TOWARDS DEVELOPMENT OF NOVEL STRATEGIES FOR SYNTHESIS OF FUSED HETEROCYCLIC AND CARBOCYCLIC FRAMEWORKS AND *HIMANIMIDE A* USING BAYLIS-HILLMAN ADDUCTS

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A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

BY

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STATEMENT

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

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

HYDERABAD

APRIL, 2010 **K. ARAVINDU**

CERTIFICATE

Certified that the work embodied in this thesis entitled "**Towards development of novel strategies for synthesis of fused heterocyclic and carbocyclic frameworks and *himanimide A* using Baylis-Hillman adducts**" has been carried out by **Mr. Kunche Aravindu**, under my supervision and the same has not been submitted elsewhere for a degree.

Professor D. BASAVAIAH
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

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Kunche Aravindu

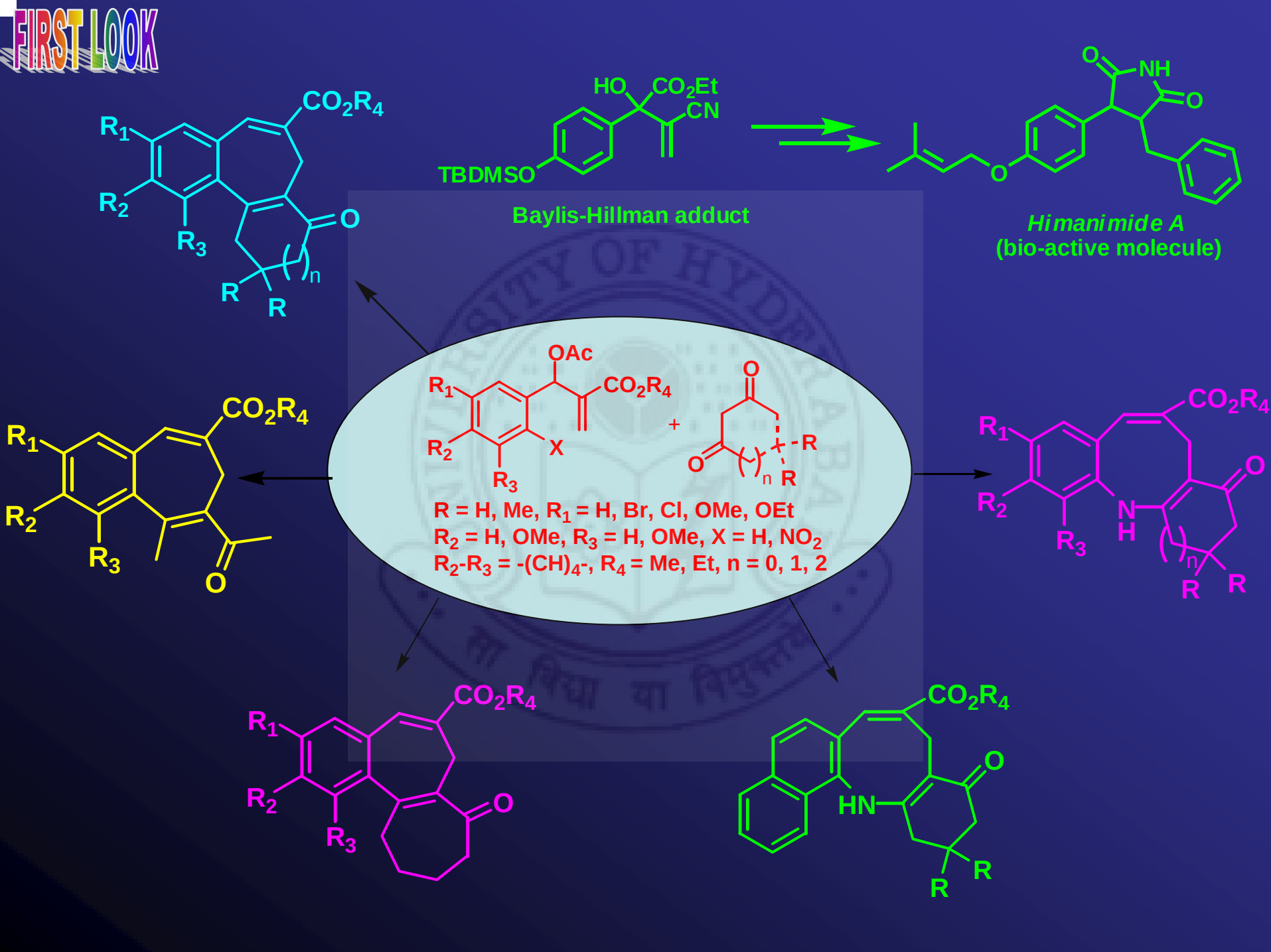
ABBREVIATIONS

Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Boc	*tert*-butoxycarbonyl
BINOL	1,1′-bi-2-naphthol
Bu or ^{n}Bu	*n*-butyl
t-Bu or Bu^{t}	*tertiar*y butyl
cat.	catalyst
Cbz	benzyloxycarbonyl
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
CSA	10-camphorsulfonic acid
c-Hex	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
dec.	decompose
DEPT	distortionless enhancement by polarization transfer
DMAP	4-(dimethylamino)pyridine
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide

ee	enantiomeric excess
Et	ethyl
Eq.	Equation
eq.	equivalent(s)
EWG	electron withdrawing group
Hex	hexyl
Hept	heptyl
HMT	hexamethylenetetramine
3-HQD	3-hydroxyquinuclidine
HTIB	hydroxy(tosyloxy)-iodobenzene
LAH	lithium aluminium hydride
LBBA	Lewis base bronsted acid
Me	methyl
Mp	melting point
MS	molecular sieves
MVK	methyl vinyl ketone
NHC	*N*-heterocyclic carbene
NMM	*N*-methylmorpholine
ORTEP	oak ridge thermal ellipsoid plot
Pent	pentyl
Ph	phenyl
PPTS	pyridinium *para*-toluenesulfonate
PTA	1,3,5-triaza-7-phosphaadamantane

Pr or *n*Pr	*n*-propyl
i-Pr or Pr^{i}	*iso*-propyl
RCM	ring closing metathesis
rt	room temperature
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDMSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TESCl	triethylsilyl chloride
TFAA	trifluoroacetic anhydride
TMEDA	tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMPDA	1,1,3,3-tetramethylpropane-1,3-diamine
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Trt	trityl
p-TsOH / *p*-TSA	*para*-toluenesulfonic acid
Ts	tosyl
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine

CONTENTS


HO
CO2Et
CN
TBDMSO
NH
O
O
Himanimide A
(bio-active molecule)
Baylis-Hillman adduct
OAc
CO2R4
R1
R2
R3
X
+
R
n
R = H, Me, R1 = H, Br, Cl, OMe, OEt
R2 = H, OMe, R3 = H, OMe, X = H, NO2
R2-R3 = -(CH)4-, R4 = Me, Et, n = 0, 1, 2
HN
NH

ABSTRACT

The Baylis-Hillman reaction is an atom-economy three component carbon-carbon bond forming reaction involving the coupling of α-position of activated alkene with an electrophile under the influence of a catalyst / catalytic system producing interesting and useful classes of highly functionalized molecules. These multifunctional molecules, usually known as Baylis-Hillman adducts, have been elegantly employed in various organic transformation methodologies and also in the synthesis of biologically active molecules and natural products. Our research group has been working on various aspects of this fascinating reaction for the last several years with the main objective of developing Baylis-Hillman adducts as a valuable source for the synthesis of various heterocyclic and carbocyclic molecules in a one-pot multistep reaction strategy.

This thesis deals with applications of Baylis-Hillman adducts in synthesis of heterocyclic / carbocyclic molecules & also synthesis of *himanimide A* and consists of three chapters 1) Introduction 2) Objectives, Results & Discussion and 3) Experimental. The first chapter, *i.e.,* Introduction presents a brief literature survey on the recent and relevant developments in the Baylis–Hillman reaction and also on applications of the Baylis–Hillman adducts in synthetic organic chemistry.

The second chapter deals with the development of simple and convenient methodologies for synthesis of heterocyclic / carbocyclic molecules from the Baylis-Hillman adducts with the following main objectives.

OBJECTIVES

1) To develop a facile methodology for synthesis of functionalized tri-/tetracyclic frameworks containing azocine moiety as one of the central rings using the Baylis-Hillman acetates as the starting materials.

2) To develop a simple, one-pot, and facile synthetic strategy for synthesis of angularly fused [6-7-5], [6-7-6], [6-7-7] and [6,7] carbocyclic ring systems containing cycloheptane as the central ring using the Baylis-Hillman acetates as the starting materials.

3) To develop a simple synthesis of *himanimide A*, biological active compound using Baylis-Hillman adduct derived from appropriate α-keto ester and acrylonitrile as the starting material.

The Baylis-Hillman acetates as a valuable source for one-pot multistep synthesis: a facile synthesis of functionalized tri-/tetracyclic frameworks containing azocine moiety

The synthesis of medium sized rings, in particular seven-, eight- and nine-membered rings, has been and continues to be a challenging and fascinating endeavour in synthetic chemistry, because unfavorable entropic and enthalpic factors prevent the adaptation of traditional methods of ring formation. An eight-membered nitrogen heterocyclic framework (particularly azocine and benzfused azocine) occupies a special place in the history of nitrogen heterocycles because of the presence of this moiety in various biologically active molecules possessing sedative, anticonvulsant, antiinflammatory, analgesic, antidepressant, and antihypertensive activities. Some dibenzazocine

derivatives are known to exhibit various biological activities such as central and blood pressure depressants, antitussive, and /or anthelmintic activities. Fascinated by these remarkable biological activities of azocines and benzfused azocines, we have developed a simple one-pot multistep synthesis of tri-/tetracyclic heterocyclic molecules containing azocine moiety as the central ring (**127-132**, **134-137**, **139**, **140**, **142** & **14**3) *via* the alkylation of alkyl 3-acetoxy-2-methylene-3-(2-nitroaryl)propanoate (**125a-h**) with various 1,3-cycloalkanediones followed by reduction and cyclization using Fe / AcOH (Schemes 52, 55, 56 and 58, Eqs. 32, 33 & Tables 2 and 3).

Simple, one-pot and facile synthesis of angularly fused [6-7-5], [6-7-6], [6-7-7] and [6,7] ring systems using Baylis-Hillman acetates

The angularly fused tricyclic carbocyclic framework containing cycloheptane as the central ring has a special and respectable place in the history of carbocyclic rings, due to the presence of this tricyclic framework in various natural products and bioactive molecules. For example, an angularly fused [6-7-5] carbocyclic skeleton is the core structure present in several natural products and bioactive molecules such as phorbol esters, frondosin C, (−)-presphaerene. An angularly fused [6-7-6] tricyclic system is present in biologically active compounds such as allocolchicine, colchinol derivative ZD6126, while an angularly fused [6-7-7] tricyclic ring system is an integral part of the well known alkaloid colchicine. Important bioactive compounds such as theaflavin, and TAK-779 contain the [6,7] bicyclic carbocyclic ring framework. Because of the remarkable medicinal importance of these fused ring frameworks and also because of unfavorable entropic factors in synthesizing seven membered rings, development of efficient protocols for the synthesis of such fused carbocyclic frameworks having

cycloheptane as the key central ring, has been and continues to be one of the attractive and challenging areas in carbocyclic chemistry.

We have developed a simple one-pot synthesis of angularly fused [6-7-5], [6-7-6], [6-7-7] tricyclic and [6,7] bicyclic molecules containing cycloheptane as the central ring (**168-180**) *via* the alkylation of Baylis-Hillman acetates (**161b-d**) with various 1,3-cycloalkanediones and 2,4-pentanedione respectively followed by the formation of vinyl chloride using oxalyl chloride and then subsequent intramolecular cyclization (Friedel-Crafts or Michael reaction) with $TiCl_4$ (Schemes 70-74, Eq. 38, & Tables 5, 7 and 8).

Synthesis of biological active compound *himanimide A*:

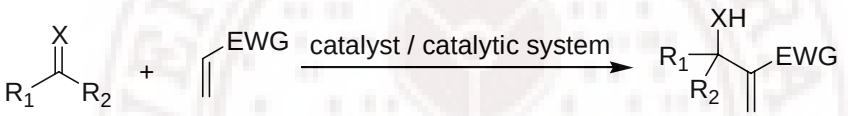
Himanimides A-D are new class of maleimide frameworks isolated from basidomycete culture in Chile. These are known to inhibit the growth of bacteria and fungi. Himanimides are also tested against filamentous fungi, yeast, and bacteria as well as different cell lines in order to evaluate potential biological activity. Due to the biological importance of these molecules, development of convenient synthetic strategy for obtaining these molecules has become a challenging endeavor in organic synthesis.

We have developed a facile synthesis of *himanimide A* (**182**), *via* the treatment of 3-(4-*tert*-butyldimethylsilyloxyphenyl)-3-ethoxycarbonyl-3-hydroxy-2-methylenepropane-nitrile (**190**) with benzene in the presence of methanesulfonic acid and subsequent alkylation of the resulting phenol derivative (**191**) with 1-bromo-3-methyl-2-butene in the presence of K_2CO_3 in acetone (Eqs. 39-41).

The third chapter deals with detailed experimental procedures, physical constants like Mp, IR, ^1H & ^{13}C NMR, mass (LCMS) spectral data & elemental analysis.

INTRODUCTION

The Baylis-Hillman reaction is a three component atom economy carbon-carbon bond forming reaction. It involves the coupling of α-position of an activated alkene (acyclic/cyclic) with an electrophile under the influence of catalyst or catalytic system (*tert*-amines, phosphines, Lewis acids, *etc*.), providing diverse classes of useful and highly densely functionalized molecules (Eq. 1).[1-8] The origin of this reaction dates back to a German patent[7] filed in the year 1972 by A. B. Baylis and M. E. D. Hillman (and also to a US patent[8] filed in the year 1973 by M. E. D. Hillman & A. B. Baylis).

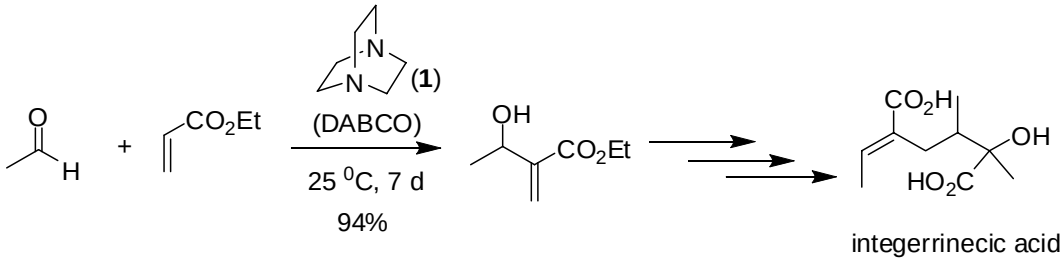


Eq. 1

EWG = COR, CO_2R, CN, CHO, SOPh, SO_2Ph, *etc.*
X = O, N-Ts, N-CO_2R, N-$PO(R)_2$, *etc.*
R_1 = alkyl, aryl, heteroaryl, *etc.*
R_2 = H, CO_2R, alkyl, *etc.*
catalyst / catalytic system = *tert.*amine, phosphine, Lewis acid, *etc.*

This reaction did not receive any attention till 1982, when Drewes and Emsile reported the synthesis of integerrinecic acid using ethyl 3-hydroxy-2-methylenebutanoate, which was obtained *via* the coupling of acetaldehyde with ethyl acrylate under the catalytic influence of DABCO (**1**), as the key starting material (Scheme 1).[9]

Scheme 1

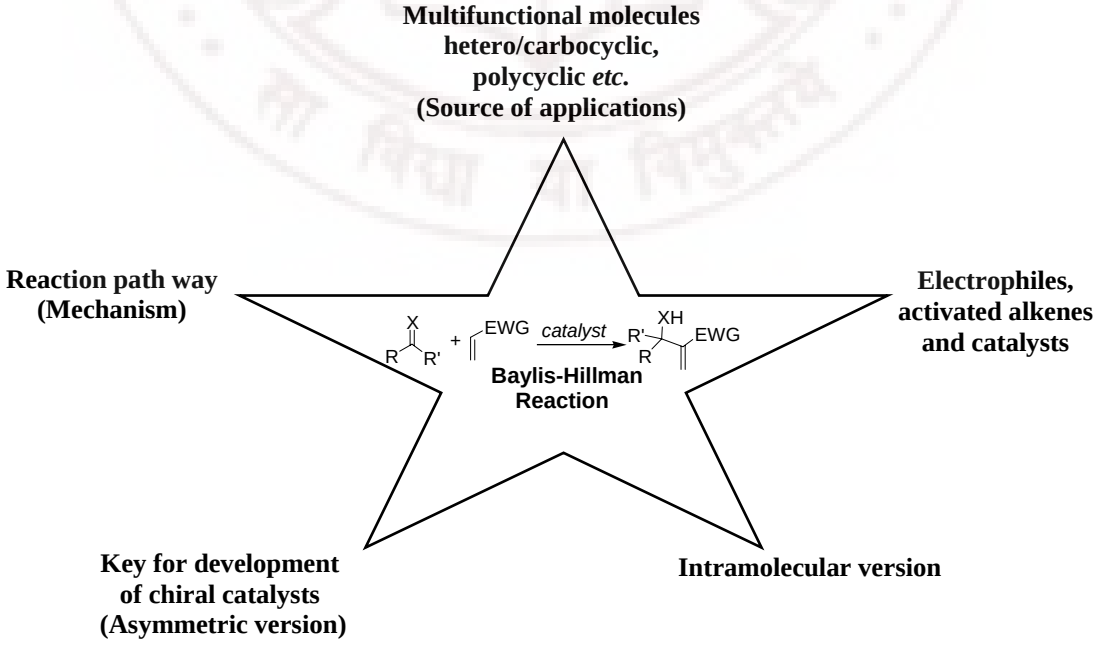


integerrinecic acid

Subsequent reports from Hoffmann (1983),[10] Perlmutter (1984),[11] Basavaiah (1986),[12] Villieras (1986),[13] Knochel and Normant (1986)[14] and Basavaiah (1987)[15] have made tremendous impact on organic chemists to look at this reaction more carefully, which resulted, in fact in exponential growth of this reaction, which is now known as the Baylis-Hillman reaction.

During the last several years the Baylis-Hillman reaction has grown tremendously in terms of all three essential components, (i) electrophiles, (ii) activated alke(y)nes, (iii) catalyst / catalytic systems (amine and non-amine catalysts) to produce highly useful densely functionalized molecules, as evidenced by large number (more than 1800) of research publications, six major reviews[1-6] and a number of mini reviews.[16-22] Also, applications of the Baylis-Hillman adducts in various novel organic transformation methodologies have been well documented in the literature.[1-6] These developments are pictorially represented in Figure 1, so as to give the growth of this reaction at a glance.

Figure 1



Since there is a vast literature available on various aspects of this fascinating reaction, it will not be possible to present all the information in this section. However, some recent, relevant and important developments, both in the reaction development and in the applications of the Baylis-Hillman adducts, are either presented or cited in this section.

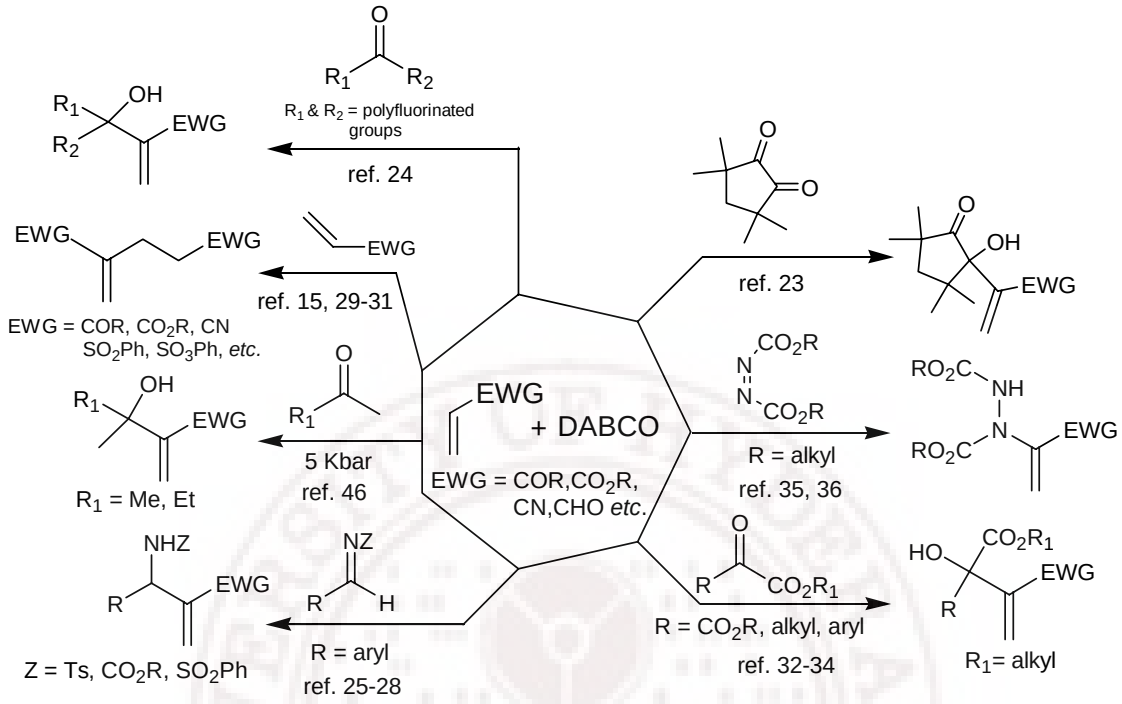
Essential Components:

(1) ELECTROPHILES:

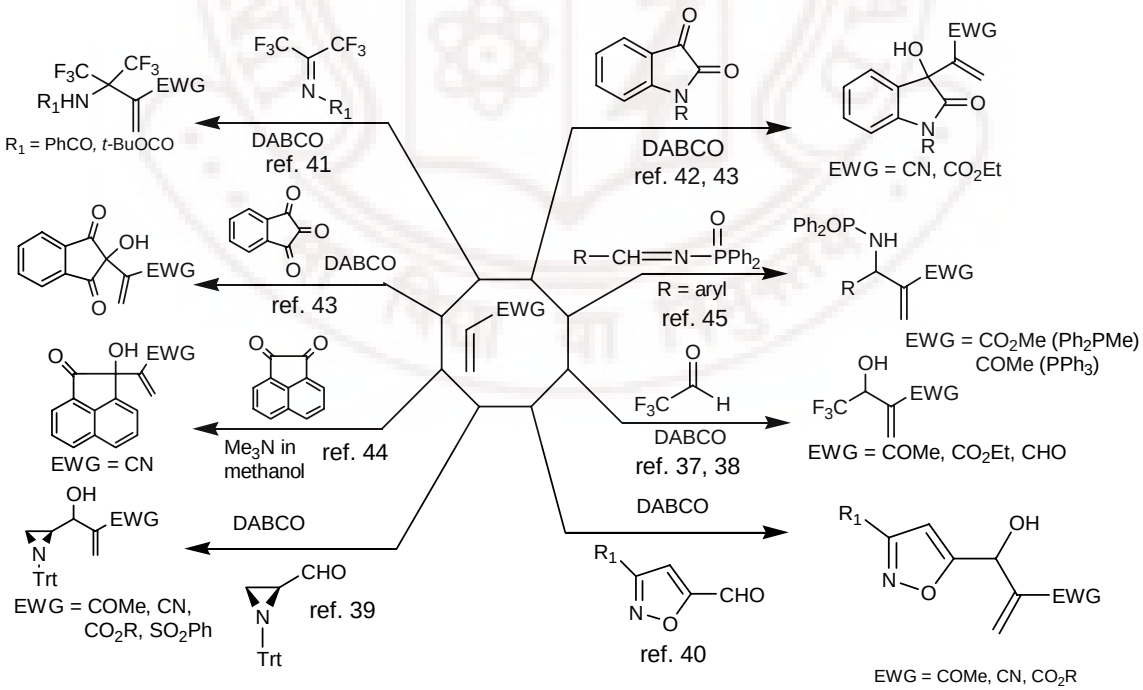
Earlier developments:

Aldehydes (aliphatic, aromatic and heteroaromatic)[3-6] are the most commonly used electrophiles for coupling with various activated alkenes to provide variety of allyl alcohol frameworks. Other carbon electrophiles such as non-enolizable 1,2-diketones,[23] fluoroketones,[24] aldimine derivatives,[25-28] activated alkenes,[15,29-31] α-keto esters,[32-34] azodicarboxylates,[35,36] have been successfully used for reaction with a variety of activated alkenes (Scheme 2). Fluorinated aldehydes & ketones,[37,38] *N*-tritylaziridine-2-(*S*)-carboxaldehyde,[39] isoxazole-5-carboxaldehyde,[40] fluoroimines,[41] various isatin derivatives,[42,43] ninhydrin,[43] acenapthoquinone,[44] and *N*-arylidenediphenylphosphinamides[45] (Scheme 3) have also been employed as electrophiles in various Baylis-Hillman coupling reactions to produce a variety of densely functionalized molecules. Normal ketones (such as acetone and butan-2-one),[46] which are less reactive, require high pressure for coupling with activated alkenes (Scheme 2).

Scheme 2



Scheme 3

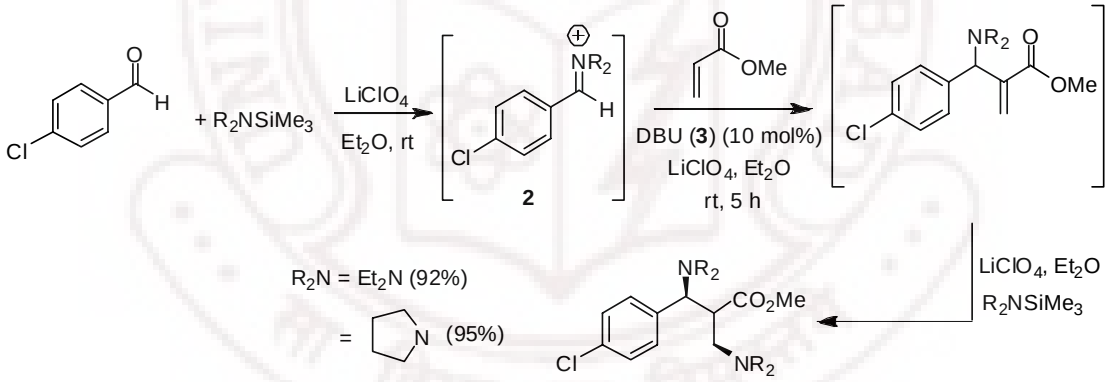


Recent developments:

In recent years a number of new electrophiles have been used for coupling with various activated alkenes under the influence of appropriate catalyst to produce multifunctional molecules. Selected examples are presented in this section.

Azizi and Saidi[47] have used *in situ* generated iminium salts (**2**) [obtained by the treatment of (trimethylsilyl)dialkylamines with aldehydes] as electrophiles in the Baylis-Hillman reaction with methyl acrylate in the presence of DBU (**3**) as a catalyst. The corresponding adducts, thus obtained, further react with (trimethylsilyl)dialkyl-amines to give the 1,3-diamines as final products. One example is presented in the Scheme 4.

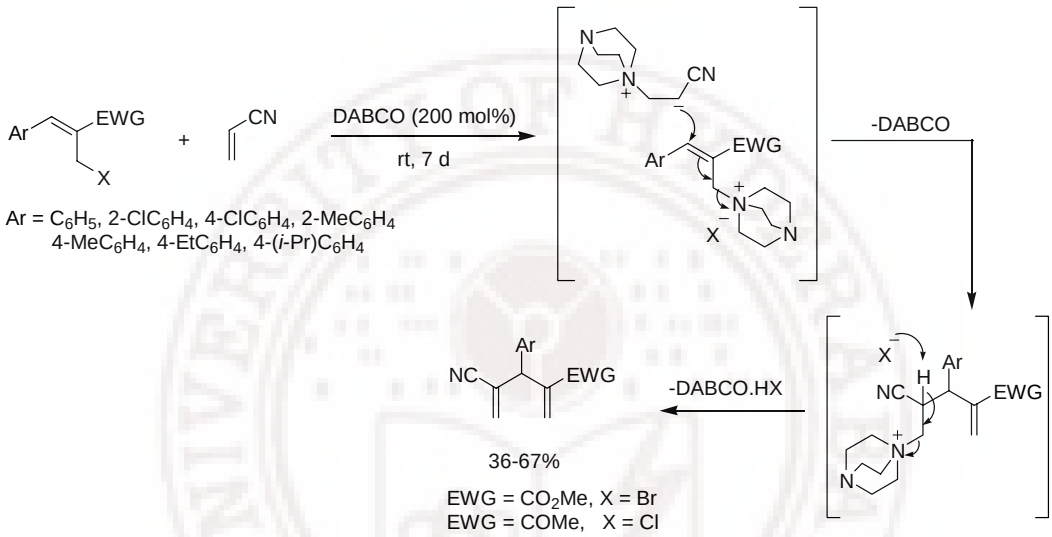
Scheme 4



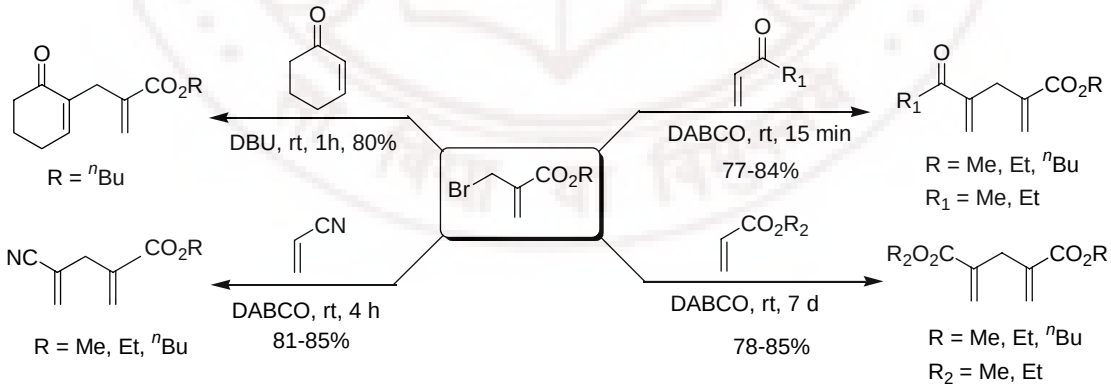
Our research group[48,49] demonstrated, for the first time, the application of allyl halides (containing electron withdrawing group α to halomethyl group) as electrophiles in the Baylis-Hillman reaction. Thus, the reaction of allyl bromides / allyl chlorides, derived from the corresponding Baylis-Hillman adducts (which were prepared from methyl acrylate and methyl vinyl ketone respectively) with acrylonitrile in the presence of DABCO provided 3-substituted functionalized 1,4-pentadienes (Scheme 5).[48] Subsequently, our research group has extended the same strategy to synthesis of a

variety of 2,4-functionalized 1,4-pentadienes *via* the Baylis-Hillman reaction of allyl bromides, derived from alkyl 3-hydroxy-2-methylenepropanoates, as electrophiles, with alkyl acrylates, alkyl vinyl ketones, acrylonitrile and cyclohex-2-enone following the reaction sequence as shown in Scheme 6.[49]

Scheme 5

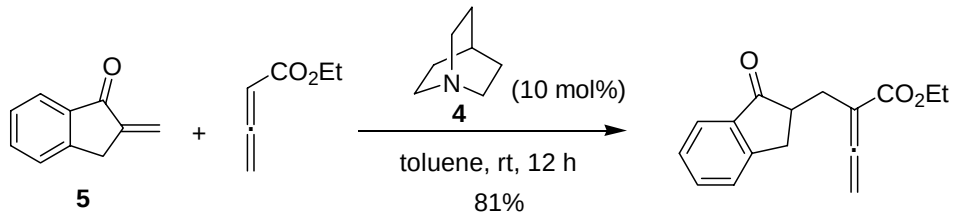


Scheme 6



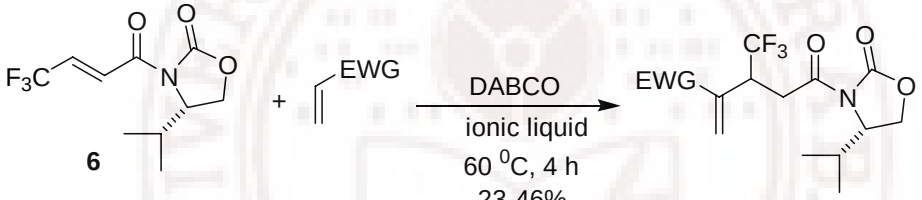
Miller and Evans[50] have elegantly reported an efficient quinuclidine (**4**) catalyzed coupling of allenic esters with α,β-unsaturated carbonyl compounds [2-methylene-

indanone (**5**)] as electrophiles to provide the corresponding Baylis-Hillman adducts in good to excellent yields. One example is presented in Eq. 2.



5 **Eq. 2**

Kitazume and coworkers[51] successfully employed 3-trifluoromethylprop-2-enamide (**6**) as electrophile in the Baylis-Hillman reaction with various activated alkenes under the influence of DABCO in ionic liquids (Eq. 3).

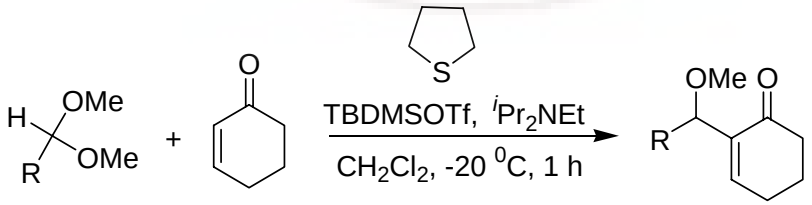


6 **Eq. 3**

EWG = CO_2Me, COMe, CN
ionic liquid = [emim][OTf], [bmim][BF_4], [bmim][PF_6]

dr = 50:50 to 55:45

Recently, Metzner and coworkers[52] have meticulously used dimethyl acetals as electrophiles in the Baylis-Hillman coupling with cyclohex-2-enone under the influence of tetrahydrothiophene and TBDMSOTf in the presence of *i*-Pr_2NEt (Hunig's base) according to Eq. 4.



Eq. 4

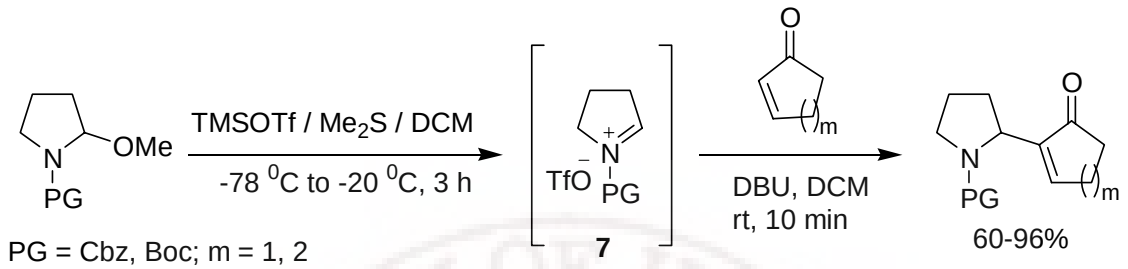
R = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$

26-83%

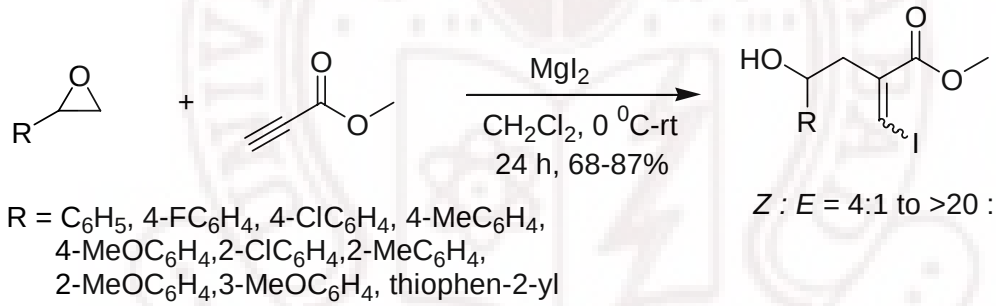
Very recently Aggarwal and coworkers[53] reported an interesting Baylis-Hillman reaction between activated alkenes and *in situ* generated iminium ions (**7**) as

electrophiles to provide the corresponding adducts according to the reaction sequence presented in Scheme 7.

Scheme 7



Li and coworkers,[54] for the first time, demonstrated the application of aryl oxiranes as electrophiles for coupling with methyl propiolate in the presence of MgI_2 to provide functionalized homoallylic alcohols in a one-pot operation (Eq. 5).



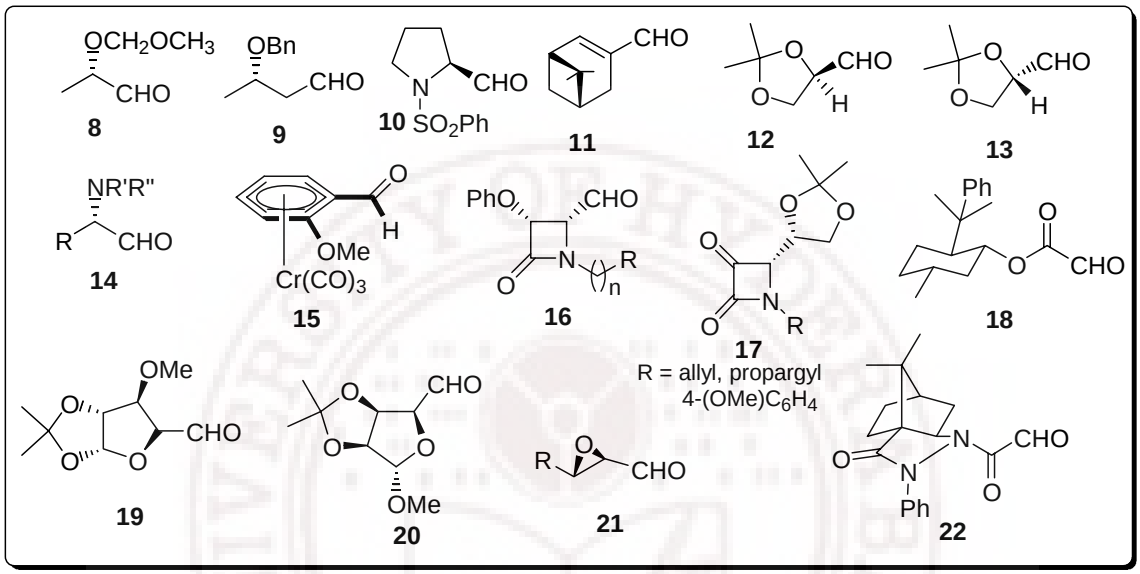
Eq. 5

Chiral (enantiopure) electrophiles:

Various chiral electrophiles such as (*S*)-O-(methoxymethyl)lactaldehyde (**8**),[55] (S)-3-benzyloxybutyraldehyde (**9**),[56] N-phenylsulfonyl-(*L*)-prolinal (**10**),[57] (*R*)-myrtenal (**11**),[58] isopropylidene (*R*)-, and (*S*)-glyceraldehydes (**12** & **13**),[58] α-dialkylamino and α-(N-acylamino)aldehydes (**14**),[57,59] enantiopure *ortho* substituted benzaldehyde tricarbonyl-chromium complexes (**15**),[60,61] 1-alkenyl- (or alkynyl) 4-oxoazetidine-2-carboxalde-hydes (**16**),[62] 3-oxo-2-azetidinones (**17**),[63] (−)-8-phenylmenthyl glyoxylate (**18**),[64] various sugar derived aldehydes (**19** & **20**),[65,66] chiral 2,3-epoxy aldehydes

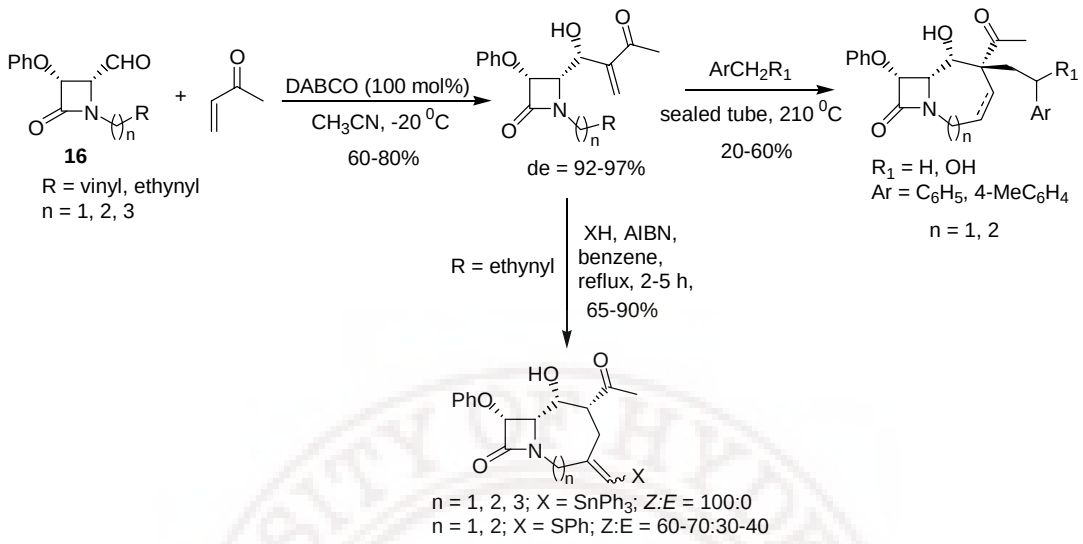
(**21**),[67] N-glyoxyloylcamphorpyrazolidinones (**22**),[68] *etc*. (Figure 2) have been used for Baylis-Hillman coupling with several activated alkenes in the presence of suitable catalyst (s) to provide the resulting products in low to high diastereoselectivities.

Figure 2

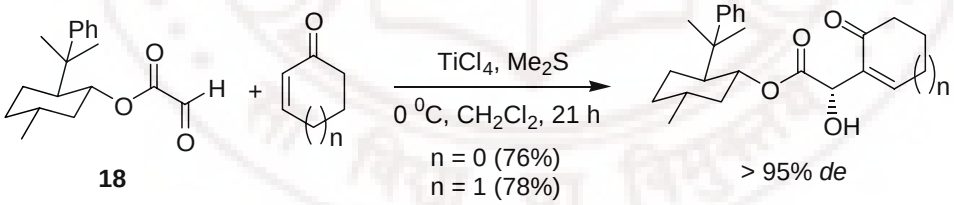


Alcaide and co-workers[62,69] employed enantiopure 1-alkenyl (alkynyl)-4-oxoazetidine-2-carboxaldehydes (**16**) as chiral electrophiles in the Baylis-Hillman reaction with methyl vinyl ketone under the influence of DABCO as catalyst which provided the resulting adducts with very high diastereoselectivities. These adducts were further transformed into functionalized β-lactams fused to medium-sized rings (Scheme 8).

Scheme 8



Bauer and Tarasiuk[64] have reported an interesting Baylis-Hillman coupling of (–)-8-phenylmenthyl glyoxylate (**18**) (enantiopure aldehyde) with cyclic enones (cyclohex-2-enone and cyclopent-2-enone) under the catalytic influence of dimethyl sulfide and in the presence of titanium tetrachloride to provide the desired adducts in high diastereoselectivities (Eq. 6).



Eq. 6

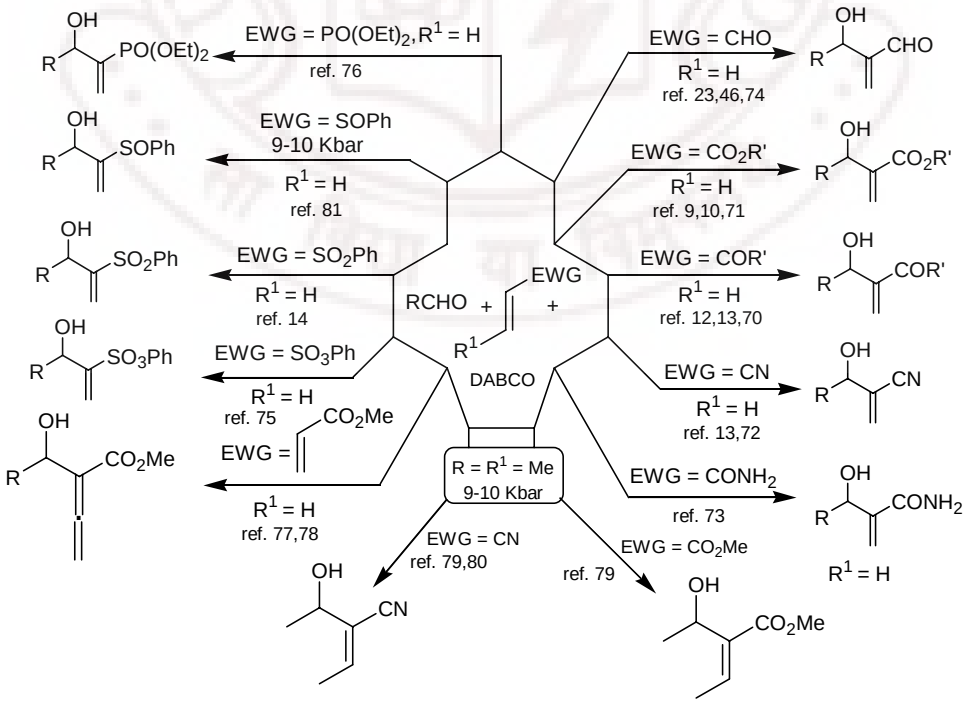
(2) Activated alkenes (acyclic / cyclic):

Earlier developments:

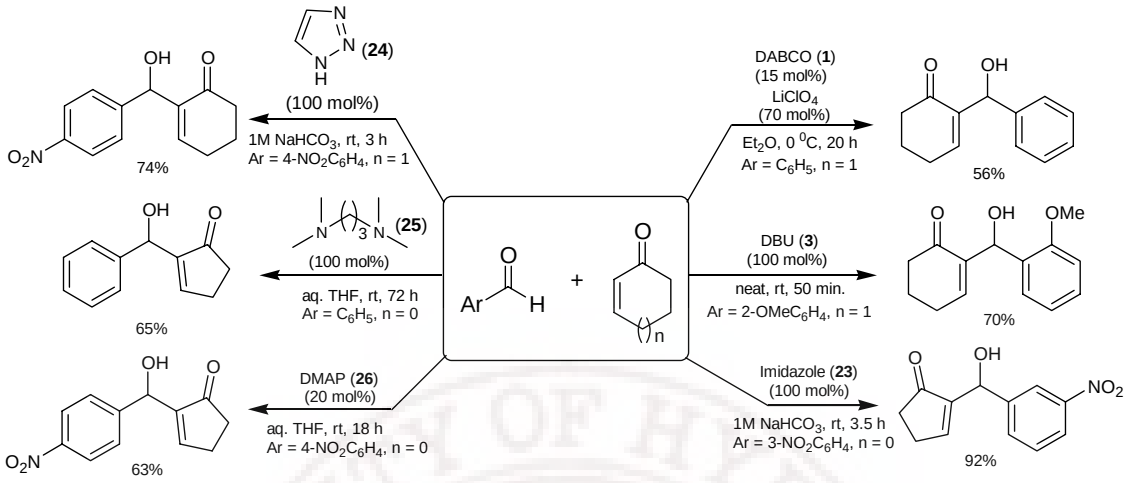
In addition to the most commonly used activated alkenes [alkyl vinyl ketones,[12,13,70] alkyl (aryl) acrylates,[9,10,71] and acrylonitrile[13,72]] variety of other activated alkenes such as acrylamides,[73] acrolein,[23,46,74] vinyl sulphones,[14] vinyl sulphonates,[75] vinyl phosphonates,[76] and allenic esters[77,78] have also been effectively employed in the Baylis-

Hillman coupling with a number of carbon electrophiles to provide the desired densely functionalized molecules (Scheme 9). Also, a variety of alkynyl esters and alkynyl ketones have been employed for coupling with electrophiles in this reaction.[19] However, the activated olefins having β-substituents such as methyl crotonate,[79] crotononitrile[79,80] and less reactive alkenes like phenyl vinyl sulfoxide[81] require high pressure to participate in this fascinating reaction (Scheme 9). In addition to various acyclic activated alkenes/alkynes several cyclic enones (most commonly cyclopent-2-enone, cyclohex-2-enone and their derivatives) were employed successfully for Baylis-Hillman coupling with a number of electrophiles in the presence of *tert*-amine catalysts, such as, DABCO (**1**),[74] DBU (**3**),[82] imidazole (**23**),[83,84] 1,2,3-triazole (**24**),[85] TMPDA (**25**),[86] and DMAP (**26**)[87,88] to provide the corresponding multifunctional molecules (Scheme 10).

Scheme 9



Scheme 10

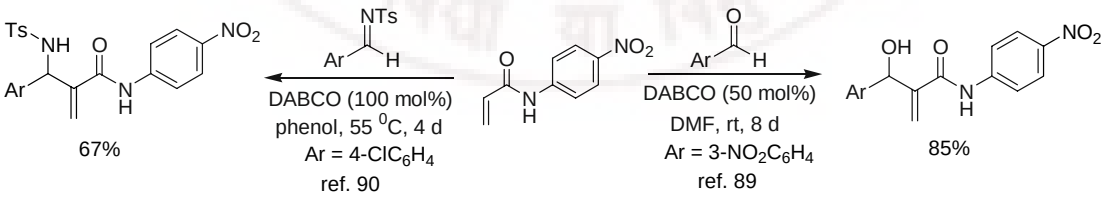


Recent developments:

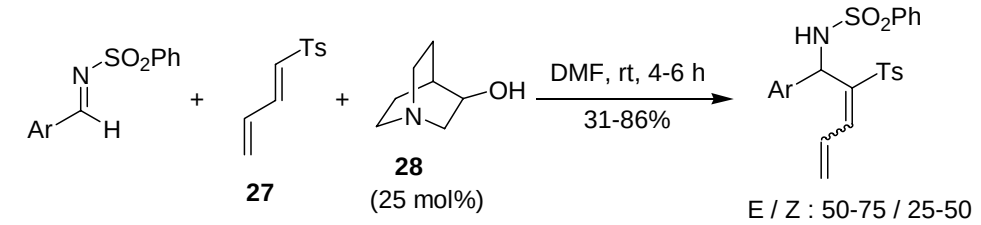
In recent years organic chemists have used several activated alkenes in Baylis-Hillman coupling with a number of electrophiles providing various classes of multifunctional molecules. Selected examples are presented in this section.

Guo and coworkers reported Baylis-Hillman coupling of *N*-aryl acrylamides with aryl aldehydes[89] or *N*-tosylated imines[90] to provide the corresponding allylic alcohols in reasonably good yields (Scheme 11).

Scheme 11



Back and coworkers[91] employed 1-(*p*-toluenesulfonyl)-1,3-butadiene (**27**) as an activated alkene for coupling with various aldimine derivatives in the presence of 3-hydroxyquinuclidine (3-HQD, **28**) as catalyst to provide the corresponding Baylis-Hillman adducts in good yields (Eq 7).

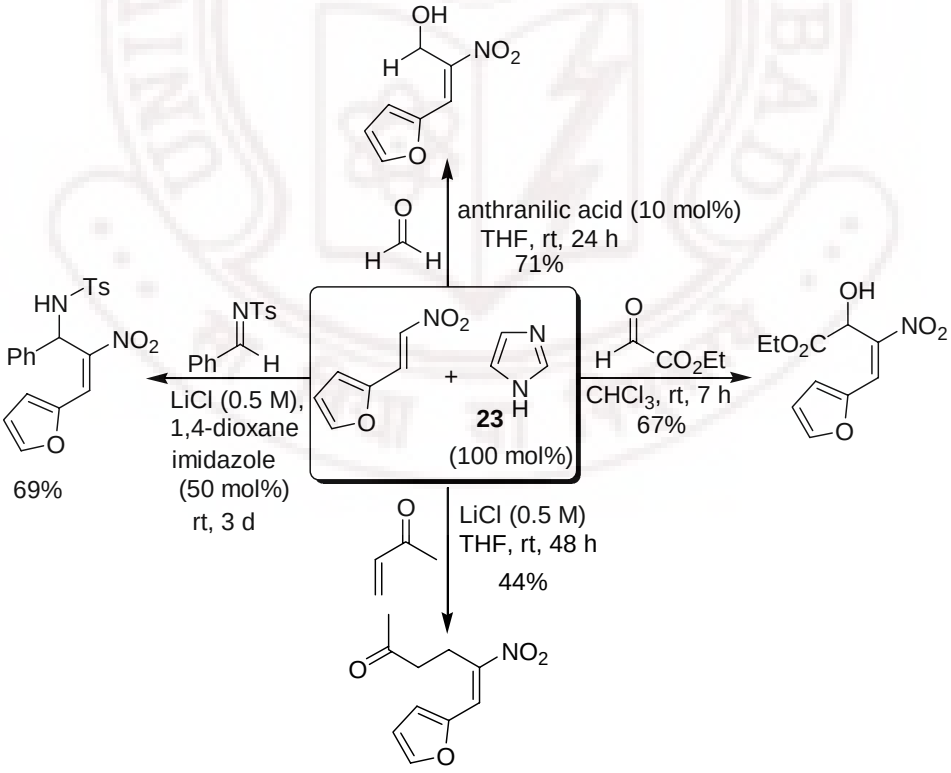


Eq. 7

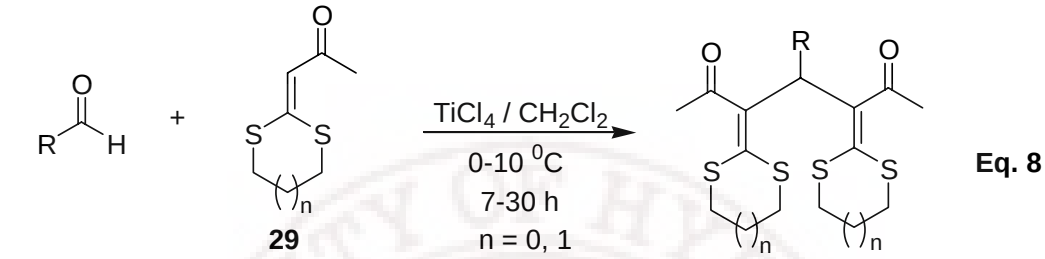
Ar = C_6H_5, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-$(CO_2Me)C_6H_4$, 1-naphthyl

Namboothiri and coworkers[92-95] systematically studied the applications of conjugated nitroalkenes as useful activated alkenes in the Baylis-Hillman coupling with formaldehyde (formalin),[92] methyl vinyl ketone,[93] ethyl glyoxylate,[94] and *N*-tosyl-imines[95] under the influence of imidazole (**23**) at room temperature. Representative examples are presented in Scheme 12.

Scheme 12



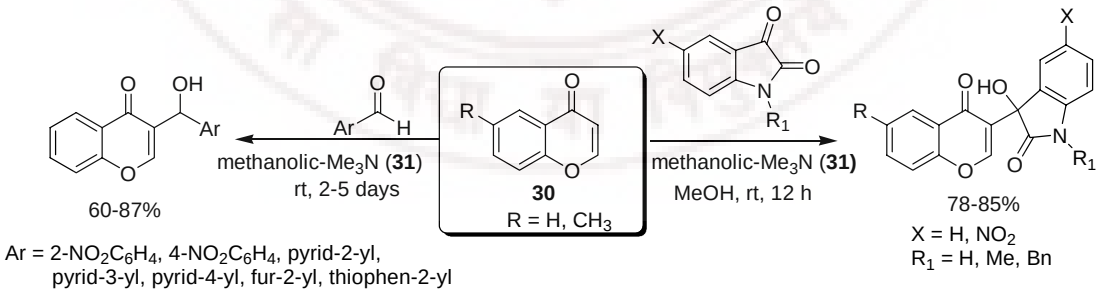
Yin and coworkers[96] has described an interesting $TiCl_4$-mediated Baylis-Hillman (type) reaction of α–oxoketene dithioacetals (**29**) with various aromatic aldehydes leading to the formation of polyfunctionalized 1,4-pentadienes *via* C-C bond formation at the α-position of α–oxoketene dithioacetals. Representative examples are presented in Eq. 8.



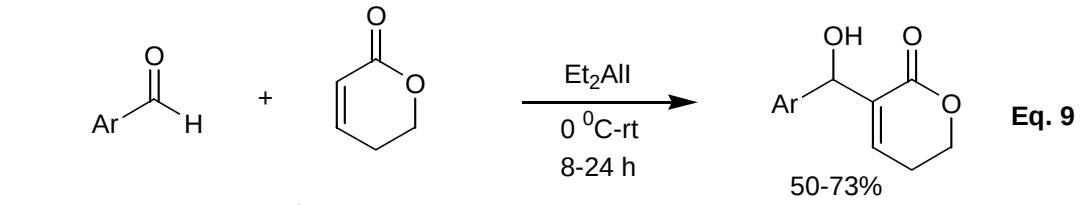
Eq. 8

Our research group[97] for the first time, used 1-benzopyran-4(4*H*)-one (**30**) derivatives, as activated alkenes in the Baylis-Hillman reaction with various electrophiles such as hetero-aromatic aldehydes, nitrobenzaldehydes and isatin derivatives under the influence of methanolic-Me_3N (**31**) to provide the corresponding adducts, as described in Scheme 13.

Scheme 13



Li and coworkers[98] have used α,β-unsaturated δ-lactone as an activated alkene for coupling with various aromatic aldehydes in the presence of diethylaluminium iodide to provide the corresponding Baylis-Hillman adducts in good yields (Eq. 9).



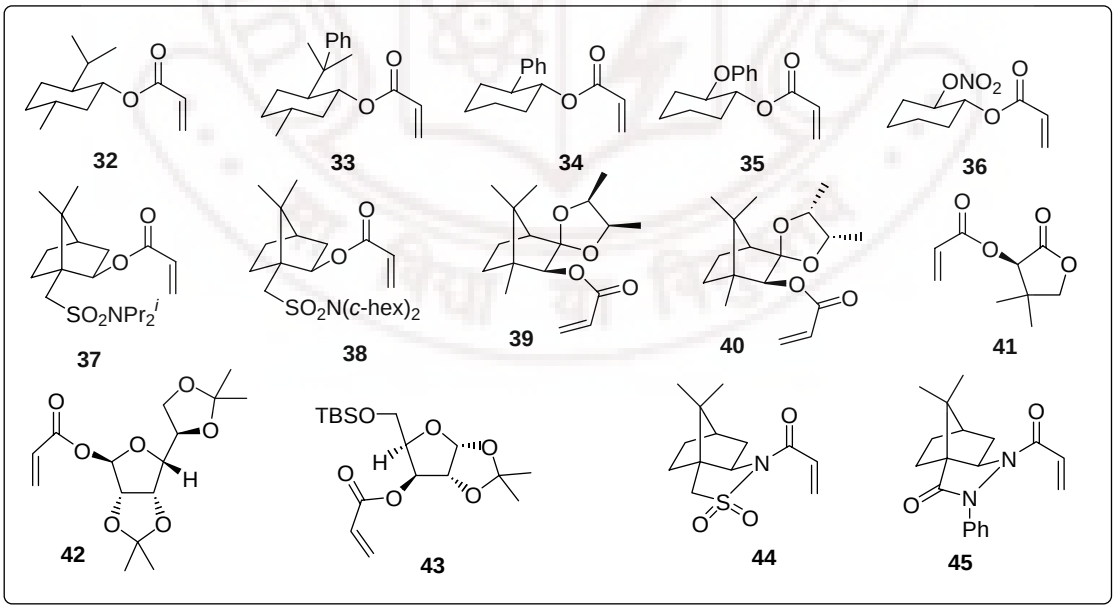
Eq. 9

Ar = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4,
4-$NO_2C_6H_4$, 2-MeC_6H_4, 4-$OMeC_6H_4$, 2-naphthyl

Chiral (enantiopure) activated alkenes:

A variety of chiral acrylates (**32-43**)[3-6,58,99-108] and chiral acrylamides (**44** & **45**)[109-111] derived from various chiral auxiliaries [cyclohexanol derivatives (**32-36**), camphor (**37-40**, **44** & **45**), and R-(+)-pentolactone (**41**), and sugar derivatives (**42**, **43**)] (Figure 3) have been employed as chiral activated alkenes in the Baylis-Hillman reaction with various electrophiles to provide the resulting adducts in low to high diastereoselectivities.

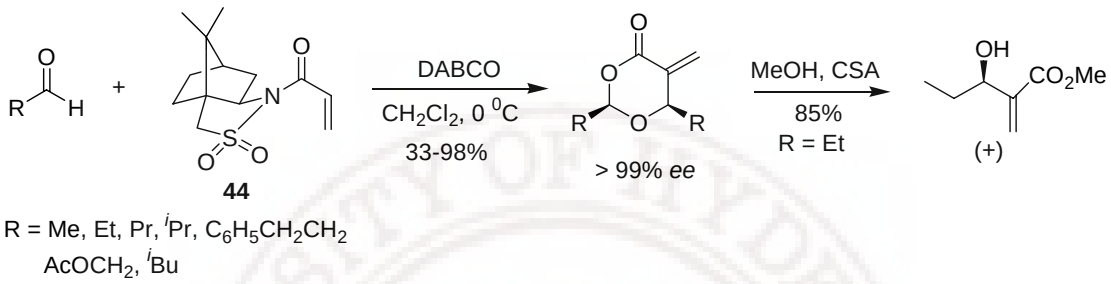
Figure 3



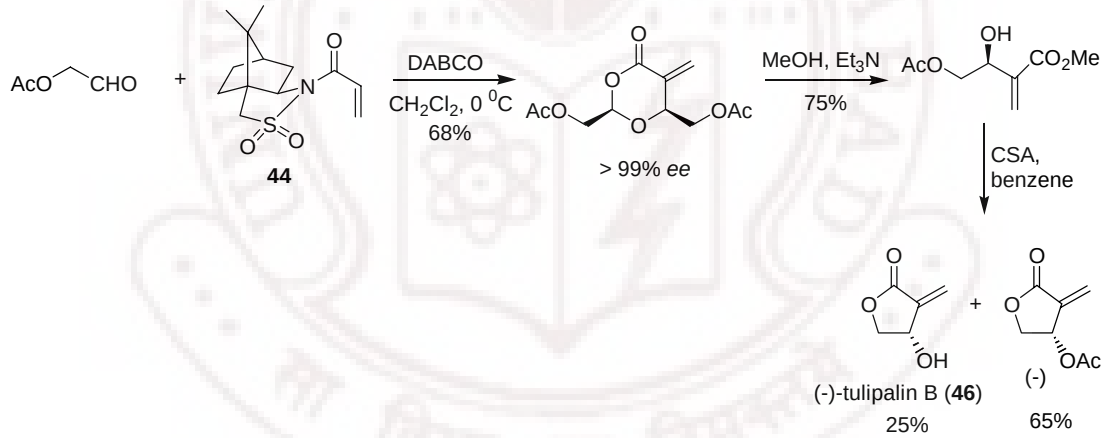
Leahy and coworkers[109,110] have employed chiral acrylamide (**44**) derived from Oppolzer′s camphor sultam, as an activated alkene in the Baylis–Hillman reaction to

provide the desired adducts in high enantioselectivities (Scheme 14). This methodology has been successfully employed for the synthesis of biologically important natural product (–)-tulipalin B (**46**) (Scheme 15).

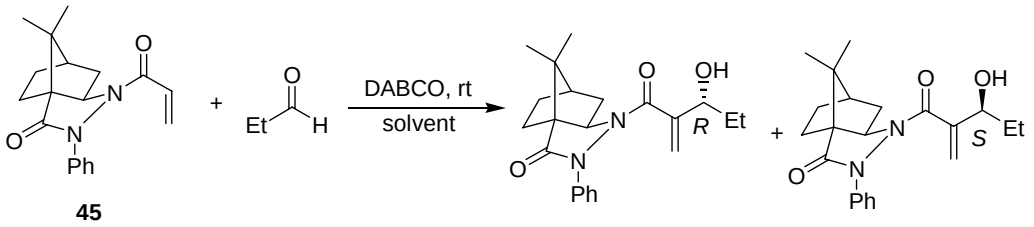
Scheme 14



Scheme 15



Yang and Chen[111] have reported a highly diastereoselective Baylis-Hillman reaction of aldehydes with enantiopure acryloylhydrazide (**45**) as chiral activated alkene. They have observed reversal of diastereoselectivity by changing the solvent from DMSO to THF/H_2O in this reaction. One such example is presented in the Eq. 10.



Eq. 10

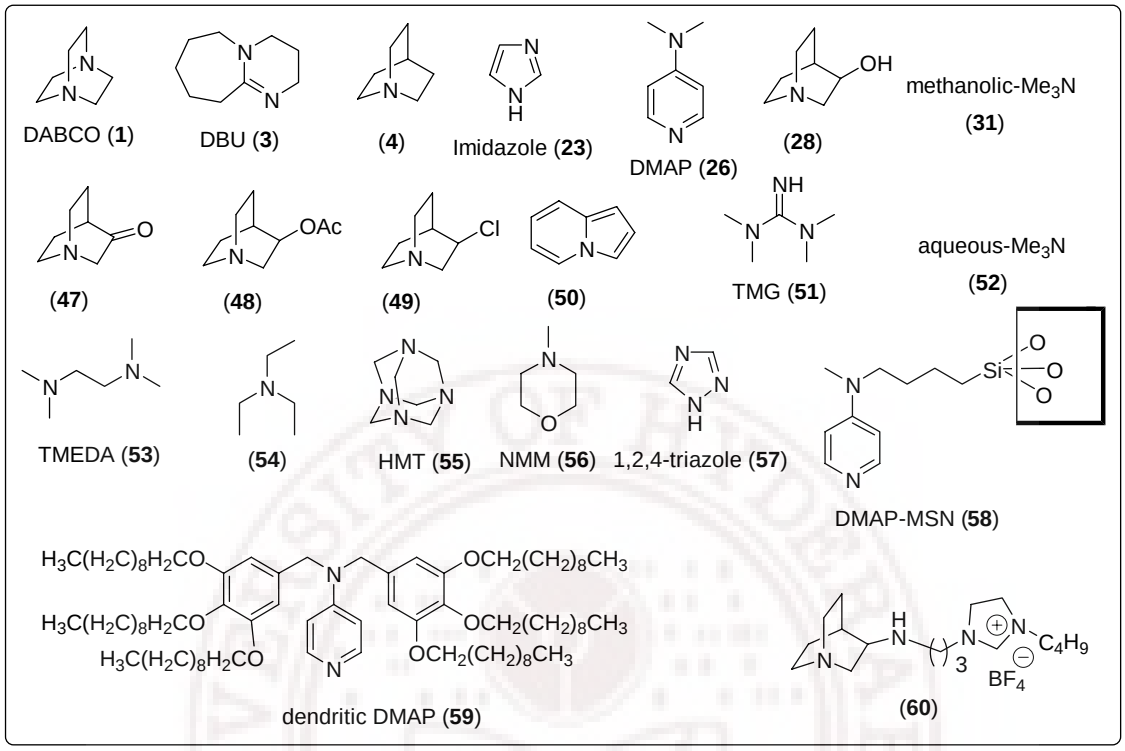
(3) Catalysts / catalytic systems:

During last several years a large variety of both amine / non-amine based catalysts have been successfully employed to catalyze the Baylis-Hillman reaction. Some of the interesting developments are presented in this section.

(a) Tertiary amine catalysts:

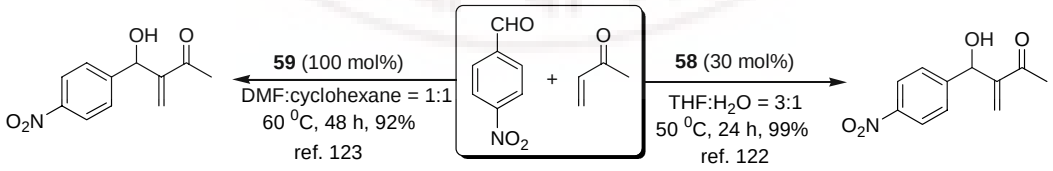
Although, DABCO (**1**)[112,113] has been used as the catalyst of choice in this fascinating reaction, various other tertiary amine catalysts such as DBU (**3**),[82] quinuclidine (**4**),[113] imidazole (**23**),[83,84,114] 4-(dimethylamino)pyridine (DMAP, **26**),[87,88] 3-hydroxyquinuclidine (**28**),[112,113] methanolic-Me_3N (**31**),[44,97,115] 3-quinuclidinone (**47**),[113] 3-acetoxyquinuclidine (**48**), [112,113] 3-chloroquinuclidine (**49**),[113] indolizine (**50**),[7] TMG (**51**),[116,117] aqueous-Me_3N (**52**),[118] TMEDA (**53**),[119] Et_3N (**54**),[46] urotropine (HMT, **55**),[120,121] NMM (**56**),[121] 1,2,4-triazole (**57**)[85] (Figure 4) have been employed as catalysts in various Baylis-Hillman reactions. Recently, polymer supported DMAP derivatives, like DMAP-MSN [meso-porous silica nano-sphere (**58**)],[122] dendritic DMAP{N,N-di[3', 4', 5'-tri(1-decyloxy)benzyl]4-aminopyridine (**59**)}[123] and also ionic liquid containing quinuclidine (**60**),[124] (Figure 4) were also found to promote Baylis-Hillman reaction.

Figure 4



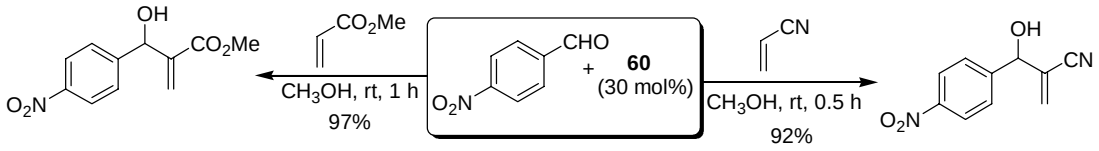
Recently, Lin and coworkers[122] have used DMAP-MSN [meso-porous silica nano-sphere (**58**)] as a catalyst while Yang and coworkers[123] employed dendritic DMAP {*N*,*N*-di[3',4',5'-tri(1-decyloxy)benzyl]-4-aminopyridine (**59**)} as catalyst in the Baylis-Hillman reaction of various activated alkenes with electrophiles (Scheme 16).

Scheme 16

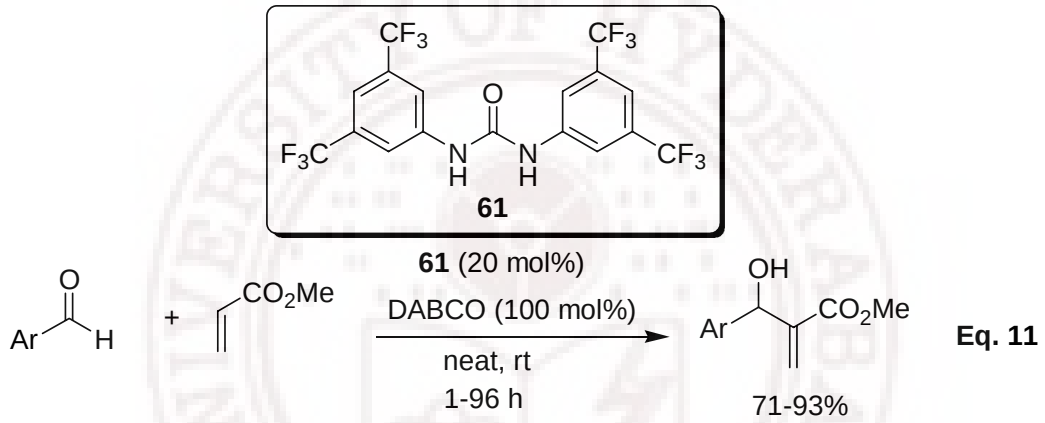


Very recently, Cheng and coworkers[124] reported an interesting application of ionic liquid containing quinuclidine component (**60**), as a catalyst for facile coupling of various activated alkenes (alkyl acrylates and acrylonitriles) with various aldehydes (Scheme 17).

Scheme 17



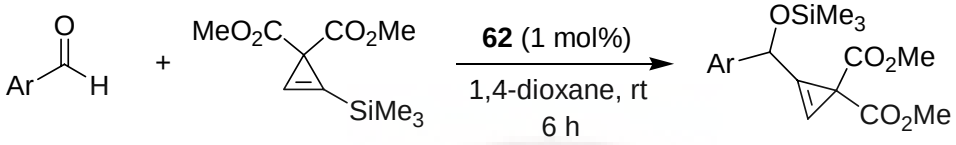
Maher and Connon[125] found that catalytic amount of bis-aryl urea (**61**) accelerate the DABCO-promoted Baylis–Hillman reaction between aromatic aldehydes and methyl acrylate in the absence of solvent. Representative examples are presented in Eq. 11.



(b) Non-amine catalysts / catalytical systems mediated Baylis-Hillman reaction:

Several non-amine compounds such as trialkylphosphines,[126-128] triarylphosphines,[129] and metal complexes like $RhH(PPh_3)_4$,[130,131] $RuH_2(PPh_3)_4$,[131,132] have been found to promote coupling of activated alkenes with aldehydes to provide the desired Baylis-Hillman adducts. Recently, R_2S–$TiCl_4$,[3,133-136] $TiCl_4$-NR_4X (X = halide),[3,137,138] $TiCl_4$-NR_3,[139] $TiCl_4$,[140,141] and R_2X–BF_3 (X = O, S)[142-144] were also successfully employed as promoters in different Baylis-Hillman reactions.

Recently, Gevorgyan and coworkers[145] found that electron rich tris(2,4,6-trimethoxyphenyl)phosphine [TTMPP, **62**] effectively catalyzes the Baylis-Hillman reaction of 1-(trimethylsilyl)cyclopropene-3,3-dicarboxylate with various aldehydes to provide the corresponding adducts in good yields (Eq. 12).



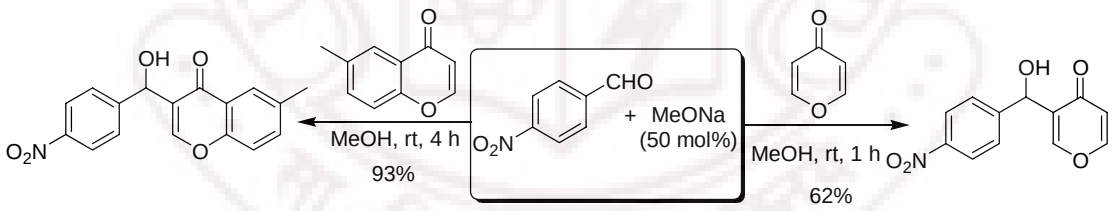
Eq. 12

Ar = C_6H_5, 3-ClC_6H_4, 3-BrC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-$(CO_2Me)C_6H_4$, fur-2-yl, *n*-Pr, *i*-Pr

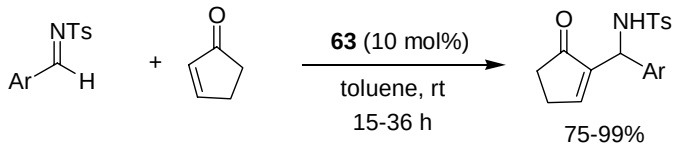
50-80%

Cheng and coworkers[146] applied, for the first time, methoxide ion as useful catalyst for Bayils-Hillman coupling of cyclic activated alkenes with various aldehydes under mild conditions to provide the corresponding Baylis-Hillman adducts in good to moderate yields (Scheme 18).

Scheme 18

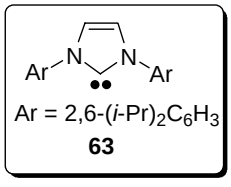


Recently, Ye and coworkers[147] have used *N*-heterocyclic carbene (NHC, **63**) as an efficient catalyst for Baylis-Hillman reaction of cyclopent-2-enone with a variety of *N*-tosylarylimines to give the corresponding adducts in high yields (Eq. 13).



75-99%

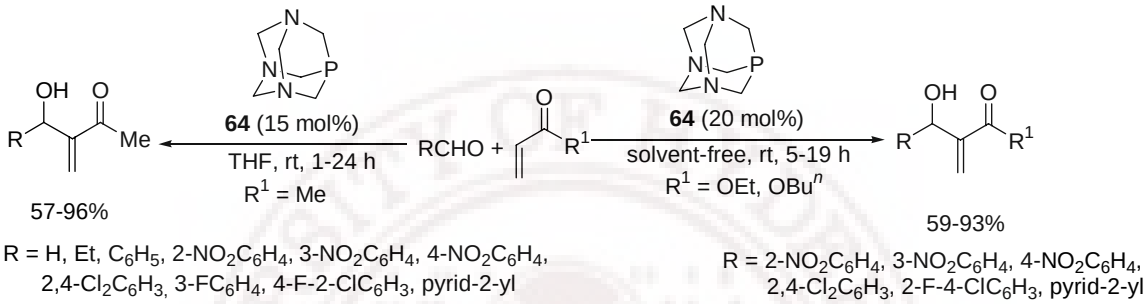
Eq. 13



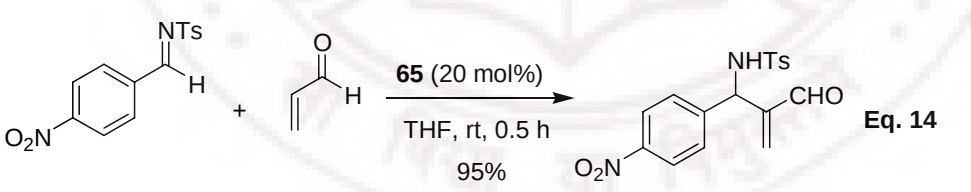
Ar = C_6H_5, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$OMeC_6H_4$, 3-ClC_6H_4, 2-$OMeC_6H_4$, fur-2-yl

He and coworkers[148] have for the first time, reported that 1,3,5,-triaza-7-phosphaadamantane (PTA, **64**) serves as an efficient catalyst for the Baylis-Hillman reaction of various aldehydes with activated alkenes to afford the corresponding adducts in good to excellent yields (Scheme 19).

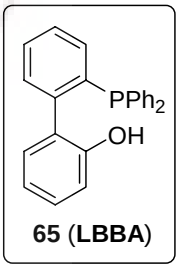
Scheme 19



Huang and coworkers[149] have employed 2-diphenylphosphine-2'-hydroxybiphenyl (LBBA, **65**) as an efficient catalyst for the coupling of various *N*-sulfonated imines with acrolein to provide the Baylis-Hillman adducts in good to excellent yields. One example is presented in Eq. 14.



Eq. 14



Chiral catalysts:

The present day challenge in this reaction is development of appropriate chiral catalysts that will be applied to most classes of activated alkenes (acyclic / cyclic) and elctrophiles. Several attempts were made towards developing asymmetric version of Baylis-Hillman reaction using various chiral catalysts.[1-6] Some of the important tertiary

amine based [chiral DABCO (**66**),[150,151] enantiopure pyrrolizidine (**67**),[152] chiral bicyclic azetidine (**68**),[153] quinidine based catalyst (**69**)[154] (Figure 5)] and a variety of bifunctional catalysts, derived from BINOL (**70-73**)[155-159] (tertiary amine / non-tertiary amine), cyclohexane based thiourea derivative (**74**)[160] and bifunctional β-isocupreidine derivative (β-ICD, **75**)[161] (Figure 6) have been successfully employed in the Baylis-Hillman reaction to achieve high enantioselectivities.

Figure 5

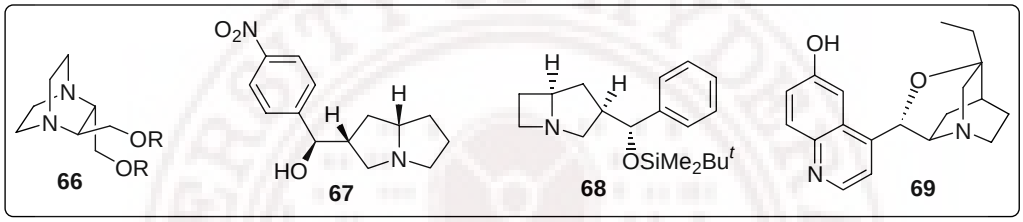
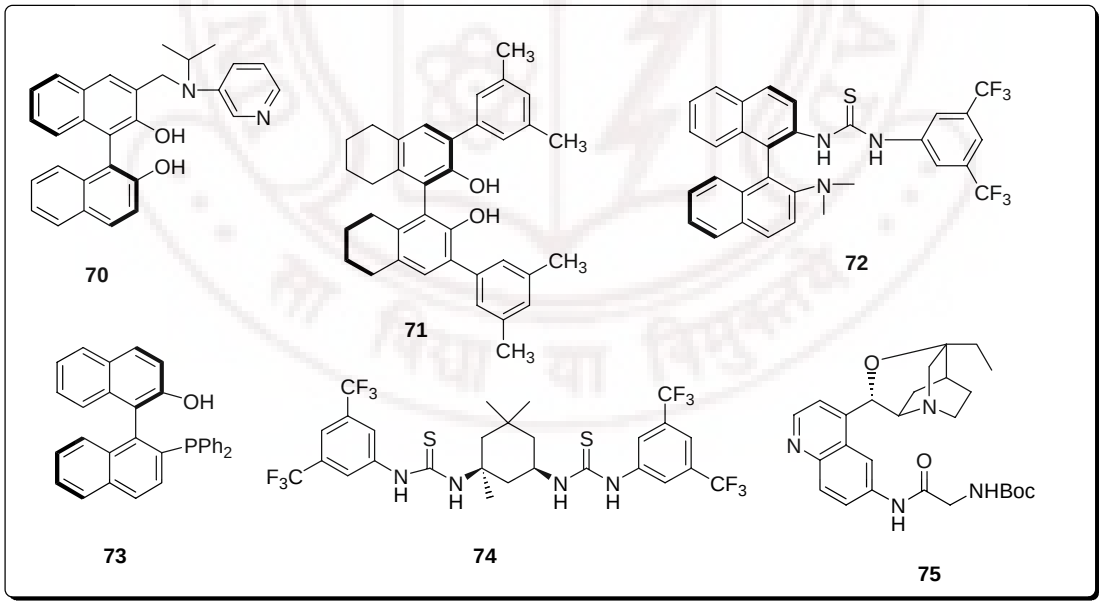
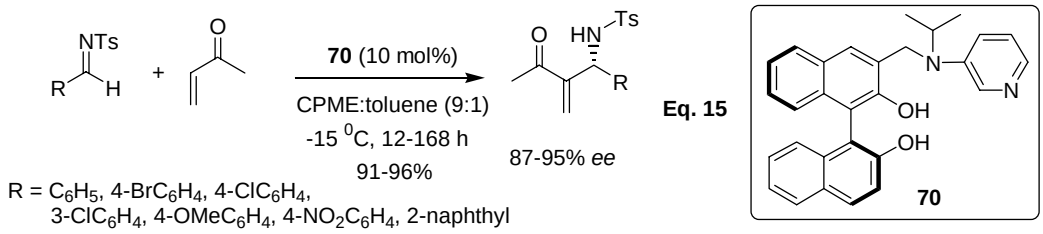


Figure 6

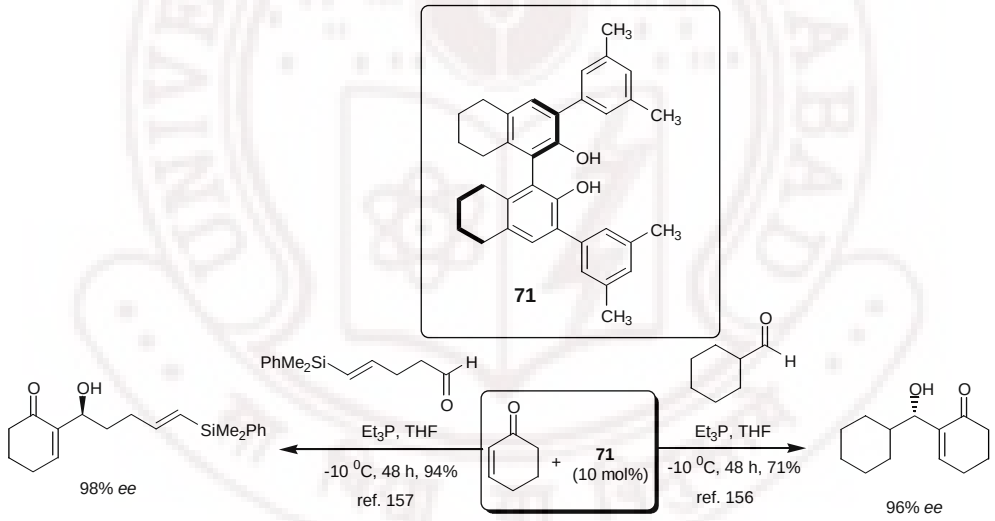


Sasai and coworkers[155] have developed an efficient and novel bifunctional organocatalyst (**70**) derived from BINOL to promote the enantioselective Baylis-Hillman reaction of various *N*-tosylimines with MVK in high enantioseletives (Eq. 15).

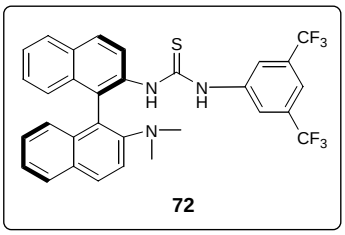


Schaus and coworkers[156,157] developed a highly enantioselective Baylis-Hillman reaction involving the coupling of cyclohex-2-enone with a variety of aldehydes (aliphatic, aromatic and silane containing aldehydes) mediated by excess Et_3P in the presence of BINOL-derived chiral co-catalyst (**71**). Representative examples are presented in Scheme 20.

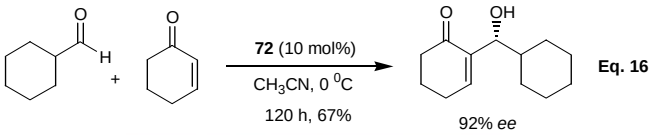
Scheme 20



Wang and coworkers[158] reported the Baylis-Hillman reaction of aldehydes with cyclohex-2-enone using binapthyl-derived amine thiourea (**72**) as efficient catalyst to afford the corresponding allyl alcohol in good yield with high enantioselective. One example is presented in Eq. 16.

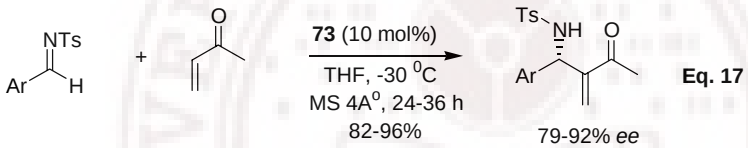


72



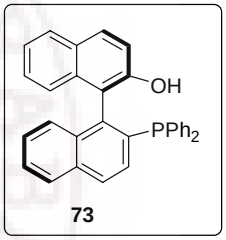
Eq. 16

Shi and Chen have developed an efficient and novel bifunctional chiral BINOL-derived phosphine catalyst (**73**) for high enantioselective Baylis-Hillman reaction of various *N*-sulfonated imines with methyl vinyl ketone (Eq. 17).[159]



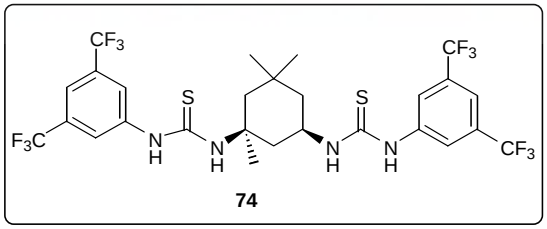
Ar = C_6H_5, 4-MeC_6H_4, 4-EtC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-FC_6H_4, 3-ClC_6H_4, 3-$NO_2C_6H_4$

Eq. 17

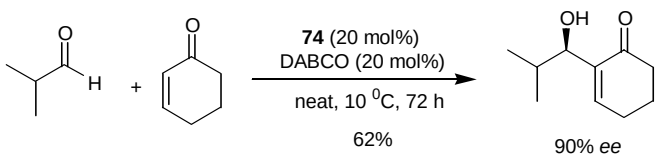


73

Berkessel and coworkers[160] have designed and synthesized, cyclohexane based thiourea derivative (**74**) and successfully employed them as efficient co-catalysts to promote the enantioselective Baylis-Hillman reaction of various aldehydes with activated alkenes (acyclic / cyclic). The resulting adducts were obtained in good yields with high enantioselective. One example is presented in Eq 18.

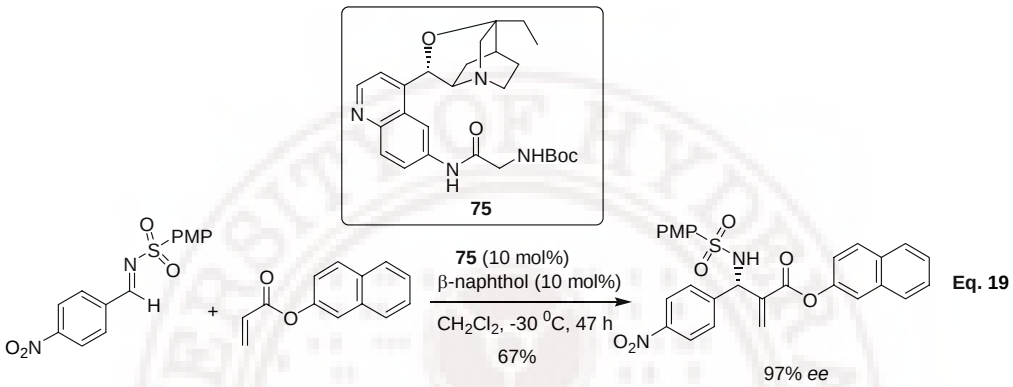


74

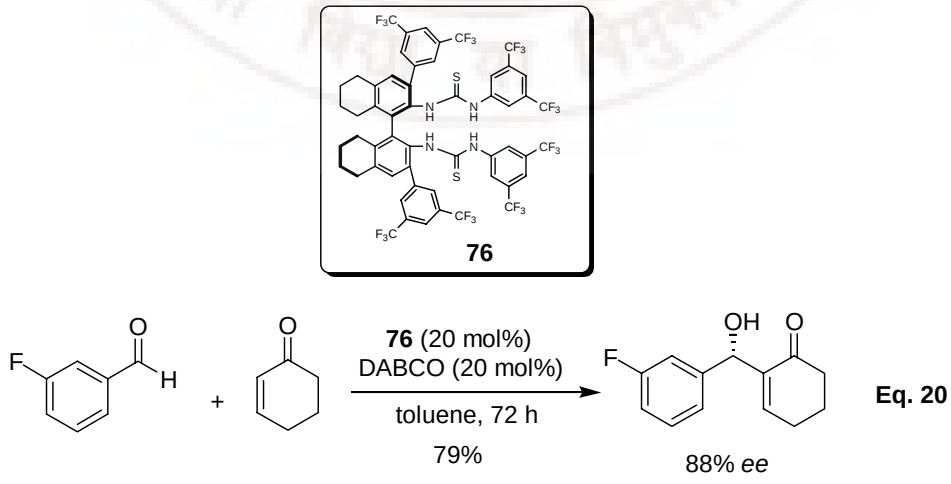


Eq. 18

Zhu and coworkers[161] have demonstrated that bifunctional β-isocupreidine (β-ICD, **75**) in combination with β-naphthol serves as a highly effective catalyst for the asymmetric Baylis-Hillman reaction between imines and β-naphthyl acrylate to provide the resulting adducts in high enantioselectivities. One representative example is presented in Eq. 19.

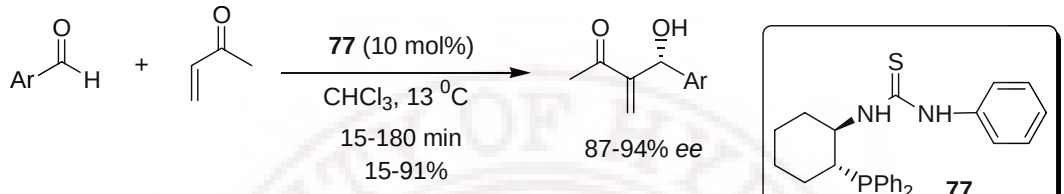


Recently, Shi and Liu have examined the asymmetric Baylis-Hillman reaction of various aromatic aldehydes with cyclohex-2-enone or cyclopent-2-enone using binaphthyl-derived bis(thio)urea derivative (**76**) as co-catalyst along with DABCO to afford the corresponding Baylis-Hillman alcohols in good yields with high enantioselectives. One representative example is presented in Eq. 20.[162]



Cyclohexane based chiral phosphinothiourea derivative (**77**) was successfully used as a catalyst for the Baylis-Hillman coupling of aromatic aldehydes with methyl vinyl ketone to provide the corresponding alcohols in good to excellent enantioselectivities by Yuan and coworkers. Representative examples are presented in Scheme 21.[163]

Scheme 21



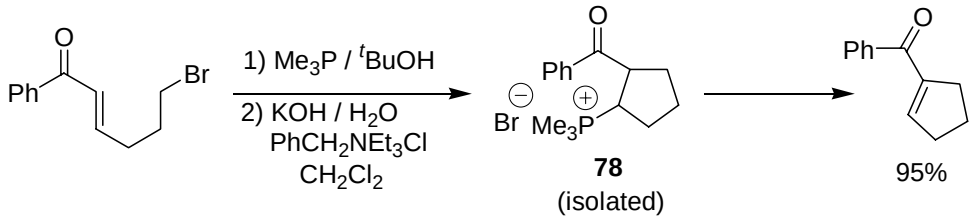
Ar = C_6H_5, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 4-$CF_3C_6H_4$, 2,4-$(Cl)_2C_6H_3$, 2-naphthyl

INTRAMOLECULAR BAYLIS-HILLMAN REACTION AND ITS ASYMMETRIC VERSION:

Although the Baylis-Hillman reaction has seen an exponential growth with respective to all the three essential components *i.e.,* activated alkene, electrophile and catalyst, during the last several years, the corresponding intramolecular version did not grow in that proportion. However in recent years this aspect has received more attention from the synthetic chemists and considerable progress has been achieved. Some of the recent and interesting developments in this direction are presented in this section.

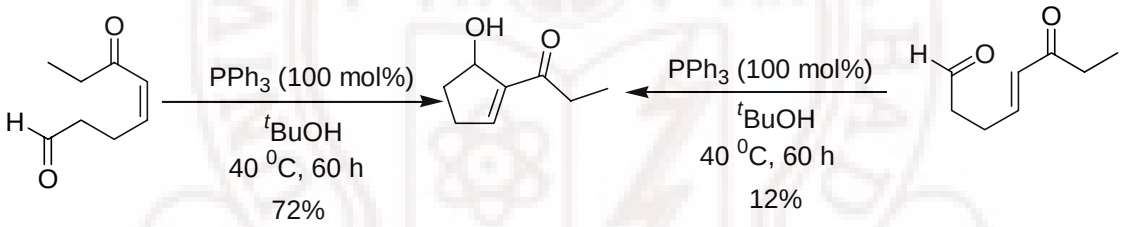
Krafft and coworkers[164] have developed an interesting organo-base mediated intra-molecular Baylis-Hillman cyclization of enone-halide system to provide the corresponding cyclic molecule in excellent yield. In order to understand the mechanism they have also isolated and characterized ketophosphinium salt (**78**), the key intermediate (Scheme 22).

Scheme 22

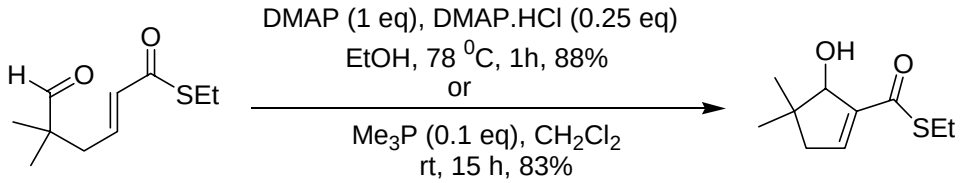


Shi and coworkers[165] reported an interesting intramolecular Baylis-Hillman reaction of enone-aldehyde under the influence of PPh_3. They have observed the role of stereo-chemistry of double bond in enone-aldehyde system. Thus the substrate with (*Z*)-stereochemistry afforded much higher yield than the corresponding substrate with (*E*)-stereochemistry (Scheme 23).

Scheme 23



Keck and Welch have described two protocols for an interesting intramolecular Baylis-Hillman reaction of substrates having both the activated alkene (ene-thioester) moiety and electrophile component (aldehyde) leading to the synthesis of cyclopentene derivatives in good yields. One representative example is presented in Eq. 21.[166]

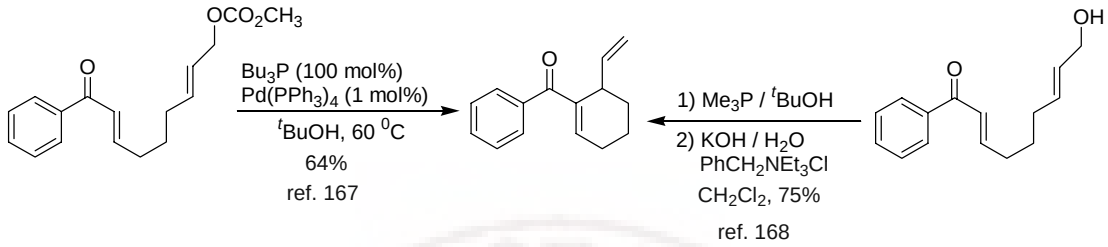


Eq. 21

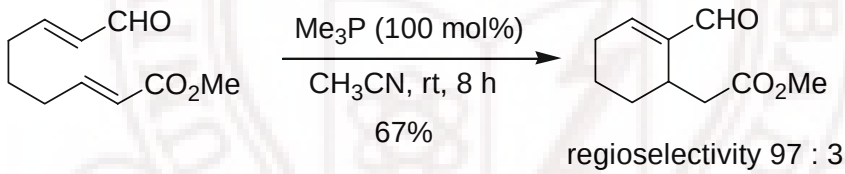
Krishe[167] and Krafft[168] have independently reported an interesting intramolecualr Baylis-Hillman reaction of the enone-allyl carbonates and enone-allyl alcohol

respectively as substrates to provide convenient methodologies for synthesis of functionalized cycloalkenes as described in Scheme 24.

Scheme 24



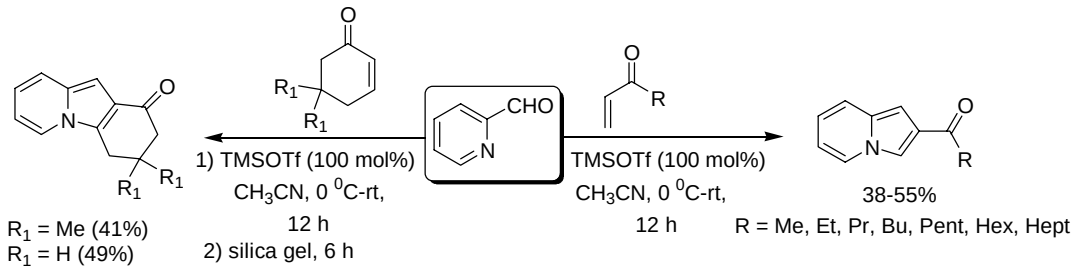
An intramolecular Baylis-Hillman reaction of enolate-enal system to provide a convenient method for the synthesis of functionalized cycloalkene derivatives was developed by Roush and coworkers.[169] One representative example is presented in Eq. 22.



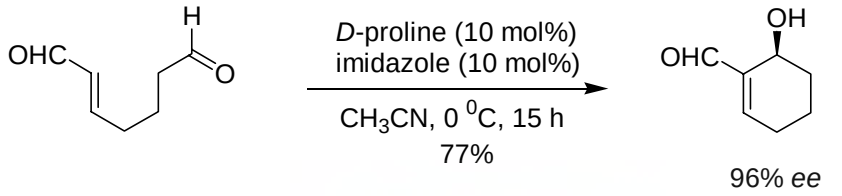
Eq. 22

Our research group[170] described an electrophile induced Baylis–Hillman reaction between activated alkenes and pyridine-2-carboxldehyde under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), leading to a novel synthesis of indolizine derivatives in one-pot operation (Scheme 25).

Scheme 25



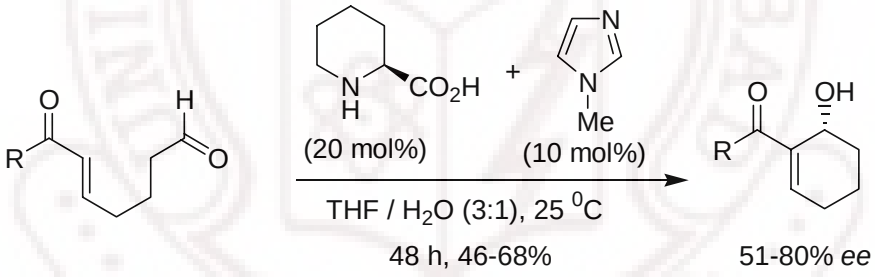
An efficient proline catalyzed enantioselective intramolecular Baylis-Hillman reaction of enal-aldehyde system under the influence of imidazole was reported by Hong and coworkers.[171] One such example is presented in Eq. 23.



Eq. 23

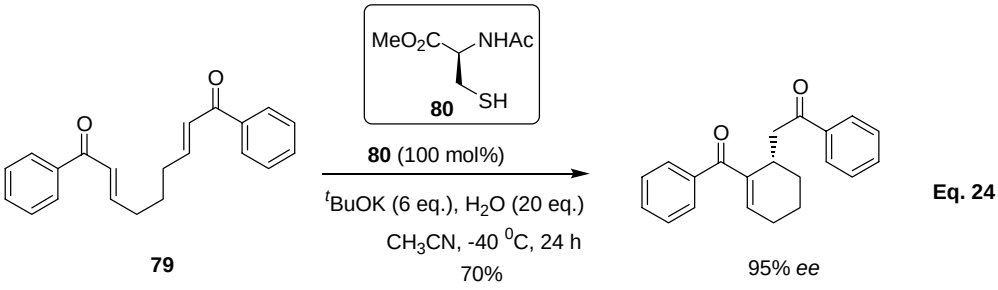
Subsequently, Miller and coworkers[172] demonstrated, the application of (*S*)-2-pipecolinic acid for promoting asymmetric intramolecular Baylis-Hillman reaction of enone-aldehyde system in the presence of *N*-methylimidazole to provide the resulting adducts in good enantioselectivities (Scheme 26).

Scheme 26



R = C_6H_5, 2-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, thiophen-2-yl

Very recently, Aroyan and Miller[173] have examined the asymmetric intramolecular Baylis-Hillman reaction of bisenone (**79**) in the presence of cysteine derivative (**80**) which provided the corresponding functionalized cyclohexene derivatives in good yields with high enantioselectives. One representative example is presented in Eq. 24.

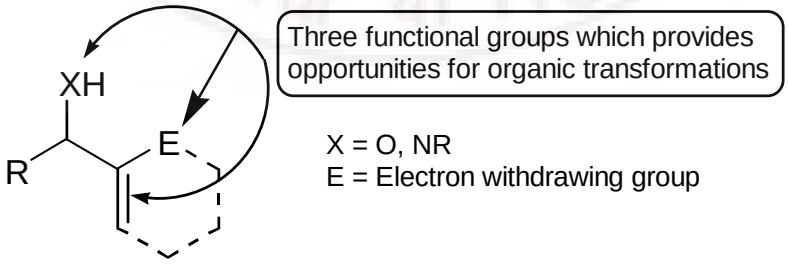


Eq. 24

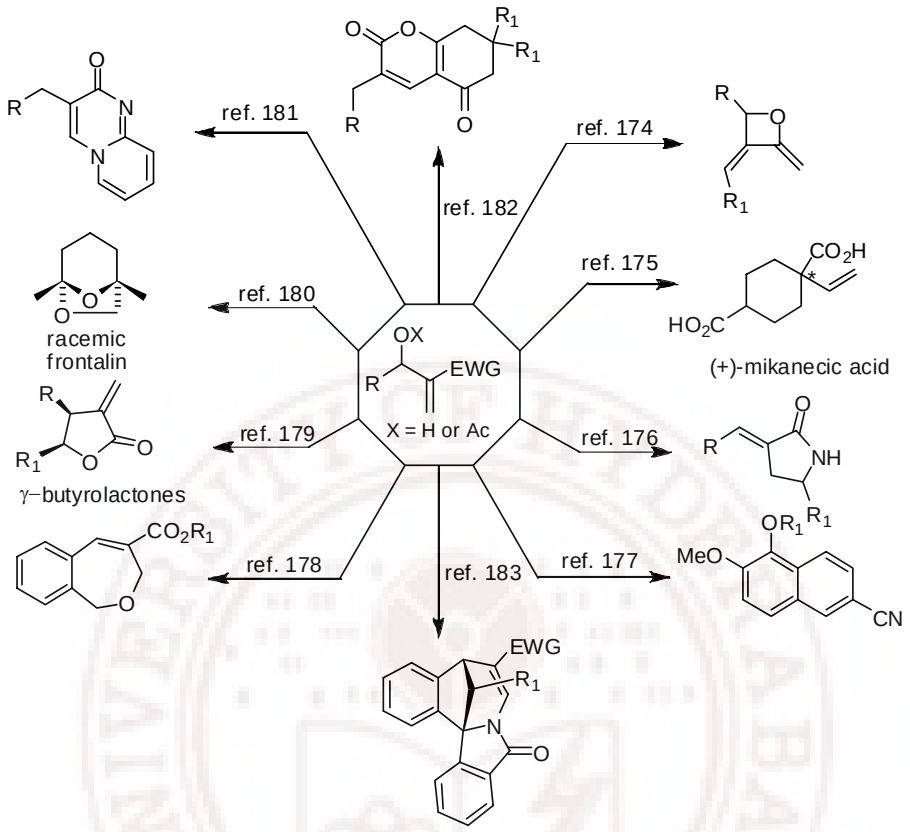
APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCT:

The Baylis-Hillman adducts play a vital place in organic synthesis as these adducts possess a minimum of three functional groups, (Figure 7) such as electron withdrawing group, olefin, and hydroxyl group (or amines) in a very close proximity which make them valuable substrates for various organic reactions like Friedel-Crafts reaction, Diels-Alder reaction, Heck reaction, radical cyclization, ring closing metathesis (RCM), hydrogenation, and hydride addition *etc.*[1-6] These adducts have been successfully employed as a valuable synthons for obtaining various organic transformation methodologies, in synthesis of hetero / carbocycles, natural products and biologically active molecules (Schemes 27 & 28).[1-6] Some of the important and relevant developments in the applications of these adducts are presented in this section.

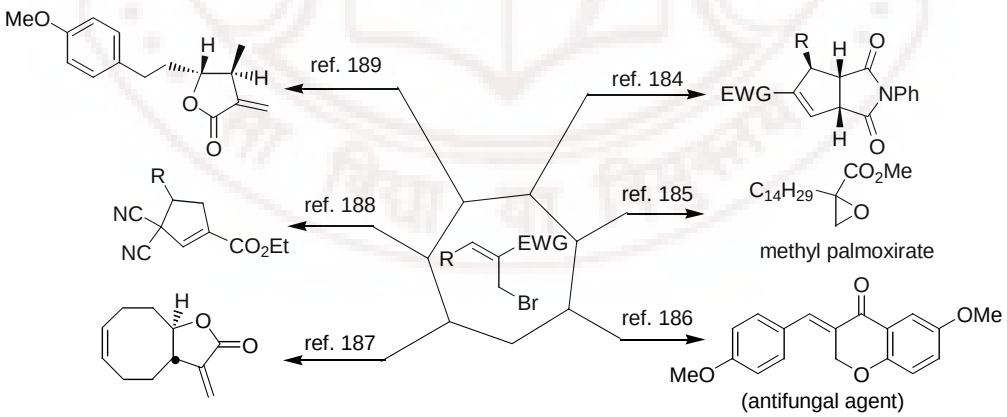
Figure 7



Scheme 27

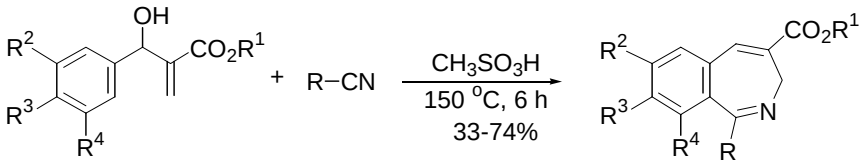


Scheme 28



Our research group[190] reported an interesting one-pot transformation of Baylis-Hillman adducts into 2-benzazepine derivatives *via* novel and tandem construction of C-N and

C-C bonds involving simultaneous Ritter and Houben-Hoesch reactions following the reaction sequence as described in Eq. 25.

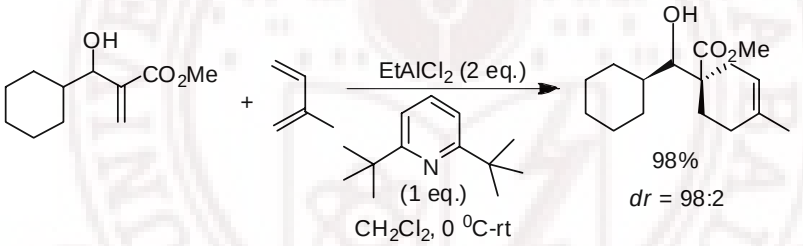


Eq. 25

R^1 = Me, Et; R^2 = OMe, OPr; R^3 = H, OMe;
R^4 = H, OMe; -R^2-R^3- = -OCH_2O-

R = Me, Et

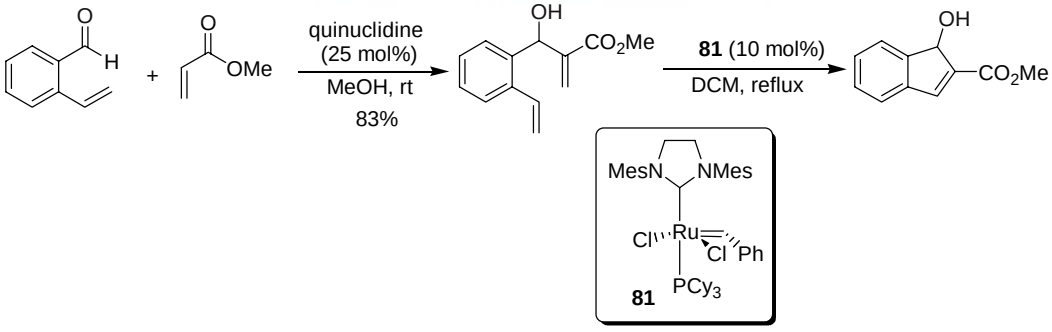
Aggarwal *et al.* successfully used Baylis-Hillman adducts as excellent dienophiles in Diels-Alder reaction with dienes to provide the corresponding adducts with complete diastereocontrol. One representative example is presented in Eq. 26.[191]



Eq. 26

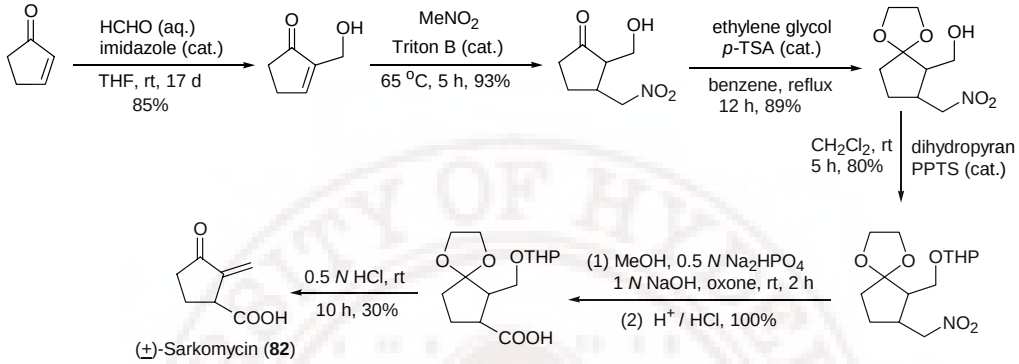
Krafft *et al.* have developed a facile synthesis of indene derivatives *via* tandem Baylis-Hillman and ring closing metathesis reactions. One representative example is presented in Scheme 29.[192]

Scheme 29



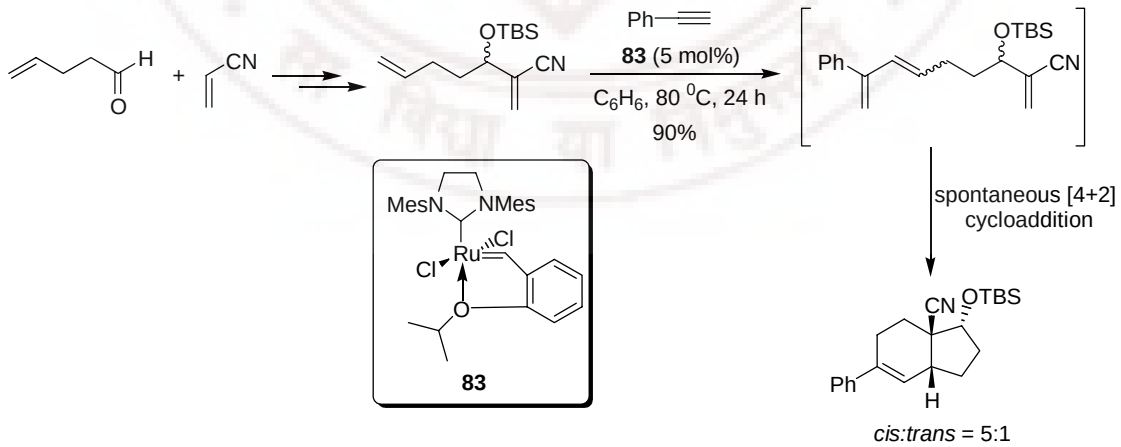
A simple and short synthesis (6 steps) of (±)-Sarkomycin (**82**) in 17% overall yield, using Baylis–Hillman reaction as the key step, was developed by Kar and Argade according to reaction sequence as presented in Scheme 30.[193]

Scheme 30



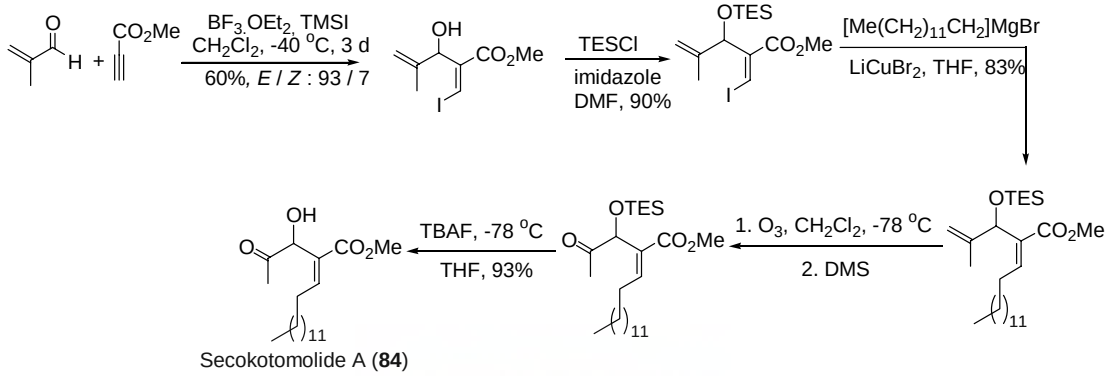
Mix and Blechert have reported the synthesis of *cis*-fused carbo-bicycles starting from Baylis-Hillman adducts *via* a reaction strategy involving sequential combination of Ru-catalyzed enyne cross-metathesis and intramolecular Diels-Alder reaction according to Scheme 31.[194]

Scheme 31



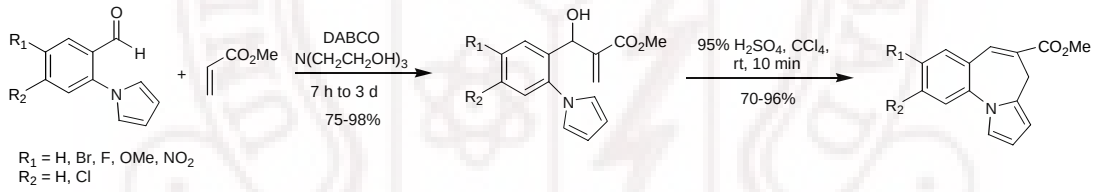
A facile five-step synthesis of Secokotomolide A (**84**) using the Baylis-Hillman reaction as a key step, was developed by Ryu and coworkers (Scheme 32).[195]

Scheme 32



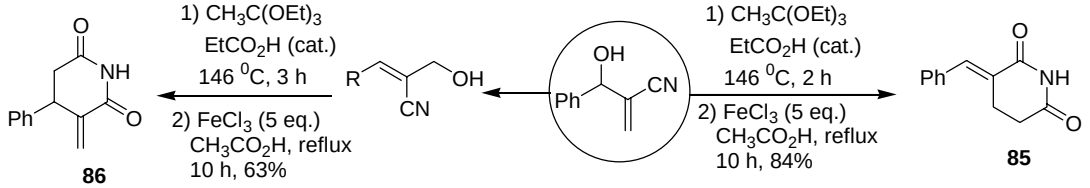
Recently, Lee and coworkers[196] have reported a facile synthesis of benzazepine derivatives from the Baylis-Hillman adducts derived from 2-pyrrolylbenzaldehydes under the influence of sulfuric acid in good to excellent yields. Representative examples are presented in Scheme 33.

Scheme 33



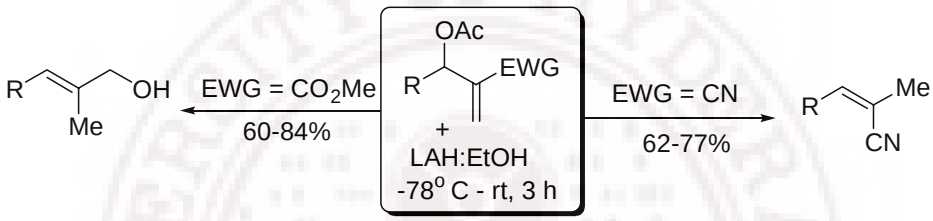
Very recently, our research group has developed simple and one-pot synthesis of piperidine-2,6-dione frameworks (**85** & **86**) from the Baylis-Hillman adducts *via* Johnson-Claisen rearrangement followed by partial hydrolysis and cyclization reaction strategy as shown in Scheme 34.[197]

Scheme 34



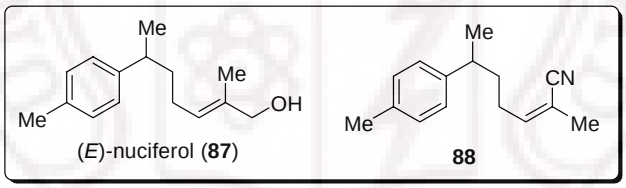
Our research group[198] has developed a simple stereoselective synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles *via* the treatment of the corresponding acetates of Baylis-Hillman adducts (obtained respectively from methyl acrylate and acrylonitrile) with LAH : EtOH (Scheme 35). Subsequently, this methodology has been successfully applied for the synthesis of (*E*)-nuciferol (**87**), a biologically active terpene and, a precursor (**88**) for (*Z*)-nuciferol (Figure 8).

Scheme 35



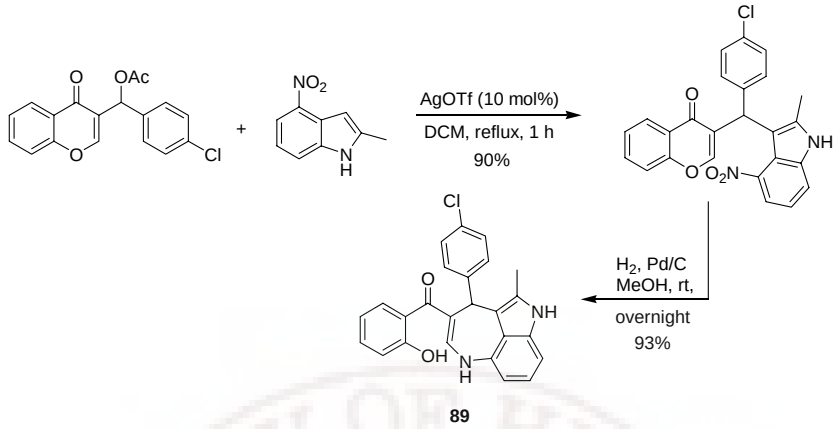
R = C_4H_9, C_5H_{11}, C_6H_{13}, C_6H_5, 4-MeC_6H_4, 3-(4-MeC_6H_4)Bu, 4-ClC_6H_4

Figure 8



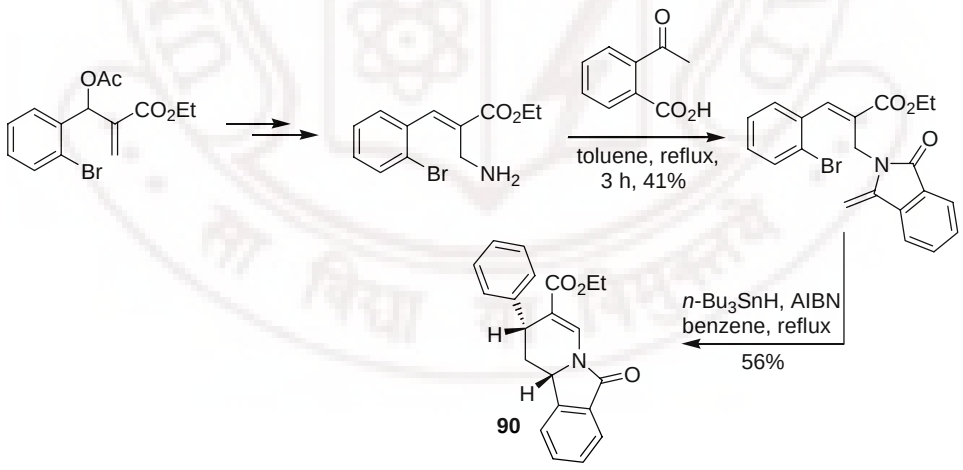
Recently, Shafiq *et al.* have reported a highly α-regioselective AgOTf catalyzed nucleophilic substitution of the Baylis-Hillman acetates with indoles. This strategy was extended to 4-NO_2-indole derivatives as nucleophile to provide a simple methodology for the synthesis of azepino-indole derivatives (**89**) *via* one-pot methodology involving reduction of nitro group, followed by an *in situ* aza-Michael addition (Scheme 36).[199]

Scheme 36



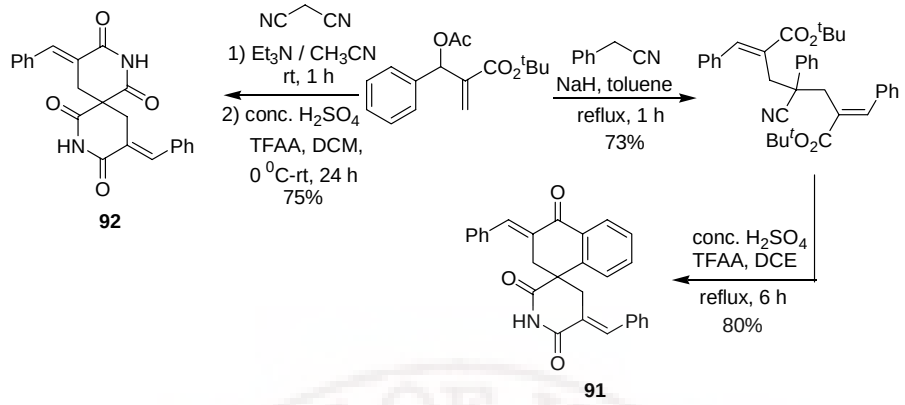
A facile synthesis of dihydropyrido[*2,1-a*]isoindolone (**90**) derivatives from the Baylis-Hillman adducts, derived from *o*-bromobenzaldehydes, using radical cyclization as the key strategy according to Scheme 37, was reported by Kim and coworkers.[200] One representative example is presented.

Scheme 37



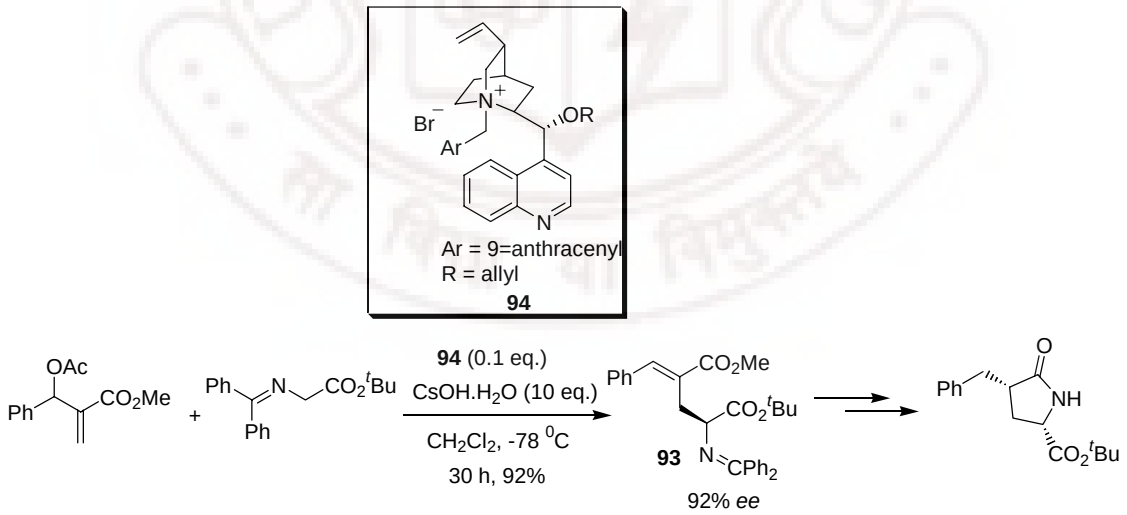
Recently, our research group has described two step procedure for the synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides (**91**) and also one-pot multistep synthesis of di(*E*)-arylidene-spiro-bisglutarimides (**92**) from the Baylis-Hillman acetates following the reaction sequence as described in Scheme 38.[201]

Scheme 38



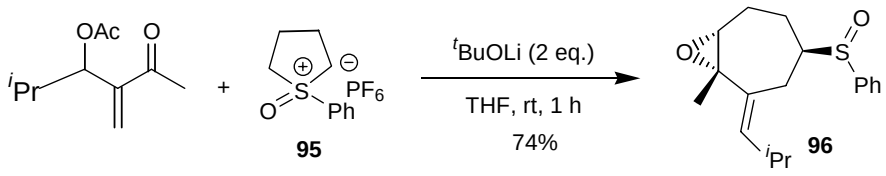
Ramachandran and coworkers[202] have reported a simple asymmetric synthesis of 4-alkylidenyl glutamic acid derivatives (**93**) *via* the alkylation of Baylis-Hillman adducts with Schiff base under the influence of chiral phase-transfer catalyst (**94**). These products (**93**) were further converted into 3,5-disubstituted pyrrolidin-2-one derivatives. One example is presented in Scheme 39.

Scheme 39



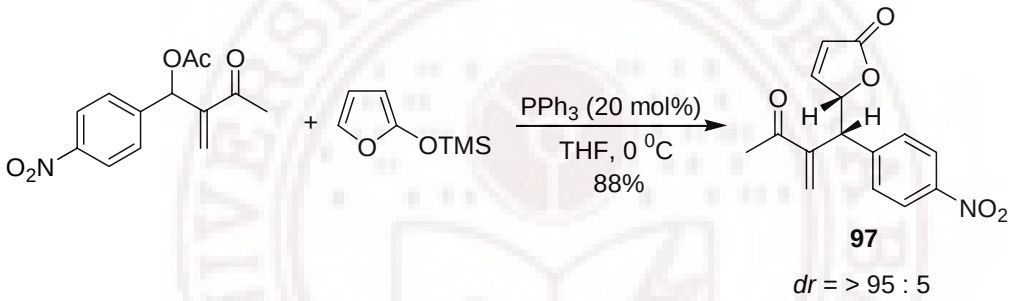
An interesting reaction of five-membered cyclic oxosulfonium ylide (**95**) with Baylis-Hillman acetates in the presence of a base to provide the cycloheptene oxide derivatives

(**96**) with stereoselectivity, involving intramolecular Corey-Chaykovsky reaction as the key step was reported by Akiyama and coworkers (Eq. 27).[203]



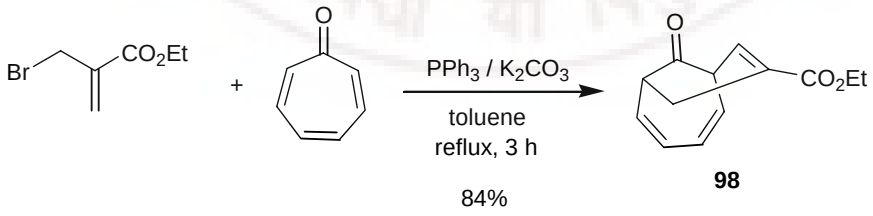
Eq. 27

Cho and Krische have reported regio and stereoselective synthesis of γ-butenolides (**97**) from the Baylis-Hillman acetates *via* the treatment with 2-trimethylsilyloxyfuran in the presence of triphenylphosphine. One representative example is presented in Eq. 28.[204]



Eq. 28

Lu and coworkers[205] have elegantly reported the phosphine-catalyzed reaction of Baylis-Hillman acetates (bromides / chlorides / *tert*-butyl carbonates) with tropone, involving [3+6] annulation strategy, to provide an interesting bicyclic compound (**98**) in excellent yields. One representative example is presented in Eq. 29.

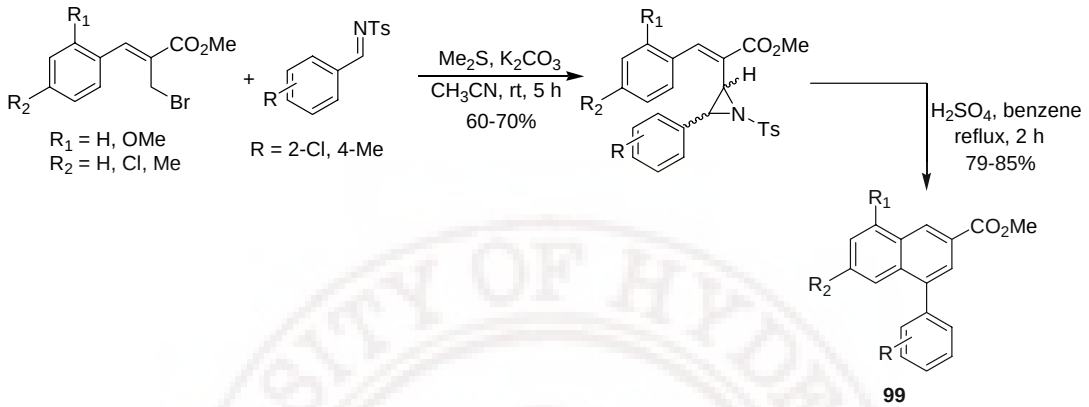


Eq. 29

A regioselective synthesis of 1-arylnaphthalenes (**99**) from *N*-tosylaziridine derivatives (which in turn were obtained *via* the reaction between *N*-tosylimines and Baylis-

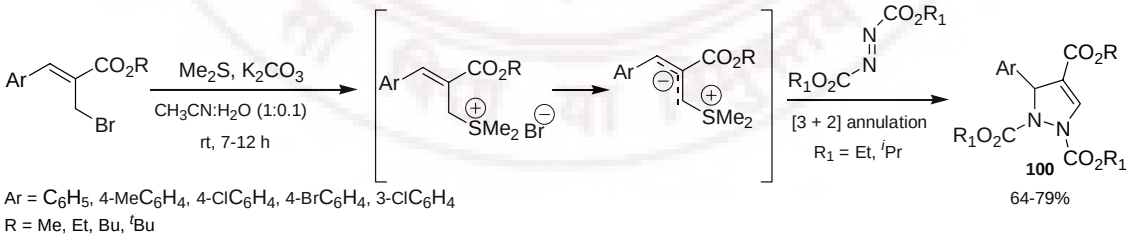
Hillman bromides), following the reaction sequence as shown in Scheme 40, was described by Kim and coworkers.[206]

Scheme 40



Recently, our research group has developed an interesting synthesis of functionalized dihydropyrazole derivatives (**100**) using Baylis-Hillman bromides *via* the treatment with dialkyl azodicarboxylates (dipolarophiles) under the influence of dimethyl sulfide in the presence of potassium carbonate in a simple one-pot [3 + 2] annulation strategy (Scheme 41).[207]

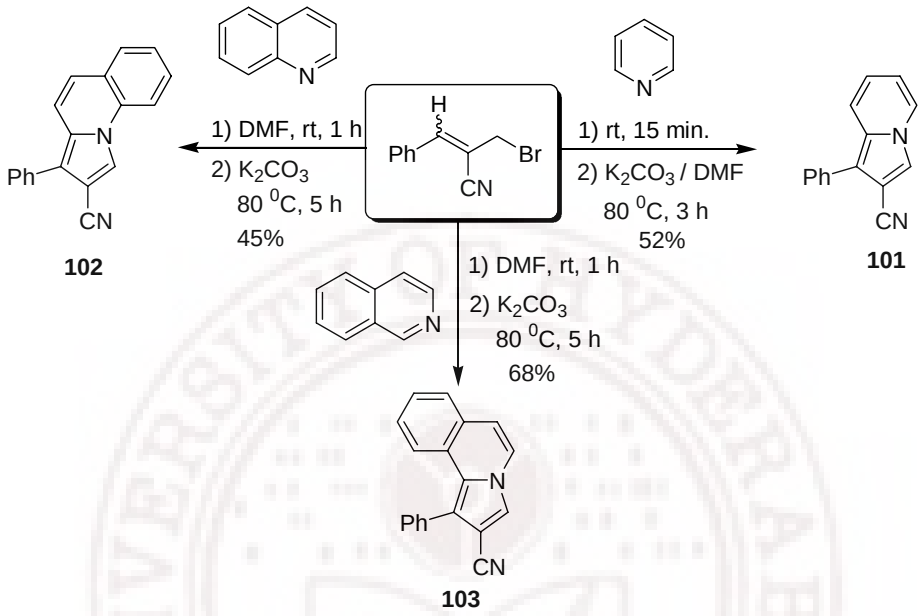
Scheme 41



Very recently, our research group has reported the convenient and one-pot synthesis of indolizine (**101**) and benzofused indolizine frameworks (**102** & **103**) *via* the reaction of Baylis-Hillman bromides with pyridine, quinoline / isoquinoline respectively in the

presence of potassium carbonate according to reaction sequence as shown in Scheme 42.[208]

Scheme 42

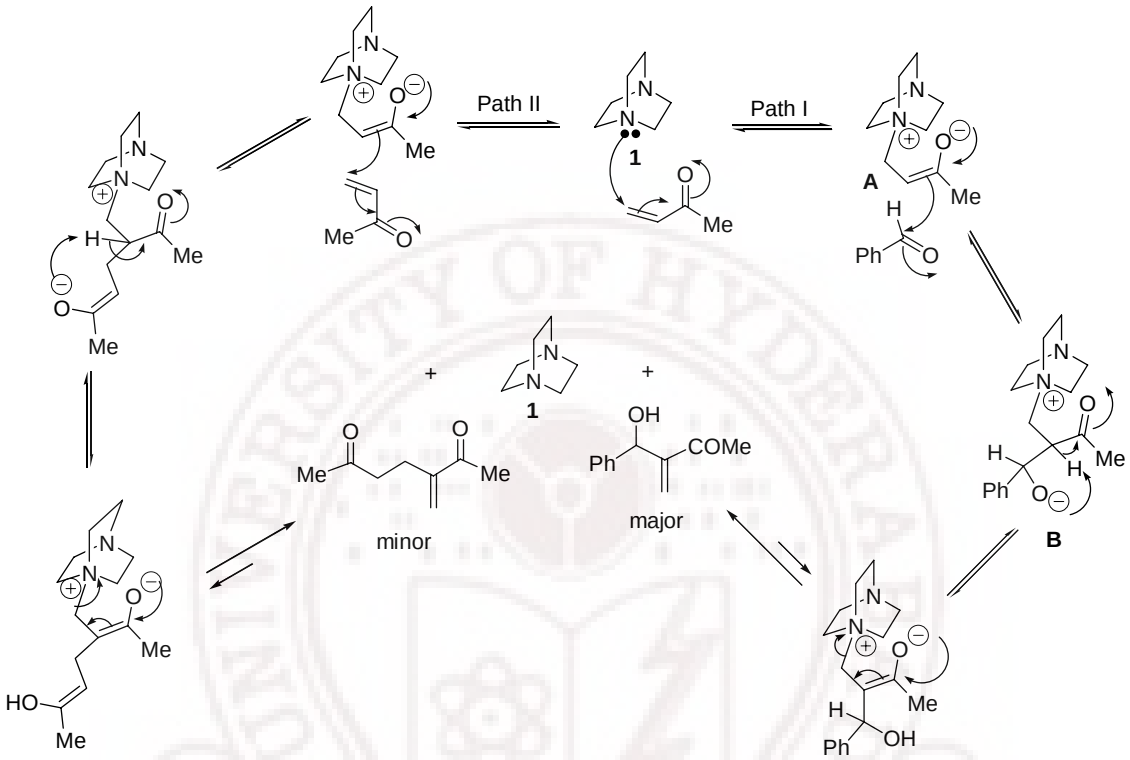


Mechanism:

Although exact mechanism of the reaction is not known, the most generally accepted mechanism[209-217] of the Baylis-Hillman reaction is illustrated in the Scheme 43 (Path I) considering the reaction between benzaldehyde (as an *electrophile*) and methyl vinyl ketone (as an *activated alkene*) under the catalytic influence of DABCO (**1**), as a model case. The first step involves the addition of catalyst (DABCO) on to the activated alkene (methyl vinyl ketone) in Michael fashion, leading to the formation of zwitterionic enolate **A**, which adds on to the electrophile (benzaldehyde) in an aldol fashion. The resulting zwitterionic species **B**, undergoes proton migration and subsequently, releases the catalyst to provide the desired multifunctional molecule. In the case of reactive activated alkenes such as methyl vinyl ketone, 3-methylene-2,6-

alkanediones (Michael type dimmers) are formed as minor products because they themselves act as electrophiles for coupling with itself (Scheme 43; Path II).

Scheme 43



All the investigations so far known in the literature suggest a similar mechanistic pathway involving the Michael, aldol and elimination sequence as shown in Scheme 43. However, many aspects of the rate limiting step (RLS) are not yet understood. Most of these mechanistic studies have been concentrated only on the acrylates (*as activated alkenes*) and aldehydes (*as electrophiles*) although several types of activated alkenes and electrophiles have been used in the Baylis-Hillman reaction. Therefore understanding the mechanism of Baylis-Hillman reaction has attracted the attention of organic chemists in recent years, indeed become an intellectual challenge for mechanistic chemists. [212-217]

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 in the literature. Our research group has been working on the Baylis-Hillman reaction for the last twenty six years with the main objective of developing this reaction into a valuable synthetic tool in organic synthesis and in fact made significant contributions in this direction. In continuation of this major research program in this fascinating reaction, we have undertaken a research project on the synthesis of heterocyclic and carbocyclic frameworks of medicinal relevance with the following objectives.

OBJECTIVES

1) To develop a facile methodology for synthesis of functionalized tri-/tetracyclic frameworks containing azocine moiety as one of the central rings using the Baylis-Hillman acetates as the starting materials.

2) To develop a simple, one-pot, and facile synthetic strategy for synthesis of angularly fused [6-7-5], [6-7-6], [6-7-7] and [6,7] carbocyclic ring systems containing cycloheptane as the central ring using the Baylis-Hillman acetates as starting materials.

3) To develop a simple synthesis of *himanimide A*, biological active compound using Baylis-Hillman adduct derived from appropriate α-keto ester and acrylonitrile as the starting material.

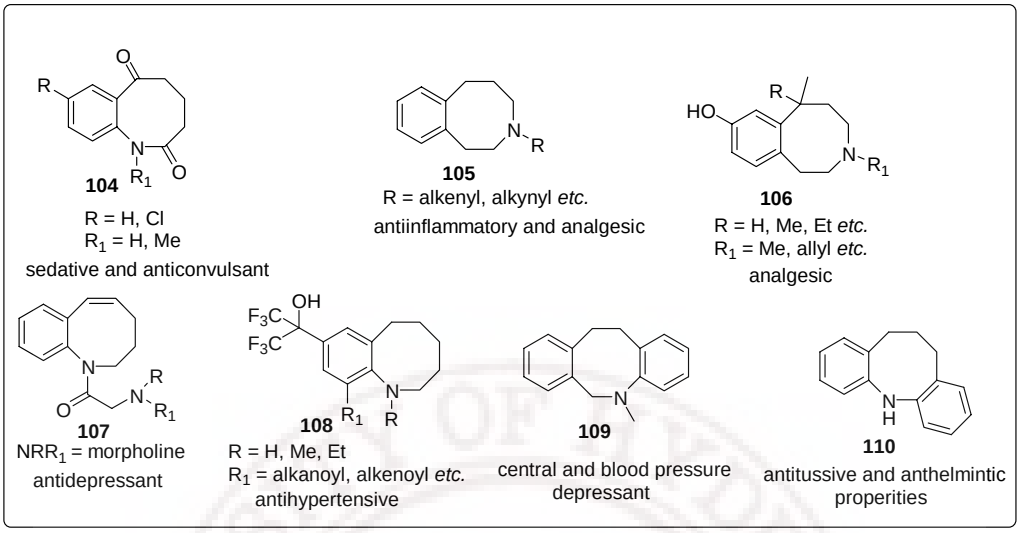
RESULTS AND DISCUSSION

The Baylis-Hillman acetates as a valuable source for one-pot multistep synthesis: a facile synthesis of functionalized tri-/tetracyclic frameworks containing azocine moiety

The synthesis of medium sized rings, in particular seven-, eight- and nine-membered rings, has been and continues to be a challenging and fascinating endeavour in synthetic chemistry, because unfavorable entropic and enthalpic factors prevent the adaptation of traditional methods of ring formation.[218-222] An eight-membered nitrogen heterocyclic framework (particularly azocines and benzfused azocines) occupies a special place in the history of nitrogen heterocycles because of the presence of this moiety in various biologically active molecules possessing **104 (**sedative, anticonvulsant)[223] **105 (**anti-inflammatory, analgesic),[224] **106 (**analgesic**)**[225] **107 (**antidepressant),[226] **108 (**antihypertensive)[227] activities [Figure 9]. Some dibenzazocine derivatives are known to exhibit various biological activities such as **109 (**central and blood pressure depressants),[228] and **110 (**antitussive, and /or anthelmintic activities)[229] [Figure 9].

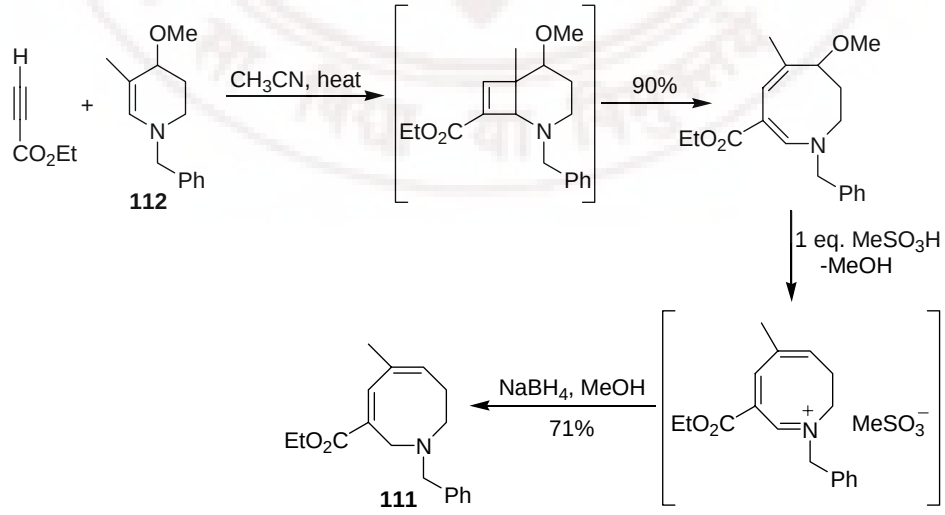
Owing to these remarkable biological activities of azocines and benzfused azocines there has been increasing interest in the development of easy and simple methodologies / strategies for the synthesis of these molecules. Some of the important methods, for the synthesis of azocine moiety, reported in the literature are presented in the following Schemes 44-47 and Eq. 30.

Figure 9



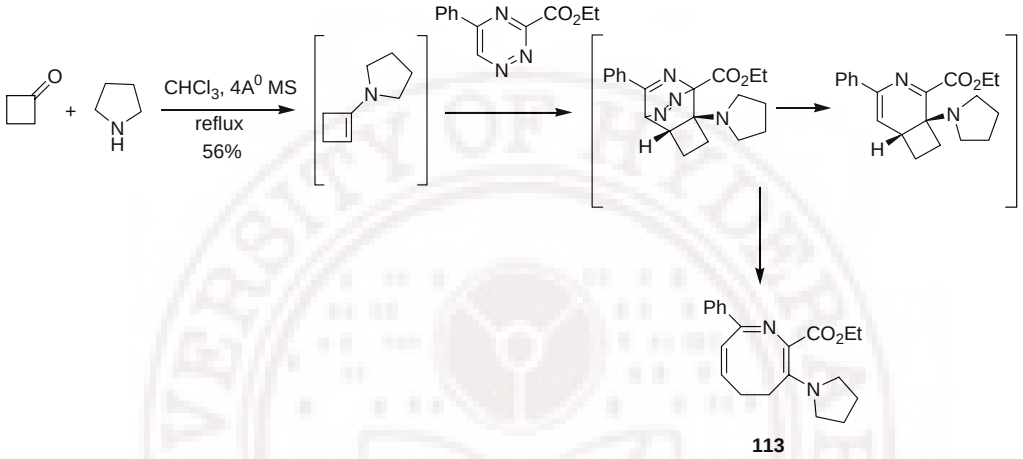
Gil and coworkers[230] have reported facile synthesis of 1,2,7,8-tetrahydroazocine derivatives (**111**). This strategy involves [2+2] cycloaddition reaction between the enamine **(112**) and ethyl propiolate to produce the cyclobutene intermediate followed by an electrocyclic ring opening to give the azocine system following the reaction sequence as described in Scheme 44.

Scheme 44

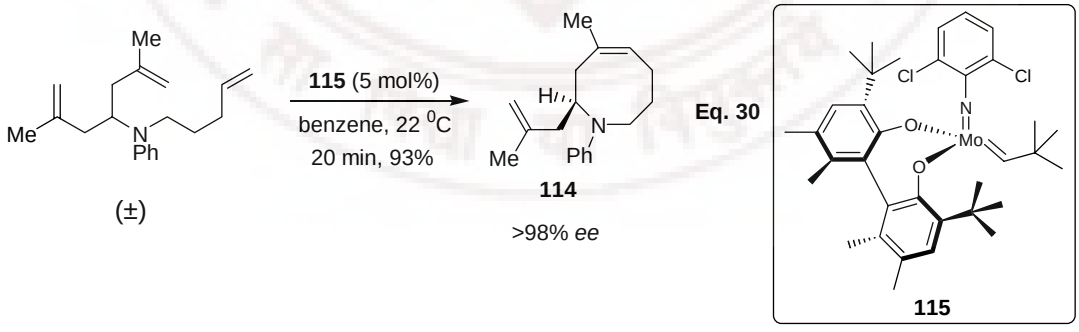


Raw and Taylor have described an interesting reaction between enamine derived from cyclobutanone and a secondary amine, with 1,2,4-triazines to produce functionalized 4,5-dihydroazocines (**113**) in one-pot operation, following cascade reaction sequence as described in the Scheme 45 (one example is presented).[231]

Scheme 45

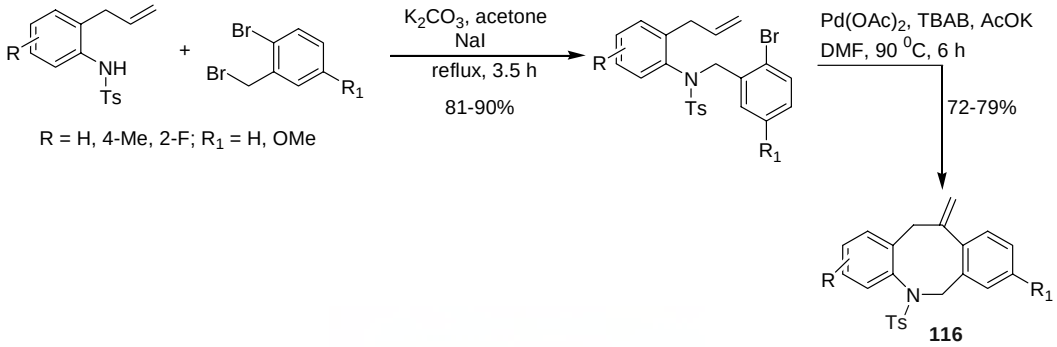


Schrock and coworkers[232] have developed an efficient enantioselective synthesis of azocine ring (**114**) through Mo-catalyzed (**115**) asymmetric ring closing metathesis of appropriate diene system, in high yields according to Eq. 30.



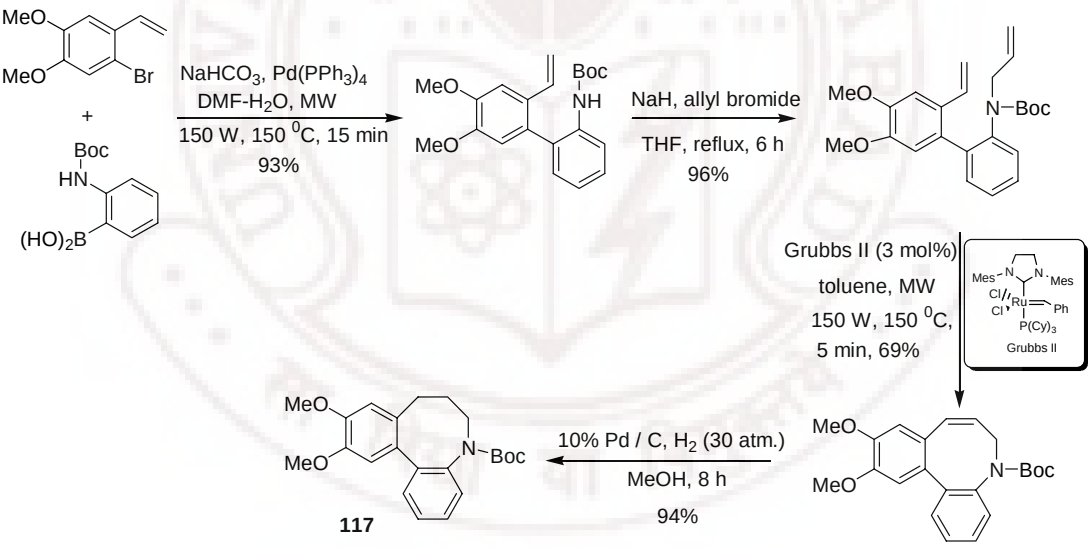
A simple protocol for the synthesis of various dibenzazocines (**116**) *via* the intramolecular Heck reaction as a key step was developed by Majumdar and coworkers, following the reaction sequence as shown in Scheme 46.[233]

Scheme 46



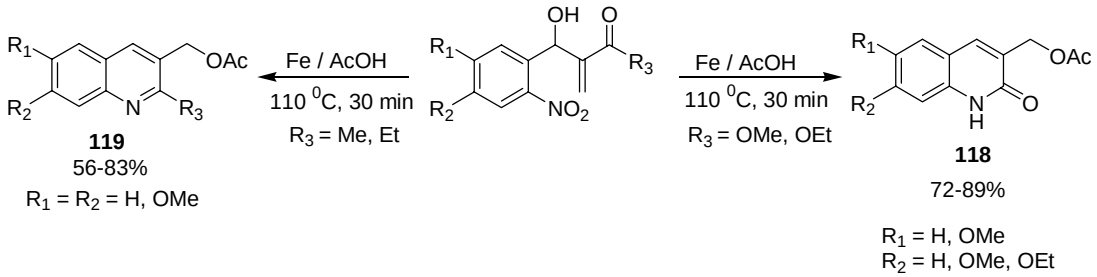
Appukkuttan *et al.* have reported an interesting synthesis of azocine frameworks (**117**) *via* microwave-enhanced Suzuki-Miyaura cross-coupling and ring-closing metathesis reactions as the key steps. One representative example is described in Scheme 47.[234]

Scheme 47

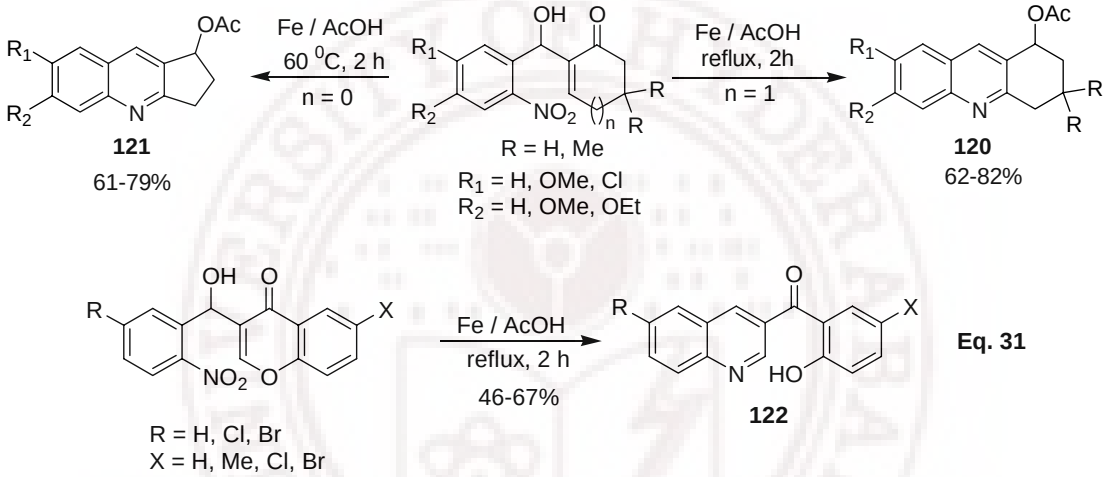


Our research group has been working on the development of one-pot synthetic protocol for the synthesis of substituted quinolines (**118** & **119**),[235] tetrahydroacridines (**120**),[236] cyclopenta[*b*]quinolines (**121**),[236] and 3-benzoylquinolines (**122**)[237] starting from Baylis-Hillman adducts, derived from various 2-nitrobenzaldehydes and acyclic / cyclic enones according to the Schemes 48 & 49 and Eq. 31.

Scheme 48

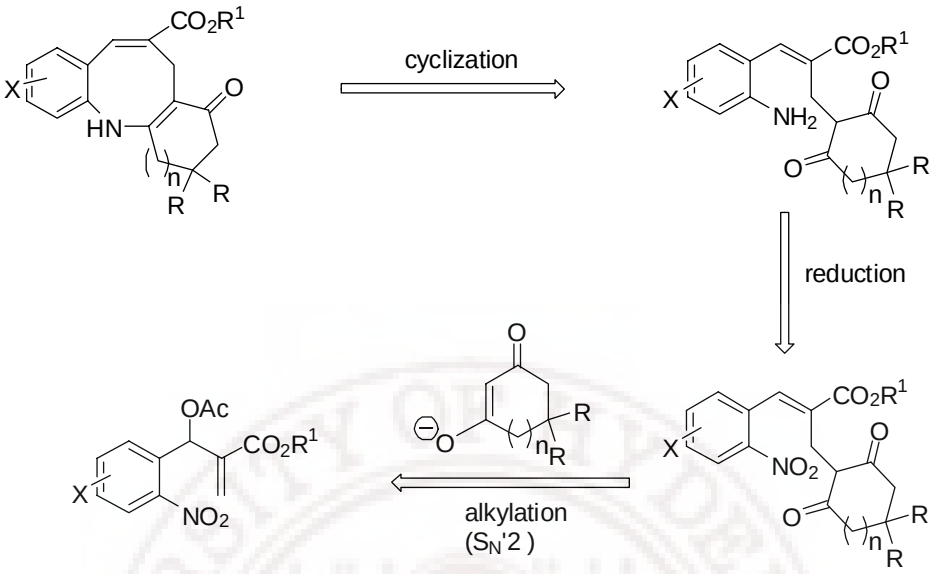


Scheme 49



On the basis of our experience we envisioned that acetates of Baylis-Hillman alcohol derived from 2-nitrobenzaldehyde and alkyl acrylate, can be in principle transformed into tri-/tetracyclic heterocyclic derivatives containing azocine moiety through an appropriate synthetic strategy. After considering some retro-synthetic strategies we arrived at a synthetic plan as shown in Scheme 50, which involves an alkylation ($S_N'2$), reduction and cyclization sequence to provide the desired azocine moiety.

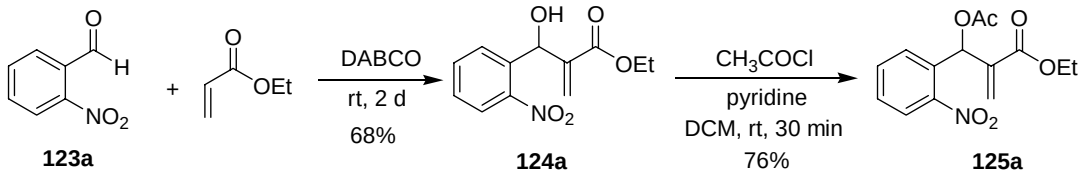
Scheme 50



Synthesis of [6-8-6] frameworks containing azocine moiety:

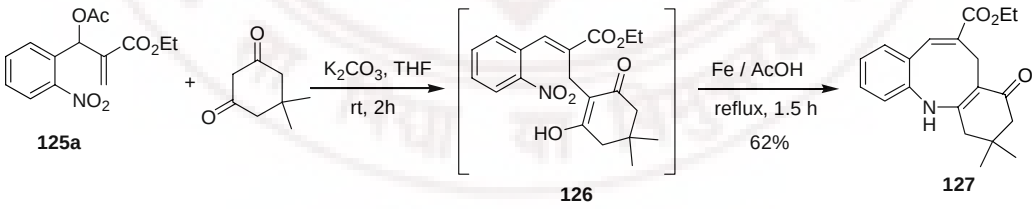
Accordingly, we have first planned synthesis of 2-aza-5,5-dimethyl-10-ethoxycarbonyl-tricyclo[10.4.0.$0^{3,8}$]hexadeca-3(8),10,12,14,16-pentaen-7-one (**127**) in a one-pot multi-step protocol starting from the Baylis-Hillman acetate (**125a**). The required acetate, ethyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125a**), was prepared *via* the acetylation of the Baylis-Hillman alcohol (**124a**) according to Scheme 51. The Baylis-Hillman adduct, *i.e.,* ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (**124a**), in turn was obtained *via* the treatment of 2-nitrobenzaldehyde (**123a**) with ethyl acrylate in the presence of DABCO as described in Scheme 51.

Scheme 51



We have examined the alkylation of 5,5-dimethyl-1,3-cyclohexanedione with ethyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125a**) as an alkylating agent. The best results were obtained when we treated Baylis-Hillman acetate (**125a**, 1 mmol) with 5,5-dimethyl-1,3-cyclohexanedione (1 mmol) in the presence of K_2CO_3 (1 mmol) in THF (1 mL) at room temperature for 2 h followed by the treatment of resulting product (obtained after removal of THF under reduced pressure) with Fe (6 mmol) / AcOH (5 mL) at reflux temperature for 1.5 h, thus providing 2-aza-5,5-dimethyl-10-ethoxycarbonyl-tricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,16-pentaen-7-one (**127**)$^{\Phi}$ in 62% isolated yield after the usual workup followed by column chromatography (Scheme 52). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 1), ^{13}C NMR (Spectrum 2), mass spectral data and elemental analysis. We have also obtained single crystal for this compound and further confirmed the structure of this molecule by single crystal X-ray data (see Figure 10 for ORTEP diagram of **127**, Table I)

Scheme 52

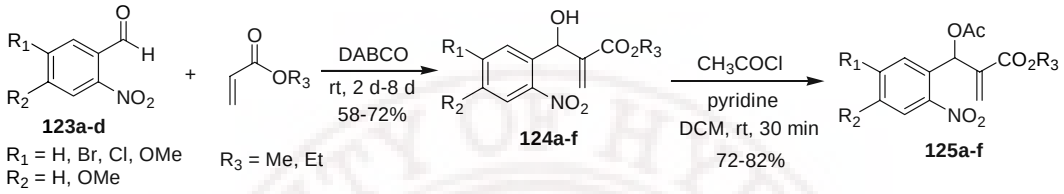


This result is indeed very interesting in the sense that the Baylis-Hillman acetate is transformed into functionalized tricyclic framework containing an important azocine moiety in one-pot operation in reasonably high yield. Encouraged by this result we have directed our attention towards understanding the generality of this methodology.

$^{\Phi}$ For easy understanding and continuation we have numbered hexahydrodibenz[*b,g*]azocine derivatives obtained from Baylis-Hillman acetates (**125a-f**) and dimedone as (**127-132**) respectively.

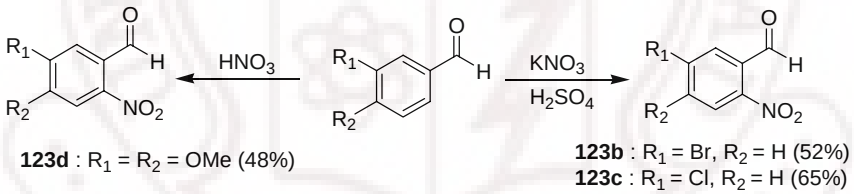
Thus we have selected representative Baylis-Hillman alcohols (**124b-f**) obtained *via* the coupling of various 2-nitrobenzaldehydes (**123a-d**) with various alkyl acrylate in the presence of DABCO and transformed them into the corresponding allyl acetates (**125b-f)** by the treatment with acetyl chloride and pyridine in CH_2Cl_2 (Scheme 53).

Scheme 53



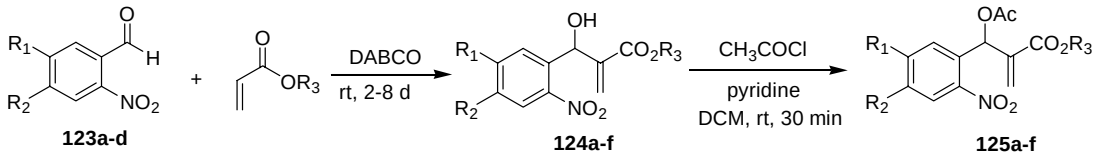
The required 5-bromo-2-nitrobenzaldehyde (**123b**), 5-chloro-2-nitrobenzaldehyde (**123c**) and 4,5-dimethoxy-2-nitrobenzaldehyde (**123d**) were prepared according to the literature procedure (Scheme 54).[238,239]

Scheme 54



We have then, subjected the Baylis-Hillman acetates (**125b-f**) to the alkylation with 5,5-dimethyl-1,3-cyclohexanedione as nucleophile, then reduction followed by cyclization to provide the desired hexahydrodibenz[*b,g*]azocine derivatives (**128-132)** in 57-68% isolated yield (Table 2). All the compounds were fully characterized by IR, ^{1}H NMR (See: spectra 3 at rt, spectra 3a at -30 ^{0}C, spectra 3b at -40 ^{0}C for the compound **128**), ^{13}C NMR (see spectra 4 at rt, spectra 4a at -30 ^{0}C, for DEPT 135, see spectra 5 at rt, spectra 5a at -30 ^{0}C and for hetero COSY see spectra 6 at rt for the compound **128**), mass spectral data and elemental analyses.

Table 1. Synthesis of Baylis-Hillman alcohols[ω,a] and acetates[χ,b]



Aldehyde	R_1	R_2	R_3	B−H alcohol[e]	Yield (%)[c]	B−H acetate[e]	Yield (%)[d]
123a	H	H	Et	**124a**	68	**125a**	76
123a	H	H	Me	**124b**	72	**125b**	82
123b	Br	H	Me	**124c**	67	**125c**	74
123c	Cl	H	Me	**124d**	61	**125d**	78
123d	OMe	OMe	Me	**124e**	62	**125e**	79
123d	OMe	OMe	Et	**124f**	58	**125f**	72

(a) All reactions were carried out on 20 mmol scale of various 2-nitrobenzaldehydes with alkyl acrylates under the influence of DABCO (15 mol%) at room temperature for 2-8 days.
(b) All reactions were carried out on 10 mmol scale of Baylis-Hillman alcohols with 20 mmol of acetyl chloride under the influence of pyridine in dichloromethane at room temperature for 30 min.
(c) Yields are based on aldehydes.
(d) Yields are based on Baylis-Hillman alcohols.
(e) All compounds gave satisfactory IR, ^{1}H NMR and ^{13}C NMR spectral data.

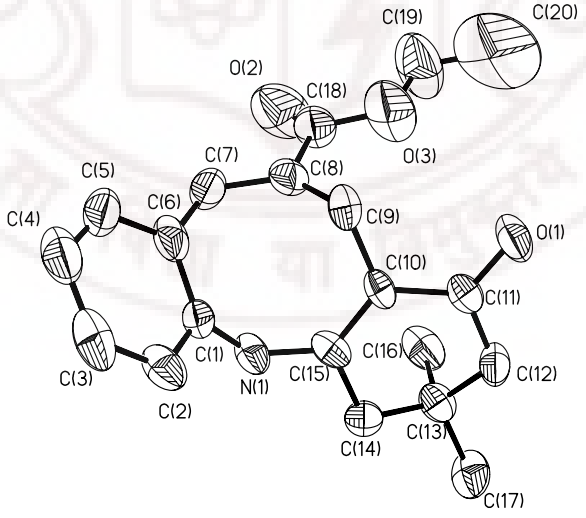


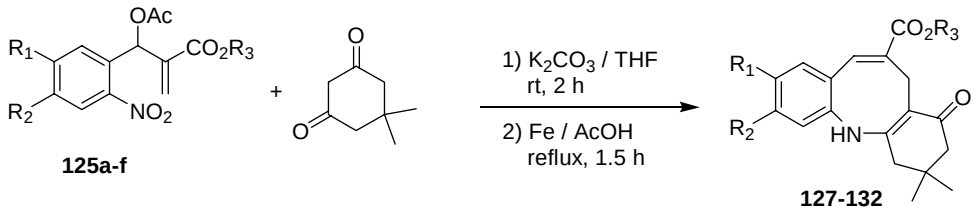
Figure 10 ORTEP diagram of compound **127**
(Hydrogen atoms were omitted for clarity)

[ω,χ] For continuity and better understanding we have numbered the B-H alcohols derived from the aldehydes (**123a-d**) and ethyl acrylate or methyl acrylate as **124a-f** respectively and the corresponding B-H acetates as **125a-f** respectively.

Table I: Crystal data collection and structure refinement for the compound **127**

Empirical formula	: $C_{20}H_{23}NO_3$
Formula weight	: 325.40
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: orthorhombic
Space group	: *P* 21 21 21
Unit cell dimensions	: a = 8.7778 (4) Å; α = 90 deg.
	: b = 14.5771 (6) Å; β = 90 deg.
	: c = 18.0574 (8) Å; γ = 90 deg.
Volume	: 2310.53(17) $Å^3$
Z, Calculated density	: 4, 1.189 g/cm^3
Absorption coefficient	: 0.083 mm^{-1}
F(000)	: 888
Crystal size	: 0.34 X 0.24 X 0.14 mm
Theta range for data collection	: 1.80 to 25.00 deg.
Limiting indices	: $-10 \le h \le 10, -17 \le k \le 17, -21 \le l \le 21$
Reflections collected / unique	: 22350 / 2330 [R(int) = 0.0351]
Completeness to theta = 25.00	: 99.9%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2330 / 1 / 276
Goodness-of-fit on F^2	: 1.042
Final R indices [I>2sigma(I)]	: R1 = 0.0494, wR2 = 0.1445
R indices (all data)	: R1 = 0.0595, wR2 = 0.1525
Largest diff. peak and hole	: 0.309 and -0.226 e. $Å^{-3}$

Table 2. Synthesis of Tricyclic Framework Containing Azocine Moiety *via* the Reaction of 5,5-Dimethyl-1,3-Cyclohexanedione with Baylis-Hillman Acetates (125a-f). [a]



B-H acetate	R_1	R_2	R_3	Product[b]	Yield (%)[c]	Mp (^{0}C)
125a	H	H	Et	**127**[d]	62	198-200
125b	H	H	Me	**128**	68	216-218 (dec.)
125c	Br	H	Me	**129**	63	246-248 (dec.)
125d	Cl	H	Me	**130**	57	250-252
125e	OMe	OMe	Me	**131**	59	232-234 (dec.)
125f	OMe	OMe	Et	**132**	64	210-212

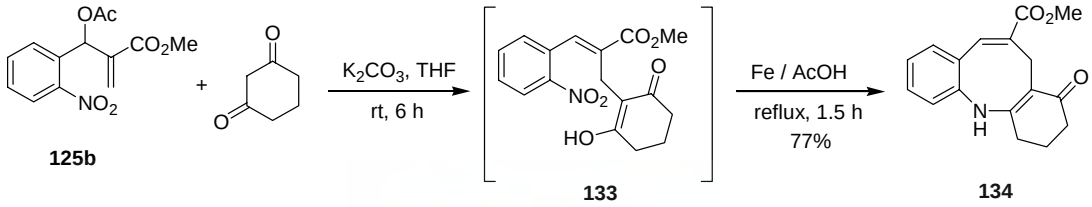
(a) All reactions were carried out on 1 mmol scale of Baylis-Hillman acetate (**125a-f)** with 1 mmol of 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3 (1 mmol) in THF at room temperature for 2 h followed by reductive cyclization using Fe / AcOH at reflux temperature for 1.5 h.
(b) All compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.
(c) Isolated yields of the pure products based on Baylis-Hillman acetates.
(d) Structure of this molecule was further confirmed by single-crystal X-ray data.

With a view to understand the generality of this reaction strategy, we have selected 1,3-cyclohexanedione as a nucleophile. Thus, treatment of methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125b**) with 1,3-cyclohexanedione in the presence of K_2CO_3 followed by reduction and cyclization using Fe / AcOH provided 2-aza-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,16-pentaen-7-one (**134**)$^{\pi}$ in 77% isolated yield (Scheme 55).

$^{\pi}$ For continuity and better understanding we have numbered hexahydrodibenz[*b,g*]azocine derivatives obtained from B-H acetates (**125b-e**) and 1,3-cyclohexanedione as **134-137** respectively.

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

Scheme 55



Then, we have subjected the Baylis-Hillman acetates (**125c-e**) for alkylation with 1,3-cyclohexanedione as a nucleophile followed by reduction and cyclization using Fe / AcOH which provided the [6-8-6] tricyclic heterocyclic molecules containing azocine moiety as the central ring (**135-137**) in 56-66% isolated yields (Table 3). All the compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses. In fact we obtained the single-crystal for the compound (**137**) and further confirmed by single-crystal X-ray data (see Figure 11 for ORTEP diagram of compound **137**, Table II).

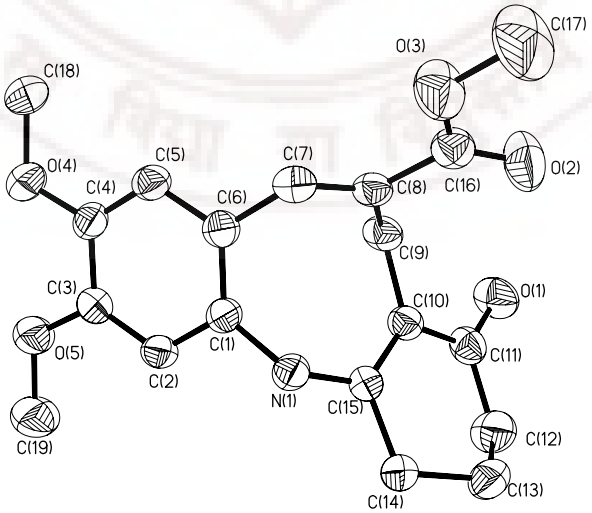
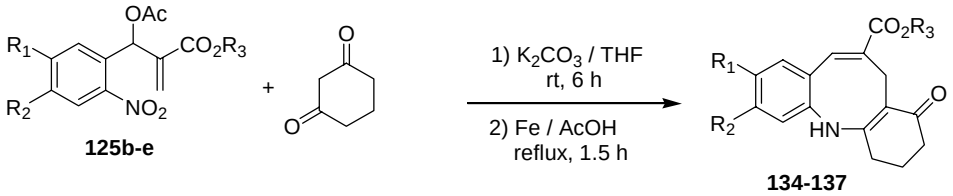


Figure 11. ORTEP diagram of compound **137**
(Hydrogen atoms were omitted for clarity)

Table II: Crystal data collection and structure refinement for the compound **137**

Empirical formula	: $C_{19}H_{21}NO_5$
Formula weight	: 343.37
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: monoclinic
Space group	: *P 21/n*
Unit cell dimensions	: a = 9.3008 (13) Å; α = 90 deg.
	: b = 13.4894 (19) Å; β = 92.959 (3) deg.
	: c = 13.871 (2) Å; γ = 90 deg.
Volume	: 1738.0 (4) $Å^3$
Z, Calculated density	: 4, 1.312 g/cm^3
Absorption coefficient	: 0.095 mm^{-1}
F(000)	: 728
Crystal size	: 0.38 X 0.25 X 0.18 mm
Theta range for data collection	: 2.11 to 25.90 deg.
Limiting indices	: $-11 \le h \le 11, -16 \le k \le 16, -17 \le l \le 16$
Reflections collected / unique	: 9216 / 3365 [R(int) = 0.0373]
Completeness to theta = 25.90	: 99.8%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3365 / 0 / 229
Goodness-of-fit on F^2	: 0.941
Final R indices [I>2sigma(I)]	: R1 = 0.0432, wR2 = 0.1060
R indices (all data)	: R1 = 0.0656, wR2 = 0.1153
Largest diff. peak and hole	: 0.378 and -0.312 e. $Å^{-3}$

Table 3. Synthesis of [6-8-6] Tricyclic Framework Containing Azocine Moiety *via* the Reaction of Baylis-Hillman Acetates (125b-e) with 1,3-Cyclohexanedione.[a]



B-H acetate	R_1	R_2	R_3	Product[b]	Yield (%)[c]	Mp (^{0}C)
125b	H	H	Me	**134**	77	208-210
125c	Br	H	Me	**135**	66	258-260 (dec.)
125d	Cl	H	Me	**136**	56	252-254 (dec.)
125e	OMe	OMe	Me	**137**[d]	62	270-272

(a) All reactions were carried out on 1 mmol scale of Baylis-Hillman acetate (**125b-e)** with 1 mmol of 1,3-cyclohexanedione in the presence of K_2CO_3 (1 mmol) in THF at room temperature for 6 h followed by reductive cyclization using Fe / AcOH at reflux for 1.5 h.
(b) All compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.
(c) Isolated yields of the pure products based on Baylis-Hillman acetates.
(d) Structure of this molecule was further confirmed by single-crystal X-ray data.

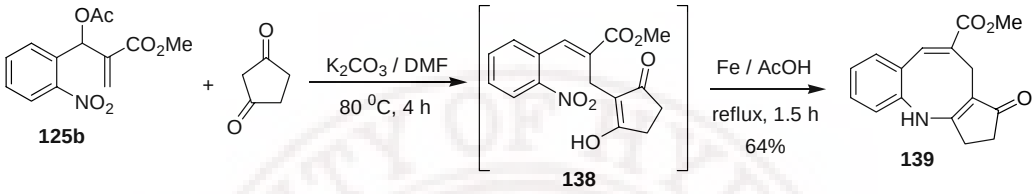
Synthesis of [6-8-5] frameworks containing azocine moiety as a central ring:

With a view to extend this strategy for obtaining [6-8-5] ring system, we employed 1,3-cyclopentanedione as a nucleophile. Thus the reaction of 1,3-cyclopentanedione with methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125b**) in the presence of potassium carbonate followed by reductive cyclization using Fe / AcOH provided the desired tricyclic molecule *i.e.* 2-aza-10-methoxycarbonyltricyclo[10.3.0.0^{3,8}]penta-deca-1(12),3,5,7,9-pentaen-13-one (**139**)[μ,σ] in 64% isolated yield (Scheme 56).

[μ] For easy understanding and continuity we have numbered [6-8-5] frameworks containing azocine moiety, obtained from B-H acetates **125b** & **125d** and 1,3-cyclopentanedione as **139** & **140** respectively.
[σ] These reactions were carried out in DMF because in THF these were very sluggish probably because of solubility problems.

Structure of this product was confirmed by IR, ^{1}H NMR (spectrum 9), ^{13}C NMR (spectrum 10), mass spectral data and elemental analysis. We have also further confirmed the structure of the molecule (**139**) by single-crystal X-ray data (see Figure 12 for ORTEP diagram of molecule **139**, Table III).

Scheme 56



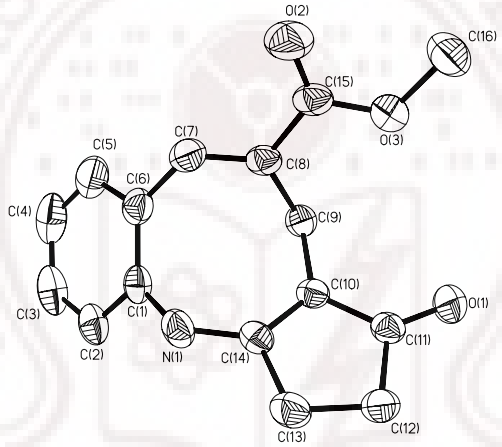
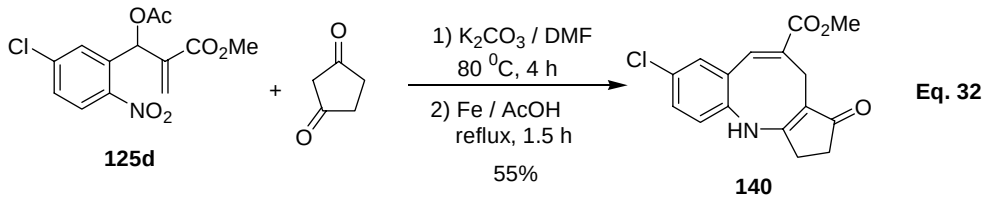


Figure 12 ORTEP diagram of compound **139**
(Hydrogen atoms were omitted for clarity)

To understand the generality of this methodology, we have also subjected methyl 3-acetoxy-3-(5-chloro-2-nitrophenyl)-2-methylenepropanoate (**125d**) to the reaction with 1,3-cyclopentanedione. The resulting product, 2-aza-6-chloro-10-methoxycarbonyltri-cyclo[10.3.0.0^{3,8}]pentadeca-1(12),3,5,7,9-pentaen-13-one (**140**) was obtained in 55% isolated yield (Eq. 32). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.

Table III: Crystal data collection and structure refinement for the compound **139**

Empirical formula	: $C_{16}H_{15}NO_3$
Formula weight	: 269.29
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: monoclinic
Space group	: *C 2/c*
Unit cell dimensions	: a = 28.377 (5) Å; α = 90 deg.
	: b = 7.1394 (12) Å; β = 121.081 (2) deg.
	: c = *15.034* (3) Å; γ = 90 deg.
Volume	: 2608.6 (8) $Å^3$
Z, Calculated density	: 8, 1.371 g/cm^3
Absorption coefficient	: 0.095 mm^{-1}
F(000)	: 1136
Crystal size	: 0.48 X 0.25 X 0.03 mm
Theta range for data collection	: 1.68 to 25.82 deg.
Limiting indices	: $-34 \le h \le 34, -8 \le k \le 8, -18 \le l \le 18$
Reflections collected / unique	: 12609 / 2503 [R(int) = 0.0608]
Completeness to theta = 25.82	: 99.5%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2503 / 0 / 182
Goodness-of-fit on F^2	: 0.995
Final R indices [I>2sigma(I)]	: R1 = 0.0483, wR2 = 0.1063
R indices (all data)	: R1 = 0.0765, wR2 = 0.1160
Largest diff. peak and hole	: 0.293 and -0.236 e. $Å^{-3}$

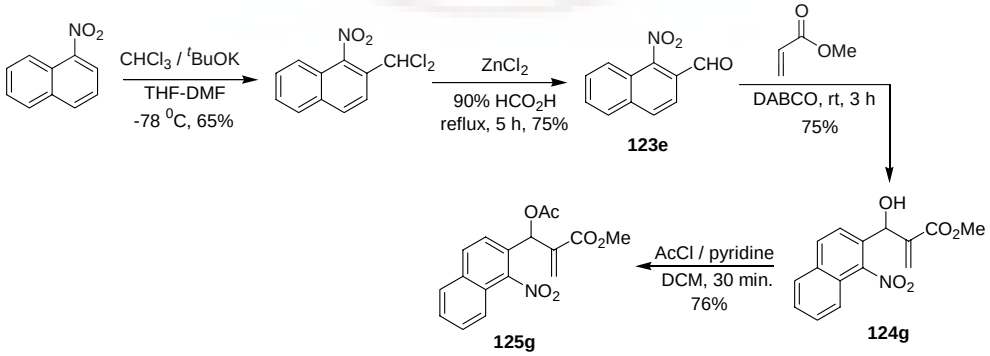


Synthesis of tetracyclic heterocyclic molecules containing azocine moiety:

After demonstrating a methodology for the synthesis of [6-8-6] / [6-8-5] frameworks containing azocine moiety as the central ring, we have directed our studies towards the synthesis of tetracyclic framework containing azocine moiety. For this purpose we have selected methyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**125g**)[ξ] as an alkylator, which was prepared from the corresponding Baylis-Hillman alcohol (methyl 3-hydroxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate, **124g**).[ξ] This alcohol was obtained *via* the coupling of 1-nitro-2-naphthaldehyde (**123e**) with methyl acrylate under the influence of DABCO (Scheme 57).

The required 1-nitro-2-naphthaldehyde (**123e**) was prepared according to Scheme 57. The reaction of 1-nitronaphthalene with chloroform in the presence of potassium *tert*-butoxide followed by hydrolysis using $ZnCl_2$ provided 1-nitro-2-naphthaldehyde (**123e**) in 75% isolated yield.[240]

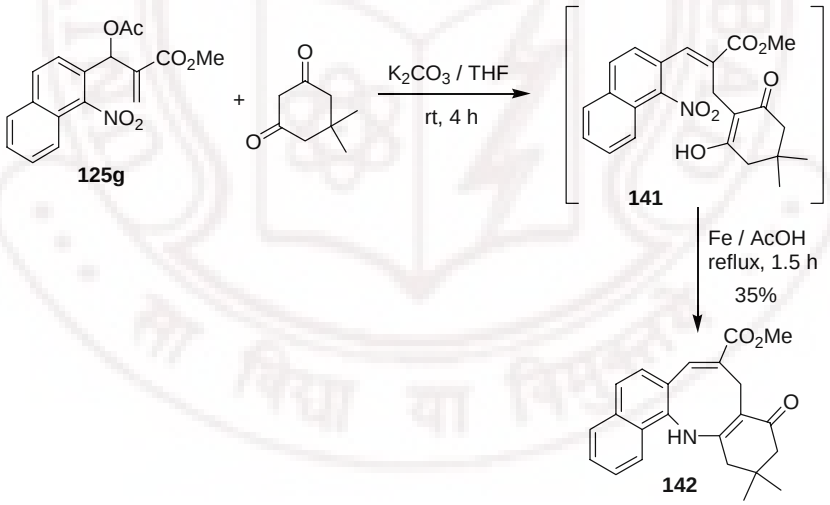
Scheme 57



[ξ] For continuity and better understanding we have numbered the B-H alcohols, B-H acetates obtained from 1-nitro-2-naphthaldehyde (**123e**) with methyl acrylate as **124g** and **125 g** respectively.

Treatment of methyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**125g**) with 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3 followed by reduction and cyclization using Fe / AcOH provided 2-aza-19,19-dimethyl-14-methoxycarbonyltetracyclo[14.4.0.0.^{3,12}0^{4,9}]eicosa-1(16),3,5,7,9,11,13-heptaen-17-one (**142**)[ψ] was obtained in 35% isolated yield (Scheme 58). Structure of this compound was fully characterized by IR, ^{1}H NMR (See: spectra 11 at rt, spectra 11a at -30 ^{0}C), ^{13}C NMR (See: spectra 12 at rt, spectra 12a at -30 ^{0}C, for DEPT 135, spectra 13 at -30 ^{0}C), mass spectral data and elemental analysis. In fact we have further confirmed the structure of this compound by single-crystal X-ray data (see Figure 13 for ORTEP diagram of compound **142**, Table IV).

Scheme 58



To examine whether the reaction was more facile and the yield of **142** would be higher using a stepwise method, we also isolated the trisubstituted alkene (**141**) in 73% isolated yield after the usual workup followed by column chromatography.

[ψ] For easy understanding and continuity we have numbered tetracyclic azocine moiety obtained from B-H acetate (**125g**) and dimedone as **142**.

Subsequent treatment of trisubstituted alkene with Fe/AcOH at reflux temperature for 1.5 h provided the desired tetracyclic azocine moiety **142** in 51% isolated yield (37% overall yield). These results clearly show that there is not much difference between two-pot and one-pot methodologies.

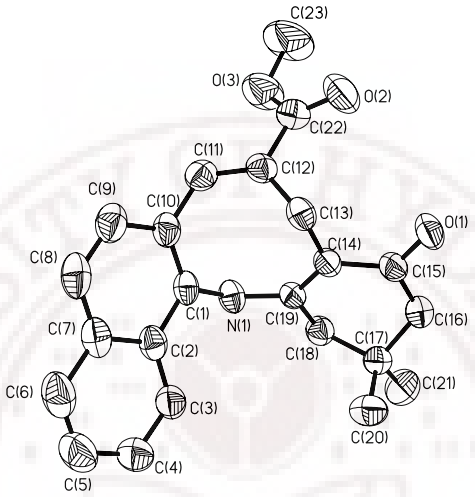
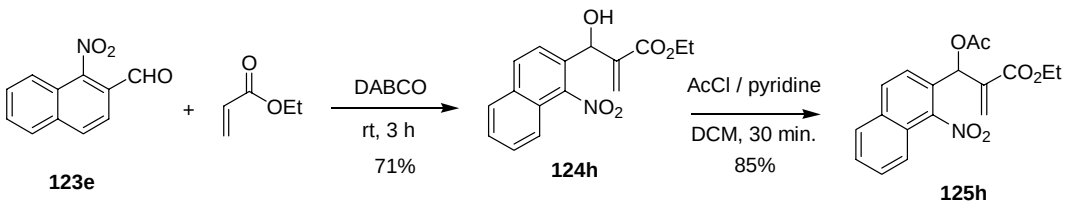


Figure 13 ORTEP diagram of compound **142**
(Hydrogen atoms were omitted for clarity)

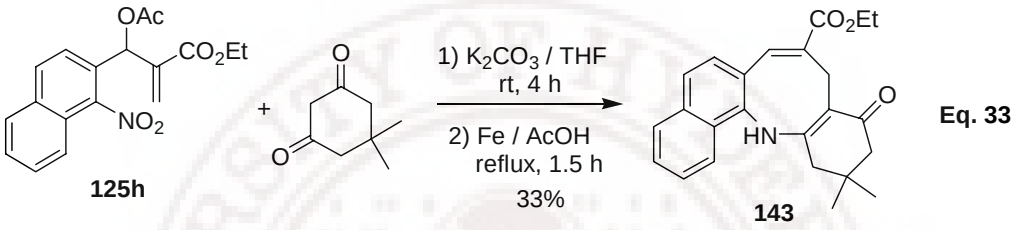
With a view to understand the generality, we have selected the Baylis-Hillman acetate, ethyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**125h**)[η] as an alkylator in the reaction strategy. The required acetate was prepared from the corresponding Baylis-Hillman alcohol (**124h**),[η] obtained *via* the coupling of 1-nitro-2-naphthaldehyde (**123e**) with ethyl acrylate according to Scheme 59.

Scheme 59



[η] For continuity and easy understanding we have numbered B-H alcohols and B-H acetates obtained from 1-nitro-2-naphthaldehyde (**123e**) with ethyl acrylate as **124h** and **125h** respectively.

Thus the treatment of Baylis-Hillman acetate (**125h**) with 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3 followed by reduction and cyclization using Fe / AcOH provided 2-aza-19,19-dimethyl-14-ethoxycarbonyltetracyclo[14.4.0.-0.^{3,12}0^{4,9}]eicosa-1(16),3,5,7,9,11,13-heptaen-17-one (**143**)$^{\kappa}$ in 33% isolated yield (Eq. 33). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.



Eq. 33

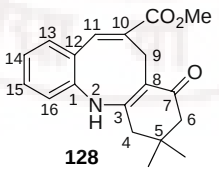
Interesting Observations in NMR Spectra:

We have noticed an interesting observation regarding the appearance of *gem*-dimethyl protons / carbons in NMR spectra for compounds **127-132**, **142**, and **143**. The *gem*-dimethyl protons in compounds **127-132** appeared as singlet in the region δ 1.01-1.03 while in the case of compounds **142** and **143** they appeared as singlets at δ 1.10 and 1.11 respectively, in ^{1}H NMR spectra at room temperature. In the ^{13}C NMR spectrum at room temperature *gem*-dimethyl carbons appeared as small peaks in the region δ 27.86-28.06 in the case of compounds **127-132** while in compounds **142** and **143** similar carbons appeared as a broad peak at δ 28.40 and 27.38, respectively, with low intensity in comparison with that of quaternary carbon (further confirmed by DEPT 135 and a hetero COSY experiment in the case of compound **128**) at room temperature.

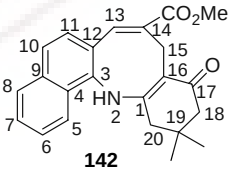
$^{\kappa}$ For better understanding we have numbered the tetracyclic azocine moiety obtained from the B-H acetate (**125h**) and dimedone as **143**.

This interesting appearance of *gem*-dimethyl carbons in the ^{13}C NMR spectra at room temperature led us to examine the NMR spectra at low temperatures to understand the conformational rigidity / flexibility. We have selected two compounds (**128** and **142**) for low temperature NMR studies. The *gem*-dimethyl protons (which appeared as singlet at room temperature) appeared as two singlets in the ^{1}H NMR spectra at -30 °C and *gem*-dimethyl carbons (which appeared as a small / broad peak at room temperature) appeared as two peaks in the ^{13}C NMR spectra at -30 °C in both compounds **128** and **142** (Table 4). We have also observed an interesting splitting pattern for three methylene groups at C-4, C-6, and C-9 (for compound **128**) and at C-15, C-18, and C-20 (for compound **142**) in the ^{1}H NMR spectrum from room temperature to -30 °C & -40 °C for compound **128** and room temperature to -30 °C for compound **142**. From these observations it appears that these compounds have conformational rigidity at low temperature, while at room temperature there may be conformational flexibility that resulted in broadening of the signals.

Table 4. Appearance and Chemical Shift Values of *gem*-Dimethyl Protons / Carbons in ^{1}H and ^{13}C NMR Spectra at Room Temperature and -30 °C for the compounds **128** and **142**.



128



142

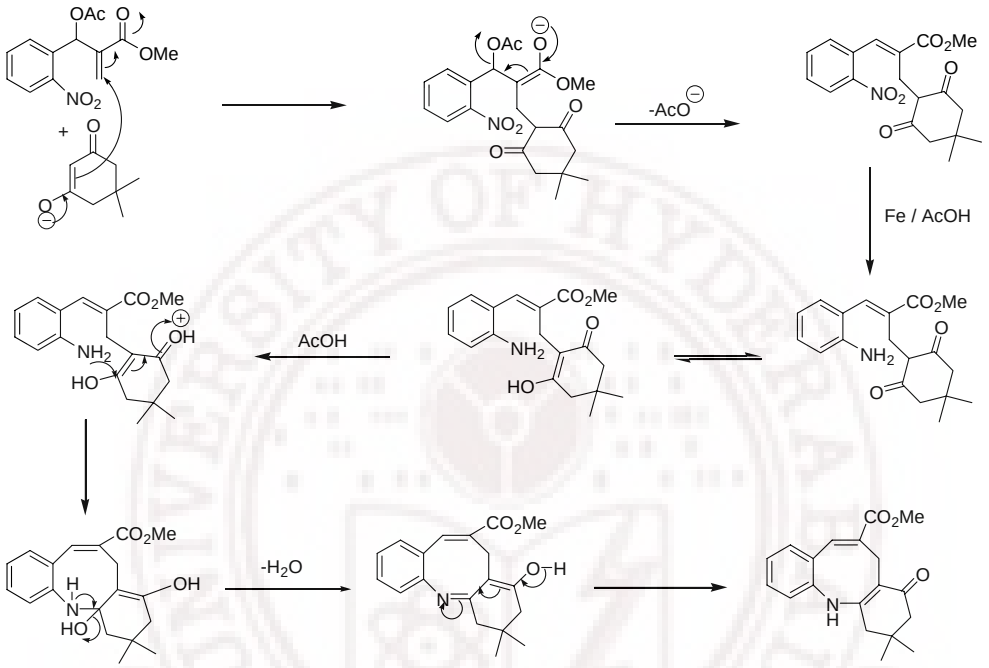
^{1}H NMR	room temperature	δ 1.02 (s)	δ 1.10 (s)
	-30 ^{0}C	δ 0.96 (s) and 1.05 (s)	δ 1.01 (s) and 1.15 (s)
^{13}C NMR	room temperature	δ 27.86	δ 28.40
	-30 ^{0}C	δ 25.84 and 29.83	δ 25.86 and 29.95

Table IV: Crystal data collection and structure refinement for the compound **142**

Empirical formula	: $C_{23}H_{23}NO_3$
Formula weight	: 361.42
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: monoclinic
Space group	: *P 21/c*
Unit cell dimensions	: a = 11.060 (2) Å; α = 90 deg.
	: b = 13.996 (3) Å; β = 112.323 (3) deg.
	: c = 13.578 (3) Å; γ = 90 deg.
Volume	: 1944.3 (6) $Å^3$
Z, Calculated density	: 4, 1.235 g/cm^3
Absorption coefficient	: 0.081 mm^{-1}
F(000)	: 768
Crystal size	: 0.42 X 0.10 X 0.04 mm
Theta range for data collection	: 1.99 to 26.03 deg.
Limiting indices	: $-13 \le h \le 13, -17 \le k \le 17, -16 \le l \le 16$
Reflections collected / unique	: 19802 / 3835 [R(int) = 0.0613]
Completeness to theta = 26.03	: 99.8%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3835 / 0 / 247
Goodness-of-fit on F^2	: 0.870
Final R indices [I>2sigma(I)]	: R1 = 0.0434, wR2 = 0.0917
R indices (all data)	: R1 = 0.0999, wR2 = 0.1071
Largest diff. peak and hole	: 0.197 and -0.186 e. $Å^{-3}$

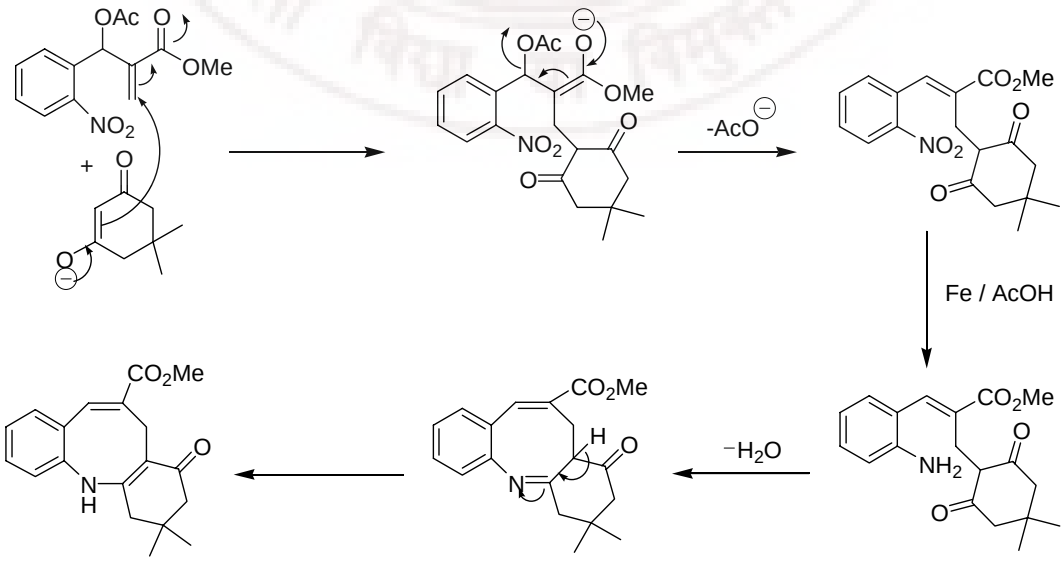
A plausible mechanism for this interesting transformation (taking **125b** as the Baylis-Hillman acetate and dimedone as the alkylating agent as a model case) is presented in Scheme 60, and also simplified mechanism was presented in Scheme 61.

Scheme 60



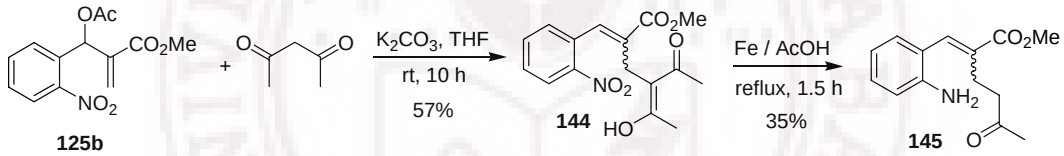
Simplified Mechanism:

Scheme 61



We have also examined the applicability of acyclic dione, that is, 2,4-pentanedione as a nucleophile. Thus the treatment of Baylis-Hillman acetate (**125b**) with 2,4-pentanedione in the presence of K_2CO_3 provided the trisubstituted alkene (**144**) in 57% isolated yield as a mixture of *E/Z* isomers *E:Z* = 78:22) [cyclicdiones provide very minor amounts of (*Z*)-isomer (<5%)]. Subsequent treatment of this trisubstituted alkene (containing *E/Z* isomers) with Fe / AcOH at reflux temperature did not provide the expected azocine moiety but resulted in the formation of (*E/Z)*-6-(2-aminophenyl)-5-methoxycarbonylhexan-2-one (**145**)[3] [reduced and mono deacetylated product] along with minor impurities (Scheme 62).

Scheme 62



In conclusion, we have developed a facile, convenient synthesis of functionalized tri / tetracyclic frameworks containing an important azocine moiety thus demonstrating the applications of the Baylis-Hillman adducts as valuable source for one-pot multistep protocol for synthesis of important and useful structural frameworks.

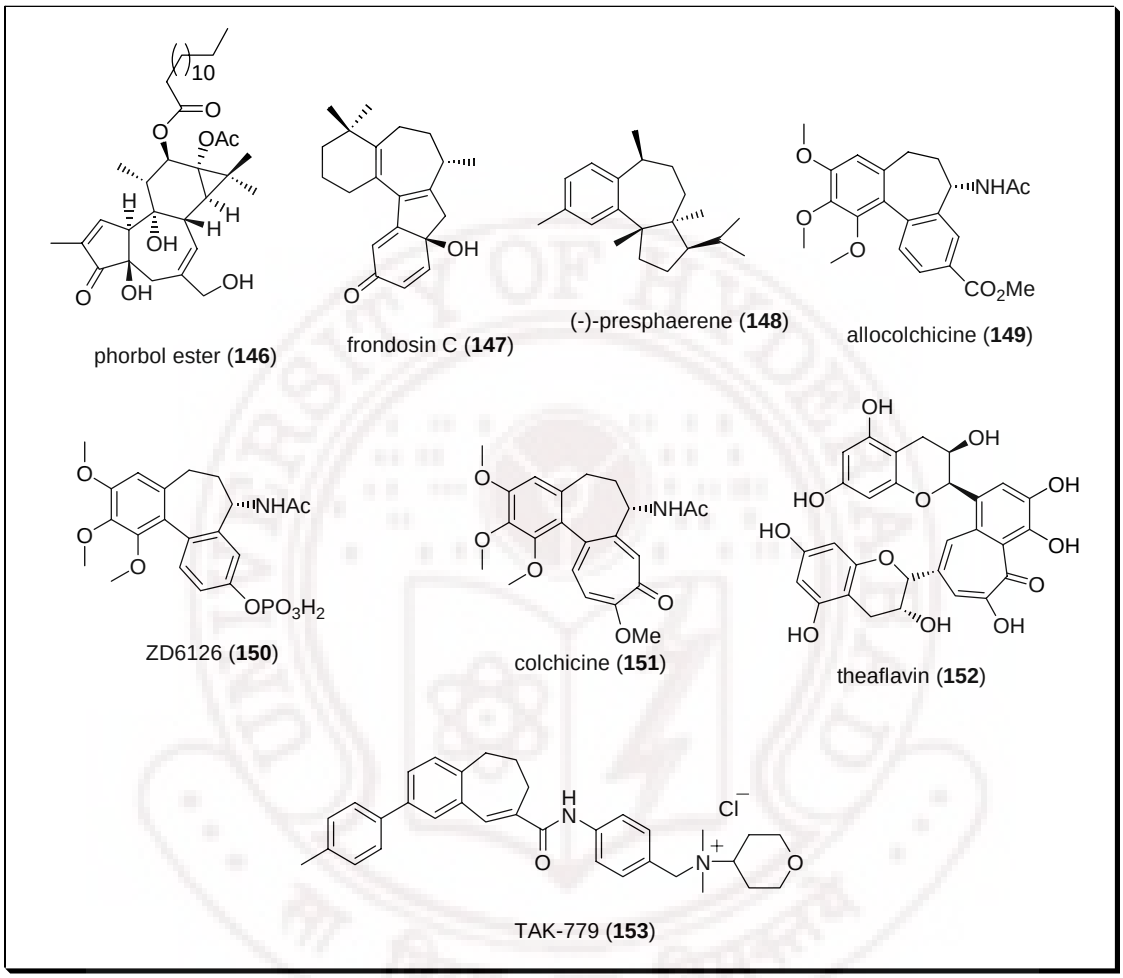
[3] For continuity and easy understanding we have numbered (*E)*-6-(2-aminophenyl)-5-methoxycarbonyl-hexan-2-one obtained from B-H acetate (**125b**) and 2,4-pentanedione as **145**.

Simple, one-pot and facile synthesis of angularly fused [6-7-5], [6-7-6], [6-7-7] and [6,7] ring systems using Baylis-Hillman acetates

After developing a facile one-pot methodology for obtaining [6-8-6] / [6-8-5] ring systems using the Baylis-Hillman acetates, we have directed our studies towards the development of angularly fused tricyclic carbocyclic molecules containing the cyclo-heptane as the central ring *i.e.* [6-7-5], [6-7-6], [6-7-7] and bicyclic molecules *i.e.* [6,7] ring systems using the Baylis-Hillman adducts as the starting material in one-pot operation. The angularly fused tricyclic carbocyclic framework containing cycloheptane as the central ring has a special and respectable place in the history of carbocyclic rings, due to the presence of this tricyclic framework in various natural products and bioactive molecules. For example, an angularly fused [6-7-5] carbocyclic skeleton is the core structure present in several natural products and bioactive molecules such as phorbol esters (**146**),[241] frondosin C (**147**),[242] and (−)-presphaerene (**148**).[243] An angularly fused [6-7-6] tricyclic system is present in biologically active compounds such as allocolchicine (**149**),[244] colchinol derivative ZD6126 (**150**)[245] while an angularly fused [6-7-7] tricyclic ring system is an integral part of the well known alkaloid colchicine (**151**).[246] Important bioactive compounds such as theaflavin (**152**),[247,248] and TAK-779 (**153**)[249,250] contain the [6,7] bicyclic carbocyclic ring framework. Because of the remarkable medicinal importance of these fused ring frameworks (Figure 14) and also because of unfavorable entropic factors in synthesizing seven membered rings, development of efficient protocols for the synthesis of such fused carbocyclic frameworks having cycloheptane as the key central

ring, has been and continues to be one of the attractive and challenging areas in carbocyclic chemistry.

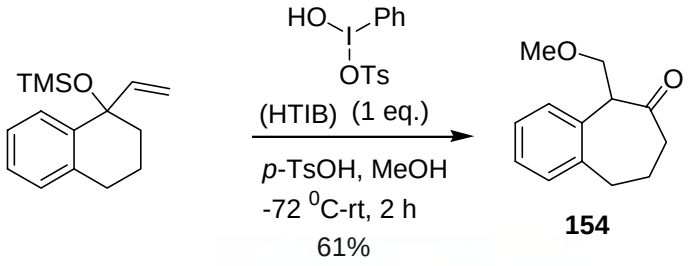
Figure 14



High applicability of these molecules with medicinal importance demands the development of simple and easy methodologies for the synthesis of seven membered carbocycles. Synthetic chemists developed various strategies / methodologies for the synthesis of seven membered carbocycles. Some recent and important strategies are presented in this section (Schemes 63, 64 & Eqs. 34-36).

Silva and coworkers[251] have reported the synthesis of seven membered carbocycles (**154**) by ring expansion of 1-vinylcycloalkanols (or the corresponding silyl ethers)

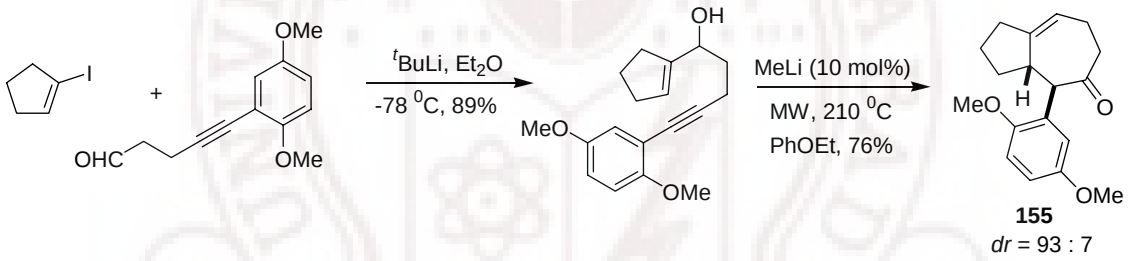
mediated by the hypervalent iodine reagent (HTIB) [hydroxy(tosyloxy)-iodobenzene] as shown in Eq. 34.



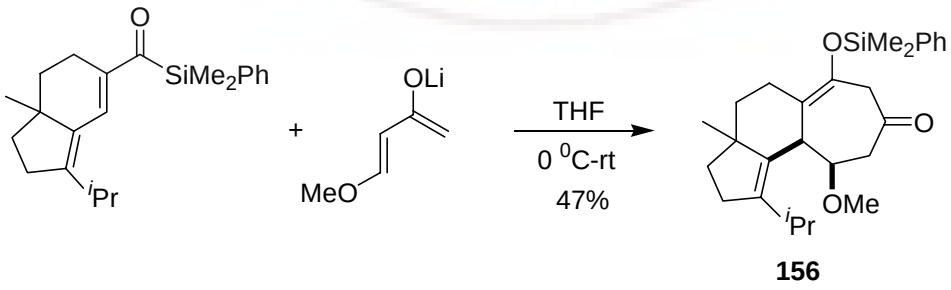
Eq. 34

An important synthesis of substituted cyclohept-4-enone derivatives (**155**) *via* a microwave-assisted tandem oxyanionic 5-*exo* cyclization / Claisen rearrangement sequence was reported according to Scheme 63, by Li and coworkers.[252]

Scheme 63



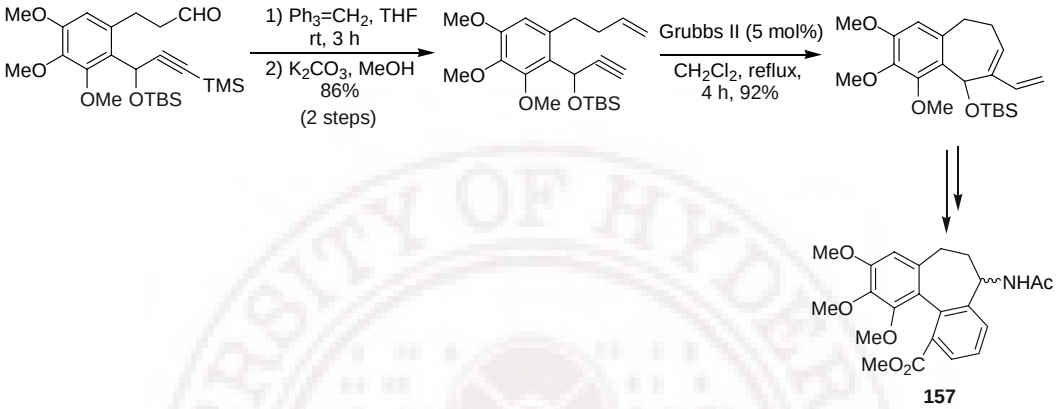
Takeda and coworkers[253] have reported an interesting synthesis of fused cycloheptane frameworks (**156**) using Brook rearrangement-mediated [3 + 4] annulation, as the key step, following the reaction sequence as shown in Eq. 35.



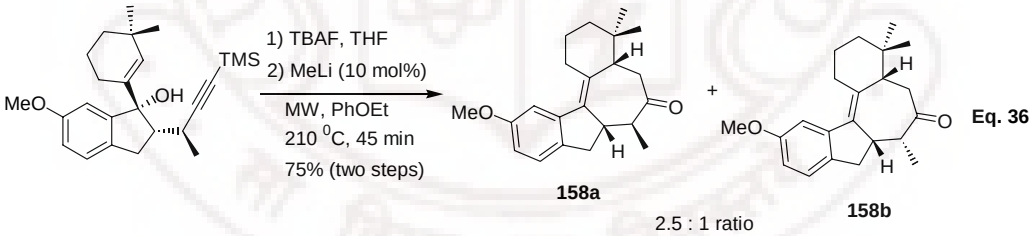
Eq. 35

Hanna and coworkers[254] have reported the synthesis of allocolchicine (**157**) [containing seven-member ring] using the enyne ring-closing metathesis as the key step following the reaction sequence as described in Scheme 64.

Scheme 64



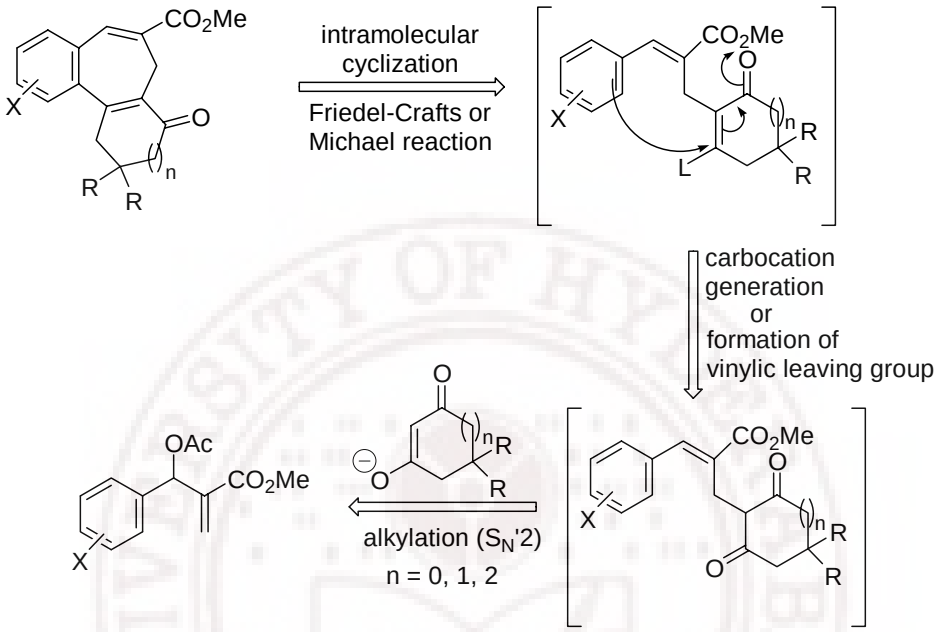
A straightforward synthesis of frondosin C (**158a** & **158b**) (containing seven membered ring), involving the strategy of one-pot, microwave-assisted 5-exo cyclization-Claisen rearrangement was described by Ovaska and coworkers (Eq. 36).[255]



We envisioned that Baylis-Hillman acetates would be excellent synthons (or alkylators) for one-pot multistep synthesis of all the three ([6-7-5], [6-7-6], and [6-7-7]) tricyclic carbocyclic frameworks. Accordingly, we planned a retro-synthetic strategy involving alkylation of suitable cyclic 1,3-diones with appropriate Baylis-Hillman acetates followed by intramolecular cyclization (*via* Friedel-Crafts or Michael reaction) after *in situ* generation of carbocation according to the reaction sequence described in Scheme 65.

General retro-synthetic strategy for the synthesis of [6-7-5], [6-7-6], and [6-7-7] carbocyclic frameworks:

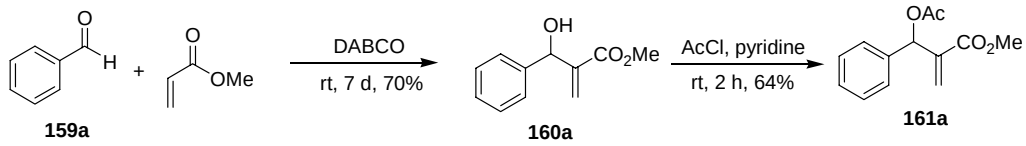
Scheme 65



Towards synthesis of [6-7-6] carbocyclic frameworks:

Accordingly, we have first focussed our attention for the development of simple methodology for the synthesis of [6-7-6] carbocyclic frameworks using the Baylis-Hillman acetates as the starting material. Thus, we have first selected methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**161a**) and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) as reaction partners. The required methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**161a**)[ρ] was prepared *via* the acetylation of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**160a**)[ρ], which was obtained *via* the Baylis-Hillman coupling of benzaldehyde (**159a**)[ρ] and methyl acrylate in the presence of DABCO (Scheme 66).

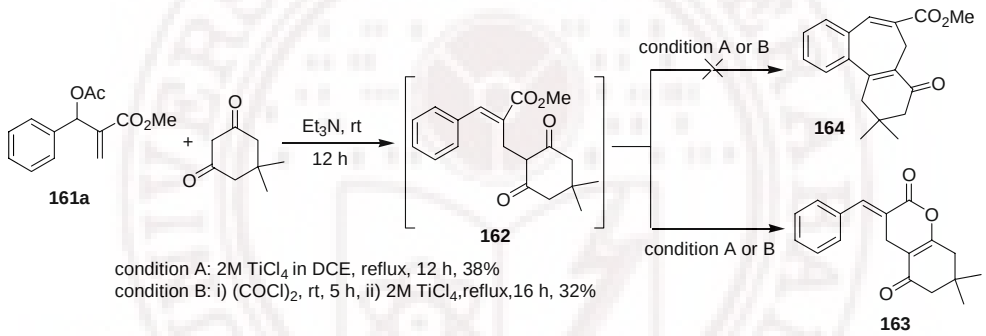
Scheme 66



159a **160a** **161a**

Our attempts to obtain the desired [6-7-6] tricyclic carbocyclic molecule (**164**) under various conditions were not successful as (*E*)-4-benzylidene-9,9-dimethyl-2-oxabicyclo[4.4.0]dec-1(6)-ene-3,7-dione (**163**)[c] was obtained as the major product (Scheme 67).

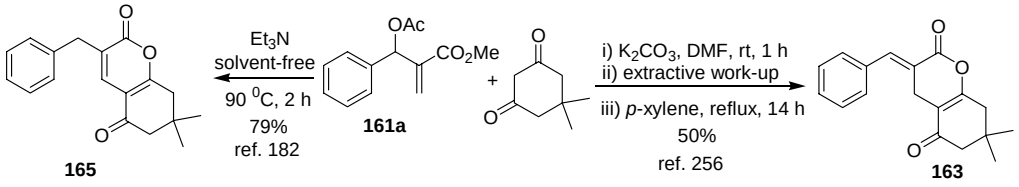
Scheme 67



161a **162** **164** **163**

It is worth mentioning here that Su[182] and Kim[256] have independently reported the synthesis of **163** and **165** according to Scheme 68. For the compound **163**, melting point, ^{1}H NMR and ^{13}C NMR are reported. Our data is in agreement with that of literature data.[182,256]

Scheme 68

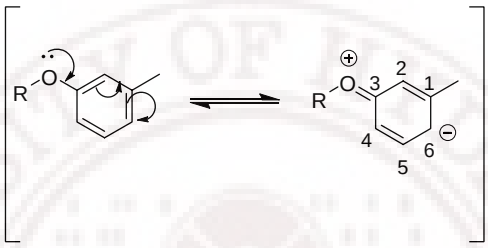


165 **161a** **163**

[ρ] For easy understanding and continuation we have numbered various aromatic aldehydes (phenyl and alkoxyphenyl), B-H alcohols and B-H acetates as **159**, **160** and **161** respectively.
[c] For better understanding we have numbered coumarin derivative obtained from B-H acetate (**161a**) and dimedone as **163**.

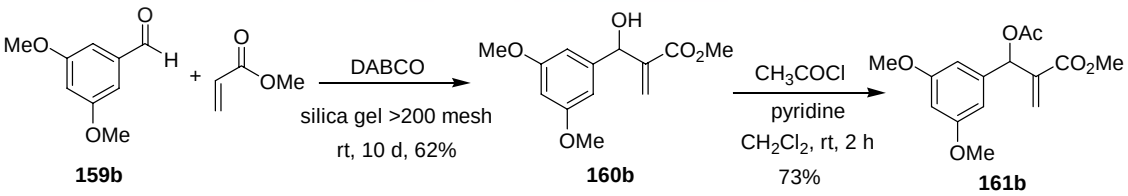
Based on our earlier studies[190,257] it occurred to us that the presence of electron donating group at 3rd / 5th position on aromatic ring of BH acetate would help in increasing electron density at 6th position thereby facilitating the intramolecular cyclization (Friedel-Crafts or Michael reaction) [Figure 15].

Figure 15



Therefore, we have selected methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methyl-enepropanoate (**161b**) as a reaction partner with dimedone. The required acetate, was prepared *via* the acetylation of the Baylis-Hillman alcohol (**160b**) according to Scheme 69. The desired Baylis-Hillman adduct, *i.e.* methyl 3-(3,5-dimethoxyphenyl)-3-hydro-xy-2-methylenepropanoate (**160b**), in turn was obtained *via* the treatment of 3,5-dimethoxybenzaldehyde (**159b**) with methyl acrylate in the presence of DABCO as described in Scheme 69.

Scheme 69



We have performed the reaction between Baylis-Hillman acetate (**161b**) and dimedone under different conditions (Table 5) and realized that the Baylis-Hillman acetate (**161b**)

provided expected [6-7-6] tricyclic carbocyclic framework (entry 10, Table 5). Thus, treatment of **161b** (1 mmol) with dimedone (1 mmol) in the presence of Et_3N provided the alkylated product which (after removal of excess triethylamine) on reaction with oxalyl chloride (5 mmol) generated *in situ* the corresponding vinyl chloride. Subsequent intramolecular cyclization (Friedel-Crafts or Michael reaction) was performed using $TiCl_4$ (2 mmol, 2M solution in DCE) in 1,2-dichloroethane (DCE) as the Lewis acid at room temperature for 4 h (after removal of DCM and oxalyl chloride under reduced pressure) to provide the desired [6-7-6] tricyclic carbocyclic molecule *i.e.* 13,15-dimethoxy-4,4-dimethyl-9-methoxycarbonyltricyclo[9.4.0.$0^{2,7}$]pentadeca-1(15),2(7),9,11,13-pentaen-6-one (**168**)[$] in 72% isolated yield after usual work up followed by column chromatography. Structure of this molecule was established by IR, ^{1}H NMR (spectrum 14), ^{13}C NMR (spectrum 15), mass spectral data and elemental analysis. Structure of this molecule was further confirmed by single crystal X-ray data (see Figure 16 for ORTEP diagram of molecule **168**, Table V).

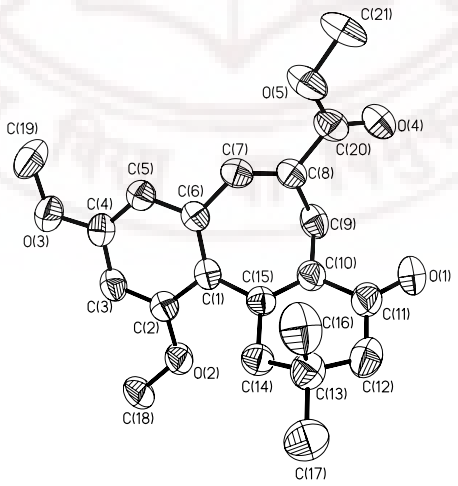
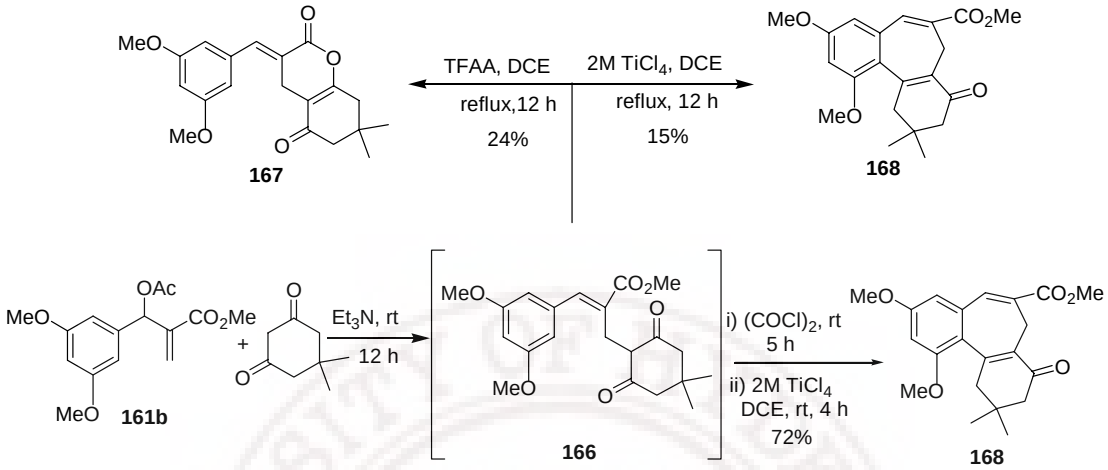


Figure 16 ORTEP diagram of compound **168**
(*Hydrogen atoms were omitted for clarity*)

[$] For continuity and better understanding we have numbered [6-7-6] carbocyclic frameworks obtained from B-H acetates **161b** & **161c** and dimedone as **168** & **169** respectively and [6-7-6] carbocyclic frameworks obtained from B-H acetates **161b-d** with 1,3-cyclohexanedione as **170-172** respectively.

Table 5. Reaction optimization: Synthesis of angularly fused [6-7-6] ring system *via* the reaction of **161b** with dimedone[a]



Entry	Conditon(s)	Product	Yield (%)
1	i) Et_3N, rt, 12 h, ii) TFAA, rt, 6 h[b]	---	---
2	i) Et_3N, rt, 12 h, ii) TFAA, reflux, 12 h	**167**	24
3	i) Et_3N, rt, 12 h, ii) $MeSO_3H$, rt, 6 h[b]	---	---
4	i) Et_3N, rt, 12 h, ii) $MeSO_3H$, reflux, 12 h[c]	---	---
5	i) Et_3N, rt, 12 h, ii) Triflic acid, rt, 6 h[b]	---	---
6	i) Et_3N, rt, 12 h, ii) Triflic acid, reflux, 12 h[c]	---	---
7	i) Et_3N, rt, 12 h, ii) $POCl_3$, rt, 6 h[b]	---	---
8	i) Et_3N, rt, 12 h, ii) $POCl_3$, reflux, 10 h[c]	---	---
9	i) Et_3N, rt, 12 h, ii) 2M $TiCl_4$, reflux,12 h	**168**	15
10	i) Et_3N, rt, 12 h, ii) $(COCl)_2$, rt, 5 h, iii) 2M $TiCl_4$, rt, 4 h	**168**	72

(a) All reactions were carried out on 1 mmol scale of Baylis-Hillman acetate **161b** with 1 mmol of dimedone.
(b) At room temperature almost all the alkylated product was intact as evidenced by TLC examination.
(c) Reaction was not clean.

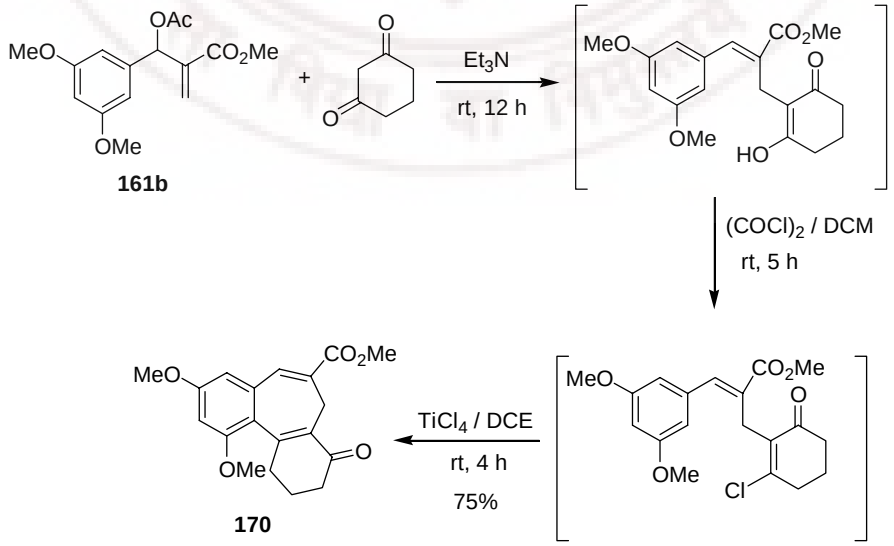
Table V: Crystal data collection and structure refinement for the compound **168**

Empirical formula	: $C_{21}H_{24}O_5$
Formula weight	: 356.40
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: monoclinic,
Space group	: *P 21/c*
Unit cell dimensions	: a = 11.868(6) Å; α = 90 deg.
	: b = 17.734(9) Å; β = 102.171(10) deg.
	: c = 9.363(5) Å; γ = 90 deg.
Volume	: 1926.3(16) $Å^3$
Z, Calculated density	: 4, 1.229 g / cm^3
Absorption coefficient	: 0.087 mm^{-1}
F(000)	: 760
Crystal size	: 0.36 X 0.22 X 0.14 mm
Theta range for data collection	: 1.76 to 26.25 deg.
Limiting indices	: $-14 \le h \le 14, -21 \le k \le 21, -11 \le l \le 11$
Reflections collected / unique	: 19893 / 3828 [R(int) = 0.0824]
Completeness to theta = 26.25	: 98.6%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3828 / 0 / 240
Goodness-of-fit on F^2	: 0.946
Final R indices [I>2sigma(I)]	: R1 = 0.0543, wR2 = 0.1123
R indices (all data)	: R1 = 0.0876, wR2 = 0.1502
Largest diff. peak and hole	: 0.206 and -0.200 e. $Å^{-3}$

To understand the generality of this reaction strategy, we have next selected another acetate (**161c**) of the B-H alcohol (**160c**) for reaction with dimedone. The required alcohol *i.e.* methyl 3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**160c**) was prepared *via* the coupling of 3-methoxybenzaldehyde (**159c**) with methyl acrylate under the influence of DABCO (Table 6). We have then subjected the Baylis-Hillman acetate (**161c**) to the reaction with 5,5-dimethyl 1,3-cyclohexanedione (dimedone) to obtain the 4,4-dimethyl-13-methoxy-9-methoxycarbonyltricyclo[9.4.0.$0^{2,7}$]pentadeca-1(15),2(7),-9,11,13-pentaen-6-one (**169**) in 67% isolated yield (Table 7). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

The same strategy has been extended to 1,3-cyclohexanedione as a nucleophile for reaction with Baylis-Hillman acetate (**161b**) which provided the desired [6-7-6] carbocyclic framework (**170**) in 75% isolated yield (Scheme 70, Table 7). Structure of this compound was confirmed by IR, ^{1}H NMR (spectrum 16), ^{13}C NMR (spectrum 17), mass spectral data and elemental analysis data.

Scheme 70



For the generality of this methodology, we have employed the Baylis-Hillman acetates (**161c** & **161d**) for reaction with 1,3-cyclohexanedione to provide the corresponding [6-7-6] tricyclic carbocyclic molecules (**171** & **172**) in 64% and 61% isolated yields respectively (Table 7). Structures of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses. The Baylis-Hillman acetate (**161d**) was prepared *via* the acetylation of the corresponding Baylis-Hillman alcohol (**160d**) which in turn was obtained *via* the coupling of 3-ethoxybenzaldehyde (**159d**) with methyl acrylate under the influence of DABCO (Table 6). The required 3-ethoxybenzaldehyde (**159d**) was prepared according to Eq. 37.

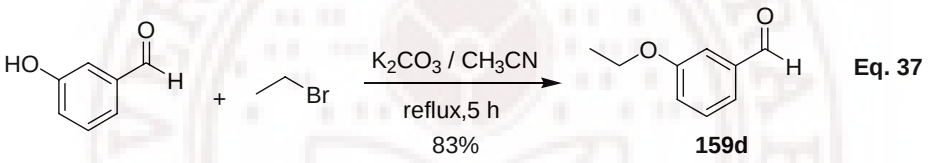
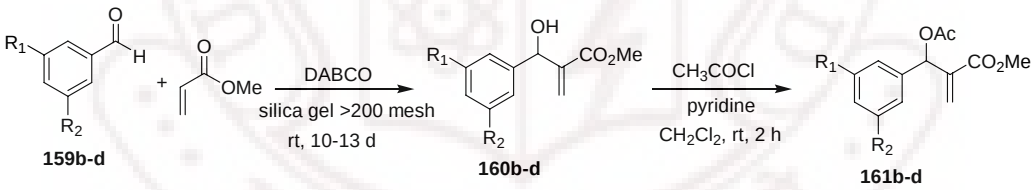


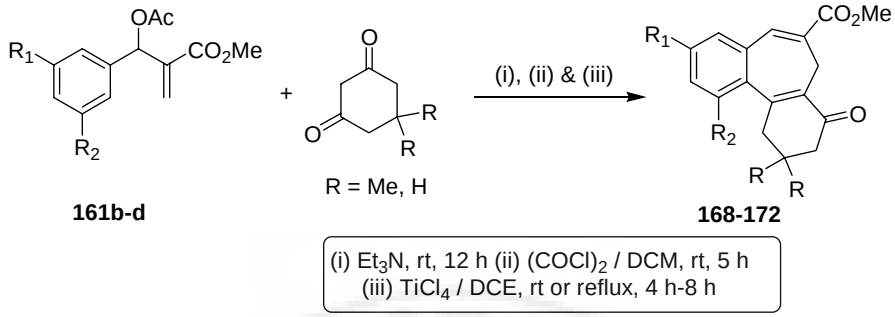
Table 6. Synthesis of Baylis-Hillman alcohols[a] and acetates[b]



Aldehyde	R_1	R_2	B–H alcohol[e]	Yield (%)[c]	B–H acetate[e]	Yield (%)[d]
159b	OMe	OMe	**160b**	62	**161b**	73
159c	OMe	H	**160c**	68	**161c**	79
159d	OEt	H	**160d**	65	**161d**	71

(a) All reactions were carried out on 50 mmol scale of various aldehydes with alkyl acrylate under the influence of DABCO (15 mol%) in the silica gel (>200 mesh)-solid phase medium at room temperature for 10-13 days.
(b) All reactions were carried out on 20 mmol scale of B.H. alcohols with 20 mmol of acetyl chloride under the influence of pyridine in dichloromethane at room temperature for 2 h.
(c) Yields are based on aldehydes.
(d) Yields are based on B.H. alcohols.
(e) All compounds gave satisfactory IR, ^{1}H NMR and ^{13}C NMR spectral data.

Table 7. Synthesis of Angularly Fused [6-7-6] Framework *via* the Reaction of **161b-d** with Dimedone & 1,3-Cyclohexanedione[a]



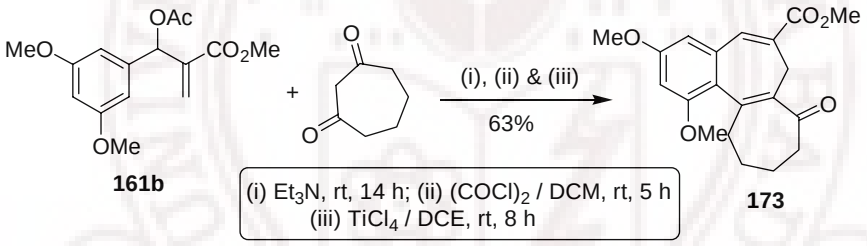
Acetate	R	R_1	R_2	Product[b]	Yield (%)[c]	Mp (^{0}C)
161b	Me	OMe	OMe	**168**[d]	72	124-126
161c	Me	OMe	H	**169**	67	84-86
161b	H	OMe	OMe	**170**	75	108-110
161c	H	OMe	H	**171**	64	---
161d	H	OEt	H	**172**	61	---

(a) All reactions were carried out on 1 mmol scale of Baylis-Hillman acetates (**161b-d**) with 1 mmol of dimedone or 1,3-cyclohexanedione in the presence of Et_3N (1 mL) at room temperature for 12 h followed by treatment with $(COCl)_2$ at room temperature for 5 h in DCM and then reaction of the resulting vinyl chloride with 2M $TiCl_4$ in DCE at rt (or reflux for 4 h-8 h).
(b) All compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis data
(c) Isolated yields of the pure products based on Baylis-Hillman acetates.
(d) Structure of this molecule was further confirmed by single crystal X-ray data.

Towards synthesis of angularly fused [6-7-7] carbocyclic ring frameworks:

With a view to extended this strategy for the synthesis of angularly fused [6-7-7] carbocyclic ring frameworks, we have selected the Baylis-Hillman acetate (**161b**) and 1,3-cycloheptanedione as reaction partners. Thus the alkylation of 1,3-cycloheptanedione with the B-H acetate (**161b**) in the presence of Et_3N provided the corresponding trisubstituted alkene, which (after removal of excess triethylamine) on reaction with oxalyl chloride (5 mmol) generated *in situ* the corresponding vinyl chloride. Intramolecular cyclization (Friedel-Crafts or Michael reaction) was performed

via the treatment with $TiCl_4$ (2 mmol, 2M solution in DCE) in 1,2-dichloroethane (DCE) as the Lewis acid at room temperature for 8 h (after removal of DCM and oxalyl chloride under reduced pressure). We were pleased to notice that the desired [6-7-7] tricyclic carbocyclic molecule *i.e.* 14,16-dimethoxy-10-methoxycarbonyltricyclo[10.4.-0.$0^{2,8}$]hexadeca-1(16),2(8),10,12,14-pentaen-7-one (**173**)© was obtained in 63% isolated yield (Eq. 38) after usual work up followed by column chromatography. Structure of this molecule was established by IR, ^{1}H NMR (spectrum 18), ^{13}C NMR (spectrum 19), mass spectral data and elemental analysis data. Structure of this molecule was further confirmed by single crystal X-ray data (see Figure 17 for ORTEP diagram of compound **173**, Table VI).



Eq. 38

For understanding the generality of this reaction strategy, we have subjected Baylis-Hillman acetates (**161c** & **161d**) for reaction with 1,3-cycloheptanedione to provide the corresponding [6-7-7] tricyclic carbocyclic molecules containing the cycloheptane as the central ring (**174** & **175**) in 59% and 57% isolated yields respectively (Scheme 71). Structures of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.

© For better understanding and continuity we have numbered [6-7-7] carbocyclic frameworks derived from B-H acetates **161b-d** and 1,3-cycloheptandione as **173-175** respectively.

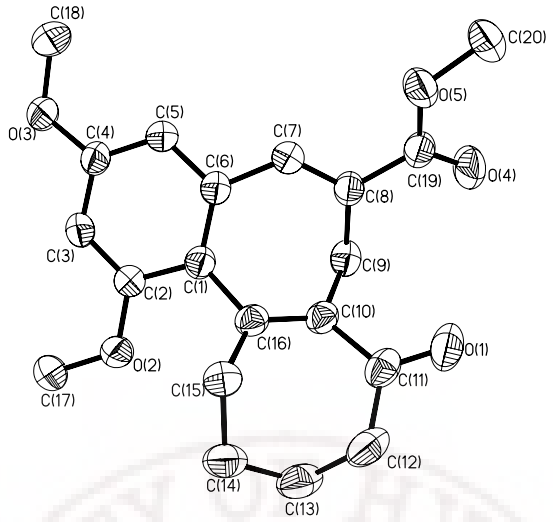


Figure 17 ORTEP diagram of compound **173**
(*Hydrogen atoms were omitted for clarity*)

Scheme 71

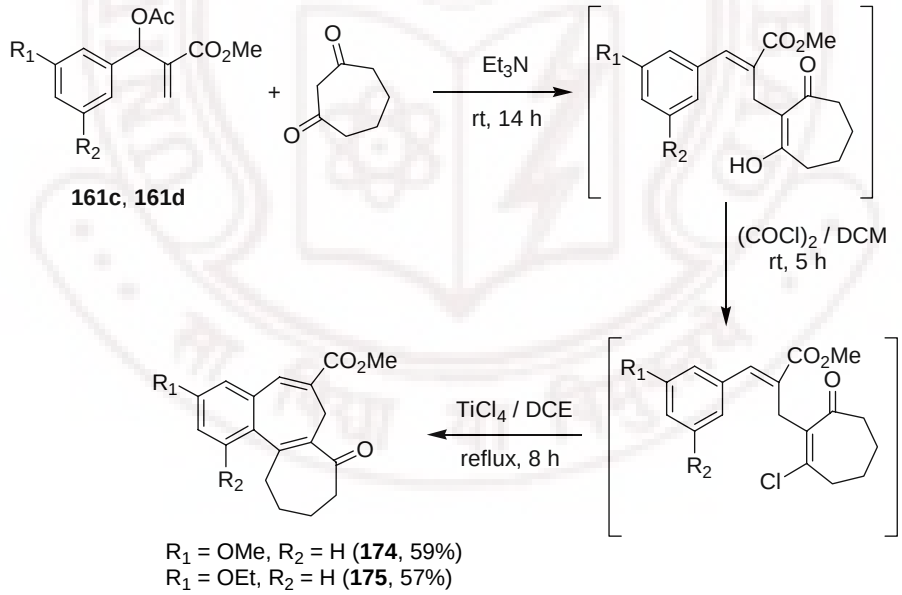


Table VI: Crystal data collection and structure refinement for the compound **173**

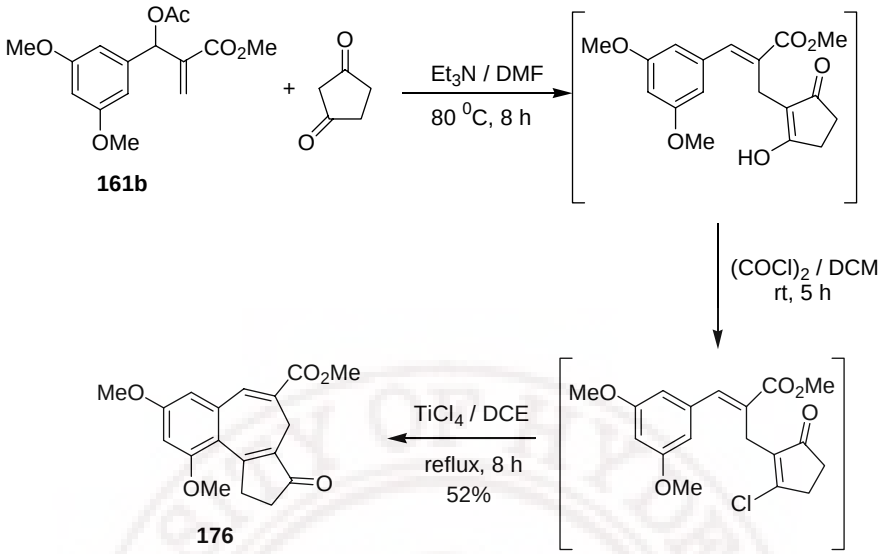
Empirical formula	: $C_{20}H_{22}O_5$
Formula weight	: 342.38
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: monoclinic,
Space group	: *P 21/c*
Unit cell dimensions	: a = 10.935(5) Å; α = 90 deg.
	: b = 7.982(4) Å; β = 102.531(10) deg.
	: c = 20.043(10) Å; γ = 90 deg.
Volume	: 1707.8(14) $Å^3$
Z, Calculated density	: 4, 1.332 g / cm^3
Absorption coefficient	: 0.095 mm^{-1}
F(000)	: 728
Crystal size	: 0.32 X 0.28 X 0.08 mm
Theta range for data collection	: 1.91 to 25.83 deg.
Limiting indices	: $-13 \le h \le 13$, $-9 \le k \le 9$, $-24 \le l \le 24$
Reflections collected / unique	: 16706 / 3292 [R(int) = 0.0680]
Completeness to theta = 25.83	: 99.6%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3292 / 0 / 229
Goodness-of-fit on F^2	: 1.036
Final R indices [I>2sigma(I)]	: R1 = 0.0472, wR2 = 0.1051
R indices (all data)	: R1 = 0.0674, wR2 = 0.1158
Largest diff. peak and hole	: 0.177 and -0.228 e. $Å^{-3}$

Towards synthesis of [6-7-5] carbocyclic ring systems:

In order to extend this strategy for the synthesis of angularly fused [6-7-5] carbocyclic ring systems, we have first employed the Baylis-Hillman acetate (**161b**) and 1,3-cyclopentanedione (nucleophile) as reaction partners. Alkylation of 1,3-cyclopentane-dione with the B-H acetate (**161b**) in the presence of Et_3N / DMF provided the corresponding alkylated product which [after removal of excess triethylamine and solvent (DMF)] on reaction with oxalyl chloride (5 mmol) generated *in situ* the corresponding vinyl chloride. Subsequent intramolecular cyclization (Friedel-Crafts or Michael reaction) using $TiCl_4$ (2 mmol, 2M solution in DCE) in 1,2-dichloroethane (DCE) as the Lewis acid at reflux temperature for 8 h (after removal of DCM and oxalyl chloride under reduced pressure) afforded the desired [6-7-5] carbocyclic ring system *i.e* 3,5-dimethoxy-9-methoxycarbonyltricyclo[9.3.0.$0^{2,7}$]tetradeca-1(11),2,4,6,8-pentaen-12-one (**176**)® in 52% isolated yield after usual work up followed by column chromatography (Scheme 72 and Table 8). Structure of this molecule was established by IR, ^{1}H NMR (spectrum 20), ^{13}C NMR (spectrum 21), mass spectral data and elemental analysis. In fact, structure of this molecule was further confirmed by single crystal X-ray data (see Figure 18 for ORTEP diagram of compound **176**, Table VII).

® For continuity and better understanding we have numbered angularly fused [6-7-5] frameworks obtained from B-H acetates **161b-d** and 1,3-cyclopentanedione as **176-178** respectively.

Scheme 72



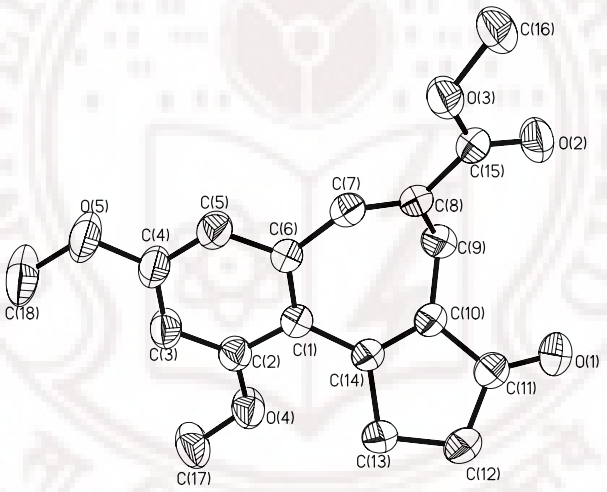


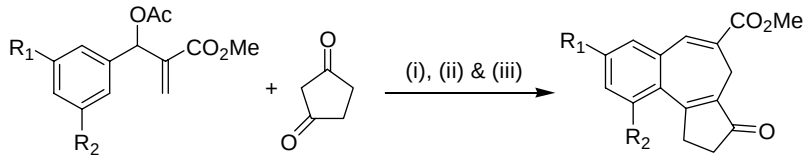
Figure 18 ORTEP diagram of compound **176**
(*Hydrogen atoms were omitted for clarity*)

With a view to examine the applicability of this strategy, we have employed Baylis-Hillman acetates (**161c** & **161d**) for the reaction with 1,3-cyclopentanedione. The resulting [6-7-5] carbocyclic frameworks (**177** & **178**) were obtained in 53% and 50% isolated yields respectively. Structures of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.

Table VII: Crystal data collection and structure refinement for the compound **176**

Empirical formula	: $C_{18}H_{18}O_5$
Formula weight	: 314.32
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: orthorhombic
Space group	: *P na2(1)*
Unit cell dimensions	: a = 22.625(4) Å; α = 90 deg.
	: b = 8.5587(15) Å; β = 90 deg.
	: c = 8.0326(14) Å; γ = 90 deg.
Volume	: 1555.5(5) $Å^3$
Z, Calculated density	: 4, 1.342 g / cm^3
Absorption coefficient	: 0.098 mm^{-1}
F(000)	: 664
Crystal size	: 0.32 X 0.24 X 0.16 mm
Theta range for data collection	: 1.80 to 25.93 deg.
Limiting indices	: $-26 \le h \le 27$, $-7 \le k \le 10$, $-9 \le l \le 9$
Reflections collected / unique	: 8327 / 2913 [R(int) = 0. 0.0640]
Completeness to theta = 25.00	: 99.8%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2913 / 1 / 211
Goodness-of-fit on F^2	: 0.959
Final R indices [I>2sigma(I)]	: R1 = 0.0451, wR2 = 0.0938
R indices (all data)	: R1 = 0.0562, wR2 = 0.0981
Largest diff. peak and hole	: 0.132 and -0.215 e. $Å^{-3}$

Table 8. Synthesis of Angularly Fused [6-7-5] Framework *via* the Reaction of Baylis-Hillman Acetates (**161b-d**) with 1,3-Cyclopentanedione[a]



161b-d **176-178**

(i) Et_3N / DMF, 80 ^{0}C, 8 h (ii) $(COCl)_2$ / DCM, rt, 5 h
(iii) $TiCl_4$ / DCE, reflux, 8 h-14 h

Acetate	R_1	R_2	Product[b]	Yield (%)[c]	M.P ^{0}C
161b	OMe	OMe	**176**[d]	52	138-140
161c	OMe	H	**177**	53	132-134
161d	OEt	H	**178**	50	140-142

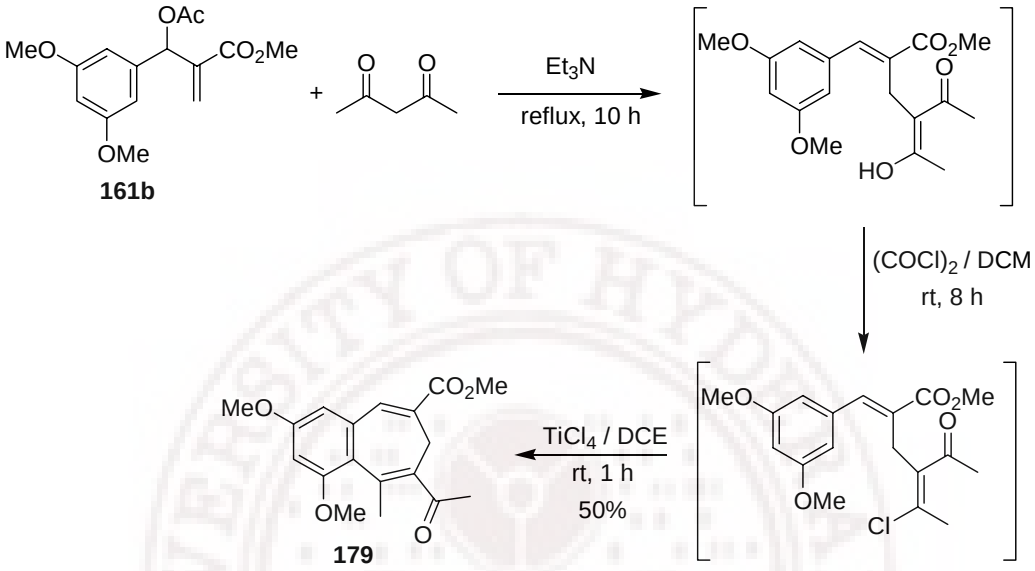
(a) All reactions were carried out on 1 mmol scale of Baylis-Hillman acetates (**161b-d**) with 1 mmol of 1,3-cyclopentanedione in the presence of Et_3N / DMF at 80 ^{0}C for 8 h followed by treatment with $(COCl)_2$ at room temperature for 5 h in DCM and then reaction of the resulting vinyl chloride with 2M $TiCl_4$ in DCE at reflux for 8 h-14 h.
(b) All the compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses.
(c) Isolated yields of the pure products based on Baylis-Hillman acetates.
(d) Structure of this molecule was further confirmed by single crystal X-ray data.

Synthesis of angularly fused [6,7] carbocyclic frameworks:

After demonstrating methodology for the synthesis of angularly fused [6-7-6], [6-7-7] and [6-7-5] carbocyclic ring systems, we have examined this strategy with acyclic diones which would provide [6,7] carbocyclic ring systems. Thus, we have employed 2,4-pentanedione as a nucleophile. Reaction of 2,4-pentanedione with Baylis-Hillman acetate (**161b**) followed by treatment of the resulting tri-substituted alkene-ester with oxalyl chloride and then with $TiCl_4$ following the same reaction strategy as in the case of tricyclic ring frameworks, provided the desired [6,7] bicylic framework (**179**) in 50% isolated yield (Scheme 73). Structure of this compound was established by IR, ^{1}H NMR (spectrum 22), ^{13}C NMR (spectrum 23), mass spectral data and elemental analysis. We

have further confirmed the structure of this compound by single crystal X-ray data (see Figure 19 for ORTEP diagram of molecule **179**,[£] Table VIII).

Scheme 73



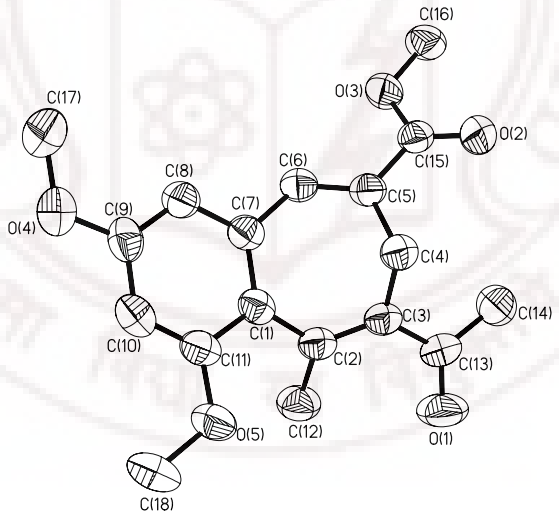


Figure 19 ORTEP diagram of compound **179**
(*Hydrogen atoms were omitted for clarity*)

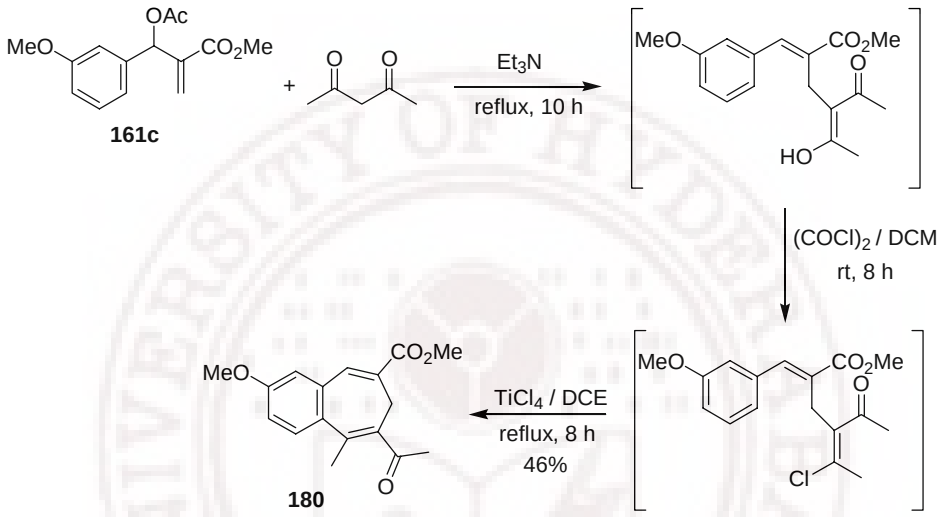
[£]For continuity and easy understanding we have numbered [6,7] bicyclic carbocyclic frameworks obtained from B-H acetates **161b** & **161c** and 2,4-pentanedione as **179** & **180** respectively.

Table VIII: Crystal data collection and structure refinement for the compound **179**

Empirical formula	: $C_{18}H_{20}O_5$
Formula weight	: 316.34
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: monoclinic,
Space group	: *P 21/n*
Unit cell dimensions	: a = 8.986(13) Å; α = 90 deg.
	: b = 16.732(12) Å; β = 105.407(3) deg.
	: c = 12.2623(18) Å; γ = 90 deg.
Volume	: 1641.4(4) $Å^3$
Z, Calculated density	: 4, 1.280 g / cm^3
Absorption coefficient	: 0.093 mm^{-1}
F(000)	: 672
Crystal size	: 0.46 X 0.34 X 0.28 mm
Theta range for data collection	: 2.11 to 25.88 deg.
Limiting indices	: $-10 \le h \le 10$, $-20 \le k \le 18$, $-14 \le l \le 15$
Reflections collected / unique	: 12374 / 3169 [R(int) = 0.4343]
Completeness to theta = 25.88	: 99.7%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3169 / 0 / 213
Goodness-of-fit on F^2	: 0.880
Final R indices [I>2sigma(I)]	: R1 = 0.0449, wR2 = 0.1005
R indices (all data)	: R1 = 0.0793, wR2 = 0.1110
Largest diff. peak and hole	: 0.232 and -0.293 e. $Å^{-3}$

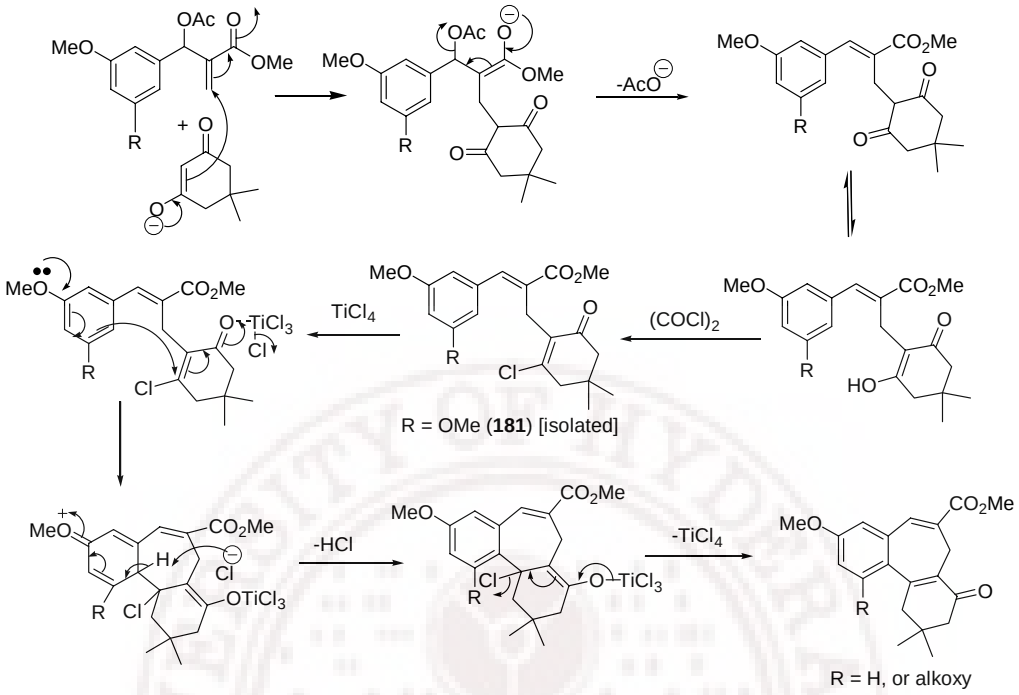
Similarly treatment of Baylis-Hillman acetate, methyl 3-acetoxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**161c**) with 2,4-pentanedione provided the [6,7] bicyclic derivative (**180**) in 46% isolated yield (Scheme 74). Structure of this compound was also confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

Scheme 74



A plausible mechanism by taking dimedone as a model case (nucleophile)] for the transformation of B-H acetates into angularly fused tricyclic carbocyclic frameworks is presented in Scheme 75. Intramolecular cyclization of the *in situ* generated vinyl chloride might involve either Friedel-Crafts or Michael reaction. In fact we have isolated the intermediate (**181**) and confirmed the structure by IR, ^{1}H NMR (spectrum 24), ^{13}C NMR (spectrum 25), and mass spectral data.

Scheme 75



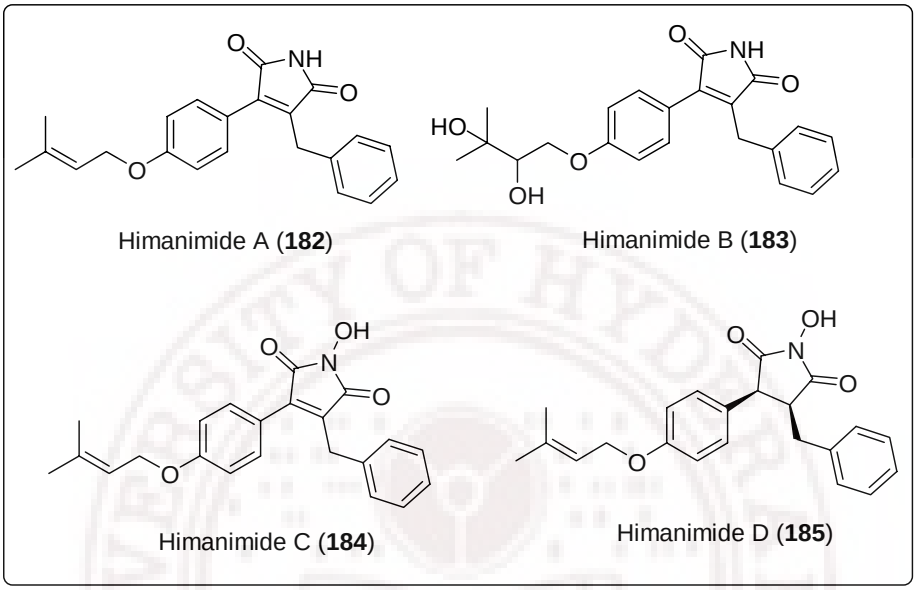
In conclusion, we have developed a simple, facile, and convenient synthesis of angularly fused [6-7-5], [6-7-6], and [6-7-7] tricyclic and [6,7] bicyclic carbocyclic frameworks, thus demonstrating the application of Baylis-Hillman adducts as valuable source for one-pot multistep protocol for the synthesis of important and useful structural frameworks.

Synthesis of biological active compound *himanimide A*:

Himanimides A-D (**182-185**)[258] are new class of maleimide frameworks (Figure 20) isolated from basidomycete culture in Chile. These are known to inhibit the growth of bacteria and fungi. *Himanimides* are also tested against filamentous fungi, yeast, and bacteria as well as different cell lines in order to evaluate potential biological activity. Due to the biological importance of these molecules, development of convenient

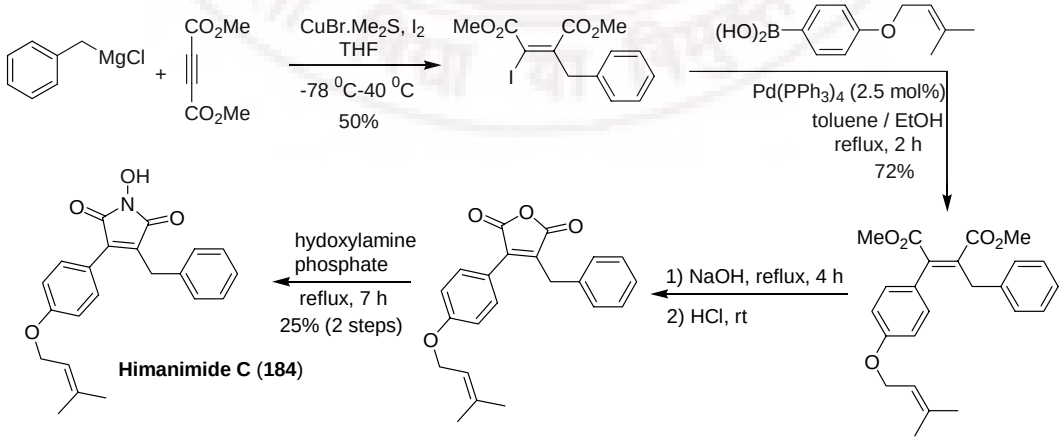
synthetic strategy for obtaining these molecules has become a challenging endeavor in organic synthesis.

Figure 20



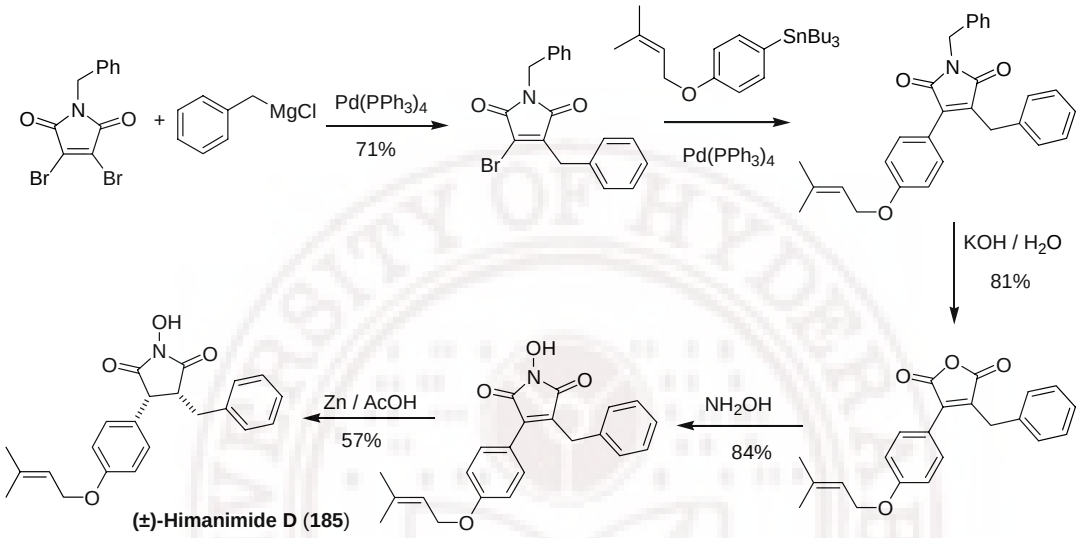
Selles has reported an interesting stereoselective synthesis of *himanimide C* (**184**) using copper-mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate as a key step following the reaction sequence as shown in Scheme 76.[259]

Scheme 76



Lee and coworkers[260] have reported the synthesis of (±)-*cis-himanimide D* (**185**), starting from *N*-benzyl 3,4-dibromomaleimide, following the reaction sequence as shown in Scheme 77.

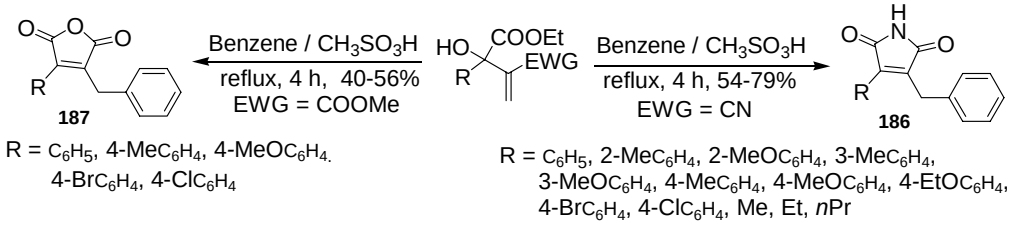
Scheme 77



Our approach

Recently, we have developed a convenient, operationally simple, one-pot procedure for the synthesis of unsymmetrical 3,4-disubstituted maleimide (**186**) and maleic anhydride (**187**) derivatives from the Baylis-Hillman alcohols (obtained *via* the reaction between α-keto esters and acrylonitrile or methyl acrylate in the presence of DABCO) involving Friedel-Crafts reaction, selective hydrolysis and cyclization strategy respectively, using methanesulfonic acid as a single reagent for all these three reactions (Scheme 78).[261,262]

Scheme 78

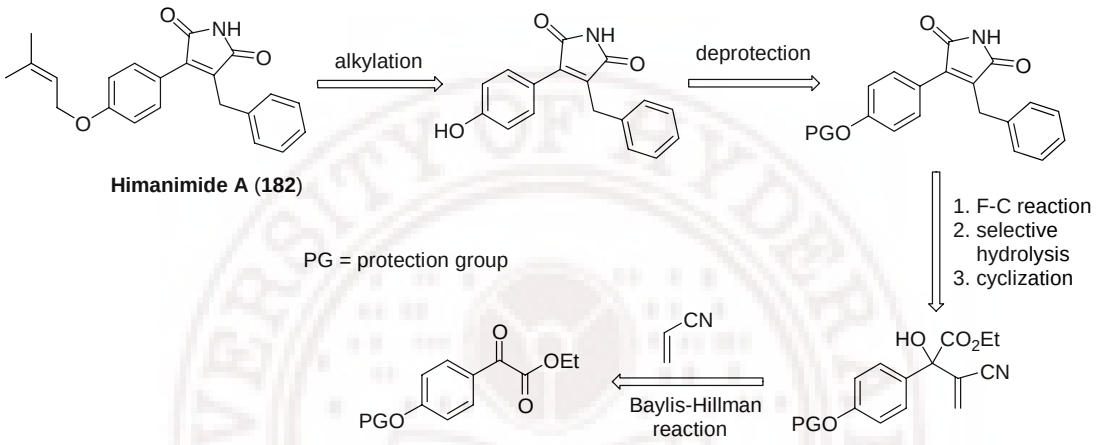


R = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4

R = C_6H_5, 2-MeC_6H_4, 2-$MeOC_6H_4$, 3-MeC_6H_4, 3-$MeOC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, Me, Et, *n*Pr

After carefully examining the structure of the *himanimide A* (**182**), it appeared that *himanimide A* can be synthesized using the Baylis-Hillman adducts as key synthon. Then, we planned the synthesis of *himanimide A* according to the retro-synthetic strategy as shown in the Scheme 79.

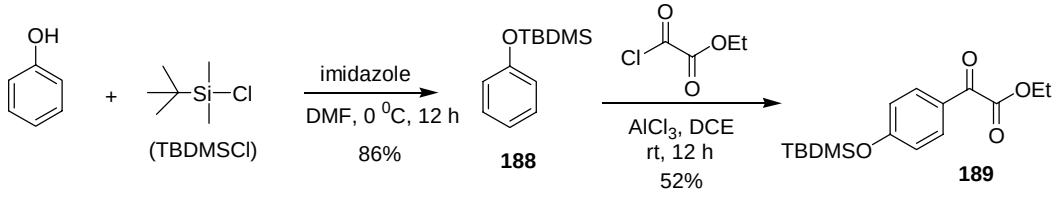
Scheme 79



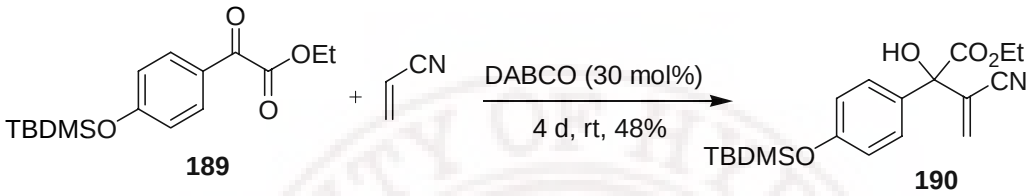
From this retro-synthetic strategy, it looks that the key starting material is the α-keto ester. Then we have selected the α-keto ester (**189**), assuming that TBDMS group will survive in the presence of methanesulfonic acid (Scheme 80).

The α-keto ester (**189**) was prepared according to the Scheme 80.[263] Phenol was protected using *tert*-butyldimethylsilyl chloride (TBDMSCl).[264] Friedel-Crafts reaction of (**188**) with ethyl chlorooxoacetate in the presence of $AlCl_3$ provided the required, ethyl (4-*tert*-butyldimethylsilyloxyphenyl)glyoxylate (**189**) in 52% isolated yield. Structure of this compound was confirmed by IR, ^{1}H NMR and ^{13}C NMR.

Scheme 80

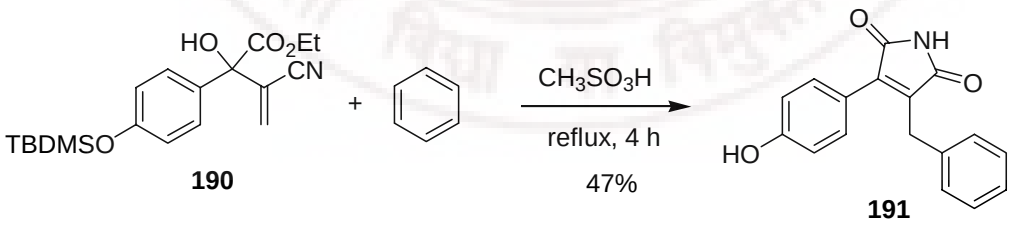


The Baylis-Hillman reaction of the α-keto ester (**189**) with acrylonitrile in the presence of DABCO provided 3-(4-*tert*-butyldimethylsilyloxyphenyl)-3-ethoxycarbonyl-3-hydroxy-2-methylenepropanenitrile (**190**) in 48% isolated yield after 4 days at room temperature (Eq. 39). Structure of this molecule was confirmed by IR, ^{1}H NMR (spectrum 26) and ^{13}C NMR (spectrum 27) and mass spectral data.



189 **190** **Eq. 39**

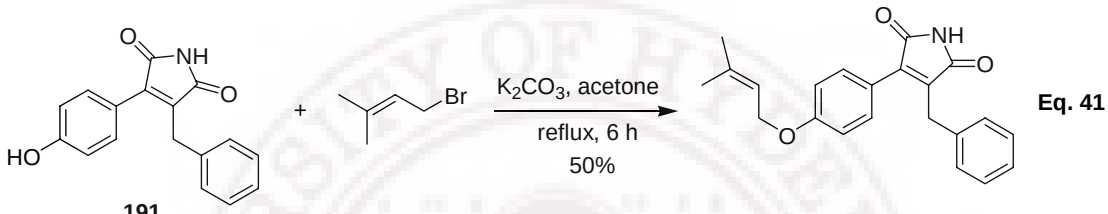
The Friedel-Crafts reaction of the Baylis-Hillman alcohol (**190**) with benzene in the presence of methanesulfonic acid at reflux temperature for 4 h, provided the 3-benzyl-4-(4-hydroxyphenyl)-1*H*-pyrrole-2,5-dione (**191**) in 47% isolated yield after usual work-up followed by column chromatography (Eq. 40). Structure of this molecule was confirmed by IR, ^{1}H NMR (spectrum 28), ^{13}C NMR (spectrum 29), mass spectral data and elemental analysis. We have also noticed that, the protective group (TBDMS) is cleaved during the course of the reaction.



190 **191** **Eq. 40**

Subsequent alkylation of the molecule (**191**) with 1-bromo-3-methyl-2-butene in the presence of K_2CO_3 in acetone at reflux for 6 h, provided the 3-benzyl-4-[4-(3-methylbut-2-enoxy)]-1*H*-pyrrole-2,5-dione (*himanimide A*, **182**) in 50% isolated after usual work-up followed by column chromatography (Eq. 41). Structure of this

molecule was confirmed by IR, ^{1}H NMR (spectrum 30), ^{13}C NMR (spectrum 31), mass spectral data and elemental analysis. *Himanimide A* is known in the literature; ^{1}H and ^{13}C NMR spectral data are reported. Our data is in agreement with that of the literature data. This compound was isolated as a liquid. We obtained this compound (**182**) as a solid [Mp: 108–110^{0}C (dec.)]. Attempts to make single-crystal of this molecule were not successful.



191 ***Himanimide A*** **(182)** **Eq. 41**

In conclusion, we have developed a facile synthesis of *himanimide A*, an important biologically active molecule, in 11.28% overall (unoptimized) yield in three steps starting from the α-keto ester (**189**). Although the yields are not high, this synthesis demonstrates the potential of the Baylis-Hillman adducts in the synthesis of natural products.

CONCLUSIONS

As we mentioned in the beginning of this section, we have made considerable success in our objectives on the applications of Baylis-Hillman adducts for synthesis of heterocyclic and carbocyclic molecules. We have successfully developed a simple one-pot and multistep synthesis of tricyclic *i.e.* [6-8-6] and [6-8-5] heterocyclic molecules containing azocine moiety as the central ring (**127-132**, **134-137**, **139** & **140**), *via* the alkylation of alkyl 3-acetoxy-2-methylene-3-(2-nitroaryl)propanoate (**125a-f**) with appropriate 1,3-cycloalkanediones followed by reduction and cyclization using Fe /

AcOH. We have also successfully transformed the methyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**125g**) and ethyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**125h**) into tetracyclic heterocyclic molecules containing azocine moiety (**142** & **143**) in one-pot multistep reaction strategy.

A simple common one-pot strategy for synthesis of angularly fused [6-7-6], [6-7-7], [6-7-5] tricyclic and [6,7] bicyclic carbocyclic frameworks (**168-180**) *via* the alkylation of Baylis-Hillman acetates (methyl 3-acetoxy-3-(3-alkoxy or 3,5-dialkoxyphenyl)-2-methylenepropanoates, **161b-d**) with 1,3-cycloalkanediones & 2,4-pentanedione followed by an *in situ* generation of vinyl chlorides using oxalyl chloride and intramolecular cyclization (Friedel-Crafts or Michael reaction) under the influence of $TiCl_4$ was developed.

We have developed a facile three step synthesis of *himanimide A* (**182**), biologically active compound, from 3-(4-*tert*-butyldimethylsilyloxyphenyl)-3-ethoxycarbonyl-3-hydroxy-2-methylenepropanenitrile (**190**) *via* Friedel-Crafts reaction with benzene in the presence of methanesulfonic acid followed by alkylation of the resulting phenol derivative (**191**) with 1-bromo-3-methyl-2-butene in the presence of K_2CO_3 in acetone.

EXPERIMENTAL

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

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.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a BRUKER-AC-200 and BRUKER-AVANCE-400 spectrometers. ^{1}H NMR (400 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned, with TMS ($\delta = 0$ ppm) as internal standard. ^{13}C NMR (50 MHz / 100 MHz) spectra for all the samples were measured in chloroform-d, with its middle peak of the triplet ($\delta = 77.10$ ppm) unless otherwise mentioned, (in the case of DMSO-d_6, $\delta = 39.70$ ppm its middle peak of the septet) as internal standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity, *i.e.* s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, b = broad, (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

Mass Spectral Analysis: Mass spectra were recorded on shimadzu LCMS 2010A mass spectrometer.

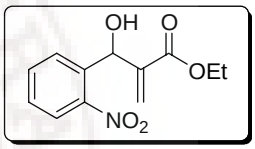
Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). 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 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.

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).

Ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (124a):

A mixture of 2-nitrobenzaldehyde (**123a**, 20 mmol, 3.02 g), ethyl acrylate (30 mmol, 3.0 g, 3.2 mL) and DABCO (15 mol%, 3.0 mmol, 0.336 g) was kept at room temperature for 2 days. The reaction mixture was diluted with ether (50 mL) and washed successively with 2N HCl, aqueous $NaHCO_3$ solution and water. Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (20% EtOAc in hexanes, silica gel) to provide the pure product (**124a**) as a pale yellow viscous liquid in 68% (3.41 g) yield.



IR (neat) : ν 3437, 1712, 1633 cm^{-1}

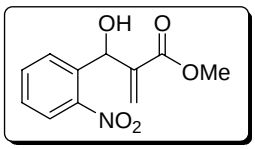
^1H NMR (400 MHz) : δ 1.21 (t, 3H, *J* = 7.2 Hz), 3.49 (d, 1H, *J* = 4.8 Hz), 4.11-4.22 (m, 2H), 5.73 (s, 1H), 6.18 (d, 1H, *J* = 4.4 Hz), 6.37 (s, 1H), 7.43-7.51 (m, 1H), 7.60-7.68 (m, 1H), 7.74 (dd, 1H, *J* = 7.6 Hz & 1.2 Hz), 7.94 (dd, 1H, *J* = 8.2 Hz & 1.2 Hz)

^{13}C NMR (50 MHz) : δ 13.93, 61.13, 67.51, 124.47, 126.12, 128.62, 128.91, 133.40, 136.31, 141.11, 148.34, 165.90.

Methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (124b):

This compound was obtained as a pale yellow viscous liquid *via* the treatment of 2-nitrobenzaldehyde with methyl acrylate under the catalytic influence of DABCO, following a similar procedure as described for the molecule **124a**.

Reaction time : 2 days



Yield : 72%

IR (neat) : ν 3437, 1716, 1638 cm^{-1}

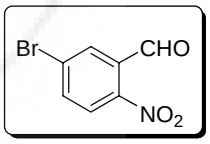
^{1}H NMR (400 MHz) : δ 3.42 (d, 1H, *J* = 4.0 Hz), 3.73 (s, 3H), 5.73 (s, 1H), 6.20 (d, 1H, *J* = 4.0 Hz), 6.37 (s, 1H), 7.41-7.49 (m, 1H), 7.60-7.65 (m, 1H), 7.73 (dd, 1H, *J* = 8.0 Hz & 1.6 Hz), 7.93 (dd, 1H, *J* = 8.0 Hz & 1.2 Hz)

^{13}C NMR (50 MHz) : δ 52.13, 67.39, 124.49, 126.36, 128.64, 128.86, 133.42, 136.21, 140.96, 148.19, 166.39.

5-Bromo-2-nitrobenzaldehyde (123b):

This was prepared according to the literature procedure with some modification.[238]

To a stirred mixture of 3-bromobenzaldehyde (20 mmol, 3.70 g) and KNO_3 (22 mmol, 2.23 g) cooled to 0 ^{0}C, was added dropwise conc. H_2SO_4. After stirring for 30 min at the same temperature, the reaction mixture was poured into ice-cold water. The solid obtained after filtration was crystallized from MeOH to provide 5-bromo-2-nitro-benzaldehyde (**123b**) as colorless needles in 52% (2.21 g) yield.



Mp : 71-73 ^{o}C [Literature: 77.5 ^{o}C] [238]

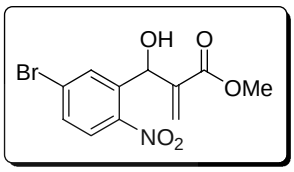
IR (KBr) : ν 1695 cm^{-1}

^{1}H NMR (400 MHz) : δ 7.88 (dd, 1H, *J* = 8.8 Hz & 2.0 Hz), 8.03 (d, 1H, *J* = 8.8 Hz), 8.05 (d, 1H, *J* = 2.0 Hz), 10.40 (s, 1H)

^{13}C NMR (100 MHz) : δ 126.19, 129.61, 132.68, 136.57, 148.10, 186.82.

Methyl 3-(5-bromo-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (124c):

This molecule was obtained *via* the Baylis-Hillman coupling of 5-bromo-2-nitrobenzaldehyde (**123b**) with methyl acrylate under the catalytic influence of DABCO, following a similar procedure as described for the molecule **124a**, as a brown viscous liquid.



Reaction time : 5 days

Yield : 67%

IR (neat) : ν 3487, 1714, 1633 cm^{-1}

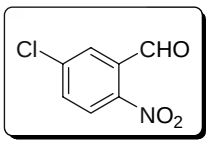
^{1}H NMR (400 MHz) : δ 3.45 (b, 1H), 3.76 (s, 3H), 5.69 (s, 1H), 6.22 (s, 1H), 6.36 (s, 1H), 7.60 (dd, 1H, *J* = 8.8 Hz & 2.0 Hz), 7.85 (d, 1H, *J* = 8.8 Hz), 7.93 (d, 1H, *J* = 2.0 Hz)

^{13}C NMR (50 MHz) : δ 52.28, 67.22, 126.14, 126.60, 128.59, 131.82, 132.16, 138.39, 140.70, 146.86, 166.26.

5-Chloro-2-nitrobenzaldehyde (123c):

This was prepared from 3-chlorobenzaldehyde following a similar procedure[238] as described for the aldehyde **123b**.

Reaction time : 30 min



Yield : 65%

Mp : 70-72 ^oC [literature: 74 ^oC] [238]

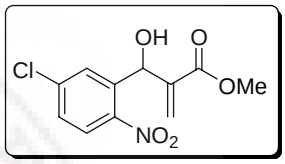
IR (KBr) : ν 1697 cm^{-1}

^{1}H NMR (400 MHz) : δ 7.71 (dd, 1H, *J* = 8.4 Hz & 2.4 Hz), 7.89 (d, 1H, *J* = 2.4 Hz), 8.12 (d, 1H, *J* = 8.4 Hz), 10.41 (s, 1H)

^{13}C NMR (100 MHz) : δ 126.24, 129.69, 132.82, 133.48, 141.30, 147.61, 186.90.

Methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (124d):

This compound was prepared *via* the treatment of 5-chloro-2-nitrobenzaldehyde (**123c**) with methyl acrylate under the catalytic influence of DABCO following a similar procedure as described for the molecule **124a**, as a brown viscous liquid.



Reaction time : 2 days

Yield : 61%

IR (neat) : ν 3466, 1716, 1631 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.46 (d, 1H, *J* = 4.0 Hz), 3.76 (s, 3H), 5.69 (s, 1H), 6.23 (d, 1H, *J* = 4.0 Hz), 6.36 (s, 1H), 7.43 (dd, 1H, *J* = 8.8 Hz & 2.0 Hz), 7.77 (d, 1H, *J* = 2.0 Hz), 7.94 (d, 1H, *J* = 8.8 Hz)

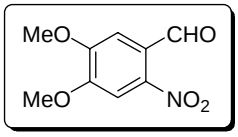
^{13}C NMR (50 MHz) : δ 52.30, 67.54, 126.22, 126.65, 128.86, 129.27, 138.47, 140.24, 140.70, 146.47, 166.36.

4,5-Dimethoxy-2-nitrobenzaldehyde (123d):

This was prepared according to the literature procedure with slight modification.[239]

To 3,4-dimethoxybenzaldehyde (30 mmol, 4.98 g), was added conc. HNO_3 (30 mL) while the reaction mixture was stirring at room temperature. The reaction mixture was then stirred at 40 ^{o}C for 30 min. and it was poured into ice-cold water. The yellow precipitate thus formed was filtered. The precipitate was washed with aqueous $NaHSO_4$ solution and filtered to remove any insoluble impurities. The filtrate was treated with aqueous KOH solution to generate the aldehyde as yellow solid. The crude solid on

crystallization from methanol at 0 ^{o}C provided the pure **123d** as yellow crystalline solid in 48% (3.16 g) yield.



Reaction time : 30 min

Mp : 125-127 ^{o}C [literature: 128 ^{o}C] [239]

IR (KBr) : ν 1685 cm^{-1}

^{1}H NMR (400 MHz) : δ 4.03 (s, 3H), 4.04 (s, 3H), 7.42 (s, 1H), 7.62 (s, 1H), 10.45 (s, 1H)

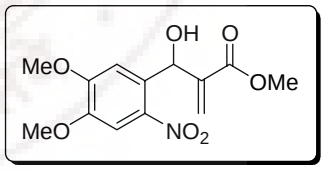
^{13}C NMR (100 MHz) : δ 56.72, 56.79, 107.17, 109.72, 125.51, 143.84, 152.38, 153.20, 187.66.

Methyl 3-(4,5-dimethoxy-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (124e):

This compound was prepared by DABCO-catalyzed Baylis-Hillman coupling of 4,5-dimethoxy-2-nitrobenzaldehyde (**123d**) with methyl acrylate, following a similar procedure as described for the molecule **124a**, as a brown viscous liquid.

Reaction time : 8 days

Yield : 62%



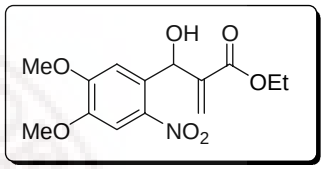
IR (neat) : ν 3499, 1724, 1612 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.54 (d, 1H, *J* = 4.0 Hz), 3.77 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 5.56 (s, 1H), 6.28 (s, 1H), 6.30 (s, 1H), 7.25 (s, 1H), 7.62 (s, 1H)

^{13}C NMR (100 MHz) : δ 52.09, 56.28, 56.33, 67.56, 107.93, 110.04, 125.63, 131.43, 140.12, 141.52, 148.02, 153.38, 166.68.

Ethyl 3-(4,5-dimethoxy-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (124f):

This product was obtained as brown viscous liquid *via* the Baylis-Hillman coupling of 4,5-dimethoxy-2-nitrobenzaldehyde (**123d**) with ethyl acrylate, under the catalytic influence of DABCO, following a similar procedure as described for the molecule **124a**.



Reaction time : 7 days

Yield : 58%

IR (neat) : ν 3512, 1714, 1614 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.28 (t, 3H, *J* = 7.2 Hz), 3.56 (b, 1H), 3.97 (s, 3H), 3.99 (s, 3H), 4.23 (q, 2H, *J* = 7.2 Hz), 5.57 (s, 1H), 6.30 (s, 2H), 7.26 (s, 1H), 7.64 (s, 1H)

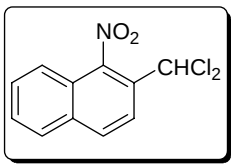
^{13}C NMR (50 MHz) : δ 14.05, 56.38, 61.16, 67.83, 108.10, 110.23, 125.44, 131.48, 140.41, 141.74, 148.19, 153.53, 166.31.

2-Dichloromethyl-1-nitronaphthalene :

This was prepared according to the literature procedure with slight modification.[240]

To a vigorously stirred solution of potassium *tert*-butoxide (80 mmol, 8.96 g) in a mixture of dry THF (35 mL) and dry DMF (15 mL) at -78 ^{0}C under nitrogen atmosphere, a solution of 1-nitronaphthalene (20 mmol, 3.46 g) and $CHCl_3$ (22 mmol, 1.56 mL) in dry DMF (8 mL) was added dropwise. The mixture was stirred at -78 ^{0}C for 10 minutes and acidified with acetic acid (10 mL) in methanol (20 mL). The reaction mixture after reaching to room temperature was poured into water (100 mL) and the products were extracted with dichloromethane (3 X 50 mL). The combined

organic layers were washed with water (3 X 75 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated followed by column chromatography (hexanes, silica gel) to provide the title compound as yellow solid in 65% yield.



Mp : 85-87 ^{0}C [literature : 88-89 ^{o}C] [240]

IR (KBr) : ν 1541 cm^{-1}

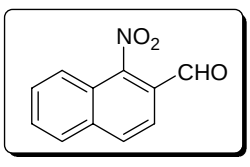
^{1}H NMR (400 MHz) : δ 6.93 (s, 1H), 7.64-7.74 (m, 2H), 7.77-7.84 (m, 1H), 7.91-7.98 (m, 1H), 8.04 (d, 1H, *J* = 8.8 Hz), 8.11 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz) : δ 65.84, 122.67, 123.62, 128.25, 128.88, 129.25, 129.56, 132.26, 134.25.

1-Nitro-2-naphthaldehyde (123e):

This was prepared according to the literature procedure with slight modification.[240]

A mixture of 2-dichloromethyl-1-nitronaphthalene (10 mmol, 2.56 g), anhydrous $ZnCl_2$ (43 mmol, 5.9 g) and 90% HCO_2H (46 mL) was refluxed for 5 hours. After cooling to room temperature, the reaction mixture was poured into water and extracted with DCM (3 X 15 mL). The extracts were dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was subjected to column chromatography (2% EtOAc in hexanes, silica gel) to provide the title compound as yellow solid in 75% (1.51 g) yield.



Mp : 97-100 ^{0}C [literature : 100 ^{o}C] [241]

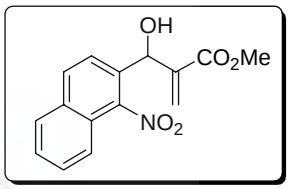
IR (KBr) : ν 1709 cm^{-1}

^{1}H NMR (400 MHz) : δ 7.72-7.79 (m, 2H), 7.91-7.96 (m, 1H), 7.97-8.03 (m, 2H), 8.11 (d, 1H, *J* = 8.4 Hz), 10.18 (d, 1H, *J* = 0.8 Hz)

^{13}C NMR (50 MHz) : δ 122.92, 123.81, 124.13, 128.45, 129.68,130.27, 131.50, 136.70, 150.52, 186.76

Methyl 3-hydroxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (124g):

This compound was prepared by DABCO-catalyzed Baylis-Hillman coupling of 1-nitro-2-naphthaldehyde (**123e**) with methyl acrylate, following a similar procedure as described for the molecule **124a**, as a pale yellow solid.



Reaction time : 3 h

Yield : 75%

Mp : 124-126 ^{0}C

IR (KBr) : ν 3474, 1711, 1633 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.30 (d, 1H, *J* = 4.4 Hz), 3.69 (s, 3H), 5.86 (d, 1H, *J* = 4.4 Hz), 5.94 (s, 1H), 6.47 (s, 1H), 7.58-7.67 (m, 3H), 7.76-7.81 (m, 1H), 7.88-7.92 (m, 1H), 7.98 (d, 1H, *J* = 8.8 Hz)

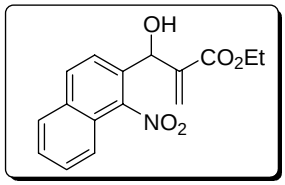
^{13}C NMR (50 MHz) : δ 52.16, 68.36, 122.02, 124.06, 124.35, 127.40, 127.70, 128.11, 128.84, 130.61, 131.29, 133.49, 139.90, 146.91, 166.12.

Ethyl 3-hydroxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (124h):

This molecule was obtained as a brown solid *via* the reaction between 1-nitro-2-naphthaldehyde (**123e**) and ethyl acrylate under the catalytic influence of DABCO, following a similar procedure as described for the molecule **124a**.

Reaction time : 3 h

Yield : 71%



Mp : 78-80 ^{0}C

IR (KBr) : ν 3476, 1709, 1633 cm^{-1}

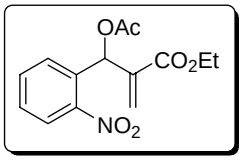
^{1}H NMR (400 MHz) : δ 1.18 (t, 3H, *J* = 7.2 Hz), 3.37 (d, 1H, *J* = 4.0 Hz), 4.14 (q, 2H, *J* = 7.2 Hz), 5.85 (d, 1H, *J* = 4.0 Hz), 5.92 (s, 1H), 6.48 (s, 1H), 7.57-7.68 (m, 3H), 7.79 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.4 Hz), 7.98 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz) : δ 13.98, 61.23, 68.46, 122.00, 124.06, 124.35, 127.21, 127.67, 128.08, 128.81, 130.75, 131.24, 133.44, 140.09, 146.93, 165.71.

Ethyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (125a):

To a stirred solution of ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (**124a**, 10 mmol, 2.51 g), pyridine (20 mmol, 1.58 g, 1.6 mL) in dry dichloromethane (25 mL) at 0 ^{o}C was added acetyl chloride (20 mmol, 1.56 g, 1.4 mL). After stirring at room temperature for 30 minutes, the reaction mixture was diluted with ether (25 mL) and washed successively with 2N HCl solution, water and saturated aqueous $NaHCO_3$ solution. Organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the crude product, thus obtained, was purified by column chromatography (10% EtOAc in hexanes, silica gel) to afford the pure ethyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125a**) as colorless liquid in 76% (2.22 g) yield.

IR (neat) : ν1749, 1722, 1639 cm^{-1}



^{1}H NMR (400 MHz) : δ 1.25 (t, 3H, *J* = 7.2 Hz), 2.13 (s, 3H), 4.15-4.30 (m, 2H), 5.53 (s, 1H), 6.44 (s, 1H), 7.30 (s, 1H), 7.48-7.54 (m, 1H), 7.56-7.61 (m, 1H), 7.63-7.69 (m, 1H), 8.03 (d, 1H, *J* = 7.6 Hz)

^{13}C NMR (50 MHz) : δ 13.88, 20.55, 61.06, 68.64, 124.82, 127.52, 128.73, 129.13, 133.31, 138.86, 148.08, 164.54, 168.94.

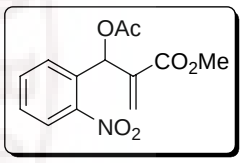
Methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (125b):

This molecule was obtained as a pale yellow solid *via* the treatment of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (**124b**) with acetyl chloride, in the presence of pyridine, following a similar procedure as described for the molecule **125a**.

Reaction time : 30 min

Yield : 82%

Mp : 62-65 ^{0}C



IR (KBr) : ν 1749, 1707, 1639 cm^{-1}

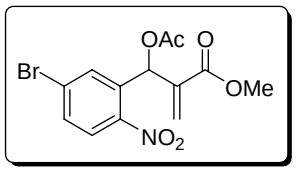
^{1}H NMR (400 MHz) : δ 2.13 (s, 3H), 3.76 (s, 3H), 5.56 (s, 1H), 6.44 (s, 1H), 7.29 (s, 1H), 7.46-7.54 (m, 1H), 7.58 (d, 1H, *J* = 7.2 Hz), 7.62-7.69 (m, 1H), 8.03 (d, 1H, *J* = 8.0 Hz)

^{13}C NMR (50 MHz) : δ 20.70, 52.18, 68.80, 124.95, 127.89, 128.76, 129.20, 133.32, 138.71, 148.19, 165.12, 169.03.

Methyl 3-acetoxy-3-(5-bromo-2-nitrophenyl)-2-methylenepropanoate (125c):

Treatment of methyl 3-(5-bromo-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (**124c**) with acetyl chloride, in the presence of pyridine, following a similar procedure as described for the molecule **125a**, provided **125c**, as a yellow solid.

Reaction time : 30 min



Yield : 74%

Mp : 116-118 ^{0}C

IR (KBr) : ν 1753, 1707, 1635 cm^{-1}

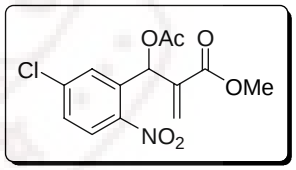
^{1}H NMR (400 MHz) : δ 2.16 (s, 3H), 3.77 (s, 3H), 5.61 (s, 1H), 6.46 (s, 1H), 7.28 (s, 1H), 7.63 (dd, 1H, *J* = 8.4 Hz & 2.0 Hz), 7.69 (d, 1H, *J* = 2.0 Hz), 7.92 (d, 1H, *J* = 8.4 Hz)

^{13}C NMR (50 MHz) : δ 20.75, 52.33, 68.36, 126.58, 128.23, 131.92, 132.40, 135.34, 138.20, 146.93, 164.91, 168.93.

Methyl 3-acetoxy-3-(5-chloro-2-nitrophenyl)-2-methylenepropanoate (125d):

This compound was prepared *via* the reaction of methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (**124d**) with acetyl chloride, in the presence of pyridine, as a yellow solid, following a similar procedure as described for the molecule **125a**.

Reaction time : 30 min



Yield : 78%

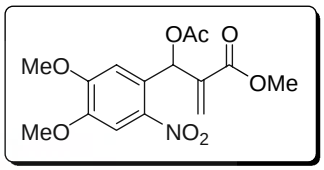
Mp : 90-92 ^{0}C

IR (KBr) : ν 1755, 1707, 1635 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.16 (s, 3H), 3.77 (s, 3H), 5.60 (s, 1H), 6.46 (s, 1H), 7.29 (s, 1H), 7.47 (dd, 1H, *J* = 8.6 Hz & 2.0 Hz), 7.54 (d, 1H, *J* = 2.0 Hz), 8.02 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR (100 MHz) : δ 20.79, 52.39, 68.31, 126.69, 128.35, 128.83, 129.36, 135.39, 138.05, 140.08, 146.18, 164.91, 169.06.

Methyl 3-acetoxy-3-(4,5-dimethoxy-2-nitrophenyl)-2-methylenepropanoate (125e): This molecule was obtained as a yellow solid *via* the treatment of methyl 3-(4,5-dimethoxy-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (**124e**) with acetyl chloride, in the presence of pyridine, following a similar procedure as described for the molecule **125a**.



Reaction time : 30 min

Yield : 79%

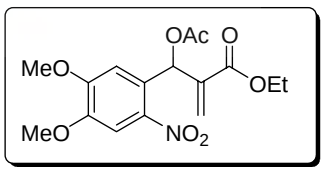
Mp : 140-142 ^{0}C

IR (KBr) : ν 1753, 1720, 1637 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.14 (s, 3H), 3.78 (s, 3H), 3.96 (s, 6H), 5.51 (s, 1H), 6.41 (s, 1H), 6.97 (s, 1H), 7.38 (s, 1H), 7.67 (s, 1H)

^{13}C NMR (50 MHz) : δ 20.67, 52.11, 56.31, 68.90, 108.19, 109.65, 127.65, 138.78, 140.41, 148.46, 153.24, 165.17, 168.96.

Ethyl 3-acetoxy-3-(4,5-dimethoxy-2-nitrophenyl)-2-methylenepropanoate (125f): Treatment of ethyl 3-(4,5-dimethoxy-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (**124f**) with acetyl chloride, in the presence of pyridine, following a similar procedure as described for the molecule **125a**, provided **125f**, as a yellow solid.



Reaction time : 30 min

Yield : 72%

Mp : 108-110 ^{0}C

IR (KBr) : ν 1747, 1720, 1630 cm^{-1}

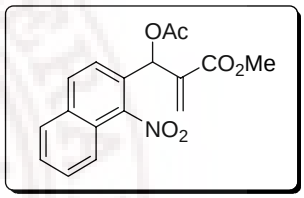
^{1}H NMR (400 MHz) : δ 1.26 (t, 3H, J = 6.8 Hz), 2.13 (s, 3H), 3.95 (s, 6H), 4.23 (q, 2H, J = 6.8Hz), 5.47 (s, 1H), 6.40 (s, 1H), 6.96

(s, 1H), 7.38 (s, 1H), 7.67 (s, 1H)

^{13}C NMR (50 MHz) : δ 14.00, 20.75, 56.36, 61.13, 68.97, 108.22, 109.70, 127.43, 127.99, 139.14, 140.48, 148.48, 153.26, 164.76, 168.96.

Methyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (125g):

This compound was prepared *via* the reaction of methyl 3-hydroxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**124g**) with acetyl chloride, in the presence of pyridine, following a similar procedure as described for the molecule **125a**, as a pale brown solid.



Reaction time : 30 min

Yield : 76%

Mp : 78-80 ^{0}C

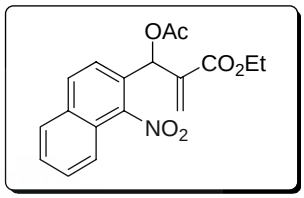
IR (KBr) : ν 1745, 1712, 1635 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.13 (s, 3H), 3.72 (s, 3H), 5.81 (d, 1H, *J* = 1.6 Hz), 6.52 (s, 1H), 6.92 (s, 1H), 7.55 (d, 1H, *J* = 8.8 Hz), 7.59-7.68 (m, 2H), 7.76-7.80 (m, 1H), 7.89-7.93 (m, 1H), 7.98 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz) : δ 20.62, 52.18, 69.21, 122.04, 124.47, 126.80, 127.96, 128.23, 128.91, 130.92, 133.64, 137.86, 147.03, 164.88, 168.88.

Ethyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (125h):

This molecule was obtained as a white solid *via* the treatment of ethyl 3-hydroxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**124h**) with acetyl chloride, in the presence of pyridine, following a similar procedure as described for the molecule **125a**.



Reaction time : 30 min

Yield : 85%

Mp : 108-110 ^{0}C

IR (KBr) : ν 1745, 1712, 1637 cm^{-1}

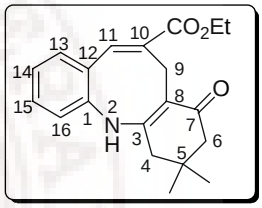
^{1}H NMR (400 MHz) : δ 1.21 (t, 3H, *J* = 6.8 Hz), 2.12 (s, 3H), 4.18 (q, 2H, *J* = 6.8 Hz), 5.77 (s, 1H), 6.52 (s, 1H), 6.92 (s, 1H), 7.53 (d, 1H, *J* = 7.6 Hz), 7.58-7.68 (m, 2H), 7.77 (d, 1H, *J* = 8.0 Hz), 7.88-7.93 (m, 1H), 7.98 (d, 1H, *J* = 8.0 Hz)

^{13}C NMR (50 MHz) : δ 14.03, 20.70, 61.35, 69.33, 122.12, 124.57, 126.92, 128.01, 128.23, 128.96, 130.95, 133.66, 138.05, 147.10, 164.52, 169.01.

2-Aza-5,5-dimethyl-10-ethoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,-16-pentaen-7-one (127):

To a stirred mixture of ethyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125a,** 1 mmol, 0.293 g) and K_2CO_3 (1 mmol, 0.138 g) in THF (1 mL) was added 5,5-dimethyl-1,3-cyclohexanedione (1 mmol, 0.140 g) at room temperature and stirring continued for 2 h at the same temperature. THF was then removed under reduced pressure, the reaction mixture was diluted with acetic acid (5 mL) and heated to reflux (at 110 ^{0}C). At this temperature electrolytic iron powder (6 mmol, 0.336 g) was added

and stirring continued at the same temperature for 1.5 h. The reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure and diluted with ethyl acetate (10 mL), stirred for 5 minutes and filtered to remove iron impurities. The insoluble iron residue was washed with ethyl acetate (2 X 5 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 (20% EtOAc in hexanes, silica gel) to afford the title compound (**127**) as a pale yellow solid in 62% (0.202 g) isolate yield.



Reaction time : (2 h + 1.5 h)

Mp : 198-200 ^{0}C

IR (KBr) : ν 3269, 1716, 1645 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.02 (s, 6H), 1.26 (t, 3H, *J* = 6.8 Hz), 2.21 (s, 2H), 2.33 (s, 2H), 3.45 (b, 2H), 4.20 (q, 2H, *J* = 6.8 Hz), 5.52 (s, 1H), 6.99 (d, 1H, *J* = 7.6 Hz), 7.14 (d, 1H, *J* = 7.6 Hz), 7.20-7.36 (m, 2H), 7.81 (s, 1H)

^{13}C NMR (100 MHz) : δ 14.30, 20.69, 28.06, 31.64, 46.66, 50.23, 60.85, 104.38, 126.70, 128.96, 129.96, 134.81, 135.90, 137.50, 137.98, 158.34, 167.31, 195.16

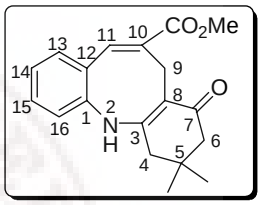
LCMS (m/z) : 326 $(M+H)^+$

Analysis calc'd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30

Found : C, 73.85; H, 7.13; N, 4.26.

2-Aza-5,5-dimethyl-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,-14,16-pentaen-7-one (128):

This molecule was obtained as a yellow solid *via* the treatment of methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125b**) with 5,5-dimethyl-1,3-cyclohexane-dione in the presence of K_2CO_3 followed by reductive cyclization using Fe / AcOH, following a similar procedure as described for the molecule **127**.



Reaction time : (2 h + 1.5 h)

Yield : 68%

Mp : 216-218 ^{0}C (dec.)

IR (KBr) : ν 3261, 1718, 1643 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.02 (s, 6H), 2.21 (s, 2H), 2.33 (s, 2H), 3.47 (b, 2H), 3.74 (s, 3H), 5.59 (s, 1H), 7.00 (d, 1H, *J* = 8.0 Hz), 7.13 (d, 1H, *J* = 6.8 Hz), 7.21-7.26 (m, 1H), 7.28-7.35 (m, 1H), 7.82 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.63, 27.86, 31.49, 46.24, 50.16, 51.88, 103.70, 126.46, 126.84, 128.75, 129.90, 134.42, 135.39, 137.91, 138.06, 159.25, 167.67, 195.32

To understand the conformational rigidity / flexibility we have recorded ^{1}H and ^{13}C NMR spectra at -30 ^{0}C.

^{1}H NMR at -30 ^{0}C (400 MHz) : δ 0.96 & 1.05 (2s, 6H), 2.20 (s, 2H), 2.29 (bs, 1H), 2.52 (bs, 1H), 2.80 (bs, 1H), 3.74 (s, 3H), 4.06 (bs, 1H), 6.24 (s, 1H), 7.06 (d, 1H, *J* = 7.6 Hz), 7.14 (d, 1H, *J* = 7.6 Hz), 7.22-7.40 (m, 2H), 7.84 (s, 1H)

^{13}C NMR at -30 ^{0}C (100 MHz) : δ 20.31, 25.84, 29.83, 31.49, 45.91, 49.79, 52.27, 103.20, 126.58, 126.80, 128.72, 129.99, 134.21, 134.85, 137.50, 138.21, 159.54, 167.80, 195.83

^{1}H NMR at -40 ^{0}C (400 MHz) : δ 0.96 & 1.08 (2s, 6H), 2.23 (s, 2H), 2.27 (d, 1H) [one of the peaks of doublet merges with the singlet at δ 2.23 (which is probably due to C-4 or C-6 methylene protons)], 2.56 (d, 1H, *J* = 15.6 Hz), 2.81 (d, 1H, *J* = 13.2 Hz), 3.76 (s, 3H), 4.08 (d, 1H, *J* = 14.4 Hz), 5.97 (s, 1H), 7.06 (d, 1H, *J* = 8.0 Hz), 7.17 (d, 1H, *J* = 7.2 Hz), 7.23-7.45 (m, 2H), 7.87 (s, 1H)

gem-Dimethyl protons (which appeared as singlet at δ 1.02 in the ^{1}H NMR spectrum at room temperature) appeared as two close singlets at δ 0.96 & 1.05 in the ^{1}H NMR spectrum at -30 ^{0}C. Protons of three methylene groups [at C-4 (or C-6), C-6 (or C-4) & C-9] which appeared at δ 2.21 (s), 2.33 (s) & 3.47 (b) at room temperature in ^{1}H NMR spectrum, appeared as singlet at δ 2.20 (2H) [probably due to C-4 or C-6 methylene protons] and four broad singlets at δ 2.29 (1H), 2.52 (1H), 2.80 (1H) & 4.06 (1H) [probably due to C-6 (or C-4) and C-9 methylene protons] in the ^{1}H NMR spectrum at -30 ^{0}C. These four broad singlets appeared as four doublets at δ 2.27 (1H) [one of the peaks of doublet probably merges with the singlet at δ 2.23 (probably due to C-4 or C-6 methylene protons)], 2.56 (1H, *J* = 15.6 Hz), 2.81 (1H, *J* = 13.2 Hz) & 4.08 (1H, *J* = 14.4 Hz) [probably due to C-6 (or C-4) and C-9 methylene protons] in ^{1}H NMR spectrum at -40 ^{0}C. The coupling constants are not perfectly matching probably

because there is no proper resolution of doublets. It is also interesting to note that there is significant change in chemical shift value of –NH–proton in ^{1}H NMR spectra at room temperature, -30 ^{0}C & -40 ^{0}C.

gem-Dimethyl carbons (which appeared as broad peak at δ 27.86 with low intensity in ^{13}C NMR spectrum at room temperature) appeared as two distinct peaks at δ 25.84 & 29.83 with low intensity in ^{13}C NMR spectrum at -30 ^{0}C. In the case of other carbons there is no significant change in chemical shift values in ^{13}C NMR spectrum at -30 ^{0}C. We have also confirmed the nature of carbons (with 3H or 2H or 1H or no H) by DEPT 135 experiment.

These differences may be attributed to the conformational changes at low temperature (rigid conformation) and room temperature (flexible conformation).

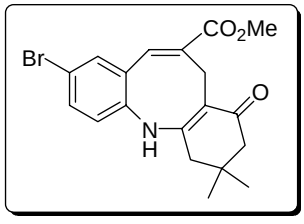
LCMS (m/z) : 312 $(M+H)^{+}$

Analysis calc'd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50

Found : C, 73.12; H, 6.83; N, 4.47.

2-Aza-14-bromo-5,5-dimethyl-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,16-pentaen-7-one (129):

Treatment of methyl 3-acetoxy-3-(5-bromo-2-nitrophenyl)-2-methylenepropanoate (**125c**) with 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3 and subsequent treatment with Fe / AcOH, following a similar procedure as described for **127**, provided the title compound **129**, as a yellow solid.



Reaction time : (2 h + 1.5 h)

Yield : 63%

Mp : 246-248 ^{0}C (dec.)

IR (KBr) : ν 3267, 1720, 1645 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.01 (s, 6H), 2.21 (s, 2H), 2.32 (s, 2H), 3.46 (b, 2H), 3.74 (s, 3H), 5.45 (s, 1H), 6.88 (d, 1H, *J* = 8.0 Hz), 7.28 (d, 1H, *J* = 2.0 Hz), 7.43 (dd, 1H, *J* = 8.0 Hz & 2.0 Hz), 7.72 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.67, 27.88, 31.55, 46.22, 50.14, 52.06, 103.78, 119.92, 128.45, 131.55, 132.83, 136.37, 136.57, 137.23, 158.95, 167.29, 195.40

LCMS (m/z) : 390 $(M+H)^+$, 392 $(M+H+2)^+$

Analysis calc'd. for $C_{19}H_{20}BrNO_3$: C, 58.47; H, 5.17; N, 3.59

Found : C, 58.59; H, 5.14; N, 3.61.

2-Aza-14-chloro-5,5-dimethyl-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,16-pentaen-7-one (130):

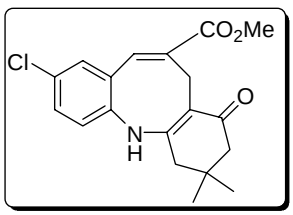
This compound was obtained as a yellow solid *via* the alkylation of methyl 3-acetoxy-3-(5-chloro-2-nitrophenyl)-2-methylenepropanoate (**125d**) with 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3 followed by reductive cyclization using Fe / AcOH, following a similar procedure as described for the molecule **127**.

Reaction time : (2 h + 1.5 h)

Yield : 57%

Mp : 250-252 ^{0}C

IR (KBr) : ν 3265, 1720, 1640 cm^{-1}



^{1}H NMR (400 MHz) : δ 1.02 (s, 6H), 2.22 (s, 2H), 2.32 (s, 2H), 3.46 (b, 2H), 3.74 (s, 3H), 5.44 (s, 1H), 6.94 (d, 1H, *J* = 8.8 Hz), 7.13 (d, 1H, *J* = 2.0 Hz), 7.28 (dd, 1H, *J* = 8.8 Hz & 2.0 Hz), 7.73 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.69, 27.88, 31.58, 46.31, 50.16, 52.08, 103.89, 128.15, 128.67, 129.87, 132.26, 136.33, 136.34, 136.45, 136.65, 158.82, 167.35, 195.39

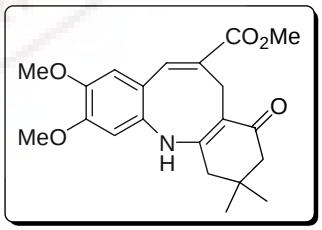
LCMS (m/z) : 346 $(M+H)^+$, 348 $(M+H+2)^+$

Analysis calc'd. for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05

Found : C, 65.90; H, 5.87; N, 3.99.

2-Aza-14,15-dimethoxy-5,5-dimethyl-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexa-deca-3(8),10,12,14,16-pentaen-7-one (131) :

This product was obtained as a yellow solid *via* the treatment of methyl 3-acetoxy-3-(4,5-dimethoxy-2-nitrophenyl)-2-methylenepropanoate (**125e**) with 5,5-dimethyl-1,3-cyclohexanedione and subsequent treatment with Fe / AcOH, following a similar procedure as described for the molecule **127**.



Reaction time : (2 h + 1.5 h)

Yield : 59%

Mp : 232-234 ^{0}C (dec.)

IR (KBr) : ν 3275, 1711, 1648 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.02 (s, 6H), 2.22 (s, 2H), 2.31 (s, 2H), 3.49 (b, 2H), 3.74 (s, 3H), 3.86 (s, 6H), 5.35 (s, 1H), 6.51 (s, 1H), 6.60 (s, 1H), 7.76 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.89, 27.88, 31.47, 46.47, 50.19, 51.93, 56.08, 103.88, 110.36, 110.80, 126.78, 130.50, 135.31, 137.95, 147.63, 149.97, 158.94, 167.84, 195.39

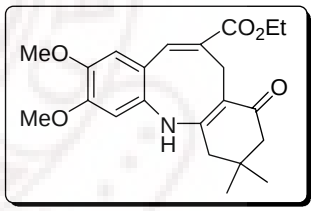
LCMS (m/z) : 370 $(M-H)^+$

Analysis calc'd. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77

Found : C, 67.86; H, 6.76; N, 3.79.

2-Aza-14,15-dimethoxy-5,5-dimethyl-10-ethoxycarbonyltricyclo[10.4.0.0^{3,8}]hexa-deca-3(8),10,12,14,16-pentaen-7-one (132):

The reaction of ethyl 3-acetoxy-3-(4,5-dimethoxy-2-nitrophenyl)-2-methylene-propanoate (**125f**) with 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3 followed by reductive cyclization using Fe / AcOH, following a similar procedure as described for the molecule **127**, provided the title compound as a yellow solid.



Reaction time : (2 h + 1.5 h)

Yield : 64%

Mp : 210-212 ^{0}C

IR (KBr) : ν 3271, 1703, 1640 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.03 (s, 6H), 1.26 (t, 3H, *J* = 6.8 Hz), 2.22 (s, 2H), 2.32 (s, 2H), 3.48 (b, 2H), 3.86 (s, 6H), 4.19 (q, 2H, *J* = 6.8 Hz), 5.43 (s, 1H), 6.52 (s, 1H), 6.61 (s, 1H), 7.75 (s, 1H)

^{13}C NMR (100 MHz) : δ 14.20, 20.85, 27.87, 31.34, 46.12, 50.17, 55.97, 60.61, 103.55, 110.40, 110.67, 126.69, 130.66, 135.65, 137.55, 147.42, 149.80, 159.17, 167.28, 195.07

LCMS (m/z) : 384 $(M-H)^+$

Analysis calc'd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63

Found : C, 68.84; H, 7.08; N, 3.68.

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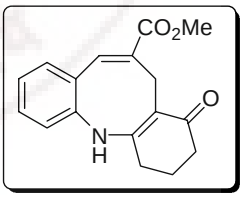
*It is interesting to note that in case of compounds **127-132** quaternary carbon appeared as a peak with high intensity (usually quaternary carbon appears with low intensity peak) at δ 31.34 to 31.64. Also the gem-dimethyl carbons appeared as single peak with low intensity at δ 27.86 to 28.06. We have in fact, confirmed this assignment by DEPT 135 experiment for the compound **128** (See spectrum 5) and also confirmed by hydrogen-carbon (hetero) COSY NMR experiment for the compound **128** (See spectrum 6).*

2-Aza-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,16-pentaen-7-one (**134**):

This molecule was obtained as a yellow solid *via* the treatment of methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125b**) with 1,3-cyclohexanedione in the presence of K_2CO_3 followed by reductive cyclization using Fe / AcOH, following a similar procedure as described for the molecule **127**.



Reaction time : (6 h + 1.5 h)

Yield : 77%

Mp : 208-210 ^{0}C

IR (KBr) : ν 3568, 1701, 1649 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.85-1.96 (m, 2H), 2.35 (t, 2H, *J* = 6.8 Hz), 2.49 (t, 2H, *J* = 6.8 Hz), 3.50 (b, 2H), 3.76 (s, 3H), 5.54 (s, 1H), 7.00 (d, 1H, *J* = 8.0 Hz), 7.13 (d, 1H, *J* = 8.0 Hz), 7.21-7.27 (m, 1H), 7.28-7.36 (m, 1H), 7.84 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.70, 21.01, 33.16, 36.59, 52.12, 105.54, 126.67, 126.70, 129.01, 130.07, 134.49, 135.55, 137.75, 138.01, 160.10, 167.65, 195.85

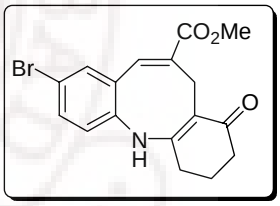
LCMS (m/z) : 284 $(M+H)^+$

Analysis calc'd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94

Found : C, 72.23; H, 6.02; N, 4.90.

2-Aza-14-bromo-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,-16-pentaen-7-one (135):

Treatment of methyl 3-acetoxy-3-(5-bromo-2-nitrophenyl)-2-methylenepropanoate (**125c**) with 1,3-cyclohexanedione in the presence of K_2CO_3 and subsequent treatment with Fe / AcOH, following a similar procedure as described for the molecule **127**, provided the title compound as a brown solid.



Reaction time : (6 h + 1.5 h)

Yield : 66%

Mp : 258-260 ^{0}C (dec.)

IR (KBr) : ν 3269, 1722, 1641 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.83-1.96 (m, 2H), 2.34 (t, 2H, *J* = 6.0 Hz), 2.49 (t, 2H, *J* = 6.0 Hz), 3.50 (b, 2H), 3.76 (s, 3H), 5.52 (s, 1H), 6.89 (d, 1H, *J* = 8.8 Hz), 7.27 (d, 1H, *J* = 2.0 Hz), 7.43 (dd, 1H, *J* = 8.8 Hz & 2.0 Hz), 7.73 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.72, 20.99, 33.10, 36.58, 52.24, 105.59, 120.08, 128.25, 131.80, 132.96, 136.43, 136.55, 136.64, 136.92, 159.64, 167.27, 195.69

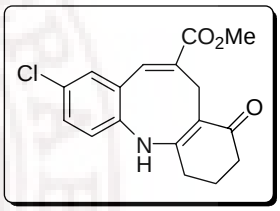
LCMS (m/z) : 360 $(M-H)^+$, 362 $(M-H+2)^+$

Analysis calc'd. for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87

Found : C, 56.23; H, 4.49; N, 3.90.

2-Aza-14-chloro-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,12,14,-16-pentaen-7-one (136):

This compound was obtained as a yellow solid *via* the treatment of methyl 3-acetoxy-3-(5-chloro-2-nitrophenyl)-2-methylenepropanoate (**125d**) with 1,3-cyclohexanedione in the presence of K_2CO_3 followed by reductive cyclization using Fe / AcOH, following a similar procedure as described for the molecule **127**.



Reaction time : (6 h + 1.5 h)

Yield : 56%

Mp : 252-254 ^{0}C (dec.)

IR (KBr) : ν 3269, 1722, 1640 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.85-1.97 (m, 2H), 2.35 (t, 2H, *J* = 6.0 Hz), 2.49 (t, 2H, *J* = 6.0 Hz), 3.50 (b, 2H), 3.77 (s, 3H), 5.48 (s, 1H), 6.95 (d, 1H, *J* = 8.8 Hz), 7.12 (d, 1H, *J* = 2.0 Hz), 7.29 (dd, 1H, *J* = 8.8 Hz & 2.0 Hz), 7.74 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.69, 20.94, 32.99, 36.57, 52.23, 105.37, 128.06, 128.79, 129.94, 132.30, 136.25, 136.38, 136.44, 136.55, 159.98, 167.28, 195.79

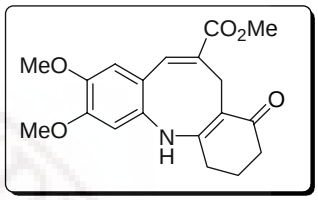
LCMS (m/z) : 318 $(M+H)^+$, 320 $(M+H+2)^+$

Analysis calc'd. for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N, 4.41

Found : C, 64.45; H, 5.07; N, 4.45.

2-Aza-14,15-dimethoxy-10-methoxycarbonyltricyclo[10.4.0.0^{3,8}]hexadeca-3(8),10,-12,14,16-pentaen-7-one (**137**)**:**

The reaction of methyl 3-acetoxy-3-(4,5-dimethoxy-2-nitrophenyl)-2-methylenepropa-noate (**125e**) with 1,3-cyclohexanedione in the presence of K_2CO_3 and subsequent treatment with Fe / AcOH, following a similar procedure as described for the molecule **127**, provided the title compound as a yellow solid.



Reaction time : (6 h + 1.5 h)

Yield : 62%

Mp : 270-272 ^{0}C

IR (KBr) : ν 3292, 1703, 1645 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.84-1.98 (m, 2H), 2.36 (t, 2H, *J* = 6.8 Hz), 2.48 (t, 2H, *J* = 6.8 Hz), 3.49 (b, 2H), 3.76 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 5.36 (s, 1H), 6.52 (s, 1H), 6.60 (s, 1H), 7.78 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.93, 20.98, 33.14, 36.67, 52.07, 56.12, 56.14, 105.38, 110.29, 110.87, 126.75, 130.30, 135.45, 138.03, 147.64, 150.04, 160.07, 167.77, 195.75

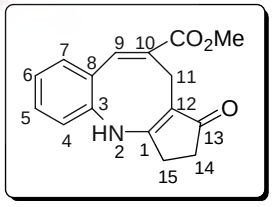
LCMS (m/z) : 342 $(M-H)^+$

Analysis calc'd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08

Found : C, 66.24: H, 6.16; N, 4.03.

Procedure for the synthesis of 2-aza-10-methoxycarbonyltricyclo[10.3.0.0^{3,8}]penta-deca-1(12),3,5,7,9-pentaen-13-one (139):

To a stirred mixture of methyl 3-acetoxy-2-methylene-3-(2-nitrophenyl)propanoate (**125b,** 1 mmol, 0.279 g) and K_2CO_3 (1 mmol. 0.138 g) in DMF (1 mL) was added 1,3-cyclopentanedione (1 mmol, 0.098 g) at room temperature. The reaction mixture was heated to 80 ^{0}C and maintained at the same temperature for 4 h. The reaction mixture was cooled to room temperature and DMF was removed under reduced pressure. Reaction mixture was diluted with acetic acid (5 mL) and heated to reflux (at 110 ^{0}C). At this temperature electrolytic iron powder (6 mmol, 0.336 g) was added and stirring continued at the same temperature for 1.5 h. Then the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure and diluted with ethyl acetate (10 mL), stirred for 5 minutes and filtered to remove iron impurities. The insoluble iron residue was washed with ethyl acetate (2 x 5 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 (100% EtOAc, silica gel) to afford the title molecule (**139**) as a pale yellow solid in 64% (0.176 g) yield.



Reaction time : (4 h + 1.5 h)

Mp : 222-224 ^{0}C (dec.)

IR (KBr) : ν 3240, 1709, 1660 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.41-2.50 (m, 2H), 2.53-2.63 (m, 2H), 3.34 (b, 2H), 3.79 (s, 3H), 6.14 (s, 1H), 6.99 (d, 1H, *J* = 8.0 Hz), 7.10 (d, 1H, *J* = 8.0 Hz), 7.21-7.38 (m, 2H), 7.81 (s, 1H)

^{13}C NMR (100 MHz) (25% DMSO-d_6 in $CDCl_3$) : δ 18.62, 26.27, 31.87, 50.75, 107.46, 124.44, 124.52, 128.27, 128.61, 130.63, 134.47, 137.10, 137.45, 165.88, 171.97, 200.51

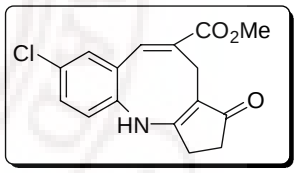
LCMS (m/z) : 270 $(M+H)^+$

Analysis calc'd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20

Found : C, 71.47; H, 5.60; N, 5.13.

2-Aza-6-chloro-10-methoxycarbonyltricyclo[10.3.0.0^{3,8}]pentadeca-1(12),3,5,7,9-pentaen-13-one (140):

This molecule was obtained as a yellow solid *via* the treatment of methyl 3-acetoxy-3-(5-chloro-2-nitrophenyl)-2-methylenepropanoate (**125d**) with 1,3-cyclopentanedione in the presence of K_2CO_3 followed by reductive cyclization using Fe / AcOH, following a similar procedure as described for the molecule **139**.



Reaction time : (4 h+1.5 h)

Yield : 55%

Mp : 230-232 ^{0}C (dec.)

IR (KBr) : ν 3234, 1714, 1651 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.39-2.46 (m, 2H), 2.53-2.63 (m, 2H), 3.34 (b, 2H), 3.78 (s, 3H), 6.51 (s, 1H), 6.98 (d, 1H, *J* = 8.4 Hz), 7.08 (d, 1H, *J* = 2.4 Hz), 7.28 (dd, 1H, *J* = 8.4 Hz & 2.4 Hz), 7.70 (s, 1H)

^{13}C NMR (100 MHz) (25% DMSO-d_6 in $CDCl_3$) : δ 18.25, 25.83, 31.47, 50.49, 106.90, 125.74, 127.50, 128.11, 129.04, 132.02, 134.99, 135.64, 135.82, 165.11, 171.30, 199.88

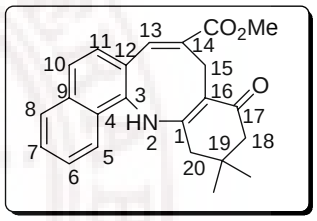
LCMS (m/z) : 304 $(M+H)^+$, 306 $(M+H+2)^+$

Analysis calc'd for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; N, 4.61

Found : C, 63.20; H, 4.67; N, 4.68.

2-Aza-19,19-dimethyl-14-methoxycarbonyltetracyclo[14.4.0.0^{3,12}.0^{4,9}]eicosa-1(16),-3,5,7,9,11,13-heptaen-17-one (142):

Treatment of methyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**125g**) with 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3, followed by reaction with Fe / AcOH following a similar procedure as described for the molecule **127**, provided the title compound as a yellow solid.



Reaction time : (4 h + 1.5 h)

Yield : 35%

Mp : 198-200 ^{0}C (dec.)

IR (KBr) : ν 3227, 1711, 1645 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.10 (s, 6H), 1.62 (s, 2H), 2.27 (s, 2H), 2.59 (b, 2H), 3.77 (s, 3H), 5.47 (s, 1H), 7.26 (d, 1H, *J* = 8.0 Hz), 7.52-7.62 (m, 2H), 7.77 (d, 1H, *J* = 8.8 Hz), 7.82-7.91 (m, 2H), 8.01 (s, 1H)

^{13}C NMR (100 MHz) : δ 21.00, 28.40, 31.74, 46.45, 50.35, 52.12, 104.08, 121.81, 125.52, 126.78, 127.36, 127.55, 128.86, 130.93, 132.31, 133.09, 134.73, 135.50, 138.38, 159.14, 167.81, 195.36

To understand the conformational rigidity / flexibility we have recorded ^{1}H and ^{13}C NMR spectra at -30 ^{0}C.

^{1}H NMR at -30 ^{0}C (400 MHz) : δ 1.01 (s, 3H), 1.15 (s, 3H), 2.24 (s, 2H), 2.45 (d, 1H, *J* = 16.0 Hz) & 2.79 (d, 1H, *J* = 16.0 Hz), 2.65 (d, 1H, *J* = 14.4 Hz) & 4.06 (d, 1H, *J* = 14.4 Hz), 3.77 (s, 3H), 5.79 (s, 1H), 7.22 (d, 1H, *J* = 8.4 Hz), 7.51-7.70 (m, 2H), 7.75 (d, 1H, *J* = 8.4 Hz), 7.81-7.97 (m, 2H), 8.01 (s, 1H)

^{13}C NMR at -30 ^{0}C (100 MHz) : δ 20.61, 25.86, 29.95, 31.59, 45.83, 49.92, 52.39, 103.23, 121.89, 125.28, 126.74, 127.28, 127.39, 128.66, 130.57, 131.87, 132.72, 134.32, 134.85, 138.66, 160.03, 167.88, 195.94

gem-Dimethyl protons (which appeared as singlet at δ 1.10 in ^{1}H NMR spectrum at room temperature) appeared as two singlets at δ 1.01 & 1.15 in the ^{1}H NMR spectrum at -30 ^{0}C. The protons of three methylene groups [at C-15, C-18 (or C-20) and C-20 (or C-18)] which appeared at δ 2.59 (b), 2.27 (s) and 1.62 (s) in ^{1}H NMR spectrum at room temperature, appeared as singlet at δ 2.24 (probably due to C-18 or C-20 methylene protons) and four doublets at δ 2.45 (1H, *J* = 16.0 Hz) & 2.79 (1H, *J* = 16.0 Hz) [probably due to C-20 (or C-18) methylene protons] and 2.65 (1H, *J* = 14.4 Hz) & 4.06 (1H, *J* = 14.4 Hz) [probably due to C-15 methylene protons] in the ^{1}H NMR spectrum at -30 ^{0}C.

gem-Dimethyl carbons (which appeared as broad peak at δ 28.40 with low intensity in ^{13}C NMR spectrum at room temperature) appeared as two distinct peaks at δ 25.86 & 29.95 with low intensity in the ^{13}C NMR spectrum at -30 ^{0}C. In the case of other carbons there is no significant change in chemical shift values in the ^{13}C NMR

spectrum at -30 ^{0}C. We have also confirmed the nature of carbons (with 3H or 2H or 1H or no H) by DEPT 135 experiment.

These differences may be attributed to the conformational changes at low temperature (rigid conformation) and room temperature (flexible conformation).

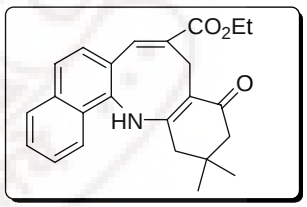
LCMS (m/z) : 362 $(M+H)^+$

Analysis calc'd. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88

Found : C, 76.46; H, 6.37; N, 3.91.

2-Aza-19,19-dimethyl-14-ethoxycarbonyltetracyclo[14.4.0.0^{3,12}.0^{4,9}]eicosa-1(16),-3,5,7,9,11,13-heptaen-17-one (143):

This molecule was obtained as a yellow solid *via* the treatment of ethyl 3-acetoxy-2-methylene-3-(1-nitronaphth-2-yl)propanoate (**125h**) with 5,5-dimethyl-1,3-cyclohexanedione in the presence of K_2CO_3 followed by reductive cyclization using Fe / AcOH, following a similar procedure as described for the molecule **127**.



Reaction time : (4 h + 1.5 h)

Yield : 33%

Mp : 210-212 ^{0}C (dec.)

IR (KBr) : ν 3256, 1707, 1682, 1630 cm^1

^{1}H NMR (400 MHz) : δ 1.11 (s, 6H), 1.29 (t, 3H, *J* = 6.8 Hz), 1.58 (s, 2H)$^{\$}$, 2.28 (s, 2H), 2.59 (b, 2H), 4.25 (q, 2H, *J* = 6.8 Hz), 5.43 (s, 1H), 7.28 (d, 1H, *J* = 7.6 Hz), 7.51-7.63 (m, 2H), 7.78 (d, 1H, *J* = 7.6 Hz), 7.84-7.91 (m, 2H), 8.01 (s, 1H)

$: *High intensity of this peak is due to the presence of moisture peak along with methylene protons peak which is confirmed by D_2O exchange.*

^{13}C NMR (100 MHz) : δ 14.29, 20.96, 27.38, 31.64, 46.24, 50.32, 60.89, 103.96, 121.90, 125.47, 126.67, 127.23, 127.42, 128.74, 130.93, 132.34, 133.13, 134.64, 135.87, 137.98, 159.20, 167.31, 195.19

LCMS (m/z) : 376 $(M+H)^+$

Analysis calc'd. for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73

Found : C, 76.64; H, 6.72; N, 3.77.

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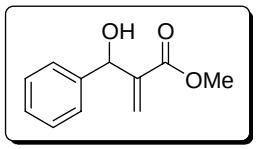
*It is interesting to note that in case of compounds **142** & **143** quaternary carbon appears as peak with high intensity at δ 31.74 & 31.64 respectively while the gem-dimethyl carbons appear as broad peak with low intensity at δ 28.40 & 27.38 respectively.*

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (160a):

A mixture of benzaldehyde (**159a**, 50 mmol, 5.30 g), methyl acrylate (75 mmol, 6.45 g, 6.75 mL) and DABCO (15 mol%, 7.5 mmol, 0.84 g) was kept at room temperature for 7 days. The reaction mixture was diluted with ether (50 mL) and washed successively with 2N HCl, aqueous $NaHCO_3$ solution and water. Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (10% EtoAc in hexanes, silica gel) to provide the pure product (**160a**) as colorless liquid in 70% (6.72 g).

IR (neat) : ν 3464, 1722, 1630 cm^{-1}



^{1}H NMR (400 MHz) : δ 3.10 (b, 1H), 3.71 (s, 3H), 5.56 (s, 1H), 5.83 (s, 1H), 6.33 (s, 1H), 7.25-7.42 (m, 5H)

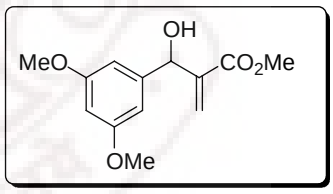
^{13}C NMR (50 MHz) : δ 51.87, 73.00, 125.85, 126.63, 127.77, 128.37, 141.40, 142.15, 166.73.

Methyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-methylenepropanoate (160b):

This was prepared according to the procedure developed in our laboratory.[265]

To a solution of 3,5-dimethoxybenzaldehyde (**159b**, 50 mmol, 8.30 g), DABCO (15 mol%, 7.5 mmol, 0.84 g) in methyl acrylate (75 mmol, 6.45 g, 6.75 mL), was added silica gel (>200 mesh) and mixed thoroughly and left at room temperature. After 10 days, reaction mixture (silica gel pack) was washed thoroughly with ethyl acetate (4 X 25 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (10% EtOAc in hexanes, silica gel) to provide the product (**160b**) as viscous liquid.

Yield : 1.56 g (62%)



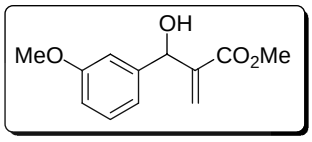
IR (neat) : ν 3483, 1714 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.11 (d, 1H, J = 6.0 Hz), 3.73 (s, 3H), 3.77 (s, 6H), 5.48 (d, 1H, J = 5.6 Hz), 5.83 (s, 1H), 6.33 (s, 1H), 6.37-6.41 (m, 1H), 6.53 (d, 2H, J = 2.0 Hz)

^{13}C NMR (100 MHz) : δ 51.96, 55.29, 73.07, 99.74, 104.56, 126.27, 141.72, 143.83, 160.79, 166.77.

Methyl 3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanoate (160c):

This compound was prepared *via* the DABCO catalyzed Baylis-Hillman coupling of 3-methoxybenzaldehyde (**159c**) with methyl acrylate following a similar procedure as described for the molecule **160b**, to provide the title compound as a colorless liquid.



Reaction time : 13 days

Yield : 68%

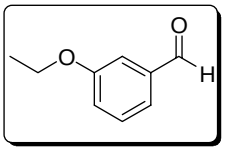
IR (neat) : ν 3510, 1716, 1601 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.07 (d, 1H, *J* = 5.6 Hz), 3.73 (s, 3H), 3.80 (s, 3H), 5.53 (d, 1H, *J* = 5.6 Hz), 5.82 (s, 1H), 6.33 (s, 1H), 6.79-6.86 (m, 1H), 6.92-6.98 (m, 2H), 7.22-7.31 (m, 1H)

^{13}C NMR (50 MHz) : δ 51.82, 55.12, 72.78, 112.20, 113.26, 118.94, 125.88, 129.32, 142.03, 143.05, 159.62, 166.70.

3-Ethoxybenzaldehyde (159d):

To a stirred solution of 3-hydroxybenzaldehyde (100 mmol, 12.21 g) and anhydrous K_2CO_3 (100 mmol, 13.8 g) in acetonitrile (150 mL), was added ethyl bromide (150 mmol, 16.34 g, 11.2 mL) and reaction mixture was heated under reflux for 5 hours. Reaction mixture was cooled to room temperature and excess acetonitrile was removed under reduced pressure. The residue thus obtained was diluted with water (100 mL) and extracted with ether (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent evaporation followed by column chromatography (3% EtOAc in hexanes, silica gel) of the resulting crude product provided the desired aldehyde **159d** as a colorless liquid.



Yield : 12.45 (83%)

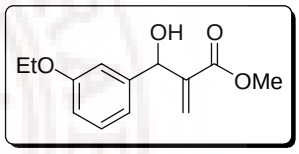
IR (neat) : ν 1699, 1599 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.44 (t, 3H, *J* = 6.8 Hz), 4.09 (q, 2H, *J* = 6.8 Hz), 7.14-7.19 (m, 1H), 7.36-7.40 (m, 1H), 7.42-7.46 (m, 2H), 9.96 (s, 1H)

^{13}C NMR (100 MHz) : δ 14.71, 63.79, 112.84, 121.95, 123.33, 130.04, 137.83, 159.55, 192.21.

Methyl 3-(3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate (160d):

This compound was obtained as a colorless liquid *via* the DABCO-catalyzed Baylis-Hillman coupling of 3-ethoxybenzaldehyde (**159d**) with methyl acrylate following a similar procedure as described for the molecule **160b**.



Reaction time : 13 days

Yield : 65%

IR (neat) : ν 3499, 1720, 1630 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.39 (t, 3H, *J* = 6.8 Hz), 3.08 (d, 1H, *J* = 6.0 Hz), 3.72 (s, 3H), 4.02 (q, 2H, *J* = 6.8 Hz), 5.51 (d, 1H, *J* = 5.2 Hz), 5.83 (d, 1H, *J* = 0.8 Hz), 6.32 (s, 1H), 6.77-6.84 (m, 1H), 6.89-6.96 (m, 2H), 7.20-7.28 (m, 1H)

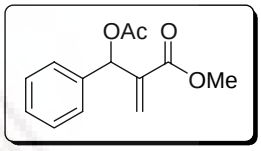
^{13}C NMR (100 MHz) : δ 14.78, 51.90, 63.34, 72.95, 112.71, 113.81, 118.80, 126.04, 129.37, 141.90, 142.95, 159.00, 166.73.

Methyl 3-acetoxy-2-methylene-3-phenylpropanoate (161a):

To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**160a**, 20 mmol, 3.84 g), pyridine (40 mmol, 3.16 g, 3.2 mL) in dry dichloromethane (25 mL) at 0 ^oC was added acetyl chloride (40 mmol, 3.12 g, 2.82 mL). After stirring at room

temperature for 2 hours, the reaction mixture was diluted with ether (50 mL) and washed successively with 2N HCl solution, saturated $NaHCO_3$ solution and water. Organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the crude product, thus obtained, was purified by column chromatography (3% EtOAc in hexanes, silica gel) to afford the pure methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**161a**) as colorless liquid in 64% (2.99 g) yield.

IR (neat) : ν 1743, 1724, 1633 cm^{-1}

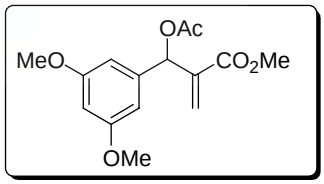


^{1}H NMR (400 MHz) : δ 2.10 (s, 3H), 3.70 (s, 3H), 5.86 (s, 1H), 6.40 (s, 1H), 6.68 (s, 1H), 7.28-7.52 (m, 5H)

^{13}C NMR (50 MHz) : δ 20.84, 51.77, 73.00, 125.59, 127.53, 128.25, 128.33, 137.74, 139.65, 165.25, 169.20.

Methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methylenepropanoate (161b):

This molecule was obtained as a colorless liquid *via* the treatment of methyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-methylenepropanoate (**160b**) with acetyl chloride, in the presence of pyridine, following a similar procedure as described for the molecule **161a**.



Reaction time : 2 h

Yield : 73%

IR (neat) : ν 1747, 1723, 1620 cm^{-1}

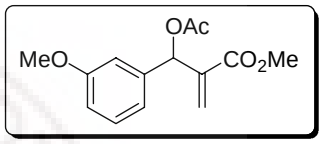
^{1}H NMR (400 MHz) : δ 2.11 (s, 3H), 3.73 (s, 3H), 3.77 (s, 6H), 5.83 (s, 1H), 6.39 (s, 2H), 6.52 (d, 2H, J = 2.4 Hz), 6.62 (s, 1H)

^{13}C NMR (50 MHz) : δ 20.89, 51.87, 55.22, 72.83, 100.12, 105.62, 126.05, 139.51, 140.04, 160.78, 165.34, 169.25.

Methyl 3-acetoxy-3-(3-methoxyphenyl)-2-methylenepropanoate (161c):

Treatment of methyl 3-hydroxy-(3-methoxyphenyl)-2-methylenepropanoate (**160c**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the molecule **161a**, provided the title compound as a colorless liquid.

Reaction time : 2 h



Yield : 79%

IR (neat) : ν 1747, 1725, 1625 cm^{-1}

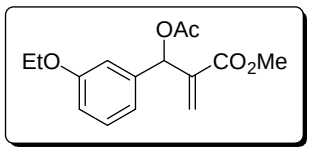
^{1}H NMR (400 MHz) : δ 2.10 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 5.84 (s, 1H), 6.39 (s, 1H), 6.66 (s, 1H), 6.81-6.88 (m, 1H), 6.91(s, 1H), 6.96 (d, 1H, *J* = 7.6 Hz), 7.21-7.30 (m, 1H)

^{13}C NMR (50 MHz) : δ 20.82, 51.77, 55.02, 72.80, 113.29, 113.60, 119.76, 125.75, 129.37, 139.29, 139.58, 159.57, 165.27, 169.18.

Methyl 3-acetoxy-3-(3-ethoxyphenyl)-2-methylenepropanoate (161d):

Treatment of methyl 3-(3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate (**160d**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the molecule **161a**, provided the title molecule as a colorless liquid.

Reaction time : 2 h



Yield : 71%

IR (neat) : ν 1747, 1726, 1633 cm^{-1}

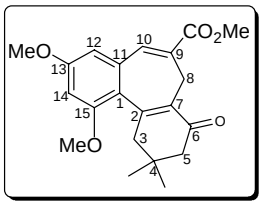
^{1}H NMR (400 MHz) : δ 1.40 (t, 3H, J = 8.0 Hz), 2.10 (s, 3H), 3.71 (s, 3H), 4.01 (q, 2H, J = 6.8 Hz), 5.84 (s, 1H), 6.39 (s, 1H), 6.65

(s, 1H), 6.82 (d, 1H, *J* = 8.0 Hz), 6.90 (s, 1H), 6.94 (d, 1H, *J* = 7.6 Hz), 7.21-7.29 (m, 1H)

^{13}C NMR (50 MHz) : δ 14.68, 20.94, 51.87, 63.32, 72.87, 113.89, 114.16, 119.74, 125.80, 129.39, 139.24, 139.63, 158.94, 165.34, 169.25.

13,15-dimethoxy-4,4-dimethyl-9-methoxycarbonyltricyclo[9.4.0.0^{2,7}]pentadeca-1(15),2(7),9,11,13-pentaen-6-one (168):

A mixture of methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methylenepropanoate (**161b**, 1 mmol, 0.294 g), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol, 0.140 g) in triethylamine (1 mL) was stirred at room temperature for 12 h. Then excess triethylamine was removed under reduced pressure and the reaction mixture was diluted with dichloromethane (3 mL). Oxalyl chloride (5 mmol, 0.635 g, 0.42 mL) was then added dropwise and stirred at room temperature for 5 h. Excess oxalyl chloride and the solvent dichloromethane were evaporated and the reaction mixture was diluted with 1,2-dichloroethane (DCE) (3 mL). A solution of $TiCl_4$ in DCE (2 mmol, 1 mL, 2M solution in DCE) was then added dropwise at 0 ^{0}C and stirring continued at room temperature for 4 h. Reaction mixture was diluted with water (10 mL) and extracted with ether (3 X 15 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (20% EtOAc in hexanes, silica gel) to provide the title compound **168**, as a colorless solid in 0.256g (72%) isolated yield.



Reaction time : 12 h + 5 h + 4 h

Mp : 124-126 ^{0}C

IR (KBr) : ν 1718, 1662, 1630, 1601 cm^{-1}

^1H NMR (400 MHz) : δ 0.79 (s, 3H), 1.09 (s, 3H), 1.76 (d, 1H, *J* = 13.2 Hz),# 2.02 (d, 1H, *J* = 16.8 Hz),# 2.26 (d, 1H, *J* = 16.4 Hz),# 2.40 (d, 1H, *J* = 16.4 Hz),# 3.20 (d, 1H, *J* = 16.8 Hz),# 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.30 (d, 1H, *J* = 13.2 Hz), # 6.52 (d, 1H, *J* = 2.0 Hz), 6.54 (d, 1H, *J* = 2.0 Hz), 7.59 (s, 1H)

#: The six protons of the three CH_2 group appears as six clear doublets.

^{13}C NMR (100 MHz) : δ 21.66, 26.62, 29.22, 34.35, 44.52, 51.43, 52.31, 55.51, 55.67, 99.56, 105.03, 123.90, 134.26, 135.96, 137.05, 137.29, 148.91, 159.05, 159.97, 166.37, 196.61

LCMS (m/z) : 357 $(M+H)^+$

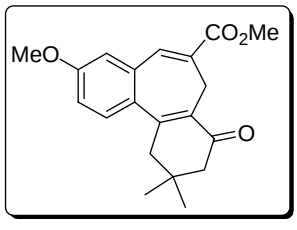
Analysis calc'd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79

Found : C, 70.65; H, 6.83.

4,4-Dimethyl-13-methoxy-9-methoxycarbonyltricyclo[9.4.0.0^{2,7}]pentadeca-1(15),-2(7),9,11,13-pentaen-6-one (169):

Treatment of 5,5-dimethyl-1,3-cyclohexanedione with methyl 3-acetoxy-3-(3-methoxy-phenyl)-2-methylenepropanoate (**161c**) in the presence of Et_3N, and subsequent treatment with oxalyl chloride in DCM followed by $TiCl_4$ in 1,2-dichloroethane, provided the title compound (**169**) as a colorless solid, following the similar procedure as described for the compound **168**.

Reaction time : (12 h + 5 h + reflux 8 h)



Yield : 67%

Mp : 84-86 ^{0}C

IR (KBr) : ν 1701, 1651, 1628, 1604 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.03 (s, 6H), 2.36 (s, 2H), 2.63 (s, 2H), 3.06 (b, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 6.91-6.96 (m, 1H),* 6.97-7.04 (m, 1H),# 7.57 (d, 1H, *J* = 8.8 Hz), 7.62 (s, 1H)

*: It is an unresolved doublet

#: It is an unresolved doublet of doublet

^{13}C NMR (100 MHz) : δ 21.03, 28.25, 33.69, 45.06, 50.89, 52.34, 55.47, 114.08, 115.47, 129.61, 133.25, 133.50, 134.29, 137.22, 148.84, 159.02, 166.38, 196.48

LCMS (m/z) : 327 $(M+H)^+$

Analysis calc'd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79

Found : C, 73.71; H, 6.74.

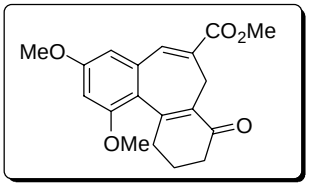
13,15-Dimethoxy-9-methoxycarbonyltricyclo[9.4.0.0^{2,7}]pentadeca-1(15),2(7),9,11,-13-pentaen-6-one (170):

This product was obtained as a colorless solid, *via* the treatment of 1,3-cyclohexanedi-one with methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methylenepropanoate (**161b**) in the presence of Et_3N, and subsequent treatment with oxalyl chloride in DCM followed by $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for product **168**.

Reaction time : (12 h + 5 h + 4 h)

Yield : 75%

Mp : 108-110 ^{0}C



IR (KBr) : ν 1714, 1660, 1630, 1597 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.69-1.87 (m, 2H), 1.97-2.09 (m, 1H), 2.15-2.26 (m, 1H), 2.42-2.58 (m, 2H), 3.22-3.36 (m, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.31 (dd, 1H, *J* = 13.2 Hz & 1.2 Hz), 6.50-6.59 (m, 2H), 7.58 (s, 1H)

^{13}C NMR (100 MHz) : δ 21.72, 23.89, 30.98, 38.03, 52.29, 55.51, 55.73, 99.58, 105.12, 123.63, 135.52, 136.03, 137.20, 137.40, 151.42, 159.01, 159.96, 166.42, 196.60

LCMS (m/z) : 329 $(M+H)^+$

Analysis calc'd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14

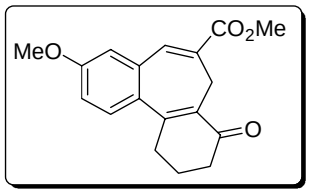
Found : C, 69.72; H, 6.13.

13-Methoxy-9-methoxycarbonyltricyclo[9.4.0.0^{2,7}]pentadeca-1(15),2(7),9,11,13-pentaen-6-one (171):

This compound was obtained as a pale yellow liquid, *via* the treatment of 1,3-cyclohexanedione with methyl 3-acetoxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**161c**) in the presence of Et_3N followed by treatment with oxalyl chloride in DCM and $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for product **168**.

Reaction time : (12 h + 5 h + reflux 8 h)

Yield : 64%



IR (neat) : ν 1707, 1660, 1601 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.98-2.14 (m, 2H), 2.50 (t, 2H, *J* = 7.2 Hz), 2.72-2.84 (m, 2H), 3.08 (b, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 6.93 (d, 1H, *J* = 2.8 Hz), 7.00 (dd, 1H, *J* = 8.8 Hz & 2.8 Hz), 7.58 (d, 1H, *J* = 8.8 Hz), 7.62 (s, 1H)

^{13}C NMR (100 MHz) : δ 21.15, 23.11, 30.99, 37.40, 52.31, 55.44, 114.13, 115.44, 129.50, 133.06, 134.18, 134.73, 137.22, 137.25, 151.26, 159.02, 166.39, 196.35

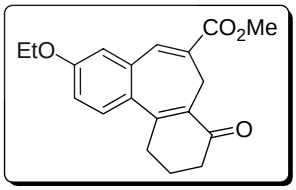
LCMS (m/z) : 299 $(M+H)^{+}$

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

Found : C, 72.28; H, 6.12.

13-Ethoxy-9-methoxycarbonyltricyclo[9.4.0.0^{2,7}]pentadeca-1(15),2(7),9,11,13-pentaen-6-one (172):

This compound was obtained as a pale yellow liquid, *via* the treatment of 1,3-cyclohexanedione with methyl 3-acetoxy-3-(3-ethoxyphenyl)-2-methylenepropanoate (**160d**) in the presence of Et_3N, and then treatment with oxalyl chloride in DCM followed by $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for product **168**.



Reaction time : (12 h + 5 h + reflux 8 h)

Yield : 61%

IR (neat) : ν 1712, 1660, 1625, 1602 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.45 (t, 3H, *J* = 6.8 Hz), 1.99-2.09 (m, 2H), 2.50 (t, 2H, *J* = 6.8 Hz), 2.72-2.80 (m, 2H), 3.07 (b, 2H), 3.84 (s, 3H), 4.10 (q, 2H, *J* = 6.8 Hz), 6.92 (d, 1H, *J* = 2.8 Hz),

6.98 (dd, 1H, *J* = 2.8 Hz & 8.8 Hz), 7.57 (d, 1H, *J* = 8.8 Hz), 7.61 (s, 1H)

^{13}C NMR (100 MHz) : δ 14.80, 21.19, 23.14, 31.03, 37.44, 52.35, 63.75, 114.71, 115.90, 129.50, 132.93, 134.11, 134.69, 137.24, 137.35, 151.34, 158.45, 166.47, 196.40

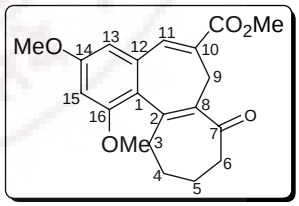
LCMS (m/z) : 313 $(M+H)^+$

Analysis calc'd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45

Found : C, 73.15; H, 6.52.

14,16-Dimethoxy-10-methoxycarbonyltricyclo[10.4.0.0^{2,8}]hexadeca-1(16),2(8),10,-12,14-pentaen-7-one (173):

Treatment of 1,3-cycloheptanedione with methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methylenepropanoate (**161b**) in the presence of Et_3N, followed by reaction with oxalyl chloride in DCM and then with $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for product **168**, provided the title compound (**173**) as a yellow solid.



Reaction time : (14 h + 5 h + 8 h)

Yield : 63%

Mp : 142-144 ^{0}C

IR (KBr) : ν 1709, 1647, 1591 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.48-1.61 (m, 1H), 1.70-1.91 (m, 3H), 1.92-2.03 (m, 1H), 2.40-2.54 (m, 2H), 2.64-2.78 (m, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.00 (dd, 1H, *J* = 13.2 Hz &

1.6 Hz), 6.50 (d, 1H, *J* = 2.4 Hz), 6.51 (d, 1H, *J* = 2.4 Hz), 7.54 (s, 1H)#

#: It is an unresolved triplet.

^{13}C NMR (100 MHz) : δ 20.50, 24.75, 26.14, 32.15, 41.17, 52.18, 55.45, 55.62, 99.43, 104.28, 125.86, 136.56, 136.67, 136.94, 140.17, 145.67, 158.76, 159.44, 166.25, 203.90

LCMS (m/z) : 343 $(M+H)^+$

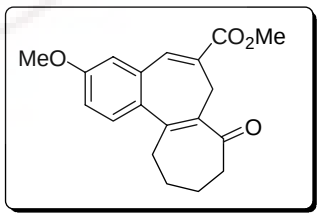
Analysis calc'd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48

Found : C, 70.22; H, 6.44.

14-Methoxy-10-methoxycarbonyltricyclo[10.4.0.0^{2,8}]hexadeca-1(16),2(8),10,12,14-pentaen-7-one (174):

This compound was obtained as a pale yellow liquid, *via* the treatment of 1,3-cycloheptanedione with methyl 3-acetoxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**161c**) in the presence of Et_3N, followed by reaction with oxalyl chloride in DCM and then with $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for product **168**.

Reaction time : (14 h + 5 h + reflux 8 h)



Yield : 59%

IR (neat) : ν 1712, 1651, 1602 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.70-1.82 (m, 4H), 2.56-2.65 (m, 2H), 2.74-2.82 (m, 2H), 2.92 (b, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 6.90 (d, 1H,

J = 2.8 Hz), 6.99 (dd, 1H, J = 2.8 Hz & 8.8 Hz), 7.56 (d, 1H, J = 8.8 Hz), 7.60 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.22, 24.26, 25.57, 32.25, 40.90, 52.25, 55.43, 113.22, 115.37, 130.13, 134.59, 134.68, 136.92, 137.06, 138.08, 145.19, 158.40, 166.26, 204.74

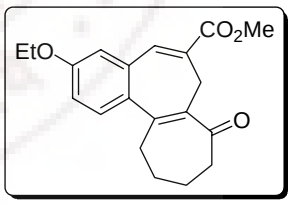
LCMS (m/z) : 313 $(M+H)^+$

Analysis calc'd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45

Found : C, 72.90; H, 6.50.

14-Ethoxy-10-methoxycarbonyltricyclo[10.4.0.0^{2,8}]hexadeca-1(16),2(8),10,12,14-pentaen-7-one (175):

This compound was obtained as a pale yellow liquid, *via* the reaction of 1,3-cycloheptanedione with methyl 3-acetoxy-3-(3-ethoxyphenyl)-2-methylenepropanoate (**161d**) in the presence of Et_3N, and subsequent treatment with oxalyl chloride in DCM followed by treatment with $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for product **168**.



Reaction time : (14 h + 5 h + reflux 8 h)

Yield : 57%

IR (neat) : ν 1716, 1651, 1630, 1600 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.44 (t, 3H, J = 6.8 Hz), 1.71-1.82 (m, 4H), 2.56-2.63 (m, 2H), 2.75-2.81 (m, 2H), 2.92 (b, 2H), 3.84 (s, 3H), 4.10 (q, 2H, J = 6.8 Hz), 6.88 (d, 1H, J = 1.6 Hz), 6.97 (dd, 1H, J = 1.6 Hz & 8.8 Hz), 7.55 (d, 1H, J = 8.8 Hz), 7.58 (s, 1H)

^{13}C NMR (100 MHz) : δ 14.84, 20.26, 24.30, 25.60, 32.28, 40.94, 52.31, 63.72, 113.82, 115.83, 130.14, 134.51, 134.56, 137.04, 137.09, 138.03, 145.32, 157.83, 166.36, 204.85

LCMS (m/z) : 327 $(M+H)^+$

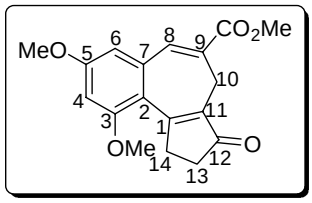
Analysis calc'd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79

Found : C, 73.72; H, 6.72.

3,5-Dimethoxy-9-methoxycarbonyltricyclo[9.3.0.0^{2,7}]tetradeca-1(11),2,4,6,8-pentaen-12-one (176):

To a stirred mixture of methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methylenepropanoate (**161b**, 1 mmol, 0.294 g) and Et_3N (1 mL) in DMF (1 mL) was added 1,3-cyclopentanedione (1 mmol, 0.098 g) at room temperature and heated to 80 ^{0}C . After stirring for 8 h at this temperature the reaction mixture was cooled to room temperature. Then DMF and excess triethylamine was removed under reduced pressure and the reaction mixture was diluted with dichloromethane (3 mL). Oxalyl chloride (5 mmol, 0.635 g, 0.42 mL) was then added dropwise and stirring continued at room temperature for 5 h. Excess oxalyl chloride and the solvent dichloromethane were removed under reduced pressure and the reaction mixture was diluted with 1,2-dichloroethane (DCE) (3 mL). A solution of $TiCl_4$ in DCE (2 mmol, 1 mL, 2M solution in DCE) was then added dropwise at 0 ^{0}C and heated under reflux for 8 h. Then the reaction mixture was allowed to cool to room temperature and diluted with water (10 mL) and extracted with ether (3 X 15 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by silica gel column

chromatography (40% EtOAc in hexanes) to provide the title compound (**176**) as a brown solid in 52% (0.163 g) isolated yield.



Reaction time : (8 h + 5 h + reflux 8 h)

Mp : 138-140 ^{0}C

IR (KBr) : ν 1703, 1682, 1630, 1597 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.48-2.55 (m, 2H), 3.05 (s, 2H), 3.06-3.15 (m, 2H), 3.83 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 6.55 (d, 1H, *J* = 2.0 Hz), 6.58 (d, 1H, *J* = 2.0 Hz), 7.61 (s, 1H)

^{13}C NMR (100 MHz) : δ 19.55, 29.06, 35.65, 52.45, 55.56, 55.70, 99.63, 106.82, 118.70, 133.47, 137.66, 137.90, 138.42, 159.98, 160.81, 164.70, 166.53, 206.68

LCMS (m/z) : 315$(M+H)^+$

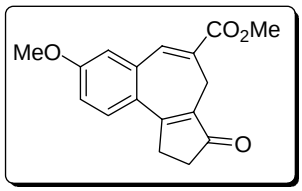
Analysis calc'd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77

Found : C, 68.74; H, 5.62.

5-Methoxy-9-methoxycarbonyltricyclo[9.3.0.0^{2,7}]tetradeca-1(11),2,4,6,8-pentaen-12-one (177):

This compound was obtained as a pale yellow solid, *via* the treatment of 1,3-cyclopentanedione with methyl 3-acetoxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**161c**) in the presence of Et_3N, followed by treatment with oxalyl chloride in DCM and then with $TiCl_4$ in 1,2-dichloroethane, following the similar procedure described for the compound **176**.

Reaction time : (8 h + 5 h + reflux 14 h)



Yield : 53%

Mp : 132-134 ^{0}C

IR (KBr) : ν 1709, 1680, 1633, 1599 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.54-2.63 (m, 2H), 2.89-2.97 (m, 2H), 3.21 (s, 2H), 3.83 (s, 3H), 3.89 (s, 3H), 6.98 (s, 1H),$^{\#}$ 7.01 (dd, 1H, *J* = 2.0 Hz & 8.4 Hz), 7.61 (d, 1H, *J* = 8.4 Hz), 7.65 (s, 1H)

#: It is an unresolved doublet.

^{13}C NMR (100 MHz) : δ 19.86, 27.56, 34.93, 52.50, 55.54, 115.52, 116.62, 128.12, 129.08, 131.32, 136.86, 136.87,138.60, 160.43, 165.03, 166.80, 206.27

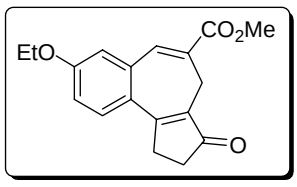
LCMS (m/z) : 285 $(M+H)^+$

Analysis calc'd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67

Found : C, 71.75; H, 5.70.

5-Ethoxy-9-methoxycarbonyltricyclo[9.3.0.0^{2,7}]tetradeca-1(11),2,4,6,8-pentaen-12-one (178):

Treatment of 1,3-cyclopentanedione with methyl 3-acetoxy-3-(3-ethoxyphenyl)-2-methylenepropanoate (**161d**) in the presence of Et_3N, and subsequent treatment with oxalyl chloride in DCM followed by treatment with $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for the molecule **176**, provided the title compound as a pale yellow solid.



Reaction time : (8 h + 5 h + reflux 14 h)

Yield : 50%

Mp : 140-142 ^{0}C

IR (KBr) : ν 1701, 1689, 1624, 1591 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.46 (t, 3H, *J* = 7.2 Hz), 2.57 (t, 2H, *J* = 4.8 Hz), 2.86-2.96 (m, 2H), 3.21 (s, 2H), 3.83 (s, 3H), 4.12 (q, 2H, *J* = 7.2 Hz), 6.97 (d, 1H, *J* = 2.4 Hz), 7.00 (dd, 1H, *J* = 2.4 Hz & 8.8 Hz), 7.60 (d, 1H, *J* = 8.8 Hz), 7.63 (s, 1H)

^{13}C NMR (100 MHz) : δ 14.75, 19.87, 27.56, 34.93, 52.50, 63.85, 115.97, 117.14, 127.95, 129.07, 131.20, 136.74, 136.85, 138.69, 159.85, 165.13, 166.84, 206.31

LCMS (m/z) : 299 $(M+H)^+$

Analysis calc'd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08

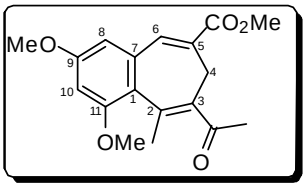
Found : C, 72.69; H, 6.10.

3-Acetyl-9,11-dimethoxy-5-methoxycarbonyl-2-methylbicyclo[5.4.0]undeca-1(7),-2,5,8,10-pentaene (179):

This compound was obtained as a colorless solid by the reaction of 2,4-pentanedione with methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methylenepropanoate (**161b**) in the presence of Et_3N, followed by treatment with oxalyl chloride in DCM and then with $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for the molecule **168**.

Reaction time : (reflux 10 h + 8 h + 1 h)

Yield : 50%



Mp : 118-120 ^{0}C

IR (KBr) : ν 1709, 1672, 1628, 1591 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.09 (d, 1H, *J* = 14.0 Hz), 2.15 (s, 3H), 2.44 (s, 3H), 3.67 (dd, 1H, *J* = 1.2 Hz & 14.0 Hz), 3.85 (s, 6H), 3.86 (s, 3H), 6.51 (d, 1H, *J* = 2.4 Hz), 6,53 (d, 1H, *J* = 2.4 Hz), 7.63 (s, 1H)

^{13}C NMR (100 MHz) : δ 21.58, 27.24, 30.56, 52.23, 55.45, 55.67, 99.82, 104.24, 126.09, 135.08, 136.34, 137.70, 139.13, 159.26, 159.34, 166.40, 201.48

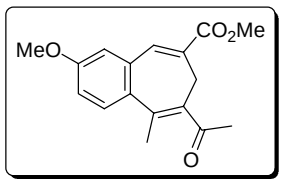
LCMS (m/z) : 317 $(M+H)^+$

Analysis calc'd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37

Found : C, 68.55; H, 6.31.

3-Acetyl-9-methoxy-5-methoxycarbonyl-2-methylbicyclo[5.4.0]undeca-1(7),2,5,8,-10-pentaene (180):

This compound was obtained as a colorless liquid, *via* the treatment of 2,4-pentanedione with methyl 3-acetoxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**161c**) in the presence of Et_3N, and subsequent treatment with oxalyl chloride in DCM followed by reaction with $TiCl_4$ in 1,2-dichloroethane, following the similar procedure as described for the product **168**.



Reaction time : (reflux 10 h + 8 h + reflux 8 h)

Yield : 46%

IR (neat) : ν 1711, 1680, 1630, 1604 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.24 (s, 3H), 2.45 (s, 3H), 2.86 (s, 2H), 3.86 (s, 6H), 6.90 (d, 1H, *J* = 2.8 Hz), 6.99 (dd, 1H, *J* = 2.8 Hz & 8.8 Hz), 7.60 (d, 1H, *J* = 8.8 Hz), 7.67 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.97, 26.60, 30.26, 52.29, 55.41, 113.43, 115.63, 130.75, 132.95, 135.06, 136.06, 136.85, 137.84, 138.24, 158.08, 166.37, 202.76

LCMS (m/z) : 287 $(M+H)^+$

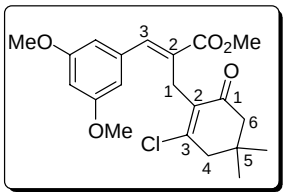
Analysis calc'd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34

Found : C, 71.14; H, 6.40.

3-Chloro-2-[(3*E*)-(3,5-dimethoxyphenyl)-2-methoxycarbonyl-prop-2-ene-1-yl]-5,5-dimethylcyclohex-2-enone (181):

A mixture of methyl 3-acetoxy-3-(3,5-dimethoxyphenyl)-2-methylenepropanoate (**161b**, 1 mmol, 0.294 g), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol, 0.140 g) in triethylamine (1 mL) was stirred at room temperature for 12 h. Then excess triethylamine was removed under reduced pressure and the reaction mixture was diluted with dichloromethane (3 mL). Oxalyl chloride (5 mmol, 0.635 g, 0.42 mL) was then added dropwise and stirred at room temperature for 5 h. Excess oxalyl chloride and the solvent dichloromethane were evaporated, the reaction mixture was diluted with ether (15 mL) and washed with saturated aqueous $NaHCO_3$ solution. Organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the crude product, thus obtained, was purified by column chromatography (10% EtOAc in hexanes, silica gel) to afford the title compound (**181**) as a pale yellow liquid in 75% (0.294 g) isolated yield.

Reaction time : 12 h + 5 h



IR (neat) : 1718, 1672 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.98 (s, 6H), 2.20 (s, 2H), 2.49 (s, 2H), 3.70 (s, 2H), 3.75 (s, 3H), 3.78 (s, 6H), 6.40 (s, 1H), 6.48 (d, 2H, J = 2.0 Hz), 7.65 (s, 1H)

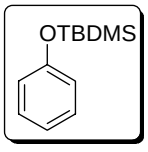
^{13}C NMR (100 MHz) : δ 25.30, 27.96, 33.10, 49.00, 50.81, 52.05, 55.42, 100.45, 106.85, 130.43, 134.20, 137.80, 139.80, 151.77, 160.61, 168.14, 195.80

LCMS (*m/z*) : 393 $(M+H)^{+}$, 395 $(M+H+2)^{+}$

***tert*-Butyldimethylsilyloxybenzene (188):**

This was prepared according to the literature procedure with slight modification.[264]

To a stirred solution of phenol (60 mmol, 5.64 g) and imidazole (90 mmol, 6.12 g) in dry DMF (200 mL) *tert*-butyldimethylsilyl chloride (66 mmol, 9.94 g) was added at 0 ^{0}C. The solution was stirred at this temperature for 12 h and allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic layer was washed with saturated NaOH (100 mL) and brine solution (100 mL) respectively. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue thus obtained was purified by column chromatography (1% EtoAc in hexanes, silica gel) to provide the desired compound as a colorless liquid.



Yield : 86%

IR (neat) : ν 2932, 1597 cm^{-1}

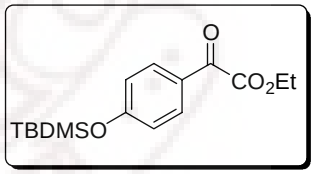
^{1}H NMR (400 MHz) : δ 0.19 (s, 6H), 0.98 (s, 9H), 6.79-6.86 (m, 2H), 6.90-6.97 (m, 1H), 7.18-7.25 (m, 2H)

^{13}C NMR (100 MHz) : δ -4.32, 18.30, 25.79, 120.21, 121.36, 129.46, 155.90

Ethyl (4-*tert*-butyldimethylsilyloxyphenyl)glyoxylate (189):

This was prepared according to the literature procedure with slight modification.[263]

To a cooled stirred solution of anhydrous $AlCl_3$ (40 mmol, 5.32 g) in dry 1,2-dichloroethane (75 mL), ethyl chlorooxoacetate (60 mmol, 8.19 g) was added dropwise over 5 min at 0 ^{0}C. Then *tert*-butyldimethylsilyloxybenzene (**188,** 40 mmol, 8.33 g) was added at this temperature. The mixture was allowed to warm to room temperature and stirred for 12 h. Then the reaction mixture was poured over crushed ice and conc. HCl (100 mL) and extracted with ethyl acetate (3 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4. The crude thus obtained was purified by column chromatography (10% EtOAc in hexanes, silica gel) to provide the title compound **189**, in 52% (6.89 g) isolated yield as a colorless liquid.



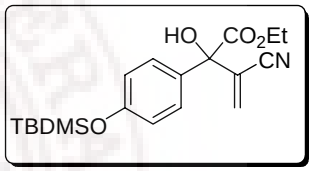
IR (neat) : ν 1738, 1682, 1597 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.25 (s, 6H), 0.99 (s, 9H), 1.41 (t, 3H, *J* = 6.8 Hz), 4.43 (q, 2H, *J* = 6.8 Hz), 6.91 (d, 2H, *J* = 8.8 Hz), 7.95 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (100 MHz) : δ -4.33, 14.13, 18.27, 25.55, 62.12, 120.37, 126.04, 132.49, 162.05, 164.21, 185.00.

3-(4-*tert*-Butyldimethylsilyloxyphenyl)-3-ethoxycarbonyl-3-hydroxy-2-methylene-propanenitrile (190):

A mixture of ethyl (4-*tert*-butyldimethylsilyloxyphenyl)glyoxylate (**189**, 25 mmol, 7.71 g), acrylonitrile (50 mmol, 2.65 g, 3.3 mL) and DABCO (30 mol%, 0.84 g) was kept at room temperature for 4 days. The reaction mixture was diluted with water (15 mL) and extracted with ether (3 X 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained, was purified by column chromatography (20% EtOAc in hexanes, silica gel) to furnish the title compound (**190**) as a colorless liquid.



Yield : 48% (4.33 g)

IR (neat) : ν 3479, 2932, 2229, 1736, 1606 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.20 (s, 6H), 0.97 (s, 9H), 1.37 (t, 3H, J = 6.8 Hz), 4.11 (s, 1H), 4.30-4.47 (m, 2H), 6.11 (s, 1H), 6.16 (s, 1H), 6.84 (d, 2H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.8 Hz)

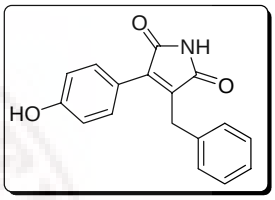
^{13}C NMR (100 MHz) : δ -4.34, 14.04, 18.25, 25.69, 63.91, 78.44, 117.03, 120.16, 125.63, 127.78, 130.19, 132.78, 156.45, 171.95

LCMS (*m/z*) : 360 $(M-H)^+$.

3-Benzyl-4-(4-hydroxyphenyl)-1*H*-pyrrole-2,5-dione (191):

To a stirred solution of 3-(4-*tert*-butyldimethylsiloxyphenyl)-3-ethoxycarbonyl-3-hydroxy-2-methylenepropanenitrile (**190**, 1 mmol, 0.361 g) in benzene (6 mL) was added methanesulfonic acid (3 mmol, 0.288 g, 0.2 mL) at room temperature and heated under reflux for 4 h. Then the reaction mixture was allowed to cool to room

temperature and diluted with water (10 mL). Aqueous $NaHCO_3$ solution was added slowly to neutralize the acid and extracted with ether (3 X 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (40% EtOAc in hexanes, silica gel) to furnish the title compound as a yellow solid in 47% (0.132 g) isolated yield.



Reaction time : 4 h

Mp : 176-178 ^{o}C (dec.)

IR (KBr) : ν 3271, 1763, 1640, 1608 cm^{-1}

^{1}H NMR (400 MHz)
(25% DMSO-d_6 in $CDCl_3$) : δ 3.89 (s, 2H), 6.86 (d, 2H, *J* = 8.8 Hz), 7.17-7.35 (m, 5H), 7.40 (d, 2H, *J* = 8.4 Hz), 9.59 (b, 1H), 10.50 (s, 1H)

^{13}C NMR (100 MHz)
(25% DMSO-d_6 in $CDCl_3$) : δ 28.19, 114.56, 118.59, 125.36, 127.02, 127.52, 129.87, 134.44, 136.52, 137.63, 157.99, 171.35, 171.91

LCMS (*m/z*) : 280 $(M+H)^{+}$

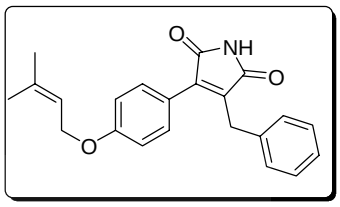
Anal. calc'd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02

Found : C, 73.23; H, 4.65; N, 5.09.

3-Benzyl-4-[4-(3-methylbut-2-enoxy)]-1*H*-pyrrole-2,5-dione (182):

A mixture of 3-benzyl-4-(4-hydroxyphenyl)-1*H*-pyrrole-2,5-dione (**191**, 0.3 mmol, 0.083 g), 1-bromo-3-methyl-2-butene (0.3 mmol, 0.044 g) and anhydrous K_2CO_3 (0.45 mmol, 0.062 g) in acetone (2 mL) was heated at reflux for 6 h. Reaction mixture was cooled to room temperature, acetone was removed under reduced pressure.The residue thus obtained was diluted with water (2 mL) and extracted with ether (3X 5 mL). The

organic layer thus obtained was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (10% EtOAc in hexanes, silica gel) to furnish the compound as a pale yellow solid in 50% (0.052 g) isolated yield.



Yield : 50% (0.052 g)

Mp : 108-110 ^{o}C (dec.)

IR (KBr) : ν 3414, 2926, 1768, 1712, 1602 cm^{-1}

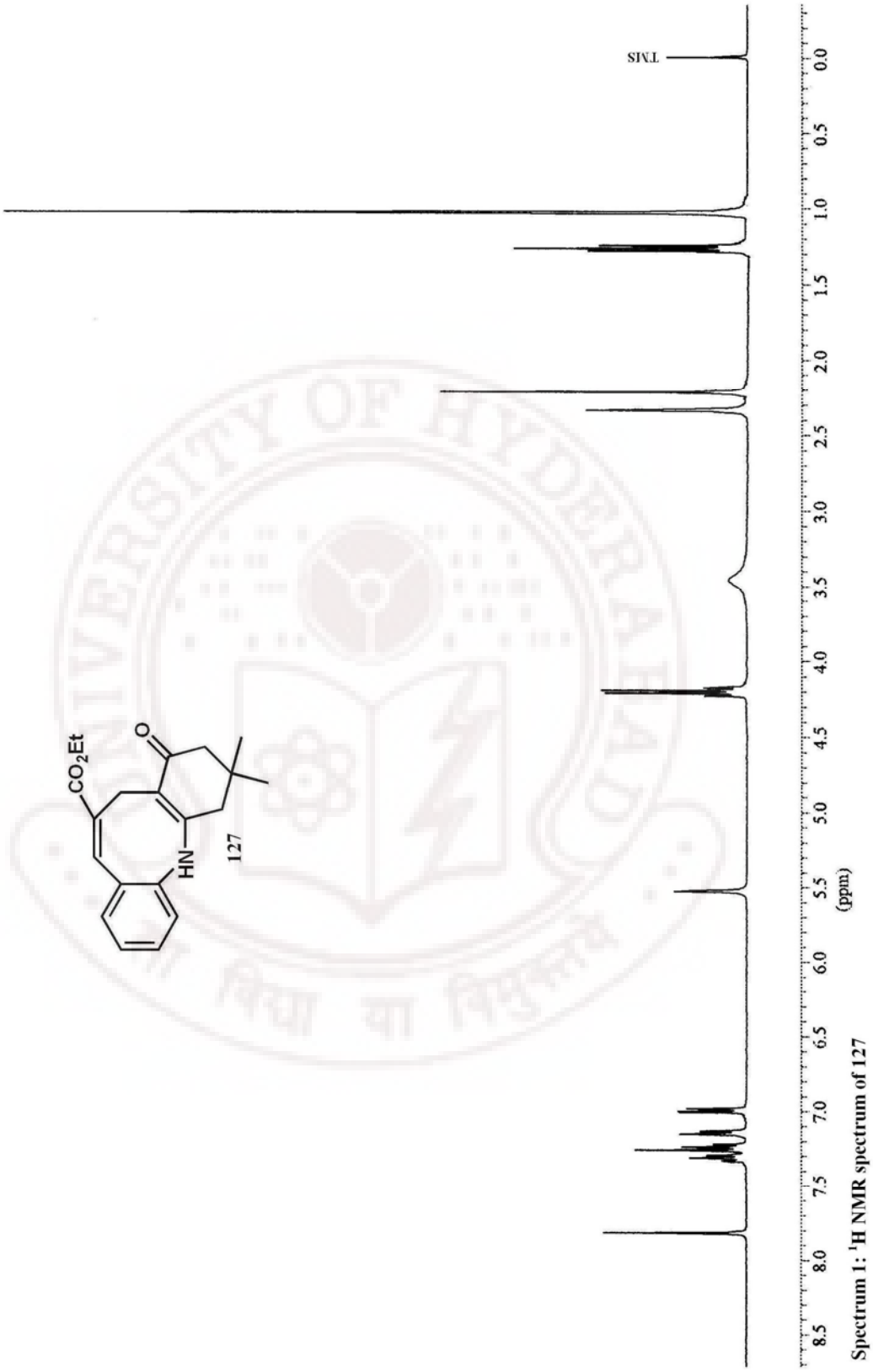
^{1}H NMR (400 MHz) : 1.74 (s, 3H), 1.80 (s, 3H), 3.94 (s, 2H), 4.54 (d, 2H, *J* = 6.8 Hz), 5.48 (t, 1H, *J* = 6.8 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 7.18-7.34 (m, 5H), 7.43 (b, 1H), 7.52 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (100 MHz) : δ 18.32, 25.91, 29.86, 65.01, 115.05, 119.24, 120.86, 126.91, 128.44, 128.96, 131.20, 136.96, 137.25, 138.84, 139.25, 160.52, 170.98, 171.47

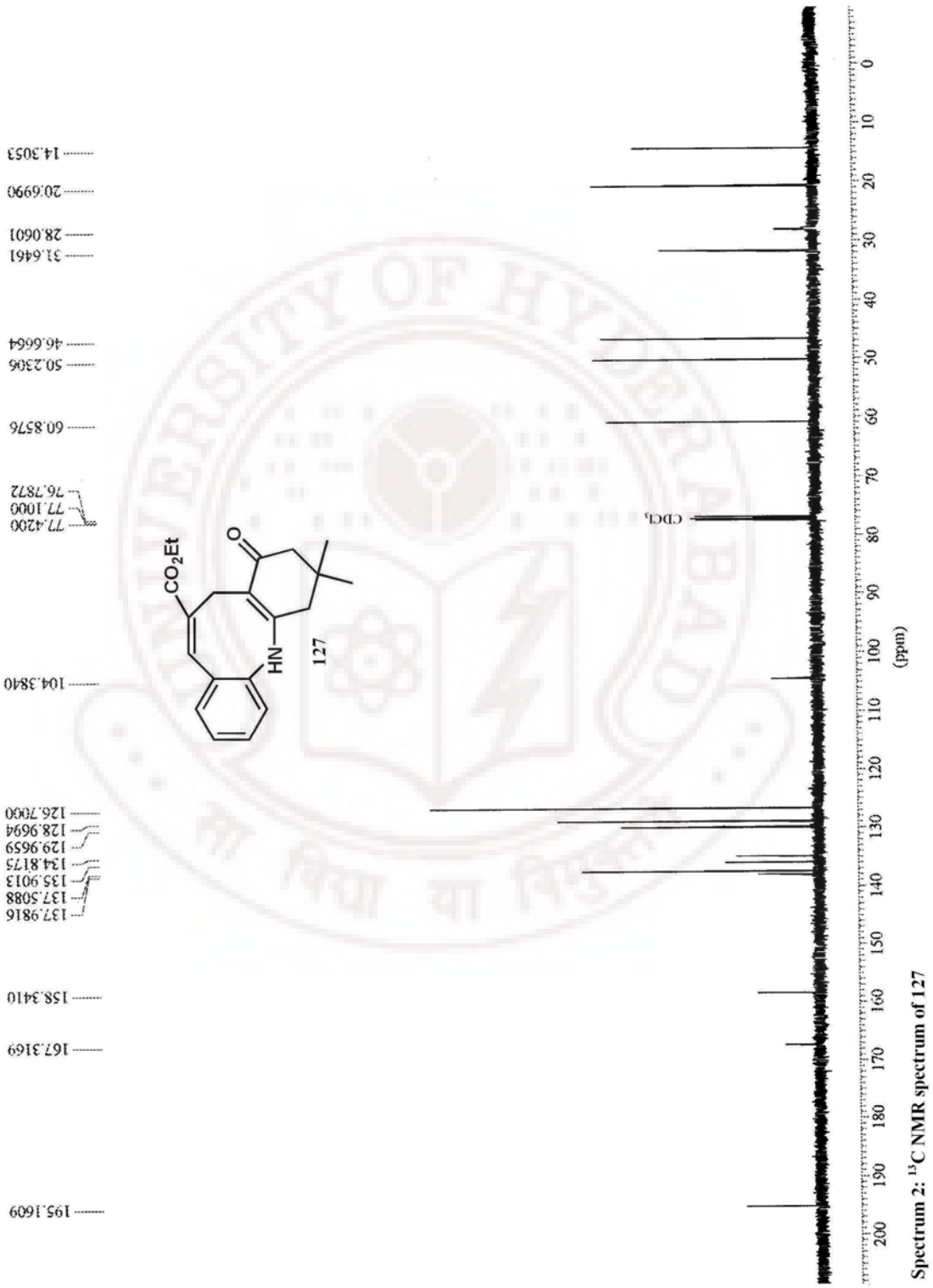
LCMS (*m/z*) : 348 $(M+H)^{+}$

Anal. calc'd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03/

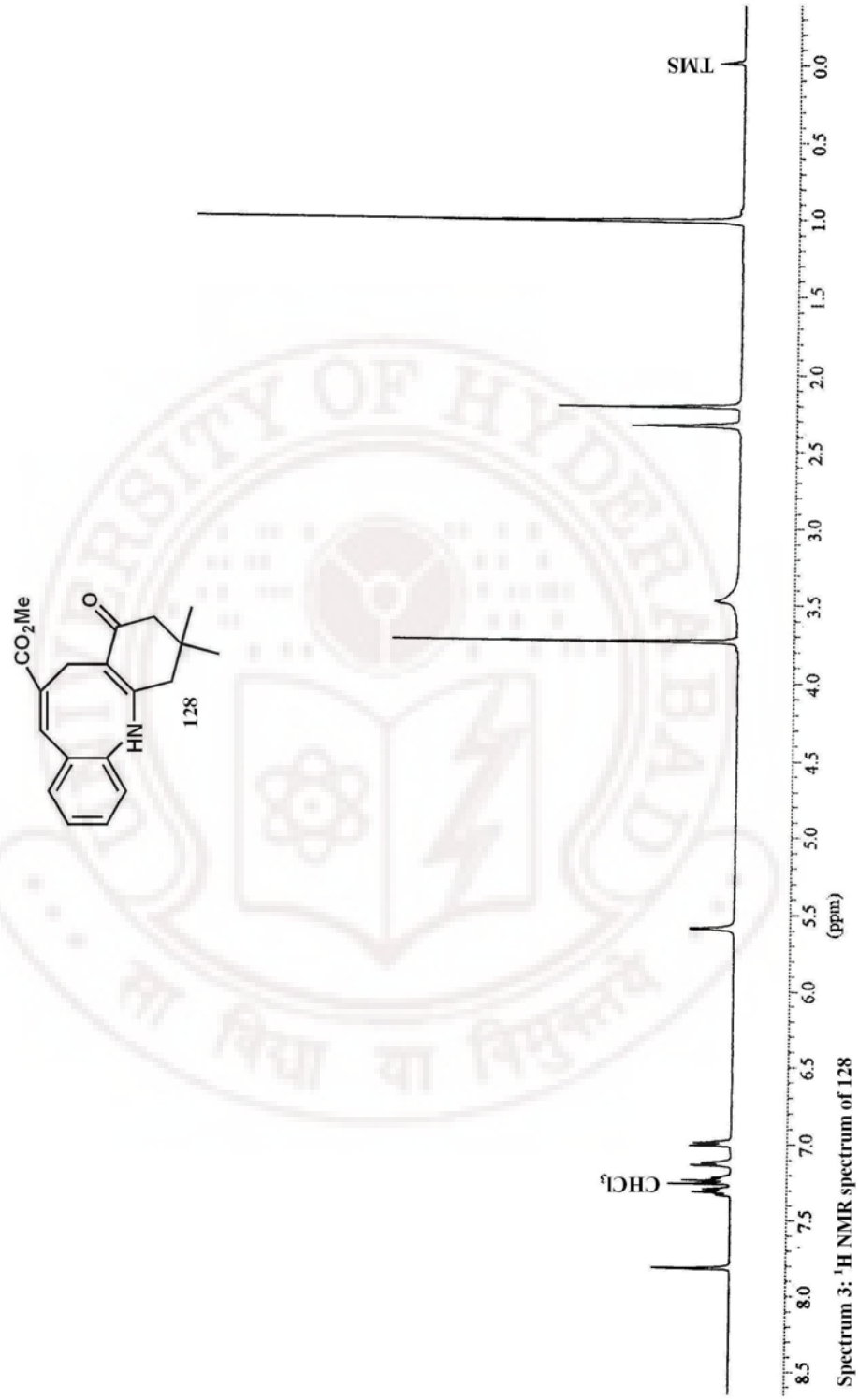
Found : C, 76.10; H, 6.03; N, 4.11.



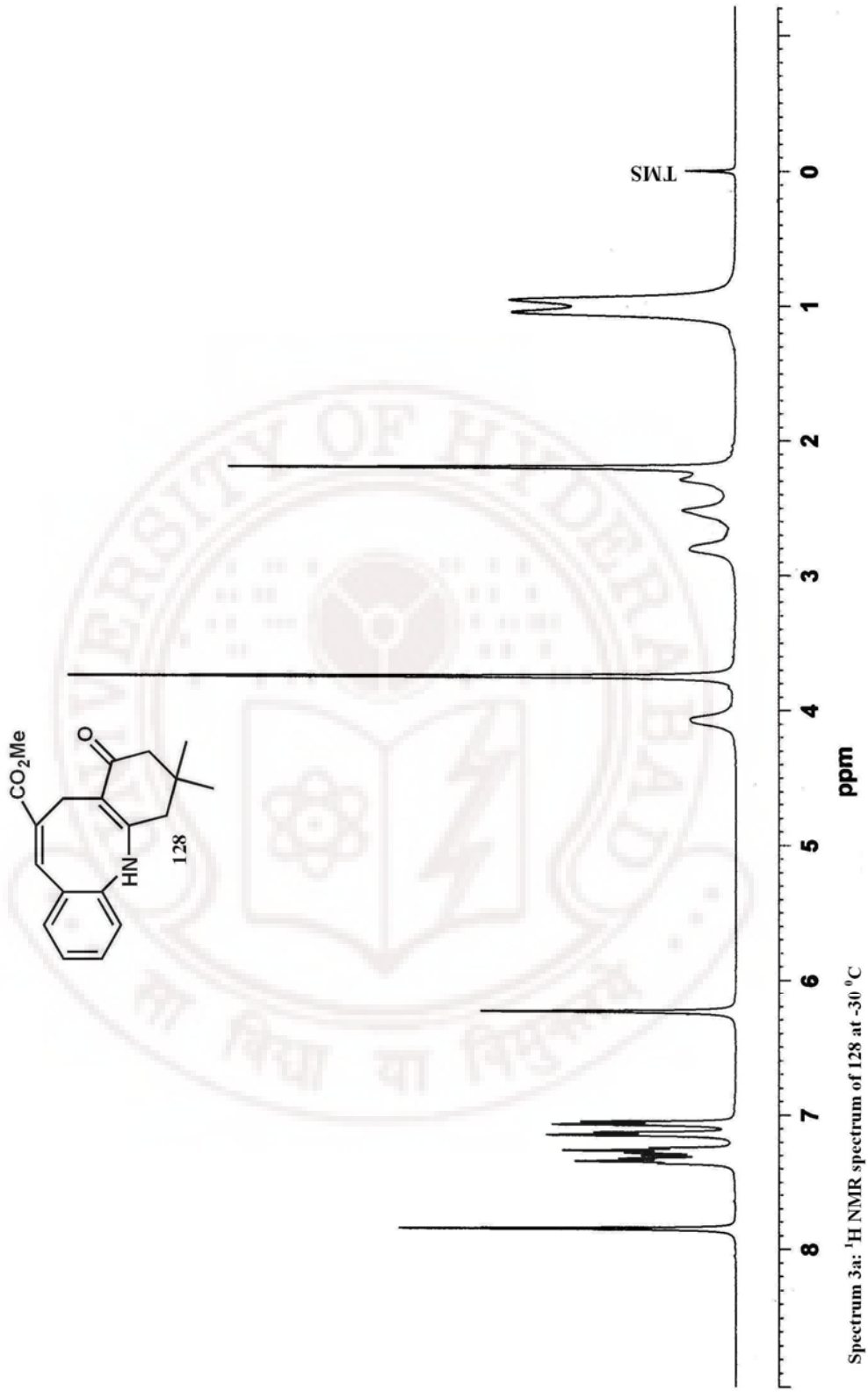
Spectrum 1: ^{1}H NMR spectrum of 127



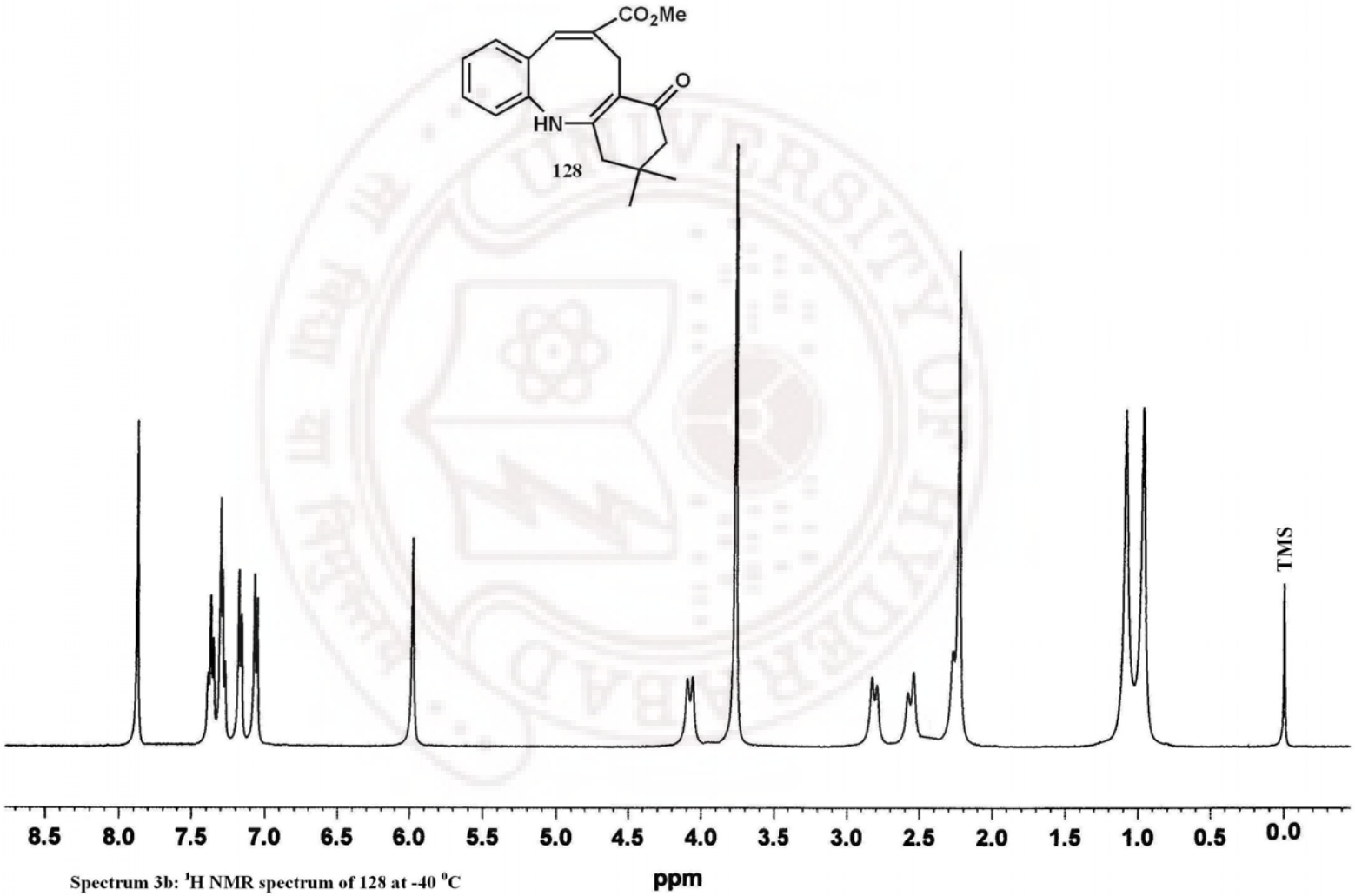
Spectrum 2: ^{13}C NMR spectrum of 127



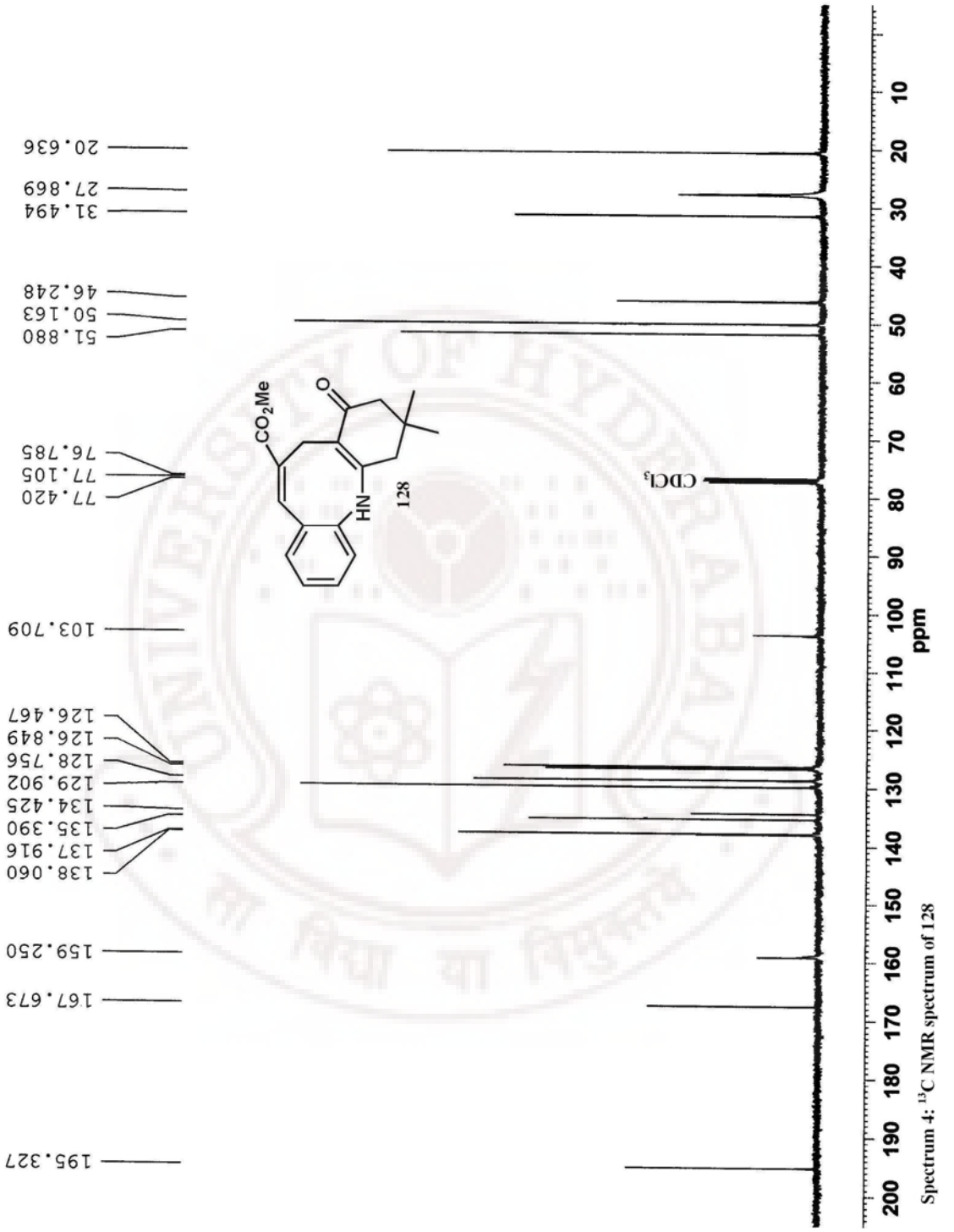
Spectrum 3: ^{1}H NMR spectrum of 128



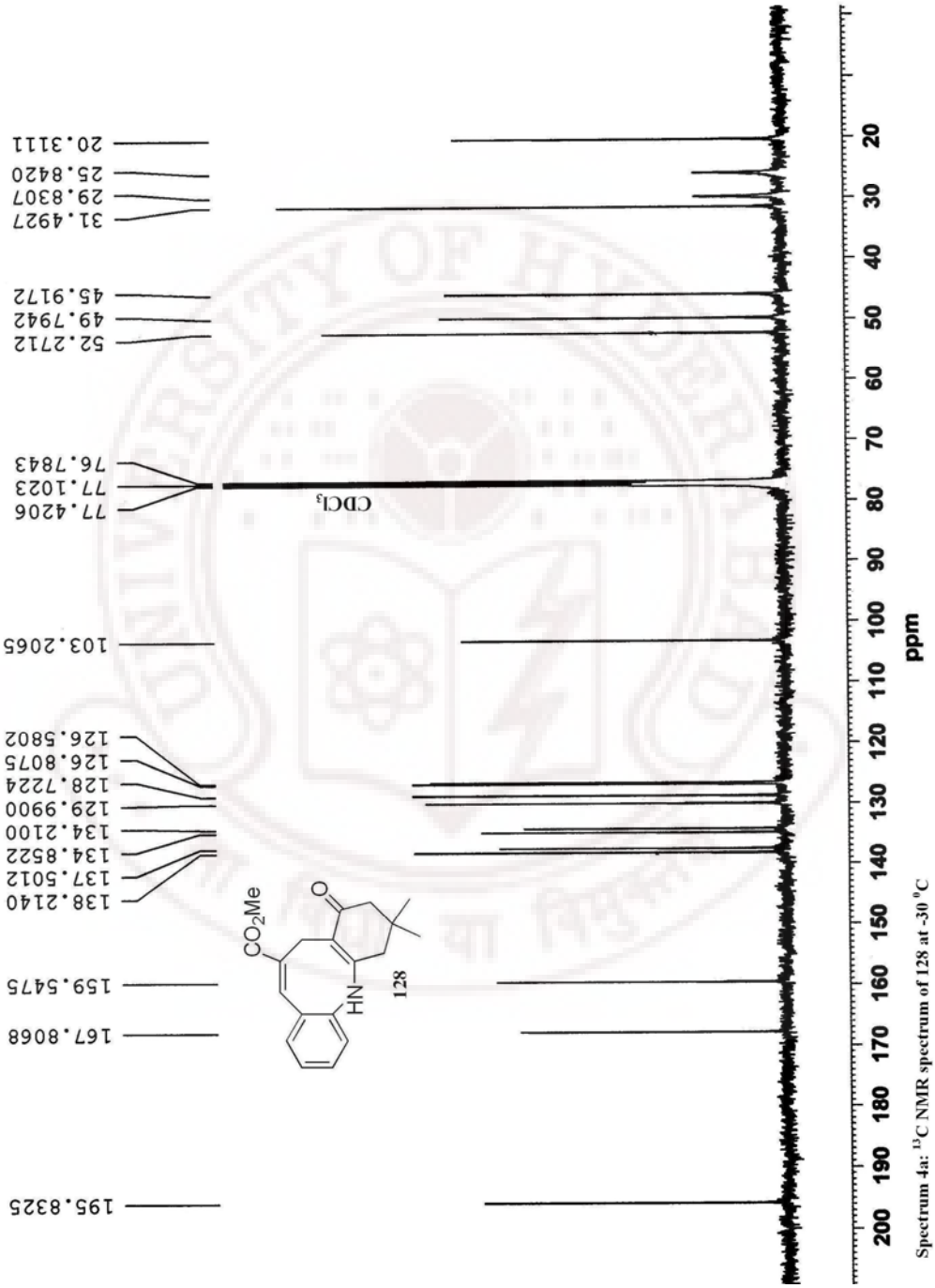
Spectrum 3a: ^{1}H NMR spectrum of 128 at -30 ^{0}C



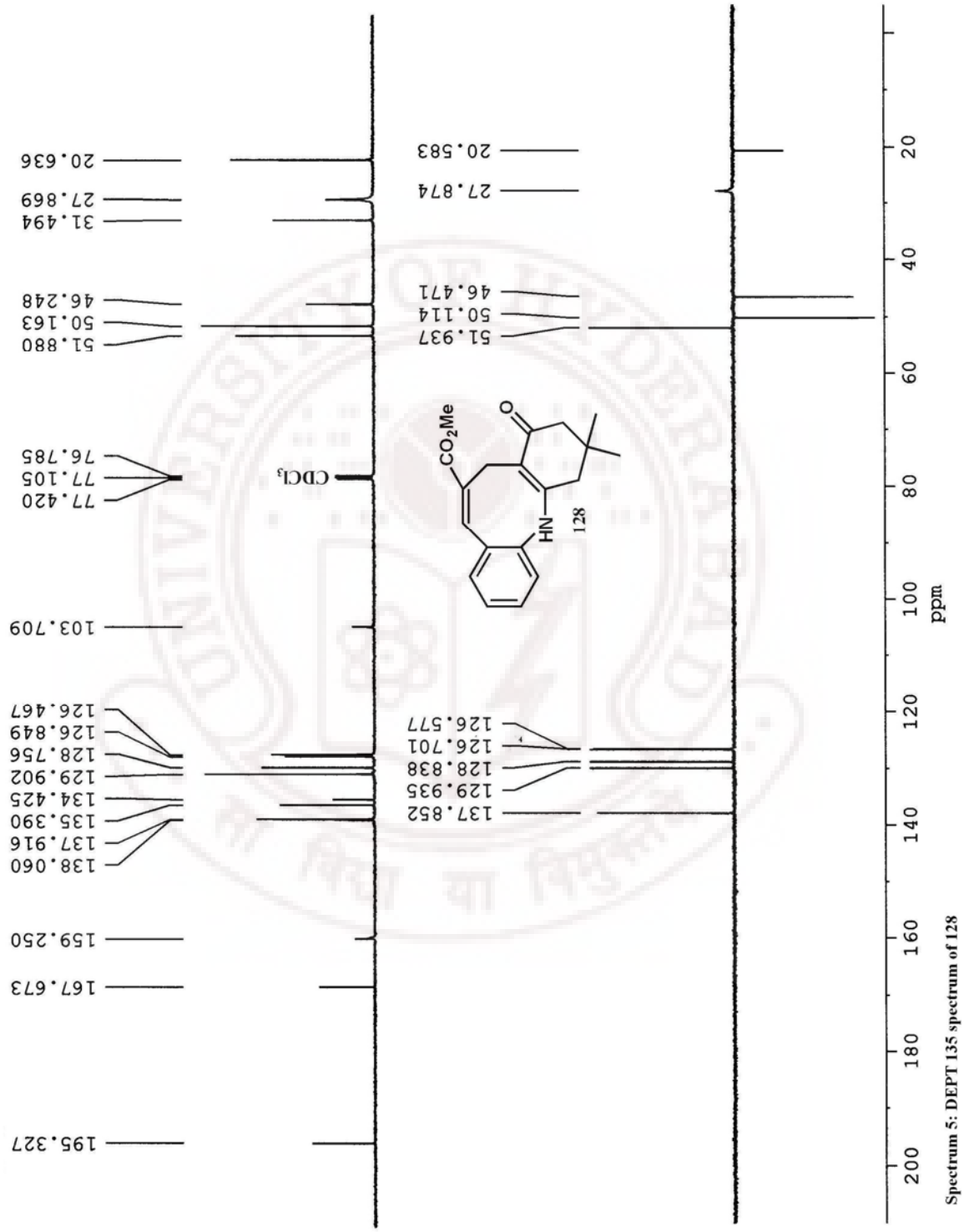
Spectrum 3b: ^{1}H NMR spectrum of 128 at -40 ^{0}C



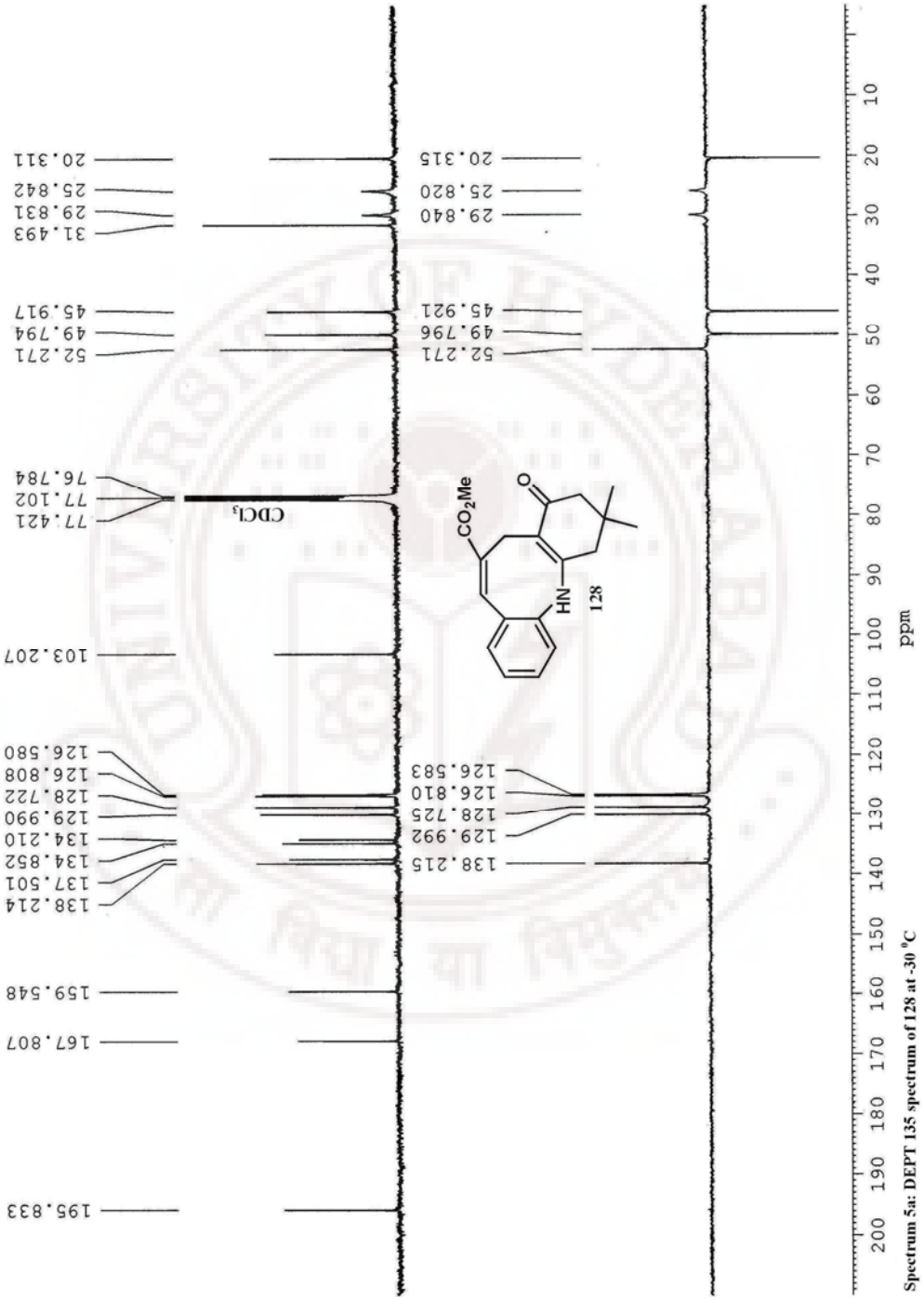
Spectrum 4: ^{13}C NMR spectrum of 128



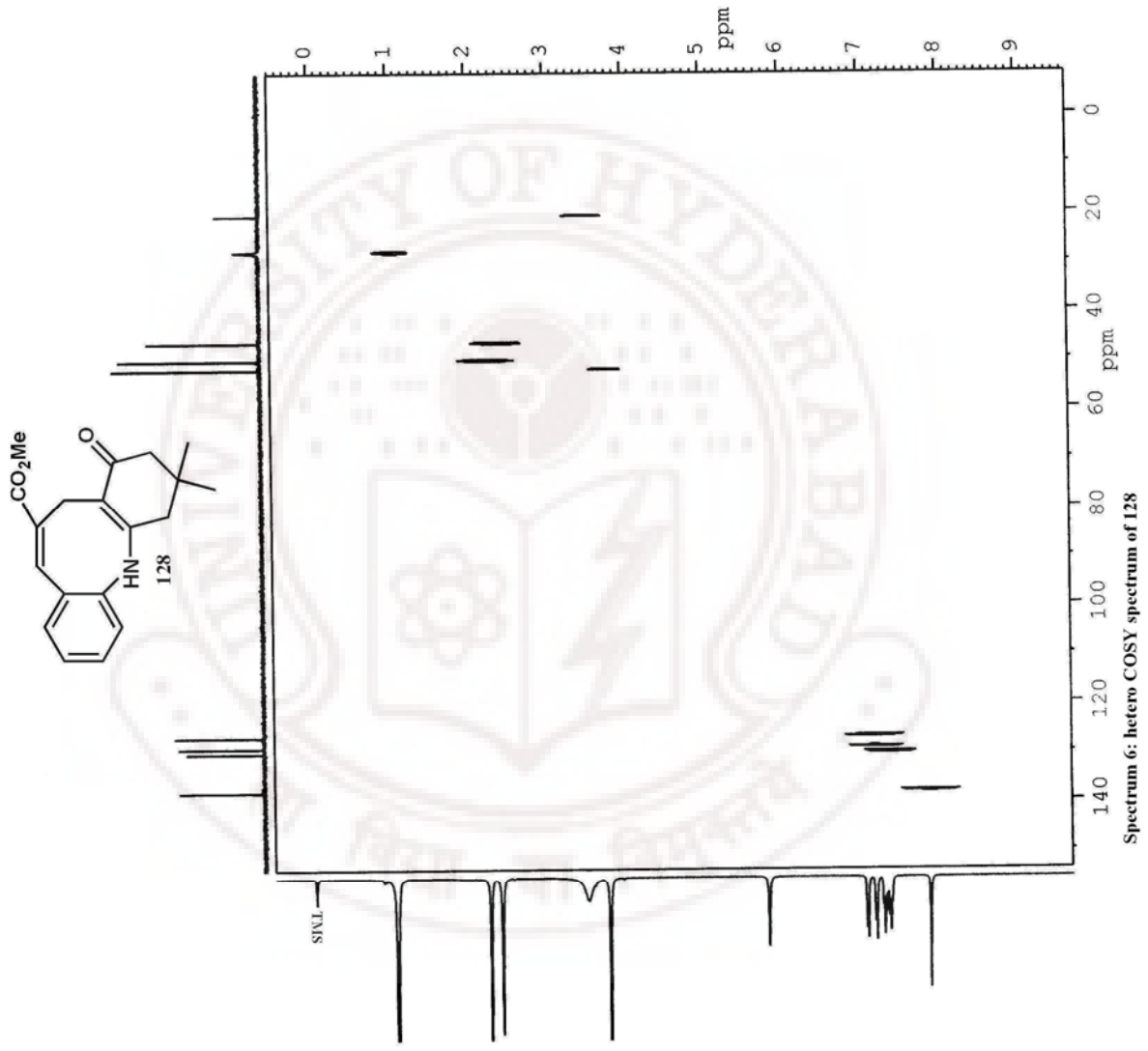
Spectrum 4a: ^{13}C NMR spectrum of 128 at -30 ^{0}C



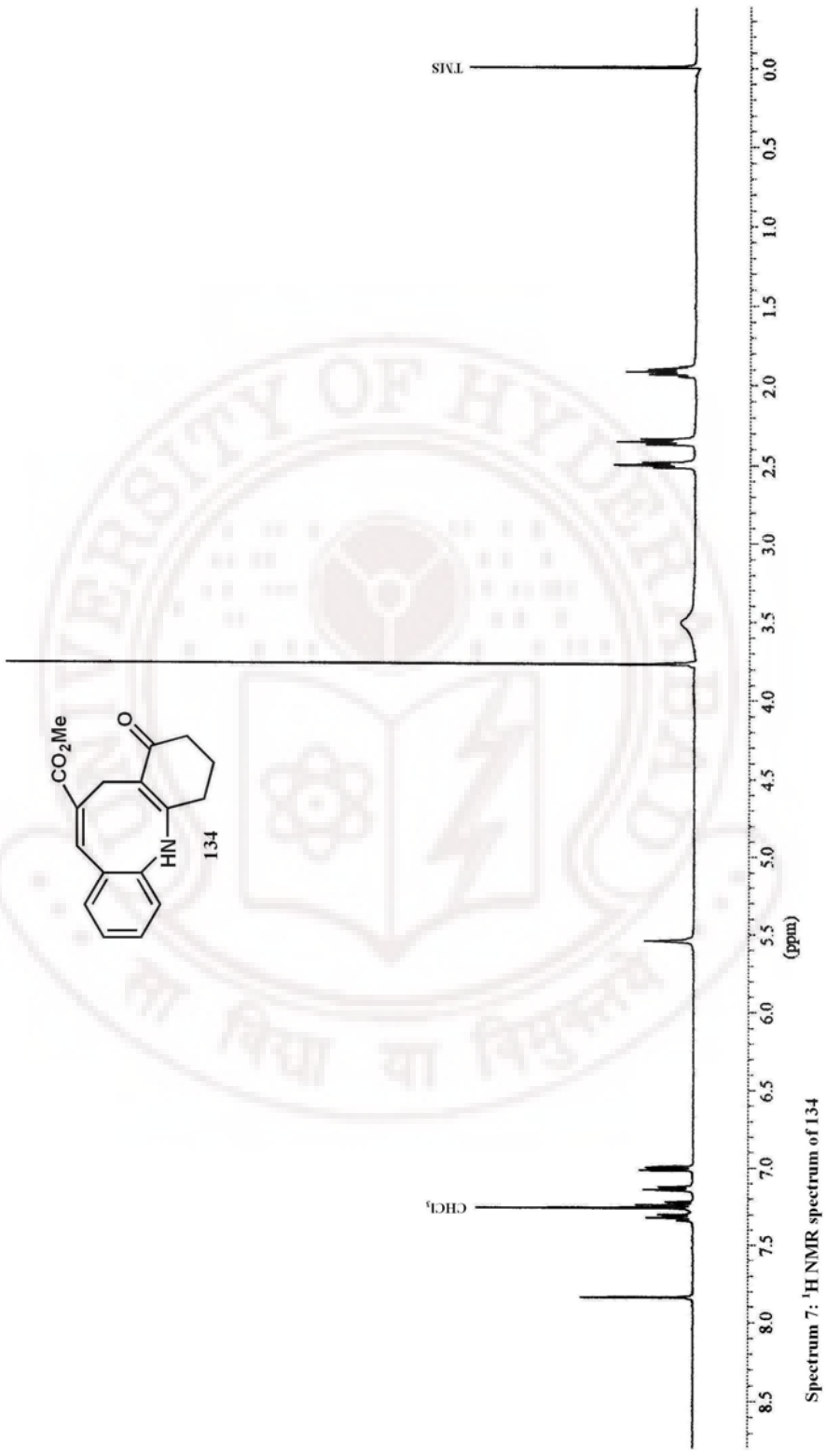
Spectrum 5: DEPT 135 spectrum of 128



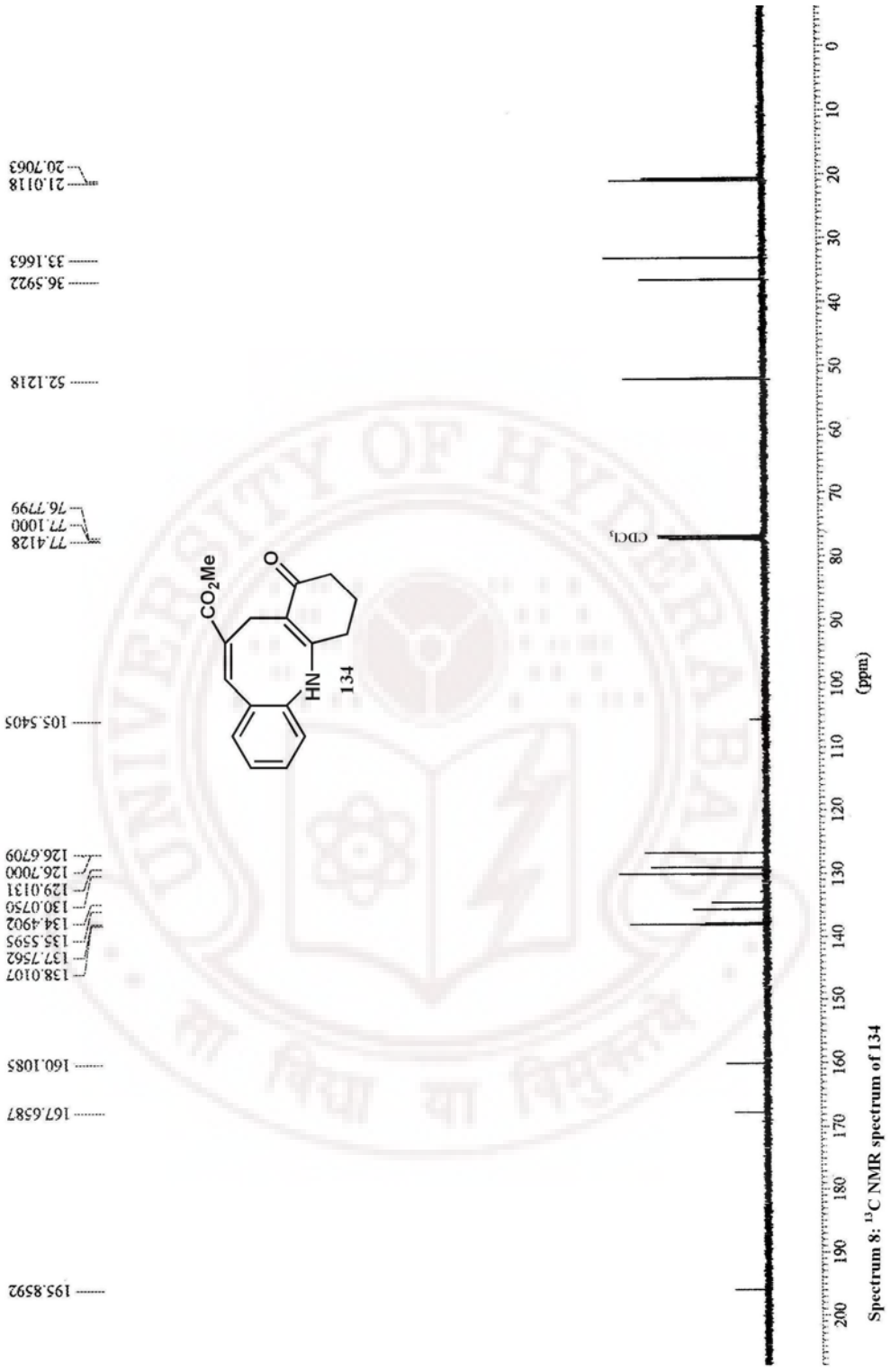
Spectrum 5a: DEPT 135 spectrum of 128 at -30 °C



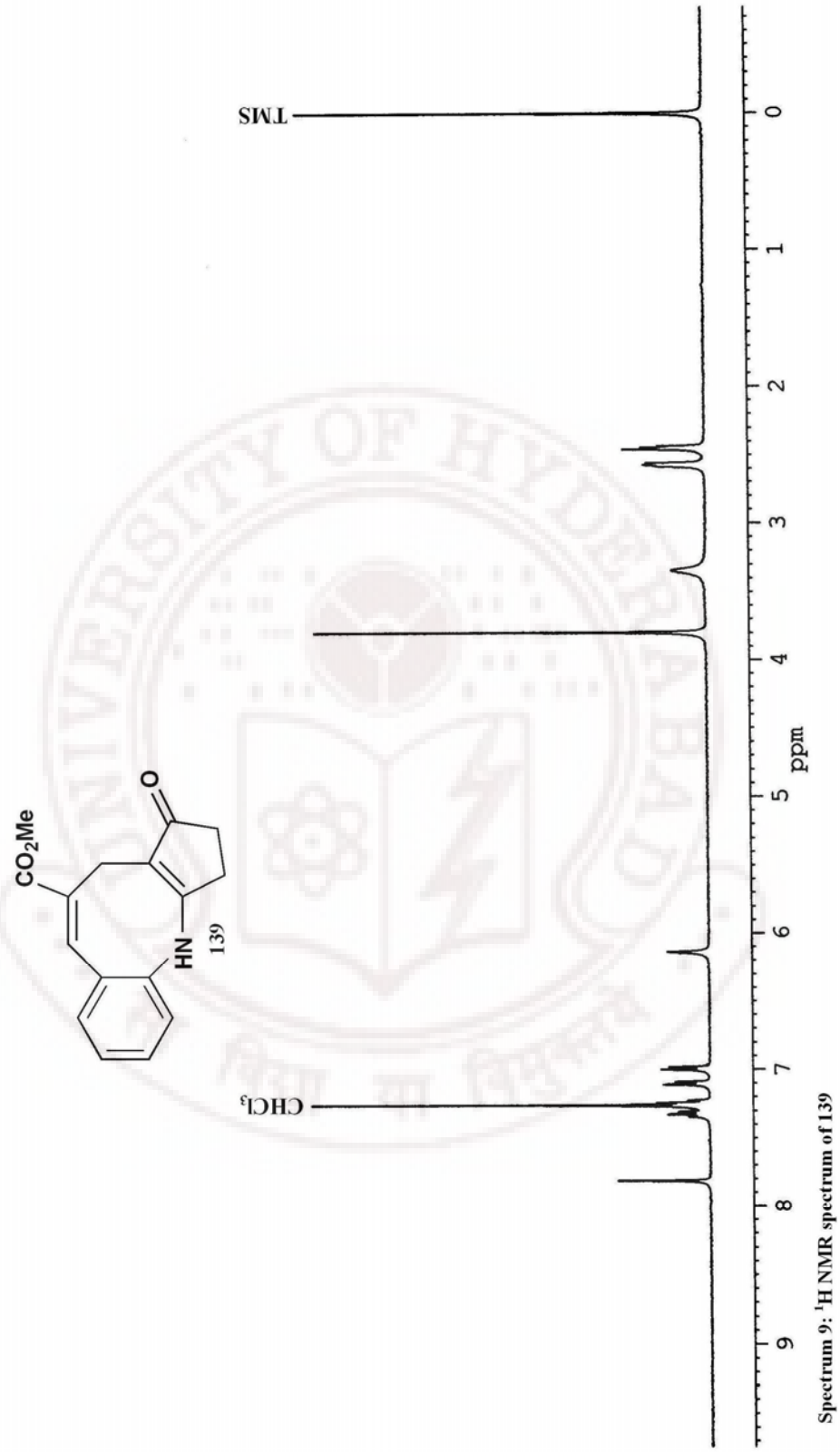
Spectrum 6: hetero COSY spectrum of 128



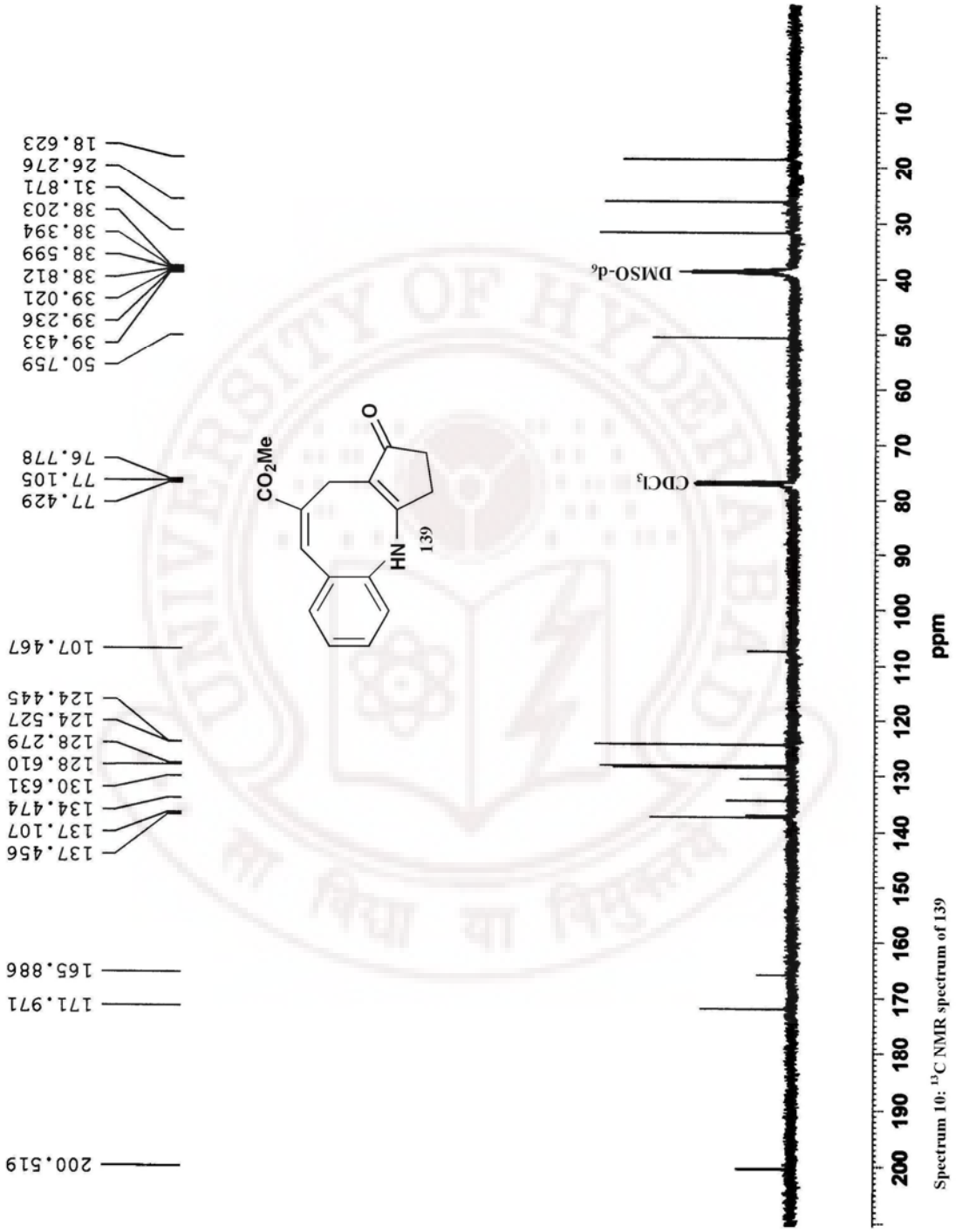
Spectrum 7: ^{1}H NMR spectrum of 134



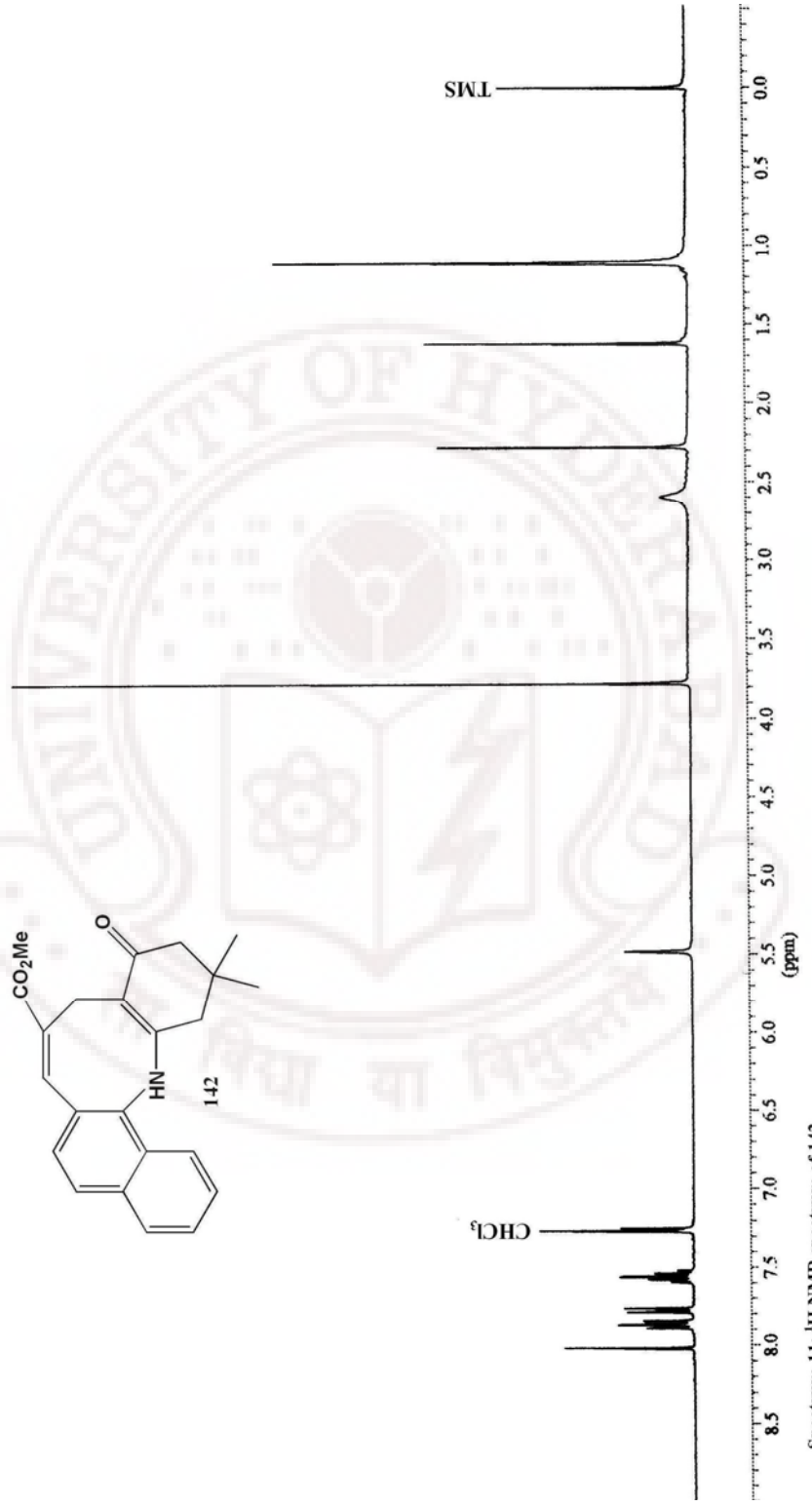
Spectrum 8: ^{13}C NMR spectrum of 134



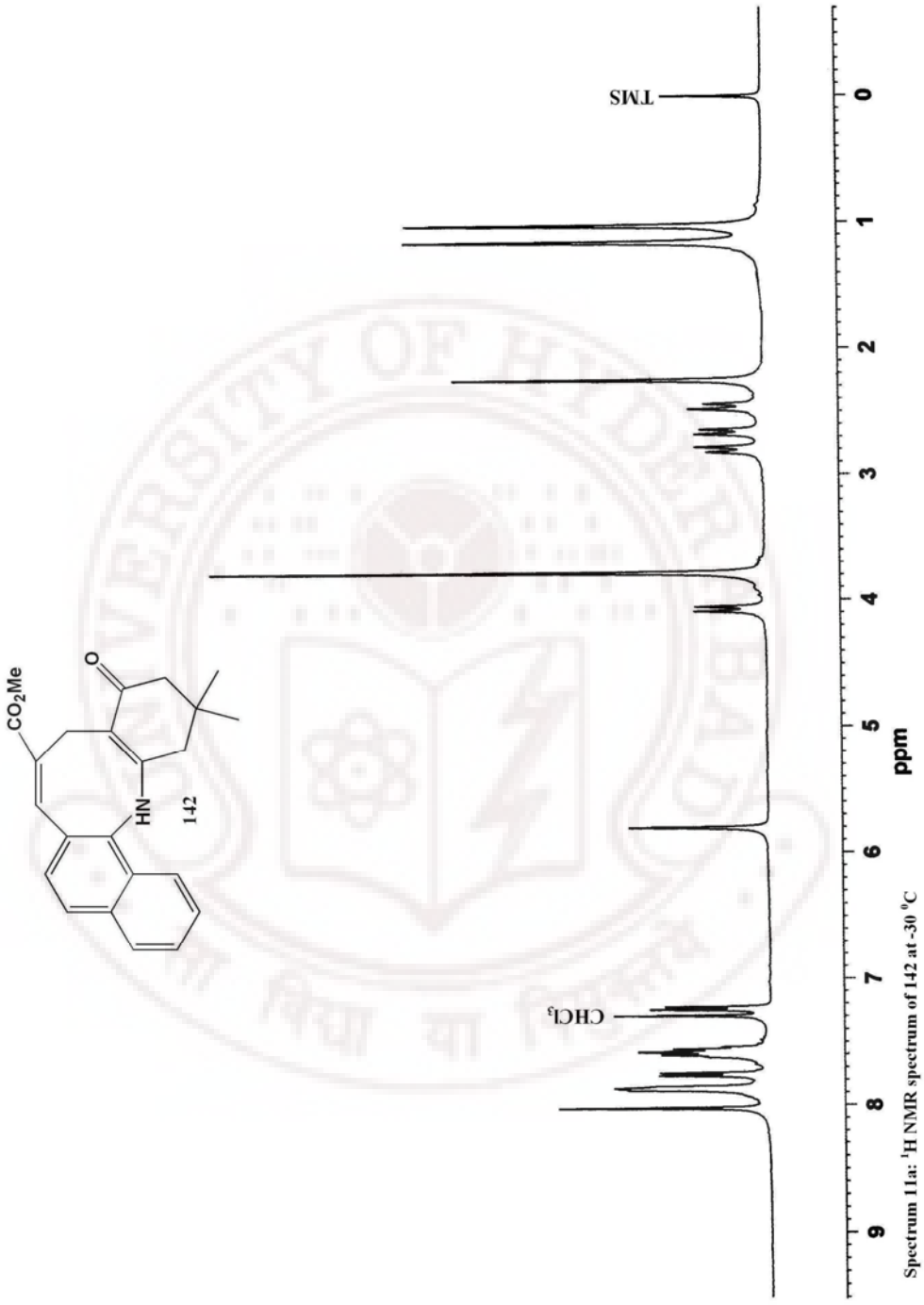
Spectrum 9: ^{1}H NMR spectrum of 139



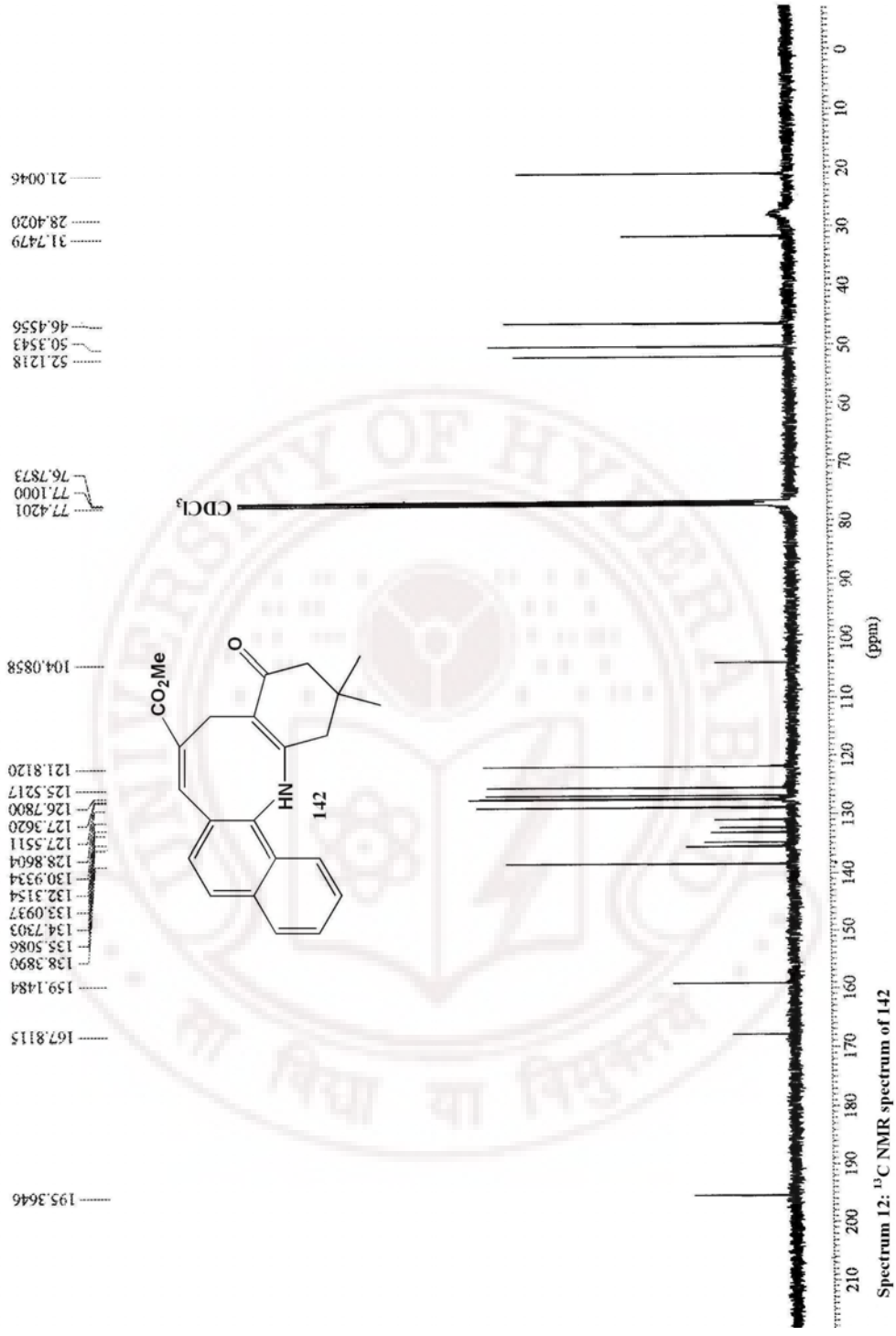
Spectrum 10: ^{13}C NMR spectrum of 139



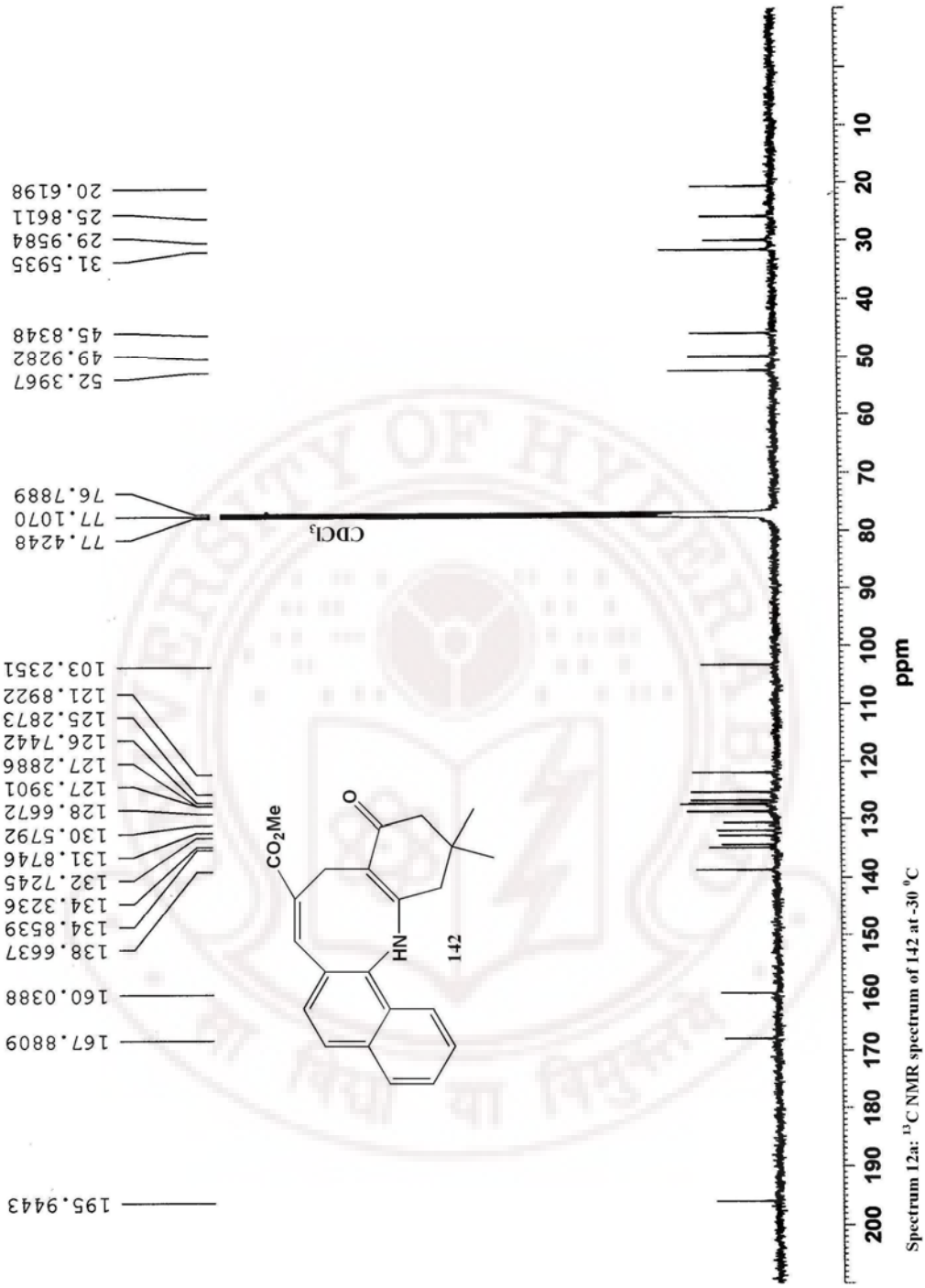
Spectrum 11: ^{1}H NMR spectrum of 142



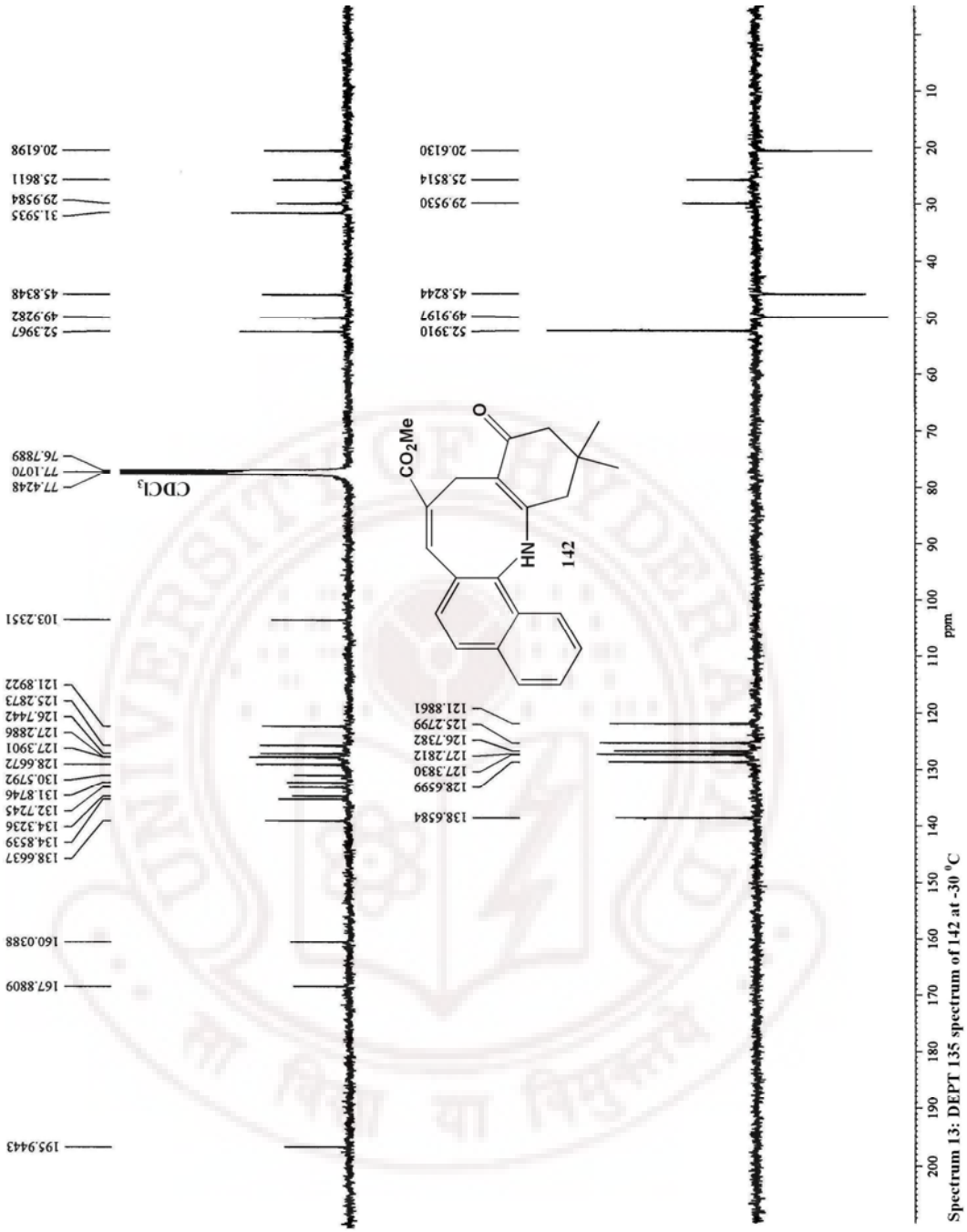
Spectrum 11a: ^{1}H NMR spectrum of 142 at -30 ^{0}C

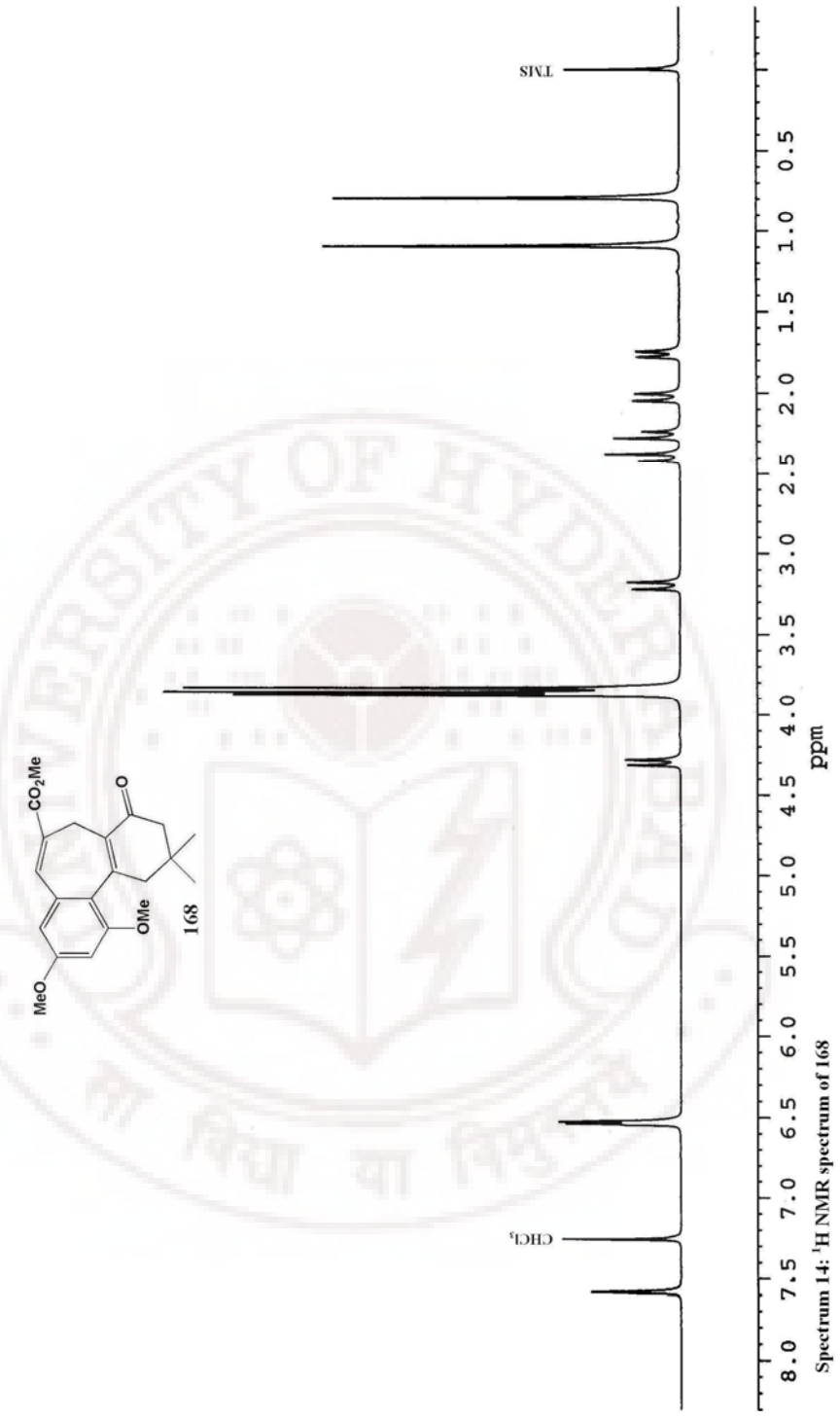


Spectrum 12: ^{13}C NMR spectrum of 142

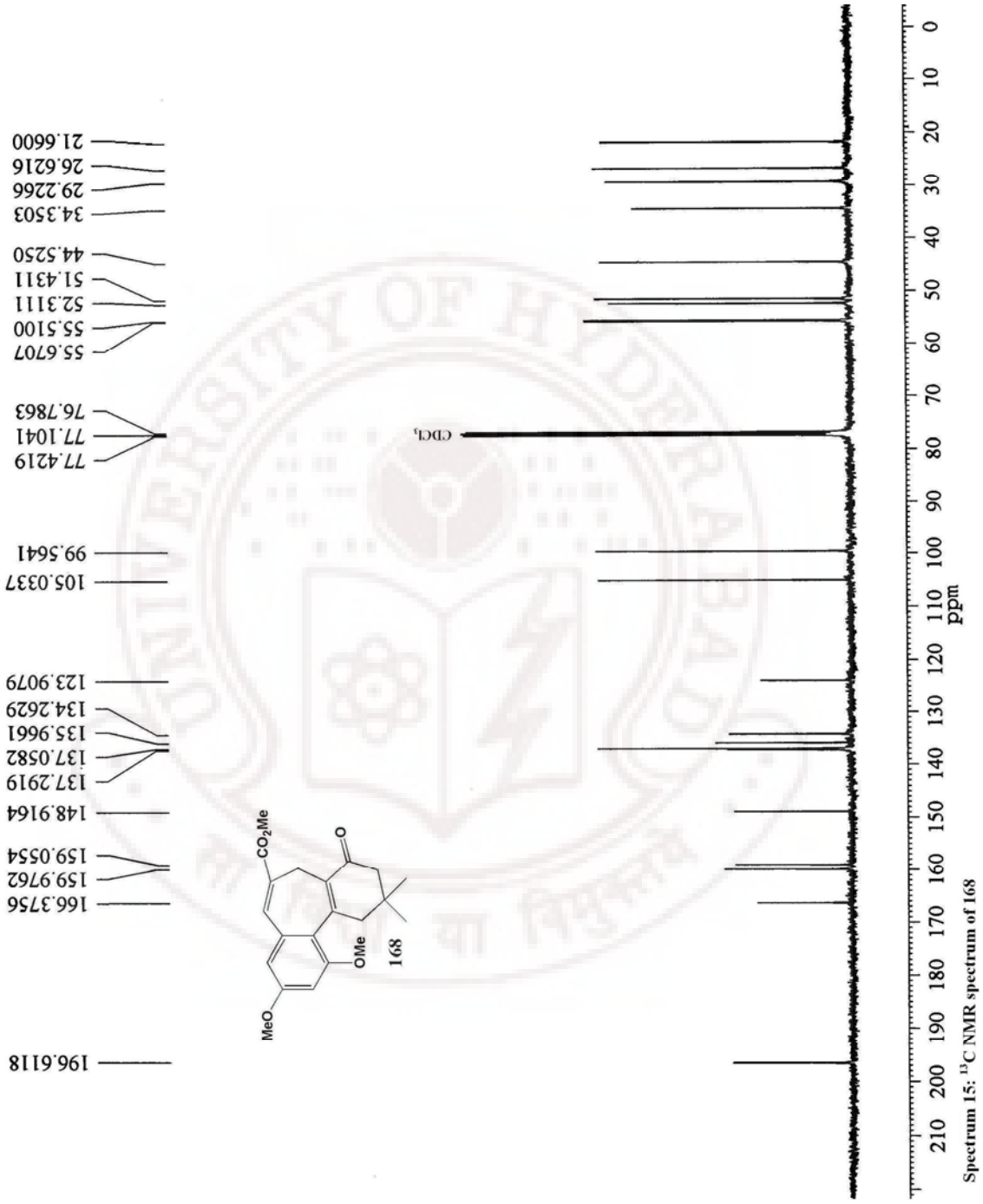


Spectrum 12a: ^{13}C NMR spectrum of 142 at -30 ^{0}C

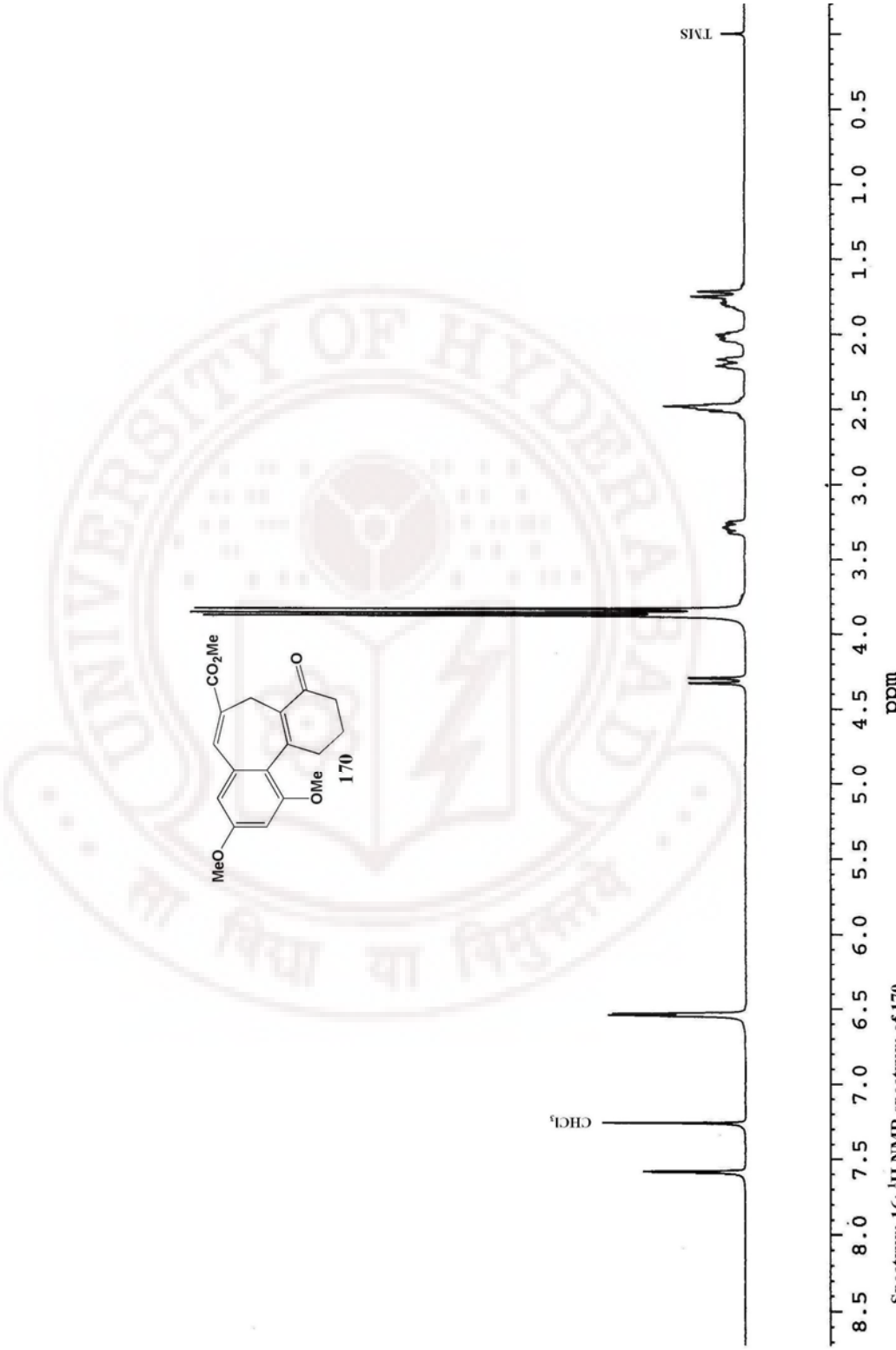

195.9443
167.8809
160.0388
138.6637
134.8539
134.3236
132.7245
131.8746
130.5792
128.6672
127.3901
127.2886
126.7442
125.2873
121.8922
103.2351
77.4248
77.1070
76.7889
CDCl3
52.3967
49.9282
45.8348
31.5935
29.9584
25.8611
20.6198
138.6584
128.6599
127.3830
127.2812
126.7382
125.2799
121.8861
52.3910
49.9197
45.8244
29.9530
25.8514
20.6130
CO2Me
O
HN
142
ppm
Spectrum 13: DEPT 135 spectrum of 142 at -30 °C



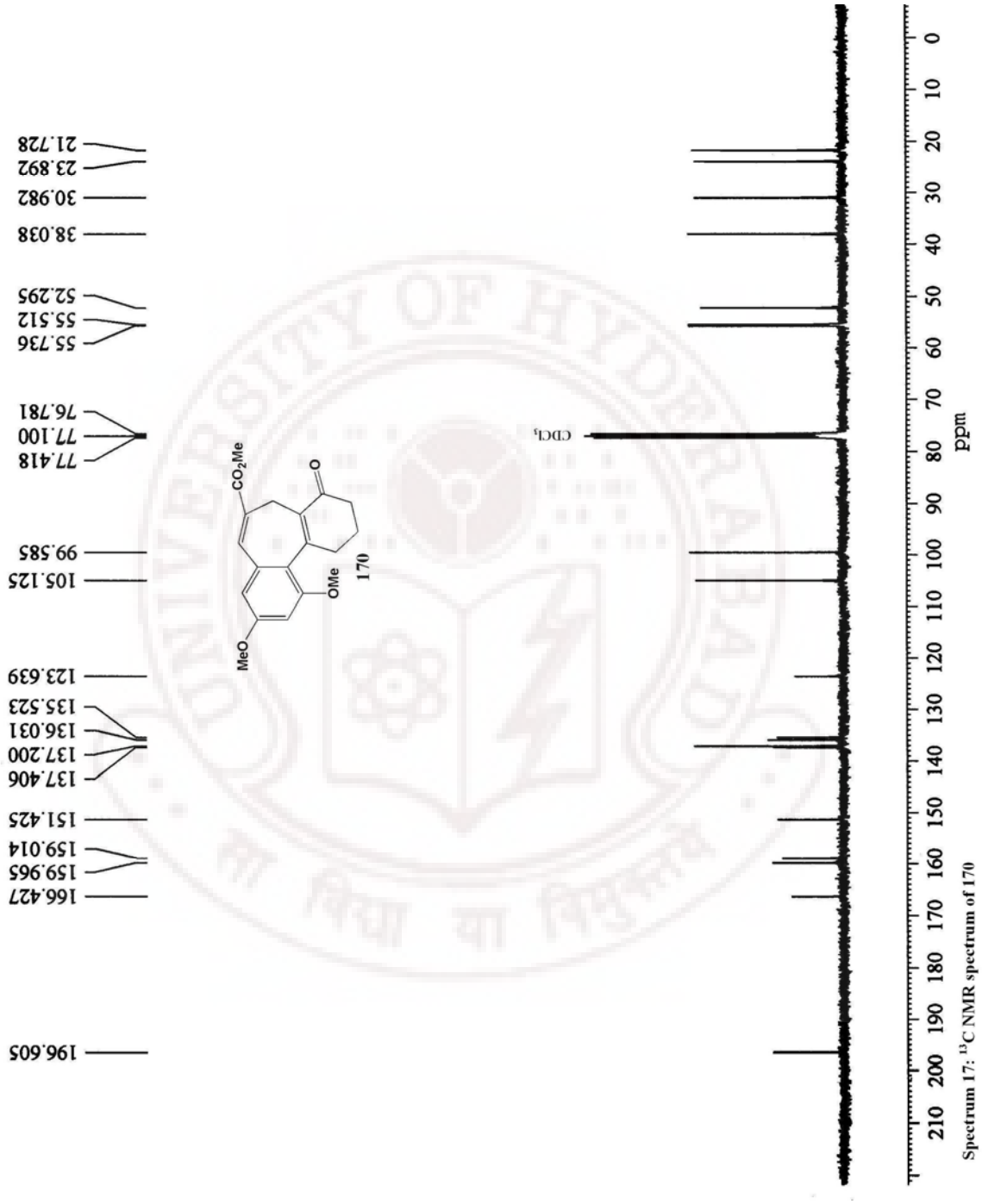
Spectrum 14: ^{1}H NMR spectrum of 168



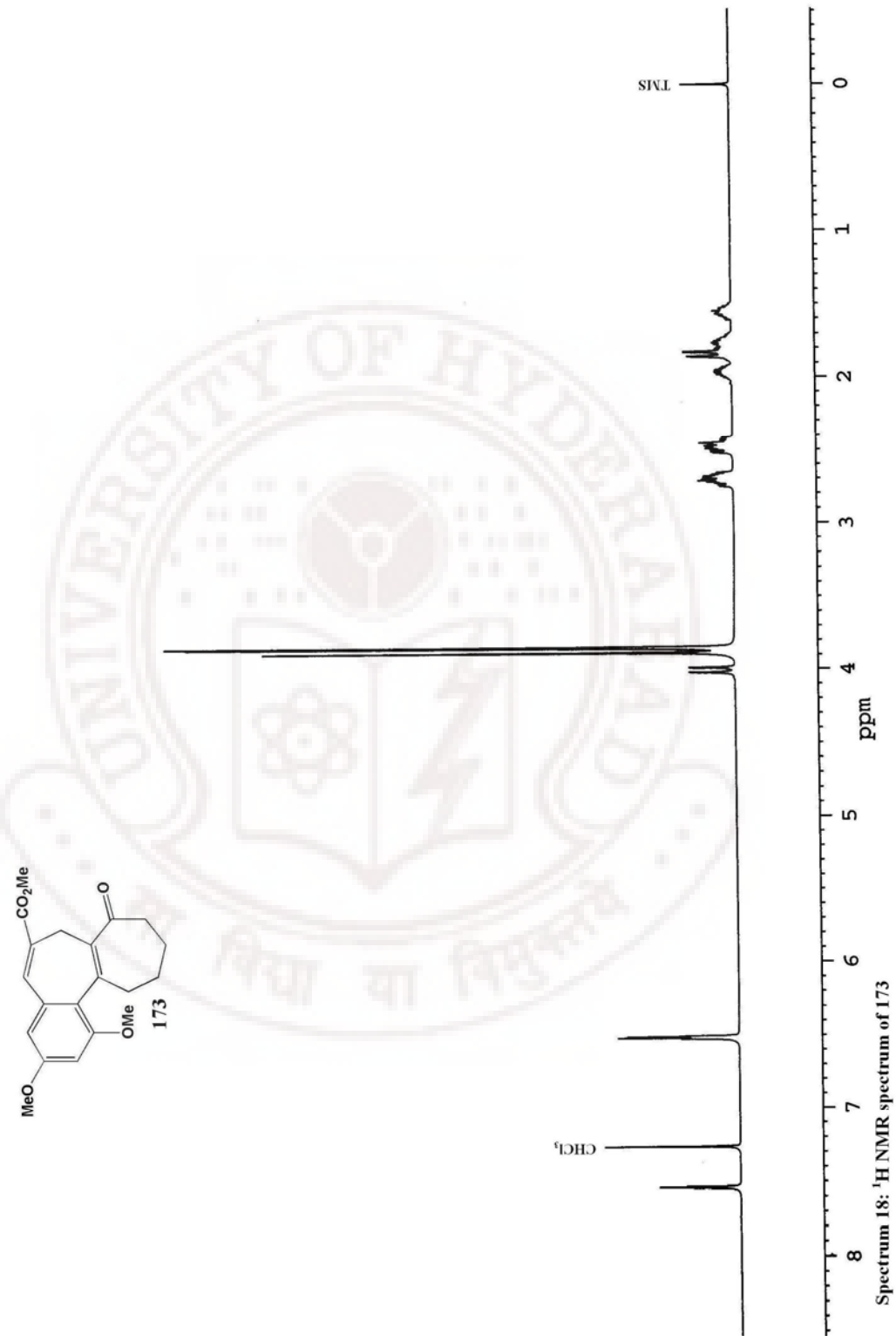
Spectrum 15: ^{13}C NMR spectrum of 168



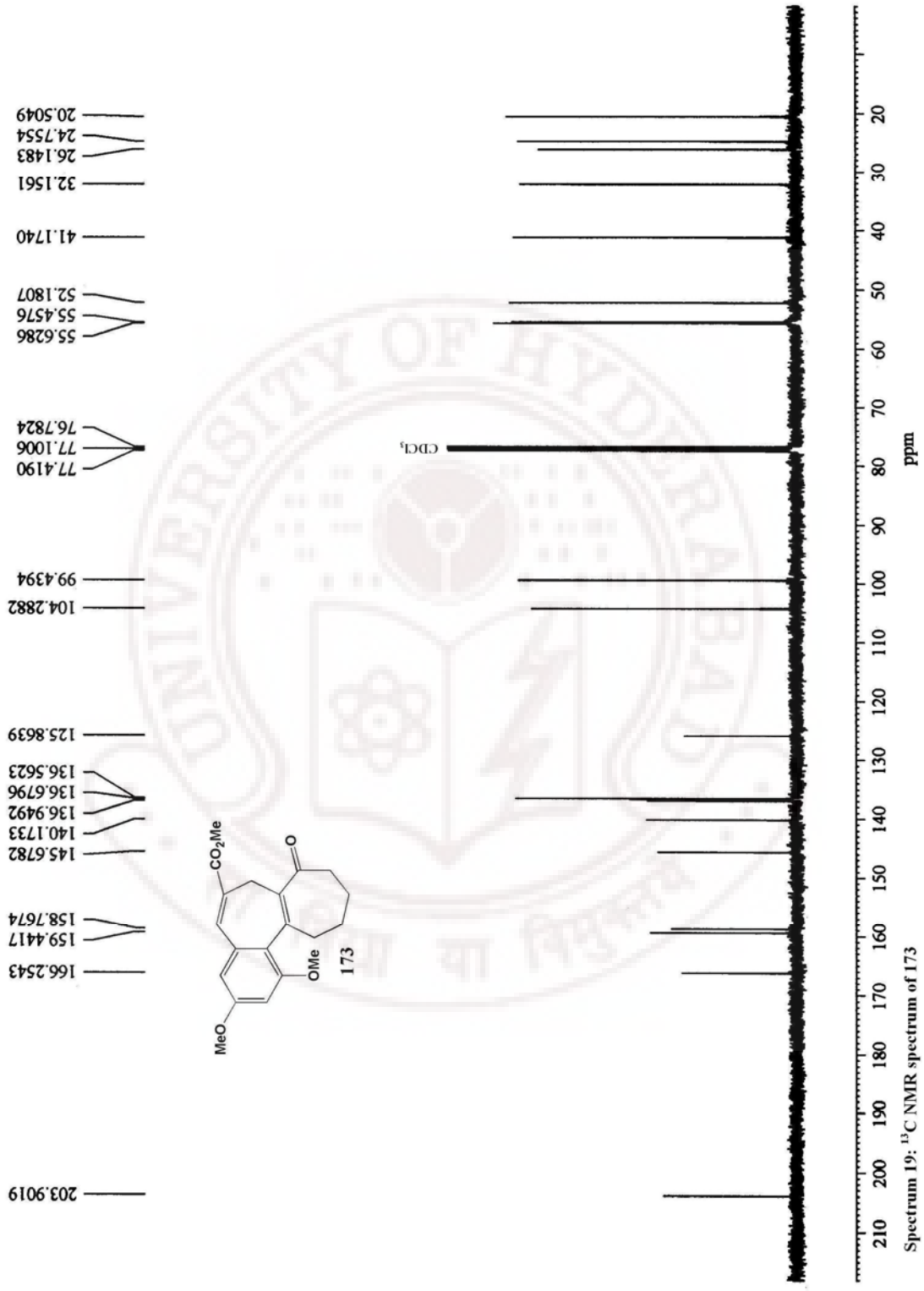
Spectrum 16: ^{1}H NMR spectrum of 170



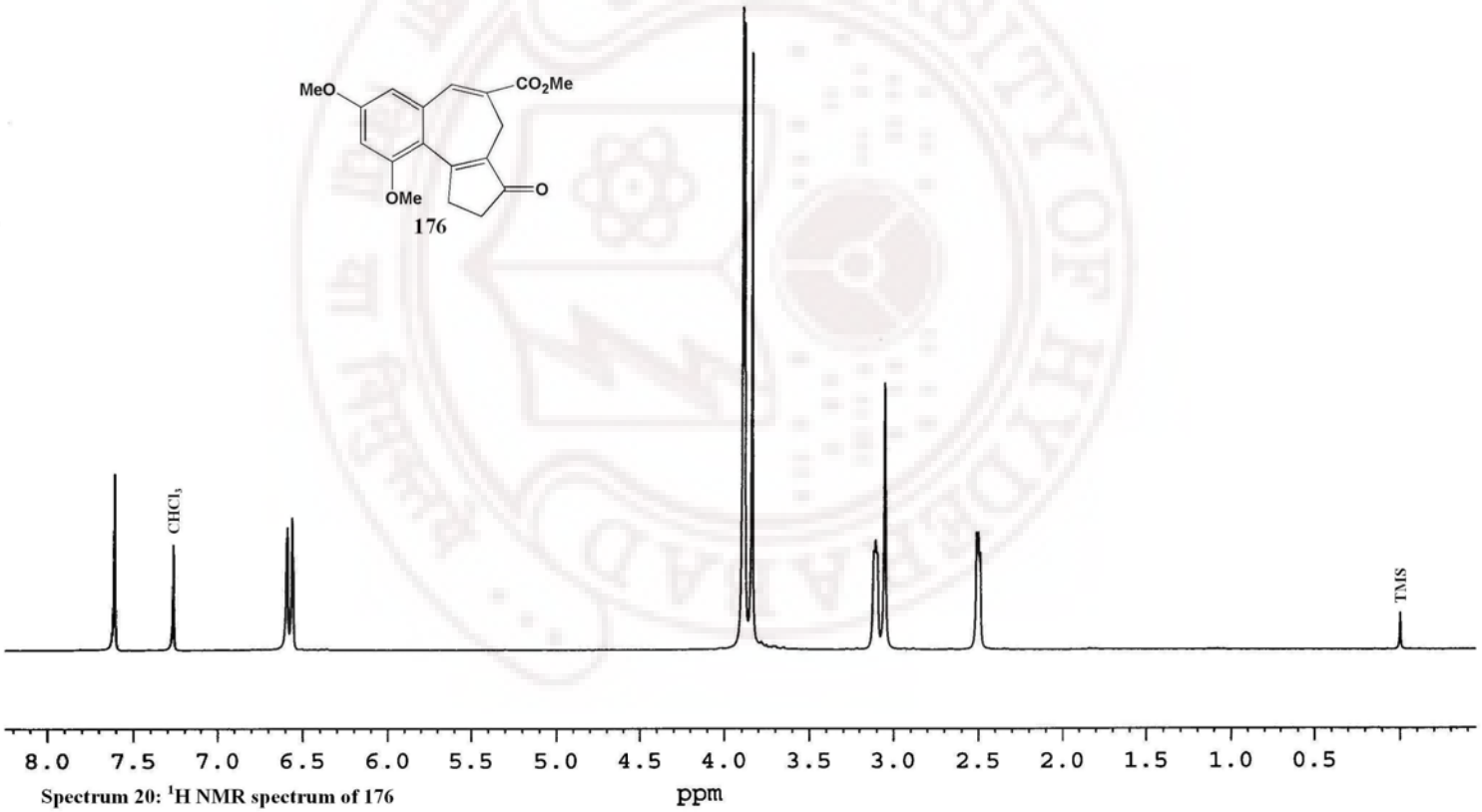
Spectrum 17: ^{13}C NMR spectrum of 170



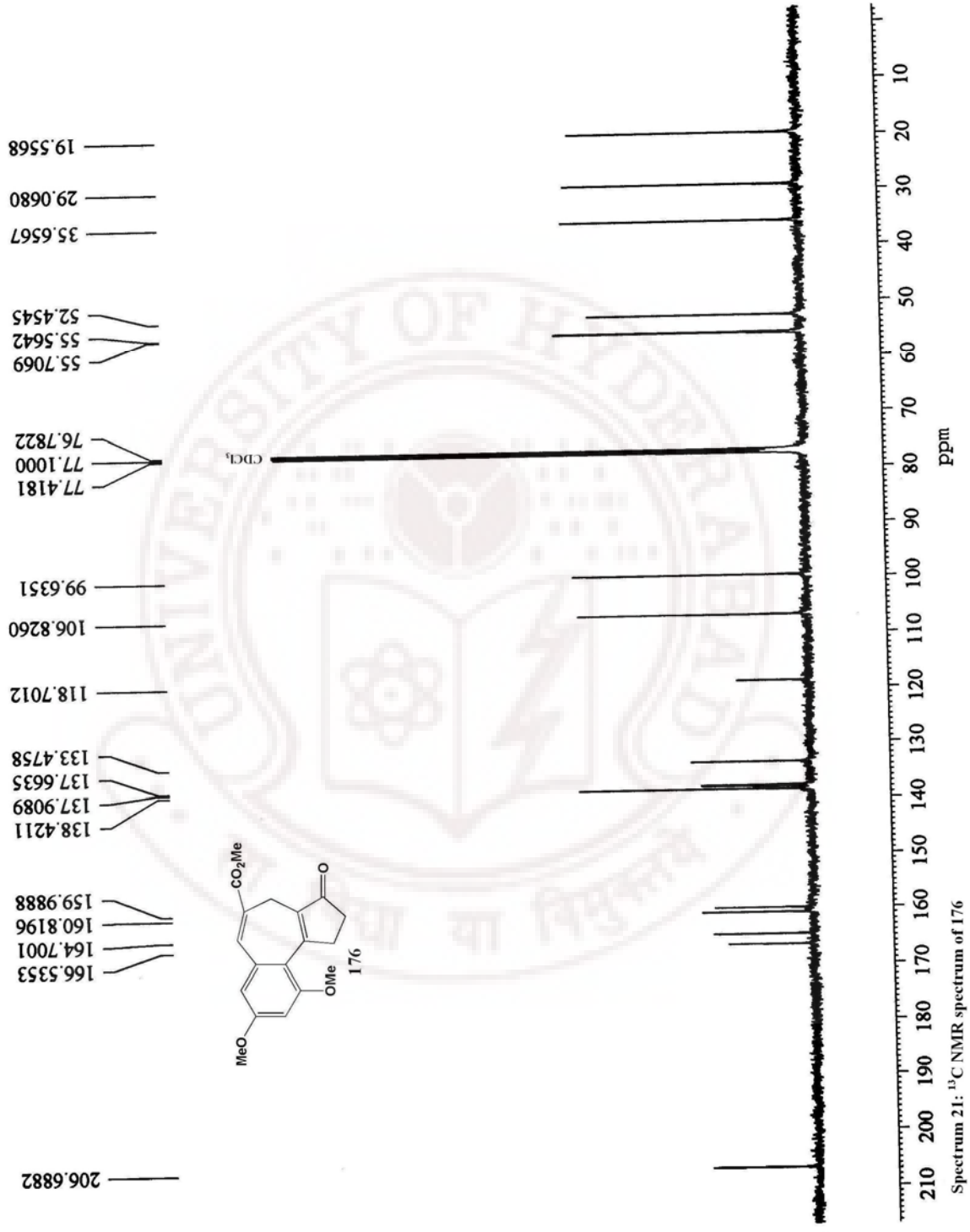
Spectrum 18: ^{1}H NMR spectrum of 173



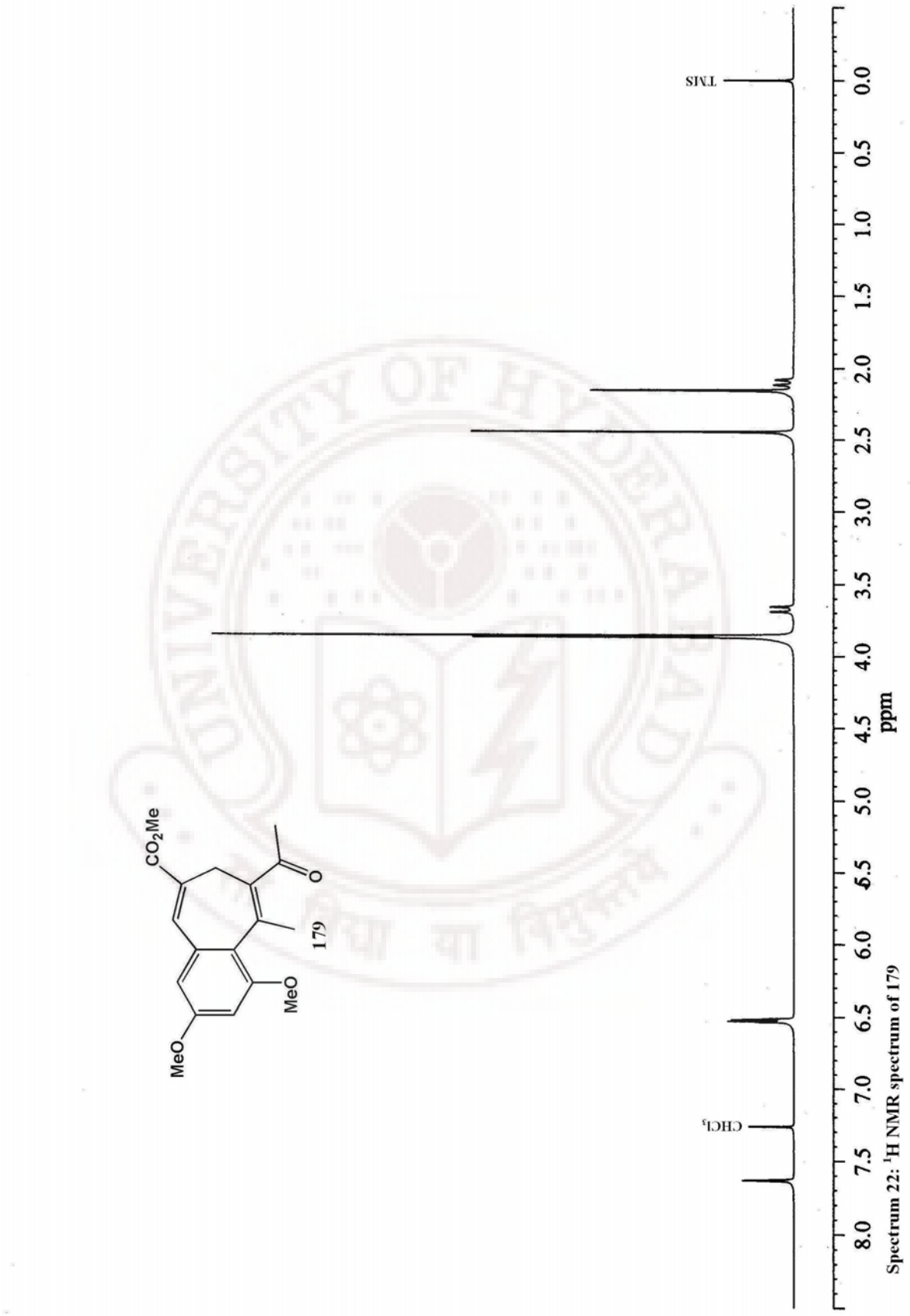
Spectrum 19: ^{13}C NMR spectrum of 173



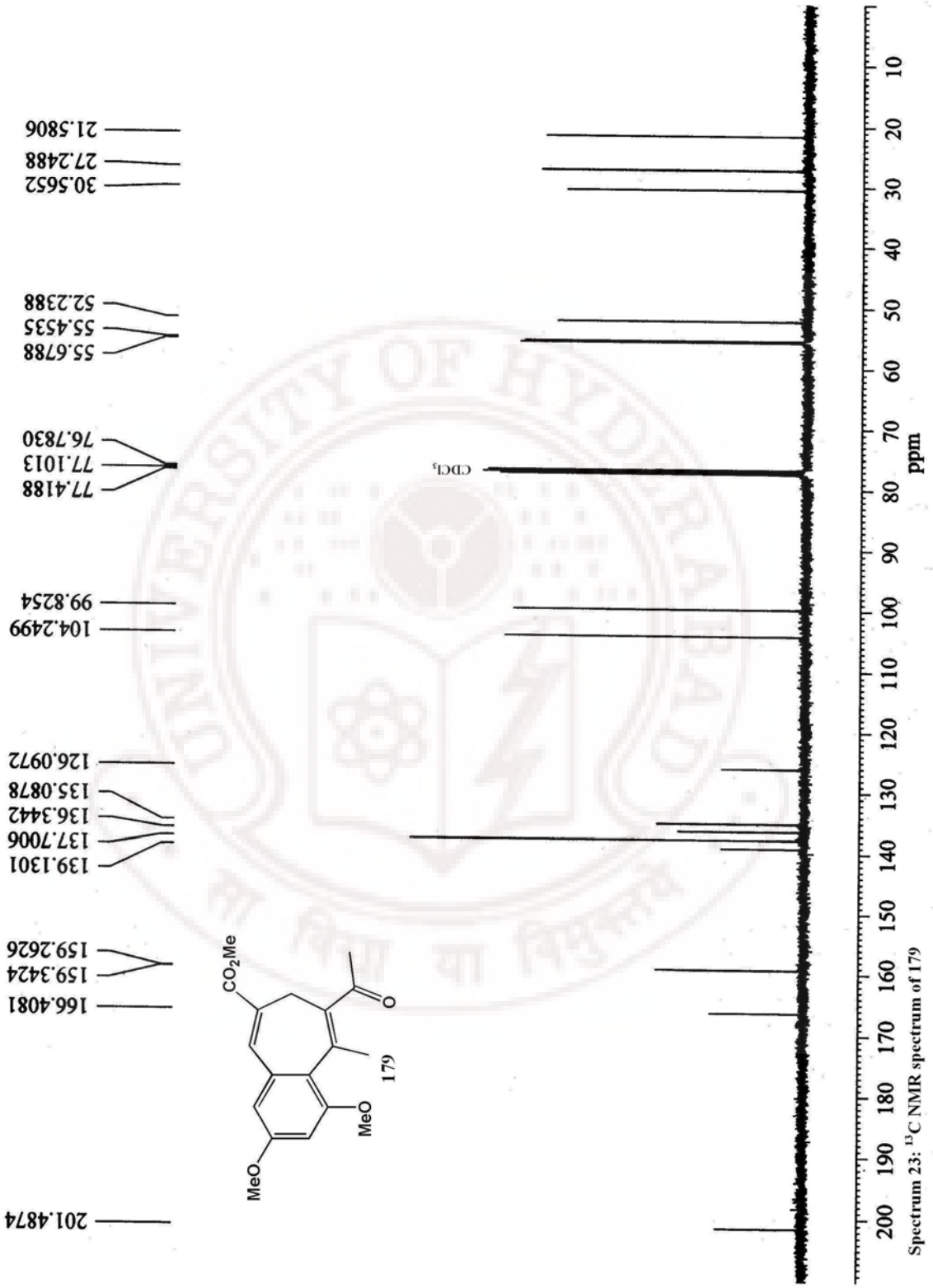
Spectrum 20: ^{1}H NMR spectrum of 176



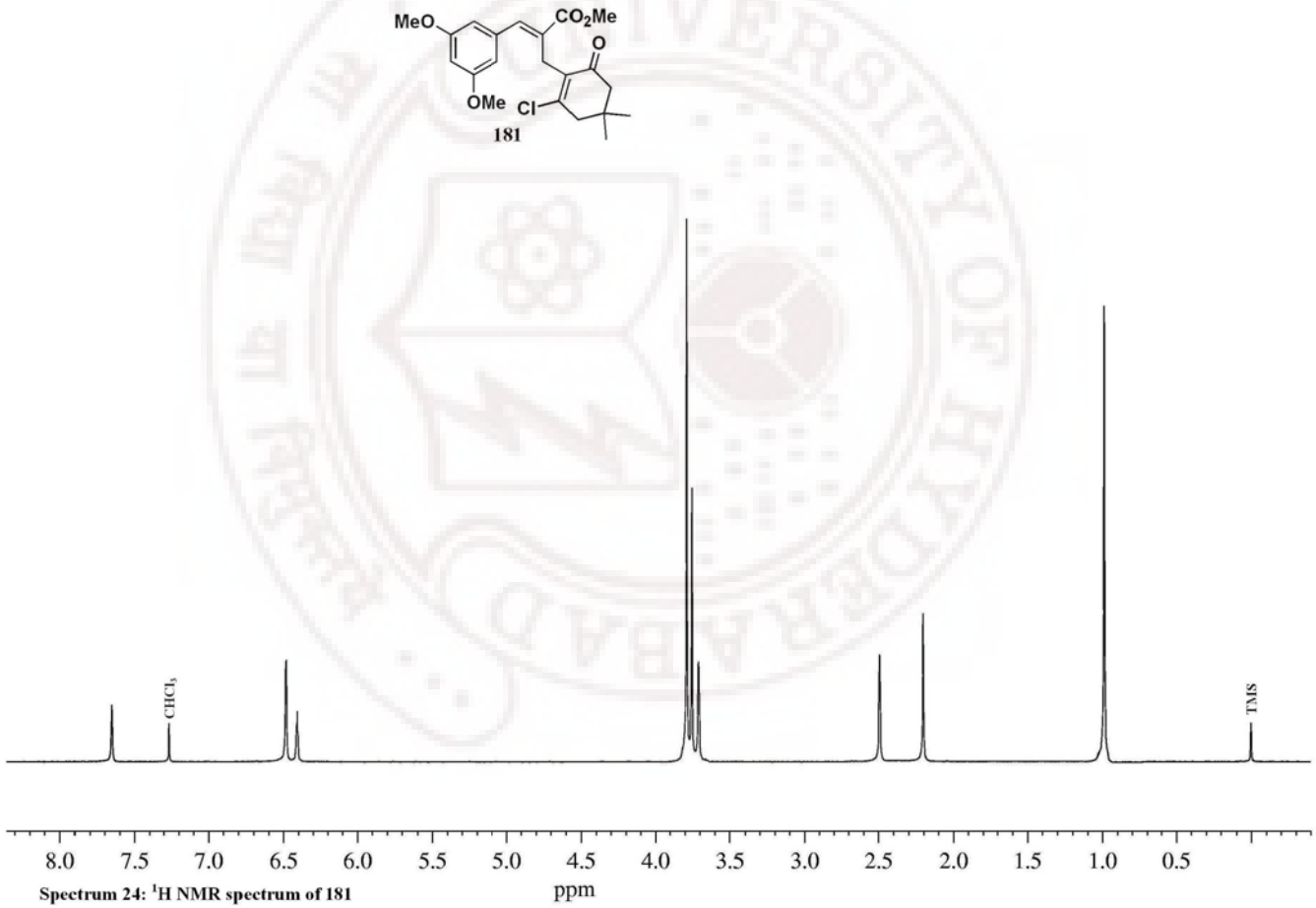
Spectrum 21: ^{13}C NMR spectrum of 176



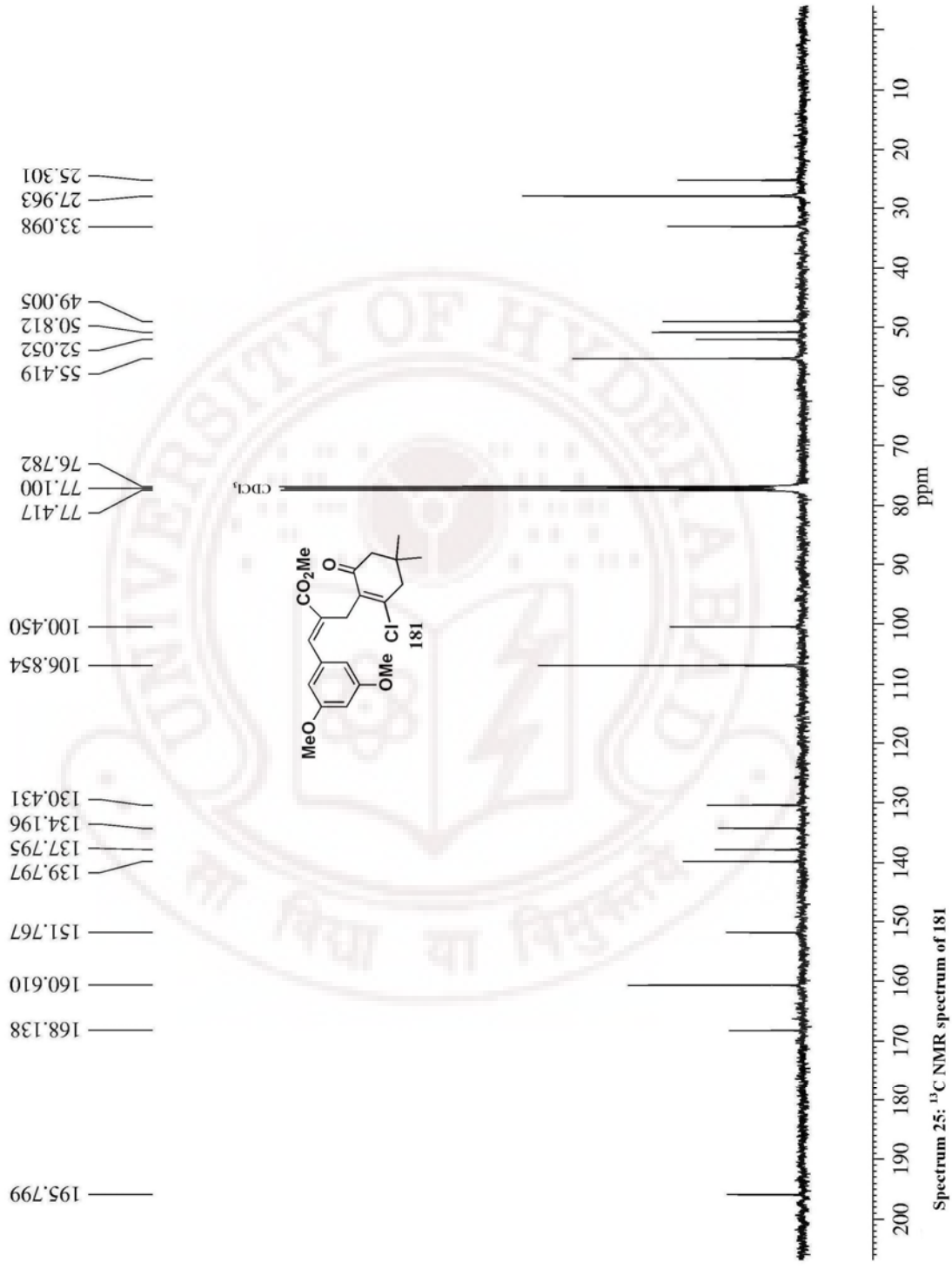
Spectrum 22: ^{1}H NMR spectrum of 179



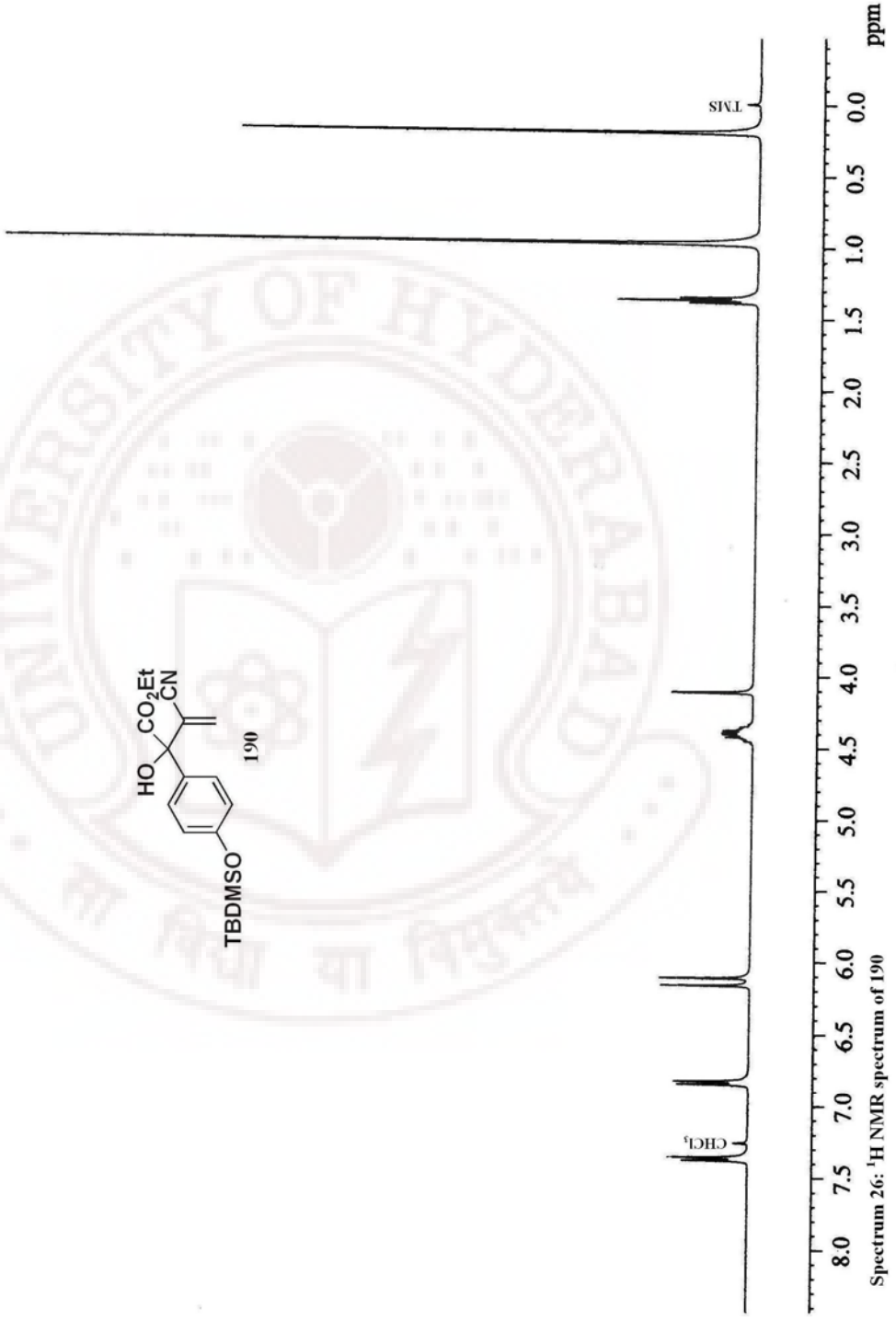
Spectrum 23: ^{13}C NMR spectrum of 179



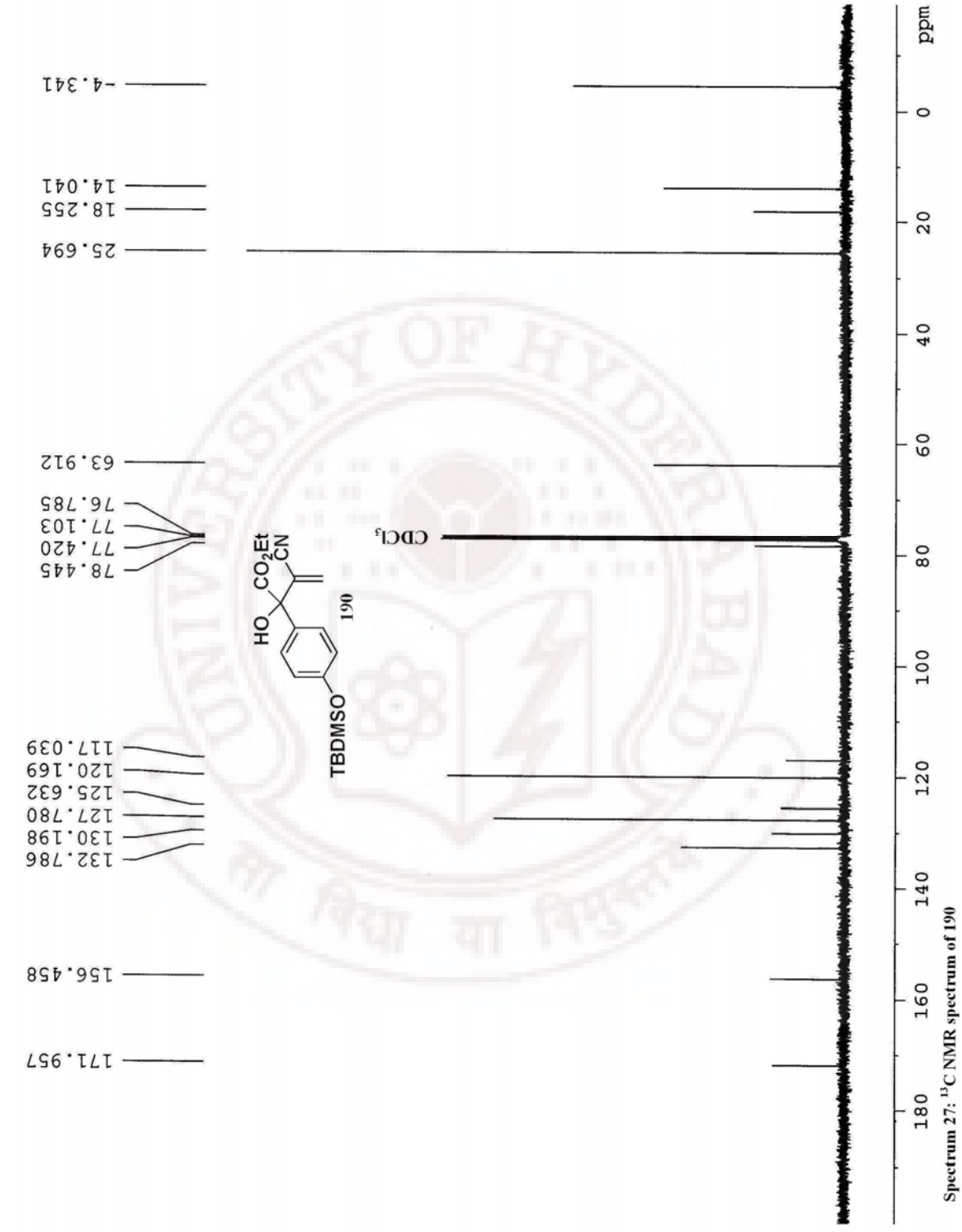
Spectrum 24: ^{1}H NMR spectrum of 181



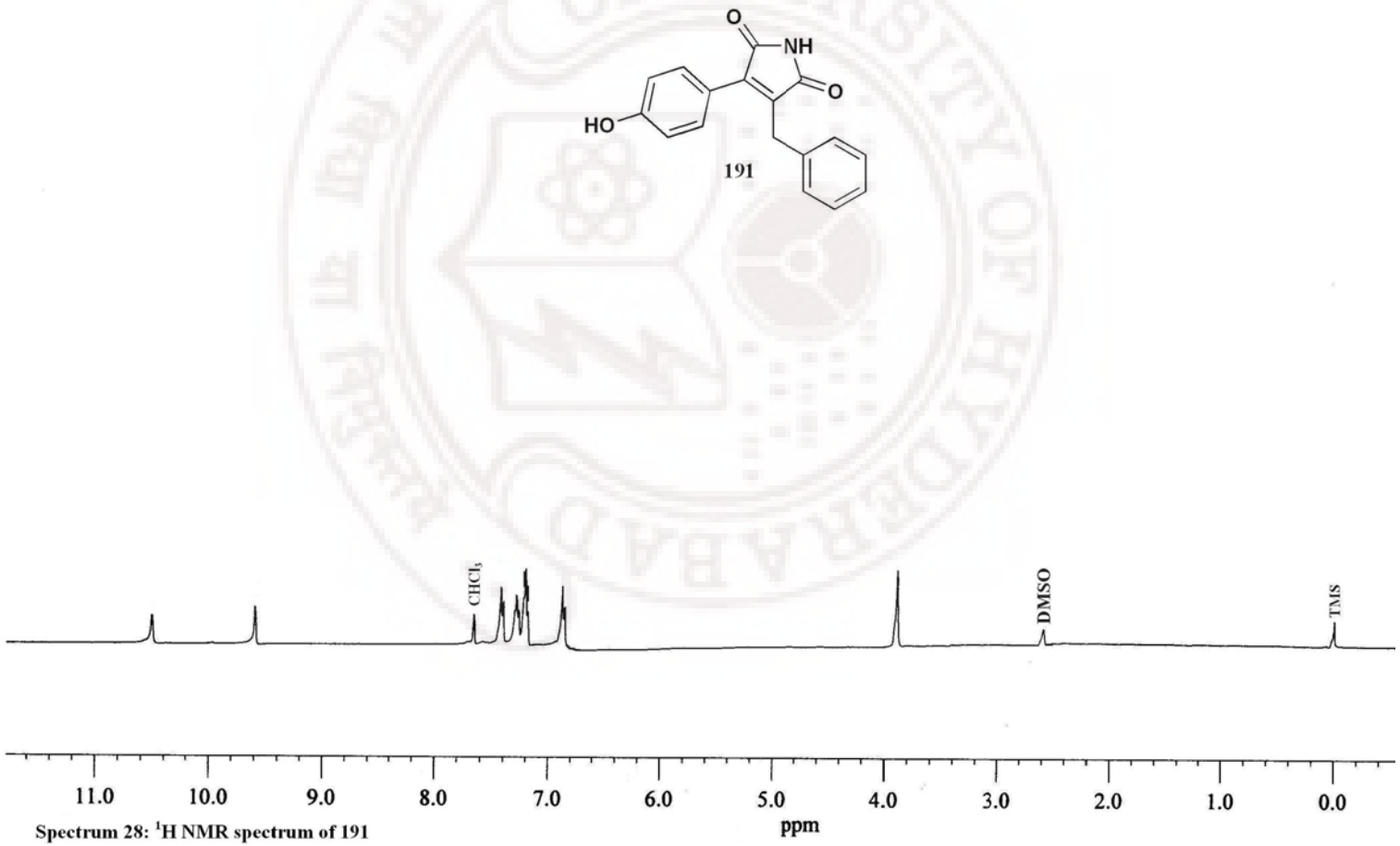
Spectrum 25: ^{13}C NMR spectrum of 181



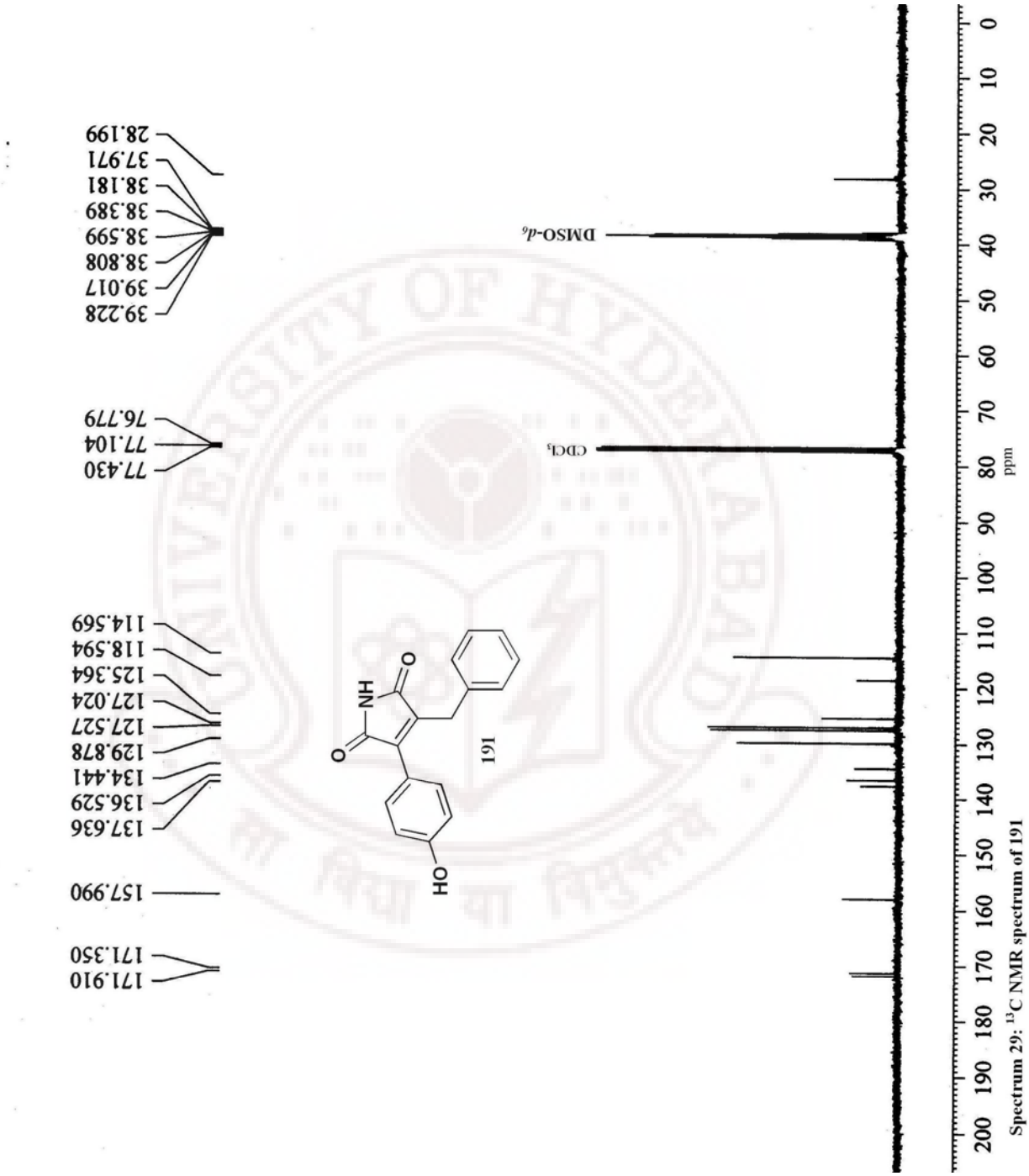
Spectrum 26: ^{1}H NMR spectrum of 190



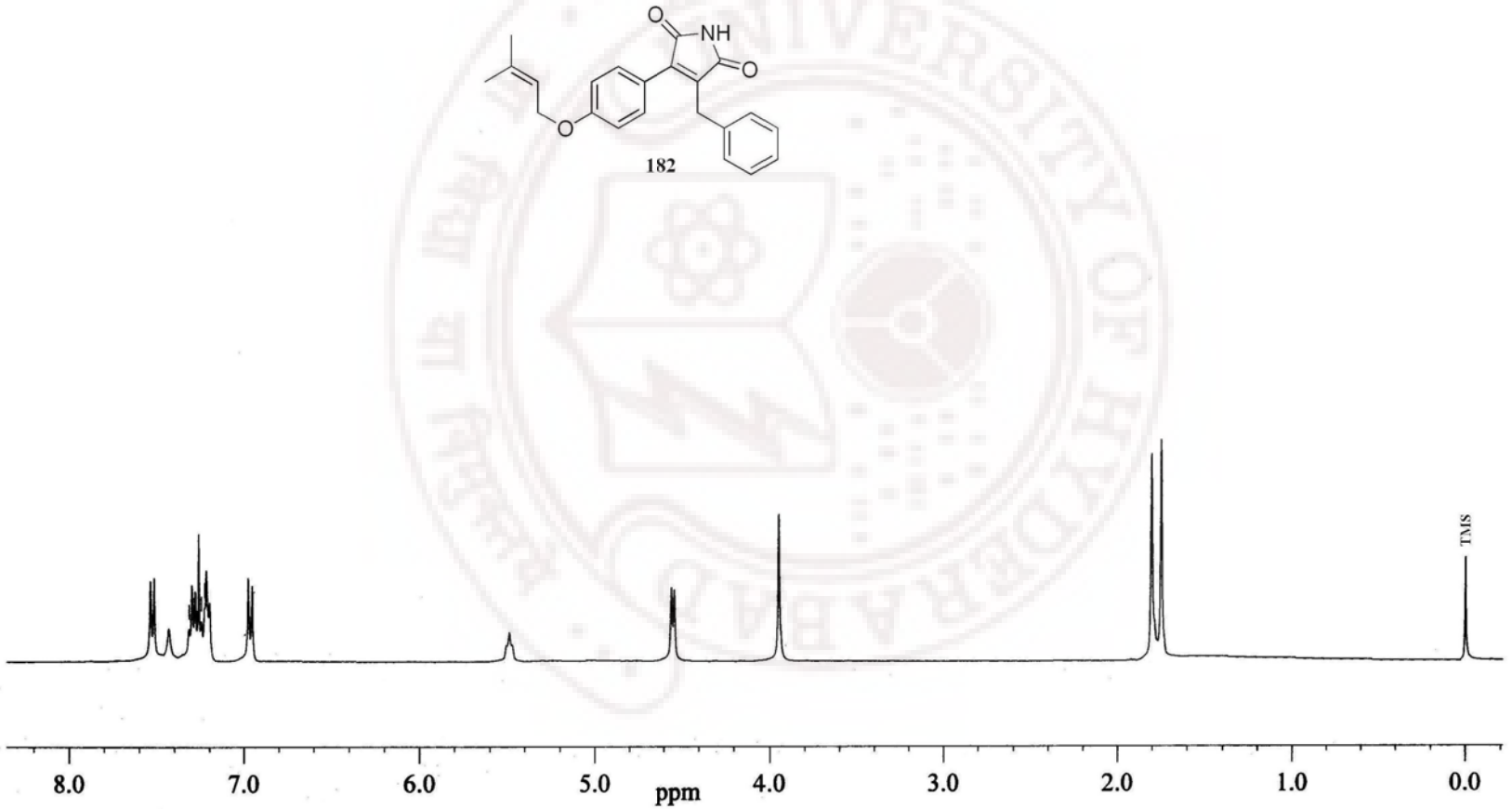
Spectrum 27: ^{13}C NMR spectrum of 190



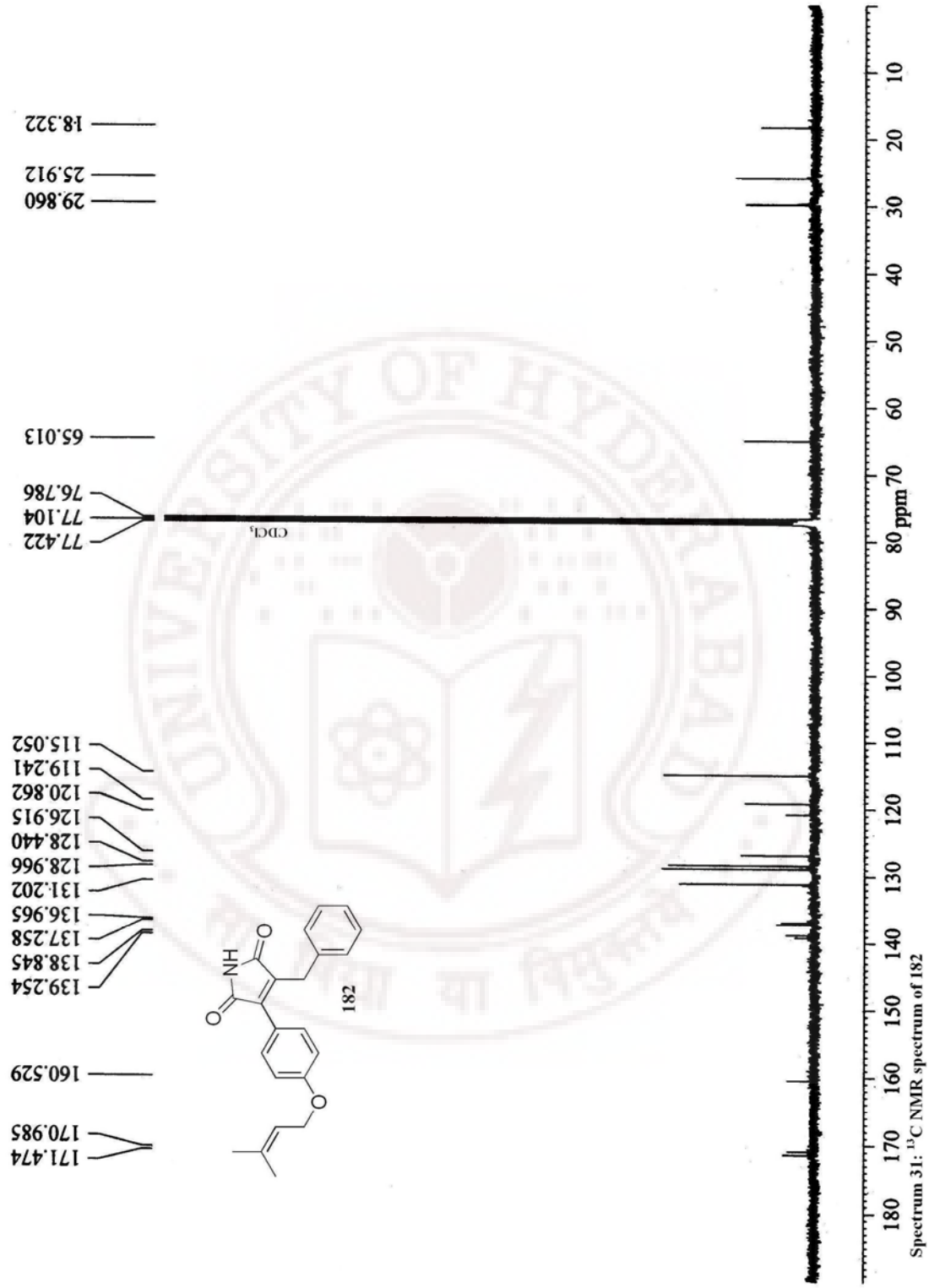
Spectrum 28: ^{1}H NMR spectrum of 191



Spectrum 29: ^{13}C NMR spectrum of 191



Spectrum 30: ^{1}H NMR spectrum of 182



Spectrum 31: ^{13}C NMR spectrum of 182

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **127**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	7629(2)	5295(1)	2557(1)	44(1)
C(2)	8259(2)	5692(1)	3180(1)	55(1)
C(3)	9709(3)	6078(2)	3147(2)	71(1)
C(4)	10499(3)	6077(2)	2498(2)	77(1)
C(5)	9890(2)	671(1)	1879(2)	65(1)
C(6)	8468(2)	5255(1)	1895(1)	48(1)
C(7)	7890(2)	4753(1)	1256(1)	51(1)
C(8)	7421(2)	3886(1)	1294(1)	47(1)
C(9)	7452(2)	3347(1)	2002(1)	41(1)
C(10)	958(2)	3401(1)	2417(1)	38(1)
C(11)	5149(2)	2562(1)	2559(1)	41(1)
C(12)	3646(2)	2621(1)	2959(1)	49(1)
C(13)	2731(2)	3478(1)	2768(1)	45(1)
C(14)	3760(2)	4297(1)	2940(1)	44(1)
C(15)	5339(2)	4223(1)	2626(1)	38(1)
C(16)	2261(3)	3464(2)	1961(1)	60(1)
C(17)	1298(2)	3526(2)	3257(1)	62(1)
C(18)	6836(3)	3455(2)	603(1)	63(1)
C(19)	6022(6)	2049(2)	65(2)	23(1)
C(20)	5924(8)	1118(3)	272(2)	162(2)
N(1)	6047(2)	5055(1)	2583(1)	43(1)
O(1)	5648(2)	1803(1)	2372(1)	56(1)
O(2)	6595(3)	3834(2)	37(1)	110(1)
O(3)	6622(3)	2567(1)	689(1)	95(1)

Table II. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **137**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	5560(2)	186(1)	8320(1)	35(1)
C(2)	4569(2)	-451(1)	7859(1)	38(1)
C(3)	3138(2)	-424(1)	8065(1)	39(1)
C(4)	2672(2)	252(1)	8753(1)	39(1)
C(5)	3666(2)	860(1)	9227(1)	39(1)
C(6)	5120(2)	842(1)	9014(1)	37(1)
C(7)	6145(2)	1543(1)	9483(1)	39(1)
C(8)	6896(2)	2172(1)	8965(1)	37(1)
C(9)	6656(2)	2251(1)	7890(1)	40(1)
C(10)	7600(2)	1598(1)	7307(1)	36(1)
C(11)	8259(2)	2056(1)	6503(1)	42(1)
C(12)	9235(2)	1443(1)	5910(2)	62(1)
C(13)	10014(2)	662(1)	6515(2)	57(1)
C(14)	8926(2)	21(1)	6995(1)	42(1)
C(15)	7808(2)	606(1)	7485(1)	34(1)
C(16)	7994(2)	2844(1)	9418(1)	44(1)
C(17)	9042(3)	3496(2)	10865(2)	103(1)
C(18)	689(2)	1008(1)	9484(2)	58(1)
C(19)	2536(2)	-1738(2)	6982(2)	78(1)
N(1)	7044(1)	57(1)	8106(1)	39(1)
O(1)	8009(2)	2925(1)	6270(1)	57(1)
O(2)	8824(2)	3325(1)	8978(1)	71(1)
O(3)	7975(2)	2873(1)	10375(1)	72(1)
O(4)	1232(1)	239(1)	8906(1)	52(1)
O(5)	2092(1)	-1026(1)	7649(1)	55(1)

Table III. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2 x 10^3) for **139**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	1167(1)	9817(2)	4115(2)	38(1)
C(2)	1094(1)	11040(3)	3335(2)	46(1)
C(3)	1533(1)	11642(3)	3266(2)	58(1)
C(4)	2057(1)	11050(3)	3990(2)	63(1)
C(5)	2130(1)	9839(3)	4764(2)	55(1)
C(6)	1694(1)	9181(3)	4840(2)	41(1)
C(7)	1803(1)	7834(3)	5660(2)	42(1)
C(8)	1581(1)	6141(3)	5493(2)	35(1)
C(9)	1175(1)	5446(3)	4421(1)	35(1)
C(10)	601(1)	6035(2)	4089(1)	32(1)
C(11)	162(1)	4758(3)	3858(1)	35(1)
C(12)	-341(1)	5861(3)	3627(2)	41(1)
C(13)	-154(1)	7884(3)	3834(2)	47(1)
C(14)	426(1)	7818(3)	4049(1)	35(1)
C(15)	1741(1)	4907(3)	6398(2)	40(1)
C(16)	1609(1)	1932(3)	6919(2)	62(1)
N(1)	690(1)	9454(2)	4175(1)	43(1)
O(1)	171(1)	3037(2)	3835(1)	49(1)
O(2)	2066(1)	5291(2)	7286(1)	61(1)
O(3)	1481(1)	3266(2)	6110(1)	52(1)

Table IV. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **142**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	7893(2)	1214(1)	6311(1)	42(1)
C(2)	7954(2)	1961(1)	5615(1)	47(1)
C(3)	9141(2)	2362(1)	5656(2)	55(1)
C(4)	9158(2)	3123(2)	5033(2)	71(1)
C(5)	7991(3)	3513(2)	4324(2)	83(1)
C(6)	6827(3)	3126(2)	4236(2)	74(1)
C(7)	6768(2)	2344(1)	4883(2)	54(1)
C(8)	5580(2)	1961(1)	4836(2)	64(1)
C(9)	547(2)	1242(1)	5497(2)	61(1)
C(10)	6708(2)	857(1)	6252(2)	48(1)
C(11)	6648(2)	71(1)	6949(1)	50(1)
C(12)	7269(2)	-755(1)	7005(1)	45(1)
C(13)	8029(2)	-968(1)	6321(1)	47(1)
C(14)	9457(2)	-705(1)	6850(1)	41(1)
C(15)	10390(2)	-1464(1)	7006(1)	48(1)
C(16)	11827(2)	-1256(1)	7514(2)	63(1)
C(17)	12212(2)	-204(1)	7546(2)	53(1)
C(18)	11288(2)	359(1)	7925(2)	48(1)
C(19)	9878(2)	179(1)	7253(1)	39(1)
C(20)	12110(2)	136(2)	6447(2)	77(1)
C(21)	13620(2)	-64(2)	8336(2)	86(1)
C(22)	7192(2)	-1533(2)	7719(2)	56(1)
C(23)	6757(3)	-1924(2)	9252(2)	127(1)
N(1)	9102(1)	962(1)	7139(1)	44(1)
O(1)	10032(1)	-2299(1)	6751(1)	60(1)
O(2)	7362(2)	-2359(1)	7601(1)	85(1)
O(3)	6898(2)	-1206(1)	8529(1)	88(1)

Table V. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **168**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	7355(2)	1197(1)	3527(3)	46(1)
C(2)	7232(3)	1537(2)	4865(3)	51(1)
C(3)	6293(3)	1963(2)	4973(3)	56(1)
C(4)	5421(3)	2078(2)	3741(3)	54(1)
C(5)	5477(2)	1745(1)	2441(3)	50(1)
C(6)	6418(2)	1287(1)	2332(3)	47(1)
C(7)	6341(2)	931(2)	904(3)	51(1)
C(8)	6758(2)	256(2)	679(3)	52(1)
C(9)	7419(2)	-197(2)	1927(3)	60(1)
C(10)	8494(3)	220(2)	2604(3)	53(1)
C(11)	9587(3)	-71(2)	2304(3)	67(1)
C(12)	10671(3)	347(2)	2930(3)	75(1)
C(13)	10511(3)	1186(2)	3172(3)	64(1)
C(14)	9560(2)	1276(2)	4033(3)	57(1)
C(15)	8457(2)	857(2)	3371(3)	48(1)
C(16)	10192(3)	1601(2)	1703(3)	91(1)
C(17)	11633(3)	1520(2)	4087(4)	96(1)
C(18)	8075(3)	1725(2)	7406(3)	73(1)
C(19)	3702(3)	2756(2)	2697(4)	89(1)
C(20)	6563(3)	-83(2)	-801(3)	61(1)
C(21)	5774(3)	95(2)	-3314(3)	87(1)
O(1)	9608(2)	-645(1)	1593(3)	103(1)
O(2)	8102(2)	1383(1)	6029(2)	62(1)
O(3)	4537(2)	2534(1)	3961(2)	74(1)
O(4)	6835(2)	-716(1)	-1053(2)	83(1)
O(5)	6026(2)	384(1)	-1844(2)	79(1)

Table VI. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **173**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	8655(1)	2335(2)	1050(1)	38(1)
C(2)	9900(1)	1933(2)	1010(1)	40(1)
C(3)	10821(1)	1639(2)	1586(1)	44(1)
C(4)	10554(1)	1810(2)	2227(1)	45(1)
C(5)	9364(1)	2199(2)	2290(1)	46(1)
C(6)	8403(1)	2419(2)	1705(1)	40(1)
C(7)	7165(1)	2719(2)	1840(1)	42(1)
C(8)	6096(1)	2127(2)	1455(1)	39(1)
C(9)	6103(1)	1183(2)	812(1)	44(1)
C(10)	6522(1)	2348(2)	314(1)	39(1)
C(11)	5494(2)	3016(2)	-237(1)	47(1)
C(12)	5754(2)	3743(2)	-881(1)	61(1)
C(13)	6859(2)	2963(2)	-1113(1)	61(1)
C(14)	8106(2)	3693(2)	-755(1)	56(1)
C(15)	8153(1)	4187(2)	-13(1)	45(1)
C(16)	7725(1)	2862(2)	427(1)	38(1)
C(17)	11332(1)	1404(2)	288(1)	50(1)
C(18)	11366(2)	1891(3)	3430(1)	68(1)
C(19)	4904(1)	2289(2)	1680(1)	44(1)
C(20)	3893(2)	3394(3)	2500(1)	67(1)
O(1)	4414(1)	2916(2)	-169(1)	64(1)
O(2)	10111(1)	1834(1)	369(1)	48(1)
O(3)	11542(1)	1544(2)	2765(1)	59(1)
O(4)	3966(1)	1522(2)	1434(1)	65(1)
O(5)	4976(1)	3334(2)	2206(1)	56(1)

Table VII. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2 x 10^3) for **176**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	3259(1)	3851(3)	3767(3)	44(1)
C(2)	4330(1)	3535(3)	4210(4)	44(1)
C(3)	3847(1)	1948(3)	1988(4)	47(1)
C(4)	3842(1)	3128(3)	3378(3)	42(1)
C(5)	5720(1)	1270(3)	3087(3)	45(1)
C(6)	4802(1)	-1421(3)	3548(4)	50(1)
C(7)	3790(1)	-1001(3)	2739(4)	49(1)
C(8)	5966(1)	3793(3)	4142(4)	55(1)
C(9)	4680(1)	274(3)	3078(3)	40(1)
C(10)	4940(1)	3027(3)	3912(3)	43(1)
C(11)	4120(1)	460(3)	2567(3)	40(1)
C(12)	6145(1)	2370(3)	3503(4)	52(1)
C(13)	4197(1)	-2207(3)	3446(4)	55(1)
C(14)	5112(1)	1533(3)	3300(3)	41(1)
C(15)	5371(1)	4109(3)	4350(4)	55(1)
C(16)	6960(1)	4636(5)	4629(6)	86(1)
C(17)	6462(1)	-573(4)	2266(5)	75(1)
C(18)	2771(1)	5929(4)	5085(5)	64(1)
O(1)	3269(1)	-1186(2)	2394(4)	73(1)
O(2)	2801(1)	3446(2)	3156(3)	62(1)
O(3)	3300(1)	5039(2)	4830(3)	57(1)
O(4)	5863(1)	-133(2)	2390(3)	62(1)
O(5)	6345(1)	4935(2)	4652(4)	79(1)

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TableVIII. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2 x 10^3) for **179**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U (eq)
C(1)	3556(3)	7314(1)	3864(2)	46(1)
C(2)	5274(3)	6976(1)	4297(2)	51(1)
C(3)	6451(3)	7369(1)	5061(2)	49(1)
C(4)	6026(3)	8154(1)	5524(2)	51(1)
C(5)	5796(3)	8788(1)	4631(2)	47(1)
C(6)	4539(3)	8726(1)	3698(2)	51(1)
C(7)	3248(3)	8113(1)	3507(2)	47(1)
C(8)	1621(3)	8367(1)	2952(2)	54(1)
C(9)	290(3)	7861(1)	2844(2)	57(1)
C(10)	553(3)	7080(1)	3238(2)	57(1)
C(11)	2152(3)	6814(1)	3725(2)	53(1)
C(12)	5600(4)	6206(1)	3728(3)	71(1)
C(13)	8220(3)	7087(1)	5458(2)	56(1)
C(14)	9589(3)	7679(2)	5796(3)	74(1)
C(15)	6935(3)	9480(1)	4841(2)	50(1)
C(16)	7788(3)	10658(1)	4104(2)	66(1)
C(17)	-1686(4)	8865(2)	1982(3)	88(1)
C(18)	1154(4)	5488(1)	3882(3)	98(1)
O(1)	8575(2)	6382(1)	5493(2)	94(1)
O(2)	7992(2)	9593(1)	5711(2)	73(1)
O(3)	6692(2)	9982(1)	3971(2)	62(1)
O(4)	-1342(2)	8059(1)	2366(2)	78(1)
O(5)	2480(2)	6056(1)	4129(2)	71(1)

LIST OF PUBLICATIONS

1. The Baylis-Hillman acetates as a valuable source for one-pot multistep synthesis: a facile synthesis of functionalized tri-/tetracyclic frameworks containing azocine moiety
   Deevi Basavaiah and **Kunche Aravindu** *Org Lett*. **2007**, *9*, 2453-2456.

2. Simple, one-pot and facile synthesis of angularly fused [6-7-5], [6-7-6], [6-7-7] and [6,7] ring systems using Baylis-Hillman acetates
   Deevi Basavaiah, **Kunche Aravindu**, Katta Santosh Kumar and Kanumuri Ramesh Reddy *Eur. J. Org. Chem.* **2010**, 1843-1848.

3. A facile one-pot transformation of Baylis–Hillman adducts into unsymmetrical disubstituted maleimide and maleic anhydrideframeworks: a facile synthesis of *himanimide A*
   Deevi Basavaiah, Badugu Devendar, **Kunche Aravindu**, and Ainelly Veerendhar *Chem. Eur. J.* **2010**, *16*, 2031-2035.

4. Simple and facile synthesis of bicyclic frameworks containing benzocycloheptane skeleton and tetracyclic-carbocyclic framework containing [6-7-6-6] ring systems from the Baylis-Hillman adducts
   Deevi Basavaiah, Kanumuri Ramesh Reddy and **Kunche Aravindu** (communicating to *Org. Bimol. Chem.*)

5. Simple and facile synthesis of propellanes from the acetates of the Baylis-Hillman adducts
   Deevi Basavaiah, Ainelly Veerendhar, and **Kunche Aravindu** (to be communicated)