TOWARDS SYNTHESIS OF SPIRO-OXINDOLES AND PROPELLANO-BISLACTONES USING THE BAYLIS-HILLMAN ADDUCTS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

AINELLY VEERENDHAR

SCHOOL OF CHEMISTRY

UNIVERSITY OF HYDERABAD

HYDERABAD–500 046

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STATEMENT

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

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

HYDERABAD
AUGUST, 2008 **AINELLY VEERENDHAR**

CERTIFICATE

Certified that the work embodied in this thesis entitled "**Towards synthesis of spiro-oxindoles and propellano-bislactones using the Baylis-Hillman adducts**" has been carried out by **Mr. Ainelly Veerendhar**, under my supervision and the same has not been submitted elsewhere for a degree.

Professor D. BASAVAIAH
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

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AINELLY VEERENDHAR

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
aq.	aqueous
BINOL	1,1′-bi-2-naphthol
Bp	boiling point
Bu	butyl
t-Bu or Bu^t	*tertiar*y butyl
cat.	catalyst
*m*CPBA	*meta*-chloroperbenzoic acid
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DEPO	diethylphosphine oxide
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio

Eq.	equation
eq.	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
Hex	hexyl
HMT	hexamethylenetetramine
3-HQD	3-hydroxyquinuclidine
KDP	ketodicyclopentadiene
KDP	ketodicyclopentadiene
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LDBB	lithium di-tert butylbiphenylide
Me	methyl
MEMCl	2-methoxyethoxymethyl chloride
Mp	melting point
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
PAP	polymer bound 4-(*N*-benzyl-*N*-methylamino)pyridine
Ph	phenyl

4-PPY	4-pyrrolidinopyridine
i-pr	isopropyl
pr	propyl
PTA	1,3,5-triaza-7-phosphaadamantane
rt	room temperature
TBAI	tetrabutylammonium iodide
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMPDA	1,1,3,3-tetramethylpropane-1,3-diamine
p-TsOH / *p*-TSA	*para*-toluenesulfonic acid

ABSTRACT

The Baylis-Hillman reaction is a three component atom economy carbon-carbon bond forming reaction. It involves the coupling of α-position of an activated alkene with an electrophile under the influence of a catalyst or catalytic system producing an interesting classes of densely functionalized molecules possessing an enormous synthetic potential. In addition to atom-economical carbon-carbon bond formation and providing multi-functional molecules, this reaction has some unique features: 1) It creates a chiral center in the case of prochiral electrophile providing opportunities to develop asymmetric version. 2) It has a provision for intramolecular version in the case of substrates having both activated alkene and electrophilic components, thus also offering challenges for developing the corresponding asymmetric version. 3) Mechanism of this reaction is not yet completely understood due to the complexities involved, therefore this aspect has become a challenging problem to organic chemists. 4) The Baylis-Hillman adducts, due to the presence of several functional groups in proximity, provide enormous competing opportunities for developing various synthetic transformations and strategies.

This thesis deals with the studies in the synthesis of spiro-oxindoles and propellano-bislactones from the Baylis-Hillman adducts and consists of three chapters 1) Introduction 2) Objectives, Results & Discussion and 3) Experimental. The first chapter i.e., Introduction presents a brief literature survey on the developments of Baylis-Hillman reac-

tion and also on the application of the Baylis-Hillman adducts in the synthetic organic chemistry.

The second chapter deals with the objectives, results & discussion. With a view to study the application of Baylis-Hillman adducts for the synthesis of spiro and heterocyclic molecules, we have undertaken a research program with following objectives.

OBJECTIVES

1. a) To develop a simple methodology for the synthesis of spiro-oxindole derivatives containing α-methylene-γ-lactone skeleton (connected by an interesting spiro bridge) *via* the treatment of methyl 2-(bromomethyl)prop-2-enoate (the allyl bromide derived from the Baylis-Hillman alcohol) with isatin derivatives under the influence of zinc.

   b) To develop a simple diastereo selective protocol for synthesis of (indolin-2-one)-3-spiro-5'-[3'-methylene-4'-aryltetrahydrofuran-2'-ones] *via* the reaction between Baylis-Hillman bromides i.e., methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates and isatin derivatives, under the influence of zinc.

2. To develop a convenient methodology for obtaining spiro-oxindole derivatives containing α-methylene-γ-lactam skeleton (connected by an interesting spiro bridge) *via* the treatment of methyl 2-(bromomethyl)prop-2-enoate with 3-(arylimino)indolin-2-ones under the influence of zinc.

3. To develop a facile methodology for the transformation of acetates of the Baylis-Hillman adducts into [4.4.4.]propellano-bislactones i.e., 4,8-bis[(*E*)-arylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.$0^{1,6}$]tetradecane-3,9,14-triones.

Simple and one pot synthesis of spiro-oxindoles having α-methylene-γ-lactone framework

The spiro-oxindole framework is an integral part of several natural products, such as spirotryprostatins A & B, welwitindolinones, horsfiline, tasmanine, aristoteline, elacomine, *etc* (Figure 8). The α-methylene-γ-lactone framework is present in many natural products such as vernolepin, euparotin, euparotin acetate, eupatundin, elephantopin, *etc* (Figure 9). Therefore development of simple and facile methodologies for synthesis of both the spiro-oxindole and α-methylene-γ-lactone derivatives has become an important and challenging endeavor in synthetic organic chemistry. It occurred to us that the molecules containing both the oxindole and α-methylene-γ-lactone frameworks connected by a spiro linkage might possess high levels of biological activity. We have therefore developed a facile one-pot methodology for synthesis of spiro-oxindoles i.e., (indolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-ones] (**133a-h**) *via* the treatment of isatin derivatives with methyl 2-(bromo-methyl)prop-2-enoate in the presence of zinc (Scheme 47, Eqs. 28 & 30, Table 1).

One-pot diastereoselective synthesis of spiro-oxindoles having α-methylene-γ-lactone framework

In continuation of our interest in spiro-oxindoles (**133a-h**), we have successfully transformed Baylis-Hillman bromides i.e., methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates (**135a-c**) into (indolin-2-one)-3-spiro-5'-[3'-methylene-4'-aryltetrahydrofuran-2'-ones] (**136a-h, 137a-f**) with high *trans* diastereoselectivity (92-100%) *via* the reaction with isatin derivatives, under the influence of zinc (Scheme 52, Eqs. 31 & 33, Tables 2 & 3).

Simple and convenient synthesis of spiro-oxindoles having α-methylene-γ-lactam framework

α-Methylene-γ-butyrolactam framework occupies an important place in heterocyclic compounds because of the presence of this skeleton in various medicinally relevant molecules. It occurred to us that the molecules containing both the oxindole and α-methylene-γ-lactam frameworks connected by a spiro linkage might serve as medicinally important molecules. Accordingly we have transformed the methyl 2-(bromomethyl)prop-2-enoate (**131**) into (indolin-2-one)-3-spiro-5′-[3'-methylene-1'-aryl-pyrrolidin-2'-ones] (**142**) in a simple and convenient methodology *via* the treatment with 3-(arylimino)indolin-2-ones (**140**) under the influence of zinc, followed by cyclization of the resulting amine-esters (**141**) in the presence of *p*-toluenesulfonic acid (Eqs. 36-41, Tables 4-6).

Simple and facile synthesis of propellanes from the acetates of the Baylis-Hillman adducts

The propellane framework is present in several natural products such as taxane, modhephene, annotinine, colombiasin A, merrilactone A, merrilactone B etc (Figure 10). Polycyclic, polylactone structural framework is present in several natural products such as sterepolide, marasmic acid, ginkgolides (A, B, C), bilobalide, anislactone A and B etc (Figure 11). Also polylactone framework with α-exo functionality is present in many biologically active molecules such as avenociolide, vernolepin, vernomenin etc (Figure 12). Because of the importance of the both propellane and polylactone frameworks simple and convenient methodologies for the synthesis of molecules having the both propellane and polylactone frame works represents an interesting and attractive endeavor in synthetic organic chemistry. We have developed simple protocol for the transformation of acetates of the Baylis-Hillman adducts into [4.4.4.]propellano-bislactones i.e., 4,8-bis[(*E*)-arylidene]-12,12-dimethyl-2,10-dioxa-tricyclo[4.4.4.$0^{1,6}$]tetradecane-3,9,14-triones (**172a-g**), involving bisalkylation, cleavage of *tert*-butyl ester group into acid group, and bislactonization without isolating any intermediate (Schemes 62, 64 & 65, Eqs. 45 & 46, Table 7).

The third chapter provides detailed experimental procedures, physical constants like boiling point, melting point, IR, ^{1}H & ^{13}CNMR mass (LC-MS) spectral data and elemental analysis.

LIST OF PUBLICATIONS

1. A facile tandem construction of C–O and C–C bonds: a novel one-pot transformation of Baylis–Hillman adducts into 2-benzoxepines
   Deevi Basavaiah, Duddu S. Sharada, and **Ainelly Veerendhar**, *Tetrahedron Lett*. **2004**, *45*, 3081.

2. Organo-base mediated Cannizzaro reaction
   Deevi Basavaiah, Duddu S. Sharada, and **Ainelly Veerendhar** *Tetrahedron Lett*. **2006**, *47*, 5771.

3. One-pot diastereoselective synthesis of spiro-oxindoles using the Baylis-Hillman bromides
   Deevi Basavaiah, **Ainelly Veerendhar**, and Badugu Devendar (*communicated*).

4. A facile one-pot transformation of the Baylis-Hillman adducts into unsymmetrical disubstituted maleimide and maleic anhydride frameworks
   Deevi Basavaiah, Badugu Devendar, and **Ainelly Veerendhar** (*communicated*).

5. Simple and convenient synthesis of spiro-oxindoles having α-methylene-γ-lactam framework
   Deevi Basavaiah and **Ainelly Veerendhar** (*to be communicated*).

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

CONTENTS

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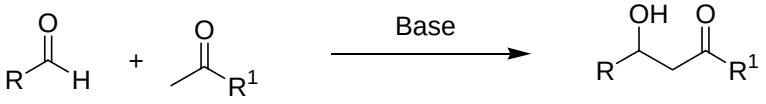
INTRODUCTION

Formation of carbon-carbon bond is one of the most fundamental reactions in organic chemistry and plays a key role in assembling carbon framework.[1-4] In recent years the concept of atom-economy has become one of the most important requirements for the development of any carbon-carbon bond forming reaction. The aldol reaction[5] is one of the oldest carbon-carbon bond forming reaction possessing the concept of atom-economy providing an interesting class of molecules having two functional groups (Eq. 1).

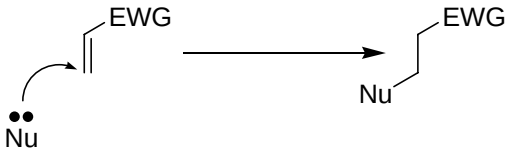
Aldol reaction



Eq. 1

Michael reaction [1,4-addition[6] of carbon nucleophile to α,β-unsaturated carbonyl or nitrile or nitro or any other elecrton withdrawing groups] is yet another oldest and important carbon-carbon bond forming reaction possessing the concept of atom-economy. Several non-carbon nucleophiles have been also used as Michael donors in various 1,4-addition reactions (Eq.2)

Michael reaction

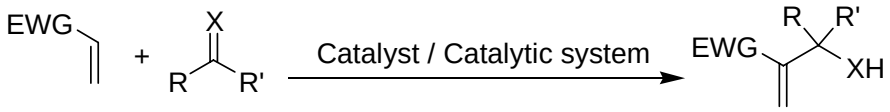


Eq. 2

Nu: carbon / non-carbon nucleophile

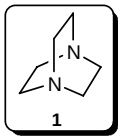
In recent years the Baylis-Hillman reaction,[7-8] a novel atom-economy carbon-carbon bond forming reaction has been developed based on the combined concepts of Michael and aldol reactions (eq.3) [for mechanism see scheme 19 (page no. 27)] and in fact this has become a powerful synthetic tool in organic chemistry because it provides densely functionalized molecules. The origin of this reaction dates back to a German patent[7] filed by Baylis and Hillman in the year 1972. This involves the coupling of α-position of an activated alkene with an electrophile under the catalytic influence of a catalyst or catalytic system [generally tertiary amine and most commonly DABCO (**1**)] producing an interesting classes of densely functionalized molecules possessing an enormous synthetic potential (Eq. 3).[7-14]

The Baylis-Hillman reaction



Eq. 3

R = alkyl, aryl, hetero-aryl, *etc.*
R' = H, alkyl, COOR *etc.*
EWG (Electron Withdrawing Group) = COOR, CN, COR, CHO, $PO(OEt)_2$, SO_3Ph, SO_2Ph, SOPh, *etc.*
Catalyst / Catalytic system = *tert*-amines, Lewis acids, phosphines, *etc.*
X = O, *N*-Ts, *N*-$PO(R)_2$, *N*-CO_2R *etc.*



During the last twenty five years, this reaction has grown in exponential fashion as evidenced by a large number of research publications, five major reviews[9-13] and several mini reviews.[14-19] In addition to atom-economical carbon-carbon bond formation and

providing multi-functional molecules, this reaction has some unique features: 1) It creates a chiral center in the case of prochiral elcetrophile providing opportunities to develop asymmetric version. 2) It provides a provision for intramolecular version in the case of substrates having both activated alkene and electrophilic components, and this aspect offers challenges for developing the corresponding asymmetric version. 3) Mechanism of this reaction is not yet completely understood due to the complexities involved, therefore this aspect has become a challenging problem to organic chemists. 4) The Baylis-Hillman adducts, due to the presence of several functional groups in proximity, provide enormous competing opportunities for developing various synthetic transformations and strategies. During the last several years all these aspects have been systematically addressed and investigated by several leading synthetic and mechanistic chemists. In fact, vast literature is now available describing all these aspects of this fascinating reaction. It is, therefore, practically impossible to describe all these aspects in this section. But every attempt is made to present relevant and recent developments on various aspects of this reaction in this section.

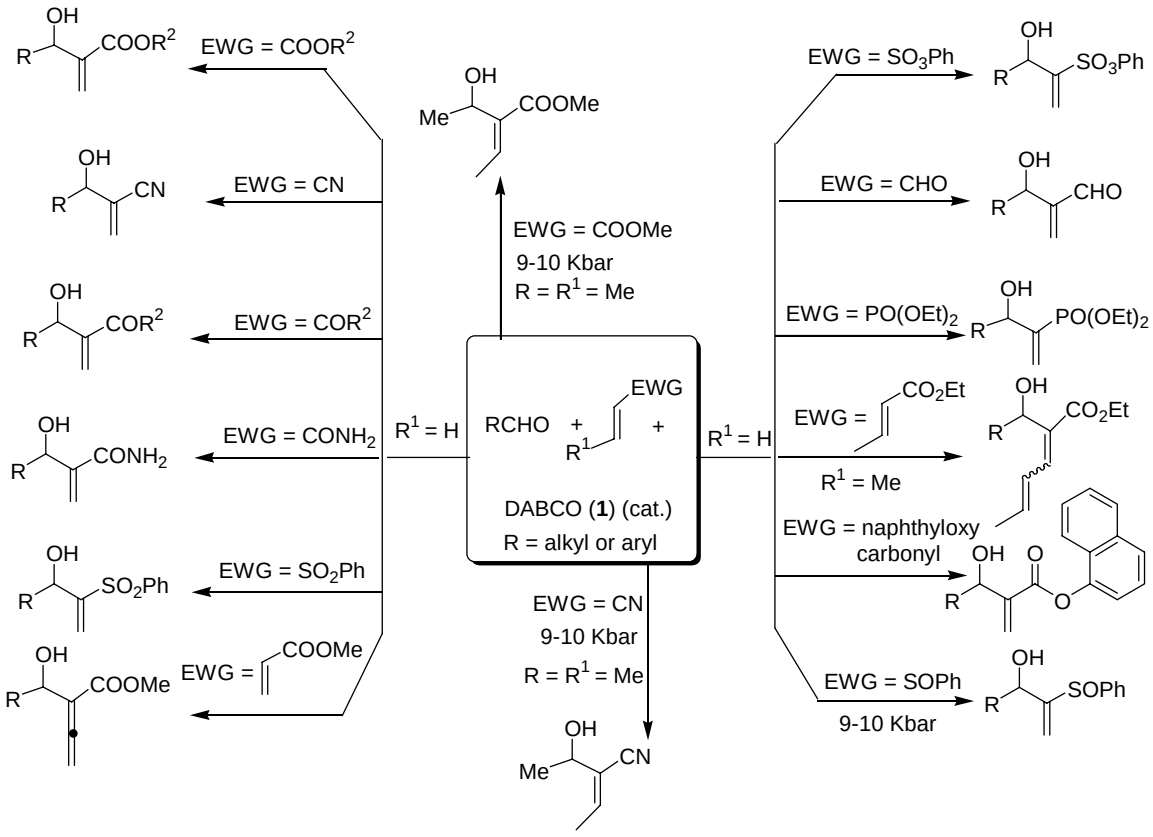
THREE ESSENTIAL COMPONENTS

During the last several years there has been an exponential growth with respect to three essential components. Several activated alkenes, number of electrophiles and large verities of catalyst/ catalytic systems have been successfully employed in this fascinating carbon-carbon bond forming reaction to provide different classes of multifunctional molecules. Some of the recent and important developments are presented in this section.

ACYCLIC ACTIVATED ALKENES:

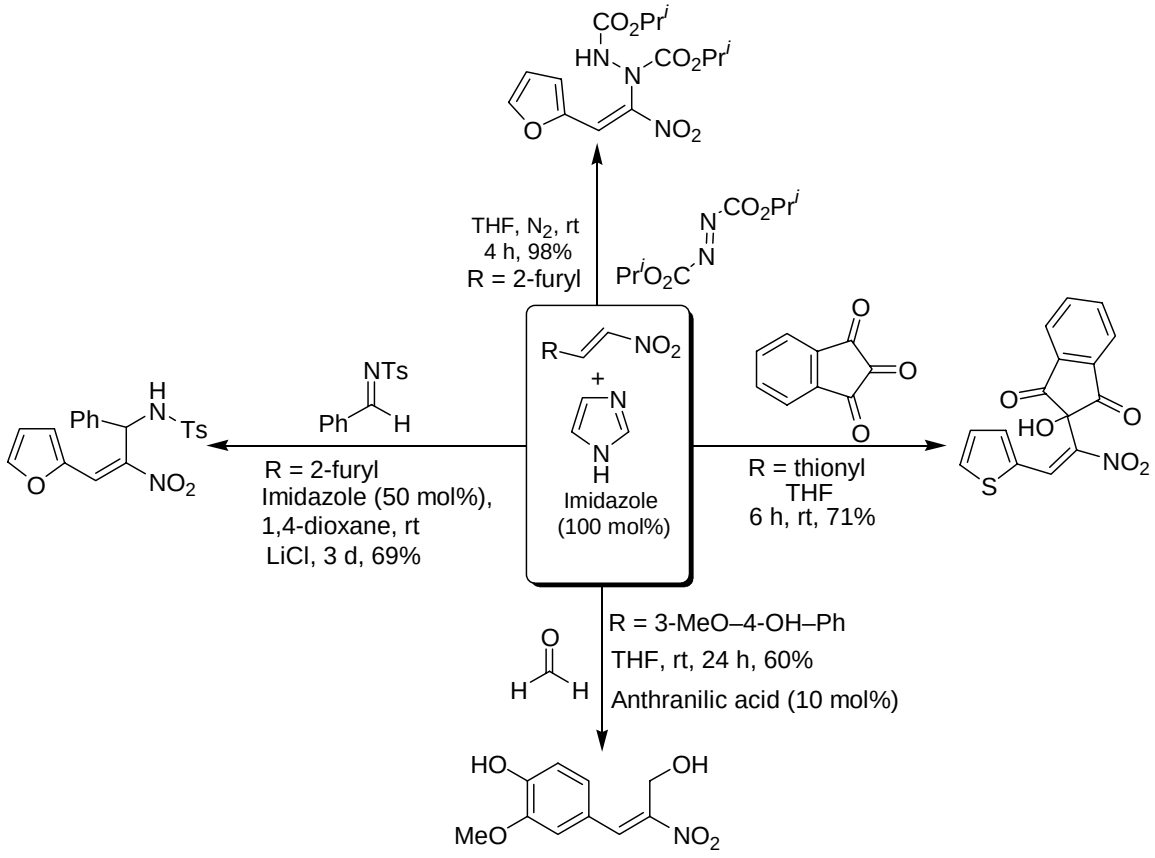
A number of acyclic activated alkenes (Scheme 1) such as alkyl (aryl) acrylates,[20-23] alkyl vinyl ketones,[24-26] acrylonitrile,[24,27] vinyl sulphones,[28] vinyl phosphonates[29] vinyl sulphonates,[30] acrolien[31-33] acrylamides,[34] allenic esters,[35,36] and ethyl sorbate[37] have been successfully employed for coupling with a number of carbon electrophiles to obtain a wide range of densely functionalized molecules, most commonly known as Baylis-Hillman adducts. However, the β-substituent activated olefins, such as, crotononitrile,[38,39] methyl crotonate[38] and less reactive alkenes like phenyl vinyl sulfoxide[40] require high pressure to couple with electrophiles (Scheme 1).

Scheme 1



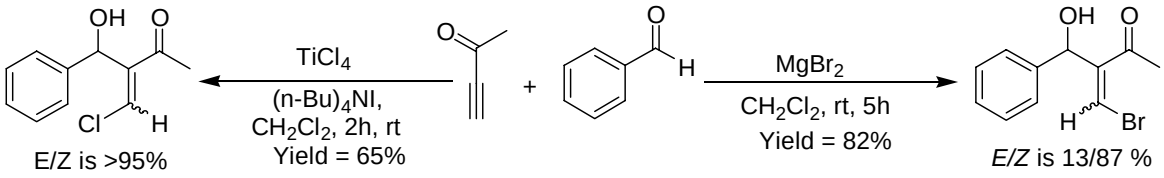
Namboothiri and co-workers[41-44] for the first time, demonstrated conjugated nitroalkenes as useful activated alkenes in the Baylis-Hillman coupling with various electrophiles such as ninhydrin,[41] formaldehyde (formalin),[42] *N*-tosylimines,[43] and diisopropyl azodicarboxylate[44] under the influence of imidazole at room temperature. Representative examples are presented in Scheme 2.

Scheme 2

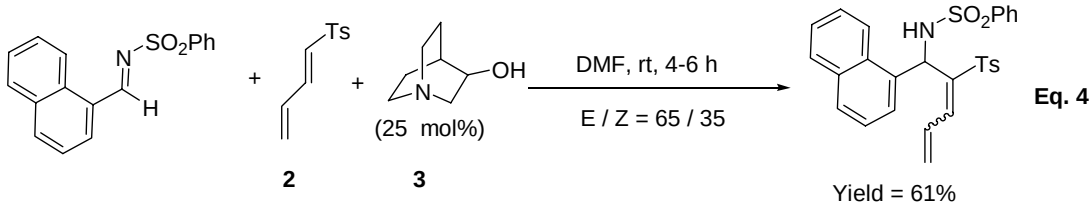


Li and co-workers,[45] and Pare and co-workers[46] independently have reported the synthesis of β-halo-Baylis-Hillman adducts via the treatment of but-3-yn-2-one with aldehydes under the influence of $TiCl_4$ and $MgBr_2$ respectively in CH_2Cl_2 (Scheme 3)

Scheme 3

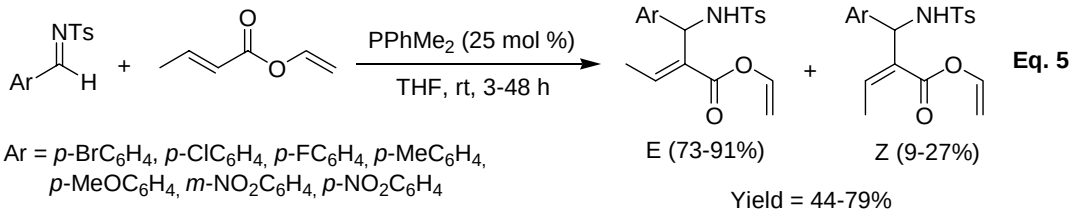


Recently, Back and co-workers[47] reported an interesting Baylis-Hillman reaction between 1-(*p*-toluenesulfonyl)-1,3-butadiene (**2**) and aldimine derivatives in the presence of 3-hydroxyquinuclidine (3-HQD, **3**) to provide the corresponding β-vinyl-Baylis-Hillman adducts. One representative example is given in Eq. 4.



Eq. 4

Shi and co-workers[48] have used vinyl crotonate as activated alkene for coupling with N-tosylimine derivatives under the influence of $PPhMe_2$ in THF at room temperature (Eq. 5).



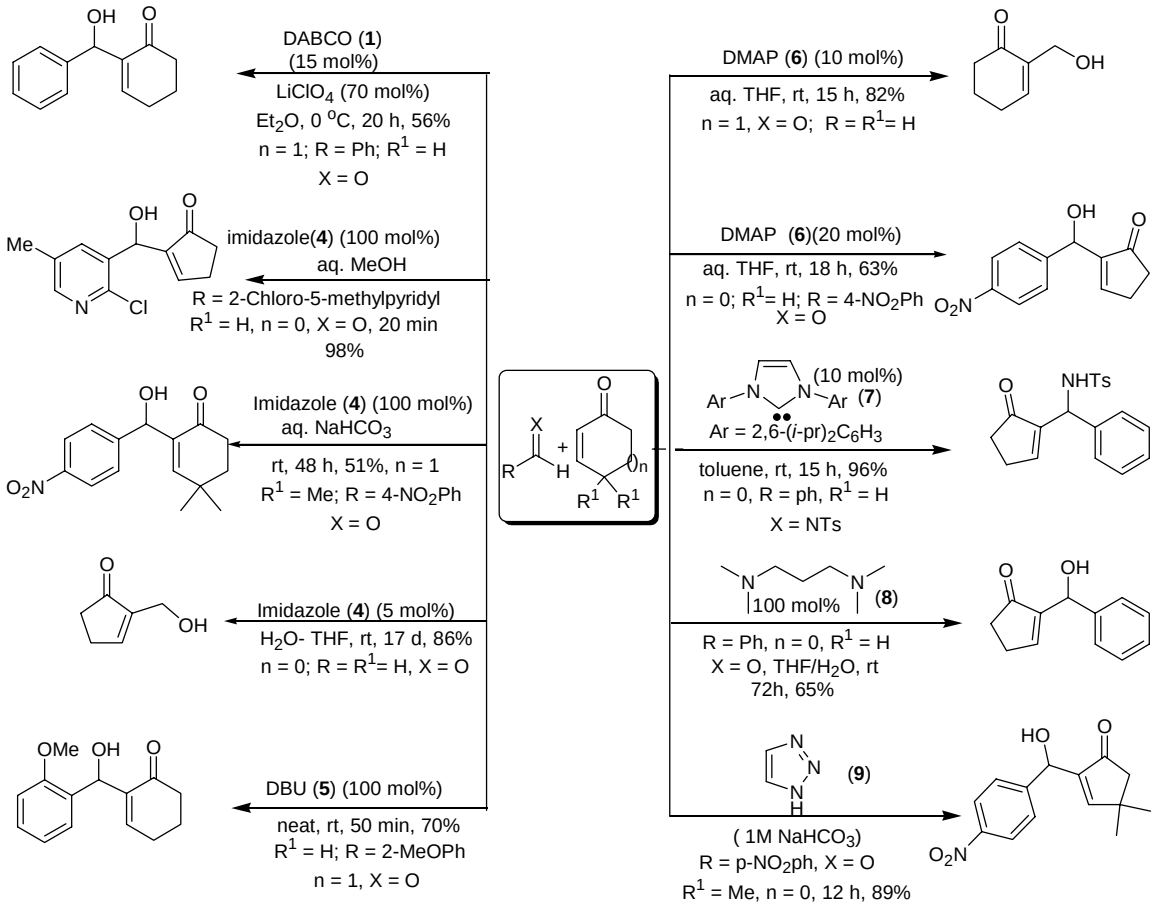
Eq. 5

CYCLIC ACTIVATED ALKENES

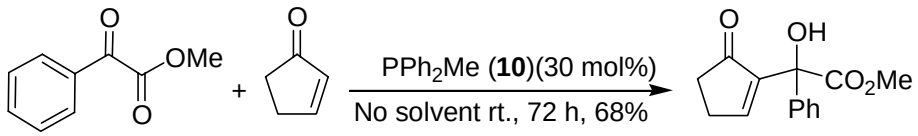
In addition to various acyclic activated alkenes/alkynes several cyclic enones (most commonly cyclopent-2-enone, cyclohex-2-enone and their derivatives) were employed

successfully for Baylis-Hillman coupling with a number of electrophiles in the presence of variety of *tert*-amine catalysts, such as, DABCO (**1**),[35] imidazole (**4**),[49-51] DBU (**5**),[52] DMAP (**6**),[53,54] N-heterocyclic carbenes (**7**) (NHC),[55] TMPDA (**8**)[56] and 1,2,3-triazole (**9**)[57] to provide corresponding multifunctional molecules (Scheme 4).

Scheme 4



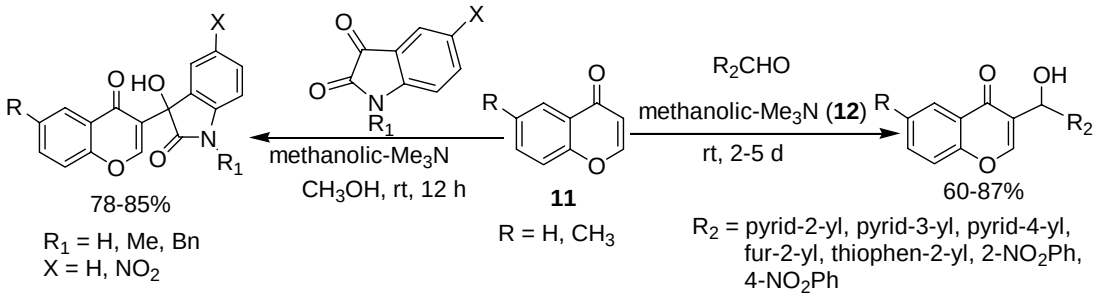
Shi and Zhang[58] reported Baylis-Hillman reaction between the α-keto esters and cyclopent-2-enone in the presence of PPh_2Me (**10**) providing the corresponding adducts. One representative example is presented in Eq. 6.



Eq. 6

Our research group[59] used 1-benzopyran-4(4*H*)-one derivatives (**11**) for the first time, as activated alkenes in the Baylis-Hillman reaction with variety of aldehydes, and isatin derivatives under the influence of methanolic-Me_3N (**12**) to provide the representative Baylis-Hillman adducts, as described in Scheme 5.

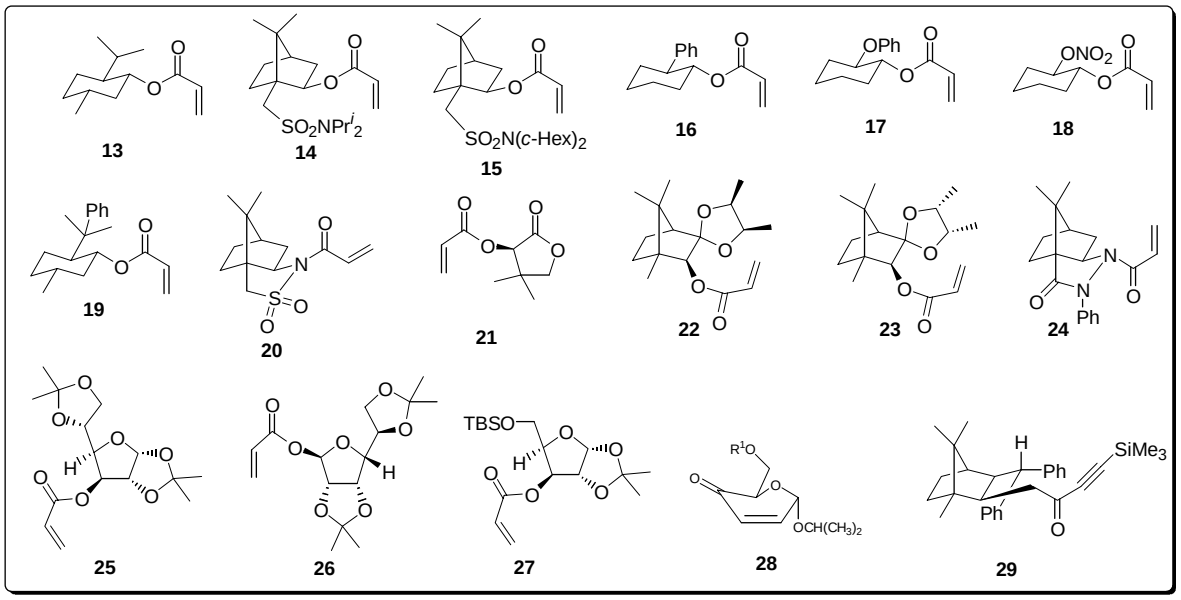
Scheme 5



CHIRAL ACTIVATED ALKENES

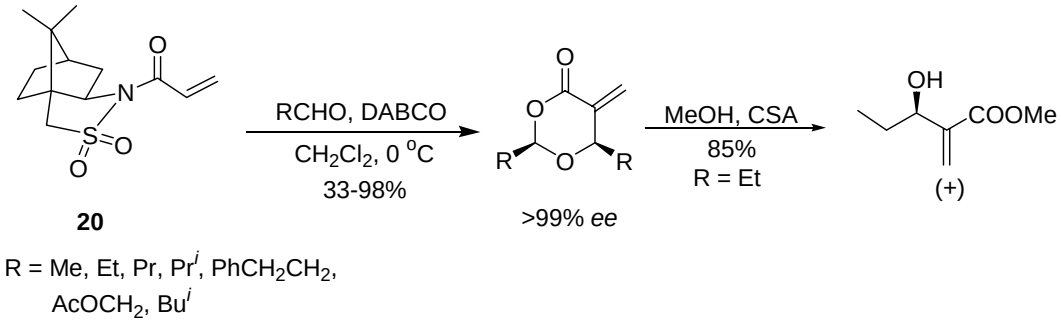
In case of prochiral electrophiles there exits a possibility of achieving high diastereoselectivities if an appropriate chiral activated alkene is used for coupling. Several attempts were in fact made in this direction and various chiral activated alkenes [mostly acrylates (**13-29**) (Figure 1)[60-76] derived from various chiral auxiliaries] were emloyed for coupling with several electrophiles to achieve high diastereoselectivities. Representative examples were described in Schemes 6,7 & Eq. 7.

Figure 1

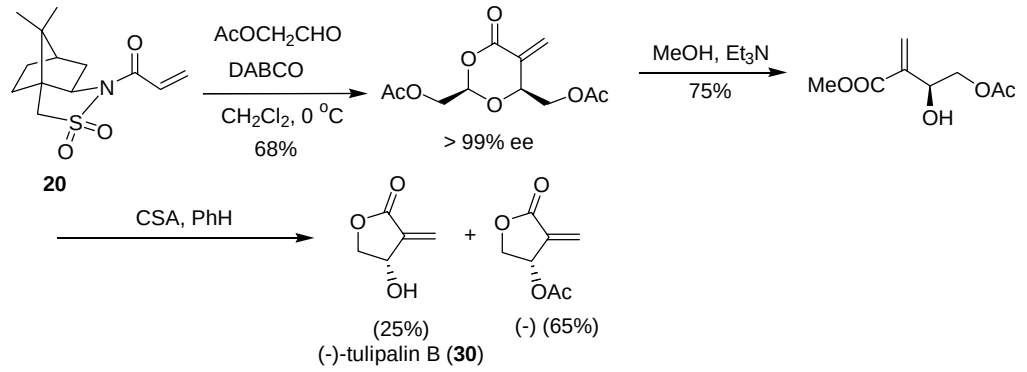


Enantiopure acrylamide (**20**) (derived from camphorsulphonic acid) has been elegantly used by Leahy and co-workers[67,68] for asymmetric Baylis-Hillman reaction to provide the resulting adducts in high diastereoselectivities (Scheme 6). This strategy was also successfully applied for the synthesis of (-)-tulipalin B (**30**), a biologically important natural product following the reaction sequence as shown in Scheme 7.

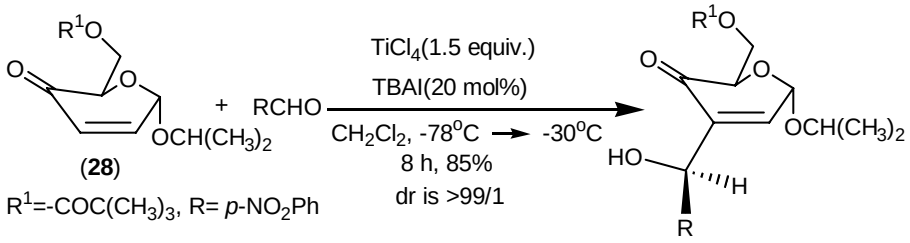
Scheme 6



Scheme 7



Shaw and co-workers[75] have employed the sugar derived chiral activated alkene (**28**) [c(6) acyl protected enuloside] for coupling with various aldehydes in the presence of $TiCl_4$ / TBAI to afford the resulting Baylis-Hillman adducts with very high diastereo-selectivities. One representative example is shown in Eq. 7.



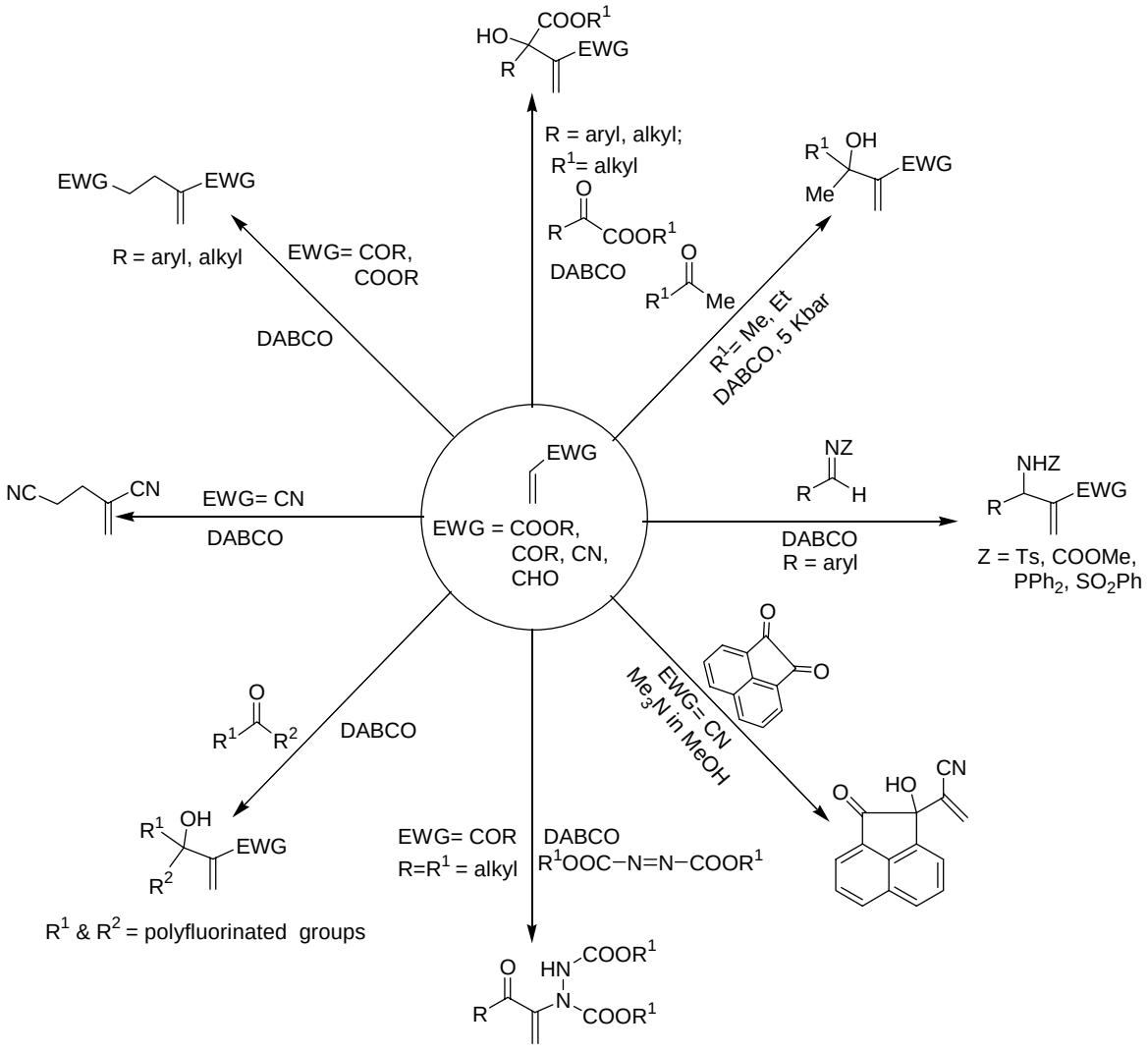
Eq. 7

ELECTROPHILES

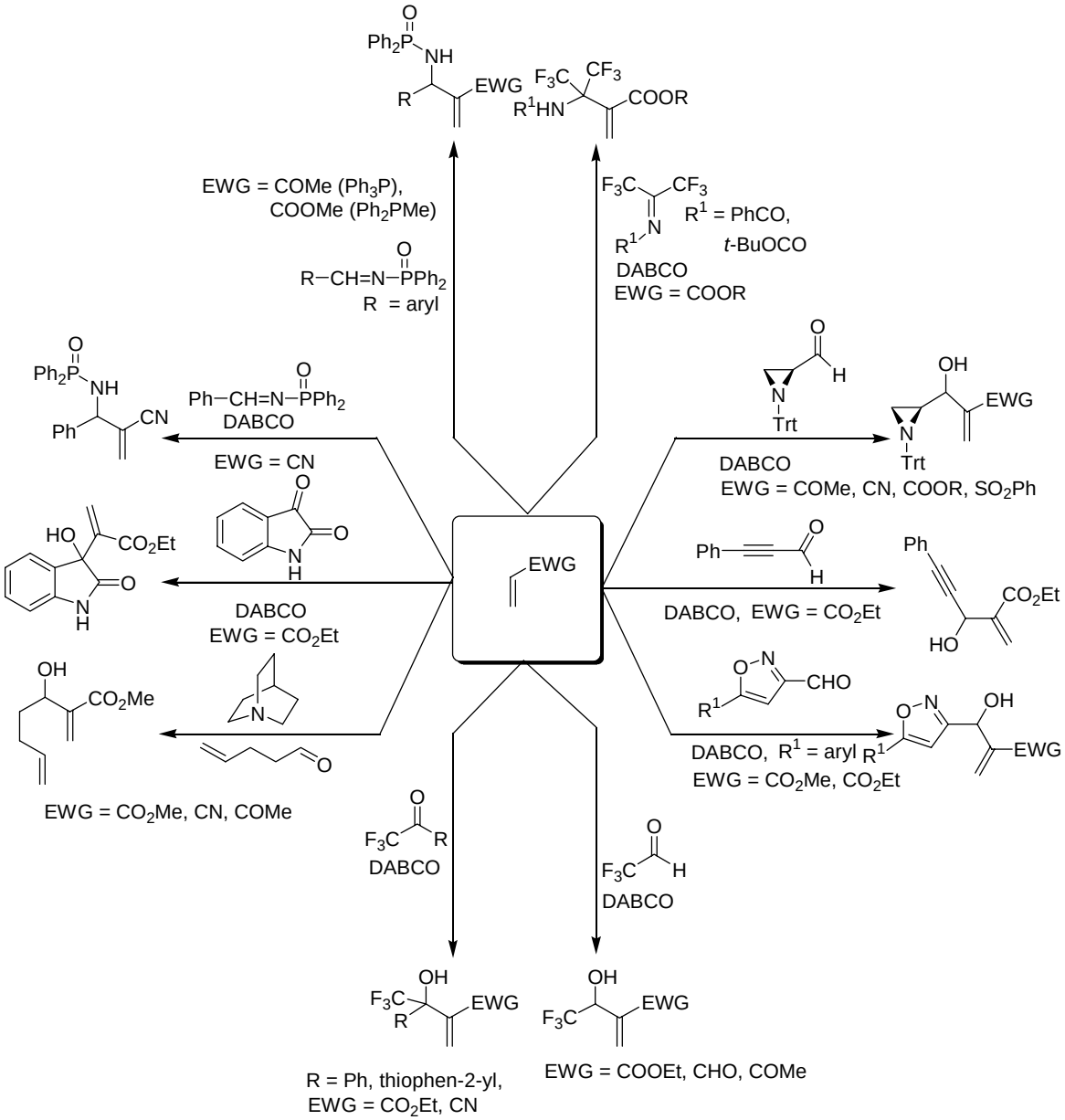
Although aldehydes are the most widely used electrophiles, other carbon electrophiles such as aldimine derivatives,[77-80] non-enolizable 1,2-diketones,[81,82] dialkyl azodicarboxylates (non-carbon electrophile),[83-84] fluoro-ketones,[85] activated alkenes,[86-89] α-keto esters,[90-92] have been utilized successively in this reaction (Scheme 8). Recently, fluoro imines,[93] *N*-tritylaziridine-2-(*S*)-carboxaldehyde,[94] acetylenic aldehydes,[95] 5-isoxazolecarboxaldehydes,[96] fluorinated aldehydes,[97] fluorinated ketones,[98] aliphatic unsaturated aldehydes,[99]

isatin derivatives,[100,101] and *N*-arylidenediphenylphosphinamides,[102] have been successfully employed as electrophiles in Baylis-Hillman reaction (Scheme 9). Less reactive electrophiles (simple ketones)[103] such as propan-2-one and butan-2-one, have been brought into the scope of the reaction under high pressure conditions (Scheme 8).

Scheme 8

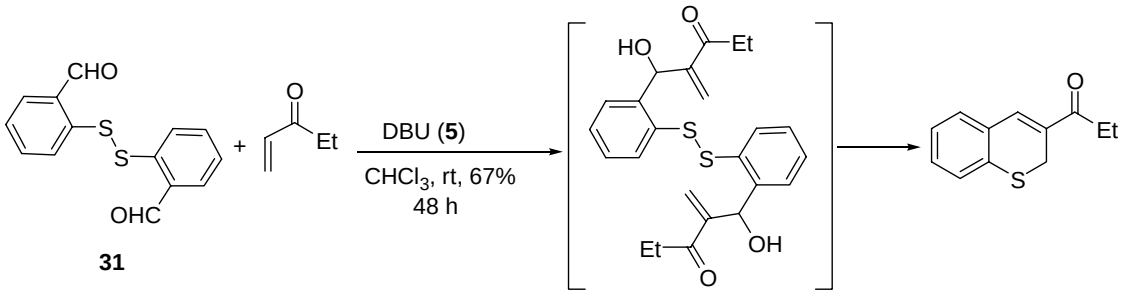


Scheme 9


EWG = COMe (Ph_3P), COOMe (Ph_2PMe)
R−CH=N−PPh_2 O
R = aryl
F_3C CF_3 R^1 = PhCO, *t*-BuOCO
DABCO
EWG = COOR
Ph−CH=N−PPh_2 O
DABCO
EWG = CN
DABCO
EWG = CO_2Et
DABCO, EWG = CO_2Et
DABCO
EWG = COMe, CN, COOR, SO_2Ph
DABCO, R^1 = aryl
EWG = CO_2Me, CN, COMe
EWG = CO_2Me, CN, COMe
DABCO
DABCO
R = Ph, thiophen-2-yl, EWG = CO_2Et, CN
EWG = COOEt, CHO, COMe

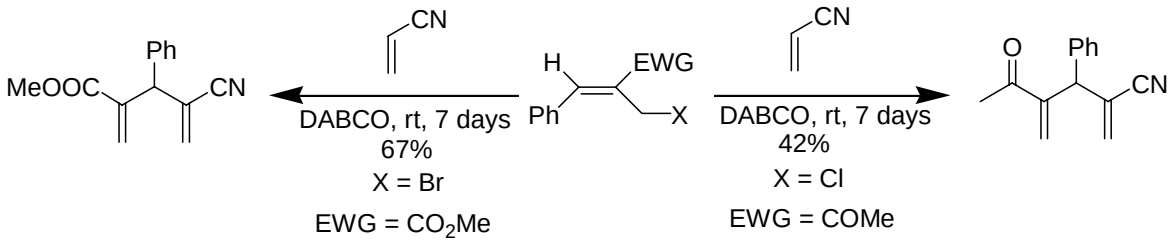
Kaye and Nocanda[104] employed 2,2′-dithiobenzaldehyde (**31**) as an electrophile for Baylis-Hillman coupling with activated alkenes in the presence of DBU, to provide benzothiopyran derivatives. One representative example is presented in the Scheme 10.

Scheme 10



Recently our research group[105a] has described for the first time, the application of (*Z*)-allyl halides (obtained from the Baylis-Hillman adducts), as suitable electrophiles in the Baylis-Hillman coupling with activated alkenes, to produce the 3-substituted 2,4-functionalized 1,4-pentadienes. One representative example is presented in Scheme 11.

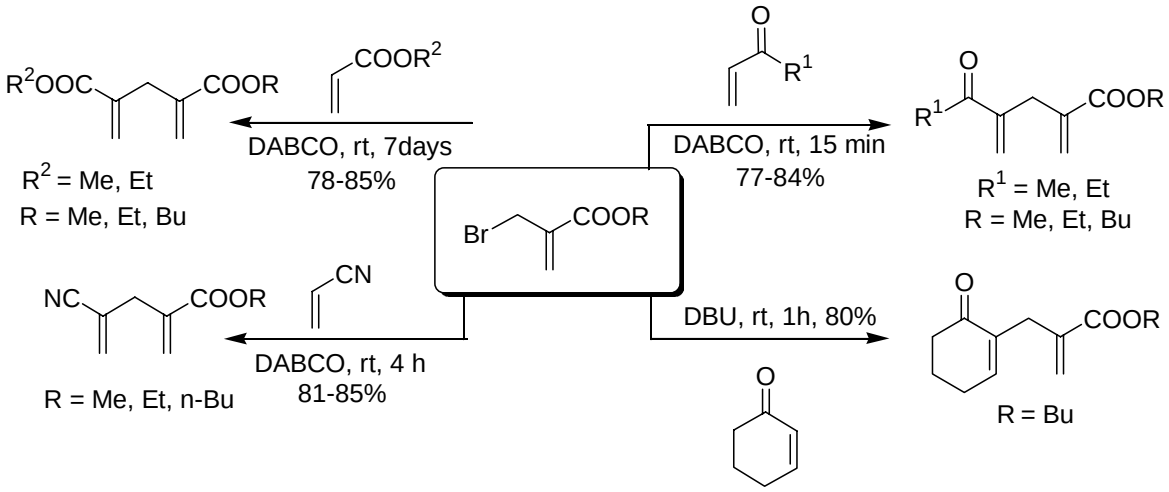
Scheme 11



Subsequently, our research group[105b] also developed a simple synthesis of a variety of 2,4-functionalized 1,4-pentadienes *via* the Baylis-Hillman reaction of the allyl bromides,

derived from alkyl 3-hydroxy-2-methylenepropanoates, as electrophiles, with alkyl acrylates, alkyl vinyl ketones and acrylonitrile (scheme 12).

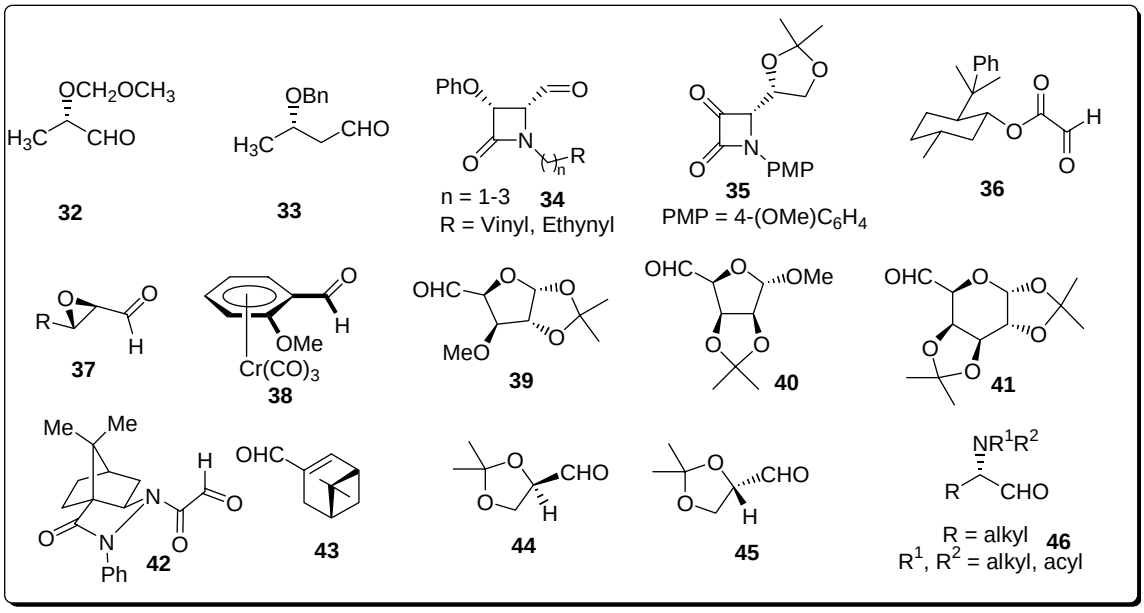
Scheme 12



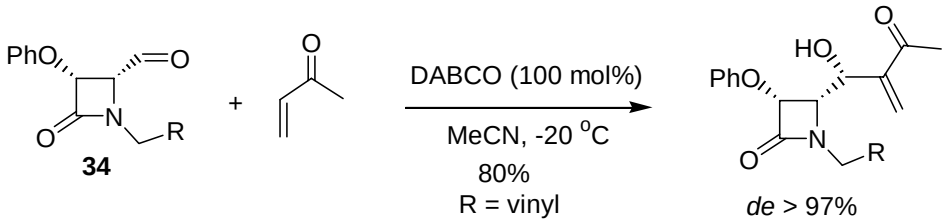
CHIRAL ELECTROPHILES

A number of enantiopure electrophiles such as (*S*)-*O*-protected lactaldehyde (**32**),[106] (*S*)-3-benzyloxybutyraldehyde (**33**),[107] 1-alkenyl- or alkynyl 4-oxoazetidine-2-carbaldehydes (**34**),[108] 3-oxo-2-azetidinones (**35**),[109] (−)-8-phenylmenthyl glyoxylate (**36**),[110] chiral 2,3-epoxy aldehydes (**37**),[111] *ortho* substituted benzaldehyde tricarbonylchromium complex (**38**),[112,113] sugar derived aldehydes (**39-41**),[114-115] *N*-glyoxyloylcamphorpyrazolidinone (**42**),[116] (*R*)-myrtenal (**43**),[61] isopropylidene (*R*)-, (S)-glyceraldehyde (**44, 45**),[61] α-dialky-lamino and α-(*N*-acylamino)aldehydes (**46**),[117] have been used for Baylis-Hillman coupling with several activated alkenes in the presence of suitable catalyst (Figure 2). The resulting products were obtained in low to good diastereoselectivities. Representative examples are presented in Eqs. 8-10.

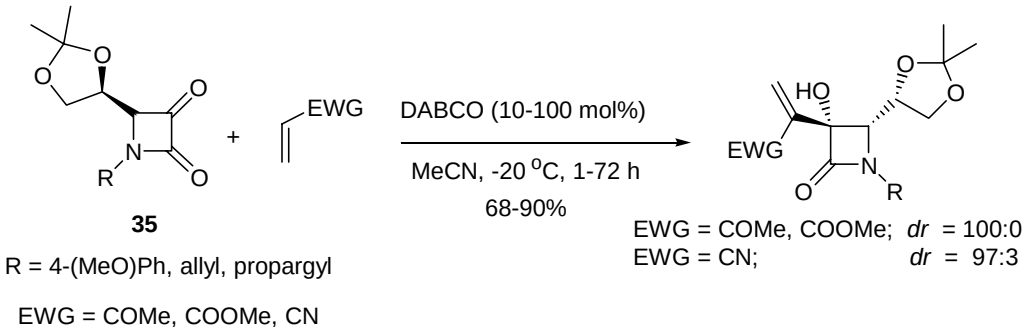
Figure 2



Recently, Alcaide and co-workers[108] have successfully utilized enantiopure 1-alkenyl(alkynyl)-4-oxoazetidine-2-carbaldehydes (**34**) as chiral electrophiles in the Baylis-Hillman reaction with MVK, which provided the Baylis-Hillman adducts with high diastereoselectivities (Eq 8). They have also successfully employed optically pure 3-oxo-2-azetidinones (**35**) for coupling with activated alkenes under the influence of DABCO to provide the resulting Baylis-Hillman adducts in high diastereoselectivities (Eq. 9).[109]



Eq. 8



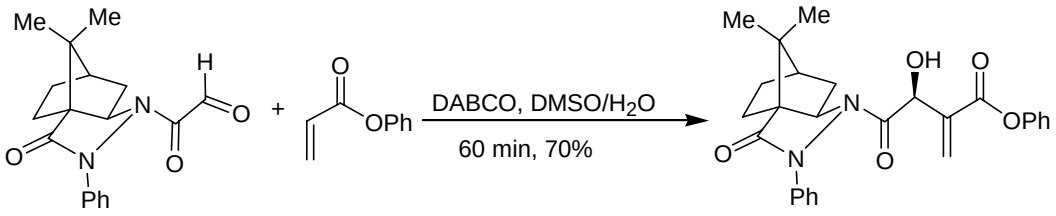
35

R = 4-(MeO)Ph, allyl, propargyl

EWG = COMe, COOMe, CN

Eq. 9

Chen and co-workers[116] have reported a highly diastereoselective Baylis-Hillman reaction using camphorpyrazolidinone derived N-glyoxylate (**42**) as electrophile for coupling with activated alkenes in the presence of DABCO. One representative example is presented in the Eq. 10.



42

dr >95:5

Eq. 10

CATALYSTS/CATALYTIC SYSTEMS

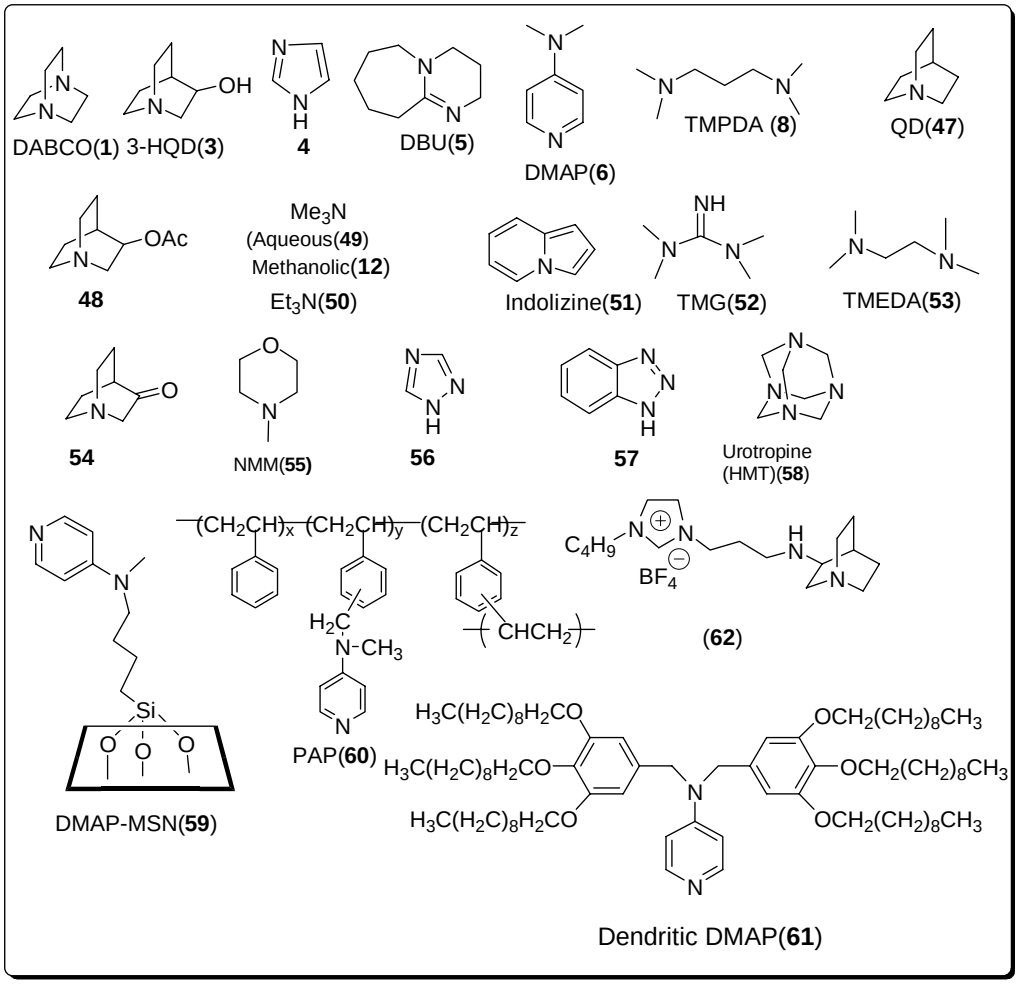
During the last two decades a large variety of both amine based catalysts, and non-amine based catalysts have been successfully employed to catalyze or promote the Baylis-Hillman reaction. Some of these interesting developments are presented in this section.

TERTIARY AMINE CATALYSTS

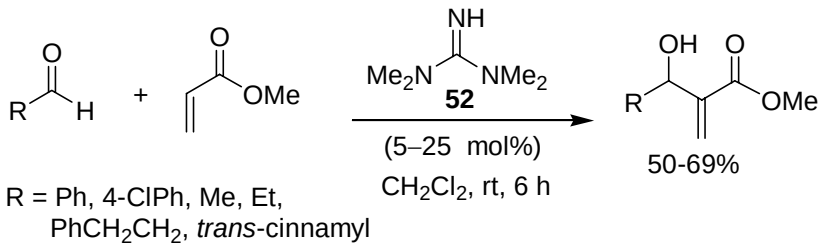
Although DABCO [12,118] has been the most frequently used catalyst in this reaction, various other tertiary amines such as, quinuclidine (**47**),[12,118] 3-hydroxyquinuclidine (**3**),[118,119] imidazole (**4**),[49,50,120], DBU (**5**),[52] DMAP (**6**),[53,54] TMPDA (**8**),[56] methanolic-Me_3N (**12**),[59,82,121] 3-acetoxyquinuclidine (**48**),[118,119] aqueous-Me_3N (**49**),[122] Et_3N (**50**),[103]

indolizine (**51**),[7] TMG (**52**),[123,124] TMEDA (**53**),[125] 3-quinuclidinone (**54**),[118] NMM (**55**),[126] 1,2,4-triazole(**56**),[57] benzotriazole(**57**),[57] and HMT (**58**)[127] have been employed in various Baylis-Hillman reactions. Recently polymer supported DMAP derivatives, like DMAP-MSN [meso-porous silica nano-sphere (**59**)],[128] PAP[4-(*N*-benzyl-*N*-methylamino)pyridine] (**60**),[129] dendritic DMAP {*N*,*N*-di[3', 4', 5'-tri(1-decyloxy)benzyl]-4-aminopyridine }(**61**)[130] and also quinuclidine containing ionic liquid (**62**), (Figure 3) have been successfully employed in certain Baylis-Hillman reactions. Some recent examples using these catalysts have been presented in Eq. 11,12 & scheme 13.

Figure 3

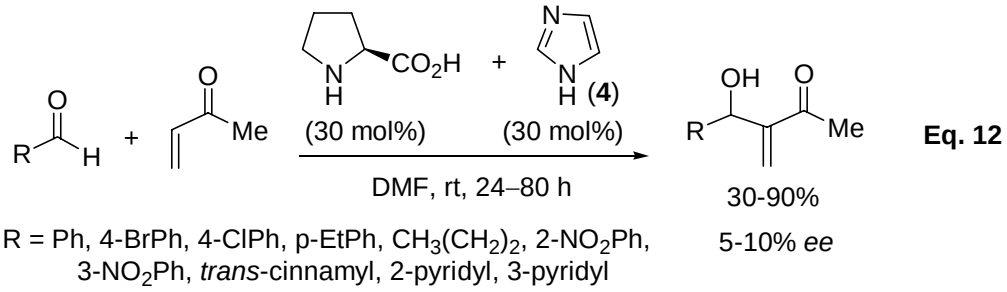


Leadbeater and co-workers[123] have reported for the first time, tetramethylguanidine (TMG, **52**) mediated Baylis-Hillman reaction between aldehydes as electrophiles and methyl acrylate as activated alkene (Eq. 11).



Eq. 11

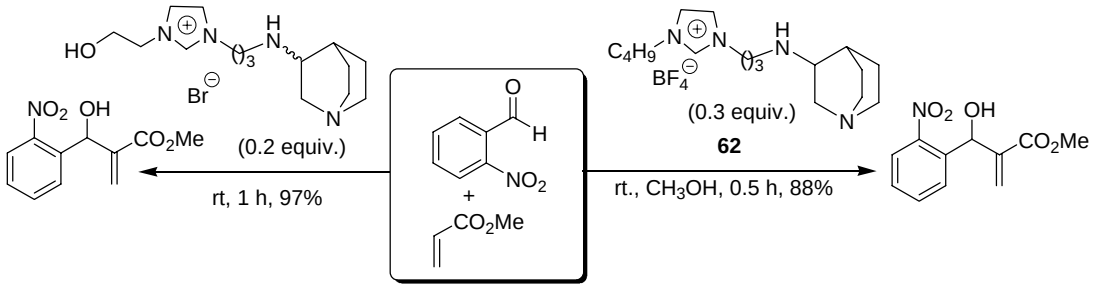
Shi and co-workers[120] have reported proline catalyzed Baylis–Hillman reaction between various aldehydes and MVK in the presence of a weak base such as imidazole (**4**). However, the enantioselectivities obtained in these reactions were found to be very low (Eq. 12)



Eq. 12

Cheng and co-workers[131,132] recently described interesting ionic liquid based quinuclidines as catalysts in the Baylis-Hillman reaction between activated alkene and electrophiles. Reprersentative examples are described in Scheme 13.

Scheme 13

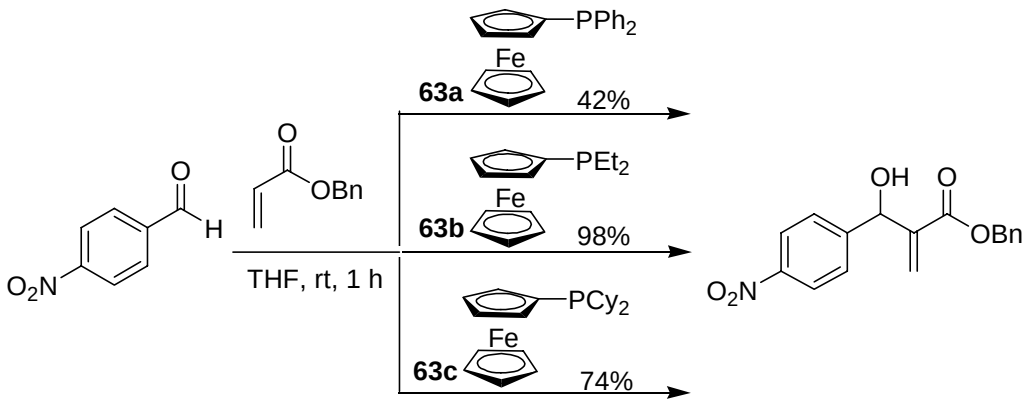


NON-AMINE CATALYZED/MEDIATED BAYLIS-HILLMAN REACTIONS

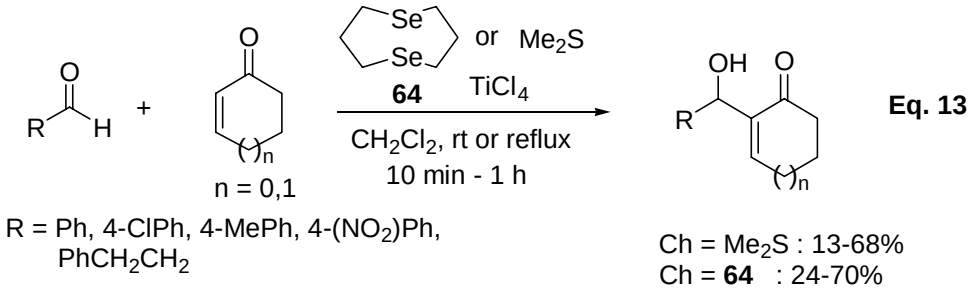
Literature survey indicates that several non-amine catalysts such as phosphines (both alkyl and aryl)[133-136] and metal complexes like $RhH(PPh_3)_4$,[137,138] $RuH_2(PPh_3)_4$,[138,139] have been also employed for coupling of activated alkenes with electrophiles such as aldehydes to provide the desired coupling adducts. In addition to amine and phosphine catalysts certain Lewis acid based reagents like $R_2S–TiCl_4$,[12,140-143] R_2XBF_3 (X = O, S),[12,144-146] , $TiCl_4$-NR_4X (X = halide),[12,147,148] $TiCl_4$-NR_3,[149] $TiCl_4$,[150] Et_2AlI,[151,152] MgI_2,[153] $MgBr_2$[46] were also successfully employed for performing the Baylis-Hillman (type) reactions.

Carretero and coworkers[154] have used air stable ferrocenyldialkylphosphines (**63a-c**) for Baylis-Hillman reaction between aldehydes and acrylates to afford the corresponding adducts in high yields at faster reaction rate (Scheme 14).

Scheme 14

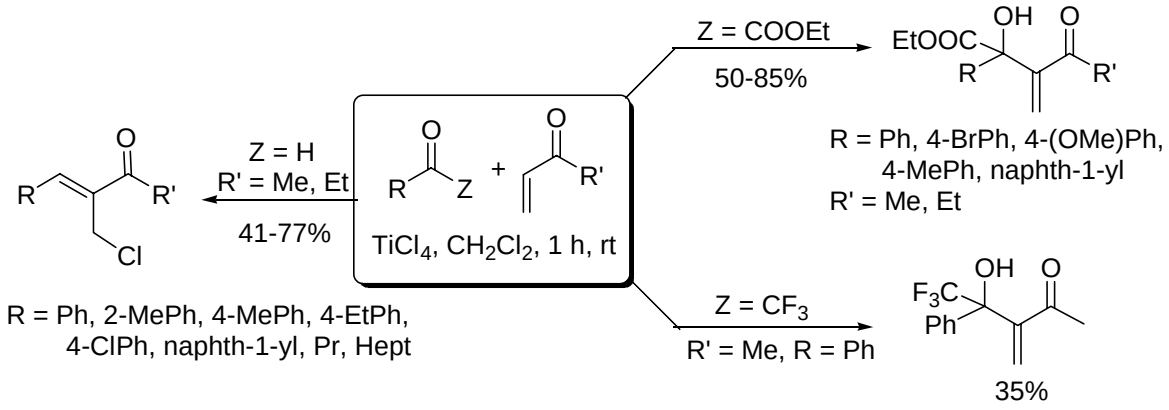


Kataoka and coworkers [140, 141] have developed an interesting chalcogenide [sulfides or selinides] catalyzed Baylis-Hillman coupling of vinyl ketones with various aldehydes in the presence of $TiCl_4$ as a Lewis acid to give the corresponding Baylis-Hillman adducts. Representative examples are presented in Eq. 13



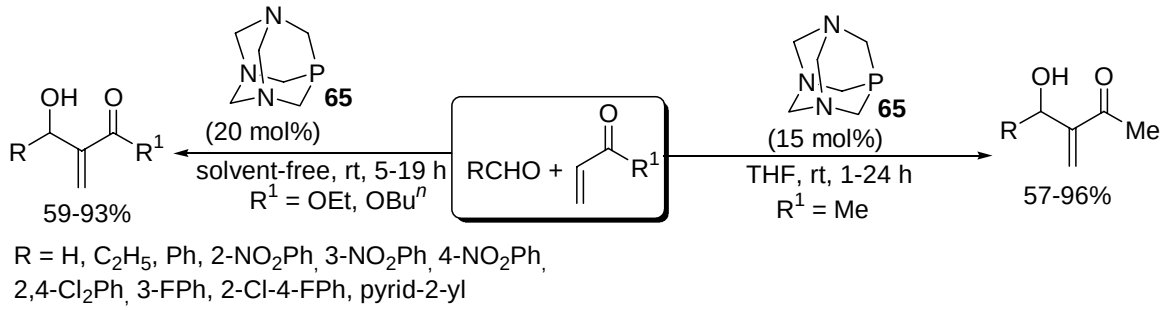
Our research group[155] reported $TiCl_4$-promoted Baylis-Hillman coupling of α-keto esters and trifluoromethyl phenyl ketone with alkyl vinyl ketones to provide the desired adducts in moderate to good yields (Scheme 15). Similar reaction with aldehydes provided (*Z*)-allyl chlorides (Scheme 15).

Scheme 15

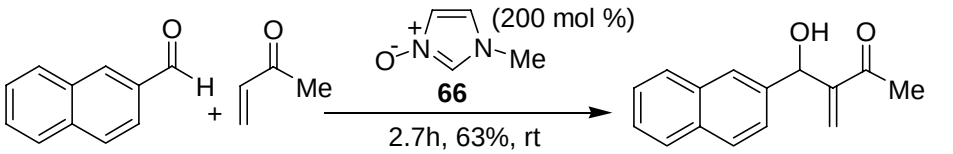


He and coworkers[156] have employed 1,3,5-triaza-7-phosphadamantane (**65**, PTA), (an air-stable nucleophilic trialkylphosphine) as an efficient catalyst for the Baylis-Hillman coupling of activated alkenes with various aldehydes (Scheme 16).

Scheme 16



Tsai and co-workers[157] have successfully carried out solvent free Baylis-Hillman reaction of various aldehydes with methyl vinyl ketone and methyl acrylate in the presence of 1-methylimidazole 3-N-oxide (**66**). One representative example is presented in the Eq. 14

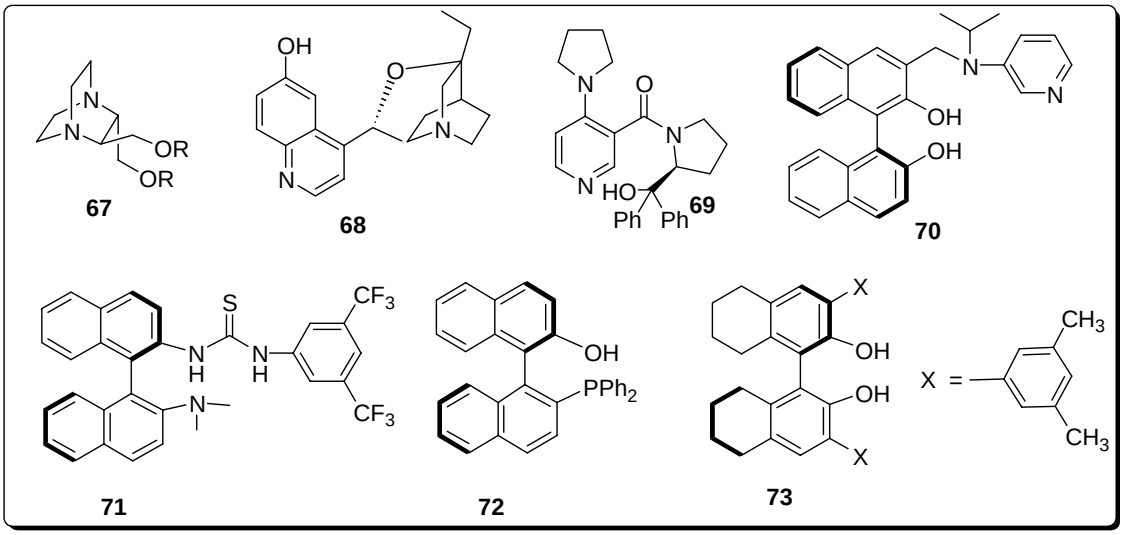


Eq. 14

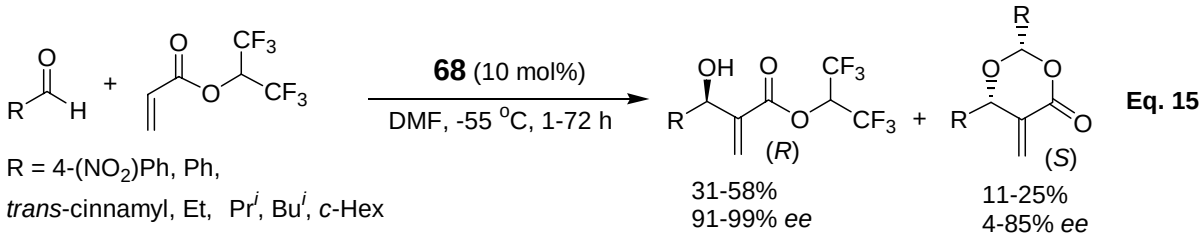
CHIRAL CATALYSTS

Efforts have been made towards developing asymmetric version of Baylis-Hillman reaction using various chiral catalysts. Some of the important tertiary amine based chiral catalysts [chiral DABCO (**67**),[158,159] quinidine based cataslyst (**68**),[160] and DMAP bifunctional chiral catalysts (**69**)[161], binaphthyl based bifunctional catalysts (**70**, **71**, **72**)[162,163,164]] are listed in Figure. 4. Some recent and relevant examples are presented in Eqs. 15,16 & scheme 17.

Figure 4



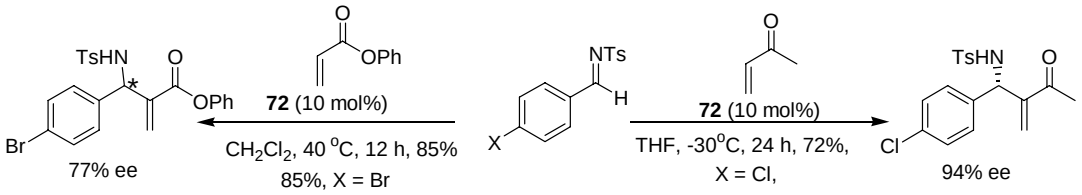
Hatakeyama and co-workers[160] have developed a highly enantioselective Baylis-Hillman reaction of 1,1,1,3,3,3-hexafluoroisopropyl acrylate with various aromatic and aliphatic aldehydes using the catalyst (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6'-hydroxy-cinchonane **(68)**. Representative examples are presented in the Eq. 15.



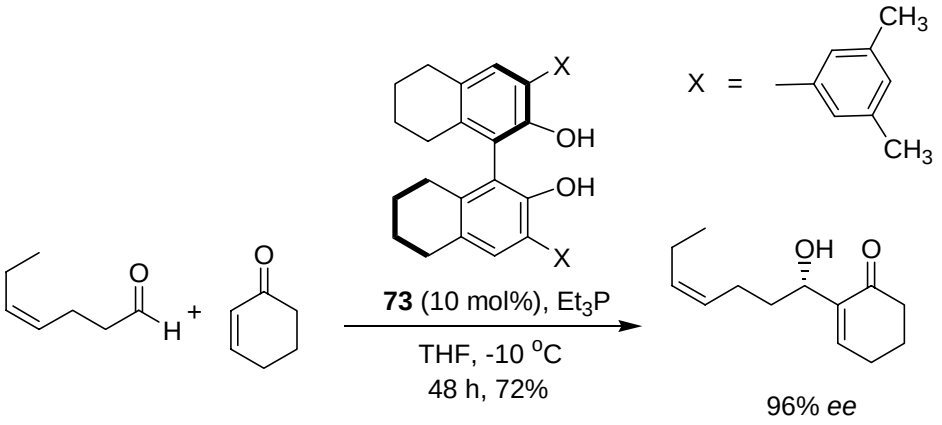
Eq. 15

Shi and co-workers[164] successfully employed (*R*)-2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-ol (**72**) as chiral catalylst in the asymmetric Baylis-Hillman coupling of *N*-tosylated imines of aromatic aldehydes with activated alkenes such as methyl vinyl ketone, phenyl acrylate to provide the resulting adducts in high enantioselectivities.(Scheme 17)

Scheme 17



Highly enantioselective Baylis-Hillman reaction using chiral tetrahydro-BINOL-derived Brønsted acids as cocatalyst along with triethyl phosphine as catalyst, was reported by Schaus and Mc Dougal.[165] One representative example is presented in the Eq. 16.

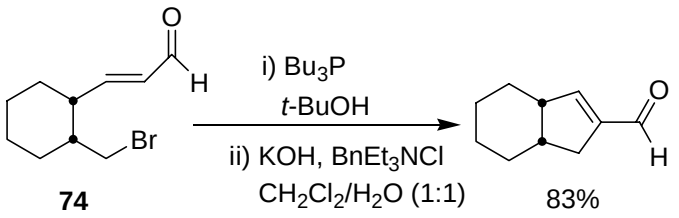


Eq. 16

INTRAMOLECULAR BAYLIS-HILLMAN REACTION

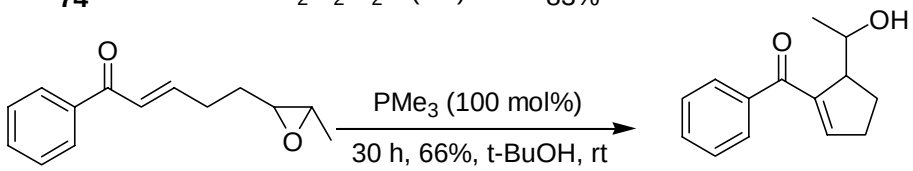
If the substrate contains both the activated alkene moiety and elctrophile component there exits a possibility of performing intramolecular Baylis-Hillman reactions under appropriate catalytic conditions. Though this aspect did not receive the expected attention in the initial years, it has attracted increased attention from the leading organic chemists in recent years. Some of the interesting developments in this direction are presented in this section.

Krafft and co-workers[166,167] reported a phosphine induced intramolecular Baylis-Hillman reaction of enone-halides to provide carbocyclic systems (one interesting example is shown in Eq. 17). Krafft also used enone-epoxides system for intramolecular Baylis-Hillman reaction (one representative example is shown in the Eq. 18).



74

Eq. 17

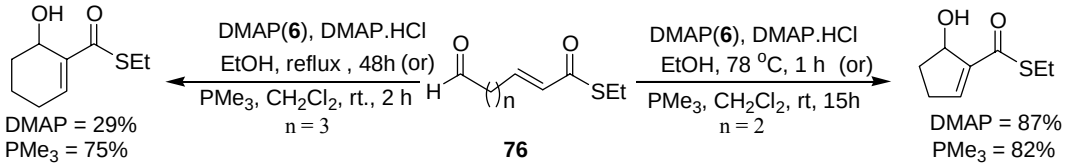


75

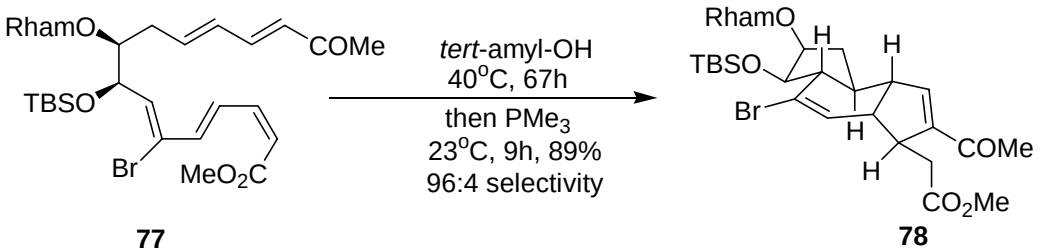
Eq. 18

Keck and Welch[168] have reported intramolecular Baylis-Hillman reaction of thioacrylate-aldehyde frameworks to provide cyclopentene and hexene ring systems (Scheme 18)

Scheme 18



Roush and co-workers[169] have developed a simple method for synthesis of spinosyn A tricyclic framework via tandem intramolecular Diels-Alder and intramolecular Baylis-Hillman rections as shown in Eq. 19

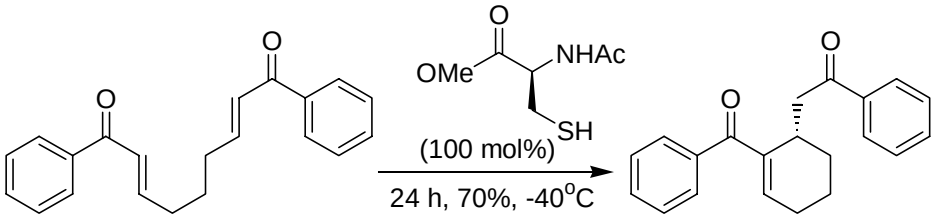


77

78

Eq. 19

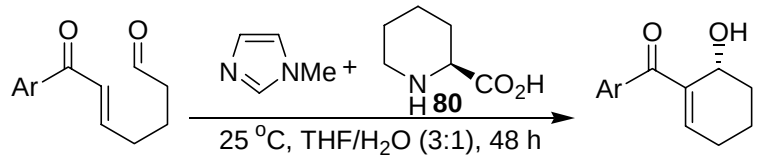
Miller and Aroyan[170] have reported highly enantioselective version of intramolecular Baylis-Hillman reaction of enone-enone frameworks under the influence of aminothiol catalyst as described in Eq 20.



79

Eq. 20

Chiral pipecolinic acid (**80**) has been successfully used as a cocatalyst in the presence of N-methylimidazole for asymmetric intramolecular Baylis-Hillman reaction of enone-aldehyde frameworks by Miller and co-workers (Eq.21).[171]



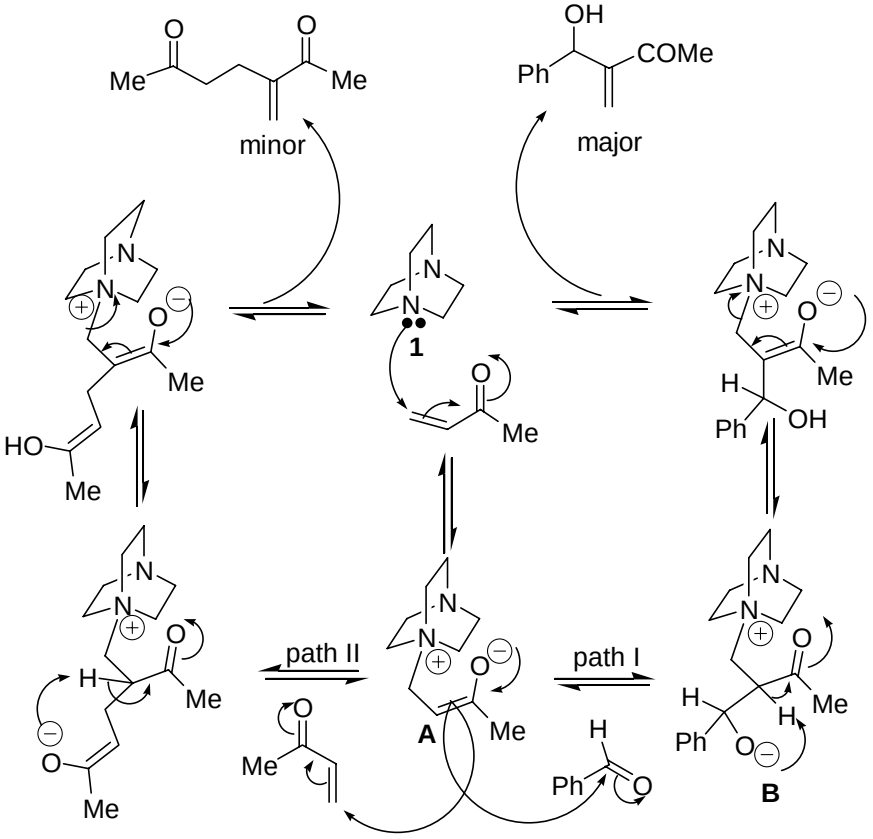
Ar = Ph, 4-ClPh, 4-BrPh, 2-MePh, 2-thionyl

Eq. 21

MECHANISM:

The most widely accepted mechanism[172-180] of the Baylis-Hillman reaction has been presented taking the reaction between methyl vinyl ketone (as an activated olefin) and benzaldehyde (as an electrophile) under the catalytic influence of DABCO (**1**) (as a catalyst), as a model case in the Scheme 19.

Scheme 19



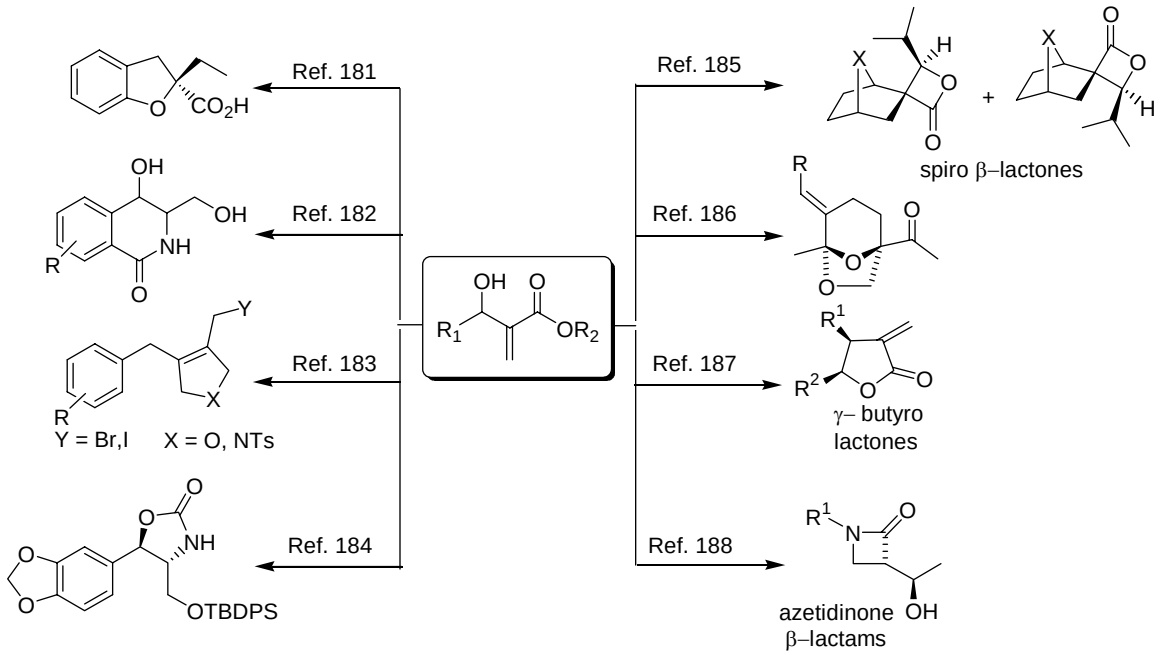
This catalytic cycle is believed to proceed through first the Michael and then aldol reactions involving the addition-elimination sequence. Thus, the first step of this catalytic cycle might involve the Michael type nucleophilic addition of DABCO to methyl vinyl ketone to generate a zwitterionic enolate **A**. This enolate **A** then makes a nucleophilic attack onto the aldehyde leading to the formation of zwitterion **B** (Path I), Subsequent proton migration followed by the release of catalyst provides highly functionalized molecules. In the case of reactive activated alkenes (such as alkyl vinyl ketones), Michael type dimers are formed as side products because these vinyl ketones themselves act as electrophiles.

APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCTS

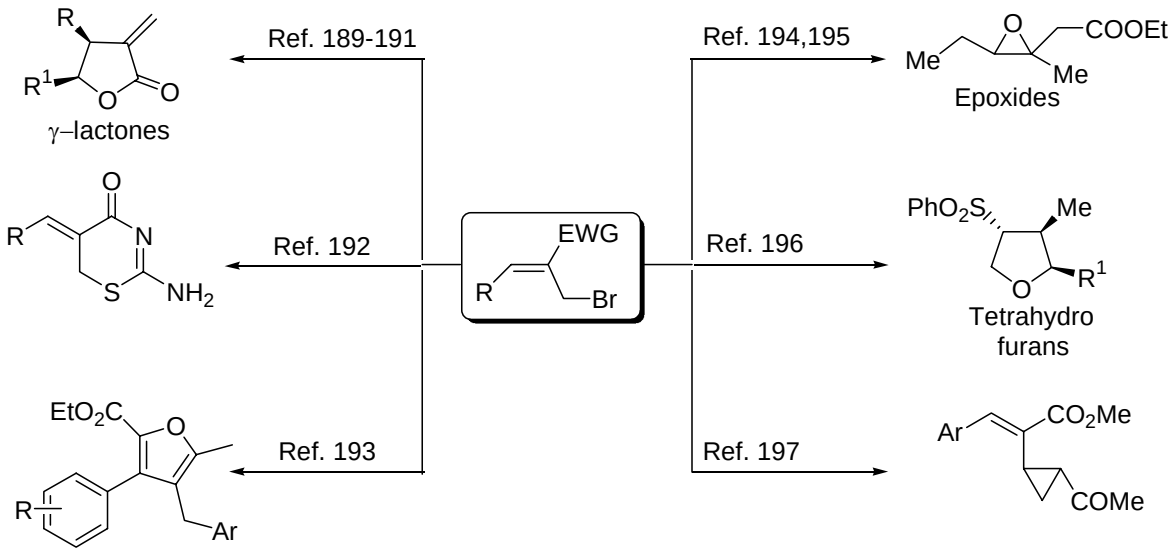
Baylis-Hillman adducts have attracted the attention of organic chemists, due to the presence of three chemospecific functional groups such as hydroxyl (or amino), olefin and electron withdrawing groups in proximity. Various organic transformation methodologies have been developed using these adducts. These adducts have also been used as valuable synthons for the synthesis of trisubstituted olefins, heterocycles, carbocycles, biologically active molecules and natural products.[9-19] Some of the recent and relevant applications of the Baylis-Hillman adducts have been presented in this section

Baylis-Hillman alcohols, bromides and acetates have been used for synthesis of various hetrocyclic and carbocyclic frameworks. Some of the important applications are presented in Schemes (20-22)[181-188,189-197,19,198-204]

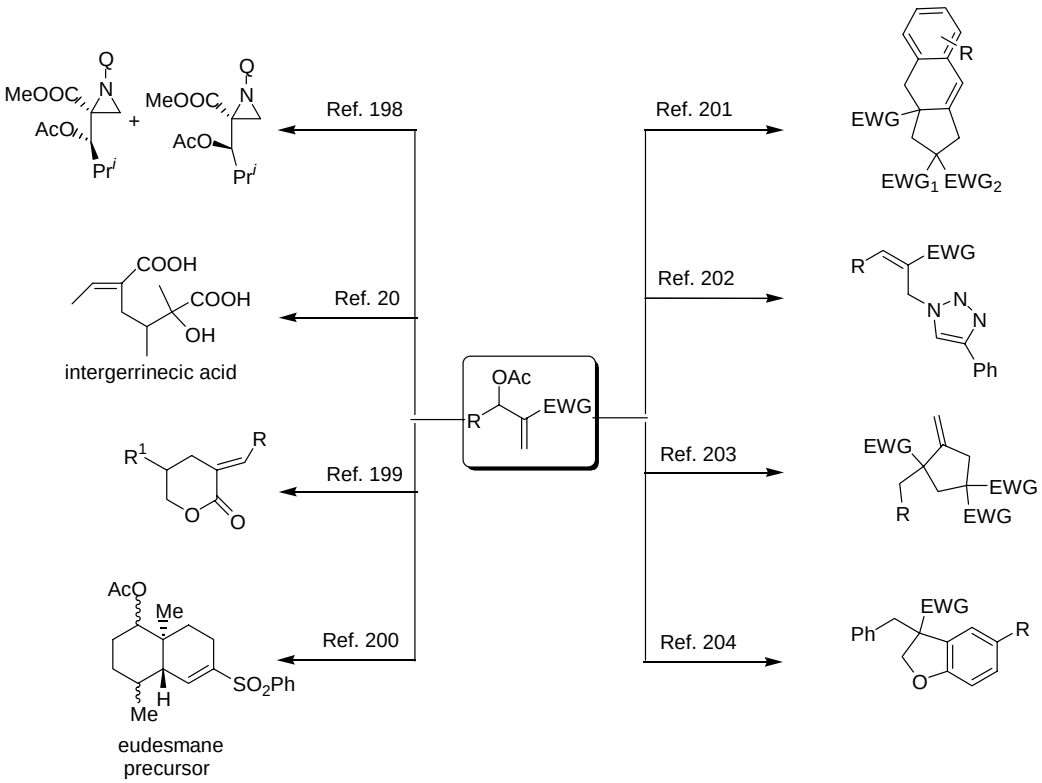
Scheme 20



Scheme 21

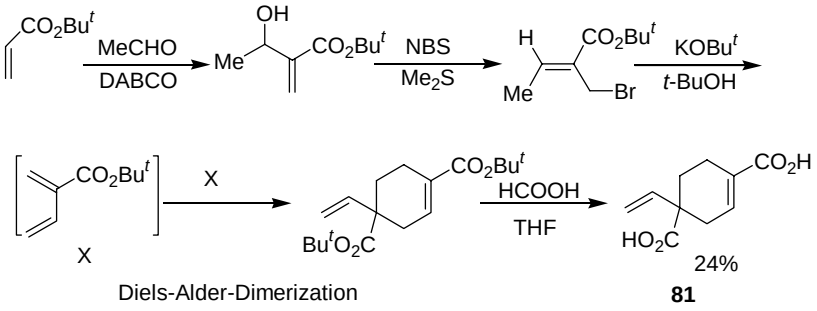


Scheme 22



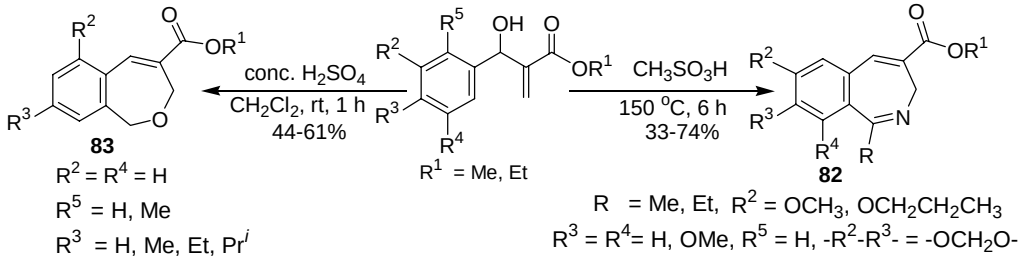
Hoffmann and Rabe[205] described an ingenious synthesis of racemic mikanecic acid (**81**) from the allyl bromide derived from the Baylis-Hillman adduct (prepared from acetaldehyde and *tert.*butyl acrylate) following the reaction sequence as shown in Scheme 23.

Scheme 23



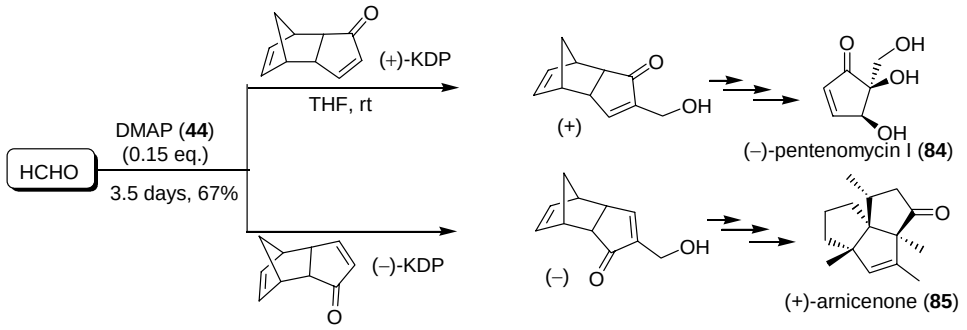
Recently our group has reported one-pot transformation of Baylis-Hillman alcohols into 2-benzazepines *via* the tandem construction of C-N and C-C bonds involving simultaneous Ritter and Houben-Hoesch reactions as described in Scheme 24.[206] Subsequently our research group has also developed a novel one-pot synthesis of 2-benzoxepines via the treatment of the Baylis-Hillman alcohols with formaldehyde in the presence of H_2SO_4 involving tandem construction of C-O and C-C bonds as described in the scheme 24.[207]

Scheme 24



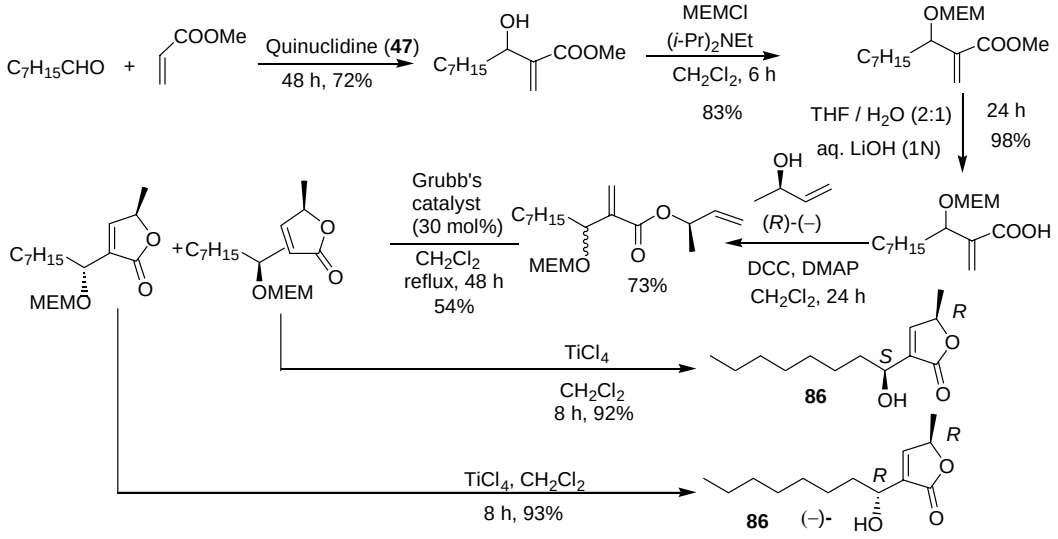
Ogasawara and co-workers have reported an elegant synthesis of cyclopentenoid antibiotic (–)-pentenomycin I (**84**)[208] and angular triquinane sesquiterpene, (+)-arnicenone (**85**),[209] isolated from *Arnica* plants, using the Baylis–Hillman adducts obtained via the coupling of chiral bicyclic enones (+)- & (–)-**KDP** with formalin under the influence of DMAP, as the key starting material (Scheme 25).

Scheme 25



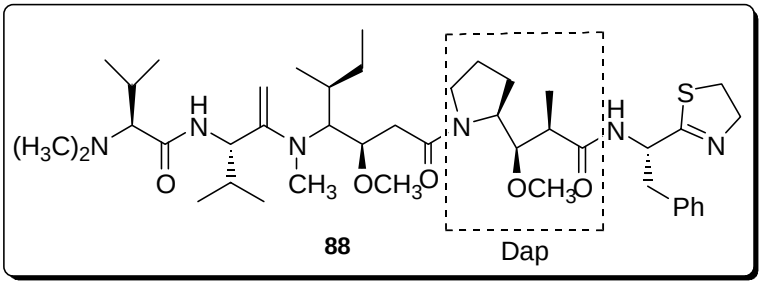
Singh and co-workers[210] have reported short synthesis of (-)-acaterin (**86**) (and its diastereo-mer), a biologically important natural product from the Baylis-Hillman adduct, derived from octanal and methyl acrylate, following the reaction sequence presented in Scheme 26.

Scheme 26

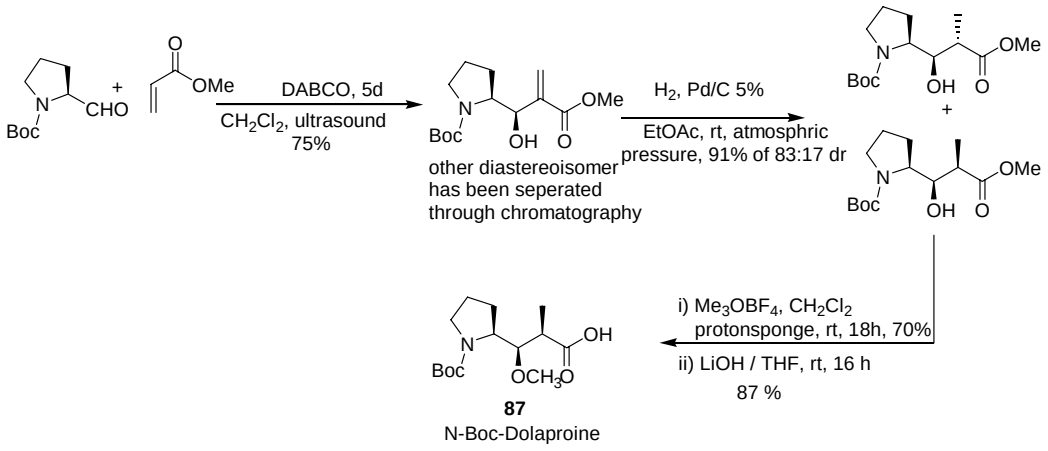


Coelho and co-workers[211] reported a stereoselective total synthesis of *N*-Boc-dolaproine (**87**) (Dap), an amino acid residue of the antineoplastic pentapeptide Dolastatin 10 (**88**), by employing the Baylis-Hillman reaction as one of the key steps according to the Scheme 27, Figure 5.

Figure 5

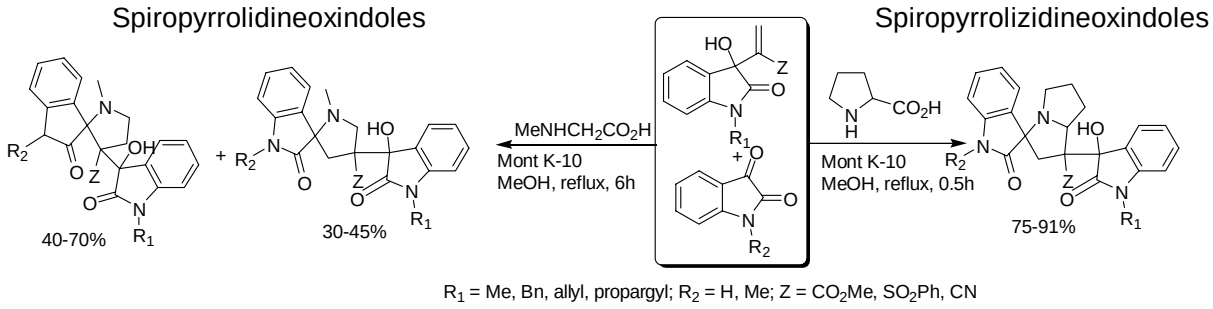


Scheme 27

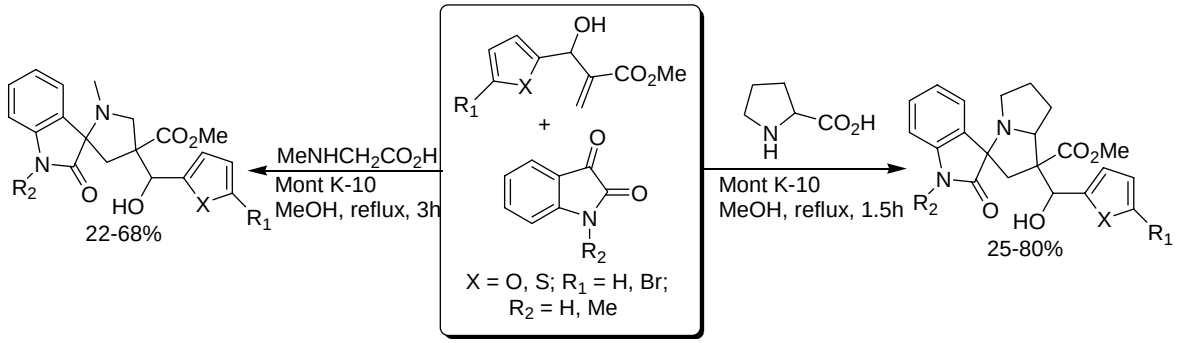


Shanmugam *et. al.*[212] have synthesized functionalized 3-spiropyrrolidine oxindoles and 3-spiropyrrolizidine oxindoles from the Baylis-Hillman adducts derived from isatin (Scheme 28) and heterocyclic aldehydes (Scheme 29).

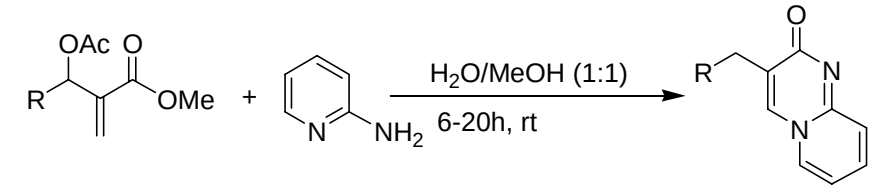
Scheme 28



Scheme 29



A facile one-pot convenient transformation of the acetates of Baylis-Hillman adducts into fused pyrimidones *via* the reaction with 2-aminopyridine in environment friendly aquous media has been reported by our research group (Eq. 22).[213]

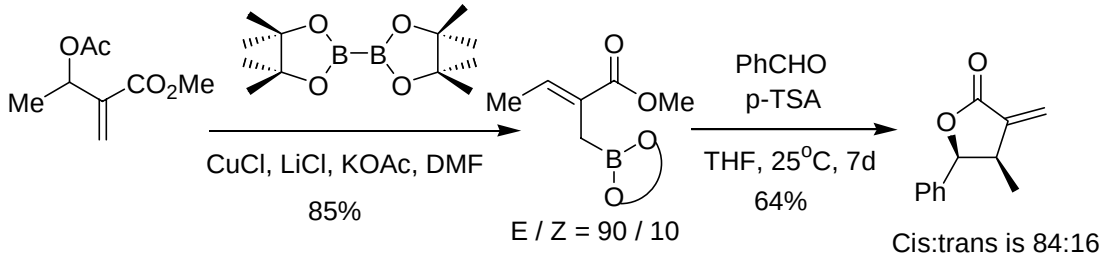


Eq. 22

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

Ramachandran and co-workers[214] have developed a simple synthesis of β-substituted α-methylene-γ-butyrolactones from the Baylis-Hillman acetates following the reaction sequence as shown in scheme 30. One representative example is shown.

Scheme 30



Our research group has developed[215] a simple stereoselective synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles *via* the treatment of methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles respectively with hydride ion from lithium aluminum hydride [LAH:EtOH (1:1)] (Scheme 31). This methodology was successfully utilized for the synthesis of (*E*)-nuciferol (**89**), a biologically active terpenoid and the precursor of (*Z*)-nuciferol (**90**) (Figure 6).

Scheme 31

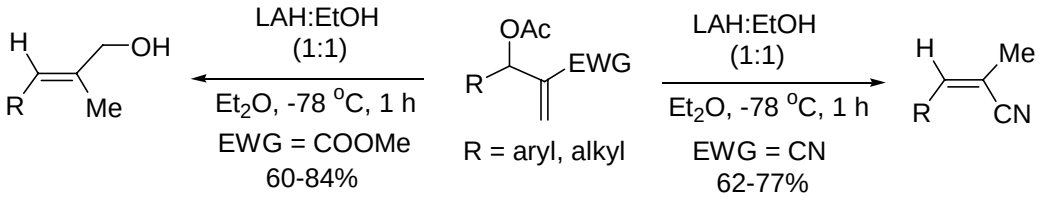
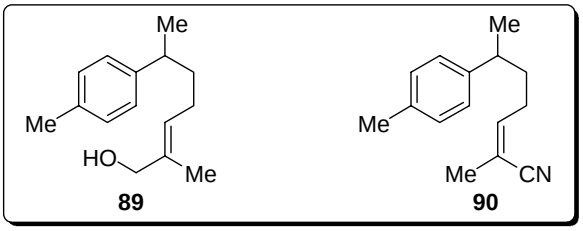
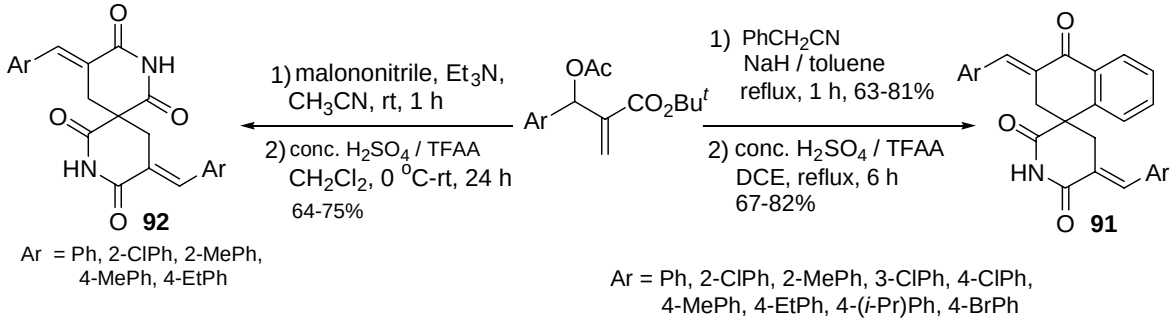


Figure 6



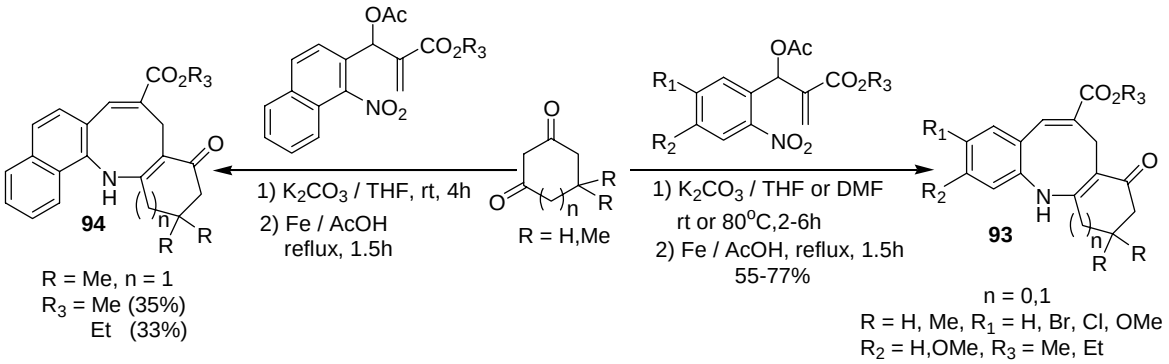
Very recently, our research group[216] has described an interesting synthesis of (*E*)-arylidene-tetralone-spiro-glutarimides (**91**) from the Baylis-Hillman acetates *via* biscyclization strategy involving facile C-C and C-N bond formation. Our research group also reported a facile one-pot multistep transformation of the Baylis-Hillman acetates into di(*E*)-arylidene-spiro-bisglutarimides (**92**) (Scheme 32).

Scheme 32



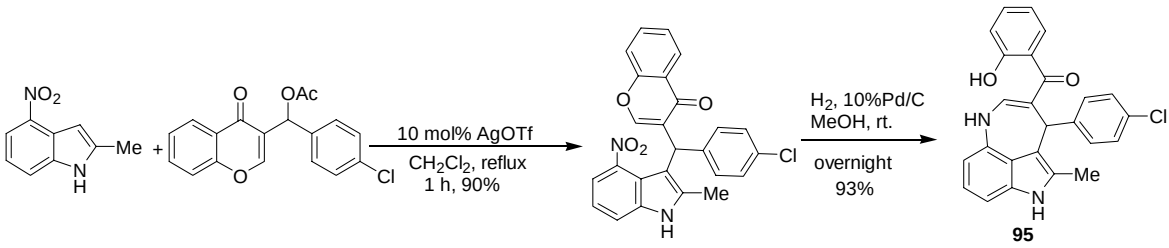
Very recently our research group[217] has conveniently transformed the Baylis-Hillman acetates into tri-/tetracyclic heterocyclic frameworks (**93** & **94**) containing an important azocine moiety *via* one-pot multistep protocol involving alkylation, reduction, and cyclization sequence.(Scheme 33)

Scheme 33



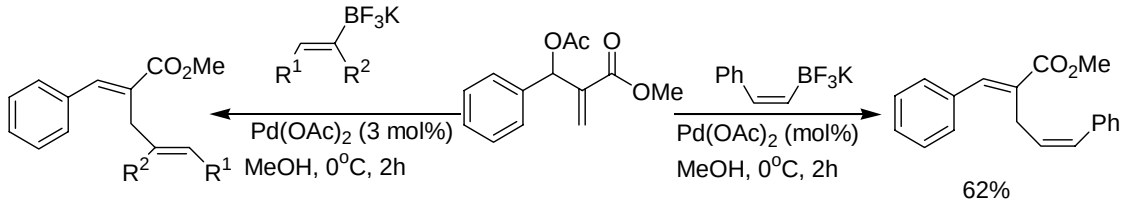
Chen and co-workers[218] have reported a mild and efficient synthesis of tricyclic compounds containing azepene (**95**) skeleton via treatment of the Baylis-Hillman acetates (obtained by the reaction of chromanone derivatives with aldehydes) with indoles followed by reductive cyclization (and cleavage of C-O bond). One representative example is presented in the Scheme 34.

Scheme 34



Kabalka and co-workers[219] have reported Heck reaction of Baylis-Hillman acetates with potassium organotrifluoroborates in the presence of $Pd(OAc)_2$, providing tri substituted alkenes. Representative examples are presented in the Scheme 35.

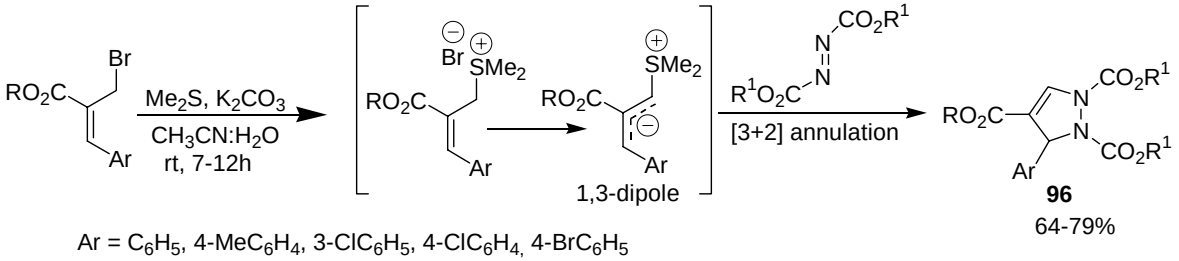
Scheme 35



R^1 = Ph, R^2 = H, 67%
R^1 = Ph, R^2 = Ph, 58%

Very recently our research group[220] has reported the synthesis of functionalized dihydropyrazole derivatives (**96**) *via* the simple one-pot [3 + 2] annulation of Baylis-Hillman bromides and dialkyl azodicarboxylates in the presence of dimethyl sulfide and potassium carbonate (Scheme 36)

Scheme 36

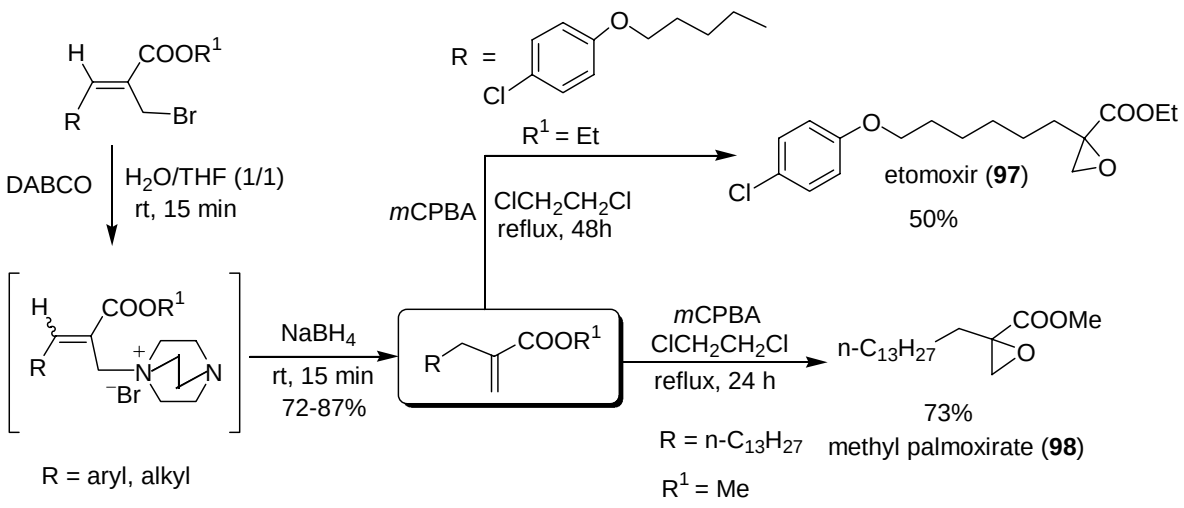


Ar = C_6H_5, 4-MeC_6H_4, 3-ClC_6H_5, 4-ClC_6H_4, 4-BrC_6H_5
R = Me, Et, Bu, Bu^t, R^1= Et, Pr^i

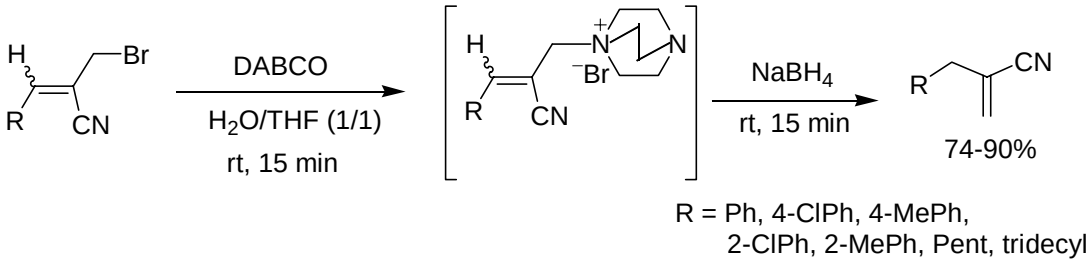
Our research group[221,222] has developed a simple and convenient procedure for the synthesis of 2-methylenealkanoates *via* the treatment of the allyl bromide (derived from Baylis-Hillman alcohol *i.e.,* 3-hydroxy-2-methylenealkanoates) with $NaBH_4$ in the presence of DABCO in aqueous media (Scheme 37).[221] This methodology was successfully applied for the synthesis of two hypoglycemic agents, etomoxir (**97**) and methyl palmoxirate (**98**) (Scheme 37).[221] Similar reaction of allyl bromides, derived from

3-hydroxy-2-methylenealkanenitriles, with DABCO followed by treatment with $NaBH_4$ in aqueous media provided 2-methylenealkanenitriles (Scheme 38).

Scheme 37



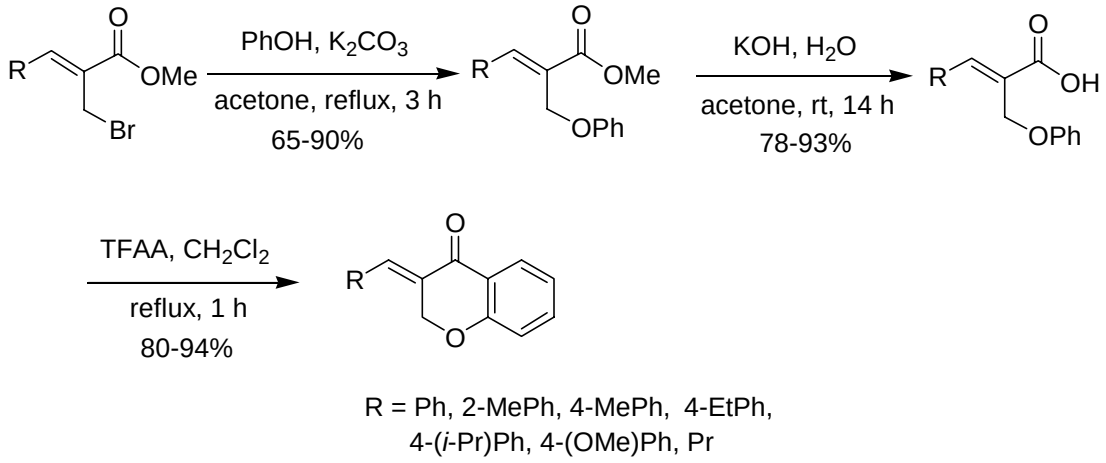
Scheme 38



Our research group[223] has developed a convenient synthesis of 3-arylidene(alkylidene)-chroman-4-ones, from the Baylis-Hillman adducts, following the reaction sequence described in Scheme 39 and has subsequently utilized this methodology for the synthesis of bonducellin methyl ether (**99**), an important natural product and 3-(4-

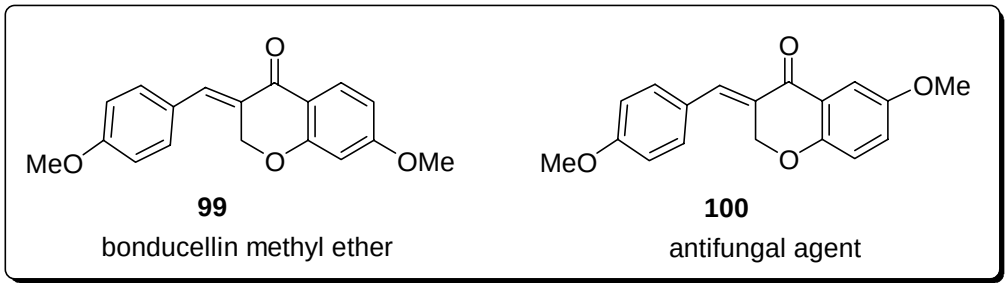
methoxybenzylidene)-6-methoxychroman-4-one, an antifungal agent (**100**) (Scheme 39) (Figure 7).

Scheme 39



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

Figure 7



OBJECTIVES, RESULTS AND DISCUSSION

OBJECTIVES

Our research group has been actively working for the last several years on various aspects of the Baylis-Hillman reaction with the main objective of developing this reaction into a valuable source for stereoselective processes. This thesis deals with applications of the Baylis-Hillman adducts[9-19] in the synthesis of spiro-oxindoles and bislactone molecules with the following objectives.

1. a) To develop a simple strategy for synthesis of spiro-oxindole derivatives containing α-methylene-γ-lactone skeleton (connected by an interesting spiro bridge) *via* the treatment of methyl 2-(bromomethyl)prop-2-enoate (the allyl bromide derived from the methyl 2-(hydroxymethyl)prop-2-enoate) with isatin derivatives under the influence of zinc.

   b) To develop a simple one-pot diastereoselective protocol for synthesis of (indolin-2-one)-3-spiro-5'-[3'-methylene-4'-aryltetrahydrofuran-2'-ones] *via* the reaction between Baylis-Hillman bromides i.e., methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates and isatin derivatives, under the influence of zinc.
2. To develop a simple protocol for obtaining spiro-oxindole derivatives containing α-methylene-γ-lactam skeleton (connected by an interesting spiro bridge) *via* the treatment of methyl 2-(bromomethyl)prop-2-enoate with 3-(arylimino)indolin-2-ones under the influence of zinc.

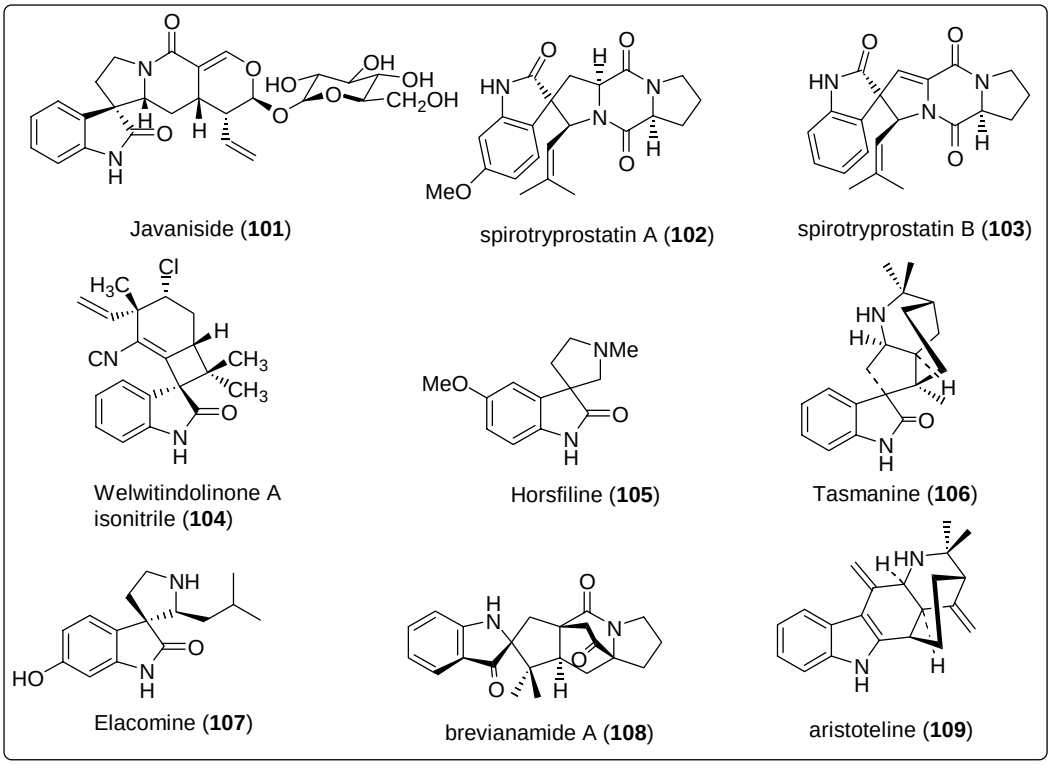
3. To develop a facile methodology for the transformation of acetates of the Baylis-Hillman adducts into [4.4.4.]propellano-bislactones *i.e.,* 4,8-bis[(*E*)-arylidene]-12,12-dime-thyl-2,10-dioxatricyclo[4.4.4.$0^{1,6}$]tetradecane-3,9,14-triones.

RESULTS AND DISCUSSION

Simple and one pot synthesis of spiro-oxindoles having α-methylene-γ-lactone framework

Spiro-oxindole framework is an integral part of several natural products, such as javaniside (**101**),[224] spirotryprostatins A & B (**102, 103**),[225] welwitindolinone A isonitrile (**104**),[226,227] horsfiline (**105**),[228] tasmanine (**106**),[229] elacomine (**107**),[230] brevianamide A (**108**),[231] and aristoteline (**109**)[229] (Figure 8) *etc*.

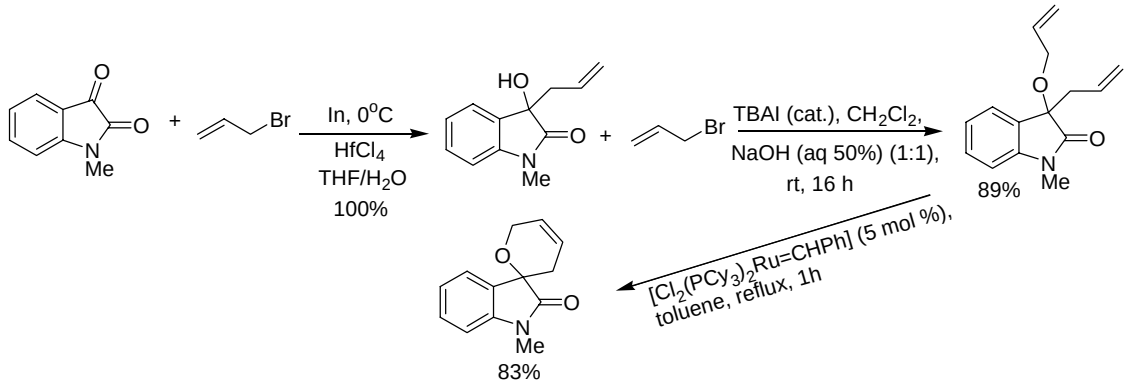
Figure 8



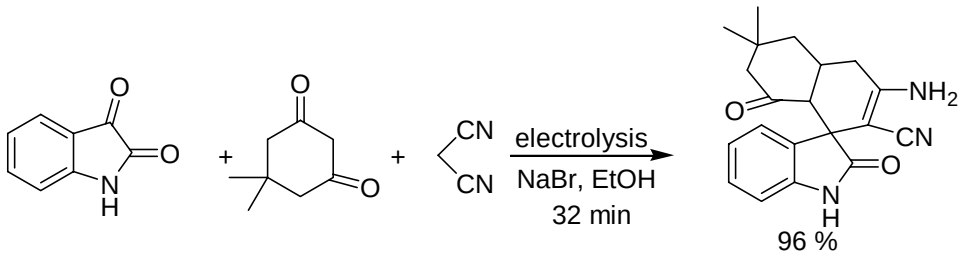
Because of the biological importance of the molecules having spiro-oxindole framework, development of simple methodologies for the synthesis of spiro-oxindole skeleton represents an interesting synthetic endeavor in organic chemistry. Therefore several synthetic methodologies have been developed for the synthesis of spiro-oxindoles (Schemes 40, 41 and Eqs. 23-26).

Almendros and co-workers[232] have reported a simple protocol for synthesis of diversely functionalized spiro-oxindoles from isatin derivatives following the reaction sequence as shown in Scheme 40.

Scheme 40

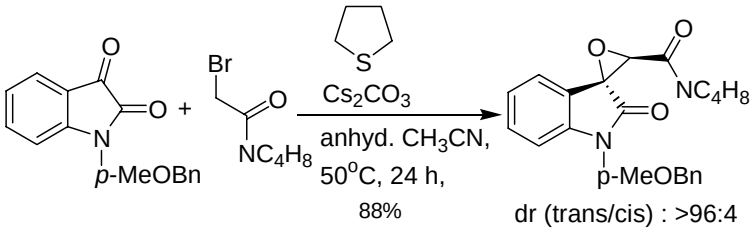


A convenient methodology for synthesis of spiro-oxindoles through electrochemically induced catalytic multicomponent transformation of cyclic 1,3-diketones, isatins, and malononitrile in alcohols was developed by Elinson[233] and co-workers (Eq. 23).



Eq 23

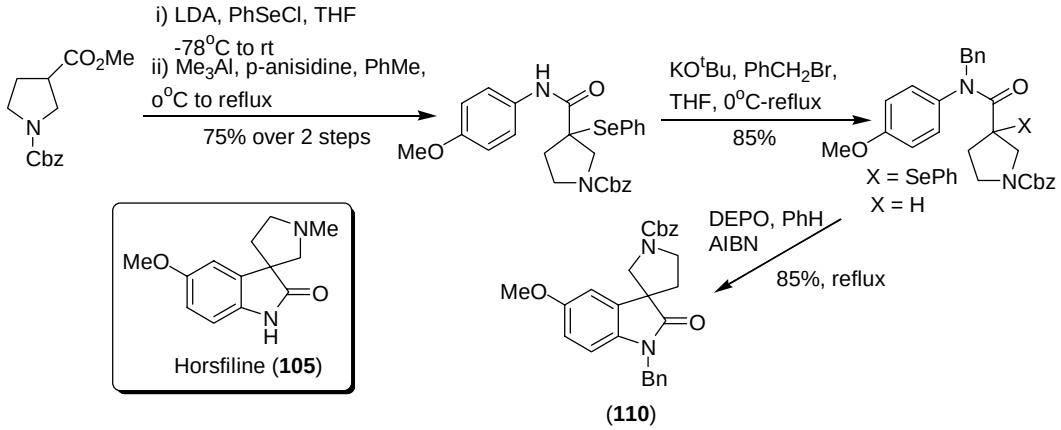
Metzner and co-workers[234] have reported an interesting synthetic protocol for biologically significant spiro-epoxyoxindoles with high diastereoselectivity *via* the treatment of isatins with *in situ* generated sulfonium ylide reagent, according to reaction strategy as described in Eq. 24.



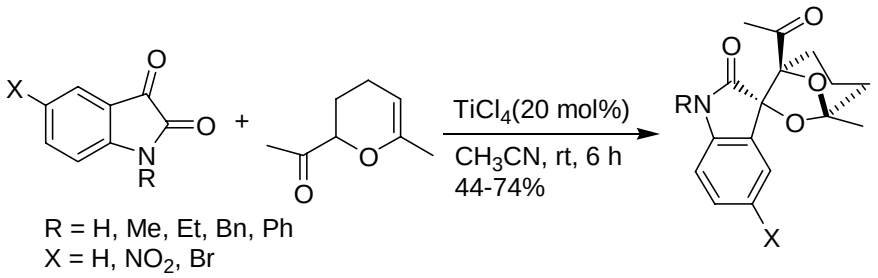
Eq. 24

Murphy and co-workers[235] have developed concise route to the compound **110**, a precursor of horsfiline (**105**) using diethylphosphine oxide (DEPO) as the key reagent according to the synthetic sequence shown in Scheme 41.

Scheme 41

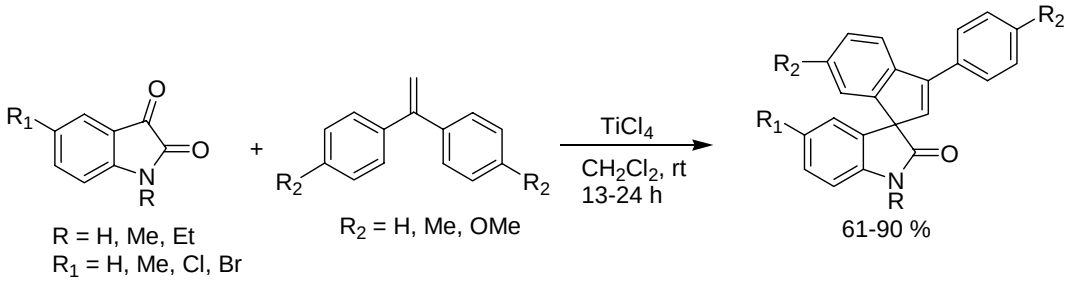


Our research group[236] has developed a simple, convenient and one-pot atom economical methodology for stereoselective synthesis of spiro-oxindoles containing both the oxindole and 6,8-dioxabicyclo(3.2.1)octane moieties *via* $TiCl_4$ catalyzed coupling of 2-acetyl-6-methyl-2,3-dihydro-4H-pyran with isatin derivatives (Eq. 25).



Eq. 25

Very recently, our research group[237] has developed a simple and one-pot $TiCl_4$-mediated strategy for synthesis of 1*H*-indene-spiro-oxindoles involving tandem Prins and Friedel-Crafts (PFC) reactions, using diarylethylenes and isatin derivatives as reacton partners (Eq 26).

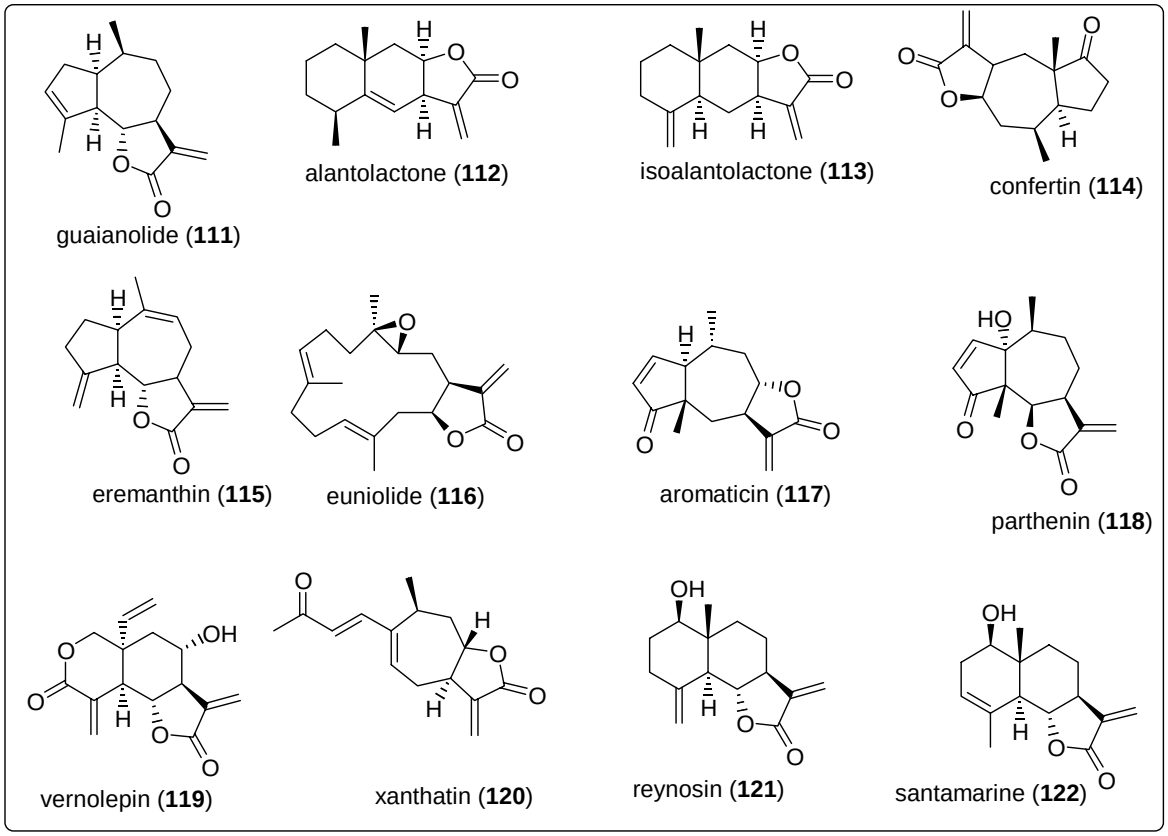


Eq. 26

The α-methylene-γ-lactone framework is present in many natural products such as guaianolide (**111**),[238] alantolactone (**112**)[239] isoalantolactone (**113**),[239] confertin (**114**),[240] eremanthin (**115**),[241] euniolide (**116**),[242] aromaticin (**117**),[243] parthenin (**118**),[244] vernolepin

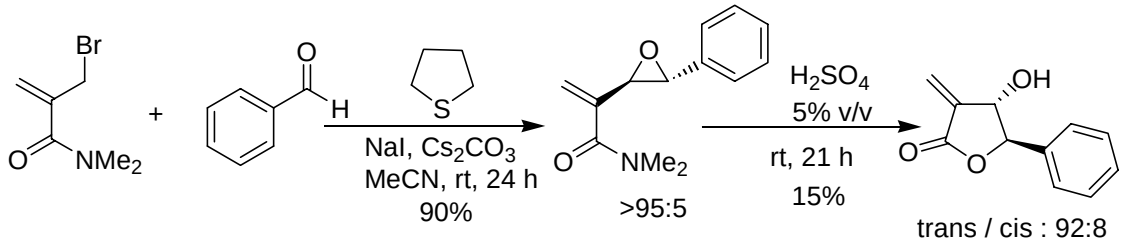
(**119**),[245] xanthatin (**120**),[246] reynosin (**121**),[244] and santamarine (**122**)[244] (Figure 9). Due to their interesting and important biological properties, development of simple and convenient methodologies for the synthesis of α-methylene-γ-lactone derivatives represents an interesting and attractive endeavor in synthetic organic and medicinal chemistry. Several systematic successful efforts are made in this direction (Schemes 42-46, Eq. 27).

Figure 9



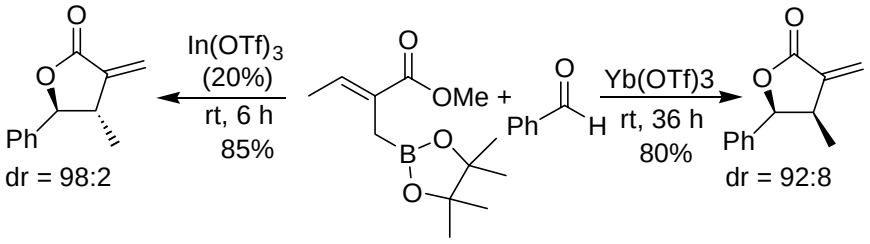
Metzner and coworkers[247] have reported stereodivergent synthesis of β-hydroxy-α-methylene lactones following the reaction sequence as described in the Scheme 42.

Scheme 42

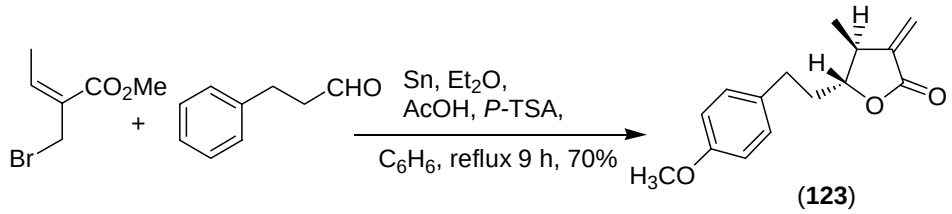


An interesting Lewis acid directed synthesis of both the *cis* and *trans* lactones was reported by Ramachandran and co-workers.[248] one representative example is described in Scheme 43.

Scheme 43



Bermejo and co-workers[249] have developed a simple procedure for synthesis of the lactone **123**, having antiproliferative activity, following the reaction sequence as described in the Eq. 27.

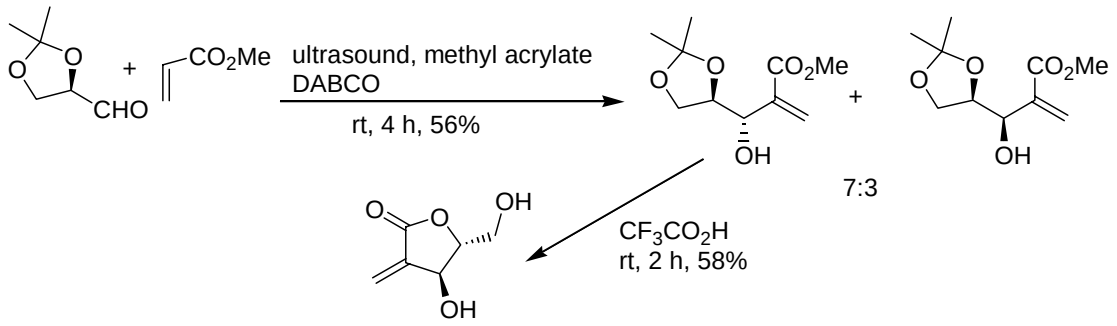


(**123**)

Eq. 27

Coelho and co-workers[250] have developed simple and convenient synthesis of α-methylene-δ-butyrolactone (**124**) starting from the Baylis-Hillman alcohol following the reaction as described in the Scheme 44.

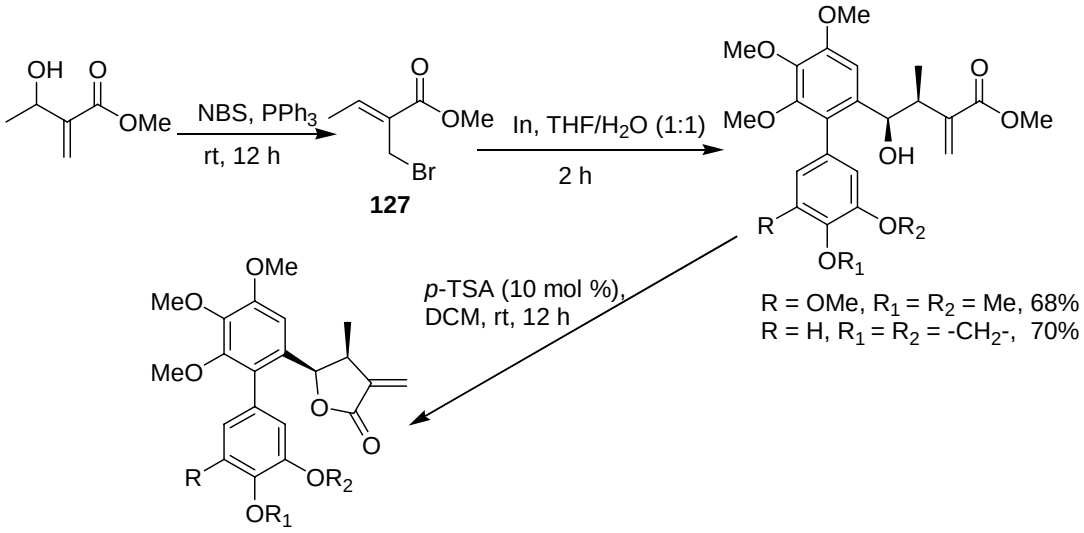
Scheme 44



(**124**)

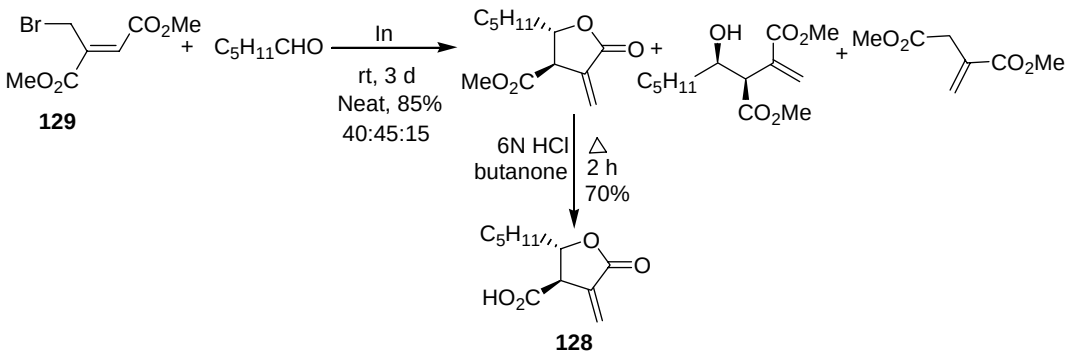
Diastereocontrolled indium mediated protocol for synthesis of natural lignans eupomatilone 2 (**125**) and 5 (**126**) using the Baylis-Hillman bromide **127** as key starting material was described by Kabalka and co-workers (Scheme 45).[251]

Scheme 45



Loh and co-workers[252] have developed a short and efficient route for the synthesis of (±)-methylenolactocin (**128**) from the bromide **129**, following the reaction as shown in Scheme 46.

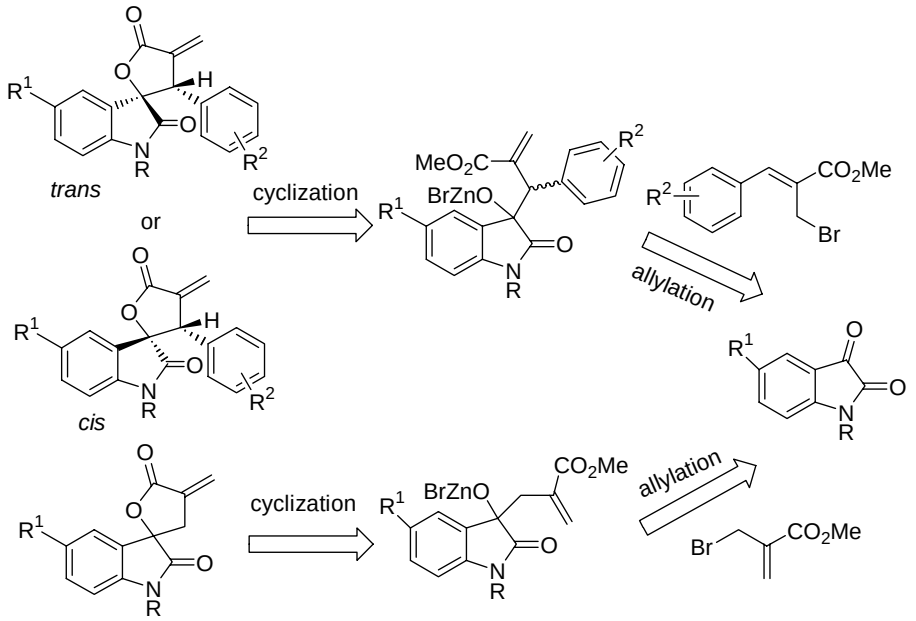
Scheme 46



Because of the biological importance of the both spiro-oxindole framework and α-methylene-γ-lactone framework, it occurred to us that the molecules containing both the oxindole and α-methylene-γ-lactone frameworks connected by a spiro linkage might possess high levels of biological activity. Although the applications of Baylis-Hillman adducts in the synthesis of various α-methylene-γ-lactone derivatives have been well documented [249-257] in the literature (Schemes 44-46, Eq. 27), their utility for synthesis of oxindole derivatives containing α-methylene-γ-lactone moiety has not been studied systematically.[253,254] We have therefore felt that the appropriate treatment of isatin derivatives with methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates (allyl bromides derived from the Baylis-Hillman alcohols i.e., 3-aryl-3-hydroxy-2-methylenepropanoates) via suitable organometallic pathway should in principle produce the desired oxindole-spiro-α-methylene-γ-lactones with high diastereoselectivity. We also felt that it would be

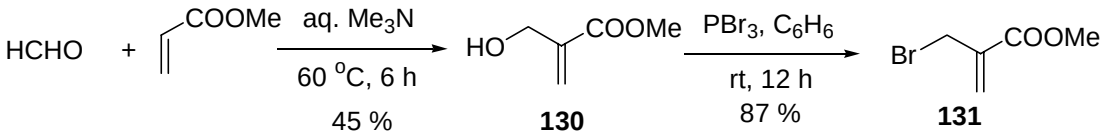
useful if we first examine the reaction of methyl 2-(bromomethyl)prop-2-enoate (the allyl bromide derived from the Baylis-Hillman alcohol) with isatin derivatives, which would lead to the formation of oxindole-spiro-α-methylene-γ-lactone framework without any stereochemistry (see retro-synthetic strategy in Scheme 47). Accordingly we have directed our efforts to develop a simple methodology for obtaining (indolin-2-one)-3-spiro-5'-[3'-methylene-tetrahydrofuran-2'-ones] using methyl 2-(bromomethyl)prop-2-enoate (retrosynthetic Scheme 47). For this purpose we have selected isatin as reaction partner.

Scheme 47

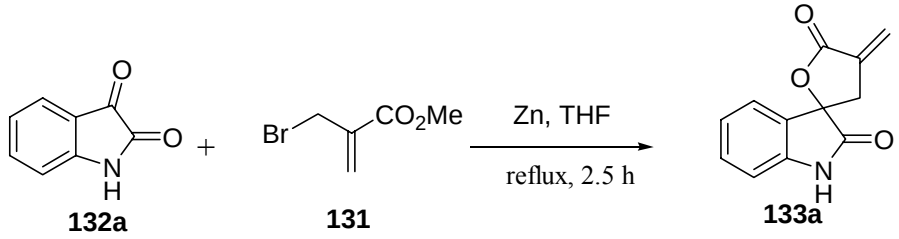


The required methyl 2-(bromomethyl)prop-2-enoate (**131**) was prepared via the treatment of methyl 2-(hydroxymethyl)prop-2-enoate (**130**) with PBr_3, following the procedure as described in the Scheme 48. Methyl 2-(hydroxymethyl)prop-2-enoate (**130**) was in turn prepared *via* the Baylis-Hillman reaction of formaldehyde with methyl acrylate (Scheme 48).

Scheme 48



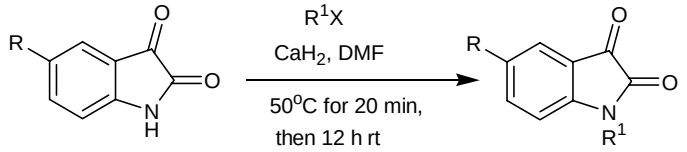
We turned our attention to perform the reaction between isatin and methyl 2-(bromomethyl)prop-2-enoate (**131**). Best results were obtained when **131** (1.1 mmol) was treated with isatin (**132a**) (1.0 mmol) under reflux in anhydrous THF (2 mL) in the presence of zinc (2 mmol) for 2.5 h, thus providing the desired product, (indolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (**133a**) in 78% isolated yield after usual workup followed by column chromatography (silica gel, 25% EtOAc in hexanes) (Eq. 28)(Table 1, entry 1). The structure of this spiro-oxindole (**133a**) is in agreement with IR, ^{1}H NMR (spectrum 1), ^{13}C NMR (spectrum 2), mass spectral data and elemental analysis. Structure of **133a** was further established by single crystal X-ray data (Fig. X1, Table I).



Eq. 28

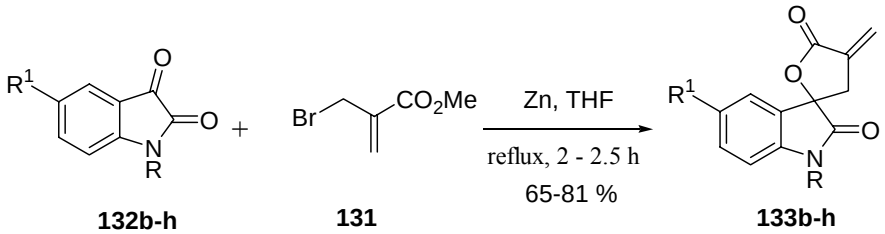
With a view to understand the generality of the reaction we have selected representative isatin derivatives (**132b-h**) for reaction with methyl 2-(bromomethyl)prop-2-enoate (**131**). Isatin derivatives **132a-d** are commercially available, and the remaining isatin derivatives (**132e-h**) were prepared *via* the alkylation of isatin derivatives with alkyl bromides in the

presence of calcium hydride in DMF in 70-86% yields (Eq. 29).



Eq. 29

Then we have successfully subjected isatin derivatives (**132b-h**) to spiro lactonization, *via* the reaction with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, to provide the corresponding spiro-oxindole derivatives (**133b-h**) in 65-81% isolated yields (Eq. 30, Table 1). The structures of spiro-oxindoles (**133b-h**) are in agreement with IR, ^{1}H NMR (See : spectra 3, 5 & 7 for compounds **133b**, **133f** & **133h** respectively), ^{13}C NMR (See: spectra 4, 6 & 8 for compounds **133b**, **133f** & **133h** respectively), mass spectral data and elemental analyses. Structure of **133f** was further established by single crystal X-ray data (Fig. X2, Table II).



Eq. 30

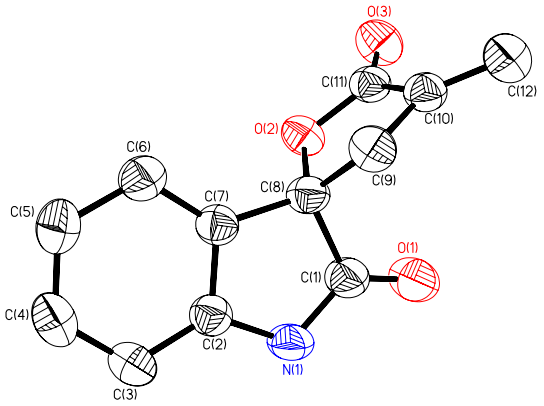


Fig. X1

ORTEP diagram of the compound 133a

(Hydrogen atoms were omitted for clarity)

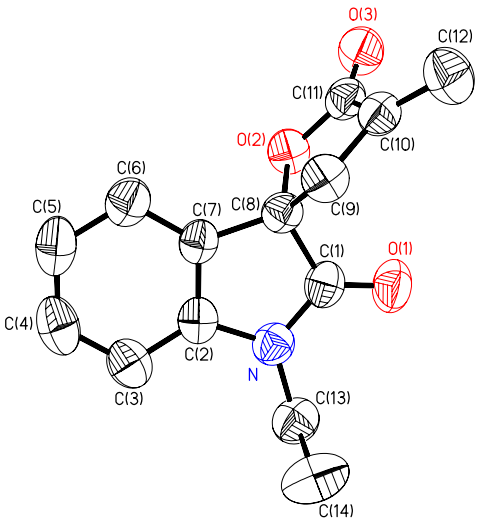


Fig. X2

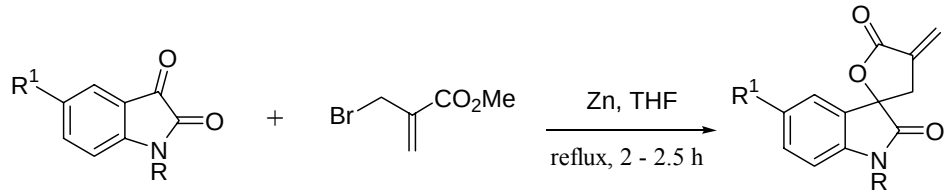
ORTEP diagram of the compound 133f

(Hydrogen atoms were omitted for clarity)

Table I: Crystal data and structure refinement for 133a

Identification code	: **133a**
Empirical formula	: $C_{12}H_9NO_3$
Formula weight	: 215.20
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system, space group	triclinic, P-1
Unit cell dimensions	: a = 9.1042(9) Å; α = 98.580(2) deg.
	: b = 9.5149(10) Å; β = 91.499(2) deg.
	: c = 13.7045(14) Å; γ = 117.583(2) deg.
Volume	: 1034.29(18) $Å^3$
Z, Calculated density	: 4, 1.382 Mg/m^3
Absorption coefficient	: 0.101 mm^{-1}
F(000)	: 448
Crystal size	: 0.38 x 0.26 x 0.18 mm^3
Theta range for data collection	: 1.51 to 26.03 deg.
Limiting indices	: $-11\leq h\leq 11$, $-11\leq k\leq 11$, $-16\leq l\leq 16$
Reflections collected / unique	: 10834 / 4039 [R(int) = 0.0398]
Completeness to theta = 26.03	: 99.4%
Absorption correction	: None
Max. and min. transmission	: 0.9821 and 0.9627
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 4039 / 0 / 297
Goodness-of-fit on F^2	: 1.041
Final R indices [I>2sigma(I)]	: R1 = 0.0478, wR2 = 0.1061
R indices (all data)	: R1 = 0.0632, wR2 = 0.1141
Largest diff. peak and hole	: 0.203 and -0.182 e. $Å^{-3}$

Table 1: Synthesis of spiro-oxindoles (133)[a]



132a-h **131** **133a-h**

Entry	Isatin	R	R^1	product[b]	Yield (%)[c]
1	**132a**	H	H	**133a**[d]	78
2	**132b**	H	Cl	**133b**	75
3	**132c**	H	Me	**133c**	81
4	**132d**	H	Br	**133d**	72
5	**132e**	Me	H	**133e**	65
6	**132f**	Et	H	**133f**[d]	69
7	**132g**	Me	Cl	**133g**	67
8	**132h**	Me	Br	**133h**	70

a) All reactions were carried out on 1 mmol scale of isatin derivatives (**132a-h**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) (1.1 mmol) in the presence of zinc (2 mmol) in anhydrous THF (2 mL) under reflux for 2-2.5 h.

b) All compounds were obtained as colorless solids and fully characterized.

c) Yields of pure products based on isatins.

d) Structures of these compounds were further confirmed by single crystal X-ray data.

Table II: Crystal data and structure refinement for 133f

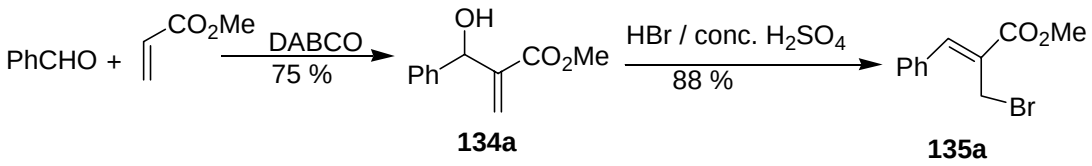
Identification code	: **133f**
Empirical formula	: $C_{14}H_{13}NO_3$
Formula weight	: 243.25
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system, space group	triclinic, P-1
Unit cell dimensions	: a = 9.0775(11) Å; α = 97.981(2) deg.
	: b = 9.1252(10) Å; β = 117.587(2) deg.
	: c = 9.2167(11) Å; γ = 106.276(2) deg.
Volume	: 616.31(12) $Å^3$
Z, Calculated density	: 2, 1.311 Mg/m^3
Absorption coefficient	: 0.093 mm^{-1}
F(000)	: 256
Crystal size	: 0.42 x 0.38 x 0.24 mm^3
Theta range for data collection	: 2.45 to 25.94 deg.
Limiting indices	: -11<=h<=11, -11<=k<=11, -11<=l<=11
Reflections collected / unique	: 6308 / 2376 [R(int) = 0.0429]
Completeness to theta = 25.94	: 99.0%
Absorption correction	: None
Max. and min. transmission	: 0.9781 and 0.9620
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2376 / 0 / 164
Goodness-of-fit on F^2	: 0.876
Final R indices [I>2sigma(I)]	: R1 = 0.0448, wR2 = 0.0772
R indices (all data)	: R1 = 0.0979, wR2 = 0.0916
Largest diff. peak and hole	: 0.118 and -0.117 $e.A^{-3}$

One-pot diastereoselective synthesis of spiro-oxindoles having α-methylene-γ-lactone framework

After developing a facile methodology for synthesis of spiro-oxindoles (**133a-h**), we have focused our studies towards diastereoselective synthesis of spiro-oxindole derivatives using methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates (**135a-c)** as a substrates for reaction with isatins (**132a-c**) (see retrosynthetic strategy in Scheme 47).

We have first selected Baylis-Hillman bromide i.e., methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**135a**) for treatment with isatin. The required Baylis-Hillman bromide (**135a**) was prepared according to the Scheme 49. Thus the treatment of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**134a**) with aq. HBr in the presence of conc. H_2SO_4, provided the allyl bromide (**135a**). The desired allyl alcohol **134a** was in turn obtained via the Baylis-Hillman reaction of benzaldehyde with methyl acrylate under the catalytic influence of DABCO.

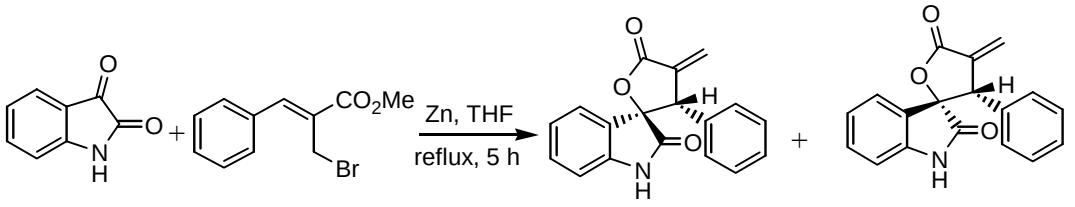
Scheme 49



134a **135a**

We have performed reaction between the Baylis-Hillman bromide **135a** and isatin under the influence of zinc in various conditions. Best results were obtained when **135a** (1.1 mmol) was treated with isatin (**132a**) (1 mmol) in the presence of zinc (2 mmol) in anhydrous THF under reflux for 5 h thus providing spiro-oxindole, (indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (**136a**) (*trans*-

configuration)[#] in 71% isolated yield after usual workup followed by column chromatography (silica gel, 20% EtOAc in hexanes) (Eq. 31, Table 2, entry 1). The structure of this spiro-oxindole (**136a**) is in agreement with IR, ^{1}H NMR (spectrum 9), ^{13}C NMR (spectrum 10), mass spectral data and elemental analysis. In addition, we have also isolated (indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-phenyltetrahydro-furan-2'-one] (**137a**) (other diastereomer) in 4% yield (^{1}H NMR of the crude mixture shows 94:6 diastereomeric ratio).[♣] The structure of this minor spiro-oxindole (**137a**) is in agreement with IR, ^{1}H NMR (spectrum 11), ^{13}C NMR (spectrum 12), spectral data. This is indeed an interesting reaction in the sense that the required spiro compound was obtained in *trans* selectivity.[♣,#]



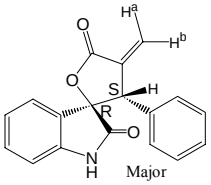
136a
Trans (racemic)
(*major isomer*)

137a
Cis (racemic)
(*minor isomer*)

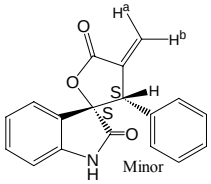
Eq. 31

It is very appropriate to mention here the work of Kim and co-workers who reported the reaction (one example) between 1-benzylisatin and methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**135a**) under the influence of indium to provide the corresponding

[♣] ^{1}H NMR of of the crude product indicates the diastereomeric ratio of 94:6 (*trans*:*cis*) (from the integration ratios of diastereomeric H^{b} protons).

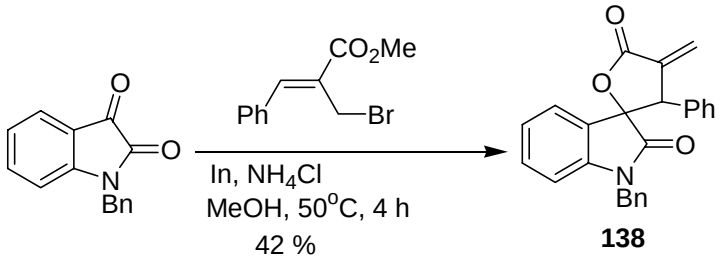


trans-isomer
racemic



cis-isomer
racemic

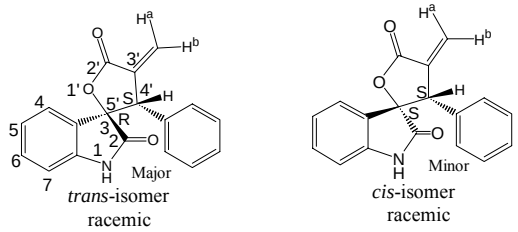
spiro-oxindole **138** in 42% yield. However, they did not report the stereochemistry of this spiro-oxindole (Eq. 32).[254]



Eq. 32

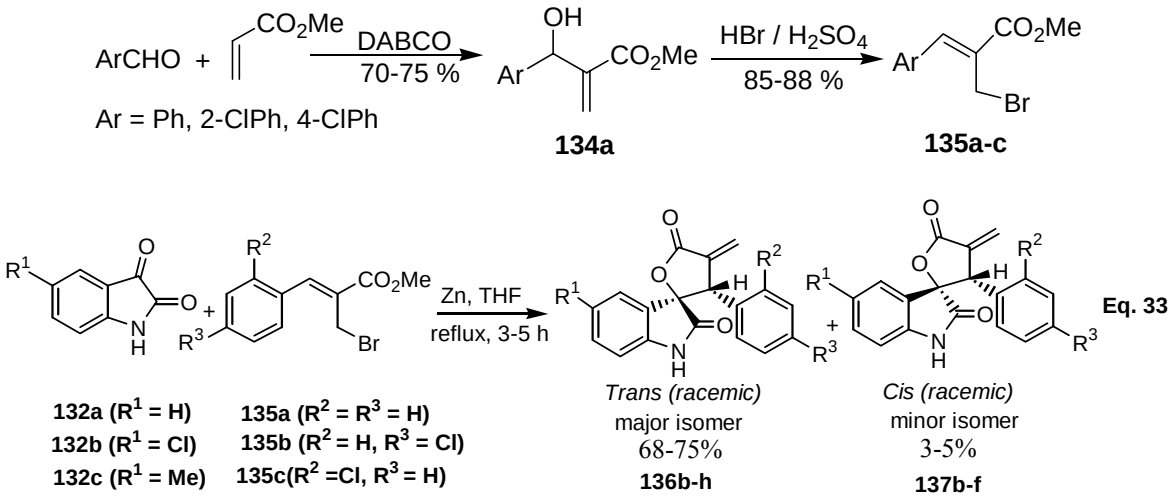
In order to understand the generality of the reaction we have selected representative allylic bromides **135a-c** which were prepared according to Scheme 50. We have then subjected all these allyl bromides **135a-c** for reaction with isatin derivatives **132a-c** in the presence of zinc under similar conditions. These reactions were found to be highly diastereoselective (92-100% *trans*)[#] (as indicated by ^{1}H NMR spectra of the crude products) and the required spiro-oxindoles (**136b-h**) were obtained in 68-75% isolated yields as colorless solids (Table 2, Eq. 33). Structures of these compouds are in full agreement with IR, ^{1}H NMR (See: spectra 13 & 17 for compouds **136d** & **136g**), ^{13}C NMR (See: spectra 14, 18 for molecules **136d**, **136g**), mass spectral data and elemental analyses. In addition, minor *cis*-diastereomers (**137b-f**) have also been isolated in 3-5% yields (Table 2)(Eq. 33) (In the case of **137g**, **137h,** ^{1}H NMR spectra of the crude mixtures did not indicate the presence of any other isomer). Structures of these molecules **137b-f** are in agreement with IR, ^{1}H NMR

[#] We have assigned the *trans* configuration when aryl group at C-4' and carbonyl group of the indoline ring are on the opposite (different) sides of the lactone ring. The *cis* configuration is assigned when these groups are on the same side of the lactone ring as shown below.



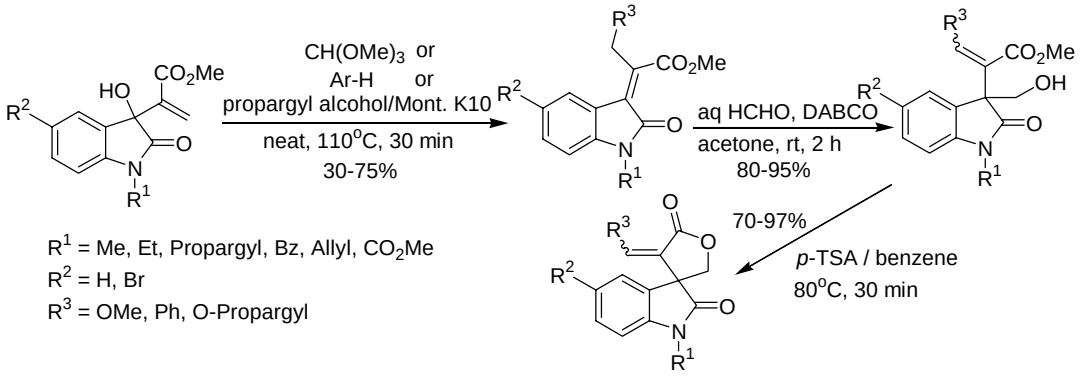
(spectrum 15 for molecule **137d**) and ^{13}C NMR (spectrum 16 for **137d**) spectral data and elemental analyses. Structures of **136c, 137c, 136e, 137e** were further established by single crystal X-ray data (Figures X3, X4, X5, X6 & Tables III, IV, V, VI).

Scheme 50



It is worth mentioning here that very recently Shanmugam and Vaithiyanathan reported the synthesis of the spiro-oxindole derivatives connected with the α-methylene-γ-lactone framework by different route, i.e., from Baylis-Hillman alcohols derived from isatin (Scheme 51).[253]

Scheme 51.



A plausible mechanism for the high diastereoselectivity (taking the reaction between **135a** and isatin **132a** as a model case) is presented in Scheme 52. The *trans* selectivity [the formation of *trans* products (**136a-h**)] might be due to the favored Transition State Model **A** having less 1,3-interactions in comparison with that of Transition State Model **B**.

Scheme 52. Diastereoslective Spiro-oxindole Formation:

Mechanism:

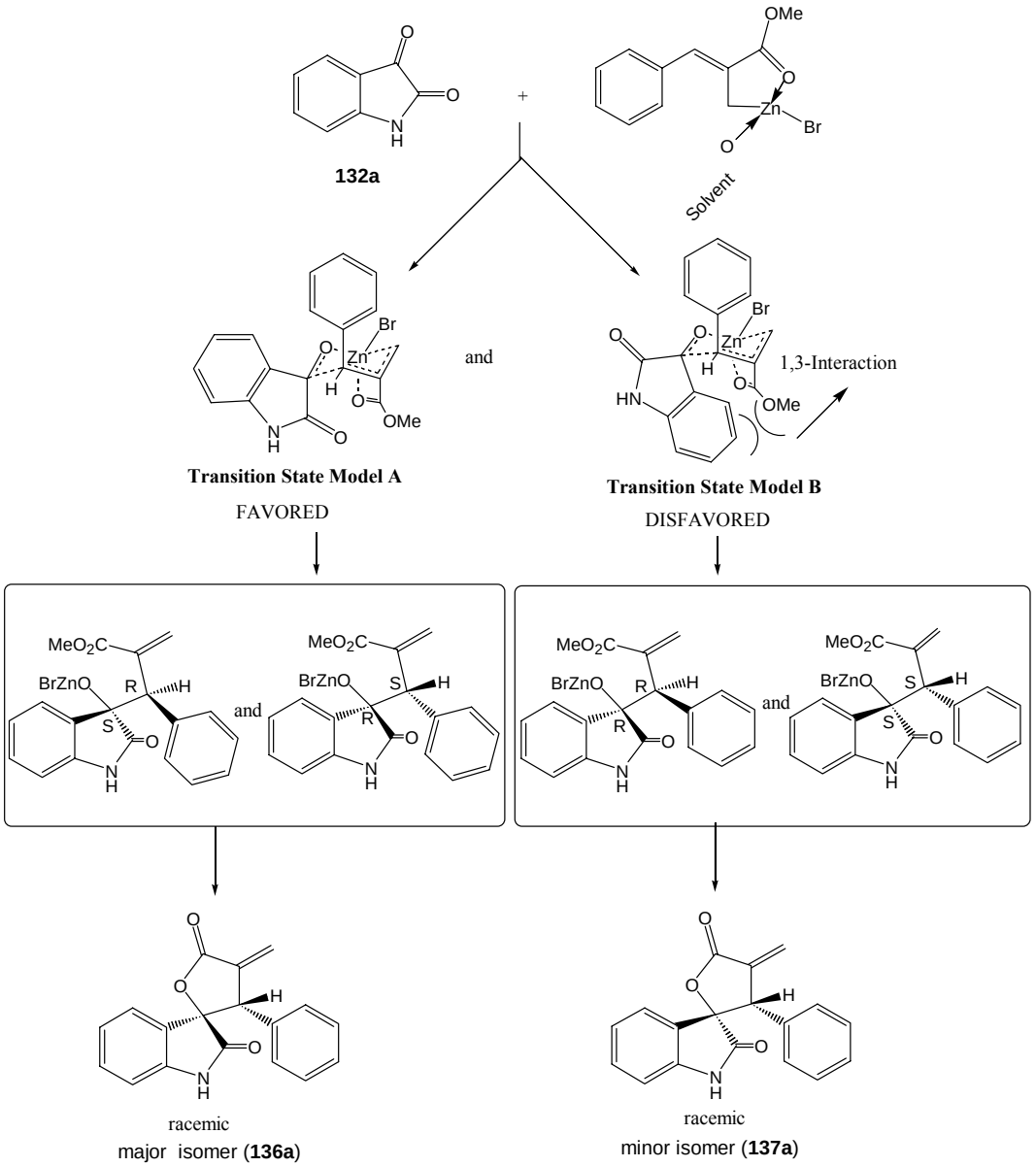
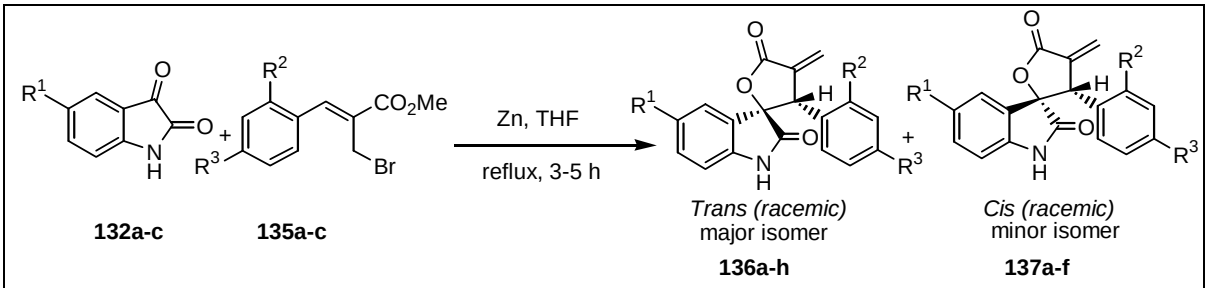


Table 2: Diastereoselective Synthesis of Spiro-Oxindoles.[a]



132a-c **135a-c**

Trans (racemic) major isomer **136a-h**

Cis (racemic) minor isomer **137a-f**

entry	bromide	Isatin	product[b] (*trans*)	yield[c] (%)	product[b] (*cis*)	yield[c](%)	*trans:cis*[d]
1	**135a**	**132a**	**136a**	71	**137a**	4	94:6
2	**135a**	**132b**	**136b**	73	**137b**	3	94:6
3	**135a**	**132c**	**136c**[e]	74	**137c**[e]	4	93:7
4	**135b**	**132a**	**136d**	70	**137d**	5	92:8
5	**135b**	**132b**	**136e**[e]	68	**137e**[e]	4	93:7
6	**135b**	**132c**	**136f**	75	**137f**	3	95:5
7	**135c**	**132a**	**136g**	72	**-----**	**-----**	100:00[f]
8	**135c**	**132b**	**136h**	69	**-----**	**-----**	100:00[f]

a) All reactions were carried out on 1 mmol scale of isatin derivatives (**132a-c**) with methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates (**135a-c**) (1.1 mmol) in the presence of zinc (2 mmol) in anhydrous THF (2 mL) under reflux for 3-5 h.

b) All compounds (**136a-h**) and (**137a-f**) were obtained as colorless solids and fully characterized.

c) Yields of pure products based on isatins.

d) Ratio of the diastereoisomers from crude ^{1}H NMR spectral data.

e) Structures of these molecules were further confirmed by single crystal X-ray data.

f) ^{1}H NMR spectra of the crude mixtures did not indicate the presence of any other isomer.

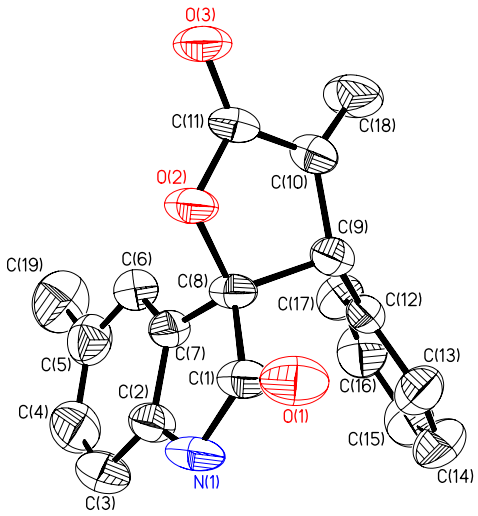


Fig. X3

ORTEP diagram of the compound 136c

(Hydrogen atoms were omitted for clarity)

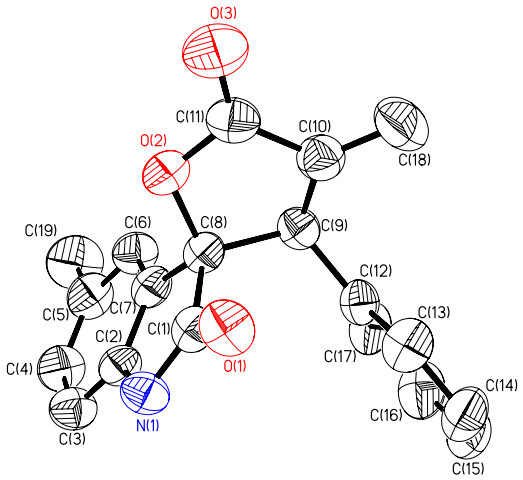


Fig. X4

ORTEP diagram of the compound 137c

(Hydrogen atoms were omitted for clarity)

Table III. Crystal data and structure refinement for 136c.

Identification code	**136c**	
Empirical formula	$C_{19}H_{15}NO_3$	
Formula weight	305.32	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system, space group	orthorhombic, P21 21 21	
Unit cell dimensions	a = 8.385(3) Å	α = 90 deg.
	b = 10.792(4) A	β = 90 deg.
	c = 17.614(6) A	γ = 90 deg.
Volume	1593.9(10) $Å^3$	
Z, Calculated density	4, 1.272 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	640	
Crystal size	0.42 x 0.32 x 0.28 mm^3	
Theta range for data collection	2.21 to 25.90 deg.	
Limiting indices	-10<=h<=10, -13<=k<=13, -21<=l<=21	
Reflections collected / unique	16361 / 3093 [R(int) = 0.0398]	
Completeness to theta = 25.90	99.9%	
Absorption correction	None	
Max. and min. transmission	0.9762 and 0.9645	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3093 / 0 / 210	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0388, wR2 = 0.0854	
R indices (all data)	R1 = 0.0441, wR2 = 0.0879	
Absolute structure parameter	-0.2(11)	
Largest diff. peak and hole	0.116 and -0.169 e.$Å^{-3}$	

Table IV. Crystal data and structure refinement for 137c.

Identification code	**137c**	
Empirical formula	$C_{19}H_{15}NO_3$	
Formula weight	305.11	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system, space group	monoclinic, C 2/c	
Unit cell dimensions	a = 17.507(2) Å	α = 90 deg.
	b = 17.788(2) Å	β = 118.715(2) deg.
	c = 13.7539(19) Å	γ = 90 deg.
Volume	3756.4(9) $Å^3$	
Z, Calculated density	8, 1.080 Mg/m^3	
Absorption coefficient	0.073 mm^{-1}	
F(000)	1280	
Crystal size	0.38 x 0.40 x 0.25 mm^3	
Theta range for data collection	1.75 to 28.30 deg.	
Limiting indices	-22<=h<=23, -23<=k<=23, -18<=l<=18	
Reflections collected / unique	21386 / 4509 [R(int) = 0.0570]	
Completeness to theta = 28.30	96.4%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4509 / 0 / 209	
Goodness-of-fit on F^2	1.381	
Final R indices [I>2sigma(I)]	R1 = 0.1332, wR2 = 0.3613	
R indices (all data)	R1 = 0.1648, wR2 = 0.3812	
Largest diff. peak and hole	1.776 and -0.343 $e.Å^{-3}$	

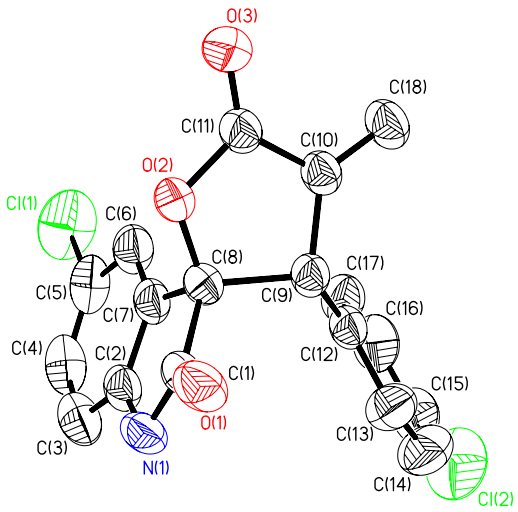


Fig. X5

ORTEP diagram of the compound 136e

(Hydrogen atoms were omitted for clarity)

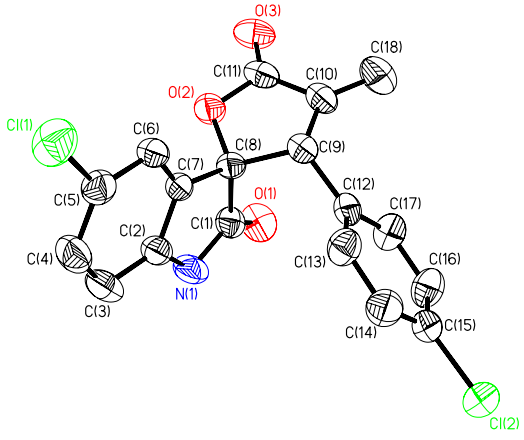


Fig. X6

ORTEP diagram of the compound 137e

(Hydrogen atoms were omitted for clarity)

Table V: Crystal data and structure refinement for 136e.

Identification code	**136e**	
Empirical formula	$C_{18}H_{11}Cl_2NO_3$	
Formula weight	360.18	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system, space group	triclinic, P-1	
Unit cell dimensions	a = 7.153(3) Å	α = 106.593(5) deg.
	b = 8.436(3) Å	β = 95.715(8) deg.
	c = 14.519(6) Å	γ = 91.467(6) deg.
Volume	834.1(6) $Å^3$	
Z, Calculated density	2, 1.434 Mg/m^3	
Absorption coefficient	0.404 mm^{-1}	
F(000)	368	
Crystal size	0.40 x 0.34 x 0.28 mm^3	
Theta range for data collection	2.52 to 25.84 deg.	
Limiting indices	-8<=h<=8, -10<=k<=10, -17<=l<=17	
Reflections collected / unique	8300 / 3179 [R(int) = 0.0193]	
Completeness to theta = 25.84	98.5%	
Absorption correction	None	
Max. and min. transmission	0.8952 and 0.8549	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3179 / 0 / 221	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.1271	
R indices (all data)	R1 = 0.0615, wR2 = 0.1375	
Largest diff. peak and hole	0.332 and -0.493 $e.A^{-3}$	

Table VI. Crystal data and structure refinement for 137e.

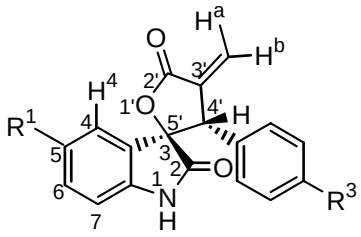
Identification code	**137e**
Empirical formula	$C_{18}H_{11}Cl_2NO_3$
Formula weight	360.18
Temperature	298 K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, P21/n
Unit cell dimensions	a = 13.642(10) Å α = 90 deg.
	b = 8.237(6) Å β = 97.011(12) deg.
	c = 14.329(11) Å γ = 90 deg.
Volume	1598(2) $Å^3$
Z, Calculated density	4, 1.497 Mg/m^3
Absorption coefficient	0.422 mm^{-1}
F(000)	736
Crystal size	0.42 x 0.14 x 0.06 mm^3
Theta range for data collection	1.95 to 24.99 deg.
Limiting indices	-16<=h<=16, -9<=k<=9, -17<=l<=17
Reflections collected / unique	12475 / 2691 [R(int) = 0.0677]
Completeness to theta = 24.99	95.8%
Absorption correction	None
Max. and min. transmission	0.9751 and 0.8426
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2691 / 0 / 221
Goodness-of-fit on F^2	1.112
Final R indices [I>2sigma(I)]	R1 = 0.0714, wR2 = 0.1087
R indices (all data)	R1 = 0.1086, wR2 = 0.1154
Largest diff. peak and hole	0.236 and -0.164 $e.A^{-3}$

Interesting Diastereomers NMR Chemical Shifts Differences:

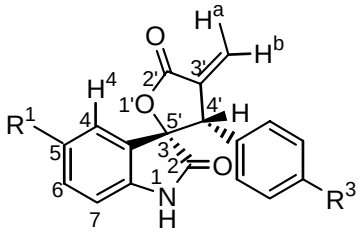
We have observed interesting chemical shift differences in ^{1}H & ^{13}C NMR spectral data of major (**136a-f**), and minor (**137a-f**) diastereomers. In ^{1}H NMR spectra, H-4 proton in the case of minor (**137a-f**) isomers appears downfield (δ 7.33-7.53), while same proton in major (**136a-f**) isomers appears upfield (δ 6.35-6.78) (Table 3). Although the chemical shift of NH protons of amides cannot be predicted appropriately, it is interesting to note that NH proton in minor (**137a-f)** isomers appears upfield (δ 7.45-7.69) where as the same NH proton in major (**136a-f**) isomers appears downfield (δ 7.97-8.81).

In ^{13}C NMR spectra, benzylic tertiary carbon (C-4') appears upfield (δ 52.33-52.84) in the case of major (**136a-f**) isomers while same carbon in minor (**137a-f**) isomers appears downfield (δ 55.25-56.01). Carbonyl carbon (C-2') in the case of major isomer (**136a-f**) appears downfield (δ 175.42-176.12), whereas in the minor isomers (**137a-f**) the same carbon appears upfield (δ 173.14-174.01). (Tabale 3). Methyl protons at C-5 appear upfield (δ 2.07 and 2.13 respectively) in the case of **136c** & **136f** (major isomers) while the same protons in **137c** & **137f** (minor isomers) appears downfield (δ 2.39 and 2.39 respectively). In conclusion we have thus developed a simple diastereoselective (*trans*) synthesis of (indolin-2-one)-3-spiro-5'-[3'-methylene-4'-aryltetrahydrofuran-2'-one] framework, demonstrating the importance of the Baylis-Hillman bromides in synthetic organic chemistry.

Table 3: Camparison of Chemical Shift Values in Major and Minor isomers



major isomer (**136a-f**)



minor isomer (**137a-f**)

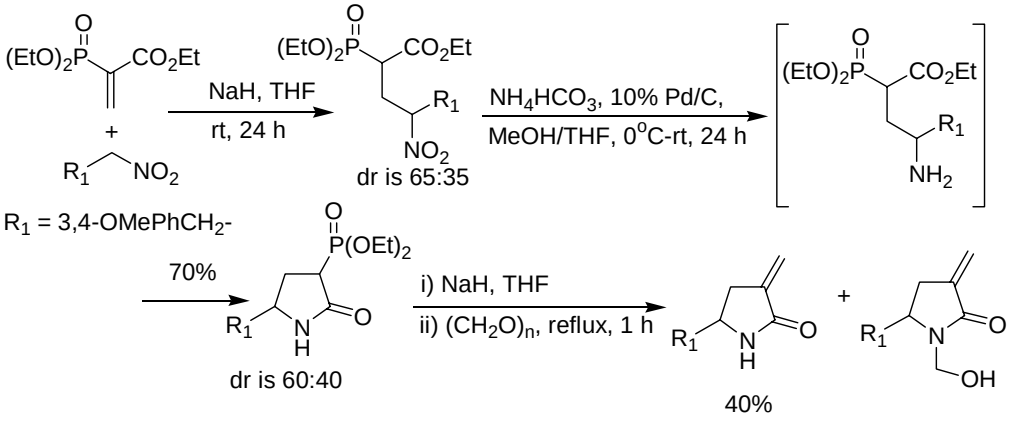
R^1	R^3	product	^{1}H NMR		^{13}C NMR	
			NH (δ)	H-4 (δ)	C-4'(ppm)	C-2' (ppm)
H	H	**136a** **137a**	7.97 7.49	6.62 (6.75)(d) 7.53 (d)	52.82 56.01	176.12 173.83
Cl	H	**136b** **137b**	8.81 7.69	6.70 (6.49) (d) 7.53 (d)	52.78 55.99	175.88 173.76
Me	H	**136c** **137c**	8.62 7.48	6.67 (6.35) (s) 7.34 (s)	52.84 55.93	176.15 174.01
H	Cl	**136d** **137d**	8.25 7.53	6.67 (6.78) (d) 7.52 (d)	52.35 55.31	175.78 173.69
Cl	Cl	**136e** **137e**	8.65 7.45	6.62 (6.70) (d) 7.52 (d)	52.36 55.36	175.42 173.14
Me	Cl	**136f** **137f**	8.32 7.46	6.45(s) 7.33 (s)	52.33 55.25	175.75 173.76

Simple and convenient synthesis of spiro-oxindoles having α-methylene-γ-lactam framework

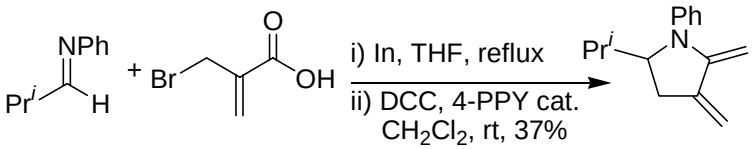
Spiro-oxindole framework is an important structural unit present in several natural products (See page no. 41, Figure 8). α-Methylene-γ-butyrolactam framework also present in natural products such as pukeleimid E (**139**) (isolated from Lyngbya majuscula)[258] and several of these derivatives are known to possess various biological activities.[259-261] α-Methylene-γ-butyrolactams exhibits less cytotoxic activity than the corresponding α-methylene-γ-butyrolactones,[262] making them suitable for cancer treatment. Due to the medicinal importance of these α-methylene-γ-butyrolactam framework several systematic efforts were made for development of simple methodology for synthesis of such derivatives.

Janecki and co-workers[259] have developed a novel, general, and straightforward route to α-methylene-γ-butyrolactams from easily available common intermediates, ethyl-2-diethoxyphosphoryl-4-nitroalkanoates. One representative example is described in Scheme 53.

Scheme 53

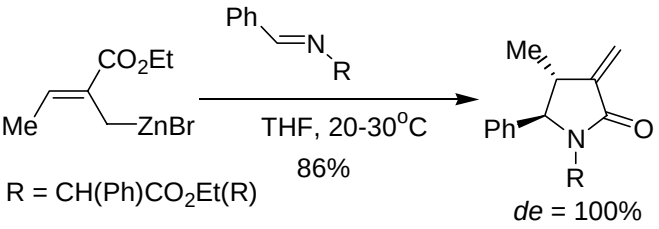


Yus and co-workers[262] have reported a simple route to preparation of α-methylene-γ-butyrolactams via indium mediated reaction between imines and 2-bromomethylprop-2-enoic acid. One representative example is described in Eq. 34.



Eq. 34

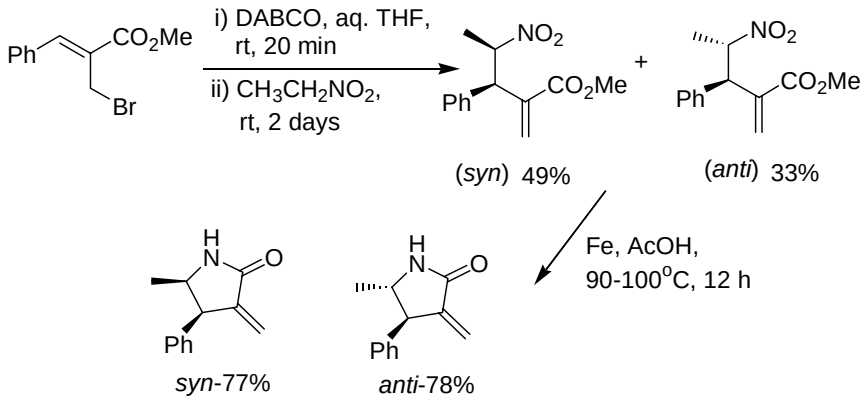
Villieras and co-workers[263] have reported the stereocontrolled synthesis of α-methylene-γ-butyrolactams using crotylzinc reagents. One example is presented in Eq. 35.



Eq. 35

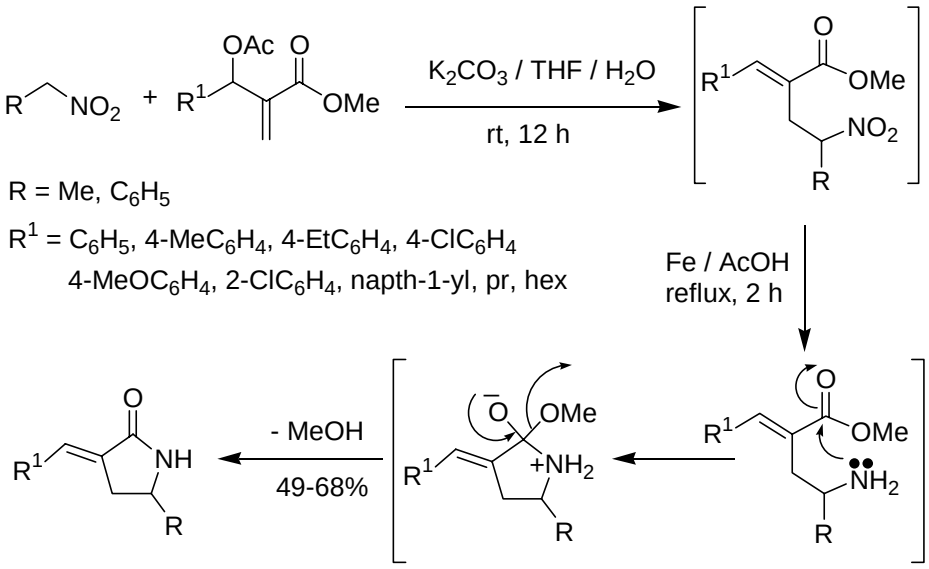
Very recently, Kim and co-workers[264] have developed efficient synthetic method for the synthesis of α-methylene-γ-butyrolactams starting from the Baylis-Hillman bromide following the reaction sequence as described in Scheme 54 (one example is presented).

Scheme 54



Recently our research group[265] has developed a simple, convenient and one-pot transformation of the Baylis-Hillman acetates into substituted γ-lactams [(*E*)-5-alkyl-3-arylidenepyrrolidin-2-ones] *via* the treatment with nitroalkane in the presence of base, followed by reductive cyclization, using Fe/AcOH (Scheme 55).

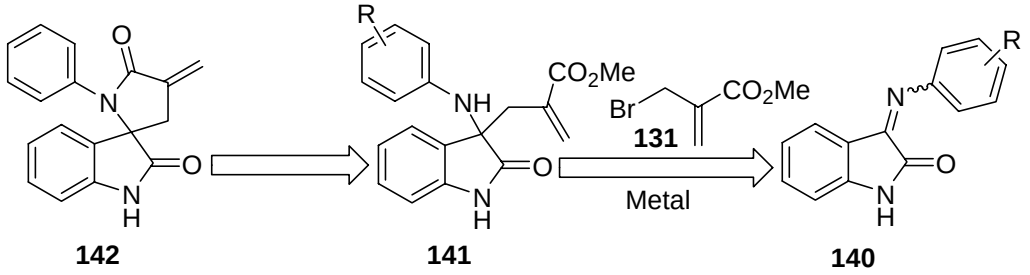
Scheme 55



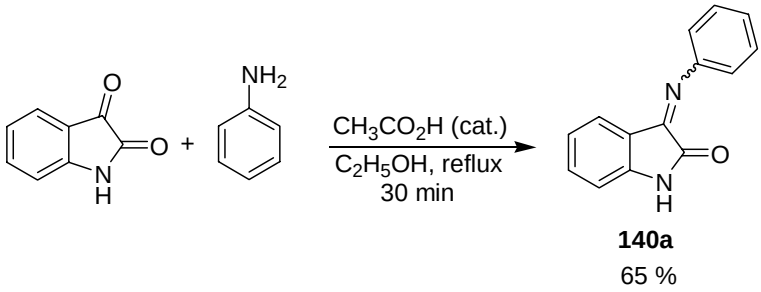
It occurred to us that molecules containing both oxindole framework and α-methylene-γ-butyrolactam skeleton connected by an spiro bridge might provide interesting compounds of medicinal relevance. We, have therefore, directed our studies towards development of simple and convenient methodology for the synthesis of molecules having oxindoles linked with α-methylene-γ-butyrolactam in spiro fashion. Although the applications of Baylis-Hillman bromides for the synthesis of α-methylene-γ-lactam derivatives[262-265] are well known (Eq. 34, 35 & Schemes 54), to the best of our knowledge their utility for the synthesis of oxindole derivatives linked with α-methylene-γ-lactam in spiro fashion is not known in the literature. We envisaged that the C-3 carbon of isatin derivatives can undergo

metal mediated allylation and subsequent cyclization might provide spiro-oxindole having α-methylene-γ-butyrolactam. The retero synthetic pathway is presented in the Scheme 56.

Scheme 56

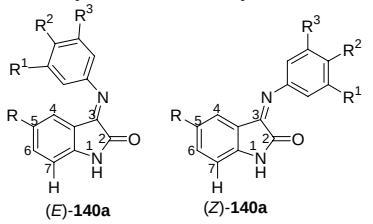


Accordingly we have first selected 3-(phenylimino)indolin-2-one (**140a**) for reaction with 2-(bromomethyl)prop-2-enoate (**131**) to provide methyl 3-(3-anilinoindolin-2-one-3-yl)-2-methylenepropanoate (**141a**). The required 3-(phenylimino)indolin-2-one (**140a**) was prepared from isatin and aniline according to Eq. 36 (Table 4).*

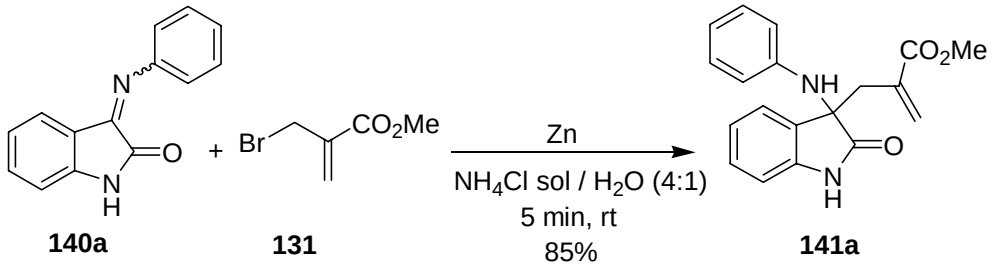


Eq. 36

* ^{1}H NMR spectral analysis clearly indicates this imine is a mixture of stereoisomers [(*E*) and (*Z*)- **140a**] (95:05) (as determined by the integration of H-7 proton signals. It can be tentatively assigned major isomer as the (*E*)- isomer and the minor isomer as the (*Z*)-isomer on the basis of stability. However, we did not proceed in this direction as the stereochemistry will be destroyed in the next step.



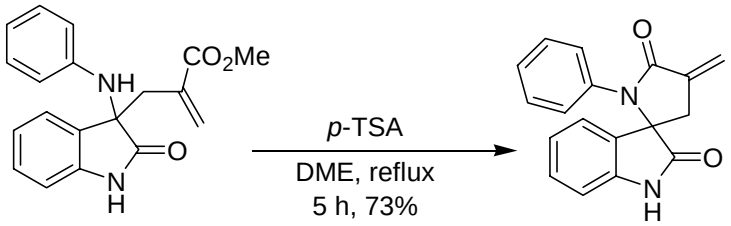
Then we have performed the reaction between 3-(phenylimino)indolin-2-one (**140a**) and methyl 2-(bromomethyl)prop-2-enoate (**131**) in various conditions. Best results were obtained when 3-(phenylimino)indolin-2-one (**140a**) was treated with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc in NH_4Cl / H_2O solution (4:1) at room temperature for 5 min, thus providing the desired oxindole (**141a***) i. e.,* methyl 3-(3-anilinoindolin-2-one-3-yl)-2-methylene propanoate (**141a**) in 85% yield after usual work-up, column chromatography (Eq. 37. Table 5). Structure of product (**141a**) was in full agreement with IR, ^{1}H NMR (Spectrum 19), ^{13}C NMR (Spectrum 20), mass spectral data, and elemental analysis (Eq. 37). Structure of **141a** was further established by single crystal X-ray data (Fig. X7, Table VII).



140a **131** **141a** **Eq. 37**

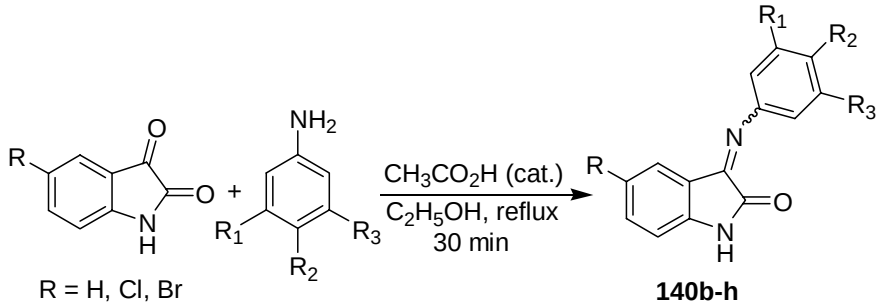
Cyclization of the allylated product (**141a**) has been carried out *via* the treatment with *p*-toluenesulfonic acid in CH_2Cl_2 at reflux for 5 h, thus providing the desired product (indolin-2-one)-3-spiro-5′-[3'-methylene-1'-phenylpyrrolidin-2'-one] (**142a**) in 73% yield after usual work-up, column chromatography (Eq. 38, Table 6). Structure of the product (**142a**) was in full agreement with IR, ^{1}H NMR (spectrum 21), ^{13}C NMR (spectrum 22),

mass (LCMS) spectral data and elemental analyses. Structure of **142a** was further established by single crystal X-ray data (Fig. X8, Table VIII).



141a **142a** **Eq. 38**

With a view to understand the generality of the reaction strategy we have prepared representative imines of isatin (**140b-h**) in 60-78% yields, by the condensation of aryl amines with isatin derivatives under reflux in C_2H_5OH in the presence of catalytic amount of CH_3CO_2H (Eq. 39).[φ] Structures of the imines (**140b-h**) were in full agreement with IR, ^1H NMR, ^{13}C NMR spectral data.

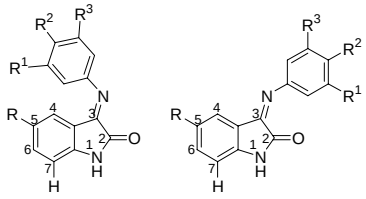


R = H, Cl, Br
R1 = R2 = R3 = H, Me

140b-h
60-78 %

Eq. 39

φ ^1H NMR spectral analysis of the imines **140b, c** indicates that these are diastereomeric mixtures (91:9, and 90:10 ratios respectively) as evidenced by the integration ratios of diastereomeric H-7 protons. ^1H NMR spectral analysis of the imines **140d-h** indicates that these are also diastereomeric mixtures [94:6 (**140d**), 91:9 (**140e**), 90:10 (**140f**), 93:7 (**140g**), 82:18 (**140h**)] as determined by the integration ratios of diastereomeric methyl group protons on the aromatic ring.



(*E*)-**140(b-h)** (*Z*)-**140(b-h)**

Then these imines (**140b-h**) were subjected to reaction with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, providing the corresponding allylated products (**141b-h**) in 70-80% isolated yields (Eq. 40, Table 5). All the products (**141b-h**) are fully characterized by IR, ^{1}H NMR (See: spectra 23 & 27 for molecules **141d** & **141g**), ^{13}C NMR (See: spectra 24 & 28 for molecules **141d** & **141g**), mass (LCMS) spectral data and elemental analyses.

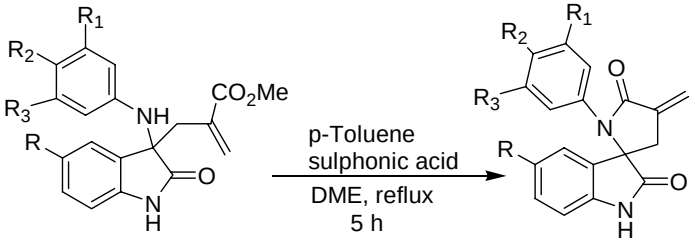
140b-h **131** **141b-h**

R = H, Cl, Br

$R_1 = R_2 = R_3$ = H,Me

Eq. 40

The allylated products (**141b-h**) were then successfully transformed into the corresponding spiro-oxindoles via treatment of p-TSA in DMF for 5 h under reflux , thus providing the products (**142b-h**) in 67-75% isolated yields (**142b-h**) (Eq. 41). All the compounds (**142b-h**) are fully characterized by IR, ^{1}H NMR (See: spectra 25 & 29 for molecules **142d** & **142g**), ^{13}C NMR (See: spectra 26 & 30 for molecules **142d** & **142g**), mass (LCMS) spectral data and elemental analyses. Structures of **142b**, **142g** were further established by single crystal X-ray data (Fig. X9 & X10, Tables IX & X).



141b-h

R = Cl, Br

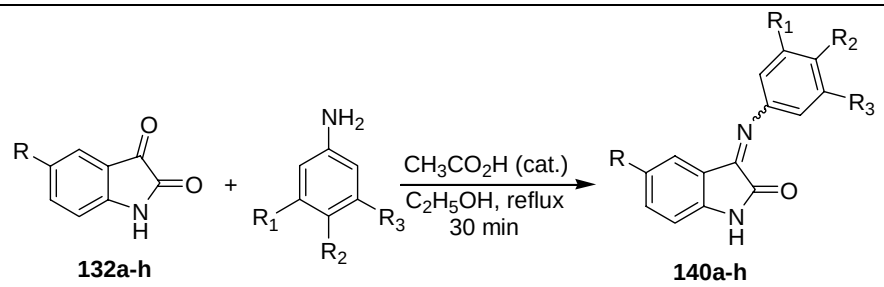
$R_1 = R_2 = R_3$ = H, Me

142b-h

67-75 %

Eq. 41

Table 4: Synthesis of imines (140a-h)[a]



132a-h **140a-h**

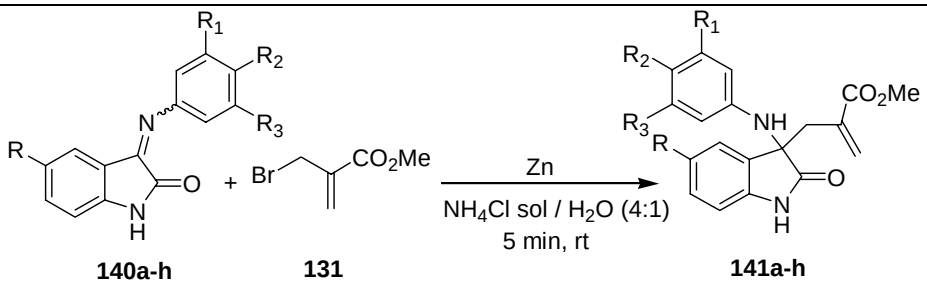
Isatin	R	Amine	R_1	R_2	R_3	Imine[b]	Yield [c](%)	Mp(°C)
132a	H	**143a**	H	H	H	**140a**	65	216-218
132b	Cl	**143a**	H	H	H	**140b**	78	252-254
132d	Br	**143a**	H	H	H	**140c**	75	260-262
132a	H	**143b**	Me	H	Me	**140d**	71	222-224
132b	Cl	**143b**	Me	H	Me	**140e**	77	256-259
132d	Br	**143b**	Me	H	Me	**140f**	72	240-242
132a	H	**143c**	H	Me	H	**140g**	65	220-222
132b	Cl	**143c**	H	Me	H	**140h**	60	286-288

a) All reactions were carried out on 10 mmols scale of isatin derivatives (**132a,b,d**) with aryl amines (**143a-c**) (10 mmols) in ethanol under reflux for 30 min in the presence of catalytic amount of acetic acid.

b) All compounds (**140a-h**) were obtained as colored solids and fully characterized.

c) Yields of pure products based on isatins.

Table 5: Allylation of imines (140a-h) with methyl 2-(bromomethyl)prop-2-enoate(131)[a]:



Imine	R	R_1	R_2	R_3	Allylated imine[b]	Yield [c](%)	Mp (°C)
140a	H	H	H	H	**141a**[d]	85	156-158
140b	Cl	H	H	H	**141b**	79	146-148
140c	Br	H	H	H	**141c**	72	158-160
140d	H	Me	H	Me	**141d**	80	152-154
140e	Cl	Me	H	Me	**141e**	77	198-200
140f	Br	Me	H	Me	**141f**	75	200-202
140g	H	H	Me	H	**141g**	70	150-152
140h	Cl	H	Me	H	**141h**	72	180-182

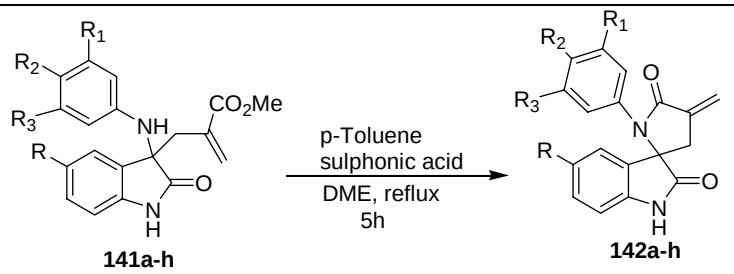
a) All reactions were carried out on 2 mmol scale of imines (**140a-h**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) (2.2 mmol) in the presence of zinc (4 mmol) in NH_4Cl sol/THF (4:1) at room temperature for 5 min.

b) All compounds (**141a-h**) were obtained as colorless solids and fully characterized.

c) Yields of pure products based on imines.

d) Structure of this molecule was further confirmed by single crystal X-ray data.

Table 6: Synthesis of spiro-oxindoles (141→142)[a]:



Allyated imine	R	R_1	R_2	R_3	Product[b]	Yield [c](%)	Mp. (°C)
141a	H	H	H	H	**142a**[d]	73	222-224
141b	Cl	H	H	H	**142b**[d]	74	226-228
141c	Br	H	H	H	**142c**	75	192-194
141d	H	Me	H	Me	**142d**	70	274-276
141e	Cl	Me	H	Me	**142e**	72	148-150
141f	Br	Me	H	Me	**142f**	67	124-126
141g	H	H	Me	H	**142g**[d]	68	266-268
141h	Cl	H	Me	H	**142h**	73	252-254

a) All reactions were carried out on 1 mmol scale of allyl amines (**141a-h**) with p-TSA in DME at reflux of 5 h.

b) All compounds (**142a-h**) were obtained as colorless solids and fully characterized.

c) Yields of pure products (**142a-h**) based on **141a-h**.

d) Structures of these products were further confirmed by single crystal X-ray data.

In conclusion we have developed a simple methodology for synthesis of (indolin-2-one)-3-spiro-5′-[3'-methylene-1'-arylpyrrolidin-2'-ones] via the treatment of methyl 2-(bromomethyl)prop-2-enoate (**131**) with aryliminoindolin-2-ones under the influence of zinc, followed by cyclization in the presence of p-TSA, thus demonstrating the potential of Baylis-Hillman bromides in organic synthesis.

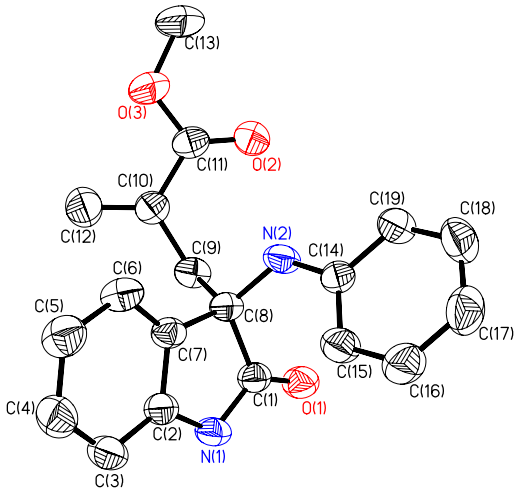


Fig. X7

ORTEP diagram of the compound 141a

(Hydrogen atoms were omitted for clarity)

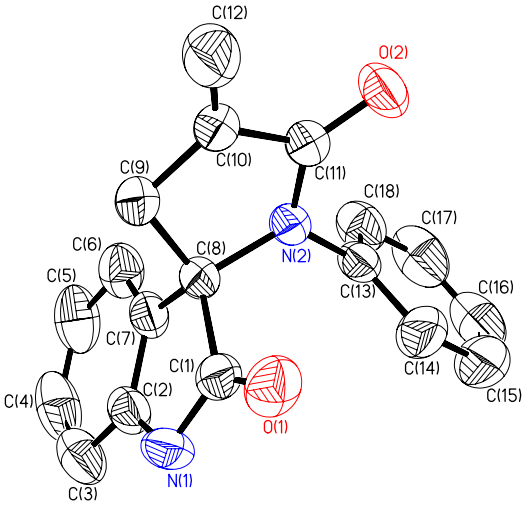


Fig. X8

ORTEP diagram of the compound 142a

(Hydrogen atoms were omitted for clarity)

Table VII. Crystal data and structure refinement for 141a

Identification code	**141a**	
Empirical formula	$C_{19}H_{18}N_2O_3$	
Formula weight	322.13	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system, space group	triclinic, P-1	
Unit cell dimensions	a = 8.8386(7) Å	α = 87.9850(10) deg.
	b = 9.5904(8) Å	β = 73.1510(10) deg.
	c = 10.8673(9) Å	γ = 67.1710(10) deg.
Volume	809.44(11) $Å^3$	
Z, Calculated density	2, 1.3232 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	340	
Crystal size	0.35 x 0.42 x 0.32 mm^3	
Theta range for data collection	1.97 to 28.12 deg.	
Limiting indices	-11<=h<=11, -12<=k<=12, -14<=l<=14	
Reflections collected / unique	9418 / 3747 [R(int) = 0.0292]	
Completeness to theta = 28.12	94.6%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3747 / 0 / 218	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0573, wR2 = 0.1623	
R indices (all data)	R1 = 0.0679, wR2 = 0.1721	
Largest diff. peak and hole	0.263 and -0.276 $e.Å^{-3}$	

Table VIII. Crystal data and structure refinement for 142a

Identification code	**142a**	
Empirical formula	$C_{18}H_{14}N_2O_2$	
Formula weight	290.11	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system, space group	monoclinic, P 21/c	
Unit cell dimensions	a = 8.7041(15) Å	α = 90 deg.
	b = 14.199(3) Å	β = 110.27 deg.
	c = 12.564(2) Å	γ = 90 deg.
Volume	1456.6(4) $Å^3$	
Z, Calculated density	4, 1.422 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	608	
Crystal size	0.31 x 0.15 x 0.26 mm	
Theta range for data collection	2.25 to 25.89 deg.	
Limiting indices	-10<=h<=10, -16<=k<=17, -13<=l<=15	
Reflections collected / unique	8959 / 2833 [R(int) = 0.0363]	
Completeness to theta = 25.89	99.8%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2833 / 0 / 199	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.1087	
R indices (all data)	R1 = 0.0602, wR2 = 0.1159	
Largest diff. peak and hole	0.134 and -0.184 $e.A^{-3}$	

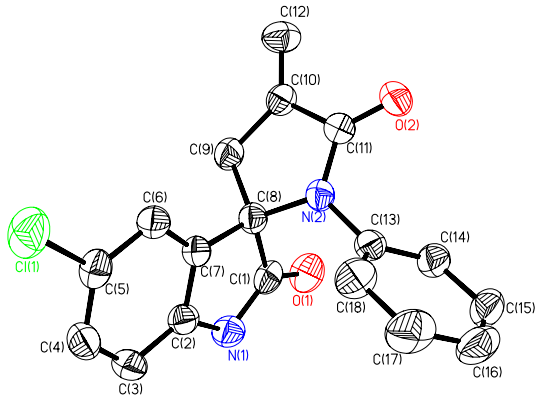


Fig. X9

ORTEP diagram of the compound 142b

(Hydrogen atoms were omitted for clarity)

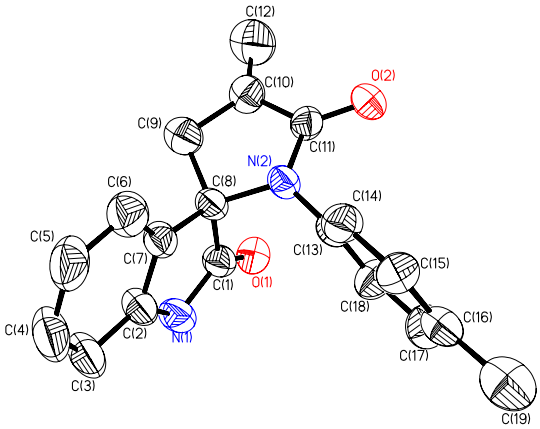


Fig. X10

ORTEP diagram of the compound 142g

(Hydrogen atoms were omitted for clarity)

Table IX. Crystal data and structure refinement for 142b.

Identification code	**142b**
Empirical formula	$C_{18}H_{13}ClN_2O_2$
Formula weight	324.07
Temperature	298K
Wavelength	0.71073 Å
Crystal system, space group	orthorhombic, P 21 21 21
Unit cell dimensions	a = 6.3047(4) Å α = 90 deg.
	b = 14.4423(10) Å β = 90 deg.
	c = 16.2202(11) Å γ = 90 deg.
Volume	1476.92(17) $Å^3$
Z, Calculated density	4, 1.459 Mg/m^3
Absorption coefficient	0.270 mm^{-1}
F(000)	672
Crystal size	0.36 x 0.15 x 0.32 mm^3
Theta range for data collection	1.89 to 25.95 deg.
Limiting indices	-7<=h<=7, -17<=k<=16, -19<=l<=19
Reflections collected / unique	15220 / 2881 [R(int) = 0.0199]
Completeness to theta = 25.95	99.7%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2879 / 0 / 208
Goodness-of-fit on F^2	1.056
Final R indices [I>2sigma(I)]	R1 = 0.0300, wR2 = 0.0772
R indices (all data)	R1 = 0.0321, wR2 = 0.0786
Absolute structure parameter	0.02(6)
Largest diff. peak and hole	0.153 and -0.161 $e.A^{-3}$

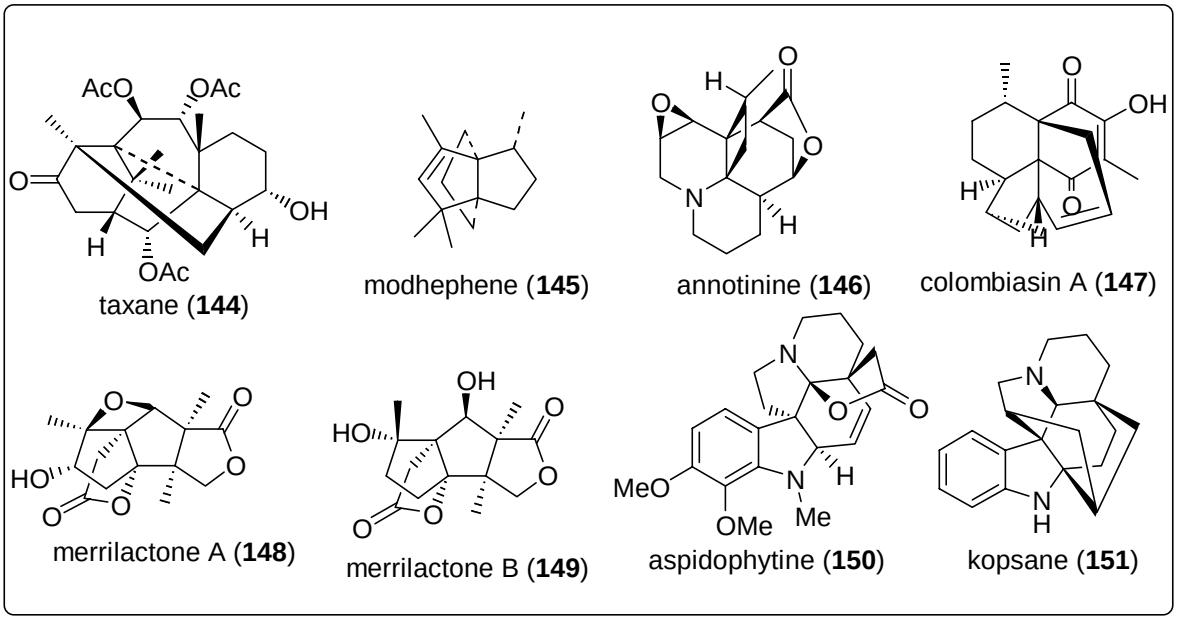
Table X. Crystal data and structure refinement for 142g.

Identification code	142g	
Empirical formula	$C_{19}H_{16}N_2O_2$	
Formula weight	304.12	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system, space group	tetragonal, P4(3)	
Unit cell dimensions	a = 10.499(2) Å	α = 90 deg.
	b = 10.499(2) Å	β = 90 deg.
	c = 14.302(6) Å	γ = 90 deg.
Volume	1576.6(8) $Å^3$	
Z, Calculated density	4, 1.279 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	640	
Crystal size	0.15 x 0.23 x 0.35 mm	
Theta range for data collection	1.94 to 26.08 deg.	
Limiting indices	-12<=h<=12, -12<=k<=12, -17<=l<=17	
Reflections collected / unique	15289 / 3096 [R(int) = 0.4289]	
Completeness to theta = 26.08	99.9%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3077 / 1 / 209	
Goodness-of-fit on F^2	0.972	
Final R indices [I>2sigma(I)]	R1 = 0.0770, wR2 = 0.1571	
R indices (all data)	R1 = 0.1026, wR2 = 0.1757	
Absolute structure parameter	1(2)	
Largest diff. peak and hole	0.137 and -0.214 $e.A^{-3}$	

Simple and facile synthesis of propellanes from the acetates of the Baylis-Hillman adducts

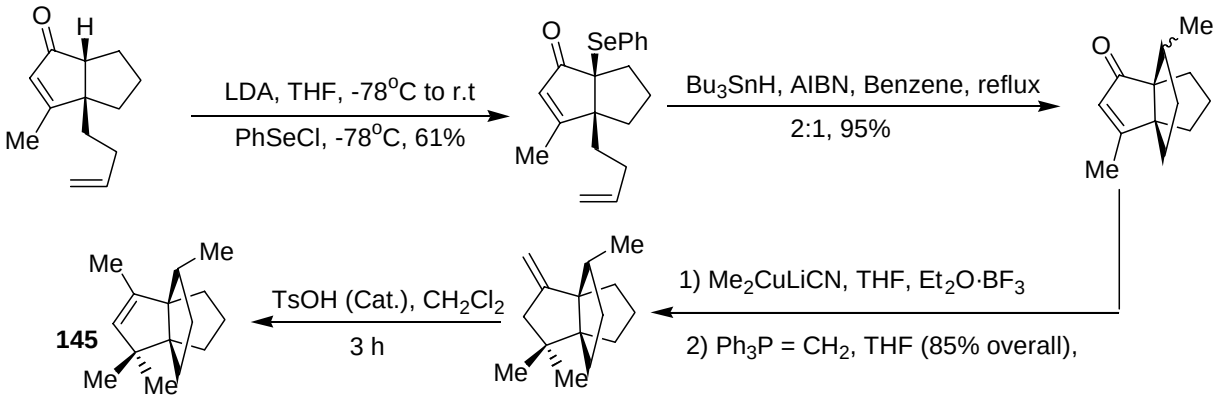
The name propellane was proposed by Ginsburg for compounds having three nonzero bridges and one zero bridge between a pair of bridgehead carbons.[266] It has attracted the organic chemists because of its unusual molecular structure, reactivity and properties.[266] This propellane framework is present in several natural products such as taxane (**144**),[267] modhephene (**145**),[268] annotinine (**146**),[269] colombiasin A (**147**),[270] merrilactone A (**148**),[271,272] merrilactone B (**149**),[273] aspidophytine (**150**),[274] kopsane (**151**)[275] *etc*., (Fig. 10). Due to the importance of propellane framework development of such derivatives has become an attractive synthetic endeavor in organic synthesis. Some of the interesting and recent literature methodologies are presented in the following section (Eq. 42-44 & Scheme 57).

Figure 10

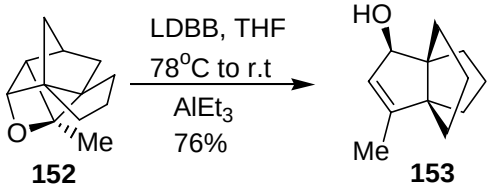


Rawal and Dvorak[276] have developed a simple synthesis of modhephene (**145**), following the reaction sequence as described in Scheme 57.

Scheme 57

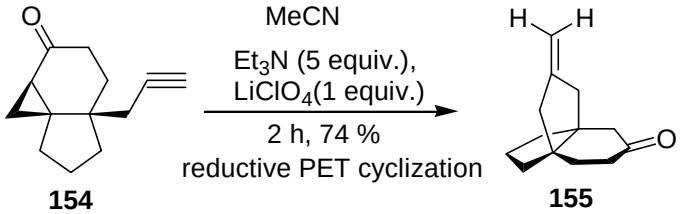


Rawal and co-workers[277] have synthesized propellane (**153**) from oxetane (**152**) using lithium di-*tert*-butylbiphenylide (LDBB)/Et_3N as key reagent (Eq. 42).



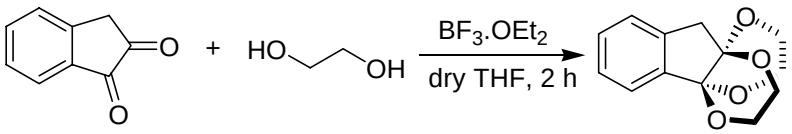
Eq. 42

Mattay and co-workers[278] have reported a facile methodology for the synthesis of propellane **155** by the photoinduced electron transfer (PET) of the compound **154** in acetonitrile as described in Eq. 43.



Eq. 43

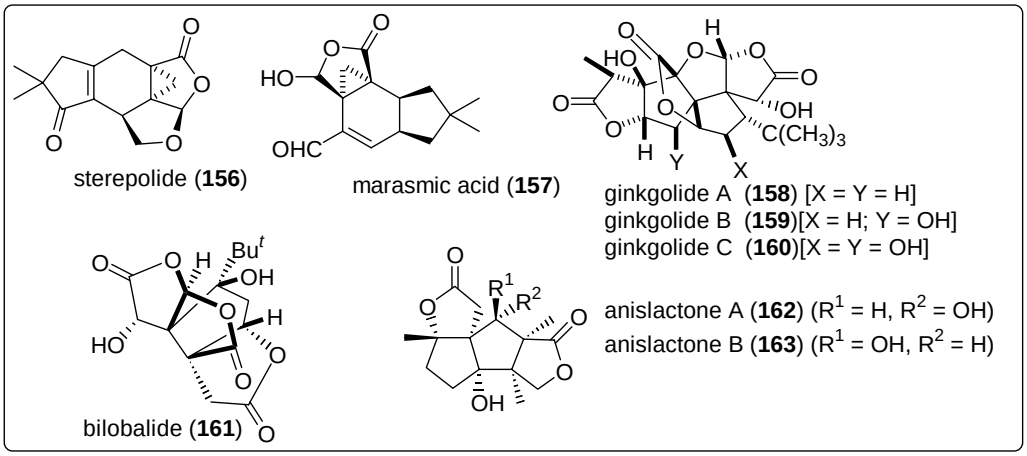
Almong and co-workers[279] have described an interesting protocol for the synthesis of propellanes by the reaction of 1,2-indanedione with ethylene glycol or with ethanedithiol in the presence of BF_3.OEt2 . One representative example is described in Eq. 44.



Eq. 44

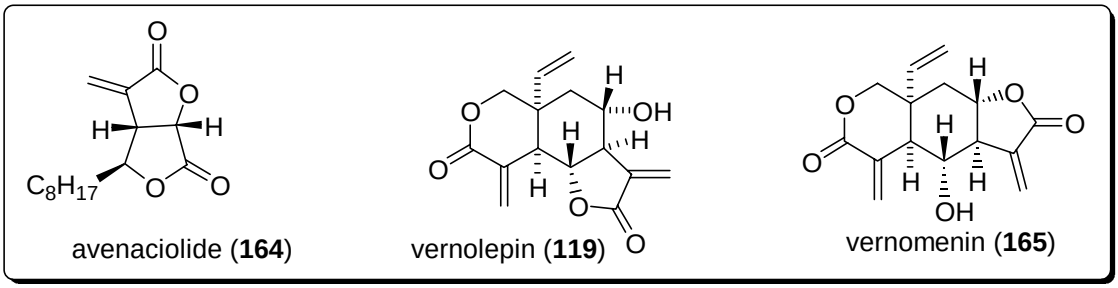
Polycyclic, polylactone structural framework is present in several natural products such as sterepolide (**156**),[280] marasmic acid (**157**),[281] ginkgolides (A, B, C) (**158**, **159**, **160**),[282, 283] bilobalide (**161**)[284,282] , anislactone A and B (**162**, **163**)[273]*etc*., (Fig. 11).

Figure 11



Also polylactone framework with α-exo functionality is present in many biologically active molecules such as avenociolide (**164**),[285] vernolepin (**119**),[245] and vernomenin (**165**)[286] *etc*., (Fig. 12).

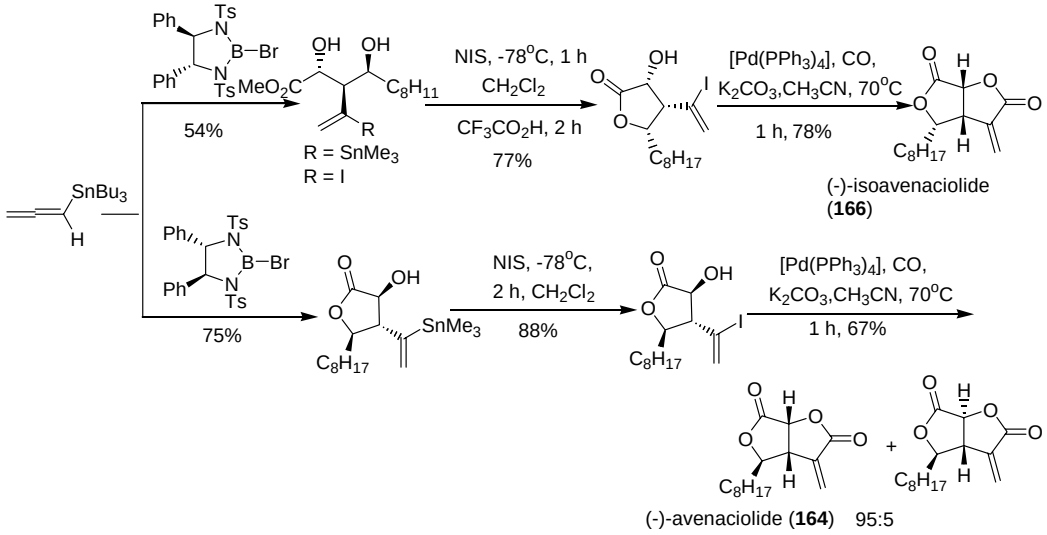
Figure 12



Due to the biological importance of the polylactone framework several synthetic strategies were reported in the literature. Some recent reports are described in this section.

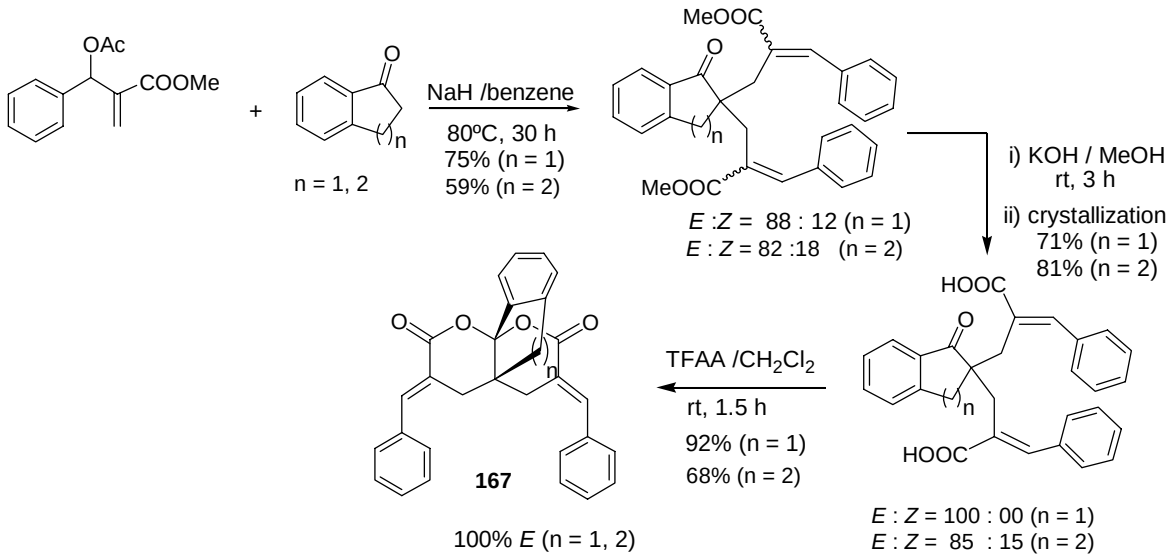
Very recently, Yu and co-workers[287] have reported the synthesis of avenaciolide (**164**) and isoavenaciolide (**166**), following the reaction as described in Scheme 58.

Scheme 58



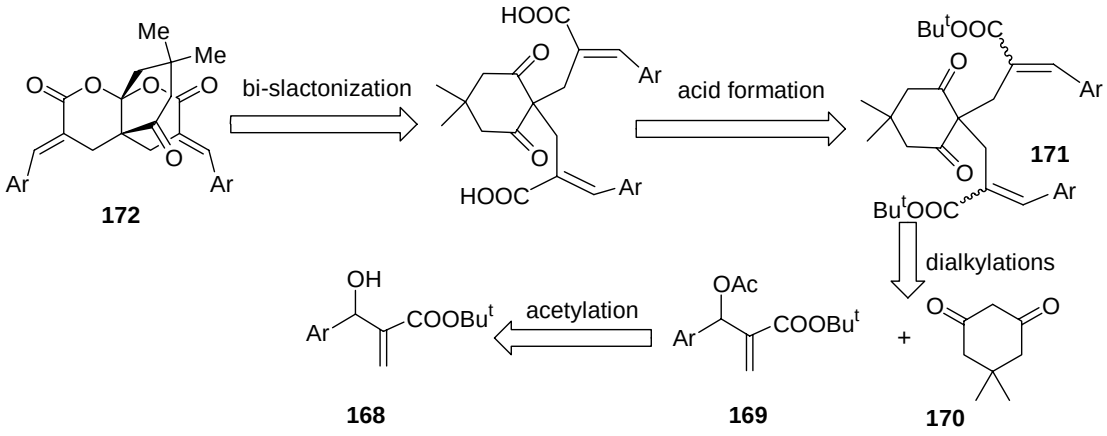
Recently our research group[288] have described a simple and convenient synthesis of 2,10-dioxa[4.4.3]propellane-3,9-diones and 2, 10-dioxa[4.4.4]propellane-3,9-dione, using acetates of the Baylis-Hillman adducts. One example is in the following Scheme 59.

Scheme 59



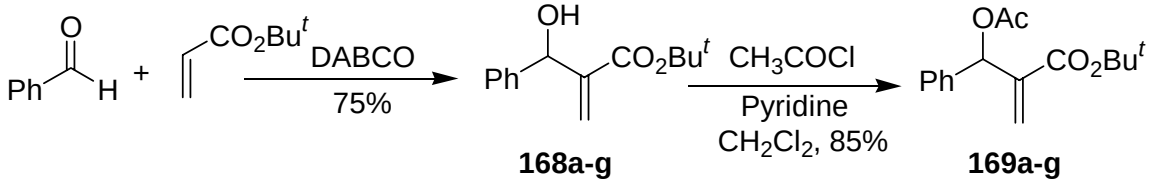
Our earlier methodology for obtaining propellano bislactones (Scheme 59) from Baylis-Hillman acetates involves three steps and we need to isolate the bis-cinnamic ester, bis-cinnamic acid and finally the bislactone. We therefore felt that it would be interesting to develop a simple strategy avoiding the isolation of the intermediates. It occurred to us the Baylis-Hillman acetate having the tert-butyl ester functionality, can be transformed into 4,8-bis[(*E*)-arylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.$0^{1,6}$]tetradecane-3,9,14-triones without isolation of any intermediate (as the tert-buty ester can be easily converted *in situ* into the corresponding acid *via* the treatment with any acid) according to the reterosynthetic strategy (Scheme 60).

Scheme 60



First we have selected, *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate **(169a)** as substrate. The required Baylis-Hillman acetate **169a** was prepared from the Baylis-Hillman alcohol *i.e.*, *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**168a**) (which was obtained by the Baylis-Hillman reaction of benzaldehyde with *tert*-butyl acrylate) according to Scheme 61.

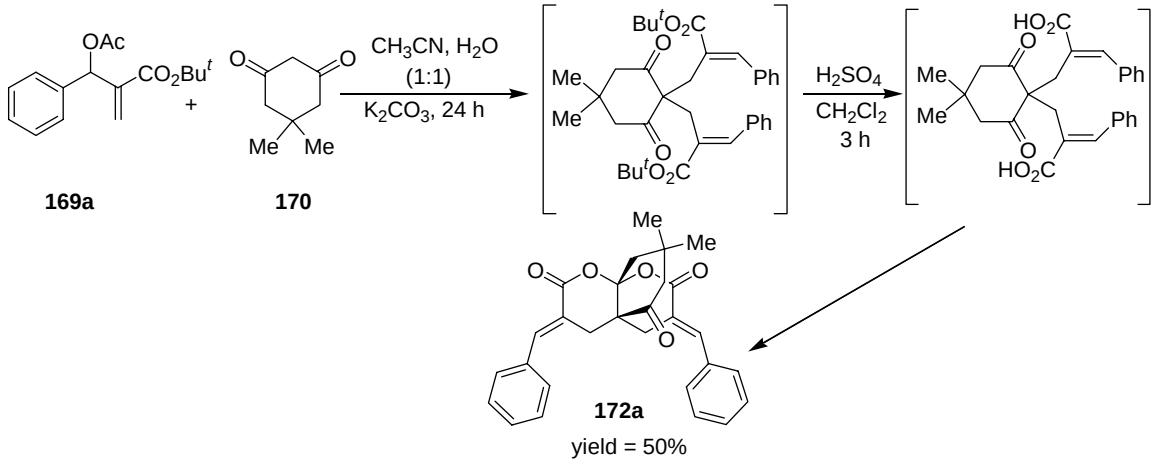
Scheme 61



We have next planned to examine the possible transformation of **169a** into the corresponding propellano-bislactone (**172a**) without isolating any bis-cinnamic ester or acid The best results in this direction were obtained when 5,5-dimethyl-1,3-cyclohexane-dione (**170**) (0.5 mmol) was treated with *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**169a**) (1.25 mmol) in the presence of K_2CO_3 (2.5 mmol) in

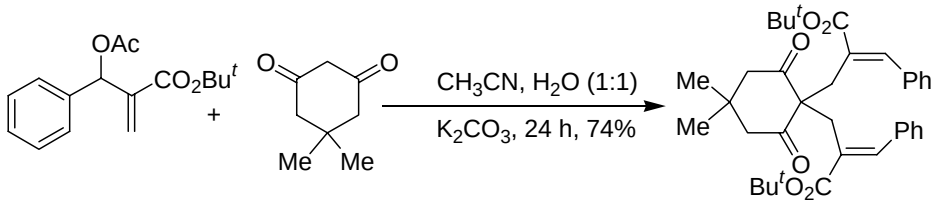
acetonitrile/water (1:1, 2 mL) under reflux for 24 hours, followed by the reaction of the resulting crude bis-ester (without isolation after usual work-up) with H_2SO_4 (1 mmol) in CH_2Cl_2 (1 mL), at room temperature for 3 hours thus providing the desired 4,8-bis[(*E*)-benzylidene]-12,12-dimethyl-2,10-dioxatricyclo-[4.4.4.$0^{1,6}$]tetradecane-3,9,14-trione (**172a**) in 50% isolated yield as colorless solid after purification through column chromatography (20% ethyl acetate in hexanes) (Scheme 62, Table 7). The structure of the product **172a** is in full agreement with the IR, ^1H, ^{13}C NMR, mass spectral data and elemental analysis. Structure of **172a** was further established by single crystal X-ray data (Fig. X11, Table XI).

Scheme 62



With a view to understand whether the treatment of the bis-cinnamic ester (after isolation) with conc. H_2SO_4 will provide better yields than treating the crude bis ester with H_2SO_4, we have isolated the bis-cinnamic ester i.e., 5, 5-dimethyl-2,2-bis [(2*E*)-2-*tert*-butoxycarbonyl-3-phenylprop-2-en-1-yl]cyclohexane-1,3-dione (**171**) in 74% yield as colorless solid after purification by column chromatrography (silica gel 10% ethyl acetate

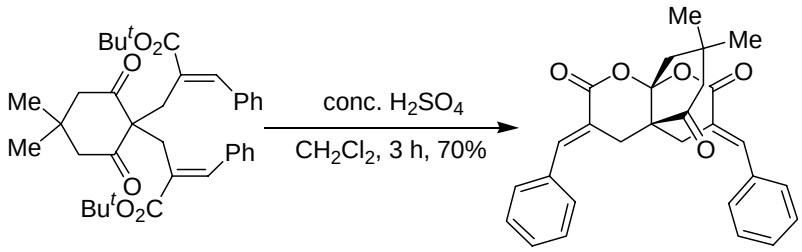
in hexanes) (Eq. 45). The structure of this bis-cinnamic ester **171** was in agreement with IR, ^{1}H NMR (spectrum 31), ^{13}C NMR (spectrum 32) spectral data. Structure of **171** was further established by single crystal X-ray data (Fig. X12, Table XII).



169a **170** **171**

Eq. 45

Bislactonization of the bis-cinnamic ester **171** was performed with conc. H_2SO_4. Thus treatment of 5, 5-dimethyl-2,2-bis [(2*E*)-2-*tert*-butoxycarbonyl-3-phenylprop-2-en-1-yl]cyclohexane-1,3-dione (**171**) (0.5 mmol) with sulfuric acid (1 mmol) in CH_2Cl_2 (1 mL) at room temperature for 3 hours provided the expected 4,8-bis[(*E*)-benzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetradecane-3,9,14-trione (**172a**) in 70% (0.155 g) yield as colorless solid (Eq. 46, Table 7). The structure of the product **172a** is in full agreement with that prepared without isolation of bislactone.



171 **172a**

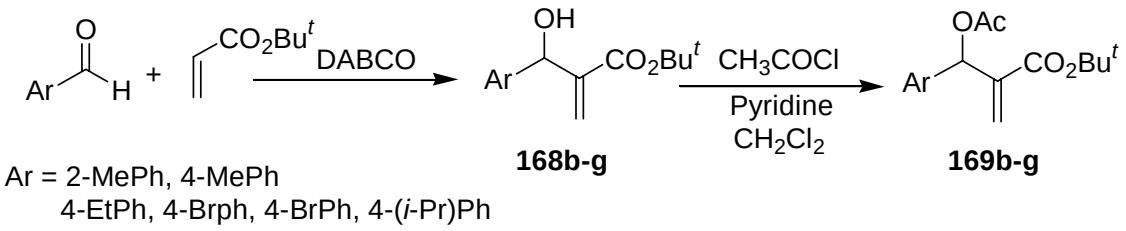
Eq. 46

We have successfully thus obtained the bislactone **172** in 52% overall yield. Since there is no much difference in the isolated yields of the bislactones in both the procedures (i.e.,without or with isolating the bis ester), we have selected the procedure having one iso-

lation procedure as the method of choice and extended this strategy to a representative class of the acetates of the Baylis-Hillman adducts.

We have then prepared representative Baylis-Hillman alcohols (**168b-g**) *via* the coupling of various aldehydes with *tert*-butyl acrylate in the presence of DABCO (**1**), using silica gel as solid phase medium and transformed them into the corresponding Baylis-Hillman acetates (**169b-g**) by treatment with acetyl chloride and pyridine in CH_2Cl_2 (Scheme 63).

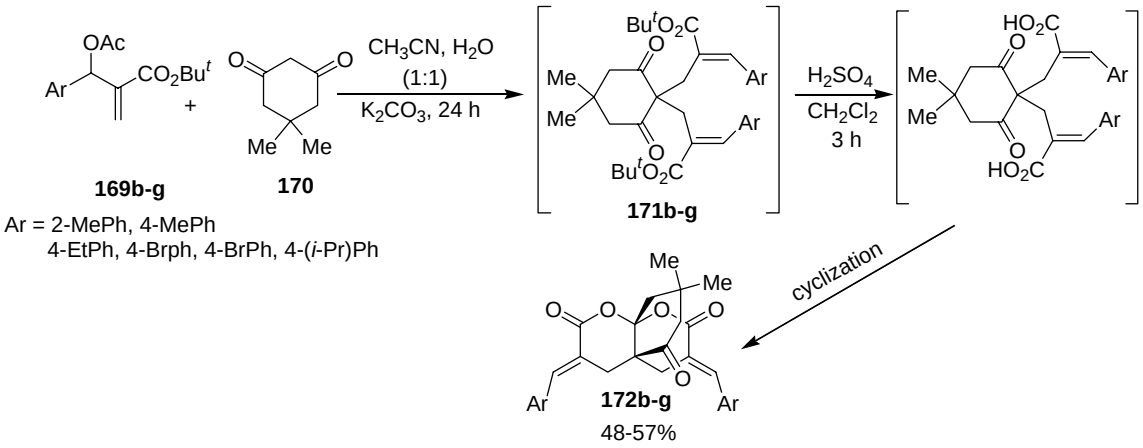
Scheme 63



Then we successfully transformed the Balis-Hillman acetates (**169b-g**) into bislactones (**172b-g**) in 48-57% isolated yields (Scheme 64, Table 7). All the bislactones (**172b-g**) were fully characterized through IR, ^{1}H NMR (See: spectra 35, 37 & 39 for molecules **172c**, **172d** & **172g**), ^{13}C NMR (See: spectra 36, 38 & 40 for molecules **172c**, **172d** & **172g**), mass spectral data, and elemental analysis.

A plausible mechanism for the formation of propellano-bislactone from the diacid is presented in the Scheme 65

Scheme 64

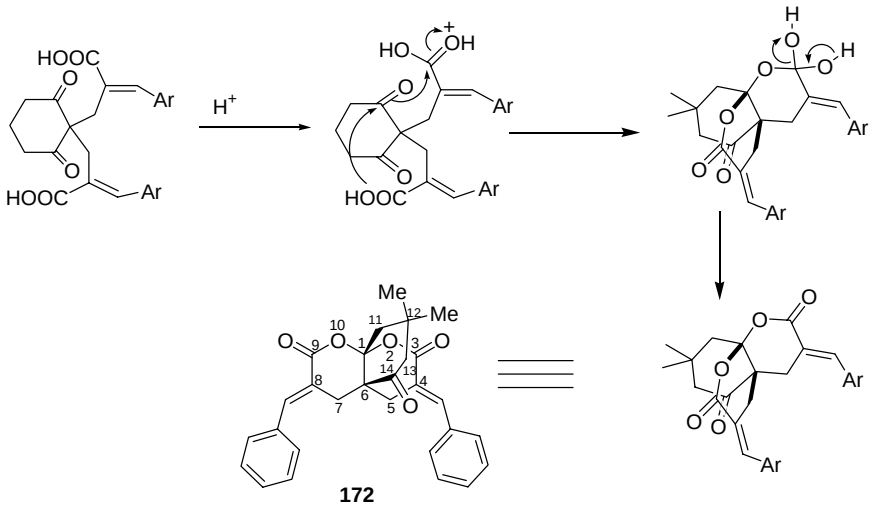


169b-g **170** **171b-g**

Ar = 2-MePh, 4-MePh
4-EtPh, 4-Brph, 4-BrPh, 4-(*i*-Pr)Ph

172b-g
48-57%

Scheme 65



172

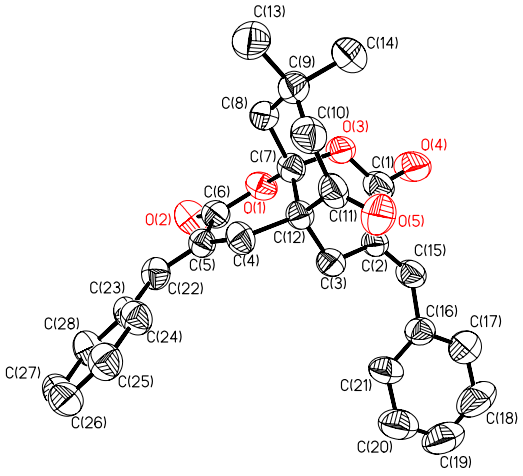


Fig. X11

ORTEP diagram of the compound 172a

(Hydrogen atoms were omitted for clarity)

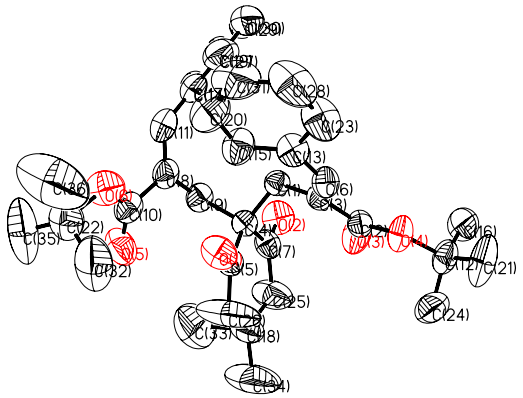


Fig. X12

ORTEP diagram of the compound 171

(Hydrogen atoms were omitted for clarity)

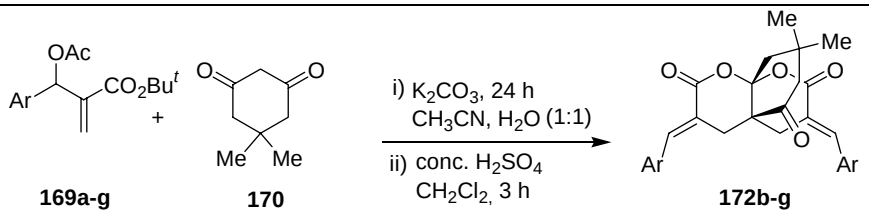
Table XI. Crystal data and structure refinement for 172a

Identification code	**172a**	
Empirical formula	$C_{28}H_{26}O_5$	
Formula weight	442.49	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system, space group	monoclinic, Cc	
Unit cell dimensions	a = 19.953(3) Å	α = 90 deg.
	b = 12.4480(15) Å	β = 111.039(2) deg.
	c = 9.9885(12) Å	γ = 90 deg.
Volume	2315.5(5) $Å^3$	
Z, Calculated density	4, 1.261 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	936	
Crystal size	0.26 x 0.35 x 0.42 mm^3	
Theta range for data collection	1.97 to 26.02 deg.	
Limiting indices	-24<=h<=24, -12<=k<=15, -12<=l<=12	
Reflections collected / unique	7266 / 4052 [R(int) = 0.0485]	
Completeness to theta = 26.02	99.8%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4052 / 2 / 300	
Goodness-of-fit on F^2	0.756	
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.0615	
R indices (all data)	R1 = 0.0936, wR2 = 0.0725	
Absolute structure parameter	-0.9(11)	
Largest diff. peak and hole	0.091 and -0.115 $e.A^{-3}$	

Table XII. Crystal data and structure refinement for 171

Identification code	db116	
Empirical formula	$C_{36}H_{44}O_6$	
Formula weight	572.31	
Temperature	298K	
Wavelength	0.71073 Å	
Crystal system, space group	triclinic, P -1	
Unit cell dimensions	a = 10.6109(9) Å	α = 74.2760(10) deg.
	b = 11.1443(10) Å	β = 84.9340(10) deg.
	c = 15.8224(14) Å	γ = 67.5850(10) deg.
Volume	1664.7(3) $Å^3$	
Z, Calculated density	2, 1.137 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	616	
Crystal size	0.34 x 0.18 x 0.38 mm	
Theta range for data collection	2.05 to 26.03 deg.	
Limiting indices	-13<=h<=13, -13<=k<=13, -19<=l<=19	
Reflections collected / unique	17409 / 6526 [R(int) = 0.0617]	
Completeness to theta = 26.03	99.4%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6526 / 0 / 387	
Goodness-of-fit on F^2	1.182	
Final R indices [I>2sigma(I)]	R1 = 0.0980, wR2 = 0.3017	
R indices (all data)	R1 = 0.1261, wR2 = 0.3323	
Largest diff. peak and hole	1.437 and -0.412 $e.A^{-3}$	

Table 7: Synthesis of prpellano-bislactones:[a]



169a-g **170** **172b-g**

Allyl Acetate	Ar	Product[b]	Yield (%)[c]	Mp (°C)
169a	Ph	**172a**[d]	50	168-170
169b	2-MePh	**172b**	52	205-207
169c	4-MePh	**172c**	48	206-208
169d	4-EtPh	**172d**	54	144-146
169e	4-BrPh	**172e**	57	266-268
169f	4-ClPh	**172f**	52	252-254
169g	4-(*i*-pr)Ph	**172g**	56	178-180

a) All reactions were carried out on 0.5 mmol scale of 5,5-dimethyl-1,3-cyclohexanedione (**170**) with 1.25 mmol of Baylis-Hillman acetates (**169a-g**) in the presence of K_2CO_3 (2.5 mmol) in CH_3CN / H_2O solvent system at reflux for 24 h, was treated with Conc. H_2SO_4 at room temperature for 3 hours.

b) All bislactones (**172a-g**) were obtained as colorless solids and gave satisfactory IR, ^1H, ^{13}C NMR, mass spectral data and elemental analyses.

c) Yields of the bislactones (**172a-g**) obtained after column chromatography (silica gel, 20% EtoAc in Hexanes)

d) Structure of this product was further confirmed by single crystal X-ray data

In conclusion we have developed a simple protocol for the transformation of acetates of the Baylis-Hillman adducts into [4.4.4.] propellano-bislactones i.e., 4,8-bis[(*E*)-arylidene]-12,12-dimethyl-2,10-dioxa-tricyclo[4.4.4.$0^{1,6}$]tetradecane-3,9,14-triones.

CONCLUSIONS

Considerable success has been achieved in our objectives on the application of the Baylis-Hillman adducts as mentioned in the beginning of the section. We have successfully prepared spiro-oxindoles i.e., (indolin-2-one)-3-spiro-5′-[3′-methylenetetrahydrofuran-2′-ones] (**133a-h**) *via* the treatment of methyl 2-(bromomethyl)prop-2-enoate (**131**) (the allyl bromide derived from the Baylis-Hillman alcohol) with isatin derivatives under the influence of zinc in a simple and one-pot methodology.

We have successfully developed simple and one pot diastereoselective synthesis of (indolin-2-one)-3-spiro-5'-[3'-methylene-4'-aryltetrahydrofuran-2'-ones] (**136a-h**) *via* the reaction between Baylis-Hillman bromides i.e., methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates (**135a-c**) and isatin derivatives, under the influence of zinc.

We have developed simple protocol for the synthesis of spiro-oxindole derivatives containing α-methylene-γ-lactam skeleton (**142a-h**) (connected by an interesting spiro bridge) *via* the treatment of methyl 2-(bromomethyl)prop-2-enoate (**131**) with 3-(arylimino)indolin-2-ones (**140a-h**) under the influence of zinc, followed by cyclization of the resulting amine esters (**141a-h**) in the presence of *p*-toluenesulfonic acid.

Simple transformation of acetates of the Baylis-Hillman adducts into [4.4.4.]propellano-bislactones i.e., 4,8-bis[(*E*)-arylidene]-12,12-dimethyl-2,10-dioxatricy-clo [4.4.4.$0^{1,6}$]tetra-decane-3,9,14-triones (**172a-g**) has been achieved.

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, t of ABq = triplet 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.

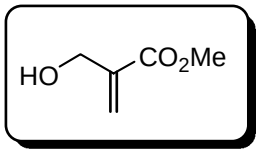
X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 A^o) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance 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).

Methyl 2-(hydroxymethyl)prop 2-enoate (130):

This compound was prepared according to the procedure developed in our laboratory.[122]

A mixture of paraformaldehyde (100 mmol, 3.003 g), aqueous trimethylamine (30 %, w/v) (120 mmol, 23.62 mL) and methyl acrylate (200 mmol, 17.2 g) was heated with stirring at 60 °C for 6 h. The reaction mixture was then cooled to room temperature. Organic layer was separated and the aqueous layer was extracted with ether (3 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained, was distilled under reduced pressure to afford the desired product **130**, as colorless oil, in 45 % (5.25 g) yield.



Bp.: 60-62 °C /1 mm(lit.[122] 71-72 °C /2 mm)

IR (neat): ν 3501, 1714, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 2.27 (t, 1H, *J* = 6.4 Hz), 3.79 (s, 3H),4.33 (d, 2H, *J* = 6.4 Hz), 5.85 (s, 1H), 6.26 (s, 1H)

^{13}C NMR (50 MHz): δ 51.84, 62.06, 125.61, 139.44, 166.77

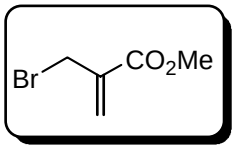
Methyl 2-(bromomethyl)prop-2-enoate (131):

This compound was prepared according to the literature procedure.[289]

Methyl 2-(hydroxymethyl)prop-2-enoate (**130**) (60 mmol, 6.96 g) was dissolved in benzene (50 mL) and PBr_3 (150 mmol, 40.6 g) was added drop wise with stirring at room temperature. After 12 h, the reaction mixture was poured into ice-cold water. Then the reaction mixture was extracted with ether (3 × 40 mL). Organic layers were combined and washed successively with water, saturated aqueous $NaHCO_3$ solution and water and dried

over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product thus obtained, was purified by column chromatography (silica gel, 2% EtOAc in hexanes), followed by distillation under reduced pressure to provide the desired product **131**, as a colorless liquid, in 87% (4.67 g) yield.

Bp.: 40-42 °C /2mm (lit.[290] 35-37 °C /1.3 mm)



IR (neat): ν 1732, 1633 cm^{-1}

^1H NMR (400 MHz): δ 3.82 (s, 3H), 4.18 (s, 2H), 5.96 (s, 1H), 6.33 (s, 1H)

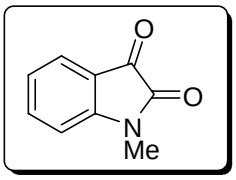
^{13}C NMR (50 MHz): δ 29.14, 52.16, 129.03, 137.35, 165.17

1-Methylisatin (132e):

This molecule was prepared following the known procedure [291]

A suspension of isatin (**132a**) (10 mmol, 1.47 g) and CaH_2(powder) (33.3 mmol, 1.4 g) in DMF (18 mL) was stirred at 40-50 °C for 20 min. Methyl iodide (50 mmol, 7.1 g, 3.1 mL) was added at the same temperature and the stirring was continued at room temperature for 12 h. The reaction mixture was poured into ice-cold HCl (0.2 M) solution and 10% aqueous NaCl solution (25 mL) was added. Then the reaction mixture was extracted with ethyl acetate (3 X 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude compound thus obtained, was purified by column chromatography (30% EtOAc in hexanes) to provide the pure compound **132e** in 70% (1.12 g) yield as brick red solid.

Mp.: 126-128 °C (lit.[292] 129-130 °C)



IR (KBr): ν 1743, 1724, 1606 cm^{-1}

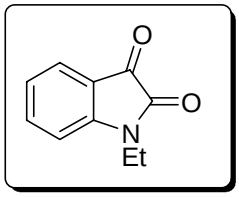
^{1}H NMR (400 MHz): δ 3.26 (s, 3H), 6.89 (d, 1H, *J* = 8.0 Hz), 7.10-7.20 (m, 1H), 7.57-7.69 (m, 2H)

^{13}C NMR (50 MHz): δ 25.91, 109.92, 117.02, 123.52, 124.71, 138.34, 151.18, 157.92, 183.10

1-Ethylisatin (132f):

Treatment of isatin (**132a**) with ethyl bromide following the similar procedure described for the compound **132e**, provided the title compound **132f** as an orange solid.

Reaction time: 12 h



Yield: 85 %

Mp.: 86-88 °C (lit.[292] 86-87 °C)

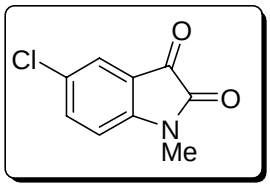
IR (KBr): ν 1734, 1608 cm^{-1}

^{1}H NMR (400 MHz): δ 1.32 (t, 3H, *J* = 7.2 Hz), 3.79 (q, 2H, *J* = 7.2 Hz), 6.90 (d, 1H, *J* = 8.0 Hz), 7.07-7.17 (m, 1H), 7.55-7.66 (m, 2H)

^{13}C NMR (50 MHz): δ 12.40, 34.84, 110.04, 117.46, 123.52, 125.22, 138.34, 150.57, 157.75, 183.58

5-Chloro-1-methylisatin (132g):

This compound was obtained *via* the reaction between 5-chloroisatin (**132b**) and methyl iodide following the similar procedure described for the compound **132e**, as an orange solid.



Reaction time: 12 h

Yield: 83 %

Mp.: 170-172 ^{o}C (lit.[293] 171-173 °C)

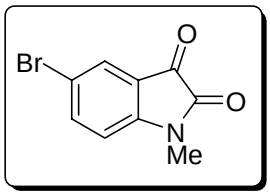
IR (KBr): ν 1755, 1728, 1608 cm^{-1}

^{1}H NMR (400 MHz): δ 3.25 (s, 3H), 6.85 (d, 1H, *J* = 8.8 Hz), 7.54-7.65 (m, 2H)

^{13}C NMR (50 MHz): δ 26.37, 111.30, 118.26, 125.12, 129.64, 137.76, 149.75, 157.70, 182.32

5-Bromo-1-methylisatin (132h):

This compound was obtained as an orange solid by the reaction of 5-bromoisatin (**132d**) with methyl iodide, following the similar procedure as described for the compound **132e**.



Reaction time: 12 h

Yield: 86 % (2.08 g)

Mp.: 148-150°C (lit.[294] 152-154 °C)

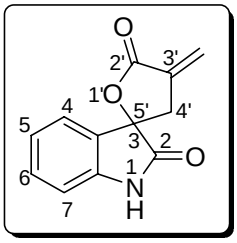
IR (KBr): ν 1747, 1732, 1606 cm^{-1}

^{1}H NMR (400 MHz): δ 3.25 (s, 3H), 6.82 (d, 1H, *J* = 8.0 Hz), 7.69-7.77 (m, 2H)

^{13}C NMR (100 MHz): δ 26.37, 111.73, 116.64, 118.56, 127.98, 140.64, 150.17, 157.50, 182.19

(Indolin-2-one)-3-spiro-5′-[3′-methylenetetrahydrofuran-2′-one] (133a):

To a stirred solution of isatin (**132a)** (1 mmol, 0.147 g), methyl 2-(bromomethyl)prop-2-enoate (**131**) (1.1 mmol, 0.197 g) in anhydrous THF (2 mL), Zn (2 mmol, 0.130 g) was added and the reaction mixture was heated under reflux for 2.5 h. THF was then removed under reduced pressure and the residue was diluted with ethyl acetate (3 mL) and 2N HCl (3 mL). Organic layer was separated and aqueous layer was extracted with ethyl acetate (3 X 20 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude product, thus obtained, was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to provide the (indolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (**133a**) as colorless solid in 78% (0.168 g) yield.



Mp: 160-162 °C

IR(KBr): 3600-2800 (multiple bands), 1770, 1726, 1650, 1616 cm^{-1}

^{1}H NMR (400 MHz): δ 3.13 & 3.33 [t of AB q, 2H, *J* = 17.6 & 2.8 (2.4) Hz], 5.82 (t, 1H, *J* = 2.4 Hz), 6.42 (t, 1H, *J* = 2.8 Hz), 6.94 (d, 1H, *J* = 7.6 Hz), 7.07-7.14 (m, 1H), 7.29-7.38 (m, 2H), 8.58 (br s, 1H)

^{13}C NMR (100 MHz, DMSO-d_6): δ 35.64, 80.08, 110.74, 122.29, 122.91, 125.40, 126.65, 131.46, 134.03, 142.74, 169.45, 175.28

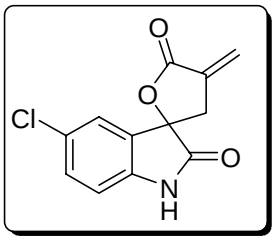
LCMS (*m/z*) : 214 $(M-H)^+$

Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51

Found: C, 66.92; H, 4.23; N, 6.68

(5-Chloroindolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (133b):

This spiro oxindole was obtained as colorless solid by the reation of 5-chloroisatin (**132b**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following the similar procedure as described for the compound **133a**.



Reaction time: 2.5 h

Yield: 75%

Mp: 192-194 °C

IR (KBr): ν 3400-2800 (multiple bands), 1765, 1738, 1660, 1622 cm^{-1}

^1H NMR (400 MHz): δ 3.06-3.16 & 3.30-3.38 (2m, 2H),* 5.82-5.86 (m, 1H),# 6.41-6.48 (m, 1H),# 6.87 (d, 1H, *J* = 8.4 Hz), 7.30 (s, 1H), 7.33 (d, 1H, *J* = 8.4 Hz), 7.88 (br s, 1H)

^{13}C NMR (100 MHz, DMSO-d_6): δ 35.43, 79.81, 112.21, 122.30, 125.87, 126.86, 128.55, 131.23, 133.77, 141.66, 169.21, 175.05

LCMS (*m/z*): 248 $(M-H)^+$

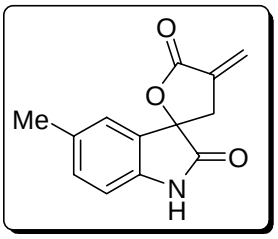
Anal. Calcd for $C_{12}H_8ClNO_3$: C, 57.73; H, 3.23; N, 5.61

Found: C, 57.70; H, 3.29; N, 5.68

* *These multiples are unresolved triplet of AB quartet.* # *Unresolved triplet.*

(5-Methylindolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (133c):

This compound was obtained *via* the zinc mediated reaction of 5-methylisatin (**132c**) with 2-(bromomethyl)prop-2-enoate (**131**), following the similar procedure as described for the compound **133a** as colorless solid.



Reaction time: 2.5 h

Yield: 81%

Mp: 182-185 °C

IR (KBr): ν 3600-2800 (multiple bands), 1765, 1724, 1650, 1631 cm^{-1}

^1H NMR (400 MHz): δ 2.32 (s, 3H), 3.11 & 3.32 (t of AB q, 2H, *J* = 17.2 & 2.8 Hz), 5.81 (t, 1H, *J* = 2.8 Hz), 6.41 (t, 1H, *J* = 2.8 Hz), 6.81 (d, 1H, *J* = 7.6 Hz), 7.09-7.17 (m, 2H), 8.01 (br s, 1H)

^{13}C NMR (100 MHz, 50% DMSO-d_6 in $CDCl_3$): δ 20.07, 35.24, 79.16, 109.84, 121.70, 124.04, 125.98, 130.58, 131.53, 132.42, 139.04, 168.34, 174.44

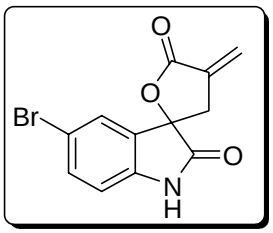
LCMS (*m/z*): 230 $(M+H)^+$

Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11

Found: C, 68.22; H, 4.83; N, 6.06

(5-Bromoindolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (133d):

This compound was prepared by the the reaction of 5-bromoisatin (**132d**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following the similar procedure as described for the compound **133a**, as colorless solid.



Reaction time: 2.5 h

Yield: 72%

Mp: 194-197°C

IR (KBr): ν 3400-2800 (multiple bands), 1768, 1736, 1660, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 3.11 & 3.34 (AB q, 2H, *J* = 17.6 Hz), 5.84 (s, 1H), 6.44 (s, 1H), 6.82 (d, 1H, *J* = 8.2 Hz), 7.44 (s, 1H), 7.48 (d, 1H, *J* = 8.2 Hz), 7.78 (br s, 1H)

^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$,): δ 35.28, 78.78, 111.96, 114.29, 122.39, 126.74, 128.19, 131.92, 133.16, 140.91, 168.14, 174.12

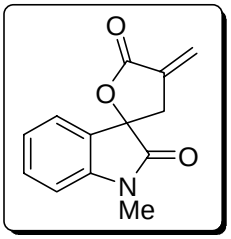
LCMS (*m/z*): 292 $(M-H)^+$, 294 $[(M+2)-H]^+$

Anal. Calcd for $C_{12}H_8BrNO_3$: C, 49.01; H, 2.74; N, 4.76

Found: C, 49.15; H, 2.79; N, 4.81

(1-Methylindolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (133e):

This compound was obtained as colorless solid by the the reaction of 1-methylisain (**132e**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following the similar procedure as described for the compound **133a**.



Reaction time: 2 h

Yield: 65%

Mp: 126-128 °C

IR (KBr): ν 1772, 1720, 1660, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 3.07-3.15 & 3.26-3.35 (2m, 2H),* 3.21 (s, 3H), 5.80 (s, 1H), 6.40 (s, 1H),# 6.88 (d, 1H, *J* = 7.8 Hz), 7.08-7.17 (m, 1H), 7.32 (d, 1H, *J* = 7.2 Hz), 7.37-7.46 (m, 1H)

^{13}C NMR (100 MHz): δ 26.43, 36.20, 79.36, 108.99, 123.07, 123.63, 124.07, 126.59, 131.30, 132.79, 143.84, 168.99, 173.43

LCMS (*m/z*): 230 $(M+H)^+$

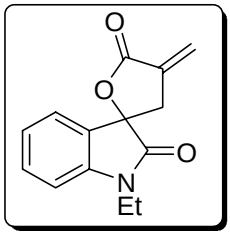
Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11

Found: C, 68.01; H, 4.80; N, 6.02

*These multiples are unresolved triplets of AB quartet. # Unresolved triplet.

(1-Ethylindolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (133f):

This compound was obtained as colorless solid *via* the zinc mediated reaction of 1-ethylisatin (**132f**) with methyl 2-(bromomethyl)prop-2-enoate (**131**), following the similar procedure as described for the molecule **133a**.



Reaction time: 2 h

Yield: 69%

Mp: 130-132 °C

IR (KBr): ν 1772, 1728, 1655, 1614 cm^{-1}

^{1}H NMR (400 MHz): δ 1.28 (t, 3H, *J* = 7.2 Hz), 3.10 & 3.30 [t of AB q, 2H, *J* = 17.2 & 2.4 (2.8) Hz], 3.66-3.85 (m, 2H), 5.80 (t, 1H, *J* = 2.8 Hz), 6.41 (t, 1H, *J* = 2.8 Hz), 6.89 (d, 1H, *J* = 7.6 Hz), 7.07-7.17 (m, 1H), 7.32 (d, 1H, *J* = 7.6 Hz), 7.36-7.45 (m, 1H)

^{13}C NMR (100 MHz): δ 12.48, 35.08, 36.24, 79.37, 109.12, 123.03, 123.45, 124.33, 126.86, 131.26, 132.88, 143.03, 169.04, 173.09

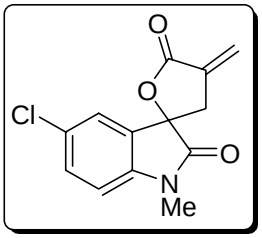
LCMS (*m/z*): 244 $(M+H)^+$

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76

Found: C, 69.30; H, 5.41; N, 5.69

(1-Methyl-5-chloroindolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (133g):

This compound was obtained as colorless solid *via* the zinc mediated reaction of 5-chloro-1-methylisatin (**132g**) with methyl 2-(bromomethyl)prop-2-enoate (**131**), following the similar procedure as described for the compound **133a**.



Reaction time: 2 h

Yield: 67%

Mp: 165-167 °C

IR (KBr): ν 1766, 1732, 1660, 1612 cm^{-1}

^{1}H NMR (400 MHz): δ 3.09 & 3.30 [t of AB q, 2H, *J* = 17.2 & 2.8 (2.4) Hz], 3.20 (s, 3H), 5.82 (t, 1H, *J* = 2.4 Hz), 6.42 (t, 1H, *J* = 2.8 Hz), 6.81 (d, 1H, *J* = 8.4 Hz), 7.30 (d, 1H, *J* = 2.0 Hz), 7.38 (dd, 1H, *J* = 8.4 & 2.0 Hz)

^{13}C NMR (100 MHz): δ 26.70, 36.22, 79.00, 110.08, 123.75, 124.76, 128.38, 129.17, 131.24, 132.23, 142.47, 168.60, 173.11

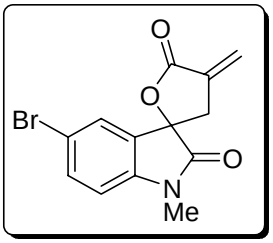
LCMS (*m/z*): 264 $(M+H)^+$, 266 $[(M+2)+H]^+$

Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31

Found: C, 59.42; H, 3.83; N, 5.29

(1-Methyl-5-bromoindolin-2-one)-3-spiro-5'-[3'-methylenetetrahydrofuran-2'-one] (133h):

This compound was prepared by the reaction of 5-bromo-1-methylisatin (**132h**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following the similar procedure as described for the compound **133a** as colorless solid.



Reaction time: 2 h

Yield: 70%

Mp: 167-169 °C

IR (KBr): ν 1768, 1734, 1664, 1608 cm^{-1}

^1H NMR (400 MHz): δ 3.09 & 3.31 (t of AB q, 2H, *J* = 17.2 & 2.4 Hz), 3.20 (s, 3H), 5.82 (t, 1H, *J* = 2.4 Hz),* 6.42 (t, 1H, *J* = 2.4 Hz),* 6.77 (d, 1H, *J* = 8.4 Hz), 7.43 (s, 1H),# 7.52 (dd, 1H, *J* = 8.4 & 1.2 Hz)

^{13}C NMR (100 MHz): δ 26.66, 36.19, 78.92, 110.55, 116.19, 123.73, 127.46, 128.68, 132.21, 134.14, 142.96, 168.57, 172.97

LCMS (*m/z*): 308 $(M+H)^+$, 310 $[(M+H)+2]^+$

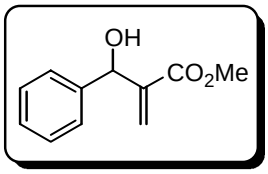
Anal. Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; N, 4.55

Found: C, 50.58; H, 3.23; N, 4.57

* *Unresolved triplets.* # *Unresolved doublet.*

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (134a):

A solution of benzaldehyde (50 mmol, 5.30 g), metyl acrylate (75 mmol, 6.45 g) and DABCO (**1**) (15 mol %, 7.5 mmol, 0.84 g) was kept at room temperature for 7 days. Ether (50 mL) was added to the reaction mixture and successively washed with 2N HCl, aqueous $NaHCO_3$ solution and water. Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product thus obtained was distilled under reduced pressure to provide the pure product (**134a**) as colorless liquid in 75 % (7.02 g) yield.



Bp: 122-124 °C/2.5 mm(lit.[222] 117-119°C /2.1mm)

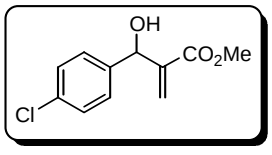
IR (neat): ν 3433, 1718, 1630 cm^{-1}

^{1}H NMR (400 MHz): δ 3.01 (d, 1H, *J* = 4.4 Hz), 3.72 (s, 3H), 5.56 (s, 1H), 5.83 (s, 1H), 6.33 (s, 1H), 7.26-7.45 (m, 5H)

^{13}C NMR (50 MHz): δ 51.87, 73.14, 125.92, 126.63, 127.82, 128.42, 141.40, 142.20, 166.77

Methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate(134b):

This compound was obtained as colorless solid via the Baylis-Hillman coupling of 4-chlorobenzaldehyde with methyl acrylate in the presence of DABCO, following the similar procedure described for the compound **134a**.



Reaction time: 7d

Yield: 73 %

Mp.: 42-44 °C

IR (KBr): ν 3368, 1720, 1635 cm^{-1}

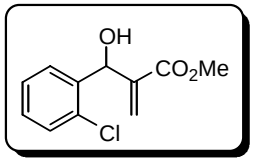
^{1}H NMR (400 MHz): δ 30.05 (d, 1H, *J* = 5.6 Hz), 3.73 (s, 3H), 5.53 (d, 1H, *J* = 5.6 Hz), 5.82 (s, 1H), 6.34 (s, 1H), 7.31 (s, 4H)

^{13}C NMR (50 MHz): δ 51.84, 72.12, 125.90, 128.01, 128.40, 133.40, 139.92, 141.79, 166.46

Methyl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate (134c):

DABCO catalyzed Baylis-Hillman reaction of 2-chlorobenzaldehyde with methyl acrylate following a similar procedure described for the compound **134a**, provided the title compound **134c** after purification through column chromatography (Silica gel, 6% EtOAc in Hexanes) as colorless viscous liquid.

Reaction time: 7d



Yield: 70 %

IR (neat): ν 3437, 1722, 1631 cm^{-1}

^{1}H NMR (400 MHz): δ 3.26 (br s, 1H), 3.78 (s, 3H), 5.58 (s, 1H), 5.98 (s, 1H), 6.33 (s, 1H), 7.18-7.45 (m, 3H), 7.57 (d, 1H, *J* = 1.4 Hz)

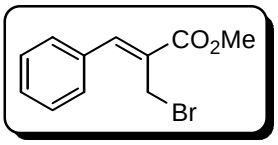
^{13}C NMR (50 MHz): δ 51.89, 68.87, 126.63, 126.85, 128.06, 128.81, 129.30, 132.72, 138.44, 140.82, 166.75

Methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (135a):

This compound was prepared according to the literature procedure[295]

To a solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**134a**) (60 mmol, 11.52 g) in CH_2Cl_2 (120 mL) was added drop wise aq. HBr (48 %, 150 mmol, 13.21 g)

followed by conc. H_2SO_4 (60 mmol, 5.88 g) with stirring at 0 °C. After 12 h at room temperature, the reaction mixture was carefully poured into ice cold water and extracted with ether (3 X 20 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 2 % ethyl acetate in hexanes) to afford **135a** as colorless liquid in 88 % (6.75 g) yield.



IR (neat): ν 1718, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 3.88 (s, 3H), 4.40 (s, 2H), 7.35-7.70 (m, 5H), 7.83 (s, 1H)

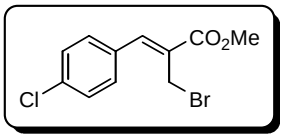
^{13}C NMR (50 MHz): δ 26.64, 52.35, 128.84, 129.56, 134.25, 142.83, 166.51

Methyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (135b):

This compound was obtained as colorless liquid *via* the treatment of methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**134b**) with aq. HBr (48 %) in the presence of conc H_2SO_4 following the similar procedure described for the molecule **135a**.

Reaction time: 12 h

Yield: 85 %



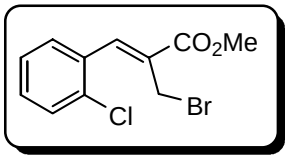
IR (neat): ν 1718, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 3.88 (s, 3H), 4.35 (s, 2H), 7.44 (d, 2H, *J* = 8.4 Hz), 7.51 (d, 2H, *J* = 8.4 Hz), 7.76 (s, 1H)

^{13}C NMR (50 MHz): δ 26.28, 52.60, 129.27, 130.97, 132.72, 135.82, 141.55, 166.41

Methyl (2Z)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate (135c):

Treatment of methyl 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**134c**) with HBr (48 %) in the presence of conc H_2SO_4 following the similar procedure described for the molecule **135a**, provided the title compound **135c** as colorless solid.



Reaction time: 12 h

Yield: 87 %

Mp.: 66-68 °C

IR (KBr): ν 1716, 1624 cm^{-1}

^{1}H NMR (400 MHz): δ 3.90 (s, 3H), 4.27 (s, 2H), 7.31-7.50 (m, 3H), 7.71 (d, 1H, *J* = 7.2 Hz), 7.92 (s, 1H)

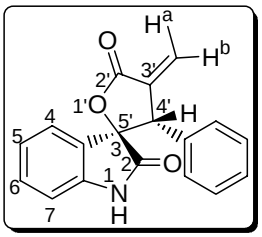
^{13}C NMR (50 MHz): δ 26.08, 52.45, 126.94, 129.51, 129.76, 130.51, 132.81, 134.44, 139.39, 165.92

(Indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (136a)

To a stirred solution of isatin (**132a**) (1 mmol, 0.147 g), methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**135a**) (1.1 mmol, 0.280 g) in anhydrous THF (2 mL), Zn (2 mmol, 0.130g) was added and the reaction mixture was heated under reflux for 5 h. THF was then removed under reduced pressure and the reaction mixture was diluted with ethyl acetate (3 mL) and 2N HCl (3 mL). Organic layer was separated and aqueous layer was extracted with ethyl acetate (3 X 20 mL). Combined organic layer was dried over anhydrous Na_2SO_4

and concentrated. The crude product, thus obtained, was purified by column chromatography (silica gel, 20% ethyl acetate in hexanes) to provide (indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (**136a**) in 71% (0.206 g) yield as colorless solid and also (indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (**137a**) (minor isomer) in 4% (0.012 g) yield.

^{1}H NMR of the crude product indicates the diastereomeric ratio of 94:6 (trans:cis) (from the integration ratios of diastereomeric H^b protons).



Mp: 126-128 °C

IR (KBr): ν 3700-2800 (multiple bands), 1782, 1728, 1675, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 4.67 (t, 1H, *J* = 2.8 Hz), 5.80 (d, 1H, *J* = 2.8 Hz), 6.62 (d, 1H, *J* = 7.6 Hz), 6.68 (d, 1H, *J* = 2.8 Hz), 6.72-6.84 (m, 2H), 6.97-7.07 (m, 2H), 7.10-7.24 (m, 4H), 7.97 (br s, 1H)

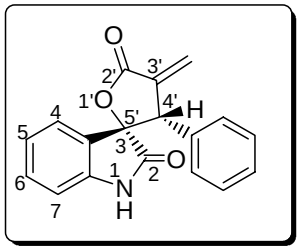
^{13}C NMR (100 MHz): δ 52.82, 84.68, 110.89, 122.68, 123.90, 125.48, 126.12, 128.23, 128.61, 128.99, 130.88, 135.36, 136.45, 140.96, 169.51, 176.12

LCMS (*m/z*): 292 $(M+H)^+$

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81

Found: C, 74.30; H, 4.52; N, 4.74

(Indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (minor isomer) (137a):



Yield: 4%

Mp: 210-212 °C

IR (KBr): ν 3600-2800 (multiple bands), 1776, 1724, 1660, 1624 cm^{-1}

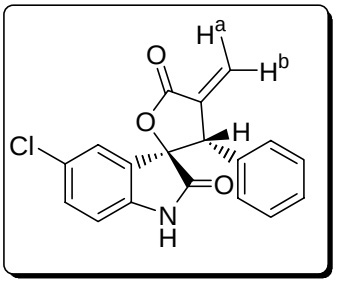
^{1}H NMR (400 MHz): δ 4.53 (t, 1H, *J* = 3.2 Hz), 5.65 (d, 1H, *J* = 3.2 Hz), 6.58 (d, 1H, *J* = 3.6 Hz), 6.72 (d, 1H, *J* = 8.0 Hz), 6.98-7.06 (m, 2H), 7.14-7.28 (m, 4H), 7.29-7.38 (m, 1H), 7.49 (br s, 1H), 7.53 (d, 1H, *J* = 7.6 Hz)

^{13}C NMR (100 MHz): δ 56.01, 85.31, 110.62, 123.53, 123.63, 124.79, 124.91, 128.70, 128.77, 129.40, 131.47, 131.66, 136.04, 141.56, 169.23, 173.83

(5-Chloroindolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (136b):

Reaction of 5-chloroisatin (**132b**) with methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**135a**) in the presence of zinc, following the similar procedure as described for the compound **136a**, provided **136b** as major isomer and **137b** as minor isomer.

^{1}H NMR of the crude product indicates the diastereomeric ratio of 94:6 (trans:cis) (from the integration ratios of diastereomeric H^b protons).



Reaction time: 3 h

Yield: 73%

Mp: 187-189 °C

IR (KBr): ν 3300-2800 (multiple bands), 1788, 1745, 1660, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 4.66 (t, 1H, *J* = 2.4 Hz), 5.84 (d, 1H, *J* = 2.4 Hz), 6.49 (d, 1H, *J* = 2.4 Hz), 6.70 (d, 1H, *J* = 2.8 Hz), 6.74 (d, 1H, *J* = 8.0 Hz), 6.97-7.05 (m, 2H), 7.12 (dd, 1H, *J* = 8.0 & 2.0 Hz), 7.22-7.30 (m, 3H), 8.81 (br s, 1H)

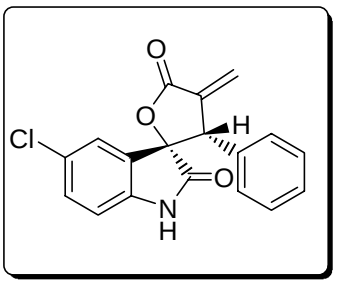
^{13}C NMR (100 MHz): δ 52.78, 84.34, 111.89, 125.58, 126.18, 126.64, 128.28, 128.62, 128.89, 130.86, 135.10, 135.82, 139.33, 169.13, 175.88

LCMS (*m/z*): 326 $(M+H)^+$, 328 $[(M+2)+H]^+$

Anal. Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30

Found: C, 66.30; H, 3.74; N, 4.21

(5-Chloroindolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (minor isomer) (137b):



Yield: 3%

Mp: 230-232 °C

IR (KBr): ν 3500-3000 (multiple bands), 1772, 1751, 1660, 1624 cm^{-1}

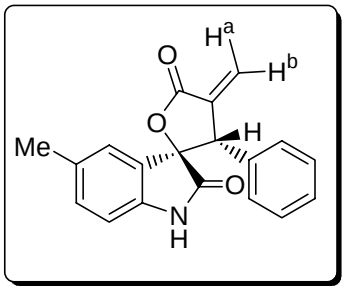
^1H NMR (400 MHz): δ 4.50 (t, 1H, *J* = 3.6 Hz), 5.66 (d, 1H, *J* = 3.6 Hz), 6.59 (d, 1H, *J* = 3.6 Hz), 6.68 (d, 1H, *J* = 8.4 Hz), 6.98-7.09 (m, 2H), 7.17-7.29 (m, 3H), 7.30 (dd, 1H, *J* = 8.4 & 2.0 Hz), 7.53 (d, 1H, *J* = 2.0 Hz), 7.69 (br s, 1H)

^{13}C NMR (100 MHz): δ 55.99, 85.09, 111.82, 124.04, 125.18, 126.66, 128.88, 128.91, 129.05, 129.34, 131.30, 131.50, 135.53, 140.10, 168.82, 173.76

(5-Methylindolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-phenyltetrahydrofuran-2'-one] (136c):

Treatment of 5-methylisatin (**132c**) with methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**135a**) in the presence of zinc, following the similar procedure as described for the compound **136a** furnished **136c** as major isomer and **137c** as minor isomer.

^1H NMR of the crude product indicates the diastereomeric ratio of 93:7(trans:cis) (from the integration ratios of diastereomeric H^b protons).



Reaction time: 5 h

Yield: 74%

Mp: 193-195 °C

IR (KBr): ν 3400-2800 (multiple bands), 1765, 1732, 1658, 1624 cm^{-1}

^{1}H NMR (400 MHz): δ 2.07 (s, 3H), 4.65 (s, 1H), 5.80 (d, 1H, *J* = 2.0 Hz), 6.35 (s, 1H), 6.62-6.72 (m, 2H), 6.93 (d, 1H, *J* = 7.6 Hz), 6.98-7.03 (m, 2H), 7.16-7.25 (m, 3H), 8.62 (br s, 1H)

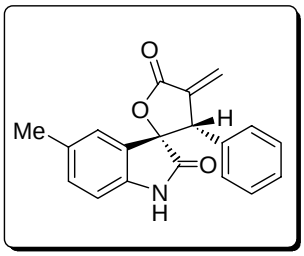
^{13}C NMR (100 MHz): δ 20.81, 52.84, 84.79, 110.51, 123.92, 125.40, 126.93, 128.18, 128.55, 129.07, 131.14, 132.32, 135.50, 136.53, 138.38, 169.53, 176.15

LCMS (*m/z*): 306 $(M+H)^+$

Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59

Found: C, 74.62; H, 4.90; N, 4.61

(5-Methylindolin-2-one)-3-spiro-5'–[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-phenyltetr-ahydrofuran-2'-one] (minor isomer) (137c):



Yield: 4%

Mp: 114-116 °C

IR (KBr): ν 3400-2800 (multiple bands), 1778, 1732, 1666, 1628 cm^{-1}

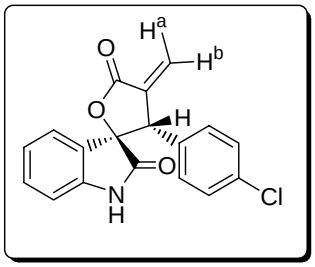
^{1}H NMR (400 MHz): δ 2.39 (s, 3H), 4.51 (t, 1H, *J* = 3.2 Hz), 5.64 (d, 1H, *J* = 3.2 Hz), 6.57 (d, 1H, *J* = 3.6 Hz), 6.60 (d, 1H, *J* = 8.0 Hz), 6.99-7.06 (m, 2H), 7.11 (d, 1H, *J* = 8.0 Hz), 7.15-7.25 (m, 3H), 7.34 (s, 1H), 7.48 (br s, 1H)

^{13}C NMR (100 MHz): δ 21.21, 55.93, 85.50, 110.40, 123.41, 124.94, 125.31, 128.64, 128.72, 129.41, 131.80, 131.82, 133.29, 136.16, 139.13, 169.28, 174.01

(Indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-(4-chlorophenyl)tetrahydrofuran-2'-one] (136d):

Reaction of isatin with methyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (**135b**), in the presence of zinc, following the similar procedure as described for the compound **136a** provided **136d** as major isomer and **137d** as minor isomer.

^{1}H NMR of the crude compound indicates the diastereomeric ratio of 92:8 (trans:cis) (from the integration ratios of diastereomeric H^b protons).



Reaction time: 5 h

Yield: 70%

Mp: 156-158 °C

IR (KBr): ν 3400-2800 (multiple bands), 1768, 1714, 1665, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 4.66 (t, 1H, *J* = 2.8 Hz), 5.77 (d, 1H, *J* = 2.8 Hz), 6.65-6.72 (m, 2H), 6.78 (d, 1H, *J* = 7.6 Hz), 6.81-6.89 (m, 1H), 6.96 (d, 2H, *J* = 8.4 Hz), 7.15-7.24 (m, 3H), 8.25 (br s, 1H)

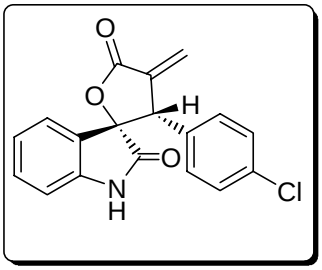
^{13}C NMR (100 MHz): δ 52.35, 84.45, 111.07, 122.94, 123.74, 125.71, 125.98, 128.87, 130.38, 131.15, 133.61, 134.23, 136.12, 140.87, 169.12, 175.78

LCMS (*m/z*): 326 $(M+H)^+$, 328 $[(M+2)+H]^+$

Anal. Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30

Found: C, 66.45; H, 3.72; N, 4.36

(Indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-(4-chlorophenyl)tetrahydrofuran-2'-one] (minor isomer) (137d):



Yield: 5%

Mp: 216-218°C

IR (KBr): ν 3300-2800 (multiple bands), 1780, 1724, 1660, 1622 cm^{-1}

^1H NMR (400 MHz): δ 4.50 (t, 1H, *J* = 3.2 Hz), 5.62 (d, 1H, *J* = 3.2 Hz), 6.59 (d, 1H, *J* = 3.6 Hz), 6.74 (d, 1H, *J* = 7.6 Hz), 6.96 (d, 2H, *J* = 8.0 Hz), 7.15-7.23 (m, 3H), 7.30-7.38 (m, 1H), 7.47-7.57 (m, 2H)

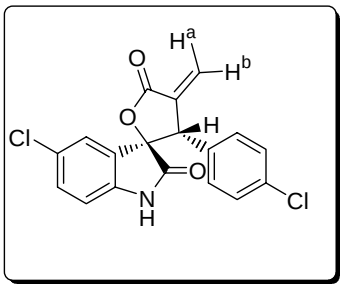
^{13}C NMR (100 MHz): δ 55.31, 85.10, 110.80, 123.65, 123.77, 124.58, 124.76, 129.04, 130.25, 130.75, 131.65, 134.77, 135.84, 141.50, 168.91, 173.69

(5-Chloroindolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-(4-chlorophenyl)tetrahydrofuran-2'-one] (136e):

Treatment of 5-chloroisatin (**132b**) with methyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (**135b**) in the presence of zinc, following the similar procedure as

described for the molecule **136a**, furnished **136e** as a major isomer and **137e** as minor isomer.

^{1}H NMR of the crude compound indicates the diastereomeric ratio of 93:7 (trans:cis) (from the integration ratios of diastereomeric H^b protons).



Reaction time: 3 h

Yield: 68%

Mp: 178-180 °C

IR (KBr): ν 3400-2800 (multiple bands), 1786, 1747, 1658, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 4.66 (s, 1H), 5.81 (d, 1H, *J* = 2.4 Hz), 6.62 (d, 1H, *J* = 1.8 Hz), 6.70 (d, 1H, *J* = 2.8 Hz), 6.74 (d, 1H, *J* = 8.2 Hz), 6.96 (d, 2H, *J* = 8.4 Hz), 7.16 (dd, 1H, *J* = 8.2 & 1.8 Hz), 7.23 (d, 2H, *J* = 8.4 Hz), 8.65 (br s, 1H)

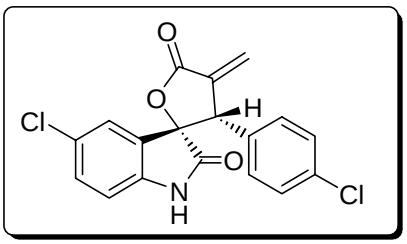
^{13}C NMR (100 MHz): δ 52.36, 84.17, 112.12, 125.45, 126.31, 126.33, 128.46, 129.10, 130.26, 131.11, 133.08, 134.65, 135.41, 139.26, 168.74, 175.42

LCMS (*m/z*): 358 $(M-H)^+$, 360 $[(M+2)-H]^+$, 362 $[(M+4)-H]^+$

Anal. Calcd for $C_{18}H_{11}Cl_2NO_3$: C, 60.02; H, 3.08; N, 3.89

Found: C, 60.07; H, 3.03; N, 3.93

(5-Chloroindolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-(4-chlorophenyl)tetrahydrofuran-2'-one] (minor isomer) (137e):



Yield: 4%

Mp: 238-240 °C

IR (KBr): ν 3500-3200 (multiple bands), 1768, 1751, 1653, 1624 cm^{-1}

^1H NMR (400 MHz): δ 4.47 (t, 1H, *J* = 3.2 Hz), 5.64 (d, 1H, *J* = 3.2 Hz), 6.60 (d, 1H, *J* = 3.6 Hz), 6.69 (d, 1H, *J* = 8.4 Hz), 6.99 (d, 2H, *J* = 8.4 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.32 (dd, 1H, *J* = 8.4 & 2.4 Hz), 7.45 (br s, 1H), 7.52 (d, 1H, *J* = 2.4 Hz)

^{13}C NMR (100 MHz): δ 55.36, 84.73, 111.80, 124.19, 125.25, 126.36, 129.19, 129.91, 130.76, 131.66, 135.01, 135.31, 139.87, 168.41, 173.14

LCMS (*m/z*): 360 $(M+H)^+$, 362 $[(M+2)-H]^+$, 364 $[(M+4)-H]^+$

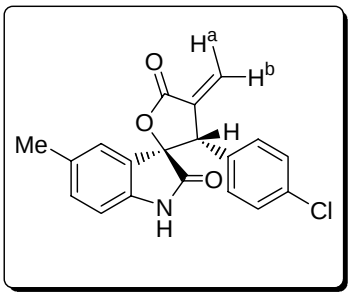
Anal. Calcd for $C_{18}H_{11}Cl_2NO_3$: C, 60.02; H, 3.08; N, 3.89

Found: C, 60.16; H, 3.02; N, 3.83

(5-Methylindolin-2-one)-3-spiro-5'-[{4'*S*(R),5'(3)*R*(S)}-3'-methylene-4'-(4-chlorophenyl)tetrahydrofuran-2'-one] (136f):

Zinc mediated reaction of 5-methylisatin (**132c**) with methyl (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (**135b**) following the similar procedure as described for the compound **136a**, provided **136f** as major isomer and **137f** as minor isomer.

^{1}H NMR of the crude product indicates the diastereomeric ratio of 95:5 (trans:cis) (from the integration ratios of diastereomeric H^b protons).



Reaction time: 5 h

Yield: 75%

Mp: 166-168 °C

IR (KBr): ν 3400-2800 (multiple bands), 1780, 1736, 1660, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 2.13 (s, 3H), 4.65 (t, 1H, *J* = 2.4 Hz), 5.77 (d, 1H, *J* = 2.4 Hz), 6.45 (s, 1H), 6.64-6.72 (m, 2H), 6.92-7.02 (m, 3H), 7.18 (d, 2H, *J* = 8.4 Hz), 8.32 (br s, 1H)

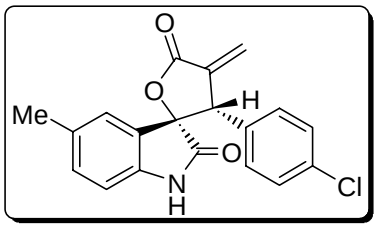
^{13}C NMR (100 MHz): δ 20.86, 52.33, 84.61, 110.73, 123.75, 125.59, 126.59, 128.75, 130.41, 131.39, 132.54, 133.65, 134.16, 136.12, 138.33, 169.16, 175.75

LCMS (*m/z*): 340 $(M+H)^+$, 342 $[(M+2)+H]^+$

Anal. Calcd for $C_{19}H_{14}ClNO_3$: C, 67.16; H, 4.15; N, 4.12

Found: C, 67.06; H, 4.16; N, 4.03

(5-Methylindolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*S*(*R*)}-3'-methylene-4'-(4-chlorophenyl)tetrahydrofuran-2'-one] (minor isomer) (137f):



Yield: 3%

Mp: 212-214°C

IR (KBr): ν 3300-2800 (multiple bands), 1780, 1732, 1626 cm^{-1}

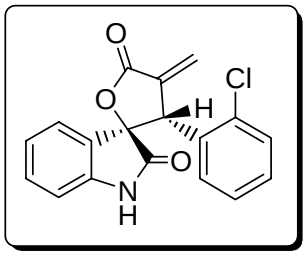
^{1}H NMR (400 MHz): δ 2.39 (s, 3H), 4.48 (t, 1H, *J* = 3.6 Hz), 5.61 (d, 1H, *J* = 3.6 Hz), 6.58 (d, 1H, *J* = 3.6 Hz), 6.63 (d, 1H, *J* = 8.0 Hz), 6.97 (d, 2H, *J* = 8.4 Hz), 7.13 (d, 1H, *J* = 8.0 Hz), 7.18 (d, 2H, *J* = 8.4 Hz), 7.33 (s, 1H), 7.46 (br s, 1H)

^{13}C NMR (100 MHz): δ 21.21, 55.25, 85.25, 110.53, 123.55, 124.62, 125.29, 129.00, 130.38, 130.78, 132.00, 133.47, 134.70, 135.95, 139.02, 168.95, 173.76

(Indolin-2-one)-3-spiro-5'-[{4'*S*(*R*),5'(3)*R*(*S*)}-3'-methylene-4'-(2-chlorophenyl)tetrahydrofuran-2'-one] (136g):

Treatment of isatin (**132a**) with methyl (2*Z*)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate (**135c**) in the presence of zinc, furnished the compound **136g** as colorless solid, following the similar procedure as described for the molecule **136a**.

^{1}H NMR spectra of the crude product did not indicate the presence of any other isomer.



Reaction time: 5 h

Yield: 72%

Mp: 183-185 °C

IR (KBr): ν 3300-2800 (multiple bands), 1784, 1724, 1662, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 5.12 (s, 1H), 5.85 (d, 1H, *J* = 2.0 Hz), 6.12 (d, 1H, *J* = 7.6 Hz), 6.62-6.69 (m, 1H), 6.75 (d, 1H, *J* = 2.0 Hz), 6.84 (d, 1H, *J* = 8.0 Hz), 7.15-7.40 (m, 5H), 8.22 (br s, 1H)

^{13}C NMR (100 MHz): δ 47.89, 83.50, 110.81, 122.51, 123.17, 126.08, 126.94, 127.13, 129.35, 129.43, 129.56, 131.05, 135.53, 135.79, 136.32, 142.03, 169.30, 176.45

LCMS (*m/z*): 326 $(M+H)^+$, 328 $[(M+2)+H]^+$

Anal. Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30

Found: C, 66.48; H, 3.74; N, 4.19

(5-Chloroindolin-2-one)-3-spiro-5'-[{4'*S*(R),5'(3)*R*(*S*)}-3'-methylene-4'-(2-chlorophenyl)tetrahydrofuran-2'-one] (136h):

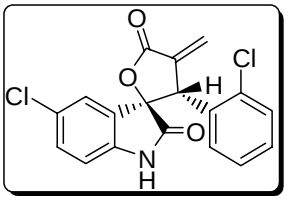
This compound was obtained as colorless solid by the reaction of 5-chloroisatin (**132b**) with methyl (2*Z*)-2-(bromomethyl)-3-(2-chlorophenyl)prop-2-enoate (**135c**) in the presence of zinc, following the similar procedure as described for the compound **136a**.

^{1}H NMR spectra of the crude product did not indicate the presence of any other isomer.

Reaction time: 3 h

Yield: 69%

Mp: 220-222 °C



IR (KBr): ν 3400-2800 (multiple bands), 1782, 1726, 1662, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 5.10 (s, 1H), 5.89 (s, 1H), 6.01 (s, 1H), 6.75-6.87 (m, 2H), 7.15-7.42 (m, 5H), 8.54 (s, 1H)

^{13}C NMR (100 MHz): δ 47.93, 83.05, 111.61, 124.82, 126.70, 127.41, 127.45, 128.05, 129.26, 129.75, 129.81, 131.01, 135.17, 135.74, 140.43, 168.84, 175.90

LCMS (*m/z*): 360 $(M+H)^+$, 362 $[(M+2)+H]^+$, 364$[(M+4)+H]^+$

Anal. Calcd for $C_{18}H_{11}Cl_2NO_3$: C, 60.02; H, 3.08; N, 3.89

Found: C, 60.06; H, 3.06; N, 3.85

3-(Phenylimino)indolin-2-one (140a):

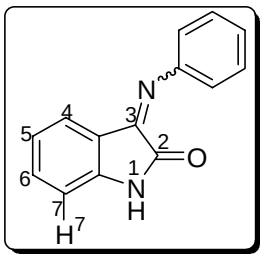
This compound was prepared according to the literature procedure.[296]

A mixture of isatin (**132a**) (10 mmol, 1.47 g), aniline (10 mmol, 0.93 g) in ethanol (25 mL) containing one drop of glacial acetic acid was heated under reflux for 30 min. The contents were cooled to room temperature and kept overnight for standing. The solid thus obtained was filtered and crystallized from ethanol to afford 3-(phenylimino)indolin-2-one (**140a**) in 65 % (1.45 g) yield as red colored solid.

*^{1}H NMR spectrum of **140a** indicates that it is a mixture of E and Z isomers (in the ratio of 95:5 as determined by the integration ratios of diastereomeric H-7 protons).*

Mp: 216-218 °C (Lit.[297] 232-234 °C)

IR (KBr): ν 3600-3000 (multiple bands), 1739, 1728,1651, 1612 cm^{-1}



^{1}H NMR (400 MHz): δ 6.66 (d, 1H, *J* = 7.2 Hz), 6.70-6.79 (m, 1H), 6.87 & 6.94 (2d, 1H, *J* = 8.0 Hz), 7.00-7.76 (m, 6H), 8.41 & 9.45 (2br s, 1H)

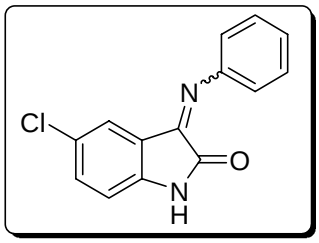
^{13}C NMR (DMSO-d_6, 100 MHz): δ 110.92, 111.70, 115.84, 117.41, 119.23, 121.60, 121.85, 122.46, 122.91, 124.61, 125.09, 125.52, 128.46, 129.75, 134.58, 145.82, 147.15, 149.18, 150.71, 152.95, 155.13, 158.60, 163.67

(*The underlined peaks are due to the minor diastereoisomer*)

5-Chloro-3-(phenylimino)indolin-2-one (140b)

This compound was obtained as red colored solid *via* the reaction between 5-chloroisatin (**132b**) and aniline in ethanol (80 mL), following similar procedure described for the compound (**140a**).

*^{1}H NMR spectrum of **140b** indicates that it is a mixture of E and Z isomers (in the ratio of 91:9 as evidenced by the integration ratios of diastereomeric H-7 protons).*



Reaction time: 30 min

Yield: 78 %

Mp: 252-254 °C

IR (KBr): ν 3600-3000 (multiple bands), 1739, 1728, 1649, 1608 cm^{-1}

^{1}H NMR (400 MHz): δ 6.64 (d, 1H, *J* = 2.0 Hz), 6.81 & 6.89 (2d, 1H, *J* = 8.0 Hz), 7.00-7.80 (m, 6H), 8.39 & 9.32 (2 br s, 1H)

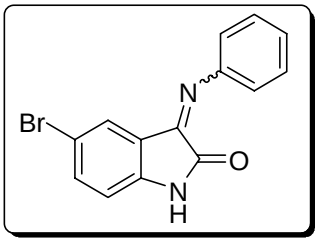
^{13}C NMR (100 MHz, DMSO-d_6): δ 112.51, 113.26, 116.95, 117.34, 119.46, 122.42, 123.18, 124.90, 125.07, 125.47, 126.63, 128.46, 129.83, 133.58, 133.87, 144.44, 145.87, 148.66, 150.32, 152.12, 154.32, 158.32, 163.35

(*The underlined peaks are due to the minor diastereoisomer*)

5-Bromo-3-(phenylimino)indolin-2-one (140c):

This compound was obtained as red color solid by the reaction of 5-bromoisatin (**132d**) with aniline in ethanol (80 mL), following the similar procedure described for the compound **140a.**

*^{1}H NMR spectrum of **140c** indicates that it is a mixture of E and Z isomers (in the ratio of 90:10 as determined by the integration ratios of diastereomeric H-7 protons).*



Reaction time: 30 min

Yield: 75%

Mp: 260-262 °C

IR (KBr): ν 3400-3000 (multiple bands), 1739, 1720, 1647, 1608 cm^{-1}

^{1}H NMR (400 MHz): δ 6.76 & 6.83(2d, 1H, *J* = 8.4 Hz), 6.78 (d, 1H, *J* = 2.0 Hz), 6.99-7.12 (m, 2H), 7.18-7.87 (m, 4H), 8.23 & 9.11 (2br s, 1H)

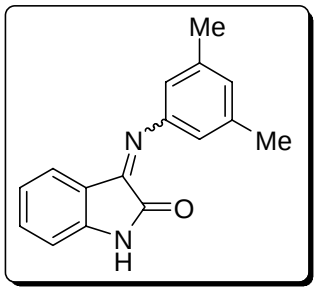
^{13}C NMR (100 MHz, DMSO-d_6): δ 112.96, 113.07, 113.69, 114.11, 117.33, 117.44, 119.46, 123.58, 125.07, 125.18, 125.44, 127.74, 128.45, 129.80, 136.37, 136.62, 144.81, 146.20, 148.63, 150.34, 151.96, 154.23, 158.15, 163.18

(*The underlined peaks are due to the minor diastereoisomer*)

3-(3,5-Dimethylphenylimino)indolin-2-one (140d):

This imine (**140d**) was obtained as pale yellow solid, by the reaction of isatin (**132a**) with 3,5-dimethylaniline, following similar procedure as described for the compound **140a**.

*^{1}H NMR spectrum of **140d** indicates that it is a mixture of E and Z isomers (in the ratio of 94:6 as determined by the integration ratios of diastereomeric methyl group protons singlets in the ^{1}H NMR spectrum).*



Reaction time: 30 min

Yield: 71%

Mp: 222-224 °C

IR (KBr): ν 3400-3000 (multiple bands), 1743,1651, 1614 cm^{-1}

^{1}H NMR (400 MHz): δ 2.31 & 2.34 (2s, 6H), 6.61-7.70 (m, 7H), 8.85 & 9.92, (2br s, 1H)

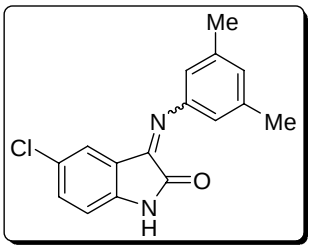
^{13}C NMR (100 MHz, DMSO-d_6): δ 21.09, 110.89, 111.63, 114.78, 115.86, 116.62, 121.64, 121.88, 122.43, 122.78, 125.60, 126.11, 126.45, 134.20, 134.43, 137.44, 139.02, 145.70, 147.03, 149.29, 150.74, 152.63, 154.81, 158.46, 163.71

(*The underlined peaks are due to the minor diastereoisomer*)

5-Chloro-3-(3,5-dimethylphenylimino)indolin-2-one (140e):

This imine (**140e**) was obtained as pale yellow solid, *via* the condensation of 5-chloroisatin (**132b**) with 3,5-dimethylaniline in ethanol (80 mL), following the similar procedure as described for the compound **140a**.

*^{1}H NMR spectrum of **140e** indicates that it is a mixture of E and Z isomers (in the ratio of 91:9 as determined by the integration ratios of diastereomeric methyl group protons singlets in the ^{1}H NMR spectrum).*



Reaction time: 30 min

Yield: 77%

Mp: 256-259 °C

IR (KBr): ν 3400-2800 (multiple bands), 1741, 1645, 1608 cm^{-1}

^{1}H NMR (400 MHz): δ 2.32 & 2.35 (2s, 6H), 6.64 & 6.70 (2s, 2H), 6.68-6.97 (m, 3H), 7.24-7.75 (1H), 8.32 & 9.34 (2br s, 1H)

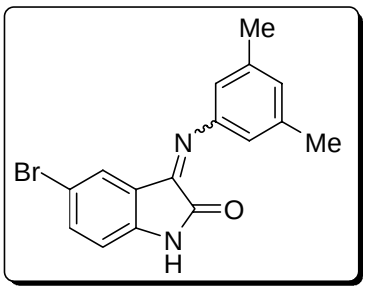
^{13}C NMR (100 MHz, DMSO-d_6): δ 21.05, 112.49, 113.21, 114.82, 116.85, 116.94, 122.30, 125.01, 125.47, 126.58, 126.80, 133.49, 133.77, 137.47, 139.15, 144.33, 145.78, 150.23, 153.93, 163.40

(*The underlined peaks are due to the minor diastereoisomer*)

5-Bromo-3-(3,5-dimethylphenylimino)indolin-2-one (140f):

This compound was obtained as pale yellow solid *via* the reaction of 5-bromoisatin (**132d**) with 3,5-dimethylaniline in ethanol (80 mL), following similar procedure described for the compound **140a**.

*^{1}H NMR spectrum of **140f** indicates that it is a mixture of E and Z isomers (in the ratio of 90:10 as determined by the integration ratios of diastereomeric methyl group protons singlets in the ^{1}H NMR spectrum).*



Reaction time: 30 min

Mp: 240-242 °C

Yield: 72%

IR (KBr): ν 3400-2800 (multiple bands), 1741, 1639, 1608, cm^{-1}

^{1}H NMR (400 MHz): δ 2.32 & 2.35 (2s, 6H), 6.64&6.69 (2s, 2H), 6.75&6.83 (2d, 1H, *J* = 8.4 Hz), 6.90-7.86 (m, 3H), 8.17 & 9.16 (2br s, 1H)

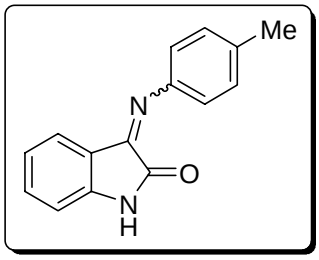
^{13}C NMR (100 MHz, DMSO-d_6): δ 21.05, 112.94, 113.09, 113.64, 114.88, 116.86, 117.42, 125.05, 126.58, 126.79, 127.89, 136.26, 136.51, 137.45, 139.12, 144.70, 146.11, 150.20, 153.82, 163.24

(*The underlined peaks are due to the minor diastereoisomer*)

3-(4-Methylphenylimino)indolin-2-one (140g):

This imine (**140g**) was obtained by the reaction of isatin (**132a**) with 4-methylaniline in ethanol (25 mL), as pale yello solid, following similar procedure as described for the compound **140a**.

*^{1}H NMR spectrum of **140g** indicates that it is a mixture of E and Z isomers (in the ratio of 93:7 as determined by the integration ratios of diastereomeric methyl group protons singlets in the ^{1}H NMR spectrum).*



Reaction time: 30 min

Yield: 65%

Mp: 220-222 °C (Lit.[298] 222 °C)

IR (KBr): ν 3400-3000 (multiple bands), 1741, 1730, 1653, 1610 cm^{-1}

^{1}H NMR (400 MHz,): δ 2.36 & 2.41 (2s, 3H), 6.70-7.75 (m, 8H), 8.76 & 9.86 (2br s, 1H)

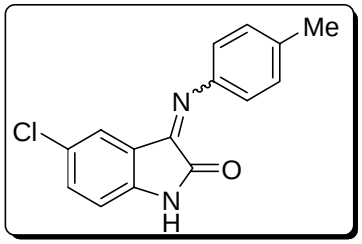
^{13}C NMR (100 MHz, DMSO-d_6): δ 20.73, 110.83, 111.65, 115.90, 117.62, 119.83, 121.84, 122.40, 122.75, 125.40, 128.92, 130.16, 134.15, 134.34, 134.46, 147.06, 148.01, 152.67, 154.91, 163.72

(*The underlined peaks are due to the minor diastereoisomer*)

5-Chloro-3-(4-methylphenylimino)indolin-2-one (140h):

This compound (**140h**) was obtained as pale yellow solid, by the condensation of 5-chloroisatin (**132b**) with 4-methyl aniline in ethanol (80 mL), following similar procedure as described for the compound **140a**.

*^{1}H NMR spectrum of **140h** indicates that it is a mixture of E and Z isomers (in the ratio of 82:18 as determined by the integration ratios of diastereomeric methyl group protons singlets in the ^{1}H NMR spectrum).*



Reaction time: 30 min

Yield: 60%

Mp: 286-288 °C (Lit.[298] 202 °C)

IR (KBr): ν 3400-3000 (multiple bands), 1739, 1732, 1651, 1612 cm^{-1}

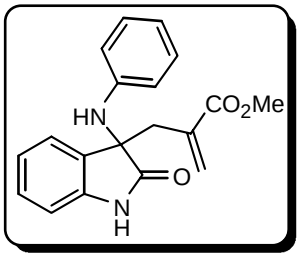
^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 & 2.36 (2s, 3H), 6.40 (s, 1H), 6.82-7.58 (m, 6H), 10.97 & 11.09 (2br s, 1H)

^{13}C NMR (100 MHz, DMSO-d_6): δ 20.74, 20.81, 112.43, 113.25, 117.04, 117.65, 120.19, 122.26, 123.49, 124.73, 125.42, 126.57, 128.94, 130.20, 133.37, 133.80, 134.82, 134.88, 144.20, 145.82, 147.54, 153.96, 158.40, 163.41

(*The underlined peaks are due to the minor diastereoisomer*)

Methyl 3-(3-anilinoindolin-2-one-3-yl)-2-methylenepropanoate (141a):

To a stirred solution of 3-(phenylimino)indolin-2-one (2 mmol, 0.444 g) (**140a**), methyl 2-(bromomethyl)prop-2-enoate (**131**) (2.2 mmol, 0.394 g) in THF (2 mL) was added zinc (4 mmol, 0.260 g) and aqueous NH_4Cl solution (8 mL). After stirring for 5 min at room temperature, the reaction mixture was cooled to 0 ^oC and diluted with $NaHCO_3$ solution (25 mL). The reaction mixture was extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound thus obtained was purified through column chromatography (20 % ethyl acetate in hexanes) to afford **141a** in 85 % (0.548 g) as colorless solid.



Mp: 156-158 °C

IR (KBr): ν 3400-2800 (multiple bands), 1716,1614 cm^{-1}

^1H NMR (400 MHz): δ 2.67 & 3.23 (ABq, 2H, *J* = 13.2 Hz), 3.69 (s, 3H), 5.22 (br s, 1H), 5.44 (s, 1H), 6.20-6.32 (m, 3H), 6.59-6.67 (m, 1H), 6.88 (d, 1H, *J* = 7.6 Hz), 6.92-7.03 (m, 3H), 7.15 (d, 1H, *J* = 7.2 Hz), 7.21-7.31 (m, 1H), 8.49 (br s, 1H)

^{13}C NMR (100 MHz): δ 41.27, 52.20, 65.30, 110.97, 114.42, 118.64, 122.41, 124.98, 129.00, 129.12, 130.75, 133.80, 139.78, 145.24, 168.10, 180.50

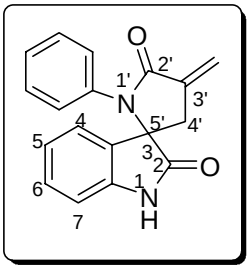
LCMS (*m/z*): 323 $(M+H)^+$

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69

Found: C, 70.78, H; 5.68; N, 8.78

(Indolin-2-one)-3-spiro-5′-[3'-methylene-1'-phenyl-pyrrolidin-2'-one] (142a):

A solution of allyl ester (1mmol, 0.322 g) (**141a**), *p*-toluenesulphonic acid (1 mmol, 0.190 g) in ethylene glycol dimethyl ether (DME) (2 mL) was heated under reflux for 5 hours. DME was removed under reduced pressure. The residue was dissolved in ethyl acetate (3 mL) and the reaction mixture was neutralized with $NaHCO_3$ solution (3 mL). The resulting mixture was then extracted with ethyl acetate (3 X 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Residue thus obtained, was purified through column chromatography (30 % ethyl acetate in hexanes) to afford (indolin-2-one)-3-spiro-5′-[3'-methylene-1'-phenyl-pyrrolidin-2'-one] (**142a**) in 73 % (0.212 g) yield as colorless solid.



Mp: 222-224 °C

IR (KBr): ν 3400-2800 (multiple bands), 1738, 1680, 1662, 1616 cm^{-1}

^1H NMR (400 MHz): δ 3.02 & 3.32 (ABq, 2H, *J* = 16.8 Hz), 5.57 (s, 1H), 6.29 (s, 1H), 6.78 (d, 1H, *J* = 7.6 Hz), 6.98-7.28 (m, 7H), 7.30 (d, 1H, *J* = 7.2 Hz), 8.26 (s, 1H)

^{13}C NMR (DMSO-*d6*, 100 MHz): δ 37.07, 67.39, 110.50, 116.65, 122.77, 124.74, 126.43, 127.42, 128.34, 129.01, 130.14, 136.69, 137.98, 141.79, 167.78, 177.14

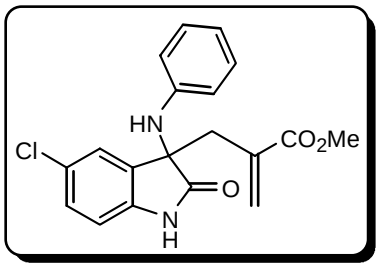
LCMS (*m/z*): 291 $(M+H)^+$

Anal. Calcd. For $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65

Found: C, 74.52; H, 4.83; N, 9.73

Methyl 3-(3-anilino-5-chloroindolin-2-one-3-yl)-2-methylenepropanoate (141b):

This compound was obtained as colorless solid *via* the reaction between 5-chloro-3-(phenylimino)indolin-2-one (**140b**) and methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following the similar procedure described for the compound **141a**.



Reaction time: 5 min

Yield: 79 %

Mp: 146-148 °C

IR (KBr): ν 3400-2800 (multiple bands), 1743, 1712, 1601 cm^{-1}

^1H NMR (400 MHz): δ 2.67 & 3.20 (ABq, 2H, *J* = 13.2 Hz), 3.73 (s, 3H), 5.23 (s, 1H), 5.47 (s, 1H), 6.22 (d, 2H, *J* = 8.0 Hz), 6.30 (s, 1H), 6.62-6.70 (m, 1H), 6.80 (d, 1H, *J* = 8.0 Hz), 6.93-7.03 (m, 2H), 7.14 (s, 1H), 7.19-7.25 (m, 1H), 8.59 (s, 1H)

^{13}C NMR (100 MHz): δ 41.27, 52.39, 65.38, 112.06, 114.24, 118.93, 125.25, 128.06, 129.15, 129.21, 130.92, 131.12, 133.54, 138.23, 144.91, 168.05, 180.20

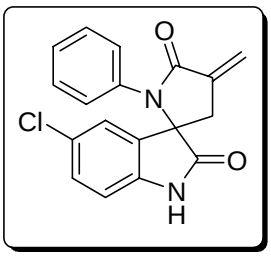
LCMS (*m/z*): 357 $(M+H)^+$, 359 $[(M+2)+H]^+$

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80, N, 7.85

Found: C, 63.85; H, 4.81; N, 7.92

(5-Chloroindolin-2-one)-3-spiro-5′-[3'-methylene-1'-phenylpyrrolidin-2'-one] (142b):

This spiro-lactam (**142b**) was obtained as colorless solid *via* the treatment of **141b** with p-toluenesulfonic acid, following similar procedure as described for the compound **142a**.



Reaction time: 5 h

Yield: 74 %

Mp: 226-228 °C

IR (KBr): ν 3450-3000 (multiple bands), 1738, 1682, 1653, 1618 cm^{-1}

^1H NMR (400 MHz): δ 3.02 & 3.33 (t of ABq, 2H, *J* = 16.8, 2.4 Hz), 5.60 (t, 1H, *J* = 2.1 Hz), 6.31 (t, 1H, *J* = 2.4 Hz), 6.72 (d, 1H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 7.13-7.28 (m, 4H), 7.30 (s, 1H), 7.84 (s, 1H)

^{13}C NMR ($CDCl_3$, DMSO-d_6, 100 MHz): δ 35.43, 65.77, 110.33, 115.41, 122.73, 124.58, 125.61, 125.75, 127.30, 128.28, 128.73, 134.80, 135.56, 138.90, 165.99, 175.02

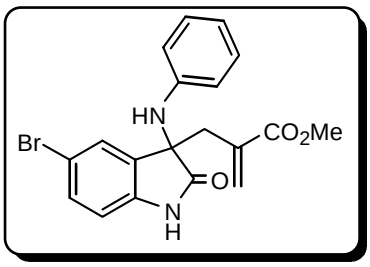
LCMS (*m/z*): 325 $(M+H)^+$, 327 $[(M+2)+H]^+$

Anal. Calcd. For $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63

Found: C, 66.34; H, 4.00; N, 8.58

Methyl 3-(3-anilino-5-bromoindolin-2-one-3-yl)-2-methylenepropanoate (141c):

This compound was obtained *via zinc mediated* reaction of 5-bromo-3-(phenylimino)indolin-2-one (**140c**) with methyl 2-(bromomethyl)prop-2-enoate (**131**), as a colorless solid, following the similar procedure described for the compound **141a**.



Reaction time: 5 min

Yield: 72 %

Mp: 158-160 °C

IR (KBr): ν 3400-2800 (multiple bands), 1745, 1707, 1631, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 2.67 & 3.20 (ABq, 2H, *J* = 13.2 Hz), 3.73 (s, 3H), 5.19 (s, 1H), 5.48 (s, 1H), 6.22 (d, 2H, *J* = 8.0 Hz), 6.30 (s, 1H), 6.62-6.71 (m, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 6.93-7.03 (m, 2H), 7.28 (s, 1H), 7.34-7.42 (m, 1H), 8.30 (s, 1H)

^{13}C NMR (100 MHz): δ 41.35, 52.47, 65.29, 112.43, 114.33, 115.43, 119.03, 128.14, 129.20, 131.13, 131.30, 132.14, 133.57, 138.66, 144.90, 168.05, 179.76

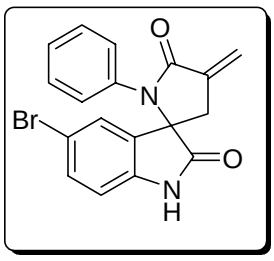
LCMS (*m/z*): 401 $(M+H)^+$, 403 $[(M+2)+H]^+$

Anal. Calcd. for $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27, N, 6.98

Found: C, 56.99; H, 4.26; N, 6.96

(5-Bromoindolin-2-one)-3-spiro-5′-[3'-methylene-1'-phenylpyrrolidin-2'-one] (142c):

This compound was obtained *via* the treatment of **141c** with p-toluenesulfonic acid as colorless solid, following the similar procedure as described for the compound **142a**.



Reaction time: 5 h

Yield: 75 %

Mp: 192-194 °C

IR (KBr): ν 3450-3000 (multiple bands), 1738, 1682, 1651, 1616 cm^{-1}

^1H NMR (400 MHz): δ 3.01 & 3.32 (t of ABq, 2H, *J* = 16.8, 2.4 Hz), 5.60 (t, 1H, *J* = 2.4 Hz), 6.30 (t, 1H, *J* = 2.4 Hz), 6.66 (d, 1H, *J* = 8.0 Hz), 6.99-7.07 (m, 2H), 7.14-7.25 (m, 3H), 7.36 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.43 (d, 1H, *J* = 2.0 Hz), 8.23 (s, 1H)

^{13}C NMR (100 MHz): δ 37.38, 67.88, 112.66, 115.96, 118.71, 126.61, 127.02, 127.96, 129.25, 130.96, 133.13, 135.91, 136.11, 139.54, 168.44, 176.75

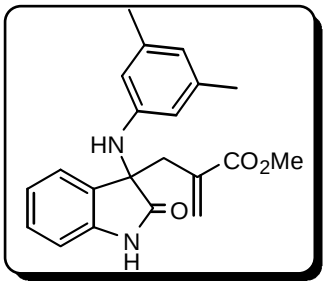
LCMS (*m/z*): 369 $(M+H)^+$, 371 $[(M+2)+H]^+$

Anal. Calcd. For $C_{18}H_{13}BrN_2O_2$: C, 58.56; H, 3.55; N, 7.59

Found: C, 58.68; H, 3.58; N, 7.65

Methyl 3-[(3,5-dimethylaniline)indolin-2-one-3-yl]-2-methylenepropanoate (141d):

Reaction of 3-(3,5-dimethylphenylimino)indolin-2-one (**140d**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following similar procedure described for the compound **141a** provided the title compound as a colorless solid.



Reaction time: 5 min

Yield: 80 %

Mp: 152-154 °C

IR (KBr): ν 3400-2800 (multiple bands), 1714, 1674, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 2.01 (s, 6H), 2.64 & 3.22 (ABq, 2H, *J* = 13.2 Hz), 3.68 (s, 3H), 5.07 (br s, 1H), 5.43 (s, 1H), 5.86 (s, 2H), 6.24 (s, 1H), 6.27 (s, 1H), 6.88 (d, 1H, *J* = 8.0 Hz), 6.93-7.02 (m, 1H), 7.14 (d, 1H, *J* = 7.2 Hz), 7.19-7.25 (m, 1H), 8.84 (s, 1H)

^{13}C NMR (100 MHz): δ 21.40, 41.26, 52.18, 65.26, 110.69, 112.49,120.81, 122.36, 125.12, 129.07, 129.27, 130.55, 133.94, 138.48, 139.82, 145.22, 168.09, 180.47

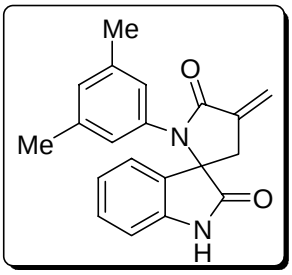
LCMS (*m/z*): 351 $(M+H)^+$

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33, N, 7.99

Found: C, 71.90; H, 6.29; N, 7.91

(Indolin-2-one)-3-spiro-5′-[3'-methylene-1'-(3,5-dimethylphenyl)pyrrolidin-2'-one] (142d):

Treatment of the amino ester (**141d**) with p-toluenesulfonic acid, following the similar procedure as described for the compound **142a**. provided the title compoundas a colorless solid.



Reaction time: 5 h

Yield: 70 %

Mp: 274-276 °C

IR (KBr): ν 3300-2800 (multiple bands), 1738, 1678, 1662, 1595 cm^{-1}

^1H NMR (DMSO-d_6, 400 MHz): δ 2.10 (s, 6H), 3.00 & 3.17 (t of ABq, 2H, *J* = 16.8, 2.4 Hz), 5.55 (s, 1H), 5.98 (s, 1H), 6.60 (s, 2H), 6.75-6.86 (m, 2H), 6.95-7.05 (m, 1H), 7.16-7.26 (m, 1H), 7.41 (d, 1H, *J* = 7.2 Hz), 10.66 (s, 1H)

^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.89, 36.98, 67.36, 110.39, 116.36, 122.68, 124.22, 124.74, 128.43. 128.98, 130.09, 136.56, 137.96, 138.05, 141.80, 167.71, 177.19

LCMS (*m/z*): 319 $(M+H)^+$

Anal. Calcd. For $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80

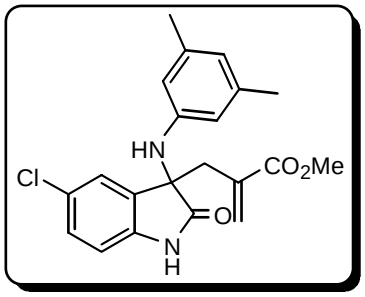
Found: C, 75.42; H, 5.75; N, 8.76

Methyl 3-[5-chloro-3-(3,5-dimethylaniline)indolin-2-one-3-yl]-2-methylenepropan-oate (141e):

Zinc mediated treatment of 5-chloro-3-(3,5-dimethylphenylimino)indolin-2-one (**140e**) with methyl 2-(bromomethyl)prop-2-enoate (**131**), following similar procedure as described for the compound **141a** furnished the title compound as a colorless solid.

Reaction time: 5 min

Yield: 77 %



Mp: 198-200 °C

IR (KBr): ν 3400-2800 (multiple bands), 1714, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 2.03 (s, 6H), 2.64 & 3.19 (ABq, 2H, *J* = 13.2 Hz), 3.71 (s, 3H), 5.11 (s, 1H), 5.45 (s, 1H), 5.85 (s, 2H), 6.28 (s, 1H), 6.31 (s, 1H), 6.80 (d, 1H, *J* = 8.0 Hz), 7.13 (s, 1H), 7.20 (d, 1H, *J* = 8.0 Hz), 9.00 (s, 1H)

^{13}C NMR (100 MHz): δ 21.45, 41.32, 52.38, 65.31, 111.70, 112.30, 121.10, 125.45, 128.03, 129.17, 130.93, 131.19, 133.69, 138.25, 138.71, 144.88, 168.03, 180.00

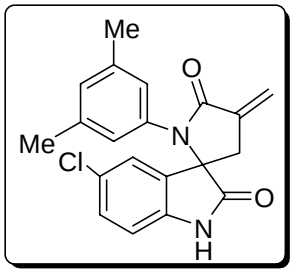
LCMS (*m/z*): 385 $(M+H)^{+}$, 387$[(M+2)+H]^{+}$

Anal. Calcd. for $C_{21}H_{21}ClN_2O_3$: C, 65.54; H, 5.50, N, 7.28

Found: C, 65.70; H, 5.54; N, 7.40

(5-Chloroindolin-2-one)-3-spiro-5′-[3'-methylene-1'-(3,5-dimethylphenyl)pyrrolidi-n-2'-one] (142e):

This spiro-lactam was obtained by the reaction of amino ester (**141e**) with p-tolunesulfonic acid as colorless solid, following the similar procedure as described for the compound **142a**.



Reaction time: 5 h

Yield: 72 %

Mp: 148-150 °C

IR (KBr): ν 3300-2800 (multiple bands), 1743, 1685, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 2.13 (s, 6H), 2.99 & 3.31 (ABq, 2H, *J* = 16.4 Hz),* 5.58 (s, 1H), 6.27-6.32 (m, 1H),# 6.63 (s, 2H), 6.72 (d, 1H, *J* = 8.4 Hz), 6.80 (s, 1H), 7.21 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.30 (d, 1H, 1.6 Hz), 8.08 (br s, 1H)

^{13}C NMR (100 MHz): δ 21.25, 37.43, 67.88, 111.83, 118.39, 124.53, 124.55, 128.95, 129.95, 130.19, 131.03, 135.77, 136.24, 138.73, 138.91, 168.26, 176.77

LCMS (*m/z*): 353 $(M+H)^+$, 355 $[(M+2)+H]^+$

Anal. Calcd. For $C_{20}H_{17}ClN_2O_2$: C, 68.09; H, 4.86; N, 7.94

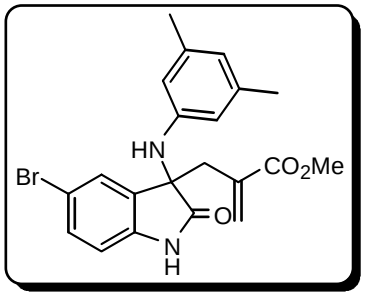
Found: C, 68.05; H, 4.85; N, 8.06

***** *Actually it is a triplet of AB quartet. Due to lack of clarity in splitting pattern we wrote as AB quartet.*

 # Actually it is a triplet. Due to lack of clarity in splitting pattern we wrote as multiplet.

Methyl 3-[5-bromo-3-(3,5-dimethylaniline)indolin-2-one-3-yl]-2-methyleneprop-anoate (141f):

This compound was prepared *via* the reaction between 5-bromo-3-(3,5-dimethyl phenylimino)indolin-2-one (**140f**) and methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc as colorless solid, following the similar procedure described for the compound **141a**.



Reaction time:	5 min
Yield:	75 %
Mp:	200-202 °C
IR (KBr):	ν3400-2800 (multiple bands), 1714, 1687, 1602 cm^{-1}
^{1}H NMR (400 MHz):	δ 2.04 (s, 6H), 2.64 & 3.19 (ABq, 2H, *J* = 13.2 Hz), 3.72 (s, 3H), 5.07 (s, 1H), 5.46 (s, 1H), 5.85 (s, 2H), 6.28 (s, 1H), 6.31 (s, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 7.27 (s, 1H), 7.36 (d, 1H, *J* = 8.0 Hz), 8.76 (br s, 1H)
^{13}C NMR (100 MHz):	δ 21.46, 41.34, 52.43, 65.24, 112.16, 112.30, 115.35, 121.12, 128.21, 130.93, 131.53, 132.07, 133.67, 138.72, 144.87, 168.01, 179.79

LCMS (*m/z*): 429 $(M+H)^+$, 431 $[(M+2)+H]^+$

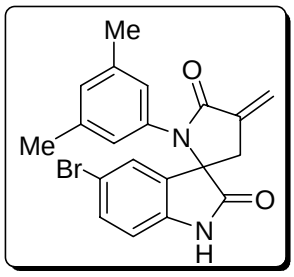
Anal. Calcd. for $C_{21}H_{21}BrN_2O_3$: C, 58.75; H, 4.93, N, 6.53

Found: C, 58.79; H, 4.94; N, 6.63

(5-Bromoindolin-2-one)-3-spiro-5′-[3'-methylene-1'-(3,5-dimethylphenyl)pyrrolidin-2'-one] (142f):

Treatment of amine ester (**141f**) with p-toluenesulfonic acid, following the similar procedure as described for the compound **142a** provided the title compound **142f** a colorless solid.

Reaction time: 5 h



Yield: 67 %

Mp: 124-126 °C

IR (KBr): ν 3300-2800 (multiple bands), 1741, 1684, 1660, 1616 cm^{-1}

^1H NMR (400 MHz): δ 2.14 (s, 6H), 2.99 & 3.31 (t of ABq, 2H, *J* = 16.8, 2.4 Hz), 5.58 (m, 1H),* 6.29 (t, 1H, *J* = 2.4 Hz), 6.63 (s, 2H), 6.67 (d, 1H, *J* = 8.0 Hz), 6.81 (s, 1H), 7.36 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.44 (d, 1H, *J* = 1.8 Hz), 7.86 (s, 1H)

^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.95, 36.81, 67.35, 112.38, 114.32, 116.50, 124.07, 127.87, 129.12, 130.69, 132.90, 136.43, 137.81, 138.12, 141.21, 167.65, 176.94

LCMS (*m/z*): 397 $(M+H)^+$, 399 $[(M+2)+H]^+$

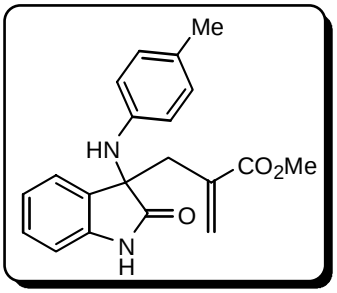
Anal. Calcd. For $C_{20}H_{17}BrN_2O_2$: C, 60.47; H, 4.31; N, 7.05

Found: C, 60.60; H, 4.36; N, 7.06

* *Actually it is triplet. Because of lack of clarity in splitting we wrote as multiplet.*

Methyl 3-[3-(4-methylaniline)indolin-2-one-3-yl)-2-methylenepropanoate (141g):

Treatment of 3-(4-methylphenylimino)indolin-2-one (**140g**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following similar procedure as described the compound **141a** , provided the title compound **141g** as colorless solid.



Reaction time: 5 min

Yield: 70 %

Mp: 150-152 °C

IR (KBr): ν 3400-2800 (multiple bands), 1712, 1664, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 2.08 (s, 3H), 2.68 & 3.22 (ABq, 2H, *J* = 13.2 Hz), 3.66 (s, 3H), 5.04 (s, 1H), 5.44 (s, 1H), 6.16 (d, 2H, *J* = 8.0 Hz), 6.23 (s, 1H), 6.73 (d, 2H, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 8.0 Hz), 6.92-7.02 (m, 1H), 7.13-7.24 (m, 2H), 9.02 (br s, 1H)

^{13}C NMR (100 MHz): δ 20.33, 41.13, 52.13, 65.58, 110.91, 114.88, 122.34, 125.02, 127.96, 129.02, 129.22, 129.51, 130.45, 133.94, 139.88, 142.86, 167.98, 180.71

LCMS (*m/z*): 337 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99, N, 8.33

Found: C, 71.27; H, 5.97; N, 8.28

(Indolin-2-one)-3-spiro-5′-[3'-methylene-1'-(4-methylphenyl)pyrrolidin-2'-one] (142g):

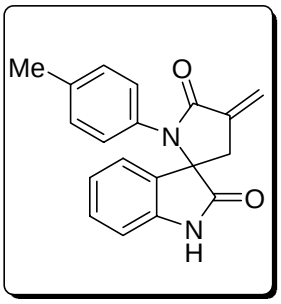
This compound was prepared *via* the treatment of amine ester (**141g**) with p-tolunesulfonic acid as colorless solid, following the similar procedure as described for the compound **142a**.

Rection time: 5 h

Yield: 68 %

Mp: 266-268 °C

IR (KBr): ν 3300-2800 (multiple bands), 1734, 1680, 1662, 1618 cm^{-1}



^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.19 (s, 3H), 3.01 & 3.17 (t of ABq, 2H, *J* = 16.8, 2.4 Hz), 5.55 (s, 1H), 5.99 (s, 1H), 6.77 (d, 1H, *J* = 7.6 Hz), 6.85 (d, 2H, *J* = 8.0 Hz), 6.94-7.02 (m, 1H), 7.04 (d, 2H, *J* = 8.0 Hz), 7.15-7.25 (m, 1H), 7.42 (d, 1H, *J* = 7.2 Hz), 10.63 (br s, 1H)

^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.68, 36.91, 67.46, 110.46, 116.44, 122.75, 124.80, 126.58, 128.43, 129.54, 130.12, 134.03, 137.01, 138.06, 141.82, 167.83, 177.20

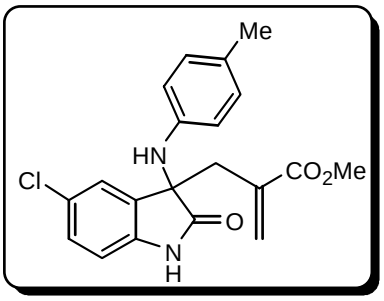
LCMS (*m/z*): 305 $(M+H)^+$

Anal. Calcd. For $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20

Found: C, 75.06; H, 5.32; N, 9.08

Methyl 3-(5-chloro-3-(4-methylaniline)-indolin-2-one-3-yl)-2-methylenepropanoate (141h):

This amine ester was obtained as colorless solid *via* the reaction of 5-chloro-3-(4-methylphenylimino)indolin-2-one (**140h**) with methyl 2-(bromomethyl)prop-2-enoate (**131**) in the presence of zinc, following the similar procedure as described for the compound **141a**.



Reaction time: 5 min

Yield: 72 %

Mp: 180-182 °C

IR (KBr): ν 3400-2800 (multiple bands), 1741, 1711, 1612 cm^{-1}

^1H NMR (400 MHz): δ 2.10 (s, 3H), 2.67 & 3.19 (ABq, 2H, *J* = 13.2 Hz), 3.70 (s, 3H), 5.05 (s, 1H), 5.47 (s, 1H), 6.15 (d, 2H, *J* = 8.0 Hz), 6.28 (s, 1H), 6.70-6.81 (m, 3H), 7.14 (s, 1H), 7.17 (d, 1H, *J* = 8.0 Hz), 8.95 (s, 1H)

^{13}C NMR (100 MHz): δ 20.38, 41.20, 52.36, 65.65, 111.92, 114.73, 125.39, 128.04, 128.37, 129.14, 129.68, 130.86, 131.14, 133.70, 138.27, 142.52, 167.95, 180.24

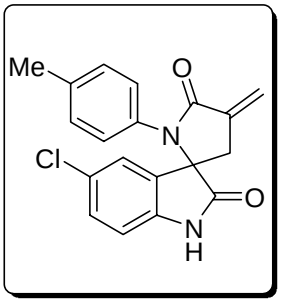
LCMS (*m/z*): 371 $(M+H)^+$, [373 (M+2)+H]$^+$

Anal. Calcd. for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16, N, 7.55

Found: C, 64.72; H, 5.10; N, 7.65

(5-Chloroindolin-2-one)-3-spiro-5′-[3'-methylene-1'-(4-methylphenyl)pyrrolidin-2'-one] (142h):

This spiro-lactam (**142h**) was obtained as colorless solid by the rection of amine ester (**141h**) with p-tolunesulfonic acid, following the similar procedure as described for the compound **142a**



Reaction time: 5 h

Yield: 73 %

Mp: 252-254 °C

IR (KBr): ν 3450-2800 (multiple bands), 1739, 1682, 1658, 1620 cm^{-1}

^1H NMR (400 MHz): δ 2.23 (s, 3H), 2.94-3.05 & 3.25-3.36 (2m, 2H),* 5.54-5.61 (m, 1H), 6.25-6.33 (m,1H), 6.70 (d, 1H, *J* = 8.0 Hz), 6.90 (d, 2H, *J* = 8.0 Hz), 7.00 (d, 2H, *J* = 8.0 Hz), 7.16-7.22 (m, 1H), 7.29 (s, 1H), 8.09 (s, 1H)

^{13}C NMR ($CDCl_3$, DMSO-d_6, 100 MHz): δ 19.23, 35.30, 65.86, 110.31, 115.26, 122.76, 124.70, 125.62, 127.90, 128.26, 128.86, 132.13, 135.49, 135.64, 138.95, 166.09, 175.11

LCMS (*m/z*): 339 $(M+H)^+$, 341$[(M+2)+H]^+$

Anal. Calcd. For $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27

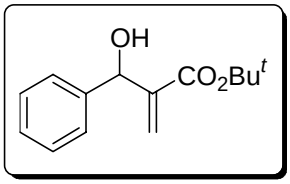
Found: C, 67.34; H, 4.43; N, 8.20

* Actually it is a triplet of ABquartet. Because of lack of clarity in splitting we wrote as two multiplets

***tert*-Butyl 3-hydroxy-2-methylene-3-phenylpropanoate (168a):**

This compound was prepared according to the procedure developed in our laboratory.[299] Benzaldehyde (100 mmol, 10.6 g, 10.1 mL), *tert*-butyl acrylate (150 mmol, 19.2 g, 22.0 mL) and DABCO (**1**) (15 mmol, 1.7 g) were thoroughly and uniformly mixed in silica gel (>200 mesh, 30.0 g) and was kept at room temperature for 36 h. Then ethyl acetate (100 mL) was added and stirred thoroughly and filtered. The solid silica gel was washed with ethyl acetate (2 X 30 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 (6% of ethyl acetate in hexanes) to afford *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**168a**) in 75% (17.5 g) as a colorless liquid.

IR (neat): ν 3443, 1711, 1631 cm^{-1}

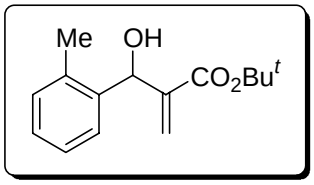


^{1}H NMR (400 MHz): δ 1.39 (s, 9H), 3.06 (d, 1H, J = 5.8 Hz), 5.50 (d, 1H, J = 5.2 Hz), 5.71 (s, 1H), 6.25 (s, 1H), 7.23-7.42 (m, 5H)

^{13}C NMR (100 MHz): δ 27.80, 73.06, 81.35, 124.74, 126.60, 127.50, 128.17, 141.68, 143.56, 165.51

***tert*-Butyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate (168b):**

This compound was obtained as viscous liquid by the reaction of 2-methylbenzaldehyde with tert-butyl acrylate in the presence of DABCO, using silica gel as solid phase medium, following the similar procedure described for the compound **168a**.



Reaction time: 12 d

Yield: 60%

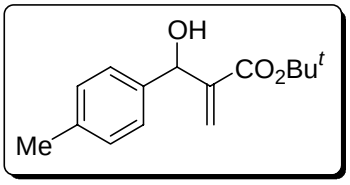
IR(neat): ν 3420, 1716, 1633 cm^{-1}

^1H NMR (400 MHz): δ 1.43 (s, 9H), 2.33 (s, 3H), 2.86 (br s, 1H), 5.50 (s, 1H), 5.75 (s, 1H), 6.23 (s, 1H), 7.10-7.47(m, 4H)

^{13}C NMR (100 MHz): δ 19.21, 28.08, 69.72, 81.66, 125.25, 126.25, 126.33, 127.82, 130.47, 135.75, 139.17, 143.33, 166.19

***tert*-Butyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (168c):**

This Baylis-Hillman alcohol was obtained as a colorless solid [after crystallization from 10% ethyl acetate in hexanes at 0 °C], *via* the the reaction of 4-methylbenzaldehyde with *tert*-butyl acrylate under the catalytic amount of DABCO (**1**), using silica gel as solid phase medium, following similar procedure described for the compound **168a**



Reaction time: 10 d

Yield: 62%

Mp: 58-60 °C (Lit.[299] 41-43 °C)

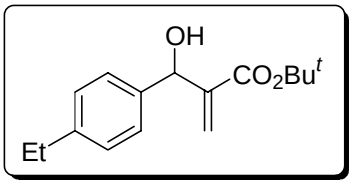
IR (KBr): ν 3327, 1714, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.40 (s, 9H), 2.33 (s, 3H), 3.04 (br s, 1H), 5.46 (s, 1H), 5.71 (s, 1H), 6.22 (s, 1H), 7.13 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.0 Hz)

^{13}C NMR (100 MHz): δ 21.11, 27.96, 73.22, 81.48, 124.87, 126.54, 129.00, 137.25, 138.76, 143.67, 165.72

***tert*-Butyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (168d):**

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 °C], using silica gel as solid phase medium, following similar procedure described for the molecule **168a**.



Reaction time: 16 d

Yield: 65%

Mp: 38-40 °C (Lit.[299] 46-48 °C)

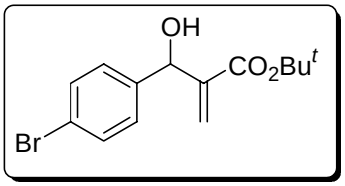
IR (KBr): ν 3321, 1714, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.22 (t, 3H, J = 7.6 Hz), 1.39 (s, 9H), 2.63 (q, 2H, J = 7.6 Hz), 3.01 (d, 1H, J = 5.8 Hz), 5.47 (d, 1H, J = 5.8 Hz), 5.71 (s, 1H), 6.23 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.26 (d, 2H, J = 8.0 Hz)

^{13}C NMR (100 MHz): δ 15.58, 27.95, 28.53, 73.23, 81.46, 124.85, 126.61, 127.80, 138.99, 143.67, 143.69, 165.73

***tert*-Butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (168e):**

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 in the presence of DABCO (cat.), using silica gel as solid phase medium, following similar procedure described for the compound **168a**.



Reaction time: 6 d

Yield: 62%

Mp: 53-55 °C (Lit. [299] 61-63 °C)

IR (KBr): ν 3325, 1714, 1635 cm^{-1}

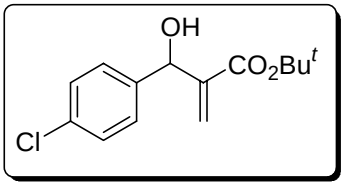
^{1}H NMR (400 MHz): δ 1.40 (s, 9H), 3.28 (d, 1H, J = 6.0 Hz), 5.43 (d, 1H, J = 6.0 Hz), 5.70 (s, 1H), 6.23 (s, 1H), 7.23 (d, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz)

^{13}C NMR (100 MHz): δ 27.98, 72.84, 81.86, 121.53, 125.48, 128.34, 131.41, 140.78, 143.08, 165.49

***tert*-Butyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (168f):**

This compound was obtained as a colorless solid [after crystallization from 15% ethyl acetate in hexanes at 0 °C], *via* the DABCO (**1**) catalyzed Baylis-Hillman coupling of 4-chlorobenzaldehyde with *tert*-butyl acrylate, using silica gel solid phase medium, following similar procedure described for the compound **168a**.

Reaction time: 14 d



Yield: 80%

Mp: 64-66 °C

IR (KBr): ν 3327, 1714, 1639 cm^{-1}

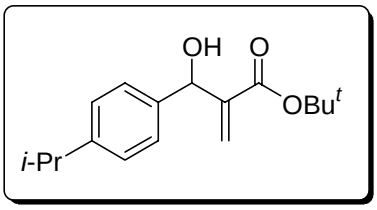
^{1}H NMR (400 MHz): δ 1.41 (s, 9H), 3.17 (d, 1H, *J* = 6.0 Hz), 5.46 (d, 1H, *J* = 6.0 Hz), 5.69 (s, 1H), 6.24 (s, 1H), 7.31 (s, 4H)

^{13}C NMR (100 MHz): δ 28.02, 72.96, 81.93, 125.56, 128.00, 128.51, 133.44, 140.26, 143.15, 165.57

***tert*-Butyl 3-(4-isopropylphenyl)-3-hydroxy-2-methylenepropanoate (168g):**

This compound was obtained as a colorless solid [after crystallization from 10% ethyl acetate in hexanes at 0 °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 **168a**.

Reaction time: 18d



Yield: 62%

Mp: 42-44 °C

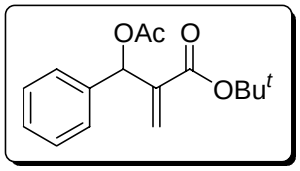
IR (KBr): ν 3319, 1712, 1633 cm^{-1}

^{1}H NMR (400 MHz): δ 1.23 (d, 6H, *J* = 6.8 Hz), 1.39 (s, 9H), 2.83-2.95 (m, 1H), 2.98 (d, 1H, *J* = 5.8 Hz), 5.48 (d, 1H, *J* = 5.8 Hz), 5.72 (d, 1H, *J* = 1.2 Hz), 6.23 (s, 1H), 7.19 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz)

^{13}C NMR (100 MHz): δ 24.00, 27.95, 33.81, 73.25, 81.49, 124.90, 126.37, 126.61, 139.10, 143.67, 148.33, 165.76

***tert*-Butyl 3-acetoxy-2-methylene-3-phenylpropanoate (169a):**

Acetyl chloride (75 mmol, 5.6 g, 5.5 mL) was added to a stirred solution of *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**168a**) (50 mmol, 11.7 g), pyridine (75 mmol, 5.6 g, 5.0 mL) in dichloromethane (50 mL) at 0 °C and stirring continued for 2 h at room temperature. The reaction mixture was diluted with ether (50 mL) and washed with water. Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product, thus obtained was purified by column chromatography (silica gel, 4% EtOAc in hexanes) to afford the pure *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**169a**) as colorless liquid in 85% (11.7 g) yield.



IR (neat): ν 1714, 1633 cm^{-1}

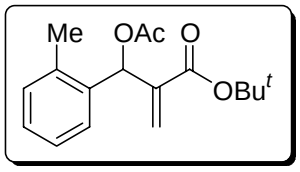
^{1}H NMR (400 MHz): δ 1.36 (s, 9H), 2.09 (s, 3H), 5.72 (s, 1H), 6.31 (s, 1H), 6.63 (s, 1H), 7.27-7.42 (m, 5H)

^{13}C NMR (100 MHz): δ 20.94, 27.77, 73.27, 81.28, 124.54, 127.75, 128.19, 128.25, 138.02, 141.12, 164.07, 169.23

***tert*-Butyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (169b):**

The treatment of *tert*-butyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate (**168b**) with acetyl chloride in the presence of pyridine, following the similar procedure described for the compound **(169a),** afforded the desired compound **169b** as colorless viscous liqulid.

Reaction time: 2h



Yield: 86%

IR (neat): ν 1743, 1714, 1637 cm^{-1}

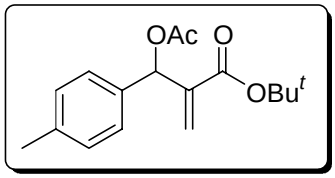
^{1}H NMR (400 MHz): δ 1.38 (s, 9H), 2.10 (s, 3H), 2.38 (s, 3H), 5.52 (s, 1H), 6.32 (s, 1H), 6.85 (s, 1H), 7.13-7.32 (m, 4H)

^{13}C NMR (100 MHz): δ 19.11, 20.87, 27.84, 70.33, 81.30, 125.37, 125.96, 127.08, 128.22, 130.47, 136.02, 136.37, 140.81, 164.38, 169.34

***tert*-Butyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (169c):**

This compound was isolated as a colorless viscous liquid, *via* the treatment of *tert*-butyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (**168c**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the compound **169a**.

Reaction time: 2 h



Yield: 86%

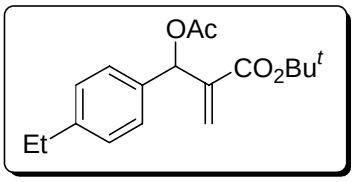
IR (neat): ν 1745, 1720, 1635 cm^{-1}

^{1}H NMR (400 MHz): δ 1.37 (s, 9H), 2.08 (s, 3H), 2.33 (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 (100 MHz): δ 21.05, 21.11, 27.86, 73.23, 81.30, 124.36, 127.76, 129.00, 135.10, 138.00, 141.29, 164.22, 169.35

***tert*-Butyl 3-acetoxy-3-(4-ethylphenyl)-2-methylenepropanoate (169d):**

The reaction of *tert*-butyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (**168d**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the molecule **169a**, provided the desired compound **169d** as a colorless viscous liquid.



Reaction time: 2h

Yield: 83%

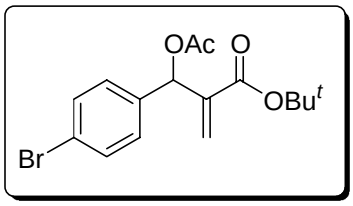
IR (neat): ν 1747, 1714, 1635 cm^{-1}

^{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), 5.70 (s, 1H), 6.29 (s, 1H), 6.61 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.26 (d, 2H, J = 8.0 Hz)

^{13}C NMR (100 MHz): δ 15.40, 21.04, 27.84, 28.51, 73.24, 81.28, 124.35, 127.78, 127.82, 135.29, 141.34, 144.33, 164.23, 169.35

***tert*-Butyl 3-acetoxy-3-(4-bromophenyl)-2-methylenepropanoate (169e):**

This compound was prepared as a colorless solid, *via* the reaction of *tert*-butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (**168e**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the molecule **169a**.



Reaction time: 2 h

Yield: 85%

Mp: 50-52 °C

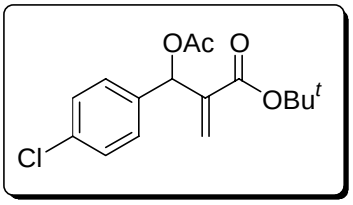
IR(KBr): ν 1738, 1705, 1626 cm^{-1}

^{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 = 8.4 Hz), 7.46 (d, 2H, J = 8.4 Hz)

^{13}C NMR (100 MHz): δ 20.97, 27.86, 72.62, 81.55, 122.27, 124.88, 129.51, 131.47, 137.24, 140.67, 163.86, 169.18

***tert*-Butyl 3-acetoxy-3-(4-chlorophenyl)-2-methylenepropanoate (169f):**

This compound was obtained as a colorless solid, *via* the acetylation of *tert*-butyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**168f**) with acetyl chloride in the presence of pyridine, following the similar procedure described for the compound **169a**.



Reaction time: 2 h

Yield: 87%

Mp: 58-60 °C

IR (KBr): ν 1743, 1703, 1633 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)

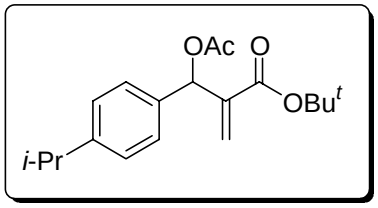
^{13}C NMR (100 MHz): δ 20.96, 27.86, 72.60, 81.55, 124.82, 128.51, 129.22, 134.10, 136.74, 140.75, 163.89, 169.21

***tert*-Butyl 3-acetoxy-3-(4-isopropylphenyl)-2-methylenepropanoate (169g):**

This acetate was prepared by the recation of *tert*-butyl 3-(4-isopropylphenyl)-3-hydroxy-2-methylenepropanoate (**168g**) with acetyl chloride in the presence of pyridine, following a similar procedure described for the molecule **169a** to obtain **169g** as as colorless viscous liquid.

Reaction time: 2h

Yield: 87%



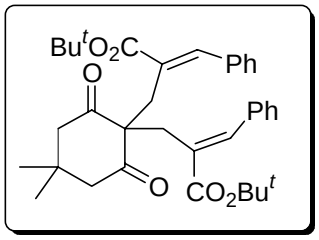
IR (neat): ν 1745, 1716, 1635 cm^{-1}

^1H NMR (400 MHz): δ 1.23 (d, 6H, J = 6.8 Hz), 1.36 (s, 9H), 2.08 (s, 3H), 2.83-2.95 (m, 1H), 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 (100 MHz): δ 21.15, 23.94, 27.90, 33.85, 73.29, 81.38, 124.44, 126.41, 127.86, 135.40, 141.38, 149.01, 164.34, 169.49

5,5-Dimethyl-2,2-bis[(2*E*)-2-*tert*-butoxycarbonyl-3-phenylprop-2-en-1-yl]cyclohexane-1,3-dione (171)

To a stirred solution of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (1.25 mmol, 0.345 g) (**169a**) in acetonitrile/water (1:1, 2 mL) was added 5,5-dimethyl-1,3-cyclohexanedione (**170**) (0.5 mmol, 0.07 g) and K_2CO_3 (2.5 mmol, 0.345 g) and heated under reflux for 24 hours. Solvents were removed under reduced pressure, and the residue was diluted with water (3 mL) and extracted with ether (3X10 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4.Solvent was removed and the crude product, thus obtained was purified by column chromatrography (silica gel 15 % ethyl acetate in hexanes) to afford 5, 5-dimethyl-2,2-bis [(2*E*)-2-*tert*-butoxycarbonyl-3-phenylprop-2-en-1-yl]cycloh-exane-1,3-dione (**171**) in 74 % (0.212 g) yield as colorless solid.



Mp: 126-128 °C

IR (KBr): ν 1699, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 1.00 (s, 6H), 1.48 (s, 18H), 2.50 (s, 4H), 2.90 (s, 4H), 7.18 (d, 4H, *J* = 7.2 Hz), 7.23-7.37 (m, 6H), 7.52 (s, 2H)

^{13}C NMR (100 MHz): δ 28.14, 29.49, 30.06, 31.99, 52.74, 65.53, 81.05, 128.03, 128.41, 129.20, 130.96, 135.85, 141.25, 167.67, 209.17

LCMS (*m/z*): 571 $(M-H)^+$

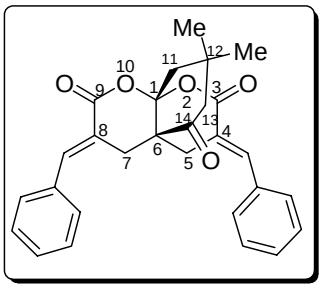
Anal. Calcd. For $C_{36}H_{44}O_6$: C, 75.50; H, 7.74

Found: C, 75.55; H, 7.71

4,8-Bis[(*E*)-benzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetradecane-3,9,14-trione (172a):

To a stirred solution of 5, 5-dimethyl-2,2-bis [(2*E*)-2-*tert*-butoxycarbonyl-3-phenylprop-2-en-1-yl]cyclohexane-1,3-dione (**171**) (0.5 mmol, 0.286 g) in CH_2Cl_2 (1 mL), conc. H_2SO_4 (1 mmol, 0.098 g) was added at 0 °C. After stirring for 3 hours at room temperature, the reaction mixture was diluted with water (3 mL), extracted with ether (3X10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed, and the crude compound thus obtained was purified through column chromatography (20 % ethyl acetate in hexanes) to afford pure 4,8-bis[(*E*)- benzylidene]-12,12-dimethyl-2,10-dioxa-

tricyclo[4.4.4.0^{1,6}]tetradecane-3,9,14-trione (**172a**) in 70 % (0.155 g) yield as colorless solid.



Mp: 166-168 °C

IR (KBr): ν 1728, 1716, 1614 cm^{-1}

^{1}H NMR (400 MHz): δ 1.18 (s, 6H), 2.33 (s, 2H), 2.58 (s, 2H), 2.71 & 3.35 (d of ABq, 4H, *J* = 16.8, 1.6 Hz), 7.29-7.48 (m, 10H), 7.97 (s, 2H)

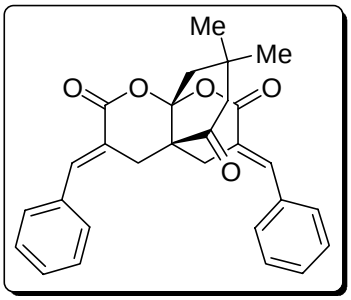
^{13}C NMR (100 MHz): δ 30.09, 30.72, 31.92, 45.45, 48.86, 49.15, 106.28, 119.94, 128.79, 129.99, 130.32, 133.96, 144.88, 162.99, 205.92

4,8-Bis[(*E*)-benzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetradecane-3,9,14-trione (172a) (without isolating the bis-cinnamic ester):

To a stirred solution of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**169a**) (1.25 mmol, 0.345 g) in acetonitrile/water (1:1, 2 mL) was added 5,5-dimethyl-1,3-cyclohexanedione (**170**) (0.5 mmol, 0.07 g), K_2CO_3 (2.5 mmol, 0.345 g) and heated under reflux for 24 hours. Reaction mixture was then cooled to room temperature and solvents were removed under reduced pressure. Residue was diluted with water (3 mL) and extracted with ether (3X10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the crude bis-adduct (5, 5-dimethyl-2,2-bis [(2*E*)-2-*tert*-butoxycarbonyl-3-phenylprop-2-en-1-yl]cyclohexane-1,3-dione) (**171**) was dissolved in CH_2Cl_2 (1 mL). Conc. H_2SO_4 (1 mmol, 0.098 g) was then added at 0 °C to the solution and stirred for 3 hours at room temperature. Then the reaction mixture was diluted with water (3 mL), extracted with ether (3X10 mL). The combined organic layer was dried over

anhydrous Na_2SO_4, solvent was removed and the crude compound thus obtained was purified through column chromatography (20 % ethyl acetate in hexanes) to afford pure 4,8-bis[(*E*)-benzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.$0^{1,6}$]tetradecane-3,9,14-trione (**172a**) in 50 % (0.111 g) yield as colorless solid.

*The spectral data (IR, ^{1}H NMR, ^{13}C NMR) is in agreement with that of the molecule **172a** page no. 163.*



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

Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92

Found: C, 76.03; H, 5.90

12,12-Dimethyl-4,8-bis-[(*E*)-2-methylbenzylidene]-2,10-dioxatricyclo[4.4.4.$0^{1,6}$]tetra-decane-3,9,14-trione (172b):

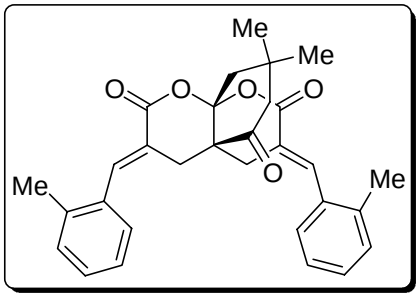
This bislactone was obtained as colorless solid *via* the reacton of *tert*-butyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (**169b**) with 5,5-dimethyl-1,3-cyclohexane-dione in the presence of K_2CO_3, followed by treatment of the resulting crude bis-adduct, with conc. H_2SO_4 (following the similar procedure described for the compound **172a)**.

Reaction time: 24 h(reflux)+3 h(rt)

Yield: 52%

Mp: 205-207 °C

IR (KBr): ν 1722, 1718, 1618 cm^{-1}



^{1}H NMR (400 MHz): δ 1.16 (s, 6H), 2.21 (s, 6H), 2.36 (s, 2H), 2.47 &3.18 (d of ABq, 4H, *J* = 16.8, 2.0 (1.4) Hz), 2.51 (s, 2H) 7.06 (d, 2H, *J* = 7.6 Hz), 7.12-7.31 (m, 6H), 8.02 (s, 2H)

^{13}C NMR (100 MHz): δ 19.74, 29.56, 30.44, 31.98, 45.73, 49.19, 49.47, 106.90, 121.42, 125.73, 128.30, 129.52, 130.50, 133.11, 137.79, 143.95, 162.96, 205.69

LCMS (*m/z*): 471 $(M+H)^+$

Anal. Calcd. For $C_{30}H_{30}O_5$: C, 76.57; H, 6.43

Found: C, 76.72; H, 6.48

12,12-Dimethyl-4,8-bis-[(*E*)-*p*-methylbenzylidene]-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetra-decane-3,9,14-trione (172c):

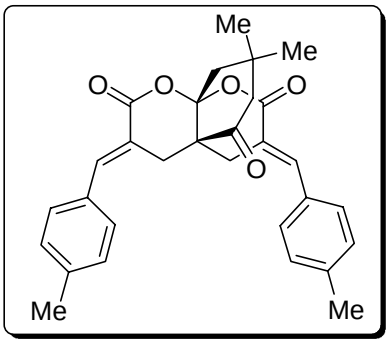
Treatment of *tert*-butyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (**169c**) with 5,5-dimethyl-1,3-cyclohexanedione (**170**) in the presence of K_2CO_3 followed by subsequent treatment of the resulting bisadduct with H_2SO_4, following the similar procedure described for the compound **172a** provided the title compound as colorless solid.

Reaction time: 24 h(reflux)+3 h(rt)

Yield: 48%

Mp: 206-208 °C

IR (KBr): ν 1734, 1714, 1602 cm^{-1}



^{1}H NMR (400 MHz): δ 1.18 (s, 6H), 2.31 (s, 2H), 2.38 (s, 6H), 2.57 (s, 2H), 2.71 & 3.35 (d of ABq, 4H, *J* = 16.8, 1.6 Hz), 7.22 (d, 4H, *J* = 8.0 Hz), 7.28 (d, 4H, *J* = 8.0 Hz), 7.95 (s, 2H)

^{13}C NMR (100 MHz): δ 21.50, 30.33, 30.91, 31.92, 45.51, 48.82, 49.28, 106.12, 118.85, 129.59, 130.60, 131.36, 140.66, 145.04, 163.20, 206.11

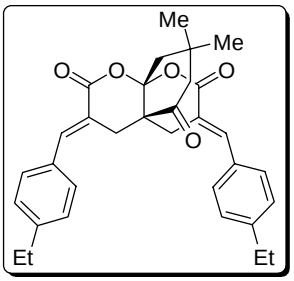
LCMS (*m/z*): 469 $(M-H)^+$

Anal. Calcd. For $C_{30}H_{30}O_5$: C, 76.57; H, 6.43

Found: C, 76.40; H, 6.47

4,8-Bis-[(*E*)-4-ethylbenzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetradecane-3,9,14-trione (172d):

This symmetrical bislactone (**172d**) was obtained as colorless solid *via* treatment of the crude bisadduct (which was obtained by the reaction of *tert*-butyl 3-acetoxy-2-methylene-3-(4-ethylphenyl)propanoate (**169d**) with 5,5-dimethyl-1,3-cyclohexanedione (**170**) in the presence of K_2CO_3), with conc. H_2SO_4 following the similar procedure described for the molecule **172a**.



Reaction time: 24 h(reflux)+3 h(rt)

Yield: 54%

Mp: 144-146 °C

IR (KBr): ν 1716, 1601 cm^{-1}

^{1}H NMR (400 MHz): δ 1.18 (s, 6H), 1.25 (t, 6H, *J* = 7.6 Hz), 2.31 (s, 2H), 2.58 (s, 2H), 2.62-2.79 (m, 6H), 3.36 (d of ABq, 2H, *J* = 16.8, 2.0

Hz),* 7.24 (d, 4H, *J* = 8.0 Hz), 7.31 (d, 4H, *J* = 8.0 Hz), 7.96 (s, 2H)

^{13}C NMR (100 MHz): δ 15.26, 28.84, 30.39, 30.98, 31.96, 45.57, 48.86, 49.35, 106.13, 118.88, 128.44, 130.74, 131.65, 145.14, 146.91, 163.23, 206.16

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

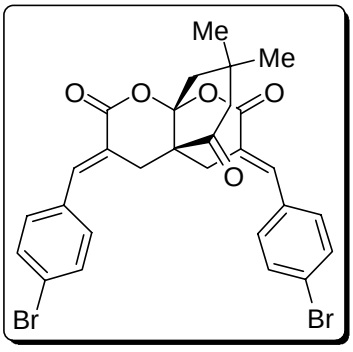
Anal. Calcd. For $C_{32}H_{34}O_5$: C, 77.08; H, 6.87

Found: C, 77.22; H, 6.80

(***** *The first part of ABq is merged with multiplet δ 2.62-2.79*)

4,8-Bis-[(*E*)-4-bromobenzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetradcane-3,9,14-trione (172e):

The crude bis-adduct (**172e**) [obtained by the reaction of of *tert*-butyl 3-acetoxy-2-methylene-3-(4-bromophenyl)propanoate (**169e**) with 5,5-dimethyl-1,3-cyclohexanedione (**170**) in the presence of K_2CO_3] was treated with conc. H_2SO_4 following the similar procedure described for the compound **172a**, to provide 4,8-bis-[(*E*)-4-bromobenzylidene]-12,12-dimethyl-2,10-dioxa-tricyclo[4.4.4.0^{1,6}]te-tradecane-3,9,14-trione (**172e**) as colorless solid.



Reaction time: 24 h(reflux)+3 h(rt)

Yield: 57%

Mp: 266-268 °C

IR (KBr): ν 1736, 1714, 1616 cm^{-1}

^1H NMR (400 MHz): δ 1.18 (s, 6H), 2.32 (s, 2H), 2.57 (s, 2H), 2.61 & 3.29 (ABq, 4H, *J* = 16.8 Hz), 7.20 (d, 4H, *J* = 8.0 Hz), 7.55 (d, 4H, *J* = 8.0 Hz), 7.86 (s, 2H)

^{13}C NMR (100 MHz): δ 30.25, 30.79, 32.06, 45.67, 49.12, 49.32, 106.41, 120.81, 124.68, 131.69, 132.23, 132.82, 143.61, 162.78, 205.77

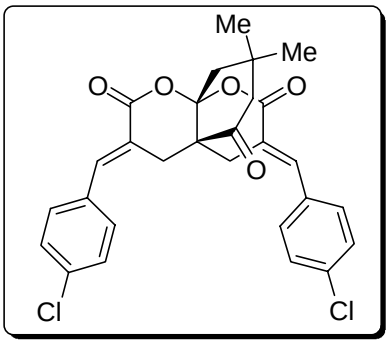
LCMS (*m/z*): 597 $(M+H)^+$, 599 $[(M+2)+H]^+$, 601 $[(M+4)+H]^+$

Anal. Calcd. For $C_{28}H_{24}Br_2O_5$: C, 56.02; H, 4.03

Found: C, 56.25; H, 4.09

4,8-Bis-[(*E*)-4-chlorobenzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetradecane-3,9,14-trione (172f):

This bislactone was obtained as colorless solid by the treatment of the crude bisadduct with conc.H_2SO_4, which was obtained *via* the reaction of *tert*-butyl 3-acetoxy-2-methylene-3-(4-chlorophenyl)propanoate (**169f**) with 5,5-dimethyl-1,3-cyclohexanedione (**170**) in the presence of K_2CO_3, following the similar procedure described for the molecule **172a**.



Reaction time: 24 h(reflux)+3 h(rt)

Yield: 52%

Mp: 252-254 °C

IR (KBr): ν 1736, 1720, 1616 cm^{-1}.

^{1}H NMR (400 MHz): δ 1.18 (s, 6H), 2.32 (s, 2H), 2.58 (s, 2H), 2.63 & 3.31 [d of ABq, 4H, *J* = 16.6, 2.0 (1.6) Hz],7.28 (d, 4H, *J* = 8.4 Hz), 7.39 (d, 4H, *J* = 8.4 Hz), 7.89 (s, 2H)

^{13}C NMR (100 MHz): δ 30.21, 30.77, 32.01, 45.61, 49.03, 49.27, 106.37, 120.65, 129.21, 131.53, 132.40, 136.25, 143.50, 162.74, 205.76

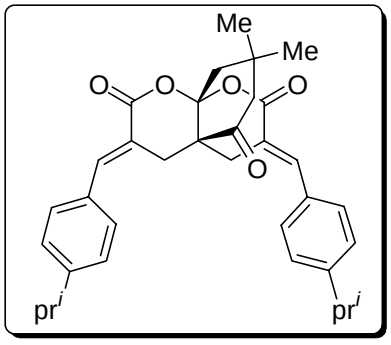
LCMS (*m/z*): 511 $(M+H)^+$, 513 $[(M+2)+H]^+$, 515 $[(M+4)+H]^+$

Anal. Calcd. For $C_{28}H_{24}C_{l2}O_5$:C, 65.76; H, 4.73

Found: C, 65.70; H, 4.70

4,8-Bis-[(*E*)-4-isopropylbenzylidene]-12,12-dimethyl-2,10-dioxatricyclo[4.4.4.0^{1,6}]tetradecane-3,9,14-trione (172g):

This bislactone was obtained as colorless solid by the reacton of *tert*-butyl 3-acetoxy-2-methylene-3-(4-isopropylphenyl)propanoate (**169g**) with 5,5-dimethyl-1,3-cyclohexanedione (**170**) in the presence of K_2CO_3, and followed by the treatment of the resulting crude bis-adduct with conc H_2SO_4, following the similar procedure described for the compound **172a**.



Reaction time: 24 h(reflux)+3 h(rt)

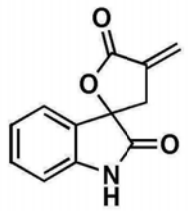
Yield: 56%

Mp: 178-180 °C

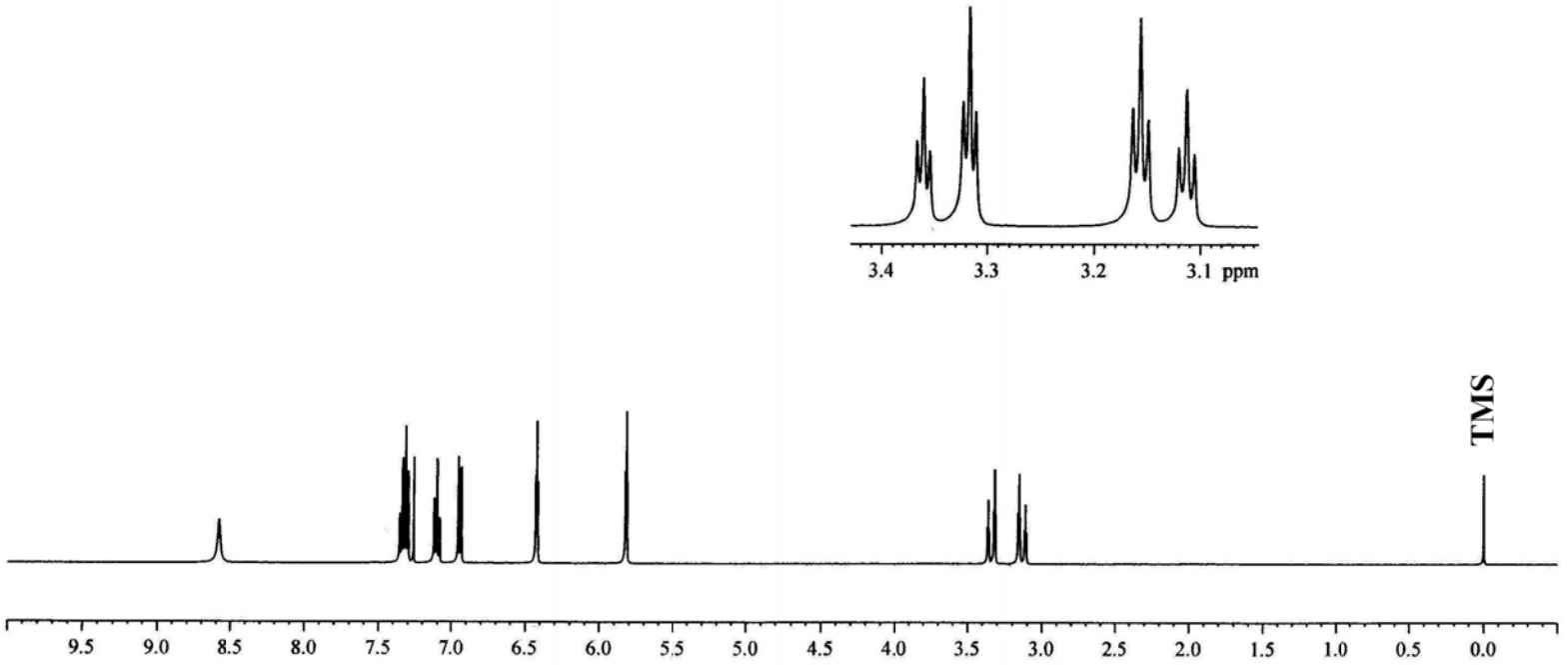
IR (KBr): ν 1726, 1616 cm^{-1}

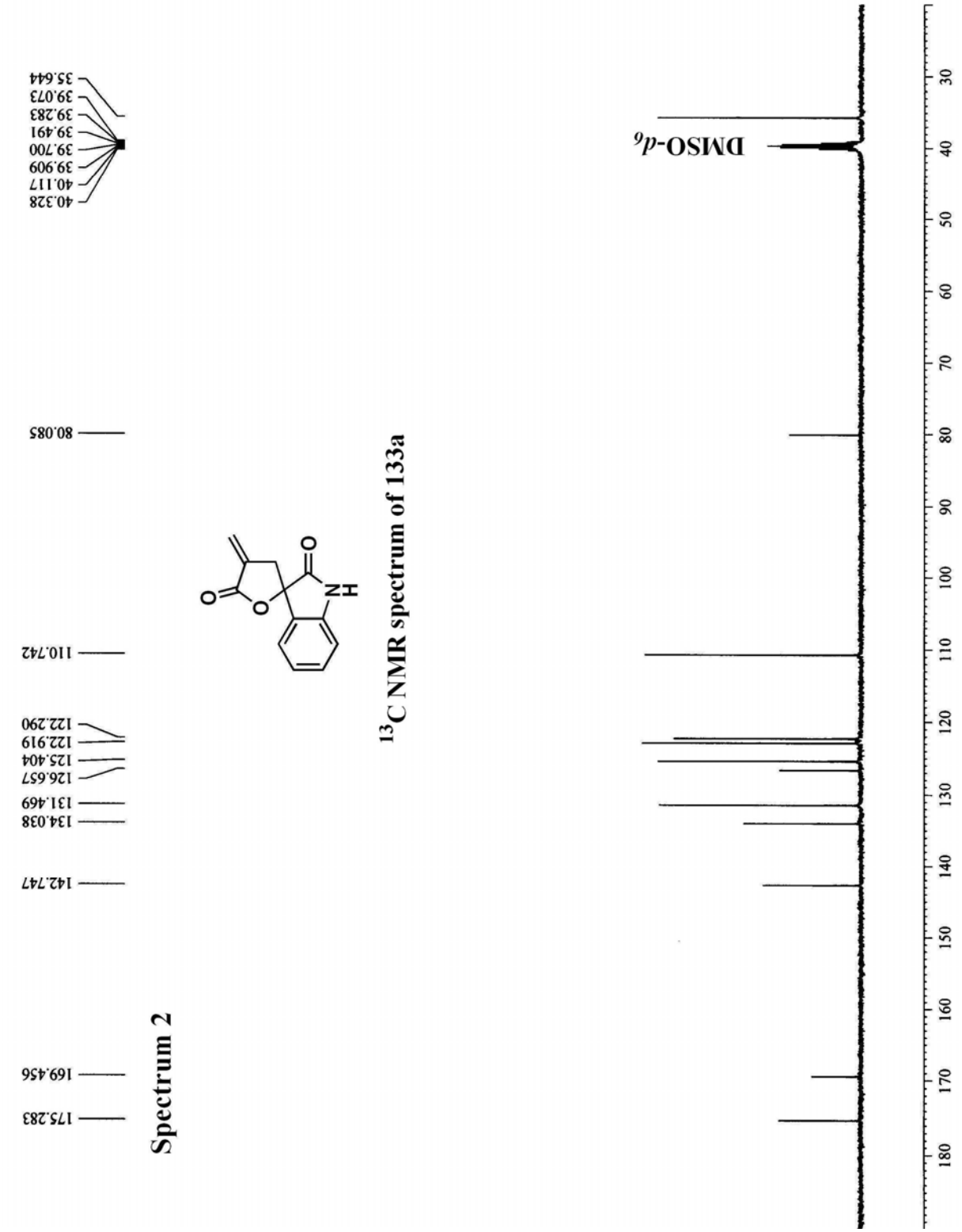
^{1}H NMR (400 MHz):	δ 1.18 (s, 6H), 1.26 (d, 12H, *J* = 6.8 Hz), 2.31 (s, 2H), 2.58 (s, 2H), 2.73 & 3.37 (ABq, 4H, *J* = 16.8 Hz), 2.93 (septet, 2H, *J* = 6.8 Hz), 7.27 (d, 4H, *J* = 8.0 Hz), 7.33 (d, 4H, *J* = 8.0 Hz), 7.97 (s, 2H)
^{13}C NMR (100 MHz):	δ 23.72, 30.33, 30.93, 31.92, 34.08, 45.49, 48.80, 49.28, 106.12, 118.85, 126.99, 130.76, 131.74, 145.06, 151.42, 163.20, 206.12
LCMS (*m/z*):	527 $(M+H)^{+}$
Anal. Calcd. For $C_{34}H_{38}O_5$:	C, 77.54; H, 7.27
Found:	C, 77.67; H, 7.20

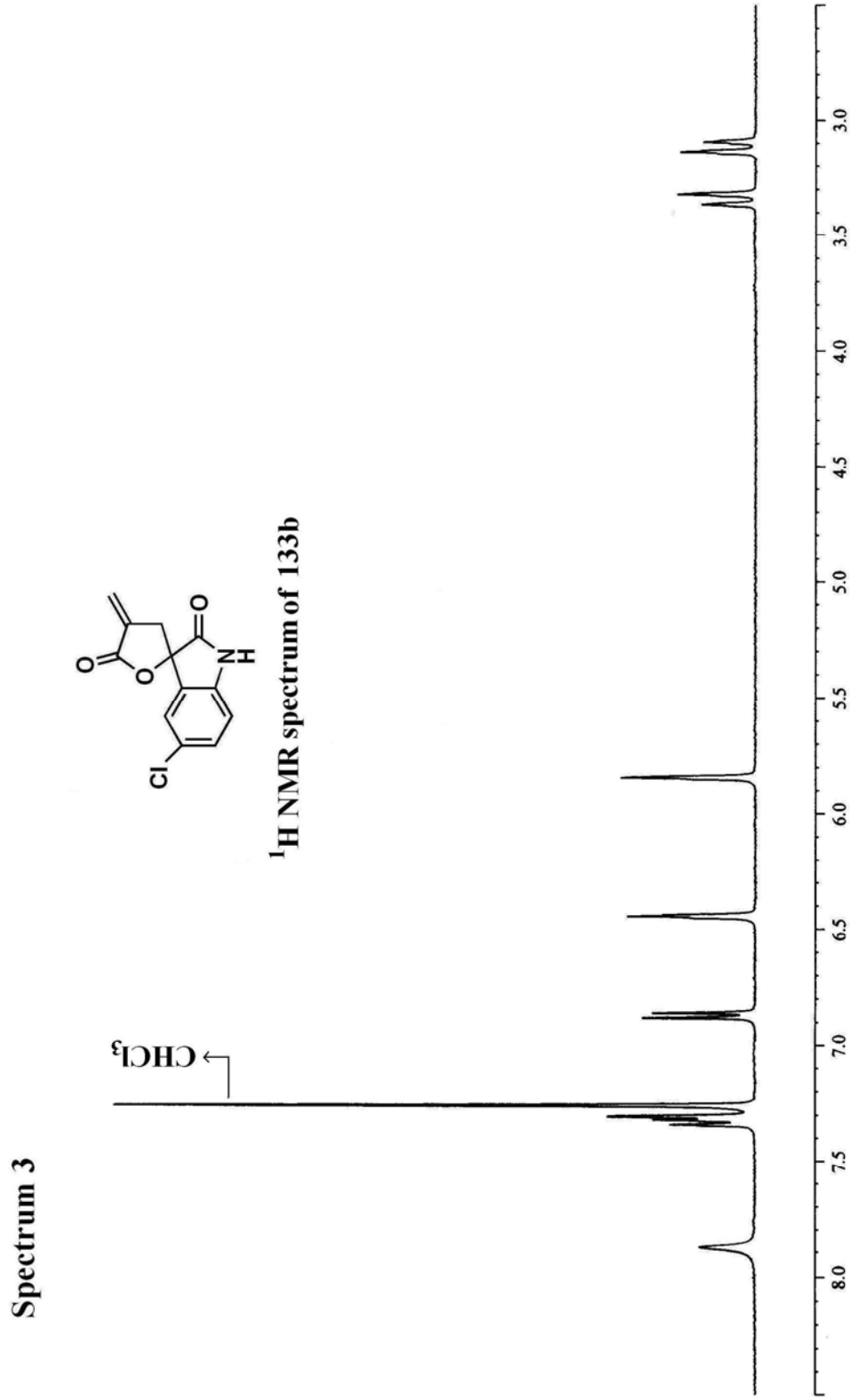
Spectrum 1



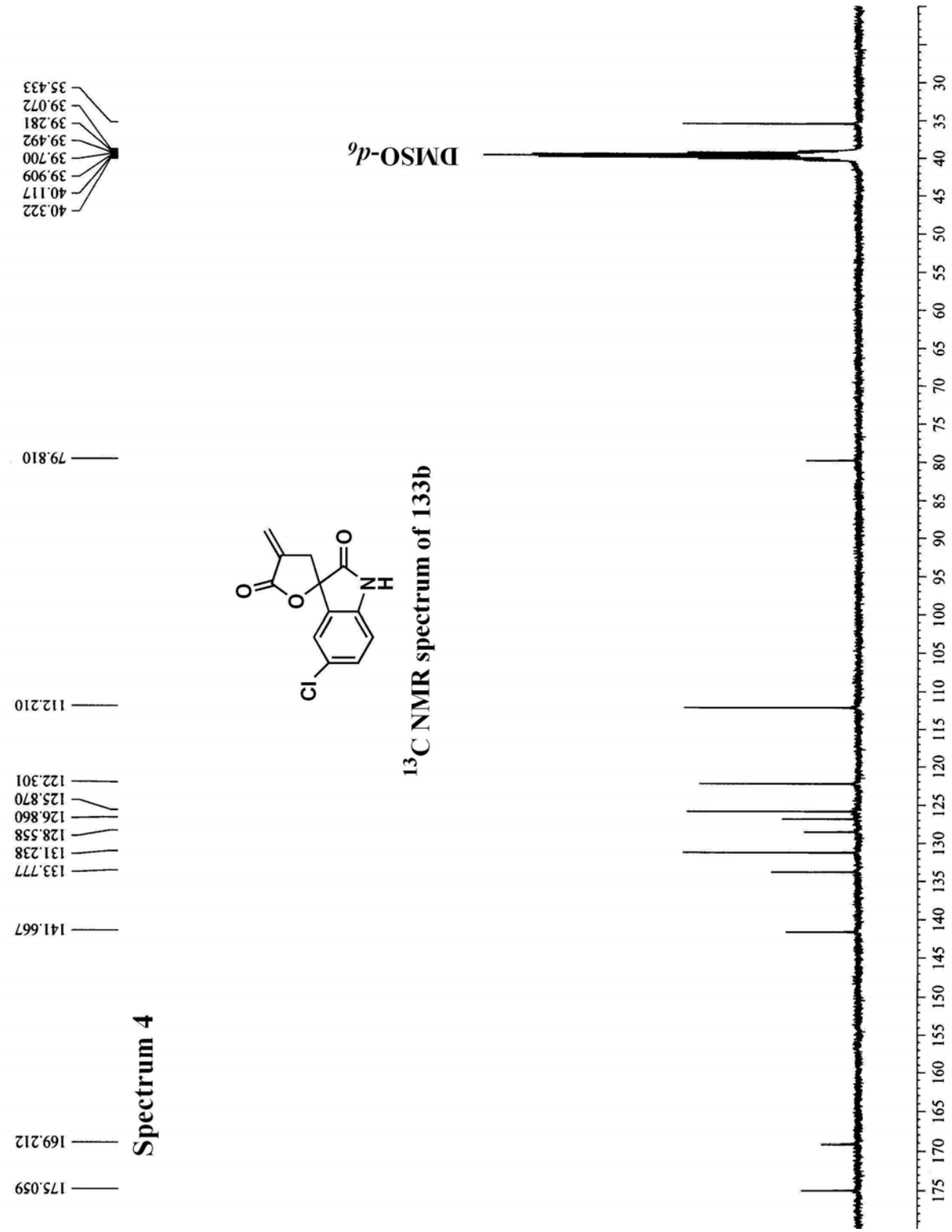
^{1}H NMR spectrum of 133a



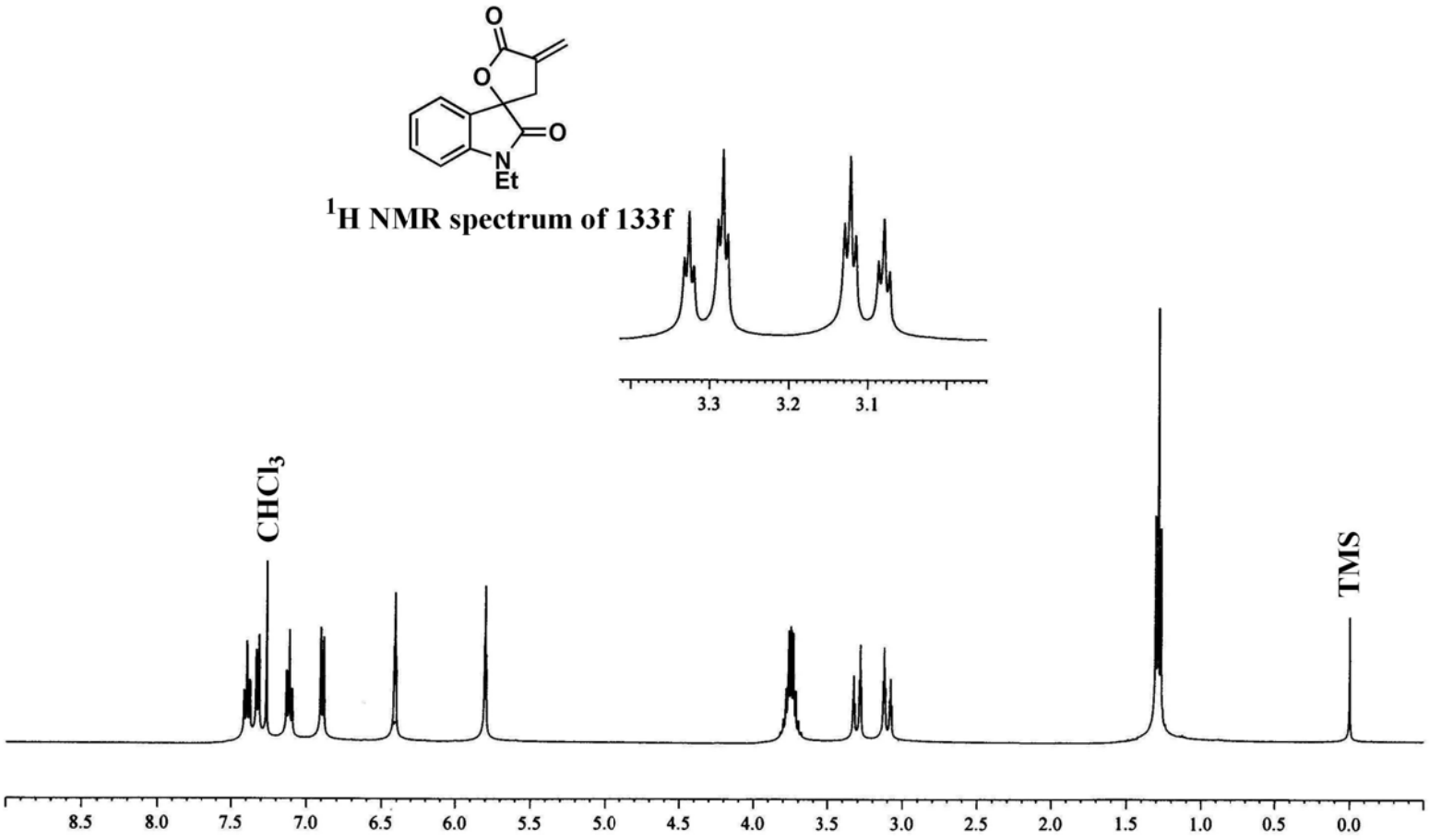

Spectrum 2
^{13}C NMR spectrum of 133a
DMSO-d_6
175.283
169.456
142.747
134.038
131.469
126.657
125.404
122.919
122.290
110.742
80.085
40.328
40.117
39.909
39.700
39.491
39.283
39.073
35.644
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180



^{1}H NMR spectrum of 133b

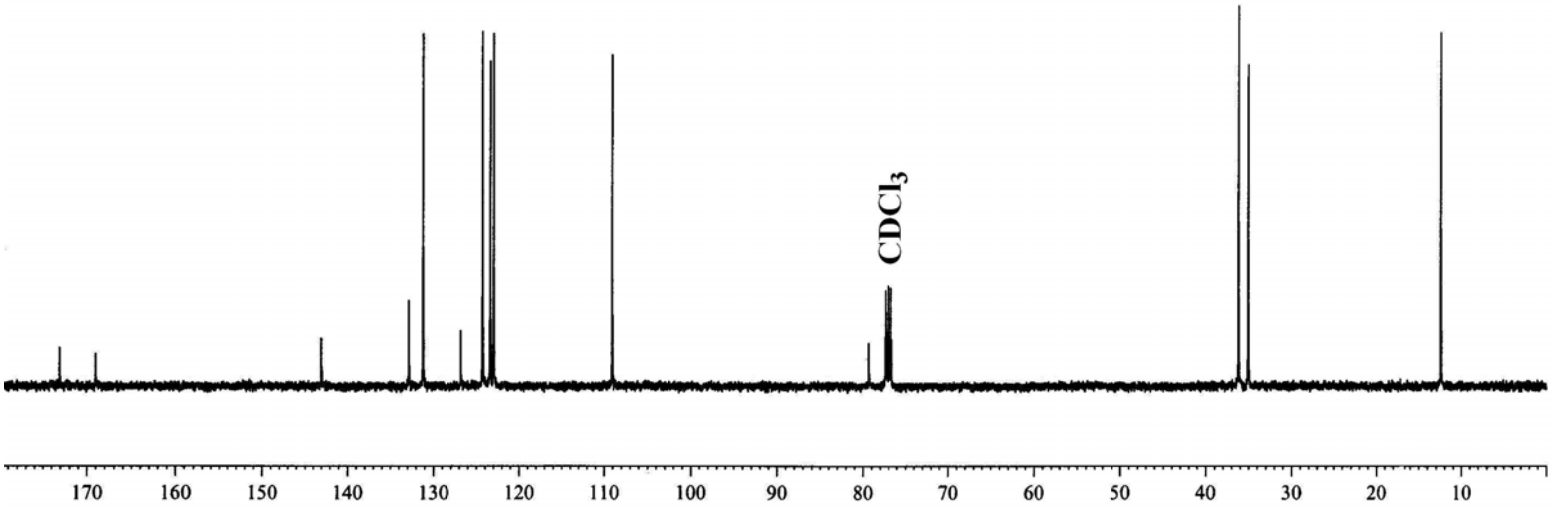

Spectrum 4
^{13}C NMR spectrum of 133b
DMSO-d_6
Cl
O
O
O
N
H
175.059
169.212
141.667
133.777
131.238
128.558
126.860
125.870
122.301
112.210
79.810
40.322
40.117
39.909
39.700
39.492
39.281
39.072
35.433

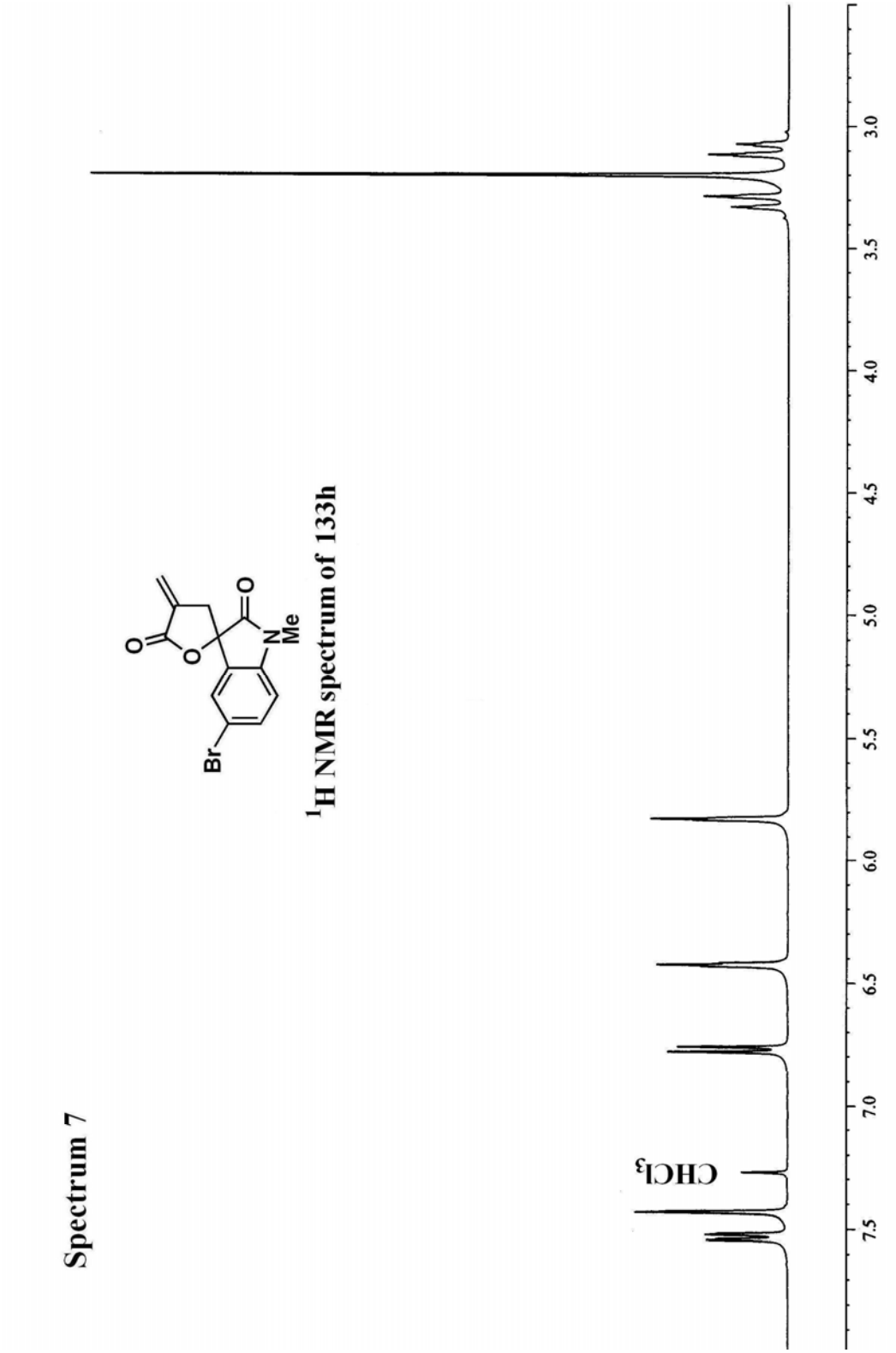
Spectrum 5

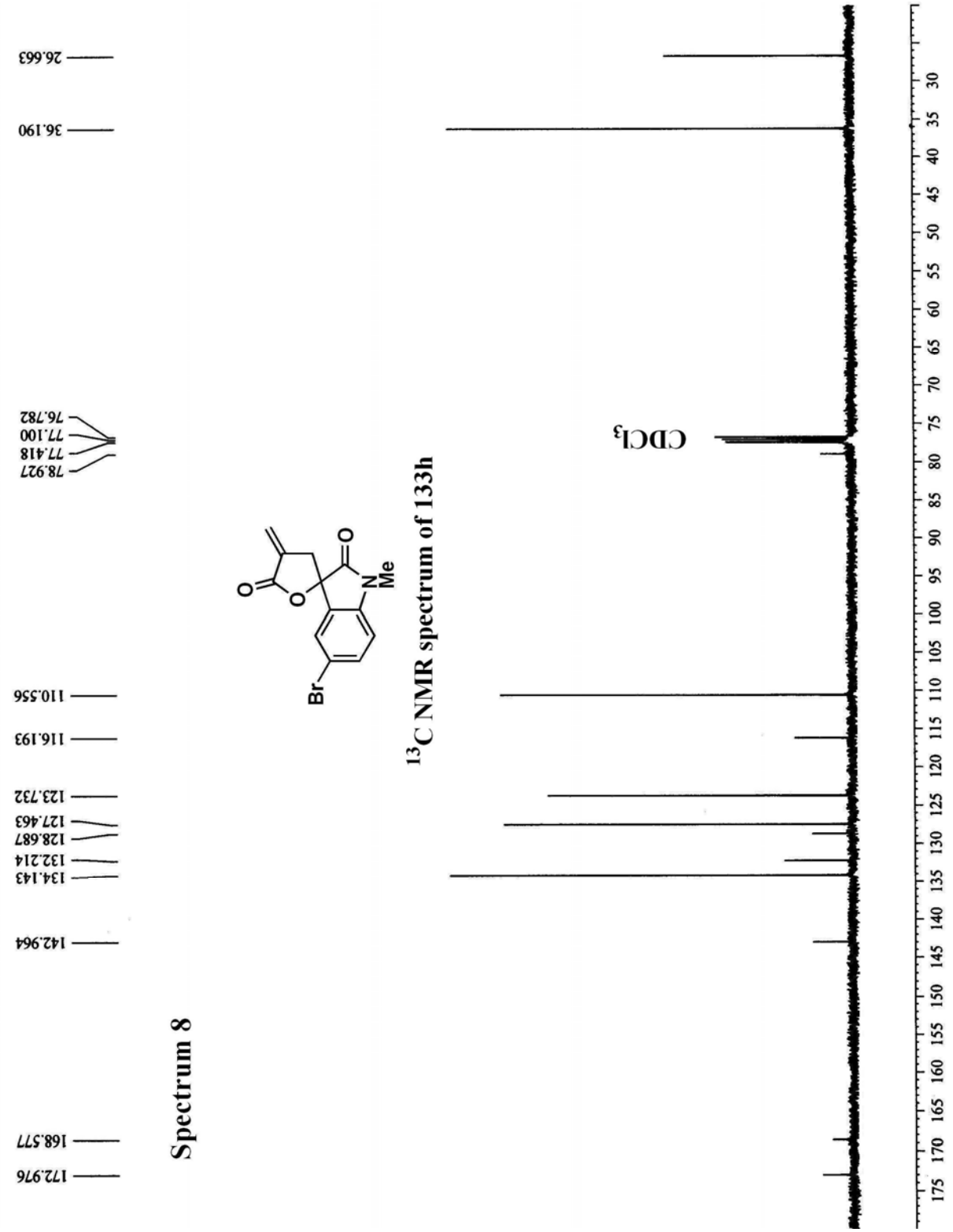

O
O
O
N
Et
^{1}H NMR spectrum of 133f
3.3
3.2
3.1
CHCl$_3$
TMS
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Spectrum 6

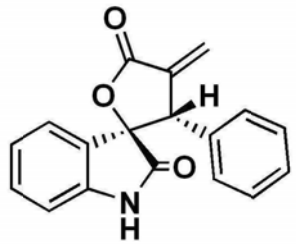
^{13}C NMR spectrum of 133f



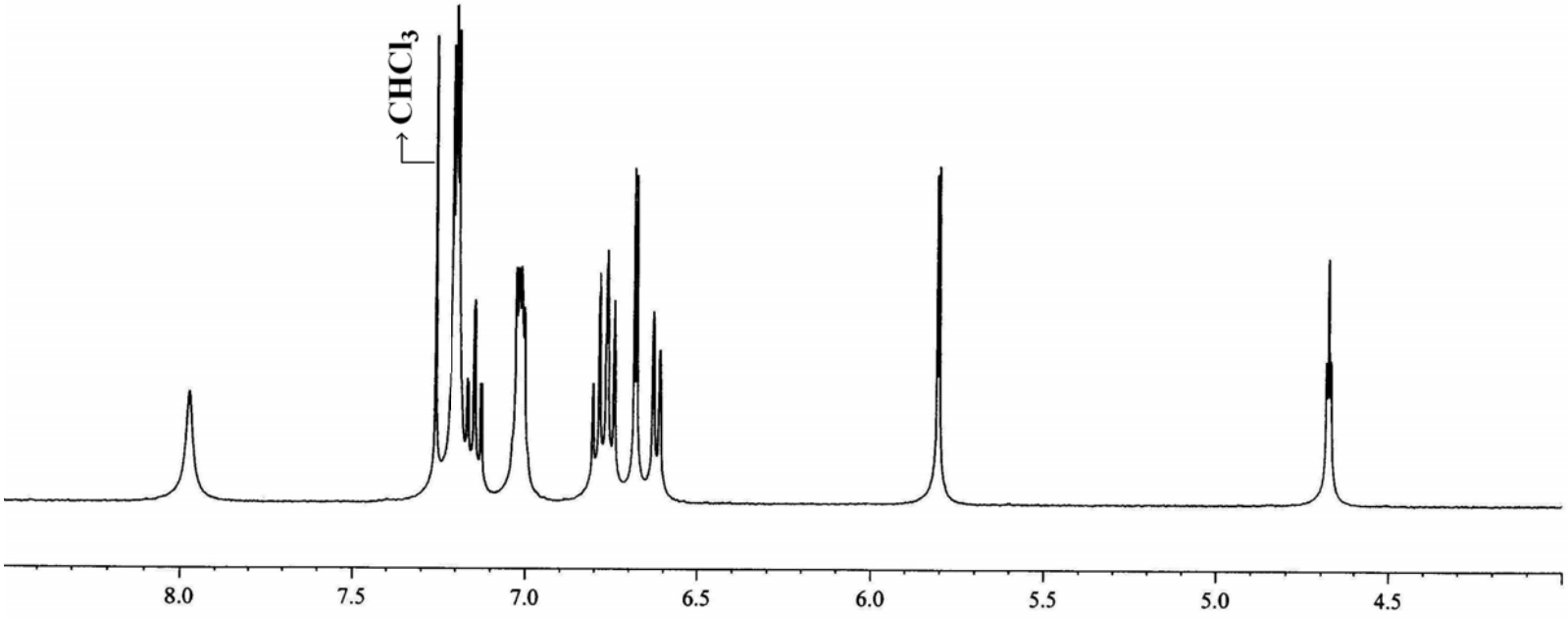

Spectrum 7
^{1}H NMR spectrum of 133h
Br
O
O
O
N
Me
CHCl$_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0


Spectrum 8
^{13}C NMR spectrum of 133h
CDCl$_3$
Br
N
Me
O
O
O
172.976
168.577
142.964
134.143
132.214
128.687
127.463
123.732
116.193
110.556
78.927
77.418
77.100
76.782
36.190
26.663

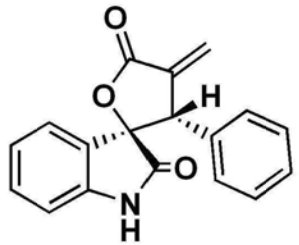
Spectrum 9



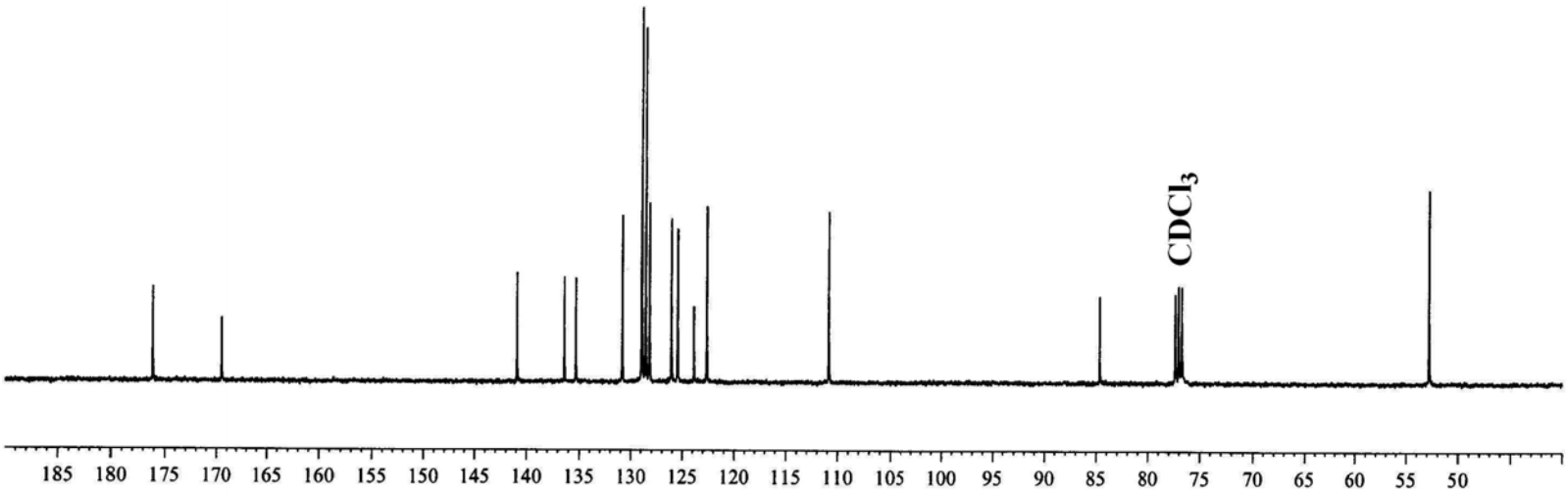
^{1}H NMR spectrum of 136a



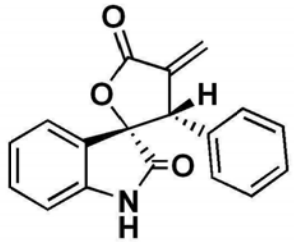
Spectrum 10



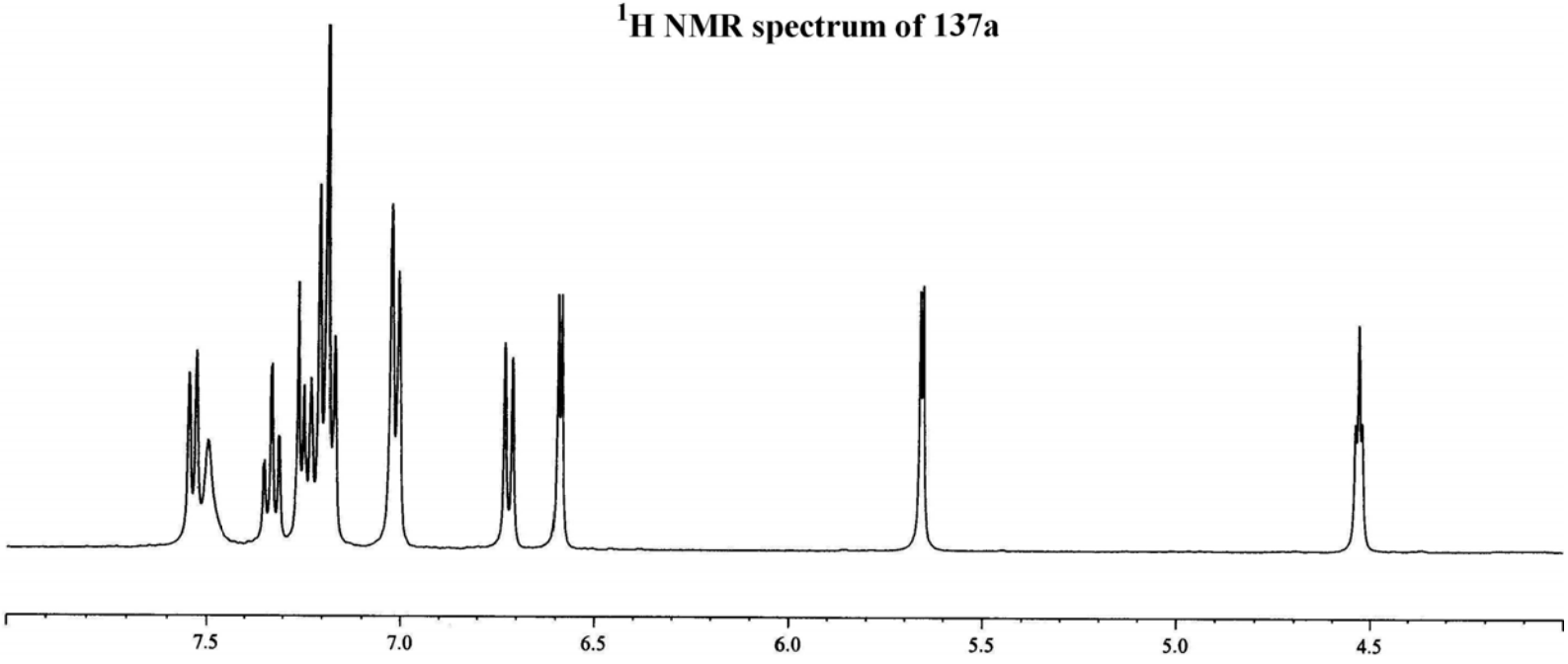
^{13}C NMR spectrum of 136a

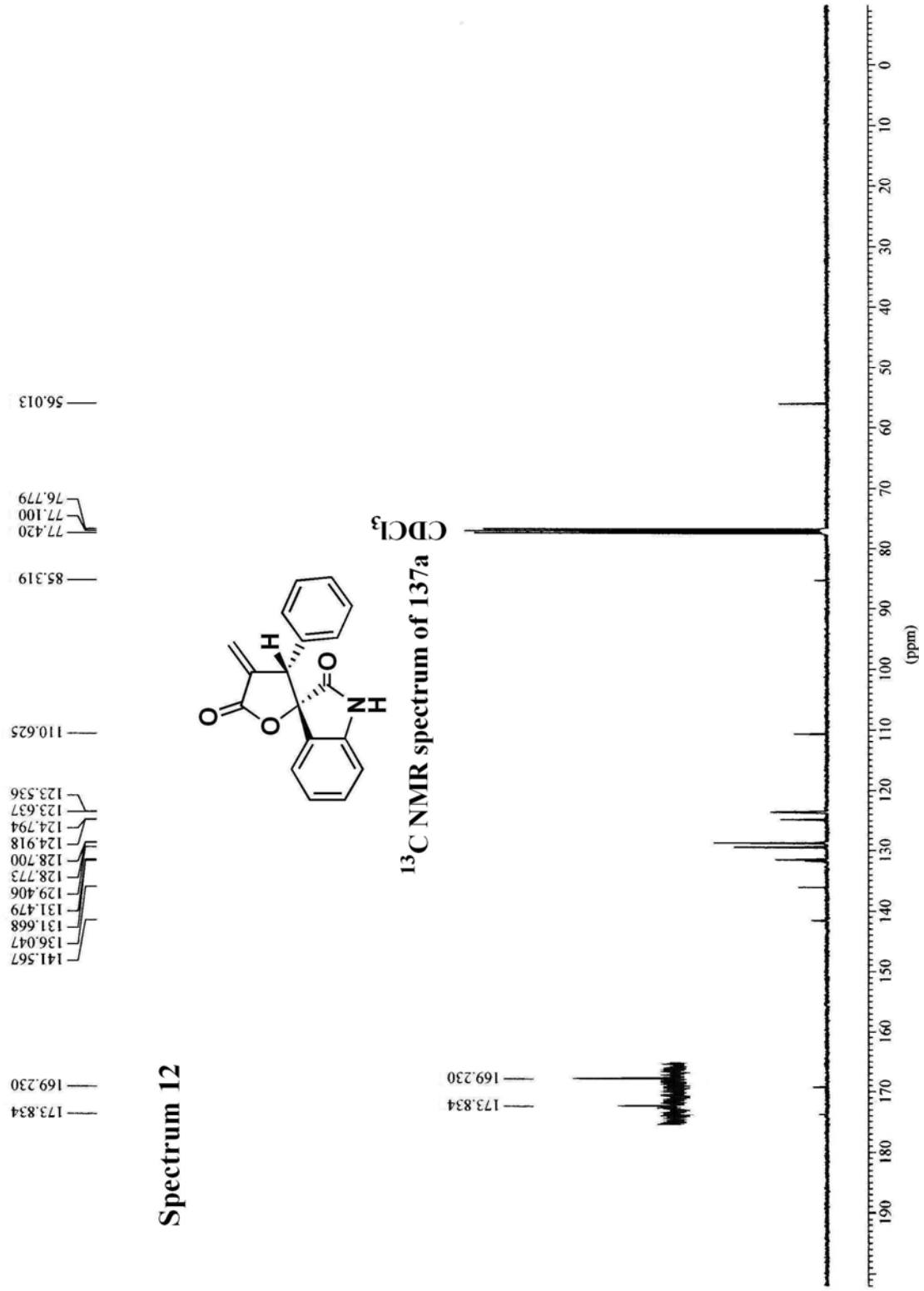


Spectrum 11

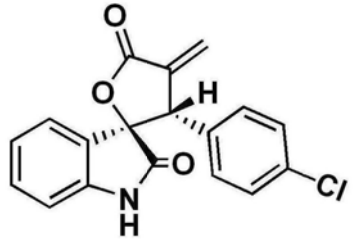


^{1}H NMR spectrum of 137a

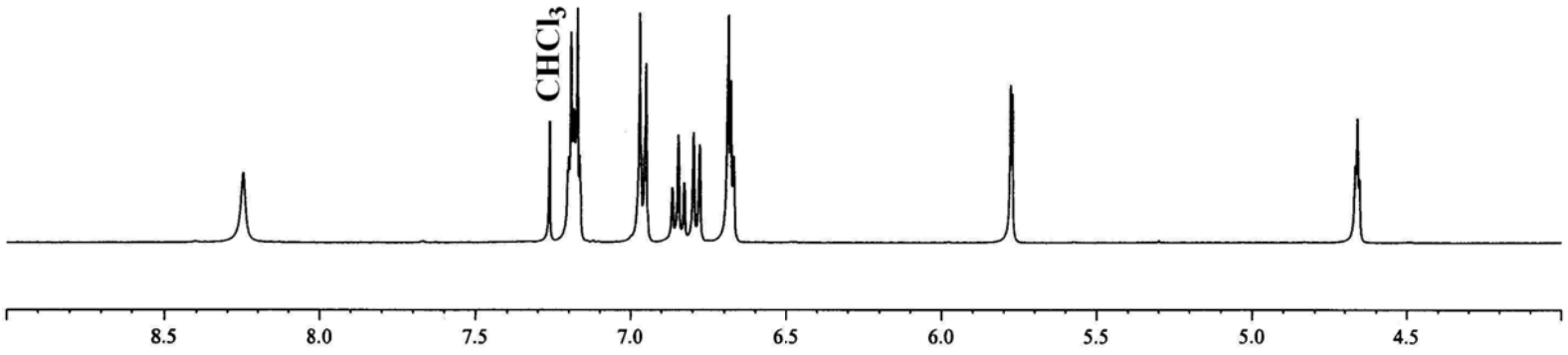



Spectrum 12
^{13}C NMR spectrum of 137a
CDCl$_3$
173.834
169.230
141.567
136.047
131.668
131.479
129.406
128.773
128.700
124.918
124.794
123.637
123.536
110.625
85.319
77.420
77.100
76.779
56.013
(ppm)

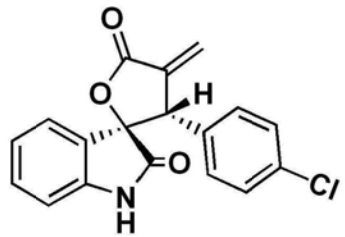
Spectrum 13



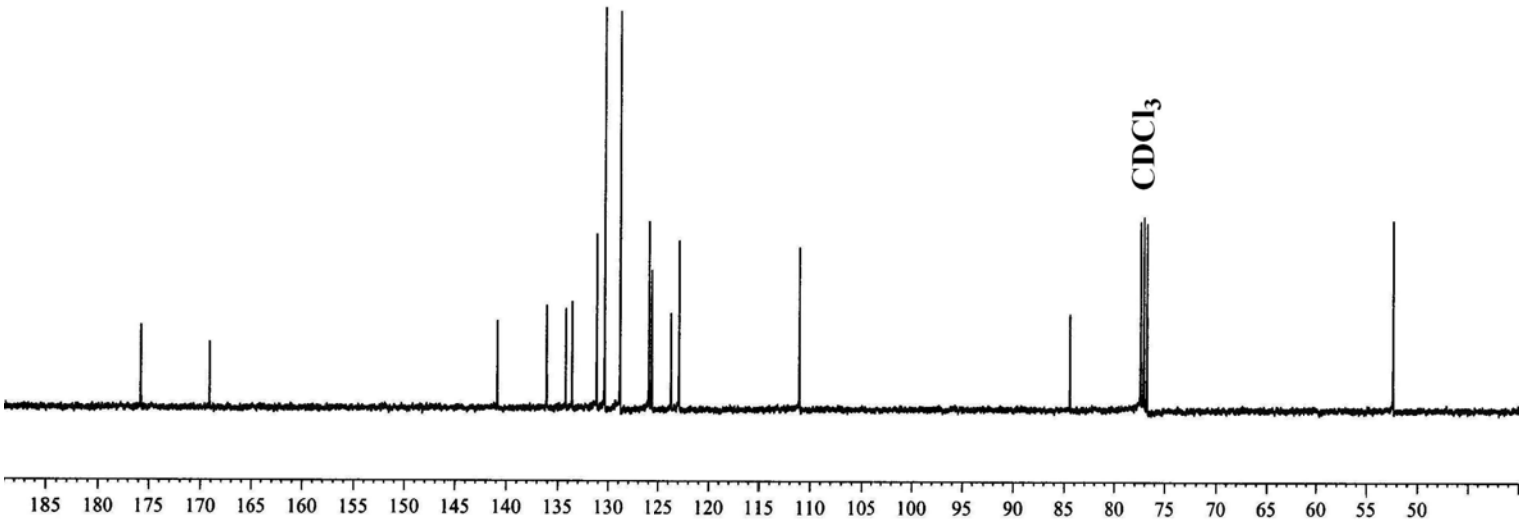
^{1}H NMR spectrum of 136d



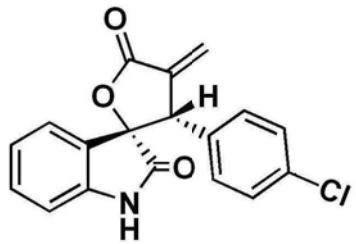
Spectrum 14



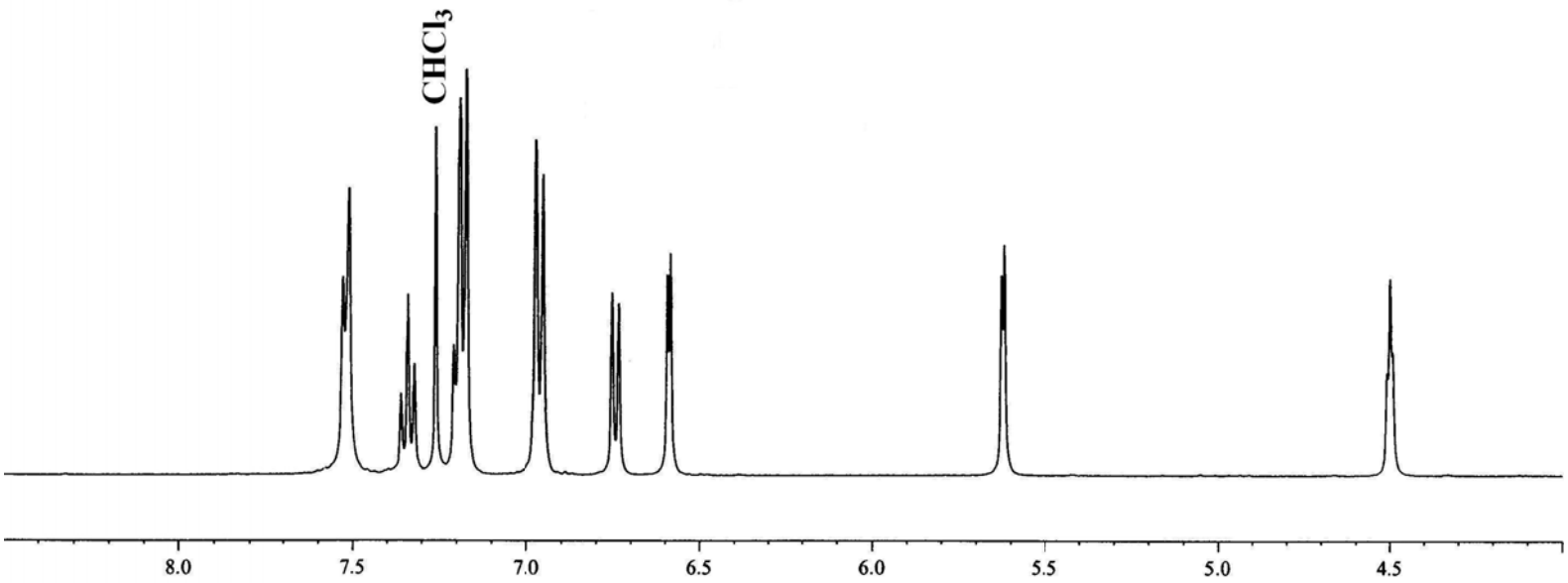
^{13}C NMR spectrum of 136d



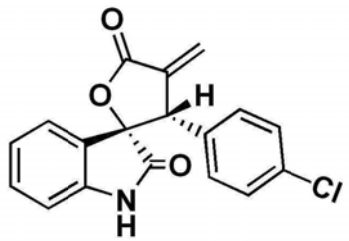
Spectrum 15



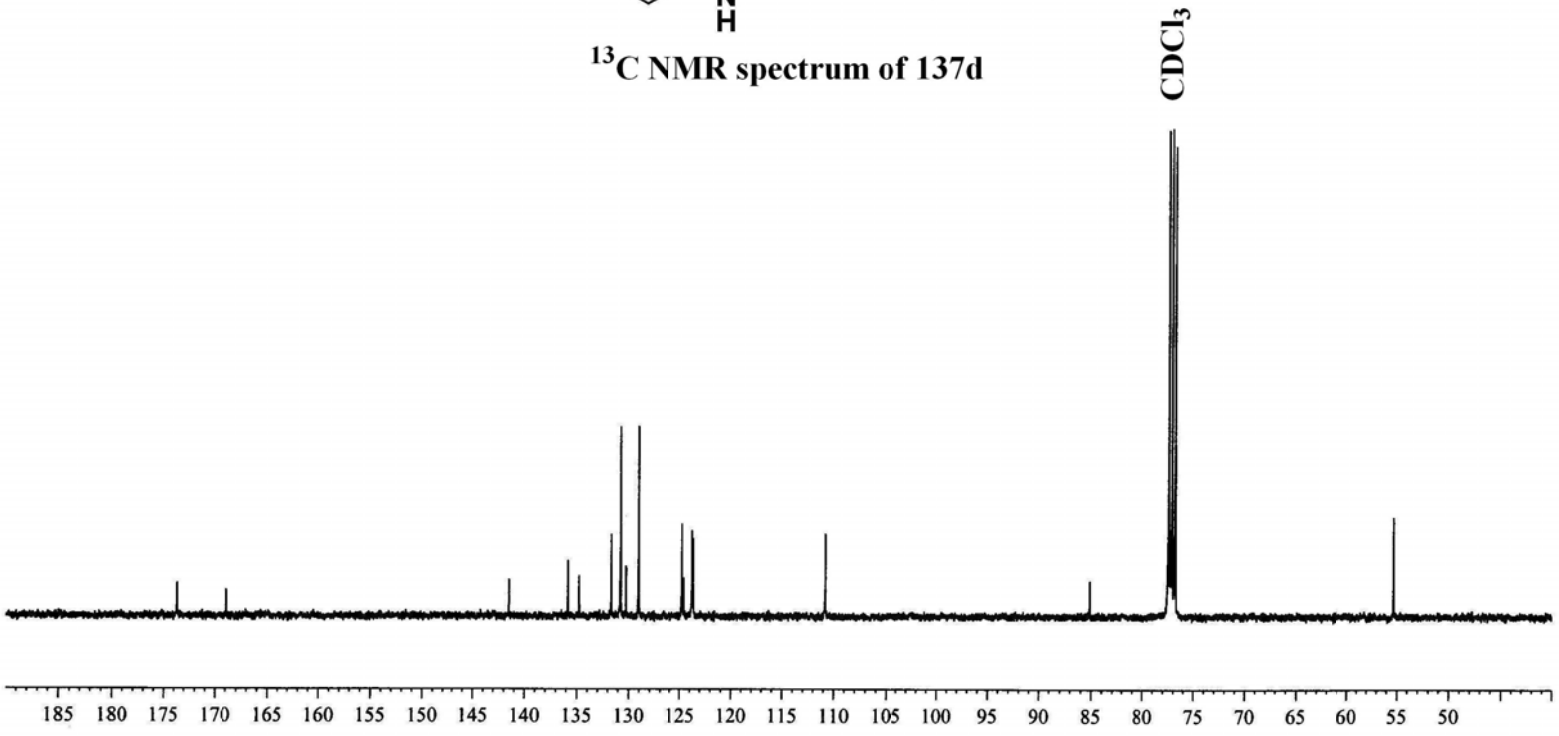
^{1}H NMR spectrum of 137d



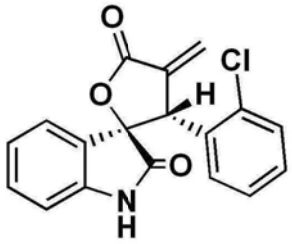
Spectrum 16



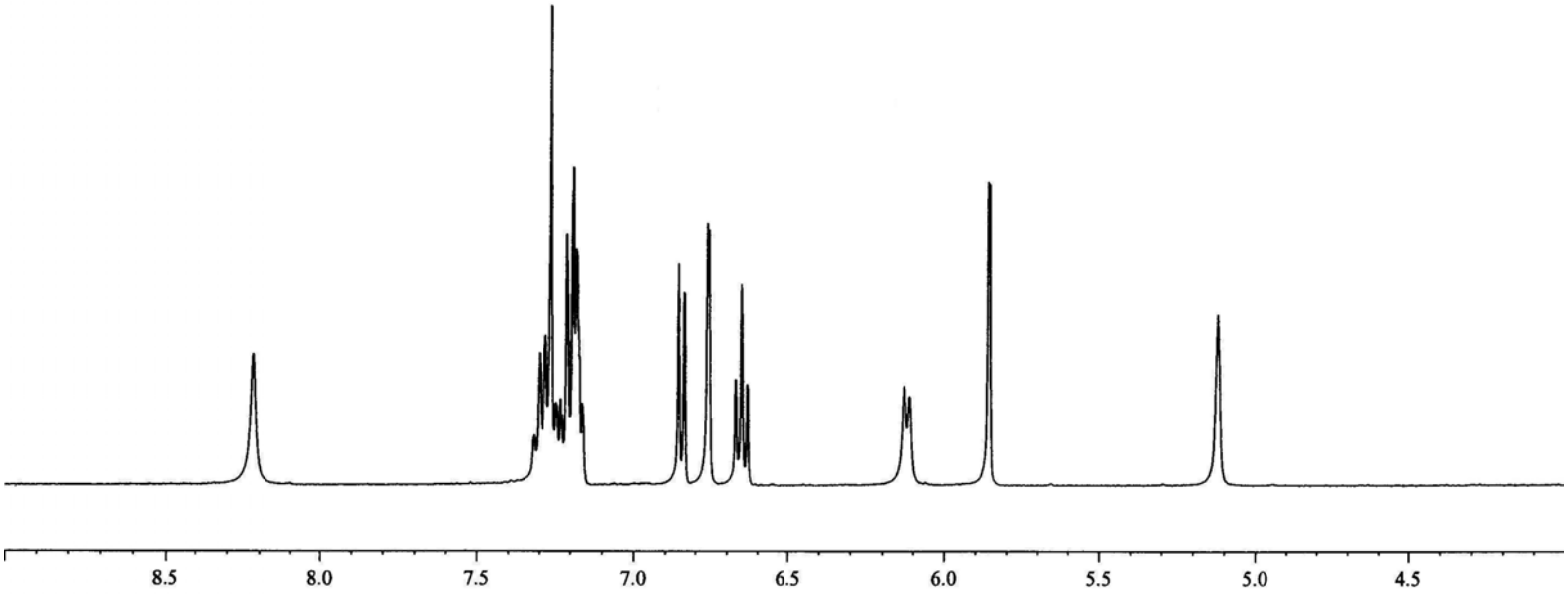
^{13}C NMR spectrum of 137d

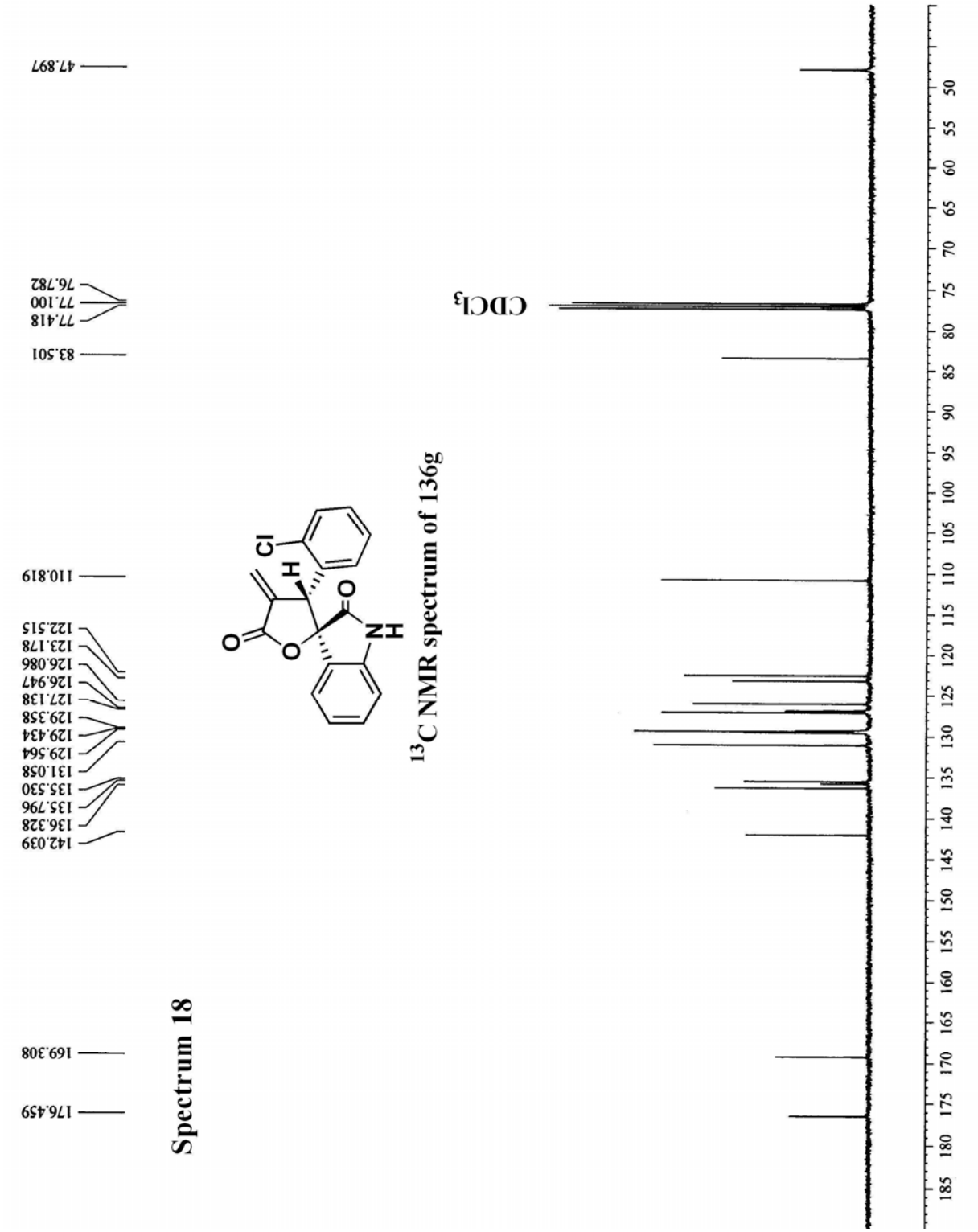


Spectrum 17

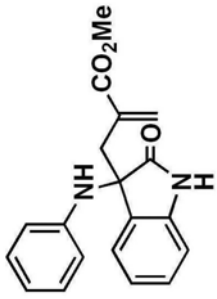


^{1}H NMR spectrum of 136g

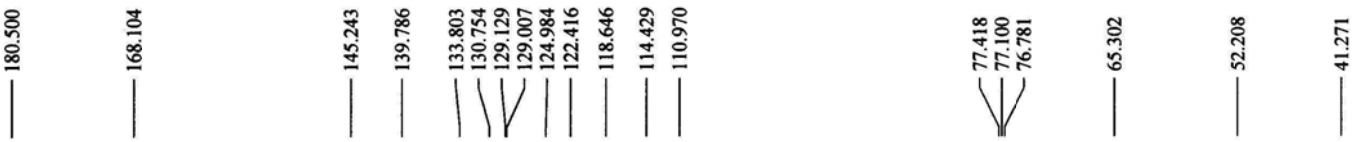



Spectrum 18
^{13}C NMR spectrum of 136g
CDCl$_3$
Cl
H
O
O
O
N
H
176.459
169.308
142.039
136.328
135.796
135.530
131.058
129.564
129.434
129.358
127.138
126.947
126.086
123.178
122.515
110.819
83.501
77.418
77.100
76.782
47.897

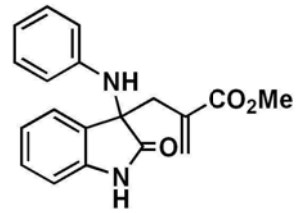
Spectrum 19



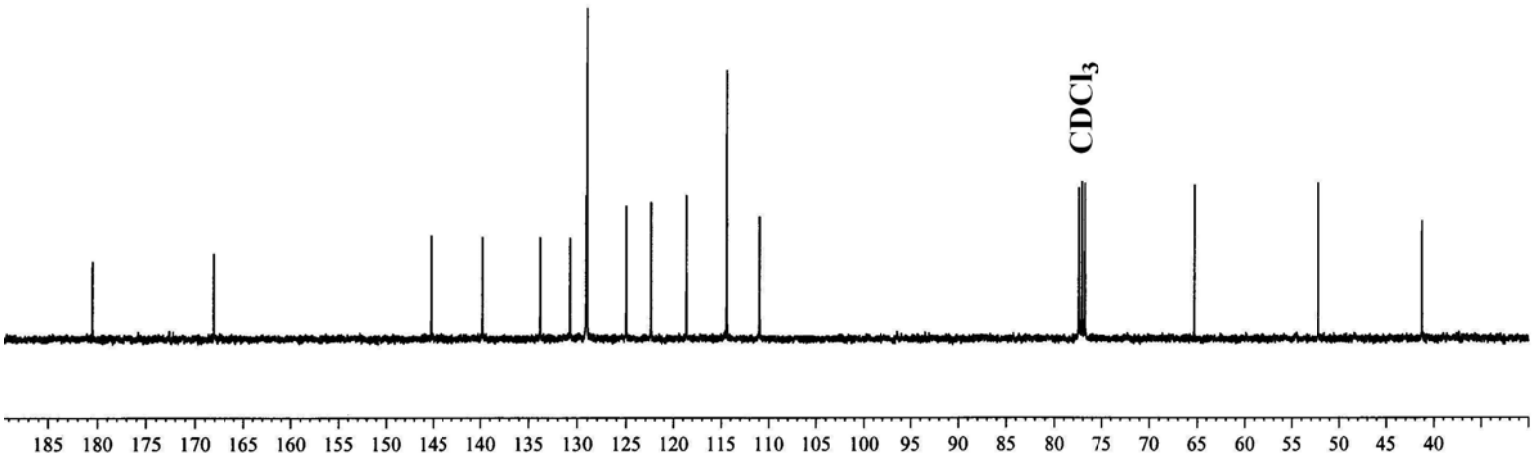
^{1}H NMR spectrum of 141a



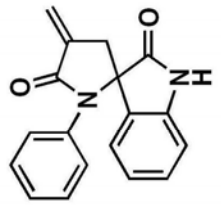
Spectrum 20



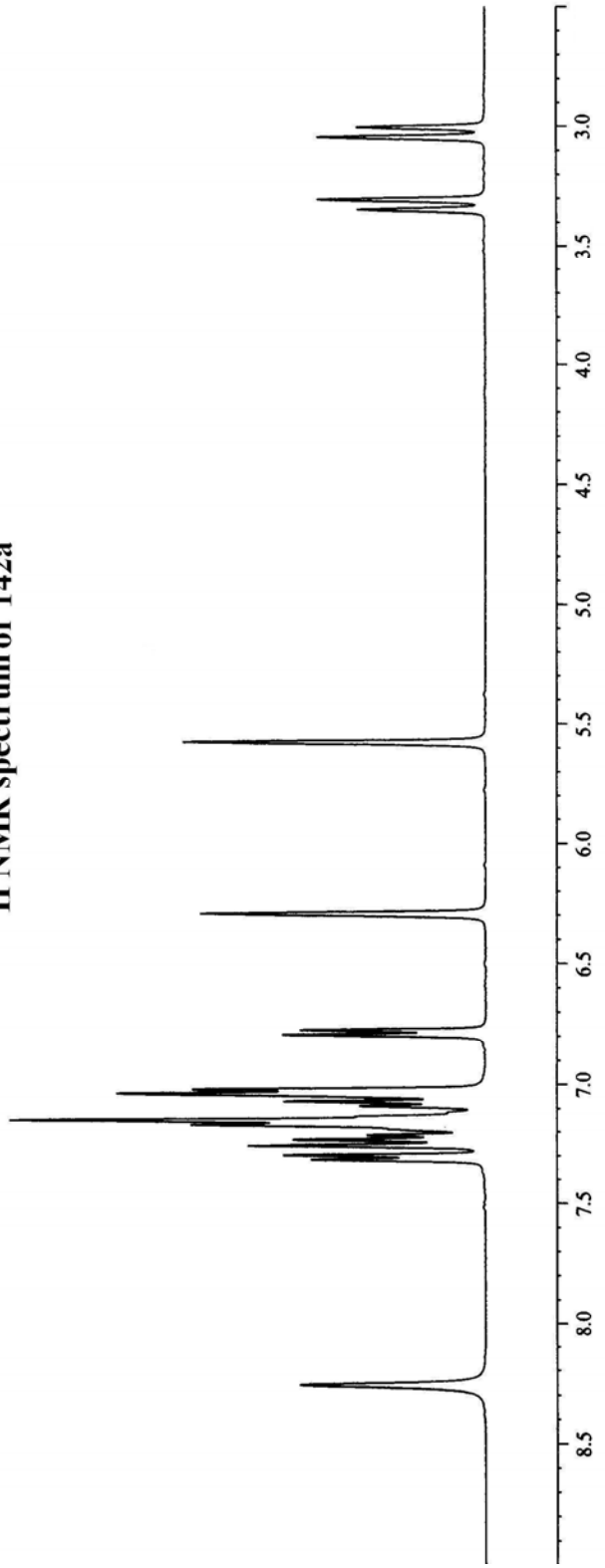
^{13}C NMR spectrum of 141a



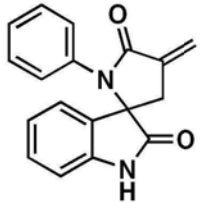
Spectrum 21



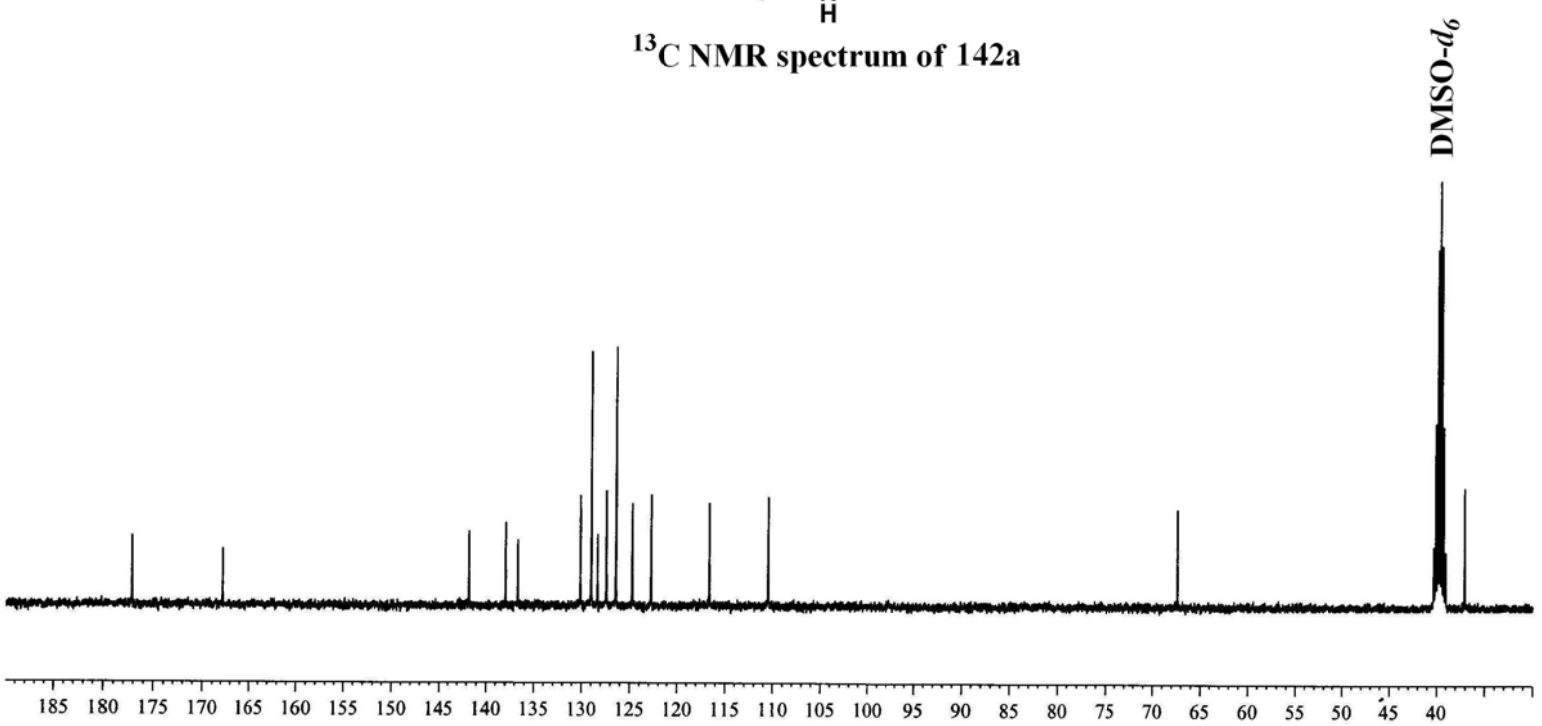
^{1}H NMR spectrum of 142a



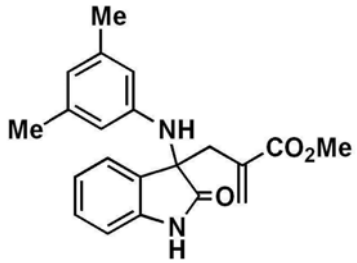
Spectrum 22



^{13}C NMR spectrum of 142a

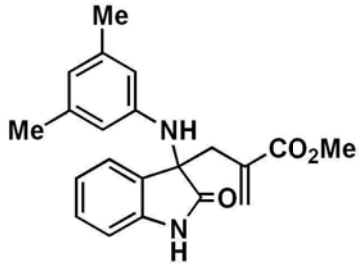


Spectrum 23

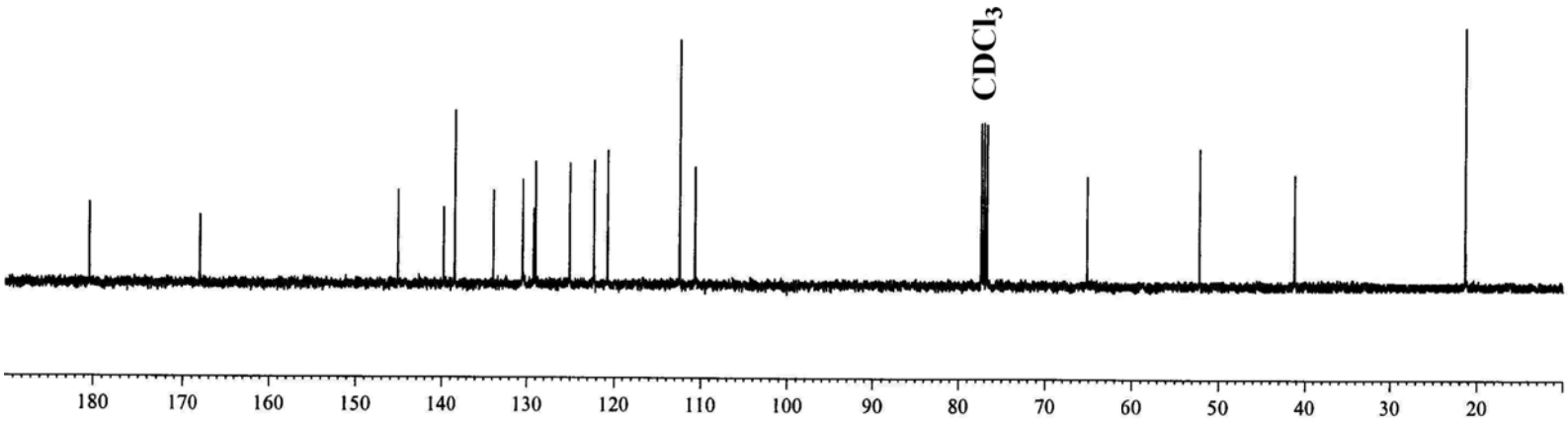


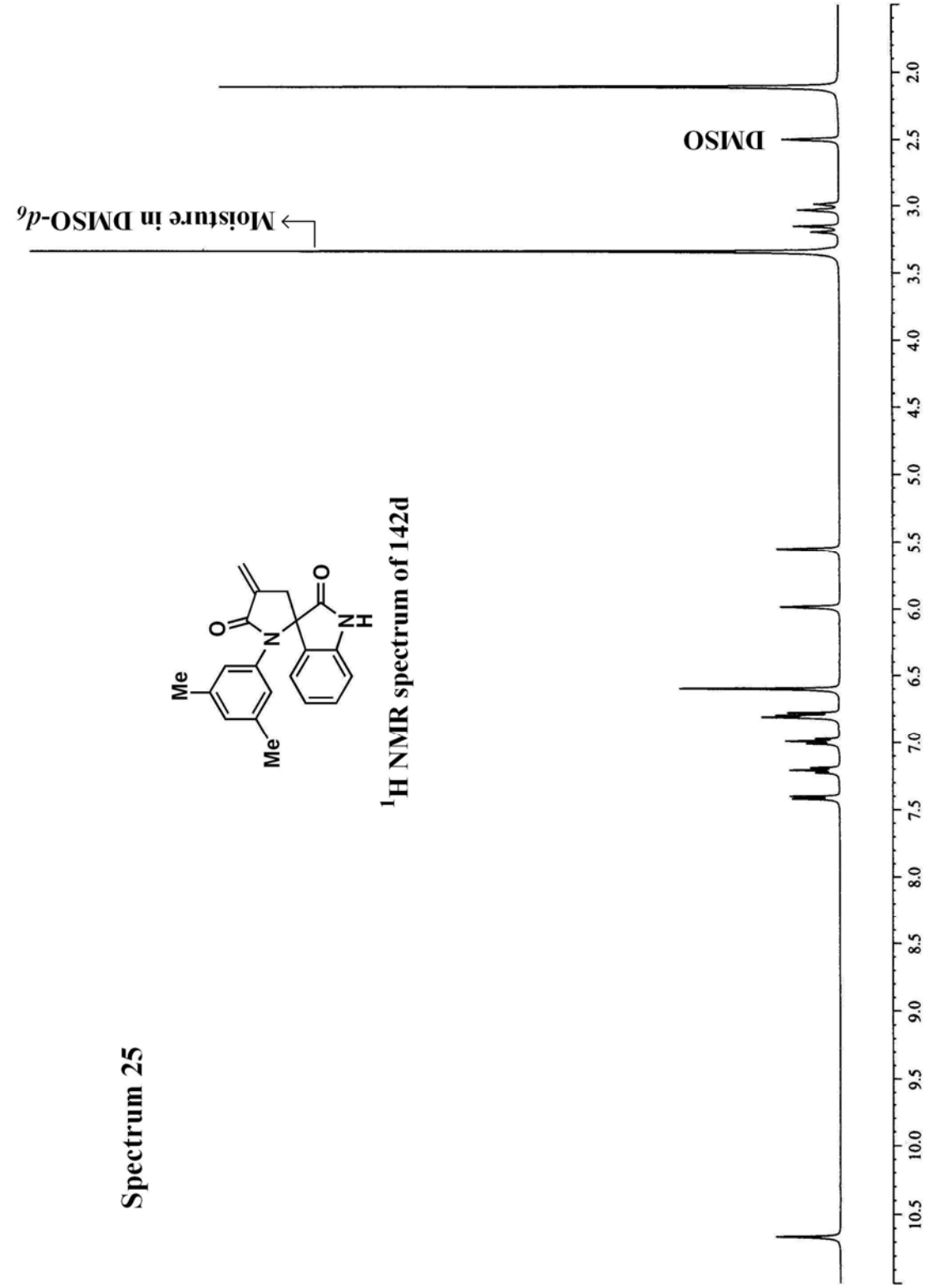
^{1}H NMR spectrum of 141d

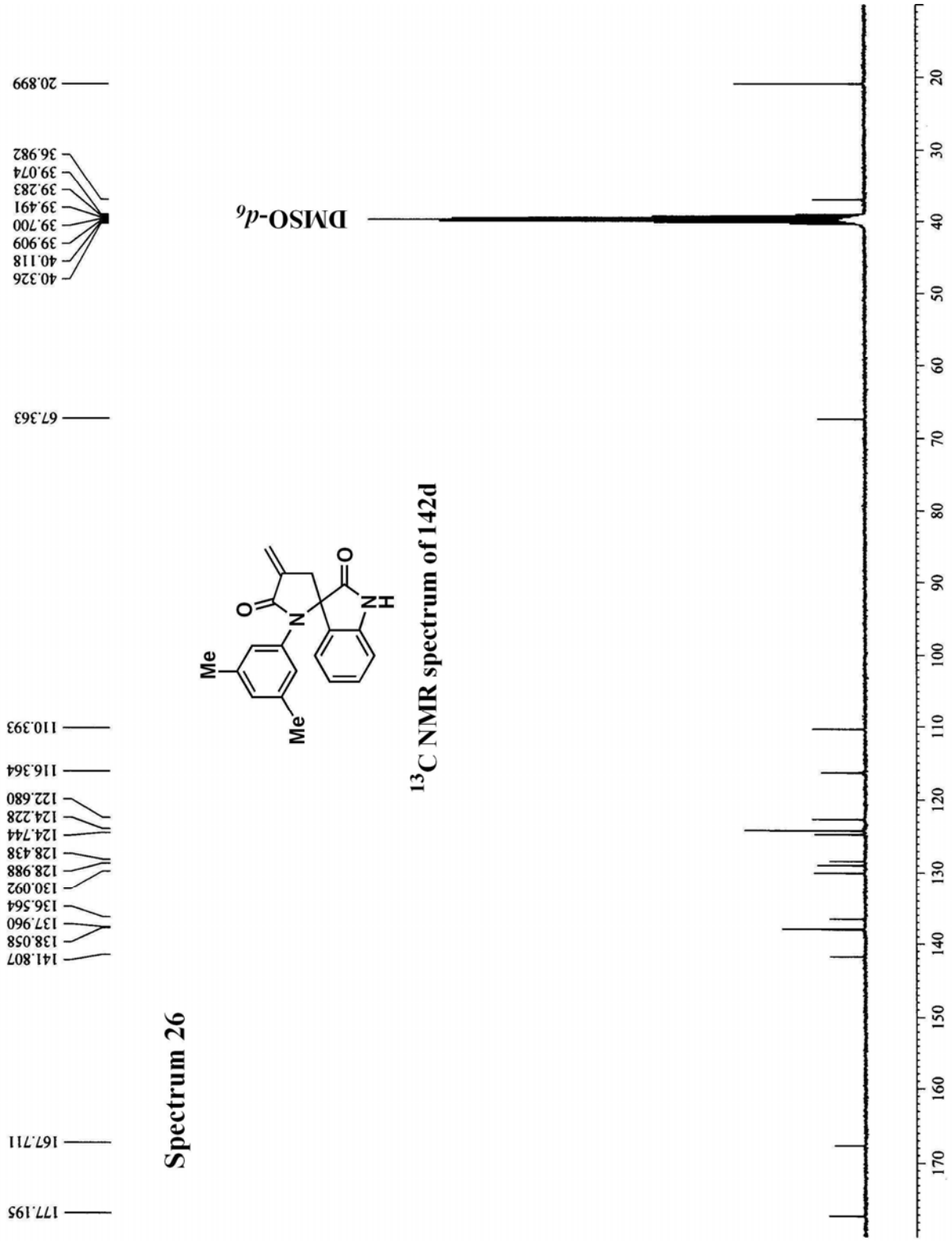
Spectrum 24



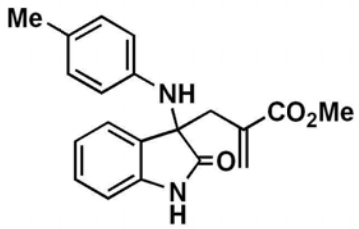
^{13}C NMR spectrum of 141d



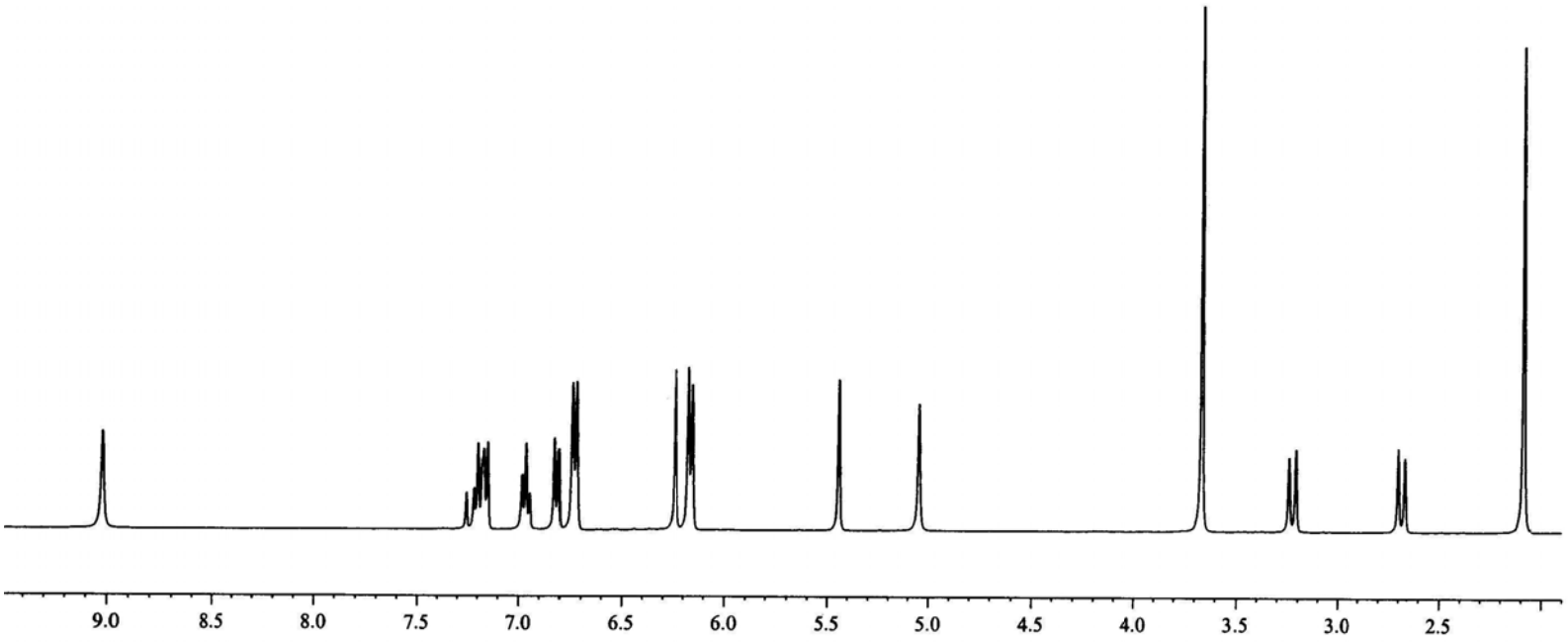

Spectrum 25
^{1}H NMR spectrum of 142d
Me
Me
O
O
N
H
DMSO
Moisture in DMSO-d_6
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

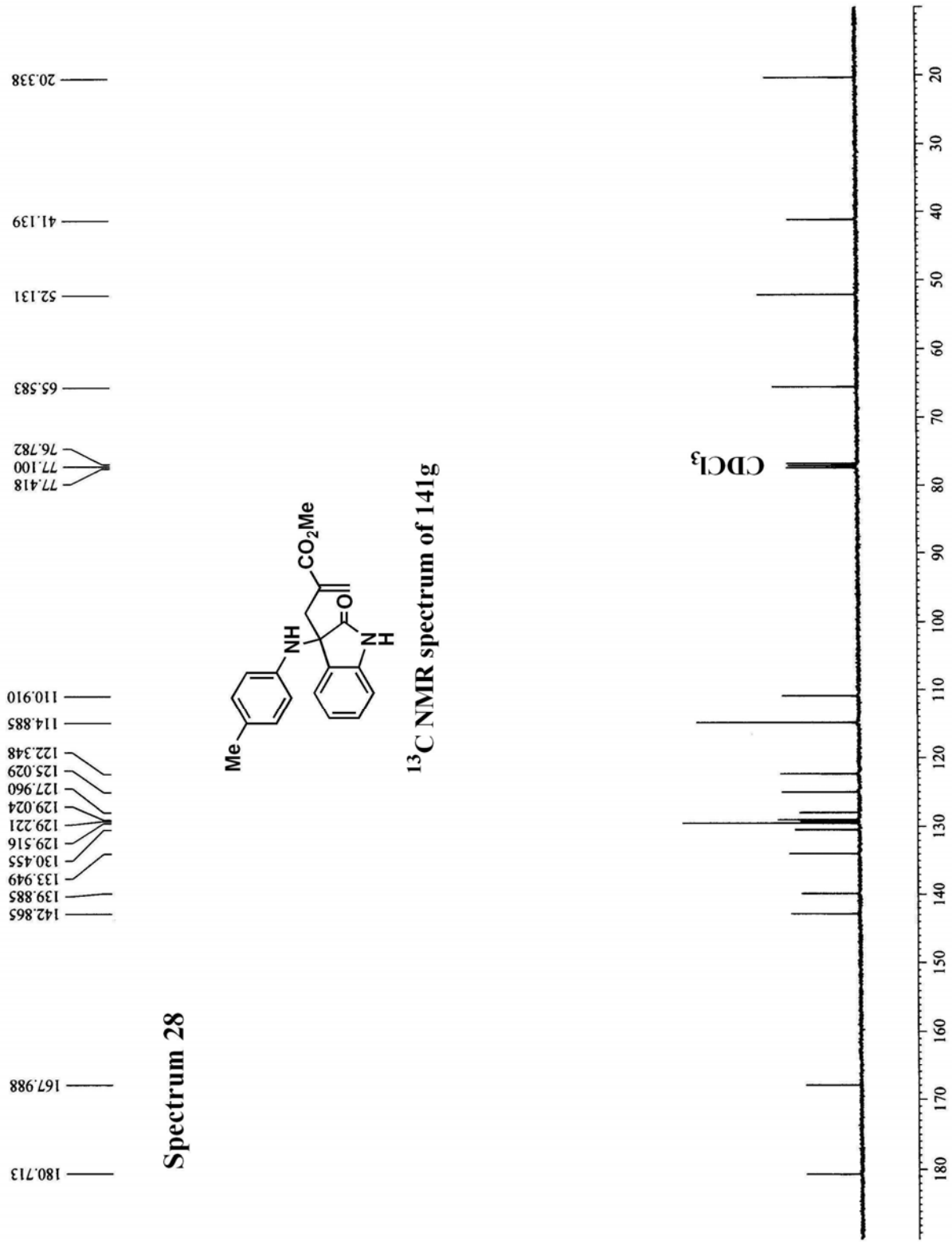

Spectrum 26
^{13}C NMR spectrum of 142d
DMSO-d_6
Me
Me
O
O
N
H
177.195
167.711
141.807
138.058
137.960
136.564
130.092
128.988
128.438
124.744
124.228
122.680
116.364
110.393
67.363
40.326
40.118
39.909
39.700
39.491
39.283
39.074
36.982
20.899
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

Spectrum 27

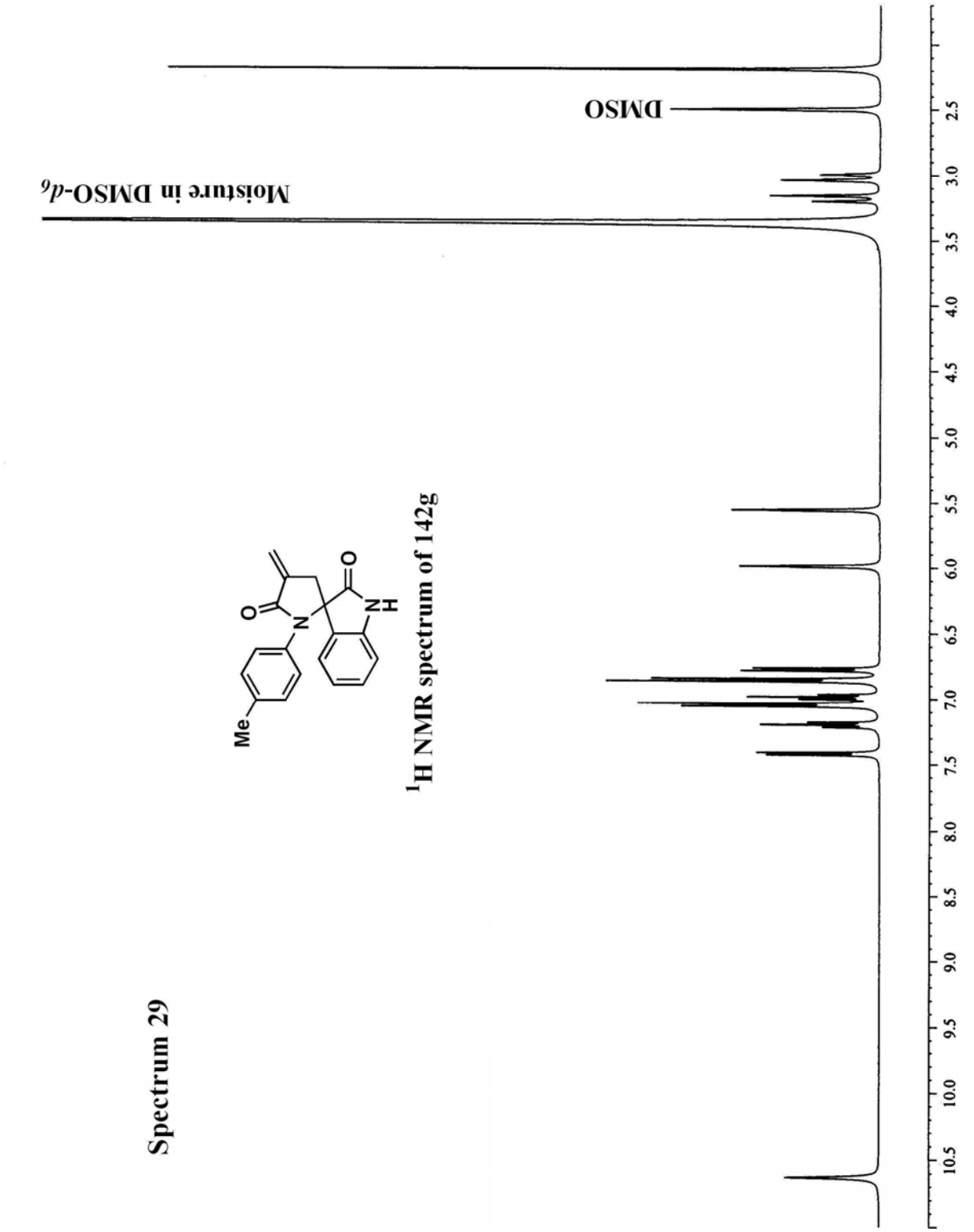


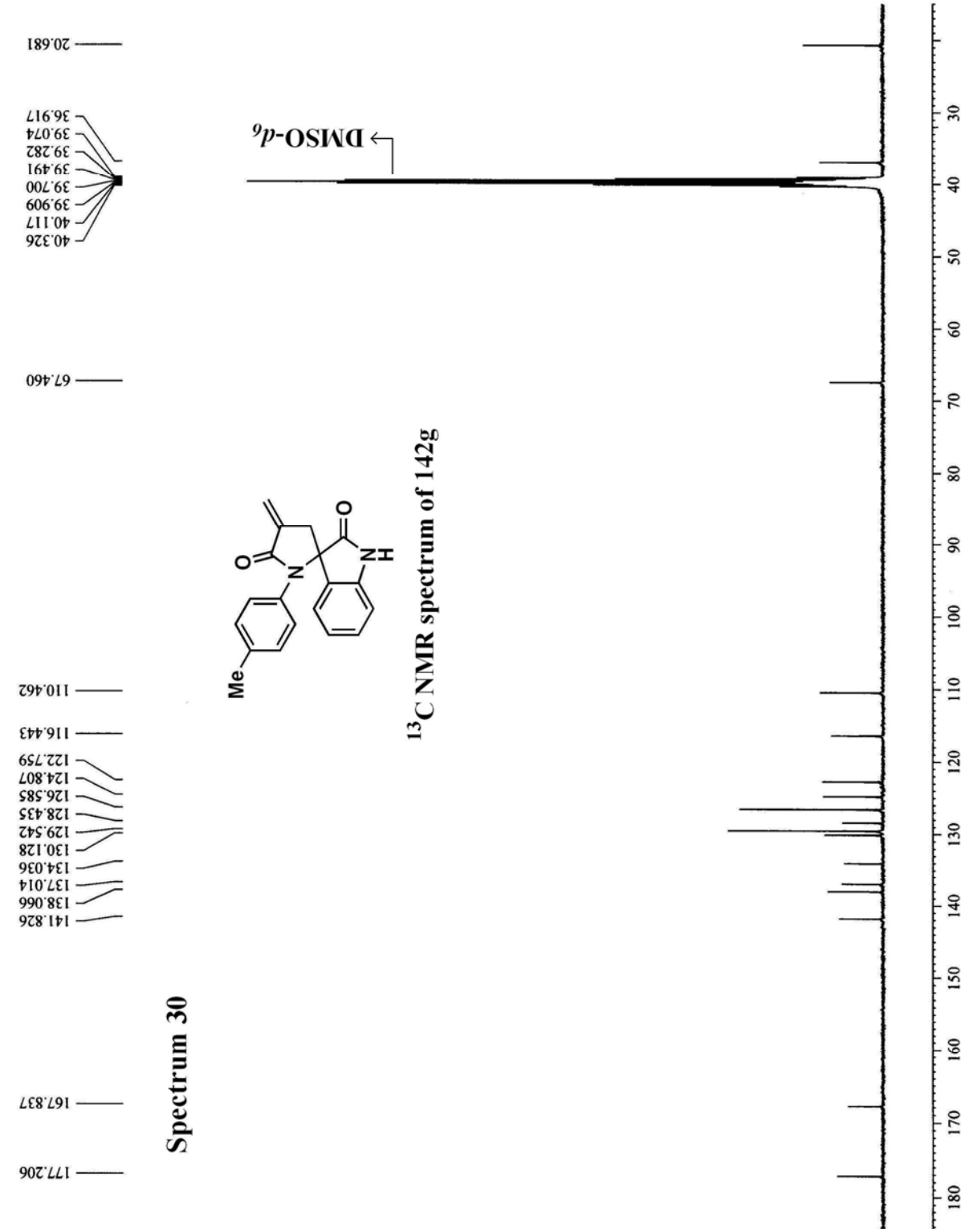
^{1}H NMR spectrum of 141g



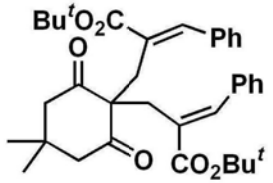


^{13}C NMR spectrum of 141g

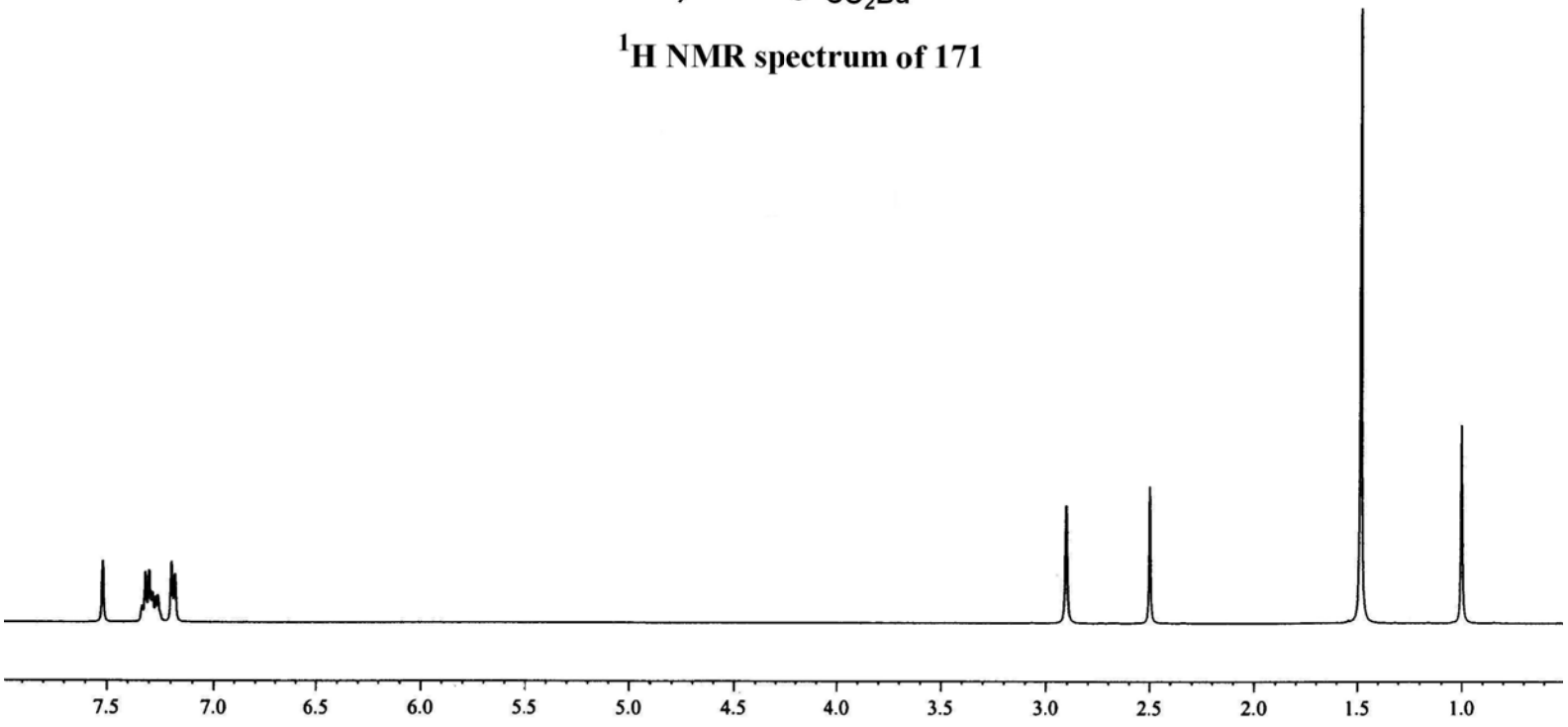

Spectrum 29
^{1}H NMR spectrum of 142g
Me
O
N
O
N
H
DMSO
Moisture in DMSO-d_6
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5


Spectrum 30
^{13}C NMR spectrum of 142g
DMSO-d_6
Me
O
N
H
O
177.206
167.837
141.826
138.066
137.014
134.036
130.128
129.542
128.435
126.585
124.807
122.759
116.443
110.462
67.460
40.326
40.117
39.909
39.700
39.491
39.282
39.074
36.917
20.681
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

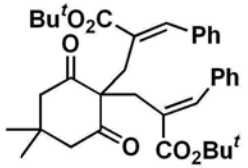
Spectrum 31



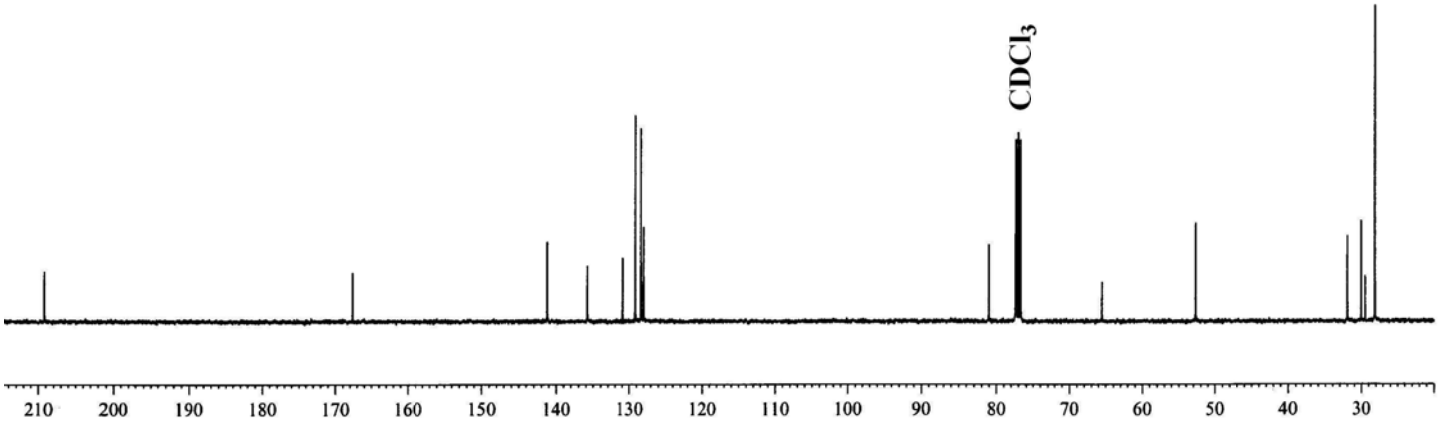
^{1}H NMR spectrum of 171



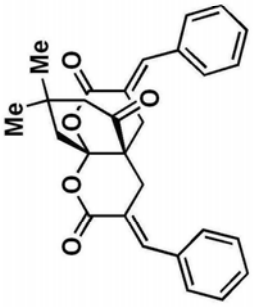
Spectrum 32



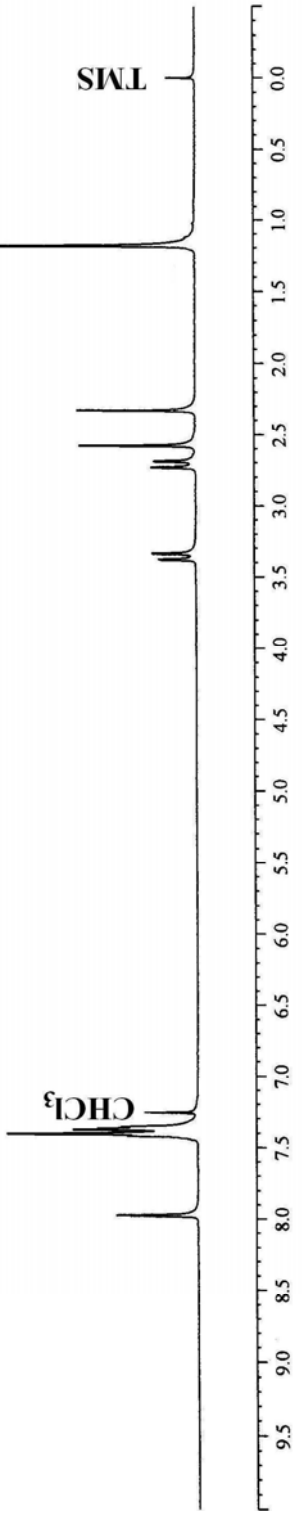
^{13}C NMR spectrum of 171

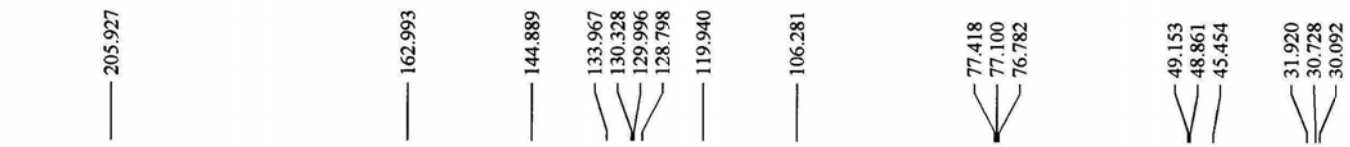


Spectrum 33

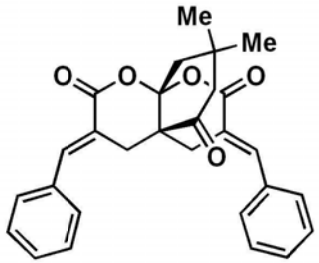


^{1}H NMR spectrum of 172a

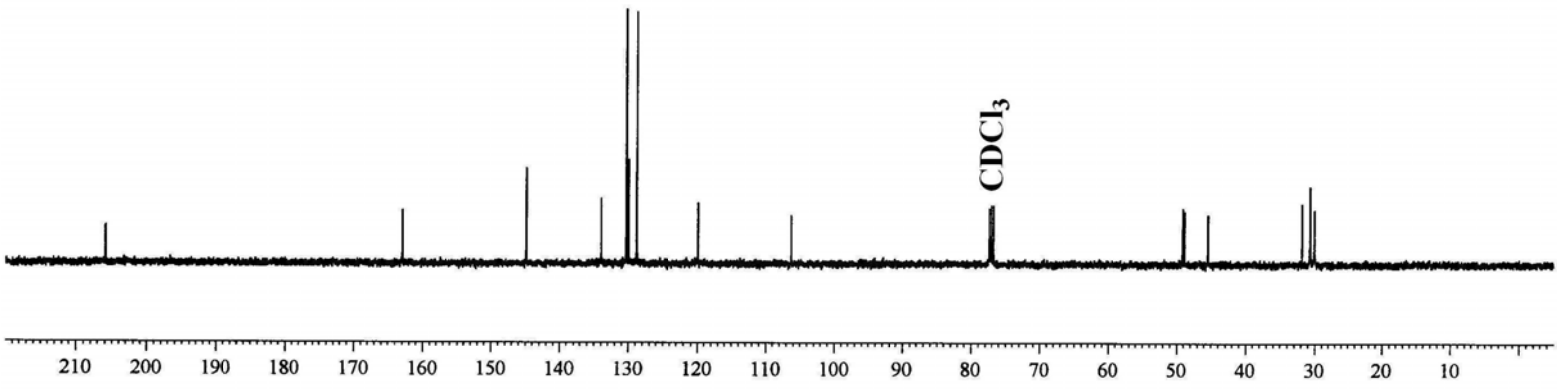




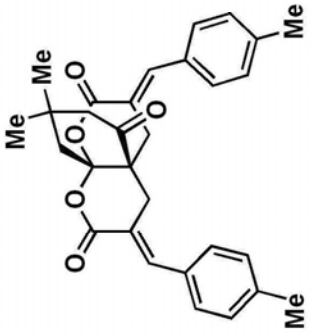
Spectrum 34



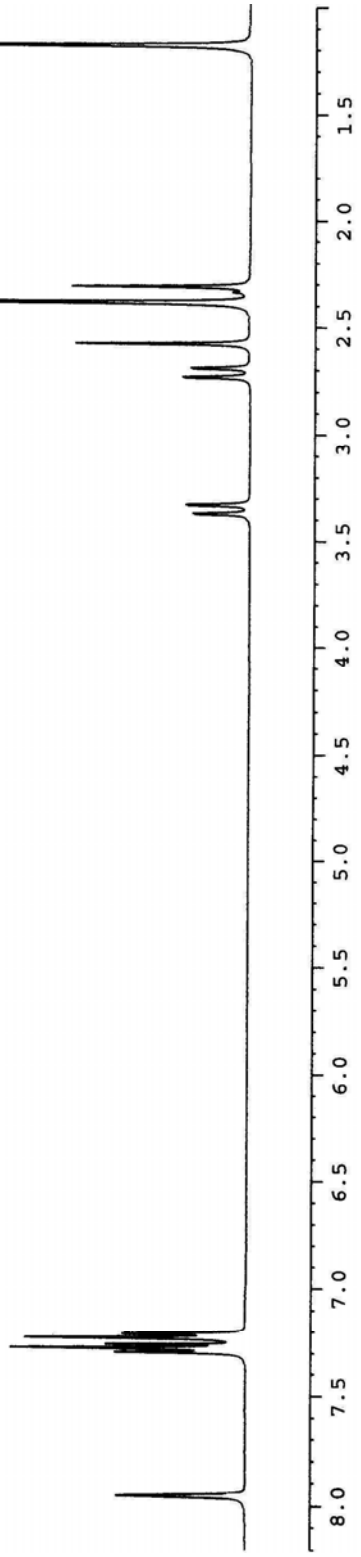
^{13}C NMR spectrum of 172a



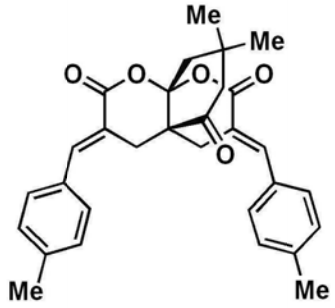
Spectrum 35



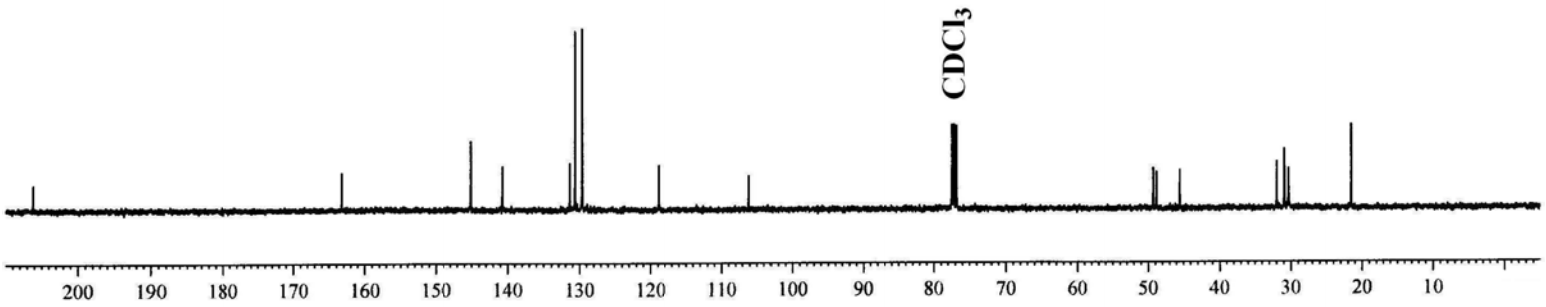
^{1}H NMR spectrum of 172c



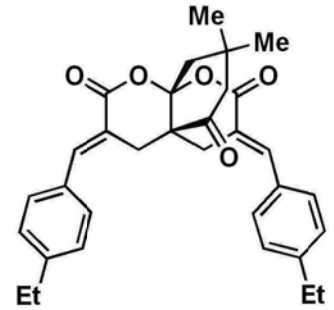
Spectrum 36



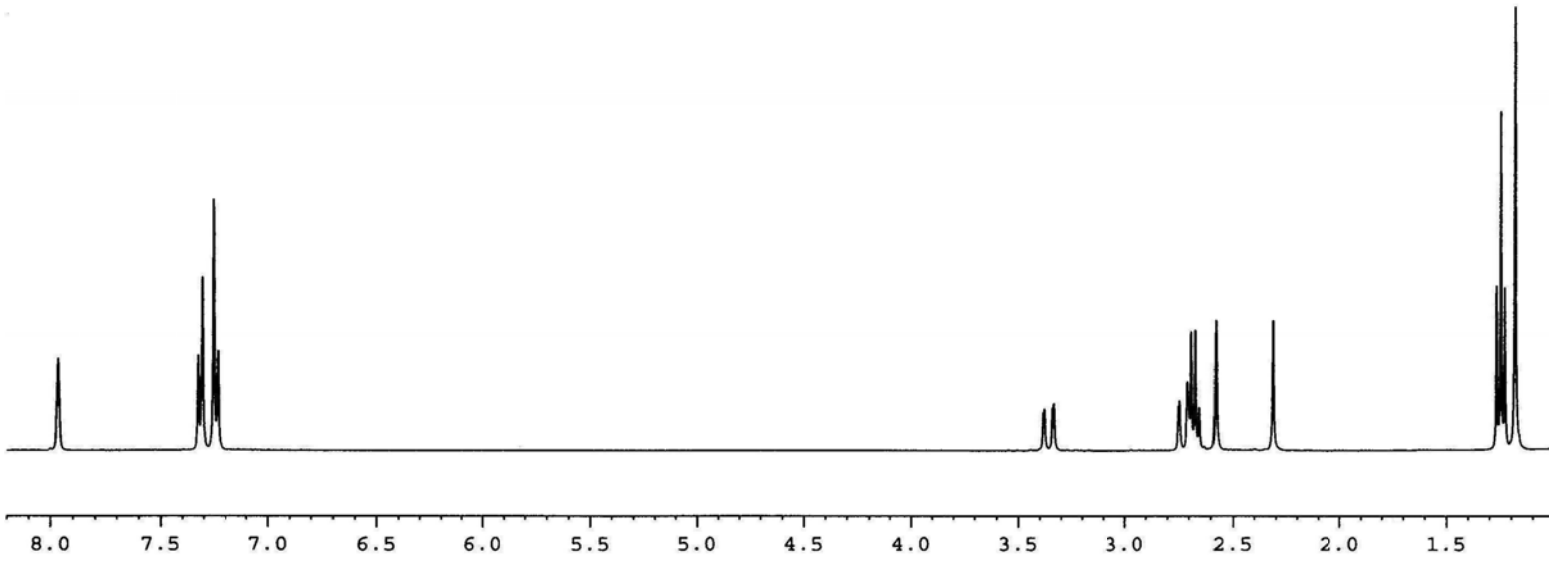
^{13}C NMR spectrum of 172c



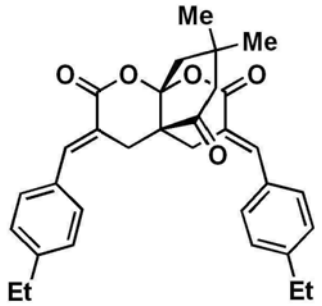
Spectrum 37



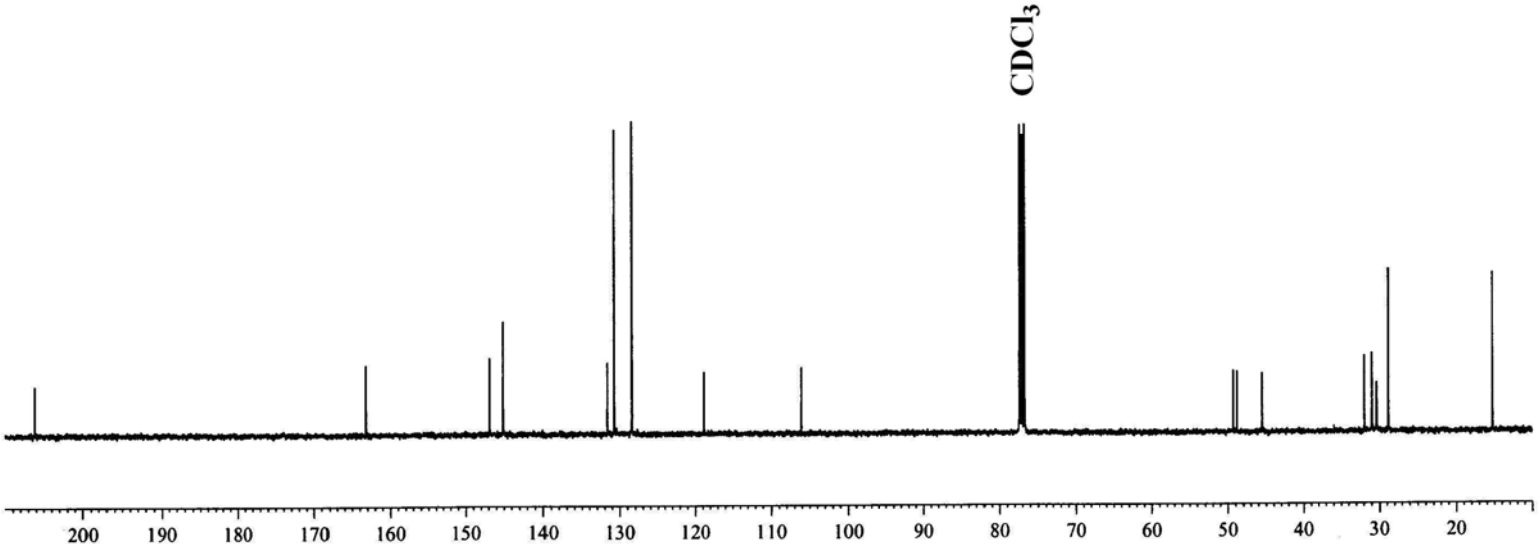
^{1}H NMR spectrum of 172d



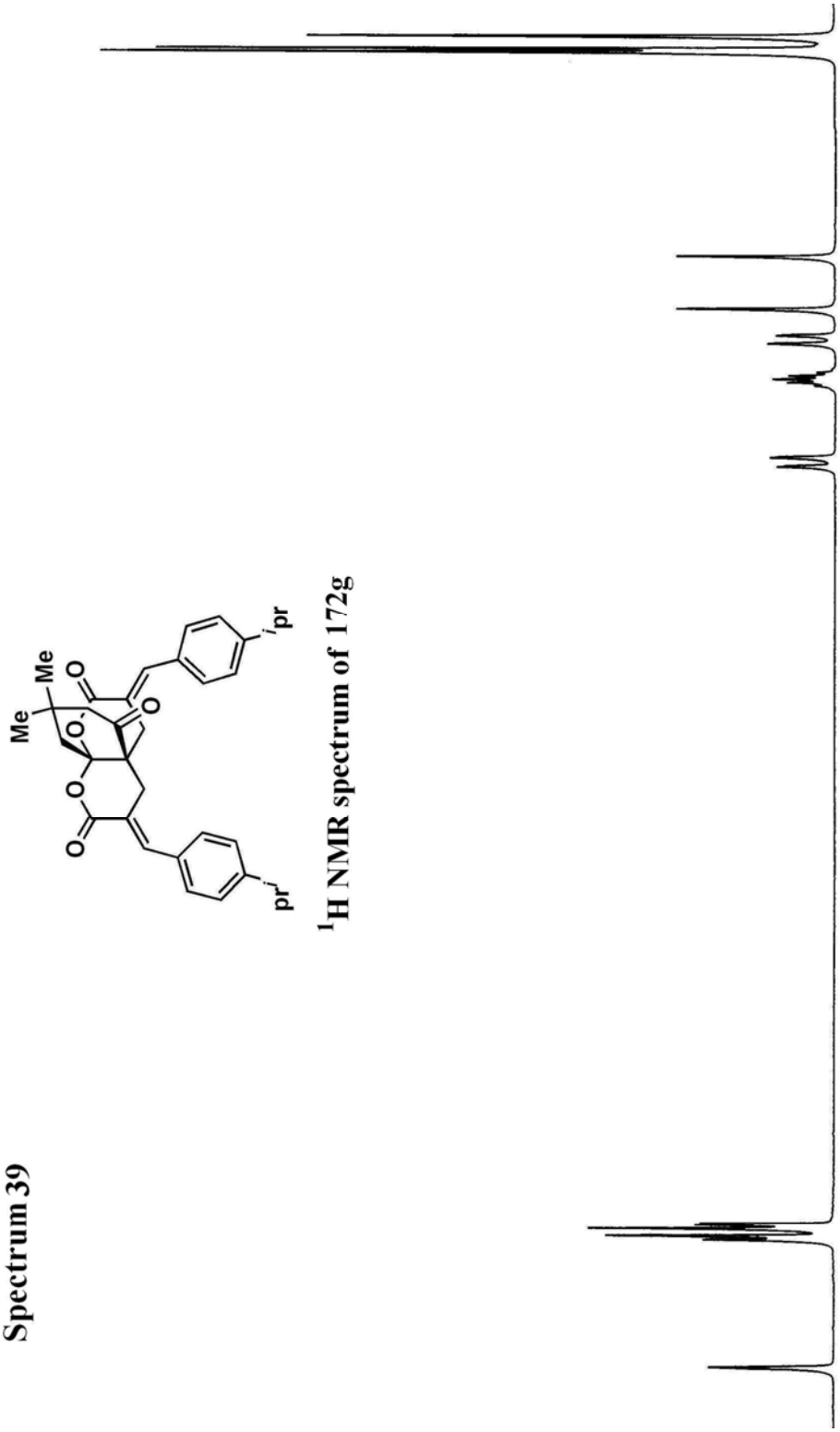
Spectrum 38



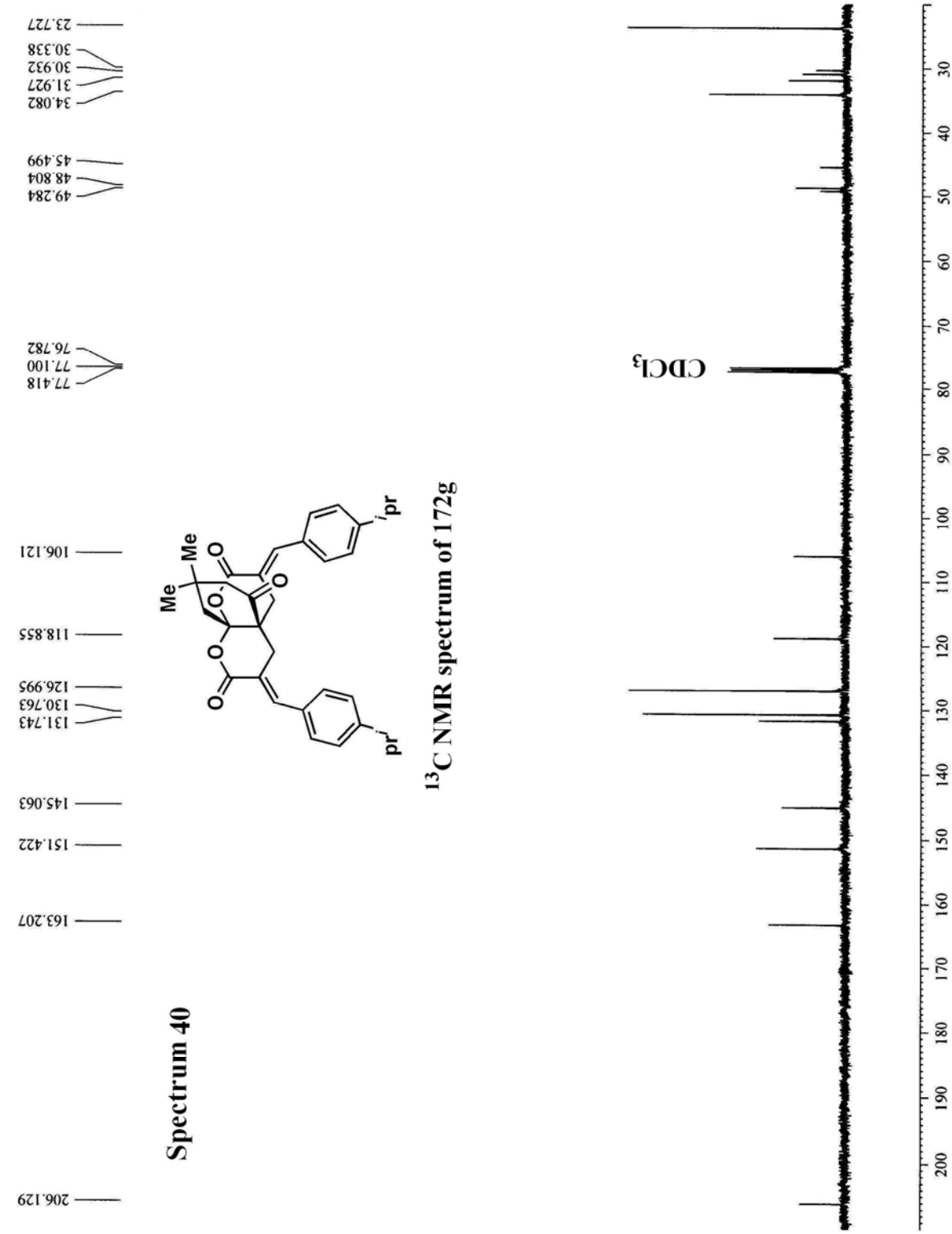
^{13}C NMR spectrum of 172d



Spectrum 39



^{1}H NMR spectrum of 172g


Spectrum 40
206.129
163.207
151.422
145.063
131.743
130.763
126.995
118.855
106.121
77.418
77.100
76.782
49.284
48.804
45.499
34.082
31.927
30.932
30.338
23.727
CDCl3
Me
Me
O
O
O
O
O
ipr
ipr
13C NMR spectrum of 172g

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **133a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	3639(2)	5960(2)	661(1)	51(1)
C(2)	3493(2)	7555(2)	-383(1)	43(1)
C(3)	3741(2)	8374(2)	-1159(1)	52(1)
C(4)	3042(3)	9394(2)	-1156(1)	57(1)
C(5)	2118(3)	9571(2)	-413(2)	57(1)
C(6)	1881(2)	8739(2)	366(1)	50(1)
C(7)	2584(2)	7739(2)	382(1)	40(1)
C(8)	2555(2)	6696(2)	1105(1)	42(1)
C(9)	869(2)	5402(2)	1314(1)	47(1)
C(10)	1227(2)	5242(2)	2347(1)	42(1)
C(11)	2716(2)	6754(2)	2794(1)	42(1)
C(12)	484(3)	4032(2)	2820(2)	57(1)
C(13)	8418(2)	5475(2)	4233(1)	41(1)
C(14)	6072(2)	3035(2)	3942(1)	39(1)
C(15)	4967(2)	1442(2)	3929(1)	49(1)
C(16)	3404(3)	836(2)	3421(1)	55(1)
C(17)	2965(2)	1781(2)	2933(1)	54(1)
C(18)	4091(2)	3382(2)	2952(1)	47(1)
C(19)	5647(2)	4002(2)	3460(1)	38(1)
C(20)	7093(2)	5655(2)	3618(1)	37(1)
C(21)	6824(2)	7047(2)	4136(1)	45(1)
C(22)	7914(2)	8414(2)	3652(2)	52(1)
C(23)	8325(2)	7724(2)	2731(2)	54(1)
C(24)	8485(3)	9963(3)	3934(2)	87(1)
N(1)	4069(2)	6471(2)	-200(1)	53(1)
N(2)	7723(2)	3951(2)	4395(1)	45(1)
O(1)	4001(2)	5078(2)	1048(1)	78(1)
O(2)	3383(1)	7639(1)	2079(1)	46(1)
O(3)	3331(2)	7248(2)	3641(1)	58(1)
O(4)	9821(2)	6559(2)	4525(1)	55(1)
O(5)	7740(2)	6111(2)	2695(1)	47(1)
O(6)	9036(2)	8357(2)	2071(1)	88(1)

Table II. Atomic coordinates (x 10^4) and equivalent isotropicdisplacement parameters (A^2 x 10^3) for compound **133f**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	-766(3)	6924(2)	1305(3)	55(1)
C(2)	-592(3)	6642(2)	-1092(3)	51(1)
C(3)	-1005(3)	6098(3)	-2759(3)	64(1)
C(4)	325(4)	6770(3)	-3100(3)	72(1)
C(5)	1987(4)	7921(3)	-1838(3)	74(1)
C(6)	2381(3)	8472(3)	-165(3)	63(1)
C(7)	1070(3)	7817(2)	187(3)	49(1)
C(8)	1074(3)	8158(2)	1816(2)	49(1)
C(9)	1336(3)	9865(2)	2625(2)	57(1)
C(10)	2332(3)	10080(2)	4507(3)	53(1)
C(11)	3131(3)	8872(3)	4745(3)	54(1)
C(12)	2523(3)	11093(3)	5798(3)	77(1)
C(13)	-3562(3)	5015(2)	-1385(3)	67(1)
C(14)	-4821(3)	5842(3)	-2180(3)	98(1)
N	-1679(2)	6129(2)	-410(2)	55(1)
O(1)	-1312(2)	6724(2)	2278(2)	75(1)
O(2)	2476(2)	7833(2)	3174(2)	56(1)
O(3)	4209(2)	8723(2)	6039(2)	71(1)

Table III. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **136c**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	7614(2)	-287(2)	2765(1)	42(1)
C(2)	6736(2)	1328(2)	2039(1)	47(1)
C(3)	5760(2)	2192(2)	1704(1)	65(1)
C(4)	6455(3)	3015(2)	1209(1)	71(1)
C(5)	8081(2)	3022(2)	1045(1)	60(1)
C(6)	9039(2)	2139(2)	1402(1)	48(1)
C(7)	8361(2)	1291(1)	1885(1)	40(1)
C(8)	9045(2)	204(1)	2298(1)	37(1)
C(9)	9793(2)	-854(1)	1808(1)	38(1)
C(10)	11523(2)	-497(2)	1821(1)	44(1)
C(11)	11764(2)	258(2)	2512(1)	41(1)
C(12)	8919(2)	-1052(1)	1065(1)	39(1)
C(13)	7653(2)	-1875(2)	1052(1)	57(1)

C(14)	6716(3)	-1989(2)	400(1)	74(1)
C(15)	7047(3)	-1302(2)	-227(1)	71(1)
C(16)	8309(3)	-505(2)	-223(1)	67(1)
C(17)	9248(2)	-384(2)	416(1)	52(1)
C(18)	12707(2)	-765(2)	1356(1)	67(1)
C(19)	8789(3)	3941(2)	494(1)	89(1)
N(1)	6338(1)	387(1)	2559(1)	51(1)
O(1)	7659(1)	-1149(1)	3205(1)	57(1)
O(2)	10330(1)	563(1)	2811(1)	44(1)
O(3)	12980(1)	598(1)	2810(1)	56(1)

Table IV. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **137c**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	1024(2)	3768(2)	2257(3)	42(1)
C(2)	2062(2)	3593(2)	4040(3)	43(1)
C(3)	2453(2)	3505(2)	5180(3)	56(1)
C(4)	3344(3)	3346(2)	5717(3)	62(1)
C(5)	3818(2)	3283(2)	5171(3)	61(1)
C(6)	3401(2)	3376(2)	4017(3)	53(1)
C(7)	2512(2)	3533(2)	3461(3)	44(1)
C(8)	1899(2)	3660(2)	2250(3)	40(1)
C(9)	2120(2)	4299(2)	1662(3)	43(1)
C(10)	1668(2)	4030(2)	489(3)	53(1)
C(11)	1542(3)	3213(2)	520(3)	56(1)
C(12)	1954(2)	5090(2)	1914(3)	43(1)
C(13)	1149(2)	5427(2)	1369(3)	57(1)
C(14)	1034(3)	6163(2)	1625(4)	66(1)
C(15)	1724(3)	6554(2)	2422(4)	70(1)
C(16)	2522(3)	6225(2)	2970(4)	73(1)
C(17)	2648(3)	5506(2)	2725(3)	59(1)
C(18)	1450(4)	4401(3)	-431(3)	79(1)
C(19)	4779(3)	3098(3)	5789(4)	91(2)
N(1)	1174(2)	3743(2)	3295(2)	48(1)
O(1)	324(1)	3849(2)	1412(2)	54(1)
O(2)	1790(2)	3002(1)	1584(2)	53(1)
O(3)	1286(3)	2758(2)	-207(3)	89(1)

Table V. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **136e**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	7754(3)	4210(3)	463(2)	43(1)
C(2)	7566(3)	6313(3)	1825(2)	47(1)
C(3)	7886(4)	7811(3)	2531(2)	62(1)
C(4)	6542(4)	8316(3)	3148(2)	67(1)
C(5)	4914(4)	7358(3)	3049(2)	64(1)
C(6)	4593(3)	5835(3)	2352(2)	55(1)
C(7)	5956(3)	5321(2)	1754(2)	44(1)
C(8)	6073(3)	3776(2)	945(1)	41(1)
C(9)	6465(3)	2150(2)	1229(1)	40(1)
C(10)	4516(3)	1341(2)	1052(1)	42(1)
C(11)	3415(3)	2036(2)	361(2)	44(1)
C(12)	7614(3)	2337(2)	2180(2)	43(1)
C(13)	9502(3)	2026(3)	2184(2)	59(1)
C(14)	10604(4)	2141(4)	3037(2)	76(1)
C(15)	9829(4)	2576(3)	3887(2)	71(1)
C(16)	7967(4)	2904(3)	3904(2)	69(1)
C(17)	6868(4)	2776(3)	3054(2)	56(1)
C(18)	3827(3)	159(3)	1366(2)	54(1)
Cl(1)	3178(2)	8079(1)	3795(1)	106(1)
Cl(2)	11204(2)	2672(1)	4961(1)	119(1)
N(1)	8653(3)	5582(2)	1090(1)	48(1)
O(1)	8181(2)	3405(2)	-311(1)	53(1)
O(2)	4413(2)	3370(2)	267(1)	45(1)
O(3)	1912(2)	1582(2)	-87(1)	60(1)

Table VI. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **137e**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	8820(2)	7672(4)	8120(2)	42(1)
C(2)	8702(2)	8935(3)	6686(2)	41(1)
C(3)	8468(2)	10053(4)	5973(2)	54(1)
C(4)	8668(2)	9610(4)	5077(2)	55(1)
C(5)	9086(2)	8135(4)	4915(2)	44(1)
C(6)	9302(2)	7013(3)	5627(2)	39(1)
C(7)	9091(2)	7429(3)	6513(2)	34(1)
C(8)	9235(2)	6498(3)	7423(2)	36(1)

C(9)	10300(2)	5920(3)	7768(2)	38(1)
C(10)	10108(2)	4373(4)	8281(2)	44(1)
C(11)	9082(3)	3853(4)	7948(2)	47(1)
C(12)	10964(2)	7215(4)	8256(2)	38(1)
C(13)	11406(2)	8323(4)	7709(2)	48(1)
C(14)	11994(2)	9566(4)	8107(2)	53(1)
C(15)	12161(2)	9689(4)	9070(2)	45(1)
C(16)	11729(2)	8622(4)	9632(2)	54(1)
C(17)	11135(2)	7391(4)	9229(2)	49(1)
C(18)	10691(3)	3490(4)	8883(2)	66(1)
Cl(1)	9326(1)	7663(1)	3770(1)	65(1)
Cl(2)	12953(1)	11195(1)	9586(1)	62(1)
N(1)	8586(2)	9072(4)	7644(2)	50(1)
O(1)	8727(2)	7361(3)	8933(1)	61(1)
O(2)	8633(2)	5040(2)	7371(1)	46(1)
O(3)	8647(2)	2633(3)	8096(2)	63(1)

Table VII. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **141a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
O(1)	4474(1)	9170(1)	8694(1)	51(1)
O(2)	6107(2)	7191(1)	4205(1)	59(1)
N(2)	6934(2)	6549(1)	6680(1)	43(1)
N(1)	7035(2)	9138(1)	8824(1)	43(1)
C(1)	8960(2)	7657(1)	6995(1)	37(1)
C(2)	6626(2)	9039(2)	5946(1)	42(1)
C(3)	7187(2)	7891(1)	6937(1)	37(1)
C(4)	6029(2)	8786(2)	8265(1)	40(1)
C(5)	6984(2)	5401(1)	7501(1)	38(1)
C(6)	8784(2)	8462(2)	8103(1)	39(1)
C(7)	7697(2)	8568(2)	4558(1)	42(1)
O(3)	8178(2)	7400(2)	2556(1)	69(1)
C(8)	7504(2)	5318(2)	8598(1)	49(1)
C(9)	10583(2)	6849(2)	6168(1)	47(1)
C(10)	7232(2)	7643(2)	3788(1)	44(1)
C(11)	10176(2)	8506(2)	8404(2)	50(1)
C(12)	6509(2)	4262(2)	7203(2)	49(1)
C(13)	7529(2)	4135(2)	9373(2)	57(1)
C(14)	11995(2)	6899(2)	6459(2)	57(1)
C(15)	11793(2)	7716(2)	7553(2)	56(1)
C(16)	6567(2)	3082(2)	7980(2)	61(1)
C(17)	7075(2)	3017(2)	9070(2)	60(1)

C(18)	8954(3)	9009(2)	4010(2)	69(1)
C(19)	7849(3)	6524(3)	1696(2)	80(1)

Table VIII. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **142a**.U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	10192(2)	2772(1)	7361(1)	42(1)
C(2)	7729(2)	3280(1)	6151(1)	47(1)
C(3)	6297(2)	3780(1)	5700(2)	66(1)
C(4)	5228(2)	3496(2)	4667(2)	79(1)
C(5)	5563(2)	2748(2)	4091(2)	73(1)
C(6)	7026(2)	2254(1)	4544(2)	58(1)
C(7)	8100(2)	2528(1)	5583(1)	42(1)
C(8)	9781(2)	2187(1)	6259(1)	38(1)
C(9)	11077(2)	2373(1)	5705(1)	46(1)
C(10)	12256(2)	1577(1)	6102(1)	42(1)
C(11)	11401(2)	821(1)	6479(1)	43(1)
C(12)	13781(2)	1517(1)	6155(2)	64(1)
C(13)	8903(2)	665(1)	6942(1)	43(1)
C(14)	9072(3)	732(1)	8061(2)	67(1)
C(15)	8020(3)	220(2)	8457(2)	90(1)
C(16)	6859(3)	-351(2)	7736(3)	87(1)
C(17)	6719(2)	-421(1)	6629(2)	80(1)
C(18)	7728(2)	97(1)	6227(2)	59(1)
N(1)	8992(2)	3416(1)	7189(1)	51(1)
N(2)	9969(1)	1177(1)	6501(1)	38(1)
O(1)	11389(1)	2661(1)	8198(1)	58(1)
O(2)	11866(1)	8(1)	6726(1)	64(1)

Table IX. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **142b**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	9730(3)	9558(1)	2737(1)	40(1)
C(2)	8108(3)	10035(1)	1555(1)	37(1)
C(3)	7663(3)	10523(1)	846(1)	47(1)
C(4)	5810(3)	10312(1)	424(1)	46(1)
C(5)	4465(3)	9646(1)	726(1)	41(1)
C(6)	4892(3)	9160(1)	1443(1)	38(1)

C(7)	6758(3)	9354(1)	1847(1)	34(1)
C(8)	7641(3)	8994(1)	2652(1)	35(1)
C(9)	6169(3)	9134(1)	3407(1)	41(1)
C(10)	5947(3)	8202(1)	3793(1)	37(1)
C(11)	7315(3)	7540(1)	3335(1)	37(1)
C(12)	4749(3)	7945(1)	4412(1)	51(1)
C(13)	9710(3)	7581(1)	2148(1)	36(1)
C(14)	11596(3)	7270(1)	2488(1)	44(1)
C(15)	13073(3)	6833(1)	1992(2)	58(1)
C(16)	12693(4)	6735(1)	1162(2)	65(1)
C(17)	10831(4)	7056(2)	827(1)	65(1)
C(18)	9315(3)	7470(1)	1320(1)	51(1)
Cl(1)	2124(1)	9426(1)	190(1)	62(1)
N(1)	9863(2)	10127(1)	2075(1)	43(1)
N(2)	8145(2)	7998(1)	2678(1)	35(1)
O(1)	10973(2)	9484(1)	3302(1)	56(1)
O(2)	7615(2)	6724(1)	3494(1)	52(1)

Table X. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **142g** U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	5237(3)	297(4)	8053(2)	46(1)
C(2)	4424(3)	1298(4)	6761(2)	49(1)
C(3)	4048(4)	1533(5)	5849(3)	67(1)
C(4)	3520(5)	2719(6)	5676(3)	78(2)
C(5)	3374(5)	3636(5)	6352(3)	75(1)
C(6)	3782(4)	3375(4)	7272(3)	62(1)
C(7)	4292(3)	2206(4)	7466(2)	45(1)
C(8)	4861(3)	1671(4)	8347(2)	42(1)
C(9)	6041(4)	2404(4)	8713(2)	56(1)
C(10)	5964(4)	2270(4)	9757(2)	51(1)
C(11)	4676(4)	1814(3)	9988(2)	45(1)
C(12)	6829(5)	2528(5)	10393(3)	83(2)
C(13)	2743(3)	1140(3)	9148(2)	41(1)
C(14)	1730(4)	1966(4)	9071(2)	50(1)
C(15)	503(4)	1492(4)	9075(3)	58(1)
C(16)	262(4)	207(4)	9164(2)	50(1)
C(17)	1291(4)	-610(4)	9236(3)	58(1)
C(18)	2529(4)	-142(4)	9229(3)	55(1)
C(19)	-1078(4)	-310(6)	9187(3)	76(1)
N(1)	4964(3)	179(3)	7125(2)	54(1)
N(2)	4021(3)	1631(3)	9174(2)	41(1)
O(1)	5697(3)	-502(3)	8557(2)	62(1)
O(2)	4214(3)	1624(3)	10773(2)	58(1)

Table XI. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **172a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	709(2)	2885(3)	4303(4)	62(1)
C(2)	1459(2)	2513(3)	4932(3)	52(1)
C(3)	1952(2)	2656(3)	4101(3)	57(1)
C(4)	2131(2)	3506(3)	1990(3)	56(1)
C(5)	2331(2)	4623(3)	2525(3)	46(1)
C(6)	1864(2)	5234(3)	3126(3)	52(1)
C(7)	986(2)	3794(3)	2401(3)	51(1)
C(8)	539(2)	4101(3)	873(3)	55(1)
C(9)	194(2)	3163(3)	-132(4)	63(1)
C(10)	750(2)	2276(3)	42(3)	69(1)
C(11)	1213(2)	2022(3)	1566(4)	60(1)
C(12)	1566(2)	2982(3)	2526(3)	49(1)
C(13)	-73(2)	3583(3)	-1673(3)	85(1)
C(14)	-462(2)	2694(3)	133(4)	81(1)
C(15)	1637(2)	2064(3)	6232(4)	60(1)
C(16)	2312(2)	1629(3)	7229(3)	57(1)
C(17)	2274(2)	1088(3)	8419(4)	83(1)
C(18)	2878(3)	679(3)	9457(5)	105(2)
C(19)	3538(3)	805(4)	9317(5)	101(2)
C(20)	3584(2)	1331(3)	8160(5)	89(1)
C(21)	2976(2)	1746(3)	7104(4)	69(1)
C(22)	2917(2)	5150(3)	2533(3)	55(1)
C(23)	3520(2)	4824(3)	2110(3)	52(1)
C(24)	3531(2)	3937(3)	1280(3)	57(1)
C(25)	4136(2)	3689(3)	983(3)	63(1)
C(26)	4737(2)	4317(3)	1513(4)	69(1)
C(27)	4741(2)	5199(3)	2338(4)	73(1)
C(28)	4128(2)	5456(3)	2606(4)	63(1)
O(1)	1278(1)	4737(2)	3222(2)	55(1)
O(2)	1987(1)	6122(2)	3625(2)	68(1)
O(3)	487(1)	3416(2)	3012(2)	59(1)
O(4)	249(1)	2741(2)	4798(2)	96(1)
O(5)	1306(2)	1120(2)	2028(3)	87(1)

Table XI2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **171**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atom	x	y	z	U(eq)
C(1)	720(3)	1160(3)	6964(2)	50(1)
C(2)	2076(3)	181(3)	5755(2)	54(1)
C(3)	1659(3)	1291(3)	6197(2)	50(1)
C(4)	1279(3)	37(3)	7822(2)	51(1)
C(5)	2679(3)	-85(3)	8064(2)	57(1)
C(6)	1987(3)	2361(3)	5834(2)	58(1)
C(7)	1230(3)	-1328(3)	7769(2)	63(1)
C(8)	64(3)	1643(3)	8811(2)	62(1)
C(9)	223(3)	405(3)	8567(2)	61(1)
C(10)	1134(3)	1483(3)	9445(2)	66(1)
C(11)	-974(4)	2820(3)	8552(2)	71(1)
C(12)	3252(3)	-619(4)	4490(2)	70(1)
C(13)	1651(3)	3646(3)	6056(2)	64(1)
C(14)	-2194(3)	3114(4)	7999(2)	74(1)
C(15)	1404(4)	3875(3)	6880(2)	77(1)
C(16)	2026(4)	-696(4)	4136(3)	87(1)
C(17)	-3032(4)	2386(4)	8248(3)	81(1)
C(18)	3626(4)	-2625(3)	8433(3)	85(1)
C(19)	-4167(4)	2693(5)	7743(3)	101(1)
C(20)	1062(5)	5154(4)	6991(3)	100(1)
C(21)	4022(6)	1(6)	3780(3)	118(2)
C(22)	2249(4)	2634(4)	10026(3)	92(1)
C(23)	1601(5)	4750(4)	5337(3)	99(1)
C(24)	4206(4)	-1958(5)	5013(3)	108(2)
C(25)	2437(5)	-2582(4)	7986(4)	115(2)
C(26)	3716(6)	-1422(5)	8428(6)	185(4)
C(27)	-2498(5)	4127(4)	7241(3)	99(1)
C(28)	1270(6)	5992(4)	5473(4)	122(2)
C(29)	-4459(5)	3676(6)	7003(4)	114(2)
C(30)	-3640(6)	4407(6)	6733(3)	117(2)
C(31)	993(5)	6200(4)	6291(4)	117(2)
C(32)	3569(5)	2019(9)	9668(4)	166(3)
C(33)	3122(9)	-2792(8)	9452(4)	175(3)
C(34)	4777(7)	-3900(6)	8635(6)	191(4)
C(35)	2062(8)	2182(9)	10931(3)	168(3)
C(36)	2001(11)	4166(7)	9741(8)	256(7)
O(1)	2958(2)	880(2)	7976(2)	79(1)
O(2)	150(3)	-1343(2)	7599(2)	82(1)
O(3)	1756(3)	-785(2)	6026(2)	88(1)
O(4)	2812(2)	343(2)	5044(1)	68(1)
O(5)	1819(3)	406(3)	9873(2)	96(1)
O(6)	1182(3)	2628(3)	9473(2)	94(1)

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