LESS REACTIVE ACRYLAMIDES AS ACTIVATED ALKENES AND KETONES AS ELECTROPHILES IN INTRAMOLECULAR BAYLIS-HILLMAN REACTION

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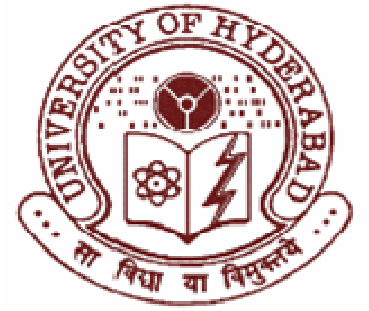
A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

GUDDETI CHANDRASHEKAR REDDY



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TO

BELOVED FAMILY MEMBERS

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.

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CERTIFICATE

Certified that the work embodied in this thesis entitled "**Less Reactive Acrylamides as Activated Alkenes and Ketones as Electrophiles in Intramolecular Baylis-Hillman Reaction**" has been carried out by **Mr. Guddeti Chandrashekar Reddy** under my supervision and the same has not been submitted elsewhere for a degree.

Professor D. BASAVAIAH
(THESIS SUPERVISOR)

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Chandrashekar Reddy

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
*i*Bu	*iso*-butyl
*n*Bu	*n*-butyl
*t*Bu	*tert*-butyl
Bz	benzoyl
Cat.	catalyst
Cbz	benzyloxycarbonyl
CDI	1,1'-CarbonylCiimidazole
C.M.	complex mixture
Conc.	concentrated
Cond.	condition
Cp	cyclopentadienyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

de	diastereomeric excesses
DMAP	dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EC	electrocyclization
ee	enantiomeric excesses
Eq.	equation
eq./equiv.	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
GLC	gas liquid chromatography
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
β-ICD	β-Isocupreidine
Me	methyl
Mes	mesityl
MOM	methoxymethyl
Mp	melting point
N. R	no reaction
ORTEP	Oak Ridge Thermal Ellipsoid Plot

Ph	phenyl
PMB	*p*-methoxybenzyl
Pr	propyl
*c*Pr	*cyclo*-propyl
*i*Pr	*iso*-propyl
*n*Pr	*n*-propyl
RRE	rev-responsive element
r.t.	room temperature
TBAB	tetrabutylammonium bromide
TBDMS/TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSOTf	trimethylsilyltrifluoromethanesulfonate
*p*Tol	*p*-tolyl
Trs	2,4,6-triisopropylbenzenesulfonyl
Ts	*p*-toluenesulfonyl

CONTENTS

ABSTRACT

The Baylis-Hillman (BH) reaction is an emerging continent in the globe of organic chemistry providing diverse classes of proximal densely functionalized molecules possessing high synthetic potential. The Baylis-Hillman (B-H) reaction involves three components 1) activated alkene 2) electrophile 3) catalyst. It involves an atom-economical construction of carbon-carbon bonds via coupling of activated alkenes with electrophiles under the influence of an appropriate catalyst. Although variety of reactive activated alkenes such as vinyl ketones, acrylates and acrylonitriles *etc.* have been extensively used, less reactive activated alkenes such as acrylamides, vinyl sulfoxides and vinyl sulfones have rarely been used in the B-H reactions. Similarly a number of reactive electrophiles such as aldehydes, α-keto esters, α-keto amides, α-diketones and α-fluoro ketones *etc.* are routinely used in coupling with various activated alkenes. However there are not many reports on the utility of normal ketones in the B-H reactions because of their inferior reactivity profile particularly in this reaction. Intramolecular Baylis-Hillman (IBH) reaction is a growing branch of Baylis-Hillman chemistry that has attracted the attention of synthetic and medicinal chemists because it produces various carbocyclic and heterocyclic compounds of different ring sizes.

This thesis deals with studies on the application of less reactive acrylamides as activated alkenes and ketones as electrophiles in intramolecular Baylis-Hillman 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 intramolecular reactions, Baylis-Hillman reaction, its intramolecular version and their applications in organic synthesis.

The second chapter deals with the objectives, results & discussion. The following are the objectives:

1) To design and synthesize substrates containing less reactive acrylamides as activated alkene components and aldehydes as electrophile components and to develop a facile protocol for their intramolecular coupling reactions.
2) To design and synthesize substrates containing less reactive acrylamides as activated alkene and ketones as electrophile components so as to perform their intramolecular cyclization.
3) To design and synthesize chiral (racemic) substrates containing less reactive acrylamide and ketone as activated alkene and electrophile components respectively and examine their potential for diastereoselective IBH-reaction

Acrylamide moiety as an activated alkene component in intramolecular Baylis-Hillman reaction: a facile synthesis of functionalized α-methylene lactam and spirolactam frameworks

Due to their less reactivity profile, acrylamides have not been well explored in the Baylis-Hillman reaction or its intramolecular molecular version. Therefore we have directed our efforts to design a substrate containing acrylamide as a activated alkene and aldehyde as a electrophile component with view to perform intramolecular cyclization reaction using appropriate catalyst. Accordingly we have synthesized substrates [N-(3-oxopropyl)-N-arylacrylamides (**72a-e**) and N-(2-oxoethyl)-N-arylacrylamides (**73a-g**)] (Schemes 51-54). We have developed a simple procedure for intramolecular Baylis-Hillman reaction of acrylamide-aldehyde substrates [(**72a-e** and (**73a-g**)]) under the influence of DABCO in *t*BuOH to provide the corresponding α-

methylene-δ-lactam (**74a-e**) and α-methylene-γ-lactam derivatives (**75a-g**) in good yields as shown in the Tables 2 and 3 respectively.

Next we have extended to this strategy to the acrylamide-aldehydes (**94a, 94b**, **100a** and **100b**) [prepared following the reaction sequence as shown in the Schemes 55 and 56 respectively] in order to obtain the corresponding IBH-products, spirolactam derivatives (**95a, 95b**, **101a** and **101b**), in good yields (Table 6).

Less reactive ketones as electrophiles and acrylamides as activated alkenes in intramolecular Baylis-Hillman reaction: facile synthesis of functionalized γ-lactam frameworks with tertiary alcoholic functionality

From the above intramolecular Baylis-Hillman reactions it is quite clear that formation of 5-membered lactams (**75a-g**) from acrylamide-aldehydes (**73a-g**) is faster than that of 6-membered lactams (**74a-e**) from acrylamide-aldehydes (**72a-e**). Therefore it occurred to us that the acrylamide-ketone (aromatic) substrates [N-(2-oxo-2-arylethyl)-N-arylacrylamides (**106a-j**) containing ketones as electrophiles and acrylamides as activated alkene components may be suitable for intramolecular Baylis-Hillman reactions in order to obtaining γ-lactam frameworks (**108a-j**) with tertiary alcoholic functionality. Accordingly we have prepared the representative substrates (**106a-j**) following reaction sequence as shown in the Schemes 59 and 60.

Subsequent intramolecular Baylis-Hillman reactions of acrylamide-ketones (**106a-j**) using DABCO as a promoter in dioxane-water solvent (1:1) system provided α-methylene-γ-lactam derivatives (**108a-j**) containing tertiary alcoholic functionality as described in Table 9.

Next we have extended this strategy to the acrylamide-ketone (aliphatic) substrates N-(2-oxopropyl)-N-arylacrylamides (**109a-c**). Accordingly we have prepared the representative substrates (**109a-c**) following reaction sequence as shown in the Schemes 61 and 62 respectively. We have then subjected N-(2-oxopropyl)-N-arylacrylamides (**109a-c**) to intramolecular Baylis-Hillman reaction in the presence of DABCO which provided the required IBH adducts, α-methylene-γ-lactam derivatives (**111a-c**) in good yields (Eq. 54 and 55).

Highly diastereoselective intramolecular Baylis-Hillman reaction of acrylamide-α-substituted ketones

After achieving reasonable success in the intramolecular Baylis-Hillman reaction using less reactive acrylamide-ketone substrates (**106a-j**) and (**109a-c**), we have focused our attention towards acrylamide-α-substituted ketones (**127a-i**) containing a chiral centre (racemic) with a view to examine the possibility of achieving diastereoselectivity in intramolecular Baylis-Hillman reaction. Accordingly we have synthesized the required acrylamide-α-substituted ketones (**127a-i**) following the reaction sequence as described in the Schemes 67-71 respectively.

Subsequent treatment of compounds **127a-i** with DABCO gave the resulting IBH adducts (**128a-i**) with high *syn*-diastereoselectivities (Eq. 58-62). We have also proposed appropriate mechanism for high diastereoselectivity in this reaction (Scheme 72).

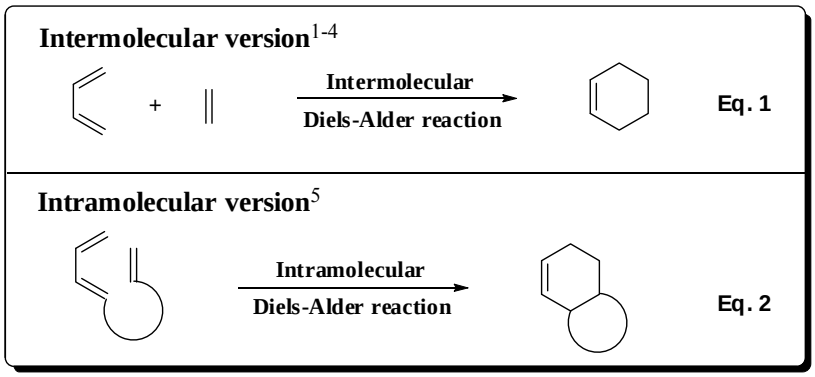
The third chapter provides detailed experimental procedures, physical constants like melting point, IR, ^{1}H & ^{13}C NMR, mass (LC-MS) spectral data, HPLC charts and HRMS spectral data.

INTRODUCTION

In chemical synthesis both intermolecular, intramolecular reactions are of fundamental importance.[1-4] In intermolecular reactions, the reaction occurs between the reaction site of one molecule and the reaction site of another molecule. But in intramolecular reactions, the reaction happens between two or more sites within the same molecule. Several intermolecular reactions, [1-4] and the corresponding intramolecular versions [5-10] have been discovered and their applications have been well documented in the literature. Intramolecular reactions can, in principle, provide cyclic compounds (or) acyclic compounds depending on the nature of the substrate and reaction performed. Since this thesis deals with intramolecular Baylis-Hillman reaction this is appropriate to present pictorially representative examples of well known intramolecular reactions from the literature. Accordingly this section presents some such examples that provide cyclic and also acyclic molecules from the literature.

Intramolecular reactions providing cyclic compounds

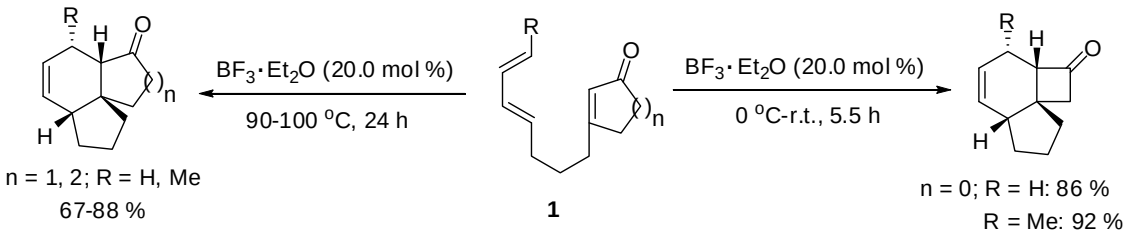
Diels-Alder reaction



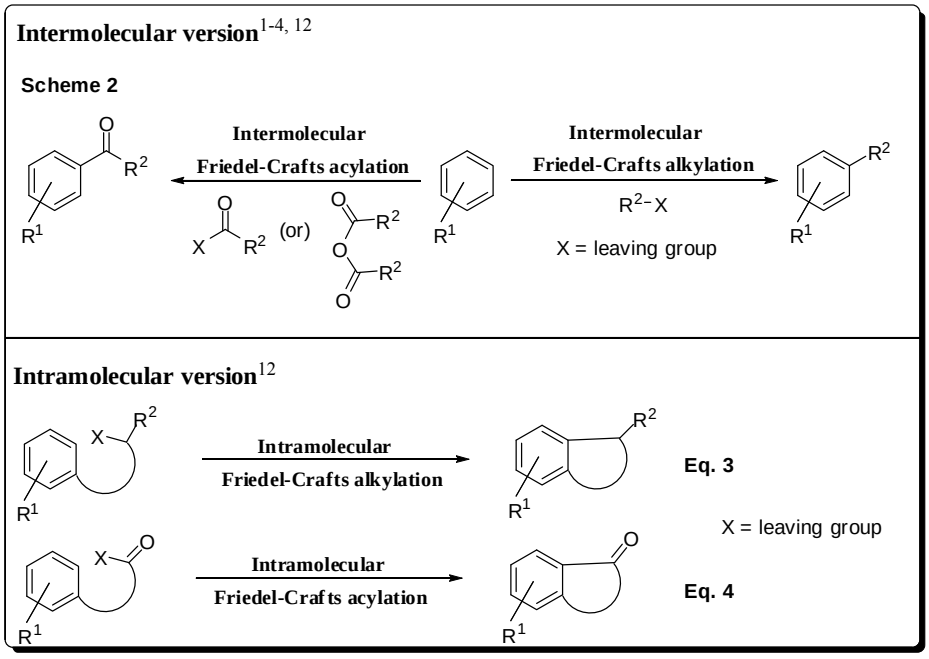
Danishefsky and co-workers[11] have reported an interesting stereoselective intramolecular Diels-Alder reaction of substrates (**1**) containing diene and dienophile

components under the influence of Lewis acid to provide synthetically useful tricyclic framework in good yields and high diastereoselectivities (Scheme 1).

Scheme 1

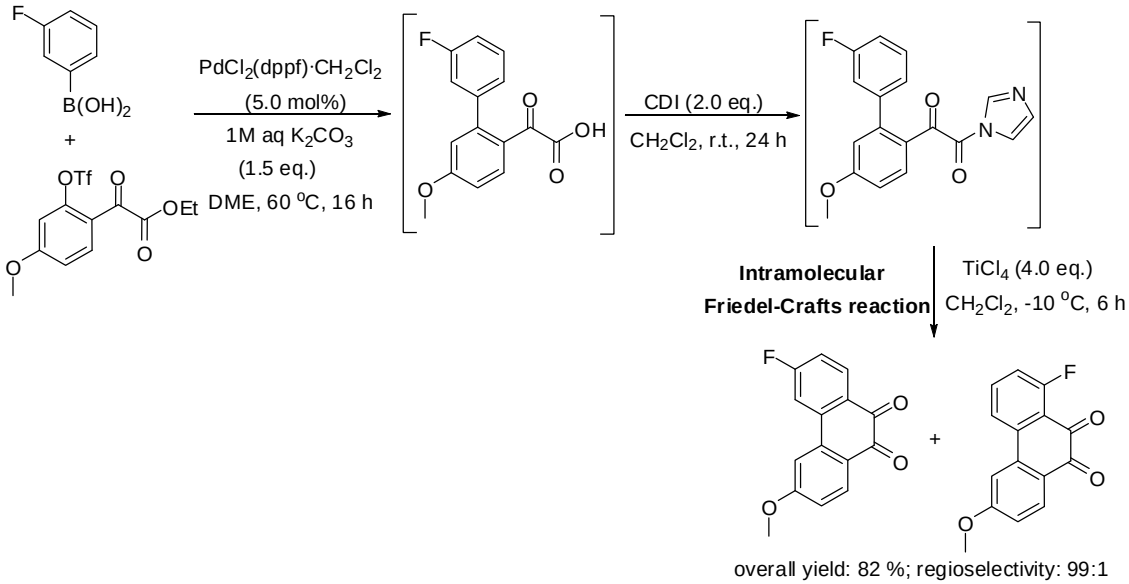


Friedel-Crafts reactions

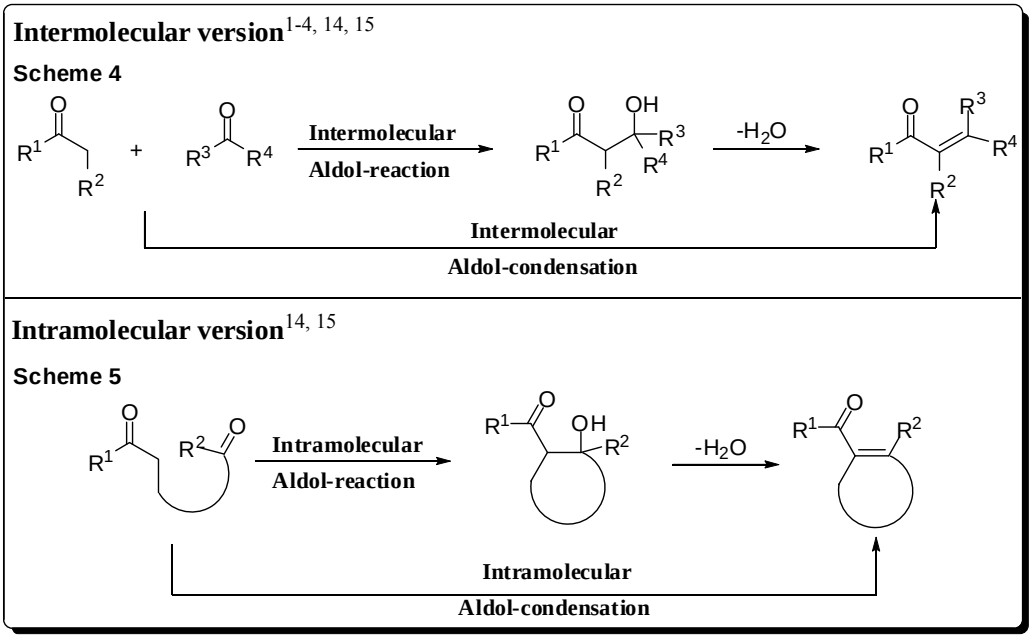


Yoshikawa and co-workers[13] have successfully utilized intramolecular Friedel-Crafts reaction as the key step in the synthesis of phenanthrene derivatives in good yields and excellent regioselectivities. One such example is shown in Scheme 3.

Scheme 3

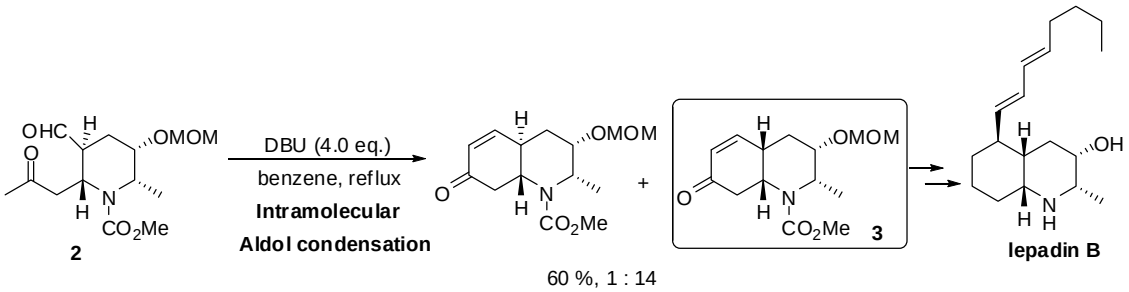


Aldol reaction

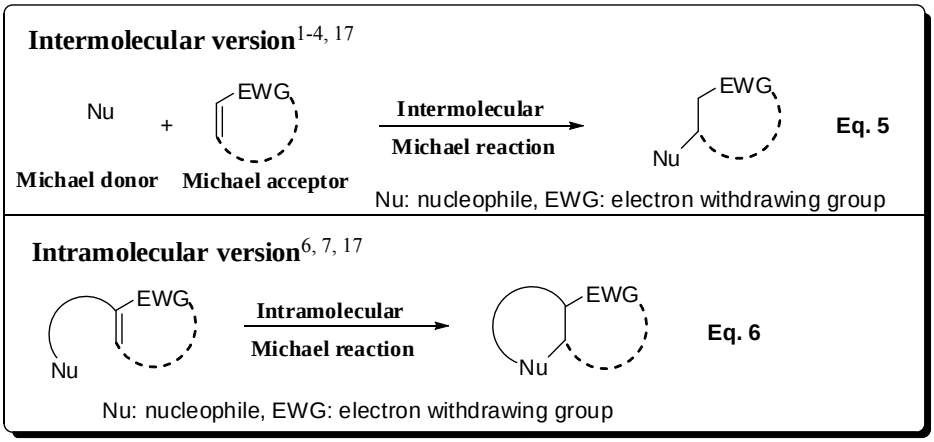


Toyooka, Nemoto and co-workers[16] have meticulously utilized intramolecular aldol reaction of substrate (**2**) for obtaining bicyclic framework (**3**) an important intermediate required in the synthesis of lepadin B (marine alkaloid) as shown in Scheme 6.

Scheme 6

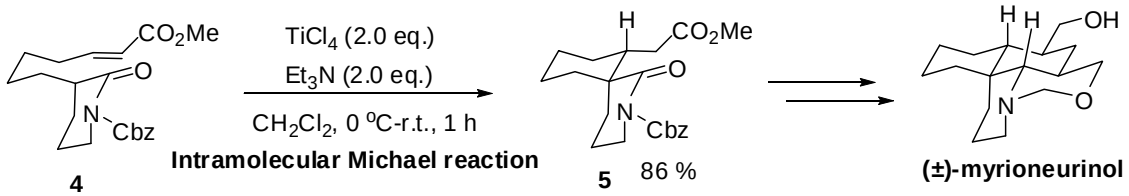


Michael reaction



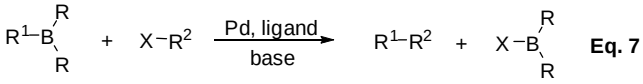
Weinreb et al.[18] successfully employed $TiCl_4/Et_3N$ mediated intramolecular Michael reaction of the substrate (**4**) to obtain the key spiro compound (**5**) during the work on synthesis of (±)-myrioneurinol (antimalarial myrioneuron alkaloid) as shown in Scheme 7.

Scheme 7



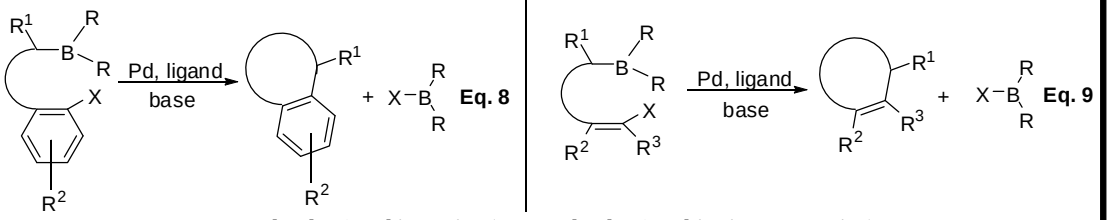
Suzuki reaction (Suzuki-Miyaura reaction)

Intermolecular version[4, 19]



Intermolecular Suzuki reaction (Intermolecular Suzuki-Miyaura reaction)

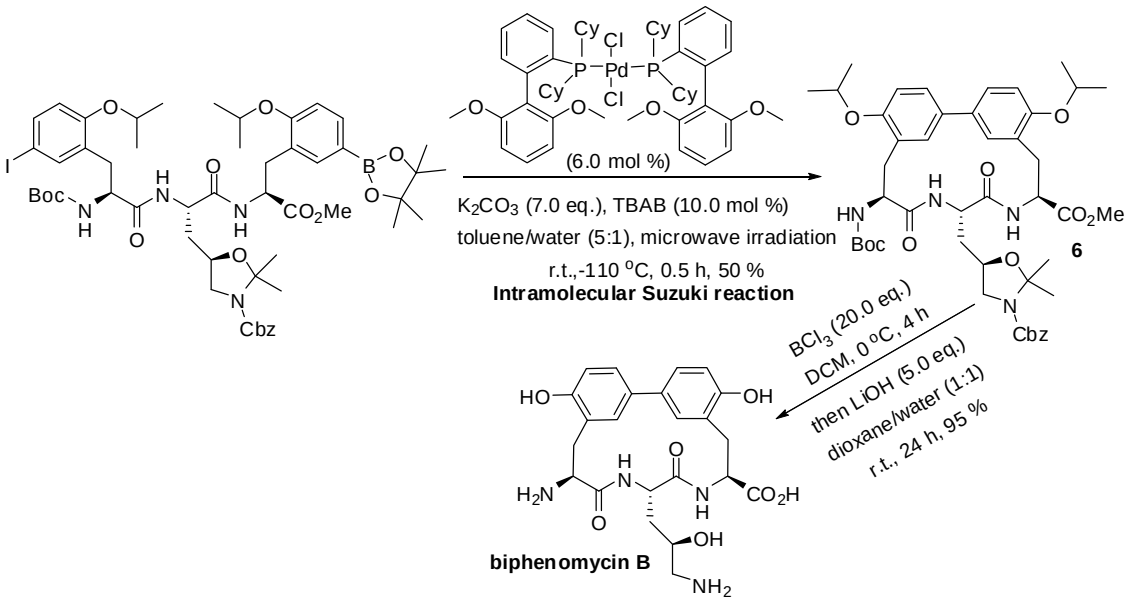
Intramolecular version[8]



Intramolecular Suzuki reaction (Intramolecular Suzuki-Miyaura reaction)

Intramolecular Suzuki reaction has been employed to obtain the key biaryl compound (**6**) containing 15-membered ring required for the synthesis of natural product biphenomycin B by Lépine and Zhu[20] according to reaction sequence presented in Scheme 8.

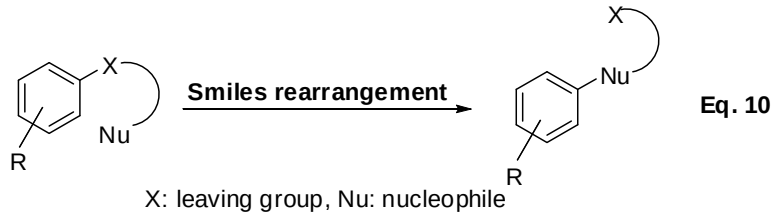
Scheme 8



Intramolecular reactions providing acyclic compounds

It is important to note that certain intramolecular reactions do not provide cyclic compounds, but give only acyclic compounds. Smiles rearrangement, Cope rearrangement and Claisen rearrangement *etc*. represent some such examples. It should be pointed out that these reactions do not have any intermolecular version by virtue of the nature of the reactions.

Smiles rearrangement[1-4, 21]

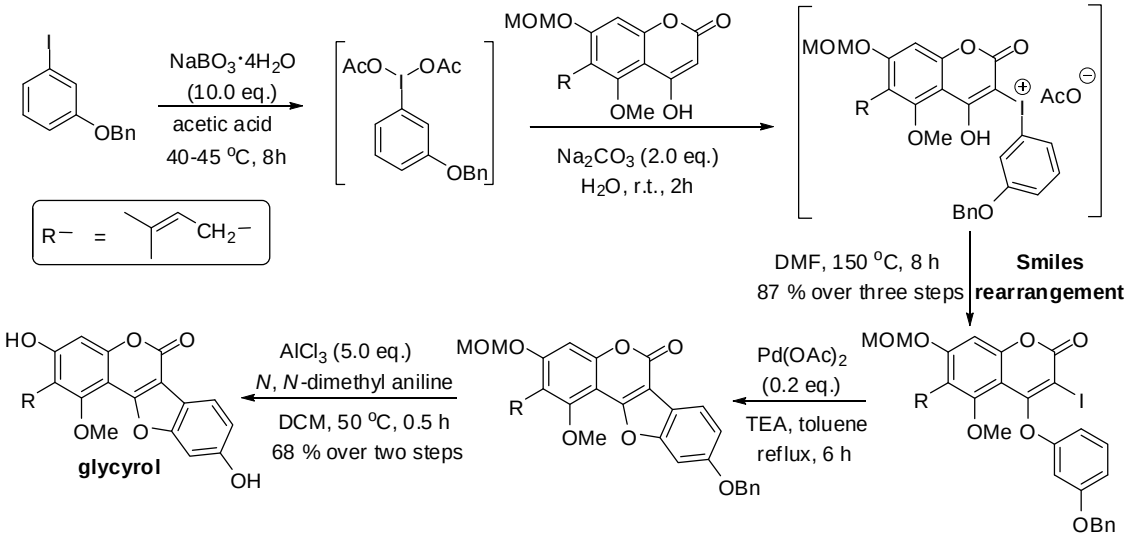


Eq. 10

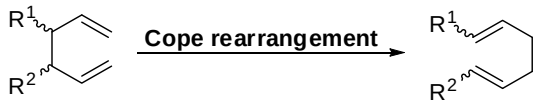
X: leaving group, Nu: nucleophile

Smiles rearrangement has been used as the key reaction by Kim and co-workers[22] during the work on the synthesis of glycyrol (isolated from glycyrrhizae radix) as described in Scheme 9.

Scheme 9



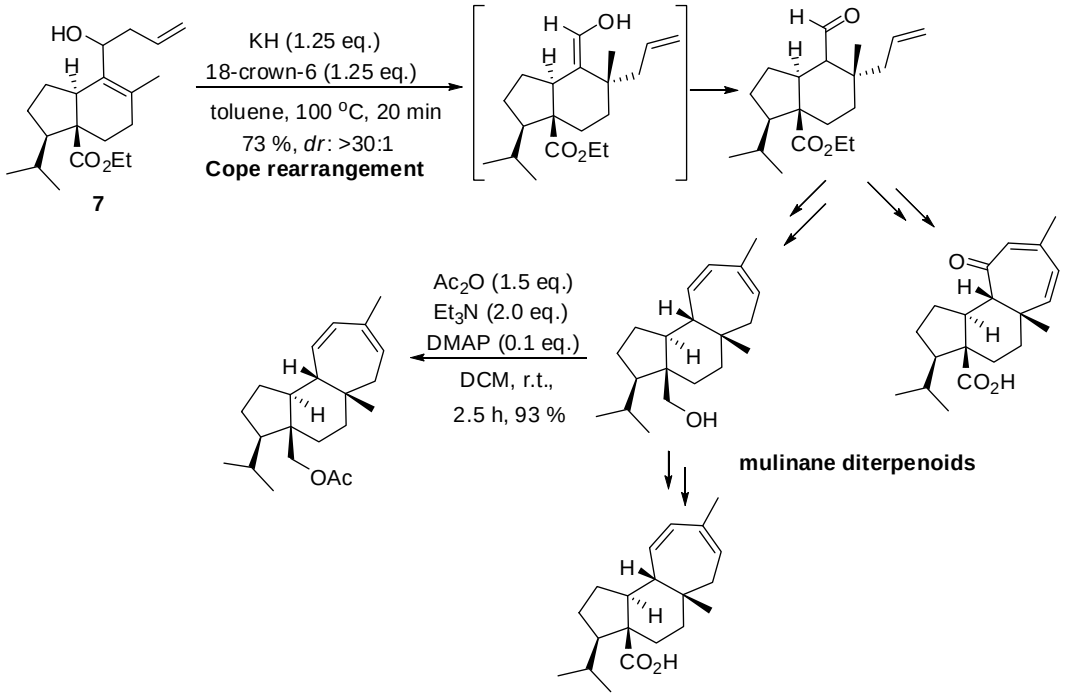
Cope rearrangement[1-4, 23, 24]



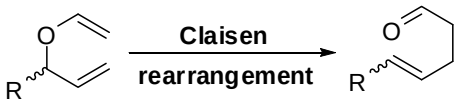
Eq. 11

Guerrero and co-workers[25] have utilized efficiently Cope rearrangement of substrate (**7**) as one of the key steps in the synthesis of biologically active natural products mulinane diterpenoids Scheme 10.

Scheme 10

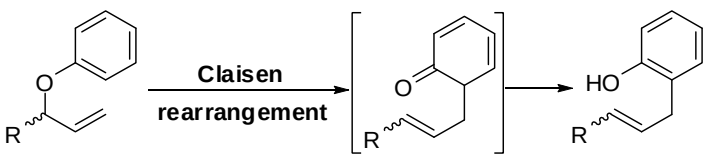


Claisen rearrangement [1-4, 23, 26-28]



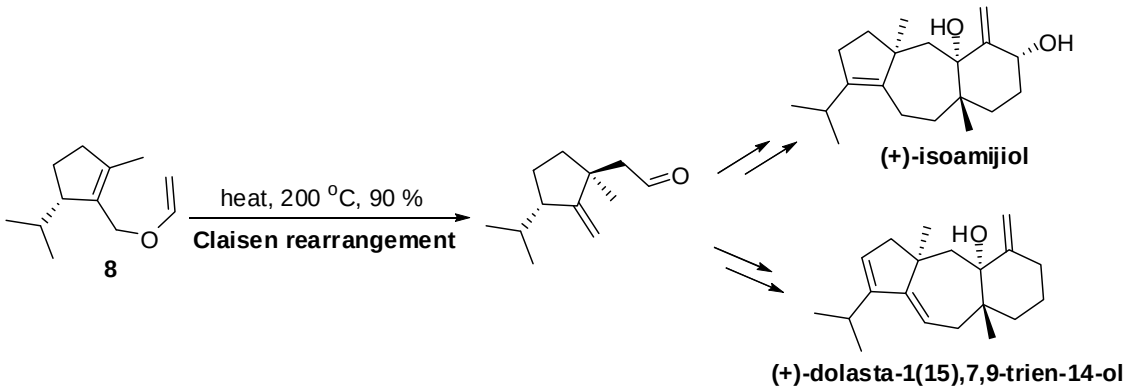
Eq. 12

Scheme 11



Natural products (+)-isoamijiol and (+)-dolasta-1(15),7,9-trien-14-ol have been synthesized by Mehta and Krishnamurthy[29] using Claisen rearrangement of the molecule (**8**) as a one of the key steps (Scheme 12).

Scheme 12



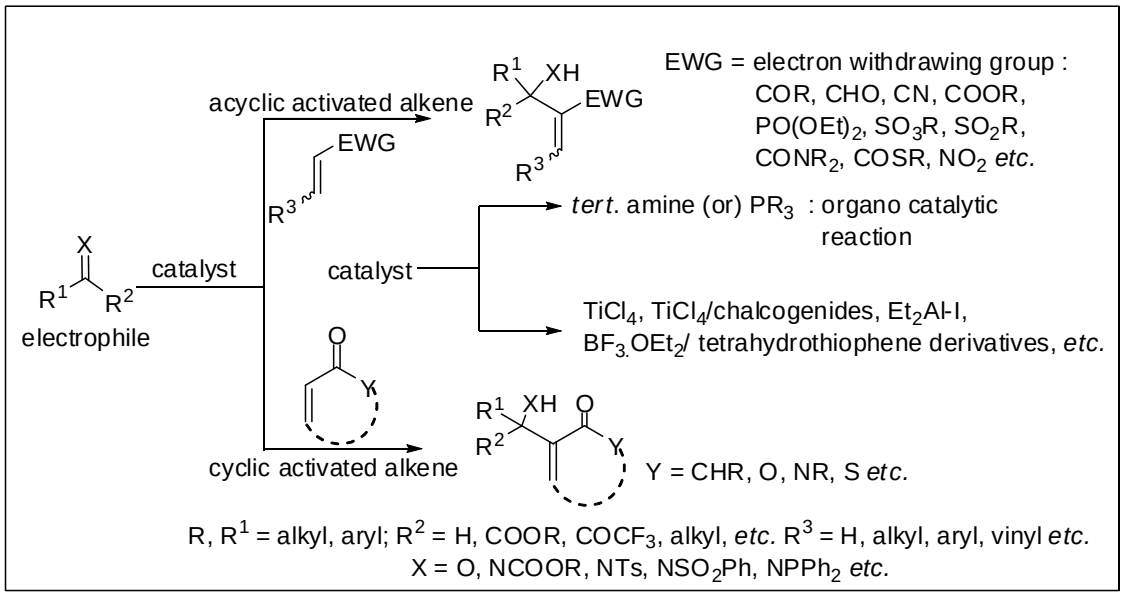
Since the thesis deals with the development of intramolecular Baylis-Hillman reactions, this section presents relevant aspects of literature on the Baylis-Hillman reaction and its intramolecular version.

Baylis-Hillman (BH) reaction

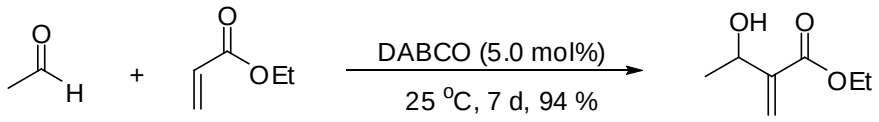
The Baylis-Hillman[30, 31] (BH) reaction is one of the most popular and useful C-C bond forming reactions. It involves atom economical coupling between the electrophile and α-position of activated alkene to produce densely functionalized molecule under the influence of appropriate catalyst (Scheme 13). It is also known as the Morita[32, 33] - Baylis-Hillman (MBH) reaction. Various activated alkenes (acrylates, alkyl vinyl ketones, acrylonitrile, acrylamides, vinyl sulfonamides, *etc*.)[34-50] have been systematically employed in coupling with a variety of electrophiles (aldehydes, imines, α-ketoesters, ketones *etc*.). [34-50] A number of catalysts such as *tert*.amines (DABCO, trimethylamine in methanol, quinuclidine, indolizine *etc*.), [34-50] phosphines (triphenyl-

phosphene, tributylphosphine, trimethylphosphine, *etc*.) and Lewis acids ($TiCl_4$, BF_3/tetrahydrothiophenes, Et_2AlI *etc*.) have been used in various BH-coupling reactions. [34-50]

Scheme 13



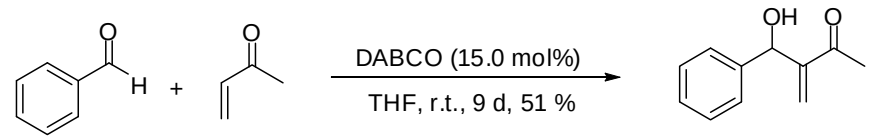
Drewes and Emslie[51] have used ethyl acrylate as an activated alkene and acetaldehyde as an electrophile in the Baylis-Hillman reaction in presence of DABCO to provide the densely functionalized molecule in 94 % yield (Eq. 13).



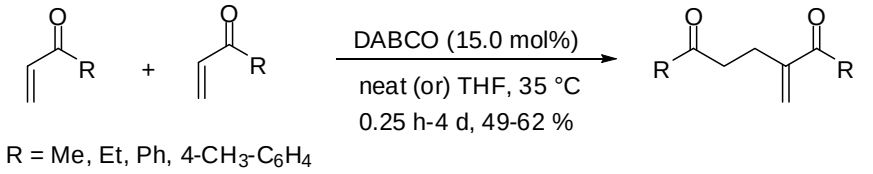
Eq. 13

Our research group[52a] has successfully utilized highly reactive methyl vinyl ketone as an activated alkene in the Baylis-Hillman reaction with aldehydes in the influence of DABCO. One example is presented in Eq. 14. Subsequently our research group[52b] has described an efficient dimerization of alkyl (aryl) vinyl ketone and acrylonitrile in

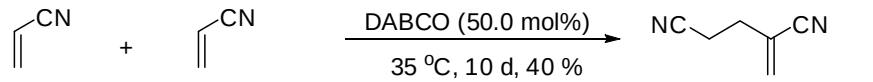
presence of DABCO to produce the corresponding Michael type dimers (Eq. 15 and Eq. 16).



Eq. 14

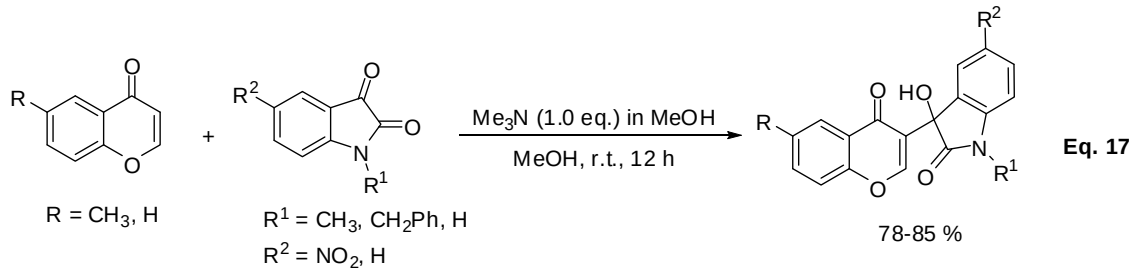


Eq. 15



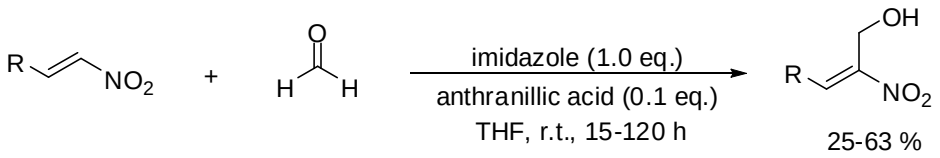
Eq. 16

Our research group[53] has also utilized 1-benzopyran-4(4*H*)-ones as activated alkenes for coupling with isatins as electrophiles under the influence of Me_3N (in MeOH) to obtain the corresponding B-H-adducts in 78-85 % yields (Representative examples are shown in Eq. 17).



Eq. 17

Namboothiri and coworkers[54a] have successfully utilized β-substituted nitroethylenes as activated alkenes for coupling with formaldehyde in presence of imidazole and anthranillic acid to obtain corresponding Baylis-Hillman adducts in moderate yields (Eq. 18).

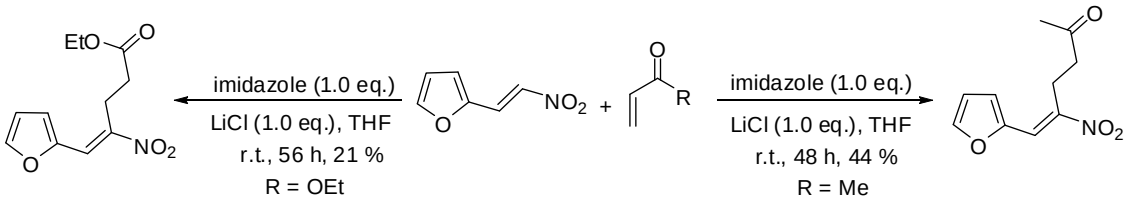


Eq. 18

R = 2-thiophenyl, 3-furyl, 3-thiophenyl, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 3, 4-$(MeO)_2C_6H_3$, 3-MeO, 4-OHC_6H_3, 4-F-C_6H_4, C_6H_5

Namboothiri and co-workers[54b] have utilized methyl vinyl ketone and ethyl acrylate as electrophiles and β-substituted nitroethylenes as activated alkenes in the Baylis-Hillman reaction to provide corresponding adducts. Two selected examples are presented in Scheme 14.

Scheme 14

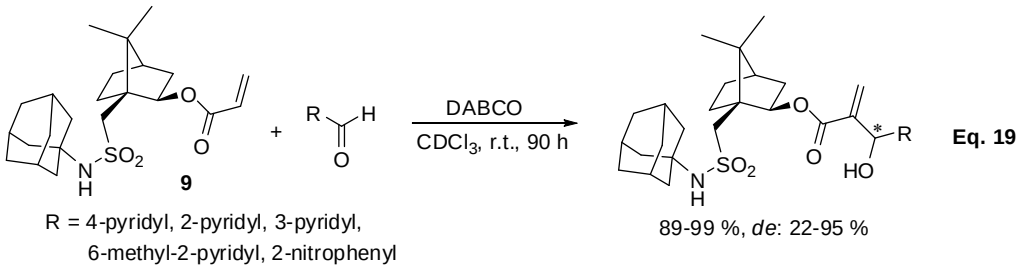


Asymmetric Baylis-Hillman reaction

Since BH-reaction creates a chiral centre in the case of prochiral electrophiles, efforts have been directed to develop different methodologies to obtain enantiomerically enriched or enantiomerically pure BH-adducts by employing either chiral electrophiles or chiral activated alkenes or chiral catalysts.[35, 38, 40]

Recent and important developments in the asymmetric Baylis-Hillman reaction: Applications of chiral activated alkenes, chiral electrophiles and chiral catalysts

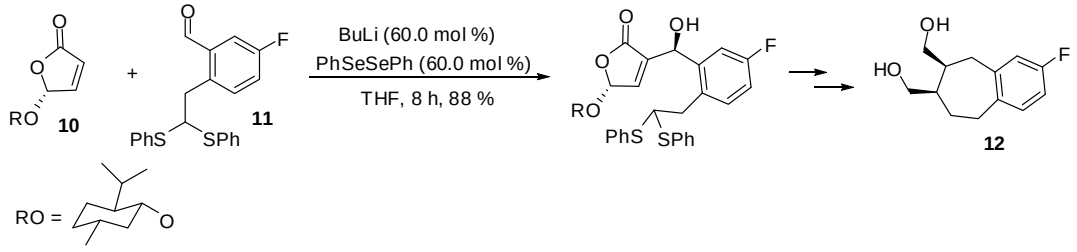
Duggan and Kaye[55] have utilized 2-exo-acryloyloxy-N-(1-adamantyl)bornane-10-sulfonamide (**9**) as a chiral activated alkene in the asymmetric Baylis-Hillman reaction with aldehydes in presence of DABCO to yield the resulting adducts in low to high diastereomeric excess (Eq. 19).



Eq. 19

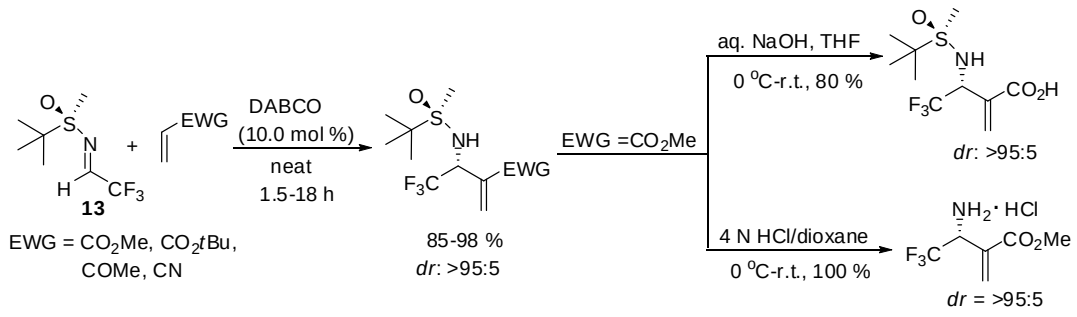
Sreedharan and Clive[56] have used chiral activated alkene (**10**) for coupling with aldehyde (**11**) to obtain the desired adduct in 100 % *de*. Thus obtained adduct was subsequently transformed into enantiomerically pure bicyclic compound (**12**) (Scheme 15).

Scheme 15



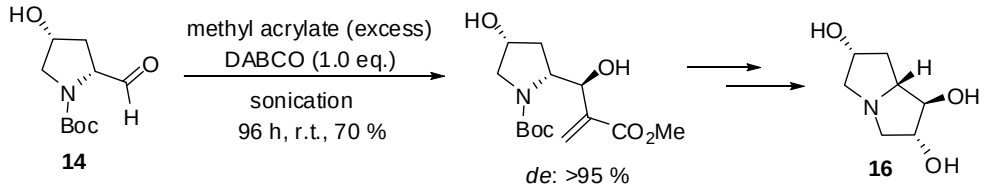
Milcent and co-workers[57] have reported Baylis-Hillman reaction of chiral CF_3-sulfinylimines (**13**) with activated alkenes under the influence of DABCO to provide Baylis-Hillman adducts in high diastereoselectivities. One such adduct derived from methyl acrylate was also converted into α-methylene β-CF_3-β-amino acids and amine ester HCl salt as described in Scheme 16.

Scheme 16

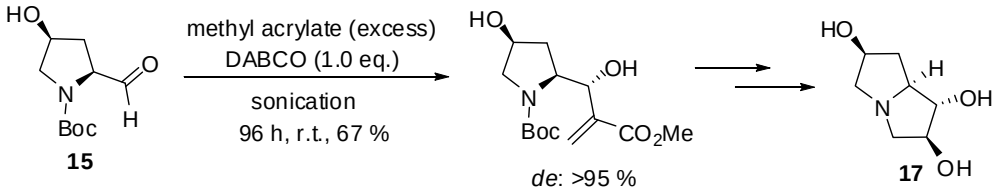


Coelho and co-workers[58] have synthesized polyhydroxylated pyrrolizidines (**16** and **17**) employing Baylis-Hillman reaction of chiral electrophiles (**14** and **15**) with methyl acrylate in the presence of DABCO as the key step as described in Schemes 17 and 18 respectively.

Scheme 17

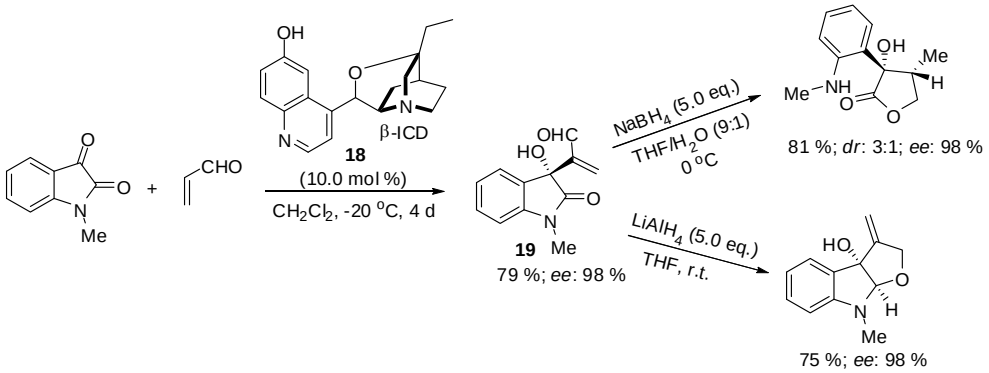


Scheme 18

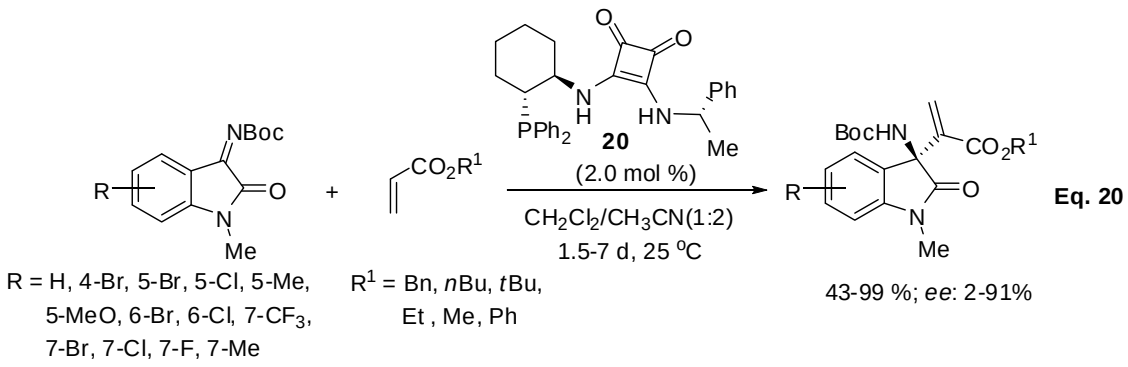


Zhou and co-workers[59] have developed highly enantioselective Baylis-Hillman reaction of acrolein with N-substituted isatins in the presence of Hatakayama catalyst (β-ICD) (**18**) to provide the resulting adducts in good to excellent yields. One such BH-adduct (**19**) obtained in 98 % *ee* was transformed into lactone via the reaction with $NaBH_4$ and also into furoindoline via treatment with $LiAlH_4$ as shown in Scheme 19.

Scheme 19



Asymmetric Baylis-Hillman reaction of acrylates with N-Boc isatin ketimines using chiral catalyst (**20**) has been described by Wu and co-workers[60] to provide the resulting adduct in a good to excellent yields and high enantioselectivities (Eq. 20).

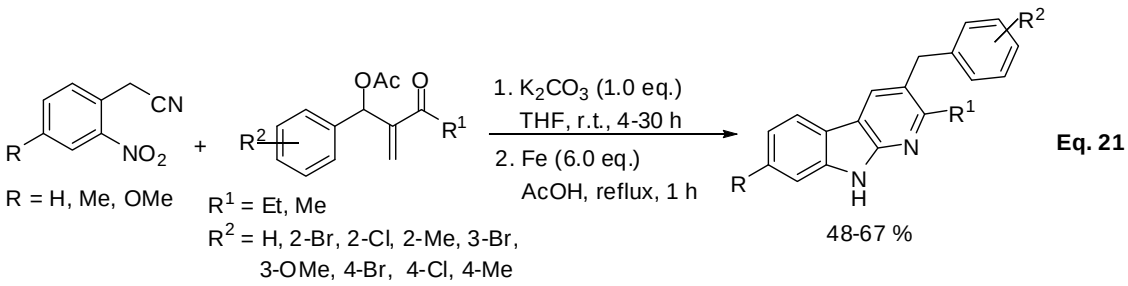


Eq. 20

Applications of Baylis-Hillman adducts

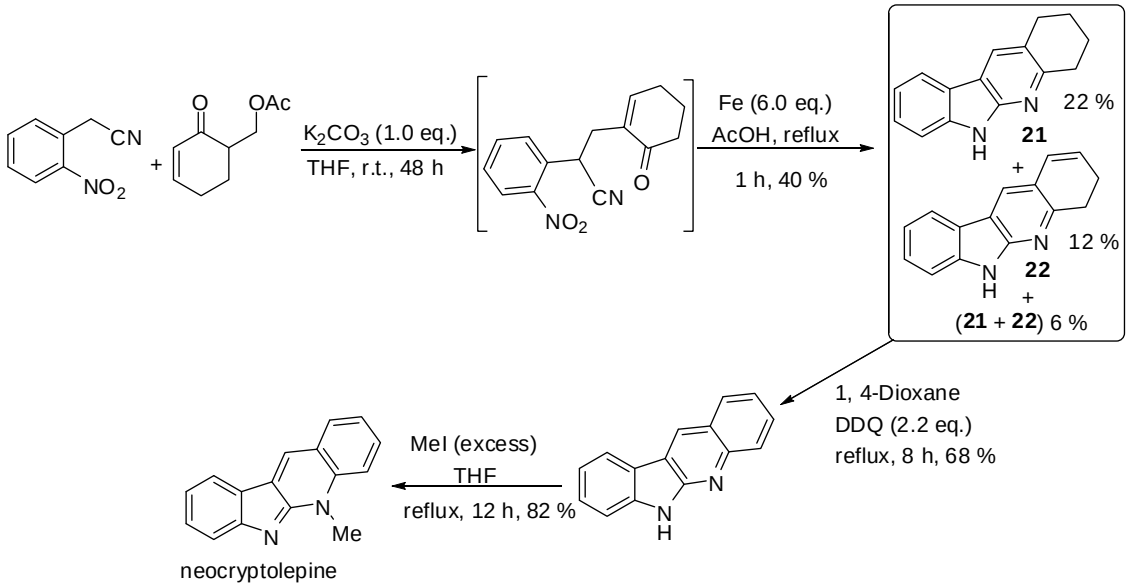
Due to the proximity of multi functional groups present in Baylis-Hillman adducts, they have been used as valuable intermediates for obtaining of variety of carbocyclic, heterocyclic frameworks, bioactive molecules and natural products. [35, 38, 40] Selected examples are described in this section.

Recently our research group[61] developed a convenient methodology for synthesis of α-carbolines from BH-adducts via a three step reaction sequence involving alkylation, reduction and cyclization (Eq. 21). This methodology has been successfully utilized for synthesis of biologically important natural product neocryptolepine as shown in the Scheme 20.



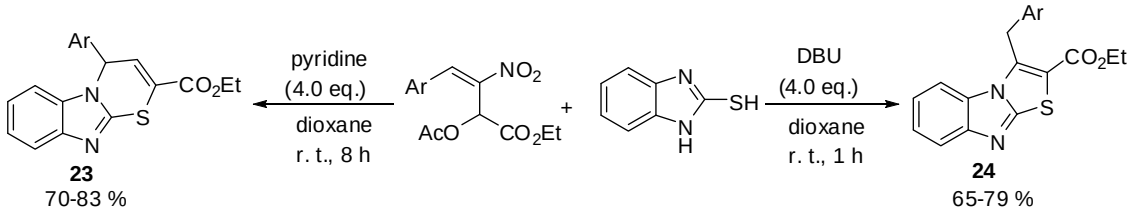
Eq. 21

Scheme 20



Gu et al.[62] have developed base-controlled regioselective reaction between 2-mercaptobenzimidazole and Baylis-Hillman acetates. It is interesting to note that in the presence of pyridine the reaction provides benzimidazo[2, 1-b]-1, 3-thiazine (**23**) while DBU provided thiazolo[3, 2-a]benzimidazole (**24**) according to Scheme 21.

Scheme 21

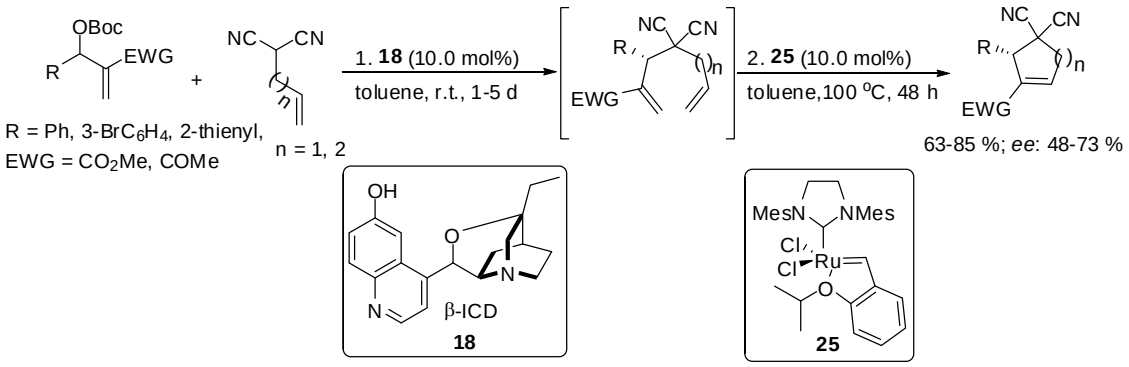


Ar = Ph, 4-$CH_3OC_6H_4$, 4-NCC_6H_4, 4-$NO_2C_6H_4$, 2, 3, 4-$(CH_3O)C_6H_2$, 1-naphthyl, 2-thiophenyl

A convenient protocol for obtaining enantiomerically enriched carbocyclic compounds via the reaction of BH-acetates with allyl (or butenyl) malononitrile in presence of chiral catalyst **18**, followed by RCM-reaction of the resulting products with Hoveyda-

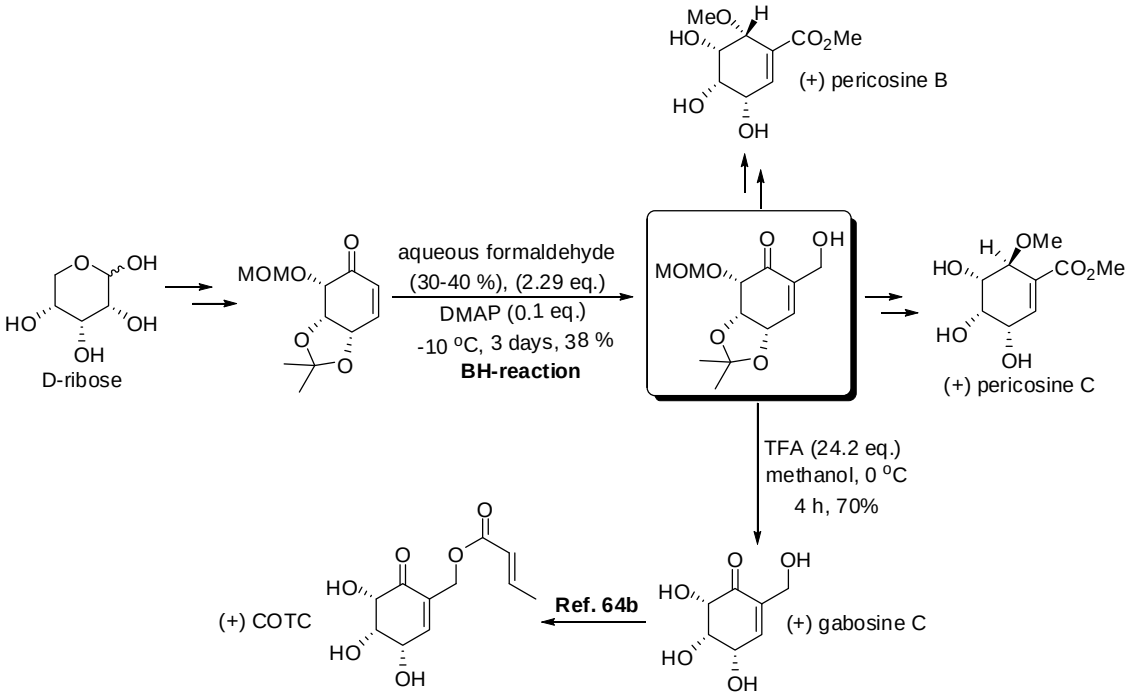
Grubbs catalyst **25** following the reaction sequence as shown in Scheme 22, was reported by Veselý and co-workers[63].

Scheme 22



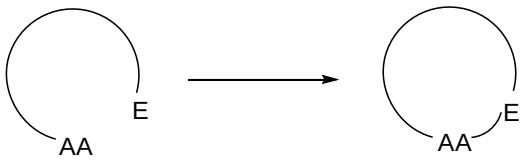
Babu and co-workers[64a] have synthesized carbosugars (+)-gabosine C, (+)-COTC, (+)-pericosine B and (+)-pericosine C by using Baylis-Hillman reaction as the key step, starting from D-ribose following the reaction strategy as described in Scheme 23.

Scheme 23



Intramolecular Baylis-Hillman (IBH) reaction

When activated alkene unit and electrophile moiety are present in a single molecule at appropriate positions, it is possible to perform intramolecular Baylis-Hillman (IBH) reaction (Eq. 22). Therefore growth of intramolecular Baylis-Hillman reaction in principle depends on the design of such unique substrates containing activated alkene (AA) and electrophile (E) components in a suitable position for coupling reaction to provide cyclic compounds.

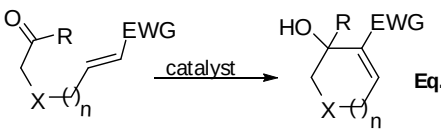


Eq. 22

Literature survey clearly shows that a number of efforts have been made for designing such special class of substrates and subsequently utilizing them in various IBH reactions to produce interesting classes of cyclic compounds (both carbocycles and hetero cycles). In fact several biologically active compounds and natural products have also been synthesized using IBH reaction as the key step.[35, 38, 40, 42]

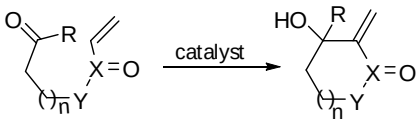
In principle IBH reactions can be designed to obtain cyclic compounds having endocyclic methylene (Eq. 23 and 25) or exocyclic methylene (Eq. 24 and 26) groups.

Intramolecular Baylis-Hillman reaction



Eq. 23

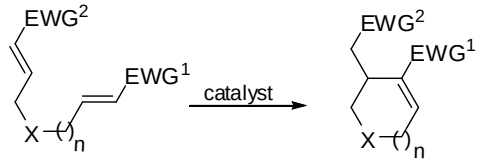
EWG = COR, COSR, CO_2R ,CN, $CONR_2$, SO_2R, $SONR_2$ *etc.*
X = CHR, O, S, NR; *etc.*; n = 0, 1, 2 *etc.*
X = CHR (carbocyclic); X = O, S, NR, *etc.* (heterocyclic);
R = H, alkyl, aryl, *etc.*



Eq. 24

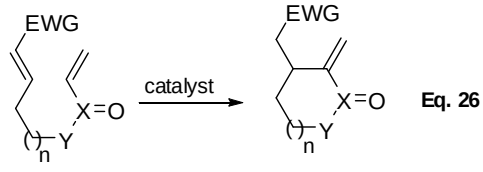
X = C, SO, *etc.*; Y = CHR, N-R, O, S, *etc.*
n = 0, 1, 2, *etc.*; X = C, Y = CHR (carbocyclic);
X = C, SO, *etc.*; Y = N-R, O, S, *etc.* (heterocyclic);
R = H, alkyl, aryl, *etc.*

Intramolecular Rauhut-Currier reaction



Eq. 25

EWG^1, EWG^2 = COR, COSR, CO_2R ,CN, $CONR_2$, SO_2R, $SONR_2$ *etc.*
X = CHR, O, S, NR; *etc.*; n = 0, 1, 2 *etc.*;
X = CHR (carbocyclic); X = O, S, NR, *etc.* (heterocyclic);
R = H, alkyl, aryl, *etc.*

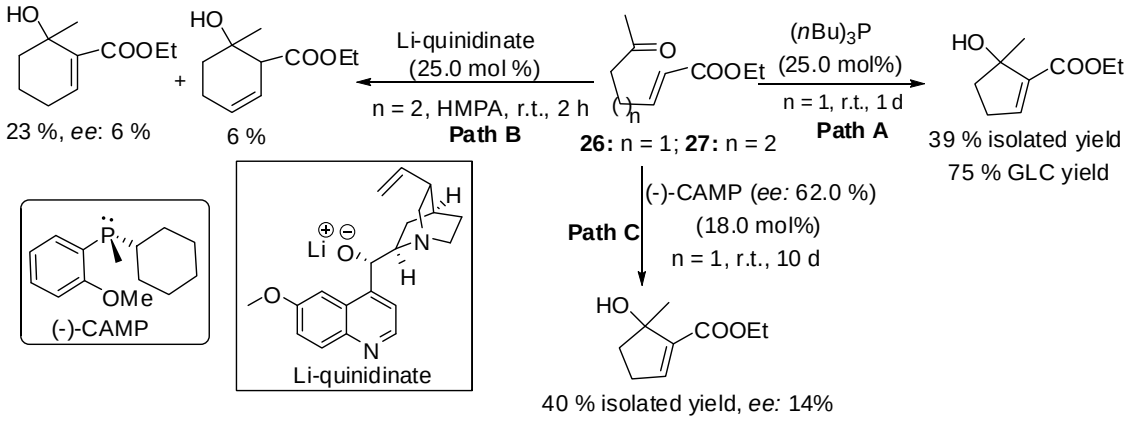


Eq. 26

EWG = COR, COSR, CO_2R ,CN, $CONR_2$, SO_2R, $SONR_2$ *etc.*
X = C, SO, *etc.*; Y = CHR, N-R, O, S, *etc.*;
n = 0, 1, 2, *etc.*; X = C, Y = CHR (carbocyclic);
X = C, SO, *etc.*; Y = N-R, O, S, *etc.* (heterocyclic);
R = H, alkyl, aryl, *etc.*

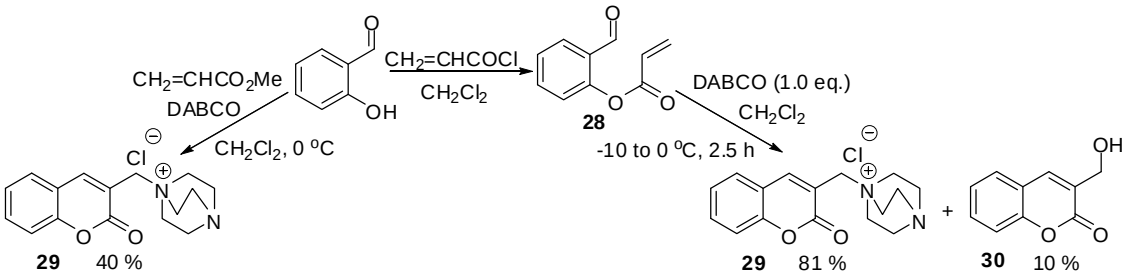
It is quite interesting and even fascinating to note that the first intramolecular Baylis-Hillman (IBH) reaction was reported as early as in 1992 by Fráter and co-workers[65] who used α,β-unsaturated ester-ketone system as substrates. The treatment of substrate (**26**) with tributyl phosphine gave the cyclopentene (n = 1) in 39 % isolated yield (GLC yield 75 %) (Scheme 24, Path A). First enantioselective intramolecular BH-reaction was also reported by Frater and co-workers in the same paper.[65] Reaction of substrate **27** (n = 2) with lithium quinidinate (Scheme 24, Path B) provided the desired cyclohexene derivative in 6 % *ee* and 23 % yield, while reaction of **26** (n = 1) with (-)-CAMP (Scheme 24, Path C) gave the expected cyclopentene derivative in 14 % *ee* and 40 % isolated yield. In spite of low enantioselectivities these studies are useful and also of importance because they showed the way and also indicated the necessity of designing appropriate catalysts for achieving better enantioselectivities.

Scheme 24



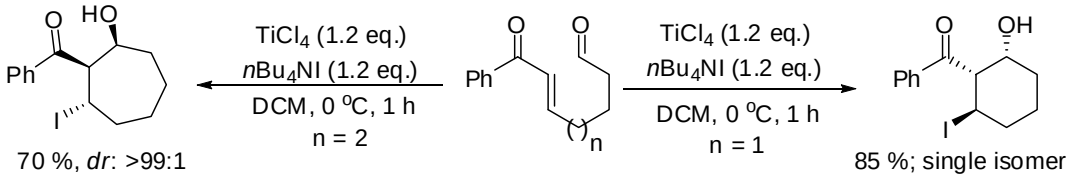
A few years later Drewes and co-workers[66] reported an interesting IBH-reaction of 2-formylphenyl acrylate (**28**) in presence of DABCO to provide coumarin salt (**29**) (as a major) in 81 % yield and rearranged BH-alcohol (**30**) (as a minor) in 10 % yield (Scheme 25). They have also prepared coumarin salt (**29**) in one step reaction via the reaction of salicylaldehyde with methyl acrylate in presence of DABCO at 0 °C in 40 % yield (Scheme 25).

Scheme 25



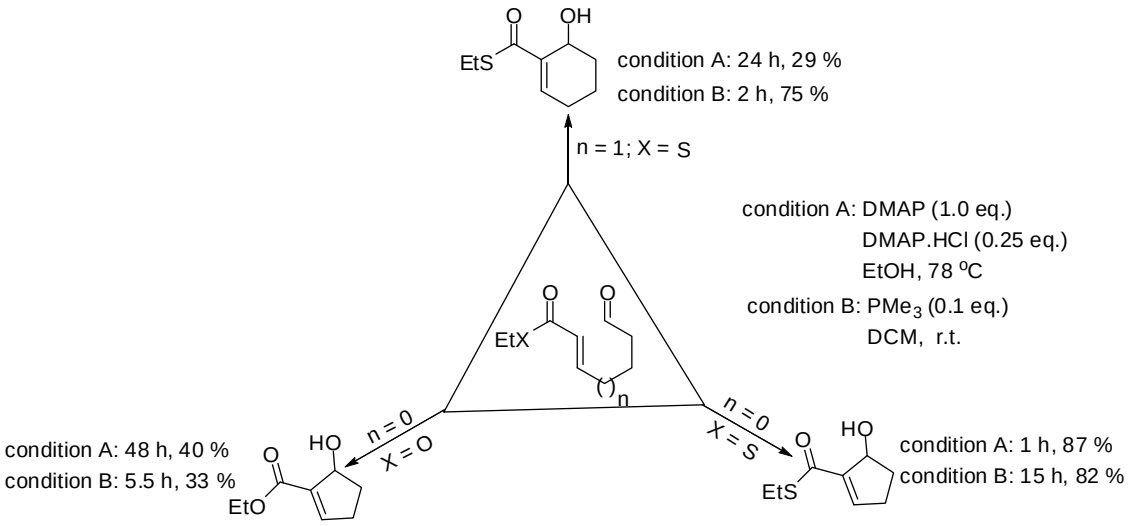
Oshima et al.[67] have developed an interesting IBH reaction of enone-aldehyde system in presence of $TiCl_4$-nBu_4NI to provide cyclic β-substituted-iodo compounds (two examples are shown in Scheme 26).

Scheme 26



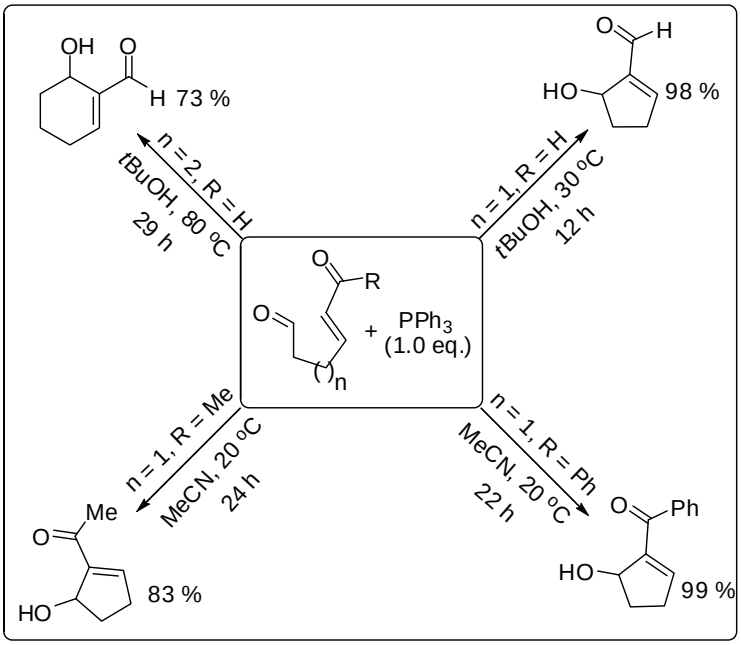
Keck and Welch[68] have described a facile intramolecular Baylis-Hillman reaction of substrates containing α,β-unsaturated thioesters and α,β-unsaturated esters as activated alkene and aldehydes as electrophile components for obtaining substituted cyclopantenols and cyclohexenols (representative examples are presented in the Scheme 27).

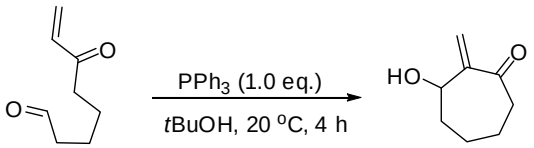
Scheme 27



Koo and co-workers[69] have used α,β-unsaturated aldehydes and α,β-unsaturated ketones as activated alkene components in the IBH reaction with aldehyde as electrophile components in the presence of triphenylphosphine to provide 5, 6, 7-membered carbocyclic ring systems (Scheme 28 and Eq. 27) in good yields (selected examples are presented).

Scheme 28



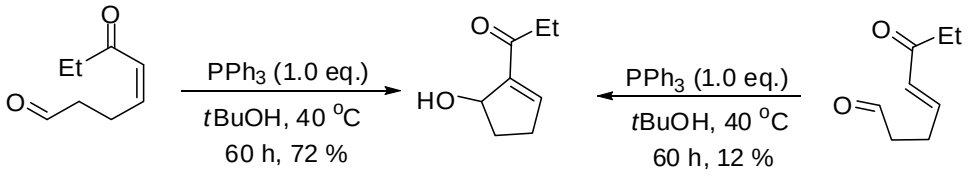


84 %

Eq. 27

Shi, Toy and co-workers[70] have systematically studied the reactivity difference between trans-enone-aldehyde and cis-enone-aldehyde systems in IBH reactions and found that reactivity of trans-substrate was less than that of corresponding cis-substrate, due to the steric hindrance for initial attack of triphenylphosphine (Scheme 29).

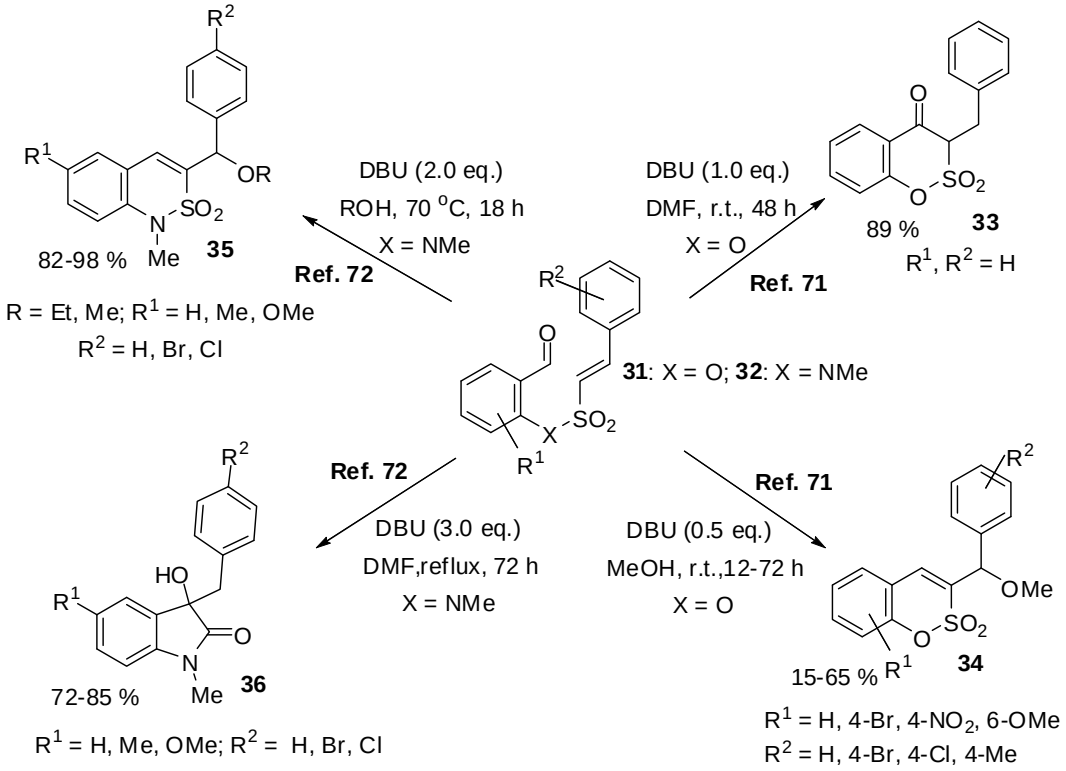
Scheme 29



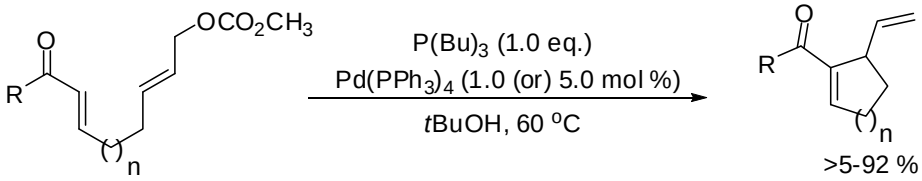
Ghandi and co-workers[71] have synthesized sultones using solvent dependant IBH reaction of 2-formylaryl-(*E*)-2-arylethylenesulfonates (**31**) in presence of DBU. Thus

DMF as a solvent gave sultone derivative (**33**) (IBH-reaction followed by isomerization involving 1,3-proton shift) (Scheme 30) while a similar reaction of 2-formylaryl-(*E*)-2-arylethylenesulfonates (**31**) with DBU in MeOH as a solvent provided ene-sultone derivatives (**34**) (IBH-reaction followed by dehydration) (Scheme 30). They[72] have extended this work to styryl-sulfonamide-aldehyde system (**32**). In these reactions alcoholic solvents gave benzo-δ-sultams (**35**) (IBH-reaction followed by dehydration) while DMF solvent provided 3-benzyl-3-hydroxyoxindoles (**36**) (Scheme 30).

Scheme 30



A facile intramolecular Baylis-Hillman reactions of enone-allyl carbonate, enolate-allyl carbonate and thioenolate-allyl carbonate systems using $P(Bu)_3$ as a coupling reagent in the presence of $Pd(PPh_3)_4$ (catalyst) providing the corresponding carbocyclic compounds were reported by Krische and co-workers[73] (Eq. 28).



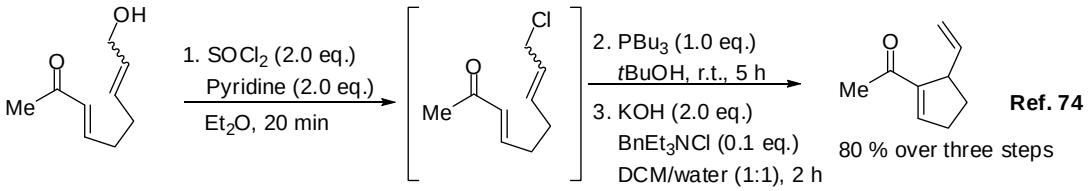
Eq. 28

R = CH_3, CH_2OBz, cyclopropyl, OEt, SEt, Ph, 2-furanyl, 2-Naphthyl

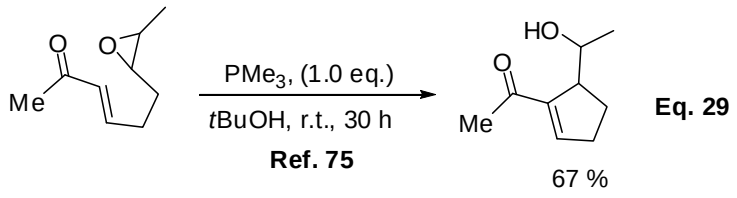
n = 1, 2

Kraft and co-workers have developed a facile strategy for synthesis of cyclopentene derivatives from enone-allyl chlorides (Scheme 31**)**,[74] enone-epoxides (Eq. 29),[75] ene thioesters-alkyl bromides (Eq. 30)[76] and enone-alkyl bromides (Scheme 32)[76] systems using PBu_3 or PMe_3 as a promoter. In fact they isolated phosphine addition intermediate (**38**) (Scheme 32)[76] in the case of enone-alkyl bromides (**37**) in order to understand the mechanism of this reaction. In this reaction they obtained the corresponding IBH-adduct in 95 % yield.

Scheme 31

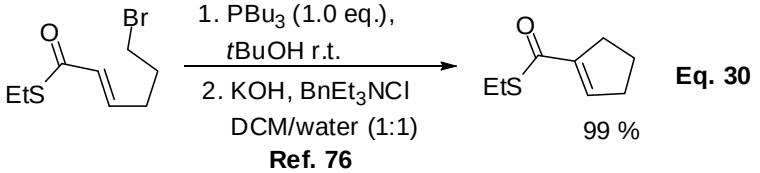


Ref. 74



Ref. 75

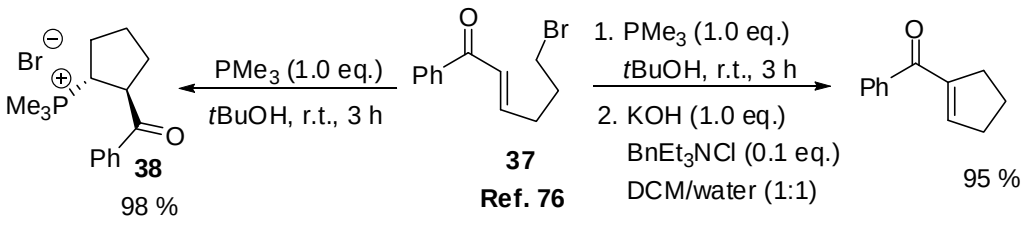
Eq. 29



Ref. 76

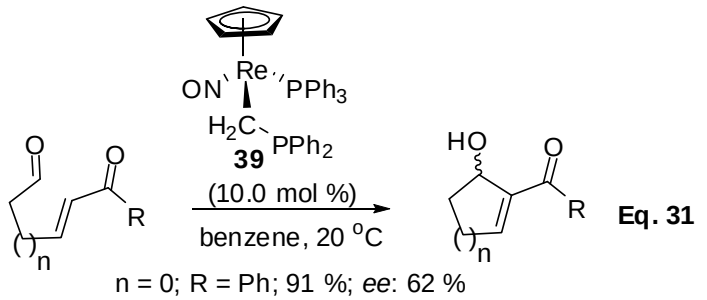
Eq. 30

Scheme 32



Asymmetric intramolecular Baylis-Hillman reaction

A chiral rhenium based catalyst (**39**) was employed by Seidel and Gladysz[77] for IBH reaction of enone-aldehyde and thioenolate-aldehyde substrates. Resulting adducts were obtained in moderate to good enantioselectivities (Eq. 31).

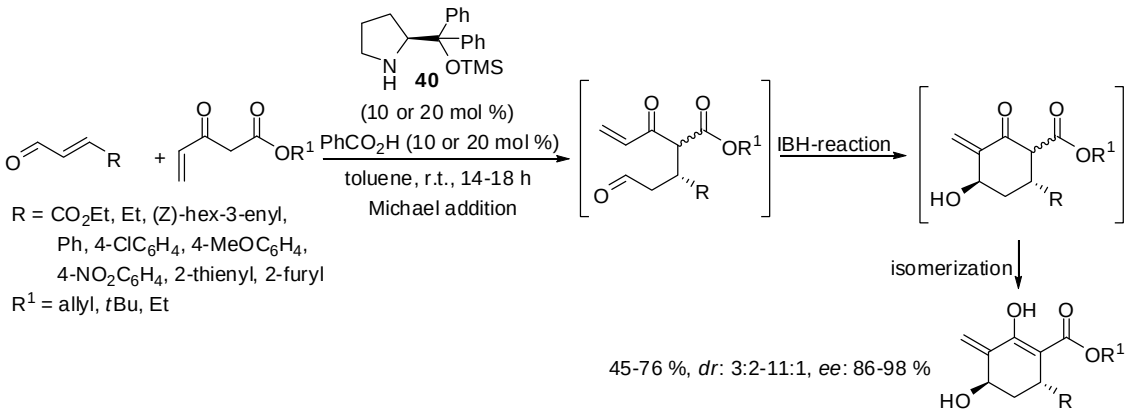


Eq. 31

n = 0; R = Ph; 91 %; *ee*: 62 %
n = 0; R = S-*i*Pr; 99 %; *ee*: 74 %
n = 1; R = *p*Tol; 91 %; *ee*: 38 %
n = 1; R = Me; 88 %; *ee*: 70 %

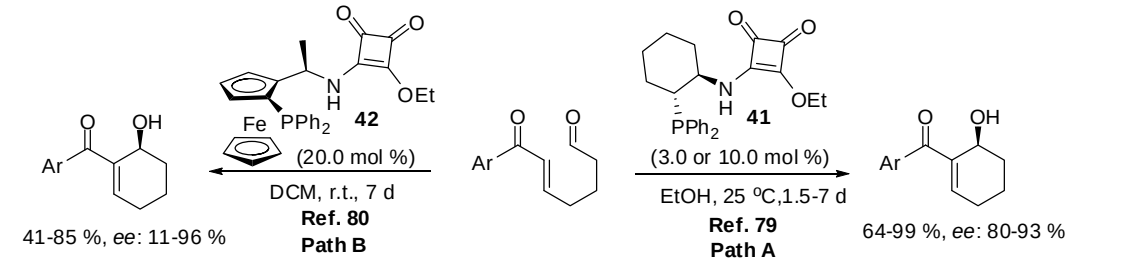
Jørgensen et al.[78] have developed a facile synthetic protocol for obtaining substituted substituted cyclohexenes in high enantioselectivities involving Michael addition reaction and intramolecular Baylis-Hillman reaction as key steps starting from ene-aldehydes and 3-oxopent-4-enoates using chiral catalyst (**40**) in the presence of benzoic acid (Scheme 33).

Scheme 33



Wu and co-workers[79] have used chiral squaramide-phosphine (**41**) as a catalyst for asymmetric intramolecular Baylis-Hillman reaction of α,β-unsaturated ketone-aldehydes to provide cyclohexenol derivatives in high enantioselectivities (Scheme 34, Path A). Recently chiral ferrocene based squaramide-phosphine catalyst (**42**) has also been successfully used in the asymmetric intramolecular Baylis-Hillman reaction of enone-aldehyde substrates by Chen et al.[80] The resulting cyclohexenol derivatives were obtained in 11-96% enantioselectivities (Scheme 34, Path B).

Scheme 34



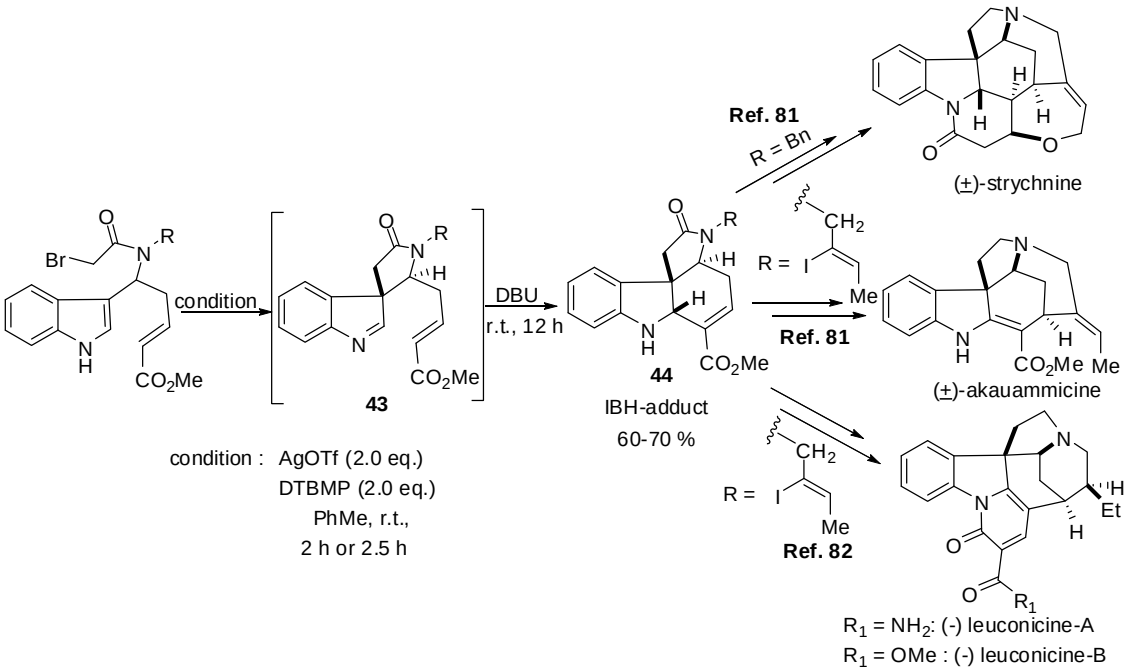
Ar = C_6H_5, 2-BrC_6H_4, 2-ClC_6H_4, 3-BrC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4, 4-$NO_2C_6H_4$, 2-Naphthyl

Ar = C_6H_5, 2-BrC_6H_4, 2-MeC_6H_4, 3-BrC_6H_4, 3-ClC_6H_4, 3-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4, 4-$NO_2C_6H_4$, 2-Naphthyl

Applications of intramolecular Baylis-Hillman reaction

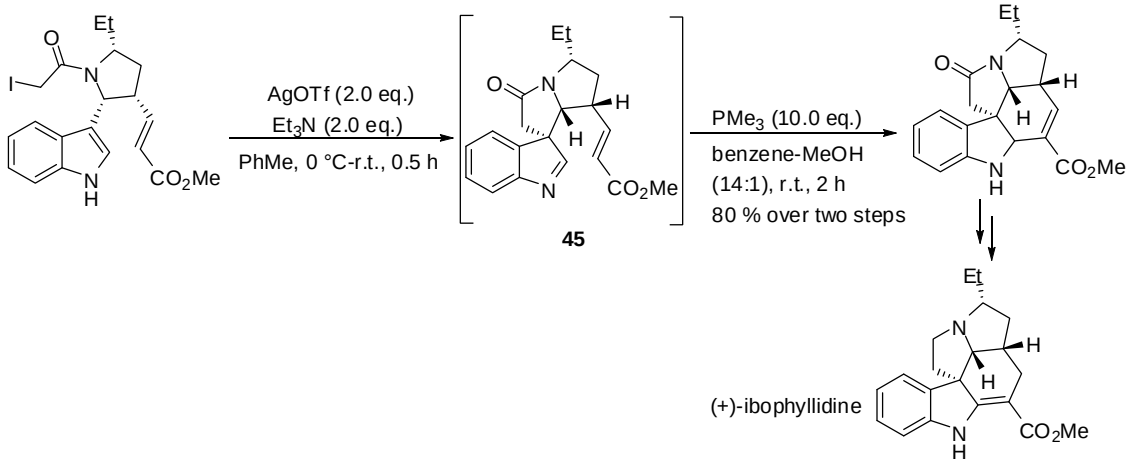
Andrade and co-workers reported the IBH reaction of enoate-imine intermediate (**43)** with DBU to provide the tetracyclic framework (**44)** which was subsequently transformed into natural products (±)-strychnine[81] (±)-akauammicine[81] in racemic form, and also (-)-leuconicine-A[82] and (-)-leuconicine-B[82] in enantiomerically pure form, (Scheme 35).

Scheme 35



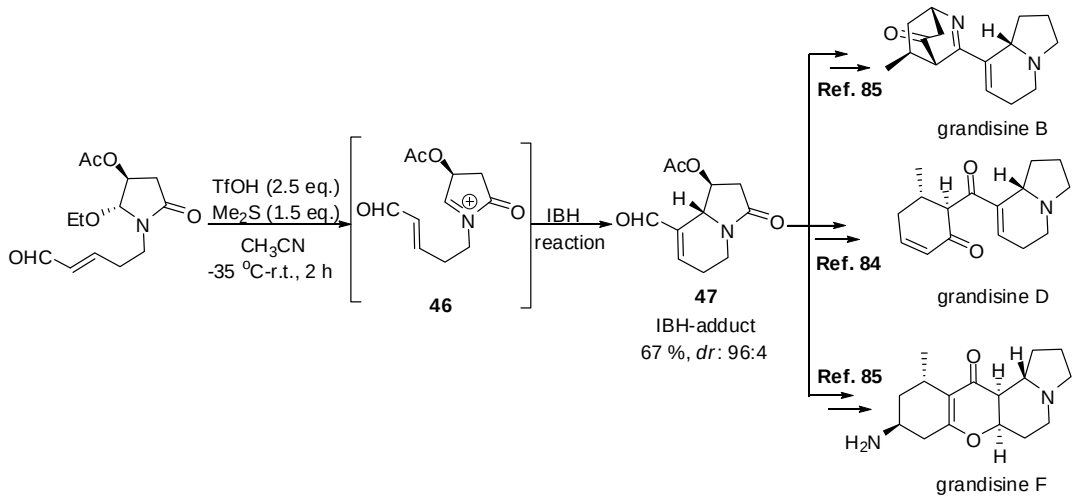
Andrews and Kwon[83] have developed a facile synthetic strategy for obtaining natural product (+)-ibophyllidine, via intramolecular Baylis-Hillman reaction of *in situ* generated enoate-imine system (**45**) as the key step (six-membered carbocyclic ring construction) following the reaction sequence as presented in the Scheme 36.

Scheme 36



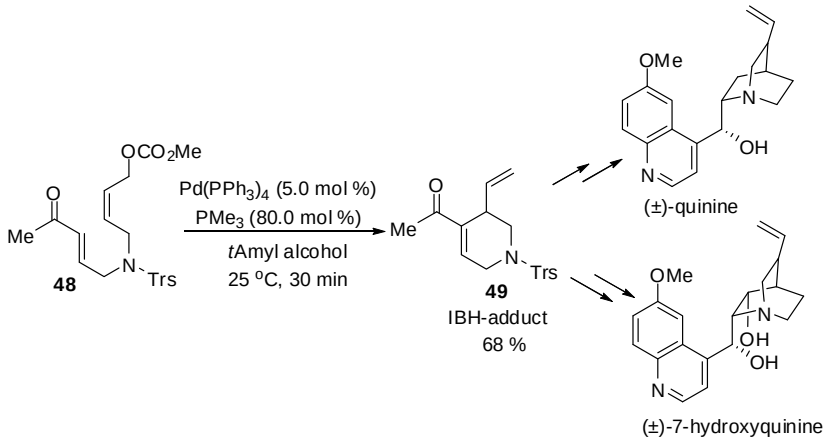
Tamura and co-workers[84, 85] have also utilized diastereoselective IBH reaction of *in situ* generated enal-iminium ion substrate (**46**) to provide the bicyclic compound (**47**), as the key step, for synthesis of natural products grandisines B, D and F (Scheme 37).

Scheme 37



Webber and Krische[86] have reported an elegant IBH reaction of substrate (**48**) containing enone-allyl carbonate using PMe_3 as a reagent to provide six member nitrogen hetero cyclic compound (**49**) which was subsequently used for the formal synthesis of (±)-quinine and also in the total synthesis of (±)-7-hydroxyquinine (Scheme 38).

Scheme 38

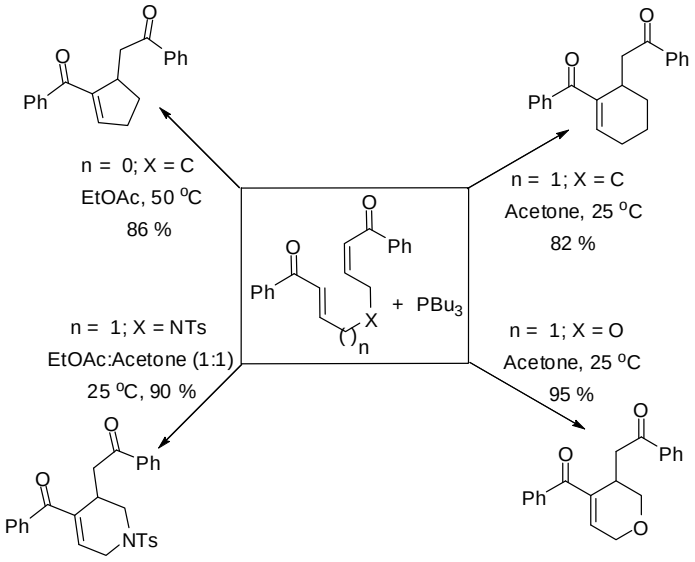


Intramolecular Rauhut-Currier reaction

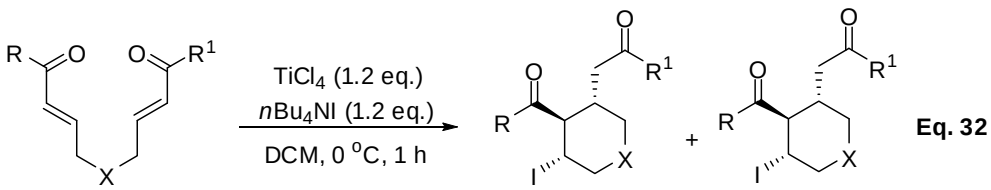
In the intramolecular Baylis-Hillman reaction (IBH), if electrophile happens to be also an activated alkene then the reaction can be also called as Intramolecular Rauhut-Currier (IRC) reaction.[35, 38, 40, 42, 87-89]

Krische and co-workers[90] reported an interesting IRC reaction of enone-enone system under influence of tributylphosphine to produce carbocyclic compounds, N- and O-heterocyclic compounds (Scheme 39).

Scheme 39



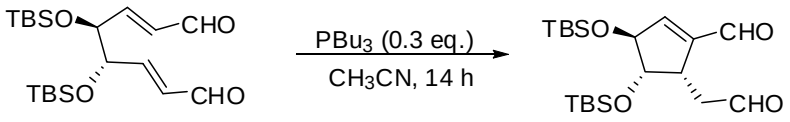
Intramolecular Rauhut-Currier reaction of enone-enone framework using $TiCl_4$-nBu_4NI as promoter producing six member heterocyclic and carbocyclic compounds was reported by Oshima and co-workers (Eq. 32).[67]



X = CH_2; R = R^1 = Ph	99 %; *dr*: >99:1	---
X = CH_2; R = R^1 = Me	77 %; *dr*: 90:10	---
X = CH_2; R = Ph; R^1 = Me	77 %; *dr*: >99:1	10 %; *dr*: >99:1
X = O; R = R^1 = Ph	85 %; *dr*: 80:20	---

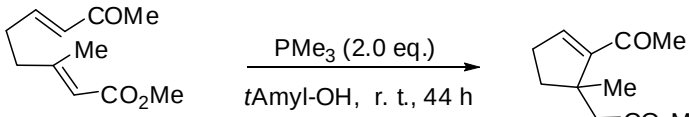
Eq. 32

Roush and co-workers[91] have described IRC reaction of enal-enal (Eq. 33), enone-enoate (Eq. 34), and funtionalized enal-enoate (Eq. 35 and Eq. 36) frameworks to provide a simple protocol for obtaining 5/6-membered carbocyclic/heterocyclic molecules.



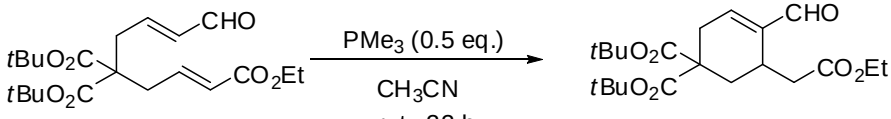
90 %; *dr*: 10:1

Eq. 33



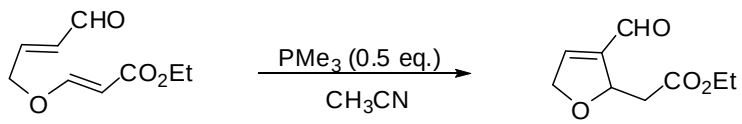
60 %

Eq. 34



74 %, regioselectivity: 97:3

Eq. 35

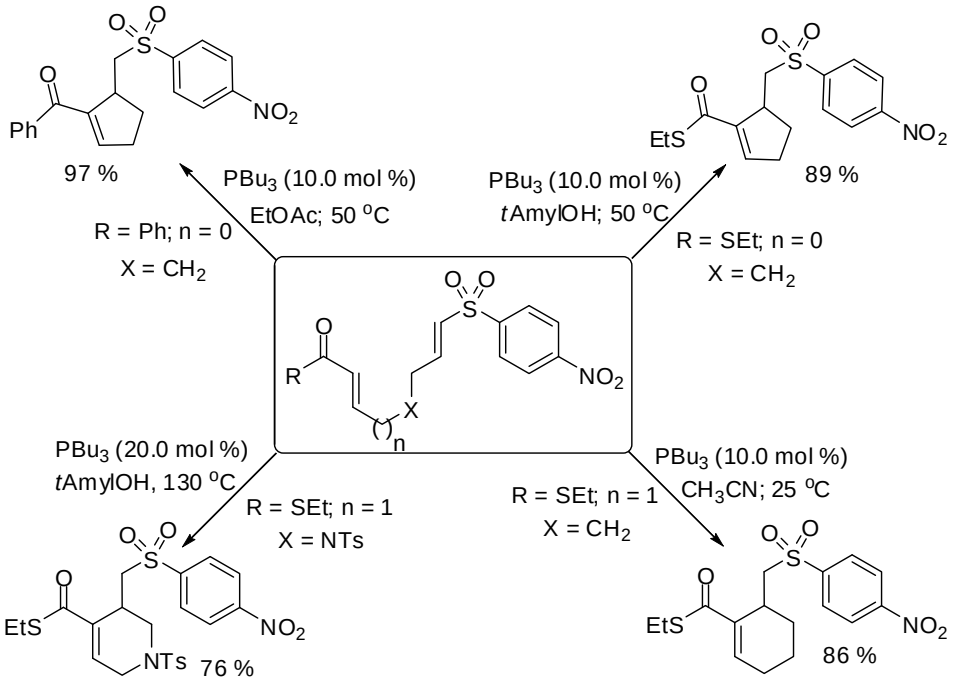


38 %

Eq. 36

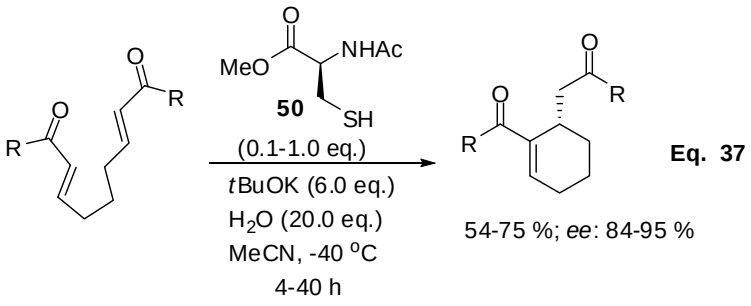
An elegant chemoselective-intramolecular Rauhut-Currier reactions of vinyl thiolate-vinyl sulfone, vinyl ketone-vinyl sulfone systems catalyzed by tributylphosphine was described by Luis and Krische (Scheme 40).[92]

Scheme 40



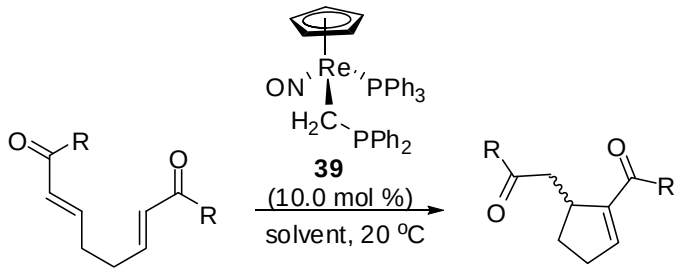
Asymmetric intramolecular Rauhut-Currier reaction

Cysteine derivative (**50**) catalyzed enantioselective IRC reaction of enone-enone system to provide the resulting cyclohexene derivatives was reported by Aroyan and Miller[93] (Eq. 37).



R = Me, C_6H_5, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-furanyl

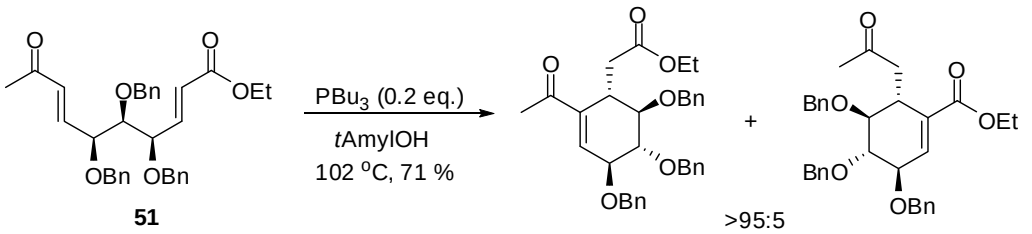
Seidel and Gladysz[77] have reported chiral rhenium phosphine (**39**) catalyzed asymmetric IRC reaction of enone-enone and thioenoate-thioenoate frameworks to produce cyclopentene derivatives (Eq. 38).



Eq. 38

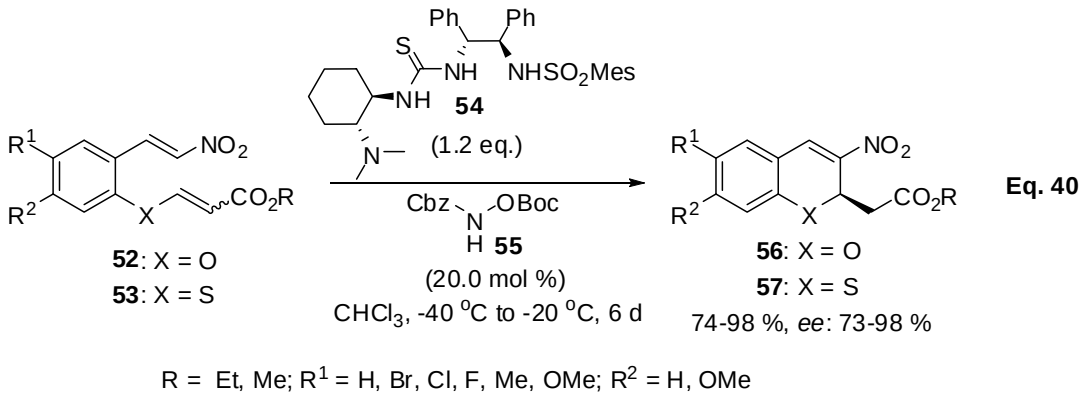
R = Ph; chlorobenzene; 67 %; *ee*: 56 %
R = Ph; benzene ; 87 %; *ee*: 42 %
R = S-*i*Pr; benzene; 81 %; *ee*: 52 %

IRC-reaction of chiral substrate (**51**) under the influence of PBu_3 to produce cyclohexene derivative in highly diastereoselective manner was reported by Krische and co-workers[90] (Eq. 39).



Eq. 39

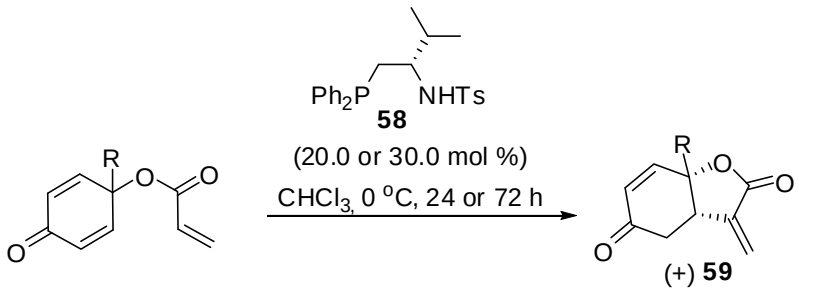
Chiral thiourea (**54**) (in the presence of **55**) catalyzed asymmetric IRC reaction of nitroalkene-alkyl(phenoxy)acrylate (**52**) and nitroalkene-alkyl(phenthio)acrylate (**53**) was reported by Xiao and co-workers.[94] The resulting chromene (**56**) and thiochromene (**57**) derivatives were obtained in high enantioselectivities (Eq. 40).



Eq. 40

R = Et, Me; R^1 = H, Br, Cl, F, Me, OMe; R^2 = H, OMe

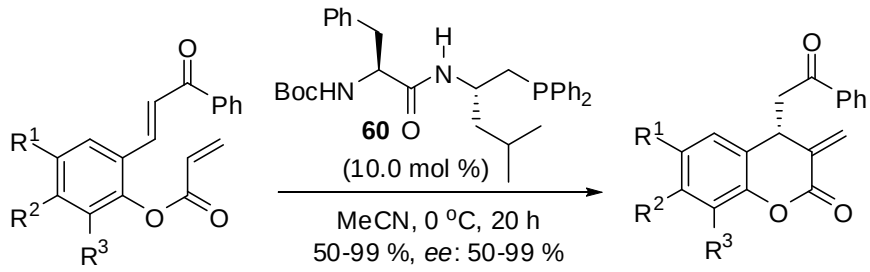
Asymmetric IRC reaction of α,β-unsaturated ketone-acrylates using chiral phosphine (**58**) as a catalyst was performed by Sasai and co-workers[95] for obtaining α-alkylidene-γ-butyrolactones (**59**) in 90-98% enantiomeric purities (Eq. 41).



Eq. 41

R = Me, Et, *n*Bu, CH_2OAc, $CH_2CH_2CO_2Me$, Ph, 4-BrC_6H_4, 4-MeC_6H_4, 3, 5-$(CF_3)_2C_6H_3$, 3,4,5-$F_3C_6H_2$

Very recently Spring and co-workers[96] have utilized α,β-unsaturated ketone-acrylate framework for IBH (IRC) reaction using peptidic phosphine (**60**) as a chiral catalyst to provide chromanone derivatives in good to very high enantioselectivities as shown in the Eq. 42.



Eq. 42

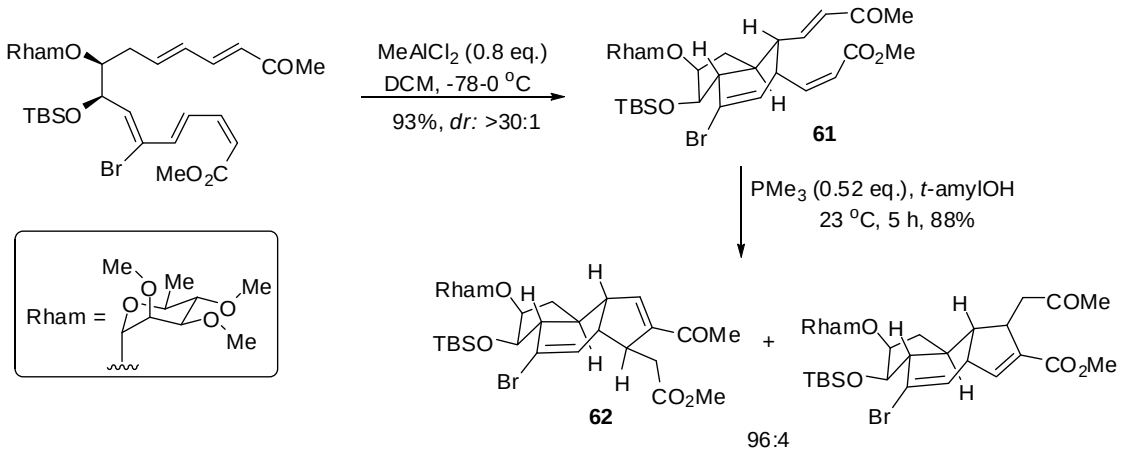
R^1 = H, Br, Cl, F, Me, OMe, NO_2, *t*Bu; R^2 = H, Cl; R^3 = H, allyl, *t*Bu

Applications of intramolecular Rauhut-Currier reaction

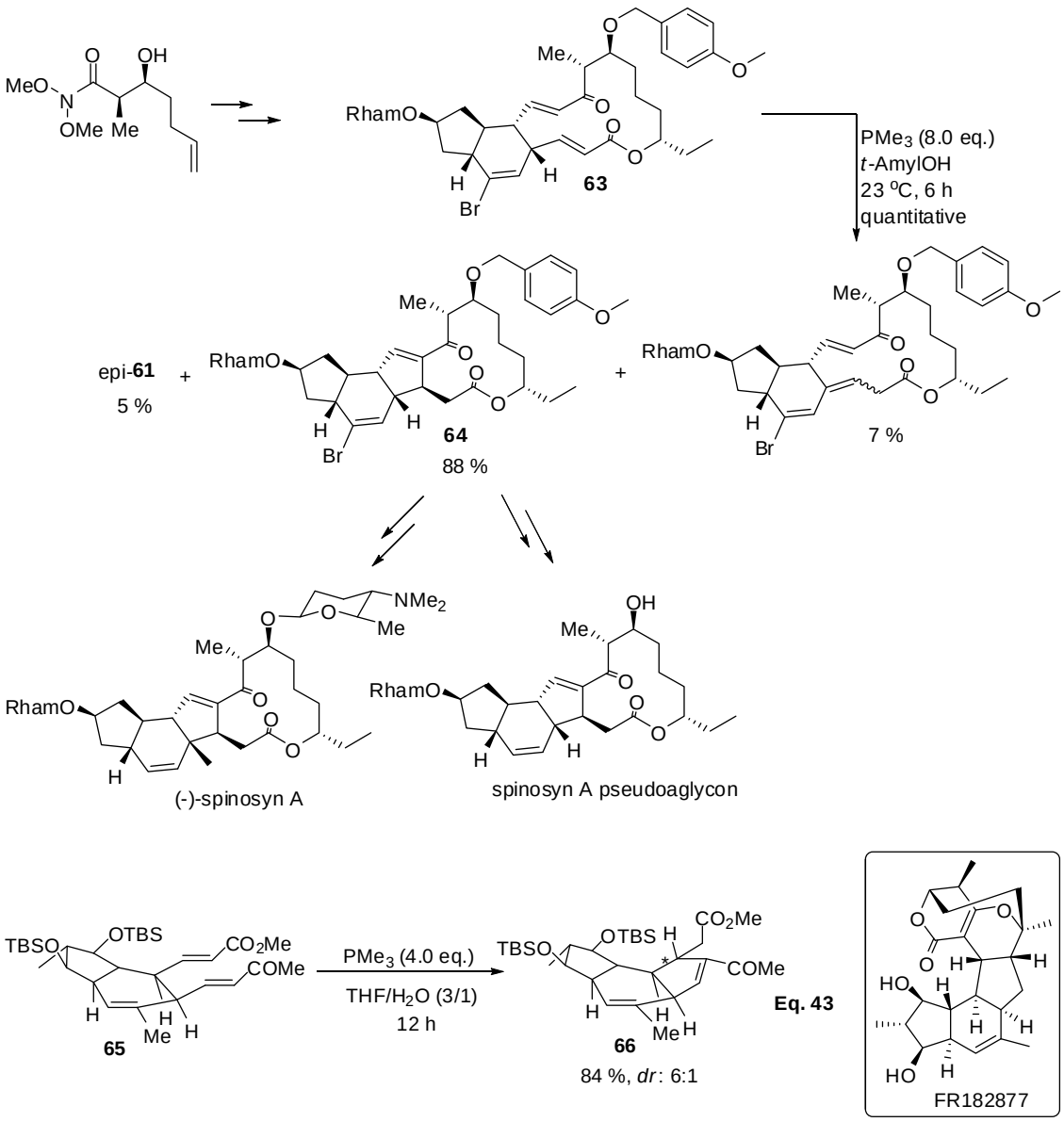
Roush and co-workers[97] have used successfully chemoselective IBH (IRC) reaction of enone-enoate framework (**61**) as a key step for obtaining the required tricyclic framework (**62**), the core structure of natural product spinosyn A (Scheme 41). Subsequently they[98, 99] extended this strategy for the synthesis of spinosyn A and spinosyn A pseudoaglycon using IRC reaction of enone-enoate framework (**63**) to obtain the required core molecule tetracyclic macrolactone (**64**) as shown in the Scheme 42.

Roush and co-workers[100] have also effectively employed the IRC reaction of enone-enoate (**65**) framework as a key step to obtain the key tricyclic framework (**66**) during their work in synthesis of FR182877 (a potent antitumor molecule) as shown in Eq. 43.

Scheme 41

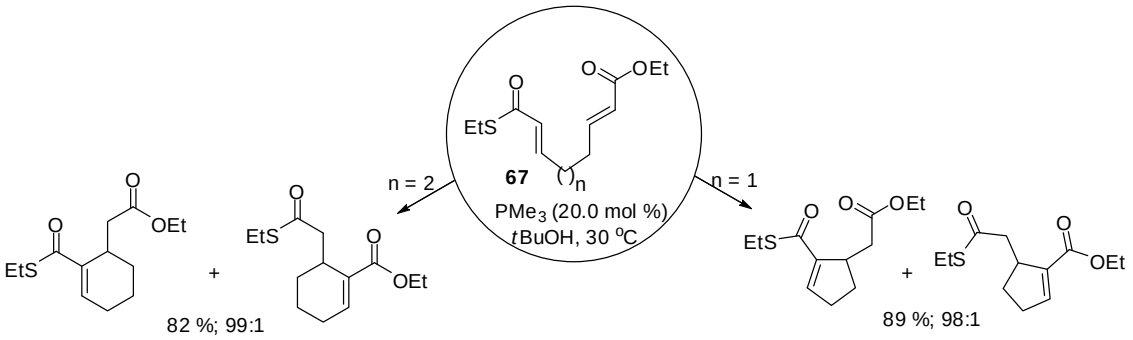


Scheme 42

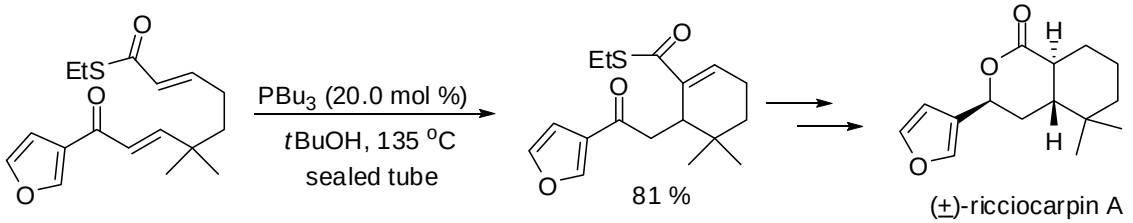


A chemoselective intramolecular IRC reaction of thioenoate-enoate framework (**67**) to provide corresponding carbocyclic compounds in highly chemoselective manner was reported by Agapiou and Krische[101] (Scheme 43). Subsequently this strategy was extended for synthesis of biologically important natural product ricciocarpin A according to synthetic strategy as in the Scheme 44.

Scheme 43

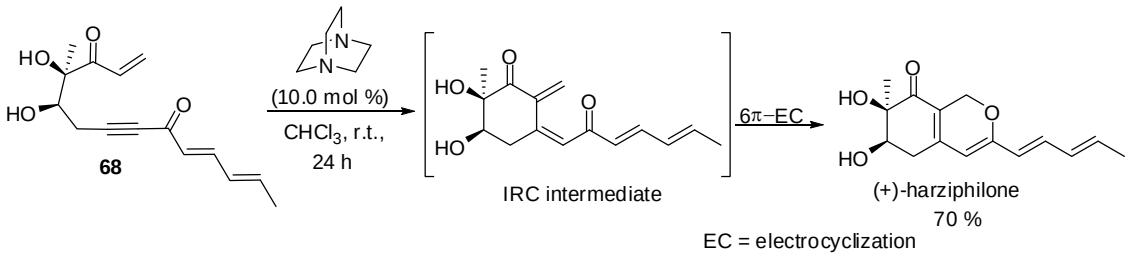


Scheme 44



Intramolecular Rauhut-Currier reaction of enone-ynone scaffold (**68**) for obtaining (+)-harziphilone (HIV-1 Rev/RRE inhibitor) was reported by Sorensen and co-workers[102] following the reaction pathway as shown in the Scheme 45.

Scheme 45



OBJECTIVES, RESULTS AND DISCUSSION

From the preceding section it is quite clear that the Baylis-Hillman (B-H) reaction involves three components 1) activated alkene 2) electrophile 3) catalyst. Although variety of reactive activated alkenes such as acrylates, vinyl ketones and acrylonitriles *etc.* have been extensively used, less reactive activated alkenes such as acrylamides, vinyl sulfoxides and vinyl sulfones have rarely been used in the B-H reactions. Similarly a number of reactive electrophiles such as aldehydes, α-keto esters, α-keto amides, α-diketones and α-fluoro ketones *etc.* are routinely used in the coupling reaction with various activated alkenes. However there are not many reports on the utility of normal ketones in the B-H reactions because of their inferior reactivity profile particularly in this reaction. Intramolecular Baylis-Hillman reaction is a growing branch of Baylis-Hillman chemistry that has attracted the attention of medicinal and synthetic chemists because it produces various carbocyclic and heterocyclic compounds of different ring sizes. Keeping the low reactivity profile of acrylamides and ketones and also importance of intramolecular Baylis-Hillman reaction in mind we have undertaken thesis work with the following objectives.

OBJECTIVES

1) To design and synthesize substrates containing less reactive acrylamides as activated alkene components and aldehydes as electrophile components and to develop a facile protocol for their intramolecular coupling reactions.

2) To design and synthesize substrates containing less reactive acrylamides as activated alkene and ketones as electrophile components so as to perform their intramolecular cyclization.

3) To design and synthesize chiral (racemic) substrates containing less reactive acrylamide and ketone as activated alkene and electrophile components respectively and examine their potential for diastereoselective IBH-reaction

All the three objectives would provide, in principle, simple protocols for obtaining α-methylene lactam derivatives, the biologically important and medicinally relevant frameworks.

RESULTS AND DISCUSSION

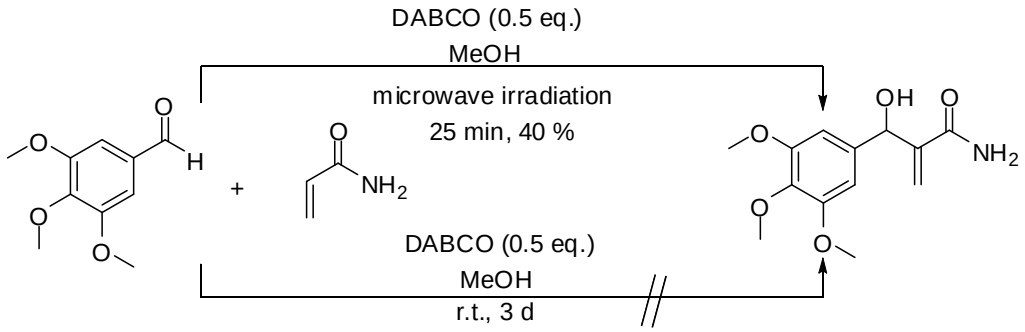
Acrylamide moiety as an activated alkene component in intramolecular Baylis-Hillman reaction: a facile synthesis of functionalized α-methylene lactam and spirolactam frameworks

Since our objective deals with utility of acrylamide moiety as an activated alkene in intramolecular Baylis-Hillman reaction it is appropriate to present relevant literature reports briefly in this section on the applications of acrylamides as activated alkenes in BH-reaction.

Acrylamides as activated alkenes in intermolecular Baylis–Hillman reaction

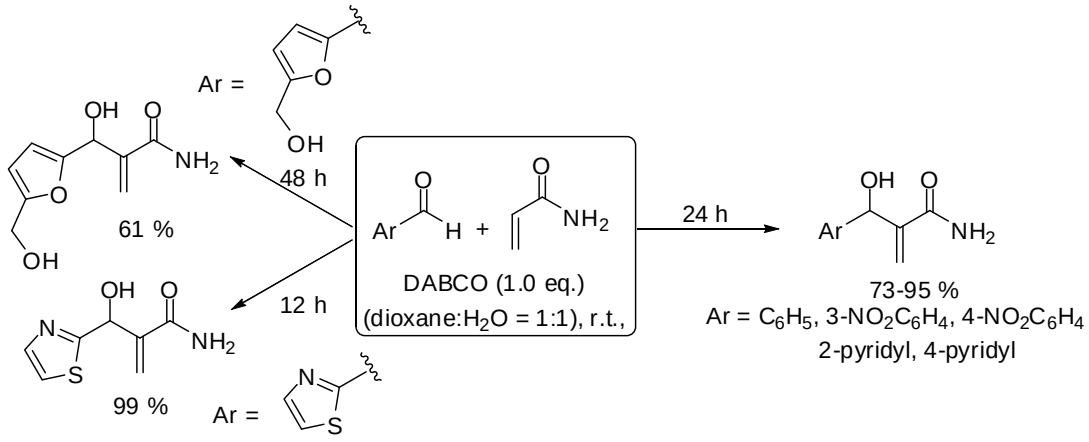
Bhat and co-workers[103a] have utilized acrylamide as a actiavated alkene and 3,4,5-trimethoxybenzaldehyde as electrophile in presence of DABCO under microwave irradiation to obtain corresponding BH-adduct in moderate yield. They observed that no reaction occurred at room temperature even after 3-days (Scheme 46).

Scheme 46



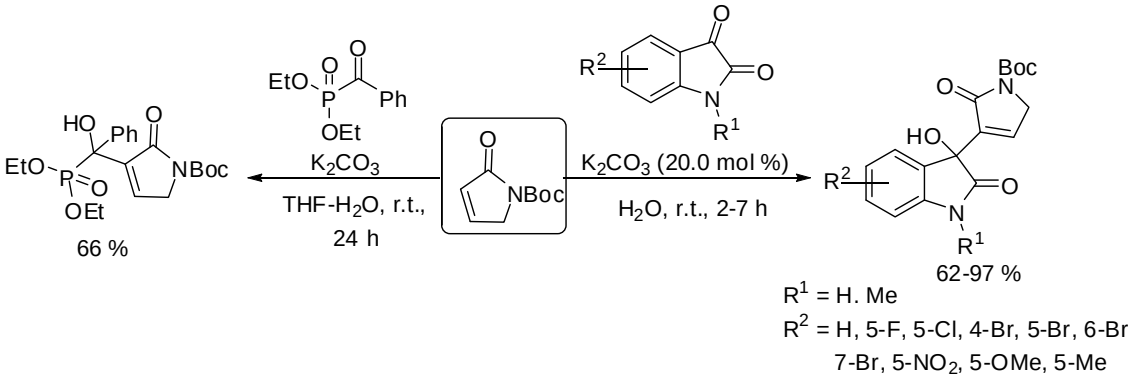
Yu and Hu[103b] have developed a simple procedure for BH-reaction of acrylamides with aromatic aldehydes using dioxane-water (1:1) solvent system in the presence of DABCO to provide the corresponding adducts in good yields (Scheme 47).

Scheme 47

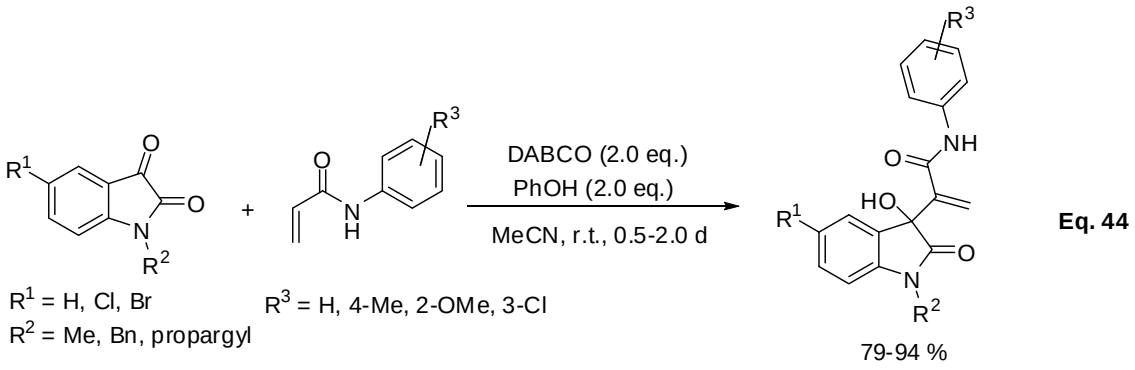


Ramreddy and Zhao[104] have reported the reaction of cyclic α, β-unsaturated amide with isatin derivatives and diethyl benzoylphosphonate in the presence of K_2CO_3 to provide the resulting adducts in high yields (Scheme 48).

Scheme 48



Recently Bharadwaj and co-workers[105] have reported a facile coupling of acrylamides with isatin derivatives in the presence of DABCO and phenol to provide the corresponding BH alcohols in high yields (Eq. 44).



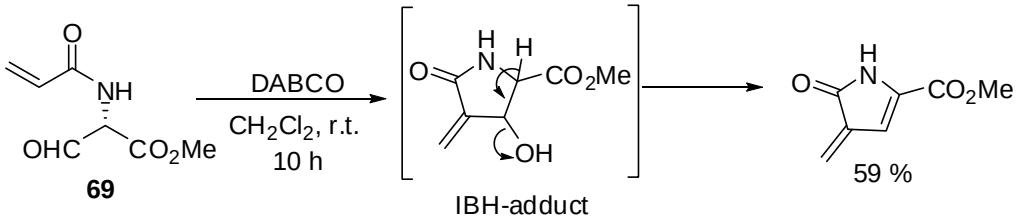
Eq. 44

Acrylamides as activated alkenes in intramolecular Baylis–Hillman reaction

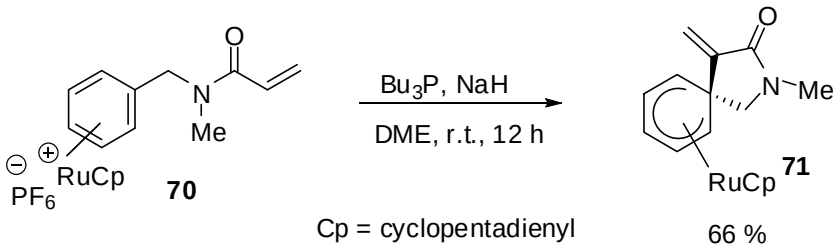
There are also some intramolecular Baylis–Hillman reactions reported in the literature involving acrylamides as activated alkene components.

Intramolecular Baylis-Hillman reaction of acrylamide-aldehyde substrate (**69**) (derived from L-serine) using DABCO as a catalyst was reported by Krishna and co-workers[106] (Scheme 49).

Scheme 49



An interesting intramolecular organometallic variation of BH reaction of substrate (**70**) containing ruthenium-arene complex as an electrophilic component and less reactive acrylamide as activated alkene component using tributylphosphine/NaH, providing spirolactam-ruthenium framework (**71**) was reported by Pigge and co-workers.[107] One such example is presented in the Eq. 45.



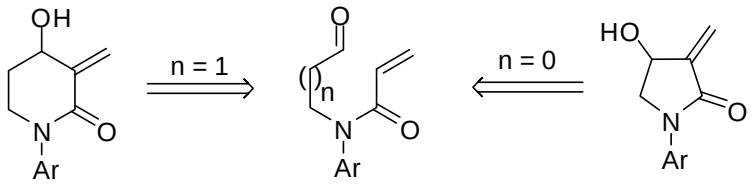
Eq. 45

Intramolecular Baylis-Hillman reaction of acrylamides (less reactive) as activated alkenes and aldehydes as electrophiles: synthesis of α-methylene lactam frameworks

In view of less reactivity nature of acrylamide, it is generally felt that development of Baylis-Hillman reactions and its intramolecular versions by employing acrylamides as

activate alkene components is considered to be a challenging and fascinating endeavor in BH-chemistry. We therefore felt that it is an appropriate problem for us to address. Accordingly we planned to design and synthesize substrates having acrylamides unit as activated alkenes, aldehydes as electrophile components and then to examine their potential in the intramolecular Baylis-Hillman reactions according to the strategy shown in the Scheme 50.

Scheme 50: Strategy for IBH reaction of acrylamide-aldehyde systems

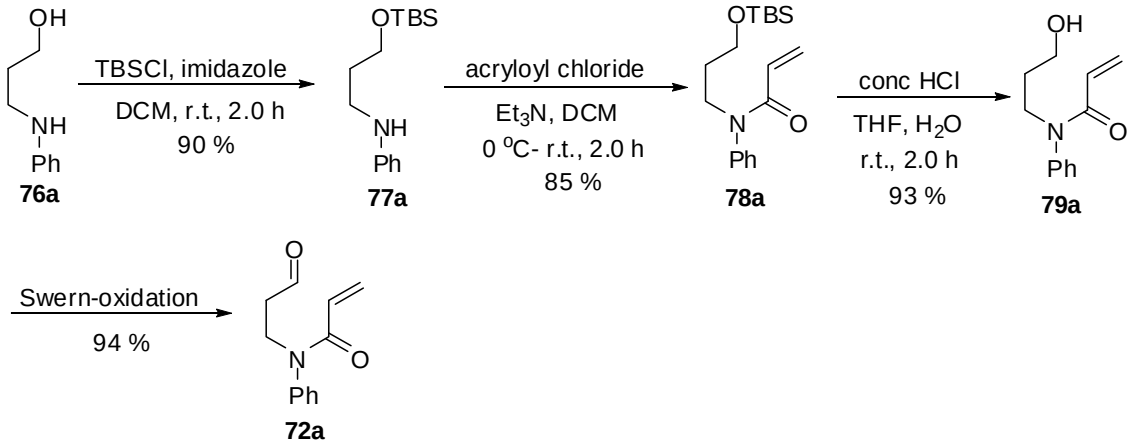


74 **72**, n = 1 **73**, n = 0 **75**

The reactions shown in the above mentioned Scheme 50, should in principle lead to the development of a simple protocol for obtaining 3-methylene-4-hydroxypiperidin-2-one (**74**) and 3-methylene-4-hydroxypyrrolidin-2-one (**75**) derivatives. We have first selected N-(3-oxopropyl)-N-phenylacrylamide (acrylamide-aldehyde) **72a** (n = 1, Ar = phenyl) as a suitable substrate for performing intramolecular B-H reaction. The required substrate (**72a**) was prepared starting from easily accessible 3-(phenylamino)propan-1-ol (**76a**)[108] following the reaction sequence as shown in the Scheme 51. This strategy involves four steps 1) TBS protection of amino alcohol (**76a**) 2) preparation of acrylamide **78a** from OTBS-amine (**77a**) 3) TBS deprotection of acrylamide (**78a**) to give acrylamide alcohol (**79a**) 4) oxidation of acrylamide alcohol (**79a**) to give

acrylamide-aldehyde **72a**. We have confirmed structures of all the intermediates (**77a**, **78a**, **79a**) (which were obtained in high yields) and the required substrate **72a** by IR, ^{1}H NMR, ^{13}C NMR and LCMS analysis.

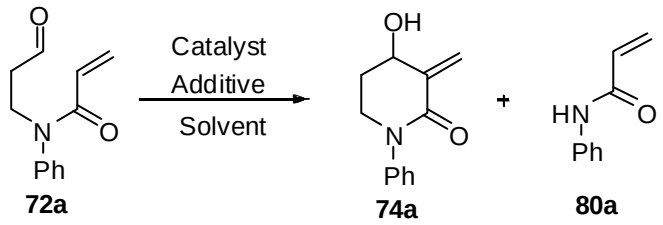
Scheme 51



Since DABCO is used as a common catalyst in the BH-reaction, we have first performed the reaction of acrylamide-aldehyde substrate (**72a**) with DABCO in acetonitrile solvent at room temperature. We were pleased to see that the reaction is reasonably clean and provided the required cyclic compound (**74a**) in 60 % yield in 24 hours time (Table 1, Entry 1). This reaction is indeed encouraging. Even though the yield is reasonably satisfactory and reaction time is quite encouraging we have directed our attempts to increase the yields and decrease the reaction time by performing the intramolecular cyclization under various conditions (Table 1). The best result was obtained when acrylamide-aldehyde substrate (**72a**) (1.0 mmol) was treated with DABCO (1.0 equiv.) in *t*BuOH (6 mL) as solvent under reflux conditions to provide the desired intramolecular Baylis-Hillman adduct (**74a**) in 75% yield in 13 h reaction time

(Table 1, Entry 22). Structure of the molecule (**74a**) was confirmed by IR, ^{1}H NMR [see Spectrum 1], ^{13}C NMR [see Spectrum 2] and HRMS analysis. From the Table 1 it is also clear that in some cases (Table 1, Entries 7–15, 19–21 and 26–31) formation of substantial amounts of *N*-phenylacrylamide (**80a**) was observed. This might be attributed to the retro-Michael reaction of **72a** as shown in the Eq. 46.

Table 1. Optimization of the reaction condition[a]



72a **74a** **80a**

Entry	Solvent	Amount mL/mmol of **72a**	Cat.(mmol)	Cond.	Additive 5 mol%	t(h)	Yield[b] % (**74a**)[c]	Yield[b] % (**80a**)[c]
1	CH_3CN	1	DABCO/(1.0)	r.t.	-	24	60	-
2	"	1	DABCO/(0.5)	"	-	60	61	-
3	"	1	DABCO/(0.25)	"	-	96	58	-
4	"	1	DABCO/(2.5)	"	-	12	59	-
5	"	3	DABCO/(1.0)	"	-	60	64	-
6	"	6	"	"	-	132	71	-
7	"	2	"	reflux	-	6	63	15
8	"	"	"	"	$MeSO_3H$	6	62	13
9	"	"	"	"	TFA	6	65	19
10	DMF	"	"	"	-	0.5	36	47
11	"	"	"	"	$MeSO_3H$	0.5	34	46
12	"	"	"	"	TFA	0.5	33	48
13	*t*BuOH	"	"	"	-	6	66	16
14	"	"	"	"	$MeSO_3H$	6	64	14
15	"	"	"	"	TFA	6	63	13
16	CH_3CN	6	"	"	-	36	67	-
17	"	"	"	"	$MeSO_3H$	36	66	-
18	"	"	"	"	TFA	36	68	-

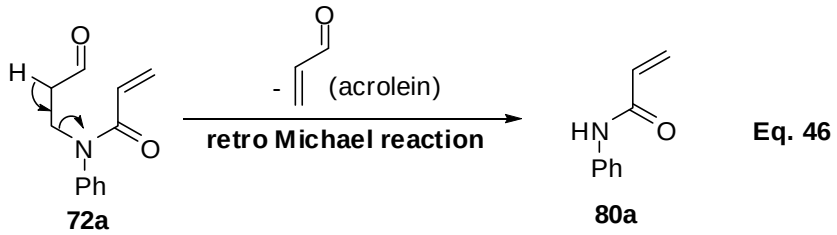
19	DMF	"	"	"	-	1	31	54
20	"	"	"	"	$MeSO_3H$	1	35	51
21	"	"	"	"	TFA	1	30	55
22	***tBuOH***	*″*	*″*	*″*	-	***13***	***75***	-
23	"	"	"	"	$MeSO_3H$	13	72	-
24	"	"	"	"	TFA	13	74	-
25	DCM	"	"	"	-	12	-	-
26	THF:H_2O (1:1)	"	"	65 ºC	-	1.5	47	15
27	CH_3CN	"	DMAP/(1.0)	reflux	-	72	30	34
28	DMF	"	"	"	-	1	-	75
29	*t*BuOH	"	"	"	-	72	26	27
30	CH_3CN	"	$P(Bu)_3$/(1.0)	r.t.	-	0.25	-	30
31	*t*BuOH	"	"	"	-	0.25	-	28

Cat.: catalyst; Cond.: condition; t: time

[a] All the reactions were carried out on a 1.0 mmol scale of acrylamide-aldehyde (**72a**).

[b] Isolated yields of pure products based on acrylamide-aldehyde (**72a**).

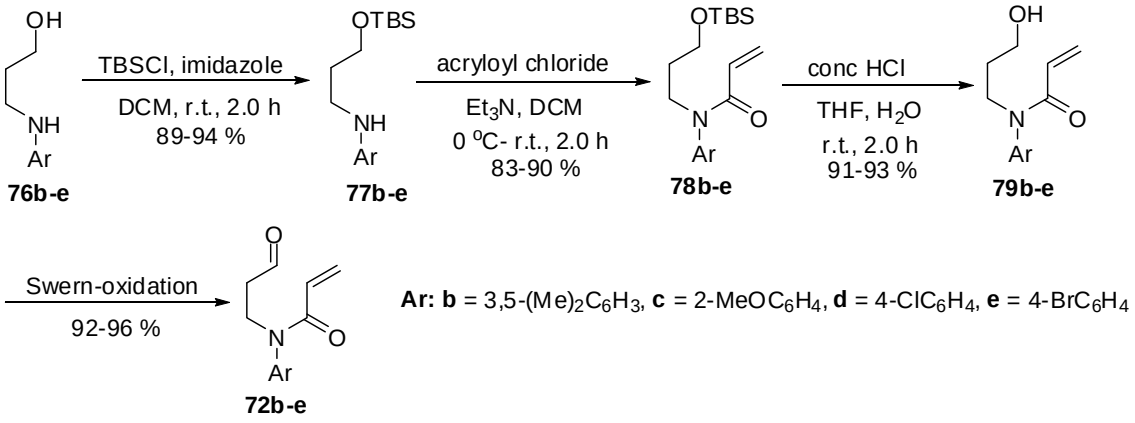
[c] Fully characterized.



Eq. 46

Encouraged by the result we have prepared representative N-(3-oxopropyl)-N-arylacrylamides (**72b-e**) following the four step protocol starting from amino alcohols (**76b-e**) as indicated in Scheme 52. Structures of all the compounds (**77b-e**, **78b-e**, **79b-e** and **72b-e**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR and LCMS spectral data analysis.

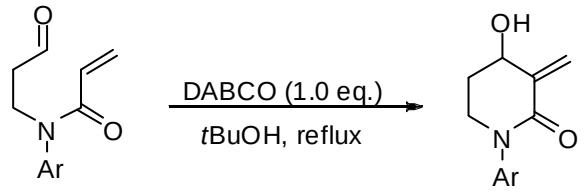
Scheme 52



Then we have subjected these acrylamide-aldehydes (**72b-e**) to the optimized reaction condition which provided the desired cyclic adducts (**74b-e**) in excellent yields (73-78 %) as shown in the Table 2. Structures of all the compounds (**74b-e**) were confirmed by IR, ^{1}H NMR [for compound **74c** see Spectrum 3 (at 23 ºC) and Spectrum 4 (at -36 ºC)], ^{13}C NMR [for compound **74c** see Spectrum 5] and HRMS spectral data analysis.

From the Table 2 it is clear that reactions are faster (6 hours) in the case of substrates (**72d** and **72e**) having electron withdrawing groups (4-Cl and 4-Br) on aromatic ring (N-aryl ring) while the substrates (**72b** and **72c**) with electron donating groups (3,5-(Me)$_2$ and 2-MeO) on aromatic ring (N-aryl ring) reduce the rate of reaction (24 and 84 hours respectively).

Table 2. Synthesis of α-methylene-δ-lactam derivatives 74a–e[a]



72a-e **74a-e**

Entry	AA	Ar	Product[b]	t(h)	Yield(%)[c]
1	**72a**	C_6H_5	**74a**	13	75
2	**72b**	3,5-$(Me)_2C_6H_3$	**74b**	24	77
3	**72c**	2-$MeOC_6H_4$	**74c**	84	73
4	**72d**	4-ClC_6H_4	**74d**	6	74
5	**72e**	4-BrC_6H_4	**74e**	6	78

AA: acrylamide-aldehyde; Ar: aryl; t: time

[a] All reactions were carried out on a 1.0 mmol scale of acrylamide-aldehydes (**72a-e**) using 1.0 equiv. of DABCO in *t*BuOH (6.0 mL) at reflux temperature.

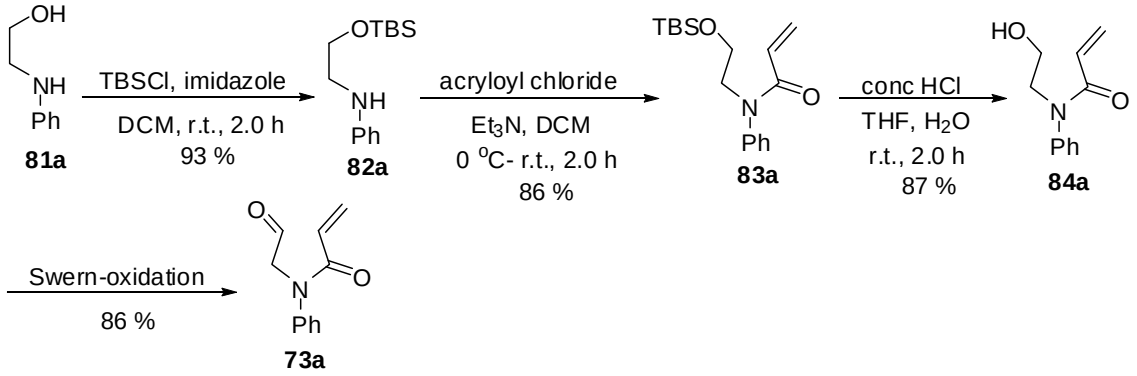
[b] All the products (**74a-e**) were obtained as white solids and fully characterized.

[c] Yields of pure isolated products (**74a-e**) based on acrylamide-aldehydes (**72a-e**).

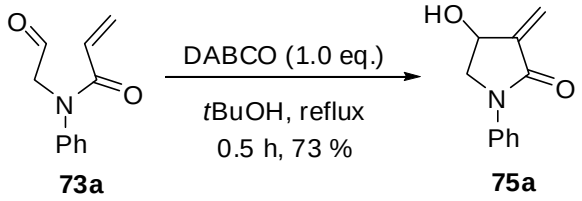
After successfully developing the intramolecular Baylis-Hillman reaction strategy for acrylamide-aldehyde units to provide 6-membered lactam derivatives, we have focused our studies towards developing intramolecular Baylis-Hillman protocol for obtaining 5-membered lactam derivatives. For this purpose we have first selected N-(2-oxoethyl)-N-phenylacrylamide (**73a**) as a substrate for the intramolecular Baylis-Hillman reaction. The required substrate (**73a**) was prepared from easily accessible 2-(phenylamino)ethanol (**81a**)[96] following the reaction sequence as shown in the Scheme 53. All these reactions were clean and provided the intermediates (**82a**, **83a** and **84a**)

and the required substrate **73a** in high yields. We have confirmed the structures of the molecules (**82a**, **83a**, **84a** and **73a**) by IR, ^{1}H NMR, ^{13}C NMR and LCMS spectral data analysis.

Scheme 53



After obtaining N-(2-oxoethyl)-N-phenylacrylamide (**73a**) in hand we have performed the IBH-reaction using the optimized condition (same as in the case of 6-membered lactam preparation). We were pleased to see the reaction is very fast taking 0.5 hour time for completion, to provide the resulting adduct (**75a**) in 73 % yield (Eq. 47). Structure of this molecule (**75a**) was established by IR, ^{1}H NMR [see Spectrum 6], ^{13}C ^{13}C NMR [see Spectrum 7] and HRMS spectral data analysis.

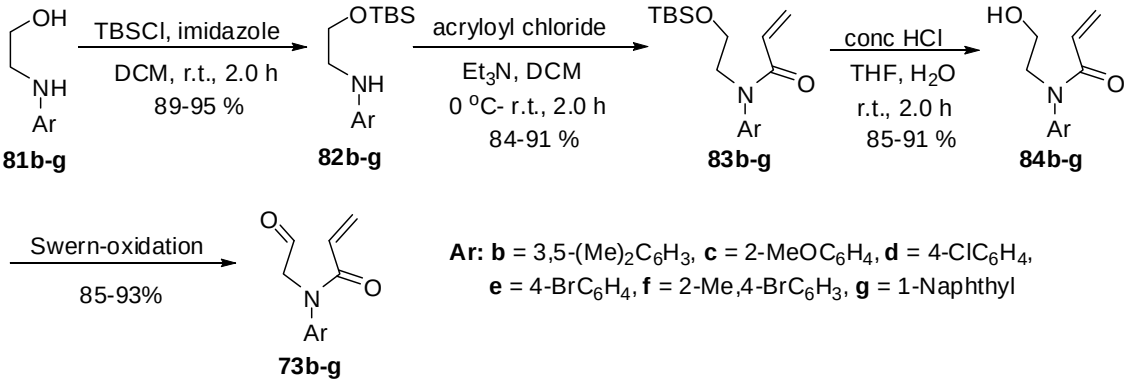


Eq. 47

We have then prepared representative acrylamide-aldehydes (**73b-g**) following the reaction sequence as shown in the Scheme 54. All the compounds (**82b-g**, **83b-g**, **84b-g**

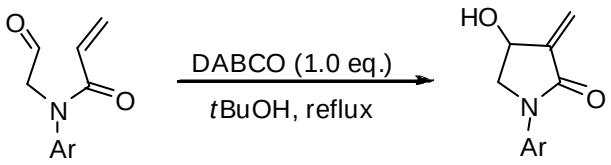
and **73b-g**) were obtained in excellent yields. Structures of the compounds were confirmed by IR, ^{1}H NMR and LCMS spectral data analysis.

Scheme 54



We have then subjected the acrylamide-aldehydes (**73b-g**) to the optimized conditions to provide the resulting 5-membered cyclic adducts (**75b-g**) in high yields and in less reaction times (0.1-2.5 h) (Table 3). It is quite clear that substrate containing electron donating groups on aromatic ring (N-aryl) (**73b** and **73c**) take longer time for completion while the substrates containing electron withdrawing groups on aromatic ring (N-aryl) having substrates (**73d** and **73e**) take remarkably less time for completion. Overall it is clear that 5-membered lactams (**75**) formation from substrates (**73**) is much faster than that of 6-membered lactams (**74**) from substrates (**72**). Structures of the molecules (**75b-g**) were in agreement with IR, ^{1}H NMR [for compound **75f** see Spectrum 8], ^{13}C NMR [for compound **75f** see Spectrum 9] and HRMS spectral data analysis. Structure of the compound (**75d**) was also confirmed by single crystal X-ray data analysis [For ORTEP diagram of the compound (**75d**) see Figure 1 and for data see Table 4].

Table 3. Synthesis of α-methylene-γ-lactam derivatives 75a–g[a]



73a-g **75a-g**

Entry	AA	Ar	Product[b]	t(h)	Yield(%)[c]
1	**73a**	C_6H_5	**75a**	0.5	73
2	**73b**	3,5-$(Me)_2C_6H_3$	**75b**	1.5	67
3	**73c**	2-$MeOC_6H_4$	**75c**	2.5	70
4	**73d**	4-ClC_6H_4	**75d**[d]	0.16	71
5	**73e**	4-BrC_6H_4	**75e**	0.16	69
6	**73f**	2-Me,4-BrC_6H_3	**75f**	1	72
7	**73g**	1-Naphthyl	**75g**	1.5	70

AA: acrylamide-aldehyde; Ar: aryl; t: time

[a] All reactions were carried out on a 1.0 mmol scale of acrylamide-aldehydes (**73a-g**) using 1.0 equiv. of DABCO in *t*BuOH (6.0 mL) at reflux temperature.

[b] All the products (**75a-g**) were obtained as (colorless/white/yellow/brown) solids and fully characterized.

[c] Yields of the pure isolated products based on acrylamide-aldehydes (**73a-g**).

[d] Structure of this compound **75d** was also confirmed by single crystal X-ray data analysis.

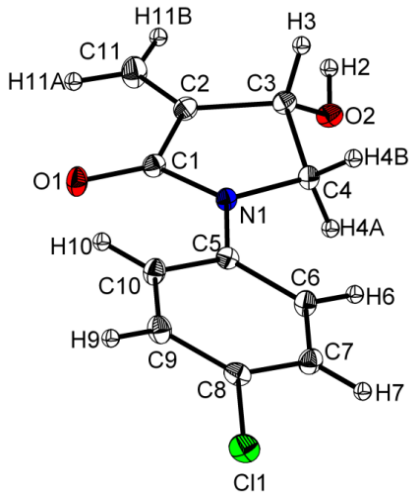
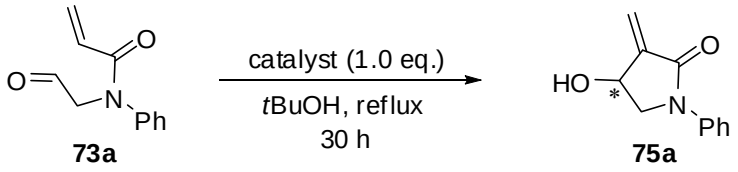


Figure 1. ORTEP diagram of the compound **75d**

***Table 4. Crystal data and structure refinement for* 75d**

Identification code	**75d**	
Empirical formula	C11 H10 Cl N O2	
Formula weight	223.65	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P 21/c*	
Unit cell dimensions	a = 4.6353(6) Å	α = 90°.
	b = 10.8365(14) Å	β = 100.292(3)°.
	c = 20.267(3) Å	γ = 90°.
Volume	1001.6(2) $Å^3$	
Z	4	
Density (calculated)	1.483 Mg/m^3	
Absorption coefficient	0.358 mm^{-1}	
F(000)	464	
Crystal size	0.28 x 0.14 x 0.10 mm^3	
Theta range for data collection	2.04 to 25.92°.	
Index ranges	-5<=h<=5, -13<=k<=13, -24<=l<=24	
Reflections collected	9948	
Independent reflections	1961 [R(int) = 0.0437]	
Completeness to theta = 25.92°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9651 and 0.9065	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1961 / 0 / 136	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0363, wR2 = 0.0931	
R indices (all data)	R1 = 0.0394, wR2 = 0.0955	
Largest diff. peak and hole	0.286 and -0.237 $e.Å^{-3}$	

After developing a facile procedure for synthesis of α-methylene-γ-lactam and α-methylene-δ-lactam derivatives via intramolecular Baylis-Hillman reaction of acrylamide-aldehyde substrates, we have directed our focus towards understanding the possibility of performing asymmetric intramolecular Baylis-Hillman reaction of substrate (**73a**). We have selected commercially available quinine and quinidine as chiral catalysts. We have performed the intramolecular Baylis-Hillman reaction of substrate (**73a**) with quinine (1.0 eq.). We were pleased to see the reaction works well though it takes longer time (30 h). The resultant adduct (**75a**) was obtained in 10 % enantioselectivity and in 65 % yield (Eq. 48). Enantioselectivity was determined by HPLC analysis [HPLC chart 1 of **75a** (racemic mixture) and HPLC chart 2 of **75a** (quinine as a promotor)] using chiral HPLC column Chiralcel-OJ-H]. We have next performed the same reaction with quinidine (1.0 eq.) as chiral catalyst; the resultant adduct (**75a**) was obtained in 5 % enantioselectivity and in 63 % yield (Eq. 48) [HPLC chart 3 of **75a** (quinidine as a promotor)]. Though the enantioselectivities are less, this study clearly indicates that there is a possibility for obtaining high enantioselectivities by designing appropriate chiral catalysts.



73a **75a** **Eq. 48**

catalyst = quinine: 65 %, *ee*: 10 %
catalyst = quinidine: 63 %, *ee*: 5%

It is interesting to mention here that α-methylene(alkylidene) lactam frameworks are present in various natural products pukeleimid E[109] (isolated from lyngbya majuscule), anatin[109], isoanatin[109] (isolated from leaves of cynometra) and gelegamine[109] (isolated from gelsemium elegans), the compounds **85**-**87**[110] (found in euphorbia humifusa) and two molecules **88**,[111] **89**[111] (isolated from the roots of polygala tricornis gagnep).

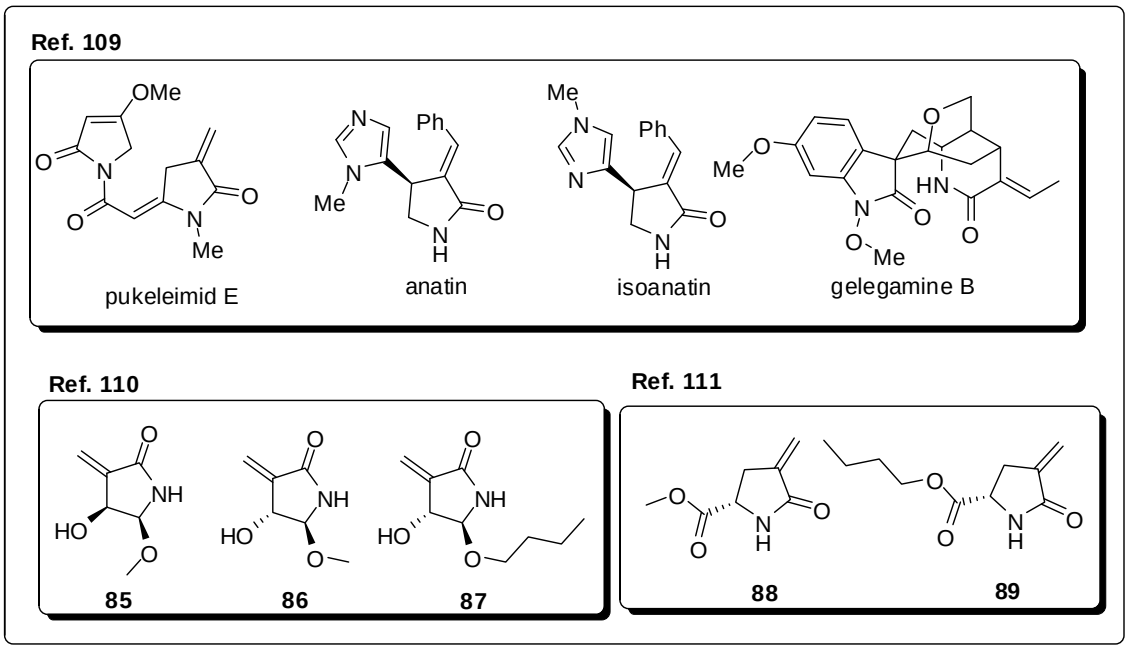
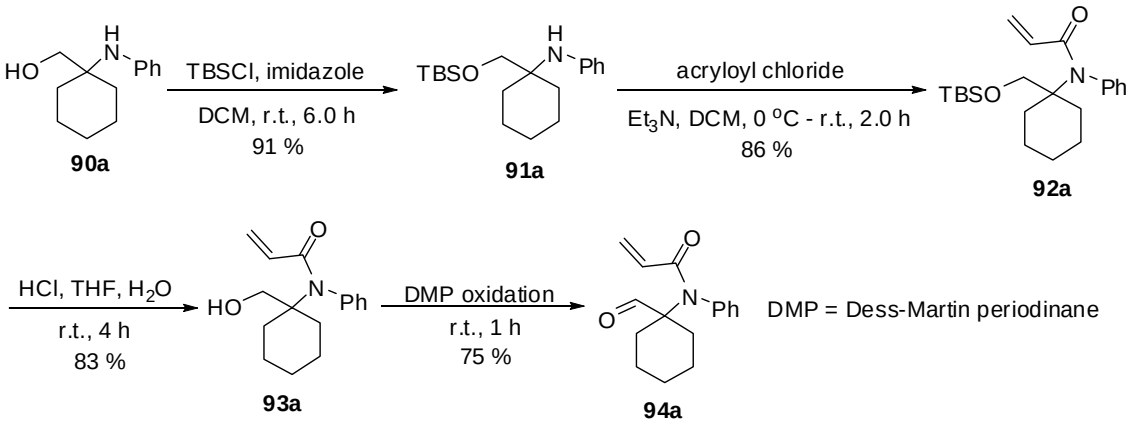


Figure 2

In view of importance of α-methylene-γ-lactam and α-methylene-δ-lactam frameworks, development of facile synthetic strategies for obtaining such derivatives is considered to be a challenging and attractive endeavor. Therefore, several strategies have been developed for obtaining such important frameworks.[112-120] In this context, the present intramolecular Baylis-Hillman methodology for obtaining α-methylene lactam derivatives (**74a-e** and **75a-g**) carries remarkable synthetic importance.

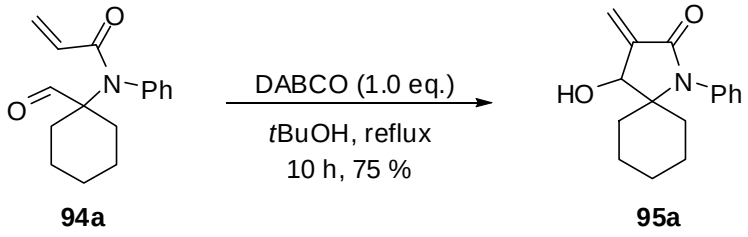
Encouraged by the success for performing intramolecular Baylis-Hillman reaction of substrates containing acrylamide and aldehyde moieties to obtain α-methylene δ –and γ-lactam derivatives we have focused our attention to extend this strategy for synthesis of spirolactam derivatives. Accordingly we have selected N-(1-formylcyclohexyl)-N-phenylacrylamide (**94a**) as a suitable substrate for intramolecular Baylis-Hillman reaction. The required substrate (**94a**) was prepared starting from easily accessible 1-(phenylamino)cyclohexylmethanol (**90a**)[121] following the reaction sequence as shown in the Scheme 55. This strategy also involves four steps as in the case of **72a** (Scheme 51). We have confirmed structures of all the intermediates (**91a**, **92a**, **93a**) and the required substrate **94a** by IR, ^{1}H NMR, ^{13}C NMR and LCMS spectral data analysis.

Scheme 55



After obtaining the required compound (**94a**), we have performed the intramolecular Baylis-Hillman reaction using reaction conditions as described for α-methylene lactam derivatives (**74a-e** and **75a-g**). This reaction was found to be clean and provided spirolactam derivative (**95a**) in 75 % yield in 10 hours time (Eq. 49). The structure of

the compound (**95a**) was confirmed by IR, ^{1}H NMR [see Spectrum 10], ^{13}C NMR [see Spectrum 11] and HRMS analysis. Structure of the compound (**95a**) was also confirmed by single crystal X-ray spectral data analysis [For ORTEP diagram of compound see Figure 3 and for data see Table 5].



94a **95a** **Eq. 49**

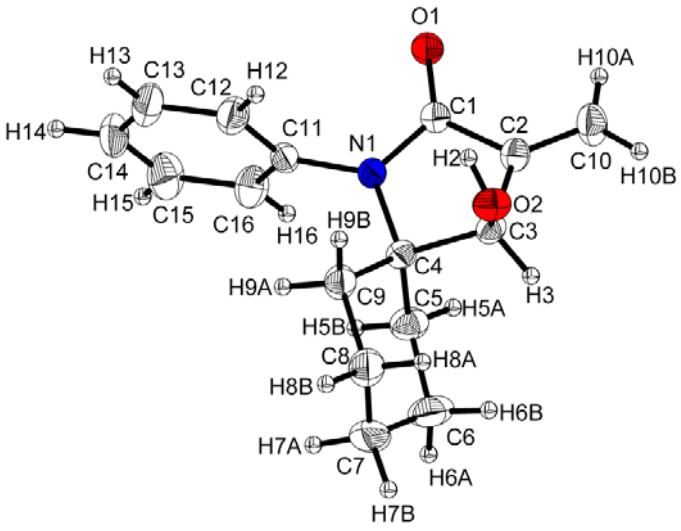


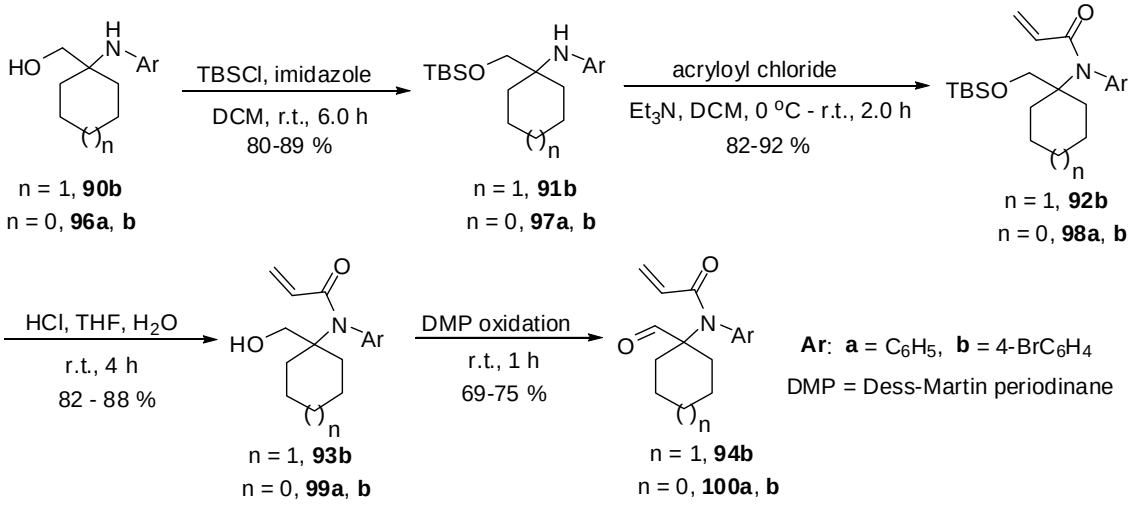
Figure 3. ORTEP diagram of the compound **95a**

***Table 5. Crystal data and structure refinement for* 95a**

Identification code	**95a**	
Empirical formula	C16 H19 N O2	
Formula weight	257.32	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P2(1)/c*	
Unit cell dimensions	a = 13.9362(17) Å	α = 90°.
	b = 14.8680(18) Å	β = 90.750(2)°.
	c = 6.5740(8) Å	γ = 90°.
Volume	1362.0(3) $Å^3$	
Z	4	
Density (calculated)	1.255 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	552	
Crystal size	0.46 x 0.25 x 0.20 mm^3	
Theta range for data collection	1.46 to 26.03°.	
Index ranges	-17<=h<=17, -18<=k<=18, -8<=l<=8	
Reflections collected	13917	
Independent reflections	2678 [R(int) = 0.0236]	
Completeness to theta = 26.03°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2678 / 0 / 173	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.1145	
R indices (all data)	R1 = 0.0481, wR2 = 0.1196	
Largest diff. peak and hole	0.156 and -0.219 $e.Å^{-3}$	

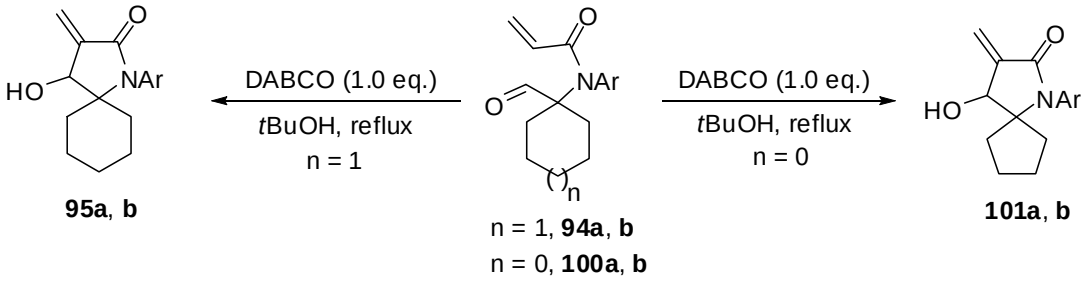
Then we have prepared three more substrates (**94b**, **100a and 100b**) following the reaction sequence as described in the Scheme 56. We have confirmed structures of all the intermediate products (**91b**, **97a**, **97b**, **92b**, **98a**, **98b**, **93b**, **99a** and **99b**) and the required BH-substrates (**94b**, **100a and 100b**) by IR, ^{1}H NMR, ^{13}C NMR and LCMS spectral data analysis.

Scheme 56



Then these acrylamide-aldehyde substrates (**94b**, **100a and 100b**) were subjected to IBH-reaction under the similar condition as described for α-methylene lactam derivatives (**74a-e** and **75a-g**). The resulting spirolactam derivatives (**95b**, **101a**, and**101 b**) were obtained in 68-72 % yields and in 0.5-2.5 hour time (Table 6). Structures of the molecules (**95b**, **101a**, and**101 b**) were in agreement with IR, ^{1}H NMR [for compound **101a** see Spectrum 12], ^{13}C NMR [for compound **101a** see Spectrum 13] and HRMS spectral data analysis.

Table 6. Synthesis of spiro-γ-lactam derivatives 95a, b and 101a, b[a]



95a, **b**

n = 1, **94a**, **b**
n = 0, **100a**, **b**

101a, **b**

Entry	AA	Ar	n	Product[b]	t(h)	Yield(%)[c]
1	**94a**	C_6H_5	1	**95a**[d]	10	75
2	**94b**	4-BrC_6H_4	1	**95b**	2.5	72
3	**100a**	C_6H_5	0	**101a**	2	68
4	**100b**	4-BrC_6H_4	0	**101b**	0.5	70

AA: acrylamide-aldehyde; Ar: aryl; t: time

[a] All the reactions were carried out on a 1.0 mmol scale of acrylamide-aldehydes (**94a**, **b** and **100a**, **b**) using 1.0 equiv. of DABCO in *t*BuOH (6.0 mL) at reflux temperature.

[b] All the products were (**95a**, **b** and **101a**, **b**) obtained as colorless (or) white solids and fully characterized.

[c] Yields of the pure isolated intramolecular products (**95a**, **b** and **101a**, **b**) based on acrylamide-aldehydes (**94a**, **b** and **100a**, **b**).

[d] Structure of this compound **95a** was also confirmed by single crystal X-ray data analysis.

It is worth mentioning here that spirolactam frameworks are present in various natural products. Some such natural products (ansalactam A,[122] stemonamide[123] and isostemonamide[123]) are presented in Figure 4. Certain spirolactam frameworks have also shown insecticidal activity and anticancer activity.[124-126] Therefore, there has been increasing interest in developing simple strategies for obtaining spirolactam

derivatives.[127-130] In view of the synthetic and biological importance of the spirolactam framework our strategy attains considerable significance.

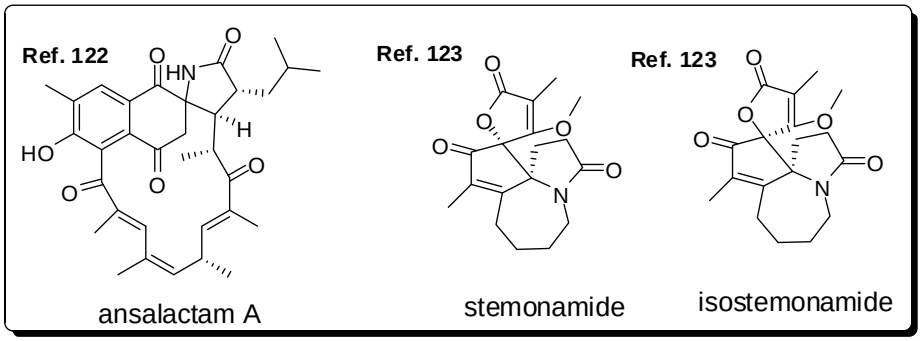


Figure 4

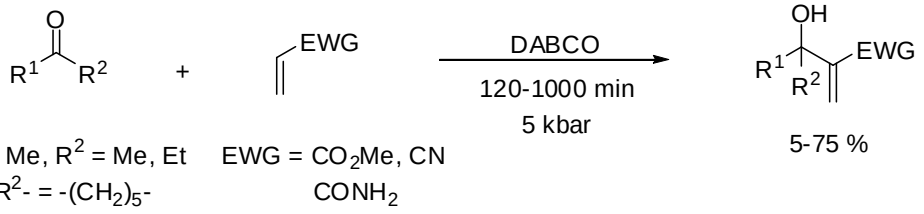
In conclusion, we have developed a facile intramolecular BH reaction of substrates containing an acrylamide as an activated alkene (less-explored activated alkene unit) component and an aldehyde as the electrophile component. This protocol provides a convenient strategy for construction of five- and six-membered α-methylene lactam and spirolactam derivatives. This methodology clearly demonstrates the importance of the acrylamide unit as a suitable activated alkene component for intramolecular BH reactions. This strategy also shows the opportunities and the way to design new classes of such substrates, which would lead to the construction of various lactam moieties with different ring sizes. Even though, enantioselectivities are low in the case of quinine and quinidine as promoters, our studies, clearly indicate that the design of appropriate catalyst would certainly provide high enantioselectivities.

Less reactive ketones as electrophiles and acrylamides as activated alkenes in intramolecular Baylis-Hillman reaction: facile synthesis of functionalized γ-lactam frameworks with tertiary alcoholic functionality

From the available literature on the Baylis-Hillman reaction it is well known that applications of ketones (except reactive ketones like α-keto esters, α-keto amides, α-diketones and α-fluoro ketones) as electrophiles in Baylis-Hillman reaction have not been well studied because of less reactivity nature of ketones in comparison to aldehydes. Literature shows that there are a very few reports on the application of ketones as electrophiles in BH-reaction.

Ketones as electrophiles in intermolecular Baylis-Hillman reaction

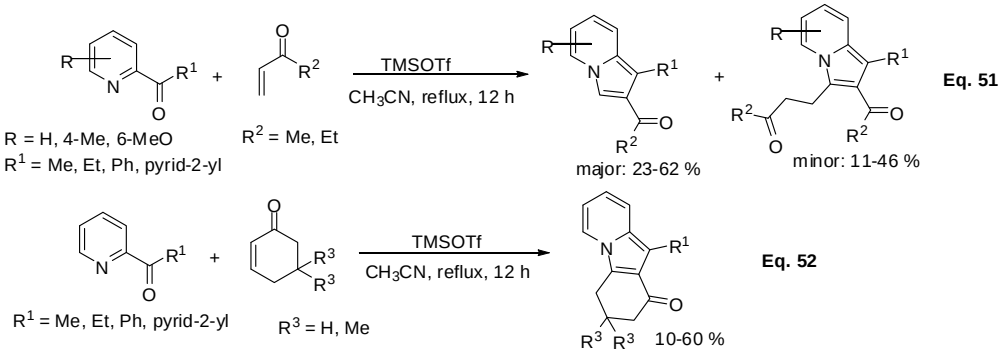
Hill and Isaacs[131] reported Baylis-Hillman reaction of ketones as electrophiles with different activated alkenes in presence of DABCO under high pressure condition to provide the resulting adducts in low to good yields (Eq. 50).



Eq. 50

Recently our research group[132] has reported an interesting two component Baylis-Hillman reaction of pyrid-2-yl alkyl(aryl) ketones (nitrogen of pyridine serving as

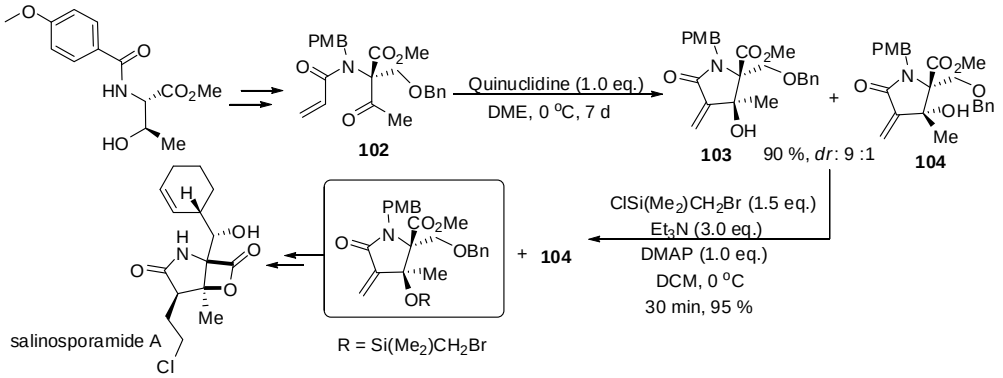
reaction initiator and ketone as an electrophile) with alkyl vinyl ketones (as activated alkenes) in the presence of TMSOTf to produce substituted indolizines (Eq. 51 and 52).



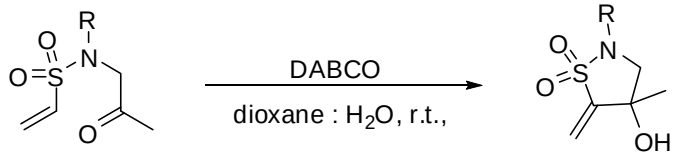
Ketones as electrophiles in intramolecular Baylis-Hillman reaction

There are also a few reports available in the literature on the applications of ketones as electrophiles in the intramolecular Baylis-Hillman reaction. Corey and co-workers[133] have successfully used substrate (**102**) containing ketone as a electrophile component and acrylamide as a activated alkene component for IBH-reaction using quinuclidine as a catalyst to provide the resulting adducts (**103** and **104**) in 9:1 diastereoselectivity in 90% yield. The major compound (**103**), thus obtained was subsequently transformed into salinosporamide A following the reaction sequence as indicated in the Scheme 57.

Scheme 57



Another important application of ketone as a electrophile component in IBH-reaction was reported by Zhou and co-workers,[134] who have described the intramolecular cyclization of substrates (**105**), having ketone and vinyl sulfonamide units, in presence of DABCO using dioxane:water solvent system at room temperature (Eq. 53).



105

74-82 %

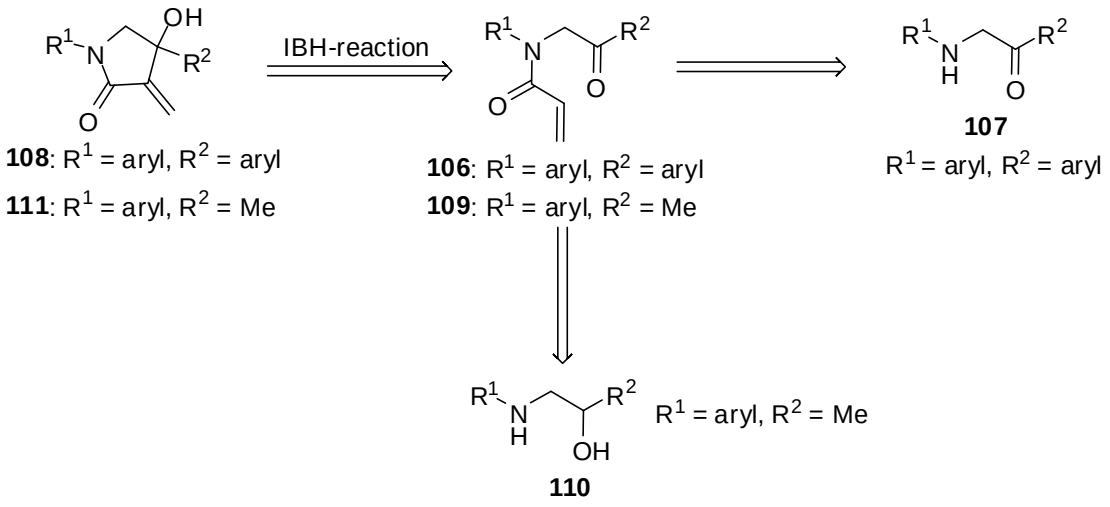
Eq. 53

R = Cy, *i*Pr, *n*Pr, *i*Bu, *t*Bu, *n*Bu, Bn, CH_2-Bn

Because of their less reactivity profile, utilizing ketones as electrophiles is considered to be a challenging and an interesting endeavor in the Baylis-Hillman reaction.

From the previous section it is clear that the formation of α-methylene-γ-lactams (**75a-g**) (5-membered lactams) from N-(2-oxoethyl)-N-arylacrylamides (**73a-g**) is faster than that of α-methylene-δ-lactams (**74a-e**) (6-membered lactams) from N-(3-oxopropyl)-N-arylacrylamides (**72a-e**). This remarkable fast reactivity profile between acrylamide and aldehyde units in the formation of α-methylene-γ-lactam frameworks has indeed made us to envisage that ketones might prove as promising electrophiles in intramolecular Baylis-Hillman coupling with acrylamides for producing functionalized γ-lactam derivatives containing tertiary alcoholic functionality (**108** and **111**) according to retro-synthetic strategy shown in Scheme 58.

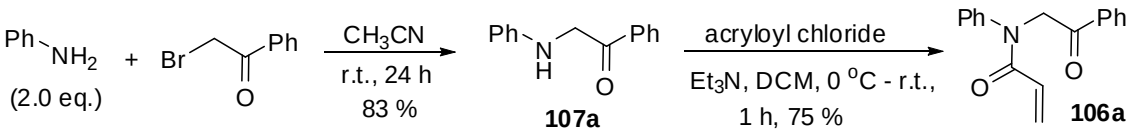
Scheme 58: Retro-synthetic strategy



IBH reaction = Intramolecular Baylis-Hillman reaction

Accordingly we have first selected the N-(2-oxo-2-phenylethyl)-N-phenylacrylamide (**106a**) as a suitable substrate for our studies. We have prepared N-(2-oxo-2-phenylethyl)-N-phenylacrylamide (**106a**) starting from readily available starting materials aniline and phenacyl bromide following the reaction sequence as shown in the Scheme 59. This strategy involves two steps 1) N-alkylation of aniline[135] 2) preparation of acrylamide-ketone (**106a**). We have confirmed the structures of the compounds (**106a** and **107a**) by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

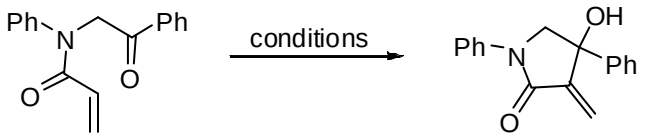
Scheme 59



We have then focused our attention in finding out appropriate reaction conditions for performing intramolecular BH reaction. In this direction we have examined the

applicability of various amines and phosphines in different solvents and reaction conditions (Table 7). After several attempts we were pleased to see highly encouraging results (Entry 21, Table 7) when we have treated **106a** (1.0 mmol) with DABCO (1.0 equiv.) in dioxane : water (1:1) solvent system (2 mL) at 65 ^{o}C for 5 h thus providing desired intramolecular Baylis Hillman adduct (4-hydroxy-3-methylene-1,4-diphenylpyrrolidin-2- one) (**108a**) in 88 % yield. Structure of the molecule (**108a**) was in agreement with IR, ^{1}H NMR [**108a** see Spectrum 14], ^{13}C NMR [**108a** see Spectrum 15] and HRMS analysis. Structure was further confirmed by single crystal X-ray data analysis [For ORTEP diagram of compound (**108a**) see Figure 5 and for data see Table 8].

Table 7. Optimization of reaction conditions.[a, b]



106a **108a**

Entry	Solvent(mL)	Catalyst	PhOH(equiv.)	T (^{o}C)	t (h)	Yield (%)[c]
1	*t*BuOH (6)	DABCO	-	Reflux	84	86
2	*t*BuOH (6)	DMAP	-	Reflux	18	N. R.
3	*t*BuOH (6)	Imidazole	-	Reflux	18	N. R.
4	*t*BuOH (6)	$P(Ph)_3$	-	Reflux	18	18
5	*t*BuOH (6)	$P(Ph)_3$	-	Reflux	144	62
6	*t*BuOH (6)	$P(Bu)_3$	-	r.t.	0.25	C.M.
7	MeCN (6)	DABCO	-	Reflux	18	20
8	MeCN (6)	DABCO	-	Reflux	120	68
9	DCE (6)	DABCO	-	Reflux	18	N. R.
10	*t*BuOH (6)	DABCO	1	Reflux	66	84
11	*t*BuOH (1)	DABCO	1	Reflux	16	82
12	DMF (6)	DABCO	-	Reflux	10	62

13	DMF (6)	DABCO	1	Reflux	8	63
14	DMF (1)	DABCO	1	100 °C	8	65
15	*t*BuOH (3) /DMF (3)	DABCO	-	82 °C	30	82
16	*t*BuOH (1) /DMF (1)	DABCO	1	82 °C	22	76
17	THF (3) /H_2O (3)	DABCO	-	65 °C	44	85
18	THF (1.5) / H_2O (1.5)	DABCO	-	65 °C	34	87
19	Dioxane (3) / H_2O (3)	DABCO	-	100 °C	2.5	79
20	Dioxane (1) / H_2O (1)	DABCO	-	80 °C	2.5	81
21	***Dioxane (1) /H_2O (1)***	***DABCO***	***-***	***65 °C***	***5***	***88***
22	Dioxane (4) / H_2O (2)	DABCO	-	100 °C	5.5	85
23	Dioxane (2) / H_2O (1)	DABCO	-	100 °C	3.5	83

T: temperature; t: time; N. R. : no reaction; C. M. : complex mixture.

[a] All the reactions were carried out on a 1.0 mmol scale of acrylamide-ketone (**106a**) using 1.0 equiv. of catalyst.

[b] The compound **108a** was fully characterized.

[c] Isolated yields of pure product based on acrylamide-ketone (**106a**).

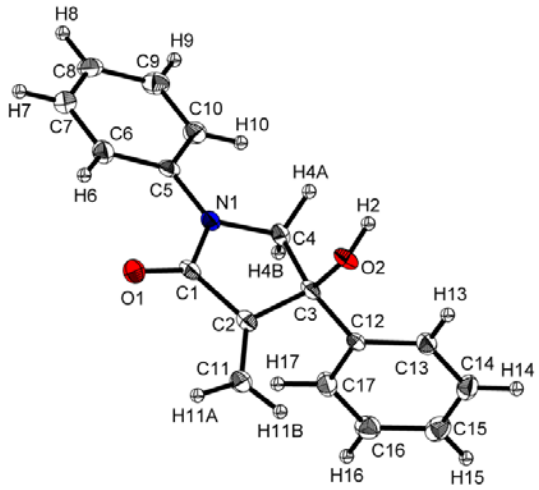


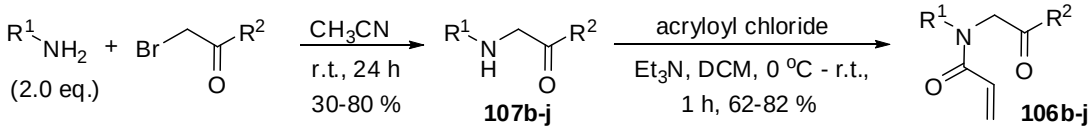
Figure 5. ORTEP diagram of the compound **108a**

***Table 8. Crystal data and structure refinement for* 108a**

Identification code	**108a**	
Empirical formula	C17 H15 N O2	
Formula weight	265.30	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P2(1)/c*	
Unit cell dimensions	a = 14.56(3) Å	α = 90°.
	b = 7.703(18) Å	β = 103.66(4)°.
	c = 11.74(3) Å	γ = 90°.
Volume	1279(5) $Å^3$	
Z	4	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	560	
Crystal size	0.28 x 0.18 x 0.10 mm^3	
Theta range for data collection	1.44 to 26.52°.	
Index ranges	-18<=h<=18, -9<=k<=9, -14<=l<=14	
Reflections collected	11578	
Independent reflections	2588 [R(int) = 0.1482]	
Completeness to theta = 26.52°	96.8 %	
Max. and min. transmission	0.9910 and 0.9751	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2588 / 0 / 182	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0923, wR2 = 0.2187	
R indices (all data)	R1 = 0.1496, wR2 = 0.2434	
Largest diff. peak and hole	0.455 and -0.462 $e.Å^{-3}$	

After having optimized reaction condition in hand, we have prepared representative class of acrylamide-ketone substrates (**106b-j**) following the reaction sequence as shown in the Scheme 60. All the compounds (**106b-j** and **107b-j**) were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

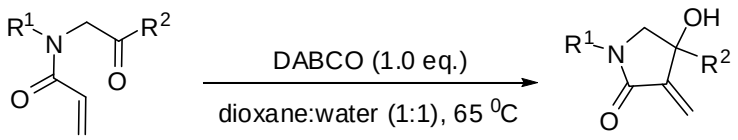
Scheme 60



107b (or) **106b**: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$
107c (or) **106c**: $R^1 = C_6H_5$, R^2 = 2-Naphthyl
107d (or) **106d**: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = C_6H_5$
107e (or) **106e**: $R^1 = C_6H_5$, $R^2 = 4\text{-}MeC_6H_4$
107f (or) **106f**: $R^1 = 4\text{-}BrC_6H_4$, $R^2 = C_6H_5$
107g (or) **106g**: $R^1 = 2\text{-}MeOC_6H_4$, $R^2 = C_6H_5$
107h (or) **106h**: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = 4\text{-}MeC_6H_4$
107i (or) **106i**: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = 4\text{-}ClC_6H_4$
107j (or) **106j**: $R^1 = 2\text{-}MeOC_6H_4$, $R^2 = 4\text{-}ClC_6H_4$

These acrylamide-aromatic ketones (**106b-j**) were then subjected to optimized reaction conditions which provided the expected functionalized γ-lactam derivatives (**108b-j**) in good to excellent yields (Table 9). Structures of the molecules (**108b-j**) were established by IR, ^{1}H NMR [for compounds **108c**, **108d**, **108g** & **108i** see Spectra 16, 18, 20 & 22 respectively], ^{13}C NMR [for compounds **108c**, **108d**, **108g** & **108i** see Spectra 17, 19, 21 & 23 respectively] and HRMS analysis. Structures of the compounds (**108b** and **108e**) were also further confirmed by X-ray data analysis [For ORTEP diagrams of compounds (**108b** and **108e**) see Figure 6 and 7, for data see Table 10 and 11 respectively].

Table 9. Synthesis of α-methylene-γ-lactam derivatives.[a, b]



106b-j **108b-j**

Entry	AK	R^1	R^2	Product	t (h)	Yield (%)[c]
1	**106a**	C_6H_5	C_6H_5	**108a**[d]	5	88
2	**106b**	C_6H_5	4-ClC_6H_4	**108b**[d]	3.5	82
3	**106c**	C_6H_5	2-Naphthyl	**108c**	12	75
4	**106d**	3,5-$Me_2C_6H_3$	C_6H_5	**108d**	20	74
5	**106e**	C_6H_5	4-MeC_6H_4	**108e**[d]	11	78
6	**106f**	4-BrC_6H_4	C_6H_5	**108f**	2.5	70
7	**106g**	2-$MeOC_6H_4$	C_6H_5	**108g**	44	84
8	**106h**	3,5-$Me_2C_6H_3$	4-MeC_6H_4	**108h**	28	72
9	**106i**	3,5-$Me_2C_6H_3$	4-ClC_6H_4	**108i**	18	76
10	**106j**	2-$MeOC_6H_4$	4-ClC_6H_4	**108j**	27	82

AK = acrylamide-ketone

[a] All the reactions were carried out on a 1 mmol scale of acrylamide-ketones (**106a-j**) using DABCO (1.0 equiv.) as a promoter in dioxane:water (1:1)(2.0 mL) solvent system at 65 ^oC temperature.

[b] All the products (**108a-j**) were obtained as (colorless/white/ yellow/orange) solids and fully characterized.

[c] Isolated yields of pure products based on acrylamide-ketones (**106a-j**).

[d] These compounds (**108a**, **108b** and **108e**) were further confirmed by single crystal X-ray data analysis.

From the Table 9 it is quite clear that the rate of reaction of the substrates (**106d**, **106e**, **106g** and **106h**) containing electron donating groups on aryl ring (N-aryl) is considerably slower than that of substrate (**106a**) containing unsubstituted phenyl ring

and substrates (**106b** and **106f**) containing electron withdrawing groups on aryl ring. We have also noticed that some rate acceleration in the case of substrates (**106i** and **106j**) containing electron withdrawing groups on carbonyl attached aryl ring. Thus we have successfully employed aryl ketones as electrophile components to provide α-methylene-γ-lactam derivatives in high yields.

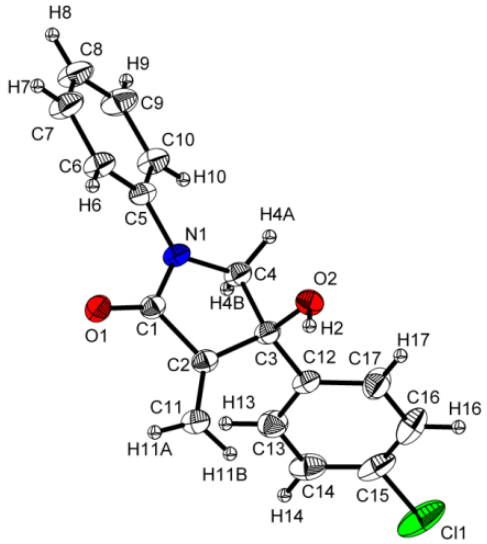


Figure 6. ORTEP diagram of the compound **108b**

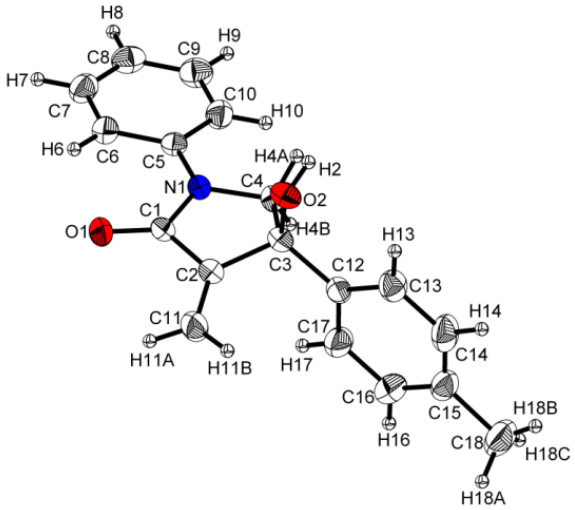


Figure 7. ORTEP diagram of the compound **108e**

***Table 10. Crystal data and structure refinement for* 108b**

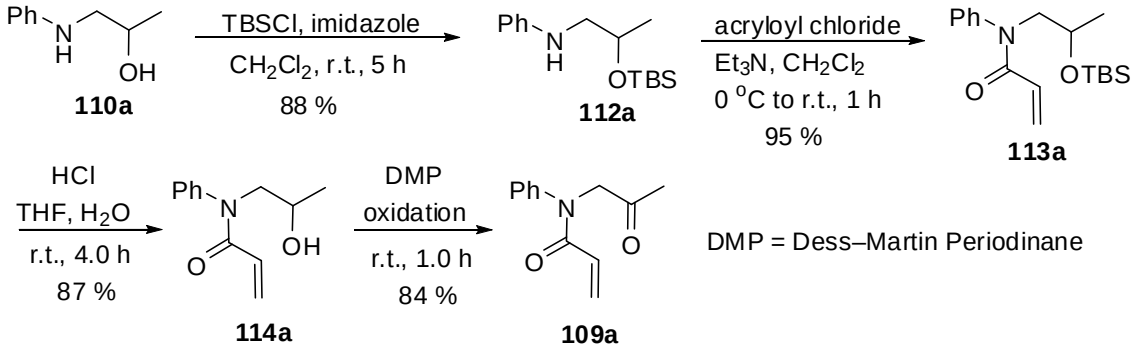
Identification code	**108b**	
Empirical formula	C17 H14 Cl N O2	
Formula weight	299.74	
Temperature	298(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	*P-1*	
Unit cell dimensions	a = 7.1058(6) Å	α = 73.219(9)°.
	b = 8.6589(9) Å	β = 78.960(7)°.
	c = 13.1659(11) Å	γ = 77.425(8)°.
Volume	749.77(12) $Å^3$	
Z	2	
Density (calculated)	1.328 Mg/m^3	
Absorption coefficient	2.283 mm^{-1}	
F(000)	312	
Crystal size	0.28 x 0.18 x 0.10 mm^3	
Theta range for data collection	3.54 to 72.00°.	
Index ranges	-8<=h<=8, -10<=k<=10, -16<=l<=13	
Reflections collected	4566	
Independent reflections	2852 [R(int) = 0.0171]	
Completeness to theta = 72.00°	96.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8039 and 0.5674	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2852 / 0 / 191	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0492, wR2 = 0.1337	
R indices (all data)	R1 = 0.0576, wR2 = 0.1431	
Largest diff. peak and hole	0.198 and -0.312 $e.Å^{-3}$	

***Table 11. Crystal data and structure refinement for* 108e**

Identification code	**108e**	
Empirical formula	C18 H17 N O2	
Formula weight	279.33	
Temperature	298(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	*I2/a*	
Unit cell dimensions	a = 11.9321(8) Å	α = 90°.
	b = 7.7953(5) Å	β = 90.160(10)°.
	c = 32.216(3) Å	γ = 90°.
Volume	2996.5(4) $Å^3$	
Z	8	
Density (calculated)	1.238 Mg/m^3	
Absorption coefficient	0.643 mm^{-1}	
F(000)	1184	
Crystal size	0.24 x 0.22 x 0.08 mm^3	
Theta range for data collection	2.74 to 67.06°.	
Index ranges	-14<=h<=10, -9<=k<=9, -38<=l<=36	
Reflections collected	9633	
Independent reflections	2668 [R(int) = 0.0238]	
Completeness to theta = 67.06°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9503 and 0.8609	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2668 / 0 / 192	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0437, wR2 = 0.1185	
R indices (all data)	R1 = 0.0530, wR2 = 0.1277	
Largest diff. peak and hole	0.190 and -0.178 $e.Å^{-3}$	

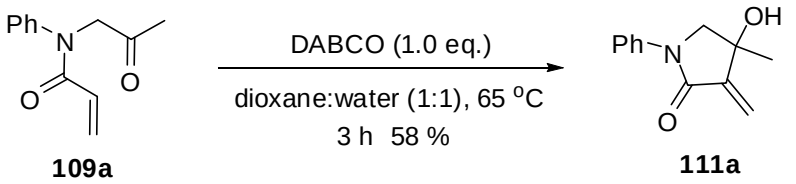
These results are highly encouraging. We have next focused our attention towards aliphatic ketones as electrophile components with a view to examine the influence of aliphatic ketones in IBH-reaction. We have accordingly first selected N-(2-oxopropyl)-N-phenylacrylamide (acrylamide-aliphatic ketone) (**109a**) as a suitable substrate for performing intramolecular B-H reaction. The required substrate (**109a**) was prepared starting from easily accessible 1-(phenylamino)propan-2-ol (**110a**)[136] following the reaction sequence as shown in the Scheme 61. This strategy involves four steps 1) TBS protection of amino alcohol (**110a**) 2) preparation of OTBS-acrylamide (**113a**) from OTBS-amine (**112a**) 3) TBS deprotection of acrylamide (**113a**) 4) oxidation of **114a** to obtain ketone (**109a**). We have confirmed structures of all the intermediates (**112a**, **113a**, **114a**) and the required substrate (**109a**) by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

Scheme 61



Then we have subjected N-(2-oxopropyl)-N-phenylacrylamide (**109a**) for intramolecular Baylis-Hillman reaction in presence of DABCO (1.0eq.) in dioxane-water (1:1) solvent system at 65 °C temperature. We pleased to see the reaction was

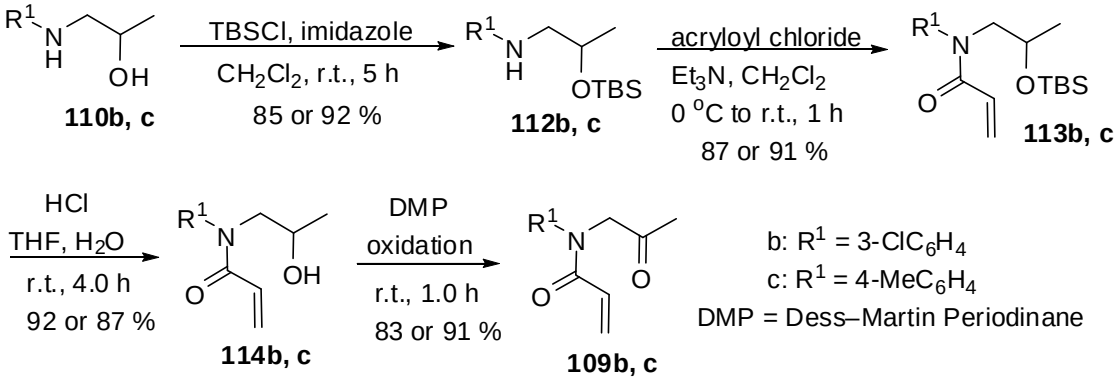
completed in 3 hours to provide the desired compound (**111a**) in 58 % yield (Eq. 54). The structure of the compound (**111a**) was confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.



109a **111a** **Eq. 54**

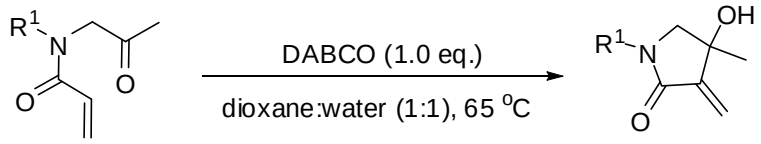
From these results it is clear that methyl ketone substrate (**109a**) reacts reasonably faster than aryl ketone substrate (**106a**). Therefore we have extended the same strategy for two more acrylamide-methyl ketones (**109b** and **109c**). The required acrylamide-methyl ketones (**109b** and **109c**) were prepared following reaction strategy as shown in the Scheme 62. The structures of the compounds (**112b**, **112c**, **113c**, **113c**, **114b**, **114c**, **109b** and **109c**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

Scheme 62



Subsequently we have examined the acrylamide-methyl ketones (**109b** and **109c**) for IBH-reaction in presence of DABCO (1.0eq.) in dioxane-water (1:1) solvent system at 65 °C temperature. The resulting adducts (**111b** and **111c**) were obtained in 55 and 52

% yields respectively in less reaction time (1 and 6 h) (Eq. 55). The structures of the IBH-adducts (**111b** and **111c**) were confirmed by IR, ^{1}H NMR [for compound **111b** see Spectrum 24], ^{13}C NMR [for compound **111b** see Spectrum 25] and HRMS analysis.



Eq. 55

109b: R^1 = 3-ClC_6H_4
109c: R^1 = 4-MeC_6H_4

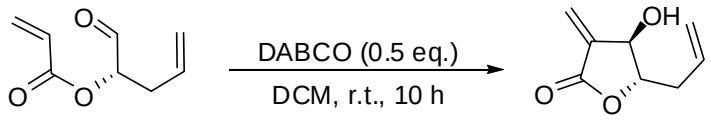
111b: R^1 = 3-ClC_6H_4; 1 h; 55 %
111c: R^1 = 4-MeC_6H_4; 6 h; 52 %

In conclusion, we have successfully employed less reactive ketones as electrophile components and acrylamides as activated alkene components in the intramolecular Baylis-Hillman reaction thus demonstrating the hidden potential of ketones as electrophiles and acrylamides as activated alkenes in IBH-reaction. This methodology provides a facile synthetic procedure for obtaining α-methylene-γ-lactam derivatives containing tertiary alcoholic functionality.

Highly diastereoselective intramolecular Baylis-Hillman reaction of acrylamide-α-substituted ketones

In the previous section we have successfully utilized less reactive acrylamides and ketones as activated alkene and electrophile components respectively providing a simple strategy for obtaining the corresponding BH-adducts *i.e.* α-methylene-γ-lactam derivatives. From this study it occurred to us that if the substrate contains a chiral centre (racemic) there is a possibility of achieving diastereoselectivity in intramolecular Baylis-Hillman reaction. Accordingly we have directed our studies towards developing diastereoselective IBH-reaction utilizing substrates containing less reactive acrylamide and ketone components and also having a chiral center (racemic). It is therefore appropriate to discuss literature reports on the diastereoselective intramolecular Baylis-Hillman reactions in this section.

Krishna and co-workers[106] have utilized chiral acrylate-aldehyde substrate (**115**) for diastereoselective intramolecular Baylis-Hillman reaction in the presence of DABCO as a catalyst and DCM as solvent to provide the corresponding BH-adduct in >95 % diastereo-selectivity (Eq. 56).



115

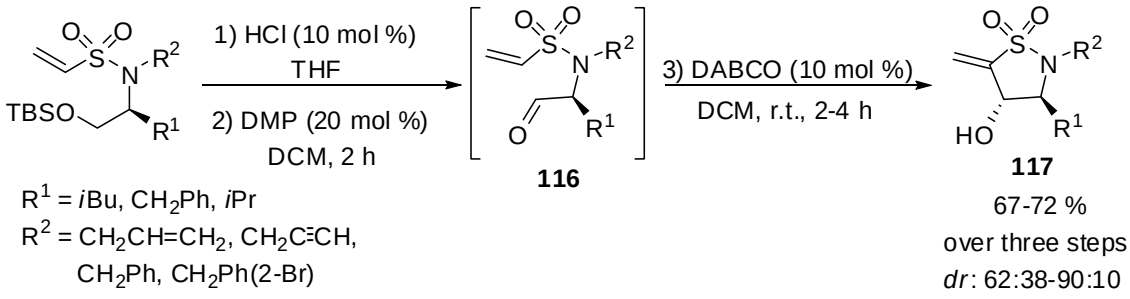
62 %
de: >95 %

Eq. 56

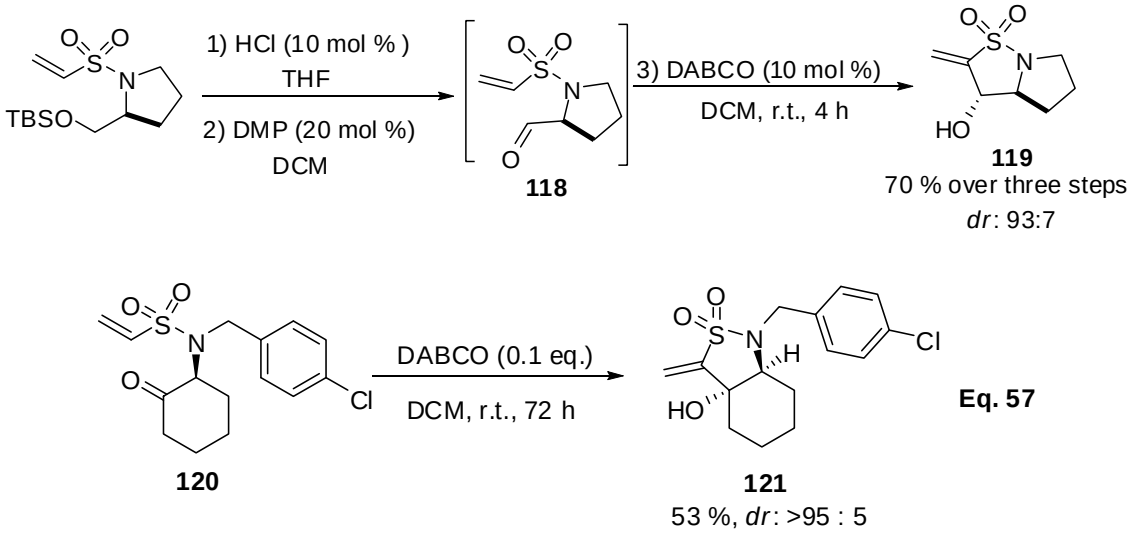
Zhou and Hanson[137] have described a facile intramolecular BH reaction of *in situ* generated chiral vinyl sulfonamide-aldehydes (**116** and **118**) to provide the resulting 5-

membered sultams (**117**) and [5.5] bicyclic sultam (**119**) respectively with high diastereo-selectivities (Scheme 63 and 64). They have also used chiral vinyl sulfonamide-ketone substrate (**120**) in IBH-reaction to give [5.6] bicyclic sultam (**121**) with more than 95% diastereoselectivity (Eq. 57).

Scheme 63



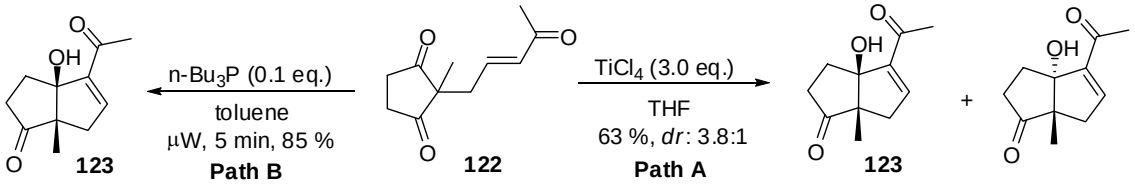
Scheme 64



Miesch and co-workers have reported an interesting diastereoselective intramolecular Baylis-Hillman reaction of substrate **122** containing enone-ketone system in the presence of $TiCl_4$[138] to produce bicyclic compound **123** with good diastereo-selectivity

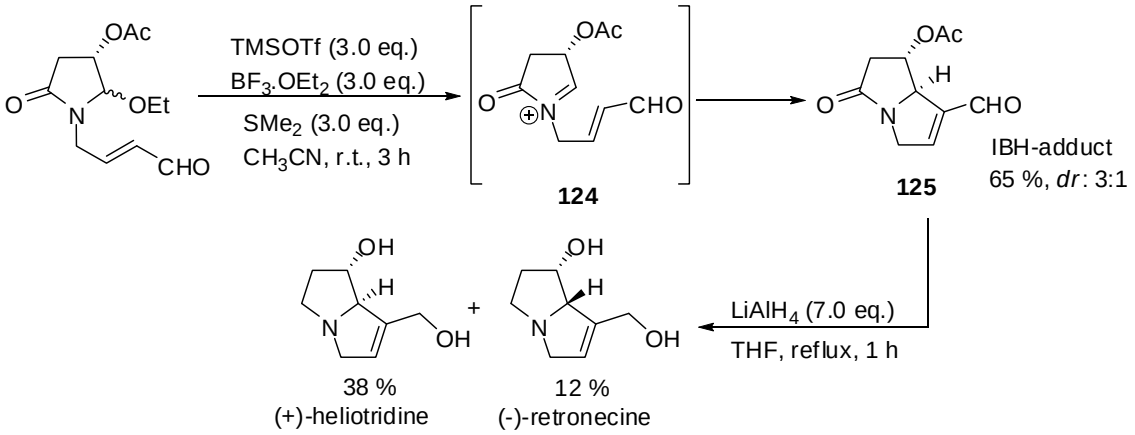
(3.8:1) (Path A). Subsequently they have also performed the same reaction using tributylphosphine[139] as a catalyst which gave **123** as a single diastereomer (Scheme 65) (Path B).

Scheme 65



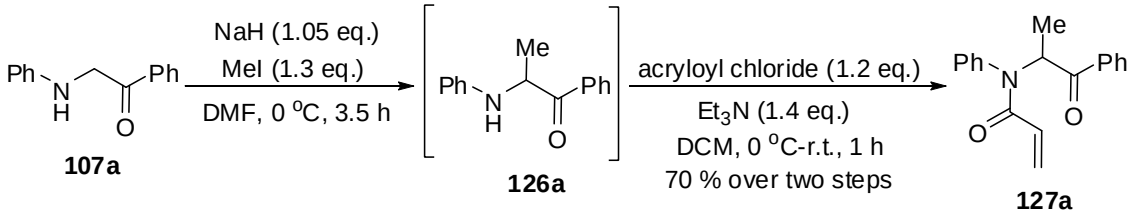
Intramolecular Baylis-Hillman reaction of *in situ* generated enal-iminium ion substrate (**124**) producing bicyclic product (**125**) was reported by Aggarwal and co-workers[140] during their work in the synthesis of natural product (+)-heliotridine and its unnatural isomer (-)-retronecine. The bicyclic product (**125**) on treatment with LAH provided the required natural product (+)-heliotridine and its unnatural isomer (-)-retronecine (Scheme 66).

Scheme 66



Based on our work reported in the previous chapter, we have chosen N-(1-oxo-1-phenylpropan-2-yl)-N-phenylacrylamide (**127a**) as a suitable substrate for diastereoselective intramolecular Baylis-Hillman reaction. This compound was prepared from easily accessible amino-ketone (**107a**) following the reaction sequence as shown in the Scheme 67. This reaction sequence involves two steps 1) amino-ketone (**107a**) was alkylated with methyl iodide in presence of NaH to provide amino-α-substituted ketone (**126a**)[141] 2) the crude amino-α-substituted ketone (**126a**) (without purification) was treated with acryloyl chloride in presence of triethylamine to provide the N-(1-oxo-1-phenylpropan-2-yl)-N-phenylacrylamide (**127a**) in 70 % isolated yield over two steps. The structure of the compound (**127a**) was confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis.

Scheme 67

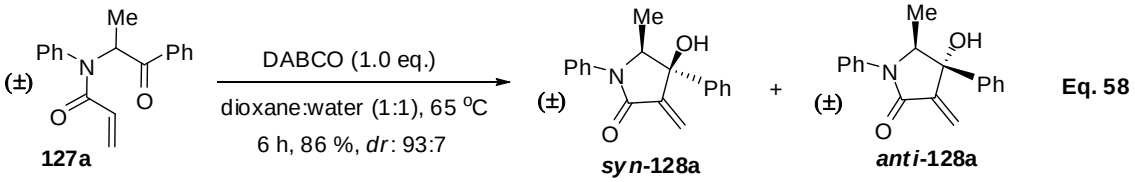


Subsequently we have subjected the acrylamide-ketone (**127a**) to the similar reaction condition as mentioned in the previous section [DABCO (1.0 eq.), dioxane-water (1:1) solvent system, at 65 °C] for intramolecular Baylis-Hillman reaction. We were pleased to see the resulting diastereomeric BH-adducts (***syn*-128a**+***anti*-128a**)[@] in 86 % diastereoselectivity[#] and 86 % yield (after purification by column chromatography) (Eq. 58). In the ^{1}H NMR spectrum of crude mixture [see Spectrum 26] as well as column

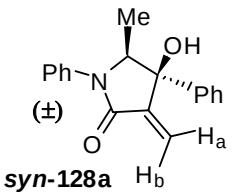
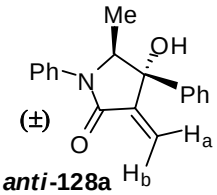
purified diastereomeric mixture (***syn*-128a**+***anti*-128a**) [see Spectrum 27] peaks of 'methyl' and 'olefinic H_a/H_b' protons of major and minor diastereomers (***syn*-128a**, ***anti*-128a**) separated nicely with the integration ratio of ≈ 93:7 and the details are presented in Table 12. However the pure major diastereomer (***syn*-128a**) was obtained by crystallization [in EtOAc-hexanes (1:2)] of column purified mixture in 60 % yield. The structure of the pure major diastereomer (***syn*-128a**) was confirmed by IR, ^{1}H NMR [see Spectrum 28], ^{13}C NMR [see Spectrum 29] and HRMS spectral data analysis. Structure of the major diastereomer (***syn*-128a**) was also confirmed by X-ray data analysis [For ORTEP diagram of compound **(*syn*-128a)** see Figure 8 and for data see Table 13].

[@] We have assigned *syn*-configuration when 'methyl' and 'OH' groups are in the same side. If 'methyl' and 'OH' groups are situated opposite to each other we assigned *anti*-configuration.

[#] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture.



Eq. 58

Table 12	 ***syn*-128a** Major diastereomer	 ***anti*-128a** Minor diastereomer
	dr: 93:7	
olefinic proton H_a	δ 5.55(s)	δ 5.67(s)
olefinic proton H_b	δ 6.38(s)	δ 6.50(s)
$CH\underline{CH}_3$	δ 1.24(d)	δ 0.72(d)

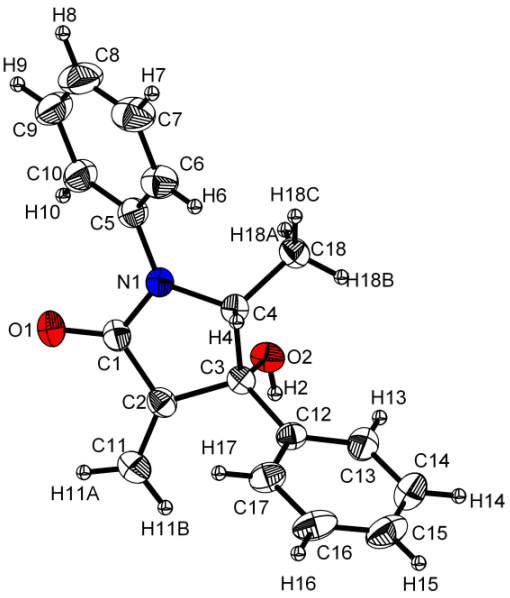


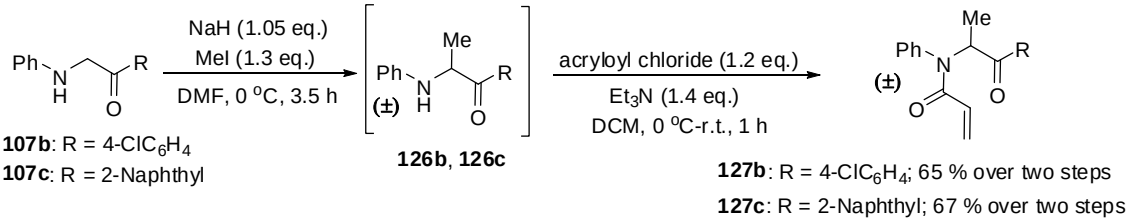
Figure 8. ORTEP diagram of the compound ***syn*-128a**

Table 13. Crystal data and structure refinement for syn-128a.

Identification code	***syn*-128a**	
Empirical formula	C18 H17 N O2	
Formula weight	279.33	
Temperature	298(2) K	
Wavelength	1.54184 Å	
Crystal system	Tetragonal	
Space group	I 41/a	
Unit cell dimensions	a = 20.2021(5) Å	a= 90°.
	b = 20.2021(5) Å	b= 90°.
	c = 14.6232(6) Å	g = 90°.
Volume	5968.1(3) $Å^3$	
Z	16	
Density (calculated)	1.244 Mg/m^3	
Absorption coefficient	0.646 mm^{-1}	
F(000)	2368	
Theta range for data collection	3.73 to 71.79°.	
Index ranges	-24<=h<=18, -21<=k<=14, -17<=l<=17	
Reflections collected	6250	
Independent reflections	2849 [R(int) = 0.0214]	
Completeness to theta = 71.79°	97.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.85720	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2849 / 0 / 192	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0520, wR2 = 0.1336	
R indices (all data)	R1 = 0.0602, wR2 = 0.1425	
Largest diff. peak and hole	0.192 and -0.243 $e.Å^{-3}$	

After reasonable success, we prepared two more acrylamide-α-methyl substituted ketones (**127b** and **127c**) (Scheme 68) using a similar strategy as described for compound **127a** (Scheme 67). The structures of these compounds (**127b** and **127c**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis.

Scheme 68



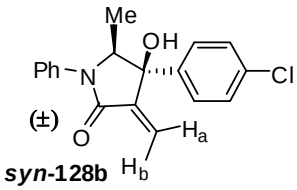
Subsequently IBH-reaction of acrylamide-α-methyl ketones (**127b** and **127c**) with DABCO (1.0 eq.), dioxane-water (1:1) solvent system, at 65 °C provided pure diastereomeric mixtures (***syn*-128b**+***anti*-128b** and ***syn*-128c**+***anti*-128c**)[@] (after column purification) in 79 and 88 % yield respectively and in 86 % diastereoselectivity[#] (Eq. 59). Diastereoselectivity was determined by the ^{1}H NMR spectrum of the crude mixture (containing ***syn*-128b**+***anti*-128b**) which showed separate peaks for 'olefinic H_a/H_b' protons of major and minor diastereomers. The integration ratio of the separated peaks clearly indicates that the reaction is 86 % diastereoselective (for details see Table 14). Similarly peaks of 'CH_3'and 'CH' a protons separated clearly in the case of major and minor diastereomers (for details see Table 14). Pure major diastereomer (***syn*-128b**) was obtained after crystallization [in EtOAc-hexanes (1:2)] in 58 % yield. The structure of this molecule (***syn*-128b**) was established by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis and the structure of the major diastereomer (***syn*-128b**) was also

confirmed by X-ray data analysis [For ORTEP diagram of compound (***syn*-128b)** see Figure 9 and for data see Table 16]. Similarly in the ^{1}H NMR spectrum of crude of diastereomeric mixture (***syn*-128c**+***anti*-128c**) 'olefinic Ha/Hb' and 'CH_3' proton signals separated clearly (for details see Table 15). However pure ***syn*-128c** was obtained by crystallization [in EtOAc-hexanes (1:2)] in 64 % isolated yield. The structure this molecule (***syn*-128c**) was established by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis.

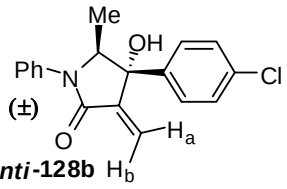
[@] We have assigned *syn*-configuration when 'methyl' and 'OH' groups are in the same side. If 'methyl' and 'OH' groups are situated opposite to each other we assigned *anti*-configuration.

[#] Diastereomeric ratios were determined by the integration ratios of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectra of the crude mixtures respectively.

Table 14



***syn*-128b** Major diastereomer

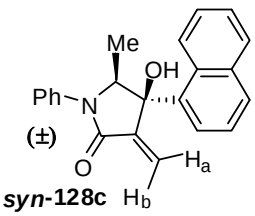


***anti*-128b** Minor diastereomer

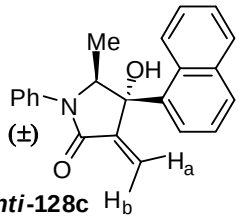
dr: 93:7

olefinic proton H_a	δ 5.53(s)	δ 5.63(s)
olefinic proton H_b	δ 6.38(s)	δ 6.49(s)
$CH\underline{CH}_3$	δ 1.21(d)	δ 0.72(d)
$\underline{CH}CH_3$	δ 4.28(q)	δ 4.36(q)

Table 15



***syn*-128c**



***anti*-128c**

	Major diastereomer	Minor diastereomer
	dr: 93:7	
olefinic proton H_a	δ 5.56(s)	δ 5.70(s)
olefinic proton H_b	δ 6.42(s)	δ 6.54(s)
$CH\underline{CH_3}$	δ 1.27(d)	δ 0.75(d)

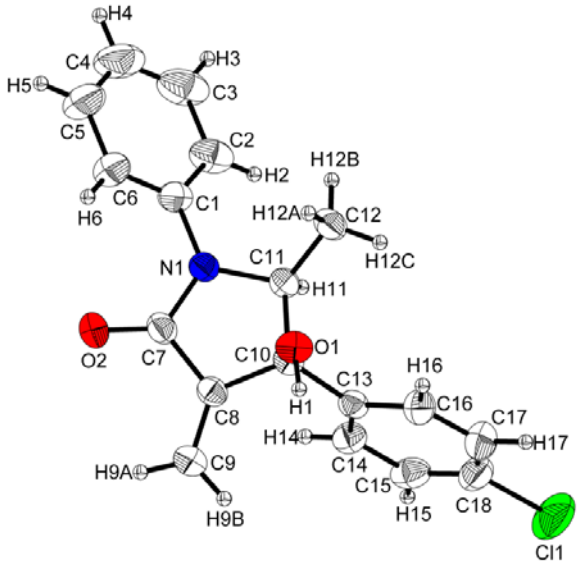


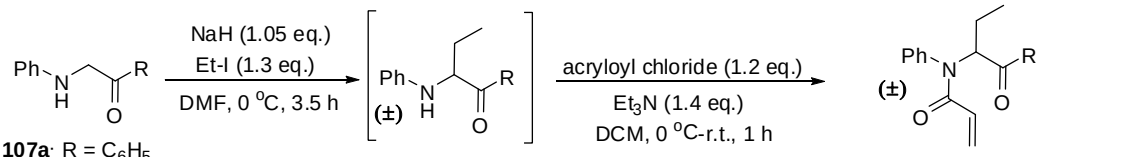
Figure 9. ORTEP diagram of the compound ***syn*-128b**

Table 16. Crystal data and structure refinement for syn-128b.

Identification code	***syn*-128b**	
Empirical formula	C18 H16 Cl N O2	
Formula weight	313.77	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I4(1)/a	
Unit cell dimensions	a = 19.9759(18) Å	a= 90°.
	b = 19.9759(18) Å	b= 90°.
	c = 16.065(3) Å	g = 90°.
Volume	6410.6(14) $Å^3$	
Z	16	
Density (calculated)	1.300 Mg/m^3	
Absorption coefficient	0.244 mm^{-1}	
F(000)	2624	
Theta range for data collection	1.63 to 26.04°.	
Index ranges	-24<=h<=24, -24<=k<=24, -19<=l<=19	
Reflections collected	32888	
Independent reflections	3163 [R(int) = 0.0363]	
Completeness to theta = 26.04°	99.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3163 / 0 / 201	
Goodness-of-fit on F^2	1.081	
Final R indices [I>2sigma(I)]	R1 = 0.0573, wR2 = 0.1351	
R indices (all data)	R1 = 0.0740, wR2 = 0.1451	
Largest diff. peak and hole	0.230 and -0.216 $e.Å^{-3}$	

After obtaining encouraging diastereoselectivities with acrylamide-α-methyl substituted ketones, we have extended our studies towards ethyl substitution at the α-position to ketone with a view to understand the effect of substitution group on the diastereoselectivity in IBH-reaction. Accordingly we have prepared α-ethyl substituted ketones (**127d** and **127e**) following the strategy shown in the Scheme 69. The structures of these compounds (**127d** and **127e**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis.

Scheme 69

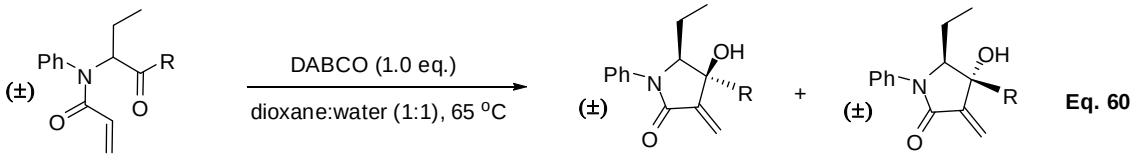


Then we have performed the intramolecular coupling of acrylamide-α-ethyl substituted ketones (**127d** and **127e**) with DABCO (1.0 eq.), dioxane-water (1:1) solvent system, at 65 °C for intramolecular Baylis-Hillman reaction which gave diastereomeric mixtures (***syn*-128d+*anti*-128d** and ***syn*-128e+*anti*-128e**)[@] in 84 & 80 % yields [after purification by column chromatagraphy (silcagel)] and in 90 & 88 % diastereoselectivities[#] respectively (Eq. 60). The diastereomeric purities in both cases (***syn*-128d+*anti*-128d** and ***syn*-128e+*anti*-128e**) were determined by the ^{1}H NMR spectra of corresponding crude reaction mixtures (for details see Tables 17 and 18). We have noticed slight increase in diastereoselectivity (86 to 90 %) from methyl substituted ketone-acrylamides (**127a-c**) to ethyl substituted ketone-acrylamides (**127d, e**). However the

pure major diastereomers (***syn*-128d** and ***syn*-128e**) in both the cases were obtained by crystallization [in EtOAc-hexanes (1:2)] of the column purified mixtures in 62 and 63 % yields respectively. The structures of the pure major diastereomers (***syn*-128d** and ***syn*-128e**) were confirmed by IR, ^{1}H NMR [for compound ***syn*-128d** see Spectrum 30], ^{13}C NMR [for compound ***syn*-128d** see Spectrum 31] and HRMS spectral data analysis.

[@] We have assigned *syn*-configuration when 'ethyl' and 'OH' groups are in the same side. If 'ethyl' and 'OH' groups are situated opposite to each other we assigned *anti*-configuration.

[#] Diastereomeric ratios were determined by the integration ratios of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectra of the crude mixtures respectively.



Eq. 60

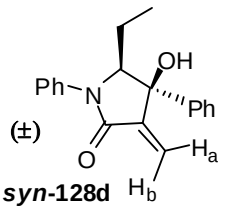
127d: R = C_6H_5

127e: R = 4-ClC_6H_4

syn*-128d**+anti*-128d**: R = C_6H_5; 13 h; 84 %; *dr*: 95:5

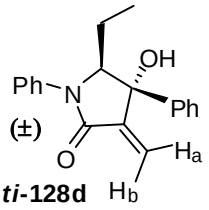
syn*-128e**+anti*-128e**: R = 4-ClC_6H_4; 11 h; 80 %; *dr*: 94:6

Table 17



***syn*-128d**

Major diastereomer



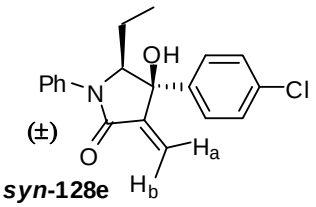
***anti*-128d**

Minor diastereomer

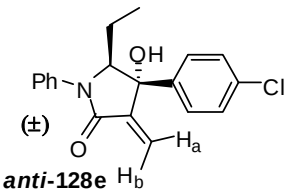
dr: 95:5

olefinic proton H_a	δ 5.51(s)	δ 5.64(s)
olefinic proton H_b	δ 6.35(s)	δ 6.46(s)
$CH_2\underline{CH}_3$	δ 0.82(t)	δ 0.29(t)
$\underline{CH}CH_2CH_3$	δ 4.29(dd)	δ 4.19(dd)

Table 18



***syn*-128e** Major diastereomer



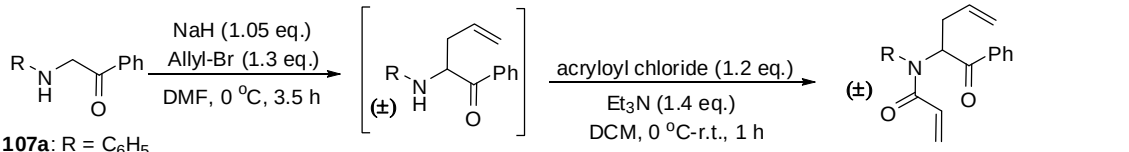
***anti*-128e** Minor diastereomer

dr: 94:6

olefinic proton H_a	δ 5.48(s)	δ 5.60(s)
olefinic proton H_b	δ 6.34(s)	δ 6.44(s)
$CH_2\underline{CH_3}$	δ 0.78(t)	δ 0.34(t)

Next we have focused our studies towards 'allyl' substitution at α-position of ketone to further understand the factors that influence diastereoselectivity in IBH-reaction. We have prepared two allyl substituted acrylamide-ketones (**127f** and **127g**) according to Scheme 70. The structures of these compounds (**127f** and **127g**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis.

Scheme 70



107a: R = C_6H_5

107d: R = 3, 5-$Me_2C_6H_3$

126f, **126g**

127f: R = C_6H_5; 50 % over two steps

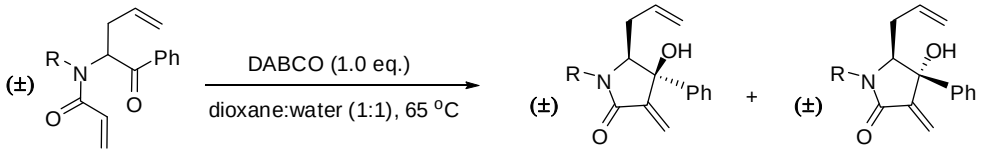
127g: R = 3, 5-$Me_2C_6H_3$; 54 % over two steps

Intramolecular BH-reaction of allyl acrylamide-ketones (**127f** and **127g**) with DABCO (1.0 eq.), dioxane-water (1:1) solvent system, at 65 °C provided diastereomeric mixtures (***syn*-128f+*anti*-128f** and ***syn*-128g+*anti*-128g**)[@] in 81 and 77 % yield respectively and in 92 % diastereoselectivity[#] (Eq. 61). The diastereomeric ratio was determined by ^{1}H NMR spectrum of the corresponding crude reaction mixture (for

details see Tables 19 and 20). Changing the substrate (**127a**) from methyl group (α-substitution to ketone) to allyl group substrate (**127f**) resulted in improving the diastereoselectivity from 86 to 92 %. It is important to note that in the case of ***syn*-128f+*anti*-128f**, we were able to separate major (***syn*-128f**) and minor (***anti*-128f**) diastereomers by column chromatography itself, in 78 and 3 % yields respectively. In the case of ***syn*-128g+*anti*-128g** we have obtained the pure major diastereomer (*syn*-**128g**) by crystallization [in EtOAc-hexanes (1:2)] of the column purified mixture in 56 % of yield. The structures of the pure major diastereomers (***syn*-128f**, and ***syn*-128g**) and minor diastereomer (***anti*-128f**) were confirmed by IR, ^{1}H NMR [for compounds ***syn*-128f**, ***anti*-128f** & ***syn*-128g** see Spectra 32, 34 & 36 respectively], ^{13}C NMR [for compounds ***syn*-128f**, ***anti*-128f** & ***syn*-128g** see Spectra 33, 35 & 37 respectively] and HRMS spectral data analysis.

[@] We have assigned *syn*-configuration when 'allyl' and 'OH' groups are in the same side. If 'allyl' and 'OH' groups are situated opposite to each other we assigned *anti*-configuration.

[#] Diastereomeric ratios were determined by the integration ratios of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectra of the crude mixtures respectively.



Eq. 61

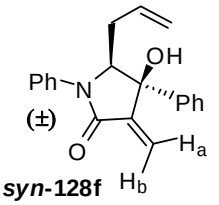
127f: R = C_6H_5

127g: R = 3, 5-$Me_2C_6H_3$

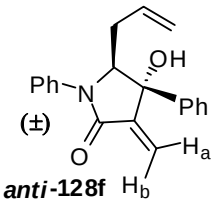
***syn*-128f+*anti*-128f**: R = C_6H_5; 13 h; 81 %; *dr*: 96:4

***syn*-128g+*anti*-128g**: R = 3, 5-$Me_2C_6H_3$; 50 h; 77 %; *dr*: 96:4

Table 19



***syn*-128f** Major diastereomer

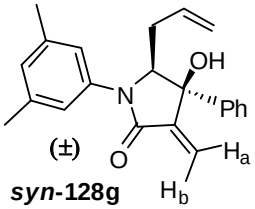


***anti*-128f** Minor diastereomer

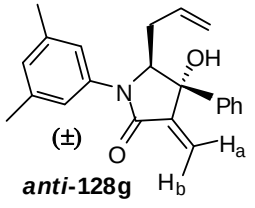
dr: 96:4

olefinic proton H_a	δ 5.58(s)	δ 5.67(s)
olefinic proton H_b	δ 6.37(s)	δ 6.48(s)
$\underline{CH}CH_2CH{=}CH_2$	δ 4.45(dd)	δ 4.35(dd)

Table 20



***syn*-128g** Major diastereomer



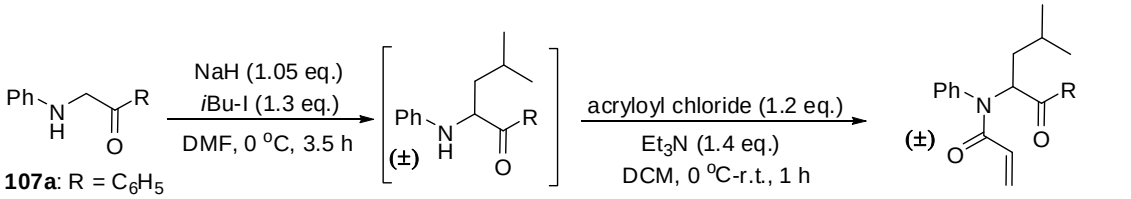
***anti*-128g** Minor diastereomer

dr: 96:4

olefinic proton H_a	δ 5.55(s)	δ 5.64(s)
olefinic proton H_b	δ 6.34(s)	δ 6.45(s)
$\underline{CH}CH_2CH{=}CH_2$	δ 4.39(dd)	δ 4.30(dd)

Finally we have directed our studies towards understanding influence of *i*Bu group substitution at α-position of ketone on diastereoselectivity. We have accordingly prepared two acrylamide-α-*i*Bu substituted ketones (**127h** and **127i**) according to the Scheme 71. The structures (**127h** and **127i**) of these compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data analysis.

Scheme 71



107a: R = C_6H_5
107e: R = 4-MeC_6H_4

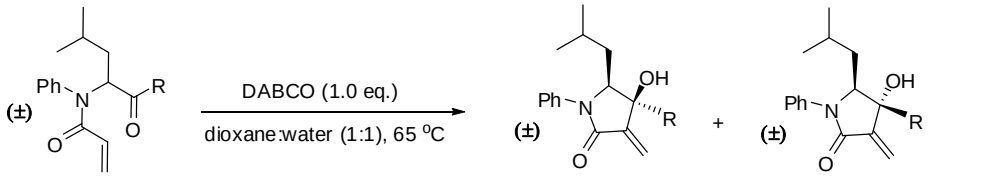
126h, **126i**

127h: R = C_6H_5; 55 % over two steps
127i: R = 4-MeC_6H_4; 57 % over two steps

Treatment of acrylamide-α-*i*Bu substituted ketones (**127h** and **127i**) with DABCO (1.0 eq.), dioxane-water (1:1) solvent system, at 65 °C for intramolecular Baylis-Hillman reaction gave diastereomeric mixtures (***syn*-128h**+***anti*-128h** and ***syn*-128i**+***anti*-128i**)[@] in 82 and 81 % yield respectively and in 92 % diastereoselectivity[#] (Eq. 62). Diastereoselectivities were determined by ^{1}H NMR spectra of the crude reaction mixtures in both the cases (for details see Table 21 and 22). From these studies, it is clear that diastereoselectivity improves from 86 to 92 % from methyl substitution to *i*Bu substitution at α-position to ketone. Pure major diastereomers (***syn*-128h** and ***syn*-128i**) in each case were obtained by crystallization [in EtOAc-hexanes (1:2)] of the column purified mixtures in 59 and 56 % of yields respectively. The structures of the pure major diastereomers (***syn*-128h** and ***syn*-128i**) were confirmed by IR, ^{1}H NMR [for compound ***syn*-128i** see Spectrum 38], ^{13}C NMR [for compound ***syn*-128i** see Spectrum 39] and HRMS spectral data analysis.

[@] We have assigned *syn*-configuration when '*iso*-butyl' and 'OH' groups are in the same side. If '*iso*-butyl' and 'OH' groups are situated opposite to each other we assigned *anti*-configuration.

[#] Diastereomeric ratios were determined by the integration ratios of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectra of the crude mixtures respectively.

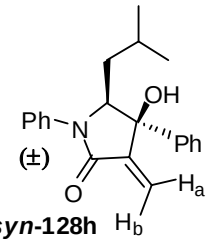


Eq. 62

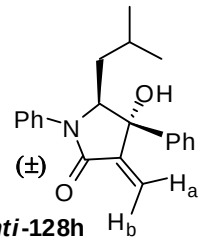
127h: R = C_6H_5
127i: R = 4-MeC_6H_4

syn-**128h**+*anti*-**128h**: R = C_6H_5; 50 h; 82 %; *dr*: 96:4
syn-**128i**+*anti*-**128i**: R = 4-MeC_6H_4; 96 h; 81 %; *dr*: 96:4

Table 21



***syn*-128h** Major diastereomer

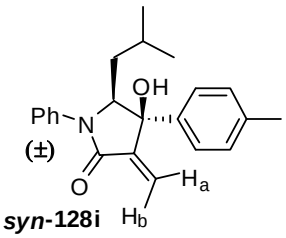


***anti*-128h** Minor diastereomer

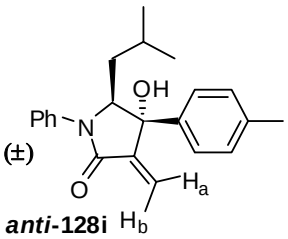
dr: 96:4

olefinic proton H_a	δ 5.48(s)	δ 5.60(s)
olefinic proton H_b	δ 6.34(s)	δ 6.44(s)
$\underline{CH}CH_2CH(CH_3)_2$	δ 4.39(dd)	δ 4.29(dd)

Table 22



***syn*-128i** Major diastereomer



***anti*-128i** Minor diastereomer

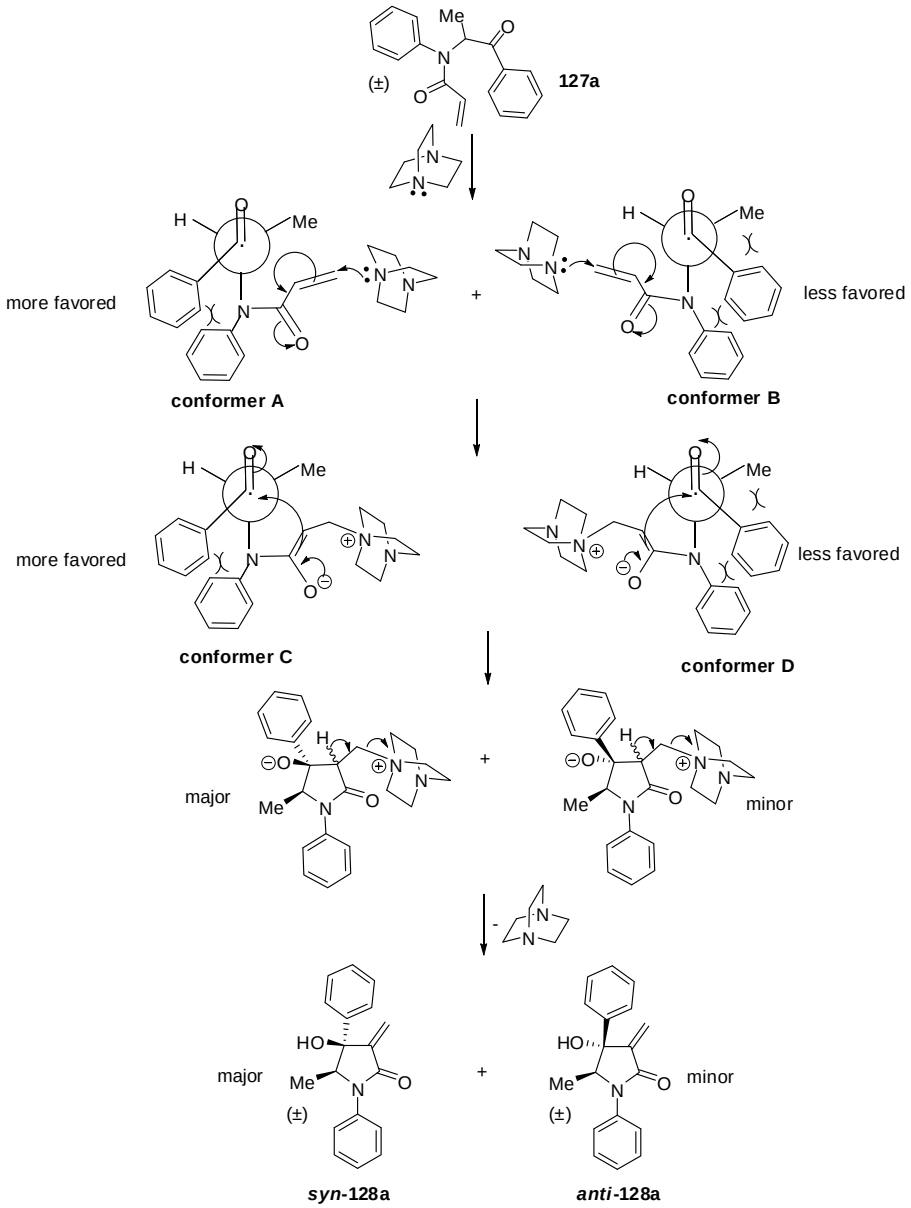
dr: 96:4

olefinic proton H_a	δ 5.48(s)	δ 5.59(s)
olefinic proton H_b	δ 6.33(s)	δ 6.42(s)
$\underline{CH}CH_2CH(CH_3)_2$	δ 4.37(dd)	δ 4.27(dd)

A plausible mechanism for high diastereoselectivities is presented in the Scheme 72 by taking example of N-(1-oxo-1-phenylpropan-2-yl)-N-phenylacrylamide (**127a**) under

the catalytic influence of DABCO as a model case. Diastereoselectivities are explained on the basis of conformers **A**, **B**, **C** and **D**. The conformers **A** and **C** are favored due to only one 1, 3-gauche interaction (Ph, Ph) while the conformers **B** and **D** are disfavored due to 1, 3 and 1, 2- interactions [(Ph, Ph) and (Ph, Me)-two gauche interactions].

Scheme 72: Plausible mechanism



In conclusion, we have examined intramolecular cyclization reaction of acrlylamide-α-substituted ketones (containing a chiral centre α to ketone) using DABCO as a catalyst to provide BH-adducts in high diastereoselectivities. We have also proposed a plausible mechanism for these selectivities in the Scheme 72. We have noticed that there is indication of increasing diastereoselectivity from the substrate containing methyl group at α-position of ketone to substrate containing allyl/*i*Bu group. This also indicates that steric factor has role on the stereochemical outcome of the IBH-reaction.

CONCLUSIONS

In conclusion, all the three objectives mentioned in the beginning of the chapter dealing with the intramolecular Baylis-Hillman reaction have been achieved with considerable progress.

1) We have designed and synthesized substrates containing less reactive acrylamide moiety as an activated alkene component and aldehydes as electrophile component and performed the intramolecular Baylis-Hillman reaction thus providing a convenient protocol for obtaining α-methylene lactam and spirolactam derivatives.

2) We have meticulously designed and synthesized substrates containing less reactive ketones and acrylamides as electrophile and activated alkene components respectively, and developed a procedure for intramolecular Baylis-Hillman coupling reaction to produce α-methylene-γ-lactam derivatives containing a tertiary alcohol functionality.

3) Finally, we have synthesized chiral (racemic) substrates having less reactive acrylamides and ketones as activated alkene and electrophile components respectively and subjected them to intramolecular cyclization to provide the resulting BH-adducts in high diastereoselectivities.

Our studies clearly demonstrate the importance of less reactive components, acrylamides and ketones in intramolecular Baylis-Hillman reactions thus expanding the scope of this reaction in synthetic chemistry. These studies also throw some light on the future projection of ketones as electrophiles which would indeed create a new platform for designing ketone substrates for diastereoselective and enantioselective BH-reactions.

EXPERIMENTAL

General: All the solvent were dried and distilled using suitable drying agents before use. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere.

Chromatography: All reactions were monitored using Thin Layer Chromatography (TLC). Analytical Thin Layer Chromatography (TLC) was performed on glass plates (7x2 cm) coated with Acme's silica gel GF 254 (254 mμ) containing 13% calcium sulphate as a binder. The spots were visualized by short exposure to UV light or iodine vapour. Column chromatography was carried out using Acme's silica gel (100-200 mesh) or Acme's neutral alumina.

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

Melting Points: Melting Points were recorded on a Superfit (India) capillary melting point apparatus or MR-Vis+ visual melting point range apparatus of LABINDIA instruments private limited and were uncorrected.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra carbon-13 magnetic resonance spectra were recorded on BRUKER-AVANCE-400 or BRUKER-AVANCE-500 spectrometers. ^{1}H NMR (400 / 500 MHz) spectra for all the samples were measured in chloroform-d, with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 MHz) spectra for all the samples were measured in chloroform-d (or in mixture of chloroform-d and DMSO-d_6) with middle peak of the triplet (δ = 77.10

ppm) of chloroform-d as an internal standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity, that is, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, td= triplet of doublet, ABq = AB quartet, bs = broad singlet, (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

X-ray Crystallographic Study: Single crystal X-ray data for the compounds (**75d**, **95a** and **108a**) were collected on a Bruker SMART APEX CCD area detector system [λ(Mo-Kα) = 0.71073 Å] at 100K and one compound (***syn*-128b**) at 298K, graphite monochromator with a ω scan width of 0.3^{o}, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software (Version 5.630) was used for the intensity data acquisition and the SAINTPLUS Software (Version 6.45) was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. Single crystal X-ray data for the compounds (**108b**, **108e** and ***syn*-128a**) were collected on Oxford Diffraction Xcalibur Eos Gemini diffractometer with graphite-monochromated Cu *Kα* radiation with the wavelength of 1.54178 Å at 298K. Data were analyzed with ‘‘CrysAlis PRO’’ software and the collected data was reduced by using the ‘‘CrysAlis PRO’’ program. An empirical absorption correction using spherical harmonics was implemented in ‘‘SCALE3 ABSPACK’’ scaling algorithm. The structures were solved 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.

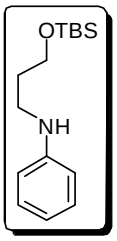
HPLC analysis: HPLC analyses were carried out on a Shimadzu SCL-10AVP instrument using the chiral column, Chiralcel-OJH.

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

HRMS Analysis: HRMS spectra were recorded on Bruker maxis ESI-TOF spectrometer.

Reprsentative procedure: Synthesis of N-[3-(*tert*-butyldimethylsilyloxy)]propyl aniline (77a)

To a stirring solution of 3-(phenylamino)propan-1-ol (**76a**) (2.87 g, 19 mmol) and imidazole (1.50 g, 22.08 mmol), in DCM (57 mL), was added TBSCl (3.15 g, 20.9 mmol) at 0 ºC. After stirring at room temperature for 2 h the reaction mixture was diluted with water (50mL) and extracted with DCM (2 x 80 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography [5 % ethyl acetate in hexanes] to provide the desired product (**77a**) in 90 % (4.53 g) yield as a brown liquid.



Reaction time : 2 h

Yield : 90 %

IR (neat) : ν 3402, 1604 cm^{-1}

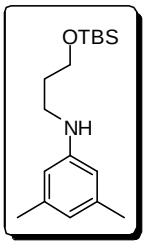
^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.92 (s, 9H), 1.79-1.88 (m, 2H), 3.23 (t, J = 6.4 Hz, 2H), 3.76 (t, J = 5.6 Hz, 2H), 4.08 (bs, 1H), 6.60 (d, J = 8.0 Hz, 2H)*, 6.63-6.71 (m, 1H), 7.14-7.19 (m, 2H)

* It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.33, 18.31, 26.01, 32.00, 42.01, 62.00, 112.68, 117.02, 129.23, 148.65

LCMS (*m/z*) : 266 $(M+H)^+$

N-[3-(*tert*-Butyldimethylsilyloxy)]propyl-3,5-dimethylaniline (77b)



Reaction time : 2 h

Yield : 94 %

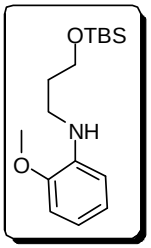
IR (neat) : ν 3404, 1602 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.92 (s, 9H), 1.76-1.85 (m, 2H), 2.23 (s, 6H), 3.21 (t, J = 6.6 Hz, 2H), 3.75 (t, J = 5.8 Hz, 2H), 3.94 (bs, 1H), 6.24 (s, 2H), 6.35 (s, 1H)

^{13}C NMR (100 MHz) : δ -5.46, 18.19, 21.46, 25.90, 32.08, 41.73, 61.73, 110.59, 118.95, 138.54, 148.64

LCMS (*m/z*) : 294 $(M+H)^+$

N-[3-(*tert*-Butyldimethylsilyloxy)]propyl-2-methoxyaniline (77c)



Reaction time : 2 h

Yield : 91 %

IR (neat) : ν 3420, 1602 cm^{-1}

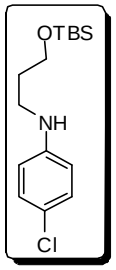
^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.91 (s, 9H), 1.82-1.91 (m, 2H), 3.24 (t, J = 6.4 Hz, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.83 (s, 3H), 4.44 (bs, 1H), 6.57-6.68 (m, 2H), 6.76 (d, J = 8.0 Hz, 1H)*, 6.83-6.90 (m, 1H)

* It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.44, 18.27, 25.91, 32.13, 41.16, 55.09, 61.57, 109.14, 109.53, 115.97, 121.21, 138.44, 146.73

LCMS (*m/z*) : 296 $(M+H)^+$

N-[3-(*tert*-Butyldimethylsilyloxy)]propyl-4-chloroaniline (77d)



Reaction time : 2 h

Yield : 89 %

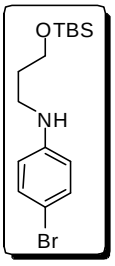
IR (neat) : ν 3404, 1602, 1502 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.91 (s, 9H), 1.76-1.86 (m, 2H), 3.19 (t, J = 6.4 Hz, 2H), 3.76 (t, J = 5.6 Hz, 2H), 4.15 (bs, 1H), 6.50 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ -5.36, 18.29, 25.98, 31.77, 42.25, 62.02, 113.66, 121.41, 129.01, 147.23

LCMS (*m/z*) : 300 $(M+H)^+$, 302 $(M+H+2)^+$

4-Bromo-N-[3-(*tert*-butyldimethylsilyloxy)]propylaniline (77e)



Reaction time : 2 h

Yield : 92 %

IR (neat) : ν 3404, 1597 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.92 (s, 9H), 1.77-1.88 (m, 2H), 3.19 (t, J = 6.4 Hz, 2H), 3.75 (t, J = 6.0 Hz, 2H), 4.19 (bs, 1H), 6.46 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H)*

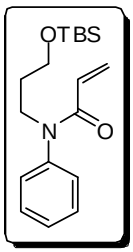
* It merges with $CHCl_3$

^{13}C NMR (100 MHz) : δ -5.39, 18.22, 25.94, 31.66, 42.07, 61.95, 108.28, 114.09, 131.79, 147.56

LCMS (*m/z*) : 344 $(M+H)^+$, 346 $(M+H+2)^+$

Reprsentative procedure: Synthesis of N-[3-(*tert*-butyldimethylsilyloxy)]propyl-N-phenylacrylamide (78a)

Acryloyl chloride (1.73 g, 19.2 mmol) was added by dropwise to a strirring solution of N-[3-(*tert*-butyldimethylsilyloxy)]propylaniline (**77a**) (4.25 g, 16.0 mmol) and Et_3N (2.26 g, 22.4 mmol) in DCM (48 mL) at 0 ºC. After stirring at room temperature for 2 h the reaction mixture was diluted with water (60 mL) and extracted with DCM (2 x 60 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by column chromatography [silica gel, 10 % ethyl acetate in hexanes] to provide the desired product (**78a**) in 85 % (4.35 g) yield as a pale yellow liquid.



Reaction time : 2 h

Yield : 85 %

IR (neat) : ν 1693, 1666, 1612 cm^{-1}

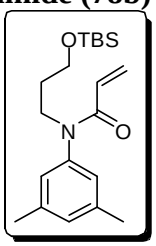
^1H NMR (400 MHz) : δ -0.02 (s, 6H), 0.83(s, 9H), 1.75-1.85 (m, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.81-3.88 (m, 2H), 5.48 (d, J = 10.4 Hz, 1H)*, 5.99 (dd, J = 16.84 and 10.4 Hz, 1H), 6.34 (dd, J = 16.8 and 2.0 Hz, 1H), 7.13-7.19 (m, 2H), 7.29-7.35 (m, 1H), 7.36-7.43 (m, 2H)

* It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.45, 18.13, 25.81, 30.92, 46.97, 60.72, 127.18, 127.58, 128.08, 128.87, 129.45, 142.15, 165.33

LCMS (*m/z*) : 320 $(M+H)^+$, 321 $(M+1+H)^+$

N-[3-(*tert*-Butyldimethylsilyloxy)]propyl-N-(3,5-dimethylphenyl)acrylamide (78b)



Reaction time : 2 h

Yield : 87 %

IR (neat) : ν 1660, 1597 cm^{-1}

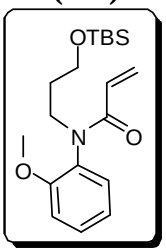
^{1}H NMR (400 MHz) : δ -0.01 (s, 6H)*, 0.84 (s, 9H), 1.76-1.84 (m, 2H), 2.31 (s, 6H), 3.64 (t, J = 6.4 Hz, 2H), 3.77-3.85 (m, 2H), 5.48 (dd, J = 10.4 and 2.4 Hz, 1H), 6.03 (dd, J = 16.8 and 10.4 Hz, 1H), 6.33 (dd, J = 16.8 and 2.4 Hz, 1H), 6.75 (s, 2H), 6.95 (s, 1H)

* It merges with TMS peak

^{13}C NMR (100 MHz) : δ -5.52, 18.07, 21.03, 25.74, 30.94, 46.76, 60.75, 125.64, 126.73, 128.96, 129.13, 139.06, 141.91, 165.19

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

N-[3-(*tert*-Butyldimethylsilyloxy)]propyl-N-(2-methoxyphenyl)acrylamide (78c)



Reaction time : 2 h

Yield : 90 %

IR (neat) : ν 1660, 1620 cm^{-1}

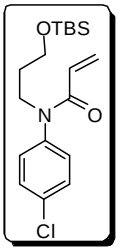
^{1}H NMR (400 MHz) : δ -0.02 (s, 3H)*, -0.10 (s, 3H), 0.82 (s, 9H), 1.71-1.81 (m, 2H), 3.57-3.66 (m, 3H), 3.78 (s, 3H), 3.87-3.97 (m, 1H), 5.43 (dd, J = 10.4 and 2.0 Hz, 1H), 5.93 (dd , J = 16.8 and 10.4 Hz, 1H), 6.31 (dd, J = 16.8 and 2.0 Hz, 1H,), 6.92-6.99 (m, 2H), 7.08-7.13 (m, 1H), 7.29-7.36 (m, 1H)

* It merges with TMS peak

^{13}C NMR (100 MHz) : δ -5.48, 18.08, 25.75, 30.82, 45.69, 55.34, 60.94, 111.80, 120.73, 126.62, 128.62, 129.26, 129.98, 130.38, 155.32, 165.91

LCMS (*m/z*) : 350 $(M+H)^+$

N-[3-(*tert*-Butyldimethylsilyloxy)]propyl-N-(4-chlorophenyl)acrylamide (78d)



Reaction time : 2 h

Yield : 83 %

IR (neat) : *v* 1664, 1620, 1589 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.01 (s, 6H)*, 0.83 (s, 9H), 1.74-1.83 (m, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.79-3.88 (m, 2H), 5.52 (d, *J* = 10.4 Hz, 1H), 5.90-6.07 (m, 1H)#, 6.35 (dd, *J* = 16.8 Hz, 1.6 Hz 1H), 7.07-7.14 (m, 2H), 7.34-7.40 (m, 2H)

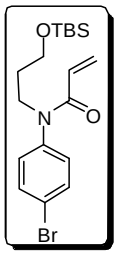
* It merges with TMS peak

It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.54, 18.03, 25.71, 30.79, 46.97, 60.45, 127.63, 128.51, 129.26, 129.54, 133.24, 140.71, 165.09

LCMS (*m/z*) : 355 $(M+H)^+$, 357 $(M+H+2)^+$

N-(4-Bromophenyl)-N-[3-(*tert*-butyldimethylsilyloxy)]propylacrylamide (78e)



Reaction time : 2 h

Yield : 85 %

IR (neat) : *v* 1662, 1620 cm^{-1}

^{1}H NMR (400 MHz) : δ -0.01 (s, 6H), 0.84 (s, 9H), 1.73-1.84 (m, 2H), 3.63 (t, J = 6.0 Hz, 2H), 3.79-3.86 (m, 2H), 5.53 (d, J = 10.4 Hz, 1H)*, 5.90-6.10 (m, 1H), 6.35 (dd, J = 16.8 and 2.0 Hz, 1H), 7.02-7.08 (m, 2H), 7.50-7.55 (m, 2H)

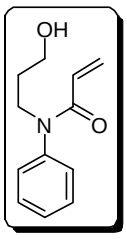
* It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.49, 18.07, 25.76, 30.83, 46.97, 60.48, 121.21, 127.71, 128.54, 129.63, 132.57, 141.26, 165.08

LCMS (*m/z*) : 398 $(M+H)^+$, 400 $(M+H+2)^+$

N-(3-Hydroxypropyl)-N-phenylacrylamide (79a)

To a stirring solution of N-[3-(*tert*-butyldimethylsilyloxy)]propyl-N-phenylacrylamide (**78a**) (2.23 g, 7 mmol) in THF-water (4:1) (17.5 mL), conc. HCl (3.5 mL) was added at room temperature. After stirring for 2 h at same temperature, the reaction mixture was neutralized by adding saturated $NaHCO_3$ solution. THF was removed and water (50 mL) was added. Then the reaction mixture extracted with ethyl acetate (60 mL x 3). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by column chromatography (75 % ethyl acetate in hexanes) to provide the desired product (**79a**) in 93 % (1.33 g) yield as a white solid.



Reaction time : 2 h

Yield : 93 %

Mp : 82-84 ºC

IR (KBr) : ν 3439,1647, 1616 cm^{-1}

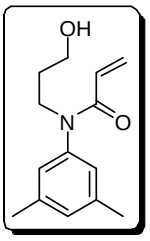
^{1}H NMR (400 MHz) : δ 1.64-1.73 (m, 2H), 3.61-3.68 (m, 2H), 3.98 (t, J = 6.4 Hz, 2H), 4.04 (t, J = 7.2 Hz, 1H), 5.56 (dd, J = 10.4 and

1.6 Hz, 1H), 5.99 (dd, *J* = 16.8 and 10.4 Hz 1H), 6.39 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.12-7.19 (m, 2H), 7.35-7.48 (m, 3H)

^{13}C NMR (100 MHz) : δ 29.90, 45.77, 58.17, 127.79, 127.89, 128.01, 129.50, 141.07, 166.30

LCMS (*m/z*) : 206 $(M+H)^+$

N-(3,5-Dimethylphenyl)-N-(3-hydroxypropyl)acrylamide (79b)



Reaction time : 2 h

Yield : 93 %

Mp : 72-74 ºC

IR (KBr) : *v* 3358, 1637, 1610 cm^{-1}

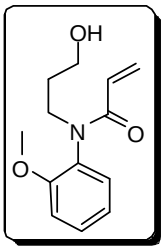
^{1}H NMR (400 MHz) : δ 1.63-1.74 (m, 2H)*, 2.34 (s, 6H), 3.60-3.69 (m, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 4.09 (t, *J* = 7.2 Hz, 1H), 5.54 (dd, *J* = 10.4 and 2.0 Hz, 1H), 6.01 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.37 (dd, *J* = 16.8 and 2.0 Hz, 1H), 6.74 (s, 2H), 6.99 (s, 1H)

* It merges with moisture peak

^{13}C NMR (100 MHz) : δ 21.11, 30.12, 45.74, 58.25, 125.59, 127.95, 128.27, 129.71, 139.54, 141.13, 166.74

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

N-(3-Hydroxypropyl)-N-(2-methoxyphenyl)acrylamide (79c)



Reaction time : 2 h

Yield : 92 %

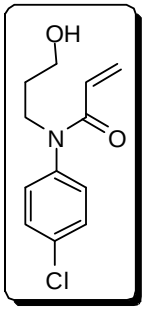
IR (neat) : ν 3447, 1653, 1612 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.59-1.68 (m, 2H), 3.57-3.67 (m, 1H), 3.69-3.85 (m, 5H), 3.92-4.02 (m, 1H), 4.16 (t, J = 7.2 Hz, 1H), 5.51 (dd, J = 10.4 and 2.0 Hz, 1H), 5.94 (dd, J = 16.8 and 10.4 Hz, 1H), 6.36 (dd, J = 16.8 and 1.6 Hz, 1H), 6.94-7.04 (m, 2 H), 7.06-7.12 (m, 1H), 7.33-7.41 (m, 1H)

^{13}C NMR (100 MHz) : δ 30.18, 44.73, 55.33, 58.22, 111.93, 120.85, 127.56, 127.84, 129.58, 129.61, 155.07, 167.19

LCMS (*m/z*) : 236 $(M+H)^+$

N-(4-Chlorophenyl)-N-(3-hydroxypropyl)acrylamide (79d)



Reaction time : 2 h

Yield : 91 %

Mp : 72-74 ºC

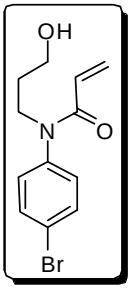
IR (KBr) : ν 3425, 1635, 1604 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.63-1.74 (m, 2H), 3.57-3.67 (m, 2H), 3.85 (t, J = 6.4 Hz, 1H), 3.91-3.98 (m, 2H), 5.59 (dd, J = 10.0 and 2.0 Hz, 1H), 5.98 (dd, 1H, J = 16.8 and 10.0 Hz), 6.36-6.44 (m, 1H), 7.07-7.13 (m, 2H), 7.38-7.44 (m, 2H)

^{13}C NMR (100 MHz) : δ 30.02, 45.96, 58.27, 127.86, 128.77, 129.32, 129.92, 133.88, 139.85, 166.53

LCMS (*m/z*) : 241 $(M+H)^+$, 243 $(M+2+H)^+$

N-(4-Bromophenyl)-N-(3-hydroxypropyl)acrylamide (79e)



Reaction time : 2 h

Yield : 93 %

Mp : 82-84 ºC

IR (KBr) : *v* 1639, 1602 cm^{-1}

^1H NMR (400 MHz) : δ 1.59-1.75 (m, 2H), 3.62 (t, *J* = 5.2 Hz, 2H), 3.84 (bs, 1H), 3.94 (t, *J* = 6.0 Hz, 2H), 5.59 (dd, *J* = 10.4 and 1.6 Hz, 1H), 5.98 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.41 (dd, *J* = 16.8 and 2.0 Hz, 1H), 7.02-7.07 (m, 2H), 7.55-7.60 (m, 2H)

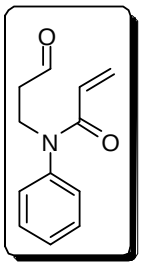
^{13}C NMR (100 MHz) : δ 30.05, 45.94, 58.27, 121.91, 127.87, 128.90, 129.69, 132.97, 140.40, 166.57

LCMS (*m/z*) : 284 $(M+H)^+$, 286 $(M+H+2)^+$

Reprsentative procedure: Synthesis of N-(3-oxopropyl)-N-phenylacrylamide (72a)*

To a stirring solution of oxalyl chloride [(2.79 g, 22 mmol) in DCM (55 mL)] at -78 ºC DMSO (3.43 g, 44 mmol) was added dropwise. After stirring for 15 min at the same temperature, the solution of N-(3-hydroxypropyl)-N-phenylacrylamide (**79a**) [(2.25 g, 11 mmol) in DCM (22 mL)] was added by drop wise. After 15 min at the same temperature, a solution of Et_3N [(6.71 g, 66 mmol) in DCM (22 mL)] was added by drop wise. After stirring for 0.5 h at the same temperature the reaction mixture was gradually brought to room temperature and stirred for an additional 0.5 h at room

temperature. The reaction mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). Organic extracts were combined and dried over anhydrous Na_2SO_4 concentrated. The crude thus obtained was purified by column chromatography (50 % ethyl acetate in hexanes) to provide the desired product (**72a**) in 94 % (2.09 g) yield as a yellow viscous liquid.



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 94 %

IR (neat) : ν 1720, 1657, 1616 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.75 (dt, J = 6.8 and 1.6 Hz, 2H), 4.13 (t, J = 6.8 Hz, 2H), 5.53 (dd, J = 10.4 and 2.0 Hz, 1H), 5.97 (dd, J = 16.8 and 10.4 Hz, 1H), 6.36 (dd, J = 16.8 and 2.0 Hz, 1H), 7.13-7.21 (m, 2H), 7.34-7.48 (m, 3H), 9.77 (t, J = 1.6 Hz, 1H)

^{13}C NMR (100 MHz) : δ 42.08, 43.46, 127.65, 127.93, 127.99, 128.16, 141.14, 165.37, 200.16

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

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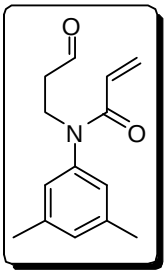
* It is worth mentioning that the aldehydes (**72a-e** and **73a-g**) were freshly prepared from alcohols (**79a-e** and **84a-g**) and used immediately for BH reaction in the presence of 3-5 mol% of hydroquinone. (Hydroquinone was added before concentration of the fraction containing pure aldehyde obtained through column chromatography).

N-(3,5-Dimethylphenyl)-N-(3-oxopropyl)acrylamide (72b)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 93 %

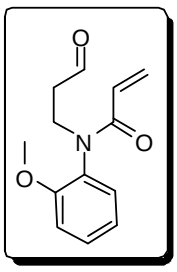
IR (neat) : ν 1720, 1657, 1610 cm^{-1}

^1H NMR (400 MHz) : δ 2.33 (s, 6H), 2.73 (dt, J = 6.8 and 1.6 Hz, 2H), 4.09 (t, J = 6.8 Hz, 2H), 5.51 (dd, J = 10.4 and 2.0 Hz, 1H), 6.00 (dd, J = 16.8 and 10.4 Hz, 1H), 6.34 (dd, J = 16.8 and 2.0 Hz, 1H), 6.75 (s, 2H), 6.99 (s, 1H), 9.77 (t, J = 1.6 Hz, 1H)

^{13}C NMR (100 MHz) : δ 20.73, 41.99, 43.26, 125.45, 127.08, 128.20, 129.38, 139.19, 140.85, 165.10, 200.06

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

N-(2-Methoxyphenyl)-N-(3-oxopropyl)acrylamide (72c)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 95 %

IR (neat) : ν 1720, 1653, 1616 cm^{-1}

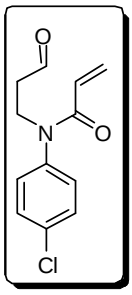
^1H NMR (400 MHz) : δ 2.68-2.76 (m, 2H), 3.80 (s, 3H), 4.05 (t, J = 6.8 Hz, 2H), 5.48 (dd, J = 10.4 and 2.0 Hz, 1H), 5.92 (dd, J = 16.8 and 10.4 Hz, 1H), 6.33 (dd, J = 16.8 and 2.0 Hz, 1H), 6.92-7.03 (m, 2H), 7.11 (dd, J = 7.6 and 1.6 Hz, 1H), 7.31-7.39 (m, 1H), 9.74-9.78 (m, 1H)*

* It is unresolved triplet

^{13}C NMR (100 MHz) : δ 42.13, 42.60, 55.31, 111.86, 120.92, 127.28, 128.05, 129.65, 129.73, 129.84, 155.14, 166.15, 200.96

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

N-(4-Chlorophenyl)-N-(3-oxopropyl)acrylamide (72d)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 92 %

IR (neat) : ν 1722, 1660, 1614 cm^{-1}

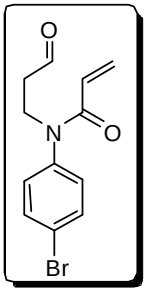
^{1}H NMR (400 MHz) : δ 2.76 (dt, J = 6.8 and 1.6 Hz, 2H), 4.09 (t, J = 6.8 Hz, 2H), 5.56 (dd, J = 10.4 and 1.6 Hz, 1H), 5.96 (dd, J = 16.8 and 10.4 Hz, 1H), 6.36 (dd, J = 16.8 and 1.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 9.78 (s, 1H)*

* It is unresolved triplet

^{13}C NMR (100 MHz) : δ 42.13, 43.58, 127.96, 128.36, 129.43, 129.86, 133.83, 139.87, 165.42, 200.09

LCMS (*m/z*) : 238 $(M+H)^+$, 240 $(M+2+H)^+$

N-(4-Bromophenyl)-N-(3-oxopropyl)acrylamide (72e)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 96 %

IR (neat) : ν 1718, 1655, 1618 cm^{-1}

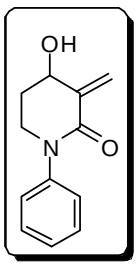
^{1}H NMR (400 MHz) : δ 2.76 (dt, J = 6.8 and 1.6 Hz, 2H), 4.09 (t, J = 6.8 Hz, 2H), 5.56 (dd, J = 10.4 and 2.0 Hz, 1H), 5.97 (dd, J = 16.8 and 10.4 Hz, 1H), 6.37 (dd, J = 16.8 and 2.0 Hz, 1H), 7.03-7.09 (m, 2H), 7.54-7.59 (m, 2H), 9.77 (t, J = 1.6 Hz, 1H)

^{13}C NMR (100 MHz) : δ 41.82, 43.24, 121.42, 127.77, 127.98, 129.55, 132.52, 140.14, 164.92, 199.82

LCMS (*m/z*) : 282 $(M+H)^+$, 284 $(M+2+H)^+$

4-Hydroxy-3-methylene-1-phenylpiperidin-2-one (74a)

A solution of N-(3-oxopropyl)-N-phenylacrylamide (**72a**)* (0.203 g, 1 mmol), DABCO (0.112 g, 1.0 mmol) in *t*BuOH (6.0 mL) was heated under reflux for 13 h with stirring (till the disappearance of the aldehyde**,** as monitored by TLC). Solvent was then removed under reduced pressure and the crude product thus obtained was purified as such by column chromatography [silica gel, EtOAc:Hexane (3:1)] to furnish 0.152 g of the title compound **74a** (75 % yield) as a white solid.



Reaction time : 13 h

Yield : 75 %

Mp : 142-144 ºC

IR (KBr) : ν 3386, 1665, 1616 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.07-2.17 (m, 2H), 2.18-2.27 (m, 1H), 3.58-3.66 (m, 1H), 3.96-4.05 (m, 1H), 4.65-4.71 (m, 1H), 5.72 (t, J = 1.6 Hz, 1H), 6.45 (t, J = 1.2 Hz, 1H), 7.25-7.32 (m, 3H)*, 7.38-7.44 (m, 2H)

* It also contains $CHCl_3$ peak

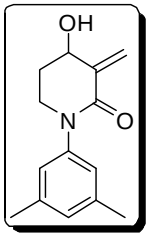
^{13}C NMR (100 MHz) : δ 30.90, 47.04, 67.93, 124.35, 126.15, 126.98, 129.13, 141.39, 142.92, 163.78

HRMS (ESI) exact mass calc′d for $C_{12}H_{13}NO_2H$ $(M+H)^+$: 204.1025

Found : 204.1021

1-(3,5-Dimethylphenyl)-4-hydroxy-3-methylenepiperidin-2-one (74b)

Reaction time : 24 h



Yield : 77 %

Mp : 194-196 ºC

IR (KBr) : ν 3402, 1660, 1616 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.04-2.24 (m, 2H), 2.27-2.41 (m, 7H)*, 3.53-3.63 (m, 1H), 3.90-4.00 (m, 1H), 4.65 (*t*, *J* = 3.6 Hz, 1H), 5.69 (s, 1H), 6.43 (s, 1H), 6.89 (s , 2H), 6.92 (s, 1H)

* It contains one singlet for 6H and a multiplet for 1H

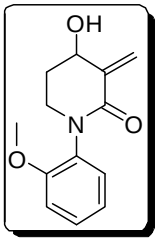
^{13}C NMR (100 MHz) : δ 20.91, 31.10, 46.95, 67.38, 122.83, 123.57, 128.28, 138.38, 141.78, 142.68, 163.29

HRMS (ESI) exact mass calc′d for $C_{14}H_{17}NO_2H$ $(M+H)^+$: 232.1338

Found : 232.1337

4-Hydroxy-1-(2-methoxyphenyl)-3-methylenepiperidin-2-one (74c)

Reaction time : 84 h



Yield : 73 %

Mp : 122-124 ºC

IR (KBr) : ν 3402, 1665, 1610 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.80-2.27 (m, 3H)* (1H, D_2O washable), 3.56 (bs, 1H), 3.70-3.90 (m, 4H)#, 4.62-4.69 (m, 1H), 5.71 (s, 1H), 6.42 (s, 1H), 6.95-7.03 (m, 2H), 7.16-7.21 (m, 1H), 7.30 (dt, J = 8.0 and 1.6 Hz, 1H)

* It also contains moisture peak

It contains a singlet at 3.83 for 3H and a multiplet for 1H

To have more clarity of the broad peak at δ 3.56 and multiplet at δ 3.70-3.90 (m, 4H) we have recorded ^{1}H NMR spectrum at -36 °C: δ 2.06-2.22 (m, 2H), 3.35-3.45 & 3.50-3.59 (2m, 1H), 3.77-4.06 (m, 5H), 4.59-4.66 (m, 1H), 5.68 (d, J = 16.8 Hz, 1H), 6.35 (d, J = 6.4 Hz,1H), 6.99-7.19 (m, 2H), 7.18-7.24 (m, 1H), 7.34-7.42 (m, 1H)

The following differences were observed between ^{1}H NMR spectra at room temperature and at -36 °C

1) OH proton which appeared in ^{1}H NMR spectrum at room temperature in the multiplet at δ 1.80-2.27 (m, 3H) now appeared in the multiplet at δ 3.77-4.06 (m, 5H) in the ^{1}H NMR spectrum at -36 °C.

2) The broad peak at δ 3.56 (bs, 1H) in the ^{1}H NMR spectrum at room temperature appeared as two multiplets at δ 3.35-3.45 & 3.50-3.59 in the ^{1}H NMR spectrum at -36 °C.

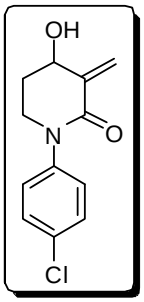
3) Singlet at δ 5.71 in ^{1}H NMR spectrum at room temperature appeared as doublet at δ 5.68 in ^{1}H NMR spectrum at -36 °C. These differences may be due to rigid conformation at low temperature (-36 °C)

^{13}C NMR (100 MHz) : δ 31.03, 46.37, 55.62, 67.86, 112.03, 120.85, 123.27, 128.75, 128.88, 131.14, 141.56, 154.49, 163.86

HRMS (ESI) exact mass calc′d for $C_{13}H_{15}NO_3H$ $(M+H)^+$: 234.1130

Found : 234.1133

1-(4-Chlorophenyl)-4-hydroxy-3-methylenepiperidin-2-one (74d)



Reaction time : 6 h

Yield : 74 %

Mp : 146-148 ºC

IR (KBr) : ν 3391, 1654, 1605 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.05-2.24 (m, 2H), 2.47 (bs, 1H) 3.53-3.62 (m, 1H), 3.94-4.04 (m, 1H), 4.62-4.68 (m, 1H), 5.71 (s, 1H), 6.42 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H)*, 7.37 (d, J = 8.4 Hz, 2H)

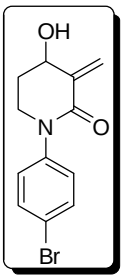
* It also contains $CHCl_3$ peak

^{13}C NMR (100 MHz) : δ 30.85, 46.81, 68.14, 124.88, 127.47, 129.29, 132.47, 141.25, 141.41, 163.61

HRMS (ESI) exact mass calc′d for $C_{12}H_{12}ClNO_2H$ $(M+H)^+$: 238.0635

Found : 238.0633

1-(4-Bromophenyl)-4-hydroxy-3-methylenepiperidin-2-one (74e)



Reaction time : 6 h

Yield : 78 %

Mp : 176-178 ºC

IR (KBr) : ν 3408, 1660, 1605 cm^{-1}

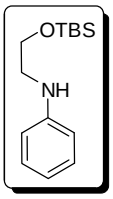
^{1}H NMR (400 MHz) : δ 2.05-2.30 (m, 3H), 3.54-3.63 (m, 1H), 3.95-4.04 (m, 1H), 4.67 (bs, 1H), 5.72 (s, 1H), 6.44 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H)

^{13}C NMR (100 MHz) : δ 30.83, 46.32, 66.97, 119.37, 123.22, 127.37, 131.45, 141.41, 141.69, 163.09

HRMS (ESI) exact mass calc′d for $C_{12}H_{12}BrNO_2H$ $(M+H)^+$: 282.0130

Found : 282.0132

N-[2-(*tert*-Butyldimethylsilyloxy)]ethylaniline (82a)



Reaction time : 2 h

Yield : 93 %

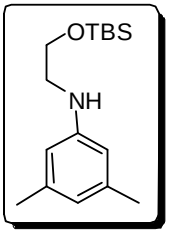
IR (neat) : ν 3408, 1604, 1506 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.90 (s, 9H), 3.22 (t, J = 5.4 Hz, 2H), 3.82 (t, J = 5.4 Hz, 2H), 4.04 (bs, 1H), 6.61-6.66 (m, 2H), 6.68-6.74 (m, 1H), 7.14-7.21 (m, 2H)

^{13}C NMR (100 MHz) : δ -5.31, 18.32, 25.94, 45.98, 61.63, 113.21, 117.53, 129.22, 148.39

LCMS (*m/z*) : 252 $(M+H)^+$

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-3,5-dimethylaniline (82b)



Reaction time : 2 h

Yield : 93 %

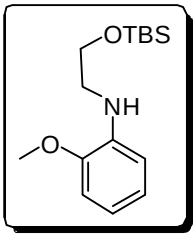
IR (neat) : ν 3408, 1605 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.91 (s, 9H), 2.24 (s, 6H),3.19 (t, J = 5.4 Hz, 2H), 3.80 (t, J = 5.4 Hz, 2H), 3.96 (bs, 1H), 6.28 (s, 2H), 6.38 (s, 1H)

^{13}C NMR (100 MHz) : δ -5.35, 18.27, 21.46, 25.90, 46.03, 61.72, 111.14, 119.50, 138.67, 148.47

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

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-2-methoxyaniline (82c)



Reaction time : 2 h

Yield : 91 %

IR (neat) : ν 3408, 1599 cm^{-1}

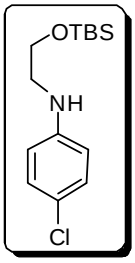
^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.91 (s, 9H), 3.23 (t, J = 5.4 Hz, 2H), 3.83 (s, 3H), 3.85 (t, J = 5.4 Hz, 2H)*, 4.62 (bs, 1H), 6.60-6.71 (m, 2H), 6.77 (dd, J = 7.8 and 1.2 Hz, 1H), 6.83-6.90 (m, 1H)

* One of the peak of the triplet merges with singlet at 3.85

^{13}C NMR (100 MHz) : δ -5.38, 18.27, 25.86, 45.66, 55.30, 61.63, 109.47, 110.16, 116.57, 121.21, 138.38, 147.17

LCMS (*m/z*) : 282 $(M+H)^{+}$

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-4-chloroaniline (82d)



Reaction time : 2 h

Yield : 95 %

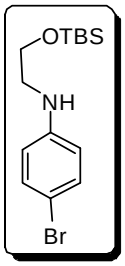
IR (neat) : ν 3406, 1602 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.06 (s, 6H), 0.90 (s, 9H), 3.18 (t, J = 5.2 Hz, 2H), 3.80 (t, J = 5.2 Hz, 2H), 4.06 (bs, 1H), 6.52-6.59 (m, 2H), 7.08-7.15 (m, 2H)

^{13}C NMR (100 MHz) : δ -5.31, 18.33, 25.93, 46.06, 61.45, 114.24, 121.97, 129.02, 146.99

LCMS (*m/z*) : 286 $(M+H)^+$

4-Bromo-N-[2-(*tert*-butyldimethylsilyloxy]ethylaniline (82e)



Reaction time : 2 h

Yield : 89 %

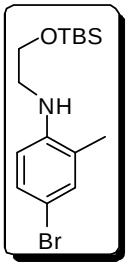
IR (neat) : ν 3393, 1597 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.06 (s, 6H), 0.90 (s, 9H), 3.17 (t, J = 5.2 Hz, 2H), 3.80 (t, J = 5.2 Hz, 2H), 4.07 (bs, 1H), 6.48-6.53 (m, 2H), 7.22-7.27 (m, 2H)

^{13}C NMR (100 MHz) : δ -5.31, 18.29, 25.92, 45.93, 61.42, 108.95, 114.70, 131.85

LCMS (*m/z*) : 330 $(M+H)^+$, 332 $(M+2+H)^+$

4-Bromo-N-[2-(*tert*-butyldimethylsilyloxy)]ethyl-2-methylaniline (82f)



Reaction time : 2 h

Yield : 93 %

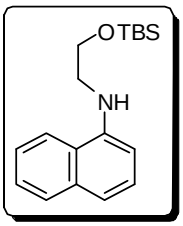
IR (neat) : ν 3412, 1599 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.08 (s, 6H), 0.90 (s, 9H), 2.10 (s, 3H), 3.16-3.28 (m, 2H), 3.86 (t, J = 5.2 Hz, 2H), 3.99 (bs, 1H), 6.47 (d, J = 8.4 Hz, 1H), 7.13-7.23 (m, 2H)

^{13}C NMR (100 MHz) : δ -5.34, 17.20, 18.23, 25.89, 45.78, 61.35, 108.66, 111.52, 124.49, 129.61, 132.45, 145.46

LCMS (*m/z*) : 344 $(M+H)^+$, 346 $(M+2+H)^+$

N-(2-(*tert*-Butyldimethylsilyloxy)ethyl)naphth-1-amine (82g)



Reaction time : 2 h

Yield : 93 %

IR (neat) : ν 3412, 1583 cm^{-1}

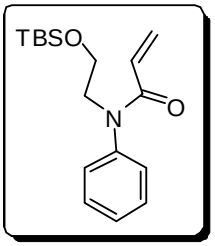
^{1}H NMR (400 MHz) : δ 0.11 (s, 6H), 0.94 (s, 9H), 3.37 (t, J = 4.8 Hz, 2H), 3.99 (t, J = 5.6 Hz, 2H), 4.86 (bs, 1H), 6.62 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H)*, 7.31-7.38 (m, 1H), 7.41-7.48 (m, 2H), 7.76-7.85 (m, 2H)

* One of the peak merges with $CHCl_3$ peak

^{13}C NMR (100 MHz) : δ -5.25, 18.32, 25.97, 46.04, 61.49, 104.69, 117.57, 119.94, 123.83, 124.75, 125.71, 126.62, 128.66, 134.36, 143.76

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

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-N-phenylacrylamide (83a)



Reaction time : 2 h

Yield : 86 %

IR (neat) : ν 1654, 1621 cm^{-1}

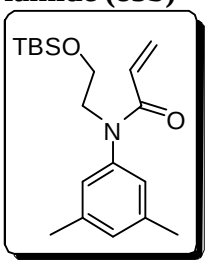
^{1}H NMR (400 MHz) : δ 0.03 (s, 6H), 0.85 (s, 9H), 3.76-3.96 (m, 4H), 5.51 (d, J = 10.4 Hz, 1H)*, 6.03 (dd, J = 16.8 and 10.4 Hz, 1H), 6.36 (dd, J = 16.8 and 2.0 Hz, 1H), 7.21-7.25 (m, 2H), 7.28-7.34 (m, 1H), 7.35-7.42 (m, 2H)

* It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.40, 18.21, 25.87, 52.35, 60.27, 127.27, 127.49, 128.18, 128.96, 129.31, 142.80, 165.68

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

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-N-(3,5-dimethylphenyl)acrylamide (83b)



Reaction time : 2 h

Yield : 91 %

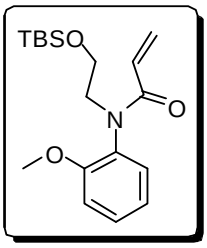
IR (neat) : ν 2931, 1660, 1620 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.04 (s, 6H), 0.86 (s, 9H), 2.31 (s, 6H), 3.83 (s, 4H), 5.49 (dd, J = 10.4 and 2.0 Hz, 1H), 6.06 (dd, J = 16.8 and 10.4 Hz, 1H), 6.34 (dd, J = 16.8 and 2.0 Hz, 1H), 6.83 (s, 2H), 6.93 (s, 1H)

^{13}C NMR (100 MHz) : δ -5.59, 18.00, 20.94, 25.68, 52.15, 60.09, 125.60, 126.67, 128.92, 138.78, 142.46, 165.37

LCMS (*m/z*) : 332 $(M-H)^+$

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-N-(2-methoxyphenyl)acrylamide (83c)



Reaction time : 2 h

Yield : 90 %

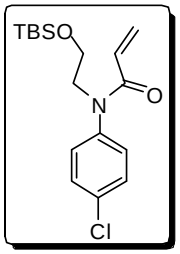
IR (neat) : ν 1665, 1621 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.02 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 3.45-3.53 (m, 1H), 3.69-3.76 (m, 1H), 3.79 (s, 3H), 3.81-3.91 (m, 1H), 4.04-4.13 (m, 1H), 5.44 (dd, J = 10.4 and 1.6 Hz, 1H), 5.95 (dd, J = 16.8 and 10.4 Hz, 1H), 6.32 (dd, J = 16.8 and 1.6 Hz, 1H), 6.90-7.01 (m, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.28-7.35 (m, 1H)

^{13}C NMR (100 MHz) : δ -5.64, -5.58, 17.93, 25.63, 50.71, 55.20, 60.02, 111.57, 120.51, 126.57, 128.32, 129.13, 130.07, 130.74, 155.00, 165.96

LCMS (*m/z*) : 336 $(M + H)^+$

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-N-(4-chlorophenyl)acrylamide (83d)



Reaction time : 2 h

Yield : 84 %

IR (neat) : ν 1664, 1620 cm^{-1}

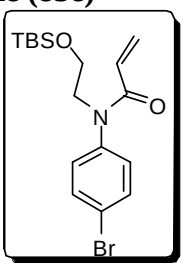
^{1}H NMR (400 MHz) : δ 0.02 (s, 6H), 0.85 (s, 9H), 3.84 (s, 4H), 5.54 (d, J = 10.0 Hz, 1H)*, 6.02 (dd, J = 16.8 and 10.4 Hz, 1H), 6.36 (dd, J = 16.8 and 2.0 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H)

* It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.50, 18.09, 25.76, 52.41, 60.27, 127.68, 128.62, 129.34, 129.39, 133.10, 141.39, 165.39

LCMS (*m/z*) : 340 $(M+H)^+$

N-(4-Bromophenyl)-N-[2-(*tert*-butyldimethylsilyloxy)]ethylacrylamide (83e)



Reaction time : 2 h

Yield : 85 %

IR (neat) : *v* 1654, 1616 cm^{-1}

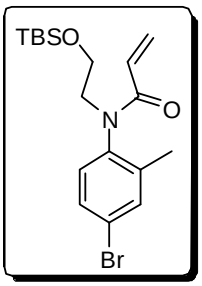
^{1}H NMR (400 MHz) : δ 0.02 (s, 6H), 0.85 (s, 9H), 3.82-3.88 (m, 4H), 5.54 (d, *J* = 10.0 Hz, 1H)*, 5.94-6.12 (m, 1H), 6.37 (dd, *J* = 16.8 and 2.0 Hz, 1H), 7.11-7.17 (m, 2H), 7.48-7.53 (m, 2H)

* It is unresolved dd

^{13}C NMR (100 MHz) : δ -5.49, 18.09, 25.77, 52.39, 60.27, 121.04, 127.74, 128.62, 129.73, 132.33, 141.91, 165.35

LCMS (*m/z*) : 384$(M+H)^+$, 386$(M+2+H)^+$

N-(4-Bromo-2-methylphenyl)-N-[2-(*tert*-butyldimethylsilyloxy)]ethylacrylamide (83f)



Reaction time : 2 h

Yield : 87 %

IR (neat) : *v* 1664, 1620 cm^{-1}

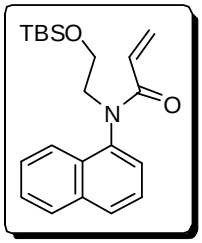
^{1}H NMR (400 MHz) : δ 0.02 (s, 6H), 0.84 (s, 9H), 2.17 (s, 3H), 3.33-3.44 (m, 1H), 3.69-3.93 (m, 2H), 4.07-4.22 (m, 1H), 5.51 (dd, *J* = 10.4 and 1.6 Hz, 1H), 5.88 (dd, *J* = 16.8 and 10.4 Hz,

1H), 6.37 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.32-7.38 (m, 1H); 7.40-7.45 (m, 1H)

^{13}C NMR (100 MHz) : δ -5.42, 17.65, 18.14, 25.80, 51.25, 60.28, 121.83, 127.86, 128.25, 130.09, 130.98, 133.98, 138.40, 140.40, 165.56

LCMS (*m/z*) : 398 $(M+H)^+$, 400 $(M+2+H)^+$

N-[2-(*tert*-Butyldimethylsilyloxy)]ethyl-N-(naphth-1-yl)acrylamide (83g)



Reaction time : 2 h

Yield : 87 %

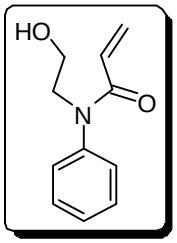
IR (neat) : *v* 1660, 1620 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.003 (s, 3H), 0.006 (s, 3H), 0.82 (s, 9H), 3.51-3.61 (m, 1H), 3.81-3.95 (m, 2H), 4.31-4.41 (m, 1H), 5.37 (dd, *J* = 10.4 and 2.0 Hz, 1H), 5.78 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.36 (dd, *J* = 16.8 and 2.0 Hz, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.45-7.58 (m, 3H), 7.76-7.83 (m, 1H), 7.85-7.95 (m, 2H)

^{13}C NMR (100 MHz) : δ -5.41, 18.17, 25.83, 51.73, 60.40, 122.85, 125.54, 126.68, 126.99, 127.33, 127.73, 128.42, 128.47, 128.72, 130.73, 134.58, 138.57, 166.46

LCMS (*m/z*) : 356 $(M+H)^+$

N-(2-Hydroxyethyl)-N-phenylacrylamide (84a)



Reaction time : 2 h

Yield : 87 %

IR (KBr) : ν 3429, 1653, 1614 cm^{-1}

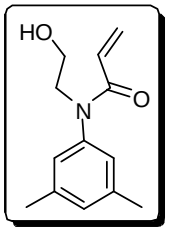
Mp : 50-52 ºC

^{1}H NMR (400 MHz) : δ 3.30 (t, J = 5.2 Hz, 1H), 3.78-3.87 (m, 2H), 3.99 (t, J = 5.2 Hz, 2H), 5.57 (dd, J = 10.4 and 1.6 Hz, 1H), 6.01 (dd, J = 16.8 and 10.4 Hz, 1H), 6.39 (dd, J = 16.8 and 1.6 Hz, 1H), 7.18-7.25 (m, 2H), 7.34-7.47 (m, 3H)

^{13}C NMR (100 MHz) : δ 52.53, 60.39, 127.86, 127.91, 127.96, 128.34, 129.52, 141.85, 166.89

LCMS (*m/z*) : 192 $(M+H)^+$

N-(3,5-Dimethylphenyl)-N-(2-hydroxyethyl)acrylamide (**84b**)



Reaction time : 2 h

Yield : 91 %

Mp : 60-62 ºC

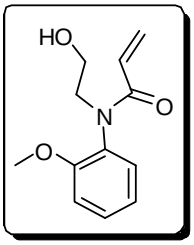
IR (KBr) : ν 3364, 1649, 1610 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.33 (s, 6H), 3.42 (t, J = 4.8 Hz, 1H), 3.77-3.84 (m, 2H) 3.95 (t, J = 5.2 Hz, 2H), 5.56 (dd, J = 10.0 and 2.0 Hz, 1H), 6.04 (dd, J = 16.8 and 10.0 Hz, 1H), 6.38 (dd, J = 16.8 and 2.0 Hz, 1H), 6.81 (s, 2H), 6.99 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.90, 52.42, 60.41, 125.44, 127.49, 128.41, 129.40, 139.21, 141.61, 166.81

LCMS (*m/z*) : 220 $(M+H)^+$

N-(2-Hydroxyethyl)-N-(2-methoxyphenyl)acrylamide (84c)



Reaction time : 2 h

Yield : 90 %

Mp : 44-46 ºC

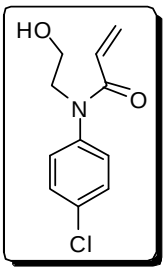
IR (KBr) : *v* 3419, 1649, 1610 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.49 (t, *J* = 5.6 Hz, 1H), 3.70-3.97 (m, 7H), 5.51 (dd, *J* = 10.4 and 2.0 Hz, 1H), 5.94 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.37 (dd, *J* = 16.8 and 2.0 Hz, 1H), 6.97-7.05 (m, 2H), 7.17 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.33-7.40 (m, 1H)

^{13}C NMR (100 MHz) : δ 51.60, 55.31, 60.33, 111.71, 120.85, 127.31, 127.90, 129.46, 129.64, 130.07, 154.70, 167.14

LCMS (*m/z*) : 220 $(M-H)^+$

N-(4-Chlorophenyl)-N-(2-hydroxyethyl)acrylamide (84d)



Reaction time : 2 h

Yield : 89 %

Mp : 44-46 ºC

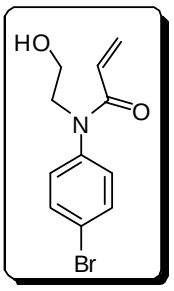
IR (KBr) : *v* 3414, 1614 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.02 (t, *J* = 4.8 Hz, 1H), 3.78-3.86 (m, 2H), 3.96 (t, *J* = 4.8 Hz, 2H), 5.60 (dd, *J* = 10.4 and 2.0 Hz, 1H), 6.00 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.40 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.15-7.21 (m, 2H), 7.38-7.44 (m, 2H)

^{13}C NMR (100 MHz) : δ 52.76, 60.74, 128.19, 128.69, 129.47, 129.89, 133.90, 140.58, 167.13

LCMS (*m/z*) : 226 $(M+H)^+$, 228 $(M+2+H)^+$

N-(4-Bromophenyl)-N-(2-hydroxyethyl)acrylamide (84e)



Reaction time : 2 h

Yield : 89 %

Mp : 76-78 ºC

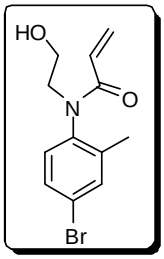
IR (KBr) : *v* 3391, 1643, 1605 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.07 (t, *J* = 4.8 Hz, 1H), 3.73-3.83 (m, 2H), 3.95 (t, *J* = 5.2 Hz, 2H), 5.59 (dd, *J* = 10.4 and 1.6 Hz, 1H), 6.01 (dd, *J* = 16.8 and 10.4, 1H), 6.40 (dd, *J* = 16.8 and 2.0 Hz, 1H), 7.09-7.16 (m, 2H), 7.53-7.60 (m, 2H)

^{13}C NMR (100 MHz) : δ 52.54, 59.94, 121.59, 128.12, 128.36, 129.71, 132.63, 140.92, 166.51

LCMS (*m/z*) : 270 $(M+H)^+$, 272 $(M+2+H)^+$

N-(4-Bromo-2-methylphenyl)-N-(2-hydroxyethyl)acrylamide (84f)



Reaction time : 2 h

Yield : 91 %

IR (neat) : *v* 3391, 1643, 1605 cm^{-1}

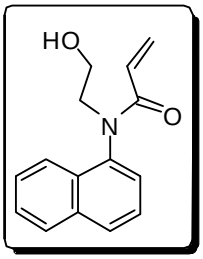
^{1}H NMR (400 MHz) : δ 2.21 (s, 3H), 3.31 (t, *J* = 5.2 Hz, 1H), 3.47-3.56 (m, 1H), 3.76-3.88 (m, 2H), 4.14-4.24 (m, 1H), 5.58 (dd, *J* = 10.4 and 1.6 Hz, 1H), 5.88 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.42 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.07 (d, *J* = 8.0

Hz, 1H), 7.39 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H)

^{13}C NMR (100 MHz) : δ 17.35, 51.34, 60.13, 122.06, 127.40, 128.80, 130.24, 130.59, 134.05, 138.09, 139.53, 166.73

LCMS (*m/z*) : 284 $(M+H)^+$, 286 $(M+2+H)^+$

N-(2-Hydroxyethyl)-N-(naphth-1-yl)acrylamide (84g)



Reaction time : 2 h

Yield : 85 %

Mp : 42-44 ºC

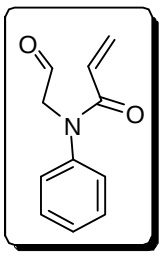
IR (KBr) : *v* 3408, 1651, 1612 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.60 (t, *J* = 5.2 Hz, 1H), 3.69 (td, *J* = 14.4 and 4.4 Hz, 1H), 3.83-3.90 (m, 2H), 4.42 (td, *J* = 14.4 and 5.6 Hz, 1H), 5.46 (dd, *J* = 10.4 and 1.6 Hz, 1H), 5.79 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.41 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.47-7.55 (m, 1H), 7.55-7.63 (m, 2H), 7.81-7.87 (m, 1H), 7.88-7.97 (m, 2H)

^{13}C NMR (100 MHz) : δ 52.16, 60.88, 122.34, 125.52, 126.67, 127.42, 127.88, 128.32, 128.38, 128.86, 130.16, 134.43, 137.74, 167.77

LCMS (*m/z*) : 242 $(M+H)^+$

N-(2-Oxoethyl)-N-phenylacrylamide (73a)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 86 %

IR (neat) : ν 1730, 1653, 1610 cm^{-1}

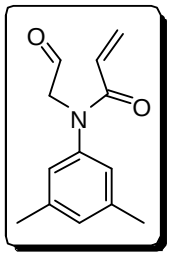
^1H NMR (400 MHz) : δ 4.52 (s, 2H), 5.62 (dd, J = 10.4 and 2.0 Hz, 1H), 6.13 (dd, J = 16.8 and 10.4 Hz, 1H), 6.43 (dd, J = 16.8 and 2.0 Hz, 1H), 7.23-7.29 (m, 2H)*, 7.34-7.47 (m, 3H), 9.69 (s, 1H)

* It merges with $CHCl_3$ peak

^{13}C NMR (100 MHz) : δ 59.46, 127.28, 127.62, 128.02, 128.49, 129.57, 141.67, 165.62, 196.40

LCMS (*m/z*) : 190 $(M + H)^+$

N-(3,5-Dimethylphenyl)-N-(2-oxoethyl)acrylamide (73b)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 93 %

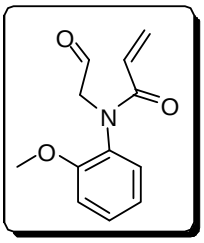
IR (neat) : ν 1734, 1657, 1610, 1595 cm^{-1}

^1H NMR (400 MHz) : δ 2.33 (s, 6H), 4.45 (s, 2H), 5.60 (dd, J = 10.4 and 2.0 Hz, 1H), 6.16 (dd, J = 16.8 and 10.0 Hz, 1H), 6.41 (dd, J = 16.8 and 2.0 Hz, 1H), 6.85 (s, 2H), 6.99 (s, 1H), 9.68 (s, 1H)

^{13}C NMR (100 MHz) : δ 20.77, 59.38, 125.06, 127.35, 128.02, 129.53, 139.29, 141.47, 165.49, 196.53

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

N-(2-Methoxyphenyl)-N-(2-oxoethyl)acrylamide (73c)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 92 %

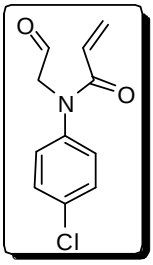
IR (neat) : ν 1730, 1658, 1618 cm^{-1}

^1H NMR (400 MHz) : δ 3.82 (s, 3H), 4.29 (d, J = 1.2 Hz, 2H), 5.58 (dd, J = 10.4 and 2.0 Hz, 1H), 6.10 (dd, J = 16.8 and 10.4 Hz, 1H), 6.42 (dd, J = 16.8 and 2.0 Hz, 1H), 6.96-7.02 (m, 2H), 7.24 (dd, J = 8.0 and 1.6 Hz, 1H), 7.33-7.40 (m, 1H), 9.70 (t, J = 1.2 Hz, 1H)

^{13}C NMR (100 MHz) : δ 55.25, 58.12, 111.76, 120.68, 127.08, 128.04, 129.55, 129.67, 129.74, 154.33, 166.19, 198.42

LCMS (*m/z*) : 220 $(M+H)^+$

N-(4-Chlorophenyl)-N-(2-oxoethyl)acrylamide (73d)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 92 %

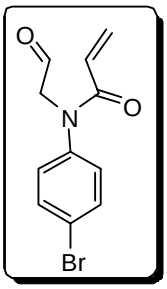
IR (neat) : ν 1732, 1657, 1620 cm^{-1}

^1H NMR (400 MHz) : δ 4.52 (s, 2H), 5.64 (dd, J = 10.4 and 1.6 Hz, 1H), 6.11 (dd, J = 16.8 and 10.4 Hz, 1H), 6.43 (dd, J = 16.8 and 1.6 Hz, 1H), 7.19-7.25 (m, 2H), 7.37-7.43 (m, 2H), 9.68 (s, 1H)

^{13}C NMR (100 MHz) : δ 59.42, 127.06, 129.10, 129.18, 129.78, 133.87, 140.31, 165.52, 196.00

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

N-(4-Bromophenyl)-N-(2-oxoethyl)acrylamide (73e)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 84 %

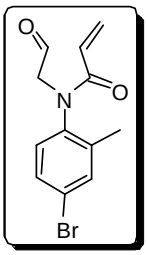
IR (neat) : *v* 1732, 1653, 1618 cm^{-1}

^{1}H NMR (400 MHz) : δ 4.52 (s, 2H), 5.64 (dd, *J* = 10.4 Hz, 2.0 Hz, 1H), 6.11 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.43 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.13-7.19 (m, 2H), 7.53-7.58 (m, 2H), 9.67 (s, 1H)

^{13}C NMR (100 MHz) : δ 59.49, 122.07, 127.13, 129.34, 129.60, 132.94, 140.94, 165.63, 195.98

LCMS (*m/z*) : 268 $(M+H)^+$, 270 $(M+2+H)^+$

N-(4-Bromo-2-methylphenyl)-N-(2-oxoethyl)acrylamide (73f)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 93 %

IR (neat) : *v* 1732, 1658, 1618 cm^{-1}

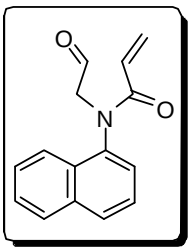
^{1}H NMR (400 MHz) : δ 2.22 (s, 3H), 3.93 and 4.79 (ABq, *J* = 18.0 Hz, 2H), 5.62 (dd, *J* = 10.4 and 1.6 Hz, 1H), 5.96 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.44 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.17 (d,

J = 8.4 Hz, 1H), 7.39 (dd, J = 8.4 and 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 9.69 (s, 1H)

^{13}C NMR (100 MHz) : δ 17.34, 58.32, 122.19, 126.41, 129.21, 130.28, 130.46, 133.96, 137.89, 139.38, 165.42, 195.73

LCMS (*m/z*) : 282 $(M+H)^+$, 284 $(M+2+H)^+$

N-(Naphth-1-yl)-N-(2-oxoethyl)acrylamide (73g)



Reaction time : [15 min + 15 min + 0.5 h] (-78 ºC) + 0.5 h (r.t.)

Yield : 91 %

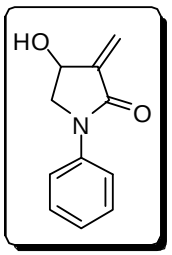
IR (neat) : v 1730, 1658, 1618 cm^{-1}

^{1}H NMR (400 MHz) : δ 4.11 and 4.98 (ABq, J = 17.6 Hz, 2H), 5.51 (dd, J = 10.4 and 1.6 Hz, 1H), 5.90 (dd, J = 16.8 and 10.4 Hz, 1H), 6.44 (dd, J = 16.8 and 1.6 Hz, 1H), 7.48-7.64 (m, 4H), 7.84-7.98 (m, 3H), 9.78 (s, 1H)

^{13}C NMR (100 MHz) : δ 59.01, 122.00, 125.54, 126.68, 126.72, 126.98, 127.48, 128.41, 128.73, 129.04, 129.91, 134.34, 137.53, 166.33, 196.14

LCMS (*m/z*) : 240 $(M+H)^+$

4-Hydroxy-3-methylene-1-phenylpyrrolidin-2-one (75a)



Reaction time : 0.5 h

Yield : 73 %

Mp : 118-120 ºC

IR (KBr) : v 3298, 1676, 1649, 1610 cm^{-1}

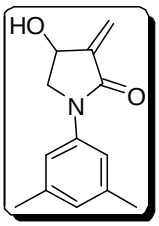
^{1}H NMR (400 MHz) : δ 2.53 (d, J = 5.6 Hz, 1H), 3.73 (dd, J = 10.4 and 3.2 Hz, 1H), 4.09 (dd, J = 10.4 and 7.2 Hz, 1H), 4.94 (bs, 1H), 5.78 (d, J = 1.6 Hz, 1H), 6.29 (d, J = 2.0 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.33-7.42 (m, 2H), 7.67 (d, J = 7.6 Hz, 2H)

^{13}C NMR (100 MHz) : δ 54.91, 64.93, 120.00, 121.00, 125.22, 128.95, 138.80, 144.07, 165.72

HRMS (ESI) exact mass calc′d for $C_{11}H_{11}NO_2H$ $(M+H)^+$: 190.0868

Found : 190.0865

1-(3, 5-Dimethylphenyl)-4-hydroxy-3-methylenepyrrolidin-2-one (75b)



Reaction time : 1.5 h

Yield : 67 %

Mp : 130-132 ºC

IR (KBr) : ν 3303, 1676, 1648, 1604 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.25-2.50 (m, 7H)*, 3.70 (dd, J = 10.4 and 3.2 Hz, 1H), 4.05 (dd, J = 10.4 and 7.2 Hz, 1H), 4.89-4.94 (m, 1H), 5.77 (d, J = 1.6 Hz, 1H), 6.28 (d, J = 2.0 Hz, 1H), 6.83 (s, 1H), 7.28 (s, 2H)

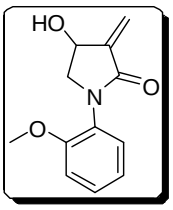
* It contains a single at 2.32 for 6H and broad peak for 1H

^{13}C NMR (100 MHz) : δ 21.43, 55.12, 64.92, 117.97, 120.47, 126.99, 138.49, 138.69, 144.27, 165.67

HRMS (ESI) exact mass calc′d for $C_{13}H_{15}NO_2H$ $(M+H)^+$: 218.1181

Found : 218.1173

4-Hydroxy-1-(2-methoxyphenyl)-3-methylenepyrrolidin-2-one (75c)



Reaction time : 2.5 h

Yield : 70 %

Mp : 119-121 ºC

IR (KBr) : ν 3347, 1676, 1654, 1610 cm^{-1}

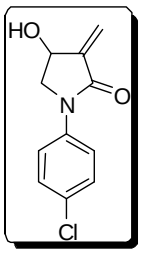
^{1}H NMR (400 MHz) : δ 2.37 (bs, 1H), 3.66 (dd, J = 10.4 and 3.2 Hz, 1H), 3.83 (s, 3H), 4.02 (dd, J = 10.4 and 6.8 Hz, 1H), 4.94 (bs, 1H), 5.78 (d, J = 1.2 Hz, 1H), 6.28 (d, J = 1.6 Hz 1H), 6.95-7.03 (m, 2H), 7.27-7.33 (m, 2H)

^{13}C NMR (100 MHz) : δ 55.45, 56.02, 65.66, 111.96, 119.75, 120.65, 126.33, 128.11, 128.90, 143.55, 154.60, 166.52

HRMS (ESI) exact mass calc′d for $C_{12}H_{13}NO_3H$ $(M+H)^+$: 220.0974

Found : 220.0975

1-(4-Chlorophenyl)-4-hydroxy-3-methylenepyrrolidin-2-one (75d)



Reaction time : 10 min

Yield : 71 %

Mp : 116-118 ºC

IR (KBr) : ν 3276, 1670, 1643, 1610 cm^{-1}

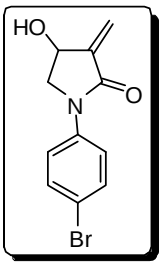
^{1}H NMR (400 MHz) : δ 2.45 (bs, 1H), 3.70 (dd, J = 10.4 and 3.2 Hz, 1H), 4.06 (dd, J = 10.4 and 7.2 Hz, 1H), 4.95 (bs, 1H), 5.81 (d, J = 1.2 Hz, 1H), 6.31 (d, J = 1.6 Hz, 1H), 7.34 (d, J = 9.2 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ 53.80, 63.51, 119.32, 120.09, 127.96, 128.63, 137.17, 143.81, 164.88

HRMS (ESI) exact mass calc′d for $C_{11}H_{10}ClNO_2H$ $(M+H)^+$: 224.0478

Found : 224.0473

1-(4-Bromophenyl)-4-hydroxy-3-methylenepyrrolidin-2-one (75e)



Reaction time : 10 min

Yield : 69 %

Mp : 114-116 ºC

IR (KBr) : ν 3358, 1687, 1648 cm^{-1}

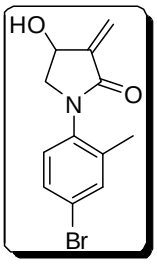
^{1}H NMR (400 MHz) : δ 2.39 (bs, 1H), 3.70 (dd, J = 10.4 and 3.2 Hz, 1H), 4.06 (dd, J = 10.4 and 7.2 Hz, 1H), 4.95 (bs, 1H), 5.81 (d, J = 1.6 Hz, 1H), 6.32 (d, J = 2.0 Hz, 1H), 7.47-7.52 (m, 2H), 7.56-7.62 (m, 2H)

^{13}C NMR (100 MHz) : δ 53.74, 63.51, 116.47, 119.39, 120.39, 130.92, 137.67, 143.83, 164.90

HRMS (ESI) exact mass calc′d for $C_{11}H_{10}BrNO_2H$ $(M+H)^+$: 267.9973

Found : 267.9970

1-(4-Bromo-2-methylphenyl)-4-hydroxy-3-methylenepyrrolidin-2-one (75f)



Reaction time : 1 h

Yield : 72 %

Mp : 94-98 ºC

IR (KBr) : ν 3353, 1681, 1659 cm^{-1}

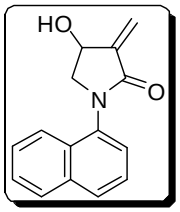
^{1}H NMR (400 MHz) : δ 2.20 (s, 3H), 2.53 (bs, 1H), 3.56 (dd, J = 10.4 and 3.2 Hz, 1H), 3.91 (dd, J = 10.4 and 6.8 Hz, 1H), 4.92-4.98 (m, 1H), 5.79 (d, J = 1.2 Hz, 1H), 6.29 (d, J = 1.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.36 (dd, J = 8.4 and 1.6 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H)

^{13}C NMR (100 MHz) : δ 17.85, 56.93, 65.79, 120.94, 121.79, 127.94, 129.99, 134.05, 135.86, 137.93, 143.06, 165.98

HRMS (ESI) exact mass calc′d for $C_{12}H_{12}BrNO_2H$ $(M+H)^+$: 282.0130

Found : 282.0134

4-Hydroxy-3-methylene-1-(naphth-1-yl)pyrrolidin-2-one (75g)



Reaction time : 1.5 h

Yield : 70 %

Mp : 102-104 ºC

IR (KBr) : ν 3364, 1687, 1659 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.87 (bs, 1H), 3.71 (dd, J = 10.8 and 2.8 Hz, 1H), 3.99 (dd, J = 10.8 and 6.8 Hz, 1H), 4.96-5.02 (m, 1H), 5.81 (d, J = 1.2 Hz, 1H), 6.33 (d, J = 1.6 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.45-7.55 (m, 3H), 7.70-7.76 (m, 1H), 7.83-7.91 (m, 2H)

^{13}C NMR (100 MHz) : δ 57.92, 65.80, 120.87, 122.70, 124.50, 125.54, 126.50, 126.90, 128.51, 128.69, 129.29, 134.41, 134.66, 143.23, 167.02

HRMS (ESI) exact mass calc′d for $C_{15}H_{13}NO_2H$ $(M+H)^+$: 240.1025

Found : 240.1025

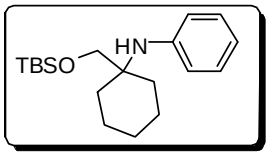
Intramolecular Baylis-Hillman reaction of 73a using quinine as a promoter:

A solution of N-(2-oxoethyl)-N-phenylacrylamide (**73a**) (0.189 g, 1.0 mmol), quinine (0.324 g, 1.0 mmol) in *t*BuOH (6.0 mL) was heated under reflux for 30 h with stirring [till the disappearance of the aldehyde (**73a**)**,** as monitored by TLC]. Solvent removal followed by purification of the crude product using column chromatography provided 0.123 g (65%) of 4-hydroxy-3-methylene-1 phenylpyrrolidin-2-one (**75a**) as a white solid in 10% *ee*. HPLC analysis of racemic **75a** using the chiral column, Chiralcel-OJ-H [hexanes:*i*PrOH (90:10), 0.5 mL/min, 254 nm] showed two peaks of equal intensity (retention times: 47.967 min and 52.708 min). Similar HPLC analysis of **75a,** obtained using quinine, as a promoter showed two peaks in the ratio of 55.2:44.8 [retention times: 48.950 min and 54.375 min] indicating that enantiomeric purity of this compound is 10 %.

Intramolecular Baylis-Hillman reaction of 73a using quinidine as a promoter:

Similar intramolecular Baylis-Hillman reaction of N-(2-oxoethyl)-N-phenylacrylamide (**73a**) using quinidine as promter provided the required 4-hydroxy-3-methylene-1 phenylpyrrolidin-2-one (**75a**) as a white solid in 63% yield in 5% ee. HPLC analysis of **75a** (obtained using quinidine as a promoter) using the chiral column, Chiralcel-OJ-H [hexanes:*i*PrOH (90:10), 0.5 mL/min, 254 nm] showed two peaks in the ratio of 47.4: 52.6 [retention times: 49.917 min and 55.950 min] indicating that enantiomeric purity of this compound is 5 %.

N-[1-(*tert*-Butyldimethylsilyloxy)methyl]cyclohexylaniline (91a)



Reaction time : 6 h

Yield : 91 %

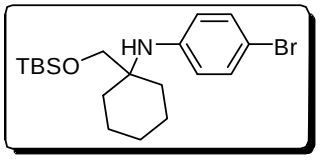
IR (neat) : ν 2925, 2854, 1605 cm^{-1}

^{1}H NMR (400 MHz) : δ -0.02 (s, 6H), 0.89 (s, 9H), 1.30-1.72 (m, 9H), 1.75-1.85 (m, 2H), 3.48 (s, 2H), 6.76-6.84 (m, 3H), 7.10-7.18 (m, 2H)

^{13}C NMR (100 MHz) : δ -5.51, 18.32, 21.81, 25.98, 26.15, 33.00, 57.60, 66.95, 119.33, 119.64, 128.71, 146.67

LCMS (*m/z*) : 320 $(M+H)^{+}$

4-Bromo-N-[1-(*tert*-butyldimethylsilyloxy)methyl]cyclohexylaniline (91b)



Reaction time : 6 h

Yield : 88 %

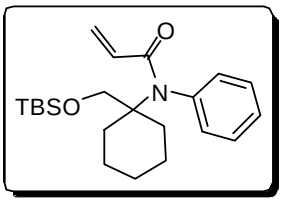
IR (neat) : ν 3419, 2931, 2854, 1594 cm^{-1}

^{1}H NMR (400 MHz) : δ -0.03 (s, 6H), 0.89 (s, 9H), 1.28-1.70 (m, 8H), 1.72-1.83 (m, 2H), 3.46 (s, 2H), 3.57 (bs, 1H), 6.68 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ -5.48, 18.31, 21.71, 25.96, 26.06, 32.91, 57.73, 66.89, 111.29, 120.95, 131.51, 145.81

LCMS (*m/z*) : 398 $(M+H)^{+}$, 400 $(M+2+H)^{+}$

N-[1-(*tert*-Butyldimethylsilyloxy)methyl]cyclohexyl-N-phenylacrylamide (92a)



Reaction time : 2 h

Yield : 86 %

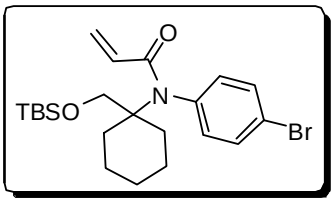
IR (neat) : ν 2931, 1654 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.08 (s, 6H), 0.92 (s, 9H), 1.11-1.58 (m, 8H), 2.19-2.28 (m, 2H), 4.30 (s, 2H), 5.26 (dd, J = 10.4 and 2.4 Hz, 1H), 5.67 (dd, J = 16.8 and 10.4 Hz, 1H), 6.14 (dd, J = 16.8 and 2.4 Hz, 1H), 7.24-7.38 (m, 5H)

^{13}C NMR (100 MHz) : δ -5.30, 18.46, 22.67, 25.58, 26.08, 32.70, 61.23, 64.97, 125.30, 127.75, 128.44, 131.51, 131.86, 141.04, 166.11

LCMS (*m/z*) : 374 $(M+H)^+$

N-(4-Bromophenyl)-N-[1-(*tert*-butyldimethylsilyloxy)methyl]cyclohexylacrylamide (92b)



Reaction time : 2 h

Yield : 89 %

IR (neat) : ν 2931, 1665, 1610 cm^{-1}

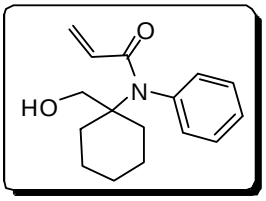
^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.91 (s, 9H), 1.11-1.61 (m, 8H), 2.11-2.24 (m, 2H), 4.27 (s, 2H), 5.30 (dd, J = 10.4 and 2.0 Hz, 1H), 5.68 (dd, J = 16.8 and 10.4 Hz, 1H), 6.16 (dd, J = 16.8 and 2.0 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H)

^{13}C NMR (100 MHz) : δ -5.34, 18.40, 22.60, 25.50, 26.03, 32.78, 61.24, 65.04, 121.71, 125.85, 131.51, 131.62, 133.13, 140.14, 165.79

LCMS (*m/z*) : 452 $(M+H)^+$, 454 $(M+2+H)^+$

N-[1-(Hydroxymethyl)cyclohexyl]-N-phenylacrylamide (93a)

To a stirring solution of (**92a**) (2.6 g, 7 mmol) [THF : Water (2 : 1), 21 mL] was added 2N HCl (7 mL) at room temperature. After stirring solution for 4 h, the reaction mixture was neutralized by saturated $NaHCO_3$ solution, and then diluted with 30 mL of water and extracted with ethyl acetate (2 x 50 mL). Organic layer were combined and dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by column chromatography [silica gel, 30 % ethyl acetate in hexanes] to give the title compound **93a** in 83 % (1.50 g) yield as a colorless viscous liquid.



Reaction time : 4 h

Yield : 83 %

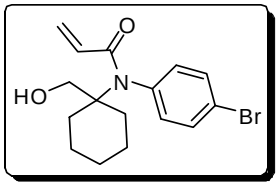
IR (neat) : *v* 3419, 2931, 1654, 1621 cm^{-1}

^1H NMR (400 MHz) : δ 0.99-1.12 (m, 1H), 1.20 (dt, *J* = 12.8 and 4.0 Hz, 2H), 1.40-1.68 (m, 5H), 2.07 (d, *J* = 12.0 Hz, 2H), 4.04 (d, *J* = 6.4 Hz, 2H), 5.33-5.44 (m, 2H), 5.69 (dd, *J* = 16.4 and 10.4 Hz, 1H), 6.25 (dd, *J* = 16.4 and 2.0 Hz, 1H), 7.09-7.17 (m, 2H), 7.37-7.45 (m, 3H)

^{13}C NMR (100 MHz) : δ 22.77, 25.03, 32.61, 65.89, 66.05, 126.68, 128.31, 129.00, 130.44, 130.90, 139.92, 167.60

LCMS (*m/z*) : 260 $(M+H)^+$

N-(4-Bromophenyl)-N-[1-(hydroxymethyl)cyclohexyl]acrylamide (93b)



Reaction time : 4 h

Yield : 85 %

IR (neat) : ν 3391, 2936, 1660, 1610 cm^{-1}

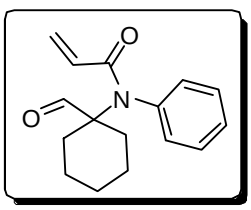
^1H NMR (400 MHz) : δ 0.99-1.12 (m, 1H), 1.18 (dt, J = 12.8 and 3.2 Hz, 2H), 1.39-1.67 (m, 5H), 2.06 (d, J = 12.8 Hz, 2H), 4.04 (d, J = 6.4 Hz, 2H), 4.98 (t, J = 6.4 Hz, 1H), 5.42 (dd, J = 10.0 and 1.6 Hz, 1H), 5.70 (dd, J = 16.4 and 10.0 Hz, 1H), 6.26 (dd, J = 16.4 and 1.6 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H)

^{13}C NMR (100 MHz) : δ 22.79, 25.10, 32.81, 65.51, 66.21, 122.40, 127.31, 130.74, 132.24, 132.28, 139.15, 167.39

LCMS (*m/z*) : 338 $(M+H)^+$, 340 $(M+2+H)^+$

Representative procedure: Synthesis of N-(1-formylcyclohexyl)-N-phenyl acrylamide (94a)*

To a stirring solution of N-[1-(hydroxymethyl)cyclohexyl]-N-phenylacrylamide **93a** (0.518 g, 2 mmol) in DCM (20 mL), Dess-Martin periodinane (1.69 g, 4 mmol) was added at room temperature. After stirring for 1h at same temperature, the reaction mixture was filtered through celite. The filterate was diluted with water and extracted with DCM (20 mL x 2), The combined organic layer was washed with saturated $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude thus obtained was purified by column chromatography (silica gel, 30 % ethyl acetate in hexanes) to provide the title compound **94a** in 75 % (0.388 g) yield as a light brown viscous liquid.



Reaction time : 1 h

Yield : 75 %

IR (neat) : ν 2931, 1726, 1643 cm^{-1}

^1H NMR (400 MHz) : δ 0.98-1.11(m, 1H), 1.20-1.35 (m, 12H), 1.50-1.71 (m, 5H), 2.45 (d, J = 12.8 Hz, 2H), 5.47 (dd, J = 10.4 and 1.6 Hz, 1H), 5.72(dd, J = 16.8 and 10.4 Hz, 1H), 6.31(dd, J = 16.8 and 10.4 Hz, 1H), 7.18-7.25 (m, 2H), 7.42-7.50 (m, 3H), 9.83 (s, 1H)

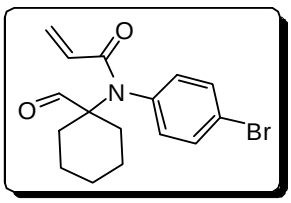
^{13}C NMR (100 MHz) : δ 22.63, 24.88, 31.51, 66.03, 128.38, 128.66, 129.00, 129.51, 130.69, 137.89, 165.45, 198.44

LCMS (*m/z*) : 258 $(M+H)^+$

***** It is worth mentioning that the aldehydes (**94a**, **94b**, **100a** and **100b**) were freshly prepared from alcohols (**93a**, **93b**, **99a** and **99b**) and used immediately for BH reaction in the presence of 3-5 mol% of hydroquinone. (Hydroquinone was added before concentration of the fraction containing pure aldehyde obtained through column chromatography).

N-(4-Bromophenyl)-N-(1-formylcyclohexyl)acrylamide (94b)

Reaction time : 1 h



Yield : 69 %

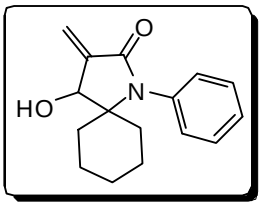
IR (neat) : ν 1726, 1649, 1616 cm^{-1}

^1H NMR (400 MHz) : δ 0.98-1.13 (m, 1H), 1.24 (dt, J = 12.8 and 4.0 Hz, 2H), 1.46-1.80 (m, 5H), 2.24 (d, J = 12.4 Hz, 2H), 5.51 (dd, J = 10.4 and 1.6 Hz, 1H), 5.72 (dd, J = 16.8 and 10.4 Hz, 1H), 6.32 (dd, J = 16.8 and 1.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 9.83 (s, 1H)

^{13}C NMR (100 MHz) : δ 22.65, 24.85, 31.69, 66.00, 116.14, 123.21, 128.10, 129.26, 132.32, 132.79, 137.00, 165.30, 198.46

LCMS (*m/z*) : 336 $(M+H)^+$, 338 $(M+2+H)^+$

4-Hydroxy-3-methylene-1-phenyl-1-azaspiro[4.5]decan-2-one (95a)



Reaction time : 10 h

Yield : 75 %

Mp : 152-154 ºC

IR (KBr) : *v* 3254, 1682, 1665, 1610 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.88-1.01 (m, 1H), 1.16 (dt, *J* = 12.8 and 4.0 Hz, 1H), 1.42-1.76 (m, 7H)*, 2.14 (d, *J* = 12.8 Hz, 1H), 2.56 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 5.80 (s, 1H), 6.29 (s, 1H), 7.07-7.13 (m, 2H), 7.36-7.46 (m, 3H)

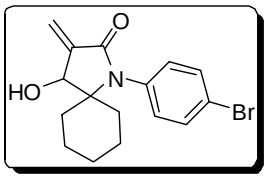
* It also contains moisture peak

^{13}C NMR (100 MHz) : δ 22.73, 23.53, 24.46, 30.21, 34.31, 67.37, 70.96, 121.83, 128.04, 128.85, 130.04, 135.44, 142.85, 167.27

HRMS (ESI) exact mass calc′d for $C_{16}H_{19}NO_2H$ $(M+H)^+$: 258.1494

Found : 258.1502

1-(4-Bromophenyl)-4-hydroxy-3-methylene-1-azaspiro[4.5]decan-2-one (95b)



Reaction time : 2.5 h

Yield : 72 %

Mp : 198-200 ºC

IR (KBr) : *v* 3276, 1682, 1665, 1615 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.88-1.02 (m, 1H), 1.12 (dt, J = 12.8 and 3.6 Hz, 1H), 1.40-1.78 (m, 7H)*, 2.13 (d, J = 12.8 Hz, 1H), 2.60 (bs, 1H), 4.63 (s, 1H), 5.80 (s, 1H), 6.28 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H)

* It contains moisture peak

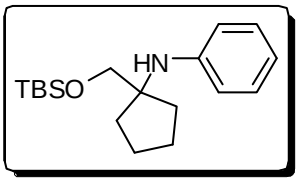
^{13}C NMR (100 MHz) : δ 22.36, 23.12, 24.11, 29.87, 34.28, 66.79, 70.48, 120.80, 121.62, 131.44, 131.70, 134.56, 143.14, 166.63

HRMS (ESI) exact mass calc′d for $C_{16}H_{18}BrNO_2H$ $(M+H)^+$: 336.0599

Found : 336.0602

N-[1-(tert-Butyldimethylsilyloxy)methyl]cyclopentylaniline (97a)

Reaction time : 6 h



Yield : 89 %

IR (neat) : ν 3402, 2947, 1600 cm^{-1}

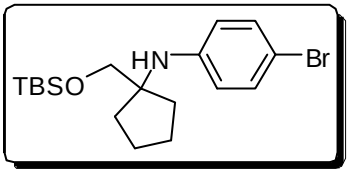
^{1}H NMR (400 MHz) : δ -0.07 (s, 6H), 0.86 (s, 9H), 1.51-1.91 (m, 8H), 3.56 (s, 2H), 4.00 (bs, 1H), 6.65 (d, J = 8.0 Hz, 2H), 6.66-6.73 (m, 1H), 7.08-7.16 (m, 2H)

^{13}C NMR (100 MHz) : δ -5.61, 18.23, 25.11, 25.89, 35.25, 65.57, 65.83, 116.00, 117.59, 128.90, 146.76

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

4-Bromo-N-[1-(*tert*-butyldimethylsilyloxy)methyl]cyclopentylaniline (97b)

Reaction time : 6 h



Yield : 80 %

IR (neat) : ν 3402, 2953, 1594 cm^{-1}

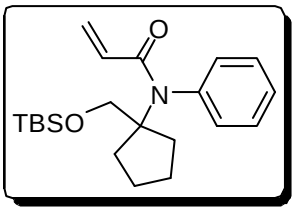
^{1}H NMR (400 MHz) : δ -0.06 (s, 6H), 0.86 (s, 9H), 1.58-1.65 (m, 2H), 1.72-1.85 (m, 6H), 3.54 (s, 2H), 4.01 (s, 1H), 6.52 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ -5.55, 18.22, 25.05, 25.88, 35.19, 65.43, 65.89, 109.25, 117.39, 131.61, 145.85

LCMS (*m/z*) : 384 $(M+H)^+$, 386 $(M+2+H)^+$

N-[1-(*tert*-Butyldimethylsilyloxy)methyl]cyclopentyl-N-phenylacrylamide (98a)

Reaction time : 2 h



Yield : 82 %

IR (neat) : v 2953, 1660, 1610 cm^{-1}

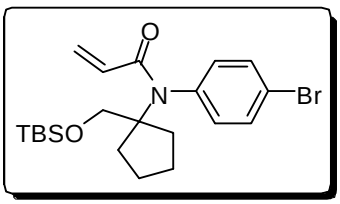
^{1}H NMR (400 MHz) : δ 0.07 (s, 6H), 0.92 (s, 9H), 1.44-1.69 (m, 6H), 1.94-2.04 (m, 2H), 3.98 (s, 2H), 5.32 (dd, J = 10.4 and 2.0 Hz, 1H), 5.75 (dd, J = 16.8 and 10.4 Hz, 1H), 6.21 (dd, J = 16.8 and 2.0 Hz, 1H), 7.24-7.40 (m, 5H)

^{13}C NMR (100 MHz) : δ -5.37, 18.41, 23.63, 26.03, 35.37, 63.86, 72.58, 125.71, 127.72, 128.70, 130.78, 131.09, 141.62, 165.73

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

N-(4-Bromophenyl)-N-[1-(*tert*-butyldimethylsilyloxy)methyl]cyclopentylacryl amide (98b)

Reaction time : 2 h



Yield : 92 %

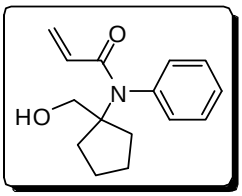
IR (neat) : v 2958, 1665, 1621 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.06 (s, 6H), 0.91 (s, 9H), 1.45-1.67 (m, 6H), 1.93-2.02 (m, 2H), 3.95 (s, 2H), 5.36 (dd, J = 10.4 and 2.0 Hz, 1H), 5.76 (dd, J = 16.4 and 10.4 Hz, 1H), 6.22 (dd, J = 16.4 and 2.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H)

^{13}C NMR (100 MHz) : δ -5.36, 18.42, 23.52, 26.04, 35.45, 63.80, 72.65, 121.67, 126.32, 130.79, 131.91, 132.51, 140.78, 165.50

LCMS (*m/z*) : 438 $(M+H)^+$, 440 $(M+2+H)^+$

N-[1-(Hydroxymethyl)cyclopentyl]-N-phenylacrylamide (99a)



Reaction time : 4 h

Yield : 88 %

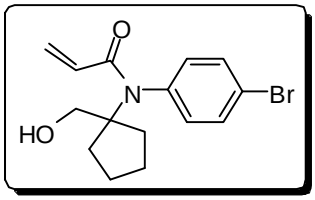
IR (neat) : v 3402, 2871, 1649, 1616 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.55-1.72 (m, 6H), 1.95-2.03 (m, 2H), 3.86 (d, J = 5.6 Hz, 2H), 4.54 (t, J = 5.6 Hz, 1H), 5.42 (dd, J = 10.4 and 2.0 Hz, 1H), 5.79 (dd, J = 16.8 and 10.4 Hz, 1H), 6.28 (dd, J = 16.8 and 2.0 Hz, 1H), 7.16-7.22 (m, 2H), 7.37-7.45 (m, 3H)

^{13}C NMR (100 MHz) : δ 23.11, 34.92, 67.09, 73.11, 126.84, 128.19, 129.13, 130.06, 130.41, 140.87, 167.72

LCMS (*m/z*) : 246 $(M+H)^+$

N-(4-Bromophenyl)-N-[1-(hydroxymethyl)cyclopentyl]acrylamide (99b)



Reaction time : 4 h

Yield : 82 %

Mp : 118-120 ºC

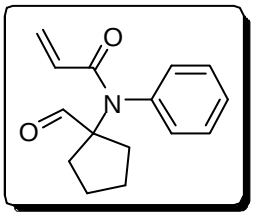
IR (KBr) : *v* 3435, 1643, 1616 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.55-1.70 (m, 6H), 1.94-2.06 (m, 2H), 3.86 (d, *J* = 5.2 Hz, 2H), 4.00-4.07 (m 1H), 5.45 (dd, *J* = 10.4 and 2.0 Hz, 1H), 5.78 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.28 (dd, *J* = 16.8 and 2.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H)

^{13}C NMR (100 MHz) : δ 23.18, 35.16, 67.02, 73.22, 122.32, 127.57, 130.25, 131.93, 132.49, 140.11, 167.60

LCMS (*m/z*) : 324 $(M+H)^{+}$, 326 $(M+2+H)^{+}$

N-(1-Formylcyclopentyl)-N-phenylacrylamide (100a)



Reaction time : 1 h

Yield : 72 %

Mp : 98-100 ºC

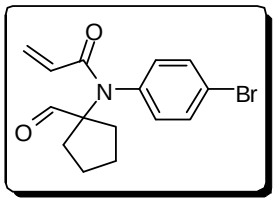
IR (KBr) : *v* 2964, 1731, 1649, 1605 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.50-1.70 (m, 6H), 2.15-2.27 (m, 2H), 5.51 (dd, *J* = 10.4 and 2.0 Hz, 1H), 5.84 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.35 (dd, *J* = 16.8 and 2.0 Hz, 1H), 7.20-7.25 (m, 2H), 7.44-7.51 (m, 3H), 9.58 (s, 1H)

^{13}C NMR (100 MHz) : δ 24.22, 33.25, 75.77, 128.34, 128.60, 128.98, 129.76, 130.25, 138.74, 166.30, 197.93

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

N-(4-Bromophenyl)-N-(1-formylcyclopentyl)acrylamide (100b)



Reaction time : 1 h

Yield : 75 %

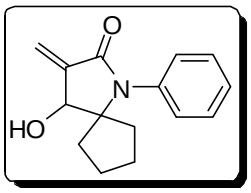
IR (neat) : *v* 2958, 1726, 1649, 1610 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.51-1.72 (m, 6H), 2.13-2.27 (m, 2H), 5.54 (dd, *J* = 10.4 and 1.6 Hz, 1H), 5.83 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.35 (dd, *J* = 16.8 and 1.6 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 9.56 (s, 1H)

^{13}C NMR (100 MHz) : δ 24.07, 33.20, 75.60, 122.90, 128.02, 128.91, 131.86, 132.87, 137.78, 165.90, 197.64

LCMS (*m/z*) : $322(M+H)^{+}$, $324(M+2+H)^{+}$

4-Hydroxy-3-methylene-1-phenyl-1-azaspiro[4.4]nonan-2-one (101a)



Reaction time : 2 h

Yield : 68 %

Mp : 114-116 ºC

IR (KBr) : *v* 3281, 1670, 1648, 1620 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.45-1.70 (m, 6H)*, 1.78-1.89 (m, 1H), 2.09-2.20 (m, 1H), 2.44 (d, *J* = 6.8 Hz, 1H), 4.48 (d, *J* = 6.8 Hz, 1H), 5.73 (d, *J* = 1.6 Hz, 1H), 6.25 (d, *J* = 1.6 Hz, 1H), 7.14-7.19 (m, 2H), 7.34-7.46 (m, 3H)

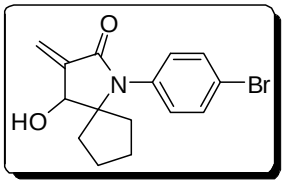
* It also contains moisture peak

^{13}C NMR (100 MHz) : δ 23.11, 23.46, 29.31, 35.40, 74.82, 74.96, 119.59, 128.09, 129.11, 129.50, 135.71, 143.00, 167.04

HRMS (ESI) exact mass calc′d for $C_{15}H_{17}NO_2H$ $(M+H)^+$: 244.1338

Found : 244.1347

1-(4-Bromophenyl)-4-hydroxy-3-methylene-1-azaspiro[4.4]nonan-2-one (101b)



Reaction time : 0.5 h

Yield : 70 %

Mp : 150-152 ºC

IR (KBr) : ν 3347, 1682, 1660, 1620 cm^{-1}

^1H NMR (400 MHz) : δ 1.47-1.70 (m, 6H)*, 1.71-1.84 (m, 1H), 2.11-2.20 (m, 1H), 2.36 (bs, 1H), 4.47 (s, 1H), 5.74 (d, J = 1.2 Hz, 1H), 6.25 (d, J = 1.6 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H)

* It also contains moisture peak

^{13}C NMR (100 MHz) : δ 22.99, 23.35, 29.25, 35.27, 74.57, 75.02, 120.28, 122.09, 131.12, 132.34, 134.71, 142.60, 167.06

HRMS (ESI) exact mass calc′d for $C_{15}H_{16}BrNO_2H$ $(M+H)^+$: 322.0443

Found : 322.0444

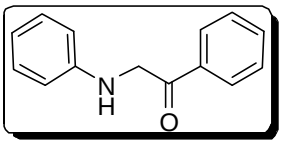
Representative procedure: Synthesis of 1-phenyl-2-(phenylamino)ethanone (107a)

This compound was prepared by using the known procedure[135]

A solution of aniline (2.79 g, 30 mmol) and phenacyl bromide (2.98 g, 15 mmol) in MeCN (30 mL) was stirred at room temperature for 24 h. Solid separated, was filtered and the filterate was concentrated in vacuo. The residue, thus obtained was purified as such by column chromatography [silica gel, 5 % ethyl acetate in hexanes] to furnish 83 % (2.62 g) yield of the title compound (**107a**) as a Yellow solid.

Reaction time : 24 h

Yield : 83 %



Mp : 92-94 ºC (lit.[135] 94-95 ºC)

IR (KBr) : ν 3364, 1687, 1600 cm^{-1}

^{1}H NMR (400 MHz) : δ 4.62 (s, 2H), 4.93 (bs, 1H), 6.69-6.79 (m, 3H), 7.19-7.27 (m, 2H), 7.49-7.56 (m, 2H), 7.60-7.66 (m, 1H), 8.02 (d, J = 7.2 Hz, 2H)

^{13}C NMR (100 MHz) : δ 50.16, 112.95, 117.67, 127.68, 128.78, 129.29, 133.74, 134.82, 147.04, 195.00

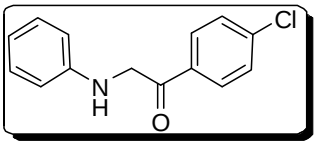
HRMS (ESI) exact mass calc′d for $C_{14}H_{13}NOH$ $(M+H)^+$: 212.1075

Found : 212.1071

1-(4-Chlorophenyl)-2-(phenylamino)ethanone (**107b**)

Reaction time : 24 h

Yield : 57 %



Mp : 86-88 ºC

IR (KBr) : ν 3391, 1676, 1620 cm^{-1}

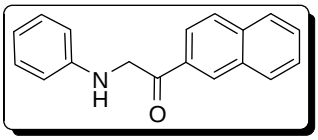
^{1}H NMR (400 MHz) : δ 4.59 (s, 2H), 4.90 (bs, 1H), 6.71 (d, J = 7.6 Hz, 2H), 6.74-6.81 (m, 1H), 7.20-7.26 (m, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 7.6 Hz, 2H)

^{13}C NMR (100 MHz) : δ 50.27, 113.03, 117.93, 129.17, 129.22, 129.40, 133.19, 140.29, 146.94, 193.98

HRMS (ESI) exact mass calc′d for $C_{14}H_{12}ClNOH$ $(M+H)^+$: 246.0686

Found : 246.0683

1-(Naphth-2-yl)-2-(phenylamino)ethanone (107c)



Reaction time : 24 h

Yield : 50 %

Mp : 116-118 ºC

IR (KBr) : ν 3396, 1681, 1626 cm^{-1}

^1H NMR (400 MHz) : δ 4.77 (s, 2H), 6.75-6.82 (m, 3H), 7.22-7.30 (m, 3H)*, 7.56-7.68 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.07 (dd, J = 8.4 and 1.6 Hz, 1H), 8.55 (s, 1H)

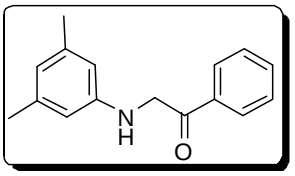
* It contains $CHCl_3$ peak.

^{13}C NMR (100 MHz) : δ 50.47, 113.19, 117.93, 123.38, 127.11, 127.92, 128.85, 129.45, 129.65, 132.22, 132.50, 135.95, 147.11, 194.98

HRMS (ESI) exact mass calc′d for $C_{18}H_{15}NONa$ $(M+Na)^+$: 284.1051

Found : 284.1054

2-(3, 5-Dimethylphenylamino)-1-phenylethanone (107d)



Reaction time : 24 h

Yield : 48 %

Mp : 100-102 ºC

IR (KBr) : ν 3386, 1693, 1605 cm^{-1}

^1H NMR (400 MHz) : δ 2.27 (s, 6H), 4.62 (s, 2H), 4.87 (bs, 1H), 6.36 (s, 2H), 6.42 (s, 1H), 7.49-7.56 (m, 2H), 7.60-7.66 (m, 1H), 8.03 (d, J = 7.6 Hz, 2H)

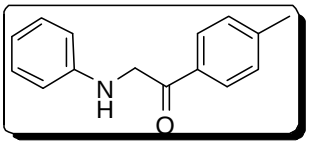
^{13}C NMR (100 MHz) : δ 21.54, 50.45, 111.03, 119.84, 127.80, 128.88, 133.82, 134.99, 139.06, 147.24, 195.20

HRMS (ESI) exact mass calc′d for $C_{16}H_{17}NOH$ $(M+H)^+$: 240.1388

Found : 240.1389

2-(Phenylamino)-1-*p*-tolylethanone (107e)

Reaction time : 24 h



Yield : 72 %

Mp : 106-108 ºC

IR (KBr) : ν 3391, 1682, 1610 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.44 (s, 3H), 4.59 (s, 2H), 4.96 (bs, 1H), 6.69-6.80 (m, 3H), 7.19-7.28 (m, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H)

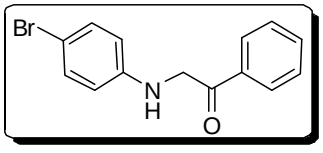
^{13}C NMR (100 MHz) : δ 21.74, 50.09, 112.99, 117.66, 127.84, 129.35, 129.53, 132.40, 144.79, 147.16, 194.62

HRMS (ESI) exact mass calc′d for $C_{15}H_{15}NOH$ $(M+H)^+$: 226.1232

Found : 226.1230

2-(4-Bromophenylamino)-1-phenylethanone (107f)

Reaction time : 24 h



Yield : 30 %

Mp : 160-162 ºC (lit.[142] 165-166 ºC)

IR (KBr) : ν 3391, 1676, 1594 cm^{-1}

^{1}H NMR (400 MHz) : δ 4.58 (s, 2H), 4.99 (bs, 1H), 6.59 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.50-7.57 (m, 2H), 7.61-7.67 (m, 1H), 8.01 (d, J = 7.6 Hz, 2H)

^{13}C NMR (100 MHz) : δ 50.19, 109.46, 114.60, 127.83, 129.01, 132.12, 134.08, 134.78, 146.10, 194.69

HRMS (ESI) exact mass calc′d for $C_{14}H_{12}BrNOH$ $(M+H)^+$: 290.0181

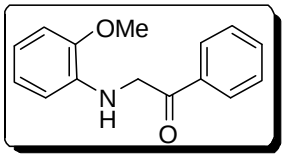
Found : 290.1079

2-(2-Methoxyphenylamino)-1-phenylethanone (107g)

Reaction time : 24 h

Yield : 52 %

Mp : 60-62 ºC



IR (KBr) : ν 3424, 1693, 1600, 1523 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.91 (s, 3H), 4.64 (s, 2H), 5.43 (bs, 1H), 6.60-6.65 (m, 1H), 6.69-6.76 (m, 1H), 6.80-6.85 (m, 1H), 6.86-6.93 (m, 1H), 7.49-7.56 (m, 2H), 7.59-7.66 (m, 1H), 8.03 (d, J = 7.6 Hz, 2H)

^{13}C NMR (100 MHz) : δ 50.15, 55.39, 109.56, 110.04, 117.01, 121.12, 127.71, 128.79, 133.66, 135.02, 137.17, 147.12, 195.02

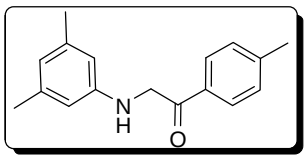
HRMS (ESI) exact mass calc′d for $C_{15}H_{15}NO_2H$ $(M+H)^+$: 242.1181

Found : 242.1183

2-(3,5-Dimethylphenylamino)-1-*p*-tolylethanone (107h)

Reaction time : 24 h

Yield : 45 %



Mp : 120-122 ºC

IR (KBr) : ν 3386, 1687, 1605 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.57 (bs, 1H), 2.27 (s, 6H), 2.44 (s, 3H), 4.58 (s, 2H), 6.36 (s, 2H), 6.42 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H)

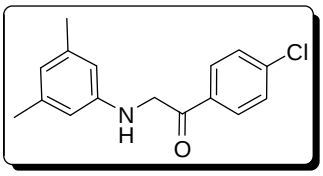
^{13}C NMR (100 MHz) : δ 21.49, 21.71, 50.25, 111.02, 119.75, 127.86, 129.49, 132.47, 138.96, 144.69, 147.24, 194.71

HRMS (ESI) exact mass calc′d for $C_{17}H_{19}NOH$ $(M+H)^+$: 254.1545

Found : 254.1548

1-(4-Chlorophenyl)-2-(3,5-dimethylphenylamino)ethanone (107i)

Reaction time : 24 h



Yield : 40 %

Mp : 118-120 ºC

IR (KBr) : ν 2904, 1682, 1589 cm^{-1}

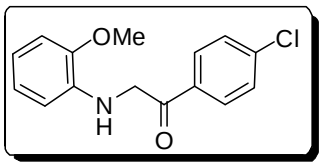
^{1}H NMR (400 MHz) : δ 2.27 (s, 6H), 4.57 (s, 2H), 4.79 (bs, 1H), 6.34 (s, 2H), 6.42 (s, 1H), 7.49(d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H)

^{13}C NMR (100 MHz) : δ 21.51, 50.42, 111.03, 119.98, 129.19, 133.27, 139.07, 140.24, 147.07, 194.08

HRMS (ESI) exact mass calc′d for $C_{16}H_{16}ClNOH$ $(M+H)^+$: 274.0999

Found : 274.0995

1-(4-Chlorophenyl)-2-(2-methoxyphenylamino)ethanone (107j)



Reaction time : 24 h

Yield : 80 %

Mp : 86-88 ºC

IR (KBr) : ν 3402, 1698, 1594 cm^{-1}

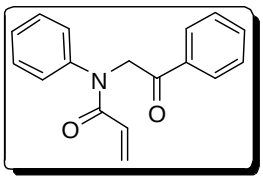
^{1}H NMR (400 MHz) : δ 3.90 (s, 3H), 4.60 (s, 2H), 5.38 (bs, 1H), 6.59 (d, J = 8.0 Hz, 2H), 6.69-6.76 (m, 1H), 6.81 (d, J = 7.2 Hz, 1H), 6.86-6.92 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H)

^{13}C NMR (100 MHz) : δ 50.10, 55.35, 109.54, 109.99, 117.12, 121.08, 129.07, 129.11, 133.28, 136.95, 139.98, 147.06, 193.90

HRMS (ESI) exact mass calc′d for $C_{15}H_{14}ClNO_2H$ $(M+H)^+$: 276.0791

Found : 276.0792

N-(2-Oxo-2-phenyl)ethyl-N-phenylacrylamide (106a)



Reaction time : 1 h

Yield : 75 %

Mp : 76-78 ºC

IR (KBr) : ν 1698, 1654, 1600 cm^{-1}

^{1}H NMR (400 MHz) : δ 5.19 (s, 2H), 5.59 (dd, J = 10.4 and 2.0 Hz, 1H), 6.17 (dd, J = 16.8 and 10.4 Hz, 1H), 6.41 (dd, J = 16.8 and 2.0 Hz, 1H), 7.30-7.52 (m, 7H), 7.54-7.62 (m, 1H), 7.94-8.02 (m, 2H)

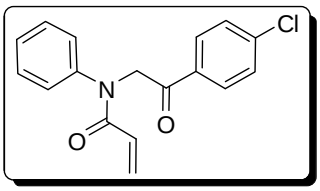
^{13}C NMR (100 MHz) : δ 56.26, 127.83, 128.10, 128.58, 129.43, 133.40, 135.02, 142.26, 165.65, 193.24

HRMS (ESI) exact mass calc′d for $C_{17}H_{15}NO_2Na$ $(M+Na)^+$: 288.1000

Found : 288.0998

N-[2-(4-Chlorophenyl)-2-oxo]ethyl-N-phenylacrylamide (106b)

Reaction time : 1 h



Yield : 76 %

Mp : 78-80 ºC

IR (KBr) : ν 1698, 1660, 1611 cm^{-1}

^{1}H NMR (400 MHz) : δ 5.14 (s, 2H), 5.59 (dd, J = 10.0 and 2.0 Hz, 1H), 6.16 (dd, J = 16.8 and 10.0 Hz, 1H), 6.41 (dd, J = 16.8 and 2.0 Hz, 1H), 7.32-7.48 (m, 7H), 7.91 (d, J = 8.4 Hz, 2H)

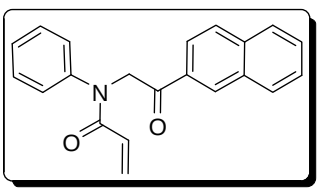
^{13}C NMR (100 MHz) : δ 56.31, 127.77, 128.16, 128.25, 128.58, 129.11, 129.46, 129.67, 133.53, 140.04, 142.27, 165.91, 192.42

HRMS (ESI) exact mass calc′d for $C_{17}H_{14}ClNO_2H$ $(M+H)^+$: 300.0791

Found : 300.0790

N-[2-(Naphth-2-yl)-2-oxo]ethyl-N-phenylacrylamide (106c)

Reaction time : 1 h



Yield : 82 %

Mp : 100-102 ºC

IR (KBr) : ν 1692, 1654 cm^{-1}

^{1}H NMR (400 MHz) : δ 5.33 (s, 2H), 5.60 (dd, J = 10.0 and 1.6 Hz, 1H), 6.20 (dd, J = 16.8 and 10.0 Hz, 1H), 6.43 (dd, J = 16.8 and 1.6

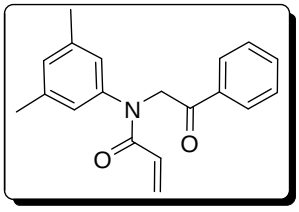
Hz, 1H), 7.31-7.38 (m, 1H), 7.39-7.44 (m, 4H), 7.52-7.64 (m, 2H), 7.84-7.97 (m, 3H), 8.01 (dd, *J* = 8.8 and 1.6 Hz, 1H), 8.50 (s, 1H)

^{13}C NMR (100 MHz) : δ 56.32, 123.40, 126.68, 127.60, 127.84, 128.11, 128.40, 128.47, 129.42, 132.16, 132.25, 135.49, 142.26, 165.71, 193.17

HRMS (ESI) exact mass calc′d for $C_{21}H_{17}NO_2Na$ $(M+Na)^+$: 338.1157

Found : 338.1160

N-(3,5-Dimethylphenyl)-N-(2-oxo-2-phenyl)ethylacrylamide (106d)



Reaction time : 1 h

Yield : 79 %

IR (neat) : *v* 1698, 1654, 1600 cm^{-1}

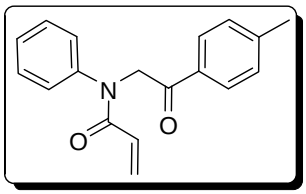
^{1}H NMR (400 MHz) : δ 2.32 (s, 6H), 5.15 (s, 2H), 5.57 (dd, *J* = 10.4 and 2.0 Hz, 1H), 6.20 (dd, *J* = 16.8 and 10.4 Hz, 1H), 6.40 (dd, *J* = 16.8 and 2.0 Hz, 1H), 6.97 (s, 3H), 7.43-7.53 (m, 2H), 7.54-7.63 (m, 1H), 7.96 (d, *J* = 7.6 Hz, 1H)

^{13}C NMR (100 MHz) : δ 21.15, 56.47, 125.73, 127.98, 128.68, 129.65, 133.48, 135.22, 139.36, 142.22, 165.82, 193.39

HRMS (ESI) exact mass calc′d for $C_{19}H_{19}NO_2H$ $(M+H)^+$: 294.1494

Found : 294.1497

N-(2-Oxo-2-*p*-tolyl)ethyl-N-phenylacrylamide (106e)



Reaction time : 1 h

Yield : 80 %

Mp : 42-44 ºC

IR (KBr) : ν 1687, 1665, 1610 cm^{-1}

^1H NMR (400 MHz) : δ 2.41 (s, 3H), 5.17 (s, 2H), 5.58 (dd, J = 10.4 and 1.6 Hz, 1H), 6.17 (dd, J = 16.8 and 10.4 Hz, 1H), 6.41 (dd, J = 16.8 and 2.0 Hz, 1H), 7.23-7.29 (m, 2H)*, 7.30-7.43 (m, 5H), 7.86 (d, J = 8.0 Hz, 2H)

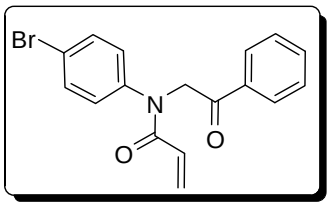
* It Contains $CHCl_3$ peak also

^{13}C NMR (100 MHz) : δ 21.55, 56.16, 127.84, 127.93, 128.09, 129.23, 129.39, 132.51, 142.29, 144.23, 165.65, 192.78

HRMS (ESI) exact mass calc′d for $C_{18}H_{17}NO_2H$ $(M+H)^+$: 280.1338

Found : 280.1338

N-(4-Bromophenyl)-N-(2-oxo-2-phenyl)ethylacrylamide (106f)



Reaction time : 1 h

Yield : 70 %

IR (neat) : ν 1698, 1654, 1616 cm^{-1}

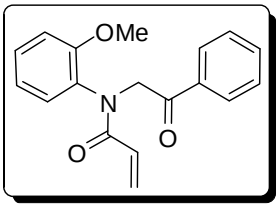
^1H NMR (400 MHz) : δ 5.16 (s, 2H), 5.62 (dd, J = 10.4 and 1.6 Hz, 1H), 6.16 (dd, J = 16.8 and 10.4 Hz, 1H), 6.42 (dd, J = 16.8 and 1.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 2H), 7.44-7.50 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.57-7.62 (m, 1H), 7.95 (d, J = 7.6 Hz, 2H)

^{13}C NMR (100 MHz) : δ 56.20, 121.88, 127.58, 127.98, 128.77, 128.92, 129.99, 132.74, 133.71, 134.97, 141.41, 165.68, 193.25

HRMS (ESI) exact mass calc′d for $C_{17}H_{14}BrNO_2Na$ $(M+Na)^+$: 366.0106

Found : 366.0107

N-(2-Methoxyphenyl)-N-(2-oxo-2-phenyl)ethylacrylamide (106g)



Reaction time : 1 h

Yield : 62 %

Mp : 94-96 ºC

IR (KBr) : ν 1693, 1654, 1610, 1600 cm^{-1}

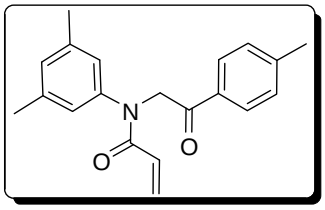
^{1}H NMR (400 MHz) : δ 3.84, (s, 3H), 4.43 (d, J = 17.6 Hz, 1H), 5.54 (dd, J = 10.4 and 1.6 Hz, 1H), 5.80 (d, J = 17.2 Hz, 1H), 6.09 (dd, J = 16.8 and 10.4 Hz, 1H), 6.39 (dd, J = 16.8 and 2.0 Hz, 1H), 6.92-7.01 (m, 2H), 7.29-7.37 (m, 1H), 7.42-7.52 (m, 3H), 7.53-7.60 (m, 1H), 7.97 (d, J = 7.2 Hz, 2H)

^{13}C NMR (100 MHz) : δ 54.60, 55.52, 111.67, 120.78, 127.68, 127.88, 128.53, 129.57, 130.10, 131.11, 133.27, 135.26, 154.74, 166.23, 193.87

HRMS (ESI) exact mass calc′d for $C_{18}H_{17}NO_3Na$ $(M+Na)^+$: 318.1106

Found : 318.1107

N-(3, 5-Dimethylphenyl)-N-(2-oxo-2-*p*-tolyl)ethylacrylamide (106h)



Reaction time : 1 h

Yield : 75 %

IR (neat) : ν 1698, 1654, 1605 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.31 (s, 6H), 2.40 (s, 3H), 5.13 (s, 2H), 5.56 (dd, J = 10.4 and 2.0 Hz, 1H), 6.20 (dd, J = 16.8 and 10.4 Hz, 1H), 6.40 (dd, J = 16.8 and 1.6 Hz, 1H), 6.93-7.00 (m, 3H), 7.25(d, J = 7.2 Hz, 2H)*, 7.86 (d, J = 8.4 Hz, 2H)

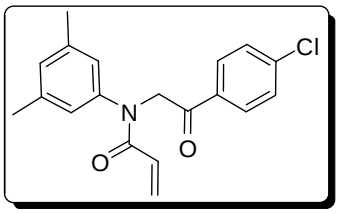
* It contains $CHCl_3$ peak also

^{13}C NMR (100 MHz) : δ 20.65, 21.14, 55.91, 125.30, 127.27, 127.58, 127.74, 128.86, 129.15, 132.25, 138.78, 141.88, 143.74, 165.16, 192.42

HRMS (ESI) exact mass calc′d for $C_{20}H_{21}NO_2H$ $(M+H)^+$: 308.1651

Found : 308.1648

N-[2-(4-Chlorophenyl)-2-oxo]ethyl-N-(3,5-dimethylphenyl)acrylamide (106i)



Reaction time : 1 h

Yield : 62 %

IR (neat) : ν 1709, 1660, 1620 cm^{-1}

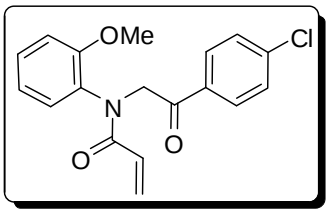
^{1}H NMR (400 MHz) : δ 2.32 (s, 6H), 5.09 (s, 2H), 5.58 (dd, J = 10.4 Hz and 2.0 Hz, 1H), 6.19 (dd, J = 16.8 and 10.4 Hz, 1H), 6.40 (dd, J = 16.8 and 2.0 Hz, 1H), 6.92-7.00 (m, 3H), 7.44 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ 20.82, 56.06, 125.39, 127.66, 127.73, 128.62, 129.12, 129.41, 133.20, 139.03, 139.40, 141.80, 165.38, 192.04

HRMS (ESI) exact mass calc′d for $C_{19}H_{18}ClNO_2H$ $(M+H)^+$: 328.1104

Found : 328.1106

N-[2-(4-Chlorophenyl)-2-oxo]ethyl-N-(2-methoxyphenyl)acrylamide (106j)



Reaction time : 1 h

Yield : 65 %

Mp : 96-98 ºC

IR (KBr) : ν 1698, 1654, 1616 cm^{-1}

^{1}H NMR (400 MHz) : δ 3.83 (s, 3H), 4.39 (d, J = 17.2 Hz, 1H), 5.55 (dd, J = 10.4 and 2.0 Hz, 1H), 5.73 (d, J = 17.2 Hz, 1H), 6.08 (dd, J = 16.8 and 10.4 Hz, 1H), 6.39 (dd, J = 16.8 and 2.0 Hz, 1H), 6.92-7.01 (m, 2H), 7.29-7.37 (m, 1H), 7.40-7.48 (m, 3H), 7.92 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ 54.33, 55.55, 11.73, 120.86, 127.58, 128.05, 128.89, 129.41, 129.69, 130.00, 131.07, 133.66, 139.66, 154.77, 166.25, 192.94

HRMS (ESI) exact mass calc′d for $C_{18}H_{16}ClNO_3H$ $(M+H)^+$: 330.0897

Found : 330.0895

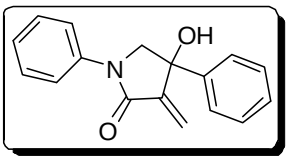
Representative procedure: Synthesis of 4-hydroxy-3-methylene-1,4-diphenyl pyrrolidin-2-one. (**108a**)

A stirring solution of N-(2-oxo-2-phenylethyl)-N-phenylacrylamide (0.265 g, 1 mmol) (**106a**), DABCO (0.112 g, 1 mmol) in dioxane (1 mL) and H_2O (1mL) (1:1) was heated at 65 ºC, for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 15 mL). Combined organic layer was washed with water (15 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude thus obtained was

purified by column chromatography [silica gel, 30% EtOAc in hexanes] to provide the title compound (**108a**) in 88% yield (0.233 g) as a colorless solid.

Reaction time : 5 h

Yield : 88 %



Mp : 160-162 ºC

IR (neat) : ν 3282, 1671, 1649 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.83 (s, 1H), 4.10 (s, 2H), 5.51 (s, 1H), 6.36 (s, 1H), 7.10-7.22 (m, 1H), 7.31-7.43 (m, 5H), 7.53 (d, J = 7.2 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H)

^{13}C NMR (100 MHz) : δ 61.72, 72.99, 118.98, 119.39, 124.05, 124.90, 126.68, 127.46, 128.12, 138.40, 143.63, 148.38, 164.69

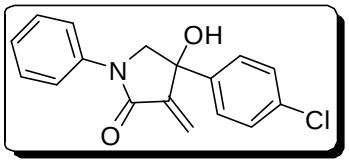
HRMS (ESI) exact mass calc′d for $C_{17}H_{15}NO_2Na$ $(M + Na)^+$: 288.1000

Found : 288.0999

4-(4-Chlorophenyl)-4-hydroxy-3-methylene-1-phenylpyrrolidin-2-one (**108b**)

Reaction time : 3.5 h

Yield : 82 %



Mp : 120-122 ºC

IR (KBr) : ν 3326, 1676, 1649 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.88 (s, 1H), 4.07 & 4.09 (ABq, J = 10.8 Hz, 2H), 5.49 (s, 1H), 6.36 (s, 1H), 7.16-7.22 (m, 1H), 7.34-7.42 (m, 4H), 7.44-7.50 (m, 2H), 7.66-7.71 (m, 2H)

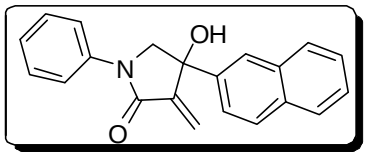
^{13}C NMR (100 MHz) : δ 62.72, 73.85, 119.92, 121.76, 125.37, 127.26, 128.49, 128.97, 133.65, 138.51, 141.73, 148.16, 165.41

HRMS (ESI) exact mass calc′d for $C_{17}H_{14}ClNO_2H$ $(M+H)^+$: 300.0791

Found : 300.0785

4-Hydroxy-3-methylene-4-(naphth-2-yl)-1-phenylpyrrolidin-2-one (**108c**)

Reaction time : 12 h



Yield : 75 %

Mp : 138-140 ºC

IR (KBr) : ν 3418, 1692, 1654 cm^{-1}

^1H NMR (400 MHz) : δ 2.75 (s, 1H), 4.16 & 4.21 (ABq, J = 10.8 Hz, 2H), 5.54 (s, 1H), 6.42 (s, 1H), 7.16-7.22 (m, 1H), 7.36-7.43 (m, 2H), 7.48 (dd, J = 8.8 and 1.6 Hz, 1H), 7.51-7.56 (m, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.83-7.91 (m, 3H), 8.12 (s, 1H)

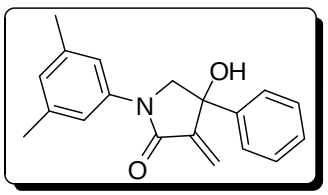
^{13}C NMR (100 MHz) : δ 62.53, 74.45, 119.89, 121.81, 123.83, 124.72, 125.22, 126.42, 126.54, 127.60, 128.34, 128.40, 128.98, 132.74, 132.87, 138.76, 140.27, 148.49, 165.57

HRMS (ESI) exact mass calc′d for $C_{21}H_{17}NO_2Na$ $(M+Na)^+$: 338.1157

Found : 338.1153

1-(3,5-Dimethylphenyl)-4-hydroxy-3-methylene-4-phenylpyrrolidin-2-one (**108d**)

Reaction time : 20 h



Yield : 74 %

Mp : 108-110 ºC

IR (KBr) : ν 3304, 1676, 1654 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.31 (s, 6H), 2.94 (s, 1H), 4.08 (s, 2H), 5.48 (s, 1H), 6.33 (s, 1H), 6.82 (s, 1H), 7.29-7.42 (m, 5H), 7.49-7.55 (m, 2H)

^{13}C NMR (100 MHz) : δ 21.43, 63.01, 74.16, 117.78, 121.15, 125.63, 126.89, 127.59, 128.28, 138.44, 138.62, 143.45, 148.63, 165.49

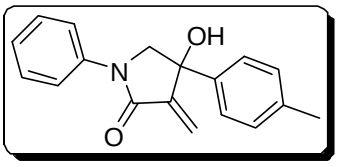
HRMS (ESI) exact mass calc′d for $C_{19}H_{19}NO_2H$ $(M+H)^+$: 294.1494

Found : 294.1496

4-Hydroxy-3-methylene-1-phenyl-4-(4-methylphenyl)pyrrolidin-2-one (**108e**)

Reaction time : 11 h

Yield : 78 %



Mp : 110-112 ºC

IR (KBr) : ν 3287, 1676, 1654 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.37 (s, 3H), 2.60 (s, 1H), 4.08 (s, 2H), 5.51 (s, 1H), 6.36 (s, 1H), 7.15-7.23 (m, 3H), 7.35-7.44 (m, 4H), 7.70 (d, J = 8.0 Hz, 2H)

^{13}C NMR (100 MHz) : δ 21.06, 62.71, 74.24, 119.86, 121.25, 125.10, 125.65, 128.93, 129.08, 137.52, 138.82, 140.20, 148.62, 165.56

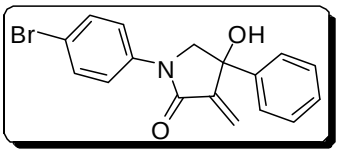
HRMS (ESI) exact mass calc′d for $C_{18}H_{17}NO_2H$ $(M + H)^+$: 280.1338

Found : 280.1335

1-(4-Bromophenyl)-4-hydroxy-3-methylene-4-phenylpyrrolidin-2-one (**108f**)

Reaction time : 2.5 h

Yield : 70 %



Mp : 55-57 ºC

IR (KBr) : ν 3391, 1676, 1649 cm^{-1}

^1H NMR (400 MHz) : δ 2.78 (s, 1H), 4.06 (s, 2H), 5.53 (s, 1H), 6.37 (s, 1H), 7.32-7.44 (m, 3H), 7.46-7.55 (m, 4H), 7.60 (d, J = 9.2 Hz, 2H)

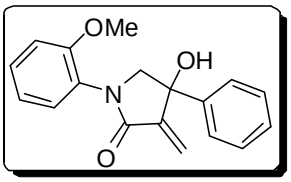
^{13}C NMR (100 MHz) : δ 62.60, 74.05, 118.07, 121.11, 121.99, 125.67, 127.85, 128.40, 131.83, 137.66, 142.75, 148.12, 165.59

HRMS (ESI) exact mass calc′d for $C_{17}H_{14}BrNO_2Na$ $(M + Na)^+$: 366.0106

Found : 366.0110

4-Hydroxy-1-(2-methoxyphenyl)-3-methylene-4-phenylpyrrolidin-2-one (**108g**)

Reaction time : 44 h



Yield : 84 %

IR (neat) : ν 3369, 1687, 1646

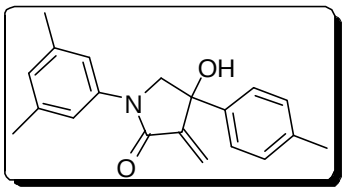
^1H NMR (400 MHz) : δ 2.84 (s, 1H), 3.82 (s, 3H), 3.98 & 4.09 (ABq, J = 10.8 Hz, 2H), 5.49 (s, 1H), 6.32 (s, 1H), 6.95-7.05 (m, 2H), 7.27-7.43 (m, 5H), 7.55-7.60 (m, 2H)

^{13}C NMR (100 MHz) : δ 55.43, 63.91, 74.98, 111.92, 120.52, 120.68, 125.37, 126.27, 127.20, 128.03, 128.21, 128.81, 144.19, 147.95, 154.56, 166.15

HRMS (ESI) exact mass calc′d for $C_{18}H_{17}NO_3H$ $(M+H)^+$: 296.1287

Found : 296.1283

1-(3,5-Dimethylphenyl)-4-hydroxy-3-methylene-4-(4-methylphenyl)pyrrolidin-2-one (**108h**)



Reaction time : 28 h

Yield : 72 %

Mp : 108-110 ºC

IR (neat) : ν 3364, 1676, 1660 cm^{-1}

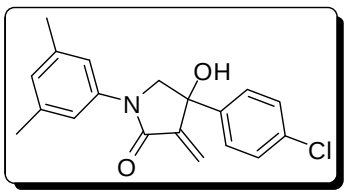
^{1}H NMR (400 MHz) : δ 2.32 (s, 6H), 2.36 (s, 3H), 2.55 (s, 1H), 4.06 (s, 2H), 5.49 (s, 1H), 6.34 (s, 1H), 6.83 (s, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.32 (s, 2H), 7.40 (d, J = 8.0 Hz, 2H)

^{13}C NMR (100 MHz) : δ 21.06, 21.51, 62.99, 74.33, 117.82, 120.92, 125.64, 126.93, 129.09, 137.52, 138.56, 138.77, 140.31, 148.87, 165.42

HRMS (ESI) exact mass calc′d for $C_{20}H_{21}NO_2Na$ $(M+Na)^+$: 330.1470

Found : 330.1465

4-(4-Chlorophenyl)-1-(3,5-dimethylphenyl)-4-hydroxy-3-methylenepyrrolidin-2-one (**108i**)



Reaction time : 18 h

Yield : 76 %

Mp : 144-146 ºC

IR (KBr) : ν 3287, 1676, 1654 cm^{-1}

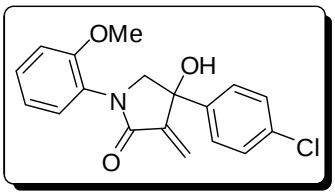
^{1}H NMR (400 MHz) : δ 2.32 (s, 6H), 2.79 (s, 1H), 4.03 & 4.07 (ABq, J = 10.8 Hz, 2H), 5.48 (s, 1H), 6.34 (s, 1H), 6.84 (s, 1H), 7.30 (s, 2H), 7.33-7.38 (m, 2H). 7.44-7.49 (m, 2H)

^{13}C NMR (100 MHz) : δ 21.49, 63.03, 73.91, 117.81, 121.46, 127.14, 127.25, 128.49, 133.65, 138.50, 138.62, 141.87, 148.46, 165.26

HRMS (ESI) exact mass calc′d for $C_{19}H_{18}ClNO_2H$ $(M+H)^+$: 328.1104

Found : 328.1104

4-(4-Chlorophenyl)-4-hydroxy-1-(2-methoxyphenyl)-3-methylenepyrrolidin-2-one (108j)



Reaction time : 27 h

Yield : 82 %

Mp : 48-50 ºC

IR (KBr) : ν 3342, 1687, 1648 cm^{-1}

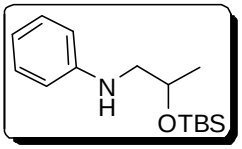
^{1}H NMR (400 MHz) : δ 2.91 (s, 1H), 3.83 (s, 3H), 3.95 & 4.04 (ABq, J = 10.8 Hz, 2H), 5.49 (s, 1H), 6.33 (s, 1H), 6.96-7.05 (m, 2H), 7.28-7.39 (m, 4H), 7.51 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ 55.56, 63.93, 74.78, 112.00, 120.86, 120.93, 126.12, 127.06, 128.28, 129.11, 133.21, 142.69, 147.76, 154.62, 166.08

HRMS (ESI) exact mass calc′d for $C_{18}H_{16}ClNO_3H$ $(M+H)^+$: 330.0897

Found : 330.0890

N-[2-(*tert*-Butyldimethylsilyloxy)]propylaniline (112a)



Reaction time : 5 h

Yield : 88 %

IR (neat) : ν 3407, 2958, 2931, 1599 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.21 (d, J = 6.0 Hz, 3H), 2.98 (dd, J = 12.8 and 8.8 Hz, 1H), 3.15 (d, J = 12.0 Hz, 1H), 3.93-4.11 (m, 2H)*, 6.57-6.63 (m, 2H), 6.66-6.73 (m, 1H), 7.13-7.21 (m, 2H)

* It contains a broad singlet of 1H at δ 3.99

^{13}C NMR (100 MHz) : δ -4.73,-4.34, 18.11, 21.80, 25.90, 51.34, 67.15, 113.06, 117.33, 129.26, 148.46

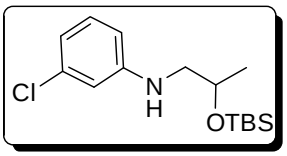
HRMS (ESI) exact mass calc′d for $C_{15}H_{27}NOSiH$ $(M+H)^+$: 266.1940

Found : 266.1941

N-[2-(*tert*-Butyldimethylsilyloxy]propyl-3-chloroaniline (112b)

Reaction time : 5 h

Yield : 85 %



IR (neat) : ν 3413, 2931, 1599 cm^{-1}

^{1}H NMR (400 MHz) : δ 0.05 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.20 (d, J = 6.0 Hz, 3H), 2.91-3.01 (m, 1H), 3.08-3.18 (m, 1H), 3.99-4.13 (m, 2H)*, 6.45 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 6.64 (d, J = 7.2 Hz, 1H), 7.02-7.10 (m, 1H)

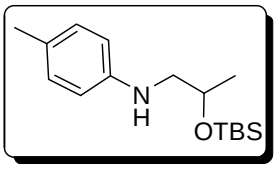
* It contains a broad singlet of 1H at δ 3.99

^{13}C NMR (100 MHz) : δ -4.73, -4.33, 18.10, 21.74, 25.89, 51.07, 67.05, 111.45, 112.51, 117.08, 130.19, 135.03, 149.65

HRMS (ESI) exact mass calc′d for $C_{15}H_{26}ClNOSiH$ $(M+H)^+$: 300.1550

Found : 300.1553

N-[2-(*tert*-Butyldimethylsilyloxy)]propyl-4-methylaniline (112c)



Reaction time : 5 h

Yield : 92 %

IR (neat) : ν 3396, 2925, 1517 cm^{-1}

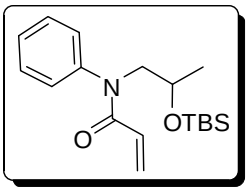
^{1}H NMR (400 MHz) : δ 0.06 (s, 6H), 0.90 (s, 9H), 1.20 (d, J = 6.0 Hz, 3H), 2.23 (s, 3H), 2.95 (dd, J = 12.0 and 7.2 Hz, 1H), 3.12 (dd, J = 12.0 and 4.0 Hz, 1H), 3.86 (bs, 1H), 4.00-4.09 (m, 1H), 6.53 (d, J = 8.4 Hz 2H), 6.98 (d, J = 8.4 Hz 2H)

^{13}C NMR (100 MHz) : δ -4.71, -4.32, 18.11, 20.44, 21.81 25.90, 51.81, 67.21, 113.25, 126.47, 129.74, 146.23

HRMS (ESI) exact mass calc′d for $C_{16}H_{29}NOSiH$ $(M+H)^{+}$: 280.2097

Found : 280.2098

N-[2-(*tert*-Butyldimethylsilyloxy)]propyl-N-phenylacrylamide (113a)



Reaction time : 1 h

Yield : 95 %

IR (neat) : ν 2936, 1659, 1615 cm^{-1}

^{1}H NMR (400 MHz) : δ -0.02 (s, 3H)*, 0.03 (s, 3H), 0.84 (s, 9H), 1.16 (d, J = 6.0 Hz, 3H), 3.58 (dd, J = 13.6 Hz, 7.2 Hz, 1H), 3.87 (dd, J = 13.6 and 5.6 Hz, 1H), 4.21-4.33 (m, 1H), 5.51 (d, J = 10.0 Hz, 1H)$^{\$}$, 6.07 (dd, J = 16.4 and 10.0 Hz, 1H), 6.36 (dd, J = 16.8 and 1.6 Hz, 1H), 7.22-7.32 (m, 3H)$^{\#}$, 7.33-7.43 (m, 2H)

* Of the three almost equal peaks, the central peak was selected as TMS peak.

$ Unresolved dd

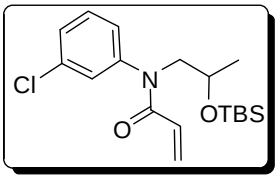
It contains $CHCl_3$ peak also

^{13}C NMR (100 MHz) : δ -4.64, 18.02, 21.078, 25.86, 58.12, 66.11, 127.22, 127.30, 127.84, 129.24, 143.41, 165.97

HRMS (ESI) exact mass calc′d for $C_{18}H_{29}NO_2SiH$ $(M+H)^+$: 320.2046

Found : 320.2048

N-[2-(*tert*-Butyldimethylsilyloxy)]propyl-N-(3-chlorophenyl)acrylamide (113b)



Reaction time : 1 h

Yield : 87 %

IR (neat) : ν 2936, 1659, 1621 cm^{-1}

^{1}H NMR (400 MHz) : δ -0.02 (s, 3H)*, 0.04 (s, 3H), 0.85 (s, 9H), 1.16 (d, J = 6.4 Hz, 3H), 3.53 (dd, J = 14 and 7.2 Hz, 1H), 3.87 (dd, J = 13.6 and 4.4 Hz, 1H), 4.3 (bs, 1H), 5.55 (d, J = 14.4 Hz, 1H), 6.09 (bs, 1H), 6.39 (dd, J = 14.4 and 1.6 Hz, 1H), 7.12-7.14 (m, 1H), 7.28-7.39 (m, 3H)#

* Of the three almost equal peaks, the central peak was selected as TMS peak. It is because its integration was lesser then other two peaks and it also showed good agreement with $CHCl_3$ peak.

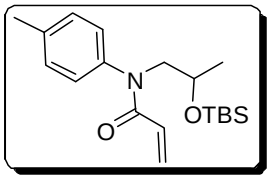
It contains $CHCl_3$ peak also.

^{13}C NMR (100 MHz) : δ -4.66, -4.60, 17.98, 21.71, 25.85, 58.32, 66.10, 126.01, 127.30, 127.97, 128.91, 130.04, 134.73, 144.79, 165.77

HRMS (ESI) exact mass calc′d for $C_{18}H_{28}ClNO_2SiH$ $(M+H)^+$: 354.1656

Found : 354.1658

N-[2-(*tert*-Butyldimethylsilyloxy)]propyl-N-(4-methylphenyl)acrylamide (113c)



Reaction time : 1 h

Yield : 91 %

IR (neat) : ν 2931, 1659, 1615 cm^{-1}

^{1}H NMR (400 MHz) : δ -0.02 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.15 (d, J = 6.0 Hz, 3H), 2.37 (s, 3H), 3.56 (dd, J = 13.6 and 7.2 Hz, 1H), 3.84 (dd, J = 13.6 and 5.6 Hz, 1H), 4.21-4.31 (m, 1H), 5.49 (dd, J = 10.0 and 1.6 Hz, 1H), 6.07 (dd, J = 16.8 and 10.4 Hz, 1H), 6.34 (dd, J = 16.8 and 1.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H)

^{13}C NMR (100 MHz) : δ -4.71, 17.94, 20.95, 21.72, 25.79, 58.01, 65.97, 126.98, 127.53, 129.18, 129.76, 137.01, 140.70, 165.92

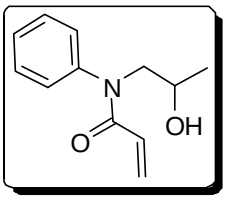
HRMS (ESI) exact mass calc′d for $C_{19}H_{31}NO_2SiH$ $(M+H)^+$: 334.2202

Found : 334.2206

N-(2-Hydroxypropyl)-N-phenylacrylamide (114a)

Deprotection reaction of N-(2-(tert-butyldimethylsilyloxy)propyl)-N-phenylacrylamide (**113a**) in presence of 2N HCl following the similar procedure as described for the molecule (**93a**) provided the title compound (**114a**) as a colorless liquid.

Reaction time : 4 h



Yield : 87 %

IR (neat) : ν 3413, 1648, 1610 cm^{-1}

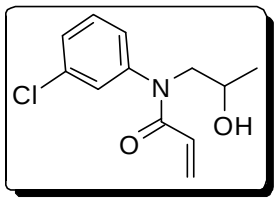
^{1}H NMR (400 MHz) : δ 1.18 (d, J = 6.4 Hz, 3H), 3.51 (dd, J = 14.0 and 2.4 Hz, 1H), 3.73 (d, J = 3.6 Hz, 1H), 3.99-4.10 (m, 1H), 4.14 (dd, J = 14.0 and 8.8 Hz, 1H), 5.57 (dd, J = 10.4 and 1.6 Hz, 1H), 6.00 (dd, J = 16.8 and 10.4 Hz, 1H), 6.39 (dd, J = 16.8 and 2.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.34-7.40 (m, 1H), 7.40-7.47 (m, 2H)

^{13}C NMR (100 MHz) : δ 21.16, 57.84, 66.33, 127.77, 127.83, 127.99, 128.26, 129.48, 142.21, 167.13

HRMS (ESI) exact mass calc′d for $C_{12}H_{15}NO_2H$ $(M+H)^+$: 206.1181

Found : 206.1180

N-(3-Chlorophenyl)-N-(2-hydroxypropyl)acrylamide (114b)



Reaction time : 4 h

Yield : 92 %

IR (neat) : ν 3418, 1659, 1621 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.19 (d, J = 6.0 Hz, 3H), 3.43 (s, 1H), 3.48-3.57 (m, 1H), 3.99-4.15 (m, 2H), 5.62 (dd, J = 10.4 and 1.6 Hz, 1H), 6.00 (dd, J = 16.8 and 10.4 Hz, 1H), 6.42 (dd, J = 16.8 and 1.6 Hz, 1H), 7.12-7.17 (m, 1H), 7.26 (s, 1H)*, 7.34-7.41 (m, 2H)

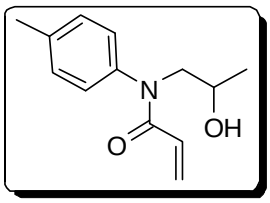
* It also contains $CHCl_3$ peak at δ 7.26

^{13}C NMR (100 MHz) : δ 21.42, 58.08, 66.69, 126.45, 128.07, 128.28, 129.04, 130.66, 135.15, 143.63, 167.31

HRMS (ESI) exact mass calc′d for $C_{12}H_{14}ClNO_2Na$ $(M+Na)^+$: 262.0611

Found : 262.0609

N-(2-Hydroxypropyl)-N-(4-methylphenyl)acrylamide (114c)



Reaction time : 4 h

Yield : 87 %

IR (neat) : ν 3424, 1643, 1610 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.17 (d, J = 6.0 Hz, 3H), 2.38 (s, 3H), 3.46 (dd, J = 14.0 and 2.4 Hz, 1H), 3.80 (d, J = 4.4 Hz, 1H), 3.98-4.08 (m, 1H), 4.13 (dd, J = 14.0 and 8.8 Hz, 1H), 5.55 (dd, J = 10.4 and 2.0 Hz, 1H), 6.01 (dd, J = 16.8 and 10.4 Hz, 1H), 6.37 (dd, J = 16.8 and 1.6 Hz, 1H), 7.09 (d, 8.0 Hz, 2H), 7.22 (d, 8.0 Hz, 2H)

^{13}C NMR (100 MHz) : δ 20.86, 21.17, 57.94, 66.46, 127.58, 127.82, 128.32, 130.09, 137.75, 139.61, 167.35

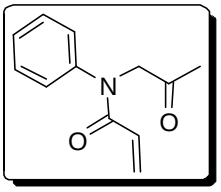
HRMS (ESI) exact mass calc′d for $C_{13}H_{17}NO_2H$ $(M+H)^+$: 220.1338

Found : 220.1339

N-(2-Oxopropyl)-N-phenylacrylamide (109a)

This compound (**109a**) was prepared *via* the treatment of N-(2-Hydroxypropyl)-N-phenylacrylamide **(114a)** with Dess-Martin periodinane in DCM, following the similar procedure as described for the molecule (**94a**) provided the title compound (**109a**), as a colorless liquid.

Reaction time : 1 h



Yield : 84 %

IR (neat) : ν 1736, 1654 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.20 (s, 3H), 4.51 (s, 2H), 5.57 (dd, J = 10.4 and 1.6 Hz, 1H), 6.11 (dd, J = 16.8 and 10.0 Hz, 1H), 6.39 (dd, J = 16.8 and 1.6 Hz, 1H), 7.25-7.44 (m, 5H)*

* It contains $CHCl_3$ peak

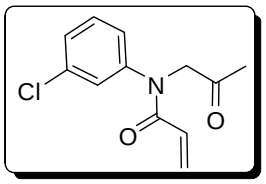
^{13}C NMR (100 MHz) : δ 27.20, 59.54, 127.70, 127.94, 127.99, 128.32, 129.57, 142.22, 165.63, 202.20

HRMS (ESI) exact mass calc′d for $C_{12}H_{13}NO_2H$ $(M+H)^+$: 204.1025

Found : 204.1023

N-(3-Chlorophenyl)-N-(2-oxopropyl)acrylamide (109b)

Reaction time : 1 h



Yield : 83 %

IR (neat) : ν 1730, 1659, 1615 cm^{-1}

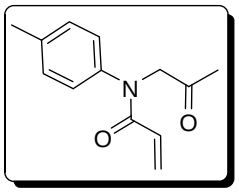
^{1}H NMR (400 MHz) : δ 2.21 (s, 3H), 4.50 (s, 2H), 5.62 (dd, J = 10.4 and 1.6 Hz, 1H), 6.00 (dd, J = 16.8 and 10.4 Hz, 1H), 6.40 (dd, J = 16.8 and 1.6 Hz, 1H), 7.18-7.24 (m, 1H), 7.30-7.37 (m, 3H)

^{13}C NMR (100 MHz) : δ 27.16, 59.31, 126.40, 127.35, 128.18, 128.27, 128.98, 130.52, 134.94, 143.36, 165.38, 201.87

HRMS (ESI) exact mass calc′d for $C_{12}H_{12}ClNO_2Na$ $(M+Na)^+$: 260.0454

Found : 260.0450

N-(2-Oxopropyl)-N-(4-methylphenyl)acrylamide (109c)



Reaction time : 1 h

Yield : 91 %

IR (neat) : ν 1736, 1654, 1615 cm^{-1}

^{1}H NMR (400 MHz) : δ 2.19 (s, 3H), 2.37 (s, 3H), 4.49 (s, 2H), 5.55 (dd, J = 10.4 and 2.0 Hz, 1H), 6.12 (dd, J = 16.8 and 10.4 Hz, 1H), 6.37 (dd, J = 16.8 and 2.0 Hz, 1H), 7.14-7.22 (m, 4H)

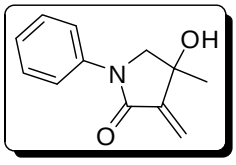
^{13}C NMR (100 MHz) : δ 20.93, 27.11, 59.53, 127.63, 127.71, 128.01, 130.07, 137.92, 139.55, 165.68, 202.25

HRMS (ESI) exact mass calc′d for $C_{13}H_{15}NO_2H$ $(M+H)^+$: 218.1181

Found : 218.1182

4-Hydroxy-4-methyl-3-methylene-1-phenylpyrrolidin-2-one (111a)

This compound (**111a**) was prepared *via* the intramolecular Baylis-Hillman reation of N-(2- oxopropyl)-N-phenylacrylamide (**109a**) in the presence of DABCO in 2 mL of dioxane : water (1:1), following the similar procedure as described for **108a**, as a light yellow solid



Reaction time : 3 h

Yield : 58 %

Mp : 108-110 ºC

IR (KBr) : ν 3336, 1682, 1654 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.60 (s, 3H)*, 2.34 (s, 1H), 3.80 & 3.89 (ABq, J = 10.0 Hz, 2H), 5.73 (s, 1H), 6.23 (s, 1H), 7.15-7.22 (m, 1H), 7.35-7.43 (m, 2H), 7.68 (d, J = 8.0 Hz, 2H)

* It contains moisture peak also

^{13}C NMR (100 MHz) : δ 27.14, 60.63, 69.75, 118.44, 119.78, 124.95, 128.75, 138.66, 147.92, 165.72

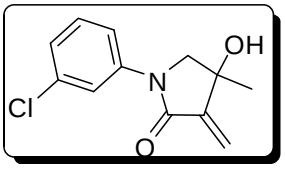
HRMS (ESI) exact mass calc′d for $C_{12}H_{13}NO_2H$ $(M+H)^+$: 204.1025

Found : 204.1033

1-(3-Chlorophenyl)-4-hydroxy-4-methyl-3-methylenepyrrolidin-2-one (111b)

Reaction time : 1 h

Yield : 55 %



Mp : 98-100 ºC

IR (KBr) : ν 3413, 1670, 1654 cm^{-1}

^{1}H NMR (400 MHz) : δ 1.60 (s, 3H)*, 2.34 (bs, 1H), 3.77 & 3.86 (ABq, J = 10.0 Hz, 2H), 5.76 (s, 1H), 6.24 (s, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.25-7.34 (m, 1H)#, 7.59 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H)

* It contains moisture peak also

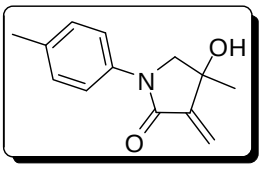
It contains $CHCl_3$ peak also at δ 7.26

^{13}C NMR (100 MHz) : δ 26.90, 60.63, 69.70, 117.44, 119.29, 119.63, 124.92, 129.82, 134.47, 139.81, 147.56, 165.91

HRMS (ESI) exact mass calc′d for $C_{12}H_{12}ClNO_2Na$ $(M+Na)^+$: 260.0454

Found : 260.0453

4-Hydroxy-4-methyl-3-methylene-1-(4-methylphenyl)pyrrolidin-2-one (111c)



Reaction time : 6 h

Yield : 52 %

IR (neat) : ν 3380, 1693, 1654, 1616 cm^{-1}

^1H NMR (400 MHz) : δ 1.58 (s, 3H), 2.34 (s, 3H), 2.48-2.55 (m, 1H), 3.76 & 3.85 (ABq, J = 10.0 Hz, 2H), 5.69 (s, 1H), 6.19 (s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H)

^{13}C NMR (100 MHz) : δ 20.84, 27.27, 60.85, 69.88, 118.18, 119.83, 129.34, 134.68, 136.30, 148.13, 165.57

HRMS (ESI) exact mass calc′d for $C_{13}H_{15}NO_2H$ $(M+H)^+$: 218.1181

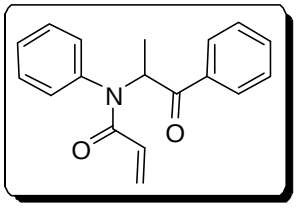
Found : 218.1184

Representative procedure: Synthesis of N-(1-oxo-1-phenylpropan-2-yl)-N-phenylacrylamide (127a)

1-Phenyl-2-(phenylamino)ethanone (**107a**) (1.055 g, 5.0 mmol) was added to suspension of NaH (0.210 g, 5.25 mmol, 60% w/w in mineral oil) in dry DMF (37 mL) at 0 ºC with stirring. After 30 min, MeI (0.923 g, 6.5 mmol) was added slowly and the stirring continued at 0 ºC for 3 h. Ice pieces were added to the reaction mixture and stirred for 10 min. Then reaction mixture was extracted with EtOAc (2 x 60 mL). The combined organic layer was washed with water (2 x 30 mL) and dried over anhydrous Na_2SO_4.Then the solvent was evaporated and the crude product thus obtained, was used without purification for the next step.

The crude product obtained above was dissolved in DCM (15 mL) and cooled at 0 ºC. To this stirring solution, Et_3N (0.707 g, 7.0 mmol) was added followed by addition of

acryloyl chloride (0.543 g, 6.0 mmol) by dropwise at 0 ºC. After stirring for 1h at same temperature, the reaction mixture was diluted with 30 mL of water and extracted with DCM (2 x 30 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by column chromatography [silica gel, 20 % ethyl acetate in hexanes] to afford the desired product (**127a**) in 70 % (0.976 g) yield (over two steps), as a reddish viscous liquid.



Reaction time : (0.5 + 3.0) h

Yield : 70 %

IR (neat) : ν 1687, 1654, 1616, 1594 cm^{-1}

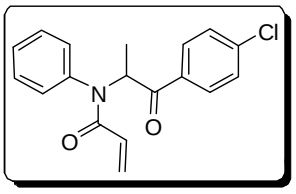
^{1}H NMR (500 MHz) : δ 1.26 (d, J = 6.0 Hz, 3H), 5.50 (dd, J = 10.5 and 2.0 Hz, 1H), 5.87 (dd, J = 17.0 and 10.5 Hz, 1H), 6.27 (q, J = 7.0 Hz, 1H), 6.37 (dd, J = 17.0 and 2.0 Hz, 1H), 7.12-7.18 (m, 2H), 7.34-7.40 (m, 3H), 7.47-7.52 (m, 2H), 7.57-7.61 (m, 1H) 8.05-8.08 (m, 2H)

^{13}C NMR (100 MHz) : δ 15.31, 55.38, 128.31, 128.41, 128.53, 128.69, 128.84, 129.33, 130.39, 133.30, 135.81, 138.24, 165.65, 198.93

HRMS (ESI) exact mass calc′d for $C_{18}H_{17}NO_2Na$ $(M+Na)^+$: 302.1157

Found : 302.1162

N-[1-(4-Chlorophenyl)-1-oxo]propan-2-yl-N-phenylacrylamide (127b)



Reaction time : (0.5 + 3.0) h

Yield : 65 %

IR (neat) : ν 1687, 1649, 1610, 1583 cm^{-1}

^{1}H NMR (500 MHz) : δ 1.25 (d, J = 7.5 Hz, 3H), 5.51 (dd, J = 10.5 and 2.0 Hz, 1H), 5.86 (dd, J = 17.0 and 10.5 Hz, 1H), 6.20 (q, J = 7.5 Hz, 1H), 6.37 (dd, J = 17.0 and 2.0 Hz, 1H), 7.10-7.15 (m, 2H), 7.35-7.40 (m, 3H), 7.45-7.49 (m, 2H), 8.00-8.03 (m, 2H)

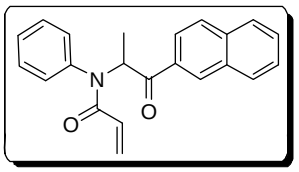
^{13}C NMR (100 MHz) : δ 15.20, 55.27, 128.24, 128.54, 128.79, 129.16, 129.40, 129.95, 130.28, 134.15, 138.05, 139.70, 165.65, 197.76

HRMS (ESI) exact mass calc′d for $C_{18}H_{16}ClNO_2Na$ $(M+Na)^+$: 336.0767

Found : 336.0769

N-[1-(Naphthalen-2-yl)-1-oxo]propan-2-yl-N-phenylacrylamide (127c)

Reaction time : (0.5 + 3.0) h



Yield : 67 %

IR (neat) : ν 1687, 1654, 1618, 1594 cm^{-1}

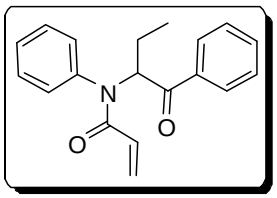
^{1}H NMR (500 MHz) : δ 1.32 (d, J = 7.0 Hz, 3H), 5.49 (dd, J = 10.5 and 2.0 Hz, 1H), 5.87 (dd, J = 16.5 and 10.5 Hz, 1H), 6.38 (dd, J = 16.5 and 2.0 Hz, 1H), 6.43 (q, J = 7.0 Hz, 1H), 7.13-7.20 (m, 2H), 7.33-7.40 (m, 3H), 7.48-7.58 (m, 1H), 7.59-7.63 (m, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.06 (dd, J = 8.5 and 1.2 Hz, 1H), 8.67 (s, 1H)

^{13}C NMR (100 MHz) : δ 15.44, 55.51, 124.38, 126.80, 127.82, 128.31, 128.51, 128.58, 128.72, 129.37, 129.89, 130.19, 130.45 132.74, 133.15, 135.80, 138.35, 165.73, 198.91

HRMS (ESI) exact mass calc′d for $C_{22}H_{19}NO_2Na$ $(M+Na)^+$: 352.1313

Found : 352.1317

N-(1-Oxo-1-phenyl)butan-2-yl-N-phenylacrylamide (127d)



Reaction time : (0.5 + 3.0) h

Yield : 62 %

IR (neat) : *v* 1693, 1654, 1616, 1594 cm^{-1}

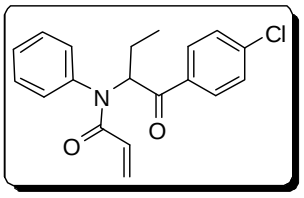
^1H NMR (500 MHz) : δ 0.97 (t, *J* = 7.0 Hz, 3H), 1.62-1.72 (m, 1H), 1.85-1.95 (m, 1H), 5.50 (dd, *J* = 10.5 and 2.0 Hz, 1H), 5.84 (dd, *J* = 16.5 and 10.5 Hz, 1H), 6.27 (t, *J* = 7.5 Hz, 1H), 6.39 (dd, *J* = 16.5 and 2.0 Hz, 1H), 6.99 (bs, 2H), 7.28-7.38 (m, 3H), 7.47-7.52 (m, 2H), 7.57-7.62 (m, 1H); 8.07-8.11 (m, 2H)

^{13}C NMR (100 MHz) : δ 11.03, 22.49, 60.25, 128.42, 128.60, 128.72, 128.91, 129.31, 130.02, 133.43, 136.40, 138.06, 165.90, 198.19

HRMS (ESI) exact mass calc′d for $C_{19}H_{19}NO_2Na$ $(M+Na)^+$: 316.1313

Found : 316.1313

N-[1-(4-Chlorophenyl)-1-oxo]butan-2-yl-N-phenylacrylamide (127e)



Reaction time : (0.5 + 3.0) h

Yield : 60 %

IR (neat) : *v* 1687, 1649, 1616, 1589 cm^{-1}

^1H NMR (500 MHz) : δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.62-1.72 (m, 1H), 1.82-1.92 (m, 1H), 5.52 (dd, *J* = 10.5 and 2.0 Hz, 1H), 5.83 (dd, *J* = 17.0 and 10.5 Hz, 1H), 6.20 (t, *J* = 7.0 Hz, 1H), 6.39 (dd,

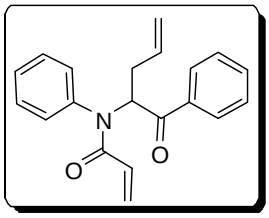
J = 16.5 and 2.0 Hz, 1H), 6.97 (bs, 2H), 7.29-7.38 (m, 3H), 7.45-7.49 (m, 2H), 8.03-8.07 (m, 2H)

^{13}C NMR (100 MHz) : δ 10.96, 22.48, 60.12, 128.26, 128.69, 128.85, 129.25, 129.40, 129.95, 130.05, 134.75, 137.89, 139.90, 165.93, 197.10

HRMS (ESI) exact mass calc′d for $C_{19}H_{18}ClNO_2Na$ $(M+Na)^+$: 350.0924

Found : 350.0929

N-(1-Oxo-1-phenylpent-4-en-2-yl)-N-phenylacrylamide (127f)



Reaction time : (0.5 + 3.0) h

Yield : 50 %

Mp : 113-116 ºC

IR (KBr) : ν 1687, 1654, 1610, 1594 cm^{-1}

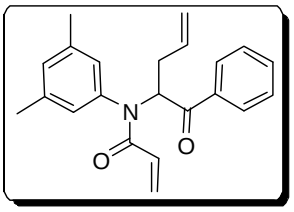
^{1}H NMR (500 MHz) : δ 2.39-2.48 (m, 1H), 2.60-2.68 (m, 1H), 5.06-5.11 (m, 1H), 5.12-5.17 (m, 1H), 5.50 (dd, J = 10.0 and 2.0 Hz, 1H), 5.76-5.86 (m, 2H), 6.39 (dd, J = 17.0 and 2.0 Hz, 1H), 6.48 (dd, J = 8.5 and 6.5 Hz, 1H), 6.99 (bs, 2H), 7.28-7.37 (m, 3H), 7.47-7.52 (m, 2H), 7.57-7.62 (m, 1H), 8.06-8.10 (m, 2 H)

^{13}C NMR (100 MHz) : δ 33.39, 58.31, 118.15, 128.33, 128.57, 128.64, 128.84, 128.94, 129.33, 130.12, 133.54, 134.04, 136.04, 137.90, 165.84, 197.47

HRMS (ESI) exact mass calc′d for $C_{20}H_{19}NO_2Na$ $(M+Na)^+$: 328.1313

Found : 328.1312

N-(3,5-Dimethylphenyl)-N-(1-oxo-1-phenylpent-4-en-2-yl)acrylamide (127g)



Reaction time : (0.5 + 3.0) h

Yield : 54 %

IR (neat) : *v* 1687, 1649, 1616, 1594 cm^{-1}

^1H NMR (500 MHz) : δ 2.22 (bs, 6 H), 2.40-2.49 (m, 1H), 2.61-2.69 (m, 1H), 5.06-5.11 (m, 1H), 5.12-5.18 (m, 1H), 5.49 (dd, *J* = 10.0 and 2.0 Hz, 1H), 5.77-5.89 (m, 2H)*, 6.34-6.65 (m, 4H)#, 7.46-7.52 (m, 2H), 7.56-7.61 (m, 2H), 8.03-8.08 (m, 2 H).

* It contains a dd (*J* = 16.5 and 10.0 Hz).

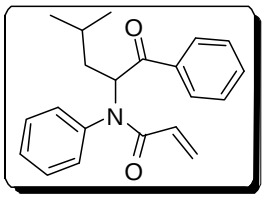
It contains a dd (*J* = 16.5 and 2.0 Hz) and it also contains another dd (*J* = 8.0 and 7.0 Hz)

^{13}C NMR (100 MHz) : δ 21.16, 33.49, 58.36, 118.03, 127.66, 128.26, 128.45, 128.59, 128.88, 130.44, 133.41, 134.28, 136.31, 137.59, 138.99, 165.77, 197.60

HRMS (ESI) exact mass calc′d for $C_{22}H_{23}NO_2Na$ $(M+Na)^+$: 356.1626

Found : 356.1624

N-(4-Methyl-1-oxo-1-phenylpentan-2-yl)-N-phenylacrylamide (127h)



Reaction time : (0.5 + 3.0) h

Yield : 55 %

IR (neat) : *v* 1693, 1660, 1610, 1594 cm^{-1}

^1H NMR (500 MHz) : δ 0.89 (d, *J* = 6.5 Hz, 3 H), 1.01 (d, *J* = 6.5 Hz, 3 H), 1.59-1.56 (m, 1H), 1.57-1.66 (m, 1H)*, 1.67-1.73 (m,

1H), 5.50 (dd, *J* = 10.0 and 2.0 Hz, 1H), 5.83 (dd, *J* = 16.5 and 10.0 Hz, 1H), 6.39 (dd, *J* = 17.0 and 2.0 Hz, 1H), 6.46 (dd, *J* = 8.0 and 6.0 Hz, 1H), 6.98 (bs, 2H), 7.28-7.38 (m, 3 H), 7.48-7.53 (m, 2H), 7.57-7.62 (m, 1H), 8.09-8.13 (m, 2 H).

* It contains moisture peak

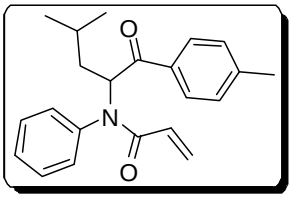
^{13}C NMR (100 MHz) : δ 22.58, 22.78, 24.83, 37.82, 56.92, 128.23, 128.38, 128.51, 128.58, 128.80, 129.17, 129.99, 133.31, 136.15, 137.93, 165.66, 198.10

HRMS (ESI) exact mass calc′d for $C_{21}H_{23}NO_2Na$ $(M+Na)^+$: 344.1626

Found : 344.1632

N-[4-Methyl-1-oxo-1-(4-methylphenyl)pentan-2-yl]-N-phenylacrylamide (127i)

Reaction time : (0.5 + 3.0) h



Yield : 57 %

Mp : 108-112 ºC

IR (KBr) : ν 1676, 1654, 1611, 1605 cm^{-1}

^{1}H NMR (500 MHz) : δ 0.90 (d, *J* = 6.5 Hz, 3 H), 1.01 (d, *J* = 6.5 Hz, 3 H), 1.48-1.55 (m, 1H), 1.56-1.65 (m, 1H)*, 1.66-1.73 (m, 1H), 2.43 (s, 3H), 5.49 (dd, *J* = 10.0 and 2.0 Hz, 1H), 5.82 (dd, *J* = 16.5 and 10.0 Hz, 1H), 6.39 (dd, *J* = 16.5 and 2.0 Hz, 1H), 6.45 (dd, *J* = 8.0 and 6.0 Hz, 1H), 6.97 (bs, 2H), 7.27-7.36 (m, 5H), 8.00 (d, 2H, *J* = 8.0 Hz, 2H).

* It contains moisture peak

^{13}C NMR (100 MHz) : δ 21.73, 22.70, 22.87, 24.91, 37.93, 56.79, 128.22, 128.53, 128.63, 128.74, 129.22, 129.59, 130.10, 133.73, 138.04, 144.24, 165.71, 197.70

HRMS (ESI) exact mass calc′d for $C_{22}H_{25}NO_2Na$ $(M+Na)^+$: 358.1783

Found : 358.1784

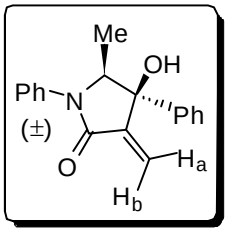
(4*S*,5*S*)/(4*R*,5*R*)[#]-4-Hydroxy-5-methyl-3-methylene-1,4-diphenylpyrrolidin-2-one (*syn*-128a)

A stirring solution of N-(1-oxo-1-phenylpropan-2-yl)-N-phenylacrylamide (0.139 g, 0.5 mmol) (**127a**), DABCO (0.056 g, 0.5 mmol) in dioxane (0.5 mL) and H_2O (0.5 mL) (1:1) was heated at 65 °C, for 6 h. The reaction mixture was diluted with water (2 mL) and extracted with DCM (2 X 15 mL). Combined organic layer was washed with water (10 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude thus obtained (in 86 % diastereoselectivity[$]) was purified by column chromatography [silica gel, EtOAc:Hexane (30:70)] to obtain diastereomeric mixture (***syn*-128a**+***anti*-128a**) in 86 % (0.120 g) isolated yield.

The major diastereomer (***syn*-128a**) was obtained by crystallization of diastereomeric mixture (***syn*-128a**+***anti*-128a**) (obtained through silicagel column chromatography) from EtOAc (3mL)-hexane (6mL) solvent system (initially diastereomeric mixture was dissolved in EtOAc at 70 °C, hexane was added to the solution and cooled at room temperature) in 60 % (0.083 g) yield as a colorless solid.

[#] It indicates the racemic nature and stereochemistry of the compound.

[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture. In the ^{1}H NMR spectrum of the crude mixture, 'CH_3'and olefinic protons (H_a and H_b) of major isomer appeared at δ 1.24(d), 5.55(s) and 6.38(s) respectively. The minor peaks appeared at δ 0.72(d), 5.67(s) and 6.50(s) are respectively due to 'CH_3' and olefinic protons (H_a and H_b) of minor diastereomer.



Yield (after crystallization) : 60 %

Mp : 183-186 ºC

IR (KBr) : ν 3227, 1687, 1650, 1594 cm^{-1}

^{1}H NMR (500 MHz) : δ 1.24 (d, J = 6.5 Hz, 3H), 2.32 (s, 1H), 4.34 (q, J = 6.5 Hz, 1H), 5.55 (s, 1H), 6.38 (s, 1H), 7.22-7.25 (m, 1H), 7.32-7.37 (m, 1H), 7.38-7.43 (m, 6H), 7.52-7.55 (m, 2H)

^{13}C NMR (100 MHz) : δ 12.56, 65.78, 76.71, 120.90, 124.23, 126.14, 126.29, 127.86, 128.42, 129.00, 137.04, 143.12, 148.17, 165.68

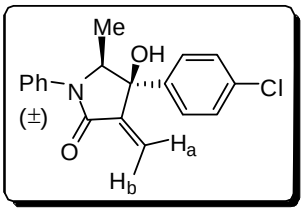
HRMS (ESI) exact mass calc′d for $C_{18}H_{17}NO_2H$ $(M+H)^+$: 280.1338

Found : 280.1332

HRMS (ESI) exact mass calc′d for $C_{18}H_{17}NO_2Na$ $(M+Na)^+$: 302.1157

Found : 302.1152

(4*S*,5*S*)/(4*R*,5*R*)[#]-4-(4-Chlorophenyl)-4-hydroxy-5-methyl-3-methylene-1-phenyl pyrrolidin-2-one (*syn*-128b)



Reaction time : 5 h

Diastereoselectivity[$] : 86 %

[#] It indicates the racemic nature and stereochemistry of the compound.

[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture. In the ^{1}H NMR spectrum of the crude mixture, 'CH_3', 'CH' and olefinic protons (H_a and H_b) of major isomer appeared at δ 1.21(d), 4.28(q), 5.53(s) and 6.38(s) respectively. The minor peaks appeared at δ 0.72(d), 4.36(q), 5.63(s) and 6.49(s) are respectively due to 'CH_3', 'CH' and olefinic protons (H_a and H_b) of minor diastereomer.

Yield of ***syn*-128b**+***anti*-128b**: 79 %
(after column purification)

Yield of ***syn*-128b** : 58 %
(after crystallization)

Mp : 188-190 ºC

IR (KBr) : ν 3326, 1676, 1649, 1589 cm^{-1}

^1H NMR (500 MHz) : δ 1.21 (d, J = 6.5 Hz, 3H), 2.66-2.71 (m, 1H), 4.27 (q, J = 6.5 Hz, 1H), 5.52 (s, 1H), 6.37 (s, 1H), 7.23-7.28 (m, 1H)*, 7.35-7.43 (m, 6H), 7.46-7.50 (m, 2H).

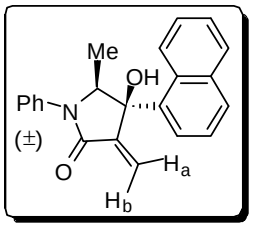
* It contains $CHCl_3$ peak

^{13}C NMR (100 MHz) : δ 12.38, 65.85, 76.36, 121.18, 124.38, 126.53, 127.74, 128.54, 129.05, 133.79, 136.79, 141.57, 147.84, 165.64

HRMS (ESI) exact mass calc′d for $C_{18}H_{16}ClNO_2Na$ $(M+Na)^+$: 336.0767

Found : 336.0770

(4*S*,5*S*)/(4*R*,5*R*)[#]-4-Hydroxy-5-methyl-3-methylene-4-(naphth-2-yl)-1-phenyl pyrrolidin-2-one (*syn*-128c)



Reaction time : 14 h

Diastereoselectivity[$] : 86 %

[#] It indicates the racemic nature and stereochemistry of the compound.

[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^1H NMR spectrum of the crude mixture. In the ^1H NMR spectrum of the crude mixture, 'CH_3' and olefinic protons (H_a and H_b) of major isomer appeared at δ 1.27(d), 5.56(s), and 6.42(s) respectively. The minor peaks appeared at δ 0.75(d), 5.70(s) and 6.54(s) are respectively due to 'CH_3'and olefinic protons (H_a and H_b) of minor diastereomer.

Yield of ***syn*-128c**+***anti*-128c**: 88 %
(after column purification)

Yield of ***syn*-128c** : 64 %
(after crystallization)

Mp : 195-197 ºC

IR (KBr) : ν 3265, 1682, 1650, 1594 cm^{-1}

^1H NMR (500 MHz) : δ 1.26 (d, J = 6.5 Hz, 3H), 2.64 (s, 1H), 4.45 (q, J = 6.0 Hz, 1H), 5.55 (s, 1H), 6.42 (s, 1H), 7.22-7.27 (m, 1H)*,

7.37-7.43 (m, 4H), 7.50-7.55 (m, 3H), 7.84-7.89 (m, 3H), 8.09 (d, J = 1.5 Hz, 1H).

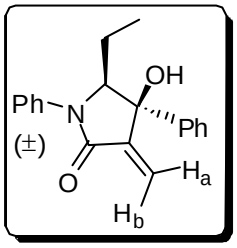
* It contains $CHCl_3$ peak

^{13}C NMR (100 MHz) : δ 12.56, 65.56, 76.89, 121.20, 124.15, 124.33, 125.35, 126.37, 126.46, 126.54, 127.63, 128.33, 128.39, 129.02, 132.84, 132.96, 137.00, 140.19, 148.15, 165.75

HRMS (ESI) exact mass calc′d for $C_{22}H_{19}NO_2Na$ $(M+Na)^+$: 352.1313

Found : 352.1310

(4*S*,5*S*)/(4*R*,5*R*)[#]-5-Ethyl-4-hydroxy-3-methylene-1,4-diphenylpyrrolidin-2-one (*syn*-128d)



Reaction time : 13 h

Diastereoselectivity[$] : 90 %

[#] It indicates the racemic nature and stereochemistry of the compound.

[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture. In the ^{1}H NMR spectrum of the crude mixture, 'CH_3', 'CH' and olefinic protons (H_a and H_b) of major isomer appeared at δ 0.82(t), 4.29(dd), 5.51(s), and 6.35(s) respectively. The minor peaks appeared at δ 0.29(t), 4.19(dd), 5.64(s) and 6.46(s) are respectively due to 'CH_3', 'CH' and olefinic protons (H_a and H_b) of minor diastereomer.

Yield of ***syn*-128d**+***anti*-128d**: 84 %
(after column purification)

Yield of ***syn*-128d** : 62 %
(after crystallization)

Mp : 124-126 ºC

IR (KBr) : ν 3210, 1682, 1660, 1594 cm^{-1}

^{1}H NMR (500 MHz) : δ 0.81 (t, J = 7.5 Hz, 3H), 1.73-1.91 (m, 2H), 2.54 (s, 1H), 4.29 (dd, J = 8.5 and 3.5 Hz, 1H), 5.50 (s, 1H), 6.34

(s, 1H), 7.21-7.25 (m, 1H), 7.29-7.34 (m, 1H), 7.35-7.45 (m, 6H), 7.49-7.54 (m, 2H)

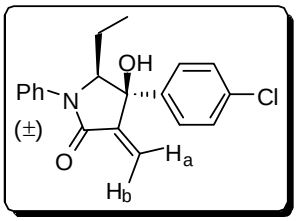
^{13}C NMR (100 MHz) : δ 10.49, 21.87, 70.88, 76.75*, 120.34, 124.07, 125.70, 126.32, 127.77, 128.50, 129.08, 137.51, 145.02, 149.07, 165.50.

* It almost merges with one of $CDCl_3$ peak

HRMS (ESI) exact mass calc′d for $C_{19}H_{19}NO_2H$ $(M+H)^+$: 294.1494

Found : 294.1495

(4*S*,5*S*)/(4*R*,5*R*)#-4-(4-Chlorophenyl)-5-ethyl-4-hydroxy-3-methylene-1-phenyl pyrrolidin-2-one (*syn*-128e)



Reaction time : 11 h

Diastereoselectivity$: 88 %

It indicates the racemic nature and stereochemistry of the compound.

$ Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture. In the ^{1}H NMR spectrum of the crude mixture , 'CH_3' and olefinic protons (H_a and H_b) of major isomer appeared at δ 0.78(t), 5.48(s) and 6.34(s) respectively. The minor peaks appeared at 0.34(t), 5.60(s) and 6.44(s) are respectively due to 'CH_3' and olefinic protons (H_a and H_b) of minor diastereomer.

Yield of ***syn*-128e**+***anti*-128e**: 80 %
(after column purification)

Yield of ***syn*-128e** : 63 %
(after crystallization)

Mp : 148-152 ºC

IR (KBr) : ν 3205, 1682, 1654, 1594 cm^{-1}

^{1}H NMR (500 MHz) : δ 0.78 (t, J = 7.5 Hz, 3H), 1.70-1.89 (m, 2H), 2.66 (s, 1H), 4.21 (dd, J = 8.5 and 3.5 Hz, 1H), 5.47 (s, 1H), 6.33

(s, 1H), 7.23-7.27 (m, 1H)*, 7.31-7.35 (m, 2H), 7.40 (d, *J* = 4.0 Hz, 4H), 7.44-7.48 (m, 2H).

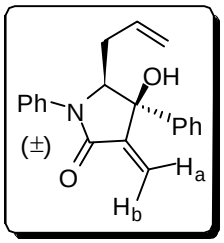
* It contains $CHCl_3$ peak

^{13}C NMR (100 MHz) : δ 10.51, 21.77, 70.96, 76.35, 120.68, 124.27, 126.56, 127.31, 128.60, 129.14, 133.65, 137.30, 143.50, 148.87, 165.37

HRMS (ESI) exact mass calc′d for $C_{19}H_{18}ClNO_2Na$ $(M+Na)^+$: 350.0924

Found : 350.0928

(4*S*,5*S*)/(4*R*,5*R*)[#]-5-Allyl-4-hydroxy-3-methylene-1,4-diphenylpyrrolidin-2-one (*syn*-128f)



Reaction time : 13 h

Diastereoselectivity[$] : 92 %

Yield of ***syn*-128f**[*] : 78 %

[#] It indicates the racemic nature and stereochemistry of the compound.
[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^1H NMR spectrum of the crude mixture. In the ^1H NMR spectrum of the crude mixture, 'CH' and olefinic protons (H_a and H_b) of major isomer appeared at δ 4.45(dd), 5.58(s) and 6.37(s) respectively. The minor peaks appeared at δ 4.35(dd), 5.67(s) and 6.48(s) are respectively due to 'CH' and olefinic protons (H_a and H_b) of minor diastereomer.
[*] It was separated by column chromotograghy.

Mp : 130-133 ºC

IR (KBr) : ν 3227, 1687, 1654, 1594 cm^{-1}

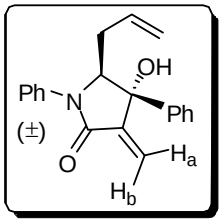
^1H NMR (500 MHz) : δ 2.55-2.66 (m, 3H), 4.45 (dd, *J* = 7.0 and 4.0 Hz, 1H), 5.00-5.04 (m, 1H), 5.05-5.10 (m, 1H), 5.58 (s, 1H), 5.71-5.81 (m, 1H), 6.37 (s, 1H), 7.21-7.25 (m, 1H), 7.30-7.34 (m, 1H), 7.35-7.43 (m, 4H), 7.46-7.51 (m, 4H)

^{13}C NMR (100 MHz) : δ 33.22, 69.31, 76.84, 118.32, 120.55, 123.86, 125.41, 126.29, 127.77, 128.50, 129.06, 134.04, 137.24, 145.08, 148.34, 165.48

HRMS (ESI) exact mass calc′d for $C_{20}H_{19}NO_2H$ $(M+H)^+$: 306.1494

Found : 306.1496

(4*R*,5*S*)/(4*S*,5*R*)[#]-5-Allyl-4-hydroxy-3-methylene-1,4-diphenylpyrrolidin-2-one (*anti*-128f)



Yield of ***anti*-128f**[*] : 3 %

Mp : 147-150 ºC

IR (KBr) : ν 3353, 1676, 1649, 1594 cm^{-1}

^{1}H NMR (500 MHz) : δ 1.89-196 (m, 1H), 1.98-2.06 (m, 1H), 2.90 (bs, 1H), 4.34 (dd, J = 8.5 and 4.0 Hz, 1H), 4.49-4.56 (m, 1H), 4.61-4.66 (m, 1H), 4.91-5.01 (m, 1H), 5.63 (s, 1H), 6.45 (s, 1H), 7.20-7.25 (m, 1H), 7.33-7.42 (m, 5H), 7.53-7.61 (m, 4H)

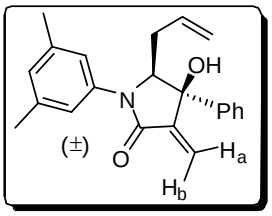
^{13}C NMR (100 MHz) : δ 35.45, 70.61, 78.17, 117.67, 121.67, 123.74, 126.16, 127.81, 128.14, 128.33, 129.12, 132.51, 137.66, 139.43, 147.28, 165.43

HRMS (ESI) exact mass calc′d for $C_{20}H_{19}NO_2Na$ $(M+Na)^+$: 328.1313

Found : 328.1317

[#] It indicates the racemic nature and stereochemistry of the compound.
[*] It was separated by column chromotograghy.

(4*S*,5*S*)/(4*R*,5*R*)[#]-5-Allyl-1-(3,5-dimethylphenyl)-4-hydroxy-3-methylene-4-phenyl pyrrolidin-2-one (*syn*-128g)



Reaction time : 50 h

Diastereoselectivity[$] : 92 %

[#] It indicates the racemic nature and stereochemistry of the compound.

[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture. In the ^{1}H NMR spectrum of the crude mixture, 'CH' and olefinic protons (H_a and H_b) of major isomer appeared at δ 4.39(dd), 5.55(s) and 6.34(s) respectively. The minor peaks appeared at δ 4.30(dd), 5.64(s) and 6.45(s) are respectively due to 'CH' and olefinic protons (H_a and H_b) of minor diastereomer.

Yield of ***syn*-128g**+***anti*-128g**: 77 %
(after column purification)

Yield of ***syn*-128g** : 56 %
(after crystallization)

Mp : 170-172 ºC

IR (KBr) : ν 3260, 1676, 1649, 1600 cm^{-1}

^{1}H NMR (500 MHz) : δ 2.31 (s, 6H), 2.53-2.63 (m, 2H), 2.66 (s, 1H), 4.39 (dd, J = 7.0 and 3.5 Hz, 1H), 5.00-5.05 (m, 1H), 5.06-5.12 (m, 1H), 5.55 (s, 1H), 5.71-5.81 (m, 1H), 6.33 (s, 1H), 6.85-6.89 (m, 1H), 7.07 (s, 2H), 7.29-734 (m, 1H), 7.35-7.40 (m, 2H), 7.47-7.50 (m, 2H)

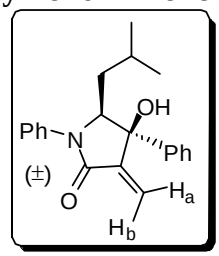
^{13}C NMR (100 MHz) : δ 21.43, 33.29, 69.35, 77.00, 118.40, 120.27, 121.72, 125.35, 127.80, 128.24, 128.57, 134.27, 137.07, 138.82, 145.20, 148.67, 165.34

HRMS (ESI) exact mass calc′d for $C_{22}H_{23}NO_2H$ $(M+H)^+$: 334.1807

Found : 334.1810

(4*S*,5*S*)/(4*R*,5*R*)[#]-4-Hydroxy-5-*iso*-butyl-3-methylene-1,4-diphenylpyrrolidin-2-one

(*syn*-128h)



Reaction time : 50 h

Diastereoselectivity[$] : 92 %

[#] It indicates the racemic nature and stereochemistry of the compound.

[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture. In the ^{1}H NMR spectrum of the crude mixture, 'CH' and olefinic protons (H_a and H_b) of major isomer appeared at δ 4.39(dd), 5.48(s) and 6.34(s) respectively. The minor peaks appeared at δ 4.29(dd), 5.60(s) and 6.44(s) are respectively due to 'CH' and olefinic protons (H_a and H_b) of minor diastereomer.

Yield of ***syn*-128h**+***anti*-128h**: 82 %
(after column purification)

Yield of ***syn*-128h** : 59 %
(after crystallization)

Mp : 160-162 ºC

IR (KBr) : ν 3232, 1682, 1650, 1594 cm^{-1}

^{1}H NMR (500 MHz) : δ 0.61 (d, J = 6.5 Hz, 3H), 0.73 (d, J = 6.5 Hz, 3H), 1.32-1.40 (m, 1H), 1.55-1.66 (m, 1H)[*], 1.78-1.85 (m, 1H), 2.39 (s, 1H), 4.38 (dd, J = 9.5 and 4.0 Hz, 1H), 5.47 (s, 1H), 6.34 (s, 1H), 7.23-7.27 (m, 1H)[@], 7.30-7.35 (m, 1H), 7.36-7.43 (m, 6H), 7.49-7.54 (m, 2H).

[*] It contains moisture peak. [@] It contains $CHCl_3$ peak

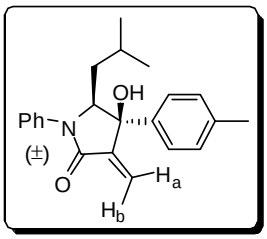
^{13}C NMR (100 MHz) : δ 21.44, 23.56, 24.67, 37.83, 67.88, 76.84[&], 120.79, 124.73, 125.93, 126.50, 127.68, 128.39, 129.02, 137.29, 144.38, 149.18, 165.57

[&] It almost merges with one of $CDCl_3$ peak

HRMS (ESI) exact mass calc′d for $C_{21}H_{23}NO_2H$ $(M+H)^+$: 322.1807

Found : 322.1805

(4*S*,5*S*)/(4*R*,5*R*)[#]-4-Hydroxy-5-*iso*-butyl-3-methylene-1-phenyl-4-(4-methylphenyl) pyrrolidin-2-one (*syn*-128i)



Reaction time : 96 h

Diastereoselectivity[$] : 92 %

[#] It indicates the racemic nature and stereochemistry of the compound.

[$] Diastereomeric ratio was determined by the integration ratio of olefinic protons (H_a or H_b) of major and minor diastereomers in the ^{1}H NMR spectrum of the crude mixture. In the ^{1}H NMR spectrum of the crude mixture, 'CH' and olefinic protons (H_a and H_b) of major isomer appeared at δ 4.37(dd), 5.48(s) and 6.33(s) respectively. The minor peaks appeared δ 4.27(dd), 5.59(s) and 6.42(s) are respectively due to 'CH' and olefinic protons (H_a and H_b) of minor diastereomer.

Yield of ***syn*-128i+*anti*-128i** : 81 %
(after column purification)

Yield of ***syn*-128i** : 56 %
(after crystallization)

Mp : 190-192 ºC

IR (KBr) : ν 3265, 1682, 1650, 1589 cm^{-1}

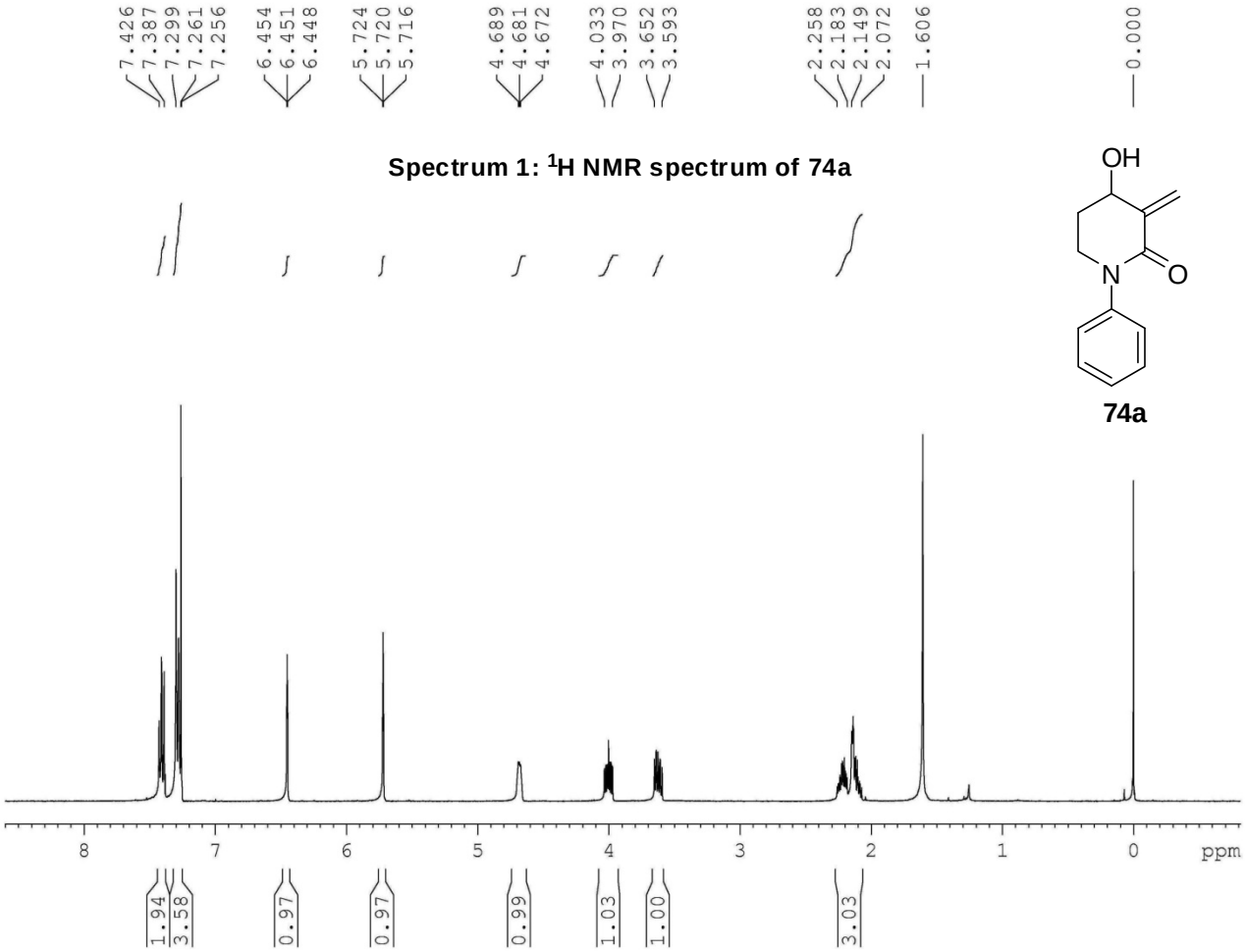
^{1}H NMR (500 MHz) : δ 0.63 (d, J = 6.5 Hz, 3H), 0.73 (d, J = 6.5 Hz, 3H), 1.31-1.38 (m, 1H), 1.57-1.67 (m, 1H)[*], 1.77-1.84 (m, 1H), 2.36 (s, 3H), 2.45 (s, 1H), 4.37 (dd, J = 9.5 and 4.0 Hz, 1H), 5.47 (s, 1H), 6.32 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.22-7.27 (m, 1H)[@], 7.36-7.41 (m, 6H).

[*] It contains moisture peak. [@] It contains $CHCl_3$ peak

^{13}C NMR (100 MHz) : δ 21.10, 21.55, 23.54, 24.70, 37.95, 67.80, 76.84, 120.54, 124.60, 125.79, 126.39, 128.98, 129.08, 137.37, 141.49, 149.19, 165.56

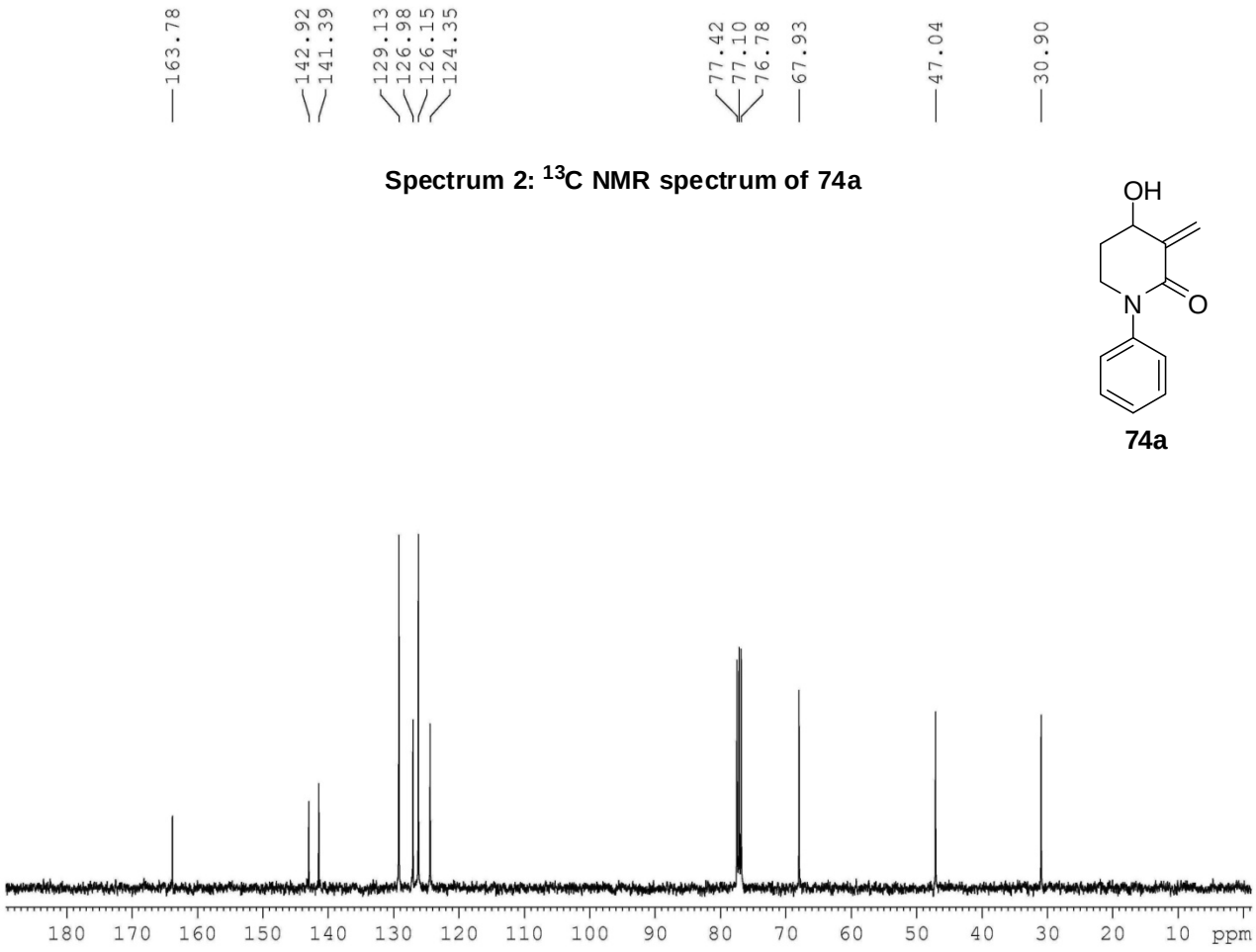
HRMS (ESI) exact mass calc′d for $C_{22}H_{25}NO_2Na$ $(M+Na)^+$: 358.1783

Found : 358.1783



Spectrum 1: ^{1}H NMR spectrum of 74a

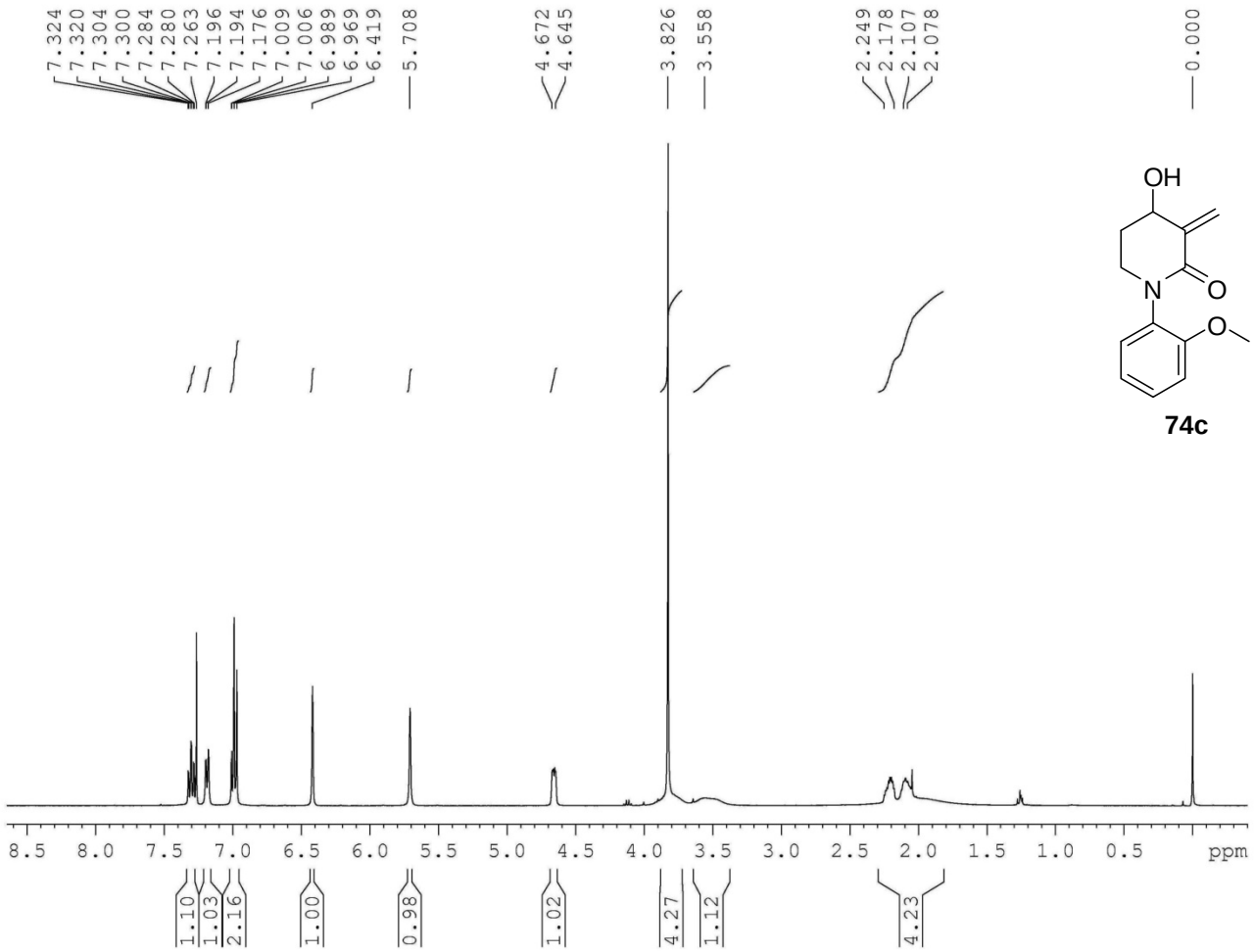
74a



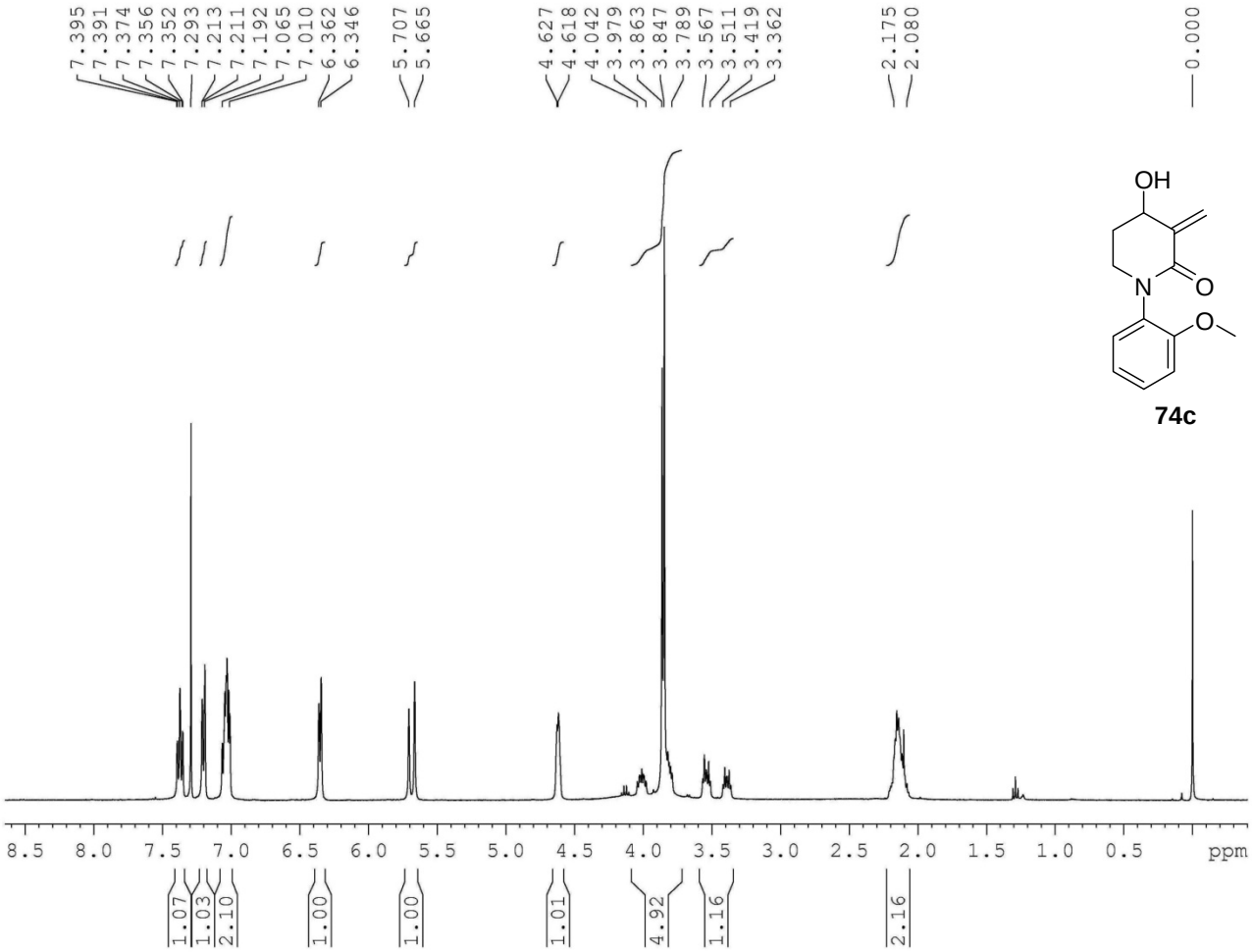
Spectrum 2: ^{13}C NMR spectrum of 74a

74a

Spectrum 3: ^{1}H NMR spectrum of 74c at 23 ^{0}C

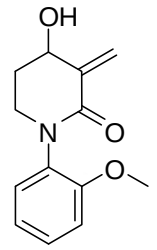


Spectrum 4: ^{1}H NMR spectrum of 74c at -36 ^{0}C

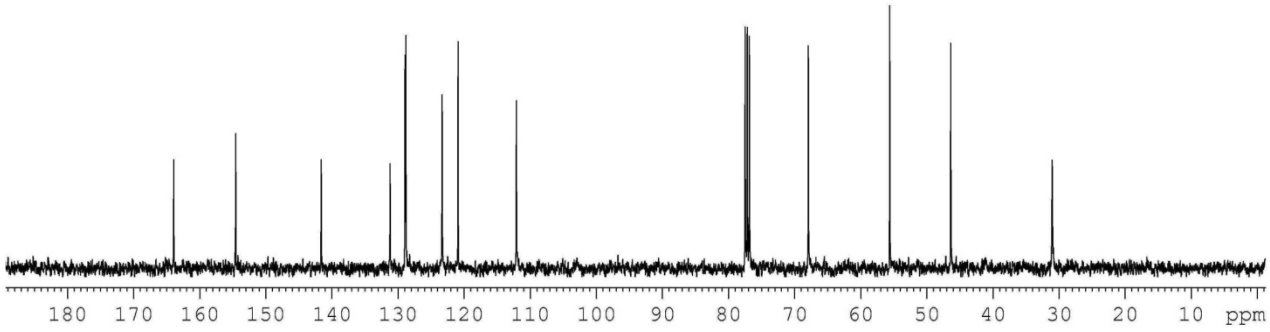


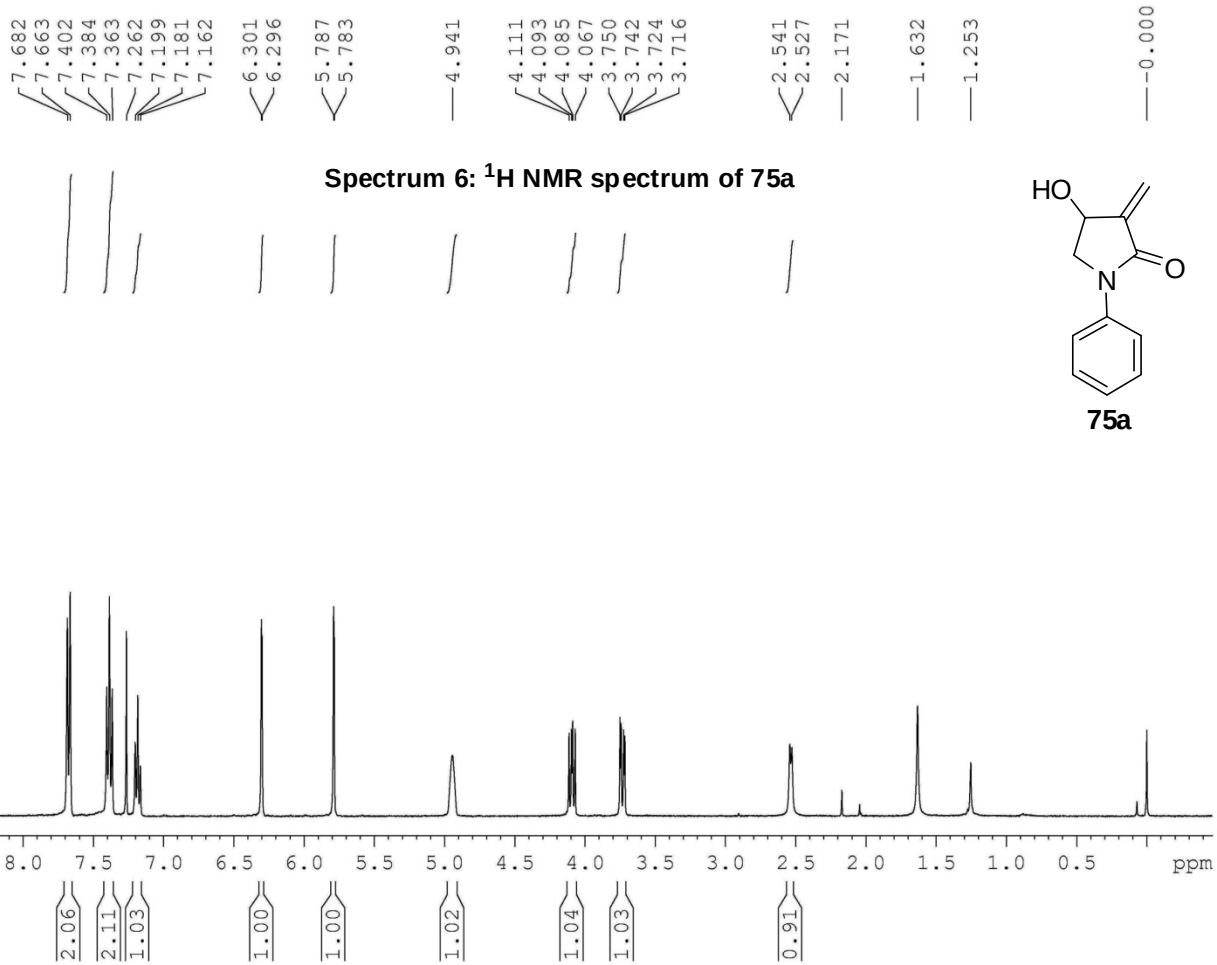
74c

Spectrum 5: ^{13}C NMR spectrum of 74c



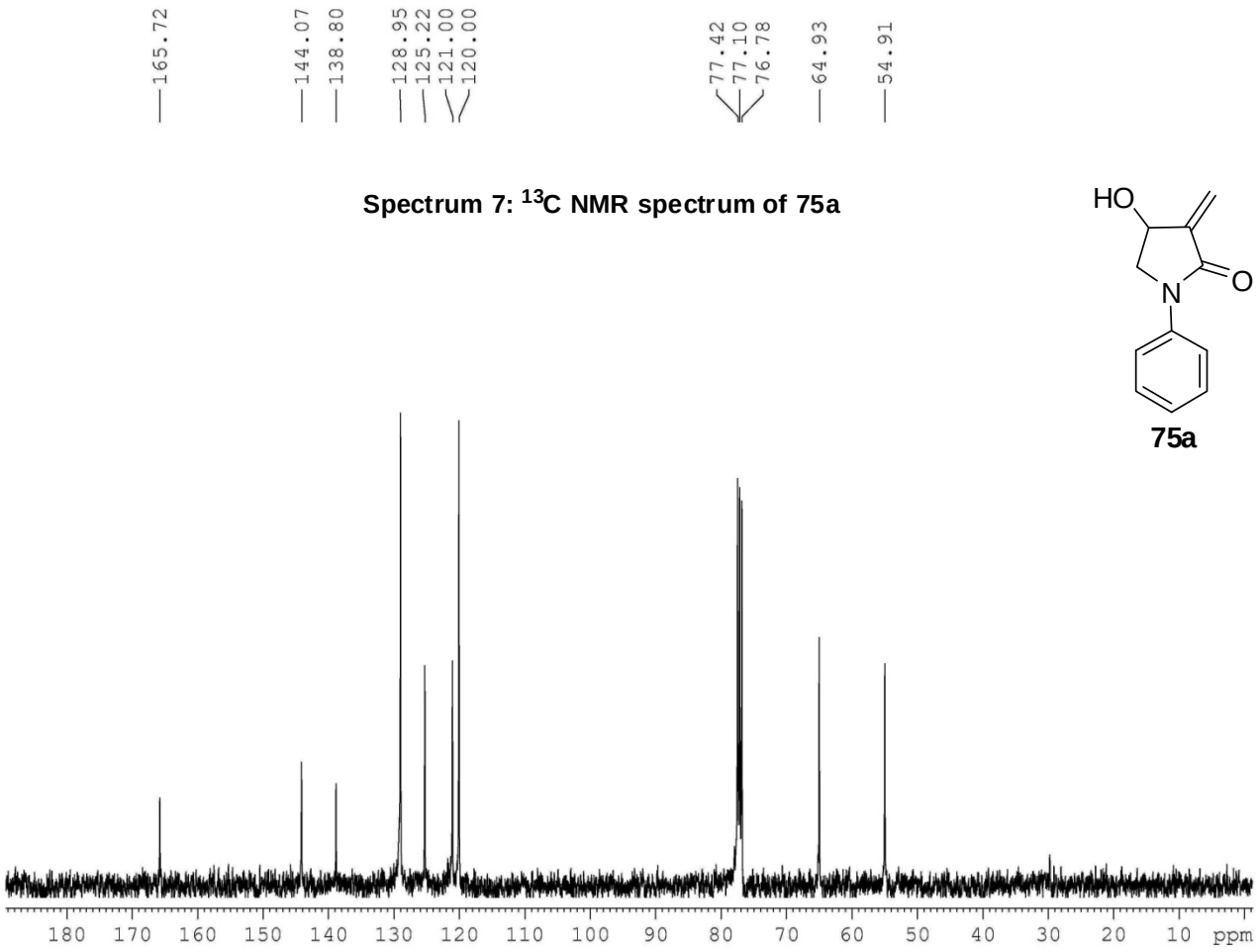
74c





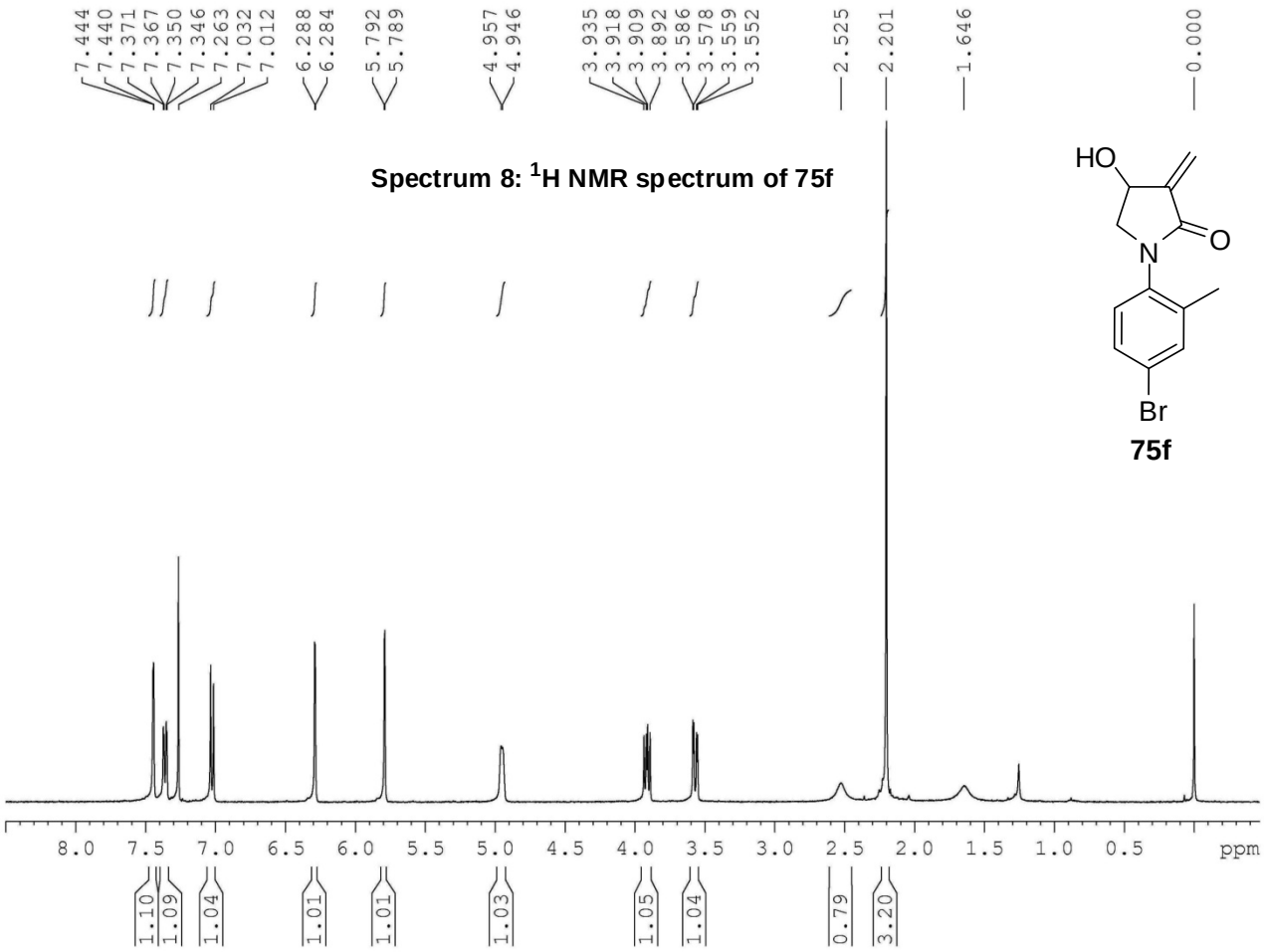
Spectrum 6: ^{1}H NMR spectrum of 75a

75a



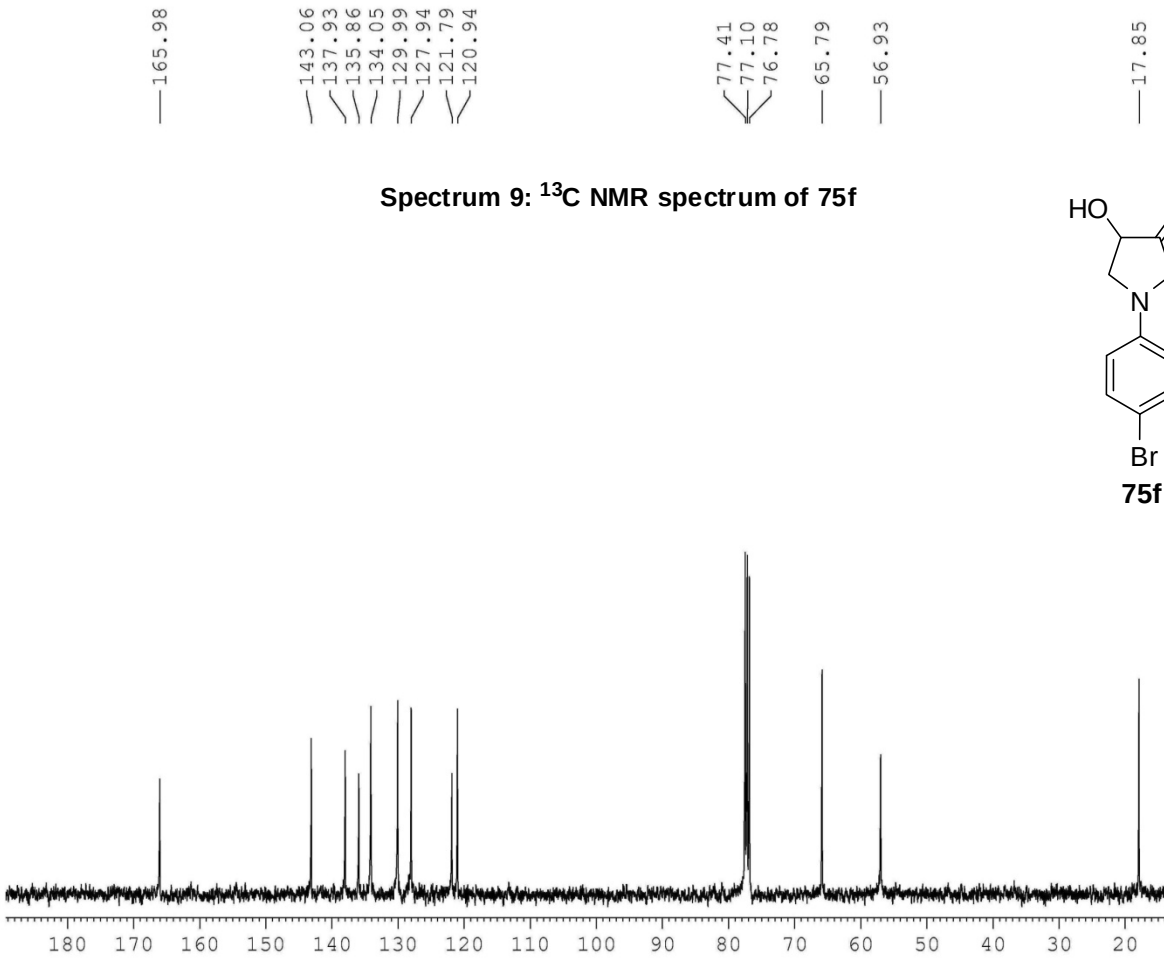
Spectrum 7: ^{13}C NMR spectrum of 75a

75a



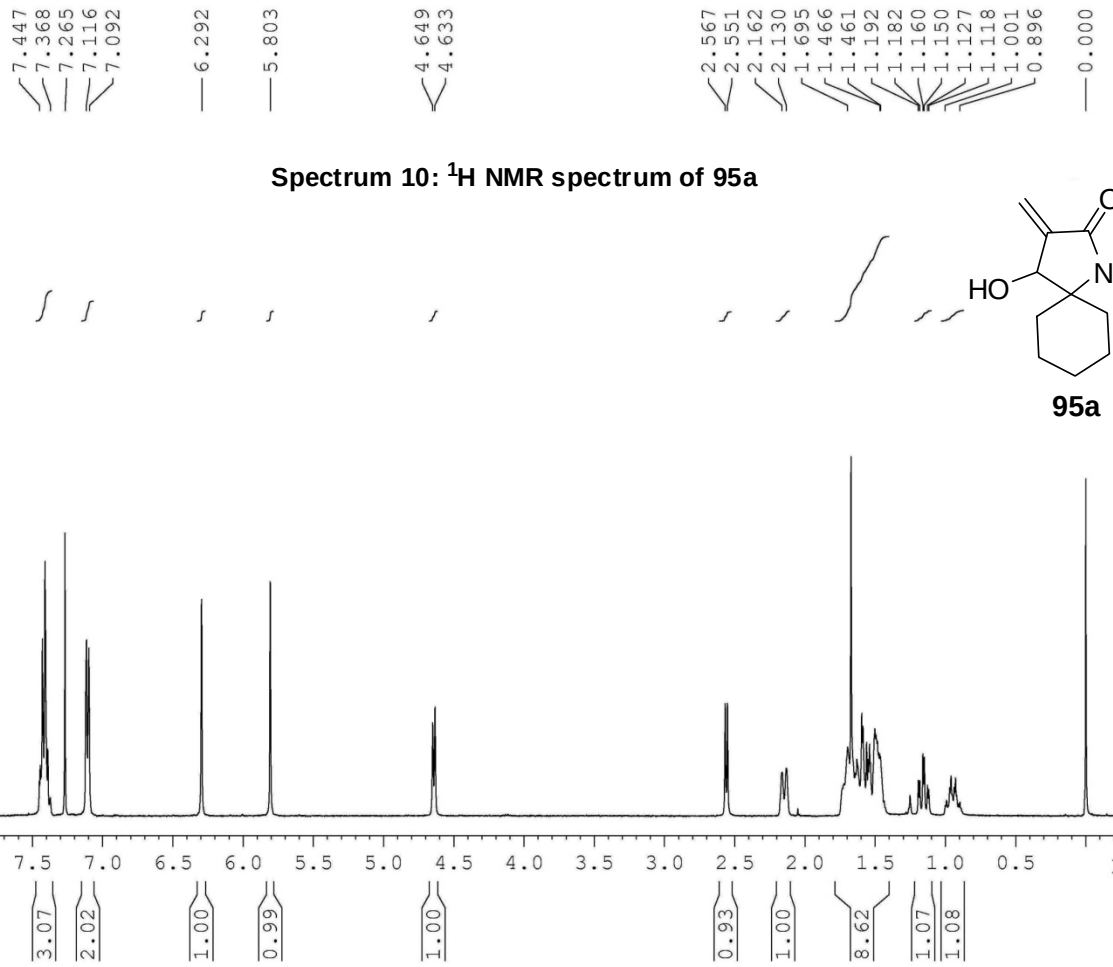
Spectrum 8: ^{1}H NMR spectrum of 75f

75f



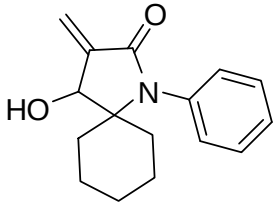
Spectrum 9: ^{13}C NMR spectrum of 75f

75f

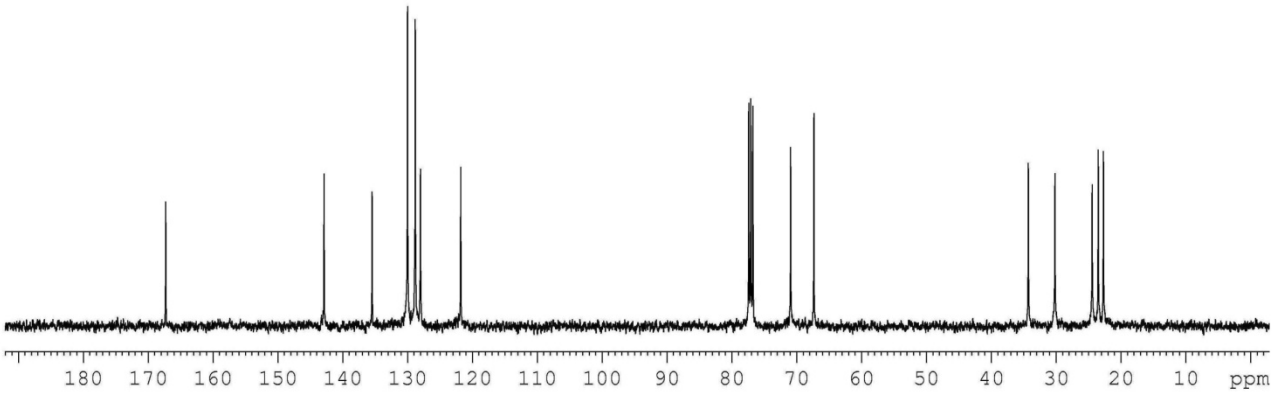


Spectrum 10: ^{1}H NMR spectrum of 95a

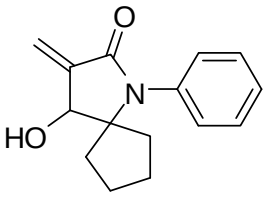
Spectrum 11: ^{13}C NMR spectrum of 95a



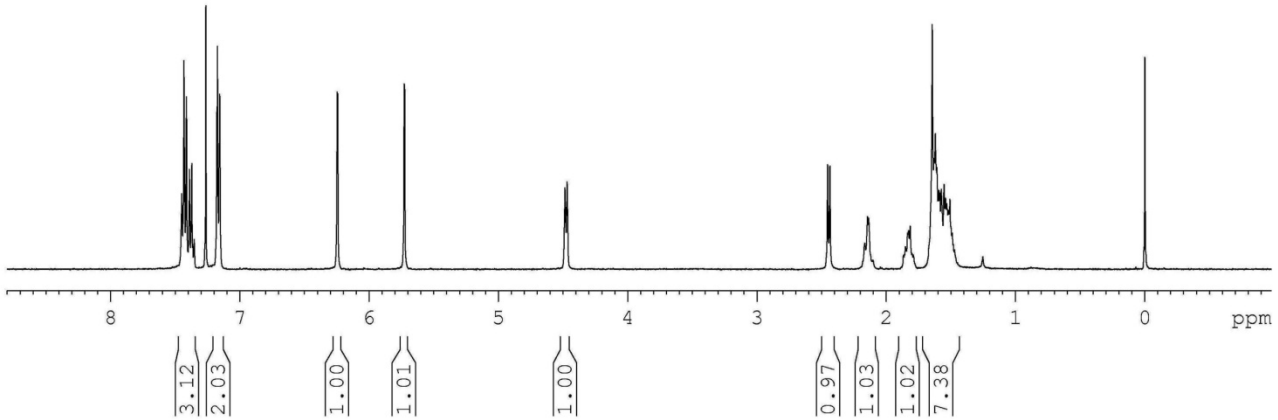
95a



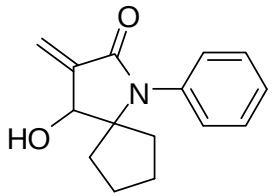
Spectrum 12: ^{1}H NMR spectrum of 101a



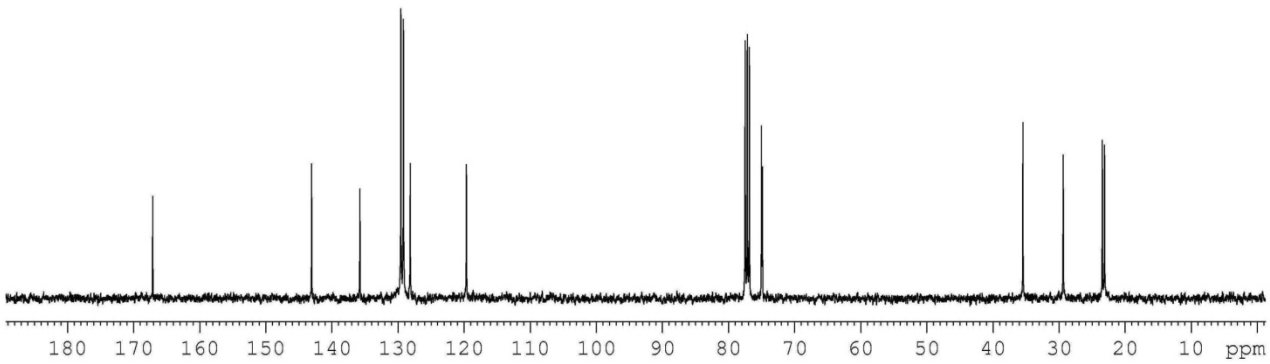
101a

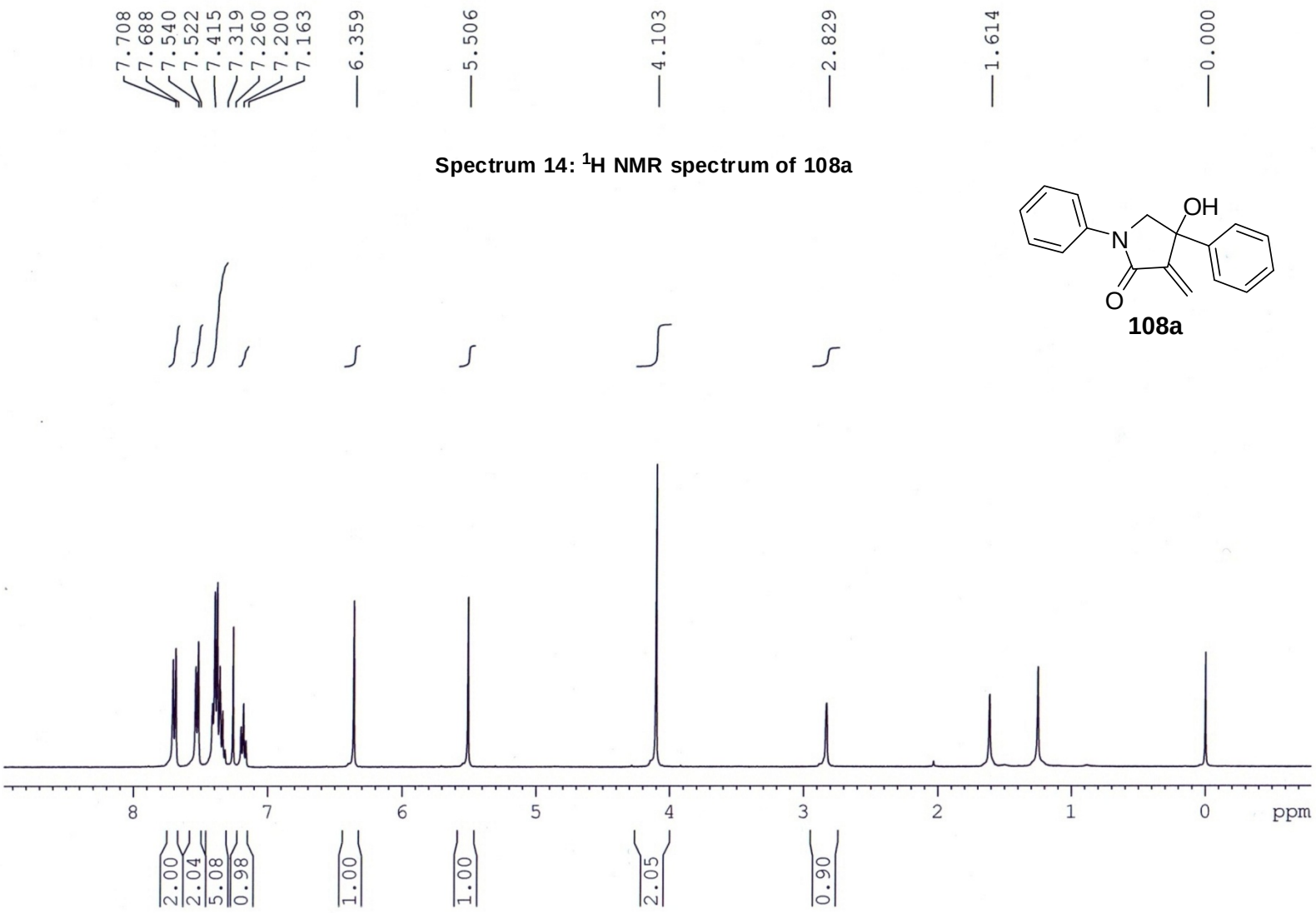


Spectrum 13: ^{13}C NMR spectrum of 101a



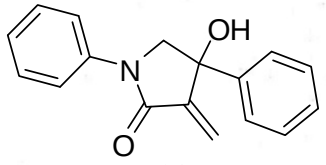
101a



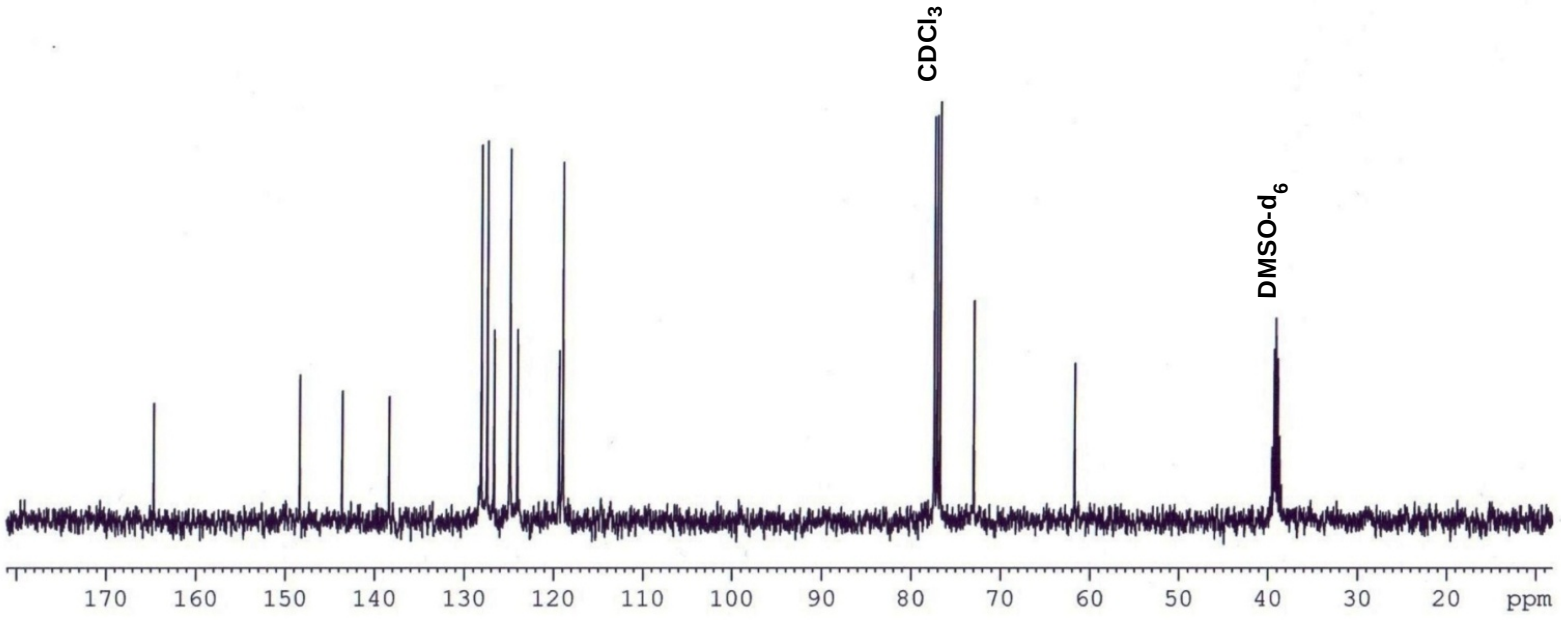


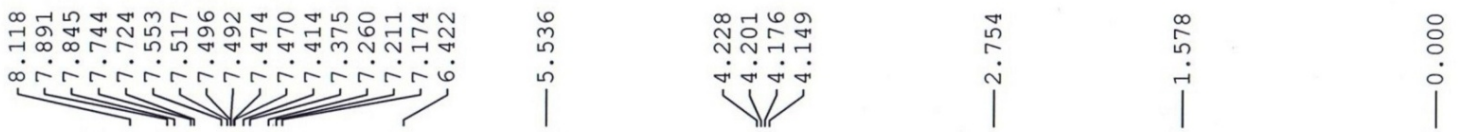
Spectrum 14: ^{1}H NMR spectrum of 108a

Spectrum 15: ^{13}C NMR spectrum of 108a

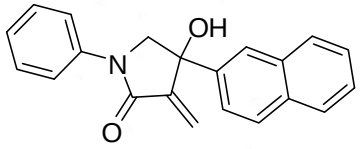


108a

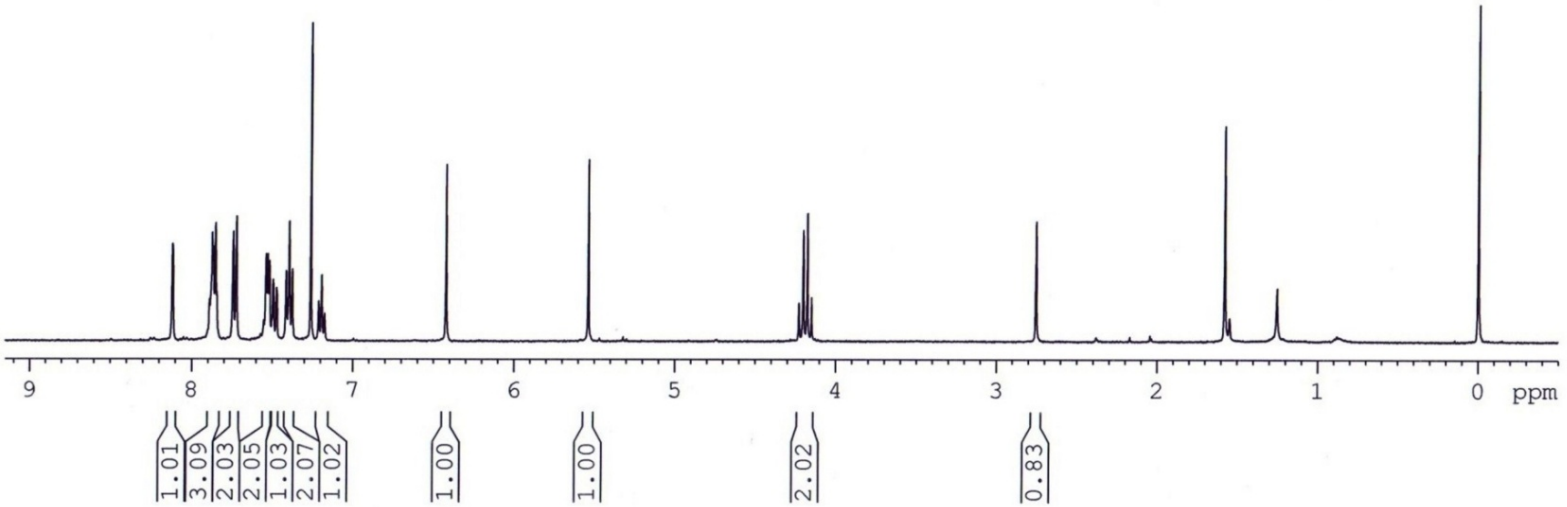


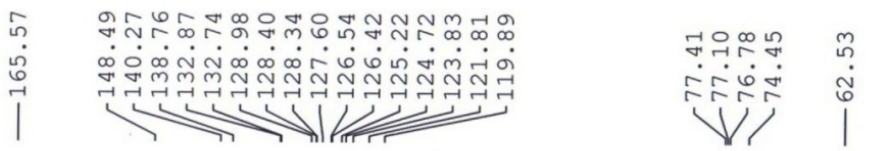


Spectrum 16: ^{1}H NMR spectrum of 108c

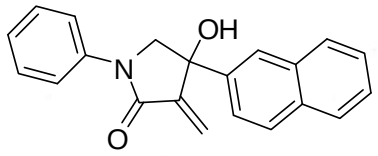


108c

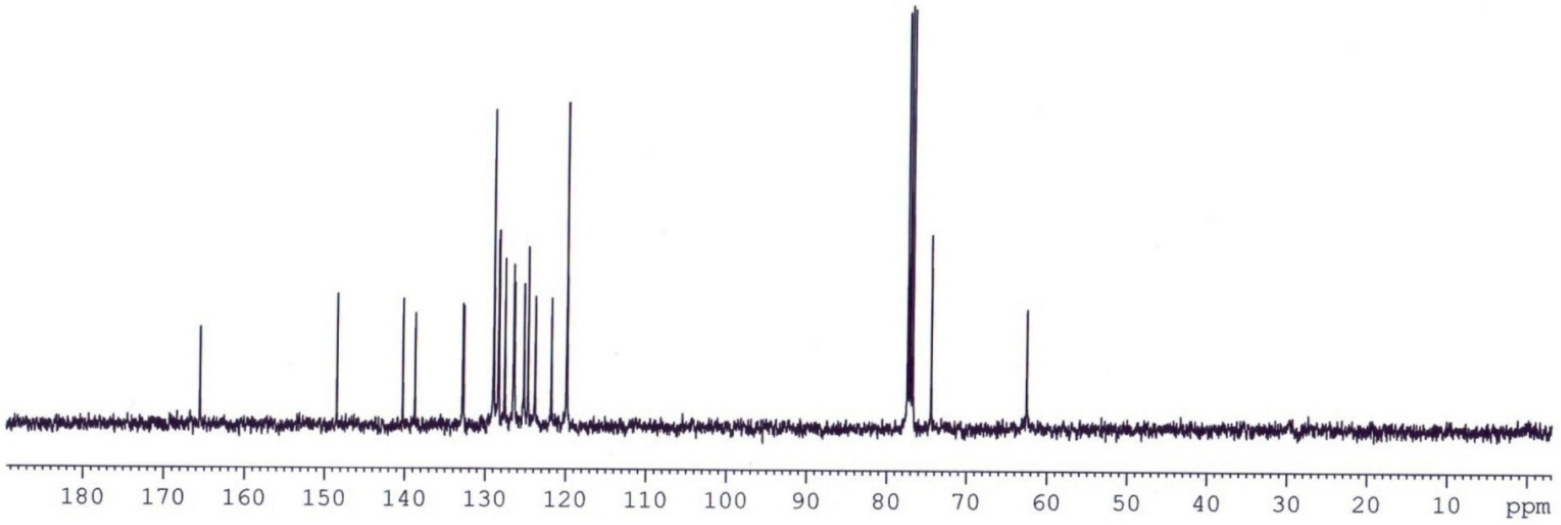


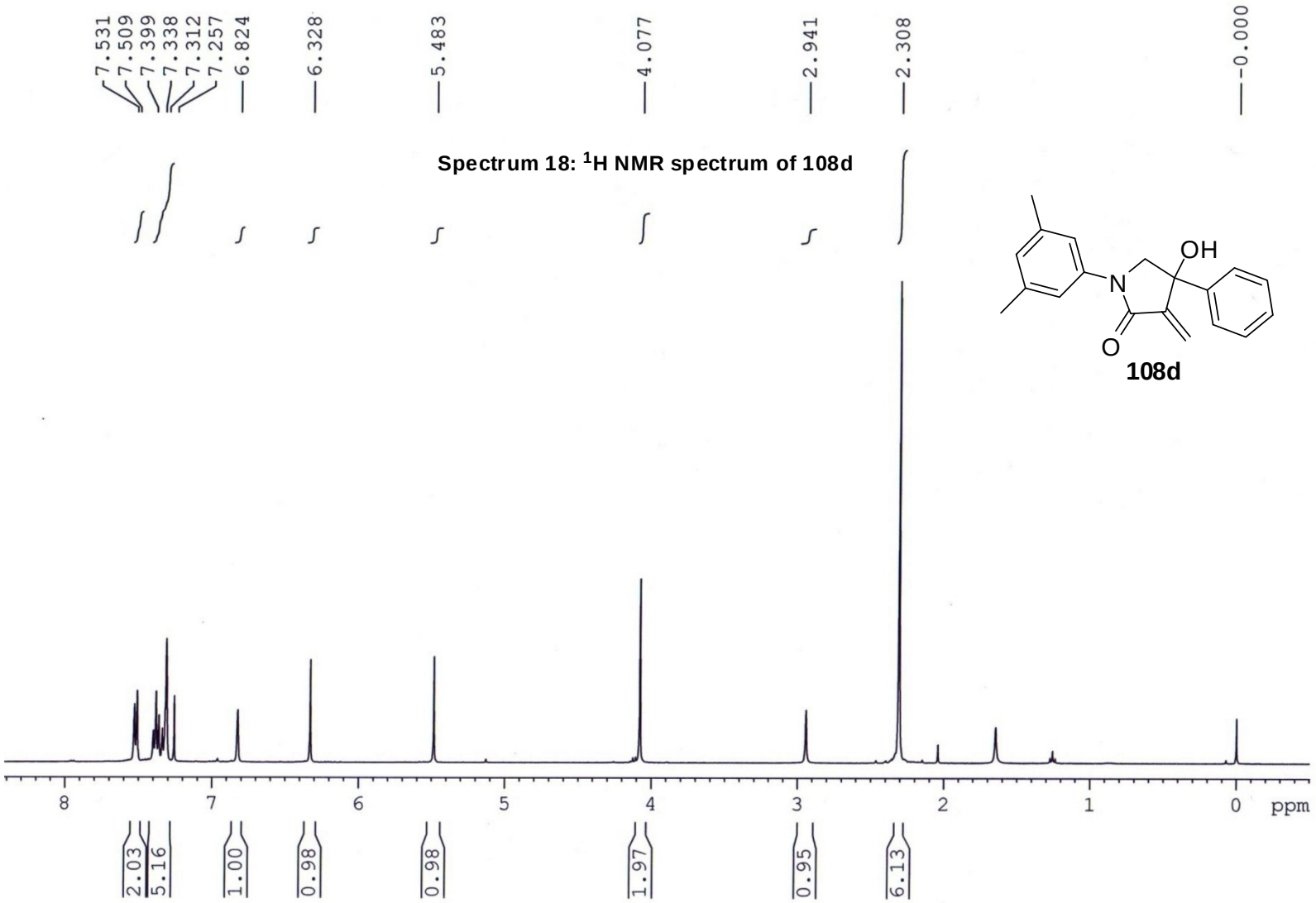


Spectrum 17: ^{13}C NMR spectrum of 108c



108c

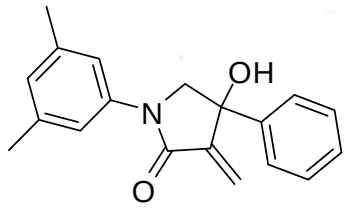




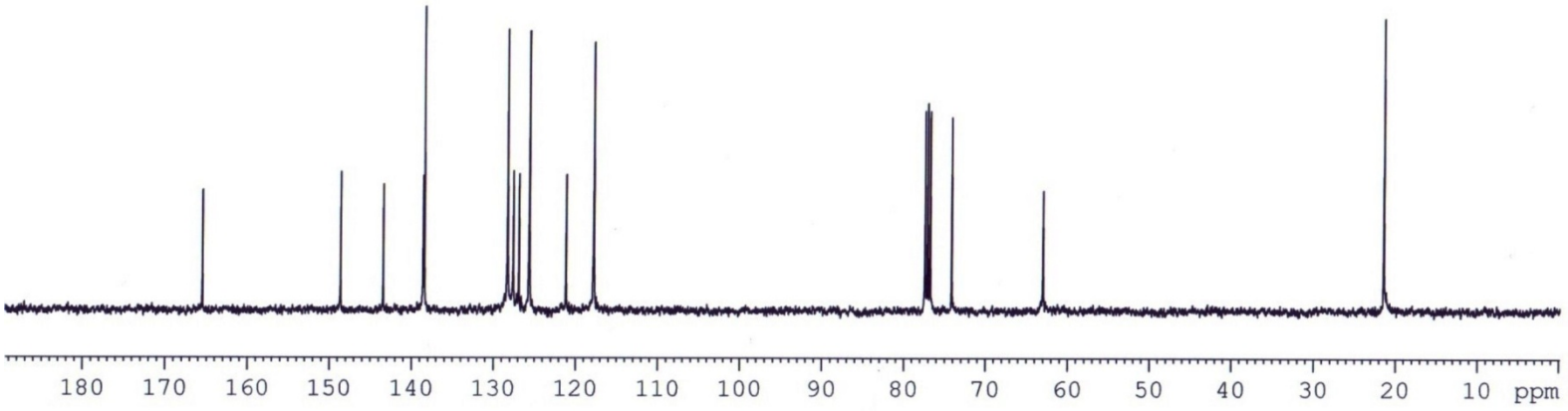
Spectrum 18: ^{1}H NMR spectrum of 108d

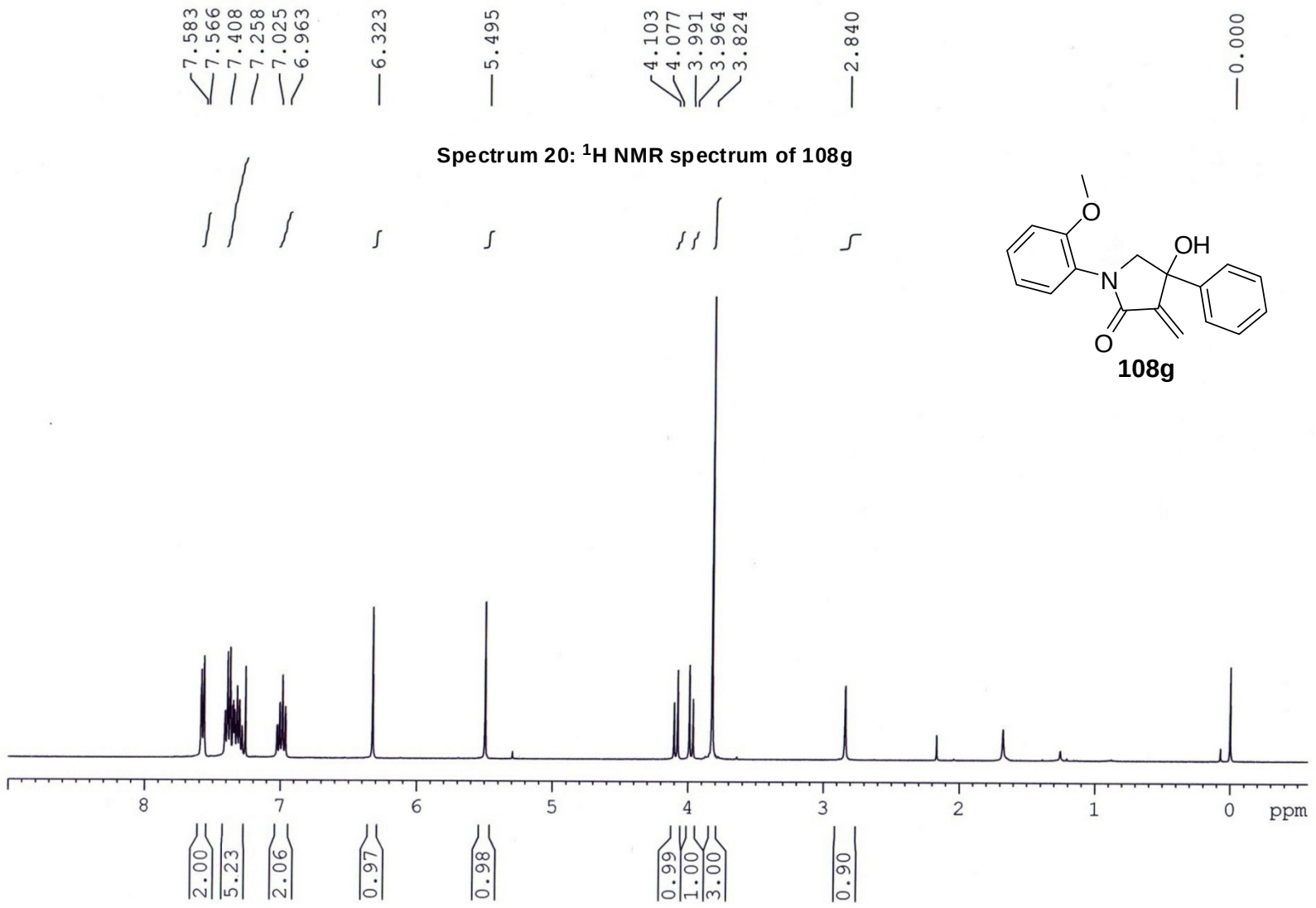
108d

Spectrum 19: ^{13}C NMR spectrum of 108d

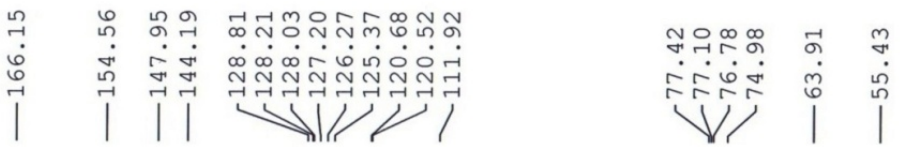


108d

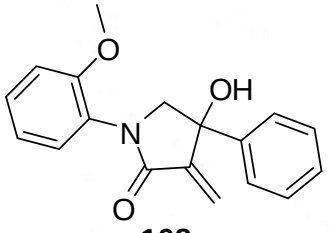




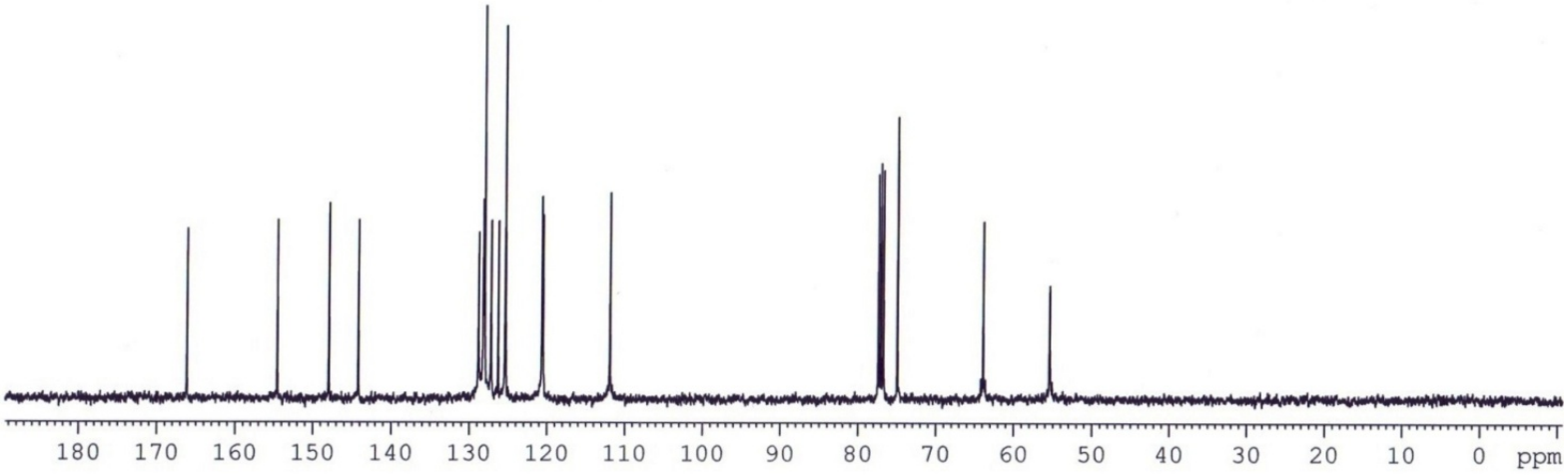
Spectrum 20: ^{1}H NMR spectrum of 108g

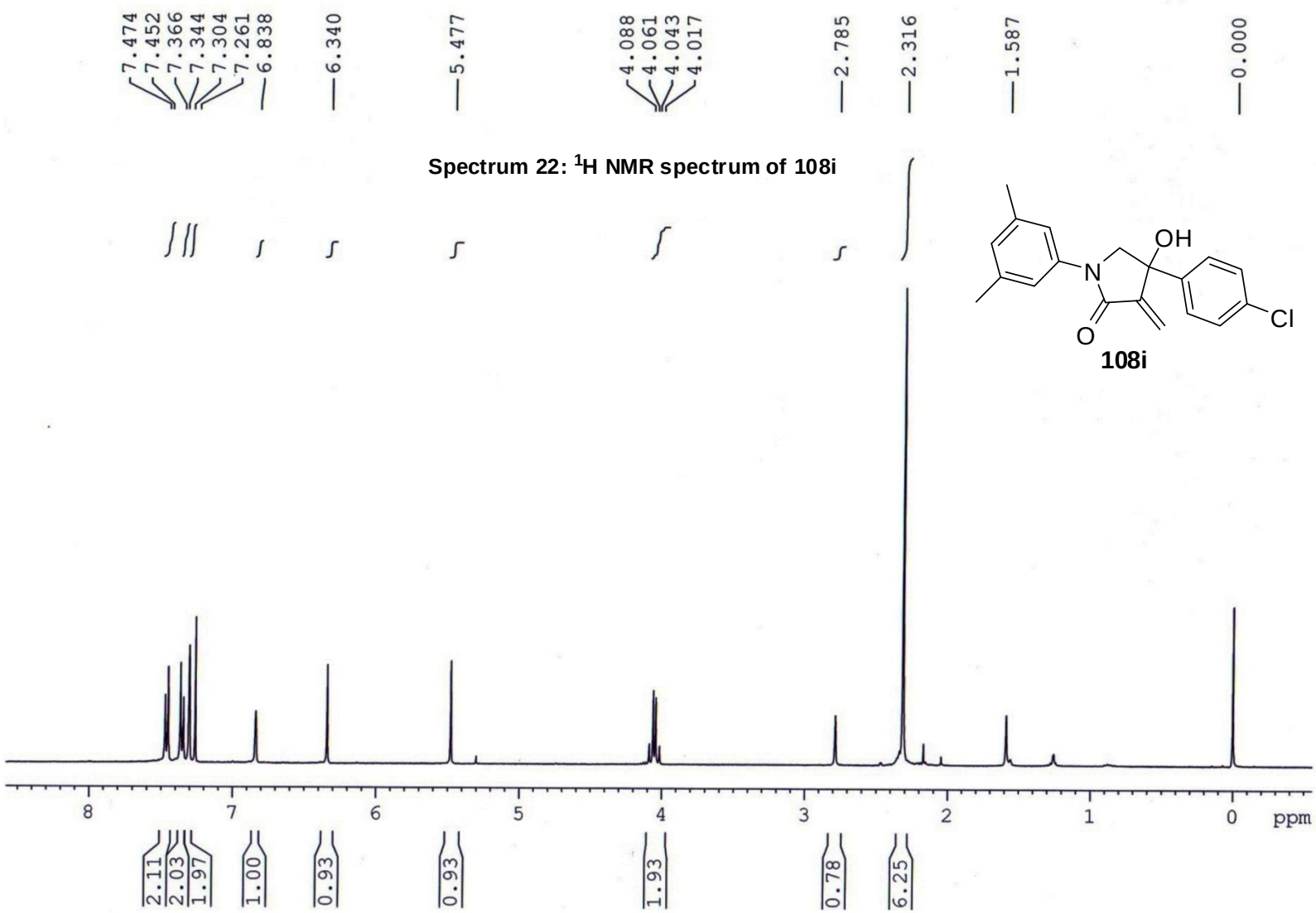


Spectrum 21: ^{13}C NMR spectrum of 108g



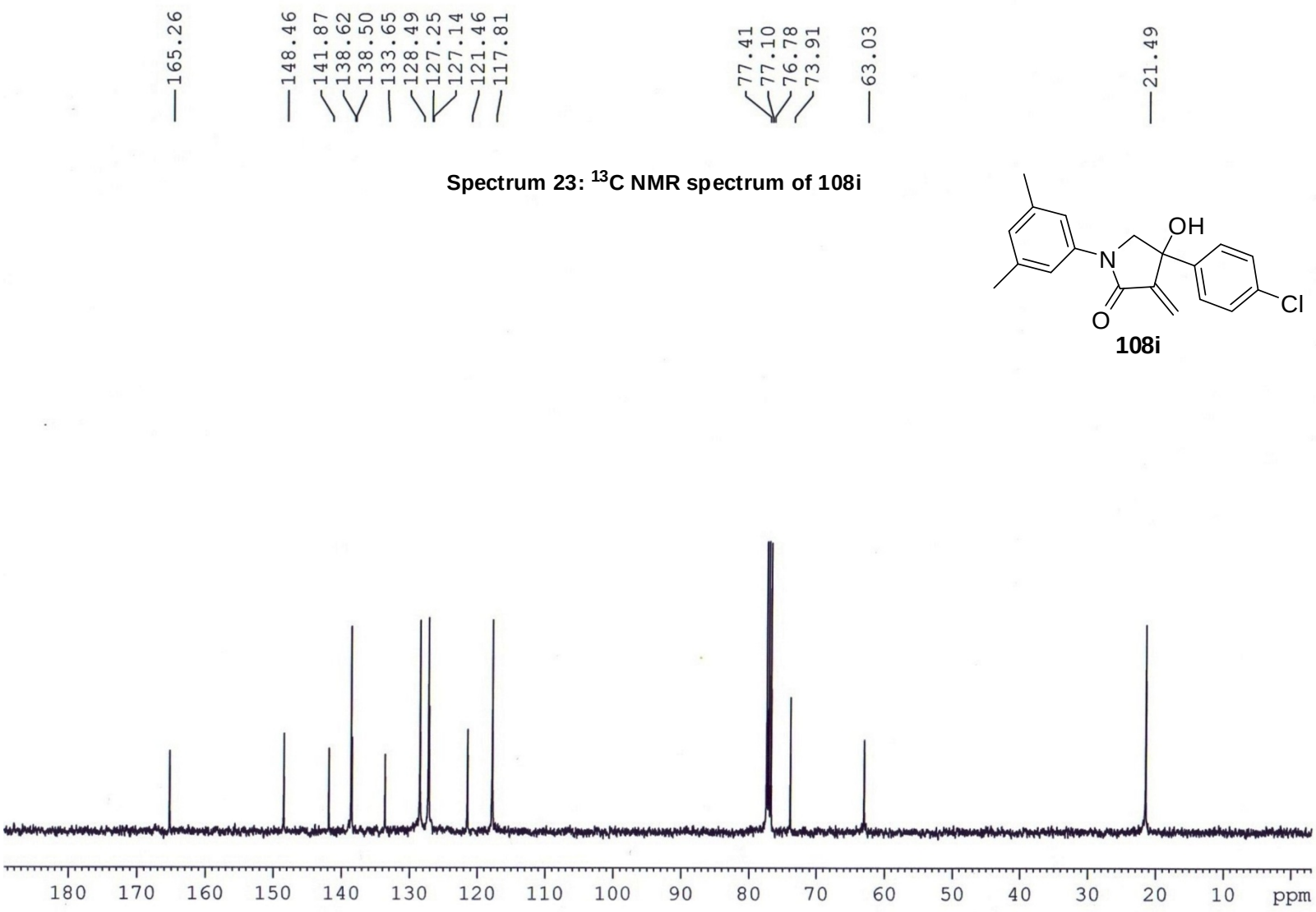
108g





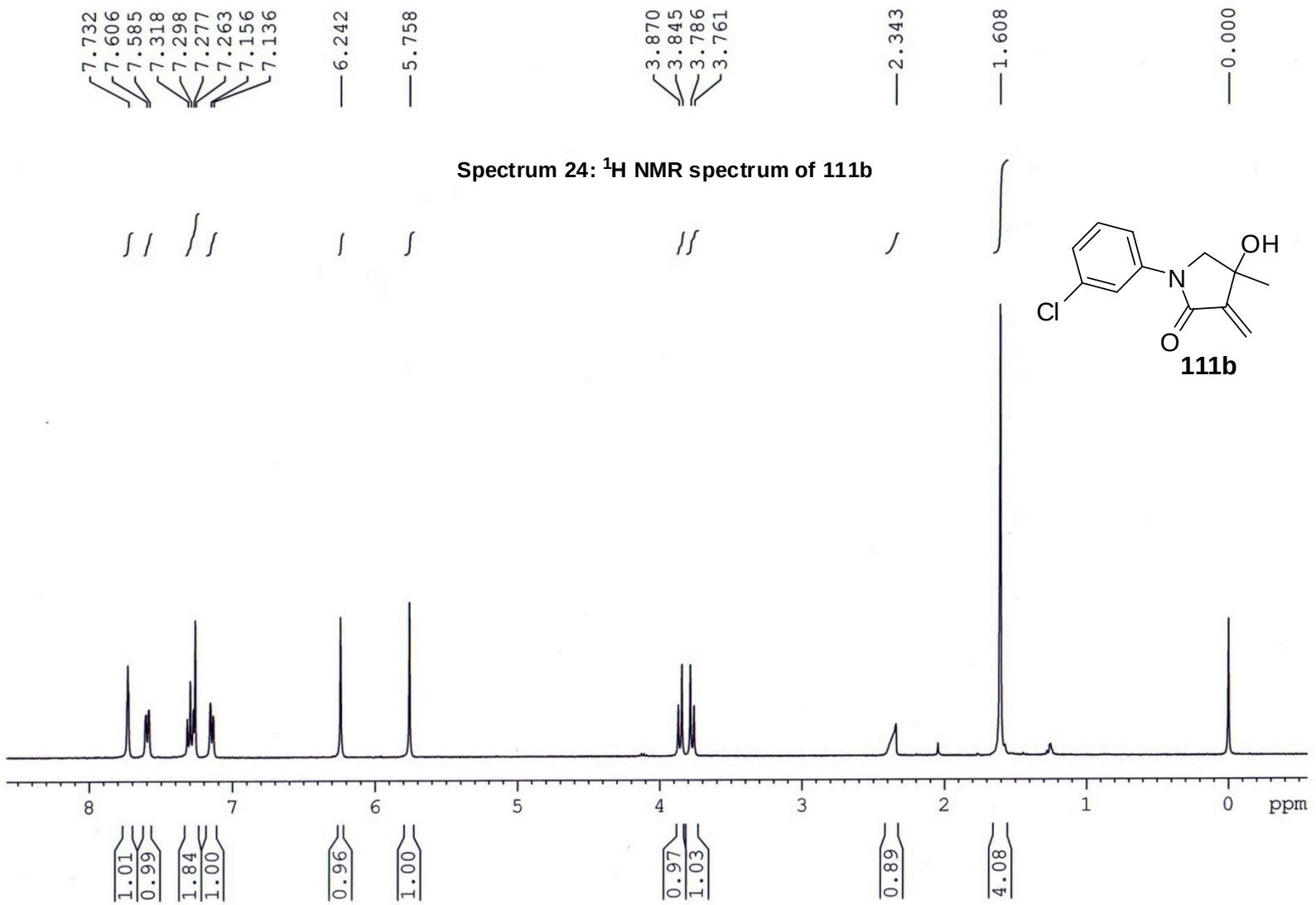
Spectrum 22: ^{1}H NMR spectrum of 108i

108i



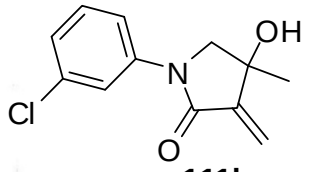
Spectrum 23: ^{13}C NMR spectrum of 108i

108i

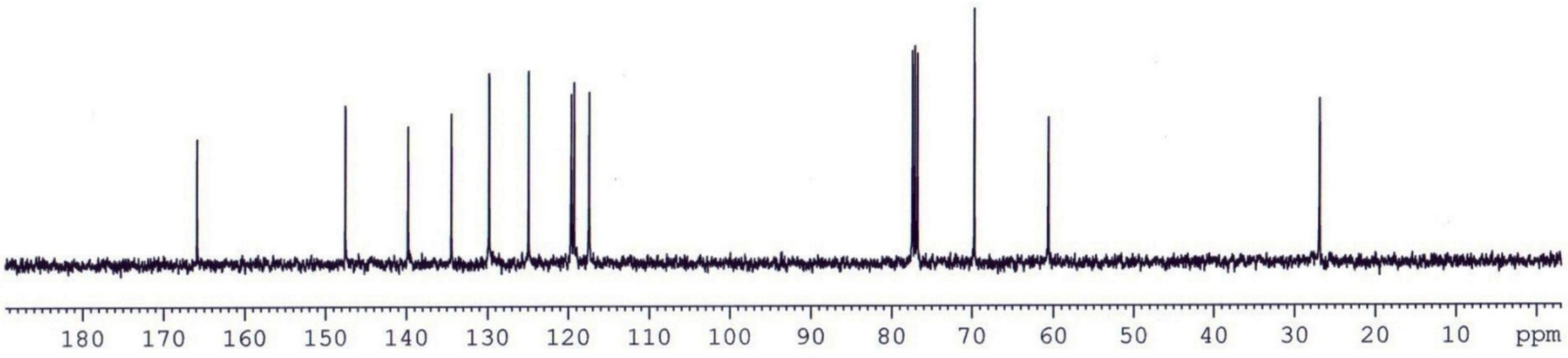


Spectrum 24: ^{1}H NMR spectrum of 111b

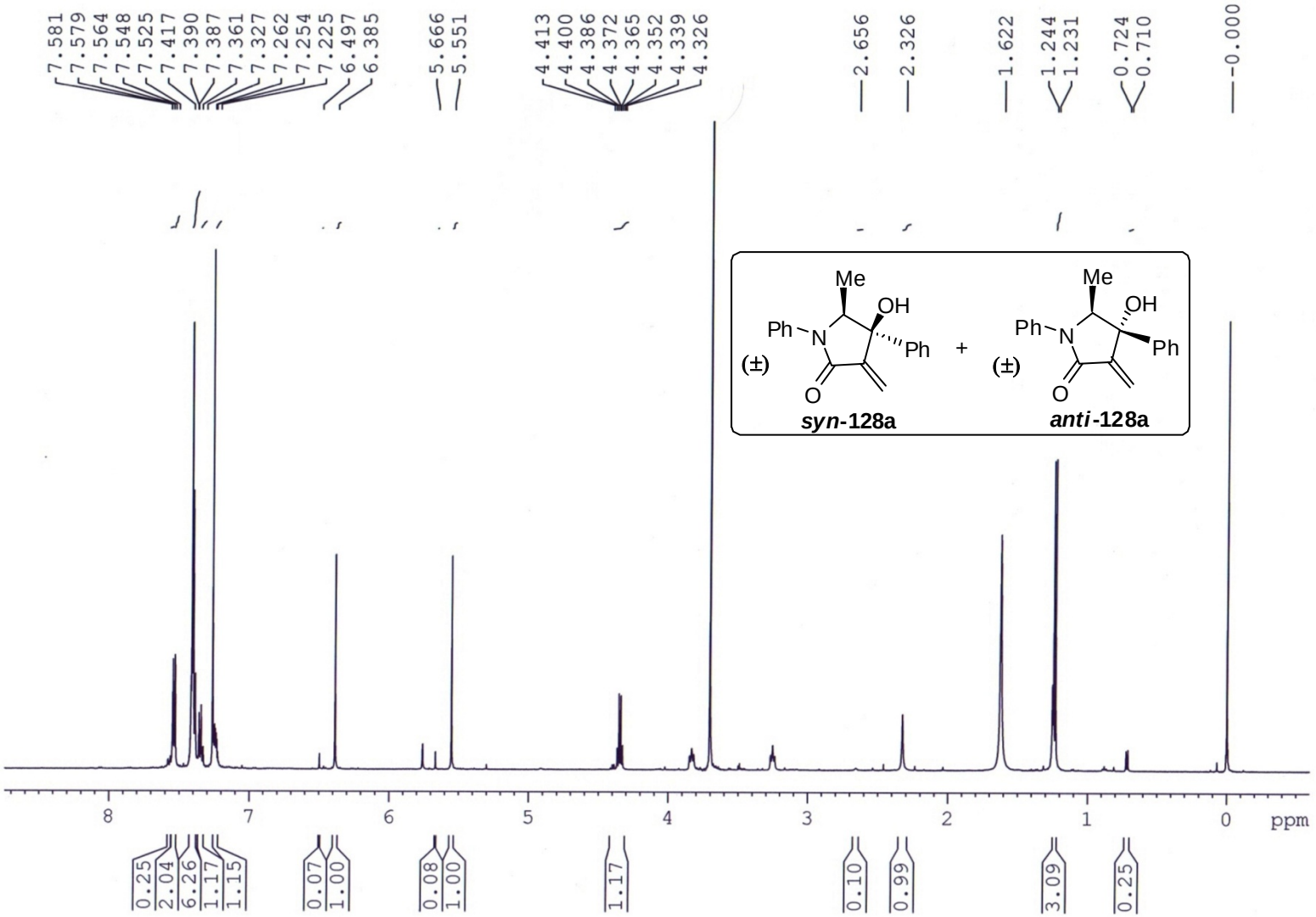
Spectrum 25: ^{13}C NMR spectrum of 111b

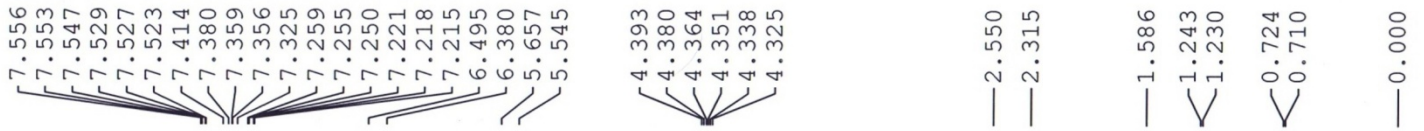


111b

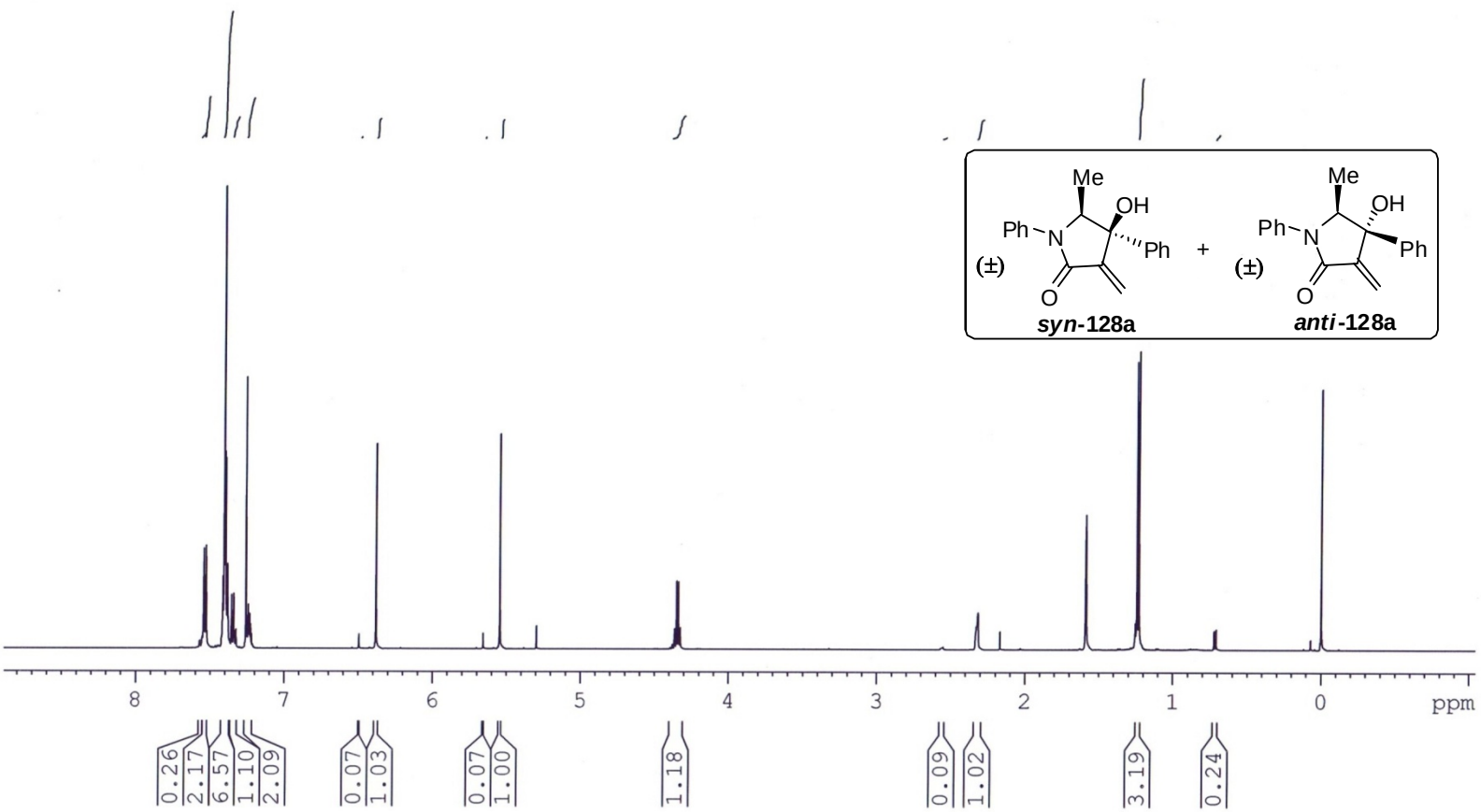


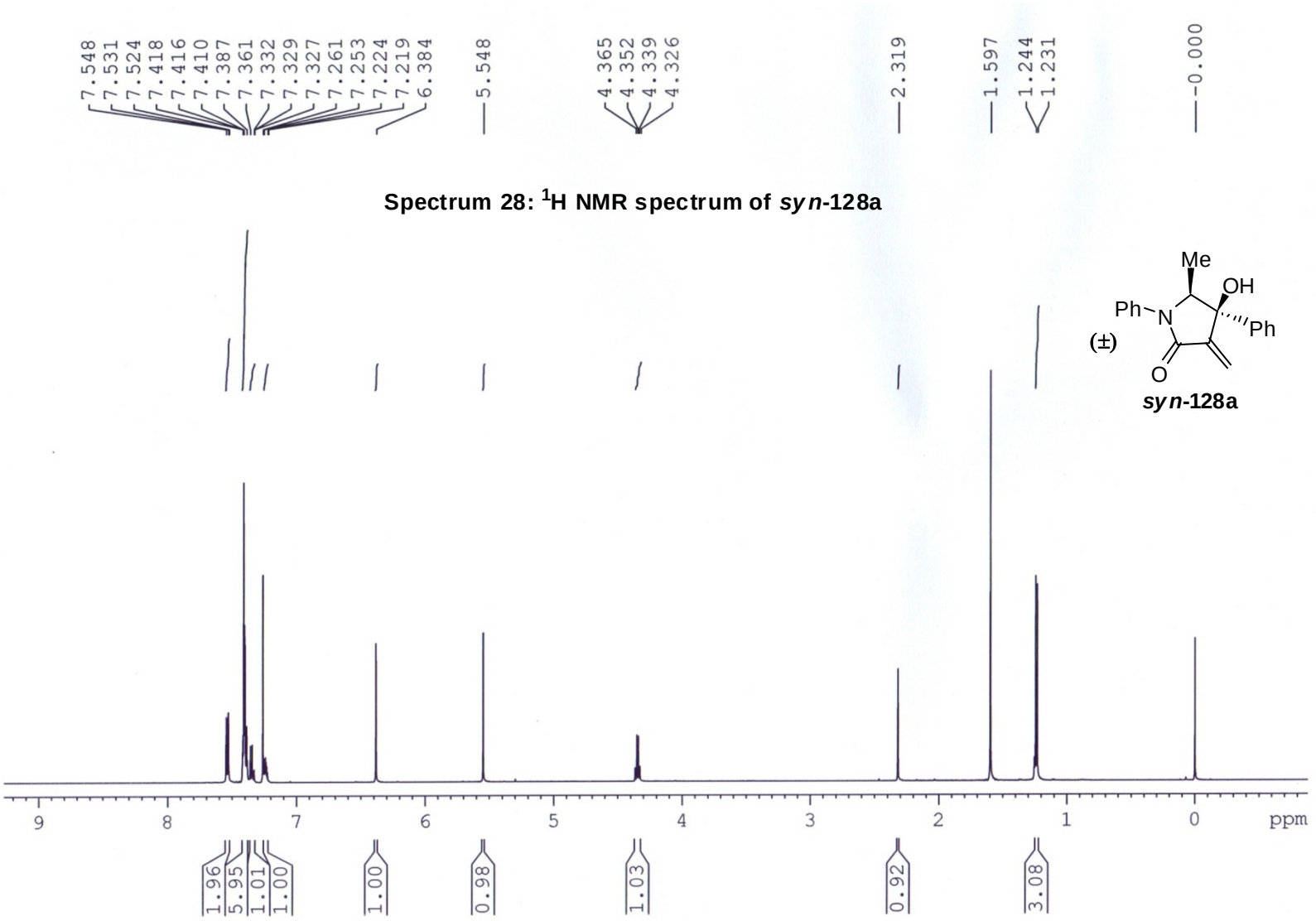
Spectrum 26: ^{1}H NMR spectrum of the crude diastereomeric mixture (*syn*-128a + *anti*-128a)





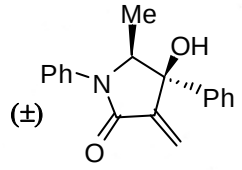
Spectrum 27: ^{1}H NMR spectrum of the column purified diastereomeric mixture (*syn*-128a + *anti*-128a)



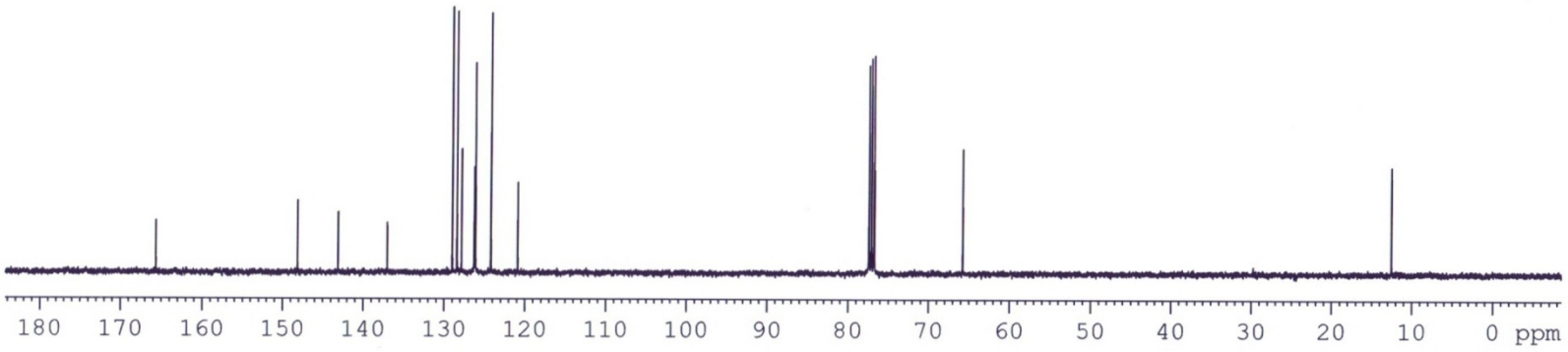


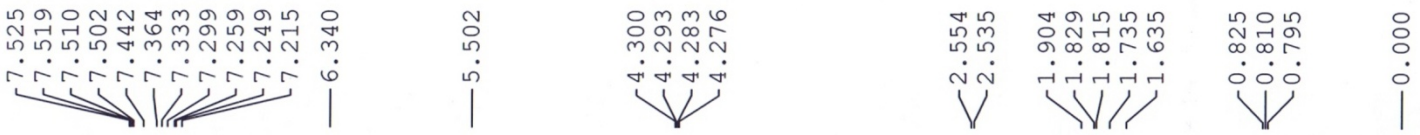
Spectrum 28: ^{1}H NMR spectrum of *syn*-128a

Spectrum 29: ^{13}C NMR spectrum of *syn*-128a

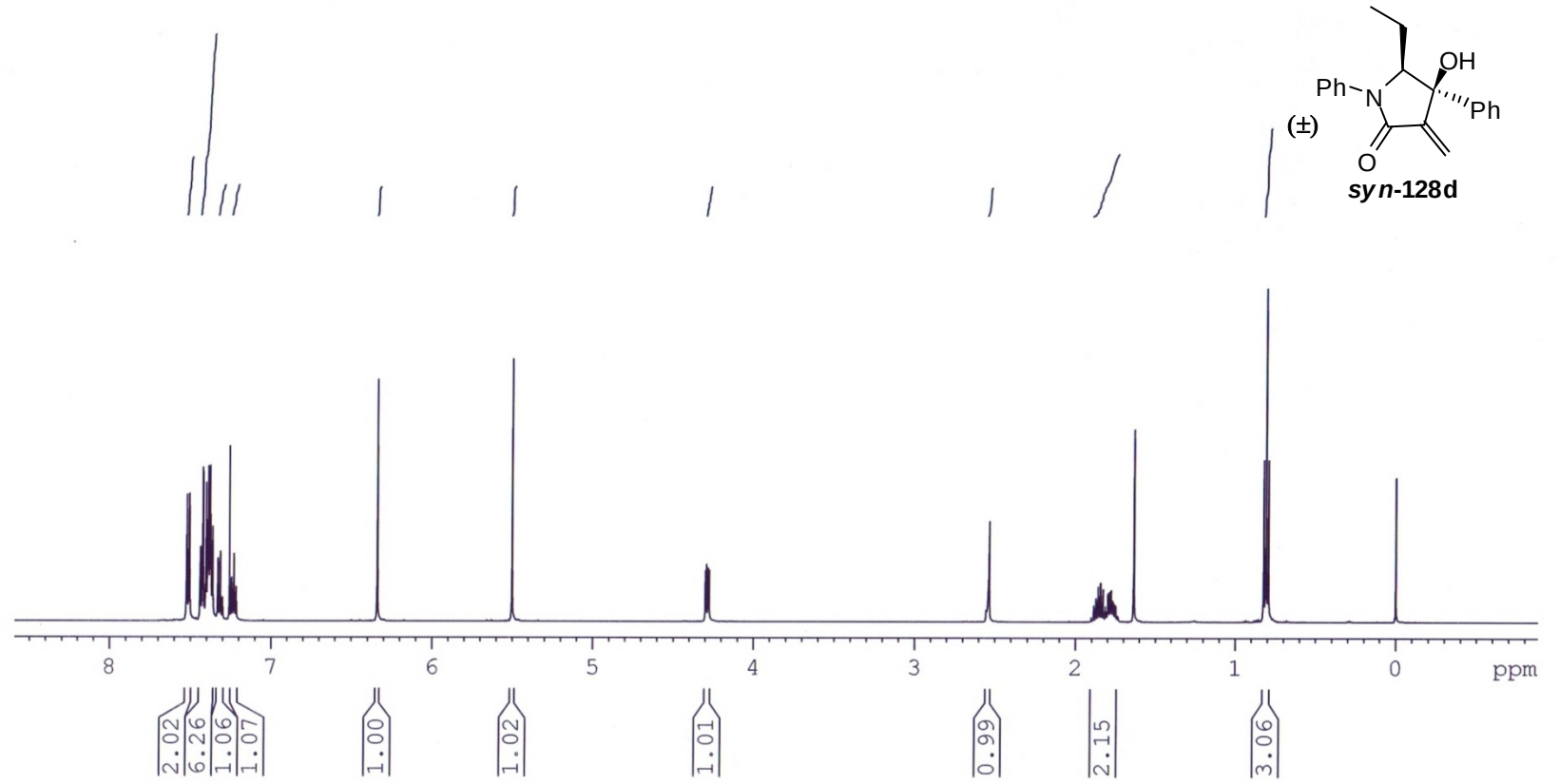


***syn*-128a**

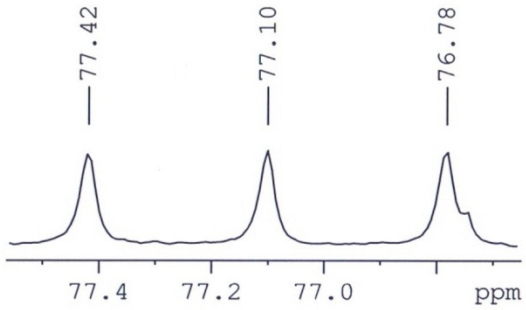


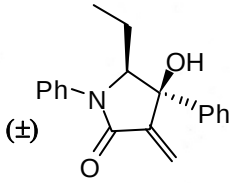


Spectrum 30: ^{1}H NMR spectrum of *syn*-128d

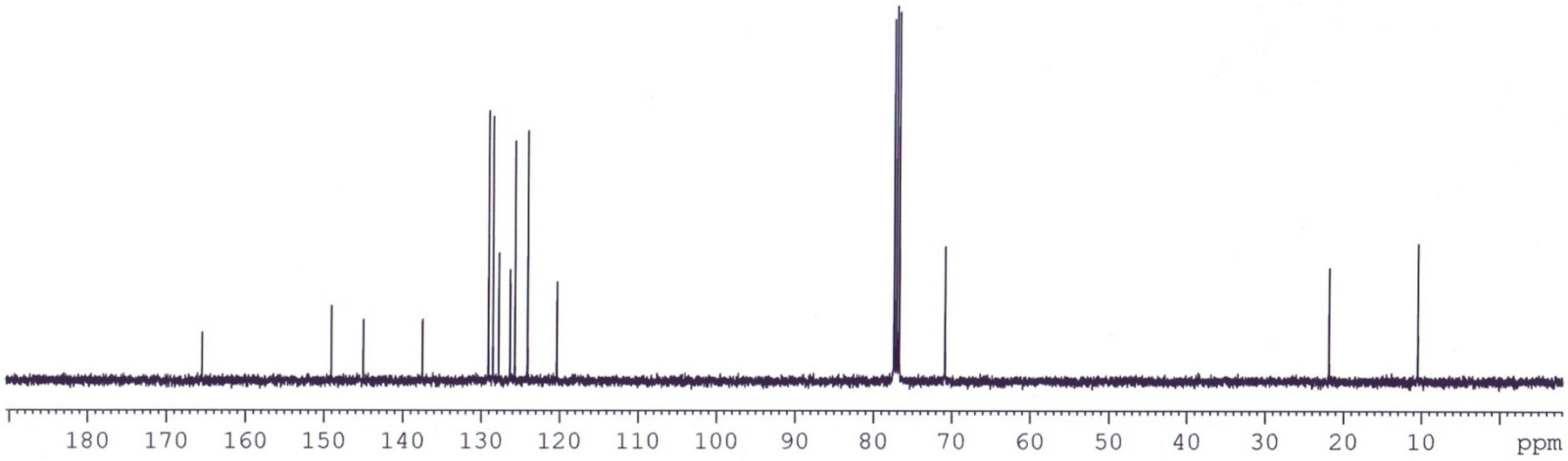


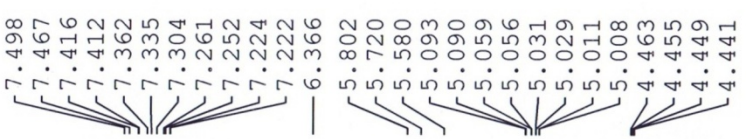
Spectrum 31: ^{13}C NMR spectrum of *syn*-128d



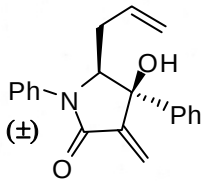


***syn*-128d**

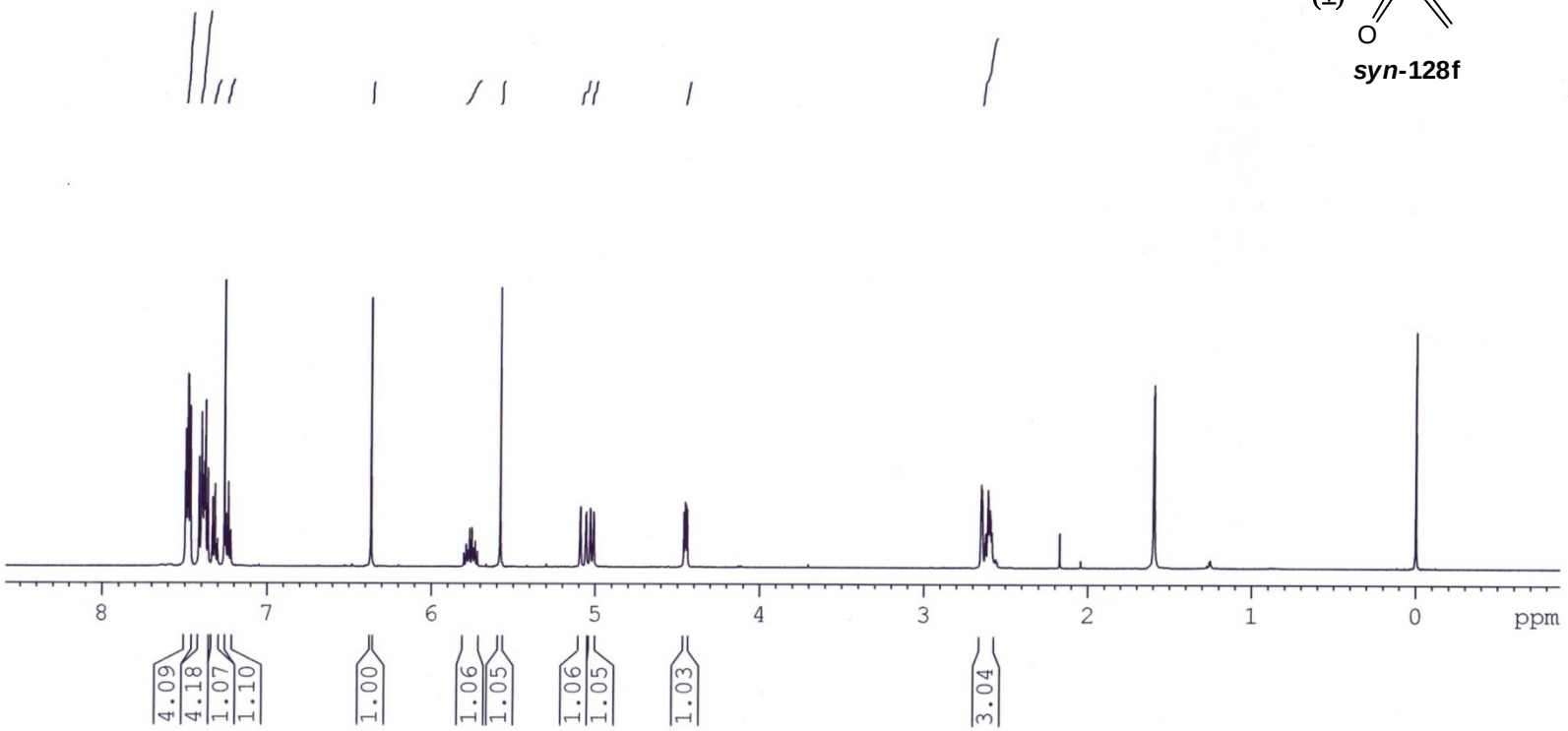




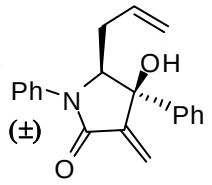
Spectrum 32: ^{1}H NMR spectrum of *syn*-128f



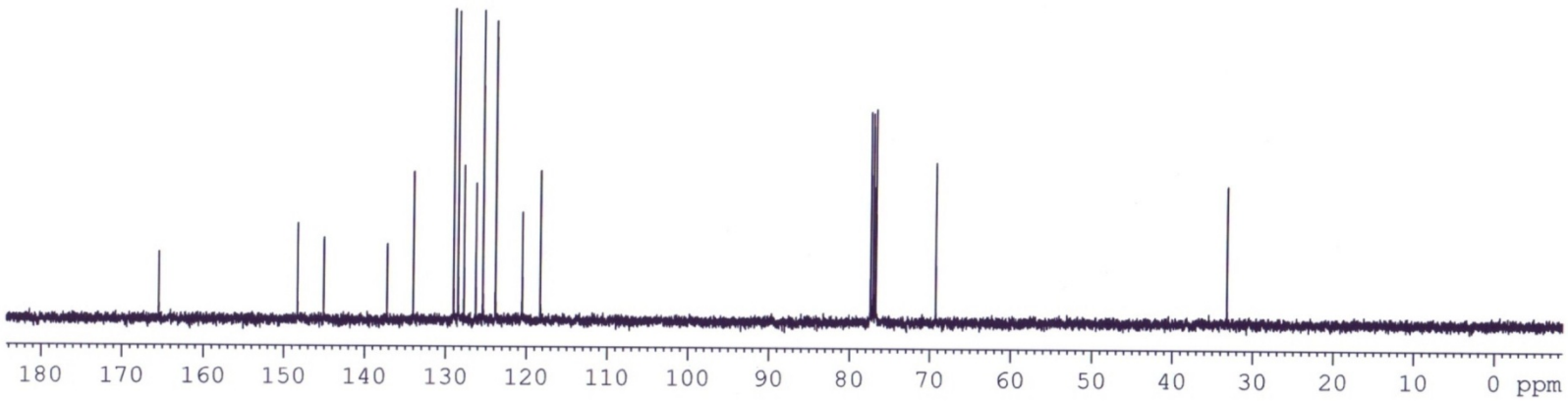
***syn*-128f**

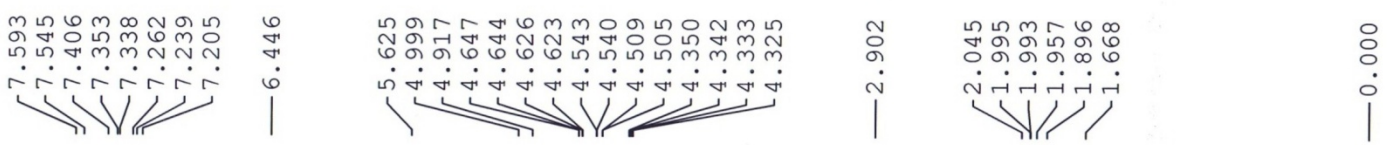


Spectrum 33: ^{13}C NMR spectrum of *syn*-128f

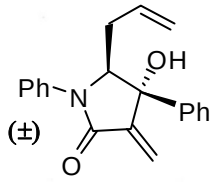


***syn*-128f**

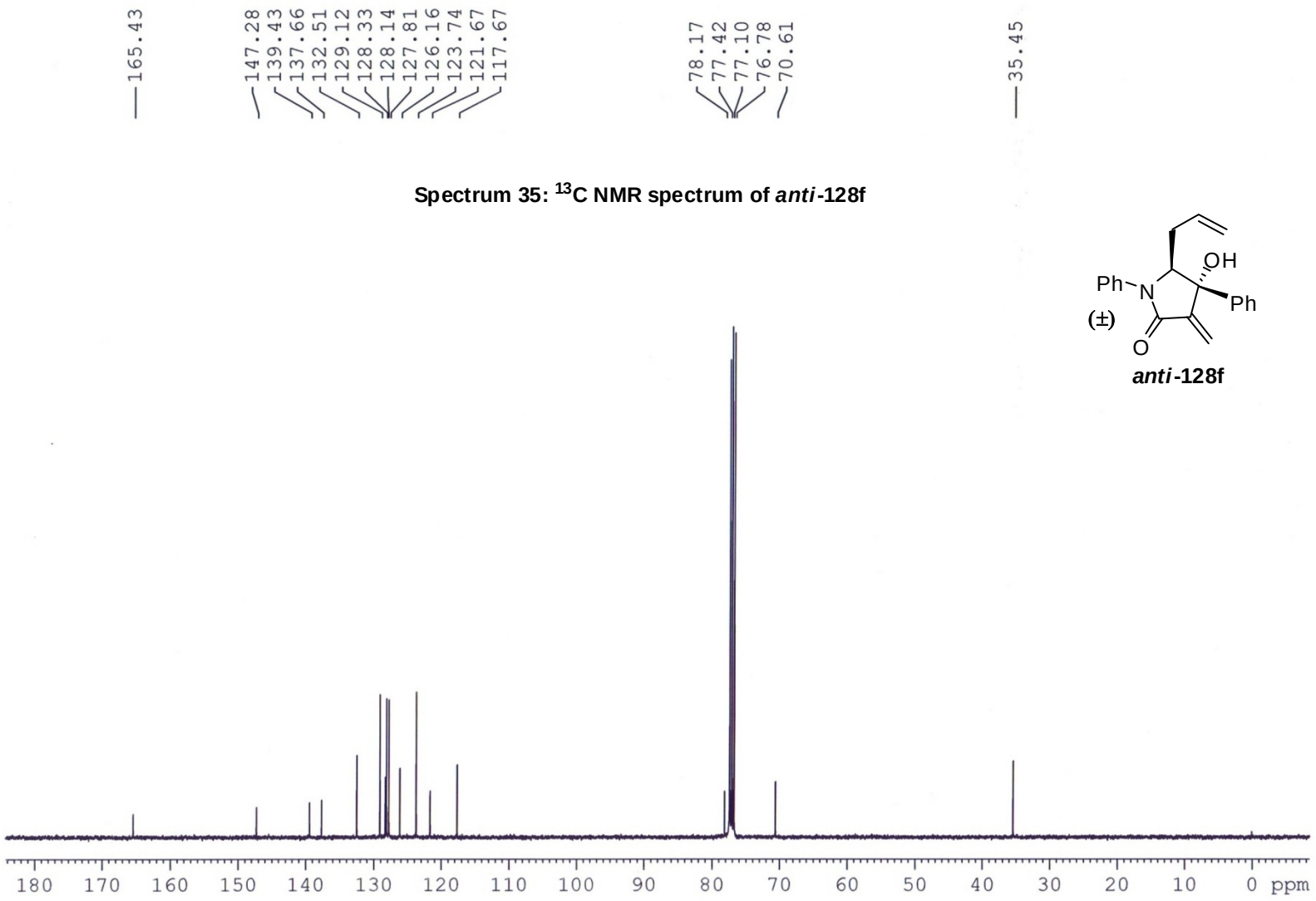




Spectrum 34: ^{1}H NMR spectrum of *anti*-128f

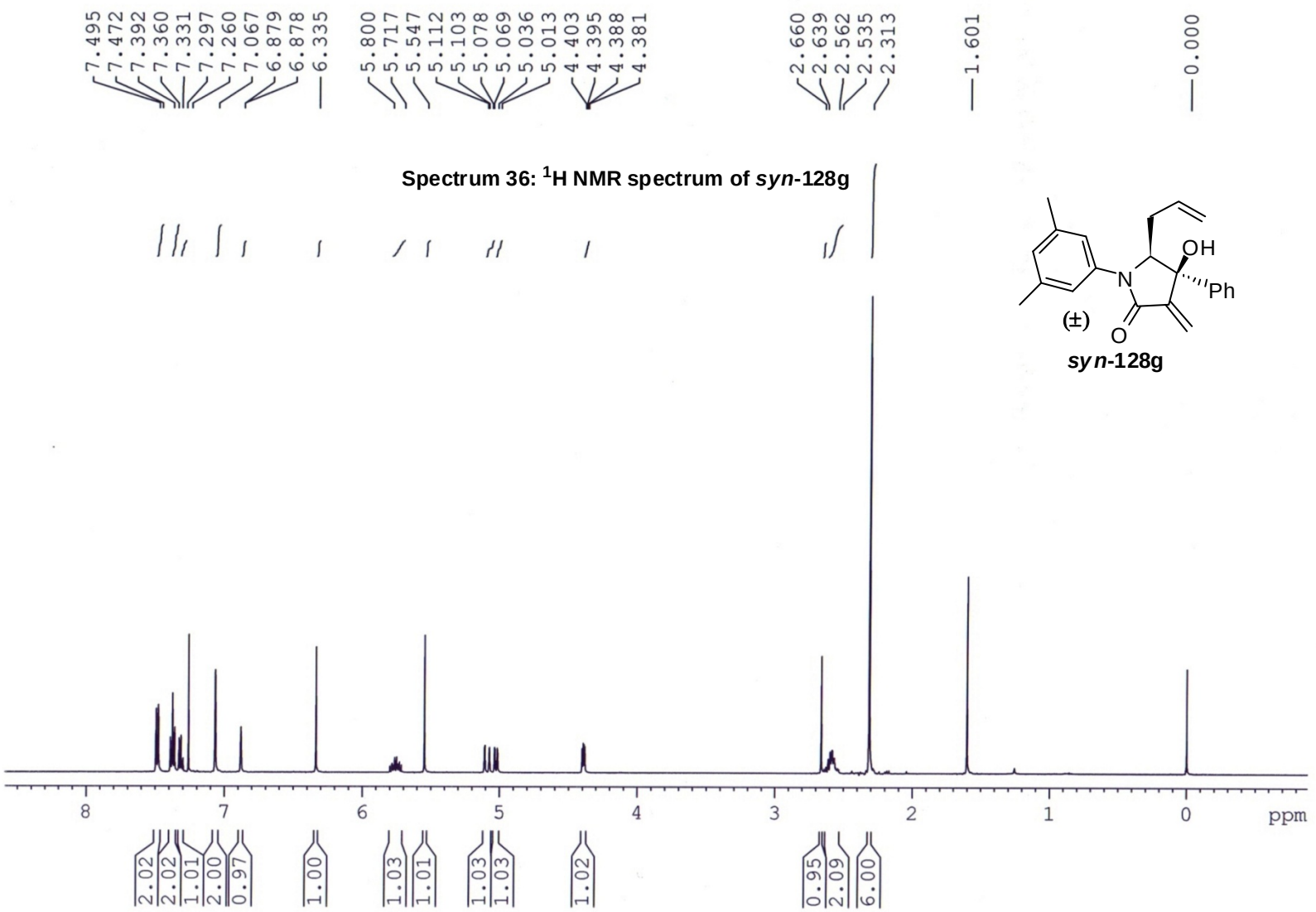


***anti*-128f**



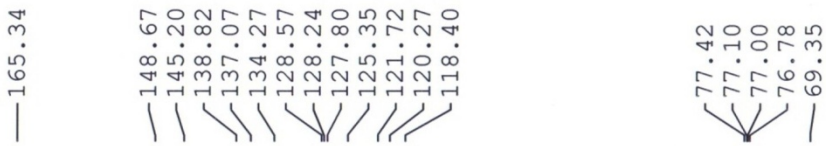
Spectrum 35: ^{13}C NMR spectrum of *anti*-128f

***anti*-128f**

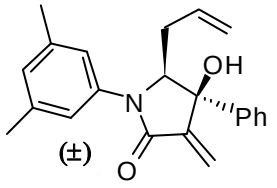


Spectrum 36: ^{1}H NMR spectrum of *syn*-128g

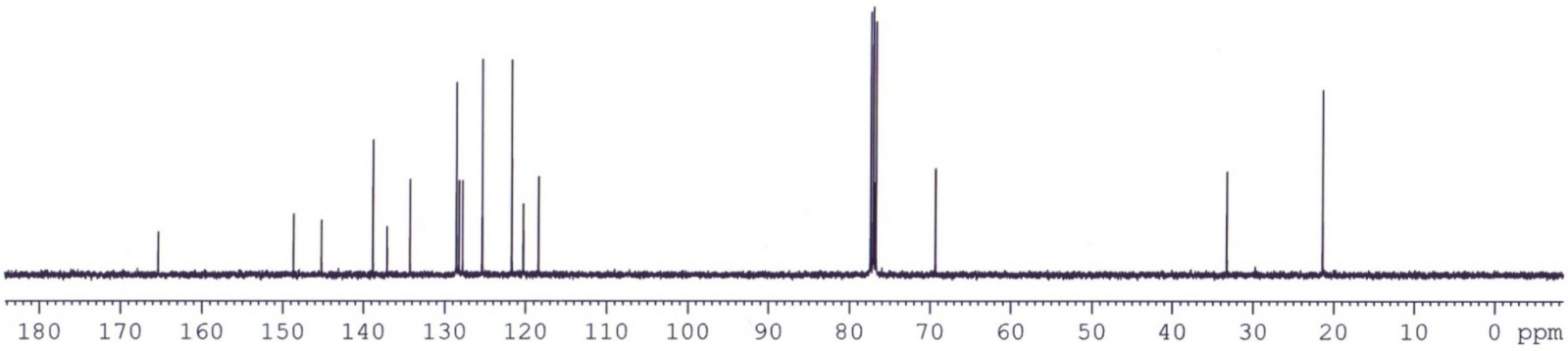
***syn*-128g**

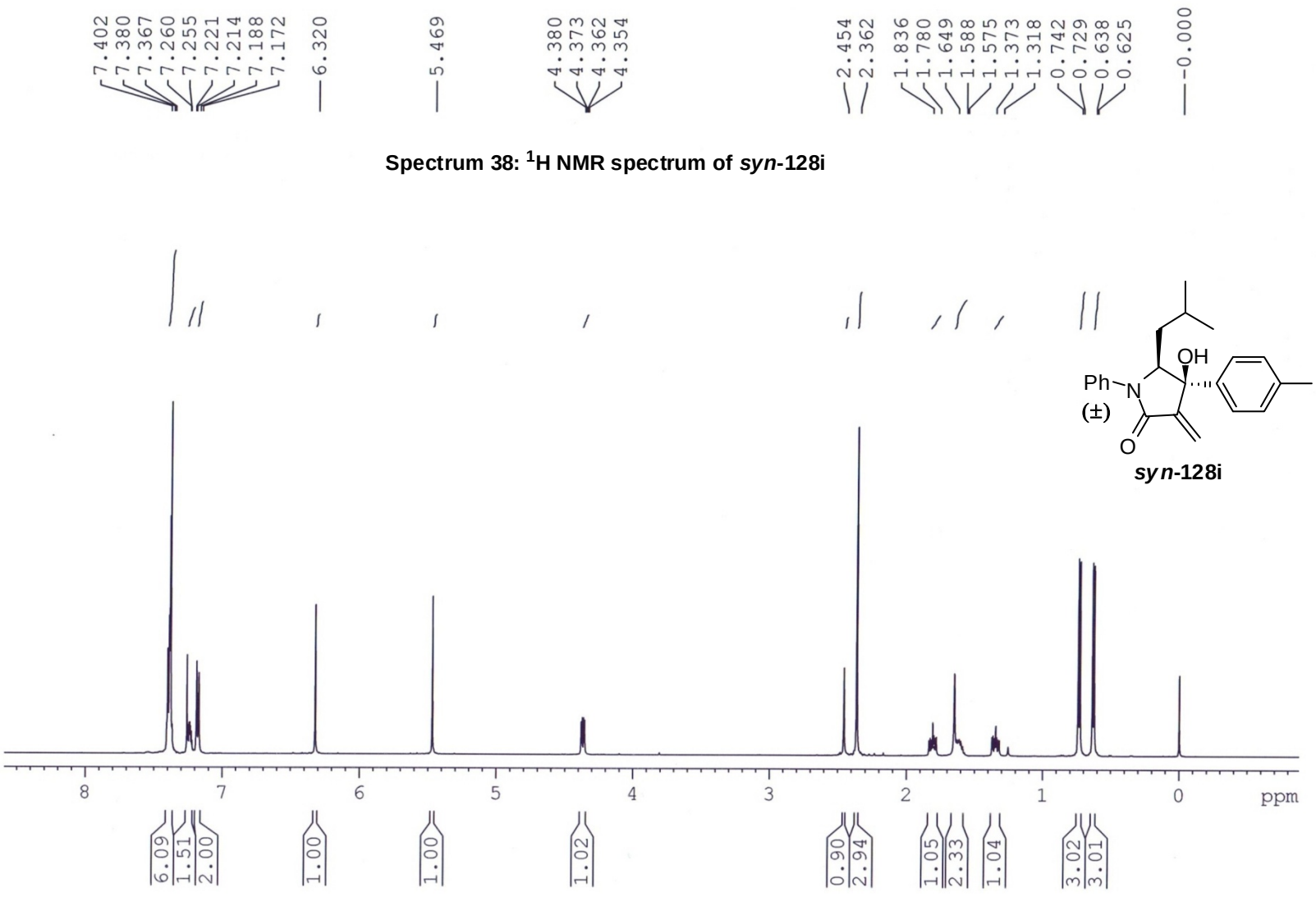


Spectrum 37: ^{13}C NMR spectrum of *syn*-128g



***syn*-128g**

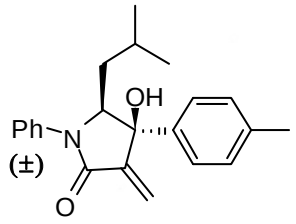




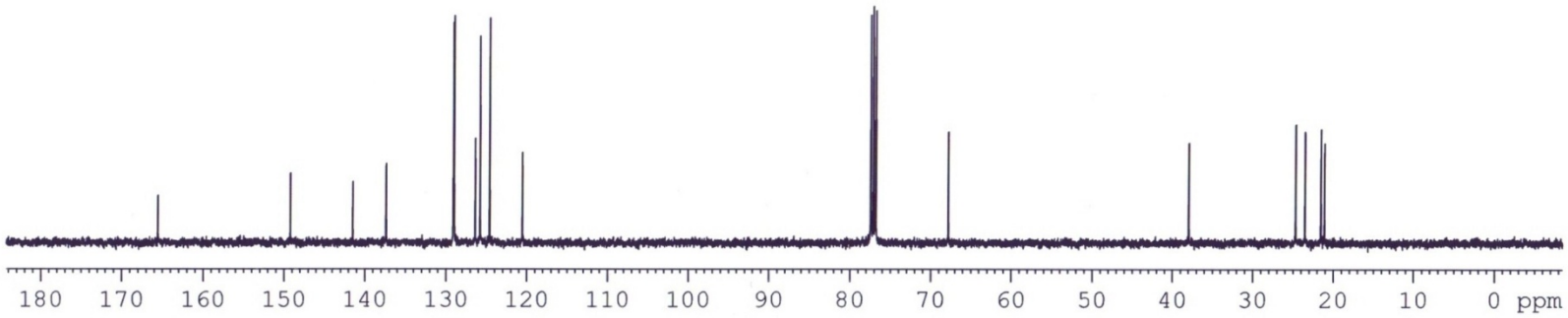
***syn*-128i**

Spectrum 38: ^{1}H NMR spectrum of *syn*-128i

Spectrum 39: ^{13}C NMR spectrum of *syn*-128i



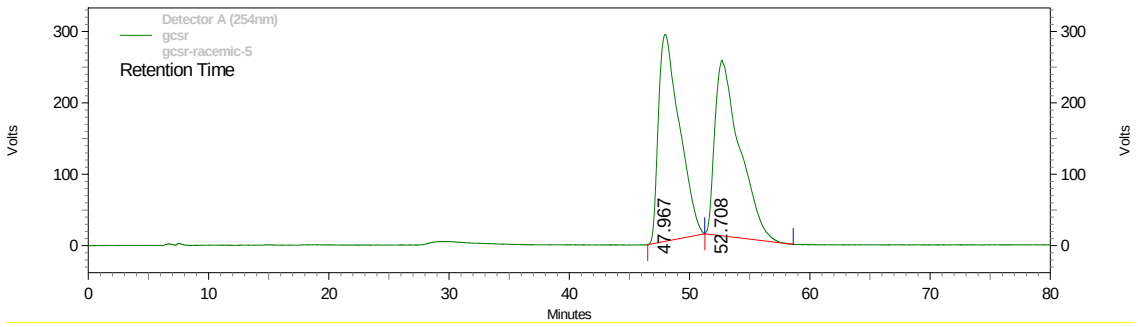
***syn*-128i**



HPLC charts

(1) HPLC chart of **75a** (racemic mixture)

Chiralcel-OJ-H [hexanes:*i*PrOH (90:10), 0.5 mL/min]

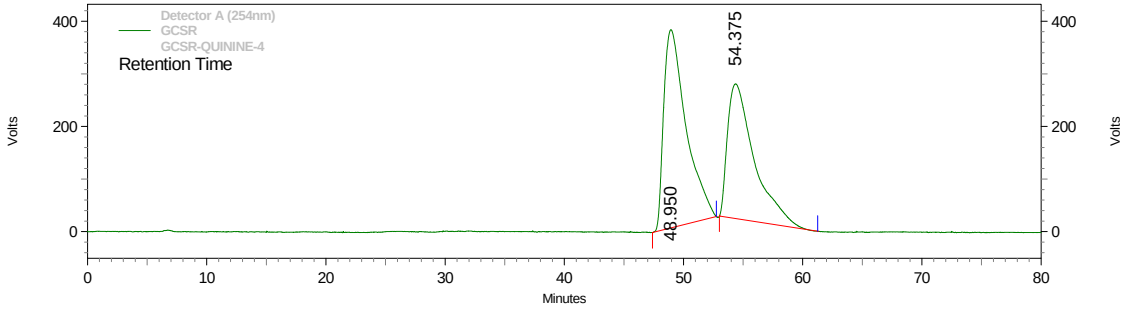


Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	47.967	35074852	49.832	289868	54.093
2	52.708	35310945	50.168	246002	45.907
Totals		70385797	100.000	535870	100.000

(2) HPLC chart of **75a** (quinine as a promoter)

Chiralcel-OJ-H [hexanes:*i*PrOH (90:10), 0.5 mL/min]

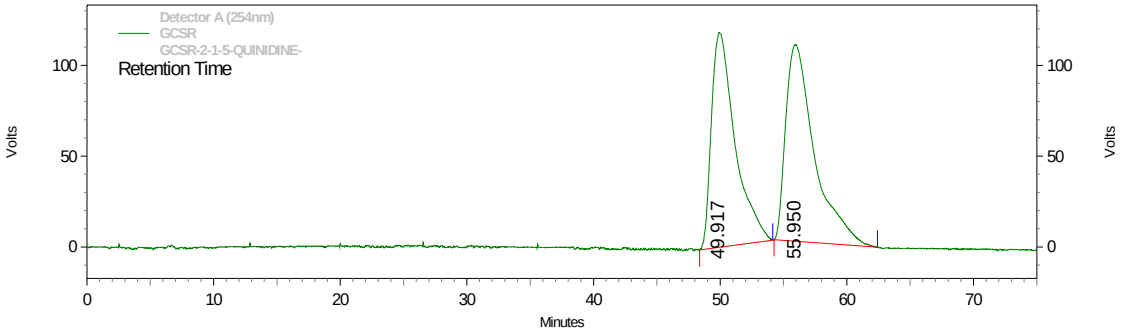


Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	48.950	48983164	55.156	376742	59.554
2	54.375	39825534	44.844	255867	40.446
Totals		88808698	100.000	632609	100.000

(3) HPLC chart of **75a** (quinidine as a promoter)

Chiralcel-OJ-H [hexanes:*i*PrOH (90:10), 0.5 mL/min]



Detector A (254nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	49.917	15318940	47.391	118309	52.228
2	55.950	17005375	52.609	108215	47.772
Totals		32324315	100.000	226524	100.000

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **75d**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	11652(3)	6929(1)	6979(1)	20(1)
C(2)	13788(3)	5993(2)	7305(1)	22(1)
C(3)	13311(3)	4821(1)	6900(1)	21(1)
C(4)	11433(3)	5239(1)	6241(1)	19(1)
C(5)	8020(3)	7009(1)	5916(1)	18(1)
C(6)	7344(3)	6502(1)	5274(1)	22(1)
C(7)	5214(3)	7020(2)	4789(1)	24(1)
C(8)	3735(3)	8049(1)	4944(1)	22(1)
C(9)	4341(4)	8566(2)	5578(1)	26(1)
C(10)	6486(3)	8049(1)	6064(1)	24(1)
C(11)	15779(4)	6192(2)	7846(1)	33(1)
Cl(1)	1090(1)	8703(1)	4325(1)	32(1)
N(1)	10210(3)	6434(1)	6393(1)	18(1)
O(1)	11249(2)	7972(1)	7186(1)	26(1)
O(2)	15884(2)	4262(1)	6760(1)	24(1)

Table II. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **95a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2733(1)	2803(1)	2163(1)	47(1)
N(1)	2396(1)	1304(1)	2583(2)	39(1)
O(2)	3895(1)	751(1)	6069(1)	51(1)
C(11)	1385(1)	1351(1)	2188(2)	41(1)

C(1)	2979(1)	2027(1)	2558(2)	38(1)
C(3)	3868(1)	761(1)	3912(2)	40(1)
C(2)	3956(1)	1705(1)	3112(2)	42(1)
C(4)	2902(1)	433(1)	2965(2)	39(1)
C(16)	1021(1)	1222(1)	252(2)	60(1)
C(5)	3071(1)	-46(1)	944(2)	56(1)
C(12)	776(1)	1509(1)	3781(2)	58(1)
C(10)	4739(1)	2191(1)	2985(3)	61(1)
C(8)	2811(1)	-1072(1)	4685(3)	66(1)
C(9)	2329(1)	-162(1)	4387(2)	51(1)
C(14)	-569(1)	1354(1)	1525(3)	72(1)
C(15)	37(1)	1216(1)	-60(3)	76(1)
C(6)	3507(2)	-984(1)	1229(3)	75(1)
C(7)	2931(1)	-1550(1)	2685(3)	80(1)
C(13)	-203(1)	1507(1)	3438(3)	72(1)

Table III. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **108a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(2)	6985(2)	1929(3)	2212(2)	34(1)
N(1)	8658(2)	1429(4)	1044(2)	26(1)
O(1)	8071(2)	3087(4)	-583(2)	39(1)
C(4)	8284(2)	281(5)	1804(3)	31(1)
C(13)	6193(2)	-1316(5)	2409(3)	31(1)
C(3)	7221(2)	612(5)	1505(3)	26(1)
C(1)	7960(2)	2094(5)	178(3)	28(1)
C(12)	6676(2)	-1065(5)	1559(3)	24(1)
C(7)	10993(3)	2600(6)	583(4)	39(1)
C(5)	9642(2)	1516(5)	1143(3)	27(1)
C(6)	10040(3)	2608(5)	466(3)	35(1)
C(11)	6252(3)	1524(5)	-471(3)	34(1)
C(17)	6714(3)	-2383(5)	794(3)	34(1)
C(15)	5815(3)	-4204(6)	1739(4)	40(1)

C(10)	10237(3)	458(5)	1944(3)	35(1)
C(9)	11188(3)	467(5)	2043(3)	38(1)
C(14)	5762(3)	-2890(5)	2495(4)	36(1)
C(8)	11579(3)	1540(5)	1363(3)	36(1)
C(2)	7053(2)	1409(5)	316(3)	27(1)
C(16)	6287(3)	-3948(6)	889(3)	39(1)

Table IV. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **108b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	1271(1)	6874(1)	10651(1)	110(1)
O(2)	-948(2)	7680(2)	5777(1)	49(1)
O(1)	3247(2)	4689(2)	4148(1)	50(1)
N(1)	2940(2)	7253(2)	4433(1)	43(1)
C(1)	2672(2)	5663(2)	4704(1)	40(1)
C(2)	1580(2)	5328(2)	5808(1)	41(1)
C(5)	3943(3)	8072(2)	3452(1)	45(1)
C(12)	946(3)	6863(2)	7270(1)	46(1)
C(3)	912(3)	6941(2)	6103(1)	43(1)
C(14)	2607(4)	5948(3)	8825(2)	68(1)
C(13)	2515(3)	5968(3)	7779(2)	57(1)
C(11)	1245(3)	3862(2)	6374(1)	50(1)
C(4)	2370(3)	7987(2)	5345(1)	46(1)
C(9)	5931(4)	10083(3)	2496(2)	70(1)
C(6)	3936(3)	7687(3)	2504(2)	56(1)
C(10)	4924(3)	9299(3)	3445(2)	56(1)
C(15)	1126(4)	6839(3)	9348(2)	70(1)
C(7)	4950(4)	8504(3)	1565(2)	70(1)
C(8)	5961(4)	9680(3)	1563(2)	74(1)
C(17)	-546(3)	7749(3)	7827(2)	65(1)
C(16)	-441(4)	7731(4)	8872(2)	80(1)

Table V. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **108e**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	1121(1)	1110(2)	3069(1)	44(1)
O(2)	-518(1)	494(2)	3788(1)	58(1)
O(1)	2571(1)	-569(2)	3317(1)	64(1)
C(5)	1275(1)	1005(2)	2633(1)	44(1)
C(3)	244(1)	1857(2)	3709(1)	46(1)
C(1)	1783(1)	420(2)	3371(1)	47(1)
C(4)	273(1)	2273(2)	3243(1)	47(1)
C(2)	1389(1)	1075(2)	3776(1)	48(1)
C(12)	7(1)	3421(2)	3977(1)	48(1)
C(10)	641(2)	2050(2)	2376(1)	57(1)
C(6)	2048(1)	-111(2)	2455(1)	54(1)
C(7)	2172(2)	-145(3)	2029(1)	62(1)
C(8)	1549(2)	900(3)	1775(1)	62(1)
C(13)	-931(2)	3517(3)	4224(1)	62(1)
C(9)	784(2)	1991(3)	1949(1)	65(1)
C(15)	-396(2)	6315(3)	4476(1)	69(1)
C(17)	728(2)	4799(3)	3979(1)	68(1)
C(11)	1963(2)	970(3)	4122(1)	74(1)
C(14)	-1122(2)	4961(3)	4468(1)	77(1)
C(16)	531(2)	6224(3)	4224(1)	78(1)
C(18)	-585(2)	7865(4)	4751(1)	105(1)

Table VI. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ***syn*-128a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(2)	6828(1)	6224(1)	922(1)	52(1)
N(1)	5992(1)	5004(1)	983(1)	48(1)
C(12)	6611(1)	6193(1)	-728(1)	47(1)

C(3)	6423(1)	5948(1)	223(1)	42(1)
C(2)	5712(1)	6050(1)	507(1)	49(1)
C(4)	6506(1)	5186(1)	303(1)	42(1)
C(17)	6186(1)	6110(1)	-1462(1)	60(1)
C(5)	5938(1)	4353(1)	1351(1)	54(1)
C(18)	7198(1)	4974(1)	577(1)	54(1)
C(1)	5523(1)	5475(1)	1078(1)	56(1)
C(13)	7221(1)	6478(1)	-875(1)	64(1)
C(6)	6144(1)	3813(1)	840(2)	68(1)
O(1)	5024(1)	5425(1)	1551(1)	90(1)
C(16)	6376(2)	6304(1)	-2332(1)	76(1)
C(11)	5317(1)	6554(1)	343(2)	68(1)
C(10)	5682(1)	4261(1)	2223(2)	70(1)
C(9)	5621(1)	3621(2)	2564(2)	91(1)
C(15)	6992(2)	6574(1)	-2474(2)	85(1)
C(14)	7412(1)	6664(1)	-1747(2)	85(1)
C(7)	6091(2)	3183(1)	1204(2)	89(1)
C(8)	5828(2)	3088(1)	2057(2)	99(1)

Table VII. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ***syn*-128b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	813(1)	4644(1)	10661(1)	139(1)
O(2)	1323(1)	4347(1)	6559(1)	60(1)
C(3)	1595(1)	3911(1)	7172(1)	46(1)
N(1)	2549(1)	3474(1)	6487(1)	51(1)
C(12)	1356(1)	4077(1)	8042(1)	49(1)
C(5)	3212(1)	3415(1)	6170(2)	60(1)
O(1)	2119(1)	2511(1)	5933(1)	87(1)
C(2)	1483(1)	3203(1)	6882(1)	49(1)
C(4)	2367(1)	3984(1)	7111(1)	48(1)
C(13)	1427(1)	3621(1)	8685(1)	59(1)
C(1)	2068(1)	3008(1)	6375(1)	56(1)

C(18)	2597(1)	4684(1)	6891(2)	64(1)
C(17)	1104(1)	4701(1)	8220(2)	68(1)
C(15)	1012(1)	4426(2)	9642(2)	80(1)
C(10)	3753(1)	3566(1)	6672(2)	79(1)
C(11)	967(1)	2808(1)	7012(2)	67(1)
C(14)	1250(1)	3792(2)	9488(1)	71(1)
C(6)	3312(1)	3213(1)	5361(2)	82(1)
C(7)	3958(2)	3154(2)	5059(3)	113(1)
C(16)	938(1)	4880(2)	9020(2)	86(1)
C(9)	4396(1)	3514(2)	6346(3)	111(1)
C(8)	4492(2)	3302(2)	5547(4)	127(2)

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LIST OF PUBLICATIONS

1. The acrylamide moiety as an activated alkene component in the intramolecular Baylis–Hillman Reaction: Facile synthesis of functionalized α-methylene lactam and spirolactam frameworks

   Basavaiah, D.; **Reddy, G. C.**; Bharadwaj, K. C. *Eur. J. Org. Chem.* **2014**, 1157.

2. Less reactive ketones as electrophiles and acrylamides as activated alkenes in intramolecular Baylis-Hillman reaction: Facile synthesis of functionalized γ-lactam frameworks

   Basavaiah, D.; **Reddy, G. C.**; Bharadwaj, K. C. *Tetrahedron* **2014**, *70*, 7991.

3. Intramolecular Baylis-Hillman reaction: Synthesis of heterocyclic molecules

   Basavaiah, D.; **Reddy, G. C.** *Arkivoc* **2016**, *ii*, 172

4. Highly diastereoselective intramolecular Baylis-Hillman reaction of acrylamide-α-substituted ketones

   Basavaiah, D.; **Reddy, G. C.** (to be communicated)

Poster and Oral Presentations

1. The acrylamide moiety as an activated alkene component in the intramolecular Baylis–Hillman Reaction: Facile synthesis of functionalized α-methylene lactam and spirolactam frameworks

   Basavaiah, D.; **Reddy, G. C.**; Bharadwaj, K. C.

   Poster cum Oral presentation at *ChemFest* **2014**

2. Less reactive ketones as electrophiles and acrylamides as activated alkenes in intramolecular Baylis-Hillman reaction: Facile synthesis of functionalized γ-lactam frameworks

   Basavaiah, D.; **Reddy, G. C.**; Bharadwaj, K. C.

   Poster presentation at *Indo-Taiwan Recent Trends in Chemical Sciences (RTCS)*-**2014**

3. Less reactive ketones as electrophiles and acrylamides as activated alkenes in intramolecular Baylis-Hillman reaction: Facile synthesis of functionalized γ-lactam frameworks

   Basavaiah, D.; **Reddy, G. C.**; Bharadwaj, K. C.

   Poster presentation at *ChemFest* **2015**

SYNOPSIS OF THE THESIS ENTITLED

LESS REACTIVE ACRYLAMIDES AS ACTIVATED ALKENES AND KETONES AS ELECTROPHILES IN INTRAMOLECULAR BAYLIS-HILLMAN REACTION

TO BE SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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The Baylis-Hillman (BH) reaction[1-11] is an emerging continent in the globe of organic chemistry providing diverse classes of proximal densely functionalized molecules possessing high synthetic potential. The Baylis-Hillman (B-H) reaction involves three components 1) activated alkene 2) electrophile 3) catalyst. It involves an atom-economical construction of carbon-carbon bonds via coupling of activated alkenes with electrophiles under the influence of an appropriate catalyst. Although variety of reactive activated alkenes such as vinyl ketones, acrylates and acrylonitriles *etc.* have been extensively used, less reactive activated alkenes such as acrylamides, vinyl sulfoxides and vinyl sulfones have rarely been used in the B-H reactions. Similarly a number of reactive electrophiles such as aldehydes, α-keto esters, α-keto amides, α-diketones and α-fluoro ketones *etc.* are routinely used in coupling with various activated alkenes. However there are not many reports on the utility of normal ketones in the B-H reactions because of their inferior reactivity profile particularly in this reaction. Intramolecular Baylis-Hillman (IBH) reaction[4,8,10] is a growing branch of Baylis-Hillman chemistry that has attracted the attention of synthetic and medicinal chemists because it produces various carbocyclic and heterocyclic compounds of different ring sizes.

This thesis deals with studies on the application of less reactive acrylamides as activated alkenes and ketones as electrophiles in intramolecular Baylis-Hillman 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 intramolecular

reactions, Baylis-Hillman reaction, its intramolecular version and their applications in organic synthesis.

The second chapter deals with the objectives, results & discussion. The following are the objectives:

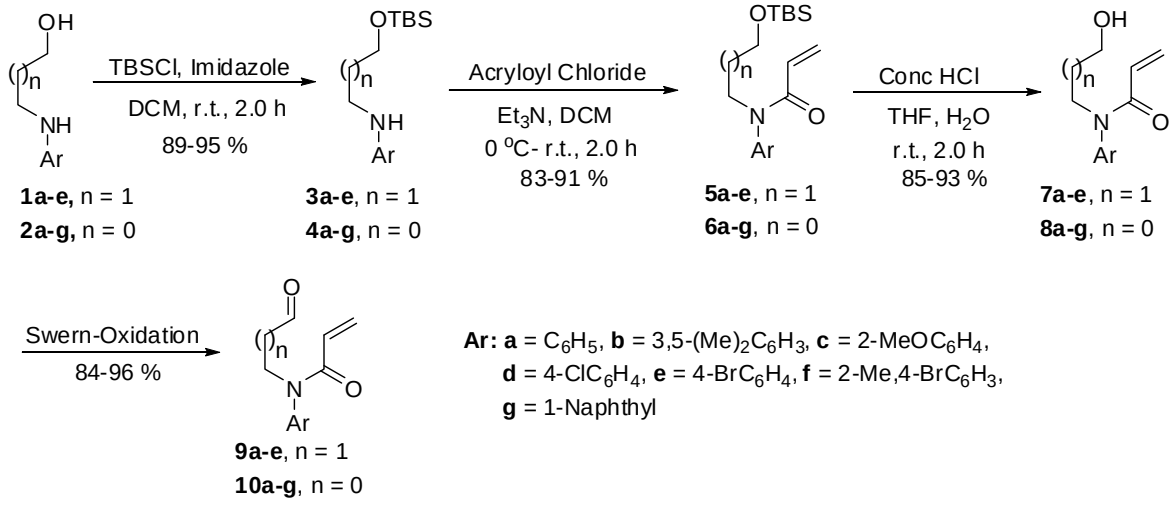
1) To design and synthesize substrates containing less reactive acrylamides as activated alkene components and aldehydes as electrophile components and to develop a facile protocol for their intramolecular coupling reactions.
2) To design and synthesize substrates containing less reactive acrylamides as activated alkene and ketones as electrophile components so as to perform their intramolecular cyclization.
3) To design and synthesize chiral (racemic) substrates containing less reactive acrylamide and ketone as activated alkene and electrophile components respectively and examine their potential for diastereoselective IBH-reaction

Acrylamide moiety as an activated alkene component in intramolecular Baylis-Hillman reaction: a facile synthesis of functionalized α-methylene lactam and spirolactam frameworks

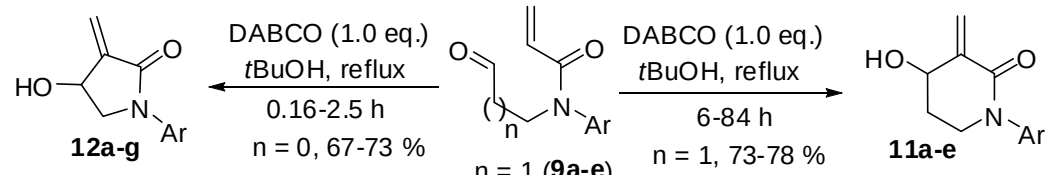
Due to their less reactivity profile, acrylamides have not been well explored in the Baylis-Hillman reaction or its intramolecular molecular version. Therefore we have directed our

efforts to design a substrate containing acrylamide as a activated alkene and aldehyde as a electrophile component with view to perform intramolecular cyclization reaction using appropriate catalyst. Accordingly we have synthesized substrates [N-(3-oxopropyl)-N-arylacrylamides (**9a-e**) and N-(2-oxoethyl)-N-arylacrylamides (**10a-g**)] following the reaction sequence as shown in the Scheme 1. We have developed a simple procedure for intramolecular Baylis-Hillman reaction of acrylamide-aldehyde substrates [(**9a-e** and (**10a-g**)]) under the influence of DABCO in *t*BuOH to provide the corresponding α-methylene-δ-lactam (**11a-e**) and α-methylene-γ-lactam derivatives (**12a-g**) in good yields as shown in the Scheme 2.

Scheme 1



Scheme 2

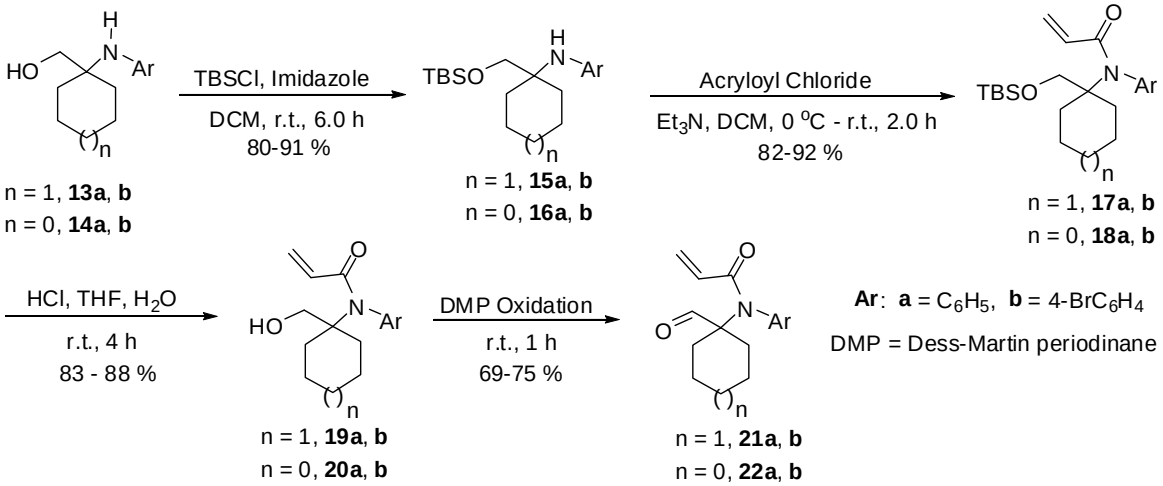


Ar: **a** = C_6H_5, **b** = 3,5-$(Me)_2C_6H_3$, **c** = 2-$MeOC_6H_4$, **d** = 4-ClC_6H_4, **e** = 4-BrC_6H_4, **f** = 2-Me,4-BrC_6H_3, **g** = 1-Naphthyl

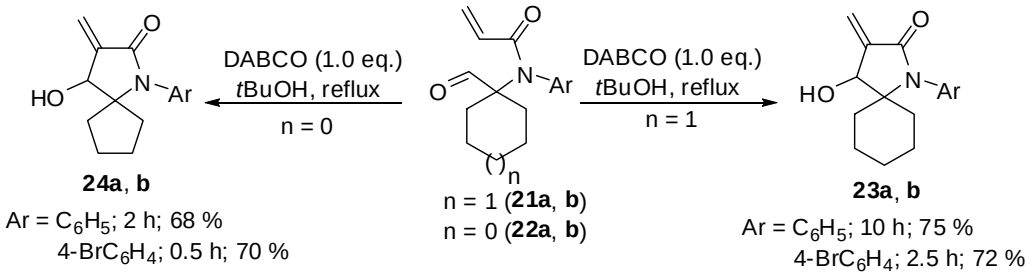
Ar: **a** = C_6H_5, **b** = 3,5-$(Me)_2C_6H_3$, **c** = 2-$MeOC_6H_4$, **d** = 4-ClC_6H_4, **e** = 4-BrC_6H_4,

Next we have extended to this strategy to the acrylamide-aldehydes (**21a**, **21b**, **22a** and **22b**) [prepared following the reaction sequence as shown in the Scheme 3] in order to obtain the corresponding IBH-products, spirolactam derivatives (**23a**, **b** and **24a**, **b**), in good yields (Scheme 4).

Scheme 3



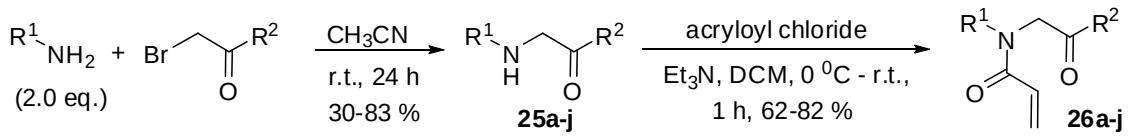
Scheme 4



Less reactive ketones as electrophiles and acrylamides as activated alkenes in intramolecular Baylis-Hillman reaction: facile synthesis of functionalized γ-lactam frameworks with tertiary alcoholic functionality

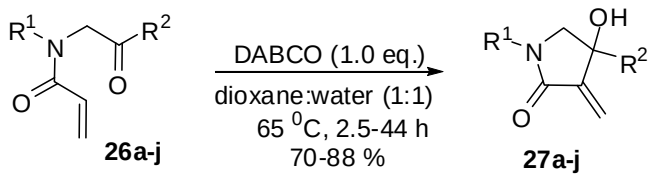
From the above intramolecular Baylis-Hillman reactions it is quite clear that formation of 5-membered lactams (**12a-g**) from acrylamide-aldehydes (**10a-g**) is faster than that of 6-membered lactams (**11a-e**) from acrylamide-aldehydes (**9a-e**). Therefore it occurred to us that the acrylamide-ketone (aromatic) substrates [N-(2-oxo-2-arylethyl)-N-arylacrylamides (**26a-j**) containing ketones as electrophiles and acrylamides as activated alkene components may be suitable for intramolecular Baylis-Hillman reactions in order to obtaining γ-lactam frameworks with tertiary alcoholic functionality. Accordingly we have prepared the representative substrates (**26a-j**) following reaction sequence as shown in the Scheme 5.

Scheme 5



25a (or) 26a: $R^1 = C_6H_5$, $R^2 = C_6H_5$
25b (or) 26b: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$
25c (or) 26c: $R^1 = C_6H_5$, $R^2 = 2$-Naphthyl
25d (or) 26d: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = C_6H_5$
25e (or) 26e: $R^1 = C_6H_5$, $R^2 = 4\text{-}MeC_6H_4$
25f (or) 26f: $R^1 = 4\text{-}BrC_6H_4$, $R^2 = C_6H_5$
25g (or) 26g: $R^1 = 2\text{-}MeOC_6H_4$, $R^2 = C_6H_5$
25h (or) 26h: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = 4\text{-}MeC_6H_4$
25i (or) 26i: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = 4\text{-}ClC_6H_4$
25j (or) 26j: $R^1 = 2\text{-}MeOC_6H_4$, $R^2 = 4\text{-}ClC_6H_4$

Subsequent intramolecular Baylis-Hillman reactions of acrylamide-ketones (**26a-j**) using DABCO as a promoter in dioxane-water solvent (1:1) system provided α-methylene-γ-lactam derivatives (**27a-j**) containing tertiary alcoholic functionality as described in Eq.1.

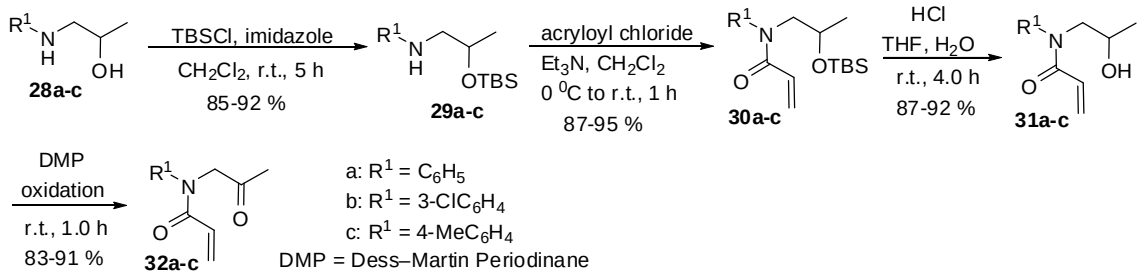


Eq.1

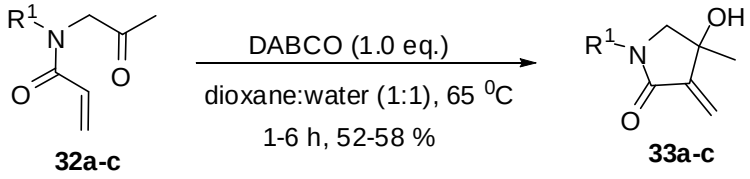
$R^1 = C_6H_5$, 2-$MeOC_6H_4$, 4-BrC_6H_4, 3, 5-$Me_2C_6H_3$
$R^2 = C_6H_5$, 2-Naphthyl, 4-ClC_6H_4, 4-MeC_6H_4

Next we have extended this strategy to the acrylamide-ketone (aliphatic) substrates N-(2-oxopropyl)-N-arylacrylamides (**32a-c**). Accordingly we have prepared the representative substrates (**32a-c**) following reaction sequence as shown in the Scheme 6.

Scheme 6



We have then subjected N-(2-oxopropyl)-N-arylacrylamides (**32a-c**) to intramolecular Baylis-Hillman reaction in the presence of DABCO which provided the required IBH adducts, α-methylene-γ-lactam derivatives (**33a-c**) in good yields (Eq.2).



Eq. 2

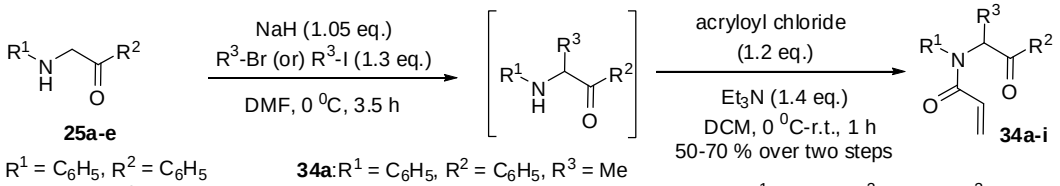
a: $R^1 = C_6H_5$; b: $R^1 = 3\text{-}ClC_6H_4$; c: $R^1 = 4\text{-}MeC_6H_4$

Highly diastereoselective intramolecular Baylis-Hillman reaction of acrylamide-α-substituted ketones

After achieving reasonable success in the intramolecular Baylis-Hillman reaction using less reactive acrylamide-ketone substrates (**26a-j**) and (**32a-c**), we have focused our attention towards acrylamide-α-substituted ketones (**34a-i**) containing a chiral centre (racemic) with a view to examine the possibility of achieving diastereoselectivity in

intramolecular Baylis-Hillman reaction. Accordingly we have synthesized the required acrylamide-α-substituted ketones (**34a-i**) following the reaction sequence as described in the Scheme 7.

Scheme 7

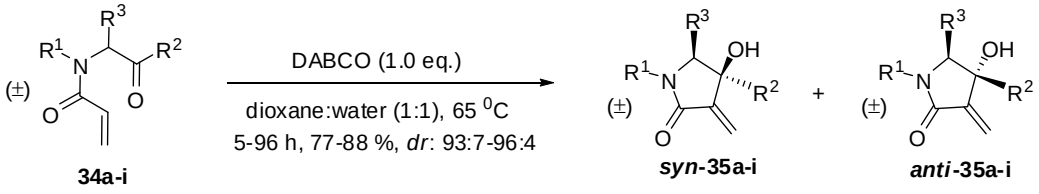


25a-e **34a-i**

25a: $R^1 = C_6H_5$, $R^2 = C_6H_5$
25b: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$
25c: $R^1 = C_6H_5$, $R^2 = 2\text{-Naphthyl}$
25d: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = C_6H_5$
25e: $R^1 = C_6H_5$, $R^2 = 4\text{-}MeC_6H_4$

34a: $R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = Me$
34b: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = Me$
34c: $R^1 = C_6H_5$, $R^2 = 2\text{-Naphthyl}$, $R^3 = Me$
34d: $R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = Et$
34e: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = Et$
34f: $R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = allyl$
34g: $R^1 = 3,5\text{-}Me_2C_6H_3$, $R^2 = C_6H_5$, $R^3 = allyl$
34h: $R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = i\text{Bu}$
34i: $R^1 = C_6H_5$, $R^2 = 4\text{-}MeC_6H_4$, $R^3 = i\text{Bu}$

Subsequent treatment of compounds **34a-i** with DABCO gave the resulting IBH adducts (**35a-i**) with high *syn*-diastereoselectivities (we have assigned *syn*-stereochemistry when 'R^3' and 'OH' groups are in the same side. If 'R^3' and 'OH' groups are situated opposite to each other we assigned *anti*-configuration) (Eq. 3). We have also proposed appropriate mechanism for high diastereoselectivity in this reaction.



34a-i ***syn*-35a-i** ***anti*-35a-i** **Eq. 3**

$R^1 = C_6H_5, 3,5\text{-}Me_2C_6H_3$; $R^2 = C_6H_5, 4\text{-}ClC_6H_4, 2\text{-Naphthyl}, 4\text{-}MeC_6H_4$
$R^3 = Me, Et, allyl, i\text{Bu}$

The third chapter provides detailed experimental procedures, physical constants like melting point, IR, ^1H & ^{13}C NMR, HRMS spectral data and HPLC Charts.

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