STUDIES IN SYNTHESIS OF HETEROCYCLIC MOLECULES USING THE BAYLIS-HILLMAN ADDUCTS

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

BY

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JULY 2004

To My

Beloved Parents

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STATEMENT

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

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

J. Srivardhana Rao 27/07/04

HYDERABAD
JULY, 2004

J. SRIVARDHANA RAO

CERTIFICATE

Certified that the work embodied in this thesis entitled **"Studies in Synthesis of Heterocyclic Molecules Using the Baylis-Hillman Adducts"** has been carried out by **Mr. J. Srivardhana Rao,** under my supervision and the same has not been submitted elsewhere for **a** degree.

D Basavaiah
July 2

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ABBREVIATIONS

Ac	acetyl
aq.	aqueous
BINAP	2,2′-bis(diphenylphosphino)-1,1'-binaphthyl
	benzyl
t-Boc	*t*-butoxycarbonyl
Bp	boiling point
Bu	butyl
/-Bu	*iso*butyl
s-Bu	*secondary-butyl*
t-Bu or Bu^t	*tert*-butyl
BINOL	1,1'-bi-2-naphthol
Bz	benzoyl
cat.	catalyst
mCPBA	*meta*-chloroperbenzoic acid
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBP	dibutyl phthalate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
(DHQD)$_2$PHAL	hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	diisobutylaluminium hydride
DIP AMP	1,2-bis(anisylphenyl)phosphinoethane

DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
EWG	electron withdrawing group
eq.	equivalents
Hept	heptyl
Hex	hexyl
c-Hex	cyclohexyl
HMPA	hexamethylphosphoramide
3-HQD	3-hydroxyquinuclidine
$Eu(fod)_3$	Europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)
$Eu(hfc)_3$	Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]
KDP	ketodicyclopentadiene
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
Me	methyl
MEM	(2-methoxyethoxy)methyl
Mp	melting point
Ms	mesyl
MS	molecular sieves
MVK	methyl vinyl ketone
MW	microwave

NMO	4-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pent	pentyl
Ph	phenyl
PLAP	pig liver acetone powder
PMP	1,2,2,6,6-pentamethylpiperidine
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr or Pr$'$	*iso*-propyl
PTC	phase transfer catalyst
Py	pyridine
RCM	ring closing metathesis
rt	room temperature
TBAF	tetrabutylammonium flouride
TBSC1	te/Y-butyldimethylsilyl chloride
tert.	tertiary
TEA	triethylamine
THF	tetrahydrofuran
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMG	1,1,3,3-tetramethylguanidine
TMS	tetramethylsilane
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Trt	trityl
Ts	tosyl

ABSTRACT

The recent developments in organic chemistry, medicinal chemistry and drug discovery demand the continuous evolution of convenient methodologies for atom economical construction of carbon-carbon bonds and functional group transformation strategies involving high levels of stereochemical control there by leading to the development of operationally simple processes for assembling the carbon structural framework. The Baylis-Hillman reaction is an emerging atom economical, carbon-carbon bond forming reaction involving the coupling of α-position of activated alkenes with carbon electrophiles under the influence of a catalyst, most commonly a tertiary amine [in particular, l,4-diazabicyclo(2.2.2)octane (DABCO)] producing multifunctional molecules, whose applications in a number of organic transformation methodologies leading to the synthesis of various trisubstituted alkenes, carbocycles, heterocycles, natural products and biologically active molecules, have been well documented in the literature.

This thesis deals with the studies in the synthesis of heterocyclic molecules using the Baylis-Hillman adducts and consists of three chapters, that is, 1. Introduction 2. Objectives, Results & Discussion and 3. Experimental. The first chapter, that is, Introduction presents a brief literature survey on the recent developments in the Baylis-Hillman reaction and also on applications of the Baylis-Hillman adducts in the organic synthesis.

The second chapter deals with the objectives, results and discussion. With a view to develop simple and convenient methodologies for synthesis of heterocyclic molecules using the Baylis-Hillman adducts we have undertaken a long range research program with the following objectives.

1. To develop a one-pot, facile methodology for synthesis of substituted γ-lactams using the acetates of the Baylis-Hillman adducts i.e., methyl 3-acetoxy-3-aryl-2-methylenepropanoates and methyl 3-acetoxy-2-methylenealkanoates.

2. a) To transform 2-[hydroxy(2-nitroaryl)methyl]cycloalk-2-enones, Baylis-Hillman adducts derived from various 2-nitrobenzaldehydes and cycloalk-2-enones, into substituted 1,2,3,4-tetrahydroacridines and cyclopenta[b]quinolines in one-pot operation.

   b) To develop a convenient methodology for synthesis of functionalized 3-benzoylquinolines from 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones, the Baylis-Hillman adducts derived from 2-nitrobenzaldehydes and chromones.

3. To develop a simple, convenient and one-pot methodology for stereoselective synthesis of spiro oxindoles containing 6,8-dioxabicyclo[3.2.1]octane skeleton involving tandem construction of C-C and C-0 bonds *via* the reaction of various isatins with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (Diels-Alder dimer of methyl vinyl ketone) under the catalytic influence of $TiCl_4$.

Facile and one-pot transformation of Baylis-Hillman adducts into substituted y-lactams

γ-Lactam framework occupies an important place in nitrogen heterocycles because of the presence of this skeleton in various natural products and biologically important molecules which **are** found to be anti-inflammatory, antihypertensive, nootropic and respiratory stimulants. Hence, the development of simple and convenient methodologies for the synthesis of γ-lactam derivatives represents an interesting and attractive endeavor in synthetic organic chemistry and medicinal chemistry. We have developed a convenient, operationally simple, one-pot procedure for synthesis of substituted γ-lactams **(118-131)** from the acetates of the Baylis-Hillman adducts **(116a-i)** in 49-68% yields (Schemes 52 & 54, eqs 38-40 and Table 3) *via* the treatment with nitroalkanes in the presence of K_2CO_3 followed by reductive cyclization using Fe/AcOH.

One-pot convenient synthesis of 1,2,3,4-tetrahydroacridines **and** cyclopenta-[b]quinolines from the Baylis-Hillman adducts

Acridine moiety is an important structural moiety present in certain natural products and in biologically important molecules which are found to be cytotoxic, antiviral, tranquillisers and antidepressants. Cyclopenta[b]quinoline derivatives are yet another class of important molecules which are found to possess biological properties such as anti-inflammatory activity, antimalarial activity, cholinesterase inhibition activity and also present in certain natural products. Hence the development of simple and convenient methodologies for synthesis of acridine and cyclopenta[b]quinoline derivatives constitutes an interesting and attractive endeavor in synthetic organic and medicinal chemistry. We have developed a simple, convenient and one-pot procedure for synthesis of substituted 1,2,3,4-tetrahydroacridines **(146a-d,148a-c)** *via* the reductive cyclization of the Baylis-Hillman alcohols **(145a-d,147a-c)** obtained, from various 2-nitrobenzaldehydes **(143a-d)** and cyclohex-2-enone (144a)/5,5-dimethylcyclohex-2-enone **(144b),** using Fe/AcOH in 62-82% yields (eqs 49, 53, Schemes 65, 66 and Table 6). We also synthesized representative cyclopenta[b]quinoline derivatives **(151a-d)** in 61-79% yields (Schemes 67,68 and Table 8) from the Baylis-Hillman alcohols **(150a-d)** obtained, from various 2-nitrobenzaldehydes **(143a-d)** and cyclopent-2-enone **(144c),** using the above methodology.

Application of Baylis-Hillman alcohols: One-pot synthesis of 3-benzoylquinolines

We have also transformed the Baylis-Hillman adducts, 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones **(153a-f),** derived from 2-nitrobenzaldehydes **(143a,c,e)** and 1-benzopyran-4(4//)-one **(152a)** / 6-methyl-l-benzopyran-4(4*H*)-one **(152b),** into functionalized 3-(2-hydroxyaryl)carbonylquinoline derivatives **(155a-f)** *via* the treatment with Fe/AcOH in 41-62% yields (Schemes 72-74, eq 56 and Table 11).

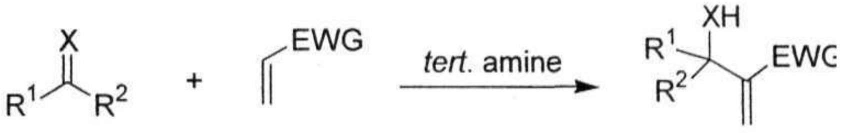
$TiCl_4$ catalyzed tandem construction of C-C and C-O bonds: a novel, simple and one-pot stereoselective synthesis of spiro oxindoles

Spiro oxindole framework occupies a special place in heterocyclic chemistry because of the presence of this framework in a number of natural products such as surugatoxin, gelsamine, horsfiline, spirotryprostatin A & B, elacomine, alstonisine, strychnofoline and tasmanin. 6,8-Dioxabicyclo[3.2.1]octane skeleton is yet another important skeleton present in certain natural products such as brevicomin, frontalin, multistriatin, bullerone and palytoxin. Hence, the development of a simple and convenient methodologies for synthesis of molecules containing both these skeletons (spiro oxindole and 6,8-dioxabicyclo[3.2.1]octane) represents an interesting and attractive endeavor in synthetic organic chemistry. We have developed a simple, convenient and one-pot stereoselective synthesis of *[1S,5S,7(3')S/IR,5R,7(3')R]* spiro oxindoles **(177a-i)** containing 6,8-dioxabicyclo[3.2.1]octane skeleton in 44-74% yields (eqs 61, 62, 64, Schemes 89-92 and Table 14) *via* the titanium tetrachloride catalyzed aldol-type reaction of 2-acetyl-6-methy 1-2,3-dihydro-4*H*-pyran with various isatin derivatives **(176a-i),** followed by cyclization, involving tandem construction of C-C and C-0 bonds. We have also successfully extended this methodology to acenaphthenequinone (178) to provide the desired spiro molecule **179** containing 6,8-dioxabicyclo[3.2.1]octane skeleton in 72 % yield (eq 65 and Table 14).

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

INTRODUCTION

The recent developments in organic chemistry, medicinal chemistry and drug discovery demand the continuous evolution of convenient methodologies for atom economical construction of carbon-carbon bonds and functional group transformation strategies involving high levels of stereochemical control there by leading to the development of operationally simple processes for assembling the carbon structural framework.[1-10] The Baylis-Hillman reaction"[16] is a novel, three component, atom economical carbon-carbon bond forming reaction, involving the coupling of a-position of activated alkenes with electrophiles under the influence of a catalyst, most commonly a tertiary amine, providing an interesting class of densely functionalized molecules (eq 1).[12-16]

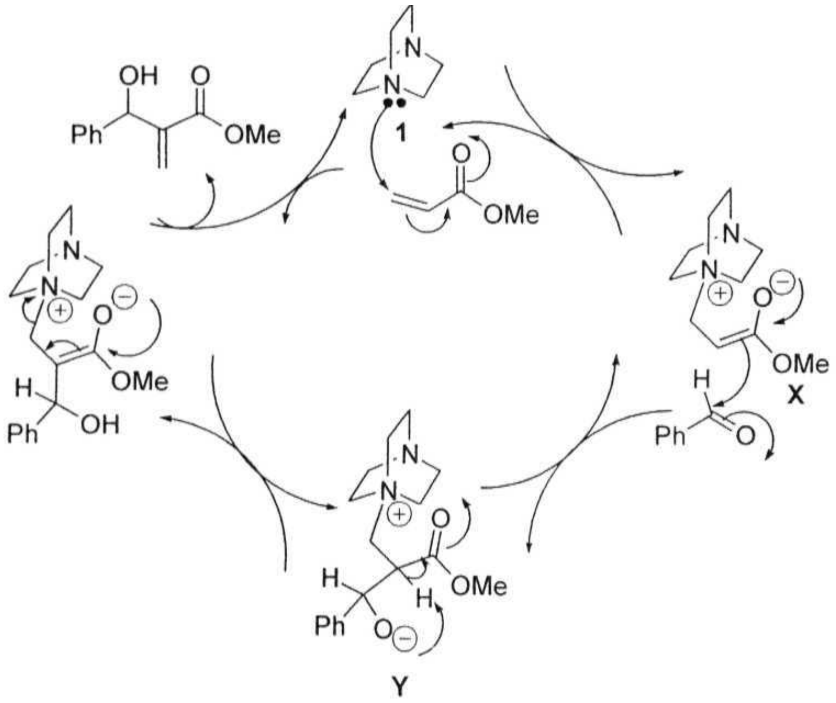


eq 1

R^1 = aryl, alkyl, aralkyl, heteroaryl
R^2 = H, alkyl, COOR   X = O, NCOOR, NTs, NSO_2Ph
EWG = COR, CN, CHO, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh

The most widely accepted mechanism[12-19] of the Baylis-Hillman reaction is shown in the Scheme 1 taking the reaction between benzaldehyde (as an electrophile) and methyl acrylate (as an activated olefin) under the catalytic influence of DABCO (1), as a model case. The first step of the reaction involves the Michael type nucleophilic addition of the tertiary amine catalyst (DABCO) to the activated alkene (methyl acrylate), leading to the formation of zwitterionic enolate X, which adds on to the electrophile (benzaldehyde) in an aldol fashion, to generate the zwitterionic species Y. The zwitterion Y undergoes proton migration and subsequently releases the catalyst to provide the desired multifunctional molecule (Scheme **1).**

Scheme 1

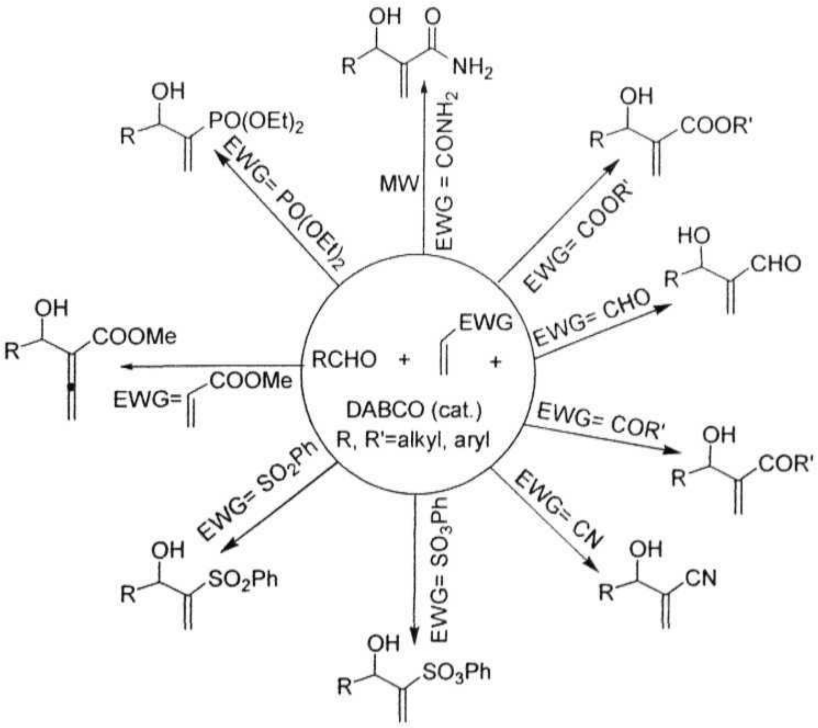


This fascinating reaction in fact originates from a German patent in the year 1972.[11] Although this reaction did not see any growth during 1972-1982, it has experienced a tremendous growth during the last 20-22 years in terms of all the three essential components that is, activated alkenes, electrophiles and catalysts and also applications of the Baylis-Hillman adducts in various organic transformation methodologies have been well documented.[12-16] This fascinating reaction has now become one of the powerful synthetic tools in organic chemistry as evidenced by four major reviews[12-14,16] and large number of publications on various aspects of this reaction. Since the available literature on various aspects of this reaction is very vast, it will not be possible to present all the developments in this section. However, some of the most recent and important developments dealing with various aspects of Baylis-Hillman reaction are presented in this section.

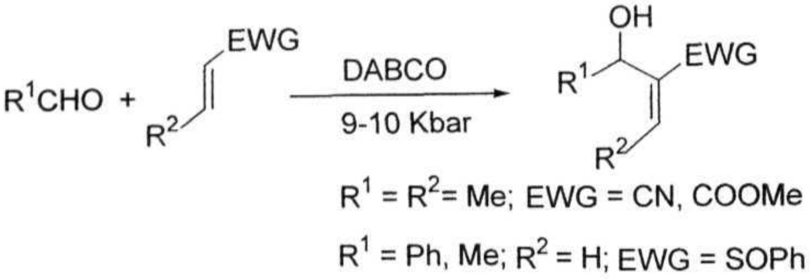
ACTIVATED ALKENES

A diverse class of activated alkenes such as alkyl (aryl) acrylates,[19-21] alkyl vinyl ketones,[22-24] acrylonitrile,[23,25,26] acrolien,[26-28] vinyl sulfones,[29] vinyl sulfonates,[30] vinyl phosphonates,[31] acrylamides,[32] and allenic esters[3334] were successfully used for coupling with a number of carbon electrophiles to obtain a wide range of densely functionalized molecules (Scheme 2).

Scheme 2

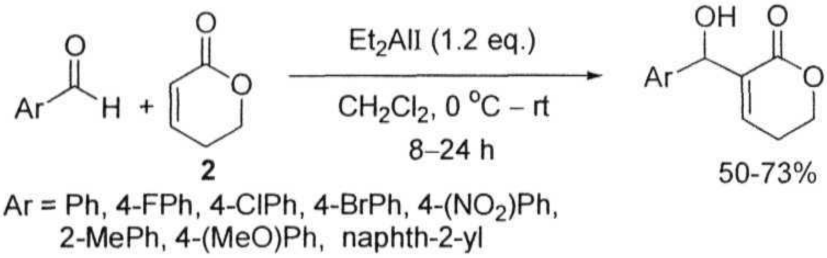


However, less reactive alkenes such as phenyl vinyl sulfoxide[35] and P-substituted activated alkenes such as crotononitrile,[36,37] and crotonic acid esters[36] require high pressures for coupling with aldehydes (eq 2).



eq 2

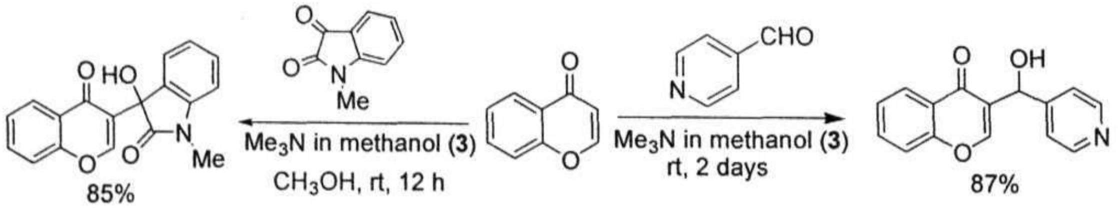
Li and co-workers[38] employed 5,6-dihydro-2*H*-pyran-2-one (2), as an activated alkene for Baylis-Hillman coupling with various aldehydes under the influence of diethylaluminum iodide (eq 3).



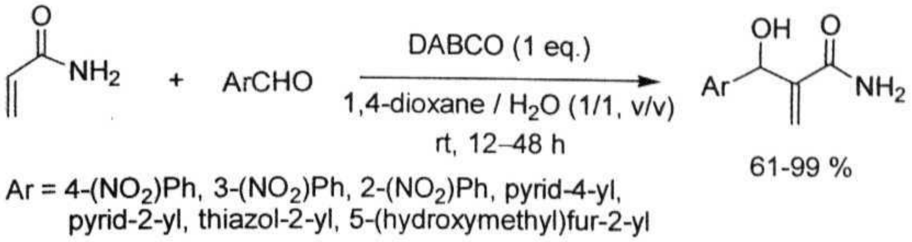
eq 3

Our research group[39] has recently used 1-benzopyran-4(4*H*)-one derivatives as activated alkenes in methanolic trimethylamine (3) mediated Baylis-Hillman coupling with heteroaromatic aldehydes, nitrobezaldehydes and isatin derivatives. Representative examples are presented in Scheme 3.

Scheme 3



Hu et al.[40] have reported acrylamide, as an activated alkene in the Baylis-Hillman coupling with various reactive aromatic and heteroaromatic aldehydes in the presence of stoichiometric amounts of DABCO in dioxane-water medium at room temperature (eq 4).

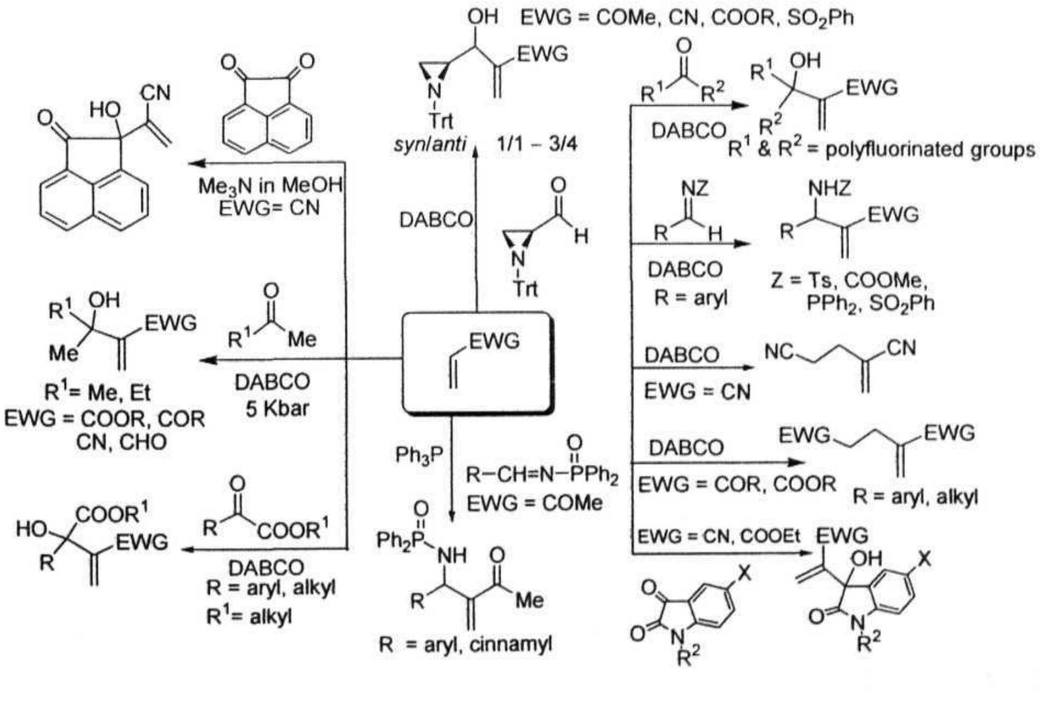


eq 4

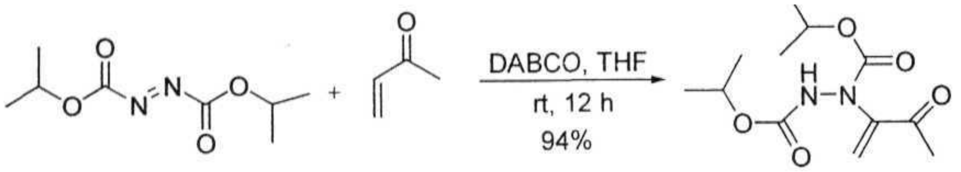
ELECTROPHILES

Although aldehydes (aliphatic, aromatic and heteroaromatic) are the most widely used electrophiles, various other carbon electrophiles such as aldimine derivatives,[41-43] α-keto esters,[44-46] non-enolizable 1,2-diketones,[26,28] *N*-tritylaziridine-2-(*S*)-carboxaldehyde,[47] *N*-arylidenediphenylphosphinamides,[48] activated alkenes,[49-52] isatin derivatives[53] and fluoro-ketones[54] have been also utilized successfully in this reaction (Scheme 4). Less reactive electrophiles such as propan-2-one and butan-2-one,[27,36] which do not undergo Baylis-Hillman reaction under normal conditions, were brought into the scope of this reaction under high pressure conditions (Scheme 4).

Scheme 4

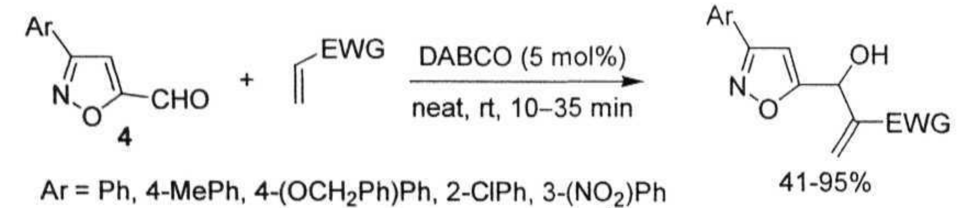


Dialkyl azodicarboxylates have been successfully employed as electrophiles for coupling with activated olefins in the presence of DABCO.[55,56] One representative example is presented in eq 5.[56]



eq 5

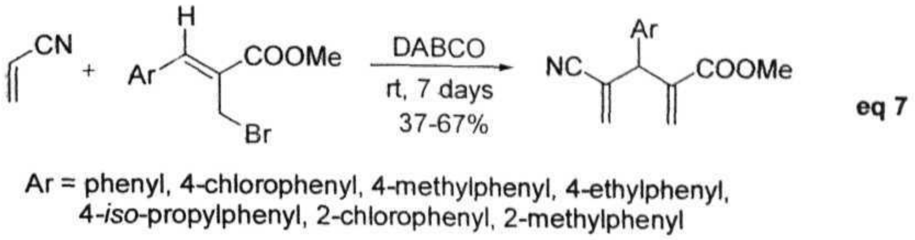
5-Isoxazolecarboxaldehydes (4) were found to be fast reacting electrophiles in the Baylis-Hillman reaction with various activated olefins by Batra and co-workers (eq 6).[57] They have also extended this reaction to solid-phase supported aldehydes and polymer supported acrylic acid esters for the generation of isoxazole based combinatorial[58] libraries and these libraries were further evaluated for their antithrombin activity *in vivo*.[59]



eq 6

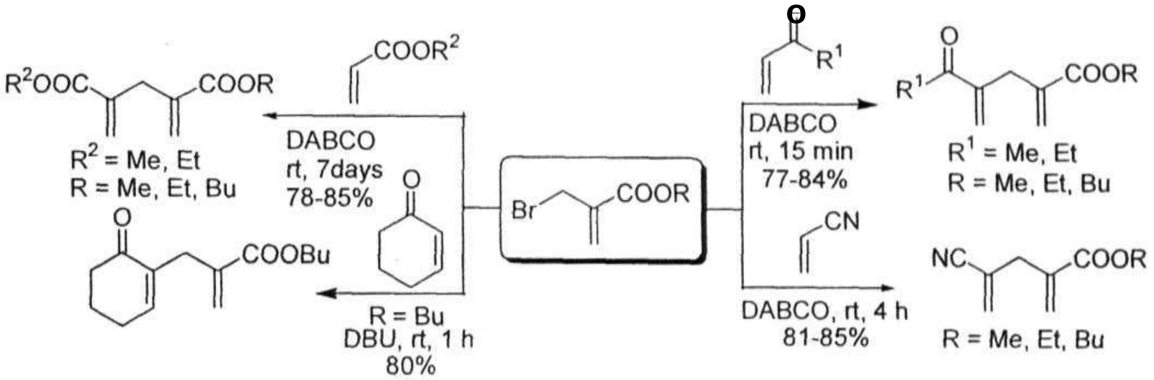
Ar = Ph, 4-MePh, 4-(OCH$_2$Ph)Ph, 2-ClPh, 3-(NO$_2$)Ph
EWG = COMe, COOMe, COOEt, COOBu, COOBu^t, CN

Our research group,[60] for the first time employed methyl 3-aryl-2-bromomethylprop-2-enoates, derived from Baylis-Hillman adducts, as electrophiles for coupling with acrylonitrile in the presence of DABCO thus providing a simple methodology for synthesis of functionalized 1,4-pentadienes with substitution at 3-position (eq 7). Subsequently, our research group extended this strategy to alkyl 3-bromomethylprop-2-enoates leading to the development of a simple methodology for one pot synthesis of functionalized 1,4-pentadienes without any substitution at 3-position (Scheme 5).[61]



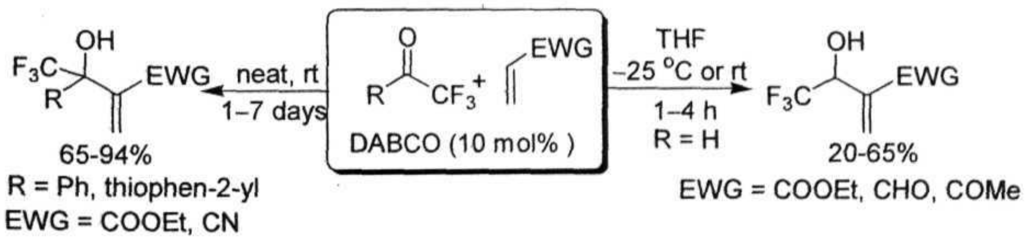
Ar = phenyl, 4-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-*iso*-propylphenyl, 2-chlorophenyl, 2-methylphenyl

Scheme 5



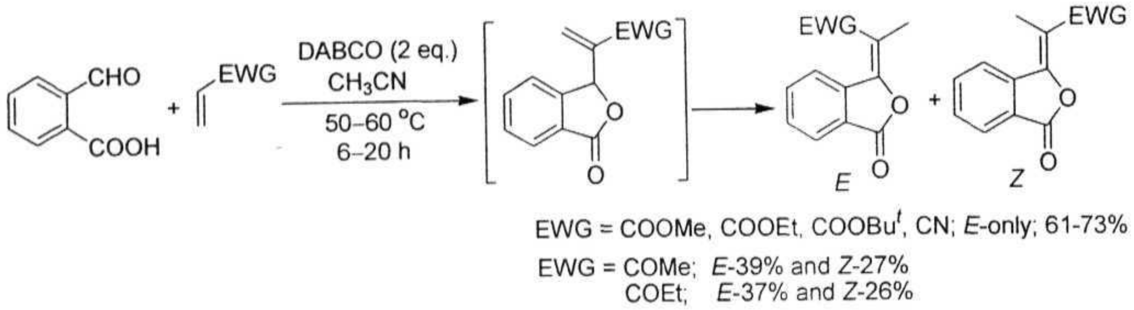
Ramachandran et al.[62,63] have successfully utilized fluorinated aldehydes and aryl trifluoromethyl ketones as electrophiles in a DABCO catalyzed Baylis-Hillman coupling with various activated alkenes (Scheme 6).

Scheme 6



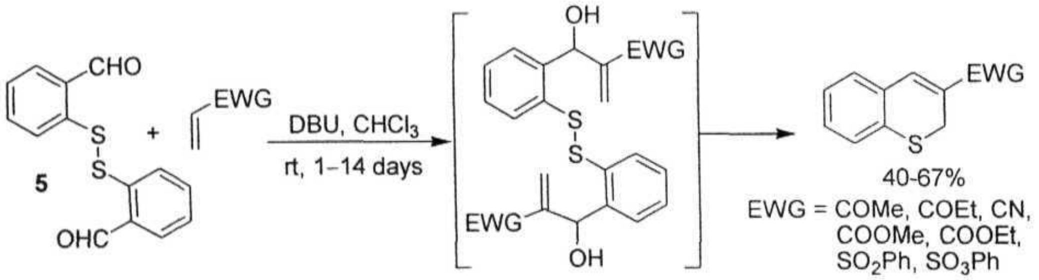
Kim and co-workers[64] have employed 2-carboxybenzaldehyde as an electrophile for the Baylis-Hillman coupling with various activated alkenes (Scheme 7).

Scheme 7



2,2′-Dithiobenzaldehyde (5) was successfully employed in the Baylis-Hillman coupling with various activated alkenes in the presence of DBU by Kaye and Nocanda to provide a convenient one-pot synthesis of benzothiopyran derivatives (Scheme 8).

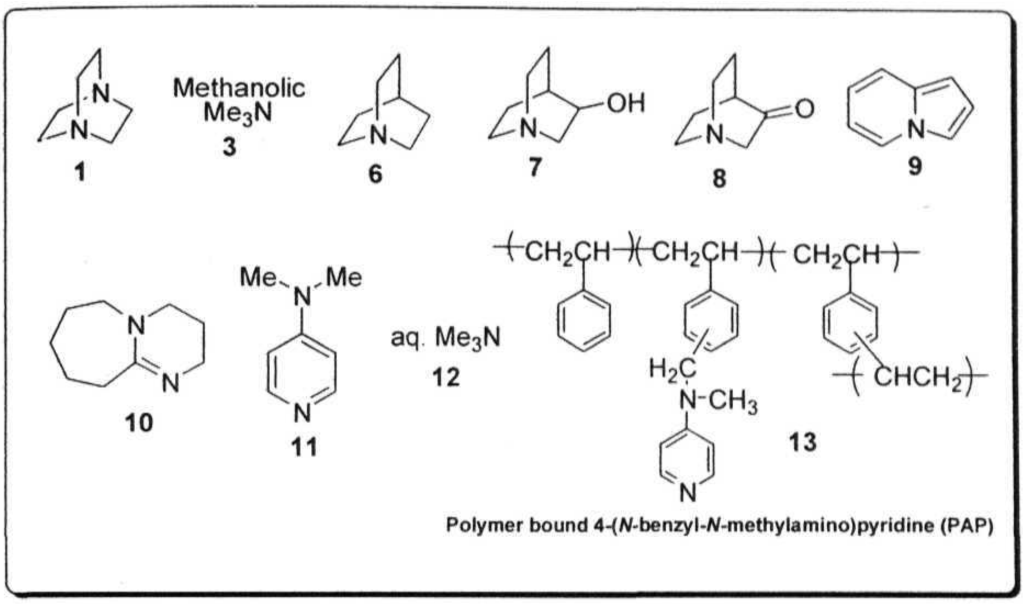
Scheme 8



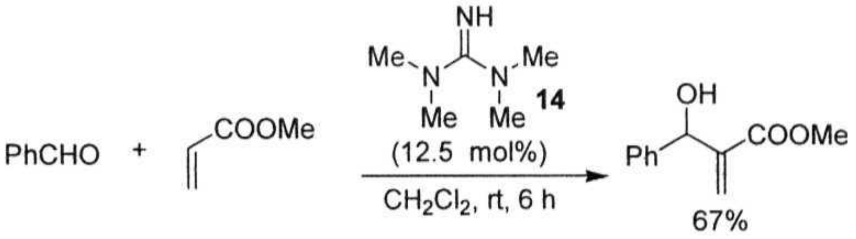
CATALYSTS/CATALYTIC SYSTEMS

Although DABCO (1) has been the most frequently used catalyst in this fascinating reaction, various other tertiary amine catalysts such as quinuclidine (6), 3-hydroxyquinuclidine (3-HQD) (7), 3-quinuclidinone (8), indolizine (9), DBU (10), DMAP (11), aqueous trimethylamine (12) and Merrifield resin containing 4-aminopyridine units (13) (Figure 1) have been also successfully employed for performing Baylis-Hillman reactions.[11-16,66-70]

Figure 1

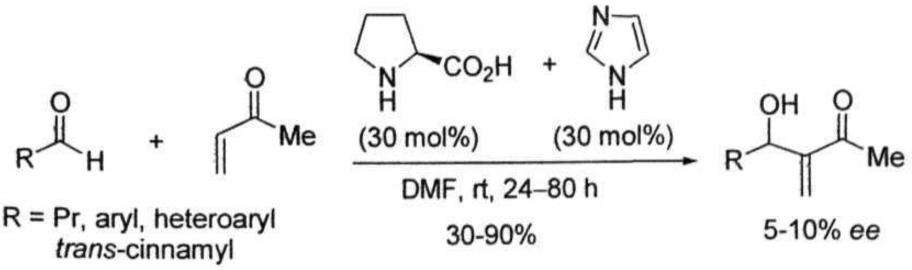


For the first time, Leadbeater et al.[71,72] have employed tetramethylguanidine (TMG) (14) as a catalyst for the Baylis-Hillman coupling of methyl acrylate with various aldehydes. One representative example is presented in eq 8.



eq 8

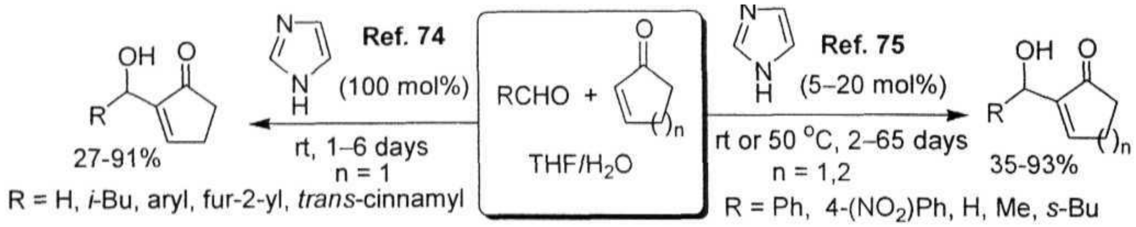
Shi and co-workers[73] have studied (*L*)-proline catalyzed Baylis-Hillman reaction between various aldehydes and MVK in the presence of imidazole as a base. However, the enantioselectivities obtained in these reactions were found to be very low (eq 9).



eq 9

Later on, Cheng and co-workers[74] & Gatri and El Gaied[75] independently used imidazole as a catalytic source for Baylis-Hillman coupling of cycloalkenones with aldehydes (Scheme 9).

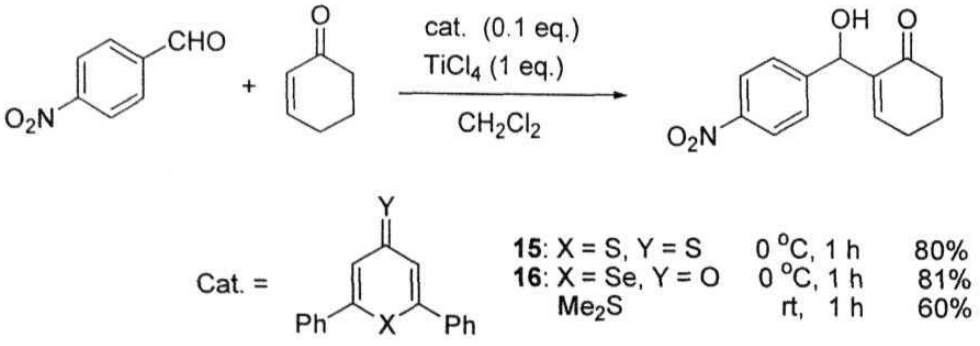
Scheme 9



NON-AMINE CATALYSTS

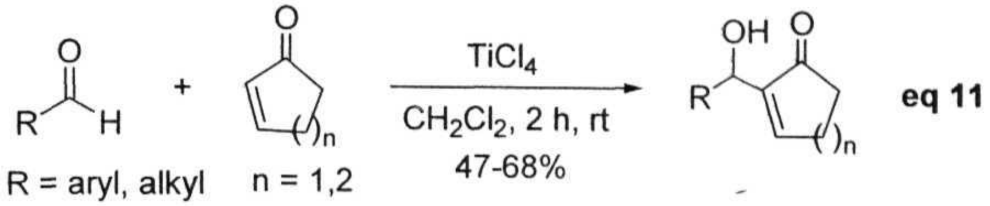
Several non-amine catalysts such as trialkyl phosphines,[76-78] triaryl phosphines[79] and metal complexes like $RhH(PPh_3)_4$,[80,81] $RuH_2(PPh_3)_4$,[81,82] have been successfully employed in the coupling of activated alkenes with aldehydes.

Kataoka et al.[83-85] demonstrated the application of sulfides or selenides (chalcogenides) as catalysts for the Baylis-Hillman coupling of vinyl ketones with various aldehydes in the presence of $TiCl_4$. They also found 2,6-diphenyl-4*H*-chalcogenopyran-4-ones (thiones) 15 and 16, to be more efficient catalysts than Me_2S for the Baylis-Hillman reaction. One representative example is presented in the eq 10.[84,85]



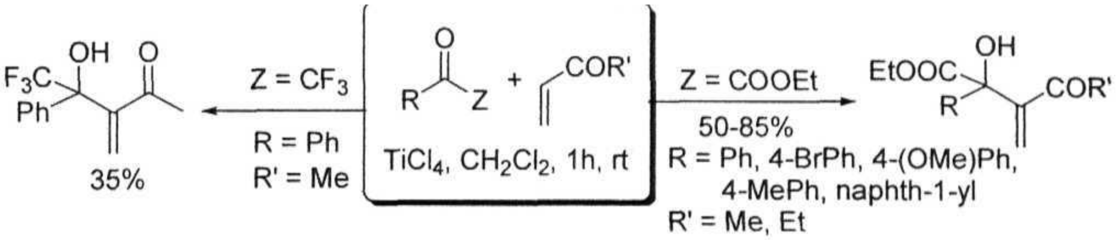
eq 10

$TiCl_4$-mediated Baylis-Hillman coupling of cyclic enones with various aldehydes in the absence of any Lewis base was reported by Li and co-workers[86] (eq 11).



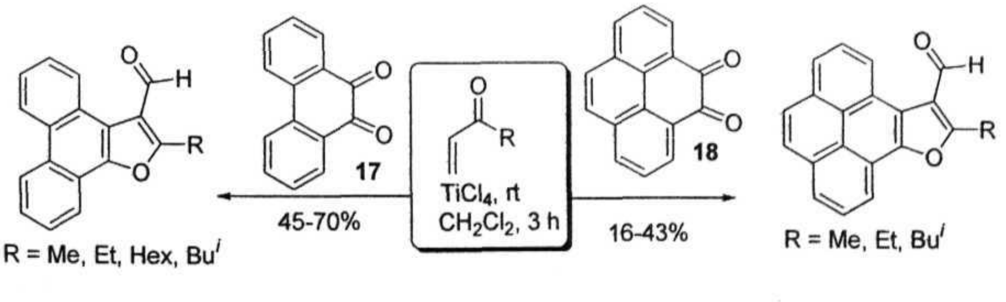
α-Keto esters and trifluoromethyl phenyl ketone have been employed as electrophiles for the Baylis-Hillman reaction with alkyl vinyl ketones under the influence of $TiCl_4$ to provide the desired tertiary alcohol derivatives, by our research group (Scheme 10).[87]

Scheme 10



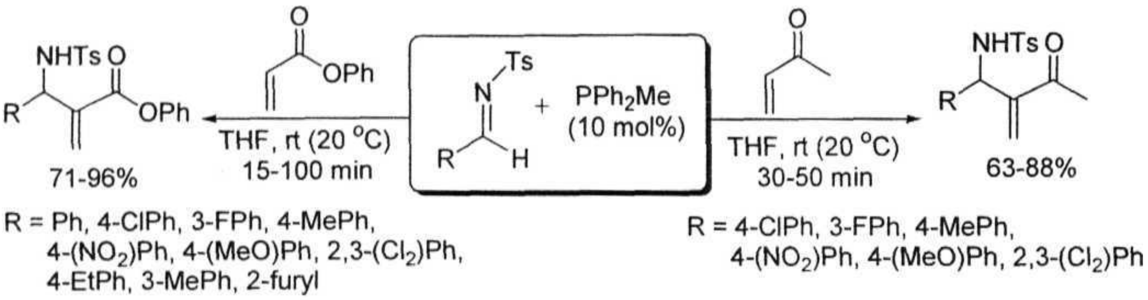
Subsequently, our research group has extended this strategy to aryl 1,2-diones 17, 18. In these cases usual Baylis-Hillman adducts were not obtained, instead an interesting class of functionalized fused furans were obtained (Scheme 11).

Scheme 11

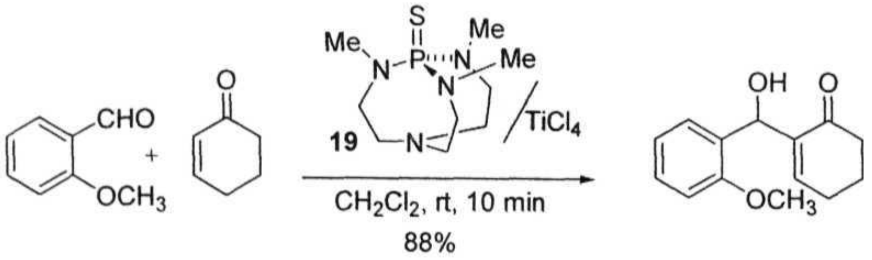


Shi and Xu[8,9] have successfully used methyl diphenylphosphine as a catalyst for Baylis-Hillman reaction between *N*-tosylated imines and different activated olefins. Representative examples are shown in Scheme 12.

Scheme 12



Verkade and co-workers[9] have developed a highly active and selective catalyst system **19**/$TiCl_4$ for Baylis-Hillman coupling of activated alkenes such as cyclic enones (including less reactive substituted derivatives), acrylates and acrylonitrile with aldehydes (eq 12). One representative example is shown below.

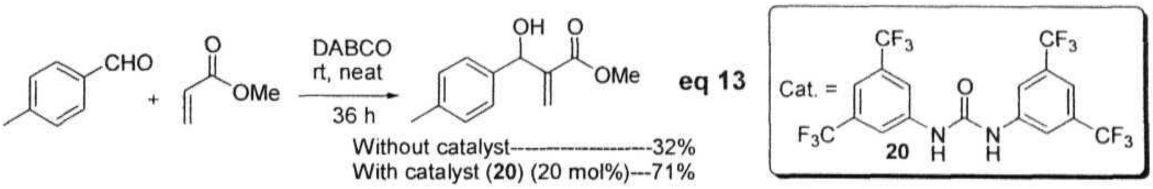


eq 12

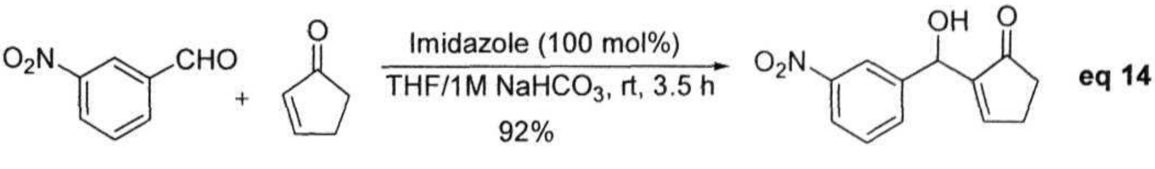
RATE ACCELERATION OF BAYLIS-HILLMAN REACTION

The normal Baylis-Hillman reaction is a slow reaction and requires a few days to a few weeks for completion depending upon the reactivity of the essential components, that is, electrophile, activated alkene and catalytic source. Several efforts have been made by the organic chemists to surmount this problem. Thus, the use of excess catalyst,[12-14,16] concept of hydrogen bonding (having a hydroxy group either in the catalyst or in the substrate),[91-94] aqueous medium,[95] microwave irradiation,[32] reactive activated alkenes,[12-14,16,96] reactive electrphiles[12-14,45] and high pressures[27,36,97] have been examined for accelerating this reaction and considerable success has been achieved in this direction. Some of the recent important and interesting developments are discussed in this section.

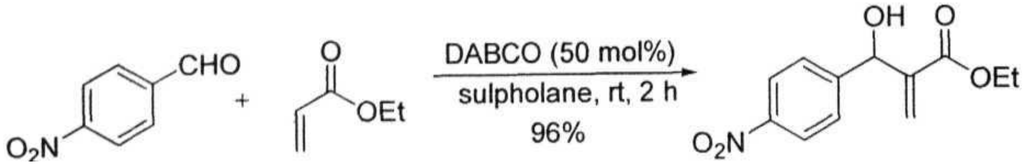
Connon and Maher[98] have found that bis-aryl ureas (20) greatly accelerate the DABCO-promoted Baylis-Hillman reaction between a variety of aryl aldehydes and methyl acrylate in the absence of solvent. One representative example is presented in eq 13.



Very recently, Cheng et al.[99] have reported a remarkable rate acceleration of imidazole promoted Baylis-Hillman reaction of cyclic enones with aldehydes in basic ($NaHCO_3$) water solution. One representative example is shown in eq 14.

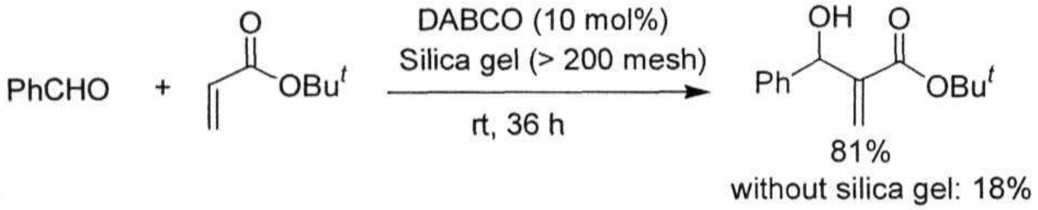


Radha Krishna et al.[100] have reported a significant rate acceleration of Baylis-Hillman reaction of various aldehydes with different activated alkenes in sulpholane as solvent. One representative example is shown in eq 15.



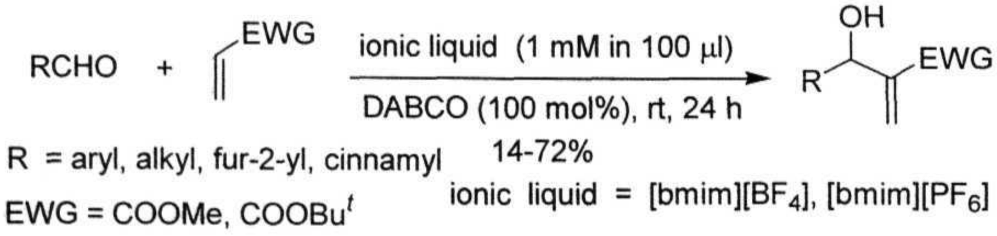
eq 15

A remarkable rate acceleration in silica gel as a solid phase medium in the Baylis-Hillman reaction was observed by our research group.[101] The less reactive activated alkene, such as *tert*-butyl acrylate reacts with benzaldehyde to provide the desired adduct in 81% yield in 36 h under these conditions (eq 16).



eq 16

Santos and co-workers [102] have observed some acceleration in the presence of ionic liquids in the Baylis-Hillman coupling between various aldehydes and alkyl acrylates (eq 17). They have also observed further rate acceleration in the presence of lithium perchlorate as an additive.



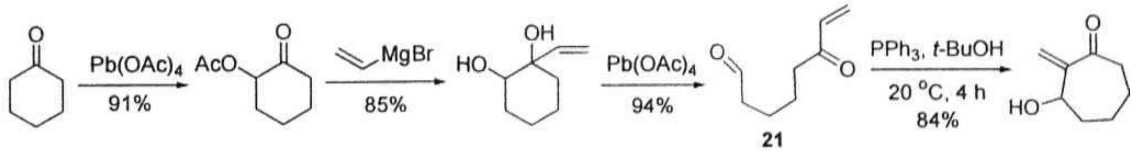
eq 17

INTRAMOLECULAR BAYLIS-HILLMAN REACTION

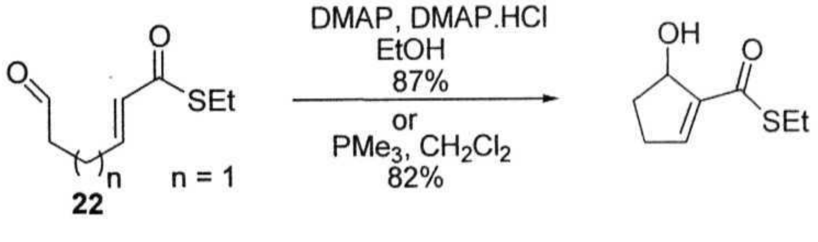
Though the normal Baylis-Hillman reaction is well studied, the intramolecular version of the Baylis-Hillman reaction is not well explored. Some of the recent advances in this aspect are presented in this section.

Very recently, Koo et al.[10] have reported an efficient method for the preparation of diverse formyl unsaturated carbonyl compounds (21) and successfully employed them in intramolecular Baylis-Hillman reactions. One representative example is shown in Scheme 13.

Scheme 13

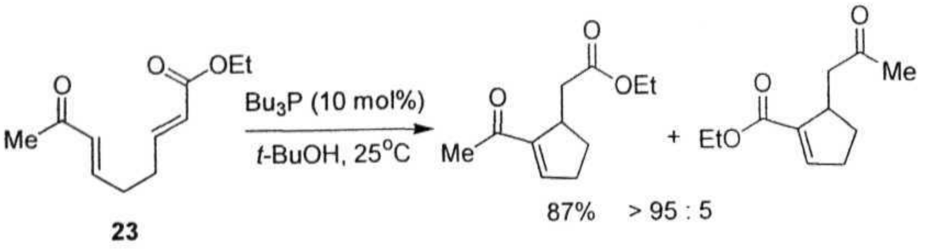


Keck and Welch have reported the intramolecular Baylis-Hillman reaction of an unsaturated thiol ester (22) under the influence of DMAP/EtOH or PMe_3/CH_2Cl_2. One representative example is shown in eq 18.

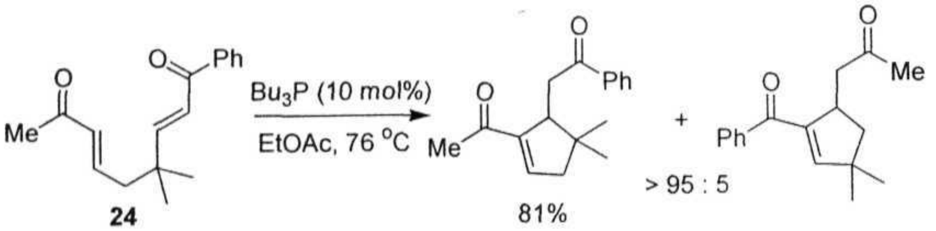


eq 18

An interesting Bu_3P catalyzed cycloisomerization of bis-enones (23 & 24) was described by Krische and co-workers. They have examined the effect of electronic (eq 19) and steric factors in these reactions (eq 20).[105]

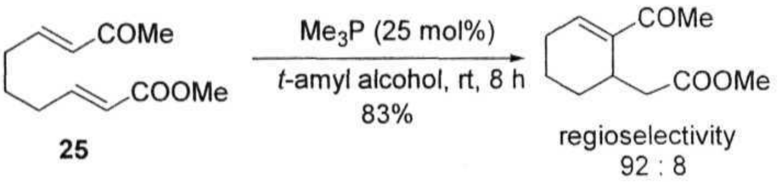


eq 19



eq 20

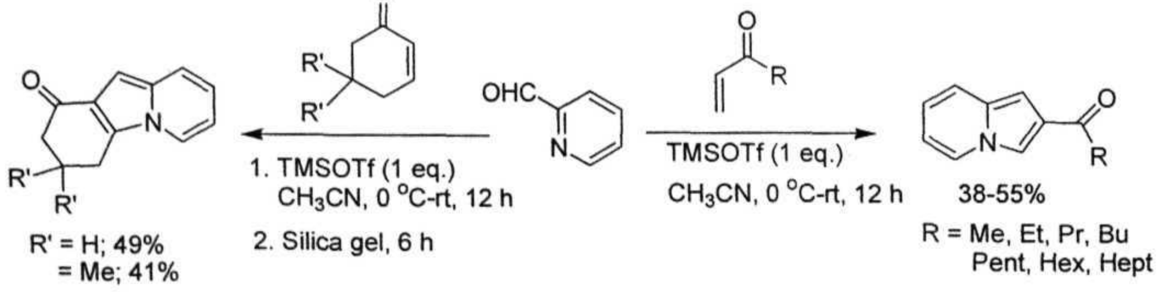
Roush and co-workers[106] reported an intramolecular Baylis-Hillman reaction of diactivated dienes (25) to provide a convenient method for synthesis of functionalized cycloalkene derivatives. A selective example is presented in eq 21.



eq 21

Our research group has developed a novel synthesis of indolizine derivatives in one-pot operation by an electrophile induced intramolecular Baylis-Hillman reaction *via* the treatment of alkyl vinyl ketones (including cyclohexenones) with pyridine-2-carboxaldehyde, under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (Scheme 14).[107]

Scheme 14



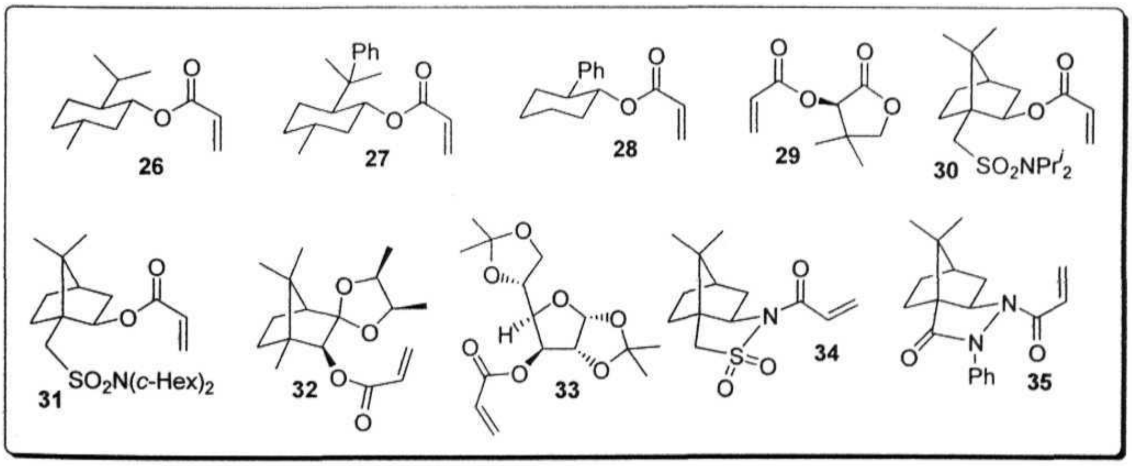
ASYMMETRIC BAYLIS-HILLMAN REACTION

In general, the asymmetric version of the Baylis-Hillman reaction can be performed by selecting appropriate chiral sources in any one (or two or three) of the essential components *i.e.,* activated alkene, electrophile and catalyst. Some of the recent developments in this direction have been described in the following.

i) Chiral activated alkenes:

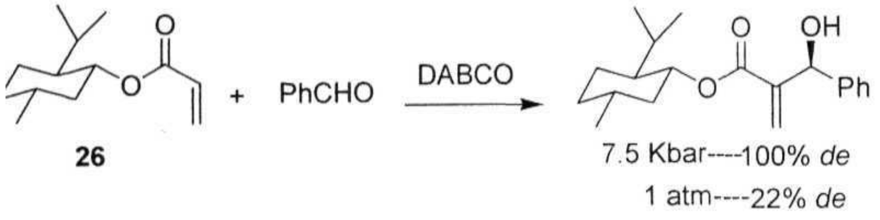
There are several reports on the asymmetric version of the Baylis-Hillman reaction using chiral activated alkenes[12,,,6] such as chiral acrylates[108-119] and chiral acrylamide derivatives.[1 0-122] A number of chiral acrylates (26-33) and chiral acrylamides (34, 35) (Figure 2) derived from various chiral auxiliaries have been employed in the Baylis-Hillman reaction, to provide the resulting adducts in low to high diastereoselectivities.[12,,16,108,,122]

Figure 2



The influence of high pressure on the diastereoselectivities of chiral auxiliary **mediated** coupling of activated alkenes with aldehydes was studied by Gilbert and co-workers.[117]

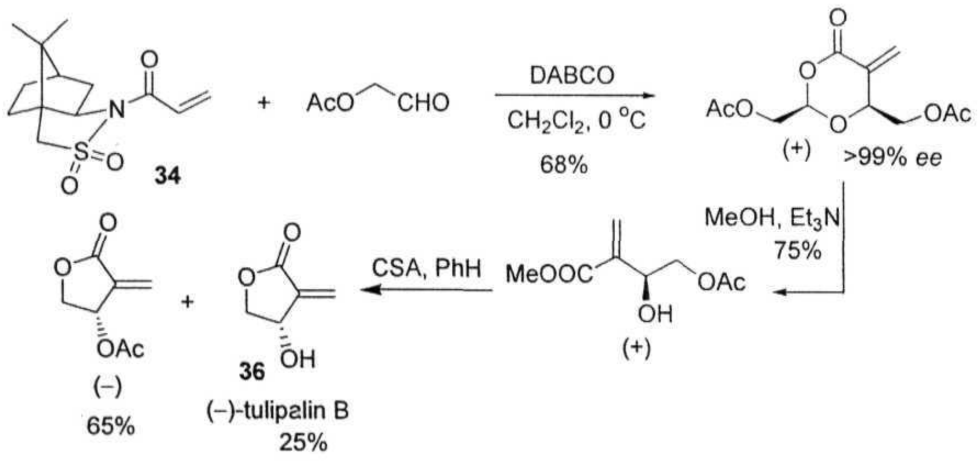
Thus, the reaction of (-)-menthyl acrylate (26) with benzaldehyde under the catalytic influence of DABCO at higher pressure provided the corresponding Baylis-Hillman adduct with 100% diastereoselectivity, whereas the similar reaction at atmospheric pressure gave the required adduct with 22% diastereoselectivity (eq 22).



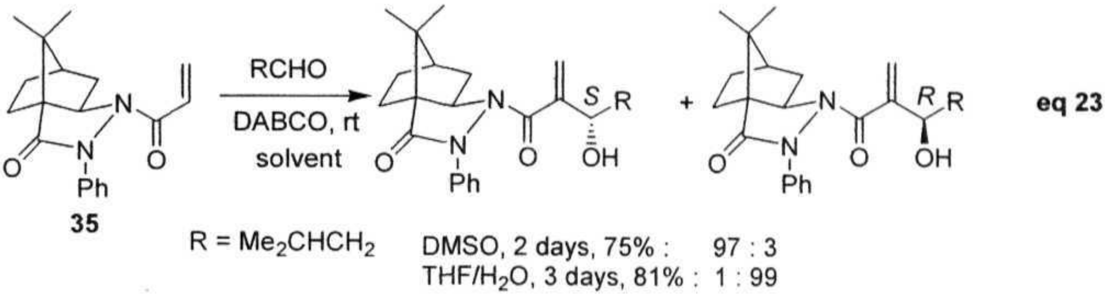
eq 22

Leahy et al.[120,121] have employed chiral acrylamide (34), derived from Oppolzer's camphor sultam, as an activated alkene in the Baylis-Hillman reaction to provide the desired adducts in high enantioselectivities. This methodology has been successfully employed for the synthesis of biologically important natural product (-)-tulipalin B (36) (Scheme 15).[120]

Scheme 15



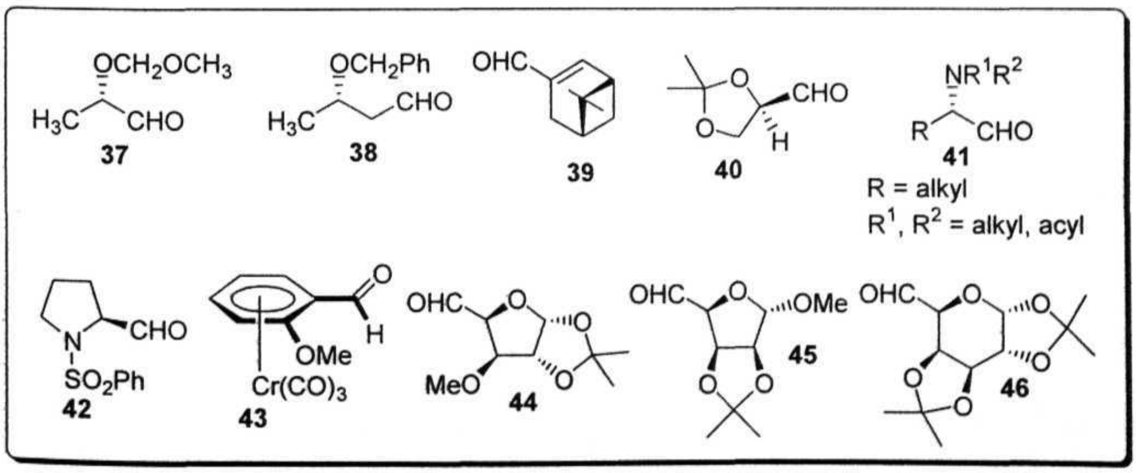
Yang and Chen have reported a highly diastereoselective Baylis-Hillman reaction of aldehydes with enantiopure acryloylhydrazide (35) as chiral activated alkene. They have observed reversal of diastereoselectivity by changing the solvent from DMSO to THF/H_2O in this reaction. One representative example is presented in the eq 23.[122]



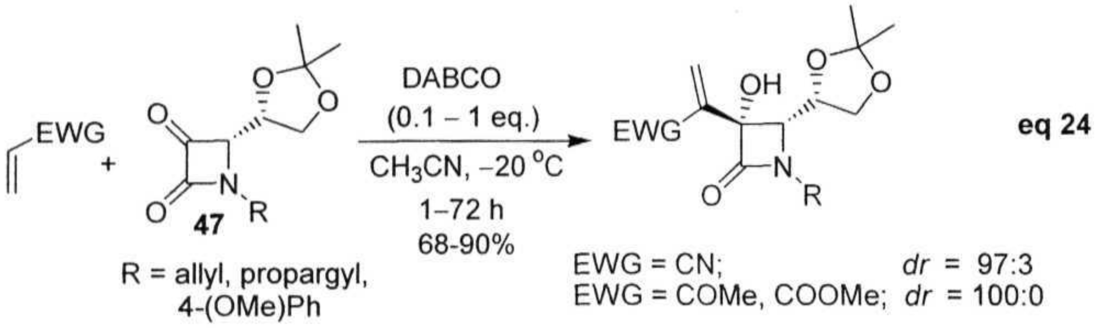
ii) Chiral electrophiles:

Several efforts have been made towards the asymmetric Baylis-Hillman reaction using chiral electrophiles. Thus, various chiral electrophiles such as (*S*)-*O*-(methoxymethyl)lactaldehyde (**37**),[123] (*S*)-3-benzyloxybutyraldehyde (**38**),[124] (*R*)-myrtenal (**39**),[117] isopropylidene (*R*)-glyceraldehyde (**40**),[117] α-dialkylamino and α-(*N*-acylamino)aldehydes (41),[125,126] *N*-phenylsulfonyl-(*L*)-prolinal (42),[126] enantiopure *o*-substituted benzaldehyde tricarbonylchromium complex (**43**)[127,128] and sugar derived aldehydes (**44-46**)[129] etc., (Figure 3), have been employed in this reaction to afford the resulting adducts with poor to high diastereoselectivities.

Figure 3

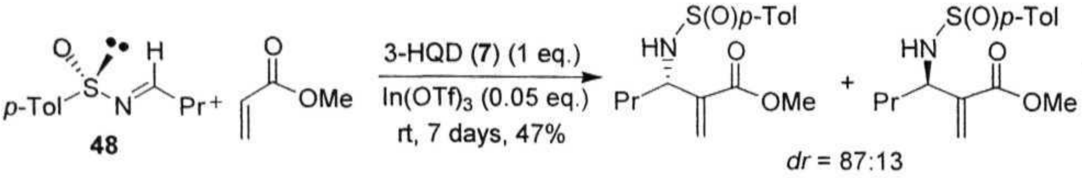


Alcaide and co-workers[130] have successfully employed enantiopure 3-oxo-2-azetidinones (47) for asymmetric Baylis-Hillman coupling with activated alkenes to provide 3-substituted-3-hydroxy β-lactam derivatives in high diastereoselectivities (eq 24).



eq 24

Enantiomerically pure N-sulfinimines (48) were used as chiral electrophiles for coupling with methyl acrylate in the presence of 3-hydroxyquinuclidine (3-HQD) (7) and $In(OTf)_3$ to provide the corresponding Baylis-Hillman adducts, β-amino-α-methylene esters in moderate to good yields and good diastereoselectivities.[131] One representative example is presented in eq 25.

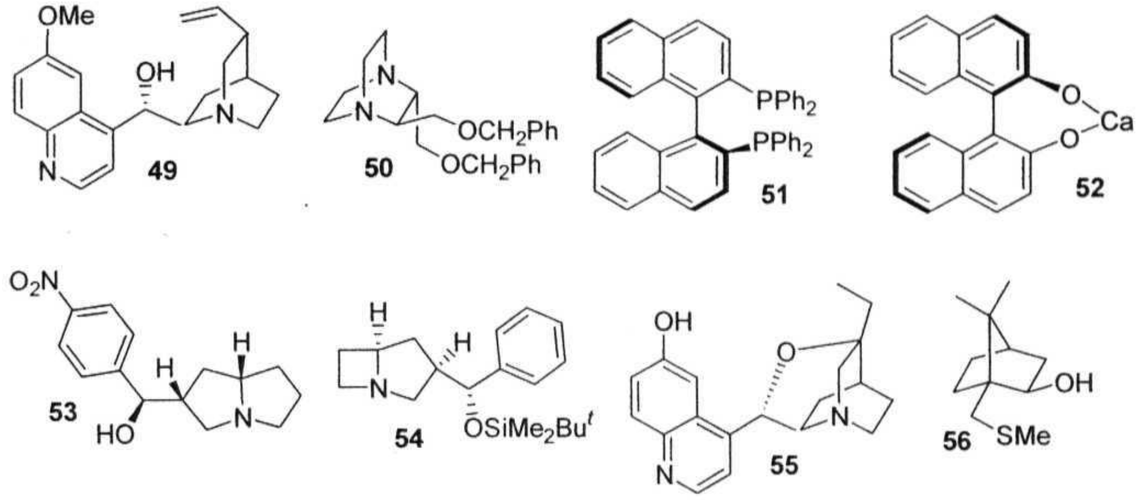


eq 25

iii) Chiral catalysts:

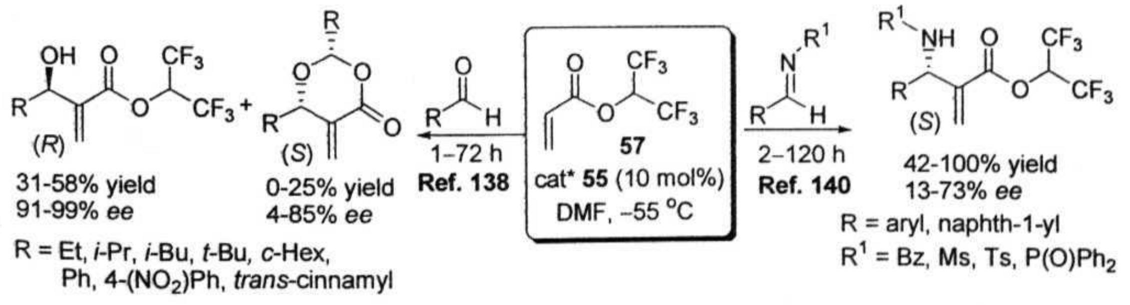
Considerable attention has been paid towards developing asymmetric version of Baylis-Hillman reaction using various chiral catalysts.[12-16] Thus, quinidine (49),[12109] chiral DABCO (50),[132,133] (*S*)-BINAP (51),[134] calcium salt of (*R*)-BINOL (52),[135] enantiopure pyrrolizidine (53),[136] chiral bicyclic azetidine (54),[137] *β*-isocupreidine (55)[138-142] and 10-methylthioisoborneol (56)[143,144] (Figure 4) have been employed as chiral catalysts in this reaction to obtain the Baylis-Hillman adducts in moderate to high selectivities (up to 99% *ee).*

Figure 4

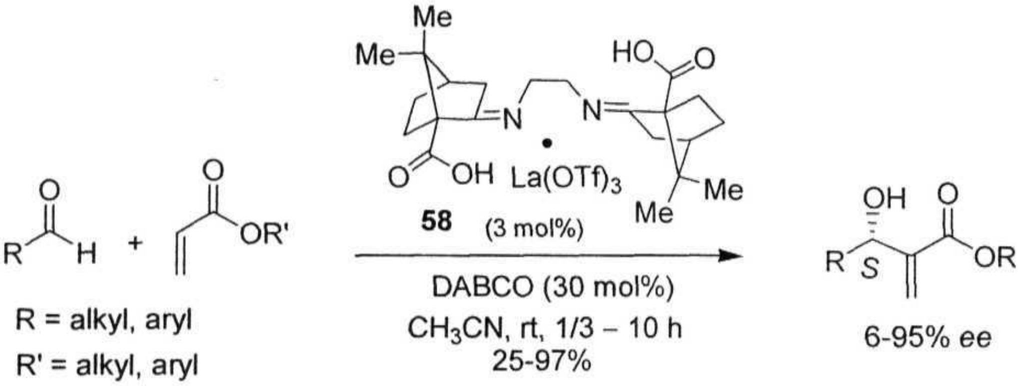


Hatakeyama and co-workers.[138,139] have developed an elegant asymmetric Baylis-Hillman reaction using *β*-isocupreidine (55), as a catalyst for the coupling between various aldehydes and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (57) (as activated alkene) to provide the desired adducts up to 99% enantiomeric purities (Scheme 16). Subsequently, they also successfully employed *β*-isocupreidine (55) as a catalyst for Baylis-Hillman reaction of aromatic imines with acrylate (57). In contrast to **the** aldehydes which afforded adducts with (*R*)-selectivity, the resulting compounds in this reaction (with aromatic imines) were formed with (*S*)-selectivity, (Scheme 16).[140]

Scheme 16



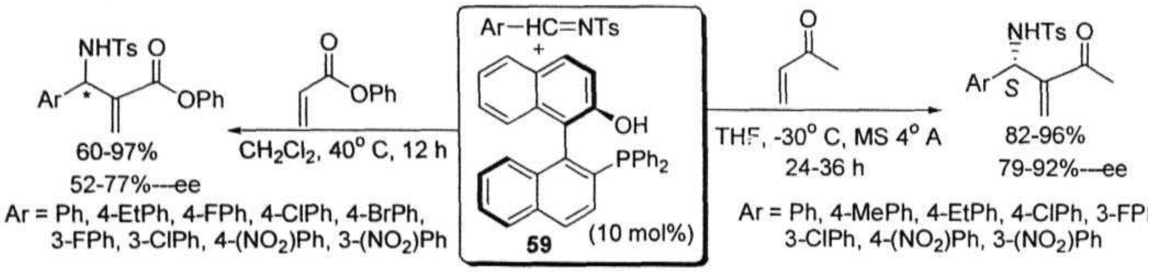
Chen and co-workers[145] have used a novel bidendate ligand (58) derived from camphor as a catalyst in the presence of Lewis acid, $La(OTf)_3$ for performing the asymmetric version of the Baylis-Hillman reaction between various aldehydes and acrylates under the influence of DABCO to provide the corresponding adducts in 6-95% enantioselectivities (eq 26).



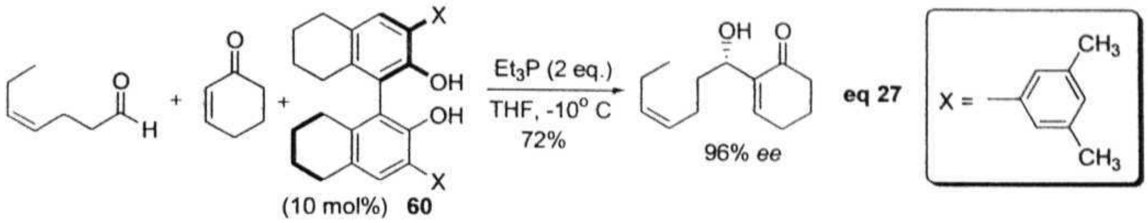
eq 26

Shi and Chen have reported an interesting chiral phoshine Lewis base (59) catalyzed asymmetric Baylis-Hillman reaction of *N*-sulfonated imines with methyl vinyl ketone and phenyl acrylate (Scheme 17).[146]

Scheme 17



Very recently, Schaus and McDougal[147] have reported a highly enantioselective Baylis-Hillman reaction of cyclohexenone with aldehydes using a chiral Bronsted acid (60) as catalyst and triethyl phosphine as the nucleophilic promoter. One representative example is shown in eq 27.

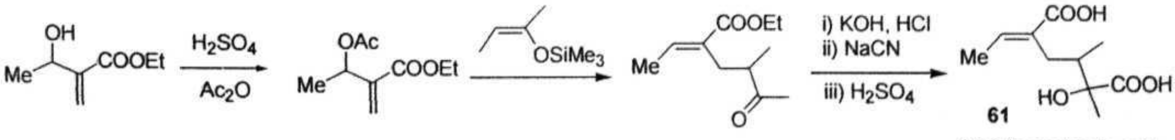


APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCTS

Due to the close proximity of three chemospecific functional groups such as hydroxy group (or amino), olefin and electron withdrawing groups in the Baylis-Hillman adducts, organic chemists have employed these adducts in various stereoselective transformation methodologies by appropriate tuning of the functional groups.[12-16] These adducts have been successfully utilized as valuable synthons for the synthesis of various trisubstituted olefins, carbocycles, biologically active molecules and natural products.[12-16] Some of such important and recent developments on applications of Baylis-Hillman adducts have been presented in this section.

Drewes et al.[20] have reported the synthesis of (±) integerrinecic acid (61) starting from the Baylis-Hillman adduct, ethyl 3-hydroxy-2-methylenebutanoate following the reaction sequence as described in Scheme 18.

Scheme 18

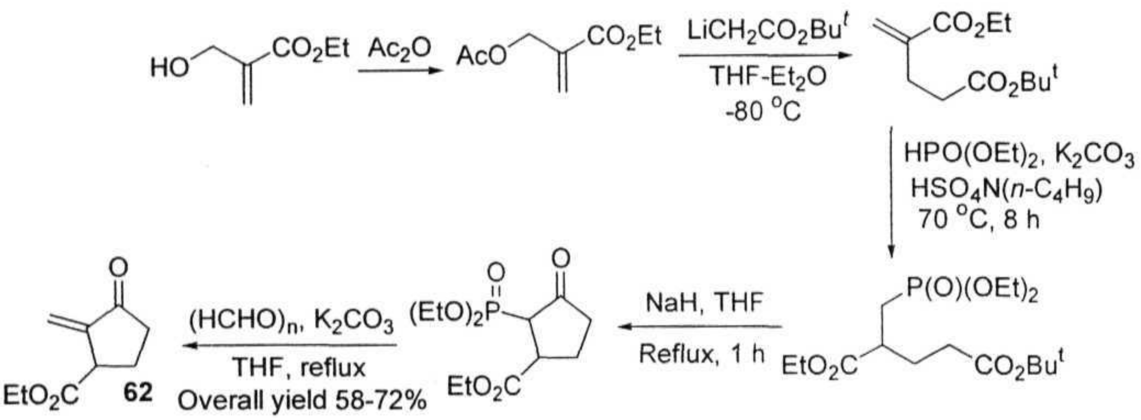


61

(±)-integerrinecic acid

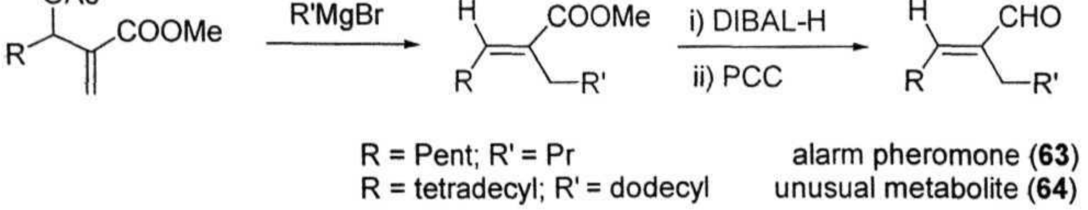
Amri et al.[52] have reported the synthesis of (±)-sarkomycin (62), an antitumor agent from ethyl 2-(hydroxymethyl)prop-2-enoate, the Baylis-Hillman adduct, obtained from ethyl acrylate and formaldehyde, according to Scheme 19.

Scheme 19



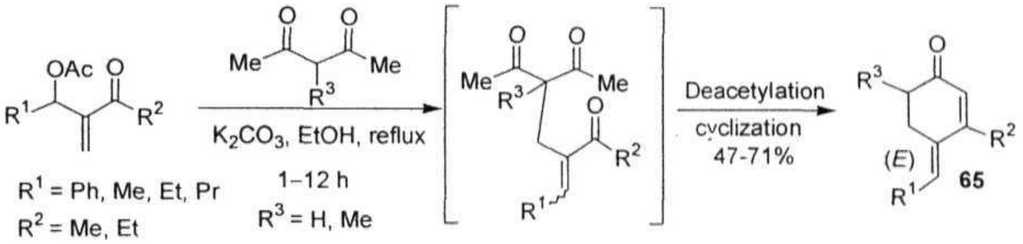
Our research group[148] developed a simple stereoselective synthesis of (2*E*)-2-substituted alk-2-enoates and (2Z)-2-substituted alk-2-enenitriles *via* the treatment of methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles respectively, with Grignard reagents. This methodology has been successfully applied for the synthesis of (2*E*)-2-butyloct-2-enal (63), an alarm pheromone component of the African weaver ant, *Oecophylla longinoda* and (2*E*)-2-tridecylheptadec-2-enal (64) an unusual metabolite from the red alga, *Laurencia* species (Scheme 20).[149]

Scheme 20



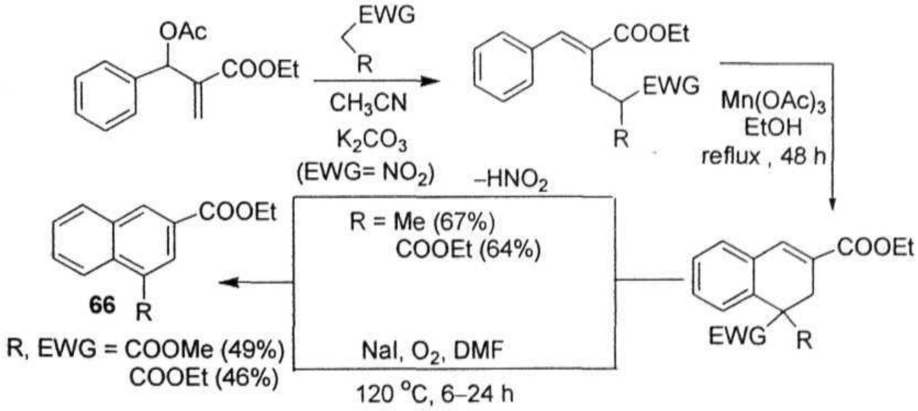
An interesting one-pot synthesis of alkylidinecyclohex-2-enones (65) *via* the treatment of acetates of the Baylis-Hillman adducts (obtained from various aldehydes and alkyl vinyl ketones) with aliphatic 1,3-diketones in the presence of K_2CO_3 in ethanol, was reported by Chamakh and Amri (Scheme 21).[150]

Scheme 21



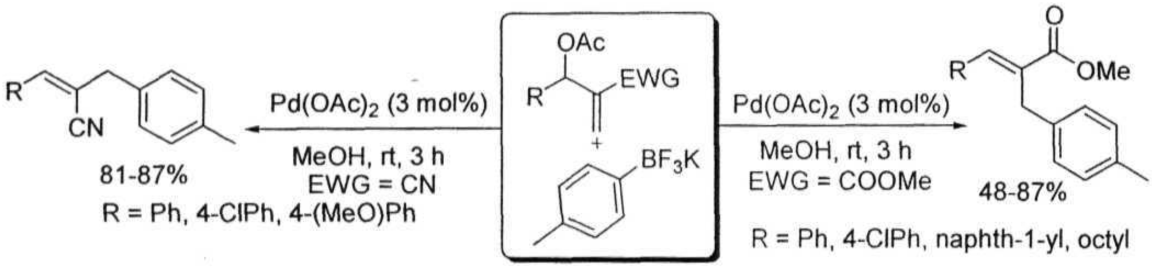
Kim and co-workers[151] have described an interesting synthesis of 1,3-disubstituted naphthalenes (66) from the acetates of the Baylis-Hillman adducts involving manganese(III) acetate assisted radical cyclization as the key step. Representative examples are presented in Scheme 22.

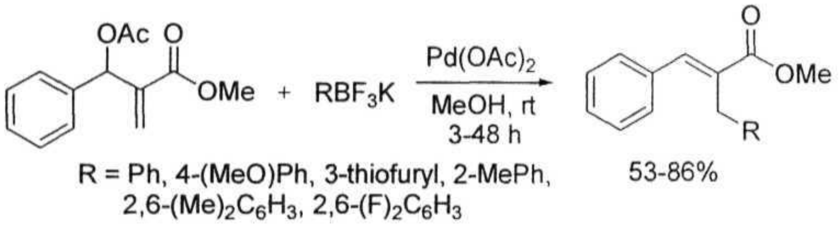
Scheme 22



Kabalka and co-workers[152] reported an interesting $Pd(OAc)_2$ catalyzed reaction between potassium organoflouroborates and acetates of Baylis-Hillman adducts providing a simple methodology for stereoselective synthesis of trisubstituted alkenes (Scheme 23 and eq 28).

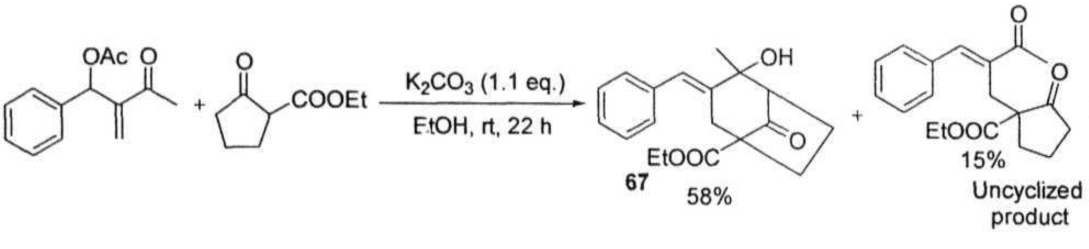
Scheme 23





eq 28

Kim et al.[153] have reported an interesting synthesis of 3-arylidenebicyclo[3.2.1]octan-8-ones (67) *via* the reaction of Baylis-Hillman acetates with 2-carboethoxycyclopentanone in the presence of K2CO3 in ethanol at room temperature. One representative example is shown in eq 29.



eq 29

Our research group have developed a simple and convenient synthesis of (*E*)-α-methylcinnamic acids *via* the nucleophilic addition of hydride ion from $NaBH_4$ to the acetates of the Baylis-Hillman adducts, followed by hydrolysis and crystallization (Scheme 24).[154] This methodology has successfully applied for synthesis of (*E*)-*p*-(myristyloxy)-α-methylcinnamic acid (68), a hypolipidemic active agent, which is also a precursor for another active hypolipidemic agent LK-903 (69) and [*E*]-*p*-(carbomethoxy)-α-methylcinnamic acid (70), a valuable synthon for an orally active serine protease inhibitor (71) (Figure 5).[154]

Scheme 24

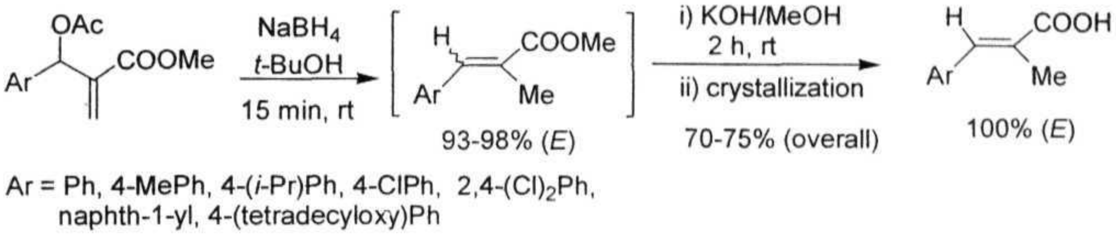
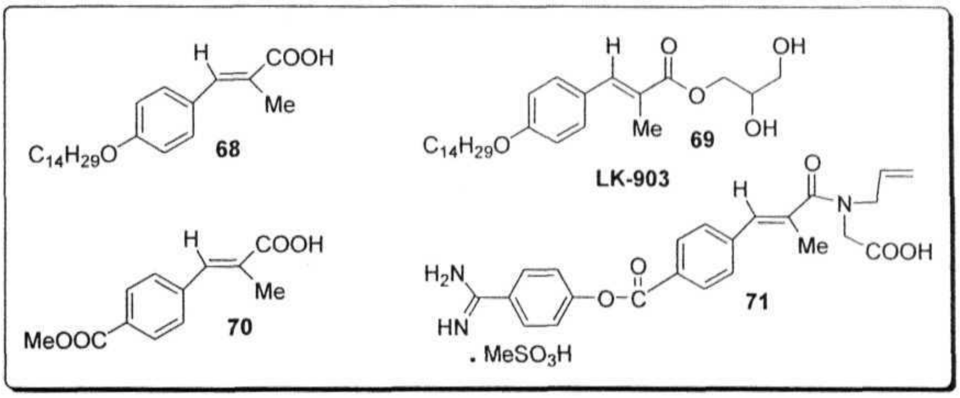
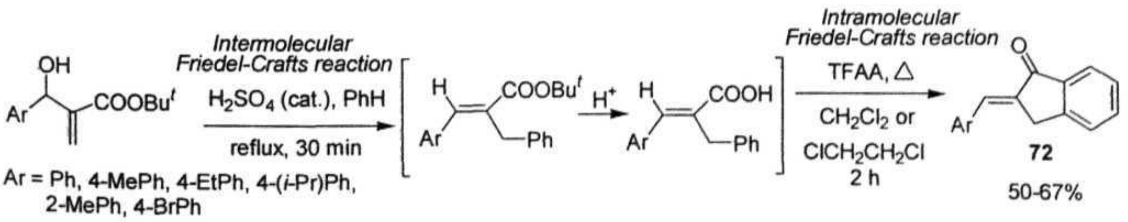


Figure 5

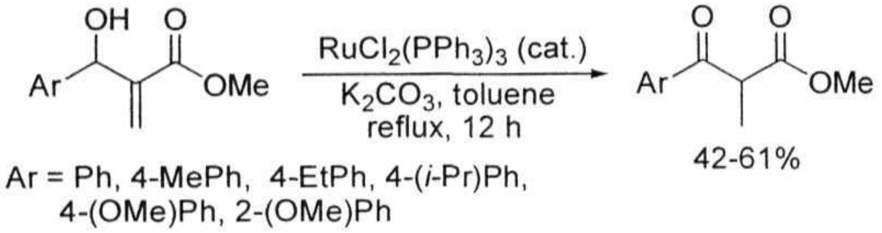


Our research group[155] has described a simple one-pot stereoselective transformation of the Baylis-Hillman adducts, obtained from aromatic aldehydes and *tert*-*butyl* acrylate into (*E*)-2-arylideneindan-1-ones (72) *via* the strategy involving one inter- and intramolecular Friedel-Crafts reactions according to Scheme 25.

Scheme 25



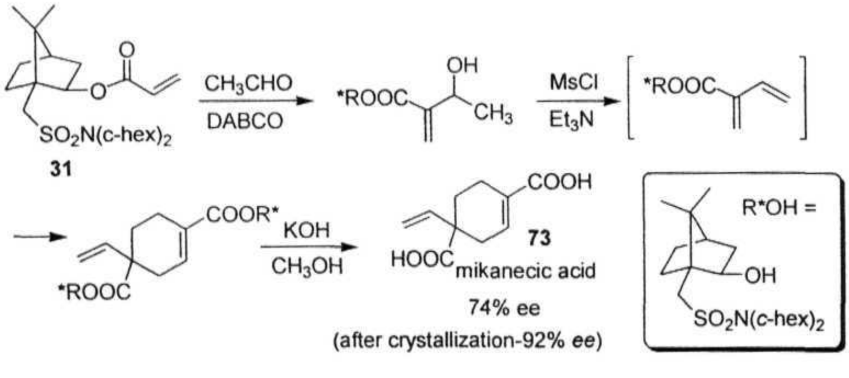
Isomerization of methyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis-Hillman adducts obtained from methyl acrylate and aromatic aldehydes, into methyl 3-aryl-2-methyl-3-oxopropanoates under the catalytic influence of $RuCl_2(PPh_3)_3$ was reported by our research group (eq 30).[156]



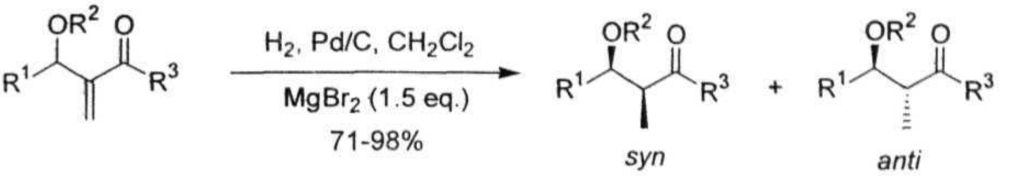
eq. 30

Our research group[157] has reported a simple enantioselective synthesis of mikanecic acid (73), a terpene dicarboxylic acid from the Baylis-Hillman adduct derived from chiral acrylate (31), following the reaction sequence as described in Scheme 26.

Scheme 26



A highly *syn*-diastereoselective heterogeneous hydrogenation of Baylis-Hillman adducts with palladium on carbon in the presence of $MgBr_2$, producing the corresponding *syn*-products (*syn*-aldol derivatives) was reported by Bouzide (eq 31).[158]

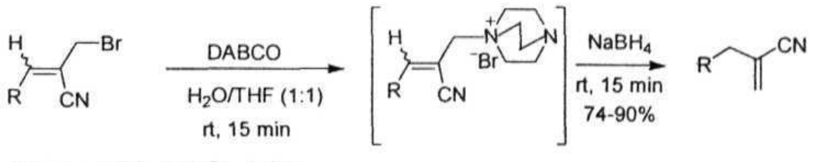


eq 31

R^1= Et, *i*-Pr, Ph; R^2= H, Me; R^3= Me, OMe, OEt *syn/anti* --- 28-88/1

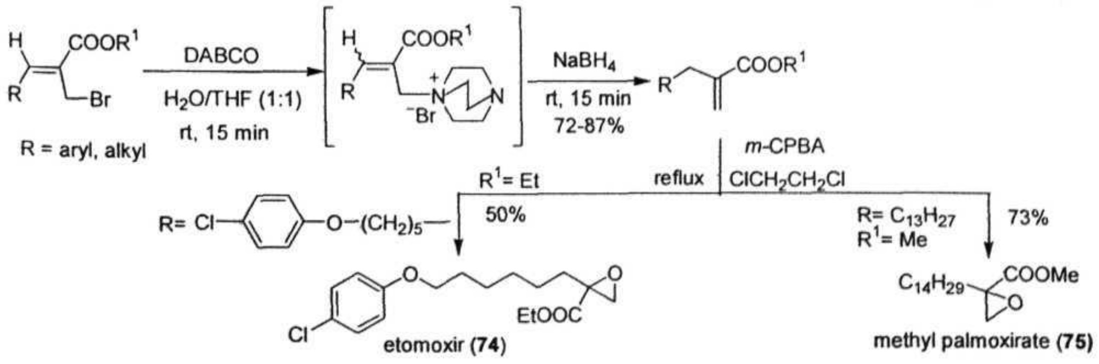
A convenient and efficient synthesis of 2-methylenealkanenitriles and alkanoates *via* the regioselective nucleophilic (S_N2') addition of hydride ion from $NaBH_4$ to the *in situ* generated DABCO-allyl bromides [2-(bromomethyl)alk-2-enenitriles and 2(Z)-2-(bromomethyl)alk-2-enoates] salts in environment friendly aqueous media was developed by our research group (Scheme 27 and Scheme 28). Subsequently, this methodology has been successfully applied for synthesis of two hypoglycemic agents, etomoxir (74) & methyl palmoxirate (75) (Scheme 28).[159]

Scheme 27



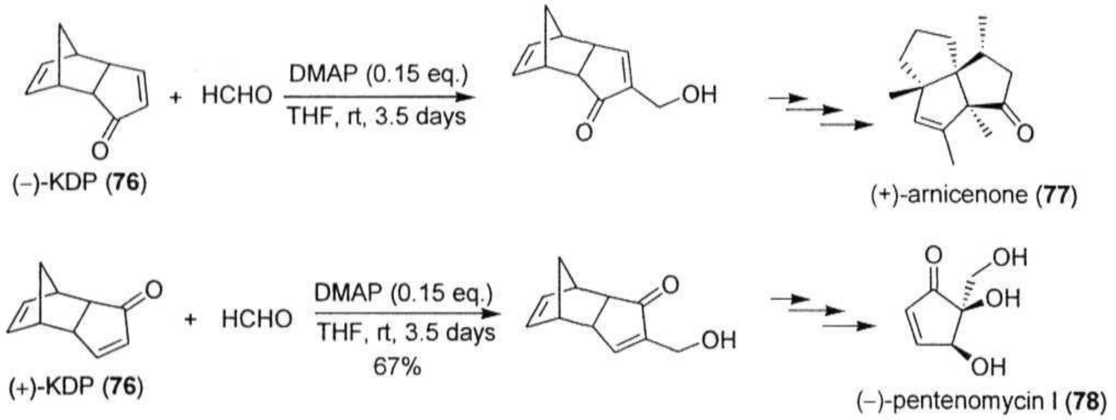
R= Ph, 4-ClPh, 4-MePh, 2-ClPh, 2-MePh, Pent, tridecyl

Scheme 28



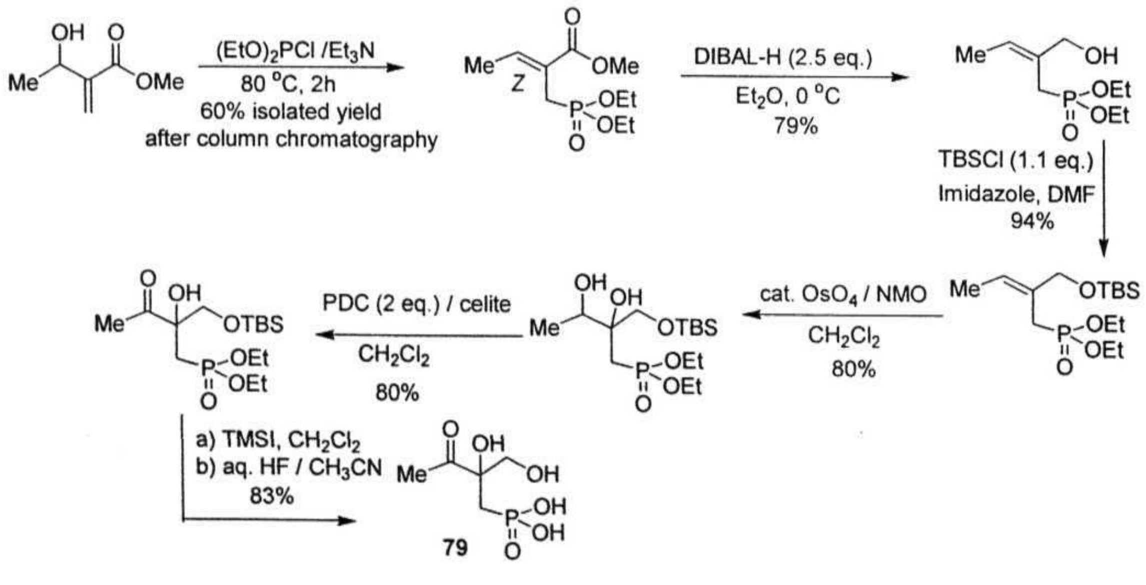
Ogasawara and co-workers[160,161] have successfully employed the Baylis-Hillman adducts, derived from chiral bicyclic enones (-)- KDP (76) & (+)-KDP (76) and formalin, in the synthesis of angular triquinane sesquiterpene (+)-arnicenone (77) and cyclopentanoid antibiotic (-)-pentenomycin I (78) according to the Scheme 29.

Scheme 29



Very recently, Fields[162] has reported a convenient synthesis of phosphonothrixin (79), an important natural product, starting from the Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate, following the reaction sequence as shown in the Scheme 30.

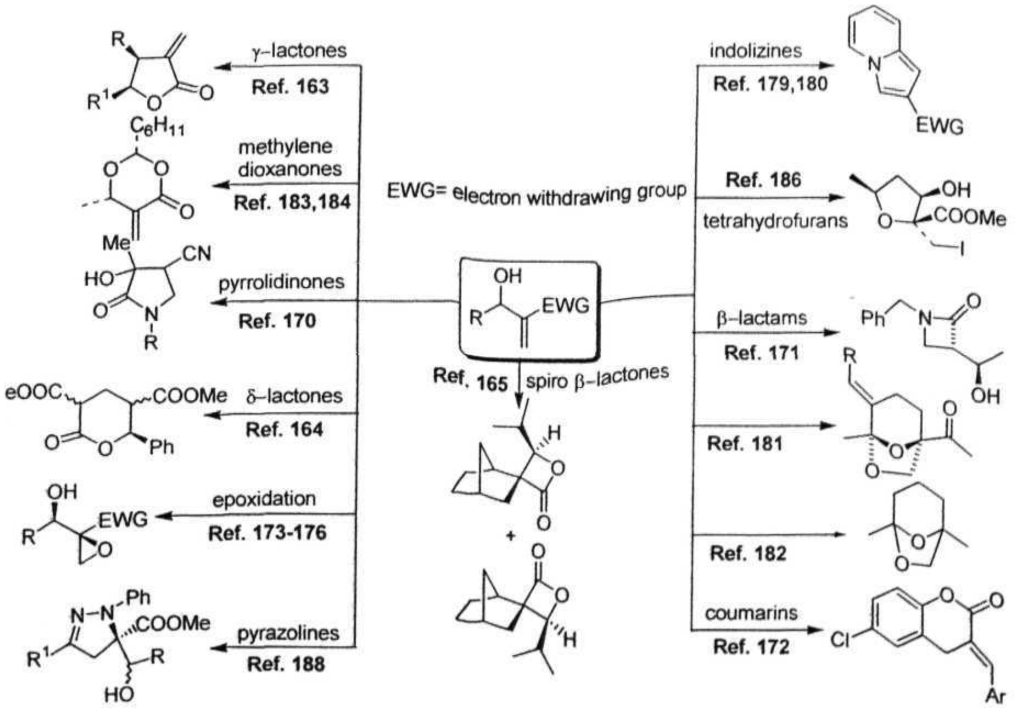
Scheme 30



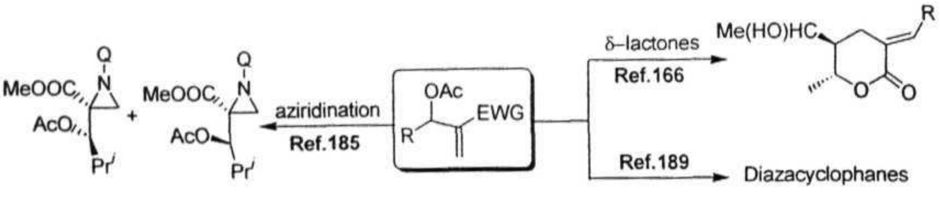
APPLICATIONS OF BAYLIS-HILLMAN ADDUCTS TO HETEROCYCLIC COMPOUNDS

Most of the important natural products, biologically active compounds, drug intermediates are heterocyclic molecules. Considerable progress has been achieved in the synthesis of heterocyclic compounds such as lactones,[163-169] lactams,[170,171] coumarines,[172] epoxides,[173-178] indolizines,[179,180] 6,8-dioxa bicyclo[3.2.1]octanes,[181,182] methylenedioxanones,[183,184] aziridines,[185] tetrahydrofurans,[186,187] pyrazolines[188] and diazacyclophanes[189] using the Baylis-Hillman adducts (pictorially presented in Schemes 31, 32 & 33). Some of the important and recent developments on the applications of Baylis-Hillman adducts to heterocyclic molecules have been presented in this section.

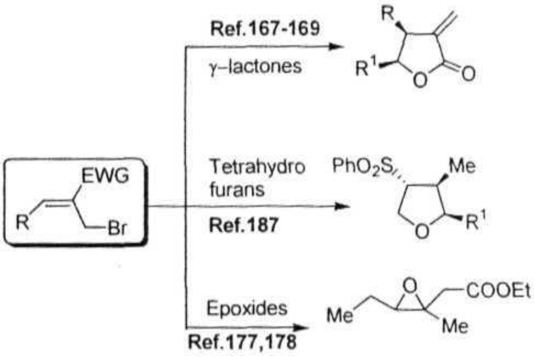
Scheme 31



Scheme 32

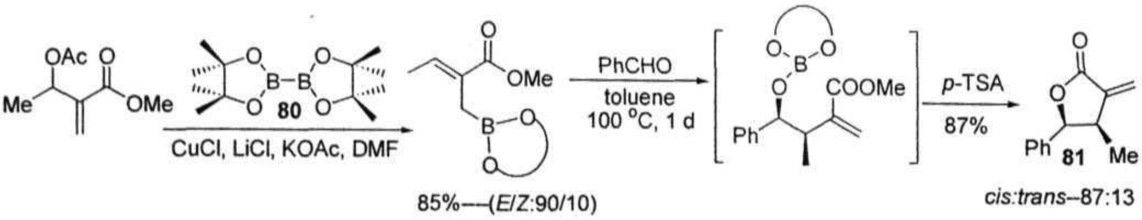


Scheme 33

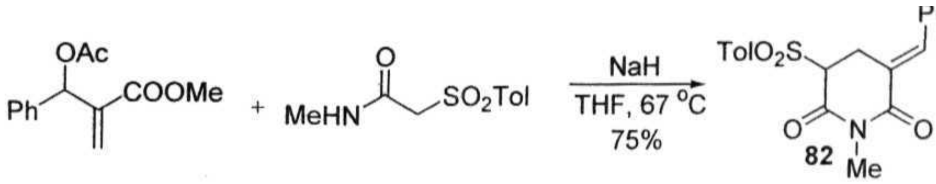


Very recently, Ramachandran et al.[190] have reported an interesting synthesis of β-substituted α-methylene γ-butyrolactones (81) *via* the nucleophilic addition of boronates (80) to the acetates of Baylis-Hillman adducts followed by the treatment of the resulting allyl boronates with aldehydes. One representative example is shown in Scheme 34.

Scheme 34

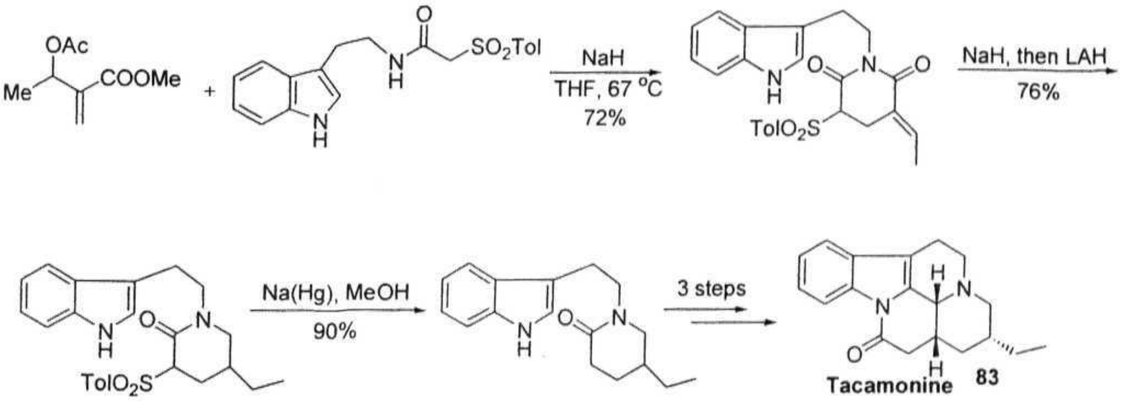


Chang and co-workers[191] have described a one-pot conversion of Baylis-Hillman adducts into alkyl-3(*E*)-aryl/alkylidene-5-substituted sulfonylpiperidine-2,6-diones (82). One representative example is shown in eq 32. This methodology has been successfully applied for synthesis of tacamonine (83), an **indole** alkaloid according to Scheme 35.



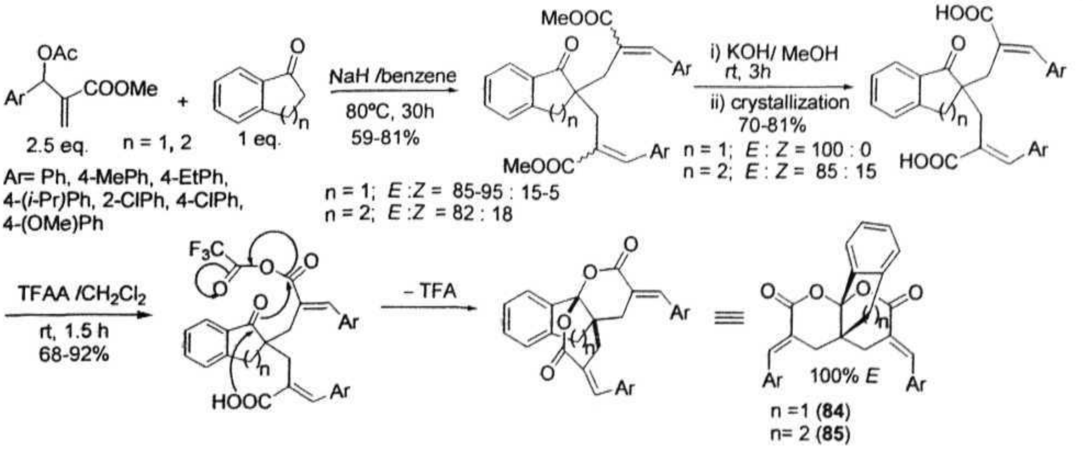
eq 32

Scheme 35



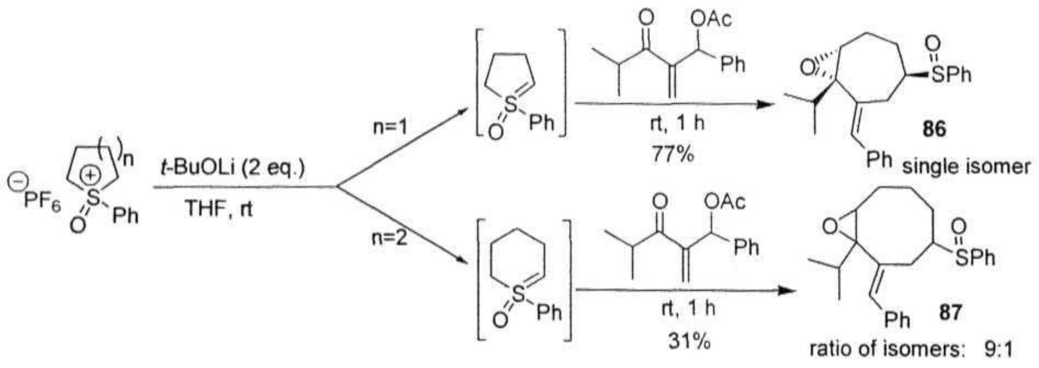
Our research group has developed a simple and convenient three-step synthesis of functionalized [4.4.3] and [4.4.4]propellano-bislactones (84) & (85) from acetates of Baylis-Hillman adducts following the reaction sequence as shown in Scheme 36.[192]

Scheme 36

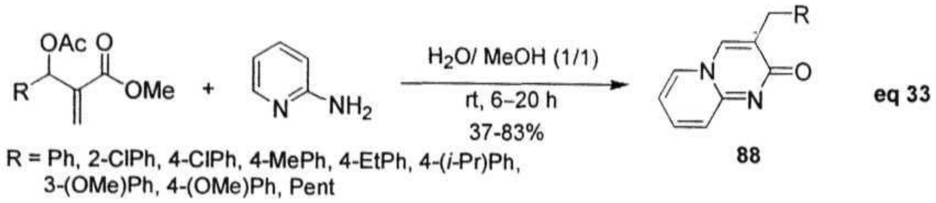


A tandem Michael-intramolecular Corey-Chaykovsky reaction of the five membered cyclic oxosulfonium ylide with acetates of the Baylis-Hillman adducts leading to the stereoselective synthesis of cycloheptene oxide derivatives (86) was reported by Fujimoto and co-workers.[193,194] A similar reaction with six membered oxosulfonium ylide provided cyclooctene oxide derivatives (87) as mixture of stereoisomers in moderate yields. Representative examples are presented in Scheme 37.

Scheme 37

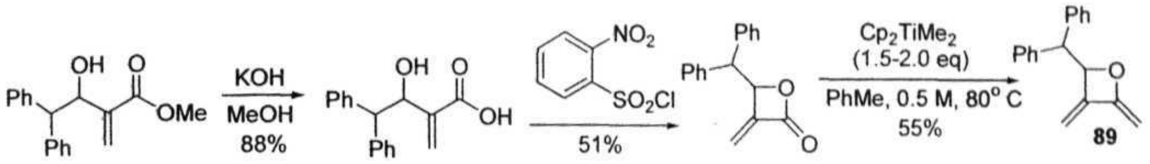


A facile, one-pot synthetic transformation of the acetates of the Baylis-Hillman adducts into fused pyrimidones (88) *via* the reaction with 2-aminopyridine in an environment-friendly aqueous media, has been developed by our research group (eq 33).[195]



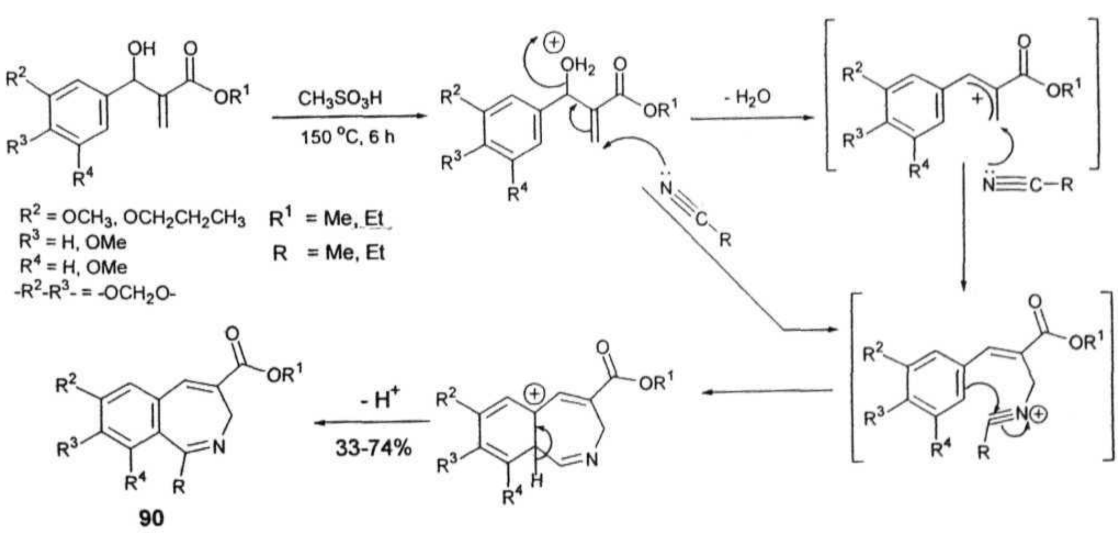
Howell et al.[196] have described an elegant synthesis of 3-alkylidene-2-methyleneoxetanes (89) *via* the treatment of α-alkylidene-β-lactones (which in turn were prepared from Baylis-Hillman adducts) with dimethyltitanocene. One representative example is shown in Scheme 38.

Scheme 38

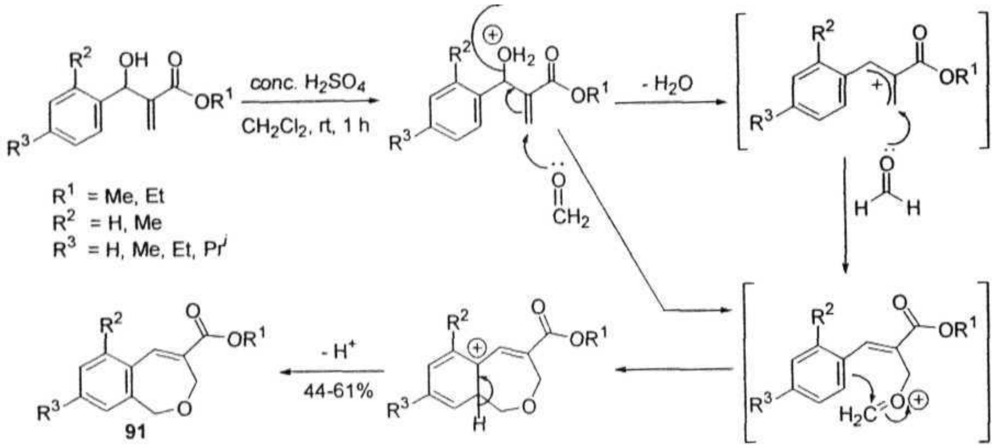


Recently, our research group reported an interesting one-pot transformation of Baylis-Hillman adducts into 2-benzazepines (90) *via* novel and tandem construction of C-N and C-C bonds involving simultaneous Ritter and Houben-Hoesch reactions as described in Scheme 39.[197] Subsequently, our research group also reported a novel one-pot synthesis of 2-benzoxepines (91) *via* the treatment of the Baylis-Hillman adducts with formaldehyde in the presence of H_2SO_4 involving tandem construction of C-O and C-C bonds as described in Scheme 40.

Scheme 39

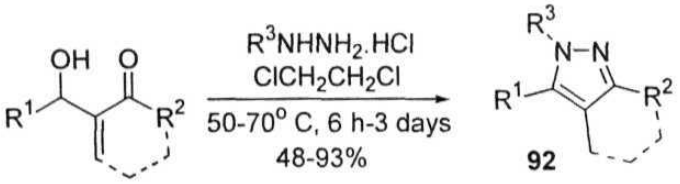


Scheme 40



91

Kim et al. have reported an interesting regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles (92) *via* the reaction of Baylis-Hillman adducts with hydrazine hydrochlorides (eq 34)."'

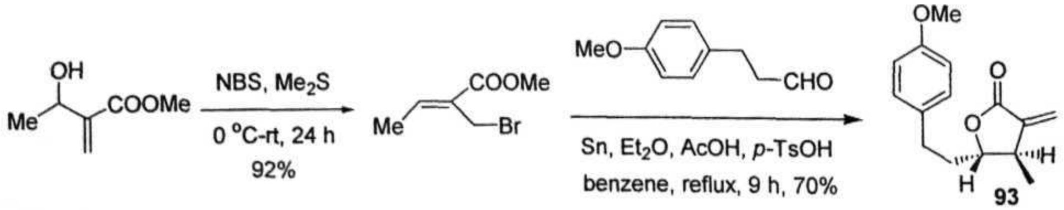


92 **eq 34**

R^1 = Ph, 4-ClPh, Pent
R^2 = Me, Et, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$
R^3 = Ph, Bu^t, 2,4-$(NO_2)_2C_6H_3$, 2,4-$(F)_2C_6H_3$

Bermejo and co-workers[200] have described an interesting synthesis of **methylene** lactone (93), from Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate according to Scheme 41. This molecule is found to possess extremely interesting properties with regard to its apoptosis **inducing** ability in HL-60 cells.

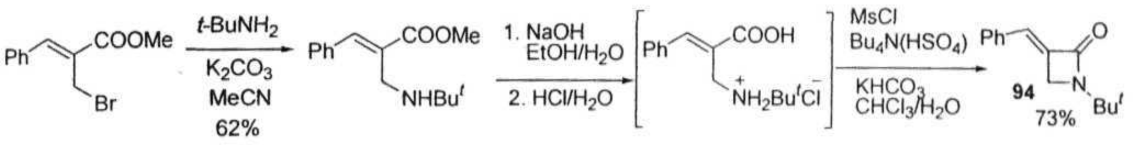
Scheme 41



93

Hoffman and Buchholz have reported an interesting synthesis of β-lactam derivatives (94) *via* the nucleophilic addition of aliphatic or aromatic primary amines to allyl bromides derived from Baylis-Hillman adducts. One representative example is presented in Scheme 42.

Scheme 42



Our research group has developed a convenient synthesis of 3-arylidene(alkylidene)-chroman-4-ones from Baylis-Hillman bromides following the reaction sequence described in Scheme 43. This methodology has been successfully applied for the synthesis of bonducellin methyl ether (95), an important natural product and 3-(4-methoxybenzylidene)-6-methoxychroman-4-one, an antifungal agent (96) (Figure 6).

Scheme 43

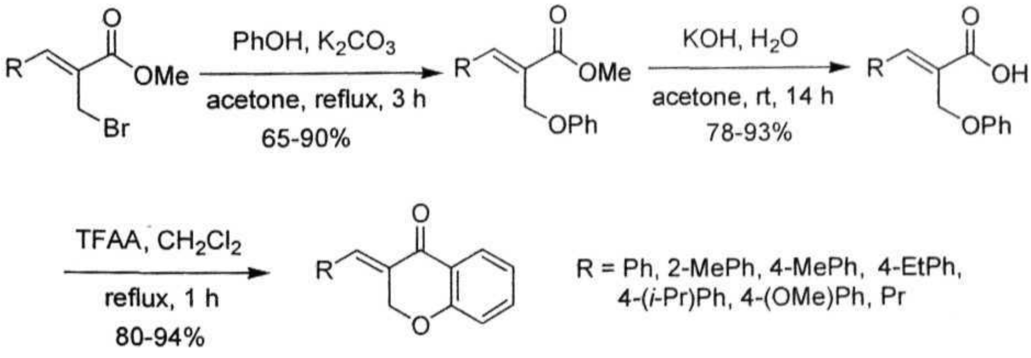
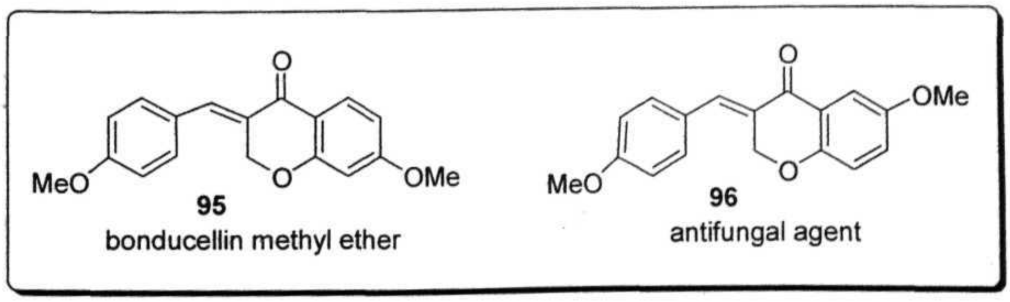


Figure 6

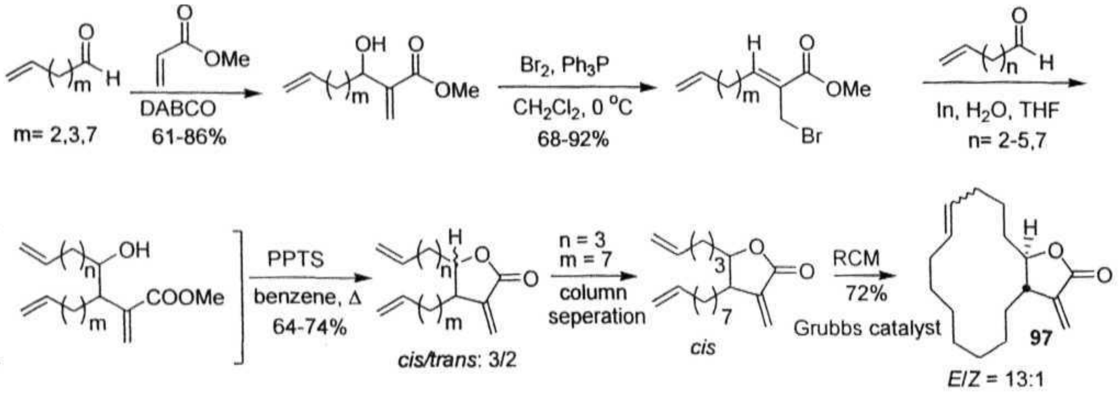


95
bonducellin methyl ether

96
antifungal agent

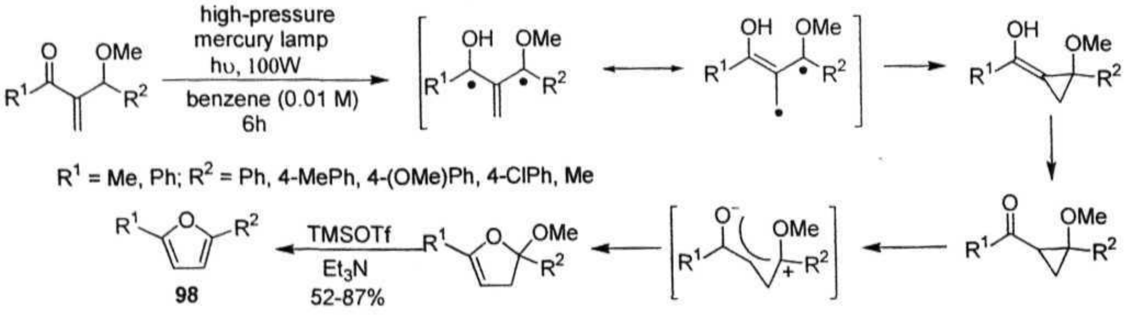
An interesting synthesis of bicyclic lactones (97) from the Baylis-Hillman adducts was reported by Paquette and Mendez-Andino following the reaction sequence as described in Scheme **44.**[203]

Scheme 44



Mikami et al.[204] have reported an interesting synthesis of substituted furan rings (98) *via* the photo chemical reaction of methyl ethers of Baylis-Hillman adducts followed by *in situ* treatment of the resulting dihydropyran derivatives with TMSOTf/Et_3N (Scheme 45).

Scheme 45



Objectives, Results and Discussion

The previous section clearly demonstrates that the Baylis-Hillman reaction is an emerging atom economical carbon-carbon bond forming reaction providing multifunctional molecules whose applications in synthesis of various natural products and biologically active molecules have been well documented.[12-14,16] Our research group has been actively working on various aspects of this reaction for the last nineteen years with the main objective of developing this reaction into a valuable synthetic tool in organic synthesis and in fact made considerable progress in this direction.[12-14,16] This thesis deals with applications of the Baylis-Hillman adducts in the synthesis of heterocyclic molecules with the following objectives.

Objectives

1. To develop a one-pot, facile methodology for synthesis of substituted γ-lactams using the acetates of the Baylis-Hillman adducts i.e., methyl 3-acetoxy-3-aryl-2-methylenepropanoates and methyl 3-acetoxy-2-methylenealkanoates.
2. a) To transform 2-[hydroxy(2-nitroaryl)methyl]cycloalk-2-enones, Baylis-Hillman adducts, derived from various 2-nitrobenzaldehydes and cycloalk-2-enones, into substituted 1,2,3,4-tetrahydroacridines and cyclopenta[b]quinolines in one-pot operation.

   b) To develop a convenient methodology for synthesis of functionalized 3-benzoylquinolines from 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones, the Baylis-Hillman adducts derived from 2-nitrobenzaldehydes and chromones.

3. To develop a simple, convenient and one-pot methodology for stereoselective synthesis of spiro oxindoles containing 6,8-dioxabicyclo[3.2.1]octane skeleton involving tandem construction of C-C and C-0 bonds *via* the reaction of various isatins with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (Diels-Alder dimer of methyl vinyl ketone) under the catalytic influence of $TiCl_4$.

Results and Discussion

Facile and one-pot transformation of Baylis-Hillman adducts into substituted γ-lactams

γ-Lactam framework occupies an important place in nitrogen heterocycles because of the presence of this skeleton in various natural products such as vitexlactam A[205] (99), cotinine[206] **(100),** convolutamides A-F[207] **(101)** (Figure 7) and biologically important molecules such as cromakalim[208] (antihypertensive) **(102),** doxapram[209] (respiratory stimulent) **(103),** etiracetam[210] (nootropic) **(104),** piperacetam[211] (nootropic) **(105),** felipyrine[212] (anti-inflammatory) **(106),** aniracetam[213] (mental performer enhancer) **(107)** and pramiracetam[214] (cognition adjuvant, nootropic) **(108)** (Figure **8).**

Figure 7

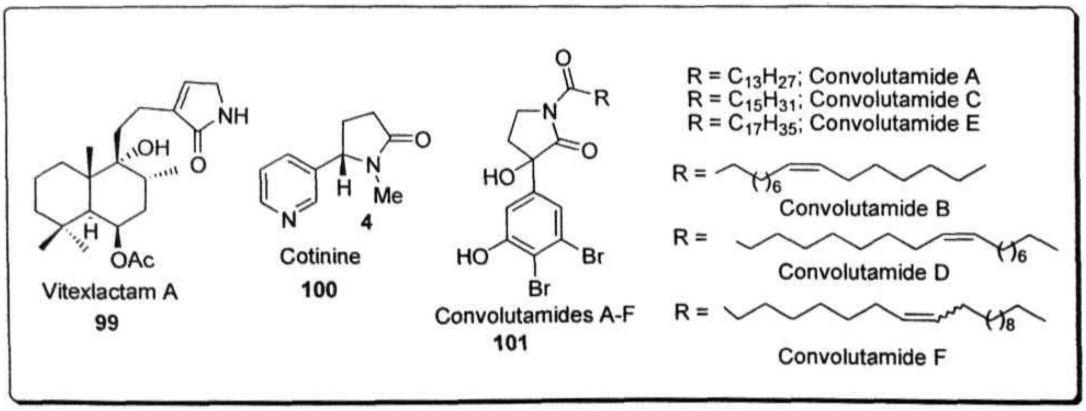
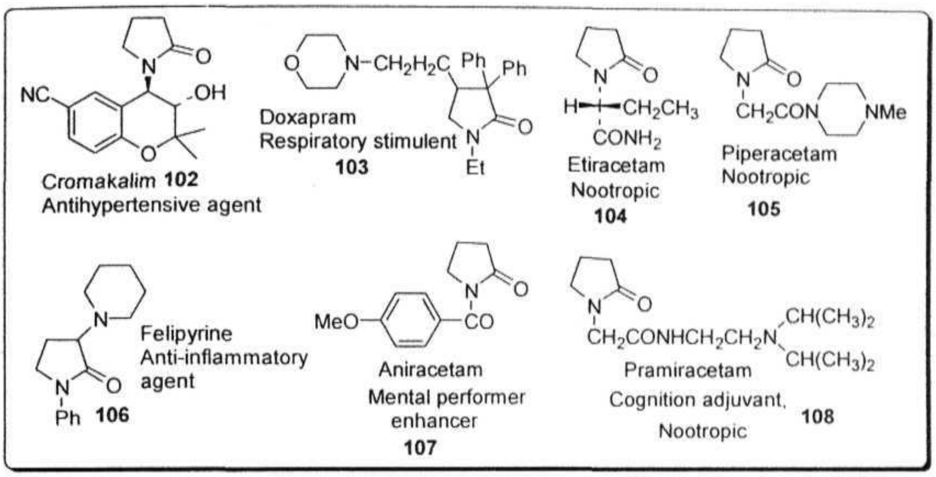


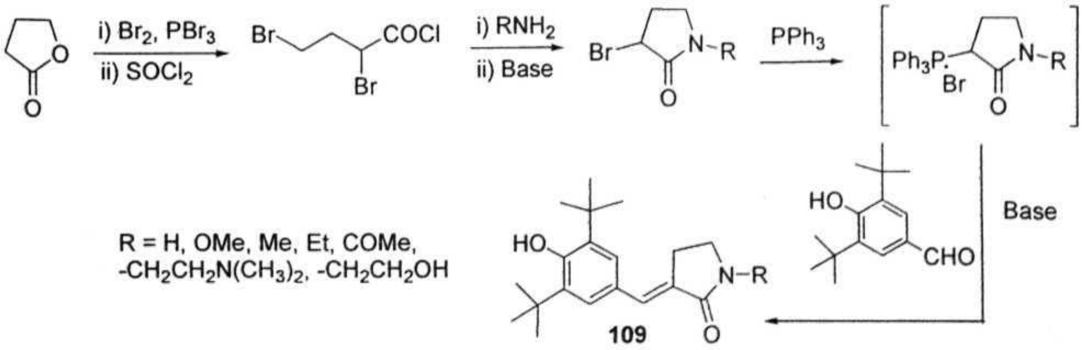
Figure 8



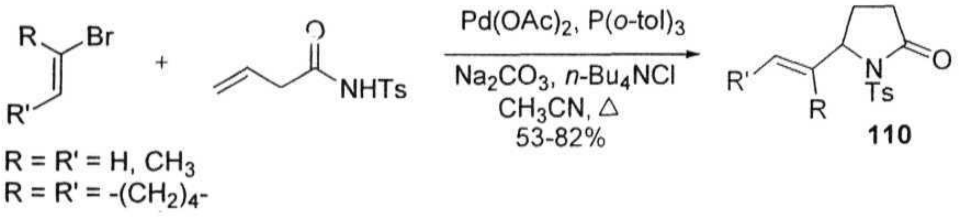
Due to their interesting and important biological properties, development of simple and convenient methodologies for synthesis of γ-lactam derivatives represent an interesting and attractive endeavor in synthetic organic chemistry and medicinal chemistry and in fact, a number of methodologies/strategies are reported in the literature for synthesis of these molecules.[215,,220] Some of the important and recent literature methods are described in the following.

Katayama and co-workers[215] have reported the synthesis of 3-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)pyrrolidin-2-ones i.e., γ-lactam derivatives **(109),** following the reaction sequence as described in the Scheme 46. They further studied these compounds for anti-inflammatory activities.

Scheme 46

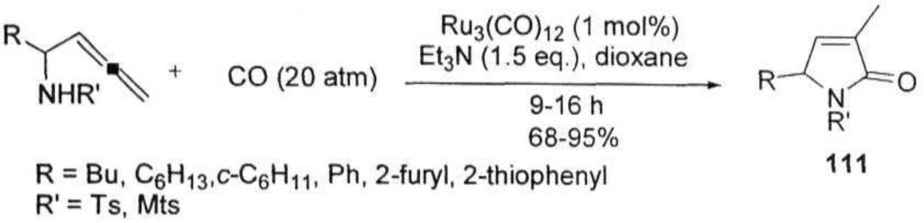


Feringa et al.[216] have described an interesting one-step synthesis of y-lactams (110) *via* palladium catalyzed tandem Heck-allylic substitution reaction between β-olefinic *N*-tosyl amides and vinyl bromides. Representative examples are shown in eq 35.



eq 35

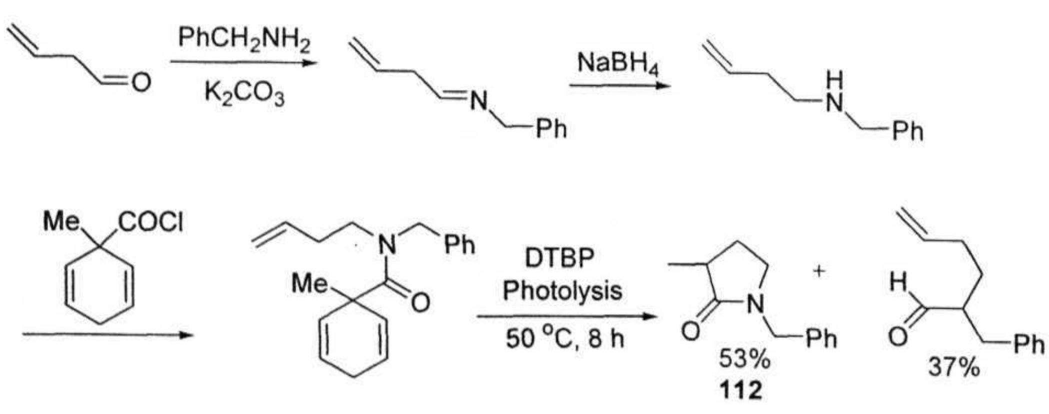
An interesting synthesis of γ-lactams (**111**) *via* $Ru_3(CO)_{12}$-catalyzed cyclocarbonylation of α-allenic sulfonamides was reported by Kang and co-workers.ˊ Representative examples are shown in eq 36.



eq 36

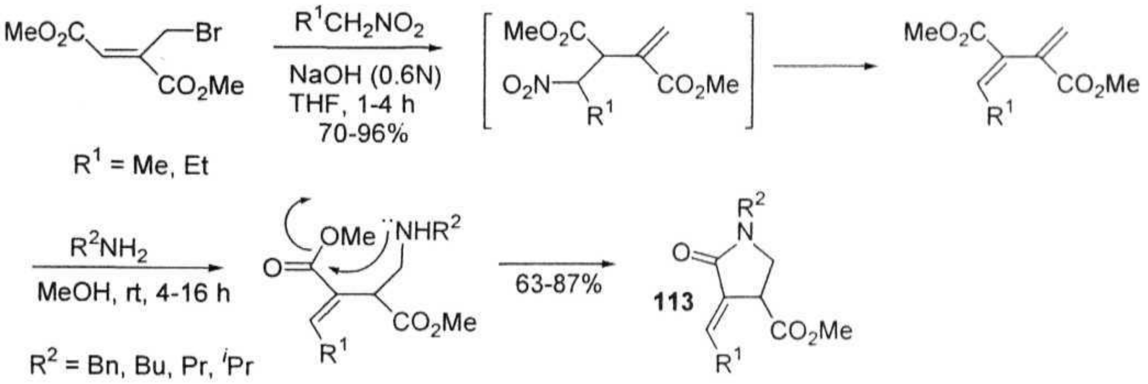
Walton and Jackson have described the synthesis of γ-lactam 112 involving the radical induced homolysis of l-carbamoy)-l-methylcyclohexa-2,5-diene as the key step (Scheme 47).

Scheme 47

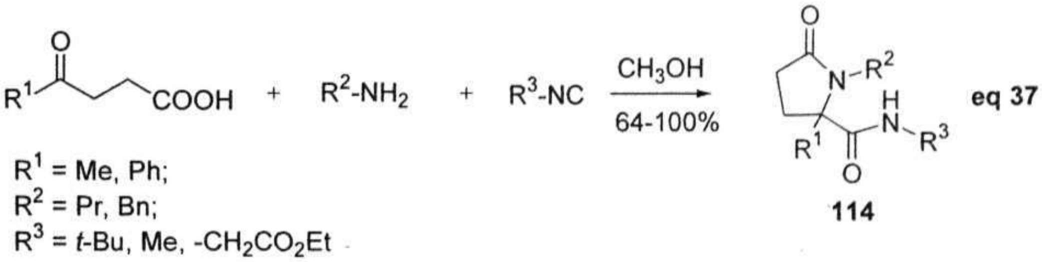


Amri et al. have developed an attractive synthesis of α-alkylidene-γ-lactams **(113)** *via* tandem alkylation-elimination of dimethyl α-(bromomethyl)fumarate followed by addition and intramolecular cyclization according to the reaction sequence described in Scheme 48.[219]

Scheme 48



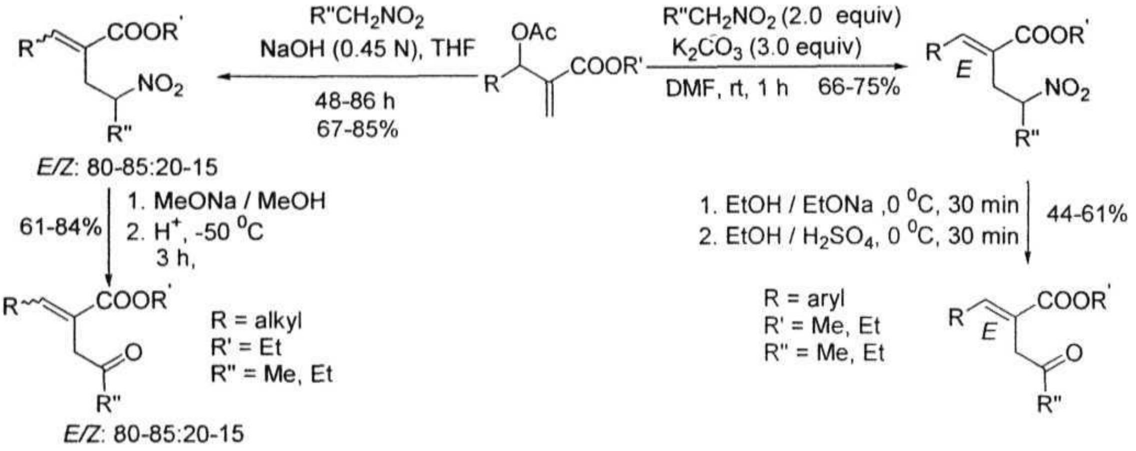
An important 4-centre-3-component one-pot synthesis of γ-lactams **(114)** involving y-keto acid, amine and isocyanide was developed by Ugi and Hanusch-Kompa (eq 37).



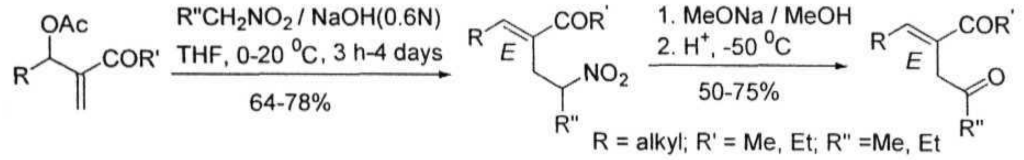
During our on going research program on the synthesis of heterocyclic molecules,[88,107,192,195,197,198,202] we required different y-lactams. The literature survey revealed that acetates of the Baylis-Hillman adducts were conveniently transformed into the corresponding alkyl (*E*)-2-alkylidene-4-nitroalkanoates[221] [or alkyl (*E*)-2-arylidene-4-nitroalkanoates[222]] (Scheme 49) and (*E*)-2-alkylidene-4-nitroalkanones[223] (Scheme 50) by the treatment with nitroalkanes in the presence of K2CO3/DMF (or NaOH/THF) and

NaOH/THF respectively. These molecules were further transformed into dicarbonyl compounds *via* Nef reaction (Scheme 49 and Scheme 50).

Scheme 49



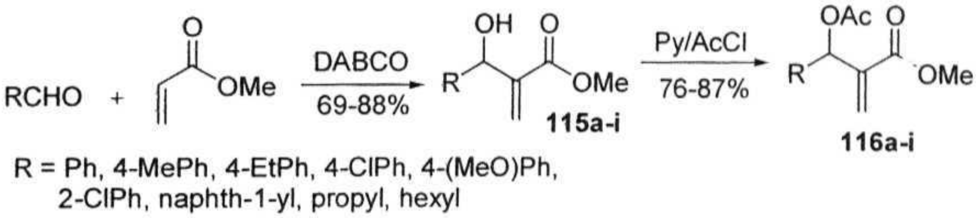
cheme 50



It occurred to us that reductive cyclization of the alkyl 2-arylidene-4-nitroalkanoates, which would be obtained *in situ via* the treatment of acetates of the Baylis-Hillman adducts with nitroalkanes, with an appropriate reagent/strategy would in principle result in one-pot formation of the desired γ-lactams.

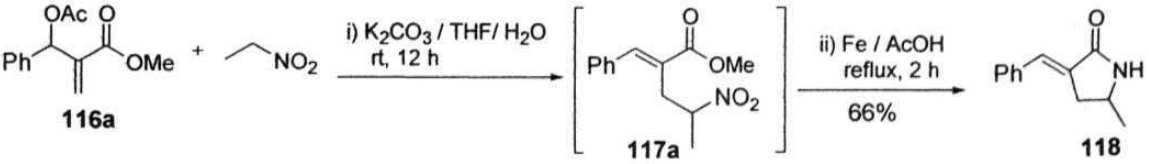
Accordingly, we have first selected the Baylis-Hillman acetate, methyl 3-acetoxy-2-methylene-3-phenylpropanoate (116a) for treatment with nitroethane in the presence of a base followed by reductive cyclization. The required methyl 3-acetoxy-2-methylene-3-phenylpropanoate (116a) was prepared from methyl 3-hydroxy-2-methylene-3-phenylpropanoate (115a), the Baylis-Hillman alcohol derived from benzaldehyde and methyl acrylate as shown in Scheme 51 [see Table 1 for Baylis-Hillman alcohol **(115a),** and Table 2 for Baylis-Hillman acetate **(116a)].**

Scheme 51



We have next planned to examine the possible transformation of **116a** into the corresponding γ-lactam derivative **(118).** The best results in this direction were obtained when methyl 3-acetoxy-2-methylene-3-phenylpropanoate **(116a)** (2 mmol) was treated with nitroethane (8 mmol) in the presence of K_2CO_3 (8 mmol) in THF (5 mL)/H_2O (0.1 mL) at room temperature for 12 h followed by the treatment with Fe/AcOH (after removal of THF and nitroethane under reduced pressure) at 110 °C for 2 h, thus providing the desired y-lactam i.e., (*E*)-5-methyl-3-benzylidenepyrrolidin-2-one **(118)*** in 66% isolated yield after work-up and purification through silica gel column chromatography (Scheme 52, Table 3). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 1), ^{13}C NMR (Spectrum 2), mass spectral data and elemental analysis.

Scheme 52



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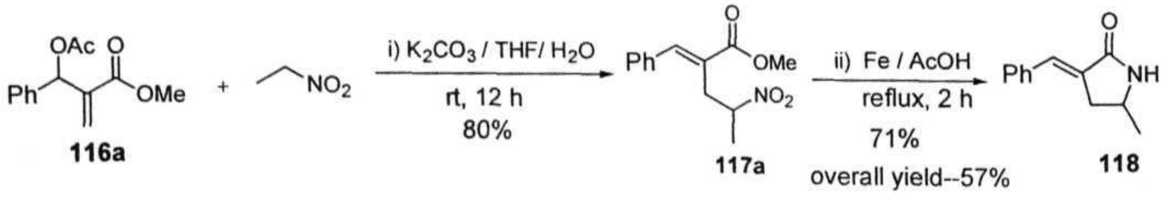
* **(*E*)-Stereochemistry** was assigned on the basis of single crystal X-ray data of the molecule 126 (see page no: 50) and on the basis of the ^{1}H NMR spectral data of 117a (see page no: 46).

With a view to examine whether the reaction is more facile and whether the yield of **118** would be higher in step-wise method, we have also isolated the trisubstituted alkene, i. e., methyl (*E*)-2-benzylidene-4-nitropentanoate **(117a).** Thus, treatment of methyl 3-acetoxy-2-methylene-3-phenylpropanoate **(116a)** (2 mmol) with nitroethane (8 mmol) in the presence of K_2CO_3 (8 mmol) in THF (5 mL) and water (0.1 mL) at room temperature for 12 h provided the desired trisubstituted alkene i.e., methyl (*E*)-2-benzylidene-4-nitropentanoate **(117a)** in 80% isolated yield after usual work-up and column chromatography. The (*E*)-stereochemistry was assigned on the basis of ^{1}H NMR spectral data which showed a singlet at 6 7.89 due to the β-vinylic proton (*cis* to the COOMe group) of major [*E*]-isomer and a singlet at 8 6.86 with low intensity (≈ 5%) due to the β-vinylic proton (*trans* to the COOMe group) of minor [*Z*]-isomer.[φ] Subsequent treatment of the molecule **117a** with Fe/AcOH at 110 °C for 2 h provided the desired γ-lactam i.e., (*E*)-5-methyl-3-benzylidenepyrrolidin-2-one **(118/** in 71% yield (overall yield amounting to 57%) (Scheme 53). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data, which are in fact in full agreement with that of the molecule prepared in one-pot method (as in Scheme 52).

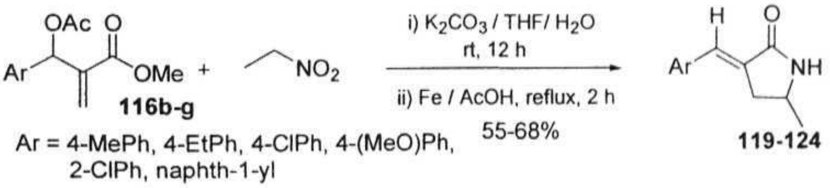
Scheme 53



[φ] In the ^{1}H NMR spectrum of the crude trisubstituted alkene (117a) with ester group, β-vinylic proton *cis* to the ester group ([*E*]-isomer) appears downfield while the same proton *trans* to the ester group ([Z]-isomer) appears upfield.[224,,226]

[ƒ] For easy understanding and continuity, the γ-lactams obtained from the acetates **116a-i** *via* the treatment with nitroethane/1-nitropropane were given continuous numbers from **118-131**.

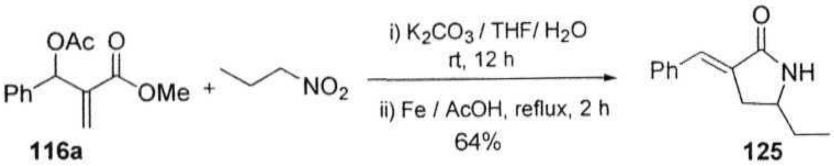
Since the yield is better in the case of one-pot method than in the case of two-pot process, we have selected the one-pot procedure as the method of choice and extended this strategy to a representative class of the acetates of the Baylis-Hillman adducts. The required Baylis-Hillman acetates **(116b-g)** were prepared according to the Scheme 51 [see Table 1 for Baylis-Hillman alcohols **(115b-g),** and Table 2 for Baylis-Hillman acetates (**116b-g**)]. Treatment of the Baylis-Hillman acetates **116b-g** with nitroethane in the presence of K_2CO_3 followed by reductive cyclization using Fe/AcOH at 110 °C for 2 h provided the desired γ-lactams i. e., (*E*)-5-methyl-3-arylidenepyrrolidin-2-ones **(119-124)** in 55-68% yields (eq 38, Table 3). Structures of these molecules were confirmed by IR, ^{1}H NMR (See: Spectrum 3 for molecule **124),** ^{13}C NMR (See: Spectrum 4 for molecule **124)** and elemental analyses.



eq 38

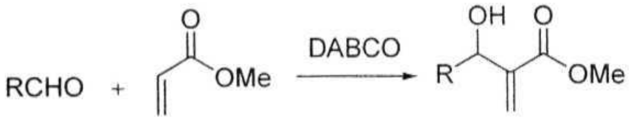
With a view to understand the generality of this methodology, we next employed another nitroalkane, 1-nitropropane for reaction with Baylis-Hillman acetates. We have first examined the reaction between 1-nitropropane and the acetate, methyl 3-acetoxy-2-methylene-3-phenylpropanoate **(116a).** Thus, treatment of the Baylis-Hillman acetate **116a** with 1-nitropropane in the presence of K_2CO_3 at room temperature for 12 h, followed by reductive cyclization using Fe/AcOH at 110 °C for 2 h (after removal of THF and 1-nitropropane under reduced pressure) provided the desired γ-lactam i. e., (*E*)-5-ethyl-3-benzylidenepyrrolidin-2-one **(125)** in 64% yield (eq 39, Table 3). Structure of this molecule

(125) was confirmed by IR, ^1H NMR (Spectrum 5), ^{13}C NMR (Spectrum 6), mass spectral data and elemental analysis.



eq 39

Table 1: Synthesis of methyl 3-aryl-3-hydroxy-2-methylenepropanoates (115a-g) and methyl 3-hydroxy-2-methylenealkanoates (115h,i)[a,b]



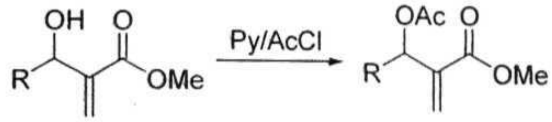
Aldehyde (R)	Time in days	Product (allyl alcohol)	Yield (%)[c]
phenyl	7	**115a**	84
4-methylphenyl	8	**115b**	75
4-ethylphenyl	7	**115c**	77
4-chlorophenyl	6	**115d**	79
4-methoxyphenyl	10	**115e**	69
2-chlorophenyl	6	**115f**	83
naphth-1-yl	7	**115g**	88
propyl	6	**115h**	71
hexyl	8	**115i**	75

a) All the reactions were carried out on 50 mmol scale of the aldehyde with methyl acrylate (75 **mmol)** in the presence of DABCO (7.5 mmol) at room temperature.

b) **All** the compounds **115a-i** were characterized by IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data.

c) Yields are of the pure products based on aldehydes.

Table 2: Synthesis of methyl 3-acetoxy-3-aryl-2-methylenepropanoates (116a-g) and methyl 3-acetoxy-2-methylenealkanoates (116h,i)[a,b]



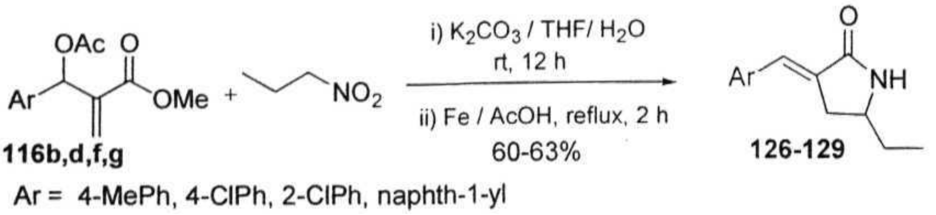
R	B-H alcohol (allyl alcohol)	Product (allyl acetate)	Yield (%)[c]
phenyl	**115a**	**116a**	85
4-methylphenyl	**115b**	**116b**	83
4-ethylphenyl	**115c**	**116c**	79
4-chlorophenyl	**115d**	**116d**	87
4-methoxyphenyl	**115e**	**116e**	77
2-chlorophenyl	**115f**	**116f**	82
naphth-1-yl	**115g**	**116g**	79
propyl	**115h**	**116h**	76
hexyl	**115i**	**116i**	86

a) All reactions were carried out on 20 mmol scale of the Baylis-Hillman alcohol with 40 mmol of acetyl chloride in the presence of pyridine at room temperature for 2 h.

b) All the compounds **116a-i** were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data.

c) Yields are of the pure products based on Baylis-Hillman alcohols after purification through silica gel column chromatography.

We have then extended this strategy to various Baylis-Hillman acetates **(116b,d,f,g)** to provide **the** desired γ-lactams i. e., (*E*)-5-ethyl-3-arylidenepyrrolidin-2-ones **(126-129)** in 60-63% yields (eq 40, Table 3). Structures of these molecules were confirmed **by** IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses.



eq 40

The (*E*)-selectivity of these molecules was established from the single crystal X-ray data for the molecule **126** (Figure X1, Table 4).

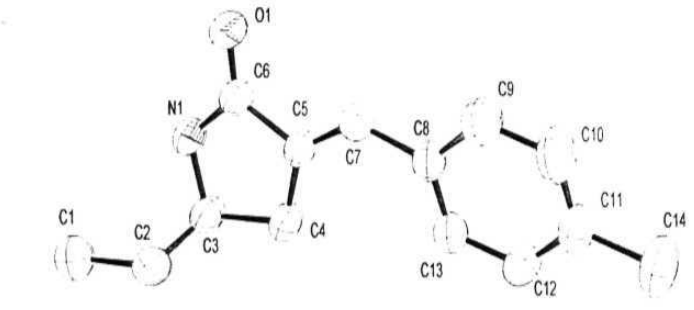
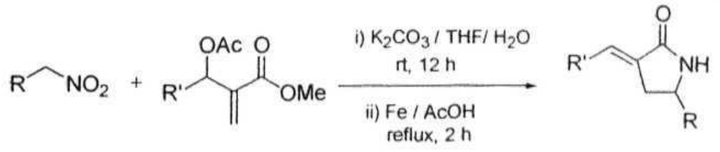


Figure X1: ORTEP diagram of compound **126.**
(Hydrogen atoms were omitted for clarity)

Later on, we extended this methodology to **the** acetates **(116h,i)** of the Baylis-Hillman adducts derived from *n*-butyraldehyde and 1-heptanal (aliphatic aldehydes) [see Table 1 for **Baylis-Hillman** alcohols **(115h,i),** and Table 2 for Baylis-Hillman acetates **(116h,i)].** **Treatment** of these Baylis-Hillman acetates **(116h,i)** with nitroethane in the presence of K_2CO_3 followed by reductive cyclization using Fe/AcOH at 110 °C for 2 h provided the desired γ-lactams i. e., (*E*)-5-methyl-3-butylidenepyrrolidin-2-one **(130)** and (*E*)-5-methyl-3-heptylidenepyrrolidin-2-one **(131)** in 52% **and** 49% yields respectively after column **purification** (Scheme 54, Table 3).[ϕ] Structures of these molecules were confirmed by IR, ^{1}H

In the ^{1}H NMR spectrum of the trisubstituted alkenes with ester group, β-vinylic proton *cis* to the ester group ([*E*]-isomer) appears downfield while the same proton *trans* to the ester group ([Z]-isomer) appears upfield.[224,226] The (*E*)-stereochemistry was assigned on the basis of ^{1}H NMR spectral data of the intermediate esters **117h,i**. ^{1}H NMR spectrum of the crude compound **117h** (uncyclized product), showed triplet for olefinic proton at 6 6.96 ([*E*]-isomer) and at 8 6.05 ([*Z*]-isomer) in the ratio 89:11. Similarly, ^{1}H NMR spectrum of the crude compound **117h** (uncyclized product), showed triplet for olefinic proton at δ 6.96 ([*E*]-isomer) and at δ 6.05 ([Z)-isomer) in the ratio 87:13.

Table 3: Synthesis of **(*E*)-5-alkyl-3-arylidene/alkylidenepyrrolidin-2-ones (118-131)**[a-f]

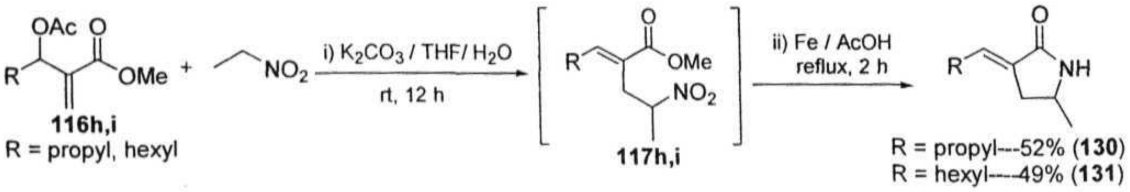


R	Acetate	R′	Product	Yield (%)	Mp (°C)
Me	**116a**	phenyl	**118**[g]	66	101-103
Me	**116b**	4-methylphenyl	**119**	65	170-172
Me	**116c**	4-ethylphenyl	**120**	68	128-130
Me	**116d**	4-chlorophenyl	**121**	64	161-163
Me	**116e**	4-methoxyphenyl	**122**	62	169-171
Me	**116f**	2-chlorophenyl	**123**	55	124-126
Me	**116g**	naphth-1-yl	**124**[g]	67	179-181
Et	**116a**	phenyl	**125**[g]	64	125-127
Et	**116b**	4-methylphenyl	**126**	62	142-144
Et	**116d**	4-chlorophenyl	**127**	63	132-134
Et	**116f**	2-chlorophenyl	**128**	60	128-130
Et	**116g**	naphth-1-yl	**129**	61	123-125
Me	**116h**	propyl	**130**[g,h]	52[i]	–
Me	**116i**	hexyl	**131**[h]	49[i]	–

a) All reactions were carried out on 2 mmol scale of Baylis-Hillman acetate with nitroalkane (8 mmol), in the presence of K_2CO_3 (8 mmol) in THF / water at room temperature for 12 h and the reaction mixture was treated with Fe powder (12 mmol) / AcOH (5mL) (after removal of THF and nitroalkane under reduced pressure) at 110 °C for 2 h. b) The compounds **118-129** were obtained as solids while the compounds **130** & **131** were obtained as viscous liquids. All the compounds **118-131** were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses. c) (*E*)-Stereochemistry of compound **126** was established by single crystal X-ray data and the stereochemistry of the other compounds was assigned in analogy to **126.** d) Yields are of the pure products (based on acetates) after purification through silica gel column chromatography. e) In the case of molecules **121, 125,** 127-129 'H NMR spectrum of the crude products shows ≈ 5-10% of uncyclized compound as evidenced by the singlet at ≈ 5 7.81-8.30 (olefinic proton) and singlet at ≈ 8 3.85-3.92 (COO<u>CH</u>$_3$) with low intensity. f) The ^{1}H NMR spectra of the crude products did not clearly indicate the presence of any isomeric impurity [on the basis of the ^{1}H NMR spectrum of the crude product of **117a** (uncyclized product) which shows the presence of ≈ (Z)-5% isomeric impurity, we believe that all these reactions are at least ≈ 95% (*E*)-selective]. g) Structures were further confirmed by mass spectral analyses. h) The ^{1}H NMR spectra of the crude products of the intermediates (nitro compounds **117h** & **117i**) derived from aliphatic acetates **116h** and **116i** indicate the presence of ≈ 11% and 13% (Z)-isomer as evidenced by the triplet at ≈ δ 6.05 (olefinic proton *trans* to the ester group). i) ^{1}H NMR and ^{13}C NMR spectral analysis of the column purified products **130** & **131** indicate the presence of ≈ 8% and ≈ 10% impurities respectively. The molecule **130** was obtained in pure form after purification through preparative HPLC (Shim pack PREP-ODS column, methanol). However similar attempt to purify the molecule **131** was unsuccessful.

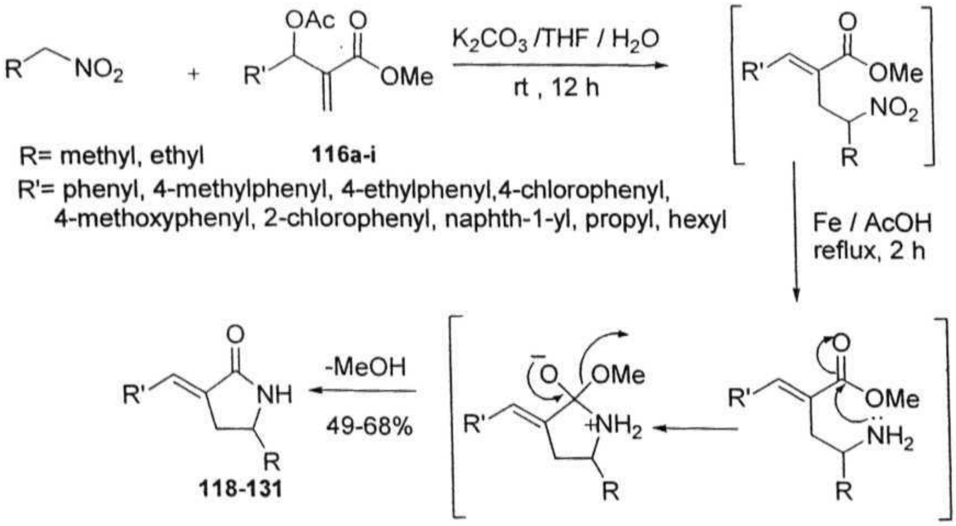
NMR (See: Spectrum 7 for molecule **130),** ^{13}C NMR (See: Spectrum 8 for molecule 130) spectral data and elemental analysis (for molecule **130).**

Scheme 54



A plausible mechanism for the one-pot transformation of the acetates of the Baylis-Hillman adducts into substituted γ-lactams **118-131** is presented in Scheme 55.

Scheme 55



In conclusion, we have successfully developed a convenient, operationally simple, one-pot procedure for the synthesis of substituted γ-lactams from the acetates of the Baylis-Hillman adducts, *via* the reductive cyclization using Fe/AcOH.

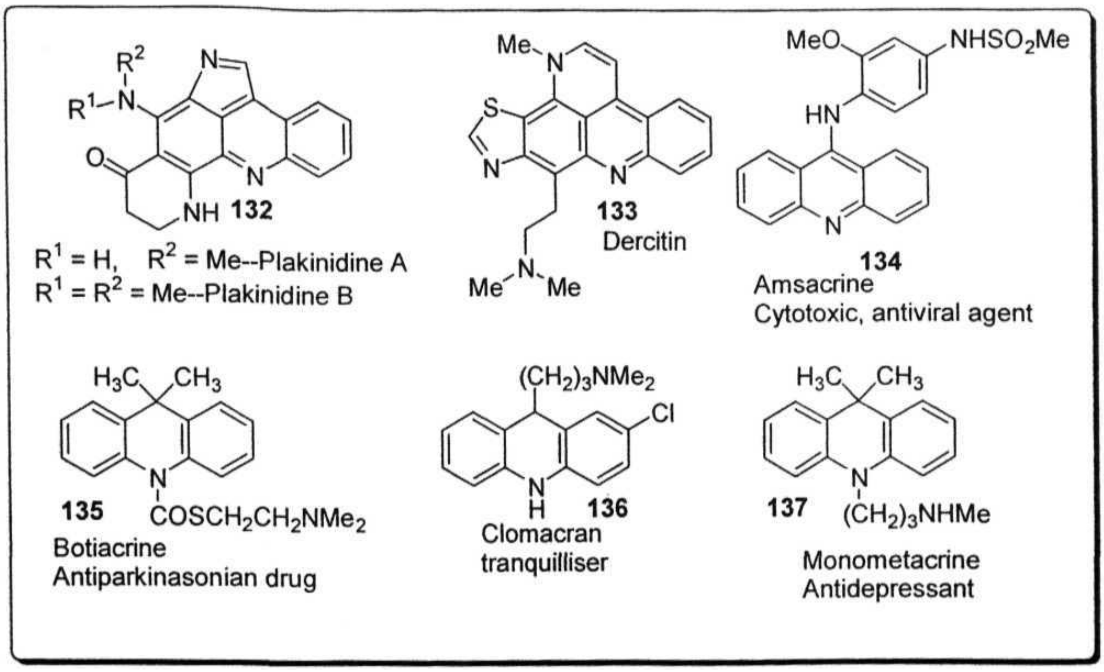
Table 4. Crystal data and structure refinement for compound 126

Identification code	**:126**
Empirical formula	: $C_{14}H_{17}NO$
Formula weight	: 215.29
Temperature	: 293(2) K
Wavelength	: 0.71073 A
Crystal system	: Monoclinic
Space group	: P21/a (Internatinal Table No. 14)
Unit cell dimensions	: a = 10.048(4) A; alpha = 90 deg.
	: b = 11.595(5) A; beta = 112.97(3) deg.
	: c = 11.158(3) A; gamma = 90 deg.
Volume	: 1196.9(8) A^3
Z, Calculated density	: 4, 1.195 Mg/m^3
Absorption coefficient	: 0.075 mm^{-1}
F(000)	: 464
Crystal size	: 0.64 x 0.55 x 0.48 mm
Theta range for data collection	: 1.98 to 27.47 deg.
Limiting indices	: $0 < h < 13$, $0 < k < 15$, $-14 < 1 < 13$
Reflections collected / unique	: 2734 / 2734 [R(int) = 0.0000]
Completeness to theta = 27.47	: 100.0%
Absorption correction	: none
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2734 / 0 / 146
Goodness-of-fit on F^2	: 1.036
Final R indices [I>3sigma(I)]	: R1 = 0.0660, wR2 = 0.1120
R indices (all data)	: R1 = 0.1914, wR2 = 0.2457
Extinction coefficient	: 0.007(6)
Largest diff. peak and hole	: 0.26 and -0.24 e. A"^{3}

One-pot convenient synthesis of 1,2,3,4-tetrahydroacridines and cyclopenta[b]quinolines from the Baylis-Hillman adducts

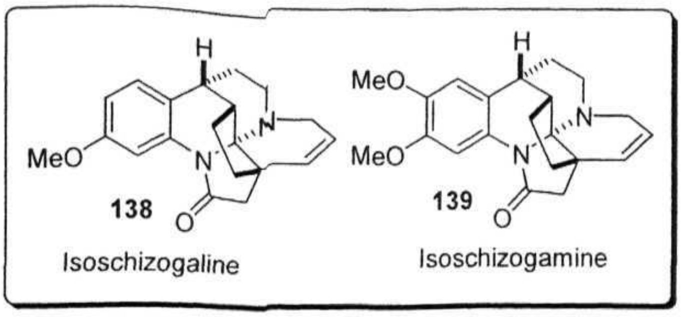
Acridine moiety is an important structural moiety present in certain natural products such as plakinidine A and B[227] (132) and dercitin[228] (133) (Figure 9) and in biologically important molecules such as amsacrine[229] (cytotoxic, antiviral agent) (134), botiacrine[230] (antiparkinasonian drug) (135), clomacran[231] (tranquilliser) (136), and monometacrine[232] (antidepressant) (137) (Figure 9). Also, acridine derivatives have been employed or examined as antitumor agents,[233] acetylcholinesterase inhibitors,[234] anticancer agents,[235] and DNA binding agents.[236]

Figure 9



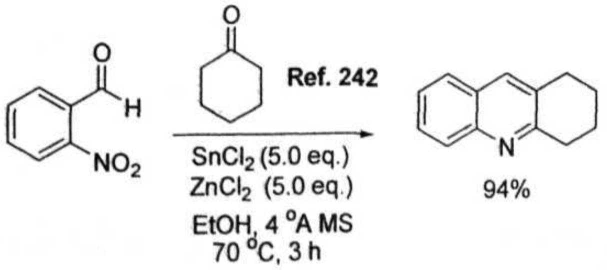
Cyclopenta[b]quinoline derivatives are yet another class of important molecules which are found to possess biological properties such as anti-inflammatory activity,[237] antimalarial activity,[238] cholinesterase inhibition activity.[239] Also, cyclopenta[b]quinoline moiety is present in certain natural products[240,241] such as isoschizogaline **(138)** and **isoschizogamine** **(139)** (Figure 10).

Figure 10



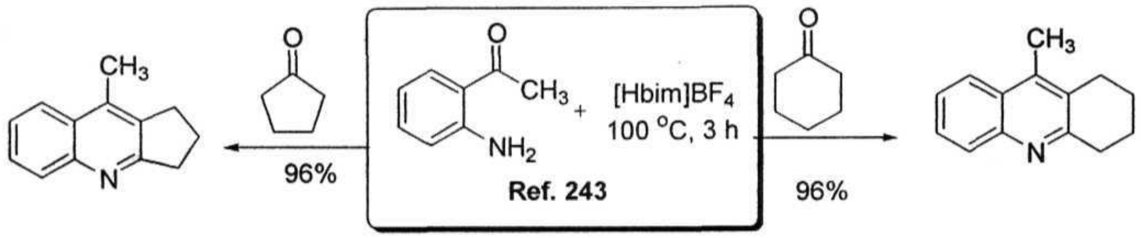
Owing to the biological importance of these molecules, development of simple and convenient methodologies for the synthesis of acridines and cyclopenta[b]quinolines constitutes an interesting and attractive endeavor in synthetic organic chemistry and in fact a number of methods were reported in the literature.[242-249] Some of the important and recent methods are presented in this section.

Miller and McNaughton[242] have developed a mild and efficient one-step synthesis of 1,2,3,4-tetrahydroacridines from 2-nitrobenzaldehydes and cyclohexanone under the influence of $SnCl_2$ and $ZnCl_2$ (one representative example is presented in eq 41). Later on, Srinivasan and co-workers[243] have reported the synthesis of 1,2,3,4-tetrahydroacridines and cyclopenta[b]quinolines *via* reaction of *o*-amino substituted aromatic carbonyls with cyclic ketones in ionic liquid medium. Representative examples are presented in Scheme 56.

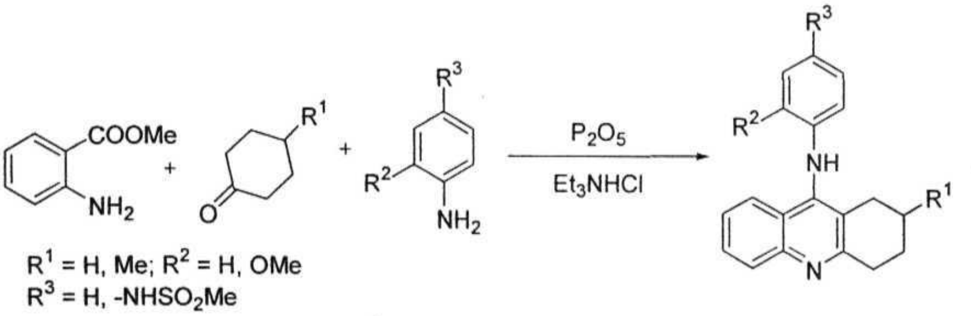


eq 41

Scheme 56



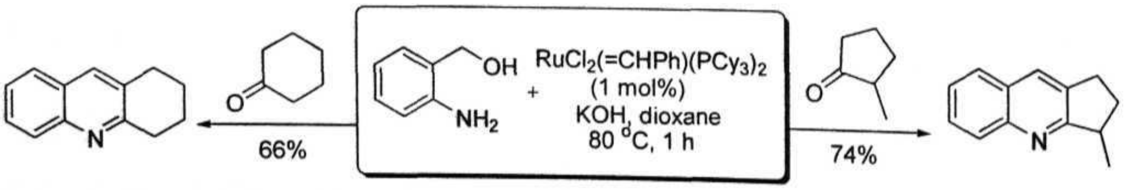
Eggert and co-workers have reported the synthesis of a series of 9-arylamino-1,2,3,4-tetrahydroacridiries following the reaction conditions as shown in eq 42 and studied their properties towards intercalative binding to DNA.[244]



eq 42

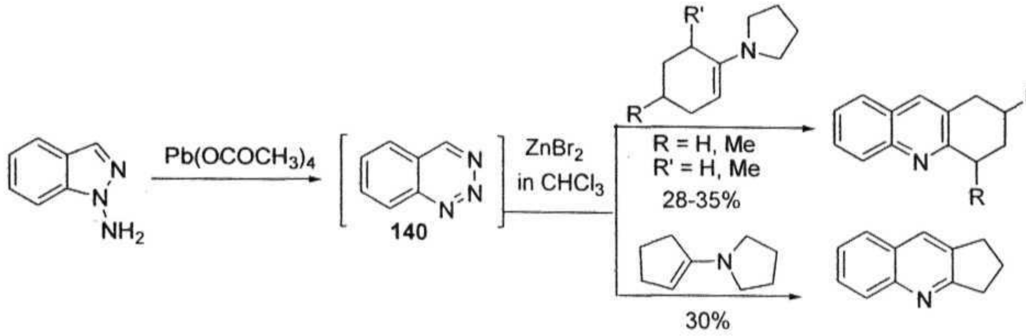
An interesting synthesis of 1,2,3,4-tetrahydroacridine derivatives *via* ruthenium-catalyzed oxidative cyclization of 2-aminobenzylalcohol with various cyclohexanones was reported by Cho and co-workers.[245] They have also reported the synthesis of cyclopenta[b]quinolines from cyclopentanones.[245] Representative examples are shown in the Scheme 57.

Scheme 57

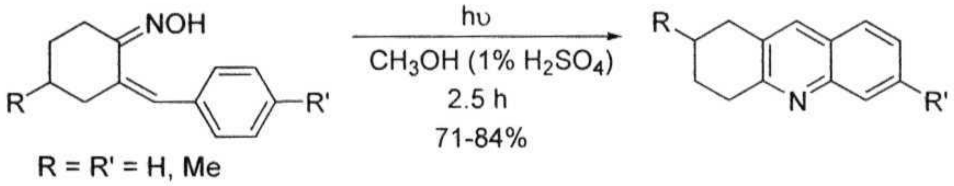


Koyama and co-workers have reported an interesting synthesis of 1.2 3 4-tetrahydroacridines and cyclopenta[b]quinoline derivative *via* Diels-Alder reaction of *in* *situ* generated 1,2,3-benzotriazine (140) with enamines derived from cyclohexanone and cyclopentanone derivatives respectively (Scheme 58).[246]

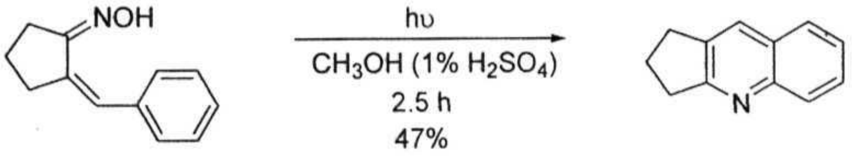
Scheme 58



Olsen[247] has developed a synthesis of 1,2,3,4-tetrahydroacridines *via* photocyclization of benzalcyclohexanone oximes in acidic methanol (eq 43). They also reported the corresponding photocyclization of benzalcyclopentanone oxime to provide cyclopenta[b]quinoline derivative (eq 44).

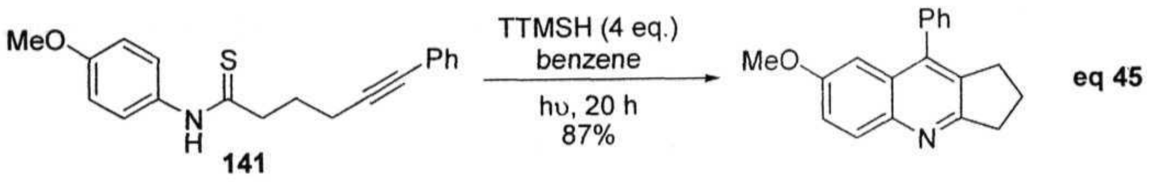


eq 43

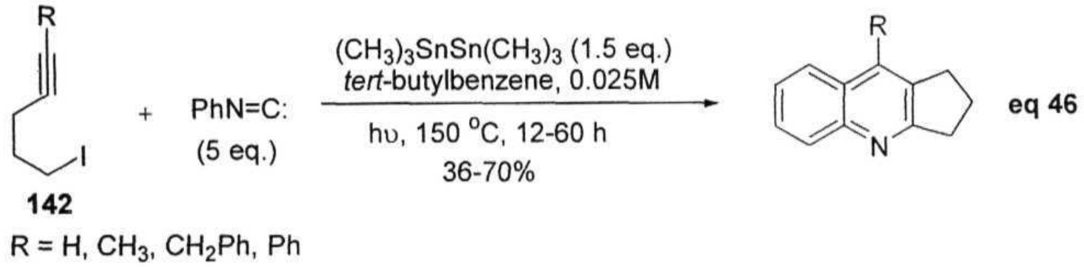


eq 44

An important tandem radical cyclization of suitably substituted thioamides (141) by exposure to *tris*(trimethylsilyl)silane (TTMSH) and UV light leading to the formation of cyclopenta[b]quinoline derivatives was described by Curran and Du (eq 45). One representative example is shown in eq 45.

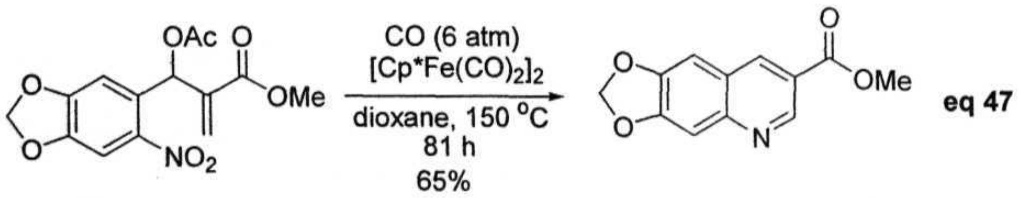


Curran and Liu[249] have reported a simple route to substituted 2,3-dihydro-1*H*-cyclopenta[b]quinolines *via* the [4+1] radical annulations of 1-substituted-5-iodo-1-pentynes (142) with phenylisocyanide in the presence of hexamethylditin (eq 46).



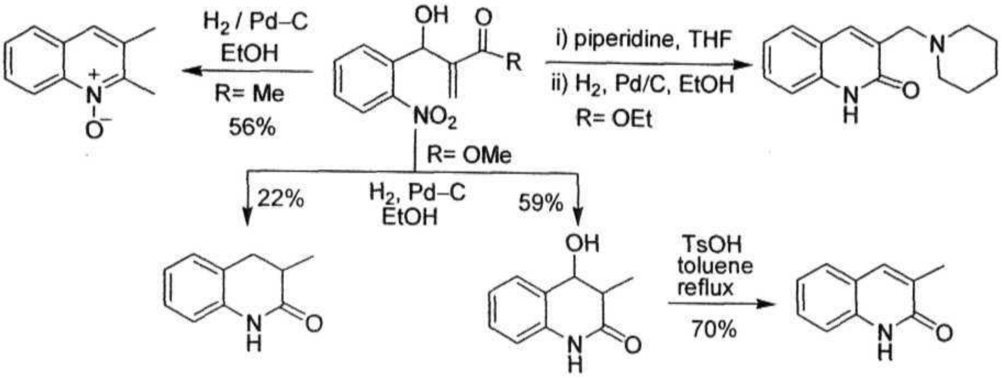
Applications of the Baylis-Hillman adducts for synthesis of various quinoline derivatives have been well documented.[250,255] Some of the recent and important methodologies are presented in the following.

Nicholas and O'Dell[250] have reported the synthesis of 3-substituted quinolines *via* transition metal catalyzed reductive cyclization of the acetates of Baylis-Hillman adducts derived from 2-nitrobenzaldehydes and methyl acrylate. One representative example is shown in eq 47.



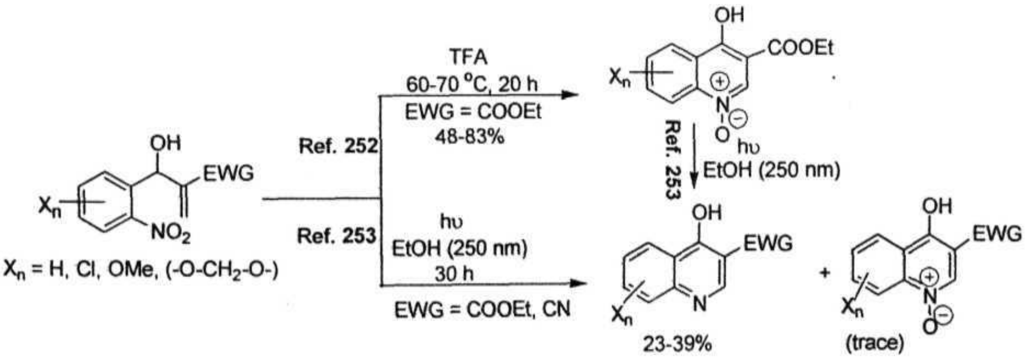
Kaye and co-workers[251] have reported an interesting transformation of the Baylis-Hillman adducts, derived from *o*-nitrobenzaldehyde and acrylates/alkyl vinyl ketones, into quinoline derivatives *via* catalytic hydrogenation using Pd/C as described in Scheme 59.

Scheme 59



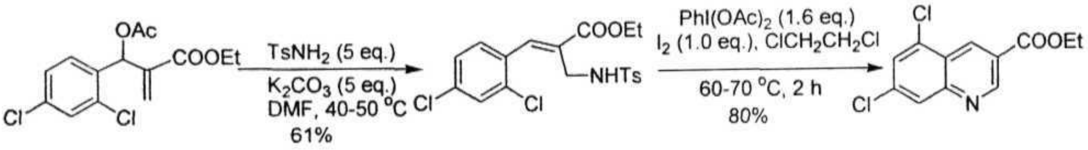
Kim and co-workers[252] have transformed the Baylis-Hillman adducts obtained from *o*-nitrobenzaldehydes and ethyl acrylate into 3-ethoxycarbonyl-4-hydroxyquinoline *N*-oxides *via* the treatment with TFA at 60-70 °C. Subsequently, they have also reported a photochemical method for the synthesis of 4-hydroxyquinolines (Scheme 60).[253]

Scheme 60



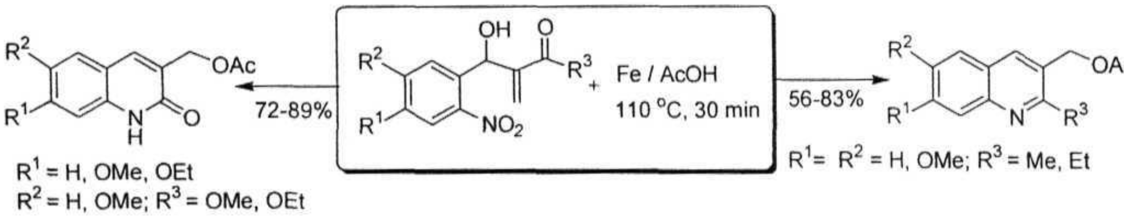
Kim et al.[254] also reported the synthesis of quinoline derivatives from the Baylis-Hillman acetates *via* the oxidative cyclization using $PhI(OAc)_2$ following the reaction sequence as shown in Scheme 61 (one representative example is presented).

Scheme 61



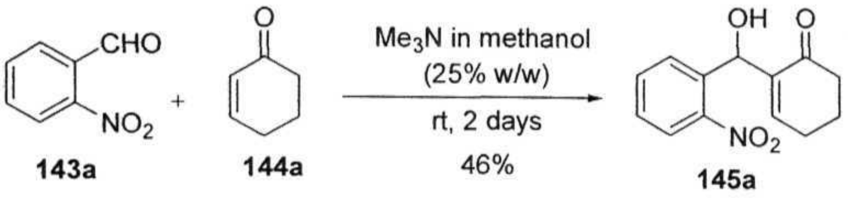
Recently, our research group have reported a simple synthesis of functionalized (1*H*)-quinol-2-ones and substituted quinolines from the Baylis-Hillman adducts (derived by the reaction of 2-nitrobenzaldehydes with alkyl acrylates and alkyl vinyl ketones respectively) *via* the treatment with Fe/AcOH (Scheme 62).[255]

Scheme 62



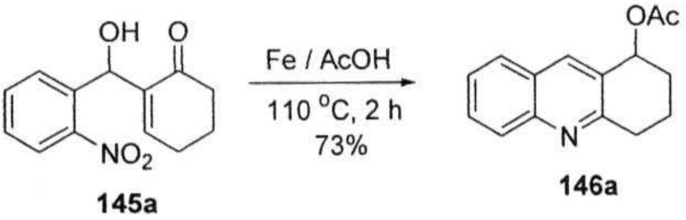
Though the applications of the Baylis-Hillman alcohols for synthesis of quinoline derivatives have been well documented, applications of the Baylis-Hillman alcohols for synthesis of acridine and cyclopenta[b]quinoline derivatives have not been examined. Therefore, we have undertaken a research project in this direction. It occurred to us that the Baylis-Hillman adducts derived from various 2-nitrobenzaldehydes and cycloalk-2-enones could be easily transformed into acridines and cyclopenta[b]quinolines by treatment with Fe/AcOH in one-pot operation. In this direction, we first selected 2-[hydroxy(2-nitrophenyl)methyl]cyclohex-2-enone (145a) for reductive cyclization with Fe powder in AcOH. The required Baylis-Hillman alcohol, 2-[hydroxy(2-nitrophenyl)methyl]cyclohex-

2-enone **(145a)**[¥] was prepared from 2-nitrobenzaldehyde and cyclohex-2-enone under **the** influence of Me_3N in methanol according to known procedure developed by our group (eq 48, Table 5).[256]



eq 48

We have then carried out the reductive cyclization of 2-[hydroxy(2-nitrophenyl)-methyl]cyclohex-2-enone **(145a)** with Fe/AcOH under various conditions. The best results were obtained when the Baylis-Hillman alcohol **(145a)** was treated with Fe powder in acetic acid al 110 °C for 2 h, thus providing the desired adduct 1-acetoxy-1,2,3,4-tetrahydroacridine **(146a)**[¥] in 73% yield (eq 49, Table 6). Structure of this molecule was confirmed by IR, ^1H NMR (Spectrum 9), ^{13}C NMR (Spectrum 10), mass spectral data and elemental analysis.



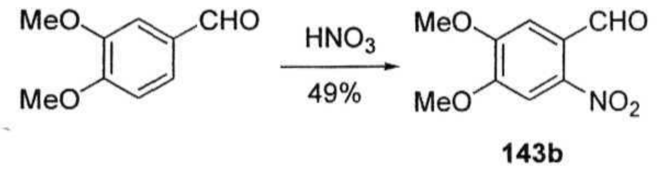
eq 49

Encouraged by the result, we extended this methodology to various Baylis-Hillman alcohols **(145b-d),** obtained from representative 2-nitrobenzaldehydes **(143b-d)** and cyclohex-2-enone **(144a).** The required 2-nitrobenzaldehydes **(143b-d)** were prepared *via* the nitration of the corresponding benzaldehydes i.e., 3,4-dimethoxybenzaldehyde (eq 50),

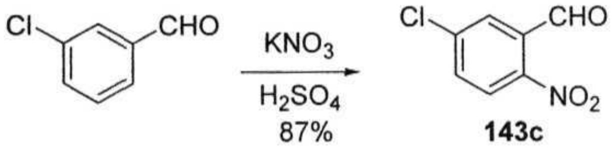
---

For continuity and easy understanding, the Baylis-Hillman alcohols obtained form 2-nitrobenzaldehydes (143a-d) and cyclohex-2-enone (144a) were numbered as 145a-d. The acridine derivatives from 145a-d were numbered as 146a-d.

3-chlorobenzaldehyde (eq 51) and 4-ethoxy-3-methoxybenzaldehyde (Scheme 63), according to the known procedures.[257,258] The required 4-ethoxy-3-methoxybenzaldehyde was prepared *via* the treatment of vanillin with ethyl bromide in the presence of K_2CO_3 (Scheme 63).

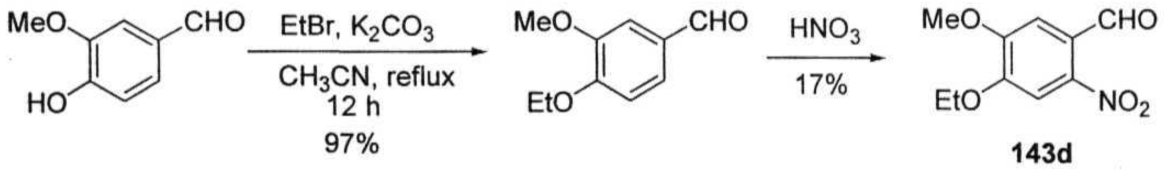


eq 50

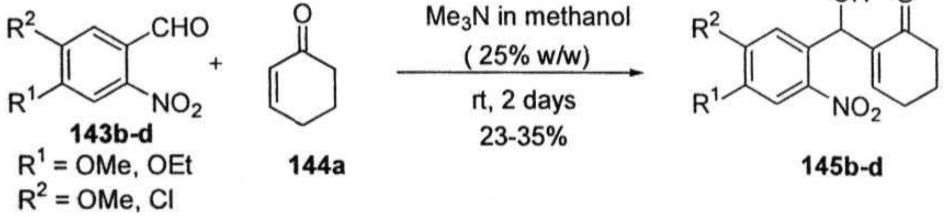


eq 51

Scheme 63



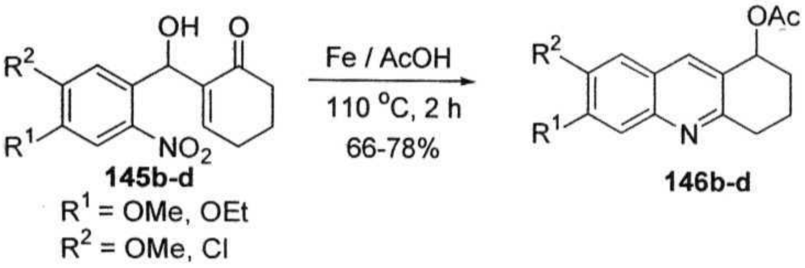
The Baylis-Hillman alcohols **(145b-d)** were obtained *via* the reaction of 2-nitrobenzaldehydes **(143b-d)** with cyclohex-2-enone **(144a)** under the influence of Me_3N in methanol (eq 52, Table 5).



eq 52

Subsequent treatment of these Baylis-Hillman alcohols **(145b-d)** with Fe/AcOH at 110 °C for 2 h, provided the desired 1,2,3,4-tetrahydroacridines **(146b-d)** in 66-78 % yields (eq 53,

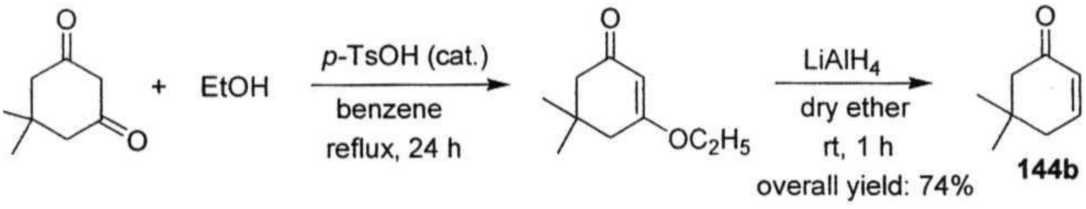
Table 6). Structures of these molecules were confirmed by IR, ^1H NMR (See: Spectrum 11 for molecule **146c),** ^{13}C NMR (See: Spectrum 12 for molecule **146c)** spectral data and elemental analyses.



eq 53

With a view to understand the generality of this methodology, we have extended this strategy to the Baylis-Hillman adduct obtained from other cyclic enone, 5,5-dimethyl cyclohex-2-enone **(144b)** and 2-nitrobenzaldehyde **(143a).** The required 5,5-dimethyl cyclohex-2-enone **(144b)** was prepared according to the known procedure (Scheme 64).[259]

Scheme **64**



The Baylis-Hillman reaction between 2-nitrobenzaldehyde **(143a)** and 5,5-dimethyl cyclohex-2-enone **(144b)** under the influence of Me_3N in methanol provided 5,5-dimethyl-2-[hydroxy(2-nitrophenyl)methyl]cyclohex-2-enone **(147a)**[§] (Scheme 65, Table 5). Subsequent treatment of this molecule with Fe/AcOH at 110 °C for 2 h, furnished the desired product 1-acetoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridine **(148a)**[§] in 82% yield

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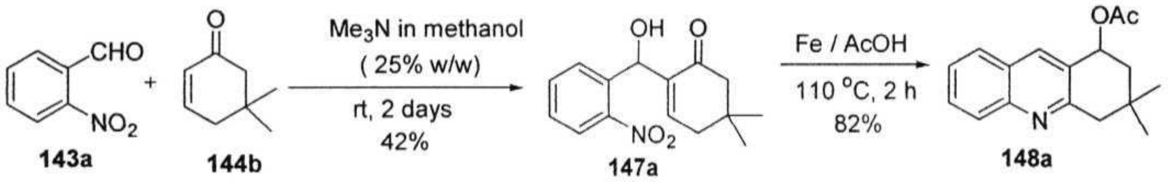
[§] For continuity and easy understanding, the Baylis-Hillman alcohols obtained form 2-nitrobenzaldehydes **(143a-c)** and 5,5-dimethylcyclohex-2-enone **(144b)** were numbered as **147a-c.** The acridine derivatives from **147a-c** were numbered as **148a-c.**

after the usual work-up and purification by silica gel column chromatography (Scheme 65, Table 6). Structure of this molecule was confirmed by IR, ^1H NMR (Spectrum 13), ^{13}C NMR (Spectrum 14), mass spectral data and elemental analysis.

Scheme 65



We later on extended this methodology to other Baylis-Hillman alcohols **(147b,c)** obtained *via* the reaction of 4,5-dimethoxy-2-nitrobenzaldehyde (143b) and 5-chloro-2-nitrobenzaldehyde **(143c)** with 5,5-dimethylcyclohex-2-enone **(144b)** under the influence of Me_3N in methanol. Treatment of these Baylis-Hillman alcohols **(147b,c)** (Scheme 66, Table 5) with Fe/AcOH at 110 °C for 2 h, provided the desired adducts 1-acetoxy-6,7-dimethoxy-3,3-dimethyl-l,2,3,4-tetrahydroacridine **(148b)** and l-acetoxy-7-chloro-3,3-dimethyl-l,2,3,4-tetrahydroacridine **(148c)** in 62% and 80% yields respectively (Scheme 66, Table 6). Structures of these molecules were confirmed by IR, ^1H NMR, ^{13}C NMR spectral data and elemental analyses.

Scheme 66

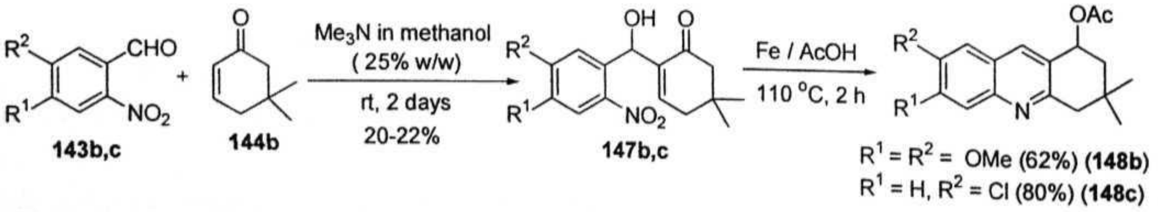
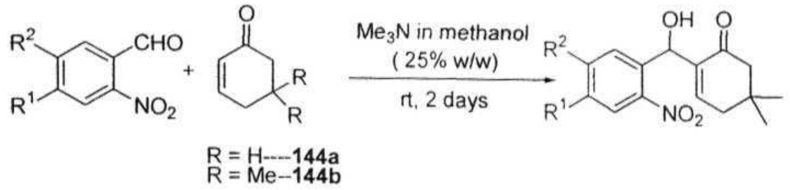


Table 5: Synthesis of **2-[hydroxy(2-nitroaryl)methyl]cyclohex-2-enones (145a-d, 147a-c)**[a]



Aldehyde	R^1	R^2	Cyclohexenone	Product[b]	Yield[c] (%)	Mp (°C)
143a	H	H	**144a**	**145a**	46	120-123
143b	OMe	OMe	**144a**	**145b**	35	112-114
143c	H	Cl	**144a**	**145c**	23	127-129
143d	OEt	OMe	**144a**	**145d**	29	138-142
143a	H	H	**144b**	**147a**	42	88-91
143b	OMe	OMe	**144b**	**147b**	20	155-158
143c	H	Cl	**144b**	**147c**	22	116-118

a) All reactions were carried out on 5 mmol scale of aldehyde with cyclohex-2-enone/5,5-dimethylcyclohex-2-enone (10 mmol) under the influence of methanolic trimethylamine (25% w/w) (5 mmol) at room temperature for 2 days.

b) All the compounds **145a-d, 147a-c** were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data.

c) Yields are of the pure products (based on aldehydes) after purification through silica gel column chromatography.

With a view to further confirm the structure, we could obtain the single crystal for the molecule 1-acetoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridine **(148a)** and the single crystal data clearly supports the proposed structure (Fig X2, Table 9).

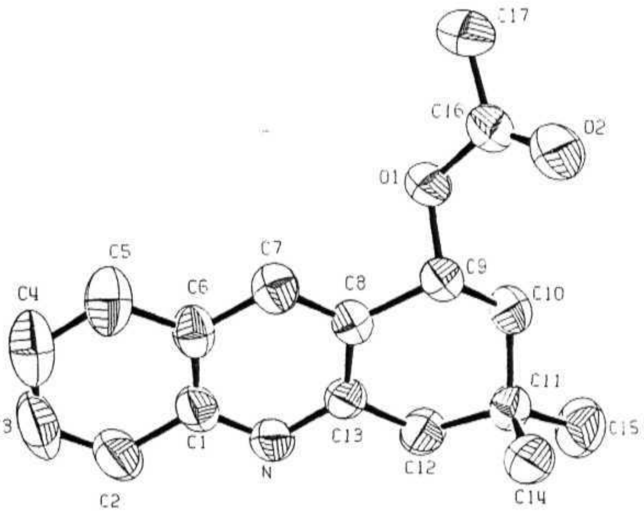
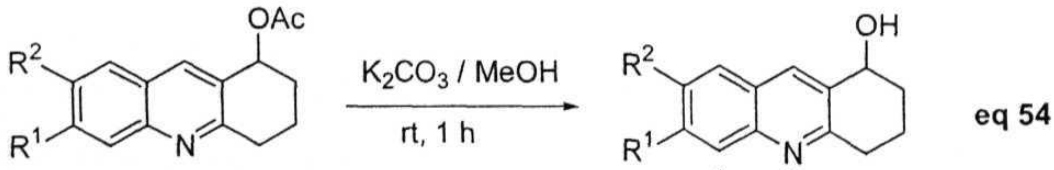


Figure X2: ORTEP diagram of compound **148a.**
(Hydrogen atoms were omitted for clarity)

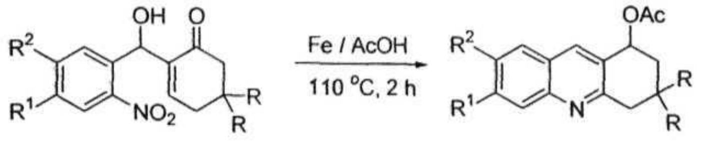
We have also transformed representative acetates **(146a)** and **(146b)** into the corresponding alcohols, 1-hydroxy-1,2,3,4-tetrahydroacridine **(149a)** and 6,7-dimethoxy-1-hydroxy-1,2,3,4-tetrahydroacridine **(149b)** by treating respectively with aqueous K_2CO_3/MeOH (eq 54). Structures of these molecules were confirmed by IR, ^{1}H NMR (See: Spectrum 15 for molecule **149a)**, ^{13}C NMR (See: Spectrum 16 for molecule **149a)** spectral data and elemental analyses.



146a ($R^1 = R^2 = H$)
146b ($R^1 = R^2 =$ OMe)

149a ($R^1 = R^2 = H$) 80%
149b ($R^1 = R^2 =$ OMe) 72%

Table 6: Synthesis of functionalized 1,2,3,4-tetrahydroacridines (146a-d, 148a-c)[a]



B-H alcohol	R^1	R^2	R	Product[b]	Yield[c] (%)	Mp (°C)
145a	H	H	H	**146a**[d]	73	71-73
145b	OMe	OMe	H	**146b**	76	98-100
145c	H	Cl	H	**146c**[d]	78	79-81
145d	OEt	OMe	H	**146d**	66	58-61
147a	H	H	Me	**148a**[d,e]	82	62-64
147b	OMe	OMe	Me	**148b**	62	112-115
147c	H	Cl	Me	**148c**[d]	80	124-126

a) All reactions were carried out on 1 mmol scale of Baylis-Hillman alcohol with Fe powder (6 mmol)/AcOH (5 mL) at reflux for 2 h.

b) All the compounds **146a-d, 148a-c** were obtained as solids and were characterized by IR, ^1H NMR (200 MHz / 400 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.

c) Yields are of the pure products (based on alcohols) after purification through silica gel column chromatography.

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

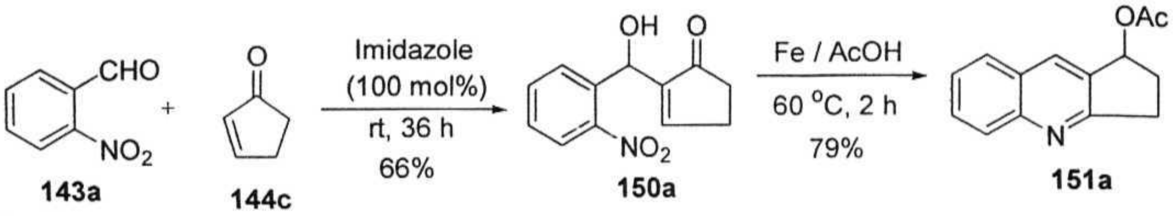
e) The structure of this molecule was also established from the single crystal X-ray data.

Synthesis of cyclopenta[b]quinolines:

We next planned to extend this methodology to the Baylis-Hillman alcohols derived from 2-nitrobenzaldehydes and cyclopent-2-enone with a view to develop a simple methodology for synthesis of cyclopenta[b]quinoline derivatives. We have therefore, first selected, 2-

[hydroxy(2-nitrophenyl)methyl]cyclopent-2-enone **(150a)** for reductive cyclization. This molecule 150a was prepared *via* the Baylis-Hillman reaction between 2-nitrobenzaldehyde **(143a)** and cyclopent-2-enone **(144c)** (Scheme 67, Table 7) according to the known procedure.[260] Subsequent treatment of this Baylis-Hillman alcohol (150a)® with Fe/AcOH at 60 °C for 2 h (the reaction was not clean at reflux) provided the desired adduct, 1-acetoxy-2,3-dihydro-1*H*-cyclopenta[b]quinoline (151a)® in 79% isolated yield (Scheme 67, Table 8). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 17), ^{13}C NMR (Spectrum 18) spectral data and elemental analysis.

Scheme 67



Encouraged by this result, we have prepared the representative Baylis-Hillman alcohols, 2-[hydroxy(2-nitroaryl)methyl]cyclopent-2-enones **(150b-d)** (Scheme 68, Table 7), *via* the reaction between 2-nitrobenzaldehydes **(143b-d)** and cyclopent-2-enone **(144c)** under the influence of imidazole. Subsequent reaction of these molecules **(150b-d)** with Fe/AcOH at 60 °C for 2 h, provided the desired substituted 1-acetoxy-2,3-dihydro-1*H*-cyclopenta-[b]quinolines **(151b-d)** in 61-74% yields (Scheme 68, Table 8). Structures of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analyses.

® For continuity and easy understanding, the Baylis-Hillman alcohols obtained form 2-nitrobenzaldehydes (143a-d) and cyclopent-2-enone (144c) were numbered as 150a-d. The cyclopenta[b]quinoline derivatives from 150a-d were numbered as **151a-d**.

Scheme 68

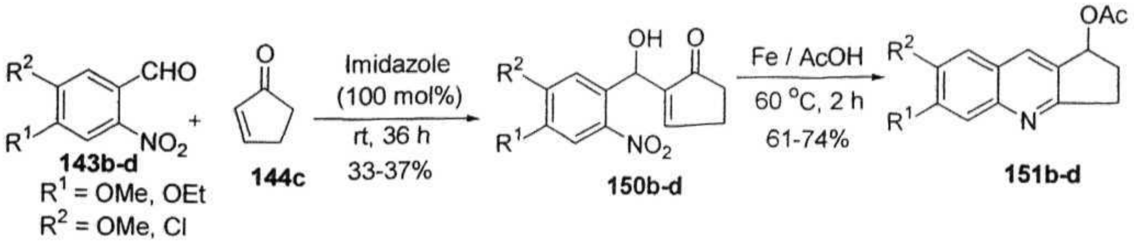
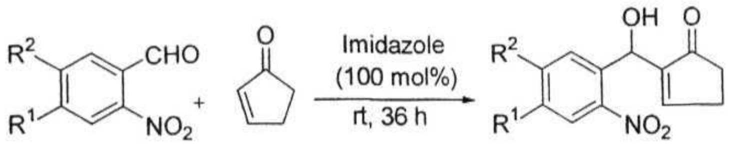


Table 7: Synthesis of 2-[hydroxy(2-nitroaryl)methyl]cyclopent-2-enones (**150a-d**)[a,b,c]

<table>
<tr><td colspan="6"> </td></tr>
<tr><th>Aldehyde</th><th>R¹</th><th>R²</th><th>Product</th><th>Yield^c (%)</th><th>Mp (°C)</th></tr>
<tr><td>143a</td><td>H</td><td>H</td><td>150a</td><td>66</td><td>98-100</td></tr>
<tr><td>143b</td><td>OMe</td><td>OMe</td><td>150b</td><td>37</td><td>125-127</td></tr>
<tr><td>143c</td><td>H</td><td>Cl</td><td>150c</td><td>35</td><td>112-114</td></tr>
<tr><td>143d</td><td>OEt</td><td>OMe</td><td>150d</td><td>33</td><td>140-142</td></tr>
</table>

a) All the reactions were carried out on 2.5 mmol scale of 2-nitrobenzaldehyde with cyclopent-2-enone (2.75 mmol) under the influence of imidazole (2.5 mmol) in aqueous THF (5+5 mL) at room temperature for 36 h.

b) All compounds 150a-d were obtained as solids and were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data.

c) Yields are of the pure products (based on aldehydes) after purification through silica gel column chromatography.

A plausible mechanism for the formation of 1,2,3,4-tetrahydroacridines and cyclopenta-[b]quinolines is presented in the Scheme 69.

Scheme 69

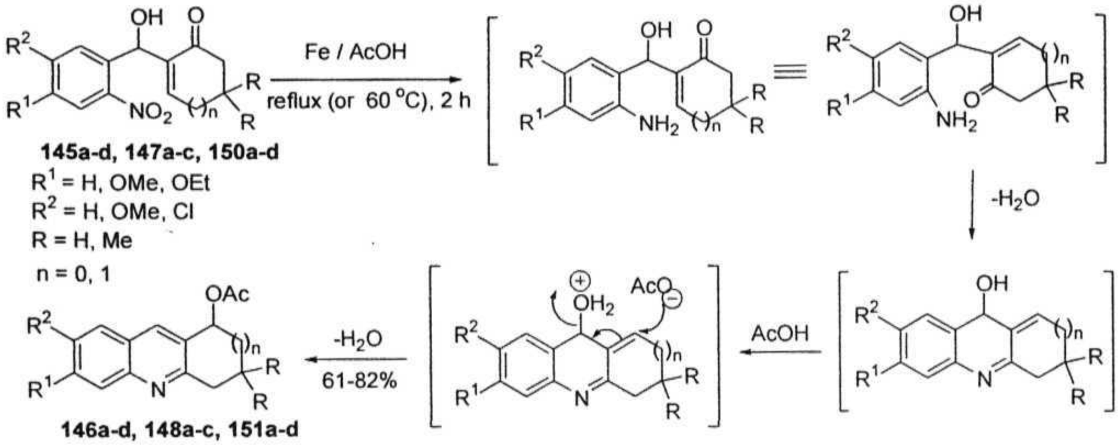
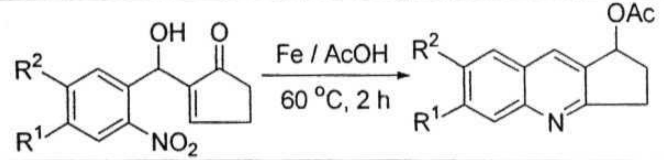


Table 8: Synthesis of functionalized cyclopenta[b]quinolines (**151a-d**)^{a,b}



B-H alcohol	R^{1}	R^{2}	Product	Yield^{c} (%)	Mp (°C)
150a	H	H	**151a**	79	-
150b	OMe	OMe	**151b**^{d}	63	108-111
150c	H	Cl	**151c**	74	90-92
150d	OEt	OMe	**151d**^{d}	61	97-99

a) All reactions were carried out on 1 mmol scale of Baylis-Hillman alcohol with Fe powder (6 mmol)/AcOH (5 mL) at 60 °C for 2 h [reactions were not clean at reflux].

b) The compounds **151b-d** were obtained as solids while the compound **151a** was obtained as a viscous liquid. All the compounds **151a-d** were characterized by IR, ^{1}H NMR (200 MHz / 400 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.

c) Yields are of the pure products (based on alcohols) after purification through silica gel column chromatography.

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

Table 9. Crystal data and structure refinement for 148a

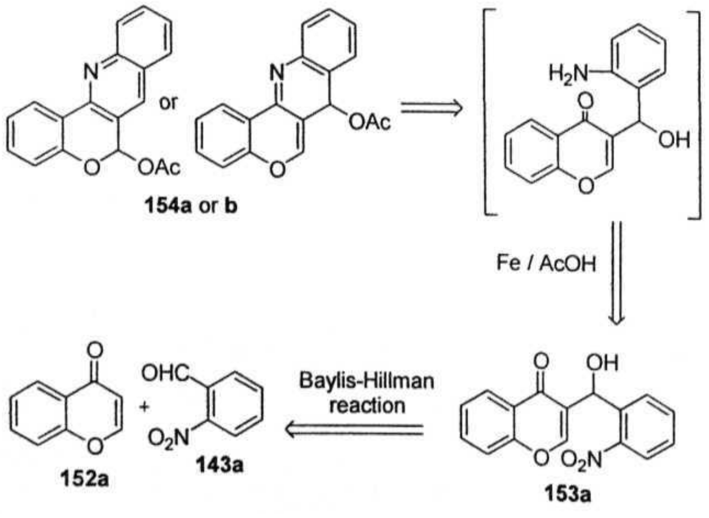
Identification code	:148a
Empirical formula	: $C_{17}H_{19}NO_2$
Formula weight	: 269.33
Temperature	: 293(2) K
Wavelength	: 0.71073 A
Crystal system	: Triclinic
Space group	: P-1 (International Table No. 2)
Unit cell dimenions	: a = 9.2092(9) A; alpha = 95.221(12) deg.
	: b = 11.5236(12) A; beta= 106.244(13) deg.
	: c = 16.450(3) A; gamma=113.528(9) deg.
Volume	: 1495.4(4) A^3
Z, Calculated density	: 1, 1.196 Mg/m^3
Absorption coefficient	: 0.078 mm^{-1}
F(000)	:576
Crystal size	: 0.6 x 0.5 x 0.4 mm
Theta range for data collection	: 1.32 to 27.47 deg.
Limiting indices	: $0 < h < 13, 0 \leq k \leq 15, -14 \leq l \leq 13$
Reflections collected / unique	: 6827 / 6827 [R(int) = 0.0000]
Completeness to theta = 27.47	: 100.0%
Absorption correction	: none
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 6827 / 0 / 362
Goodness-of-fit on F^2	: 1.149
Final R indices [I>3sigma(I)]	: R1 = 0.0565, wR2 = 0.1068
R indices (all data)	: R1 = 0.1353, wR2 = 0.1806
Extinction coefficient	: 0.007(6)
Largest diff. peak and hole	: 0.20 and -0.15 e. A^{-3}

In conclusion, we have successfully developed a simple, convenient one-pot procedure for the synthesis of substituted 1,2,3,4-tetrahydroacridines and cyclopenta[b]quinolines from the Baylis-Hillman alcohols, obtained from various 2-nitrobenzaldehydes and cyclohex-2-enone/5,5-dimethylcyclohex-2-enone and Baylis-Hillman alcohols, derived from 2-nitrobenzaldehydes and cyclopent-2-enone, respectively *via* the reductive cyclization using Fe/AcOH.

Application of Baylis-Hillman alcohols: One-pot synthesis of 3-benzoylquinolines

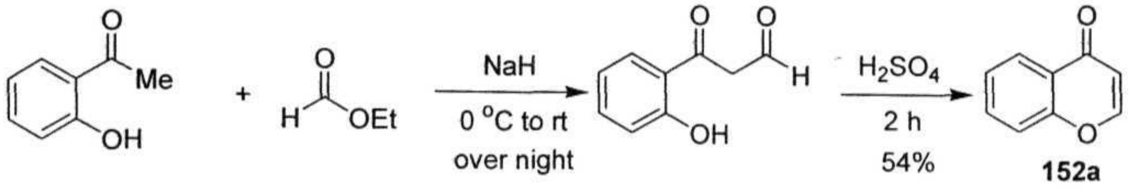
Our successful work on the synthesis 1,2,3,4-tetrahydroacridines and cyclopenta[b]quinolines led us to examine the possibility of synthesizing the tetracyclic heterocyclic molecules **154a** or **b** *via* reductive cyclization of the Baylis-Hillman adduct, 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one **(153a)** derived from 2-nitrobenz-aldehyde **(143a)** and 1-benzopyran-4(4*H*)-one **(152a)** using Fe/AcOH (according to the retrosynthetic pathway as described in Scheme 70).

Scheme 70



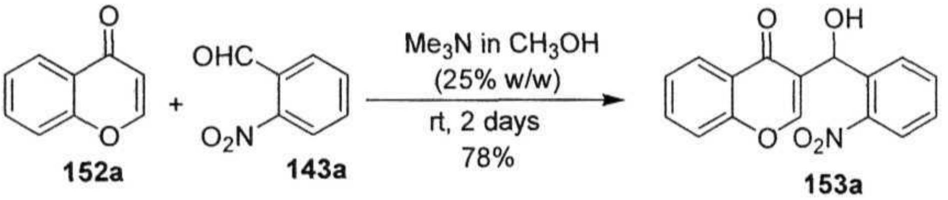
The required chromone derivative, 1-benzopyran-4(4*H*)-one **(152a)** was prepared according to the known procedure (Scheme 71).[261]

Scheme 71



152a

Treatment of the activated alkene **152a** with 2-nitrobenzaldehyde **(143a)** under the influence of methanolic trimethylamine according to the procedure developed in our laboratory furnished the required Baylis-Hillman alcohol, 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one **(153a)*** (eq 55, Table 10).[39]



eq 55

Our attempts to synthesize the tetracyclic heterocyclic molecule **154a** or **b** *via* the reductive cyclization of the Baylis-Hillman alcohol **153a,** with Fe/AcOH under various conditions were not successful. Instead, to our surprise, 3-(2-hydroxyphenyl)carbonylquinoline or [3-(2-hydroxybenzoyl)quinoline] **(155a)** was obtained. Thus, treatment of the Baylis-Hillman alcohol, 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one **(153a)** with Fe/AcOH at reflux for 2 h, provided 3-(2-hydroxyphenyl)carbonylquinoline **(155a)*** in **56% yield**

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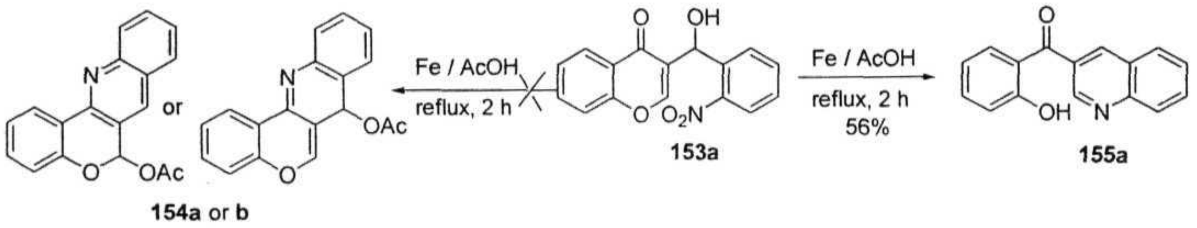
* For continuity and easy understanding, the Baylis-Hillman alcohols obtained form 2-nitrobenzaldehydes (**143a,c,e**) and 1-benzopyran-4(4*H*)-one (152a) were numbered as 153a-c. The quinoline derivatives from **153a-c** were numbered as 155a-c.

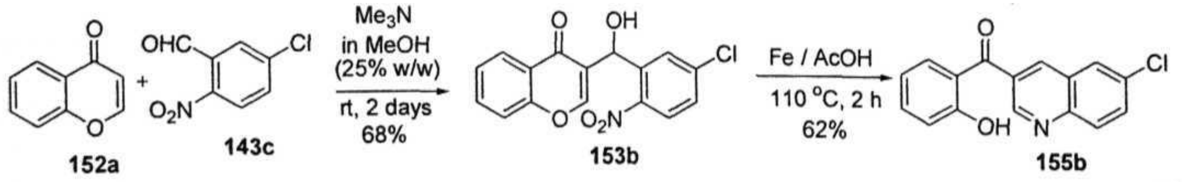
(Scheme 72, Table 11). The structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 19), ^{13}C NMR (Spectrum 20), mass spectral data and elemental analysis.

Scheme 72



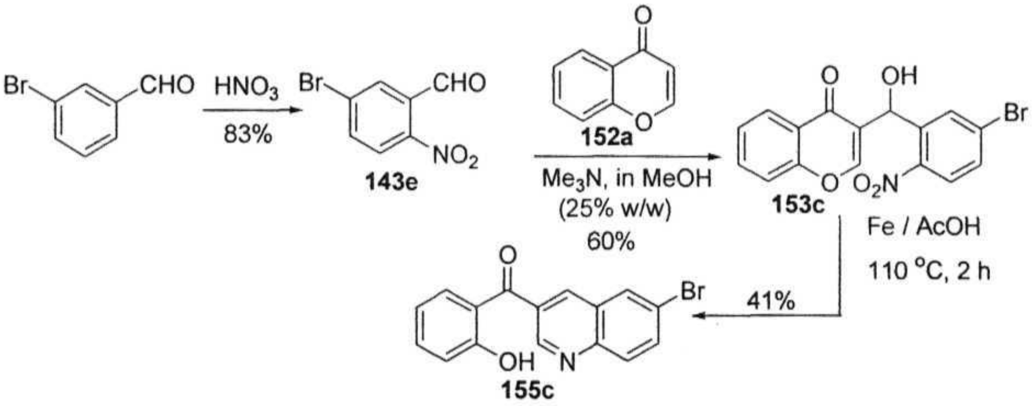
This reaction was encouraging in the sense that this strategy provides the quinoline derivatives containing 3-benzoyl substitution. With a view to understand the generality of this reaction, we extended this methodology to the Baylis-Hillman alcohol, 3-[hydroxy(5-chloro-2-nitrophenyl)methyl]-4*H*-chromen-4-one **(153b)** (Scheme 73, Table 10), obtained from 5-chloro-2-nitrobenzaldehyde **(143c)** and 1-benzopyran-4(4*H*)-one **(152a).** Reductive cyclization of the Baylis-Hillman alcohol **(153b),** with Fe/AcOH provided, 6-chloro-3-(2-hydroxyphenyl)carbonylquinoline **(155b)** in 62% isolated yield (Scheme 73, Table 11). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.

Scheme 73



We then extended this strategy to the Baylis-Hillman alcohol, 3-[hydroxy(5-bromo-2-nitrophenyl)methyl]-4*H*-chromen-4-one **(153c)** (Scheme 74, Table 10), obtained *via* **the reaction** of 5-bromo-2-nitrobenzaldehyde **(143e)** with 1-benzopyran-4(4*H*)-one **(152a). The** required 5-bromo-2-nitrobenzaldehyde **(143e)** was prepared *via* the nitration of 3-bromobenzaldehyde following the literature procedure (Scheme 74).[258] Treatment of Baylis-Hillman alcohol **153c,** with Fe/AcOH provided, 6-bromo-3-(2-hydroxyphenyl)carbonylquinoline **(155c)** in 41% isolated yield (Scheme 74, Table 11). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 21), ^{13}C NMR (Spectrum 22), mass spectral data and elemental analysis.

Scheme 74

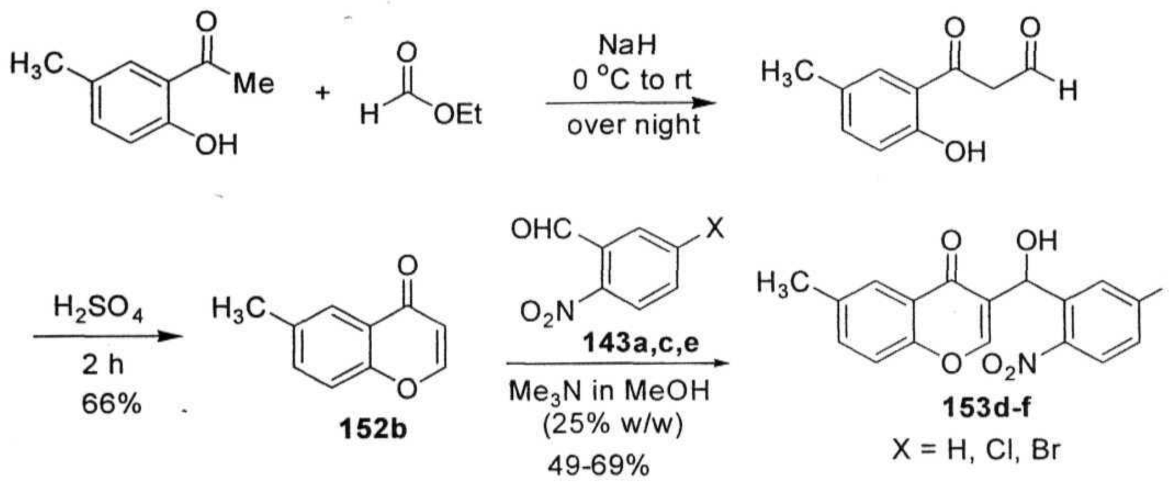


With a view to understand the generality of this methodology, we have planned to examine the possible application of 3-[hydroxy(2-nitroaryl)methyl]-6-methyl-4*H*-chromen-4-ones **(153d-f),** the Baylis-Hillman alcohols obtained from 6-methyl-1-benzopyran-4(4*H*)-one **(152b)** and 2-nitrobenzaldehyde derivatives **(143a,c,e)** for the preparation of the corresponding 3-aroylquinolines (Scheme 75).

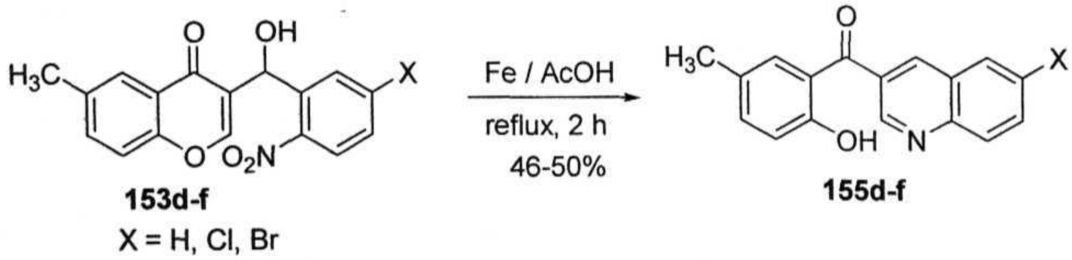
The required chromone derivative, 6-methyl-1-benzopyran-4(4*H*)-one **(152b)** was prepared according to literature procedure (Scheme 75).[261] We have prepared three representative

Baylis-Hillman alcohols **(153d-f)**[$] *via* the reaction of 6-methyl-1-benzopyran-4(4*H*)-one **(152b)** with 2-nitrobenzaldehydes **(143a,c,e)** (Scheme 75, Table 10).

Scheme 75



We then successfully converted the Baylis-Hillman alcohols **153d-f,** *via* the reaction with Fe/AcOH at reflux for 2 h, into the desired 3-benzoylquinoline derivatives **155d-f** in 46-50% yields (eq 56, Table 11). Structures of these molecules were confirmed by IR, ^{1}H NMR (See: Spectrum 23 for molecule **155d),** ^{13}C NMR (See: Spectrum 24 for molecule **155d)** spectral data and elemental analyses.



eq 56

[$] For continuity and easy understanding, the Baylis-Hillman alcohols obtained form 2-nitrobenzaldehydes **(143a,c,e)** and 6-methyl-benzopyran-4(4*H*)-one **(152b)** were numbered as 153d-f. The quinoline derivatives from **153d-f** were numbered as **155d-f.**

We have also established the structure for the molecule, 6-bromo-3-(2-hydroxy-5-methylbenzoyl)quinoline **(155f)** by single crystal X-ray data (Figure X3, Table 12).

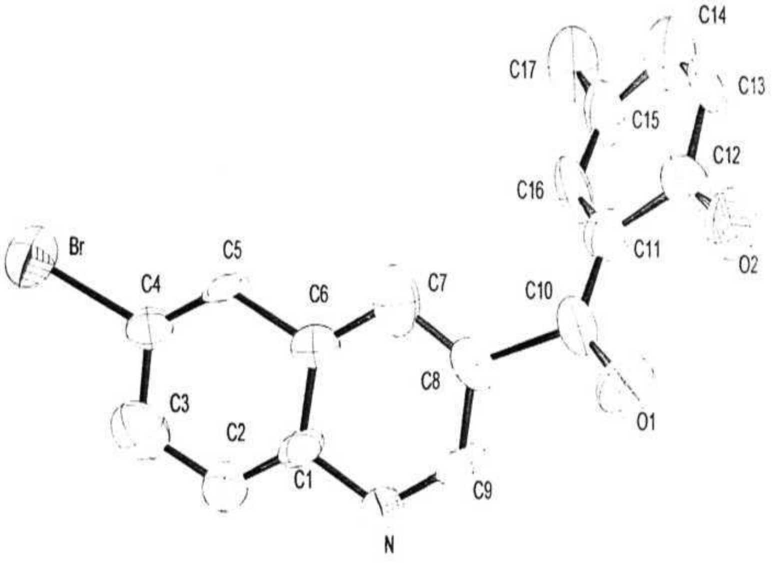


Figure X3: ORTEP diagram of compound **155f.**
(Hydrogen atoms were omitted for clarity)

A plausible mechanism for the formation of 3-benzoylquinolines (155a-f) is presented in Scheme 76. The reaction is believed to proceed through the formation of tetracyclic system C, which might form through pyran moiety (oxonium ion) A or **B** *(via* the nucleophilic attack of amine onto the oxonium ion). Finally, the tetracyclic system C, which is like O-C-N system, might cleave to provide the 3-benzoylquinoline derivatives **(155a-f).** These results also suggest that the usual Schiff s base formation could not be possible because of formation of pyran system (oxonium ion) (A or B) in the reaction.

Scheme 76

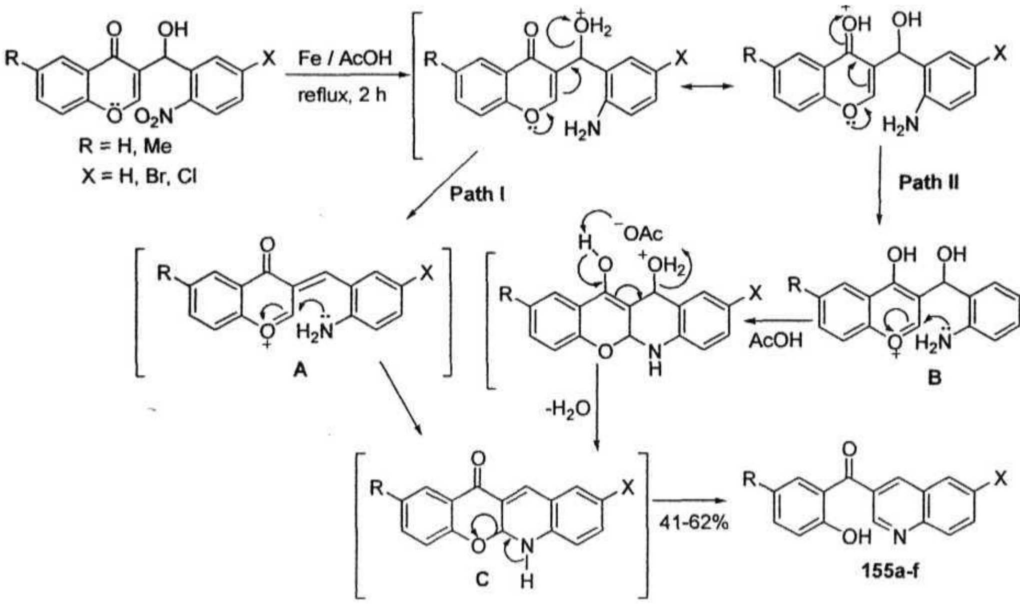
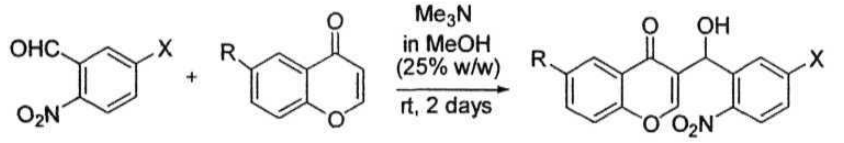


Table 10: Synthesis of 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones (153a-f)[a,b]



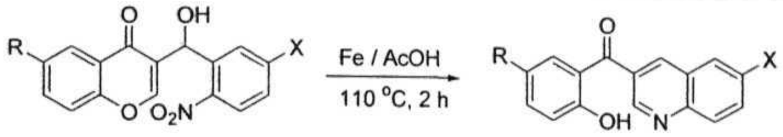
Aldehyde	X	Chromone	R	Product[b]	Yield[c] (%)	Mp (°C)
143a	H	**152a**	H	**153a**	78	148-151
143c	Cl	**152a**	H	**153b**	68	165-168
143e	Br	**152a**	H	**153c**	60	151-154
143a	H	**152b**	Me	**153d**	69	168-170
143c	Cl	**152b**	Me	**153e**	49	139-141
143e	Br	**152b**	Me	**153f**	52	145-147

a) All the reactions were carried out on 2 mmol scale of aldehyde with 1-benzopyran-4(4*H*)-one (**152a**) (2 mmol)/6-methyl-1-benzopyran-4(4*H*)-one (**152b**) (2 mmol) under the influence of methanolic trimethylamine (25% w/w) (2 mmol) at room temperature for 2 days.

b) All compounds **153a-f** were characterized by IR, ^{1}H NMR (400 MHz), ^{13}C NMR (50 MHz/100 MHz) spectral data.

c) Yields are of the pure products after purification through silica gel column chromatography.

Table 11: Synthesis of functionalized 3-benzoylquinolines (155a-f)[a]



B-H alcohol	R	X	Product[b]	Yield[c] (%)	Mp. (°C)
153a	H	H	**155a**[d]	56	70-73
153b	H	Cl	**155b**	62	116-119
153c	H	Br	**155c**[d]	41	119-121
153d	Me	H	**155d**[d]	50	79-81
153e	Me	Cl	**155e**[d]	48	116-118
153f	Me	Br	**155f**[e]	46	123-125

a) All reactions were carried out on 1 mmol scale of Baylis-Hillman alcohol with Fe powder (6 mmol)/AcOH (5 mL) at reflux for 2 h.

b) All the compounds **155a-f** were obtained as solids and were characterized by IR, ^{1}H NMR (400 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.

c) Yields are of the pure products (based on alcohols) after purification through silica gel column chromatography.

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

e) The structure of this molecule was also established from the single crystal X-ray data.

In conclusion, we have developed a simple and convenient methodology **for** synthesis of functionalized 3-(2-hydroxyaryl)carbonylquinoline derivatives from the Baylis-Hillman adducts, derived from chromones and 2-nitrobenzaldehydes, *via* **the treatment with** Fe/AcOH.

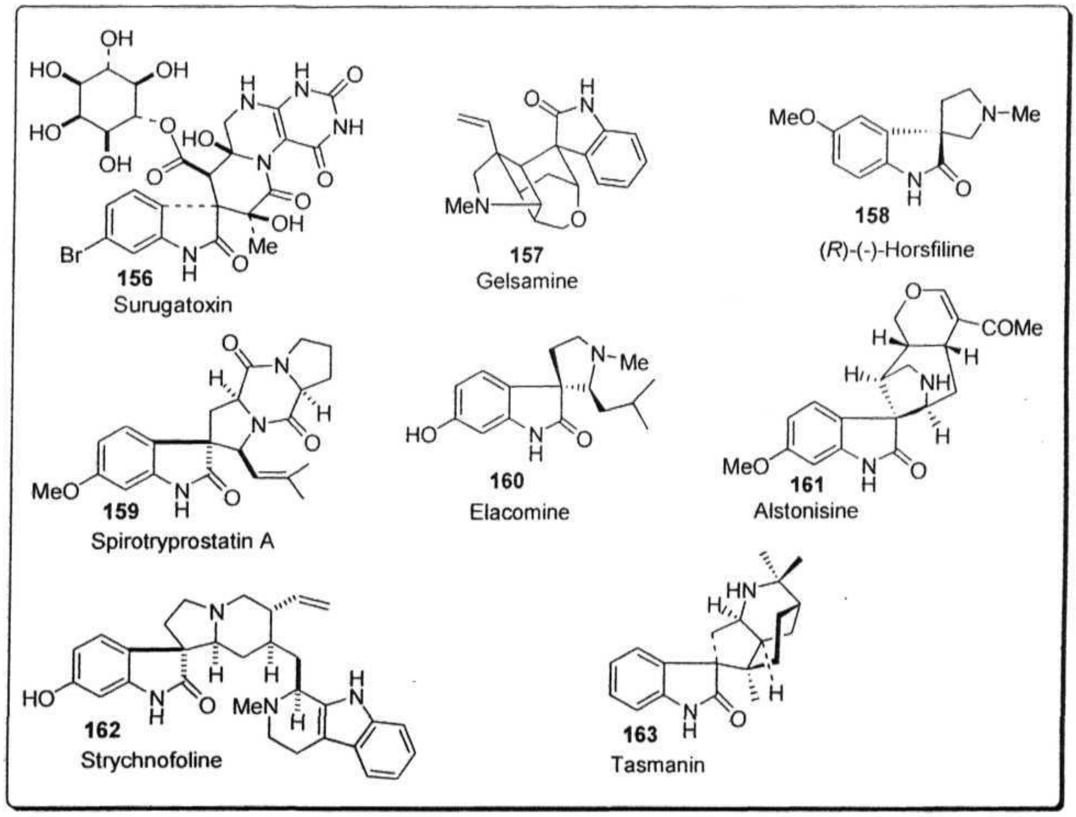
Table 12: Crystal data and structure refinement for **155f**

Identification code	**:155f**
Empirical formula	: $C_{17}H_{12}BrNO_2$
Formula weight	: 342.19
Temperature	: 100(2) K
Wavelength	: 0.71073 A
Crystal system	: triclinic
Space group	: P1 (Internatinal Table No. 2)
Unit cell dimenions	: a = 8.8737(12) A; alpha = 82.070(2) deg.
	: b = 11.4541(15) A; beta = 79.169(2) deg.
	: c = 15.187(2) A; gamma = 72.976(2) deg.
Volume	: 1444.0(3) A^3
Z, Calculated density	:4, 1.574 g/m^3
Absorption coefficient	: 2.850 mm'^{1}
F(000)	:688
Crystal size	: 0.52 x 0.48 x 0.42 mm
Theta range for data collection	: 1.87 to 26.02 deg.
Limiting indices	: $0 < h < 13$, $0 < k < 15$, $-14 < 1 < 13$
Reflections collected / unique	: 14866 / 11039 [R(int) = 0.0000]
Completeness to theta = 27.47	: 99.3 %
Absorption correction	: multi-scan technique (SADABS)
Max. and min. transmission	: 0.4624 and 0.3299
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 11039/0/146
Goodness-of-fit on F^2	: 1.016
Final R indices [I>3sigma(I)]	: R1 = 0.0400, wR2 = 0.0939
R indices (all data)	: R1 = 0.0704, wR2 = 0.1092
Largest diff. peak and hole	: 0.590 and -0.482 e. $Å^{-3}$

$TiCl_4$ catalyzed tandem construction of C-C and C-O bonds: a novel, simple and one-pot stereoselective synthesis of spiro oxindoles

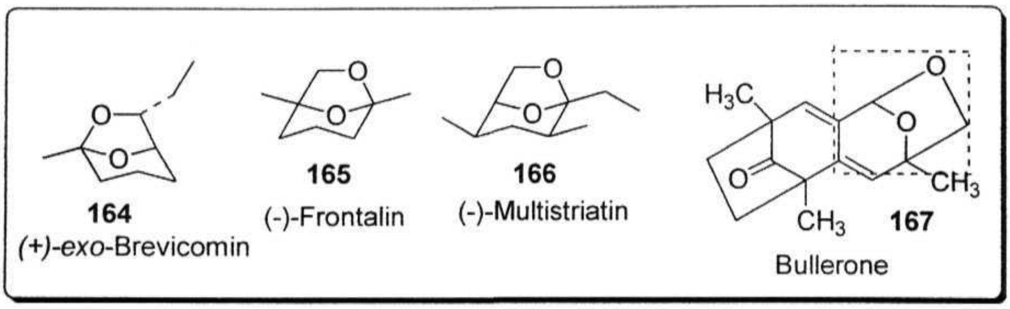
Spiro oxindole framework occupies a special place in heterocyclic chemistry because of the presence of this framework in a number of natural products such as surugatoxin[262] **(156),** gelsamine[263] **(157),** horsfiline[264,265] **(158),** spirotryprostatin A[265] **(159),** elacomine[265] **(160),** alstonisine[265] **(161),** strychnofoline[266] **(162)** and tasmanin[267] **(163)** (Figure 11).

Figure **11**



6,8-Dioxabicyclo[3.2.1]octane skeleton is yet another important skeleton present in certain natural products such as (+)-*exo*-brevicomin[268] **(164),** (-)-frontalin[269] **(165),** (-)-multistriatin[270] **(166),** bullerone[271] **(167)** (Figure 12) and palytoxin.[272]

Figure 12

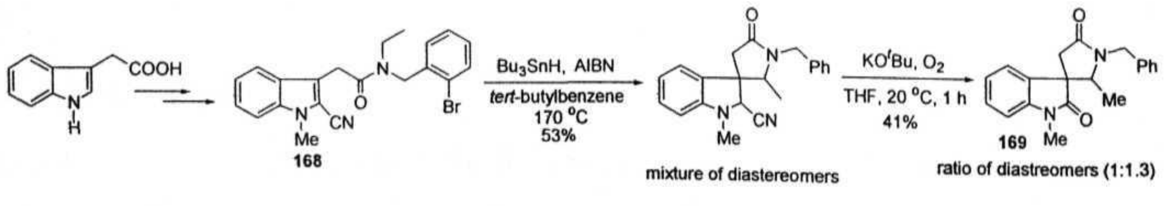


Due to the biological importance of these molecules, i. e., spiro oxindoles and 6,8-dioxabicyclo[3.2.1]octanes, development of a simple and convenient methodologies for synthesis of these molecules represents an attractive endeavor in synthetic organic chemistry. Some of the important and recent literature methods for synthesis of spiro oxindoles and 6,8-dioxabicyclo[3.2.1]octanes are presented in this section.

Spiro oxindoles:

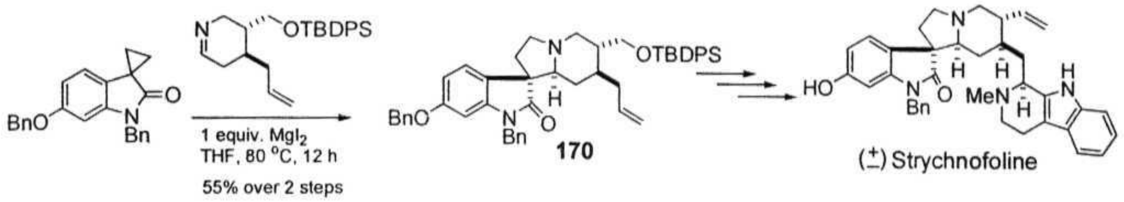
Jones et al.[265] have reported an interesting reaction of indole amide **168** with tributylstannane to provide spiroindolenines which are readily converted into spiropyrrolidinyloxindoles **169** according to Scheme 77. The tricyclic system present in **169** is found in a number of interesting natural products such as horsfiline **(158),** spirotryprostatin (159), elacomine (160) and alstonisine (161) (Figure 11).

Scheme 77



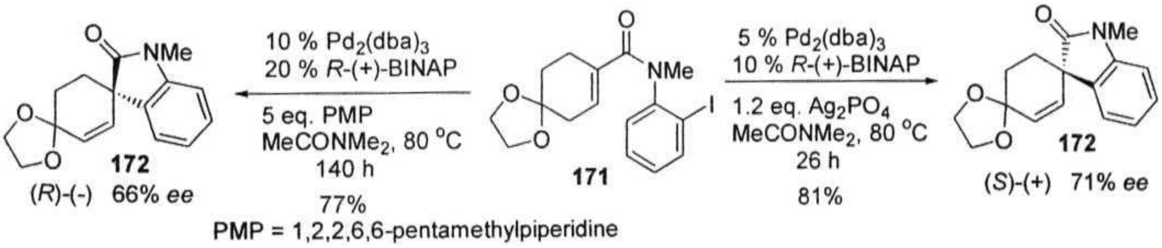
Carriera and Lerchner have reported an elegant synthesis of a spiro oxindole framework 170, which was further transformed into alkaloid, (±) strychnofoline (162) according to the Scheme 78.[266]

Scheme 78



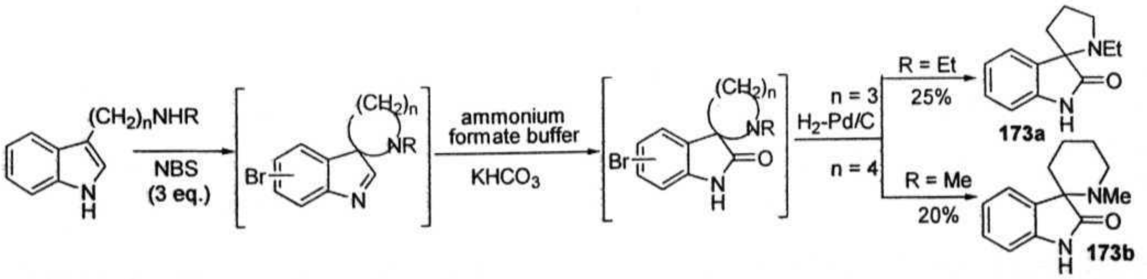
Overman and Ashimori[273] have described the synthesis of both enantiomers of spiro oxindoles (172), from acryloyl 2'-iodoanilide (171) by palladium-catalyzed cyclizations in the presence of the single enantiomer of a chiral diphoshine ligand *R*-(+)-BINAP by employing different conditions. Representative examples are shown in Scheme 79.

Scheme 79



Kornet and Thio[274] have reported the synthesis of oxindole-3-spiropyrrolidine (173a) and oxindole-3-spiropiperidine (173b) according to the Scheme 80. They further studied these compounds for local anasthetic activity.

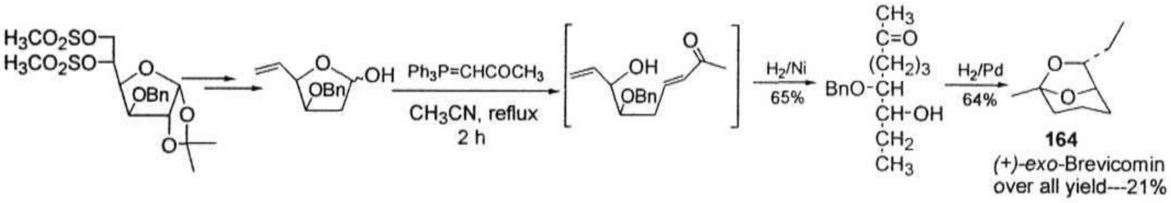
Scheme 80



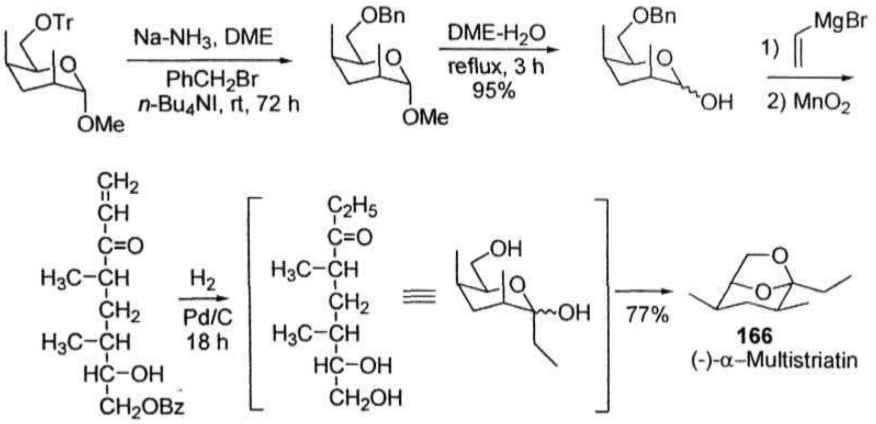
6,8-Dioxabicyclo[3.2.1]octanes:

Fraser-Reid and co-workers have reported a series of papers for synthesis of 6,8-dioxabicyclo[3.2.1]octane skeleton, which is an important moiety present in several pheromones such as *exo*-brevicomin[268] **(164)** (Scheme 81) and (-)-α-multistriatin[270] **(166)** (Scheme 82) from D-glucose derivatives.

Scheme 81

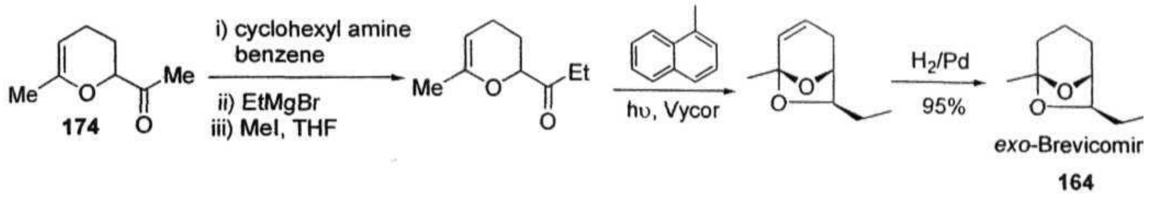


Scheme 82



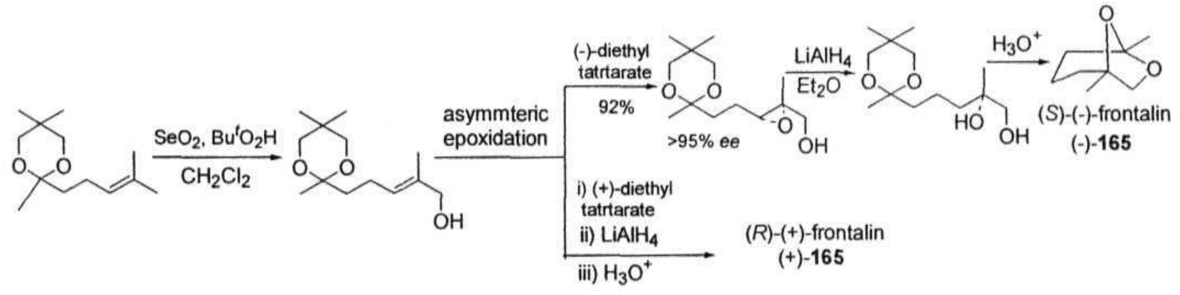
Kossanyi et al.[275] have reported an easy access to *exo*-brevicomin **(164)**, by selective irradiation of the carbonyl group of 2-propionyl-6-methyl-2,3-dihydro-4*H*-pyran [prepared from 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)]**, which on catalytic hydrogenation provided *exo*-brevicomin **(164)** (Scheme 83).

Scheme 83



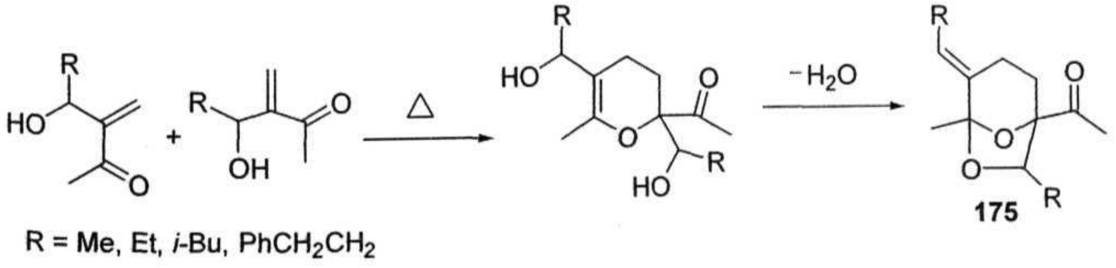
Lee[276] has reported the total synthesis of both the enantiomers of frontalin (165) in high optical purity using Katsuki-Sharpless asymmetric epoxidation as a key step according to the Scheme 84.

Scheme 84



Hoffmann and co-workers[181] reported an intermolecular dehydrative double cyclization of the Baylis-Hillman adducts, obtained from methyl vinyl ketone, leading to the formation of functionalized 6,8-dioxabicyclo[3.2.1]octane moiety (175) (Scheme 85).

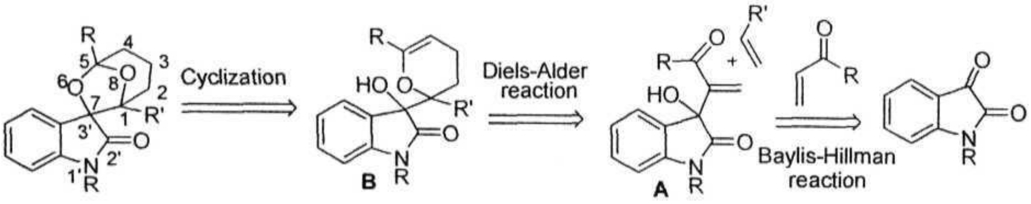
Scheme 85



Due to the importance of these skeletons, i. e., spiro oxindole and 6,8-dioxabicyclo[3.2.1]octane, development of a simple and convenient methodology for synthesis of molecules containing both these two skeletons in appropriately and aesthetically appealing way represents an interesting and attractive endeavor in synthetic organic and medicinal chemistry. We therefore undertaken a research program in this direction with an aim of developing an one-pot convenient synthesis of [6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-indolin-2'-ones.

After considering some possible retrosynthetic strategies for synthesis of [6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-indolin-2'-ones (spiro oxindoles containing 6,8-dioxabicyclo[3.2.1]octane skeleton), we arrived at two different retrosynthetic strategies (Scheme 86 and Scheme 87). Scheme 86 will involve Baylis-Hillman reaction between isatins and methyl vinyl ketone followed by Diels-Alder reaction of the expected Baylis-Hillman adducts (A) with appropriate dienophile leading to the dihydropyran derivative (B) which will be expected to cyclize to provide the desired spiro oxindole molecules.

Scheme 86



Scheme 87 is expected to proceed through tandem construction of C-C and C-0 bonds essentially involving aldol-type reaction of 2-alkanoyl-6-alkyl-2,3-dihydro-4*H*-pyran with isatin derivatives followed by cyclization. Since Scheme 87 is expected to create a

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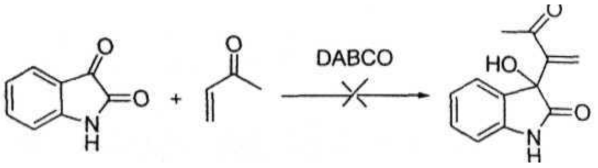
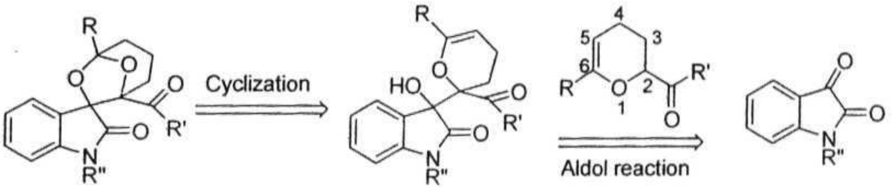
[Σ] In fact our attempts to synthesize the Baylis-Hillman alcohol *via* the reaction of isatin with methyl vinyl ketone in the presence of DABCO under various conditions were not successful (eq 57).



eq 57

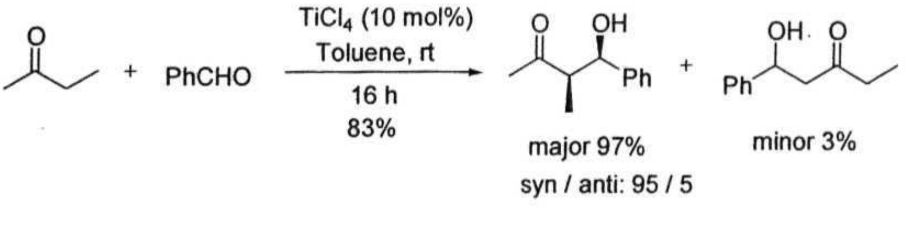
quaternary chiral center *via* the aldol reaction of dihydropyran derivatives with isatin derivatives at carbon 2 (Scheme 87) under the influence of appropriate reagent, this route looked us more challenging. Thereby, we have directed our attention in examining the applicability of Scheme 87 for synthesis of spiro oxindole derivatives.

Scheme 87



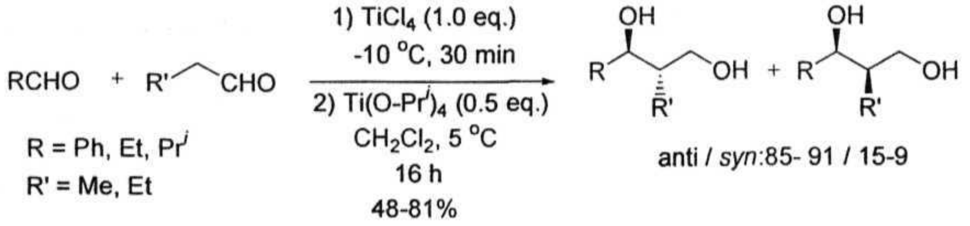
A careful literature survey reveals that $TiCl_4$ has been used for mediating aldol reactions between ketones and aldehydes. Some of the important literature methods are described in the following section.

Mahrwald and Gundogen[277] have reported a highly diastereoselective aldol addition reaction at the more encumbered a-side of unsymmetrical ketones with aldehydes under the catalytic influence of TiCU. One representative example is presented in eq 58.



eq 58

Later on Mahrwald and co-workers reported an interesting synthesis of *anti* 1,3-diols using $TiCl_4/Ti(OPr^i)_4$ system following the reaction sequence involving one-pot aldol and reduction process according to eq 59.

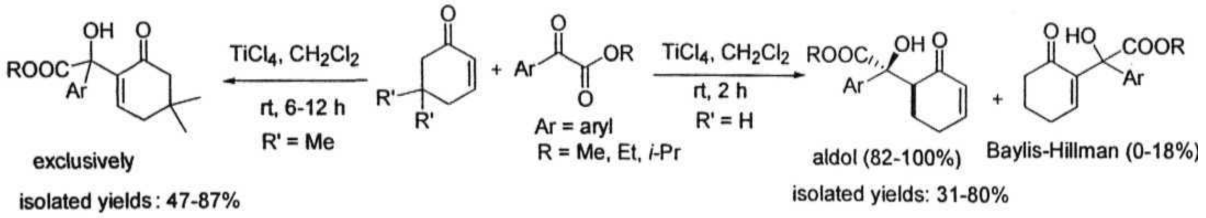


eq 59

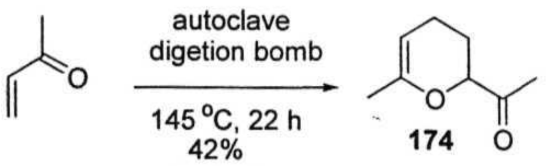
8 7 oo 279

Our earlier work on the $TiCl_4$ mediated Baylis-Hillman reaction ' and an recent work on the steric factors directed Baylis-Hillman or aldol reactions between cyclohex-2-enones and a-keto esters under the influence of $TiCl_4$ (Scheme 88), led us to examine the possible aldol reaction between 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174) (Diels-Alder dimer of methyl vinyl ketone) and isatin derivatives under the influence of titanium tetrachloride as this strategy might provide one-pot synthesis of the desired spiro oxindole derivatives with possible stereo control during the formation of C-C and C-0 bonds.

Scheme 88



The required 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174) was prepared *via* the Diels-Alder dimerization of methyl vinyl ketone following the known procedure (eq 60).[280]



eq 60

We have then carried out the reaction between isatin (176a) and 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174) under the influence of different catalytic quantities of titanium tetrachloride (See: Table 13). The best results were obtained when isatin **(176a)**$^{@}$ **(1 mmol)** was treated with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** (2 mmol) in acetonitrile as solvent in the presence of $TiCl_4$ (20 mol%, 0.2 mmol) at room temperature for 6 h, thus providing the desired spiro oxindole, [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]$^{\nabla}$-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(indolin-2′-one) **(177a)**$^{@,\otimes}$ in 74% isolated yield after usual work-up **and** purification through silica gel column chromatography **(eq 61, Table** 14). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 25), ^{13}C NMR (Spectrum 26), mass spectral data and elemental analysis. The structure and stereochemistry of the compound **177a** was further confirmed by single crystal X-ray data (Fig. X4, Table 15).

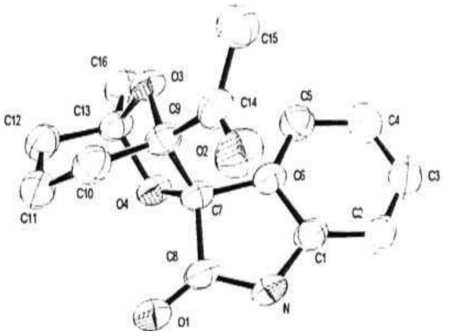


Figure X4: ORTEP diagram of compound **177a.**
{Hydrogen atoms were omitted for clarity)

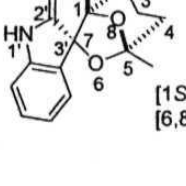
® For continuity and easy understanding, isatin was numbered as 176a and the spiro oxindole from **176a** was numbered as **177a**.

$^{\nabla}$ We have written [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]before all the names of spiro oxindoles to indicate the **racemic** nature and **also** stereochemistry.

For easy understanding, we have written the structures with [1*S*,5*S*,7(3′)*S*] configuration for all the compounds **117a-i** throughout this section.

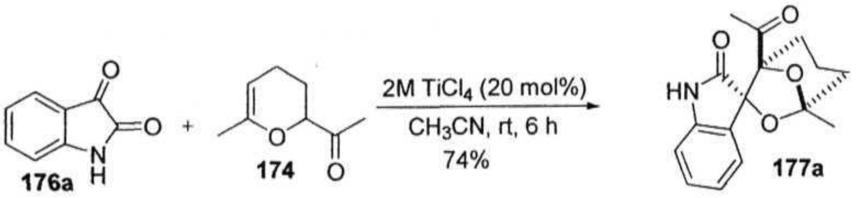
® For easy understanding, we have numbered the spiro oxindoles as mentioned below and named accordingly.

For example 177a



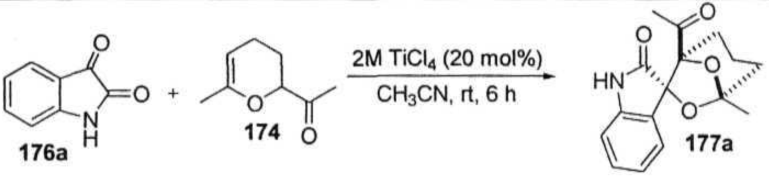
is named as

[1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3' -(indolin-2'-one)



eq 61

Table 13: Synthesis of [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]$^{∇,⊗}$-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane)]-7-spiro-3'-(indolin-2'-one) (177a) under various conditions[a]



Isatin (**176a**) (eq.)	2-Acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**174**) (eq.)	$TiCl_4$ (eq.)	Yield of **177a** (%)[b]
1	2	1	24
1	2	2	32
1	5	1	73
1	1	0.2	49
1	**2**	**0.2**	**74**
1	1.2	0.1	43

a) All the reactions were carried out in CH3CN (5 mL) at room temperature for 6 h.

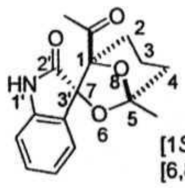
b) Yields are of the pure product [based on isatin (176a)] after purification through column chromatography (silica gel, 10% EtOAc in hexanes).

[∇] We have written [1*S*,5*S*,7(3′)*S*/′*R*,5*R*,7(3′)*R*] before all the names of spiro oxindoles to indicate the racemic nature and also stereochemistry.

For easy understanding, we have written the structures with [1*S*,5*S*,7(3′)*S*] configuration for all the compounds **117a-i** throughout this section.

® For easy understanding, we have numbered the spiro oxindoles as mentioned below and named accordingly.

For example **177a**

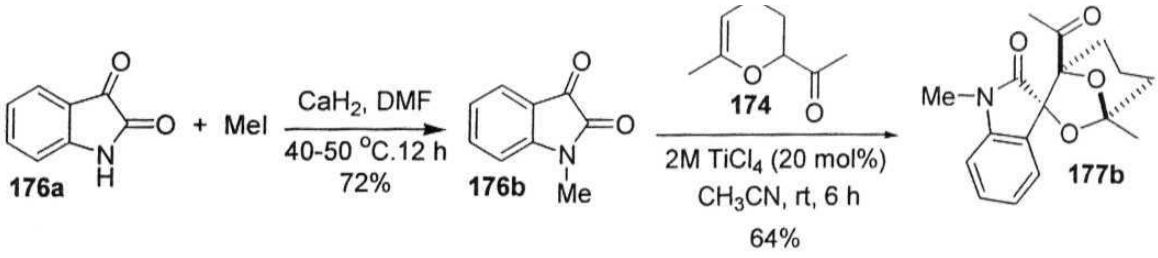


is named as

[1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3' -(indolin-2'-one)

Encouraged by this result, we extended the same methodology to the other isatin derivative **1-methylisatin (176b).** The required isatin derivative (176b) was prepared *via* the reaction of isatin **(176a)** with methyl iodide in the presence of CaH_2 according to the literature procedure (Scheme 89).[281] Treatment of the isatin **176b**[@] with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** in the presence of $TiCl_4$ (20 mol%) at room temperature for 6 h provided the desired product, [1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*][∇]-1-acetyl-5-methyl-[6,8-dioxabicyclo-(3.2.1)octane]-7-spiro-3'-(l'-methylindolin-2'-one) **(177b)**[@] in 64% yield (Scheme 89, Table 14). Structure of this molecule was confirmed by IR, ^1H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

Scheme 89



With a view to understanding the generality of this methodology, we have employed two more isatin derivatives, 1-ethylisatin (176c) and 1-benzylisatin (176d). The required isatin derivatives **176c,d**[@] were prepared *via* the reaction of isatin (176a) with the corresponding bromides in the presence of CaH_2 according to the literature procedure (Scheme 90).[281] Treatment of the isatin derivatives 176c,d with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the influence of $TiCl_4$ (20 mol%) at room temperature for 6 h, provided the

---

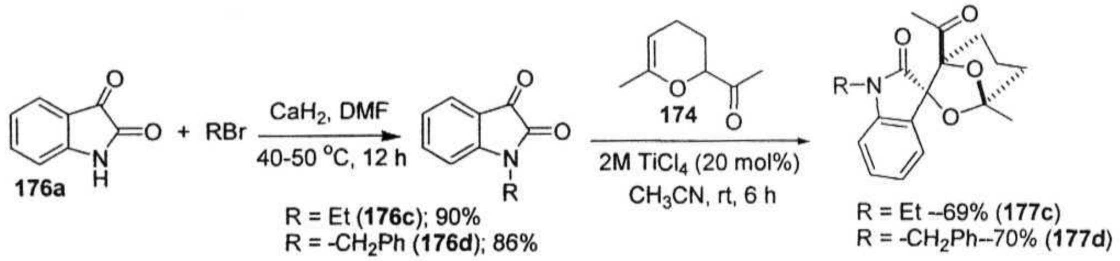
® For continuity and easy understanding, isatin derivatives were numbered as **176a-i** and the spiro oxindoles from **176a-i** were numbered as **177a-i**.

[∇] We have written *[\S,SS,7(3')S/\R,5R,7(3')R)* before **all** the names of spiro oxindoles to indicate the **racemic** nature and also stereochemistry.

For easy understanding, we have written the structures with [1*S*,5*S*,7(3')*S*] configuration for all the compounds **117a-i throughout this** section.

desired spiro oxindole derivatives, [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]$^{\nabla}$-1-acetyl-5-methyl-[6,8-dioxabi-cyclo(3.2.1)octane]-7-spiro-3'-(l'-ethylindolin-2'-one) **(177c)**$^{@}$ and [1*S*,5*S*,7(3′)*S*/-1*R*,5*R*,7(3′)*R*]$^{\nabla}$-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-benzylindolin-2′-one) **(177d)**$^{@}$ in 69% and 70% yields respectively (Scheme 90, Table 14). Structures of these molecules were confirmed by IR, ^{1}H NMR (See: Spectrum 27 for molecule **177d),** ^{13}C NMR (See: Spectrum 28 for molecule **177d),** mass spectral data and elemental analyses.

Scheme 90



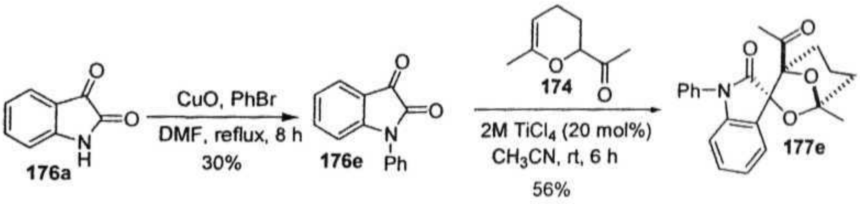
With a view to understand the effect of phenyl group on nitrogen of isatin, we extended this methodology to 1-phenylisatin **(176e).** The required isatin 176e was prepared *via* the reaction of isatin **(176a)** with bromobenzene under the influence of CuO according to the known procedure (Scheme 91). Reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** with 1-phenylisatin **(176e)**$^{@}$ under the influence of $TiCl_4$ (20 mol%) at room temperature for 6 h, furnished the desired spiro oxindole [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]$^{\nabla}$1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-(1'-phenylindolin-2'-one) **(177e)**$^{@}$

$^{\nabla}$ We have written [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*] before all the names of spiro oxindoles to indicate the racemic nature and also stereochemistry.
For easy understanding, we have written the structures with [1*S*,5*S*,7(3′)*S*] configuration for all the compounds **117a-i** throughout this section.

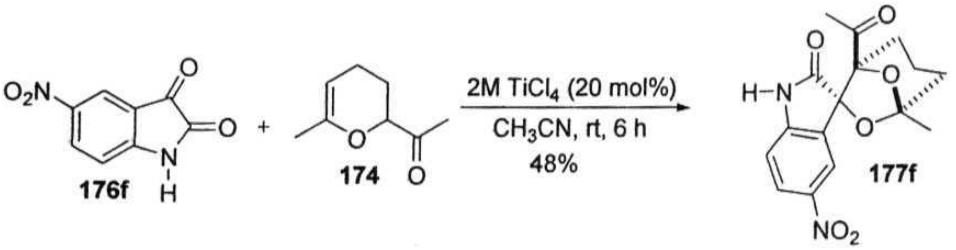
® For continuity and easy understanding, isatin derivatives were numbered as 176a-i and the spiro oxindoles from **176a-i** were numbered as **177a-i.**

in 56% yield (Scheme 91, Table 14). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

Scheme 91



We have also examined the application of isatin derivative, 5-nitroisatin **(176f)**$^@$ as a substrate in this methodology. Thus, treatment of 176f with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** in the presence of $TiCl_4$ (20 mol%) at room temperature for 6 h, provided the desired spiro oxindole derivative, [1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]$^\nabla$-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-(5'-nitroindolin-2'-one) **(177f)**$^@$ in 48% yield (eq 62, Table 14). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 29), ^{13}C NMR (Spectrum 30), mass spectral data and elemental analysis. Though the yield is little less, this reaction is still encouraging in the sense that this shows the generality of the reaction.



eq 62

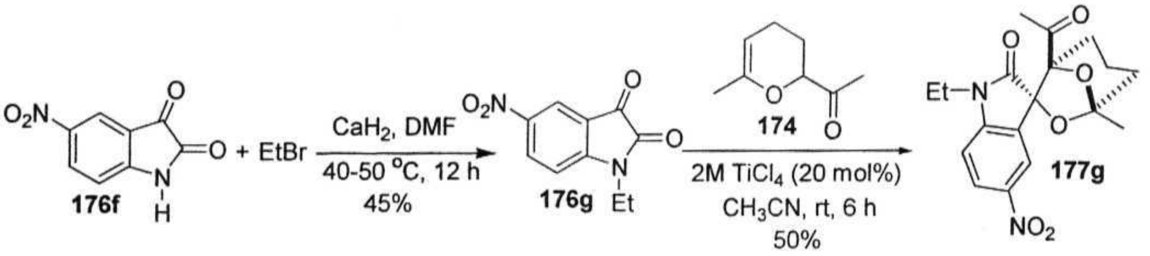
® For continuity and easy understanding, isatin derivatives were numbered as 176a-i and the spiro oxindoles from **176a-i** were numbered as **177a-i.**

$^\nabla$ We have written [1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*] before all the names of spiro oxindoles to indicate the racemic nature and also stereochemistry.

For easy understanding, we have written the structures with [1*S*,5*S*,7(3')*S*] configuration for all the compounds **117a-i** throughout this section.

We have next used **1-ethyl-5-nitroisatin (176g)** as a substrate in this strategy. The required isatin **176g** was prepared *via* the reaction of isatin **176f** with ethyl bromide in the presence of CaH_2 (Scheme 92). Treatment of **176g**[@] with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** in the presence of $TiCl_4$ (20 mol%) at room temperature for 6 h, resulted in the formation of the desired product, [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*][∇]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-ethyl-5′-nitroindolin-2′-one) **(177g)**[@] in 50% yield (Scheme 92, Table 14). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

Scheme 92

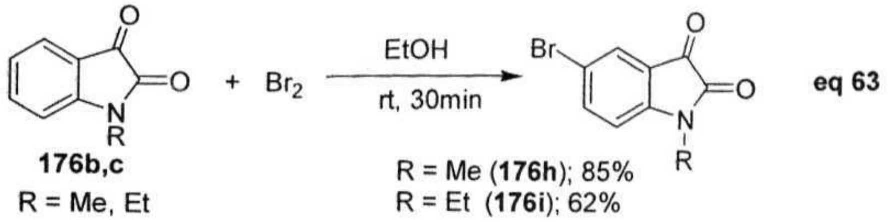


With a view to understand the scope of this strategy, we have employed two more isatin derivatives **5-bromo-1-methylisatin (176h)** and **5-bromo-1-ethylisatin (176i)** having bromo substituent on the aromatic ring of the isatin molecules. The required isatin derivatives **176h,i** were prepared by the action of bromine on 1-methylisatin **(176b)** and 1-ethylisatin **(176c)** respectively in ethanol (eq 63).

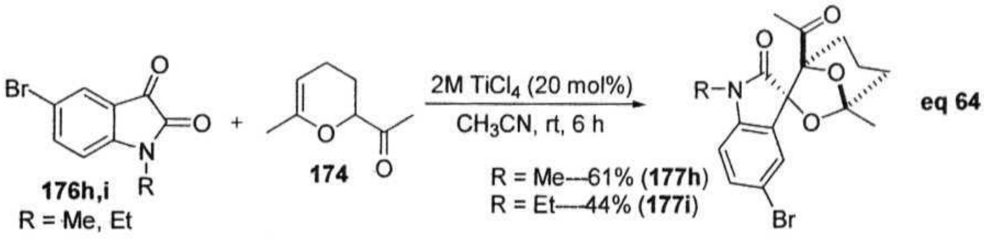
® For continuity and easy understanding, isatin derivatives were numbered as **176a-i** and the spiro oxindoles from **176a-i** were numbered as **177a-i.**

[∇] We have written [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*] before all the names of spiro oxindoles to indicate the racemic nature and also stereochemistry.

For easy understanding, we have written the structures with [1*S*,5*S*,7(3′)*S*] configuration for **all the** compounds **117a-i** throughout this section.



Subsequent reaction of bromo isatins **176h,i**[@] with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the influence of $TiCl_4$ (20 mol%) at room temperature for 6 h, furnished the desired spiro oxindole derivatives, [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*][∇]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(5′-bromo-1′-methylindolin-2′-one) **(177h)**[@] and [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*][∇]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(5′-bromo-1′-ethylindolin-2′-one) **(177i)**[@] in 61% and 44% yields respectively (eq 64, Table 14). Structures of these molecules were confirmed by 1R, ^1H NMR (See: Spectrum 31 for molecule **177h),** ^{13}C NMR spectral data (See: Spectrum 32 for molecule 177h), mass spectral data and elemental analyses.



The structure and stereochemistry of the compound **177i** was further confirmed by single crystal X-ray data (Fig. X5, Table 16).

® For continuity and easy understanding, isatin derivatives were numbered as 176a-i and the spiro oxindoles from **176a-i** were numbered as 177a-i.

[∇] We have written [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*] before all the names of spiro oxindoles to indicate the racemic nature and also stereochemistry.
For easy understanding, we have written the structures with [1*S*,5*S*,7(3′)*S*] configuration for **all the** compounds **117a-i throughout this** section.

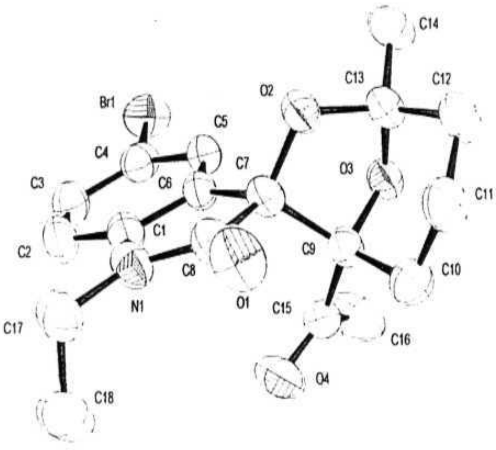
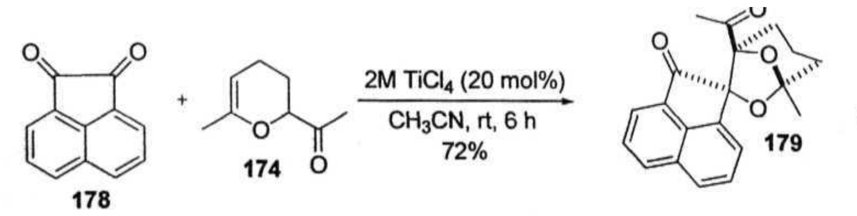


Figure X5: ORTEP diagram of compound 177i.
(Hydrogen atoms were omitted for clarity)

With a view to understanding the application of this strategy to aromatic 1,2-diketones, we have selected acenaphthenequinone **(178).** Thus, the reaction of acenaphthenequinone **(178)** with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the catalytic influence of 20 mol% of $TiCl_4$ provided the desired spiro derivative, [1*S*,5*S*,7(1')*S*/1*R*,5*R*,7(1')*R*][∞]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-1'-(1',2'-dihydroacenaphthalene-2'-one) **(179)** in 72% yield (eq 65, Table 14). Structure of this molecule was confirmed by IR, ^1H NMR (Spectrum 33), ^{13}C NMR (Spectrum 34), mass spectral data and elemental analysis. The structure and stereochemistry of the compound **179** was further confirmed by single crystal X-ray data (Fig. X6, Table 17).



eq 65

[∞] We have written [1*S*,5*S*,7(1')*S*/1*R*,5*R*,7(1')*R*] before the name of the spiro compound 179 to indicate the racemic nature and also stereochemistry.
For easy understanding, we have written the structure with [1*S*,5*S*,7(1')*S*] configuration for compound 179.

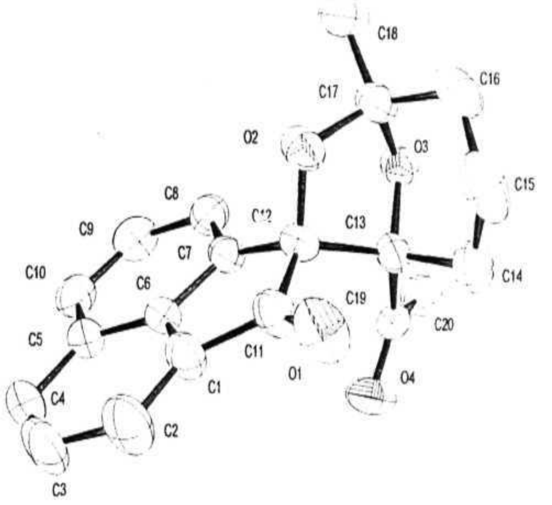
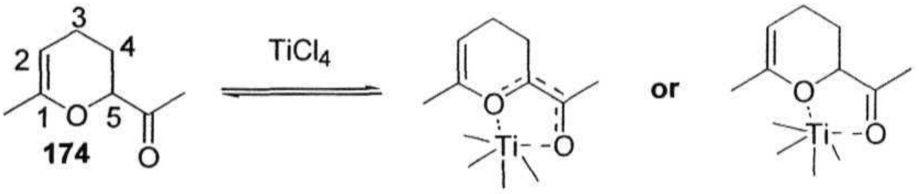


Figure X6: ORTEP diagram of compound **179.**
(Hydrogen atoms were omitted for clarity)

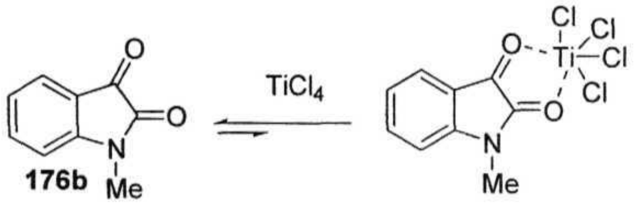
With a view to understand the nature of the activated species formed in the reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** with $TiCl_4$.[∅] we have recorded the ^1H NMR and ^{13}C NMR spectra of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** (1.0 eq.) in the presence of $TiCl_4$ (0.1 eq.) in $CDCl_3$ (eq 66). In the ^1H NMR spectrum (Spectrum 35), the multiplet originally at 8 4.55 appears now as a singlet at 8 4.49 (due to olefinic proton). The multiplet originally at 8 4.27-4.33 appears now as two multiplets, one at 8 4.22-4.30 (major) and the other one at 8 4.31-4.40 (minor) due to methine proton. There is also some change in splitting pattern in the region 8 1.22-2.20. Similarly, ^{13}C NMR spectrum (Spectrum 36) shows some additional peaks at 8 207.44 (C=O), 106.29 <C2), 78.79 (C5), 39.45 and 33.64. These results clearly indicate the possible formation of titanium enolate or complexation as shown in eq 66.

We also noticed very small variations in quantity of $TiCl_4$ effects the intensity of additional peaks in the ^1H NMR and ^{13}C NMR spectra.



eq 66

We have also recorded the ^{1}H NMR and ^{13}C NMR spectra of the 1-methylisatin (176b) (1.0 eq.) in the presence of $TiCl_4$ (0.2 eq.)[0] in $CDCl_3$ (eq 67). ^{1}H NMR spectrum (Spectrum 37) shows there is not any significant changes in the chemical shift values and the pattern of the peaks from the original spectrum. Similar trend was also observed in the ^{13}C NMR spectrum (Spectrum 38). These results do not give any clear indication for strong complexation between 1-methylisatin and titanium tetrachloride in the present reaction conditions. However, we can not rule out some kind of complexation (eq 67).

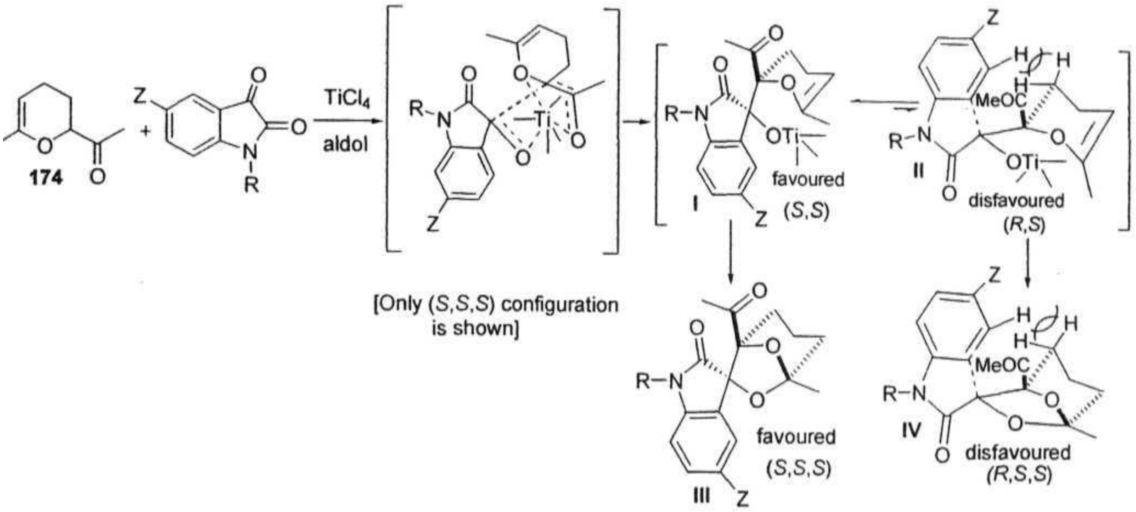


eq 67

A plausible mechanism with possible transition state models **(I,II,III** and **IV)** for the one-pot formation of spiro oxindoles 177a-i from 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** and isatin derivatives 176a-i is presented in Scheme 93. The reaction might probably proceed through titanium enolate followed by C-C bond formation through aldol-type reaction with isatin derivatives and then cyclization (C-0 bond formation) leading to the formation of desired spiro oxindoles. Stereoselectivity is possibly explained by the transition state models **(I,II,IH** and **IV).**

[θ] We also noticed that very minor variations in $TiCl_4$ quantity influence the chemical shifts of the ^{1}H NMR and ^{13}C NMR spectra. However, the pattern remains the same.

Scheme 93



It is worth mentioning here the work of Nair and co-workers,[283] who reported a facile dipolar cycloaddition reactions of isatins with carbonyl ylides, generated *in situ,* by $Rh_2(OAc)_4$ catalyzed reaction of diazoketones, providing novel spiro oxindole derivatives **(180)** containing 6,8-dioxabicyclo[3.2.1]octane skeleton. One representative example is shown in Scheme 94.

Scheme 94

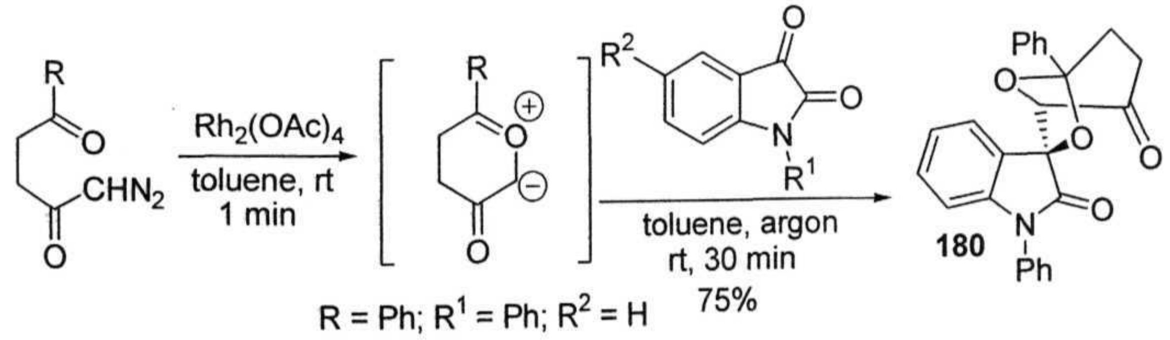
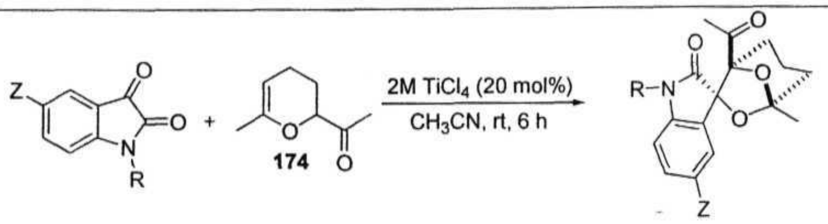


Table 14: Synthesis of functionalized spiro oxindoles (177a-i, 179)[a]



Isatin	Z	R	Product[b]	Yield[c] (%)	Mp (°C)
176a	H	H	**177a**[d]	74	163-165
176b	H	Me	**177b**	64	148-150
176c	H	Et	**177c**	69	130-132
176d	H	CH_2Ph	**177d**	70	141-143
176e	H	Ph	**177e**	56	125-127
176f	NO_2	H	**177f**	48	212-216
176g	NO_2	Et	**177g**	50	168-171
176h	Br	Me	**177h**	61	177-180
176i	Br	Et	**177i**[d]	44	137-140
178	-	-	**179**[d]	72	147-149

a) All reactions were carried out on 1 mmol scale of isatin with 2 mmol of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**174**) in acetonitrile (5 mL) under the influence of 20 mol% of $TiCl_4$ (2M solution in CH_2Cl_2) at room temperature for 6 h.

b) All the compounds 177a-i, **179** were obtained as solids and were characterized by IR, ^1H NMR (200 MHz/400 MHz), ^{13}C NMR (50 MHz/100 MHz), mass spectral data and elemental analyses.

c) Yields are of the pure products (based on isatins) after purification through silica gel column chromatography.

d) The structures of these molecules were further established from the single crystal X-ray data.

Table 15: Crystal data and structure refinement for 177a

Identification code	: 177a
Empirical formula	: $C_{16}H_{17}NO_4$
Formula weight	: 287.31
Temperature	: 293(2) K
Wavelength	: 0.71073 A
Crystal system	: Triclinic
Space group	: P-1 (Internatinal Table No. 2)
Unit cell dimensions	: a = 7.508(17) A; alpha = 77.46(6) deg.
	: b = 8.223(7) A; beta = 83.05(10) deg.
	: c = 12.453(8) A; gamma = 74.89(10) deg.
Volume	: 722.8(18) A^3
Z, Calculated density	: 2, 1.320 Mg/m^3
Absorption coefficient	: 0.1 mm^{-1}
F(000)	: 304
Crystal size	: 0.52 x 0.48 x 0.42 mm
Theta range for data collection	: 1.68 to 27.47 deg.
Limiting indices	: $0 < h < 9, -9 < k < 10, -15 < l < -16$
Reflections collected / unique	: 3322 / 3322 [R(int) = 0.0000]
Completeness to theta = 27.47	: 100.0%
Absorption correction	: none
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3322 / 0 / 192
Goodness-of-fit on F^2	: 1.008
Final R indices [I>3sigma(I)]	: R1 = 0.0667, wR2 = 0.0895
R indices (all data)	: R1 = 0.2056, wR2 = 0.2056
Extinction coefficient	: 0.050(11)
Largest diff. peak and hole	: 0.41 and -0.32 e. $A^{"3}$

Table 16: Crystal data and structure refinement for 177i

Identification code : **177i**

Empirical formula : $C_{18}H_{20}BrNO_4$

Formula weight : 394.26

Temperature : 100(2) K

Wavelength : 0.71073 A

Crystal system : Monoclinic

Space group : P21/n (Internatinal Table No. 14)

Unit cell dimensions : a = 12.5767(8) A; alpha = 90 deg.

: b = 9.3151(5) A; beta = 109.086(10) deg.

: c = 15.5341(11) A; gamma = 90 deg.

Volume : 1719.8(2) A^3

Z, Calculated density : 4, 1.523 Mg/m^3

Absorption coefficient : 2.412 mm^{-1}

F(000) : 808

Crystal size : 0.50 x 0.54 x 0.48 mm

Theta range for data collection : 1.82 to 28.26 deg.

Limiting indices : $-16 < h < 16$, $-12 < k < 12$, $-20 < 1 < 20$

Reflections collected / unique : 19184 / 4090 [R(int) = 0.0000]

Completeness to theta = 27.47 : 96 %

Absorption correction : multi-scan technique (SADABS)

Max. and min. transmission : 0.5315 and 0.4070

Refinement method : Full-matrix least-squares on F^2

Data / restraints / parameters : 4090 / 0 / 220

Goodness-of-fit on F^2 : 0.994

Final R indices [I>3sigma(I)] : R1 = 0.0401, wR2 = 0.0560

R indices (all data) : R1 = 0.1152, wR2 = 0.1152

Largest diff. peak and hole : 0.883 and -0.650 e. A^{-3}

Table 17: **Crystal data and structure refinement for** 179

Identification code	: **179**
Empirical formula	: $C_{20}H_{18}O_4$
Formula weight	: 322.34
Temperature	: 293(2) K
Wavelength	: 0.71073 A
Crystal system	: Monoclinic
Space group	: P 21/c (Internatinal Table No. 14)
Unit cell dimensions	: a = 11.901(2) A; alpha = 90 deg.
	: b = 9.0504(13) A; beta = 90.66(2) deg.
	: c = 114.859(6) A; gamma = 90 deg.
Volume	: 1600.4(7) A^{3}
Z, Calculated density	: 4, 1.338 Mg/m^{3}
Absorption coefficient	: 0.09 mm'^{1}
F(000)	: 680
Crystal size	: 0.50 x 0.45 x 0.40 mm
Theta range for data collection	: 1.71 to 27.47 deg.
Limiting indices	: $0<h<15, 0<k<11, -19<l<19$
Reflections collected / unique	: 3587 / 3587 [R(int) = 0.0000]
Completeness to theta = 27.47	: 100.0%
Absorption correction	: none
Refinement method	: Full-matrix least-squares on F^{2}
Data / restraints / parameters	: 3587/0/218
Goodness-of-fit on F^{2}	: 1.015
Final R indices [I>3sigma(I)]	: R1 = 0.0720, wR2 = 0.1367
R indices (all data)	: R1 = 0.2015, wR2 = 0.2967
Extinction coefficient	: 0.009(5)
Largest diff. peak and hole	: 0.32 and -0.24 e. A'^{3}

In conclusion, we have developed a simple, convenient and one-pot stereoselective synthesis of [1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)-octane]-7-spiro-3'-(l'-alkyl(aryI)indolin-2'-ones) (177a-i) *via* the titanium tetrachloride catalyzed aldol-type reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran with various isatin derivatives followed by cyclization, involving tandem construction of C-C and C-0 bonds with stereochemical control.

CONCLUSIONS

We have achieved considerable success in our objectivities on the applications of Baylis-Hillman adducts as mentioned in the beginning of this section. We have successfully transformed methyl 3-acetoxy-3-aryl-2-methylenepropanoates **(116a-g)** and methyl 3-acetoxy-2-methylenealkanoates **(116h,i)**, acetates of the Baylis-Hillman adducts, into substituted γ-lactams i.e., (*E*)-5-alkyl-3-aryl(alkyl)idene-pyrrolidin-2-ones **(118-131)** in a facile, one-pot operation *via* the treatment with nitroalkanes in the presence of K_2CO_3 followed by reductive cyclization using Fe/AcOH.

We have successfully developed a convenient, one-pot facile methodology for synthesis of functionalized 1,2,3,4-tetrahydroacridines **(146a-d, 148a-c)** from the Baylis-Hillman adducts i.e., 2-[hydroxy(2-nitroaryI)methyl]cyclohex-2-enones **(145a-d, 147a-c),** [derived from various 2-nitrobenzaldehydes **(143a-d)** and cyclohex-2-enone (144a)/5,5-dimethyl-cyclohex-2-enone **(144b)]** *via* the reductive cyclization using Fe/AcOH. We have also synthesized representative cyclopenta[b]quinolines **(151a-d)** from the Baylis-Hillman adducts i.e., 2-[hydroxy(2-nitroaryl)methyi]cyclopent-2-enones (150a-d), [derived from various 2-nitrobenzaldehydes (143a-d) and cyclopent-2-enone (144c)] *via* the reductive cyclization using Fe/AcOH.

We have also transformed the Baylis-Hillman adducts, 3-[hydroxy(2-nitroaryl)methyl]-4*H*-chromen-4-ones (153a-f), derived from various 2-nitrobenzaldehydes (**143a,c,e**) and 1-benzopyran-4(4*H*)-one (**152a**)/6-methyl-1-benzopyran-4(4*H*)-one (152b), into the corresponding substituted 3-benzoylquinolines (155a-f) in one-pot operation *via* the treatment with Fe/AcOH.

We have also developed a one-pot, facile and novel synthesis of substituted spiro oxindoles i.e., [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-[1′-alkyl(aryl)indolin-2′-ones] (177a-i) *via* the reaction of various isatins (176a-i) with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (Diels-Alder dimer of methyl vinyl ketone) (174) under the catalytic influence of $TiCl_4$ essentially involving tandem construction of C-C and C-0 bonds with stereochemical control. We have also synthesized [1*S*,5*S*,7(1′)*S*/1*R*,5*R*,7(1′)*R*]-1-acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-1′-(1′,2′-dihydro-acenaphthalene-2'-one) (179) *via* the reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174) with acenaphthenequinone (178) under the catalytic influence of $TiCl_4$.

Our studies clearly demonstrate the potential of Baylis-Hillman adducts as valuable substrates for synthesis of various heterocyclic molecules.

EXPERIMENTAL

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

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

Elemental Analyses: Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyzer or Thermo Finnigan Flash 1112 CHN analyzer.

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

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a BRUKER-AC-200/Avance-400 spectrometer. ^{1}H NMR (200 MHz) (other wise specified) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, with TMS (5 = 0 ppm) as internal standard. ^{13}C NMR (50 MHz) (other wise specified) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, with its middle peak of the triplet (8 = 77.10 ppm) as internal standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity, that is, s =

singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, ABq = AB quartet, b = broad, (3) number of hydrogens integrated for the signal, (4) coupling constant J in Hertz.

Mass Spectral Analyses: Mass spectra were recorded either on VG7070H mass spectrometer using EI technique or Shimadzu LCMS 2010A or Shimadzu GC-2010 mass spectrometer.

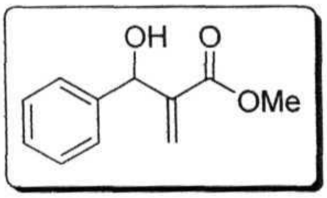
X-ray Crystallography: The X- ray diffraction measurements were carried out at 293 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Ka (λ = 0.71073 A^0) radiation with CAD4 software. The single crystal was fixed to a capillary head by an appropriate fixing material. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. Stability of the crystal during the measurements was monitored measuring the intensity of the standard reflections after every one and half hour intervals. No appreciable variation of the crystal was detected. The data were reduced using XTAL program. The structure was resolved by direct methods and refined by full-matrix least-squares using the SHELXS-86 and SHELXL-93 program packages respectively OR the X-ray intensity data were measured at 100(2) K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ = 0.71073Å) operated at 1500 W power (50 kV, 30 tnA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame integration algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package.

Chromatography: Analytical Thin Layer Chromatography (TLC) was performed on glass plates (7 × 2 cm) coated with Acme's silica gel GF 254 (254 mμ) containing 13% calcium Sulfate as a binder. The spots were visualized by short exposure to iodine vapour or UV light. Column chromatography was carried out using Acme's silica gel (100-200 mesh). High-pressure liquid chromatography (HPLC) analysis was carried out on Shimadzu LC-10AD Chromatopac equipped with SPD-10A UV-VIS detector using HPLC grade solvents.

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

Methyl **3-hydroxy-2-methylene-3-phenylpropanoate (115a):**

A mixture of benzaldehyde (50 mmol, 5.306 g), methyl acrylate (75 mmol, 6.456 g) and DABCO (15 mol%, 7.5 mmol, 0.841 g) was kept at room temperature for 7 days. The reaction mixture was diluted with ether (50 mL) and washed successively with 2N HC1 solution, water and saturated $NaHCO_3$ solution. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained, was distilled under reduced pressure, to afford the desired product (**115a**), as a colorless liquid.



Yield : 84% (8.06 g)
Bp. : 121-122 °C/2.5 mm
IR (Neat) : v3341, 1716, 1633 cm^{-1}
^{1}H NMR : 8 3.16 (b, 1H), 3.71 (s, 3H), 5.56 (s, 1H), 5.84 (s, 1H), 6.33 (s, 1H), 7.23-7.60 (m,5H)
^{13}C NMR : δ 51.53, 72.32, 125.29, 126.51, 127.45, 128.06, 141.28, 142.06, 166.39

Methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (115b):

This molecule was prepared *via* the Baylis-Hillman reaction of 4-methylbenzaldehyde with methyl acrylate in the presence of a catalytic amount of DABCO as a colorless liquid, following the similar procedure described for the molecule **115a**.

Reaction time : 8 days
Yield : 75%
Bp. : 141-142 °C/5.1 mm

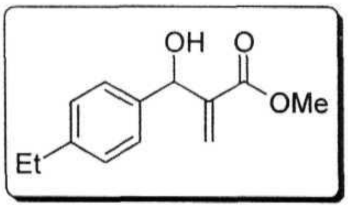
IR (Neat) : ν 3503, 1714, 1626 cm''^{1}

^{1}H NMR : 5 2.33 (s, 3H), 2.93 (b, 1H), 3.71 (s, 3H), 5.53 (s, 1H), 5.84 (s, 1H), 6.32 (s, 1H), 7.14 (d, 2H, *J*= 7.8 Hz), 7.26 (d, 2H, *J* = 7.8 Hz)

^{13}C NMR : 5 21.09, 51.85, 72.97, 125.67, 126.58, 129.11, 137.49, 138.47, 142.25, 166.79

Methyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (115c):

This molecule was obtained as a colorless liquid *via* the Baylis-Hillman reaction of 4-ethylbenzaldehyde with methyl acrylate in the presence of a catalytic amount of DABCO, following the similar procedure described for the molecule **115a**.



Reaction tim< : 7 days

Yield : 77%

Bp. : 152-154 °C/5.0 mm

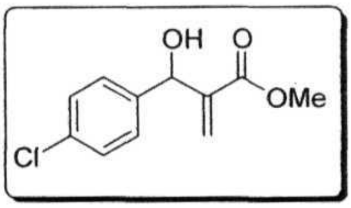
IR (Neat) : ν 3466, 1722, 1630 cm^{-1}

^{1}H NMR : 5 1.23 (t, 3H, *J*= 7.8 Hz), 2.64 (q, 2H, *J* = 7.8 Hz), 2.83 (b, 1H), 3.72 (s, 3H), 5.54 (s, 1H), 5.86 (s, 1H), 6.33 (s, 1H), 7.17 (d, 2H, *J* = 7.8 Hz), 7.29 (d, 2H, *J*= 7.8 Hz)

^{13}C NMR : 5 15.29, 28.39, 51.65, 72.58, 125.32, 126.60, 127.72, 138.66, 142.27, 143.61, 166.63

Methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (115d):

This was prepared as a colorless liquid *via* the treatment of 4-chlorobenzaldehyde with methyl acrylate in the presence of a catalytic amount of DABCO, following the similar procedure described for the molecule **115a**.



Reaction time : 6 days

Yield : 79%

Bp. : 126-128 °C/1 mm

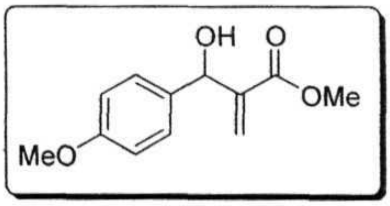
IR (Neat) : ν 3265, 1716, 1635 cm''^{1}

^{1}H NMR : *8* 3.08 (b, 1H), 3.73 (s, 3H), 5.53 (s, 1H), 5.82 (s, 1H), 6.34 (s, 1H), 7.31 (s,4H)

^{13}C NMR : 6 51.87, 72.24, 125.97, 128.01, 128.45, 133.44, 139.95, 141.81, 166.51

Methyl **3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate** (115e):

This was prepared *via* the DABCO catalyzed Baylis-Hillman reaction of 4-methoxybenzaldehyde with methyl acrylate as a colorless solid, following the similar procedure described for the molecule **115a.**



Reaction time : 10 days

Yield : 69%

Mp. : 60-62 °C

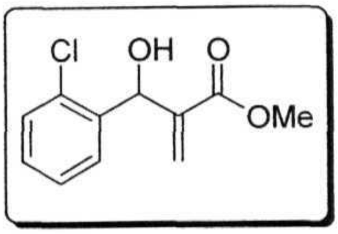
IR (KBr) : ν 3462, 1722, 1630 cm*^{1}

^{1}H NMR : 8 2.82 (b, 1H), 3.70 (s, 3H), 3.79 (s, 3H), 5.51 (s, 1H), 5.85 (s, 1H), 6.31 (s, 1H), 6.86 (d, 2H, *J*= 7.8 Hz), 7.28 (d, 2H, *J*=7.8 Hz)

^{13}C NMR :6 51.72, 55.14, 72.29, 113.77, 125.05, 128.01, 133.78, 142.59, 159.18,166.70

Methyl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate (115f):

This molecule was obtained as a colorless liquid *via* the Baylis-Hillman reaction between 2-chlorobenzaldehyde and methyl acrylate in the presence of a catalytic amount of DABCO, following the similar procedure described for the molecule **115a.**



Reaction time : 6 days

Yield : 83%

Bp. : 116-117 °C/0.4 mm

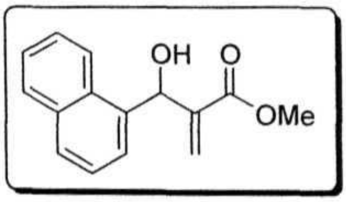
IR (Neat) : v3429, 1722, 1631 cm^{-1}

^1H NMR : 5 3.27 (b, 1H), 3.78 (s, 3H), 5.58 (s, 1H), 5.98 (s, 1H), 6.34 (s, 1H), 7.20-7.41 (m, 3H), 7.55-7.61 (m, 1H)

^{13}C NMR : 8 51.96, 69.26, 126.68, 126.99, 128.23, 128.96, 129.47, 132.91, 138.56, 140.96, 166.92

Methyl 3-hydroxy-2-methylene-3-(naphth-l-yl)propanoate (115g):

This was obtained as a colorless solid *via* the reaction of 1-naphthaldehyde with methyl acrylate in the presence of a catalytic amount of DABCO, following the similar procedure described for the molecule **115a.**



Reaction time : 7 days

Yield : 88%

Mp. : 107-110 °C

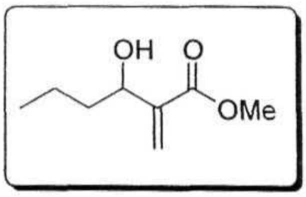
IR (KBr) : v 3211, 1724,1628 cm^{-1}

^{1}H NMR : 5 3.18 (b, 1H), 3.78 (s, 3H), 5.59 (s, 1H), 6.36 (s, 1H), 6.38 (s, 1H), 7.43-7.56 (m, 3H), 7.61-7.67 (m, 1H), 7.79-7.94 (m, 2H), 7.96-8.07 (m, 1H)

^{13}C NMR : 8 52.06, 69.21, 123.86, 124.54, 125.39, 125.65, 126.21, 127.06, 128.61, 128.78, 130.92, 133.88, 136.67, 142.08, 167.23

Methyl 3-hydroxy-2-methylenehexanoate (115h):

This molecule was prepared *via* the treatment of butyraldehyde with methyl acrylate in the presence of a catalytic amount of DABCO as a colorless liquid, following the similar procedure described for the molecule **115a**.



Reaction tirr : 6 days

Yield : 71%

Bp. : 81-82 °C/2 mm

IR (Neat) : ν 3437, 1718, 1631 cm^{-1}

^{1}H NMR : 8 0.94 (t, 3H, *J*= 7.8 Hz), 1.21-1.71 (m, 4H), 2.30 (b, 1H), 3.78 (s, 3H), 4.41 (t, 1H, *J* = 6.8 Hz), 5.79 (s, 1H), 6.22(s, 1H)

^{13}C NMR : 8 13.64, 18.78, 38.38, 51.58, 70.69, 124.40, 142.95, 166.94

Methyl 3-hydroxy-2-methylenenonanoate (115i):

This was obtained as a colorless liquid *via* the Baylis-Hillman reaction of 1-heptanal with methyl acrylate in the presence of a catalytic amount of DABCO, following the similar procedure described for the molecule **115a.**

Reaction time : 8 days

Yield : 75%

Bp. : 110-111 °C/4.1 mm

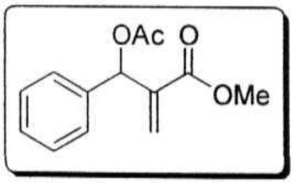
IR (Neat) : ν 3437, 1718, 1630 cm^{-1}

^{1}H NMR :8 0.88(t, 3H, J = 6.8 Hz), 1.12-1.78 (m, 10H), 2.52 (b, 1H), 3.78 (s, 3H), 4.30-4.49 (m, 1H),5.79(s, 1H),6.22(s. 1H)

^{13}C NMR : δ 13.83, 22.42, 25.57, 28.94, 31.64. 36.27, 51.53, 70.91, 124.35, 142.98, 166.87

Methyl 3-acetoxy-2-methylene-3-phenylpropanoate (116a):

To a solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(115a)** (20 mmol, 3.84 g) and pyridine (40 mmol, 3.16 g) in CH_2Cl_2 at 0 °C was added acetyl chloride (40 mmol, 3.14 g) slowly and stirred at room temperature for 3 h. Reaction mixture was diluted with ether (10 mL) and washed successively with aqueous 2N HC1 solution, water and $NaHCO_3$ solution. Organic layer was dried over anhyd. Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 3% EtOAc in hexanes) to provide the required compound **116a** as a colorless liquid.



Yield : 85% (3.77 g)

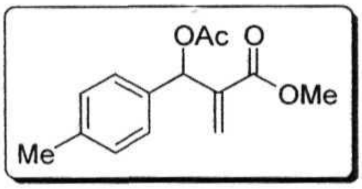
IR (Neat) : ν 1743, 1726 cm^{-1}

^{1}H NMR : 8 2.10 (s, 3H), 3.71 (s, 3H), 5.86 (s, 1H), 6.40 (s, 1H), 6.69 (s, 1H), 7.30-7.40 (m, 5H)

^{13}C NMR : 8 20.91, 51.84, 73.05, 125.66, 127.57, 128.37, 137.77, 139.68, 165.28, 169.28

Methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (116b):

This molecule was obtained as a colorless liquid *via* the treatment of methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate **(115b)** with acetyl chloride in the presence of pyridine following the similar procedure described for the molecule **116a.**



Yield : 83%

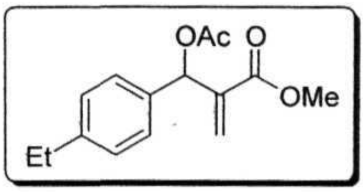
IR (Neat) : v 1745, 1728 cm^{-1}

^{1}H NMR : 8 2.09 (s, 3H), 2.33 (s, 3H), 3.70 (s, 3H), 5.86 (s, 1H), 6.38 (s, 1H), 6.65 (s, 1H), 7.14 (d, 2H, *J*= 8.0 Hz), 7.27 (d, 2H, *J*= 8.0 Hz)

^{13}C NMR : δ 20.89, 20.99, 51.74, 72.98, 125.24, 127.57, 129.06, 134.90, 138.05, 139.90, 165.34, 169.17

Methyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate (116c):

This was obtained *via* the reaction of methyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate **(115c)** with acetyl chloride in the presence of pyridine as a colorless liquid following the similar procedure described for the molecule **116a.**



Yield : 79%

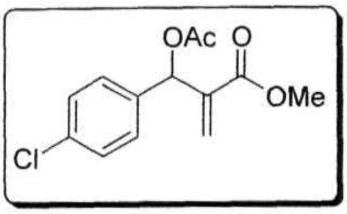
IR (Neat) : v 1745, 1728 cm^{-}

^{1}H NMR : 8 1.22 (t, 3H, *J* = 7.6 Hz), 2.09 (s, 3H), 2.64 (q, 2H, J = 7.6 Hz), 3.70 (s, 3H), 5.86 (s, 1H), 6.38 (s, 1H), 6.67 (s, 1H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz)

^{13}C NMR : 8 15.29, 20.98, 28.53, 51.83, 73.05, 125.34, 127.69, 127.93, 135.14, 139.97, 144.42, 165.42, 169.21

Methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (116d):

This molecule was obtained *via* the treatment of methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate **(115d)** with acetyl chloride in the presence of pyridine as a colorless liquid following the similar procedure described for the molecule **116a**.



Yield : 87%

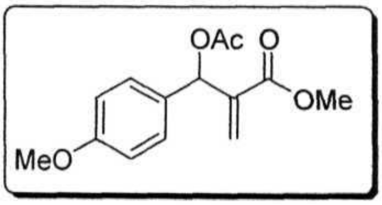
IR(Neat) :v 1745, 1720 cm"^{1}

^{1}H NMR : 8 2.10 (s, 3H), 3.70 (s, 3H), 5.88 (s, 1H), 6.40 (s, 1H), 6.63 (s, 1H),7.31(s,4H)

^{13}C NMR : 8 20.97, 51.99, 72.45, 125.81, 128.66, 129.09, 134.27, 136.50, 139.36, 165.19, 169.21

Methyl 3- acetoxy-3-(4-methoxyphenyl)-2-methylenepropanoate (116e):

This was obtained as a colorless liquid *via* the reaction of methyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate **(115e)** with acetyl chloride in the presence of pyridine following the similar procedure described for the molecule **116a.**



Yield : 77%

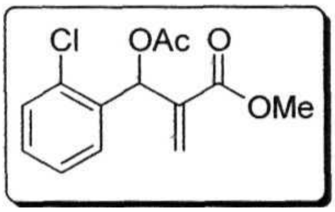
IR (Neat) : ν 1739, 1718 cm^{-1}

^{1}H NMR : 8 2.09 (s, 3H), 3.70 (s, 3H), 3.79 (s, 3H), 5.87 (s, 1H), 6.38 (s, 1H), 6.64 (s, 1H), 6.87 (d, 2H, J= 8.8 Hz), 7.30 (d, 2H, J= 8.8 Hz)

^{13}C NMR : 8 20.89, 51.77, 55.11, 72.82, 113.86, 124.95, 129.07, 129.92, 139.97,159.71, 165.36,169.24

Methyl 3-acetoxy-3-(2-chlorophenyl)-2-methylenepropanoate (116f):

This molecule was obtained as a colorless liquid *via* the treatment of methyl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate **(115f)** with acetyl chloride in the presence of pyridine following the similar procedure described for the molecule **116a.**



Yield : 82%

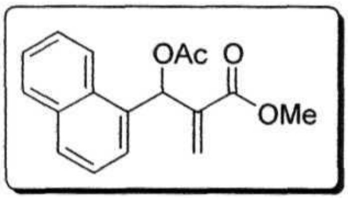
IR (Neat) :v 1745, 1724 cm^{-1}

^{1}H NMR : 6 2.12 (s, 3H), 3.74 (s, 3H), 5.65 (s, 1H), 6.46 (s, 1H), 7.04 (s, 1H), 7.23-7.42 (m,4H)

^{13}C NMR : 8 20.72, 51.97, 70.14, 126.85, 127.65, 128.45, 129.55, 129.85, 133.69, 135.47, 138.37, 165.29, 169.00

Methyl 3-acetoxy-2-methylene-3-(naphth-1-yl)propanoate (116g):

This was obtained *via* the reaction of methyl 3-hydroxy-2-methylene-3-(naphth-l-yl)propanoate **(115g)** with acetyl chloride in the presence of pyridine following the similar procedure described for the molecule **116a,** as a colorless liquid.



Yield : 79%

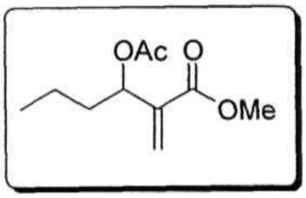
IR (Neat) :v 1745, 1722 cm''^{1}

^{1}H NMR : δ 2.13 (s, 3H), 3.72 (s, 3H), 5.71 (s, 1H), 6.47 (s, 1H), 7.33-7.63 (m, 5H), 7.75-7.92 (m, 2H), 8.00-8.12 (m, 1H)

^{13}C NMR : δ 20.94, 52.03, 69.96, 123.62, 125.12, 125.39, 125.87, 126.58, 127.42, 128.78, 129.24, 131.01, 133.51, 133.95, 139.48, 165.73, 169.49

Methyl 3-acetoxy-2-methylenehexanoate (116h):

This molecule was obtained *via* the treatment of methyl 3-hydroxy-2-methylene-hexanoate **(115h)** with acetyl chloride in the presence of pyridine as a colorless liquid following the similar procedure described for the molecule 116a.



Yield : 76%

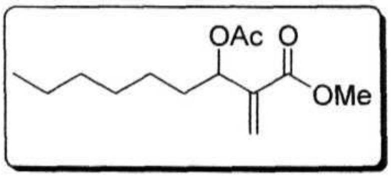
IR (Neat) : v 1745, 1720 cm^{-1}

^{1}H NMR : 5 0.92 (t, 3H, *J*= 6.8 Hz), 1.21-1.49 (m, 2H), 1.51-1.80 (m, 2H), 2.07 (s, 3H), 3.77 (s, 3H), 5.63 (t, 1H, *J*= 6.8 Hz), 5.75 (s, 1H), 6.27 (s, 1H)

^{13}C NMI : 8 13.10, 18.10, 20.24, 36.00, 51.21, 71.08, 124.11, 140.16,

Methyl 3-acetoxy-2-methylenenonanoate (116i):

This was obtained as a colorless liquid *via* the reaction of methyl 3-hydroxy-2-methylenenonanoate **(115i)** with acetyl chloride in the presence of pyridine following the similar procedure described for the molecule **116a**.



Yield : 86%

IR (Neat) :v 1745, 1724 cm^{-1}

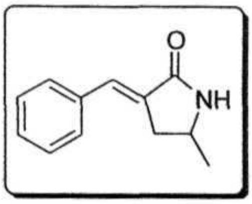
^{1}H NMR : 8 0.87 (t, 3H, *J* =6.8 Hz), 1.05-1.45 (m, 8H), 1.49-1.88 (m, 2H), 2.08 (s, 3H), 3.78 (s, 3H), 5.53-5.67 (m, 1H), 5.75 (s, 1H), 6.27 (s, 1H)

^{13}C NMR : 8 13.97, 20.99, 22.51, 25.23, 28.87, 31.62, 34.27, 51.85, 71.88, 124.93, 140.35, 165.78, 169.89

(*E*)-5-Methyl-3-benzylidenepyrrolidin-2-one (118):

One-pot procedure:

To a stirred mixture of nitroethane (8 mmol, 0.6 g) and K_2CO_3 (8 mmol, 1.104 g) in THF (5 mL) and water (0.1 mL) was added methyl 3-acetoxy-2-methylene-3-phenylpropanoate **(116a)** (2 mmol, 0.468 g) at room temperature. After stirring at room temperature for 12 h, THF and nitroethane were removed under reduced pressure. The reaction mixture was diluted with acetic acid (5 mL) and electrolytic Fe powder (12 mmol, 0.67 g) was added. The reaction mixture was heated under reflux (at 110 °C) for 2 h and then was allowed to cool to room temperature. Acetic acid was removed under reduced pressure and the reaction mixture was diluted with EtOAc (10 mL), stirred for 2 min and filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (2 x 10 mL). The filtrate and washings were combined and dried over anhydrous Na_2SO_4. Solvent (EtOAc) was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel) using 70% EtOAc in hexanes to afford (*E*)-5-methyl-3-benzylidenepyrrolidin-2-one **(118)** as a light yellow solid in 66% yield (0.247 g).



Mp. : 101-103 °C

IR (KBr) : ν 3200-2800 (multiple bands), 1685, 1647 cm^{-1}

^1H NMR : δ 1.32 (d, 3H, J = 6.0 Hz), 2.58-2.77 (m, 1H), 3.32 (ddd, 1H, J = 2.6, 7.8 & 17.6 Hz), 3.82-4.03 (m, 1H), 7.04 (b, 1H), 7.28-7.54 (m, 6H)

^{13}C NMR : 5 23.26, 34.95, 47.52, 128.35, 128.54, 129.41, 130.12, 131.33, 135.73, 172.05

EIMS (*m/z*) : 187 (M^+)

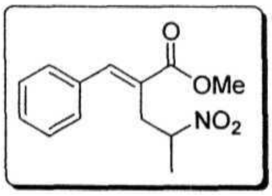
Analysis calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48

Found : C, 76.85; H, 7.03; N, 7.52

Two-step procedure:

First step: Methyl *(E)*-2-benzylidene-4-nitropentanoate (117a):

To a stirred mixture of nitroethane (8 mmol, 0.6 g) and K_2CO_3 (8 mmol, 1.104 g) in THF (5 mL) and water (0.1 mL) was added methyl 3-acetoxy-2-methylene-3-phenylpropanoate **(116a)** (2 mmol, 0.468 g) at room temperature. After stirring at room temperature for 12 h, THF and nitroethane were removed under reduced pressure and the reaction mixture was diluted with water and extracted with EtOAc (2 × 5 mL). The EtOAc layer was dried over anhydrous Na_2SO_4. Solvent (EtOAc) was evaporated [^{1}H NMR of the crude reaction mixture showed the presence of ≈ 5% (Z)-isomeric impurity as evidenced by the appearance of singlet at 8 6.86 (olefinic proton) in very low intensity] and the residue thus obtained was purified by silica gel column chromatography using 7% EtOAc in hexanes to afford methyl (*E*)-2-benzylidene-4-nitropentanoate **(117a)** in 80% isolated yield (0.4 g).



IR (Neat) : v 1712, 1633 cm^{-1}

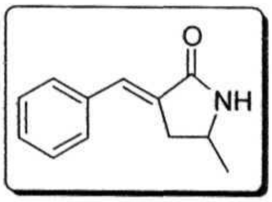
^{1}H NMR : δ 1.45 (d, 3H, *J* = 6.8 Hz), 2.95 & 3.29 (doublet of ABq, 2H, *J* = 7.8 & 13.6 Hz), 3.83 (s, 3H), 4.78-5.00 (m, 1H), 7.25-7.45 (m, 5H),7.88(s, 1H)

^{13}C NMR : δ 18.75, 32.80, 52.30, 81.68, 127.31, 128.77, 128.94, 134.64, 143.51, 167.65

^{1}H NMR spectra of this molecule is known in the literature and our data is in agreement with that of reported data.[222]

Second step: (*E*)-5-Methyl-3-benzylidenepyrrolidin-2-one (118):

Methyl (*E*)-2-benzylidene-4-nitropentanoate (1.6 mmol, 0.4 g) **(117a)** obtained above, was diluted with acetic acid (5 mL) and Fe powder (12 mmol, 0.67 g) was added. The reaction mixture was heated at 110 °C for 2 h. The reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The reaction mixture was diluted with EtOAc (10 mL) and stirred for 2 min and filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (2 ×10 mL). The filtrate and washings were combined and dried over anhydrous Na_2SO_4. Solvent (EtOAc) was removed under reduced pressure and the crude product thus obtained was purified by column chromatography (silica gel) using 70% EtOAc in hexanes to afford (*E*)-5-methyl-3-benzylidenepyrrolidin-2-one **(118)** as a light yellow solid in 71% yield (0.21 g) (the overall yield amounting to 57%).

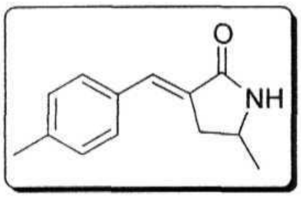


Mp. : 101-103 °C

The spectral data (IR, ^{1}H and ^{13}C NMR) are in full agreement with that of the molecule prepared in one-pot procedure.

(*E*)-5-Methyl-3-(4-methylbenzylidene)pyrrolidin-2-one (119):

This molecule was obtained as a light yellow solid *via* the treatment of methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (116b) with nitroethane and subsequent treatment of the *in situ* formed nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118**.



Yield : 65%

Mp. : 170-172 °C

IR (KBr) : ν 3100-2800 (multiple bands), 1668, 1635 cm^{-1}

^{1}H NMR : δ 1.31 (d, 3H, *J*= 6.6 Hz), 2.37 (s, 3H), 2.58-2.74 (m, 1H), 3.30 (ddd, 1H, *J* = 2.8, 7.8 & 17.4 Hz), 3.84-4.01 (m, 1H), 6.93(b, 1H), 7.21 (d, 2H, *J* = 8.0 Hz), 7.28-7.46 (m, 3H)

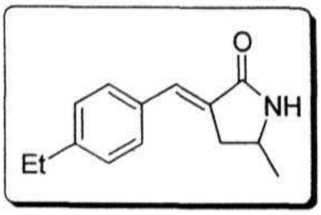
^{13}C NMR : δ 21.25, 23.33, 35.01, 47.53, 129.33, 129.47, 130.16, 132.98, 138.54, 172.25

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

Found : C, 77.50; H, 7.56; N, 6.90

(*E*)-5-Methyl-3-(4-ethylbenzylidene)pyrrolidin-2-one (120):

This was obtained *via* the reaction of methyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate **(116c)** with nitroethane and subsequent treatment of the resulting nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118** as a light yellow solid.



Yield : 68%

Mp. : 128-130 °C

IR (KBr) : v 3100-2820 (multiple bands), 1682, 1647 cm"^{1}

^{1}H NMR :8 1.24 (t, 3H,./= 7.4 Hz), 1.31 (d, 3H, J = 6.6 Hz), 2.58-2.75 (m, 3H), 3.31 (ddd, 1H,./= 2.4, 7.6 & 17.5 Hz), 3.82-4.00 (m, 1H), 6.98 (b, 1H), 7.23 (d, 2H, J = 8.0 Hz), 7.33 (t, 1H, J= 2.4 Hz), 7.40 (d, 2H, J = 8.0 Hz)

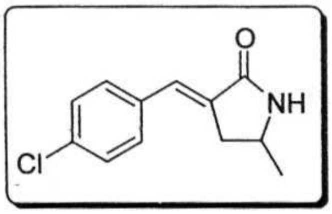
^{13}C NMR : 8 15.24, 23.31, 28.60, 34.99, 47.51, 128.09, 129.54, 130.12, 130.24, 133.22, 144.82, 172.26

Analysis calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. N, 6.51

Found : C, 78.34; H, 7.90; N, 6.46

(*E*)-5–Methyl-3-(4-chlorobenzylidene)pyrrolidin-2-one (121):

This molecule was prepared as a light yellow solid *via* the treatment of methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate **(116d)** with nitroethane and subsequent treatment of the *in situ* generated nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118.**



Yield : 64%

Mp. : 161-163 °C

IR (KBr) : v 3100-2800 (multiple bands), 1689, 1649 cm'^{1}

^{1}H NMR : δ 1.32 (d, 3H, J = 6.4 Hz), 2.55-2.70 (m, 1H), 3.29 (ddd, 1H, J = 2.8, 7.8 & 17.6 Hz), 3.84-4.02 (m, 1H), 7.16 (b, 1H), 7.29 (t, 1H, J= 2.8 Hz),7.35-7.47 (m, 4H)

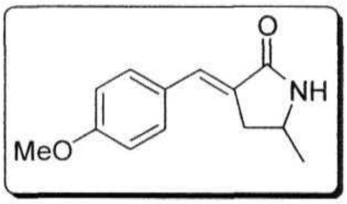
^{13}C NMR : 8 23.43, 35.07, 47.54, 128.98, 129.27, 130.74, 131.67, 134.31, 134.47, 171.62

Analysis calcd for $C_{12}H_{12}NOCl$: C, 65.01; H, 5.46; N, 6.32

Found : C, 64.87; H, 5.42; N, 6.38

(*E*)-5–Methyl-3-(4-methoxybenzylidene)pyrrolidin-2-one (122):

This compound was prepared by the treatment of methyl 3-acetoxy-3-(4-methoxyphenyl)-2-methylenepropanoate (116e) with nitroethane and subsequent treatment of the resulting nitro ester with Fe / AcOH as a light yellow solid following the one-pot procedure described for the molecule **118**



Yield : 62%

Mp. : 169-171 °C

IR (KBr) : v 3100-2900 (multiple bands), 1691, 1645 cm^{-1}

^1H NMR :5 1.31 (d, 3H, *J* = 6.0 Hz), 2.54-2.72 (m, 1H), 3.29 (ddd, 1H, *J*= 2.4, 7.8 & 17.4 Hz), 3.81-4.02 (m, 4H), 6.93 (d, 2H, *J* = 8.6 Hz), 7.09 (b, 1H), 7.29 (t, 1H, *J* =2.4 Hz), 7.42 (d, 2H, *J*= 8.6 Hz)

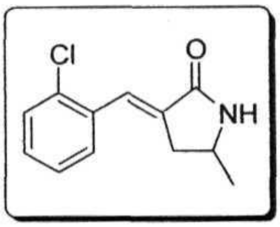
^{13}C NMR : 8 23.41, 34.99, 47.46, 55.27, 114.16, 128.56, 129.93, 131.07, 159.82, 172.33

Analysis calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45

Found : C, 72.11; H, 6.99; N, 6.52

(*E*)-5–Methyl-3-(2-chlorobenzylidene)pyrrolidin-2-one (123):

This molecule was prepared as a light yellow solid *via* the treatment of methyl 3-acetoxy-3-(2-chloropheny!)-2-methylenepropanoate **(116f)** with nitroethane and subsequent treatment of the *in situ* generated nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118**.



Yield : 55%

Mp. : 124-126 °C

IR (KBr) : v 3200-2820 (multiple bands), 1682, 1647 cm"^{1}

^{1}H NMR : 5 1.31 (d, 3H, J = 6.6 Hz), 2.52-2.69 (m, 1H), 3.23 (ddd, 1H, J= 2.4, 7.4 & 17.6 Hz), 3.80-4.00 (m, 1H), 7.14 (b, 1H), 7.19-7.52 (m, 4H), 7.67 (t, 1H, J=2.4 Hz)

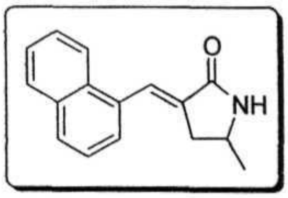
^{13}C NMR : 5 23.10, 34.75, 47.63, 126.42, 126.55, 129.16, 129.35, 129.88, 133.91, 134.06, 134.88, 171.46

Analysis calcd for $C_{12}H_{12}NOCl$: C, 65.01; H, 5.46; N, 6.32

Found : C, 64.81; H, 5.50; N, 6.27

(*E*)-5–Methyl-3-(1-naphthylidene)pyrrolidin-2-one (124):

This compound was prepared as a colorless solid by the reaction of methyl 3-acetoxy-2-methylene-3-(naphth-l-yl)propanoate **(116g)** with nitroethane and subsequent **treatment** of the resulting nitro ester with Fe / AcOH following the one-pot procedure described **for** the molecule **118.**



Yield : **67%**

Mp. : 179-181 °C

IR **(KBr)** : v 3200-2800 **(multiple** bands), 1691, 1651 cm"^{1}

^{1}H NMR : 8 1.31 (d, 3H, J= 6.4 Hz), 2.53-2.72 (m, 1H), 3.24 (ddd, 1H, J= 2.8, 7.6 & 17.6 Hz), 3.81-4.01 (m, 1H), 7.12 (b, 1H), 7.43-7.66 (m, 4H), 7.78-7.96 (m, 2H), 8.08 (t, 1H, J=2.8 Hz), 8.12-8.25 (m, 1H)

^{13}C NMR : δ 23.16, 34.99, 47.67, 124.24, 125.15, 125.99, 126.13, 126.46, 127.55, 128.61, 128.90, 131.90, 132.77, 133.70, 171.68

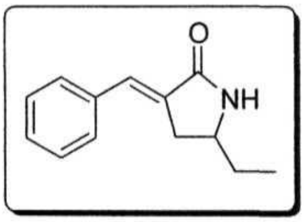
EIMS *(m/z)* : 237 (M^{+})

Analysis calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90

Found : C, 81.09; H, 6.39; N, 5.82

(*E*)-5-Ethyl-3-benzylidenepyrrolidin-2-one (125):

This molecule was obtained *via* the treatment of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (116a) with 1-nitropropane and subsequent treatment of the *in situ* generated nitro ester with Fe / AcOH as a light yellow solid following the one-pot procedure described for the molecule **118**.



Yield : 64%

Mp. : 125-127 °C

IR (KBr) : v 3200-2800 (multiple bands), 1685, 1651 cm'^{1}

^{1}H NMR : 8 0.99 (t, 3H, J= 7.8 Hz), 1.52-1.74 (m, 2H), 2.64-2.82 (m, 1H), 3.27 (ddd, 1H, J= 2.0, 7.6 & 17.6 Hz), 3.64-3.81 (m, 1H), 6.50 (b, 1H), 7.28-7.60 (m, 6H)

^{13}C NMR : 8 9.55, 30.18, 32.60, 53.27, 128.28, 128.50, 129.37, 129.87, 131.22, 135.68, 172.22

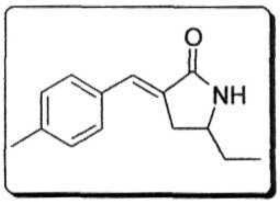
EIMS (*m/z*) : 201 (M^+)

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

:C, 77.40; H, 7.46; N, 7.01

(*E*)-5-Ethyl-3-(4-methylbenzylidene)pyrrolidin-2-one (126):

This compound was obtained as a light yellow solid *via* the treatment of methyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (116b) with 1-nitropropane and subsequent treatment of the resulting nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118**.



Yield : 62%

Mp. : 142-144 °C

IR (KBr) : ν 3200-2800 (multiple bands), 1691, 1651 cm^{-1}

^{1}H NMR : δ 0.98 (t, 3H, *J*= 7.6 Hz), 1.52-1.70 (m, 2H), 2.37 (s, 3H), 2.62-2.78 (m, 1H), 3.26 (ddd, 1H, *J*= 2.8, 7.8 & 17.6 Hz), 3.63-3.79 (m, 1H), 6.80 (b, 1H), 7.21 (d, 2H, *J* = 7.8 Hz), 7.31 (t, 1H, *J* =2.8 Hz), 7.37 (d, 2H, *J* =7.8 Hz)

^{13}C NMR : δ 9.58, 21.21, 30.26, 32.70, 53.28, 129.30, 129.44, 129.93, 130.12, 133.01, 138.46, 172.39

Analysis calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51

Found : C, 77.95; H, 7.99; N, 6.55

(*E*)-5–Ethyl-3-(4-chlorobenzylidene)pyrrolidin-2-one (127):

This molecule was prepared by the reaction of methyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (**116d**) with 1 -nitropropane and subsequent treatment of the *in situ* generated nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118** as a light yellow solid.

Yield : 63%

Mp. : 132-134 °C

IR (KBr) : v 3200-2800 (multiple bands), 1697, 1653 cm^{-1}

^{1}H NMR : 8 0.99 (t, 3H, *J*= 7.4 Hz), 1.52-1.72 (m, 2H), 2.61-2.78 (m, 1H), 3.23 (ddd, 1H, *J* = 2.8, 7.8 & 17.6 Hz), 3.65-3.81 (m, 1H), 7.05 (b, 1H), 7.29 (t, 1H, *J*= 2.8 Hz), 7.33-7.49 (m, 4H)

^{13}C NMR : δ 9.67, 30.32, 32.75, 53.33, 128.92, 130.69, 131.74, 134.33, 171.89

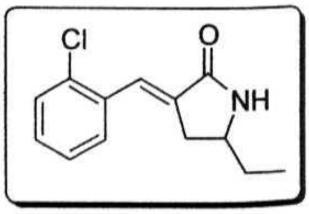
Analysis calcd for $C_{13}H_{14}NOCl$: C, 66.24; H, 5.99; N, 5.94

Found : C, 66.43; H, 5.99; N, 5.90

(*E*)-5–Ethyl-3-(2-chlorobenzylidene)pyrrolidin-2-one (128):

This molecule was obtained as a light yellow solid *via* the treatment of methyl 3-acetoxy-3-(2-chlorophenyl)-2-methylenepropanoate **(116f)** with 1-nitropropane and subsequent treatment of the resulting nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118.**

Yield : 60%



Mp. : 128-130 °C

IR (KBr) : v 3500-2800 (multiple bands), 1682, 1651 cm^{-1}

^{1}H NMR :6 1.01 (t, 3H, *J* = 7.0 Hz), 1.51-1.74 (m, 2H), 2.56-2.72 (m, 1H), 3.17 (ddd, 1H, *J* = 3.0, 7.8 & 17.6 Hz), 3.61-3.78 (m, 1H), 6.87 (b, 1H), 7.19-7.55 (m, 4H), 7.65 (t, 1H, *J*= 3.0 Hz)

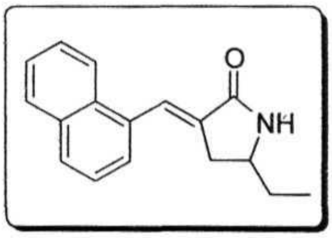
^{13}C NMR : 8 9.60, 30.06, 32.47, 53.37, 126.39, 126.56, 129.16, 129.34, 129.89, 133.86, 134.88, 171.57

Analysis calcd for $C_{13}H_{14}NOCl$: C, 66.24; H, 5.99; N, 5.94

Found : C, 66.06; H, 6.01; N, 6.00

(*E*)-5–Ethyl-3-(1-naphthylidene)pyrrolidin-2-one (129):

This compound was prepared by the reaction of methyl 3-acetoxy-2-methylene-3-(naphth-l-yl)propanoate **(116g)** with 1-nitropropane and subsequent treatment of the *in situ* generated nitro ester with Fe / AcOH as a colorless solid following the one-pot procedure described for the molecule **118**.



Yield :61%

Mp. : 123-125 °C

IR (KBr) : v 3200-2800 (multiple bands), 1693, 1649 cm$^{'1}$

^{1}H NMR : § 0.96 (t, 3H, *J*= 7.6 Hz), 1.48-1.72 (m, 2H), 2.57-2.74 (m, 1H), 3.18 (ddd, 1H, *J* =2.6, 7.6 & 17.4 Hz), 3.61-3.76 (m, 1H), 6.89 (b, 1H), 7.42-7.61 (m, 4H), 7.78-7.95 (m, 2H), 8.05 (t, 1H, *J* =2.6 Hz), 8.12-8.24 (m, 1H)

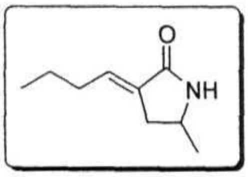
^{13}C NMR : 8 9.65, 30.10, 32.60, 53.42, 124.13, 125.09, 125.90, 126.03, 126.34, 127.13, 128.52, 128.77, 131.80, 132.70, 133.58, 133.77, 171.89

Analysis calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57

Found : C, 80.98; H, 6.76; N, 5.54

(*E*)-5-Methyl-3-butylidenepyrrolidin-2-one (130):

This molecule was obtained as a colorless liquid *via* the treatment of methyl 3-acetoxy-2-methylenehexanoate (116h) with nitroethane and subsequent treatment of the resulting nitro ester with Fe / AcOH following the one-pot procedure described for the molecule 118.



Yield : **52%**

IR (Neat) : v 3360-2820 (multiple bands), 1699, 1672 cm^{-1}

^{1}H NMR : 8 0.92 (t, 3H, J= 7.6 Hz), 1.24 (d, 3H, *J*= 6.2 Hz), 1.39-1.62 (m, 2H), 1.98-2.17 (m, 2H), 2.18-2.32 (m, 1H), 2.81-3.01 (m, 1H), 3.72-3.92 (m, 1H), 6.37-6.52 (m, 1H), 7.09 (b, 1H)

^{13}C NMR : 8 13.88, 21.84, 23.38, 31.47, 32.66, 47.23, 131.40, 133.56, 171.28

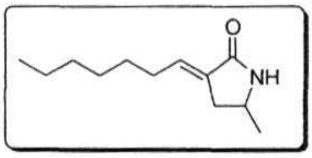
EIMS (*m/z*) : 153 (M^{+})

Analysis calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14

Found : C, 70.70; H, 9.96; N, 9.22

(*E*)-5-Methyl-3-heptylidenepyrrolidin-2-one (131):

This compound was prepared by the reaction of methyl 3-acetoxy-2-methylenenonanoate **(116i)** with nitroethane and subsequent treatment of the *in situ* generated nitro ester with Fe / AcOH following the one-pot procedure described for the molecule **118** as a colorless liquid.



Yield : 49%

IR (Neat) : v 3248, 3000-2820 (multiple bands), 1701, 1672 cm"^{1}

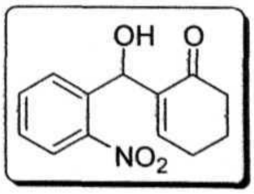
^{1}H NMR : 5 0.88 (t, 3H, *J* = 6.8 Hz), 1.18-1.57 (m, 11H), 2.05-2.20 (m, 2H), 2.21-2.37 (m, 1H), 2.84-3.01 (m, 1H), 3.71-3.91 (m, 1H), 6.38-6.51 (m, lH),6.55(b, 1H)

^{13}C NMR : 5 13.88, 22.39, 23.17, 28.09, 29.26, 31.39, 32.43, 47.33, 131.43, 133.56, 171.60

2-[Hydroxy(2-nitrophenyl)methyllcyclohex-2-enone (145a):

This molecule was prepared according to the procedure developed in our laboratory.[256]

A solution of 2-nitrobenzaldehyde **(143a)** (5 mmol, 0.755 g) and cyclohex-2-enone **(144a)** (10 mmol, 0.961 g) in methanolic trimethylamine (25% w/w) (5 mmol, 1.55 mL) was kept at room temperature for 2 days. Low boiling liquids were evaporated and the crude product thus obtained was purified by silica gel column chromatography (30% EtOAc in hexanes) to afford the desired Baylis-Hillman alcohol **145a** in 46% (0.568 g) yield, as a light yellow solid.



Mp, : 120-123 °C (lit.[284] 124-125 °C)

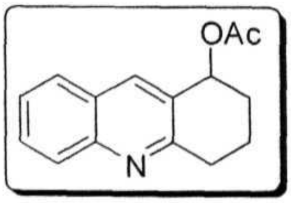
IR (KBr) : v3393, 1658, 1608 cm"^{1}

^{1}H NMR : 5 1.91-2.12 (m, 2H), 2.30-2.52 (m, 4H), 3.70 (b, 1H), 6.18 (s, 1H), 6.62 (t, 1H, *J* = 3.8 Hz), 7.40-7.51 (m, 1H), 7.60-7.71 (m, 1H), 7.81 (d, 1H, *J* = 7.8 Hz), 7.98 (d, 1H, *J*= 6.8 Hz)

^{13}C NMR : 8 22.40, 25.71, 38.23, 67.06, 124.37, 128.28, 128.94, 133.20, 136.65. 139.85. 147.09. 148.10, 199.57

1-Acetoxy-1,2,3,4-tetrahydroacridine (146a):

To a stirred solution of Baylis-Hillman alcohol i e., 2-[hydroxy(2-nitrophenyl)-methyl]cyclohex-2-enone **(145a)** (1 mmol, 0.247 g) in acetic acid (5 mL) was added electrolytic Fe powder (6 mmol, 0.335 g) and the reaction mixture was heated under reflux for 2 h. Then the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The reaction mixture was diluted with EtOAc (10 mL) and stirred for 2 min and filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (10 mL). The filtrate and washings were combined and dried over anhydrous Na_2SO_4. Solvent (EtOAc) was removed under reduced pressure and the crude product thus obtained was purified by column chromatography (silica gel) using 10% EtOAc in hexanes to afford the desired l-acetoxy-l,2,3,4-tetrahydroacridine **(146a)** as a light yellow solid in 73% (0.176 g) yield.



Mp. : 71-73 °C

IR (KBr) :v 1726, 1620 cm^{-1}

^{1}H NMR (400 MHz) : 8 1.98-2.31 (m, 7H), 3.07-3.32 (m, 2H), 6.23 (t, 1H, *J*= 5.2 Hz), 7.48-7.54 (m, 1H), 7.68-7.75 (m, 1H), 7.80 (d, 1H, *J*= 7.6 Hz), 8.02 (d, 1H, *J* = 8.8 Hz), 8.14 (s, 1H)

^{13}C NMR : 6 18.55, 21.30, 28.75, 32.85, 69.84, 125.80, 126.82, 127.65, 128.27, 128.77, 129.72, 136.62, 147.56, 158.45, 170.50

EIMS (*m/z*) : 241 (M^+)

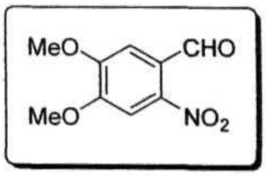
Anal calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80

Found : C, 74.87; H, 6.26; N, 5.75

4,5-Dimethoxy-2-nitrobenzaldehyde (143b):

This molecule is prepared according to the known procedure.[257]

To 4,5-dimethoxybenzaldehyde (30 mmol, 4.98 g), conc. HNO_3 (30 mL) was added with stirring at room temperature and the reaction mixture was heated at 40 °C for 30 min. The reaction mixture was poured into ice-cold water and the yellow precipitate thus obtained was filtered. The precipitate was shaken with aqueous sodium bisulfate solution **and** filtered **to** remove any insoluble solid. The filtrate was treated with aqueous sodium hydroxide solution to regenerate the aldehyde as a yellow solid. The crude solid thus obtained was crystallized from methanol at 0 °C to afford the pure 4,5-dimethoxy-2-nitrobenzaldehyde **(143b)** as a yellow crystalline solid in 49% (3.24 g) yield.



Mp. : 126-127 °C (lit.[257] 128 °C)

IR (KBr) : v 1685 cm"^{1}

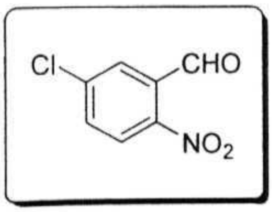
^{1}H NMR (400 MHz) : 8 4.05 (s, 3H), 4.06 (s, 3H), 7.44 (s, 1H), 7.64 (s, 1H), 10.47 (s, 1H)

^{13}C NMR : 8 56.69, 107.13, 109.67, 125.44, 143.75, 152.34, 153.14, 187.54

5-Chloro-2-nitrobenzaldehyde (143c):

This molecule is prepared according to the literature procedure.

To a stirred mixture of 3-chlorobenzaldehyde (20 mmol, 2.81 g) and KNO_3 (20.2 mmol, 2.04 g) at 0 °C was added slowly drop-wise conc. H_2SO_4 (20.5 mL) at 0 °C and the stirring was continued at the same temperature for 30 min. The reaction mixture was poured into ice-cold solution. The solid thus obtained was filtered and recrystallized from methanol to furnish 5-chloro-2-nitrobenzaldehyde (**143c**) as colorless needles in 87% (3.23 g) yield



Mp. : 72-75 °C (lit.[258] 77.5 °C)

IR (KBr) :v 1697 cm^{-1}

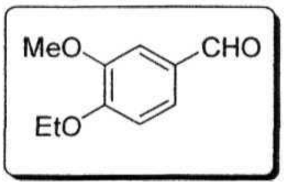
^1H NMR : δ 7.71 (dd, 1H, J = 2.2, 8.6 Hz), 7.88 (d, 1H, J = 2.2 Hz), 8.11 (d, 1H, J = 8.6 Hz), 10.40 (s, 1H)

^{13}C NMR : 5 126.20, 129.68, 132.90, 133.44, 141.26, 147.71, 186.72

4-Ethoxy-5-methoxy-2-nitrobenzaldehyde (143d):

4-Ethoxy-3-methoxybenzaldehyde:

To a stirred mixture of vanillin (30 mmol, 4.56 g) and anhydrous K_2CO_3 (90 mmol, **12.43** g) in acetonitrile (50 mL) was added ethyl bromide (60 mmol, 4.47 mL) at room temperature. After stirring at 45 °C for 36 h, the reaction mixture was cooled to room temperature and the solvent was evaporated. The residue was diluted with water (10 mL) and extracted with ether (2 x 20 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated. The product thus obtained was purified by column chromatography (silica gel, 15% EtOAc in hexanes) to afford the pure 4-ethoxy-3-methoxybenzaldehyde as a light brown solid in 87% (4.7 g) yield.



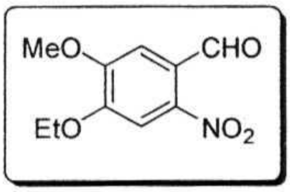
M.p : 55-57 °C

IR (KBr) : 1678 cm^{-1}

^{1}H NMR : 5 1.51 (t, 3H, *J* = 6.8 Hz), 3.93 (s, 3H), 4.19 (q, 2H, *J* = 6.8 Hz), 6.96 (d, 1H, *J* = 7.8 Hz), 7.39-7.54 (m, 2H), 9.84 (s, 1H)

^{13}C NMR : 5 14.37, 55.75, 64.41, 109.09, 111.18, 126.48, 129.76, 149.58, 153.77, 190.59

The reaction of HNO_3 with 4-ethoxy-3-methoxybenzaldehyde (obtained above) at 40 °C following the similar procedure described for the molecule **143b,** provided 4-ethoxy-3-methoxy-2-nitrobenzaldehyde as a light yellow crystalline solid.



Yield : 17%

Mp. : 157-161 °C

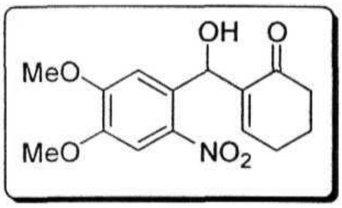
IR (KBr) : v 1689 cm^{1}

^{1}H NMR : 8 1.54 (t, 3H, *J* = 6.8 Hz), 4.01 (s, 3H), 4.25 (q, 2H, *J* = 6.8 Hz), 7.41 (s, 1H), 7.59 (s, 1H), 10.44 (s, 1H)

^{13}C NMR (400 MHz) : δ 14.39, 56.71, 65.53, 107.85, 109.81, 125.27, 143.89, 151.84, 153.34, 187.76

2-[Hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclohex-2-enone (145b):

This molecule was prepared *via* the reaction between 4,5-dimethoxy-2-nitrobenzaldehyde **(143b)** and cyclohex-2-enone **(144a)** under the influence of methanolic trimethylamine, following the similar procedure described for the molecule **145a** as a light yellow solid.



Yield : 35%

Mp. : 112-114 °C

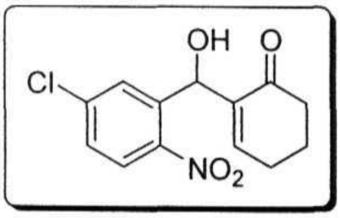
IR (KBr) : v 3352, 1658, 1616 cm^{1}

^{1}H NMR : 6 1.90-2.08 (m, 2H), 2.26-2.40 (m, 2H), 2.44-2.60 (m, 2H), 3.83 (d, 1H, *J* = 4.0 Hz), 3.94 (s, 3H), 3.99 (s, 3H), 6.31 (d, 1H, J = 4.0 Hz), 6.43 (t, 1H, *J* = 3.8 Hz), 7.34 (s, 1H), 7.63 (s, 1H)

^{13}C NMR : 6 22.32, 25.54, 38.07, 56.17, 56.24, 66.67, 107.83, 110.11, 132.12, 139.63, 140.38, 146.08, 147.66, 153.33, 199.48

2-[Hydroxy(5-chloro-2-nitrophenyl)methyl]cyclohex-2-enone (145c):

This molecule was prepared *via* the Baylis-Hillman reaction of 5-chloro-2-nitrobenzaldehyde **(143c)** with cyclohex-2-enone (144a) under the influence of methanolic trimethylamine, following the similar procedure described for the molecule **145a** as a light yellow solid.



Yield : 23%

Mp. : 127-129 °C

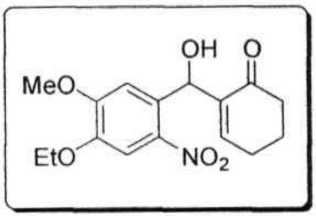
IR (KBr) : v 3391, 1655, 1602 cm^{1}

^{1}H NMR : 8 1.91-2.10 (m, 2H), 2.30-2.55 (m, 4H), 3.66 (b, 1H), 6.20 (s, 1H), 6.60 (t, 1H, *J* = 5.0 Hz), 7.41 (dd, 1H, *J* = 2.0, 8.8 Hz), 7.83 (d, 1H, *J* = 2.0 Hz), 7.92 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR : 8 22.37, 25.71, 38.16, 66.68, 126.02, 128.39, 129.20, 139.07, 139.63, 139.99, 146.13, 147.19, 199.40

2-[Hydroxy(4-ethoxy-5-methoxy-2-nitrophenyl)methyl]cyclohex-2-enone (145d):

This compound was obtained as a light yellow solid *via* the treatment of 4-ethoxy-5-methoxy-2-nitrobenzaldehyde **(143d)** with cyclohex-2-enone **(144a)** under the influence of methanolic trimethylamine, following the similar procedure described for the molecule **145a.**



Yield : 29%

Mp. : 138-142 °C

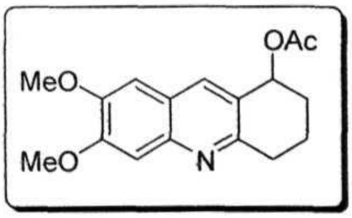
IR (KBr) : v3431, 1666, 1612 cm"1

^{1}H NMR (400 MHz) : 5 1.52 (t, 3H, *J* = 6.8 Hz), 1.95-2.05 (m, 2H), 2.28-2.40 (m, 2H), 2.45-2.60 (m, 2H), 3.81 (b, 1H), 4.05 (s, 3H), 4.18 (q, 2H, *J* = 6.8 Hz), 6.33 (s, 1H), 6.44 (t, 1H, *J* = 4.0 Hz), 7.35 (s, 1H), 7.65 (s, 1H)

^{13}C NMR : 5 14.45, 22.42, 25.64, 38.19, 56.32, 64.89, 66.96, 108.97, 110.33, 131.84, 139.75, 140.45, 146.13, 147.11, 153.71, 199.68

1-Acetoxy-6,7-dimethoxy-1,2,3,4-tetrahydroacridine(146b):

This molecule was obtained as a colorless solid *via* the reaction of 2-[hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclohex-2-enone **(145b)** with Fe / AcOH, following the similar procedure described for the molecule **146a.**



Yield : 76%

Mp. : 98-100 °C

IR (KBr) : v 1730, 1620 cm"1

^{1}H NMR : 6 1.88-2.29 (m, 7H), 2.91-3.30 (m, 2H), 3.99 (s, 3H), 4.01 (s, 3H), 6.17 (t, 1H, *J* =4.8 Hz), 7.01 (s, 1H), 7.34 (s, 1H), 7.97 (s, 1H)

^{13}C NMR : 5 18.63, 21.40, 28.87, 32.46, 55.94, 56.08, 69.96, 104.99, 106.83, 122.35, 126.82, 135.36, 144.67, 149.43, 152.97, 155.93, 170.72

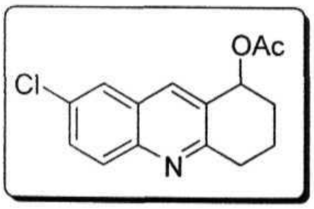
MS (*m/z*) : 302 (M^++H)

Anal calcd for $C_{17}H_{19}NO_4$:C, 67.76; H, 6.36; N, 4.6

Found :C, 67.87; H, 6.35; N, 4.6

1-Acetoxy-7-chloro-1,2,3,4-tetrahydroacridine (146c):

This molecule was obtained as a light brown solid by the reductive cyclization of 2-[hydroxy(5-chloro-2-nitrophenyl)methyl]cyclohex-2-enone (145c) using Fe / AcOH following the similar procedure described for the molecule 146a.



Yield : 78%

Mp. : 79-81 °C

IR (KBr) :v 1734, 1620 cm^{-1}

^{1}H NMR (400 MHz) : 5 1.94-2.27 (m, 7H), 2.99-3.11 (m, 1H), 3.15-3.25 (m, 1H), 6.15 (t, 1H, *J* =4.0 Hz), 7.57 (dd, 1H, *J*= 2.0 & 8.8 Hz), 7.71 (d, 1H, *J* = 2.0 Hz), 7.90 (d, 1H, *J*= 8.8 Hz), 8.00 (s, 1H)

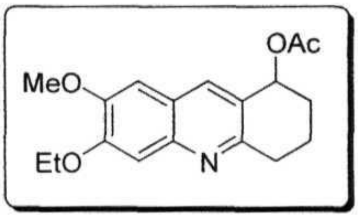
^{13}C NMR : 5 18.61, 21.38, 28.77, 32.87, 69.79, 126.34, 127.50, 130.00, 130.75, 131.60, 135.70, 145.99, 159.01, 170.58

Anal calcd for $C_{15}H_{14}NO_2Cl$: C, 65.34; H, 5.12; N, 5.08

Found : C, 65.40; H, 5.09; N, 5.10

1-Acetoxy-6-ethoxy-7-methoxy-1,2,3,4-tetrahydroacridine (146d):

This compound was prepared *via* the treatment of 2-[hydroxy(4-ethoxy-5-methoxy-2-nitrophenyl)methyl]cyclohex-2-enone **(145d)** with Fe / AcOH, as a colorless solid following the similar procedure described for the molecule **146a.**



Yield : 66%

Mp. : 58-61 °C

IR (KBr) : v 1707, 1622 cm^{-1}

^{1}H NMR : δ 1.55 (t, 3H, J = 7.4 Hz), 1.90-2.29 (m, 7H), 2.90-3.28 (m, 2H), 3.98 (s, 3H), 4.25 (q, 2H, J = 7.4 Hz), 6.17 (t, 1H, J = 4.8 Hz), 7.00 (s, 1H), 7.31 (s, 1H), 7.95 (s, 1H)

^{13}C NMR : δ 14.54, 18.78, 21.45, 29.02, 32.68, 56.04, 64.43, 70.11, 105.18, 107.76, 122.29, 126.77, 135.22, 144.97, 149.72, 152.32, 155.98, 170.78

EIMS (*m/z*) : 315 (M$^+$)

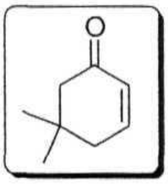
Anal calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44

Found : C, 68.39; H, 6.78; N, 4.41

5,5-Dimethylcyclohex-2-enone (144b):

This molecule was prepared according to the known procedure."

A mixture of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (275 mmol, 38.5 g), absolute ethanol (35 mL), benzene (300 mL) and *p*-toluenesulfonic acid (1 g) was heated under reflux with continuous removal of water. After the complete removal of water (≈ 24 h), the mixture was fractionally distilled to give enol ether as colorless liquid, which on immersing in a dry-ice bath (liquid N_2/EtOAc) set to a glass and crystallized on warming (Mp.: 56 °C). This enol ether was then dissolved in dry ether (300 mL) and was added lithium aluminum hydride (100 mmol, 3.8 g) with stirring over a period of 5 minutes at room temperature. A vigorous reaction occurred. After stirring for 1 h at room temperature, reaction mixture was poured into water and diluted with aqueous H2SO4. Organic layer was separated and the water layer was extracted with ether (3 x 25 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and the residue thus obtained, was distilled to afford the desired enone **144b** in 74% (25.2 g) yield, as a colorless liquid.



Bp. : 60-62 °C/5 mm (lit.[259] 74-75 °C/11 mm)

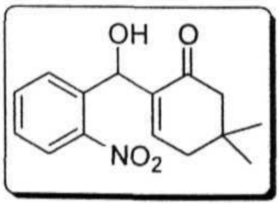
IR (Neat) : ν 1672 cm^{-1}

^1H NMR : 5 1.05 (s, 6H), 2.12-2.36 (m, 4H), 6.04 (td, 1H, *J* = 10.0 & 2.0 Hz), 6.86 (td, 1H, *J* = 10.0 & 4.0 Hz)

^{13}C NMR : 8 28.02, 33.58, 39.62, 51.50, 128.64, 148.20, 199.48

5,5-Dimethyl-2-[hydroxy(2-nitrophenyl)methyl]cyclohex-2-enone(147a):

This molecule was prepared *via* the reaction between 2-nitrobenzaldehyde **(143a)** and 5,5-dimethylcyclohex-2-enone **(144b)** under the influence of methanolic trimethylamine, following the similar procedure described for the molecule **145a** as a light yellow solid.



Yield : 42%

Mp. : 88-91 °C

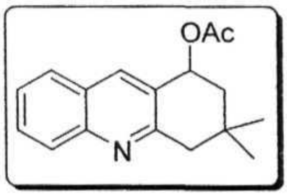
IR (KBr) : ν 3375, 1660, 1610 cm^{-1}

^1H NMR : 8 1.03 (s, 6H), 2.24 (d, 2H, *J* = 4.8 Hz), 2.33 (s, 2H), 3.65 (d, 1H, *J* = 5.0 Hz), 6.22 (d, 1H, *J* = 5.0 Hz), 6.44 (t, 1H, *J* = 4.8 Hz), 7.40-7.54 (m, 1H), 7.61-7.73 (m, 1H), 7.84 (d, 1H, J = 7.8 Hz), 7.95 (d, 1H, J = 9.8 Hz)

^{13}C NMR : 5 27.81, 28.32, 33.86, 39.67, 51.72, 66.60, 124.35, 128.20, 128.89, 133.19, 136.72, 139.16, 144.65, 147.89, 199.53

1-Acetoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridine (148a):

This molecule was obtained as a colorless solid *via* the reaction of 5,5-dimethyl-2-[hydroxy(2-nitrophenyl)methyl]cyclohex-2-enone **(147a)** with Fe / AcOH following the similar procedure described for the molecule **146a.**



Yield : 82%

Mp. : 62-64 °C

IR (KBr) : v 1732, 1622 cm^{-1}

^{1}H NMR : 5 1.08 (s, 3H), 1.17 (s, 3H), 1.75-1.89 (m, 1H), 2.05-2.27 (m, 4H), 2.92 & 3.03 (ABq, 2H, J = 17.2 Hz), 6.25 (t, 1H, J =7.4 Hz), 7.40-7.55 (m, 1H), 7.60-7.71 (m, 1H), 7.77 (d, 1H, J= 7.8 Hz), 8.00 (d, 1H, J = 8.6 Hz), 8.05 (s, 1H)

^{13}C NMR : 5 21.25, 27.23, 30.28, 30.61, 41.67, 47.11, 69.46, 125.81, 126.90, 127.53, 128.03, 128.33, 129.53, 135.16, 147.54, 157.86, 170.66

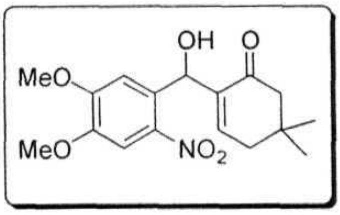
EIMS (*m/z*) : 269 (M^+)

Anal calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20

Found :C, 75.88; H, 7.17; N, 5.19

5,5-Dimethyl-2-[hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclohex-2-enone (147b):

This molecule was prepared *via* the reaction between 4,5-dimethoxy-2-nitrobenzaldehyde **(143b)** and 5,5-dimethylcyclohex-2-enone **(144b)** under the influence of methanolic trimethylamine, following the similar procedure described for the molecule **145a** as a light yellow solid.



Yield : 20%

Mp. : 155-158 °C

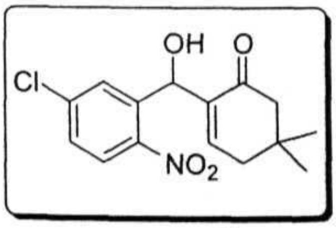
IR (KBr) : v 3387, 1657, 1614 cm^{-1}

^{1}H NMR (400 MHz) : 5 1.04 (s, 6H), 2.22 (d, 2H, *J* = 4.0 Hz), 2.33 & 2.40 (ABq, 2H, *J* = 16.0 Hz), 3.75 (b, 1H), 3.97 (s, 3H), 4.01 (s, 3H), 6.30 (t, 1H, *J* = 4.0 Hz), 6.34 (s, 1H), 7.37 (s, 1H), 7.66 (s, 1H)

^{13}C NMR : 8 27.70, 28.38, 33.86, 39.62, 51.71, 56.23, 56.33, 66.61, 107.90, 110.12, 132.19, 139.66, 143.86, 147.70, 153.39, 199.67

5,5-Dimethyl-2-[hydroxy(5-chloro-2-nitrophenyl)methyl]cyclohex-2-enone (147c):

This compound was obtained *via* the Baylis-Hillman reaction of 5-chloro-2-nitrobenzaldehyde **(143c)** with 5,5-dimethylcyclohex-2-enone **(144b)** under the influence of methanolic trimethylamine, following the similar procedure described for the molecule **145a,** as a light brown solid.



Yield : 22%

Mp. : 116-118 °C

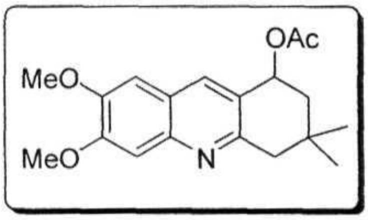
IR (KBr) : v 3335, 1653, 1606 cm''^{1}

^{1}H NMR : 5 1.03 (s, 6H), 2.24 (d, 2H,./ = 4.0 Hz), 2.34 (s, 2H), 3.64 (b, 1H), 6.24 (s, 1H), 6.41 (t, 1H, *J* = 4.0 Hz), 7.42 (dd, 1H, *J* = 1.8, 8.8 Hz), 7.87 (d, 1H, *J* = 1.8 Hz), 7.94 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR : 5 27.90, 28.36, 33.96, 39.73, 51.72, 66.49, 126.11, 128.39, 129.24, 138.95, 139.09, 140.11, 144.82, 145.98, 199.57

1-Acetoxy-6,7-dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridine (148b):

This molecule was obtained as a colorless solid *via* the reaction of 5,5-dimethyl-2-[hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclohex-2-enone (147b) with Fe / AcOH following the similar procedure described for the molecule 146a.



Yield : 62%

Mp. : 112-115 °C

IR (KBr) :v 1732, 1622 cm"

^{1}H NMR : 5 1.06 (s, 3H), 1.15 (s, 3H), 1.70-1.89 (m, 1H), 2.05-2.24 (m, 4H), 2.84 & 2.96 (ABq, 2H, *J* = 16.6 Hz), 3.99 (s, 3H), 4.01 (s, 3H), 6.22 (t, 1H, *J* = 6.8 Hz), 7.01 (s, 1H), 7.33 (s, 1H), 7.90 (s, 1H)

^{13}C NMR : 8 21.19, 27.20, 30.06, 30.59, 41.68, 46.78, 55.76, 55.82, 69.59, 104.87, 106.98, 122.32, 125.90, 133.54, 144.66, 149.35, 152.66, 155.20, 170.68

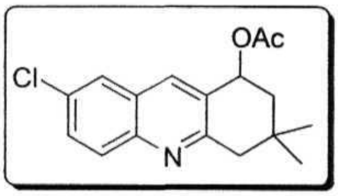
MS (*m/z*) : 330 (M^++H)

Anal calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25

Found : C, 69.16; H, 7.00; N, 4.29

1-Acetoxy-7-chloro-3,3-dimethyl-1,2,3,4-tetrahydroacridine (148c):

This compound was prepared *via* the treatment of 5,5-dimethyl-2-[hydroxy(5-chloro-2-nitrophenyl)methy!]cyclohex-2-enone (147c) with Fe / AcOH as a light brown solid following the similar procedure described for the molecule **146a.**



Yield : 80%

Mp. : 124-126 °C

IR (KBr) :v 1726, 1614 cm"^{1}

^{1}H NMR : 5 1.07 (s, 3H), 1.16 (s, 3H), 1.71-1.90 (m, 1H), 2.06-2.31 (m, 4H), 2.88 & 2.99 (ABq, 2H, *J* = 18.6 Hz), 6.22 (t, 1H, *J* = 6.8 Hz), 7.59 (dd, 1H, *J* = 1.8 & 8.8 Hz), 7.76 (d, 1H, *J* = 1.8 Hz), 7.92 (d, 1H, *J* = 8.8 Hz), 7.96 (s, 1H)

^{13}C NMR : 5 21.28, 27.25, 30.40, 30.67,41.66, 47.09, 69.33, 126.19, 127.53, 129.20, 130.05, 130.46, 131.50, 134.17, 145.94, 158.38, 170.68

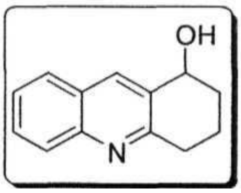
EIMS (*m/z*) : 303 (M$^+$), 305 (M$^+$+2)

Anal calcd for $C_{17}H_{18}NO_2Cl$: C, 67.21; H, 5.97; N, 4.61

Found : C, 67.49; H, 6.00; N, 4.58

l-Hydroxy-l,2,3,4-tetrahydroacridine(149a):

A mixture of l-acetoxy-l,2,3,4-tetrahydroacridine **(146a)** (0.5 mmol, 0.120 g), K_2CO_3 (1.5 mmol, 0.207 g) in methanol (2 mL) containing a drop of water was stirred at room temperature for 1 h. The salts were removed by filtration and washed with methanol (2 x 5 mL). The filtrate and washings were combined. Solvent was removed and the crude product obtained was subjected to crystallization from methanol at 0 °C to provide 1 hydroxy-l,2,3,4-tetrahydroacridine **(149a)** as a colorless solid in 80% (0.079 g) yield.



Mp. : 161-163 °C

IR (KBr) : ν 3196 cm^{-1}

^{1}H NMR : 6 1.84-2.33 (m, 5H), 3.05-3.23 (m, 2H), 4.95-5.10 (m, 1H), 7.41-7.56 (m, 1H), 7.61-7.74 (m, 1H), 7.78 (dd, 1H, J = 1.2 & 8.0 Hz), 7.99 (d, 1H, J = 8.6 Hz), 8.25 (s, 1H)

^{13}C NMR : 5 18.95, 32.51, 33.12, 68.58, 125.85, 127.26, 127.67, 128.28, 129.54, 133.40, 135.39, 147.37, 158.53

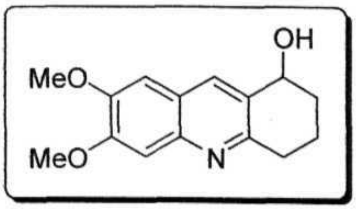
MS (*m/z*) : 200 (M$^+$+H)

Anal calcd for C$_{13}$H$_{13}$NO : C, 78.36; H, 6.58; N, 7.03

Found : C, 78.49; H, 6.55; N, 7.10

6,7-Dimethoxy-1-hydroxy-1,2,3,4-tetrahydroacridine (149b):

This compound was obtained as colorless solid by the hydrolysis of 1-acetoxy-6,7-dimethoxy-l,2,3,4-tetrahydroacridine **(146b)** with aqueous K$_2$CO$_3$ in methanol following the similar procedure described for the molecule **149a.**



Yield : 72%

Mp. : 133-136°C

IR (KBr) : ν 3119 cm^{-1}

^{1}H NMR : 6 1.80-2.45 (m, 5H), 2.90-3.20 (m, 2H), 3.97 (s, 3H), 3.98 (s, 3H), 4.90-5.01 (m, 1H), 6.94 (s, 1H), 7.30 (s, 1H), 8.05 (s, 1H)

^{13}C NMR : 5 18.97, 32.58, 32.80, 56.02, 56.09, 68.46, 104.99, 107.03, 122.65, 131.33, 133.98, 144.46, 149.41, 152.68, 155.83

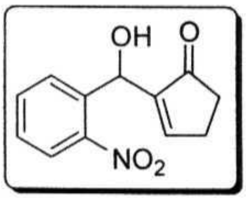
Anal calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40

Found : C, 69.26; H, 6.64; N, 5.36

2-[Hydroxy(2-nitrophenyl)methyl]cyclopent-2-enone (150a):

This molecule was prepared following the procedure as reported in the literature.

A solution of 2-nitrobenzaldehyde **(143a)** (2.5 mmol, 0.377 g), cyclopent-2-enone **(144c)** (2.75 mmol, 0.225 g) and imidazole (2.5 mmol, 0.17 g) in 5 mL of THF was charged with 5 mL of deionized water and stirred at room temperature for 36 h. The reaction mixture was extracted with ethyl acetate (3 x 20 mL). The ethyl acetate layer was dried over anhyd. Na_2SO_4 and concentrated and the residue thus obtained was purified by column chromatography (silica gel, 15% EtOAc in hexanes) to furnish the title compound **(150a)** as a colorless solid in 66% (0.378 g) yield.



Mp. : 98-100 °C

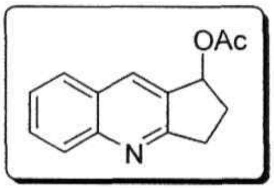
IR (KBr) : v3342, 1687, 1628 cm^{-1}

^{1}H NMR : 8 2.43-2.76 (m, 4H), 4.14 (d, 1H, *J* = 4.4 Hz), 6.18 (d, 1H, *J* = 4.4 Hz), 7.23 (t, 1H, *J* = 2.0 Hz), 7.40-7.55 (m, 1H), 7.61-7.75 (m, 1H), 7.87 (d, 1H, *J* = 7.8 Hz), 7.98 (d, 1H, *J* = 7.6 Hz)

^{13}C NMR : δ 26.64, 34.96, 64.86, 124.44, 128.44, 128.82, 133.54, 136.64, 145.92, 147.61, 160.02,209.13

1-Acetoxy-2,3-dihydro-1*H*-cyclopenta[b]quinoline (151a):

To a stirred solution of 2-[hydroxy(2-nitrophenyl)methyl]cyclopent-2-enone **(150a)** (1 mmol, 0.233 g) in acetic acid (5 mL) was added Fe powder (6 mmol, 0.335 g) and the reaction mixture was heated at 60 °C for 2 h. Then the reaction mixture was worked-up following the similar procedure as mentioned for the molecule **146a** and the product thus obtained, was purified by column chromatography (silica gel, 8% EtOAc in hexanes) to afford 1-acetoxy-2,3-dihydro-1*H*-cyclopenta[b]quinoline **(151a)** as a viscous colorless liquid in 79% yield (0.179 g).



IR(Neat) : v 1736, 1626 cm''^{1}

^{1}H NMR (400 MHz) : 5 2.11 (s, 3H), 2.25-2.36 (m, 1H), 2.56-2.68 (m, 1H), 3.11-3.21 (m, 1H), 3.35-3.46 (m, 1H), 6.31-6.37 (m, 1H), 7.50-7.57 (m, 1H), 7.69-7.76 (m, 1H), 7.84 (dd, 1H, *J* = 1.2 & 8.4 Hz), 8.07 (d, 1H, *J* = 8.4 Hz), 8.22 (s, 1H)

^{13}C NMR : 6 21.02, 30.51, 31.96, 75.53, 125.76, 127.03, 128.24, 128.55, 129.60, 132.82, 133.36, 148.81, 166.03, 170.76

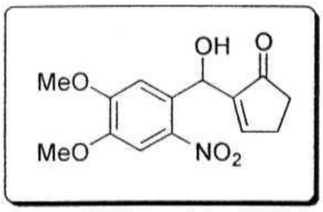
Anal calcd for $C_{14}H_{13}NO_2$:C, 73.99; H, 5.77; N, 6.16

Found :C, 73.77; H, 5.82; N, 6.09

2-[Hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclopent-2-enone (150b):

This molecule was obtained as a white solid *via* the reaction of 4,5-dimethoxy-2-nitrobenzaldehyde **(143b)** with cyclopent-2-enone **(144c)** in the presence of imidazole as catalyst following the similar procedure described for the molecule **150a.**

Yield : **37%**



Mp. : 125-127 °C

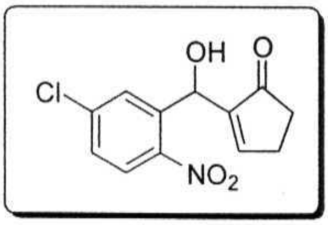
IR (KBr) : v3497, 1689, 1626 cm$^{"1}$

^{1}H NMR (400 MHz) : 5 2.48-2.70 (m, 4H), 3.97 (s, 3H), 4.01 (s, 3H), 4.23 (b, 1H), 6.30 (s, 1H), 7.13 (t, 1H, *J* = 2.4 Hz), 7.39 (s, 1H), 7.66 (s, 1H)

^{13}C NMR : 6 26.49, 34.95, 56.26, 56.35, 64.82, 107.78, 109.91, 132.28, 139.42, 146.12, 147.88, 153.63, 159.55,209.33

2-[Hydroxy(5-chloro-2-nitrophenyl)methyl]cyclopent-2-enone (150c):

This molecule was obtained as a brown solid *via* the Baylis-Hillman reaction of 5-chloro-2-nitrobenzaldehyde **(143c)** with cyclopent-2-enone **(144c)** using imidazole as catalyst following the similar procedure described for the molecule 150a.



Yield : 35%

Mp. : 112-114 °C

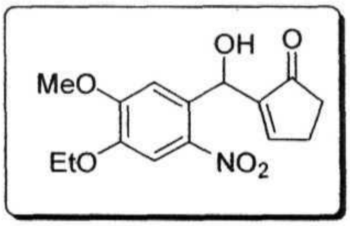
IR (KBr) : v 3337, 1684, 1620 cm$^{"1}$

^{1}H NMR (400 MHz) : 5 2.48-2.71 (m, 4H), 4.13 (b, 1H), 6.23 (s, 1H), 7.20-7.24 (m, 1H), 7.46 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.90 (d, 1H, *J* = 2.4 Hz), 8.00 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR : 8 26.76, 34.96, 64.53, 126.19, 128.64, 129.07, 139.04, 140.45, 145.59, 160.17,209.20

2-[Hydroxy(4-ethoxy-5-methoxy-2-nitrophenyl)methyl]cyclopent-2-enone (150d):

This compound was prepared *via* the treatment of 4-ethoxy-5-methoxy-2-nitrobenzaldehyde **(143d)** with cyclopent-2-enone **(144c)** in the presence of imidazole as catalyst as a light brown solid following the similar procedure described for the molecule 150a.



Yield : 33%

Mp. : 140-142 °C

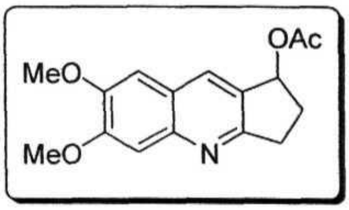
IR (KBr) : ν 3302, 1684, 1630 cm^{-1}

^{1}H NMR (400 MHz) : 8 1.53 (t, 3H, *J*= 7.0 Hz), 2.45-2.68 (m, 4H), 4.01 (s, 3H), 4.11-4.25 (m, 3H), 6.30 (s, 1H), 7.13-7.17 (m, 1H), 7.38 (s, 1H), 7.66 (s, 1H)

^{13}C NMR : 8 14.51, 26.59, 35.06, 56.43, 64.99, 65.23, 108.92, 110.11, 131.94, 139.56, 146.11, 147.34, 154.01, 159.55,209.59

1-Acetoxy-2,3-dihydro-6,7-dimethoxy-1*H*-cyclopenta[b]quinoline (151b):

This compound was obtained as a colorless solid *via* the treatment of 2-[hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclopent-2-enone **(150b)** with Fe / AcOH following the similar procedure described for the molecule **151a.**



Yield : 63%

Mp. : 108-111 °C

IR (KBr) : v 1728, 1620 cm"^{1}

^{1}H NMR : 8 2.07 (s, 3H), 2.17-2.35 (m, 1H), 2.47-2.69 (m, 1H), 2.97-3.16 (m, 1H), 3.25-3.44 (m, 1H), 3.99 (s, 3H), 4.02 (s, 3H), 6.28 (dd, 1H, *J*= 3.6 & 7.0 Hz), 7.05 (s, 1H), 7.39 (s, 1H), 8.04 (s, 1H)

^{13}C NMR : 8 21.03, 30.44, 31.76, 55.80, 55.86, 75.96, 105.75, 107.39, 122.32, 130.93, 131.80, 145.89, 149.14, 152.55, 163.61, 170.83

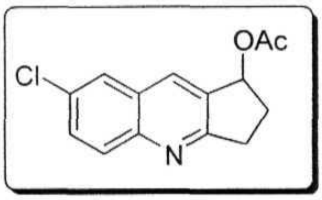
EIMS (*m/z*) : 287 (M$^+$)

Anal calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87

Found : C, 67.08; H, 5.94; N, 4.91

1-Acetoxy-7-chloro-2,3-dihydro-1*H*-cyclopenta[b]quinoline (151c):

This compound was obtained as a light green solid by the reaction of 2-[hydroxy(5-chloro-2-nitrophenyl)methyl]cyclopent-2-enone (150c) with Fe / AcOH following the similar procedure as described for the molecule 151a.



Yield : 74%

Mp. : 90-92 °C

IR (KBr) :v 1724, 1622 cm^{-1}

^1H NMR : 8 2.09 (s, 3H), 2.18-2.38 (m, 1H), 2.52-2.73 (m, 1H), 3.05-3.21 (m, 1H), 3.28-3.48 (m, 1H), 6.29 (dd, 1H, *J* = 4.0 & 6.8 Hz), 7.63 (dd, 1H, *J* = 2.0 & 8.8 Hz), 7.79 (d, 1H, *J* = 2.0 Hz), 7.98 (d, 1H, *J* = 8.8 Hz), 8.10 (s, 1H)

^{13}C NMR : 8 21.01, 30.61, 32.02, 75.44, 126.92, 127.84, 130.26, 130.46, 131.62, 132.40, 134.00, 147.39, 166.55, 170.77

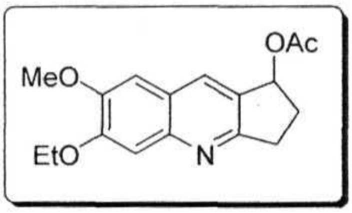
EIMS *(m/z)* : 261 (M^+), 263 (M^++2)

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

Found : C, 64.35; H, 4.62; N, 5.40

1-Acetoxy-2,3-dihydro-6-ethoxy-7-methoxy-1*H*-cyclopenta[b]quinoline (151d):

This molecule was prepared by the reductive cyclization of 2-[hydroxy(4-ethoxy-5-methoxy-2-nitrophenyl)methyl]cyclopent-2-enone **(150d)** with Fe / AcOH as a light green solid following the similar procedure described for the molecule **151a.**



Yield : 61%

Mp. : 97-99 °C

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

^{1}H NMR : δ 1.55 (t, 3H, *J*= 6.8 Hz), 2.08 (s, 3H), 2.16-2.36 (m, 1H), 2.49-2.70 (m, 1H), 2.99-3.20 (m, 1H), 3.24-3.47 (m, 1H), 3.99 (s, 3H), 4.26 (q, 2H, *J* = 6.8 Hz), 6.28 (dd, 1H, *J* = 3.8 & 6.8 Hz), 7.05 (s, 1H), 7.37 (s, 1H), 8.05 (s, 1H)

^{13}C NMR : δ 14.46, 21.21, 30.57, 31.88, 55.94, 64.34, 76.12, 105.91, 108.14, 122.31, 130.95, 132.01, 146.03, 149.48, 152.00, 163.69, 171.07

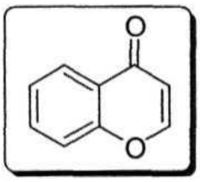
Anal calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65

Found : C, 67.71; H, 6.40; N, 4.63

1-Benzopyran-4(4*H*)-one (152a):

This molecule is prepared according to the literature procedure.[261]

To a stirred solution of 2-hydroxyacetophenone (25 mmol, 3.4 g, 3 mL) in ethyl formate (375 mmol, 27.8 g, 30.3 mL) was added NaH (60% dispersion in oil) (125 mmol, 5 g) in portions for 15 minutes at 0 °C. The reaction mixture was kept at room temperature for 12 h. Ice cold water was then added carefully and the resulting solution was extracted with ether (2 x 30 mL) to remove any starting materials. The separated aqueous layer was then acidified with acetic acid and extracted with ether (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product, thus obtained, was treated with dilute sulfuric acid (16 mL of 98% H_2SO_4 mixed with 70 mL of H_2O) and heated under reflux for 2 h. The reaction mixture was cooled to room temperature and diluted with ether. Organic layer was separated and washed with water, saturated aqueous $NaHCO_3$ solution and was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was subjected to column chromatography (silica gel, 10% EtOAc in hexanes) to afford the desired compound **152a** in 54% (1.97 g) yield as a colorless solid.

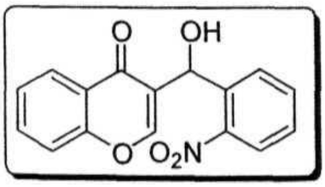


Mp.	: 55-57 °C (lit.[261] 59 °C)
IR (KBr)	:v 1651, 1610 cm^{-1}
^{1}H NMR (400 MHz)	: 8 6.36 (d, 1H, *J* = 6.0 Hz), 7.43-7.53 (m, 2H), 7.66-7.74 (m, 1H), 7.88 (d, 1H, *J* = 6.0 Hz), 8.23 (d, 1H, *J* = 6.8 Hz)
^{13}C NMR (100 MHz)	: 8 112.78, 118.05, 124.69, 125.08, 125.55, 133.63, 155.27, 156.32, 177.42

3-[Hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (153a):

This was prepared according to the procedure developed by our research group.[39]

A solution of 1-benzopyran-4(4*H*)-one (152a) (2 mmol, 0.292 g) and 2-nitro-benzaldehyde **(143a)** (2 mmol, 0.302 g) in methanolic trimethylamine (25% w/w) (2 mmol, 0.118 g, 0.62 mL) was kept at room temperature for 2 days. Solvent was evaporated and the residue thus obtained, was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to provide the desired adduct **(153a)** in 78% (0.463 g) yield, as a colorless solid.

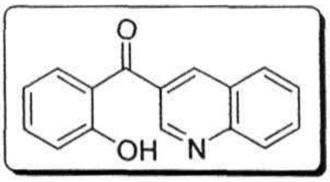


Mp.	: 148-151 °C (lit.[39] 150-152 °C)
IR (KBr)	: v 3339, 1639, 1604 cm^{-1}
^{1}H NMR (400 MHz)	:8 4.57(b, 1H), 6.49(s, 1H), 7.41-7.57 (m, 3H), 7.67-7.78 (m, 2H), 7.80 (s, 1H), 7.95 (d, 1H, *J* =8.0 Hz), 8.00 (d, 1H, *J* = 8.0 Hz), 8.21 (d, 1H, *J* = 8.0Hz)

^{13}C NMR : 6 66.28, 118.28, 123.86, 124.69, 125.54, 125.83, 128.86, 129.30, 133.61, 134.20, 136.06, 148.34, 153.84, 156.42, 177.88

3-(2-Hydroxyphenyl)carbonylquinoline(155a):

To a stirred solution of 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one **(153a)** (1 mmol, 0.297 g) in acetic acid (5 mL) was added Fe powder (6 mmol, 0.335 g) and the reaction mixture was refluxed for 2 h. Then, the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The reaction mixture was diluted with EtOAc (10 mL) and stirred for 2 min and filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (10 mL). The filtrate and washings were combined and dried over anhydrous Na$_2$SO$_4$. Solvent (EtOAc) was removed under reduced pressure and the crude product thus obtained was purified by column chromatography (silica gel) using 70% EtOAc in hexanes to afford 3-(2-hydroxyphenyl)carbonylquinoline (155a) as a light yellow solid in 56% yield (0.14 g).



Mp. : 70-73 °C

IR (KBr) : v 1628, 1606, 1587 cm"^{1}

^{1}H NMR (400 MHz) : 8 6.90-7.00 (m, 1H), 7.13 (d, 1H, *J* = 8.4 Hz), 7.55-7.78 (m, 3H), 7.85-7.93 (m, 1H), 7.95 (d, 1H, *J*= 8.4 Hz), 8.21 (d, 1H, *J*= 8.4 Hz), 8.50 (d, 1H, *J*= 2.0 Hz), 9.21 (d, 1H, *J* =2.0 Hz), 11.91 (s 1H, D$_2$O exchangeable)

^{13}C NMR : 8 118.67, 119.04, 126.43, 127.72, 128.91, 129.44, 130.51, 131.75, 133.06, 136.84, 137.81, 149.16, 149.31, 163.21, 199.11

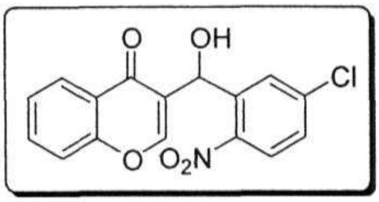
MS *(m/z)* : 250 (M$^+$+H)

Analysis calcd for $C_{16}H_{11}NO_2$: C, 77.10; H,4.45;N, 5.62

Found : C, 77.38; H, 4.48; N, 5.63

3-[Hydroxy(5-chloro-2-nitrophenyl)methyl]-4*H*-chromen-4-one (153b):

This compound was prepared *via* the treatment of 1 -benzopyran-4(4*H*)-one **(152a)** with 5-chloro-2-nitrobenzaldehyde **(143c)** under the influence of methanolic Me_3N as a colorless solid, following the similar procedure described for the molecule **153a.**



Yield : 68%

Mp. : 165-168 °C

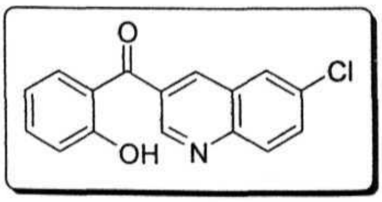
IR (KBr) : v3393, 1630, 1602 cm"^{1}

^{1}H NMR (400 MHz) : 5 4.55 (b, 1H), 6.50 (s, 1H), 7.42-7.55 (m, 3H), 7.69-7.80 (m, 1H), 7.82 (s, 1H), 7.96 (d, 1H, *J* = 2.0 Hz), 7.99 (d, 1H, *J*= 8.8 Hz), 8.21 (dd, 1H, *J*= 2.0, 8.8 Hz)

^{13}C NMR (100 MHz) : 8 66.01, 118.29, 123.70, 124.03, 125.63, 125.76, 126.27, 128.99, 129.45, 134.34, 138.22, 140.45, 146.26, 153.76, 156.33, 177.76

6-Chloro-3-(2-hydroxyphenyl)carbonylquinoline(155b):

This molecule was obtained *via* the treatment of 3-[hydroxy(5-chloro-2-nitrophenyl)methyl]-4*H*-chromen-4-one **(153b)** with Fe / AcOH following the similar procedure described for the molecule **155a** as a light yellow solid.



Yield : 62%

Mp. : 116-119 °C

IR (KBr) : v 1626, 1608, 1585 cm^{-1}

^{1}H NMR (400 MHz) : 8 6.90-7.05 (m, 1H), 7.15 (d, 1H, *J*= 8.4 Hz), 7.56-7.74 (m, 2H), 7.81 (d, 1H, *J* = *92* Hz), 7.95 (s, 1H), 8.16 (d, 1H, *J*= 8.8 Hz), 8.41 (s, 1H),9.19(s, 1H), 11.86 (s 1H)

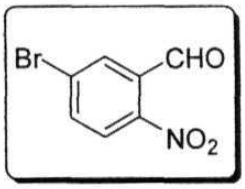
^{13}C NMR : 6 118.96, 119.23, 127.26, 127.48, 131.26, 131.50, 132.69, 133.06, 133.78, 136.67, 137.18, 147.68, 149.58, 163.50, 198.91

Analysis calcd for $C_{16}H_{10}NO_2Cl$: C, 67.74; H, 3.55; N, 4.94

Found : C, 67.57; H, 3.52; N, 4.96

5-Bromo-2-nitrobenzaldehyde (143e):

This molecule was prepared *via* the reaction of 3-bromobenzaldehyde with KNO_3 and conc. H_2SO_4 following the similar procedure described for the molecule 143c.



Yield : 83%

Mp. : 69-72 °C (lit.[258] 74 °C)

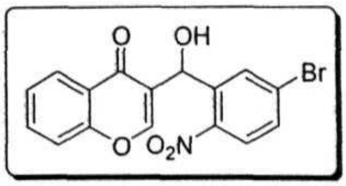
IR (KBr) : v 1695, 1599 cm^1

^{1}H NMR (400 MHz) : 8 7.85-7.93 (m, 1H), 8.00-8.11 (m, 2H), 10.43 (s, 1H)

^{13}C NMR : δ 126.07, 129.41, 132.52, 136.47, 148.04, 186.68

3-[Hydroxy(5-bromo-2-nitrophenyl)methyl]-4*H*-chromen-4-one (153c):

This compound was obtained as a colorless solid *via* the Baylis-Hillman reaction of 1-benzopyran-4(4*H*)-one **(152a)** with 5-bromo-2-nitrobenzaldehyde **(143e)** under the influence of methanolic Me_3N, following the similar procedure described for **the** molecule **153**



Yield : 60%

Mp. : 151-154°C

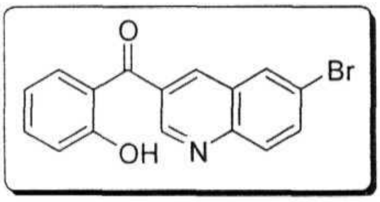
IR (KBr) : v3400, 1631, 1602 cm$^{"1}$

^{1}H NMR (400 MHz) :84.54(b, lH),6.49(s, 1H), 7.41-7.56 (m, 2H), 7.64 (dd, 1H, *J* = 2.0, 8.8 Hz), 7.70-7.77 (m, 1H), 7.81 (s, 1H), 7.89 (d, 1H, *J* = 8.8 Hz), 8.11 (d, 1H, *J* =2.0 Hz), 8.21 (dd, 1H, *J* = 2.0, 8.8 Hz)

^{13}C NMR (100 MHz) : 8 65.96, 118.34, 123.75, 124.16, 125.67, 125.82, 126.27, 128.97, 132.09, 132.48, 134.38, 138.17, 146.86, 153.82, 156.39, 177.77

6-Bromo-3-(2-hydroxyphenyl)carbonylquinoline (155c):

This compound was obtained as a light yellow solid *via* the treatment of 3-[hydroxy(5-bromo-2-nitrophenyl)methyl]-4*H*-chromen-4-one (153c) with Fe / AcOH following the similar procedure described for the molecule 155a.



Yield :41%

Mp. : 119-121 °C

IR (KBr) :v 1624, 1608, 1585 cm$^{"1}$

^{1}H NMR (400 MHz) : 8 6.90-7.00 (m, 1H), 7.16 (d, 1H, *J* = 8.8 Hz), 7.52-7.66 (m, 2H), 7.95 (dd, 1H, *J* = 2.0, 8.8 Hz), 8.10 (d, 1H, *J* =8.8 Hz), 8.13 (d, 1H, *J* = 2.0 Hz), 8.41 (d, 1H, *J* = 2.0 Hz), 9.21 (d, 1H, .7= 2.0 Hz), **11.87** (s **1H)**

^{13}C NMR : δ 118.89, 119.16, 121.80, 127.67, 130.80, 131.26, 131.38, 132.98, 135.14, 136.50, 137.08, 147.83, 149.67, 163.40, 198.72

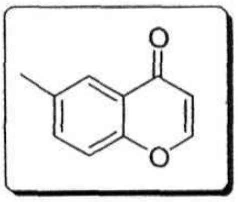
MS (*m/z*) : 328 (M$^+$+H); 330 [(M$^+$+H)+2]

Analysis calcd for $C_{16}H_{10}NO_2Br$: C, 58.56; H, 3.07; N, 4.27

Found : C, 58.76; H, 3.09; N, 4.23

6-Methyl-1-benzopyran-4(4*H*)-one (152b):

This molecule was prepared from 2-hydroxy-5-methylacetophenone and ethyl formate following the similar procedure described for the molecule 152a.



Yield : 66%

Mp. : 85-87 °C (lit.^{261} 88-89 °C

IR (KBr) : v 1649, 1620 cm"^{1}

^{1}H NMR (400 MHz; : 5 2.46 (s, 3H), 6.34 (d, 1H, *J* = 6.0 Hz), 7.37 (d, 1H, *J* = 8.4 Hz), 7.49(d, 1H, *J* = 8.4 Hz), 7.85 (d, 1H, *J* = 6.0 Hz), 8.01 (s, 1H)

^{13}C NMR : 6 20.74, 112.70, 117.82, 124.56, 125.02, 134.81, 135.09, 154.76, 155.05, 177.44

3-[Hydroxy(2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (153d):

This compound was prepared *via* the treatment of 6-methyl-1-benzopyran-4(4*H*)-one **(152b)** with 2-nitrobenzaldehyde **(143a)** under the influence of methanolic Me_3N as a colorless solid, following the similar procedure described for the molecule **153a.**

Yield : 69%

Mp. : 168-170 °C

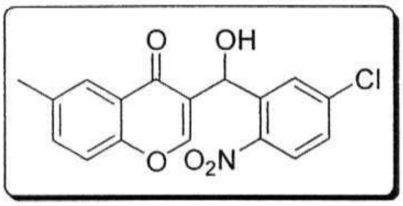
IR (KBr) : v 3321, 1637, 1601 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.47 (s, 3H), 4.64 (d, 1H, *J*= 6.0 Hz), 6.48 (d, 1H, *J*= 6.0 Hz), 7.38 (d, 1H, J= 8.8 Hz), 7.48-7.56 (m, 2H), 7.67-7.74 (m, 1H), 7.76 (s, 1H), 7.94-8.03 (m, 3H)

^{13}C NMR (100 MHz, DMSO-d_6) : 5 20.29, 62.29, 118.11, 122.68, 123.80, 124.08, 125.93, 128.40, 129.08, 132.82, 134.98, 135.25, 136.89, 148.31, 153.82, 154.04, 175.02

3-[Hydroxy(5-chloro-2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (153e):

This compound was obtained *via* the Baylis-Hillman reaction of 6-methyl-1-benzopyran-4(4*H*)-one **(152b)** with 5-chloro-2-nitrobenzaldehyde (143c) under the influence of methanolic Me_3N as a colorless solid, following the similar procedure described for the molecule **15:**



Yield : 49%

Mp. : 139-141 °C

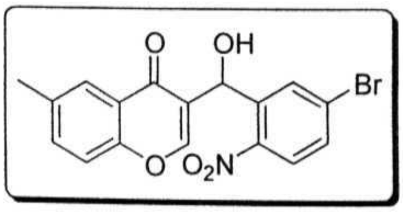
IR (KBr) : ν 3232, 1651, 1628, 1601 cm^{-1}

^{1}H NMR (400 MHz) : 8 2.47 (s, 3H), 4.60 (b, 1H), 6.49 (s, 1H), 7.39 (d, 1H, *J* = 8.8 Hz), 7.46 (dd, 1H, *J*= 2.0, 8.8 Hz), 7.53 (dd, 1H, *J*= 2.0, 8.8 Hz), 7.79 (s, 1H), 7.94-8.02 (m,3H)

^{13}C NMR (100 MHz) : 8 21.03, 66.11, 118.06, 123.42, 123.86, 125.01, 126.28, 128.96, 129.52, 135.66, 135.76, 138.43, 140.44, 146.30, 153.71, 154.69, 177.88

3-[Hydroxy(5-bromo-2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (153f):

This molecule was prepared as a colorless solid *via* the treatment of 6-methyl-1-benzopyran-4(4*H*)-one **(152b)** with 5-bromo-2-nitrobenzaldehyde **(143e)** under the influence of methanolic Me_3N, following the similar procedure described for the molecule **153a.**



Yield : 52%

Mp. : 145-147 °C

IR (KBr) : ν 3217, 1649, 1630 cm^{1}

^{1}H NMR (400 MHz) : 8 2.45 (s, 3H), 2.85 (b, 1H), 6.49 (s, 1H), 7.37 (d, 1H, *J* = 8.8

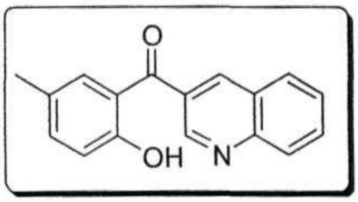
Hz), 7.51 (d, 1H, *J* = 8.8 Hz), 7.60 (dd, 1H, *J* = 2.0 & 8.8 Hz), 7.79(s, 1H),7.86(d, 1H, *J*= 8.8 Hz), 7.95 (s, 1H),8.10(d, 1H, *J*= 2.0 Hz)

^{13}C NMR (100 MHz) : 8 21.02, 65.97, 118.05, 123.39, 123.91, 125.01, 126.22, 128.91, 132.00, 132.46, 135.65, 135.74, 138.31, 146.81, 153.70, 154.67, 177.84

3-(2-Hydroxy-5-methylphenyl)carbonylquinoline (155d):

This compound was prepared *via* the treatment of 3-[hydroxy(2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (153d) with Fe / AcOH following the similar procedure described for the molecule 155a as a light yellow solid.

Yield ; 50%



Mp. : 79-81 °C

IR (KBr) : v 1630, 1609, 1587 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.28 (s, 3H), 7.06 (d, 1H, *J*= 9.6 Hz), 7.38-7.44 (m, 2H), 7.67-7.74 (m, 1H), 7.88-7.94 (m, 1H), 7.99 (d, 1H, *J*= 8.0 Hz), 8.23 (d, 1H, *J* = 8.8 Hz), 8.52 (d, 1H, *J* = 2.0 Hz), 9.21 (d, 1H, *J* = 2.0 Hz), 11.75 (s 1H)

^{13}C NMR : 8 20.43, 118.50, 118.96, 126.63, 127.67, 128.28, 128.93, 129.54, 130.85, 131.67, 132.67, 137.64, 137.93, 149.36, 161.27, 199.06

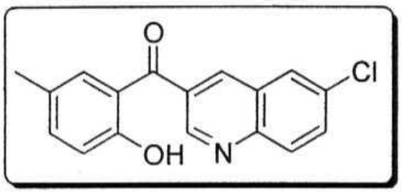
MS *(m/z)* : 264 (M$^+$+H)

Analysis calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32

Found : C, 77.71; H, 5.02; N, 5.35

6-Chloro-3-(2-hydroxy-5-methylphenyl)carbonylquinoline(155e):

This molecule was obtained as a light yellow solid *via* the reaction of 3-[hydroxy(5-chloro-2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (153e) with Fe / AcOH following the similar procedure described for the molecule **155a.**



Yield : 48%

Mp. : 116-118 °C

IR (KBr) : ν 1624, 1608, 1587 cm^{-1}

^1H NMR (400 MHz) : δ 2.28 (s, 3H), 7.06 (d, 1H, *J* = 8.4 Hz), 7.35 (s, 1H), 7.41 (d, 1H, *J* = 8.4 Hz), 7.82 (d, 1H, *J* = 9.2 Hz), 7.96 (s, 1H), 8.17 (d, 1H, *J* = 9.2 Hz), 8.41 (s, 1H), 9.18 (s, 1H), 11.70 (s 1H)

^{13}CNMR : δ 20.53, 118.72, 118.87, 127.48, 128.50, 131.26, 131.75, 132.62, 133.74, 136.53, 138.32, 147.64, 149.60, 161.46, 198.82

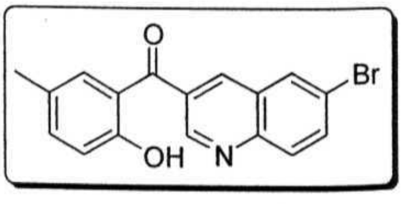
MS (*m/z*) : 298 (M^++H); 300 [(M^++H)+2]

Analysis calcd for $C_{17}H_{12}NO_2Cl$: C, 68.58; H, 4.06; N, 4.70

Found : C, 68.49; H, 4.02; N, 4.65

6-Bromo-3-(2-hydroxy-5-methylphenyl)carbonylquinoline (155f):

This compound was prepared *via* the treatment of 3-[hydroxy(5-bromo-2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (153f) with Fe / AcOH as a light yellow solid following the similar procedure described for the molecule **155a.**



Yield : 46%

Mp. : 123-125 °C

IR (KBr) : ν 1630, 1604, 1582 cm^{1}

^{1}H NMR (400 MHz) : 5 2.28 (s, 3H), 7.06 (d, 1H, *J* = 8.8 Hz), 7.34 (d, 1H, *J* = 2.0 Hz), 7.41 (dd, 1H, *J* = 2.0, 8.8 Hz), 7.94 (dd, 1H, .7= 2.0, 8.8 Hz), 8.10 (d, 1H, *J* = 8.8 Hz), 8.14 (d, 1H, *J*= 2.0 Hz), 8.40 (d, 1H, *J* = 2.0 Hz), 9.19 (d, 1H, *J* = 2.0 Hz), 11.69 (s 1H)

^{13}C NMR : 5 20.45, 118.60, 118.77, 121.68, 127.70, 128.37, 130.75, 131.19, 131.55, 132.47, 135.00, 136.33, 138.17, 147.68, 149.65, 161.32, 198.55

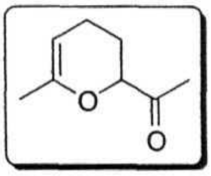
Analysis calcd for $C_{17}H_{12}NO_2Br$: C, 59.67; H, 3.53; N, 4.09

Found :C, 59.73; H, 3.50; N, 4.13

2-Acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174):

This molecule was prepared according to the procedure reported in the literature.

Methyl vinyl ketone (150 mmol, 10.5 g) and hydroquinone (0.95 mmol, 0.105 g) were taken in a steel bomb and kept in a thermostat at 145 °C for 22 h. The reaction mixture was cooled and distilled under reduced pressure to obtain the pure title compound **174** in 42 % (4.40 g) yield.



Bp. : 55-57 °C / 10 mm (lit.^{280} 68-69 °C / 13 mm)

IR (Neat) :v 1720, 1684 cm$^{''1}$

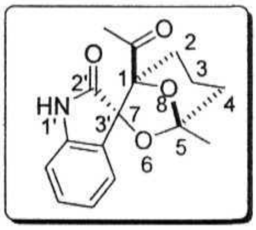
^{1}H NMR : 8 1.74-2.10 (m, 7H), 2.24 (s, 3H), 4.22-4.31 (m, 1H), 4.52 (t, 1H, *J*= 3.4 Hz)

^{13}C NMR : 8 19.14, 19.90, 23.51, 25.77, 80.32, 96.28, 149.92, 209.22

EIMS (*m/z*) : 140 (M$^+$)

[1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-(indolin-2'-one) (177a):

To a stirred solution of isatin (176a) (1 mmol, 0.147 g) and 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174) (2 mmol, 0.280 g), in acetonitrile (5 mL) was added $TiCl_4$ (2 M solution in CH_2Cl_2, 0.1 mL) at room temperature and the reaction mixture was stirred at the same temperature for 6 h. Water was added to the reaction mixture and extracted with ethyl acetate (2 x 10 mL). Ethyl acetate layer was dried over anhyd. Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to afford the desired compound **177a** as a colorless soli



Yield : 74% (0.212 g)

Mp. : 163-165 °C

IR (KBr) : v 3200-2800 (multiple bands), 1720, 1620 cm"^{1}

^{1}H NMR (400 MHz) : 5 1.65-2.00 (m, 7H), 2.04 (s, 3H), 2.22 (dd, 1H, *J* = 6.0 & 13.6 Hz), 3.05-3.22 (m, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 6.96-7.04 (m, 1H), 7.19-7.25 (m, 1H), 7.43 (d, 1H, *J*= 7.6 Hz), 7.94 (b, 1H)

^{13}C NMR : 8 17.50, 25.48, 26.08, 27.42, 33.19, 83.67, 94.24, 110.18, 110.67, 122.70, 124.74, 129.35, 130.22, 140.33, 174.22,205.83

EIMS (*m/z*) : 287 (M^+)

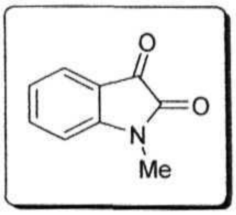
Analysis calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87

Found : C, 66.72; H, 5.98; N, 4.87

1-Methylisatin (176b):

This molecule is prepared according to the literature procedure.[281]

A suspension of isatin (176a) (20 mmol, 2.94 g) and powdered calcium hydride (66.6 mmol, 2.79 g) in 36 mL of DMF was stirred at 40-50 °C for 20 min. Methyl iodide (100 mmol, 14.19 g) was added and the stirring was continued at the same temperature for 12 h. The reaction mixture was poured into aqueous, acidified (0.2 M HC1), 10% sodium chloride solution (50 mL) and extracted with ethyl acetate (3 x 25 mL). Organic layer was dried over anhyd. Na_2SO_4. Solvent was removed and the residue thus obtained was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to provide 1-methylisatin **(176b)** as an orange solid.



Yield : 72% (2.32 g)

Mp. : 128-131 °C (lit.[281] 133-134 °C)

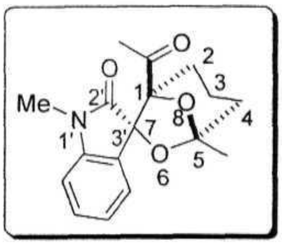
IR (KBr) : v 1747, 1728, 1604 cm"^{1}

^{1}H NMR : 6 3.25 (s, 3H), 6.89 (d, 1H, *J* = 7.8 Hz), 7.04-7.19 (m, 1H), 7.53-7.67 (m, 2H)

^{13}C NMR : 6 26.01, 109.96, 117.14, 123.62, 124.83, 138.39, 151.25, 158.02, 183.20

[1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-(1'-methylindolin-2'-one) (177b):

This molecule was prepared as a colorless solid *via* the reaction of 1-methylisatin **(176b)** with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the influence of $TiCl_4$ following the similar procedure described for the molecule **177a.**



Yield : 64 %

Mp. : 148-150 °C

IR (KBr) :v 1718, 1707, 1608 cm"^{1}

^{1}H NMR (400 MHz) : 5 1.62-2.00 (m, 7H), 2.01 (s, 3H), 2.20 (dd, 1H, *J*= 5.6 & 13.6Hz), 3.08-3.40 (m, 4H), 6.75 (d, 1H, *J* = *1.6* Hz), 6.96-7.11 (m, 1H), 7.24-7.40 (m, 1H), 7.44 (d, 1H, *J* = 7.6 Hz)

^{13}C NMR : 6 17.43, 25.40, 26.00, 26.43, 27.37, 33.16, 83.34, 94.00, 108.16, 110.48, 122.67, 124.24, 128.88, 130.19, 143.08, 171.99,205.66

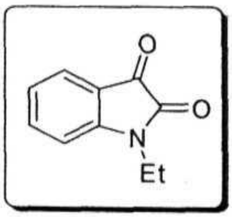
MS (*m/z*) : 302 $(M^{+}+H)$

Analysis calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65

Found : C, 67.99; H, 6.35; N, 4.61

1-Ethylisatin (176c):

This molecule was obtained as an orange solid *via* the reaction of isatin **(176a)** with ethyl bromide following the similar procedure described for the molecule **176b.**



Yield : 90%

Mp. : 82-85 °C (lit.[285] 86-87 °C)

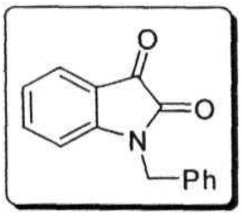
IR (KBr) : v 1745, 1734, 1610 cm"^{1}

^{1}H NMR : 5 1.29 (t, 3H, *J* = 7.2 Hz), 3.77 (q, 2H, *J* = 7.2 Hz), 6.90 (d, 1H, *J* = 7.8 Hz), 7.03-7.20 (m, 1H), 7.52-7.68 (m, 2H)

^{13}C NMR : 5 12.31, 34.77, 110.00, 117.37, 123.44, 125.10, 138.30, 150.48, 157.68, 183.52

1-Benzylisatin (176d):

This molecule was obtained as an orange solid *via* the reaction of isatin **(176a)** with benzyl bromide in the presence of calcium hydride following the similar procedure described for the molecule 176b.



Yield : 86%

Mp. : 130-133 °C (lit.[281] 133-134 °C)

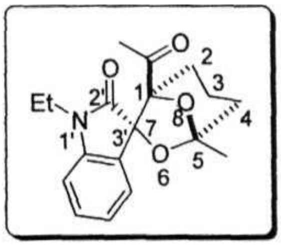
IR (KBr) :ν 1732, 1612 cm^{-1}

^{1}H NMR : 8 4.92 (s, 2H), 6.78 (d, 1H, J = 7.8 Hz), 7.03-7.13 (m, 1H), 7.26-7.40 (m, 5H), 7.44-7.54 (m, 1H), 7.59 (d, 1H, J = 7.8 Hz)

^{13}C NMR : 8 43.89, 110.96, 117.53, 123.74, 125.17, 127.23, 128.01, 128.91, 134.49, 138.30, 150.59, 158.19, 183.15

[1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-(l'-ethylindolin-2'-one) (177c):

This molecule was prepared as a colorless solid *via* the reaction of 1-ethylisatin **(176c)** with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the catalytic influence of TiCl$_4$ following the similar procedure described for the molecule 177a.



Yield : 69 %

Mp. : 130-132 °C

IR (KBr :ν 1720, 1709, 1610 cm''

^{1}H NMR : 8 1.27 (t, 3H, J = 6.8 Hz), 1.56-1.94 (m, 7H), 1.98 (s, 3H), 2.12-2.29 (m, 1H), 3.06-3.30 (m, 1H), 3.64-3.88 (m, 2H), 6.75 (d, 1H, J

=7.8 Hz), 6.94-7.03 (m, 1H), 7.20-7.31 (m, 1H), 7.43 (d, 1H, *J* = 8.0 Hz)

^{13}C NMR : 5 12.16, 17.37, 25.35, 25.91, 27.29, 33.12, 34.86, 83.28, 94.00, 108.19, 110.42, 122.43, 124.45, 128.98, 130.07, 142.08, 171.50, 205.46

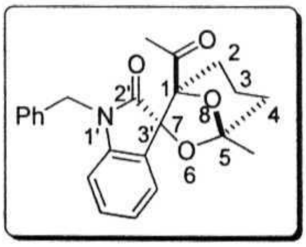
EIMS (*m/z*) : 315 (M^+)

Analysis calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44

Found : C, 68.42; H, 6.74; N, 4.49

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-benzylindolin-2′-one) (177d):

This compound was obtained *via* the treatment of 1-benzylisatin **(176d)** with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the influence of $TiCl_4$ (cat.) as a colorless solid following the similar procedure described for the molecule 177a.



Yield : 70 %

Mp. : 141-143 °C

IR (KBr) : v 1716, 1608 cm^{-1}

^{1}H NMR : 5 1.63-2.00 (m, 7H), 2.04 (s, 3H), 2.19-2.37 (m, 1H), 3.09-3.36 (m, 1H), 4.79 & 5.07 (ABq, 2H, *J* = 15.8 Hz), 6.59 (d, 1H, *J* = 7.8 Hz), 6.92-7.035(m, 1H), 7.08-7.20 (m, 1H), 7.21-7.51 (m, 6H)

^{13}C NMR : 5 17.52, 25.50, 26.11, 27.56, 33.26, 44.23, 83.45, 94.24, 109.33, 110.64, 122.80, 124.32, 127.21, 127.57, 128.79, 129.10, 130.12, 135.48,142.42,172.35,205.93

MS (*m/z*) : 377 (M^+)

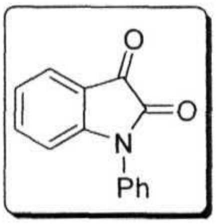
Analysis calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71

Found :C, 73.01; H, 6.19; N, 3.71

1-Phenylisatin (176e):

This molecule is prepared according to the literature procedure.[282]

A mixture of isatin (176a) (10 mmol, 1.47 g), bromobenzene (14 mmol, 2.198 g), and cupric oxide (20 mmol, 1.59 g) in 25 mL of DMF was refluxed for 8 h. While hot, any insoluble material was filtered from the reaction mixture. The filtrate was poured into cold water and the resulting precipitate was filtered, dried and recrystallized from chloroform to provide 1-phenylisatin (176e) as orange crystals.



Yield : 30% (0.67 g)

Mp. : 133-136 °C (lit.[282] 137-139 °C)

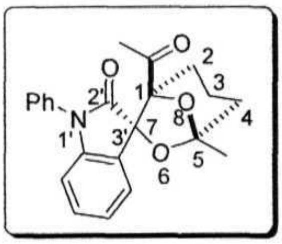
IR (KBr) :v 1739, 1608 cm^{-1}

^{1}H NMR : 6 6.90 (d, 1H, *J* = 8.0 Hz), 7.12-7.23 (m, 1H), 7.37-7.65 (m, 6H), 7.70 (d, 1H, *J* =7.4 Hz)

^{13}C NMR : 8 111.28, 117.47, 124.27, 125.48, 125.96, 128.77, 129.91, 132.91, 138.34, 151.62, 157.31, 182.83

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-(l'-phenylindolin-2'-one)(177e):

This molecule was prepared as a colorless solid *via* the reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174) with 1-phenylisatin (176e) under the catalytic influence of $TiCl_4$ following the similar procedure described for the molecule 177a.



Yield : 56 %

Mp. : 125-127 °C

IR (KBr) :v 1728, 1707, 1610 cm^{1}

^{1}H NMR : 5 1.62-2.00 (m, 7H), 2.04 (s, 3H), 2.15-2.30 (m, 1H), 3.06-3.32 (m, 1H), 6.64 (d, 1H, *J* = 7.8 Hz), 6.94-7.08 (m, 1H), 7.11-7.23 (m, 1H), 7.35-7.60 (m,6H)

^{13}C NMR : 8 17.32, 25.47, 26.06, 27.43, 33.17, 83.60, 94.49, 109.36, 110.82, 123.06, 124.54, 126.88, 128.26, 128.52, 129.58, 130.06, 134.36, 143.30, 171.48,205.83

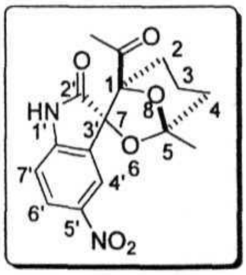
EIMS (*m/z*) : 363 (M^{+})

Analysis calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85

Found : C, 72.93; H, 5.85; N, 3.88

[1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo-(3.2.1)-octane]-7-spiro-3'-(5'-nitroindolin-2'-one)(177f):

This compound was obtained *via* the treatment of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** with 5-nitroisatin (176f) under the influence of $TiCl_4$ (cat.) as a colorless **solid following** the similar procedure described for the molecule **177a.**



Yield : 48 %

Mp. :212-216 °C

IR (KBr) : v 3263, 3100-2800 (multiple bands), 1751, **1716,** 1628 cm^{4}

^{1}H NMR : δ 1.65-2.05 (m, 7H), 2.08-2.26 (m, 4H), 2.96-3.20 (m, 1H), 6.88 (d, 1H, *J* = 8.6 Hz), 8.20(dd, 1H,./=8.6& 1.8 Hz), 8.26 (d, 1H, *J* = 1.8 Hz), 8.44 (b, 1H)

^{13}C NMR :6 17.29,25.53,26.43,27.26,32.90,83.04,94.73, 110.07, 111.63, 120.17, 127.15, 130.63, 143.58, 146.18, 174.20,206.98

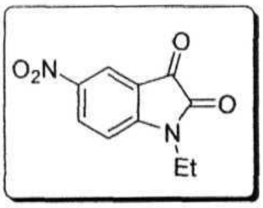
E1MS (*m/z*) : 332 (M$^+$)

Analysis calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43

Found : C, 57.98; H, 4.82; N, 8.38

1-Ethyl-5-nitroisatin (176g):

This molecule was obtained as an orange solid *via* the reaction of 5-nitroisatin **(176f)** with ethyl bromide in the presence of calcium hydride following the similar procedure described for the molecule **176b.**



Yield : 45%

Mp. : 183-187 °C

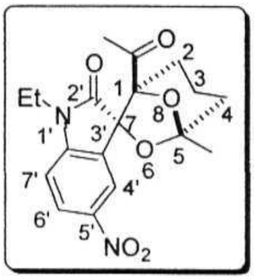
1R (KBr) :v 1761, 1736, 1610 cm^1

^{1}H NMR : 8 1.36 (t, 3H, *J* = 7.4 Hz), 3.88 (q, 2H, J = 7.4 Hz), 7.07 (d, 1H, *J* = 8.6 Hz), 8.47 (d, 1H, *J* = 2.0 Hz), 8.54 (dd, 1H, *J* = 2.0, 8.6 Hz)

^{13}C **NMR** (400 MHz) : 8 12.51, 35.69, 110.18, 117.24, 121.13, 133.66, 144.05, 154.81, 157.60, 181.46

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-ethyl-5′-nitroindolin-2′-one) (177g):

This molecule was obtained as a colorless solid *via* the reaction of 1-ethyl-5-nitroisatin (176g) with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the catalytic influence of $TiCl_4$ following the similar procedure described for the molecule 177a.



Yield : 50 %

Mp. : 168-171 °C

IR (KBr) : v 1738, 1711, 1608 cm$^{'1}$

^{1}H NMR : 8 1.31 (t, 3H, *J* = 7.8 Hz), 1.62-2.21 (m, 11H), 2.95-3.28 (m, 1H), 3.65-4.00 (m, 2H), 6.84 (d, 1H, *J* = 7.8 Hz), 8.20-8.31 (m, 2H)

^{13}C NMR : δ 12.13, 17.25, 25.50, 26.15, 27.27, 33.00, 35.57, 82.67, 94.66, 107.85, 111.42, 119.86, 127.14, 130.39, 143.32, 148.02, 171.80, 206.12

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

Analysis calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77

Found : C, 59.80; H, 5.60; N, 7.81

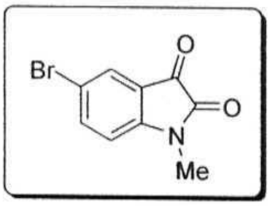
5-Bromo-1-methylisatin (176h):

To a stirred solution of 1-methylisatin **(176b)** (4 mmol, 0.644 g) in 4 mL of ethanol was added bromine (20 mmol, 3.196 g) slowly at room temperature. After stirring 30 min at room temperature, ethanol was removed from the reaction mixture and the solid thus obtained was recrystallized from ethyl acetate in hexanes to afford the title compound as an orange solid.

Yield : 85% (0.815 g)

Mp. : 167-169 °C (lit.^{286} 170-172 °C)

IR (KBr) : v 1747, 1724, 1606 cm^{-1}



^{1}H NMR (400 MHz; : δ 3.29 (s, 3H), 6.84 (d, 1H, J = 7.2 Hz), 7.68-7.85 (m, 2H)

^{13}C NMR : 5 27.00, 111.88, 116.71, 118.72, 128.18, 140.70, 150.23, 157.58, 182.23

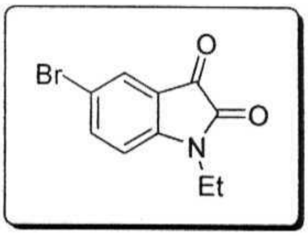
5-Bromo-1-ethylisatin (176i):

This molecule was prepared *via* the bromination of 1-ethylisatin (176c) with bromine following the similar procedure described for the molecule **176h** as an orange solid.

Yield : 62%

Mp. : 144-146 °C (lit.^{287} 148-149 °C)

IR (KBr) : v 1734, 1602 cm^{-1}

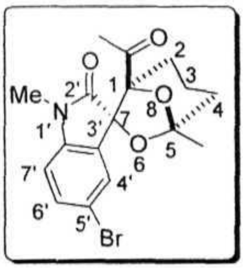


^{1}H NMR : 5 1.30 (t, 3H, J= 7.0 Hz), 3.78 (q, 2H, J = 7.0 Hz), 6.83 (d, 1H, J = 8.8 Hz), 7.66-7.77 (m, 2H)

^{13}C NMR : 6 12.35, 35.08, 111.83, 116.29, 118.67, 127.99, 140.53, 149.31, 157.05, 182.44

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(5′-bromo-1′-methylindolin-2′-one) (177h):

This molecule was obtained *via* the reaction of 5-bromo-1-methylisatin **(176h)** with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** under the influence of TiCl$_4$ (cat.) as a colorless solid following the similar procedure described for the molecule **177a.**



Yield :61 %

Mp. : 177-180 °C

IR (KBr) : v 1728, 1709, 1606 cm^1

^{1}H NMR : 5 1.62-2.22 (m, 11H), 3.00-3.28 (m, 4H), 6.62 (d, 1H, J = 8.8 Hz), 7.40 (dd, 1H, J = 8.8 & 2.0 Hz), 7.50 (d, 1H, J = 2.0 Hz)

^{13}C NMR (100 MHz) : 6 17.35, 25.55, 26.31, 26.64, 27.33, 33.04, 83.12, 94.20, 109.75, 110.89, 115.28, 127.23, 131.02, 132.95, 142.17, 171.43,206.03

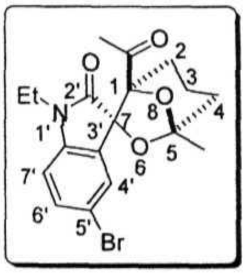
MS *(m/z)* : 379 (M$^+$), 381 (M$^+$+2)

Analysis calcd for $C_{17}H_{18}NO_4Br$: C, 53.69; H, 4.77; N. 3.68

Found :C, 53.79: H, 4.72; N, 3.64

[1*S*,5*S*,7(3')*S*/1*R*,5*R*,7(3')*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3'-(5'-bromo-1'-ethylindolin-2'-one) (177i):

This compound was prepared as a colorless solid *via* the reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran **(174)** with 5-bromo-1-ethylisatin (176i) under the catalytic influence of $TiCl_4$ following the similar procedure described for the molecule **177a.**



Yield : 44 %

Mp. : 137-140 °C

IR (KBr) :v 1724, 1707, 1604 cm^{-1}

^{1}H NMR : 5 1.25 (t, 3H, J = 6.8 Hz), 1.62-2.00 (m, 7H), 2.03-2.22 (m, 4H), 3.04-3.28 (m, 1H), 3.59-3.90 (m, 2H), 6.63 (d, 1H, J = 7.8 Hz), 7.38 (dd, 1H, J =7.8 & 2.0 Hz), 7.52 (d, 1H, J= 2.0 Hz)

^{13}C NMR : 6 12.06, 17.30, 25.47, 26.08, 27.32, 33.06, 35.08, 83.11, 94.26, 109.72, 110.81, 114.98, 127.47, 131.28, 132.83, 141.28, 170.99, 205.65

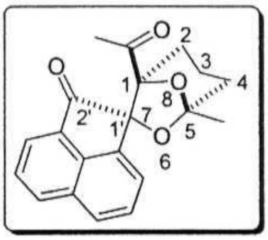
MS(*m/z*) : 394 (M$^+$+H); 396 [(M$^+$+H)+2]

Analysis calcd for $C_{18}H_{20}NO_4Br$: C, 54.83; H, 5.11; N, 3.55

Found :C, 54.63; H, 5.13; N, 3.58

[1*S*,5*S*,7(1′)*S*/1*R*,5*R*,7(1′)*R*]-1-Acetyl-5-methyl-[6,8-dioxabicyclo(3.2.1)octane]-7-spiro-1′-(1′,2′-dihydroacenaphthalene-2′-one) (179):

This molecule was obtained as a colorless solid *via* the treatment of acenaphthenequinone **(178)** with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (174) under the influence of $TiCl_4$ (cat.) following the similar procedure described for the molecule 177a.



Yield : 72 %

Mp. : 147-149 °C

IR (KBr) : v 1726, 1712, 1622 cm$^{"1}$

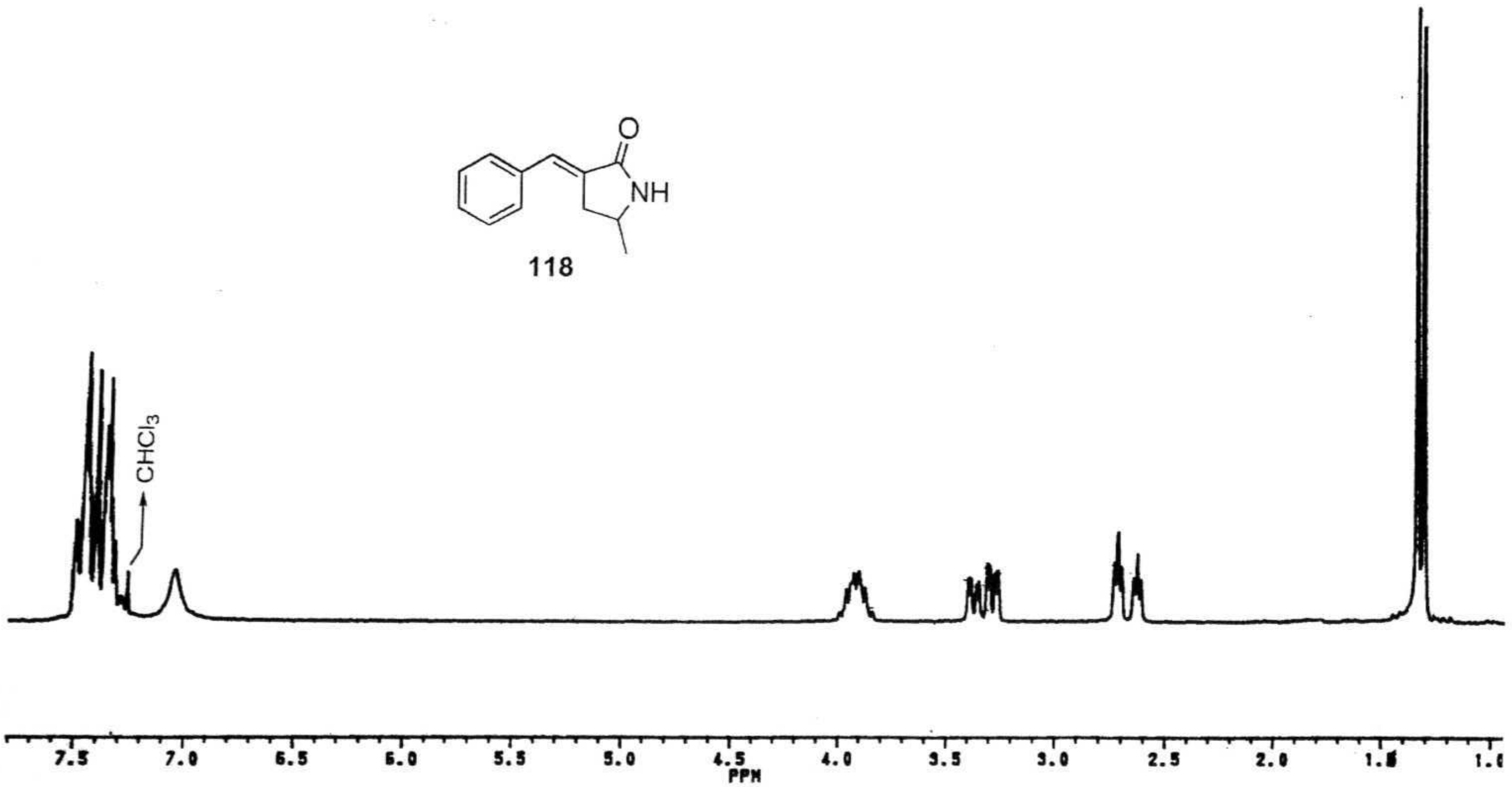
^{1}H NMR (400 MHz) : 8 1.71-2.10 (m, 1 0H), 2.17 (dd, 1H, *J* = 7.6 & 14.8 Hz), 3.19-3.38 (m, 1H), 7.59-7.66 (m, 1H), 7.71-7.83 (m, 2H), 7.87 (d, 1H, *J* = 8.8 Hz), 8.00 (d, 1H, *J* = 6.8 Hz), 8.09 (d, 1H, *J* = 7.6 Hz)

^{13}C NMR : 8 17.57, 25.48, 25.72, 28.10, 33.38, 87.23, 94.95, 110.52, 120.95, 121.80, 125.85, 128.33, 128.50, 130.36, 131.63, 132.91, 138.93, 141.01,198.91,205.88

EIMS (*m/z*) : 322 (M$^+$)

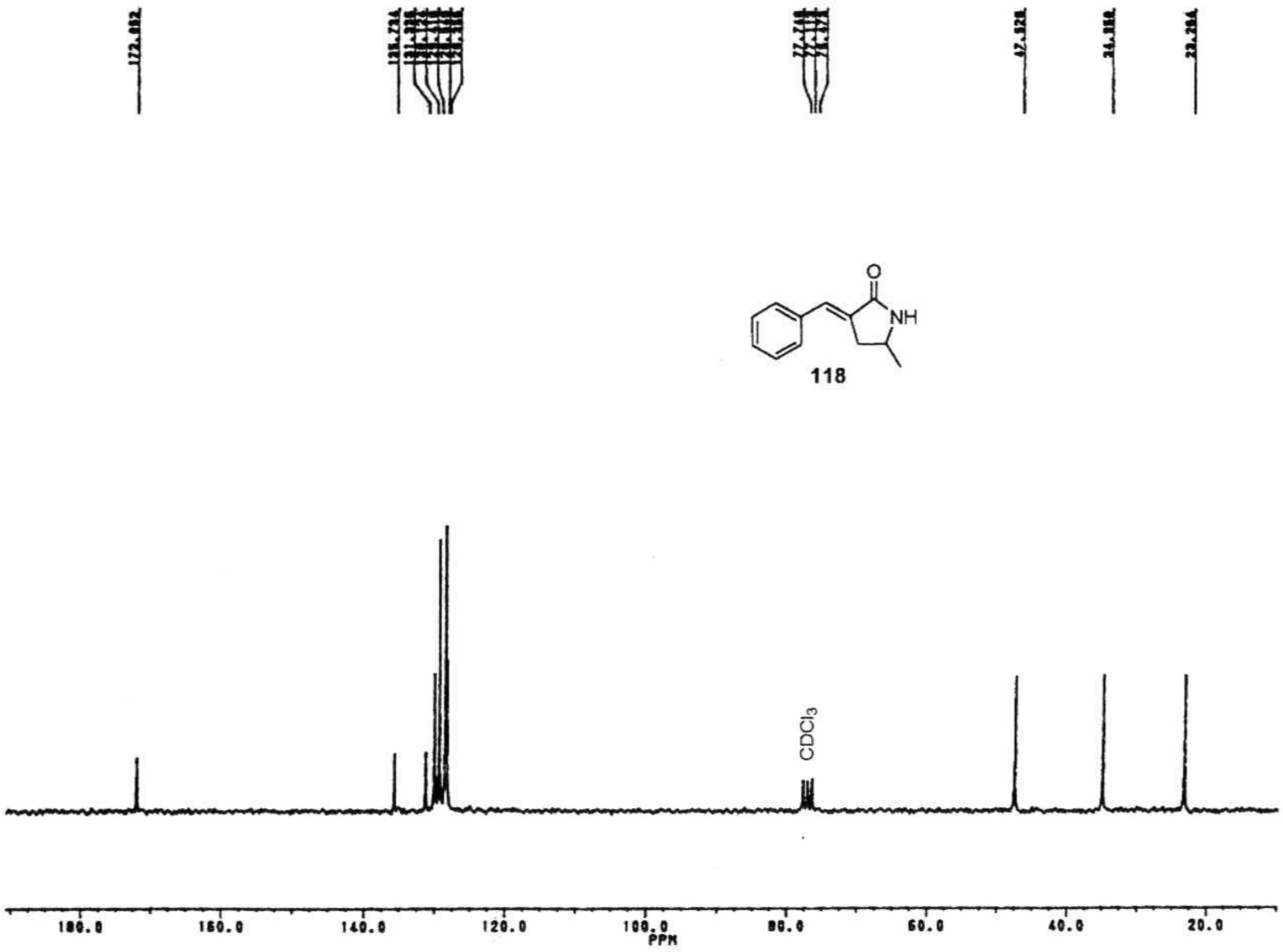
Analysis calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63

Found : C, 74.70; H, 5.65



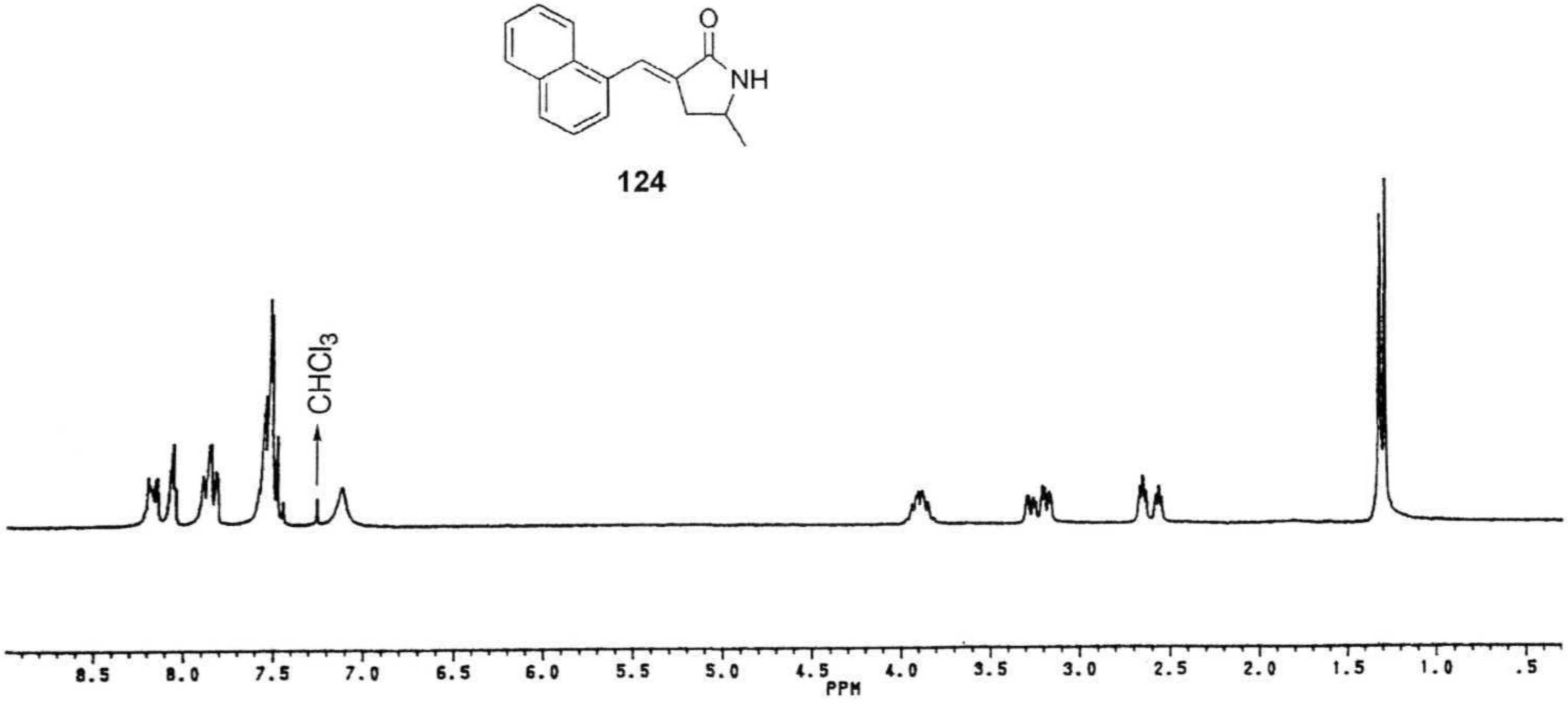
^{1}H NMR spectrum of 118

Spectrum 1



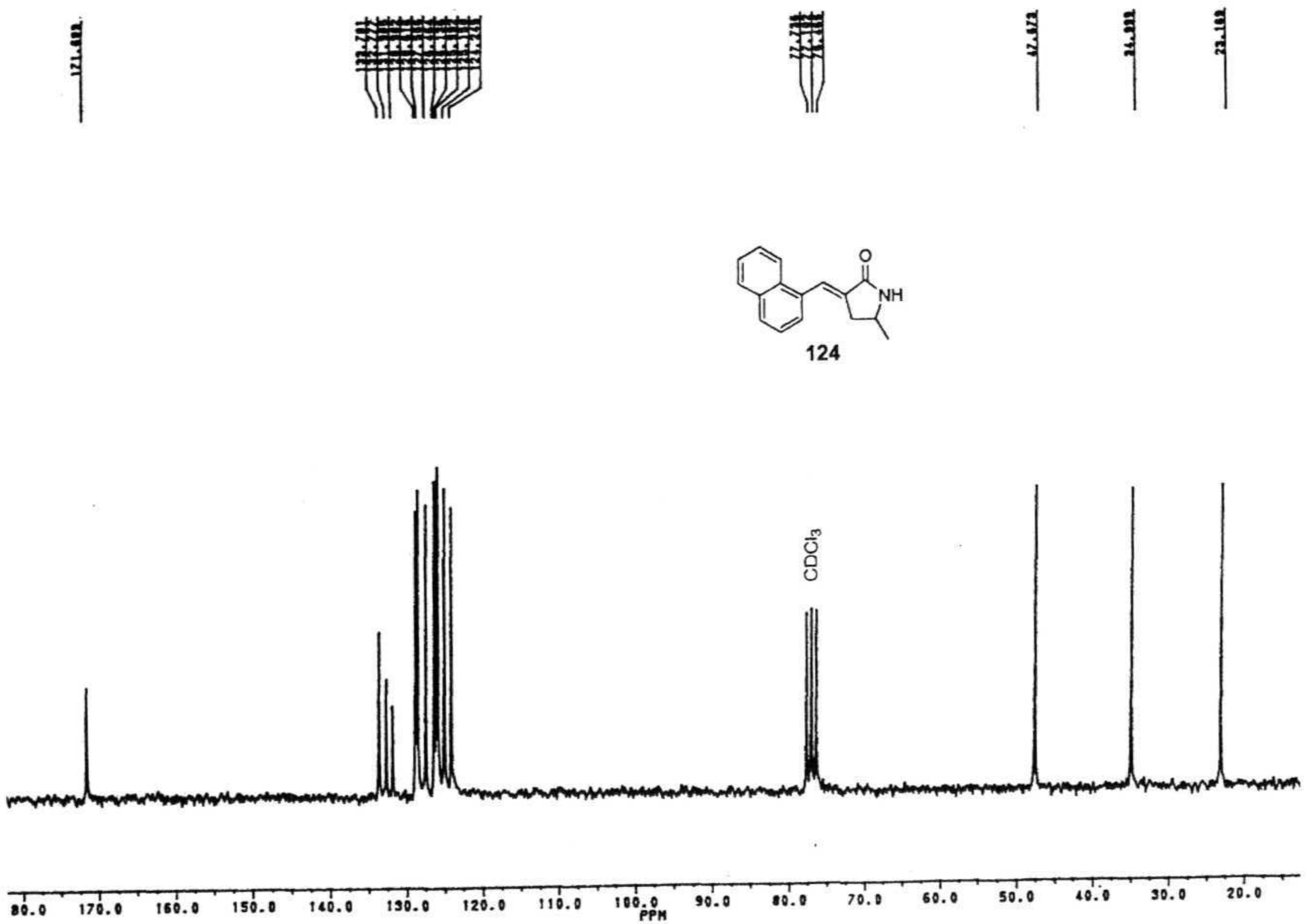
^{13}C NMR spectrum of 118

Spectrum 2



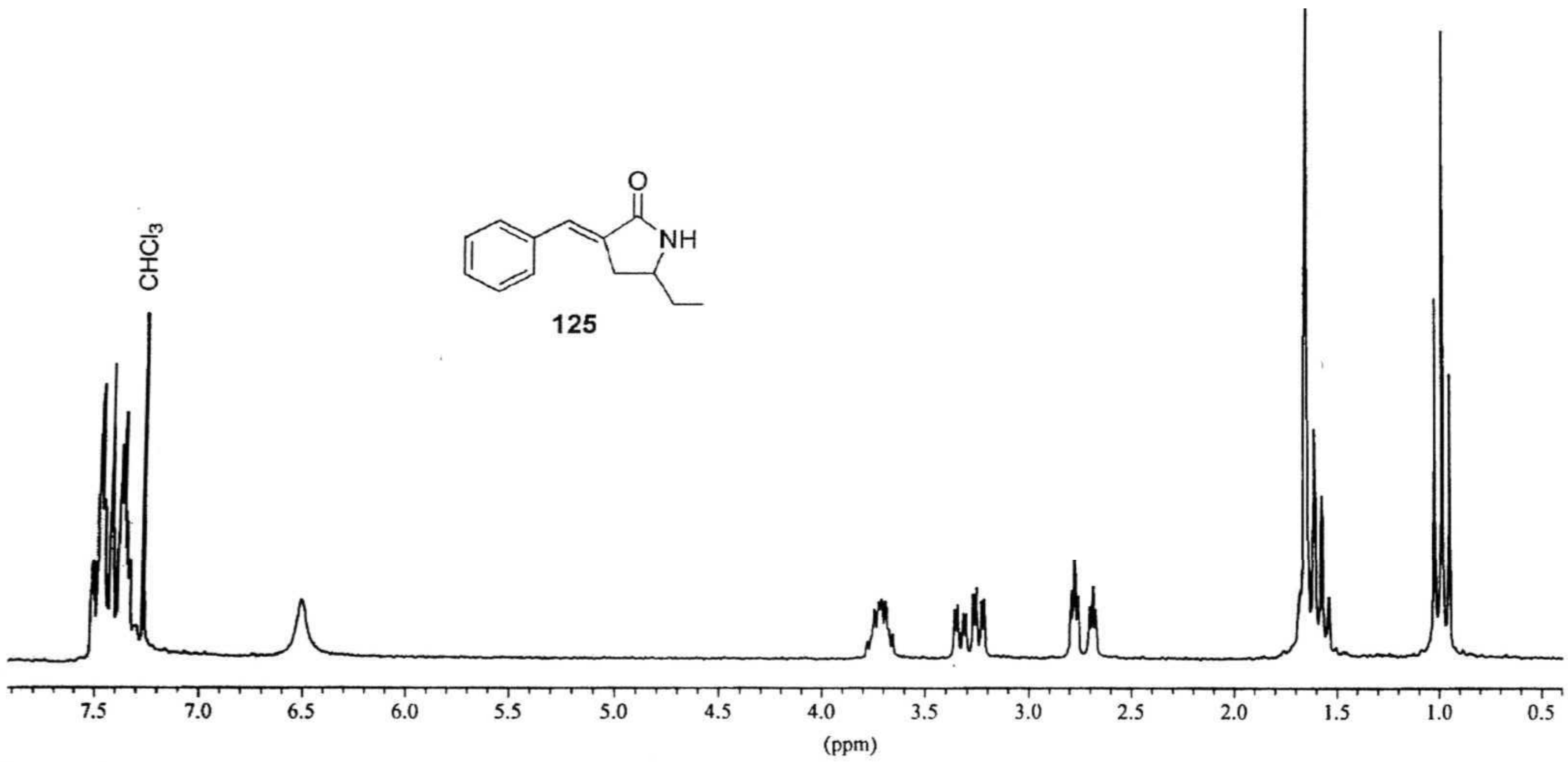
^{1}H NMR spectrum of 124

Spectrum 3



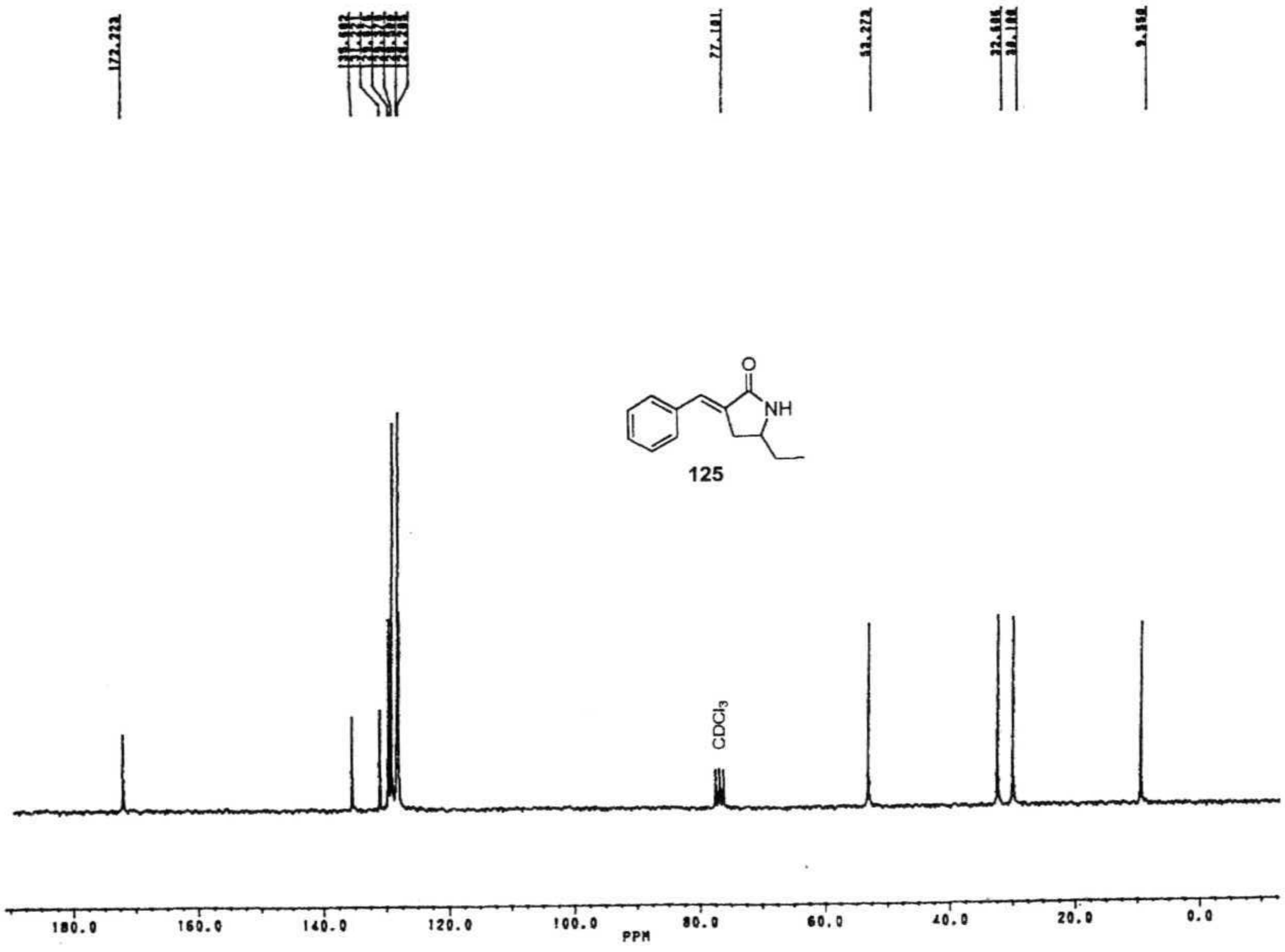
^{13}C NMR spectrum of 124

Spectrum 4



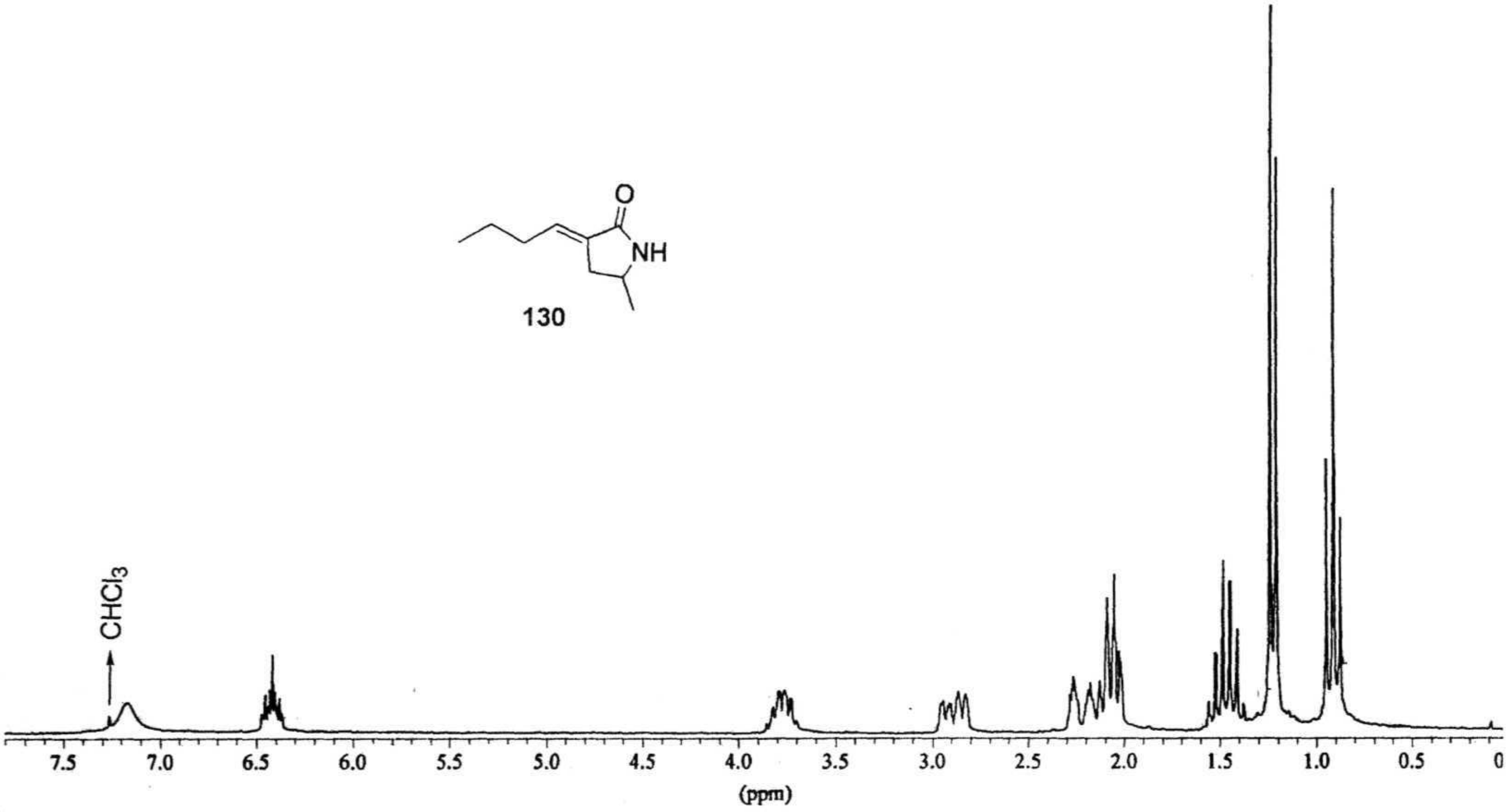
^{1}H NMR spectrum of 125

Spectrum 5



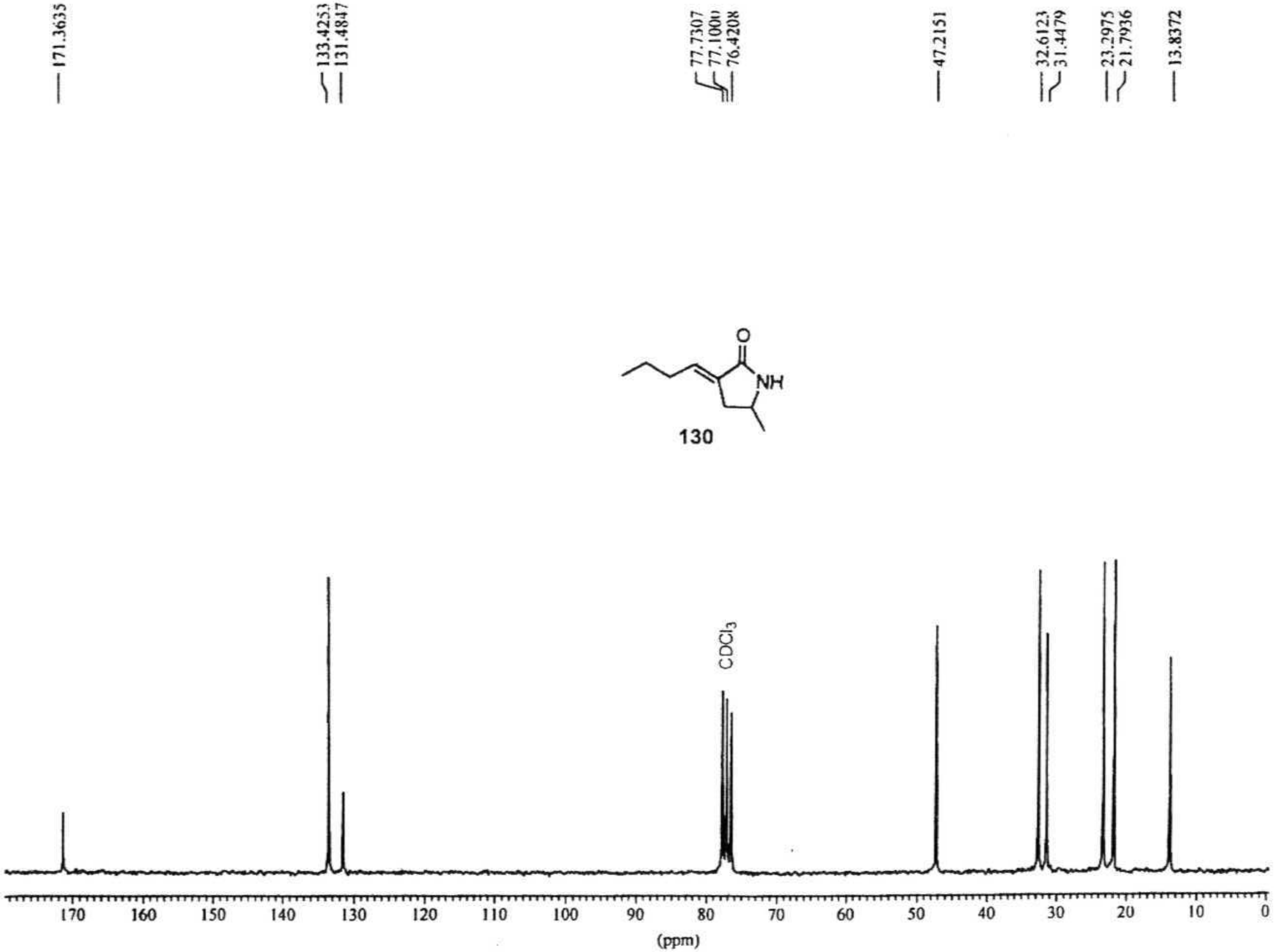
^{13}C NMR spectrum of 125

Spectrum 6



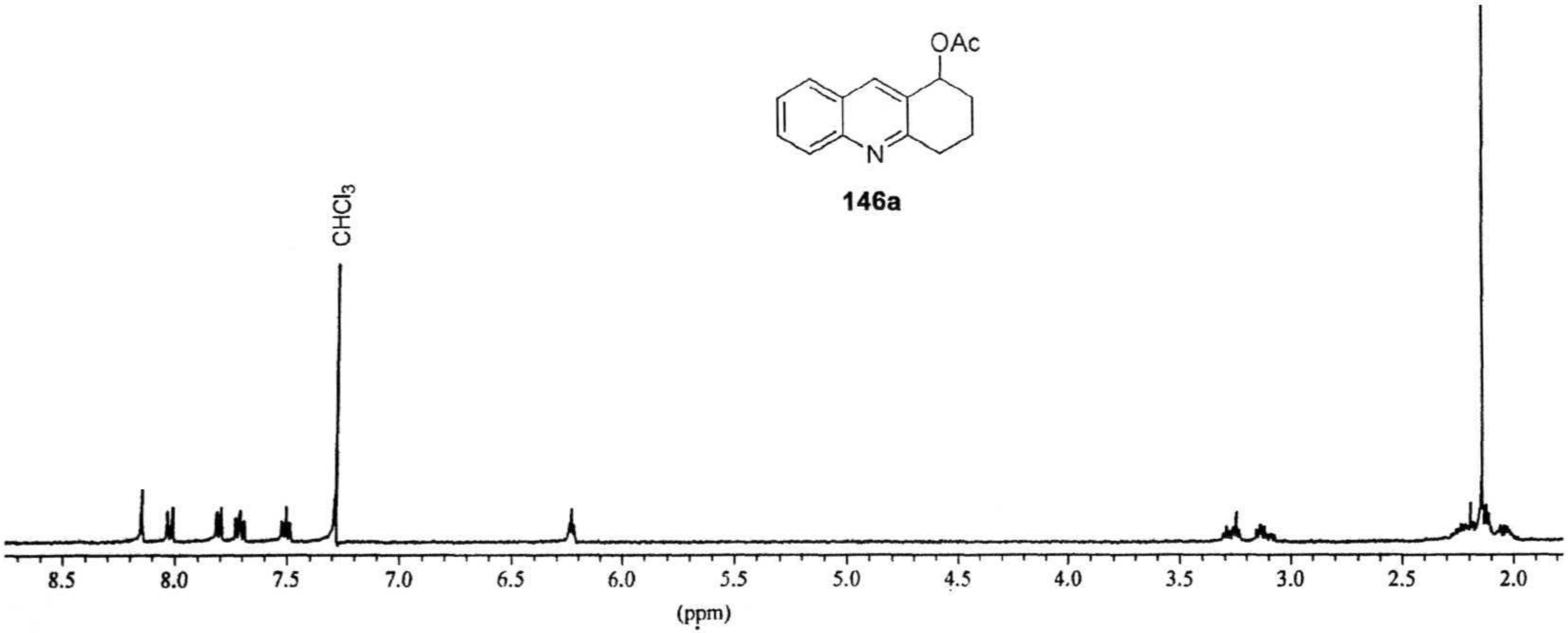
^{1}H NMR spectrum of 130

Spectrum 7



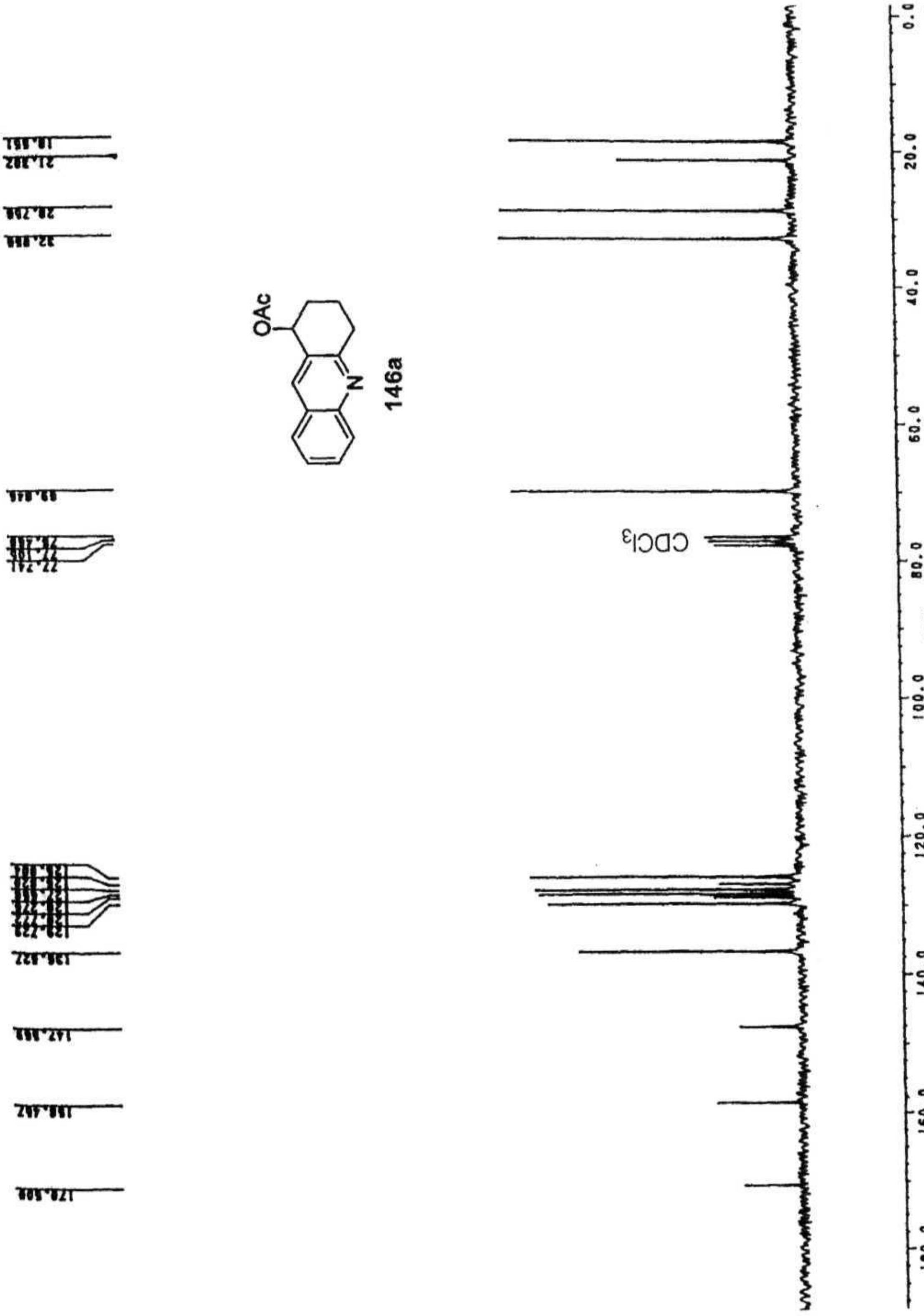
^{13}C NMR spectrum of 130

Spectrum 8



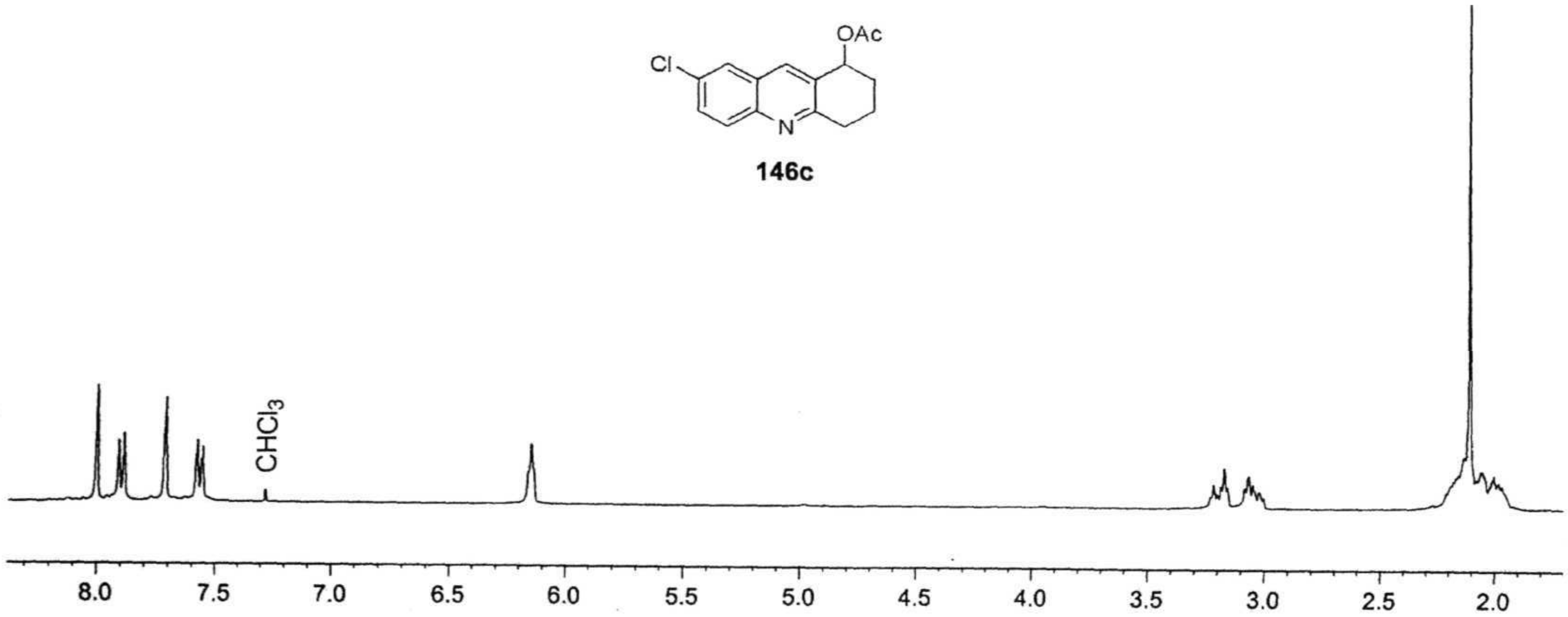
^{1}H NMR spectrum of 146a

Spectrum 9



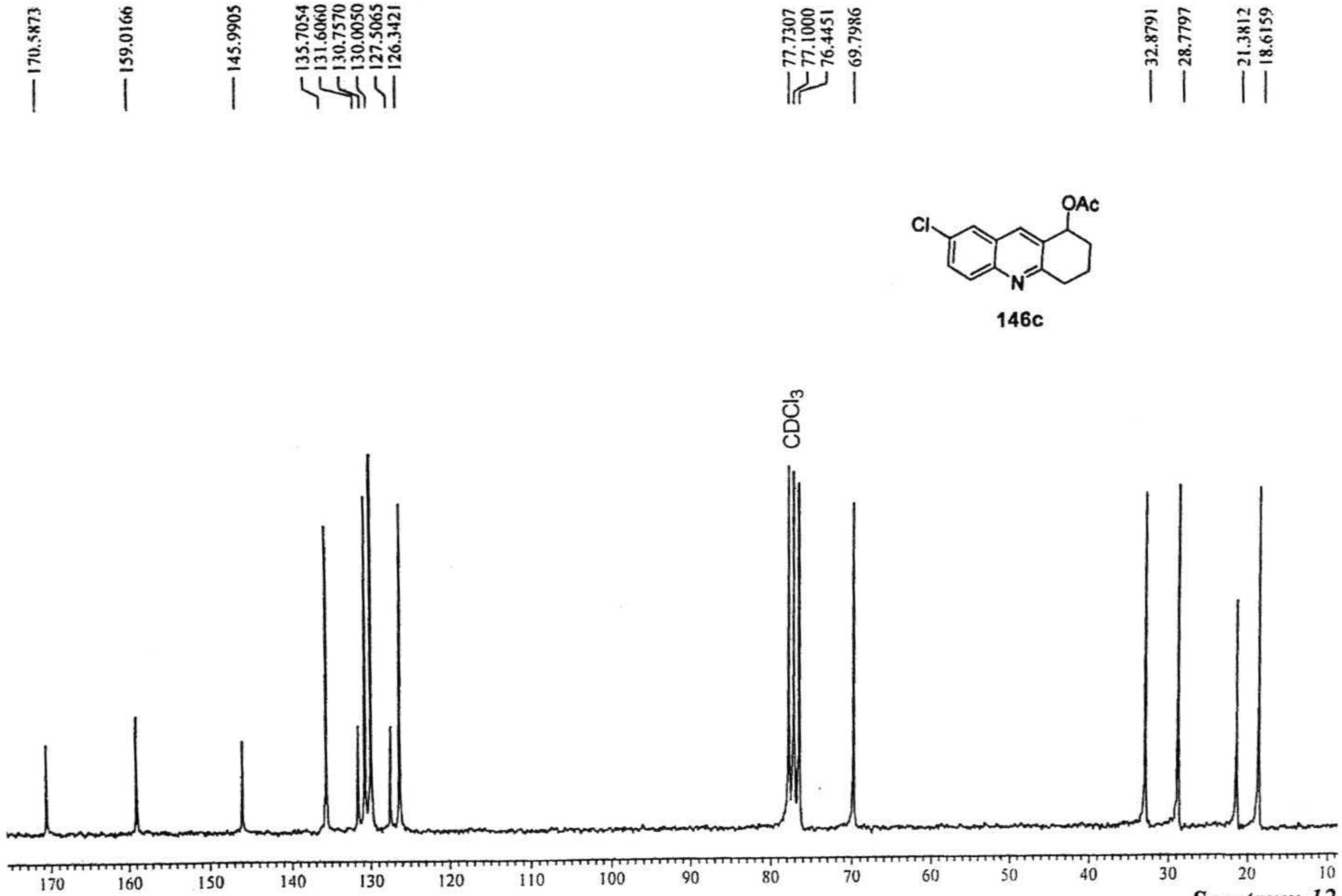
Spectrum 10

^{13}C NMR spectrum of 146a



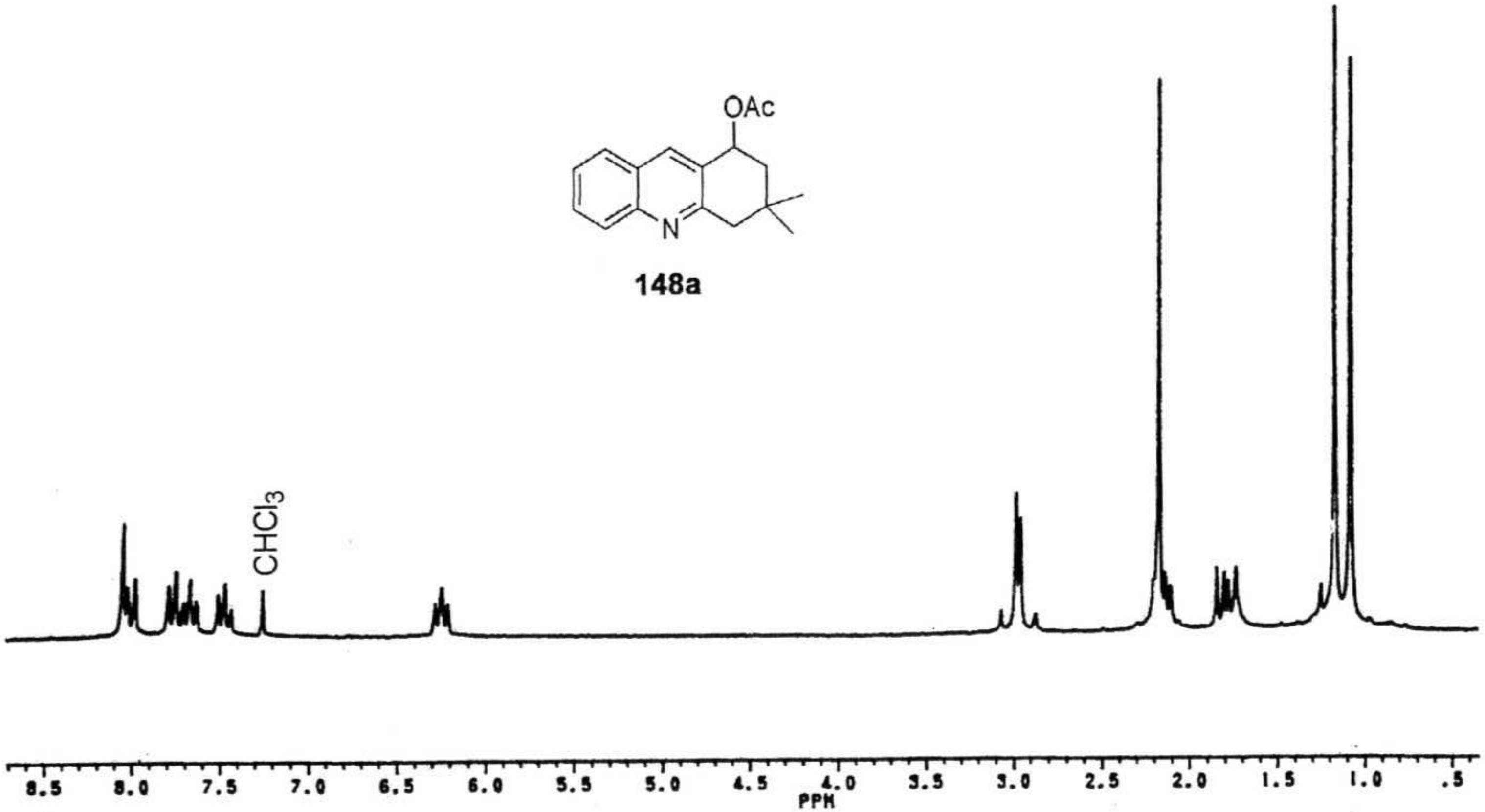
^{1}**H NMR spectrum of 146c**

Spectrum 11



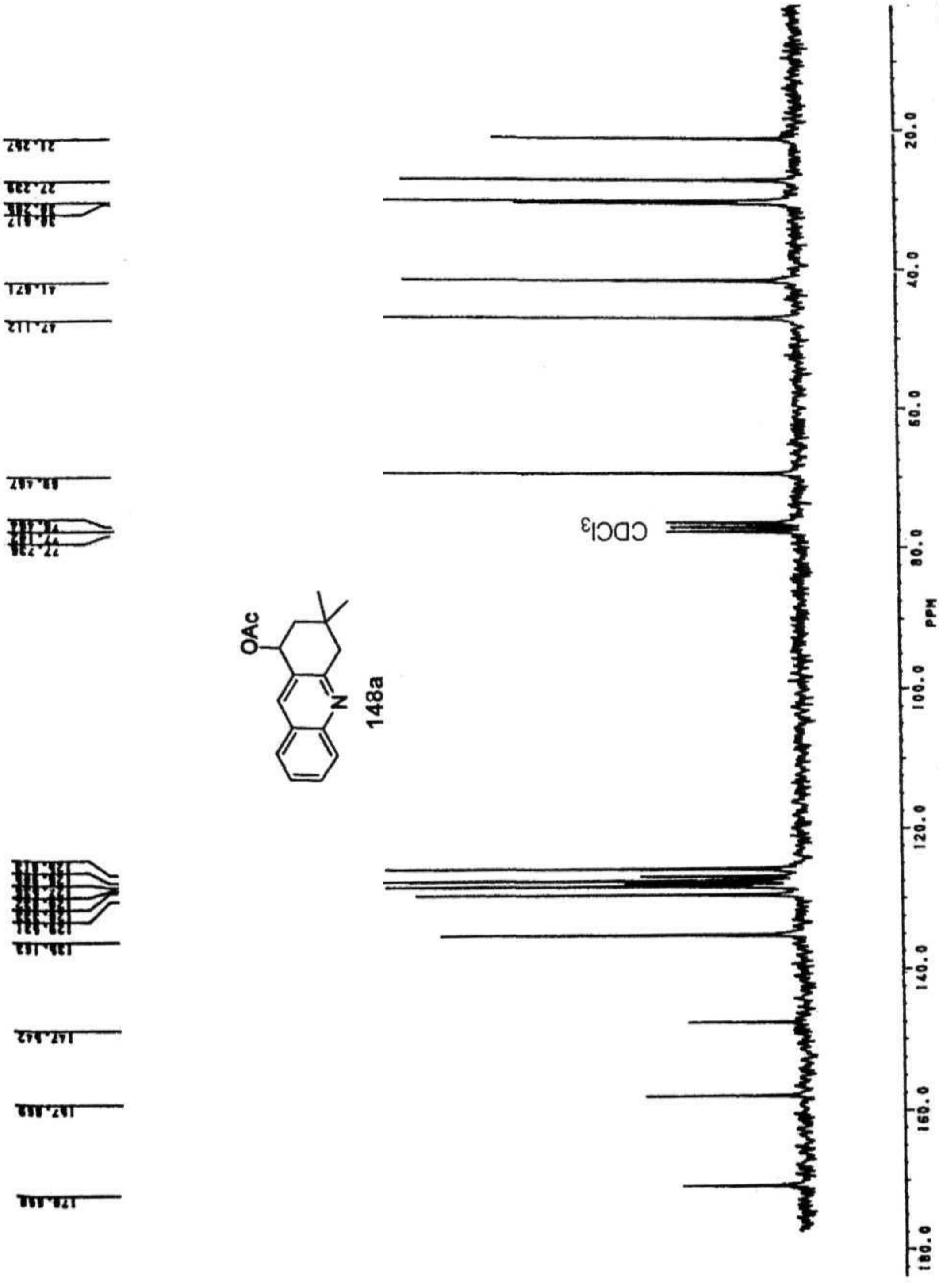
Spectrum 12

^{13}C NMR spectrum of 146c



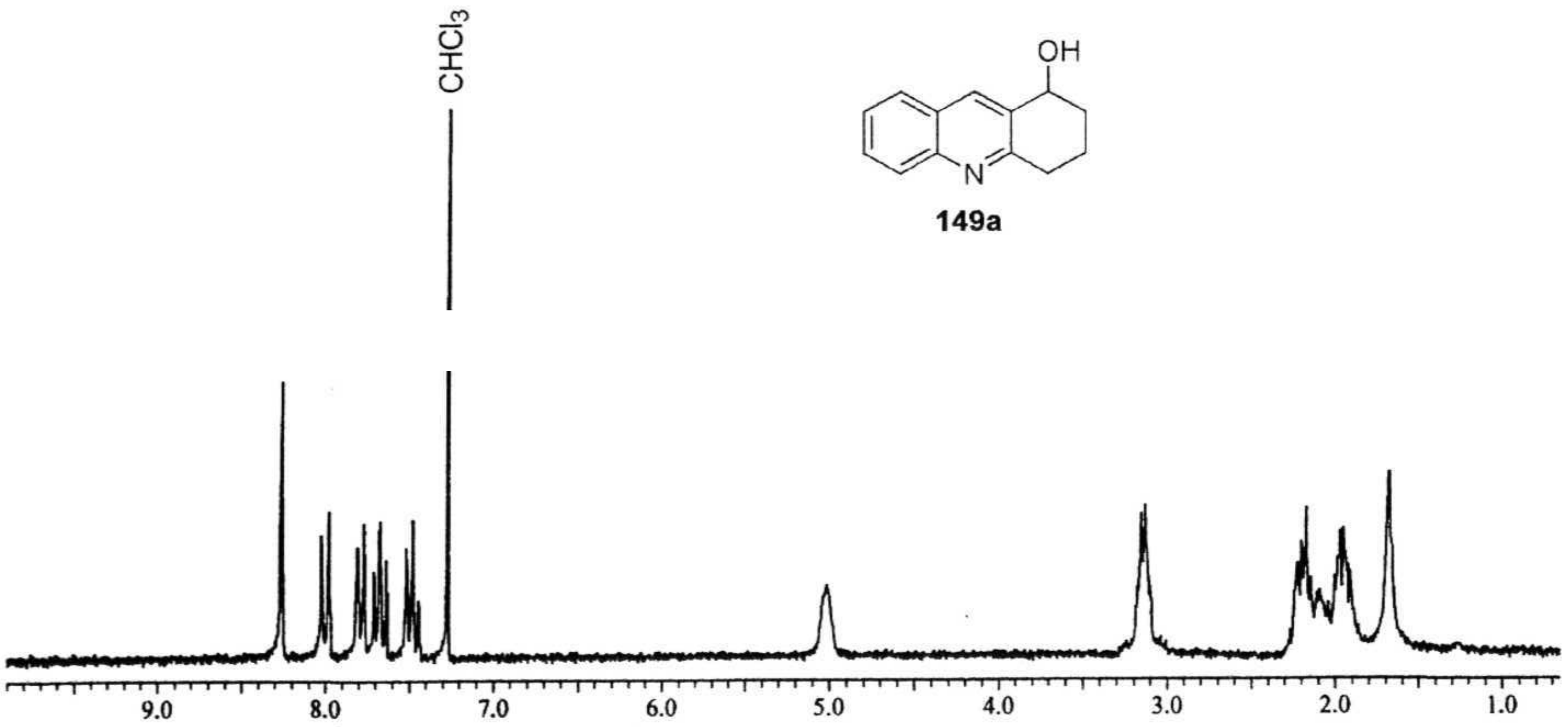
^{1}H NMR spectrum of 148a

Spectrum 13



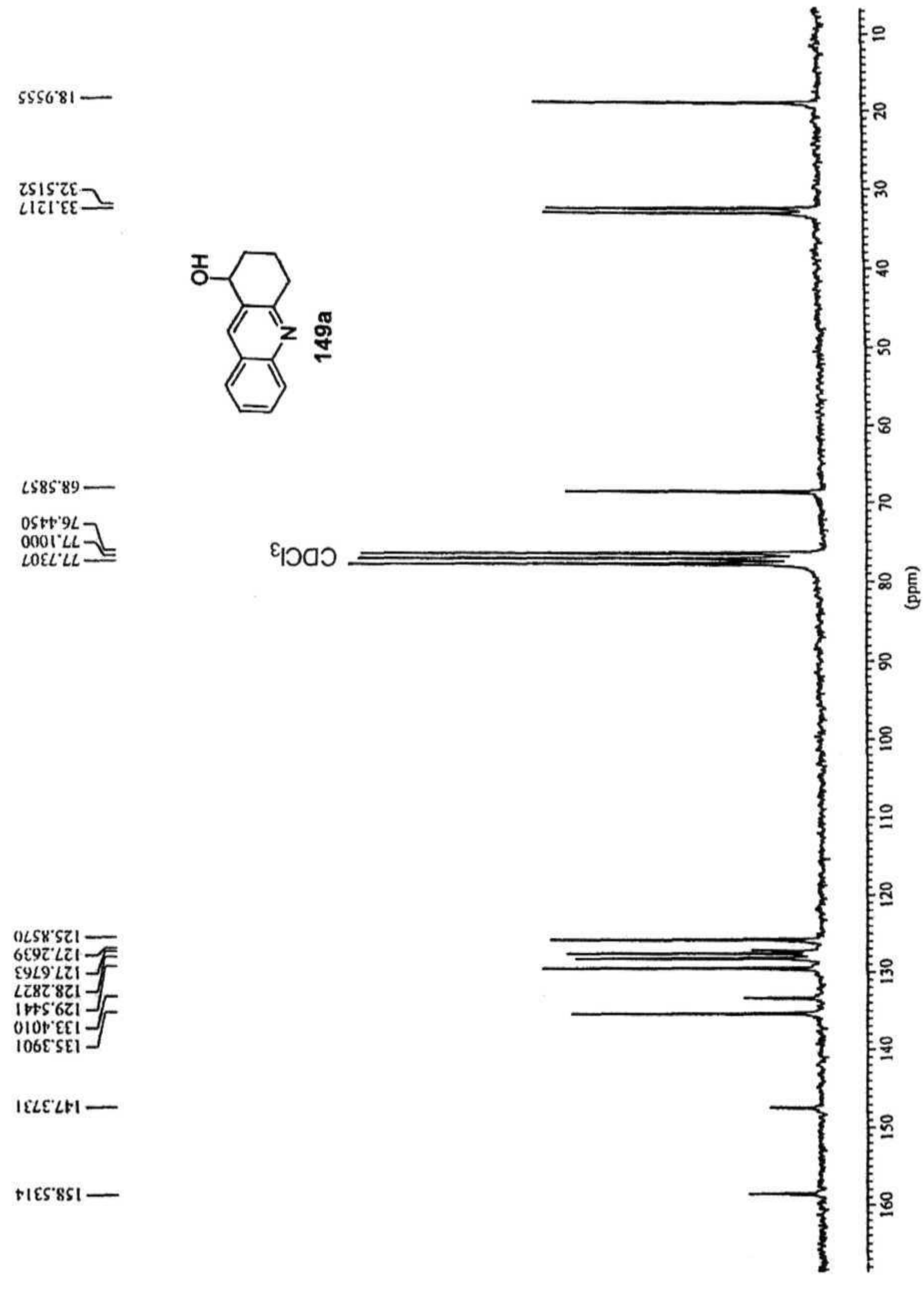
Spectrum 14

^{13}C NMR spectrum of 148a



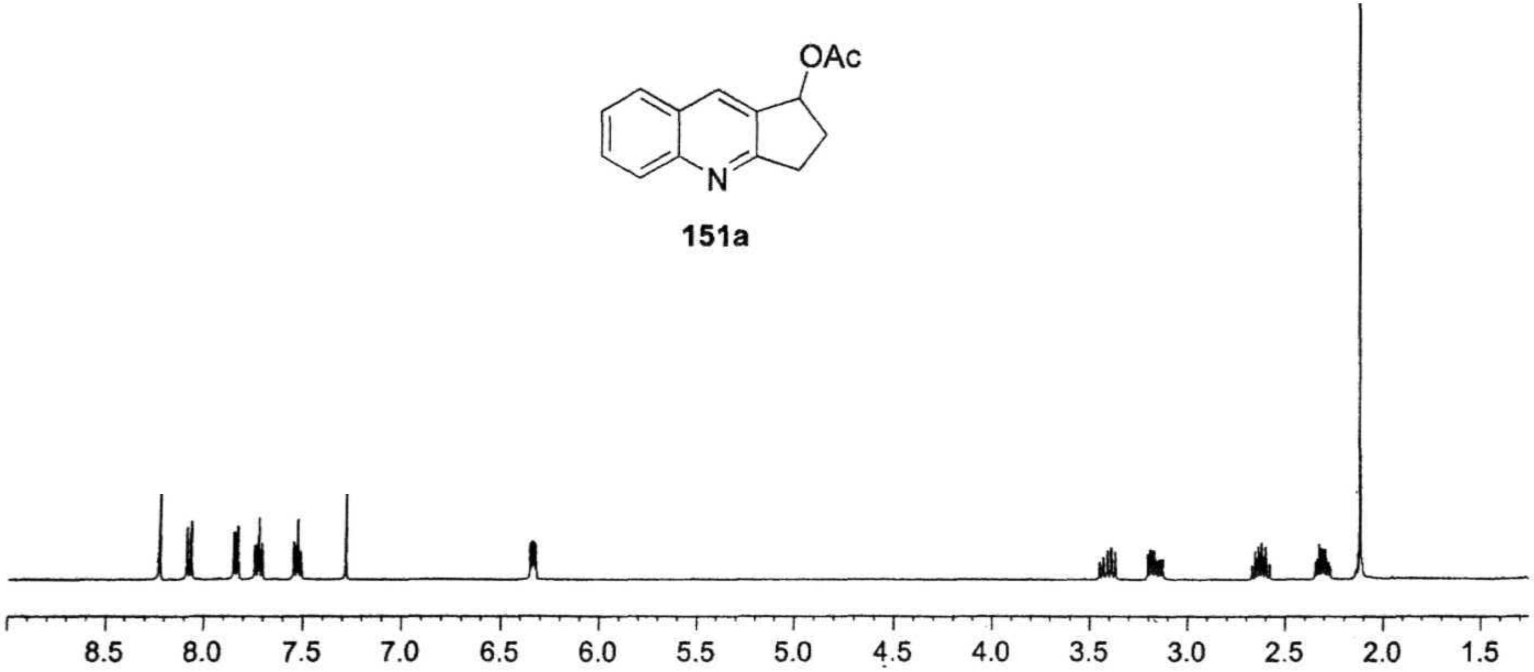
^{1}H NMR spectrum of 149a

Spectrum 15



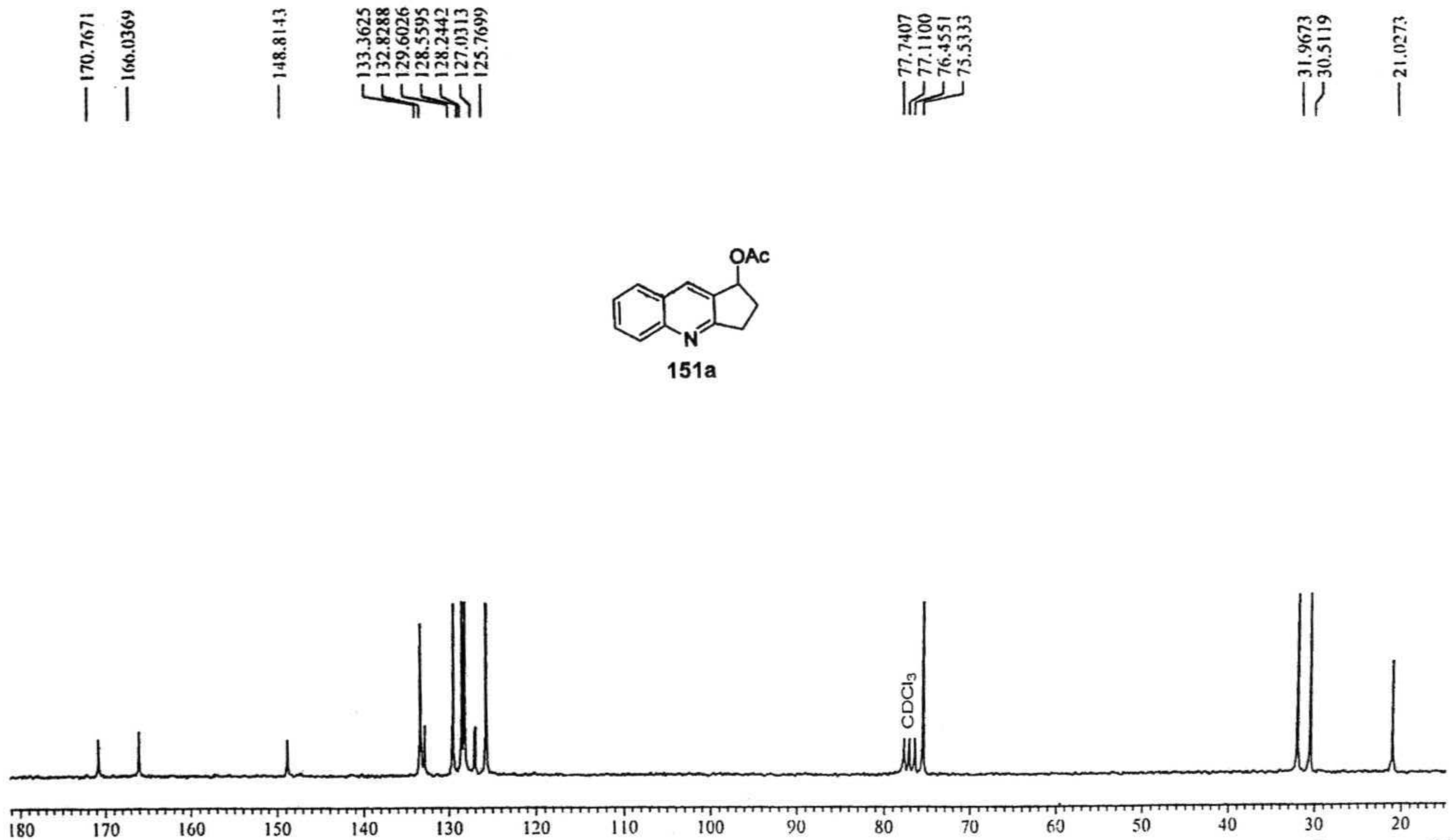
^{13}C NMR spectrum of 149a

Spectrum 16



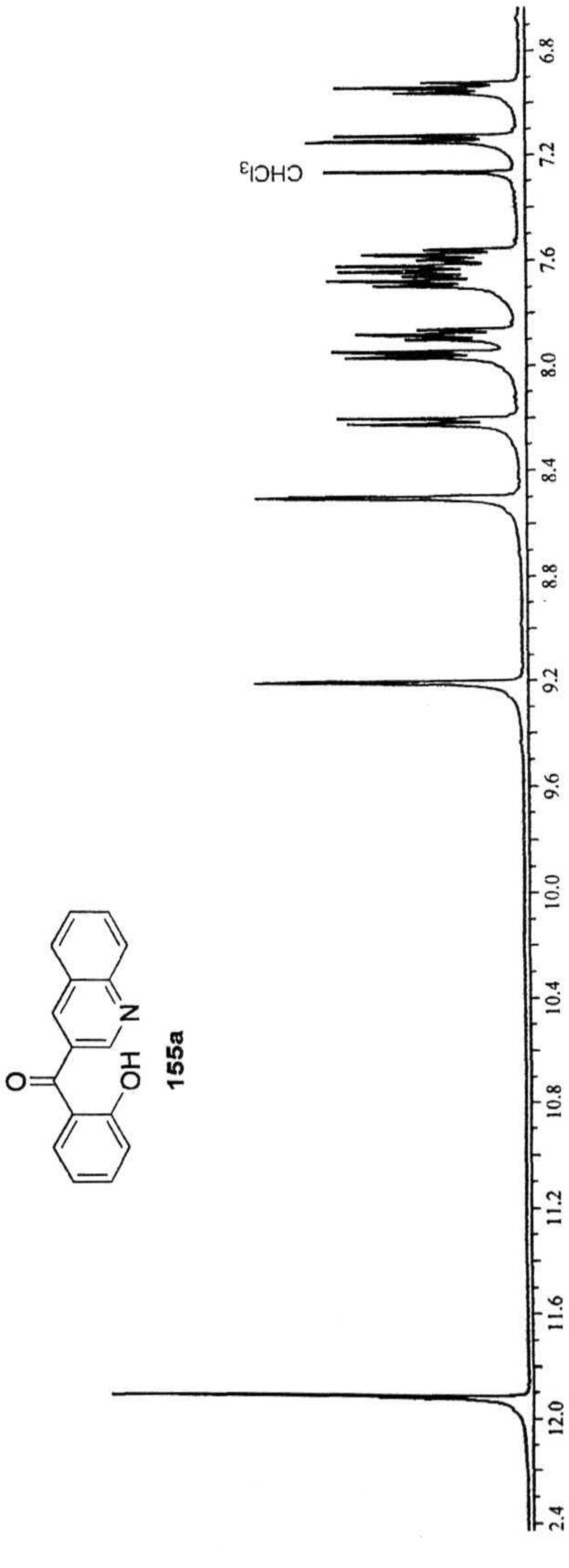
151a

^{1}H NMR spectrum of 151a *Spectrum 17*



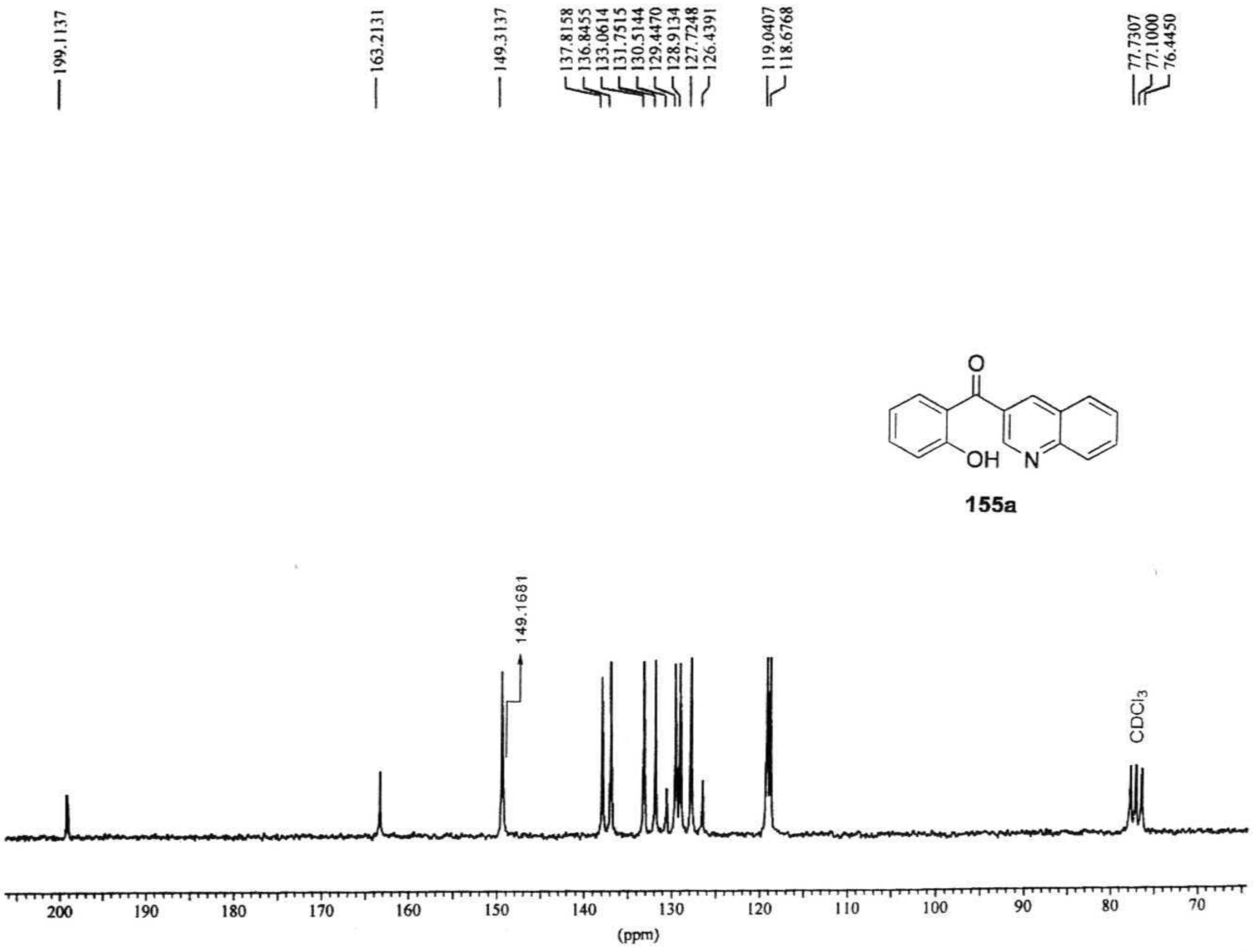
Spectrum 18

^{13}C NMR spectrum of 151a



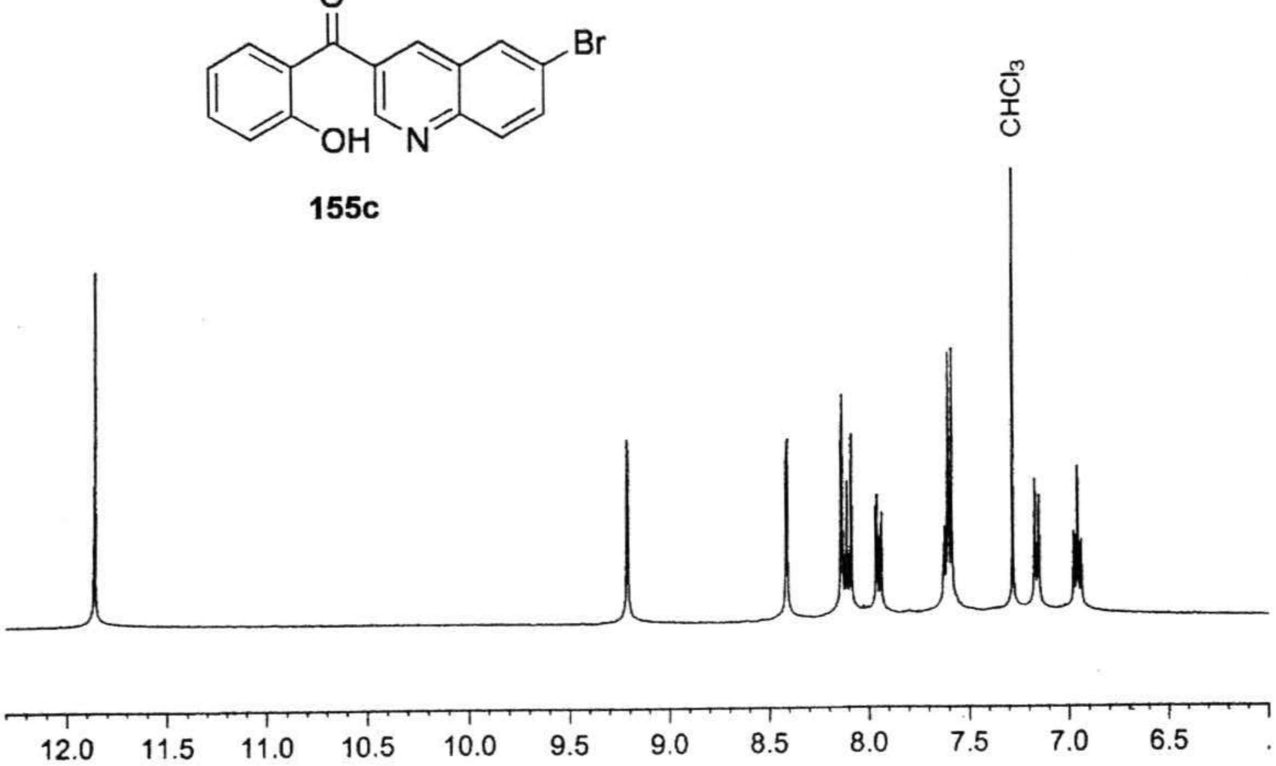
Spectrum 19

^{1}H NMR spectrum of 155a



^{13}C NMR spectrum of 155a

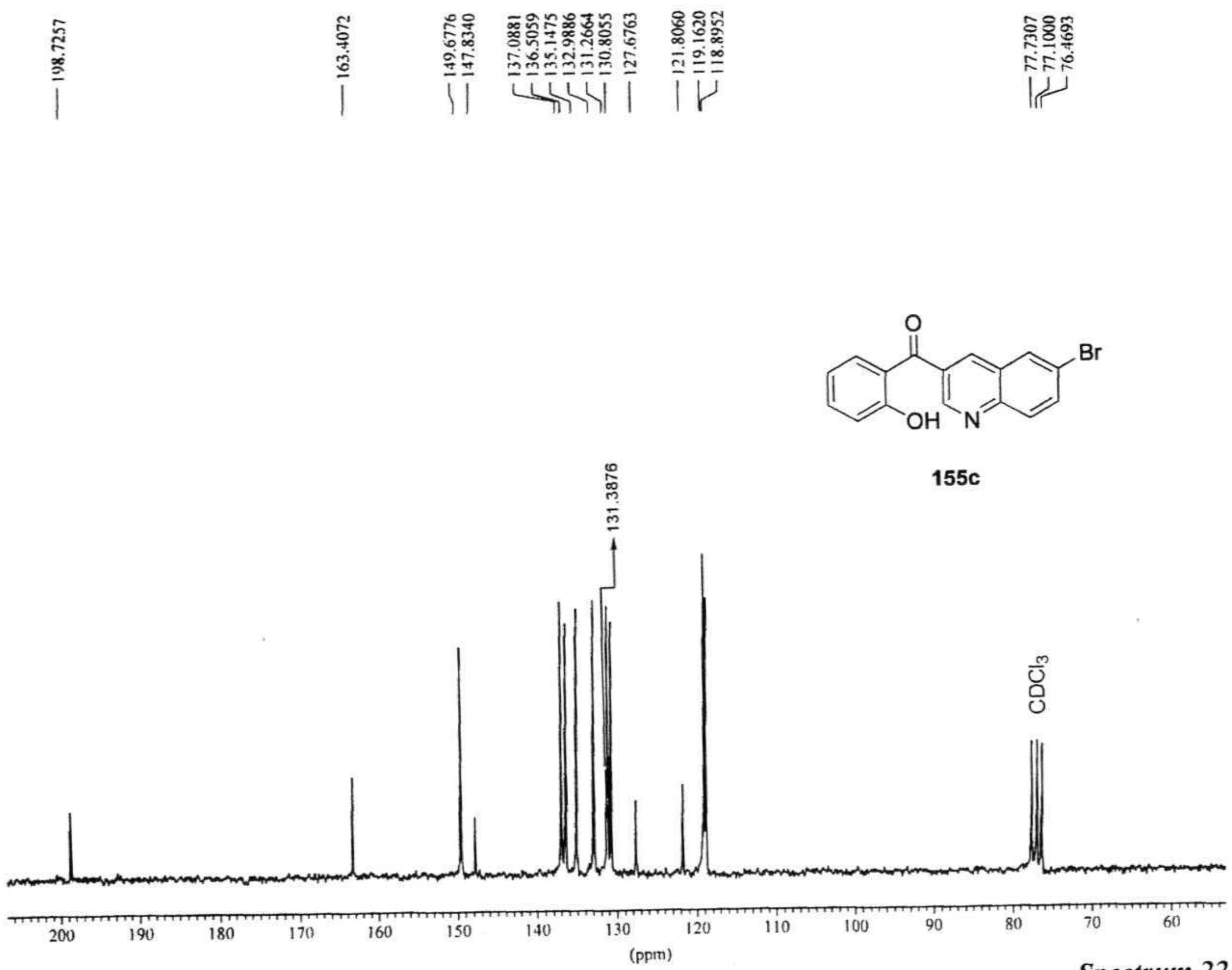
Spectrum 20



155c

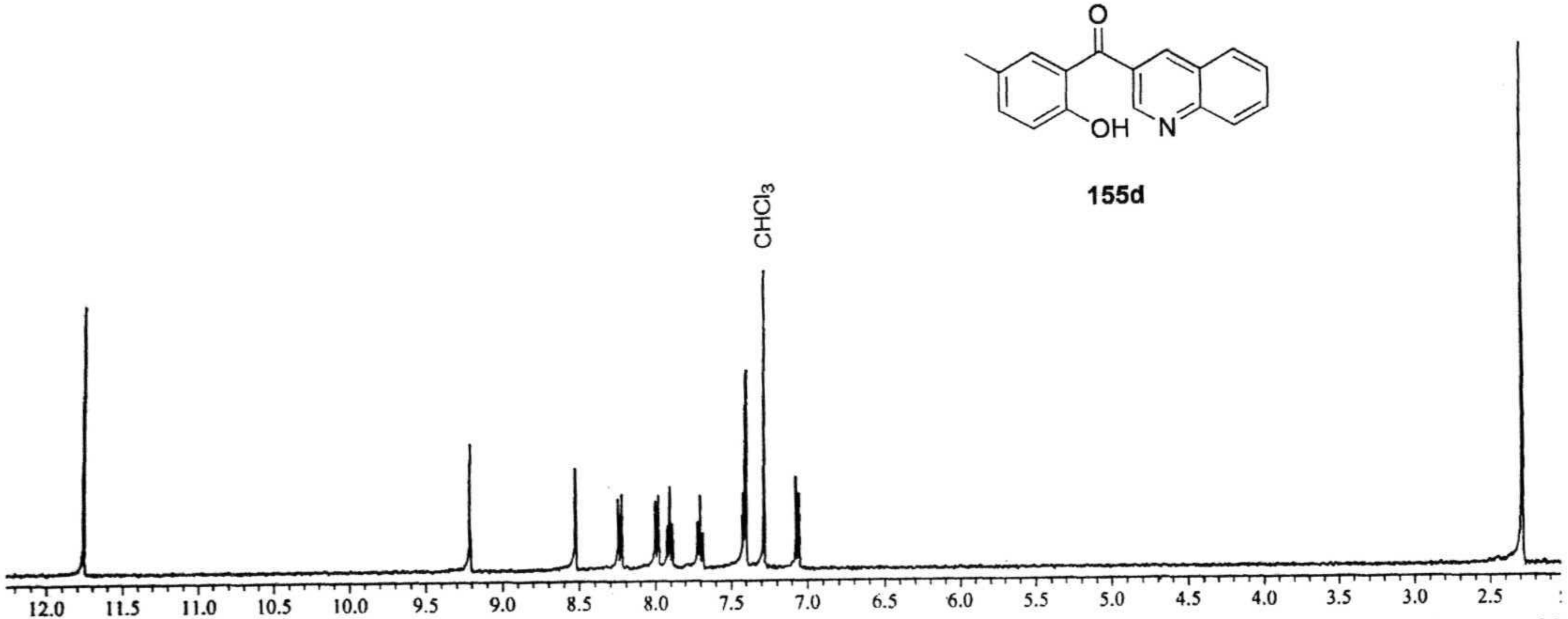
^{1}H NMR spectrum of 155c

Spectrum 21



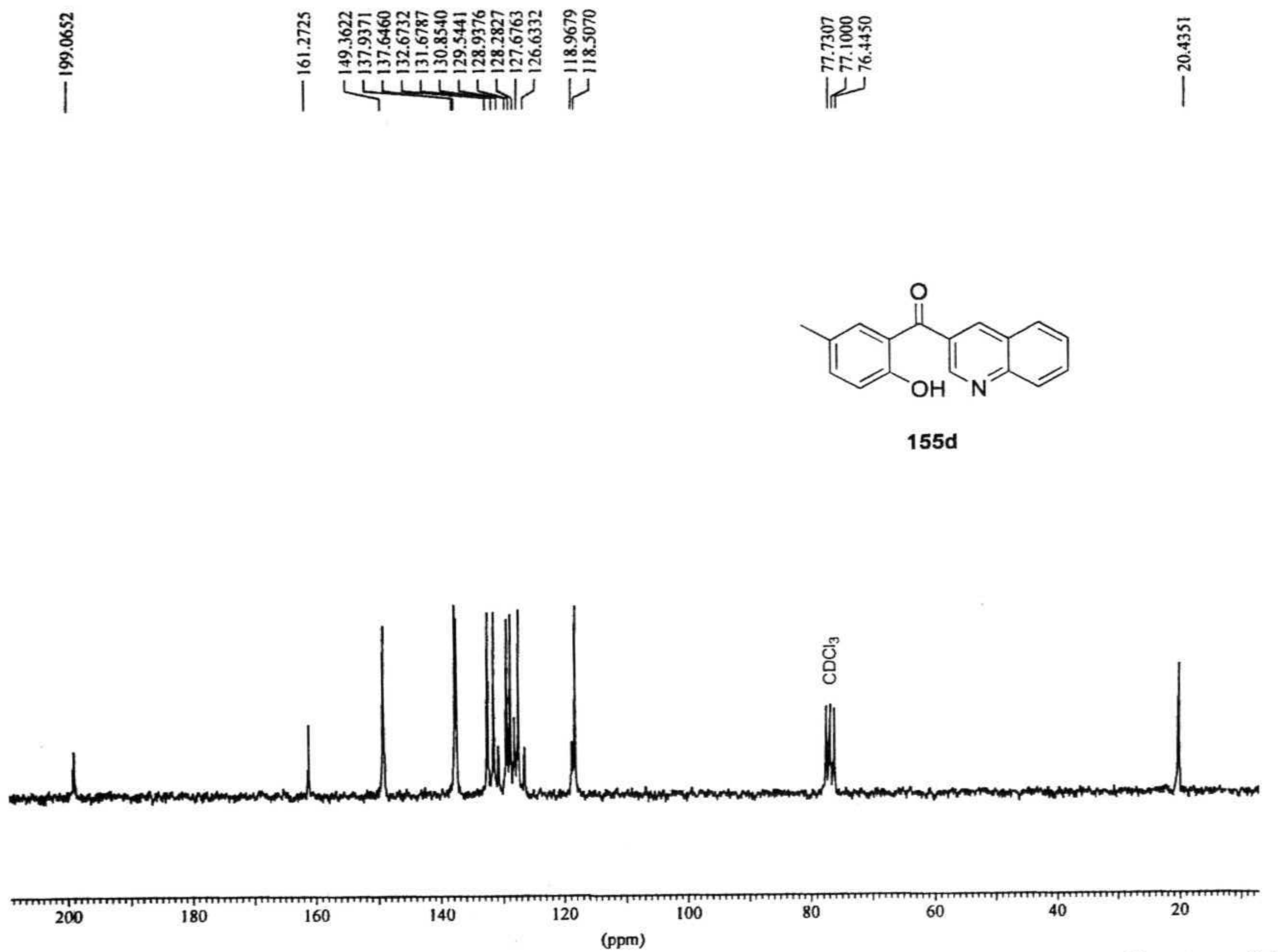
^{13}C NMR spectrum of 155c

Spectrum 22



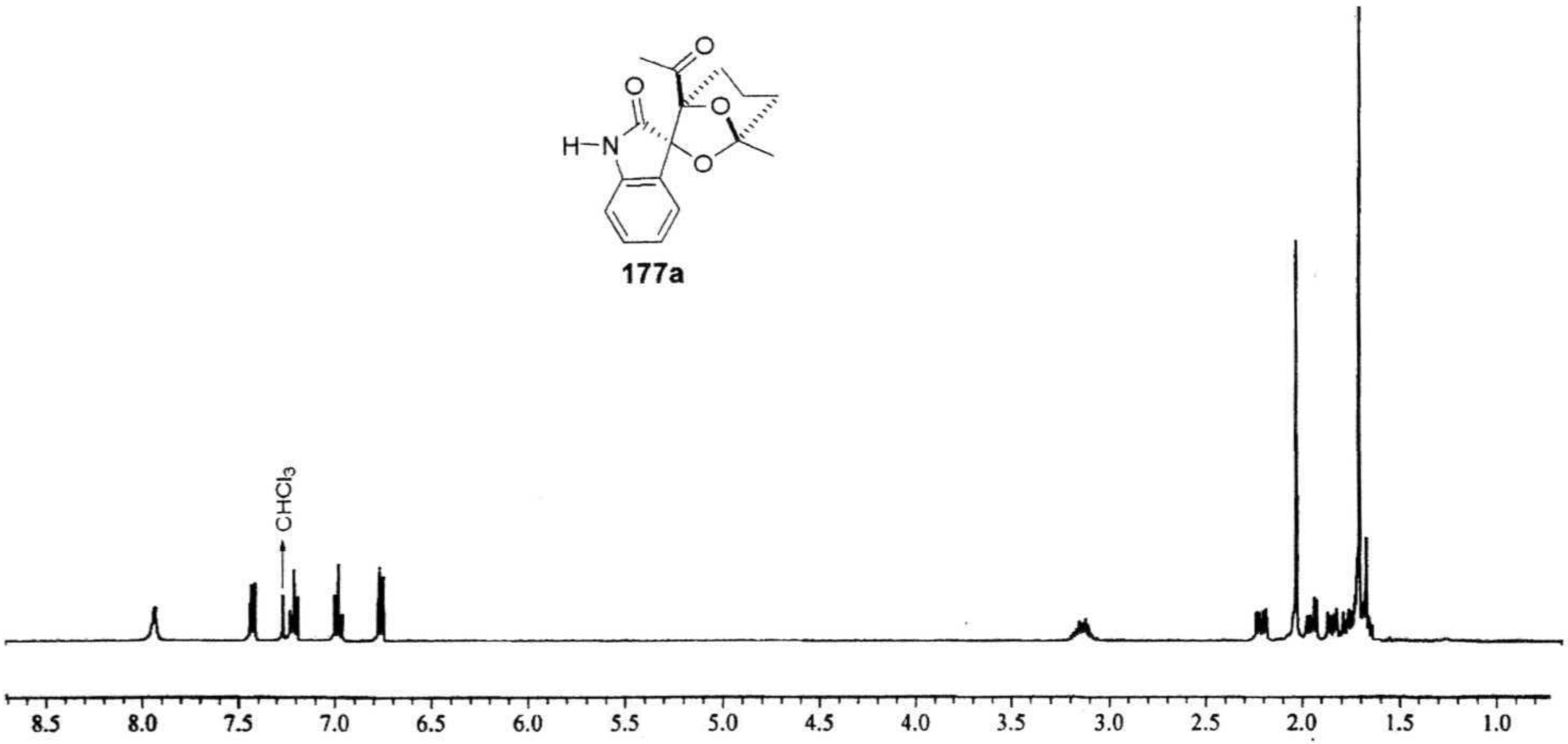
Spectrum 23

^{1}H NMR spectrum of 155d



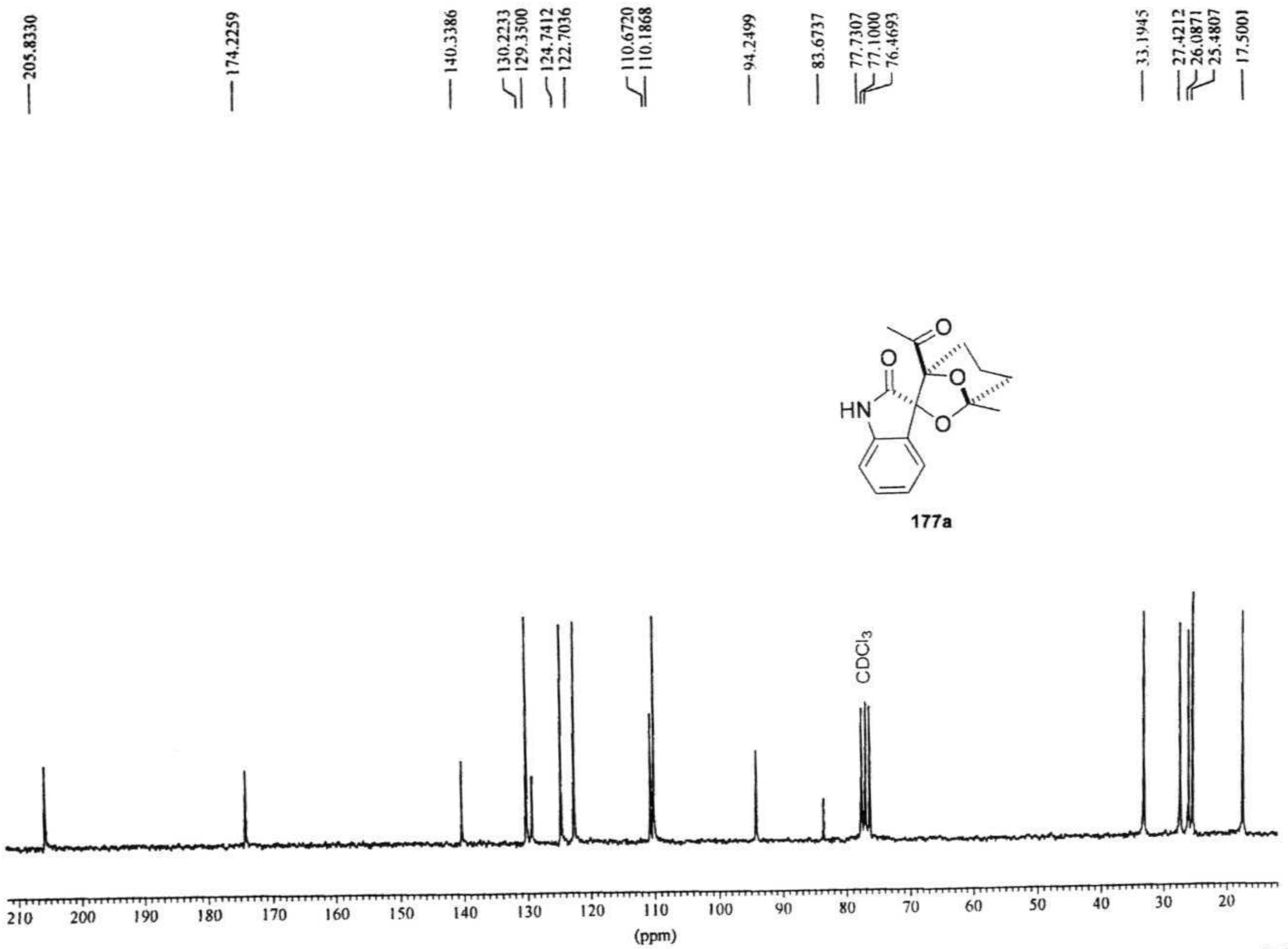
^{13}C NMR spectrum of 155d

Spectrum 24



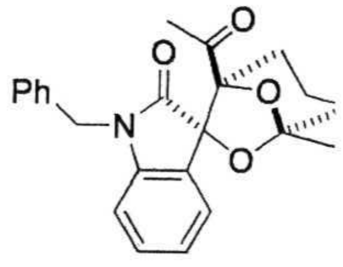
^{1}H NMR spectrum of 177a

Spectrum 25

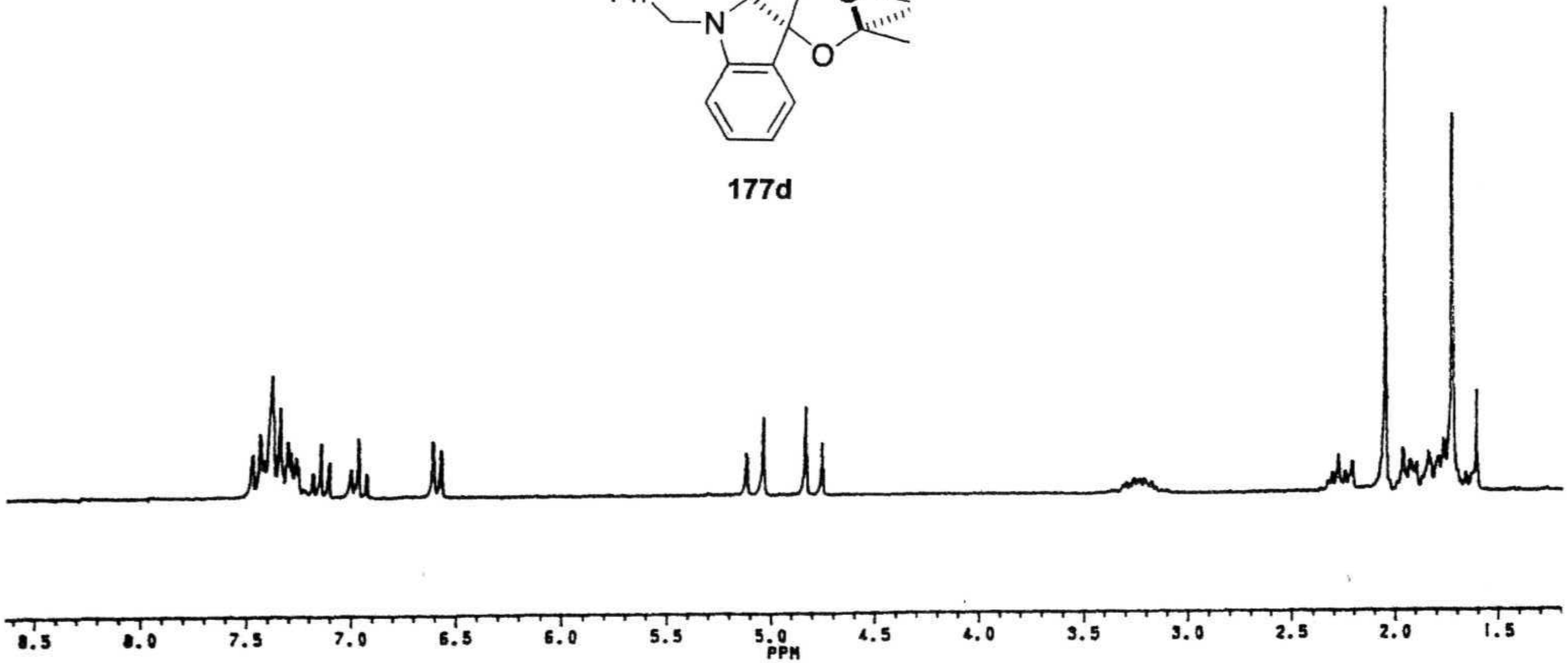


Spectrum 26

^{13}C NMR spectrum of 177a

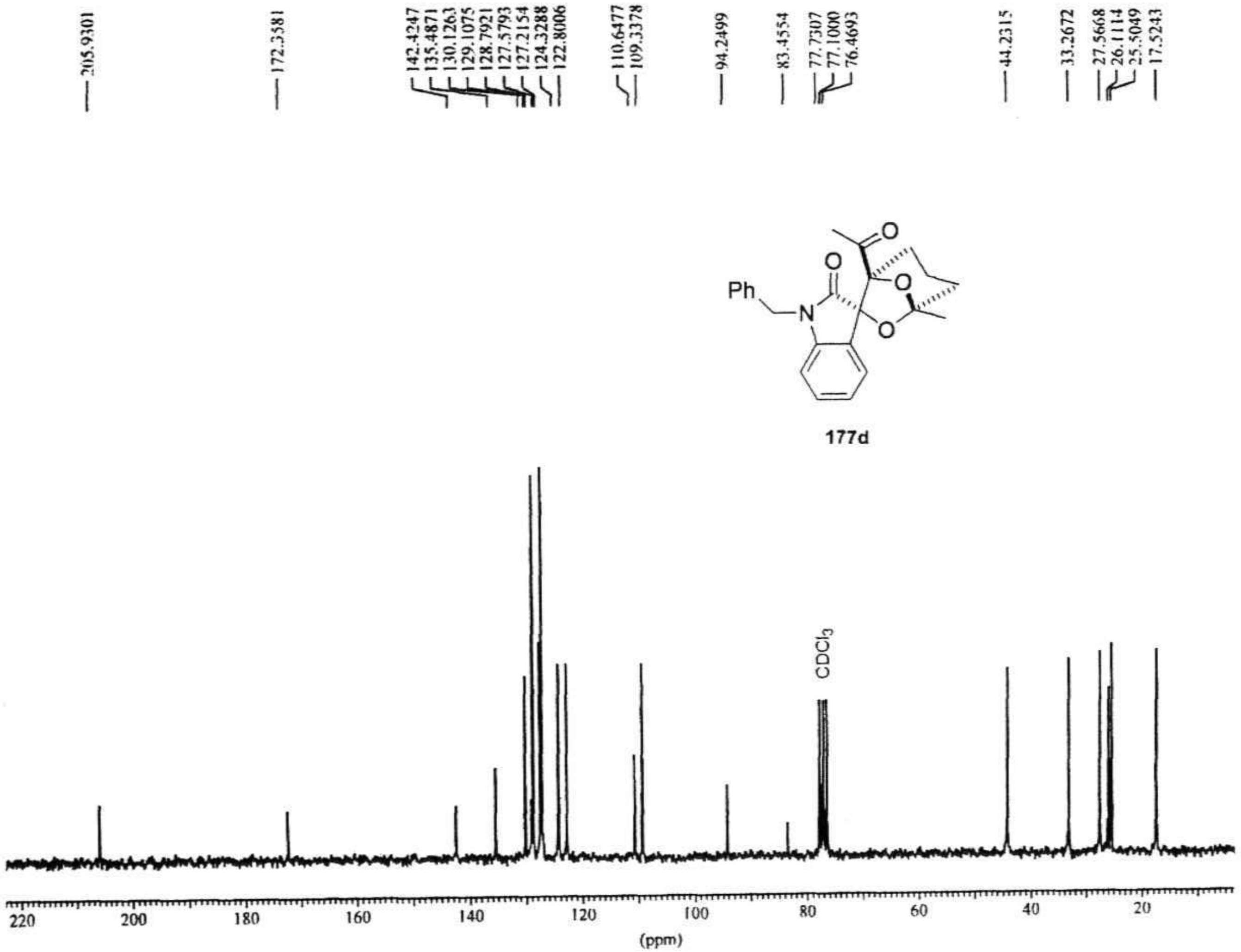


177d



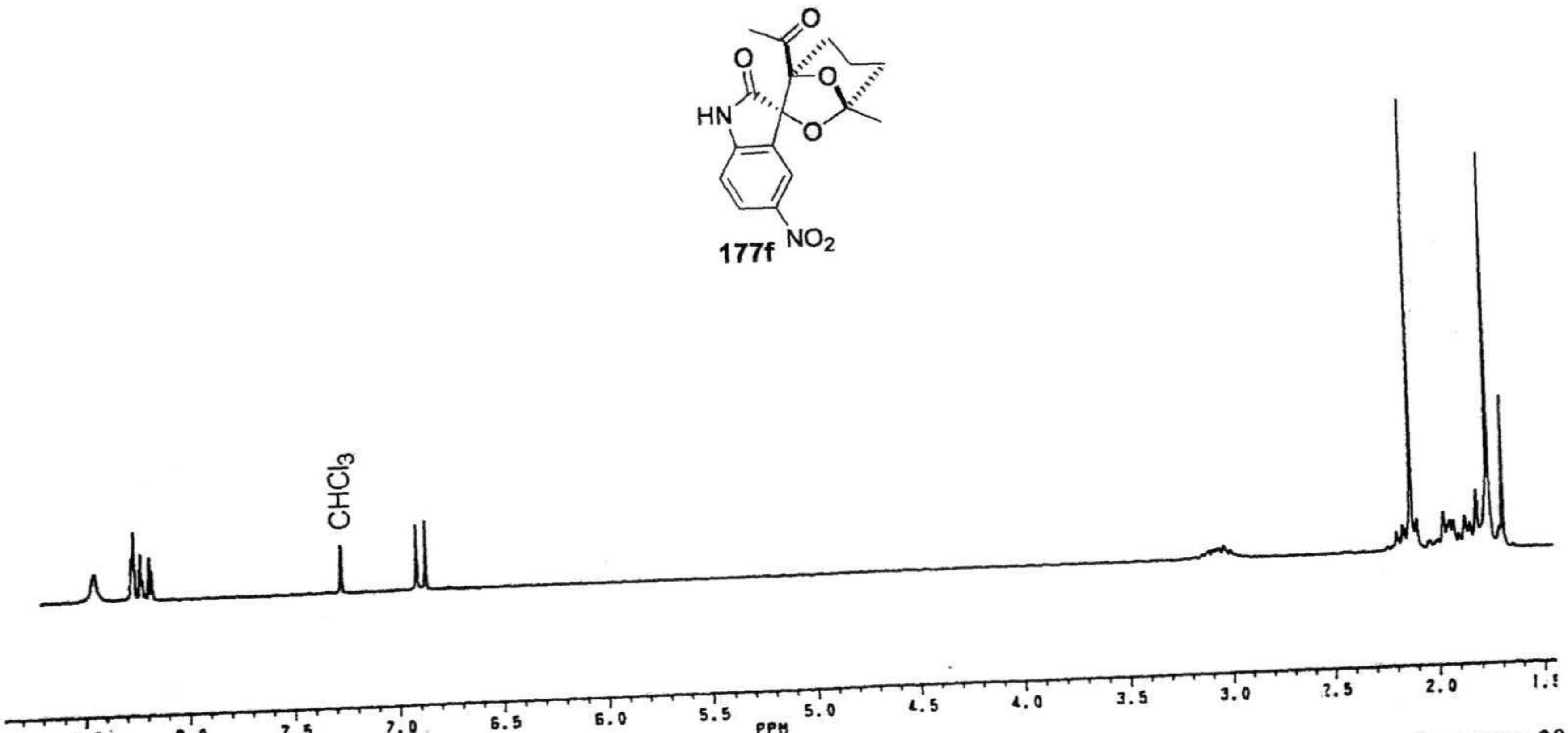
^{1}H NMR spectrum of 177d

Spectrum 27



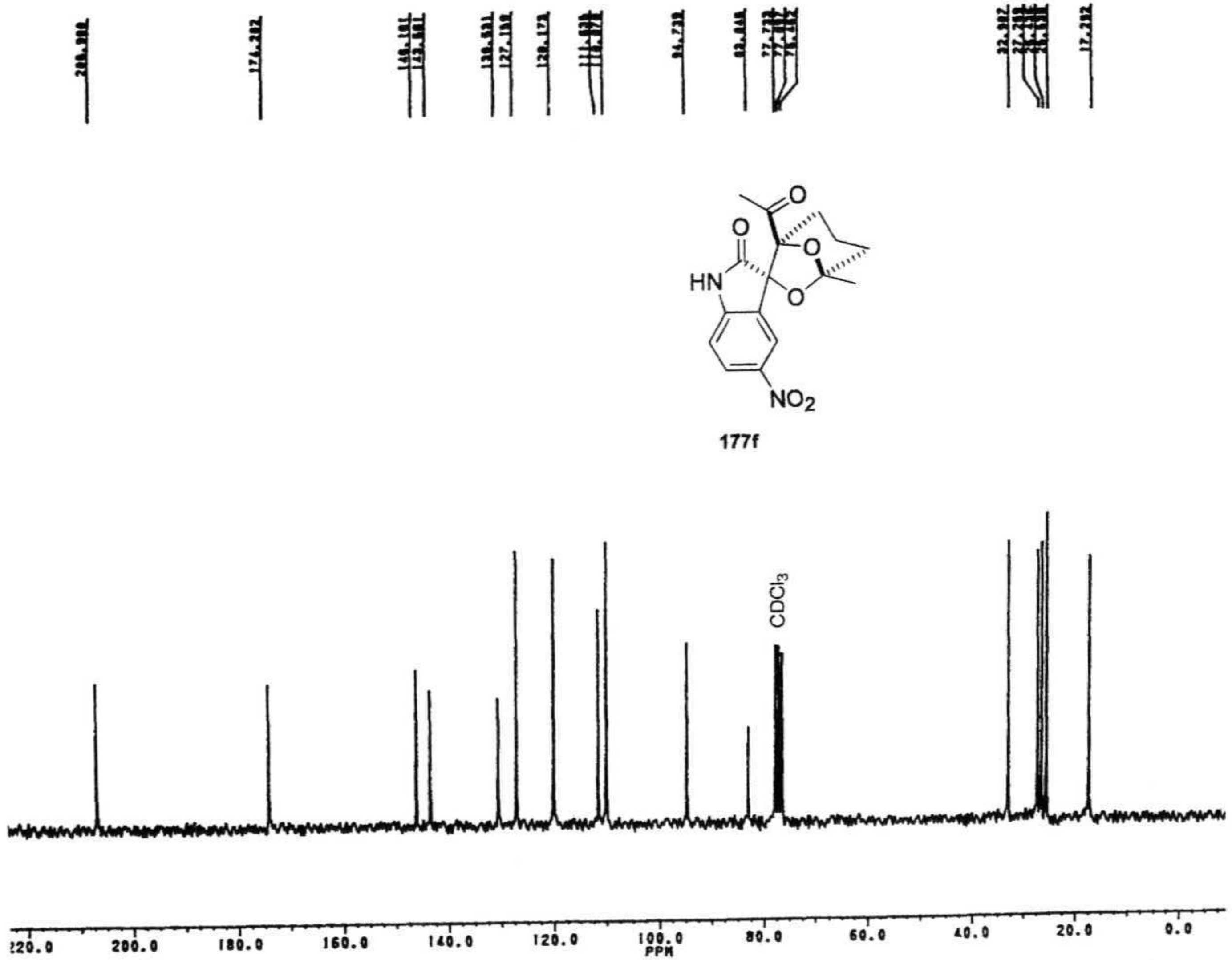
^{13}C NMR spectrum of 177d

Spectrum 28



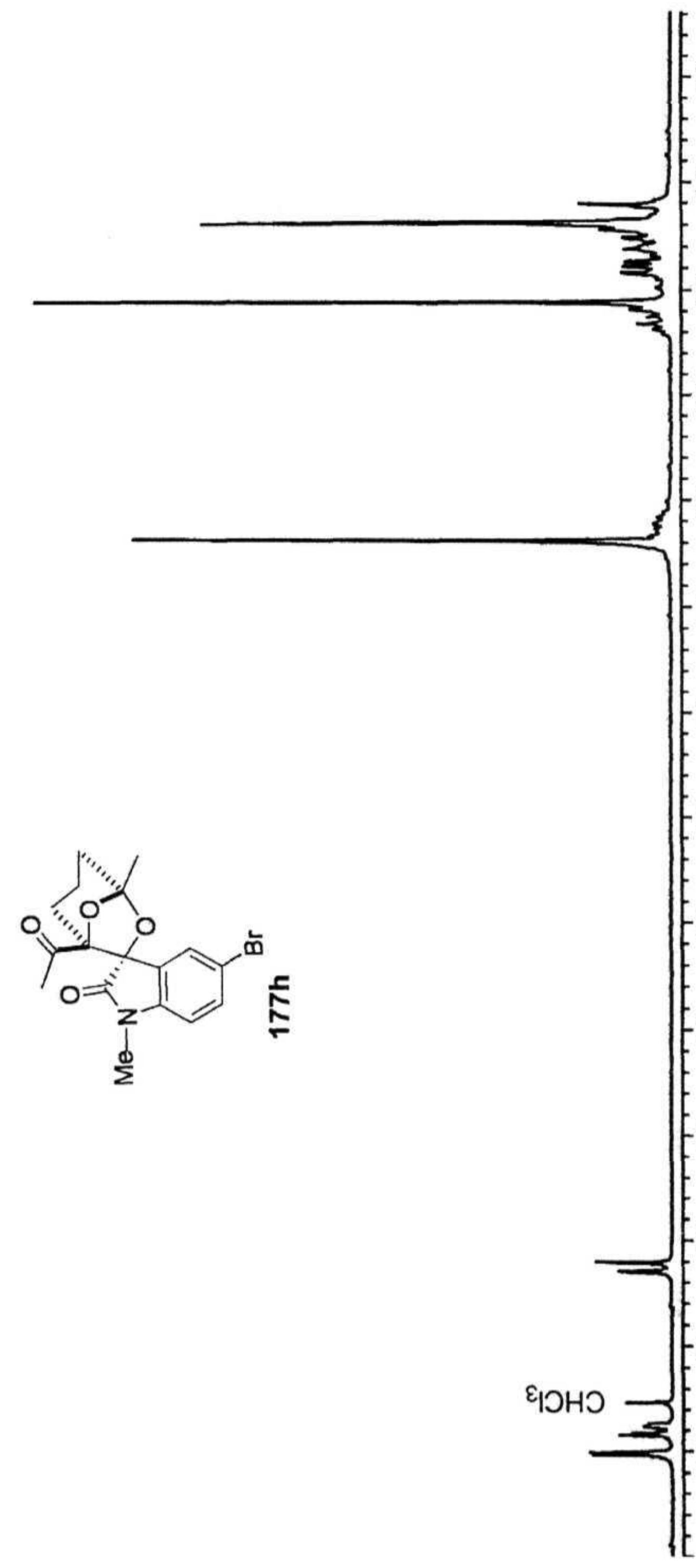
Spectrum 29

^{1}H NMR spectrum of 177f



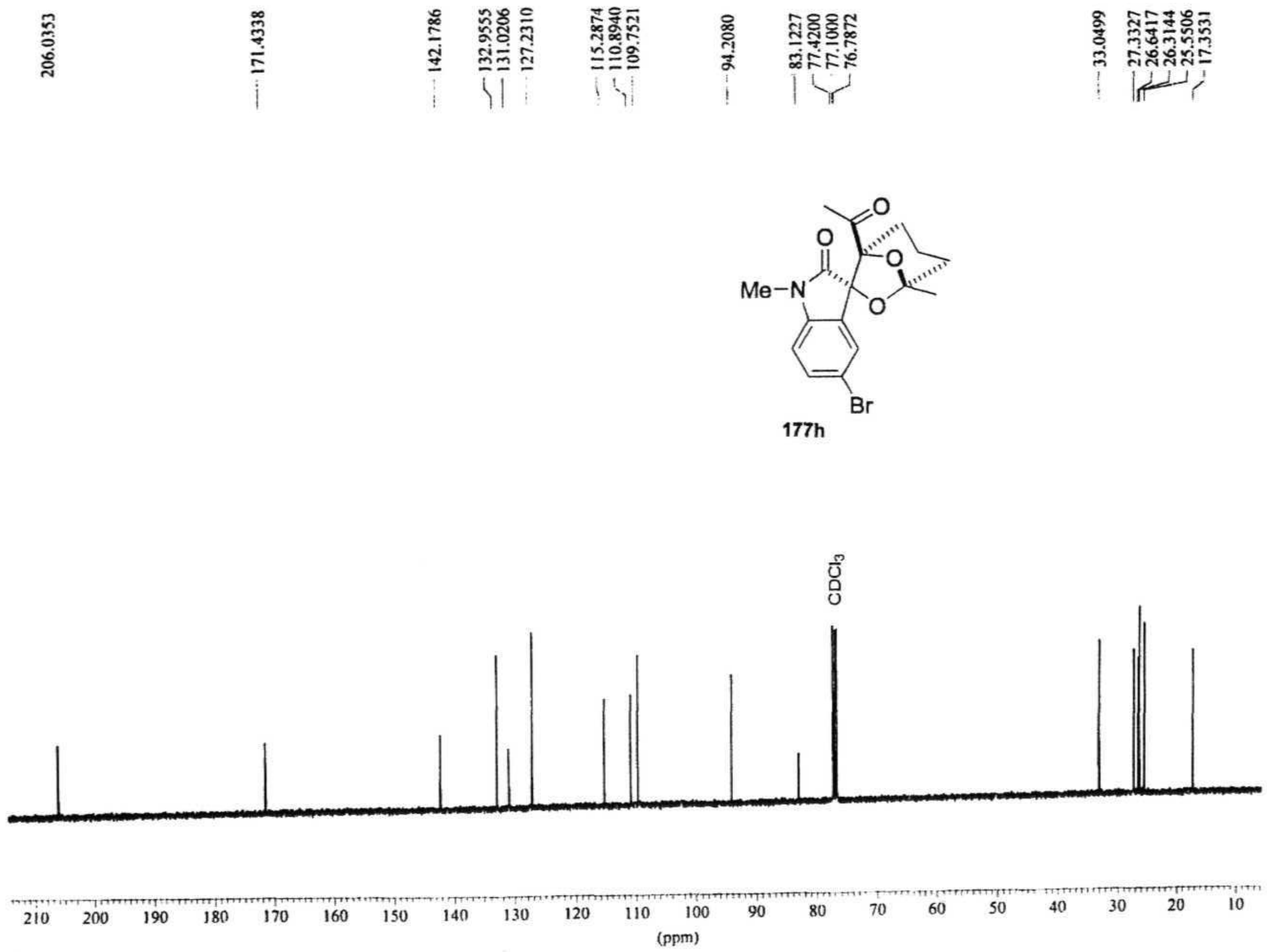
Spectrum 30

^{13}C NMR spectrum of 177f



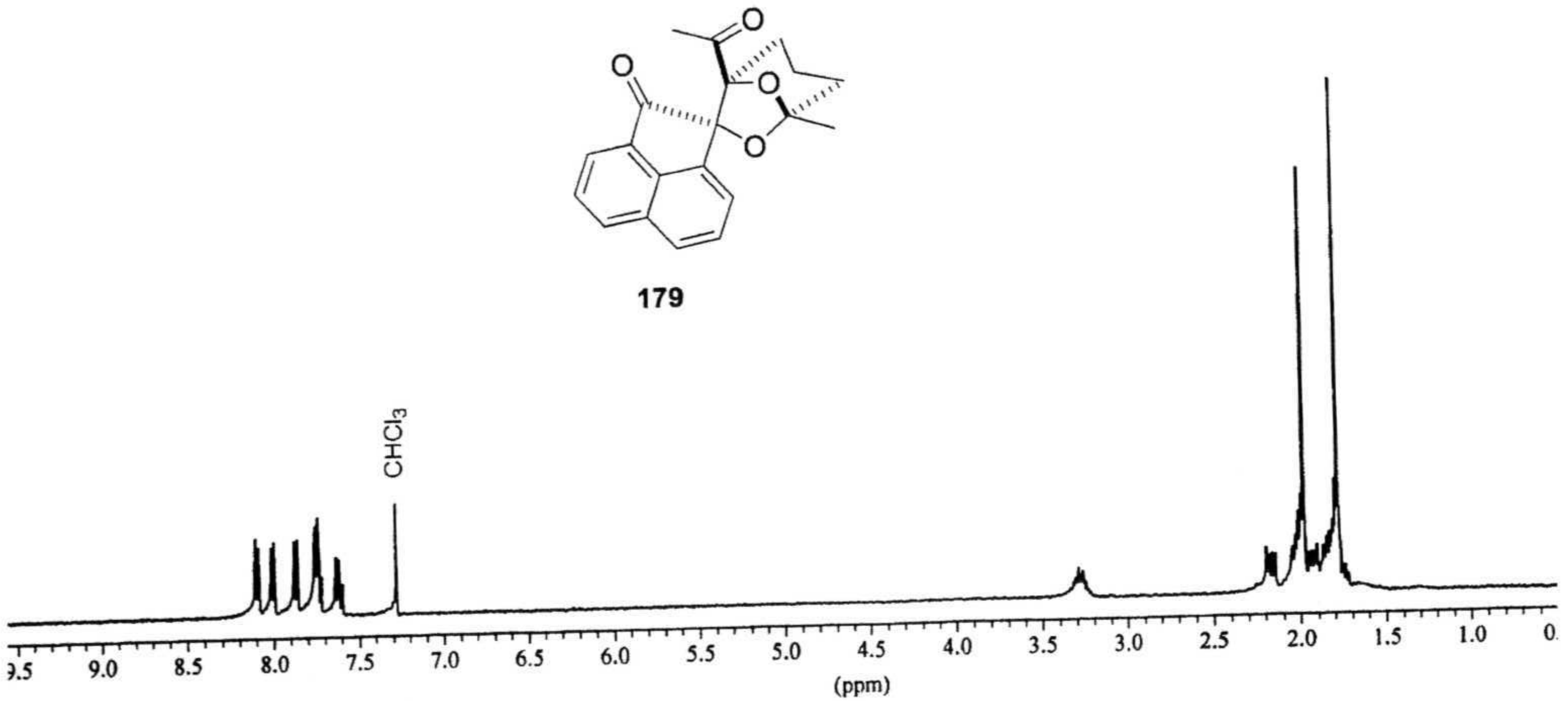
^{1}H NMR spectrum of 177h

Spectrum 31



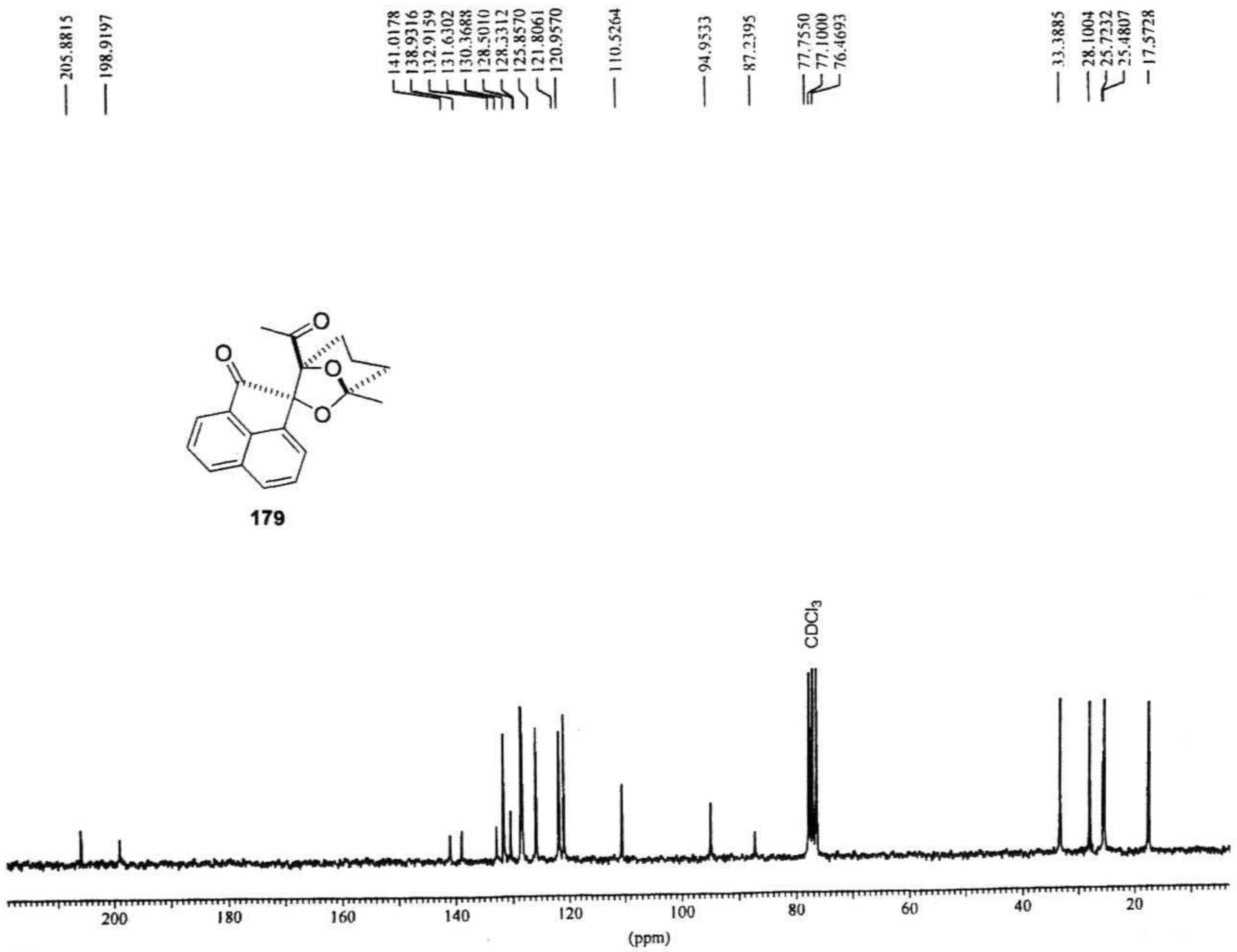
^{13}C NMR spectrum of 177h

Spectrum 32



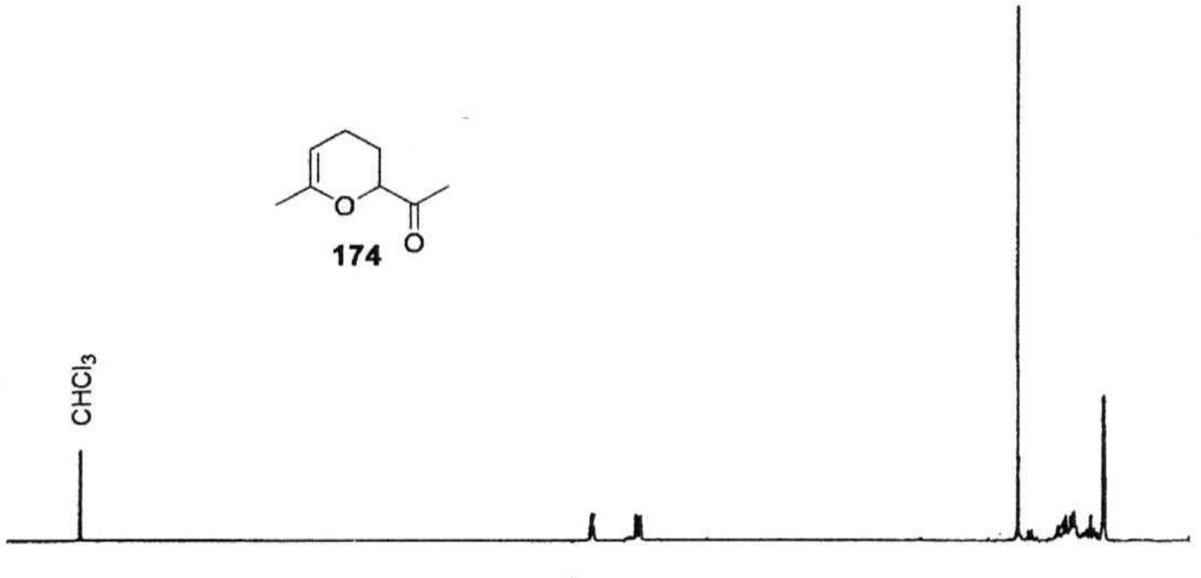
Spectrum 33

^{1}H NMR spectrum of 179

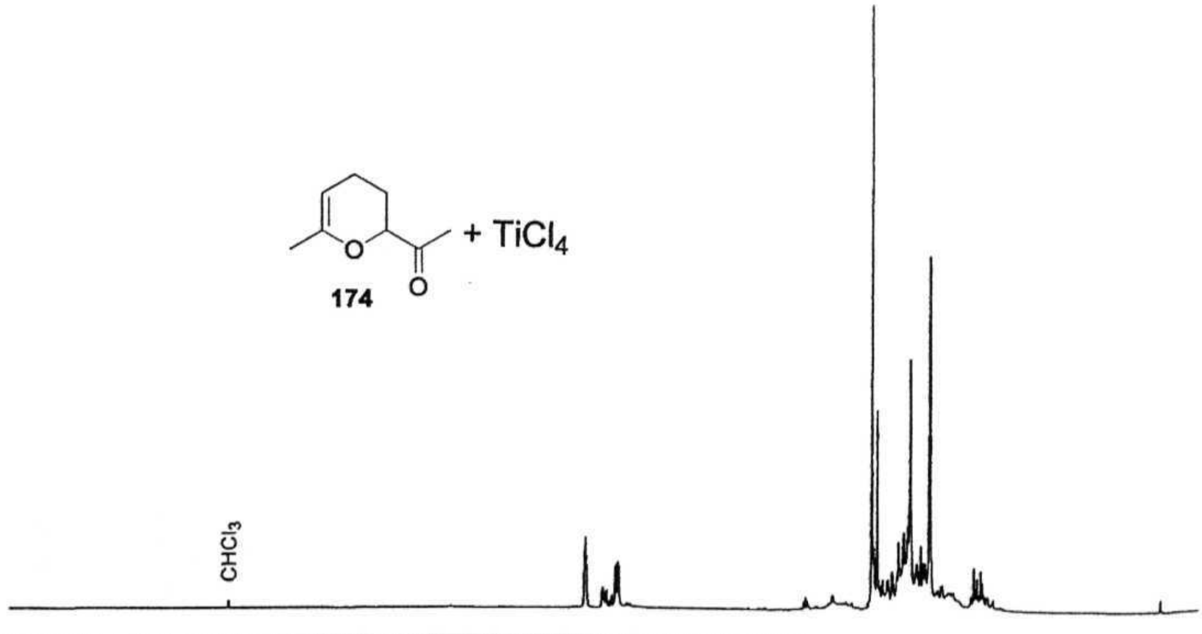


^{13}C NMR spectrum of 179

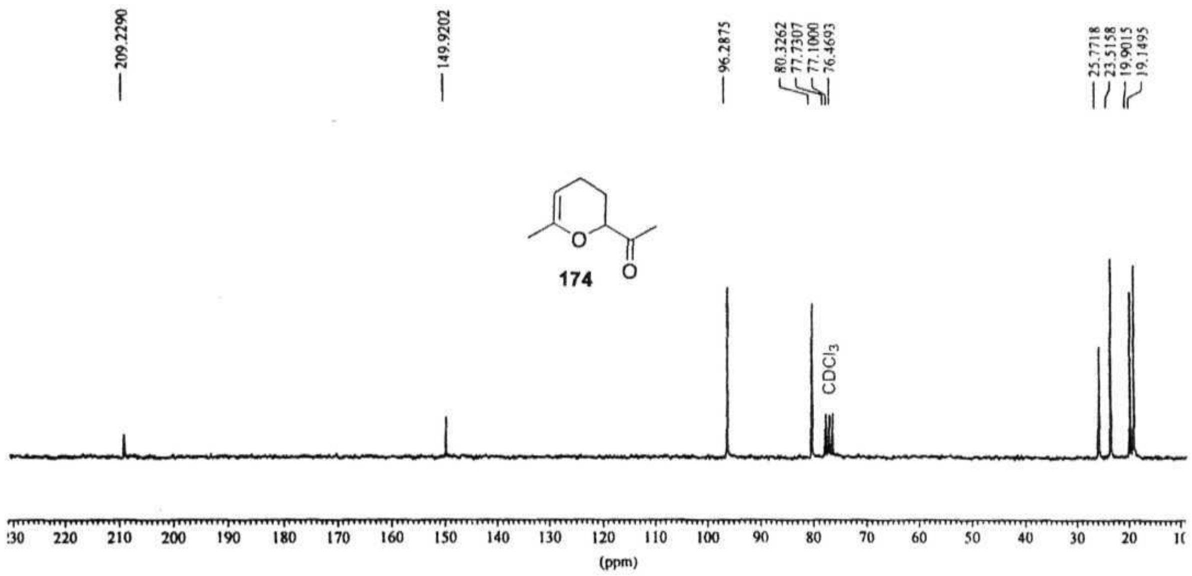
Spectrum 34



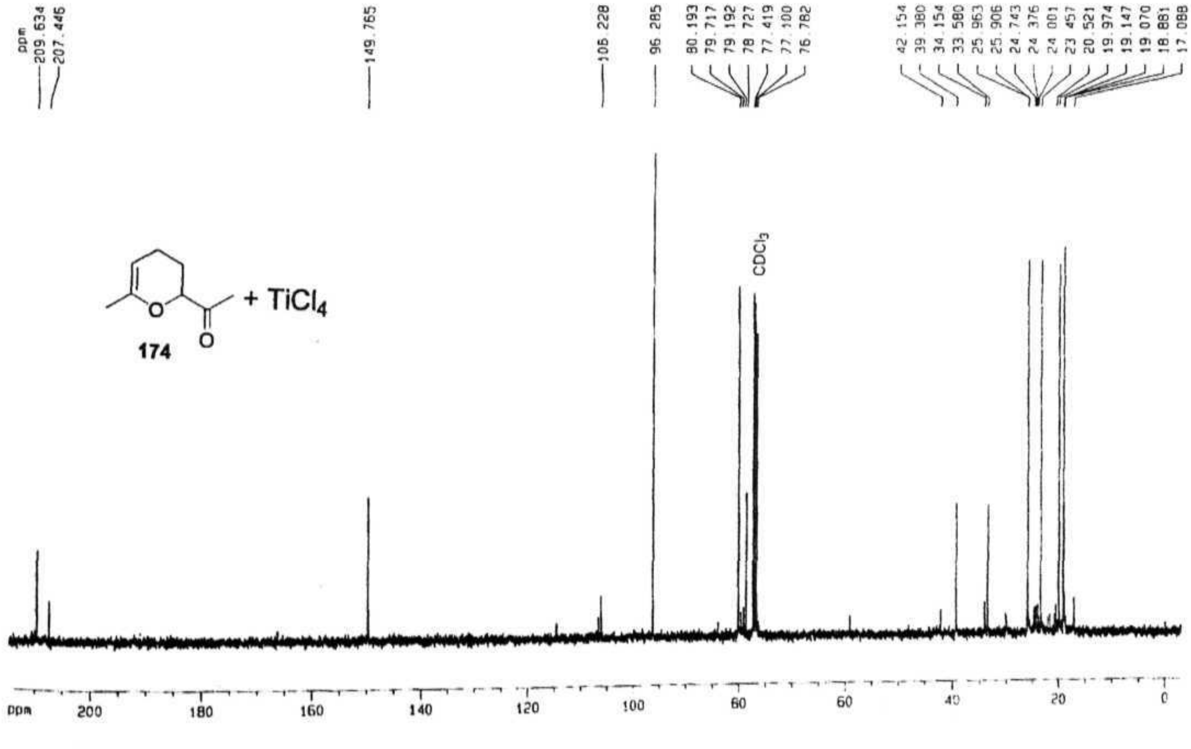
a) ^{1}H NMR spectrum of 174



b) ^{1}H NMR spectrum of 174 (1.0 eq.)+TiCl$_4$ (0.1 eq.) ***Spectrum 35***

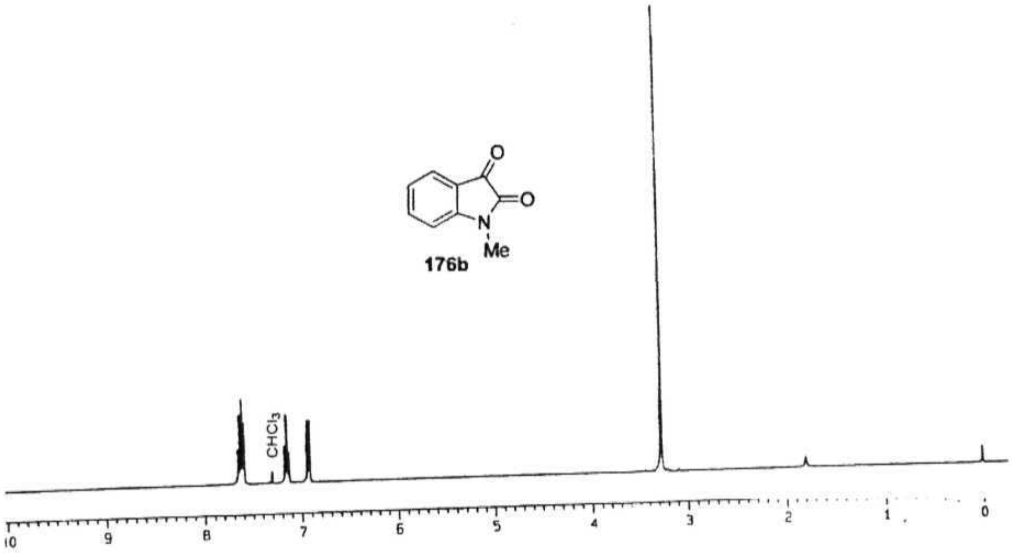


a) ^{13}C NMR spectrum of 174

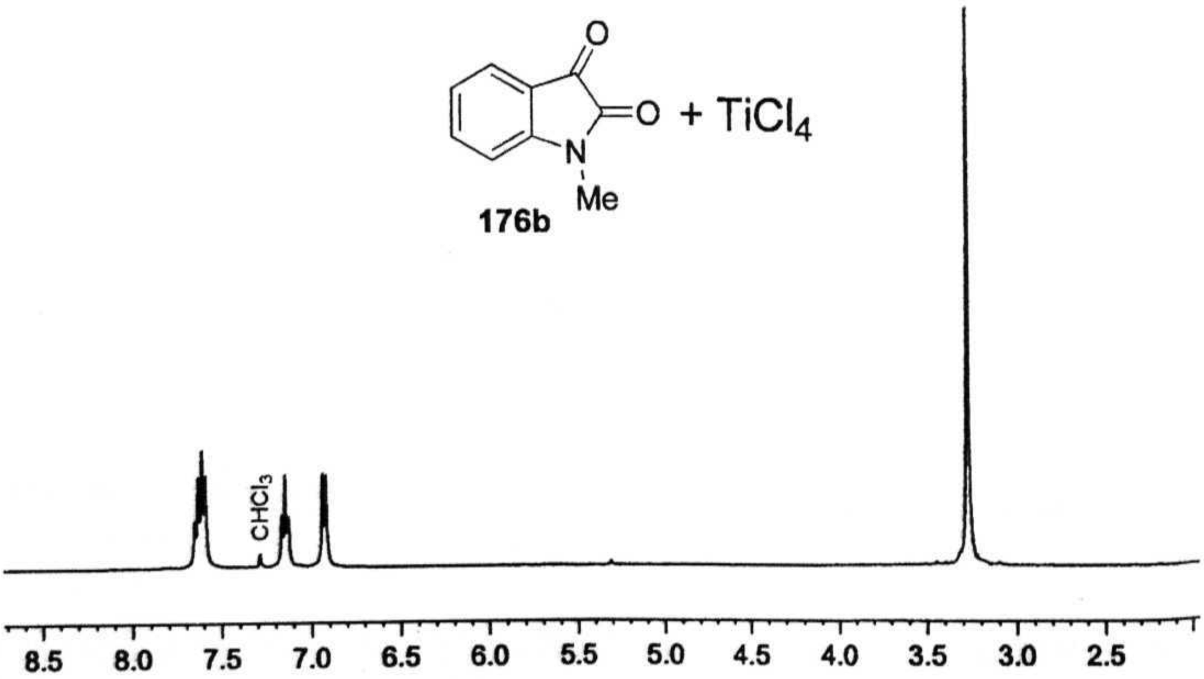


b) ^{13}C NMR spectrum 174 (1.0 eq.)+TiCl$_4$ (0.1 eq.)

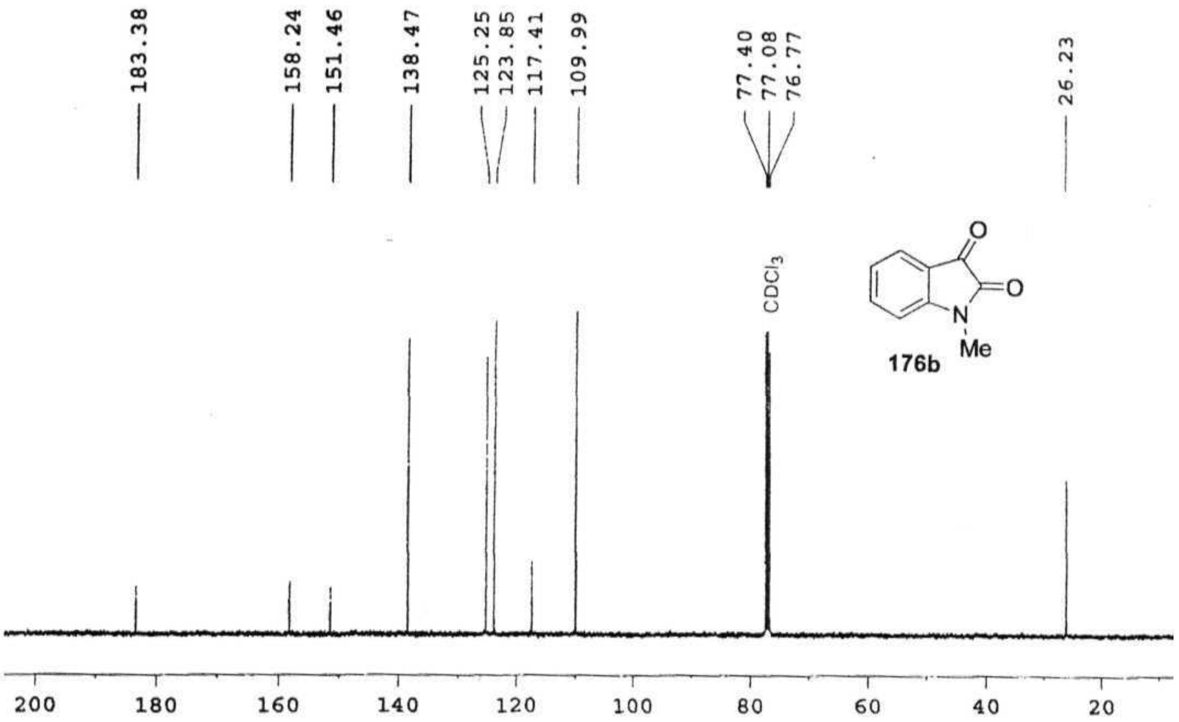
Spectrum 36



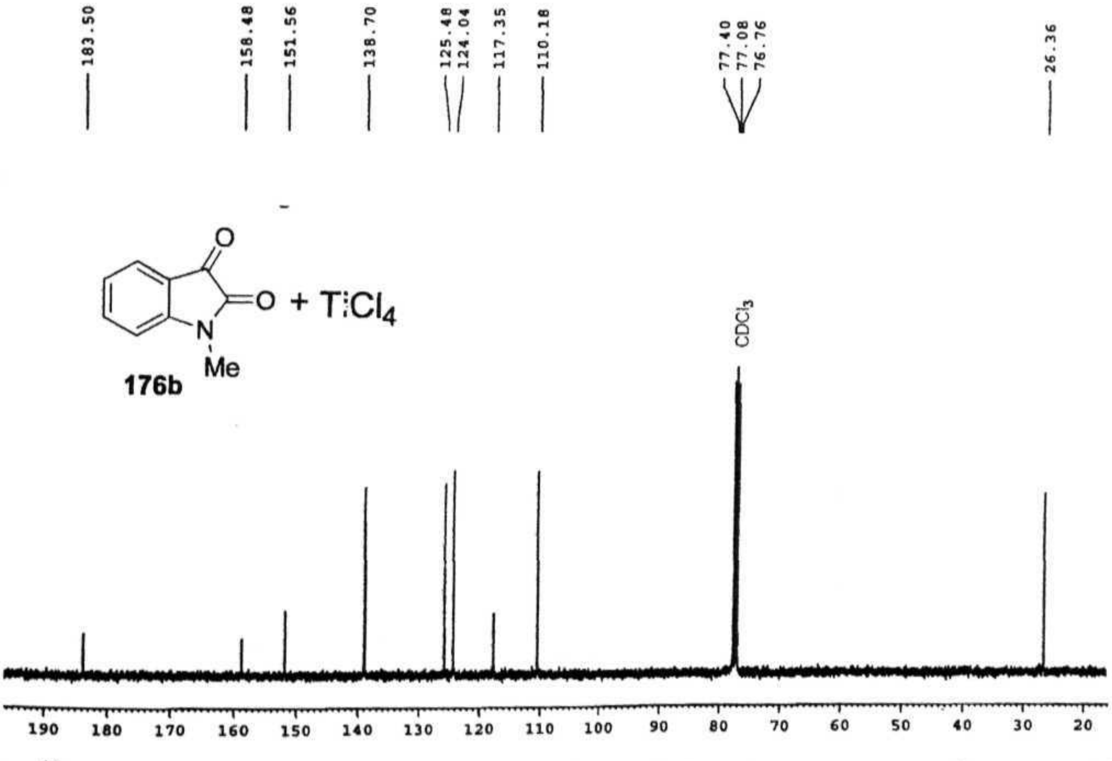
a) ^{1}**H NMR spectrum of 176b**



b) ^{1}**H NMR spectrum of 176b (1.0 eq.)+**$TiCl_4$ **(0.2 eq.)** ***Spectrum 37***



a) ^{13}C NMR spectrum of 176b



b) ^{13}C NMR spectrum of 176b (1.0 eq.)+TiCl$_4$ (0.2 eq.) *Spectrum 38*

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule **126.** U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	998(2)	511(2)	4002(2)	63(1)
C(5)	740(2)	-933(2)	2349(2)	46(1)
C(8)	1836(3)	-665(2)	665(2)	47(1)
C(7)	1516(3)	-378(2)	1803(2)	49(1)
N(l)	-260(2)	-1169(2)	3849(2)	54(1)
C(3)	-570(3)	-2263(2)	3154(2)	51(1)
C(13)	1237(3)	-1580(2)	-164(2)	54(1)
C(4)	-54(3)	-2054(2)	2034(2)	53(1)
C(6)	532(3)	-430(2)	3486(2)	48(1)
C(1l)	2528(3)	-1076(3)	-1519(2)	59(1)

C(12)	1570(3)	-1771(2)	-1237(2)	60(1)
C(9)	2783(3)	35(3)	372(3)	68(1)
C(2)	190(4)	-3251(2)	4018(3)	66(1)
C(l)	-291(5)	-3450(3)	5141(3)	84(1)
C(10)	3103(3)	-162(3)	-707(3)	74(1)
C(14)	2880(4)	-1297(3)	-2693(3)	82(1)

Table II: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule **148a.** U(eq) is defined as one third of the trace of the orthogonal ized U_{ij} tensor.

	x	y	z	U(eq)
0(1)	984(2)	3716(2)	1220(1)	57(1)
N(l)	1124(3)	7773(2)	934(1)	56(1)
C(8)	1258(3)	5861(2)	1350(1)	43(1)
C(13)	377(3)	6598(2)	1056(2)	46(1)
C(9)	379(3)	4567(2)	1560(2)	46(1)
C(7)	2934(3)	6377(2)	1467(2)	53(1)
C(6)	3777(3)	7615(2)	1326(2)	54(1)

C(10)	-1528(3)	3984(2)	1176(2)	54(1)
C(l)	2817(3)	8294(2)	1074(2)	55(1)
0(2)	244(3)	2416(2)	2115(2)	88(1)
C(12)	-1504(3)	6032(3)	845(2)	56(1)
C(ll)	-2200(3)	4972(2)	1314(2)	51(1)
C(16)	842(4)	2675(3)	1559(2)	64(1)
C(14)	-1683(4)	5561(3)	2274(2)	66(1)
C(5)	5520(3)	8225(3)	1453(2)	78(1)
C(2)	3639(5)	9572(3)	965(2)	79(1)
C(15)	-4133(3)	4267(3)	923(2)	83(1)
C(3)	5323(5)	10115(3)	1105(2)	91(0
C(4)	6271(4)	9446(4)	1349(2)	92(1)
C(17)	1497(5)	1887(3)	1133(3)	97(1)

Table III: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A x 10) for molecule **155f.** U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(5)	629(13)	8261(12)	4136(9)	53(3)
C(7)	1477(13)	8002(9)	5633(7)	49(3)
C(4)	414(14)	8952(12)	3341(7)	49(3)
C(6)	1171(14)	8625(10)	4778(9)	45(3)
C(l)	1467(14)	9828(10)	4596(8)	50(3)
C(8)	2051(14)	8439(9)	6238(8)	44(3)
C(10)	2646(14)	7700(11)	7039(8)	49(3)
C(ll)	1750(13)	6872(11)	7571(8)	46(3)
C(3)	666(17)	10075(14)	3177(9)	65(4)
C(12)	2365(14)	5931(13)	8159(8)	55(3)
C(16)	58(15)	7124(11)	7558(7)	58(3)
C(2)	1141(16)	10528(11)	3797(9)	56(3)
C(9)	2308(16)	9592(13)	5973(9)	59(4)
C(15)	-815(16)	6358(15)	8058(9)	64(4)
C(13)	1610(20)	5108(13)	8588(10)	75(4)

C(14)	18(19)	5360(15)	8535(8)	90(5)
C(17)	-2637(18)	6651(17)	8085(11)	108(6)
O(1)	3893(10)	7736(9)	7215(6)	69(3)
0(2)	3930(12)	5722(10)	8254(8)	80(3)
N(l)	2062(13)	10296(9)	5218(8)	55(3)
Br(l)	-268(1)	8277(1)	2426(1)	70(1)

Table IV: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule 177a. U(eq) is defined as one third of the trace of the orthogonalized Uy tensor.

	x	y	z	U(eq)
0(3)	915(2)	3069(2)	6204(1)	43(1)
0(4)	659(2)	3428(2)	7983(1)	44(1)
0(1)	4370(2)	1961(2)	8919(2)	61(1)
C(6)	776(3)	357(3)	8226(2)	42(1)
C(9)	2568(3)	2023(3)	6690(2)	43(1)
N(l)	230(3)	-444(2)	9305(2)	51(1)
0(2)	4552(3)	-704(2)	6652(2)	72(1)

C(10)	4068(3)	3032(3)	6410(2)	52(1)
C(13)	287(3)	4355(3)	6868(2)	44(1)
C(1)	1718(3)	-932(3)	9033(2)	47(1)
C(8)	3304(3)	1160(3)	8769(2)	47(1)
C(14)	3203(3)	346(3)	6271(2)	49(1)
C(5)	-833(3)	206(3)	7880(2)	49(1)
C(7)	1798(3)	1763(3)	7921(2)	42(1)
C(12)	1449(3)	5659(3)	6537(2)	51(1)
C(11)	3465(3)	4793(3)	6745(2)	56(1)
C(16)	-1746(3)	5093(3)	6783(2)	58(1)
C(2)	1112(4)	-2394(3)	9481(2)	58(1)
C(4)	-1477(4)	-1253(3)	8330(2)	57(1)
C(3)	-500(4)	-2531(3)	9116(2)	62(1)
C(15)	2192(4)	74(4)	5396(2)	63(1)

Table V: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule **177i.** U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Br(l)	12058(1)	5638(1)	854(1)	62(1)
0(2)	10483(1)	8199(2)	3624(1)	43(1)
0(3)	9049(1)	6850(2)	2714(1)	40(1)
C(14)	10439(2)	5645(3)	3912(2)	56(1)
C(6)	10670(2)	8615(2)	2130(1)	38(1)
C(9)	8804(2)	8309(2)	2423(1)	39(1)
C(5)	10996(2)	7338(2)	1852(1)	41(1)
C(15)	8273(2)	8423(3)	1396(1)	44(1)
C(13)	9755(2)	6990(2)	3638(1)	43(1)
C(8)	10089(2)	10574(2)	2852(2)	46(1)
N(l)	10580(2)	11053(2)	2240(1)	48(1)
0(1)	9751(2)	11336(2)	3338(1)	65(1)
C(17)	10734(2)	12561(3)	2093(2)	58(1)
C(4)	11575(2)	7389(3)	1231(2)	46(1)
C(12)	9044(2)	7376(3)	4225(2)	53(1)

C(10)	7987(2)	8918(3)	2879(2)	52(1)
C(7)	10024(2)	8909(2)	2774(1)	40(1)
C(1)	10938(2)	9913(2)	1812(2)	43(1)
C(2)	11498(2)	9959(3)	1184(2)	54(1)
C(3)	11809(2)	8679(3)	888(2)	55(1)
C(ll)	8449(2)	8794(3)	3914(2)	57(1)
C(18)	9805(3)	13136(3)	1308(2)	88(1)
0(4)	8148(2)	9596(2)	1055(1)	61(1)
C(16)	7879(3)	7102(3)	860(2)	79(1)

Table VI: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for molecule **179.** U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
0(4)	1033(4)	1395(6)	1114(4)	60(2)
C(20)	1813(6)	168(9)	-132(5)	51(2)
0(3)	3825(3)	1417(4)	356(3)	36(1)
0(2)	4261(4)	3502(5)	1144(3)	44(1)
C(6)	1773(5)	5207(6)	949(4)	35(1)

C(7)	2437(5)	4164(6)	503(4)	33(1)
C(13)	2998(5)	1570(7)	1050(4)	37(1)
C(12)	3070(5)	3264(7)	1192(4)	34(1)
0(1)	2901(6)	3450(7)	2836(3)	68(2)
C(5)	1100(5)	6254(7)	508(5)	42(2)
C(8)	2450(6)	4200(7)	-427(4)	42(2)
C(19)	1855(5)	1068(7)	688(4)	41(1)
C(ll)	2628(6)	3882(8)	2098(4)	45(2)
C(10)	1114(6)	6248(8)	-437(5)	46(2)
C(9)	1767(6)	5250(8)	-883(4)	48(2)
C(l)	1831(6)	5084(7)	1877(4)	45(2)
C(14)	3352(7)	619(8)	1841(5)	52(2)
C(17)	4764(5)	2228(7)	708(5)	42(2)
C(4)	476(6)	7227(8)	1076(6)	54(2)
C(3)	545(8)	7114(9)	1983(6)	66(2)
C(2)	1206(8)	6005(10)	2414(5)	64(2)
C(15)	4565(8)	962(11)	2187(6)	72(3)
C(16)	5353(7)	1300(9)	1430(6)	60(2)
C(18)	5497(6)	2709(9)	-61(6)	58(2)

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LIST OF PUBLICATIONS

1. Applications of Baylis-Hillman acetates: one-pot, facile and convenient synthesis of substituted γ-lactams
   Deevi Basavaiah,* and **Jamjanam Srivardhana Rao** *Tetrahedron Lett.,* **2004,** *45,* 1621-1625.

2. A novel Baylis-Hillman protocol for the synthesis of functionalized fused furans
   Deevi Basavaiah,* Bandaru Sreenivasulu and **Jamjanam Srivardhana Rao**
   Tetrahedron Lett., **2001,** *42,* 1147-1149.

3. Simple, facile and one-pot conversion of the Baylis-Hillman adducts into functionalized 1,2,3,4-tetrahydroacridines and cyclopenta[b]quinolines
   Deevi Basavaiah,* **Jamjanam Srivardhana Rao** and Raju Jannapu Reddy
   Accepted for publication as a note in the Journal of Organic Chemistry.

4. $TiCl_4$ catalyzed tandem construction of C-C and C-0 bonds: a novel, simple and one-pot stereoselective synthesis of spiro oxindoles.
   Deevi Basavaiah,* **Jamjanam Srivardhana Rao,** Raju Jannapu Reddy and Anumolu Jaganmohan Rao, *to be communicated.*

5. Applications of Baylis-Hillman adducts: one-pot, facile and convenient synthesis of 3-benzoylquinolines
   Deevi Basavaiah,* **Jamjanam Srivardhana Rao** and Raju Jannapu Reddy, *manuscript under preparation.*