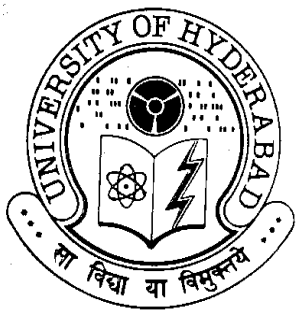
APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCTS: TOWARDS DEVELOPMENT OF NOVEL STRATEGIES FOR SYNTHESIS OF SPIRO AND HETEROCYCLIC COMPOUNDS

RAJU JANNAPU REDDY



SCHOOL OF CHEMISTRY

UNIVERSITY OF HYDERABAD

HYDERABAD–500 046

INDIA

DECEMBER 2007

APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCTS: TOWARDS DEVELOPMENT OF NOVEL STRATEGIES FOR SYNTHESIS OF SPIRO AND HETEROCYCLIC COMPOUNDS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

RAJU JANNAPU REDDY

SCHOOL OF CHEMISTRY

UNIVERSITY OF HYDERABAD

HYDERABAD–500 046

INDIA

DECEMBER 2007

CONTENTS

STATEMENT

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

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

HYDERABAD
DECEMBER, 2007 **RAJU JANNAPU REDDY**

CERTIFICATE

Certified that the work embodied in this thesis entitled "**Applications of the Baylis-Hillman adducts: Towards development of novel strategies for synthesis of spiro and heterocyclic compounds**" has been carried out by **Mr. Raju Jannapu Reddy**, 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

ACKNOWLEDGEMENTS

I express my sincere gratitude and profound respect to my research supervisor **Professor D. Basavaiah**, for his inspiring guidance, constant encouragement, advices, timely suggestions and criticisms throughout my research tenure.

I thank the Dean and all the faculty members of the School of Chemistry for their timely help and cooperation during my Ph. D. program.

I am thankful to Professor S. Pal for helpful discussions regarding the X-ray data analysis.

It is a great privilege to express my heartfelt regards to all my teachers during the entire tenure of my educational career, especially to Dr. Ravinder Rao & Dr. Ramachary.

I acknowledge the help rendered by my senior colleagues and present labmates Dr. S. Bhaskar raju, Dr. P. Rama Krishna, Dr. K. Muthukumaran, Dr. M. Krishnamacharyulu, Dr. A. Bakthadoss, Dr. R. Mallikarjuna Reddy, Dr. B. Sreenivasulu, Dr. M. Jagan Mohan Rao, Dr. G. Jayapal Reddy, Dr. D. S. Sharada, Dr. J. Srivardhana Rao, Dr. T. Satyanarayana, Dr. V. Chandrashaker, Dr. K. Venkateswara Rao, Mr. D. V. Lenin Babu, Mr. B. Devender, Ms. P. Anupama, Mr. A. Veerendhar, Mr. K. Ramesh Reddy, Mr. K. Aravindu, Ms. Suparna Roy, Mr. B. Sekhara Reddy, Mr. B. Satpal Singh and Mr. K. Santosh Kumar for their timely help and pleasant association.

Words are poor substitute to express my profound gratitude and love to my parents & my wife for their unfailing love, affection and encouragements. I take this opportunity to express my deepest affection to my Brother-in-law (Bavagaru, **PSN Reddy**) and my Sister for their support, encouragement, love and affection deserves a great appreciation, which words cannot do & their children's Sushee and Sheshi for their cheerful company. I am extremely thankful to all my family members, especially my Cosines (Rajitha, Rama & Naveen) and their family members & also my Uncle and Anti for their support.

I am thankful to Mr. G. Vikram is indeed of great help to me and also thank to Dr. L. Srinivasa Reddy, Mr. Phani, and Mr. Jagadeesh for their timely help.

I thank all my **FRIENDS** for their help and support especially, Mr. I. Rambabu, Mr. A. Earrana, Mr. N. Vijay kumar, Mr. B. Rajendhar, Mr. Satyanarayana Reddy, Mr. Raghu, Mrs. Lavanya, Mr. Narendhar, Mr. Mohan, Dr. Suresh, Dr. Narsi Reddy, Dr. Venu, Dr. Basavoju, Dr. Balu, Dr. Malla Reddy, Dr. Guptha, Dr. Sateesh, Dr. Pavan, Mr. Shyamraj, Mrs. Kavitha, Mr. Bhuvan, Mr. Narahari, Mr. Anwar, Mr. Balaraman, Mr. Venu, Mr. Kishana Kishore, Mr. Satish, Mr. Nagaraju, Mr. Venu, Mr. Mallesh, Mr. Sanjeev, Mr. Silva, Mr. Ramu, Mr. Kishore, Mr. Narayana, Mr. Ramukumar and Mr. K. Srikanth.

I gratefully acknowledge the help provided by the technical and office staff of the School of Chemistry. I also thank Mr. V. Bhaskara Rao, Mrs. Asia Perwej, Mrs. Vijaya Laxmi, Mr. S. Satyanarayana, Mr. M. Shetty, Mr. R. Raghavaiah and Mr. Vijay Bhaskar for their timely help.

National Single Crystal X-ray Facility, funded by DST (New Delhi) in School of Chemistry is highly acknowledged.

Financial assistance by CSIR (New Delhi) and DST (New Delhi) is gratefully acknowledged.

Raju

ABBREVIATIONS

Ac	acetyl
aq.	aqueous
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Boc	butoxycarbonyl
Bp	boiling point
BINOL	1,1′-bi-2-naphthol
Bu	*n*-butyl
t-Bu or Bu^t	*tertiar*y butyl
Bn	benzyl
cat.	catalyst
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimdazole
*m*CPBA	*meta*-chloroperbenzoic acid
Cp	cyclopentyl
CPME	cyclopentyl methyl ether
c-Hex	cyclohexyl
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
dba	dibenzylideneacetone
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
de	diastereomeric excess
dec.	decompose
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide (Me_2S)

DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl
Eq.	Equation
eq.	equivalent(s)
$Eu(fod)_3$	Europium tris[6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octane-dionate]
EWG	electron withdrawing group
Hex	hexyl
Hept	heptyl
HMT	hexamethylenetetramine
3-HQD	3-hydroxyquinuclidine
LAH	lithium aluminum hydride
KDP	ketodicyclopentadiene
Me	methyl
MEMCl	(2-methoxyethoxy)methyl chloride
Mp	melting point
MS	molecular sieves
MsCl	mesyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
PAP	polymer bound 4-(*N*-benzyl-*N*-methylamino)pyridine
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pent	pentyl
Ph	phenyl
PMP	*p*-methoxyphenyl

PPTS	pyridinium *p*-toluenesulfonate
PTA	1,3,5-triaza-7-phosphaadamantane
Pr	*n*-propyl
i-Pr or Pr^i	*iso*-propyl
RCM	ring-closing metathesis
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDMSCl / TBSCl	*tert*-butyldimethylsilyl chloride
TBDMSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TEA	triethylamine
TESCl	chlorotriethylsilane
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	chlorotriisopropylsilane
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
TsCl	tosyl chloride

ABSTRACT

The Baylis-Hillman reaction is a successful and useful carbon-carbon bond forming reaction well equipped with the concepts of atom-economy and generation of useful multifunctional molecules. This is an essentially a three component reaction involving the coupling of α-position of activated alkene with an electrophile in the presence of a catalyst or catalytic system, providing an interesting classes of highly synthetically useful densely functionalized molecules. These multifunctional molecules, usually known as Baylis-Hillman adducts, have been elegantly employed in a variety of stereoselective organic transformation methodologies and also in the synthesis of several important heterocycles, carbocycles, natural products and biologically active molecules. During the last twenty three years, our research group has been working on various aspects of this fascinating reaction with the main aim of developing Baylis-Hillman adducts / chemistry into a valuable source for synthesis of various structural frameworks which ultimately would lead to the production of important molecules of medicinal relevance.

This thesis deals with the development of novel strategies for synthesis of various spiro and heterocyclic frameworks using the Baylis-Hillman adducts, and consists of three chapters 1) Introduction 2) Objectives, Results & Discussion and 3) Experimental. The first chapter, that is, 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 development of novel strategies / methodologies for synthesis of spiro and heterocyclic compounds from the Baylis-Hillman adducts with following main objectives.

OBJECTIVES

1) To develop a simple and facile two step procedure for the synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides [di(*E*)-arylidene alonomids] from the Baylis-Hillman acetates.

2) To develop the Baylis-Hillman acetates as a valuable source for one-pot multistep synthesis: A convenient synthesis of di(*E*)-arylidene-spiro-bisglutarimides.

3) To develop the Baylis-Hillman adducts as a valuable source for one-pot multistep synthesis: A facile synthesis of substituted-2-piperidones.

4) To develop a simple methodology for regioselective phenylation of the Baylis-Hillman adducts, derived *via* the coupling of various chromones with 3- / 4-nitro-benzaldehydes, through the Friedel-Crafts reaction with benzene.

5) To develop a facile methodology for one-pot conversion of Baylis-Hillman adducts, obtained *via* the reaction of chromone derivatives with 2-nitro- / 2,4-dinitrobenzaldehydes, into tetra / penta cyclic chromone fused quinoline *N*-oxides.

A simple and facile two step procedure for the synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides from the Baylis-Hillman acetates

Tetralone and spiro-tetralone derivatives occupy an important place in organic and medicinal chemistry because of the presence of this moiety in a number of natural products, such as, palmarumycins (possess antifungal, antibacterial, and herbicidal activites), humicolone (possesses cytotoxic activity), daldinone A, & aristelegone A-C *etc*. The glutarimide framework represents yet another important structural organization present in a number of bioactive molecules, such as, thalidomide (sedative & hypnotic), migrastatin (antitumor), sesbanimide A & B (antitumor), amino-glutethimide (antineoplastic), cinperene (antipsychotic & neuroleptic) & phenglut-arimide (antiparkinsonian & anticholinergic) *etc*. Due to the biological importance of the spiro-tetralone structural unit and glutarimide framework, it occurred to us that the development of a simple and facile synthesis of an interesting and aesthetically appealing molecular architecture containing both the tetralone and glutarimide structural units linked by an appropriate spiro bridge as in the case of alonimid (**157**), *i.e*. [1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′, 6′-dione] (well known for sedative and hypnotic activities), would certainly provide an easy access to the different derivatives of alonimids (**162**) (Figure 12) and also would provide attractive spiro and heterocyclic compounds with possible medicinal relevance and hence represents challenging endeavor in organic and medicinal chemistry.

In this direction, we have successfully developed a novel, convenient and operationally simple two-step procedure for the synthesis of di(*E*)-arylidene alonimids (**162a-i**) *via* the bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates (**160a-i**) followed by an interesting biscyclization strategy involving the successive C-C and C-N bonds formation through an intramolecular Friedel-Crafts reaction and hydrolysis of nitrile group with subsequent formation of glutarimide framework (Schemes 66 & 68 and Table 1).

The Baylis-Hillman acetates as a valuable source for one-pot multistep synthesis: A convenient synthesis of di(*E*)-arylidene-spiro-bisglutarimides

Recent developments in organic and medicinal chemistry created a need for synthesizing important and potential biologically active frameworks in an operationally simple procedure, if possible in one-pot operation, even though a number of steps / reactions are involved in actual synthetic processes.

Accordingly, we have developed a simple and facile one-pot multistep synthesis of spiro-bisglutarimides (**165a-g**) *via* bisalkylation of malononitrile with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates (**160a-g**) followed by the hydrolysis of nitrile groups and subsequent cyclization (Schemes 71 & 72 and Table 2). The most interesting aspect of this methodology is that two C-C and two C-N bonds are formed in one pot-operation.

The Baylis-Hillman adducts as a valuable source for one-pot multistep synthesis: A facile synthesis of substituted-2-piperidones

The 2-piperidone moiety occupies a special place in nitrogen heterocyclic chemistry because of the presence of this moiety in a variety of biologically important natural products and also in a number of medicinally relevant molecules, such as, peptidase / protease inhibitors, EP_4 receptor agonists, and selective antagonists of the neurokinin-2 (NK_2) receptor. High applicability of these molecules with medicinal importance demands the development of simple and easy methodologies for the synthesis of 2-piperidone framework with a provision to have a wide range of substitution profile.

We have developed a convenient and operationally simple one-pot multistep procedure for the synthesis of 5-substituted / 3,5-disubstituted-2-piperidones (**181a-j**) from the Baylis-Hillman alcohols (**179a-i**), *via* the Johnson-Claisen rearrangement, reduction of α, β-unsaturated nitrile to amine followed by cyclization (Schemes 80-82 and Table 3), thus demonstrating the versatility of Baylis-Hillman adducts as a valuable source for one-pot multistep synthesis.

Regioselective phenylation of the Baylis-Hillman adducts via the Friedel-Crafts reaction with benzene

Friedel-Crafts reaction is one of the most popular carbon-carbon bond forming reactions and has been extensively used in various aspects of organic synthesis including the

preparation of important natural and bioactive molecules. We have transformed the Baylis-Hillman alcohols (**187a-i**), [obtained by the treatment of chromone derivatives (**186a-f)** with 3-/4-nitrobenzaldehydes in the presence of NaOMe], *via* the Friedel-Crafts reaction with benzene, into 3-[(3-/4-nitrophenyl)phenylmethyl]-4*H*-chromen-4-one derivatives (**188a-i**) (Schemes 90-92, 96 & 97 and Tables 5 & 6), thus demonstrating the importance of Baylis-Hillman adducts in synthetic organic chemistry.

A facile methodology for one-pot conversion of Baylis-Hillman adducts into tetra / penta cyclic chromone fused quinoline *N*-oxides

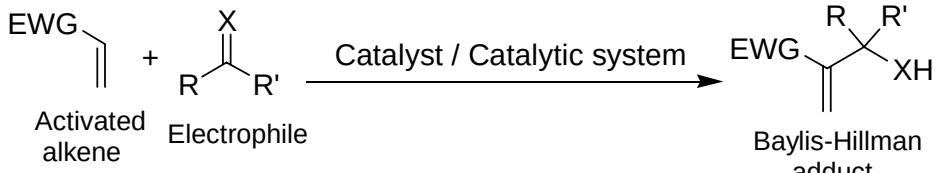
A facile methodology for the synthesis of tetra / penta cyclic chromone fused quinoline *N*-oxide frameworks (**195a-g**), from the Baylis-Hillman alcohols, *i.e.,* 3-[hydroxy(2-nitro / 2,4-dinitrophenyl)methyl]-4*H*-chromen-4-one derivatives (**187j-p**), derived from representative chromone derivatives (**186a-f**) and 2-nitrobenzaldehyde / 2,4-dinitrobenzaldehyde, in a convenient and operationally simple one-pot procedure has been developed (Eq. 32, Schemes 107, 109 & 110 and Table 8).

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

INTRODUCTION

ORIGIN & GROWTH OF THE BAYLIS-HILLMAN REACTION

The Baylis-Hillman reaction[1-6] is a successful and useful carbon-carbon bond forming reaction well equipped with the concepts of atom-economy and generation of useful multifunctional molecules. The origin of this reaction dates back to a German patent[1] filed in the year 1972 by A. B. Baylis & M. E. D. Hillman (and also to a US patent[2] filed in the year 1973 by M. E. D. Hillman & A. B. Baylis). This is an essentially three component reaction involving the coupling of α-position of activated alkene with an electrophile in the presence of a catalyst or catalytic system, providing an interesting class of highly synthetically useful densely functionalized molecules (Eq. 1).[3-6]



Eq. 1

R = alkyl, aryl, hetero-aryl, *etc.*
R' = H, COOR, alkyl, *etc.*
X = O, *N*-Ts, *N*-CO_2R, *N*-$PO(R)_2$, *etc.*

Catalyst / Catalytic system = *tert*-amines, phosphines, Lewis acids, *etc.*

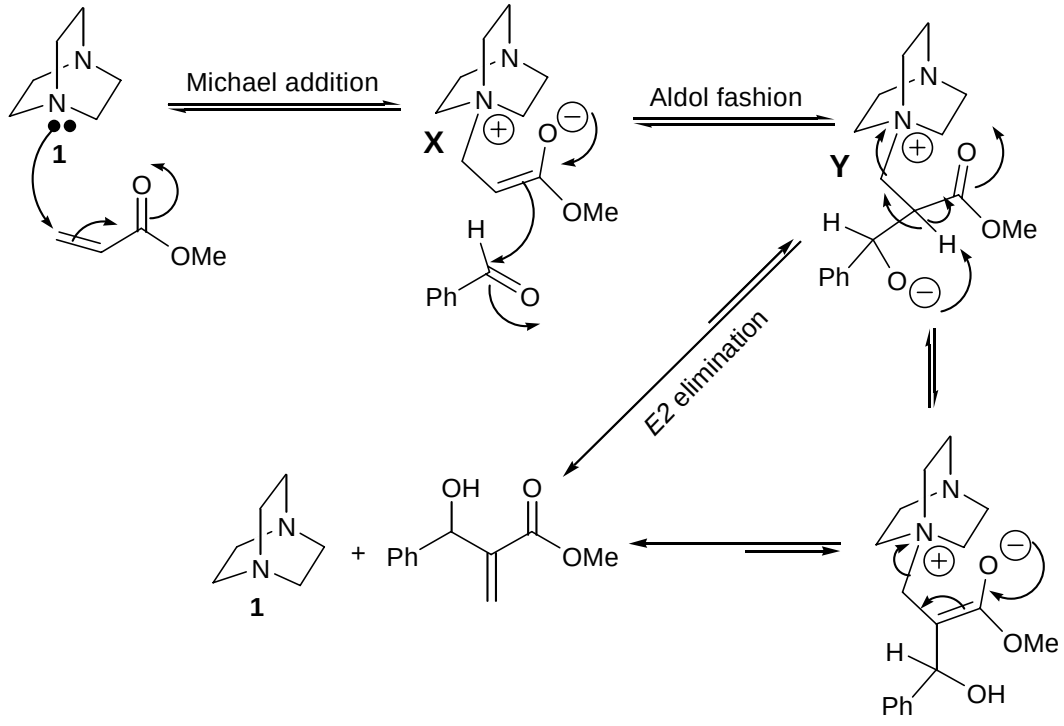
EWG (Electron Withdrawing Group) = COOR, COR, CHO, CN, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh, *etc.*

MECHANISM OF THE BAYLIS-HILLMAN REACTION

The most widely accepted mechanism[7-15] of the Baylis-Hillman reaction is shown in the Scheme 1 taking the reaction between benzaldehyde (*as an electrophile*) and methyl acrylate (*as an activated olefin*) under the catalytic influence of DABCO (**1**), as a

model case. The first step of the reaction involves the Michael (nucleophilic) type addition of the tertiary amine catalyst (DABCO) to the activated alkene (*methyl acrylate*), leading to the formation of zwitterionic enolate **X**, which adds on to the electrophile (*benzaldehyde*) in an aldol fashion, to generate the zwitterionic species **Y**. The zwitterion **Y** undergoes proton migration and releases the catalyst to provide the desired multifunctional molecule (Scheme 1). 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 1.[7-15] However, many aspects of the rate limiting step (RLS) are not yet understood.[7-15] 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.

Scheme 1



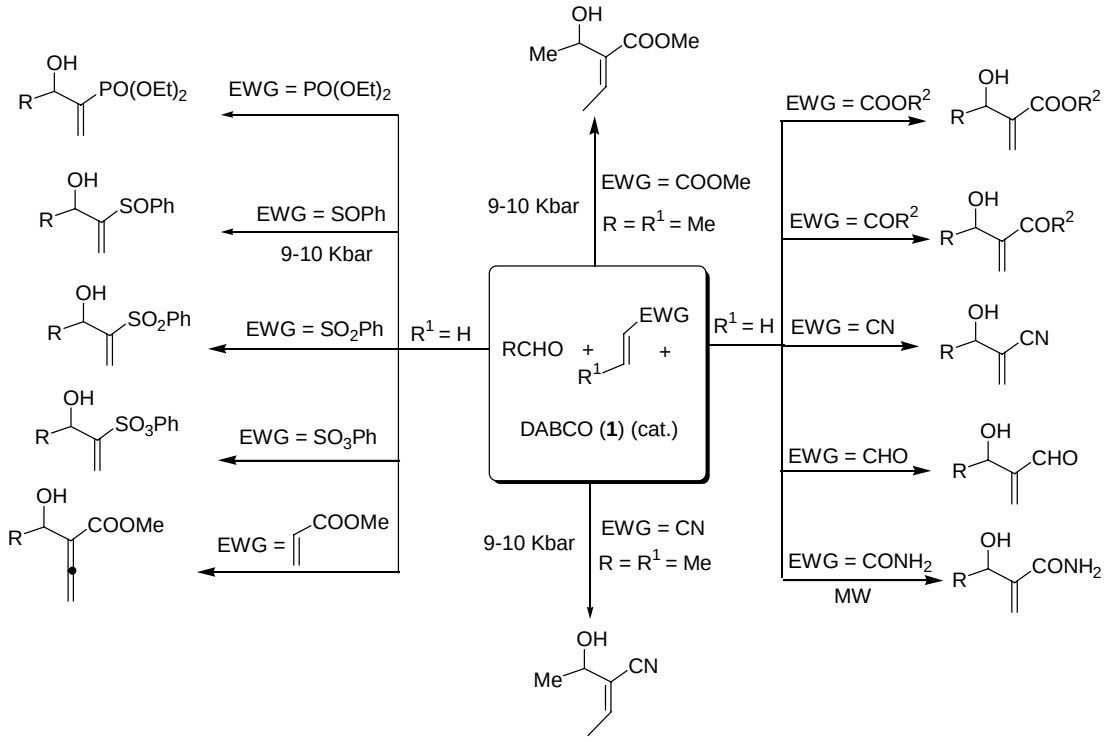
THREE ESSENTIAL COMPONENTS—DEVELOPMENTS

During the past two decades the Baylis–Hillman reaction has seen a tremendous growth in terms of all the three essential components, *i.e.* (1) activated alkenes (*acyclic / cyclic*), (2) electrophiles (*carbon / non-carbon*), and (3) catalyst (or catalytic system) / reagents (*tert-amine / non-amine*) to produce densely functionalized molecules, as evidenced by four major reviews,[3-6] many mini reviews[16-22] and large number (more than 1000) of research publications. Also, applications of the Baylis-Hillman adducts in various new synthetic transformation methodologies have been well documented in the literature.[3-6] Since the available literature on various aspects of this reaction is very vast, it will not be possible to present all the developments in this section. However, some of the recent, relevant and important developments on various aspects of this reaction are presented in this section.

(1) ACTIVATED ALKENES

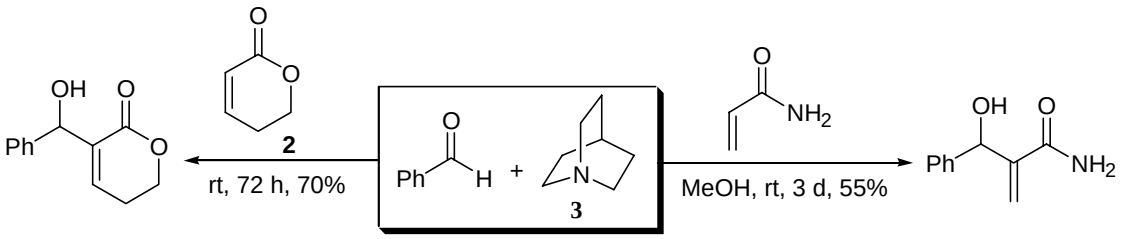
Acyclic activated alkenes: A large number of acyclic activated alkenes, such as, alkyl (aryl) acrylates,[23-25] alkyl vinyl ketones,[26-28] acrylonitrile[27,29] vinyl sulphones,[30] acrylamides,[31] allenic esters,[32,33] vinyl sulphonates,[34] vinyl phosphonates[35] and acrolien[36-38] have been effectively employed in the Baylis-Hillman coupling with a number of electrophiles to provide the desired densely functionalized molecules (Scheme 2). Also, a variety of alkynyl esters and alkynyl ketones have been employed for coupling with electrophiles in this reaction.[19] However, the β-substituent activated olefins, such as, crotononitrile[39,40] & methyl crotonate[39] and less reactive alkenes like phenyl vinyl sulfoxide[41] require high pressure to participate in this reaction (Scheme 2).

Scheme 2

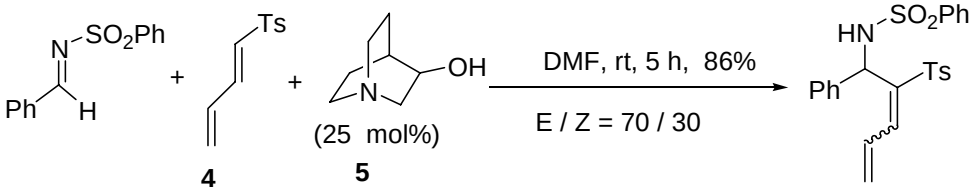


Recently, Aggarwal and coworkers,[42] have employed 5,6-dihydro-2*H*-pyran-2-one (**2**) as an activated alkene for coupling with aldehydes in the presence of quinuclidine (**3**). They have also used acrylamide as activated alkene for coupling with aldehydes under the catalytic influence of quinuclidine (**3**) in the presence of methanol. Representative examples are presented in Scheme 3.

Scheme 3



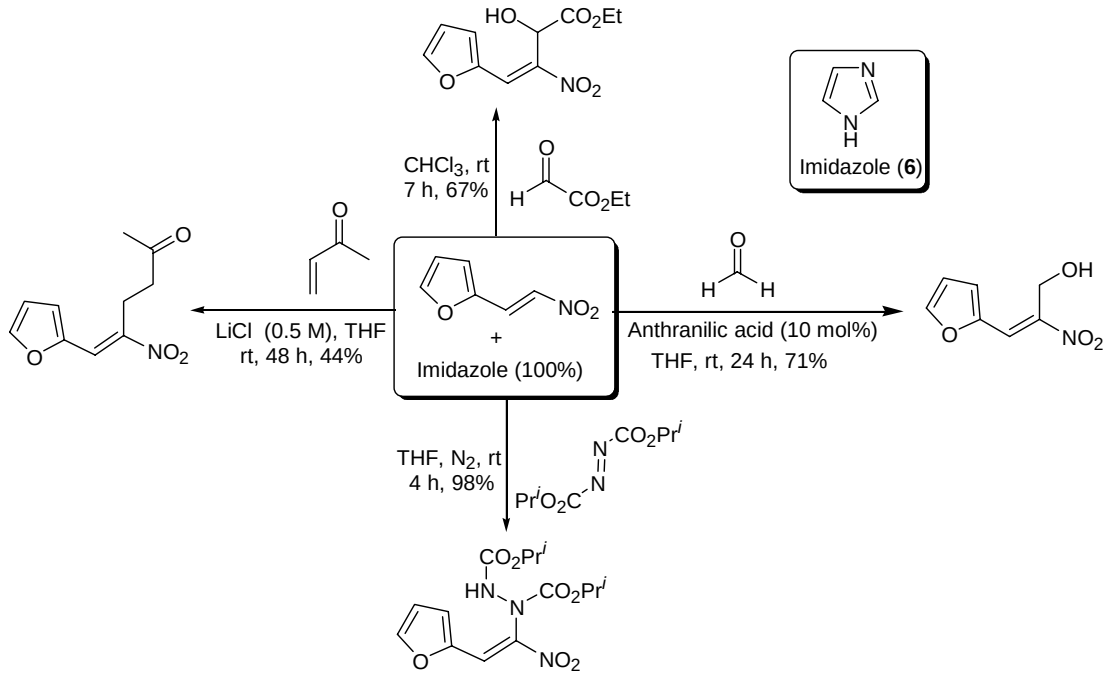
Recently, Back and coworkers[43] employed 1-(*p*-toluenesulfonyl)-1,3-butadiene (**4**) as activated alkene for coupling with aldimine derivatives in the presence of 3-hydroxyquinuclidine (3-HQD, **5**) as catalyst to provide the corresponding Baylis-Hillman adducts (Eq. 2).[43b]



4 **5** **Eq. 2**

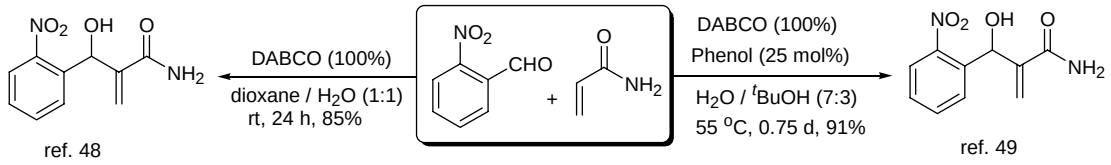
Namboothiri and coworkers[44-47] systematically studied the applications of conjugated nitroalkenes as useful activated alkenes in the Baylis-Hillman coupling with formaldehyde (formalin),[44] methyl vinyl ketone,[45] ethyl glyoxylate,[46] and diisopropyl azodicarboxylate[47] under the influence of imidazole (**6**) at room temperature. Representative examples are presented in Scheme 4.

Scheme 4



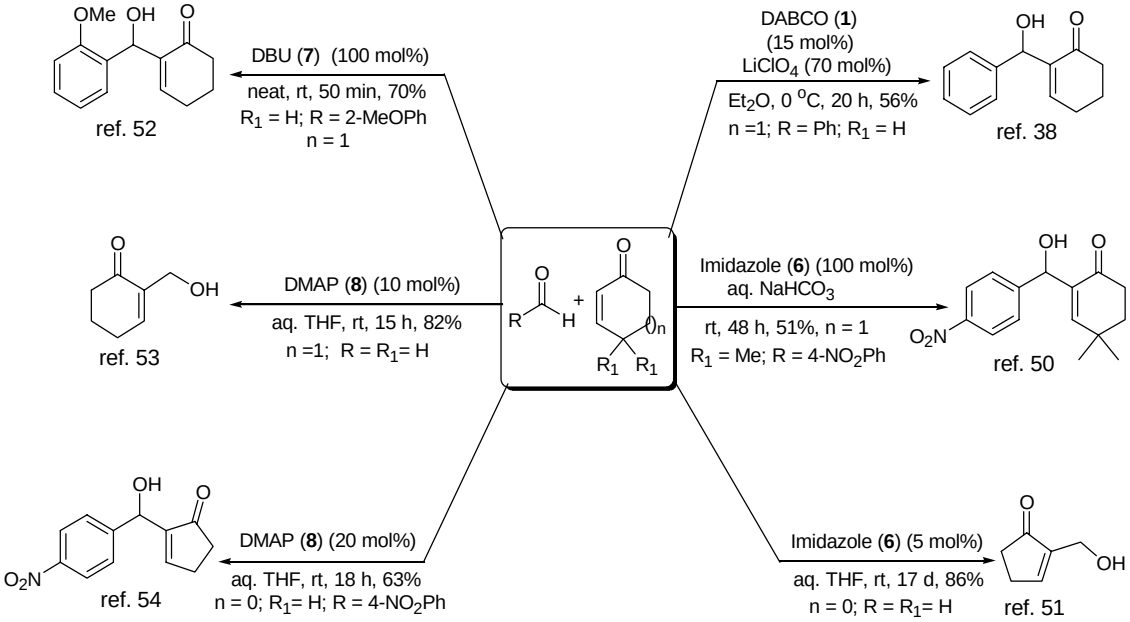
Hu and Connon independently reported[48,49] a facile coupling of acrylamide with aldehydes using DABCO (**1**) as a catalyst in the presence of protic solvent system. Representative examples are presented in Scheme 5.

Scheme 5



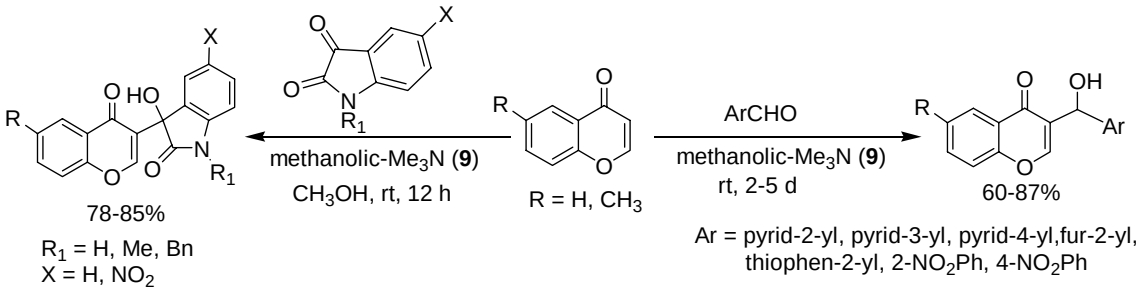
Cyclic activated alkenes: Cyclic enones (most commonly cyclopent-2-enone, cyclohex-2-enone and their derivatives)[6] are another interesting class of activated alkenes that are successfully employed for coupling with various aldehydes in the presence of variety of *tert*-amine catalysts, such as, DABCO (**1**),[38] imidazole (**6**),[50,51] DBU (**7**)[52] and DMAP (**8**)[53,54] to provide corresponding multifunctional molecules (Scheme 6).

Scheme 6



Our research group[55] for the first time, used 1-benzopyran-4(4*H*)-one derivatives, as activated alkenes in the Baylis-Hillman reaction with various electrophiles such as hetero-aromatic aldehydes, nitrobezaldehydes and isatin derivatives under the influence of methanolic-Me_3N (**9**) to provide the representative Baylis-Hillman adducts, as described in Scheme 7.

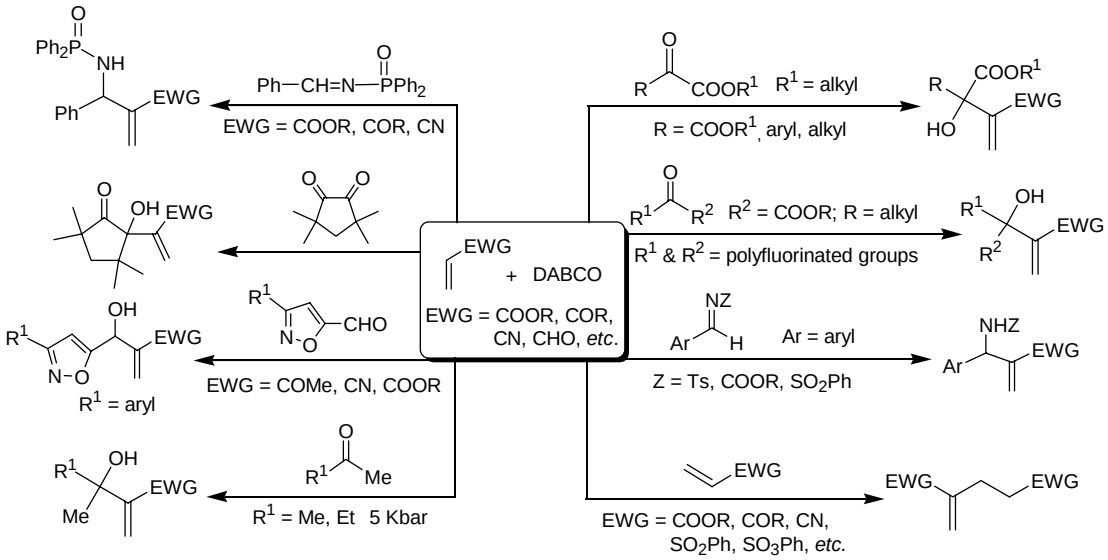
Scheme 7



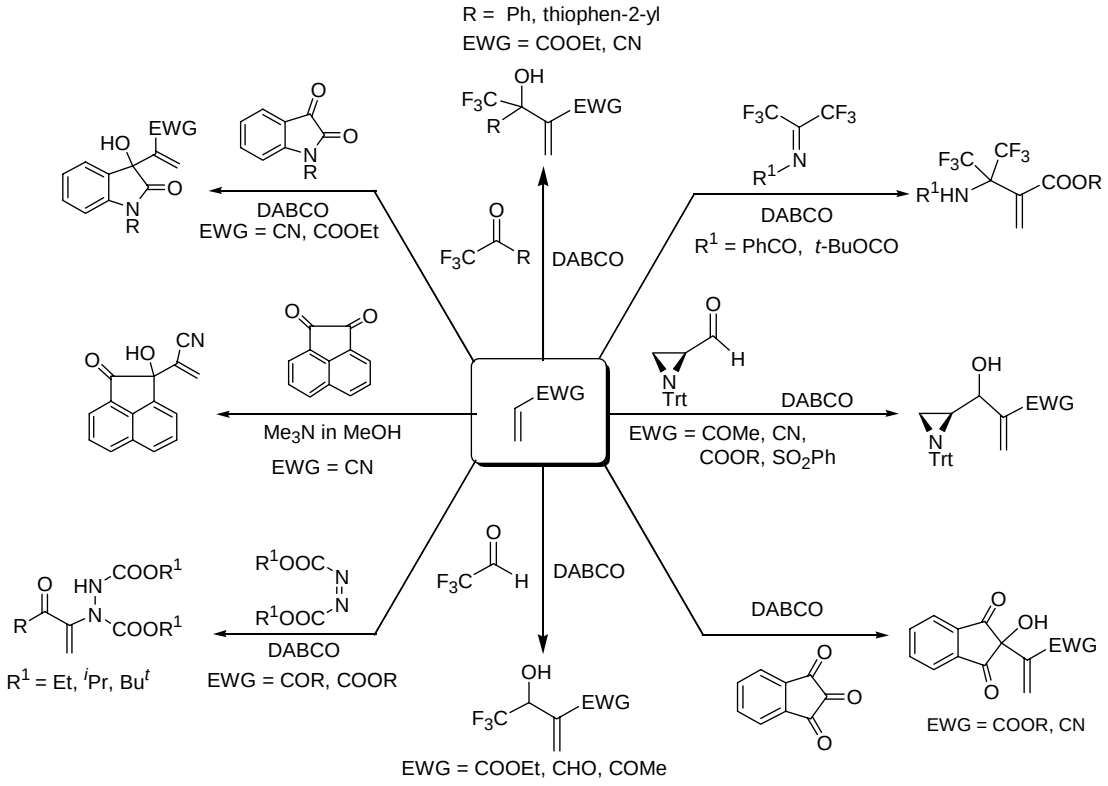
(2) ELECTROPHILES

Aldehydes (aliphatic, aromatic, and hetero-aromatic)[3-6] are the primary source of electrophiles, to produce densely functionalized Baylis-Hillman adducts. In addition, other electrophiles such as α-keto esters,[56-58] fluoro ketones,[59] aldimine derivatives,[60-63] activated alkenes,[64-67] *N*-benzylidenediphenylphosphinamide,[68] non-enolizable 1,2-diketones[37] and isoxazole-5-carboxaldehydes[69] have also been successfully employed in this reaction (Scheme 8). However, simple ketones (acetone & 2-butanone)[36] which are usually less reactive require high pressure conditions for coupling with activated alkenes (Scheme 8). Recently, fluoro imines,[70] fluorinated aldehydes & ketones,[71,72] isatin derivatives,[73,74] ninhydrin,[74] *N*-trityl-aziridine-2-(*S*)-carboxaldehyde,[75] acenaptho-quinone,[76] and azodicarboxylates[77,78] have been successfully employed as electrophiles in the Baylis-Hillman reaction (Scheme 9).

Scheme 8

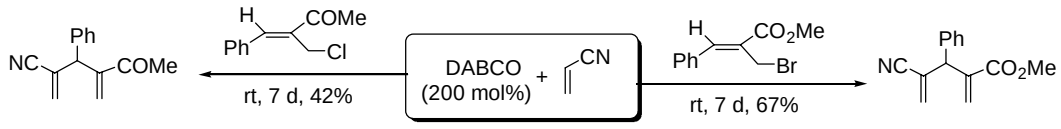


Scheme 9

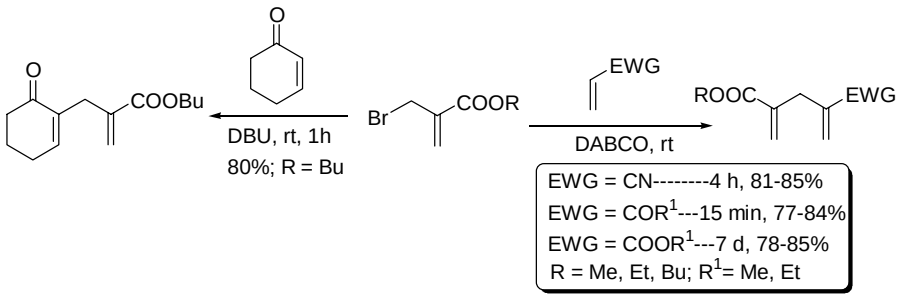


Our research group[79,80] demonstrated, for the first time, the application of allyl halides as electrophiles in the Baylis-Hillman reaction. Thus, the reaction of allyl bromides / allyl chlorides, derived from the corresponding Baylis-Hillman adducts (obtained, from the activated alkenes, methyl acrylate and methyl vinyl ketone) with acrylonitrile in the presence of DABCO resulted in the formation of 3-substituted functionalized 1,4-pentadienes (Scheme 10).[79] Subsequently, our research group has extended same strategy to allyl bromides derived from alkyl 3-hydroxy-2-methylenepropanoates, thus developing a simple methodology for one-pot synthesis of 2,4-functionalized 1,4-pentadienes (Scheme 11).[80]

Scheme 10



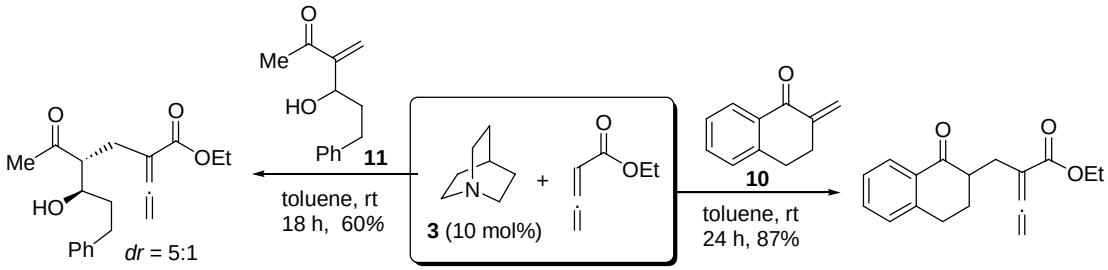
Scheme 11



Recently Miller and coworkers[81] reported an efficient quinuclidine (**3**) catalyzed coupling of allenic esters with α, β-unsaturated carbonyl compounds [α-methylene tetralone (**10**)] as electrophiles to provide the corresponding Baylis-Hillman adducts. Quinuclidine (**3**) also comfortably mediates the coupling of ethyl allenoate with the

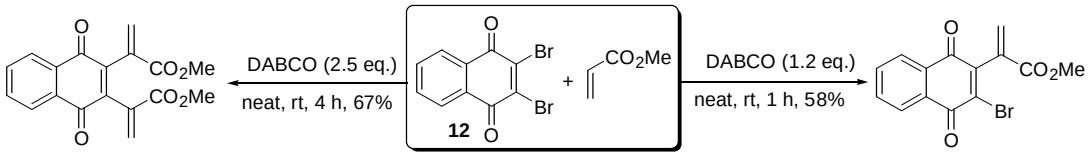
Baylis-Hillman alcohol (**11**) as an electrophile. Representative examples are presented in Scheme 12.

Scheme 12



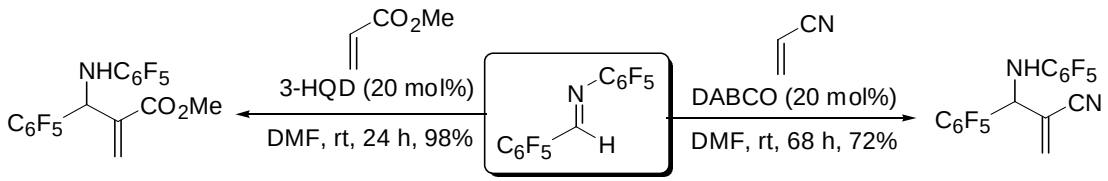
A facile coupling of 2,3-dibromo-1,4-naphthoquinone (**12**) with activated alkenes to provide the corresponding mono- / di-substituted products was reported by Lee and coworkers.[82] Representative examples are presented in Scheme 13.

Scheme 13



Zhu and coworkers[83] reported aza-Baylis-Hillman reactions of polyfluoroaldimines with methyl acrylate and acrylonitrile in the presence of various tertiary amine catalysts. Representative examples are presented in Scheme 14.

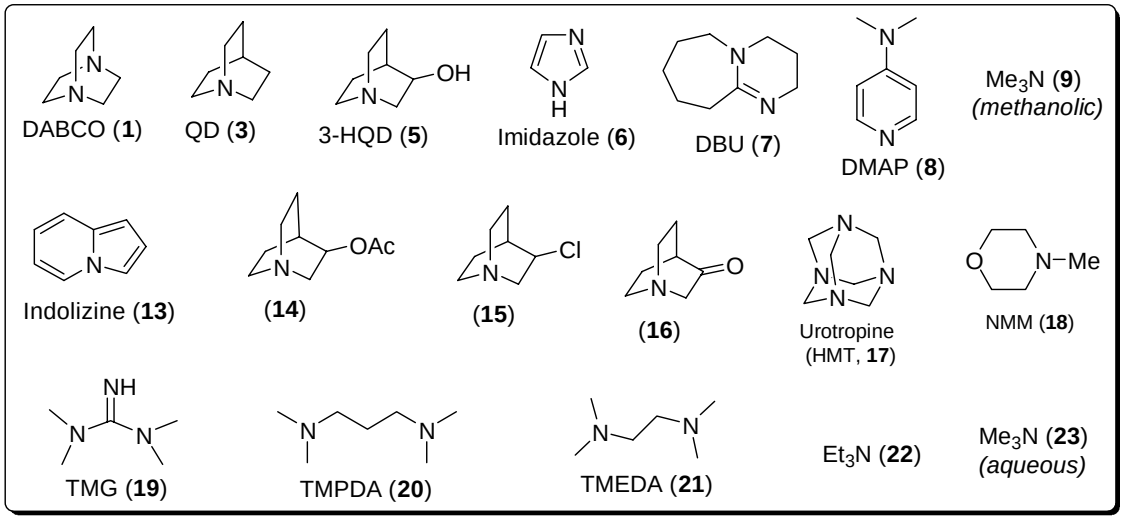
Scheme 14



(3) TERTIARY AMINE CATALYSTS

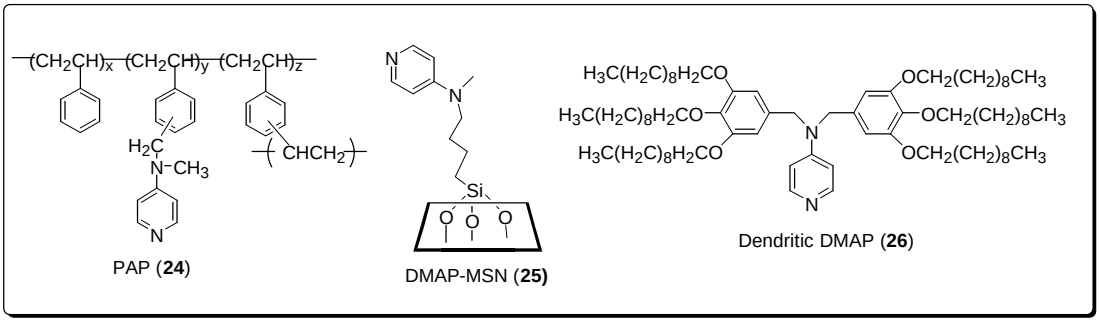
Although a variety of tertiary amine catalysts, such as, DABCO (**1**),[1,42,.84] quinuclidine (**3**),[1,42] 3-hydroxyquinuclidine (**5**),[42,84] imidazole (**6**),[50,51,85] DBU (**7**),[52] DMAP (**8**),[53,54] methanolic-Me_3N (**9**),[55,76,86] indolizine (**13**),[1] 3-acetoxyquinuclidine (**14**),[42,84] 3-chloro-quinuclidine (**15**),[42] 3-quinuclidinone (**16**),[42] HMT (**17**),[87,88] NMM (**18**),[88] TMG (**19**),[89,90] TMPDA (**20**),[91] TMEDA (**21**),[92] Et_3N (**22**)[36] and aqueous-Me_3N (**23**)[93] (Figure 1) have been successfully employed in various and specific Baylis-Hillman reactions, DABCO (**1**) has been the most frequently used common catalyst for the Baylis-Hillman reaction.

Figure 1

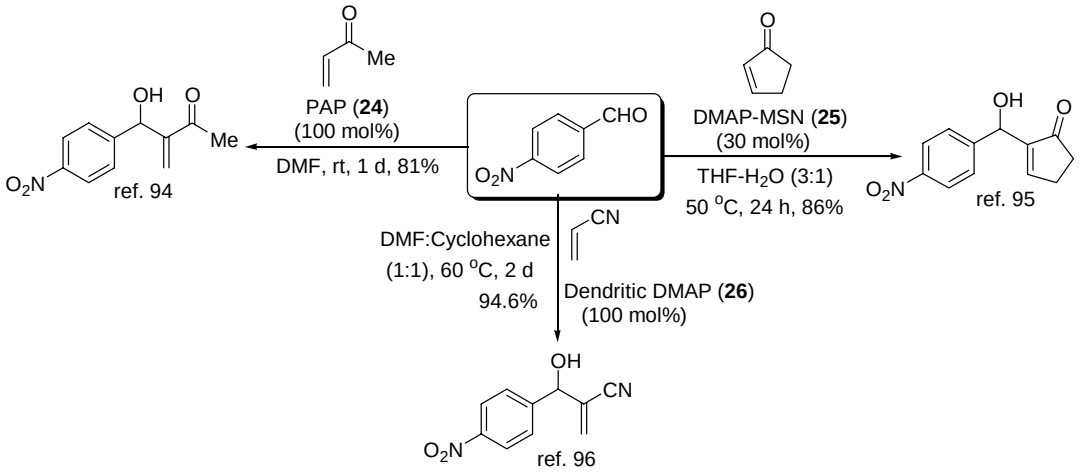


Recently, various polymer supported DMAP derivatives, such as, PAP [polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine (**24)**],[94] DMAP-MSN [meso-porous silica nano-sphere (**25**)],[95] and dendritic DMAP {*N*,*N*-di[3', 4', 5'-tri(1-decyloxy)benzyl]-4-amino-pyridine (**26)**}[96] (Figure 2) have been successfully employed as catalysts for the Baylis-Hillman reaction of various activated alkenes with electrophiles (Scheme 15).

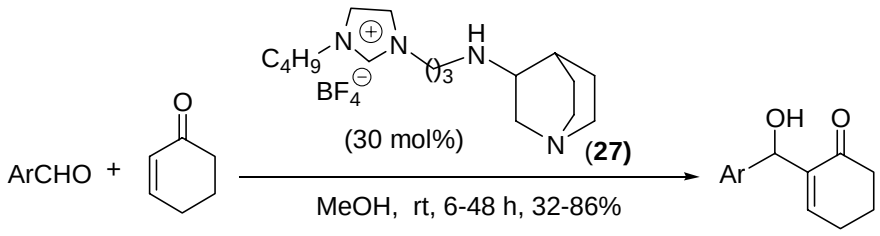
Figure 2



Scheme 15



Very recently, Cheng and coworkers[97] reported an interesting application of quinuclidine containing the ionic liquid component (**27**), as a catalyst for facile coupling of various activated alkenes (acyclic and cyclic enones) with electrophiles (Eq. 3).



Eq. 3

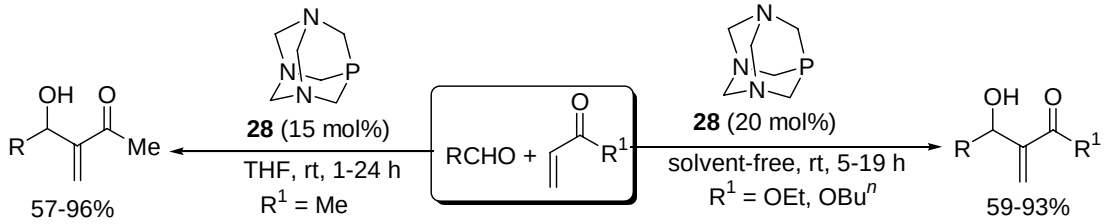
Ar = C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 3,4-$(OCH_2O)C_6H_3$

NON-AMINE CATALYSTS (CATALYTIC SYSTEMS) / REAGENTS MEDIATED BAYLIS-HILLMAN REACTIONS

Various non-amine catalysts / catalytic system, such as, trialkyl phosphines,[98-100] triaryl phosphines,[101] and metal complexes like $RhH(PPh_3)_4$,[102,103] $RuH_2(PPh_3)_4$,[103,104] have been found to promote coupling of activated alkenes with aldehydes to provide the coupling adducts. In addition, $R_2S–TiCl_4$,[6,105-108] $TiCl_4$-R_4NX (X = halide),[6,109,110] $TiCl_4$-R_3N,[111] $TiCl_4$,[112,113] $R_2X–BF_3$ (X = O, S),[114-116] and Et_2AlI[117,118] were also successfully employed as catalysts / catalytic systems in Baylis-Hillman (type) coupling reactions.

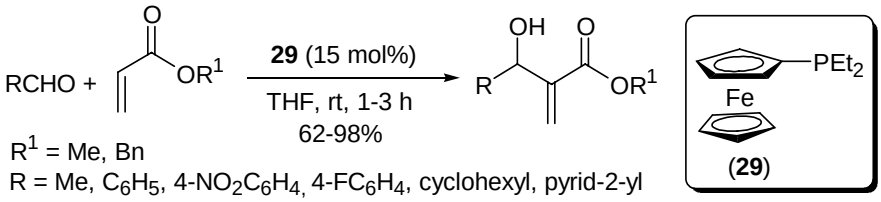
He and coworkers[119] demonstrated that 1,3,5-triaza-7-phosphaadamantane (**28,** PTA), an air-stable nucleophilic trialkylphosphine, comfortably catalyzes the Baylis-Hillman coupling of various aldehydes with activated alkenes (Scheme 16).

Scheme 16



R = H, C_2H_5, C_6H_5, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 3-FC_6H_4, 2-Cl-4-FC_6H_3, pyrid-2-yl

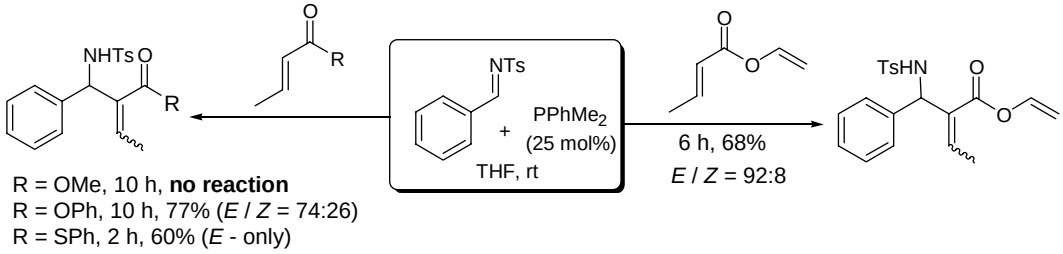
An air-stable ferrocenediethylphosphine (**29**) has been successfully used as an effective catalyst for the Baylis-Hillman reaction between various aldehydes and acrylates to afford the corresponding adducts in high yields, by Carretero and coworkers[120] as described in Eq. 4.



Eq. 4

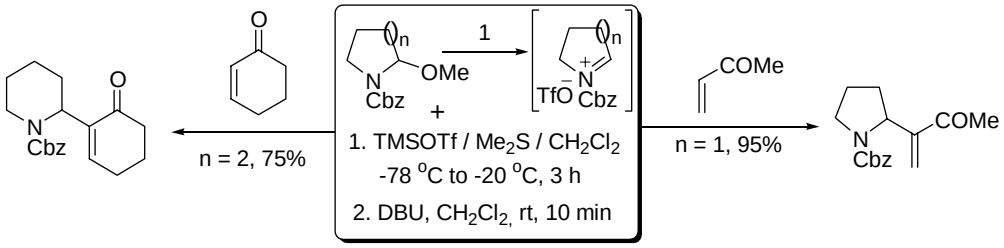
Shi *et.al.,* reported aza-Baylis-Hillman reaction of β-substituted α, β-unsaturated esters with *N*-tosylated imines in the presence of phosphine ($PPhMe_2$) catalyst to provide the corresponding Baylis-Hillman adducts in moderate to good yields (Scheme 17).[121]

Scheme 17



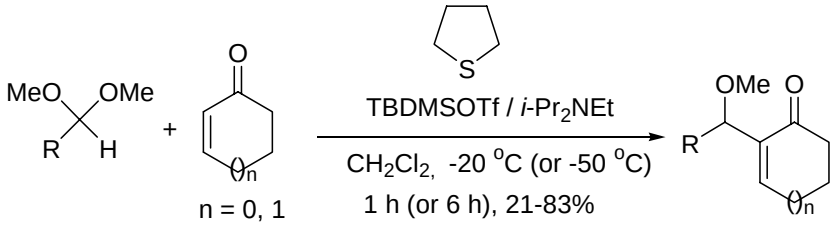
Very recently Aggarwal and coworkers[122] reported an interesting Baylis-Hillman reaction between activated alkenes and *in situ* generated iminium ions as electrophiles to produce the corresponding adducts according to reaction sequence presented in Scheme 18.

Scheme 18



Recently, Metzner and coworkers[123] have successfully used dimethyl acetals as electrophiles in the Baylis-Hillman coupling with cyclic enones under the influence of

tetrahydrothiophene and TBDMSOTf in the presence of *i*-Pr_2NEt (Hunig's base) as described in Eq. 5.

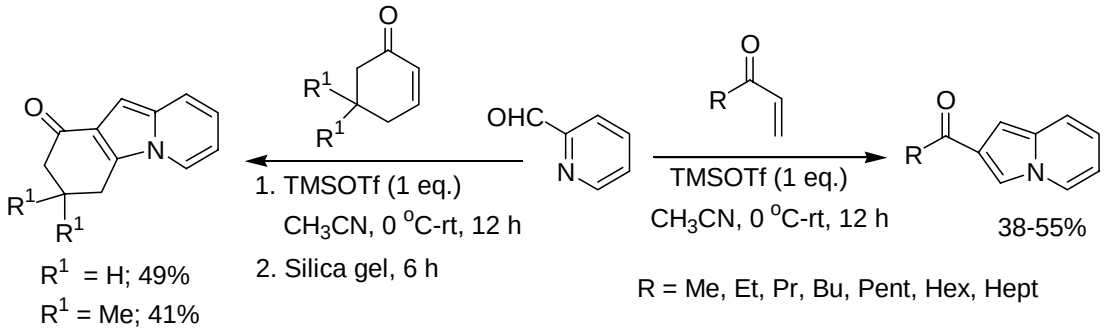


Eq. 5

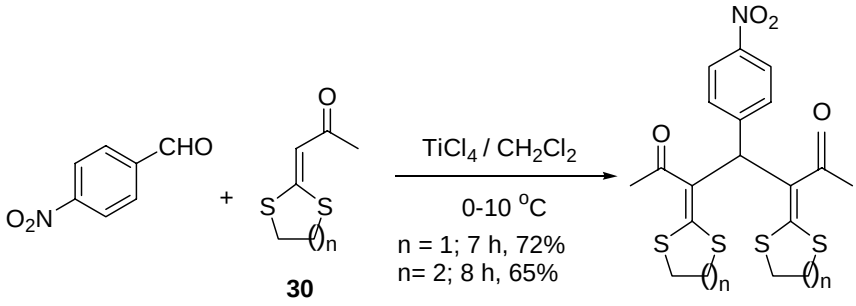
R = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, $C_6H_5CH{=}CH$, $C_6H_5CH_2CH_2$

Our research group described an electrophile induced intramolecular 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 19).[124]

Scheme 19



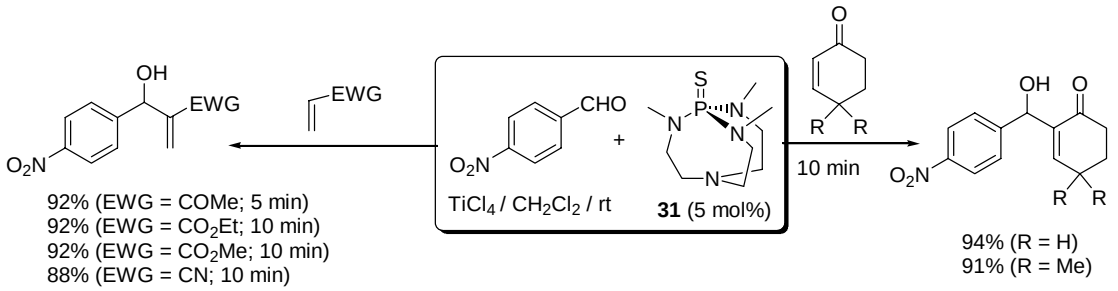
An interesting $TiCl_4$-mediated Baylis-Hillman type reaction of α–oxoketene dithioacetals (**30**) with various aldehydes leading to the formation of polyfunctionalized 1,4-pentadienes *via* C-C bond formation at the α-position of α–oxoketene dithioacetals has been described by Yin and coworkers.[125] Representative examples are presented in Eq. 6.



Eq. 6

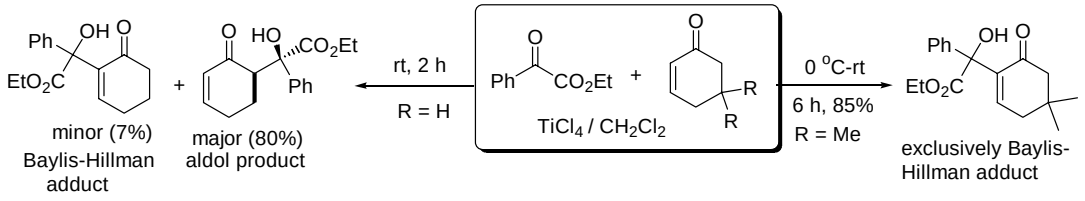
Verkade and coworkers[126] reported an interesting protocol for the Baylis-Hillman coupling reaction between various acyclic / cyclic activated alkenes and variety of aldehydes at faster reaction rate using the aza-phosphine catalyst (**31**) to provide corresponding adducts in excellent yields. Representative examples are presented in Scheme 20.

Scheme 20

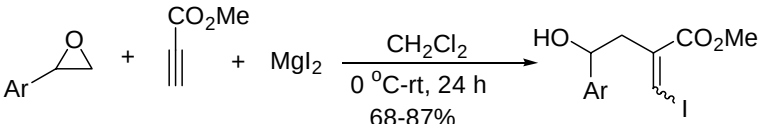


Our research group[127] has developed steric factors directed Baylis-Hillman and aldol reactions in $TiCl_4$ mediated coupling between α-keto esters with cyclohex-2-enone derivatives. Thus, 5,5-dimethylcyclohex-2-enone provides the corresponding Baylis-Hillman adducts exclusively in reaction with α-keto esters under the influence of $TiCl_4$, whereas a similar reaction of α-keto esters with cyclohex-2-enone furnishes the corresponding aldol adducts with high *syn*-diastereoselectivity as the major product along with the Baylis-Hillman adduct as the minor product. Representative examples are described in Scheme 21.

Scheme 21



Li and coworkers,[128] for the first time, demonstrated the application of oxirane as an electrophile for coupling with methyl propiolate in the presence of MgI_2 to provide densely functionalized homoallylic alcohols (Eq. 7).

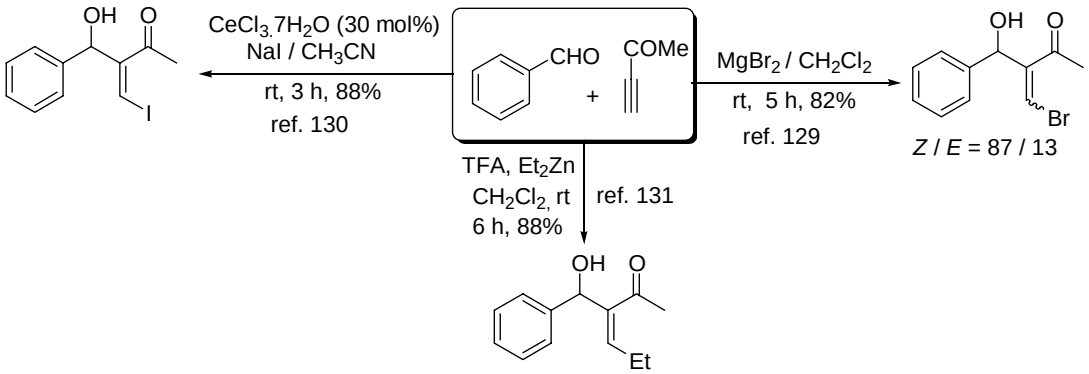


Eq. 7

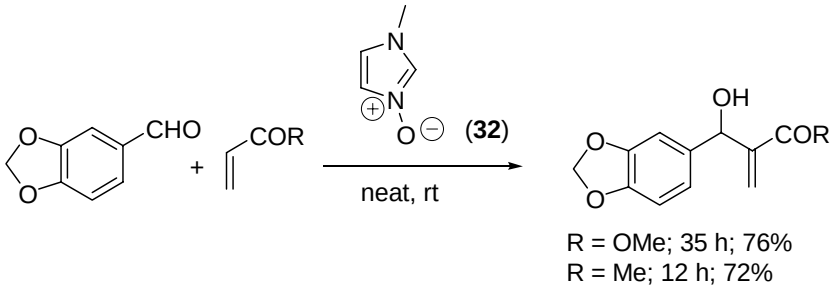
Ar = C_6H_5, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, thiophen-2-yl

Recently various research groups[129-131] developed independently simple methods for synthesis of β-substituted Baylis-Hillman adducts *via* one-pot three-component reaction protocol involving the treatment of α, β-acetylenic ketones (*in situ* generation of allenoates) with various aldehydes in the presence of various catalysts / reagents to provide allyl alcohols (Scheme 22).

Scheme 22



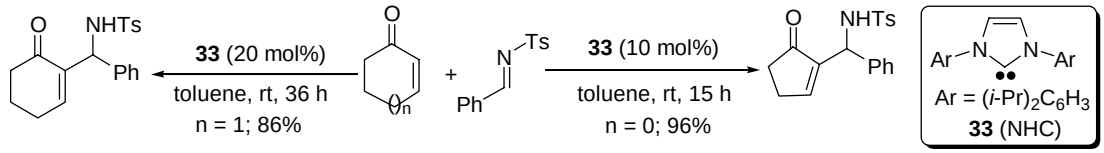
1-Methylimidazole 3*N*-oxide (**32**) catalyzed Baylis-Hillman coupling of various aldehydes with methyl acrylate / methyl vinyl ketone to provide corresponding adducts in good yields was reported by Tsai and coworkers (Eq. 8).[132]



Eq. 8

Very recently, Ye and coworkers[133] reported an interesting, *N*-heterocyclic carbene (NHC, **33**) catalyzed aza-Baylis-Hillman coupling of cyclic enones with a variety of *N*-tosylimines to provide the corresponding adducts in high yields. Representative examples are presented in Scheme 23.

Scheme 23



ASYMMETRIC BAYLIS-HILLMAN REACTION

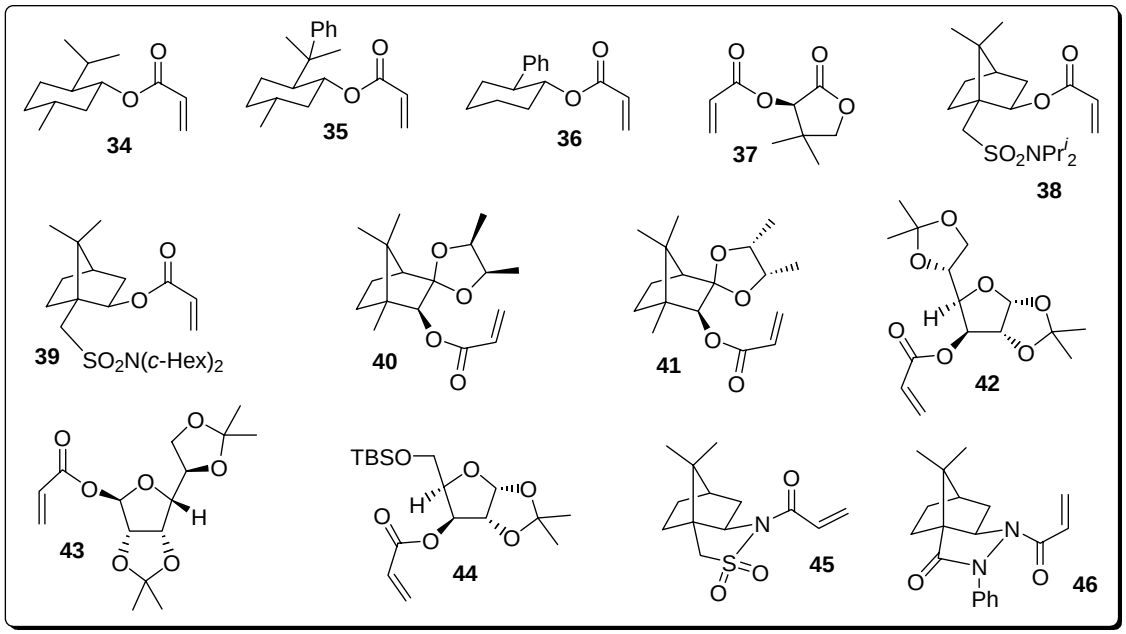
In general, the asymmetric version of the Baylis-Hillman reaction can be performed in four different ways by selecting appropriate chiral sources, *i.e.,* (1) using the enantiopure (chiral) activated alkene system, (2) using the enantiopure (chiral) electrophile component, (3) using a chiral catalyst, and also (4) using chiral catalytic sources such as solvent or any other chiral medium / additives. In fact, efforts were

made in all these directions and reasonable success was accomplished in certain aspects.

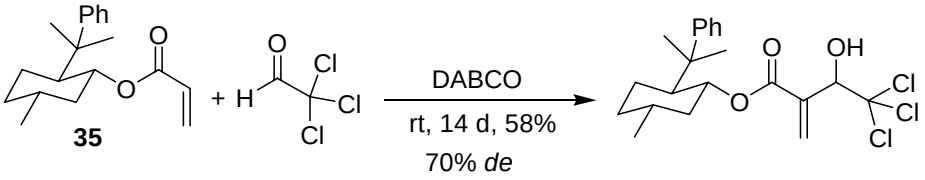
(1) ENANTIOPURE (CHIRAL) ACTIVATED ALKENES

A number of chiral acrylates (**34-44**)[3-6,134-142] and chiral acrylamides (**45**[143,144] & **46**[145]) derived from various chiral auxiliaries [cyclohexanol derivatives (**34-36**), (*R*)-(+)-pentolactone (**37**), camphor (**38-41, 45 & 46**) and sugar derivatives (**42-44**)] 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).

Figure 3

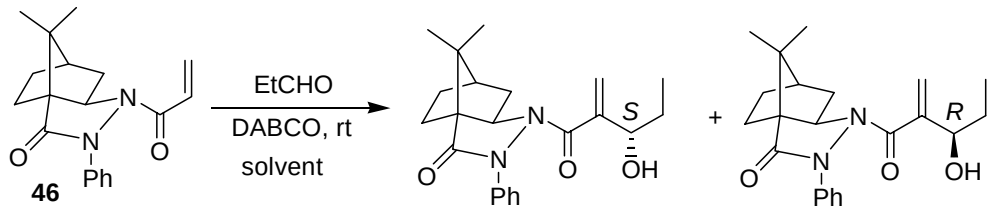


Drewes and coworkers[139] have successfully employed (-)-8-phenylmenthyl acrylate (**35**) as a chiral activated alkene for Baylis-Hillman coupling with various aldehydes. The best result with the diastereoselectivity of 70% was achieved in the case of trichloroacetaldehyde (Eq. 9).



Eq. 9

Yang and Chen have reported a highly diastereoselective Baylis-Hillman reaction of aldehydes with enantiopure acryloylhydrazide (**46**) as chiral activated alkene. They have observed reversal of diastereoselectivity by changing the solvent from DMSO to THF/H_2O in this reaction. One representative example is presented in the Eq. 10.[145]



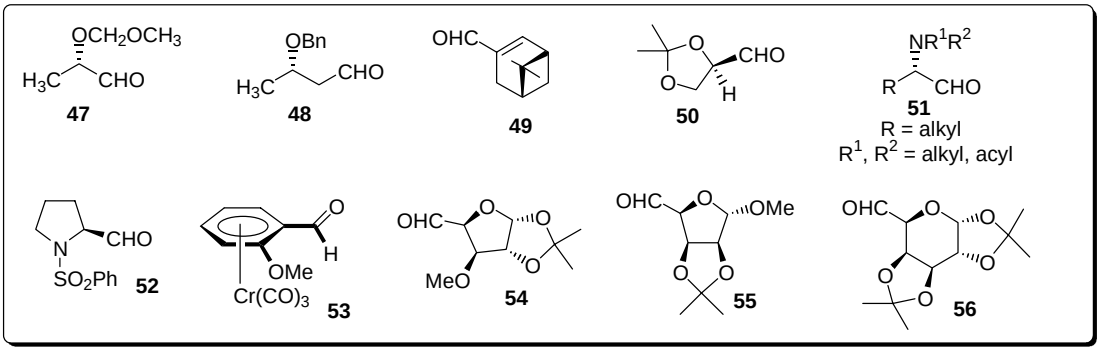
99 : 1 (DMSO, 4 d, 85%)
1 : 99 (THF/H_2O, 3 d, 85%)

Eq. 10

(2) ENANTIOPURE (CHIRAL) ELECTROPHILES

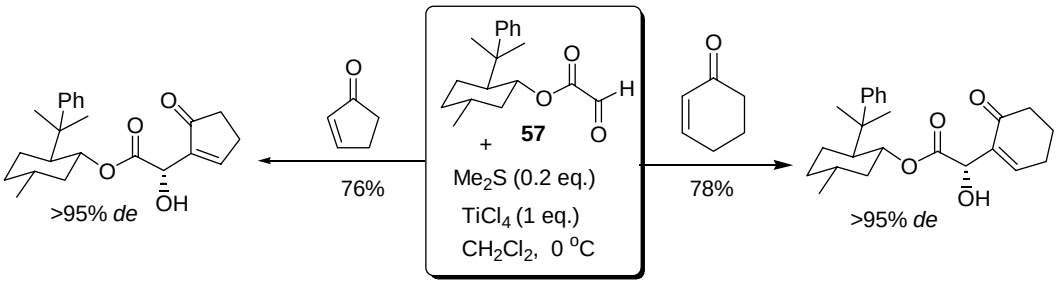
Several efforts have been made towards the asymmetric Baylis-Hillman reaction using enantiopure electrophiles. Thus, various chiral electrophiles such as (*S*)-*O*-(methoxymethyl)lactaldehyde (**47**),[146] (*S*)-3-benzyloxybutyraldehyde (**48**),[147] (*R*)-myrtenal (**49**),[137] isopropylidene (*R*)-glyceraldehyde (**50**),[137] α-dialkylamino and α-(*N*-acylamino)aldehydes (**51**),[148,149] *N*-phenylsulfonyl-(*L*)-prolinal (**52**),[149] enantiopure *o*-substituted benzaldehyde tricarbonyl-chromium complex (**53**)[150,151] and sugar derived aldehydes (**54**-**56**),[152,153] *etc.* (Figure 4), have been employed for coupling with various activated alkenes to afford the resulting adducts with poor to high diastereoselectivities.

Figure 4



Bauer and Tarasiuk have reported an interesting Baylis–Hillman coupling of enantiopure aldehyde, that is, (–)-8-phenylmenthyl glyoxylate (**57**) with cyclic enones (cyclohex-2-enone and cyclopent-2-enone) under the catalytic influence of dimethyl sulfide in the presence of stoichiometric amounts of titanium tetrachloride to provide the desired adducts in high diastereoselectivities (Scheme 24).[154]

Scheme 24



(3) CHIRAL CATALYSTS

Considerable attention has been paid towards developing asymmetric version of Baylis-Hillman reaction using various chiral catalysts.[3-6] Thus, chiral DABCO (**58**),[155,156] (*S*)-enantiopure pyrrolizidine (**59**),[157] chiral bicyclic azetidine (**60**),[158] proline derivatives (**61-63**),[159-161] and quinidine & its derivatives (**64-68**),[162-165] have been examined as chiral catalysts in this reaction to provide the resulting adducts in moderate to good

enantioselectivities (Figure 5). Very recently, a variety of bifunctional catalysts, derived from BINOL (**69-74**),[166-171] have been successfully employed in the Baylis-Hillman reaction to achieve high enantioselectivity (Figure 6).

Figure 5

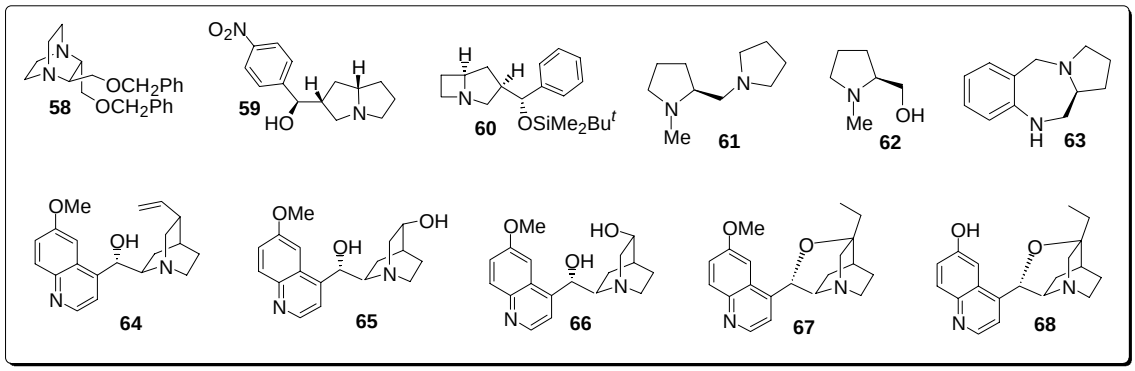
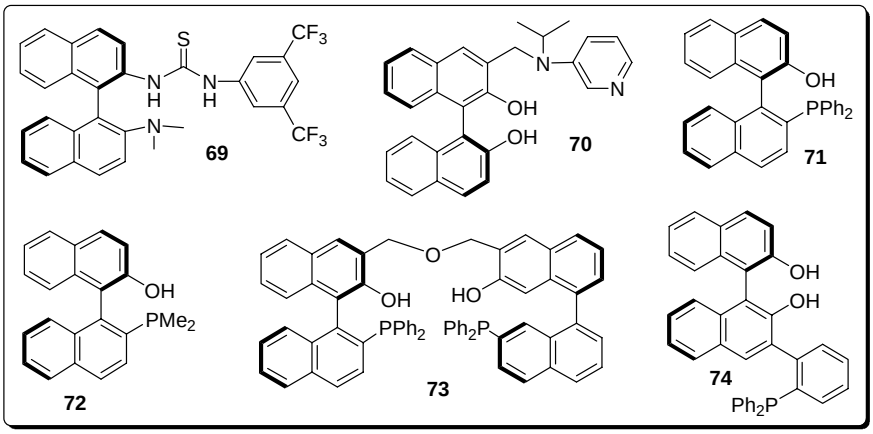
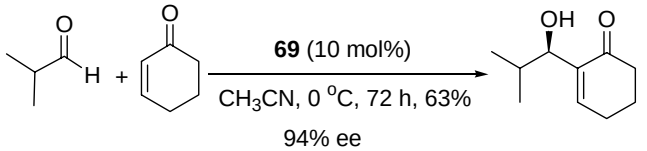


Figure 6



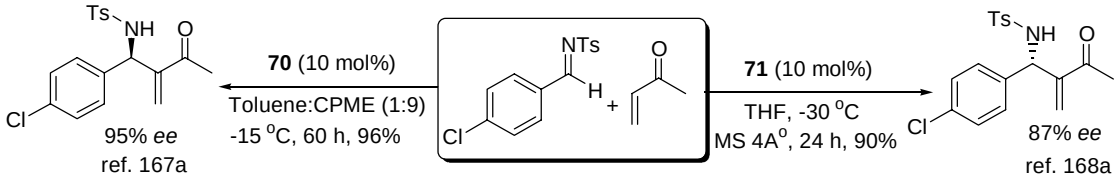
Wang and coworkers,[166] reported a bifunctional binapthyl-derived amine thiourea organocatalyst **69** promoted enantioselective Baylis-Hillman reaction of cyclohex-2-enone with various aldehydes to afford the resulting adducts in good yields with high enantioselectivites. One representative example is described in Eq. 11.



Eq. 11

Sasai and Shi research groups, independently developed, an efficient and novel BINOL based bifunctional organocatalysts **70**[167a] & **71**[168a] respectively for high enantioselective Baylis-Hillman reaction of various *N*-tosylimines with MVK (Scheme 25).

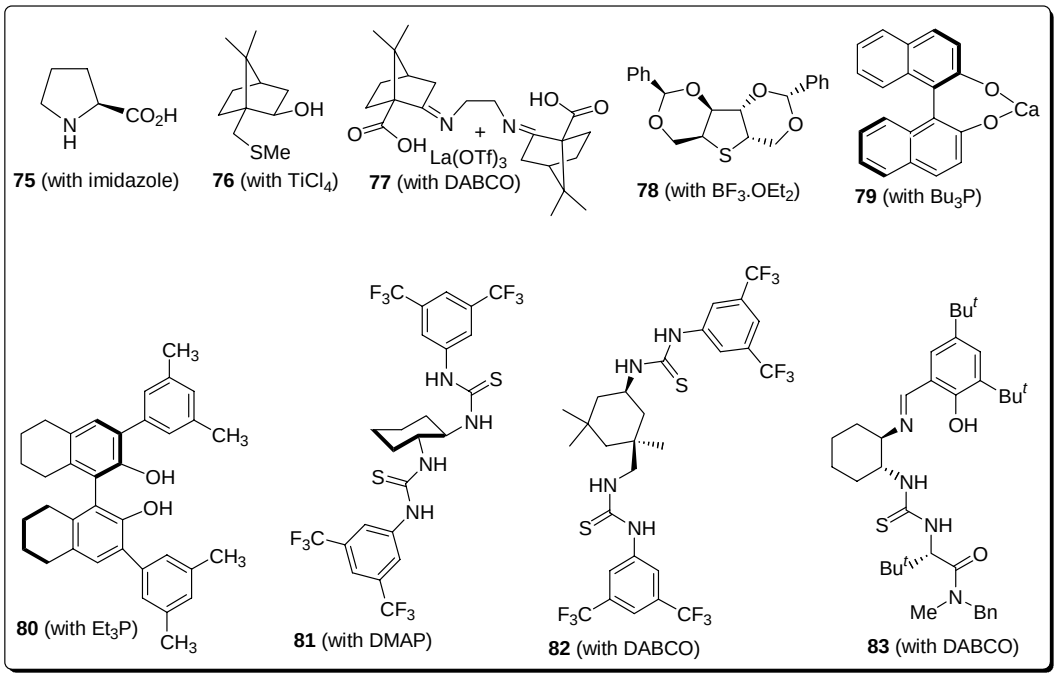
Scheme 25



(4) CHIRAL CATALYTIC SOURCES / ADDITIVES

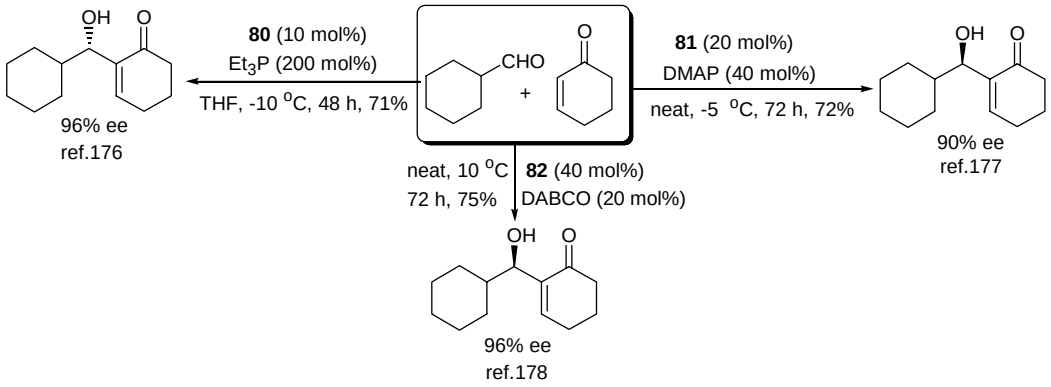
Recently, several enantiopure catalytic sources / additives, such as, *L*-proline (**75**),[85] 10-methylthioisoborneol (**76**),[172] camphor derivative (**77**),[173] enantiopure sulfide (**78**),[116] calcium salt of (*R*)-BINOL (**79**),[174] (*R*)-BINOL derivative (**80**),[175,176] and also many other thiourea derivatives (**81**-**83**)[177-179] were used as chiral additives (along with the catalysts) to perform asymmetric Baylis-Hillman reaction (Figure 7).

Figure 7



McDougal and Schaus[175,176] developed a highly enantioselective Baylis-Hillman reaction involving the coupling of cyclohex-2-enone with a variety of aldehydes mediated by excess Et_3P in the presence of BINOL-derived chiral co-catalyst (**80**) (Scheme 26).[176] Later on, Nagasawa[177] and Berkessel[178] research groups, independently designed and synthesized, cyclohexane based thiourea derivatives **81** & **82** respectively and successfully employed them as efficient co-catalysts for Baylis-Hillman reaction of various aldehydes with cyclohex-2-enone to afford the corresponding allyl alcohol with high enantioselectivities. Representative examples are given in Scheme 26.

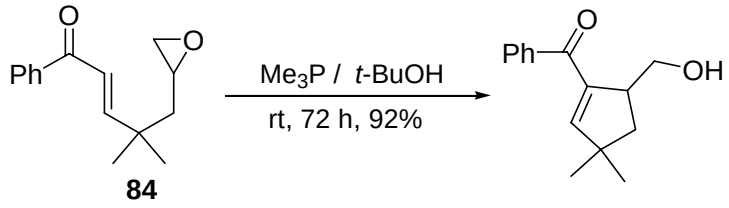
Scheme 26



INTRAMOLECULAR (RING CLOSING) BAYLIS-HILLMAN REACTION AND ITS ASYMMETRIC VERSION

Although the intramolecular Baylis-Hillman reaction did not grow earlier as expected, in recent years this aspect has, indeed, received much attention from the organic chemists. Some of the recent and interesting developments in this direction are presented in this section.[180-187]

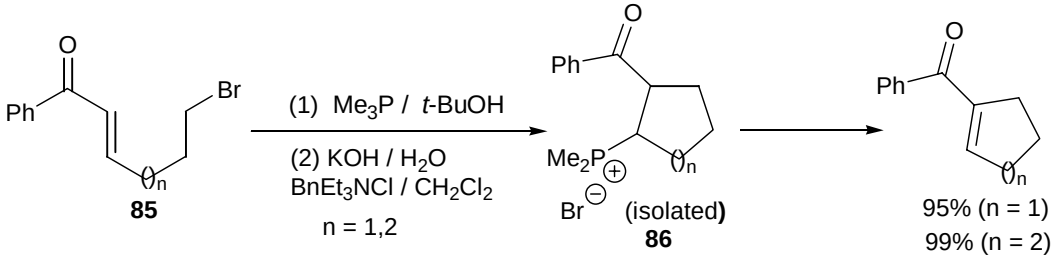
Kraft and Wright[180] described an interesting trialkyl phosphine mediated Baylis-Hillman ring closing reaction of enone-epoxide system (**84**) to provide cyclic adducts in good yields. One representative example is presented in Eq. 12.



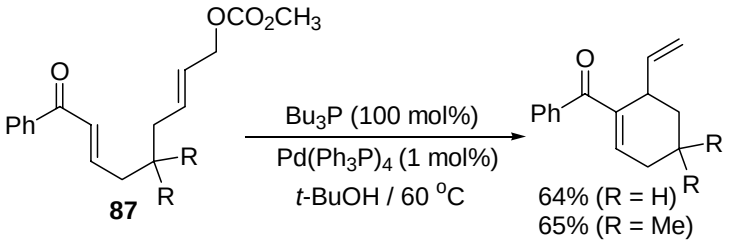
84 **Eq. 12**

Krafft and coworkers[181] described an organo-base mediated intramolecular Baylis-Hillman cyclization of enones (**85**) to provide the corresponding cyclic molecules (five and six-membered rings) in excellent yields. With a view to understand the mechanism they have also isolated and characterized ketophosphinium salt (**86**) which is the key intermediate (Scheme 27).[181a]

Scheme 27



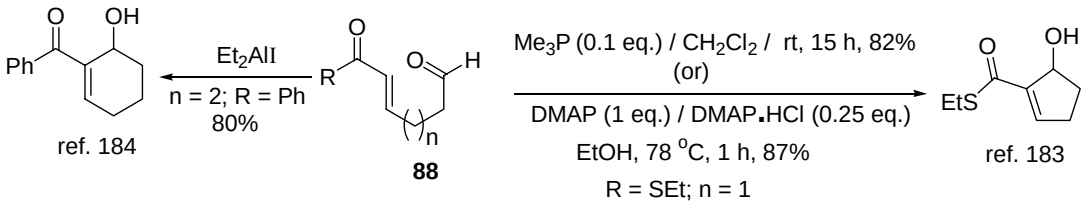
An interesting intramolecualr ring closing reaction of the enone-carbonates (**87**) under the influence of Bu_3P in the presence of catalytic amount of $Pd(Ph_3P)_4$ to provide a convenient method for synthesis of functionalized cycloalkenes was described by Krische and coworkers.[182] Representative examples are described in Eq. 13.



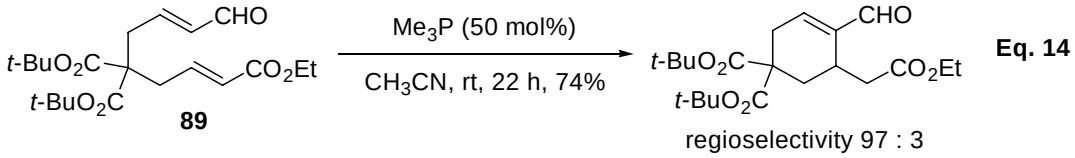
Eq. 13

Keck[183] and Oshima[184] reported independently an interesting intramolecular Baylis-Hillman reaction of substrates (**88**) having both the activated alkene moiety and electrophile component leading to the synthesis of cyclopentene (R = SEt; n = 1) and cyclohexene (R = Ph; n = 2) derivatives as described in Scheme 28.

Scheme 28

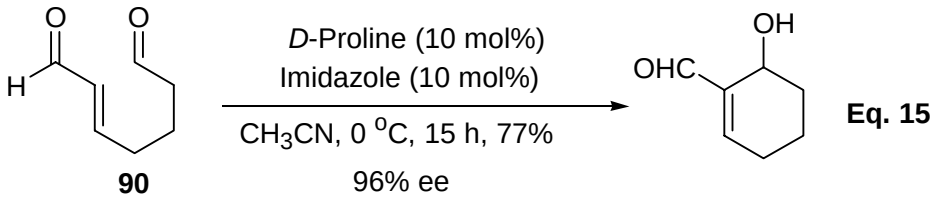


An intramolecular Baylis-Hillman ring closing reaction of diactivated alkenes (**89**) to provide a convenient method for synthesis of functionalized cycloalkene derivatives was described by Roush and coworkers.[185] One representative example is presented in Eq. 14.



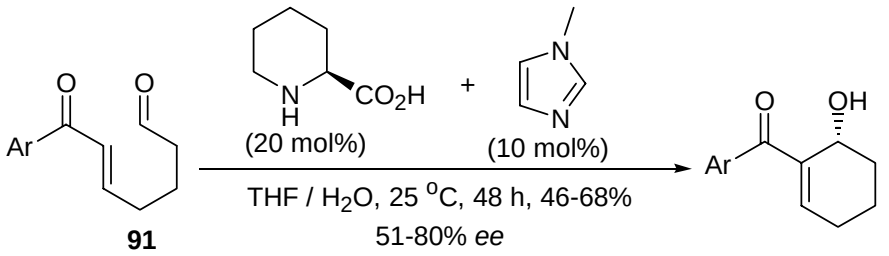
Eq. 14

For the first time, Hong and coworkers[186] reported, an efficient proline catalyzed enanatioselective intramolecular Baylis-Hillman reaction of enone-aldehyde system (**90**) under the influence of imidazole. One representative example is shown in Eq. 15.



Eq. 15

Subsequently, Miller and coworkers[187] demonstrated, the application of (*S*)-2-pipecolinic acid for promoting asymmetric intramolecular Baylis-Hillman reaction of enone-aldehyde system (**91**) in the presence of *N*-methylimidazole to provide the resulting adduct in good enantioselectivities (Eq. 16).



Eq. 16

Ar = Phenyl, 2-methylphenyl, 4-chlorophenyl, 4-bromophenyl, thiophen-2-yl

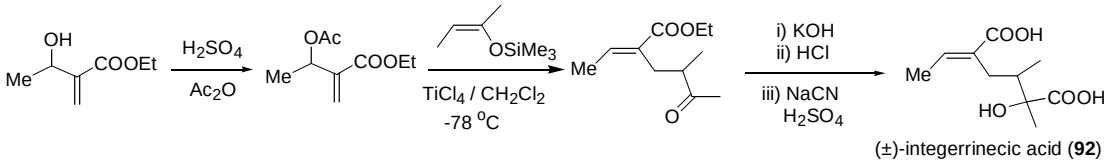
APPLICATIONS OF THE BAYLIS–HILLMAN ADDUCTS

The Baylis-Hillman adducts play an important role in organic synthesis as these adducts possess a minimum three functional groups (electron withdrawing group, olefin and hydroxyl or amino groups) in a very close proximity which, in fact, make them valuable substrates for various organic reactions like Friedel-Crafts reaction, Diels-Alder reaction, Heck reaction, Claisen & Arbuzov rearrangements, isomerization, hydrogenation, and photochemical reactions, *etc.*[3-6] These adducts have also been elegantly employed as valuable synthons in the stereodefined synthesis of various trisubstituted olefins and several important natural products, biologically active molecules and hetero / carbocycles.[3-6] Some of the important and recent developments in the application of these adducts are presented in this section so as to provide a glimpse of the importance of Baylis-Hillman adducts.

I. SYNTHESIS OF NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE MOLECULES FROM THE BAYLIS-HILLMAN ADDUCTS

Drewes *et.al.*[23] reported a facile synthesis of (±) integerrinecic acid (**92**) an interesting natural product starting from the Baylis-Hillman adduct, ethyl 3-hydroxy-2-methylene-butanoate following the reaction sequence as described in Scheme 29.

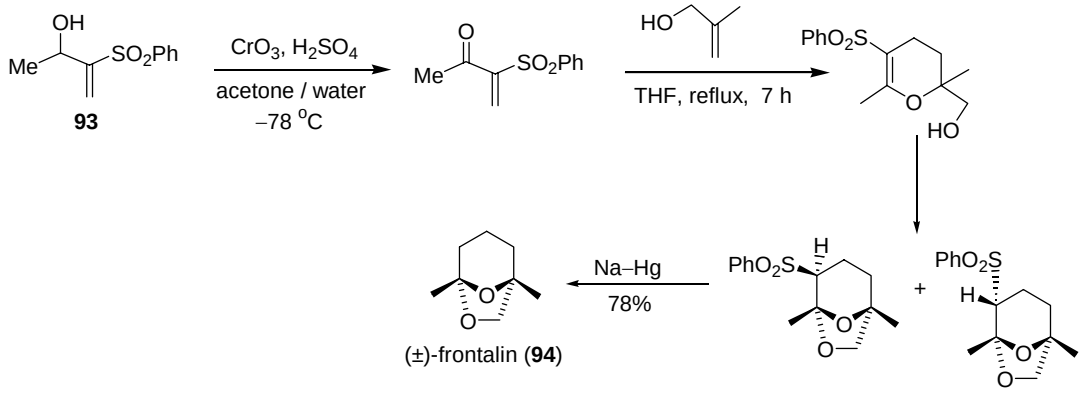
Scheme 29



(±)-integerrinecic acid (**92**)

Weichert and Hoffmann elegantly transformed 3-hydroxy-2-(phenylsulphonyl)but-1-ene (**93**) the Baylis-Hillman adduct, derived *via* the reaction of phenyl vinyl sulfone with acetaldehyde, into racemic frontalin (**94**), an interesting biologically active phermone, according to synthetic sequence as described in Scheme 30.[188]

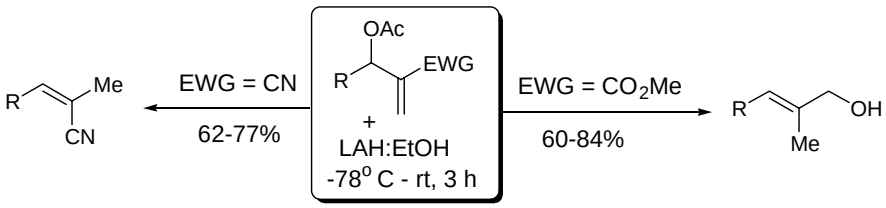
Scheme 30



Our research group 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

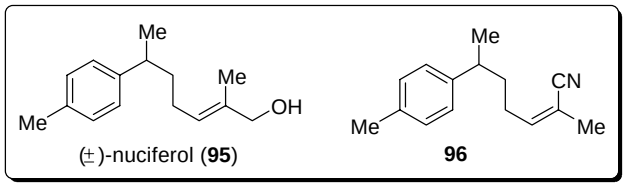
corresponding acetates of Baylis-Hillman adducts (obtained respectively from methyl acrylate and acrylonitrile) with LAH:EtOH (Scheme 31). Subsequently, this methodology has been successfully applied for the synthesis of (*E*)-nuciferol (**95**), a biologically active terpene and **96**, a precursor for (*Z*)-nuciferol (Figure 8).[189]

Scheme 31



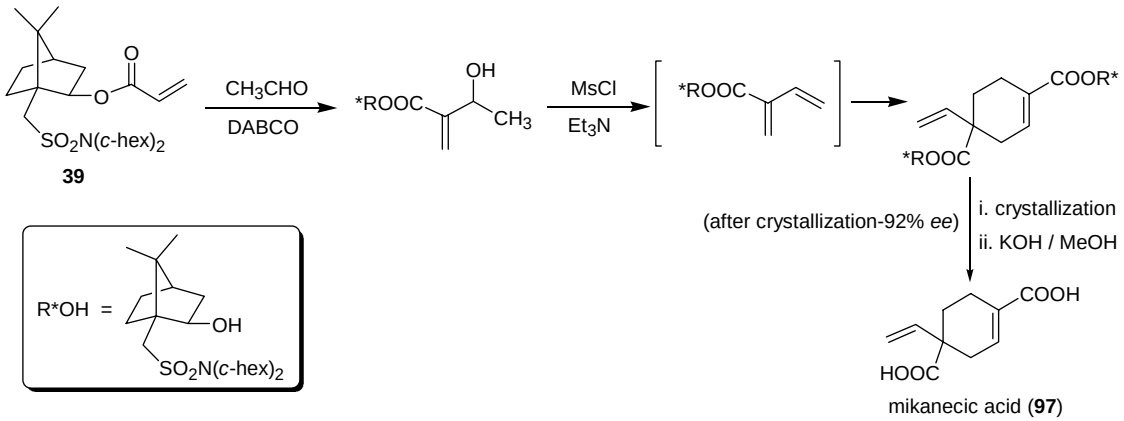
R = C_4H_9, C_5H_{11}, C_6H_{13}, C_6H_5, 4-MeC_6H_4, 3-(4-MeC_6H_4)Bu, 4-ClC_6H_4

Figure 8



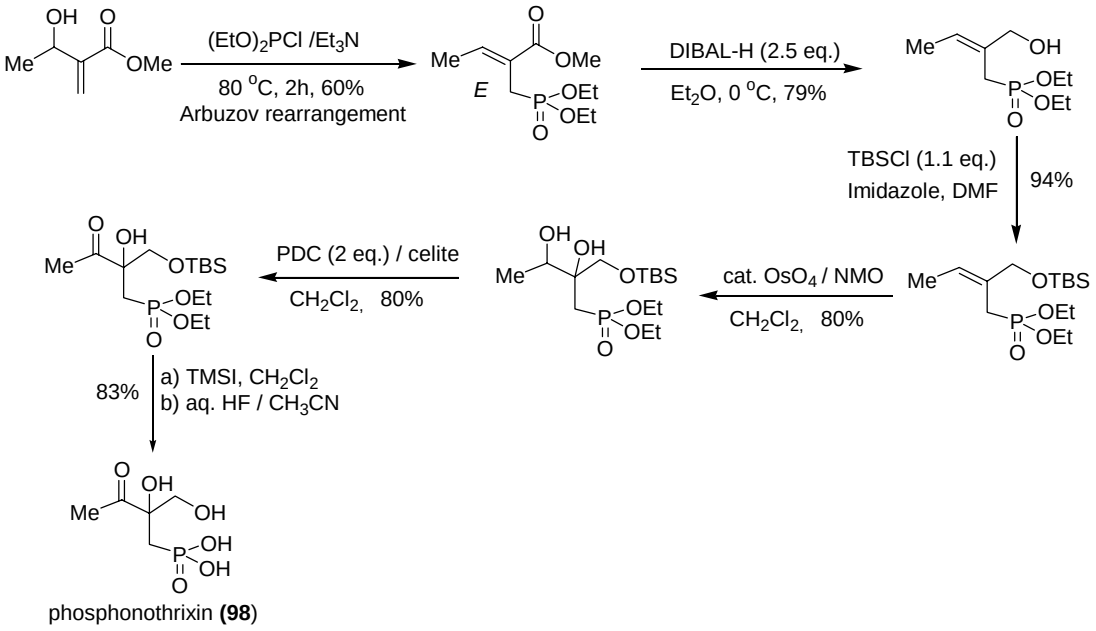
Our research group[190] has reported a simple enantioselective synthesis of mikanecic acid (**97**), a terpene dicarboxylic acid having a chiral quartering carbon centre from the Baylis-Hillman adduct derived from chiral acrylate (**39**) and acetaldehyde, following the reaction sequence as described in Scheme 32.

Scheme 32



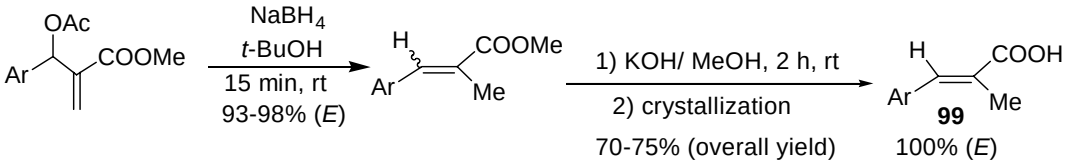
Very recently, Fields[191] reported a convenient synthesis of phosphonothrixin (**98**), an important natural product, starting from the Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate, following the reaction sequence as described in Scheme 33.

Scheme 33



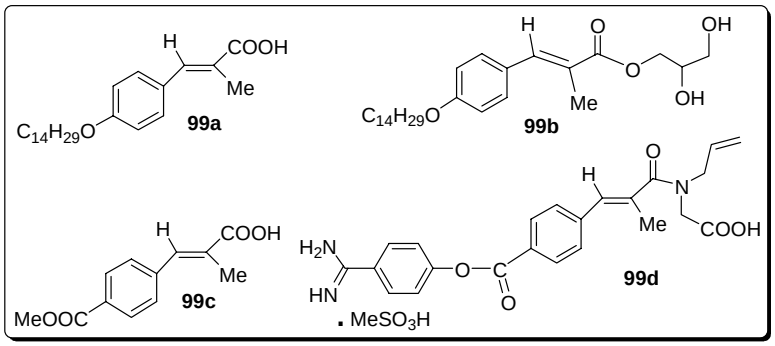
A simple and convenient synthesis of (*E*)-α-methylcinnamic acids (**99**) has been developed by our research group *via* the nucleophilic addition of hydride ion from $NaBH_4$ to the acetates of the Baylis–Hillman adducts, followed by hydrolysis and crystallization (Scheme 34).[192] This methodology has been successfully applied for the synthesis of (*E*)-*p*-(myristyloxy)-α-methylcinnamic acid (**99a**), a hypolipidemic active agent [which is also a precursor for another active hypolipidemic agent LK-903 (**99b**)] and [*E*]-*p*-(carbomethoxy)-α-methylcinnamic acid (**99c**) which is valuable synthon for orally active serine protease inhibitor (**99d**) (Figure 9).[192]

Scheme 34



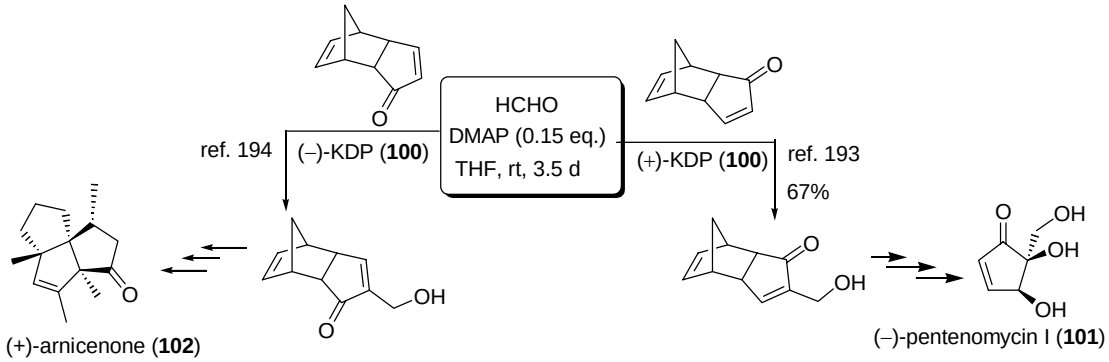
Ar= Ph, 4-ClPh, 4-(*i*-Pr)Ph, 4-MePh, 2,4-$(Cl)_2$Ph, naphth-1-yl, 4-(tetradecyloxy)Ph

Figure 9



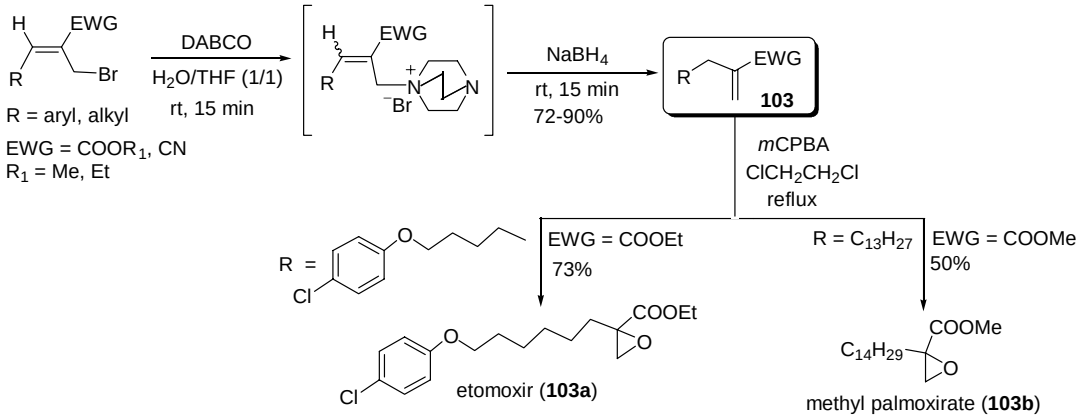
Ogasawara and coworkers[193,194] have reported an elegant synthesis of cyclopentenoid antibiotic (–)-pentenomycin I (**101**)[193] and angular triquinane sesquiterpene (+)-arnicenone (**102**),[194] isolated from *Arnica* plants, using the Baylis–Hillman adducts, obtained *via* the coupling of chiral bicyclic enones (+)- & (–)-**100** with formalin, under the influence of DMAP (Scheme 35).

Scheme 35

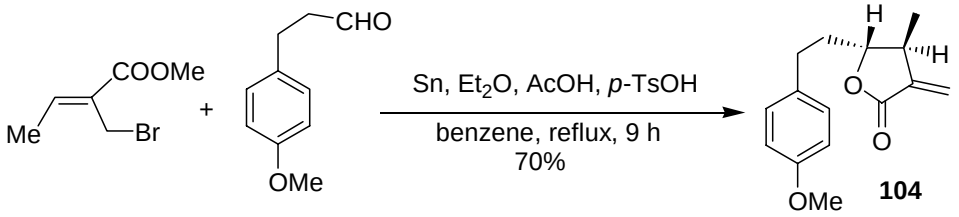


Our research group[195,196] has developed a convenient methodology for synthesis of 2-methylenealkanoates (**103**) *via* the treatment of the Baylis-Hillman bromide (derived from Baylis-Hillman alcohol *i.e.,* 3-hydroxy-2-methylenealkanoates) with $NaBH_4$ in the presence of DABCO in aqueous media. This methodology has been successfully applied for the synthesis of two hypoglycemic agents, etomoxir (**103a**) and methyl palmoxirate (**103b**) as described in Scheme 36.

Scheme 36



Bermejo and coworkers[197] have successfully employed methyl 2-bromomethylbut-2-enoate for synthesis of a biological active compound **104**, possessing apoptosis-inducing ability in HL-60 cells (Eq. 17).

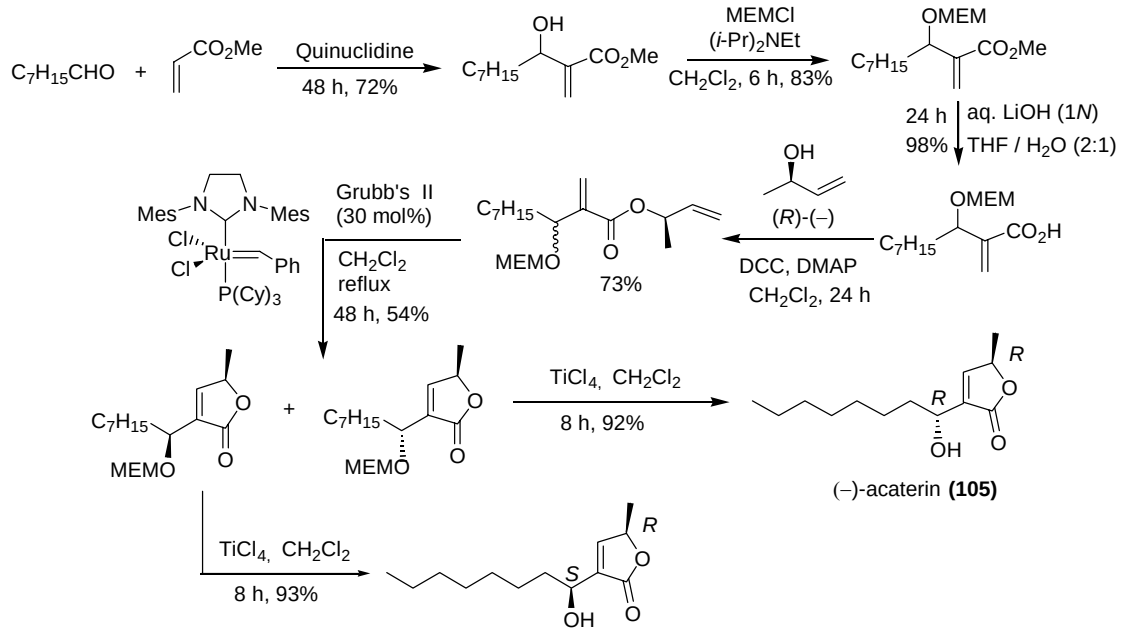


Eq. 17

Recently, (−)-acaterin (**105**), a biologically important natural product, was synthesized by Singh and coworkers[198] utilizing the Baylis-Hillman adduct, derived from octanal

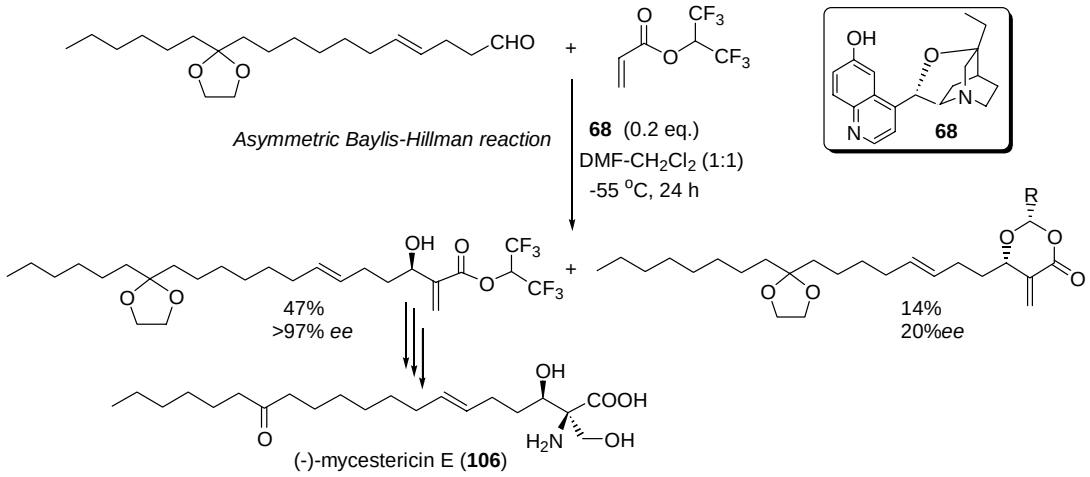
and methyl acrylate, as the key starting material following the reaction sequence as presented in Scheme 37.

Scheme 37



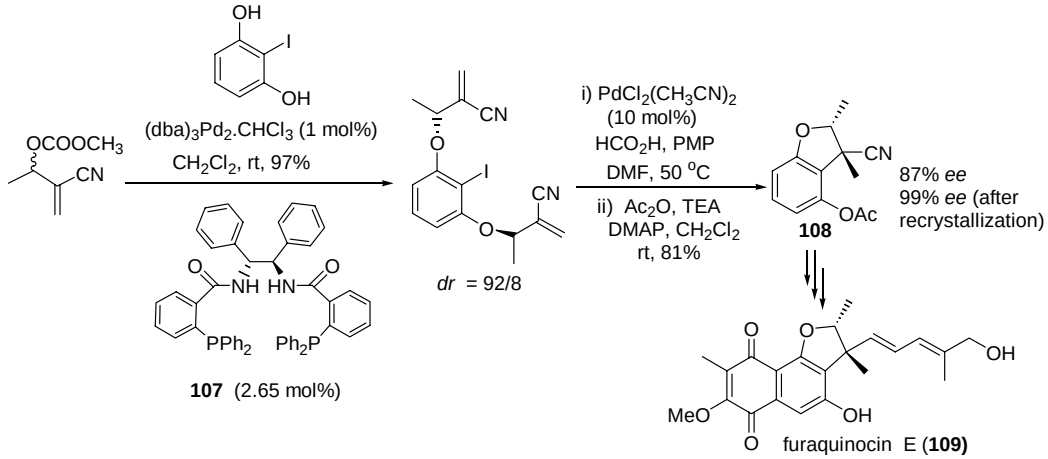
Hatakeyama and coworkers[199] reported an elegant synthesis of (-)-mycestericin E (**106**), a potent immunosuppressive agent, which involves asymmetric Baylis-Hillman reaction catalyzed by **68**, as the key step as described in Scheme 38.

Scheme 38



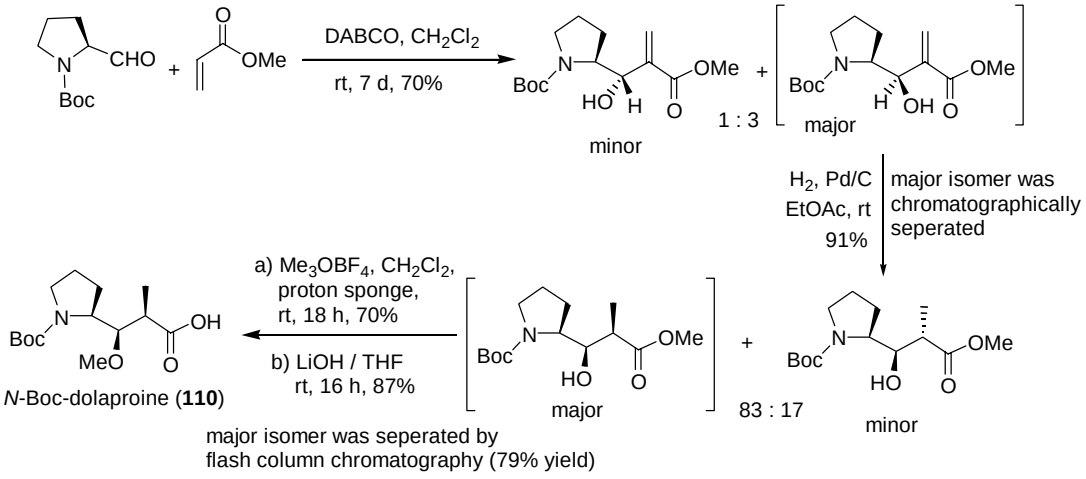
Trost *et. al.*[200] have reported elegant deracemization of Baylis-Hillman adducts involving the principle of DYKAT using the enantiopure ligand **107** in the presence of $(dba)_3Pd_2.CHCl_3$. Subsequently, this methodology has been extended to the synthesis of enantiomerically pure dihydrobenzfuran derivative **108** which was further transformed into furaquinocin E (**109**) as described in Scheme 39.

Scheme 39



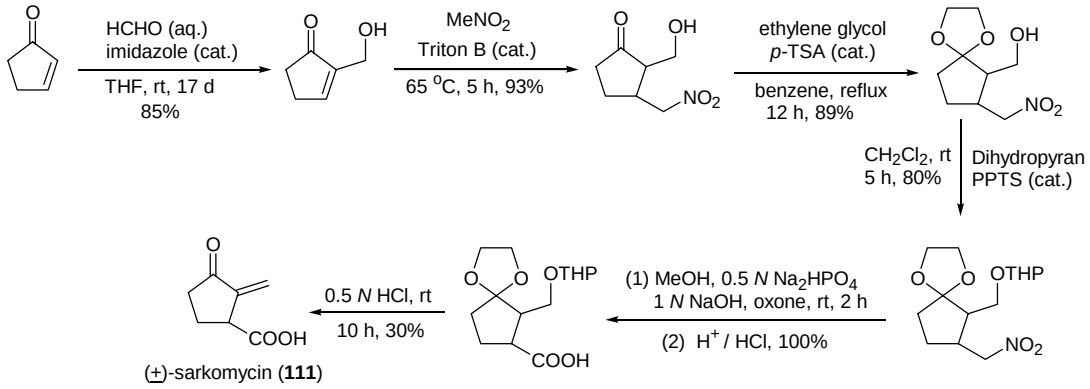
Recently, Almeida and Coelho have employed the Baylis-Hillman reaction as the key step for the synthesis of *N*-Boc-dolaproine (**110**), an amino acid residue of the antineoplastic pentapeptide, Dolastatin-10, as described in Scheme 40.[201]

Scheme 40



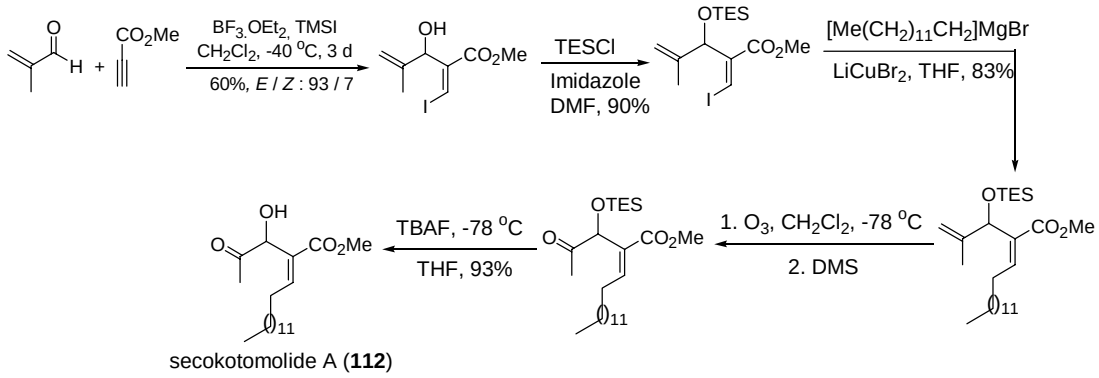
A simple and short synthesis (6 steps) of (±)-sarkomycin (**111**) in 17% overall yield, using Baylis–Hillman reaction as the key step, was developed by Kar and Argade according to reaction sequence as presented in Scheme 41.[202]

Scheme 41



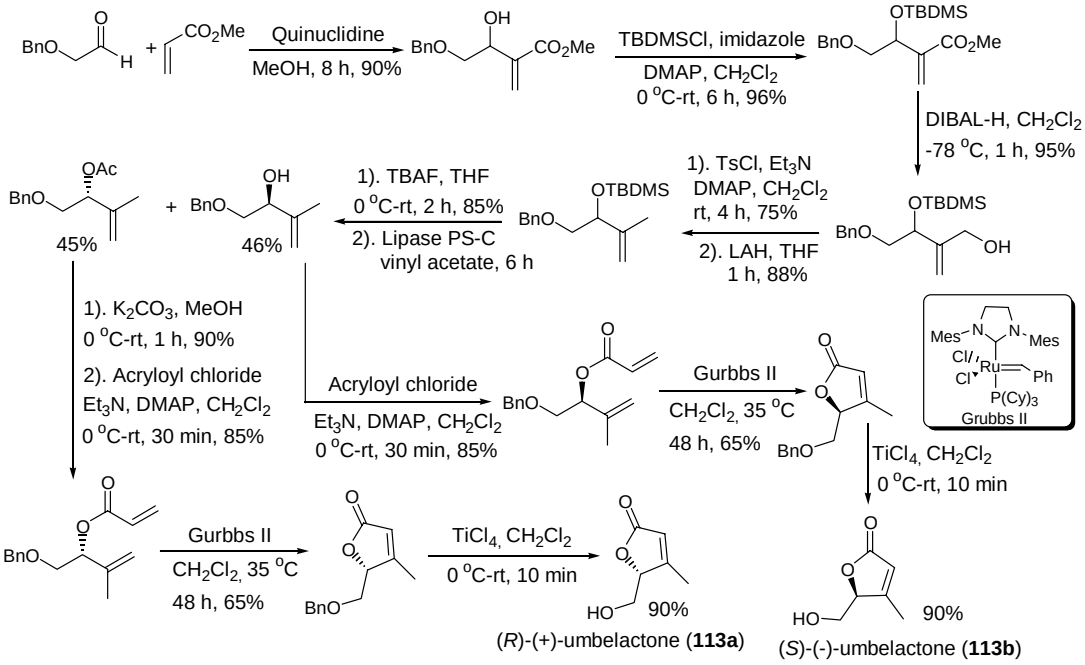
Very recently, Ryu and coworkers[203] developed a facile five-step synthesis of secokotomolide A (**112**) using the Baylis-Hillman reaction as a key step (Scheme 42).

Scheme 42



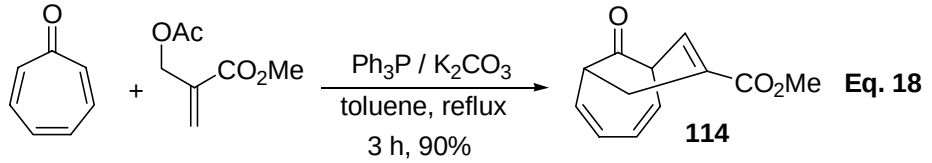
A facile synthesis of enantiomerically pure umbelactones (*R*-**113a** & *S*-**113b**) have been developed by Kamal and coworkers[204] employing the Baylis-Hillman reaction, lipase-mediated resolution protocol and ring closing metathesis as the key steps (Scheme 43).

Scheme 43



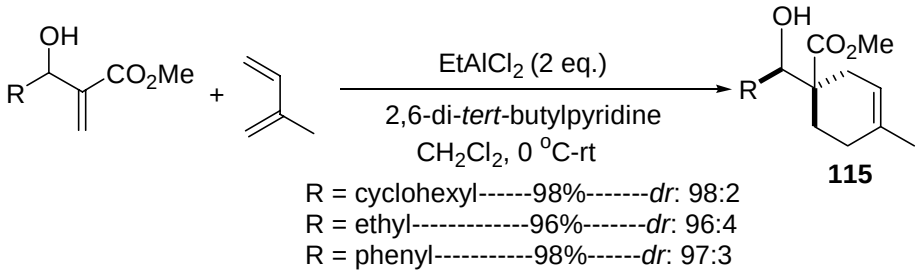
II. SYNTHESIS OF CARBOCYCLIC AND HETEROCYCLIC MOLECULES FROM THE BAYLIS-HILLMAN ADDUCTS

A simple and convenient method for synthesis of bridged nine-membered carbocycles (**114**) in excellent yields *via* the phosphine-catalyzed reaction of Baylis-Hillman acetate (bromide / chloride / *tert*-butyl carbonate) with tropone involving [3+6] annulation strategy was developed by Lu and coworkers (Eq. 18).[205]



Eq. 18

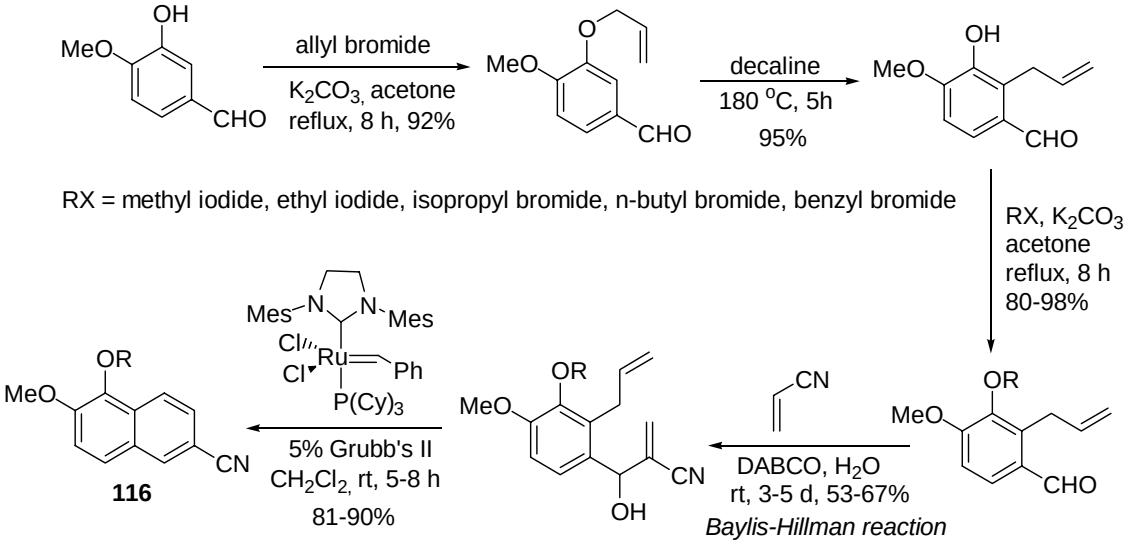
Very recently Aggarwal *et.al*.[206] successfully used Baylis-Hillman adducts as excellent dienophiles in Diels-Alder reaction with dienes to provide the corresponding adducts (**115**) with complete diastereocontrol. Representative examples are presented in Eq. 19.



Eq. 19

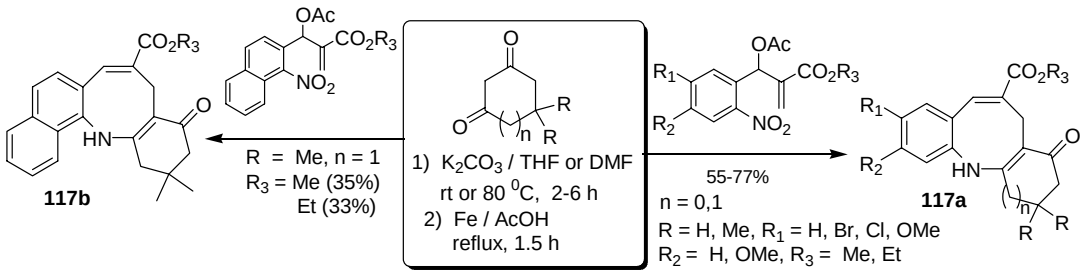
Wang and coworkers,[207] reported a simple synthesis of substituted cyanonaphthalenes (**116**), employing the Baylis-Hillman reaction as a key step. Representative examples are presented in Scheme 44.

Scheme 44



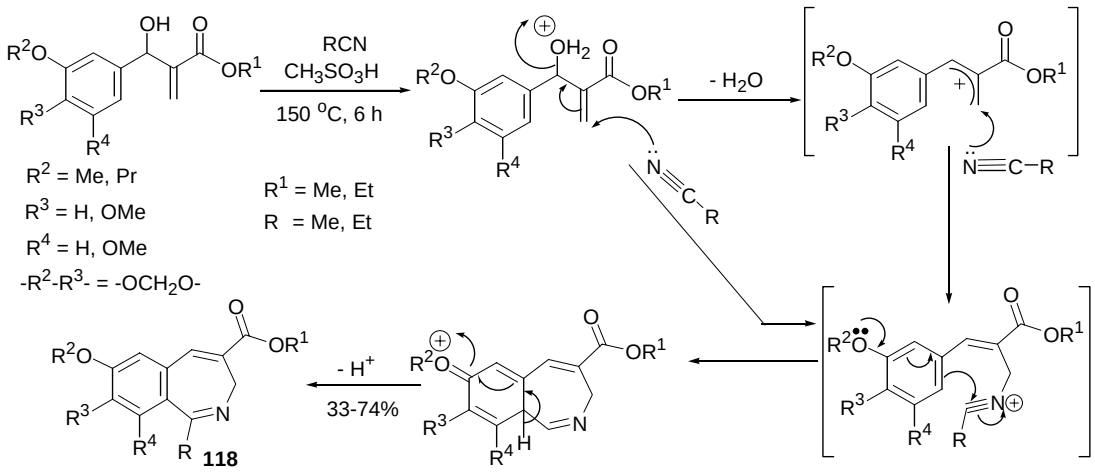
Very recently our research group[208] has developed a simple, convenient, and one-pot synthesis of functionalized tri / tetracyclic frameworks (**117a** & **117b**) containing an important azocine moiety, from the acetates of Baylis-Hillman adducts following the reaction sequence involving alkylation, reduction, and cyclization steps, as described in Scheme 45.

Scheme 45

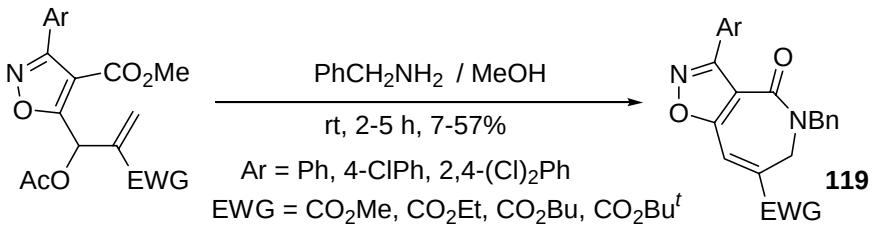


Our research group[209] reported an interesting one-pot transformation of Baylis-Hillman adducts into 2-benzazepines (**118**) *via* novel and tandem construction of C-N and C-C bonds involving simultaneous Ritter and Houben-Hoesch reactions as described in Scheme 46 (Representative examples are presented).

Scheme 46

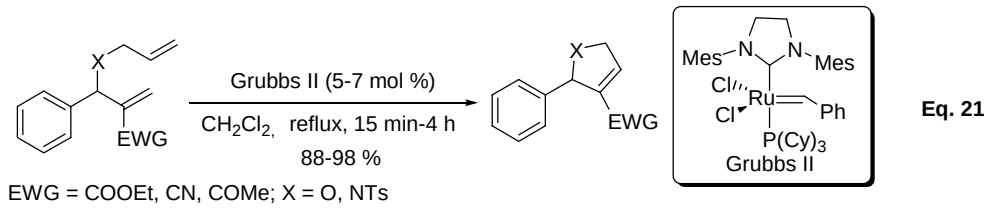


A simple synthesis of azipine derivatives (**119**) from the acetates of Baylis-Hillman adducts has been recently reported by Batra and coworkers (Eq. 20).[210]



Eq. 20

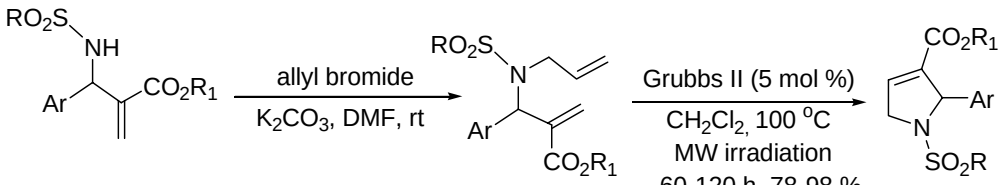
Kim and coworkers[211] have reported an efficient method for synthesis of 2,5-dihydrofuran and 2,5-dihydropyrrole derivatives from the Baylis-Hillman adducts employing the ring-closing metathesis (RCM) as one of the key step (Eq. 21). Later on, Adolfsson and coworkers[212] reported an interesting transformation of *N*-allylated aza-Baylis-Hillman adducts into functionalized 2,5-dihydropyrrole derivatives *via* ring-closing metathesis (RCM) under microwave irradiation (Scheme 47).



Eq. 21

EWG = COOEt, CN, COMe; X = O, NTs

Scheme 47



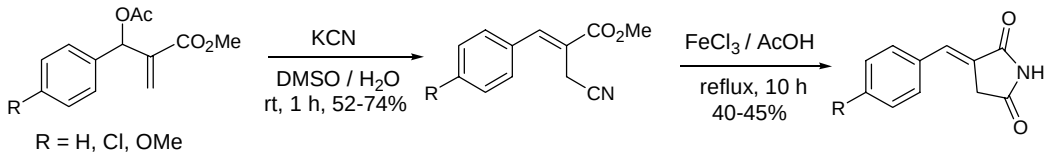
Ar = Ph, 3-ClC_6H_4, 4-$MeOC_6H_4$, naphth-1-yl, pyrid-2-yl

R = 4-MeC_6H_4, 4-$NO_2C_6H_4$

R_1 = Me, Bu^t

A simple synthesis of arylidinesuccinimide derivatives from the Baylis-Hillman acetates was described by Lee and coworkers according to the Scheme 48.[213]

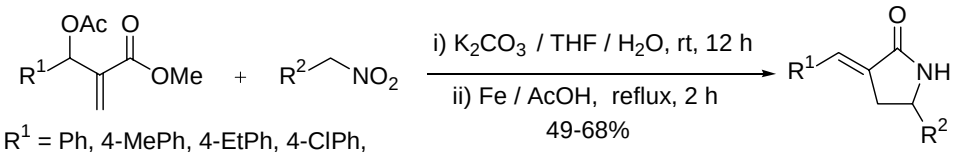
Scheme 48



R = H, Cl, OMe

Recently, our research group[214] reported a convenient one-pot synthesis of (*E*)-5-alkyl-3-arylidenepyrrolidin-2-one (γ-lactam) derivatives *via* the treatment of acetates of

Baylis-Hillman adducts with nitroalkanes in the presence of a base, followed by reductive cyclization, using Fe / AcOH (Eq. 22).



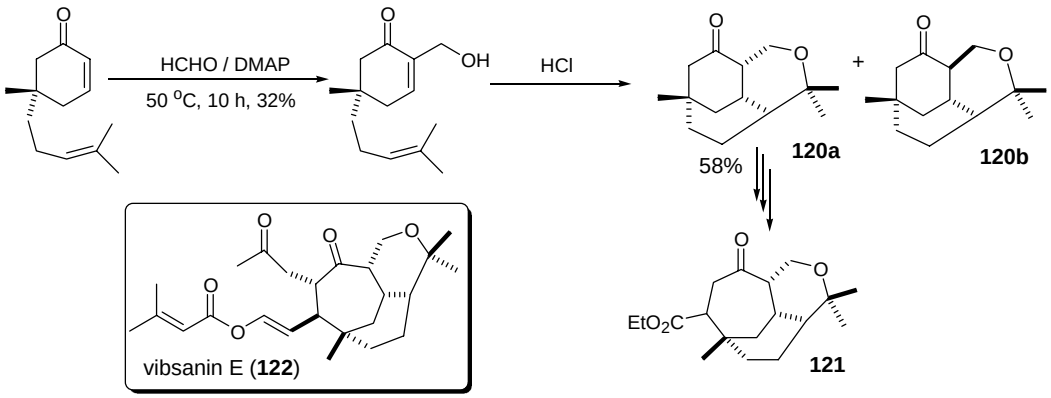
Eq. 22

R^1 = Ph, 4-MePh, 4-EtPh, 4-ClPh, 4-MeOPh, 2-ClPh, naphth-1-yl, *n*-Pr, *n*-Hex

R^2 = Me, Et

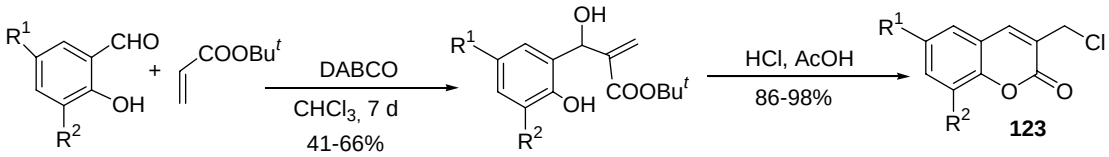
Williams *et. al.,* has developed an elegant protocol for synthesis of tricyclic system (**120a** & **120b**) which was transformed subsequently in to the core framework (**121**) of vibsanin E (**122**) employing the Baylis-Hillman reaction as key step (Scheme 49).[215]

Scheme 49



A simple synthesis of 3-(chloromethyl)coumarin derivatives (**123**) has been developed by Kaye and coworkers[216] following the Baylis-Hillman protocol as described in Scheme 50.

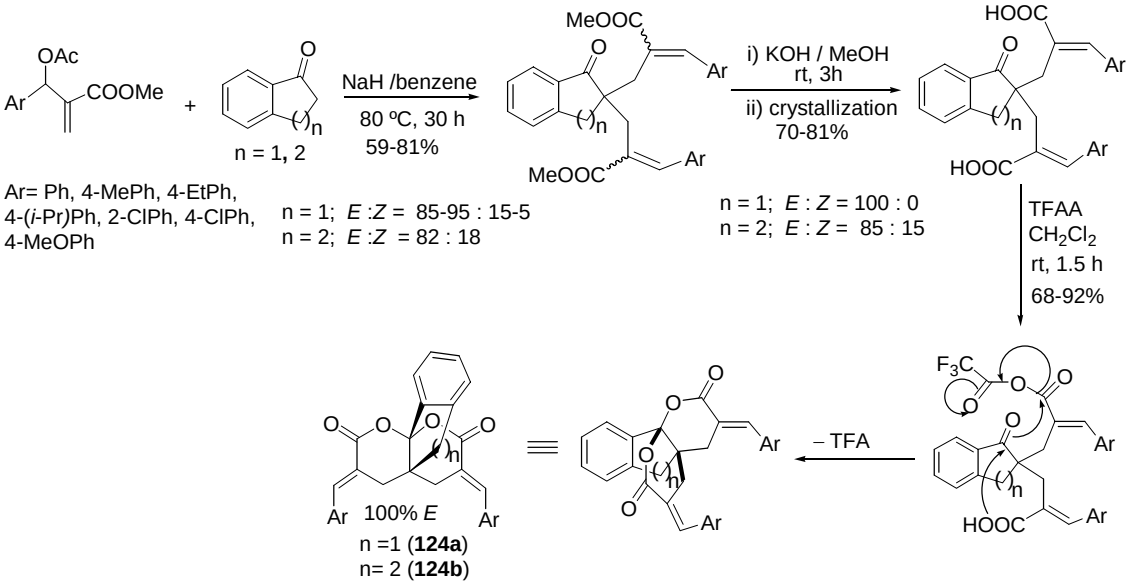
Scheme 50



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

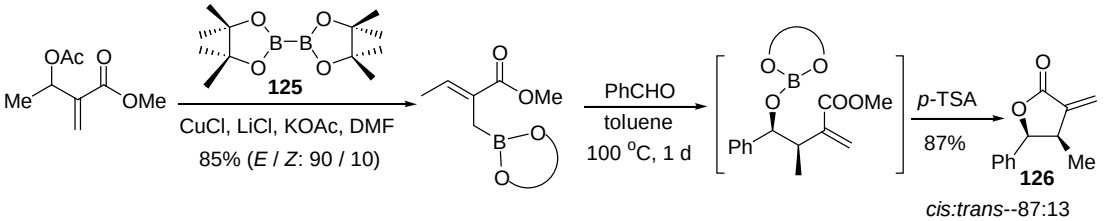
Our research group[217] has developed a simple and convenient three-step synthesis of functionalized [4.4.3] and [4.4.4]propellano-bislactones (**124a** & **124b**) from the acetates of Baylis-Hillman adducts following the reaction sequence as shown in Scheme 51.

Scheme 51

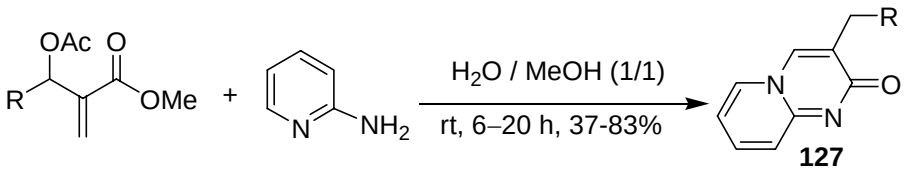


Recently, Ramachandran *et. al*. have reported an interesting synthesis of α-substituted β-methylene β-butyrolactone (**126**) *via* the nucleophilic addition of boronates **125,** to the acetates of Baylis-Hillman adducts, followed by the treatment of the resulting allyl boronates with aldehydes. One representative example is shown in Scheme 52.[218]

Scheme 52



A facile one-pot synthetic transformation of the acetates of the Baylis–Hillman adducts into fused pyrimidones (**127**) *via* the reaction with 2-aminopyridine in environment-friendly aqueous media was reported by our research group (Eq. 23).[219]

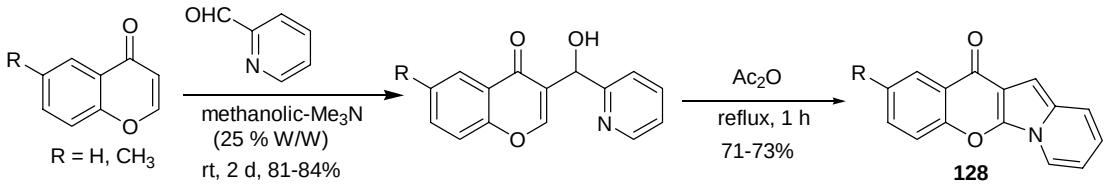


Eq. 23

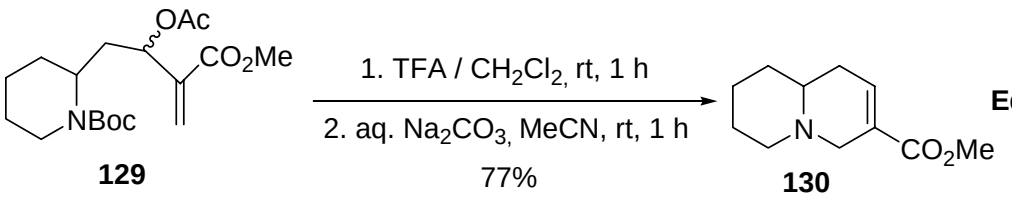
R= Ph, 4-MePh, 4-EtPh, 4-(*i*-Pr)Ph, 2-ClPh, 4-ClPh, 3-MeOPh, 4-MeOPh, Pent

Our research group[55] has successfully employed Baylis-Hillman adducts, obtained from chromone derivatives and pyridine-2-carboxaldehyde into tetracyclic indolizine fused chromone systems (**128**). Representative examples are presented in Scheme 53.

Scheme 53



The acetate of the Baylis-Hillman adducts (**129**), derived from *N*-protected β-amino aldehydes with methyl acrylate, have been transformed into nitrogen fused heterocycles (**130**) by Clive *et.al.* [220] One representative example is presented in Eq. 24.



Eq. 24

OBJECTIVES, RESULTS AND DISCUSSION

From the preceding chapter it is quite clear that the Baylis–Hillman reaction is one of the useful carbon-carbon bond forming reactions, providing an unique class of multifunctional molecules having enormous synthetic potential.[3-6] These multifunctional molecules, usually known as Baylis-Hillman adducts, have been elegantly employed in a variety of stereoselective transformation methodologies and in the synthesis of several important heterocycles, carbocycles, natural products and biologically active molecules.[3-6] During the last twenty three years, our research group has been working on various aspects of this fascinating reaction with the main aim of developing Baylis-Hillman adducts / chemistry into a valuable source for synthesis of various structural frameworks which ultimately would lead to the production of important molecules of medicinal relevance and has in fact contributed significantly to this effect.[3-6] With a view to further expand the scope of this fascinating reaction in synthetic organic chemistry, we have undertaken this research project with the following objectives:

OBJECTIVES

1) To develop a simple and facile two step procedure for the synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides [di(*E*)-arylidene alonomids] from the Baylis-Hillman acetates.
2) To develop the Baylis-Hillman acetates as a valuable source for one-pot multistep synthesis: A convenient synthesis of di(*E*)-arylidene-spiro-bisglutarimides.

3) To develop the Baylis-Hillman adducts as a valuable source for one-pot multistep synthesis: A facile synthesis of substituted-2-piperidones.
4) To develop a simple methodology for regioselective phenylation of Baylis-Hillman adducts, derived *via* the coupling of various chromones with 3- / 4-nitro-benzaldehydes, through the Friedel-Crafts reaction with benzene.
5) To develop a facile methodology for one-pot conversion of Baylis-Hillman adducts, obtained *via* the reaction of chromone derivatives with 2-nitro-benzaldehyde / 2,4-dinitrobenzaldehyde, into tetra / penta cyclic chromone fused quinoline *N*-oxides.

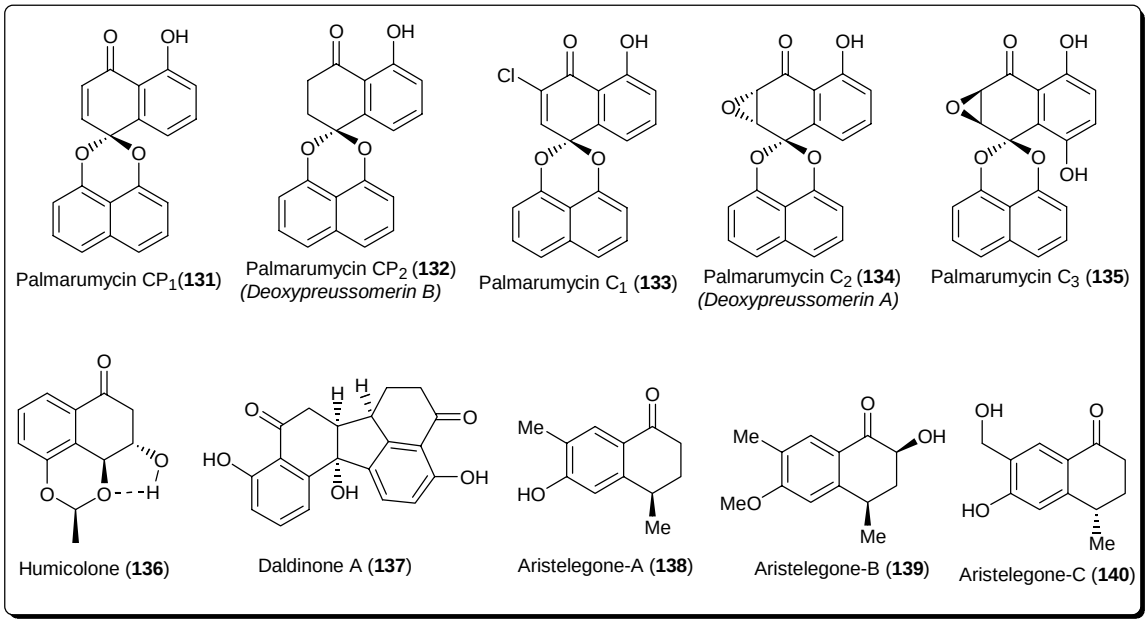
RESULTS AND DISCUSSION

A simple and facile two step procedure for the synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides from the Baylis-Hillman acetates

Tetralone and spiro-tetralone derivatives occupy an important place in organic and medicinal chemistry because of the presence of this moiety in a number of natural products such as palmarumycins (**131-135**)[221-224] (possess antifungal, antibacterial, and herbicidal activites), humicolone (**136**)[225] (possesses cytotoxic activity), daldinone A (**137**),[226] & aristelegone A-C (**138-140**)[227] *etc.* (Figure 10). Due to their interesting and important biological properties, development of simple and convenient methodologies for synthesis of tetralone and spiro-tetralone derivatives represents an interesting and attractive endeavor in organic and medicinal chemistry. Several synthetic strategies / methodologies have been

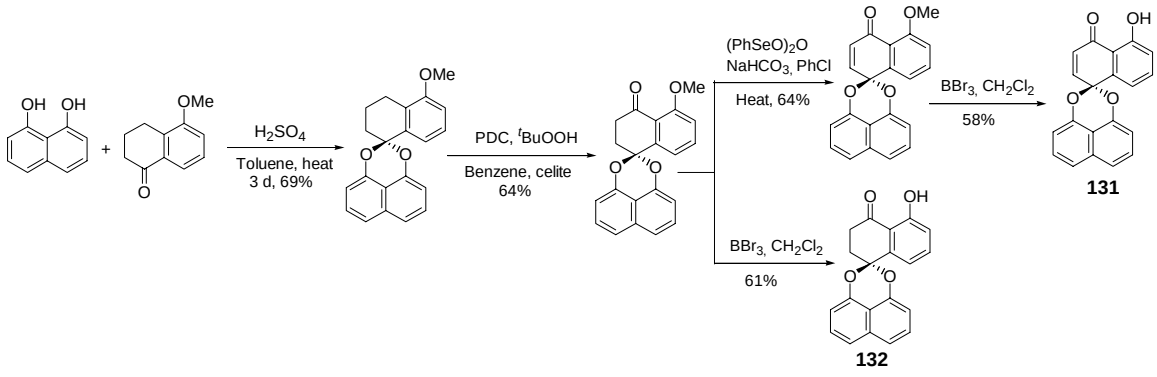
developed for these frameworks and some of the important & recent literature synthetic methods are described in the following Schemes 54-57.

Figure 10



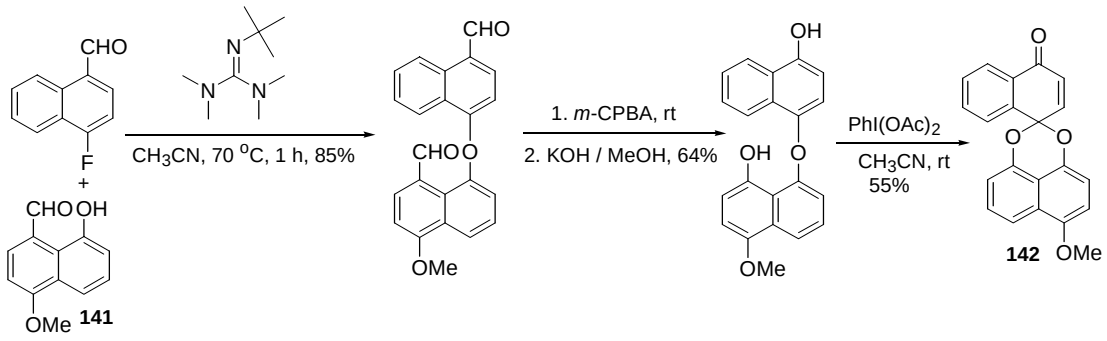
Taylor and coworkers[222] developed an important protocol for the synthesis of palmarumycin CP_1 (**131**) & CP_2 (**132**) *via* an interesting spiro-cyclization of 1,8-dihydroxynaphthalene with 5-methoxytetralone in the presence of H_2SO_4 following the reaction sequence as described in Scheme 54.

Scheme 54



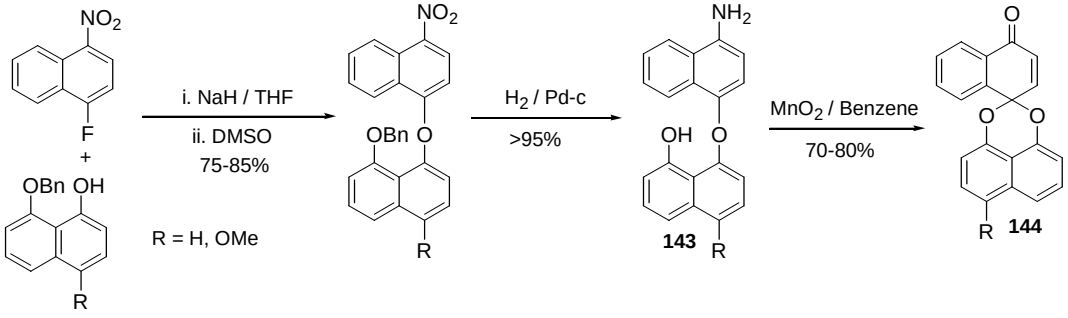
Wipf and Lynch[228] reported an interesting synthesis of spiro-tetralone derivative (**142**) from 4-fluoronaphthaldehyde *via* S_NAr coupling with naphthol derivative (**141**) in the presence of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base) followed by oxidative spiro-cyclization to palmarumycin analogue as described in Scheme 55.

Scheme 55



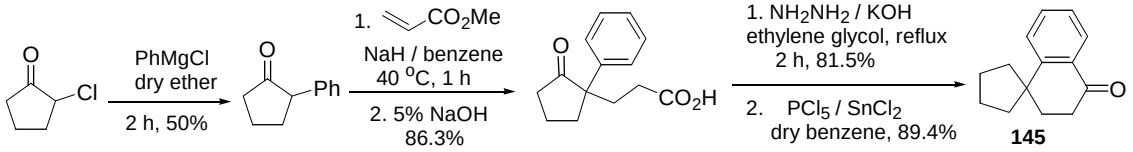
Coutts and coworkers[229] reported an oxidative spiro-cyclization of dinaphthyl ethers (**143**) (obtained from 4-fluoro-1-nitronaphthalene) with activated manganese dioxide leading to the formation of palmarumycin analogues (**144**) as presented in Scheme 56.

Scheme 56



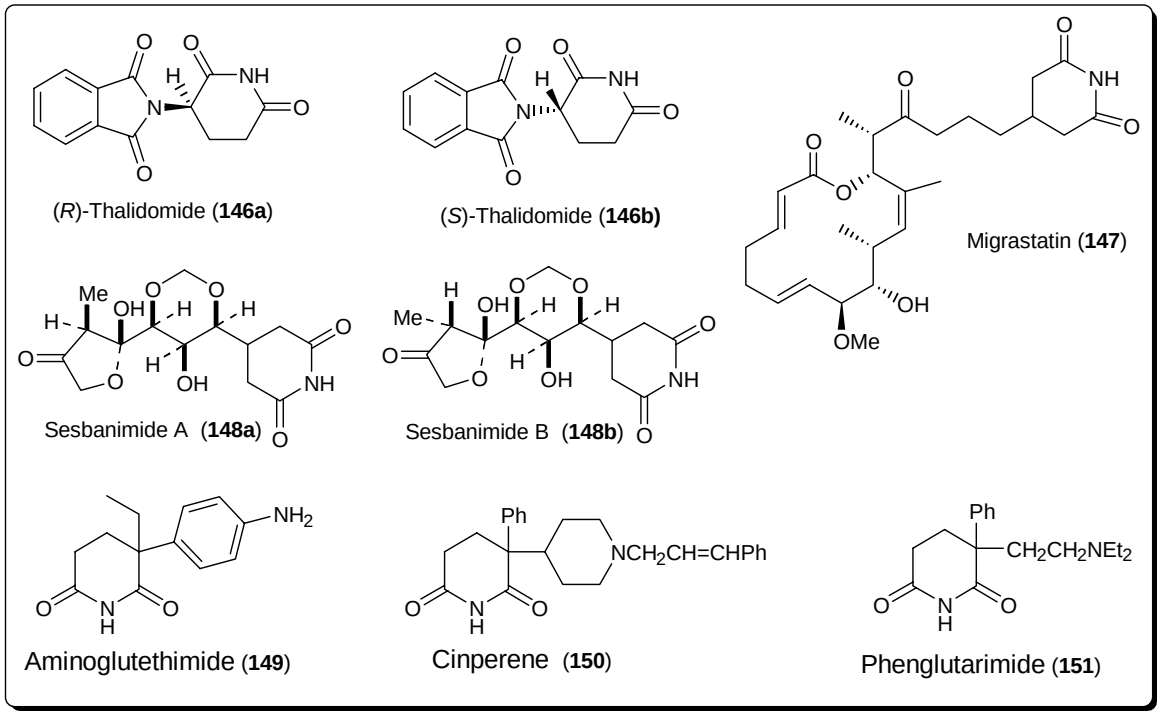
An interesting synthesis of spiro-tetralone (**145**), starting from 2-chloropentanone, was reported by Arnold *et. al.,*[230] following the reaction sequence according to Scheme 57, involving Michael and intramolecular Friedel-Crafts reactions as the key steps.

Scheme 57



The glutarimide framework represents yet another important structural organization present in a number of bioactive molecules, such as, (*R*) & (*S*)-thalidomides (**146a** & **146b**)[231,232] (sedative & hypnotic), migrastatin (**147**)[233] (antitumor), sesbanimide A & B (**148a** & **148b**)[234] (antitumor), aminoglutethimide (**149**)[235,236] (antineoplastic) cinperene (**150**)[237] (antipsychotic & neuroleptic) & phenglutarimide (**151**)[238] (antiparkinsonian & anticholinergic) *etc.* (Figure 11).

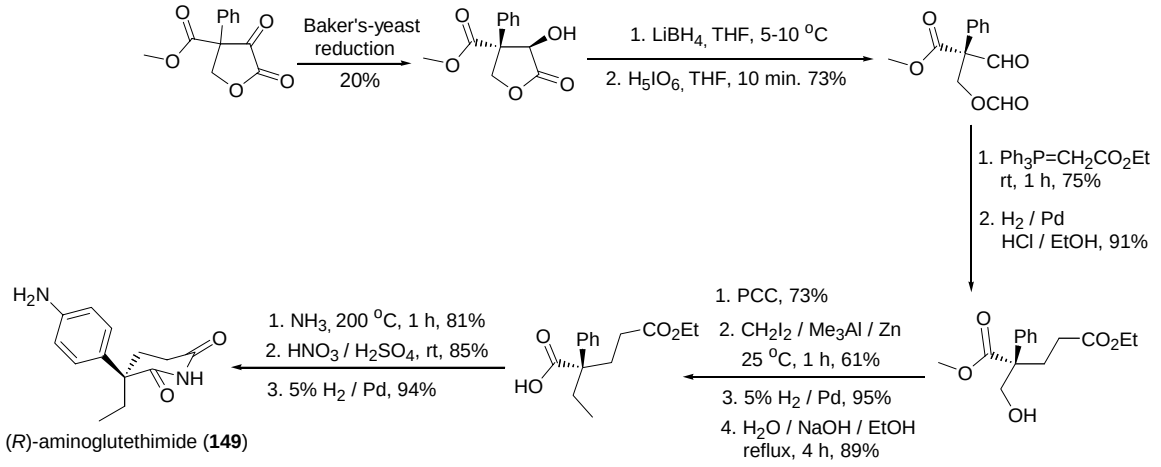
Figure 11



Due to the biological importance of the molecules containing glutarimide framework, development of simple and facile methodologies for the synthesis of glutarimide structural unit represents an interesting endeavor in synthetic organic chemistry. Several synthetic strategies have been reported in the literature for synthesis of glutarimide framework and some of the recent and important methods are discussed in the following.

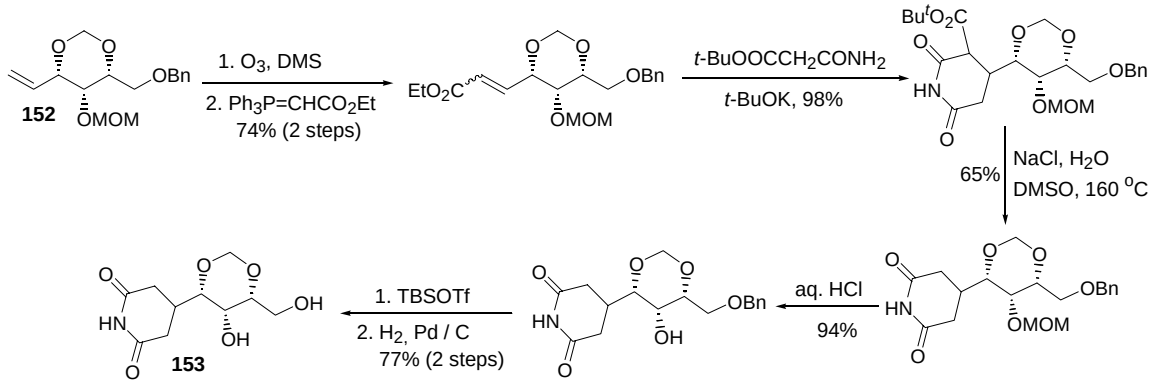
Fuganti and coworkers[236] reported an interesting synthesis enantiomerically pure (*R*)-aminoglutethimide (**149**) starting from the ketolactone following the reaction sequence as described in Scheme 58.

Scheme 58



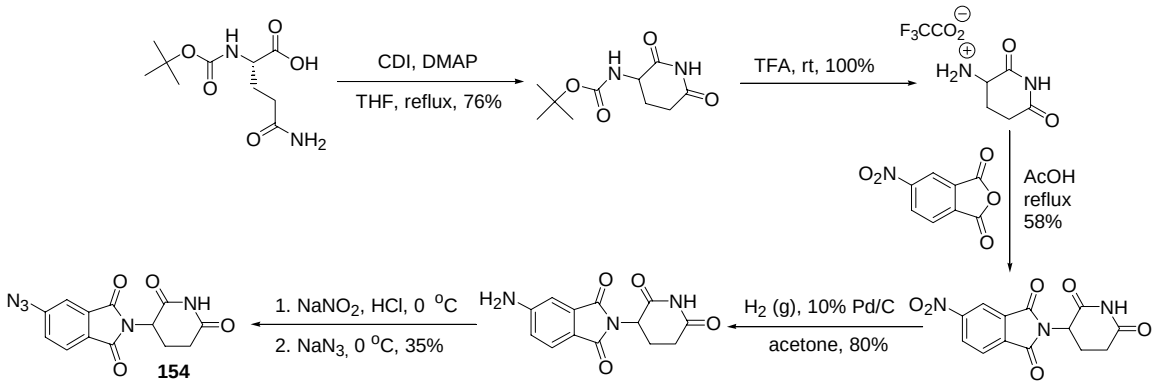
An asymmetric synthesis of the A,B-ring system (**153**) of (+)-sesbanimide A (**148a**) starting from an enantiopure chiral starting material (**152**) was reported by Cirillo and Panek following the reaction sequence as described in Scheme 59.[239]

Scheme 59



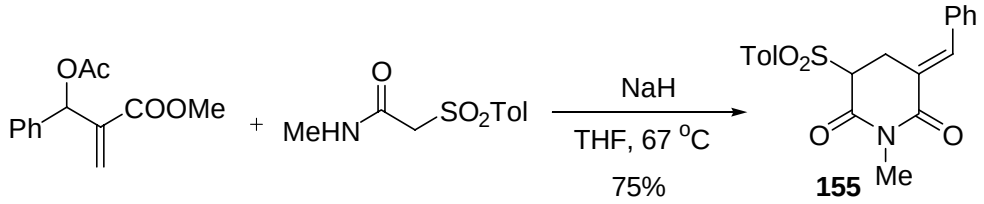
Brown and coworkers[240] reported five-step synthesis of an azido-thalidomide analogue (**154**) following the reaction sequence as described in Scheme 60. These azido-labeled analogues of thalidomide have been found to be valuable in aiding in the identification of relevant protein interactions and in elucidating putative binging sites.

Scheme 60



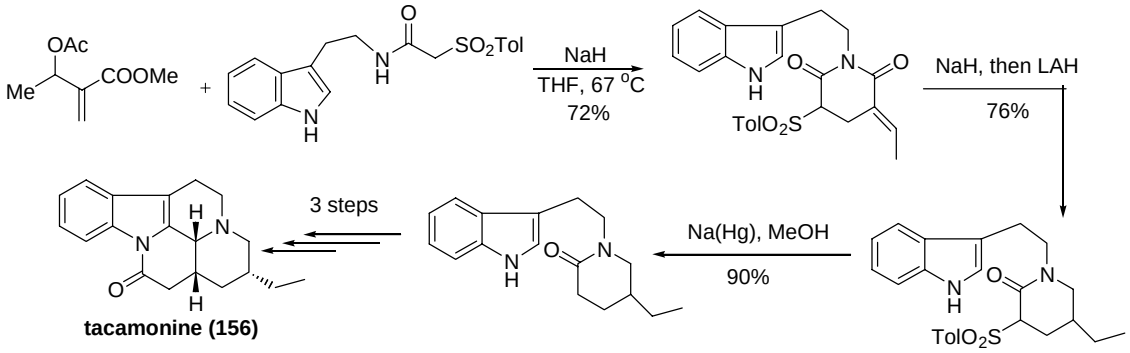
Chang and coworkers[241] have described a one-pot conversion of Baylis-Hillman adducts into *N*-alkyl-3(*E*)-arylidene/alkylidene-5-substituted sulfonyl piperidine-2,6-diones (**155**).

One representative example is shown in Eq. 25. This methodology has been successfully applied for synthesis of tacamonine (**156**), an indole alkaloid according to Scheme 61.



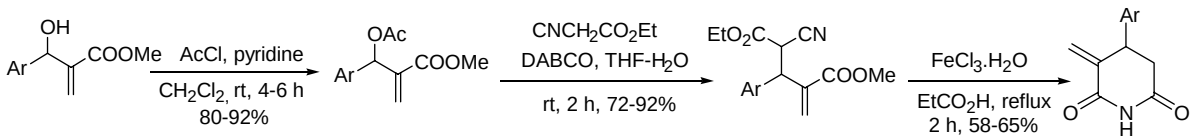
Eq. 25

Scheme 61



Batra and coworkers[242] described a convenient synthesis of 3-methylene-4-aryl-piperidine-2,6-diones *via* the nucleophilic addition of ethyl cyanoacetate onto the Baylis-Hillman acetates followed by hydrolysis & cyclization using $FeCl_3.H_2O$ in propanoic acid as described in Scheme 62.

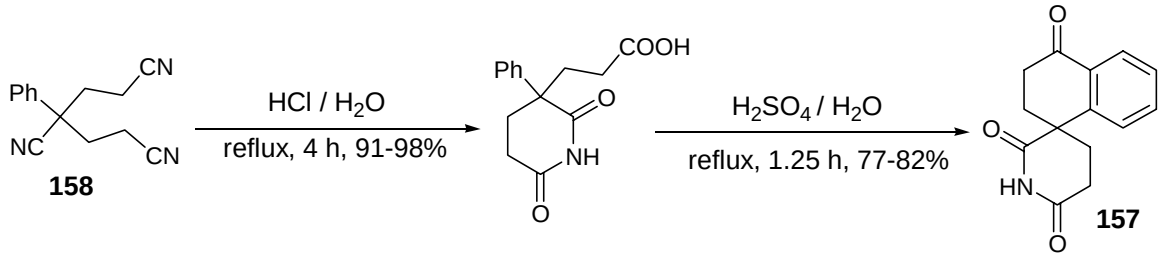
Scheme 62



Due to the biological importance of the spiro-tetralone structural unit and glutarimide framework, it occurred to us that the development of a simple and facile synthesis of an interesting and aesthetically appealing molecular architecture containing both the tetralone and glutarimide structural units linked by an appropriate spiro bridge as in the case of alonimid (**157**),[243] *i.e.* [1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′, 6′-dione] (well known for sedative and hypnotic activities), would certainly provide an easy access to the different derivatives of alonimid (Figure 12) and also provide attractive compounds with possible medicinal relevance and hence represents a challenging endeavor in organic and medicinal chemistry.

It is worth mentioning here the work of Koelsch[244] who developed, a simple two-step synthesis of tetralone-spiro-glutarimide (alonomid, **157**) from γ-cyano-γ-phenyl pimelonitrile (**158**) *via* the hydrolysis of nitrile group leading to the formation of glutarimide ring followed by formation of tetralone ring through an intramolecular Friedel-Crafts reaction according to reaction sequence as described in Scheme 63.

Scheme 63



In continuation of our interest in developing, simple and useful methodologies for synthesis of hetero and carbocyclic molecules,[55,124,190,195,208,209,214,217,219] we have undertaken a research program for developing a convenient synthesis of di(*E*)-arylidene-tetralone-spiro-glutarimides [di(*E*)-arylidene alonimids] from the acetates of the Baylis-Hillman adducts according to the retro-synthetic strategy as described in Scheme 64. Thus, the Baylis-Hillman (B-H) acetates (**160**) *i.e. tert*-butyl 3-acetoxy-3-aryl-2-methylenepropnoates [obtained from the Baylis-Hillman alcohols (**159**)], would in principle serve as a good alkylating agents for bisalkylation of benzyl cyanide and then one of the ester group in the bisadduct (**161**) would be used for intramolecular Friedel-Crafts reaction while the other ester group would be utilized in the formation of the glutarimide framework thus leading to the generation of the spiro molecule, that is, di(*E*)-arylidene alonimid (**162**), with appropriate substitution profile (Scheme 64).

Scheme 64

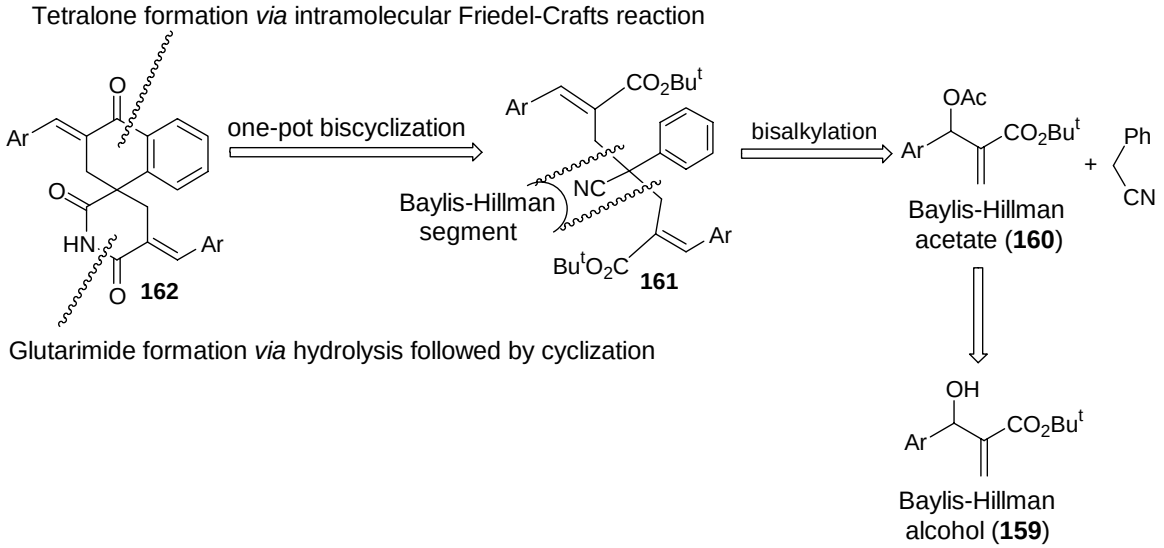
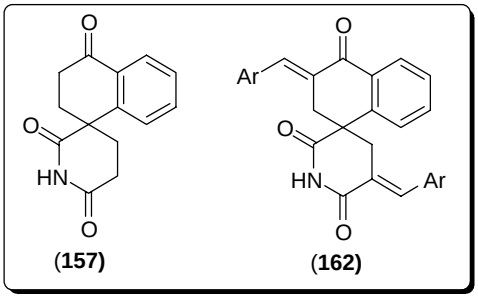
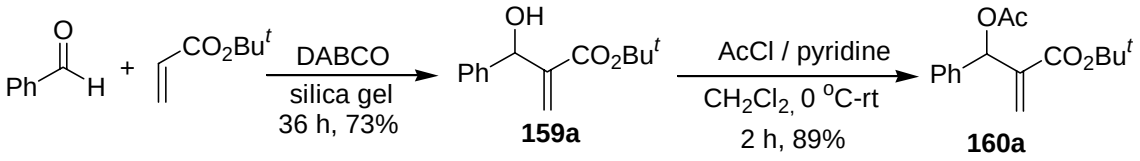


Figure 12



Accordingly, we have first planned synthesis of di(*E*)-benzylidene-tetralone-spiro-glutarimide (**162a**) *i.e.* di(*E*)-benzylidene alonimid. The required acetate, *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**), was prepared *via* the acetylation of the Baylis-Hillman adduct (**159a**) according to Scheme 65. The desired Baylis-Hillman adduct, *i.e.*, *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**159a**), in turn was obtained *via* the treatment of benzaldehyde with *tert*-butyl acrylate in the presence of DABCO as described in Scheme 65.

Scheme 65



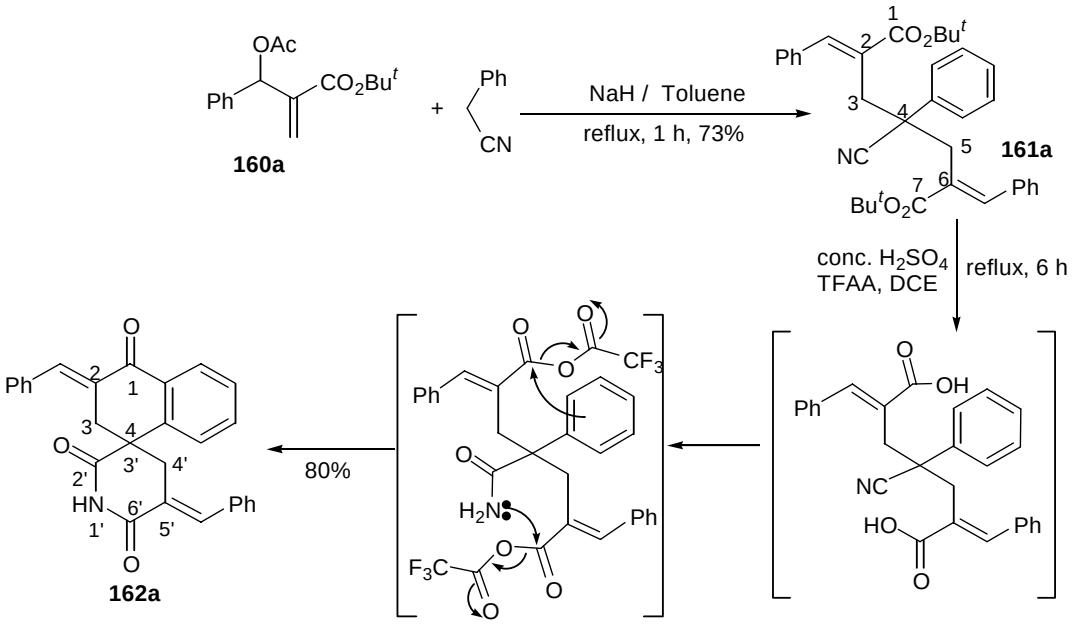
Next we have examined the bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) as an alkylating agent. The best results were achieved when benzyl cyanide (2 mmol) was treated with B-H acetate **160a** (5 mmol) in the presence of excess NaH (10 mmol) in anhydrous toluene under reflux for 1 h to provide the desired bisadduct, di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-

heptanedioate **(161a)** in 73% isolated yield after column chromatography (silica gel, 5% EtOAc in hexanes), followed by crystallization from 3% EtOAc in hexanes at 0 ^{o}C, to provide exclusively (*E*)-stereoselectivity♣ (Scheme 66 & Table 1). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 1), ^{13}C NMR (Spectrum 2), mass (LCMS) spectral data and elemental analysis. Subsequent treatment of this bisadduct **161a** (0.5 mmol) with conc. H_2SO_4 (2.5 mmol) / trifluoracetic anhydride (TFAA) (2.5 mmol) in 1,2-dichloroethane (DCE, 3 mL) under reflux for 6 h provided the desired 2,5′-di[(*E*)-benzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (**162a**) as a colorless solid in 80% isolated yield after column chromatography using silica gel (30% EtOAc in hexanes) (Scheme 66 & Table 1) with (*E*)-stereochemistry.♣ Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 3), ^{13}C NMR (Spectrum 4), mass (LCMS) spectral data and elemental analysis.

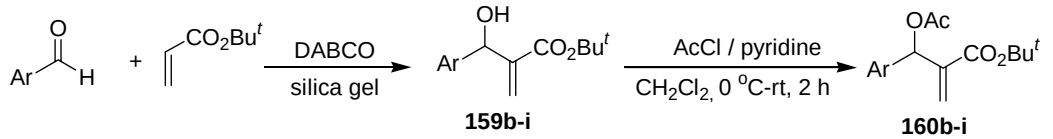
This result is indeed very interesting and encourging in the sense that the Baylis-Hillman acetate (**160a**) is transformed into 2,5′-di[(*E*)-benzylidene] alonimid (**162a**) in two steps in 58% overall yield. We have then prepared a representative class of Baylis-Hillman adducts (**159b-i**) *via* the coupling of various aromatic aldehydes with *tert*-butyl acrylate in the presence of DABCO and transformed them into the corresponding allyl acetates (**160b-i**) by the treatment with acetyl chloride and pyridine in CH_2Cl_2 (Scheme 67).

♣ In the ^{1}H NMR spectra of trisubstituted alkenes (with ester group at α-position), the β-vinylic proton *cis* to the ester group appears downfield while the β-vinylic proton *trans* to the ester appears upfield.[245-247] ^{1}H NMR spectra of crude product of bisadduct **161a** indicated the presence of ≈8% minor (*Z*)-isomer. The *E*/*Z* selectivity was determined by the integration ratio of isomeric β-vinylic protons [^{1}H NMR spectrum of **161a** (the crude), shows a singlet at δ 7.65 (for *E*-isomer) and a singlet at δ 6.85 (*Z*-isomer) in 92:8 ratio]. However, crystallization provides pure (*E*)-isomer.

Scheme 66



Scheme 67



Ar = 2-ClC_6H_4 (**159b**), 2-MeC_6H_4 (**159c**), 3-ClC_6H_4 (**159d**), 4-ClC_6H_4 (**159e**), 4-MeC_6H_4 (**159f**), 4-EtC_6H_4 (**159g**), 4-(*i*-Pr)C_6H_4 (**159h**), 4-BrC_6H_4 (**159i**)

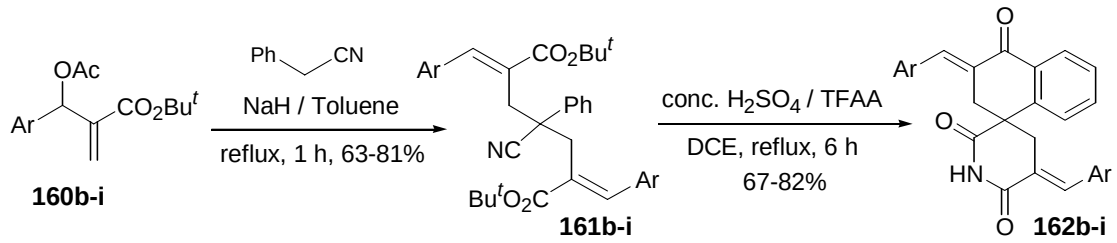
Ar = 2-ClC_6H_4 (**160b**), 2-MeC_6H_4 (**160c**), 3-ClC_6H_4 (**160d**), 4-ClC_6H_4 (**160e**), 4-MeC_6H_4 (**160f**), 4-EtC_6H_4 (**160g**), 4-(*i*-Pr)C_6H_4 (**160h**), 4-BrC_6H_4 (**160i**)

We have, then, successfully extended this methodology to the Baylis-Hillman acetates (**160b-i**) for bisalkylation of benzyl cyanide, which provides corresponding bisadducts, di-*tert*-butyl 2,6-di[(*E*)-arylidene]-4-cyano-4-phenyl-1,7-heptanedioates (**161b-i**) in 63-81% isolated yields with pure (*E*)-stereoselectivity.[Θ] Subsequently, these bisadducts (**161b-i**) were transformed into di(*E*)-arylidene alonimids (**162b-i**) in 67-82% isolated yields, *via*

[Θ] In the case of **161b**,**d-i**, crude compounds show the presence of 5-14% *(Z)*-isomer. However, crystallization provides pure (*E*)-isomers. In the case of **161c**, ^{1}H NMR of the crude products did not show the presence of any (*Z*)-isomer. The *E*/*Z* selectivity was determined by the integration ratio of isomeric β-vinylic protons [the β-vinylic proton *cis* to ester group (*E*-isomer) appeared at δ 7.53-7.63 while the same proton *trans* to ester group (*Z*-isomer) appeared at δ 6.76-6.88].

the treatment with H_2SO_4 / TFAA (Scheme 68 & Table 1). All the bisadducts (**161b-i**) and di(*E*)-arylidene alonomids (**162b-i**) were characterized by IR, ^{1}H NMR [Spectrum 5 (for compound **162c**) & Spectrum 6 (for compound **162g**)], ^{13}C NMR [Spectrum 7 (for compound **162c**) & Spectrum 8 (for compound **162g**)] and mass (LCMS) spectral data and elemental analyses. In fact, we obtained single crystals, in the case of bisadduct **161h** (Figure X1 & Table I), di(*E*)-arylidene alonimids **162a** (Figure X2 & Table II) & **162b** (Figure X3 & Table III), and established the structures of these molecules by single crystal X-ray data analyses.

Scheme 68



Ar = 2-ClC_6H_4, 2-MeC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-EtC_6H_4, 4-(*i*-Pr)C_6H_4, 4-BrC_6H_4

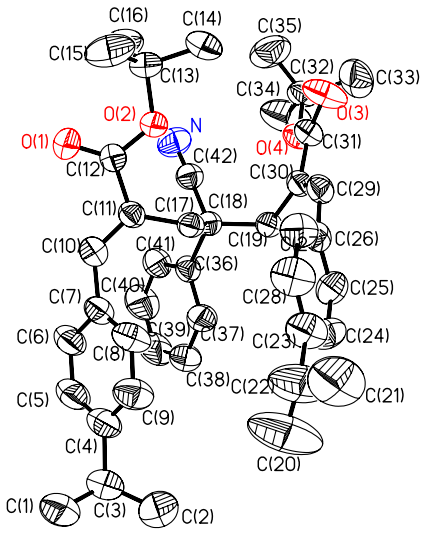
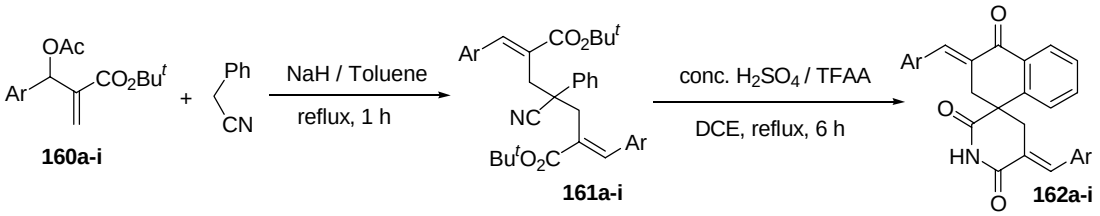


Figure X1 ORTEP diagram of compound **161h**
(Hydrogen atoms were omitted for clarity)

Table 1 Synthesis of bisadducts (**161a-i**)[a] and di(*E*)-arylidene alonomids (**162a-i**)[b] from the B-H acetates (**160a-i**)



B-H acetate	Ar	Product[c]	Yield[d] (%)	Mp (^oC)	Product[c]	Yield[d] (%)	Mp (^oC)
160a	C_6H_5	**161a**	73	118-120	**162a**[e]	80	184-186
160b	2-ClC_6H_4	**161b**	70	140-142	**162b**[e]	82	187-189
160c	2-MeC_6H_4	**161c**	81	127-129	**162c**	75	232-234
160d	3-ClC_6H_4	**161d**	65	151-152	**162d**	67	229-231
160e	4-ClC_6H_4	**161e**	66	184-186	**162e**	77	236-238
160f	4-MeC_6H_4	**161f**	80	124-126	**162f**	77	227-229
160g	4-EtC_6H_4	**161g**	78	80-82	**162g**	78	150-152
160h	4-(*i*-Pr)C_6H_4	**161h**[e]	72	110-111	**162h**	75	179-180
160i	4-BrC_6H_4	**161i**	63	187-189	**162i**	71	233-235

(a) All reactions were carried out on a 2 mmol scale of benzyl cyanide with 5 mmol of B-H acetate (**160a-i**) in the presence of excess NaH (10 mmol) in anhydrous toluene under reflux for 1 h in N_2 atm.

(b) All reactions were carried out on a 0.5 mmol scale of bisadducts (**161a-i)** with conc. H_2SO_4 (2.5 mmol) and TFAA (2.5 mmol) in 1,2-dichloroethane (DCE, 3 mL) under reflux for 6 h.

(c) All the products (**161a-i** & **162a-i**)$^{\Theta}$ were obtained as colorless solids and fully characterized by IR, ^1H, ^{13}C NMR, mass (LCMS) spectral data and elemental analyses.

(d) Isolated yields of the pure products **161a-i** (based on benzyl cyanide) & **162a-i** (based on bisadducts).

(e) The structures of these molecules with (*E*)-stereochemistry were also established from the single crystal X-ray data (Figures X1-X3 & Tables I-III) and in analogy (*E*)-stereochemistry is assigned to the other compounds.

$^{\Theta}$ In the case of **161a,b**,**d-i**, crude compounds show the presence of 5-14% *(Z)*-isomer. However, crystallization provides pure (*E*)-isomers. In the case of **161c**, ^1H NMR of the crude products did not show the presence of any (*Z*)-isomer. The *E*/*Z* selectivity was determined by the integration ratio of isomeric β-vinylic protons [the β-vinylic proton *cis* to ester group (*E*-isomer) appeared at δ 7.53-7.63 while the same proton *trans* to ester group (*Z*-isomer) appeared at δ 6.76-6.88].

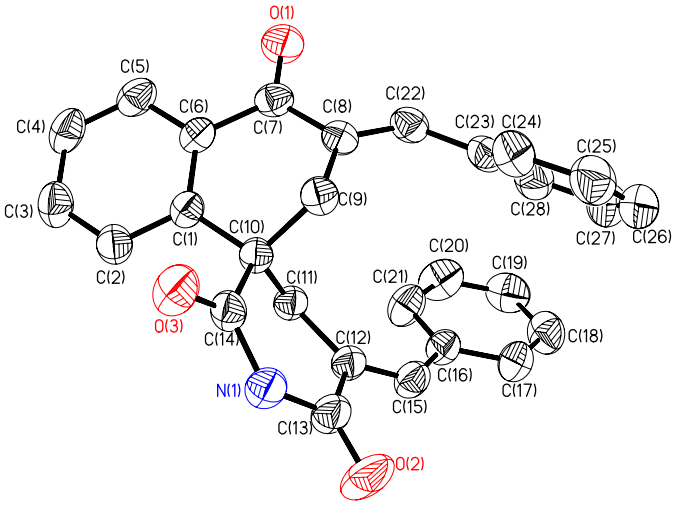


Figure X1 ORTEP diagram of compound **162a**
(Hydrogen atoms were omitted for clarity)

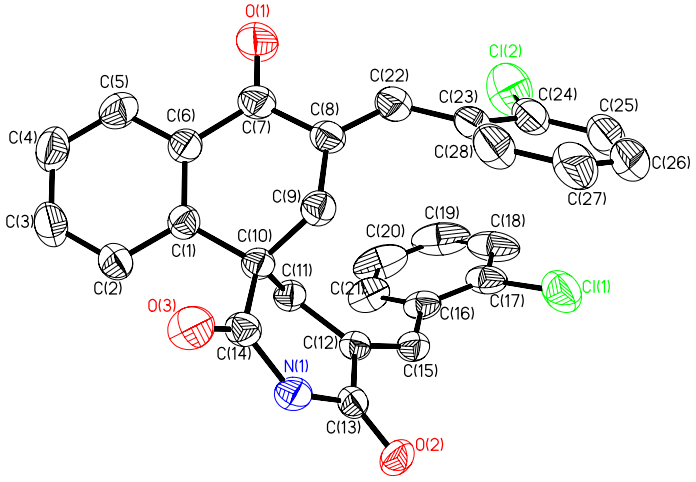


Figure X2 ORTEP diagram of compound **162b**
(Hydrogen atoms were omitted for clarity)

Table I: Crystal data collection and structure refinement for the compound **161h**

Empirical formula	: $C_{42}H_{51}NO_4$
Formula weight	: 633.84
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: $P2_1/n$ (*International Table #14*)
Unit cell dimensions	: a = 11.799(2) Å; α = 90 deg.
	: b = 14.900(3) Å; β = 98.298(3) deg.
	: c = 21.767(4) Å; γ = 90 deg.
Volume	: 3786.6(11) $Å^3$
Z, Calculated density	: 4, 1.112 g/cm^3
Absorption coefficient	: 0.070 mm^{-1}
F(000)	: 1368
Crystal size	: 0.41 X 0.28 X 0.16 mm
Theta range for data collection	: 1.66 to 25.00 deg.
Limiting indices	: $-14 \le h \le 14$, $-17 \le k \le 17$, $-25 \le l \le 25$
Reflections collected / unique	: 26807 / 6661 [R(int) = 0.0393]
Completeness to theta = 25.00	: 100%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 6661 / 0 / 434
Goodness-of-fit on F^2	: 1.041
Final R indices [I>2sigma(I)]	: R1 = 0.0580, wR2 = 0.1491
R indices (all data)	: R1 = 0.0970, wR2 = 0.1687
Largest diff. peak and hole	: 0.258 and -0.237 e. $Å^{-3}$

Table II: Crystal data collection and structure refinement for the compound **162a**

Empirical formula	: $C_{28}H_{21}NO_3$
Formula weight	: 419.46
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: $P2_1/n$ (*International Table # 14*)
Unit cell dimensions	: a = 9.0369(18) Å; α = 90 deg.
	: b = 25.751(5) Å; β = 96.103(3) deg.
	: c = 9.2740(18) Å; γ = 90 deg.
Volume	: 2145.9(7) $Å^3$
Z, Calculated density	: 4, 1.298 g/cm^3
Absorption coefficient	: 0.084 mm^{-1}
F (000)	: 880
Crystal size	: 0.44 X 0.28 X 0.22 mm
Theta range for data collection	: 1.58 to 25.00 deg.
Limiting indices	: $-10 \le h \le 9$, $-22 \le k \le 30$, $-11 \le l \le 11$
Reflections collected / unique	: 12584 / 3780 [R(int) = 0.0233]
Completeness to theta = 25.00	: 100%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3780 / 0 / 293
Goodness-of-fit on F^2	: 1.065
Final R indices [I>2sigma (I)]	: R1 = 0.0427, wR2 = 0.1031
R indices (all data)	: R1 = 0.0528, wR2 = 0.1081
Largest diff. peak and hole	: 0.197 and -0.282 e. $Å^{-3}$

Table III: Crystal data collection and structure refinement for the compound **162b**

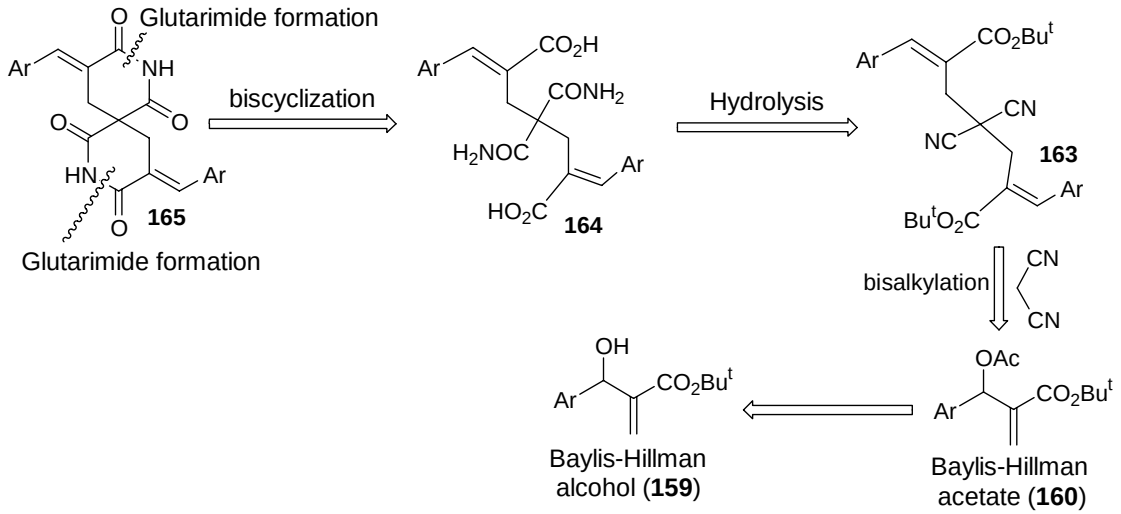
Empirical formula	: $C_{28}H_{19}NCl_2O_3$
Formula weight	: 488.34
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P–1 (*International Table # 2*)
Unit cell dimensions	: a = 9.0278 (7) Å; α = 79.2200(10) deg.
	: b = 10.5146(9) Å; β = 75.2250(10) deg.
	: c = 13.4184(11) Å; γ = 72.0250(10) deg.
Volume	: 1163.34(16) $Å^3$
Z, Calculated density	: 2, 1.394 g/cm^3
Absorption coefficient	: 0.311 mm^{-1}
F(000)	: 504
Crystal size	: 0.41 X 0.22 X 0.18 mm
Theta range for data collection	: 1.58 to 25.00 deg.
Limiting indices	: $-10 \le h \le 10$, $-12 \le k \le 12$, $-15 \le l \le 15$
Reflections collected / unique	: 11260 / 4080 [R(int) = 0.0353]
Completeness to theta = 25.00	: 99.7%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 6080 / 0 / 311
Goodness-of-fit on F^2	: 0.997
Final R indices [I>2sigma(I)]	: R1 = 0.0412, wR2 = 0.1006
R indices (all data)	: R1 = 0.0557, wR2 = 0.1064
Largest diff. peak and hole	: 0.241 and -0.260 e. $Å^{-3}$

In conclusion, we have successfully developed a convenient and operationally simple two step procedure for the synthesis of di(*E*)-arylidene alonimids (**162a-i**) *via* the bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates (**160a-i**) followed by an interesting biscyclization strategy involving the successive C-C and C-N bonds formation through an intramolecular Friedel-Crafts reaction and hydrolysis of nitrile group with subsequent formation of glutarimide framework.

The Baylis-Hillman acetates as a valuable source for one-pot multistep synthesis: A convenient synthesis of di(*E*)-arylidene-spiro-bisglutarimides

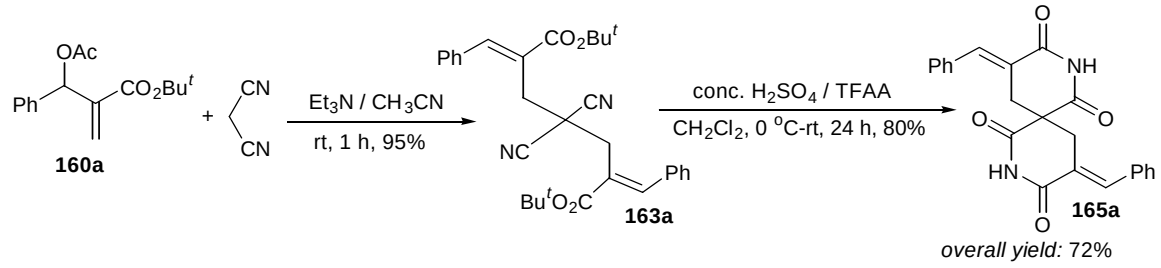
After successfully developing a convenient methodology for synthesis of di(*E*)-arylidene alonimids, it occurred to us that Baylis-Hillman acetates (**160**) would in principle serves as a valuable source for synthesis of spiro-bisglutarimide derivatives (**165**), *via* bisalkylation of malononitrile followed by the hydrolysis of bisadduct (**163**) of nitrile groups into amide groups (**164**) and subsequent cyclization as shown in Scheme 69 (retro-synthetic strategy).

Scheme 69



We have first selected *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) as a substrate for this strategy. Thus, the treatment of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) (2 mmol) with malononitrile (1 mmol) in the presence of triethylamine (1 mmol) in acetonitrile (3 mL) at room temperature for 1 h provided the desired bisadduct, *i.e.*, di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4,4-dicyano-1,7-heptanedioate (**163a**), as a colorless solid in 95% isolated yield after usual workup and column chromatography with pure (*E*)-stereoselectivity.[Φ] Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 9), ^{13}C NMR (Spectrum 10), mass (LCMS) spectral data and elemental analysis. Subsequent reaction of bisadduct (**163a**) with conc. H_2SO_4 (2 mmol) and TFAA[ℜ] (2 mmol) (addition at 0 ^{o}C) at room temperature for 24 h in dichloromethane (5 mL) followed by usual workup provided the desired 3,3′-spiro-bis[5-{(*E*)-benzylidene}-piperidine-2,6-dione] **(165a**) in 80% yield (Scheme 70). Structure of this molecule was confirmed by IR, ^{1}H NMR & ^{13}C NMR spectral data and elemental analysis. Thus, we have successfully transformed Baylis-Hillman acetate (**160a**) into spiro-bisglutarimide (**165a**) in two-steps in 72% overall yield.

Scheme 70

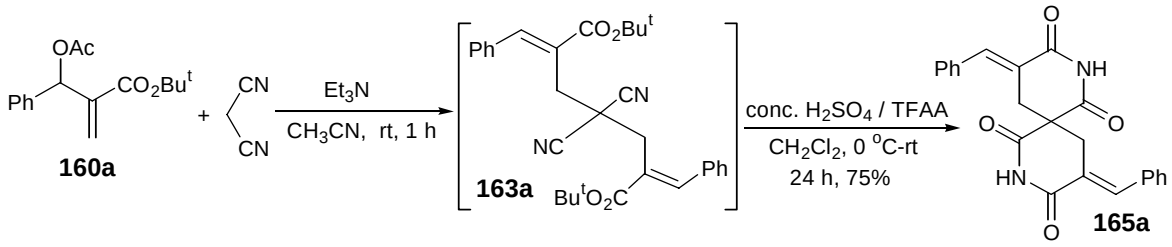


[Φ] In the ^{1}H NMR spectra of trisubstituted alkenes (with ester group at α-position), the β-vinylic proton *cis* to the ester group appears downfield while the β-vinylic proton *trans* to the ester appears upfield.[245-247] In the ^{1}H NMR spectrum of **163a**, only one singlet at δ 7.91 (for *E*-isomer) was observed and no peak was observed in the region δ 6.55-7.00 (indicating the absence of any *Z*-isomer).

[ℜ] In the absence of TFAA (trifluoroacetic anhydride) the reaction mixture is non-homogeneous and sluggish.

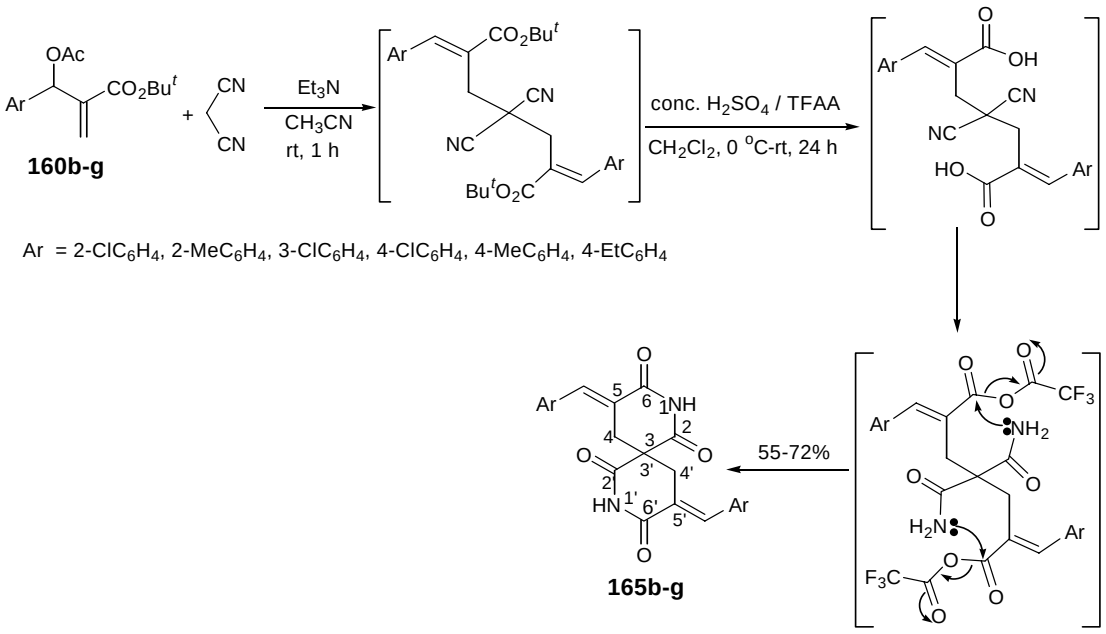
In recent developments in organic and medicinal chemistry created a need for synthesizing important and potential biologically active frameworks in an operationally simple procedure, if possible in one-pot operation, even though a number of steps / reactions are involved in actual synthetic processes.[208,214,248-250] Accordingly, we directed our studies towards the development of one-pot multistep procedure for transformation of Baylis-Hillman acetates into spiro-bisglutarimides. In this direction, we have first selected *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) as a substrate for bisalkylation. Thus, the treatment of **160a** (2 mmol) in acetonitrile (3 mL) with malononitrile (1 mmol) in the presence of triethylamine (1 mmol) at room temperature for 1 h provided the bisadduct, which on, subseqeuent reaction (after removing acetonitrile & triethylamine under reduced pressure) with conc. H_2SO_4 (2 mmol) and TFAA (2 mmol) (addition at 0 ^oC) at room temperature for 24 h in dichloromethane (5 mL) followed by usual workup provided the desired 3,3′-spiro-bis[5-{(*E*)-benzylidene}-piperidine-2,6-dione] **(165a**) in 75% yield (Scheme 71 & Table 2). Structure of this molecule was confirmed by IR, ^1H NMR (Spectrum 11), ^{13}C NMR (Spectrum 12), mass (LCMS) spectral data and elemental analysis. In fact, spectral data is in full agreement with that of the molecule prepared in two-step methods as in Scheme 70.

Scheme 71



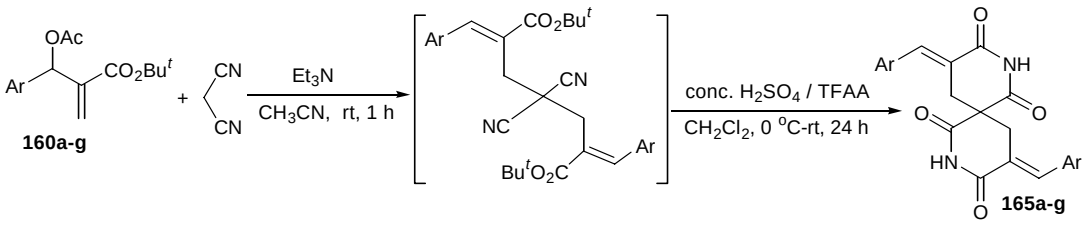
This is indeed very encouraging result in the sense that two-steps, actually involving two C-C and two C-N bonds forming reaction, were performed in one-pot operation in 75% yield [while 72% overall yield in two-steps (Scheme 70)]. With a view to understand the generality of this one-pot multistep methodology we have extended this strategy to representative Baylis-Hillman acetates (**160b-g**) which provided the resulting spiro-bisglutarimides (**165b-g**)[Δ] in 55-72% yields (Scheme 72 & Table 2). All the products (**165b-g**) were fully characterized by IR, ^{1}H NMR [Spectrum 13 (for product **165b**) & Spectrum 14 (for product **165g**)], ^{13}C NMR [Spectrum 15 (for product **165b**) & Spectrum 16 (for product **165g**)], and mass (LCMS) spectral data and elemental analyses. In fact, we obtained single crystal for compound **165g** and further established the structure of this molecule by single crystal X-ray data (Figure X4 & Table IV).

Scheme 72



[Δ] The (*E*)-stereochemistry was assigned of the products **165a-g** on the basis of ^{1}H NMR spectral data of **163a** and also in analogy with that single crystal X-ray data of **165g**.

Table 2 One-pot multistep synthesis of di(*E*)-arylidene-spiro-bisglutarimides (**165a-g**)[a] from the B-H acetates (**160a-g**)



B-H acetate	Ar	Product[b]	Yield[c] (%)	Mp (°C)
160a	C_6H_5	**165a**	75	255 (dec.)
160b	2-ClC_6H_4	**165b**	55	240-241
160c	2-MeC_6H_4	**165c**	56	190-192
160d	3-ClC_6H_4	**165d**	61	222 (dec.)
160e	4-ClC_6H_4	**165e**	72	230 (dec.)
160f	4-MeC_6H_4	**165f**	64	245 (dec.)
160g	4-EtC_6H_4	**165g**[d]	59	218-220

(a) All reactions were carried out on a 1 mmol scale of malononitrile with 2 mmol of B-H acetate (**160a-g**) in the presence of Et_3N in acetonitrile at room temperature for 1 h. Solvent acetonitrile and Et_3N were removed under reduced pressure and the residue, thus obtained was treated with conc. H_2SO_4 (2 mmol) / TFAA (2 mmol) in dichloromethane (5 mL) at room temperature for 24 h.

(b) All the pure products **165a-g** were obtained as colorless solids [with (*E*)-stereochemistry$^{\Delta}$ as evidenced by the ^{1}H NMR spectral analysis and also in analogy with that of **165g**] and characterized by IR, ^{1}H, ^{13}C NMR, mass (LCMS) spectral data and elemental analyses.

(c) Yields of the pure products **165a-g** based on B-H acetates **160a-g**.

(d) The structure of this molecule [with (*E*)-stereochemistry] was also established by the single crystal X-ray data (Figure X4 & Table IV).

Table IV: Crystal data collection and structure refinement for the compound **165g**

Empirical formula	: $C_{27}H_{26}N_2O_4$
Formula weight	: 442.50
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P–1 (*International Table # 2*)
Unit cell dimensions	: a = 10.0689(7) Å; α = 101.1420(10) deg.
	: b = 10.7855(7) Å; β = 108.9140(10) deg.
	: c = 12.4469(9) Å; γ = 105.6280(10) deg.
Volume	: 1171.60(15) $Å^3$
Z, Calculated density	: 2, 1.254 g/cm^3
Absorption coefficient	: 0.085 mm^{-1}
F(000)	: 468
Crystal size	: 0.40 X 0.32 X 0.26 mm
Theta range for data collection	: 1.82 to 25.00 deg.
Limiting indices	: $-11 \le h \le 11$, $-12 \le k \le 12$, $-14 \le l \le 14$
Reflections collected / unique	: 11347 / 4099 [R(int) = 0.0266]
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	: 4099 / 0 / 308
Goodness-of-fit on F^2	: 1.070
Final R indices [I>2sigma(I)]	: R1 = 0.0617, wR2 = 0.1824
R indices (all data)	: R1 = 0.0803, wR2 = 0.1963
Largest diff. peak and hole	: 0.448 and -0.310 e. $Å^{-3}$

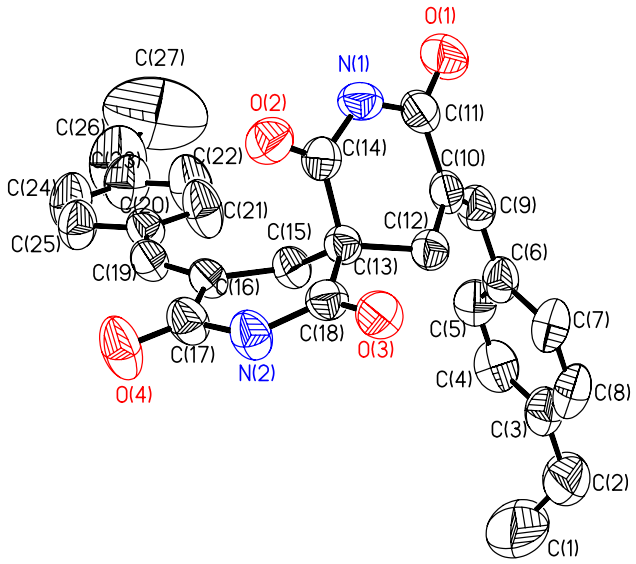
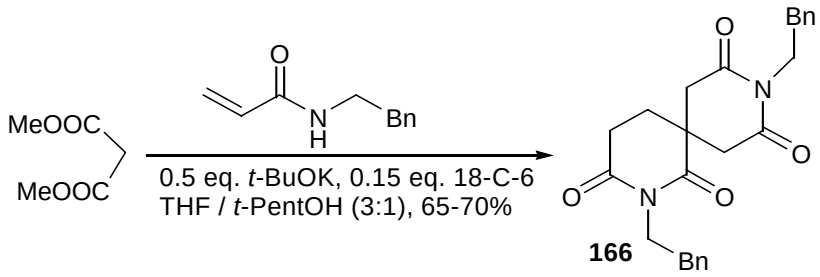


Figure X4 ORTEP diagram of compound **165g**
(Hydrogen atoms were omitted for clarity)

It is interesting to note that there are not many methods known in literature for synthesis of spiro-bisglutarimides.[251,252] Two known synthetic strategies are reported in the following Eq. 26 & Scheme 73.

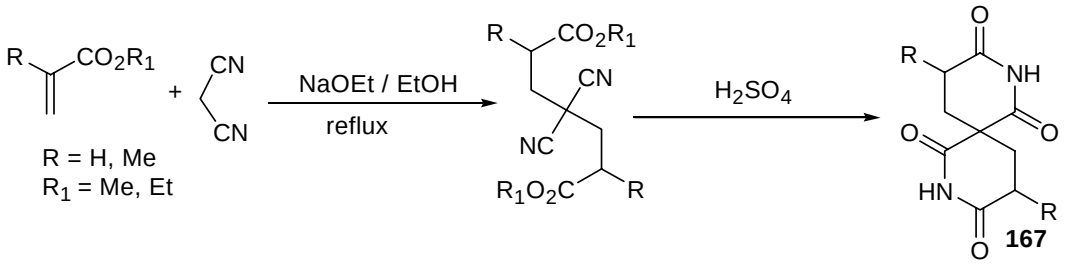
The spiro-bisglutarimide (**166**) is prepared by Ivanovic and coworkers *via* the bisalkylation (bis-Michael addition) of dimethyl malonate with *N*-phenethylacrylamide followed by cyclization in the presence of *t*-BuOK (Eq. 26).[251]



Eq. 26

Victory and Jose reported an interesting synthesis of substituted spiro-bisglutarimides (**167**) *via* the bis-Michael addition of malononitrile to ethyl acrylate (or methyl methacrylate) followed by hydrolysis and then cyclization as described in Scheme 73.[252]

Scheme 73



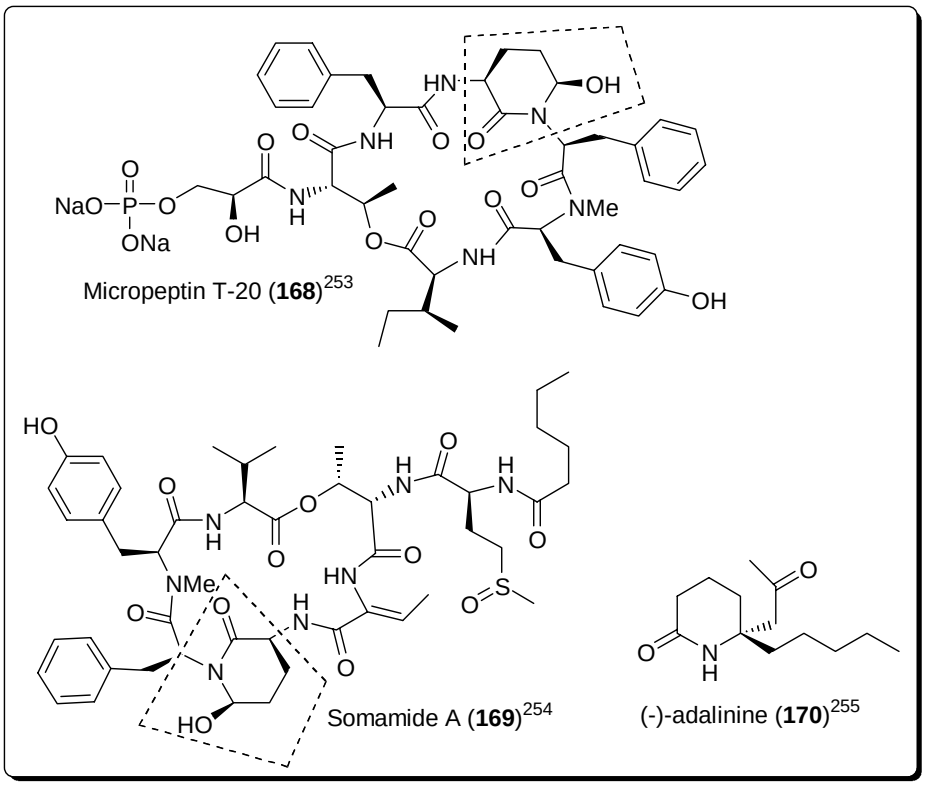
In conclusion, we have successfully developed a facile one-pot multistep synthesis of spiro-bisglutarimides (**165a-g**) *via* bisalkylation of malononitrile with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates (**160a-g**) followed by the hydrolysis of nitrile groups and subsequent cyclization. The most interesting aspect of this methodology is that two C-C and two C-N bonds are formed in one pot-operation.

The Baylis-Hillman adducts as a valuable source for one-pot multistep synthesis: A facile synthesis of substituted-2-piperidones

The 2-piperidone moiety occupies a special place in nitrogen heterocyclic chemistry because of the presence of this moiety in a variety of biologically important natural products, such as, micropeptin T-20 (**168**),[253] somamide A (**169**)[254] and (-)-adalinine (**170**)[255] (Figure 13) and also in a number of medicinally relevant molecules, such as, peptidase / protease inhibitors, EP_4 receptor agonists, and selective antagonists of the

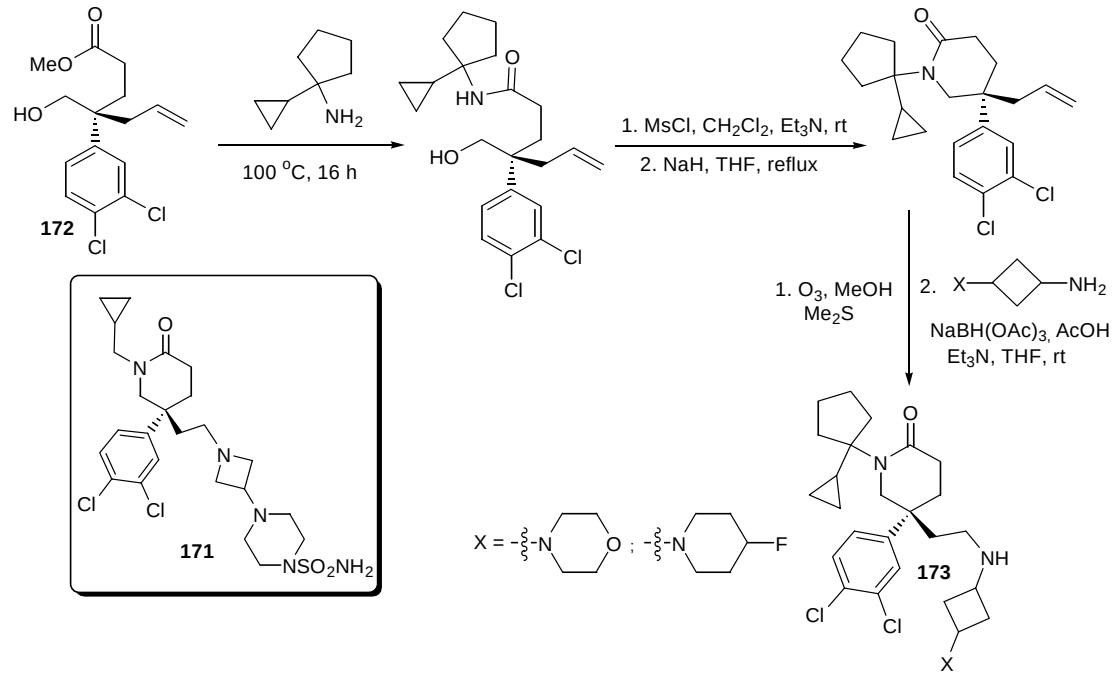
neurokinin-2 (NK_2) receptor.[256-261] High applicability of these molecules with medicinal importance demands the development of simple and easy methodologies for the synthesis of 2-piperidone framework with a provision to have a wide range of substitution profile. Synthetic chemists developed various strategies / methodologies for the synthesis of 2-piperidone framework. Some recent and important strategies are presented in the following Schemes 74-78.

Figure 13



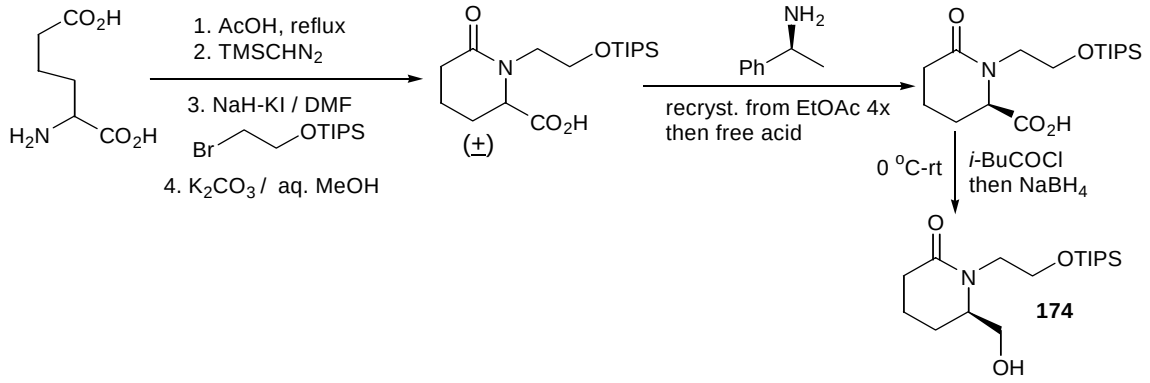
During their studies for finding replacements for sulphonamide moiety in **171**, with a view to improve oral absorption, Middleton and coworkers[257] developed a successful synthetic strategy for synthesis of 2-piperidone framework (**173**) from enantiopure starting material **172** according to the reaction sequence as described in Scheme 74.

Scheme 74



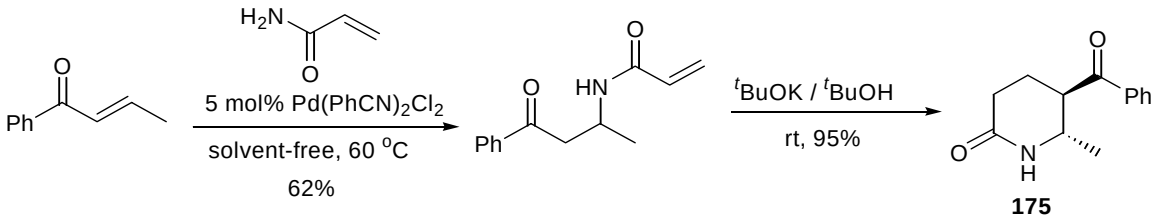
Elworthy and coworkers[258] described an interesting synthesis of enantiomerically pure *N*-substituted 6(*R)*-hydroxymethyl-2-piperidone (**174**) following the reaction sequence as shown in Scheme 75.

Scheme 75



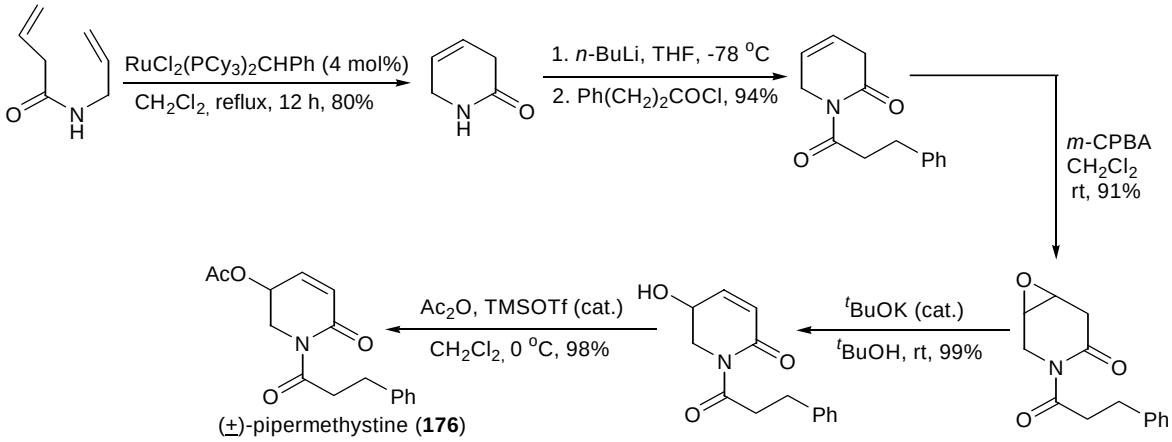
Highly facile synthesis of disubstituted-2-piperidones (**175**) framework involving an interesting sequence of aza-Michael (hydroamidation) reaction and an intramolecular aza-Michael reaction was described by Ihara and coworkers[262] according to Scheme 76.

Scheme 76



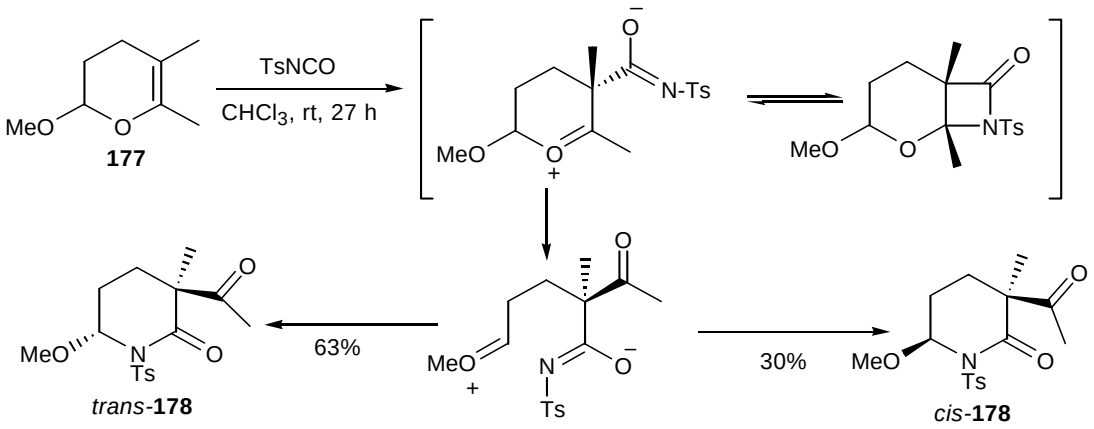
Liebeskind and coworkers[263] described an interesting protocol for synthesis of (±)-pipermethystine (**176**) using a ring closing metathesis as a key step following synthetic sequence as described in Scheme 77.

Scheme 77

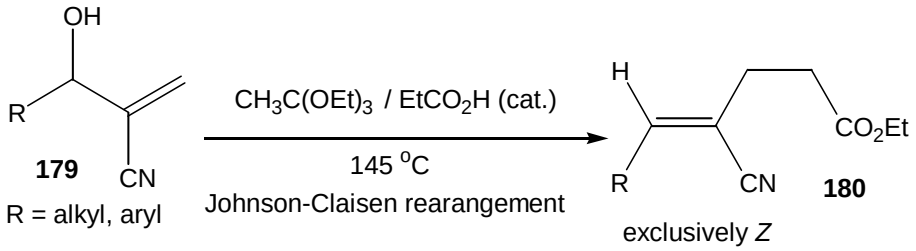


Hall and coworkers[264] reported synthesis of a separable *cis* / *trans* mixture of highly substituted 2-piperidone (**178**) starting from 3,4-dihydro-2-methoxy-5,6-dimethyl-2*H*-pyran (**177**) following the reaction sequence as described in Scheme 78.

Scheme 78



We have sometime ago developed an interesting stereo-defined synthesis of functionalized trisubstituted alkenes *i.e.* ethyl (4*Z*)-4-cyanoalk-4-enoates (**180**) *via* the Johnson-Claisen (Claisen orthoester) rearrangement[265] of the Baylis-Hillman alcohols, *i.e.* 3-hydroxy-2-methylenealkanenitriles (**179**) with triethyl orthoacetate (Eq. 27).[266]

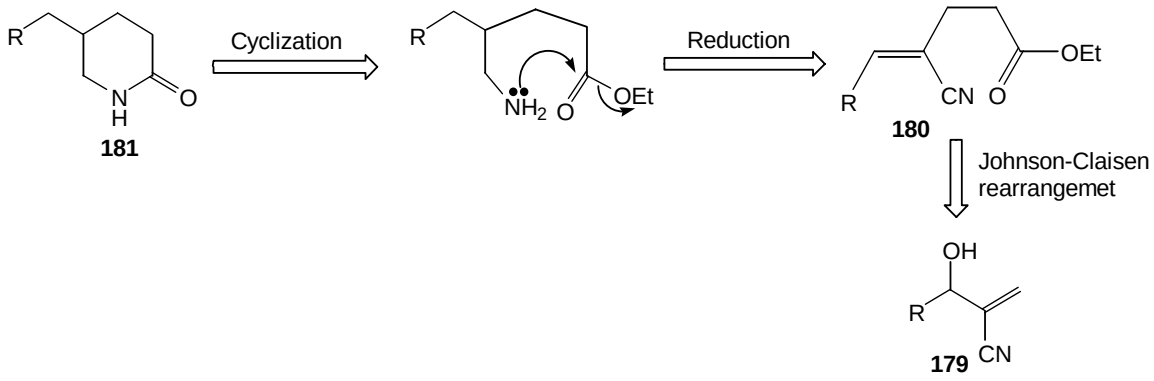


Eq. 27

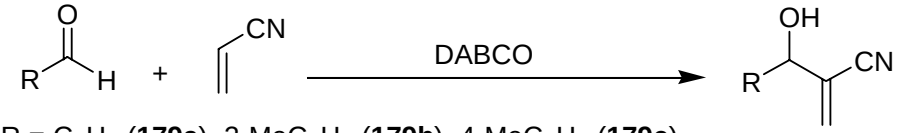
It occurred to us that (4*Z*)-4-cyanoalk-4-enoates (**180**) would be an excellent starting materials for synthesis of 2-piperidone derivatives (**181**) *via* the reduction of cyano group to amino group which would be located in the proximity of ester group for possible cyclization to generate a six membered heterocyclic framework with a provision to have a

different substitution profile at 3rd & 5th position. It also occurred to us that the entire operation can be done in one-pot starting from the Baylis-Hillman adducts involving the Johnson-Claisen rearrangement, reduction of α, β-unsaturated nitrile moiety into amine-skeleton followed by cyclization to 2-piperidone framework (retro-synthetic strategy shown in Scheme 79).

Scheme 79



Accordingly, we have first selected the Baylis-Hillman alcohol, *i.e.*, 3-hydroxy-2-methylene-3-phenylpropanenitrile (**179a**) as a substrate for Johnson-Claisen rearrangement followed by reductive cyclization. The required Baylis-Hillman alcohol was prepared *via* the treatment of benzaldehyde with acrylonitrile in the presence of DABCO (Eq. 28).



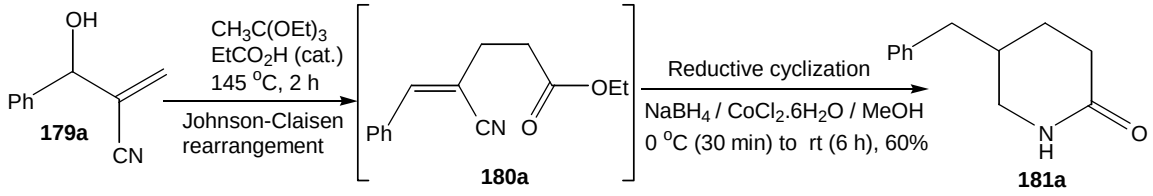
Eq. 28

R = C_6H_5 (**179a**), 2-MeC_6H_4 (**179b**), 4-MeC_6H_4 (**179c**), 4-(*i*-Pr)C_6H_4 (**179d**), 2-ClC_6H_4 (**179e**), 4-ClC_6H_4 (**179f**), $C_6H_5CH_2CH_2$ (**179g**), Pent (**179h**), Hept (**179i**)

179a-i

We have then carried out the Johnson-Claisen rearrangement of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**179a)** with triethyl orthoacetate in the presence of catalytic amount of propanoic acid. Our next target was to develop an *in situ* methodology for reduction of α, β-unsaturated nitrile into amino group. The best results in this direction were obtained using $NaBH_4$ / $CoCl_2.6H_2O$ (Scheme 80).[267,268] Thus, the reaction of **179a** (1 mmol) with triethyl orthoacetate (1 mL) at 145 ^oC in the presence of propanoic acid (3 drops) for 2 h, followed (after removing excess orthoester under reduced pressure) by treatment with $NaBH_4$ (10 mmol) / $CoCl_2.6H_2O$ (2 mmol) in methanol at 0 ^oC for 30 min and then for 6 h at room temperature, provided 5-benzyl-2-piperidone (**181a**) as a colorless solid in 60% isolated yield, after workup and purification by column chromatography (Scheme 80 & Table 3). Structure of this molecule was confirmed by IR, ^1H NMR (Spectrum 17), ^{13}C NMR (Spectrum 18), mass (LCMS) spectral data and elemental analysis.

Scheme 80



This was indeed a very interesting result in the sense that three steps were performed in one-pot to produce the desired 5-benzyl-2-piperidone **181a** in encouraging yield. We have then prepared representative Baylis-Hillman alcohols (**179b-f**) from various aromatic aldehydes and acrylonitrile (Eq. 28). These alcohols were subjected to Johnson-Claisen rearrangement followed by treatment with $NaBH_4$ (10 mmol) / $CoCl_2.6H_2O$ (2 mmol) to

provide the 5-(substituted-benzyl)-2-piperidones (**181b-f**) in 53-64% isolated yields (Scheme 81 & Table 3). Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 19, for compound **181d**), ^{13}C NMR (Spectrum 20, for compound **181d**), mass (LCMS) spectral data and elemental analyses.

With a view to understand the generality of this strategy we have also prepared the representative Baylis-Hillman alcohols (**179g-i**), from corresponding aliphatic aldehydes (hydrocinnamaldehyde, hexanal & octanal) and acrylonitrile as shown in Eq. 28. We have also successfully transformed Baylis-Hillman alcohols (**179g-i)** into 5-alkyl-2-piperidones (**181g-i)** into 59-67% isolated yields *via* the Johnson-Claisen rearrangement followed by reductive cyclization using $NaBH_4$ / $CoCl_2.6H_2O$ (Scheme 81 & Table 3). Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 21, for compound **181i**), ^{13}C NMR (Spectrum 22, for compound **181i**), mass (LCMS) spectral data and elemental analyses. We obtained, single crystals for **181c** & **181g** and further confirmed the structures of these molecules by the single crystal X-ray data (Figures X5 & X6 and Tables V & VI).

Scheme 81

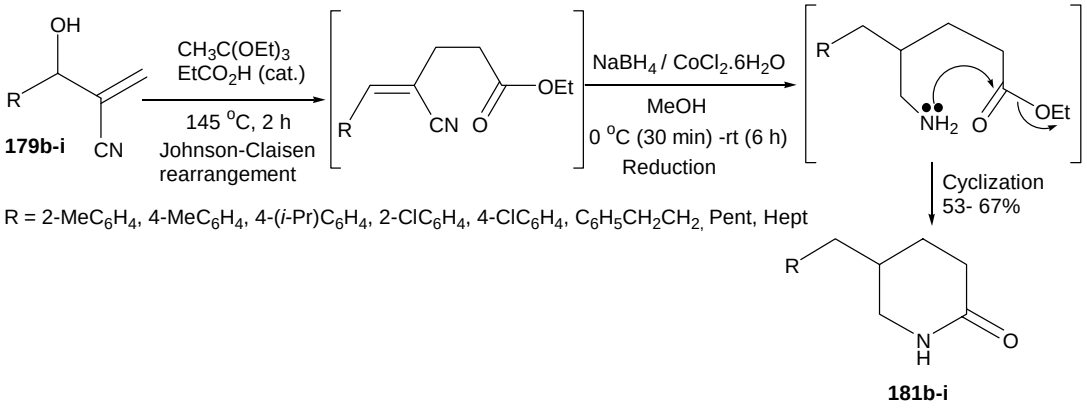
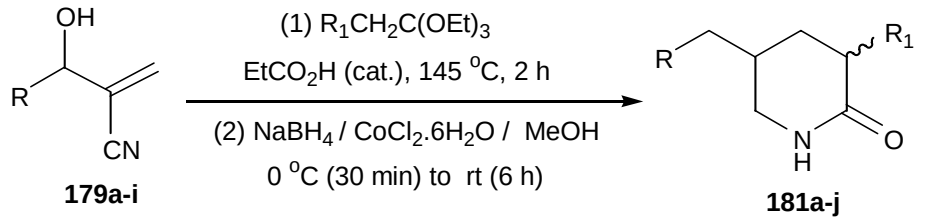


Table 3 One-pot multistep synthesis of substituted-2-piperidones (**181a-j**)[a] from the Baylis-Hillman alcohols (**179a-i**)



179a-i **181a-j**

B-H alcohol	R	R_1	Product[b]	Yield[c] (%)	Mp (°C)
179a	C_6H_5	H	**181a**	60	107-109
179b	2-MeC_6H_4	H	**181b**	58	103-105
179c	4-MeC_6H_4	H	**181c**[d]	64	111-113
179d	4-(*i*-Pr)C_6H_4	H	**181d**	56	91-93
179e	2-ClC_6H_4	H	**181e**	53	106-108
179f	4-ClC_6H_4	H	**181f**	55	109-111
179g	$C_6H_5CH_2CH_2$	H	**181g**[d]	59	88-90
179h	Pent	H	**181h**	67	43-45
179i	Hept	H	**181i**	65	59-61
179a[e]	C_6H_5	Me	**181j**[e]	61	84-86

(a) All reactions were carried out on a 1 mmol scale of Baylis-Hillman alcohols (**179a-i**) with orthoacetate (1 mL) at 145 °C in the presence of catalytic amount of propanoic acid (3 drops) for 2 h. Excess orthoester was distilled off under reduced pressure. The residue, thus obtained, was treated with $NaBH_4$ (10 mmol) in the presence of $CoCl_2.6H_2O$ (2 mmol) in methanol (8 mL) at 0 °C for 30 min and then room temperature for 6 h.

(b) All the compounds (**181a-j**) were obtained as colorless solids and were characterized by IR, ^1H NMR (400 MHz), ^{13}C NMR (50 MHz), mass (LCMS) spectral data and elemental analyses.

(c) Yields are of the pure products **181a-j** (based on B-H alcohols) after purification through silica gel column chromatography (silica gel, 100% EtOAc).

(d) The structures of these molecules were also established from the single crystal X-ray data (Figures X5 & X6 and Tables V & VI).

(e) This reaction was performed with triethyl orthopropanoate and the product was obtained as a 1:1 mixture of diastereomers as evidenced by NMR spectral analysis.

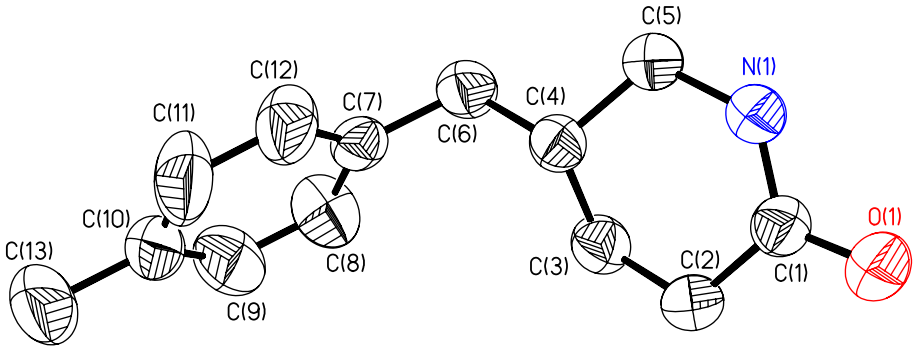


Figure X5 ORTEP diagram of compound **181c**
(Hydrogen atoms were omitted for clarity)

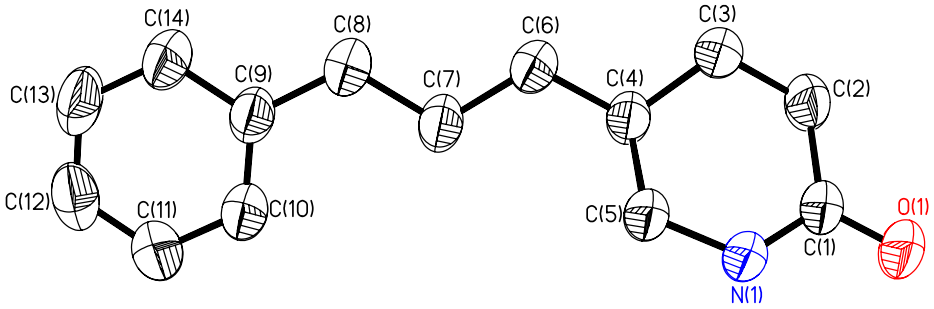
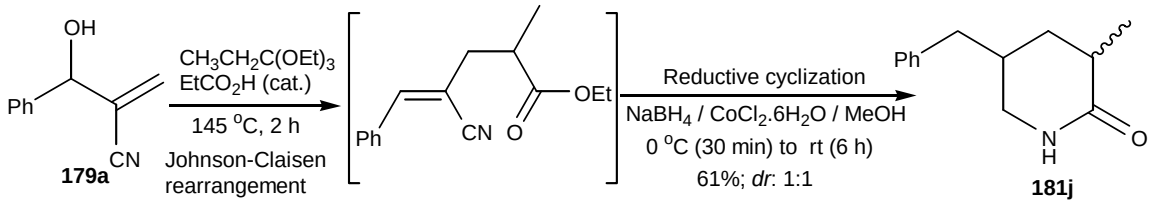


Figure X6 ORTEP diagram of compound **181g**
(Hydrogen atoms were omitted for clarity)

With a view to extend the possibility of this strategy for the preparation of 3,5-disubstututed-2-piperidone framework we have used triethyl orthopropanoate for the Johnson-Claisen rearrangement. Thus, the Baylis-Hillman alcohol **179a** on successive treatment with triethyl orthopropanoate and $NaBH_4$ / $CoCl_2{\cdot}6H_2O$ following the same

strategy (as in case of triethyl orthoacetate) provided 5-benzyl-3-methyl-2-piperidone (**181j**) in 61% isolated yield (Scheme 82 & Table 3). However, ^{1}H and ^{13}C NMR spectra clearly indicate that this molecule is ≈1:1 mixture of diastereomers. In ^{1}H NMR (Spectrum 23) methyl protons (at C-3 position) on the 2-piperidone ring appeared as two doublets of equal intensities at δ 1.19 & 1.23, thus indicating this molecule as a ≈1:1 mixture of diastereomers. Two singlets of equal intensities at δ 6.46 & 6.50 are attributed to the NH–protons of the diastereomers (≈1:1 ratio). ^{13}C NMR (Spectrum 24) shows two peaks at δ 175.68 & 176.23 for one carbonyl carbon, two peaks at δ 139.17 & 139.39 for one quaternary aromatic carbon and twelve aliphatic peaks for six aliphatic carbons (of similar intensities), which clearly indicate that this compound is a mixture of diastereomers.

Scheme 82



In conclusion, we have successfully developed a convenient and operationally simple one-pot multistep procedure for the synthesis of 5-substituted / 3,5-disubstituted-2-piperidones (**181a-j**) from the Baylis-Hillman alcohols (**179a-i**), *via* the Johnson-Claisen rearrangement, reduction of α, β-unsaturated nitrile to amine followed by cyclization, thus demonstrating the application of Baylis-Hillman adducts as a valuable source for one-pot multistep synthesis.

Table V: Crystal data collection and structure refinement for the compound **181c**

Empirical formula	: $C_{13}H_{17}NO$
Formula weight	: 203.28
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: $P2_1/c$ (*International Table # 14*)
Unit cell dimensions	: a = 14.335(5) Å; α = 90 deg.
	: b = 5.812(2) Å; β = 96.357(6) deg.
	: c = 14.026(5) Å; γ = 90 deg.
Volume	: 1161.4(7) $Å^3$
Z, Calculated density	: 4, 1.163 g/cm^3
Absorption coefficient	: 0.073 mm^{-1}
F(000)	: 440
Crystal size	: 0.42 X 0.21 X 0.07 mm
Theta range for data collection	: 1.43 to 26.27 deg.
Limiting indices	: $-17 \le h \le 17$, $-7 \le k \le 7$, $-17 \le l \le 17$
Reflections collected / unique	: 11271 / 2316 [R(int) = 0.0270]
Completeness to theta = 25.00	: 98.7%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2316 / 0 / 138
Goodness-of-fit on F^2	: 1.041
Final R indices [I>2sigma(I)]	: R1 = 0.0464, wR2 = 0.1246
R indices (all data)	: R1 = 0.0684, wR2 = 0.1386
Largest diff. peak and hole	: 0.227 and -0.131 e. $Å^{-3}$

Table VI: Crystal data collection and structure refinement for the compound **181g**

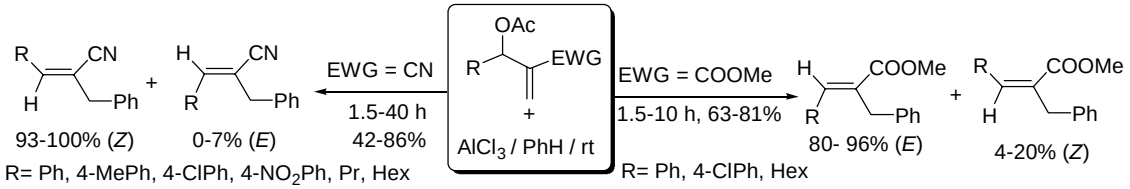
Empirical formula	: $C_{14}H_{19}NO$
Formula weight	: 217.30
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P–1 (*International Table # 2*)
Unit cell dimensions	: a = 5.8744(15) Å; α = 74.375 deg.
	: b = 8.040(2) Å; β = 89.430(4) deg.
	: c = 14.260(4) Å; γ = 73.780 deg.
Volume	: 621.2(3) $Å^3$
Z, Calculated density	: 2, 1.162 g/cm^3
Absorption coefficient	: 0.072 mm^{-1}
F(000)	: 236
Crystal size	: 0.46 X 0.38 X 0.23 mm
Theta range for data collection	: 1.49 to 26.07 deg.
Limiting indices	: $-7 \le h \le 7$, $-9 \le k \le 9$, $-17 \le l \le 17$
Reflections collected / unique	: 4966 / 4966 [R(int) = 0.0000]
Completeness to theta = 26.07	: 99.2%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2438 / 0 / 150
Goodness-of-fit on F^2	: 1.023
Final R indices [I>2sigma(I)]	: R1 = 0.0571, wR2 = 0.1589
R indices (all data)	: R1 = 0.0716, wR2 = 0.1714
Largest diff. peak and hole	: 0.225 and -0.205 e. $Å^{-3}$

Regioselective phenylation of the Baylis-Hillman adducts via the Friedel-Crafts reaction with benzene

Friedel-Crafts reaction is one of the most popular carbon-carbon bond forming reaction and has been extensively used in various aspects of organic synthesis including the preparation of important natural and bioactive molecules.[269,270] The Baylis-Hillman adducts / acetates have been successfully employed as a valuable substrate for Friedel-Crafts reaction.[271-275] Some of the interesting developments on the applications of Baylis-Hillman adducts / acetates as substrates for Friedel-Crafts reaction are presented in the section.

Our research group has demonstrated the utility of acetates of the Baylis-Hillman adducts as novel stereo-defined β-electrophiles in the Friedel-Crafts reaction with benzene under the influence of $AlCl_3$ leading to the stereoselective synthesis of (*Z*)- and (*E*)-functionalized trisubstitued alkenes (Scheme 83).[271]

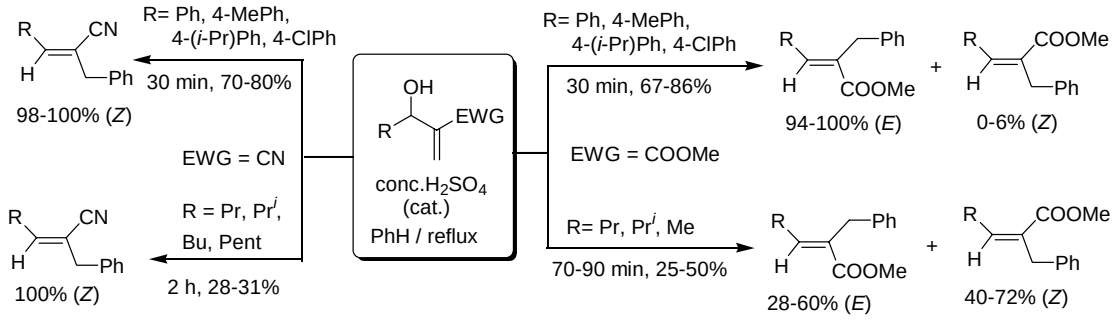
Scheme 83



Subsequently, our research group[272] has developed a simple and convenient methodology for the stereoselective synthesis of both (*E*)- and (*Z*)-trisubstituted olefins *via* the sulfuric

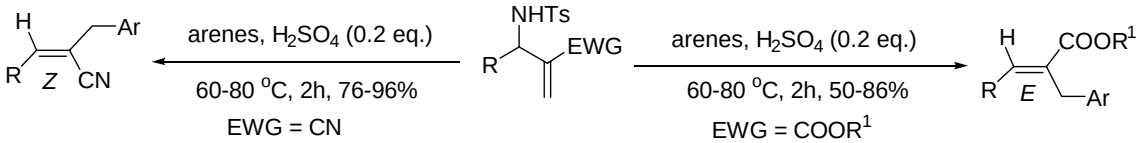
acid (thus avoiding the use of $AlCl_3$ in performing the Friedel-Crafts reaction) catalyzed Friedel-Crafts reaction of Baylis-Hillman adducts with benzene as described in Scheme 84.

Scheme 84



Later on, Kim and coworkers[273] have reported the Friedel-Crafts reaction of the Baylis-Hillman adducts of *N*-tosylimine derivatives with arenes in the presence of sulfuric acid providing a stereoselctive methodology for the synthesis of (*E*)- and (*Z*)-2-benzyl trisubstituted olefins (Scheme 85). They have also employed chlorobenzene and toluene for the Friedel-Crafts reaction which provided the products as a mixture of *ortho*- and *para*-isomers.

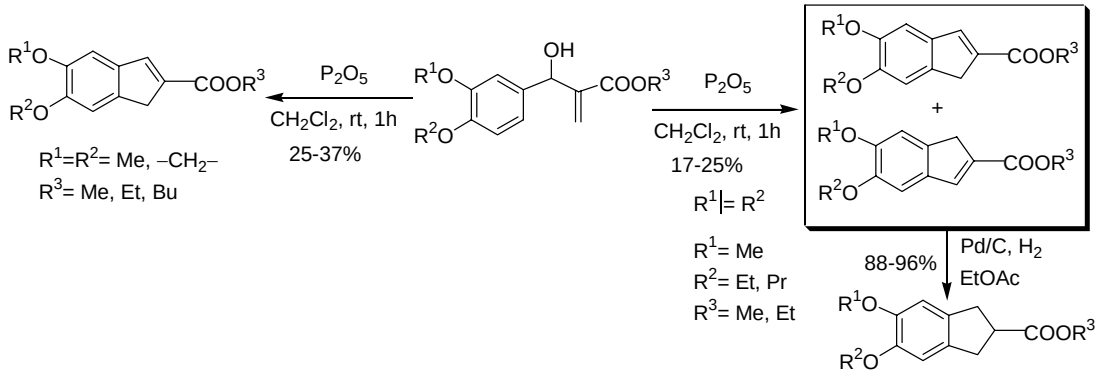
Scheme 85



Our research group[274] has described an interesting intramolecular Friedel-Crafts reaction of the Baylis-Hillman adducts, containing electron releasing group on aromatic ring, in the presence of P_2O_5, thus providing a convenient process for the synthesis of indene

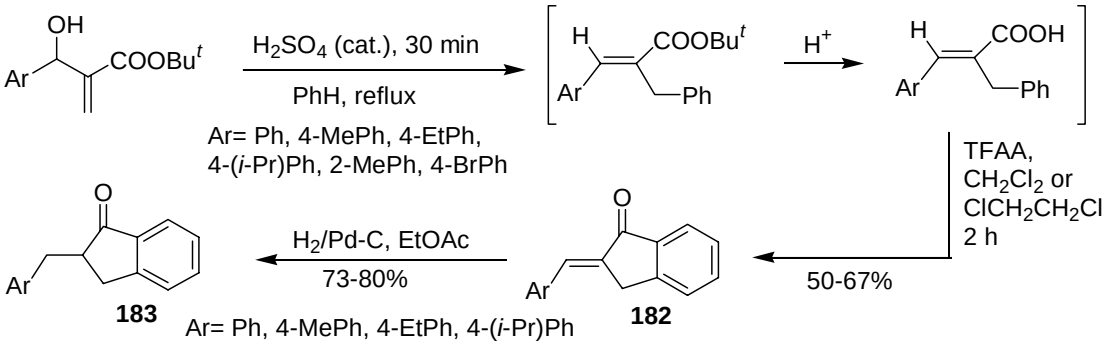
derivatives though in low yields and as a mixture of isomers**.** These indene derivatives were further hydrogenated to the corresponding indane derivatives (Scheme 86).

Scheme 86



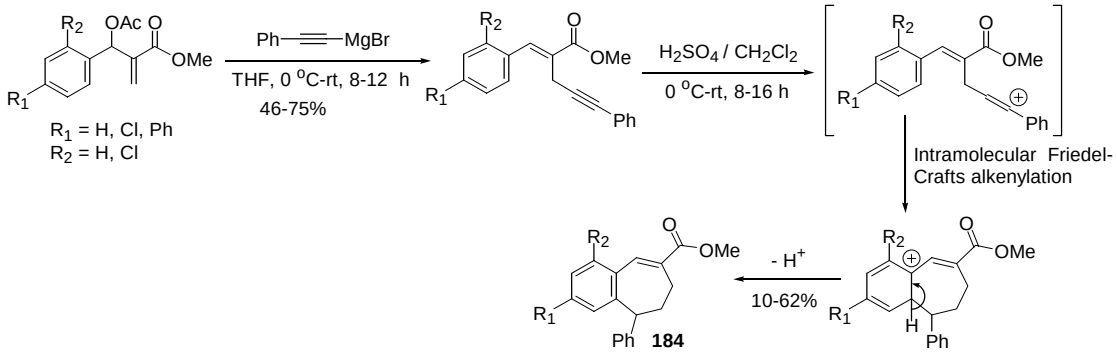
Subsequently, a simple one-pot stereoselective transformation of *tert*-butyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis-Hillman adducts obtained from *tert*-butyl acrylate and aromatic aldehydes, into (*E*)-2-arylideneindan-1-ones (**182**) involving one inter- and one intramolecular Friedel-Crafts reactions has been developed by our research group[275] according to the Scheme 87. These compounds were further transformed to the corresponding 2-arylmethylindan-1-ones (**183**) *via* the catalytic hydrogenation (5% Pd / C) as shown in Scheme 87.

Scheme 87



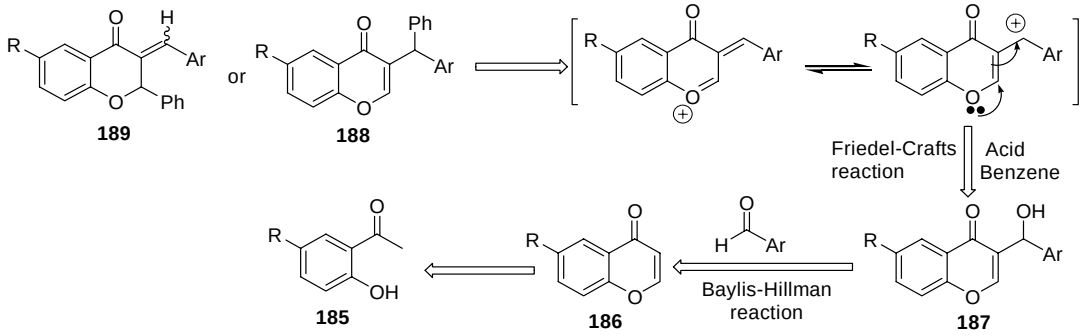
A facile synthesis of 7*H*-benzocycloheptene derivatives (**184**) from acetates of the Baylis-Hillman adducts was developed by Kim and coworkers[276] according to reaction sequence as described in Scheme 88.

Scheme 88

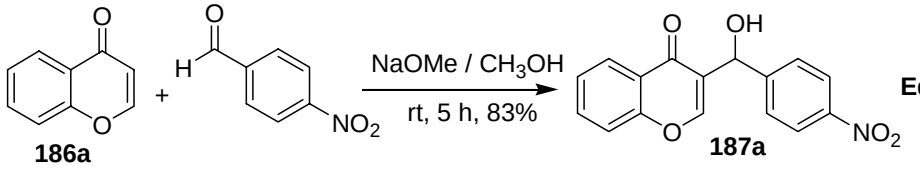


Although the chromone derivatives were employed as activated alkenes in Baylis-Hillman reaction, the applications of these adducts are not well studied in organic synthesis. Therefore, we have, undertaken to examine the possible application of these adducts, *i.e.* 3-[hydroxy(aryl)methyl]-4*H*-chromen-4-ones (**187**), obtained from chromones (**186**) (derived from 2′-hydroxyacetophenones **185**) and aldehydes, as substrates in the Friedel-Crafts reaction with benzene and also with a view to understand the regioselectivity of phenylation (**188** & **189**) in this reaction, as described in retro-synthetic Scheme 89.

Scheme 89



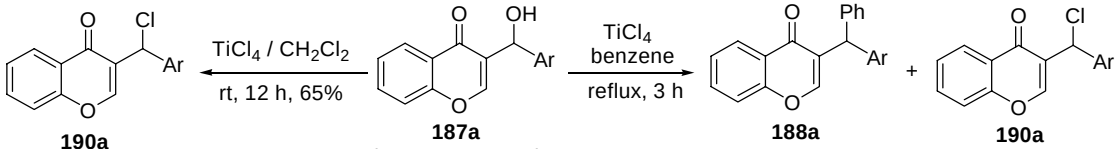
Accordingly, we have first selected the Baylis-Hillman alcohol, *i.e.*, 3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187a**) as a substrate for our study. The required Baylis-Hillman alcohol (**187a**), was obtained *via* the treatment of 1-benzopyran-4(4*H*)-one (**186a**) with 4-nitrobenzaldehyde in the presence of NaOMe[$] in methanol, according to literature procedure,[277] as described in Eq. 29 (Table 4).



186a **187a** **Eq. 29**

Next we have planned to examine the Friedel-Crafts reaction of 3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187a**) with benzene in the presence of various Lewis acids / acids. In this direction, we have first carried out, the reaction of **187a** with benzene in the presence of $TiCl_4$ (Scheme 90 & Table 5). We have, in fact, obtained the desired product (**188a)** though in low yield (19%) along with the allyl chloride (**190a)** as the major product (81%) as evidenced by ^1H & ^{13}C NMR spectral data analysis. With view to obtain the allyl chloride (**190a)** exclusively**,** we have conducted the same reaction in dichloromethane without benzene for 12 h and indeed obtained the allyl chloride (**190a**), as a colorless solid in 65% yield (Scheme 90). Structure of this molecule was confirmed by IR, ^1H NMR, ^{13}C NMR and mass (LCMS) spectral data.

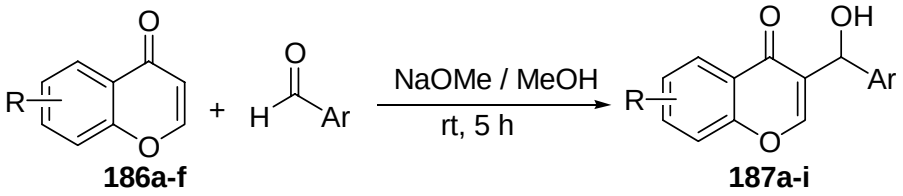
Scheme 90



190a **187a** (Ar = 4-$NO_2C_6H_4$) **188a** mixture of **188a**:**190a** = 19 : 81 **190a**

[$] Due to the faster reaction rate we have used NaOMe / MeOH instead of methanolic-Me_3N.[55]

Table 4 Synthesis of 3-[hydroxy(3- / 4-nitrophenyl)methyl]-4*H*-chromen-4-ones (**187a-i**)[a]



186a-f **187a-i**

Chromones	R	Ar	Product[b]	Yield[c] (%)	Mp (^{o}C)
186a	H	4-$NO_2C_6H_4$	**187a**	83	188-189
186a	H	3-$NO_2C_6H_4$	**187b**	75	135-137
186b	6-Me	4-$NO_2C_6H_4$	**187c**	87	199-200
186b	6-Me	3-$NO_2C_6H_4$	**187d**	71	155-157
186c	6-Cl	4-$NO_2C_6H_4$	**187e**	60	175-177
186d	6-Br	4-$NO_2C_6H_4$	**187f**	64	186-188
186e	5,6-benzo-	4-$NO_2C_6H_4$	**187g**	79	160-161
186e	5,6-benzo-	3-$NO_2C_6H_4$	**187h**	68	151-153
186f	7,8-benzo-	4-$NO_2C_6H_4$	**187i**	78	201-203

(a) All reactions were carried out on a 5 mmol scale of chromones (**186a-f**) with 5 mmol of various 3- / 4-nitrobezaldehydes in the presence of 50 mol% of NaOMe in MeOH (10 mL) at room temperature for 5 h.

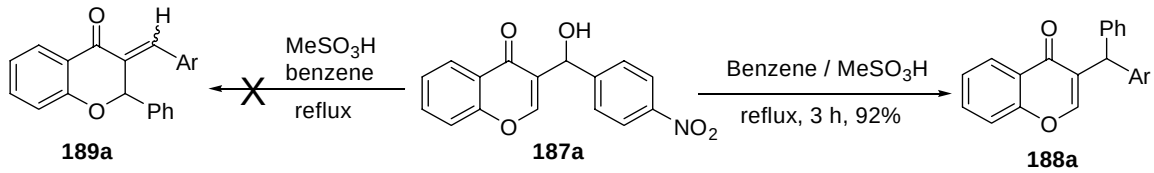
(b) All the compounds (**187a-i)** were characterized by by IR, ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectral data.

(c) Yields are of the pure products **187a-i** based on chromone derivatives **186a-f**.

These results clearly show that $TiCl_4$ is not the appropriate Lewis acid for the phenylation reaction. Therefore, we have selected other Lewis acids, such as, $FeCl_3$ & $BF_3{\cdot}OEt_2$ and also various non-nucleophilic protic acids (H_2SO_4, TFA, *p*-TSA & $MeSO_3H$) to perform the Friedel-Crafts reaction of **187a** with benzene (Table 5 & entries 2-10). The best results,

in this direction were obtained, when we treated **187a** (1 mmol) with benzene (5 mL) in the presence of methanesulfonic acid (2 mmol) at reflux temperature for 3 hrs, thus providing 3-[(4-nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (**188a**), as a colorless solid in 92% yield (Scheme 91, Table 5 & entry 9) after workup followed by purification through silica gel column chromatography (15% EtOAc in hexanes). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 25), ^{13}C NMR (Spectrum 26), mass (LCMS) spectral data and elemental analysis. The structure of this molecule (**188a**) was further confirmed by single crystal X-ray data (Figure X7 & Table VII). It is interesting to note this Friedel-Crafts reaction did not provide any traces of the other (theoretically possible) regio-isomer (**189a**) as mentioned in retro-synthetic Scheme 89.

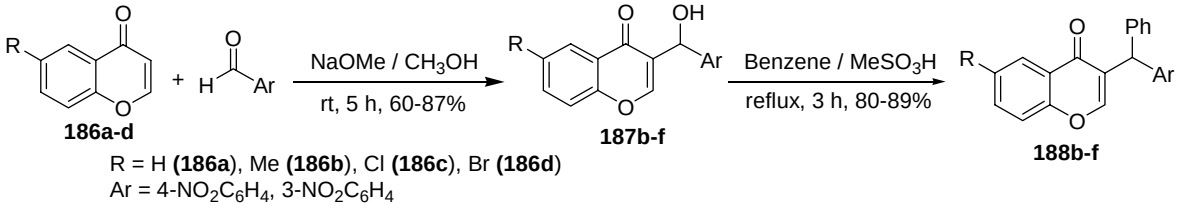
Scheme 91



With a view to understand the generality this reaction we have prepared a representative class of Baylis-Hillman alcohols, *i.e.* 3-[hydroxy(3 / 4-nitrophenyl)methyl]-4*H*-chromen-4-ones (**187b-f)**, *via* the reaction of various chromones (**186a-d**) with 3 / 4-nitrobenzaldehydes in the presence of sodium methoxide in methanol (Scheme 92 & Table 4). Structures of these molecules were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. We have then successfully transformed these Baylis-Hillman alcohols (**187b-f**)^{f} *via* the reaction of benzene under the influence of methanesulfonic acid, into 3-[(3- / 4-nitro-

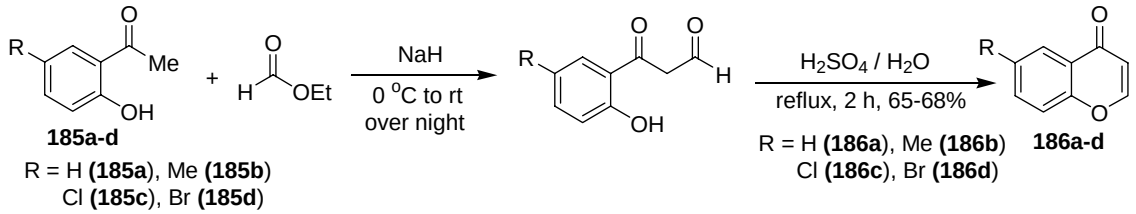
phenyl)phenylmethyl]-4*H*-chromen-4-ones (**188b-f**)[f] in 80-89% isolated yields (Scheme 92 & Table 6). Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 27, for compound **188c**), ^{13}C NMR (Spectrum 28, for compound **188c**), mass (LCMS) spectral data and elemental analysis.

Scheme 92



The required 1-benzopyran-4(4*H*)-one derivatives (**186a-d**), were prepared starting from the corresponding 2′-hydroxyacetophenones (**185a-d**), according to the literature procedure as described in Scheme 93.[278]

Scheme 93



The required 5′-halo-2′-hydroxyacetophenones (**185c & d**), were prepared from the corresponding 4-halophenols, according to literature as described Scheme 94.[279]

---

[f] For continuity and easy understanding the Baylis-Hillman alcohols (derived from various chromones **186a-f** and 3 / 4-nitrobezaldehydes) are numbered as **187a-i** respectively. Similarly, the Friedel-Crafts products, derived from B-H alcohols (**187a-i),** are numbered as **188a-i** respectively.

Scheme 94

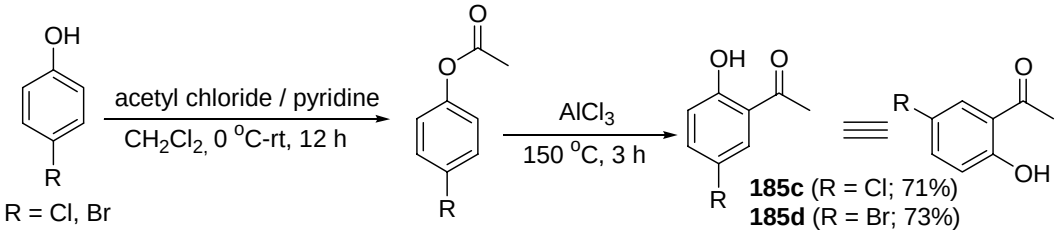
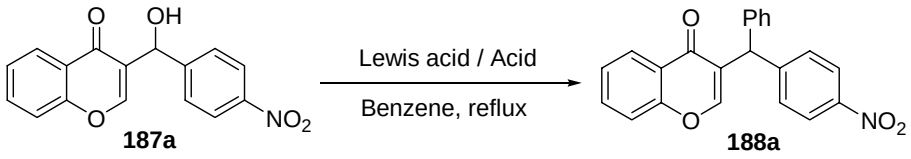


Table 5 Standardization: Phenylation of the 3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187a**)[a] with various Lewis acids / acids in benzene



Entry	Lewis acid / Acid	Time (hrs)	Yield (%)
1	$TiCl_4$ (1.5 mmol)	3	Mixture[b]
2	$FeCl_3$ (1.5 mmol)	3	78
3	$BF_3.OEt_2$ (1.5 mmol)	5	70
4	H_2SO_4 (1.5 mmol)	5	68
5	*p*-TSA (1.5 mmol)	10	52[c]
6	TFA (1.5 mmol)	5	67[c]
7	$MeSO_3H$ (1 mmol)	8	80
8	$MeSO_3H$ (1.5 mmol)	4	88
9	**$MeSO_3H$ (2 mmol)**	**3**	**92**
10	$MeSO_3H$ (2.5 mmol)	3	90

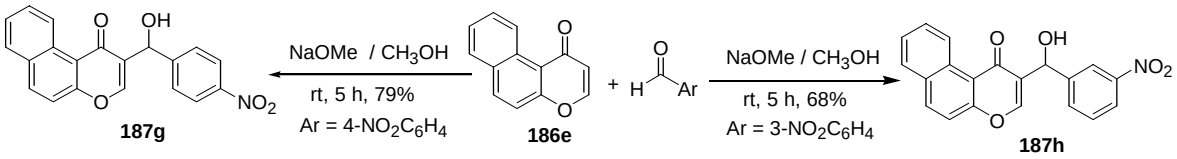
(a) All reactions were carried out on a 1 mmol scale of Baylis-Hillman alcohol (**187a**) with benzene (5 mL) in the presence of various Lewis acids / acids at reflux temperature.

(b) Obtained as a mixture of **188a** and allyl chloride **190a** (confirmed by ^{1}H NMR and ^{13}C NMR spectral data analysis).

(c) In the case of entries 5 & 6, starting material **187a** was recovered, 30% & 20% respectively.

With a view to extended the scope of this methodology we have next selected 5,6-benzochromone (**186e**). We have prepared the required Baylis-Hillman alcohols, *i.e.* 3-[hydroxy(3 /4-nitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-ones (**187g** & **187h**), *via* the treatment of 5,6-benzochromone (**186e**) with 3 / 4-nitrobenzaldehydes in the presence of sodium methoxide in methanol, as described in Scheme 95 (Table 4). Structures of these molecules were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Scheme 95



We have then successfully employed the Baylis-Hillman alcohols (**187g** & **187h)**, for the Friedel-Crafts reaction with benzene under the influence of methanesulfonic acid to provide the desired products **188g** & **188h** in 86% & 83% isolated yields respectively (Scheme 96 & Table 6). Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 29, for compound **188h**), ^{13}C NMR (Spectrum 30, for compound **188h**), mass (LCMS) spectral data and elemental analyses. We have, in fact, obtained single crystal for the compound **188g** and further confirmed the structure of this molecule by the single crystal X-ray data (Figure X8 & Table VIII).

Scheme 96

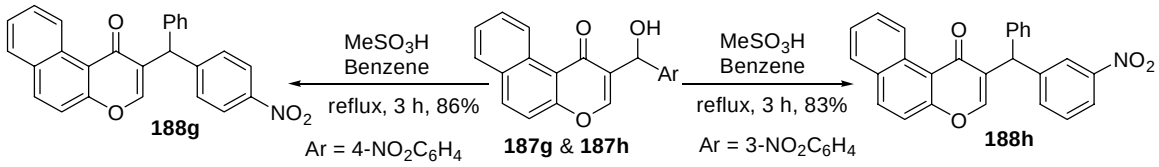
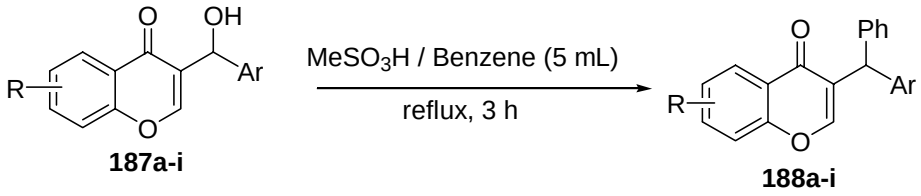


Table 6 Regioselective phenylation[#] of 3-[hydroxy(3- /4-nitrophenyl)methyl]-4*H*-chromen-4-one derivatives (**187a-i**)[a]



187a-i **188a-i**

B-H alcohol	R	Ar	Product[b]	Yield[c] (%)	Mp (^{o}C)
187a	H	4-$NO_2C_6H_4$	**188a**[d]	92	116-118
187b	H	3-$NO_2C_6H_4$	**188b**	80	111-113
187c	6-Me	4-$NO_2C_6H_4$	**188c**	89	168-169
187d	6-Me	3-$NO_2C_6H_4$	**188d**	82	79-81
187e	6-Cl	4-$NO_2C_6H_4$	**188e**	84	163-165
187f	6-Br	4-$NO_2C_6H_4$	**188f**	81	171-173
187g	5,6-benzo-	4-$NO_2C_6H_4$	**188g**[d]	86	179-181
187h	5,6-benzo-	3-$NO_2C_6H_4$	**188h**	83	142-144
187i	7,8-benzo-	4-$NO_2C_6H_4$	**188i**	78	168-170

(a) All reactions were carried out on a 1 mmol scale of Baylis-Hillman alcohols (**187a-i**), with benzene (5 mL) in the presence of $MeSO_3H$ (2 mmol) at reflux for 3 h.

(b) All the compounds (**188a-i)** were obtained as colorless solids and were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass (LCMS) spectral data and elemental analyses.

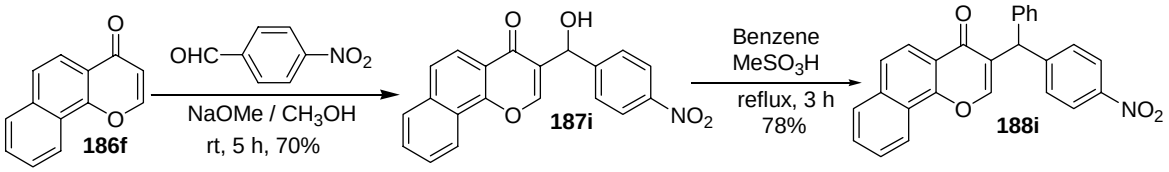
(c) Yields are of the pure products (**188a-i**) based on B-H alcohols (**187a-i**) after purification through silica gel column chromatography (silica gel, 15% EtOAc in hexanes).

(d) The structures of these molecules were also established from the single crystal X-ray data (Figures X7 & X8 and Tables VII & VIII).

[#] The regioselective phenylation of **187a-i** (leading to the exclusive formation of **188a-i**) may be attributed to the steric factors present either in the transition state in the formation of **189** or in the product (**189**) itself (page nos. 85 & 88).

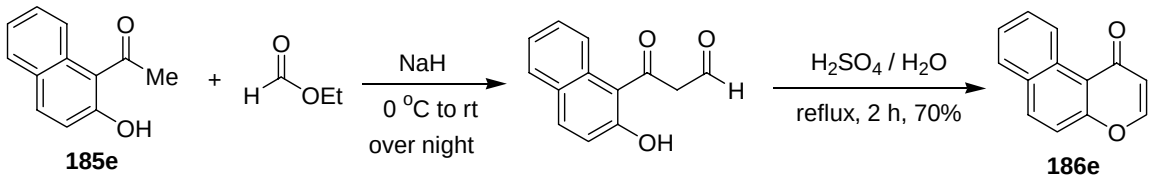
Encouraged by these results, we have also prepared the Baylis-Hillman alcohol *i.e*., 3-[hydroxy(4-nitrophenyl)methyl]-7,8-benzo-4*H*-chromen-4-one (**187i**) *via* the reaction of 7,8-benzochromone (**186f**) with 4-nitrobenzaldehyde in the presence of sodium methoxide in methanol as described in Scheme 97 (Table 4). Structure of this molecule (**187i**) was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. Then, we have also successfully transformed the Baylis-Hillman alcohol (**187i**), into the desired Friedel-Crafts products, 3-[(4-nitrophenyl)phenylmethyl]-7,8-benzo-4*H*-chromen-4-one (**188i**) under similar reaction condition (Scheme 97 & Table 6). Structure of this molecule (**188i**) was confirmed by IR, ^{1}H NMR (Spectrum 31), ^{13}C NMR (Spectrum 32), mass (LCMS) spectral data and elemental analysis.

Scheme 97

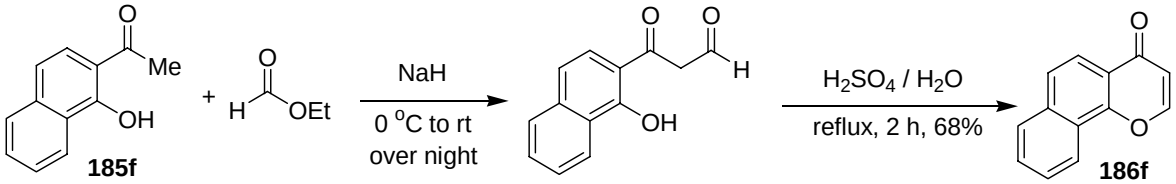


The required 5,6-benzochromone (**186e**) & 7,8-benzochromone (**186f**), were prepared *via* the reaction of 1-acetyl-2-naphthol (**185e**) & 2-acetyl-1-naphthol (**185f**) with ethyl formate respectively, according to the literature procedure,[278] as described in Schemes 98 & 99.

Scheme 98



Scheme 99



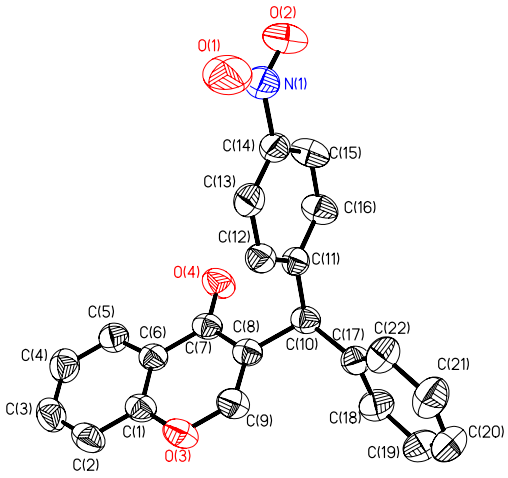


Figure X7 ORTEP diagram of compound **188a**
(Hydrogen atoms were omitted for clarity)

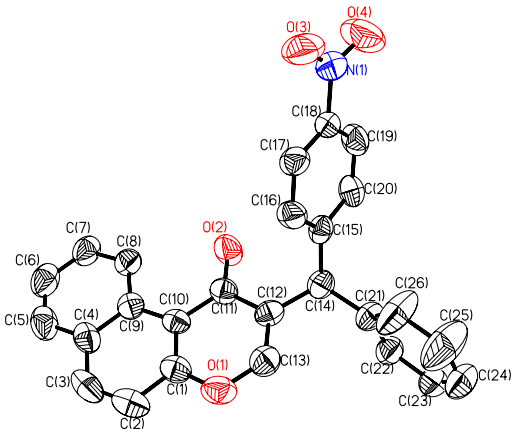
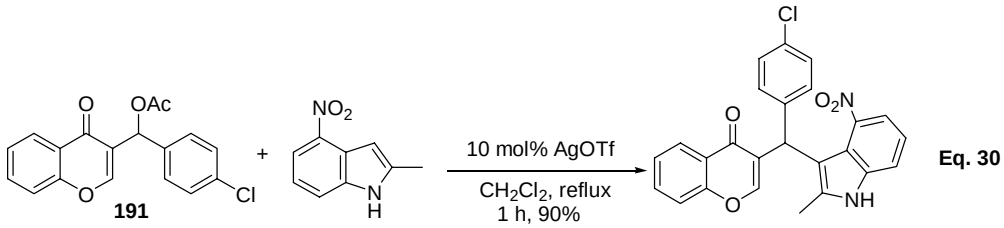


Figure X8 ORTEP diagram of compound **188g**
(Hydrogen atoms were omitted for clarity)

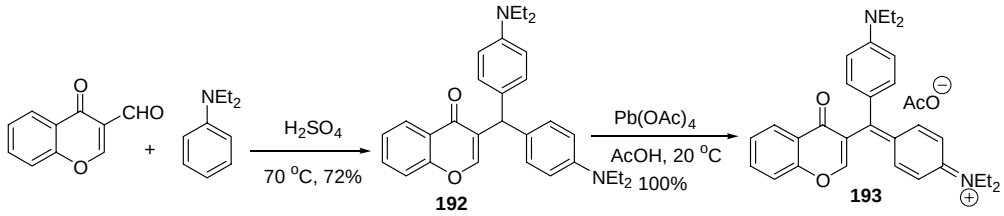
It is worth describing here the work of Chen and coworkers[280] who reported a mild and efficient regioselective nucleophilic substitution of acetate of the Baylis-Hillman adduct (**191**) with indoles under the catalytic influence of AgOTf (Eq. 30).



Eq. 30

It is also quite appropriate to mention here the work of Harnisch who reported the formation of di(4-diethylphenylamine)methylchromone (**192**), *via* the addition of diethylaniline to the 3-formylchromone, in the presence of H_2SO_4. This product was subsequently oxidized to the diarylmethine dye (**193**) with $Pb(OAc)_2$ in AcOH as described in Scheme 100.[281]

Scheme 100



In conclusion, we have developed a facile and operationally simple methodology for regioselective phenylation of Baylis-Hillman alcohols, *i.e.,* 3-[hydroxy(3- / 4-nitrophenyl)-methyl]-4*H*-chromen-4-one derivatives (**187a-i**), derived from various chromone derivatives (**186a-i**) and 3-/4-nitrobenzaldehydes, *via* the Friedel-Crafts reaction with benzene, thus demonstrating the application of Baylis-Hillman adducts in synthetic organic chemistry.

Table VII: Crystal data collection and structure refinement for the compound **188a**

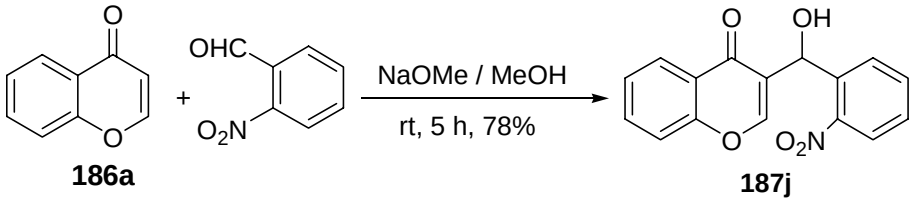
Empirical formula	: $C_{22}H_{15}NO_4$
Formula weight	: 357.36
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: $P2_1/n$ (*International Table # 14*)
Unit cell dimensions	: a = 16.1911(14) Å; α = 90 deg.
	: b = 5.7489(5) Å; β = 92.6340(10) deg.
	: c = 19.2077(16) Å; γ = 90 deg.
Volume	: 1786.0(3) $Å^3$
Z, Calculated density	: 4, 1.440 g/cm^3
Absorption coefficient	: 0.129 mm^{-1}
F(000)	: 792
Crystal size	: 0.41 X 0.36 X 0.21 mm
Theta range for data collection	: 1.68 to 26.03 deg.
Limiting indices	: $-19 \le h \le 19$, $-7 \le k \le 7$, $-23 \le l \le 23$
Reflections collected / unique	: 17596 / 3509 [R(int) = 0.0547]
Completeness to theta = 26.03	: 99.9%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3509 / 0 / 244
Goodness-of-fit on F^2	: 1.045
Final R indices [I>2sigma(I)]	: R1 = 0.0446, wR2 = 0.1131
R indices (all data)	: R1 = 0.0571, wR2 = 0.1199
Largest diff. peak and hole	: 0.165 and -0.201 e. $Å^{-3}$

Table VIII: Crystal data collection and structure refinement for the compound **188g**

Empirical formula	: $C_{26}H_{17}NO_4$
Formula weight	: 357.36
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: $P2_1/n$ (*International Table # 14*)
Unit cell dimensions	: a = 15.810(3) Å; α = 90 deg.
	: b = 12.487(5) Å; β = 91.263(3) deg.
	: c = 10.2660(16) Å; γ = 90 deg.
Volume	: 2026.2(6) $Å^3$
Z, Calculated density	: 4, 1.446 g/cm^3
Absorption coefficient	: 0.130 mm^{-1}
F(000)	: 902
Crystal size	: 0.42 X 0.38 X 0.30 mm
Theta range for data collection	: 2.08 to 26.01 deg.
Limiting indices	: $-19 \le h \le 19$, $-15 \le k \le 15$, $-12 \le l \le 12$
Reflections collected / unique	: 20396 / 3962 [R(int) = 0.0971]
Completeness to theta = 26.01	: 99.3%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3962 / 0 / 280
Goodness-of-fit on F^2	: 0.997
Final R indices [I>2sigma(I)]	: R1 = 0.0669, wR2 = 0.1289
R indices (all data)	: R1 = 0.1611, wR2 = 0.1556
Largest diff. peak and hole	: 0.152 and -0.129 e. $Å^{-3}$

A facile methodology for one-pot conversion of Baylis-Hillman adducts into tetra / penta cyclic chromone fused quinoline *N*-oxides

After successfully developing phenylation of various Baylis-Hillman alcohols, derived from the chromone derivatives and 3- / 4-nitrobenzaldehydes, with a view to understand the generality and also to extend the scope of this reaction, we have examined the possible Friedel-Crafts reaction of the Baylis-Hillman alcohol, *i.e.* 3-[hydroxy(2-nitrophenyl)-methyl]-4*H*-chromen-4-one (**187j**),[∇] obtained *via* the treatment of 1-benzopyran-4(4*H*)-one (**186a**) with 2-nitrobenzaldehyde in the presence of NaOMe / methanol, (Eq. 31 & Table 7), with benzene.



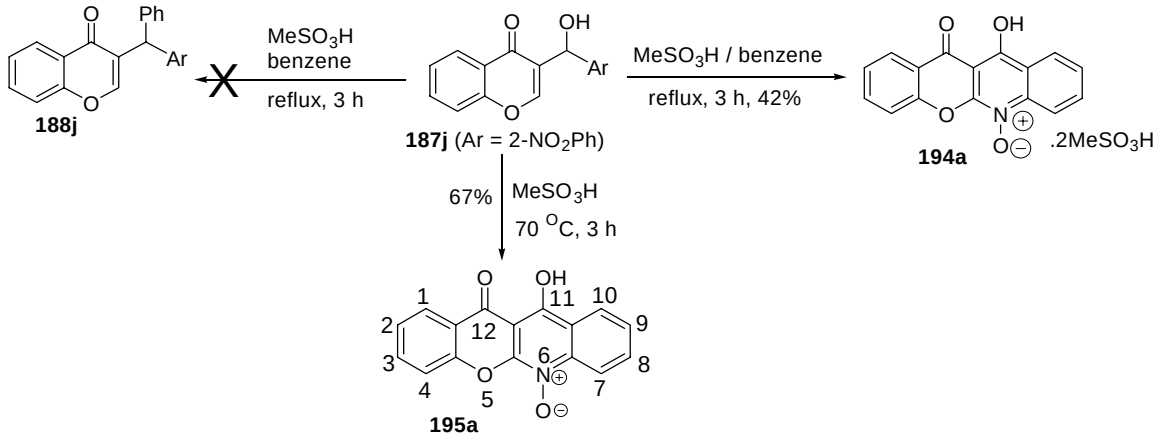
186a **187j** **Eq. 31**

Treatment of Baylis-Hillman alcohol **187j** with benzene in the presence of $MeSO_3H$, under similar reaction condition (as in the case of **188a**, Scheme 91) did not provide the desired Friedel-Crafts product, *i.e.*, 3-[(2-nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (**188j**). Instead, we have obtained another interesting tetra cyclic chromone fused quinoline *N*-oxide (**194a**)[Σ] (Scheme 101). Structure of this molecule[Ω] was confirmed by IR, ^{1}H NMR (Spectrum 33), and ^{13}C NMR (Spectrum 34) spectral data. The structure of this molecule

[∇] To have continuity and easy understanding the Baylis-Hillman alcohols derived from **186a-f** and 2-nitro-benzaldehyde / 2,4-dinitrobenzaldehyde are numbered as **187j-p**.
[Σ] To have easy understanding the chromone fused quinoline *N*-oxide derivatives obtained from **187j-p** are numbered as **195a-g** and the chromone fused quinoline *N*-oxide with $MeSO_3H$ is numbered as **194a**.

was further confirmed by single crystal X-ray data (Figure X9 & Table IX).[Ω] The fact, that the product, obtained, does not contain phenyl group any where, clearly shows that benzene has certainly no role to play in this reaction. To ascertain this fact, we have performed the reaction of **187j** (1 mmol) with methanesulfonic acid (2 mL) at 70 ^{o}C for 2 h, in the absence of benzene. We are indeed pleased to obtain 6-aza-11-hydroxy-5-oxa-6-oxy-naphthacen-12-one (**195a**),[@] as a colorless solid in 67% yield (Scheme 101).

Scheme 101



Even though the reaction is promising the yields are low. With view to improve the yields we have examined the application of various acids to effect of cyclization. In this direction, the best results were obtained, when we used trifluoroacetic acid (TFA) (Eq. 32). Thus, the reaction of 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (**187j)** (1 mmol) with TFA (3 mL) at 70 ^{o}C for 2 h, provided 6-aza-11-hydroxy-5-oxa-6-oxy- naphthacen-12-one

---

[Ω] From NMR studies and single crystal X-ray data analysis (see Figure X9) clearly shows that compound **194a** contains two equivalents of $MeSO_3H$.

[@] The products **195a-i** were not soluble in $CDCl_3$, MeOH-d_4 and DMSO-d_6, therefore we have recorded NMR in 10% TFA (or 10% TFA-*d*) in $CDCl_3$.

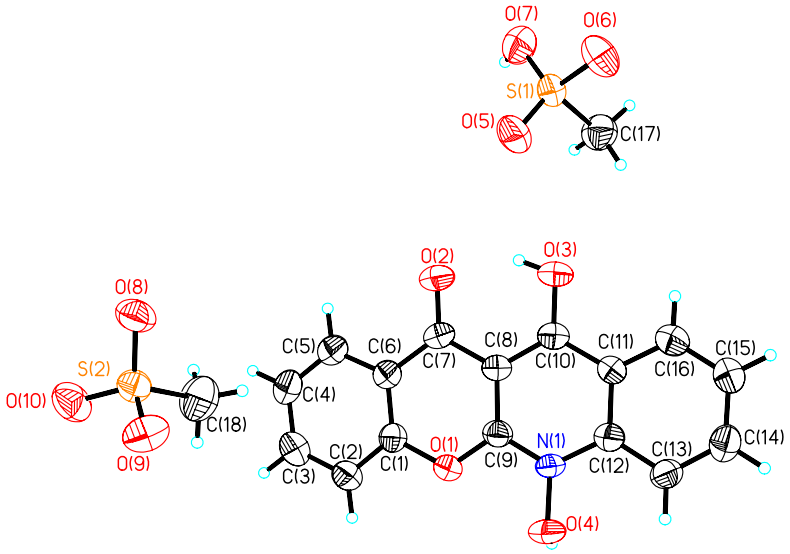
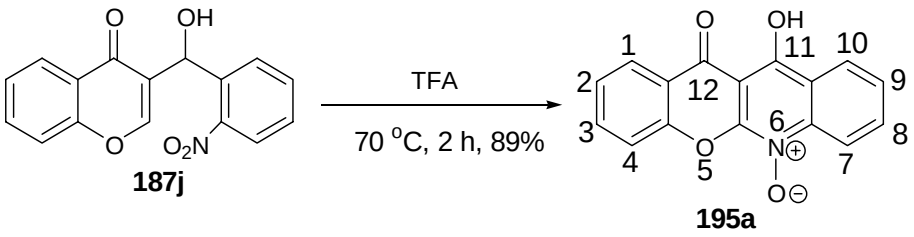


Figure X9 ORTEP diagram of compound **194a**
(Single crystal X-ray data analysis clearly
shows crystal has two equivalents of $MeSO_3H$).

(**195a**),[@] as a colorless solid in 89% yield, after workup and without any further purification (Eq. 32 & Table 8). Structure of this molecule was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass (LCMS) spectral data and elemental analysis. We have, in fact, obtained single crystal, from 10% TFA in $CHCl_3$, for the compound **195a** and further confirmed the structure of this molecule by the single crystal X-ray data (Figure X10 & Table X).



Eq. 32

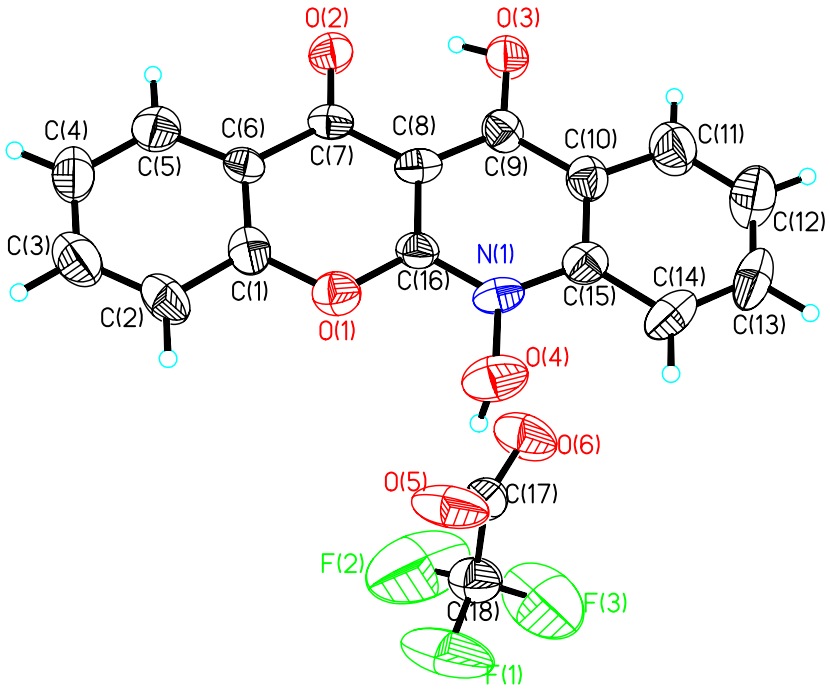
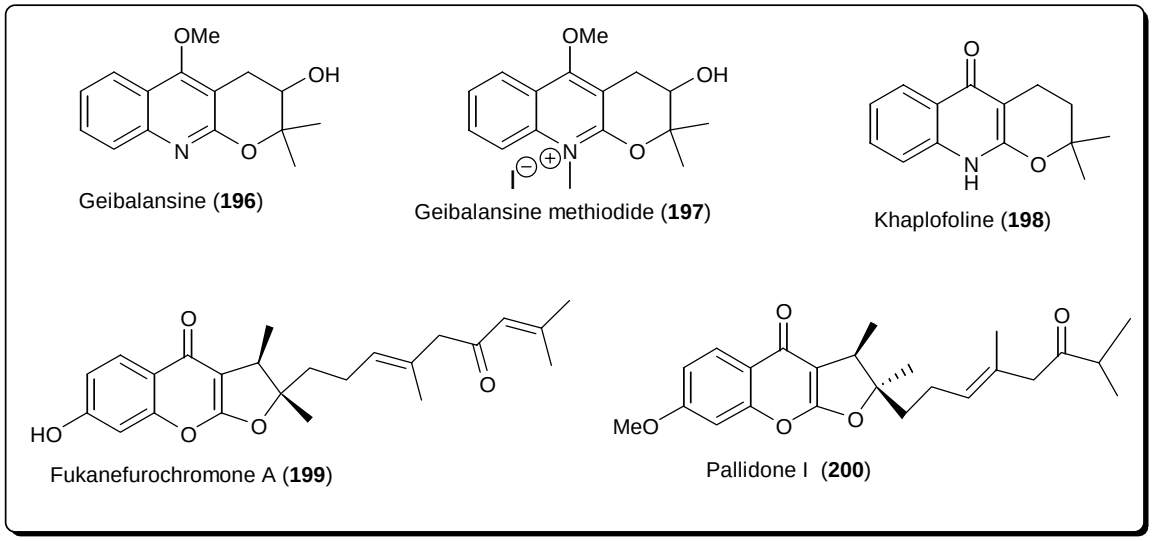


Figure X10 ORTEP diagram of compound **195a**
(Single crystal X-ray data analysis clearly
shows crystal has one equivalent TFA)

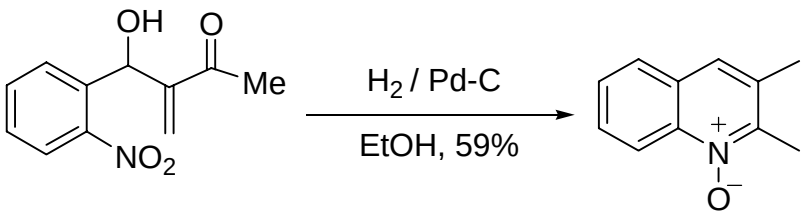
It is well known that fused quinoline framework[282-284] and fused chromone structural unit[285,286] continue to occupy an important place in heterocyclic chemistry due to the presence of these moieties in variety of natural products [such as geibalansine (**196**),[282,283] geibalansine methiodide (**197**),[283] khaplofoline (**198**),[284] fukanefurochromone A (**199**)[285] and pallidone I (**200**)[286]] possessing wide spectrum of physiological activities (Figure 14).

Figure 14



Literature survey reveals that applications of the Baylis-Hillman adducts, derived from 2-nitrobenzaldehydes, for synthesis of various quinoline *N*-oxides and quinoline derivatives have been well documented. Some of the relevant and important methodologies are presented in the following.

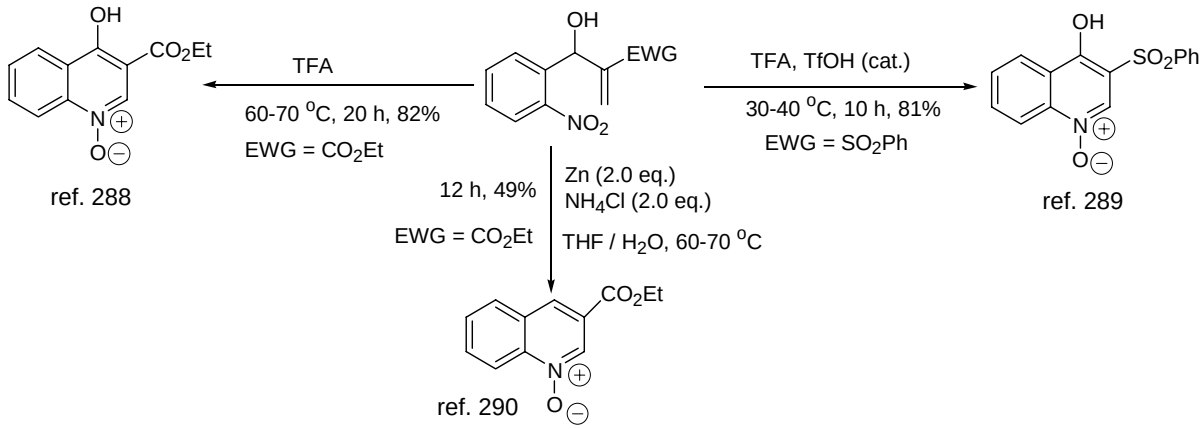
Kaye and coworkers[287] have reported an elegant synthesis of 4-hydroxyquinoline *N*-oxides *via* catalytic hydrogenation of the Baylis-Hillman adducts, derived from 2-nitro-benzaldehyde and methyl vinyl ketone, in the presence of Pd/C. One representative example is shown in Eq. 33.



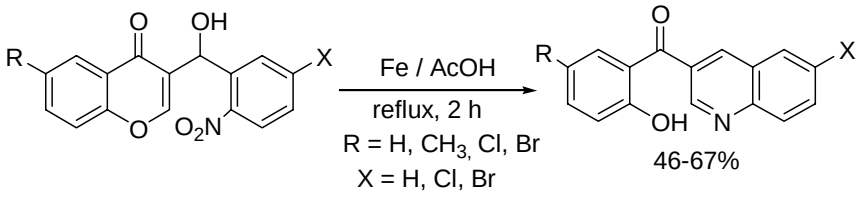
Eq. 33

Later on, Kim and coworkers[288-290] have transformed the Baylis-Hillman adducts, obtained from 2-nitrobenzaldehyde and various activated alkenes, into quinoline *N*-oxides *via* the treatment with TFA or with Zn / NH_4Cl (for partial reduction of nitro group). Some of representative examples are presented in Scheme 102.

Scheme 102



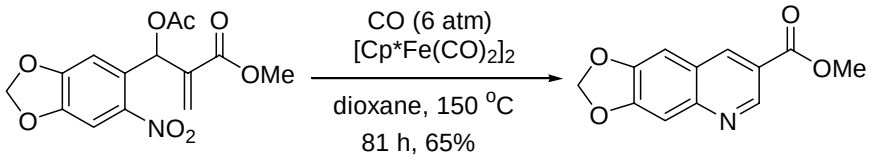
Recently, we have reported a simple synthesis of 3-benzoylquinolines, from the Baylis-Hillman alcohols, obtained from various chromones and 2-nitrobenzaldehydes, *via* the treatment with Fe / AcOH in Eq. 34.[291]



Eq. 34

Nicholas and O'Dell have reported the synthesis of 3-substituted quinolines *via* transition metal catalyzed reductive cyclization of the acetates of Baylis-Hillman adducts (derived

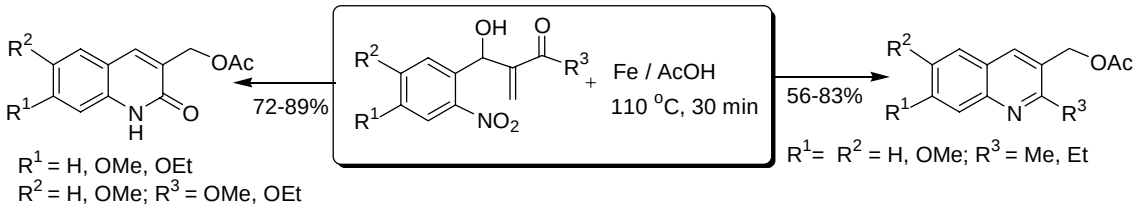
from 2-nitrobenzaldehydes and methyl acrylate). One representative example is shown in Eq. 35.[292]



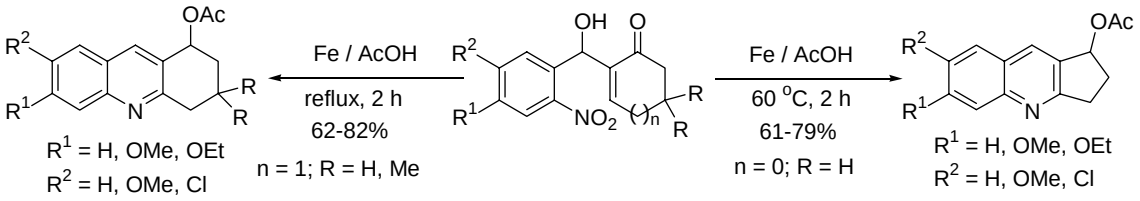
Eq. 35

Our research group has reported a facile synthesis of functionalized (1*H*)-quinol-2-ones and substituted quinolines from the Baylis-Hillman adducts (derived by the reaction of 2-nitrobenzaldehydes with alkyl acrylates and alkyl vinyl ketones respectively) *via* the treatment with Fe/AcOH (Scheme 103).[293] Later on, our research group extended the same strategy to one-pot synthesis of functionalized 1, 2, 3, 4-tetrahydroacridines and cyclo-penta[*b*]quinolines from the Baylis-Hillman alcohols (Scheme 104).[294]

Scheme 103



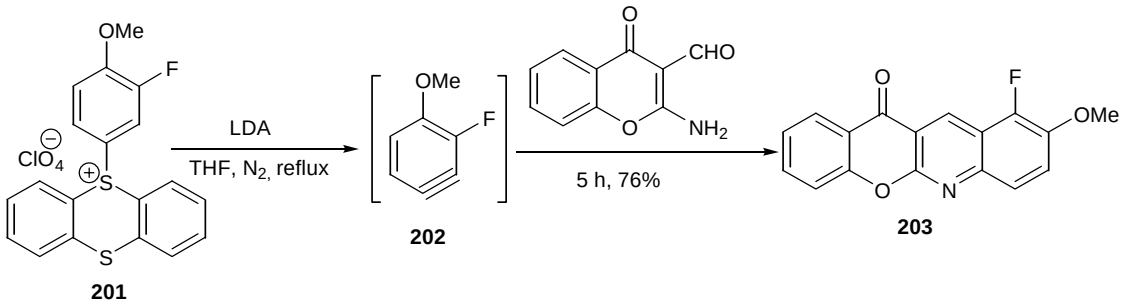
Scheme 104



It is also worth mentioning here the work of Kim and coworkers,[295] who prepared tetra cyclic system (**203**) *via* the reaction of 3-halogeno-4-methoxybenynes (**202**) [*in situ*

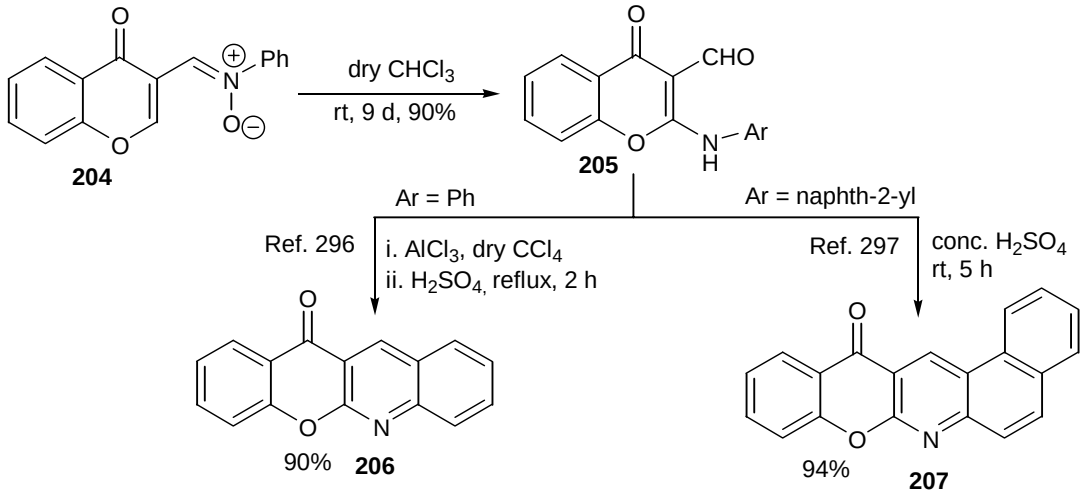
generated from 5-(3-halogeno-4-methoxyphenyl)thioanthrenium perchlorates (**201**)] with 2-amino-3-formylchromone. One representative example is presented in Scheme 105.

Scheme 105



Ishar and coworkers[296,297] also reported an interesting transformation of 2-arylamino-3-formylchromones (**205**) (obtained *via* the rearrangement of **204)** into chromone fused quinolines (**206** & **207**) through intramolecular cyclization as described in Scheme 106.

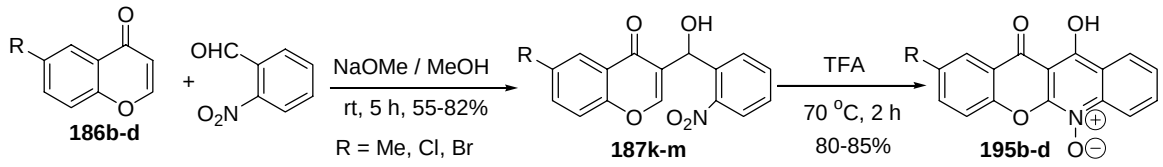
Scheme 106



Since our methodology provides a simple and convenient synthesis of chromone fused quinoline *N*-oxides and due to the importance these frameworks for certain biological

activities,[282-286] we thought that it would be interesting to understand the generality of our synthetic strategy for the production of tetra / penta cyclic chromone fused quinoline *N*-oxides. Accordingly, we have extended this strategy to various representative Baylis-Hillman alcohols (**187k-m**), obtained from 1-benzopyran-4(4*H*)-one derivatives (**186b-d**) and 2-nitrobenzaldehyde (Scheme 107 & Table 7). Thus, the treatment of the alcohols (**187k-m**) with TFA at 70 ^{o}C for 2 h, provided the desired tetracyclic compounds **195b-d**, as colorless solids in 80-85% yields (Scheme 107 & Table 8). Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 35, for compound **195d**), and ^{13}C NMR (Spectrum 36, for compound **195d**), mass (LCMS) spectral data and elemental analysis.

Scheme 107



Next, we have turned our attention towards benzochromone fused quinoline *N*-oxide derivatives. In this direction, we have prepared representative Baylis-Hillman alcohols, *i.e.* 3-[hydroxy(2-nitro / 2,4-dinitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-ones (**187n** & **187o**), *via* the reaction of 5,6-benzochromone (**186e**) with 2-nitrobenzaldehyde / 2,4-dinitrobenzaldehyde respectively, in the presence of sodium methoxide in methanol (Scheme 108 & Table 7). Structures of these molecules were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Scheme 108

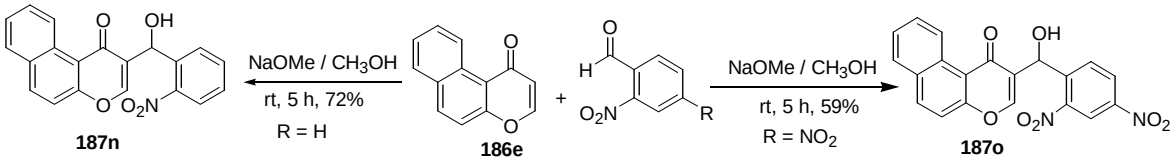
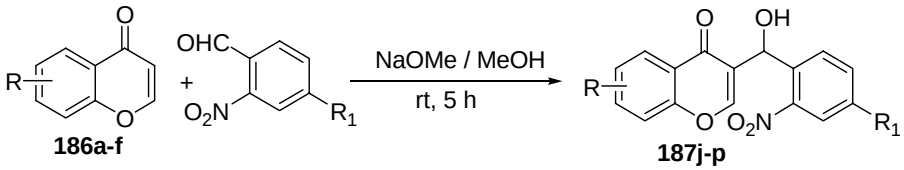


Table 7 Synthesis of 3-[hydroxy(2-nitro / 2,4-dinitrophenyl)methyl]-4*H*-chromen-4-one derivatives (**187j-p**)[a]



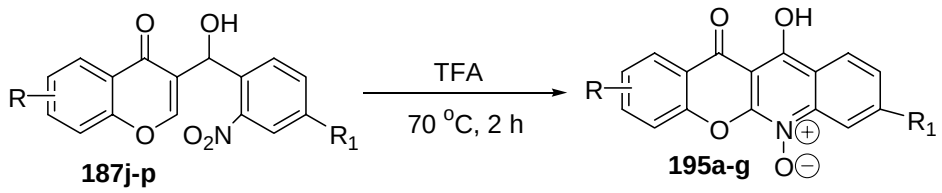
Chromones	R	R_1	Product[b]	Yield[c] (%)	Mp (°C)
186a	H	H	**187j**	78	149-151
186b	6-Me	H	**187k**	82	184-186
186c	6-Cl	H	**187l**	55	148-150
186d	6-Br	H	**187m**	61	179-181
186e	5,6-benzo-	H	**187n**	72	157-159
186e	5,6-benzo-	NO_2	**187o**	59	208-209
186f	7,8-benzo-	H	**187p**	70	166-168

(a) All reactions were carried out on a 5 mmol scale of chromones (**186a-f**) with 5 mmol of 2-nitrobezaldehyde / 2,4-dinitrobenzaldehyde in the presence of 50 mol% of NaOMe in methanol (10 mL) at room temperature for 5 h.

(b) All the compounds (**187j-p)** were characterized by IR, ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectral data.

(c) Yields are of the pure products (**187j-p)** based on chromones (**186a-f**).

Table 8 A facile and one-pot synthesis of chromone fused quinoline *N*-oxides (**195a-g**)[a] from the Baylis-Hillman alcohols (**187j-p**)



187j-p **195a-g**

B-H alcohol	R	R^1	Product[b]	Yield[c] (%)	Mp (°C)
187j	H	H	**195a**[d]	89	268-269
187k	6-Me	H	**195b**	85	249-251
187l	6-Cl	H	**195c**	80	261-263
187m	6-Br	H	**195d**	81	270-272
187n	5,6-benzo-	H	**195e**	86	235-238
187o	5,6-benzo-	NO_2	**195f**[d]	84	265 (dec.)
187p	7,8-benzo-	H	**195g**	75	279 (dec.)

(a) All reactions were carried out on a 1 mmol scale of Baylis-Hillman alcohols (**187j-p**) with trifluoroacetic acid (3 mL) at 70 °C for 2 h.

(b) All the compounds (**195a-g)** were obtained as colorless solids and were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass (LCMS) spectral data and elemental analyses (NMR recorded in 10% TFA in $CDCl_3$ for the products **195a, 195e** & **195f** & also recorded in 10% TFA-*d* in $CDCl_3$ for the products **195b-d,g**).

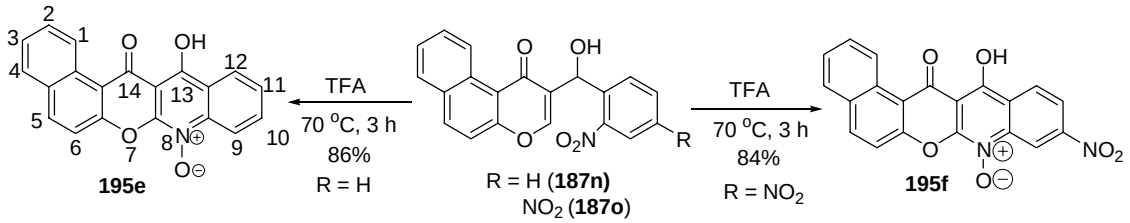
(c) Yields are of the pure products (**195a-g**) based on B-H alcohols (**187j-p**).

(d) The structures of these molecules were also established from the single crystal X-ray data (Figures X10 & X11 and Tables X & XI).

We have then examined reaction of the Baylis-Hillman alcohols (**187n** & **o**) with trifluoroacetic acid (3 mL) at 70 °C for 2 h. The resulting 8-aza-13-hydroxy-7-oxa-8-oxy-benzo[*a*]naphthacen-14-one (**195e**) and 8-aza-13-hydroxy-10-nitro-7-oxa-8-oxy-benzo[*a*]-naphthacen-14-one (**196f**) in 86% & 84% yields respectively (Scheme 109 & Table 8).

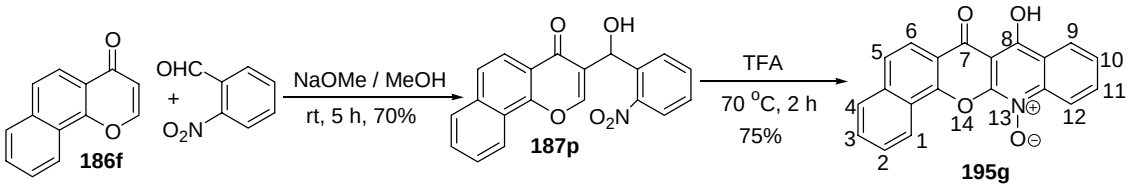
Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 37, for molecule **195e**), ^{13}C NMR (Spectrum 38, for molecule **195e**), mass (LCMS) spectral data and elemental analyses. The structure of the compound **195f** was further confirmed by single crystal X-ray data analysis (Figure X11 & Table XI).

Scheme 109



We have also next selected the Baylis-Hillman alcohol, *i.e.*, 3-[hydroxy(2-nitrophenyl)-methyl]-7,8-benzo-4*H*-chromen-4-one (**187p**), for our study. The required Baylis-Hillman alcohol (**187p**), was prepared *via* the coupling of 7,8-benzochromone (**186f**) with 2-nitrobenzaldehyde in the presence of NaOMe in methanol (Scheme 110 & Table 7). Treatment of this alcohol (**187p**) with trifluoroacetic acid under similar reaction condition provided, 13-aza-8-hydroxy-14-oxa-13-oxy-benzo[*a*]naphthacen-7-one (**195g**), in 75% yield (Scheme 110 & Table 8). Structure of this molecule (**195g**) was confirmed by IR, ^{1}H NMR (Spectrum 39), ^{13}C NMR (Spectrum 40), mass (LCMS) spectral data and elemental analysis.

Scheme 110



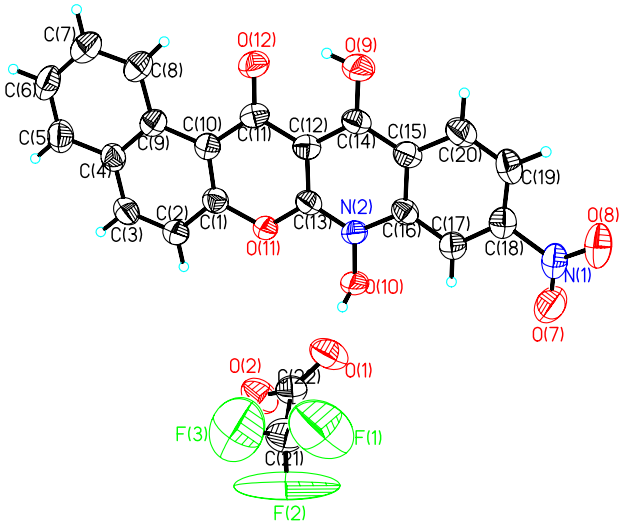


Figure X11 ORTEP diagram of compound **195f**
(Single crystal X-ray data analysis clearly
shows crystal has one equivalent TFA)

A plausible mechanism for the formation of chromone fused quinoline *N*-oxides is presented in Scheme 111, on the basis of similar mechanism proposed by Coelho and coworkers.[298]

Scheme 111

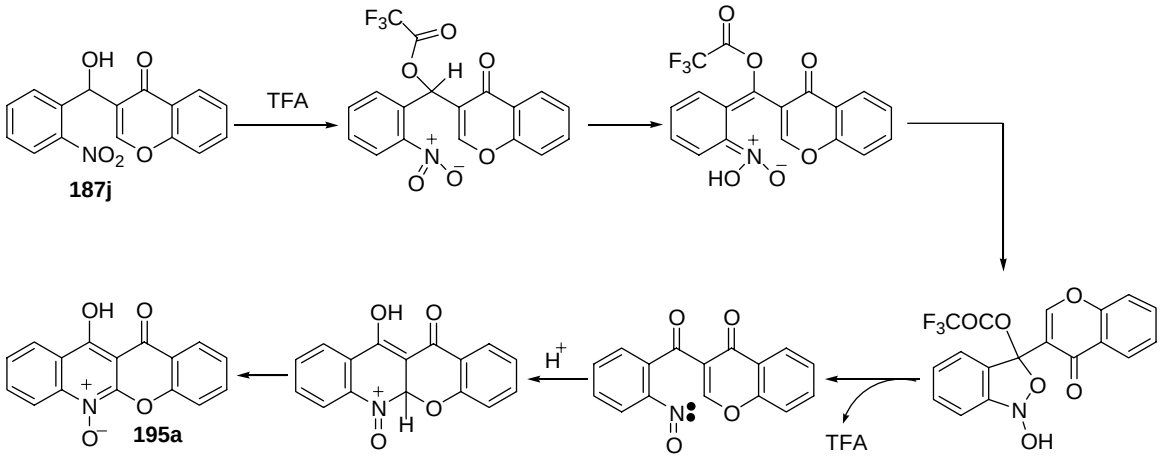


Table IX: Crystal data collection and structure refinement for the compound **194a**

Empirical formula	: $C_{16}H_9NO_4 \cdot 2CH_3SO_3H$
Formula weight	: 471.47
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P–1 (*International Table # 2*)
Unit cell dimensions	: a = 8.454(2) Å; α = 101.904(6) deg.
	: b = 10.445(3) Å; β = 108.145(4) deg.
	: c = 13.176(4) Å; γ = 105.274(5) deg.
Volume	: 1012.4(5) $Å^3$
Z, Calculated density	: 2, 1.601 g/cm^3
Absorption coefficient	: 0.766 mm^{-1}
F(000)	: 494
Crystal size	: 0.39 X 0.28 X 0.19 mm
Theta range for data collection	: 1.71 to 25.00 deg.
Limiting indices	: $-10 \le h \le 9$, $-9 \le k \le 12$, $-15 \le l \le 9$
Reflections collected / unique	: 4891 / 3293 [R(int) = 0.0270]
Completeness to theta = 25.00	: 92.6%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3293 / 0 / 285
Goodness-of-fit on F^2	: 1.033
Final R indices [I>2sigma(I)]	: R1 = 0.0557, wR2 = 0.1386
R indices (all data)	: R1 = 0.0813, wR2 = 0.1517
Largest diff. peak and hole	: 0.321 and -0.288 e. $Å^{-3}$

Table X: Crystal data collection and structure refinement for the compound **195a**

Empirical formula	: $C_{16}H_9NO_4 \cdot CF_3CO_2H$
Formula weight	: 393.27
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: $P2_1/c$ (*International Table # 14*)
Unit cell dimensions	: a = 4.9085(10) Å; α = 90 deg.
	: b = 15.560(3) Å; β = 93.431(4) deg.
	: c = 21.096(4) Å; γ = 90 deg.
Volume	: 1608.3(5) $Å^3$
Z, Calculated density	: 1, 1.624 g/cm^3
Absorption coefficient	: 0.145 mm^{-1}
F(000)	: 800
Crystal size	: 0.39 X 0.28 X 0.18 mm
Theta range for data collection	: 1.63 to 25.00 deg.
Limiting indices	: $-5 \le h \le 5$, $-18 \le k \le 18$, $-24 \le l \le 25$
Reflections collected / unique	: 15257 / 2835 [R(int) = 0.1331]
Completeness to theta = 25.00	: 100%
Absorption correction	: Multi-scan method (SADABS)
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2835 / 0 / 255
Goodness-of-fit on F^2	: 1.227
Final R indices [I>2sigma(I)]	: R1 = 0.1303, wR2 = 0.2690
R indices (all data)	: R1 = 0.1614, wR2 = 0.2890
Largest diff. peak and hole	: 0.634 and -0.293 e. $Å^{-3}$

Table XI: Crystal data collection and structure refinement for the compound **195f**

Empirical formula	: $C_{20}H_{10}N_2O_6 \cdot CF_3CO_2H$
Formula weight	: 671.37
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P–1 (*International Table # 2*)
Unit cell dimensions	: a = 7.843(6) Å; α = 108.262(12) deg.
	: b = 12.622(10) Å; β = 99.098(13) deg.
	: c = 15.572(12) Å; γ = 100.997(13) deg.
Volume	: 1397.2(18) $Å^3$
Z, Calculated density	: 2, 1.695 g/cm^3
Absorption coefficient	: 0.190 mm^{-1}
F(000)	: 713
Crystal size	: 0.44 X 0.20 X 0.18 mm
Theta range for data collection	: 1.76 to 25.00 deg.
Limiting indices	: $-9 \le h \le 9$, $-15 \le k \le 15$, $-18 \le l \le 18$
Reflections collected / unique	: 13463 / 4909 [R(int) = 0.0316]
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	: 4909 / 0 / 449
Goodness-of-fit on F^2	: 1.050
Final R indices [I>2sigma(I)]	: R1 = 0.0993, wR2 = 0.2588
R indices (all data)	: R1 = 0.1213, wR2 = 0.2826
Largest diff. peak and hole	: 0.843 and -0.465 e. $Å^{-3}$

In conclusion, we have successfully developed a simple methodology for the synthesis of tetra / penta cyclic chromone fused quinoline *N*-oxide frameworks (**195a-g**), from the Baylis-Hillman alcohols, *i.e.,* 3-[hydroxy(2-nitro / 2,4-dinitrophenyl)methyl]-4*H*-chromen-4-one derivatives (**187j-p**), derived from representative chromone derivatives (**186a-f**) and 2-nitro-benzaldehyde / 2,4-dinitrobenzaldehyde, in a convenient and operationally simple one-pot operation.

CONCLUSIONS

All the objectives mentioned in the beginning of the chapter have been achieved with considerable success. We have successfully developed a convenient and operationally simple two steps procedure for the synthesis of di(*E*)-arylidene-tetralone-spiro-glutaramides [di(*E*)-arylidene alonimids] **(162a-i)**, *via* the bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates (**160a-i**) followed by an interesting bis-cyclization strategy involving the successive C-C and C-N bonds formation through an intramolecular Friedel-Crafts reaction and hydrolysis of nitrile group with subsequent glutarimide ring formation.

A novel one-pot multistep strategy for synthesis of spiro-bisglutarimides **(165a-g**) *via* bisalkylation of malononitrile with *tert*-butyl 3-acetoxy-3-aryl-2-methylenepropanoates (**160a-g**) (acetates of the Baylis-Hillman adducts), followed by the hydrolysis of nitrile groups and subsequent cyclization was developed. We have described a convenient and

operationally simple one-pot multistep procedure for the synthesis of 2-piperidone derivatives (**181a-j**) from the Baylis-Hillman alcohols (**179a-i**), *via* the Johnson-Claisen rearrangement, reduction of α, β-unsaturated nitrile to amine followed by cyclization, thus demonstrating the application of Baylis-Hillman adducts as a valuable source for one-pot multistep synthesis.

A facile and operationally simple methodology for regioselective phenylation of Baylis-Hillman alcohols, *i.e.,* 3-[hydroxy(3- / 4-nitrophenyl)methyl]-4*H*-chromen-4-one derivatives (**187a-i**), *via* the Friedel-Crafts reaction with benzene was developed, leading to the formation of 3-[(3- /4-nitrophenyl)phenylmethyl]-4*H*-chromen-4-one frameworks (**188a-i**).

We have also successfully transformed the Baylis-Hillman alcohols, *i.e.,* 3-[hydroxyl(2-nitro/2,4-dinitrophenyl)methyl]-4*H*-chromen-4-one derivatives (**187j-p**), obtained from various chromone derivatives (**186a-f**) and 2-nitrobenzaldehyde / 2,4-dinitrobenzaldehyde, into tetra / penta cyclic chromone fused quinoline *N*-oxides (**195a-g**) in a convenient and operationally simple one-pot process.

Our studies clearly demonstrate the importance of the Baylis-Hillman adducts as a valuable source in organic transformation methodologies, particularly for one-pot multistep / reaction strategies.

EXPERIMENTAL

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

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

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

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a BRUKER-AC-200 and BRUKER-AVANCE-400 spectrometers. ^1H NMR (400 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned (δ = 2.50 ppm for ^1H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (50 MHz / 100 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-d_6, δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity,

that is, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet, br = broad, d of ABq = doublet of AB quartet, (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer.

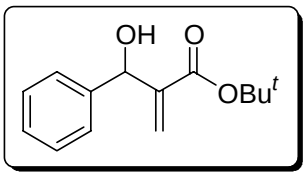
Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 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 A^o) 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).

tert-Butyl 3-hydroxy-2-methylene-3-phenylpropanoate (159a):

This compound was prepared according to the procedure developed in our laboratory.[299] Bezaldehyde (100 mM, 10.6 g, 10.0 mL), *tert*-butyl acrylate (150 mM, 19.2 g, 22.0 mL) and DABCO (15 mM, 3.36 g), silica gel (>200 mesh, 30.0 g) were thoroughly and uniformly mixed and this mixture was kept at room temperature. After 36 h, ethyl acetate (100 mL) was added and stirred thoroughly and filtered. The solid silica gel was washed with ethyl acetate (2 X 25 mL). The filtrates and washings were combined and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained was purified by column chromatography (6% of ethyl acetate / hexanes) to afford *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**159a**) in 73% (17.0 g) as a colorless liquid.



IR (neat): ν 3445, 1714, 1631 cm^{-1}

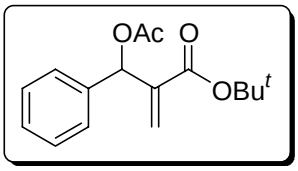
^{1}H NMR (400 MHz): δ 1.39 (s, 9H), 3.14 (br s, 1H), 5.49 (s, 1H), 5.71 (s, 1H), 6.24 (s, 1H), 7.22-7.40 (m, 5H)

^{13}C NMR (50 MHz): δ 27.85, 73.12, 81.39, 124.74, 126.63, 127.53, 128.20, 141.76, 143.66, 165.56

tert-Butyl 3-acetoxy-2-methylene-3-phenylpropanoate (160a):

To a stirred solution of *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**159a**) (50 mmol, 11.7 g), pyridine (75 mmol, 5.6 g, 5.0 mL) in dichloromethane (50 mL) at 0 ^oC was added acetyl chloride (75 mmol, 5.6 g, 5.5 mL). After stirring at room temperature for 2 h, the reaction mixture was diluted with ether (50 mL) and washed with water. Organic layer

was dried over anhydrous Na_2SO_4. Solvent was removed and the crude product, thus obtained was purified by column chromatography (silica gel, 4% EtOAc in hexanes) to afford the pure *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) as a pale-yellow liquid in 89% (12.3 g) yield.



IR (neat): ν 1745, 1718, 1635 cm^{-1}

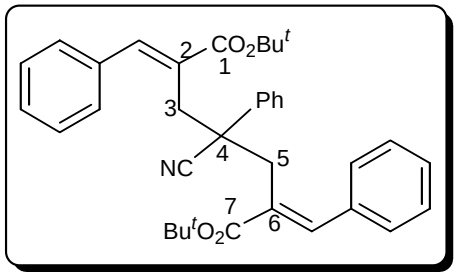
^{1}H NMR (400 MHz): δ 1.36 (s, 9H), 2.08 (s, 3H), 5.72 (s, 1H), 6.31 (s, 1H), 6.64 (s, 1H), 7.20-7.40 (m, 5H)

^{13}C NMR (50 MHz): δ 20.77, 27.68, 73.17, 81.12, 124.37, 127.65, 128.08, 128.16, 138.00, 141.16, 163.94, 169.03

Di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161a):

To a stirred suspension of oil free excess NaH (10 mmol, 0.24 g) in anhydrous toluene were added benzyl cyanide (2 mmol, 0.234 g) and *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) (5 mmol, 1.38 g) at room temperature and heated under reflux for 1 h under N_2 atmosphere. Then the reaction mixture was allowed to come to room temperature and cooled to 0 ^oC. Excess NaH was carefully quenched with very slow addition of water at 0 ^oC. Reaction mixture was extracted with ether (3 X 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated. The residue, thus obtained, was purified by column chromatography (5% ethyl acetate in hexanes) followed by crystallization$^{\#}$ (from 3% ethyl acetate in hexanes at 0 ^oC) to afford

di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**161a**), as a colorless solid, in 73 % (0.80 g) yield**.**



Mp: 118-120 ^{o}C

IR (KBr): ν 2235, 1711, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.44 (s, 18H), 3.09 & 3.34 (ABq, 4H, J = 13.6 Hz), 6.98-7.38 (m, 15H), 7.62 (s, 2H)

^{13}C NMR (50 MHz): δ 28.00, 35.95, 48.28, 81.34, 120.39, 126.53, 127.50, 128.04, 128.16, 128.42, 128.84, 130.27, 135.60, 137.54, 142.01, 166.94

LCMS (*m/z*): 548 $(M-H)^{-}$

Anal. Calcd. for $C_{36}H_{39}NO_4$: C, 78.66; H, 7.15; N, 2.55

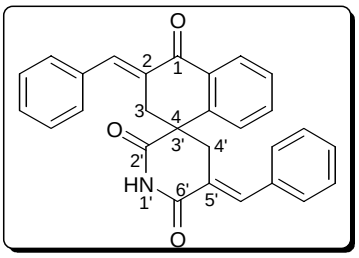
Found: C, 78.67; H, 7.11; N, 2.64

[#]*The crude product contains 8% (Z)-isomer, as indicated by the* ^{1}*H NMR spectral analysis. However crystallization provides pure (E)-isomer.*

2,5′-Di[(*E*)-benzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162a):

To a stirred solution of di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**161a**) (0.5 mmol, 0.275 g) in 1,2-dichloroethane (DCE, 3 mL) were added

conc. H_2SO_4 (2.5 mmol, 0.245 g, 0.13 mL) and tirfluoroacetic anhydride (TFAA, 2.5 mmol, 0.525 g, 0.35 mL) at room temperature. The reaction mixture was heated under reflux for 6 h and then allowed to cool to room temperature. Reaction mixture was poured into aqueous K_2CO_3 solution and extracted with EtOAc (3 X 25 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 (30% ethyl acetate in hexanes) to provide, 2,5′-di[(*E*)-benzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (**162a**), as a colorless solid in 80% (0.168 g) yield.



Mp: 184-186 ^oC

IR (KBr): ν 3300-2800 (multiple bands), 1711, 1693, 1651, 1624 cm^{-1}

^1H NMR (400 MHz): δ 3.08 (s, 2H), 3.38 & 3.48 (ABq, 2H, J = 14.8 Hz), 6.88 (d, 2H, J = 6.6 Hz), 7.13-7.41 (m, 9H), 7.43-7.51 (m, 1H), 7.53-7.62 (m, 1H), 7.72 (s, 1H), 7.85 (s, 1H), 8.20 (d, 1H, J = 7.2 Hz), 8.68 (s, 1H, D_2O exchangeable)

^{13}C NMR (100 MHz): δ 35.23, 36.15, 48.25, 124.07, 126.64, 128.64, 128.67, 129.10, 129.17, 129.42, 129.55, 129.74, 129.87, 132.58, 133.63, 133.90, 134.60, 140.29, 142.49, 166.30, 174.45, 185.72

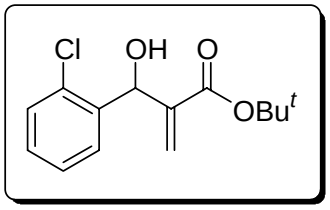
LCMS (*m/z*): 420 $(M+H)^+$

Anal. Calcd. for $C_{28}H_{21}NO_3$: C, 80.17; H, 5.05; N, 3.34

Found: C, 80.27; H, 5.00; N, 3.35

***tert*-Butyl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate (159b):**

This was obtained as a colorless viscous liquid [after silica gel column chromatography, 8% ethyl acetate in hexanes], *via* the DABCO catalyzed Baylis-Hillman reaction of 2-chlorobenzaldehyde with *tert*-butyl acrylate, following similar procedure described for the compound **159a**.



Reaction time: 14 d

Yield: 81%

IR (neat): ν 3435, 1714, 1633 cm^{-1}

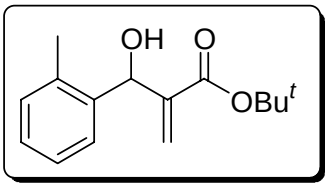
^{1}H NMR (400 MHz): δ 1.43 (s, 9H), 3.28 (d, 1H, J = 4.8 Hz), 5.54 (s, 1H), 5.94 (d, 1H, J = 4.8 Hz), 6.26 (s, 1H), 7.18-7.38 (m, 3H), 7.48-7.58 (m, 1H)

^{13}C NMR (50 MHz): δ 27.95, 69.31, 81.63, 125.54, 126.97, 128.13, 128.91, 129.39, 133.03, 138.88, 142.37, 165.73

***tert*-Butyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate (159c):**

This compound was obtained as a colorless viscous liquid [after crystallization from 10% ethyl acetate in hexanes at 0 ^oC], *via* the reaction between 2-methylbenzaldehyde and *tert*-butyl acrylate catalyzed by DABCO, following simlar procedure described for the compound **159a**.

Reaction time: 12 d



Yield: 57%

Mp: 52-54 ^{o}C (Lit.[299] 54-55^{o}C)

IR (KBr): ν 3400, 1714, 1633 cm^{-1}

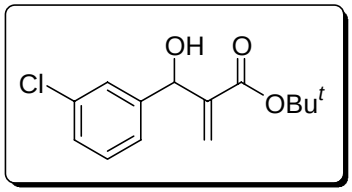
^{1}H NMR (400 MHz): δ 1.42 (s, 9H), 2.32 (s, 3H), 2.90 (br s, 1H), 5.51 (s, 1H), 5.73 (s, 1H), 6.23 (s, 1H), 7.10-7.26 (m, 3H), 7.37-7.44 (m, 1H)

^{13}C NMR (50 MHz): δ 19.02, 27.93, 69.43, 81.34, 124.78, 126.05, 126.26, 127.65, 130.34, 135.68, 139.27, 143.51, 165.97

tert-Butyl 3-(3-chlorophenyl)-3-hydroxy-2-methylenepropanoate (159d):

This compound was obtained as a colorless viscous liquid [after silica gel column chromatography, 8% ethyl acetate in hexanes], *via* the reaction of 3-chlorobenzaldehyde with *tert*-butyl acrylate in the presence of DABCO (cat), following similar procedure described for the molecule **159a**.

Reaction time: 14 d



Yield: 85%

IR (neat): ν 3449, 1709, 1631 cm^{-1}

^{1}H NMR (400 MHz): δ 1.40 (s, 9H), 3.35 (br s, 1H), 5.44 (s, 1H), 5.73 (s, 1H), 6.25 (s, 1H), 7.18-7.28 (m, 3H), 7.36 (s, 1H)

^{13}C NMR (50 MHz): δ 27.73, 72.27, 81.49, 124.74, 124.93, 126.77, 127.48, 129.37, 133.95, 143.15, 143.97, 165.17

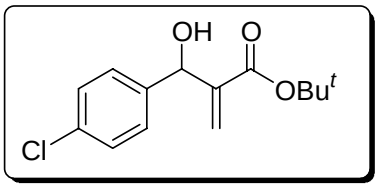
***tert*-Butyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (159e):**

This compound was obtained as a colorless solid [after crystallization from 15% ethyl acetate in hexanes at 0 ^{o}C], *via* the DABCO catalyzed Baylis-Hillman coupling of 4-chlorobenzaldehyde with *tert*-butyl acrylate, following similar procedure described for the compound **159a**.

Reaction time: 14 d

Yield: 87%

Mp: 63-65 ^{o}C



IR (KBr): ν 3321, 1714, 1639 cm^{-1}

^{1}H NMR (400 MHz): δ 1.41 (s, 9H), 3.21(br s, 1H), 5.46 (s, 1H), 5.70 (s, 1H), 6.24 (s, 1H), 7.30 (s, 4H)

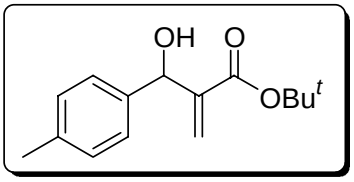
^{13}C NMR (50 MHz): δ 28.00, 72.87, 81.87, 125.39, 128.01, 128.47, 133.44, 140.33, 143.24, 165.54

***tert*-Butyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (159f):**

This Baylis-Hillman alcohol was obtained as a colorless solid [after crystallization from 10% ethyl acetate in hexanes at 0 ^{o}C], *via* the coupling of 4-methylbenzaldehyde with *tert*-butyl acrylate under the catalytic influence of DABCO, following similar procedure described for the compound **159a**.

Reaction time: 12 d

Yield: 68%



Mp: 40-42 ^{o}C (Lit.[299] 41-43 ^{o}C)

IR (KBr): ν 3335, 1714, 1635 cm^{-1}

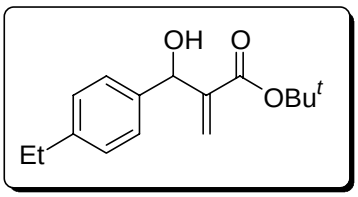
^{1}H NMR (400 MHz): δ 1.39 (s, 9H), 2.32 (s, 3H), 3.09 (br s, 1H), 5.45 (s, 1H), 5.72 (s, 1H), 6.22 (s, 1H), 7.13 (d, 2H, J = 7.6 Hz), 7.23 (d, 2H, J = 7.6 Hz)

^{13}C NMR (50 MHz): δ 21.01 27.90, 73.04, 81.32, 124.57, 126.53, 128.91, 137.11, 138.81, 143.78, 165.63

tert-Butyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (159g):

This compound was prepared *via* the Baylis-Hillman reaction between 4-ethyl-benzaldehyde and *tert*-butyl acrylate catalyzed by DABCO, as a colorless solid [after crystallization from 10% ethyl acetate in hexanes at 0 ^{o}C], following similar procedure described for the molecule **159a**.

Reaction time: 16 d



Yield: 69%

Mp: 45-47 ^{o}C (Lit.[299] 46-48 ^{o}C)

IR (KBr): ν 3310, 1716, 1635 cm^{-1}

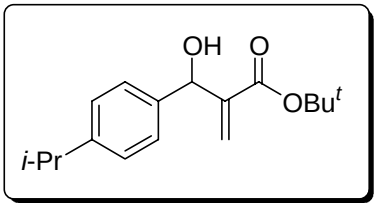
^{1}H NMR (400 MHz): δ 1.21 (t, 3H, J = 7.6 Hz), 1.39 (s, 9H), 2.62 (q, 2H, J = 7.6 Hz), 3.10 (d, 1H, J = 5.8 Hz), 5.46 (d, 1H, J = 5.8 Hz), 5.72

(s, 1H), 6.23 (s, 1H), 7.15 (d, 2H, J = 8.0 Hz), 7.26 (d, 2H, J = 8.0 Hz)

^{13}C NMR (50 MHz): δ 15.51, 27.88, 28.65, 73.09, 81.34, 124.61, 126.60, 127.72, 139.02, 143.58, 143.78, 165.66

tert-Butyl 3-(4-isopropylphenyl)-3-hydroxy-2-methylenepropanoate (159h):

This compound was obtained as a colorless solid [after crystallization from 10% ethyl acetate in hexanes at 0 ^{o}C], *via* the treatment of 4-isopropylbenzaldehyde with *tert*-butyl acrylate in the presence of DABCO (cat.), following similar procedure described for the Baylis-Hillman adduct **159a**.



Reaction time: 18 d

Yield: 59%

Mp: 44-46 ^{o}C (Lit.[299] 43-45 ^{o}C)

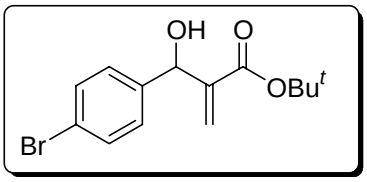
IR (KBr): ν 3344, 1716, 1637 cm^{-1}

^{1}H NMR (400 MHz): δ 1.23 (d, 6H, J = 6.8 Hz), 1.39 (s, 9H), 2.89 (sept, 1H, J = 6.8 Hz), 3.08 (br s, 1H), 5.47 (d, 1H, J = 4.8 Hz), 5.72 (s, 1H), 6.23 (s, 1H), 7.19 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz)

^{13}C NMR (50 MHz): δ 24.00, 27.95, 33.82, 73.26, 81.46, 124.78, 126.36, 126.63, 139.17, 143.78, 148.34, 165.76

***tert*-Butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (159i):**

This allylic alcohol was obtained as a colorless solid [after crystallization from 15% ethyl acetate in hexanes at 0 ^{o}C], *via* the reaction between 4-bromobenzaldehyde and *tert*-butyl acrylate under the catalytic influence of DABCO, following similar procedure described for the compound **159a**.



Reaction time: 10 d

Yield: 65%

Mp: 59-61 ^{o}C (Lit.[299] 61-63 ^{o}C)

IR (KBr): ν 3325, 1716 , 1637 cm^{-1}

^{1}H NMR (400 MHz): δ 1.41 (s, 9H), 3.21 (br s, 1H), 5.44 (s, 1H), 5.70 (s, 1H), 6.24 (s, 1H), 7.24 (d, 2H, J = 8.4 Hz), 7.46 (d, 2H, J = 8.4 Hz)

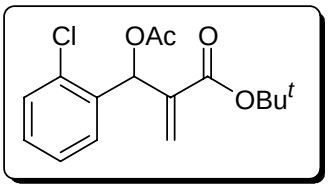
^{13}C NMR (50 MHz): δ 27.97, 72.78, 81.80, 121.51, 125.34, 128.35, 131.38, 140.82, 143.15, 165.46

***tert*-Butyl 3-acetoxy-3-(2-chlorophenyl)-2-methylenepropanoate (160b):**

This acetate was obtained as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**159b**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the compound **160a**.

Reaction time: 2 h

Yield: 86%



IR (neat): ν 1749, 1720, 1637 cm^{-1}

^1H NMR (400 MHz): δ 1.38 (s, 9H), 2.12 (s, 3H), 5.51 (s, 1H), 6.38 (s, 1H), 7.02 (s, 1H), 7.20-7.43 (m, 4H)

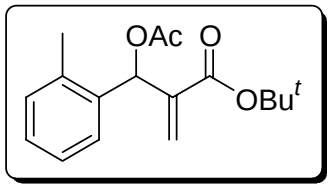
^{13}C NMR (50 MHz): δ 20.75, 27.88, 70.23, 81.51, 126.12, 126.82, 128.50, 129.54, 129.73, 133.78, 135.80, 139.95, 163.98, 168.98

***tert*-Butyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (160c):**

This allyl acetate was prepared as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate (**159c**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the compound **160a**.

Reaction time: 2 h

Yield: 88%



IR (neat): ν 1745, 1722, 1635 cm^{-1}

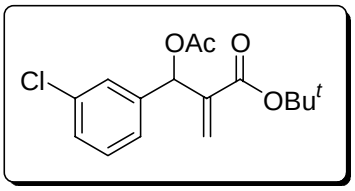
^1H NMR (400 MHz): δ 1.38 (s, 9H), 2.09 (s, 3H), 2.38 (s, 3H), 5.52 (s, 1H), 6.32 (s, 1H), 6.86 (s, 1H), 7.09-7.31 (m, 4H)

^{13}C NMR (50 MHz): δ 19.12, 20.89, 27.90, 70.42, 81.34, 125.34, 126.00, 127.14, 128.25, 130.51, 136.09, 136.43, 140.94, 164.45, 169.35

***tert*-Butyl 3-acetoxy-3-(3-chlorophenyl)-2-methylenepropanoate (160d):**

This Baylis-Hillman acetate was prepared as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-(3-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**159d**) with acetyl

chloride in the presence of pyridine, following a similar procedure described for the molecule **160a**.



Reaction time: 2 h

Yield: 88%

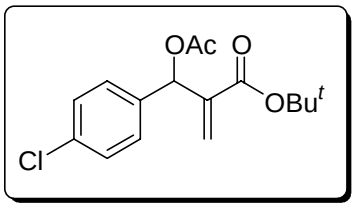
IR (neat): ν 1749, 1714, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.38 (s, 9H), 2.10 (s, 3H), 5.76 (s, 1H), 6.34 (s, 1H), 6.58 (s, 1H), 7.20-7.42 (m, 4H)

^{13}C NMR (50 MHz): δ 20.79, 27.78, 72.51, 81.49, 124.95, 125.90, 127.77, 128.28, 129.54, 134.12, 140.24, 140.65, 163.74, 169.01

***tert*-Butyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (160e):**

This compound was obtained as a colorless solid, *via* the acetylation of *tert*-butyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**159e**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the compound **160a**.



Reaction time: 2 h

Yield: 90%

Mp: 60-61 ^{o}C

IR (KBr): ν 1745, 1699, 1631 cm^{-1}

^{1}H NMR (400 MHz): δ 1.38 (s, 9H), 2.09 (s, 3H), 5.75 (s, 1H), 6.32 (s, 1H), 6.59 (s, 1H), 7.30 (s, 4H)

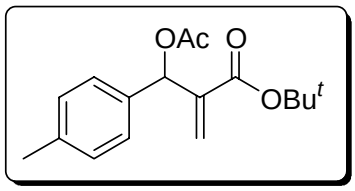
^{13}C NMR (50 MHz): δ 20.79, 27.76, 72.49, 81.36, 124.66, 128.40, 129.13, 133.98, 136.72, 140.75, 163.77, 168.98

***tert*-Butyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (160f):**

This compound was prepared as a colorless viscous liquid, *via* the treatment of *tert*-butyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (**159f**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the compound **160a**.

Reaction time: 2 h

Yield: 84%



IR (neat): ν 1745, 1720, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.37 (s, 9H), 2.07 (s, 3H), 2.32 (s, 3H), 5.71 (s, 1H), 6.29 (s, 1H), 6.60 (s, 1H), 7.13 (d, 2H, J = 8.0 Hz), 7.24 (d, 2H, J = 8.0 Hz)

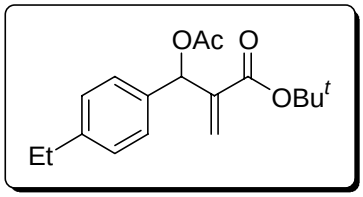
^{13}C NMR (50 MHz): δ 20.96, 21.01, 27.80, 73.19, 81.22, 124.28, 127.70, 128.93, 135.09, 137.91, 141.33, 164.15, 169.22

***tert*-Butyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate (160g):**

Treatment of *tert*-butyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (**159g**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the molecule **160a**, provided the title compound as a colorless viscous liquid.

Reaction time: 2 h

Yield: 88%



IR (neat): ν 1747, 1718, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.21 (t, 3H, J = 7.6 Hz), 1.37 (s, 9H), 2.08 (s, 3H), 2.63 (q, 2H, J = 7.6 Hz), 5.71 (s, 1H), 6.29 (s, 1H), 6.61 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz)

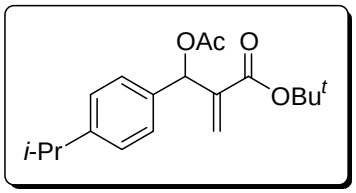
^{13}C NMR (50 MHz): δ 15.36, 20.99, 27.83, 28.48, 73.24, 81.22, 124.28, 127.77, 135.34, 141.43, 144.29, 164.23, 169.27

***tert*-Butyl 3-acetoxy-3-(4-isopropylphenyl)-2-methylenepropanoate (160h):**

This compound was prepared as a colorless viscous liquid, *via* the treatment of *tert*-butyl 3-(4-isopropylphenyl)-3-hydroxy-2-methylenepropanoate (**159h**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the molecule **160a**.

Reaction time: 2 h

Yield: 85%



IR (neat): ν 1747, 1718, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.22 (d, 6H, J = 6.8 Hz), 1.36 (s, 9H), 2.08 (s, 3H), 2.88 (sept, 1H, J = 6.8 Hz), 5.70 (s, 1H), 6.29 (s, 1H), 6.61 (s, 1H), 7.18 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz)

^{13}C NMR (50 MHz): δ 21.11, 23.92, 27.93, 33.87, 73.31, 81.34, 124.37, 126.41, 127.87, 135.51, 141.52, 149.02, 164.35, 169.42

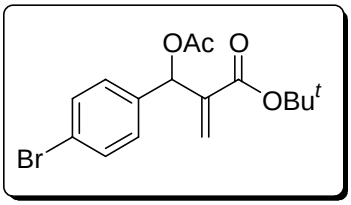
***tert*-Butyl 3-acetoxy-3-(4-bromophenyl)-2-methylenepropanoate (160i):**

This compound was prepared as a colorless solid, *via* the reaction of *tert*-butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (**159i**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the molecule **160a**.

Reaction time: 2 h

Yield: 87%

Mp: 53-54 ^{o}C



IR(KBr): ν 1738, 1703, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 1.38 (s, 9H), 2.09 (s, 3H), 5.75 (s, 1H), 6.32 (s, 1H), 6.57 (s, 1H), 7.24 (d, 2H, J = 8.0 Hz), 7.46 (d, 2H, J = 8.0 Hz)

^{13}C NMR (50 MHz): δ 20.92, 27.85, 72.61, 81.49, 122.24, 124.81, 129.47, 131.43, 137.28, 140.72, 163.81, 169.08

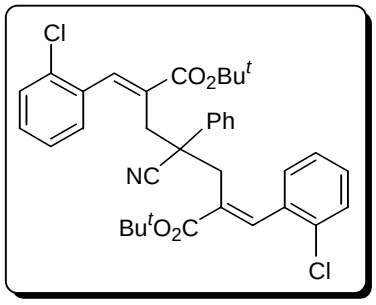
Di-*tert*-butyl 2,6-di[(*E*)-2-chlorobenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161b):

This product was obtained as a colorless solid, *via* the treatment of benzyl cyanide with *tert*-butyl 3-acetoxy-3-(2-chlorophenyl)-2-methylenepropanoate (**160b**) in the presence of NaH, following the similar procedure described for product **161a**.

Reaction time: 1 h

Yield: 70%

Mp: 140-142 ^{o}C



IR (KBr): ν 2239, 1707, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.47 (s, 18H), 2.99 & 3.24 (ABq, 4H, J = 13.6 Hz), 6.95-7.10 (m, 7H), 7.12-7.32 (m, 6H), 7.63 (s, 2H)

^{13}C NMR (50 MHz): δ 28.00, 35.95, 47.67, 81.66, 120.10, 126.29, 126.51, 127.50, 127.50, 128.25, 129.25, 129.71, 131.67, 134.15, 134.32, 136.86, 139.22, 166.34

LCMS (*m/z*): 640 $(M+Na)^+$, 642 $[(M+2)+Na]^+$, 644 $[(M+4)+Na]^+$

Anal. Calcd. for $C_{36}H_{37}Cl_2NO_4$: C, 69.90; H, 6.03; N, 2.26

Found: C, 69.75; H, 6.07; N, 2.34

Di-*tert*-butyl 2,6-di[(*E*)-2-methylbenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161c):

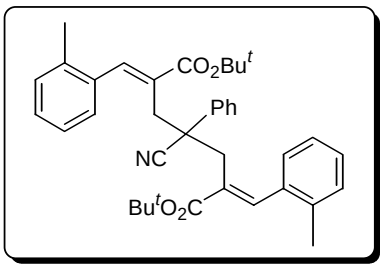
This bisadduct was obtained as a colorless solid, *via* the reaction of benzyl cyanide with *tert*-butyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (**160c**) in the presence of NaH, following the similar procedure described for compound **161a**.

Reaction time: 1 h

Yield: 81%

mp: 127-129 ^{o}C

IR (KBr): ν 2237, 1718, 1628 cm^{-1}



^{1}H NMR (400 MHz): δ 1.50 (s, 18H), 1.92 (s, 6H), 2.98 & 3.14 (ABq, 4H, J = 13.6 Hz), 6.82-6.92 (m, 6H), 6.98-7.22 (m, 7H), 7.62 (s, 2H)

^{13}C NMR (50 MHz): δ 19.73, 27.97, 35.42, 47.84, 81.34, 120.10, 125.49, 126.09, 127.14, 127.99, 130.12, 130.29, 134.88, 137.11, 137.28, 141.67, 166.70

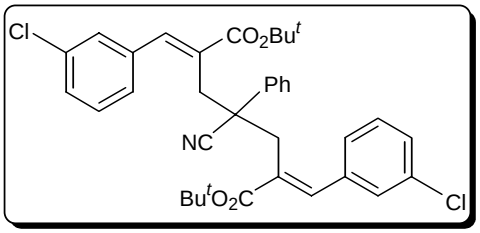
LCMS (*m/z*): 578 $(M+H)^+$

Anal. Calcd. for $C_{38}H_{43}NO_4$: C, 79.00; H, 7.50; N, 2.42

Found: C, 79.05; H, 7.49; N, 2.41

Di-*tert*-butyl 2,6-di[(*E*)-3-chlorobenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161d):

This product was prepared *via* the reaction between benzyl cyanide and *tert*-butyl 3-acetoxy-3-(3-chlorophenyl)-2-methylenepropanoate (**160d**) in the presence of NaH following the similar procedure described for compound **161a**, as a colorless solid.



Reaction time: 1 h

Yield: 65%

Mp: 151-152 ^{o}C

IR (KBr): ν 2235, 1709, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.46 (s, 18H), 3.10 & 3.30 (ABq, 4H, J = 13.6 Hz), 6.92-7.25 (m, 13H), 7.54 (s, 2H)

^{13}C NMR (50MHz): δ 27.97, 36.10, 48.20, 81.68, 120.13, 126.48, 126.70, 127.70, 128.06, 128.11, 128.62, 129.64, 131.41, 134.34, 136.94, 137.35, 140.33, 166.43

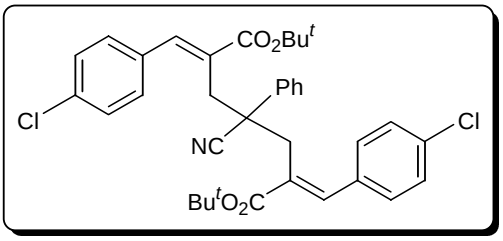
LCMS (*m/z*): 618 $(M+H)^+$, 620 $[(M+2)+H]^+$, 622 $[(M+4)+H]^+$

Anal. Calcd. for $C_{36}H_{37}Cl_2NO_4$: C, 69.90; H, 6.03; N, 2.26

Found: C, 69.72; H, 6.03; N, 2.22

Di-*tert*-butyl 2,6-di[(*E*)-4-chlorobenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161e):

This molecule was prepared, *via* the bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (**160e**) in the presence of NaH, following the similar procedure described for compound **161a**, as a colorless solid.



Reaction time: 1 h

Yield: 66%

Mp: 184-186 ^{o}C

IR (KBr): ν 2235, 1714, 1633 cm^{-1}

^{1}H NMR (400 MHz): δ 1.44 (s, 18H), 3.09 & 3.13 (ABq, 4H, J = 13.6 Hz), 6.99 (d, 4H, J = 8.4 Hz), 7.04-7.18 (m, 5H), 7.23 (d, 4H, J = 8.4 Hz), 7.56 (s, 2H)

^{13}C NMR (50 MHz): δ 28.00, 36.20, 48.40, 81.61, 120.22, 126.60, 127.74, 128.28, 128.67, 130.17, 130.87, 133.98, 137.33, 140.67, 166.65

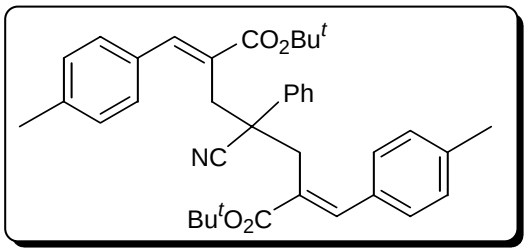
LCMS (*m/z*): 640 $(M+Na)^{+}$, 642 $[(M+2)+Na]^{+}$, 644 $[(M+4)+Na]^{+}$

Anal. Calcd. for $C_{36}H_{37}Cl_2NO_4$: C, 69.90; H, 6.03; N, 2.26

Found: C, 69.96; H, 5.99; N, 2.16

Di-*tert*-butyl 2,6-di[(*E*)-4-methylbenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161f):

This bisadduct was prepared *via* the reaction between benzyl cyanide and *tert*-butyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (**160f**) in the presence of NaH, following the similar procedure described for compound **161a**, as a colorless solid.



Reaction time: 1 h

Yield: 80%

mp: 124-126 ^{o}C

IR (KBr): ν 2235, 1709, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.42 (s, 18H), 2.35 (s, 6H), 3.12 & 3.38 (ABq, 4H, J = 13.6 Hz), 6.96-7.13 (m, 11H), 7.16-7.21 (m, 2H), 7.60 (s, 2H)

^{13}C NMR (50 MHz): δ 21.33, 27.97, 36.03, 48.45, 81.12, 120.47, 126.60, 127.48, 128.11, 129.03, 129.10, 129.47, 132.64, 137.81, 138.08, 142.06, 167.14

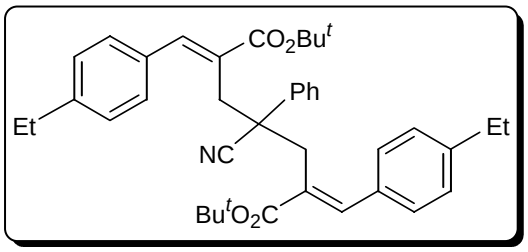
LCMS (*m/z*): 576 (M-H)$^{-}$

Anal. Calcd. for $C_{38}H_{43}NO_4$: C, 79.00; H, 7.50; N, 2.42

Found: C, 78.91; H, 7.51; N, 2.46

Di-*tert*-butyl 2,6-di[(*E*)-4-ethylbenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161g):

This bisadduct was obtained *via* the reaction of benzyl cyanide with *tert*-butyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate (**160g**) in the presence of NaH, as a colorless solid, following the similar procedure described for compound **161a**.



Reaction time: 1 h

Yield: 78%

Mp: 80-82 ^{o}C

IR(KBr): ν 2361, 1703, 1633 cm^{-1}

^1H NMR (400 MHz): δ 1.23 (t, 6H, J = 7.6 Hz), 1.44 (s, 18H), 2.64 (q, 4H, J = 7.6 Hz), 3.13 & 3.39 (ABq, 4H, J = 13.6 Hz), 6.98-7.22 (m, 13H), 7.60 (s, 2H)

^{13}C NMR (50 MHz): δ 15.43, 28.02, 28.68, 36.10, 48.45, 81.17, 120.49, 126.63, 127.45, 127.91, 128.08, 129.08, 129.49, 132.91, 137.79, 142.13, 144.38, 167.16

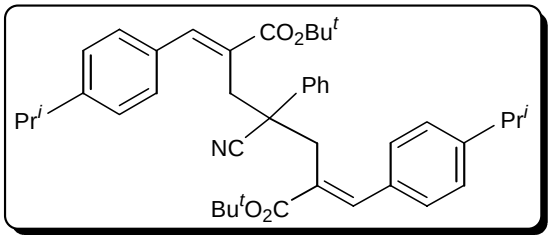
LCMS (*m/z*): 604 $(M-H)^-$

Anal. Calcd. for $C_{40}H_{47}NO_4$: C, 79.30; H, 7.82; N, 2.31

Found: C, 79.20; H, 7.82; N, 2.38

Di-*tert*-butyl 2,6-di[(*E*)-4-isopropylbenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161h):

This molecule was prepared, *via* bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy--3-(4-isopropylphenyl)-2-methylenepropanoate (**160h**) in the presence of NaH, as a colorless solid, following the similar procedure described for product **161a**.



Reaction time: 1 h

Yield: 72%

Mp: 110-111 ^oC

IR (KBr): ν 2239, 1711, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 1.25 (d, 12H, J = 6.8 Hz), 1.45 (s, 18H), 2.89 (sept, 2H, J = 6.8 Hz), 3.14 & 3.39 (ABq, 4H, J = 13.6 Hz), 6.97-7.07 (m, 7H), 7.08-7.19 (m, 6H), 7.60 (s, 2H)

^{13}C NMR (50 MHz): δ 23.90, 28.02, 33.94, 36.12, 48.45, 81.17, 120.47, 126.46, 126.60, 127.40, 128.04, 129.05, 129.47, 133.03, 137.74, 142.13, 148.97, 167.16

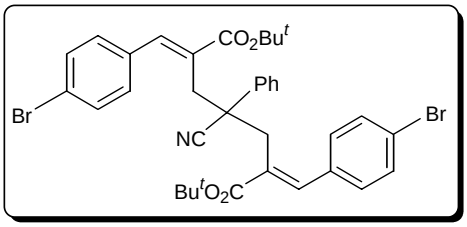
LCMS (*m/z*): 632 $(M\text{-H})^-$

Anal. Calcd. For $C_{42}H_{51}NO_4$: C, 79.58; H, 8.11; N, 2.21

Found: C, 79.63; H, 8.13; N, 2.32

Di-*tert*-butyl 2,6-di[(*E*)-4-bromobenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (161i):

This bisadduct was obtained as a colorless solid, *via* the bisalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-3-(4-bromophenyl)-2-methylenepropanoate (**160i**) in the presence of NaH, following the similar procedure described for molecule **161a**.



Reaction time: 1 h

Yield: 63%

Mp: 187-189 ^{o}C

IR (KBr): ν 2235, 1712, 1633 cm^{-1}

^{1}H NMR (400 MHz): δ 1.44 (s, 18H), 3.08 & 3.31 (ABq, 4H, J = 13.6 Hz), 6.92 (d, 4H, J = 8.4 Hz), 7.02-7.18 (m, 5H), 7.36 (d, 4H, J = 8.4 Hz), 7.53 (s, 2H)

^{13}C NMR (50 MHz): δ 27.97, 36.17, 48.33, 81.61, 120.18, 122.26, 126.58, 127.74, 128.28, 130.39, 130.92, 131.60, 134.41, 137.23, 140.67, 166.60

LCMS (*m/z*): 727 $(M+Na)^+$, 729 $[(M+2)+Na]^+$, 731 $[(M+4)+Na]^+$

Anal. Calcd. for $C_{36}H_{37}Br_2NO_4$: C, 61.12; H, 5.27; N, 1.98

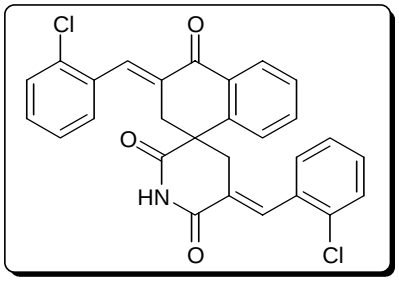
Found: C, 61.29; H, 5.25; N, 1.98

---

*In the case of **161b**,**d-i** crude compounds show the presence of 5-14% (Z)-isomer. However, crystallization (3% ethyl acetate in hexanes for **161b**,**d,f-h** and 8% ethyl acetate in hexanes for **161e** &**161i**), provides the pure (E)-isomer. In the case of **161c**, ^{1}H NMR of the crude product did not show the presence of any (Z)-isomer.*

2,5′-Di[(*E*)-2-chlorobenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162b):

This product was prepared *via* the reaction of di-*tert*-butyl 2,6-di[(*E*)-2-chloro-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**161b**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane, as a colorless solid, following the similar procedure described for molecule **162a**.



Reaction time: 6 h

Yield: 82%

Mp: 187-189 ^{o}C

IR (KBr): ν 3200-3050 (multiple bands), 1720, 1680, 1612 cm^{-1}

^{1}H NMR (400 MHz): δ 2.83 & 3.53 (ABq, 2H, J = 14.4 Hz), 3.05 & 3.09 (2s, 2H), 6.64 (d, 1H, J = 5.8 Hz), 7.08-7.64 (m, 10H), 7.89 (s, 1H), 7.97 (s, 1H), 8.21 (d, 1H, J = 6.3 Hz), 8.39 (s, 1H)

^{13}C NMR (100 MHz): δ 35.70, 36.12, 47.92, 125.79, 126.12, 126.75, 128.83, 129.31, 129.52, 129.93, 129.98, 130.12, 130.28, 130.67, 131.79, 132.09, 132.23, 133.34, 134.05, 134.59, 134.85, 137.15, 139.69, 142.22, 165.83, 173.97, 185.35

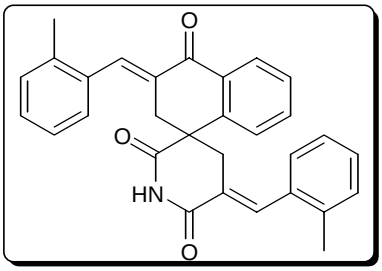
LCMS (*m/z*): 488 $(M+H)^{+}$, 490 $[(M+2)+H]^{+}$, 492 $[(M+4)+H]^{+}$

Anal. Calcd. for $C_{28}H_{19}Cl_2NO_3$: C, 68.86; H, 3.92; N, 2.87

Found: C, 68.80; H, 3.90; N, 2.98

2,5′-Di[(*E*)-2-methylbenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162c):

This compound was obtained as a colorless solid, *via* the treatment of di-*tert*-butyl 2,6-di[(*E*)-2-methylbenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**161c**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane, following the similar procedure described for product **162a**.

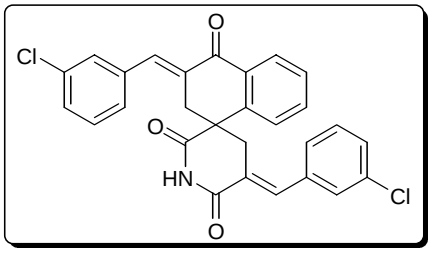


Reaction time:	6 h
Yield:	75%
Mp:	232-234 ^{o}C
IR (KBr):	ν 3300-2800 (multiple bands), 1718, 1684, 1650, 1624 cm^{-1}
^{1}H NMR (400 MHz): (50 % DMSO-d_6 in $CDCl_3$)	δ 1.92 (s, 3H), 2.05 (s, 3H), 2.87 & 3.36 (ABq, 2H, J = 15.0 Hz)*, 3.00-3.12 (m, 2H), 6.73 (d, 1H, J = 7.5 Hz), 7.00-7.36 (m, 8H), 7.44-7.52 (m, 1H), 7.55-7.65 (m, 1H), 7.71 (s, 1H), 7.81 (s, 1H), 8.10 (d, 1H, J = 7.6 Hz), 11.21 (br s, 1H)
^{13}C NMR (100 MHz): (50% DMSO-d_6 in $CDCl_3$)	δ 18.16, 18.34, 33.90, 33.98, 46.01, 124.21, 124.30, 125.17, 126.75, 126.88, 126.99, 127.06, 127.61, 127.69, 128.83, 128.96, 129.31, 131.24, 131.57, 132.24, 135.96, 136.31, 136.39, 137.92, 141.62, 165.04, 173.07, 184.00
LCMS (m/z):	448 $(M+H)^{+}$
Anal. Calcd. for $C_{30}H_{25}NO_3$:	C, 80.51; H, 5.63; N, 3.13
Found:	C, 80.55; H, 5.61; N, 3.16

**One of the doublets (second part) of the AB quartet arising from one of the methylenes (two protons) partly merges with moisture peak in DMSO-d_6 at δ 3.27. When we recorded in the presence of Eu(fod)$_3$ as a shift reagent, a multiplet at δ 2.84-3.15 for two methylenes (four protons) was observed.*

2,5′-Di[(*E*)-3-chlorobenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162d):

This compound was obtained *via* the treatment of di-*tert*-butyl 2,6-di[(*E*)-3-chloro-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**161d**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane, following the similar procedure described for molecule **162a**, as a colorless solid.



Reaction time: 6 h

Yield: 67%

Mp: 229-231 ^{o}C

IR (KBr): ν 3300-2950 (multiple bands), 1714, 1697, 1666, 1628 cm^{-1}

^{1}H NMR (400 MHz): (66.6% DMSO-d_6 in $CDCl_3$) δ 3.08 & 3.42 (ABq, 2H, J = 15.4 Hz), 3.17-3.29 (m, 2H),* 7.00-7.70 (m, 13H), 8.06 (d, 1H, J = 7.6 Hz), 11.36 (s, 1H)

^{13}C NMR (100 MHz): (66.6% DMSO-d_6 in $CDCl_3$) δ 32.98, 33.39, 45.08, 124.72, 125.69, 125.81, 126.28, 126.34, 126.48, 126.93, 127.01, 127.09, 127.47, 128.40, 128.42, 130.32, 130.75, 131.69, 131.72, 131.92, 134.14, 134.28, 134.75, 135.85, 140.89, 164.01, 172.16, 183.15

LCMS (*m/z*): 486 (M-H)$^{-}$, 488 [(M+2)-H]$^{-}$, 490 [(M+4)-H]$^{-}$

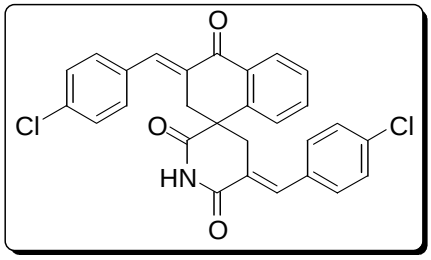
Anal. Calcd. for $C_{28}H_{19}Cl_2NO_3$: C, 68.86; H, 3.92; N, 2.87

Found: C, 68.73; H, 3.93; N, 2.83

**One of the methylenes (two protons) appears as multiplet at δ 3.17-3.29 which partly merges with moisture peak in DMSO-d_6 at δ 3.32.*

2,5′-Di[(*E*)-4-chlorobenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162e):

Treatment of di-*tert*-butyl 2,6-di[(*E*)-4-chlorobenzylidene]-4-cyano-4-phenyl-1,7-heptane-dioate (**161e**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane, provided title compound as a colorless solid, following the similar procedure described for molecule **162a**.



Reaction time: 6 h

Yield: 77%

Mp: 236-238 ^{o}C

IR (KBr): ν 3300-3000 (multiple bands), 1712, 1685, 1652, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 3.04 (s, 2H), 3.33 & 3.47 (ABq, 2H, J = 14.8 Hz), 6.82 (d, 2H, J = 7.3 Hz), 7.08-7.40 (m, 7H), 7.41-7.54 (m, 1H), 7.55-7.63 (m, 1H), 7.66 (s, 1H), 7.80 (s, 1H), 8.21 (d, 1H, J = 7.2 Hz), 8.35 (s, 1H)

^{13}C NMR (400 MHz): (50% DMSO-d_6 in $CDCl_3$) δ 34.00, 34.45, 46.35, 124.84, 125.57, 127.20, 127.27, 127.54, 129.55, 129.76, 129.98, 131.23, 131.31, 131.90, 132.60, 133.36, 133.50, 136.25, 137.64, 141.61, 165.06, 173.21, 184.11

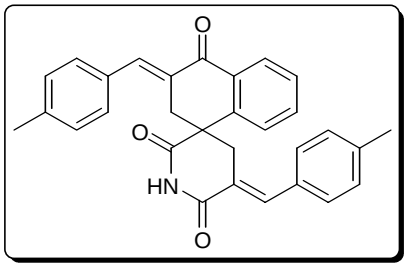
LCMS (*m/z*): 488 $(M+H)^+$, 490 $[(M+2)+H]^+$, 492 $[(M+4)+H]^+$

Anal. Calcd. for $C_{28}H_{19}Cl_2NO_3$: C, 68.86; H, 3.92; N, 2.87

Found: C, 68.66; H, 3.95; N, 2.86

2,5′-Di[(*E*)-4-methylbenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162f):

This compound was prepared *via* the reaction of di-*tert*-butyl 2,6-di[(*E*)-4-methyl-benzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**161f**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane, as a colorless solid, following the similar procedure described for product **162a**.



Reaction time: 6 h

Yield: 77%

Mp: 227-229 ^{o}C

IR (KBr): ν 3200-2950 (multiple ands), 1718, 1674, 1655, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 2.34 (s, 3H), 2.39 (s, 3H), 3.08 (s, 2H), 3.39 & 3.48 (ABq, 2H, J = 14.9 Hz), 6.81 (d, 2H, J = 7.6 Hz), 7.04-7.34 (m, 7H), 7.44-7.51 (m, 1H), 7.53-7.61 (m, 1H), 7.70 (s, 1H), 7.85 (s, 1H), 8.20 (d, 1H, J = 7.6 Hz), 8.41 (s, 1H, D_2O exchangeable)

^{13}C NMR (100 MHz): δ 21.47, 21.53, 35.34, 36.23, 48.25, 123.16, 126.59, 128.61, 129.08, 129.38, 129.41, 129.58, 130.00, 130.88, 131.83, 132.67, 133.82, 139.52, 139.98, 140.50, 142.51, 142.66, 166.56, 174.61, 185.89

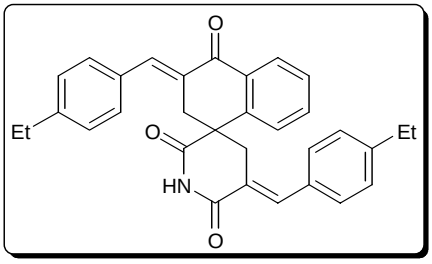
LCMS (*m/z*): 448 $(M+H)^+$

Anal. Calcd. for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63; N, 3.13

Found: C, 80.66; H, 5.62; N, 3.16

2,5′-Di[(*E*)-4-ethylbenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162g):

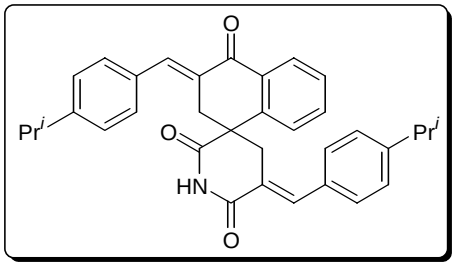
Treatment of di-*tert*-butyl 2,6-di[(*E*)-4-ethylbenzylidene]-4-cyano-4-phenyl-1,7-heptane-dioate (**161g**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane, furnished **162g** as a colorless solid, following the similar procedure described for molecule **162a**.



Reaction time:	6 h
Yield:	78%
Mp:	150-152 ^oC
IR (KBr):	ν 3200-2800 (multiple bands), 1714, 1684, 1650, 1630 cm^{-1}
^1H NMR (400 MHz):	δ 1.10-1.38 (m, 6H), 2.55-2.81 (m, 4H), 3.10 (s, 2H), 3.41 & 3.49 (ABq, 2H, J = 14.6 Hz), 6.83 (d, 2H, J = 7.6 Hz), 7.05-7.34 (m, 7H), 7.42-7.51 (m, 1H), 7.52-7.61 (m, 1H), 7.71 (s, 1H), 7.85 (s, 1H), 8.21 (d, 1H, J = 7.6 Hz), 8.66 (br s, 1H, D_2O exchangeable)
^{13}C NMR (100 MHz):	δ 15.30, 15.38, 28.77, 28.83, 35.29, 36.19, 48.29, 123.07, 126.59, 128.18, 128.22, 128.61, 129.01, 129.05, 129.68, 130.08, 131.07, 132.03, 132.65, 133.82, 140.49, 142.50, 142.65, 145.75, 146.23, 166.53, 174.59, 185.93
LCMS (*m/z*):	476 $(M+H)^+$
Anal. Calcd. for $C_{32}H_{29}NO_3$:	C, 80.82; H, 6.15; N, 2.95
Found:	C, 80.84; H, 6.19; N, 2.91

2,5′-Di[(*E*)-4-isopropylbenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162h):

This product was obtained as a colorless solid, *via* the reaction of di-*tert*-butyl 2,6-di[(*E*)-4-isopropylbenzylidene]-4-cyano-4-phenyl-1,7-hept-anedioate (**161h**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane, following the similar procedure described for molecule **162a**.



Reaction time: 6 h

Yield: 75%

Mp: 179-180 ^oC

IR (KBr): ν 3250-2900 (multiple bands), 1718, 1693, 1652, 1628 cm^{-1}

^1H NMR (400 MHz): δ 1.22-1.32 (m, 12H), 2.82-3.00 (m, 2H), 3.12 (s, 2H), 3.33-3.59 (m, 2H), 6.84 (d, 2H, J = 6.5 Hz), 7.03-7.34 (m, 7H), 7.41-7.51 (m, 1H), 7.52-7.62 (m, 1H), 7.70 (s, 1H), 7.84 (s, 1H), 8.21 (d, 1H, J = 6.7 Hz), 8.53 (s, 1H)

^{13}C NMR (100 MHz): δ 23.81, 34.05, 34.09, 35.26, 36.15, 48.32, 123.01, 126.62, 126.75, 126.81, 128.61, 128.99, 129.03, 129.75, 130.11, 131.19, 132.15, 133.82, 140.45, 142.54, 142.59, 150.29, 150.80, 166.62, 174.64, 185.98

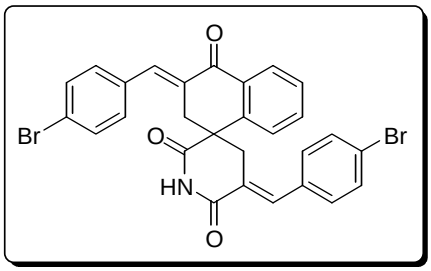
LCMS (*m/z*): 504 $(M+H)^+$

Anal. Calcd. for $C_{34}H_{33}NO_3$: C, 81.08; H, 6.60; N, 2.78

Found: C, 81.18; H, 6.61; N, 2.81

2,5′-Di[(*E*)-4-bromobenzylidene]-[1,2,3,4-tetrahydronaphthalen-1-one]-4-spiro-3′-[piperidine-2′,6′-dione] (162i):

This compound was obtained as a colorless solid *via* the treatment of di-*tert*-butyl 2,6-di[(*E*)-4-bromobenzylidene]-4-cyano-4-phenyl-1,7-heptanedioate (**161i**) with conc. H_2SO_4 / TFAA in 1,2-dichloroethane following the similar procedure described for molecule **162a**.



Reaction time: 6 h

Yield: 71%

Mp: 233-235 ^{o}C

IR (KBr): ν 3300-3050 (multiple bands), 1707, 1684, 1650, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 3.03 (s, 2H), 3.33 & 3.46 (ABq, 2H, J = 15.0 Hz), 6.74 (d, 2H, J = 8.4 Hz), 7.05 (d, 2H, J = 8.4 Hz), 7.24-7.54 (m, 6H), 7.56-7.73 (m, 1H), 7.64 (s, 1H), 7.78 (s, 1H), 8.22 (d, 1H, J = 7.8 Hz), 8.28 (s, 1H)

^{13}C NMR (100 MHz): (50% DMSO-d_6 in $CDCl_3$) δ 33.98, 34.41, 46.32, 121.78, 121.92, 124.91, 125.56, 127.19, 127.24, 129.75, 129.84, 130.18, 130.46, 131.29, 131.63, 132.30, 132.59, 136.24, 137.63, 141.60, 165.03, 173.18, 184.10

LCMS (*m/z*): 574 $(M-H)^-$, 576 $[(M+2)-H]^-$, 578 $[(M+4)-H]^-$

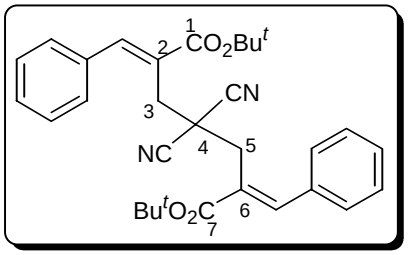
Anal. Calcd. for $C_{28}H_{19}Br_2NO_3$: C, 58.26; H, 3.32; N, 2.43

Found: C, 58.38; H, 3.33; N, 2.44

Two-step procedure to 3,3′-spiro-bis[5-{(*E*)-benzylidene}piperidine-2,6-dione] (165a):

Step 1: Di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4,4-dicyano-1,7-heptanedioate (163a):

A solution of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) (2 mmol, 0.550 g) in acetonitrile (3 mL) were added malononitrile (1 mmol, 0.07 g, 0.06 mL) and triethylamine (1 mmol, 0.131 mL) at room temperature. After stirring at room temperature for 1 h, solvent acetonitrile and Et_3N were evaporated under the reduced pressure, the residue, thus obtained was subjected to column chromatoghaphy (5% of ethyl acetate / hexanes) to afford di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4,4-dicyano-1,7-heptanedioate (**163a**) in 95% (0.434 g) as a colorless solid.



Mp: 109-111 ^{o}C

IR (KBr): ν 2251, 1711, 1630 cm^{-1}

^{1}H NMR (400 MHz): δ 1.54 (s, 18H), 3.20 (s, 4H), 7.22-7.29 (m, 4H), 7.32-7.42 (m, 6H), 7.91 (s, 2H)

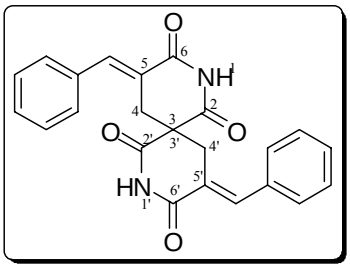
^{13}C NMR (50 MHz): δ 27.95, 33.89, 36.44, 82.31, 114.84, 127.31, 128.71, 128.86, 134.58, 144.63, 165.68

LCMS (*m/z*): 499 $(M+H)^{+}$

Step 2: 3,3′-Spiro-bis[5-{(*E*)-benzylidene}piperidine-2,6-dione] (165a):

To a stirred solution of di-*tert*-butyl 2,6-di[(*E*)-benzylidene]-4,4-dicyano-1,7-heptanedioate (**163a**) (1 mmol, 0.493 g) in dichloromethane (5 mL) at 0 ^{o}C conc. H_2SO_4 (2 mmol, 0.42 g,

0.28 mL) and trifluoroacetic anhydride (TFAA, 2 mmol, 0.196 g, 0.1 mL) were added. Then the reaction mixture was allowed to come to room temperature and stirred for 24 h. Reaction mixture was poured into aqueous K_2CO_3 solution and separated solid was filtered and well washed with water (to remove salts) followed by ethyl acetate (to remove any other organic impurities) and dried over under *vaccuo,* to provide the title compound (**165a**) as a colorless solid in 80% (0.31 g).



Mp: 255 ^{o}C (dec.)

IR (KBr): ν 3250-2830 (multiple bands), 1711, 1678, 1610 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 3.00 & 3.34* (ABq, 4H, J = 16 Hz), 7.13-7.50 (m, 8H),7.76 (s, 2H), 11.25 (s, 2H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 31.04, 50.85, 125.59, 128.89, 129.86, 129.88, 134.35, 138.91, 165.98, 170.55

Anal. Calcd. for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25

Found: C, 71.33; H, 4.71; N, 7.17

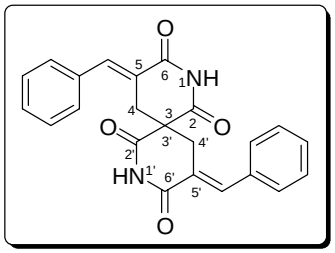
******One of the doublet of AB quartet for CH_2 protons (four protons) is merged with moisture in DMSO-d_6. When we recorded in pyridine-d_5 as a deuterated solvent clear appearence of AB quartet at δ 2.91 & 3.57 (4H, J =15.7 Hz) was observed.*

One-pot procedure of 3,3′-spiro-bis[5-{(*E*)-benzylidene}piperidine-2,6-dione] (165a):

To a stirred solution of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**160a**) (2 mmol, 0.552 g) in acetonitrile (3 mL) were added malononitrile (1 mmol, 0.066 g, 0.06

mL) and triethylamine (1 mmol, 0.131 mL) at room temperature. After stirring at room temperature for 1 h, solvent acetonitrile and Et_3N were evaporated under the reduced pressure. The resulting residue was diluted with dichloromethane (5 mL) & cooled to 0 ^oC. To this stirred solution at 0 ^oC conc. H_2SO_4 (2 mmol, 0.192 g, 0.10 mL) and trifluoroacetic anhydride (TFAA, 2 mmol, 0.42 g, 0.28 mL) were added. Then the reaction mixture was allowed to warm to room temperature. After stirring for 24 h at room temperature the reaction mixture was poured into aqueous K_2CO_3 solution. The solid separated was filtered and well washed with water followed by ethyl acetate (10 mL). Thus obtained solid was dried under *vaccuo,* to provide pure 3,3′-spiro-bis[5-{(*E*)-benzylidene}piperidine-2,6-dione] (**165a**), as a colorless solid in 75% (0.289 g) yield.

Mp: 255 ^oC (dec.)



The spectral data (IR, ^1H NMR & ^{13}C NMR) is in full agreement and identical with that of the molecule prepared in two-step methods.

IR (KBr): ν 3200-2830 (multiple bands), 1711, 1680, 1610 cm^{-1}

^1H NMR (400 MHz): (50% DMSO-d_6 in $CDCl_3$) δ 2.86 & 3.34 (ABq, 4H, J = 15.2 Hz), 7.19-7.41 (m, 10H), 7.72 (s, 2H), 11.08 (br s, 2H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 31.02, 50.84 125.59, 128.88, 129.34, 129.87, 134.34, 138.90, 165.97, 170.54

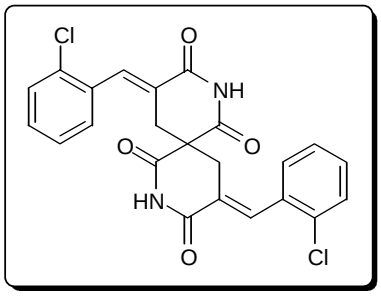
LCMS (*m/z*): 387 $(M+H)^+$

Anal. Calcd. for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25

Found: C, 71.33; H, 4.71; N, 7.17

3,3′-Spiro-bis[5-{(*E*)-2-chlorobenzylidene}piperidine-2,6-dione] (165b):

This was obtained as a colorless solid *via* the reaction of malononitrile with *tert*-butyl 3-acetoxy-3-(2-chlorophenyl)-2-methylenepropanoate (**160b**) in the presence of Et_3N, and subsequent treatment with conc. H_2SO_4 / TFAA in dichloromethane, following the similar one-pot procedure described for compound **165a**.



Reaction time: 1+24 h

Yield: 55%

mp: 240-241 ^oC

IR (KBr): ν 3200-2800 (multiple bands), 1716, 1687, 1639 cm^{-1}

^1H NMR (400 MHz): (DMSO-d_6) δ 2.90 & 3.17 (ABq, 4H, J = 15.6 Hz), 7.34 (d, 2H, J = 7.6 Hz), 7.38-7.48 (m, 4H), 7.56 (d, 2H, J = 7.6 Hz), 7.68 (s, 2H), 11.42 (s, 2H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 30.87, 50.84, 127.42, 127.90, 129.88, 130.58, 130.99, 132.64, 133.55, 135.51, 165.60, 170.42

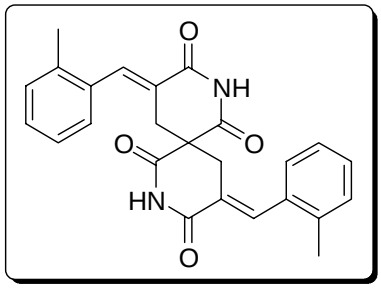
LCMS (*m/z*): 455 $(M+H)^+$; 457 $[(M+2)+H]^+$, 459 $[(M+4)+H]^+$

Anal. Calcd. for $C_{23}H_{16}Cl_2N_2O_4$: C, 60.67; H, 3.54; N, 6.15

Found: C, 60.55; H, 3.51; N, 6.11

3,3′-Spiro-bis[5-{(*E*)-2-methylbenzylidene}piperidine-2,6-dione] (165c):

This spiro-bisglutarimides was obtained as a colorless solid, *via* the reaction of malononitrile with *tert*-butyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (**160c**) in the presence of Et_3N, and subsequent treatment with conc. H_2SO_4 / TFAA in dichloromethane (5 mL), following the similar one-pot procedure described for compound **165a**.



Reaction time: 1+24 h

Yield: 56%

Mp: 190-192 ^{o}C

IR (KBr): ν 3200-2830 (multiple bands), 1711, 1680, 1622 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 2.15 (s, 6H), 2.80 & 3.10 (ABq, 4H, J = 15.4 Hz), 6.92-7.41 (m, 8H), 7.69 (s, 2H), 11.29 (br s, 2H)*

^{13}C NMR (100 MHz): (DMSO-d_6) δ 19.58, 30.95, 51.05, 125.89, 126.38, 128.61, 129.16, 130.38, 133.66, 137.21, 138.26, 166.16, 170.94

LCMS (*m/z*): 415 $(M+H)^+$

Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76

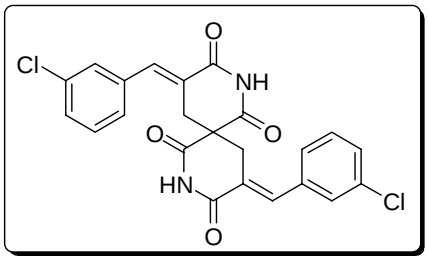
Found: C, 72.23; H, 5.34; N, 6.74

**For observation of -NH- proton we recorded the ^{1}H NMR spectrum with more sample.*

3,3′-Spiro-bis[5-{(*E*)-3-chlorobenzylidene}piperidine-2,6-dione] (165d):

This product was obtained as a colorless solid, *via* the reaction of malononitrile with *tert*-butyl 3-acetoxy-3-(3-chlorophenyl)-2-methylenepropanoate (**160d**) in the presence of Et_3N

/ CH_3CN, and subsequent treatment with conc. H_2SO_4 / TFAA in dichloromethane, following the similar procedure described for molecule **165a**.



Reaction time: 1+24 h

Yield: 61%

Mp: 222 ^oC (dec.)

IR (KBr): ν 3200-2800 (multiple bands), 1711, 1682, 1633, 1614 cm^{-1}

^1H NMR (400 MHz): (DMSO-d_6) δ 3.04 & 3.29* (ABq, 4H, J = 15.6 Hz), 5.00 (br s, 2H),* 7.35-7.50 (m, 8H), 7.65 (s, 2H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 31.17, 50.92, 127.60, 128.34, 129.00, 129.39, 130.70, 133.58, 136.72, 166.20, 170.97

LCMS (*m/z*): 455 $(M+H)^+$ 457 $(M+2+H)^+$

Anal. Calcd. for $C_{23}H_{16}Cl_2N_2O_4$: C, 60.67, H, 3.54, N, 6.15

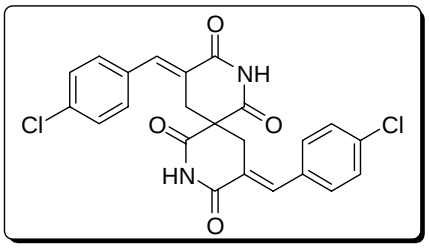
Found: C, 60.60; H, 3.54; N, 6.30.

******One of the doublet of AB quartet for CH_2 protons (four protons) is partly merges with moisture in DMSO-d_6. To prove this, we recorded in pyridine-d_5 as a deuterated solvent clear appearence of AB quartet at δ 3.30 & 3.93 (4H, J =15.6 Hz) was observed. And also we observed –NH- proton at δ 5.00.*

3,3′-Spiro-bis[5-{(*E*)-4-chlorobenzylidene}piperidine-2,6-dione] (165e):

Treatment of malononitrile with *tert*-butyl 3-acetoxy3-(4-chlorophenyl)-2-methylene-propanoate (**160e**) in the presence of Et_3N / CH_3CN, and subsequent treatment with conc.

H_2SO_4 / TFAA in dichloromethane, provided the title compound as a colorless solid, following the similar procedure described for molecule **165a**.



Reaction time: 1+24 h

Yield: 72%

Mp: 230 ^{o}C (dec.)

IR (KBr: ν 3250-2800 (multiple bands), 1710, 1685, 1647, 1618 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 2.88 & 3.23* (ABq, 4H, J = 15.16 Hz), 7.30-7.56 (m, 8H), 7.60 (s, 2H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 31.54, 51.12, 127.70, 128.84, 131.57, 133.56, 133.75, 136.00, 167.32, 172.32

LCMS (*m/z*): 455 $(M+H)^+$ 457 $(M+2+H)^+$

Anal. Calcd. for $C_{23}H_{16}Cl_2N_2O_4$: C, 60.67, H, 3.54, N, 6.15

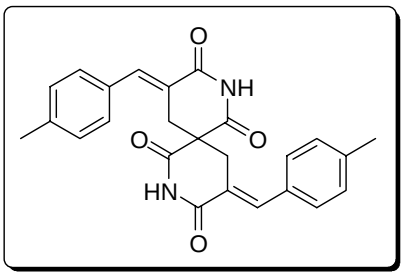
Found: C, 60.63, H, 3.53, N, 6.13

******One of the doublet of AB quartet for CH_2 protons (four protons) is parlty merges with moisture in DMSO-d_6. We did not observe –NH- proton peak due to low-solubility.*

3,3′-Spiro-bis[5-{(*E*)-4-methylbenzylidene}piperidine-2,6-dione] (165f):

This was obtained as a colorless solid, *via* the reaction of malononitrile with *tert*-butyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (**160f**) in the presence of Et_3N, and

subsequent treatment with conc. H_2SO_4 / TFAA in dichloromethane, following the similar one-pot procedure described for compound **160a**.



Reaction time: 1+24 h

Yield: 64%

mp: 245 ^oC (dec.)

IR (KBr): ν 3200-2800 (multiple bands), 1711, 1684, 1618 cm^{-1}

^1H NMR (400 MHz): (DMSO-d_6) δ 2.33 (s, 6H), 3.08 & 3.32* (ABq, 4H, J = 15.8 Hz), 7.19-7.41 (m, 8H), 7.68 (s, 2H), 11.20 (br s, 2H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 21.13, 31.12, 50.82, 124.60, 129.53, 130.01, 131.51, 139.11, 139.34, 166.08, 170.59

LCMS (*m/z*): 415 $(M+H)^+$

Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76

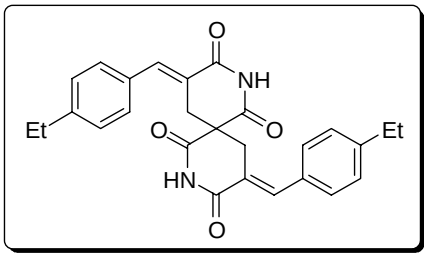
Found: C, 72.63; H, 5.37; N, 6.84

******One of the doublet of AB quartet for CH_2 protons (four protons) is merged with moisture in DMSO-d_6. To prove this, our attempts using in the presence of Eu(fod)$_3$ as a shift reagent, were unsuccessful. However, when we recorded in pyridine-d_5 as a deuterated solvent clear appearence of AB quartet at δ 3.32 & 3.97 (4H, J =15.6 Hz) was observed.*

3,3′-Spiro-bis[5-{(*E*)-4-ethylbenzylidene}piperidine-2,6-dione] (165g):

This was obtained as a colorless solid, *via* the reaction between malononitrile and *tert*-butyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate (**160g**) in the presence of Et_3N,

and subsequent treatment with conc. H_2SO_4 / TFAA in dichloromethane, following the similar one-pot procedure described for compound **165a**.



Reaction time: 1+24 h

Yield: 59%

Mp: 218-220 ^{o}C

IR (KBr): ν 3200-2850 (multiple bands), 1724, 1699, 1630 cm^{-1}

^{1}H NMR (400 MHz): δ 1.27 (t, 6H, J = 7.6 Hz), 2.70 (q, 4H, J = 7.6 Hz), 2.94 & 3.53 (ABq, 4H, J = 15.6 Hz), 7.17-7.30 (m, 8H), 7.93 (s, 2H), 8.23 (s, 2H, D_2O exchangeable)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 15.46, 28.20, 31.18, 50.85, 124.65, 128.36, 130.14, 131.80, 139.08, 145.52, 166.12, 170.61

LCMS (*m/z*): 443 $(M+H)^+$

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92; N, 6.33

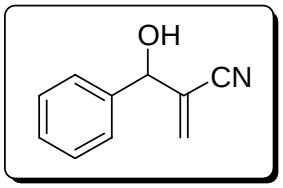
Found: C, 73.07; H, 5.92; N, 6.23

3-Hydroxy-2-methylene-3-phenylpropanenitrile (179a):

This was prepared according the procedure developed in our laboratory.[29,196]

Benzaldehyde (30 mmol, 3.18 g, 3.0 mL), acrylonitrile (75 mmol, 3.97 g, 4.9 mL) and DABCO (7.5 mmol, 0.84 g) were mixed and the resulting solution was kept at room temperature for 2 days. The reaction mixture was diluted with ether (50 mL) and washed

successively with 2*N* HCl solution, water and aqueous $NaHCO_3$ solution. Ogranic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was distilled under reduced pressure to afford 3-hydroxy-2-methylene-3-phenylpropanenitrile (**179a**) as a colorless liquid in 70% (4.0 g) yield.



Bp: 118-120 °C / 2.0 mm (Lit.[196] 125-126°C / 2.2 mm)

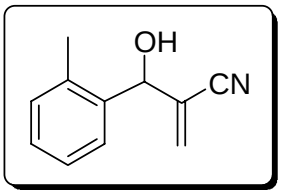
IR (neat): ν 3431, 2229, 1622 cm^{-1}

^1H NMR (400 MHz): δ 3.18 (br s, 1H), 5.17 (s, 1H), 5.93 (s, 1H), 6.01 (s, 1H), 7.25-7.42 (m, 5H)

^{13}C NMR (50 MHz): δ 73.63, 116.88, 125.97, 126.31, 128.57, 130.07, 139.05

3-Hydroxy-2-methylene-3-(2-methylphenyl)propanenitrile (179b):

This compound was prepared via the treatment of 2-methylbenzaldehyde with acrylonitrile in the presence of DABCO (cat.) following the similar procedure described for the molecule **179a**, as a colorless liquid.



Reaction time: 2 d

Bp: 144-146 °C / 1.5 mm (Lit.[196] 130-132 °C / 1.3 mm)

Yield: 68%

IR (neat): ν 3468, 2227, 1624 cm^{-1}

^{1}H NMR (400 MHz): δ 2.39 (s, 3H), 2.44 (br s, 1H), 5.55 (s, 1H), 6.04 (d, 1H, J = 1.2 Hz), 6.08 (d, 1H, J = 1.2 Hz), 7.15-7.32 (m, 3H), 7.38-7.50 (m, 1H)

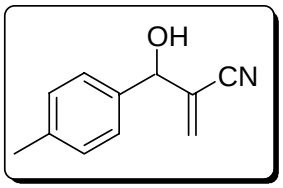
^{13}C NMR (50 MHz): δ 19.02, 70.76, 117.17, 125.73, 126.43, 126.63, 128.74, 130.15, 130.87, 135.68, 137.13

3-Hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (179c):

This allylic alcohol was obtained as a colorless liquid, *via* the Baylis-Hillman coupling of 4-methylbenzaldehyde with acrylonitrile in the presence of DABCO (cat.), following the similar procedure described for the molecule **179a**.

Reaction time: 2 d

Bp: 136-138 °C / 0.4 mm (Lit.[196] 122-125°C / 0.3 mm)



Yield: 77%

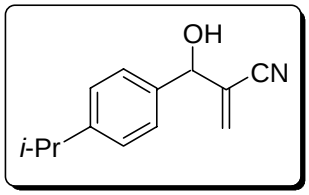
IR (neat): ν 3439, 2229, 1616 cm^{-1}

^{1}H NMR (400 MHz): δ 2.30 (s, 3H), 3.57 (d, 1H, J = 4.0 Hz), 5.04 (d, 1H, J = 4.0 Hz), 5.85 (s, 1H), 5.94 (s, 1H), 7.07-7.20 (m, 4H)

^{13}C NMR (50 MHz): δ 20.94, 73.58, 116.97, 126.34, 129.32, 129.66, 136.21, 138.39

3-(4-Isopropylphenyl)-3-hydroxy-2-methylenepropanenitrile (179d):

This compound was obtained as a colorless liquid, *via* the DABCO catalyzed coupling of 4-isopropylbenzaldehye with acrylonitrile, following the similar procedure described for the compound **179a**.



Reaction time: 2 d

Yield: 65%

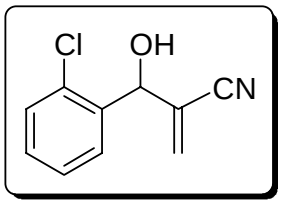
IR (neat): ν 3449, 2229, 1616 cm^{-1}

^1H NMR (400 MHz): δ 1.24 (d, 6H, J = 6.8 Hz), 2.76 (br s, 1H), 2.89 (sept, 1H, J = 6.8 Hz), 5.23 (s, 1H), 5.99 (s, 1H), 6.07 (s, 1H), 7.24 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz)

^{13}C NMR (50 MHz): δ 23.85, 33.77, 73.82, 117.07, 126.29, 126.53, 126.87, 129.71, 136.57, 149.58

3-(2-Chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (179e):

This molecule was prepared as a colorless liquid, *via* the Baylis-Hillman coupling of 2-chlorobenzaldehyde with acrylonitrile in the presence of catalytic amount of DABCO, following the similar procedure described for the product **179a**.



Reaction time: 2 d

Bp: 136-138 °C / 1.0 mm (Lit.[196] 143-145 °C / 1.2 mm)

Yield: 70%

IR (neat): ν 3456, 2231, 1622 cm^{-1}

^{1}H NMR (400 MHz): δ 3.00 (d, 1H, J = 4.0 Hz), 5.74 (d, 1H, J = 4.0 Hz), 6.04 (s, 2H), 7.22-7.43 (m, 3H), 7.60 (d, 1H, J = 7.6 Hz)

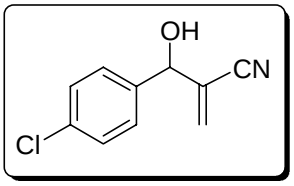
^{13}C NMR (50 MHz): δ 70.12, 116.66, 124.49, 127.40, 127.85, 129.55, 129.79, 131.43, 132.40, 136.46

3-(4-Chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (179f):

It was obtained as a colorless liquid, *via* the Baylis-Hillman reaction between 4-chlorobezaldehyde and acrylonitrile under the catalytic influence of DABCO, following the similar procedure described for the molecule **179a**.

Reaction time: 2 d

Bp: 138-142 °C / 1.0 mm (Lit.[196] 139-141 °C / 0.7 mm)



Yield: 78%

IR (neat): ν 3495, 2231, 1618 cm^{-1}

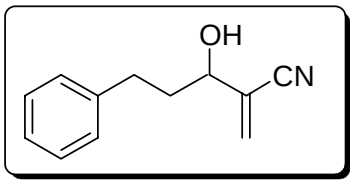
^{1}H NMR (400 MHz): δ 2.66 (br s, 1H), 5.27 (s, 1H), 6.03 (d, 1H, J = 1.2 Hz), 6.10 (d, 1H, J = 1.2 Hz), 7.27-7.45 (m, 4H)

^{13}C NMR (50 MHz): δ 73.21, 116.73, 125.85, 127.84, 128.91, 130.41, 134.51, 137.67

3-Hydroxy-2-methylene-5-phenylpentanenitrile (179g):

This compound was prepared as a colorless liquid (after silica gel column chromatography, 5% EtOAc in hexanes), *via* the treatment of hydrocinnamaldehyde with acrylonitrile in the

presence of DABCO (cat), following the similar procedure described for the compound **179a**.



Reaction time: 2 d

Yield: 73%

IR (neat): ν 3462, 2226, 1628 cm^{-1}

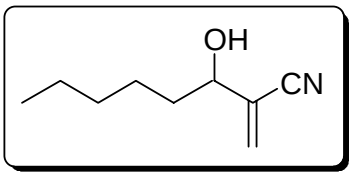
^{1}H NMR (400 MHz): δ 1.88-2.20 (m, 3H), 2.62-2.85 (m, 2H), 4.20-4.29 (m, 1H), 6.00 (s, 2H), 7.15-7.36 (m, 5H)

^{13}C NMR (50 MHz): δ 31.08, 36.88, 71.13, 116.97, 126.00, 126.56, 128.28, 128.37, 130.22, 140.67

3-Hydroxy-2-methyleneoctanenitrile (179h):

This Baylis-Hillman alcohol was obtained as a colorless liquid, *via* the coupling of hexanal with acrylonitrile in the presence of catalytic amount of DABCO, following the similar procedure described for the product **179a**.

Reaction time: 2 d



Bp: 98-100 °C / 2.0 mm (Lit.[196] 110-111 °C / 2.4 mm)

Yield: 78%

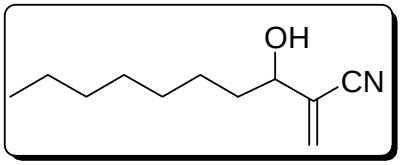
IR (neat): ν 3481, 2227, 1624 cm^{-1}

^{1}H NMR (400 MHz): δ 0.90 (t, 3H, J = 6.5 Hz), 1.25-1.50 (m, 6H), 1.59-1.85 (m, 2H), 2.15 (br s, 1H), 4.20-4.29 (m, 1H), 5.98 (s, 1H), 5.99 (s, 1H)

^{13}C NMR (50 MHz): δ 13.81, 22.35, 24.60, 31.30, 35.40, 72.05, 117.05, 126.90, 129.93

3-Hydroxy-2-methylenedecanenitrile (179i):

This Baylis-Hillman adduct was obtained as a colorless liquid (after silica gel column chromatography, 5% EtOAc in hexanes), *via* the Baylis-Hillman reaction of octanal with acrylonitrile in the presence of catalytic amount of DABCO, following the similar procedure described for the compound **179a**.



Reaction time: 2 d

Yield: 75%

IR (neat): ν 3477, 2227, 1622 cm^{-1}

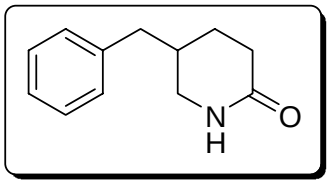
^{1}H NMR (400 MHz): δ 0.85 (t, 3H, J = 7.0 Hz), 1.26-1.50 (m, 10H), 1.60-1.79 (m, 2H), 2.15 (d, 1H, J = 5.0 Hz), 4.18-4.28 (m, 1H), 5.97 (s, 1H), 5.99 (s, 1H)

^{13}C NMR (50 MHz): δ 13.91, 22.49, 24.99, 29.04, 29.14, 31.64, 35.52, 72.10, 117.07, 126.99, 129.83

5-Benzyl-2-piperidone (181a):

A stirred solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**179a**) (1 mM, 0.159 g) in triethyl orthoacetate (1 mL) was heated at 145 ^{o}C in the presence of catalytic amount of propanoic acid (3 drops) for 2 h. Excess orthoester (along with propanoic acid) was distilled off under reduced pressure. The residue was diluted with methanol (8 mL) and

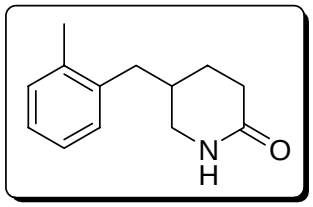
$CoCl_2.6H_2O$ (2 mM, 0.476 g) was added. Resulting solution was cooled to 0 ^oC and $NaBH_4$ (10 mM, 0.38 g) was added portion-wise (three portions) in 15 min duration (hydrogen gas evolution was observed). The reaction mixture (black precipitate formed) was stirred for 30 min at 0 ^oC, and then allowed to warm to room temperature and stirred for 6 h. Methanol was removed under reduced pressure. Residue was diluted with 4 *N* HCl (15 mL) and extracted with EtOAc (3 X 20 mL). Combined organic layer was washed with water (20 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 100% EtOAc) to furnish 5-benzyl-2-piperidone **(181a)** as a colorless solid in 60% (0.114 g) yield.



Mp:	107-109 ^oC
IR (KBr):	ν 3300-2800 (multiple bands), 1662 cm^{-1}
^1H NMR (400 MHz):	δ 1.46-1.60 (m, 1H), 1.85-1.96 (m, 1H), 2.00-2.15 (m, 1H), 2.25-2.49 (m, 2H), 2.55-2.70 (m, 2H), 2.95-3.04 (m, 1H), 3.20-3.29 (m, 1H), 6.27 (br s, 1H, D_2O exchangeable), 7.14 (d, 2H, J = 6.8 Hz), 7.19-7.34 (m, 3H)
^{13}C NMR (50 MHz):	δ 26.86, 30.67, 35.13, 39.62, 47.33, 126.46, 128.57, 128.91, 139.24, 172.60
LCMS (*m/z*):	190 $(M+H)^+$
Anal. Calcd. For $C_{12}H_{15}NO$:	C, 76.16; H, 7.99; N 7.40
Found:	C, 76.18; H, 8.04; N, 7.45

5-(2-Methylbenzyl)-2-piperidone (181b):

This product was obtained as a colorless solid, *via* the treatment of 3-hydroxy-2-methylene-3-(2-methylpheny)propanenitrile (**179b**) with triethyl orthoacetate followed by the treatment with $NaBH_4$ / $CoCl_2.6H_2O$ in methanol, following the similar procedure described for the compound **181a**.



Reaction time: 6.5 h

Yield: 58%

Mp: 103-105 ºC

IR (KBr): ν 3300-2800 (multiple bands), 1666 cm^{-1}

^1H NMR (400 MHz): δ 1.49-1.64 (m, 1H), 1.83-1.97 (m, 1H), 2.00-2.12 (m, 1H), 2.25-2.50 (m, 5H), 2.63 (d, 2H, J = 7.2 Hz), 2.97-3.07 (m, 1H), 3.21-3.30 (m, 1H), 6.35 (br s, 1H, D_2O exchangeable), 7.05-7.20 (m, 4H)

^{13}C NMR (50 MHz): δ 19.39, 26.98, 30.59, 33.94, 36.68, 47.23, 125.85, 126.46, 129.66, 130.46, 135.94, 137.45, 172.67

LCMS (*m/z*): 204 $(M+H)^+$

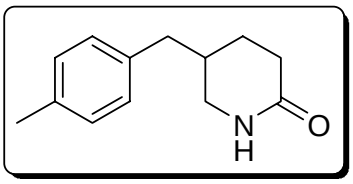
Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89

Found: C, 76.77; H, 8.49; N, 6.93

5-(4-Methylbenzyl)-2-piperidone (181c):

This compound was prepared *via* successive treatment of 3-hydroxy-2-methylene-3-(4-methylpheny)propanenitrile (**179c**) with triethyl orthoacetate and $NaBH_4$ / $CoCl_2.6H_2O$ in

methanol, following the similar procedure described for the product **181a**, as a colorless solid.



Reaction time: 6.5 h

Yield: 64%

Mp: 111-113 ºC

IR (KBr): ν 3200-2850 (multiple bands), 1662 cm^{-1}

^1H NMR (400 MHz): δ 1.45-1.58 (m, 1H), 1.85-1.94 (m, 1H), 1.99-2.10 (m, 1H), 2.25-2.49 (m, 5H), 2.51-2.65 (m, 2H), 2.94-3.03 (m, 1H), 3.20-3.28 (m, 1H), 6.19 (br s, 1H), 7.03 (d, 2H, J = 7.6 Hz), 7.10 (d, 2H, J = 7.6 Hz)

^{13}C NMR (50 MHz): δ 20.96, 26.81, 30.62, 35.15, 39.16, 47.23, 128.74, 129.15, 135.87, 136.14, 172.60

LCMS (*m/z*): 204 $(M+H)^+$

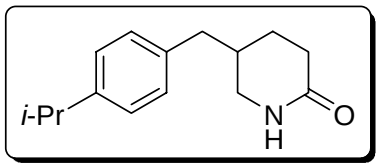
Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89

Found: C, 76.70; H, 8.41; N, 7.00

5-(4-Isopropylbenzyl)-2-piperidone (181d):

The Johnson-Claisen rearrangement of 3-(4-isopropylphenyl)-3-hydroxy-2-methylene-propanenitrile (**179d**) with triethyl orthoacetate and then treatment with $NaBH_4$ / $CoCl_2.6H_2O$ in methanol, following the similar procedure described for the product **181a**, provided the title compound as a colorless solid.

Reaction time: 6.5 h



Yield: 56%

Mp: 95-96 ºC

IR (KBr): ν 3320-2850 (multiple bands), 1664 cm^{-1}

^1H NMR (400 MHz): δ 1.23 (d, 6H, J = 6.8 Hz), 1.45-1.59 (m, 1H), 1.86-1.95 (m, 1H), 1.99-2.12 (m, 1H), 2.25-2.67 (m, 4H), 2.83-3.04 (m, 2H), 3.21-3.28 (m, 1H), 6.11 (br s, 1H, D_2O exchangeable), 7.06 (d, 2H, J = 7.8 Hz), 7.15 (d, 2H, J = 7.8 Hz)

^{13}C NMR (50 MHz): δ 24.00, 26.86, 30.62, 33.67, 35.11, 39.18, 47.23, 126.51, 128.79, 136.50, 146.93, 172.67

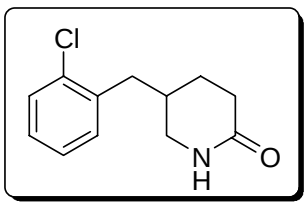
LCMS (*m/z*): 232 $(M+H)^+$

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05

Found: C, 77.96; H, 9.17; N, 6.03

5-(2-Chlorobenzyl)-2-piperidone (181e):

Treatment of 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (**179e**) with triethyl orthoacetate and subsequent reaction with $CoCl_2.6H_2O$ in the presence of $NaBH_4$ in methanol, following the similar procedure described for the molecule (**181a**), furnished **181e** as a colorless solid.



Total reaction time: 6.5 h

Yield: 53%

Mp: 106-108 ºC

IR (KBr): ν 3200-2950 (multiple bands), 1672 cm^{-1}

^1H NMR (400 MHz): δ 1.48-1.60 (m, 1H), 1.85-1.96 (m, 1H), 2.01-2.14 (m, 1H), 2.27-2.50 (m, 2H), 2.54-2.70 (m, 2H), 2.94-3.05 (m, 1H), 3.21-3.30 (m, 1H), 6.05 (br s, 1H), 7.08 (d, 1H, J = 7.6 Hz), 7.11-7.33 (m, 2H), 7.36 (d, 1H, J = 8.0 Hz)

^{13}C NMR (50 MHz): δ 26.88, 30.59, 33.65, 37.02, 47.16, 126.82, 127.99, 129.81, 131.14, 134.22, 137.06, 172.45

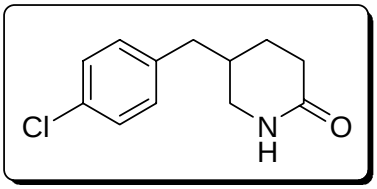
LCMS (*m/z*): 224 $(M+H)^+$, 226 $(M+2+H)^+$

Anal. Calcd. for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26

Found: C, 64.47; H, 6.39; N, 6.25

5-(4-Chlorobenzyl)-2-piperidone (181f):

This was prepared as a colorless solid, *via* the reaction of 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (**179f**) with triethyl orthoacetate and followed by the treatment with $NaBH_4$ / $CoCl_2.6H_2O$ in methanol, following the similar procedure described for the compound **181a**.



Reaction time: 6.5 h

Yield: 55%

Mp: 109-111 ºC

IR (KBr): ν 3300-2950 (multiple bands), 1657 cm^{-1}

^{1}H NMR (400 MHz): δ 1.45-1.59 (m, 1H), 1.83-1.93 (m, 1H), 1.98-2.12 (m, 1H), 2.24-2.49 (m, 2H), 2.52-2.68 (m, 2H), 2.92-3.03 (m, 1H), 3.18-3.29 (m, 1H), 6.15 (br s, 1H), 7.06 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz)

^{13}C NMR (50 MHz): δ 26.69, 30.50, 34.98, 38.84, 47.06, 128.62, 130.17, 132.21, 137.67, 172.45

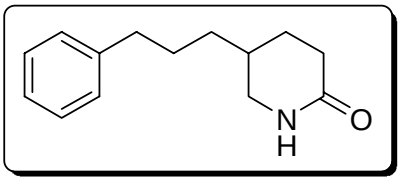
LCMS (*m/z*): 224 $(M+H)^+$, 226 $(M+2+H)^+$

Anal. Calcd. for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26

Found: C, 64.48; H, 6.30; N, 6.21

5-(3-Phenylpropyl)-2-piperidone (181g):

This product was prepared *via* the Johnson-Claisen (using triethyl orthoacetate) rearrangement of 3-hydroxy-2-methylene-5-phenylpentanenitrile (**179g**) followed by treatment with $NaBH_4$ / $CoCl_2.6H_2O$ in methanol, following the similar procedure described for the compound **181a**, as a colorless solid.



Total reaction time: 6.5 h

Yield: 59%

Mp: 88-90 ºC

IR (KBr): ν 3300-2840 (multiple bands), 1664 cm^{-1}

^{1}H NMR (400 MHz): δ 1.29-1.50 (m, 3H), 1.56-1.95 (m, 4H), 2.26-2.47 (m, 2H), 2.56-2.66 (m, 2H), 2.88-2.97 (m, 1H), 3.28-3.38 (m, 1H), 6.06 (br s, 1H), 7.13-7.31 (m, 5H)

^{13}C NMR (50 MHz): δ 26.88, 28.60, 30.59, 32.56, 32.95, 35.81, 47.36, 125.73, 128.23, 141.93, 172.64

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

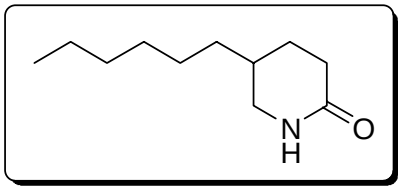
Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45

Found: C, 77.55; H, 8.81; N, 6.48

5-Hexyl-2-piperidone (181h):

This product was prepared *via* the successive treatment of 3-hydroxy-2-methyleneoctane-nitrile (**179h**) with triethyl orthoacetate and $NaBH_4$ / $CoCl_2.6H_2O$ in methanol, following the similar procedure described for the molecule **181a**, as a colorless solid.

Total reaction time: 6.5 h



Yield: 67%

Mp: 43-45^o C

IR (KBr): ν 3300-2800, 1670, 1504 cm^{-1}

^{1}H NMR (400 MHz): δ 0.86 (t, 3H, J = 6.8Hz), 1.20-1.50 (m, 11H), 1.69-2.05 (m, 2H), 2.26-2.43 (m, 2H), 2.85-2.92 (m, 1H), 3.28-3.35 (m, 1H), 6.51 (s, 1H)

^{13}C NMR (50 MHz): δ 13.91, 22.47, 26.79, 27.00, 29.24, 30.64, 31.61, 33.02, 47.43, 172.81

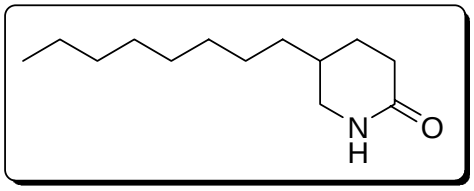
LCMS (*m/z*): 184 $(M+H)^+$

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08: H, 11.55; N, 7.64

Found: C, 72.08: H, 11.55; N, 7.64

5-Octyl-2-piperidone (181i):

This product was obtained as a colorless solid, *via* the successive treatment of 3-hydroxy-2-methylenedecanenitrile (**179i**) with triethyl orthoacetate and $NaBH_4$ / $CoCl_2.6H_2O$ in methanol following the similar procedure described for the compound **181a**.



Total reaction time: 6.5 h

Yield: 65%

Mp: 59-61 ºC

IR (KBr): ν 3300-2800 (multiple bands), 1674 cm^{-1}

^1H NMR (400 MHz): δ 0.88 (t, 3H, J = 6.8 Hz), 1.20-1.51 (m, 15H), 1.71-1.80 (m, 1H), 1.84-1.95 (m, 1H), 2.24-2.48 (m, 2H), 2.89-2.98 (m, 1H), 3.29-3.38 (m, 1H), 6.19 (br s, 1H, D_2O exchangeable)

^{13}C NMR (50 MHz): δ 14.10, 22.66, 26.96, 27.10, 29.26, 29.50, 29.72, 30.79, 31.86, 33.14, 47.65, 172.81

LCMS (*m/z*): 212 $(M+H)^+$

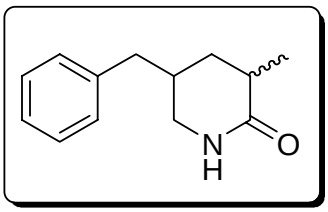
Anal. Calcd. for $C_{13}H_{25}NO$: C, 73.88; H 11.92; N, 6.63

Found: C, 73.89; H, 11.99; N, 6.60

5-Benzyl-3-methyl-2-piperidone (181j):

The reaction of 3-hydroxy-2-methylene-3-phenypropanenitrile (**179a**) with triethyl orthopropanoate and then subsequent reaction with $CoCl_2.6H_2O$ in the presence of $NaBH_4$

in methanol, following the similar procedure described for the compond **181a**, gave the title compound, as a colorless solid.



Total reaction time: 6.5 h

Yield: 61%

Mp: 84-86 ºC

IR (KBr): ν 3300-2900 (multiple bands), 1658 cm^{-1}

^1H NMR (400 MHz): δ 1.17-2.78 (m, 9H),* 2.92-3.05 (m, 1H), 3.15-3.30 (m, 1H), 6.46 & 6.50 (br 2s, 1H, diastereomeric NH protons, 1:1 ratio), 7.05-7.38 (m, 5H)

^{13}C NMR (50 MHz): δ 17.08, 18.51, 31.73, 33.82, 34.26, 35.71, 35.93, 36.27, 39.23, 40.25, 46.94, 47.87, 126.31, 128.45, 128.79, 139.17, 139.39, 175.68, 176.23

LCMS (*m/z*): 204 $(M+H)^+$

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89

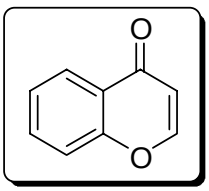
Found: C, 76.97; H, 8.48; N, 6.95

*This multiplet contains two doublets at δ 1.19 & 1.23 (in almost 1:1 ratio) indicating that this molecule is a mixture of diastereomers.

1-Benzopyran-4(4*H*)-one (186a)

This compound was prepared according to the literature procedure with minor modification.[278]

To a stirred solution of 2′-hydroxyacetophenone (**185a**) (50 mmol, 6.8 g, 6.0 mL) in ethyl formate (750 mmol, 55.5 g, 60.0 mL) at 0 ^{o}C was added NaH (55-60% dispersion in oil) (250 mmol, 11.0 g) portion wise in 20-30 min. After keeping the reaction mixture for 12 h at room temperature, cold water was added carefully and the resulting solution was extracted twice with ether (2 X 30 mL) to remove any starting materials. The aqueous layer was then acidified with acetic acid ($P^H \approx 4$) and extracted with ether (3 X 60 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product, thus obtained, was treated with dilute sulfuric acid (32 mL of 98% H_2SO_4 mixed with 140 mL of H_2O) and heated under reflux for 2 h. The reaction mixture was cooled to room temperature and diluted with ether. Organic layer was separated and successively washed with water, saturated aqueous $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was subjected to column chromatography (silica gel, 15% EtOAc in hexanes) to afford the desired compound **186a** in 56% (4.1 g) yield as a pale-yellow solid.



Mp: 52-54 ^{o}C (lit.[278] 59 ^{o}C)

IR (KBr): ν 1651, 1618 cm^{-1}

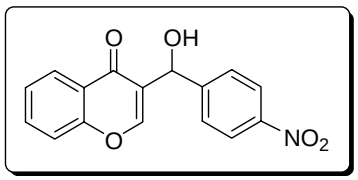
^{1}H NMR (400 MHz): δ 6.34 (d, 1H, J = 6.0 Hz), 7.34-7.50 (m, 2H), 7.63-7.72 (m, 1H), 7.82-7.91 (m, 1H), 8.20 (d, 1H, J = 7.8 Hz)

^{13}C NMR (100 MHz): δ 112.68, 117.94, 124.64, 124.95, 125.44, 133.49, 155.15, 156.25, 177.20

3-[Hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (187a):

This compound was prepared following the procedure as reported in the literature.[277]

A solution of 1-benzopyran-4(4*H*)-one (**186a**) (5 mmol, 0.73 g), 4-nitrobenzaldehyde (5 mmol, 0.755 g) and sodium methoxide (2.5 mmol, 0.132 g) in methanol (10 mL) was stirred for 5 h at room temperature. Methanol was removed under reduced pressure and residue thus obtained was quenched with 1*N* HCl (10 mL) and extracted with dichloromethane (3 X 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Thus crude solid obtained was crystallized from methanol / acetonitrile (1:1) to afford as a pale-yellow solid in 83% (1.23 g) yield.



Mp: 188-189 ^{o}C (Lit.[55] 186-187 ^{o}C)

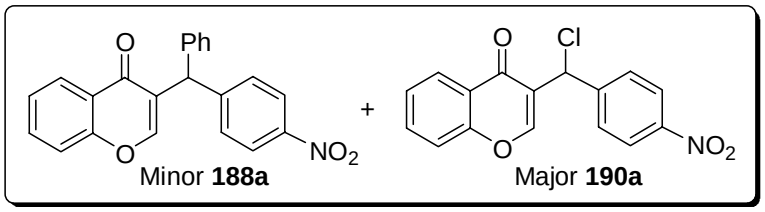
IR (KBr): ν 3379, 1626, 1593 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 5.91 (s, 1H), 6.28 (s, 1H), 7.40-7.50 (m, 1H), 7.62 (d, 1H, *J* = 8.4 Hz), 7.68-7.82 (m, 3 H), 7.99 (d, 1H, *J* = 7.8 Hz), 8.16 (d, 2H, *J* = 8.4 Hz), 8.44 (s, 1H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 66.91, 118.59, 123.37, 123.44, 125.10, 125.65, 126.57, 127.99, 134.41, 146.73, 151.45, 154.61, 155.95, 175.27

A mixture of 3-[(4-nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (188a) & 3-[chloro(4-nitrophenyl)methyl]-4*H*-chromen-4-one (190a):

To a stirred solution of 3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187a**) (1 mmol, 0.297 g) in benzene (5 mL), $TiCl_4$ (1.5 mmol, 0.75 mL, 2 M solution in dichloromethane) was added, and heated under reflux for 3 hours. The reaction mixture cooled to room temperature and benzene was removed under reduced pressure. Thus obtained residue was diluted with ethyl acetate (50 mL) and the EtOAc layer was successfully washed with water and aq. K_2CO_3. Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 15% EtOAc in hexanes) to afford the 19:81 mixture of **188a: 190a**.



Minor **188a** Major **190a**

IR (KBr): ν 1641, 1614, 1572 cm^{-1}

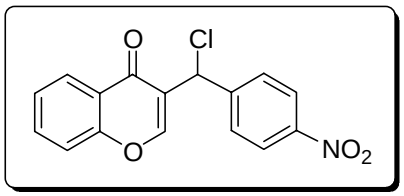
^{1}H NMR (400 MHz): δ 5.81 (s, 0.19H), 6.38 (s, 0.81H), 7.06-8.46 (m, 10H)

^{13}C NMR (100 MHz): δ 47.37, 54.38, 118.17, 118.31, 123.51, 123.84, 123.97, 124.26, 125.43, 125.86, 126.00, 126.18, 126.78, 127.48, 128.56, 129.05, 129.10, 129.66, 133.99, 134.42, 139.80, 146.47, 146.87, 147.76, 149.31, 155.19, 155.46, 156.33, 175.17, 176.44

*The underlined chemical shift values are due to minor product of **188a**. ^{13}C NMR of mixure of products should account for 32 carbons. Here only 30 carbons appeared. The missing two peaks of the minor product probably merges with some peaks.*

3-[Chloro(4-nitrophenyl)methyl]-4*H*-chromen-4-one (190a):

A solution of 3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187a**) (1 mmol, 0.297 g) and $TiCl_4$ (1.5 mmol, 0.75 mL, 2 M solution in dichloromethane) in 3 mL of dichloromethane was stirred for 12 hours at room temperature. Water was added to the reaction mixture and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 15% EtOAc in hexanes) to afford the desired pure 3-[chloro(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**190a**) as a colorless solid in 65% (0.205 g) yield.



Mp: 124-126 ^oC

IR (KBr): ν 1624, 1599 cm^{-1}

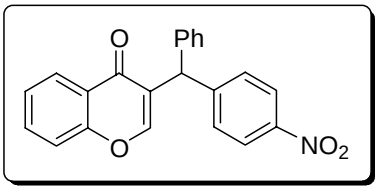
^1H NMR (400 MHz): δ 6.29 (s, 1H), 7.29-7.38 (m, 1H), 7.40 (d, 1H, J = 8.4 Hz), 7.56-7.67 (m, 3H), 8.04-8.16 (m, 3 H), 8.17 (s, 1H)

^{13}C NMR (100 MHz): δ 54.56, 118.28, 123.47, 123.93, 124.21, 125.82, 125.95, 128.54, 134.39, 146.44, 147.71, 155.18, 156.28, 175.13

LCMS (*m/z*): 316 $(M+H)^+$ 318 $[(M+2)+H]^+$

3-[(4-Nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (188a):

To a stirred solution of 3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187a**) (1 mmol, 0.297 g) in benzene (5 mL), methanesulfonic acid (2 mmol, 0.192 g, 0.13 mL) was added, and heated under reflux for 3 hours. The reaction mixture was cooled to room temperature and benzene was removed under reduced pressure. Thus obtained residue was diluted with ethyl acetate (50 mL) and was successfully washed with water and aq. K_2CO_3. Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 15% EtOAc in hexanes) to afford the desired pure 3-[(4-nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (**188a**) as a colorless solid in 92% (0.328 g) yield.



Mp: 116-118 ^{o}C

IR (KBr): ν 1635, 1606 cm^{-1}

^{1}H NMR (400 MHz): δ 5.81 (s, 1H), 7.15 (d, 2H, J = 7.2 Hz), 7.23-7.48 (m, 8H), 7.62-7.71 (m, 1H), 8.12-8.22 (m, 3H)

^{13}C NMR (100 MHz): δ 47.34, 118.14, 123.68, 123.79, 125.39, 126.11, 126.71, 127.44, 129.01, 129.06, 129.62, 133.96, 139.75, 146.79, 149.29, 155.43, 156.29, 176.38

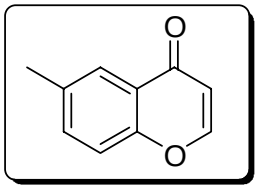
LCMS (*m/z*): 358 $(M+H)^{+}$

Anal. Calcd. for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23; N, 3.92

Found: C, 73.88; H, 4.27; N, 4.00

6-Methyl-1-benzopyran-4(4*H*)-one (186b):

This compound was prepared as a colorless solid, *via* the treatment of 5′-methyl-2′-hydroxyacetophenone (**185b**) with ethyl formate in the presence of NaH, following the similar procedure described for the molecule **186a**.



Yield: 62%

Mp: 82-84 ^{o}C (Lit.[278] 88-89 ^{o}C)

IR (KBr): ν 1649, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 2.43 (s, 3H), 6.31 (d, 1H, J = 6.0 Hz), 7.33 (d, 1H, J = 8.4 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 6.0 Hz), 7.97 (s, 1H)

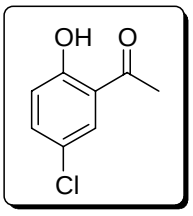
^{13}C NMR (100 MHz): δ 20.55, 112.37, 117.63, 124.18, 124.66, 134.66, 134.85, 154.45, 155.03, 177.30

5′-Chloro-2′-hydroxyacetophenone (185c):

This compound was prepared according to the literature procedure with minor modification.[279]

To a stirred solution of 4-chlorophenol (50 mmol, 6.42 g, 4.9 mL), pyridine (75 mmol, 5.88 g, 5.6 mL) in dichloromethane (50 mL) at 0 ^{o}C was added acetyl chloride (75 mmol, 5.9 g, 6.0 mL) dropwise. After stirring 12 h at room temperature, the reaction mixture was diluted with 4 *N* HCl and water and then extracted with ether (3 X 60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concerted. Thus obtained crude pale-yellow oil was treated with anhydrous $AlCl_3$ (150 mmol, 20.0 g) and the mixture was

heated to 150 ^{o}C. After 3 hours, water was added carefully at 0 ^{o}C and extracted with ether (3 X 60 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concerted and the residue, thus obtained, was purified by column chromatography (silica gel, 5% EtOAc / hexanes) to furnish pale-yellow solid in 71% (6.0 g) yield.



Mp: 55-57 ^{o}C (Lit.[300] 54-56 ^{o}C)

IR (KBr): ν 3010, 1645, 1618 cm^{-1}

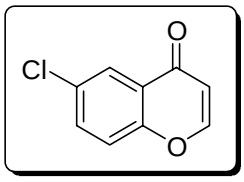
^{1}H NMR (400 MHz): δ 2.61 (s, 3H), 6.93 (d, 1H, J = 9.0 Hz), 7.40 (dd, 1H, J = 2.5 & 9.0 Hz), 7.68 (d, 1H, J = 2.5 Hz), 12.13 (s, 1H)

^{13}C NMR (50 MHz): δ 26.64, 120.05, 120.22, 123.50, 129.83, 136.26, 160.83, 203.57

6-Chloro-1-benzopyran-4(4*H*)-one (186c):

This compound was prepared *via* the treatment of 5′-chloro-2′-hydroxyacetophenone (**185c**) with ethyl formate in the presence of NaH, following the similar procedure described for the compound **186a**.

[Upon completion, reaction mixture was extracted with ethyl acetate and then the combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the residue, thus obtained, was crystallized from dichloromethane / hexanes (1:1) at 0 ^{o}C to afford the pure product as a colorless solid].



Yield: 65%

Mp: 133-135 ^{o}C (Lit.[301] 136-138 ^{o}C)

IR (KBr): ν 1641, 1620 cm^{-1}

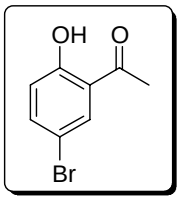
^{1}H NMR (400 MHz): δ 6.35 (d, 1H, *J* = 6.0 Hz), 7.42 (d, 1H, *J* = 9.0 Hz), 7.57-7.64 (m, 1H), 7.86 (d, 1H, *J* = 6.0 Hz), 8.16 (d, 1H, *J* = 2.2 Hz)

^{13}C NMR (50 MHz): δ 112.85, 119.93, 125.12, 125.75, 131.16, 133.91, 154.79, 155.42, 176.16

5′-Bromo-2′-hydroxyacetophenone (185d):

This molecule was prepared via the treatment of 4-bromophenol in the presence of pyridine in dichlormethane (50 mL) at 0 ^oC with added acetyl chloride followed by the treatment with $AlCl_3$, following the similar procedure described for the compound **185c**.

Yield: 73%



Mp: 60-62 ^oC (Lit.[302] 58-61 ^oC)

IR (KBr): ν 3072, 1645, 1612 cm^{-1}

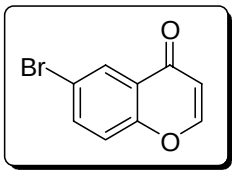
^{1}H NMR (400 MHz): δ 2.60 (s, 3H), 6.85 (d, 1H, *J* = 8.8 Hz), 7.50 (d, 1H, *J* = 8.8 Hz), 7.79 (s, 1H), 12.13 (s, 1H)

^{13}C NMR (100 MHz): δ 26.63, 110.37, 120.43, 120.85, 132.86, 139.01, 161.25, 203.49

6-Bromo-1-benzopyran-4(4*H*)-one (186d):

This molecule was prepared *via* the reaction of 5′-bromo-2′-hydroxyacetophenone (**185d**) with ethyl formate in the presence of NaH, following the similar procedure described for the compound **186a**.

[Upon completion, reaction mixture was extracted with ethyl acetate and then the organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the residue, thus obtained, was crystallized from dichloromethane / hexanes (1:1) at 0 ^oC to afford the pure product as a colorless solid].



Yield: 68%

Mp: 139-141 ^oC (Lit.[303] 135-139 ^oC)

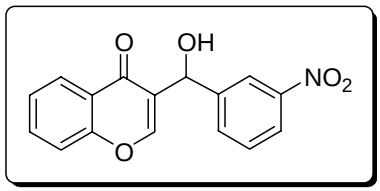
IR (KBr): ν 1639, 1599 cm^{-1}

^1H NMR (400 MHz): δ 6.35 (d, 1H, J = 6.0 Hz), 7.36 (d, 1H, J = 8.8 Hz), 7.74 (dd, 1H, J = 2.0 & 8.8 Hz), 7.87 (d, 1H, J = 6.0 Hz), 8.30 (d, 1H, J = 2.0 Hz)

^{13}C NMR (50 MHz): δ 112.97, 118.70, 120.15, 126.17, 128.40, 136.69, 155.28, 155.45, 176.04

3-[Hydroxy(3-nitrophenyl)methyl]-4*H*-chromen-4-one (187b):

This Baylis-Hillman alcohol was prepared as a colorless solid, by the reaction of 1-benzopyran-4(4*H*)-one (**186a**) with 3-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.



Reaction time: 5 h

Yield: 75%

Mp: 135-137 ^oC (Lit.[277] 134-136 ^oC)

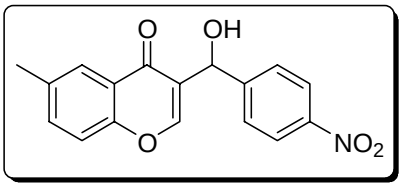
IR (KBr): ν 3371, 1626, 1593 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 5.92 (d, 1H, J = 4.2 Hz), 6.28 (d, 1H, J = 4.2 Hz), 7.41-7.50 (m, 1H), 7.55-7.70 (m, 2H), 7.75-7.86 (m, 1H), 7.90 (d, 1H, J = 7.6 Hz), 8.00 (d, 1H, J = 7.6 Hz), 8.09 (d, 1H, J = 8.0 Hz), 8.31 (s, 1H), 8.47 (s, 1H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 66.83, 118.59, 121.38, 122.23, 123.44, 125.09, 125.63, 126.56, 129.68, 133.53, 134.41, 146.13, 147.77, 154.56, 155.97, 175.33

3-[Hydroxy(4-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (187c):

This alcohol was obtained as a pale-yellow solid, *via* the Baylis-Hillman reaction of 6-methyl-1-benzopyran-4(4*H*)-one (**186b**) with 4-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.



Reaction time: 5 h

Yield: 87%

Mp: 199-200 ^{o}C (Lit.[277] 198-199 ^{o}C)

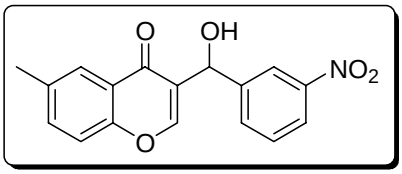
IR (KBr): ν 3391, 1622, 1591 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 2.37 (s, 3H), 5.91 (d, 1H, J = 4.0 Hz), 6.25 (d, 1H, J = 4.0 Hz), 7.51 (d, 1H, J = 8.4 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.71 (d, 2H, J = 8.8 Hz), 7.76 (s, 1H), 8.15 (d, 2H, J = 8.4 Hz), 8.39 (s, 1H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 20.56, 66.84, 118.35, 123.14, 123.35, 124.29, 126.41, 127.92, 135.21, 135.45, 146.69, 151.54, 154.24, 154.44, 175.20

3-[Hydroxy(3-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (187d):

This compound was prepared as a colorless solid, *via* the reaction of 6-methyl-1-benzopyran-4(4*H*)-one (**186b**) with 3-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.



Reaction time: 5 h

Yield: 71%

Mp: 155-157 ^{o}C (Lit.[277] 153-154 ^{o}C)

IR (KBr): ν 3371, 1626, 1593 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 2.33 (s, 3H), 5.94 (s, 1H), 6.29 (d, 1H, J = 3.0 Hz), 7.40-7.64 (m, 3H), 7.74 (s, 1H), 7.90 (d, 1H, J = 7.2 Hz), 8.07 (d, 1H, J = 7.2 Hz), 8.32 (s, 1H), 8.41 (s, 1H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 20.54, 66.82, 118.28, 121.37, 122.19, 123.16, 124.31, 126.46, 129.64, 133.48, 135.14, 135.37, 146.29, 147.78, 154.24, 154.33, 175.31

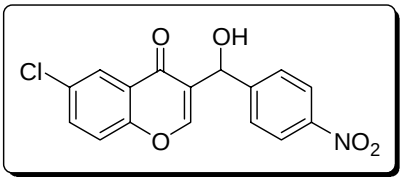
6-Chloro-3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (187e):

This compound was prepared by the reaction between 6-chloro-1-benzopyran-4(4*H*)-one (**186c**) and 4-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**, as a colorless solid.

Reaction time: 5 h

Yield: 60%

Mp: 175-177 ^{o}C



IR (KBr): ν 3398, 1622, 1593 cm^{-1}

^{1}H NMR (400 MHz) (DMSO-d_6): δ 5.88 (s, 1H), 6.30 (d, 1H, J = 3.3 Hz), 7.67-7.96 (m, 5H), 8.16 (d, 2H, J = 8.6 Hz), 8.48 (s, 1H)

^{13}C NMR (100 MHz) (DMSO-d_6): δ 66.86, 121.17, 123.37, 124.05, 124.51, 126.57, 128.04, 130.15, 134.35, 146.77, 151.14, 154.55, 155.00, 174.19

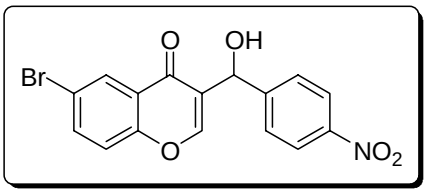
6-Bromo-3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (187f):

This molecule was obtained as a colorless solid, *via* the Baylis-Hillman coupling of 6-bromo-1-benzopyran-4(4*H*)-one (**186d**) with 4-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.

Reaction time: 5 h

Yield: 64%

Mp: 186-188 ^{o}C



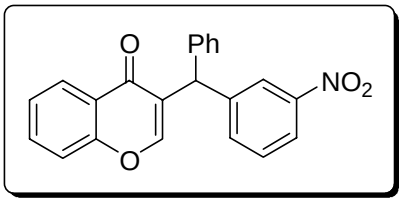
IR (KBr): ν 3485, 1639, 1601 cm^{-1}

^{1}H NMR (400 MHz) (DMSO-d_6): δ 5.88 (d, 1H, J = 3.8 Hz), 6.31 (d, 1H, J = 3.8 Hz), 7.64 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.4 Hz), 7.87-8.15 (m, 2H), 8.16 (d, 2H, J = 8.4 Hz), 8.47 (s, 1H)

^{13}C NMR (100 MHz) (DMSO-d_6): δ 66.86, 118.07, 121.32, 123.37, 124.89, 126.66, 127.18, 128.03, 137.03, 146.77, 151.13, 154.91, 154.97, 174.06

3-[(3-Nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (188b):

This molecule was prepared, *via* the reaction of 3-[hydroxy(3-nitrophenyl)methyl]-4*H*-chromen-4-one (**187b**) with benzene in the presence of methanesulfonic acid, following the similar procedure described for the molecule **188a**, as a colorless solid.



Reaction time: 3 h

Yield: 80%

Mp: 111-113 ^{o}C

IR (KBr): ν 1639, 1612 cm^{-1}

^{1}H NMR (400 MHz): δ 5.83 (s, 1H), 7.15 (d, 2H, *J* = 7.2), 7.23-7.52 (m, 7H), 7.59 (d, 1H, *J* = 7.6 Hz), 7.62-7.71 (m, 1H), 8.06-8.12 (m, 2H), 8.17 (dd, 1H, *J* = 1.2 & 7.8 Hz)

^{13}C NMR (100 MHz): δ 47.11, 118.16, 121.95, 123.39, 123.71, 125.35, 126.08, 126.70, 127.41, 129.00, 129.04, 129.49, 133.93, 135.13, 139.86, 143.79, 148.50, 155.51, 156.29, 176.39

LCMS (*m/z*): 358 (M+H)$^{+}$

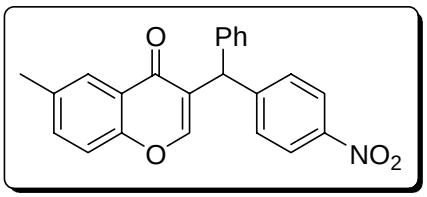
Anal. Calcd. for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23; N, 3.92

Found: C, 74.63; H, 4.30; N, 3.96

3-[(4-Nitrophenyl)phenylmethyl]-6-methyl-4*H*-chromen-4-one (188c):

This compound was obtained as a colorless solid, *via* treatment of 3-[hydroxy(4-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (**187c**) with benzene under the influence of methanesulfonic acid, following the similar procedure described for the compound **188a**.

Reaction time: 3 h



Yield: 89%

Mp: 168-169 ^{o}C

IR (KBr): ν 1639, 1606 cm^{-1}

^{1}H NMR (400 MHz): δ 2.43 (s, 3H), 5.81 (s, 1H), 7.14 (d, 2H, J = 7.2 Hz), 7.23-7.43 (m, 7H), 7.48 (d, 1H, J = 8.6 Hz), 7.95 (s, 1H), 8.15 (d, 2H, J = 8.6 Hz)

^{13}C NMR (100 MHz): δ 20.97, 47.35, 117.90, 123.39, 123.79, 125.39, 126.48, 127.41, 128.99, 129.10, 129.64, 135.23, 135.42, 139.90, 146.79, 149.44, 154.60, 155.32, 176.44

LCMS (*m/z*): 372 (M+H)$^{+}$

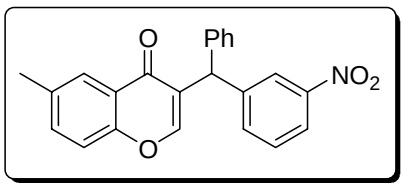
Anal. Calcd. for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77

Found: C, 74.18; H, 4.63; N, 3.74

3-[(3-Nitrophenyl)phenylmethyl]-6-methyl-4*H*-chromen-4-one (188d):

This compound was obtained as a colorless solid, *via* Friedel-Crafts reaction of 3-[hydroxy(3-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (**187d**) with benzene in the presence of methanesulfonic acid, following the similar procedure described for the compound **188a**.

Reaction time: 3 h



Yield: 82%

Mp: 79-81 ^{o}C

IR (KBr): ν 1643, 1616 cm^{-1}

^{1}H NMR (400 MHz): δ 2.42 (s, 3H), 5.82 (s, 1H), 7.15 (d, 2H, *J* = 7.0 Hz), 7.23-7.52 (m, 7H), 7.59 (d, 1H, *J* = 7.6 Hz), 7.95 (s, 1H), 8.05-8.13 (m, 2H)

^{13}C NMR (100 MHz): δ 20.96, 47.12, 117.91, 121.92, 123.40, 125.36, 126.46, 127.37, 128.98, 129.07, 129.45, 135.16, 135.20, 135.37, 140.00, 143.93, 148.51, 154.60, 155.40, 176.45

LCMS (*m/z*): 372 $(M+H)^+$

Anal. Calcd. for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77

Found: C, 74.41; H, 4.62; N, 3.81

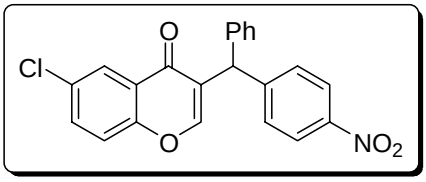
6-Chloro-3-[(4-nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (188e):

This molecule was prepared, by the reaction of 6-chloro-3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187e**) with benzene under the influence of $MeSO_3H$, following the similar procedure described for the compound **188a**, as a colorless solid.

Reaction time: 3 h

Yield: 84%

Mp: 163-165 ^oC



IR (KBr): ν 1643, 1606 cm^{-1}

^{1}H NMR (400 MHz): δ 5.78 (s, 1H), 7.14 (d, 2H, *J* = 7.6 Hz), 7.24-7.46 (m, 7H), 7.61 (dd, 1H, *J* = 1.2 & 8.8 Hz), 8.11 (s, 1H), 8.15 (d, 2H, *J* = 8.0 Hz)

^{13}C NMR (100 MHz): δ 47.29, 119.94, 123.84, 124.59, 125.47, 126.85, 127.57, 129.02, 129.07, 129.61, 131.35, 134.21, 139.47, 146.87, 148.95, 154.62, 155.56, 175.28

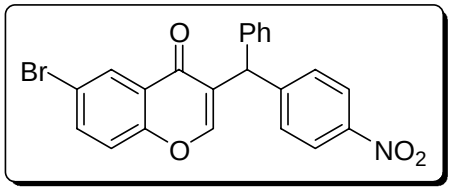
LCMS (*m/z*): 392 $(M+H)^+$, 394 $[(M+2)+H]^+$

Anal. Calcd. for $C_{22}H_{14}ClNO_4$: C, 67.44; H, 3.60; N, 3.57

Found: C, 67.34; H, 3.65; N, 3.55

6-Bromo-3-[(4-Nitrophenyl)phenylmethyl]-4*H*-chromen-4-one (188f):

Treatment of 6-bromo-3-[hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (**187f**) with benzene in the presence of methanesulfonic acid, following the similar procedure described for the compound (**188a**), furnished the title compound as a colorless solid.



Reaction time: 3 h

Yield: 81%

Mp: 171-173 ^{o}C

IR (KBr): ν 1641, 1610 cm^{-1}

^{1}H NMR (400 MHz): δ 5.78 (s, 1H), 7.14 (d, 2H, *J* = 6.6 Hz), 7.24-7.47 (m, 7H), 7.71-7.80 (m, 1H), 8.15 (d, 2H, *J* = 8.4 Hz), 8.29 (s, 1H)

^{13}C NMR (100 MHz): δ 47.31, 118.82, 120.15, 123.84, 124.98, 126.96, 127.58, 128.72, 129.03, 129.08, 129.62, 136.96, 139.46, 146.87, 148.93, 155.05, 155.56, 175.12

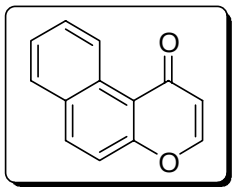
LCMS (*m/z*): 436 $(M+H)^+$, 438 $[(M+2)+H]^+$

Anal. Calcd. for $C_{22}H_{14}BrNO_4$: C, 60.57; H, 3.23; N, 3.21

Found: C, 60.55; H, 3.22; N, 3.30

5,6-Benzochromen-4(4*H*)-one (186e)

This molecule was prepared, *via* the treatment of 1-acetyl-2-naphthol (**185e**) ethyl formate in the presence of NaH, following the similar procedure described for the compound **185a**. [Upon completion, reaction mixture was extracted with ethyl acetate and then the organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the residue, thus obtained, was crystallized from dichloromethane / hexanes (1:1) at 0 ^oC to afford the pure product as a colorless solid].



Yield: 70%

Mp: 99-101 ^oC (Lit.[304] 102-103 ^oC)

IR (KBr): ν 1643, 1610 cm^{-1}

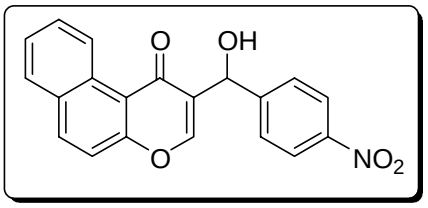
^1H NMR (400 MHz): δ 6.40-6.50 (m, 1H), 7.38-8.08 (m, 6H), 10.01 (d, 1H, J = 8.4 Hz)

^{13}C NMR (50 MHz): δ 115.62, 117.26, 117.82, 126.34, 126.80, 127.89, 128.86, 130.22, 135.07, 152.39, 157.31, 178.98

3-[Hydroxy(4-nitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (187g)

The Baylis-Hillman coupling reaction of 5,6-benzochromen-4(4*H*)-one (**186e**) with 4-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**, provided the title compound as a colorless solid.

Reaction time: 5 h



Yield: 79%

Mp: 160-161 ^{o}C

IR (KBr): ν 3418, 1641, 1591 cm^{-1}

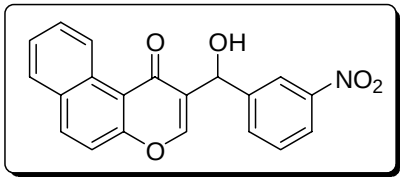
^{1}H NMR (400 MHz): (DMSO-d_6) δ 6.01 (d, 1H, J = 4.0 Hz), 6.31 (d, 1H, J = 4.0 Hz), 7.59-7.85 (m, 5H), 8.05 (d, 1H, J = 8.4 Hz), 8.18 (d, 2H, J = 8.4 Hz), 8.30 (d, 1H, J = 8.8 Hz), 8.52 (s, 1H), 9.83 (d, 1H, J = 8.6 Hz)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 67.10, 116.27, 118.12, 123.39, 126.17, 126.79, 128.17, 128.78, 129.21, 129.27, 129.83, 130.44, 136.06, 146.74, 151.53, 152.32, 157.41, 177.14

3-[Hydroxy(3-nitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (187h)

This alcohol was prepared as a colorless solid, *via* the Baylis-Hillman coupling of 5,6-benzochromen-4(4*H*)-one (**186e**) with 3-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.

Reaction time: 5 h



Yield: 68%

Mp: 151-153 ^{o}C

IR (KBr): ν 3422, 1641, 1593 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 6.04 (d, 1H, J = 4.0 Hz), 6.33 (d, 1H, J = 4.0 Hz), 7.55-

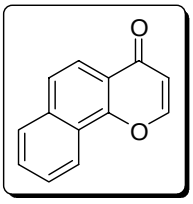
7.79 (m, 4H), 7.92-8.07 (m, 2H), 8.09 (d, 1H, *J* = 8.0 Hz), 8.24 (d, 1H, *J* = 8.8 Hz), 8.38 (s, 1H), 8.55 (s, 1H), 9.82 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 67.04, 116.27, 118.06, 121.55, 122.25, 126.17, 126.73, 128.72, 129.22, 129.66, 129.82, 130.38, 133.72, 135.96, 146.26, 147.81, 152.24, 157.38, 177.20

7,8-Benzochromen-4(4*H*)-one (186f):

This molecule was prepared, *via* the reaction of 2-acetyl-1-naphthol (**185f**) with ethyl formate in the presence of NaH, following the similar procedure described for the compound **186a**.

[Upon completion, reaction mixture was extracted with ethyl acetate and then the organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the residue, thus obtained, was crystallized from dichloromethane / hexanes (1:1) at 0 ^{o}C to afford the pure product as a colorless solid].



Yield: 68%

Mp: 127-129 ^{o}C (Lit.[304] 124-125 ^{o}C)

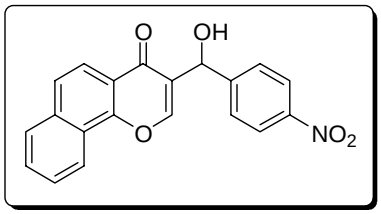
IR (KBr): ν 1657, 1641 cm^{-1}

^{1}H NMR (400 MHz): δ 6.50 (d, 1H, *J* = 5.8 Hz), 7.60-7.81 (m, 3H), 7.89 (d, 1H, *J* = 8.0 Hz), 8.02 (d, 1H, *J* = 5.8 Hz), 8.12 (d, 1H, *J* = 8.8 Hz), 8.43 (d, 1H, *J* = 8.0 Hz)

^{13}C NMR (50 MHz): δ 114.26, 120.64, 121.17, 122.24, 123.94, 125.29, 127.09, 128.04, 129.27, 135.80, 153.92, 154.45, 177.28

3-[Hydroxy(4-nitrophenyl)methyl]-7,8-benzo-4*H*-chromen-4-one (187i):

This alcohol was prepared as a colorless solid, *via* the Baylis-Hillman reaction between 7,8-benzochromen-4(4*H*)-one (**186f**) and 4-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.



Reaction time: 5 h

Yield: 78%

Mp: 201-203 ^{o}C

IR (KBr): ν 3395, 1639, 1620, 1587 cm^{-1}

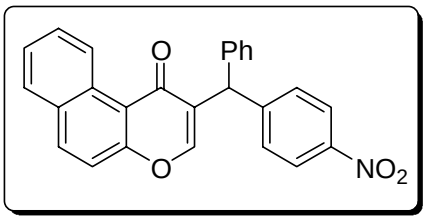
^{1}H NMR (400 MHz): (DMSO-d_6) δ 5.97 (s, 1H), 6.34 (br s, 1H), 7.70-7.96 (m, 6H), 8.05 (d, 1H, J = 6.8 Hz), 8.12-8.23 (m, 2H), 8.43 (d, 1H, J = 7.6 Hz), 8.61 (s, 1H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 66.99, 119.71, 120.08, 121.98, 123.38, 123.45, 125.58, 127.86, 127.98, 128.09, 128.37, 129.83, 135.38, 146.77, 151.33, 153.26, 153.83, 174.98

3-[(4-Nitrophenyl)phenylmethyl]-5,6-benzo-4*H*-chromen-4-one (188g)

Friedel-Crafts alkylation of 3-[hydroxy(4-nitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (**187g**) with benzene under the inflrence of methanesulfonic acid, following the similar

procedure described for the compound **188a**, provided the title compound as a colorless solid.



Reaction time: 3 h

Yield: 86%

Mp: 179-181 ^{o}C

IR (KBr): ν 1639, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 5.92 (s, 1H), 7.17 (d, 2H, *J* = 7.2 Hz), 7.27-7.46 (m, 6H), 7.47 (d, 1H, *J* = 8.8 Hz), 7.56-7.63 (m, 1H), 7.65-7.72 (m, 1H), 7.89 (d, 1H, *J* = 7.8 Hz), 8.08 (d, 1H, *J* = 8.8 Hz), 8.16 (d, 2H, *J* = 8.8 Hz), 9.96 (d, 1H, *J* = 8.8 Hz)

^{13}C NMR (100 MHz): δ 47.52, 117.06, 117.54, 123.91, 126.86, 127.21, 127.47, 128.33, 129.07, 129.17, 129.34, 129.47, 129.63, 130.55, 130.70, 135.91, 140.09, 146.86, 149.59, 153.25, 157.63, 177.87

LCMS (*m/z*): 408 $(M+H)^{+}$

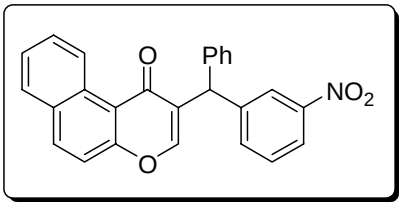
Anal. Calcd. for $C_{26}H_{17}NO_4$: C, 76.65; H, 4.21; N, 3.44

Found: C, 76,62; H, 4.25; N, 3.41

3-[(3-Nitrophenyl)phenylmethyl]-5,6-benzo-4*H*-chromen-4-one (188h):

This molecule was obtained as a colorless solid, *via* the treatment of 3-[hydroxy(3-nitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (**187h**) with benzene in the presence of

methanesulfonic acid in benzene, following the similar procedure described for the compound **188a**.



Reaction time: 3 h

Yield: 83%

Mp: 142-144 ^{o}C

IR (KBr): ν 1637, 1612 cm^{-1}

^{1}H NMR (400 MHz): δ 5.94 (s, 1H), 7.17 (d, 1H, J = 7.6 Hz), 7.25-7.73 (m, 9H), 7.87 (d, 1H, J = 8.0 Hz), 8.03-8.20 (m, 3H), 9.95 (d, 1H, J = 8.8 Hz)

^{13}C NMR (100 MHz): δ 47.27, 117.06, 117.56, 121.97, 123.43, 126.79, 127.17, 127.42, 128.32, 129.05, 129.13, 129.31, 129.39, 129.55, 130.54, 130.67, 135.11, 135.86, 140.20, 144.06, 148.60, 153.32, 157.61, 177.85

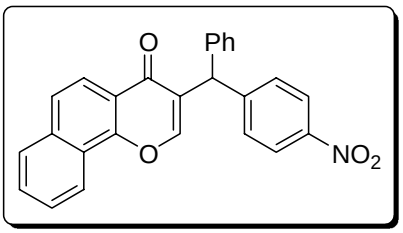
LCMS (*m/z*): 408 $(M+H)^{+}$

Anal. Calcd. for $C_{26}H_{17}NO_4$: C, 76.65; H, 4.21; N, 3.44

Found: C, 76.70; H, 4.18; N, 3.36

3-[(4-Nitrophenyl)phenylmethyl]-7,8-benzo-4*H*-chromen-4-one (188i):

Friedel-Crafts reaction of 3-[hydroxy(4-nitrophenyl)methyl]-7,8-benzo-4*H*-chromen-4-one (**187i**) with benzene under the influence of methanesulfonic acid, following the similar procedure described for the compound **188a**, affored the title compound as a colorless solid.



Reaction time: 3 h

Yield: 78%

Mp: 168-170 ^{o}C

IR (KBr): ν 1643, 1612 cm^{-1}

^{1}H NMR (400 MHz): δ 5.88 (s, 1H), 7.17-7.50 (m, 7H), 7.54-7.85 (m, 4H), 7.90 (d, 1H, J = 7.2 Hz), 8.05-8.23 (m, 3H), 8.40 (d, 1H, J = 7.2 Hz)

^{13}C NMR (100 MHZ): δ 47.43, 120.03, 120.89, 122.16, 123.84, 123.93, 125.60, 127.34, 127.50, 128.19, 129.07, 129.12, 129.54, 129.67, 135.90, 139.77, 146.85, 149.24, 153.83, 154.66, 176.15

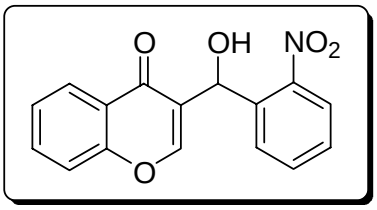
LCMS (*m/z*): 408 $(M+H)^{+}$

Anal. Calcd. for $C_{26}H_{17}NO_4$: C, 76.65; H, 4.21; N, 3.44

Found: C, 76.67; H, 4.23; N, 3.53

3-[Hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (187j)

This compound was obtained as a colorless solid, *via* the treatment of 1-benzopyran-4(4*H*)-one (**186a**) with 2-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the molecule **187a**.



Reaction time: 5 h

Yield: 78%

Mp: 149-151 ^{o}C (Lit.[55] 150-152 ^{o}C)

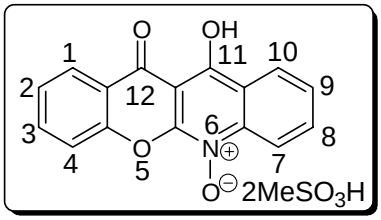
IR (KBr): ν 3531, 1639, 1600 cm^{-1}

^{1}H NMR (400 MHz): δ 4.61 (br s, 1H), 6.47 (s, 1H), 7.35-7.58 (m, 3H), 7.61-7.76 (m, 2H), 7.74 (s, 1H), 7.89-8.09 (m, 2H), 8.16 (d, 1H, J = 8.0 Hz)

^{13}C NMR (100 MHz): δ 66.18, 118.27, 123.79, 124.65, 124.69, 125.52, 125.78, 128.86, 129.24, 133.63, 134.22, 136.01, 148.24, 153.86, 156.38, 177.89

6-Aza-11-hydroxy-5-oxa-6-oxy-naphthacen-12-one as bismethanesulfonic acid salt (194a):

A solution of 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (**187j**) (1 mmol, 0.297 g) and methanesulfonic acid (1.5 mmol, 0.144 g, 0.97 mL) in benzene (5 mL) was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature and benzene was removed under reduced pressure and thus obtained crude solid was crystallized from chloroform to afford the yellowish crystals (from the single crystals data it is clear indicates that the product crystallization as with two equivalents of $MeSO_3H$) in 42% (0.199 g) yield.



Mp: 260-262 ^{o}C

IR (KBr): ν 3028, 1637, 1606, 1585, 1523, 1466, 1280 cm^{-1}

^{1}H NMR (400 MHz): δ 2.70 (s, 6H),* 7.62-7.75 (m, 1H), 7.82-7.92 (m, 1H), 7.93-8.11 (m, 2H), 8.21-8.33 (m, 1H), 8.38 (d, 1H, *J* = 8.0 Hz), 8.52 (d, 1H, *J* = 8.4 Hz), 8.60 (d, 1H, *J* = 8.0 Hz), 12.73 (br s, 3H)**

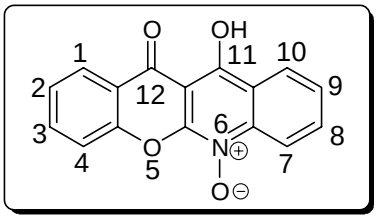
***It looks the broad peak contains one of –O<u>H</u> peak at C11 of the compound merges with two eqvivalent of $MeSO_3$<u>H</u> peak at δ 12.73.*

^{13}C NMR (50 MHz): δ 39.01,* 99.68, 117.22, 117.46, 119.38, 125.54, 126.63, 127.70, 128.37, 138.56, 138.95, 140.09, 154.55, 154.62, 173.08, 181.43

**This is attributed to methyl group of $MeSO_3H$.*

6-Aza-11-hydroxy-5-oxa-6-oxy-naphthacen-12-one (*via* the reaction of 187j with $MeSO_3H$) (195a):

A solution of 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (**187j**) (1 mmol, 0.297 g) in methanesulfonic acid (2 mL) was stirred at 70 ^{o}C for 3 hours. Reaction mixture was cooled to room temperature and diluted with ethyl acetate. Resulting solution was poured into water and stirred for 10 min and thus separated colorless solid was filtered and dried under *vacuo* to afford pure title product in 67% (0.180 g) yield.



Mp: 268-269 ^{o}C

IR (KBr): ν 3074, 1637, 1512, 1466, 1394, 1350, 1217 cm^{-1}

^{1}H NMR (400 MHz): (10% TFA in $CDCl_3$) δ 7.70-7.80 (m, 1H), 7.85 (d, 1H, *J* = 8.4 Hz), 7.90-8.02 (m, 1H), 8.05-8.14 (m, 1H), 8.26-8.40 (m, 1H), 8.45 (d, 1H, *J* = 8.0 Hz), 8.49 (d, 1H, *J* = 8.0 Hz), 8.70 (d, 1H, *J* = 8.4 Hz), 11.30 (br s, 1H)*

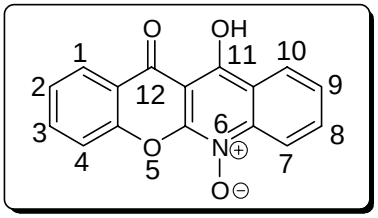
**It looks that –OH (at C11) peak of the compound merges with COOH peak of the TFA at* δ *10.76.*

^{13}C NMR (100 MHz): (10% TFA in $CDCl_3$) δ 99.45, 116. 87, 117.60, 119.05, 119.48, 126.25, 127.21, 128.79, 129.43, 139.59, 139.93, 140.20, 154.89, 154.94, 174.52, 181.86; In addition two quartets, one at δ 114.82 [q, *J* = 282 Hz; (signals at 110.59, 113.41, 116.23, 118.99)] and second one at δ 162.56 [q, *J* = 42 Hz; (signals at δ 161.91, 162.35, 162.78, 163.21)] arising from trifluoroacetic acid (TFA) also appeared.

6-Aza-11-hydroxy-5-oxa-6-oxy-naphthacen-12-one (*via* the reaction of 187j with TFA) (195a):

A solution of 3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (**187j**) (1 mmol, 0.297 g) in trifluoroacetic acid (3 mL) was stirred at 70 ^{o}C for 2 hours. Reaction mixture was

cooled to room temperature and diluted with ethyl acetate. Resulting solution was poured into water and stirred for 10 min and thus separated colorless solid was filtered and dried under *vacuo* to afford pure 6-aza-11-hydroxy-5-oxa-6-oxy-naphthacen-12-one (**195a**) product in 89% (0.248 g) yield.



Mp: 268-269 ^{o}C

IR (KBr): ν 3105, 1660, 1610, 1529, 1452, 1348, 1277 cm^{-1}

^{1}H NMR (400 MHz): (10% TFA in $CDCl_3$) δ 7.66-7.77 (m, 1H), 7.84 (d, 1H, J = 8.0 Hz), 7.87-7.96 (m, 1H), 7.99-8.10 (m, 1H), 8.22-8.33 (m, 1H), 8.40 (d, 1H, J = 7.2 Hz), 8.47 (d, 1H, J = 8.2 Hz), 8.64 (d, 1H, J = 8.0 Hz), 10.76 (br s, 1H)*

**It looks that –O<u>H</u> (at C11) peak of the compound merges with COO<u>H</u> peak of the TFA at δ 10.76.*

^{13}C NMR (100 MHz): (10% TFA in $CDCl_3$) δ 99.20, 116. 88, 117.17, 118.76, 119.17, 125.82, 126.88, 128.27, 128.95, 139.07, 139.63, 139.70, 154.34, 154.47, 173.55, 181.29; In addition two quartets, one at δ 114.63 [q, J = 284 Hz; (signals at 110.38, 113.21, 116.05, 118.88)] and second one at δ 160.94 [q, J = 42 Hz; (signals at δ 160.31,

160.73, 161.15, 161.58)] arising from trifluoroacetic acid (TFA) also appeared.

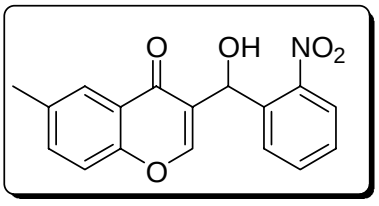
LCMS (*m/z*): 280 $(M+H)^+$

Anal. Calcd. for $C_{16}H_9NO_4$: C, 68.82; H, 3.25; N, 5.02

Found: C, 68.84; H, 3.24; N, 5.05

3-[Hydroxy(2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (187k):

This compound was obtained as a colorless solid, *via* the Baylis-Hillman coupling of 6-methyl-1-benzopyran-4(4*H*)-one (**186b**) with 2-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the product **187a**.



Reaction time: 5 h

Yield: 82%

Mp: 184-186 °C (Lit.[277] 183-184 °C)

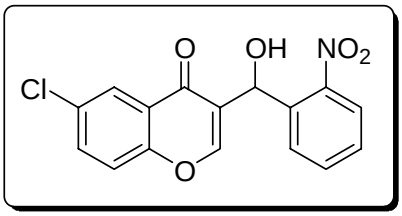
IR (KBr): ν 3339, 1639, 1602 cm^{-1}

^1H NMR (400 MHz): (DMSO-d_6) δ 2.35 (s, 3H), 6.29 (d, 1H, J = 3.5 Hz), 6.41 (s, 1H), 7.44-7.59 (m, 3H), 7.61-7.80 (m, 3H), 7.88 (d, 1H, J = 8.0 Hz), 8.20 (s, 1H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 20.54, 62.62, 118.31, 122.97, 124.07, 124.35, 126.22, 128.64, 129.37, 133.06, 135.21, 135.44, 137.21, 148.61, 154.05, 154.29, 175.30

6-Chloro-3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (187l):

This compound was obtained as a colorless solid, *via* NaOMe mediated Baylis-Hillman reaction of 6-chloro-1-benzopyran-4(4*H*)-one (**186c**) with 2-nitrobenzaldehyde following the similar procedure described for the compound **187a**.



Reaction time: 5 h

Yield: 55%

Mp: 148-150 ^{o}C

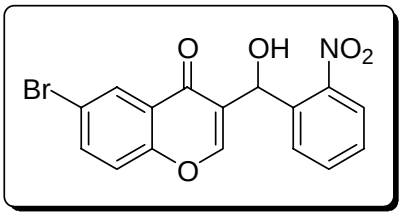
IR (KBr): ν 3329, 1637, 1604 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 6.32-6.42 (m, 2H), 7.47-7.56 (m, 1H), 7.61-7.95 (m, 6H), 8.29 (s, 1H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 62.59, 121.12, 124.10, 124.11, 124.32, 126.41, 128.76, 129.42, 130.16, 133.13, 134.34, 136.85, 148.55, 154.59, 154.66, 174.31

6-Bromo-3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (187m):

This compound was obtained as a colorless solid, *via* the NaOMe mediated coupling of 6-bromo-1-benzopyran-4(4*H*)-one (**187d**) with 2-nitrobenzaldehyde in methanol, following the similar procedure described for the compound **187a**.



Reaction time: 5 h

Yield: 61%

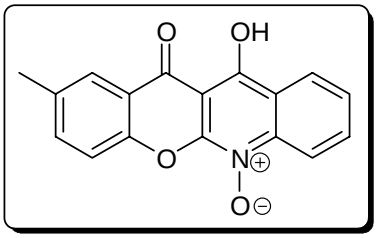
Mp: 179-181 ^{o}C

IR (KBr): ν 3341, 1643, 1604 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6)	δ 6.30-6.49 (m, 2H), 7.44-7.78 (m, 4H), 7.89 (d, 2H, J = 8.0 Hz), 8.02 (s, 1H), 8.28 (s, 1H)
^{13}C NMR (100 MHz): (DMSO-d_6)	δ 62.60, 118.07, 121.26, 124.13, 124.70, 126.51, 127.24, 128.76, 129.43, 133.13, 136.86, 137.01, 148.54, 154.61, 154.95, 174.18

6-Aza-11-hydroxy-2-methyl-5-oxa-6-oxy-naphthacen-12-one (195b):

This molecule was obtained as a colorless solid, *via* the treatment of 3-[hydroxy(2-nitro-phenyl)methyl]-6-methyl-4*H*-chromen-4-one (**187k**) with trifluoroacetic acid, following the similar procedure described for the compound **195a**.



Reaction time:	2 h
Yield:	85%
Mp:	249-251 ^{o}C
IR (KBr):	ν 3504, 1660, 1610, 1527, 1477, 1446, 1348, 1277 cm^{-1}
^{1}H NMR (400 MHz): (10% TFA-*d* in $CDCl_3$)	δ 2.57 (s, 3H), 7.72 (d, 1H, J = 7.8 Hz), 7.80-7.98 (m, 2H), 8.16 (s, 1H), 8.23-8.34 (m, 1H), 8.46 (d, 1H, J = 7.8 Hz), 8.63 (d, 1H, J = 7.6 Hz), 12.24 (br s, 1H)* **It looks that –O<u>H</u> (at C11) peak of the compound merges with COO<u>H</u> peak of the TFA at δ 12.24.*
^{13}C NMR (100 MHz): (10% TFA-*d* in $CDCl_3$)	δ 20.85, 99.24, 116.79, 116.97, 118.47, 118.88, 125.75,

126.22, 128.83, 139.13, 139.56, 139.65, 140.12, 152.71, 154.40, 173.28, 181.13; In addition two quartets, one at δ 114.86 [q, J = 282 Hz; (110.61, 113.44, 116.29, 119.03)] and second one at δ 160.87 [q, J = 42 Hz; (160.25, 160.66, 161.08, 161.49)] due to the carbons of CF_3COOH also appeared.

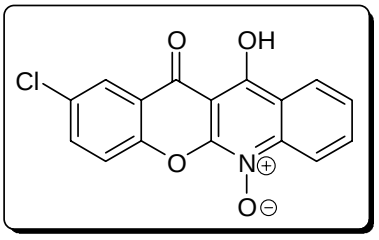
LCMS (*m/z*): 294 $(M+H)^+$

Anal. Calcd. for $C_{17}H_{10}NO_4$: C, 69.92; H, 3.78; N, 4.78

Found: C, 69.63; H, 3.77; N, 4.85

6-Aza-2-chloro-11-hydroxy-5-oxa-6-oxy-naphthacen-12-one (195c):

This product was obtained, *via* the treatment of 6-chloro-3-[hydroxy(2-nitro-phenyl)methyl]-4*H*-chromen-4-one (**187l)** with trifluoroacetic acid, as a colorless solid, following the similar procedure described for the product **195a**.



Reaction time: 2 h

Yield: 80%

Mp: 261-263 ^oC

IR (KBr): ν 3117, 1657, 1610, 1535, 1466, 1336, 1261 cm^{-1}

^1H NMR (400 MHz): (10% TFA-*d* in $CDCl_3$) δ 7.81 (d, 1H, J = 7.8 Hz), 7.89-8.02 (m, 2H), 8.22-8.41 (m, 2H), 8.48 (d, 1H, J = 7.6 Hz), 8.65 (d, 1H, J = 6.8 Hz), 12.03 (br s, 1H)*

**It looks that –OH (at C11) peak of the compound merges with COOH peak of the TFA at δ 12.03.*

^{13}C NMR (100 MHz): (10% TFA-*d* in $CDCl_3$) δ 99.37, 116.99, 117.54, 120.35, 120.45, 125.49, 125.98, 128.67, 133.94, 138.43, 139.16, 140.37, 152.71, 153.75, 175.52, 180.21; In addition two quartets, one at δ 115.10 [q, *J* = 284 Hz; (signals at δ 110.85, 113.68, 116.53, 119.37)] and second one at δ 160.00 [q, *J* = 40 Hz; (signals at δ 159.41, 159.80, 160.20, 160.60)] due to the presence of CF_3COOH also appeared.

LCMS (*m/z*): 312 $(M-H)^-$, 314 $[(M+2)-H)]^-$

Anal. Calcd. for $C_{16}H_8ClNO_4$: C, 61.26; H, 2.57; N, 4.47

Found: C, 61.44; H, 2.55; N, 4.42

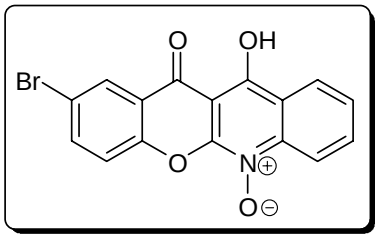
6-Aza-2-bromo-11-hydroxy-5-oxa-6-oxy-naphthacen-12-one (195d):

This compound was obtained as a colorless solid, *via* the reaction between 6-bromo-3-[hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (**187m**) and trifluoroacetic acid, following the similar procedure described for the compound **195a**.

Reaction time: 2 h

Yield: 81%

Mp: 270-272 °C



IR (KBr): ν 3117, 1657, 1610, 1537, 1462, 1448, 1336, 1261 cm^{-1}

^{1}H NMR (400 MHz): (10% TFA-*d* in $CDCl_3$) δ 7.73 (d, 1H, *J* = 8.4 Hz), 7.87-8.00 (m, 1H), 8.10 (d, 1H, *J* = 8.8 Hz), 8.20-8.38 (m, 1H), 8.44-8.56 (m, 2H), 8.63 (d, 1H, *J* = 7.8 Hz), 13.00 (br s, 1H)*

**It looks that –O<u>H</u> (at C11) peak of the compound merges with COO<u>H</u> peak of the TFA at δ 13.00.*

^{13}C NMR (100 MHz): (10% TFA-*d* in $CDCl_3$) δ 99.26, 116.95, 117.06, 120.53, 120.59, 121.65, 125.72, 129.02, 129.22, 139.72, 139.86, 141.50, 153.15, 154.11, 172.66, 179.93; In addition two quartets, one at δ 114.78 [q, *J* = 284 Hz; (signals at δ 110.54, 113.36, 116.21, 119.05)] and second one at δ 160.30 [q, *J* = 42 Hz; (signals at δ 159.68, 160.10, 160.51, 160.92)] arising from the CF_3COOH also appeared.

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

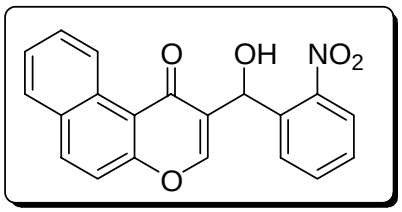
Anal. Calcd. for $C_{16}H_8BrNO_4$: C, 53.66; H, 2.25; N, 3.91

Found: C, 53.82; H, 2.28; N, 4.00

3-[Hydroxy(2-nitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (187n):

This compound was obtained as a colorless solid, *via* the treatment of 5,6-benzochromen-4(4*H*)-one (**186e**) with 2-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.

Reaction time: 5 h



Yield: 72%

Mp: 157-159 ^{o}C

IR (KBr): ν 3339, 1641, 1597 cm^{-1}

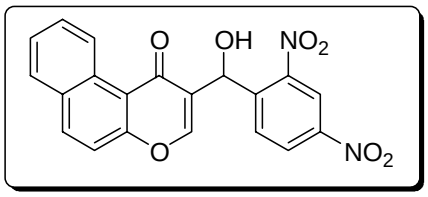
^{1}H NMR (400 MHz) (DMSO-d_6): δ 6.35 (d, 1H, J = 4.8 Hz), 6.51 (d, 1H, J = 4.8 Hz), 7.43-7.79 (m, 6H), 7.91 (d, 1H, J = 7.8 Hz), 8.02 (d, 1H, J = 7.8 Hz), 8.26 (d, 1H, J = 9.0 Hz), 8.37 (s, 1H), 9.78 (d, 1H, J = 8.6 Hz)

^{13}C NMR (100 MHz) (DMSO-d_6): δ 62.75, 116.08, 118.07, 124.04, 126.15, 126.77, 128.65, 128.73, 129.10, 129.26, 129.40, 129.80, 130.38, 133.05, 136.02, 137.20, 148.80, 152.00, 157.44, 177.21

3-[Hydroxy(2,4-dinitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (187o):

This compound was obtained as a colorless solid, *via* the Baylis-Hillman reaction of 5,6-benzochromen-4(4*H*)-one (**186e**) with 2,4-dinitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.

Reaction time: 5 h



Yield: 59%

Mp: 208-209 ^{o}C

IR (KBr): ν 3391, 1637, 1595 cm^{-1}

^{1}H NMR (400 MHz): δ 6.52 (d, 1H, J = 4.0 Hz), 6.72 (d, 1H, J = 4.0 Hz), 7.58-

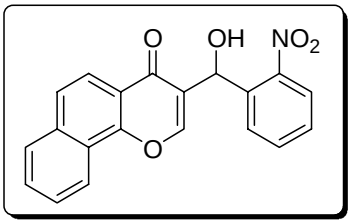
(DMSO-d_6)

7.76 (m, 3H), 8.04 (d, 2H, J = 8.4 Hz), 8.29 (d, 1H, J = 9.0 Hz), 8.38-8.48 (m, 2H), 8.68 (d, 1H, J = 2.0 Hz), 9.74 (d, 1H, J = 8.4 Hz)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 62.94, 116.09, 118.10, 119.64, 126.15, 126.92, 127.25, 128.33, 128.82, 129.39, 129.74, 130.46, 131.35, 136.27, 143.99, 146.74, 148.44, 152.48, 157.56, 177.18

3-[Hydroxy(2-nitrophenyl)methyl]-7,8-benzo-4*H*-chromen-4-one (187p):

This compound was obtained as a colorless solid, *via* the treatment of 7,8-benzochromen-4(4*H*)-one (**186f**) with 2-nitrobenzaldehyde in the presence of NaOMe in methanol, following the similar procedure described for the compound **187a**.



Reaction time: 5 h

Yield: 70%

Mp: 166-168 ^{o}C

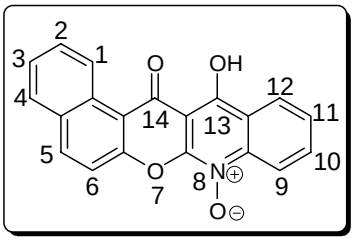
IR (KBr): ν 3393, 1641, 1621, 1604 cm^{-1}

^{1}H NMR (400 MHz): (DMSO-d_6) δ 6.40 (br s, 1H), 6.47 (s, 1H), 7.47-7.56 (m, 1H), 7.63-7.97 (m, 7H), 8.04 (d, 1H, J = 7.6 Hz), 8.35-8.48 (m, 2 H)

^{13}C NMR (100 MHz): (DMSO-d_6) δ 62.70, 119.52, 120.08, 121.96, 123.43, 124.11, 125.55, 127.83, 128.35, 128.72, 129.48, 129.81, 133.12, 135.37, 137.03, 148.63, 153.31, 153.52, 175.07

8-Aza-13-hydroxy-7-oxa-8-oxy-benzo[*a*]naphthacen-14-one (195e):

The treatment of 3-[hydroxy(2-nitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (**187n**) with trifluoroacetic acid, provided the title compound as a colorless solid, following the similar procedure described for the product **195a**.



Reaction time: 2 h

Yield: 86%

Mp: 235-238 ^{o}C

IR (KBr): ν 3111, 1655, 1608, 1506, 1450, 1373, 1336, 1267 cm^{-1}

^{1}H NMR (400 MHz): (10% TFA in $CDCl_3$) δ 7.64-7.75 (m, 1H), 7.76-8.00 (m, 3H), 8.00 (d, 1H, J = 8.0 Hz), 8.20-8.38 (m, 1H), 8.42 (d, 1H, J = 8.4 Hz), 8.50 (d, 1H, J = 8.4 Hz), 8.62 (d, 1H, J = 7.6 Hz), 9.67 (d, 1H, J = 8.0 Hz), 11.96 (br s, 1H)*

**It looks that –O<u>H</u> (at C13) peak of the compound merges with COO<u>H</u> peak of the TFA at δ 11.96.*

^{13}C NMR (100 MHz): (10% TFA in $CDCl_3$) δ 99.58, 112.39, 117.22, 125.44, 126.19, 128.29, 128.62, 129.29, 129.35, 131.43, 131.54, 139.17, 139.40, 141.25, 152.74, 156.54, 173.19, 182.30; In addition two quartets, one at δ 115.18 [q, J = 292 Hz; (signals at δ 110.71, 113.63, 116.73, 119.32)] and second one at δ 160.20 [q, J = 40 Hz; (signals at δ 159.60, 160.00, 160.41, 160.81)] arising from CF_3COOH also appeared.

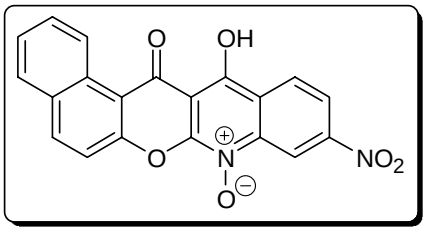
LCMS (*m/z*): 330 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{11}NO_4$: C, 72.95; H, 3.37; N, 4.25

Found: C, 72.93; H, 3.41; N, 4.32

8-Aza-13-hydroxy-10-nitro-7-oxa-8-oxy-benzo[*a*]naphthacen-14-one (195f):

This molecule was obtained as a colorless solid, *via* the reaction between 3-[hydroxy(2,4-dinitrophenyl)methyl]-5,6-benzo-4*H*-chromen-4-one (**187o**) and trifluoroacetic acid, following the similar procedure described for the compound **195a**.



Reaction time: 2 h

Yield: 84%

Mp: 265 ^oC (dec.)

IR (KBr): ν 3113, 1658, 1585, 1543, 1508, 1442, 1342, 1234 cm^{-1}

^1H NMR (400 MHz): (10% TFA in $CDCl_3$) δ 7.78-7.90 (m, 1H), 7.91 (d, 1H, *J* = 8.8 Hz), 7.93-8.06 (m, 1H), 8.14 (d, 1H, *J* = 8.0 Hz), 8.58 (d, 1H, *J* = 8.8 Hz), 8.63 (d, 1H, *J* = 8.8 Hz), 8.91 (d, 1H, *J* = 8.8 Hz), 9.32 (s, 1H), 9.74 (d, 1H, *J* = 8.4 Hz), 11.77 (br s, 1H)*

**It looks that –O<u>H</u> (at C13) peak of the compound merges with COO<u>H</u> peak of the TFA at δ 11.77.*

^{13}C NMR (100 MHz): (10% TFA in $CDCl_3$) δ 101.24, 112.75, 113.30, 116.56, 121.23, 122.32, 126.85, 128.61, 129.22, 129.73, 130.05, 132.25, 132.59, 139.93, 142.97, 153.62, 154.95, 157.40, 174.86, 182.74; In addition

two quartets, one at δ 114.65 [q, J = 282 Hz; (signals at δ 110.42, 113.24, 116.07, 118.89)] and second one at δ 161.67 [q, J = 43 Hz; (signals at δ 161.46, 161.89, 162.32, 162.75)] arising from the carbons of CF_3COOH also appeared.

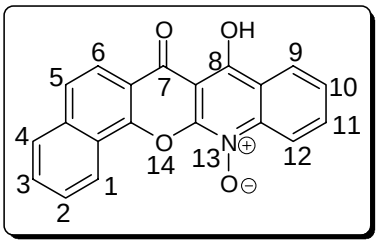
LCMS (*m/z*): 375 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{10}N_2O_6$: C, 64.18; H, 2.69; N, 7.48

Found: C, 64.08; H, 2.68; N, 7.42

13-Aza-8-hydroxy-14-oxa-13-oxy-benzo[*a*]naphthacen-7-one (195g):

This compound was obtained as a colorless solid, *via* treatment of 3-[hydroxy(2-nitrophenyl)methyl]-7,8-benzo-4*H*-chromen-4-one (**187p**) with trifluoroacetic acid, following the similar procedure described for the product **195a**.



Reaction time: 2 h

Yield: 75%

Mp: 279 ^oC (dec.)

IR (KBr): ν 3111, 1655, 1608, 1521, 1450, 1385, 1338, 1265 cm^{-1}

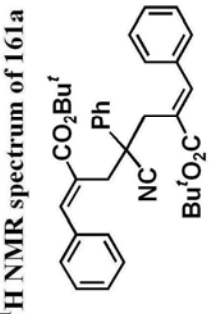
^1H NMR (400 MHz): (10% TFA-*d* in $CDCl_3$) δ 7.80-7.99 (m, 3H), 8.00-8.11 (m, 2H), 8.19 (d, 1H, J = 8.8 Hz), 8.28-8.38 (m, 1H), 8.54 (d, 1H, J = 8.8 Hz), 8.67 (d, 1H, J = 8.4 Hz), 8.72 (d, 1H, J = 8.4 Hz), 11.99 (br s, 1H)*

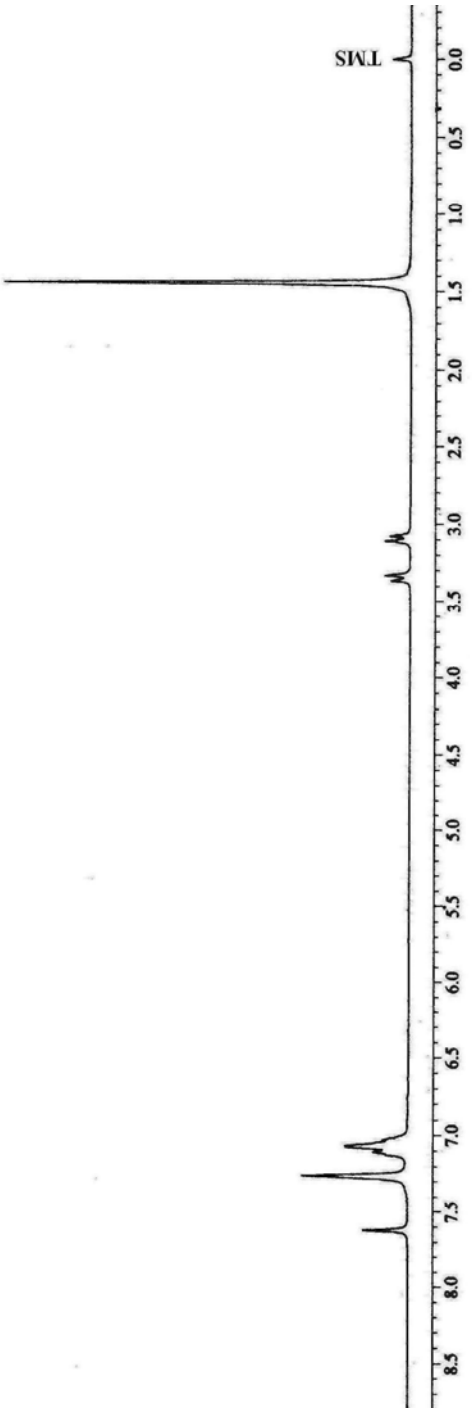
**It looks that –O<u>H</u> (at C8) peak of the compound merges with COO<u>H</u> peak of the TFA at δ 11.99.*

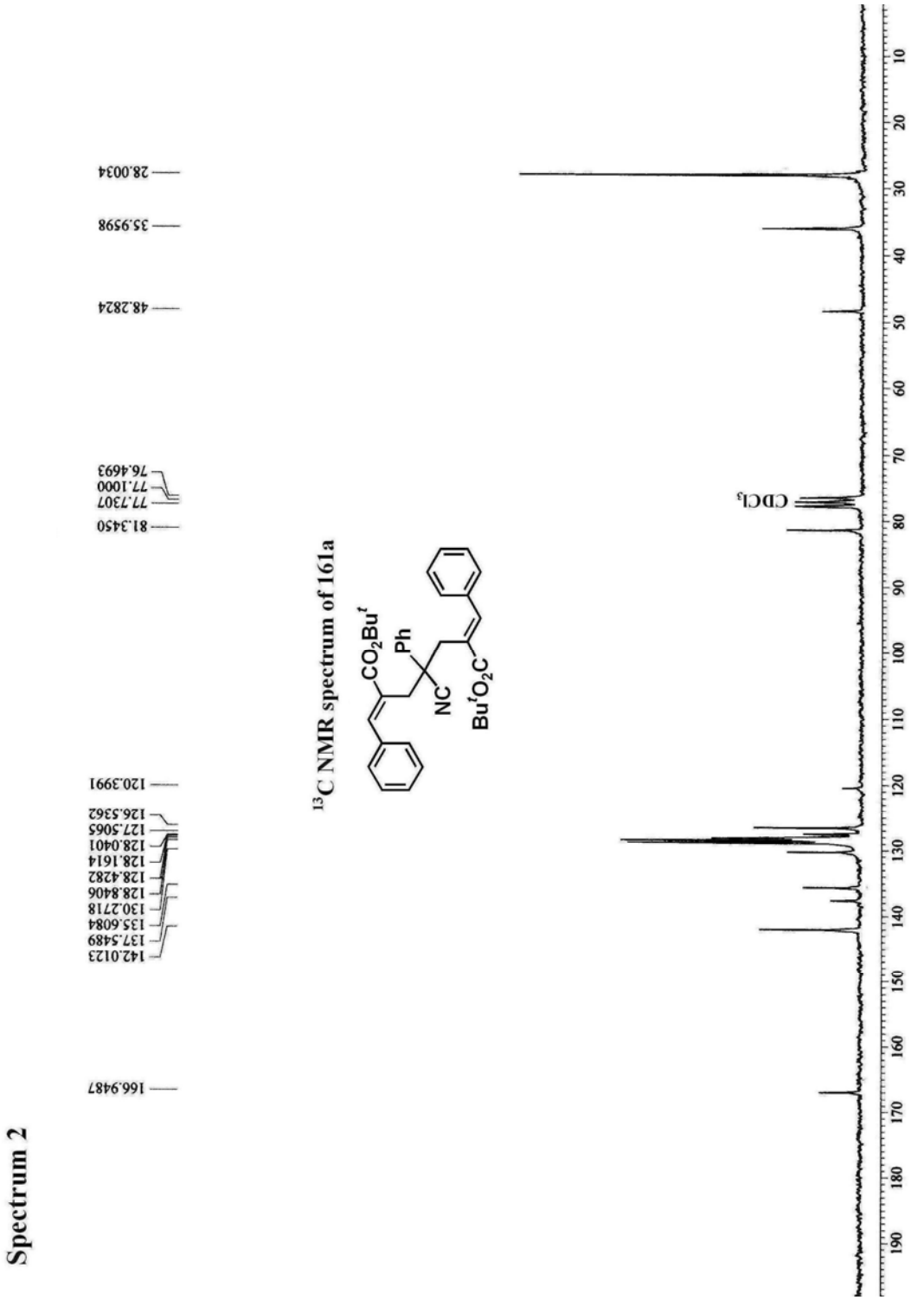
^{13}C NMR (100 MHz): (10% TFA-*d* in $CDCl_3$)	δ 99.60, 115.49, 116.85, 117.29, 119.04, 122.73, 125.80, 125.83, 128.56, 128.72, 129.05, 129.43, 132.51, 138.43, 139.74, 153.04, 154.10, 173.42, 180.78; In addition two quartets, one at δ 114.71 [q, J = 282 Hz; (signals at δ 110.47, 113.29, 116.13, 118.97)] and second one at δ 161.27 [q, J = 42 Hz; (signals at δ 160.64, 161.06, 161.49, 161.91)] due to the presence of CF_3COOH also appeared.
LCMS (*m/z*):	330 $(M+H)^+$
Anal. Calcd. for $C_{20}H_{11}NO_4$:	C, 72.95; H, 3.37; N, 4.25
Found:	C, 73.08; H, 3.40; N, 4.13

Spectrum 1

^{1}H NMR spectrum of 161a

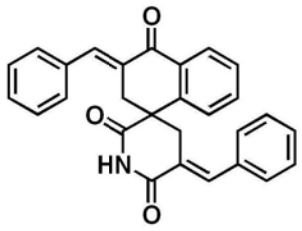


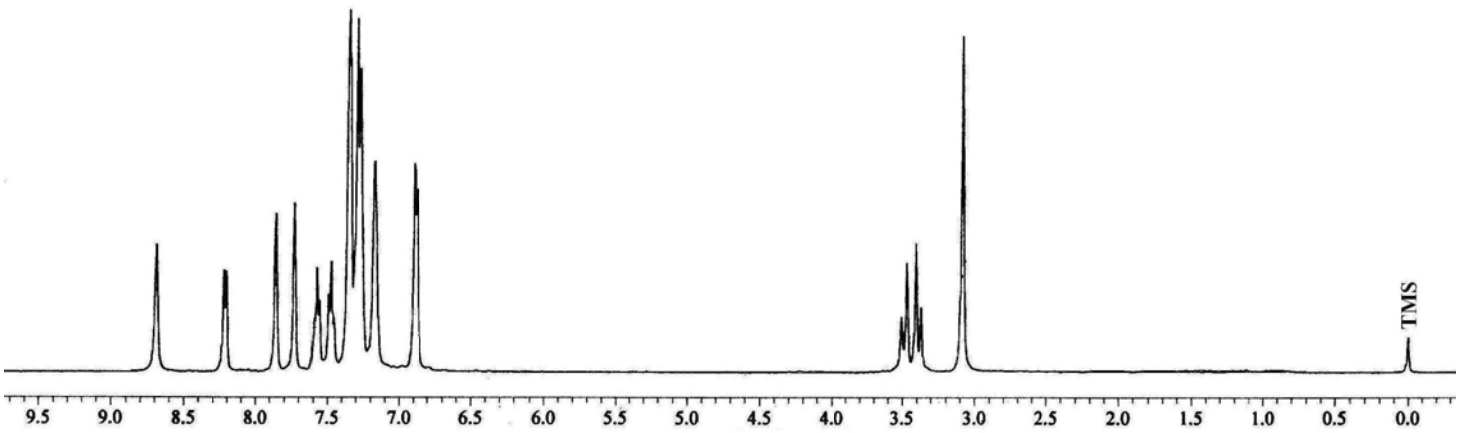


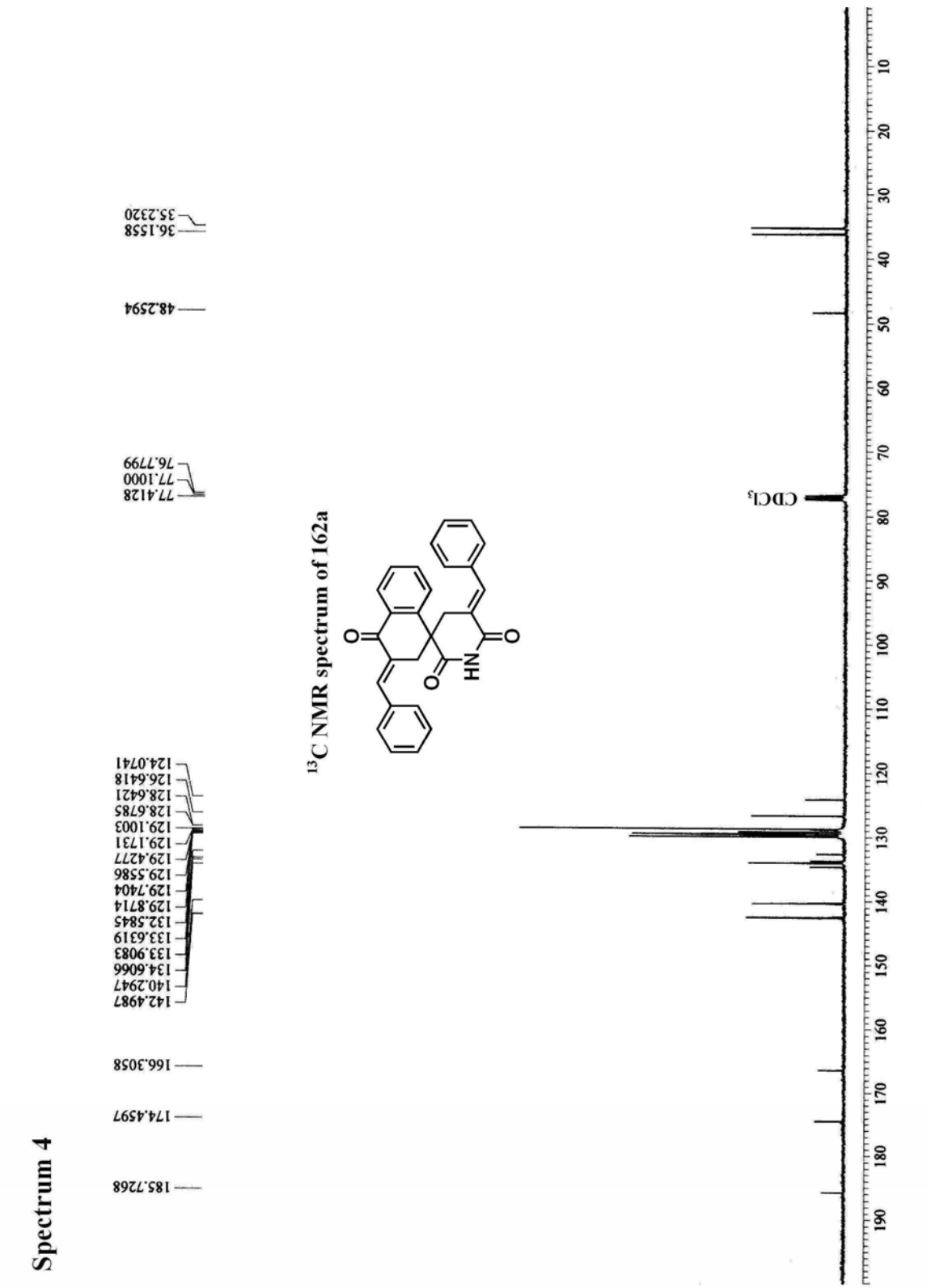

Spectrum 2
^{13}C NMR spectrum of 161a
CO2But
Ph
NC
But O2C
CDCl3
166.9487
142.0123
137.5489
135.6084
130.2718
128.8406
128.4282
128.1614
128.0401
127.5065
126.5362
120.3991
81.3450
77.7307
77.1000
76.4693
48.2824
35.9598
28.0034

Spectrum 3

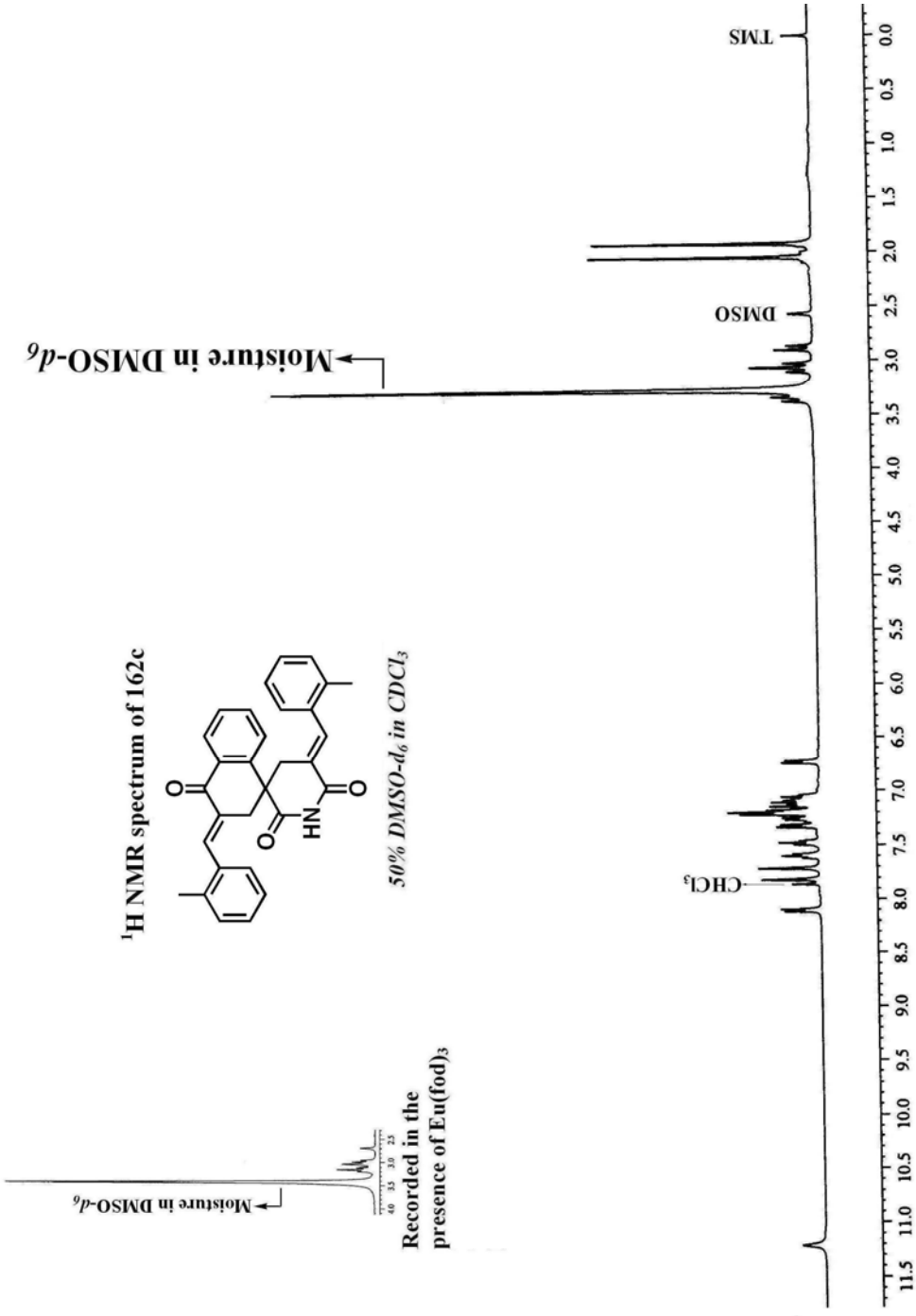
^{1}H NMR spectrum of 162a





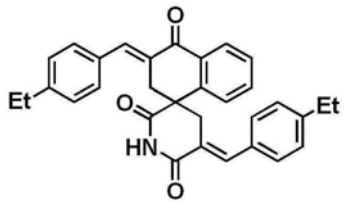

Spectrum 4
^{13}C NMR spectrum of 162a
CDCl$_3$
185.7268
174.4597
166.3058
142.4987
140.2947
134.6066
133.9083
133.6319
132.5845
129.8714
129.7404
129.5586
129.4277
129.1731
129.1003
128.6785
128.6421
126.6418
124.0741
77.4128
77.1000
76.7799
48.2594
36.1558
35.2320
HN
O

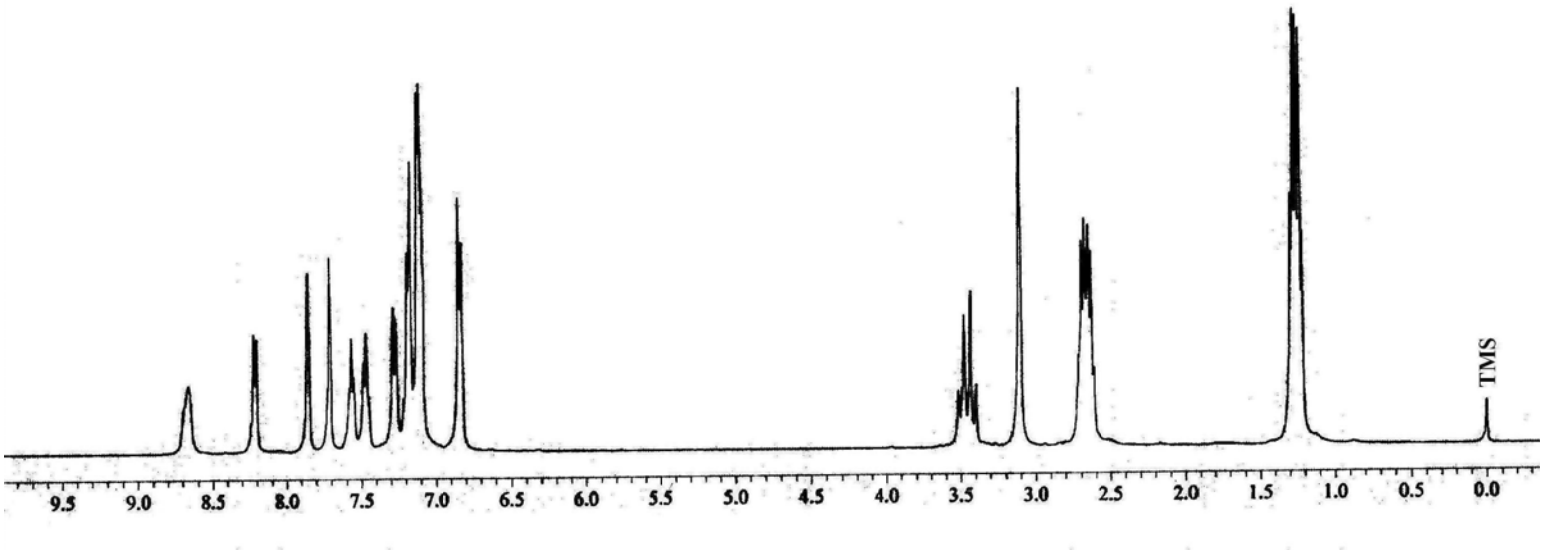
Spectrum 5

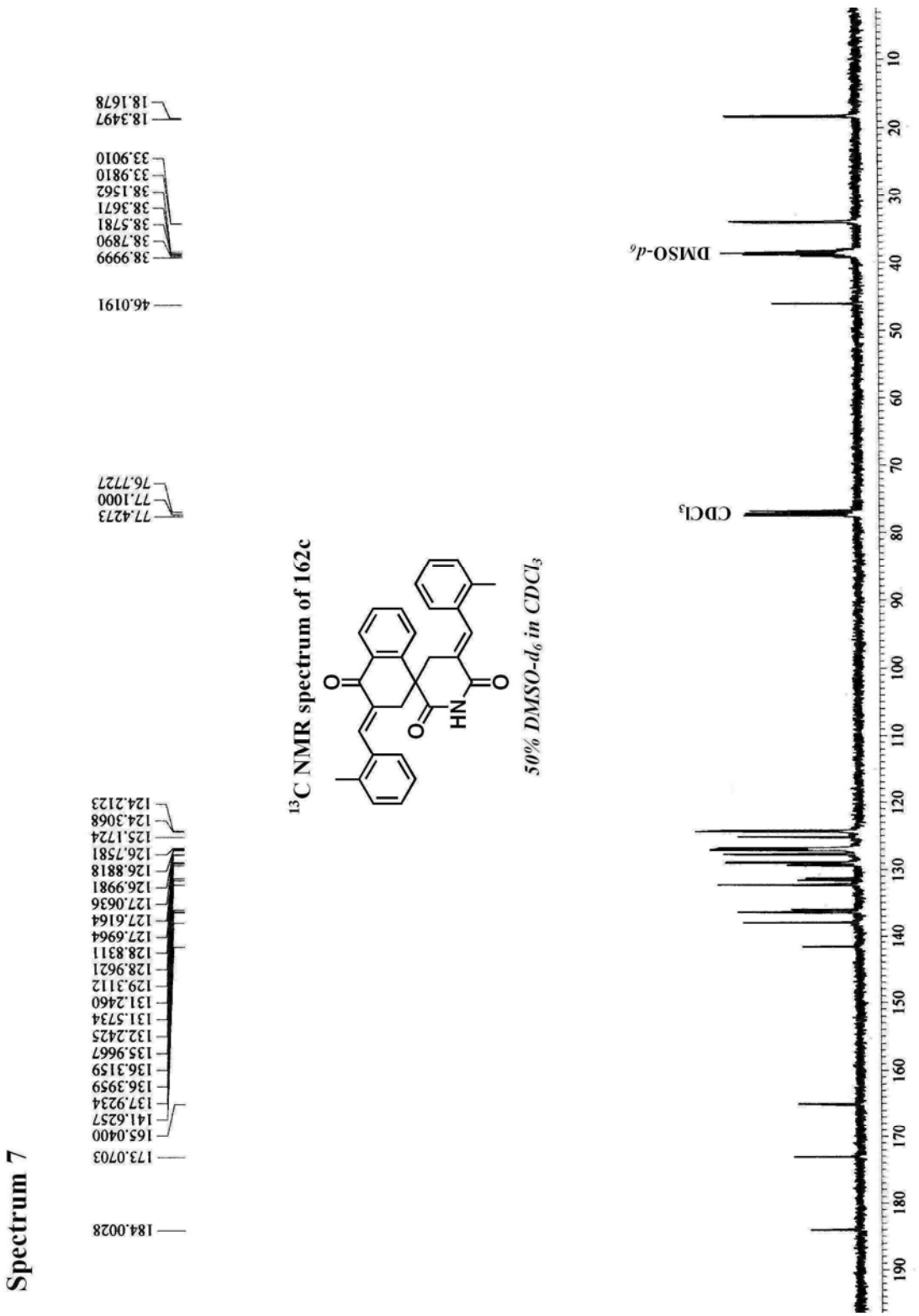

Moisture in DMSO-d_6
^{1}H NMR spectrum of 162c
HN
O
O
O
50% DMSO-d_6 in $CDCl_3$
Recorded in the presence of Eu(fod)$_3$
Moisture in DMSO-d_6
DMSO
TMS
$CHCl_3$
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

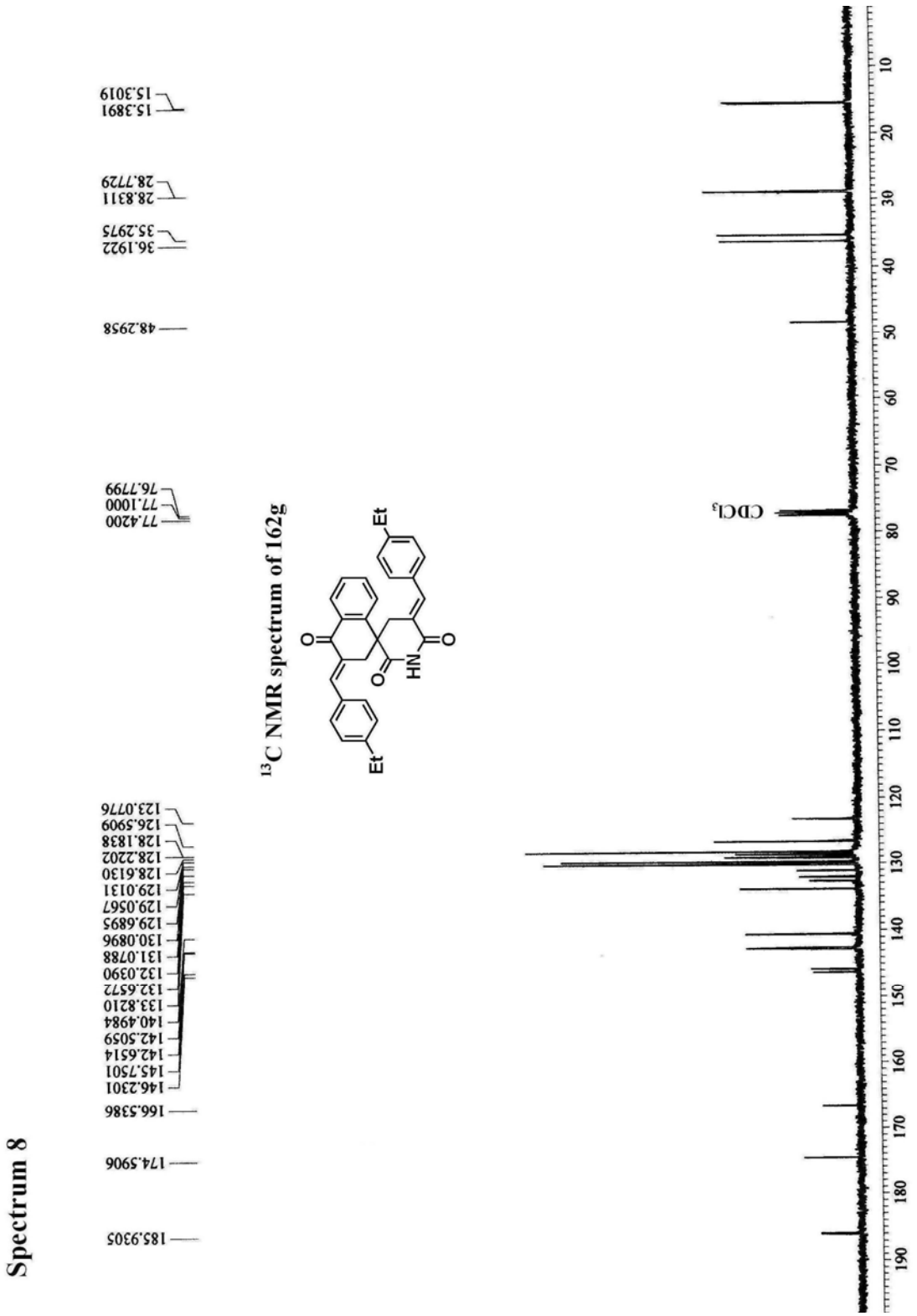
Spectrum 6

^{1}H NMR spectrum of 162g



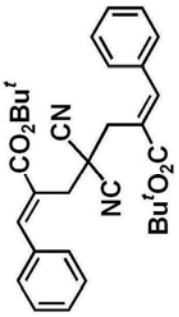


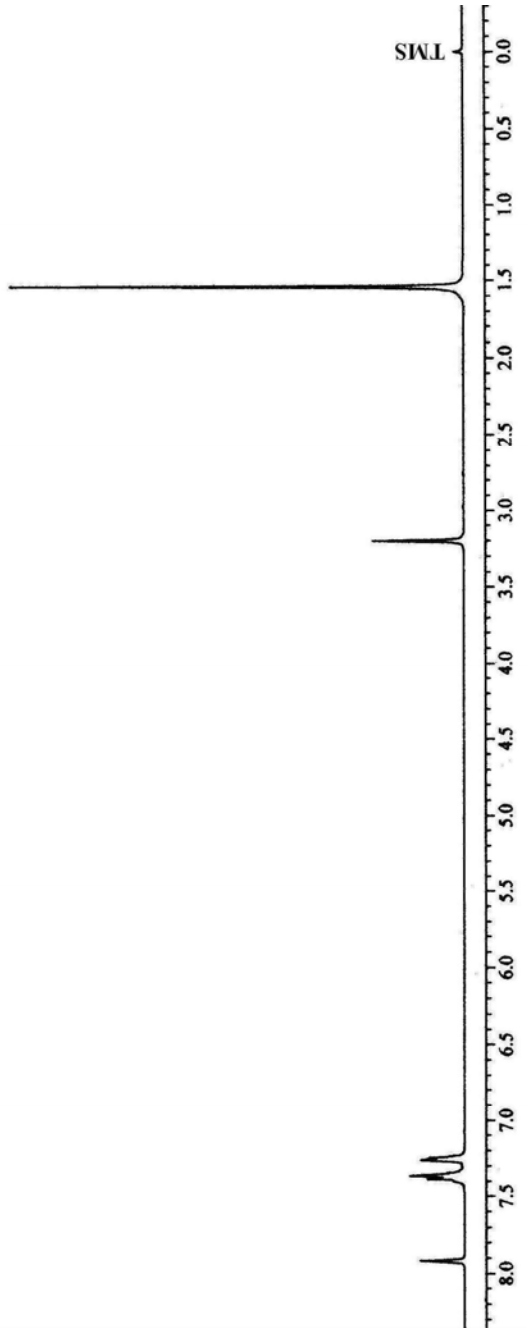

Spectrum 7
^{13}C NMR spectrum of 162c
50% DMSO-d_6 in $CDCl_3$
$CDCl_3$
DMSO-d_6
HN
O
O
O
18.1678
18.3497
33.9010
33.9810
38.1562
38.3671
38.5781
38.7890
38.9999
46.0191
76.7727
77.1000
77.4273
124.2123
124.3068
125.1724
126.7581
126.8818
126.9981
127.0636
127.6164
127.6964
128.8311
128.9621
129.3112
131.2460
131.5734
132.2425
135.9667
136.3159
136.3959
137.9234
141.6257
165.0400
173.0703
184.0028

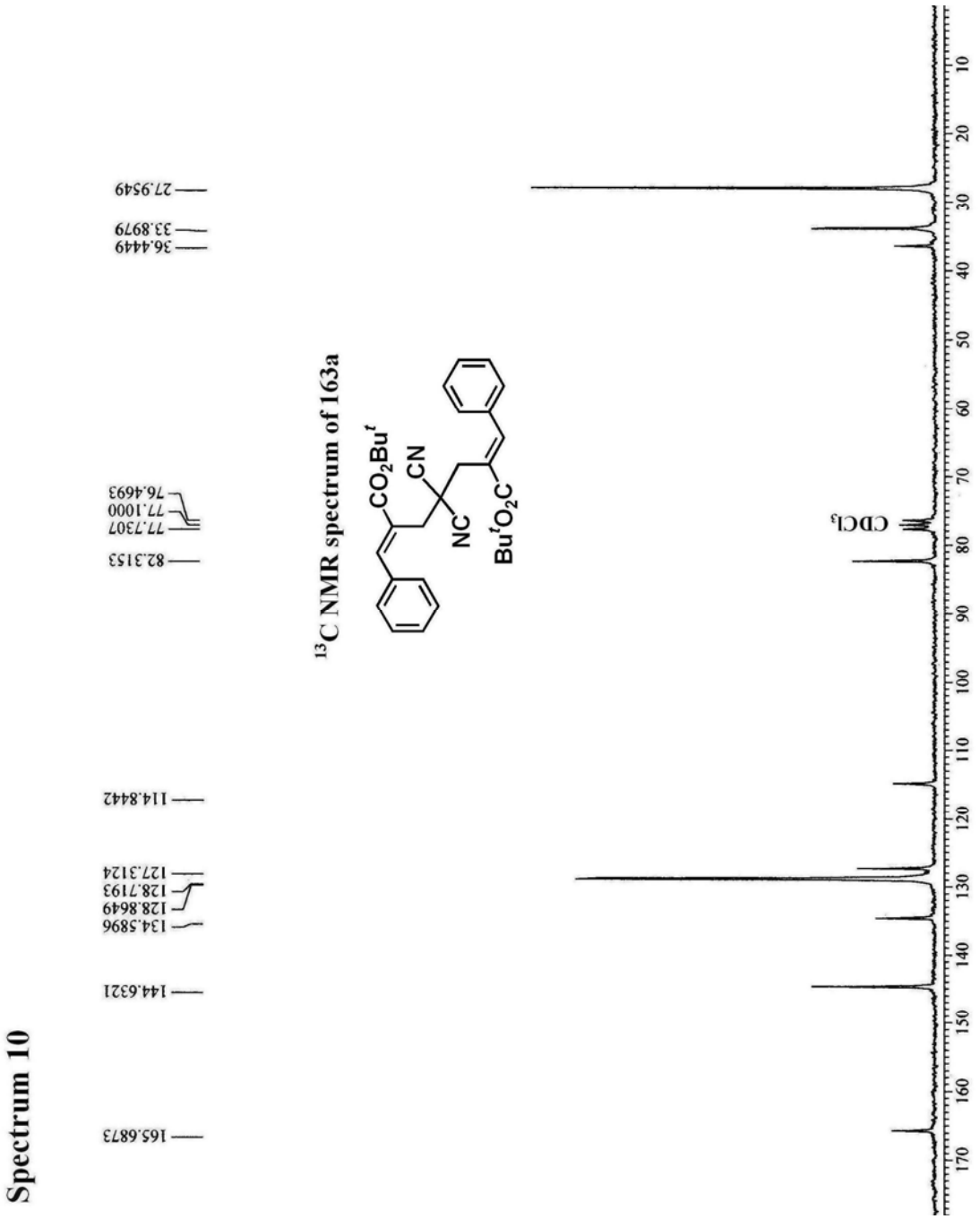

Spectrum 8
^{13}C NMR spectrum of 162g
Et
Et
O
O
HN
O
CDCl$_3$
15.3019
15.3891
28.7729
28.8311
35.2975
36.1922
48.2958
76.7799
77.1000
77.4200
123.0776
126.5909
128.1838
128.2202
128.6130
129.0131
129.0567
129.6895
130.0896
131.0788
132.0390
132.6572
133.8210
140.4984
142.5059
142.6514
145.7501
146.2301
166.5386
174.5906
185.9305

Spectrum 9

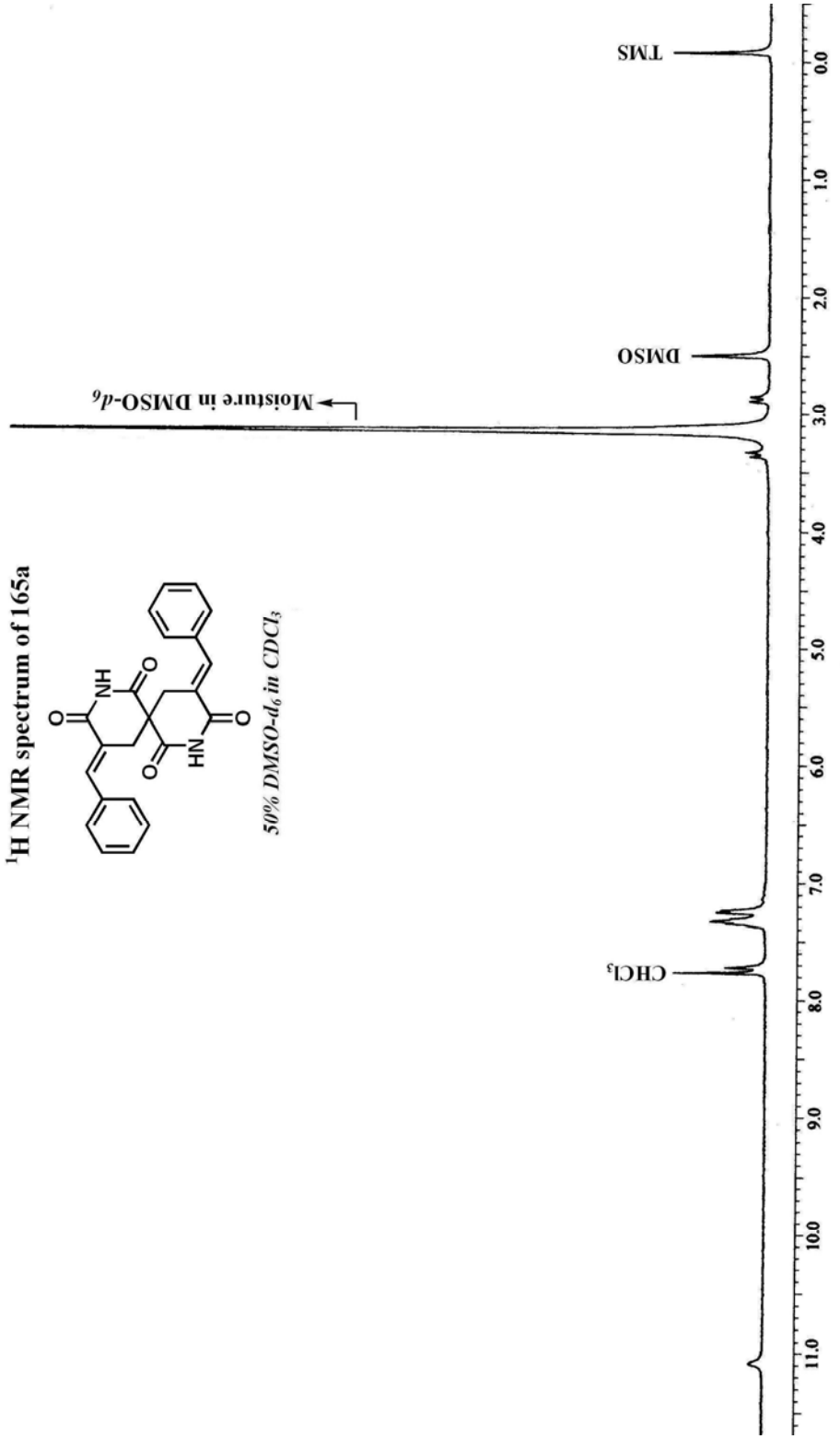
^{1}H NMR spectrum of 163a

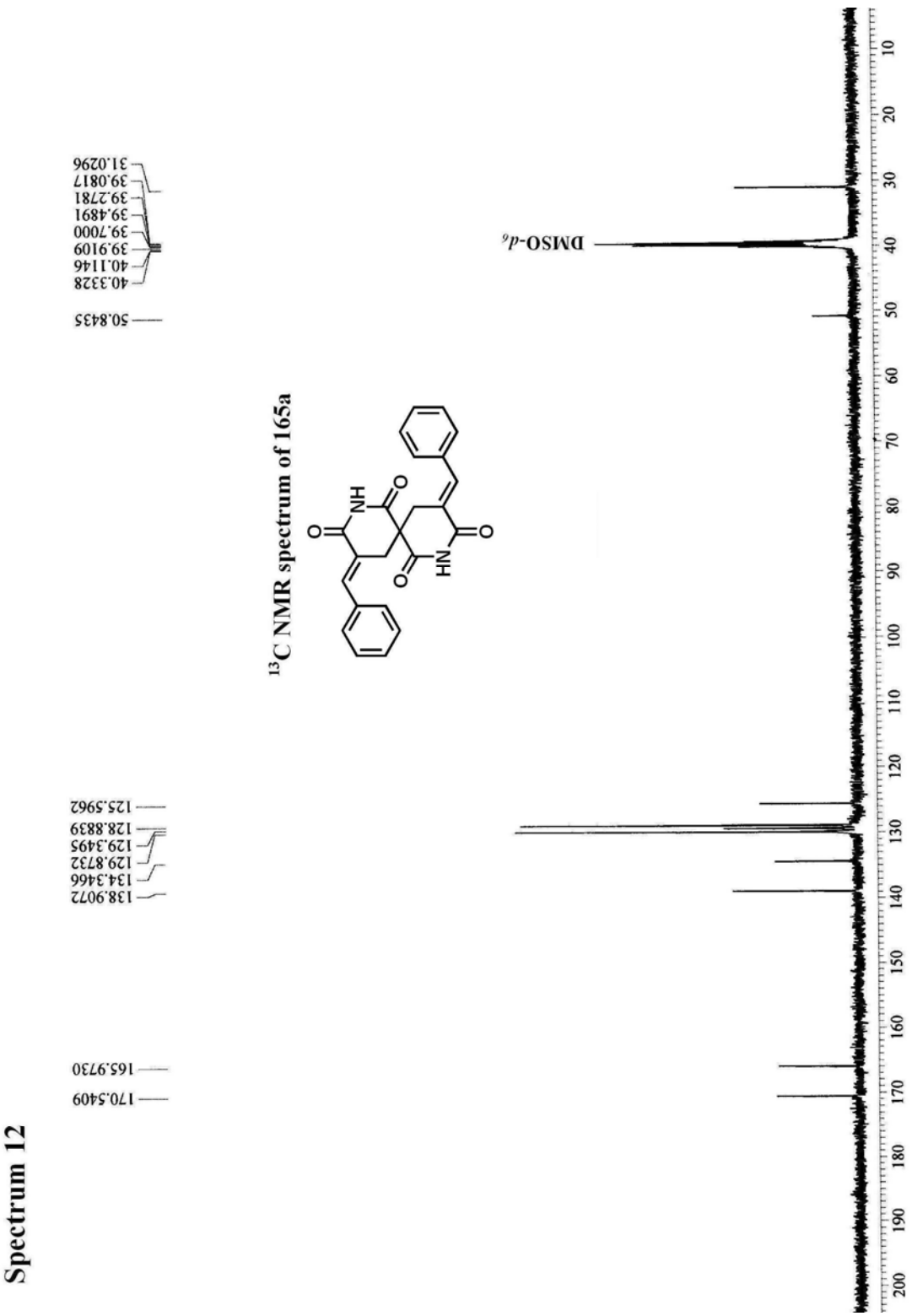





Spectrum 10
^{13}C NMR spectrum of 163a
CO2But
CN
NC
But O2C
CDCl3
165.6873
144.6321
134.5896
128.8649
128.7193
127.3124
114.8442
82.3153
77.7307
77.1000
76.4693
36.4449
33.8979
27.9549

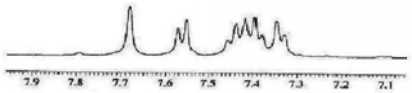
Spectrum 11


^{1}H NMR spectrum of 165a
50% DMSO-d_6 in $CDCl_3$
Moisture in DMSO-d_6
DMSO
TMS
$CHCl_3$
NH
HN
O
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


Spectrum 12
^{13}C NMR spectrum of 165a
DMSO-d_6
170.5409
165.9730
138.9072
134.3466
129.8732
129.3495
128.8839
125.5962
50.8435
40.3328
40.1146
39.9109
39.7000
39.4891
39.2781
39.0817
31.0296
NH
NH
O
O
O
O

Spectrum 13

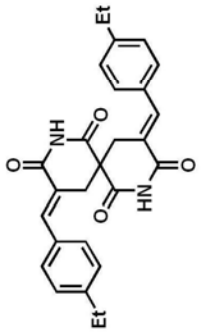
^{1}H NMR spectrum of 165b

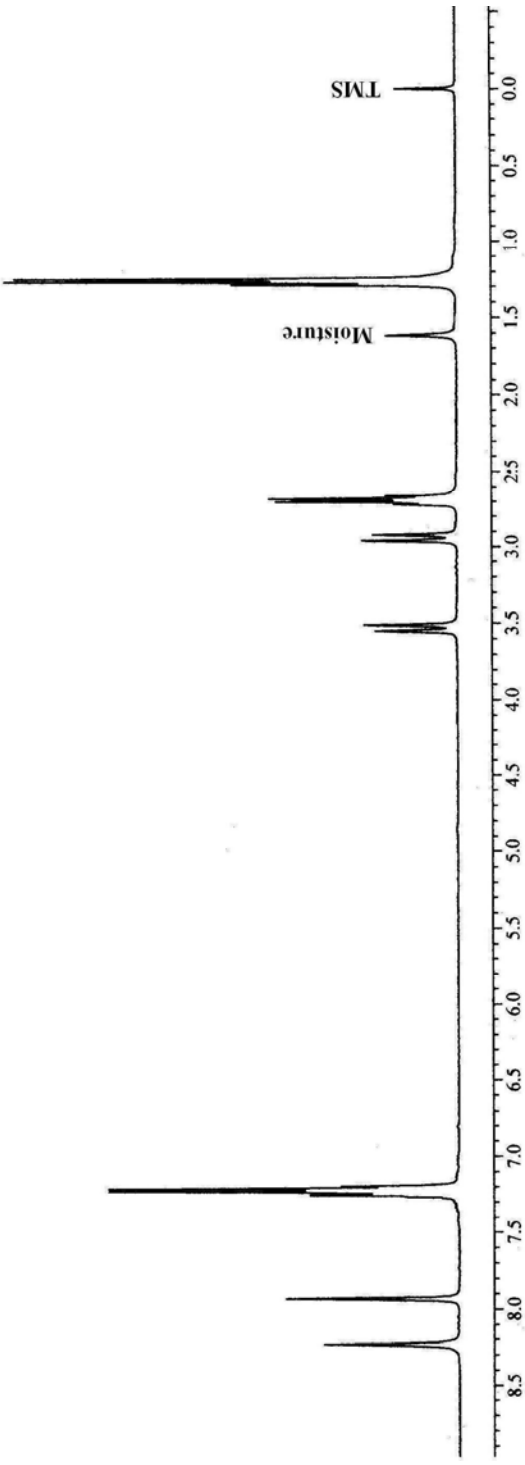


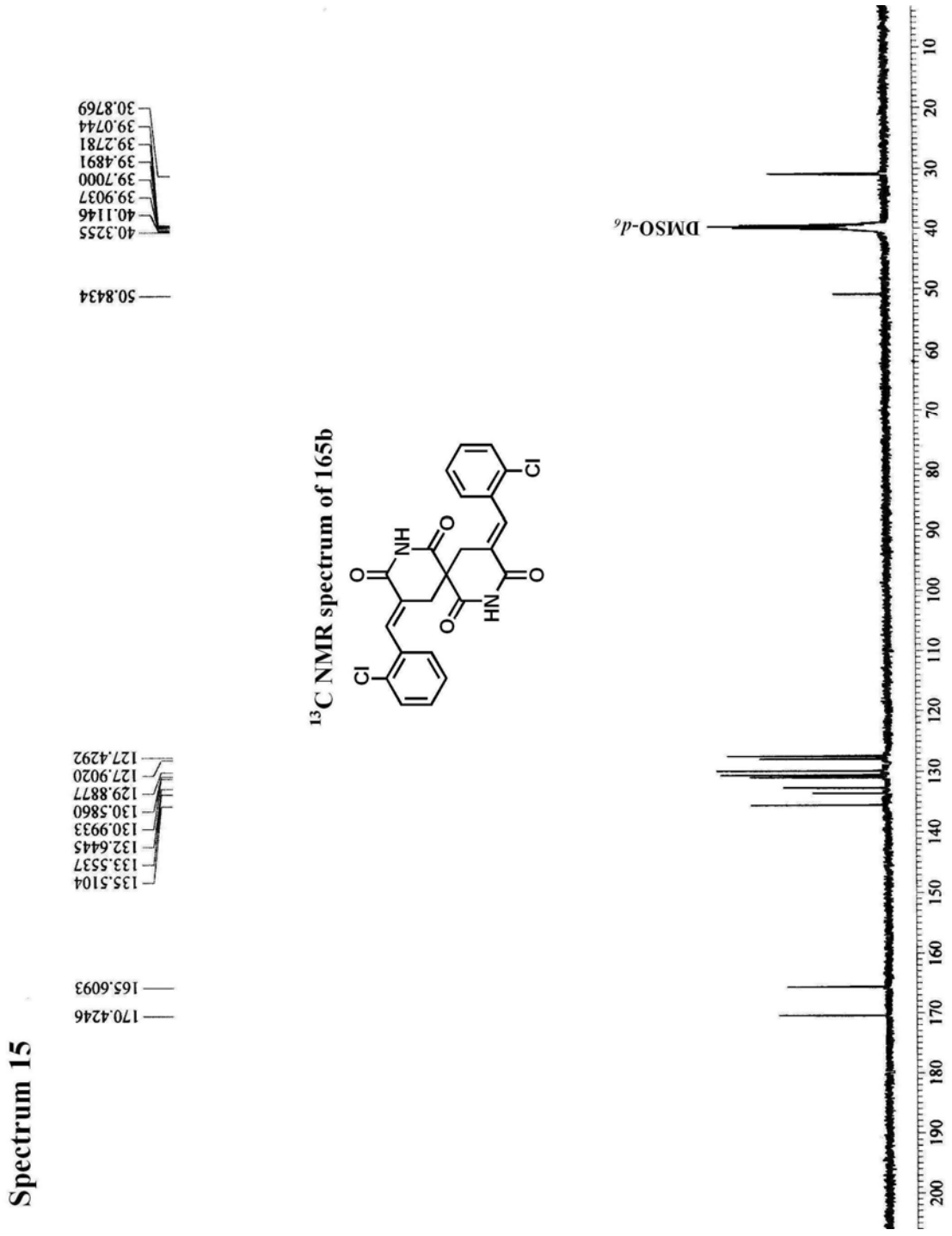
Expansion of the region 7.10-7.90

Spectrum 14

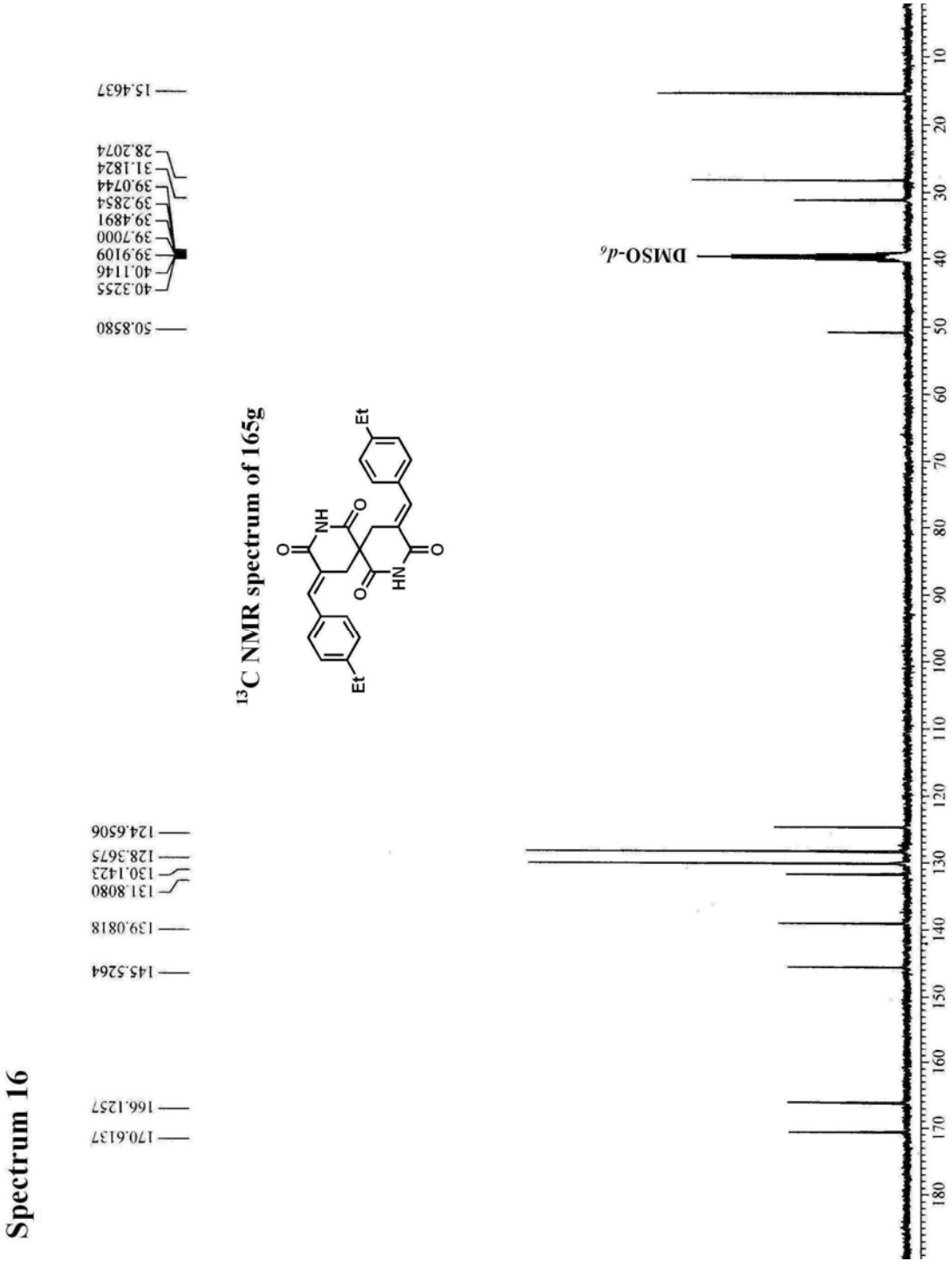
^{1}H NMR spectrum of 165g





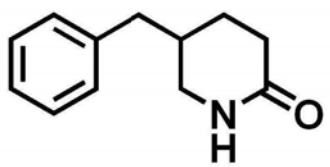

Spectrum 15
170.4246
165.6093
135.5104
133.5537
132.6445
130.9933
130.5860
129.8877
127.9020
127.4292
50.8434
40.3255
40.1146
39.9037
39.7000
39.4891
39.2781
39.0744
30.8769
DMSO-d_6
^{13}C NMR spectrum of 165b
Cl
Cl
NH
HN
O
O
O
O

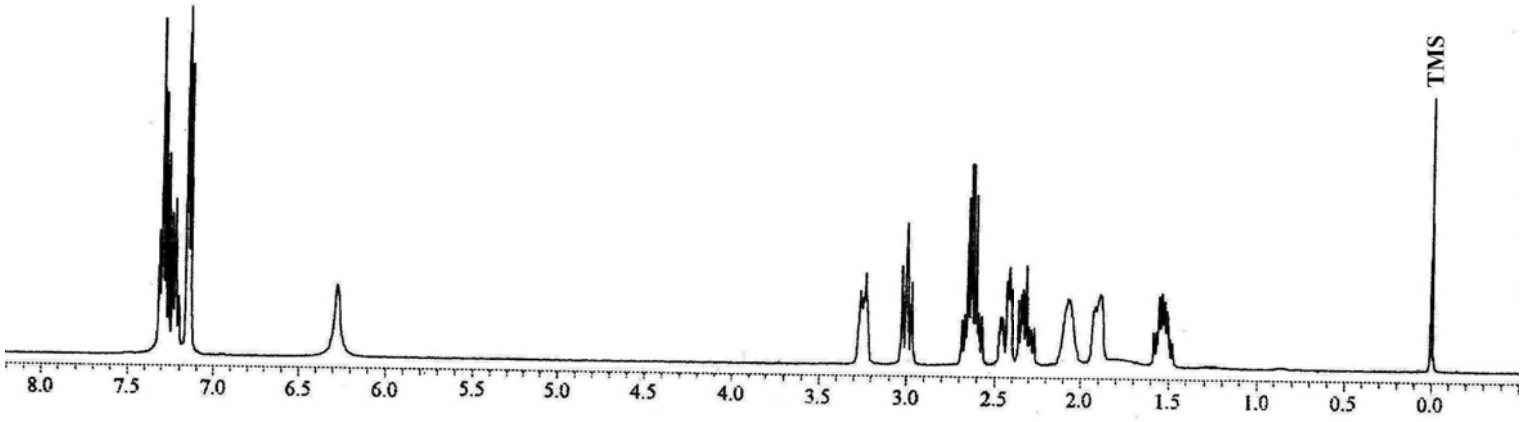
Spectrum 16

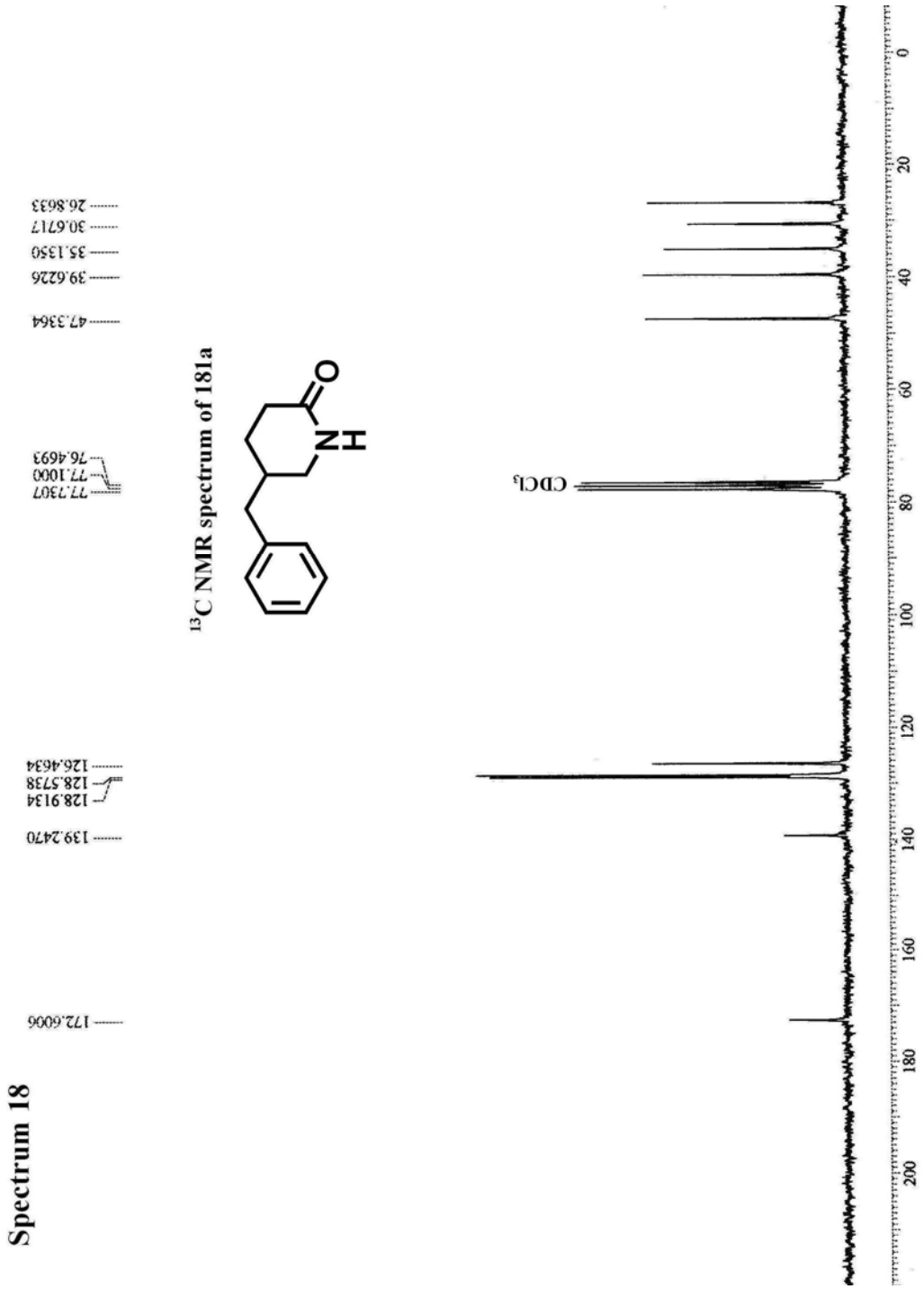

^{13}C NMR spectrum of 165g
DMSO-d_6
15.4637
28.2074
31.1824
39.0744
39.2854
39.4891
39.7000
39.9109
40.1146
40.3255
50.8580
124.6506
128.3675
130.1423
131.8080
139.0818
145.5264
166.1257
170.6137
Et
Et
NH
NH
O
O
O
O

Spectrum 17

^{1}H NMR spectrum of 181a

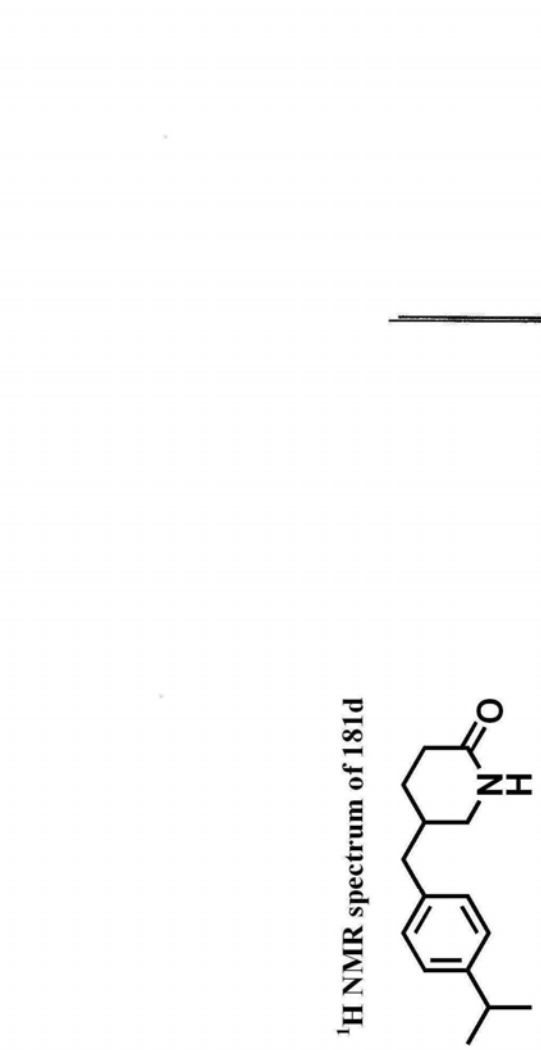


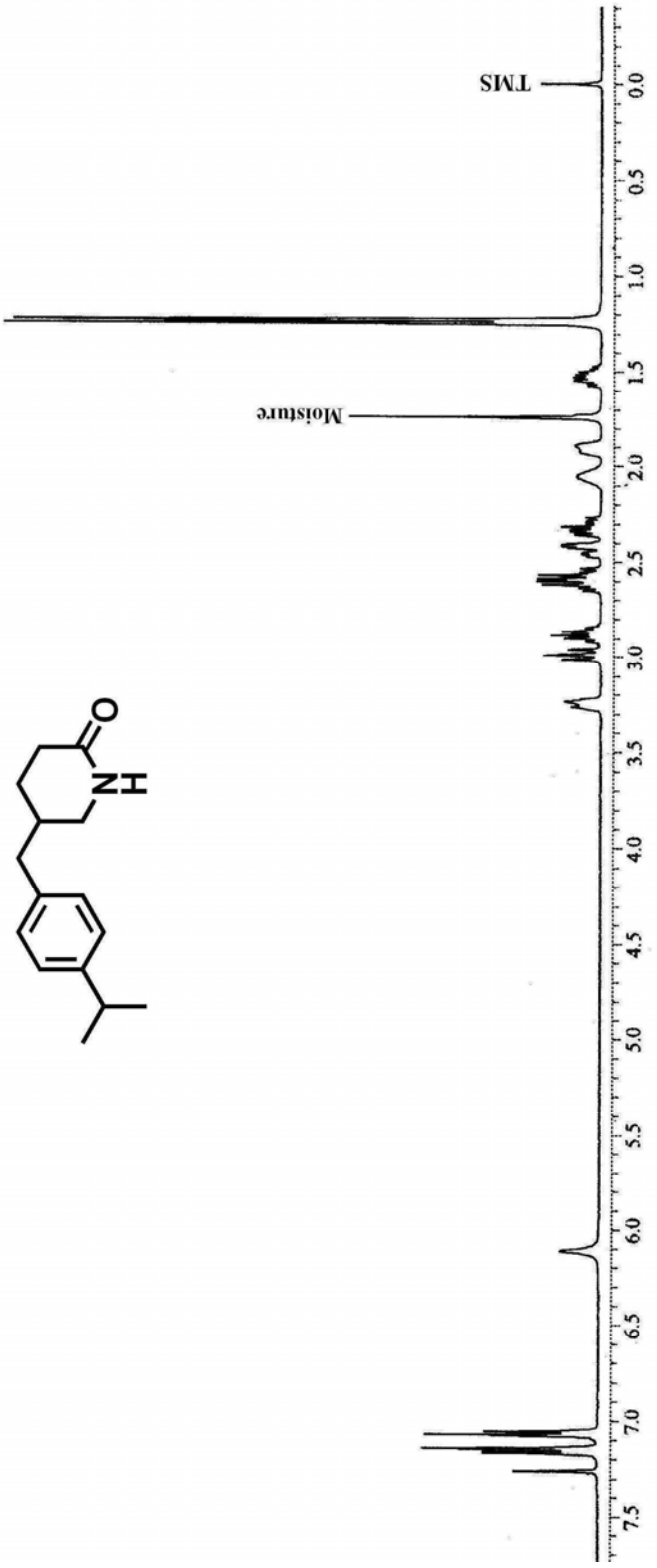


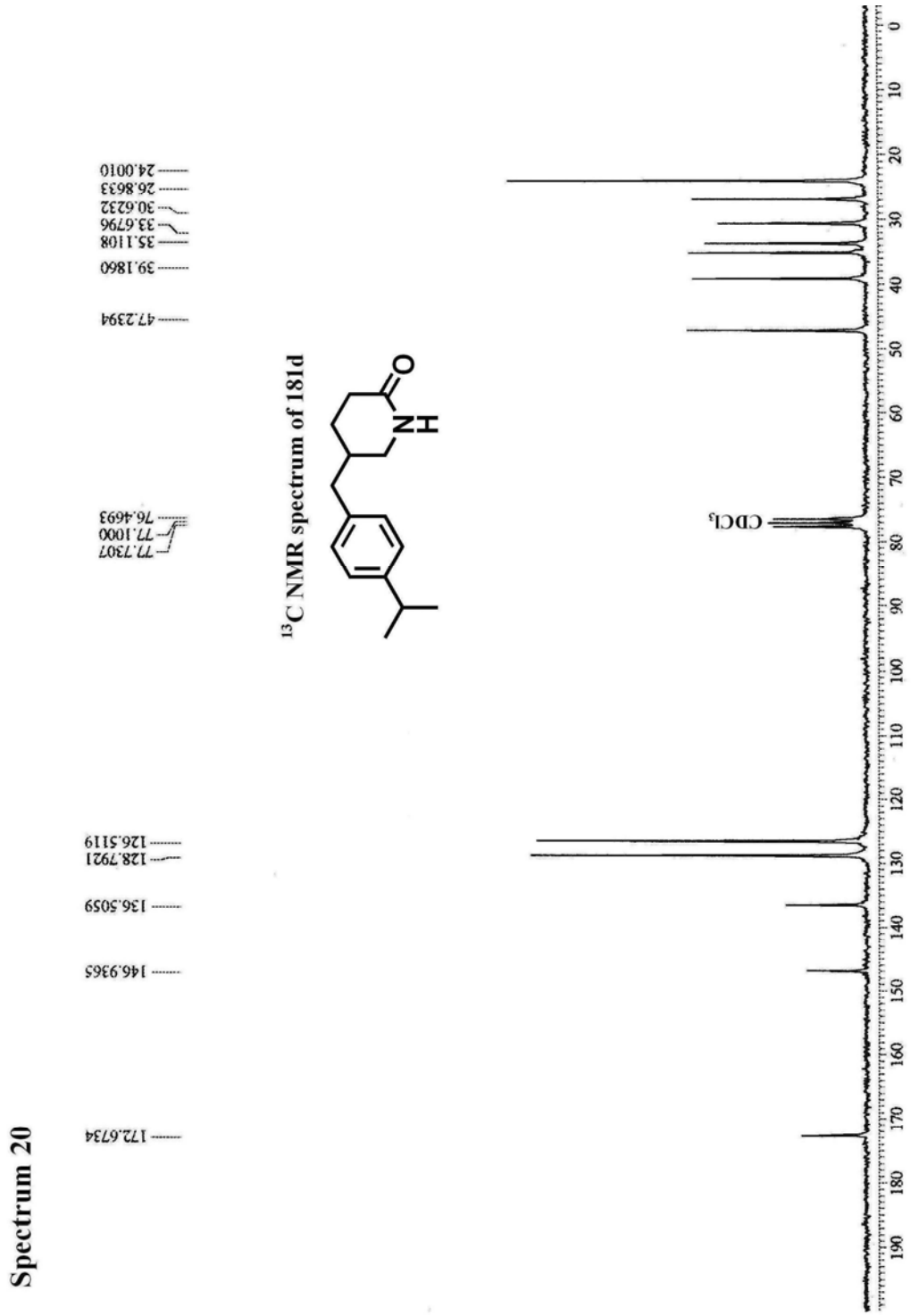

Spectrum 18
^{13}C NMR spectrum of 181a
CDCl$_3$
172.6066
139.2470
128.9134
128.5738
126.4634
77.7307
77.1000
76.4693
47.3364
39.6226
35.1350
30.6717
26.8633
0
20
40
60
80
100
120
140
160
180
200

Spectrum 19

^{1}H NMR spectrum of 181d

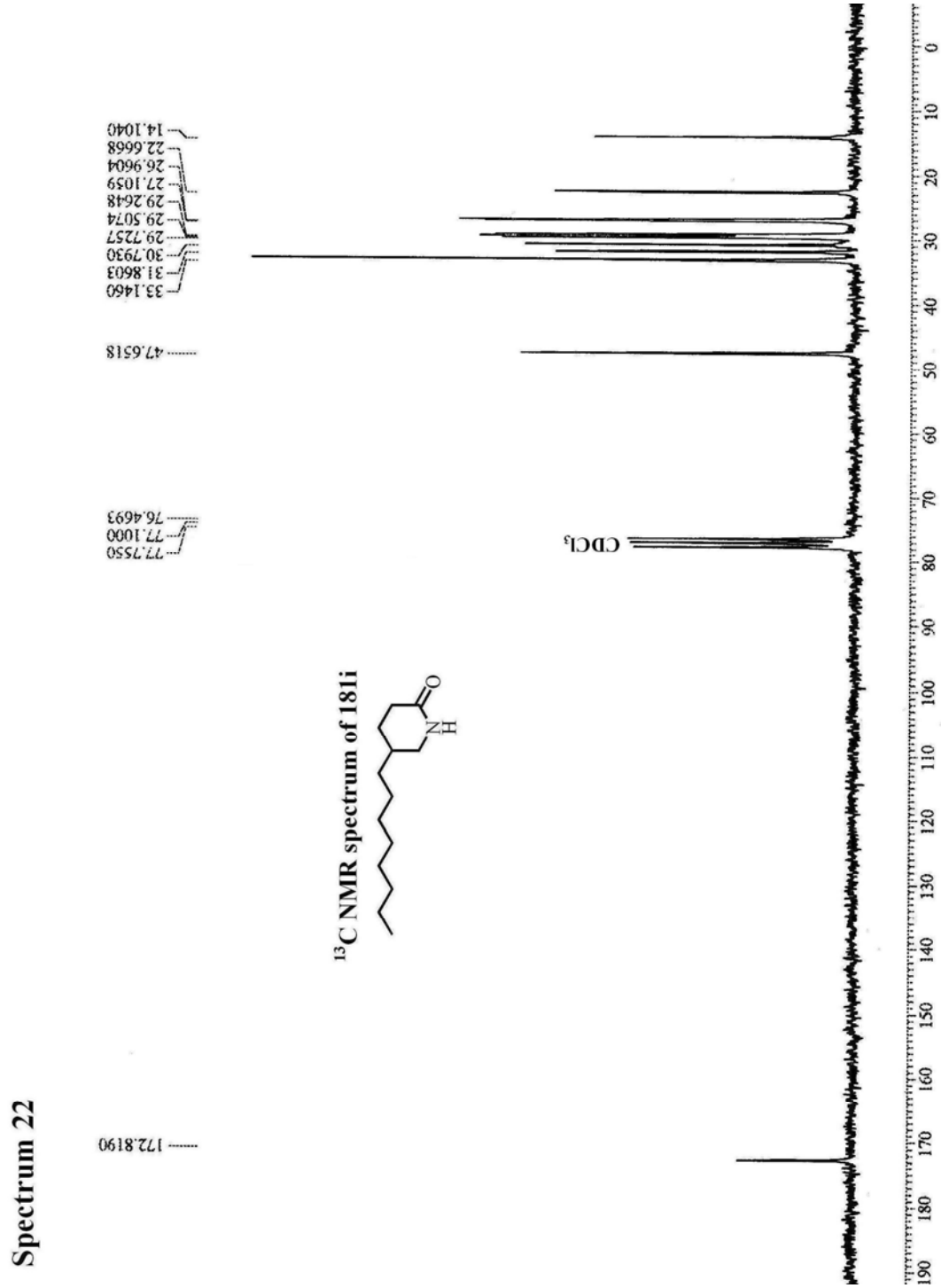





Spectrum 20
172.6734
146.9365
136.5059
128.7921
126.5119
77.7307
77.1000
76.4693
47.2394
39.1860
35.1108
33.6796
30.6232
26.8633
24.0010
^{13}C NMR spectrum of 181d
CDCl$_3$

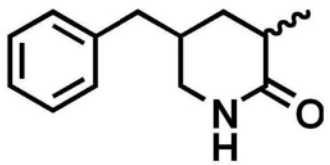
Spectrum 21

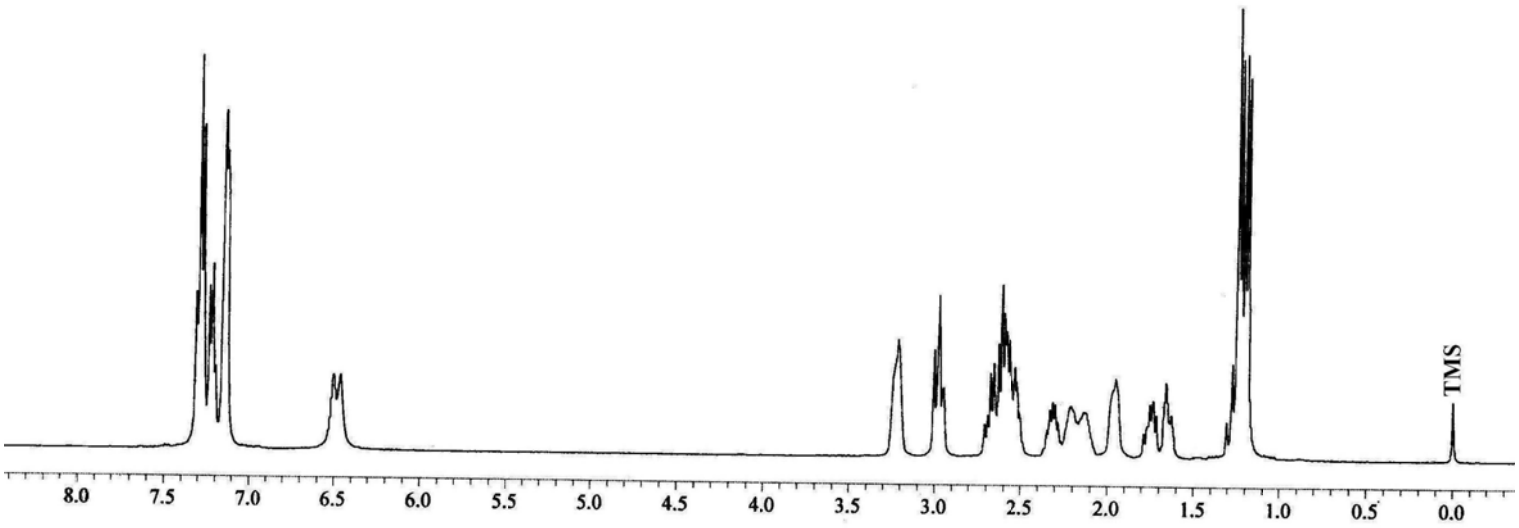
^{1}H NMR spectrum of 181i

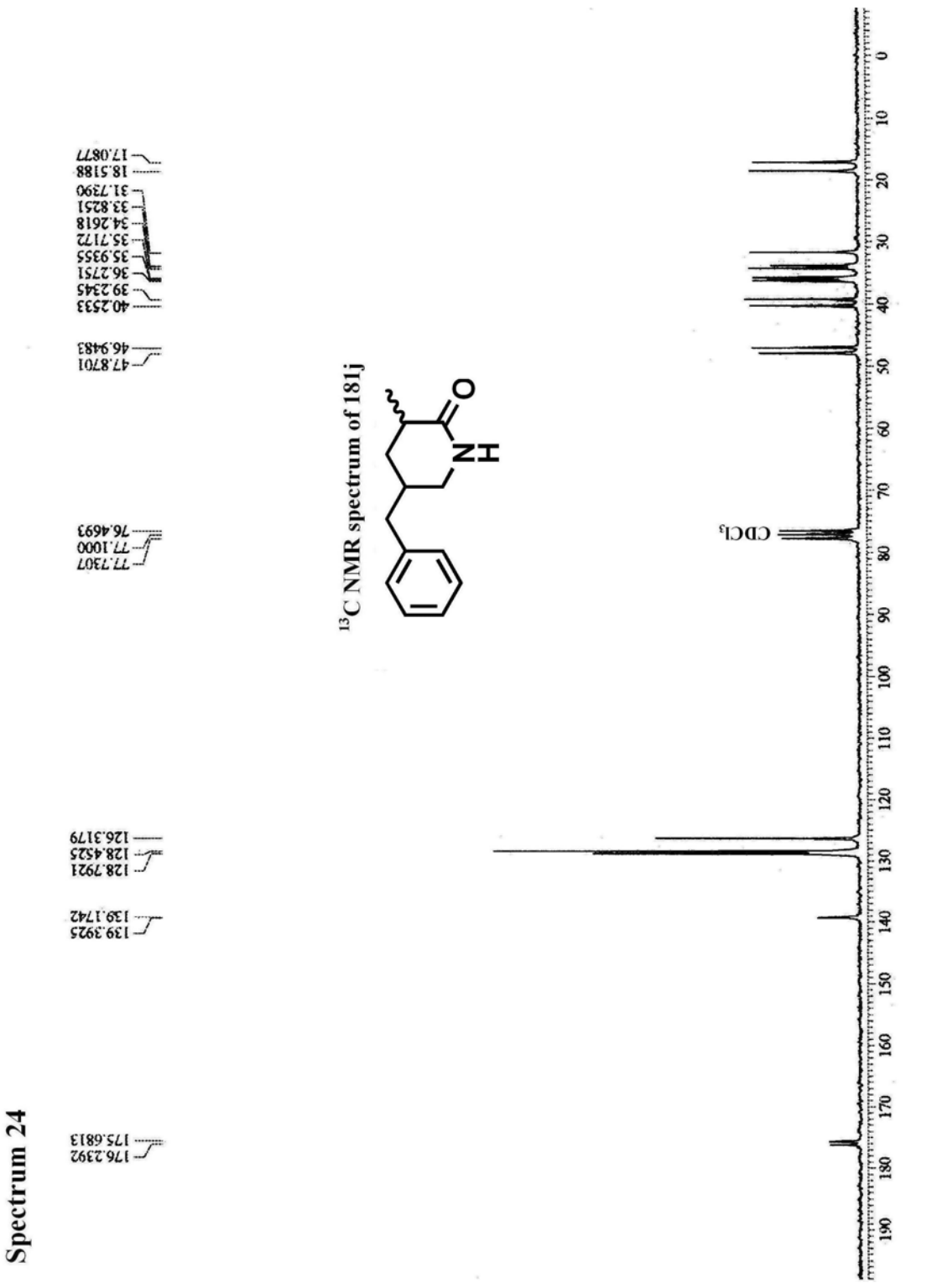

Spectrum 22
^{13}C NMR spectrum of 181i
CDCl$_3$
172.8190
77.7550
77.1000
76.4693
47.6518
33.1460
31.8603
30.7930
29.7257
29.5074
29.2648
27.1059
26.9604
22.6668
14.1040

Spectrum 23

^{1}H NMR spectrum of 181j

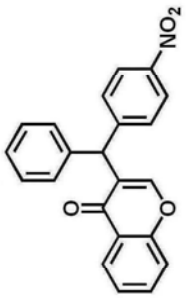


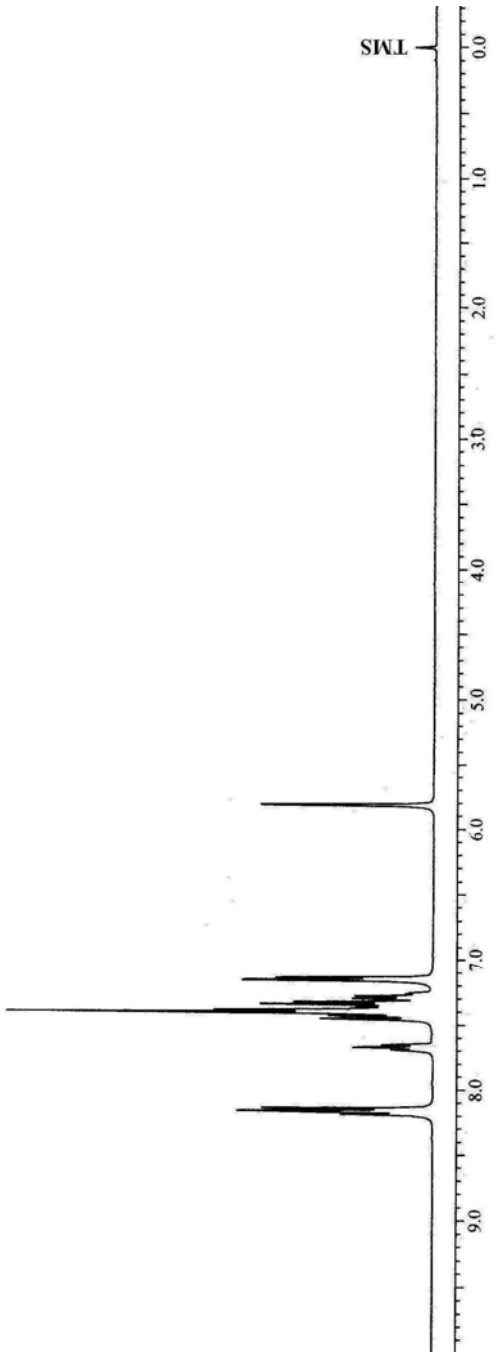


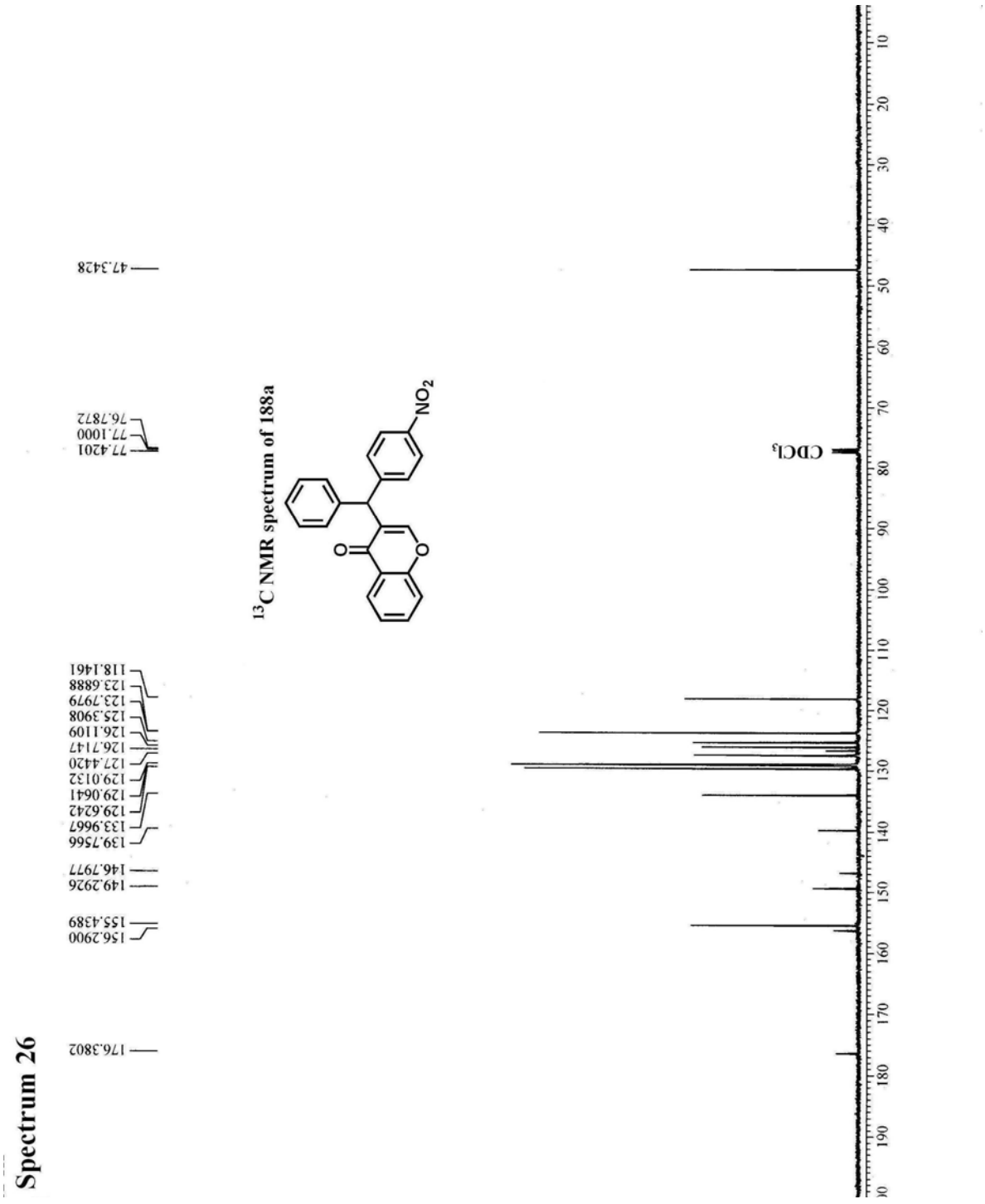

Spectrum 24
^{13}C NMR spectrum of 181j
CDCl$_3$
176.2392
175.6813
139.3925
139.1742
128.7921
128.4525
126.3179
77.7307
77.1000
76.4693
47.8701
46.9483
40.2533
39.2345
36.2751
35.9355
35.7172
34.2618
33.8251
31.7390
18.5188
17.0877

Spectrum 25

^{1}H NMR spectrum of 188a

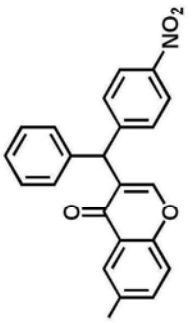


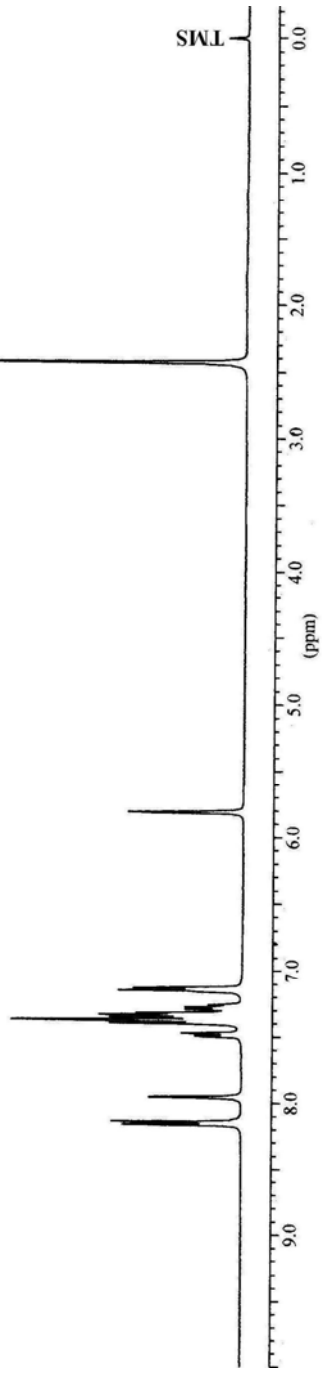


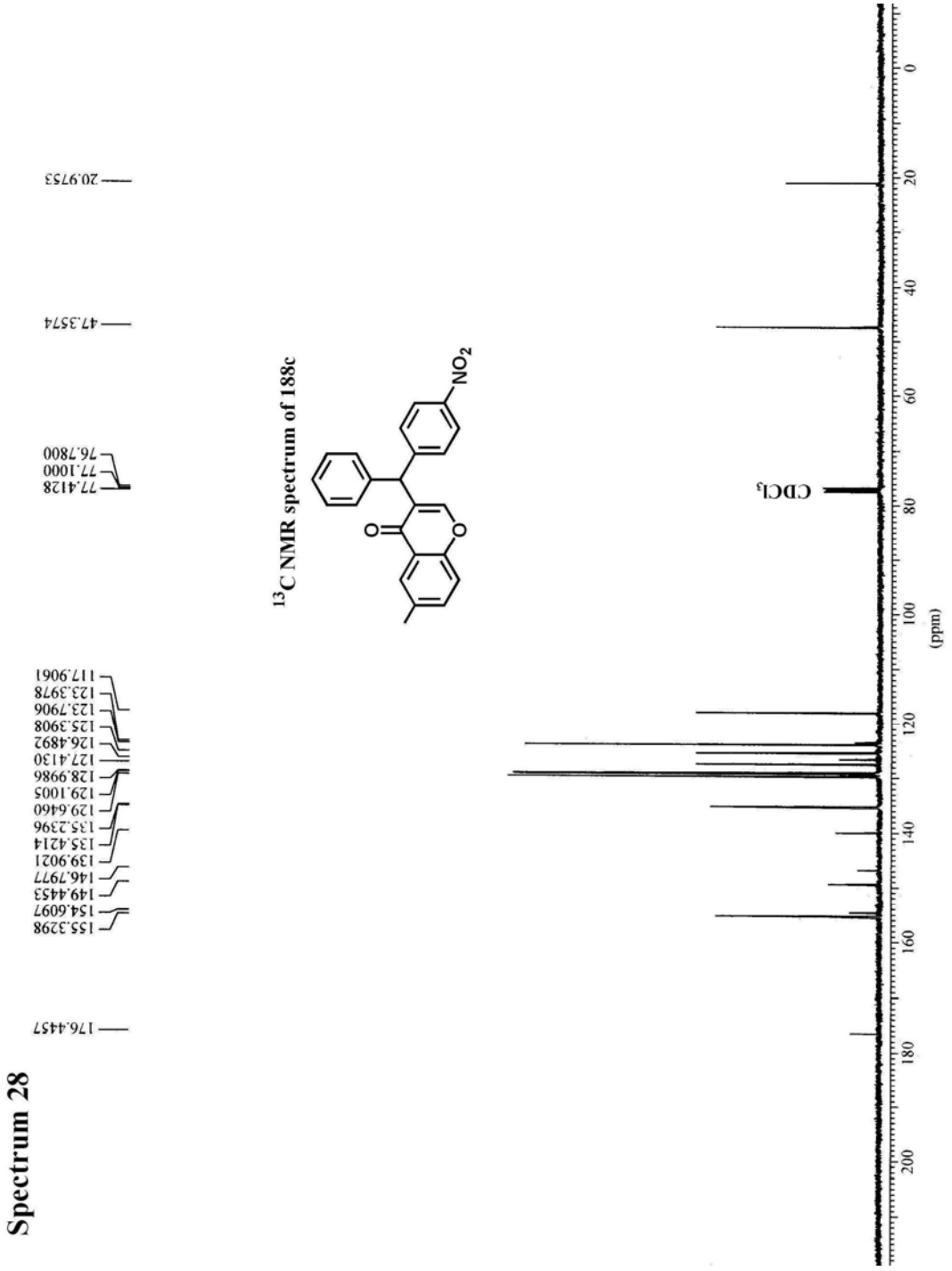

Spectrum 26
176.3802
156.2900
155.4389
149.2926
146.7977
139.7566
133.9667
129.6242
129.0641
129.0132
127.4420
126.7147
126.1109
125.3908
123.7979
123.6888
118.1461
77.4201
77.1000
76.7872
47.3428
^{13}C NMR spectrum of 188a
NO_2
O
O
$CDCl_3$
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

Spectrum 27

^{1}H NMR spectrum of 188c

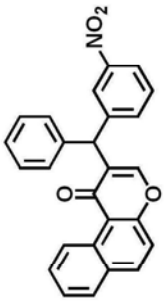


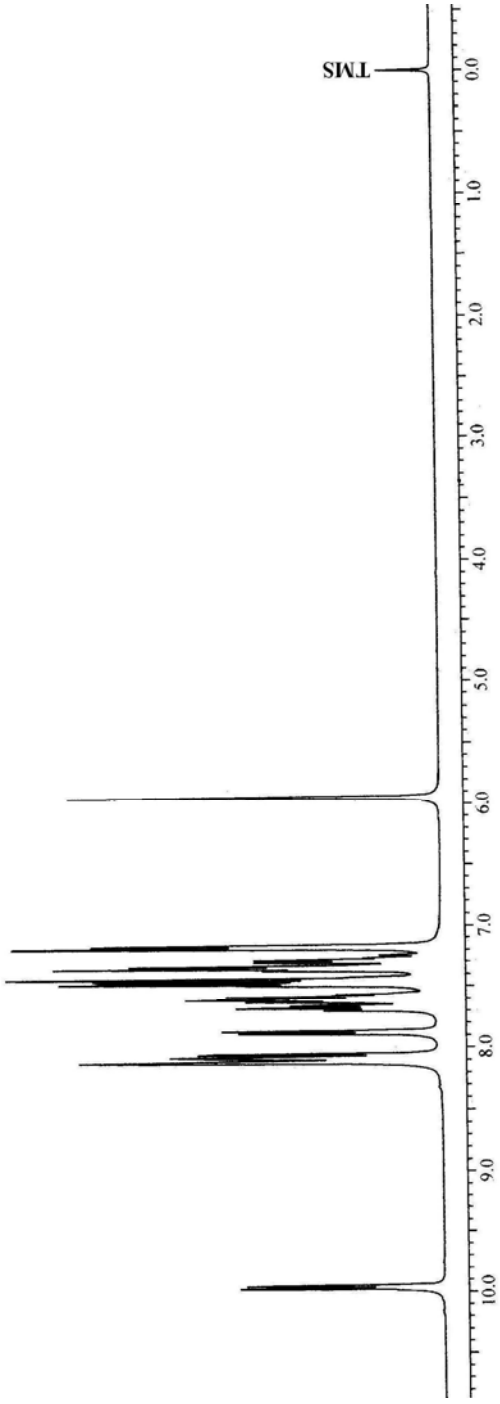


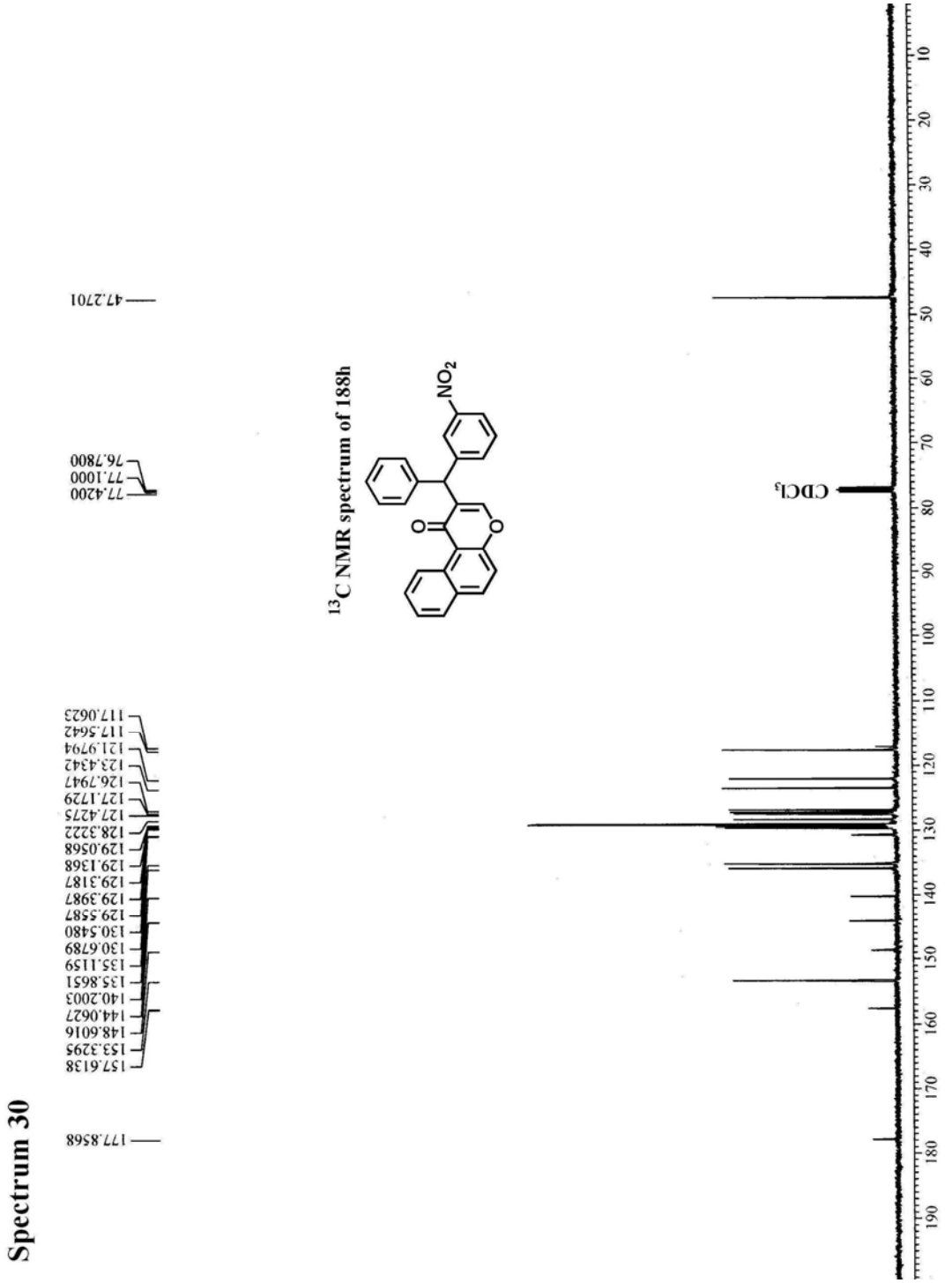

Spectrum 28
176.4457
155.3298
154.6097
149.4453
146.7977
139.9021
135.4214
135.2396
129.6460
129.1005
128.9986
127.4130
126.4892
125.3908
123.7906
123.3978
117.9061
77.4128
77.1000
76.7800
47.3574
20.9753
^{13}C NMR spectrum of 188c
NO_2
O
O
CDCl$_3$
0
20
40
60
80
100
120
140
160
180
200
(ppm)

Spectrum 29

^{1}H NMR spectrum of 188h

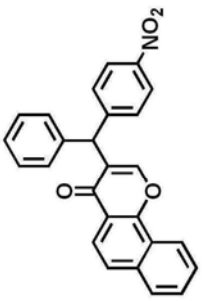


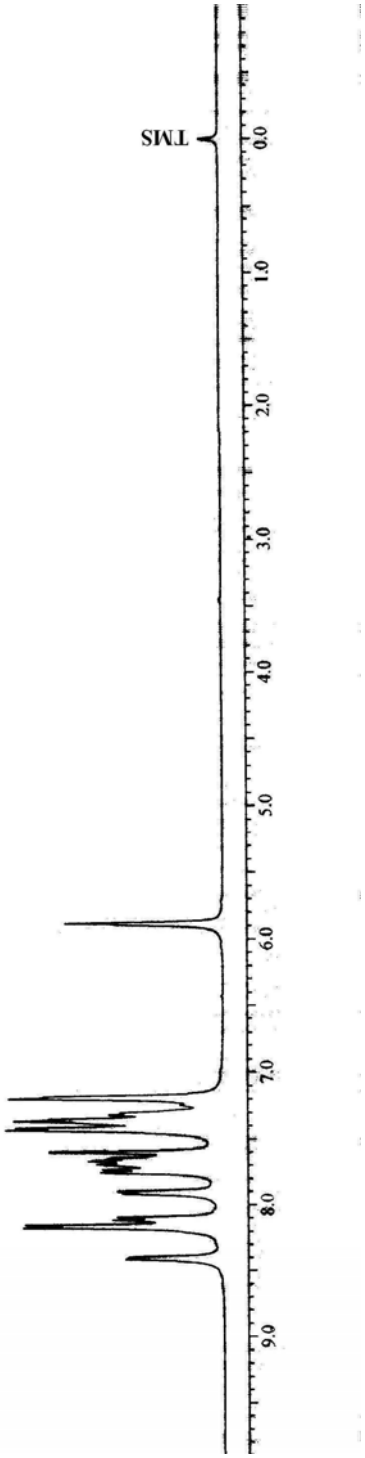


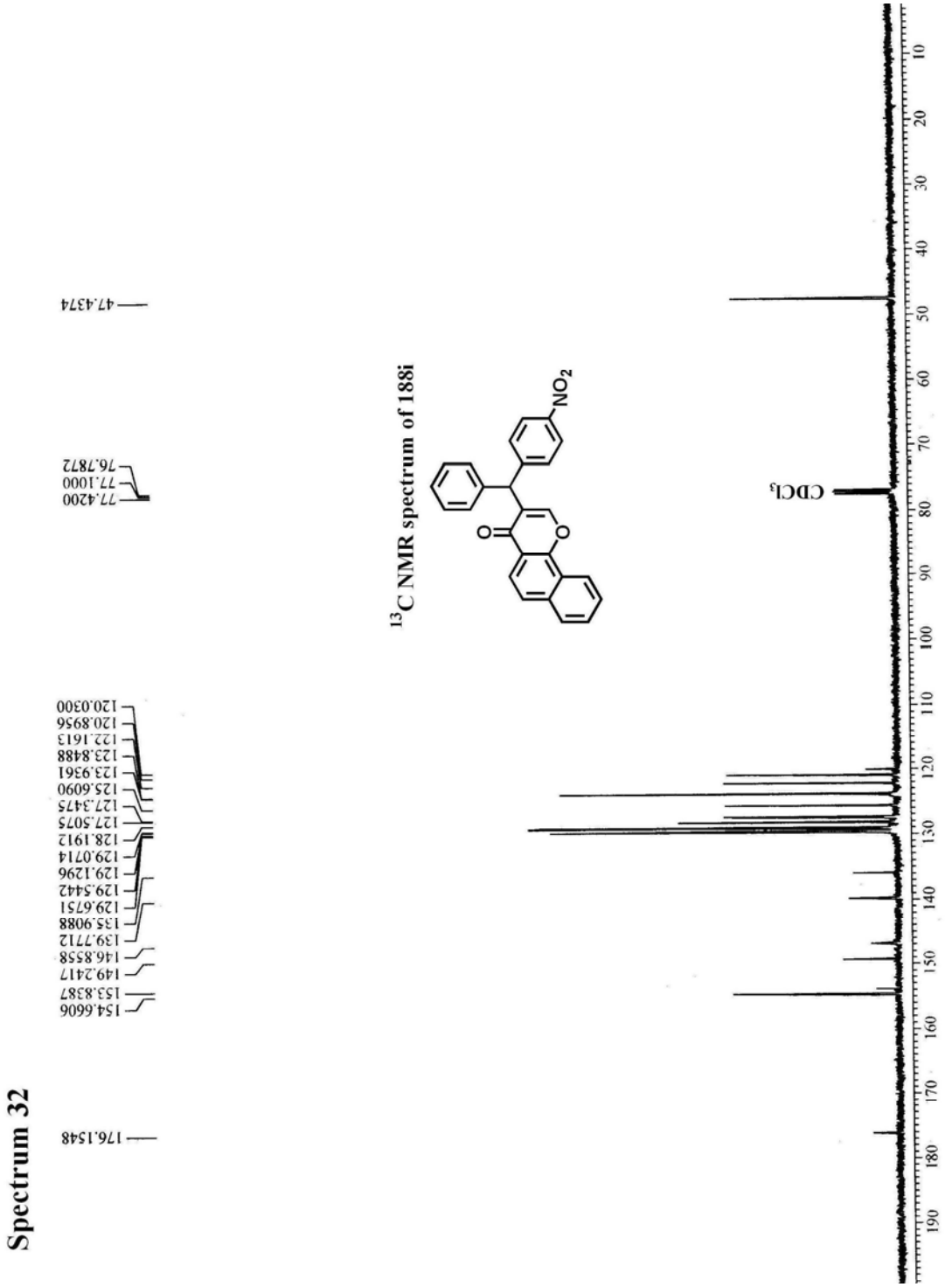

Spectrum 30
177.8568
157.6138
153.3295
148.6016
144.0627
140.2003
135.8651
135.1159
130.6789
130.5480
129.5587
129.3987
129.3187
129.1368
129.0568
128.3222
127.4275
127.1729
126.7947
123.4342
121.9794
117.5642
117.0623
77.4200
77.1000
76.7800
47.2701
^{13}C NMR spectrum of 188h
NO_2
O
O
$CDCl_3$
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

Spectrum 31

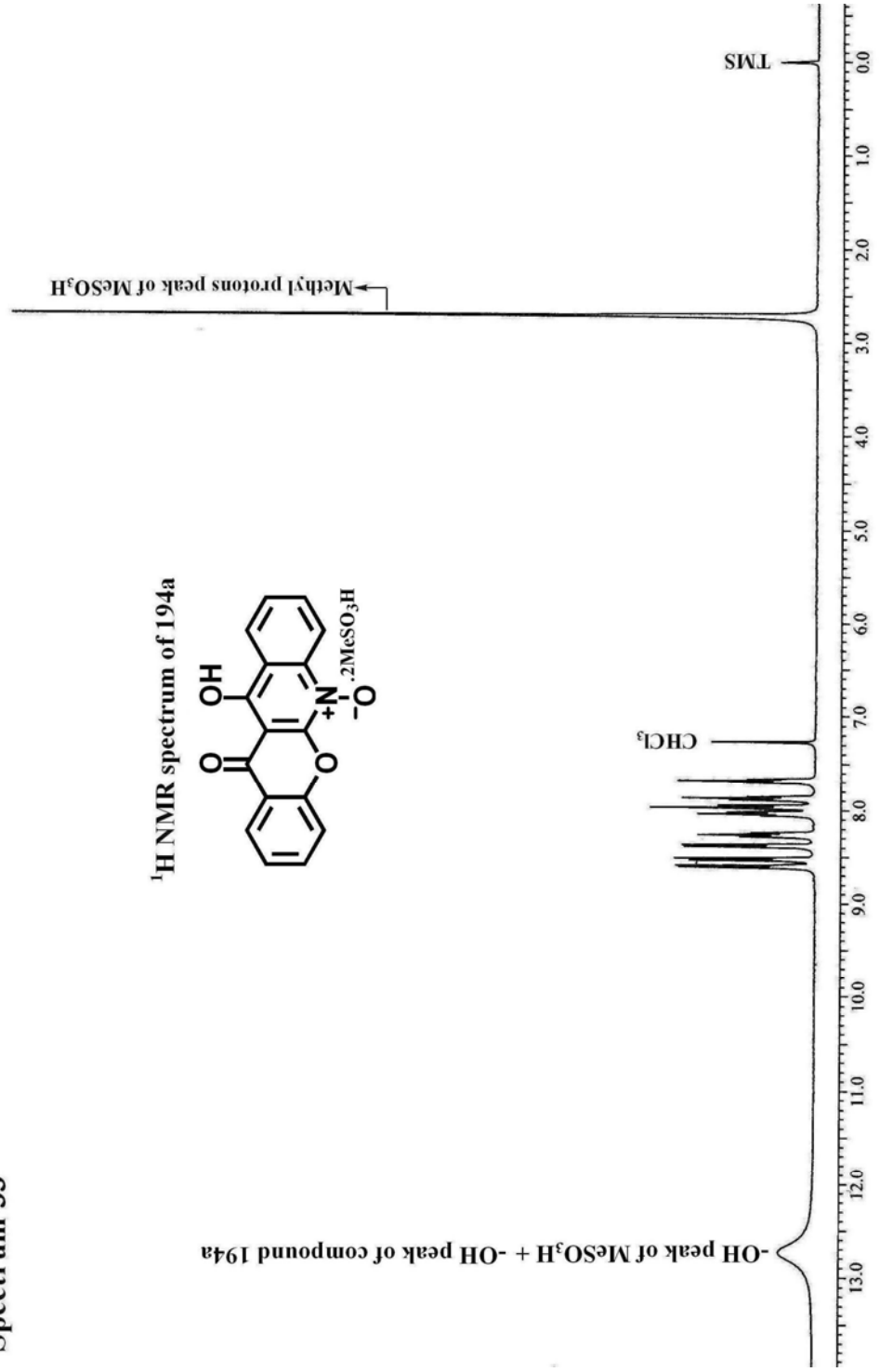
^{1}H NMR spectrum of 188i






Spectrum 32
176.1548
154.6606
153.8387
149.2417
146.8558
139.7712
135.9088
129.6751
129.5442
129.1296
129.0714
128.1912
127.5075
127.3475
125.6090
123.9361
123.8488
122.1613
120.8956
120.0300
77.4200
77.1000
76.7872
47.4374
^{13}C NMR spectrum of 188i
NO_2
O
O
CDCl$_3$
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

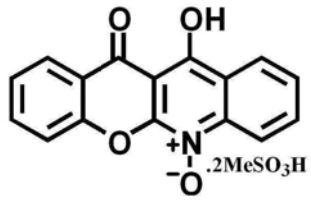
Spectrum 33

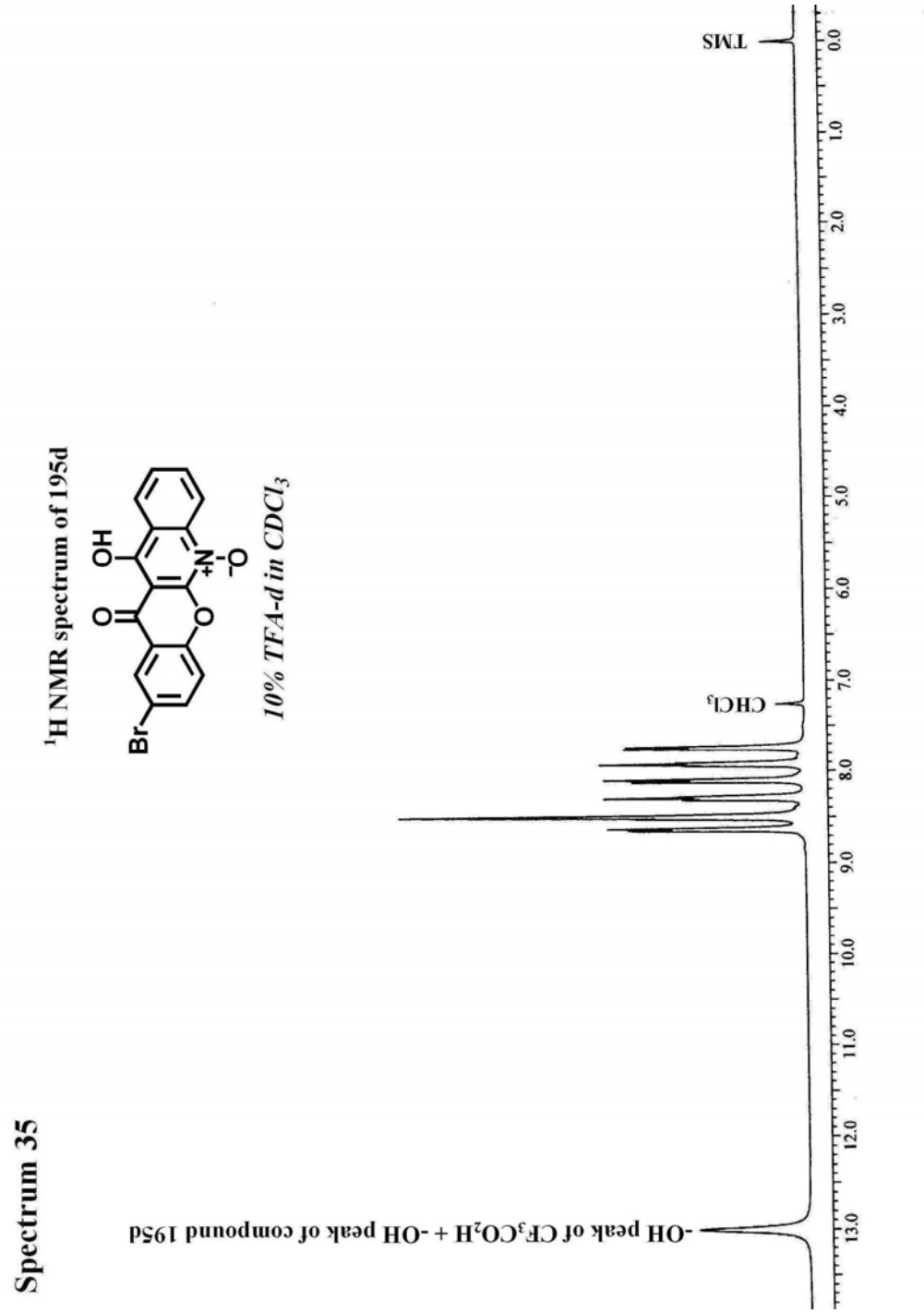

^{1}H NMR spectrum of 194a
OH
O
O
+N
O
.2MeSO$_3$H
-OH peak of MeSO$_3$H + -OH peak of compound 194a
CHCl$_3$
Methyl protons peak of MeSO$_3$H
TMS
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

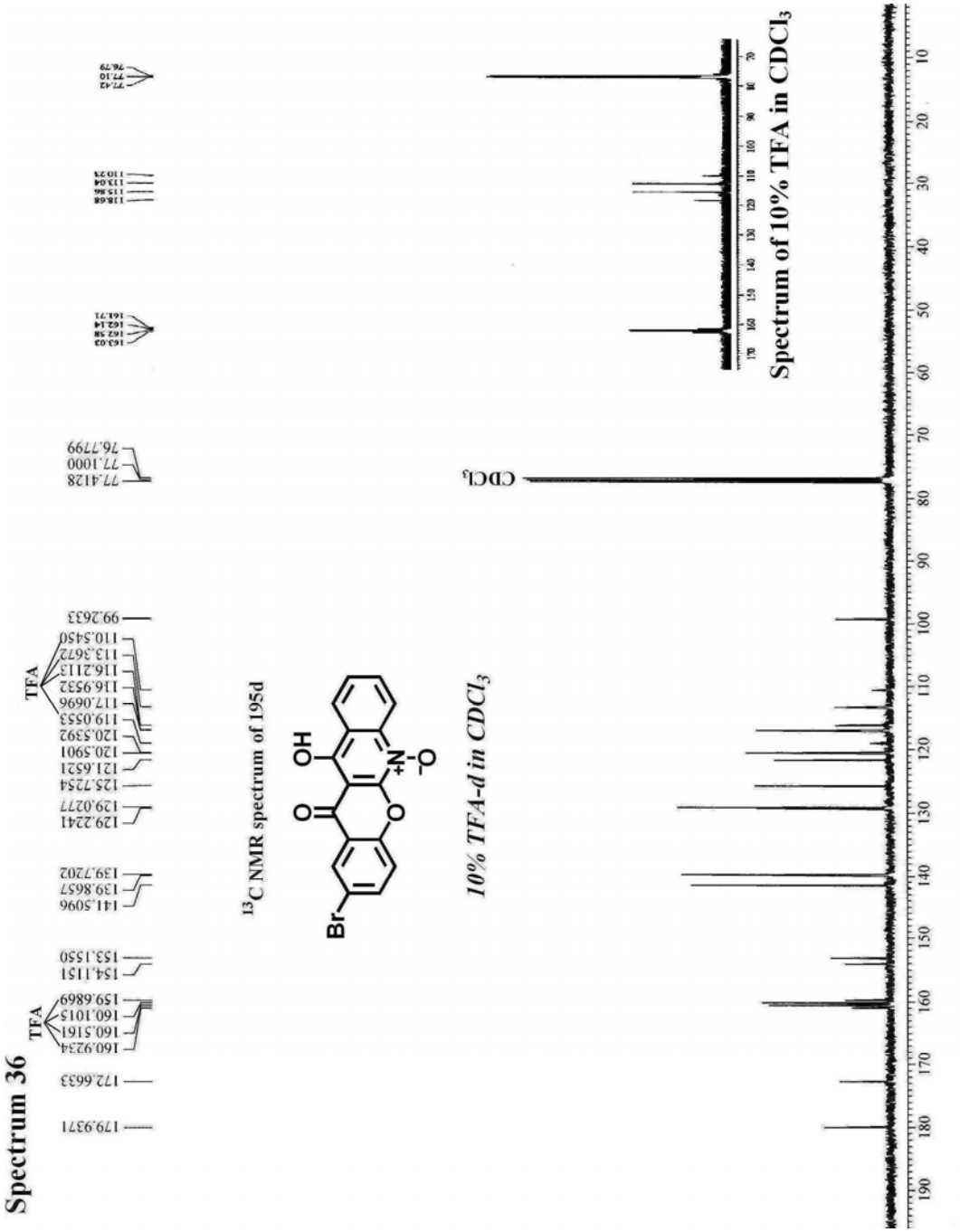
Spectrum 34

181.4303
173.0858
154.6261
154.5533
140.0960
138.9559
138.5678
128.3798
127.7006
126.6332
125.5417
119.3803
117.4640
117.2214
99.6835
77.7307
77.1000
76.4693
39.0162

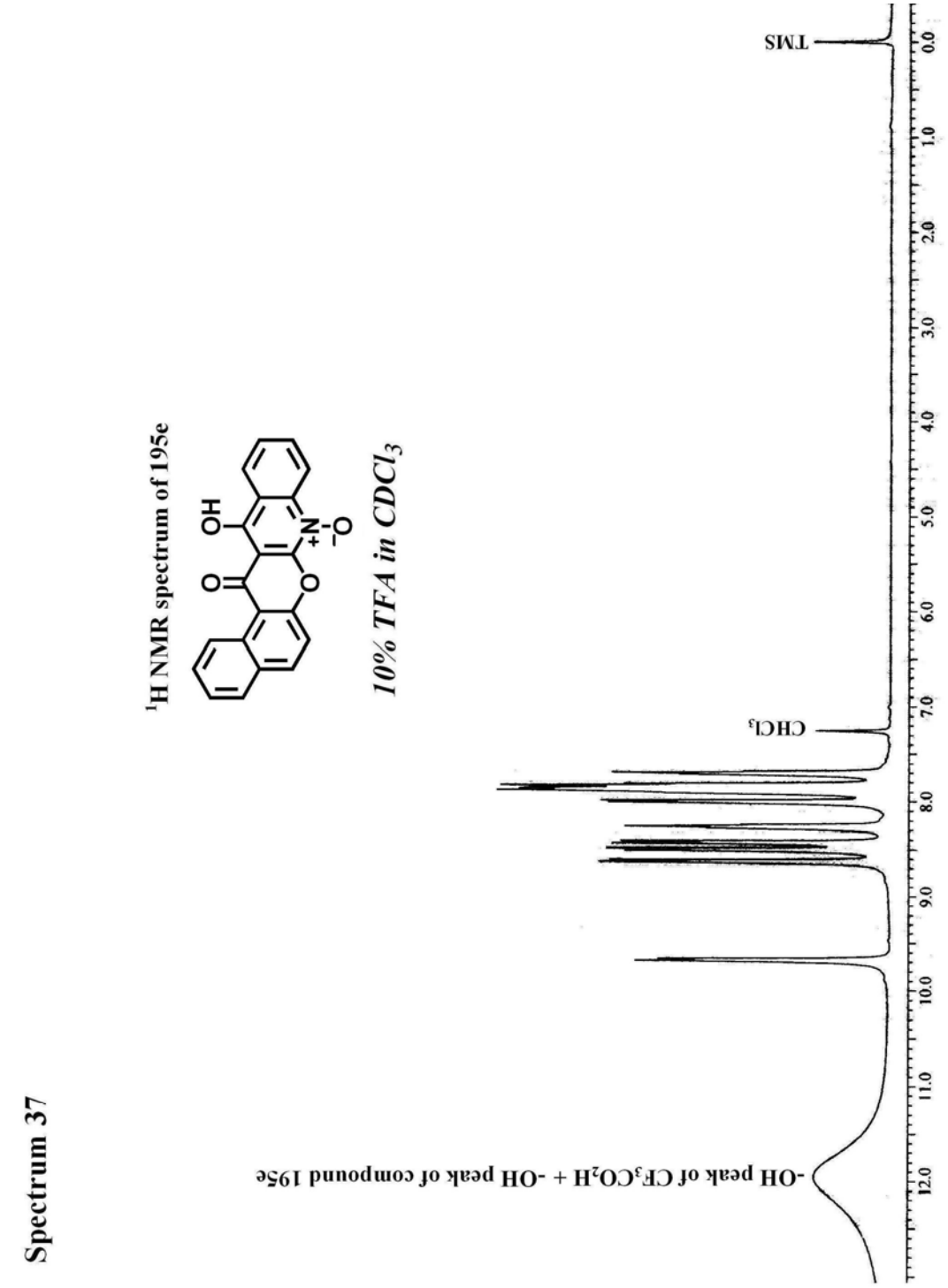
^{13}C NMR spectrum of 194a




Spectrum 35
^{1}H NMR spectrum of 195d
10% TFA-d in $CDCl_3$
-OH peak of CF_3CO_2H + -OH peak of compound 195d
$CHCl_3$
TMS
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

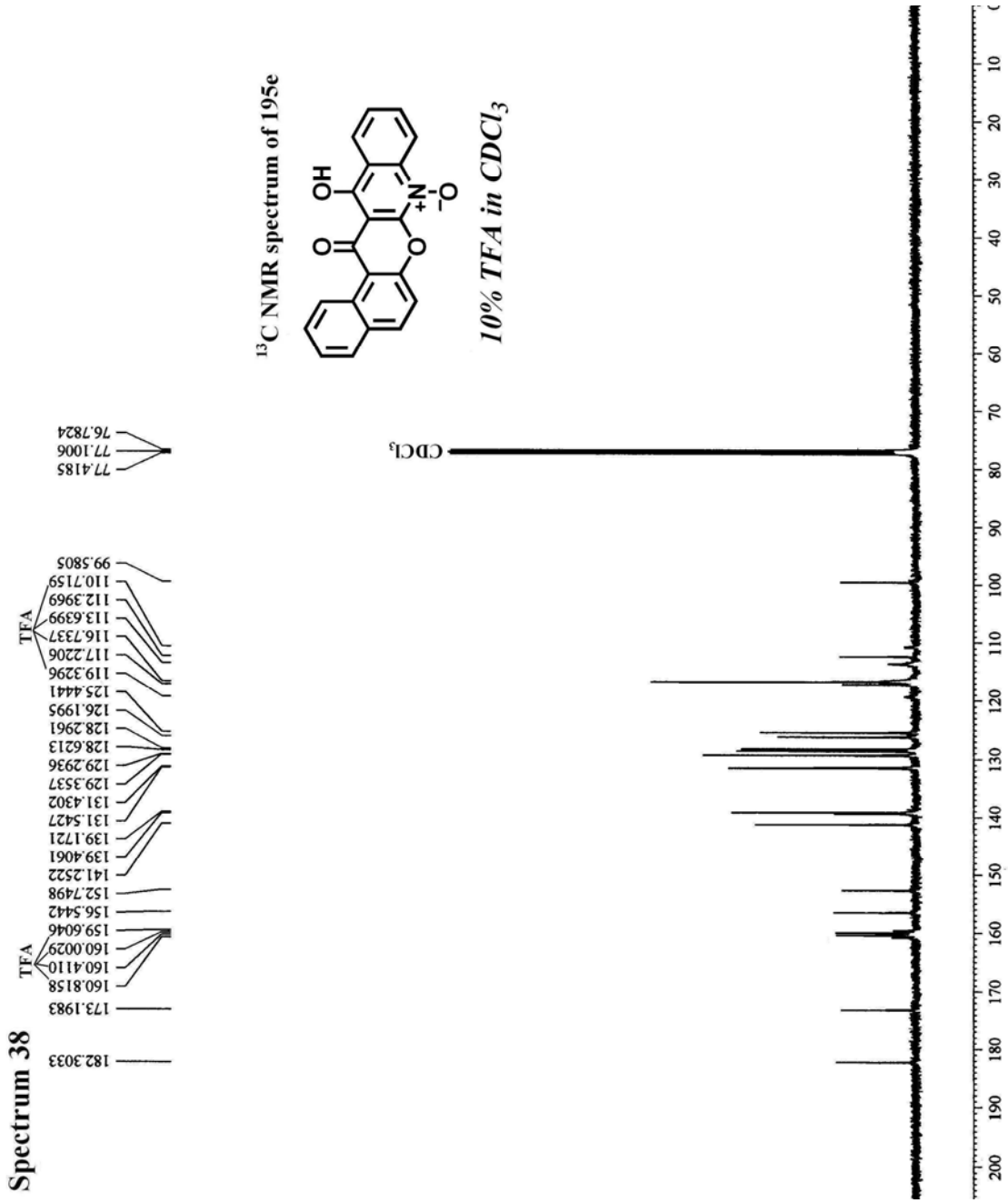

Spectrum 36
TFA
TFA
179.9371
172.6633
160.9234
160.5161
160.1015
159.6869
154.1151
153.1550
141.5096
139.8657
139.7202
129.2241
129.0277
125.7254
121.6521
120.5901
120.5392
119.0553
117.0696
116.9532
116.2113
113.3672
110.5450
99.2633
77.4128
77.1000
76.7799
163.03
162.58
162.14
161.71
118.68
117.86
117.64
110.23
^{13}C NMR spectrum of 195d
10% TFA-d in CDCl$_3$
CDCl$_3$
Spectrum of 10% TFA in CDCl$_3$

Spectrum 37



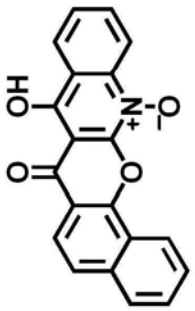
^{1}H NMR spectrum of 195e

10% TFA in $CDCl_3$

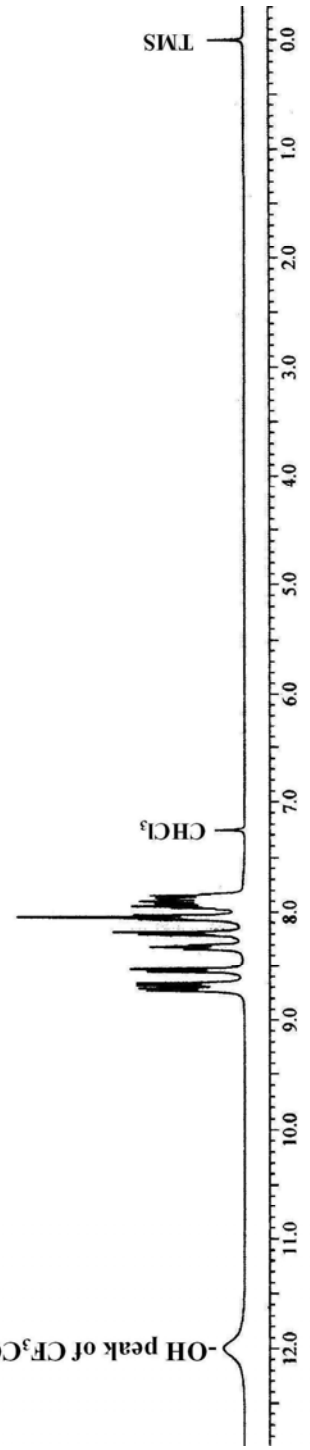

Spectrum 38
182.3033
173.1983
TFA
160.8158
160.4110
160.0029
159.6046
156.5442
152.7498
141.2522
139.4061
139.1721
131.5427
131.4302
129.3537
129.2936
128.6213
128.2961
126.1995
125.4441
119.3296
117.2206
116.7337
113.6399
112.3969
110.7159
TFA
99.5805
77.4185
77.1006
76.7824
CDCl3
13C NMR spectrum of 195e
10% TFA in CDCl3

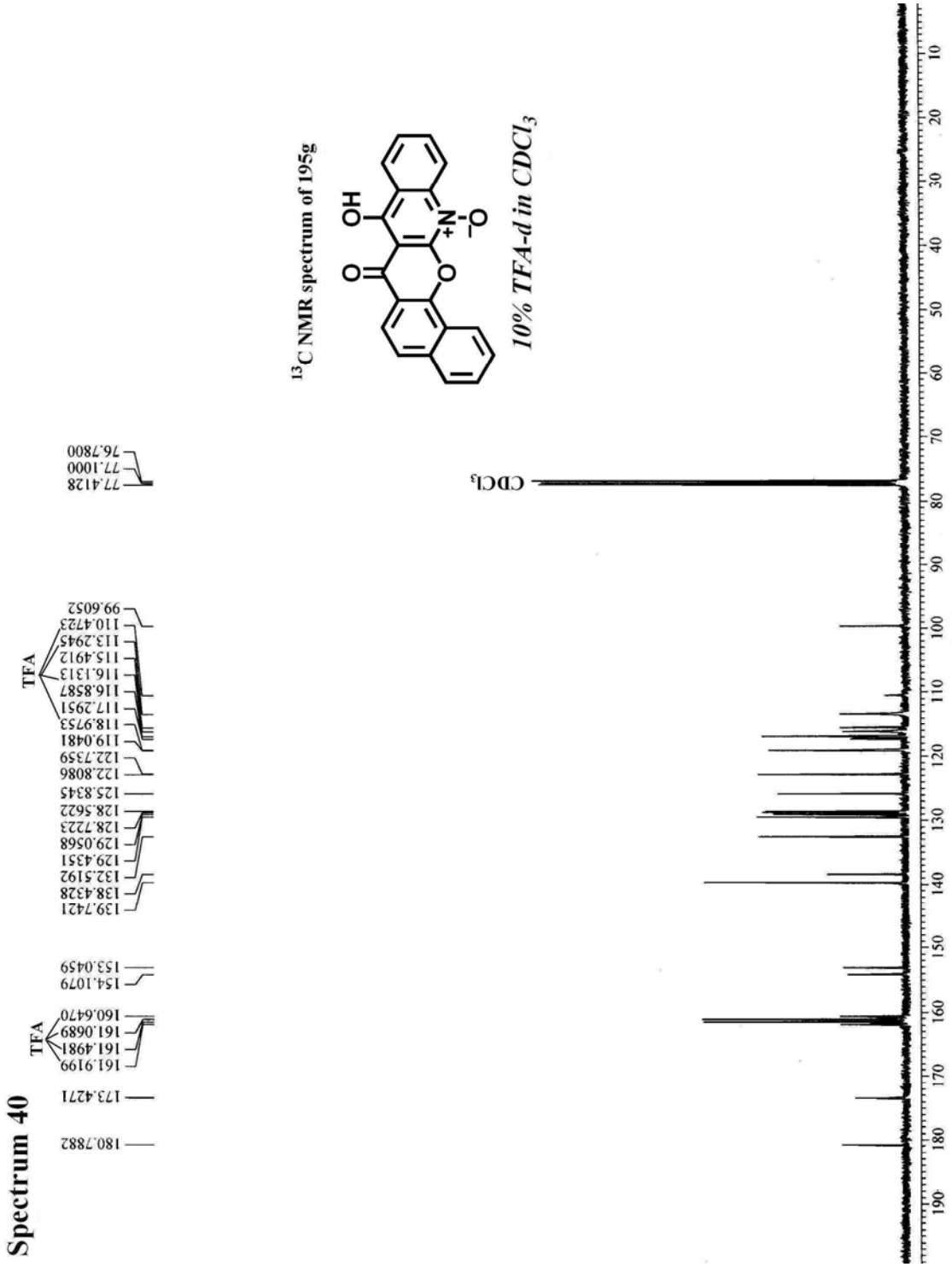
Spectrum 39

^{1}H NMR spectrum of 195g



10% TFA-d in $CDCl_3$




Spectrum 40
TFA
TFA
TFA
CDCl3
^{13}C NMR spectrum of 195g
10% TFA-d in CDCl3
OH
O
O
N+
O-

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **161h**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
O(1)	1482(2)	7879(1)	905(1)	88(1)
O(2)	2580(1)	6698(1)	759(1)	57(1)
O(3)	4882(2)	4244(1)	1373(1)	90(1)
O(4)	5157(1)	4863(1)	2318(1)	58(1)
N	3153(2)	6424(2)	2255(1)	72(1)
C(1)	6527(3)	12466(2)	907(2)	122(1)
C(2)	8113(3)	11414(2)	1217(2)	128(1)
C(3)	6960(3)	11703(2)	1332(2)	89(1)
C(4)	6066(2)	10946(2)	1274(1)	72(1)
C(5)	5204(3)	10942(2)	1639(2)	81(1)
C(6)	4370(2)	10293(2)	1584(1)	76(1)
C(7)	4376(2)	9599(2)	1165(1)	60(1)
C(8)	5232(2)	9595(2)	794(1)	73(1)
C(9)	6053(3)	10265(2)	849(1)	80(1)
C(10)	3450(2)	8925(2)	1090(1)	60(1)
C(11)	3518(2)	8034(1)	1074(1)	48(1)
C(12)	2411(2)	7545(2)	913(1)	54(1)
C(13)	1620(2)	6073(2)	567(1)	67(1)
C(14)	2251(3)	5215(2)	477(3)	146(2)
C(15)	890(3)	5968(2)	1071(2)	96(1)
C(16)	923(3)	6409(2)	-26(2)	102(1)
C(17)	4609(2)	7496(1)	1196(1)	46(1)
C(18)	4935(2)	7171(1)	1878(1)	45(1)
C(19)	5943(2)	6487(1)	1932(1)	47(1)
C(20)	8675(6)	9160(3)	-64(2)	184(3)
C(21)	8487(4)	8126(3)	-966(2)	134(2)
C(22)	8144(4)	8461(3)	-383(2)	132(2)
C(23)	7657(3)	7717(2)	-19(1)	79(1)
C(24)	8148(2)	7456(2)	567(1)	75(1)
C(25)	7677(2)	6784(2)	891(1)	64(1)

C(26)	6690(2)	6347(1)	630(1)	52(1)
C(27)	6223(2)	6586(2)	34(1)	69(1)
C(28)	6695(3)	7257(2)	-277(1)	83(1)
C(29)	6123(2)	5646(2)	952(1)	54(1)
C(30)	5782(2)	5680(1)	1509(1)	46(1)
C(31)	5216(2)	4851(2)	1715(1)	54(1)
C(32)	4614(2)	4131(2)	2636(1)	66(1)
C(33)	5284(3)	3282(2)	2610(2)	106(1)
C(34)	4705(4)	4484(2)	3286(2)	125(2)
C(35)	3387(3)	4020(2)	2356(2)	110(1)
C(36)	5305(2)	7962(1)	2315(1)	50(1)
C(37)	6263(2)	8461(2)	2227(1)	66(1)
C(38)	6640(2)	9157(2)	2625(2)	81(1)
C(39)	6065(3)	9370(2)	3106(2)	91(1)
C(40)	5115(3)	8890(2)	3188(1)	90(1)
C(41)	4735(2)	8195(2)	2799(1)	64(1)
C(42)	3926(2)	6737(2)	2082(1)	50(1)

Table II: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **162a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	**x**	**y**	**z**	**U(eq)**
O(1)	3966(1)	2429(1)	5002(1)	60(1)
O(2)	4907(2)	1269(1)	-2776(1)	78(1)
O(3)	3043(1)	2762(1)	-1350(1)	59(1)
N(1)	4235(2)	2049(1)	-1998(1)	51(1)
C(1)	4768(2)	2785(1)	1410(2)	37(1)
C(2)	5471(2)	3188(1)	755(2)	48(1)
C(3)	5863(2)	3639(1)	1499(2)	55(1)
C(4)	5558(2)	3701(1)	2920(2)	55(1)
C(5)	4898(2)	3304(1)	3595(2)	49(1)
C(6)	4517(2)	2841(1)	2860(2)	39(1)
C(7)	3963(2)	2401(1)	3684(2)	41(1)
C(8)	3436(2)	1931(1)	2857(2)	39(1)
C(9)	3071(2)	2008(1)	1248(2)	40(1)
C(10)	4380(2)	2281(1)	602(1)	36(1)

C(11)	5763(2)	1931(1)	721(2)	38(1)
C(12)	5616(2)	1470(1)	-276(2)	40(1)
C(13)	4915(2)	1571(1)	-1770(2)	51(1)
C(14)	3829(2)	2397(1)	-985(2)	41(1)
C(15)	6071(2)	984(1)	9(2)	46(1)
C(16)	6795(2)	737(1)	1320(2)	44(1)
C(17)	6722(2)	197(1)	1390(2)	52(1)
C(18)	7300(2)	-72(1)	2599(2)	61(1)
C(19)	8002(2)	189(1)	3763(2)	65(1)
C(20)	8120(2)	717(1)	3712(2)	66(1)
C(21)	7539(2)	995(1)	2504(2)	55(1)
C(22)	3433(2)	1480(1)	3572(2)	44(1)
C(23)	2929(2)	971(1)	3015(2)	45(1)
C(24)	1597(2)	906(1)	2125(2)	56(1)
C(25)	1125(2)	420(1)	1667(2)	67(1)
C(26)	1968(2)	-11(1)	2073(2)	70(1)
C(27)	3281(2)	44(1)	2947(2)	67(1)
C(28)	3751(2)	530(1)	3432(2)	56(1)

Table III: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **162b**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	**x**	**y**	**z**	**U(eq)**
Cl(1)	2680(1)	4847(1)	4191(1)	69(1)
Cl(2)	5955(1)	1421(1)	4677(1)	83(1)
O(1)	5718(2)	-2081(1)	2779(1)	67(1)
O(2)	277(2)	5107(1)	1206(1)	47(1)
O(3)	2296(2)	1403(1)	-421(1)	55(1)
N(1)	1186(2)	3178(2)	474(1)	40(1)
C(1)	2560(2)	-451(2)	1402(1)	36(1)
C(2)	1390(2)	-795(2)	1089(2)	46(1)
C(3)	1427(3)	-2125(2)	1137(2)	57(1)
C(4)	2614(3)	-3131(2)	1502(2)	59(1)
C(5)	3734(3)	-2813(2)	1850(2)	53(1)
C(6)	3720(2)	-1474(2)	1812(1)	39(1)
C(7)	4897(2)	-1184(2)	2275(1)	43(1)

C(8)	5010(2)	224(2)	2109(1)	39(1)
C(9)	4187(2)	1160(2)	1300(1)	38(1)
C(10)	2504(2)	1017(2)	1374(1)	34(1)
C(11)	1338(2)	1573(2)	2351(1)	35(1)
C(12)	1026(2)	3065(2)	2319(1)	33(1)
C(13)	802(2)	3881(2)	1319(1)	36(1)
C(14)	1986(2)	1840(2)	399(1)	37(1)
C(15)	904(2)	3719(2)	3113(1)	38(1)
C(16)	955(2)	3148(2)	4189(1)	41(1)
C(17)	1713(2)	3616(2)	4770(2)	50(1)
C(18)	1737(3)	3121(3)	5789(2)	72(1)
C(19)	969(4)	2165(3)	6269(2)	85(1)
C(20)	169(3)	1697(2)	5731(2)	77(1)
C(21)	171(3)	2174(2)	4700(2)	55(1)
C(22)	5850(2)	535(2)	2672(2)	45(1)
C(23)	6257(2)	1802(2)	2589(2)	47(1)
C(24)	6357(2)	2296(2)	3457(2)	54(1)
C(25)	6726(2)	3496(2)	3383(2)	67(1)
C(26)	7050(3)	4211(2)	2432(2)	72(1)
C(27)	7024(3)	3739(2)	1559(2)	72(1)
C(28)	6641(2)	2548(2)	1626(2)	60(1)

Table IV: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **165g**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	**x**	**y**	**z**	**U(eq)**
O(3)	4056(2)	1499(2)	8259(2)	60(1)
O(2)	6133(2)	1519(2)	11035(2)	64(1)
N(1)	7251(2)	159(2)	10394(2)	56(1)
N(2)	5587(2)	3534(2)	9559(2)	58(1)
O(4)	6906(2)	5533(2)	10990(2)	84(1)
C(18)	5307(3)	2224(2)	8984(2)	49(1)
C(12)	6406(3)	632(2)	8200(2)	50(1)
O(1)	8314(2)	-1289(2)	9827(2)	81(1)

C(11)	7742(3)	-462(2)	9598(2)	57(1)
C(14)	6615(2)	1135(2)	10316(2)	50(1)
C(13)	6615(2)	1726(2)	9299(2)	45(1)
C(16)	8278(3)	4108(2)	10662(2)	49(1)
C(19)	9507(3)	4957(2)	11612(2)	54(1)
C(10)	7559(3)	-17(2)	8520(2)	53(1)
C(15)	8132(3)	2901(2)	9745(2)	51(1)
C(17)	6919(3)	4469(2)	10453(2)	59(1)
C(9)	8488(3)	-136(3)	7982(2)	63(1)
C(20)	11067(3)	5040(2)	12082(2)	54(1)
C(6)	8551(3)	299(3)	6946(2)	60(1)
C(5)	9906(3)	1108(3)	6999(3)	70(1)
C(25)	12071(3)	6151(3)	13055(2)	70(1)
C(7)	7298(3)	-72(3)	5897(2)	72(1)
C(8)	7396(4)	345(3)	4940(3)	82(1)
C(21)	11683(3)	4189(3)	11591(3)	85(1)
C(3)	8739(4)	1159(3)	4989(3)	78(1)
C(4)	9987(4)	1530(3)	6034(3)	81(1)
C(22)	13192(3)	4413(3)	12091(3)	97(1)
C(24)	13583(3)	6371(4)	13520(3)	90(1)
C(23)	14175(3)	5498(4)	13055(3)	89(1)
C(26)	15830(4)	5779(6)	13544(5)	151(2)
C(2)	8827(6)	1617(4)	3942(3)	114(1)
C(1)	9149(12)	2942(6)	4077(5)	281(5)
C(27)	16308(7)	4726(9)	13595(9)	278(5)

Table V: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **181c**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	**x**	**y**	**z**	**U(eq)**
O(1)	4218(1)	8614(2)	10708(1)	72(1)
N(1)	4437(1)	7574(2)	9212(1)	56(1)
C(1)	4012(1)	7352(3)	10003(1)	54(1)
C(2)	3257(1)	5578(3)	10018(1)	65(1)
C(3)	3208(1)	3818(3)	9220(1)	59(1)
C(4)	3347(1)	4936(3)	8273(1)	51(1)

C(5)	4283(1)	6143(3)	8357(1)	57(1)
C(6)	3266(1)	3238(3)	7429(1)	62(1)
C(7)	2269(1)	2660(3)	7061(1)	52(1)
C(8)	1830(1)	700(3)	7299(2)	78(1)
C(9)	903(2)	244(4)	6961(2)	87(1)
C(10)	381(1)	1709(4)	6381(1)	76(1)
C(11)	817(2)	3686(4)	6143(2)	100(1)
C(12)	1740(2)	4140(4)	6467(1)	83(1)
C(13)	-632(2)	1206(6)	6014(2)	120(1)

Table VI: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **181g**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	**x**	**y**	**z**	**U(eq)**
O(1)	357(2)	7226(2)	-480(1)	74(1)
N(1)	2242(3)	5181(2)	884(1)	59(1)
C(1)	1819(3)	6777(2)	227(1)	56(1)
C(2)	3130(4)	8053(2)	377(1)	67(1)
C(3)	5288(3)	7184(2)	1095(1)	62(1)
C(4)	4771(3)	5899(2)	2006(1)	52(1)
C(5)	3983(3)	4456(2)	1720(1)	58(1)
C(6)	6900(3)	5079(2)	2754(1)	60(1)
C(7)	6475(3)	3906(2)	3724(1)	60(1)
C(8)	8578(3)	3230(3)	4449(1)	74(1)
C(9)	8376(3)	2054(2)	5446(1)	57(1)
C(10)	6570(4)	1261(3)	5670(1)	73(1)
C(11)	6494(4)	154(3)	6595(2)	79(1)
C(12)	8223(4)	-198(2)	7309(1)	73(1)
C(13)	10000(4)	596(3)	7106(1)	75(1)
C(14)	10079(4)	1707(3)	6189(1)	71(1)

Table VII: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **188a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
N(1)	1624(1)	6403(3)	12335(1)	62(1)
O(1)	1984(1)	7982(3)	12631(1)	95(1)
O(2)	1232(1)	4951(3)	12640(1)	84(1)
O(3)	3790(1)	7858(2)	8665(1)	58(1)
O(4)	3033(1)	2082(2)	9683(1)	60(1)
C(1)	4359(1)	6177(3)	8861(1)	47(1)
C(2)	5173(1)	6609(3)	8705(1)	57(1)
C(3)	5759(1)	4968(4)	8881(1)	64(1)
C(4)	5547(1)	2929(3)	9213(1)	63(1)
C(5)	4741(1)	2537(3)	9372(1)	54(1)
C(6)	4128(1)	4175(3)	9200(1)	44(1)
C(7)	3266(1)	3829(2)	9380(1)	43(1)
C(8)	2707(1)	5704(2)	9170(1)	42(1)
C(9)	2994(1)	7534(3)	8833(1)	51(1)
C(10)	1810(1)	5497(2)	9369(1)	43(1)
C(11)	1751(1)	5803(2)	10152(1)	41(1)
C(12)	2139(1)	7628(3)	10506(1)	47(1)
C(13)	2097(1)	7852(3)	11219(1)	50(1)
C(14)	1661(1)	6225(3)	11573(1)	47(1)
C(15)	1256(1)	4425(3)	11242(1)	59(1)
C(16)	1300(1)	4234(3)	10529(1)	55(1)
C(17)	1229(1)	7050(3)	8930(1)	47(1)
C(18)	1092(1)	6554(3)	8227(1)	63(1)
C(19)	598(1)	7977(4)	7804(1)	76(1)
C(20)	229(1)	9894(4)	8076(1)	77(1)
C(21)	339(1)	10379(3)	8769(1)	71(1)
C(22)	834(1)	8963(3)	9196(1)	57(1)

Table VIII: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **188g**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
N(1)	920(2)	9522(2)	1208(3)	67(1)
O(1)	4421(2)	4419(2)	1282(2)	70(1)
O(2)	3381(1)	6416(2)	3903(2)	71(1)
O(3)	1298(2)	10118(2)	476(3)	102(1)
O(4)	250(2)	9768(2)	1684(3)	106(1)
C(1)	4930(2)	4938(3)	2170(3)	56(1)
C(2)	5797(3)	4703(3)	2028(4)	74(1)
C(3)	6366(2)	5181(3)	2837(4)	76(1)
C(4)	6114(2)	5905(3)	3825(4)	59(1)
C(5)	6715(2)	6389(3)	4656(4)	76(1)
C(6)	6470(3)	7069(3)	5614(4)	82(1)
C(7)	5623(2)	7275(3)	5792(3)	69(1)
C(8)	5022(2)	6821(2)	5005(3)	58(1)
C(9)	5244(2)	6124(2)	3987(3)	49(1)
C(10)	4633(2)	5628(2)	3094(3)	45(1)
C(11)	3724(2)	5810(2)	3132(3)	49(1)
C(12)	3200(2)	5222(2)	2183(3)	49(1)
C(13)	3577(2)	4571(3)	1343(3)	62(1)
C(14)	2249(2)	5322(2)	2262(3)	51(1)
C(15)	1936(2)	6451(2)	2007(3)	46(1)
C(16)	2323(2)	7149(2)	1162(3)	55(1)
C(17)	1996(2)	8153(2)	902(3)	54(1)
C(18)	1272(2)	8454(2)	1502(3)	50(1)
C(19)	872(2)	7805(3)	2357(3)	61(1)
C(20)	1201(2)	6805(3)	2601(3)	56(1)
C(21)	1766(2)	4509(2)	1435(3)	52(1)
C(22)	1635(2)	3503(3)	1927(3)	58(1)
C(23)	1224(2)	2720(3)	1221(4)	70(1)
C(24)	924(2)	2934(4)	9(5)	88(1)
C(25)	1030(3)	3938(4)	-494(4)	130(2)
C(26)	1448(3)	4714(3)	223(4)	102(2)

Table IX: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **194a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
S(1)	2179(1)	2522(1)	1251(1)	47(1)
S(2)	3431(1)	10419(1)	8301(1)	47(1)
N(1)	6477(3)	2967(3)	7673(2)	38(1)
O(1)	4611(3)	3911(2)	8142(2)	43(1)
O(2)	2131(4)	3761(4)	4878(2)	79(1)
O(3)	4216(4)	2581(4)	4364(2)	71(1)
O(4)	7306(3)	3181(3)	8808(2)	50(1)
O(5)	2933(4)	3615(3)	2302(2)	65(1)
O(6)	3586(4)	2725(3)	730(2)	64(1)
O(7)	534(4)	2398(3)	455(2)	72(1)
O(8)	3092(4)	10553(3)	7197(2)	59(1)
O(9)	5302(3)	11021(3)	9034(2)	63(1)
O(10)	2337(3)	10960(3)	8809(2)	65(1)
C(1)	3155(4)	4354(4)	7852(3)	42(1)
C(2)	2640(5)	4790(4)	8719(3)	49(1)
C(3)	1209(5)	5229(4)	8478(3)	53(1)
C(4)	293(5)	5214(4)	7397(3)	55(1)
C(5)	818(5)	4765(4)	6548(3)	54(1)
C(6)	2266(5)	4320(4)	6761(3)	47(1)
C(7)	2842(5)	3801(4)	5876(3)	50(1)
C(8)	4291(5)	3286(4)	6207(3)	43(1)
C(9)	5124(4)	3394(3)	7340(3)	40(1)
C(10)	4906(5)	2679(4)	5434(3)	47(1)
C(11)	6300(4)	2144(4)	5784(3)	44(1)
C(12)	7097(4)	2308(3)	6940(3)	40(1)
C(13)	8495(4)	1828(4)	7327(3)	46(1)
C(14)	9054(5)	1187(4)	6575(3)	55(1)
C(15)	8270(5)	987(4)	5423(3)	64(1)
C(16)	6904(5)	1456(4)	5042(3)	58(1)
C(17)	2024(5)	941(4)	1513(3)	63(1)
C(18)	2767(6)	8637(4)	8166(4)	79(1)

Table X: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **195a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
O(1)	4795(8)	2983(3)	1612(2)	42(1)
O(2)	9175(9)	4263(3)	319(2)	46(1)
O(3)	6422(9)	5633(3)	564(2)	48(1)
O(4)	997(10)	3666(3)	2206(2)	59(1)
O(5)	3646(13)	3439(3)	3210(2)	76(2)
O(6)	5367(12)	4746(3)	3150(3)	72(2)
N(1)	2467(10)	4179(3)	1823(2)	38(1)
F(1)	5145(15)	3343(4)	4401(2)	125(2)
F(2)	8622(14)	3850(8)	4127(3)	194(5)
F(3)	5700(30)	4622(5)	4433(3)	196(5)
C(1)	6725(12)	2551(4)	1283(3)	40(2)
C(2)	7068(15)	1690(4)	1427(3)	51(2)
C(3)	8965(16)	1230(5)	1114(4)	60(2)
C(4)	10475(15)	1597(4)	657(4)	55(2)
C(5)	10102(13)	2454(4)	509(3)	47(2)
C(6)	8238(12)	2943(4)	820(3)	35(1)
C(7)	7839(12)	3859(4)	697(3)	35(1)
C(8)	5766(12)	4285(4)	1048(3)	36(1)
C(9)	5208(11)	5157(4)	970(3)	38(1)
C(10)	3224(13)	5545(4)	1341(3)	42(2)
C(11)	2585(15)	6430(5)	1300(4)	60(2)
C(12)	700(16)	6779(5)	1669(4)	68(2)
C(13)	-623(15)	6268(5)	2092(4)	63(2)
C(14)	-81(13)	5407(5)	2156(3)	51(2)
C(15)	1864(12)	5037(4)	1778(3)	38(1)
C(16)	4366(12)	3815(4)	1493(3)	35(1)
C(17)	4929(13)	4079(4)	3416(3)	44(2)
C(18)	6067(17)	3987(5)	4095(4)	59(2)

Table XI: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **195f**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
N(1)	8183(5)	10590(4)	11105(3)	55(1)
N(2)	6130(4)	9103(3)	7732(2)	41(1)
F(1)	2400(10)	5313(5)	8320(4)	181(3)
F(2)	3371(10)	3984(6)	7644(8)	260(5)
F(3)	1357(7)	4464(7)	7031(5)	185(3)
F(4)	381(9)	3853(5)	5053(3)	170(3)
F(5)	444(13)	2250(6)	4301(7)	271(6)
F(6)	-1411(8)	2984(8)	3862(4)	198(3)
F(7)	2768(9)	5241(5)	485(4)	162(2)
F(8)	726(10)	3928(6)	-467(3)	174(3)
F(9)	3211(12)	3655(8)	-182(6)	234(4)
O(1)	4671(5)	6646(3)	7834(3)	73(1)
O(2)	4714(5)	5179(3)	6610(3)	74(1)
O(3)	3122(6)	3956(4)	4145(3)	74(1)
O(4)	819(6)	3712(4)	3001(3)	96(2)
O(5)	1744(7)	4442(4)	1696(3)	80(2)
O(6)	1083(9)	2645(5)	735(4)	133(2)
O(7)	9008(6)	9860(4)	11043(3)	82(1)
O(8)	7942(6)	11201(4)	11830(2)	82(1)
O(9)	4065(5)	11849(3)	7795(2)	61(1)
O(10)	6984(4)	8238(2)	7702(2)	51(1)
O(11)	5133(4)	8255(2)	6183(2)	43(1)
O(12)	2929(4)	10899(3)	6040(2)	54(1)
C(1)	4189(6)	8204(3)	5321(3)	43(1)
C(2)	4175(6)	7214(4)	4589(3)	50(1)
C(3)	3279(7)	7059(4)	3724(3)	55(1)
C(4)	2407(6)	7875(4)	3542(3)	47(1)
C(5)	1495(7)	7688(4)	2621(3)	61(1)
C(6)	712(6)	8494(5)	2440(3)	61(1)
C(7)	769(6)	9501(5)	3155(4)	59(1)
C(8)	1602(6)	9708(4)	4059(3)	51(1)
C(9)	2452(5)	8902(4)	4285(3)	43(1)
C(10)	3383(5)	9059(3)	5216(3)	40(1)
C(11)	3538(5)	10059(3)	6042(3)	41(1)
C(12)	4496(5)	10054(3)	6927(3)	41(1)

C(14)	4709(6)	10965(3)	7763(3)	44(1)
C(13)	5253(5)	9142(3)	6946(3)	39(1)
C(16)	6349(5)	9958(3)	8589(3)	41(1)
C(15)	5641(6)	10922(3)	8619(3)	44(1)
C(17)	7227(5)	9866(4)	9407(3)	43(1)
C(18)	7342(5)	10724(4)	10225(3)	47(1)
C(19)	6691(6)	11689(4)	10295(3)	55(1)
C(20)	5851(6)	11787(4)	9495(3)	53(1)
C(21)	2905(8)	4822(5)	7579(4)	71(2)
C(22)	4214(6)	5636(4)	7312(3)	51(1)
C(23)	307(10)	3180(6)	4259(4)	82(2)
C(24)	1478(8)	3656(4)	3726(4)	61(1)
C(25)	1610(7)	3677(6)	928(4)	74(2)
C(26)	2159(11)	4116(7)	187(4)	90(2)

REFERENCES

(1) Baylis, A. B.; Hillman, M. E. D. *German patent* 2155113, **1972**; *Chem. Abstr.* **1972**, *77*, 34174q

(2) Hillman, M. E. D.; Baylis, A. B. *U. S. Patent* 3743669, **1973**.

(3) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(4) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001.

(5) Ciganek, E. *Organic Reactions*; Paquette, L. A., Ed; Wiley, New York: 1997, vol. 51, p 201.

(6) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev*. **2003**, *103*, 811.

(7) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem*. **1990**, *3*, 285.

(8) Bode, M. L.; Kaye, P.T.; *Tetrahedron Lett.* **1991**, *32*, 5611.

(9) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371.

(10) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem. Int. Ed*. **2004**, *43*, 4330.

(11) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed*. **2005**, *44*, 2.

(12) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc*. **2005**, *127*, 16762.

(13) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147

(14) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980.

(15) Roy, D.; Sunoj, R. B. *Org. Lett.* **2007**, *9*, 4873.

(16) Langer, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049.

(17) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12.

(18) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(19) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45.

(20) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614.

(21) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905.

(22) Basavaiah, D.; Rao, K. V.; Reddy. R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581.

(23) Drewes, S. E.; Emslie, N. D. *J. Chem. Soc. Perkin Trans. I* **1982**, 2079.

(24) (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795; (b) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849.

(25) Basavaiah, D.; Sarma, P. K. S. *Synth. Commun.* **1990**, *20*, 1611.

(26) Basavaiah, D.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1986**, *27*, 2031.

(27) Amri, H.; Villieras, J. *Tetrahedron Lett.* **1986**, *27*, 4307.

(28) Basavaiah, D.; Bharathi, T. K.; Gowriswari, V. V. L. *Synth. Commun.* **1987**, *17*, 1893.

(29) Basavaiah, D.; Gowriswari, V. V. L. *Synth. Commun.* **1987**, *17*, 587.

(30) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5095.

(31) Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444.

(32) Tsuboi, S.; Takatsuka, S.; Utaka, M. *Chem. Lett.* **1988**, 2003.

(33) Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem*. **1993**, *58*, 5952.

(34) Wang, S.-Z., Yamamoto, K.; Yamada, H.; Takahashi, T. *Tetrahedron* **1992**, *48*, 2333.

(35) Amri, H.; El Gaied, M. M.; Villieras, J. *Synth. Commun.* **1990**, *20*, 659.

(36) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007.

(37) Strunz, G. M.; Bethell, R.; Sampson, G.; White, P. *Can. J. Chem.* **1995**, *73*, 1666.

(38) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 1539.

(39) Hill, J. S.; Isaacs, N. S. *J. Chem. Res. (S)*, **1988**, 330.

(40) van Rozendaal, E. L. M.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, *49*, 6931.

(41) Ando, D.; Bevan, C.; Brown, J. M.; Price, D. W. *J. Chem. Soc. Chem. Commun.* **1992**, 592.

(42) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692.

(43) (a) Sorbetti, J. M.; Clary, K. N.; Rankic, D. A.; Wulff, J. E.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3326; (b) Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett*. **2005**, *7*, 2377.

(44) Rastogi, N.; Namboothiri, I. N. N.; Cojocaru, M. *Tetrahedron Lett*. **2004**, *45*, 4745.

(45) Dadwal, M.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothiri, I. N. N. *Chem. Commun.* **2006**, 338.

(46) Deb, I.; Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2006**, *8*, 1201.

(47) Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Biomol. Chem.* **2006**, *4*, 2525.

(48) Yu, C.; Hu, L. *J. Org. Chem.* **2002**, *67*, 219.

(49) Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496.

(50) Luo, S.; Wang, P. G.; Cheng, J-P. *J. Org. Chem.* **2004**, *69*, 555.

(51) Gatri, R.; El Gaied, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835.

(52) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311.

(53) Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965.

(54) Lee, K. Y.; Gong, J. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 659.

(55) Basavaiah, D.; Jaganmohan Rao, A. *Tetrahedron Lett.* **2003**, *44*, 4365.

(56) Grundke, C.; Hoffmann, H. M. R. *Chem. Ber.* **1987**, *120*, 1461.

(57) Basavaiah, D.; Bharathi, T. K.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1987**, *28*, 4351.

(58) Basavaiah, D.; Gowriswari, V. V. L. *Synth. Commun.* **1989**, *19*, 2461.

(59) Golubev, A. S.; Galakhov, M. V.; Kolomiets, A. F.; Fokin, A. V. *Bull. Russian Acad. Sci.* **1992**, *41*, 2193.

(60) Yamamoto, K.; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 319.

(61) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869.

(62) Shi, Y.-L..; Xu, Y.-M.; Shi, M. *Adv. Synth. Catal.* **2004**, *346*, 1220.

(63) Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417.

(64) Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K. *Tetrahedron Lett*. **1987**, *28*, 4591.

(65) Basavaiah, D.; Gowriswari, V. V. L.; Dharma Rao, P.; Bharathi, T. K. *J. Chem. Res*. (*S*) **1995**, 267 & (*M*) 1656.

(66) Drewes, S. E.; Emslie, N. D.; Karodia, N. *Synth. Commun*. **1990**, *20*, 1915.

(67) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc. Perkin Trans. I* **2002**, 1318.

(68) Shi, M.; Zhao, G.–L. *Tetrahedron Lett.* **2002**, *43*, 4499.

(69) Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276.

(70) Sergeeva, N. N.; Golubev, A. S.; Burger, K. *Synthesis* **2001**, 281.

(71) Ram Reddy, M. V.; Rudd, M. T.; Ramchandran, P. V. *J. Org. Chem.* **2002**, *67*, 5382.

(72) Ramachandran, P. V.; Ram Reddy, M. V.; Rudd, M. T. *Chem. Commun.* **2001**, 757.

(73) Garden, S. J.; Skakle, J. M. S. *Tetrahedron Lett*. **2002**, *43*, 1969.

(74) Chung, Y. M.; Im, Y. J.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002**, *23*, 1651.

(75) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981.

(76) Basavaiah, D.; Jaganmohan Rao, A.; Krishnamacharyulu, M. *ARKIVOC* **2002**, *VII*, 136.

(77) Kamimura, A.; Gunjigake, Y.; Mitsudera, H.; Yokoyama, S. *Tetrahedron Lett.* **1998**, *39*, 7323.

(78) Shi, M.; Zhao, G.-L. *Tetrahedron* **2004**, *60*, 2083.

(79) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett*. **2001**, *42*, 85.

(80) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Mallikarjuna Reddy, R. *J. Org. Chem.* **2002**, *67*, 7135.

(81) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc*. **2003**, *125*, 12394.

(82) Lee, C. H.; Lee K.-J. *Synthesis* **2004**, 1941.

(83) Liu, X.; Chai, Z.; Zhao, G.; Zhu, S. *J. Fluorine Chem*. **2005**, *126*, 1215.

(84) Drewes, S. E.; Freese, S. D.; Emsile, N. D.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1565.

(85) Shi, M.; Jiang, J. -K.; Li, C. -Q. *Tetrahedron Lett*. **2002**, *43*, 127.

(86) Cai, J.; Zhou, Z.; Zhao, G. ; Tang, C. *Org. Lett.* **2002**, *4*, 4723.

(87) de Souza, R. O. M. A.; Meireles, B. A.; Aguiar, L. C. S.; Vasconcellos, M. L. A. A. *Synthesis* **2004**, 1595.

(88) Krishna, P. R.; Sekhar, E. R.; Kannan, V. *Synthesis* **2004**, 857.

(89) Leadbeater, N. E.; Van der Pol, C. *J. Chem. Soc. Perkin Trans. I* **2001**, 2831.

(90) Grainger, R. S.; Leadbeater, N. E.; Pamies, A. M. *Catalysis Commun*. **2002**, *3*, 449.

(91) Lee, K. Y.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett*. **2004**, *45*, 5485.

(92) Zhao, S.; Chen, Z. *Synth*. *Commun.* **2005**, *35*, 121.

(93) Basavaiah, D.; Krishnamacharyulu, M.; Jaganmohan Rao, A. *Synth. Commun.* **2000**, *30*, 2061.

(94) Corma, A.; Garcia, H.; Leyva, A. *Chem. Commun*. **2003**, 2806.

(95) Chen, H.-T.; Huh, S.; Wiench, J. W.; Pruski, M.; Lin, V. S-Y. *J. Am. Chem. Soc*. **2005**, *127*, 13305.

(96) Yang, N-F.; Gong, H.; Tang, W-J.; Fan, Q-H.; Cai, C-Q.; Yang, L-W. *Journal of Molecular Catalysis A: Chemical* **2005**, *233*, 55.

(97) Mi, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem*. **2005**, *70*, 2338.

(98) Rauhut, M. M.; Currier, H. (*American Cyanamid Co.*) *U. S. patent* 3074999, **1963**; *Chem. Abstr*. **1963**, *58*, 11224a.

(99) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(100) Imagawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, M. *Synth. Commun.* **1984**, *14*, 1267.

(101) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731.

(102) Sato, S.; Matsuda, I.; Izumi, Y. *Chem. Lett.* **1985**, 1875.

(103) Sato, S.; Matsuda, I.; Shibata, M. *J. Organomet. Chem.* **1989**, *377*, 347.

(104) Matsuda, I.; Shibata, M.; Sato, S. *J. Organomet. Chem.* **1988**, *340*, C_5.

(105) Kataoka, T.; Iwama, T.; Tsujiyama, S.-i. *Chem. Commun.* **1998**, 197.

(106) Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Iwamura, T.; Watanabe, S.-i. *Tetrahedron* **1998**, *54*, 11813.

(107) Iwama, T.; Kinoshita, H.; Kataoka, T. *Tetrahedron Lett.* **1999**, *40*, 3741.

(108) Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synlett* **1999**, 1249.

(109) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383.

(110) Li, G.; Gao, J.; Wei, H.–X.; Enright, M. *Org. Lett.* **2000**, *2*, 617.

(111) Shi, M.; Jiang, J.-K.; Feng, Y.–S. *Org. Lett.* **2000**, *2*, 2397.

(112) Li, G.; Wei, H. –X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.

(113) Basavaiah, D.; Sreenivasulu, B. Mallikarjuna Reddy, R.; Muthukumaran, K.; *Synth. Commun.* **2001**, *31*, 2987.

(114) Kataoka, T.; Kinoshita, S.; Kinoshita, H.; Fujita, M.; Iwamura, T.; Watanabe, S.-i. *Chem. Commun.* **2001**, 1958.

(115) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; *J. Chem. Soc. Perkin Trans. I* **2002**, 2043.

(116) Walsh, L. M.; Winn, C. L.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 8219.

(117) Zhu, Y-H.; Vogel, P. *Synlett* **2001**, 79.

(118) Pei, W.; Wei, H-X.; Li, G. *Chem. Commun.* **2002**, 2412.

(119) He, Z.; Tang, X.; Chen, Y.; He, Z. *Adv*. *Synth*. *Catal*. **2006**, *348*, 413.

(120) Pereira, S. I.; Adrio, J.; Silva, A. M. S. Carretero, J. C. *J. Org. Chem*. **2005**, *70*, 10175.

(121) Shi, Y.-L.; Shi, M. *Tetrahedron* **2006**, *62*, 461.

(122) Myers, E. L.; deVries, J. G.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1.

(123) Srivardhana Rao, J.; Briere, J.-F., Metzner, P.; Basavaiah, D. *Tetrahedron Lett.* **2006**, *47*, 3553.

(124) Basavaiah, D.; Jaganmohan Rao, A. *Chem. Commun*. **2003**, 604.

(125) Yin, Y.-B.; Wang, M.; Liu, Q.; Hu, J.-L.; Sun, S.-G.; Kang, J. *Tetrahedron Lett.* **2005**, *46*, 4399.

(126) You, J.; Xu, J.; Verkade, J. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 5054.

(127) Basavaiah, D.; Sreenivasulu, B.; Jaganmohan Rao, A. *J. Org. Chem*. **2003**, *68*, 5983.

(128) Kattuboina, A.; Kaur, P.; Timmons, C.; G. Li, *Org. Lett*. **2006**, *8*, 2771.

(129) Wei, H.-X.; Jasoni, R. L.; Hu, J.; Li, G.; Pare, P. W. *Tetrahedron* **2004**, *60*, 10233.

(130) Yadav, J. S.; Reddy, B. V. S.; Gupta, M. K.; Eeshwaraiah, B. *Synthesis* **2005**, 57.

(131) Xue, S.; He, L.; Han, K.-Z.; Liu, Y.-K.; Guo, Q.-X. *Synlett* **2005**, 1247.

(132) Lin, Y.-S.; Liu, C.-W.; Tsai, T. Y. R. *Tetrahedron Lett*. **2005**, *46*, 1859.

(133) He, L.; Jain, T.-Y.; Ye, S. *J. Org. Chem*. **2007**, *72*, 7466.

(134) Basavaiah, D.; Gowriswari, V. V. L.; Sarma, P. K. S.; Dharma Rao, P. *Tetrahedron Lett.* **1990**, *31*, 1621.

(135) (a) Gowriswari, V. V. L. *Ph. D. thesis*, University of Hyderabad **1989**; (b) Sarma, P. K. S. *Ph. D. thesis*, University of Hyderabad **1993**.

(136) Jensen, K. N.; Roos, G. H. P. *S. Afr. J. Chem.* **1992**, *45*, 112.

(137) Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 969.

(138) Drewes, S. E.; Emslie, N. D.; Karodia, N.; Khan, A. A. *Chem. Ber*. **1990**, 1*23*, 1447.

(139) Drewes, S. E.; Emslie, N. D.; Khan, A. A. *Synth. Commun.* **1993**, *23*, 1215.

(140) Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A. *Tetrahedron Lett.* **1993**, *34*, 1205.

(141) Evans, M. D.; Kaye, P. T. *Synth. Commun.* **1999**, *29*, 2137.

(142) Krishna, P. R.; Kannan, V.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2001**, *12*, 829.

(143) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317.

(144) Piber, M.; Leahy, J. W. *Tetrahedron Lett.* **1998**, *39*, 2043.

(145) Yang, K.–S.; Chen, K. *Org. Lett.* **2000**, *2*, 729.

(146) Drewes, S. E.; Manickum, T.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1065.

(147) Drewes, S. E.; Njamela, O. L.; Roos, G. H. P. *Chem. Ber.* **1990**, *123*, 2455.

(148) Manickum, T.; Roos, G. H. P. *Synth. Commun.* **1991**, *21*, 2269.

(149) Drewes, S. E.; Khan, A. A.; Rowland, K. *Synth. Commun.* **1993**, *23*, 183.

(150) Kundig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett*. **1993**, *34*, 7049.

(151) Kundig, E. P.; Xu, L. H.; Schnell, B. *Synlett* **1994**, 413.

(152) Krishna, P. R.; Kannan, V.; Sharma, G. V. M. Ramana Rao, M. H. V. *Synlett* **2003**, 888.

(153) Krishna, P. R.; Manjuvani, A.; Kannan, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2691.

(154) Bauer, T.; Tarasiuk, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1741.

(155) Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 639.

(156) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.

(157) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533.

(158) Barrett, A. G. M.; Dozzo, P.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2002**, *58*, 7303.

(159) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal*. **2004**, *346*, 1106.

(160) Krishna, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603.

(161) Tang, H.; Zhao, G.; Zhou, Z.; Zhou, Q.; Tang, C. *Tetrahedron Lett*. **2006**, *47*, 5717.

(162) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.

(163) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

(164) (a) Nakano, A.; Ushiyama, M.; Iwabuchi, Y.; Hatakeyama, S. *Adv. Synth. Catal.* **2005**, *347*, 1790; (b) Nakano, A.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2006**, *8*, 5357.

(165) Shi, M.; Xu, Y.-M.; Shi, Y.-L. *Chem. Eur. J*. **2005**, *11*. 1794.

(166) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.

(167) (a) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc*. **2005**, *127*, 3680; (b) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2006**, *17*, 578.

(168) (a) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310; (b) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc*. **2005**, *127*, 3790.

(169) Shi, M.; Li, C.-Q. *Tetrahedron: Asymmetry* **2005**, *16*, 1385.

(170) Liu, Y.-H.; Chen, L.-H.; Shi, M. *Adv. Synth. Catal.* **2006**, *348*, 973.

(171) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761.

(172) (a) Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Kanematsu, K.; Iwamura, T.; Watanabe, S.-i. *Chem. Lett.* **1999**, 257. (b) Iwama, T.; Tsujiyama, S.-i.; Kinoshita, H.; Kanematsu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.-i.; Kataoka, T. *Chem. Pharm. Bull.* **1999**, *47*, 956.

(173) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem*. **2003**, *68*, 915.

(174) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165.

(175) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231.

(176) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc*. **2003**, *125*, 12094.

(177) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.

(178) Berkessel, A.; Roland, K.; Neudorfl, J. M. *Org. Lett.* **2006**, *8*, 4195.

(179) Raheem, I. T.; Jacobsen, E. N. *Adv*. *Synth*. *Catal*. **2005**, *347*, 1701

(180) Krafft, M. E.; Wright, J. A. *Chem*. *Commun*. **2006**, 2977.

(181) (a) Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Abboud, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 4174; (b) Krafft, M. E.; Seibert, K. A.; Haxell, T. F. N. Hirosawa, C. *Chem*. *Commun*. **2005**, 5772.

(182) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc*. **2003**, *125*, 7758.

(183) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687.

(184) Yagi, K.; Turitani. T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111.

(185) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.

(186) Chen, S.-H.; Hong, B.-C.; Su, C.-F.; Sarshar, S. *Tetrahedron Lett*. **2005**, *46*, 8899.

(187) Aroyan, C. E.; Vasbinder, M. M.; Miller, S. J. *Org*. *Lett*. **2005**, ***7***, 3849.

(188) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098.

(189) Basavaiah, D.; Sarma, P. K. S. *J. Chem. Soc. Chem. Commun.* **1992**, 955.

(190) Basavaiah, D.; Pandiaraju, S.; Sarma, P. K. S. *Tetrahedron Lett.* **1994**, *35*, 4227.

(191) Fields, S. C. *Tetrahedron Lett.* **1998**, *39*, 6621.

(192) Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197.

(193) Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419.

(194) Iura, Y.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 291.

(195) Basavaiah, D.; Kumaragurubaran, N. *Tetrahedron Lett.* **2001**, *42*, 477.

(196) Basavaiah, D.; Reddy, K. R.; Kumaragurubaran, N. *Nature Protocols*, **2007**, *2*, 667.

(197) Gonzalez, A. G.; Silva, M. H.; Padron, J. I.; Leon, F.; Reyes, E.; Alvarez-Mon, M.; Pivel, J. P.; Quintana, J.; Estevez, F.; Bermejo, J. *J. Med. Chem.* **2002**, *45*, 2358.

(198) Anand, R. V.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 5393.

(199) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030.

(200) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616.

(201) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **2003**, *44*, 937.

(202) Kar, A.; Argade, N. P. *Synthesis* **2005**, 1234.

(203) Lee, S.; Hwang, G.-S.; Shin, S. C.; Lee, T. G.; Jo, R. H.; Ryu, D. H. *Org. Lett*. **2007**, *9*, 5087.

(204) Kamal, A.; Krishnaji, T.; Reddy, P.V. *Tetrahedron Lett.* **2007**, *48*, 7232.

(205) Du, Y.; Feng, J.; Lu, X. *Org. Lett*. **2005**, *7*, 1987.

(206) Aggarwal, V. K.; Patin, A.; Tisserand, S. *Org. Lett*. **2005**, *7*, 2555.

(207) Chen, P. Y.; Chen, H.-M.; Chen, L.-Y.; Tzeng, J.-Y.; Tsai, J.-C.; Chi, P.-C.; Li, S.-R.; Wang, E.-C. *Tetrahedron*, **2007**, *63*, 2824.

(208) Basavaiah, D.; Aravindu, K. *Org. Lett*. **2007**, *9*, 2453.

(209) Basavaiah, D.; Satyanarayana, T. *Chem. Commun.* **2004**, 32.

(210) Batra, S.; Roy, A. K. *Synthesis* **2004**, 2550.

(211) Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 2805.

(212) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2004**, *45*, 3089.

(213) Hong, W. P.; Lim, H. N.; Park, H. W.; Lee, K.-J. *Bull. Korean. Chem. Soc.* **2005**, *26*, 655.

(214) Basavaiah, D.; Srivardhana Rao, J. *Tetrahedron Lett*. **2004**, *45*, 1621.

(215) Heim, R.; Wiedemann, S.; Willams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327.

(216) Kaye, P. T.; Musa, M. A.; Nocanda, X. W. *Synthesis* **2005**, 531.

(217) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, *3*, 3619.

(218) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481.

(219) Basavaiah, D.; Satyanarayana, T. *Tetrahedron Lett.* **2002**, *43*, 4301.

(220) Clive, D. L. J.; Yu, M.; Li, Z. *Chem. Commun.* **2005**, 906.

(221) Jiao, P.; Swenson, D. C.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *J. Nat. Prod.* **2006**, *69*, 1667.

(222) Ragot, J. P.; Alcaraz, M.-L.; Taylor, R. J. K. *Tetrahedron Lett*. **1998**, *39*, 4921.

(223) Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem*. **2002**, *67*, 2735.

(224) Wipf, P.; Jung, J.-K.; Rodriguez, S.; Lazo, J. S.; *Tetrahedron* **2001**, *57*, 283.

(225) Laurent, D.; Guella, G.; Mancini, I.; Roquebert, M.-F.; Farinole, F.; Pietra, F. *Tetrahedron*, **2002**, *58*, 9163.

(226) Quang, D. N.; Hashimoto, T.; Tanaka, M.; Baumgartner, M.; Stadler, M.; Asakawa, Y. *J. Nat. Prod*. **2002**, *65*, 1869.

(227) Wu, T.-S.; Tsai, Y.-L.; Damu, A. G.; Kuo, P.-C.; Wu, P.-L. *J. Nat. Prod*. **2002**, *65*, 1522.

(228) Wipf, P.; Lynch, S. M. *Org. Lett*. **2003**, *5*, 1155.

(229) Coutts, I. G. C.; Allcock, R. W.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 9105.

(230) Arnold, R. T.; Buckley Jr., J. S.; Dodson, R. M. *J. Am. Chem. Soc*. **1950**, *72*, 3153.

(231) Yamada, T.; Okada, T.; Sakaguchi, K.; Ohfune, Y.; Ueki, H.; Soloshonok, V. A. *Org. Lett*. **2006**, *8*, 5625.

(232) Xiao, Z.; Schaefer, K.; Firestine, S.; Li, P.-K. *J. Comb. Chem*. **2002**, *4*, 149.

(233) Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K.-D. Tong, W. P.; Huang, X.-Y. Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2004**, *126*, 11326.

(234) Grieco, P. A.; Henry, K. J.; Nunes, J. J.; Matt, Jr., J. E. *J. Chem. Soc. Chem. Commun*. **1992**, 368.

(235) *Dictionary of Drugs*: Elks, J.; Ganellin, C. R. Eds.; 1st Ed.; Chapman and Hall: Lodon, 1990, p 70 (*A-00305*).

(236) Fogliato, G.; Fronza, G.; Fuganti, C.; Grasselli, P.; Servi, S. *J. Org. Chem.* **1995**, *60*, 5693.

(237) *Dictionary of Drugs*: Elks, J.; Ganellin, C. R. Eds.; 1st Ed.; Chapman and Hall: Lodon, 1990, p 281 (*C-00380*).

(238) *Dictionary of Drugs*: Elks, J.; Ganellin, C. R. Eds.; 1st Ed.; Chapman and Hall: Lodon, 1990, p 960 (*P-00155*).

(239) Cirillo, P. F.; Panek, J. S. *J. Org. Chem.* **1994**, *59*, 3055.

(240) Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Org. Lett*. **2003**, *5*, 2865.

(241) Chen C.-Y. Chang, M.-Y.; Hsu, R.-T.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett*. **2003**, *44*, 8627.

(242) Singh, V.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Tetrahedron* **2006**, *62*, 8731.

(243) (a) *Dictionary of Drugs*: Elks, J.; Ganellin, C. R. Eds.; 1st Ed.; Chapman and Hall: Lodon, 1990, p 32 (*A-00142*). (b) *German patent* 2035636, **1971**.

(244) Koelsch, C. F. *J. Org. Chem*. **1960**, *25*, 164.

(245) Tanaka, K.; Yamagishi, N.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 3619.

(246) (a) Larson, G. L.; de Kaifer, C. F.; Seda, R.; Torres, L. E.; Ramirez, J. R. *J. Org. Chem.* **1984**, *49*, 3385. (b) Baraldi, P. G.; Guarneri, M.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *J. Chem. Soc., Perkin Trans I* **1984**, 2501.

(247) Basavaiah, D.; Pandiaraju, S.; Krishnamacharyulu, M. *Synlett* **1996**, 747.

(248) Satyanarayana, T. *Ph.D. Thesis*, University of Hyderabad, **2004**.

(249) (a) Ishikawa, T.; Miyahara, T.; Asakura, M.; Higuchi, S.; Miyauchi, Y.; Saito, S. *Org. Lett.* **2005**, *7*, 1211; (b) Yao, S.-P.; Lu, D.-S.; Wu, Q.; Cai, Y.; Xu, S.-H.; Lin, X.-F. *Chem. Commun*. **2004**, 2006.

(250) (a) Son, S. Uk.; Park, K. H.; Chung, Y. K. *J. Am. Chem. Soc.* **2002**, *124*, 6838; (b) Harwig, C. W.; Hoffman, T. Z.; Wentworth, A. D.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2001**, *10*, 915.

(251) Popovic-Dordevic, J. B.; Ivanovic, M. D.; Kiricojevic, V. D. *Tetrahedron Lett*. **2005**, *46*, 2611.

(252) Victory, P.; Jose, D. *Afinidad*, **1978**, *35*, 161; *Chem. Abstr*. **1978**, *89*, 179515j.

(253) Yokokawa, F.; Inaizumi, A.; Shioiri, T. *Tetrahedron* **2005**, *61*, 1459.

(254) Nogle, L. M.; Williamson, T. R.; Gerwick, W. H. *J. Nat. Prod*. **2001**, *64*, 716.

(255) Yamazki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739.

(256) Kumar, S.; Flamant-Robin, C.; Wang, Q.; Chiaroni, A.; Sasaki, N. A. *J. Org. Chem*. **2005**, *70*, 5946.

(257) Middleton, D. S.; MacKenzie, A. R.; Newman, S. D.; Corless, M.; Warren, A.; Marchington, A. P.; Jones, B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3957.

(258) Elworthy, T. R.; Brill, E. R.; Caires, C. C.; Kim, W.; Lach, L. K.; Tracy, J. L.; Chiou, S.-S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2523.

(259) Lee, H. K.; Chun, J. S.; Pak, C. S. *Tetrahedron* **2003**, *59*, 6445.

(260) MacKenzie, A. R.; Marchington, A. P.; Middleton, D. S.; Newman, S. D.; Jones, B. C. *J. Med. Chem.* **2002**, *45*, 5365.

(261) Bonjouklian, R.; Smitka, T. A.; Hunt, A. H.; Occolowitz, J. L.; Perun Jr. T. J.; Doolin, L.; Stevenson, S.; Knauss, L.; Wijayaratne, R.; Szewczyk, S.; Patterson, G. M. L. *Tetrahedron* **1996**, *52*, 395.

(262) Takasu, K.; Nishida, N.; Ihara, M. *Synlett* **2004**, 1844.

(263) Arrayas, R. G.; Alcudia, A.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 3381.

(264) Jao, E.; Slifer, P. B.; Lalancette, R.; Hall, S. S. *J. Org. Chem*. **1996**, *61*, 2865.

(265) (a) Castro, A. M. M. *Chem. Rev*. **2004**, *104*, 2939; (b) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(266) Basavaiah, D.; Pandiaraju, S. *Tetrahedron Lett.* **1995**, *36*, 757.

(267) (a) Osby, J, O.; Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67; (b) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801.

(268) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron* **1969**, *36*, 4555.

(269) *Friedel-Crafts Chemistry*; Olah, G. A., Ed; New York: Wiley, **1973**.

(270) Olah, G. A.; Krishnmurti, R.; Prakash, G. K. S. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Eds, New York: Pergamon, **1990**, vol. 3, p 293 and references cited there in.

(271) Basavaiah, D.; Pandiaraju, S.; Padmaja, K. *Synlett* **1996**, 393.

(272) Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Pandiaraju, S. *Tetrahedron Lett.* **1997**, *38*, 2141.

(273) Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett.* **1998**, *39*, 6223.

(274) Basavaiah, D.; Bakthadoss, M.; Jayapal Reddy, G. *Synthesis* **2001**, 919.

(275) Basavaiah, D.; Reddy, R. M. *Tetrahedron Lett.* **2001**, *42*, 3025.

(276) GowriSankar, S.; Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 6141.

(277) Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.–P. *J. Org. Chem.* **2004**, *69*, 8413.

(278) Schonberg, A.; Sina, A. *J. Am. Chem. Soc.* **1950**, *72*, 3396.

(279) Davies, S. G.; Mobbs, B. E.; Goodwin, C. J. *J. Chem. Soc. Perkin Trans. I* **1987**, 2597.

(280) Shafiq, Z.; Liu, L.;Wang, D.; Chen, Y. J. *Org. Lett.*. **2007**, *9*, 2525.

(281) Harnisch, V. H. *Liebigs Ann. Chem*. **1972**, *765*, 8.

(282) Morel, A. F.; Larghi, E. L. *Tetrahedron: Asymmetry* **2004**, *15*, 9.

(283) Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Carroll, J. G.; Mackerracher, D.; Malone, J. F. *J. Chem. Soc. Perkin Trans. I* **2000**, 3397.

(284) Sekar, M.; Prasad, K. J. R. *J. Nat. Prod.* **1998**, *61*, 294.

(285) Motai, T.; Kitanaka, S. *J. Nat. Prod.* **2005**, *68*, 1732.

(286) Su, B.-N.; Takaishi, Y.; Honda, G.; Itoh, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2000**, *63*, 520.

(287) Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *Chem. Commun.* **1998**, 2563.

(288) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343.

(289) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385.

(290) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1109.

(291) Basavaiah, D.; Reddy, R. J.; Srivardhana Rao, J.; *Tetrahedron Lett.* **2006**, *47*, 73.

(292) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem*. **2003**, *68*, 6427.

(293) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693.

(294) Basavaiah, D.; Srivardhana Rao, J.; Reddy, R. J. *J. Org. Chem*. **2004**, *69*, 7379.

(295) Yoon, K.; Ha, S. M.; Kim, K. *J. Org. Chem*. **2005**, *70*, 5741.

(296) Ishar, M. P. S.; Kumar, K.; Singh, R. *Tetrahedron Lett.* **1998**, *39*, 6547.

(297) Singh, G.; Singh. R.; Girdhar, N. K.; Ishar, M. P. S. *Tetrahedron* **2002**, *58*, 2471.

(298) Amarante, G. W.; Benassi, M.; Sabino, A. A.; Esteves, P. M.; Coelho, F.; Eberlin, M. N. *Tetrahedron Lett.* **2006**, *47*, 8427.

(299) Basavaiah, D.; Reddy, R. M. *Indian J. Chem.* **2001**, *40B*, 985.

(300) Aldrich, *Catalog Handbook of fine chemicals*, **2007-2008**, p 673.

(301) Aldrich, *Catalog Handbook of fine chemicals*, **2005-2006**, p 646.

(302) Aldrich, *Catalog Handbook of fine chemicals*, **2005-2006**, p 479.

(303) Aldrich, *Catalog Handbook of fine chemicals*, **2007-2008**, p 453.

(304) Singh, O. V.; George, V.; Kapil, R. S. *Indian J. Chem.***1995**, *34B*, 856.