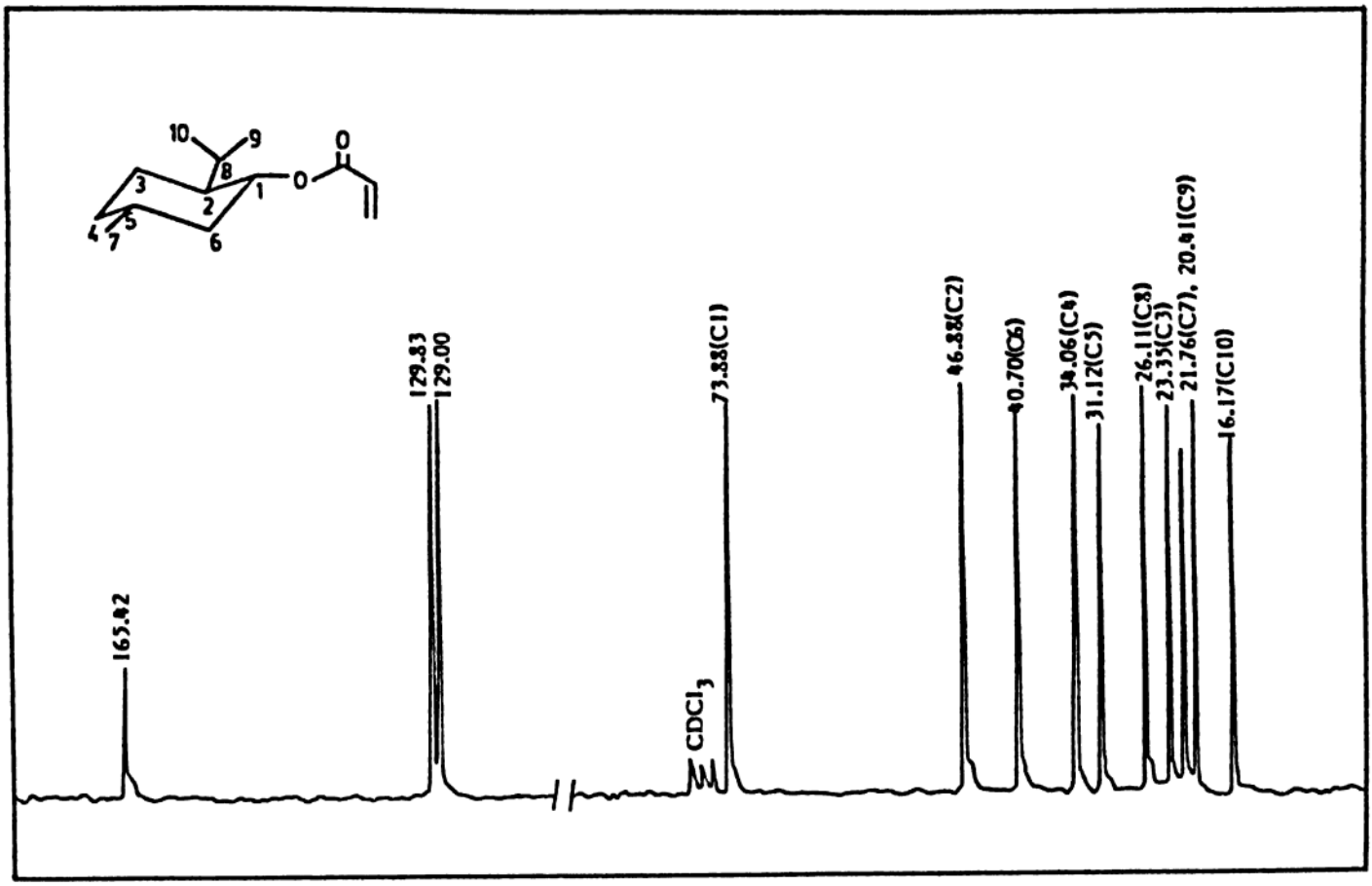


Fig. 17 : ^{13}C NMR spectrum of **116.**

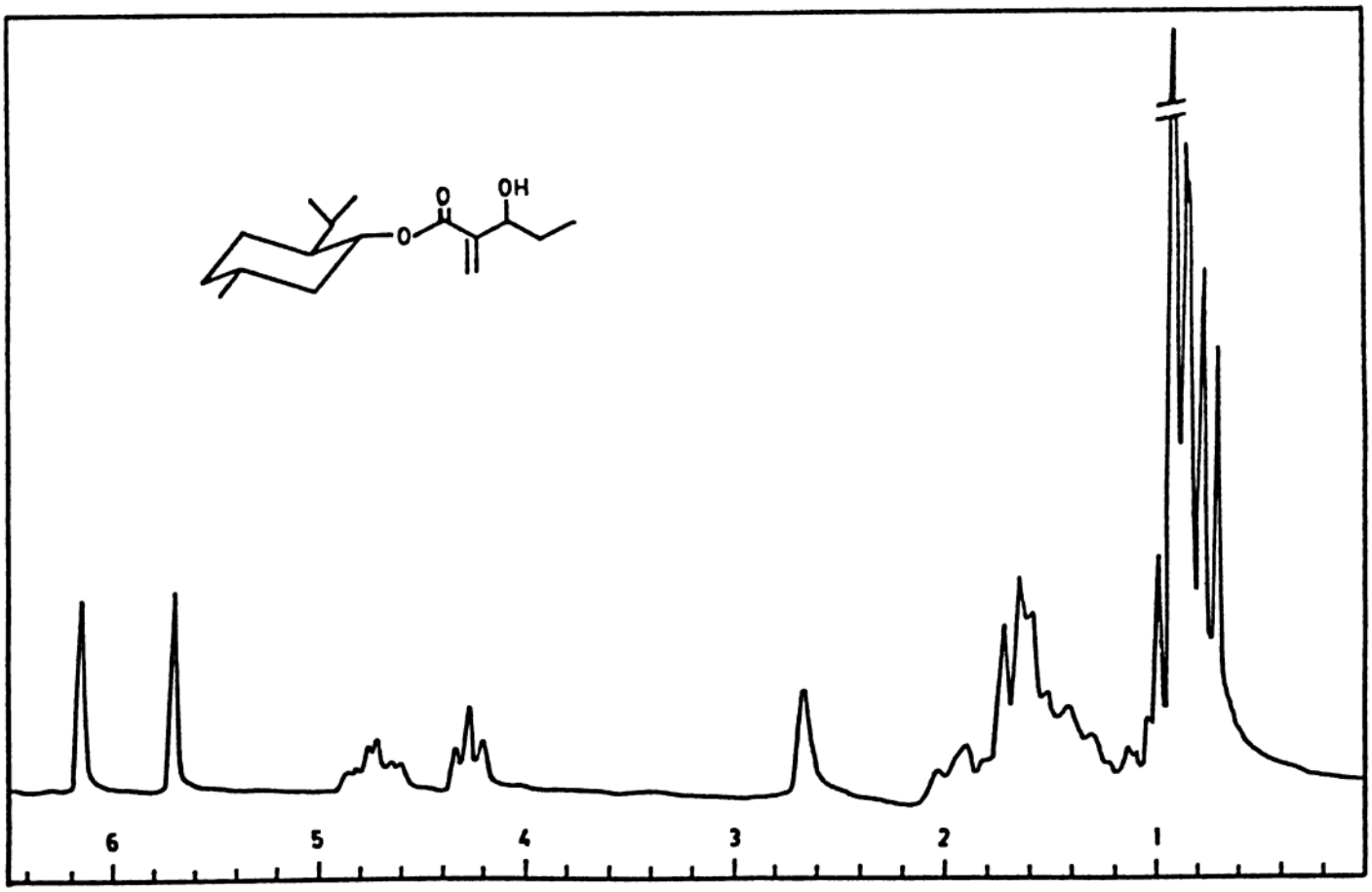


Fig. 18 : ^{1}H NMR spectrum of **119a.**

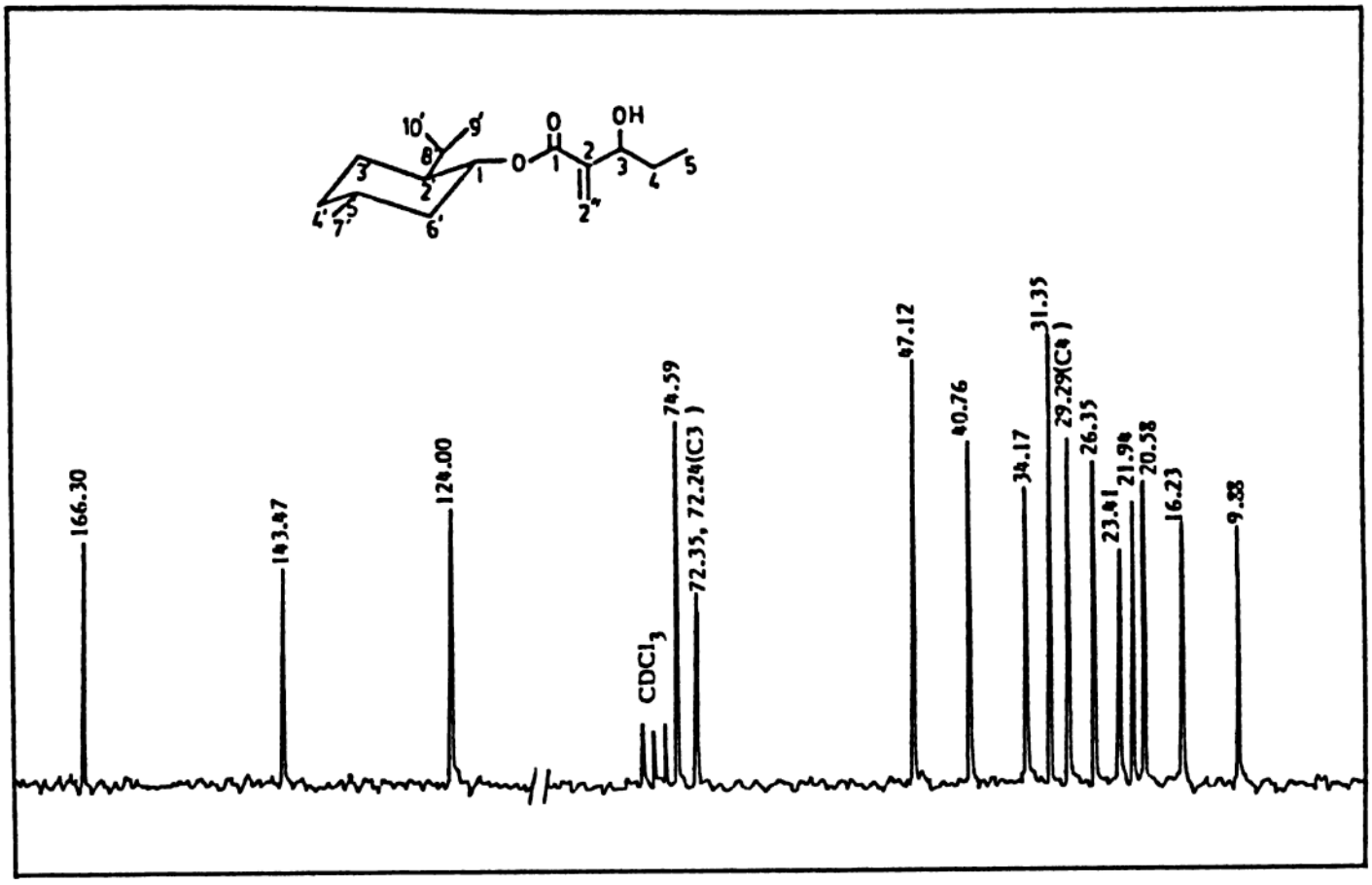


Fig. 19 : ^{13}C NMR spectrum of **119a.**

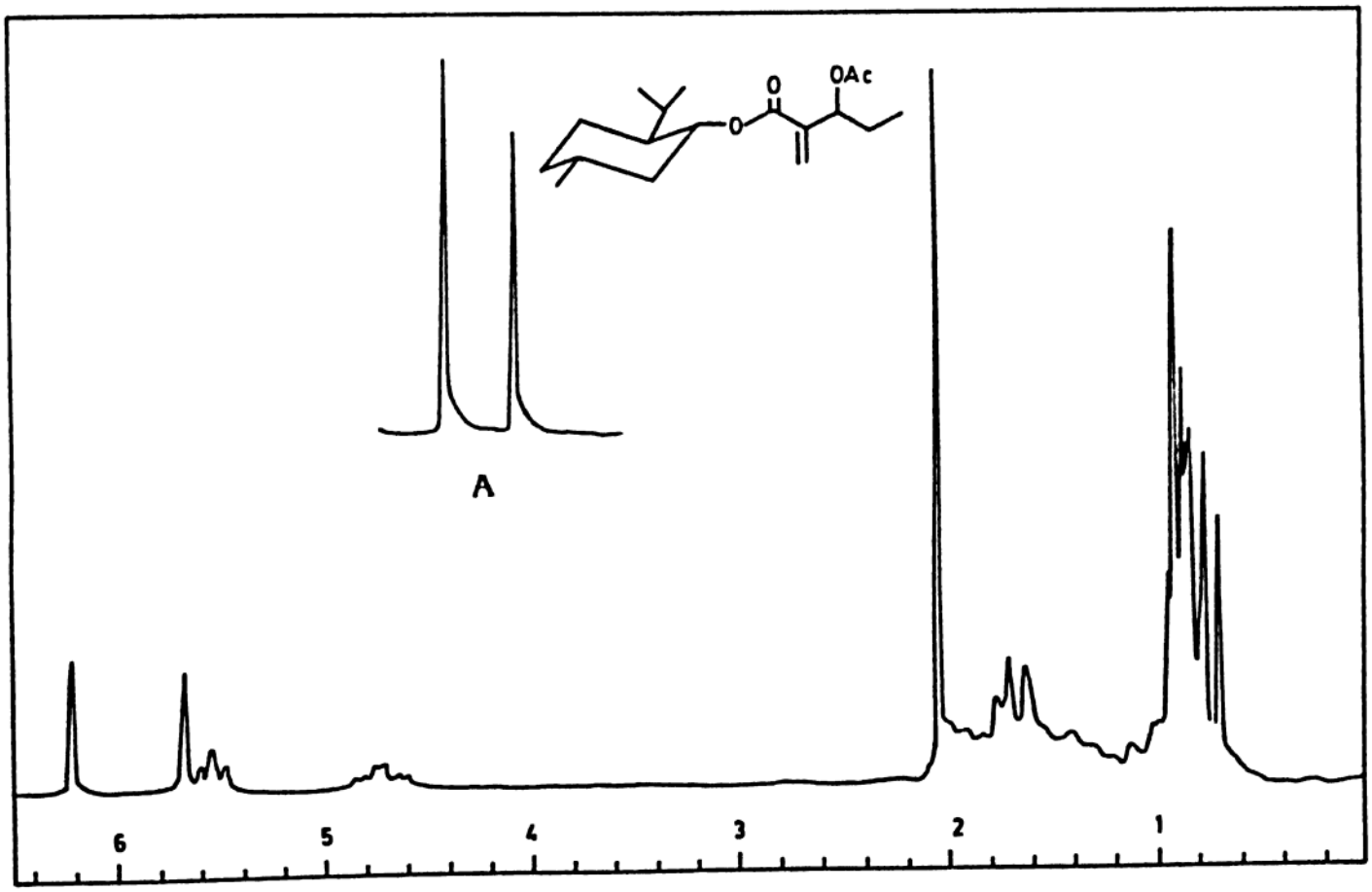


Fig. 20 : ^{1}H NMR spectrum of **120a.** **A.** splitting of $O{=}CCH_3$ signal in the presence of $Eu(hfc)_3$.

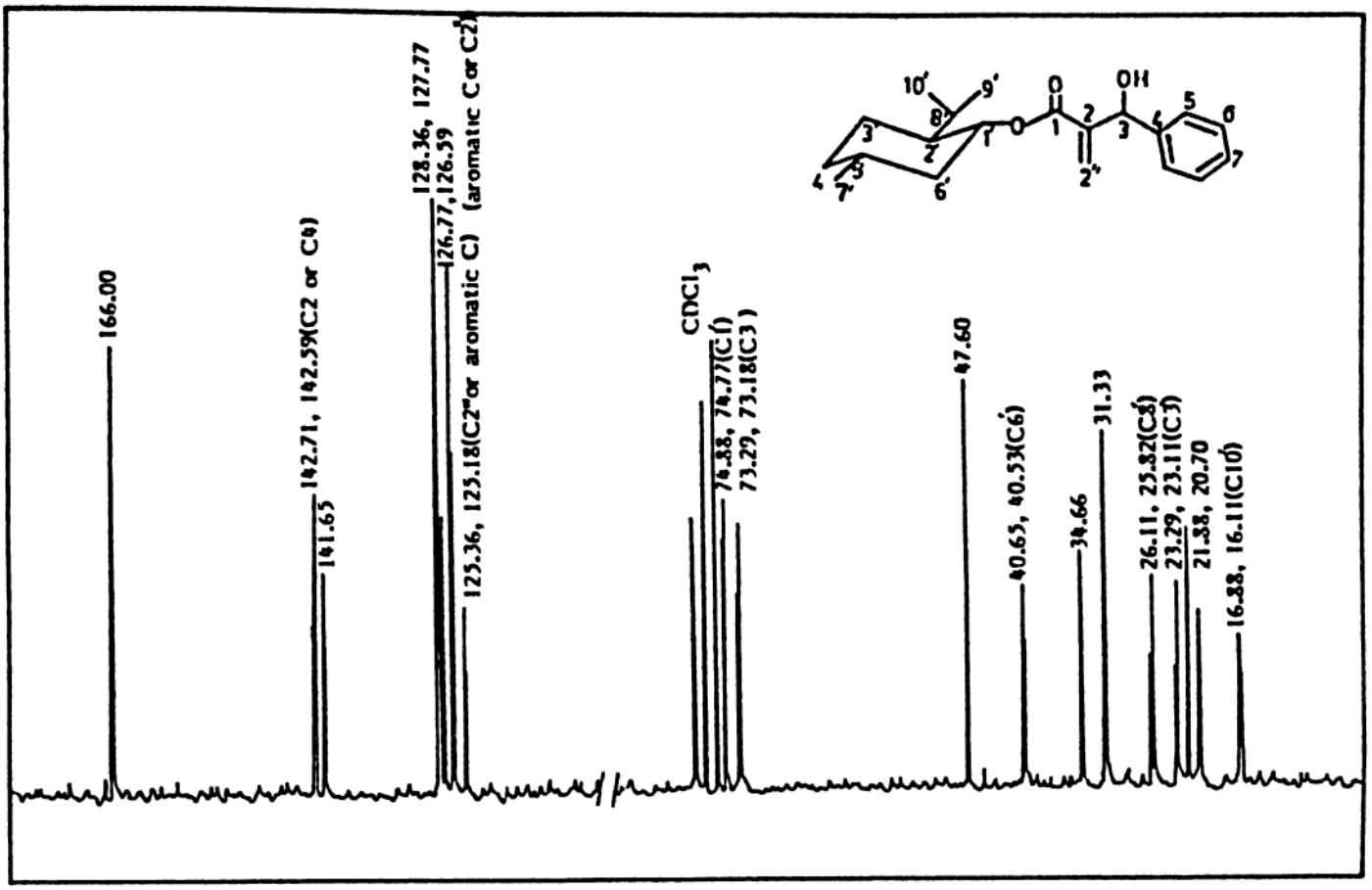


Fig. 21 : ^{13}C NMR spectrum of **119e.**

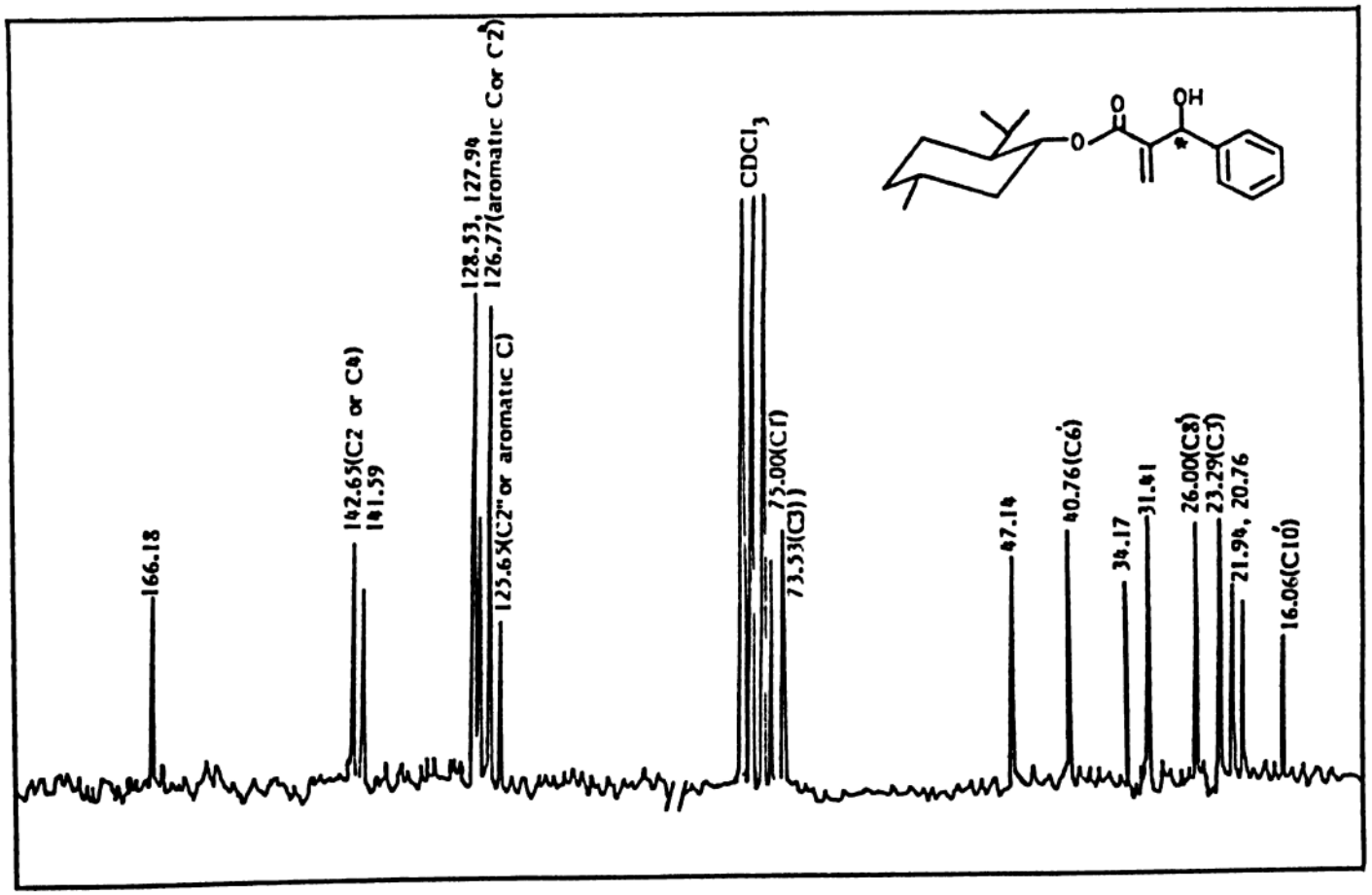


Fig. 22 : ^{13}C NMR spectrum of **119'e.**

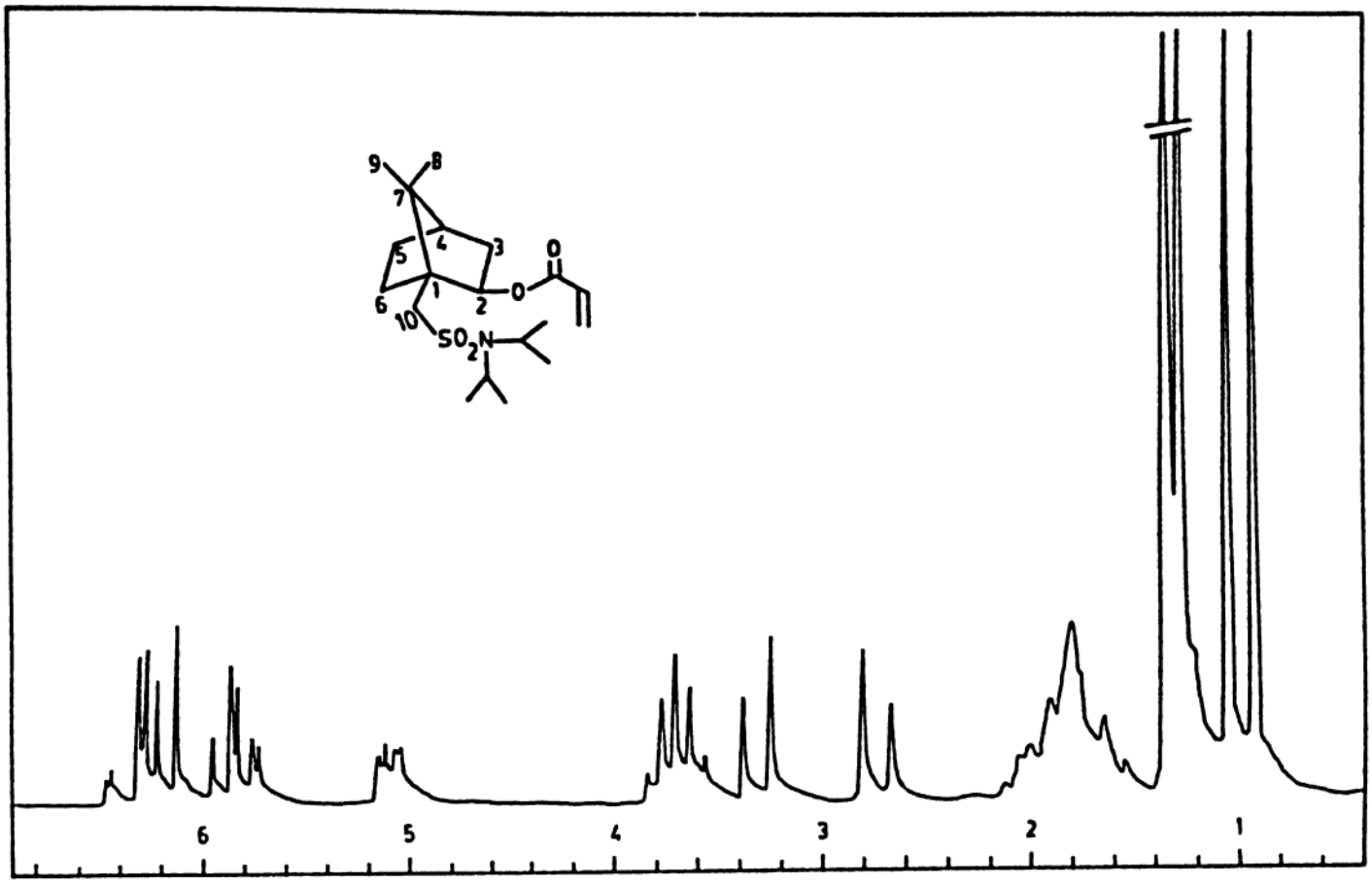


Fig. 23 : ^{1}H NMR spectrum of **118.**

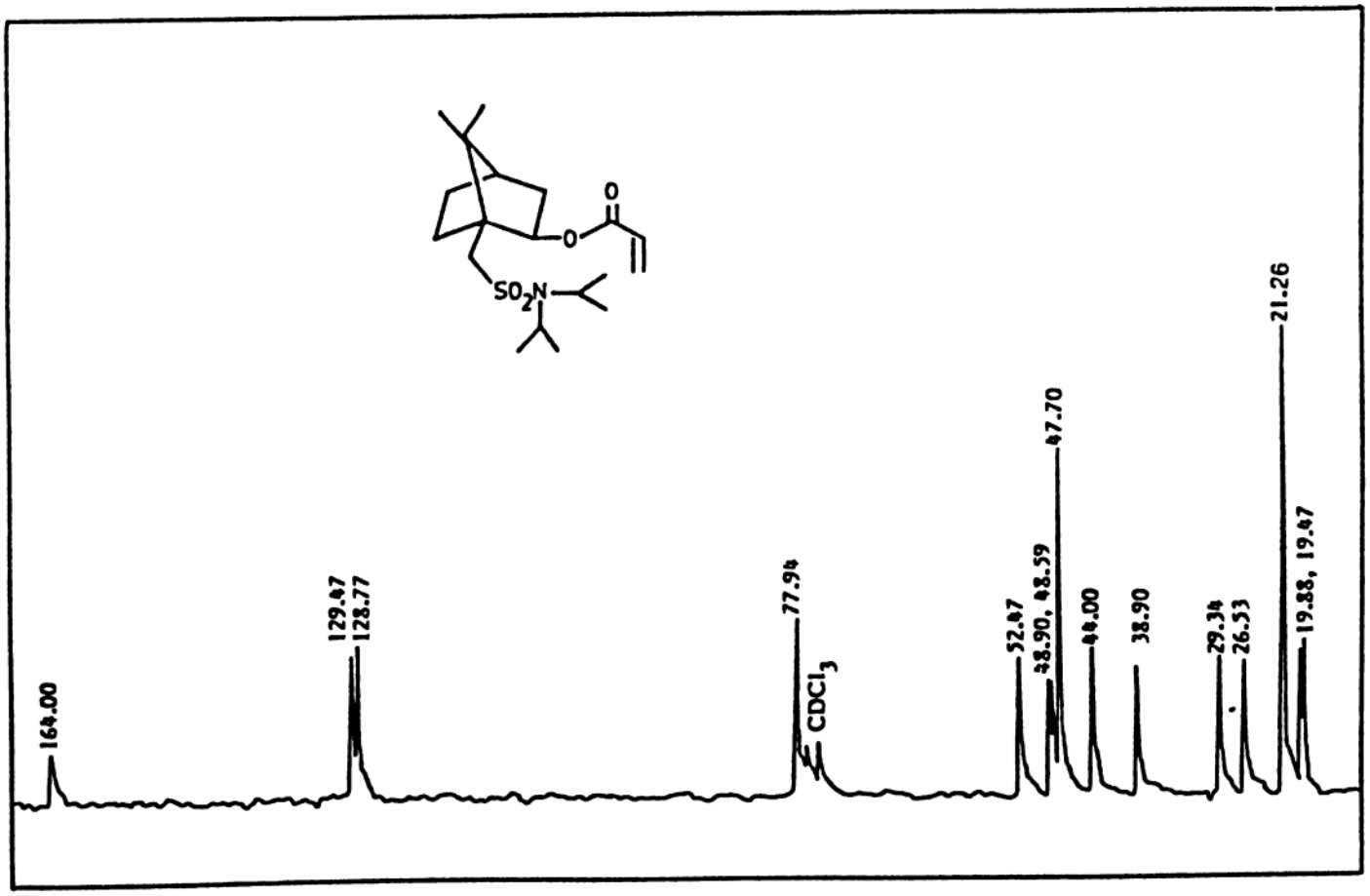


Fig. 24 : ^{13}C NMR spectrum of **118.**

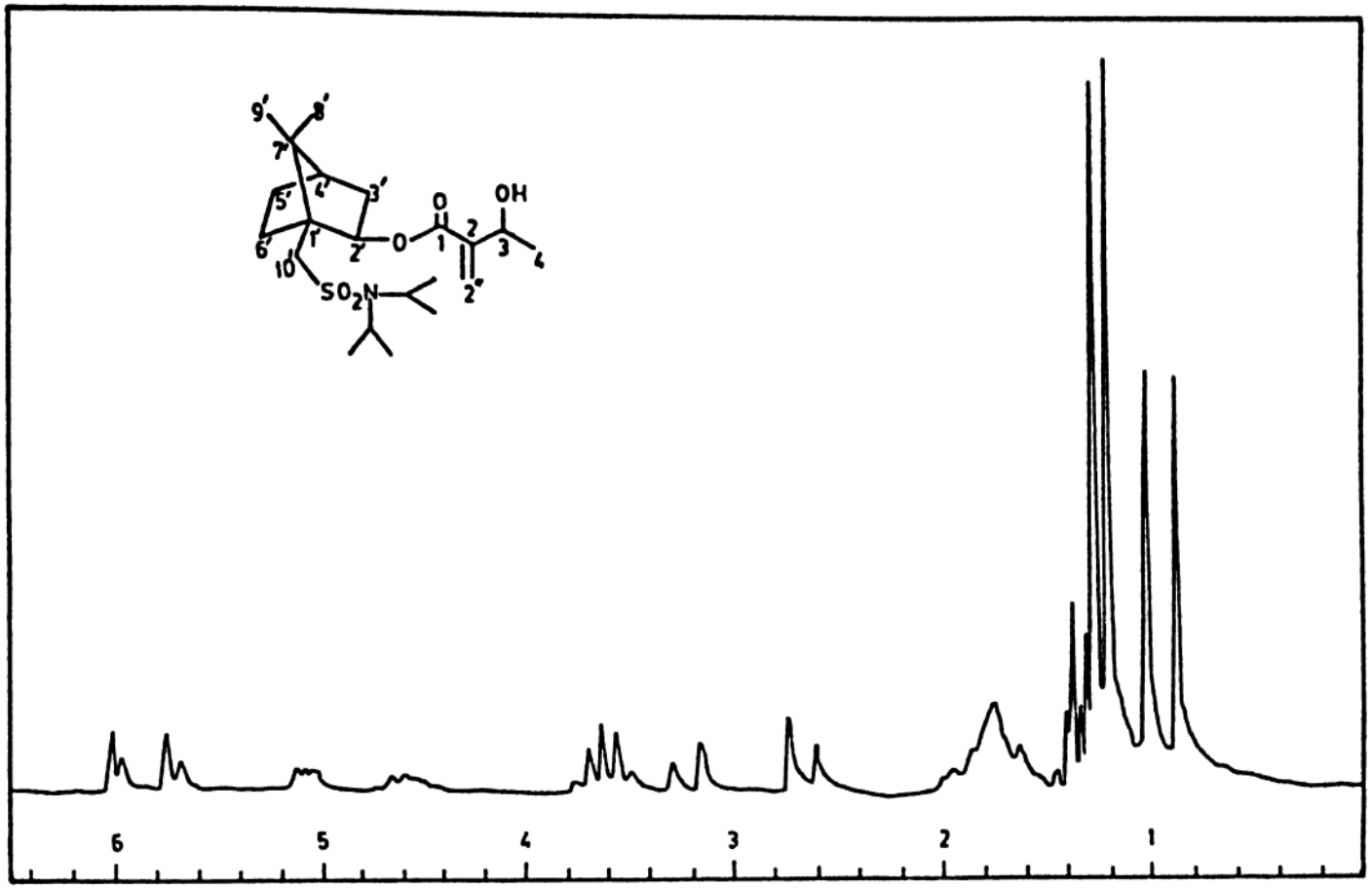


Fig. 25 : ^{1}H NMR spectrum of **127a.**

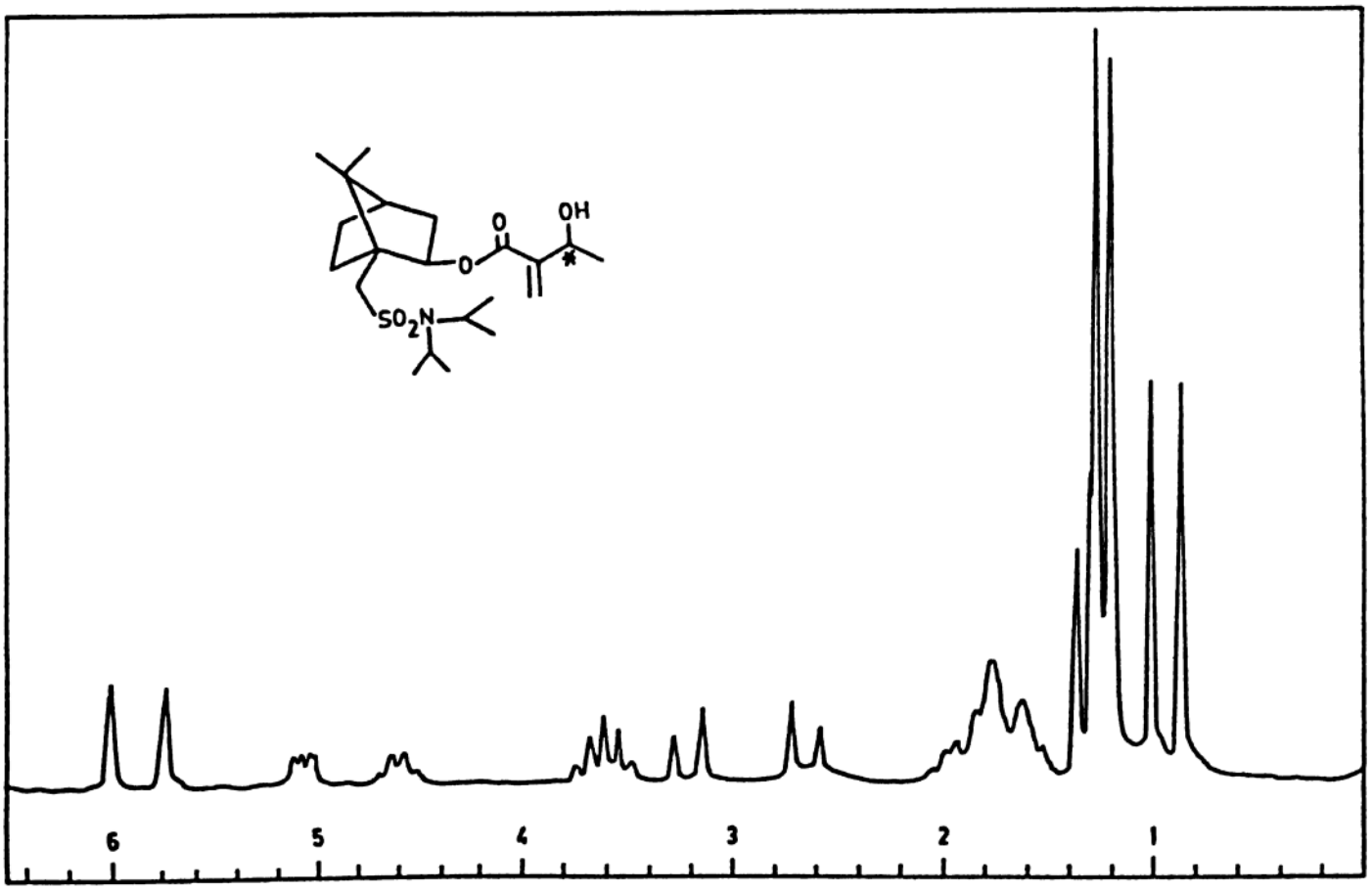


Fig. 26 : ^{1}H NMR spectrum of **127'a.**

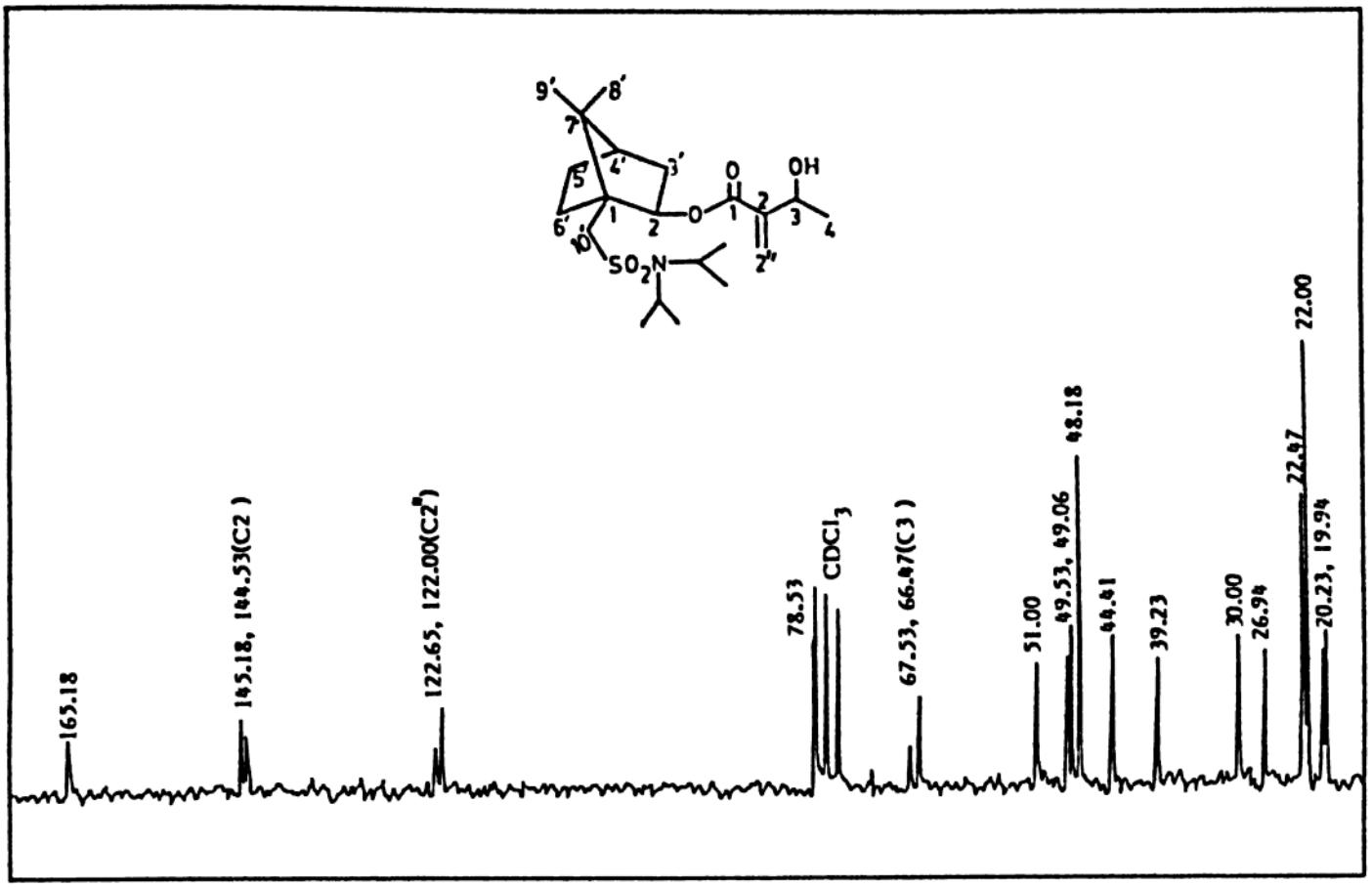


Fig. 27 : ^{13}C NMR spectrum of **127a.**

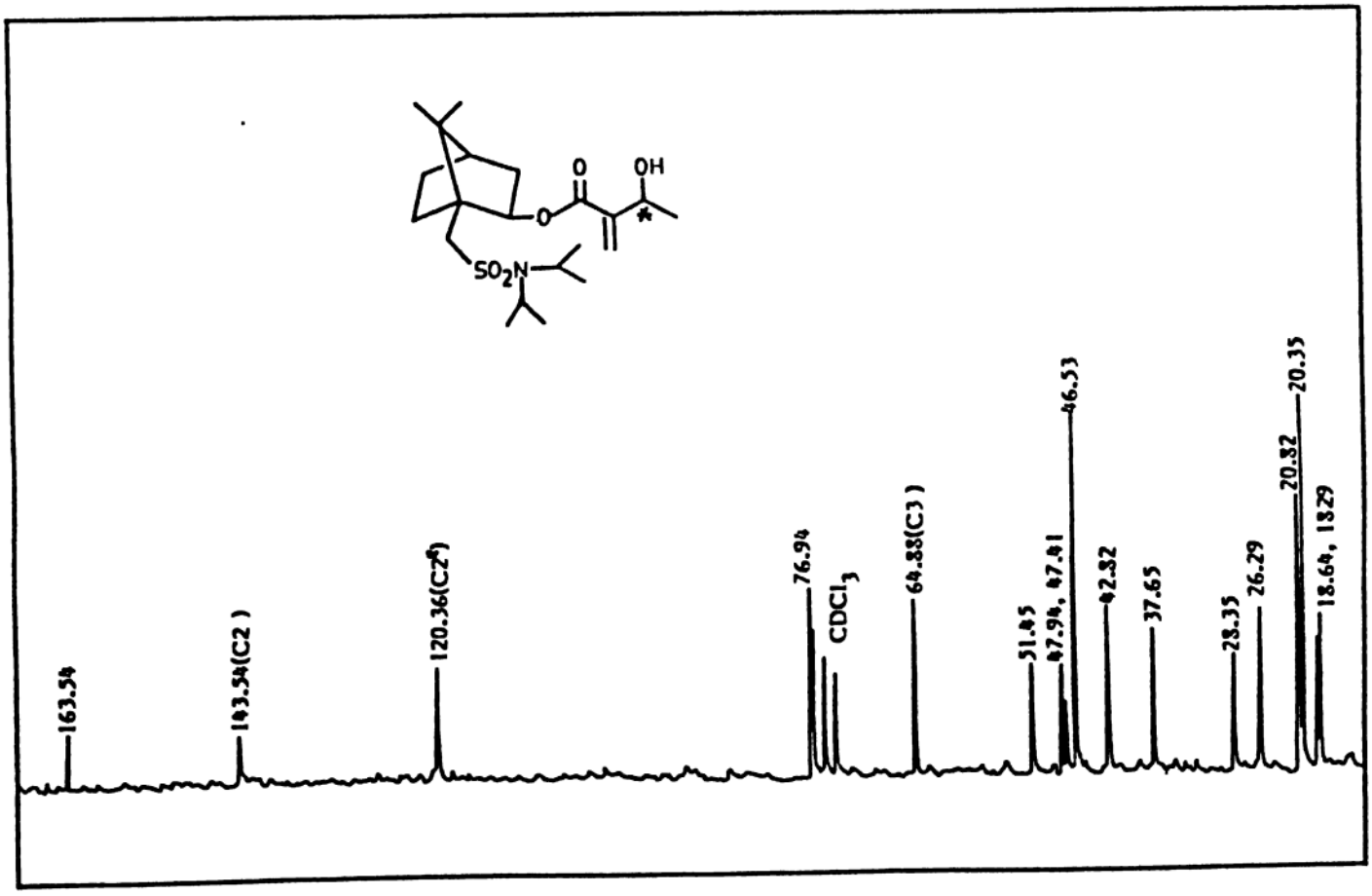


Fig. 28: ^{13}C NMR spectrum of **127'a.**

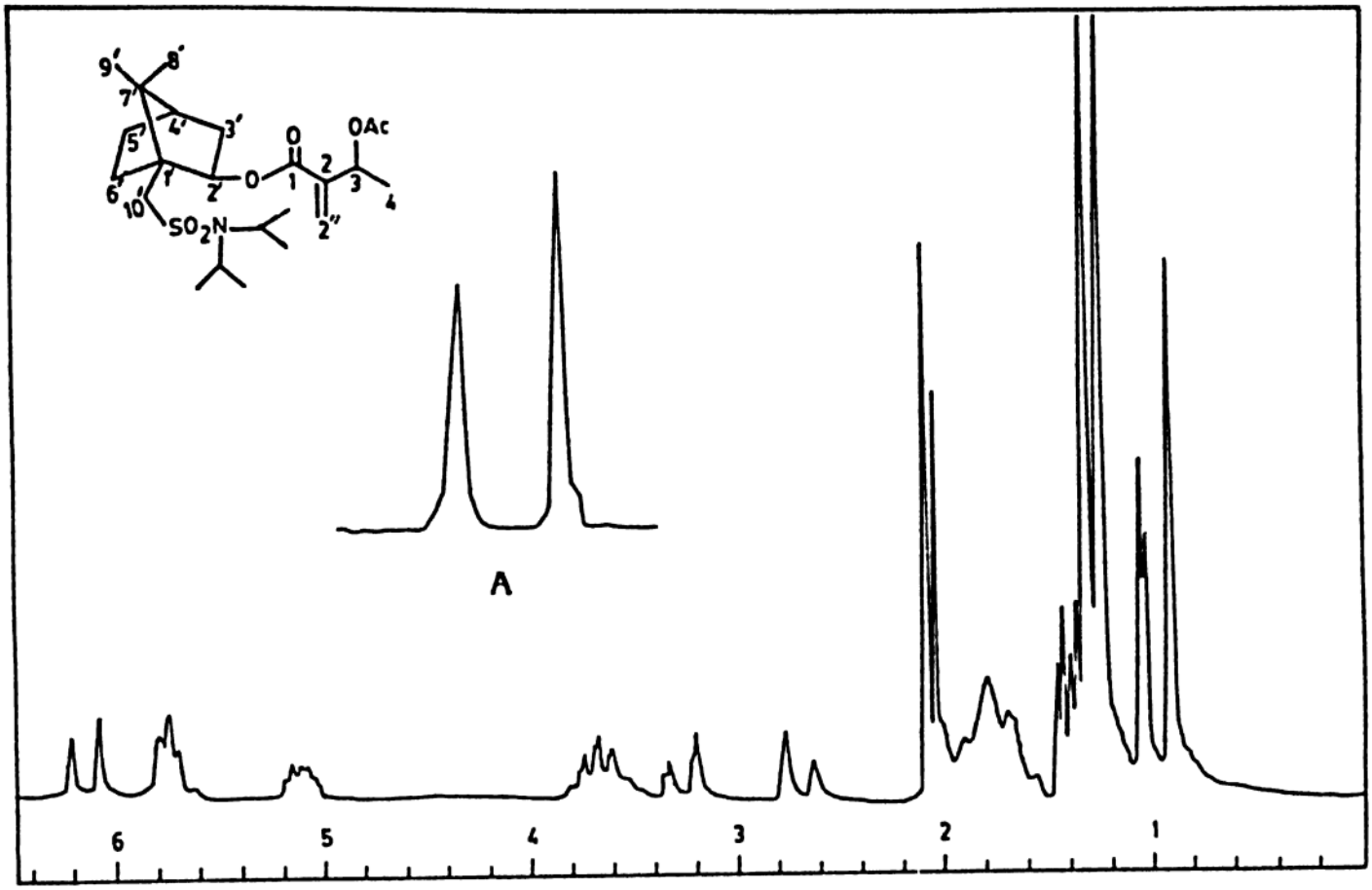


Fig. 29 : ^{1}H NMR spectrum of **128a**. **A.** splitting of O-CCH_3 signal in the presence of $Eu(hfc)_3$.

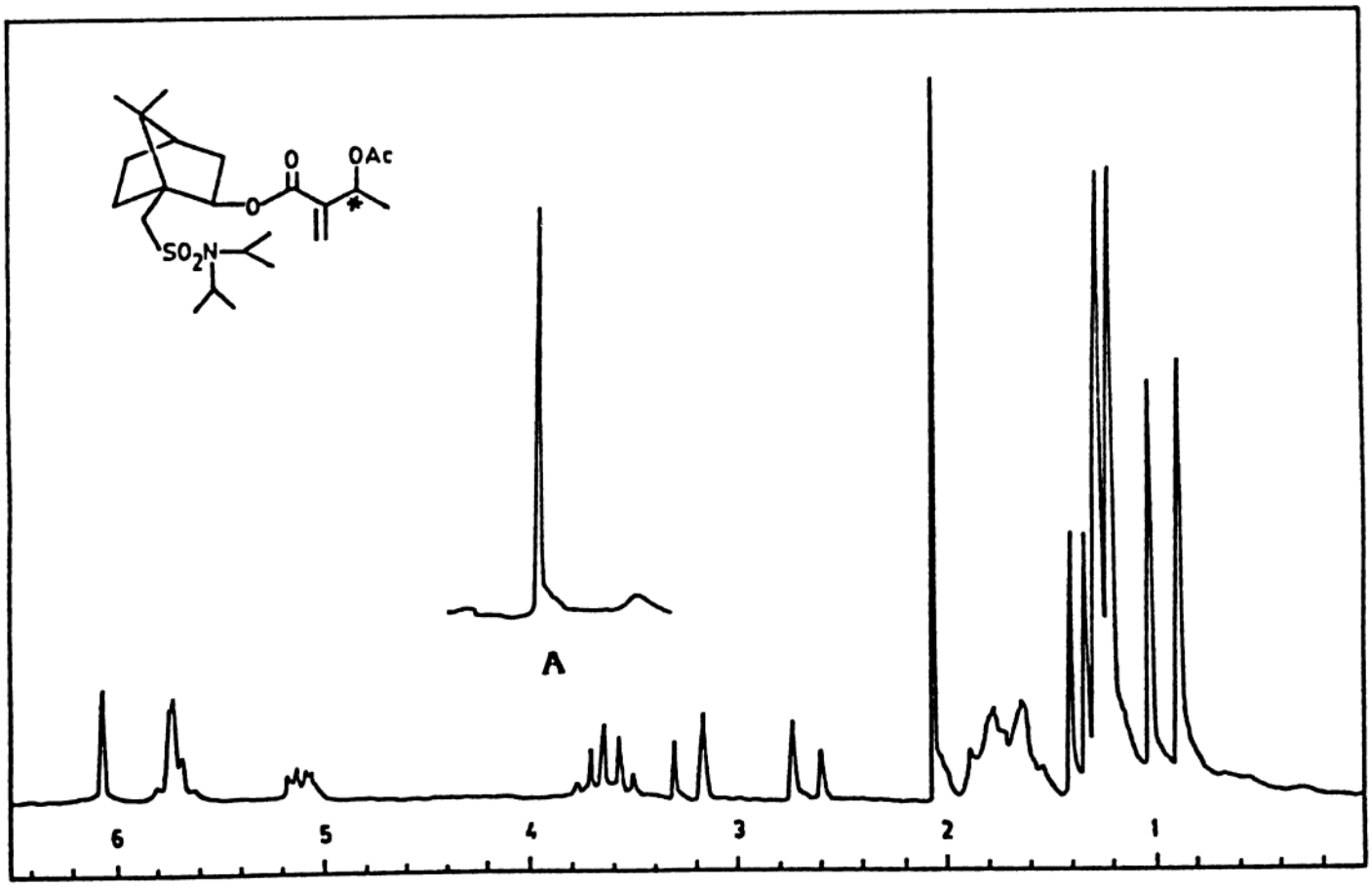


Fig. 30 : ^{1}H NMR spectrum of **128'a**. **A.** O=CCH_3 signal in the presence of $Eu(hfc)_3$ [No splitting, 100% de].

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