# DEVELOPMENT OF A TWO COMPONENT BAYLIS–HILLMAN REACTION AND STEREOSELECTIVE SYNTHESIS OF TETRASUBSTITUTED ALKENES AND DIHYDROFURAN-FUSED-SPIROOXINDOLES USING THE BAYLIS–HILLMAN ADDUCTS

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**INDIA**

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A THESIS SUBMITTED FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY**

BY

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**INDIA**

**OCTOBER 2015**

TO

BELOVED FAMILY MEMBERS

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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** and it has not been submitted elsewhere for the award of any degree or diploma or membership etc. This work is also free from plagiarism. I hereby agree that my thesis can be deposited in Shodhganga/INFLIBNET.

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**
**OCTOBER, 2015**

**G. VEERARAGHAVAIAH**

# CERTIFICATE

Certified that the work embodied in this thesis entitled "**Development of a Two Component Baylis-Hillman reaction and Stereoselective Synthesis of Tetrasubstituted Alkenes and Dihydrofuran-fused-spirooxindoles using the Baylis-Hillman Adducts**" has been carried out by **Mr. Gorre Veeraraghavaiah** 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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*Veeraraghavaiah*

# ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AcOH | acetic acid |
| $Ac_2O$ | acetic anhydride |
| aq. | aqueous |
| Ar | aryl |
| BH | Baylis-Hillman |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BINOL | 1, 1’-bi-2-naphthol |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bu or *n*-Bu | *n*-butyl |
| *s*-Bu | *sec*-butyl |
| $^t$Bu or *t*-Bu | *tert*-butyl |
| cat. | catalytic |
| Cbz | benzyloxycarbonyl |
| CDK | cyclin-dependent kinase |
| Conc. | concentrated |
| COD | 1,5-cyclooctadiene |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| CPME | cyclopentyl methyl ether |
| Cy | cyclohexyl |
| DABCO | 1,4-diazabicyclo(2.2.2)octane |

| | |
|---|---|
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo(5.4.0)undec-7-ene |
| DCB | dichlorobenzene |
| DCC | dicyclohexylcarbodiimide |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| *de* | diastereomeric excess |
| DEAD | diethyl azodicarboxylate |
| DIAD | diisopropyl azodicarboxylate |
| DIBAL-H | diisobutylaluminium hydride |
| DMA | *N,N*-dimethylacetamide |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | dimethylaminopyridine |
| DMF | *N,N*-dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| *dr* | diastereomeric ratio |
| DYKAT | dynamic kinetic asymmetric transformation |
| *ee* | enantiomeric excess |
| Eq. | equation |

| | |
|---|---|
| eq. or equiv. | equivalent(s) |
| Et | ethyl |
| EWG | electron withdrawing group |
| Hex | hexyl |
| *n*-Hept | *n*-heptyl |
| HMPA | hexamethylphosphoramide |
| HMT | hexamethylenetetramine |
| 3-HQD | 3-hydroxyquinuclidine |
| EVK | ethyl vinyl ketone |
| *β*-ICD | *β*-isocupreidine |
| Im | imidazole |
| LAH | lithium aluminum hydride |
| LHMDS | lithium hexamethyldisilazide |
| LDA | lithium di-isopropyl amide |
| Me | methyl |
| Mp | melting point |
| MS | molecular seives |
| MVK | methyl vinyl ketone |
| MW | microwave |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |
| NHC | *N*-heterocyclic carbene |
| NMP | *N*-methyl 2-pyrrolidinone |

| | |
|---|---|
| NMM | *N*-methylmorpholine |
| NOESY | nuclear overhauser effect spectroscopy |
| Np | naphthyl |
| Nu | nucleophile |
| ORTEP | Oak Ridge Thermal Ellipsoid Plot |
| PEG | poly ethyleneglycol |
| *n*-Pent | *n*-pentyl |
| PG | protecting group |
| Ph | phenyl |
| PPTS | pyridinium *p*-toluenesulfonate |
| 4-PPY | 4-pyrrolidinopyridine |
| $^{i}$Pr | *iso*-propyl |
| Pr | propyl |
| PTA | 1,3,5-triaza-7-phosphaadamantane |
| PTSA | *p*-toluenesulfonic acid |
| RC | Rauhut-Currier |
| ref. | reference |
| rt or RT | room temperature |
| SDS | sodium dodecyl sulfate |
| TBAB | tetrabutylammonium bromide |
| TBAF | tetrabutylammonium fluoride |
| TBAHS | tetrabutylammonium hydrogensulfate |
| TBAI | tetrabutylammonium iodide |

| | |
|---|---|
| TBDMS/TBS | *tert*-butyldimethylsilyl |
| TBDMSOTf | tert-butyldimethylsilyl trifluoromethanesulfonate |
| TBDPS | tert-butyldiphenylsilyl |
| TBHP | *tert*-butyl hydroperoxide |
| TBME | *tert*-butyl methyl ether |
| Tf | trifluoromethanesulfonyl |
| TfOH | trifluoromethanesulfonic acid |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| TFSA | trifluoromethanesulfonic acid |
| THF | tetrahydrofuran |
| TMEDA | tetramethylethylenediamine |
| TMG | 1,1,3,3-tetramethylguanidine |
| TMPDA | 1,1,3,3-tetramethylpropane-1,3-diamine |
| TMS | trimethylsilyl |
| TMSI | 1-(trimethylsilyl)imidazole |
| TMSOTf | trimethylsilyltrifluoromethanesulfonate |
| Tol | *p*-tolyl |
| Ts | *p*-toluenesulfonyl |
| *p*-TsOH | *p*-toluenesulfonic acid |

# ABSTRACT

In a broad sense, the chemical synthesis is nothing but a process involving bond formation and/or bond cleavage. Organic synthesis essentially deals with construction of C—C bond, C—X (X = H, heteroatom) bonds and/or their cleavage. Among these, carbon–carbon bond formation is the most fundamental process in organic chemistry to create molecular complexity and diversity. Baylis-Hillman reaction is one such three component atom economy C—C bond forming reaction involving the coupling of α-position of activated alkene with electrophile in the presence of a catalyst to provide diverse classes of densely functionalized molecules. The Baylis-Hillman adducts, containing a minimum of three functional groups in close proximity, have been employed successfully in various organic transformation methodologies and also in the synthesis of carbocyclic & heterocyclic molecules of medicinal importance. Our research group has been working on this fascinating reaction for the last three decades on various aspects of this reaction and contributed significantly for the growth of the reaction.

This thesis deals with the development of two component Baylis-Hillman reaction and synthesis of stereoselective tetrasubstituted alkenes (Baylis-Hillman bromides) and their application to [3+2]-annulation strategies/cycloaddition reaction 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 important developments of BH-reaction with respect to all the three essential components along with its asymmetric version and also describes briefly the applications of the Baylis-Hillman bromides in organic synthesis.

The second chapter deals with the objectives, results & discussion. Although BH reaction has seen significant development in many directions, it is surprising to note that two component (containing electrophile and reaction initiation site components) BH reaction, yet another aspect of this reaction, was not received adequate attention during all these years. Even though BH bromides derived from aldehydes as electrophiles have received considerable attention from chemists, the bromides of the BH adducts obtained from α–keto esters, as electrophiles, did not receive any attention from chemists. We have therefore, in continuation of our ongoing research program on BH reaction, undertaken this thesis work with the following key objectives.

1) To develop a facile two component Baylis-Hillman reaction using substrates containing less reactive components, ketones, as electrophile component and nitrogen of pyridine/isoquinoline as a promoter for coupling with alkyl vinyl ketones as activated alkene component. This process would, in principle, result in the development of simple protocol for synthesis of indolizine derivatives.
2) To develop a convenient and facile protocol, from BH adducts derived from α–keto esters via coupling with alkyl acrylates/acrylonitrile, for obtaining stereodefined tetrasubstituted alkenes containing allylbromide functionality.
3) To study the possible applications of the above mentioned tetrasubstituted alkenes (containing allyl bromide functionality) as a source of dipoles for reaction with isatins as dipolarophiles with a view to develop a facile [3+2] annulation strategy for stereoselective synthesis of dihydrofuran-fused-spirooxindoles containing ester group or nitrile functionality.

## Ketones as electrophiles in two component Baylis-Hillman reaction: A facile one-pot synthesis of substituted indolizines

Several years ago our research group has reported for the first time, that the coupling of pyridine-2-carboxaldehyde with alkyl vinyl ketones under the influence of TMSOTf, provided a facile methodology for obtaining indolizine derivatives. In this strategy, the pyridine nitrogen acts as initiator site and induces the reaction while the aldehyde group acts as an electrophile.

At that time our research group felt that ketones may not be suitable electrophile components in the above strategy as it was generally understood that ketones are less reactive electrophiles in BH reaction. However recently we felt that this is not that absurd to examine the potential of ketones as electrophiles in these reactions on the assumption that intramlecular reactions are normally faster than the corresponding intermolecular reactions. Accordingly we have developed a facile coupling of 2-alkanoyl(aroyl) pyridines (**80a-f**) with representative alkyl vinyl ketones (**81a**, **b**) under the influence of TMSOTf to provide indoziline derivatives **82a-j** in 23–62% yields along with the side products **83a-j** in 0–46% yields (Eq. 37, Table 2). With a view to further expand the scope of this strategy we also used isoquinolin-1-yl phenyl ketone (**84**) for coupling with MVK (**81a**) which furnished 12-acetyl-1-aza-11-phenyltricyclo-[8.3.0.0$^{4,9}$]trideca-2,4(9),5,7,10,12-hexaene (**85**) in 55% yield (Eq. 38). Next we have directed our efforts towards understanding the application of cyclic activated alkenes such as cyclohex-2-enone (**86a**) & 5,5-dimethylcyclohex-2-enone (**86b**) in this methodology under similar conditions to provide indolizine derivatives **87a-f** in 10–60% yields (Table 3). Similar coupling of isoquinolin-1-yl phenyl ketone (**84**) with cyclohex-2-enone (**86a**) also gave the desired product 2-aza-14-oxo-12-phenyltetracyclo[11.4.0.$0^{2,11}$,$0^{5,10}$]-heptdeca-1(13),3,5-(10),6,8,11-hexaene (**88**) in 45% yield (Eq. 39). This strategy clearly demonstrates the applications of certain ketones as suitable electrophiles in BH reaction and also opens up the ground for design of appropriate substrates for two component Baylis-Hillman reactions.

## A facile and stereoselective synthesis of tetrasubstituted alkenes from Baylis-Hillman alcohols

Tetrasubstituted alkene framework with defined stereochemistry occupies a special place in organic and medicinal chemistry because of the presence of such moiety in various biologically active molecules [tamoxifen, panomifene], natural products. Due to their congested nature and the challenges involved in their synthesis, development of facile and convenient strategies for obtaining tetrasubstituted alkenes with defined stereochemistry has been and continuous to be a facinating and attractive problem in synthetic chemistry.

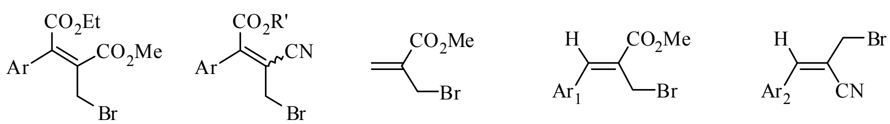
Based on the importance of synthesis of tetrasubstituted alkenes with defined stereochemistry and also based on the bromination of BH alcohols derived from aldehydes it occured to us that the BH alcohols, obtained from α–keto esters as electrophiles and acrylates/acrylonitrile as activated alkenes should, in principle, provide tetrasubstituted alkenes having allyl bromide fuctionality. If it is so, what could be its stereochemistry?

Accordingly, we have developed a facile methodology for stereoselective synthesis of tetrasubstituted alkenes via the treatment of Baylis-Hillman alcohols obtained from the reaction of methyl acrylate and α-ketoseters with NBS/DMS reagent system. The bromination of BH-alcohol (**91a**) was tried under different conditions (for optimization of reaction condition see Table 4). The best results were obtained when the methyl 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanoate **(91a)** was treated with NBS(2.0 eq.)/DMS(4.0 eq.) providing the desired allylic bromide (**93a**) containing tetrasubstituted olefin double bond with (*E*)-configuration [(*E*)-4-ethyl 1-methyl 2-(bromomethyl)-3-phenyl-maleate (**93a**)] at room temperature for 12 h in 94% yield (see entry 5, Table 4). To understand the generality of this strategy we have subjected BH alcohols (**91a–h**), to optimized reaction condition to provide tetrasubstituted alkenes, 4-ethyl 1-methyl 2-bromomethyl-3-arylmaleates (**93a–h**) with *E*-selectivity exclusively in excellent yields (Table 7). We have then extended this methodology for aliphatic congener, methyl 3-ethoxycarbonyl-3-hydroxy-2-methylenebutanoate (**91i**), which gave the resulting allyl bromide **93i** was obtained with (*E*)-stereoselectivity in 84% yield (Eq. 46).

Similar treatment of Baylis-Hillman alcohols **105a-e** obtained via the reaction of acrylonitile and α-keto esters in the presence of NBS/DMS as reagent system provided the resulting allyl bromides as a separable (2:1) mixtures of (*E*)**-106a–e** and (*Z*)**-106a–e** in good yields (Table 9). We have then extended this methodology for aliphatic congener **105f**. Thus the bromination of BH alcohol **105f** gave two allyl bromides (*E*)-**106f**/(*Z*)-**106f** in 81% overall yield as a separable (3:1) mixture of (*E*)-**106f** and (*Z*)-**106f** (Eq. 48). Appropriate reaction mechanisms for formation of tetrasubstituted alkenes with exclusively (*E*)-stereochemistry (BH alcohols derived from α-keto esters and methyl acrylate) in ester case (Scheme 41) and *E*/*Z*-isomeric mixture (BH alcohols derived from α-keto esters and acrylonitrile) in nitrile case (Scheme 47) were provided.

## Application of tetrasubstituted alkenes (allyl bromides) obtained from BH-adducts in [3+2] annulation strategy: Stereoselective synthesis of dihydrofuran-fused-spirooxindoles

The 1,3-dipolar cycloaddition reactions or [3+2] annulation strategies are fundamentally important methods for building five membered ring frameworks. Recently, our research group has reported a facile steric factors directed synthesis of spiroepoxy and spirodihydrofuran oxindoles via [3+2] cycloaddition reaction of BH bromides **121–123** (as 1,3-dipoles) and isatins (as dipolarophiles).



**93** **(*E*/*Z*)-106** **121** **(*Z*)-122** **(*E*)-123**

This study clearly demonstrated the influence of steric factors arising from three BH bromides **121**, **122**, and **123** in [3+2] annulation reactions with isatins as dipolarophiles. This study also puts before us a big question, that is, what would be the possible application of tetrasubstituted allyl bromides (**93** & **106**) as dipoles and isatin derivatives as dipolarophiles in [3+2] annulation reactions.

i) **Application of tetrasubstituted alkenes of ester derivative as a source of dipole for [3+2] annulation with isatin derivatives**

We have undertaken the study of [3+2] annulation strategy between the diploes generated from BH bromides [tetrasubstituted alkenes described in the previous objective of this section] and isatin derivatives as dipolarophiles. Thus we examined the reaction of the allyl bromide [4-ethyl 1-methyl 2-bromomethyl-3-phenylmaleate (**93a**)] with *N*-methylisatin (**124a**) under various conditions (for optimization see Table 11). The best result was obtained when the bromide (**93a**) (1.5 mmol) was treated with *N*-

methylisatin (**124a**) (1.0 mmol) in DMF (3.0 mL) in the presence of $Me_2S$ (2.0 mmol) and $Cs_2CO_3$ (2.0 mmol) at room temperature for 24 h, thus providing the resulting spirooxindole containing dihydrofuran ring, [3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (**125a**), in 86% isolated yield. To understand generality of this methodology we have performed the reaction between various substituted isatins **124a-g** and different BH bromides **93a-f**. The resulting dihydrofuran-fused-spirooxindoles (±)-**125a-l** were obtained in 72–86% yields and high diastereoselectivity (Table 13). A plausible mechanism has been provided for understanding of the stereochemical course of the reaction (Scheme 49).

ii) **Application of (*E*) and (*Z*) tetrasubstituted alkenes of nitrile derivative as a source of dipoles for [3+2] annulation with isatin derivatives**

After developing stereoselective synthesis of dihydrofuran-fused-spirooxindoles from the tetrasubstituted alkene containing allyl bromides with ester functionality **93**, we have directed our attention to examine the application of tetrasubstituted alkene **106** containing nitrile functionality in a similar [3+2] annulation reaction with isatin derivatives **124**. Accordingly we have first selected (*E*)-ethyl 4-bromo-3-cyano-2-phenylbut-2-enoate (**106a**) as a source of 1,3-dipole and *N*-methylisatin (**124a**) as a dipolarophile (Eq. 58). The resulting dihydrofuran-fused-spirooxindoles (**127a** & **127a′**) were obtained as a seperable mixture of diastereomers in 2:1 ratio.

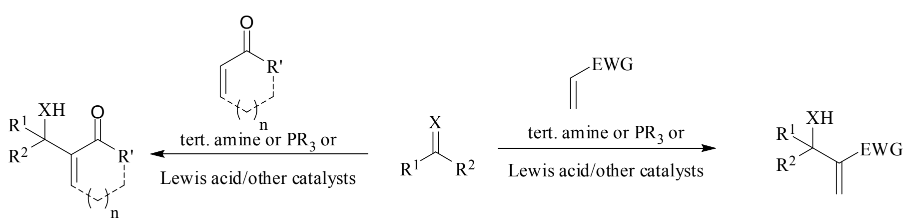
Then we have extended the same strategy to (*Z*)-allyl bromide **106a** with a view to understand the stereochemical course of the reaction (Eq. 59). In this case also the resulting dihydrofuran-fused-spirooxindoles (**127a** & **127a′**) were obtained as a seperable mixture of diastereomers in 2:1 ratio.

Thus both (*E*) and (*Z*)-allyl bromides containing tetrasubstituted alkene motif provided the same products in almost same ratio. Therefore we have subjected (*E*/*Z*)-mixture of allyl bromides **106a** (without seperation) to a similar [3+2]-annulation strategy with *N*-methylisatin (**124a**) (Eq. 60). As expected it provided a mixture of syn and anti (**127a** and **127a′**) (2:1) of dihydrofuran-fused-spirooxindoles. This would mean that both the (*E*)- and (*Z*)-isomeric bromides involve the same reaction pathway and in both cases the reaction is proceeding through the same reactive intermediate/transition state. To understand the generality of this observation we have subsequently subjected two more ally bromides **106b** & **106e** (as a mixture of *E*/*Z* isomers) to [3+2] annulation strategy with *N*-methylisatin (**124a**) (Table 14). In both the cases the products were obtained as a seperable mixture of (ratio ≈ 2:1) diastereomers. Structures and stereochemistry of the major and minor diastereomers were confirmed by single crystal X-ray diffraction data analysis (in the case of compounds **127a/a′** and **127b/b′**). A plausible mechanism has been provided for understanding of the stereochemical course of the reaction (Scheme 50).

The third chapter provides detailed experimental procedures, physical constants like boiling point, melting point, IR, $^{1}H$ & $^{13}C$ NMR, mass (LC-MS) spectral data, elemental analyses and HRMS spectral data and representative spectral copies.

# INTRODUCTION

In a broad sense, the chemical synthesis is nothing but a process involving bond formation and/or bond cleavage. Organic synthesis essentially deals with construction of C—C bond, C—X (X = H, heteroatom) bonds and/or their cleavage.[1–9] Among these, carbon–carbon bond formation is the most fundamental process in organic chemistry to create molecular complexity and diversity.[10] It is quite clear from the literature, that there are many named/unnamed C—C bond forming reactions well known and established.[9–14] To mention a few such examples: aldol reaction,[15] Diels-Alder reaction,[16] Friedel-Crafts reaction,[17] Grignard reaction,[18] Michael reaction,[19] Olefin metathesis,[20] Wittig reaction,[21] etc. were discovered and developed systematically and their applications have been well documented. The Baylis-Hillman reaction is one such C—C bond forming reaction which has grown recently from unknown patent level to the high level of popularity and utility during past three decades.[22–48]




$R^1$= alkyl, aryl, heteroaryl etc.
$R^2$= H, COOR, alkyl, etc.; R' = $CH_2$, O, NH, N–R, etc.; n = 0, 1, 2,...
X= O, NCOOR, NTs, $NSO_2Ph$ etc.
EWG= electron withdrawing group: COR, CHO, CN, COOR, $PO(OEt)_2$, SOPh, $SO_2Ph$, $SO_3Ph$ etc.

**Scheme 1**

Baylis-Hillman (BH) reaction [also known as the Morita-Baylis-Hillman (MBH) reaction] is an atom economy, three component process involving C—C bond formation. Three components are i) activated alkene, ii) electrophile iii) catalyst/catalytic system. The carbon–carbon bond is constructed via the coupling between α–position of activated alkene with electrophile using a catalyst to provide interesting classes of molecules containing proximal functional groups

(Scheme 1).[22–48] The resulting proximal multifunctional molecules are generally known as the Baylis-Hillman adducts. The main and important features of this C—C bond forming reaction are: i) it is an atom-economy-three component [activated alkenes (alkynes), electrophiles & catalysts] organocatalytic reaction, ii) it creates a chiral center, iii) understanding its mechanistic aspects is yet another challenge due to variation of parameters in performing this reaction, iv) it provides proximal densely functionalized products of high synthetic potential, v) it offers opportunities to develop its intramolecular version. These are pictorially represented in Figure 1.

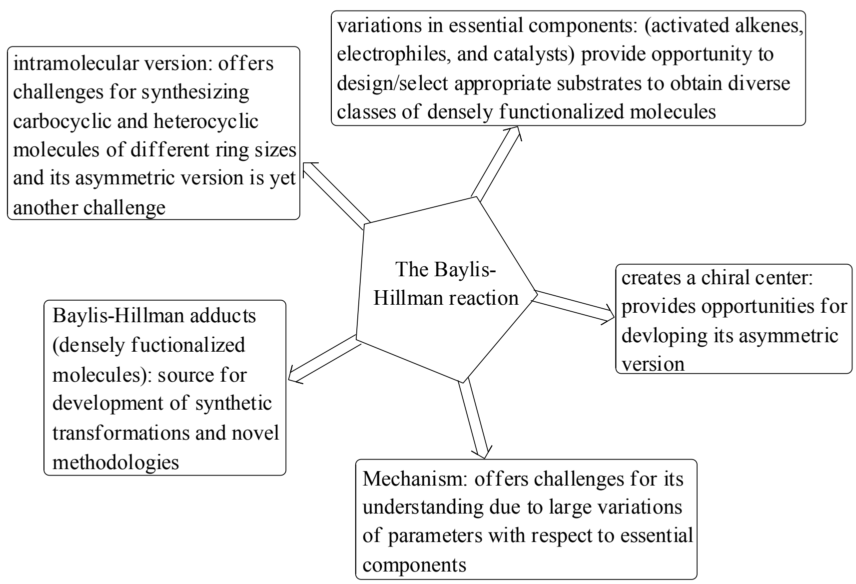



**Figure 1.** Schematic presentation of opportunities offered by Baylis-Hillman adducts

Several major[24-32] and mini[33-43] reviews and thousands of research papers published on this fascinating reaction during the past three decades are in fact testimony for its growing popularity and continuous growth.

Since this thesis deals with the development of two component Baylis-Hillman reaction and synthesis of stereospecific tetrasubstituted alkenes (Baylis-Hillman bromides) and their application in [3+2]-annulation strategies/cycloaddition reaction, this chapter presents the important developments of BH-reaction with respect to all the three essential components along with its asymmetric version and also describes briefly the applications of the Baylis-Hillman bromides in organic synthesis.

Various essential components, that is, activated alkenes, electrophiles & catalysts that have been frequently utilized in BH reaction to produce the corresponding adducts containing a minimum of three functional groups in close proximity are listed in Figures 2–4.[25, 26, 29, 31, 32] It is quite clear from the literature survey that umpteen number of activated alkenes and electrophiles have been used successfully in the Baylis-Hillman reaction that led to development of this reaction. In this section applications of representative and important activated alkenes, electrophiles and catalysts/additives have been presented.

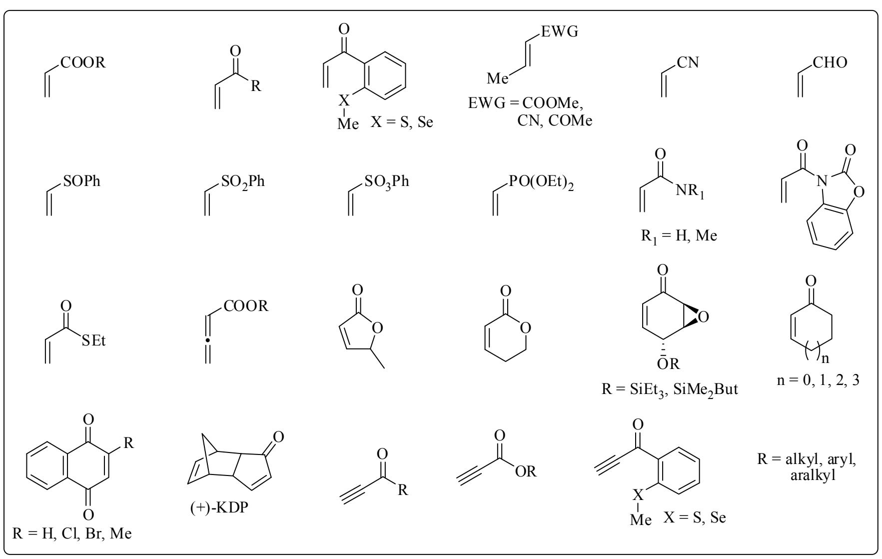
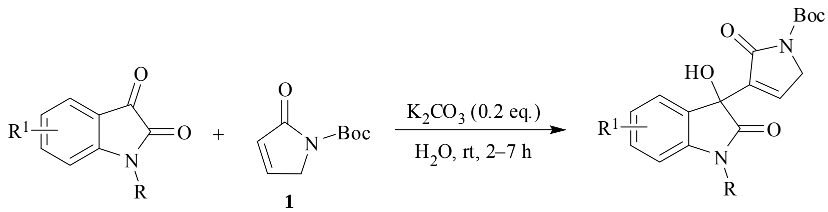



**Figure 2.** Representative activated alkenes used in BH reaction[25, 26, 29, 31, 32]

Zhao and coworkers have successfully utilized the *N*-Boc-3-pyrrolin-2-one (**1**) as an activated alkene for coupling with isatins in the presence of $K_2CO_3$ to provide the resulting adducts in high yields (Eq. 1).[49]




(Eq. 1)

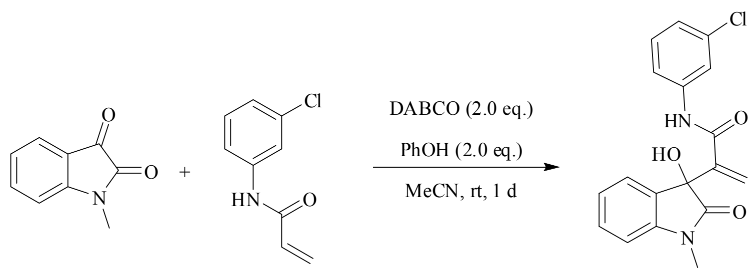
1

R = H, Me

$R^1$ = H, 5-F, 5-Cl, 5-Br, 5-$NO_2$, 5-OMe, 5-Me, 4-Br, 6-Br, 7-Br

62–97%

Bharadwaj and coworkers have reported the application of *N*-phenyacrylamide (**2**) as an activated alkene in the BH coupling with isatins under the influence of DABCO and phenol. Eq. 2 presents one such example.[50]

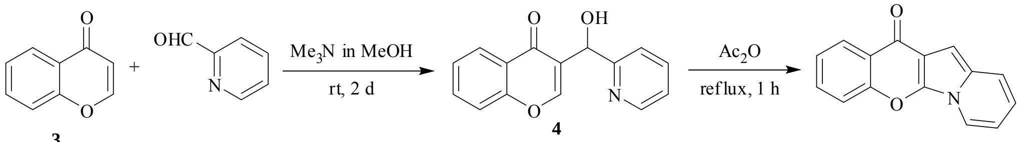



(Eq. 2)

2

94%

Our research group have meticulously used 1-benzopyran-4(4*H*)-one (**3**) as an activated alkene in Baylis-Hillman reaction with isatin-derivatives and aldehydes under the influence of methanolic trimethylamine. One such BH coupling product **4** derived from 1-benzopyran-4(4*H*)-one (**3**) and pyridine-2-carboxaldehyde has been conveniently converted into a highly important indolizine-fused-chromone derivative as shown in Scheme 2.[51]




3

4

84%

71%

**Scheme 2**

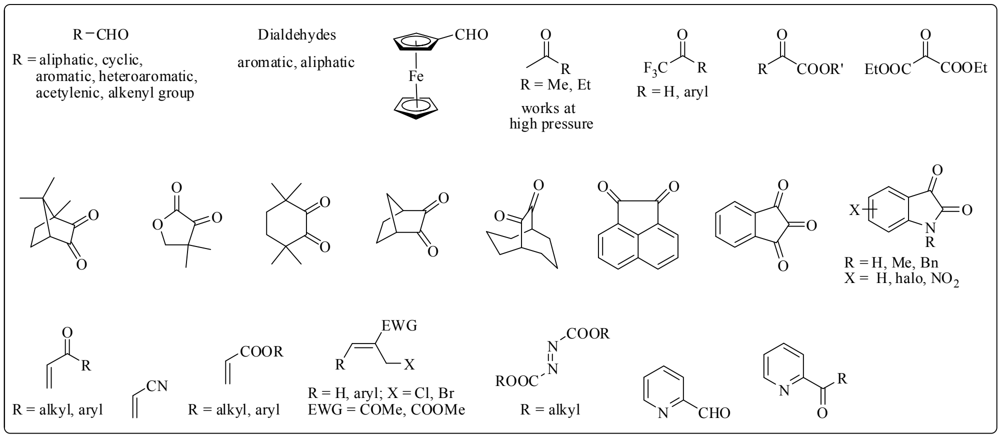
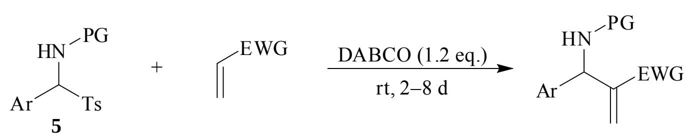



**Figure 3.** Representative electrophiles used in BH reaction[25, 26, 29, 31, 32]

A fascinating application of α-amidoaryl-*p*-tosylsulfones **5** as electrophiles in BH coupling with acrylates and acrylonitriles as activated alkenes was reported by Gajda and Gajda (Eq. 3).[52]

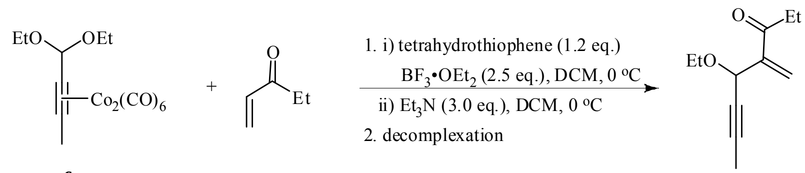



(Eq. 3)

PG = Boc, Cbz
EWG = $CO_2Me$, $CO_2Et$, CN
Ar = Ph, 4-$MeOC_6H_4$, 4-$BrC_6H_4$, 2-$MeOC_6H_4$, 2-$ClC_6H_4$, 2-furyl, 3-pyridyl, 1-Np

51–79 %

Application of dicobalthexacarbonyl coordinated acetylenic acetals as electrophiles for Baylis-Hillman coupling with different alkyl or aryl vinyl ketones under the influence of $BF_3{\cdot}OEt_2$ and tetrahydrothiophene system has been reported by Krafft and coworkers. One such example dealing with dicobalthexacarbonyl coordinated 1,1-diethoxybut-2-yne (**6**) as electrophile and EVK as activated alkene is shown in Eq. 4.[53]

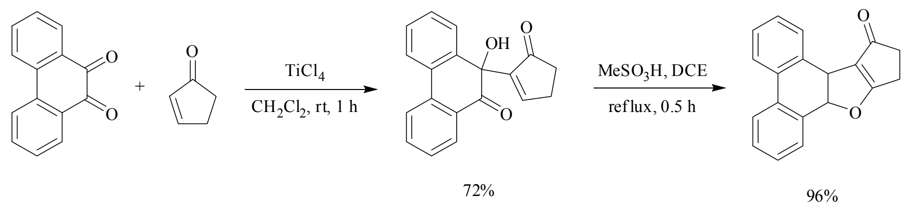



**6**

71%

(Eq. 4)

Our research group described Lewis acid mediated Baylis-Hillman reaction of cyclic 1,2-diones as electrophiles with cycloalk-2-enones as activated alkenes. The resulting BH adducts were successfully transformed into furan derivatives via methanesulfonic acid mediated cyclization. Scheme 3 represents one such example.[54]




**Scheme 3**

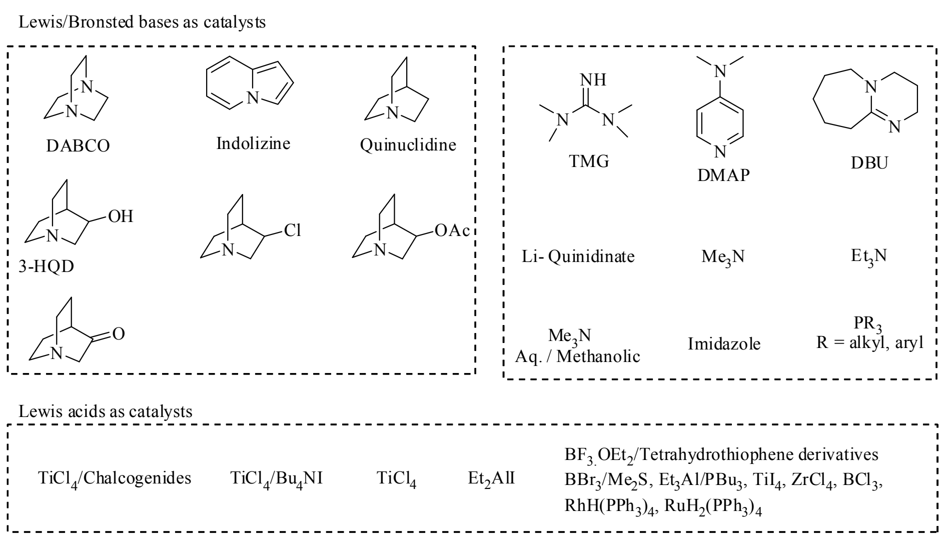
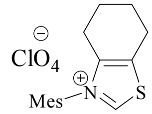
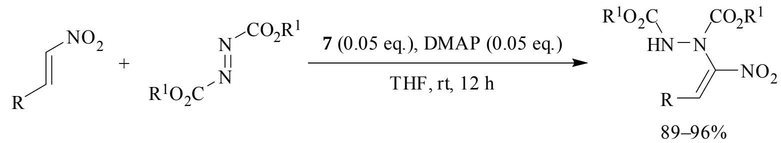



**Figure 4.** Representative catalysts/catalytic systems used in BH reaction[25, 26, 29, 31, 32]

Ye and coworkers have utilized *N*-heterocyclic carbene **7** as a catalyst for the Baylis-Hillman coupling of azodicarboxylates with β–substituted nitroalkenes (Eq. 5).[55]



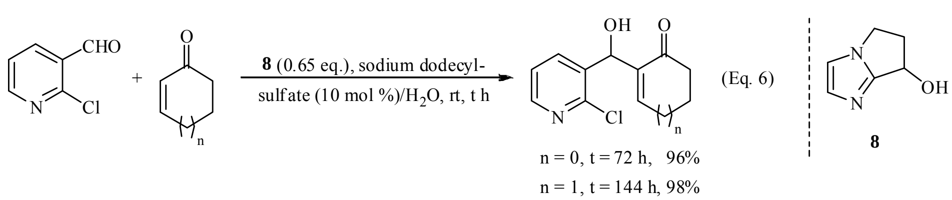
**7**



(Eq. 5)

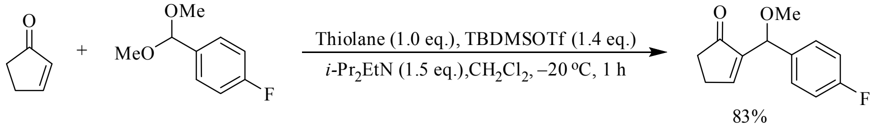
R = Ph, 4-$MeOC_6H_4$, 4-$MeC_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$, 4-$NO_2C_6H_4$,
4-$CNC_6H_4$, 3-$ClC_6H_4$, 2-$ClC_6H_4$, 2-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 2-thienyl
$R^1$ = Et, *i*-Pr, *t*-Bu

Bicyclic imidazolyl alcohol **8** was successfully utilized as a catalyst in Baylis-Hillman reaction of aromatic aldehydes with cycloalk-2-enones by Coelho and coworkers. 2-Chloro-3-pyridinecarboxaldehyde couples with cyclohex-2-enone and cyclopent-2-enone under the catalytic influence of catalyst **8** to provide the resulting adducts in high yields (Eq. 6).[56]



(Eq. 6)

An interesting thiolane/TBDMSOTf mediated BH coupling of cyclopent-2-enone with 4-fluorobenzaldehyde dimethoxy acetal was reported by Metzner and coworkers. (Eq. 7 reveals one such example).[57]



(Eq. 7)

## Asymmetric Baylis-Hillman reaction

In Baylis-Hillman reaction there is a possibility of achieving enantioselectivity if the electrophile is prochiral.[25, 26, 29, 39–43] From the existing literature it is well established that the asymmetric Baylis-Hillman reaction can be performed by using i) substrate having chirality in any one (two or all) of the three essential components (activated alkenes, electrophiles, chiral/achiral catalyst), ii) chiral additives or media, and iii) methods of resolution/deracemization of racemic BH adducts.

**i) *BH Reactions using chiral activated alkenes and/or electrophiles*:**

Applications of several chiral activated alkenes built on chiral auxiliaries have been well documented in the literature for coupling with prochiral electrophiles thus providing the resulting BH adducts in high diastereoselectivities.[25, 26, 29, 39–43] Chiral activated alkenes that gave high diastereoselectivities in BH coupling reactions with

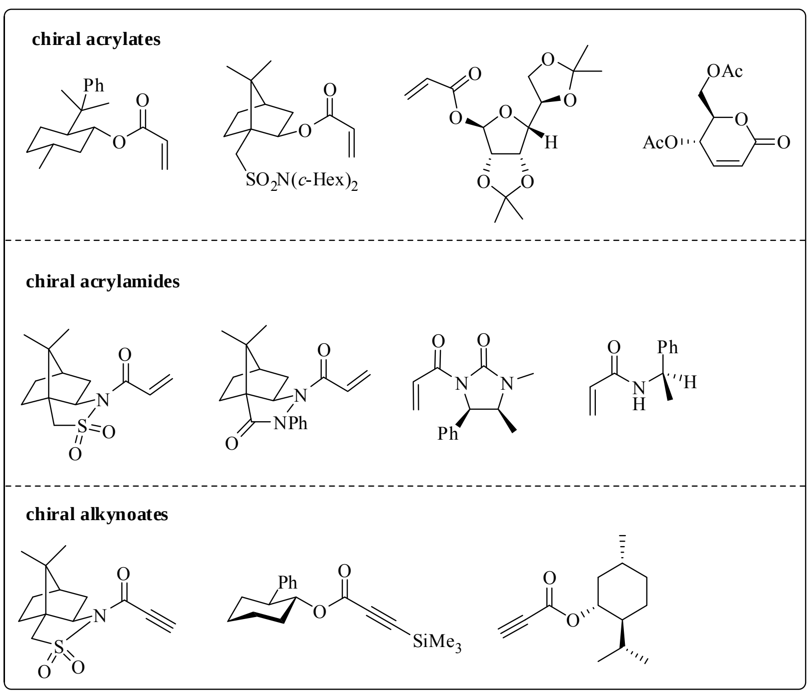
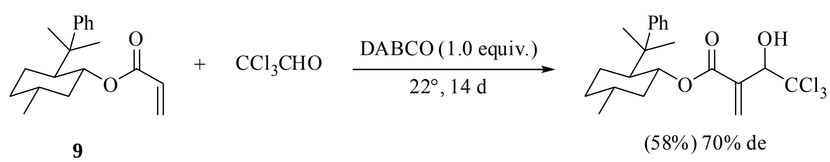



**Figure 5.** Representative chiral activated alkenes used in BH reaction[25, 26, 29, 39-43]

various electrophiles are listed in Figure 5.[25, 26, 29, 39–43] Representative examples describing the utility of selected chiral activated alkenes for coupling with electrophiles providing the resultant adducts in low to high diastereoselectivities are presented in Eqs. 8–11.

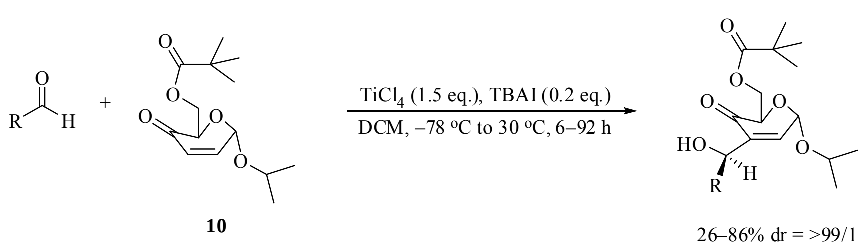
(–)-8-Phenylmenthyl acrylate (**9**) was meticulously used by Drewes and coworkers in BH coupling reaction with various electrophiles.[58] Coupling of **9** with trichloroacetaldehyde provided the BH-adduct in 70% de (Eq. 8).[58]




**9**

(Eq. 8)

The cyclic enone enuloside **10**, obtained from sugar, has been employed as a chiral activated alkene for BH coupling with aldehydes under the influence of $TiCl_4$/TBAI by Shaw and cowokers. The resulting adducts were obtained in high diastereoselectivities (Eq. 9).[59]

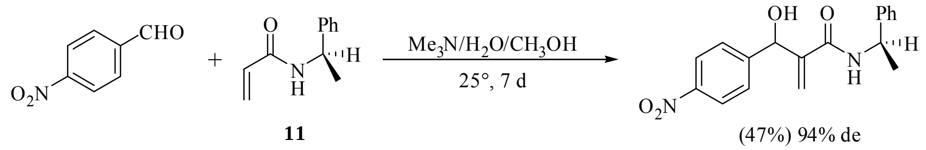



**10**

R = $C_6H_5$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-$FC_6H_4$, *n*-Pr, *n*-nonyl,

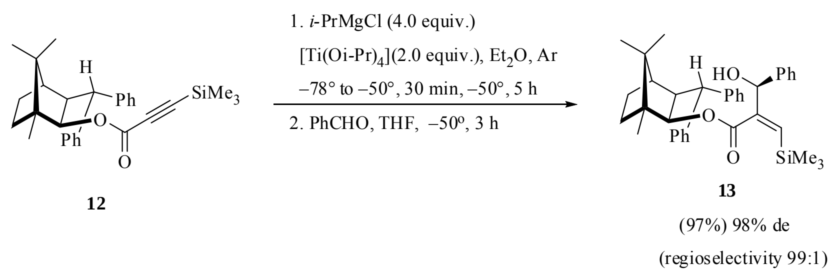
(Eq. 9)

(+)-*N*-α-Phenylethyl acrylamide (**11**), derived from α–methylbenzylamine, was employed as an activated alkene for coupling with aldehydes. In this strategy the best result of 94% diastereoselectivity was achieved in the case of coupling with 4-nitrobenzaldehyde (Eq. 10).[60, 61]



(Eq. 10)

In addition to chiral activated alkenes, chiral alkynoates have also been employed as activated alkenes in BH reaction for coupling with aldehydes. Chiral molecule **12** was one such alkynoate which on coupling with different electrophiles in presence of [Ti(O*i*-Pr)$_4$]/*i*-PrMgCl provided the β–substituted Baylis-Hillman adducts **13** in excellent geometric, regio and diastereoselectivities (See Eq. 11 for one example).[62]



(Eq. 11)

Various chiral electrophiles such as chiral aldehydes, chiral aldimines, chiral azitidine-2,3-diones, and chiral metal coordinated aldehydes/aldimines have been successfully employed for coupling with a number of activated alkenes to achieve high diastereoselectivities.[25, 26, 29, 39–43] Representative chiral electrophiles which are used in BH reaction are shown in Figure 6 and selected relevant examples are given in Eqs. 12–13.

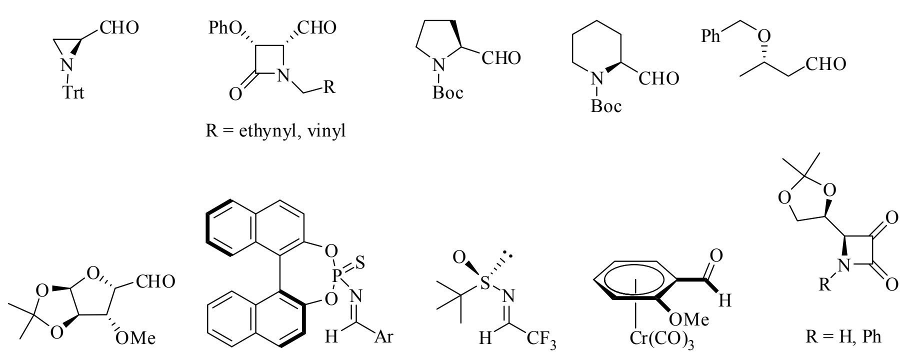
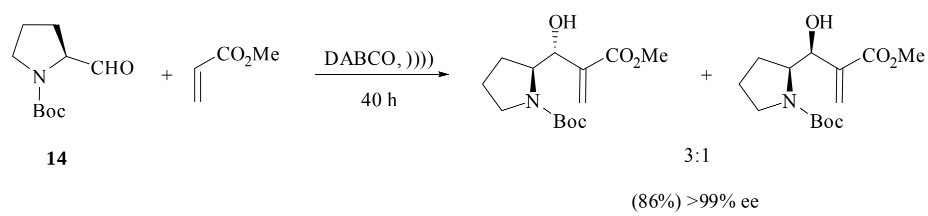


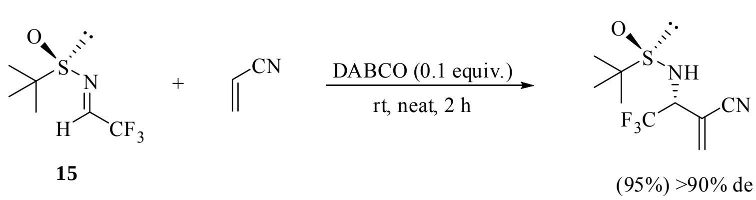
**Figure 6.** Representative chiral electrophiles used in BH reaction[25, 26, 29, 39-43]

Coelho and coworkers used *N*-Boc-prolinal (**14**) as electrophile for coupling with methyl acrylate under ultrasound reaction conditions. The resultant adduct was obtained in moderate facial (*syn*/*anti*) selectivity and excellent enantioselectivity (Eq.12).[63]



(Eq. 12)

Coupling of (*R*)-*N*-tert-butanesulfinyl-3,3,3-trifluoroacetaldimine (**15**) as a electrophile with acrylates and acrylonitrile provided the resulting BH adducts in high diastereoselectivities. One such example using acrylonitrile as an activated alkene is presented in Eq. 13.[64]



(Eq. 13)

**ii)** ***BH Reactions using chiral catalysts/ligands/additives***

Although a number of chiral activated alkenes and electrophiles have been developed and meticulously used in various asymmetric BH reactions, such efforts can not address certain problems of asymmetric BH reaction. Therefore designing of appropriate chiral catalysts or ligands or additives has become an attractive and challenging endeavor in BH chemistry to synthesize BH adducts in enantiomerically pure/enriched form. Representative catalysts (chiral amines, phosphines, ureas/thioureas), chiral ligands and additives that have been developed for asymmetric BH reactions are depicted in Figure 7.[25, 26, 29, 39–43]

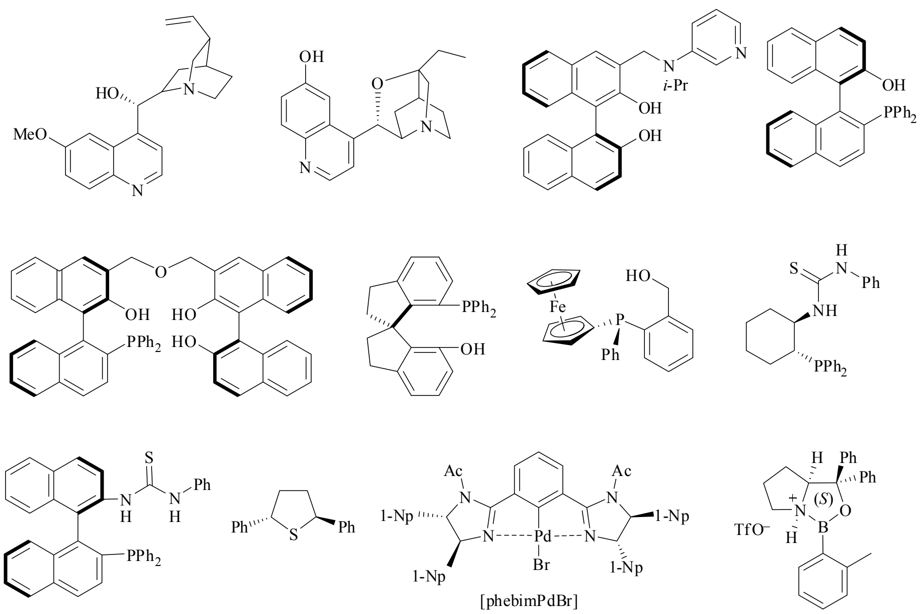
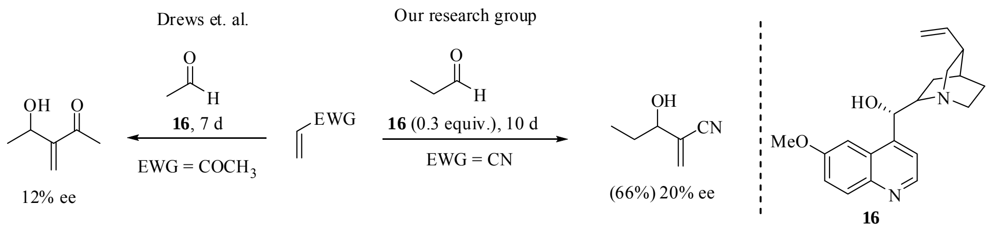


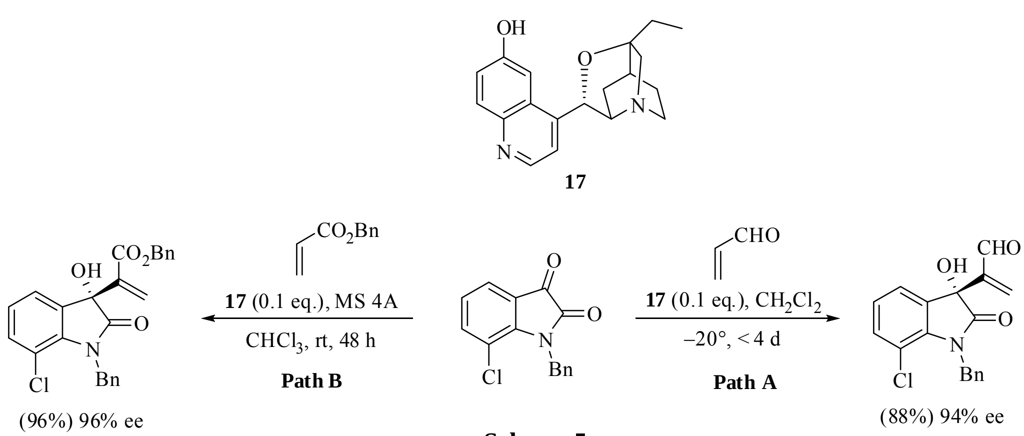
**Figure 7.** Representative chiral catalysts/ligands/additives used in BH reaction[25, 26, 29, 39-43]

Initially, Drewes[32] and our research groups[31, 65] explored the asymmetric Baylis-Hillman reactions using the naturally occurring quinidine (**16**) as a catalyst. Drewes reported an interesting coupling of MVK with acetaldehyde using quinidine (**16**) as a catalyst to provide the resulting adduct in 12% ee. Our research group reported that the reaction of acrylonitrile with propionaldehyde under the influence of quinidine (**16**) provided the resulting alcohol in 20% ee (Scheme 4).[31, 32, 65] Even though these initial enantioselectivities were low, these observations helped and showed the way towards achieving the better selectivities by designing the catalysts appropriately.



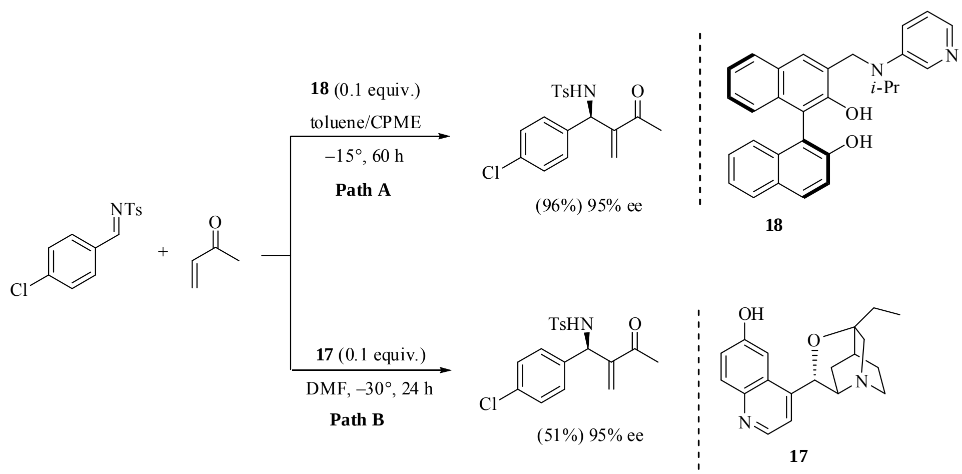

**Scheme 4**

*β*-ICD (**17**) is found to be one of the most successful chiral amine catalysts for asymmtric BH reactions.[25, 26, 29, 39–43] Zhou and coworkers have reported an asymmetric coupling of isatins with acrolein using chiral catalyst *β*-ICD (**17**) to provide the resulting adducts in high ee (Path A-Scheme 5 presents one such example).[66] Later, Lu and coworkers reported a facile reaction of isatins with acrylates as activated alkenes in presence of *β*-ICD (**17**) to afford the enantio-enriched BH adducts in good yields (Path B-Scheme 5 reveals one such example).[67]



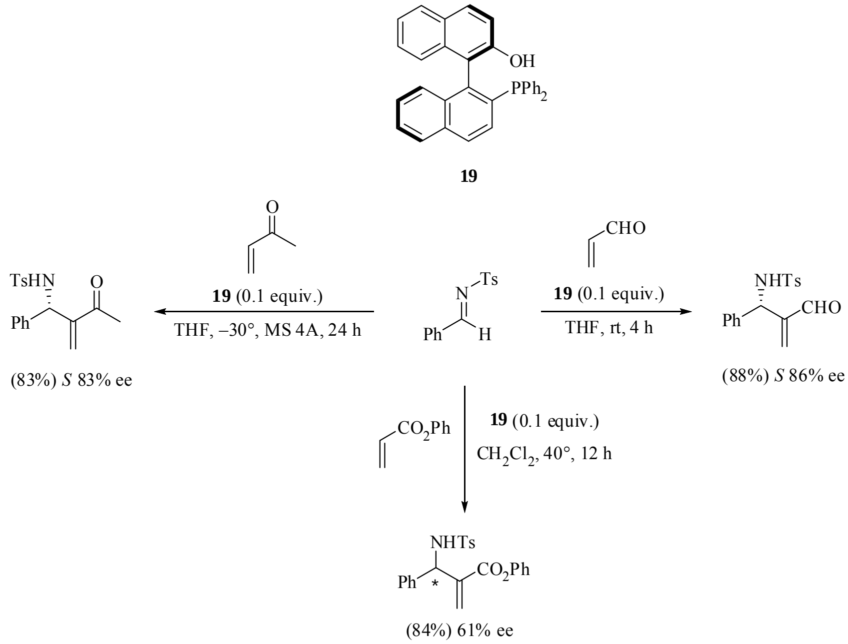

**Scheme 5**

Bifunctional-BINOL based framework **18** has been successfully employed as catalyst in BH reaction by Sasai and coworkers to provide the resulting adducts up to 95% ee (Path A-Scheme 6).[68] Shi and coworkers performed similar reaction with *β*-ICD (**17**) and found similar kind of enantioselectivities (Path B-Scheme 5). One such example in each case is given in Scheme 6.[69]



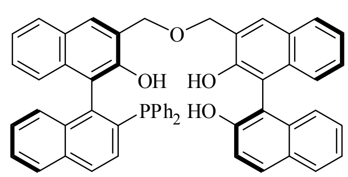

**Scheme 6**

Shi and coworkers developed the chiral phosphine **19** as a powerful catalyst and extensively used in reactions of acrylates, acrolein and alkyl vinyl ketones with aldimine derivatives in asymmetric BH reaction. Scheme 7 shows one such example in each case.[70, 71]

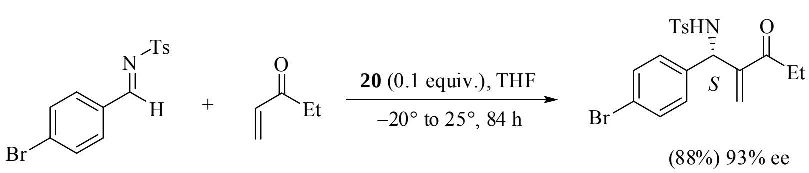


**Scheme 7**

Chiral phosphine **20** containing mutiple phenol groups was successfully used by Shi and coworkers in BH coupling of *N*-tosyl benzaldimine derivative with ethyl vinyl ketone to provide the resulting adduct in high enantioselectivity. One such example is described in Eq. 14.[72]

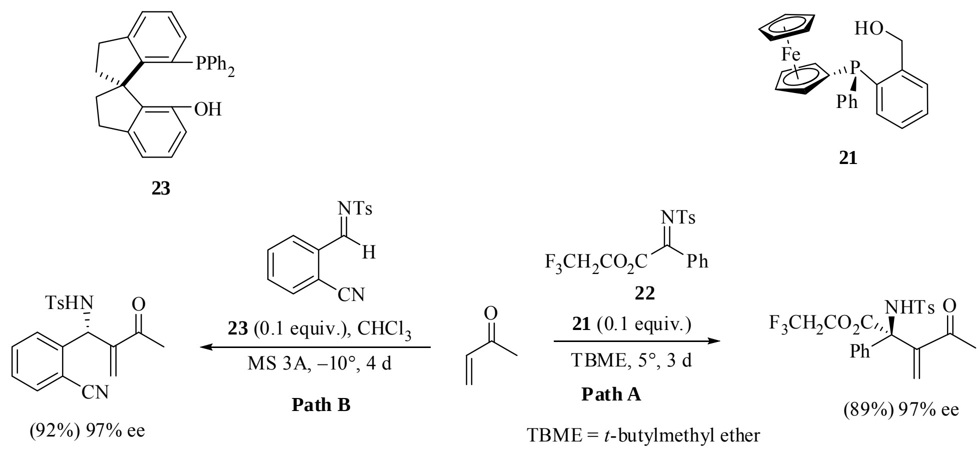


**20**



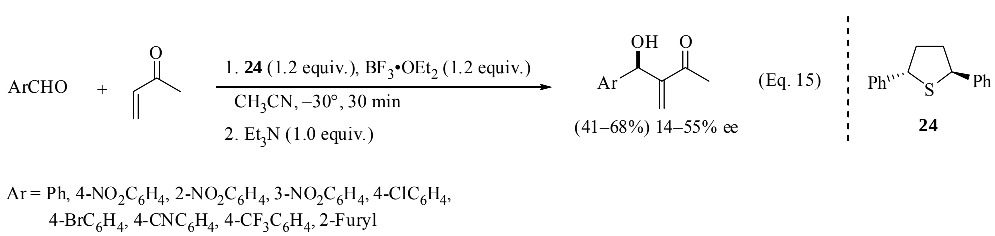
(Eq. 14)

Ferrocenyl based catalyst **21** containing P-chirogenic center was successfully used in BH reaction. Coupling of ketimine **22** with MVK under the influence of **21** gave the resulting adduct in 97% enantiopurity (Path A-Scheme 8).[73] Subsequently a novel spiro bifunctional organophosphrous derivative **23** containing phenolic OH group was developed and used as a catalyst in BH reaction (Path B-Scheme 8).[74] Scheme 8 describes one such example in each case.

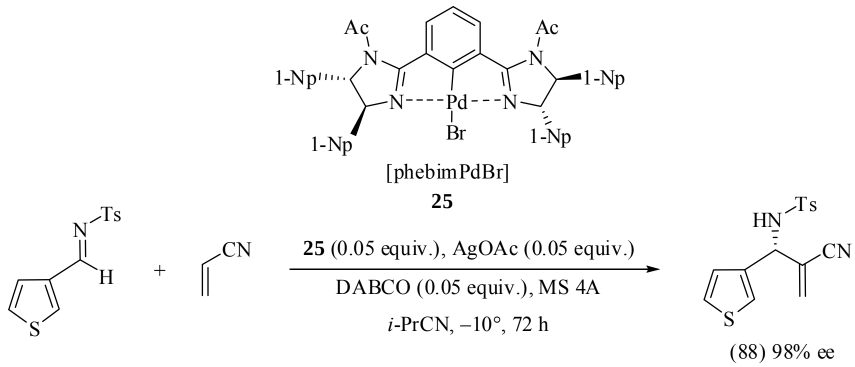



**Scheme 8**

Periasamy and coworkers have successfully used chiral thiophene **24** as a promoter for the asymmetric BH reaction of MVK with aldehydes to produce corresponding adducts up to 55% ee (Eq. 15).[75]

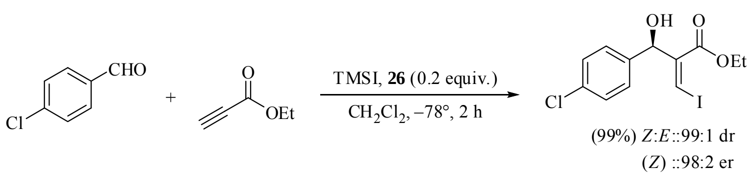



Shibata et. al. reported application of $C_2$-symmetric chiral ligand of Palladium(II) Pincer complex **25** in asymmetric BH reaction. The highest ee of 98% was achieved in the coupling of acrylonitrile with *N*-tosyl-3-thiphenecarbaldehyde imine under the influence of **25** in presence of AgOAc and DABCO (Eq. 16).[76]

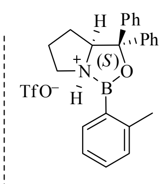



(Eq. 16)

Ryu and coworkers have described an interesting method for synthesis of (*Z*)-iodo substituted BH adducts in very high enantioselectivities using (*S*/*R*)-oxazaborolidium salt **26** as catalyst system. Thus the BH reaction of 4-chlorobenzaldehyde, ethyl propiolate and TMSI in presence of (*S*)-oxazaborolidium salt **26** gave the resultant adduct in excellent geometric and enantioselectivity (Eq. 17).[77]




(Eq. 17)

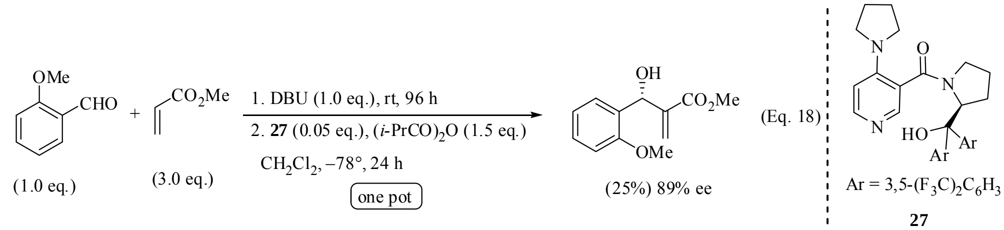



26

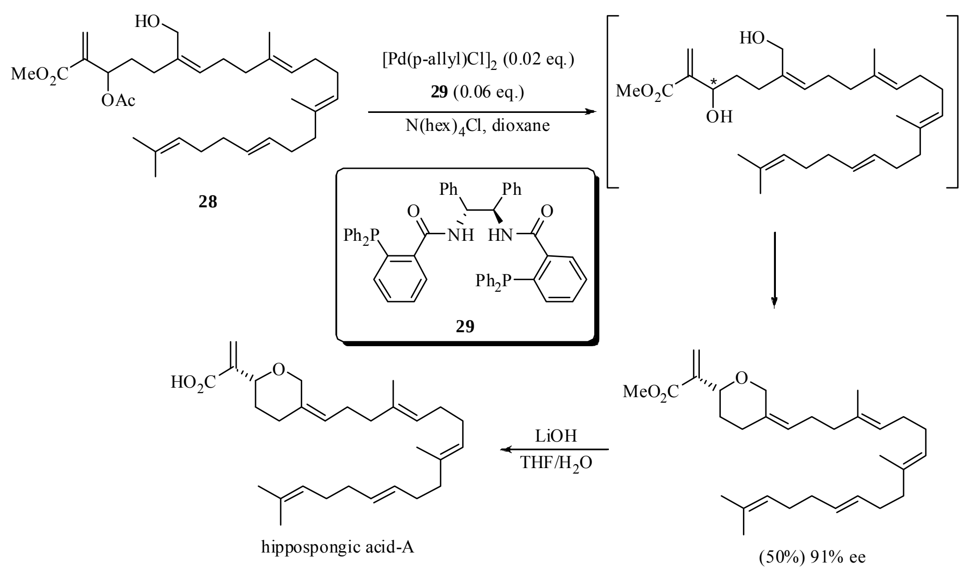
### iii) ***Resolution/deracemization of racemic BH adducts***

In addition to above mentioned strategies, protocols for resolution or deracemization of racemic BH adducts using enzymatic as well as non-enzymatic methodologies have also been developed for obtaining enantiomerically pure/enriched BH alcohols. Some such enantiomerically pure BH adducts thus obtained were successfully utilized for syntheses of various natural/bioactive compounds.[25, 26, 29] This section deals representative examples involving resolution/deracemization of racemic BH adducts/ its derivatives (Eqs. 18-21)and their applications (Scheme 9).

Connon and Dalaigh reported one pot process for BH reaction and first acylative nonenzymatic kinetic resolution of in situ generated BH adducts using 4-aminopyridine derivative **27** containing proline moiety as catalyst. One such example dealing with 2-anisaldehyde and methyl acrylate is shown in Eq. 18.[78]

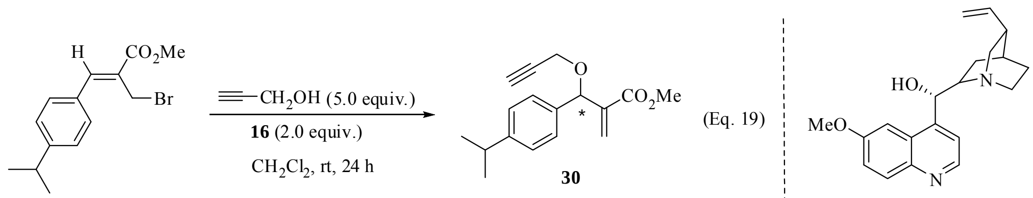


An elegant synthesis of hippospongic acid-A, a gastrulation inhibitor, was reported by Trost and coworkers using dynamic asymmetric kinetic transformation process (DYKAT) of BH acetate **28** with a palladium-catalyst in presence of chiral ligand **29** as the key step (Scheme 9).[79]



**Scheme 9**

Our research group have successfully converted the BH bromides into chiral propiolate ethers **30** using quinidine (**16**) as chiral leaving group. One such example is given in Eq. 19.[80]



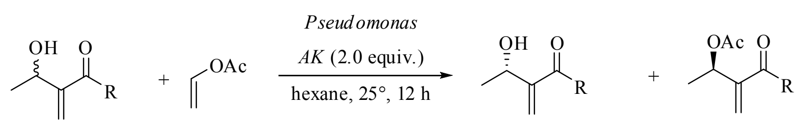

**30**

(36%) 40% de

(Eq. 19)

**16**

Burgess and Jennings reported a facile synthesis of enantiomerically pure BH adducts via the resolution of racemic BH alcohols using *Pseudomonas AK* via transesterification process with vinyl acetate. Eq. 20 presents two such examples.[81]

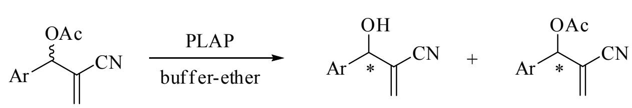



R = OMe (22%) 87% ee

R = Bu (23%) >95% ee

(Eq. 20)

Our research group have effectively utilized the pig liver acetone powder (PLAP) for asymmetric hydrolysis of racemic acetates to provide the resulting adduct in good enantioselectivity. Eq. 21 provides two such examples.[82]

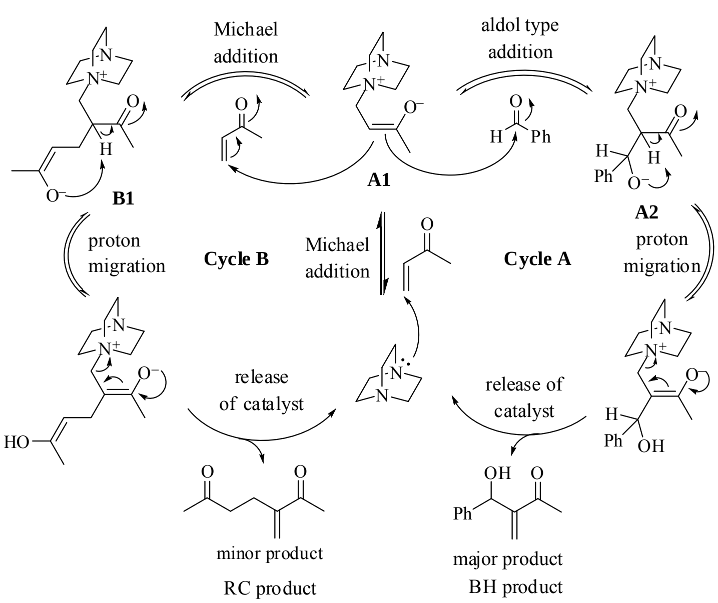



(Eq. 21)

| | | |
|---|---|---|
| Ar = Ph | (81%) 60% ee | (87%) |
| Ar = 1-Np | (87%) 86% ee | (95%) |

## Mechanism

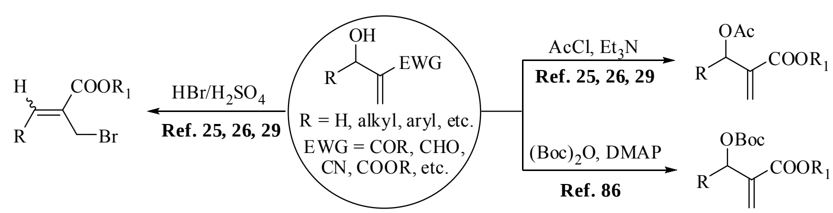
A plausible mechanism of this interesting reaction is depicted in Scheme 10 with methyl vinyl ketone (MVK) as an activated alkene, PhCHO as an electrophile, under the catalytic influence of DABCO as a model case. Two catalytic cycles **A** and **B** are, in principle, possible. Initially, DABCO makes a nucleophilic attack on MVK in Michael fashion to generate zwitterionic enolate **A1**. In **Cycle A**, the freshly in situ generated zwitterionic enolate **A1** adds to the benzaldehyde in aldol fashion to give zwitterionic enolate **A2**. Then the zwitterionic enolate **A2** might undergo proton migration. Subsequent release of catalyst might provide the required Baylis-Hillman adduct as a major product. In **Cycle B**, the newly in situ generated zwitterionic enolate **A1** adds to the another MVK molecule in Michael fashion to generate zwitterionic enolate **B1**. Subsequent proton migration and release of catalyst provide the minor product as shown in Scheme 10.[25, 26, 29, 83–85]




**Scheme 10**

## Applications of Baylis-Hillman adducts

Due to the presence of a minimum of three proximal functional groups, the Baylis-Hillman adducts represents a special class of molecules with rich chemistry and thus offers umpteen number of opportunities for developing various organic transformations.[25, 26, 29, 39–43] The Baylis-Hillman alcohols can be easily transformed into the corresponding acetates, bromides, carbonates and other derivatives (Scheme 11).[25, 26, 29, 86] Since all these derivatives possesses a minimum of three functional groups in proximity organic chemists have effectively harnessed these functionalized molecules and meticulously developed a large number of organic transformations and key methodologies. Some such methodologies have been systematically employed for the syntheses of various carbo/heterocyclic molecules of biological importance.[25, 26, 29, 39–43] These are pictorially depicted in Figures 8 & 9.




**Scheme 11**

### Applications of Baylis-Hillman alcohols and acetates: *Selected important earlier reports*

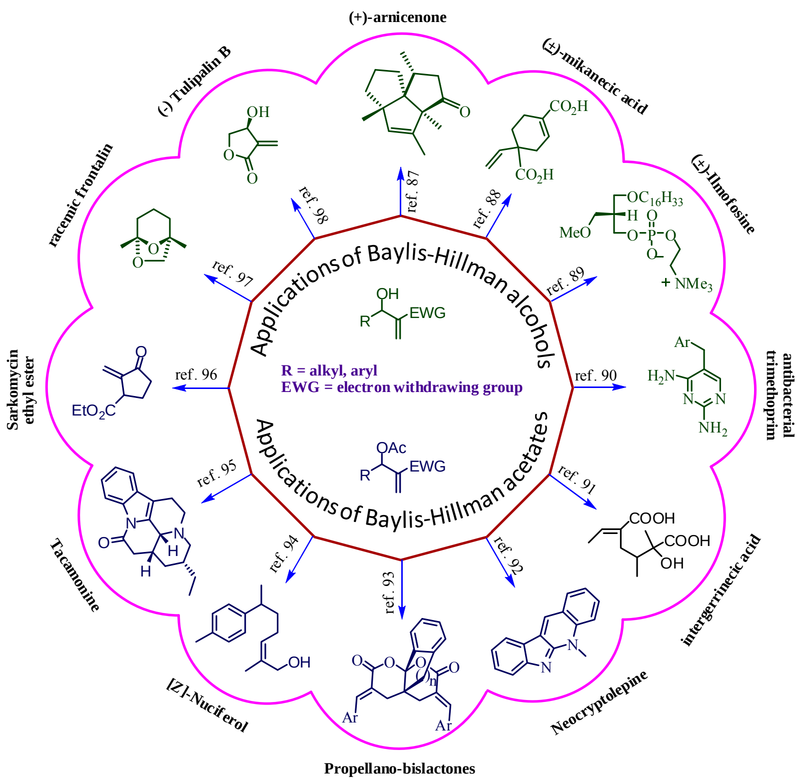



**Figure 8.** Applications of Baylis-Hillman alcohols and acetates: Selected important earlier reports

## Applications of Baylis-Hillman bromides*: Selected important earlier reports*

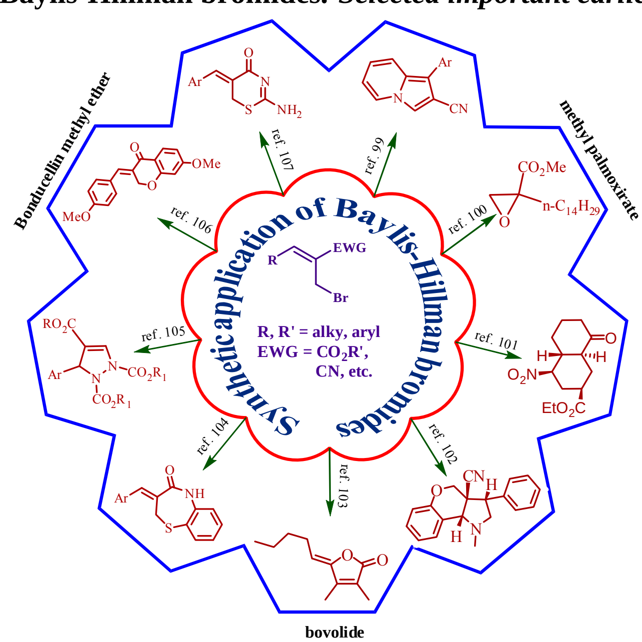
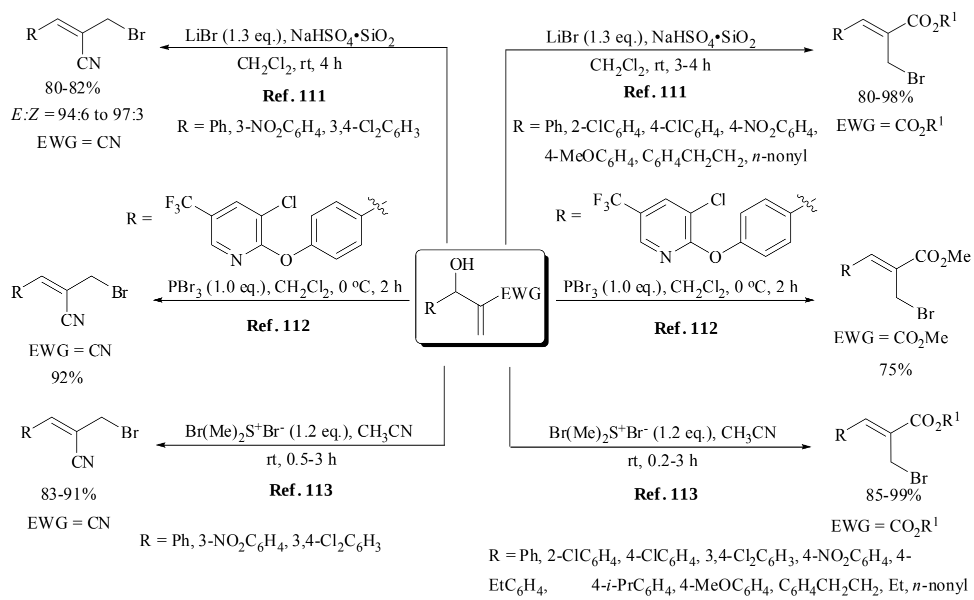



**Figure 9.** Applications of Baylis-Hillman bromides: Selected important earlier reports

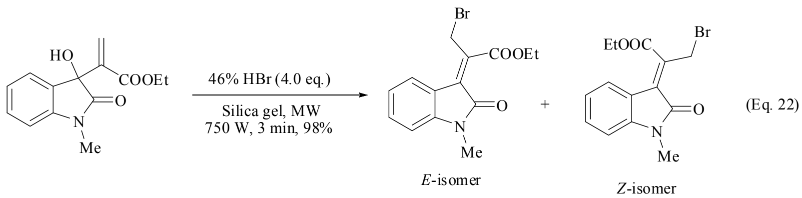
Since the part of the thesis deals with the applications of Baylis-Hillman bromides in synthesis of biologically important spirooxindoles, a few recent and relevant literature reports highlighting the importance of BH bromides and their application in synthesis of biological and medicinally important organic frameworks are presented in this section.

**General synthesis of Baylis-Hillman bromides:**

Due to synthetic importance of BH bromide a number of methods have been developed for synthesizing the allyl bromides. Baylis-Hillman alcohols were directly converted into corresponding allyl bromides using variety of reagents such as hydrogen bromide along with acids ($HBr–H_2SO_4$),[91, 108] NCS/NBS-$Me_2S$,[109] KSF/NaBr clay under microwave,[110] LiBr/$NaHSO_4$•$SiO_2$,[111] $PBr_3$,[112] $[Br(Me)_2S^+Br^–]$,[113] etc. Some such selected synthetic methodologies for preparation of Baylis-Hillman bromides are shown in Scheme 12[111–113] and Eq. 22.[114]

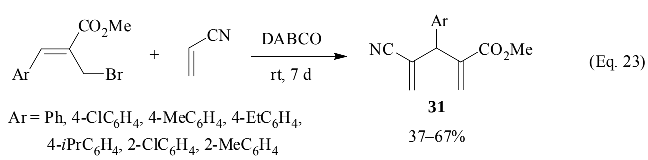


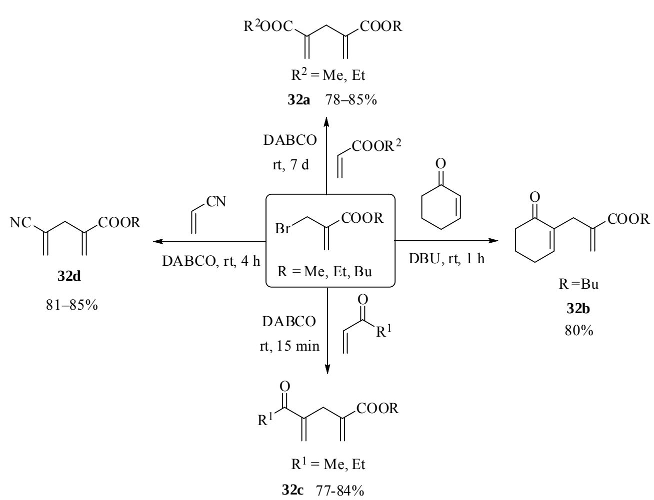

**Scheme 12**




## Applications of Baylis-Hillman bromides*:*

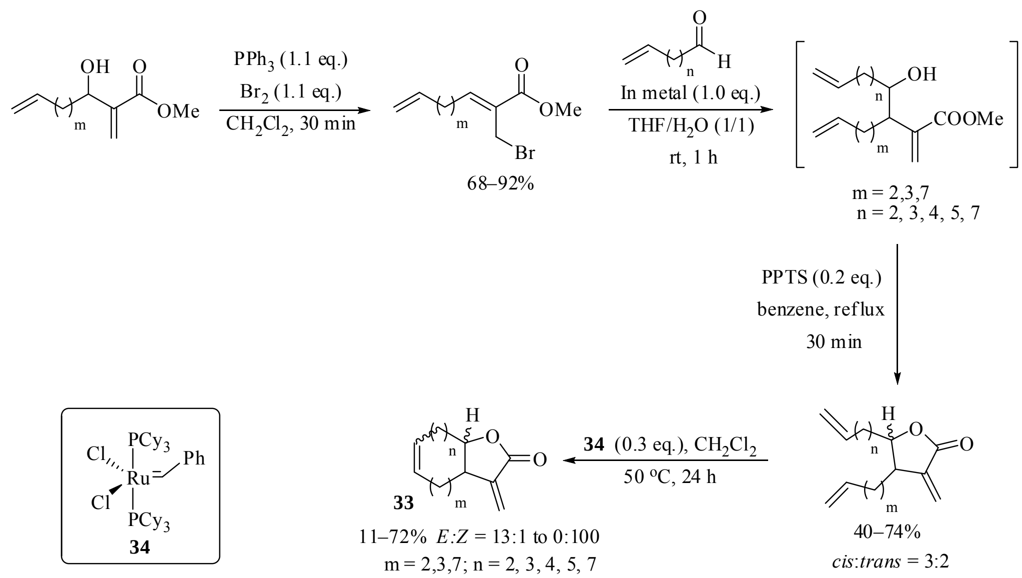
Our research group demonstrated a fascinating application of Baylis-Hillman bromides as electrophiles in BH reaction with acrylonitrile as activated alkene in the presence of DABCO to produce 3-substituted 2,4-functionalized 1,4-penatadiene derivatives **31** in encouraging yields as shown in Eq. 23.[115a] Subsequently, our research group extended this protocol to synthesize 2,4-functionalized 1,4-pentadienes **32** (without substitution at 3-position) by employing allyl bromides obtained from alkyl 3-hydroxy-2-methylenepropanoates as electrophiles for coupling with various activated alkenes (Scheme 13).[115b]



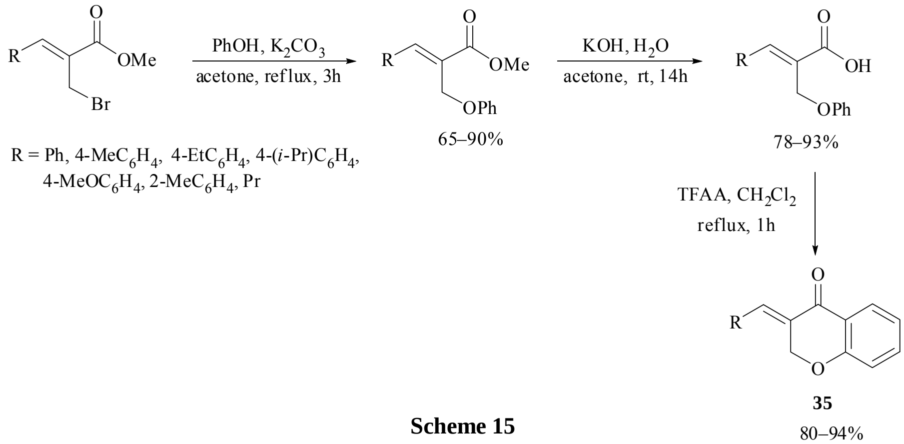

**Scheme 13**

A facile protocol for obtaining larger rings fused with $\alpha$-methylene-$\gamma$-lactone moiety **33** was developed Mendez-Andino and Paquette using the BH bromide as starting material. In this strategy indium mediated C—C bond formation and ring-closing metathesis (RCM) have been employed as the key steps (Scheme 14).[116]

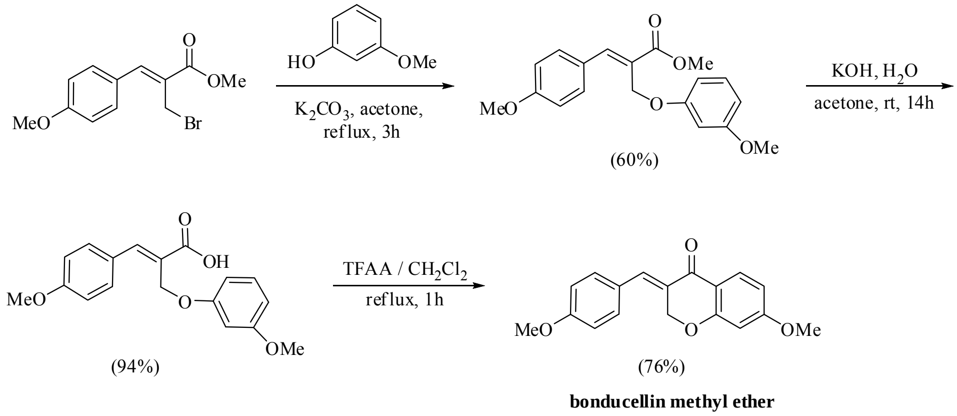



**Scheme 14**

Our research group has effectively utilized the bromides of the BH alcohols, obtained from methyl acrylate and aldehydes, for synthesis of 3-arylidene(alkylidene)chroman-4-ones (**35**) via intramolecular Friedel-Crafts reaction following the reaction sequence as shown in Scheme 15.[106] This strategy was meticulously utilized for synthesis of bonducellin methyl ether, a biologically active compound, following synthetic strategy presented in Scheme 16.[106]

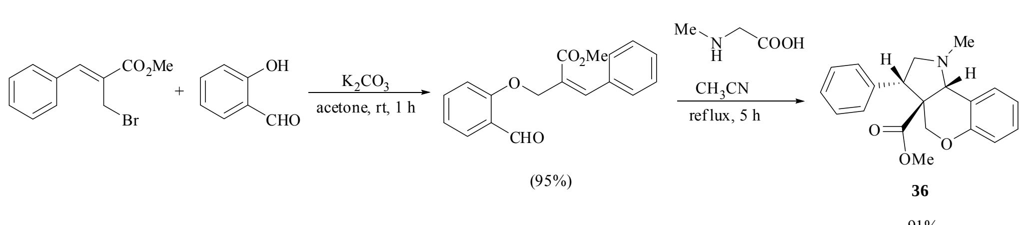


**Scheme 15**



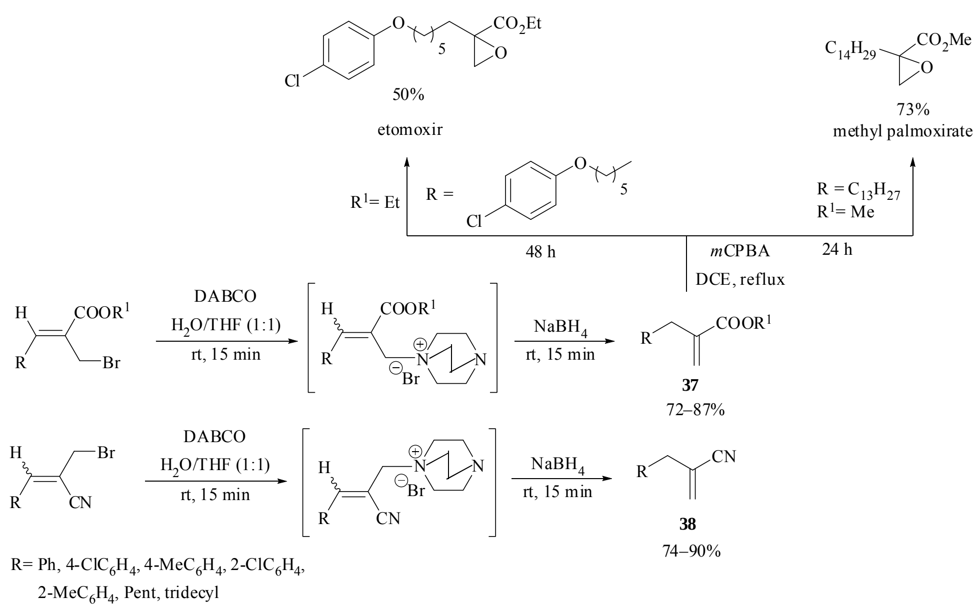
**Scheme 16**

Bakthadoss and co-workers have reported a facile synthetic protocol for synthesis of tricyclic chromeno-pyrrolidine derivatives **36** from BH-bromides via the treatment with salicylaldehyde followed by [3+2]-cycloaddition reaction with *N*-methylglycine as described in Scheme 17.[117]



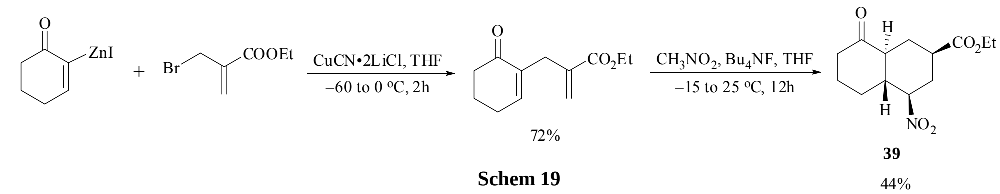
**Scheme 17**

Our research group has developed a facile and convenient methodology for the synthesis of 2-methylenealkanoates **37** and alkanenitriles **38** via regioselective nucleophilic addition ($S_N2'$) of hydride ion generated from $NaBH_4$ to in situ obtained DABCO-allylbromide salt in eco-friendly aqueous media (Scheme 18).[100] This methodology has been successfully extended to synthesis of hypoglycemic agents etomoxir and methyl palmoxirate according to Scheme 18.[100]



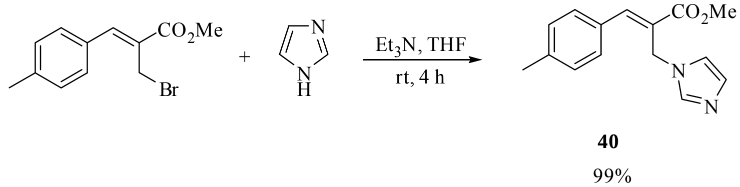

**Scheme 18**

A facile synthetic methodology for obtaining polyfunctionalized decalin **39** via treatment of BH bromide, ethyl 2-(bromomethyl)prop-2-enoate, with 2-zincated cyclohexenone in the presence of Cu(I) catalyst, followed by reaction with nitromethane according to the reaction sequence shown in Scheme 19 was reported by Prasad and Knochel.[101]



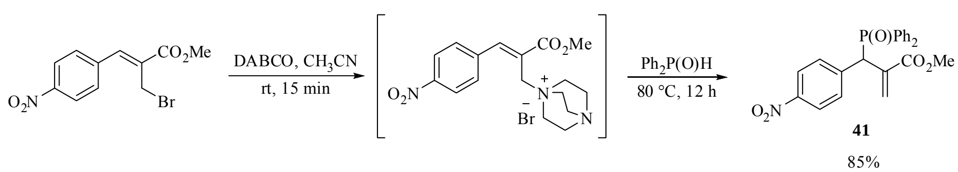
Schem 19

Jia and coworkers have used BH bromide for synthesis of *N*-substituted imidazole **40** by treatment with imidazole in presence of triethylamine (Eq. 24 discloses one such example).[118]



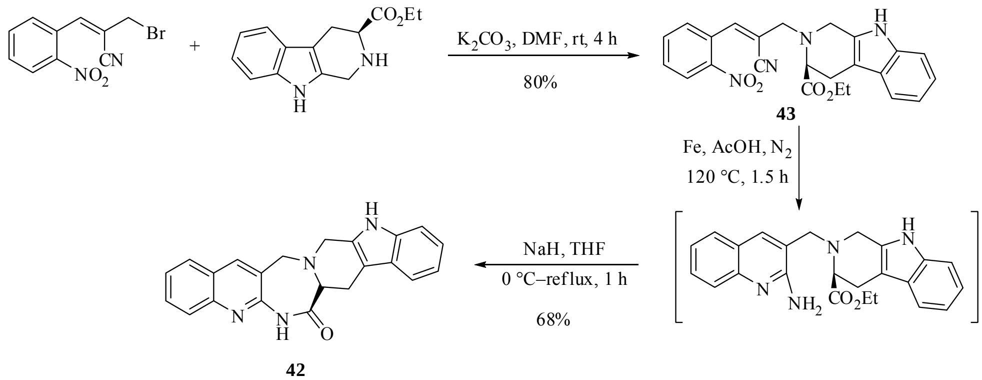
(Eq. 24)

Yang and coworkers have developed an efficient phosphorylation protocol for BH-bromides to provide the corresponding 2-methylene-3-phosphorylalkanoates **41** in encouraging yields as shown in Eq. 25.[119]



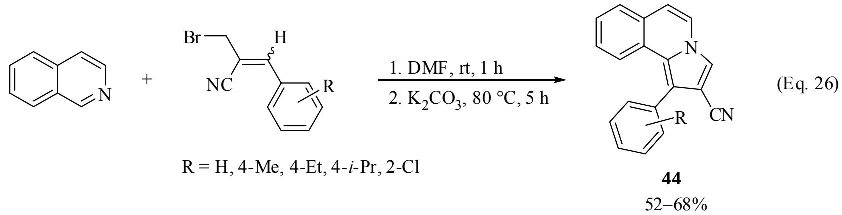
(Eq. 25)

Batra and coworkers reported an elegant approach for synthesis of polycyclic quinolines **42** using the reductive cyclization of the allyl amine derivatives **43** that are obtained from BH bromides as the key step as shown in Scheme 20.[120]

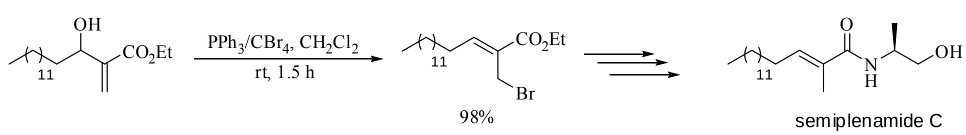


**Scheme 20**

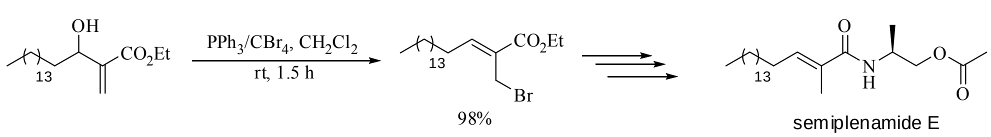
Our research group has developed a simple one-pot procedure for synthesis of benzofused indolizines **44** from BH bromides using the concept of 1,5-cyclization following the reaction strategy shown in Eq. 26.[99]



Das and coworkers have reported a facile synthetic strategy for obtaining semiplenamides C and E, naturally occurring bioactive fatty acid amides, using the BH bromides as key synthons (Scheme 21 & 22).[121]

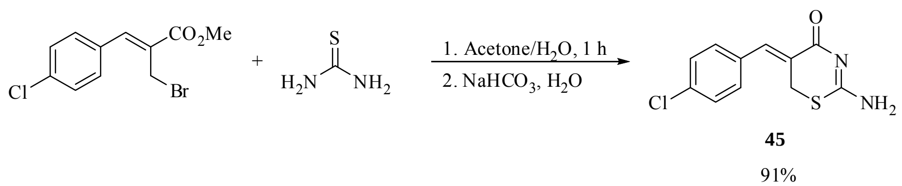


**Scheme 21**



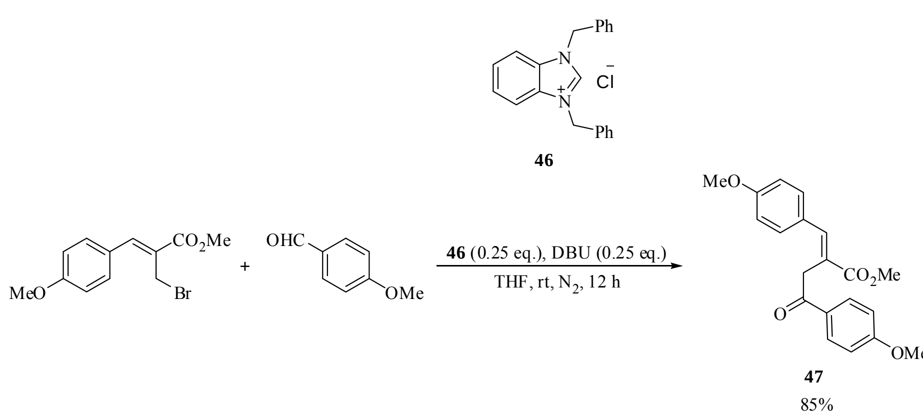
**Scheme 22**

Sa and coworkers have successfully utilized BH bromides for synthesis of 2-amino-1,3-thiazin-4-ones **45** in good yields by treatment with various thiourea derivatives followed by a base-promoted intramolecular cyclization (Eq. 27 represents one such example).[122]



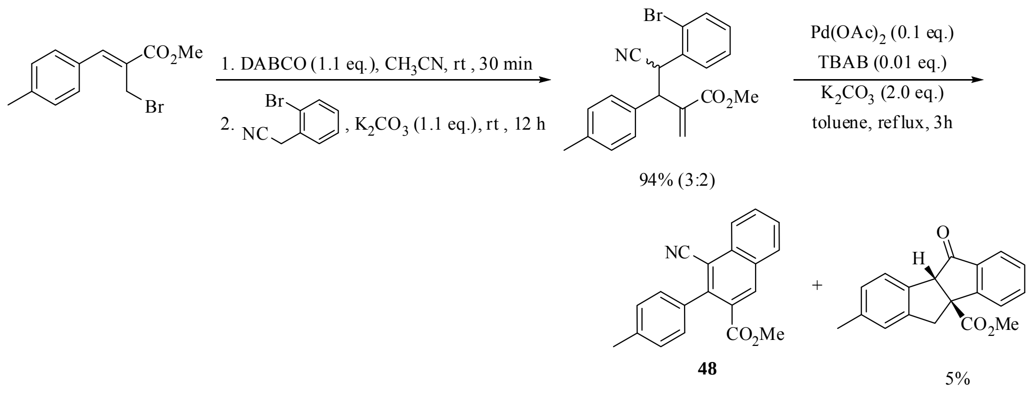

(Eq. 27)

Yadav and coworkers have developed an interesting methodology for coupling of BH bromides with aromatic aldehydes in presence of *N*-heterocyclic carbene (Breslow intermediate) **46** for obtaining α-arylidene-γ-keto esters **47**, synthetically important precursors (Eq. 28 shows one such example).[123]



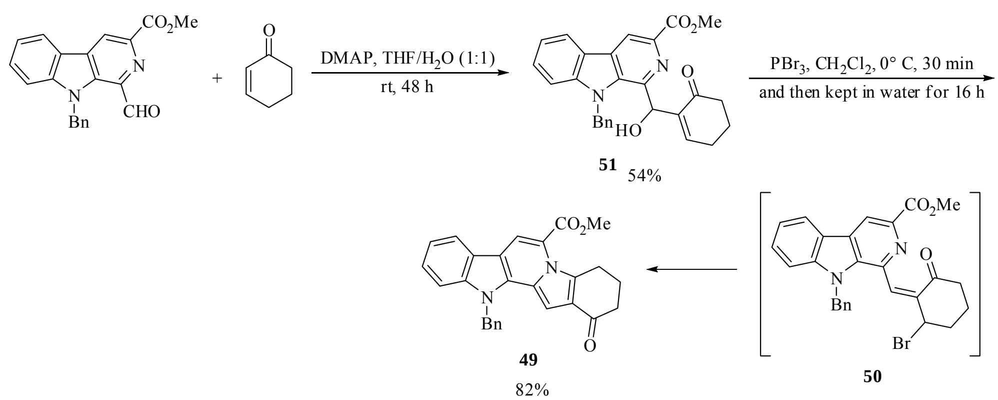

(Eq. 28)

A facile synthetic strategy for synthesis of poly-substituted naphthalenes **48** using BH bromides as the starting materials was developed by Kim and coworkers following the reaction protocol as presented in Scheme 23.[124]



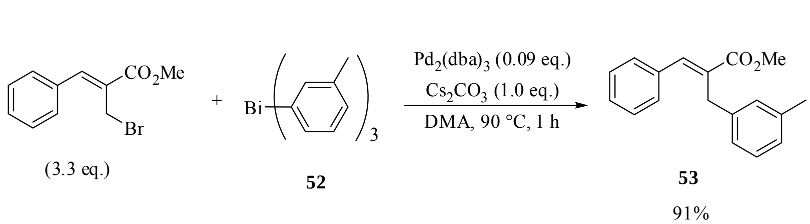
**Scheme 23**

Batra and coworkers have reported a facile synthetic strategy for obtaining pentacyclic compound **49** via the intramolecular cyclization of the the BH bromide **50** generated in situ from the BH alcohol **51** (Scheme 24).[125]



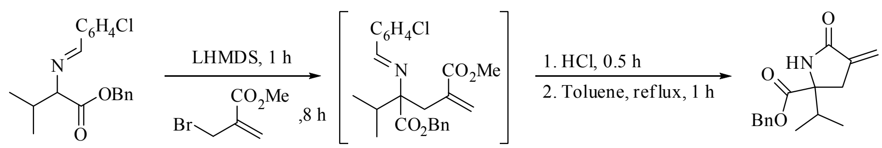
**Scheme 24**

Rao and coworkers have developed a facile strategy for synthesis of trisubstituted (*E*)-alkenes **53** in high yields via the treatment of BH bromides with triarylbismuth derivatives **52** under palladium-catalyzed conditions (Eq. 29).[126]



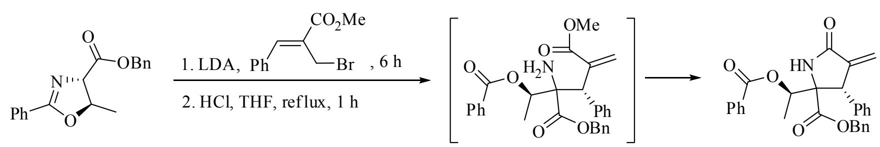
(Eq. 29)

A convenient protocol for obtaining *α*-methylene-*γ*-carboxy-*γ*-lactams **54** was reported by Mereddy and coworkers using BH bromide as key synthon (Representative example is shown in Eq. 30).[127] Later on, they have also extended this methodology for the synthesis of *β*-methyl/phenyl pyroglutamates **55** in stereoselective manner as shown in Eq. 31.[128]



**54**
67%

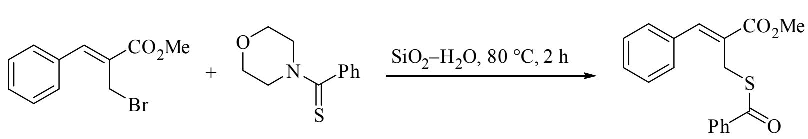
(Eq. 30)



**55**
69%

(Eq. 31)

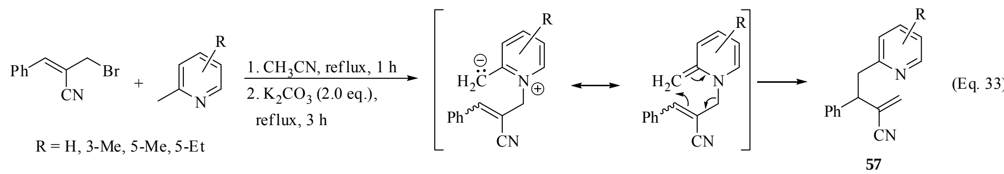
Yadav and coworkers have reported a novel and one-pot synthesis of allyl thioester derivatives **56** via the treatment of BH bromides with *N*-thioaroylmorpholines in silica gel-water system. This reaction proceeds via *S*-alkylation followed by hydrolysis as shown in Eq. 32.[129]



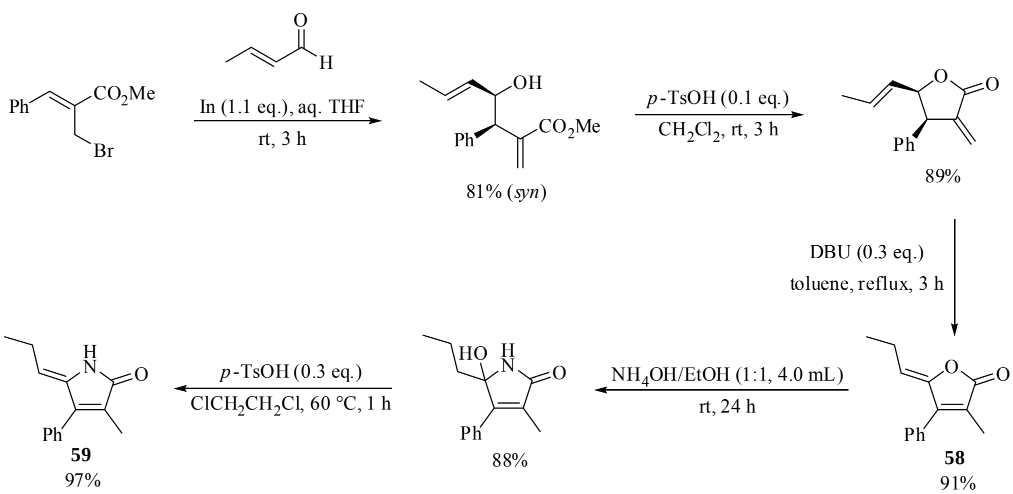
**56**
94%

(Eq. 32)

An interesting alkylation of methyl group of 2-methylpyridine with BH bromide was reported to produce acrylonitrile derivatives **57** by Kim and coworkers following the reaction strategy shown in Eq. 33. This reaction is believed to proceed through aza-Cope rearrangement (Eq. 34 resembles one such example).[130]

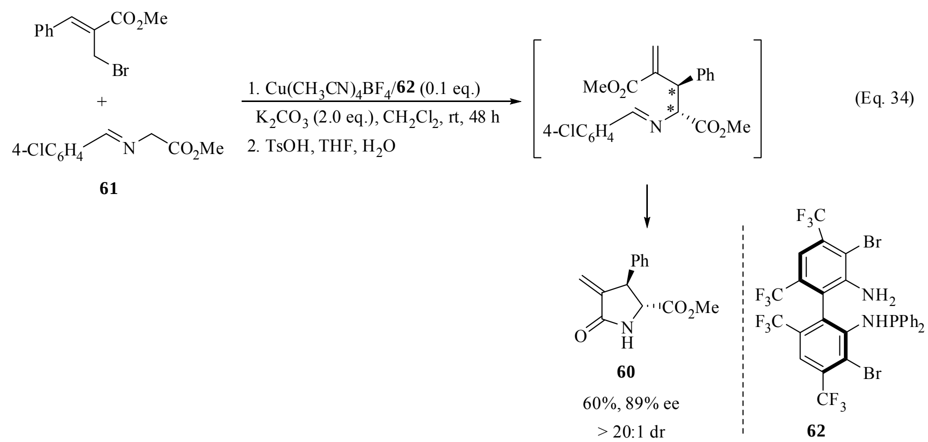


Kim and coworkers have reported an efficient synthesis of γ-alkenylbutenolides **58** and 5-alkylidene-1,5-dihydropyrrol-2-ones **59** from BH bromides in a stereoselective manner and excellent yields (Scheme 25 presents one such example).[103, 131]



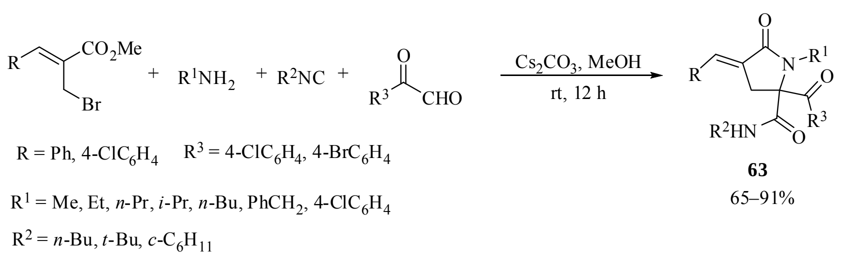
**Scheme 25**

Wang and coworkers have described an efficient synthetic protocol for synthesis of enantioenriched pyroglutamate 60 via the treatment of BH bromides with glycine-derived imino ester 61 under the influence of Cu(I)-catalyst. This strategy involves tandem γ-Michael addition-elimination followed by deprotection /lactamization reactions (Eq. 34).[132]



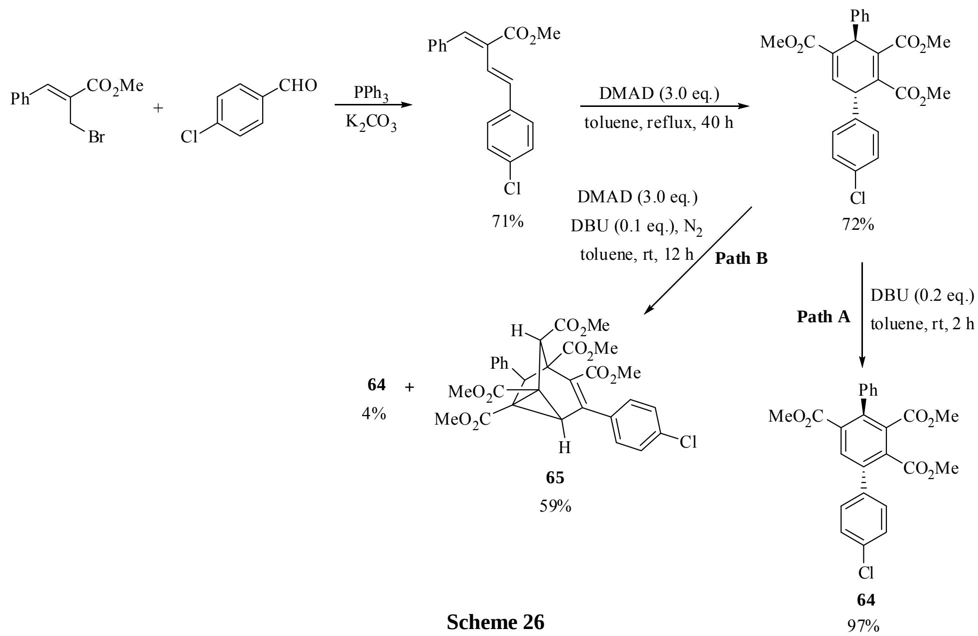
(Eq. 34)

An interesting reaction strategy have been developed for the synthesis of 5-oxopyrrolidine-2-carboxamides **63** in high yields using BH bromides as starting materials under Ugi conditions (using isocyanides, primary amines and arylglyoxals) in the presence of $Cs_2CO_3$ (cat.) in a one pot operation (Eq. 35).[133]



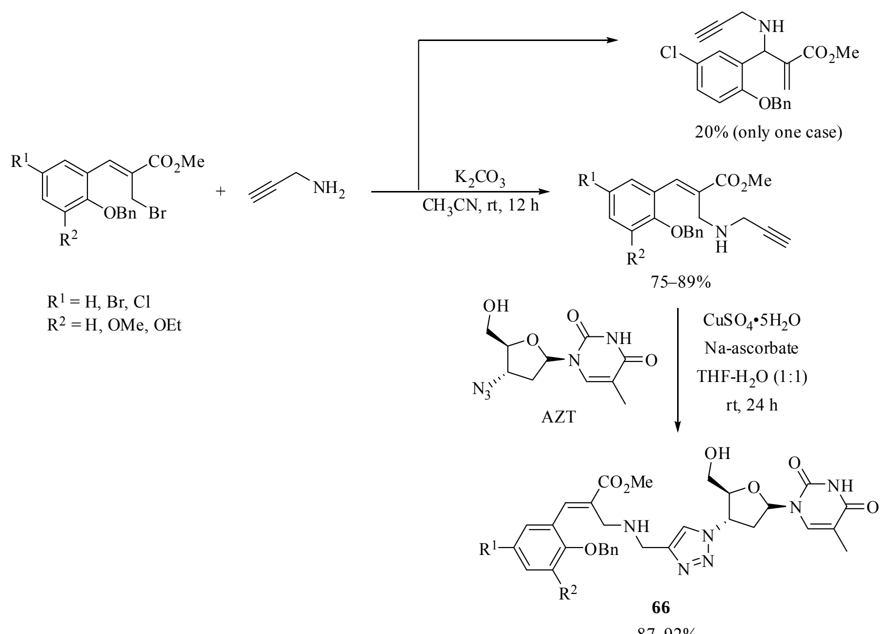
(Eq. 35)

BH bromides have been conveniently transformed into biphenyl compounds **64**. This strategy involves sequential Wittig reaction and Diels–Alder reaction (with DMAD) as key steps (Path A-Scheme 26).[134] In the presence of excess DMAD, tricyclo[3.2.1.0$^{2,7}$]oct-3-ene scaffold **65** was obtained following the reaction sequence as shown in Path B-Scheme 26.[134]



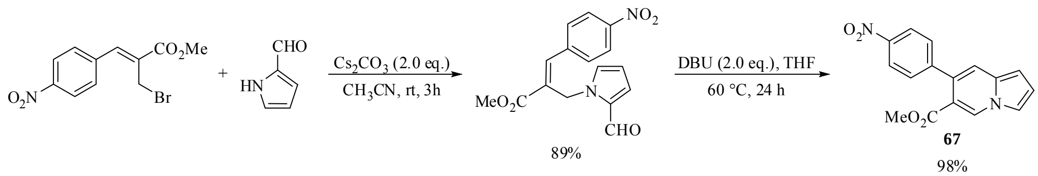

**Scheme 26**

Kaye and coworkers have reported a facile protocol for synthesis of cinnamate ester AZT conjugate **66** from BH bromide following the reaction sequence as shown in Scheme 27.[135] Click reaction is the key step in this strategy.



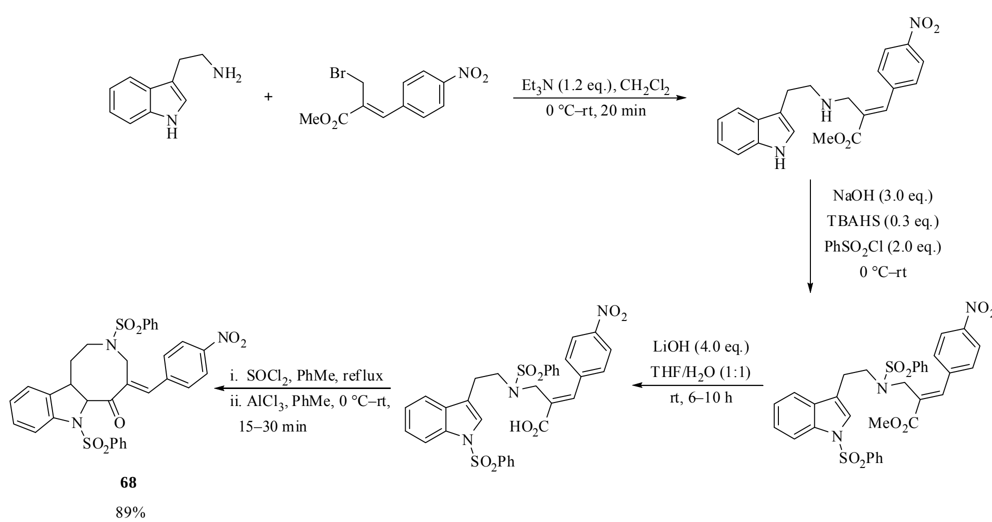

**Scheme 27**

Kim and Park have described an interesting [3+3] cycloaddition protocol for synthesis of 6,7-disubstituted indolizine derivatives **67** using BH bromide as the starting material via the reaction with pyrrole-2-carboxaldehyde following the reaction sequence as shown in Scheme 28 (Given one such example).[136]



**Scheme 28**

Batra and coworkers have reported a simple methodology for synthesis of indoloazocines **68** starting from BH bromide. This methodology involves intramolecular Friedel-Crafts reaction as the key step. Scheme 29 describes one such example.[137]



**Scheme 29**

# OBJECTIVES, RESULTS AND DISCUSSION

Preceding section clearly demonstrates the importance and also applications of Baylis-Hillman reaction in organic synthesis. Although BH reaction has seen significant developments in many directions, it is surprising to note that two component (containing electrophile and reaction initiating sites) BH reaction, yet another important aspect of this reaction was not received adequate attention during all these years. Even though BH bromides derived from aldehydes as electrophiles have received considerable attention from chemists, the corresponding bromides of the BH adducts obtained from α–keto esters, as electrophiles, did not also receive any attention from chemists. We have therefore, in continuation of our ongoing research program on BH reaction, undertaken this thesis work with the following key objectives.

## OBJECTIVES

1) To develop a facile two component Baylis-Hillman reaction using substrates containing less reactive components, ketones, as electrophile component and nitrogen of pyridine/isoquinoline as a promoter for coupling with alkyl vinyl ketones as activated alkene component. This process would, in principle, result in the development of simple protocol for synthesis of indolizine derivatives.
2) To develop a convenient and facile protocol, from BH adducts derived from α–keto esters via coupling with alkyl acrylates/acrylonitrile, for obtaining stereodefined tetrasubstituted alkenes containing allylbromide functionality.

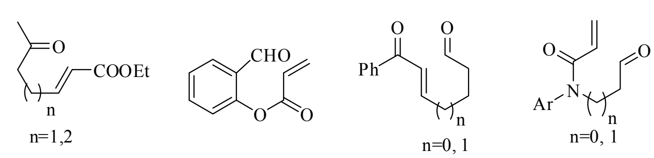
3) To study the possible applications of the above mentioned tetrasubstituted alkenes (containing allyl bromide functionality) as a source of dipoles for reaction with isatins as dipolarophiles with a view to develop a facile [3+2] annulation strategy for stereoselective synthesis of dihydrofuran-fused-spirooxindoles containing ester group or nitrile functionality.

# RESULTS AND DISCUSSION

## Development of a novel two component Baylis-Hillman reaction

As already discussed in earlier chapter, the Baylis-Hillman reaction is an atom-economic C—C bond forming reaction to produce densely functionalized molecules in a three component atom-economical organocatalytic process. It is also possible, in principle, to design substrates having two components inbuilt and to perform the coupling reaction with third component. Thus the two component BH reactions, in principle, can be performed in three different ways:

i. By designing substrates containing activated alkene and electrophile components in a molecule to perform the coupling between them in the presence of appropriate catalyst/medium. This procedure, in fact, is a well known intramolecular BH reaction. Selected such substrates are listed in Figure 10.[138, 139]




Ref. 138a Ref. 138b Ref. 138c Ref. 139

**Figure 10.** Substrates containing both activated alkene and electrophile components used in BH reaction

ii. By designing of substrate having activated alkene and reaction promoting sites to perform the BH coupling with electrophiles to produce cyclic compounds. Representative known substrates are listed in Figure 11.[140, 141]

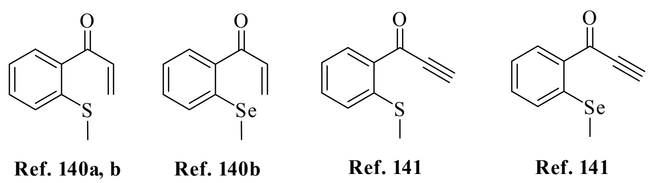



**Figure 11.** Substrates containing activated alkene and catalytic sites used in BH reaction

iii. By designing substrates containing electrophilic and reaction promoting sites to carry out reaction with activated alkene. Such substrates are shown in Figure 12.[142]

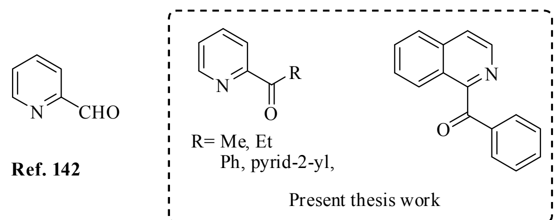
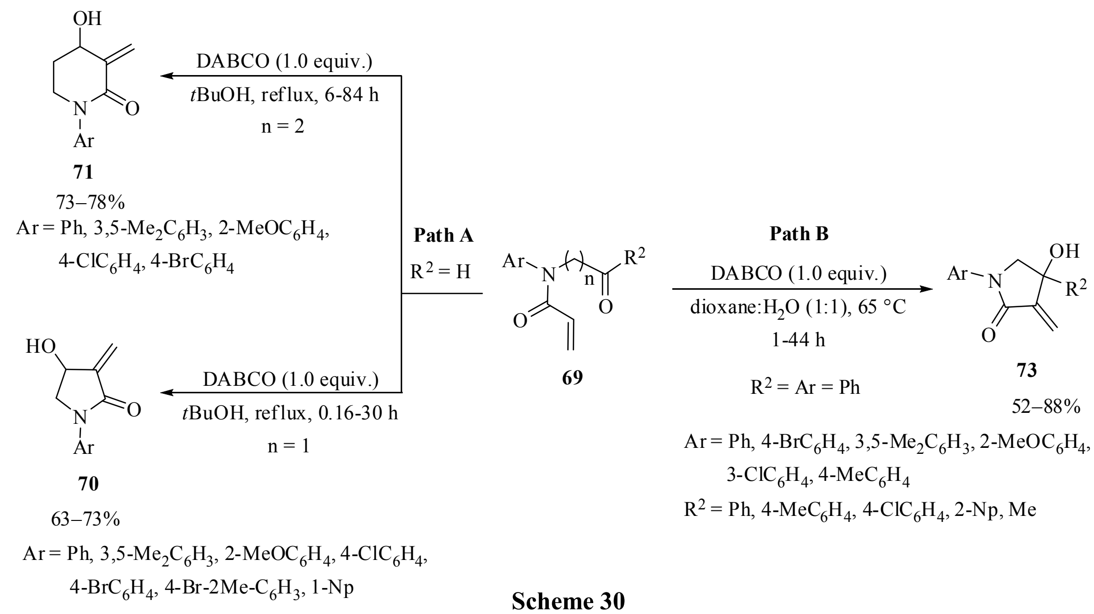


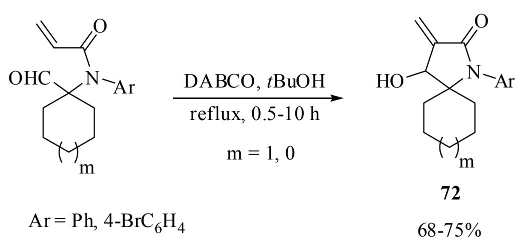

**Figure 12.** Substrates containing electrophilic and catalytic sites used in BH reaction

**i) Intramolecular (BH) cyclization of substrates containing both activated alkene and electrophile components under the influence of a catalyst/medium**[25, 26, 29, 31–33]

Very recently our research group has effectively employed two component substrates **69** containing less reactive acrylamide moiety as an activated alkene and aldehyde as an electrophile component in intramolecular Baylis-Hillman reaction using DABCO as a catalyst to provide 5- and 6-membered α-methylene lactam (**70** & **71**) and spirolactam derivatives **72** (Path A, Scheme 30 & Eq. 36).[139] Later on, our research group has successfully used less reactive ketone as electrophile and acrylamide as activated alkene components in intramolecular BH-reaction, leading to the development of facile protocol for obtaining α-methylene-γ-lactam derivatives **73** containing tertiary alcohol functionality (Path B, Scheme 30).[143]

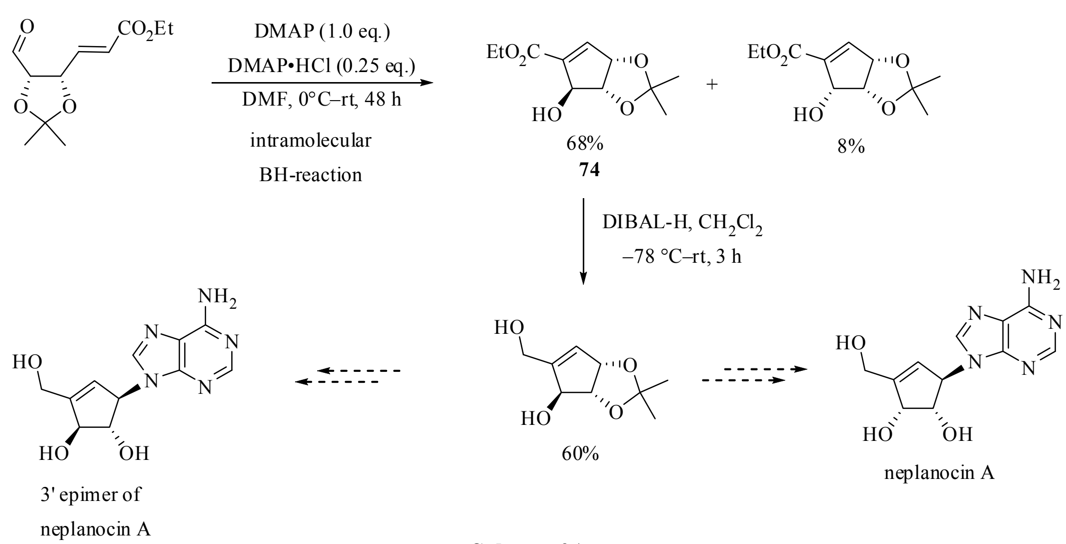



**Scheme 30**




(Eq. 36)

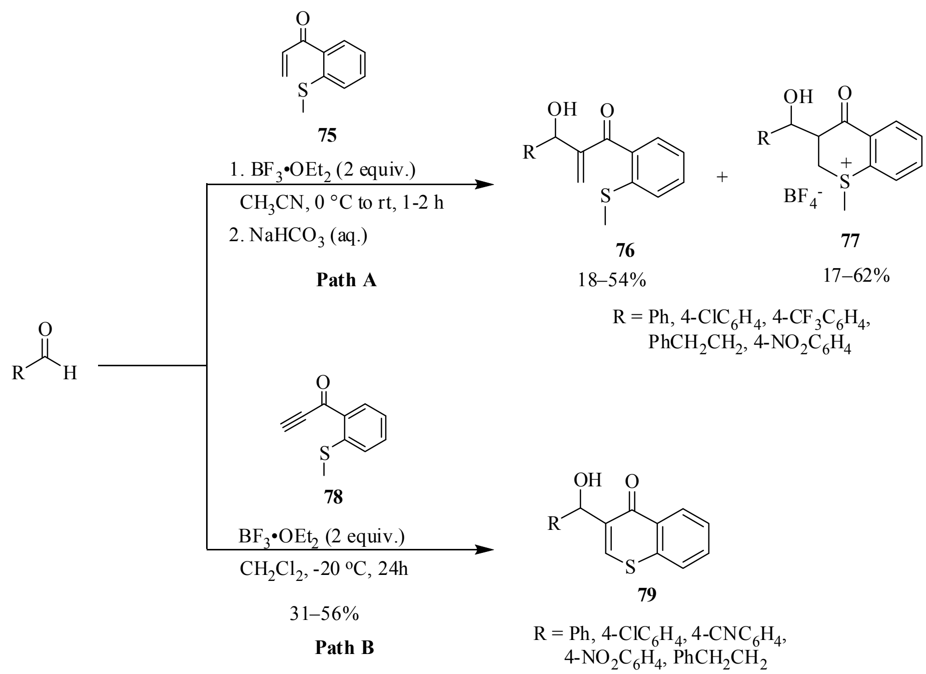
Enoate-aldehyde substrate has been meticulously employed for intramolecular BH-reaction to provide cyclopentenyl intermediate **74** which was used as a key synthon for synthesis of neplanocin A, a potent antiviral molecule, following the reaction strategy as shown in Scheme 31.[144]



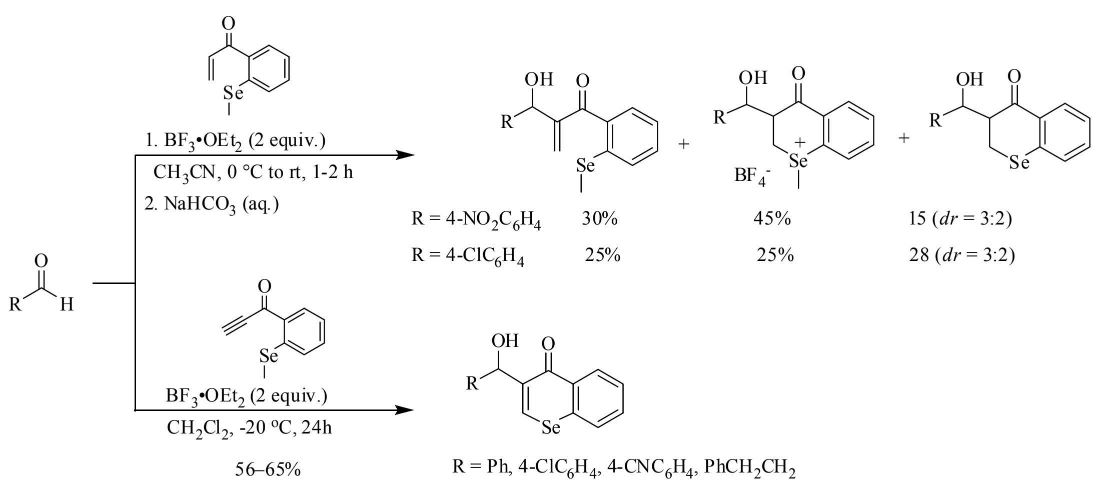

**Scheme 31**

**ii) Coupling of substrates containing activated alkene and catalytic sites with electrophiles**

Kataoka and coworkers described a self induced (intramolecular) chalcogeno-Baylis-Hillman reaction of 1-[2-(methylsulfanyl)phenyl]prop-2-enone (**75**) with aryl aldehydes in the presence of $BF_3$•$OEt_2$ to provide the resulting adducts **76** and onium salts **77** (Path A, Scheme 32).[140b] They have also reported the coupling of 1-(2-(methylthio)phenyl)prop-2-yn-1-one (**78**) with representative aldehydes in the presence of $BF_3$•$OEt_2$ leading to the formation of 3-(hydroxy(alkyl)methyl)-4*H*-thiochromen-4-one (**79**) (Path B, Scheme 32).[141] This strategy was also extended to substrates containing the selenium as shown in Scheme 33.[140b, 141]

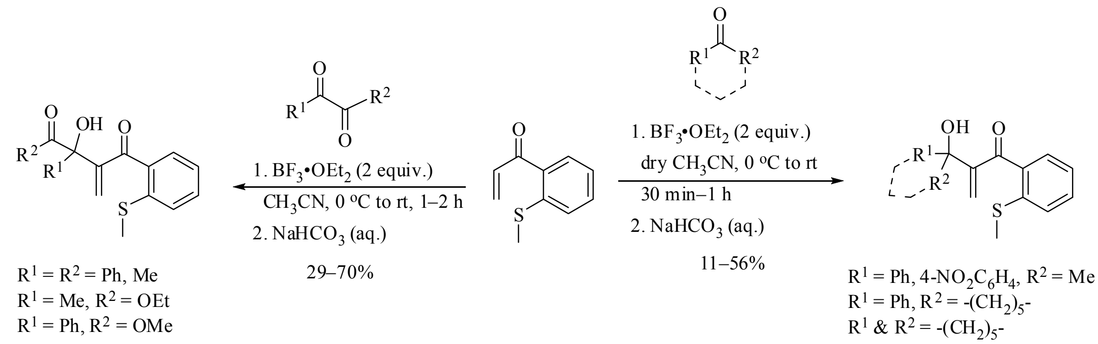



**Scheme 32**




**Scheme 33**

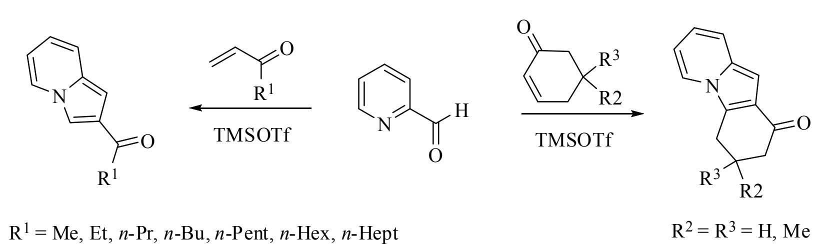
However it is interesting to note from the reports of Kataoka and coworkers that the coupling of ketones, α-diketones and α-keto esters in the presence of $BF_3$•$OEt_2$ provided exclusively the usual Baylis-Hillman adducts in moderate yields (Scheme 34).[140a] In all these reactions there was no cyclization observed.




**Scheme 34**

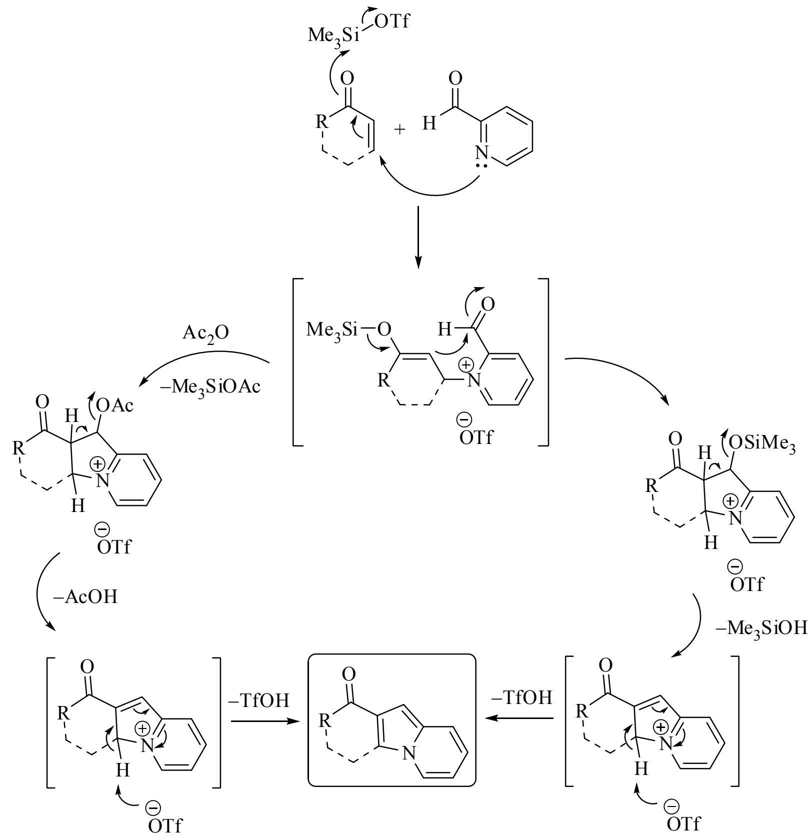
**iii) Coupling of substrates containing electrophilic and catalytic sites with activated alkenes**

Several years ago our research group has reported, for the first time, the coupling of pyridine-2-carboxaldehyde with alkyl vinyl ketones under the influence of TMSOTf, to provide a facile methodology for obtaining indolizine derivatives.[142] In this strategy, the pyridine nitrogen acts as initiator site and induces the reaction while the aldehyde group acts as an electrophile (Scheme 35).[142] The plausible mechanism is presented in Scheme 36.




**Scheme 35**

At that time our research group felt that ketones may not be suitable electrophile components in the above strategy as it was generally understood that ketones are less reactive electrophiles in BH reaction. However recently we felt that this is not that absurd to examine the potential of ketones as electrophiles in these reactions on the assumption that intramolecular reactions are normally faster than the corresponding intermolecular reactions.

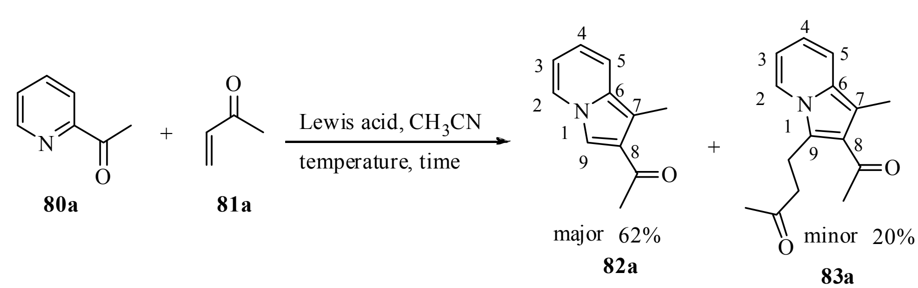



**Scheme 36**

Accordingly we have first selected 2-acetylpyridine as a two component substrate, for coupling with methyl vinyl ketone (MVK) under the influence of appropriate Lewis acid catalyst.

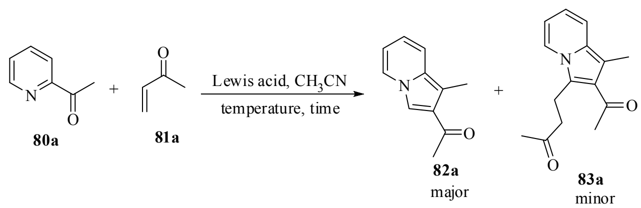
## Ketones as Electrophiles in Two Component Baylis-Hillman Reaction: A Facile One-Pot Synthesis of Substituted Indolizines

On the basis of our earlier experience we have treated 2-acetyl-pyridine (**80a**) with methyl vinyl ketone (MVK) (**81a**) under the influence of TMSOTf in $CH_3CN$ at room temperature for 12 hours which provided the desired 8-acetyl-1-aza-7-methybicyclo-[4.3.0]nona-2,4,6,8-tetraene (**82a**) in 24% yield. We also noticed the formation of 8-acetyl-1-aza-7-methyl-9-(3-oxobutyl)bicyclo-[4.3.0]nona-2,4,6,8-tetraene (**83a**) (MVK addition product of **82a**) in 8% yield. This reaction was indeed encouraging. We have then immediately directed our attention towards optimization of this reaction under different Lewis acids and conditions (Table 1). Best result was obtained when **80a** was treated with **81a** in the presence of TMSOTf at reflux temperature in acetonitrile for 12 hours thus providing the desired indolizine derivative **82a** in 62% yield along with the side product **83a** (MVK addition product of **82a**) in 20% yield (Table 1, entry 5) (combined yield 82%, see Eq. 37). The structures of **82a** and **83a** were established by IR, $^1$H NMR [see Spectrum 1 for compound **82a** & Spectrum 3 for compound **83a**], $^{13}$C NMR [see Spectrum 2 for compound **82a** & Spectrum 4 for compound **83a**] and HRMS spectroscopic studies.




(Eq. 37)

**Table 1: Optimization of reaction conditions for coupling of 2-acetylpyridine with MVK**[a]

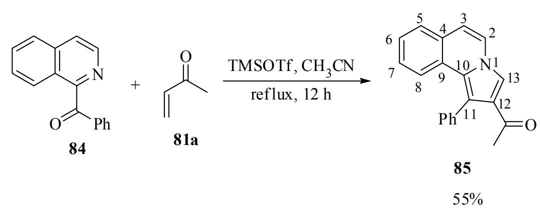



| Entry | Lewis Acid | Temp.(°C) | Time (h) | Product **82a**[b] Yield (%)[c] | Product **83a**[b] Yield (%)[c] | **82a**+**83a** Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1[d] | $TiCl_4$ | rt | 12 | — | — | — |
| 2[e] | TMSOTf | rt | 12 | 24 | 8 | 32 |
| 3 | TMSOTf | rt | 12 | 54 | 23 | 77 |
| 4 | TMSOTf | rt | 24 | 55 | 21 | 76 |
| **5** | **TMSOTf** | **80** | **12** | **62** | **20** | **82** |
| 6 | $Zn(OTf)_2$ | rt | 12 | 45 | 13 | 58 |
| 7 | $Sc(OTf)_3$ | rt | 12 | 51 | 16 | 67 |
| 8 | $Sc(OTf)_3$ | 80 | 12 | 56 | 19 | 75 |

[a]All reactions were carried out on 1.0 mmol scale of 2-acetylpyridine and 2.0 mmol of methyl vinyl ketone under the influence of various Lewis acids (1.0 mmol) in acetonitrile (containing 1% $H_2O$, v/v) (2 mL). [b]All compounds (**82a** & **83a**) were characterized by IR, $^{1}$H NMR, $^{13}$C NMR, and HRMS spectroscopic studies. [c]Yields were calculated on the basis of 2-acetylpyridine (**80a**). [d]Reaction was not clean. [e]Reaction was carried out on 1.0 mmol scale of 2-acetylpyridine and 1.0 mmol of methyl vinyl ketone.

In order to understand the generality of this strategy we have treated various 2-alkanoyl-(aroyl) pyridines (**80a-e**) with methyl vinyl ketone (**81a**) and ethyl vinyl ketone (**81b**) under similar conditions which provided indolizine derivatives **82a-j** in 23–62% yields along with the side products **83a-j** in 0–46% yields (Table 2). All products were fully characterized using IR, $^{1}$H NMR, $^{13}$C NMR spectroscopy and HRMS analyses. Further, the compounds **82f**, **83f**, **82h** and **83h** were confirmed by single crystal X-ray diffraction data analysis [See Tables I–IV; for data of **82f**, **83f**, **82h** and **83h** respectively]. For ORTEP diagrams see Figures X1–X4 of compounds **82f**, **83f**, **82h** and **83h** respectively.

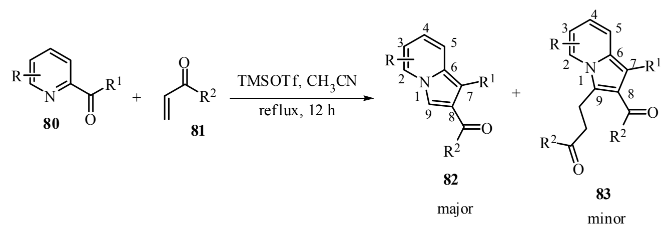
With a view to further expand the scope of this strategy we also used isoquinolin-1-yl phenyl ketone (**84**) for coupling with MVK (**81a**) which furnished 12-acetyl-1-aza-11-phenyltricyclo-[8.3.0.0$^{4,9}$]trideca-2,4(9),5,7,10,12-hexaene (**85**) in 55% yield (Eq. 38). We did not observe formation of any side product here. The structure of **85** was established by IR, $^{1}$H [see Spectrum 5], $^{13}$C NMR [see Spectrum 6] spectroscopy and HRMS analyses.




(Eq. 38)

Next we have directed our efforts towards understanding the application of cyclic activated alkenes such as cyclohex-2-enone (**86a**) & 5,5-dimethylcyclohex-2-enone (**86b**) in this methodology. Thus coupling of **86a** and **86b** with selected 2-alkanoyl(aroyl) pyridines **80** under similar conditions provided indolizine derivatives **87a-f** in 10–60% yields (Table 3). Similar coupling of isoquinolin-1-yl phenyl ketone (**84**) with cyclohex-2-enone (**86a**) also gave the desired product 2-aza-14-oxo-12-phenyltetracyclo[11.4.0.0$^{2,11}$,0$^{5,10}$]-heptdeca-1(13),3,5-(10),6,8,11-hexaene (**88**) in 45% yield (Eq. 39). The structure of **88** was established by IR, $^{1}$H NMR [see Spectrum 7], $^{13}$C NMR [see Spectrum 8] and HRMS spectroscopic studies and further confirmed by single crystal X-ray diffraction data analysis [See Table V; for data of **88**] (for ORTEP diagram see Figure X5).

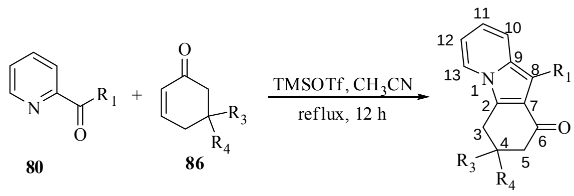
**Table 2: Synthesis of indolizines 82 and 83 via the treatment of 2-alkanoyl(aroyl) pyridines 80 with methyl(ethyl) vinyl ketones 81 under optimized reaction conditions[a]**



| Entry | R | $R^1$ | $R^2$ | Product[b] | Yield (%)[c] | Product[b] | Yield (%)[c] | **82**+**83** Yield (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | H | Me(**80a**) | Me(**81a**) | **82a** | 62 | **83a** | 20 | 82 |
| 2 | H | Me(**80a**) | Et(**81b**) | **82b** | 37 | **83b** | 13 | 50 |
| 3 | H | Et(**80b**) | Me(**81a**) | **82c** | 57 | **83c** | 23 | 80 |
| 4 | H | Et(**80b**) | Et(**81b**) | **82d** | 23 | **83d** | 14 | 37 |
| 5 | 4-Me | Me(**80c**) | Me(**81a**) | **82e** | 33 | **83e** | 46 | 79 |
| 6 | 6-MeO | Me(**80d**) | Me(**81a**) | **82f**[d] | 59 | **83f**[d] | 13 | 72 |
| 7 | 6-MeO | Me(**80d**) | Et(**81b**) | **82g** | 41 | **83g** | — | 41 |
| 8 | H | Ph(**80e**) | Me(**81a**) | **82h**[d] | 49 | **83h**[d] | 11 | 60 |
| 9 | H | Pyrid-2-yl(**80f**) | Me(**81a**) | **82i** | 31 | **83i** | — | 31 |
| 10 | H | Pyrid-2-yl(**80f**) | Et(**81b**) | **82j** | 27 | **83j** | — | 27 |

[a]All reactions were carried out on 1.0 mmol scale of 2-alkanoyl(aroyl)pyridines (**80**) with 2.0 mmol of activated alkene (**81**) in the presence of TMSOTf (1.0 mmol) in acetonitrile (containing 1% $H_2O$, v/v) (2 mL). [b]All compounds (**82a–j** & **83a–f**, **83h**) were characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS analyses. [c]Yields were calculated on the basis of 2-alkanoyl(aroyl) pyridines (**80**). [d]Structure of these molecules were further confirmed by single crystal X-ray diffraction data analysis.

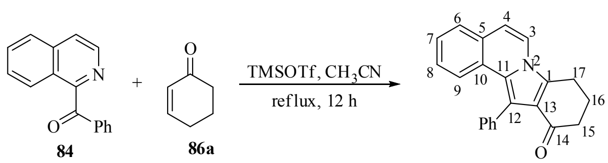
**Table 3: Synthesis of indolizines 87 via the treatment of 2-alkanoyl(aroyl) pyridines 80 with cyclic activated alkenes 86 under optimized reaction conditions**[a]




80 86 87

| Entry | R[1] | R3 | R[4] | Product[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | Me (**80a**) | H | H (**86a**) | **87a** | 60 |
| 2 | Me (**80a**) | Me | Me (**86b**) | **87b** | 31 |
| 3 | Et (**80b**) | H | H (**86a**) | **87c** | 26 |
| 4 | Ph (**80e**) | H | H (**86a**) | **87d** | 35 |
| 5 | Ph (**80e**) | Me | Me (**86b**) | **87e** | 10 |
| 6 | Pyrid-2-yl (**80f**) | H | H (**86a**) | **87f** | 59 |

[a]All reactions were carried out on 1.0 mmol scale of 2-alkanoyl(aroyl) pyridines (**80**) with 1.0 mmol of cyclic activated alkene (**86**) in the presence of TMSOTf (1.0 mmol) in acetonitrile (containing 1% $H_2O$, v/v) (2 mL). [b]All compounds (**87a–f**) were characterized by IR, $^1$H NMR, $^{13}$C NMR and HRMS spectroscopic studies. [c]Yields were calculated on the basis of 2-alkanoyl(aroyl) pyridines (**80**).




84 86a 88 45% (Eq. 39)

It is very appropriate to mention here the importance of indolizine framework.[145–150] Several natural products such as (–)-swainsonine[145], slaframine[146], castanospermine[147], cryptaustoline[148], 219F[149], camptothecin[150] contain the indolizine structural unit (Figure 13). Also good number of compounds having indolizine framework exhibit various biological activities such as antibacterial activity against mycobacterium tuberculosis[151], antioxidant[152], inhibitors of phosphatase[153] and aromatase[154], antidepressant[155], antileukemic[156], and calcium entry blocker activities[157] etc. It is also worth mentioning here that the Baylis-Hillman adducts have already been used as useful synthons for obtaining indolizine frameworks.[51, 99, 142, 158] Because of the importance of indolizine derivatives there has been increasing interest in the development of useful strategies for synthesis of diverse classes of such framework.[51, 99, 142, 145–150, 158–166] In this context it is certainly appropriate to say that this present work also shows significant relevance as a strategy in obtaining such useful derivatives.

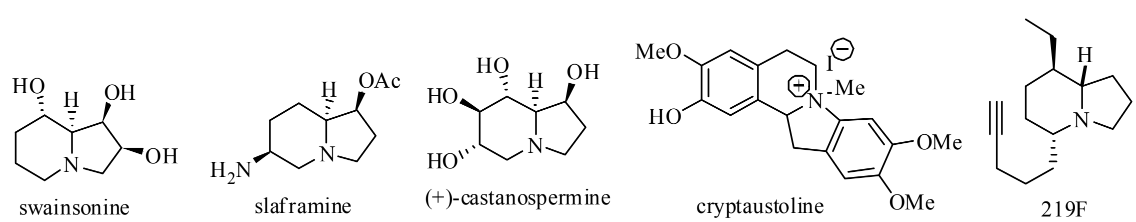



**Figure 13.** Representative natural products and biologically active compounds containing indolizine framework

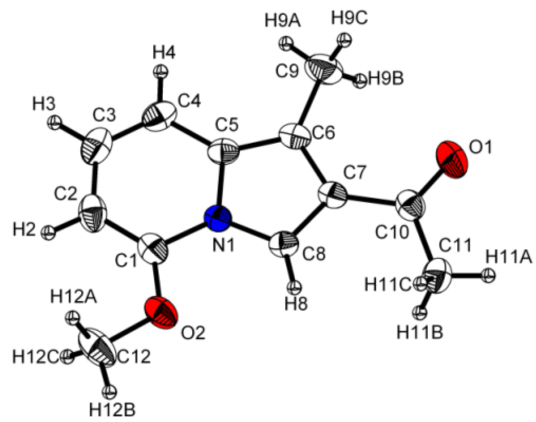



**Figure X1.** ORTEP diagram of compound **82f**

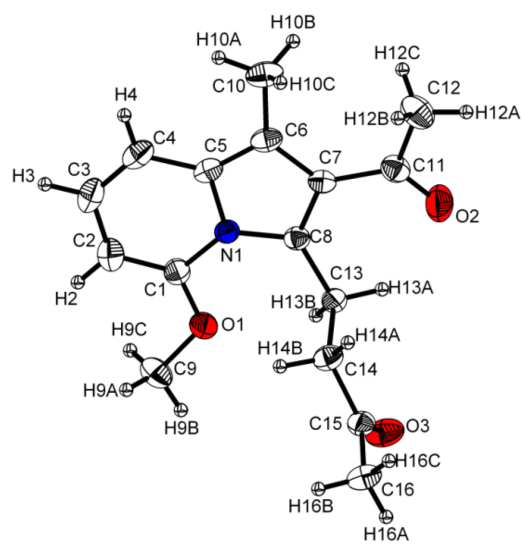



**Figure X2.** ORTEP diagram of compound **83f**

**Table I.** Crystal data and structure refinement for **82f**

| | | |
|---|---|---|
| Identification code | 82f | |
| Empirical formula | C12 H13 N O2 | |
| Formula weight | 203.23 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | Pbca | |
| Unit cell dimensions | a = 14.886(4) Å | α= 90°. |
| | b = 8.048(2) Å | β= 90°. |
| | c = 17.590(4) Å | γ = 90°. |
| Volume | 2107.2(9) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.281 $Mg/m^3$ | |
| Absorption coefficient | 0.088 $mm^{-1}$ | |
| F(000) | 864 | |
| Crystal size | 0.24 x 0.16 x 0.14 $mm^3$ | |
| Theta range for data collection | 2.32 to 26.03°. | |
| Index ranges | -18<=h<=18, -9<=k<=9, -21<=l<=21 | |
| Reflections collected | 20200 | |
| Independent reflections | 2070 [R(int) = 0.0415] | |
| Completeness to theta = 26.03° | 100.0 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2070 / 0 / 139 | |
| Goodness-of-fit on $F^2$ | 1.170 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0635, wR2 = 0.1385 | |
| R indices (all data) | R1 = 0.0792, wR2 = 0.1466 | |
| Largest diff. peak and hole | 0.158 and -0.162 e.$Å^{-3}$ | |

**Table II.** Crystal data and structure refinement for **83f**

| | | |
|---|---|---|
| Identification code | 83f | |
| Empirical formula | C16 H19 N O3 | |
| Formula weight | 273.32 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1) | |
| Unit cell dimensions | a = 4.9759(15) Å | $\alpha$= 90°. |
| | b = 13.292(4) Å | $\beta$= 90.818(5)°. |
| | c = 10.625(3) Å | $\gamma$ = 90°. |
| Volume | 702.7(4) Å$^3$ | |
| Z | 2 | |
| Density (calculated) | 1.292 Mg/m$^3$ | |
| Absorption coefficient | 0.089 mm$^{-1}$ | |
| F(000) | 292 | |
| Crystal size | 0.23 x 0.20 x 0.18 mm$^3$ | |
| Theta range for data collection | 1.92 to 26.02°. | |
| Index ranges | -6<=h<=6, -16<=k<=16, -13<=l<=13 | |
| Reflections collected | 7205 | |
| Independent reflections | 2749 [R(int) = 0.0294] | |
| Completeness to theta = 26.02° | 99.6 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 2749 / 1 / 185 | |
| Goodness-of-fit on F$^2$ | 1.090 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0462, wR2 = 0.1194 | |
| R indices (all data) | R1 = 0.0552, wR2 = 0.1238 | |
| Largest diff. peak and hole | 0.130 and -0.178 e.Å$^{-3}$ | |

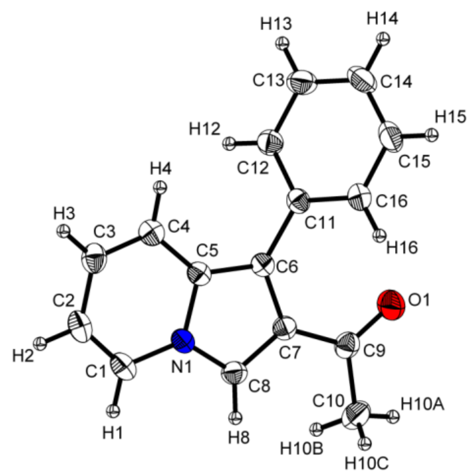



**Figure X3.** ORTEP diagram of compound **82h**

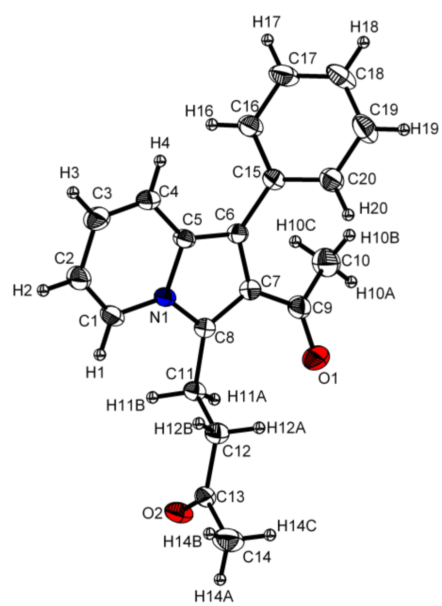



**Figure X4.** ORTEP diagram of compound **83h**

**Table III.** Crystal data and structure refinement for **82h**

| | | |
|---|---|---|
| Identification code | 82h | |
| Empirical formula | C16 H13 N O | |
| Formula weight | 235.27 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 9.286(2) Å | $\alpha$= 90°. |
| | b = 11.358(3) Å | $\beta$= 98.495(4)°. |
| | c = 11.827(3) Å | $\gamma$ = 90°. |
| Volume | 1233.8(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.267 $Mg/m^3$ | |
| Absorption coefficient | 0.079 $mm^{-1}$ | |
| F(000) | 496 | |
| Crystal size | 0.8 x 0.4 x 0.2 $mm^3$ | |
| Theta range for data collection | 2.22 to 25.89°. | |
| Index ranges | -11<=h<=11, -13<=k<=13, -14<=l<=14 | |
| Reflections collected | 12115 | |
| Independent reflections | 2380 [R(int) = 0.0325] | |
| Completeness to theta = 25.89° | 99.6 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2380 / 0 / 164 | |
| Goodness-of-fit on $F^2$ | 1.145 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0552, wR2 = 0.1225 | |
| R indices (all data) | R1 = 0.0637, wR2 = 0.1272 | |
| Largest diff. peak and hole | 0.197 and -0.152 e.$Å^{-3}$ | |

**Table IV.** Crystal data and structure refinement for **83h**

| | | |
|---|---|---|
| Identification code | 83h | |
| Empirical formula | C20 H19 N O2 | |
| Formula weight | 305.36 | |
| Temperature | 273(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 9.1844(10) Å | α= 81.098(2)°. |
| | b = 9.6681(11) Å | β= 65.775(2)°. |
| | c = 10.4799(12) Å | γ = 79.753(2)°. |
| Volume | 831.62(16) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.219 $Mg/m^3$ | |
| Absorption coefficient | 0.079 $mm^{-1}$ | |
| F(000) | 324 | |
| Crystal size | 0.6 x 0.4 x 0.2 $mm^3$ | |
| Theta range for data collection | 2.14 to 26.04°. | |
| Index ranges | -11<=h<=11, -11<=k<=11, -12<=l<=12 | |
| Reflections collected | 8707 | |
| Independent reflections | 3258 [R(int) = 0.0346] | |
| Completeness to theta = 26.04° | 99.3 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3258 / 0 / 210 | |
| Goodness-of-fit on $F^2$ | 1.264 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0887, wR2 = 0.1860 | |
| R indices (all data) | R1 = 0.0932, wR2 = 0.1889 | |
| Largest diff. peak and hole | 0.263 and -0.381 e.$Å^{-3}$ | |

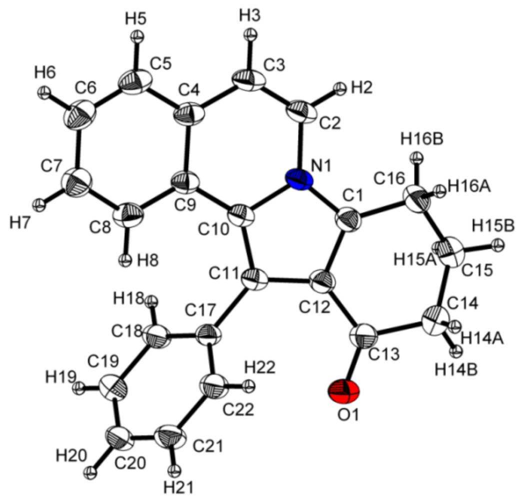
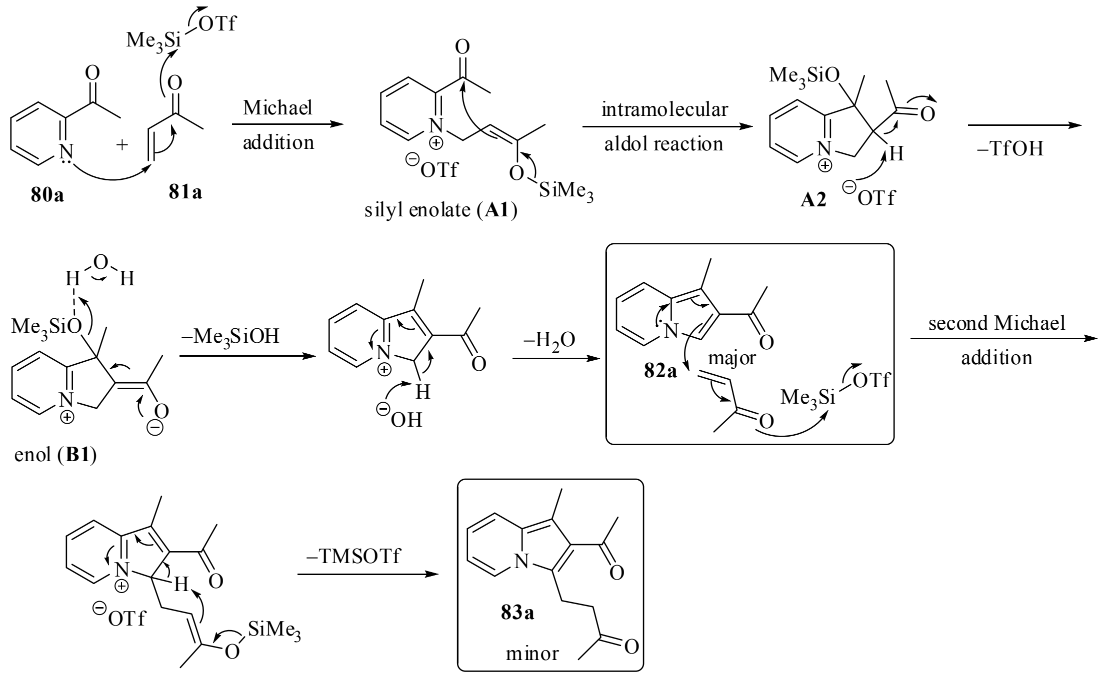



**Figure X5.** ORTEP diagram of compound **88**

A plausible mechanism has been described taking the reaction of 2-acetylpyridine (**80a**) with MVK (**81a**) as a model case in Scheme 37. The first step involves the initial Michael addition of pyridine (via N—C bond formation) with MVK leading to the formation of the silyl enolate (**A1**) followed by intramolecualr aldol addition to produce pyridinium salt **A2**. Subsequent removal of trimethylsilyloxy group (as silanol or its ether) and TfOH followed by neutralization of positive charge on the nitrogen provided the desired product **82a** (major). The minor compound **83a** was formed via the Michael addition of indolizine **82a** onto MVK as shown in Scheme 37.

**Table V.** Crystal data and structure refinement for **88**

| | | |
|---|---|---|
| Identification code | 88 | |
| Empirical formula | C22 H17 N O | |
| Formula weight | 311.37 | |
| Temperature | 273(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 10.5099(15) Å | $\alpha$= 90°. |
| | b = 17.731(3) Å | $\beta$= 115.207(2)°. |
| | c = 9.3383(13) Å | $\gamma$ = 90°. |
| Volume | 1574.5(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.314 $Mg/m^3$ | |
| Absorption coefficient | 0.080 $mm^{-1}$ | |
| F(000) | 656 | |
| Crystal size | 0.2 x 0.18 x 0.16 $mm^3$ | |
| Theta range for data collection | 2.14 to 25.86°. | |
| Index ranges | -12<=h<=12, -21<=k<=21, -11<=l<=11 | |
| Reflections collected | 15907 | |
| Independent reflections | 3046 [R(int) = 0.0384] | |
| Completeness to theta = 25.86° | 99.9 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3046 / 0 / 217 | |
| Goodness-of-fit on $F^2$ | 1.010 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0434, wR2 = 0.1014 | |
| R indices (all data) | R1 = 0.0705, wR2 = 0.1143 | |
| Largest diff. peak and hole | 0.135 and -0.148 e.$Å^{-3}$ | |




**Scheme 37.** Plausible Mechanism

In conclusion, we have developed a facile protocol for coupling of 2-alkanoyl(aroyl) pyridines with representative alkyl vinyl ketones under the influence of TMSOTf leading to the formation of indoziline derivatives. This strategy clearly demonstrates the applications of certain ketones as suitable electrophiles in BH reaction and also opens up the ground for design of appropriate substrates for two component Baylis-Hillman reactions.

## A Facile and Stereoselective Synthesis of Tetrasubstituted Alkenes from Baylis-Hillman Alcohols

Tetrasubstituted alkene[167] framework with defined stereochemistry occupies a special place in organic and medicinal chemistry because of the presence of such moiety in various biologically active molecules [tamoxifen,[168, 169] panomifene[168, 169]], natural products (abudinol A & B,[170] isodomoic acids G & H[171]) (Fig. 14), drug molecules,[169, 172] liquid crystals.[173] Tetrasubstituted alkene units are also widely implicated in material research such as reversible optical data storage devices,[174] molecular switches[175] due to rotationally locked and highly congested nature of olefinic double bond. Due to the above-mentioned applications and also because of the challenges involved in synthesis due to its congested nature, development of facile and convenient strategies for obtaining tetrasubstituted alkene framework with defined stereochemistry has been and continuous to be a facinating and attractive problem in synthetic chemistry.[167, 176–179]

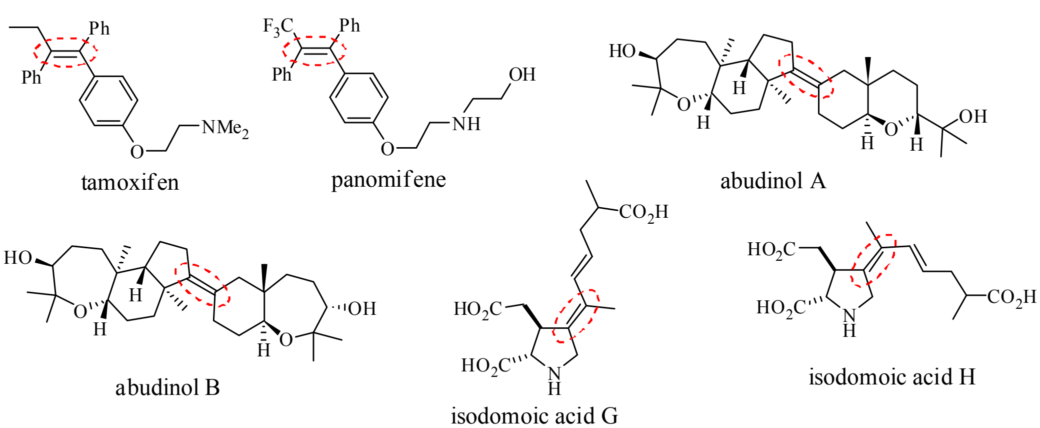
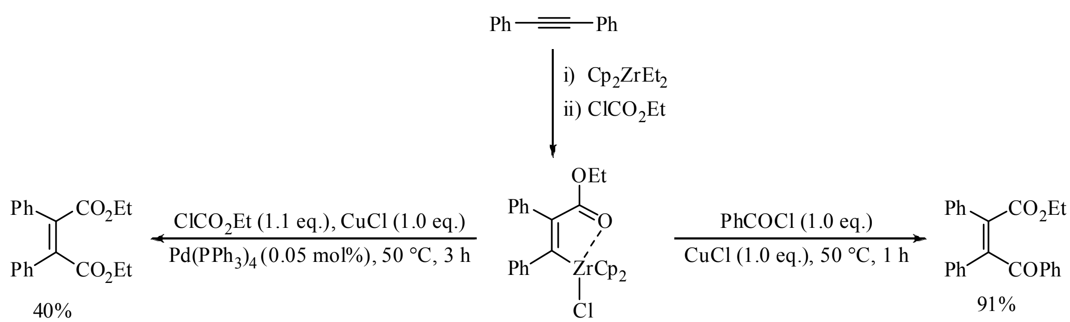



**Figure 14.** Representative natural products and biologically active molecules containing tetrasubstituted alkene framework

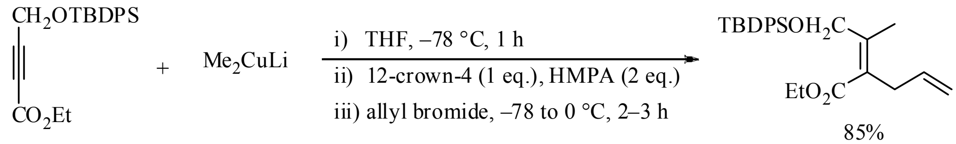
The most significant challenge in synthesis of tetrasubstituted alkenes is the difficulty in establishing the stereochemistry without X-ray diffraction data and NOESY (2D NMR). Despite these difficulties, there are some reports in the literature on the synthesis of tetrasubstituted alkenes. A few such methodologies are discussed in this section.

Takahashi and coworkers have reported an elegant strategy for synthesis of the tetrasubstituted alkenes via carbozirconation of diphenylacetylenes (by treating with $Cp_2ZrEt_2$ and ethyl chloroformate) followed by the treatment of the resulting zirconated intermediate **89** with various electrophiles under the influence of $Pd(PPh_3)_4$/CuCl or CuCl following the reaction sequence as shown in Scheme 38.[176]



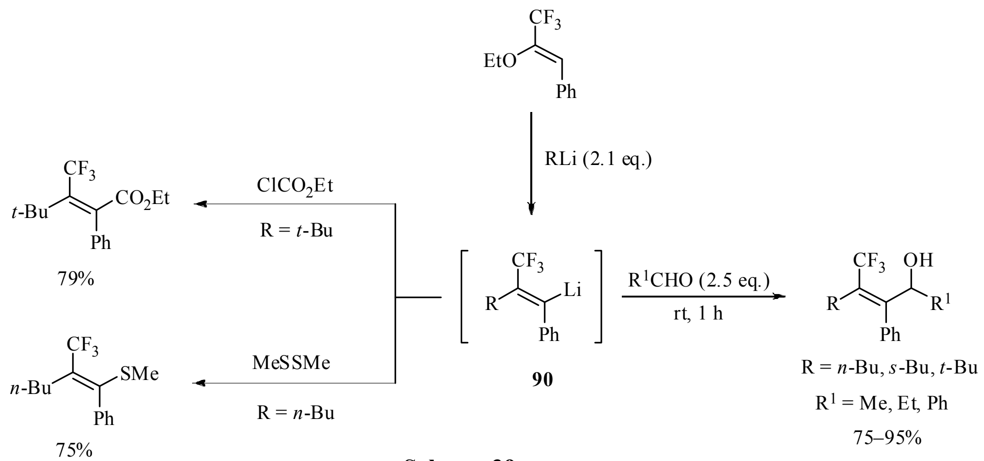

**Scheme 38**

Hall and Zhu have developed a facile protocol for synthesis of tetrasubstituted alkenes via electrophilic addition of vinyl cuprates onto substituted acetylenic esters followed by alkylation (see Eq. 40 for one example).[177]



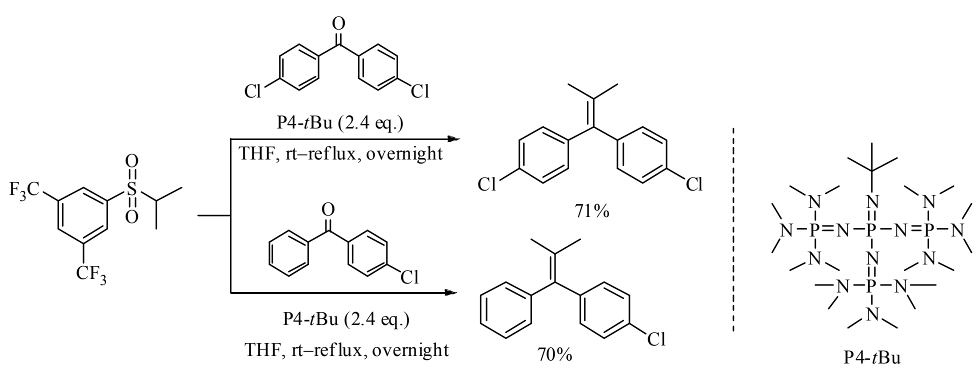

(Eq. 40)

Bonnet-Delpon and coworkers have developed an interesting strategy for the stereoselective synthesis of tetrasubstituted alkenes via carbolithiation of enol ethers [using alkyl lithium reagents (2.1 equiv.) such as *n*-BuLi or *s*-BuLi or *t*-BuLi] followed by the reaction of resulting intermediate **90** with various electrophiles according to Scheme 39.[178]




**Scheme 39**

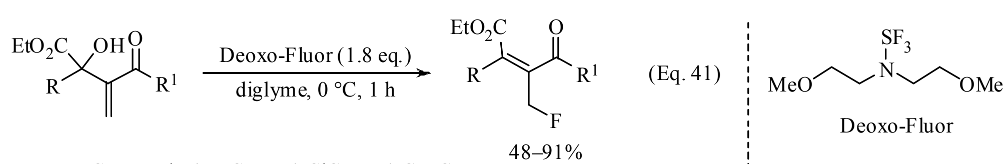
Najera and coworkers have synthesized the tetrasubstituted alkenes via Schwesinger's base (P4-*t*Bu) promoted Julia-Kocienski olefination of 3,5-bis(trifluoromethyl)phenyl sulfones with ketones as shown in Scheme 40.[179]




**Scheme 40**

The Baylis-Hillman alcohols derived from activated alkenes (acrylates, acrylonitrile, alkyl vinyl ketones, etc.) and aldehydes have been systematically and extensively employed for obtaining trisubstituted alkenes (containing allyl bromide moiety) with defined stereochmistry.[26, 29, 31, 32] Representative examples were already presented in the preceding section, that is, Introduction chapter-Scheme 12. There is also a report on the synthesis of tetrasubstituted alkenes from BH alcohols derived from *N*-alkylated isatins and acrylates but the stereochemical aspects of the reaction were not described (see Eq. 22, in Introduction chapter).

Literature reveals that Sasai and coworkers have reported a convenient stereoselective synthesis of tetrasubstituted allyl BH fluorides from BH alcohols, obtained from α–keto esters as electrophiles and alkyl vinyl ketones/acrylates as activated alkenes via the treatment with Deoxo-Fluor [bis(2-methoxyethyl)aminosulfur trifluoride] (Eq. 41).[180]

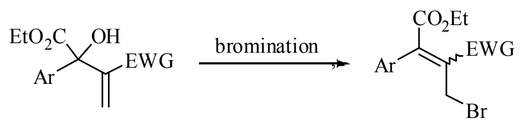



(Eq. 41)

R = Me, $c$-$C_6H_{11}$, Ph, 4-$BrC_6H_4$, 4-$ClC_6H_4$, 4-$CF_3C_6H_4$, 3-$ClC_6H_4$, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 1-Np

$R^1$ = Me, Et, Ph

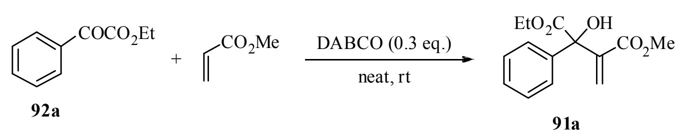
Even though the BH alcohols derived from aldehydes and various activated alkenes have been systematically converted into trisubstituted alknes having an allyl bromide unit, there was not any report on the transformation of BH alcohols obtained from α–keto esters into the corresponding allyl bromides. Such allyl bromides in principle would contain tetrasubstituted alkene moiety with defined stereochemistry. Therefore, it occured to us that it is appropriate to examine the bromination of BH alcohols obtained from α–keto esters as electrophiles and acrylates/acrylonitrile as activated alkenes (Eq. 42).




(Eq. 42)

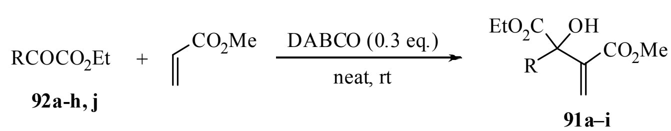
Accordingly, our focus was directed to examine i) the bromination of BH alcohols obtained from methyl acrylate and α–keto esters with a view to understand the stereochemistry of the resulting tetrasubstituted alkenes ii) the bromination of BH alcohols obtained from acrylonitrile and α–keto esters with a view to understand the role of CN group in stereochemical path of the reaction and also to obtain the resulting tetrasubstituted alkenes having allyl bromide functionality with defined stereochemistry.

For this purpose first we selected the BH alcohol, methyl 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanoate (**91a**) for bromination studies. Required alcohol (**91a**) was obtained from traditional DABCO catalyzed BH reaction of commercially available ethyl phenylglyoxalate (**92a**) and methyl acrylate (Eq. 43) following the known procedure.[181]



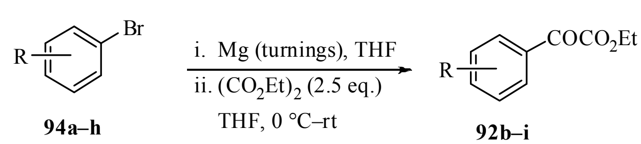

(Eq. 43)

Next the bromination of BH-alcohol (**91a**) was tried under different conditions (for optimization of reaction condition see Table 4). The best results were obtained when the methyl 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanoate **(91a)** was treated with NBS(2.0 eq.)/DMS(4.0 eq.) providing the desired allylic bromide (**93a**) containing tetrasubstituted olefin double bond with (*E*)-configuration [4-ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (**93a**)] at room temperature for 12 hours in 94% yield (see entry 5, Table 4). The structure of the resulting tetrasubstituted olefin **93a** was confirmed by IR, $^1$H NMR [see Spectrum 9], $^{13}$C NMR [see Spectrum 10] and HRMS spectroscopic studies. The (*E*)-stereochemistry of this tetrasubstituted olefin was confirmed by single crystal X-ray diffraction data analysis [See Table VI; for data of **93a**] (for ORTEP diagram see Figure X6). We were pleased to see the reaction is clean and also complete stereoselective. This result was indeed encouraging. Subsequently we extended this strategy for various BH alcohols (**91a**–**i**) prepared from representative α–keto esters (**92a**–**h**, **j**) and methyl acrylate (Eq. 44, Table 5). Structures of all the BH alcohols (**91a**–**i**) were confirmed by IR, $^1$H NMR, $^{13}$C NMR and LCMS spectroscopic studies.



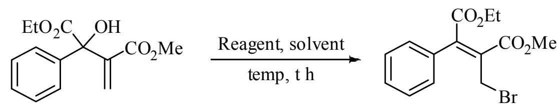

(Eq. 44)

The desired α–keto esters **92b–i** were prepared following the literature procedure by the treatment of arylmagnesium bromides [obtained from Grignard reaction of corresponding aryl bromides **94a–h** with magnesium turnings] with diethyl oxalate as shown in Eq 45 (Table 6).[182] Structures of all the α–keto esters **92b–i** were confirmed by IR, $^1$H NMR, $^{13}$C NMR and LCMS spectroscopic studies.




(Eq. 45)

**Table 4. Optimization of reaction conditions for bromination of BH-alcohol**[a]




| Entry | Reagent (eq.) | Solvent | Temp. (°C) | Time (h) | Product yield (%)[b,c] |
|---|---|---|---|---|---|
| 1[d] | HBr(2.0)/$H_2SO_4$(1.0) | DCM | rt | 12 | — |
| 2[d] | HBr(2.0)/$H_2SO_4$(1.0) | DCM | reflux | 12 | — |
| 3[e] | HBr(2.0)/$H_2SO_4$(1.0) | DCE | reflux | 12 | Trace |
| 4 | HBr(2.0)/$H_2SO_4$(1.0) | DCE | reflux | 24 | 13 |
| **5** | **NBS(2.0)/DMS(4.0)** | **DCM** | **rt** | **12** | **94** |

[a]All reactions were carried out on 2.5 mmol scale of methyl 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanoates (**91a**) under different brominating reaction condtitions in different solvents (5.0 mL). [b]Product **93a** characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS spectroscopic studies. [c]Yield was calculated on the basis of BH-alcohol **91a**. [d]No reaction was observed and starting material **91a** was intact. [e]Trace amount of product **93a** was observed and starting material **91a** was recovered.

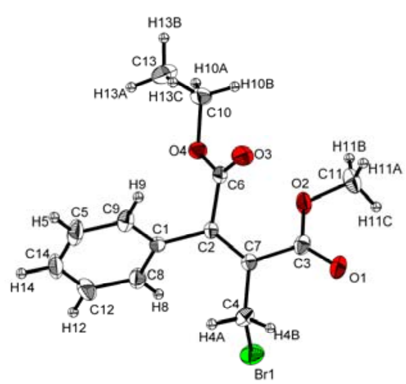
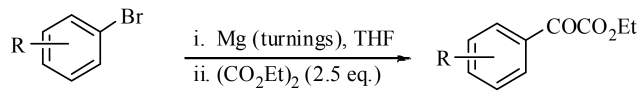



**Figure X6.** ORTEP diagram of the compound **93a**

**Table VI**. Crystal data and structure refinement for **93a**

| | | |
|---|---|---|
| Identification code | 93a | |
| Empirical formula | C14 H15 Br O4 | |
| Formula weight | 327.17 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P 1 21/n 1 | |
| Unit cell dimensions | a = 9.1638(12) Å | α= 90°. |
| | b = 8.6022(10) Å | β= 101.841(13)°. |
| | c = 18.039(3) Å | γ = 90°. |
| Volume | 1391.7(3) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.561 $Mg/m^3$ | |
| Absorption coefficient | 2.960 $mm^{-1}$ | |
| F(000) | 664 | |
| Theta range for data collection | 3.28 to 24.17°. | |
| Index ranges | -9<=h<=10, -9<=k<=6, -20<=l<=20 | |
| Reflections collected | 4608 | |
| Independent reflections | 2229 [R(int) = 0.0329] | |
| Completeness to theta = 24.17° | 99.8 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2229 / 0 / 174 | |
| Goodness-of-fit on $F^2$ | 1.028 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0423, wR2 = 0.1064 | |
| R indices (all data) | R1 = 0.0627, wR2 = 0.1195 | |
| Largest diff. peak and hole | 0.331 and -0.461 e.$Å^{-3}$ | |

**Table 5. Preparation of ethyl arylglyoxylates from aryl bromides[a#]**



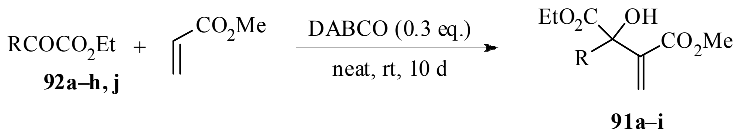
**94a–h** **92b–i**

| Entry | R | Aryl bromide | Product | Yield (%)[b,c] |
|---|---|---|---|---|
| 1 | 4-Me | **94a** | **92b** | 69 |
| 2 | 3-Me | **94b** | **92c** | 64 |
| 3 | 3-MeO | **94c** | **92d** | 65 |
| 4 | 4-MeO | **94d** | **92e** | 62 |
| 5 | 4-EtO | **94e** | **92f** | 66 |
| 6 | 4-Br | **94f** | **92g** | 73 |
| 7 | 4-Cl | **94g** | **92h** | 84 |
| 8 | 2-MeO | **94h** | **92i** | 67 |

[a]All reactions were carried out on 100.0 mmol scale of arylmagnesium bromide (**94a–h**) [obtained from Grignard reaction of corresponding aryl bromides with magnesium turnings in THF (100 mL)] with diethyl oxalate (250.0 mmol) in THF (100 mL) at –10 °C for 1 h. [b]All compounds (**92b–i**) were characterized by IR, $^{1}$H NMR, $^{13}$C NMR, and LCMS spectroscopic studies. [c]Yields were calculated on the basis of aryl bromides (**94a–h**). [#]Ethyl phenylglyoxylate (**92a**) and ethyl pyruvates (**92j**) are commercially available and purchased from Sigma-Aldrich.

To understand the generality of this strategy we have subjected BH alcohols (**91a–h**), to optimized reaction condition to provide tetrasubstituted alkenes, 4-ethyl 1-methyl 2-bromomethyl-3-arylmaleates (**93a–h**) with *E*-selectivity exclusively in excellent yields (Table 7). The structures of the resulting tetrasubstituted olefins were confirmed by IR, $^{1}$H

**Table 6. Preparation of BH-alcohols of ethyl arylglyoxylates and methyl acrylate[a]**



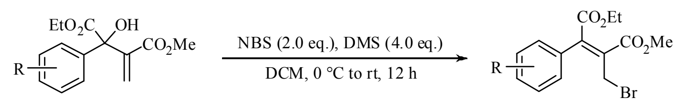

| Entry | R | Ethyl arylglyoxylate | Product | Yield (%)[b,c] |
|---|---|---|---|---|
| 1 | Ph | **92a** | **91a** | 71 |
| 2 | 4-Me$C_6H_4$ | **92b** | **91b** | 74 |
| 3 | 3-Me$C_6H_4$ | **92c** | **91c** | 69 |
| 4 | 3-MeO$C_6H_4$ | **92d** | **91d** | 76 |
| 5 | 4-MeO$C_6H_4$ | **92e** | **91e** | 78 |
| 6 | 4-EtO$C_6H_4$ | **92f** | **91f** | 81 |
| 7 | 4-Br$C_6H_4$ | **92g** | **91g** | 82 |
| 8 | 4-Cl$C_6H_4$ | **92h** | **91h** | 81 |
| 9[d] | Me | **92j** | **91i** | 41 |

[a]All reactions were carried out on 40.0 mmol scale of various ethyl arylglyoxylates (**92a–h, j**) with methyl acrylate (80.0 mmol) under the catalytic influence of DABCO (30 mol%) at room temperature for 10 days. [b]All compounds (**91a–i**) were characterized by IR, $^1$H NMR, $^{13}$C NMR, and LCMS spectroscopic studies. [c]Yields were calculated on the basis of ethyl arylglyoxylates (**92a–h, j**). [d]Reaction was performed for 7 days.

NMR, $^{13}$C NMR and HRMS spectroscopic studies.

We have then extended this methodology for aliphatic congener **91i** which was conveniently prepared via the reaction of commercially available ethyl pyruvate (**92j**) and methyl acrylate.[181] The resulting allyl bromide **93i** was obtained in (*E*)-stereoselectivity in 84% yield (Eq. 46). The structure of the resulting tetrasubstituted olefin **93i** was confirmed

**Table 7. Bromination of BH-alcohols of methyl acrylate[a]**

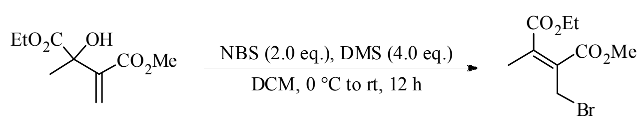


91a-h

93a-h

| Entry | BH alcohol | R | Product | Yield (%)[b,c] |
|---|---|---|---|---|
| 1 | **91a** | H | **93a**[d] | 94 |
| 2 | **91b** | 4-Me | **93b** | 92 |
| 3 | **91c** | 3-MeO | **93c** | 93 |
| 4 | **91d** | 3-Me | **93d** | 90 |
| 5 | **91e** | 4-MeO | **93e** | 94 |
| 6 | **91f** | 4-EtO | **93f** | 91 |
| 7 | **91g** | 4-Br | **93g** | 90 |
| 8 | **91h** | 4-Cl | **93h** | 88 |

[a]All reactions were carried out on 10.0 mmol scale of BH-alcohol (**91a–h**) with NBS (20.0 mmol) and DMS (40.0 mmol) in $CH_2Cl_2$ (50.0 mL). [b]All compounds (**93a–h**) were characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS spectroscopic studies. [c]Yields were calculated on the basis of BH-alcohols (**91a–h**). [d]Structure of this molecule was further confirmed by single crystal X-ray diffraction data analysis.



91i

93i

84%

(Eq. 46)

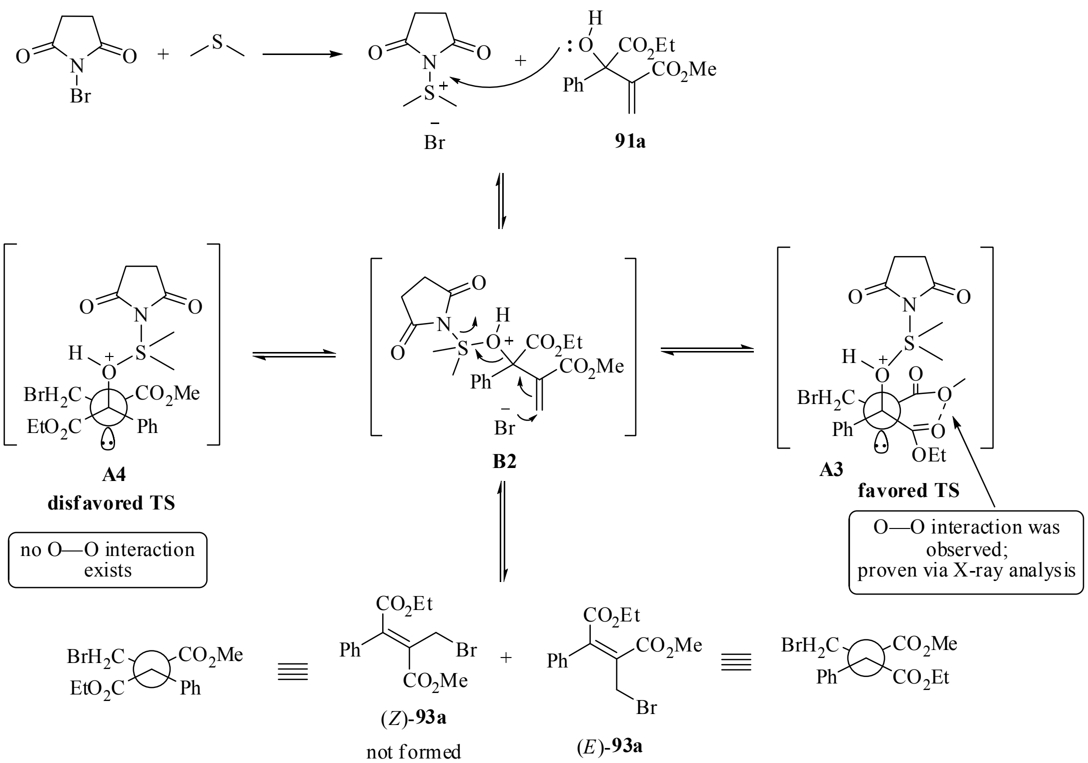
by IR, $^1$H NMR [see Spectrum 11], $^{13}$C NMR [see Spectrum 12] and HRMS spectroscopic studies. (*E*)-Stereochemistry was further confirmed by NOESY (2D NMR) [see Spectrum 13] experiment (the correlation between allylic protons and protons of double bond attached methyl group). A plausible mechanism for stereoselective formation of, 4-ethyl 1-methyl 2-bromomethyl-3-aryl/alkylmaleates (**93a-i**) with (*E*)-selectivity is presented in Scheme 41.

Initially, dimethyl sulfide gives a sulfonium salt on reaction with NBS. This salt then reacts with BH alcohol possibly to generate oxonium ion complex (**B2**) having **O–S–N** type bonding pattern. Then bromide ion attacks this species in $S_N2$ fashion to provide allylic bromides exclusively with (*E*)-stereochemistry. The stereochemistry of the product **93a** was assigned by single crystal X-ray diffraction data analysis. We were pleased to notice and it revealed that there is an O—O interaction[183] as shown in Figure P1.


**Figure P1.** O—O interaction in compound **93a** (within the range of H-bond distance)

Based on the O—O attractive interaction as evidenced by single crystal X-ray diffraction data analysis in the case of product **93a** and also on the basis of the fact that the aromatic groups and methyl group provide similar stereochemical directions, we tend to propose that transition state (**A3**) containing O—O attractive interactions is favored than the transition state (**A4**) thus providing the resulting allyl bromide exclusively with (*E*)-

stereochemistry. Thus O—O attractive interactions may indirectly result in COOEt–COOMe attractions to provide the resulting tetrasubstituted alkenes containing both the ester moieties *cis* to each other as presented in Scheme 41.

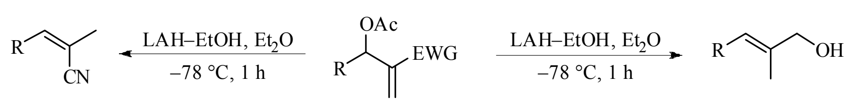



**Scheme 41.** Plausible Mechanism

**The bromination of BH alcohols obtained from acrylonitrile and α–keto esters with a view to understand the role of CN group in stereochemical path of the reaction**

It has been well documented in the literature that the Baylis-Hillman adducts obtained from methyl acrylate and acrylonitrile have shown opposite stereochemical directions in various reactions. Representative such examples are given in Schemes 42–46.[94, 184–187]

Our research group has reported a remarkable reversal of stereoselectivity in the reduction of acetates of BH alcohols derived from methyl acrylate to acrylonitrile. The reduction of BH acetates, methyl 3-acetoxy-2-methylenealkanoates, with $LiAlH_4$/EtOH gave the (2*E*)-2-methylalk-2-en-1-ols (**95**) whereas the similar reduction of 3-acetoxy-2-methylene-alkanenitriles provided the (2*Z*)-2-methylalk-2-enenitriles (**96**) as shown in Scheme 42.[94] Similarly Friedel-Crafts reaction of BH alcohols, obtained from methyl acrylate, with benzene provided (*E*)-trisubstituted alkenes **97** as a major compound along with (*Z*)-isomeric products in respectable amounts while BH alcohols, derived from acrylonitrile, gave alkenes with high (*Z*)-selectivity **98** under similar Friedel-Crafts reaction conditions as shown in Scheme 43.[184]



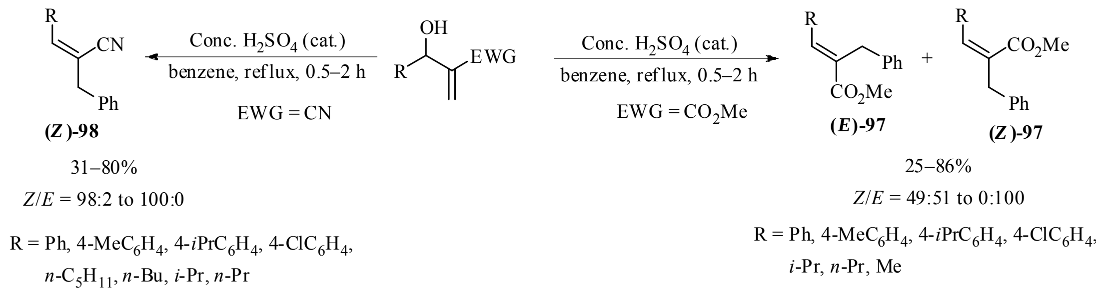

**(*Z*)-96**
62–77%

R = $n$-$C_4H_9$, $n$-$C_5H_{11}$, $n$-$C_6H_{13}$, Ph, 4-$MeC_6H_4$, 3-(4-$MeC_6H_4$)Bu

**(*E*)-95**
60–84%

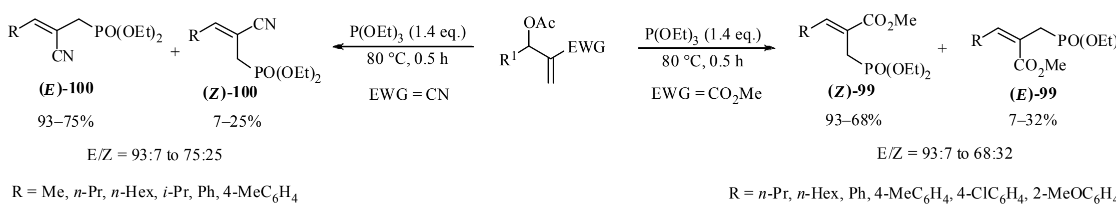
R = $n$-$C_4H_9$, $n$-$C_5H_{11}$, $n$-$C_6H_{13}$, Ph, 4-$MeC_6H_4$, 3-(4-$MeC_6H_4$)Bu, 4-$ClC_6H_4$

**Scheme 42**



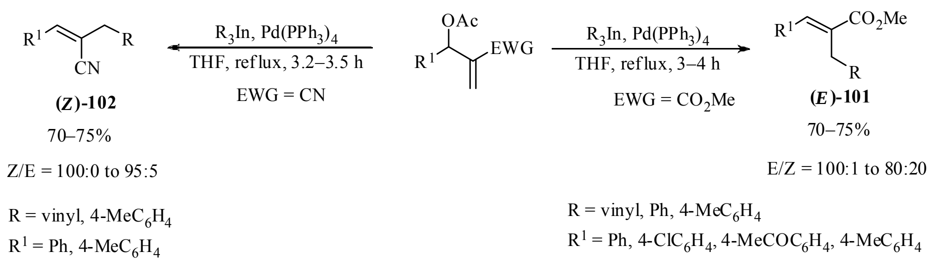
**Scheme 43**

Subsequently, our research group studied the phosphrylation reaction of acetates of BH alcohols derived from methyl acrylate and acrylonitrile via the nucleophilic addition with $P(OEt)_3$ and noticed the significant stereochemical reversal in the products formed **99** and **100** (from esters to nitriles) (Scheme 44).[185]



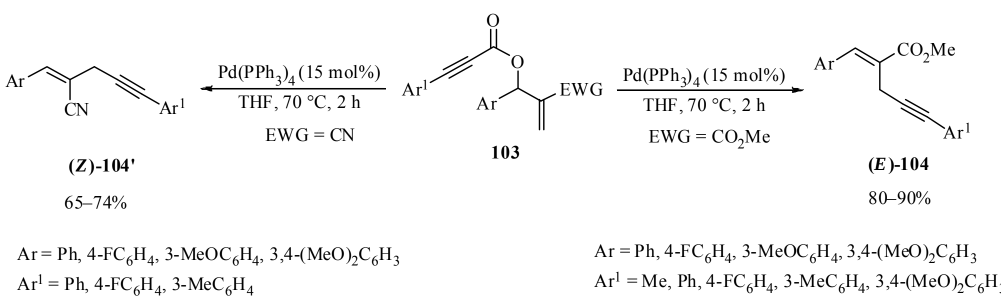
**Scheme 44**

Ranu and coworkers have also reported a similar reversal of stereochemistry in the alkylation reaction (products **101** and **102** respectively) of acetates of BH alcohols derived from methyl acrylate and acrylonitrile via the treatment with triarylindium in the presence of catalytic $Pd(PPh_3)_4$ as described in Scheme 45.[186]



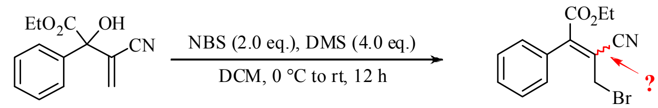

**Scheme 45**

Recently, Tummanapalli and coworkers have disclosed a fascinating regio- and stereoselective tandem allylic rearrangement/intramolecular decarboxilative coupling of aryl propiolates **103** of BH-adducts (prepared from methyl acrylate and acrylonitrile) using $Pd(PPh_3)_4$ catalyst. They have also observed a remarkable stereochemical reversal in the products formed (*E*)-**104** and (*Z*)-**104′** (Scheme 46).[187]




**Scheme 46**

Based on the above mentioned observations, we have undertaken to examine the bromination of BH-adducts obtained from α–keto esters and acrylonitrile to have an understanding of the stereochemical course of the reaction (Eq. 46). Accordingly, we have first selected the BH alcohol, ethyl 3-cyano-2-hydroxy-2-phenylbut-3-enoate (**105a**), obtained from ethyl phenylglyoxylate and acrylonitrile for treatment with NBS/DMS (Eq. 47).



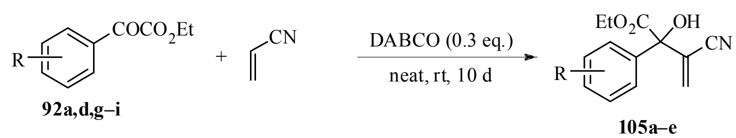

**105a** **(*E*/*Z*)-106a** (Eq. 47)

Thus BH-alcohol, ethyl 3-cyano-2-hydroxy-2-phenylbut-3-enoate (**105a**), on treatment with NBS/DMS at room temperature [following the similar procedure as in the case of esters (**93**)] provided the resulting allyl bromide, ethyl 4-bromo-3-cyano-2-(2-methoxyphenyl)but-2-enoate, as a separable mixture of (*E*)-**106a** and (*Z*)-**106a** in the ratio of 2:1 [determined by the ratio of isomeric allylic protons in $^1$H NMR spectrum of the crude mixture]. Both (*E*)- and (*Z*)-bromides were separated by silica gel column chromatography. Their structures were determined by IR, $^1$H NMR [see Spectrum 14 for (*E*)-**106a** & Spectrum 16 for (*Z*)-**106a**], $^{13}$C NMR [see Spectrum 15 for (*E*)-**106a** & Spectrum 17 for (*Z*)-**106a**] and HRMS spectral analyses. Stereochemistry was assigned on the basis of chemical shift values of allylic methylene protons[184,185,188] in $^1$H NMR spectra of (*E*)-**106a** and (*Z*)-**106a**. The allylic methylene protons (*trans* to ester group) of (*E*)-isomer appeared at δ 3.98 while that of (*Z*)-isomer (*cis* to ester group) appeared at δ 4.30.

We have then prepared representative BH-alcohols **105b–e** [ethyl 3-cyano-2-hydroxy-2-arylbut-3-enoates] via the reaction of various α–keto esters with acrylonitrile following the known procedure (see Table 8).[181] Subsequently these alcohols **105b–e** were subjected to bromination reaction with NBS/DMS. The resulting allyl bromides **106b–e** were obtained as a separable mixtures of (*E*)-(major) and (*Z*)-(minor) isomers in 2:1 ratio in overall good yields (Table 9). Structures of all these allyl bromides were confirmed by IR, $^{1}H$ NMR, $^{13}C$ NMR and HRMS spectroscopic studies.

The stereochemistry was further confirmed by single crystal X-ray diffraction data analysis in the case of (*E*)-**106e** and (*Z*)-**106e** [for data of (*E*)-**106e** and (*Z*)-**106e** see Tables VII & VIII and ORTEP diagrams see Figures X7 & X8 respectively]. In the case of (*Z*)-**106b–e**, the allylic protons appeared at δ 4.28, 4.32, 4.32, 4.49 [downfield in comparison to that of

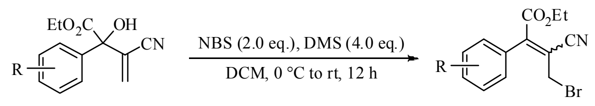
**Table 8. Preparation of BH-alcohols of ethyl arylglyoxylate and acrylonitrile**[a,@]




| Entry | R | Ethyl arylglyoxylate | Product | Yield (%)[b,c] |
|---|---|---|---|---|
| 1 | H | **92a** | **105a** | 77 |
| 2 | 3-MeO | **92d** | **105b** | 82 |
| 3 | 4-Br | **92g** | **105c** | 85 |
| 4 | 4-Cl | **92h** | **105d** | 84 |
| 5 | 2-MeO | **92i** | **105e** | 84 |

[a]All reactions were carried out on 40.0 mmol scale of various ethyl arylglyoxylates (**92**) with acrylonitrile (80.0 mmol) under the catalytic influence of DABCO (30 mol%) at room temperature for 10 days. [b]All compounds **105a–e** were characterized by IR, $^{1}H$ NMR, $^{13}C$ NMR, and LCMS spectroscopic studies. [c]Yields were calculated on the basis of ethyl arylglyoxylates (**92**). [@]In order to have continuity and easy understanding the BH alcohols obtained from α-keto esters **92a,d,g–i** are numbered as **105a–e** respectively.

**Table 9. Bromination of BH-alcohols of acrylonitrile**[a]




| Entry | BH alcohol | R | Product | Yield (%)[b,c] | Overall Yield (%) (*E*)+(*Z*) |
|---|---|---|---|---|---|
| 1 | **105a** | H | **(*E*)-106a** | 58 | 87 |
| | | | **(*Z*)-106a** | 29 | |
| 2 | **105b** | 3-MeO | **(*E*)-106b** | 61 | 94 |
| | | | **(*Z*)-106b** | 33 | |
| 3 | **105c** | 4-Br | **(*E*)-106c** | 59 | 87 |
| | | | **(*Z*)-106c** | 28 | |
| 4 | **105d** | 4-Cl | **(*E*)-106d** | 62 | 92 |
| | | | **(*Z*)-106d** | 30 | |
| 5 | **105e** | 2-MeO | **(*E*)-106e**[d] | 60 | 92 |
| | | | **(*Z*)-106e**[d] | 32 | |

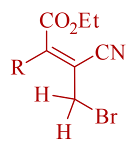
[a]All reactions were carried out on 10.0 mmol scale of BH-alcohol (**105a-e**) with NBS (20.0 mmol) and DMS (40.0 mmol) in $CH_2Cl_2$ (50.0 mL). [b]All compounds [**(*E*)-106a-e** and **(*Z*)-106a-e**] were characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS analyses. [c]Yields were calculated on the basis of BH-alcohols (**105a-e**). [d]Structures of these molecules were further confirmed by single crystal X-ray diffraction data analysis.

(*E*)-isomer] respectively while that of (*E*)-**106b–e**, the allylic protons appeared at δ 3.99, 3.97, 3.96, 3.99 respectively in $^1$H NMR spectra.

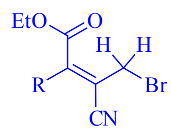
This difference is due to the deshielding effect of the ester carbonyl group on allylic protons of (*Z*)-isomers in $^1$H NMR spectrum. In$^{13}$C NMR spectra, the allylic carbons of

(*Z*)-**106a–e** appeared at δ 26.99, 26.99, 26.65, 26.63, 26.52 respectively while that of (*E*)-**106a–e**, the same allylic carbons appeared at δ 27.80, 28.54, 28.61, 27.59, 27.61 respectively (Table 10). Even though there is no significant difference in these $^{13}$C NMR chemical shift values we felt that it is appropriate to present these values in Table 10 to have some understanding/comparison.

**Table 10. The $^{1}$H &$^{13}$C NMR correlation between (*E*)-and (*Z*)-isomers of compounds 106**



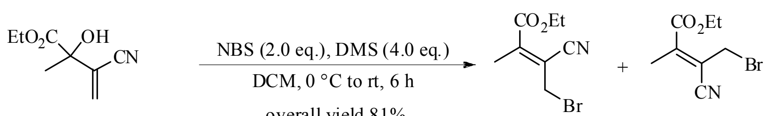
(*E*)-isomer



(*Z*)-isomer

| R | $^{1}$H NMR Chem. Shift (δ) | | $^{13}$C NMR Chem. Shift (δ) | |
|---|---|---|---|---|
| | (*E*)- | (*Z*)- | (*E*)- | (*Z*)- |
| Ph (**106a**) | 3.98 | 4.30 | 27.80 | 26.99 |
| 3-MeO$C_6H_4$ (**106b**) | 3.99 | 4.28 | 28.54 | 26.99 |
| 4-Br$C_6H_4$ (**106c**) | 3.97 | 4.32 | 27.61 | 26.65 |
| 4-Cl$C_6H_4$ (**106d**) | 3.96 | 4.32 | 27.59 | 26.63 |
| 2-MeO$C_6H_4$ (**106e**) | 3.99 | 4.49 | 28.61 | 26.52 |
| $CH_3$ (**106f**) | 4.15 | 4.37 | 26.78 | 25.82 |

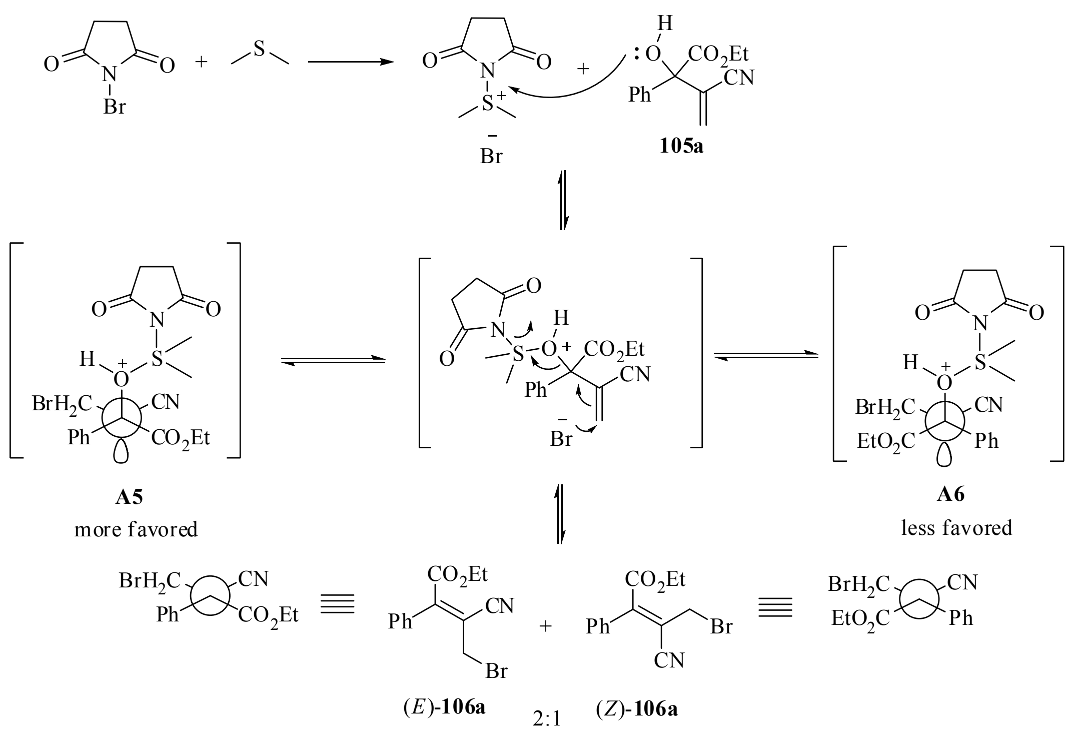
We have then extended this methodology for aliphatic congener **105f** which was prepared via the reaction of ethyl pyruvate (**92j**) and acrylonitrile following the literature procedure.[181] Thus the bromination of BH alcohol **105f** gave allyl bromide as a mixture of (*E*)-1**06f** and (*Z*)-**106f** in 81% overall yield (Eq. 48). $^{1}$HNMR spectrum [(*E*)-allylic methylene protons appeared at δ 4.14 (*trans* to ester group) while that of (*Z*)-isomer appeared at δ 4.37] of the crude mixture shows that (*E*)-isomer is predominating [(*E*):(*Z*) is 3:1]. Both the isomers were seperated using silica-gel column chromatography. The structures of both the resulting (*E*)- and (*Z*)- tetrasubstituted olefins were confirmed by IR, $^{1}$H NMR [see Spectrum 18 for (*E*)-**106f** & Spectrum 20 for (*Z*)-**106f**], $^{13}$C NMR [see Spectrum 19 for (*E*)-**106f** & Spectrum 21 for (*Z*)-**106f**] and HRMS spectroscopic studies.




**105f** **(*E*)-106f** 61% 3:1 **(*Z*)-106f** 20% (Eq. 48)

(*E*)-Stereochemistry of the major isomer of **106f** was further confirmed by NOESY (2D NMR) [see Spectrum 22] experiment, which showed the correlation between allylic methylene protons and allyl methyl protons. (*Z*)-Stereochemistry of the minor isomer of **106f** was also futher established by NOESY (2D NMR) [see Spectrum 23] experiment which does not give any indication for correlation between allylic methylene protons and allyl methyl protons.

A plausible mechanism has been described for the bromination of BH-alcohol **105a** with NBS/DMS reagent system in Scheme 47. We have proposed a similar pathway as in the case of ester (Scheme 41). The product formation clearly indicates that the transition state **A5** in which ester and nitrile are *cis* to each other (in Gauche conformation) is favored than that one (TS **A6**) having nitrile and ester *trans* to each other. These results would indicate to some extent that phenyl is sterically less demanding than ester or there may be some kind of CN—COOEt attractive interaction that might be directing the stereochemical course of the reaction to provide (*E*)-allylic bromide as a major product. In the case of methy derivative of BH alcohol, ethyl 3-cyano-2-hydroxy-2-methylbut-3-enoate **(105f)**, the resulting bromides were obtained with (*E*)-isomer (75%) as major and (*Z*)-isomer (25%) as minor. Since methyl group is smaller than the COOEt, the formation of (*E*)-isomer as a major product certainly indicates the possibiliy of CN—COOEt attractive interactions in the transition state (Gauche conformation as shown in transition state **TS A5**). Therefore we reasoned that the moderate (*E*)-stereoselectivity might be due to the CN—COOEt attractive interactions. We also feel that this mechanism explains the results reasonably well. However we can not rule out any other alternative mechanism(s).




**Scheme 47.** Plausible Mechanism

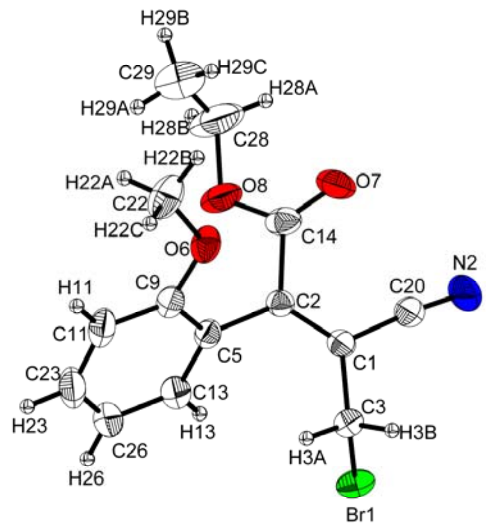



**Figure X7.** ORTEP diagram of the compound (*E*)-**106e**

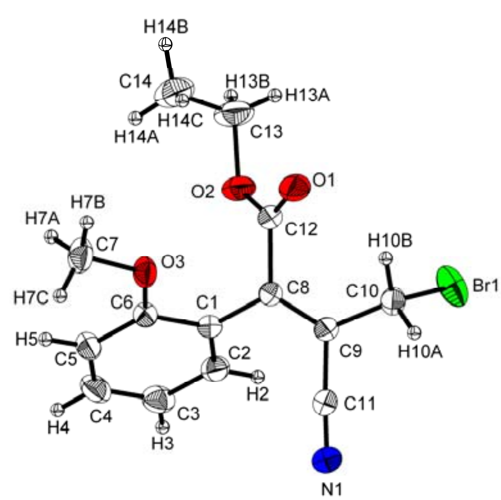



**Figure X8.** ORTEP diagram of the compound (*Z*)-**106e**

**Table VII.** Crystal data and structure refinement for (*E*)-**106e**

| | | |
|---|---|---|
| Identification code | (*E*)-106e | |
| Empirical formula | C14 H14 Br N O3 | |
| Formula weight | 324.17 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 10.127(5) Å | α= 90°. |
| | b = 37.316(17) Å | β= 115.066(7)°. |
| | c = 8.741(4) Å | γ = 90°. |
| Volume | 2992(2) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.439 $Mg/m^3$ | |
| Absorption coefficient | 2.750 $mm^{-1}$ | |
| F(000) | 1312 | |
| Theta range for data collection | 1.09 to 25.95°. | |
| Index ranges | -12<=h<=12, -45<=k<=45, -10<=l<=10 | |
| Reflections collected | 28938 | |
| Independent reflections | 5750 [R(int) = 0.0672] | |
| Completeness to theta = 25.95° | 98.0 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 5750 / 1 / 347 | |
| Goodness-of-fit on $F^2$ | 0.690 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0454, wR2 = 0.1403 | |
| R indices (all data) | R1 = 0.0780, wR2 = 0.1763 | |
| Largest diff. peak and hole | 0.653 and -0.412 e.$Å^{-3}$ | |

**Table VIII.** Crystal data and structure refinement for (*Z*)-**106e**

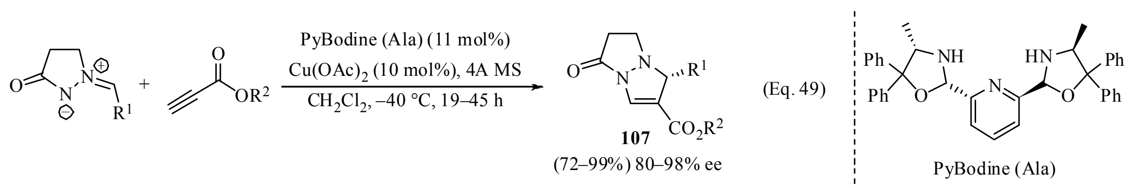
| | | |
|---|---|---|
| Identification code | (*Z*)-106e | |
| Empirical formula | C14 H14 Br N O3 | |
| Formula weight | 324.17 | |
| Temperature | 298(2) K | |
| Wavelength | 1.54184 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 8.9401(7) Å | α= 105.015(8)°. |
| | b = 9.5710(8) Å | β= 106.930(8)°. |
| | c = 9.7936(11) Å | γ = 102.773(7)°. |
| Volume | 733.35(12) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.468 $Mg/m^3$ | |
| Absorption coefficient | 3.860 $mm^{-1}$ | |
| F(000) | 328 | |
| Theta range for data collection | 5.03 to 66.59°. | |
| Index ranges | -8<=h<=10, -11<=k<=10, -11<=l<=11 | |
| Reflections collected | 4178 | |
| Independent reflections | 2596 [R(int) = 0.0226] | |
| Completeness to theta = 66.59° | 99.8 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2596 / 0 / 176 | |
| Goodness-of-fit on $F^2$ | 1.000 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0554, wR2 = 0.1370 | |
| R indices (all data) | R1 = 0.0614, wR2 = 0.1443 | |
| Largest diff. peak and hole | 0.379 and -0.834 e.$Å^{-3}$ | |

In conclusion, we have developed a facile and simple synthetic methodology for obtaining of sterically congested and geometrically defined tetrasubstituted alkenes using Baylis-Hillman alcohols as key synthons. This methodology clearly demonstrates the applicability of NBS/DMS system as a suitable reagent for transformation of BH alcohols (obtained from ethyl arylglyoxylates and methyl acrylate/acrylonitrile) into tetrasubstituted alkenes containing allyl bromide functionality with defined stereochemistry. We have also further confirmed the (*E*)-and (*Z*)-stereochemistry of tetrasubstituted alkenes using single crystal X-ray diffraction data analysis in the case of (*E*)-**106e** and (*Z*)-**106e.**

## Application of Tetrasubstituted Alkenes (Allyl Bromides) obtained from BH-Adducts in [3+2] Annulation Strategy: Stereoselective Synthesis of Dihydrofuran-fused-spirooxindoles

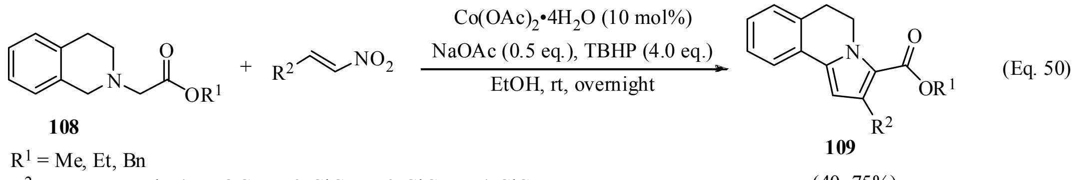
The 1,3-dipolar cycloaddition or [3+2] annulation reactions are synthetically important strategies for building five membered ring frameworks. Various examples were presented in the literature and a few such methods are discussed in this section.

Arai and coworkers have described an interesting strategy for synthesis of fused bicyclic pyrazolone skeleton **107** via [3+2] annulation strategy involving azomethine imine, as dipolarophile, and propiolate, as a dipole, according to Eq. 49.[189]



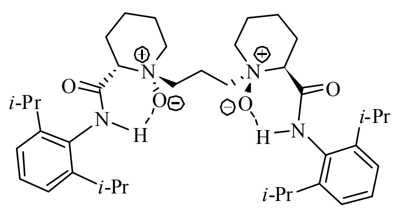

$R^1$ = *i*-Pr, *c*-$C_6H_{11}$, Ph, 4-Me$C_6H_4$, 2-Me$C_6H_4$, 3-Cl$C_6H_4$, 4-F$C_6H_4$, 4-I$C_6H_4$, 4-MeO$C_6H_4$
$R^2$ = Me, Et, *t*-Bu

An oxidative [3+2] cycloaddition of nitroolefins with dihydroisoquinoline esters **108** producing dihydropyrrolo[2,1-a]isoquinolines **109** was reported by Wang and coworkers (Eq. 50).[190]

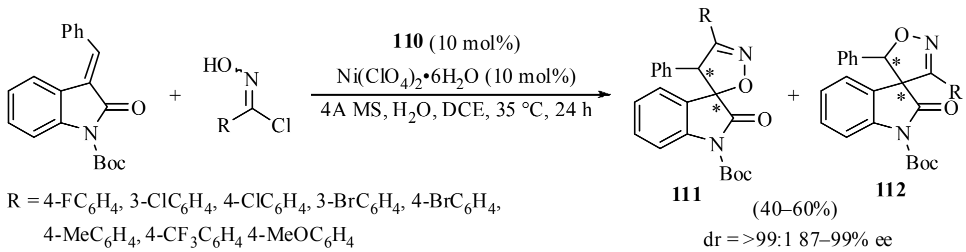



$R^1$ = Me, Et, Bn
$R^2$ = *n*-Pr, *i*-Pr, Ph, 4-MeO$C_6H_4$, 2-Cl$C_6H_4$, 3-Cl$C_6H_4$, 4-Cl$C_6H_4$, 4-$CF_3C_6H_4$, 4-F$C_6H_4$, 4-Br$C_6H_4$, 1-Np, 2-Np, 2-furyl

Feng and coworkers have reported 1,3-dipolar cycloaddition reaction of 3-arylidene-2-oxindoles with nitrile oxides using chiral *N*,*N*'-dioxide-nickel(II) complex **110** as a catalyst to provide the resulting isomeric spiro-oxindoles **111** & **112** in high enantioselectivities following the reaction sequence shown in Eq. 51.[191]

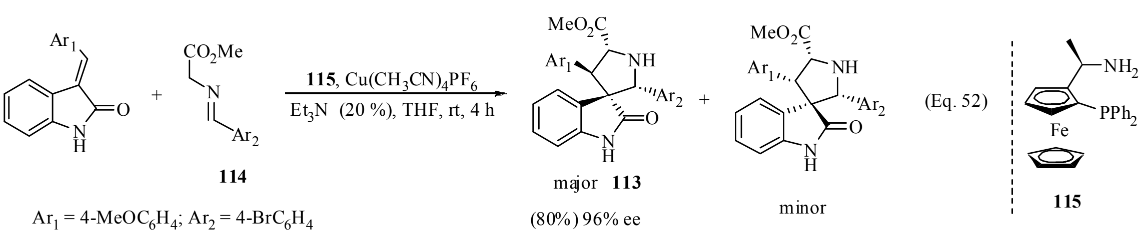



**110**



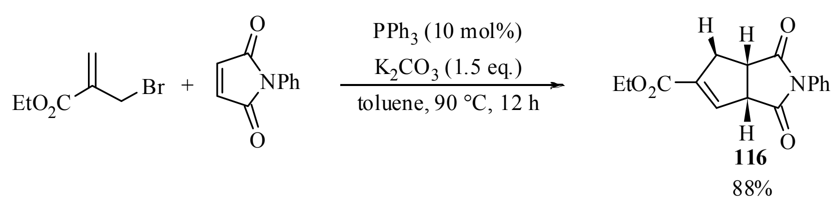

(Eq. 51)

An efficient enantioselective synthesis of spiro-oxindoles **113** containing pyrrolizidine ring via 1,3-dipolar cycloaddition reaction between azomethine ylides (generated from imine **114**) and 3-arylidene-2-oxindoles using chiral phosphine **115** as catalyst (Eq. 52) was described by Waldmann and coworkers.[192]



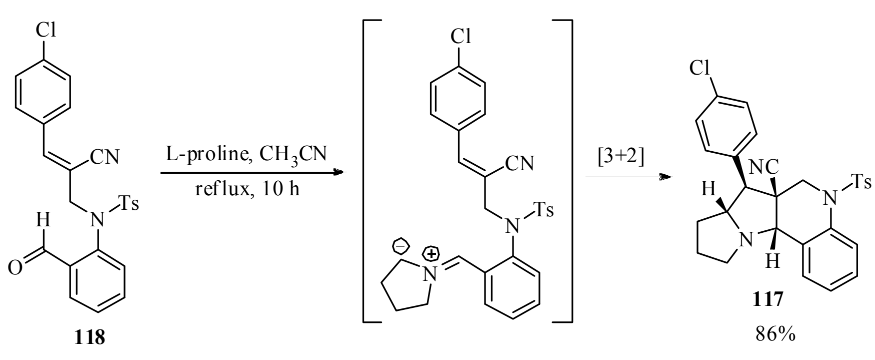
BH-adducts and their derivatives have also been effectively utilized in [3+2] cycloaddition reactions as dipolarophiles (with azomethine ylides[193, 194] and benzonitrile oxide[195] *etc*. as dipoles) and also as dipoles (with DEAD/DIAD,[105] enones,[196] methyleneindolinones,[197] isatylidene malononitriles,[198] *N*-phenylmaleimide,[199, 200] propargyl sulfones[201] *etc*. as dipolarophiles) to produce a variety of carbocylic and heterocylic compounds of medicinal importance. Representative examples are presented in Eqs. 53–56 and Scheme 48.

Lu and coworkers have utilized the Baylis-Hillman bromides as dipoles for [3+2] addition with *N*-phenylsuccinimide as dipolarophile under the catalytic influence of $PPh_3$ to produce cyclopentene fused pyrrolozidine-dione framework **116** in good yields (Eq. 53).[200]



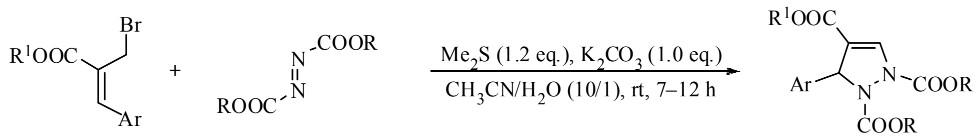

(Eq. 53)

Recently, Bakthadoss and coworkers have synthesized the pyrroloquinolines **117** via an intramolecular [3+2] annulation strategy involving allylamine **118**, derived from BH bromides and L-proline (One example is given in Eq. 54).[202]




(Eq. 54)

Few years ago our research group has disclosed an efficient reaction strategy for synthesis of substituted dihydropyrazole derivatives **119**, by effective utilization of BH bromides as dipoles and dialkyl azodicarboxylates as dipolarophiles, in the presence of DMS/$K_2CO_3$ in a facile one-pot [3+2] annulation strategy (Eq. 55).[105]

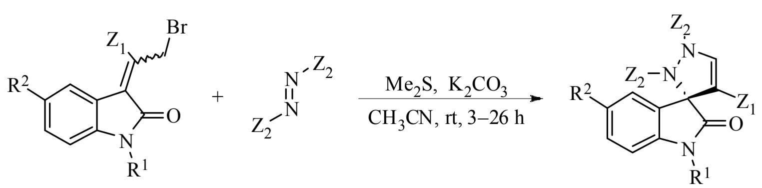


**119**
64–79%

(Eq. 55)

Ar = $C_6H_5$, 4-Me$C_6H_4$, 3-Cl$C_6H_4$, 4-Cl$C_6H_4$, 4-Br$C_6H_4$
$R^1$ = Me, Et, *i*-Bu; R = Et, *i*-Pr

Later on Shanmugam and coworkers have extended a similar 1,3-dipolar cycloaddition reaction of bromides obtained from BH alcohols (derived from *N*-alkylated isatins and methyl acrylate and acrylonitrile) to the stereoselective synthesis of spirocyclopyrazole-oxindoles **120** in good yields (Eq. 56).[203]

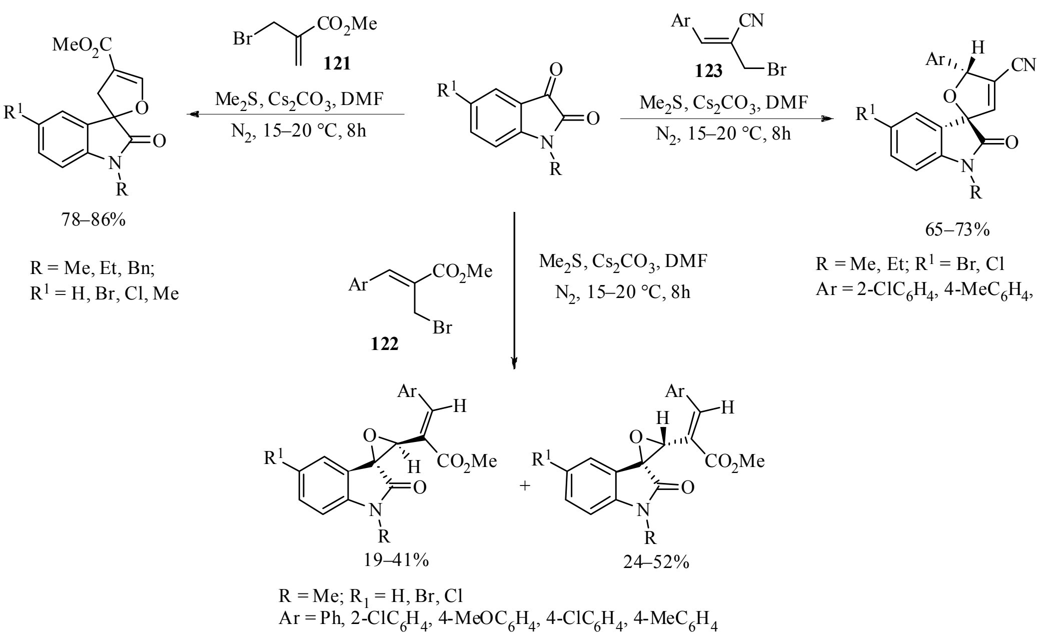


**120**
66–91%

(Eq. 56)

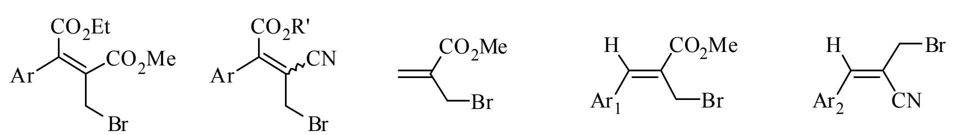
$R^1$ = Me, $CH_2CCH$, Bn; $R^2$ = H, Me, F, CHO
$Z_1$ = $CO_2$Me, CN: $Z_2$ = $CO_2$Et, $CO_2$*i*-Pr, $CO_2$*t*-Bu

Recently, our research group has reported a facile steric factors directed synthesis of spiroepoxy and spirodihydrofuran oxindoles via [3+2] cycloaddition reaction of BH bromides **121–123** (as 1,3-dipoles) with isatins (as dipolarophiles) according to the reaction strategy shown in Scheme 48.[204]

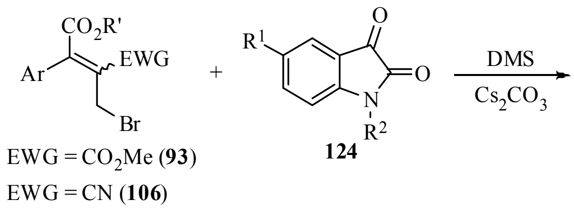


**Scheme 48**

This study clearly demonstrated the influence of steric factors arising from three BH bromides **121**, **122**, and **123** in [3+2] annulation reactions with isatins as dipolarophiles. This study also puts before us a big question, that is, what would be the possible application of tetrasubstituted allyl bromides **93** and **106** (both *E*- and *Z*-isomers) as dipoles and isatin derivatives **124** as dipolarophiles in [3+2] annulation reactions (Eq. 57).



**93** **(*E*/*Z*)-106** **121** **(*Z*)-122** **(*E*)-123**

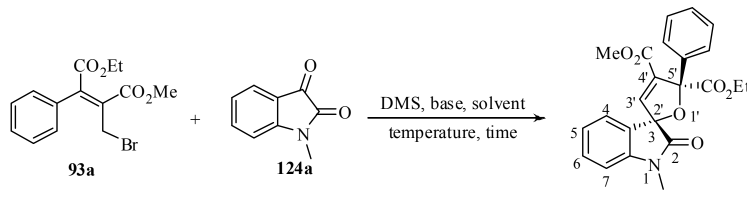


(Eq. 57)

i) **Application of tetrasubstituted alkenes of ester derivative as a source of dipole for [3+2] annulation with isatin derivatives**

Accordingly we have first undertaken the study of [3+2] annulation strategy between the dipoles generated from BH bromides, 4-ethyl 1-methyl 2-bromomethyl-3-arylmaleates **93** (tetrasubstituted alkenes described in the previous section of this chapter), and isatin derivatives as dipolarophiles. Thus we examined the reaction of the allyl bromide [4-ethyl 1-methyl 2-bromomethyl-3-phenylmaleate (**93a**)] with *N*-methylisatin (**124a**) under various conditions (for optimization see Table 11). The best result was obtained when the bromide (**93a**) (1.5 mmol) was treated with *N*-methylisatin (**124a**) (1.0 mmol) in DMF (3.0 mL) in the presence of $Me_2S$ (2.0 mmol) and $Cs_2CO_3$ (2.0 mmol) at room temperature for 24 hours, thus providing the resulting spirooxindole containing dihydrofuran ring, [3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (**125a**), in 86% isolated yield. The structure of the compound was confirmed by IR, $^1$H NMR [see Spectrum 24], $^{13}$C NMR [see Spectrum 25] and HRMS spectroscopic studies. Stereochemistry was assigned on the basis of single crystal X-ray diffraction data analysis [for data see Table IX and ORTEP diagram see Figure X9].

**Table 11. Optimization of [3+2]-cycloaddition reaction conditions[a]**



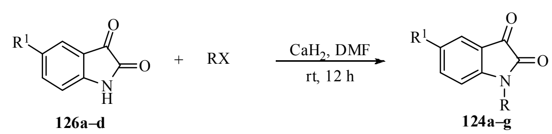

| S.No. | Base | Solvent | Temp. (°C) | Time (h) | Product yield (%)[b,c] |
|---|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | DMF | rt | 8 | 56 |
| **2** | **$Cs_2CO_3$** | **DMF** | **rt** | **24** | **86** |
| 3 | $Cs_2CO_3$ | DMF | rt | 48 | 58 |
| 4 | $Cs_2CO_3$ | DMF | 80 | 24 | 44 |
| 5 | $Cs_2CO_3$ | DMF | 80 | 5 | 23 |
| 6 | $Cs_2CO_3$ | DMF | 120 | 5 | 11 |
| 7 | $K_2CO_3$ | DMF | rt | 24 | 23 |
| 8[d] | KO*t*-Bu | DMF | rt | 24 | — |
| 9[d] | NaH | DMF | rt | 24 | — |
| 10[d] | $Cs_2CO_3$ | THF | rt | 24 | — |
| 11 | $Cs_2CO_3$ | $CHCl_3$ | rt | 24 | 32 |
| 12 | $Cs_2CO_3$ | $CH_3CN$ | rt | 24 | 39 |

[a]All reactions were carried out on 1.0 mmol scale of 1-methylisatin (**124a**) and 1.5 mmol of BH-bromide **93a** under the influence of DMS (2.0 mmol) and various bases (2.0 mmol) in different solvents (3.0 mL). [b]Product **125a** was characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS analyses. [c]Yield was calculated on the basis of 1-methylisatin (**124a**). [d]No reaction was observed and starting material **124a** was intact.

To understand generality of this methodology we have performed the reaction between various substituted isatins **124a–g** and different BH bromides (**93a-f**). The resulting dihydrofuran-fused-spirooxindoles (**125a–l**) were obtained in 72–86% yields (Table 13). Structures of all the compounds were confirmed by IR, $^{1}$H NMR [see Spectrum 26 for compound **125e**], $^{13}$C NMR [see Spectrum 27 for compound **125e**] and HRMS spectroscopic studies. Stereochemistry was assigned on the basis of single crystal X-ray diffraction data analysis of componuds **125i–k** [for data see Tables X–XII and ORTEP diagrams see Figures X10–X12 respectively].

The required *N*-alkylated isatins **124a–g** were prepared from isatins **126a–d** via the treatment with corresponding alkyl halide following the literature procedure (Table 12).[205]

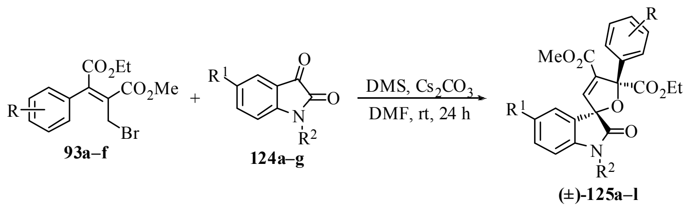
**Table 12. Synthesis of isatin derivatives**[a]




| Entry | $R^1$ | RX | Product | Yield (%)[b,c] |
|---|---|---|---|---|
| 1 | H(**126a**) | MeI | **124a** | 83 |
| 2 | H(**126a**) | EtBr | **124b** | 80 |
| 3 | H(**126a**) | BnBr | **124c** | 74 |
| 4 | H(**126a**) | *n*-PrBr | **124d** | 77 |
| 5 | Cl(**126b**) | MeI | **124e** | 72 |
| 6 | Me(**126c**) | MeI | **124f** | 75 |
| 7 | Br(**126d**) | MeI | **124g** | 72 |

[a]All reactions were carried out on 100 mmol scale of isatin (**126a–d**) and $CaH_2$ (200 mmol) with RX (250 mmol) in DMF (100 mL) were heated 40–50 °C for 12 h. [b]All compounds (**124a–g**) were characterized by IR, $^{1}$H NMR, $^{13}$C NMR, and LCMS spectroscopic studies. [c]Yields were calculated on the basis isatin (**126**).

**Table 13**. **Synthesis of dihydrofuran fused spirooxindoles via [3+2]-cycloaddition reaction**[a]



| S.No. | R | $R^1$ | $R^2$ | Product | Yield (%)[b,c] |
|---|---|---|---|---|---|
| 1 | H (**93a**) | H | Me (**124a**) | **125a**[d] | 86 |
| 2 | H (**93a**) | H | Et (**124b**) | **125b** | 77 |
| 3 | H (**93a**) | H | Bn (**124c**) | **125c** | 75 |
| 4 | H (**93a**) | H | *n*-Pr (**124d**) | **125d** | 80 |
| 5 | H (**93a**) | Cl | Me (**124e**) | **125e** | 78 |
| 6 | H (**93a**) | Me | Me (**124f**) | **125f** | 72 |
| 7 | H (**93a**) | Br | Me (**124g**) | **125g** | 73 |
| 8 | 4-Me (**93b**) | H | Me (**124a**) | **125h** | 81 |
| 9 | 3-MeO (**93c**) | H | Me (**124a**) | **125i**[d] | 79 |
| 10 | 3-Me (**93d**) | H | Me (**124a**) | **125j**[d] | 77 |
| 11 | 4-MeO (**93e**) | H | Me (**124a**) | **125k**[d] | 83 |
| 12 | 4-EtO (**93f**) | H | Me (**124a**) | **125l** | 82 |

[a] All reactions were carried out on 1.0 mmol scale of isatins **124a–g** and 1.5 mmol of BH-bromides **93a–f** under the influence of DMS (2.0 mmol) and $Cs_2CO_3$ (2.0 mmol) in DMF (3.0 mL). [b]All compounds (**125a-l**) were characterized by IR, $^1$H NMR, $^{13}$C NMR, and HRMS spectroscopic studies. [c]Yields were calculated on the basis of isatin **124**. [d]Structure of these molecules were further confirmed by single crystal X-ray diffraction data analysis.

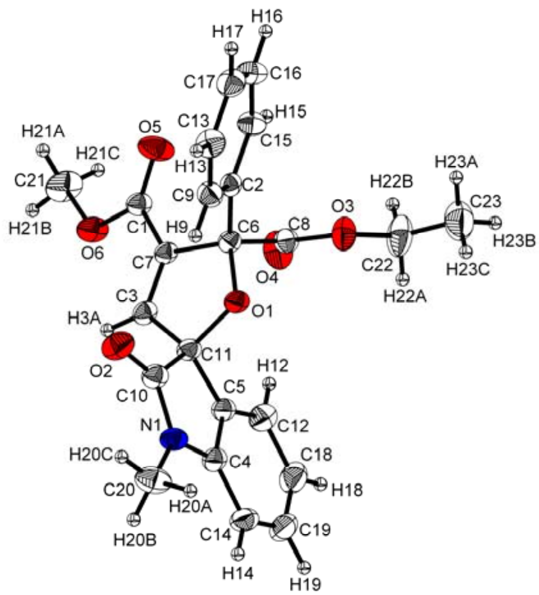



**Figure X9.** ORTEP diagram of the compound (±)-**125a**

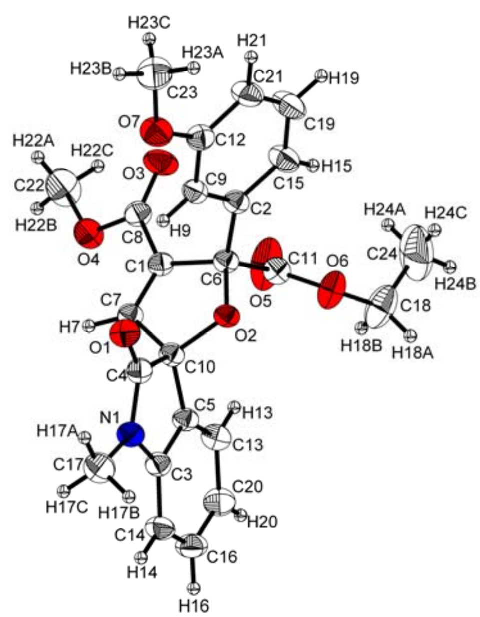



**Figure X10.** ORTEP diagram of the compound (±)-**125i**

**Table IX.** Crystal data and structure refinement for (±)-**125a**

| | | |
|---|---|---|
| Identification code | (±)-125a | |
| Empirical formula | C23 H21 N O6 | |
| Formula weight | 407.41 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P 1 21/n 1 | |
| Unit cell dimensions | a = 9.0237(5) Å | α= 90°. |
| | b = 14.1300(12) Å | β= 91.934(6)°. |
| | c = 15.9401(10) Å | γ = 90°. |
| Volume | 2031.3(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.332 $Mg/m^3$ | |
| Absorption coefficient | 0.097 $mm^{-1}$ | |
| F(000) | 856 | |
| Crystal size | 0.45 x 0.30 x 0.20 $mm^3$ | |
| Theta range for data collection | 2.88 to 24.71°. | |
| Index ranges | -10<=h<=10, -16<=k<=14, -18<=l<=18 | |
| Reflections collected | 7528 | |
| Independent reflections | 3451 [R(int) = 0.0432] | |
| Completeness to theta = 24.71° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9809 and 0.9577 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3451 / 0 / 274 | |
| Goodness-of-fit on $F^2$ | 1.031 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0558, wR2 = 0.1096 | |
| R indices (all data) | R1 = 0.0996, wR2 = 0.1310 | |
| Largest diff. peak and hole | 0.263 and -0.272 e.$Å^{-3}$ | |

**Table X.** Crystal data and structure refinement for (±)-**125i**

| | | |
|---|---|---|
| Identification code | (±)-125i | |
| Empirical formula | C24 H23 N O7 | |
| Formula weight | 437.43 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 12.4289(17) Å | α= 90°. |
| | b = 11.9630(16) Å | β= 110.550(2)°. |
| | c = 15.722(2) Å | γ = 90°. |
| Volume | 2188.8(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.327 $Mg/m^3$ | |
| Absorption coefficient | 0.098 $mm^{-1}$ | |
| F(000) | 920 | |
| Theta range for data collection | 2.19 to 26.05°. | |
| Index ranges | -15<=h<=15, -14<=k<=14, -19<=l<=19 | |
| Reflections collected | 22267 | |
| Independent reflections | 4313 [R(int) = 0.0318] | |
| Completeness to theta = 26.05° | 99.6 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 4313 / 0 / 293 | |
| Goodness-of-fit on $F^2$ | 1.029 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0491, wR2 = 0.1269 | |
| R indices (all data) | R1 = 0.0580, wR2 = 0.1351 | |
| Largest diff. peak and hole | 0.248 and -0.295 e.$Å^{-3}$ | |

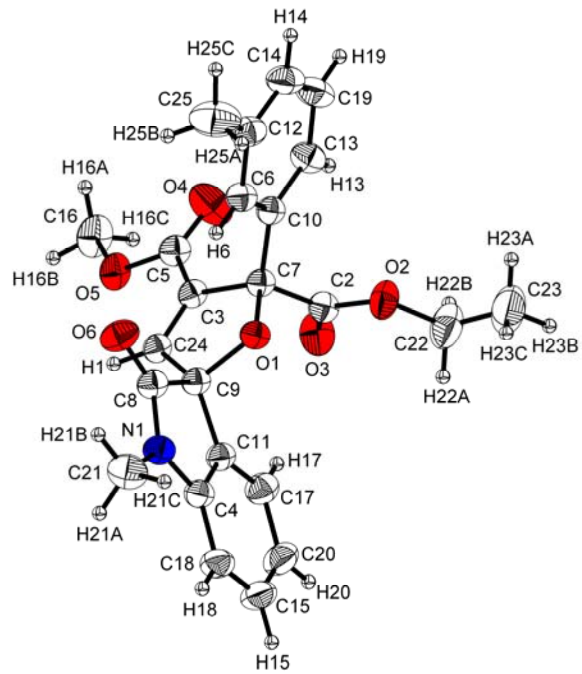



**Figure X11.** ORTEP diagram of the compound (±)-**125j**

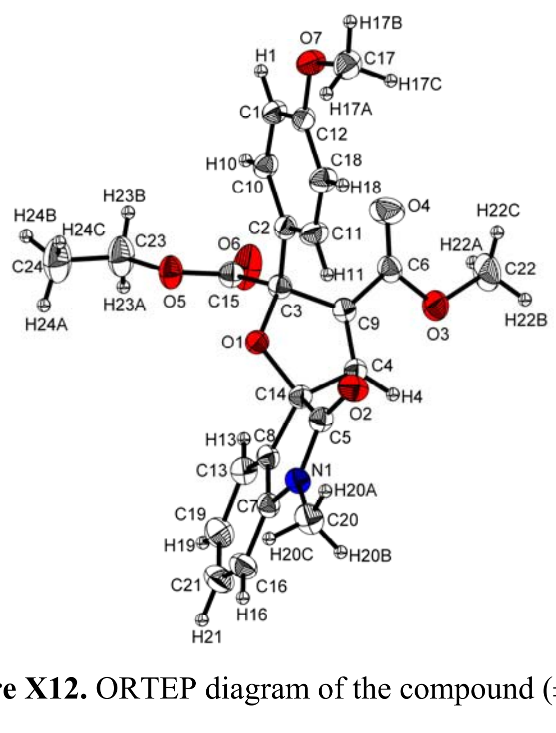



**Figure X12.** ORTEP diagram of the compound (±)-**125k**

**Table XI.** Crystal data and structure refinement for (±)-**125j**

| | | |
|---|---|---|
| Identification code | (±)-125j | |
| Empirical formula | C24 H23 N O6 | |
| Formula weight | 421.43 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 9.109(3) Å | α= 90°. |
| | b = 14.664(4) Å | β= 96.109(4)°. |
| | c = 16.335(4) Å | γ = 90°. |
| Volume | 2169.4(10) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.290 $Mg/m^3$ | |
| Absorption coefficient | 0.093 $mm^{-1}$ | |
| F(000) | 888 | |
| Theta range for data collection | 1.87 to 26.21°. | |
| Index ranges | -11<=h<=11, -18<=k<=18, -20<=l<=20 | |
| Reflections collected | 22090 | |
| Independent reflections | 4336 [R(int) = 0.0305] | |
| Completeness to theta = 26.21° | 99.4 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 4336 / 0 / 284 | |
| Goodness-of-fit on $F^2$ | 1.039 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0543, wR2 = 0.1410 | |
| R indices (all data) | R1 = 0.0629, wR2 = 0.1494 | |
| Largest diff. peak and hole | 0.319 and -0.245 e.$Å^{-3}$ | |

**Table XII.** Crystal data and structure refinement for (±)-**125k**

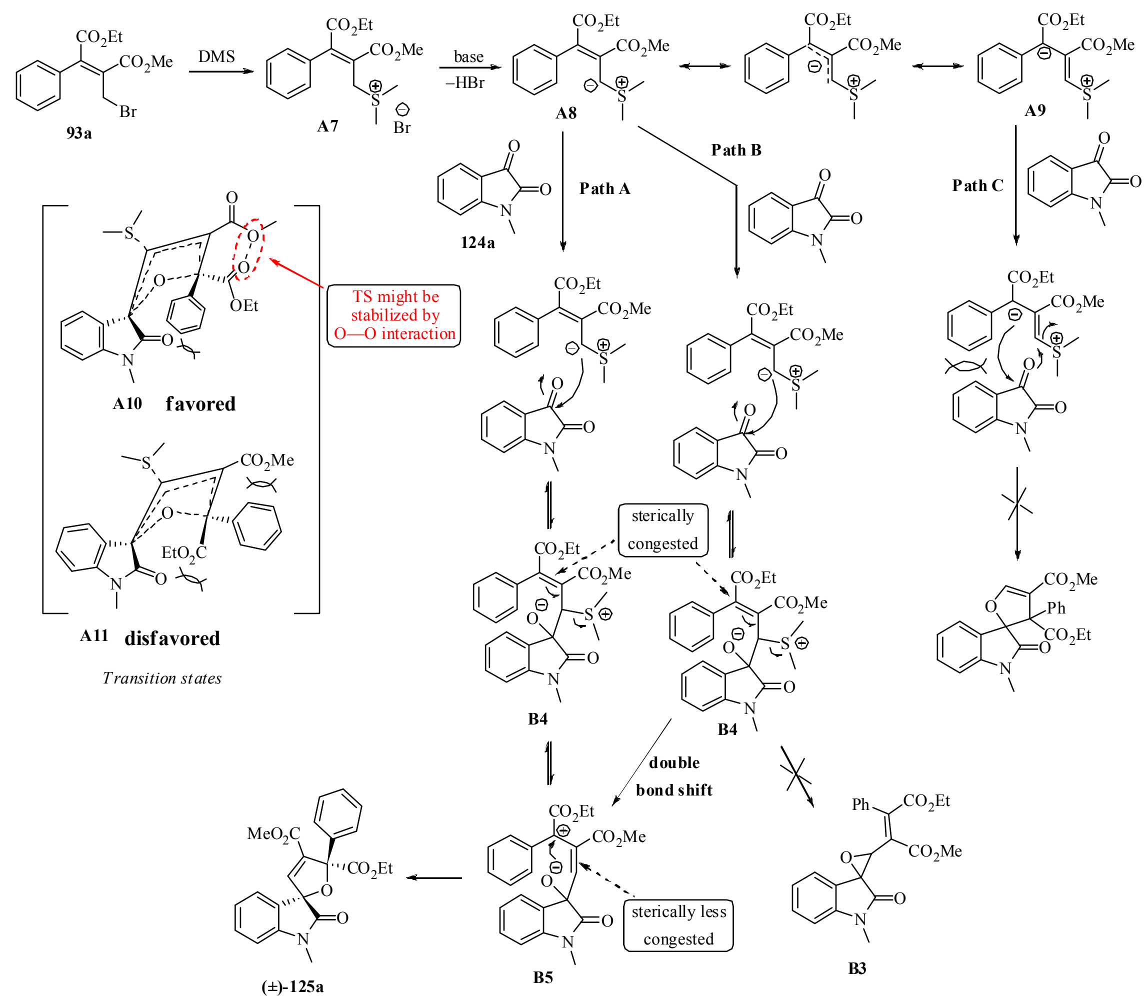
| | | |
|---|---|---|
| Identification code | (±)-125k | |
| Empirical formula | C24 H23 N O7 | |
| Formula weight | 437.43 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 11.986(7) Å | α= 90°. |
| | b = 9.637(6) Å | β= 92.551(10)°. |
| | c = 19.051(12) Å | γ = 90°. |
| Volume | 2198(2) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.322 Mg/m$^3$ | |
| Absorption coefficient | 0.098 mm$^{-1}$ | |
| F(000) | 920 | |
| Theta range for data collection | 1.70 to 25.68°. | |
| Index ranges | -14<=h<=14, -11<=k<=11, -23<=l<=23 | |
| Reflections collected | 18110 | |
| Independent reflections | 4086 [R(int) = 0.0371] | |
| Completeness to theta = 25.68° | 97.8 % | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 4086 / 0 / 293 | |
| Goodness-of-fit on F$^2$ | 1.121 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0496, wR2 = 0.1297 | |
| R indices (all data) | R1 = 0.0724, wR2 = 0.1675 | |
| Largest diff. peak and hole | 0.328 and -0.297 e.Å$^{-3}$ | |

A plausible mechanism has been described for the [3+2] annulation strategy[206a] using the BH bromide **93a** as a dipole and *N*-methylisatin (**124a**) as a dipolarophile, as a model case, in Scheme 49. Initially, DMS forms a sulfonium bromide (**A7**) on reaction with BH bromide **93a**. This salt gets deprotanated in the presence of base to generate in situ a dipole **A8**. Subsequently the in situ formed dipole **A8** adds to the dipolarophile to produce dihydrofuran-fused-spirooxindole (±)-**125a** with defined stereochemistry (aryl ring of the dipolarophile is anti to the aryl group of the dipole).

Theoritically there are three possible reaction pathways A, B, C. Among these three possible pathways, Path C is disfavored due to highly sterically hindered tertiary carbanion **A9** (which can't make any nucleophilic attack on carbonyl of isatin **124a**).

In fact, on the basis of our earlier work (Scheme 48), we expected the formation of epoxide **B3**. Surprisingly no such epoxide formation was observed. Epoxide formation is possible only if dipole **A8** (carbanion α to sulfonium moiety) makes a nucleophilic attack on carbonyl of isatin followed by the attack of in situ formed oxy anion ($O^{\ominus}$) (TS **B4**) on to the carbon (α to the sulfonium moiety). But it looks that once **B4** is formed via the attack of carbanion (α to the sulfonium moiety) onto carbonyl of isatin, the tetrasubstituted alkene double bond might spontaneously shift so as to relieve the steric crowding thus allowing $SMe_2$ group to leave to generate more stable allyl benzylic carbocation **B5**. These points do not favor the Path B. Most probably due to this reason epoxide formation was not observed. After the remarkable steric relaxation, the oxy anion ($O^{\ominus}$) might add comfortably to the benzylic allylic carbocation (**B5**) to provide five membered dihydrofuran derivative

**(125a)**. Our results, to some extent, might derive support from the mechanism proposed by Firestone for 1,3-dipolar cycloaddition reactions (see footnote page no. 103).[206b]




**Scheme 49**. Plausible mechanism

All the above-mentioned considerations favor the Path A. In this pathway two transition states **A10** and **A11** are possible. The transition state **A10** has i) O—O attractive interactions ($CO_2Me$—$CO_2Et$ attraction) and ii) phenyl and N-CO (of isatin) steric interactions, while **A11** has two interactions i) COOMe–phenyl (steric/repulsive) interactions ii) N-CO (of isatin)-COOEt (probably less attractive) interactions. Since transition state **A10**, has one very attractive interaction and one steric interaction, it is more favored than the transition state **A11** which has one steric interactions and one less attractive interaction. Thus, the resulting dihydrofuran derivative was obtained with complete stereoselectivity such that the aryl ring of dipole is anti to aryl group of the dipolariphile.

**Firestone's hypothesis:**

It is worth mentioning here that the work of Firestone on the mechanism of 1,3-dipolar cycloadditions. Firestone mentioned "*unsymmetrical dipolarophiles can add to unsymmetrical 1,3-dipoles in two directions, of which one only is usually found. An understanding of this problem requires consideration of both steric and electronic factors as well as the principle of maximum gain in σ-bond energy.*"

In the discussion he also said "*the electronic factors, when the others are controlled, should direct the course of a concerted cycloaddition toward that orientation in which the more electrophilic end of the dipolarophile links with the negative end of the dipole. For a two-step cycloaddition with a dipolar intermediate the prediction is the same*" (Figure 15).[206b]

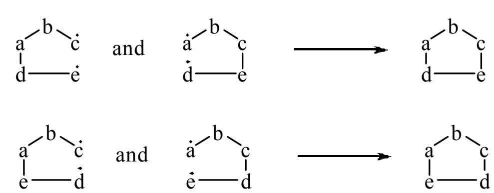
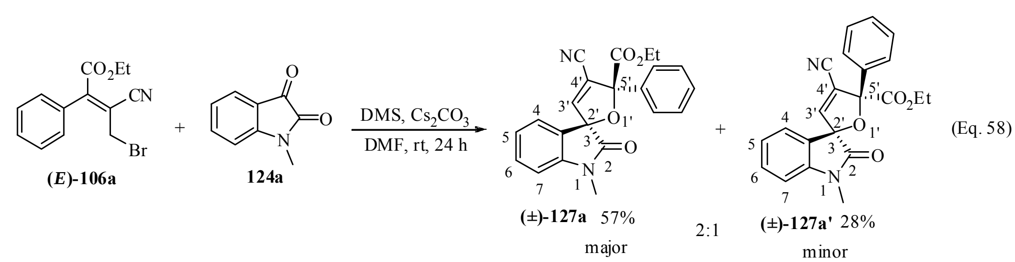


Figure 15

**ii) Application of (*E*)- and (*Z*)-tetrasubstituted alkenes of nitrile derivative as a source of dipoles for [3+2] annulation with isatin derivatives**

After examining the application of tetrasubstituted ally bromides **93** containing ester functionality as a source of dipole for [3+2] annulation reaction with isatin derivatives producing dihydrofuran-fused-spirooxindole with defined stereochemistry, we have directed our attention to examine the application of tetrasubstituted alkene **106** containing nitrile functionality in a similar [3+2] annulation reaction with isatin derivatives **124**. Accordingly we have first selected (*E*)-ethyl 4-bromo-3-cyano-2-phenylbut-2-enoate (**106a**) as a source of 1,3-dipole and *N*-methylisatin (**124a**) as a dipolarophile (Eq. 58). Thus the reaction of (*E*)-allyl bromide **106a** with *N*-methylisatin (**124a**) in DMF (3.0 mL) in the presence of $Me_2S$ (2.0 mmol) and $Cs_2CO_3$ (2.0 mmol) at room temperature for 24 h provided the spirooxindole fused dihydrofuran derivatives as a seperable mixture (*syn* and *anti*) of diastereomers that is [3*R* (2′*R*),5′*S*]/[3*S* (2′*S*),5′*R*]-(1-methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-cyano-2′, 5′-dihydrofuran] (**127a**) and [3*R* (2′*R*),5′*R*]/[3*S* (2′*S*),5′*S*]-(1-methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbo-nyl-5′-phenyl-4′-cyano-2′, 5′-dihydrofuran] (**127a′**) in 57% and 28% isolated yields respectively. Structures of both the diastereomers have been thoroughly confirmed using IR, $^1$H NMR



[see Spectra 28 & 30 for (±)-**127a** and (±)-**127a′** respectively], $^{13}$C NMR [see Spectra 29 & 31 for (±)-**127a** and (±)-**127a′** respectively] and HRMS spectroscopic studies. Stereochemistry was, in each case, established by single crystal X-ray diffraction analysis (for data see Tables XIII and XIV). For ORTEP diagrams see Figure X13 and Figure X14.

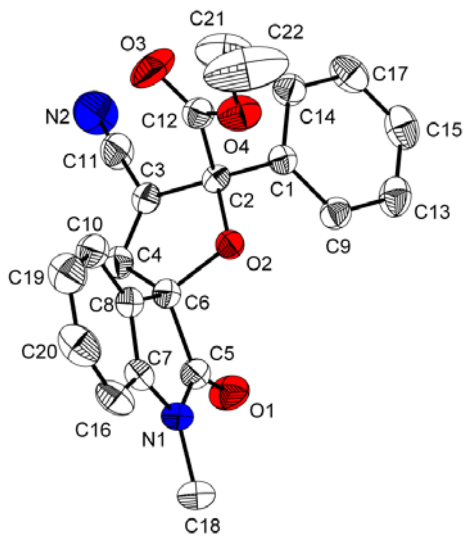



**Figure X13.** ORTEP diagram of the compound (±)-**127a** [from (*E*)-**106a**]

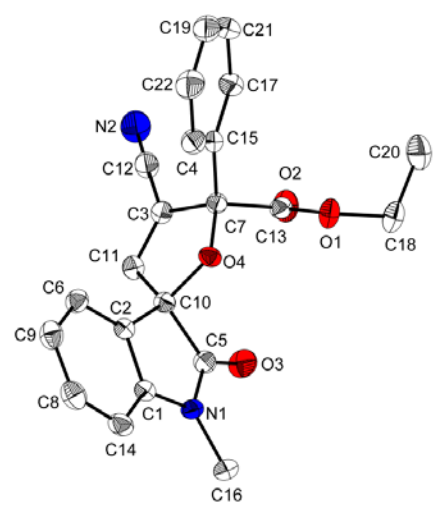



**Figure X14.** ORTEP diagram of the compound (±)-**127a′** [from (*E*)-**106a**]

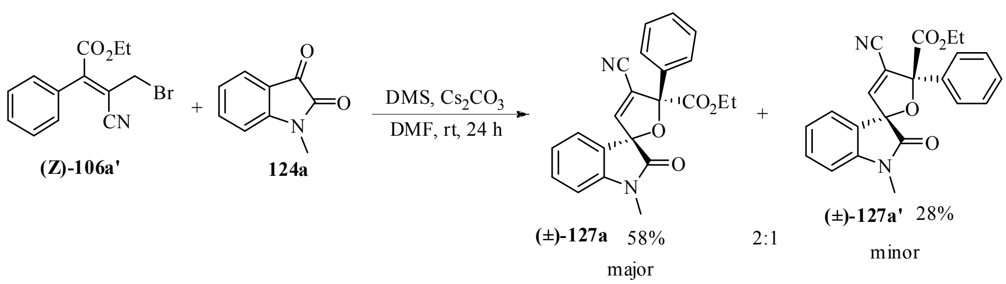
**Table XIII.** Crystal data and structure refinement for (±)-**127a** [from (*E*)-**106a**]

| | | |
|---|---|---|
| Identification code | (±)-127a [from (*E*)-106a] | |
| Empirical formula | C22 H18 N2 O4 | |
| Formula weight | 374.38 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 12.0864(15) Å | α= 90°. |
| | b = 13.1490(16) Å | β= 99.463(2)°. |
| | c = 12.6206(15) Å | γ = 90°. |
| Volume | 1978.4(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.257 $Mg/m^3$ | |
| Absorption coefficient | 0.088 $mm^{-1}$ | |
| F(000) | 784 | |
| Theta range for data collection | 2.16 to 26.07°. | |
| Index ranges | -14<=h<=14, -16<=k<=16, -15<=l<=15 | |
| Reflections collected | 20307 | |
| Independent reflections | 3904 [R(int) = 0.0342] | |
| Completeness to theta = 26.07° | 99.8 % | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3904 / 1 / 255 | |
| Goodness-of-fit on $F^2$ | 1.049 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0622, wR2 = 0.1522 | |
| R indices (all data) | R1 = 0.0754, wR2 = 0.1615 | |
| Largest diff. peak and hole | 0.402 and -0.278 e.$Å^{-3}$ | |

**Table XIV.** Crystal data and structure refinement for (±)-**127a′** [from (*E*)-**106a**]

| | | |
|---|---|---|
| Identification code | (±)-127a′ [from (*E*)-106a] | |
| Empirical formula | C22 H18 N2 O4 | |
| Formula weight | 374.38 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 14.803(8) Å | α= 90°. |
| | b = 7.071(4) Å | β= 96.768(8)°. |
| | c = 18.105(9) Å | γ= 90°. |
| Volume | 1882.0(17) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.321 $Mg/m^3$ | |
| Absorption coefficient | 0.092 $mm^{-1}$ | |
| F(000) | 784 | |
| Crystal size | 0.28 x 0.25 x 0.20 $mm^3$ | |
| Theta range for data collection | 1.39 to 26.05°. | |
| Index ranges | -18<=h<=18, -8<=k<=8, -22<=l<=22 | |
| Reflections collected | 18358 | |
| Independent reflections | 3700 [R(int) = 0.0298] | |
| Completeness to theta = 26.05° | 99.3 % | |
| Absorption correction | None | |
| Max. and min. transmission | 0.9818 and 0.9747 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3700 / 0 / 255 | |
| Goodness-of-fit on $F^2$ | 1.045 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0447, wR2 = 0.1157 | |
| R indices (all data) | R1 = 0.0562, wR2 = 0.1228 | |
| Largest diff. peak and hole | 0.210 and -0.209 e.$Å^{-3}$ | |

Then we have extended the same strategy to allyl bromide (*Z*)-**106a** with a view to understand the stereochemical course of the reaction. Thus treatment of (*Z*)-ethyl 4-bromo-3-cyano-2-phenylbut-2-enoate [(*Z*)-**106a**] with *N*-methylisatin (**124a**) in DMF (3.0 mL) in the presence of $Me_2S$ (2.0 mmol) and $Cs_2CO_3$ (2.0 mmol) at room temperature for 24 h provided the spirooxindole fused dihydrofuran derivatives as a seperable mixture (*syn* and *anti* in 2:1 ratio) of diastereomers in 58% and 28% yields respectively (Eq. 59).




(Eq. 59)

Spectral data [IR, $^{1}$H NMR, $^{13}$C NMR and HRMS spectral analyses] clearly indicated that major compound is nothing but (±)-**127a** {[3*R* (2′*R*),5′*S*]/[3*S* (2′*S*),5′*R*]-(1-methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-cyano-2′, 5′-dihydrofuran]} and minor compound is (±)-**127a′** {[3*R* (2′*R*),5′*R*]/[3*S* (2′*S*),5′*S*]-(1-methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbo-nyl-5′-phenyl-4′-cyano-2′, 5′-dihydrofuran]}.

To further confirm the structures we took single crystal X-ray diffraction data for the major (for data see Table XV and for ORTEP diagram see Figure X15) and minor isomers (for data see Table XVI and for ORTEP diagram see Figure X16). This data unequivocally confirmed the major product is (±)-**127a** while the minor is (±)-**127a′**.

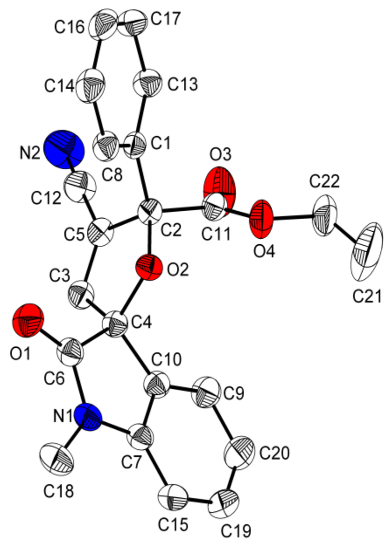



**Figure X15.** ORTEP diagram of the compound (±)-**127a** [from (*Z*)-**106a**]

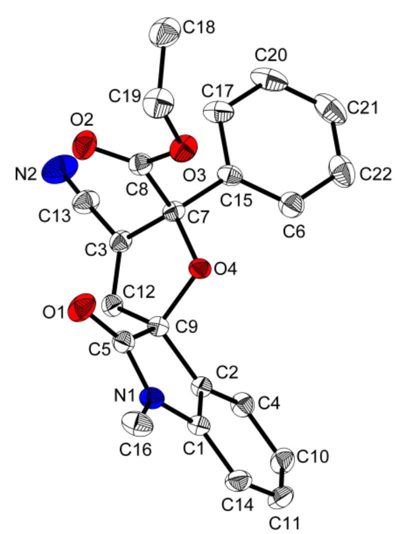



**Figure X16.** ORTEP diagram of the compound (±)-**127a′** [from (*Z*)-**106a**]

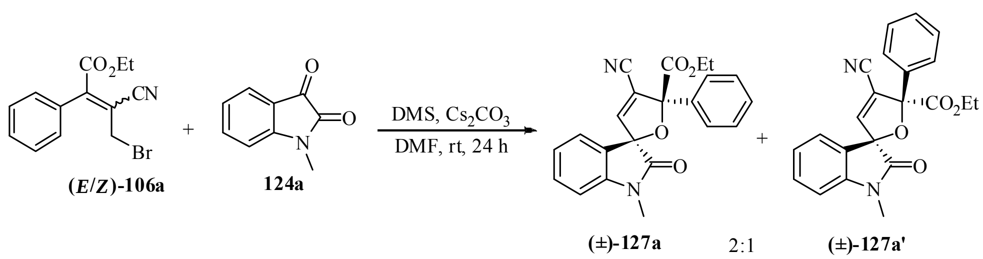
**Table XV.** Crystal data and structure refinement for (±)-**127a** [from (*Z*)-**106a**]

| | | |
|---|---|---|
| Identification code | (±)-127a [from (*Z*)-106a] | |
| Empirical formula | C22 H18 N2 O4 | |
| Formula weight | 374.38 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 12.0806(16) Å | α= 90°. |
| | b = 13.1507(18) Å | β= 99.424(2)°. |
| | c = 12.6249(17) Å | γ= 90°. |
| Volume | 1978.6(5) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.257 Mg/m$^3$ | |
| Absorption coefficient | 0.088 mm$^{-1}$ | |
| F(000) | 784 | |
| Theta range for data collection | 2.16 to 26.04°. | |
| Index ranges | -14<=h<=14, -16<=k<=16, -15<=l<=15 | |
| Reflections collected | 20061 | |
| Independent reflections | 3901 [R(int) = 0.0273] | |
| Completeness to theta = 26.04° | 99.8 % | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 3901 / 1 / 255 | |
| Goodness-of-fit on F$^2$ | 1.039 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0592, wR2 = 0.1547 | |
| R indices (all data) | R1 = 0.0683, wR2 = 0.1622 | |
| Largest diff. peak and hole | 0.437 and -0.312 e.Å$^{-3}$ | |

**Table XVI.** Crystal data and structure refinement for (±)-**127a′** [from (*Z*)-**106a**]

| | | |
|---|---|---|
| Identification code | (±)-127a′ [from (*Z*)-106a] | |
| Empirical formula | C22 H18 N2 O4 | |
| Formula weight | 374.38 | |
| Temperature | 298(2) K | |
| Wavelength | 1.54184 Å | |
| Crystal system | Monoclinic | |
| Space group | P 21/c | |
| Unit cell dimensions | a = 14.8424(2) Å | α= 90°. |
| | b = 7.08492(12) Å | β= 96.8001(15)°. |
| | c = 18.1098(3) Å | γ= 90°. |
| Volume | 1890.98(6) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.315 $Mg/m^3$ | |
| Absorption coefficient | 0.751 $mm^{-1}$ | |
| F(000) | 784 | |
| Crystal size | 0.38 x 0.31 x 0.22 $mm^3$ | |
| Theta range for data collection | 3.00 to 67.07°. | |
| Index ranges | -17<=h<=16, -8<=k<=7, -21<=l<=18 | |
| Reflections collected | 6685 | |
| Independent reflections | 3383 [R(int) = 0.0137] | |
| Completeness to theta = 67.07° | 99.9 % | |
| Max. and min. transmission | 0.8522 and 0.7633 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3383 / 0 / 255 | |
| Goodness-of-fit on $F^2$ | 1.065 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0476, wR2 = 0.1241 | |
| R indices (all data) | R1 = 0.0515, wR2 = 0.1272 | |
| Largest diff. peak and hole | 0.245 and -0.273 $e.Å^{-3}$ | |

Thus in cycloaddition reaction with *N*-methylisatin, both (*E*)- and (*Z*)-allyl bromides containing tetrasubstituted alkene motif and nitrile functionality provided the same products in almost same ratio. Therefore it looks to us that both the *E*)- and (*Z*)-allyl bromides follow the same reaction pathway. In order to understand further in this direction we have subjected the (*E*/*Z*)-mixture of allyl bromides **106a** (without seperation) to [3+2]-annulation reaction with *N*-methylisatin (**124a**) (Eq. 60). As expected it provided as a mixture of *syn* and a*nti* [(±)-**127a** and (±)-**127a′**] (2:1) which were seperated by column chromatography and analyzed thoroughly by IR, $^{1}$H NMR [see Spectra 28 & 30 for (±)-**127a** and (±)-**127a′** respectively], $^{13}$C NMR [see Spectra 29 & 31 for (±)-**127a** and (±)-**127a′** respectively] and HRMS spectral analyses.



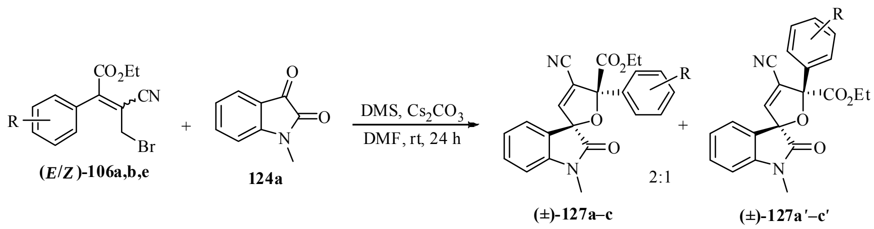

(Eq. 60)

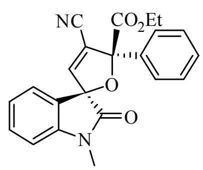
This would mean that the same reactive intermediate/transition state is involved in the cycloaddition reactions of (*E*)- and (*Z*)-isomeric bromides with *N*-methylisatin. To understand the generality of this observation we have subsequently subjected two more ally bromides **106b** & **106e**[$] (as a mixture of *E*/*Z*) to [3+2] annulation strategy with *N*-methylisatin (**124a**). In both the cases the products (dihydrofuran derivatives) were obtained as a seperable mixture of major **127b** and **127c**[$] and minor **127b′** and **127c′**[$]

[$]In order to have continuity and easy understanding the major and minor products obtained from BH bromide **106e** is numbered as (±)-**127c** and (±)-**127c′** respectively.

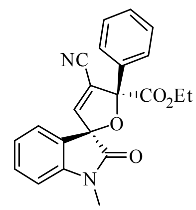
diastereomers (approximately in 2:1). In each case the diastereomers were seperated and thoroughly analysed by IR, $^{1}H$ NMR, $^{13}C$ NMR and HRMS spectral analyses.

**Table 14**. **Synthesis of dihydrofuran fused spirooxindoles via [3+2]-cycloaddition reaction**[a]

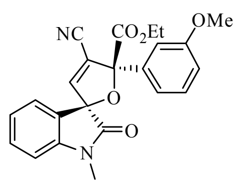


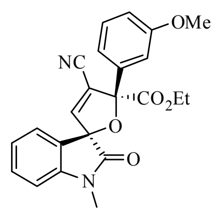
**(±)-127a 59%**



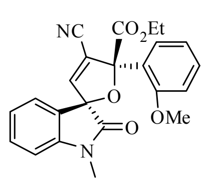
**(±)-127a' 28%**



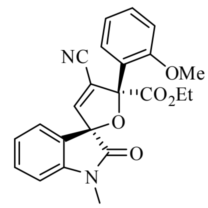
**(±)-129b**[d] **62%**



**(±)-127b'**[d] **28%**



**(±)-127c 63%**



**(±)-127c' 27%**

[a]All reactions were carried out on 1.0 mmol scale of 1-methylisatin (**124a**) and 1.5 mmol of BH-bromide **106** under the influence of DMS (2.0 mmol) and $Cs_2CO_3$ (2.0 mmol) in DMF (3.0 mL). [b]All compounds (±)-**127a-c**/(±)-**127a′-c′** were fully characterized by IR, $^{1}H$ NMR, $^{13}C$ NMR, and HRMS spectroscopic studies. [c]Yields were calculated on the basis of 1-methylisatin (**124a**). [d]Structure of these molecules were further confirmed by single crystal X-ray diffraction data analysis.

Stereochemistry was further confirmed by single crystal X-ray diffraction data analysis for the compounds (±)-**127b** and (±)-**127b′** (for data see Tables XVII and XVIII). For ORTEP diagrams see Figure X17 and Figure X18.

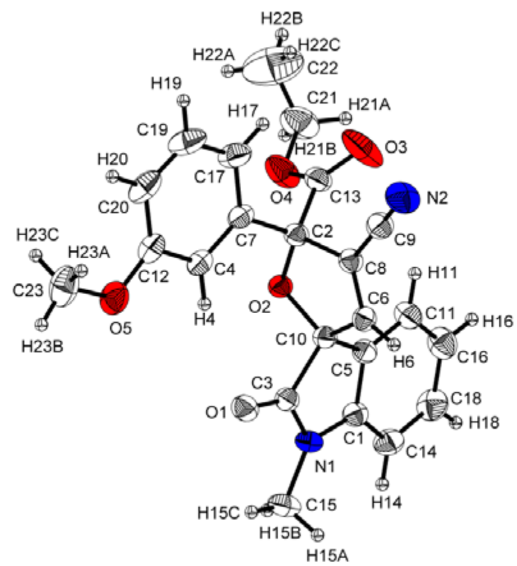



**Figure X17.** ORTEP diagram of compound (±)-**127b** [from (*E*/*Z*)-**106b**]

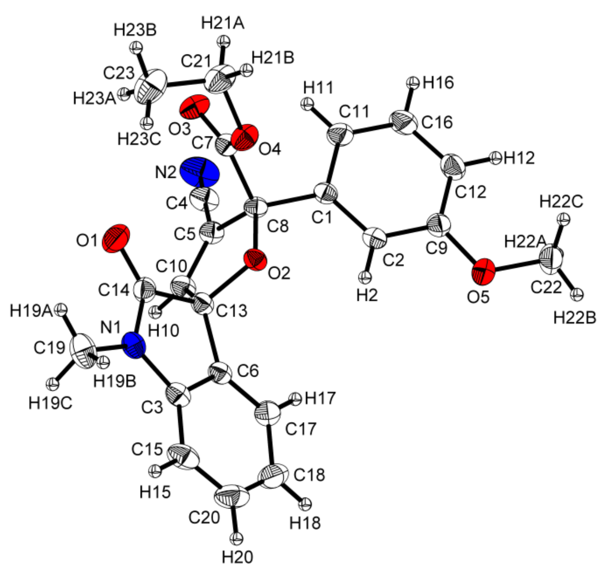


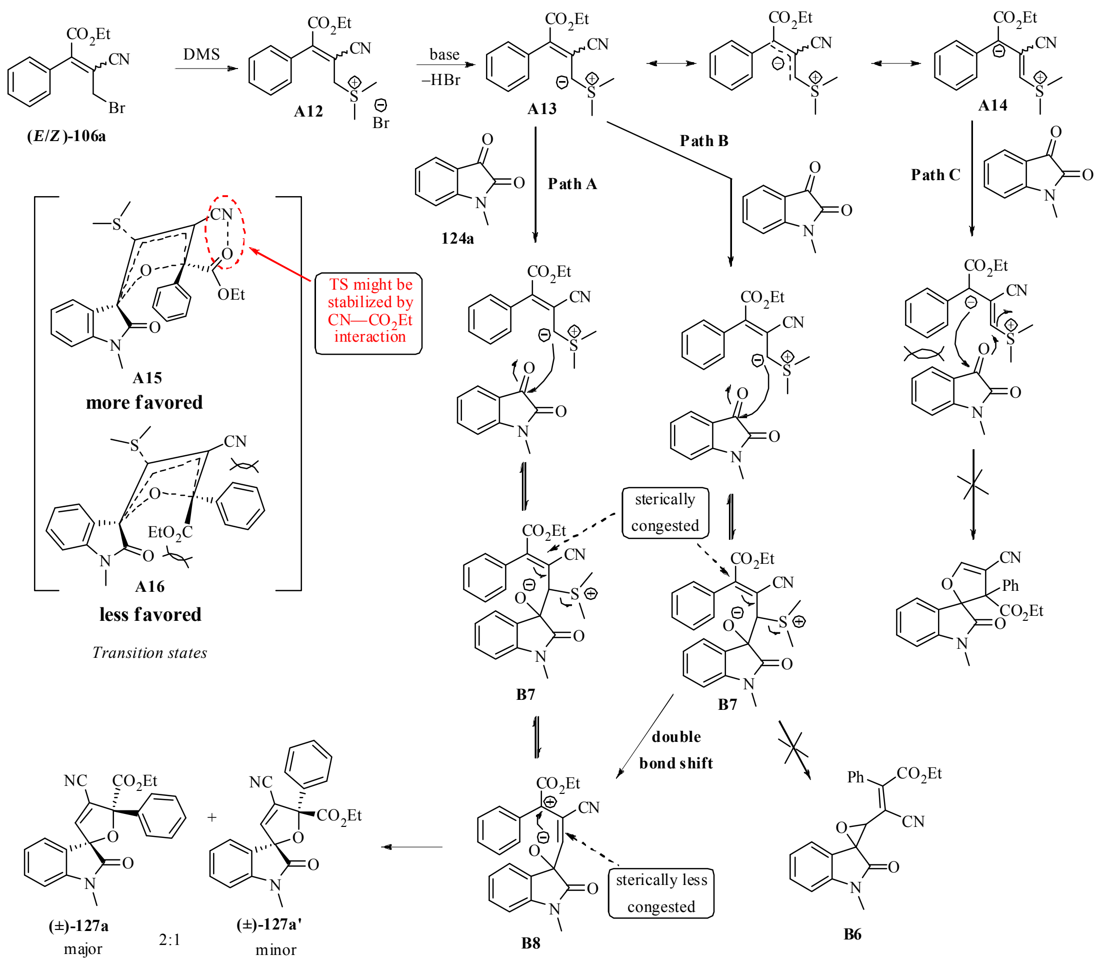

**Figure X18.** ORTEP diagram of compound (±)-**127b′** [from (*E*/*Z*)-**106b**]

**Table XVII.** Crystal data and structure refinement for (±)-**127b** [from (*E*/*Z*)-**106b**]

| | | |
|---|---|---|
| Identification code | (±)-127b [from (*E*/*Z*)-106b] | |
| Empirical formula | C23 H20 N2 O5 | |
| Formula weight | 404.41 | |
| Temperature | 273(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 11.7965(14) Å | α= 90°. |
| | b = 11.0766(14) Å | β= 109.599(2)°. |
| | c = 16.691(2) Å | γ = 90°. |
| Volume | 2054.6(4) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.307 Mg/m$^3$ | |
| Absorption coefficient | 0.093 mm$^{-1}$ | |
| F(000) | 848 | |
| Theta range for data collection | 1.83 to 26.04°. | |
| Index ranges | -14<=h<=14, -13<=k<=13, -20<=l<=20 | |
| Reflections collected | 20675 | |
| Independent reflections | 4045 [R(int) = 0.0337] | |
| Completeness to theta = 26.04° | 99.8 % | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 4045 / 6 / 274 | |
| Goodness-of-fit on F$^2$ | 1.051 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0558, wR2 = 0.1502 | |
| R indices (all data) | R1 = 0.0679, wR2 = 0.1622 | |
| Largest diff. peak and hole | 0.323 and -0.324 e.Å$^{-3}$ | |

**Table XVIII.** Crystal data and structure refinement for (±)-**127b′** [from (*E*/*Z*)-**106b**]

| | | |
|---|---|---|
| Identification code | (±)-127b′ [from (*E*/*Z*)-106b] | |
| Empirical formula | C23 H20 N2 O5 | |
| Formula weight | 404.41 | |
| Temperature | 298(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 11.476(3) Å | α= 90°. |
| | b = 12.967(4) Å | β= 111.425(4)°. |
| | c = 14.827(4) Å | γ = 90°. |
| Volume | 2053.9(11) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.308 Mg/m$^3$ | |
| Absorption coefficient | 0.093 mm$^{-1}$ | |
| F(000) | 848 | |
| Theta range for data collection | 1.91 to 26.07°. | |
| Index ranges | -14<=h<=14, -16<=k<=15, -18<=l<=18 | |
| Reflections collected | 20704 | |
| Independent reflections | 4056 [R(int) = 0.0250] | |
| Completeness to theta = 26.07° | 99.7 % | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 4056 / 0 / 274 | |
| Goodness-of-fit on F$^2$ | 1.049 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0403, wR2 = 0.1024 | |
| R indices (all data) | R1 = 0.0474, wR2 = 0.1076 | |
| Largest diff. peak and hole | 0.196 and -0.229 e.Å$^{-3}$ | |




**Scheme 50**. The plausible mechanism

A plausible mechanism was described for the [3+2] annulation strategy[206a] using the BH bromide (*E*/*Z*)-**106a** as a dipole and *N*-methylisatin (**124a**) as a dipolarophile (Scheme 50). Initially, both the isomers of BH bromide (*E*/*Z*)-**106a** reacts with DMS to form a sulfonium bromide **A12** which then on treatment with base generate dipole **A13**. The in situ formed dipole **A13** undergoes [3+2] annulation reaction with isatin.

In this case also the [3+2] addition can proceed in three different pathways, Paths A, B and C as in the case of esters (Scheme 49 see page 102). Eventhough, it is similar to previous mechanism in ester derivative, we felt that it is appropriate to provide explanation for easy understanding.

Reaction Path C is disfavored because of tertiary carbanion **A14** is highly sterically hindered and it is not in position to make any nucleophilic attack on carbonyl of isatin **124a**.

On similar grounds discussed in the case of esters, the Path B is disfavored due to the presence of sterically hindered double bond as shown in TS **B7**. The spontaneous double bond shift occurs to release the steric crowding thus generating the allylic benzylic carbocation **B8**. Since both the (*E*)- and (*Z*)-isomers proceeds through the same reactive intermediate **B8** and they provide the same products.

Thus in both the cases of (*E*)- and (*Z*)-allyl bromides the reaction proceeds through Path A and reactive intermediate **B8**. The product formation clearly indicates tha transition state **A15** is more favored than transition state **A16** probably due to some kind of CN and ester attractive interactions thus leading to the formation of the separable diastereomeric mixture of dihydrofuran-fused-spirooxindoles (±)-**127a** and (±)-**127a′** in 2:1 ratio. In the case of ester–allyl bromides (**93**) O—O interactions keeps the both ester groups *cis* to each other thus allowing the formation of single stereochemically pure dihydrofuran-fused-spirooxindole derivatives.

In conclusion, we have developed a facile and stereoselective one pot methodology for synthesis of dihydrofuran-fused-spirooxindoles in good yields. Our studies clearly show that O–O interactions (ester-ester attractive interactions) are strong and in fact, have the power of controling the streochemical course of the reactions. Also ester–nitrile attractive interactions are moderately strong (not to the extent of ester–ester interaction) and has the ability to direct the stereochemical path of the reactions to a reasonable extent.

# CONCLUSION

In conclusion, we have made sincere efforts towards achieving the all three objectives mentioned in the beginning of this chapter and we were pleased to see that we have made reasonble success in our endeavors. Thus we have effectively used ketones, which are thought to be less reactive, as electrophiles in two component BH reactions. These efforts resulted in development of a facile protocol for obtaining functionalized indolizine derivatives.

We have also effectively employed the BH alcohols derived from α-keto esters and methyl acrylate for stereodefined synthesis of (*E*)-tetrasubstituted alkenes containing allyl bromide moiety. Similarly we have also used the BH alcohols obtained from α-keto esters and acrylonitrile for synthesis of tetrasubstituted alkenes containing allyl bromide moiety and we have obtained a seperable *E*/*Z*-mixture in 2:1 ratio using NBS/DMS reagent system under mild reaction conditions.

Finally, we have successfully utilized the above synthesized tetrasubstituted alkenes (BH bromides) as a source of dipoles in [3+2] cycloaddition reactions with different substituted isatins as dipolarophiles under the influence of DMS/$Cs_2CO_3$ for developing a protocol for synthesis of highly medicinal and therapeutic important dihydrofuran-fused-spirooxindole frameworks. Our studies also throw some light on the importance of O—O attractions in ester groups in controlling the sterteochemical course of certain reactions.

# EXPERIMENTAL

**General:** All the required solvents were dried and distilled prior to use under suitable drying agents. Moisture sensitive reactions were carried out under $N_2$ (nitrogen) atmosphere using standard syringe-septum techniques.

**Chromatography:** All reactions were monitored using TLC (Thin Layer Chromatography). Analytical TLC (Thin Layer Chromatography) was performed on glass plates (7×2 cm) coated with FINAR's silica gel GF 254 (254 mμ) containing 13% calcium sulfate as a binder. The spots were visualized/recognized by short exposure to UV (ultraviolet) light or iodine vapour. Column chromatography was carried out using FINAR's silica gel (60-120 mesh or 100-200 mesh or 230-400 mesh).

**Infrared Spectra:** Infrared spectra were recorded on a JASCO FT-IR 5300 or NICOLET 5700 FT-IR spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 $cm^{-1}$. Liquid samples as thin film between NaCl plates and solid samples were recorded as KBr wafers, peaks are reported in $cm^{-1}$.

**Melting Points:** Melting points were determined on MR-Vis+ visual melting point range apparatus of LABINDIA instruments private limited and were uncorrected.

**Nuclear Magnetic Resonance Spectra:** Proton magnetic resonance ($^1H$ NMR) spectra, carbon-13 magnetic resonance ($^{13}C$ NMR) spectra and NOESY (2D NMR) spectra were recorded on BRUKER-AVANCE-400 or 500 spectrometers. $^{1}$H NMR (400 or 500 MHz) spectra for all the compounds were measured in chloroform-*d* ($CDCl_3$) with TMS ($\delta = 0$ ppm) as an internal standard. $^{13}$C NMR (100 or 125 MHz) spectra for all the samples were measured in chloroform-*d* ($CDCl_3$) with its middle peak of the triplet ($\delta = 77.10$ ppm) as an internal standard. The spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for peaks multiplicity, that is, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet, dABq = doublet of AB quartet, (3) coupling constant *J* in Hertz, (4) number of hydrogens integrated for the signal.

**Single Crystal X-ray Diffraction Study:** Single crystal X-ray diffraction data for compounds **82f**, **83f**, **82h**, **83h**, **88**, (*E*)-**106e**, **125i–k**, **127a** [from (*E*)-**106a**], **127a′** [from (*E*)-**106a**], **127a** [from (*Z*)-**106a**], **127b**, and **127b′** were collected on a Bruker SMART APEX CCD area detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3°, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software (Version 5.630) was used for the intensity data acquisition and for the data extraction SAINTPLUS Software (Version 6.45) was used. In each case, absorption correction was performed by using SADABS program, an empirical absorption correction with equivalent reflections was carried out using the program. Single crystal X-ray data for compounds **93a** and **125a** were collected on Oxford Diffraction Xcalibur Eos Gemini diffractometer with graphite-monochromated Mo *Kα* radiation with the wavelength of 0.71073 Å at 298K. Single crystal X-ray data for compounds (*Z*)-**106e** and **127a′** [from (*Z*)-**106a**] were collected on Oxford

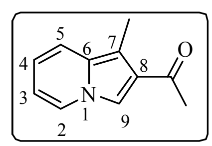
Diffraction Xcalibur Eos Gemini diffractometer using graphite-monochromated Cu *Kα* radiation with the wavelength of 1.54184 Å at 298K. Data were analyzed by using the ''CrysAlis PRO'' software and the collected data were also reduced with ''CrysAlis PRO'' program. An empirical absorption correction using spherical harmonics was implemented in ''SCALE3 ABSPACK'' scaling algorithm. The structures were solved by using SHELXS-97, and full-matrix least-squares refinement against $F^2$ was carried out using SHELXL-97. All non-hydrogen atoms were refined anisotropically. The software used to prepare the material is *WinGx* v1.70.01 (L. Farrugia, 2005). The DIAMOND (Version 2.1e) software was used for molecular graphics.

**Mass Spectral Analysis:** Mass spectral data were collected on Shimadzu LCMS 2010A spectrometer.

**HRMS Analysis:** HRMS spectra were recorded on Bruker maXis ESI-TOF mass spectrometer.

**8-Acetyl-1-aza-7-methylbicyclo[4.3.0]nona-2,4,6,8-tetraene (82a):**

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.0 mmol, 0.222 g, 0.18 mL) was added at 0 °C to a stirring solution of 2-acetylpyridine (**80a**) (1.0 mmol, 0.121 g, 0.11 mL) and methyl vinyl ketone (**81a**) (2.0 mmol, 0.140 g, 0.16 mL) in acetonitrile (containing 1% $H_2O$, v/v) (2 mL). Reaction mixture was then heated under reflux for 12 hours and allowed to come to room temperature (25–30 °C). The reaction mixture was diluted with dichloromethane (10 mL) and saturated aqueous $K_2CO_3$ solution (10 mL) was added. Organic layer was separated and aqueous layer was washed with dichloromethane (2 X 5 mL). Combined organic layer was dried over anhydrous sodium sulfate ($Na_2SO_4$). Solvent was evaporated. Thus obtained crude [TLC (10% ethyl acetate in hexanes) showed three spots indicating that it is a mixture of three compounds] was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to provide two products **82a** (0.107 g) in 62% and **83a** (0.049 g) in 20% yields as viscous liquids along with very small amounts of the strarting material (**80a**, 10 mg). Starting material elutes first. Afterwards the title compound **82a** (less polar) was collected follwed by the collection of the byproduct **83a** (more polar).

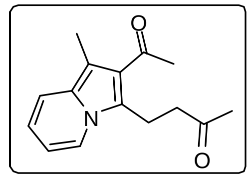



| | |
|---|---|
| Yield | :62% |
| IR (KBr) | :$\upsilon$ 1659, 1484, 1435, 1220, 739 $cm^{-1}$ |
| $^1$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 2.527 (s, 3H), 2.53 (s, 3H), 6.44–6.51 (m, 1H), 6.57–6.64 (m, 1H), 7.33 (d, $J$ = 9.2 Hz, 1H), 7.71 (s, 1H), 7.77 (d, $J$ = 7.2 Hz, 1H) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 10.15, 28.63, 109.87, 112.31, 115.93, 116.75, 118.78, 125.11, 125.93, 131.04, 195.78 |

HRMS (ESI) exact mass calcd. for $C_{11}H_{11}NO+Na$ $(M+Na)^+$ :196.0738

Found :196.0739

**8-Acetyl-1-aza-7-methyl-9-(3-oxobutyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene(83a):**




Time :12 h

Yield :20%

IR (neat) :$\upsilon$ 1709, 1648, 1495, 1418, 1237, 739 $cm^{-1}$

$^1H$ NMR (400 MHz, $CDCl_3$) :$\delta$ 2.16 (s, 3H), 2.52 (s, 3H), 2.60 (s, 3H), 2.80 (t, $J$ = 7.6 Hz, 2H), 3.36 (t, $J$ = 7.6 Hz, 2H), 6.51–6.57 (m, 1H), 6.58–6.64 (m, 1H), 7.32–7.38 (m, 1H), 7.85 (d, $J$ = 7.2 Hz, 1H)

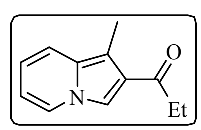
$^{13}C$ NMR (100 MHz, $CDCl_3$) :$\delta$ 11.35, 19.13, 29.76, 31.80, 41.52, 107.74, 112.21, 115.87, 118.59, 121.67, 124.35, 126.40, 129.55, 197.62, 208.20

HRMS (ESI) exact mass calcd. for $C_{15}H_{17}NO_2+H$ $(M+H)^+$ :244.1337

Found :244.1335

**1-Aza-7-methyl-8-(1-oxopropyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (82b):**

The indolizines **82b** and **83b** were obtained by the reaction between 2-acetylpyridine (**80a**) and ethyl vinyl ketone (**81b**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as viscous liquids.




Time :12 h

Yield :37%

IR (KBr) :$\upsilon$ 1670, 1484, 1435, 1193, 739 cm$^{-1}$

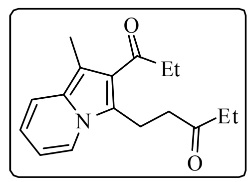
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.22 (t, $J$ = 7.2 Hz, 3H), 2.54 (s, 3H), 2.91 (q, $J$ = 7.2 Hz, 2H), 6.44–6.51 (m, 1H), 6.56–6.64 (m, 1H), 7.33 (d, $J$ = 9.2 Hz, 1H), 7.72 (s, 1H), 7.77 (d, $J$ = 6.8 Hz, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 8.57, 10.27, 33.85, 110.10, 112.33, 115.26, 116.70, 118.90, 125.19, 125.58, 131.11, 199.00

HRMS (ESI) exact mass calcd for $C_{12}H_{13}NO$ $(M)^+$ :187.0997

Found :187.0995

**1-Aza-7-methyl-9-(3-oxopentyl)-8-(1-oxopropyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (83b):**




Time :12 h

Yield :13%

IR (neat) :$\upsilon$ 1714, 1654, 1489, 1451, 1215, 733 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.04 (t, $J$ = 7.2 Hz, 3H), 1.22 (t, $J$ = 7.2 Hz, 3H), 2.44 (q, $J$ = 7.2 Hz, 2H), 2.52 (s, 3H), 2.79 (t, $J$ = 7.6 Hz, 2H), 2.94 (q, $J$ = 7.2 Hz, 2H), 3.35 (t, $J$ = 7.2 Hz, 2H), 6.49–6.55 (m, 1H), 6.57–6.64 (m, 1H), 7.34 (d, $J$ = 8.8 Hz, 1H), 7.86 (d, $J$ = 7.2 Hz, 1H)

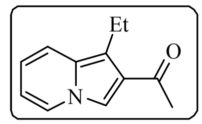
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 7.78, 8.28, 11.60, 19.48, 35.99, 36.69, 40.47, 107.29, 112.19, 115.95, 118.67, 121.87, 124.48, 126.52, 129.68, 201.03, 211.18

HRMS (ESI) exact mass calcd for $C_{17}H_{21}NO_2$+Na $(M+Na)^+$ : 294.1470

Found :294.1467

**8-Acetyl-1-aza-7-ethylbicyclo[4.3.0]nona-2,4,6,8-tetraene (82c):**

The compounds **82c** and **83c** were obtained by the reaction between 2-propanoylpyridine (**80b**) and methyl vinyl ketone (**81a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as viscous liquids.



Time :12 h

Yield :57%

IR (neat) :$\upsilon$ 1660, 1484, 1430, 1210, 745 $cm^{-1}$

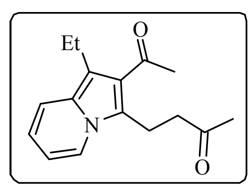
$^1H$ NMR (400 MHz, $CDCl_3$) :$\delta$ 1.20 (t, $J$ = 7.6 Hz, 3H), 2.53 (s, 3H), 3.02 (q, $J$ = 7.6 Hz, 2H), 6.44–6.54 (m, 1H), 6.56–6.66 (m, 1H), 7.34 (d, $J$ = 9.2 Hz, 1H), 7.70 (s, 1H), 7.77 (d, $J$ = 7.2 Hz, 1H)

$^{13}C$ NMR (100 MHz, $CDCl_3$) :$\delta$ 15.79, 17.80, 28.58, 112.38, 116.29, 116.91, 117.04, 118.71, 125.17, 130.56, 195.43

HRMS (ESI) exact mass calcd for $C_{12}H_{13}NO+Na$ $(M+Na)^+$ :210.0889

Found :210.0892

**8-Acetyl-1-aza-7-ethyl-9-(3-oxobutyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (83c):**



Time :12 h

Yield :23%

IR (neat) :$\upsilon$ 1715, 1654, 1495, 1441, 1249, 745 $cm^{-1}$

$^1H$ NMR (400 MHz, $CDCl_3$) :$\delta$ 1.24 (t, $J$ = 7.6 Hz, 3H), 2.17 (s, 3H), 2.62 (s, 3H), 2.80 (t, $J$ = 7.6 Hz, 2H), 2.98 (q, $J$ = 7.6 Hz, 2H), 3.32 (t,

$J$ = 7.6 Hz, 2H), 6.51–6.57 (m, 1H), 6.58–6.65 (m, 1H),7.35 (d, $J$ = 9.2 Hz, 1H), 7.83 (d, $J$ = 7.2 Hz, 1H)

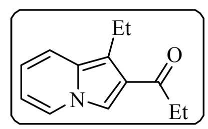
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 16.76, 18.35, 19.25, 29.93, 31.28, 41.69, 112.40, 114.91, 116.09, 118.59, 121.84, 124.11, 125.93, 129.16, 198.06, 208.30

HRMS (ESI) exact mass calcd for $C_{16}H_{19}NO_2$+Na $(M+Na)^+$ :280.1313

Found :280.1315

**1-Aza-7-ethyl-8-(1-oxopropyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (82d):**

Reaction between 2-propanoylpyridine (**80b**) and ethyl vinyl ketone (**81b**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, provided the compounds **82d** and **83d** as viscous liquids.




Time :12 h

Yield :23%

IR (KBr) :$\upsilon$ 1665, 1489, 1435, 1215, 755 cm$^{-1}$

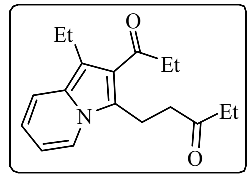
$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.21 (t, $J$ = 7.6 Hz, 3H), 1.22 (t, $J$ = 7.6 Hz, 3H), 2.92 (q, $J$ = 7.6 Hz, 2H), 3.03 (q, $J$ = 7.6 Hz, 2H), 6.45–6.52 (m, 1H), 6.57–6.64 (m, 1H), 7.33–7.38 (m, 1H), 7.71 (s, 1H), 7.75–7.80 (m, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 8.56, 15.86, 17.90, 33.71, 112.35, 115.52, 116.83, 117.20, 118.75, 124.73, 125.21, 130.55, 198.66

HRMS (ESI) exact mass calcd for $C_{13}H_{15}NO$+Na $(M+Na)^+$ :224.1051

Found :224.1065

**1-Aza-7-ethyl-9-(3-oxopentyl)-8-(1-oxopropyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (83d):**



Time :12 h

Yield :14%

IR (neat) :$\upsilon$ 1715, 1660, 1446, 1413, 1210, 742 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.05 (t, $J$ = 7.2 Hz, 3H), 1.22 (t, $J$ = 7.2 Hz, 3H), 1.23 (t, $J$ = 7.6 Hz, 3H), 2.44 (q, $J$ = 7.2 Hz, 2H), 2.79 (t, $J$ = 7.6 Hz, 2H), 2.91–3.01 (m, 4H), 3.31 (t, $J$ = 7.6 Hz, 2H), 6.50–6.56 (m, 1H), 6.57–6.64 (m, 1H), 7.32–7.38 (m, 1H), 7.83 (d, $J$ = 7.2 Hz, 1H)

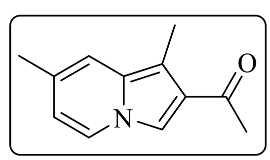
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 7.77, 8.49, 16.82, 18.49, 19.41, 36.00, 36.16, 40.46, 112.20, 114.38, 115.99, 118.52, 121.87, 124.18, 125.64, 129.14, 201.52, 211.01

HRMS (ESI) exact mass calcd for $C_{18}H_{23}NO_2$+Na (M+Na)$^+$ :308.1626

Found :308.1627

**8-Acetyl-1-aza-4,7-dimethylbicyclo[4.3.0]nona-2,4,6,8-tetraene (82e):**

Treatment of 4-methyl 2-acetylpyridine (**80c**) with methyl vinyl ketone (**81a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, provided the title compound **82e** and the corresponding Michael addition product **83e** as solids.



Time :12 h

Yield :33%

M.p. :56–58 °C

IR (neat) :$\upsilon$ 1654, 1484, 1419, 1232, 789 $cm^{-1}$

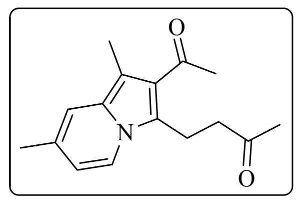
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 2.25 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 6.32 (dd, $J$ = 1.2, 6.8 Hz, 1H), 7.06 (s, 1H), 7.64 (s, 1H), 7.68 (d, $J$ = 6.8 Hz, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 10.11, 21.13, 28.59, 108.08, 115.28, 115.42, 116.44, 124.63, 126.13, 126.83, 131.31, 195.93

HRMS (ESI) exact mass calcd. for $C_{12}H_{13}NO$+H $(M+H)^+$ :188.1075

Found :188.1072.

**8-Acetyl-1-aza-4,7-dimethyl-9-(3-oxobutyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (83e):**



Time :12 h

Yield :46%

M.p. : 91–93 °C

IR (neat) :$\upsilon$ 1715, 1649, 1495, 1463, 1419, 1243, 772 $cm^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 2.15 (s, 3H), 2.26 (s, 3H), 2.48 (s, 3H), 2.58 (s, 3H), 2.79 (t, $J$ = 7.6 Hz, 2H), 3.33 (t, $J$ = 7.6 Hz, 2H), 6.38 (d, $J$ = 7.6 Hz, 1H),* 7.07 (s, 1H), 7.78 (d, $J$ = 7.6 Hz, 1H,); *unresolved dd.

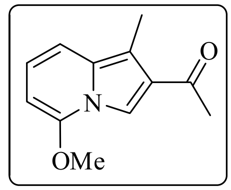
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 11.43, 19.31, 21.00, 29.91, 31.89, 41.84, 105.94, 115.19, 116.37, 121.38, 124.45, 125.99, 129.82, 197.81, 208.54

HRMS (ESI) exact mass calcd. for $C_{16}H_{19}NO_2$+H $(M+H)^+$ :258.1494

Found :258.1498

**8-Acetyl-1-aza-2-methoxy-7-methylbicyclo[4.3.0]nona-2,4,6,8-tetraene (82f):**

The indolizines **82f** and **83f** were obtained by the reaction between 6-methoxy 2-acetylpyridine (**80d**) and methyl vinyl ketone (**81a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as solids.

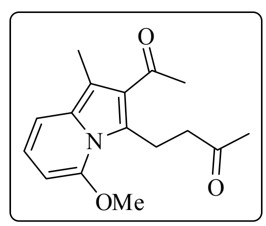


| | |
|---|---|
| Time | :12 h |
| Yield | :59% |
| M.p. | :126–127 °C |
| IR (neat) | :$\upsilon$ 1654, 1632, 1490, 1430, 1210, 739 $cm^{-1}$ |
| $^1H$ NMR (400 MHz, $CDCl_3$) | :$\delta$ 2.53 (s, 3H), 2.56 (s, 3H), 4.06 (s, 3H), 5.77 (d, $J$ = 7.2 Hz, 1H), 6.65–6.71 (m, 1H), 7.02 (d, $J$ = 9.2 Hz, 1H), 7.86 (s, 1H) |
| $^{13}C$ NMR (100 MHz, $CDCl_3$) | :$\delta$ 10.41, 28.57, 55.98, 86.17, 109.68, 110.87, 111.80, 118.08, 126.04, 132.65, 148.84, 196.16; |

HRMS (ESI) exact mass calcd. for $C_{12}H_{13}NO_2$+H $(M+H)^+$ :204.1024

Found :204.1022.

**8-Acetyl-1-aza-2-methoxy-7-methyl-9-(3-oxobutyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (83f):**

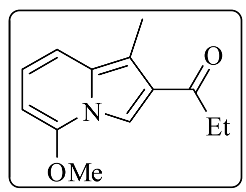


| | |
|---|---|
| Time | :12 h |
| Yield | :13% |
| M.p. | :129–131 °C |
| IR (neat) | :$\upsilon$ 1704, 1649, 1621, 1473, 1424, 1232, 750 $cm^{-1}$ |

| | |
|---|---|
| $^{1}$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 2.19 (s, 3H), 2.45 (s, 3H), 2.57 (s, 3H), 2.82 (t, $J$ = 8.0 Hz, 2H), 3.59 (t, $J$ = 8.0 Hz, 2H), 3.91 (s, 3H), 5.66 (d, $J$ = 7.2 Hz, 1H), 6.53–6.61 (m, 1H), 6.95 (d, $J$ = 9.2 Hz, 1H) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 11.46, 22.51, 29.88, 32.25, 45.62, 56.01, 87.24, 107.09, 111.11, 117.12, 126.72, 127.01, 132.25, 151.94, 198.94, 208.68 |
| HRMS (ESI) exact mass calcd. for $C_{16}H_{19}NO_3$+H $(M+H)^+$ | :274.1443 |
| Found | :274.1445 |

**1-Aza-2-methoxy-7-methyl-8-(1-oxopropyl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (82g):**

Reaction between 6-methoxy 2-acetylpyridine (**80d**) and ethyl vinyl ketone (**81b**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, provided the indolizine **82g** as a solid.



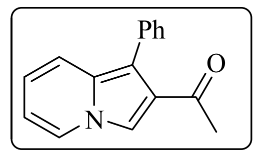
| | |
|---|---|
| Time | :12 h |
| Yield | :41% |
| M.p. | :88–90 °C |
| IR (neat) | :$\upsilon$ 1671, 1638, 1484, 1463, 1282, 756 $cm^{-1}$ |
| $^{1}$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 1.23 (t, $J$ = 7.2 Hz, 3H), 2.54 (s, 3H), 2.94 (q, $J$ = 7.2 Hz, 2H), 4.05 (s, 3H), 5.76 (d, $J$ = 6.8 Hz, 1H), 6.61–6.70 (m, 1H), 7.02 (d, $J$ = 8.8 Hz, 1H), 7.87 (s, 1H) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 8.66, 10.48, 33.70, 56.00, 86.15, 109.85, 110.92, 111.10, 117.97, 125.58, 132.63, 148.90, 199.34 |

HRMS (ESI) exact mass calcd. for $C_{13}H_{15}NO_2$+H $(M+H)^+$ :218.1181

Found :218.1176

**8-Acetyl-1-aza-7-phenylbicyclo[4.3.0]nona-2,4,6,8-tetraene (82h):**

The molecules **82h** and **83h** were obtained by the reaction between 2-benzoylpyridine (**80e**) and methyl vinyl ketone (**81a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as solids.



Time :12 h

Yield :49%

M.p. :142–144 °C

IR (neat) :$\upsilon$ 1660, 1484, 1424, 1205, 783 $cm^{-1}$

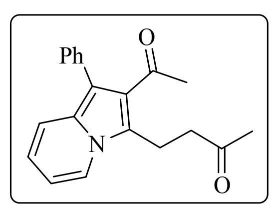
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 2.33 (s, 3H), 6.53–6.61 (m, 1H), 6.63–6.70 (m, 1H), 7.28–7.39 (m, 2H), 7.40–7.48 (m, 4H), 7.81 (s, 1H), 7.84–7.90 (m, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 29.56, 113.00, 114.99, 116.14, 118.70, 119.42, 125.29, 126.60, 126.80, 128.19, 130.67, 131.49, 134.48, 195.90

HRMS (ESI) exact mass calcd for $C_{16}H_{13}NO$+H $(M+H)^+$ :236.1070

Found :236.1075.

**8-Acetyl-1-aza-9-(3-oxobutyl)-7-phenylbicyclo[4.3.0]nona-2,4,6,8-tetraene (83h):**



Time :12 h

Yield :11%

M.p. :122–123 °C

IR (neat) :$\upsilon$ 1709, 1656, 1517, 1419, 1236, 763 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 2.09 (s, 3H), 2.20 (s, 3H), 2.91 (t, $J$ = 7.6 Hz, 2H), 3.35 (t, $J$ = 7.6 Hz, 2H), 6.59–6.69 (m, 2H), 7.27–7.32 (m, 1H), 7.34–7.40 (m, 3H), 7.42–7.48 (m, 2H), 7.95 (d, $J$ = 6.8 Hz, 1H)

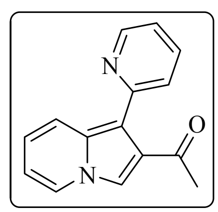
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 18.96, 29.89, 31.46, 42.02, 112.73, 114.74, 117.81, 119.18, 122.05, 125.01, 126.17, 126.85, 128.50, 129.76, 130.58, 135.22, 199.24, 208.15;

HRMS (ESI) exact mass calcd for $C_{20}H_{19}NO_2$+H (M+H)$^+$ :306.1494

Found :306.1489.

**8-Acetyl-1-aza-7-(pyrid-2-yl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (82i):**

Treatment of di(2-pyridyl) ketone (**80f**) with methyl vinyl ketone (**81a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, provided the title compound **82i** as a viscous liquid.




Time :12 h

Yield :31%

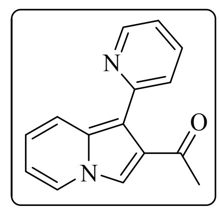
IR (neat) :$\upsilon$ 1665, 1473, 1413, 1200, 739 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 2.47 (s, 3H), 6.57–6.66 (m, 1H), 6.74–6.84 (m, 1H), 7.15–7.23 (m, 1H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.68–7.78 (m, 2H), 7.80 (s, 1H), 7.89 (d, $J$ = 6.8 Hz, 1H), 8.68 (d, $J$ = 4.0 Hz, 1H)

| | |
|---|---|
| $^{13}C$ NMR (100 MHz, $CDCl_3$) | :$\delta$ 29.35, 113.20, 113.50, 117.05, 119.95, 120.15, 120.91, 125.36, 125.63, 126.37, 132.67, 135.64, 149.02, 153.96, 195.51 |
| HRMS (ESI) exact mass calcd for $C_{15}H_{12}N_2O$+H $(M+H)^+$ | :237.1028 |
| Found | :237.1029. |

**1-Aza-8-(1-oxopropyl)-7-(pyrid-2-yl)bicyclo[4.3.0]nona-2,4,6,8-tetraene (82j):**

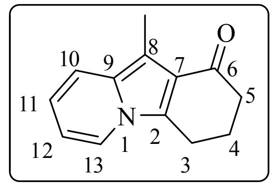
The compound **82j** was obtained by the reaction between di(2-pyridyl) ketone (**80f**) and ethyl vinyl ketone (**81b**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as a solid.



| | |
|---|---|
| Time | :12 h |
| Yield | :27% |
| M.p. | :101–103 °C |
| IR (neat) | :$\upsilon$ 1665, 1484, 1413, 1194, 750 $cm^{-1}$ |
| $^{1}H$ NMR (400 MHz, $CDCl_3$) | :$\delta$ 1.16 (t, $J$ = 7.2 Hz, 3H), 2.84 (q, $J$ = 7.2 Hz, 2H), 6.58–6.65 (m, 1H), 6.76–6.82 (m, 1H), 7.15–7.22 (m, 1H), 7.53–7.60 (m, 1H), 7.68–7.76 (m, 2H), 7.79 (s, 1H), 7.89 (d, $J$ = 7.2 Hz, 1H), 8.65–8.70 (m, 1H) |
| $^{13}C$ NMR (100 MHz, $CDCl_3$) | :$\delta$ 8.49, 34.58, 113.18, 113.55, 116.36, 120.02, 120.10, 120.93, 125.39, 125.65, 126.09, 132.66, 135.69, 149.07, 154.15, 198.81 |
| HRMS (ESI) exact mass calcd for $C_{16}H_{14}N_2O$+H $(M+H)^+$ | :251.1179 |
| Found | :251.1184. |

**1-Aza-8-methyl-6-oxotricyclo[7.4.0.0$^{2,7}$]trideca-2(7),8,10,12-tetraene (87a):**

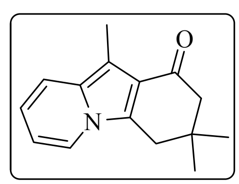
Tricyclic compound **87a** was obtained by the reaction between 2-acetylpyridine (**80a**) and cyclohex-2-enone (**86a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as a solid.




| | |
|---|---|
| Time | :12 h |
| Yield | :60% |
| M.p. | :123–125 °C |
| IR (neat) | :$\upsilon$ 1654, 1435, 1402, 1232, 734 cm$^{-1}$ |
| $^1$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 2.22–2.32 (m, 2H), 2.55 (s, 3H), 2.58–2.63 (m, 2H), 2.93 (t, $J$ = 6.0 Hz, 2H), 6.47–6.53 (m, 1H), 6.54–6.62 (m, 1H), 7.30–7.36 (m, 1H), 7.56 (d, $J$ = 6.8 Hz, 1H) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 9.63, 21.15, 23.53, 39.44, 107.75, 112.09, 116.03, 119.12, 121.00, 121.85, 129.96, 130.86, 197.23; |
| HRMS (ESI) exact mass calcd for $C_{13}H_{13}NO$ (M)$^+$ | :199.0997; |
| Found | :199.1031. |

**1-Aza-6-oxo-4,4,8-trimethyltricyclo[7.4.0.0$^{2,7}$]trideca-2(7),8,10,12-tetraene (87b):**

Reaction between 2-acetylpyridine (**80a**) and 5,5-dimethylcyclohex-2-enone (**86b**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, afforded the title compound **87b** as a solid.




| | |
|---|---|
| Time | :12 h |
| Yield | :31% |
| M.p. | :89–91 °C |
| IR (neat) | :$\upsilon$ 1665, 1457, 1408, 1227, 734 cm$^{-1}$ |

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.17 (s, 6H), 2.48 (s, 2H), 2.54 (s, 3H), 2.78 (s, 2H), 6.47–6.53 (m, 1H), 6.54–6.61 (m, 1H), 7.33 (d, $J$ = 9.2 Hz, 1H), 7.54 (d, $J$ = 6.8 Hz, 1H)

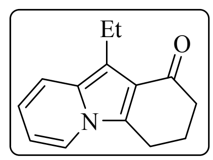
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 9.58, 28.94, 35.31, 35.38, 53.57, 107.74, 112.09, 115.91, 119.24, 120.01, 121.79, 129.80, 130.36, 196.80

HRMS (ESI) exact mass calcd for $C_{15}H_{17}NO$ $(M)^+$ :227.1310

Found :227.1307

**1-Aza-8-ethyl-6-oxotricyclo[7.4.0.0$^{2,7}$]trideca-2(7),8,10,12-tetraene (87c):**

The indolizine **87c** was obtained by the reaction between 2-propanoylpyridine (**80b**) and cyclohex-2-enone (**86a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as a solid.




Time :12 h

Yield :26%

M.p. :94–96 °C

IR (neat) :$\upsilon$ 1665, 1457, 1433, 1232, 734 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.23 (t, $J$ = 7.2 Hz, 3H), 2.23–2.33 (m, 2H), 2.61 (t, $J$ = 6.8 Hz, 2H), 2.93 (t, $J$ = 6.4 Hz, 2H), 3.02 (q, $J$ = 7.2 Hz, 2H), 6.48–6.54 (m, 1H), 6.55–6.61 (m, 1H), 7.35 (d, $J$ = 9.2 Hz, 1H), 7.56 (d, $J$ = 6.8 Hz, 1H)

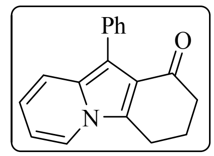
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 15.93, 17.75, 21.25, 23.54, 39.57, 112.17, 115.02, 116.21, 119.11, 120.37, 121.93, 129.42, 131.10, 196.84;

HRMS (ESI) exact mass calcd for $C_{14}H_{15}NO$ $(M)^+$ :213.1154

Found :213.1162.

**1-Aza-6-oxo-8-phenyltricyclo[7.4.0.0$^{2,7}$]trideca-2(7),8,10,12-tetraene (87d):**

Reaction between 2-benzoylpyridine (**80e**) and cyclohex-2-enone (**86a**) in acetonitrile under the influence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, produced the title compound **87d** as a solid.



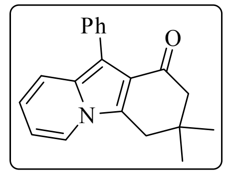

| | |
|---|---|
| Time | :12 h |
| Yield | :35% |
| M.p. | :113–115 °C |
| IR (neat) | :$\upsilon$ 1665, 1463, 1430, 1227, 767 cm$^{-1}$ |
| $^1$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 2.22–2.36 (m, 2H), 2.55–2.67 (m, 2H), 2.96 (t, $J$ = 6.0 Hz, 2H), 6.53–6.60 (m, 1H), 6.61–6.68 (m, 1H), 7.22–7.31 (m, 1H), 7.35–7.43 (m, 2H), 7.46 (d, $J$ = 8.8 Hz, 1H), 7.54 (d, $J$ = 7.6 Hz, 2H), 7.62 (d, $J$ = 7.2 Hz, 1H) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 21.38, 23.27, 39.75, 112.84, 112.99, 118.49, 119.76, 119.81, 122.08, 126.39, 127.84, 130.38, 130.47, 132.20, 133.80, 195.42; |

HRMS (ESI) exact mass calcd for $C_{18}H_{15}NO$ $(M)^+$ :261.1154;

Found :261.1178.

**1-Aza-4,4-dimethyl-6-oxo-8-phenyltricyclo[7.4.0.0$^{2,7}$]trideca-2(7),8,10,12-tetraene (87e):**

Tricyclic compound **87e** was obtained by the reaction between 2-benzoylpyridine (**80e**) and 5,5-dimethylcyclohex-2-enone (**86b**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as a solid.



Time :12 h

Yield :10%

M.p. :140–142 °C

IR (neat) :$\upsilon$ 1654, 1452, 1430, 1232, 745 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.22 (s, 6H), 2.53 (s, 2H), 2.87 (s, 2H), 6.57–6.63 (m, 1H), 6.64–6.72 (m, 1H), 7.27–7.33 (m, 1H), 7.37–7.45 (m, 2H), 7.50 (d, $J$ = 9.2 Hz, 1H), 7.54–7.60 (m, 2H), 7.64 (d, $J$ = 7.2 Hz, 1H)

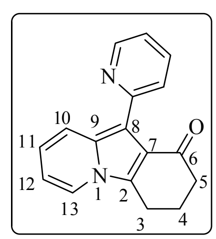
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 28.87, 35.20, 35.46, 53.87, 112.81, 112.91, 118.38, 118.73, 119.90, 122.00, 126.40, 127.89, 130.38, 130.77, 131.09, 133.70, 195.09

HRMS (ESI) exact mass calcd for $C_{20}H_{19}NO$ +Na $(M+Na)^+$ :312.1364

Found :312.1365.

**1-Aza-6-oxo-8-(pyrid-2-yl)tricyclo[7.4.0.0$^{2,7}$]trideca-2(7),8,10,12-tetraene (87f):**

Treatment of di(2-pyridyl) ketone (**80f**) with cyclohex-2-enone (**86a**) in acetonitrile in the presence of TMSOTf, following similar reaction procedure described for molecules **82a** & **83a**, provided the title compound **87f** as a solid.



Time :12 h

Yield :59%

M.p. :141–143 °C

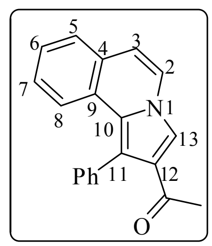
IR (neat) :$\upsilon$ 1665, 1473, 1424, 1232, 745 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 2.30–2.40 (m, 2H), 2.68 (t, $J$ = 6.0 Hz, 2H), 3.03 (t, $J$ = 6.4 Hz, 2H), 6.64–6.72 (m, 1H), 6.78–6.85 (m, 1H),

| | |
|---|---|
| | :7.10–7.17 (m, 1H), 7.67–7.75 (m, 2H), 7.87–7.95 (m, 1H), 8.04–8.11 (m, 1H), 8.61–8.70 (m, 1H) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 21.43, 23.11, 39.86, 111.68, 113.35, 119.82, 120.02, 120.57, 121.36, 121.99, 125.94, 132.32, 132.83, 135.42, 148.56, 153.87, 195.55 |
| HRMS (ESI) exact mass calcd for $C_{17}H_{14}N_2O$+H $(M+H)^+$ | :263.1179 |
| Found | :263.1184 |

**12-Acetyl-1-aza-11-phenyltricyclo[8.3.0.0$^{4,9}$]trideca-2,4(9),5,7,10,12-hexaene (85):**

The tricyclic compound **85** was obtained by the reaction between isoquinolin-1-yl phenyl ketone (**84**) and methyl vinyl ketone (**81a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, as a solid.

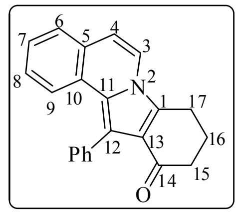


| | |
|---|---|
| Time | :12 h |
| Yield | :55% |
| M.p. | :118–120 °C |
| IR (neat) | :$\upsilon$ 1671, 1473, 1430, 1221, 761 cm$^{-1}$ |
| $^1$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 2.14 (s, 3H), 6.81 (d, *J* = 7.2 Hz, 1H), 7.08–7.16 (m, 1H), 7.21–7.32 (m, 2H), 7.41–7.56 (m, 6H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.85 (s, 1H) |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 29.51, 113.94, 118.62, 118.75, 122.85, 124.16, 126.18, 126.51, 126.85, 127.07, 127.25, 127.64, 127.75, 128.98, 130.70, 136.81, 195.29 |
| HRMS (ESI) exact mass calcd for $C_{20}H_{15}NO$+Na $(M+Na)^+$ | :308.1051 |

Found :308.1052.

**2-Aza-14-oxo-12-phenyltetracyclo[11.4.0.0$^{2,11}$,0$^{5,10}$]heptdeca-1(13),3,5(10),6,8,11-hexaene (88):**

Reaction between isoquinolin-1-yl phenyl ketone (**84**) and cyclohex-2-enone (**86a**) in acetonitrile in the presence of TMSOTf, following the similar reaction procedure described for the molecules **82a** & **83a**, gave the title compound **88** as a solid.




Time :12 h

Yield :45%

M.p. :249–251 °C

IR (neat) :$\upsilon$ 1660, 1471, 1424, 1216, 765 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 2.28–2.38 (m, 2H), 2.58 (t, $J$ = 7.2 Hz, 2H), 3.05 (t, $J$ = 6.4 Hz, 2H), 6.83 (d, $J$ = 7.6 Hz, 1H), 7.08–7.18 (m, 1H), 7.23–7.31 (m, 1H), 7.38–7.53 (m, 7H), 7.56 (d, $J$ = 7.6 Hz, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 21.36, 23.30, 39.32, 113.55, 116.74, 120.46, 120.80, 123.07, 125.74, 126.12, 127.20, 127.25, 127.48, 127.60, 128.49, 130.44, 134.38, 136.02, 194.63

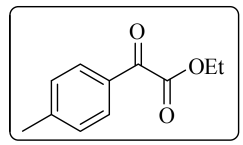
HRMS (ESI) exact mass calcd for $C_{22}H_{17}NO+H$ $(M+H)^+$ :312.1388

Found :312.1391.

**Ethyl (4-methylphenyl)glyoxylate (92b):**

This compound was prepared according to the literature procedure.[182]

To a stirred solution of diethyl oxalate (250 mmol, 36.5g, 33.85 mL) in THF (100 mL) was added a solution of 4-methylphenylmagnesium bromide (100 mmol) [prepared from 4-bromotoluene (**94a**) (100 mmol, 17.10 g, 12.3 mL) and magnesium turnings (100 mmol, 2.43 g)] in THF (100 mL) slowly at –10 °C over a period of 1 hour. The reaction mixture was quenched immediately with 2N HCl solution to a pH of 4.0 and extracted with ether (3 X 100 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered and solvent was evaporated. Excess diethyl oxalate was distilled off. Residue thus obtained was purified by column chromatography to provide the ethyl (4-methylphenyl)glyoxylate (**92b**) in 13.28 g (69%).




IR (Neat) :ν 1738, 1676 $cm^{-1}$

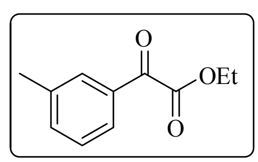
$^{1}$H NMR (400 MHz, $CDCl_3$) :δ 1.42 (t, *J* = 7.2 Hz, 3H), 2.45 (s, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :δ 13.86, 21.82, 63.06, 128.64, 129.58, 130.08, 146.19, 164.01, 186.06

LCMS (*m/z*) :193.00 $(M+H)^+$

**Ethyl (3-methylphenyl)glyoxylate (92c):**

The title compound was obtained as a colorless liquid via the reaction of 3-methyl phenylmagnesium bromide with diethyl oxalate in THF, following the similar reaction procedure described for the molecule **92b**.




Time :1 h

Yield :64%

IR (Neat) :ν 1744, 1687 $cm^{-1}$

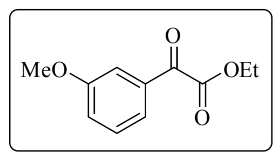
$^{1}$H NMR (400 MHz, $CDCl_3$) :δ 1.38 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.37–7.44 (m, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.77–7.86 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :δ 14.03, 21.17, 62.21, 127.27, 128.72, 130.19, 132.36, 135.72, 138.79, 163.98, 186.66

LCMS (*m/z*) :191.00 $(M–H)^+$

**Ethyl (3-methoxyphenyl)glyoxylate (92d):**

Reaction of 3-methoxy-phenylmagnesium bromide with diethyl oxalate in THF, following the similar procedure described for the molecule **92b**, gave the title compound as a colorless liquid.




Time :1 h

Yield :65%

IR (Neat) :ν 1737, 1682 $cm^{-1}$

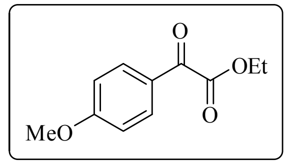
$^{1}$H NMR (400 MHz, $CDCl_3$) :δ 1.43 (t, *J* = 6.8 Hz, 3H), 3.87 (s, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.21 (dd, *J* = 2.0 Hz & 8.4 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :δ 13.68, 55.25, 62.85, 113.08, 121.53, 122.79, 129.75, 133.47, 159.76, 163.68, 186.13

LCMS (*m/z*) :209.00 $(M+H)^+$

**Ethyl (4-methoxyphenyl)glyoxylate (92e):**

Treatment of 4-methoxy-phenylmagnesium bromide with diethyl oxalate in THF, following the similar reaction procedure described for the molecule **92b**, provided the title compound as a colorless liquid.



Time :1 h

Yield :62%

IR (Neat) :ν 1740, 1666 $cm^{-1}$

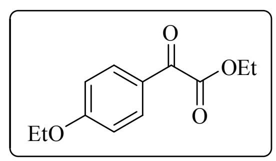
$^{1}$H NMR (400 MHz, $CDCl_3$) :δ 1.42 (t, *J* = 7.2 Hz, 3H), 3.90 (s, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :δ 14.09, 55.62, 62.14, 114.22, 125.43, 132.52, 164.17, 165.01, 184.90

LCMS (*m/z*) :209.00 $(M+H)^+$

**Ethyl (4-ethoxyphenyl)glyoxylate (92f):**

The title compound was obtained via the reaction of 4-ethoxy-phenylmagnesium bromide with diethyl oxalate in THF, following the similar reaction procedure described for the molecule **92b**, as a colorless liquid.



Time :1 h

Yield :66%

IR (Neat) :ν 1733, 1676 $cm^{-1}$

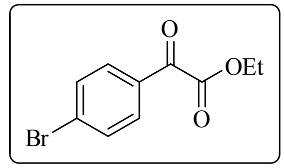
$^{1}$H NMR (400 MHz, $CDCl_3$) :δ 1.42 (t, *J* = 7.2 Hz, 3H),* 1.45 (t, *J* = 7.2 Hz, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.44 (q, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H); *One of the triplet peak merged with the triplet peaks at δ 1.45.

$^{13}$C NMR (100 MHz, $CDCl_3$) :δ 14.06, 14.50, 62.04, 63.99, 114.63, 125.30, 132.48, 164.21, 164.45, 184.85

LCMS (*m/z*) :223.00 $(M+H)^+$

**Ethyl (4-bromophenyl)glyoxylate (92g):**

Reaction of 4-bromophenylmagnesium bromide with diethyl oxalate in THF, following the similar procedure described for the molecule **92b**, produced the title compound as a colorless liquid.




Time :1 h

Yield :73%

IR (Neat) :ν 1737, 1688, 1584 $cm^{-1}$

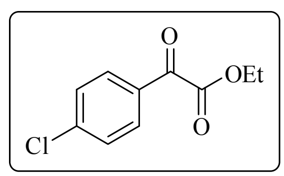
$^{1}$H NMR (400 MHz, $CDCl_3$) :δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.46–7.53 (m, 2H), 7.96–8.03 (m, 2H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :δ 14.03, 62.47, 129.25, 131.38, 141.52, 157.86, 163.17, 184.83

LCMS (*m/z*) :257.00 $(M+H)^+$

**Ethyl (4-chlorophenyl)glyoxylate (92h):**

This molecule was obtained as a colorless liquid via the reaction between 4-chlorophenylmagnesium bromide with diethyl oxalate in THF, following the similar procedure described for the molecule **92b**.




Time :1 h

Yield :84%

IR (Neat) :ν 1731, 1682 $cm^{-1}$

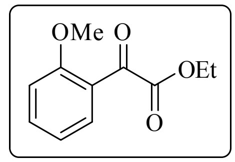
$^{1}$H NMR (400 MHz, $CDCl_3$) :δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :δ 14.03, 62.47, 129.25, 131.37, 141.51, 157.86, 163.17, 184.83

LCMS (*m/z*) :213.00 $(M+H)^+$

**Ethyl (2-methoxyphenyl)glyoxylate (92i):**

Treatment of 2-methoxy-phenylmagnesium bromide with diethyl oxalate in THF, following the similar procedure described for the molecule **92b**, gave the α-keto ester **92i** as a colorless liquid.




Time :1 h

Yield :67%

IR (Neat) :ν 1732, 1688 $cm^{-1}$

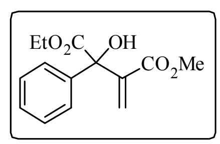
$^1H$ NMR (400 MHz, $CDCl_3$) :δ 1.38 (t, *J* = 7.2 Hz, 3H), 3.87 (s, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.55–7.63 (m, 1H), 7.88 (d, *J* = 7.6 Hz, 1H)

$^{13}C$ NMR (100 MHz, $CDCl_3$) :δ 14.05, 55.93, 61.70, 112.01, 121.20, 122.63, 130.58, 136.35, 160.23, 165.27, 186.57

LCMS (*m/z*) :209.00 $(M+H)^+$

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanoate (91a):**

This compound was prepared following the literature procedure.[181]




A mixture of ethyl phenylglyoxylate (**92a**) (40.0 mmol, 7.12 g), methyl acrylate (80.0 mmol, 6.88 g, 7.0 mL) and DABCO (12.0 mmol, 1.344 g) was kept at room temperature for 10 days. The reaction mixture was diluted with water (20.0 mL) and extracted with ether (3 X 20 mL). Combined organic layers were dried over anhydrous sodium sulfate, solvent was evaporated and the residue thus obtained was purified by using column chromatography (silica gel, 10% EtOAc in hexanes) to provide **91a** in 71% (7.51 g) yield as a colorless liquid.

IR (KBr) :$\upsilon$ 3496, 1731, 1687, 1627 $cm^{-1}$

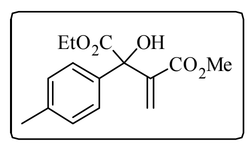
$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.29 (t, $J$ = 7.5 Hz, 3H), 3.81 (s, 3H), 4.30 (q, $J$ = 7.0 Hz, 2H), 4.32 (s, 1H), 5.38 (s, 1H), 6.38 (s, 1H), 7.32–7.42 (m, 3H), 7.61–7.66 (m, 2H).

$^{13}$C NMR (125 MHz, $CDCl_3$) : $\delta$ 14.00, 52.21, 62.55, 78.78, 126.84, 128.18, 128.35, 129.12, 137.88, 142.98, 166.86, 173.32.

LCMS ($m/z$) :265.00 $(M+H)^+$

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-methylphenyl)-2-methylenepropanoate (91b):**

The title compound was obtained via Baylis-Hillman coupling between ethyl (4-methylphenyl)glyoxylate (**92b**) and methyl acrylate following the similar reaction procedure described for **91a**.



Time :10 d

Yield :74%

IR (neat) :$\upsilon$ 3490, 1736, 1698, 1638 $cm^{-1}$

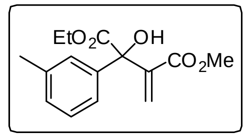
$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.29 (t, $J$ = 7.0 Hz, 3H), 2.36 (s, 3H), 3.81 (s, 3H), 4.283 (s, 1H), 4.284 (q, $J$ = 7.5 Hz, 2H), 5.40 (s, 1H), 6.37 (s, 1H), 7.19 (d, $J$ = 8.0 Hz, 2H), 7.50 (d, $J$ = 8.5 Hz, 2H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.99, 21.03, 52.16, 62.44, 78.64, 126.71, 128.86, 129.05, 134.87, 138.05, 143.01, 166.88, 173.41.

LCMS ($m/z$) :279.00 $(M+H)^+$

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-(3-methylphenyl)-2-methylenepropanoate (91c):**

Baylis-Hillman reaction between ethyl (3-methylphenyl)glyoxylate (**92c**) and methyl acrylate following the similar reaction procedure described for **91a**, gave the title compound as a colorless liquid.




Time :10 d

Yield :69%

IR (neat) :$\upsilon$ 3496, 1775, 1742, 1625, 1605 $cm^{-1}$

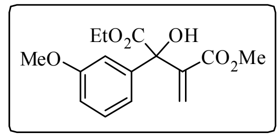
$^1H$ NMR (400 MHz, $CDCl_3$) :$\delta$ 1.28 (t, $J$ = 7.2 Hz, 3H), 2.36 (s, 3H), 3.81 (s, 3H), 4.25–4.40 (m, 3H),* 5.40 (s, 1H), 6.37 (s, 1H), 7.15 (d, $J$ = 7.6 Hz, 1H), 7.25 (t, $J$ = 8.0 Hz, 1H), 7.35–7.44 (m, 1H), 7.47 (s,1H); *It merged with quartet at $\delta$ 4.25 ($J$ = 7.2 Hz).

$^{13}C$ NMR (100 MHz, $CDCl_3$) :$\delta$ 14.00, 21.59, 52.25, 62.52, 78.75, 123.92, 127.33, 128.01, 129.07, 129.29, 137.61, 137.90, 142.86, 166.95, 173.41.

LCMS ($m/z$) :279.00 $(M+H)^+$

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanoate (91d):**

Coupling between ethyl (3-methoxyphenyl)glyoxylate (**92d**) and methyl acrylate following the similar reaction procedure described for **91a**, produced the BH adduct **91d**.




Time :10 d

Yield :76%

IR (neat) :$\upsilon$ 3485, 1737, 1633 cm$^{-1}$

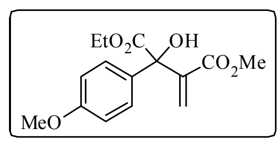
$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.5 Hz, 3H), 3.811 & 3.815 (2s, 6H), 4.30 (q, $J$ = 7.5 Hz, 2H), 4.33 (s, 1H), 5.42 (s, 1H), 6.39 (s, 1H), 6.89 (dd, $J$ = 2.5 & 8.5 Hz, 1H), 7.18 (d, $J$ = 7.5 Hz, 1H), 7.23 (t, $J$ = 2.0 Hz, 1H), 7.29 (t, $J$ = 8.0 Hz, 1H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.98, 52.18, 55.22, 62.53, 78.65, 112.46, 114.00, 119.19, 129.08, 129.20, 139.41, 142.71, 159.55, 166.79, 173.19.

LCMS ($m/z$) :293.20 (M–H)$^+$

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropano-ate (91e):**

This compound was obtained via Baylis-Hillman reaction of ethyl (4-methoxyphenyl)glyoxylate (**92e**) with methyl acrylate following the similar reaction procedure described for **91a**.




Time :10 d

Yield :78%

IR (neat) :$\upsilon$ 3474, 1742, 1709, 1627 cm$^{-1}$

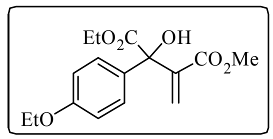
$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.29 (t, $J$ = 7.0 Hz, 3H), 3.81 & 3.82 (2s, 6H), 4.28 (s, 1H), 4.29 (q, $J$ = 7.0 Hz, 2H), 5.42 (s, 1H), 6.37 (s, 1H), 6.90 (d, $J$ = 8.5 Hz, 2H), 7.54 (d, $J$ = 8.5 Hz, 2H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 14.10, 52.27, 55.37, 62.56, 78.54, 113.62, 128.19,

| | |
|---|---|
| | 129.12, 129.88, 143.22, 159.67, 167.00, 173.56. |
| LCMS (*m/z*) | :293.20 (M–H)$^+$ |

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-ethoxyphenyl)-2-methylenepropano-ate (91f):**

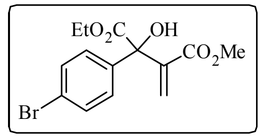
Baylis-Hillman coupling between ethyl (4-ethoxyphenyl)glyoxylate (**92f**) and methyl acrylate following the similar reaction procedure described for **91a**, gave the title compound.




| | |
|---|---|
| Time | :10 d |
| Yield | :81% |
| Mp. | :140–141 °C |
| IR (neat) | :$\upsilon$ 3457, 1753, 1731, 1698, 1633 cm$^{-1}$ |
| $^1$H NMR (500 MHz, CDCl$_3$) | :$\delta$ 1.28 (t, $J$ = 7.0 Hz, 3H), 1.41 (t, $J$ = 7.0 Hz, 3H), 3.80 (s, 3H), 4.04 (q, $J$ = 7.0 Hz, 2H), 4.26 (s, 1H), 4.28 (q, $J$ = 7.0 Hz, 2H), 5.41 (s, 1H), 6.36 (s, 1H), 6.89 (d, $J$ = 9.0 Hz, 2H), 7.52 (d, $J$ = 9.0 Hz, 2H). |
| $^{13}$C NMR (125 MHz, CDCl$_3$) | :$\delta$ 14.06, 14.86, 52.21, 62.48, 63.51, 78.51, 114.10, 128.11, 129.05, 129.66, 143.21, 159.00, 166.96, 173.52. |
| LCMS (*m/z*) | :307.15 (M–H)$^+$ |

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-bromophenyl)-2-methylenepropanoate (91g):**

The title compound was obtained via coupling between ethyl (4-bromophenyl)glyoxylate (**92g**) and methyl acrylate following the similar reaction procedure described for **91a**.




Time :10 d

Yield :82%

IR (neat) :$\upsilon$ 3468, 1748, 1698, 1633 $cm^{-1}$

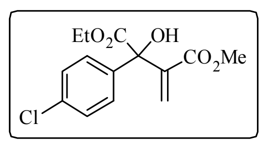
$^{1}H$ NMR (500 MHz, $CDCl_3$) :$\delta$ 1.28 (t, $J$ = 7.0 Hz, 3H), 3.81 (s, 3H), 4.29 (q, $J$ = 7.0 Hz, 2H), 4.34 (s, 1H), 5.39 (s, 1H), 6.39 (s, 1H), 7.49–7.55 (m, 4H).

$^{13}C$ NMR (125 MHz, $CDCl_3$) :$\delta$ 13.98, 52.30, 62.76, 78.42, 122.67, 128.72, 129.06, 131.31, 136.97, 142.58, 166.62, 172.89.

LCMS (*m/z*) :341.00 $(M–H)^+$

**Methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-chlorophenyl)-2-methylenepropanoate (91h):**

Baylis-Hillman reaction between ethyl (4-chlorophenyl)glyoxylate (**92h**) and methyl acrylate following the similar reaction procedure described for **91a**, gave the BH adduct **91h**.




Time :10 d

Yield :81%

IR (neat) :$\upsilon$ 3479, 1731, 1698, 1632, 1588 $cm^{-1}$

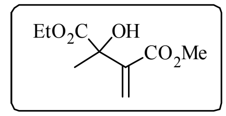
$^{1}H$ NMR (500 MHz, $CDCl_3$) :$\delta$ 1.28 (t, $J$ = 7.0 Hz, 3H), 3.81 (s, 3H), 4.29 (q, $J$ = 7.0 Hz, 2H), 4.36 (s, 1H), 5.38 (s, 1H), 6.39 (s, 1H), 7.35 (d, $J$ = 8.5 Hz, 2H), 7.59 (d, $J$ = 8.5 Hz, 2H).

$^{13}C$ NMR (125 MHz, $CDCl_3$) :$\delta$ 13.98, 52.31, 62.76, 78.36, 128.35, 128.38, 129.08, 134.41, 136.38, 142.63, 166.65, 172.97.

LCMS (*m/z*) :296.00 $(M–2)^+$

**Methyl 3-ethoxycarbonyl-3-hydroxy-2-methylenebutanoate (91i):**

The title compound was obtained via reaction between ethyl pyruvate (**92j**) and methyl acrylate following the similar reaction procedure described for **91a**.



Time :7 d

Yield :41%

IR (neat) :$\upsilon$ 3479, 1748, 1709, 1622 cm$^{-1}$

$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.26 (t, $J$ = 7.5 Hz, 3H), 3.77 (s, 3H), 3.93 (s, 1H), 4.23 (q, $J$ = 7.0 Hz, 2H), 5.98 (s, 1H), 6.37 (s, 1H).

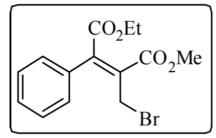
$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 14.00, 23.73, 52.09, 62.02, 73.70, 125.61, 141.82, 166.53, 174.81.

LCMS (*m/z*) :203.00 $(M+H)^+$

**4-Ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (93a):**

To a stirred suspension of *N*-bromosuccinimide (20.0 mmol, 3.559 g) in $CH_2Cl_2$ (50.0 mL) dimethyl sulfide (40.0 mmol, 2.485g, 2.94 mL) was added slowly under nitogen atmosphere at 0 °C and the stirring was continued for 1 hour at same temperature. To this resultant yellow suspension methyl 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methy-lenepropanoate (**91a**) (10.0 mmol, 2.643 g) was added portion wise. After stirring for 12 hours at room temperature the reaction mixture was treated with aqueous $NaHCO_3$ solution (10.0 mL) and organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2X10 mL). Combined organic layer was dried over anhydrous sodium sulfate ($Na_2SO_4$), solvent was evaporated. Thus the obtained crude mixture was purified by column chromatography (silica gel 100–200 mesh, 10% EtOAc in hexanes) to provide **93a** in 94% (3.084 g) yield as a colorless solid.

Yield :94%



Mp. :57–59 °C

IR (KBr) :$\upsilon$ 1726, 1627 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 3.87 (s, 3H), 4.13 (s, 2H), 4.27 (q, $J$ = 7.2 Hz, 2H), 7.40–7.51 (m, 5H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 13.94, 27.49, 52.68, 61.88, 127.71, 128.83, 129.57, 129.84, 133.42, 145.44, 165.59, 167.62.

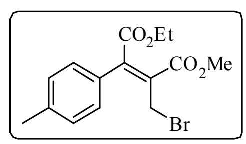
HRMS (ESI) exact mass calcd for $C_{14}H_{15}BrO_4$+Na (M+Na)$^+$ : 349.0051

Found :349.0056.

**4-Ethyl 1-methyl 2-(bromomethyl)-3-(4-methylphenyl)maleate (93b):**

The title compound was obtained via bromination of methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-methylphenyl)-2-methylenepropanoate (**91b**) using *N*-bromosuccinimide, following the similar reaction procedure described for **93a**.

Time :12 h



Yield :92%

Mp. :57–58 °C

IR (neat) :$\upsilon$ 1731, 1605 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.29 (t, $J$ = 7.2 Hz, 3H), 2.39 (s, 3H), 3.86 (s, 3H), 4.15 (s, 2H), 4.27 (q, $J$ = 7.2 Hz, 2H), 7.25 (d, $J$ = 7.2 Hz, 2H),* 7.37 (d, $J$ = 8.0 Hz, 2H). *It also contains $CHCl_3$ peak.

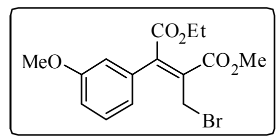
$^{13}$C NMR (100 MHz, $CDCl_3$) : $\delta$ 13.95, 21.34, 27.79, 52.62, 61.82, 127.68, 129.18, 129.54, 130.51, 139.81, 145.81, 165.65, 167.85.

HRMS (ESI) exact mass calcd for $C_{15}H_{17}BrO_4$+Na $(M+Na)^+$ :363.0208

Found :363.0211

**4-Ethyl 1-methyl 2-(bromomethyl)-3-(3-methoxyphenyl)maleate (93c):**

Bromination of methyl 3-ethoxycarbonyl-3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**91c**) using *N*-bromosuccin-imide, following the similar reaction procedure described for **93a**, provided the ally bromide **93c**.




Time :12 h

Yield :93%

Mp. :62–63 °C

IR (neat) :$\upsilon$ 1715, 1600 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.15 (s, 2H), 4.28 (q, $J$ = 7.2 Hz, 2H), 6.94–7.00 (m, 1H), 7.00–7.06 (m, 2H), 7.35 (t, $J$ = 8.0 Hz, 2H).

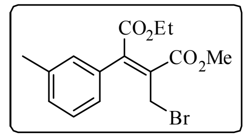
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 13.96, 27.68, 52.71, 55.36, 61.94, 112.70, 115.79, 119.92, 129.72, 129.98, 134.56, 145.49, 159.69, 165.55, 167.57.

HRMS (ESI) exact mass calcd for $C_{15}H_{17}BrO_5$+Na $(M+Na)^+$ :379.0157

Found :379.0159.

**4-Ethyl 1-methyl 2-(bromomethyl)-3-(3-methylphenyl)maleate (93d):**

This allyl bromide **93d** was obtained via bromination of methyl 3-ethoxycarbonyl-3-hydroxy-3-(3-methylphenyl)-2-methylenepropanoate (**91d**) using *N*-bromosuccinimide, following the similar reaction procedure described for **93a**.



Time :12 h

Yield :90%

IR (neat) :$\upsilon$ 1726, 1622 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) :$\delta$ 1.29 (t, $J$ = 7.2 Hz, 3H), 2.38 (s, 3H), 3.86 (s, 3H), 4.13 (s, 2H), 4.27 (q, $J$ = 7.2 Hz, 2H), 7.20–7.36 (m, 4H).

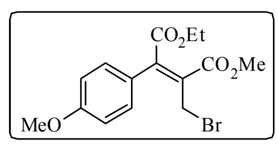
$^{13}$C NMR (100 MHz, CDCl$_3$) :$\delta$ 13.95, 21.40, 27.64, 52.65, 61.86, 124.76, 128.19, 128.72, 129.48, 130.39, 133.34, 138.66, 145.83, 165.61, 167.76.

HRMS (ESI) exact mass calcd for $C_{15}H_{17}BrO_4$+Na (M+Na)$^+$ : 363.0208

Found :363.0207

**4-Ethyl 1-methyl 2-(bromomethyl)-3-(4-methoxyphenyl)maleate (93e):**

Treatment of methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-methoxyphenyl)-2-methylene-propanoate (**91e**) with *N*-bromosuccinimide, following the similar reaction procedure described for **93a**, gave the required allyl bromide **93e**.



Time :12 h

Yield :94%

Mp. :82–83 °C

IR (KBr) :$\upsilon$ 1725, 1710, 1620, 1599 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) :$\delta$ 1.30 (t, $J$ = 5.6 Hz, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.19 (s, 2H), 4.28 (q, $J$ = 5.6 Hz, 2H), 6.94–7.00 (m, 2H), 7.41–7.46 (m, 2H).

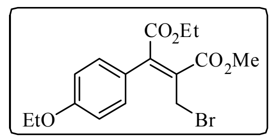
$^{13}$C NMR (100 MHz, CDCl$_3$) :$\delta$ 13.88, 28.05, 52.46, 55.25, 61.69, 114.27, 125.58, 128.58, 145.61, 160.60, 165.62, 167.89.

HRMS (ESI) exact mass calcd for $C_{15}H_{17}BrO_5$+Na $(M+Na)^+$ :379.0157

Found :379.0160.

**4-Ethyl 1-methyl 2-(bromomethyl)-3-(4-ethoxyphenyl)maleate (93f):**

This molecule was obtained via treatment of methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-ethoxyphenyl)-2-methylenepropanoate (**91f**) with *N*-bromosuccinimide, following the similar reaction procedure described for **93a**.




Time :12 h

Yield :91%

Mp. :89–91 °C

IR (KBr) :$\upsilon$ 1731, 1600 $cm^{-1}$

$^1H$ NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 1.44 (t, $J$ = 7.2 Hz, 3H), 3.85 (s, 3H), 4.07 (q, $J$ = 7.2 Hz, 2H), 4.20 (s, 2H), 4.28 (q, $J$ = 7.2 Hz, 2H), 6.93–6.98 (m, 2H), 7.40–7.45 (m, 2H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) :$\delta$ 14.04, 14.79, 28.29, 52.68, 61.89, 63.64, 114.82, 125.46, 128.36, 129.54, 145.98, 160.11, 165.82, 168.20.

HRMS (ESI) exact mass calcd for $C_{16}H_{19}BrO_5$+Na $(M+Na)^+$ :393.0314

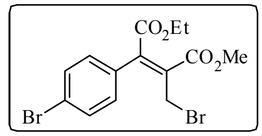
Found :393.0310.

**4-Ethyl 1-methyl 2-(bromomethyl)-3-(4-bromophenyl)maleate (93g):**

This molecule was obtained via treatment of methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-bromophenyl)-2-methylenepropanoate (**91g**) with *N*-bromosuccinimide, following the similar procedure described for **93a**.

Time :12 h

Yield :90%



Mp. :78–79 °C

IR (KBr) :$\upsilon$ 1726, 1709, 1611 cm$^{-1}$

$^{1}$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.29 (t, $J$ = 7.5 Hz, 3H), 3.87 (s, 3H), 4.08 (s, 2H), 4.26 (q, $J$ = 7.0 Hz, 2H), 7.31–7.36 (m, 2H), 7.56–7.62 (m, 2H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 14.02, 27.16, 52.87, 62.17, 124.18, 129.54, 132.24, 144.03, 165.55, 167.26.

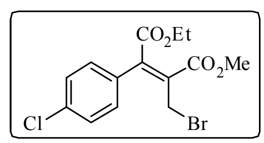
HRMS (ESI) exact mass calcd for $C_{14}H_{14}Br_2O_4$+Na (M+Na)$^+$ :426.9157

Found :426.9165.

**4-Ethyl 1-methyl 2-(bromomethyl)-3-(4-chlorophenyl)maleate (93h):**

Reaction of methyl 3-ethoxycarbonyl-3-hydroxy-3-(4-chlorophenyl)-2-methylene-propanoate (**91h**) with *N*-bromosuccinimide, following the similar procedure described for **93a**, produced the title compound.

Time :12 h



Yield :88%

Mp. :59–60 °C

IR (KBr) :$\upsilon$ 1726, 1622 cm$^{-1}$

$^{1}$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.29 (t, $J$ = 7.0 Hz, 3H), 3.87 (s, 3H), 4.09 (s, 2H), 4.27 (q, $J$ = 7.0 Hz, 2H), 7.38–7.47 (m, 4H).

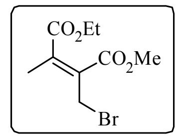
$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.95, 27.15, 52.80, 62.08, 129.19, 129.24, 130.67, 131.82, 135.82, 143.97, 165.45, 167.27.

HRMS (ESI) exact mass calcd for $C_{14}H_{14}BrClO_4$+Na (M+Na)$^+$ :382.9662

Found :382.9665.

**4-Ethyl 1-methyl 2-(bromomethyl)-3-methylmaleate (93i):**

The allyl bromide **93i** was obtained via bromination of methyl 3-ethoxycarbonyl-3-hydroxy-2-methylenebutanoate **(91i)** using *N*-bromosuccinimide, following the similar procedure described for **93a**.




Time :12 h

Yield :84%

IR (KBr) :$\upsilon$ 1726, 1633 $cm^{-1}$

$^1H$ NMR (500 MHz, $CDCl_3$) :$\delta$ 1.32 (t, $J$ = 7.5 Hz, 3H), 2.09 (s, 3H), 3.80 (s, 3H), 4.21 (s, 2H), 4.26 (q, $J$ = 7.0 Hz, 2H).

$^{13}C$ NMR (125 MHz, $CDCl_3$) :$\delta$ 13.98, 16.70, 25.39, 52.50, 61.62, 129.80, 142.56, 165.66, 168.88.

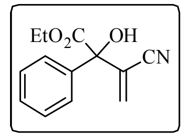
HRMS (ESI) exact mass calcd for $C_9H_{13}BrO_4$+Na $(M+Na)^+$ :286.9895

Found :286.9893.

**3-Ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (105a):**

This compound was prepared following the literature procedure.[181]

A mixture of ethyl phenylglyoxylate (**92a**) (40.0 mmol, 7.12 g), acrylonitrile (80.0 mmol, 4.24 g, 5.2 mL) and DABCO (12.0 mmol, 1.344 g) was kept at room temperature for 10 days. The reaction mixture was diluted with water (20.0 mL) and extracted with ether (3X20 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$, solvent was evaporated and the residue thus obtained was purified by using column chromatography (silica gel, 10% EtOAc in hexanes) to provide **105a** in 77% (7.11 g) yield as a colorless liquid.



Yield :77%

IR (KBr) :$\upsilon$ 3463, 2230, 1748, 1616 cm$^{-1}$

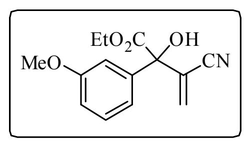
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.39 (t, $J$ = 7.2 Hz, 3H), 4.18 (s, 1H), 4.34–4.51 (m, 2H), 6.16 (s, 1H), 6.21 (s, 1H), 7.35–7.46 (m, 3H), 7.49–7.58 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 13.88, 63.86, 78.57, 116.86, 125.15, 126.28, 128.61, 129.05, 132.96, 137.49, 171.58.

LCMS (*m/z*) :232.00 $(M+H)^+$

**3-Ethoxycarbonyl-3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanenitrile (105b):**

The title compound was obtained via Baylis-Hillman coupling between ethyl (3-methoxyphenyl)glyoxylate (**92d**) and acrylonitrile following the similar reaction procedure described for **105a**.



Time :10 d

Yield :82%

Mp. :134–135 °C

IR (KBr) :$\upsilon$ 3425, 2230, 1748, 1600 cm$^{-1}$

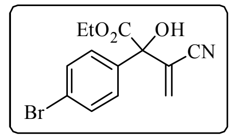
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.39 (t, $J$ = 7.2 Hz, 3H), 3.81 (s, 3H), 4.20 (s, 1H), 4.33–4.50 (m, 2H), 6.14 (s, 1H), 6.19 (s, 1H), 6.87–6.96 (m, 1H), 7.06–7.15 (m, 2H), 7.31 (t, $J$ = 8.4 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 13.97, 55.30, 63.91, 78.55, 112.20, 114.53, 116.93, 118.62, 125.14, 129.70, 133.03, 139.02, 159.75, 171.52.

LCMS (*m/z*) :262.00 M+H)$^+$

**3-Ethoxycarbonyl-3-hydroxy-3-(4-bromophenyl)-2-methylenepropanenitrile (105c):**

Baylis-Hillman coupling between ethyl (4-bromophenyl)glyoxylate (**92g**) and acrylonitrile following the similar reaction procedure described for **105a**, provided the title compound.




Time :10 d

Yield :85%

IR (KBr) :$\upsilon$ 3468, 2225, 1737, 1589 $cm^{-1}$

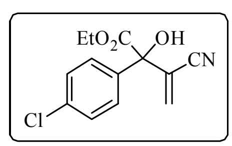
$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.37 (t, $J$ = 7.0 Hz, 3H), 4.27 (s, 1H), 4.33–4.47 (m, 2H), 6.15 (s, 1H), 6.20 (s, 1H), 7.41–7.47 (m, 2H), 7.51–7.56 (m, 2H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.97, 64.25, 78.19, 116.67, 123.53, 126.39, 128.22, 131.85, 132.98, 136.63, 171.25.

LCMS (*m/z*) :309.00 $(M)^+$

**3-Ethoxycarbonyl-3-hydroxy-3-(4-chlorophenyl)-2-methylenepropanenitrile (105d):**

Reaction between ethyl (4-chlorophenyl)glyoxylate (**92h**) and acrylonitrile following the similar reaction procedure described for **105a**, gave the desired BH adduct.




Time :10 d

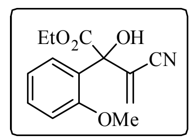
Yield :84%

IR (KBr) :$\upsilon$ 3463, 2225, 1742, 1589 $cm^{-1}$

| | |
|---|---|
| $^{1}$H NMR (500 MHz, $CDCl_3$) | :$\delta$ 1.37 (t, $J$ = 7.0 Hz, 3H), 4.33 (s, 1H), 4.35–4.47 (m, 2H), 6.15 (s, 1H), 6.19 (s, 1H), 7.35–7.39 (m, 2H), 7.47–7.52 (m, 2H). |
| $^{13}$C NMR (125 MHz, $CDCl_3$) | :$\delta$ 13.92, 64.17, 78.11, 116.66, 125.06, 127.90, 128.82, 132.96, 135.19, 136.04, 171.25. |
| LCMS ($m/z$) | :265.00 $(M)^+$ |

**3-Ethoxycarbonyl-3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropanenitrile (105e):**

This allyl alcohol was prepared via Baylis-Hillman coupling between ethyl (2-methoxyphenyl)glyoxylate (**92i**) and acrylonitrile following the similar reaction procedure described for **105a**.

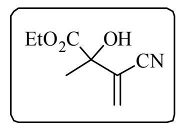



| | |
|---|---|
| Time | :10 d |
| Yield | :84% |
| Mp. | :164–165 °C |
| IR (neat) | :$\upsilon$ 3425, 2225, 1748, 1605 cm$^{-1}$ |
| $^{1}$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 1.31 (t, $J$ = 7.2 Hz, 3H), 3.81 (s, 3H), 4.26–4.44 (m, 3H), 6.38 (s, 1H), 6.59 (s, 1H), 6.93 (d, $J$ = 8.4 Hz, 1H), 7.01 (t, $J$ = 7.6 Hz, 1H), 7.31 (d, $J$ = 8.0 Hz, 1H), 7.34–7.42 (m, 1H). |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 13.98, 55.53, 63.21, 77.54, 111.67, 116.92, 120.97, 123.76, 127.11, 128.34, 130.75, 134.41, 156.74, 172.26. |
| LCMS ($m/z$) | :262.00 $(M+H)^+$ |

**Ethyl 3-cyano-2-hydroxy-2-methylbut-3-enoate (105f):**

This compound was prepared following the literature procedure.[181]

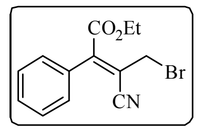
To a mixture of acrylonitrile (100.0 mmol, 5.30 g) and DABCO (1.5 mmol, 0.168 g) was added ethyl pyruvate (10.0 mmol, 1.02 g) and allowed to stand at room temperature for 24 hours. Reaction mixture was diluted with dichloromethane (25 mL) and washed with 2N HCl, aqueous $NaHCO_3$ solution and dried over anhydrous sodium sulphate. After concentration, crude mixture was subjected to column chromatography (10% EtOAc in hexanes) to provide the pure product **105f** in 49% yield (0.83 g), as a liquid.



| | |
|---|---|
| Time | :1 d |
| Yield | :49% |
| IR (neat) | :$\upsilon$ 3468, 2230, 1737, 1616 cm$^{-1}$ |
| $^1$H NMR (500 MHz, $CDCl_3$) | :$\delta$ 1.36 (t, $J$ = 7.0 Hz, 3H), 1.68 (s, 3H), 3.88 (s, 1H), 4.28–4.40 (m, 2H), 6.11 (s, 1H), 6.30 (s, 1H). |
| $^{13}$C NMR (125 MHz, $CDCl_3$) | :$\delta$ 13.99, 24.76, 63.53, 74.02, 116.66, 125.65, 131.58, 173.18. |
| LCMS (*m/z*) | :170 (M+H)$^+$ |

**(*Z*)-Ethyl 4-bromo-3-cyano-2-phenylbut-2-enoate [(*Z*)-106a]:**

To a stirred suspension of *N*-bromosuccinimide (20.0 mmol, 3.559 g) in $CH_2Cl_2$ (50.0 mL) dimethyl sulfide (40.0 mmol, 2.485g, 2.94 mL) was added slowly at 0 °C under nitogen atmosphere and stirring was continued for 1 hour at the same temperature. To this resultant yellow suspension ethyl 3-cyano-2-hydroxy-2-phenylbut-3-enoate (**105a**) (10.0 mmol, 2.643 g) was added portion wise. After stirring for 12 hours at room temperature the reaction mixture was treated with aqueous $NaHCO_3$ solution (10.0 mL) and organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2X10 mL). Combined organic layer was dried over anhydrous sodium sulfate ($Na_2SO_4$). Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel 230–400 mesh, 5% EtOAc in hexanes) to provide (*Z*)-**106a** (elutes first) in 29% (0.854 g) yield as a colorless viscous liquid and then the corresponding (*E*)-**106a** in 58% (1.71 g) yield as a colorless viscous liquid.




Yield :29%

IR (neat) :$\upsilon$ 2225, 1720, 1611 $cm^{-1}$

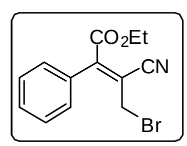
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.32 (t, $J$ = 7.2 Hz, 3H), 4.30 (s, 2H), 4.35 (q, $J$ = 7.2 Hz, 2H), 7.40–7.48 (m, 3H), 7.48–7.54 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.04, 26.99, 62.80, 114.56, 116.35, 128.32, 128.81, 130.73, 132.74, 149.49, 165.11.

HRMS (ESI) exact mass calcd for $C_{13}H_{12}BrNO_2$+Na (M+Na)$^+$ :315.9949

Found :315.9946.

**(*E*)-Ethyl 4-bromo-3-cyano-2-phenylbut-2-enoate [(*E*)-106a]**[#]**:**




Time :12 h

Yield :58%

IR (neat) :$\upsilon$ 2225, 1726, 1605 $cm^{-1}$

$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.35 (t, $J$ = 7.0 Hz, 3H), 3.99 (s, 2H), 4.36 (q, $J$ = 7.0 Hz, 2H), 7.34–7.39 (m, 2H), 7.45–7.50 (m, 3H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.83, 27.80, 62.87, 115.86, 115.96, 128.03, 128.88, 130.13, 131.62, 149.00, 164.50.

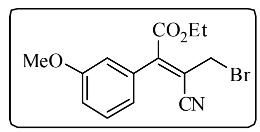
#It contains ≈ 2% *Z*-isomer.

HRMS (ESI) exact mass calcd for $C_{13}H_{12}BrNO_2$+Na (M+Na)$^+$ :315.9949

Found :315.9949.

**(*Z*)-Ethyl 4-bromo-3-cyano-2-(3-methoxyphenyl)but-2-enoate [(*Z*)-106b]:**

(*E*)- and (*Z*)-isomers of **106b** were obtained via bromination of ethyl 3-cyano-2-hydroxy-2-(3-methoxyphenyl)but-3-enoate (**105b**) using *N*-bromosuccinimide, following the similar reaction procedure described for **(*E*/*Z*)-106a**.

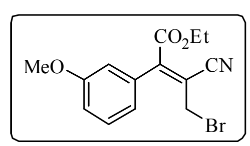


| | |
|---|---|
| Time | :12 h |
| Yield | :33% |
| IR (neat) | :$\upsilon$ 2225, 1726, 1594 cm$^{-1}$ |
| $^1$H NMR (500 MHz, $CDCl_3$) | :$\delta$ 1.33 (t, *J* = 7.0 Hz, 3H), 3.83 (s, 3H), 4.28 (s, 2H), 4.35 (q, *J* = 7.0 Hz, 2H), 6.98–7.02 (m, 1H), 7.03–7.09 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 1H). |
| $^{13}$C NMR (125 MHz, $CDCl_3$) | :$\delta$ 14.07, 26.99, 55.44, 62.83, 113.51, 114.38, 116.32, 116.73, 120.65, 129.97, 133.79, 149.41, 159.61, 165.07. |

HRMS (ESI) exact mass calcd for $C_{14}H_{14}BrNO_3$+Na (M+Na)$^+$ :346.0055

Found :346.0055.

**(*E*)-Ethyl 4-bromo-3-cyano-2-(3-methoxyphenyl)but-2-enoate [(*E*)-106b]:**



| | |
|---|---|
| Time | :12 h |
| Yield | :61% |
| Mp. | :62–64 °C |
| IR (KBr) | :$\upsilon$ 2219, 1720, 1600 cm$^{-1}$ |

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 3.80 (s, 3H), 4.00 (s, 2H), 4.32 (q, $J$ = 7.2 Hz, 2H), 6.96 (d, $J$ = 8.4 Hz, 1H), 7.06 (t, $J$ = 7.2 Hz, 1H), 7.31 (d, $J$ = 7.6 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 1H).

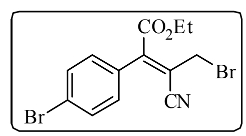
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 13.83, 28.54, 55.61, 62.33, 111.22, 115.97, 117.01, 120.73, 121.33, 129.35, 131.92, 146.40, 156.78, 164.37.

HRMS (ESI) exact mass calcd for $C_{14}H_{14}BrNO_3$+Na (M+Na)$^+$ :346.0055

Found :346.0056.

**(*Z*)-Ethyl 4-bromo-3-cyano-2-(4-bromophenyl)but-2-enoate [(*Z*)-106c]:**

(*E*)- and (*Z*)-isomers of **106c** were obtained via bromination of ethyl 3-cyano-2-hydroxy-2-(4-bromophenyl)but-3-enoate (**105c**) using *N*-bromosuccinimide, following the similar reaction procedure described for **(*E*/*Z*)-106a**.




Time :12 h

Yield :28%

IR (neat) :$\upsilon$ 2225, 1715, 1589 cm$^{-1}$

$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.33 (t, $J$ = 7.5 Hz, 3H), 4.32 (s, 2H), 4.35 (q, $J$ = 7.0 Hz, 2H), 7.41–7.47 (m, 4H).

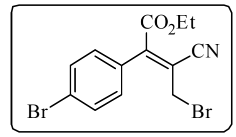
$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 14.04, 26.65, 62.99, 115.71, 116.15, 129.17, 129.82, 131.26, 137.00, 148.09, 164.71.

HRMS (ESI) exact mass calcd for $C_{13}H_{11}Br_2NO_2$+Na (M+Na)$^+$ :393.9055

Found :393.9056.

**(*E*)-Ethyl 4-bromo-3-cyano-2-(4-bromophenyl)but-2-enoate [(*E*)-106c]:**

Time :12 h




Yield :59%

IR (KBr) :$\upsilon$ 2214, 1720, 1589 cm$^{-1}$

$^{1}$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.34 (t, $J$ = 7.0 Hz, 3H), 3.97 (s, 2H), 4.35 (q, $J$ = 7.0 Hz, 2H), 7.30–7.35 (m, 2H), 7.44–7.49 (m, 2H).

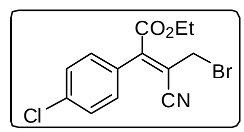
$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.87, 27.61, 63.13, 115.68, 116.88, 129.29, 129.58, 130.07, 136.50, 147.66, 164.11.

HRMS (ESI) exact mass calcd for $C_{13}H_{11}Br_2NO_2$+Na (M+Na)$^+$ :393.9055

Found :393.9057.

**(*Z*)-Ethyl 4-bromo-3-cyano-2-(4-chlorophenyl)but-2-enoate [(*Z*)-106d]:**

(*E*)- and (*Z*)-isomers of **106d** were obtained via bromination of ethyl 3-cyano-2-hydroxy-2-(4-chlorophenyl)but-3-enoate (**105d**) using *N*-bromosuccinimide, following the similar reaction procedure described for **(*E*/*Z*)-106a**.




Time :12 h

Yield :30%

IR (neat) :$\upsilon$ 2219, 1726, 1594 cm$^{-1}$

$^{1}$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.33 (t, $J$ = 7.0 Hz, 3H), 4.32 (s, 2H), 4.35 (q, $J$ = 7.0 Hz, 2H), 7.41–7.47 (m, 4H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 14.05, 26.63, 62.99, 115.76, 116.14, 129.18, 129.84, 131.30, 137.03, 148.11, 164.73.

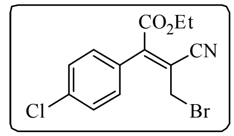
HRMS (ESI) exact mass calcd for $C_{13}H_{11}BrClNO_2$+Na (M+Na)$^+$ :349.9560

Found :349.9557.

**(*E*)-Ethyl 4-bromo-3-cyano-2-(4-chlorophenyl)but-2-enoate [(*E*)-106d]:**

Time :12 h

Yield :62%



IR (KBr) :$\upsilon$ 2219, 1720, 1589 cm$^{-1}$

$^{1}$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.34 (t, $J$ = 7.5 Hz, 3H), 3.96 (s, 2H), 4.35 (q, $J$ = 7.0 Hz, 2H), 7.30–7.34 (m, 2H), 7.43–7.49 (m, 2H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.89, 27.59, 63.14, 115.68, 116.88, 129.31, 129.59, 130.11, 136.54, 147.71, 164.14.

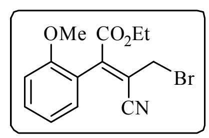
HRMS (ESI) exact mass calcd for $C_{13}H_{11}BrClNO_2$+Na (M+Na)$^+$ :349.9560

Found :349.9561.

**(*Z*)-Ethyl 4-bromo-3-cyano-2-(2-methoxyphenyl)but-2-enoate [(*Z*)-106e]#:**

(*E*)- and (*Z*)-isomers of **106e** were obtained via treatment of ethyl 3-cyano-2-hydroxy-2-(2-methoxyphenyl)but-3-enoate (**105e**) with *N*-bromosuccinimide, following the similar reaction procedure described for **(*E*/*Z*)-106a**.

Time :12 h



Yield :32%

Mp. :80–82 °C

IR (KBr) :$\upsilon$ 2225, 1721, 1600 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.25 (t, $J$ = 7.2 Hz, 3H), 3.81 (s, 3H), 4.28 (q, $J$ = 7.0 Hz, 2H), 4.49 (s, 2H), 6.92 (d, $J$ = 8.4 Hz, 1H), 7.02–7.08 (m, 1H), 7.41–7.50 (m, 2H).

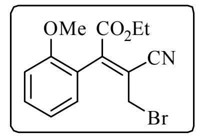
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 13.91, 26.52, 55.52, 62.10, 110.84, 116.70, 117.88, 120.81, 123.41, 130.69, 132.23, 146.64, 156.98, 164.99.

#Minor peaks at $\delta$ 1.30 (t), 3.98 (s) indicates that the presence of ≈ 2–3% of *E*-isomer.

HRMS (ESI) exact mass calcd for $C_{14}H_{14}BrNO_3$+Na (M+Na)$^+$ :346.0055

Found :346.0053.

**(*E*)-Ethyl 4-bromo-3-cyano-2-(2-methoxyphenyl)but-2-enoate [(*E*)-106e]:**




Time :12 h

Yield :60%

Mp. :65–67 °C

IR (KBr) :$\upsilon$ 2219, 1742, 1594 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 3.80 (s, 3H), 4.00 (s, 2H), 4.32 (q, $J$ = 7.2 Hz, 2H), 6.95 (d, $J$ = 8.4 Hz, 1H), 7.06 (t, $J$ = 7.6 Hz, 1H), 7.31 (dd, $J$ = 1.2 & 7.6 Hz, 1H), 7.41–7.49 (m, 1H).

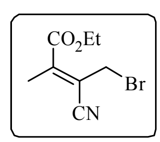
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 13.91, 28.61, 55.67, 62.42, 111.25, 116.05, 117.08, 120.81, 121.39, 129.42, 132.00, 146.48, 156.84, 164.46.

HRMS (ESI) exact mass calcd for $C_{14}H_{14}BrNO_3$+Na (M+Na)$^+$ :346.0055

Found :346.0057.

**(*Z*)-Ethyl 4-bromo-3-cyano-2-methylbut-2-enoate [(*Z*)-106f]:**

(*E*)- and (*Z*)-isomers of **106f** were obtained via bromination of ethyl 3-cyano-2-hydroxy-2-methylbut-3-enoate **(105f)** using *N*-bromosuccinimide, following the similar reaction procedure described for **(*E*/*Z*)-106a**.




Time :6 h

Yield :20%

IR (KBr) :$\upsilon$ 2219, 1720, 1610 cm$^{-1}$

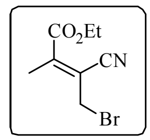
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.36 (t, $J$ = 7.2 Hz, 3H), 2.31 (s, 3H), 4.32 (q, $J$ = 7.2 Hz, 2H), 4.37 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.11, 20.28, 25.82, 62.47, 116.19, 118.59, 145.82, 165.14.

HRMS (ESI) exact mass calcd for $C_8H_{10}BrNO_2$+Na $(M+Na)^+$ :253.9793

Found :253.9790.

**(*E*)-Ethyl 4-bromo-3-cyano-2-methylbut-2-enoate [(*E*)-106f]:**




Time :6 h

Yield :61%

IR (KBr) :$\upsilon$ 2225, 1731, 1616 cm$^{-1}$

$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 1.38 (t, $J$ = 7.5 Hz, 3H), 2.14 (s, 3H), 4.14 (s, 2H), 4.35 (q, $J$ = 7.0 Hz, 2H).

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 13.85, 15.47, 26.76, 62.56, 116.17, 146.31, 164.63.

HRMS (ESI) exact mass calcd for $C_8H_{10}BrNO_2$+Na $(M+Na)^+$ :253.9793

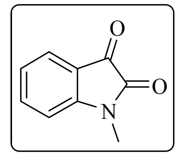
Found :253.9797.

**1-Methylisatin (124a):**

This compound was prepared following the known procedure.[205]

A stirred suspension of isatin (**126a**) (100 mmol, 14.713 g) and powdered $CaH_2$ (300 mmol, 12.6 g) in DMF (100 mL) was heated at 40–50 $^oC$ for 20 minutes. Methyl iodide (500 mmol, 70.9 g) was added at the same temperature and stirring was continued at room temperature for 12 hours. Then the reaction mixture was poured into ice-cold HCl solution and aq. NaCl solution was added. Reaction mixture was extracted with ethyl acetate (3 X 100 mL). Combined organic layer was dried over anhydrous $Na_2SO_4$.

Solvent was evaporated and the crude product thus obtained was subjected to crystallization to provide the desired product in 83% yield as brick red solid.



M.P :132–134 ºC (lit. 133–134 ºC)

IR (KBr) :$\nu$ 1748, 1709, 1605 $cm^{-1}$

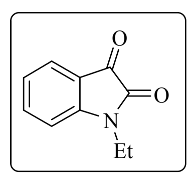
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 3.25 (s, 3H), 6.92 (d, $J$ = 8.0 Hz, 1H), 7.13 (dt, $J$ = 0.8 & 7.2 Hz, 1H), 7.57 (dd, $J$ = 0.8 & 7.6 Hz, 1H), 7.62 (dt, $J$ = 1.2 & 8.0 Hz, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 26.17, 109.99, 117.39, 123.79, 125.13, 138.45, 151.44, 158.21, 183.32

LCMS ($m/z$) :162.00 $(M+H)^+$

**1-Ethylisatin (124b):**

This compound was obtained via the reaction between isatin (**126a**) and ethyl bromide in the presence of $CaH_2$, following the similar procedure as described for the compound **124a**, as orange solid.




Time :12 h

M.p. :87–88 ºC (lit 86–87 ºC)

Yield :80%

IR (KBr) :$\nu$ 1737, 1715, 1605 $cm^{-1}$

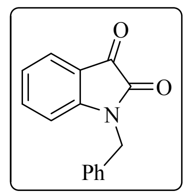
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.32 (t, $J$ = 7.2 Hz, 3H), 3.80 (q, $J$ = 7.2 Hz, 2H), 6.93 (d, $J$ = 7.6 Hz, 1H), 7.11 (t, $J$ = 7.2 Hz, 1H), 7.56–7.65 (m, 2H)

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 12.50, 34.95, 110.06, 117.63, 123.61, 125.39, 138.36, 150.68, 157.87, 183.67

LCMS (*m/z*) :176.10 $(M+H)^+$

**1-Benzylisatin (124c):**

Reaction between isatin (**126a**) and benzyl bromide in the presence of $CaH_2$, following the similar procedure as described for the compound **124a**, provided the title compound as an orange solid.



Time :12 h

M.p. :133–134 ºC (lit 133–134 ºC)

Yield :74%

IR (KBr) :$\nu$ 1748, 1710, 1611 cm$^{-1}$

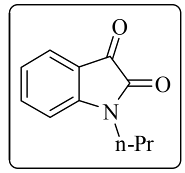
$^{1}$H NMR (500 MHz, $CDCl_3$) :$\delta$ 4.92 (s, 2H), 6.79 (d, $J$ = 7.5 Hz, 1H), 7.08 (t, $J$ = 7.5 Hz, 1H), 7.25–7.39 (m, 5H), 7.48 (t, $J$ = 8.0 Hz, 1H), 7.59 (d, $J$ = 7.5 Hz, 1H)

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 44.02, 111.04, 117.65, 123.87, 125.35, 127.43, 128.14, 129.04, 134.53, 138.36, 150.71, 158.28, 183.25

LCMS (*m/z*) :238.00 $(M+H)^+$

**1-(*n*-Propyl)isatin (124d):**

This molecule was obtained via the reaction between isatin (**126a**) and *n*-propyl bromide in the presence of $CaH_2$, following the similar procedure as described for the compound **124a**, as orange solid.



Time :12 h

M.p. :131–133 ºC (lit 133–134 ºC)

Yield :77%

IR (KBr) :*ν* 1748, 1726, 1611 $cm^{-1}$

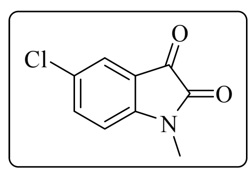
$^1$H NMR (500 MHz, $CDCl_3$) :*δ* 1.00 (t, *J* = 7.5 Hz, 3H), 1.75 (sex, *J* = 7.5 Hz, 2H), 3.70 (t, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 7.11 (dt, *J* = 0.5 & 7.5 Hz, 1H), 7.56–7.63 (m, 2H)

$^{13}$C NMR (125 MHz, $CDCl_3$) :*δ* 11.31, 20.61, 41.77, 110.23, 117.52, 123.59, 125.33, 138.37, 151.09, 158.19, 183.64

LCMS (*m/z*) :190.00 $(M+H)^+$

**5-Chloro-1-methylisatin (124e):**

Treatment of 5-chloroisatin (**126b**) with methyl iodide in the presence of $CaH_2$, following the similar procedure as described for the compound **124a**, provided the desired product as a red solid.



Time :12 h

M.p. :171–173 ºC (lit 172–174 ºC)

Yield :72%

IR (KBr) :*ν* 1764, 1726, 1611 $cm^{-1}$

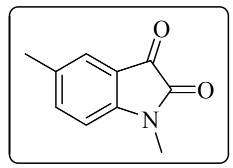
$^1$H NMR (500 MHz, $CDCl_3$) :*δ* 3.27 (s, 3H), 6.90 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.59 (dd, *J* = 2.0 & 8.5 Hz, 1H)

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 26.40, 111.32, 118.21, 125.17, 129.65, 137.81, 149.72, 157.69, 182.38

LCMS (*m/z*) :195.00 $(M)^+$

**1,5-Dimethylisatin (124f):**

This compound was obtained via the reaction between 5-methylisatin (**126c**) and methyl iodide in the presence of $CaH_2$, following the similar procedure as described for the compound **124a**, provided the desired product as a red solid.




Time :12 h

M.p. :173–14 ºC (lit 172–174 ºC)

Yield :75%

IR (KBr) :$\nu$ 1742, 1731, 1622 cm$^{-1}$

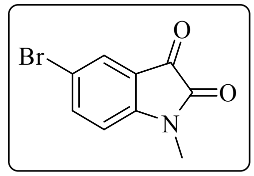
$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 2.34 (s, 3H), 3.23 (s, 3H), 6.80 (d, $J$ = 7.5 Hz, 1H), 7.38 (s, 1H), 7.41 (dd, $J$ = 0.5 & 8.0 Hz, 1H)

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 20.65, 26.19, 109.79, 117.38, 125.53, 133.65, 138.81, 149.26, 158.33, 183.62

LCMS (*m/z*) :176.10 $(M+H)^+$

**5-Bromo-1-methylisatin (124g):**

Reaction between 5-bromolisatin (**126d**) and methyl iodide in the presence of $CaH_2$, following the similar procedure as described for the compound **124a**, gave the title molecule as a red solid.




Time :12 h

Yield :72%

M.p. :181–182 ºC

IR (KBr) :$\nu$ 1753, 1726, 1605 cm$^{-1}$

$^1$H NMR (500 MHz, $CDCl_3$) :$\delta$ 3.26 (s, 3H), 6.85 (d, $J$ = 8.5 Hz, 1H), 7.67 (d, $J$ = 2.0 Hz, 1H), 7.73 (dd, $J$ = 2.0 & 8.0 Hz, 1H)

$^{13}$C NMR (125 MHz, $CDCl_3$) :$\delta$ 26.38, 111.75, 116.63, 118.53, 128.98, 140.65, 150.14, 157.48, 182.20

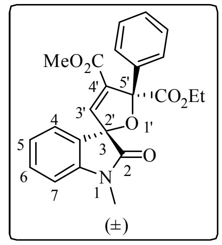
LCMS (*m/z*) :240.0 (M)$^+$

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125a):**

To a stirred solution of 4-ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (**93a**) (1.5 mmol, 0.491 g) in DMF (3.0 mL) were added dimethyl sulfide (2.0 mmol, 0.124 g, 0.15 mL), $Cs_2CO_3$ (2.0 mmol, 0.652 g) and 1-methylisatin (**124a**) (1.0 mmol, 0.161 g) at room temperature. After stirring for 24 hours at the same temperature the reaction mixture was diluted with water (2.0 mL) and extracted with EtOAc (3X10 mL). Combined organic layer was washed with water (2x5 mL) and dried over anhydrous sodium sulfate ($Na_2SO_4$). Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to provide **125a** in 86% (0.348 g) yield as a colorless solid.

Yield :86%

Mp. :163–164 °C



IR (KBr) :$\upsilon$ 1742, 1720, 1625, 1501, 1473, 1369 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 3.23 (s, 3H), 3.70 (s, 3H), 4.37 (q, $J$ = 7.2 Hz, 2H), 6.70 (s, 1H), 6.85 (d, $J$ = 8.0 Hz, 1H), 7.08 (t, $J$ = 7.6 Hz, 1H), 7.28–7.46 (m, 5H), 7.89 (d, $J$ = 7.2 Hz, 1H).

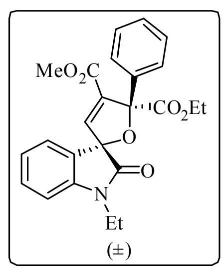
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.07, 26.63, 52.01, 62.24, 90.31, 95.17, 108.75, 123.53, 125.58, 126.69, 127.71, 128.43, 131.07, 137.25, 138.06, 138.60, 143.35, 161.66, 171.17, 172.75.

HRMS (ESI) exact mass calcd for $C_{23}H_{21}NO_6$+H (M+H)$^+$ :408.1447

Found :408.1449

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Ethylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbon-yl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125b):**

The title compound was obtained via [3+2] cycloaddition reaction between 1-ethylisatin (**124b**) and 4-ethyl 1-methyl 2-(bromometh-yl)-3-phenylmaleate (**93a**), following the similar reaction procedure described for **125a**.



Time :24 h

Yield :77%

Mp. :164–165 °C

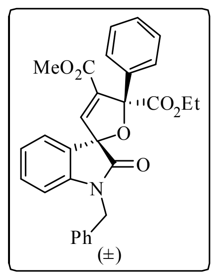
IR (neat) :$\upsilon$ 1731, 1625, 1490, 1463, 1337 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 1.31 (t, $J$ = 7.2 Hz, 3H), 3.70

| | |
|---|---|
| | (s, 3H), 3.73–3.88 (m, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.28–7.44 (m, 5H), 7.88–7.93 (m, 2H). |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 12.52, 14.09, 35.28, 52.00, 62.27, 90.38, 95.23, 108.86, 123.34, 125.80, 126.94, 127.73, 128.45, 130.99, 137.27, 138.21, 138.47, 142.45, 161.68, 171.22, 172.39. |
| HRMS (ESI) exact mass calcd for $C_{24}H_{23}NO_6$ $(M+H)^+$ | : 421.1525 |
| Found | :422.1606. |

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Benzylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125c):**

Reaction between 1-benzylisatin (**124c**) and 4-ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (**93a**), following the similar reaction procedure described for **125a**, gave the title compound.




| | |
|---|---|
| Time | :24 h |
| Yield | :75% |
| Mp. | :134–135 °C |
| IR (KBr) | :$\upsilon$ 1720, 1610, 1496, 1468, 1353, 1260 cm$^{-1}$ |
| $^1$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 1.31 (t, *J* = 7.2 Hz, 3H), 3.71 (s, 3H), 4.33–4.47 (m, 2H), 4.88 & 4.96 (ABq, *J* = 15.6 Hz, 2H), 6.74 (d, *J* = 5.6 Hz, 1H),# 6.75 (s, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 7.22–7.38 (m, 8H),* 7.39–7.46 (m, 2H), 7.92–7.97 (m, 2H); #One of these peak merged with singlet at $\delta$ 6.75; *It contains $CHCl_3$ peak. |

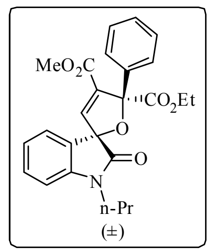
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.08, 44.27, 52.03, 62.31, 90.40, 95.33, 109.75, 123.57, 125.67, 126.72, 127.38, 127.75, 127.88, 128.50, 128.92, 130.93, 135.07, 137.20, 138.12, 138.55, 142.38, 161.64, 171.18, 172.95.

HRMS (ESI) exact mass calcd for $C_{29}H_{25}NO_6$ $(M+Na)^+$ :506.1580

Found :506.1583

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-*n*-Propylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125d):**

[3+2] Cycloaddition reaction between 1-(*n*-propyl)isatin (**124d**) and 4-ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (**93a**), following the similar reaction procedure described for **125a**, produced the required dihydrofuran derivative.




Time :24 h

Yield :80%

Mp. :128–130 °C

IR (neat) :$\upsilon$ 1737, 1631, 1490, 1468, 1342, 1260 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 0.99 (t, $J$ = 7.2 Hz, 3H), 1.31 (t, $J$ = 7.2 Hz, 3H), 1.68–1.80 (m, 2H), 3.69 (t, $J$ = 7.6 Hz, 2H),# 3.70 (s, 3H), 4.38 (t, $J$ = 7.2 Hz, 2H), 6.70 (s, 1H), 6.86 (d, $J$ = 8.0 Hz, 1H), 7.06 (t, $J$ = 7.6 Hz, 1H), 7.25–7.44 (m, 5H),* 7.91 (d, $J$ = 7.6 Hz, 2H); #One of the triplet peak merged with singlet at $\delta$ 3.70; * It contains $CHCl_3$ peak.

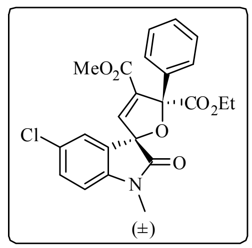
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 11.41, 14.08, 20.63, 42.12, 52.01, 62.27, 90.34, 95.22, 109.01, 123.32, 125.73, 126.84, 127.72, 128.44, 130.96, 137.24, 138.25, 138.43, 142.80, 161.67, 171.23, 172.76.

HRMS (ESI) exact mass calcd for $C_{25}H_{26}NO_6$ $(M+H)^+$ :436.1760

Found :436.1758.

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methyl-5-chloroindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125e):**

The title compound was obtained via the reaction between 1-methyl-5-chloroisatin (**124e**) and 4-ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (**93a**), following the similar reaction procedure described for **125a**.




Time :24 h

Yield :78%

Mp. :138–139 °C

IR (KBr) :$\upsilon$ 1715, 1626, 1490, 1446, 1337, 1260, 1205 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.34 (t, $J$ = 7.6 Hz, 3H), 3.22 (s, 3H), 3.72 (s, 3H), 4.32–4.47 (m, 2H), 6.68 (s, 1H), 6.78 (d, $J$ = 8.4 Hz, 1H), 7.30–7.46 (m, 5H), 7.81–7.89 (m, 2H).

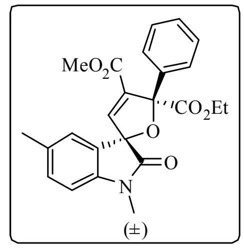
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.04, 26.72, 52.09, 62.47, 90.08, 95.26, 109.80, 126.07, 127.66, 127.73, 128.25, 128.52, 128.87, 130.90, 136.99, 137.30, 139.12, 141.87, 161.46, 170.78, 172.28.

HRMS (ESI) exact mass calcd for $C_{23}H_{21}ClNO_6$ $(M+H)^+$ :442.1057

Found :442.1047.

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1,5-Dimethylindolin-2-one)-3-spiro-2′-[5′-ethoxy-carbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125f):**

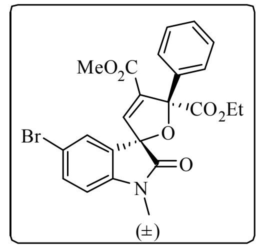
[3+2] Cycloaddition reaction between 1,5-dimethylisatin (**124f**) and 4-ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (**93a**), following the similar reaction procedure described for **125a**, gave the title compound.




| | |
|---|---|
| Time | :24 h |
| Yield | :72% |
| Mp. | :140–141 °C |
| IR (KBr) | :*υ* 1715, 1631 $cm^{-1}$ |
| $^1$H NMR (400 MHz, $CDCl_3$) | :*δ* 1.32 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 3.21 (s, 3H), 3.70 (s, 3H), 4.30–4.48 (m, 2H), 6.70 (s, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.31–7.44 (m, 3H), 7.89 (d, *J* = 7.2 Hz, 2H). |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :*δ* 14.03, 20.97, 26.59, 51.95, 62.18, 90.43, 95.07, 108.49, 126.23, 126.62, 127.67, 128.37, 131.21, 133.12, 137.31, 138.22, 138.43, 140.93, 161.66, 171.14, 172.64. |
| HRMS (ESI) exact mass calcd for $C_{24}H_{24}NO_6$ $(M+H)^+$ | :422.1604 |
| Found | :422.1602. |

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methyl-5-bromoindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125g):**

The title compound was obtained via [3+2] cycloaddition of 1-methyl-5-bromoisatin (**124g**) with 4-ethyl 1-methyl 2-(bromomethyl)-3-phenylmaleate (**93a**), following the similar reaction procedure described for **125a**.



Time :24 h

Yield :73%

Mp. :176–177 °C

IR (neat) :$\upsilon$ 1731, 1620 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.35 (t, $J$ = 7.2 Hz, 3H), 3.22 (s, 3H), 3.72 (s, 3H), 4.32–4.48 (m, 2H), 6.68 (s, 1H), 6.73 (d, $J$ = 8.0 Hz, 1H), 7.30–7.53 (m, 5H), 7.85 (d, $J$ = 7.2 Hz, 1H).

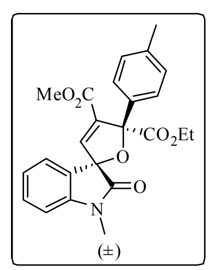
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.12, 26.76, 52.14, 62.54, 90.04, 95.30, 110.29, 116.10, 127.70, 127.79, 128.57, 128.64, 128.89, 133.85, 137.00, 137.30, 139.21, 142.42, 161.51, 170.79, 172.22.

HRMS (ESI) exact mass calcd for $C_{23}H_{21}BrNO_6$ $(M+H)^+$ :486.0552

Found :486.0579.

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(4-methylphenyl)-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125h):**

The title compound was obtained via treatment of 1-methylisatin (**124a**) with 4-ethyl 1-methyl 2-(bromomethyl)-3-(4-methylphenyl)maleate (**93b**), following the similar reaction procedure described for **125a**.



Time :24 h

Yield :81%

Mp. :142–144 °C

IR (neat) :$\upsilon$ 1753, 1737, 1715, 1626 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 2.35 (s, 3H), 3.23 (s, 3H), 3.70 (s, 3H), 4.36 (q, $J$ = 7.2 Hz, 2H), 6.69 (s, 1H), 6.84

(d, $J$ = 7.6 Hz, 1H), 7.08 (t, $J$ = 7.6 Hz, 1H), 7.20 (d, $J$ = 8.0 Hz, 2H), 7.29 (d, $J$ = 6.8 Hz, 1H), 7.36 (t, $J$ = 7.6 Hz, 1H), 7.76 (d, $J$ = 8.0 Hz, 2H).

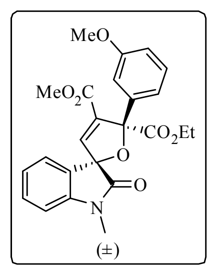
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.10, 21.26, 26.62, 52.01, 62.19, 90.22, 95.16, 108.72, 123.51, 125.61, 126.79, 127.60, 128.50, 131.02, 134.38, 137.95, 138.16, 138.65, 143.39, 161.75, 171.30, 172.81.

HRMS (ESI) exact mass calcd for $C_{24}H_{24}NO_6$ $(M+H)^+$ :422.1604

Found :422.1607.

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(3-methoxyphenyl)-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125i):**

The title compound was obtained via reaction between 1-methylisatin (**124a**) and 4-ethyl 1-methyl 2-(bromomethyl)-3-(3-methoxyphenyl)-maleate (**93c**), following the similar reaction procedure described for **125a**.




Time :24 h

Yield :79%

Mp. :172–173 °C

IR (KBr) :$\upsilon$ 1736, 1630 cm$^{-1}$

$^{1}$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 3.24 (s, 3H), 3.70 (s, 3H), 3.87 (s, 3H), 4.37 (q, $J$ = 7.2 Hz, 2H), 6.70 (s, 1H), 6.85 (d, $J$ = 7.6 Hz, 1H), 6.85–6.91 (m, 1H), 7.08 (t, $J$ = 7.6 Hz, 1H), 7.28–7.40 (m, 3H),* 7.74 (s, 1H); *It contains $CHCl_3$ peak.

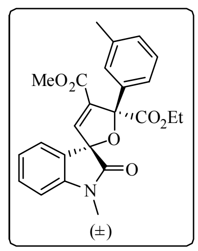
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.03, 26.58, 51.94, 55.34, 62.17, 90.28, 95.03, 108.72, 112.72, 114.88, 120.02, 123.45, 125.44, 126.62, 128.38, 131.02, 137.91, 138.50, 138.67, 143.27, 159.27, 161.54, 170.98, 172.69.

HRMS (ESI) exact mass calcd for $C_{24}H_{24}NO_7$ $(M+H)^+$ :438.1553

Found :438.1555.

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(3-methylphenyl)-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125j):**

Reaction between 1-methylisatin (**124a**) and 4-ethyl 1-methyl 2-(bromomethyl)-3-(3-methylphenyl)maleate (**93d**), following the similar reaction procedure described for **125a**, gave the title compound.




Time :24 h

Yield :77%

Mp. :152–153 °C

IR (neat) :$\upsilon$ 1731, 1605, 1490, 1468, 1375, 1249, 1085, 1025 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 2.40 (s, 3H), 3.23 (s, 3H), 3.70 (s, 3H), 4.37 (q, $J$ = 7.2 Hz, 2H), 6.70 (s, 1H), 6.84 (d, $J$ = 7.6 Hz, 1H), 7.09 (t, $J$ = 7.6 Hz, 1H), 7.14 (d, $J$ = 7.6 Hz, 1H), 7.24–7.32 (m, 2H), 7.33–7.41 (m, 1H), 7.65 (d, $J$ = 8.0 Hz, 1H), 7.74 (s, 1H).

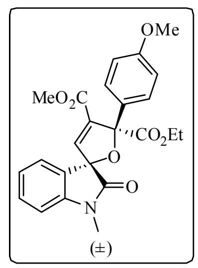
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.10, 21.69, 26.66, 52.02, 62.20, 90.24, 95.22, 108.72, 123.51, 124.82, 125.58, 126.77, 127.59, 128.36, 129.26, 131.04, 137.15, 137.28, 138.06, 138.60, 143.37, 161.69, 171.29, 172.76.

HRMS (ESI) exact mass calcd for $C_{24}H_{24}NO_6$ $(M+H)^+$ :422.1604

Found :422.1601.

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(4-methoxyphenyl)-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125k):**

This molecule was obtained via treatment of 1-methylisatin (**124a**) with 4-ethyl 1-methyl 2-(bromomethyl)-3-(4-methoxyphenyl)maleate (**93e**), following the similar reaction procedure described for **125a**.




Time :24 h

Yield :83%

Mp. :148–150 °C

IR (neat) :$\upsilon$ 1742, 1720, 1621 $cm^{-1}$

$^1H$ NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 3.23 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 4.36 (q, $J$ = 7.2 Hz, 2H), 6.68 (s, 1H), 6.84 (d, $J$ = 7.6 Hz, 1H), 6.93 (d, $J$ = 8.8 Hz, 2H), 7.08 (t, $J$ = 7.6 Hz, 1H), 7.29 (d, $J$ = 7.6 Hz, 1H), 7.33–7.41 (m, 1H), 7.81 (d, $J$ = 8.8 Hz, 2H).

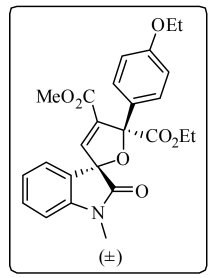
$^{13}C$ NMR (100 MHz, $CDCl_3$) :$\delta$ 14.00, 26.50, 51.91, 55.08, 62.10, 90.08, 94.88, 108.70, 113.02, 123.41, 125.44, 126.67, 129.01, 129.38, 130.95, 137.70, 138.56, 143.27, 159.48, 161.67, 171.17, 172.77.

HRMS (ESI) exact mass calcd for $C_{24}H_{24}NO_7$ $(M+H)^+$ :438.1553

Found :438.1552.

**[3*S* (2′*S*),5′*R*]/[3*R* (2′*R*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(4-ethoxyphenyl)-4′-methoxycarbonyl-2′, 5′-dihydrofuran] (125l):**

The title compound was obtained via [3+2] cycloaddition reaction between 1-methylisatin (**124a**) and 4-ethyl 1-methyl 2-(bromomethyl)-3-(4-ethoxyphenyl)maleate (**93f**), following the similar procedure described for **125a**.




Time :24 h

Yield :82%

Mp. :122–123 °C

IR (neat) :$\upsilon$ 1726, 1620 cm$^{-1}$

$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.30 (t, $J$ = 7.2 Hz, 3H), 1.40 (t, $J$ = 7.2 Hz, 3H), 3.23 (s, 3H), 3.70 (s, 3H), 4.04 (q, $J$ = 7.2 Hz, 2H), 4.36 (q, $J$ = 7.2 Hz, 2H), 6.68 (s, 1H), 6.84 (d, $J$ = 7.6 Hz, 1H), 6.88–6.94 (m, 2H), 7.05–7.11 (m, 1H), 7.27–7.31 (m, 1H), 7.36 (dt, $J$ = 1.2 & 7.6 Hz, 1H), 7.75–7.83 (m, 2H).

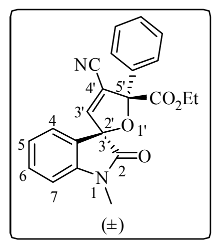
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.11, 14.87, 26.63, 52.00, 62.20, 63.32, 90.13, 95.04, 108.73, 113.66, 123.53, 125.59, 126.83, 129.07, 129.25, 131.02, 137.73, 138.73, 143.38, 159.00, 161.79, 171.35, 172.92.

HRMS (ESI) exact mass calcd for $C_{25}H_{26}NO_7$ $(M+H)^+$ :452.1709

Found :452.1707.

**[3*R* (2′*R*),5′*S*]/[3*S* (2′*S*),5′*R*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-cyano-2′, 5′-dihydrofuran] (127a):**

To a stirred solution of (*E*/*Z*)-ethyl 4-bromo-3-cyano-2-phenylbut-2-enoate (**106a**) (1.5 mmol, 0.491 g) in DMF (3.0 mL) were added dimethyl sulfide (2.0 mmol, 0.124 g, 0.15 mL), $Cs_2CO_3$ (2.0 mmol, 0.652 g) and 1-methylisatin (**124a**) (1.0 mmol, 0.161 g) at room temperature. After stirring for 24 hours at the same temperature the reaction mixture was diluted with water (2.0 mL) and extracted with EtOAc (3X10 mL). Combined organic layer was washed with water (2x5 mL) and dried over anhydrous sodium sulfate ($Na_2SO_4$). Solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 20% EtOAc in hexanes) thus provided two seperable diastereomers, that is, **127a** (elutes first) in 59% (0.222 g) yield and then **127a′** in 27% (0.101 g) yield as colorless solids.




Yield :59%

Mp. :207–209 °C

IR (KBr) :$\upsilon$ 2230, 1731, 1611 $cm^{-1}$

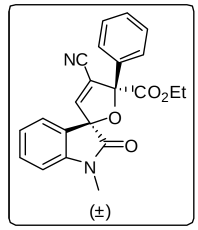
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.34 (t, $J$ = 7.2 Hz, 3H), 3.23 (s, 3H), 4.40 (q, $J$ = 7.2 Hz, 2H), 6.60 (s, 1H), 6.88 (d, $J$ = 8.0 Hz, 1H), 7.09–7.16 (m, 1H), 7.16–7.22 (m, 1H), 7.38–7.52 (m, 4H), 7.75–7.85 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.07, 26.75, 62.93, 91.52, 94.76, 109.13, 112.38, 119.81, 123.78, 125.31, 125.43, 125.87, 128.84, 129.39, 131.68, 135.84, 142.08, 143.53, 169.85, 171.62.

HRMS (ESI) exact mass calcd for $C_{22}H_{18}N_2O_4$+Na $(M+Na)^+$ :397.1164

Found :397.1162.

**[3*R* (2′*R*),5′*R*]/[3*S* (2′*S*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-phenyl-4′-cyano-2′, 5′-dihydrofuran] (127a′):**




Yield :27

Mp. :157–159 °C

IR (neat) :$\upsilon$ 2236, 1748, 1726, 1611 $cm^{-1}$

$^{1}H$ NMR (500 MHz, $CDCl_3$) :$\delta$ 1.37 (t, $J$ = 7.0 Hz, 3H), 3.21 (s, 3H), 4.40 (dq, $J$ = 1.0 & 7.0 Hz, 2H), 6.59 (s, 1H), 6.88 (d, $J$ = 7.0 Hz, 1H), 7.09–7.14 (m, 1H), 7.17–7.21 (m, 1H), 7.40–7.50 (m, 4H), 7.68–7.73 (m, 2H).

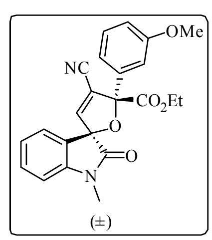
$^{13}C$ NMR (100 MHz, $CDCl_3$) :$\delta$ 14.02, 26.71, 62.77, 91.02, 93.70, 109.11, 112.82, 120.85, 123.62, 124.87, 125.62, 129.09, 129.43, 131.75, 136.67, 142.20, 144.17, 168.72, 171.72.

HRMS (ESI) exact mass calcd for $C_{22}H_{18}N_2O_4$+Na $(M+Na)^+$ :397.1164

Found :397.1165.

**[3*R* (2′*R*),5′*S*]/[3*S* (2′*S*),5′*R*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(3-methoxyphenyl)-4′-cyano-2′, 5′-dihydrofuran] (127b):**

Both the diastereomers of **127b** were obtained via [3+2] cycloaddition reaction of 1-methylisatin (**124a**) with (*E*/*Z*)-ethyl 4-bromo-3-cyano-2-(3-methoxyphenyl)but-2-enoate (**106b**), following the similar reaction procedure described for **127a**/**127a′**.




Time :24 h

Yield :62%

Mp. :182–184 °C

IR (KBr) : $\upsilon$ 2225, 1731, 1605 cm$^{-1}$

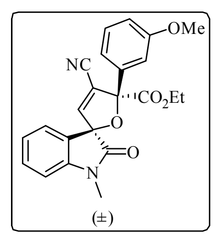
$^{1}$H NMR (500 MHz, $CDCl_3$) : $\delta$ 1.34 (t, $J$ = 7.0 Hz, 3H), 3.21 (s, 3H), 3.86 (s, 3H), 4.35–4.45 (m, 2H), 6.58 (s, 1H), 6.86 (d, $J$ = 7.5 Hz, 1H), 6.91–6.97 (m, 1H), 7.08–7.13 (m, 1H), 7.15–7.17 (m, 1H), 7.24–7.28 (m, 1H), 7.34 (t, $J$ = 8.0 Hz, 1H), 7.39 (dt, $J$ = 1.5 & 8.0 Hz, 1H), 7.51 (t, $J$ = 2.0 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) : $\delta$ 14.09, 26.77, 55.42, 62.92, 91.51, 94.69, 109.12, 111.02, 112.34, 115.83, 117.83, 119.91, 123.76, 125.32, 125.33, 129.77, 131.67, 137.18, 141.78, 143.50, 160.04, 169.78, 171.62.

HRMS (ESI) exact mass calcd for $C_{23}H_{21}N_2O_5$ $(M+H)^+$ :405.1450

Found :405.1454

**[3*R* (2′*R*),5′*R*]/[3*S* (2′*S*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(3-methoxyphenyl)-4′-cyano-2′, 5′-dihydrofuran] (127b′):**




Yield :28%

Mp. :195–197 °C

IR (neat) : $\upsilon$ 2230, 1726, 1611 cm$^{-1}$

$^{1}$H NMR (500 MHz, $CDCl_3$) : $\delta$ 1.37 (t, $J$ = 7.0 Hz, 3H), 3.20 (s, 3H), 3.81 (s, 3H), 4.33–4.45 (m, 2H), 6.58 (s, 1H), 6.88 (d, $J$ = 8.0 Hz, 1H), 6.93–6.99 (m, 1H), 7.11 (dt, $J$ = 0.5 & 7.5 Hz, 1H), 7.20 (dd, $J$ = 1.0 & 7.5 Hz, 1H), 7.25 (t, $J$ = 2.0 Hz, 1H), 7.27–7.32 (m, 1H), 7.38 (t, $J$ = 8.0 Hz, 1H), 7.42 (dt, $J$ = 1.0 & 8.0 Hz, 1H).

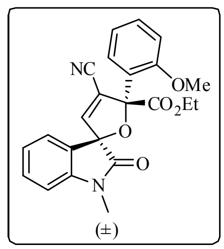
$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.05, 26.73, 55.34, 62.84, 91.02, 93.50, 109.15, 110.14, 112.83, 115.29, 116.95, 120.78, 123.62, 124.96, 125.61, 130.23, 131.79, 138.03, 142.10, 144.14, 160.08, 168.66, 171.69.

HRMS (ESI) exact mass calcd for $C_{23}H_{21}N_2O_5$ $(M+H)^+$ :405.1450

Found :405.1455

**[3*R* (2′*R*),5′*R*]/[3*S* (2′*S*),5′*S*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(2-methoxyphenyl)-4′-cyano-2′, 5′-dihydrofuran] (127c):**

Both the diastereomers of **127c** were obtained via [3+2] cycloaddition reaction between 1-methylisatin (**124a**) and (*E*/*Z*)-ethyl 4-bromo-3-cyano-2-(2-methoxyphenyl)but-2-enoate (**106e**), following the similar procedure described for **127a**/**127a′**.




Time :24 h

Yield :63%

Mp. :251–253 °C

IR (KBr) :$\upsilon$ 2241, 1742, 1611 cm$^{-1}$

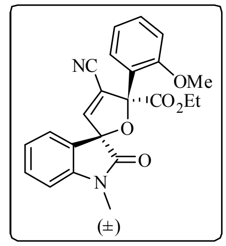
$^1$H NMR (400 MHz, $CDCl_3$) :$\delta$ 1.27 (t, $J$ = 6.8 Hz, 3H), 3.21 (s, 3H), 3.84 (s, 3H), 4.23–4.38 (m, 2H), 6.58 (s, 1H), 6.84 (d, $J$ = 8.0 Hz, 1H), 6.92 (d, $J$ = 8.4 Hz, 1H), 7.07–7.15 (m, 2H), 7.34–7.42 (m, 3H), 7.98 (dd, $J$ = 1.6 & 8.0 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) :$\delta$ 14.06, 26.73, 55.14, 62.31, 91.60, 93.57, 108.86, 110.52, 112.51, 119.63, 121.31, 123.87, 125.37, 125.73, 126.18, 127.80, 130.61, 131.46, 142.79, 143.47, 155.72, 169.95, 171.94.

HRMS (ESI) exact mass calcd for $C_{23}H_{21}N_2O_5$ $(M+H)^+$ :405.1450

Found :405.1450.

**[3*R* (2′*R*),5′*S*]/[3*S* (2′*S*),5′*R*]-(1-Methylindolin-2-one)-3-spiro-2′-[5′-ethoxycarbonyl-5′-(2-methoxyphenyl)-4′-cyano-2′, 5′-dihydrofuran] (127c′):**



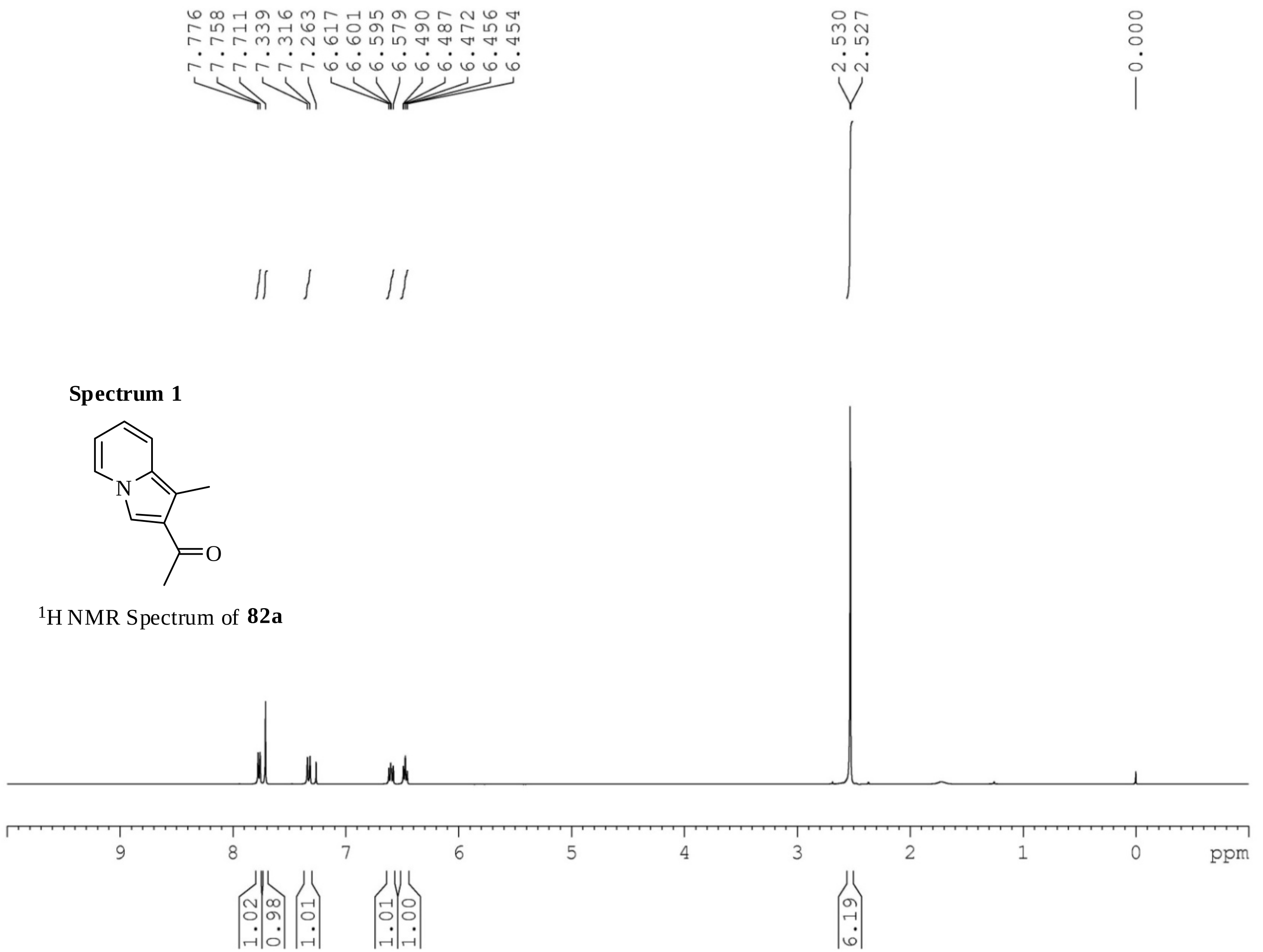

| | |
|---|---|
| Yield | :27% |
| Mp. | :244–246 °C |
| IR (KBr) | :$\upsilon$ 2241, 1742, 1611 $cm^{-1}$ |
| $^1$H NMR (400 MHz, $CDCl_3$) | :$\delta$ 1.27 (t, $J$ = 6.8 Hz, 3H), 3.20 (s, 3H), 3.83 (s, 3H), 4.23–4.39 (m, 2H), 6.58 (s, 1H), 6.84 (d, $J$ = 8.0 Hz, 1H), 6.92 (d, $J$ = 8.4 Hz, 1H), 7.07–7.16 (m, 2H), 7.34–7.43 (m, 3H), 7.98 (dd, $J$ = 1.6 & 8.0 Hz, 1H). |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | :$\delta$ 14.05, 26.71, 55.13, 62.30, 91.59, 93.55, 108.86, 110.51, 112.50, 119.60, 121.29, 123.85, 125.36, 125.71, 126.15, 127.79, 130.60, 131.45, 142.79, 143.46, 155.71, 169.94, 171.93. |

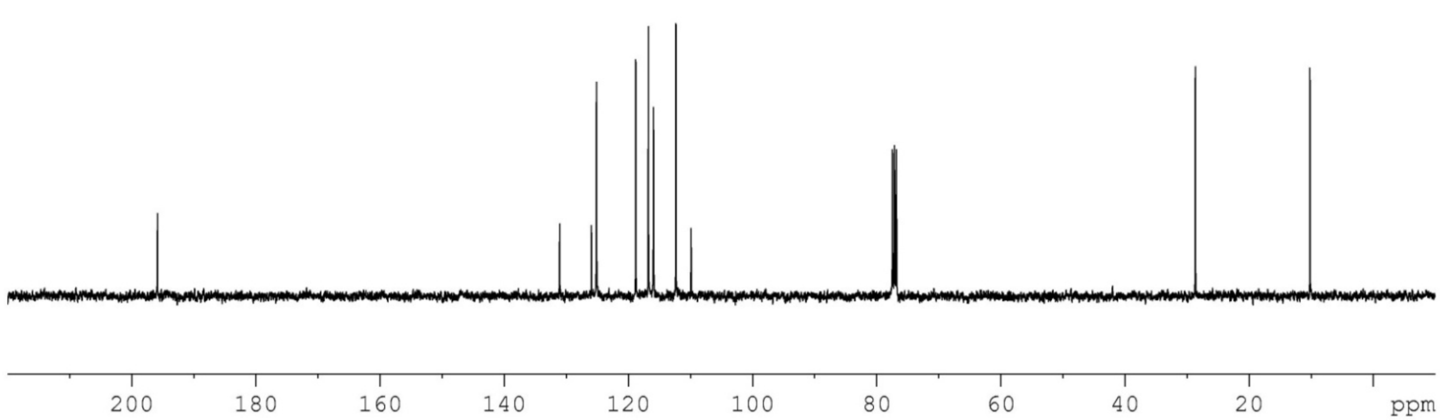
HRMS (ESI) exact mass calcd for $C_{23}H_{21}N_2O_5$ $(M+H)^+$ :405.1450

Found :405.1451.

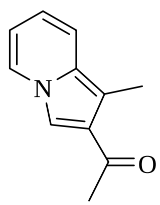
Spectrum 1

$^1$H NMR Spectrum of **82a**



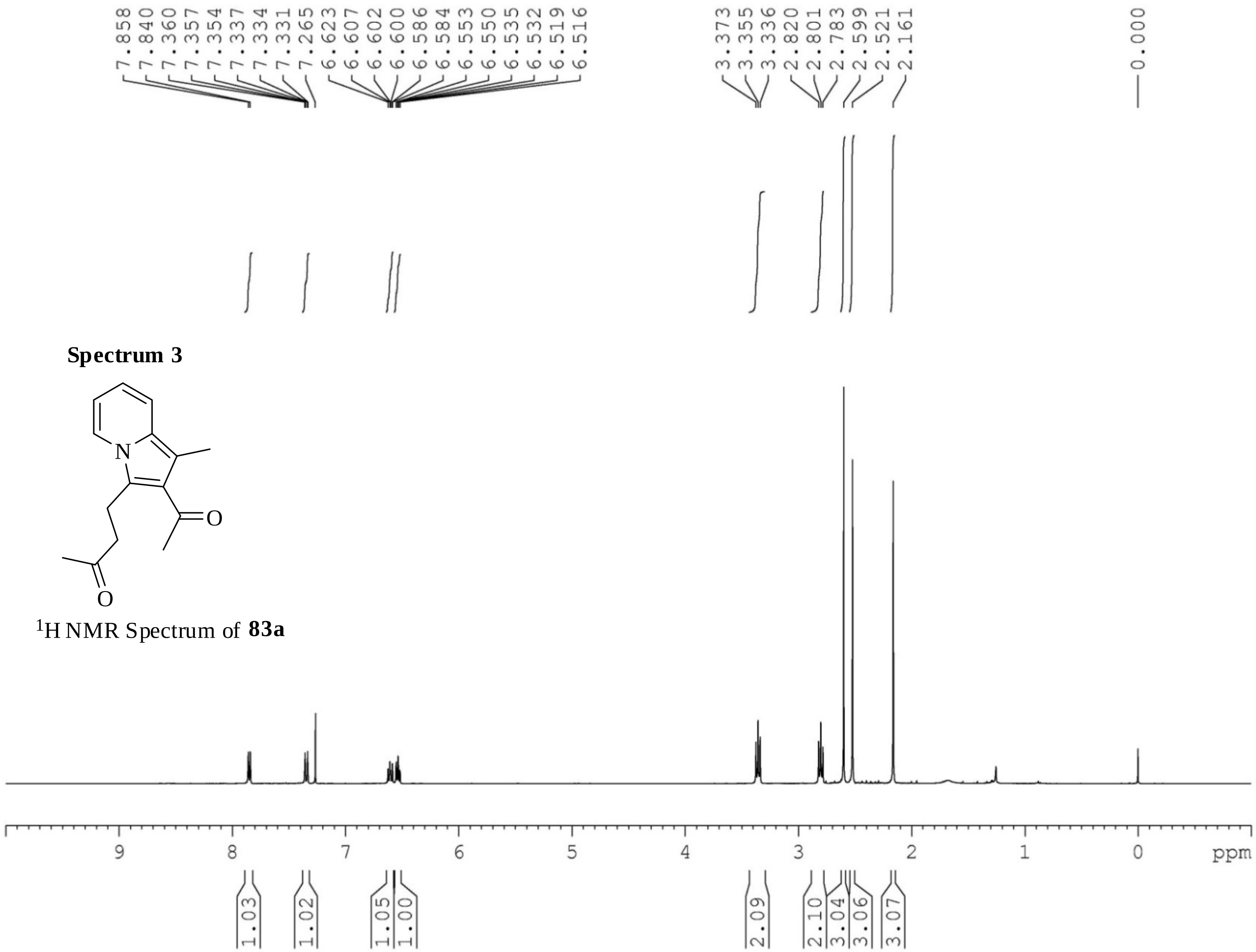



**Spectrum 2**



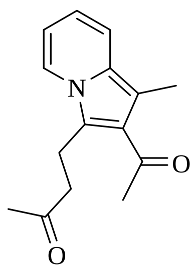

$^{13}$C NMR Spectrum of **82a**

**Spectrum 3**

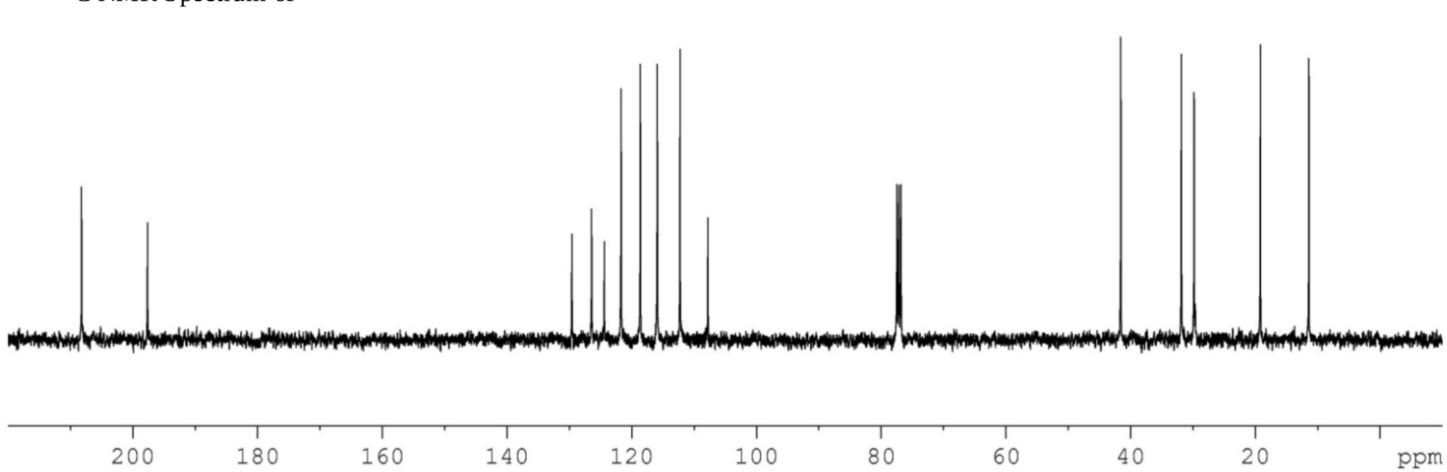



$^{1}$H NMR Spectrum of **83a**

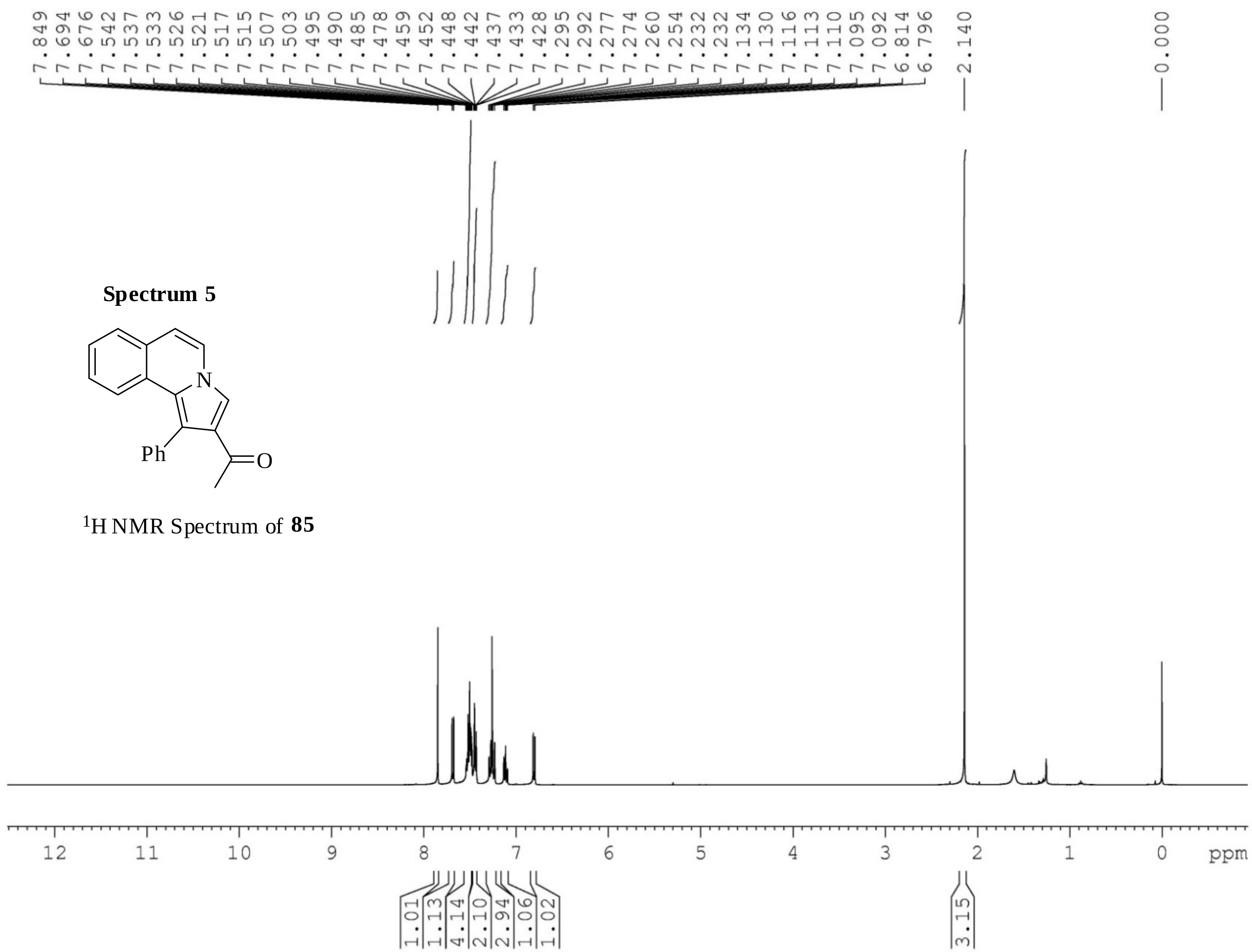
**Spectrum 4**



$^{13}C$ NMR Spectrum of **83a**



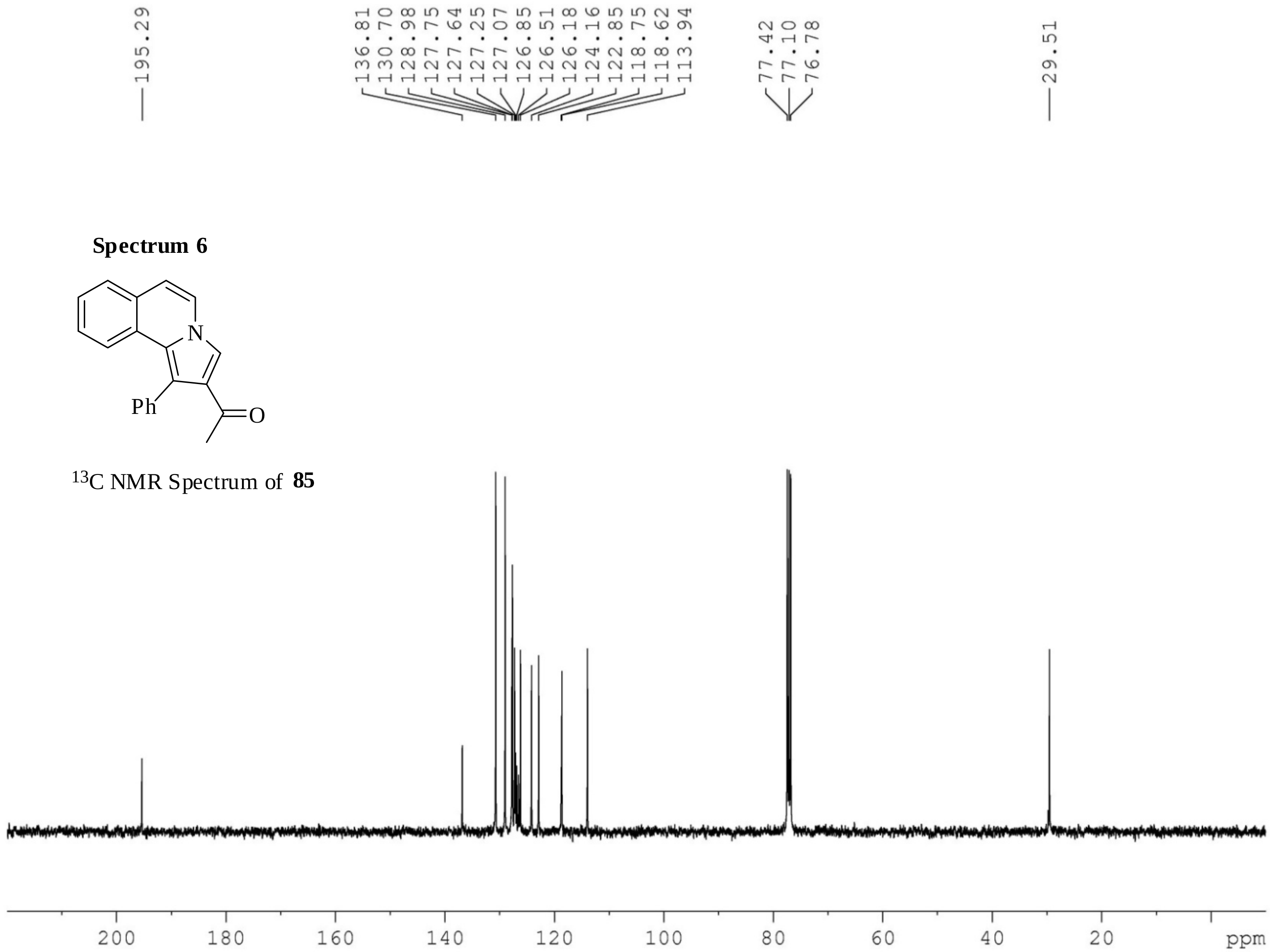
**Spectrum 5**



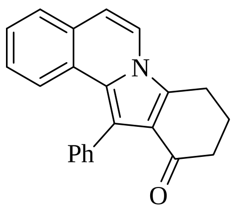

$^{1}$H NMR Spectrum of **85**

**Spectrum 6**

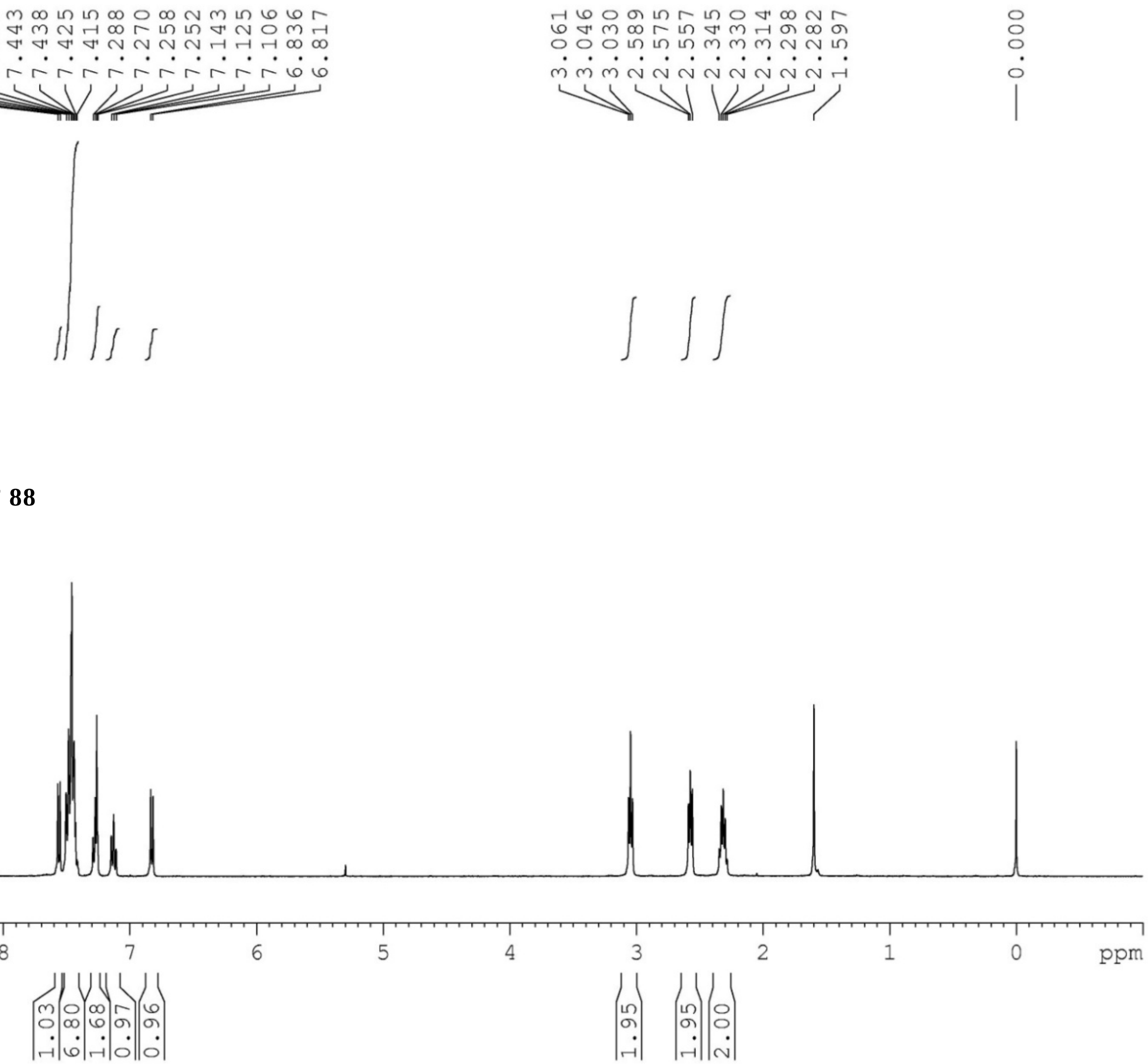
$^{13}$C NMR Spectrum of **85**

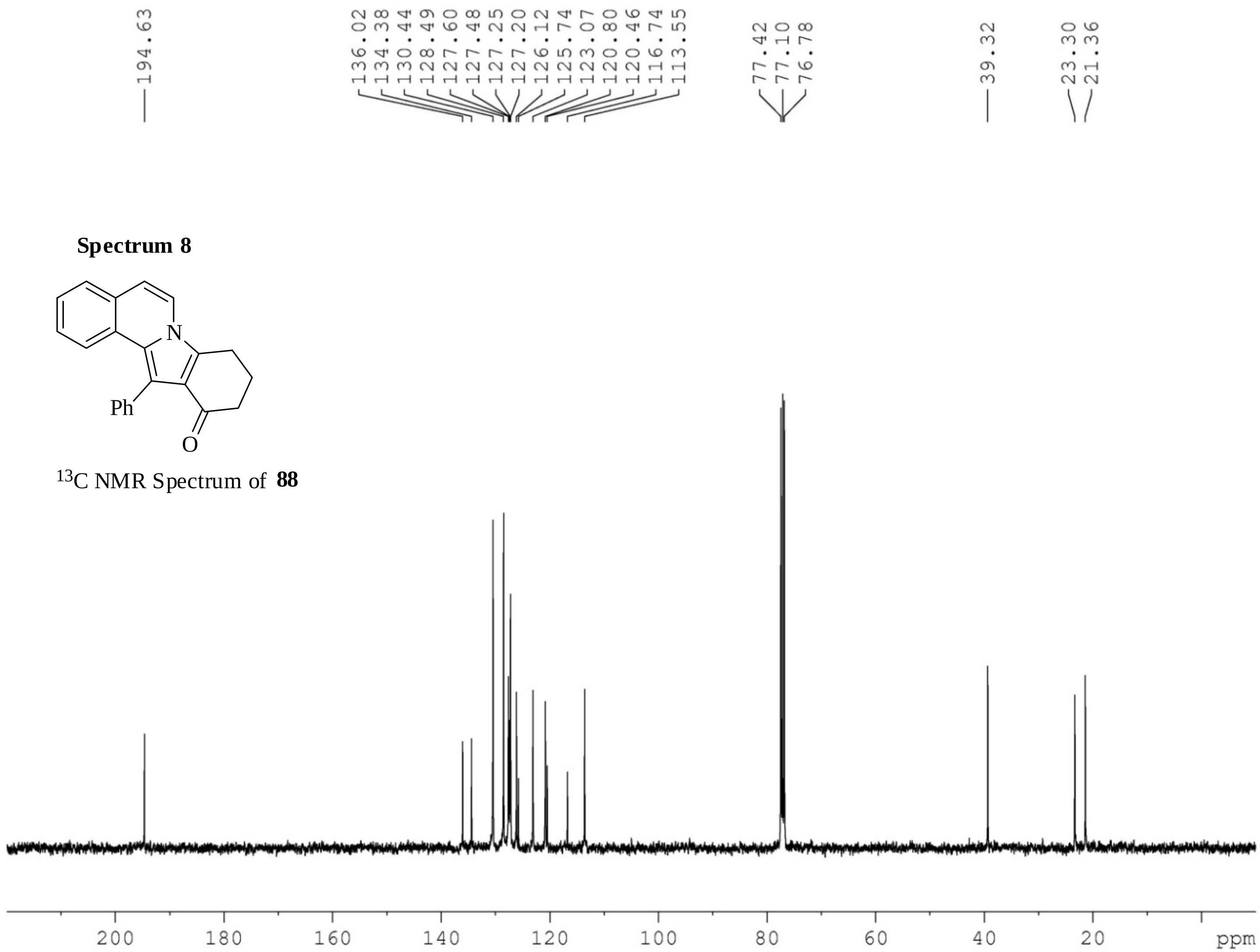


**Spectrum 7**




$^1$H NMR Spectrum of **88**

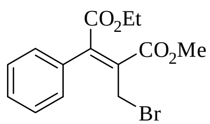




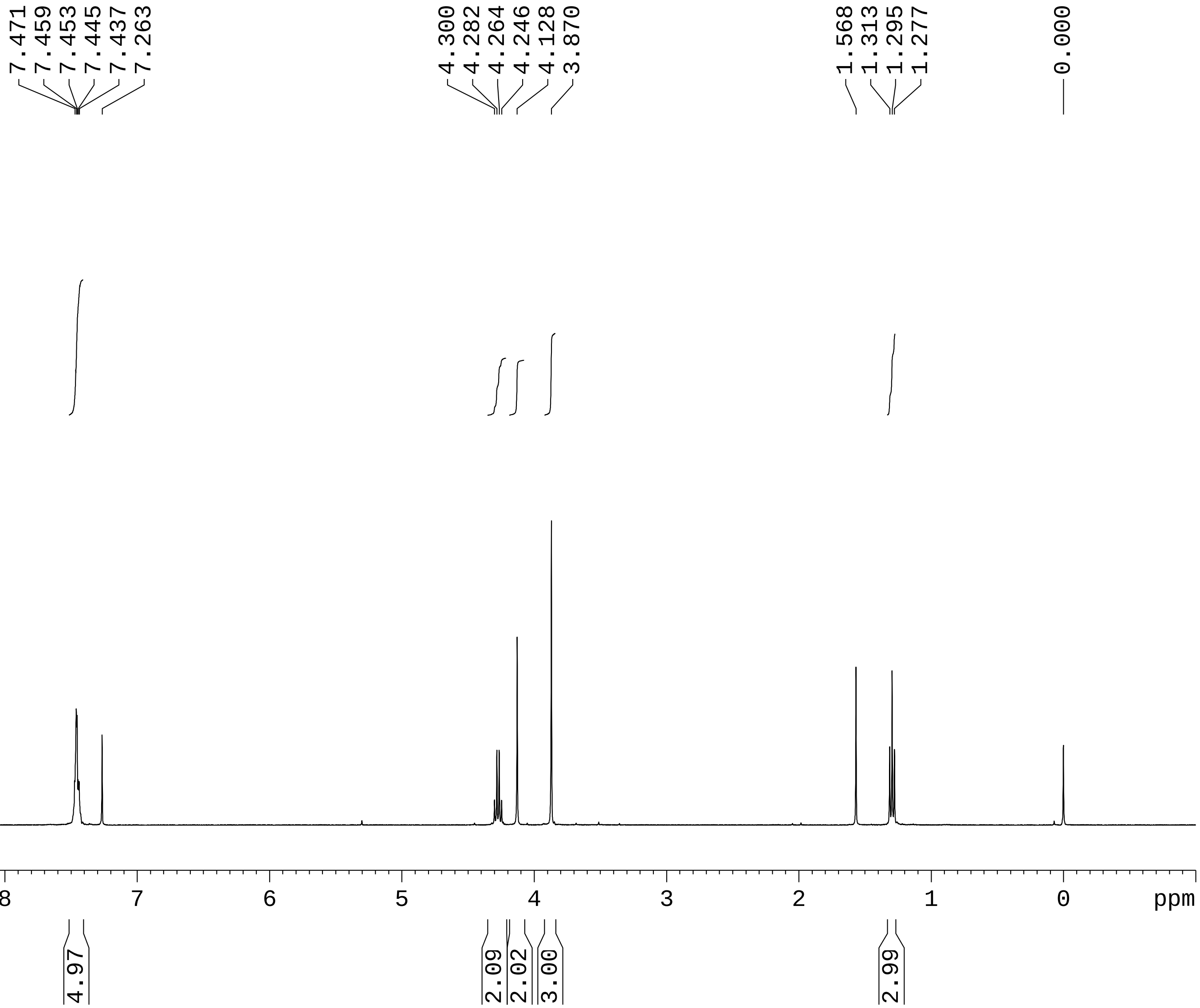

**Spectrum 8**

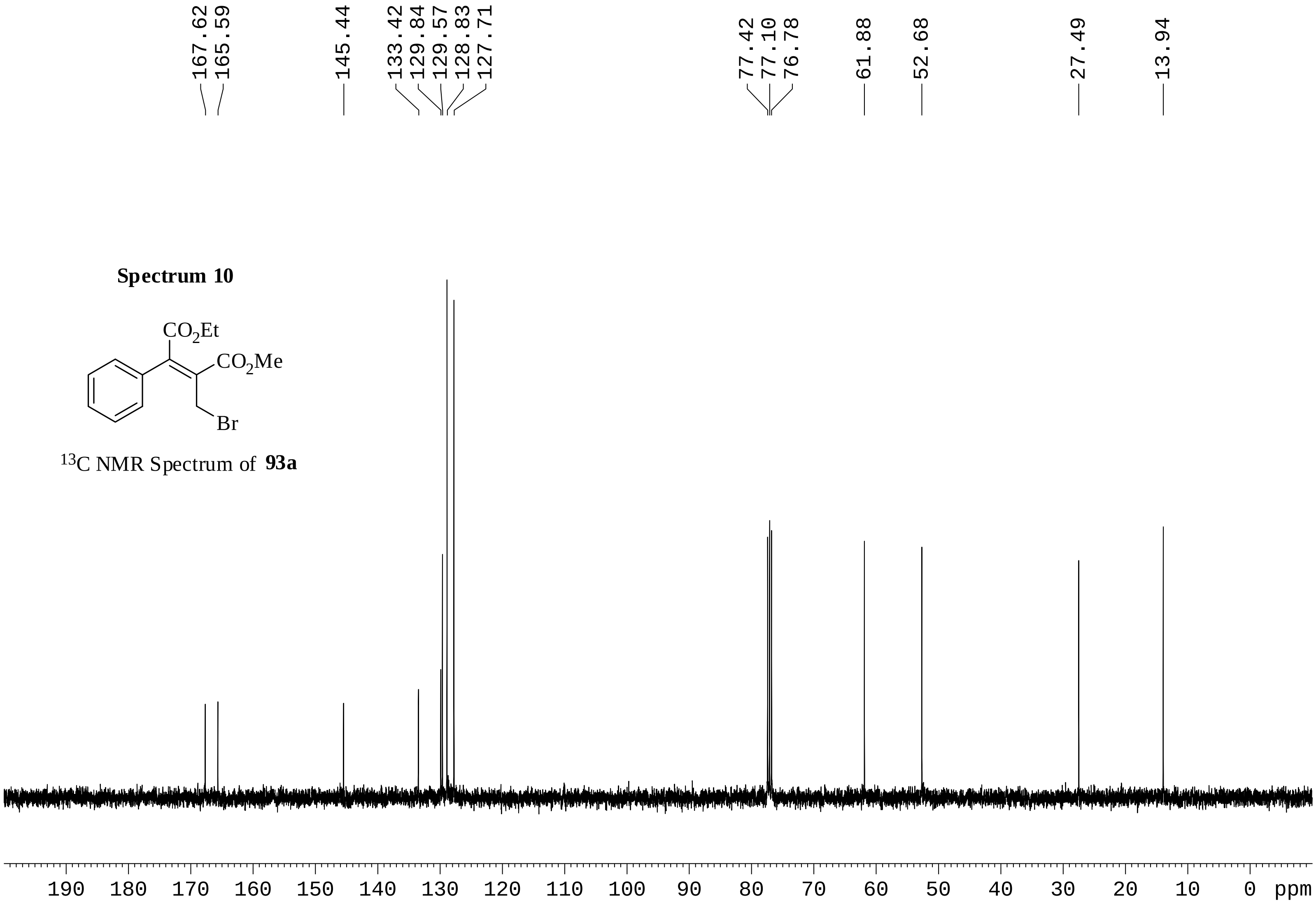
$^{13}$C NMR Spectrum of **88**

**Spectrum 9**



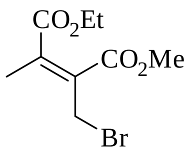

$^1H$ NMR Spectrum of **93a**



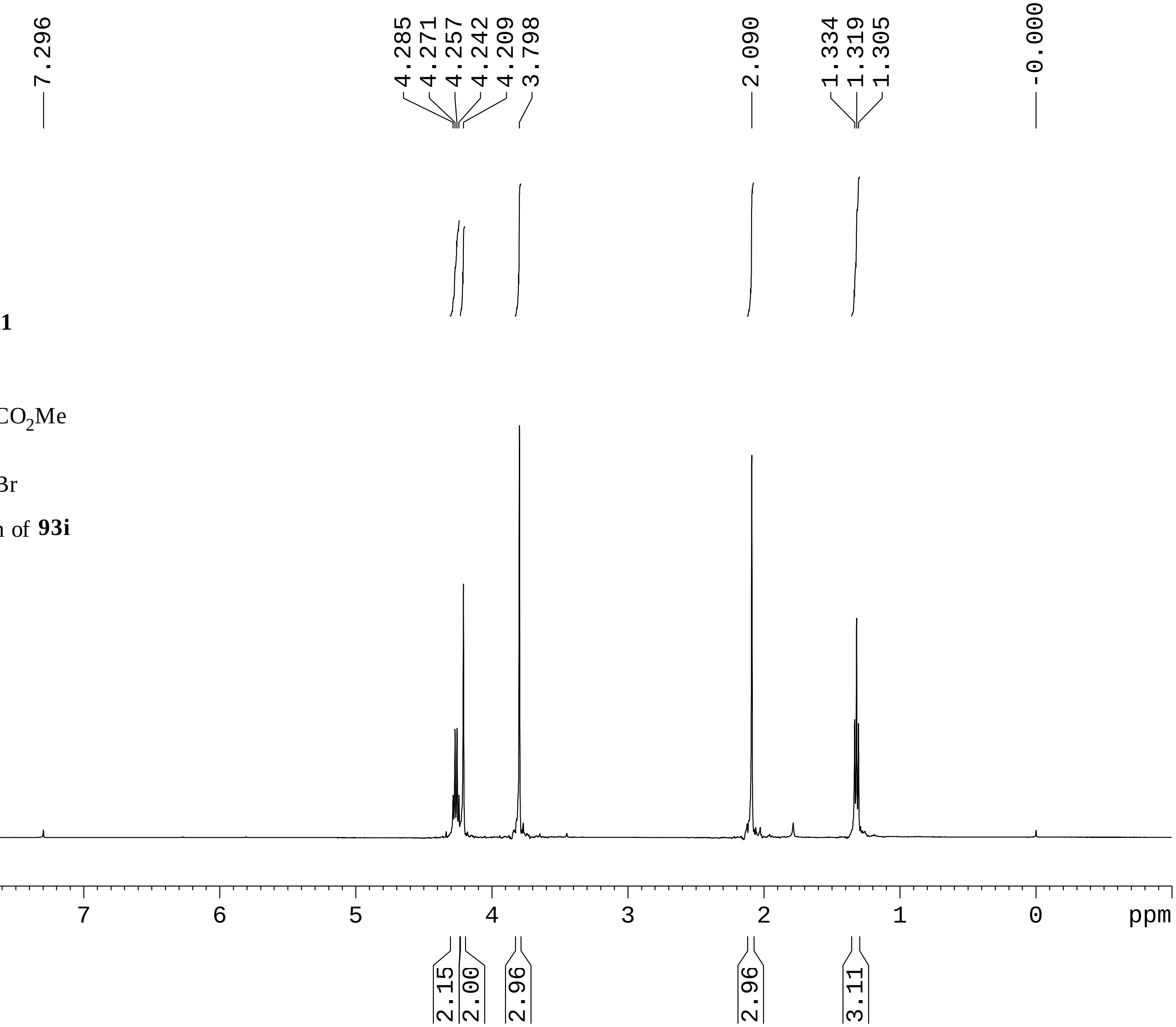


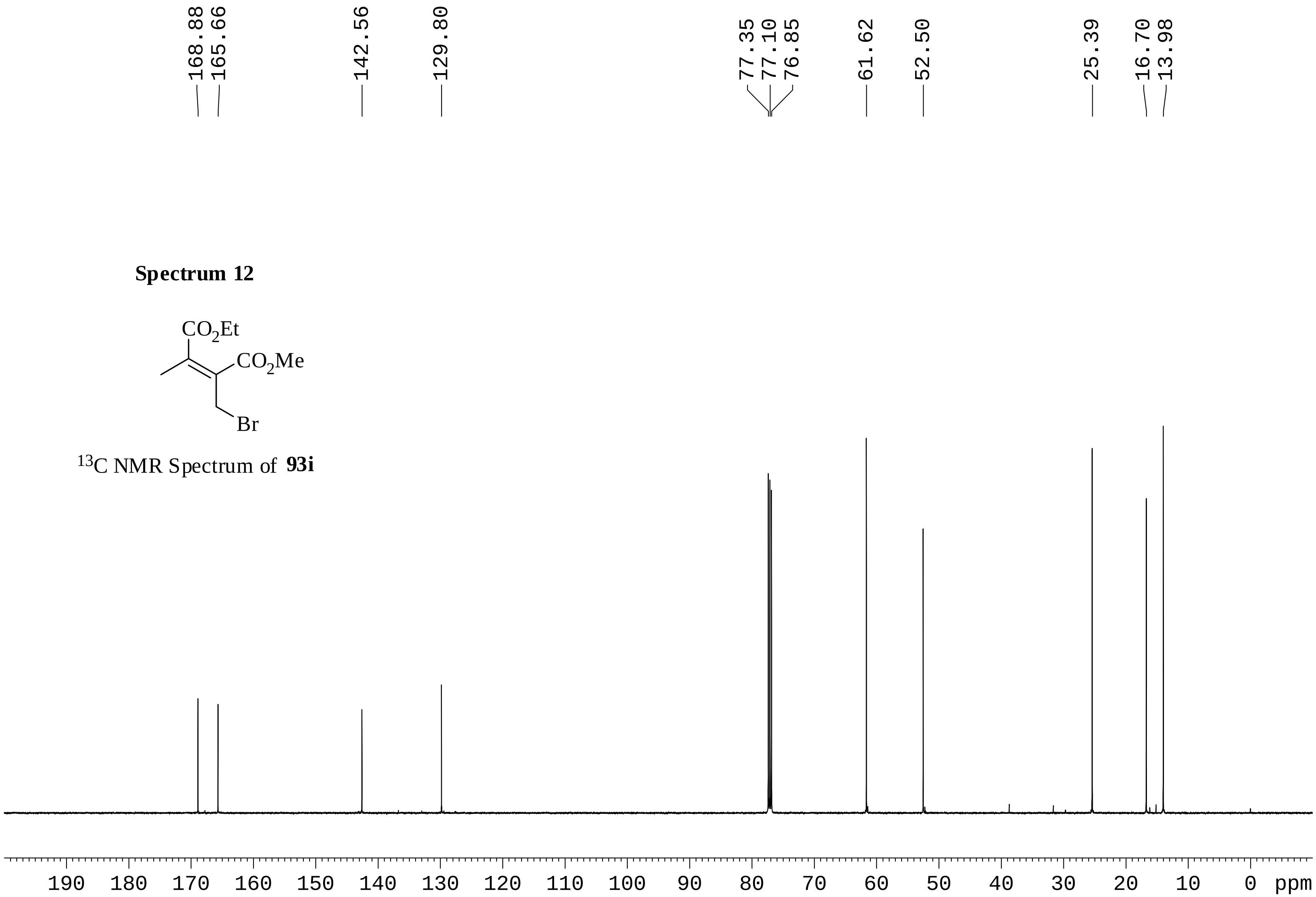

$^{13}$C NMR Spectrum of **93a**

**Spectrum 11**




[1]H NMR Spectrum of **93i**

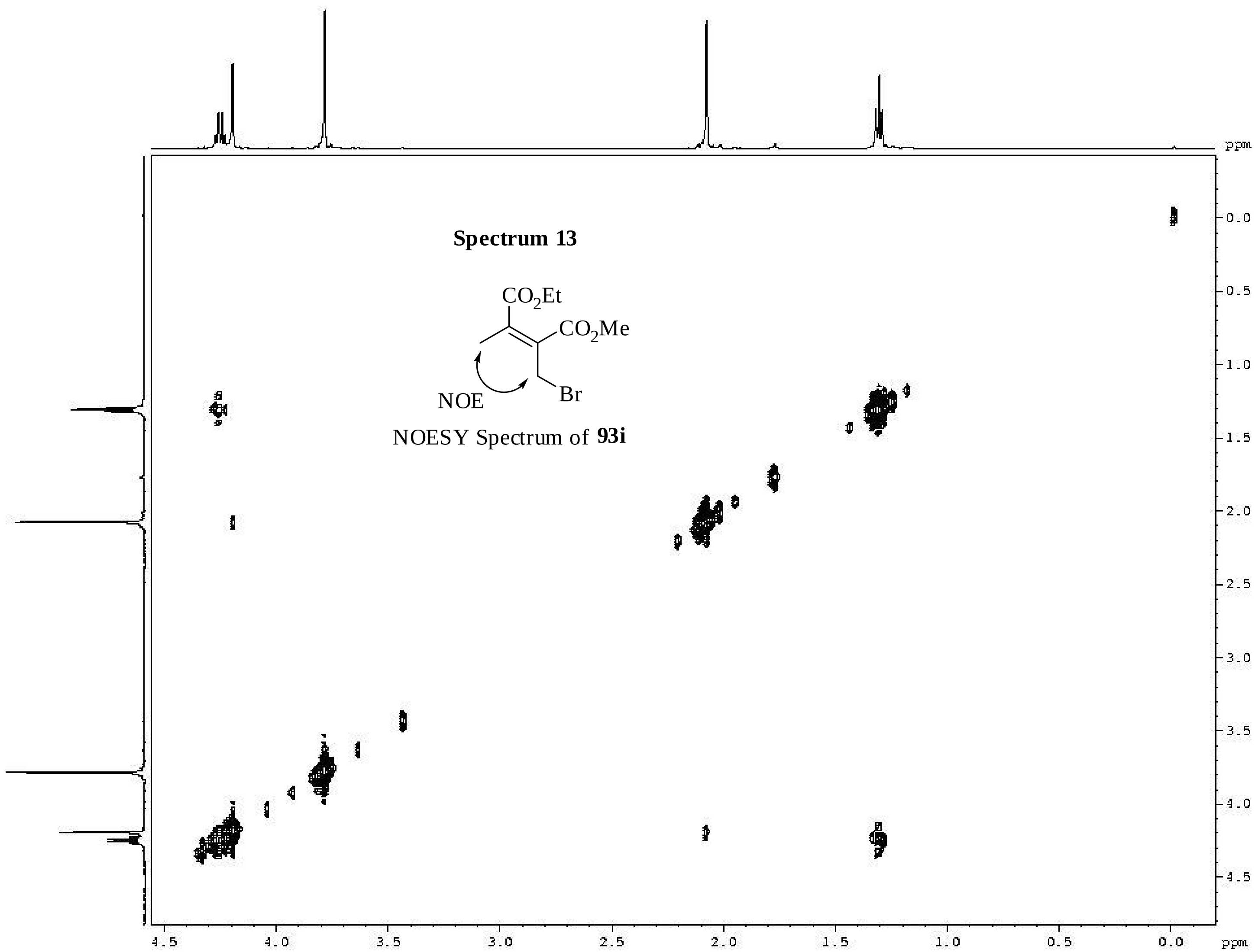




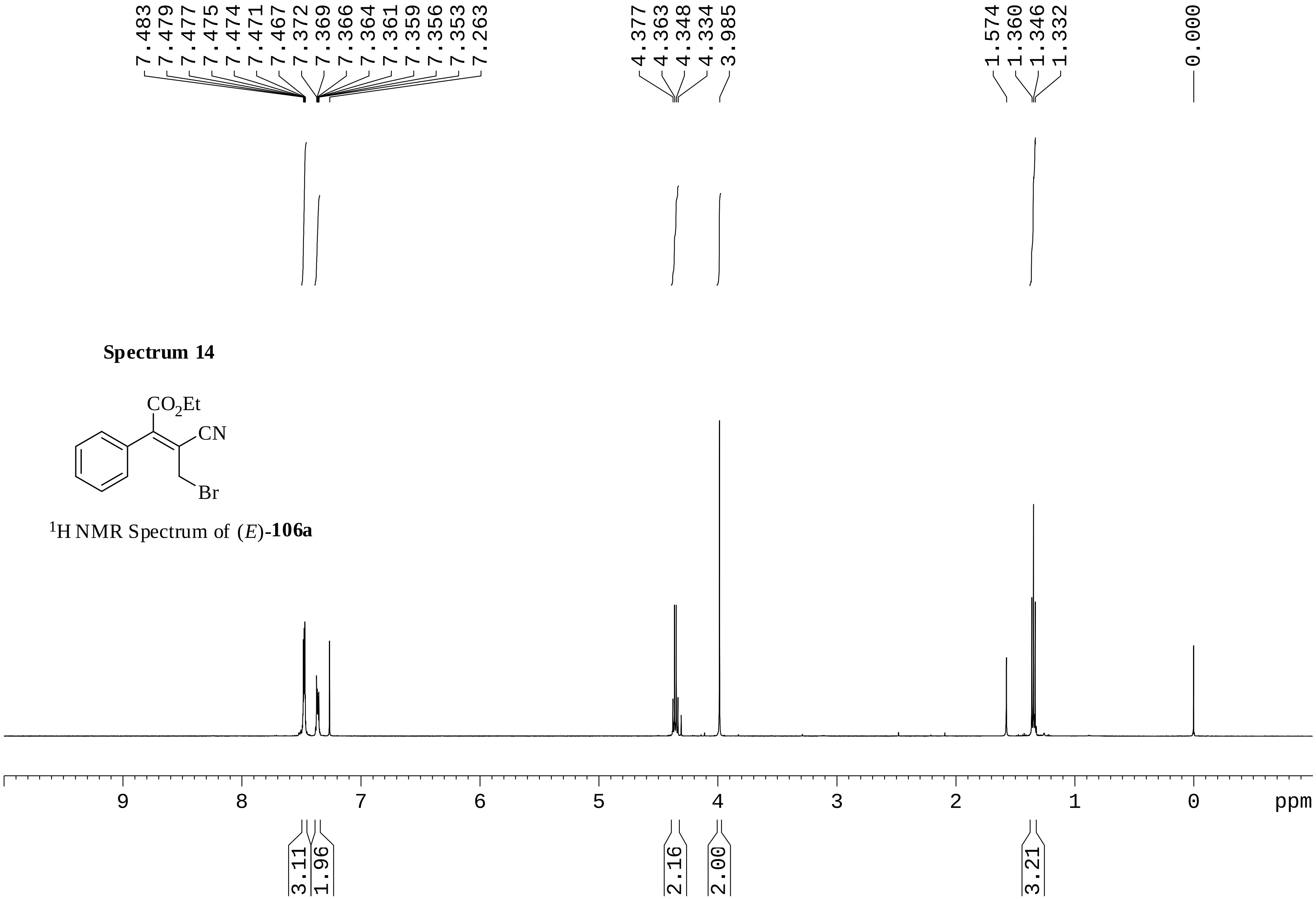

**Spectrum 12**



$^{13}$C NMR Spectrum of **93i**



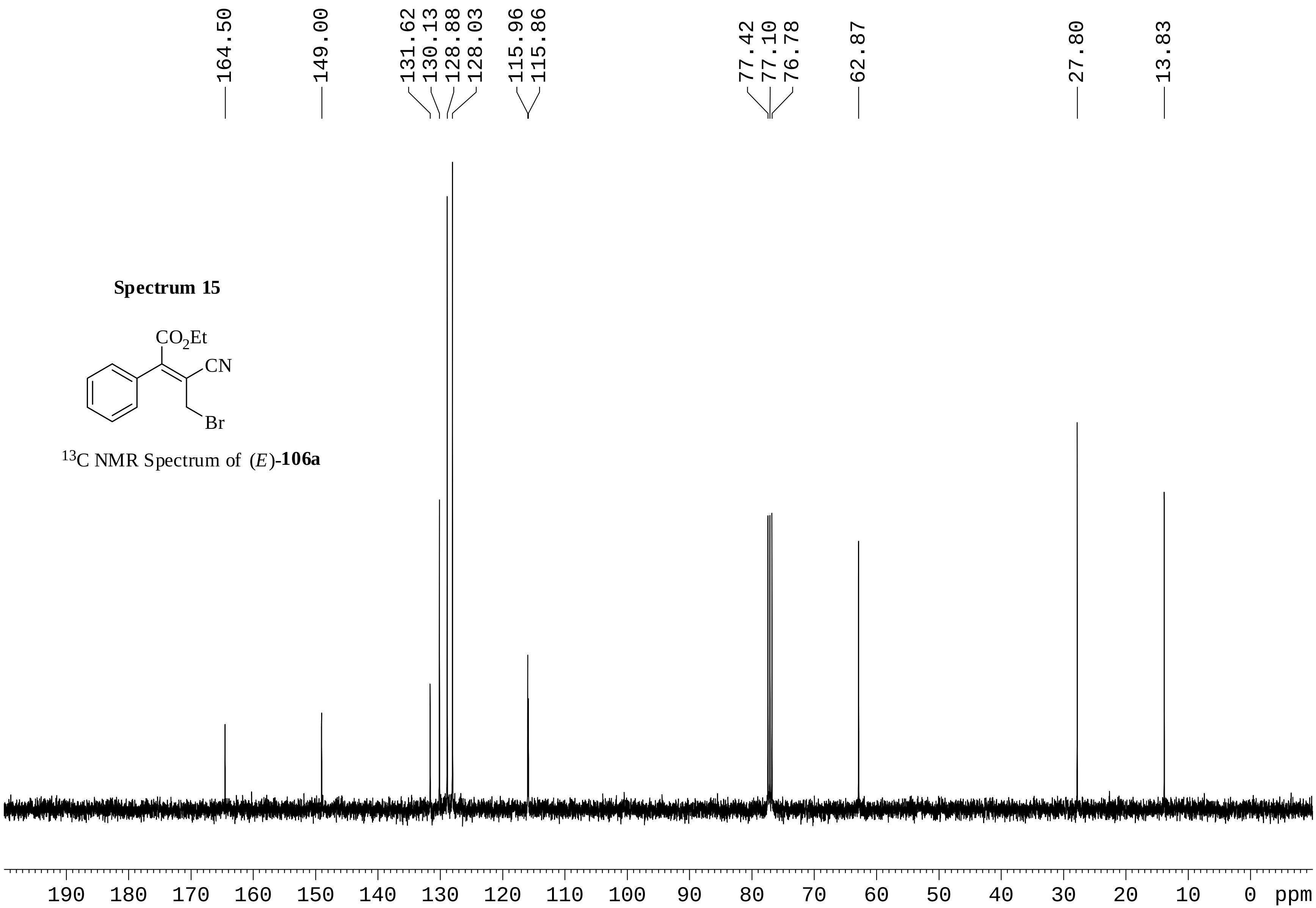
Spectrum 13
CO2Et
CO2Me
Br
NOE
NOESY Spectrum of 93i
ppm




**Spectrum 14**

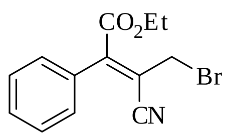
$^1$H NMR Spectrum of (*E*)-**106a**

**Spectrum 15**

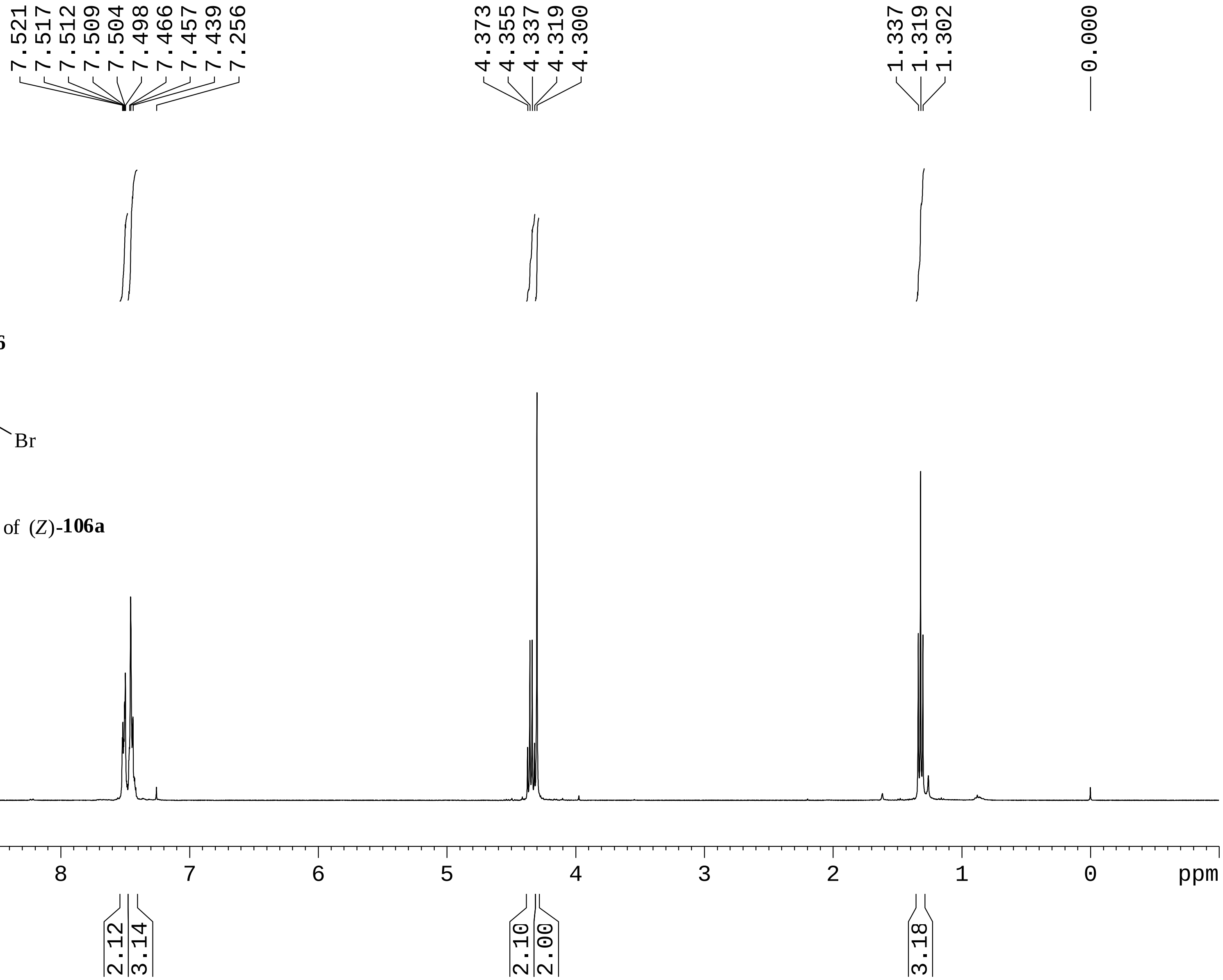



$^{13}$C NMR Spectrum of (*E*)-**106a**

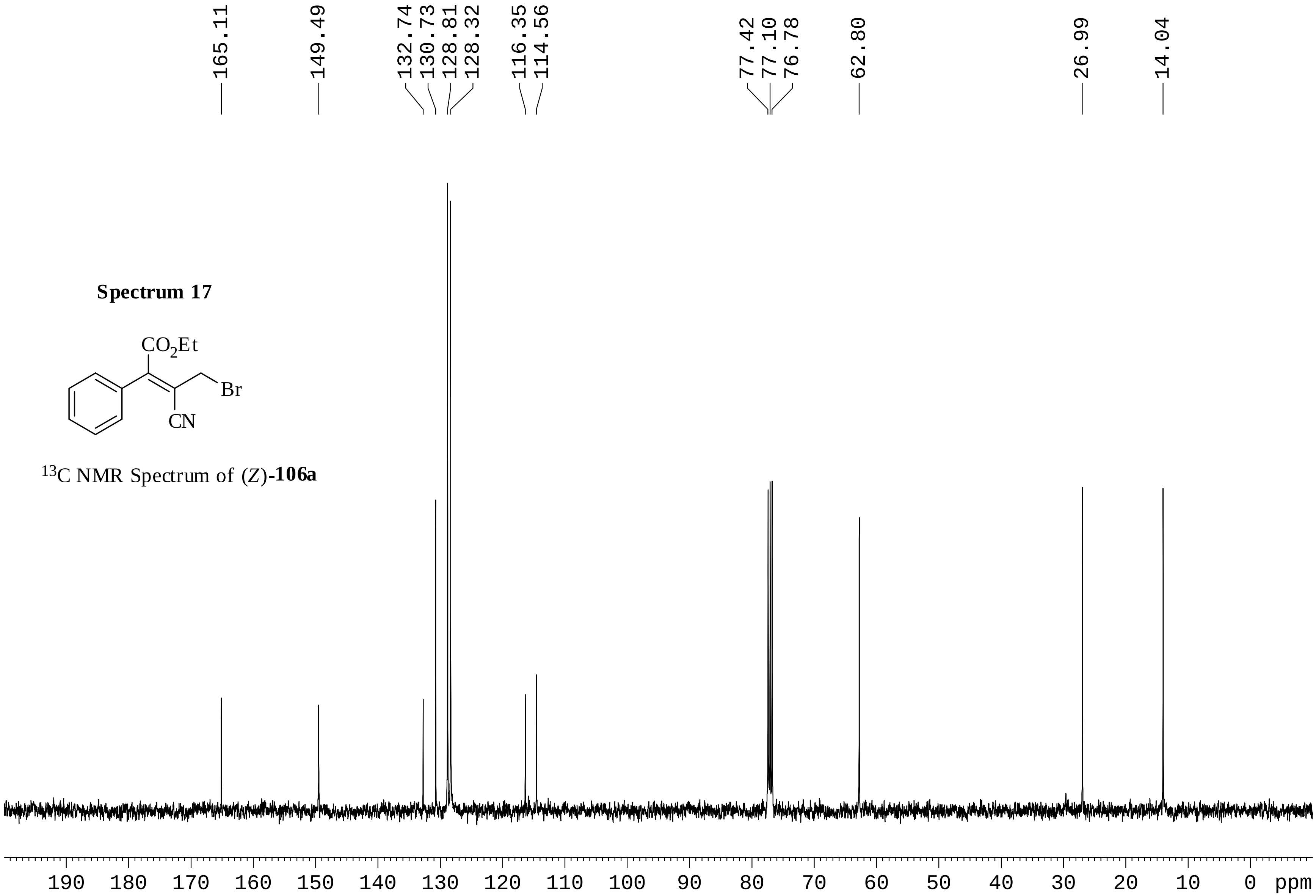
**Spectrum 16**




[1]H NMR Spectrum of (*Z*)-**106a**

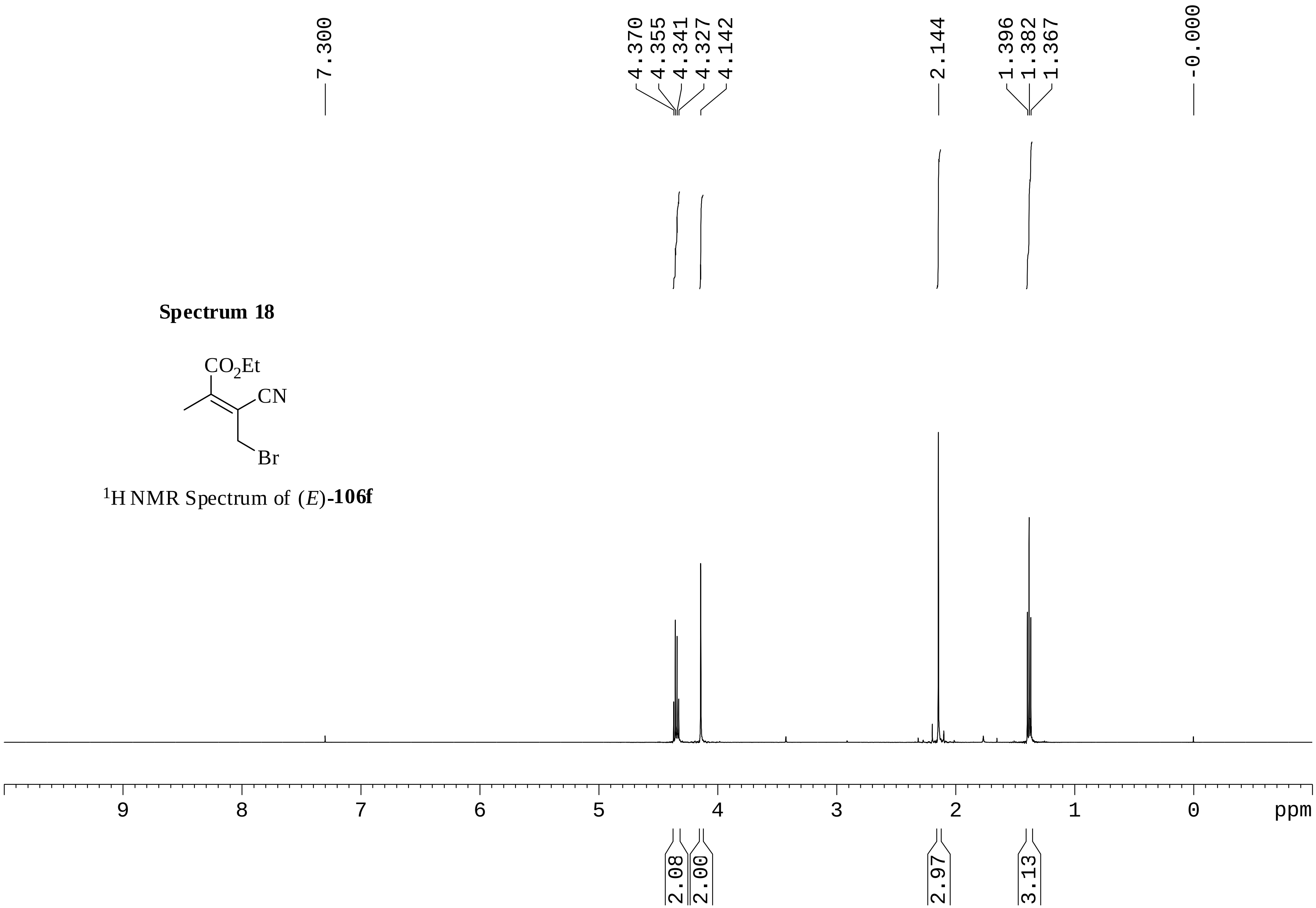


**Spectrum 17**



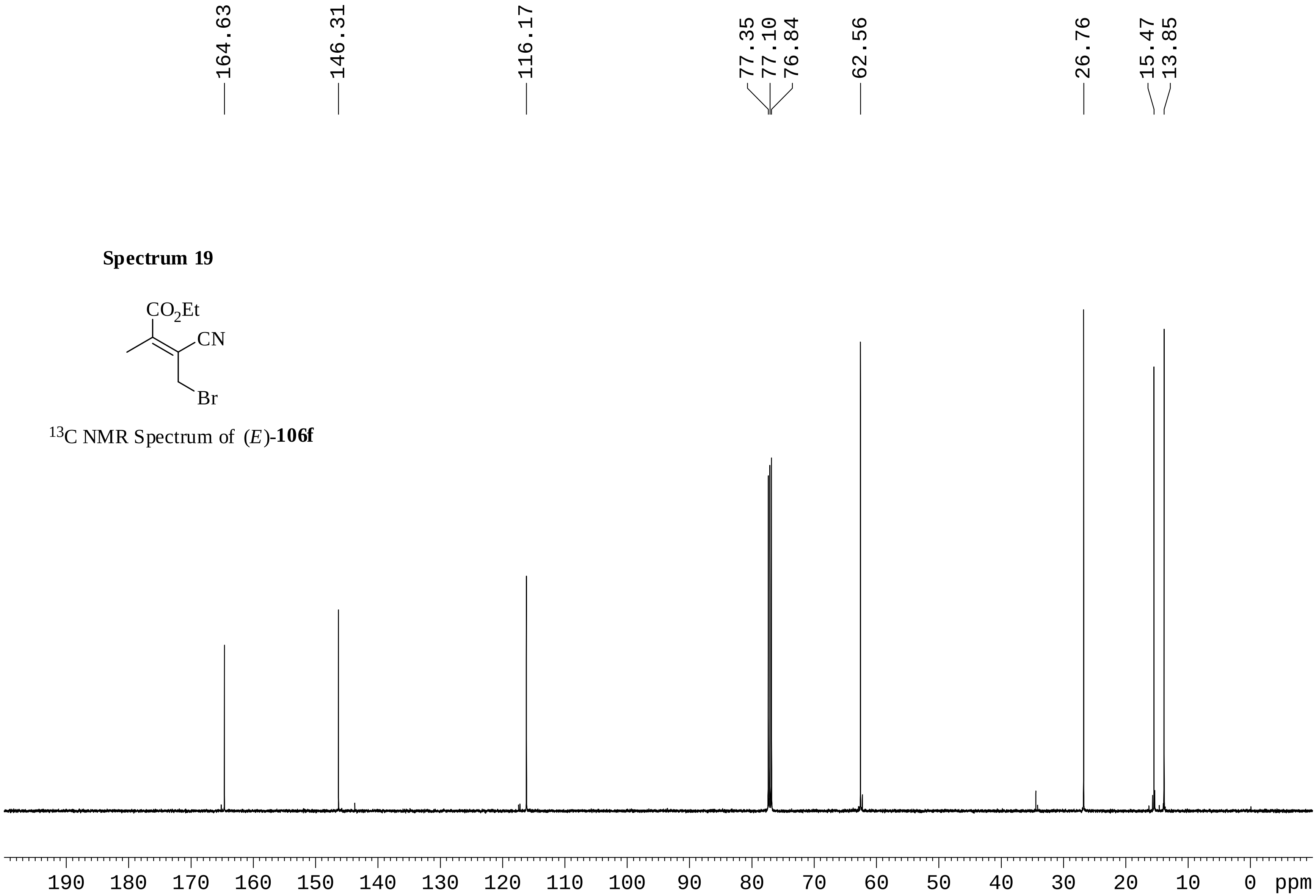

$^{13}$C NMR Spectrum of (*Z*)-**106a**

**Spectrum 18**



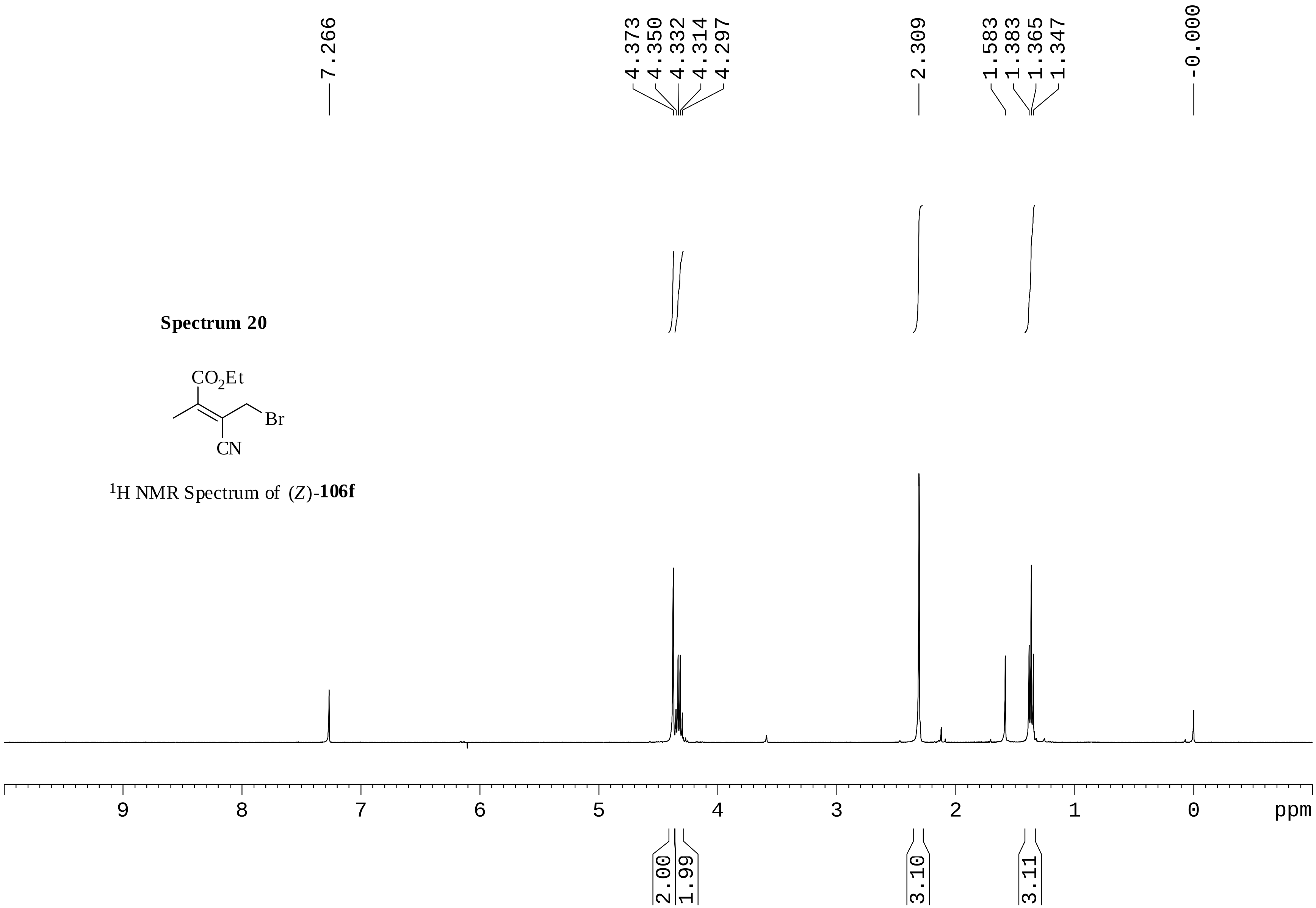

[1]H NMR Spectrum of (*E*)-**106f**

**Spectrum 19**

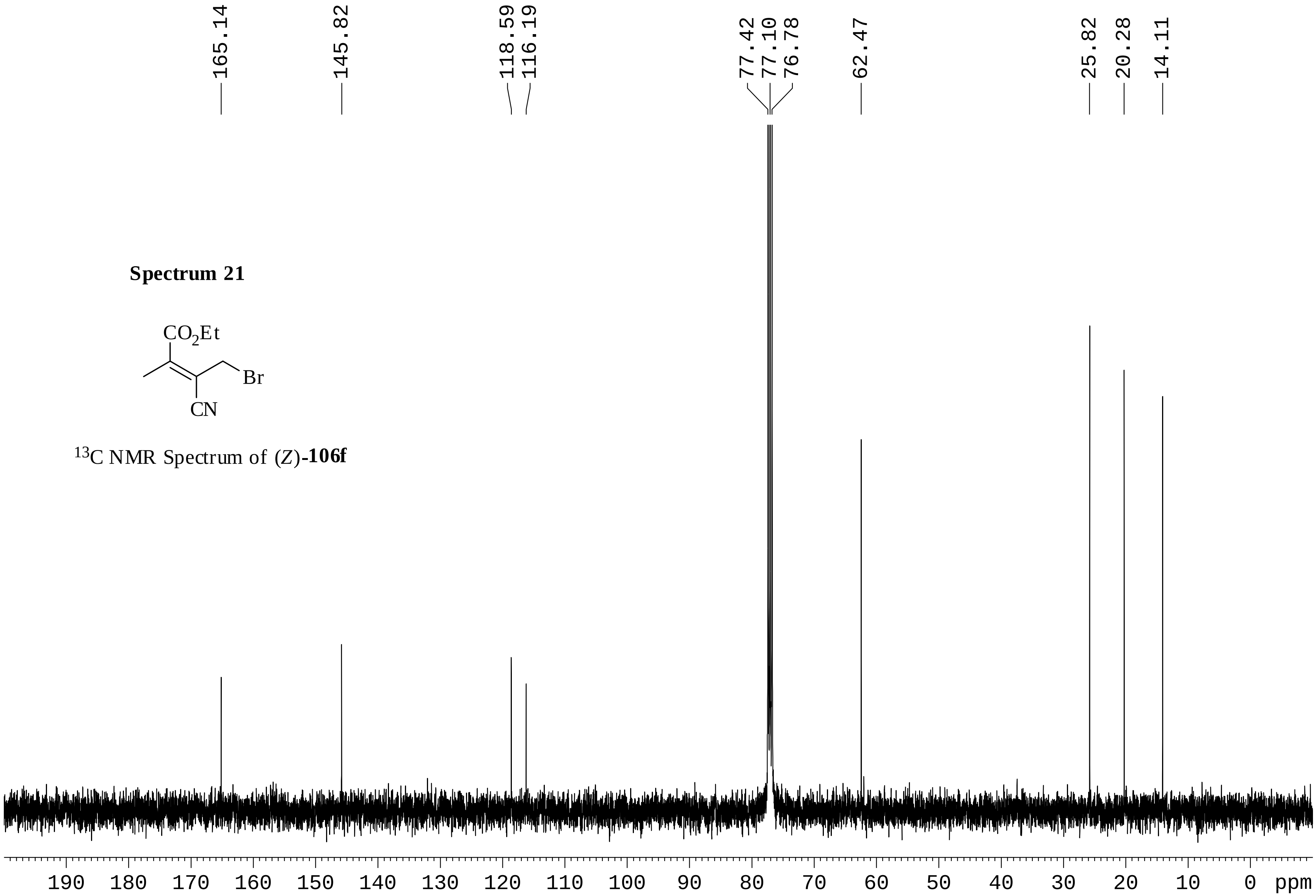



$^{13}$C NMR Spectrum of (*E*)-**106f**

**Spectrum 20**

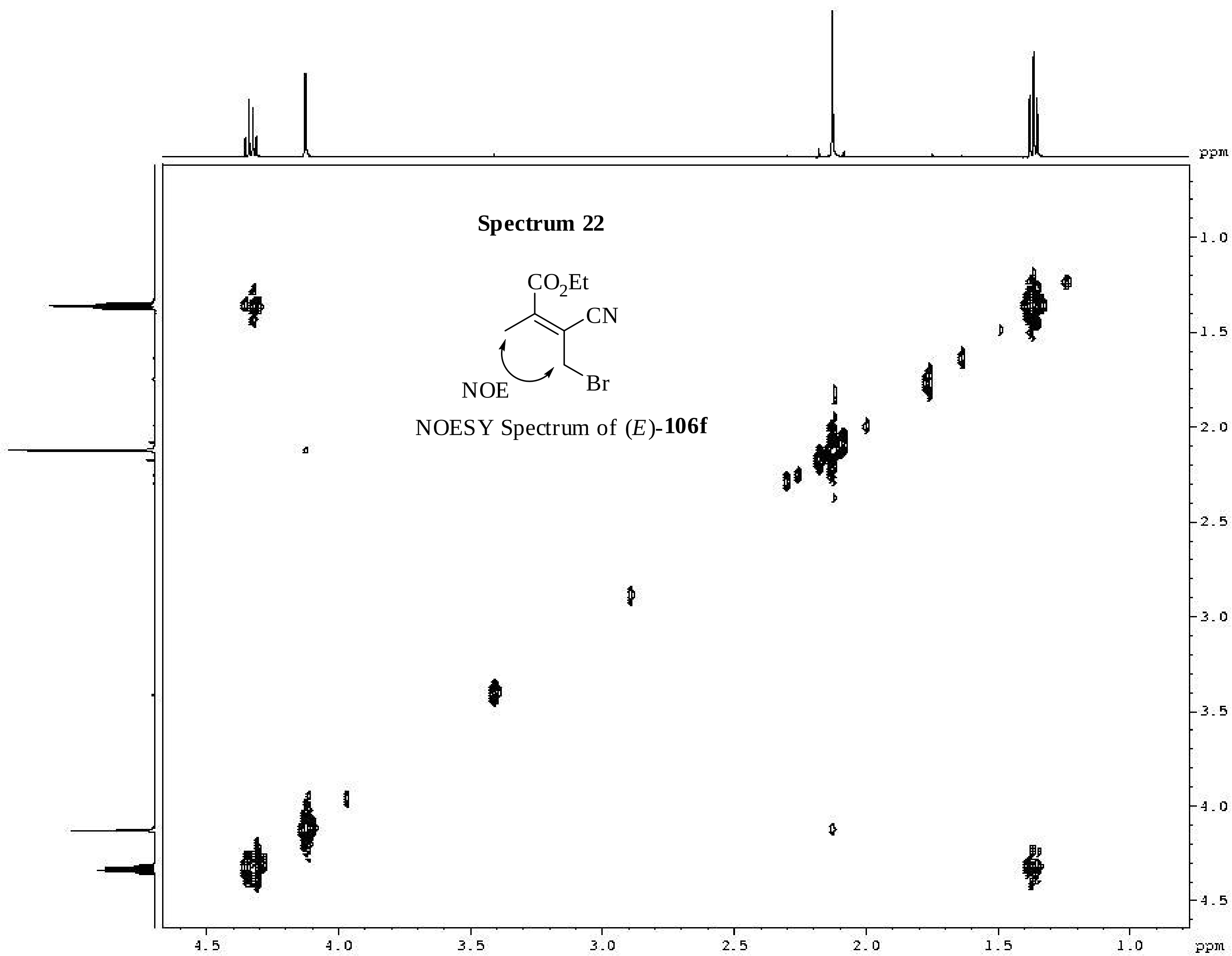



[1]H NMR Spectrum of (*Z*)-**106f**

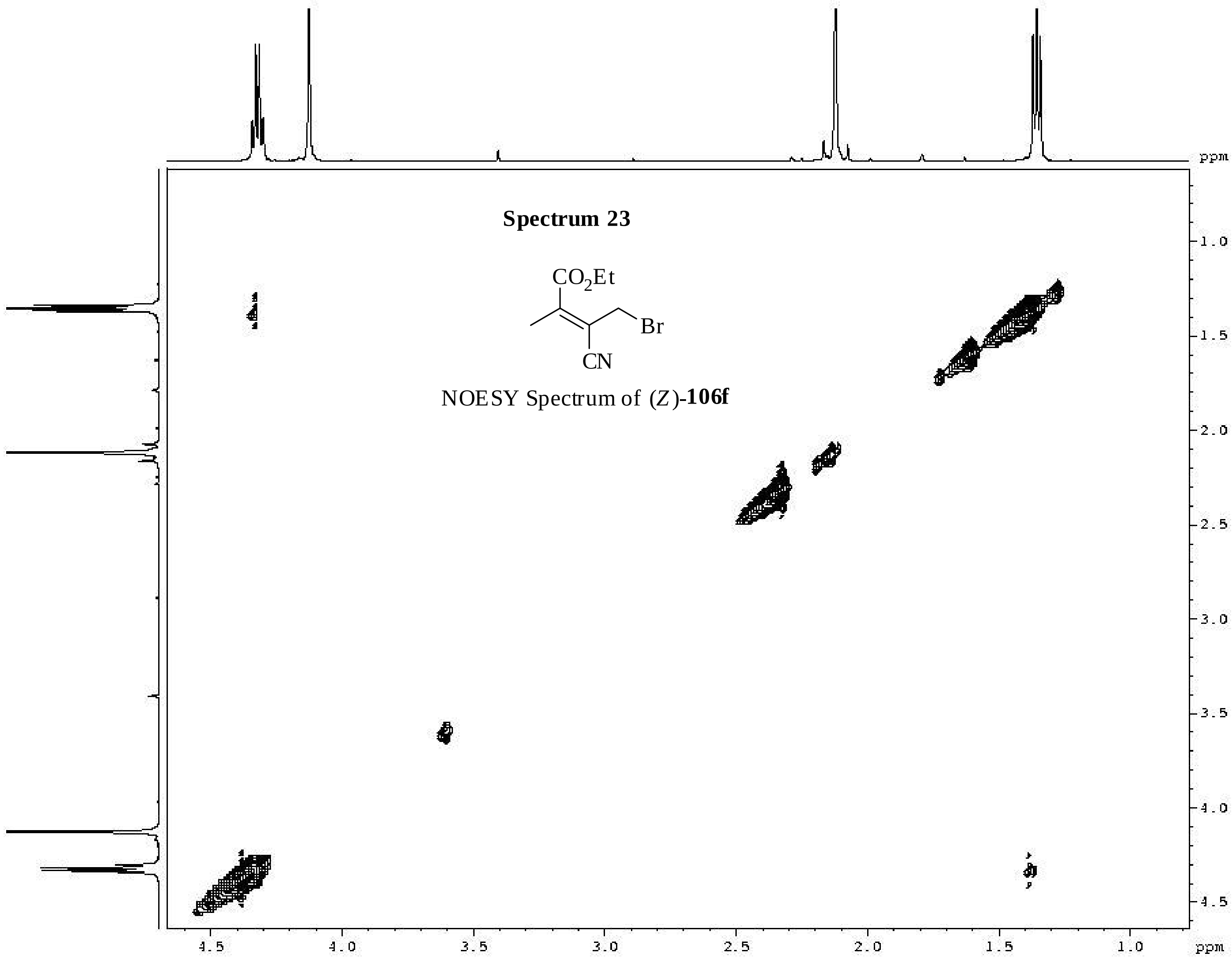



**Spectrum 21**

$^{13}$C NMR Spectrum of (*Z*)-**106f**

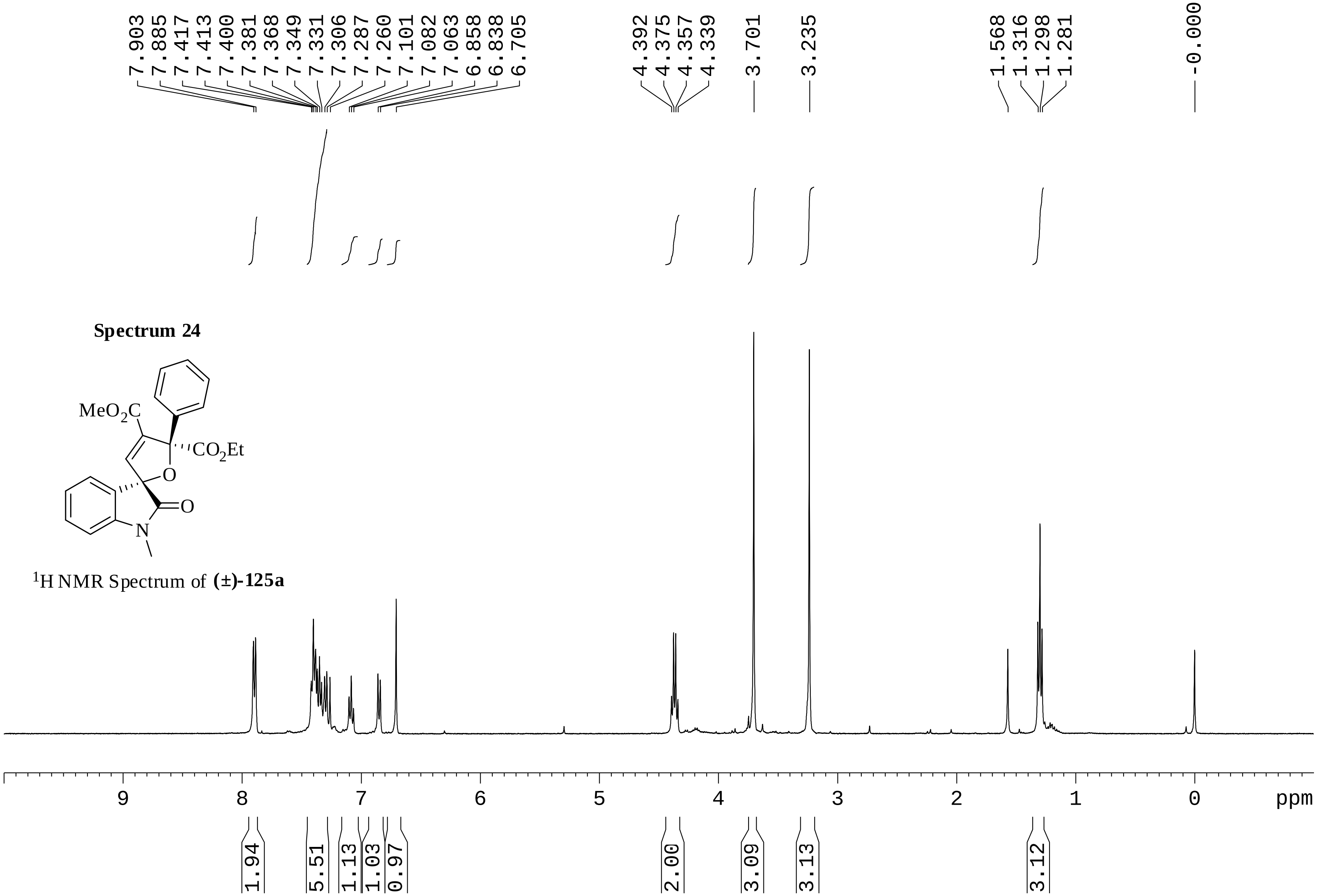

Spectrum 22
CO2Et
CN
Br
NOE
NOESY Spectrum of (E)-106f
ppm
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

**Spectrum 23**



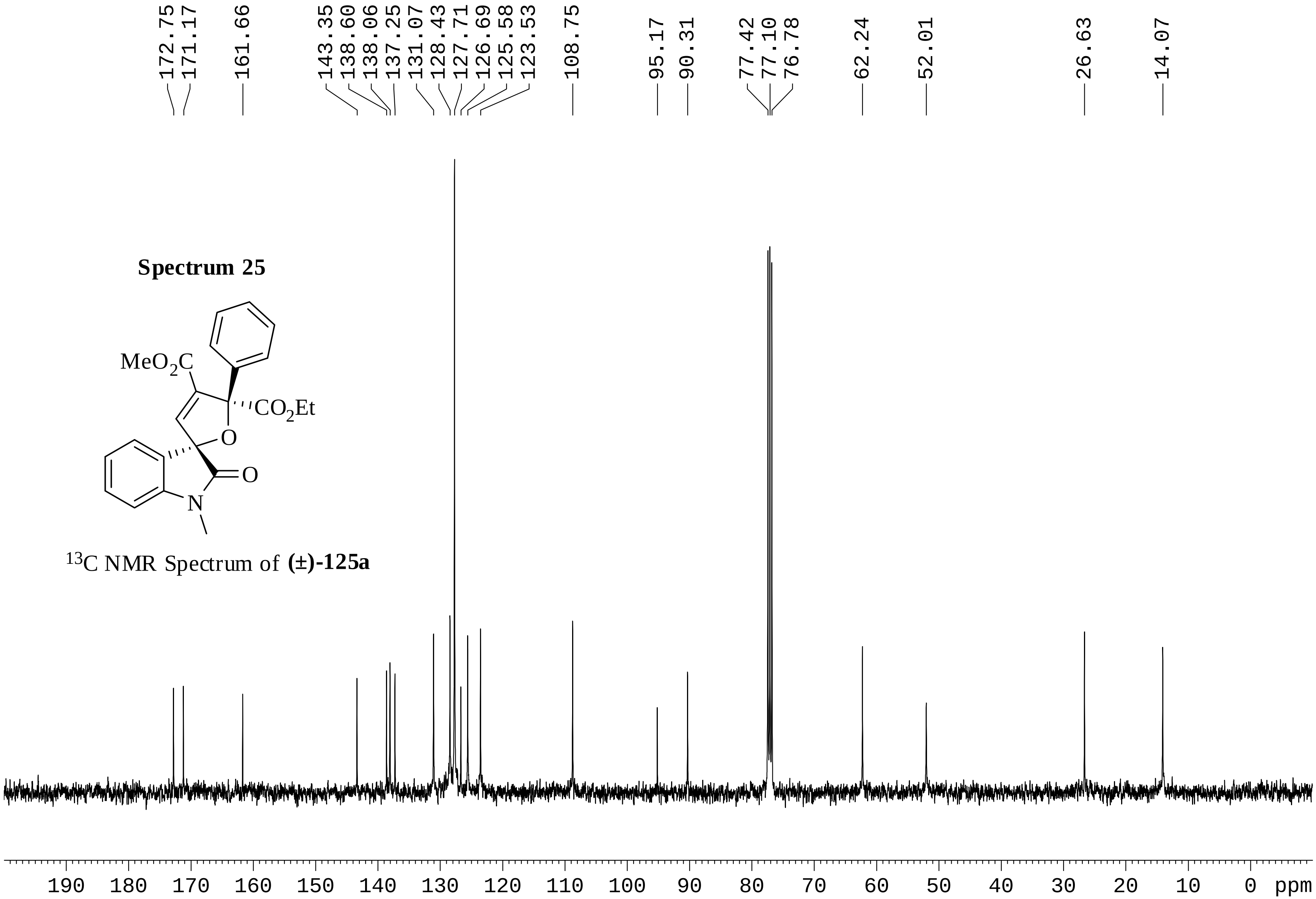

NOESY Spectrum of (*Z*)-**106f**

**Spectrum 24**



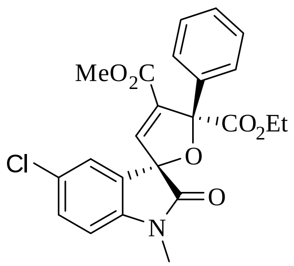

$^1$H NMR Spectrum of **(±)-125a**

**Spectrum 25**

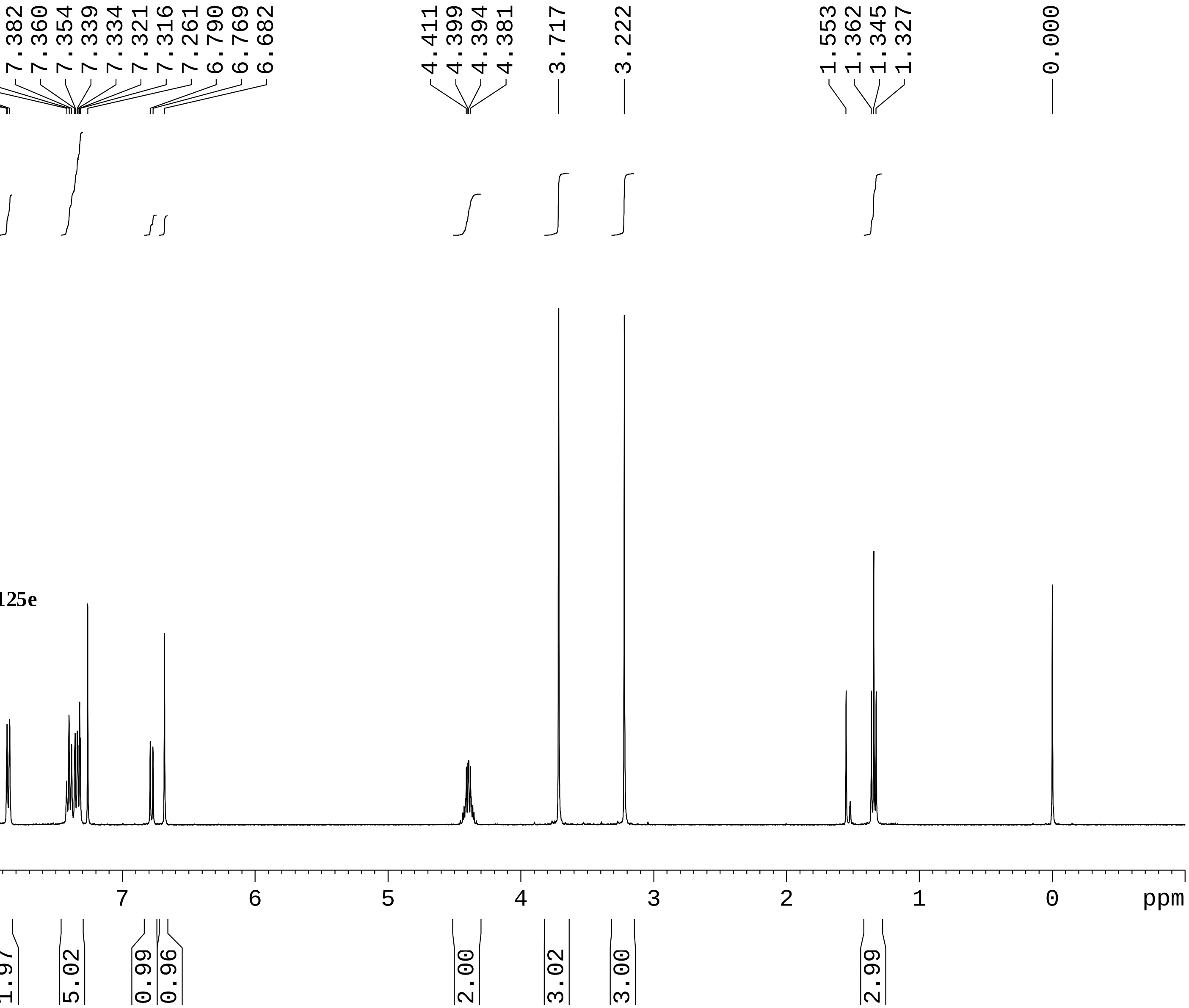



$^{13}C$ NMR Spectrum of **(±)-125a**

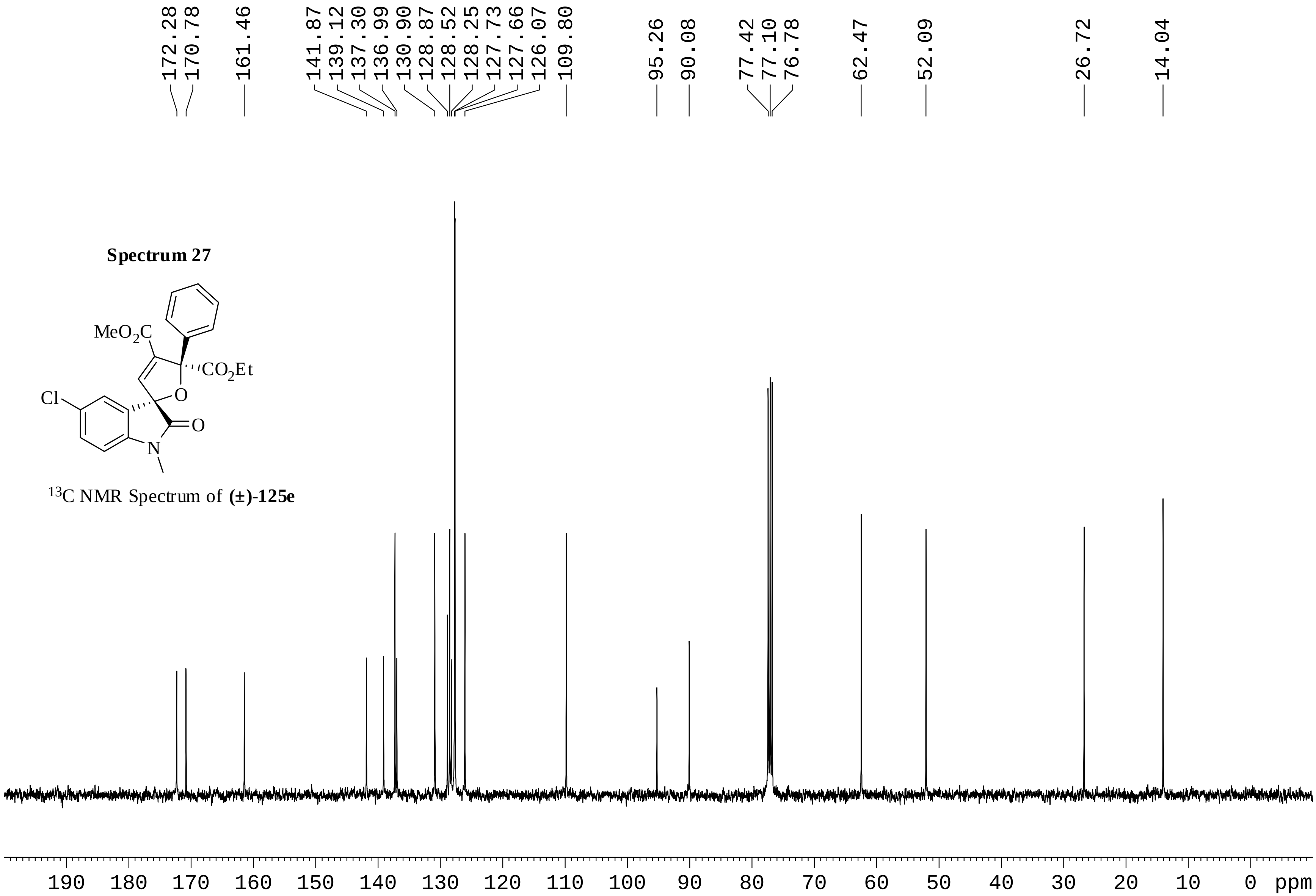
**Spectrum 26**




$^1$H NMR Spectrum of **(±)-125e**

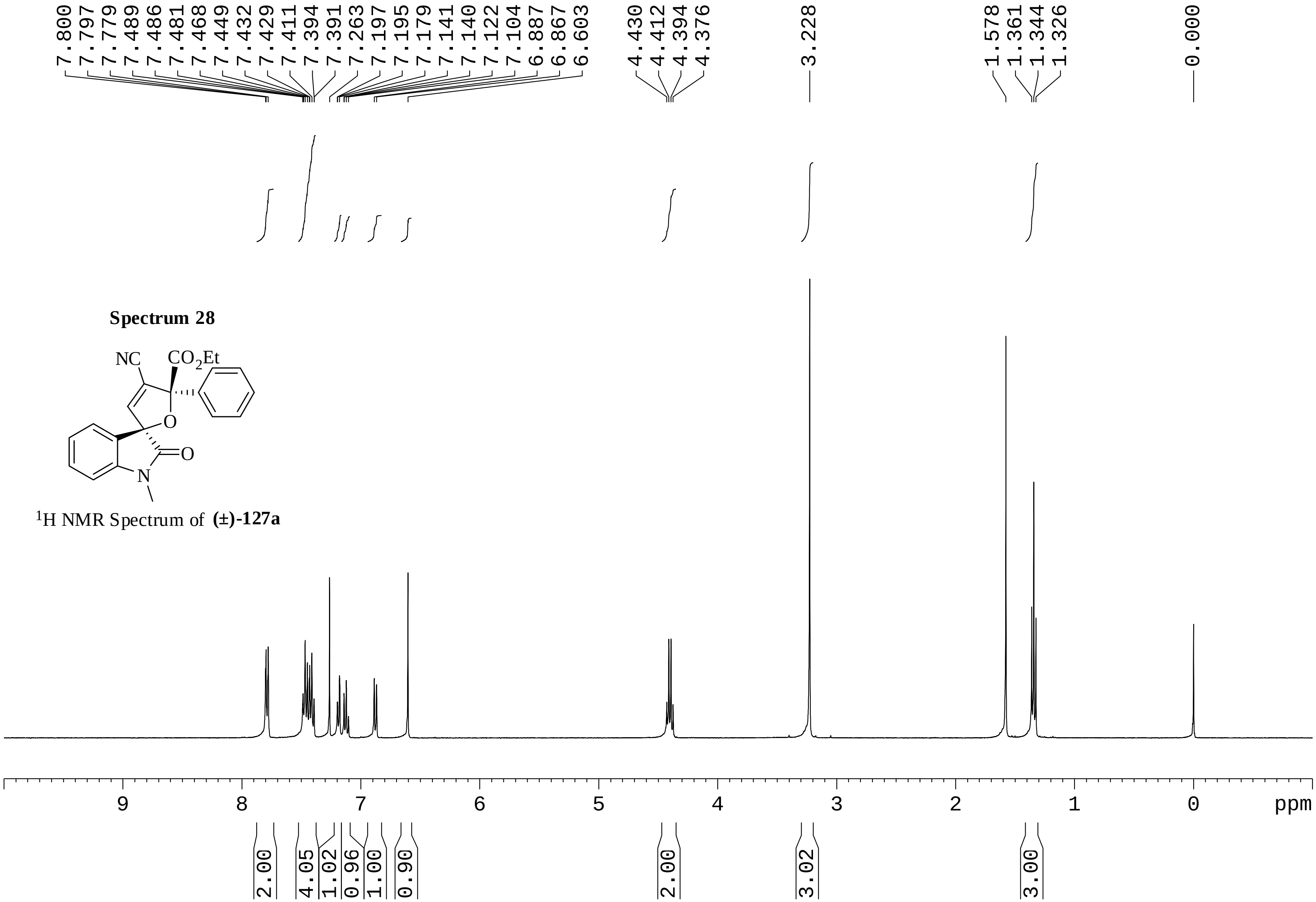


**Spectrum 27**

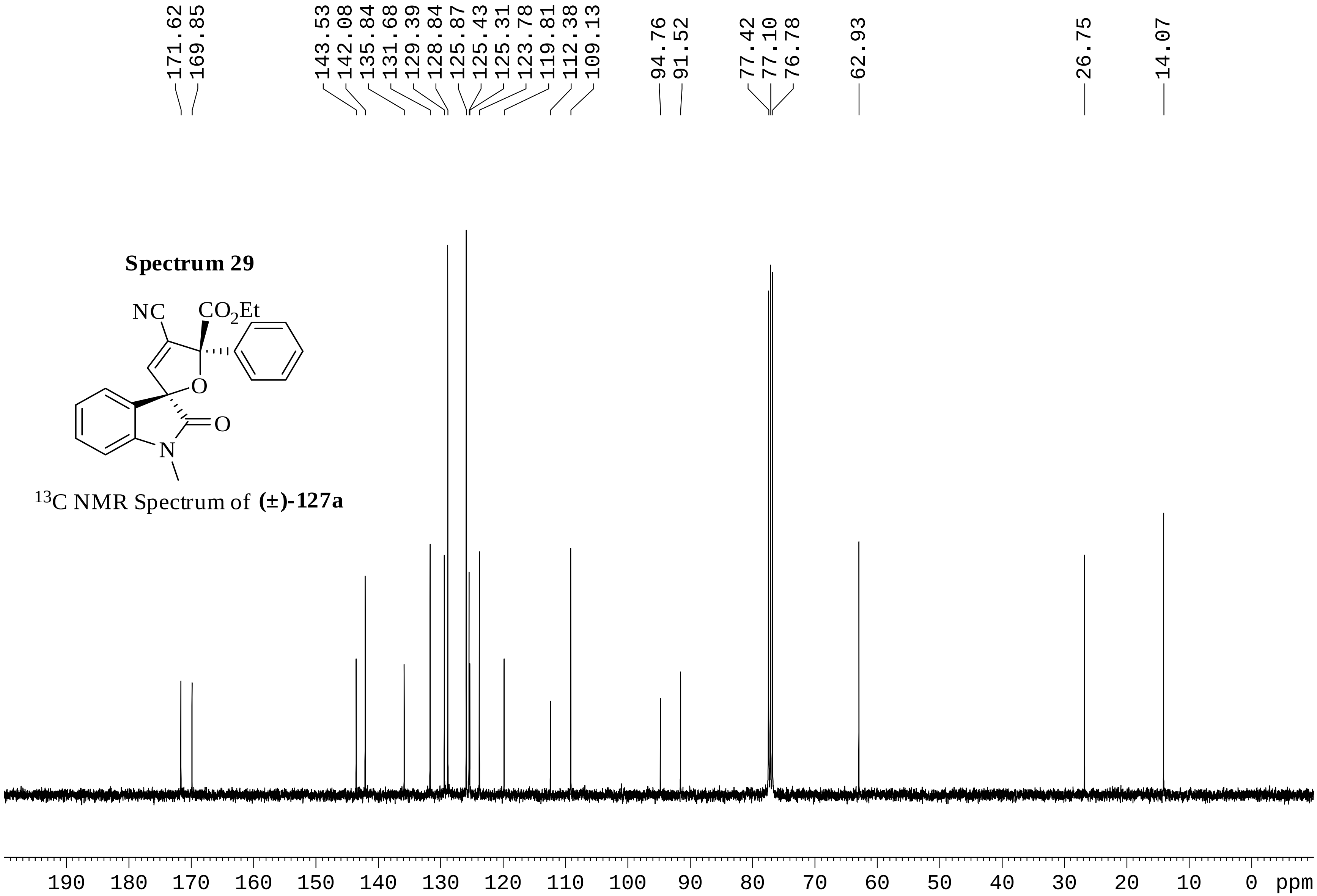



$^{13}$C NMR Spectrum of **(±)-125e**

**Spectrum 28**



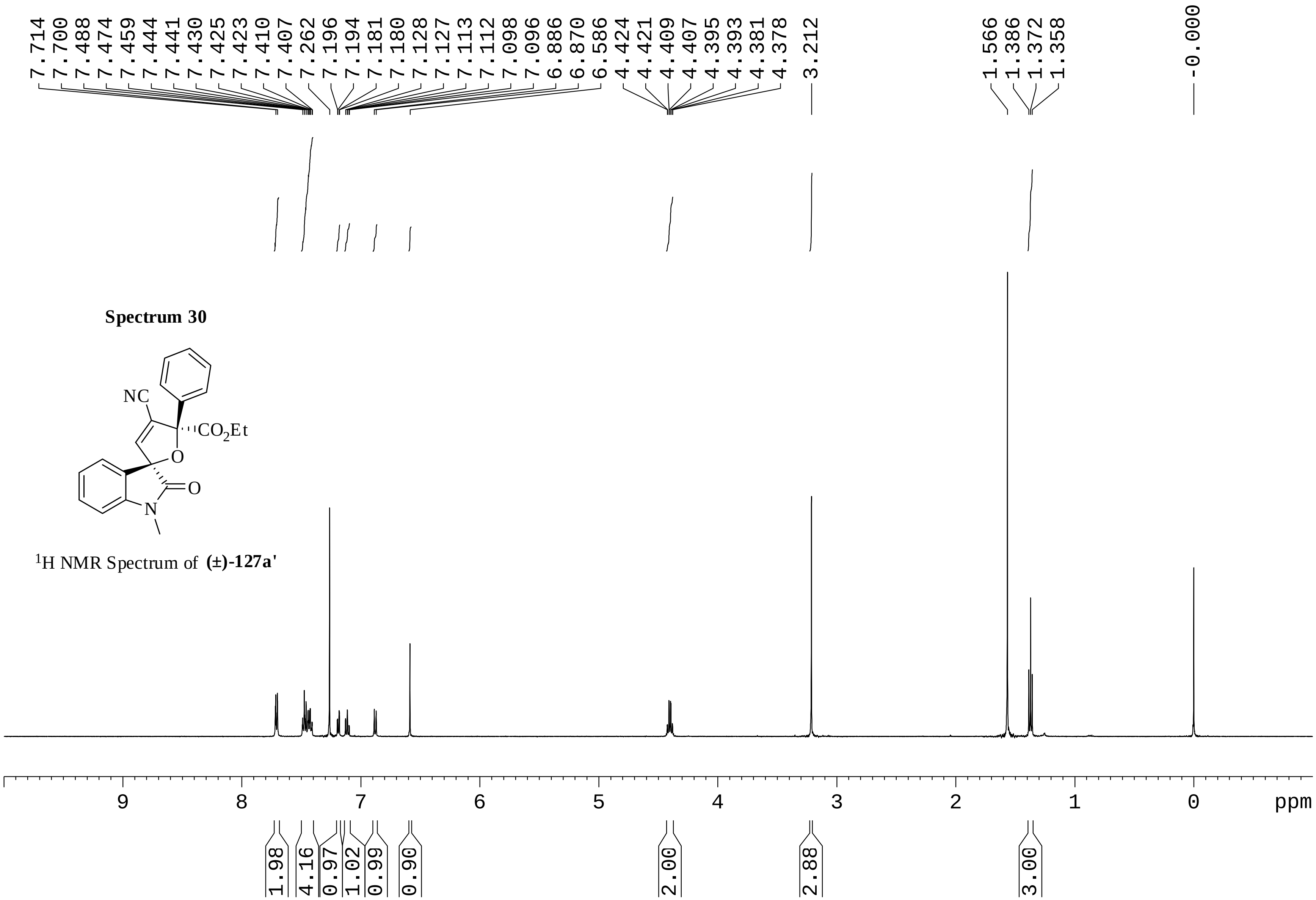

$^1$H NMR Spectrum of **(±)-127a**




**Spectrum 29**

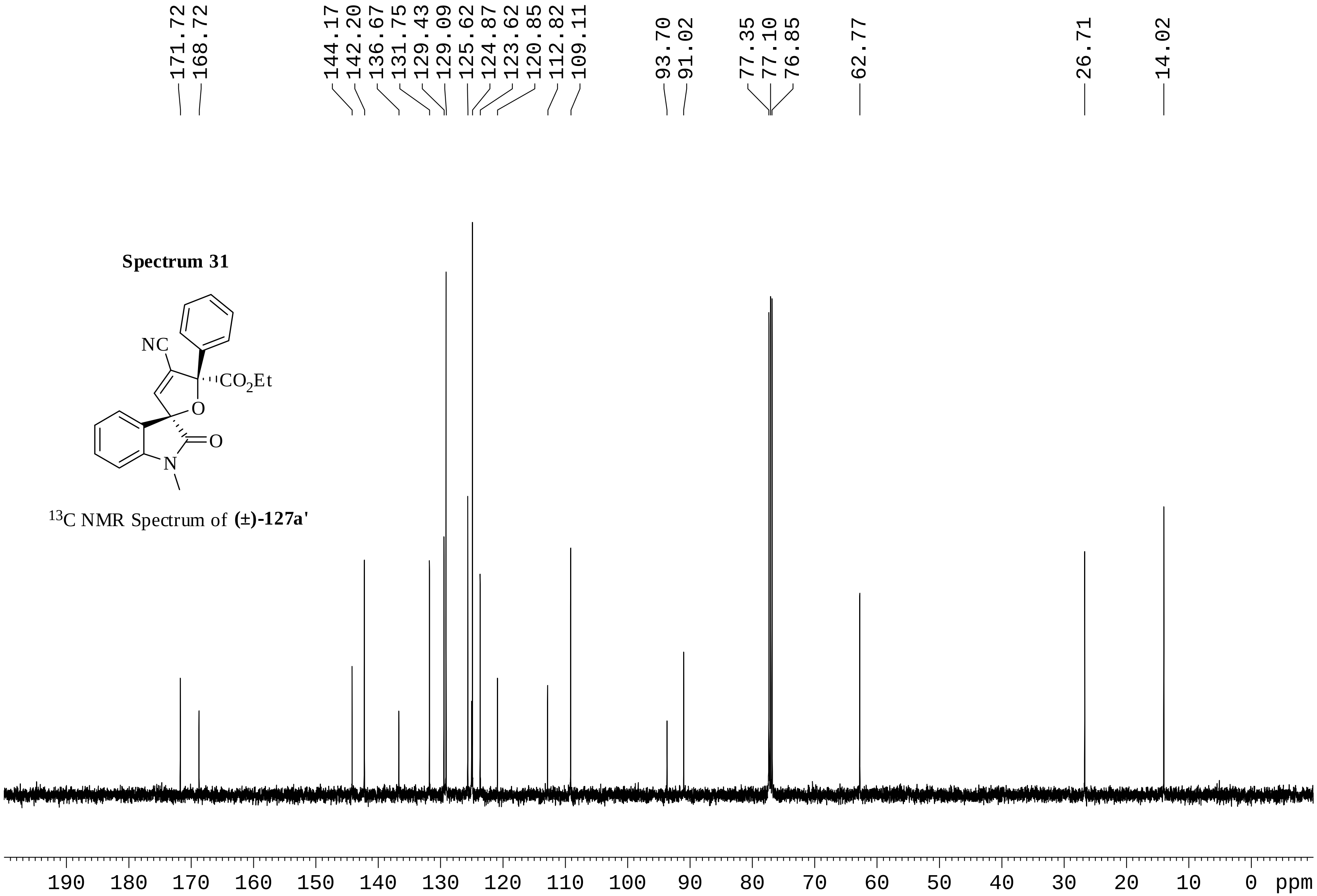
$^{13}$C NMR Spectrum of **(±)-127a**

**Spectrum 30**




[1]H NMR Spectrum of **(±)-127a'**

**Spectrum 31**




$^{13}$C NMR Spectrum of **(±)-127a'**

# APPENDIX

## (X-RAY CRYSTALLOGRAPHIC DATA)

**Table I**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **82f**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 2659(1) | 1907(2) | 3413(1) | 44(1) |
| C(5) | 3604(1) | 1924(2) | 3375(1) | 48(1) |
| O(2) | 1308(1) | 2508(2) | 3905(1) | 66(1) |
| C(1) | 2196(2) | 2688(3) | 3993(1) | 53(1) |
| C(8) | 2327(1) | 1028(2) | 2820(1) | 45(1) |
| C(6) | 3849(1) | 1017(2) | 2741(1) | 49(1) |
| C(7) | 3044(1) | 460(2) | 2392(1) | 45(1) |
| C(10) | 2948(2) | -489(3) | 1685(1) | 54(1) |
| C(11) | 2020(2) | -763(3) | 1387(1) | 64(1) |
| C(2) | 2666(2) | 3495(3) | 4538(1) | 65(1) |
| C(3) | 3615(2) | 3549(3) | 4509(1) | 69(1) |
| O(1) | 3594(1) | -1027(3) | 1339(1) | 87(1) |
| C(4) | 4072(2) | 2798(3) | 3951(1) | 61(1) |
| C(9) | 4799(1) | 715(3) | 2499(2) | 76(1) |
| C(12) | 754(2) | 3172(3) | 4498(2) | 88(1) |

**Table II**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **83f**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| O(1) | 1131(4) | 966(1) | 6272(2) | 56(1) |
| N(1) | 4461(4) | 1657(1) | 7470(2) | 41(1) |
| C(1) | 2837(5) | 823(2) | 7247(2) | 45(1) |
| C(8) | 4621(5) | 2574(2) | 6860(2) | 41(1) |
| C(5) | 6299(5) | 1655(2) | 8507(2) | 46(1) |
| O(3) | 1187(4) | 2843(2) | 3146(2) | 73(1) |
| C(6) | 7593(5) | 2565(2) | 8533(2) | 48(1) |
| C(13) | 3237(5) | 2802(2) | 5636(2) | 44(1) |
| C(7) | 6548(4) | 3147(2) | 7514(2) | 42(1) |
| C(3) | 4910(7) | -31(2) | 8992(3) | 67(1) |
| C(11) | 7261(5) | 4192(2) | 7180(3) | 53(1) |
| O(2) | 5993(5) | 4664(2) | 6386(2) | 88(1) |
| C(9) | -542(6) | 132(2) | 5909(3) | 66(1) |
| C(15) | 3374(5) | 2459(2) | 3271(2) | 48(1) |
| C(14) | 4670(5) | 2313(2) | 4537(2) | 50(1) |
| C(2) | 3050(6) | -2(2) | 7978(3) | 61(1) |
| C(4) | 6479(6) | 772(2) | 9249(2) | 59(1) |
| C(10) | 9739(6) | 2803(3) | 9509(3) | 65(1) |
| C(16) | 4919(6) | 2105(3) | 2166(2) | 63(1) |
| C(12) | 9559(7) | 4702(3) | 7821(4) | 75(1) |

**Table III**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **82h**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 8762(2) | 11078(1) | 4396(1) | 41(1) |
| C(5) | 7786(2) | 10143(2) | 4417(2) | 38(1) |
| O(1) | 9189(2) | 8581(1) | 1454(1) | 66(1) |
| C(6) | 7926(2) | 9415(2) | 3507(1) | 37(1) |
| C(7) | 9021(2) | 9923(2) | 2934(2) | 39(1) |
| C(11) | 6990(2) | 8380(2) | 3207(2) | 39(1) |
| C(9) | 9632(2) | 9473(2) | 1953(2) | 46(1) |

| | | | | |
|---|---|---|---|---|
| C(3) | 6942(2) | 11072(2) | 6010(2) | 52(1) |
| C(8) | 9506(2) | 10932(2) | 3510(2) | 44(1) |
| C(12) | 6804(2) | 7533(2) | 4012(2) | 47(1) |
| C(4) | 6877(2) | 10167(2) | 5272(2) | 44(1) |
| C(16) | 6188(2) | 8270(2) | 2126(2) | 48(1) |
| C(1) | 8839(2) | 11989(2) | 5171(2) | 51(1) |
| C(2) | 7947(2) | 11996(2) | 5953(2) | 55(1) |
| C(14) | 5059(3) | 6525(2) | 2675(2) | 64(1) |
| C(13) | 5847(2) | 6614(2) | 3744(2) | 60(1) |
| C(15) | 5230(2) | 7352(2) | 1868(2) | 60(1) |
| C(10) | 10861(3) | 10135(2) | 1565(2) | 65(1) |

**Table IV**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **83h**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 4120(2) | 1773(2) | 6606(2) | 41(1) |
| O(2) | -1440(2) | 294(2) | 9348(2) | 57(1) |
| C(13) | -482(3) | -443(3) | 8477(3) | 42(1) |
| C(15) | 5773(3) | 3482(3) | 3018(3) | 40(1) |
| O(1) | 760(3) | 2537(3) | 4749(3) | 73(1) |
| C(7) | 3139(3) | 2662(3) | 5003(3) | 41(1) |
| C(8) | 2761(3) | 1985(3) | 6343(3) | 40(1) |
| C(5) | 5384(3) | 2319(3) | 5441(3) | 40(1) |
| C(12) | 1025(3) | 47(3) | 7372(3) | 46(1) |
| C(11) | 1207(3) | 1559(3) | 7421(3) | 42(1) |
| C(4) | 6892(3) | 2195(3) | 5528(3) | 48(1) |
| C(6) | 4786(3) | 2878(3) | 4433(3) | 40(1) |
| C(16) | 6652(4) | 4572(3) | 2846(3) | 52(1) |
| C(1) | 4349(4) | 1143(3) | 7797(3) | 51(1) |
| C(20) | 5874(4) | 2960(3) | 1824(3) | 54(1) |
| C(9) | 1920(3) | 3152(3) | 4408(3) | 49(1) |

| | | | | |
|---|---|---|---|---|
| C(18) | 7677(5) | 4592(4) | 360(3) | 72(1) |
| C(2) | 5786(4) | 1055(4) | 7851(3) | 62(1) |
| C(17) | 7596(4) | 5112(4) | 1528(4) | 66(1) |
| C(19) | 6819(5) | 3519(4) | 503(3) | 70(1) |
| C(3) | 7091(4) | 1592(4) | 6697(4) | 61(1) |
| C(14) | -737(5) | -1910(4) | 8438(4) | 76(1) |
| C(10) | 2068(4) | 4477(4) | 3437(4) | 72(1) |

**Table V**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **88**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 9145(1) | 897(1) | 5661(2) | 48(1) |
| O(1) | 4591(1) | 940(1) | 5053(2) | 69(1) |
| C(12) | 6958(2) | 921(1) | 5406(2) | 48(1) |
| C(9) | 9010(2) | 1421(1) | 3185(2) | 47(1) |
| C(4) | 10477(2) | 1309(1) | 3767(2) | 52(1) |
| C(11) | 6933(2) | 1173(1) | 3949(2) | 45(1) |
| C(10) | 8305(2) | 1169(1) | 4126(2) | 45(1) |
| C(3) | 11225(2) | 960(1) | 5288(2) | 59(1) |
| C(1) | 8325(2) | 751(1) | 6431(2) | 50(1) |
| C(2) | 10586(2) | 778(1) | 6195(2) | 56(1) |
| C(17) | 5675(2) | 1408(1) | 2522(2) | 45(1) |
| C(18) | 5222(2) | 992(1) | 1136(2) | 55(1) |
| C(13) | 5833(2) | 847(1) | 5915(2) | 54(1) |
| C(8) | 8315(2) | 1803(1) | 1749(2) | 58(1) |
| C(22) | 4941(2) | 2055(1) | 2522(2) | 56(1) |
| C(5) | 11169(2) | 1562(1) | 2863(2) | 63(1) |
| C(16) | 8833(2) | 453(1) | 8070(2) | 63(1) |
| C(20) | 3344(2) | 1854(1) | -177(2) | 63(1) |
| C(19) | 4060(2) | 1210(1) | -198(2) | 63(1) |
| C(6) | 10458(2) | 1923(1) | 1455(3) | 68(1) |

| | | | | |
|---|---|---|---|---|
| C(7) | 9021(2) | 2049(1) | 902(2) | 65(1) |
| C(21) | 3791(2) | 2274(1) | 1178(2) | 64(1) |
| C(14) | 6314(2) | 667(1) | 7644(2) | 76(1) |
| C(15) | 7591(2) | 169(1) | 8338(2) | 79(1) |

**Table VI**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **93a**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 6029(1) | 3431(1) | 451(1) | 60(1) |
| O(4) | 10346(3) | 5167(3) | 3024(2) | 40(1) |
| C(1) | 7779(4) | 3175(4) | 2775(2) | 32(1) |
| C(2) | 8902(4) | 3288(4) | 2300(2) | 29(1) |
| C(3) | 9809(4) | 3262(4) | 1105(2) | 39(1) |
| O(2) | 10606(3) | 4487(3) | 1343(2) | 51(1) |
| C(4) | 7350(4) | 2092(4) | 1158(2) | 40(1) |
| O(1) | 9931(4) | 2516(4) | 566(2) | 66(1) |
| O(3) | 11487(3) | 2982(3) | 2800(2) | 57(1) |
| C(5) | 7124(6) | 2506(5) | 3945(3) | 61(1) |
| C(6) | 10405(4) | 3789(4) | 2724(2) | 37(1) |
| C(7) | 8671(4) | 2932(4) | 1568(2) | 31(1) |
| C(8) | 6370(5) | 3792(4) | 2530(3) | 46(1) |
| C(9) | 8152(5) | 2551(4) | 3492(2) | 45(1) |
| C(10) | 11712(5) | 5739(5) | 3488(3) | 53(1) |
| C(11) | 11780(5) | 4919(5) | 967(3) | 61(1) |
| C(12) | 5362(5) | 3744(6) | 3000(3) | 63(1) |
| C(13) | 11986(6) | 5098(6) | 4254(3) | 73(1) |
| C(14) | 5748(6) | 3104(6) | 3708(3) | 67(2) |

**Table VII**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for (*E*)**-106e**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 6083(1) | 2051(1) | 6539(1) | 64(1) |
| Br(2) | 3161(1) | -212(1) | 2355(1) | 83(1) |
| C(1) | 5814(4) | 2041(1) | 3117(5) | 46(1) |
| O(3) | 7823(3) | 862(1) | 2256(4) | 69(1) |
| O(6) | 2835(3) | 2102(1) | -1324(4) | 67(1) |
| C(2) | 4767(4) | 1881(1) | 1770(5) | 44(1) |
| C(3) | 5575(4) | 2286(1) | 4338(5) | 48(1) |
| O(2) | 7802(3) | 837(1) | 5713(4) | 60(1) |
| C(4) | 8072(4) | 503(1) | 2607(5) | 56(1) |
| C(5) | 3179(4) | 1905(1) | 1364(5) | 48(1) |
| C(6) | 7234(5) | -33(1) | 3477(5) | 57(1) |
| C(7) | 5957(4) | 558(1) | 3354(5) | 51(1) |
| C(8) | 6455(5) | 887(1) | 4471(6) | 59(1) |
| O(8) | 4312(4) | 1377(1) | -34(5) | 86(1) |
| C(9) | 2207(4) | 2016(1) | -254(6) | 52(1) |
| C(10) | 7082(4) | 333(1) | 3130(5) | 50(1) |
| C(11) | 713(5) | 2036(1) | -703(7) | 70(1) |
| O(1) | 5742(4) | 1152(1) | 4305(6) | 95(1) |
| C(12) | 3855(5) | 179(1) | 1367(6) | 68(1) |
| C(13) | 2633(5) | 1812(1) | 2530(6) | 63(1) |
| C(14) | 5192(5) | 1661(1) | 575(5) | 63(1) |
| C(15) | 3446(6) | 685(2) | 2932(7) | 74(1) |
| C(16) | 9176(5) | 302(1) | 2452(6) | 64(1) |
| C(17) | 4518(4) | 483(1) | 2608(5) | 58(1) |
| C(18) | 9288(5) | -66(1) | 2819(6) | 68(1) |
| C(19) | 8337(5) | -235(1) | 3339(6) | 68(1) |
| C(20) | 7351(5) | 1989(1) | 3526(6) | 64(1) |
| C(21) | 8427(6) | 1138(1) | 6874(7) | 80(2) |
| N(2) | 8587(5) | 1959(2) | 3979(7) | 99(2) |
| C(22) | 1945(7) | 2132(2) | -3091(7) | 87(2) |
| C(23) | 208(6) | 1949(1) | 512(9) | 82(2) |
| C(25) | 9933(7) | 1046(2) | 8046(9) | 107(2) |

| | | | | |
|---|---|---|---|---|
| C(26) | 1148(5) | 1837(2) | 2106(8) | 77(2) |
| N(1) | 2500(6) | 814(2) | 3107(9) | 115(2) |
| C(27) | 8913(6) | 1073(2) | 2048(10) | 104(2) |
| O(7) | 6198(4) | 1738(1) | 244(4) | 87(1) |
| C(28) | 4609(10) | 1131(3) | -1164(9) | 145(4) |
| C(29) | 3731(12) | 1195(3) | -2810(12) | 158(4) |

**TableVIII**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for (*Z*)-**106e**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 7246(1) | 5556(1) | 6869(1) | 88(2) |
| O(3) | 2735(3) | 1181(3) | 8926(3) | 55(3) |
| O(2) | 2270(3) | 2151(3) | 6068(3) | 64(3) |
| O(1) | 3241(3) | 4380(3) | 8013(4) | 74(3) |
| N(1) | 8931(4) | 2963(4) | 9651(5) | 70(3) |
| C(1) | 4574(3) | 1046(3) | 7674(3) | 42(3) |
| C(9) | 6377(4) | 3718(3) | 8522(4) | 42(3) |
| C(8) | 4861(4) | 2687(3) | 7901(3) | 42(3) |
| C(6) | 3472(4) | 288(4) | 8212(4) | 44(3) |
| C(2) | 5376(4) | 226(4) | 6920(4) | 52(3) |
| C(10) | 6831(4) | 5368(4) | 8667(4) | 50(3) |
| C(11) | 7786(4) | 3250(4) | 9133(4) | 49(3) |
| C(4) | 4051(5) | -2025(4) | 7272(5) | 65(3) |
| C(12) | 3382(4) | 3199(4) | 7363(4) | 50(3) |
| C(3) | 5107(5) | -1305(4) | 6710(5) | 63(3) |
| C(5) | 3223(5) | -1239(4) | 8028(4) | 56(3) |
| C(7) | 1543(5) | 471(5) | 9447(5) | 67(3) |
| C(13) | 751(5) | 2500(7) | 5421(6) | 84(3) |
| C(14) | -447(6) | 2015(8) | 6096(7) | 92(3) |

**Table IX.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **125a**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 7120(2) | 2252(1) | 1112(1) | 44(1) |
| O(3) | 7764(2) | 4232(2) | 1113(1) | 62(1) |
| O(6) | 5074(2) | 2371(2) | -1564(1) | 59(1) |
| C(1) | 4991(3) | 2860(2) | -861(2) | 43(1) |
| O(2) | 5795(2) | 292(2) | 1233(1) | 65(1) |
| C(2) | 4962(2) | 3237(2) | 1172(2) | 37(1) |
| N(1) | 8321(2) | 88(2) | 1299(1) | 48(1) |
| O(5) | 4276(2) | 3566(2) | -801(1) | 81(1) |
| C(3) | 6559(2) | 1605(2) | -188(2) | 41(1) |
| C(4) | 9556(3) | 559(2) | 985(2) | 45(1) |
| C(5) | 9117(3) | 1350(2) | 540(2) | 42(1) |
| C(6) | 6252(2) | 2941(2) | 641(1) | 38(1) |
| C(7) | 5868(2) | 2422(2) | -171(1) | 36(1) |
| C(8) | 7319(3) | 3754(2) | 444(2) | 45(1) |
| O(4) | 7764(2) | 3892(2) | -244(1) | 70(1) |
| C(9) | 4419(3) | 2614(2) | 1749(2) | 48(1) |
| C(10) | 7045(3) | 544(2) | 1079(2) | 47(1) |
| C(11) | 7459(2) | 1448(2) | 595(2) | 40(1) |
| C(12) | 10137(3) | 1935(2) | 191(2) | 57(1) |
| C(13) | 3243(3) | 2864(2) | 2242(2) | 58(1) |
| C(14) | 11041(3) | 323(2) | 1089(2) | 59(1) |
| C(15) | 4309(3) | 4114(2) | 1089(2) | 49(1) |
| C(16) | 3125(3) | 4357(2) | 1576(2) | 58(1) |
| C(17) | 2602(3) | 3734(2) | 2149(2) | 57(1) |
| C(18) | 11630(3) | 1706(3) | 297(2) | 68(1) |
| C(19) | 12056(3) | 913(3) | 735(2) | 68(1) |
| C(20) | 8381(3) | -779(2) | 1781(2) | 68(1) |
| C(21) | 4297(3) | 2758(3) | -2295(2) | 77(1) |
| C(22) | 8843(4) | 4990(3) | 951(2) | 84(1) |

| | | | | |
|---|---|---|---|---|
| C(23) | 9130(4) | 5526(3) | 1696(2) | 94(1) |

**Table X.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **125i**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(2) | 2631(1) | 6159(1) | 998(1) | 45(1) |
| O(1) | 542(1) | 5284(1) | 1236(1) | 61(1) |
| C(1) | 2195(1) | 5375(1) | -434(1) | 44(1) |
| C(2) | 1804(1) | 7429(1) | -259(1) | 45(1) |
| N(1) | 1877(1) | 4083(1) | 2169(1) | 53(1) |
| O(3) | 1875(2) | 6093(1) | -1907(1) | 79(1) |
| O(4) | 1943(1) | 4252(1) | -1694(1) | 70(1) |
| O(6) | 4413(1) | 7324(1) | 832(1) | 76(1) |
| C(3) | 3026(1) | 3795(1) | 2323(1) | 48(1) |
| C(4) | 1469(1) | 4830(1) | 1480(1) | 47(1) |
| C(5) | 3408(1) | 4344(1) | 1705(1) | 45(1) |
| C(6) | 2611(1) | 6441(1) | 99(1) | 43(1) |
| C(7) | 2069(1) | 4579(1) | 102(1) | 45(1) |
| O(7) | -1183(1) | 7976(1) | -643(1) | 75(1) |
| C(8) | 1988(2) | 5306(1) | -1417(1) | 51(1) |
| C(9) | 689(1) | 7324(1) | -291(1) | 48(1) |
| C(10) | 2418(1) | 4992(1) | 1059(1) | 43(1) |
| C(11) | 3851(1) | 6666(1) | 160(1) | 51(1) |
| C(12) | -98(1) | 8176(2) | -639(1) | 54(1) |
| C(13) | 4513(2) | 4206(2) | 1729(1) | 55(1) |
| C(14) | 3732(2) | 3085(2) | 2971(1) | 61(1) |
| O(5) | 4264(2) | 6249(2) | -325(1) | 112(1) |
| C(15) | 2145(2) | 8404(2) | -566(1) | 66(1) |
| C(16) | 4850(2) | 2956(2) | 2993(1) | 67(1) |
| C(17) | 1222(2) | 3675(2) | 2709(1) | 71(1) |
| C(18) | 5629(2) | 7494(3) | 1011(2) | 101(1) |

| | | | | |
|---|---|---|---|---|
| C(19) | 1356(2) | 9243(2) | -909(2) | 80(1) |
| C(20) | 5241(2) | 3507(2) | 2393(1) | 65(1) |
| C(21) | 234(2) | 9142(2) | -955(1) | 69(1) |
| C(22) | 1740(3) | 4107(2) | -2648(2) | 111(1) |
| C(23) | -2058(2) | 8756(2) | -1100(2) | 89(1) |
| C(24) | 5850(3) | 8346(4) | 441(3) | 167(2) |

**Table XI.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **125j**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 2138(1) | 2259(1) | 1060(1) | 50(1) |
| O(5) | -458(2) | 2244(1) | -1518(1) | 65(1) |
| O(2) | 2749(2) | 4161(1) | 1046(1) | 73(1) |
| C(24) | 1401(2) | 1594(1) | -198(1) | 48(1) |
| N(1) | 3345(2) | 170(1) | 1295(1) | 56(1) |
| O(6) | 841(2) | 393(1) | 1246(1) | 74(1) |
| C(2) | 2275(2) | 3688(1) | 386(1) | 56(1) |
| C(3) | 742(2) | 2392(1) | -200(1) | 47(1) |
| C(4) | 4535(2) | 599(1) | 967(1) | 54(1) |
| C(5) | -249(2) | 2800(1) | -880(1) | 55(1) |
| O(4) | -757(2) | 3546(1) | -868(1) | 105(1) |
| C(6) | -523(2) | 2616(1) | 1636(1) | 55(1) |
| C(7) | 1222(2) | 2914(1) | 584(1) | 46(1) |
| C(8) | 2054(2) | 613(1) | 1075(1) | 53(1) |
| C(9) | 2411(2) | 1469(1) | 576(1) | 47(1) |
| C(10) | -6(2) | 3218(1) | 1085(1) | 49(1) |
| C(11) | 4046(2) | 1360(1) | 512(1) | 51(1) |
| O(3) | 2684(2) | 3805(1) | -275(1) | 84(1) |
| C(12) | -1656(2) | 2854(2) | 2107(1) | 67(1) |
| C(13) | -628(2) | 4079(1) | 999(1) | 65(1) |
| C(14) | -2256(2) | 3711(2) | 2008(1) | 75(1) |

| | | | | |
|---|---|---|---|---|
| C(15) | 6976(2) | 895(2) | 692(2) | 81(1) |
| C(16) | -1333(3) | 2596(2) | -2240(1) | 82(1) |
| C(17) | 5024(2) | 1896(2) | 148(1) | 66(1) |
| C(18) | 6003(2) | 352(2) | 1060(1) | 70(1) |
| C(19) | -1756(3) | 4319(2) | 1459(1) | 79(1) |
| C(20) | 6509(2) | 1653(2) | 243(2) | 80(1) |
| C(21) | 3455(3) | -649(2) | 1797(2) | 80(1) |
| C(22) | 3829(3) | 4878(2) | 922(2) | 101(1) |
| C(23) | 4150(4) | 5373(2) | 1669(2) | 129(1) |
| C(25) | -2193(4) | 2178(2) | 2702(2) | 110(1) |

**Table XII.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **125k**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 2981(1) | 8365(2) | 431(1) | 43(1) |
| O(2) | 4418(1) | 9217(2) | 1699(1) | 59(1) |
| O(5) | 1823(1) | 6928(2) | -584(1) | 59(1) |
| O(3) | 1(1) | 9410(2) | 1766(1) | 64(1) |
| N(1) | 4730(1) | 10898(2) | 881(1) | 45(1) |
| O(7) | 3024(2) | 2442(2) | 1908(1) | 56(1) |
| C(1) | 1986(2) | 3776(2) | 1094(1) | 47(1) |
| C(2) | 2302(2) | 6223(2) | 933(1) | 41(1) |
| C(3) | 1987(2) | 7618(2) | 609(1) | 41(1) |
| C(4) | 2018(2) | 9758(2) | 1184(1) | 42(1) |
| O(4) | 18(2) | 7140(2) | 1533(1) | 77(1) |
| C(5) | 4134(2) | 9881(2) | 1180(1) | 43(1) |
| C(6) | 412(2) | 8269(3) | 1479(1) | 48(1) |
| C(7) | 4118(2) | 11546(2) | 329(1) | 42(1) |
| C(8) | 3090(2) | 10890(2) | 219(1) | 41(1) |
| C(9) | 1434(2) | 8600(2) | 1108(1) | 40(1) |
| C(10) | 1725(2) | 5009(2) | 763(1) | 45(1) |
| C(11) | 3162(2) | 6145(3) | 1441(1) | 52(1) |

| | | | | |
|---|---|---|---|---|
| C(12) | 2842(2) | 3718(2) | 1605(1) | 43(1) |
| C(13) | 2330(2) | 11377(3) | -277(1) | 51(1) |
| C(14) | 3012(2) | 9726(2) | 745(1) | 40(1) |
| C(15) | 1254(2) | 7438(2) | -68(1) | 47(1) |
| C(16) | 4406(2) | 12678(3) | -65(1) | 56(1) |
| C(17) | 3794(2) | 2344(3) | 2493(1) | 60(1) |
| C(18) | 3436(2) | 4904(2) | 1778(1) | 50(1) |
| O(6) | 291(2) | 7704(3) | -112(1) | 88(1) |
| C(19) | 2606(2) | 12529(3) | -672(1) | 63(1) |
| C(20) | 5807(2) | 11367(3) | 1156(1) | 61(1) |
| C(21) | 3633(3) | 13158(3) | -565(1) | 66(1) |
| C(22) | -941(2) | 9241(4) | 2201(2) | 85(1) |
| C(23) | 1196(3) | 6624(4) | -1236(1) | 81(1) |
| C(24) | 1962(3) | 6164(5) | -1760(2) | 99(1) |

**Table XIII.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **127a** [from (*E*)**-106a**]. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(2) | 6750(1) | 16(1) | 8092(1) | 50(1) |
| N(1) | 5608(2) | -1394(1) | 9798(1) | 56(1) |
| C(1) | 8425(2) | 505(2) | 7393(2) | 46(1) |
| O(1) | 7505(2) | -1480(2) | 9811(1) | 80(1) |
| O(4) | 6084(2) | 1460(1) | 6645(2) | 81(1) |
| C(2) | 7252(2) | 51(2) | 7149(2) | 45(1) |
| C(3) | 7241(2) | -1055(2) | 6802(2) | 51(1) |
| C(4) | 6668(2) | -1611(2) | 7390(2) | 54(1) |
| C(5) | 6556(2) | -1317(2) | 9368(2) | 55(1) |
| C(6) | 6227(2) | -956(2) | 8189(2) | 49(1) |
| C(7) | 4655(2) | -1119(2) | 9054(2) | 54(1) |
| C(8) | 4969(2) | -882(2) | 8079(2) | 51(1) |
| C(9) | 8983(2) | 559(2) | 8436(2) | 57(1) |

| | | | | |
|---|---|---|---|---|
| C(10) | 4179(2) | -607(2) | 7213(2) | 67(1) |
| C(11) | 7789(2) | -1396(2) | 5951(2) | 70(1) |
| C(12) | 6521(2) | 665(2) | 6268(2) | 56(1) |
| C(13) | 10062(2) | 944(2) | 8655(2) | 73(1) |
| C(14) | 8959(2) | 841(2) | 6571(2) | 61(1) |
| O(3) | 6395(2) | 429(2) | 5357(2) | 105(1) |
| C(15) | 10581(2) | 1280(2) | 7843(3) | 77(1) |
| C(16) | 3556(2) | -1058(2) | 9205(2) | 74(1) |
| C(17) | 10042(2) | 1228(2) | 6802(3) | 74(1) |
| C(18) | 5603(3) | -1708(2) | 10902(2) | 79(1) |
| N(2) | 8242(3) | -1644(2) | 5279(2) | 110(1) |
| C(19) | 3070(2) | -546(3) | 7356(3) | 85(1) |
| C(20) | 2777(2) | -760(2) | 8335(3) | 89(1) |
| C(21) | 5367(3) | 2078(3) | 5839(3) | 115(1) |
| C(22) | 4638(4) | 2634(5) | 6285(4) | 196(3) |

**Table XIV.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **127a′** [from (*E*)-**106a**]. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 7782(1) | 12153(2) | 5632(1) | 51(1) |
| O(4) | 7919(1) | 9564(1) | 6781(1) | 36(1) |
| O(2) | 6994(1) | 9877(2) | 4979(1) | 57(1) |
| C(1) | 9464(1) | 6899(2) | 7649(1) | 36(1) |
| O(3) | 8960(1) | 7386(2) | 5746(1) | 59(1) |
| C(2) | 8530(1) | 7147(2) | 7634(1) | 33(1) |
| N(1) | 9703(1) | 6959(2) | 6919(1) | 39(1) |
| C(3) | 6692(1) | 7863(2) | 6237(1) | 36(1) |
| C(4) | 6704(1) | 11761(3) | 7420(1) | 47(1) |
| C(5) | 8969(1) | 7265(2) | 6413(1) | 38(1) |
| C(6) | 8132(1) | 7085(2) | 8281(1) | 41(1) |
| C(7) | 7081(1) | 9849(2) | 6319(1) | 33(1) |

| | | | | |
|---|---|---|---|---|
| C(8) | 9604(1) | 6643(3) | 8956(1) | 52(1) |
| C(9) | 8680(1) | 6828(3) | 8949(1) | 49(1) |
| C(10) | 8137(1) | 7570(2) | 6849(1) | 34(1) |
| C(11) | 7286(1) | 6608(2) | 6531(1) | 37(1) |
| C(12) | 5801(1) | 7514(2) | 5866(1) | 47(1) |
| C(13) | 7273(1) | 10600(2) | 5553(1) | 38(1) |
| C(14) | 10018(1) | 6665(2) | 8308(1) | 46(1) |
| C(15) | 6492(1) | 11245(2) | 6687(1) | 36(1) |
| C(16) | 10623(1) | 6812(3) | 6724(1) | 53(1) |
| C(17) | 5730(1) | 12000(3) | 6279(1) | 51(1) |
| N(2) | 5088(1) | 7286(3) | 5577(1) | 74(1) |
| C(18) | 8000(1) | 13032(3) | 4945(1) | 60(1) |
| C(19) | 5395(2) | 13740(3) | 7347(1) | 68(1) |
| C(20) | 7257(2) | 14288(3) | 4624(1) | 69(1) |
| C(21) | 5183(1) | 13241(3) | 6617(1) | 66(1) |
| C(22) | 6149(2) | 13015(3) | 7748(1) | 63(1) |

**Table XV.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **127a** [from (*Z*)-**106a**]. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(2) | 1751(1) | 9984(1) | 8092(1) | 50(1) |
| C(1) | 3425(1) | 9495(1) | 7394(2) | 46(1) |
| N(1) | 609(1) | 11394(1) | 9799(1) | 57(1) |
| O(1) | 2504(1) | 11479(2) | 9811(1) | 80(1) |
| C(2) | 2251(1) | 9949(1) | 7149(1) | 45(1) |
| O(4) | 1083(2) | 8540(1) | 6643(1) | 81(1) |
| C(3) | 1667(2) | 11612(2) | 7391(2) | 53(1) |
| C(4) | 1224(2) | 10955(1) | 8189(1) | 49(1) |
| C(5) | 2239(2) | 11056(2) | 6804(2) | 51(1) |
| C(6) | 1559(2) | 11317(2) | 9367(2) | 55(1) |
| C(7) | -345(2) | 11120(2) | 9055(2) | 54(1) |

| | | | | |
|---|---|---|---|---|
| C(8) | 3981(2) | 9442(2) | 8437(2) | 58(1) |
| C(9) | -822(2) | 10607(2) | 7214(2) | 67(1) |
| C(10) | -32(2) | 10884(2) | 8078(2) | 52(1) |
| C(11) | 1521(2) | 9333(2) | 6268(2) | 55(1) |
| C(12) | 2790(2) | 11395(2) | 5949(2) | 70(1) |
| C(13) | 3960(2) | 9157(2) | 6572(2) | 61(1) |
| C(14) | 5060(2) | 9056(2) | 8654(2) | 72(1) |
| C(15) | -1444(2) | 11058(2) | 9206(2) | 73(1) |
| C(16) | 5584(2) | 8718(2) | 7846(2) | 77(1) |
| O(3) | 1396(2) | 9571(2) | 5356(1) | 106(1) |
| C(17) | 5042(2) | 8771(2) | 6802(2) | 75(1) |
| C(18) | 601(2) | 11708(2) | 10901(2) | 79(1) |
| N(2) | 3245(3) | 11644(2) | 5279(2) | 110(1) |
| C(19) | -2224(2) | 10759(2) | 8337(3) | 89(1) |
| C(20) | -1931(2) | 10547(2) | 7355(2) | 86(1) |
| C(21) | -361(4) | 7365(5) | 6286(4) | 197(3) |
| C(22) | 368(3) | 7922(3) | 5838(3) | 113(1) |

**Table XVI.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **127a′** [from (*Z*)-**106a**]. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(4) | 7919(1) | 436(2) | 1782(1) | 34(1) |
| O(3) | 7783(1) | -2157(2) | 632(1) | 48(1) |
| O(2) | 6995(1) | 123(2) | -21(1) | 54(1) |
| C(1) | 9463(1) | 3102(2) | 2649(1) | 34(1) |
| O(1) | 8961(1) | 2615(2) | 746(1) | 57(1) |
| C(2) | 8531(1) | 2854(2) | 2634(1) | 32(1) |
| C(3) | 6691(1) | 2138(2) | 1236(1) | 34(1) |
| N(1) | 9704(1) | 3041(2) | 1918(1) | 37(1) |
| C(4) | 8130(1) | 2914(2) | 3280(1) | 39(1) |
| C(5) | 8969(1) | 2736(2) | 1413(1) | 36(1) |

| | | | | |
|---|---|---|---|---|
| C(6) | 6705(1) | -1758(3) | 2421(1) | 45(1) |
| C(7) | 7079(1) | 152(2) | 1319(1) | 32(1) |
| C(8) | 7274(1) | -602(2) | 553(1) | 36(1) |
| C(9) | 8136(1) | 2427(2) | 1848(1) | 32(1) |
| C(10) | 8680(1) | 3170(3) | 3949(1) | 48(1) |
| C(11) | 9605(1) | 3357(3) | 3958(1) | 51(1) |
| C(12) | 7286(1) | 3394(2) | 1531(1) | 35(1) |
| C(13) | 5803(1) | 2488(3) | 867(1) | 45(1) |
| C(14) | 10019(1) | 3337(3) | 3307(1) | 44(1) |
| C(15) | 6493(1) | -1248(2) | 1688(1) | 35(1) |
| C(16) | 10621(1) | 3187(3) | 1723(1) | 50(1) |
| C(17) | 5729(1) | -2003(3) | 1278(1) | 49(1) |
| N(2) | 5088(1) | 2712(3) | 578(1) | 71(1) |
| C(18) | 7256(2) | -4292(4) | -376(1) | 66(1) |
| C(19) | 8001(2) | -3029(3) | -55(1) | 57(1) |
| C(20) | 5183(2) | -3247(3) | 1618(1) | 63(1) |
| C(21) | 5395(2) | -3744(3) | 2348(1) | 66(1) |
| C(22) | 6152(2) | -3018(3) | 2750(1) | 60(1) |

**Table XVII.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **127b**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(2) | 3269(1) | 6110(1) | 971(1) | 46(1) |
| O(1) | 5619(1) | 5197(1) | 1054(1) | 57(1) |
| N(1) | 5223(1) | 3918(2) | 2004(1) | 51(1) |
| C(1) | 4206(2) | 3566(2) | 2206(1) | 48(1) |
| C(2) | 2388(2) | 6421(2) | 171(1) | 46(1) |
| C(3) | 4929(2) | 4694(2) | 1334(1) | 45(1) |
| C(4) | 4044(2) | 7505(2) | -156(1) | 51(1) |
| C(5) | 3185(2) | 4130(2) | 1661(1) | 46(1) |
| C(6) | 2923(2) | 4397(2) | 130(1) | 45(1) |

| | | | | |
|---|---|---|---|---|
| O(5) | 5676(2) | 8343(2) | -438(1) | 78(1) |
| C(7) | 2836(2) | 7433(2) | -265(1) | 51(1) |
| C(8) | 2236(2) | 5254(2) | -330(1) | 46(1) |
| O(4) | 1414(1) | 7447(2) | 993(1) | 91(1) |
| C(9) | 1474(2) | 5164(2) | -1201(1) | 56(1) |
| C(10) | 3540(2) | 4843(2) | 1013(1) | 43(1) |
| C(11) | 2077(2) | 3913(2) | 1728(1) | 59(1) |
| C(12) | 4463(2) | 8365(2) | -590(1) | 60(1) |
| C(13) | 1222(2) | 6765(2) | 330(1) | 57(1) |
| C(14) | 4145(2) | 2786(2) | 2829(1) | 62(1) |
| N(2) | 874(2) | 5101(2) | -1894(1) | 81(1) |
| C(15) | 6453(2) | 3572(2) | 2484(2) | 67(1) |
| O(3) | 271(2) | 6437(3) | -90(2) | 126(1) |
| C(16) | 2006(2) | 3125(2) | 2360(2) | 71(1) |
| C(17) | 2030(2) | 8205(2) | -832(2) | 74(1) |
| C(18) | 3022(2) | 2578(2) | 2893(2) | 72(1) |
| C(19) | 2451(3) | 9044(2) | -1265(2) | 87(1) |
| C(20) | 3657(3) | 9149(2) | -1150(2) | 79(1) |
| C(23) | 6161(3) | 9200(2) | -875(2) | 95(1) |
| C(21) | 387(3) | 7789(3) | 1255(2) | 98(1) |
| C(22) | -126(6) | 8835(5) | 844(4) | 193(2) |

**Table XVIII.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **127b′**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(2) | 8469(1) | 4841(1) | 1500(1) | 37(1) |
| O(4) | 6252(1) | 5801(1) | 853(1) | 50(1) |
| O(3) | 6517(1) | 6266(1) | 2370(1) | 54(1) |
| N(1) | 10507(1) | 6452(1) | 1099(1) | 45(1) |
| C(1) | 7126(1) | 3873(1) | 2120(1) | 36(1) |
| C(2) | 7487(1) | 2993(1) | 1773(1) | 39(1) |

| | | | | |
|---|---|---|---|---|
| O(5) | 7296(1) | 1247(1) | 1384(1) | 61(1) |
| C(3) | 11108(1) | 5496(1) | 1168(1) | 41(1) |
| C(4) | 8536(1) | 5176(1) | 3978(1) | 49(1) |
| C(5) | 8778(1) | 5167(1) | 3097(1) | 38(1) |
| C(6) | 10651(1) | 4793(1) | 1665(1) | 38(1) |
| O(1) | 8949(1) | 7106(1) | 1559(1) | 64(1) |
| C(7) | 6789(1) | 5754(1) | 1803(1) | 39(1) |
| C(8) | 7778(1) | 4897(1) | 2123(1) | 35(1) |
| C(9) | 6887(1) | 2060(1) | 1767(1) | 43(1) |
| C(10) | 9844(1) | 5379(1) | 2994(1) | 42(1) |
| C(11) | 6164(1) | 3820(1) | 2478(1) | 49(1) |
| C(12) | 5932(1) | 2008(1) | 2123(1) | 50(1) |
| C(13) | 9671(1) | 5319(1) | 1946(1) | 38(1) |
| C(14) | 9640(1) | 6419(1) | 1519(1) | 43(1) |
| C(15) | 12011(1) | 5223(1) | 811(1) | 57(1) |
| C(16) | 5583(1) | 2891(1) | 2472(1) | 56(1) |
| C(17) | 11106(1) | 3805(1) | 1823(1) | 49(1) |
| N(2) | 8334(2) | 5167(1) | 4671(1) | 78(1) |
| C(18) | 12020(2) | 3524(1) | 1461(1) | 63(1) |
| C(19) | 10746(2) | 7358(1) | 620(1) | 64(1) |
| C(20) | 12452(2) | 4224(2) | 965(1) | 67(1) |
| C(21) | 5284(2) | 6586(1) | 473(1) | 65(1) |
| C(22) | 6645(2) | 294(1) | 1268(1) | 63(1) |
| C(23) | 5831(2) | 7625(1) | 497(2) | 79(1) |

# LIST OF PUBLICATIONS

1. Synthesis of substituted maleimide derivatives using the Baylis-Hillman adducts

   Basavaiah, D., Lenin, D.V., **Veeraraghavaiah, G.** *Current Sci.* **2011**, *101*, 888.

2. The Baylis-Hillman reaction: A novel concept for creativity in chemistry

   Basavaiah, D., **Veeraraghavaiah, G.** *Chem. Soc.Rev.* **2012**, *41*, 68.

3. Baylis-Hillman carbonates in organic synthesis: A convenient one-pot strategy for nitrone-spiro-oxindole frameworks

   Basavaiah, D., Badsara, S.S., **Veeraraghavaiah, G.** *Tetrahedron* **2013**, *69*, 7995.

4. Ketones as electrophiles in two component Baylis-Hillman reaction: A facile one-pot synthesis of substituted indolizines

   Basavaiah, D., **Veeraraghavaiah, G.**, Badsara, S.S. *Org. Biomol. Chem.* **2014**, *12*, 1551.

5. The Baylis-Hillman acetates as a source of ambiphilic molecules: A simple synthesis of 1,3-thiazinane-2-thione frameworks

   Basavaiah, D., Pal, S., **Veeraraghavaiah, G.**, Bharadwaj, K.C. *Tetrahedron* **2015**, *71*, 4659.

6. A facile and stereoselective synthesis of tetrasubstituted alkenes from Baylis-Hillman alcohols

   Basavaiah, D., **Veeraraghavaiah, G.**, Pal, S., Naganaboina, R. T. (to be communicated)

7. Baylis-Hillman bromides containing tetrasubstituted alkene motif as a source of dipoles in [3+2] annulation strategy: Stereoselective synthesis of dihydrofuran-fused-spirooxindoles

   Basavaiah, D., **Veeraraghavaiah, G.** (to be communicated)

## Book Chapter

"ASYMMETRIC MORITA-BAYLIS-HILLMAN REACTION"-The chapter in Organic Reactions

Basavaiah, D., **Veeraraghavaiah, G.**, Ciganek, E. (will be published shortly)

## Poster and Oral Presentations

1. Synthesis of substituted maleimide derivatives using the Baylis-Hillman adducts

   Basavaiah, D., Lenin, D.V., **Veeraraghavaiah, G.**

   Poster presentation at *ChemFest* **2012**

2. Ketones as electrophiles in two component Baylis-Hillman reaction: A facile one-pot synthesis of substituted indolizines

   Basavaiah, D., **Veeraraghavaiah, G.**, Badsara, S.S.

   Poster cum Oral presentation at *ChemFest* **2014**

3. Two component Baylis-Hillman reaction using ketones as electrophiles: A convenient synthesis of substituted indolizines

   Basavaiah, D., **Veeraraghavaiah, G.**, Badsara, S.S.

   Poster presentation at *Indo-Taiwan Recent Trends in Chemical Sciences (RTCS)*-**2014**

4. Baylis-Hillman adducts in organic synthesis: One-pot synthesis of nitrone-spiro-oxindole frameworks

   Basavaiah, D., Badsara, S.S., **Veeraraghavaiah, G.**

   Poster presentation at *ChemFest* **2015**

SYNOPSIS OF THE THESIS ENTITLED

**DEVELOPMENT OF A TWO COMPONENT BAYLIS–HILLMAN REACTION AND STEREOSELECTIVE SYNTHESIS OF TETRASUBSTITUTED ALKENES AND DIHYDROFURAN-FUSED-SPIROOXINDOLES USING THE BAYLIS–HILLMAN ADDUCTS**

TO BE SUBMITTED FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY**

BY

**VEERARAGHAVAIAH GORRE**

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**INDIA**

**OCTOBER 2015**

In a broad sense, the chemical synthesis is nothing but a process involving bond formation and/or bond cleavage. Organic synthesis essentially deals with construction of C—C bond, C—X (X = H, heteroatom) bonds and/or their cleavage. Among these, carbon–carbon bond formation is the most fundamental process in organic chemistry to create molecular complexity and diversity. Baylis-Hillman reaction[1] is one such three component atom economy C—C bond forming reaction involving the coupling of α-position of activated alkene with electrophile in the presence of a catalyst to provide diverse classes of densely functionalized molecules. The Baylis-Hillman adducts, containing a minimum of three functional groups in close proximity, have been employed successfully in various organic transformation methodologies and also in the synthesis of carbocyclic & heterocyclic molecules of medicinal importance.[1] Our research group has been working on this fascinating reaction for the last three decades on various aspects of this reaction and contributed significantly for the growth of the reaction.[1b]

This thesis deals with the development of two component Baylis-Hillman reaction and synthesis of stereoselective tetrasubstituted alkenes (Baylis-Hillman bromides) and their application to [3+2]-annulation strategies/cycloaddition reaction 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 important developments of BH-reaction with respect to all the three essential components along with its asymmetric version and also describes briefly the applications of the Baylis-Hillman bromides in organic synthesis.

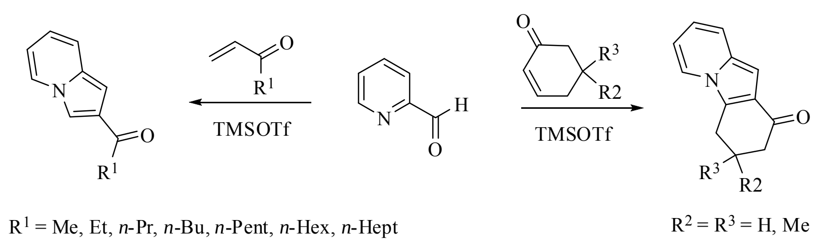
The second chapter deals with the objectives, results & discussion. Although BH reaction have seen significant development in many directions, it is surprising to note that two component (containing electrophile and reaction initiation site components) BH reaction, yet another aspect of this reaction, was not received adequate attention during all these years. Even though BH bromides derived from aldehydes as electrophiles have received considerable attention from chemists, the bromides of the BH adducts obtained from α–keto esters, as electrophiles, did not receive any attention from chemists. We have therefore, in continuation of our ongoing research program on BH reaction, undertaken this thesis work with the following key objectives.

1) To develop a facile two component Baylis-Hillman reaction using substrates containing less reactive components, ketones, as electrophile component and nitrogen of pyridine/isoquinoline as a promoter for coupling with alkyl vinyl ketones as activated alkene component. This process would, in principle, result in the development of simple protocol for synthesis of indolizine derivatives.
2) To develop a convenient and facile protocol, from BH adducts derived from α–keto esters via coupling with alkyl acrylates/acrylonitrile, for obtaining stereodefined tetrasubstituted alkenes containing allylbromide functionality.

3) To study the possible applications of the above mentioned tetrasubstituted alkenes (containing allyl bromide functionality) as a source of dipoles for reaction with isatins as dipolarophiles with a view to develop a facile [3+2] annulation strategy for stereoselective synthesis of dihydrofuran-fused-spirooxindoles containing ester group or nitrile functionality.

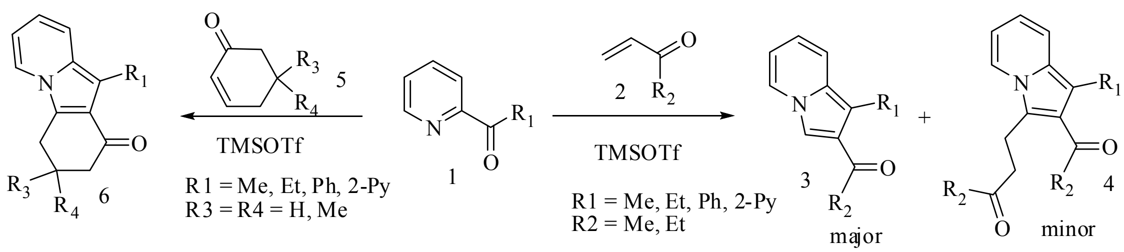
## Ketones as Electrophiles in Two Component Baylis-Hillman Reaction: A Facile One-Pot Synthesis of Substituted Indolizines

Several years ago our research group has reported for the first time, that the coupling of pyridine-2-carboxaldehyde with alkyl vinyl ketones under the influence of TMSOTf, provided a facile methodology for obtaining indolizine derivatives.[2] In this strategy, the pyridine nitrogen acts as initiator site and induces the reaction while the aldehyde group acts as an electrophile (Scheme 1).[2]

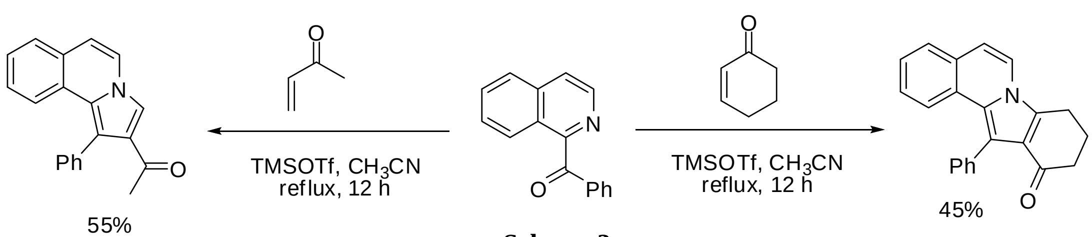



**Scheme 1**

At that time our research group felt that ketones may not be suitable electrophile components in the above strategy as it was generally understood that ketones are less reactive electrophiles in BH reaction. However recently we felt that this is not that absurd to examine the potential of ketones as electrophiles in these reactions on the assumption that intramlecular reactions are normally faster than the corresponding intermolecular reactions. Accordingly we have developed a facile protocol for coupling of 2-alkanoyl(aroyl) pyridines with representative alkyl vinyl ketones (both acyclic and cyclic) under the influence of TMSOTf to provide indoziline derivatives. This strategy clearly demonstrates the applications of certain ketones as suitable electrophiles in BH reaction and also opens up the ground for design of appropriate substrates for two component Baylis-Hillman reactions (Scheme 2 & 3).



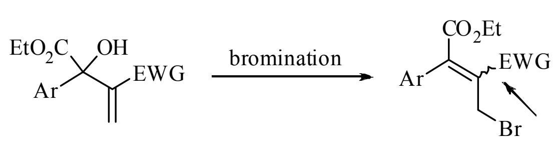

**Scheme 2**




**Scheme 3**

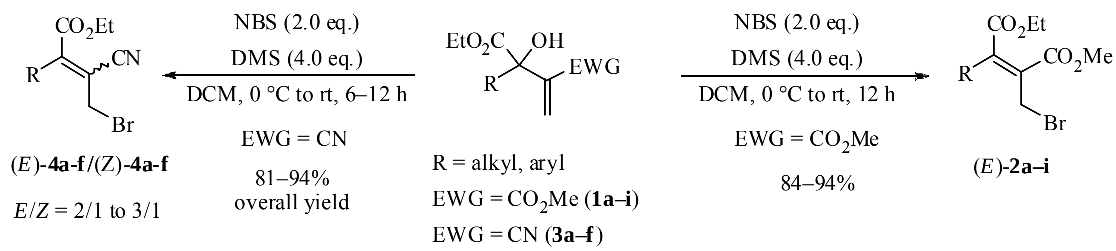
## A Facile and Stereoselective Synthesis of Tetrasubstituted Alkenes from Baylis-Hillman Alcohols

Tetrasubstituted alkene[3] framework with defined stereochemistry occupies a special place in organic and medicinal chemistry because of the presence of such moiety in various biologically active molecules [tamoxifen, panomifene], natural products. Due to their congested nature and the challenges involved in their synthesis, development of facile and convenient strategies for obtaining tetrasubstituted alkenes with defined stereochemistry has been and continuous to be a facinating and attractive problem in synthetic chemistry.[3] Based on the importance of synthesis of tetrasubstituted alkenes with defined stereochemistry and also based on the bromination of BH alcohols derived from aldehydes[1] it occured to us that the BH alcohols, obtained from α–keto esters as electrophiles and acrylates/acrylonitrile as activated alkenes should, in principle, provide tetrasubstituted alkenes having allyl bromide fuctionality. If it is so, what could be its stereochemistry (Eq. 1).



(Eq. 1)

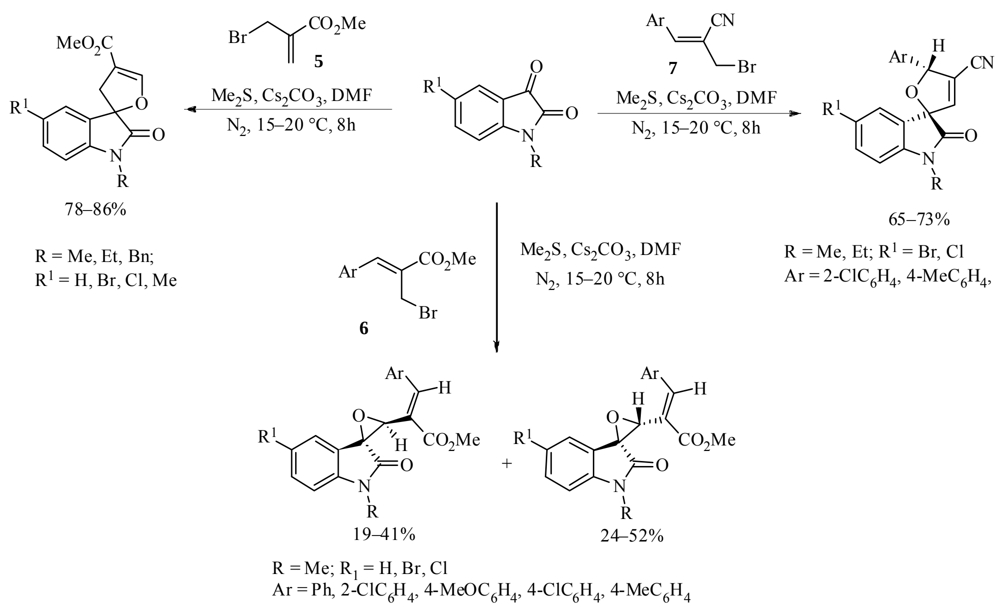
Our efforts in this direction resulted in developing a facile methodology for stereoselective synthesis of tetrasubstituted alkenes via the treatment of Baylis-Hillman alcohols obtained from the reaction of methyl acrylate and α-ketoseters with NBS/DMS system. Resultant tetrasubstituted alkenes were obtained with exclusively (*E*)-stereochemistry. Similar treatment of Baylis-Hillman alcohols obtained via the reaction of acrylonitile and α-ketoseters in the presence of NBS/DMS as reagent system provided the resulting allyl bromides as a separable (2:1) mixture of (*E*/*Z*)-isomers (Scheme 4). Appropriate reaction mechanisms for formation of tetrasubstituted alkenes with exclusively (*E*)-stereochemistry (BH alcohols derived from α-keto esters and methyl acrylate) in ester case and *E*/*Z*-isomeric mixture (BH alcohols derived from α-keto esters and acrylonitrile) in nitrile case were provided.




**Scheme 4**

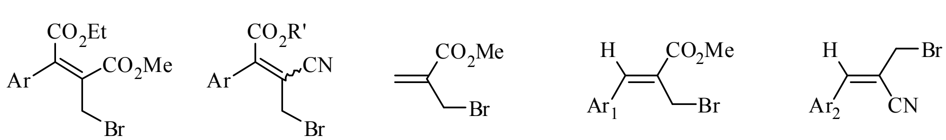
## Application of Tetrasubstituted Alkenes (allyl bromides) obtained from BH-adducts in [3+2] Annulation Strategy: Stereoselective Synthesis of Dihydrofuran-fused-spirooxindoles

The 1,3-dipolar cycloaddition reactions or [3+2] annulation strategies are fundamentally important methods for building five membered ring frameworks. Recently, our research group has reported a facile steric factors directed synthesis of spiroepoxy and spirodihydrofuran oxindoles via [3+2] cycloaddition reaction of BH bromides **5**–**7** (as 1,3-dipoles) and isatins (as dipolarophiles) as shown in Scheme 5.[4]

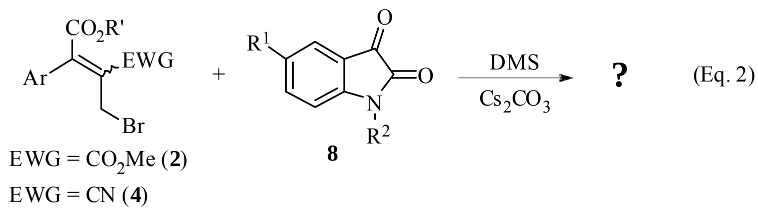



**Scheme 5**

This study clearly demonstrated the influence of steric factors arising from three BH bromides **5**, **6**, and **7** in [3+2] annulation reactions with isatins as dipolarophiles. This study also puts before us a big question, that is, what would be the possible application of tetrasubstituted allyl bromides (**2** & **4**) as dipoles and isatin derivatives as dipolarophiles in [3+2] annulation reactions (Eq. 2).

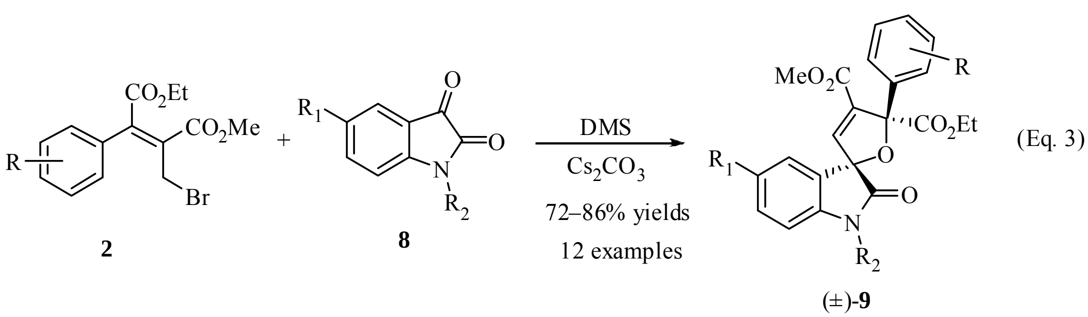


**2** **(*E*/*Z*)-4** **5** **(*Z*)-6** **(*E*)-7**



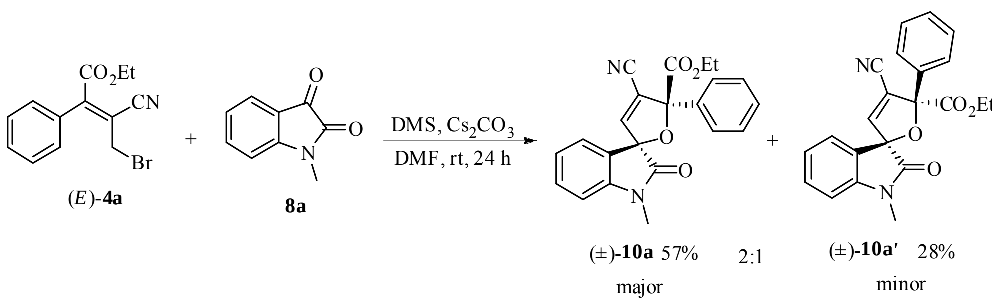

**i) Application of tetrasubstituted alkenes of ester derivative as a source of dipole for [3+2] annulation with isatin derivatives**

Accordingly we have undertaken the study of [3+2] annulation strategy between the diploes generated from BH bromides [tetrasubstituted alkenes described in the previous objective of this section] and isatin derivatives as dipolarophiles. Accordingly we have performed the reaction between various substituted isatins **8** and different BH bromides **2**, the resulting dihydrofuran-fused-spirooxindoles **9** were obtained in high diastereoselectivity (having phenyl group of isatin and aryl group of dipole anti to each other) 72–86% yields (Eq. 3).



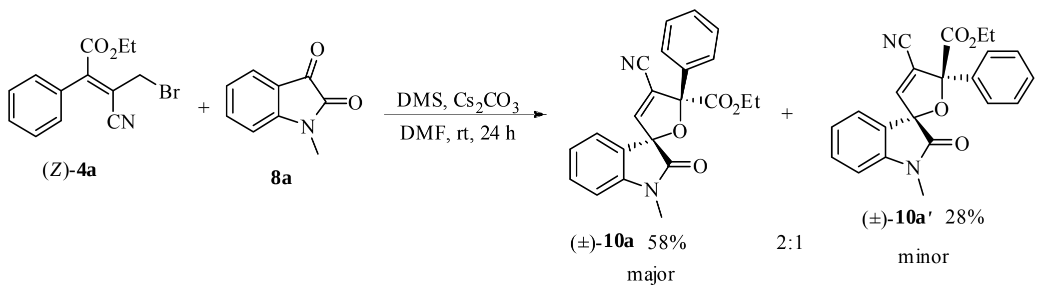
### ii) Application of (*E*) and (*Z*) tetrasubstituted alkenes of nitrile derivative as a source of dipoles for [3+2] annulation with isatin derivatives

After developing stereoselective synthesis of spirooxindole fused dihydrofuran frameworks from the tetrasubstituted alkene containing allyl bromides **2**, we have directed our attention to examine the application of tetrasubstituted alkene **4** containing nitrile functionality in a similar [3+2] annulation reaction with isatin derivatives **8**. Accordingly we have first selected (*E*)-ethyl 4-bromo-3-cyano-2-phenylbut-2-enoate (**4a**) as a source of 1,3-dipole and *N*-methylisatin (**8a**) as a dipolarophile (Eq. 4). The resulting dihydrofuran-fused-spirooxindoles were obtained as a seperable mixture of diastereomers in 2:1 ratio.



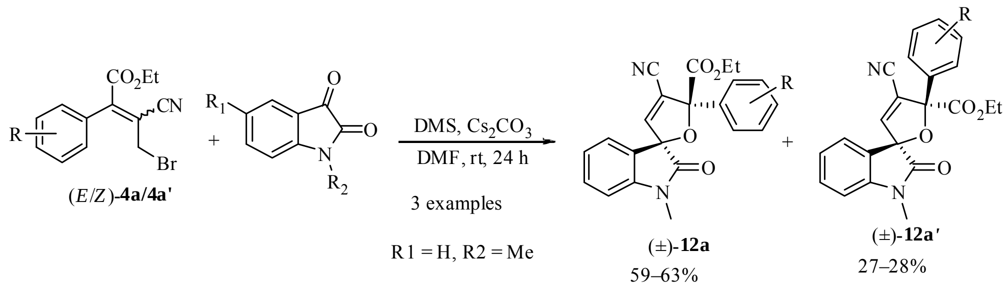

(Eq. 4)

Then we have extended the same strategy to allyl bromide (*Z*)-**4a** with a view to understand the stereochemical course of the reaction (Eq. 5). This case also the resulting dihydrofuran-fused-spirooxindoles were obtained as a seperable mixture of diastereomers in 2:1 ratio.




(Eq. 5)

Thus both (*E*)- and (*Z*)-allyl bromides containing tetrasubstituted alkene motif provided the same products in almost same ratio. Therefore we have performed the reaction of (*E*/*Z*)-mixture of allyl bromides (*E*)-**4a**/(*Z*)-**4a** (without seperation) to a similar [3+2]-annulation strategy with *N*-methylisatin (**8a**) (Eq. 6). As expected it provided as a mixture of syn and anti (**10a** and **10a′**) (2:1) which were seperated by column chromatography and analysed by IR, $^{1}$H NMR, $^{13}$C NMR and HRMS spectral analysis. This would mean that both the (*E*)- and (*Z*)- isomeric bromides involve the same reaction pathway and in both cases the reaction is proceeding through the same reactive intermediate/transition state. To understand the generality of this observation we have subsequently subjected two more ally bromides (as a mixture of *E*/*Z*) to [3+2] annulation strategy with *N*-methylisatin. In both the cases the products were obtained as a seperable mixture of diastereomers. A plausible mechanism has been provided for understanding of the stereochemical course of the reaction.




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

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