Novel Synthetic Approaches to Aza-heterocycles, Oxo-α-Amino Acids and (*E*)-α,β-Unsaturated Carboxylic Acids/Esters

A thesis

Submitted in partial fulfillment of the requirements

Of the degree of

Doctor of Philosophy

By

Amar R. Mohite

ID: 20083004

INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH, PUNE

February 2014

Dedicated to My Parents

And

My Sister

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH (IISER), PUNE
(An Autonomous Institution, Ministry of Human Resource Development, Govt. of India)
900 NCL Innovation Park, Dr. Homi Bhabha Road, Pune 411008

Dr. Ramakrishna G. Bhat
Associate Professor
Department of Chemistry
IISER, Pune.

CERTIFICATE

Certified that the work incorporated in this thesis entitled "***Novel Synthetic Approaches to Oxo-α-Amino Acids, Aza-heterocycles and (E)-α,β-Unsaturated Carboxylic Acids/Esters"*** submitted by **Mr. Amar R. Mohite** was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

Date: 7th Feb. 2014, Pune

Ramakrishna G. Bhat
(Research Supervisor)

DECLARATION

I declare that, this written submission represents my ideas in my own words and where others' ideas have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea / data / fact/ source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Date: 7th Feb. 2014, Pune

Mr. Amar R. Mohite
(Senior Research Fellow)
ID: 20083004

ACKNOWLEDGEMENTS

It has been a long journey for the completion of this degree and it would not have been possible without the support of many individuals. First of all, I am grateful to my mentor Professor Ramakrishna G. Bhat (RGB) who continuously encouraged me to pursue this research work. As a first and new student to research field, he spent extra time to teach and helped to achieve clear structure of my research work. He helped me lot during my research work till the completion of my thesis at each and every step of my PhD. I thank him for believing in my abilities, and for his guidance in chemistry, and general optimism in life. It is difficult to compose appropriate sentence to express my gratefulness to him for his guidance and keen interest which made this work possible.

I sincerely thank Director Prof. K. N. Ganesh for giving me an opportunity to work in the prestigious and state of art research facility provided by the IISER-Pune, also for the access to his lab, at the NCL during the construction of IISER-P research laboratories. I am also grateful to the Research Advisory Committee (RAC) members Dr. H. N. Gopi and Dr. C. V. Ramana for their valuable suggestions and their insights for improving the projects. I specially thank Dr. V. G. Anand and other faculty members of chemistry department for their valuable discussions.

I am grateful to work with my colleagues Prakash, Rajesh, Balu, Tushar and Trimbak who made friendly environment for research work. They are the best colleagues and friends that I have ever met. I am also happy to work with Digvijay Int. MS student and Anand who brought the fresh perspective and help during my research work.

I would like to acknowledge the support from DK (Dnyaneshwar) and Shekhar for fluorescent studies. Thanks to Bapu for helping me in doing TGA study. I am grateful to the technical staff and non-technical staff of IISER-Pune. I would like to thank Sachin and Sandip for recording mass samples in the absence of technical staff during the initial days. I am also thankful to Kudu and Dr. Ravi Ghorpade for their help during my initial stages of research work. I am thankful to Shekhar for his continuous help during the research work.

I would like to acknowledge the financial assistance from IISER-Pune for my entire research work and graduate research fellowship.

I had a great time with my friends Shekhar, Deepak, Prakash, Sandip, Alex, Sachin, Maroti, Nitin, Anupam, Anurag, D. K., Shivaji, Kanika, Vijay, Murthy, Mayur, Dharma, Sharad, Resmi, Arthur, Arun during my stay and this will etched ever in my memory. I always enjoyed adventurous trekking trips with Somu, Harsha and Anurag. I will always remember the quality time spent with my friends at my hostels (HR2), Deghe Bungalow and sipping tea along with my room-mate Murthy.

I enjoyed and shared my life experiences with my friendz Shraddha, Pravin, Sagar, Samir, Khudu, Kapil, Sunny, Ram (Pappu), Sandy, Vijaaa, Sushma, Dipti, Akshay (Akyaa) who always there for me.

I thank my sister for her endless love and thanks are also due to the charming, curious and lovable my nephew: Arya who always made me to smile. At this stage, I would like to thank my mama (uncle) who helped me a lot during the period. At last but not the least, I am humbly grateful and indebted to my parents, for their constant love and encouragement. Thank you.

Amar R. Mohite

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ABBREVIATIONS

Ac	Acyl
Ar	Aryl
Bn	Benzyl
^{t}Boc	*tert*-butoxycarbonyl
bs	broad singlet
Calcd.	Calculated
Cat.	Catalytic
Cbz	benzyloxycarbonyl
DME	Dimethoxymethane
DBU	1,8-Diazabicycloundec-7-ene
d	doublet
DCC	*N*,*N*’-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
DEPT	Distortionless Enhancement by Polarization Transfer
DMAP	*N*,*N*'-dimethylaminopyridine
DMSO	dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimehtylaminopropyl)carbodiimide
EI	electron impact
EtOAc	ethyl acetate
GHz	Gigahertz
g	gram
h	hour
HMBC	Heteronuclear Multiple-Bond Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IR	Infra red
J	Spin coupling consatant
LDA	Lithium diisopropylamide
m	multiplet
m/z	mass/charge
MA	Meldrum's Acid or 2,2-dimethyl-1,3-dioxane-4,6-dione
MALDI TOF/TOF	Matrix Assisted Laser Desorption Ionization Time of Flight
Me	methyl
mg	milligram
min	minute
mL	milliliters
mmol	millimole

MOM	Methoxymethyl
mol	mole
mp	melting point
MsOH	Methanesulfonic acid
MS	Molecular sieve
MW	Microwave
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methylmorpholine *N*-Oxide
nOe	Nuclear Overhauser Effect
OMC	Octyl methoxycinnamate
*p*TSA	*p*-Toluenesulfonic acid
Ph	phenyl
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
t	triplet
^{t}Bu	*tert*-butyl
td	triplet of doublet
TES	triethylsilane
TEA	triethyl amine
TFA	trifluoroacetic acid
TGA	Thermogravimetric Analysis
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TOF	Turnover frequency
TON	Turnover number

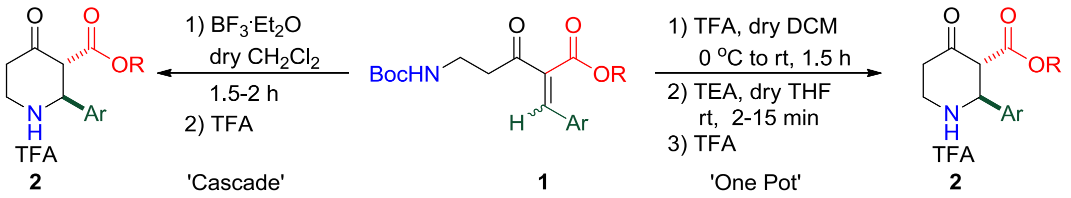
SYNOPSIS

The thesis entitled ***"Novel Synthetic Approaches to Oxo α-Amino acids, Aza-Heterocycles and α,β-Unsaturated Carboxylic acids/esters"*** comprises of four chapters.

Chapter 1: *Synthesis of trans-2,3-disubstituted piperidones and their derivatives from amino acids.*

In this chapter two new protocols for the diastereoselective synthesis of 2,3-disubstituted piperidones have been described. The approach has been utilized to make the precursor of pipecolic acid as well. Diastereoselective *trans*-2,3-disubstituted piperidones and piperidines have been synthesized by the intramolecular aza-Michael addition of alkylidene β-ketoesters **1** derived from β-alanine. Alkylidene β-ketoesters **1** on treatment with Lewis acid: $BF_3{\cdot}Et_2O$ afforded piperidone derivatives **2** in very good yields (up to 85%) following cascade reaction type pathway. $BF_3{\cdot}Et_2O$ activated the double bond for Michael addition and also deprotected ^{t}Boc group in cascade manner to furnish substituted piperidones. In addition one pot synthesis of piperidones from alkylidene β-ketoesters has been achieved by the use of trifluoroacetic acid (TFA) followed by the addition of triethylamine (Table **1**).

Table 1: Synthesis of Piperidones by Cascade and One pot method



R	**Ar** (One Pot Method)	R	**Ar** (Cascade Method)
Me	4-Methoxyphenyl (**2a**, 84%)	Me	Phenyl (**2b**, 64%)
Me	Phenyl (**2b**, 85%)	Me	3-Bromophenyl (**2c**, 64%)
Me	3-Bromophenyl (**2c**, 82%)	Me	4-^{t}Butylphenyl (**2d**, 64%)
Me	4-^{t}Butylphenyl (**2d**, 88%)	Me	4-Methylphenyl (**2e**, 66%)
Me	4-Methylphenyl (**2e**, 81%)	Bn	4-^{t}Butylphenyl (**2i**, 85%)
Me	3,4-Dimethoxyphenyl (**2f**, 86%)	Bn	Phenyl (**2j**, 84%)
Me	4-Bromophenyl (**2g**, 80%)		
Me	Furyl (**2h**, 72%)		
Bn	4-^{t}Butylphenyl (**2i**, 85%)		
Bn	Phenyl (**2j**, 84%)		

Various 2,3-disubstituted piperidone derivatives (**2a**–**2j**) have been synthesized starting from alkylidene β-ketoesters. The stereochemistry at C-2 and C-3 position of piperidone has been unequivocally confirmed by ^{1}H-NMR (coupling constant) and single crystal X-ray diffraction of compound **2e**.

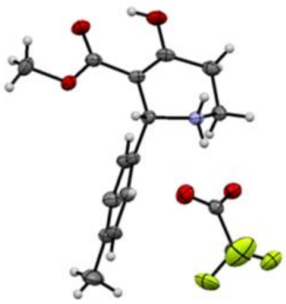
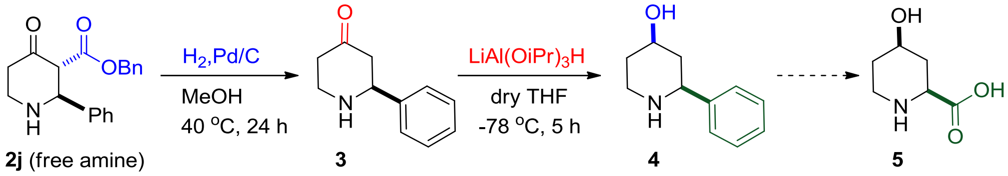


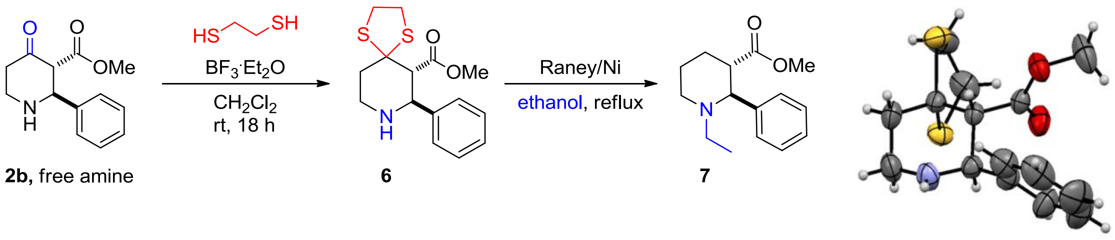
Fig 1: Molecular structure of compound **2e**

Further this method has been effectively utilized in synthesizing the precursor of 4-hydroxy pipecolic acid **4** (Scheme **1**). One pot debenzylation followed by decarboxylation of compound **2j** (free amine) afforded 2-phenyl piperidone **3**, which upon treatment with sterically hindered reducing agent LiAl(O^{i}Pr)$_3$H furnished 2-phenyl 4-hydroxy piperidine **4**: a precursor of 4-hydroxy pipecolic acid **5**.



Scheme 1: Synthesis of precursor of 4-hydroxypipecolic acid

The keto-enol tautomerism in piperidone derivatives has been observed. This observation has been studied in two different solvents by ^{1}H-NMR spectroscopy. In order to understand the stereochemistry at C-2 and C-3 positions, the keto group of **2b** (free amine) was protected using ethane-1,2-dithiol to afford compound **6** (Scheme **2**). The single crystal X-ray diffraction analysis of **6** unequivocally confirmed the *trans* geometry. We observed the formation of *N*-ethylated piperidine derivative **7** during the reduction of compound **6** with Raney/Ni in ethanol.



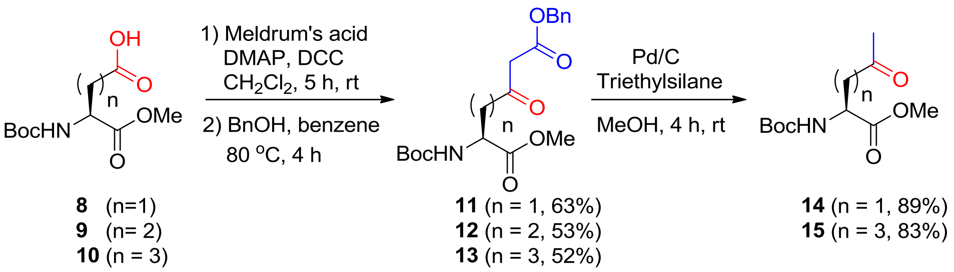
Scheme 2: Synthesis of *N*-alkylated piperidine and crystal structure of **6**

Convenient and efficient diastereoselective syntheses of *trans*-2,3-disubstituted piperidone derivatives by one pot method as well as using cascade reaction pathway have been explored.These protocols involve simple and convenient experimental procedures, short reaction time and high yields.

Chapter 2: *Synthesis of side chain modified Oxo-α-Amino acids and cis-5-alkyl Prolines.*

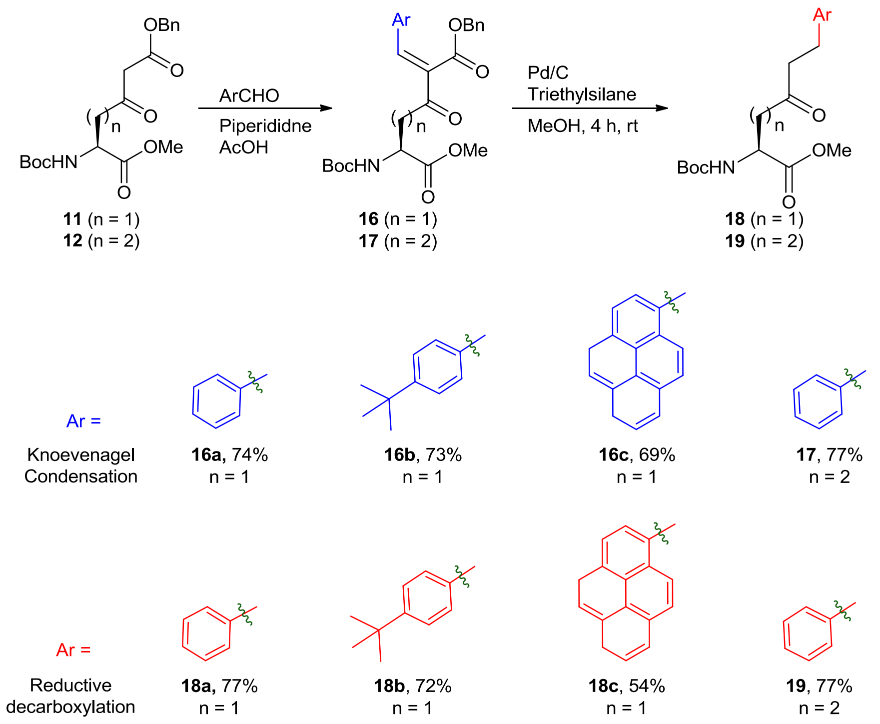
This chapter presents a brief overview on the importance and the synthesis of side chain modified α-amino acids. Oxo-α-amino acids have been successfully employed in site specific modification and these side chain modified amino acids are also present in the inhibitors of oligosaccharyltransferase. Such kind of amino acids have been effectively utilized in organocatalysis and the molecular scaffolds derived from these amino acids have been utilized in peptidomimetics. Similarly, unnatural amino acids such as *cis*-5-alkylated prolines have been effectively used in the restriction of amide bond rotation in peptides. In this chapter novel and practical method has been described to synthesize various oxo-α-amino acids and *cis*-5-alkyl prolines starting from commercially available α-amino acids.

Oxo-amino acids such as 4-oxo-L-norvaline **14** and 6-oxo-L-homonorleucine **15** have been synthesized in very good yields by the reductive decarboxylation of the corresponding β-ketoesters (**11** and **13**) respectively using Pd/C and triethylsilane (Scheme **3**).



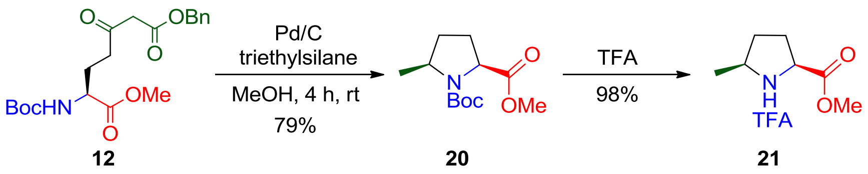
Scheme 3: Reductive decarboxylation of β-ketoesters

These β-ketoesters have been prepared from the corresponding L-aspartic acid **8** and L-homoglutamic acid **10** derivatives. The optical purity of 4-oxo-L-norvaline has been confirmed by HPLC analysis using chiral column. Its optical purity has been further supported by the literature values of specific optical rotation of the corresponding compounds. Further, Knoevenagel condensation of aminocarboxylate derived β-ketoesters (**11** and **12**, Scheme **4**) with different aldehydes afforded corresponding derivatives (**16a–c**, **17**). These derivatives under reductive decarboxylation conditions afforded the side chain modified oxo-α-amino acids in good yields (**18a–18c**, **19**).



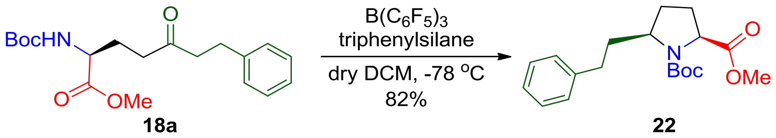
Scheme 4: Synthesis of Oxo-α-amino acids

To illustrate the application of this methodology a fluorescent amino acid **18c** has been synthesized. These studies have shown that aminocarboxylate derived β-ketoesters are very useful intermediates and the method employed is both general and practical for the preparation of β(γ)-oxo-α-amino acids. Interestingly, L-glutamic acid derived β-keto ester **12** under similar reductive decarboxylation conditions resulted unanticipated 5-methyl-*N*-Boc-L-proline methyl ester **20** exclusively in 79% yield. The compound **20** on treatment with trifluoroacetic acid gave 5-methyl proline methyl ester **21** (Scheme **5**). The *cis*-stereochemistry has been confirmed by HMQC and nOe studies of **21**.



Scheme 5: Synthesis of 5-*cis*-Methyl Proline

However, oxo-amino acid **18a** resulted in the *cis*-alkyl proline derivative **22** only under Lewis acid condition (Scheme **6**).



Scheme 6: Synthesis of 5-*cis*-Methyl Proline

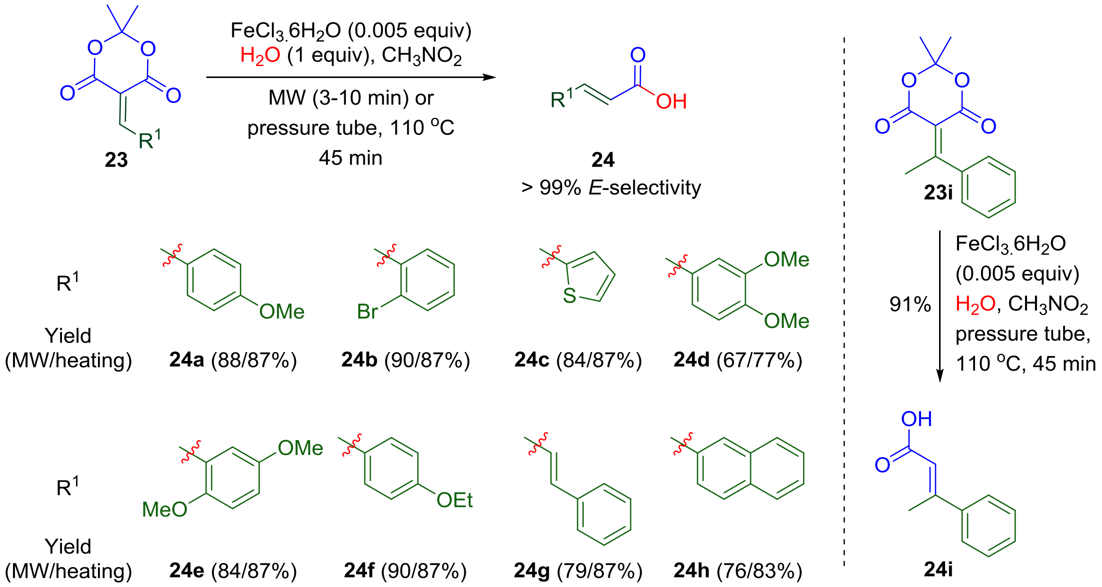
We have described an effective and practical method for the synthesis of oxo-α-amino acids and 5-*cis* alkyl substituted L-proline derivatives.

Chapter 3: *$FeCl_3·6H_2O$ catalyzed Novel and Expedient Synthesis of α,β-Unsaturated carboxylic acids/esters from alkylidene Meldrum's acids.*

This chapter is divided into two sections. Section-A describes the novel catalytic access to important and useful α,β-unsaturated carboxylic acids starting from the corresponding derivatives of alkylidene Meldrum's acid using a new catalyst system comprising of $FeCl_3·6H_2O$ (0.1-0.5 mol%) and (1 equiv) H_2O in dry CH_3NO_2. Section-B illustrates the rapid and efficient synthesis of various α,β-unsaturated carboxylic esters using $FeCl_3·6H_2O$ (0.1-0.5 mol%) and (1 equiv) alcohol in CH_3NO_2 both under conventional heating and microwave conditions.

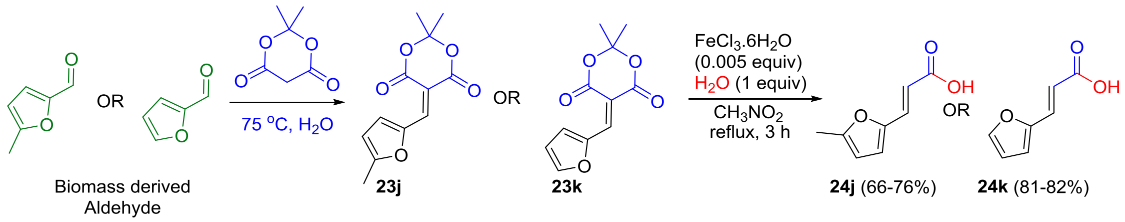
Section A: *Synthesis of α,β-unsaturated carboxylic acids and applications*

This section briefly outlines the importance of α,β-unsaturated carboxylic acids and their utility in organic synthesis with the recent literature findings. These are significant structural motifs in many natural products, pheromones and bioactive compounds. In this section we have described the facile synthesis of α,β-unsaturated carboxylic acids. Alkylidene Meldrum's acid when treated with optimized catalyst system comprising of $FeCl_3 \cdot 6H_2O$ (0.1-0.5 mol%) and (1 equiv) H_2O in CH_3NO_2 undergoes an efficient ring cleavage to furnish α,β-unsaturated carboxylic acids in relatively short time. Initially, in order to optimize the efficient catalytic transformation, many Lewis acids were screened under both conventional heating and microwave irradiation (2.5 GHz) conditions in a pressure tube. Various α,β-unsaturated carboxylic acids (**24a**–**24i**) have been synthesized from the corresponding alkylidene derivatives of Meldrum's acid (MA) (**23a**–**23i**) using this protocol (Scheme **7**).



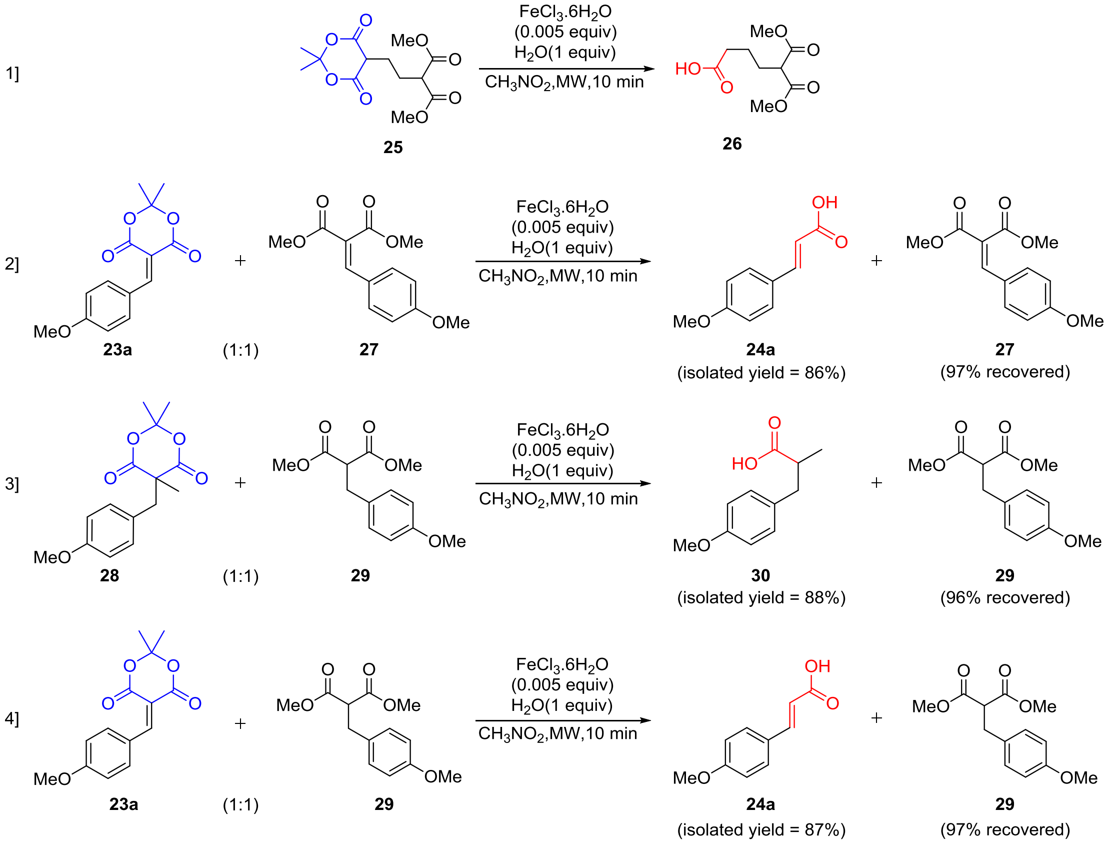
Scheme 7: Substrate scope for α,β-unsaturated carboxylic acids

Notably, we observed that *(E)*-isomers have been obtained as major products (>99%, Scheme **7**). Besides, the catalyst system tolerated many functional moieties under the reaction conditions. Further, biomass derived aldehydes such as furfural and 5-methyl furfural have been utilized in synthesizing the corresponding alkylidene Meldrum's acid derivatives **23j** and **23k** respectively. These compounds when subjected to optimized catalytic conditions afforded the expected α,β-unsaturated carboxylic acids **24j**, **24k** respectively in good yields (Scheme **8**).



Scheme 8: Biomass derived aldehydes in the synthesis of α,β-unsaturated carboxylic acids

These unsaturated acids have been considered as potential candidates for fuel additives and for fine chemicals. Further, the series of competitive experiments have shown that the catalytic protocol is very selective towards cyclic 1,3-diesters (Scheme **9**).

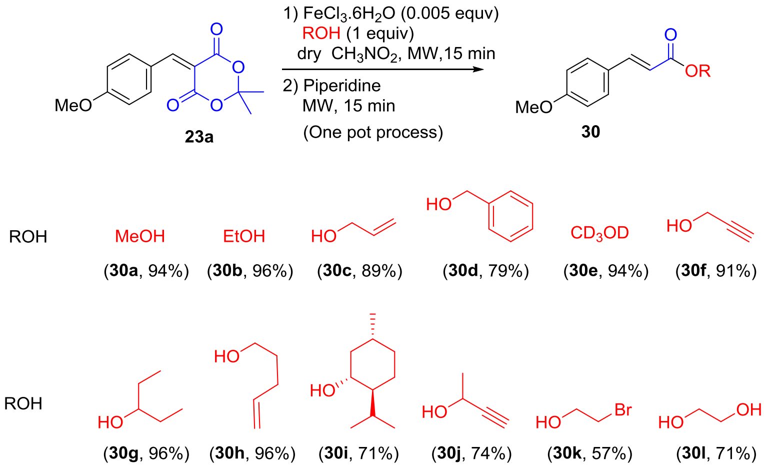


Scheme 9: Competitive experiments

It has been shown that catalyst $FeCl_3{\cdot}6H_2O$ loading as low as 0.01 mol% (0.001 equiv) would be enough for the very efficient catalytic transformation. Gram scale (53 g) synthesis has been demonstrated under conventional refluxing conditions. This catalytic transformation leads to volatile by-products such as CO_2 and acetone.

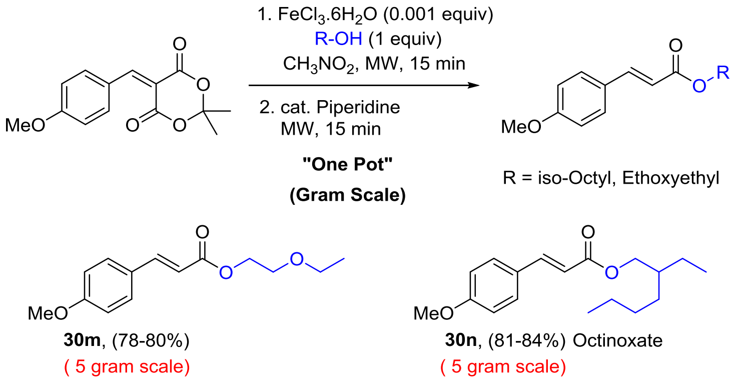
Section B: *Synthesis of α,β-unsaturated esters and applications*

This section begins with a brief account on the importance of α,β-unsaturated carboxylic esters and outlines the recent synthetic procedures. α,β-Unsaturated carboxylic esters such as *p*-methoxycinnamates have been used as important UV-B sun screens. In this section we have described the development of novel protocol for the rapid and convenient synthesis of α,β-unsaturated esters starting from very reactive alkylidine 1,3-cyclic diesters. Treatment of compound **23a** with $FeCl_3{\cdot}6H_2O$ (0.005 equiv) and MeOH (1 equiv) in CH_3NO_2 under microwave irradiation (2.5 GHz) for 15 minutes afforded the corresponding half methyl ester, which upon treatment with catalytic amount piperidine under microwave irradiation (15 min) furnished the desired methyl *p*-methoxy cinnamate **30a** in one pot in excellent yield (94%, Scheme **10**). Encouraged by the initial success, we treated compound **23a** with various alcohols to synthesize different *p*-methoxycinnamtes in moderate to excellent yields (57–96%) in short time (Scheme **10**). We observed that in most of the cases the (*E*)-isomers were obtained as major products (>98-99%).



Scheme 10: $FeCl_3.6H_2O$ catalyzed synthesis of α,β-unsaturated esters

Further, we explored this methodology by synthesizing well known sunscreen filters **30m** and **30n** (Octinoxate) in excellent yields with high *E*-selectivity (Scheme **11**). Owing to the commercial importance of sunscreen filters and to make this approach more practical, we carried out this catalytic transformation on a 5 gram scale under microwave irradiation to afford **30m** and **30n** in very good yields (80%, 84%). Notably, $FeCl_3{\cdot}6H_2O$ catalyst loading was reduced to 0.001 equiv on a large scale.



Scheme 11: Synthesis of sunscreen filters

In order to establish the generality and efficiency of this protocol different alkylidene MA derivatives were prepared and subjected to $FeCl_3\cdot6H_2O$ (0.005 equiv) and alcohol (1 equiv) in CH_3NO_2 under microwave irradiation to afford **30o**–**30s** (Fig **2**).

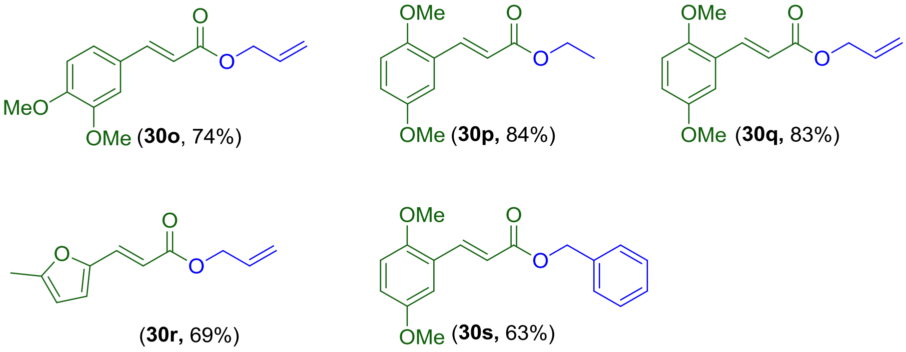


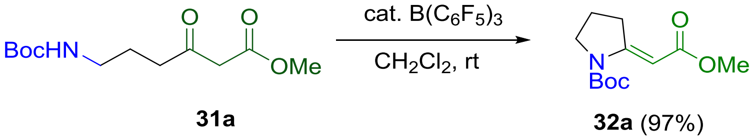
Fig 2: Substrates scope for α,β-unsaturated carboxylic esters

We have described the development of a novel methodology for an easy access of α,β-unsaturated esters from derivatives of alkylidine Meldrum's acids (cyclic 1,3-diesters). This approach is very rapid and highly *E*-stereoselective.

Chapter 4: *Lewis acid catalyzed one pot synthesis of heterocyclic β-enamino esters starting from amino acid β-ketoesters.*

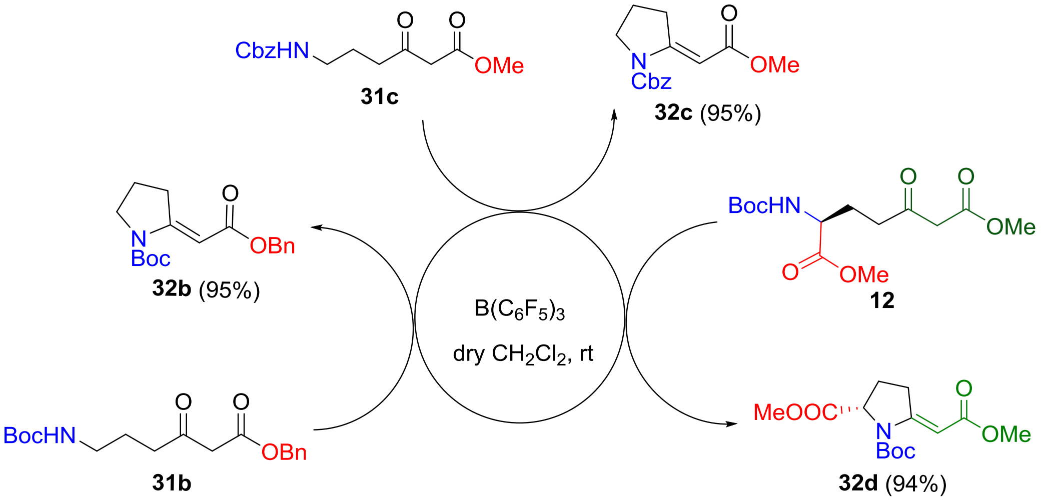
This chapter begins with the overview of the utility and the synthesis of alkylidene pyrrolidines and piperidines which are precursors of pyrrolidine and piperidine containing natural products respectively. Alkylidene pyrrolidines and piperidines have been used in the synthesis of functionalized pyrroles. They have also been employed in variety of synthetic transformations. We have described the initial stages of work on

Lewis acid: $B(C_6F_5)_3$ catalyzed synthesis of alkylidene pyrrolidines and piperidines from β-ketoesters. β-Ketoestershave been prepared starting from amino acids. The β-ketoester **31a** on treatment with catalytic amount of $B(C_6F_5)_3$ (10 mol %) in dry dichloromethane (DCM) furnished the alkylidene pyrrolidine **32a** in very high yield (Scheme **12**).



Scheme 12: Synthesis of chiral Alkylidene pyrrolidine

In order to explore the scope of this methodology, different β-ketoesters (**31b**, **31c** and **12**) were synthesized and subjected to catalytic amount of $B(C_6F_5)_3$ (10 mol %). The instantaneous reaction resulted in the formation of corresponding 5-membered heterocyclic β-enamino esters (**32b** and **32c**) and chiral heterocyclic β-enamino esters (**32d**) in excellent yields (Scheme **13**).



Scheme 13: Synthesis of chiral Alkylidene pyrrolidine

We have developed a novel catalytic protocol for the synthesis of 5-membered heterocyclic β-enamino esters. This initial study has been standardized for the synthesis of β-enamino esters. This protocol would be very useful in synthesizing piperazine and morpholine derivatives.

(*Numbers of substrates and products in the synopsis are different from those in thesis*)

LIST OF PUBLICATIONS

Journal Articles

1. **Amar R. Mohite** and Ramakrishna G. Bhat; A Practical and Convenient Protocol for the Synthesis of (*E*)-α,β-Unsaturated Carboxylic Acids; *Org. Lett.* **2013**, *15*, 4564–4567.

2. **Amar R. Mohite** and Ramakrishna G. Bhat; Enantiopure Synthesis of Side Chain-Modified α-Amino Acids and 5-*cis*-Alkylprolines; *J. Org. Chem.* **2012**, *77*, 5423–5428.

3. **Amar R. Mohite**, Prakash R. Sultane and Ramakrishna G. Bhat; $BF_3 \cdot Et_2O$ and Trifluoroacetic acid/Triethyl amine mediated synthesis of Functionalized Piperidines; *Tetrahedron Lett.* **2012**, *53*, 30–35; (Abstarct selected in **ChemInform** 2012, 43 (17); DOI:10.1002/chin.201217154.)

4. Prakash R. Sultane, **Amar R. Mohite** and Ramakrishna G. Bhat; Total synthesis of 1-deoxy-7,8a-di-*epi*-castanospermine and formal synthesis of pumiliotoxin-251D; *Tetrahedron Lett.* **2012**, *53*, 5856–5858.

5. **Amar R. Mohite** and Ramakrishna G. Bhat; An Expedient Stereoselective Synthesis of (*E*)-α,β-Unsaturated Esters Using $FeCl_3 \cdot 6H_2O$. *Communicated.*

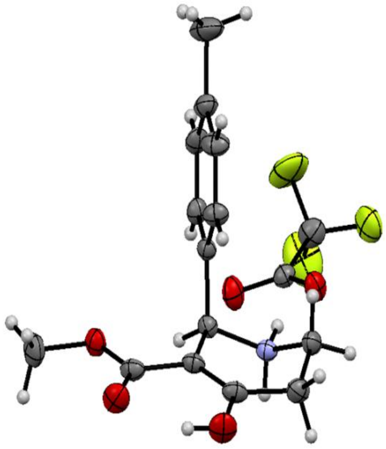
6. L.V. R. BabuSyamala, **Amar R. Mohite** and Ramakrishna G. Bhat; $FeCl_3 \cdot 6H_2O$ catalyzed enantioselective synthesis of 2,3 and 2,6-disubstituted piperidines: A Greener Approach; *Manuscript under preparation.*

Patent

1. **Amar R. Mohite** and Ramakrishna G. Bhat; Synthesis of (*E*)-α,β-unsaturated carboxylic acids and esters; Provisional patent filed in India application No. **2437/MUM/2013**.

Chapter One

Synthesis of *trans*-2,3-disubstituted piperidones and their derivatives from amino acids



2,3-disubstitutedpiperidone.TFA
enol form (X-ray crystal structure)

Chapter 1

In this chapter a two-step one pot synthesis of disubstituted piperidones and piperidines (only trans-configuration) starting from α,β-unsaturated keto esters has been developed. Cascade type reaction using $BF_3{\cdot}Et_2O$ *or one pot deprotection of* ^{t}*Boc group by TFA/then TEA facilitated the intramolecular aza-Michael addition of α,β-unsaturated keto esters to afford trans-2,3-disubstituted piperidines.*

1.1 Introduction

Alkaloids of Hemlock extract poisoned the ancient Greek philosopher Socrates in 399 B. C. by possible combined chemical effects of coniine and γ-coniceine found in it.[1] These are secondary metabolites containing basic nitrogen in their six-membered saturated heterocyclic ring (Fig **1.1**), however their enantiomeric metabolites[2] are rare in Nature. Alkaloids are group of natural products produced by a large variety of organisms including bacteria, fungi, plants and animals. Though some alkaloids are poisonous, most of the alkaloids often have pharmacological effects and are used as medications, as recreational drugs. The black pepper (*Piper nigrum*) is a flowering vine in the family *Piperaceae*, found mostly in southern India, and usually used as spice. Its pungent smell is due to the presence of 'piperine' an alkaloid.

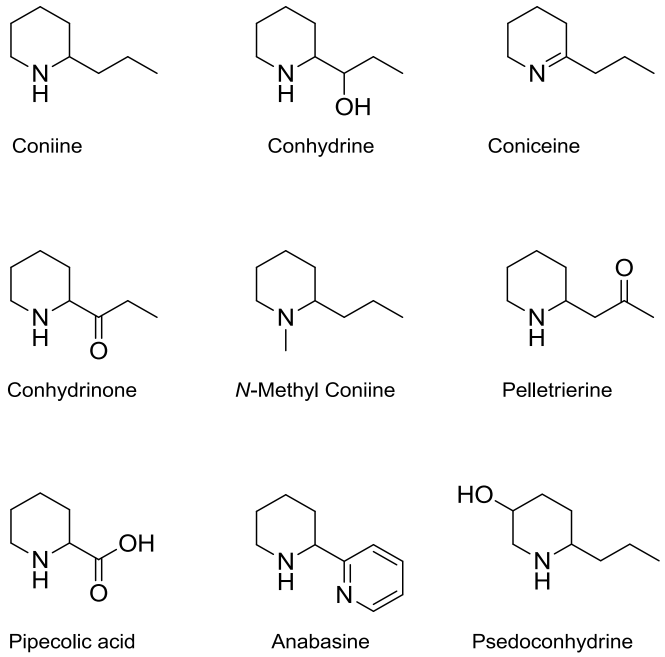


Fig 1.1: Some piperidine alkaloids found in plants

The ‘solenopsins’ are piperidine alkaloids derived from the venom of the red fire ant *Solenopsis invicta*. These piperidine alkaloids are known to inhibit angiogenesis via the phosphoinositol-3 kinase (PI3-K) signalling pathway[3] (Fig **1.2**). Dart frog found in central and south America secretes many lipophilic alkaloids through their skin as their protecting mechanism against predation.[4]

Fig 1.2: Solenopsin alkaloid in fire ants (courtesy: Wikipedia)

There are several drugs in the market that contain piperidine ring as main core. The drug Ritalin®[5] used for the treatment of attention-deficit-hyperactivity disorder and the insect repellent Bayrepel®[6] also contain a 2-substituted piperidine core (Fig **1.3**). These are privileged structures and viable scaffolds in the drug discovery. Piperidine containing small molecule APIs (active pharmaceutical ingredients) used in the drugs are listed below (Fig **1.3**).

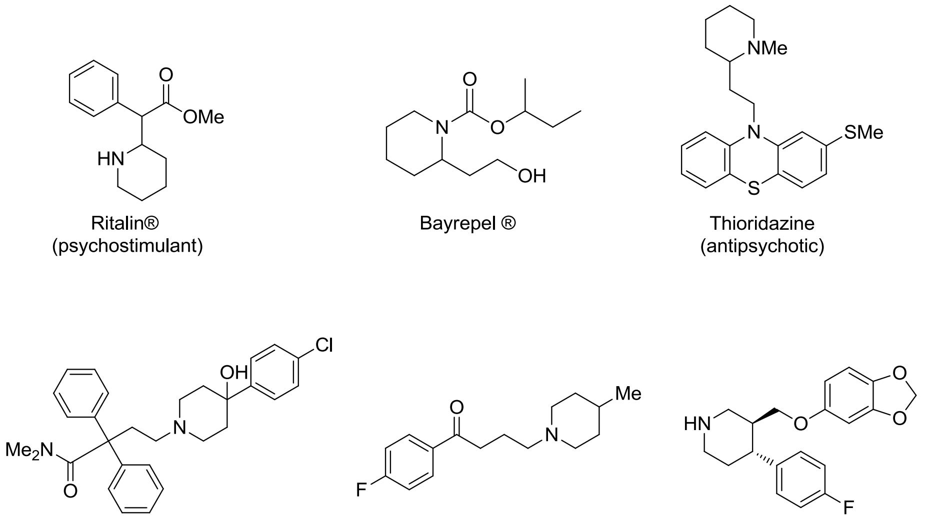
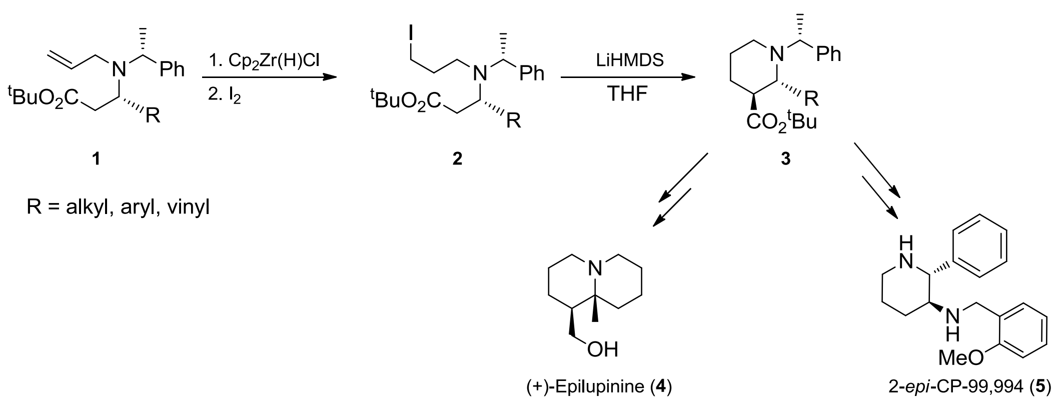

Ritalin® (psychostimulant)
Bayrepel ®
Thioridazine (antipsychotic)
Loperanide opioid
Melperane (antipscychotic)
Paroxetine (antidepressant)

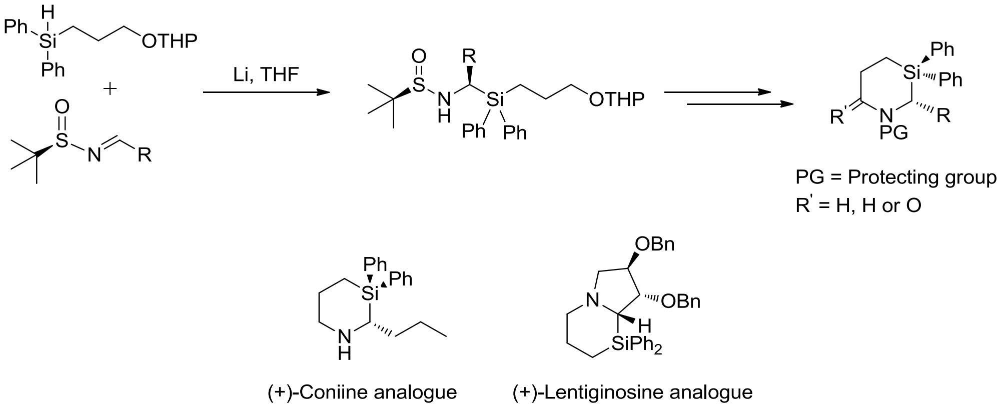
Fig 1.3: Some APIs containing piperidine core

Clearly, synthesis of such important piperidines is subject of study. Some of the synthetic methods have been applied[7] mostly starting from substituted pyridines,[8] amino alcohols,[9] imines.[10] Other methods rely on aldol reaction,[11] reductive amination reaction,[12] ring expansion and heterocyclic rearrangements,[13] aza-conjugate additions.[14] Various metal and acid catalyzed cyclizations,[15] and Mannich type reactions[16] have been explored. Recently, olefin metathesis,[17] and multicomponent reactions[18] have been employed for the constructions of piperidines. Szmoniak *et al.* used hydrozirconation cyclization strategy[19] for synthesis of pyrrolidines and further this methodology was extended for synthesis of *trans*-2,3-disubstituted piperidines (Scheme **1.1**).



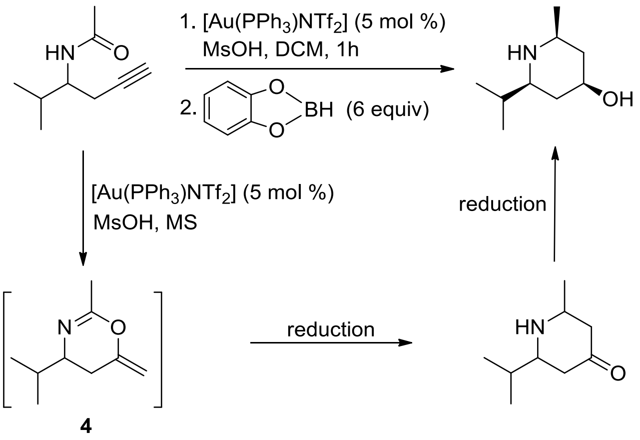
Scheme 1.1: Hydrozirconation cyclization

The chemoselective hydrozirconation of *N*-allyl-amino ester followed by iodination (generation of an electrophilic site) gave an iodo compound **2** which upon treatment with LiHMDS afforded diastereomerically pure piperidines **3** in good yields. The stereochemical outcome of this reaction is due to chair like transition state involving a non-chelated *E*-enolate. While, in another method, Skrydstrup *et al.* demonstrated an efficient synthesis of 1,3-azasilaheterocycles[20] and related alkaloids by using chiral α-silylsulfinamide (Scheme **1.2**).



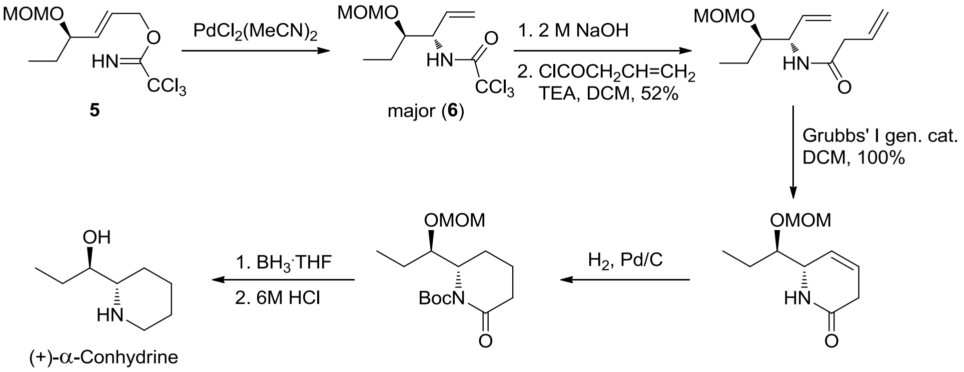
Scheme 1.2: Silicon containing piperidines

Addition of alkyldiphenylsilane to sulfinimine in presence of lithium metal gives a series of *α*-silylsulfinamide derivatives, which upon treatment with base or coupling agent (water soluble carbodiimide, EDC·HCl) afforded aza-piperidines. The stereochemical outcome was greatly dependent upon chiral sulphamine. Several alkaloid analogues of (+)-coniine, indolizidine and (+)-lentiginosine have been synthesized using this methodology. (+)-Subcosine II, a member of *Lythraceae* family of natural products was isolated from *Lagerstroemia subcostata*. Zhang and co-workers showed an elegant method for the stereoselective synthesis of piperidin-4-ones,[21] an alternative method to aza-Petasis-Ferrier rearrangement (Scheme **1.3**).



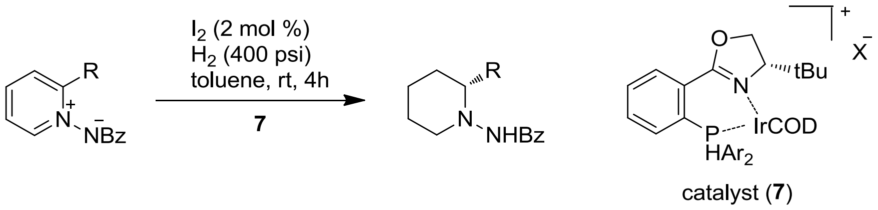
Scheme 1.3: Gold catalyzed Ferrier rearrangement towards piperidines

Gold catalyzed cyclization of *N*-homopropargyl amide offered the cyclic intermediate **4**, an imidate that underwent Ferrier rearrangement to furnish piperidine-4-ones. Further, chemoselective reduction afforded piperidin-4-ols. The stereochemical outcome has been substrate controlled and dependent on the stereochemistry of *N*-homopropargyl amide. (+)-α-Conhydrine, a piperidine alkaloid was isolated from the leaves of the poisonous plant, *Conium maculatum* L. Sutherland *et al.* explored Pd catalyzed MOM-ether directed aza-Claisen rearrangement for the stereoselective synthesis of (+)-α-conhydrine and its pyrrolidine analogues (Scheme **1.4**).[22] The allylic trichloroacetimidate **5** in presence of palladium (II) catalyst underwent aza-Claisen rearrangement by affording *erythro* isomer **6** as a major product. Further, *N*-acylation followed by Grubbs' metathesis gave (+)-α-conhydrine (Scheme **1.4**).



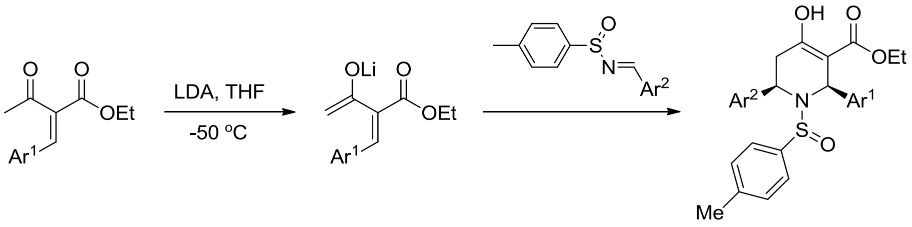
Scheme 1.4: Overman rearrangement

Carette and co-workers[23] showed an elegant method to synthesize 2-substituted piperidine derivatives. The catalytic asymmetric hydrogenation of *N*-iminopyridinium ylides by using chiral iridium complex **7** and iodine afforded enantiopure piperidine derivatives in one pot (Scheme **1.5**).



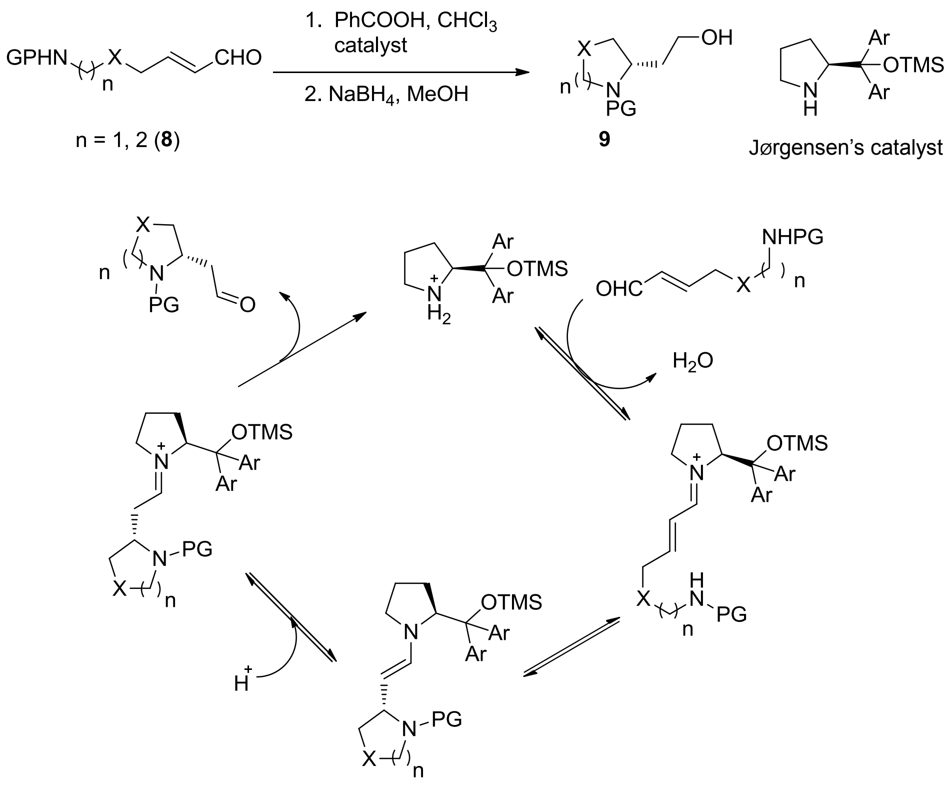
Scheme 1.5: Asymmetric hydrogenation of *N*-iminopyridinium ylides

Ghorai and co-workers used the domino imino-aldol-aza-Michael strategy for synthesis of 2,6-*cis*-disubstituted piperidines.[24] In this strategy, enolate of α-alkylidine-β-ketoester was generated followed by the subsequent addition to *N*-sulfonylaldimines afforded the corresponding disubstituted piperidines (Scheme **1.6**).



Scheme 1.6: Domino imino-aldol-aza-Michael reaction

This method gave an access to enantioselective and distereoselective 2,6-*cis*-piperidines. Hemlock (*Conium maculatum* L. *Umbelliferae*) has long been known as a poisonous plant and great interest has been devoted for the synthesis and study of alkaloids derived from this plant. Fustero and co-workers described a very simple method for the synthesis of several alkaloids such as (+)-coniine, (+)-sedamine and (+)-allosedamine by organocatalytic intramolecular aza-Michael reaction.[25] Compound **8** (containing a carbamate as well as α,β-unsaturated aldehyde moieties at remote positions) on treatment with Jørgensen's catalyst underwent aza-Michael addition to afford five and six membered heterocycles **9** in moderate yields with good enantioselectivity (Scheme **1.7**).



Scheme 1.7: Organocatalytic Michael addition of carbamate and its reaction mechanism

There are several synthetic methods available for the preparation of piperidines as described above. Every method is unique with respect to starting material, catalyst and way of transformation. Most of these methods are engineered to synthesize piperidine derivatives with specific stereochemistry and property. Some of these methods use expensive and/or complex catalysts, and some of them consist of low yielding steps and demand chromatographic purification, hence decreasing the overall chemical efficiency of the reactions. Some of the drawbacks can be avoided by subjecting reactants to successive chemical transformations in just one reaction flask or by carrying out consecutive series of intramolecular chemical reactions in one pot. This would minimize tedious purifications or chromatographic purification of each step, thus minimizing chemical waste generation, and saving time. In spite of these available methods it is still a challenge to develop a method that is cost effective and practical for the synthesis of substituted piperidines.

In this chapter we describe a two-step short and efficient strategy for the synthesis of substituted piperidones and piperidines in high diastereoselectivity (only *trans*-configuration), by employing cascade type reaction using $BF_3 \cdot Et_2O$ or by carrying out one pot deprotection of ^{t}Boc group followed by intramolecular aza-Michael addition of α,β-unsaturated β-ketoesters.

1.2 Results and Discussion

In the literature, several interesting natural products with piperidine scaffold have been reported. Most of these piperidines have substitutions at 2, 3 or 4 positions (Fig **1.4**). Interestingly, less attention has been given for the synthesis of these natural products from a common intermediate.

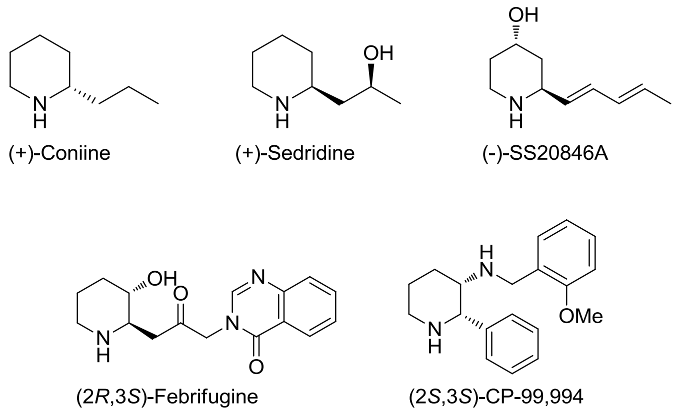


Fig 1.4: Substituted piperidine alkaloids

We planned to design an intermediate **10** that can be converted into different substituted piperidines of biological importance (Fig **1.5**). Hence, we envisaged that, intermediate **10** can be explored for synthesis of 2-substituted, (2,4)-disubstituted and (2,3)-disubstituted piperidines.

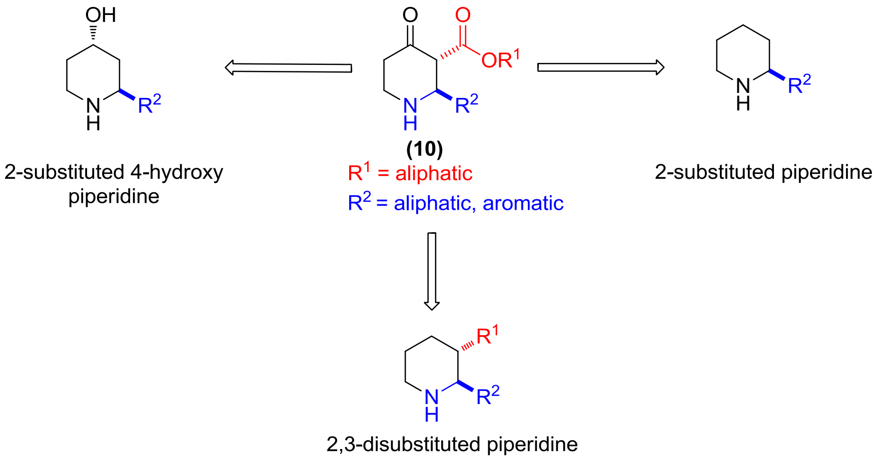


Fig 1.5: Planned intermediate for synthesis of substituted piperidines

In order to synthesize piperidines in a cost effective and convenient pathway, simple and commercially available starting materials would be ideal. In our retrosynthetic analysis (Fig **1.6**) we envisioned that functionalized piperidines can be constructed conveniently by the intramolecular aza-Michael reaction of α,β-unsaturated β-ketoester **12**. In turn, compound **12** can be synthesized from Masamune-Claisen β-ketoester **11** by condensing with various aldehydes using Knoevenagel condensation. Compound **11** can be easily synthesized starting from commercially available inexpensive naturally occurring β-alanine.

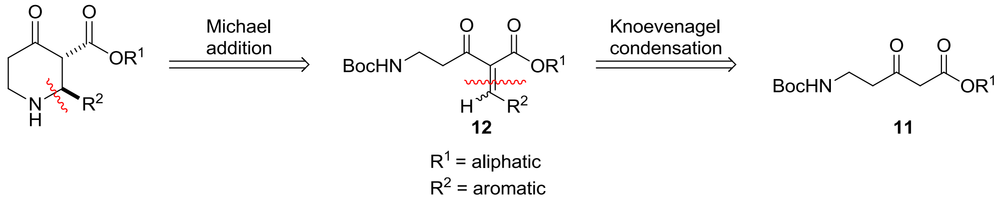


Fig 1.6: Retrosynthetic analysis

1.2.1 Synthesis of β-ketoester

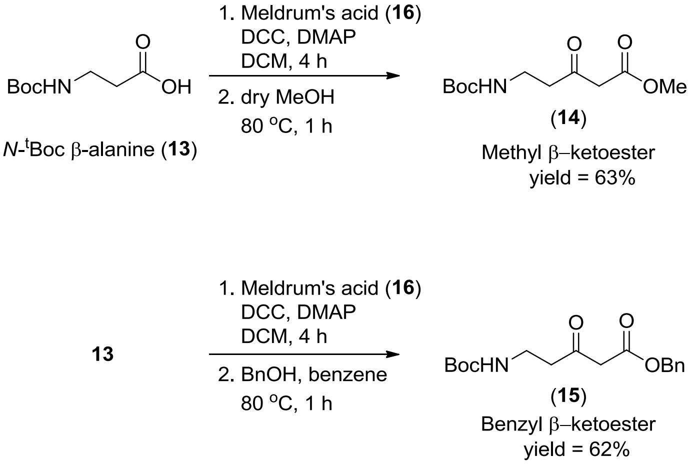
Though there are many approaches for the synthesis of β-ketoesters[26] but only few methods are available in literature for the synthesis of β-ketoesters starting from carboxylic acids.[27] It is known in the literature that alcohols can readily react with an intermediate, obtained from the coupling of Meldrum's acid with carboxylic acid to afford the corresponding β-ketoesters.[28] Different alcohols can be used as nucleophiles for the construction of different β-ketoesters.

12

R^1 = Aliphatic
R^2 = Aliphatic, Aromatic

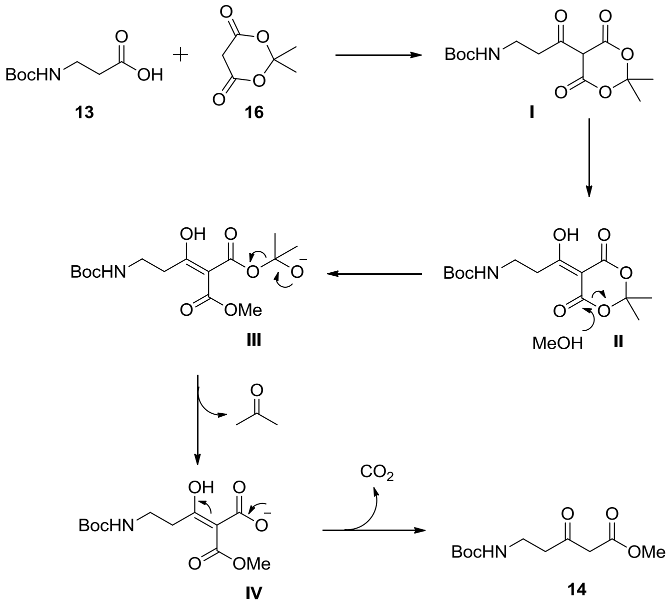
Scheme 1.8: Proposed strategy for synthesis of piperidones

In order to explore the synthetic strategy we began our study with the preparation of Masamune-Claisen β-ketoester (**14**, Scheme **1.9)** starting from *N*-^{t}Boc-β-alanine **13** using Meldrum's acid (**16**) approach in one pot. In order to study the effect of ester functionality if any, benzyl β-ketoester **15** was also prepared from **13** using Meldrum's acid and benzyl alcohol.



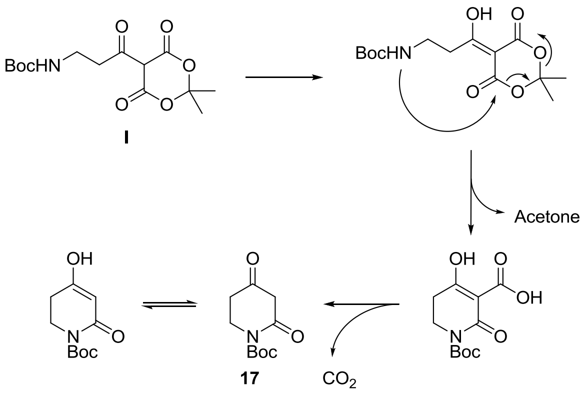
Scheme 1.9: Synthesis of β-ketoesters (**14**, **15**) from β-Alanine

Meldrum's acid (MA) **16** is distinguished from other 1,3-dicarbonyl compounds in two main ways: it is extremely acidic and also highly electrophilic. In terms of acidity, pKa of MA in DMSO is 7.3.[29] This makes MA more reactive for the coupling. The electrophilicity of Meldrum's acid, coupled with its simple and versatile derivatization, make MAs very attractive reagent for organic synthesis. The plausible mechanism for the formation of β-ketoester has been described in Scheme **1.10**. MA reacts with *N*-^{t}Boc-β-alanine to form a coupled product **I**, which then undergoes keto-enol tautomerism to form a stable enol isomer **II**. Under heating conditions methanol reacts with adduct **II** by attacking one of the carbonyl carbons of cyclic diester to form an intermediate **III**. This intermediate instantaneously loses acetone to afford an intermediate **IV** that undergoes thermal decarboxylation to furnish β-ketoester **14**.



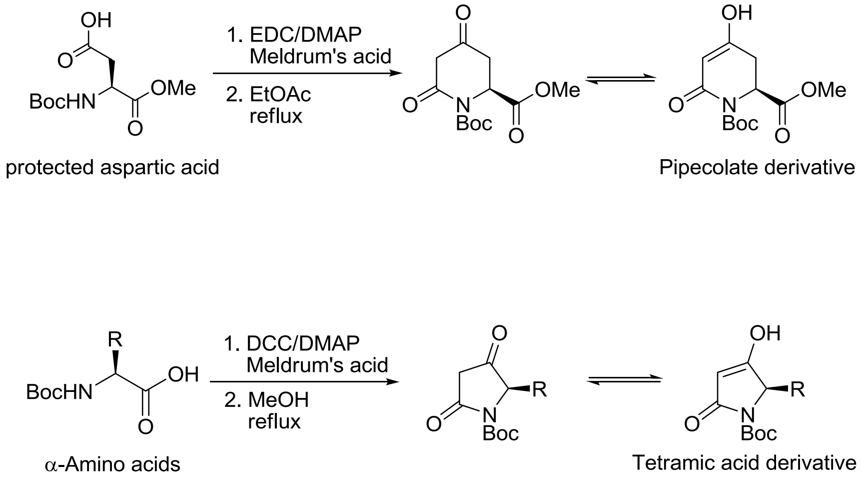
Scheme 1.10: Mechanism of β-ketoester formation by Meldrum's acid method

It is known in the literature that adduct **I** under heating conditions cyclizes[30] to form piperidine derivative **17** (Scheme **1.11**), which are potentially useful intermediates for synthesis of several natural products.



Scheme 1.11: Synthesis of piperidine derivatives from intermediate I

Similarly, β-ketoesters derived from optically pure α-amino acids are known to yield optically pure piperidines[31] and tetramic acids (Scheme **1.12**).[32]

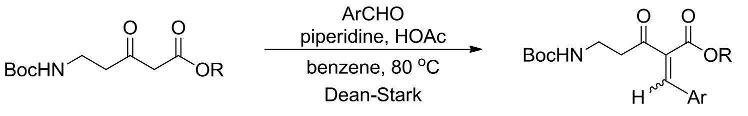


Scheme 1.12: Synthesis of enantiopure pipecolate and Tetramic acid derivatives

1.2.2 Preparation of unsaturated β-ketoesters using Knoevenagel condensation

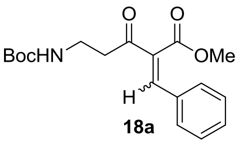
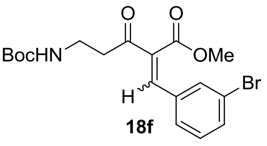
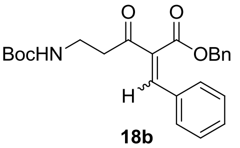
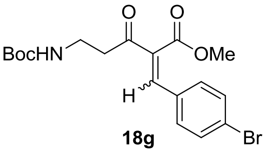
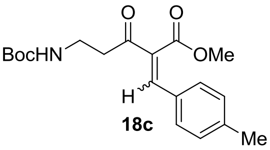
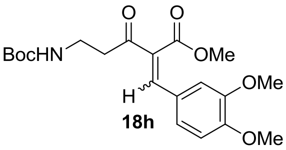
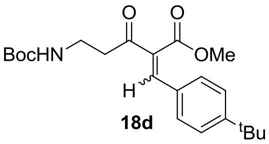
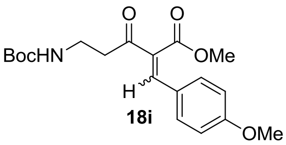
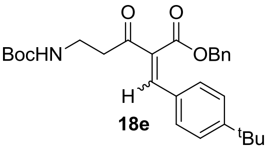
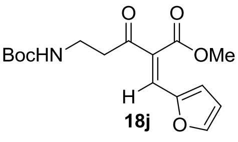
As per the concept outlined (Scheme **1.8**), we set out for the synthesis of unsaturated β-ketoesters. It is very well established in the literature that active methylene in β-ketoester and aldehyde will undergo Knoevenagel condensation to furnish unsaturated β-ketoesters.[33] In order to study the proposed reaction a series α,β-unsaturated β-ketoesters (**18a–18j**) have been prepared by condensing β-ketoesters (**14**, **15**) with different aldehydes in good to excellent yields (63–88%, Table **1.1**).

Table 1.1: Substrates synthesized by Knoevenagel condensation



R = Me, **14**
R = Bn, **15**

Ar = aromatic/heteroaromatic (**18**)

unsaturated β-ketoester	**(*E*:*Z*)^a (yield %)**	**unsaturated β–ketoester**	**(*E*:*Z*)^a (yield %)**
 **18a**	(*E*:*Z* = 44:56) (78%)	 **18f**	(*E*:*Z* = 36:64) (82%)
 **18b**	(*E*:*Z* = 27:73) (88%)	 **18g**	(*E*:*Z* = 54:46) (76%)
 **18c**	(*E*:*Z* = 38:62) (75%)	 **18h**	(*E*:*Z* = 58:42) (79%)
 **18d**	(*E*:*Z* = 36:38) (82%)	 **18i**	(*E*:*Z* = 55:45) (77%)
 **18e**	(*E*:*Z* = 22:78) (77%)	 **18j**	*Z* (63%)

^{a}isolated yield of *cis* and *trans* mixture

These unsaturated β-ketoesters were obtained as a mixture of (*E*)-*trans* and (*Z*)-*cis* isomers in variable ratios (Table **1.1**). *E*/*Z* ratio was determined based on proton

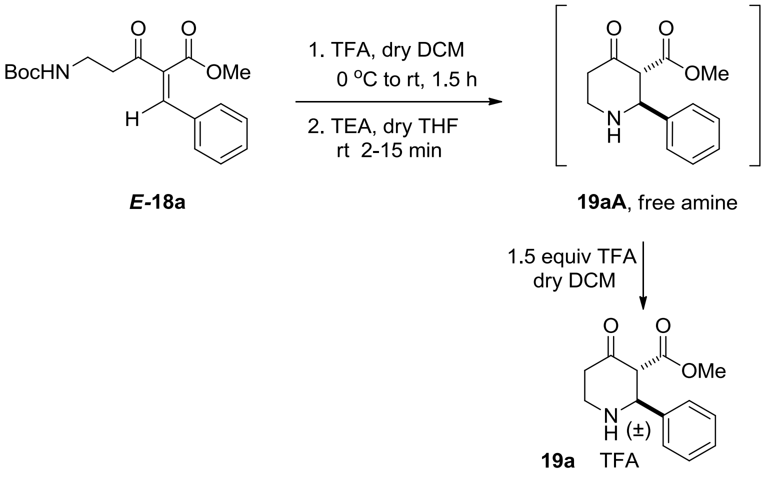
NMR. Geometric isomers were unequivocally determined by nOe studies of all the compounds. In order to study the effect of geometrical isomers on the cyclization, *E* and *Z* isomers of **18a**–**18e** were isolated by column chromatography. Attempted isolation of *E* isomer of (**18j**) was unsuccessful.

1.2.3 Aza-Michael Addition

Having obtained the unsaturated β-ketoester, further we planned to explore its reactivity towards the intramolecular aza-Michael reaction. It is anticipated that suitably placed (compounds synthesized see Table **1.1**) α,β-unsaturation, activated by keto and ester groups, can act as 'Michael accepter' and the protected amine would react with highly activated 'Michael acceptor' under suitable conditions. We believed that activation of either donor carbamate or the Michael acceptor would facilitate the cyclization to afford the piperidones. We believed that synthesis of piperidine derivatives by both the mode of activations would certainly a subject of study.

1.2.4 Aza-Michael addition by deprotection: One-pot protocol

We began our study for the activation of relatively less nucleophilic Michael donor: carbamate in the unsaturated β-ketoester (*E*-**18a**, Scheme **1.13**) for the synthesis of piperidone derivative. Presumably, removal of amine protecting group (^{t}Boc) would enhance the nucleophilicity as well as facilitate the instantaneous cyclization. In order to facilitate the cyclization unsaturated β-ketoester **18a** (*E*-isomer) was treated with trifluoroacetic acid (TFA) in anhydrous dichloromethane at 0 °C for 1.5 h.



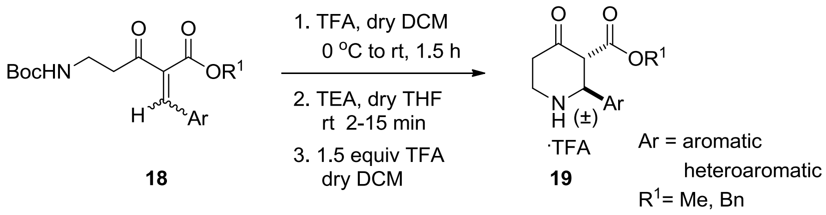
Scheme 1.13: Aza-Michael addition using TFA/TEA method

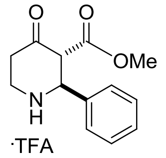
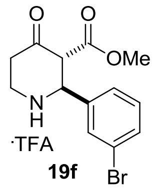
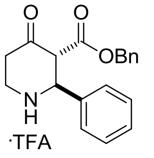
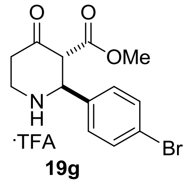
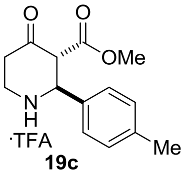
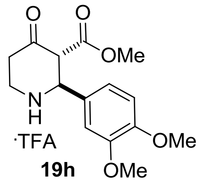
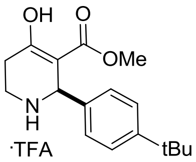
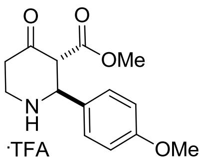
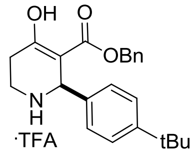
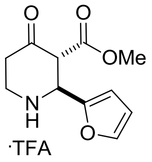
Then, excess TFA was evaporated under reduced pressure and resultant TFA salt was dissolved in anhydrous THF and to this solution triethyl amine was added dropwise at room temperature. The reaction was monitored by thin layer chromatography (TLC). Within 15 min corresponding 2,3-disubstituted piperidone derivative (**19aA**) was obtained. However, we observed that **19aA** found to decompose gradually over a period of time. We surmised that reactive secondary amine might have reacted with the methyl ester moiety thus leading to side reaction. In order to arrest this side reaction, compound **19aA** was treated with TFA (1 equiv) to afford 2,3-disubstitued piperidone **19a** as stable and crystalline solid. Further this two step one pot synthesis was found to be very rapid and efficient.

Furthermore, we observed that reaction was highly regioselective and stereoselective by yielding *trans*-2,3-disubstituted piperidone exclusively starting from the *E*-isomer of *E*-**18a**. The *trans* relationship of the substituents at C-2 and C-3 in compound **19a** was unambiguously deduced from the J_{2-3} coupling constant (J = 12 Hz). We did not observe any trace of amide product resulting from the reaction of free secondary amine with the ester. Also, we did not observe any side reaction products stemming out of oligomerization, and intermolecular Michael addition. The reaction was found to be very neat and isolated the single product (**19a**). We optimized the protocol for cyclization with TFA/TEA in CH_2Cl_2 at 0 ^oC.

In order to study the role of geometrical isomer on the stereochemistry if any during cyclization, we further embarked on the synthesis of piperidones starting from *Z*-unsaturated β-ketoester (*Z*-**18a**). Under identical reaction conditions compound *Z*-**18a** afforded the corresponding *trans*-2,3-disubstitued piperidone **19a** as a single product in good yield (82%). ^{1}H-NMR spectrum did not reveal the formation of trace amount of corresponding *cis*-isomer of piperidone. Finally, we observed that an equimolar mixture of both *Z*-**18a** and *E*-**18a** under optimized reaction conditions afforded compound **19a** in very good yield (85%). We presumed that both the isomers undergo cyclization via the similar transition states. Encouraged by this initial success, we treated several unsaturated β-ketoesters (**18b**–**18j**) under optimized reaction conditions to afford the corresponding 2,3-disubstituted piperidone derivatives **19b–19j** in good to excellent yields (Table **1.2**). The relation of C-2 and C-3 substituents in all the obtained products (**19b**–**19j**) found to be *trans* from the coupling constants (Table **1.2**).

Table 1.2: Substrate scope of aza-Michael addition using TFA/TEA



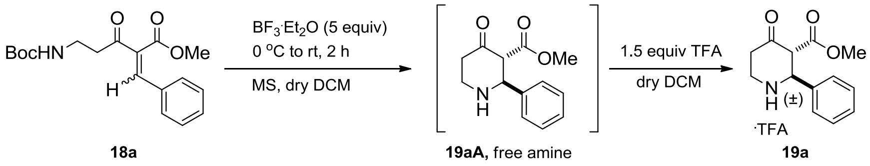
oxo-piperidines[a]	**yield**[b] **(%)**	**oxo-piperidine**[a]	**yield**[b] **(%)**
 **19a**	(85%)	 **19f**	(82%)
 **19b**	(84%)	 **19g**	(80%)
 **19c**	(81%)	 **19h**	(86%)
 **19d**	(88%)	 **19i**	(84%)
 **19e**	(85%)	 **19j**	(72%)

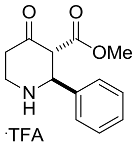
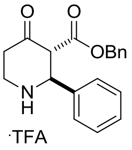
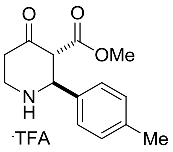
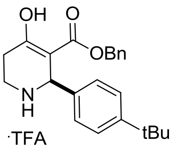
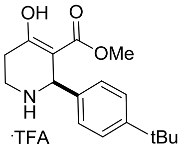
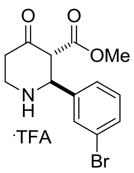
[a] Alkylidene derivatives of β–ketoesters (2 mmol in dry DCM), TFA (40 mmol) 0 °C for 1.5 h, then TEA (10 mmol) in dry THF for 2-15 min, prodcut obtained as a single diastereoisomer in all cases, [b] isolated yields

1.2.5 Cascade protocol

After the successful synthesis of piperidones via the activation of carbamates, we turned our attention towards the activation of unsaturation to facilitate the cyclization of unsaturated β-ketoesters to afford the disubstituted piperidines. In order to activate the unsaturation, suitable Lewis acid may be ideal, that in turn would facilitate the aza-Michael addition. It is known in the literature that Lewis acid: $BF_3 \cdot Et_2O$ can deprotect tertiary-butyloxy carbonyl (^{t}Boc) group in almost neutral reaction condition.[34] Also, $BF_3 \cdot Et_2O$ as a Lewis acid would coordinate with oxo species.[35] We planned to explore the use of $BF_3 \cdot Et_2O$ for the possible cyclization. The unsaturated β-ketoester **18a** (*E* and *Z* mixture) on treatment with $BF_3 \cdot Et_2O$ gave corresponding piperidone free amine **19aA**, which was then treated with trifluoroacetic acid to afford the stable *trans*-2,3-disubstituted piperidone TFA salt **19a** in good yield (Table **1.3**).

Table 1.3: Aza-Michael addition using $BF_3 \cdot Et_2O$



oxo-piperidine[a]	yield[b] (%)	oxo-piperidine[a]	yield[b] (%)
	(**19a**, 64%)		(**19b**, 84%)
	(**19c**, 66%)		(**19d**, 83%)
	(**19e**, 88%)		(**19f**, 62%)

[a] prodcut obtained as a single diastereoisomer in all cases
[b] isolated yields

The compound did not require any chromatographic purification and the purity of **19a** was evident from the ^{1}H-NMR spectrum. The reaction involved a sequence of transformations in a cascade pathway. At first, facile deprotection of ^{t}Boc group took place followed by the instantaneous aza-Michael addition, a cascade type pathway. Encouraged by this success and to make the methodology general, unsaturated β-keto esters (**18b–18f**) were treated with the optimized reaction conditions (Table **1.3**) to afford the corresponding *trans*-2,3-disubstituted piperidones (**19b–19f**) in good to excellent yields in 1.5 to 2 h (Table **1.3**). To the best of our knowledge we utilized for the first time $BF_3{\cdot}Et_2O$ as Lewis acid for the intramolecular aza-Michael addition for synthesizing piperidine derivatives in a cascade pathway.

1.2.6 Keto-enol tautomerism

It was observed from the ^{1}H NMR spectra that most of the disubstituted piperidone derivatives gradually converted into enolic form, from the initial keto form. This led to a great difficulty in assigning the stereochemistry initially. It is known in the literature that keto-enol tautomerism greatly depends on the polarity of the solvent used. We studied the keto-enol tautomerism of **19aA** and **19a** of the products in chloroform-d_3 and DMSO-d_6 by recording ^{1}H NMR spectra at different time intervals. We observed that the products rapidly converted from keto to enolic form in chloroform-d_3 (Fig **1.7**, Eq. 1), whereas keto form was relatively stable in DMSO-d_6 (Fig **1.7**, Eq. 2) and however, gradually converted into the respective enolic form (Fig **1.7**, Eq. 3 and Fig **1.8**).

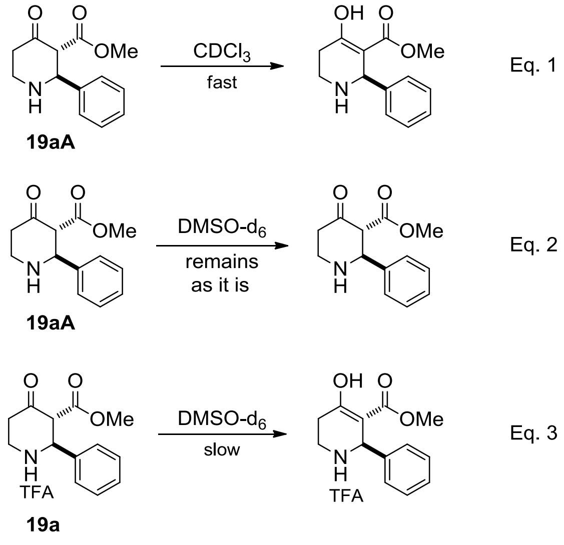


Fig 1.7: Keto-enol tautomerism in different solvents

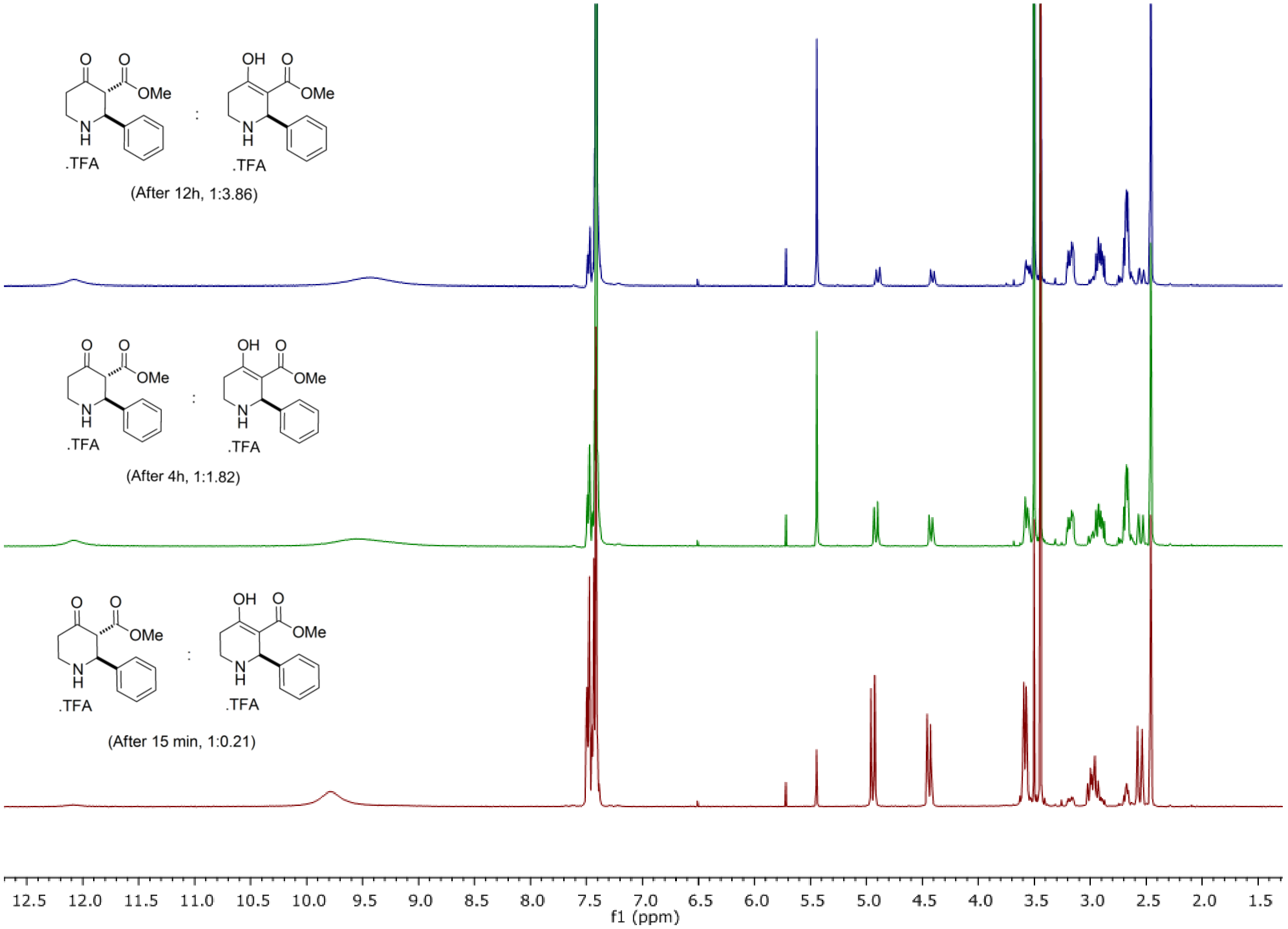


Fig 1.8: Stacked ^{1}H NMR spectra of compound **19a** reveal the gradual conversion of keto to enol form.

This behaviour of keto-enol tautomerism has been explained schematically (Fig **1.9**). Generally, 1,3-diketones and related derivatives mostly exist in three different tautomeric forms a) *cis*-enolic form, b) diketone form, c) *trans*-enolic form.

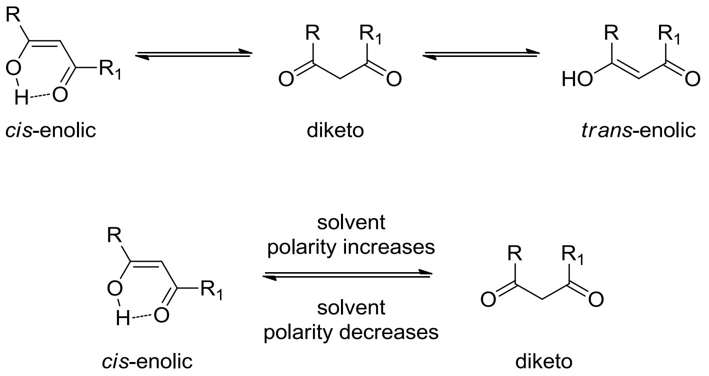


Fig 1.9: Tautomeric forms of 1,3-dicarbonyl compounds

In solution, open chain 1,3-dicarbonyl compounds enolize to *cis*-enolic form as they are stabilized by intramolecular hydrogen bonding. In contrast, cyclic 1,3-dicarbonyl compounds attain *trans* enol form in case of smaller rings and converts into *cis* enols in cases of large sized rings. The diketo form is more dipolar than chelated *cis*-enolic form, the keto-enol ratio often depends on solvent polarity. In principle, on the dissolution of 1,3-dicarbonyl compound in low polarity solvents, enhances the population of *cis*-enolic form, whereas polar solvent displaces the equilibrium towards the diketo form.[36] The phenomenon can be understood based on intramolecular chelation of the enol. The intramolecular hydrogen bonding reduces the dipole-dipole repulsion of the carbonyl groups. Furthermore the enol stabilization due to intramolecular hydrogen bonding is more predominant. Thus more polar solvent tends to stabilize the intermolecular hydrogen bonding and thus reduces enol content.

1.2.7 Characterization

It was evident from the coupling constant (J = 12 Hz) that the substituent at C-2 position (Ar group) and C-3 position (-CO_2R group) in piperidones were in *trans* arrangement in all the compounds (**19a**–**19j**). Though, by ^{1}H-NMR we confirmed *trans* geometry of substituents, however we observed that the molecular structure of **19c** by X-ray single crystal analysis revealed the enolic form of **19c** and thus the arrangement of the substituents was not confirmed by X-ray analysis (Fig **1.10**). It was evident that

19c attained enol form during crystallization process. Hence, in order to confirm the stereochemical arrangements of the substituents, we decided to mask the keto group by protecting it with 1,2-ethane dithiol (Fig **1.11**). The compound **19aA** (free amine) was treated with 1,2-ethanedithiol and $BF_3{\cdot}Et_2O$ in dry DCM to obtain the corresponding the protected piperidine derivative, **20**.

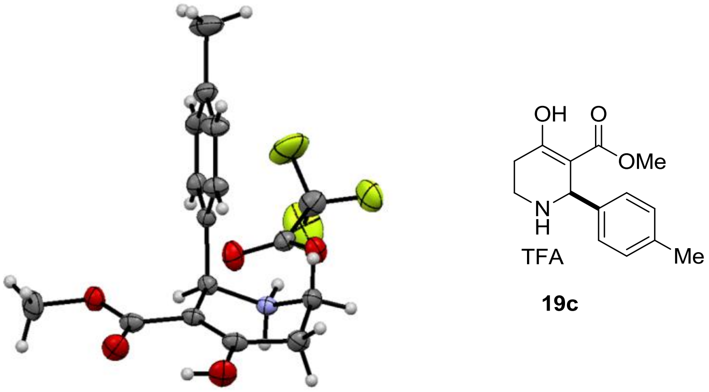


Fig 1.10: Crystal structure of compound **19c**

^{1}H NMR coupling constant (*J* = 12 Hz*)* of compound **20** confirmed that *trans* relation of C-2 and C-3 substituents. Molecular structure of **20** elucidated by X-ray single crystal analysis confirmed unequivocally the *trans* arrangement (Fig **1.11**). Hence, identical configuration was assumed for the rest of the disubstituted piperidones.

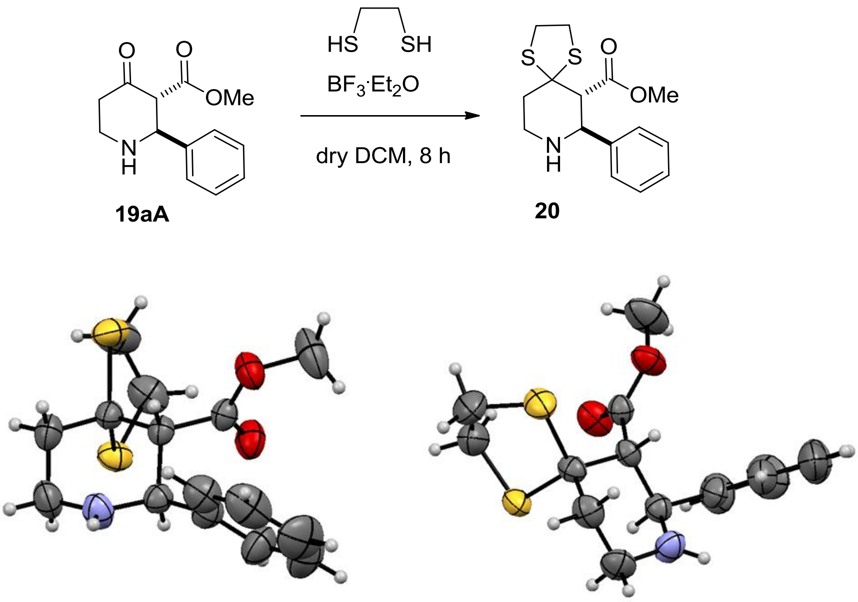
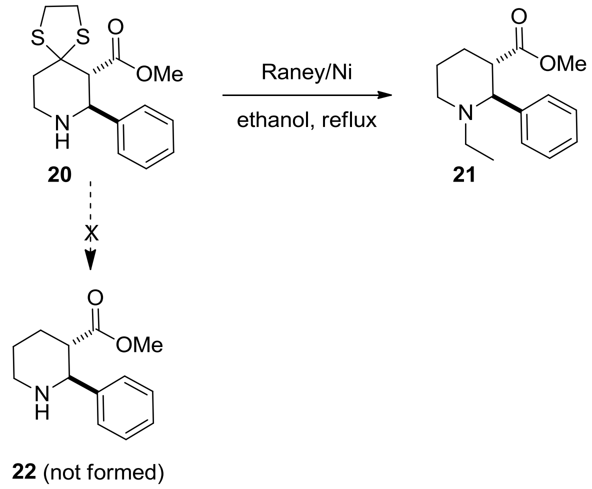


Fig 1.11: Synthesis and crystal structure of compound

1.2.8 Applications of the methodology

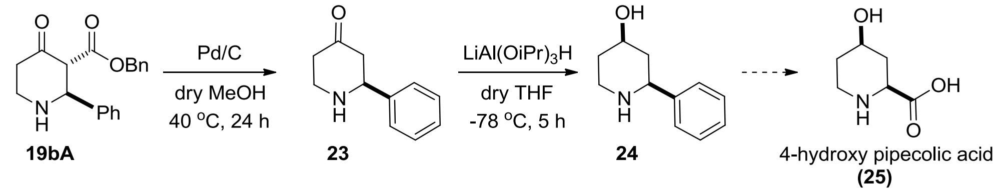
After successfully synthesizing different piperidone derivatives by two different strategies, we turned our attention to maximize the scope of this methodology. Compound **20** upon treatment with Raney/Ni under refluxing conditions in ethanol furnished the unanticipated *N*-ethyl-2,3-disubstituted piperidone (**21**), instead of the expected 2,3-disubstituted piperidone derivative **22** (Scheme **1.14**).



Scheme 1.14: Unusual reactivity of compound **20** with Raney/Ni

Having obtained an interesting result, we then gleaned through the literature regarding such type of reactions. We learnt that, amines react with alcohols in presence of an excess amount of Raney nickel to afford the corresponding *N*-alkylated products.[37] Due to this observation we did not pursue this study further. We then turned our attention for utilizing 2,3-disubstituted derivative for the formal synthesis of pipecolic acid derivative. 2-phenyl piperidinol **24** has been used as a key intermediate for the synthesis of 4-hydroxy pipecolic acid.[38,39] Encouraged by this, we then focused our attention towards the synthesis of 2-phenyl piperidine-4-ol **24** by employing our methodology. We subjected compound **19bA** for the β-keto decarboxylation using methanolic NaOH (NaOH/MeOH). However, we were unable to isolate the pure product; 2-phenyl piperidone **23**. However, compound **19bA** (free amine) under hydrogenolysis conditions with Pd/C, H_2 underwent facile β-keto decarboxylation,[40] to afford compound **23** in good yield (63% over two steps from **18b**). 2-Phenyl piperidone, **23** was further reduced by lithium trialkoxyaluminum hydride to afford 2-

phenylpiperidinol, **24** (Scheme **1.15**) in good yield (84%). This method proved to be very efficient and accessible for the synthesis of racemic 4-hydroxy pipecolic acid in good yield.



Scheme 1.15: Formal synthesis of 4-hydroxy pipecolic acid

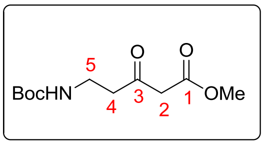
1.3 Conclusions

In conclusion, we have developed an efficient two step one pot diastereoconvergent strategy that provides a straightforward access to a number of *trans* disubstituted piperidines, using simple experimental protocols. Piperidine derivatives have been efficiently synthesized by employing cascade type reaction using $BF_3 \cdot Et_2O$ and by using TFA/TEA have been described. We have effectively utilized the well known reagent such as Meldrum's acid in building β-ketoesters. Using a similar strategy, a short access to hydroxyl pipecolic acid is also described. Very simple and rapid experimental procedures involving mild conditions and only one or two chromatographic purifications are the main features of the process.

1.4 Experimental Section

General: Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. THF, CH_2Cl_2, MeOH, EtOAc, Diethyl ether, Pet. Ether, Chloroform were purified and dried by using regular procedures using “Purification of Laboratory Chemicals” by Perrin and stored over activated 4 Å molecular sieves. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Merck, Spectrochem and AVRA). Removal of solvent or concentration under reduced pressure was performed using a rotary evaporator. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm). ^{1}H-NMR spectra were recorded on a JEOL ECS-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, DMSO-d_6: 2.5 ppm). Data are reported as follows: chemical shift, multiplicity bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of triplet, ddd = doublet of doublet of doublet), coupling constants (Hz) and integration. ^{13}C-NMR spectra were recorded on JEOL ECS-400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$ 77.00 ppm, DMSO-d_6: 39.52 ppm). High-resolution mass spectrometry was performed on Waters Q-TOF Micro ESI (Time of Flight LC/MS) and MALDI TOF/TOF (Applied Biosciences). Data for X-ray structure determination were obtained from Bruker APEXII DUO diffractometer using Mo-Kα (λ = 0.71073 Å) graphite monochromated radiation. (FT-IR) spectra were obtained using a NICOLET 6700 FT-IR spectrophotometer as a thin film on sodium chloride and KBr disc in wave numbers and reported in cm^{-1}.

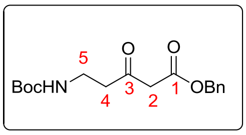
Methyl 5-((*tert*-butoxycarbonyl) amino)-3-oxopentanoate (14)



To a well stirred mixture of 3-((tert-butoxycarbonyl) amino) propanoic acid (18.91 g, 100 mmol), Meldrum’s acid (14.41 g, 100 mmol), DMAP (17.1 g, 140 mmol) in dry dichloromethane (300 mL) at 0 °C was added portion-wise dicyclohexyl carbodiimide (DCC) (28.8 g, 140 mmol) over 15 minutes maintaining 0 °C. Then the reaction mixture was allowed to warm to room temperature and stirred for

5 h. The precipitate formed was removed by filtration through a sintered glass funnel. Filtrate was washed with aqueous 1M $KHSO_4$ solution (2 x 200 mL) then with brine solution (2 x 175 mL) and dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give brownish residue. Then the residue was dissolved in anhydrous methanol (250 mL) and refluxed for 4h. After which the methanol was removed under reduced pressure to afford crude compound (14) which was further purified by column chromatography over silica gel eluting with Pet. Ether/EtOAc (90:10) affording as light yellow oil in 63% (15.5 g); R_f = 0.32 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 3401, 2971, 1711, 1518, 1259, 1165; δ_H (400 MHz, $CDCl_3$) 4.97 (bs, 1H), 3.74 (s, 3H), 3.46 (s, 2H), 3.38 (q, *J* = 6 Hz, 2H), 2.78 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_c (100 MHz, $CDCl_3$) 202.4, 167.5, 155.9, 79.6, 52.6, 49.2, 43.2, 35.1, 28.5; MALDI TOF/TOF m/z Calcd for $C_{11}H_{19}NO_5$ $[M + K]^+$ 284.0900, observed 284.0899.

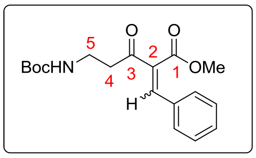
Benzyl 5-((*tert*-butoxycarbonyl)amino)-3-oxopentanoate (15)



To a well stirred mixture of 3-((tert-butoxycarbonyl) amino) propanoic acid (9.5 g, 50 mmol), Meldrum's acid (7.21 g, 50 mmol), DMAP (9.2 g, 75 mmol) in anhydrous dichloromethane (120 mL) at 0 °C was added portion-wise dicyclohexyl carbodiimide (DCC) (15.45 g, 75 mmol) over 10 minutes maintaining 0 °C. Then reaction mixture was allowed to warm to room temperature and stirred for 5 h. The precipitate formed was removed by filtration through sintered glass funnel. Filtrate was washed with aq 1M $KHSO_4$ solution (2 x 70 mL) then brine (2 x 75 mL) and dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give brownish residue. The residue was dissolved in dry benzene (80 mL) and benzyl alcohol (7.8 mL, 75 mmol) was added then refluxed for 4 h and the solvent was removed under reduced pressure to give crude material which was purified by column chromatography over silica gel eluting with Pet. Ether/EtOAc (97:3 to 90:10) light yellow oil in 62% yield (10 g). R_f = 0.37 Pet. Ether/EtOAc (70:30); IR (Neat) cm^{-1}: 2977, 1746, 1712, 1512, 1366, 1274, 1252, 1168, 750; δ_H (400 MHz, $CDCl_3$) 7.37 (m, 5H), 5.17 (s, 2H), 5.01 (bs, 1H), 3.49 (s, 2H), 3.34 (q, *J* = 6 Hz, 2H), 2.75 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_c (100 MHz, $CDCl_3$) 202.3, 166.8, 155.9, 135.2, 128.7, 128.6, 128.5, 79.4, 67.3, 49.3, 43.1, 35.0, 28.4; MALDI TOF/TOF m/z Calcd for $C_{17}H_{23}NO_5$ $[M + K]^+$ 344.1474, observed 344.1470.

General Experimental procedure for Knoevenagel condensation

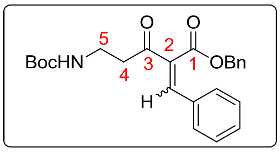
(*E*,*Z*)-Methyl 2-benzylidene-5-(*tert*-butoxycarbonylamino)-3-oxopentanoate (18a)



To a well stirred mixture of beta-keto ester (7 g, 28.57mmol), benzaldehyde (3.19 mL, 31.47 mmol) in benzene (175 mL), were added piperidine (0.3 mL, 0.28 mmol), acetic acid (0.32 mL, 0.57 mmol). Then the reaction mixture was refluxed using Dean-Stark apparatus to remove the water formed during the course of the reaction. After the completion of reaction (2.5-3 h) benzene was evaporated under vacuum and the residue was purified by flash chromatography over silica gel eluting with Pet. Ether/EtOAc (98:2 to 70:30) affording 18a as pale yellow oil in 78% yield (7.4 g, *E:Z* = 44:56); (*E*) isomer: pale yellow oil; R_f = 0.47 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2976, 1705, 1621, 1509, 1449, 1258, 1170, 768; δ_H (400 MHz, $CDCl_3$) 7.73 (s, 1H), 7.41-7.32 (m, 5H), 5.05 (bs, 1H), 3.82 (s, 3H), 3.4 (q, *J* = 6 Hz, 2H), 2.76 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_c (100 MHz, $CDCl_3$) 205.3, 164.9, 155.9, 141.6, 133.1, 132.7, 130.8, 129.8, 129.1, 79.4, 52.8, 43.6, 35.1, 28.6; (*Z*) isomer: pale yellow oil; R_f = 0.39 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2977, 1713, 1623, 1508, 1436, 1227, 1170, 756, 692; δ_H (400 MHz, $CDCl_3$) 7.59 (s, 1H), 7.42-7.38 (m, 5H), 5.1 (bs, 1H), 3.83 (s, 3H), 3.47 (q, *J* = 6 Hz, 2H), 2.96 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_C(100 MHz, $CDCl_3$) 196.3, 168.2, 156, 141.8, 133.8, 132.8, 131.1, 129.6, 129, 79.4, 52.8, 38.8, 35.3, 28.5; HRMS (ESI TOF) m/z Calcd for $C_{18}H_{23}NO_5$ $[M + Na]^+$ 356.1474, observed 356.1476.

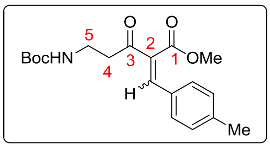
Similar procedure as mentioned above for 18a was used for Knoevenagel condensation with various aldehydes.

(*E*,*Z*)-Benzyl-2-benzylidene-5-((*tert*-butoxycarbonyl)amino)-3-oxopentanoate (18b)



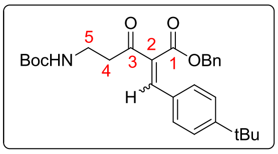
Yield = 88%, (*E:Z* = 27:73), (*Z*) isomer: a pale yellow solid; R_f = 0.47 Pet. Ether/EtOAc (70:30); IR (KBr) cm^{-1}: 2927, 1714, 1600, 1509, 1170, 754; δ_H (400 MHz, $CDCl_3$) 7.59 (s, 1H), 7.38-7.23 (m, 10H), 5.3 (s, 2H), 5.1 (bs, 1H), 3.46 (q, *J* = 6 Hz, 2H), 2.95 (t, *J* = 6 Hz, 2H), 1.43 (s, 9H); δ_c (100 MHz, $CDCl_3$) 196.2, 167.5, 156, 141.9, 134.7, 133.9, 132.7, 130.9, 129.7, 129.2, 129, 128.8, 79.5, 67.8, 38.9, 35.3, 28.5; MALDI TOF/TOF m/z Calcd for $C_{24}H_{27}NO_5$ $[M + K]^+$ 448.1526, observed 448.1528; (mixture of *E* and *Z*) δ_H (400 MHz, $CDCl_3$) 7.74 (s, 1H, *E*), 7.59 (s, 1H, *Z*), 7.37-7.23 (m, 20H, *E* and *Z*), 5.29 (s, 2H, *Z*), 5.27 (s, 2H, *E*), 5.07-5.02 (m, 2H, *E* and *Z*), 3.48-3.39 (m, 4H, *E* and *Z*), 2.95 (t, *J* = 6 Hz, 2H, *Z*), 2.75 (t, *J* = 6 Hz, 2H, *E*), 1.43 (s, 9H, *Z*), 1.41 (s, 9H, *E*); δ_c (100 MHz, $CDCl_3$) 205.1, 196.2, 167.5, 164.3, 156, 155.9, 141.9, 141.8, 135.4, 134.7, 133.9, 133.2, 132.7, 130.9, 130.8, 129.8, 129.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 79.4, 67.8, 67.4, 43.8, 38.8, 35.3, 35.1, 28.5.

(*E*,*Z*)-Methyl-5-((*tert*-butoxycarbonyl)amino)-2-(4-methylbenzylidene)-3-oxopentanoate (18c)



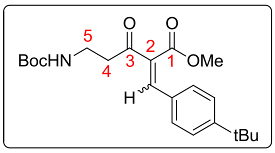
Yield = 75% (*E*:*Z* = 38:62); (*E*) isomer: a pale yellow oil; R_f = 0.34 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2963, 1709, 1616, 1513, 1375, 1260, 1175; δ_H (400 MHz, $CDCl_3$) 7.69 (s, 1H), 7.24-7.15 (m, 4H), 5.07 (bs, 1H), 3.81 (s, 3H), 3.40 (q, *J* = 6 Hz, 2H), 2.76 (t, *J* = 6 Hz, 2H), 2.35 (s, 3H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 205.5, 164.9, 155.9, 141.6, 141.3, 131.9, 129.9, 129.8, 79.3, 52.6, 43.5, 35.1, 28.5, 21.5; (*Z*) isomer: a pale yellow oil; R_f = 0.29 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2970, 1715, 1520, 1253, 1170; δ_H (400 MHz, $CDCl_3$) 7.57 (s, 1H), 7.31 (d, *J* = 8 Hz, 2H), 7.17 (d, *J* = 8 Hz, 2H), 5.1 (bs, 1H), 3.85 (s, 3H), 3.45 (q, *J* = 6 Hz, 2H), 2.96 (t, *J* = 6 Hz, 2H), 2.37 (s, 3H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 196.3, 168.4, 155.9, 141.89, 141.85, 132.9, 129.89, 129.85, 129.77, 79.4, 52.7, 38.6, 35.3, 28.5, 21.6; HRMS (ESI TOF) m/z Calcd for $C_{19}H_{25}NO_5$ $[M + Na]^+$ 370.1630, observed 370.1631.

(*E*,*Z*)-Benzyl-5-(*tert*-butoxycarbonylamino)-2-(4-*tert*-butylbenzylidene)-3-oxopentanoate (18d)



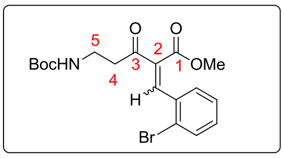
Yield = 77% (*E*:*Z* = 22:78); IR (neat) cm^{-1}: mixture of *E* and *Z*; δ_H (400 MHz, $CDCl_3$) 7.68 (s, 1H, *E*), 7.55 (s, 1H, *Z*), 7.37-7.25 (m, 8H, *E* and *Z*), 5.3 (s, 2H, *Z*), 5.25 (s, 2H, *E*), 5.08 (bs, 2H, *E* and *Z*), 3.46-3.39 (m, 4H, *E* and *Z*), 3.45-3.41 (m, 4H, *E* and *Z*), 2.93 (t, *J* = 6 Hz, 2H, *Z*), 2.81 (t, *J* = 6 Hz, 2H, *E*), 1.41 (s, 18H, *E* and *Z*), 1.29 (s, 9H, *Z*), 1.28 (s, 9H, *E*); δ_C (100 MHz, $CDCl_3$) 205.4, 196.2, 167.7, 164.5, 155.9, 154.7, 154.5, 141.8, 141.7, 135.5, 134.8, 132.9, 131.9, 129.7, 129.2, 128.7, 125.9, 79.4, 67.7, 67.2, 53.5, 43.7, 38.7, 35.3, 35, 31.1, 28.5; MALDI TOF/TOF m/z Calcd for $C_{28}H_{35}NO_5$ $[M + K]^+$ 504.2152, observed 504.2199.

(*E*,*Z*)-Methyl-5-((*tert*-butoxycarbonyl)amino)-2-(4-(*tert*-butyl)benzylidene)-3-oxopentanoate (18e)



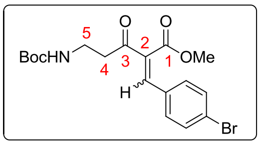
Yield = 78% (*E*:*Z* = 37:63); mixture of *E* and *Z*; IR (neat) cm^{-1}: 2958, 1712, 1605, 1510, 1374, 1256, 1172; Mixture of *E* and *Z*; δ_H (400 MHz, $CDCl_3$) 7.64 (s, 1H, *E*), 7.53 (s, 1H, *Z*), 7.39-7.23 (m, 8H, *E* and *Z*), 5.08 (bs, 2H, *E* and *Z*), 3.83 (s, 3H, *Z*), 3.87 (s, 3H, *E*), 3.45-3.41 (m, 4H, *E* and *Z*), 2.93 (t, *J* = 6 Hz, 2H, *Z*), 2.79 (t, *J* = 6 Hz, 2H, *E*), 1.39 (s, 9H, *E*), 1.38 (s, 9H, *Z*), 1.28 (s, 9H, *Z*), 1.26 (s, 9H, *E*); δ_C (100 MHz, $CDCl_3$) 205.7, 196.5, 168.5, 165.1, 156.0, 155, 154.5, 141.7, 141.5, 132.9, 131.8, 129.9, 129.8, 126.2, 126.2, 79.5, 79.4, 53.6, 52.8, 52.7, 50.9, 43.6, 38.7, 35.2, 35.07, 31.2, 28.6, 28.5; HRMS (ESI TOF) m/z Calcd for $C_{21}H_{29}NO_5$ $[M + Na]^+$ 412.2100, observed 412.2100.

(*E*,*Z*)-Methyl-2-(3-bromobenzylidene)-5-((*tert*-butoxycarbonyl)amino)-3-oxopentanoate (18f)



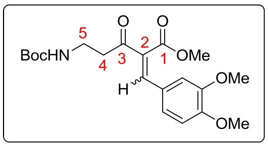
Yield = 82%; (*E*:*Z* = 39:64) a pale yellow oil; R_f = 0.31 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2970, 1709, 1511, 1373, 1252, 1171; δ_H (400 MHz, $CDCl_3$) 7.6 (s, 1H, *E*), 7.52-7.46 (m, 5H, *E* and *Z*), 7.32-7.19 (m, 4H, *E* and *Z*), 5.05 (bs, 2H, *E* and *Z*), 3.82 (s, 3H, *E*), 3.80 (s, 3H, *Z*), 3.46-3.37 (m, 4H, *E* and *Z*), 2.93 (t, *J* = 6 Hz, 2H, *Z*), 2.73 (t, 2H, *E*), 1.40 (s, 9H, *E*), 1.38 (s, 9H, *Z*); δ_C (100 MHz, $CDCl_3$) 204.7, 195.9, 167.6, 164.5, 155.9, 139.9, 139.7, 134.9, 134.7, 134.5, 133.8, 133.5, 132.6, 132.3, 130.5, 127.9, 127.8, 123.1, 123, 79.5, 79.48, 79.4, 52.9, 43.7, 39, 35.3, 35.1, 28.5; MALDI TOF/TOF m/z Calcd for $C_{18}H_{22}BrNO_5$ $[M + K]^+$ 450.0318, observed 450.0311.

(*E*,*Z*)-Methyl-2-(4-bromobenzylidene)-5-((*tert*-butoxycarbonyl)amino)-3-oxopentanoate (18g)



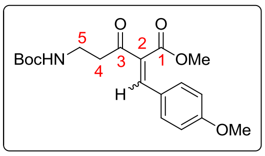
Yield = 76% (*E*:*Z* = 54:46); a pale yellow solid on standing; R_f = 0.33 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2968, 1707, 1507, 1258, 1172; δ_H (400 MHz, $CDCl_3$) 7.64 (s, 1H, *E*), 7.54-7.49 (m, 5H, *E* and *Z*), 7.29-7.2 (m, 4H, *E* and *Z*), 5.05 (bs, 2H, *E* and *Z*), 3.84 (s, 3H, *E*), 3.83 (s, 3H, *Z*), 3.48-3.4 (m, 4H, *E* and *Z*), 2.96 (t, *J* = 6 Hz, 2H, *Z*), 2.77 (t, *J* = 6 Hz, 2H, *E*), 1.42 (s, 18H, *E* and *Z*); δ_C (100 MHz, $CDCl_3$) 204.9, 196, 167.8, 164.6, 155.9, 155.8, 140.3, 140.1, 134.3, 133.7, 132.4, 131.7, 131.6, 131, 130.9, 125.6, 125.3, 79.5, 52.9, 52.8, 43.7, 38.9, 35.3, 34.9, 28.49, 28.47; HRMS (ESI TOF) m/z Calcd for $C_{18}H_{22}BrNO_5$ $[M + Na]^+$ 434.0579, observed 434.0577.

(*E*,*Z*)-Methyl-5-((*tert*-butoxycarbonyl)amino)-2-(3,4-dimethoxybenzylidene)-3-oxopentanoate (18h)



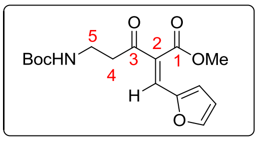
Yield = 79% (*E*:*Z* = 58:42); (*E*) isomer: a pale yellow oil; R_f = 0.51 Pet. Ether/EtOAc (50:50); IR (neat) cm^{-1}: 2960, 1713, 1595, 1515, 1261, 1160, 1021; δ_H (400 MHz, $CDCl_3$) 7.64 (s, 1H), 6.98-6.96 (m, 1H), 6.88-6.82 (m, 2H), 5.06 (bs, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.42 (q, *J* = 6 Hz, 2H), 2.81 (t, *J* = 6 Hz, 2H), 1.40 (s, 9H); δ_C (100 MHz, $CDCl_3$) 206, 165.2, 155.9, 151.4, 149.2, 141.6, 130.6, 125.6, 124.3, 112.1, 111.2, 79.4, 56.1, 56, 52.6, 43.7, 35.4, 28.5; (*Z*) isomer: a pale yellow oil; R_f = 0.4 Pet. Ether/EtOAc (50:50); IR (neat) cm^{-1}: 2971, 1711, 1520, 1260, 1160; δ_H (400 MHz, $CDCl_3$) 7.53 (s, 1H), 7.06 (dd, *J* = 2 Hz, 6 Hz, 1H), 6.97 (d, *J* = 2 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 5.09 (bs, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.45 (q, *J* = 6 Hz, 2H), 2.94 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 196.3, 168.7, 156, 151.9, 149.2, 141.8, 131.8, 125.4, 124.8, 111.7, 111.2, 79.4, 56.1, 55.9, 52.7, 38.6, 35.4, 28.5; HRMS (ESI TOF) m/z Calcd For $C_{20}H_{27}NO_7$ $[M + Na]^+$ 416.1685, observed 416.1685.

(*E*,*Z*)-Methyl-5-((*tert*-butoxycarbonyl)amino)-2-(4-methoxybenzylidene)-3-oxopentanoate (18i)



Yield = 77% (*E*:*Z* = 55:45); (*E*) isomer: a pale yellow oil; R_f = 0.26 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2930, 1708, 1600, 1513, 1258, 1171, 835; δ_H (400 MHz, $CDCl_3$) 7.66 (s, 1H), 7.25 (d, *J* = 9 Hz, 2H), 6.87 (d, *J* = 9 Hz, 2H), 5.08 (bs, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.42 (q, *J* = 6 Hz, 2H), 2.8 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 205.9, 165.2, 161.8, 155.9, 141.4, 131.9, 130.5, 125.3, 114.63, 79.4, 55.5, 52.6, 43.6, 35.3, 28.6; (*Z*) isomer: a pale yellow oil; R_f = 0.21 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2976, 1715, 1612, 1250, 1171, 1027, 830; δ_H (400 MHz, $CDCl_3$) 7.54 (s, 1H), 7.38 (d, *J* = 9 Hz, 2H), 6.9 (d, *J* = 9 Hz, 2H), 5.1 (bs, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.45 (q, *J* = 6 Hz, 2H), 2.94 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 196.3, 168.7, 162.1, 156, 141.6, 131.9, 131.5, 125.2, 114.7, 79.4, 55.6, 52.8, 38.6, 35.4, 28.5; HRMS (ESI TOF) m/z Calcd for $C_{19}H_{25}NO_6$ $[M + Na]^+$ 386.1580, observed 386.1580.

(*Z*)-Methyl-5-((*tert*-butoxycarbonyl)amino)-2-(furan-2-ylmethylene)-3-oxopentanoate (18j)

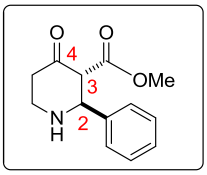


Yield = 63%; a pale yellow oil; R_f = 0.31 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2963, 1711, 1618, 1514, 1373, 1255, 1172, 759; δ_H (400 MHz, $CDCl_3$) 7.56 (d, *J* = 2 Hz, 1H), 7.33 (s, 1H), 6.83 (d, *J* = 4 Hz, 1H), 6.53 (q, *J* = 2 Hz, 1H), 5.1 (bs, 1H), 3.9 (s, 3H), 3.45 (q, *J* = 6 Hz, 2H), 2.91 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 195.7, 167.9, 156, 148.9, 147, 129, 126.8, 119.6, 113.2, 79.4, 52.7, 38.8, 35.3, 28.5; MALDI TOF/TOF m/z Calcd for $C_{16}H_{21}NO_6$ $[M + K]^+$ 362.1006, observed 362.1009.

General Experimental procedure for one-pot aza-Michael reaction of Piperidones

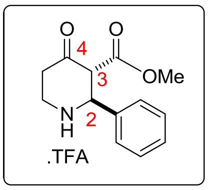
To a well stirred mixture of Knoevenagel product (**19a–19j**) (2 mmol) in anhydrous dichloromethane (DCM) (5 mL) at 0 °C, was added drop-wise Trifluoro acetic acid (TFA) (40 mmol) maintaining temperature of the reaction mixture at 0 °C. The reaction mixture was allowed to stir for 1.5 h. Excess of TFA was evaporated on rotary evaporator to furnish pale yellow residue. Then the residue was dissolved in anhydrous THF (70 mL) under inert atmosphere. To this solution triethyl amine (TEA) (10 mmol) was added drop-wise at room temperature (time required for completion of reaction 2-15 min). Reaction mixture was concentrated to dryness under reduced pressure to get light yellow residue, dissolved in ethyl acetate (25 mL), washed with distilled water (2 x 20 mL), brine (2 x 20 mL), dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give light yellow residue as a single diastereomer as showed by ^{1}H NMR Further, product in above reaction was converted to TFA salt and submitted for characterization.

***trans*-Methyl 4-oxo-2-phenylpiperidine-3-carboxylate (19aA)**



Pale yellow oil (Yield = 98%); R_f = 0.34 Pet. Ether/EtOAc (50:50); δ_H (400 MHz, DMSO-d_6) 7.39-7.21 (m, 5H), 4.06 (d, J = 10.4 Hz, 1H), 3.75 (d, J = 10.8 Hz, 1H), 3.43 (s, 3H), 3.33-3.30 (m, 1H), 2.88 (dt, J = 2.4 Hz, 10 Hz, 1H), 2.64-2.63 (m, 1H), 2.30-2.27 (m, 1H); δ_C (100 MHz, DMSO-d_6) 204.7, 168.7, 141.2, 128.4, 127.8, 127.7, 127.3, 64.9, 64.2, 51.4, 45.6, 41.7.

***trans*-Methyl 4-oxo-2-phenylpiperidine-3-carboxylate (19a)**

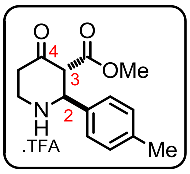


White solid (Yield = 85%); IR (KBr) cm^{-1}: 3440, 2965, 1710, 1580, 1444, 1160, 1141, 826, 735; mixture of keto−enol (1: 0.21); δ_H (400 MHz, DMSO-d_6) 12.11 (bs, 1H, enol), 7.54-7.43 (m, 10H, keto and enol), 5.49 (s, 1H, enol), 5.00 (d, J = 12 Hz, 1H, keto), 4.49 (d, J = 12 Hz, 1H, keto), 4.63 (m, 2H, keto), 3.54 (s, 3H, enol), 3.49 (s, 3H, keto), 3.24-3.20 (m, 1H, enol), 3.06-2.91 (m, 2H, keto and enol), 2.74-2.70 (m, 2H, enol), 2.62-2.58 (m, 1H, keto); δ_C (100 MHz, DMSO-d_6) 199.4, 169.5, 169.1, 166.5, 135.3, 134.3, 129.8, 129.4, 129.3, 129.1, 128.8, 128.1, 95.2, 59.9, 52.8, 52.1, 42.4, 37.2, 35.0, 25.5; HRMS (ESI TOF) m/z Calcd for $C_{13}H_{15}NO_3$ [M + Na]$^+$ 256.0950, observed 256.0949.

Benzyl 4-oxo-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (19b)

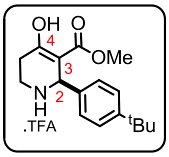
White solid (Yield = 84%); enol form; δ_H (400 MHz, DMSO-d_6) 12.1 (bs, 1H), 7.43 (s, 4 H), 7.22-7.12 (m, 4H), 6.77-6.75 (m, 2H), 5.49 (s, 1H), 5.1 (d, J = 12 Hz, 1H), 4.99 (d, J = 12 Hz, 1H), 3.22-3.18 (m, 1H), 2.99-2.96 (m, 1H), 2.72-2.68 (m, 2H); enol form; δ_C (100 MHz, DMSO-d_6) 170.4, 169, 135.9, 135.8, 129.9, 129.8, 129.3, 128.8, 128.7, 128.3, 127.4, 95.9, 66.3, 53.4, 35.7, 26.1; MALDI TOF TOF m/z Calcd for $C_{19}H_{19}NO_3$ [M + Na]$^+$ 332.1263, observed 332.1265.

Methyl 4-oxo-2-(*p*-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (19c)



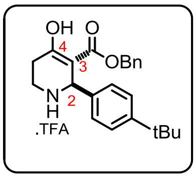
White solid (Yield = 81%); IR (KBr) cm^{-1}: 3448, 2969, 1669, 1581, 1436, 1184, 1142, 826; mixture of keto:enol (0.26:1); δ_H (400 MHz, DMSO-d_6) 12.13 (bs, 1H, enol), 7.41-7.24 (m, 8H, keto and enol), 5.44 (s, 1H, enol), 4.89 (d, J = 12.4 Hz, 1H, keto), 4.45 (d, J = 12.8 Hz, 1H, keto), 3.60-3.58 (m, 2H, keto), 3.55 (s, 3H, enol), 3.49 (s, 3H, keto), 3.23-2.19 (m, 1H, enol), 3.03-2.89 (m, 2H, keto and enol), 2.77-2.65 (m, 2H, enol), 2.59-2.50 (m, 1H, keto), 2.3 (s, 6H, enol and keto); enol form: δ_C (100 MHz, DMSO-d$_6$) 169.4, 169.2, 138.9, 132.3, 129.6, 129.3, 129.2, 128.0, 95.3, 52.5, 52.1, 34.9, 25.5, 20.8; HRMS (ESI TOF) m/z Calcd for $C_{14}H_{17}NO_3$ [M + H]$^+$ 248.1287, observed 248.1290.

***trans*-Methyl-2-(4-(*tert*-butyl)phenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate (19d)**



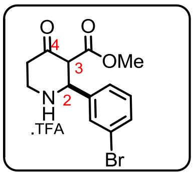
White solid (Yield = 88%); IR (KBr) cm^{-1}: 3436, 2965, 1672, 1588, 1435, 1302, 1196, 1138. 835; enol form; δ_H (400 MHz, DMSO-d$_6$) 12.1 (bs, 1H), 7.48 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 5.47 (s, 1H), 3.57 (s, 3H), 3.21-3.17 (m, 1H), 2.96-2.89 (m, 1H), 2.78-2.64 (m, 2H), 1.29 (s, 9H); δ_C (100 MHz, DMSO-d$_6$) 169.5, 169.3, 151.8, 132.4, 129, 125.6, 95.4, 52.4, 52.1, 34.9, 34.5, 31.1, 25.5; HRMS (ESI TOF) m/z Calcd for $C_{17}H_{23}NO_3$ [M + H]$^+$ 290.1756, observed 290.1753.

Benzyl 2-(4-*tert*-butylphenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate (19e)



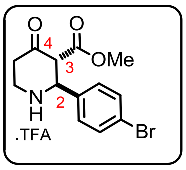
White solid (Yield = 85%); IR (KBr) cm^{-1}: 3447, 2966, 1681, 1619, 1497, 1455, 1415, 1296, 840, 722; mixture of keto: enol (0.21: 1); δ_H (400 MHz, DMSO-d$_6$) 12.06 (bs, 1H, enol), 7.46-7.34 (m, 10H, keto and enol), 7.22-7.10 (m, 6H, keto and enol), 6.72 (d, *J* = 8 Hz, 2H), 5.45 (s, 1H, enol), 5.13 (d, *J* = 12 Hz, 1H, enol), 4.99-4.93 (m, 3H, keto and enol), 4.87 (d, *J* = 12 Hz, 1H, keto), 4.45 (d, *J* = 12 Hz, 1H, keto), 3.55 (d, *J* = 12 Hz, 2H, keto), 3.20-3.17 (m, 1H, enol), 3.03-2.96 (m, 2H, keto and enol), 2.76 (m, 2H, enol), 2.56-2.52 (m, 1H, keto),1.28 (s, 9H, enol), 1.25 (s, 9H, keto); δ_C (100 MHz, DMSO-d$_6$) enol form; 170.3, 169.1, 152.5, 135.9, 133.1, 129.7, 128.7, 127.4, 126, 95.9, 66.2, 53, 35.7, 34.9, 31.6, 26.1; MALDI TOF/TOF m/z Calcd for $C_{23}H_{27}NO_3$ [M + K]$^+$ 404.1628, observed 404.1857.

Methyl 2-(3-bromophenyl)-4-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (19f)



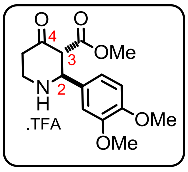
White solid (Yield = 82%); IR (KBr) cm^{-1}: 3456, 2998, 2792, 1693, 1578, 1439, 1185, 1143, 830, 709; mixture of keto: enol (0.19: 1); δ_H (400 MHz, DMSO-d$_6$) 12.13 (bs, 1H, enol), 7.77-7.64 (m, 2H, enol and keto), 7.50-7.39 (m, 6H, enol and keto), 5.51 (s, 1H, enol), 4.87 (d, *J* = 12 Hz, 1H, keto), 4.43 (d, *J* = 12.8 Hz, 1H, keto) (one signal lost due to overlap corresponding for 2H keto), 3.56 (s, 3H, enol), 3.51 (s, 3H, keto), 3.29-3.21 (m, 1H, enol), 2.98-2.91 (m, 2H, enol and keto), 2.71 (bs, 2H, enol), 2.57-2.53 (m, 1H, keto); enol form: δ_C (100 MHz, DMSO-d_6) 170.3, 169.4, 138.5, 132.8, 132.6, 131.3, 128.8, 122.5, 95.3, 52.7, 35.7, 26.1; HRMS (ESI TOF) m/z Calcd for $C_{13}H_{14}BrNO_3$ $[M + H]^+$ 312.0235, observed 312.0250.

Methyl 2-(4-bromophenyl)-4-oxopiperidine-3-carboxylate (19g)



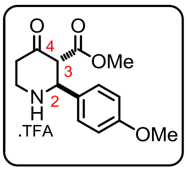
White solid (Yield = 80%); IR (KBr) cm^{-1}: 3444, 1669, 1579, 1435, 1187, 1142, 826, 642; keto: enol (0.29: 1); δ_H (400 MHz, DMSO-d_6) 12.1 (bs, 1H), 7.7-7.65 (m, 4H, keto and enol), 7.48-7.42 (m, 4H, keto and enol), 5.48 (s, 1H, enol), 4.93 (d, *J* = 12 Hz, 1H, keto), 4.42 (d, *J* = 12.4 Hz, 1H, keto) (one signal lost due to overlap corresponding to 2H, keto), 3.55 (s, 3H, enol), 3.51 (s, 3H, keto), 3.27-3.22 (m, 1H), 2.98-2.91 (m, 2H, keto and enol), 2.73-2.71 (m, 2H, enol), 2.59-2.56 (m, 1H, keto); δ_C (100 MHz, DMSO-d_6) 169.7, 168.9, 134.8, 131.7, 131.6, 122.9, 95, 52.2, 35.1, 25.6; MALDI TOF/TOF m/z Calcd for $C_{13}H_{14}BrNO_3$ $[M + K]^+$ 349.9794, observed 349.9803.

Methyl 2-(3,4-dimethoxyphenyl)-4-oxopiperidine-3-carboxylate (19h)



White solid (Yield = 86%); IR (KBr) cm^{-1}: 3456, 2956, 1682, 1585, 1437, 1254, 1144, 1024, 831, 643; keto form; δ_H (400 MHz, DMSO-d_6) 7.19 (s, 1H), 7.02 (s, 2H), 4.93 (d, *J* = 12.8 Hz, 1H), 4.53 (d, *J* = 12.8 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.61-3.58 (m, 2H), 3.52 (s, 3H), 3.07-2.98 (m, 1H), 2.62-2.58 (m, 1H); keto and enol form; δ_C (100 MHz, DMSO-d_6) 199.4, 169.4, 169.3, 166.6, 149.7, 149.5, 148.8, 148.7, 127.3, 126.2, 121.4, 120.9, 112.8, 111.6, 111.2, 111.1, 95.4, 59.8, 59.7, 55.5, 55.4, 52.5, 52.2, 42.2, 37.01, 34.8, 25.5; HRMS (ESI TOF) m/z Calcd for $C_{15}H_{19}NO_5$ $[M + Na]^+$ 316.1161, observed 316.1164.

trans-Methyl 2-(4-methoxyphenyl)-4-oxopiperidine-3-carboxylate (19i)



White solid (Yield = 84%); IR (KBr) cm^{-1}: 2967, 2724, 2496, 1753, 1705, 1667, 1437, 1260, 1032, 828, 724, 516; keto form; δ_H (400 MHz, DMSO-d_6) 7.45 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.93 (d, *J* = 12.8 Hz, 1H), 4.45 (d, *J* = 12.8 Hz, 1H), 3.77 (s, 3H), 3.60 (d, *J* = 8.8 Hz, 2H), 3.49 (s, 3H), 3.04-2.98 (m, 1H), 2.60-2.56 (m, 1H); δ_C (100 MHz, DMSO-d_6) 199.5, 166.6, 160.2, 129.7, 125.9, 114.4, 59.8, 59.4, 55.3, 52.2, 42.2, 36.9; HRMS (ESI TOF) m/z Calcd for $C_{14}H_{17}NO_4$ $[M + Na]^+$ 286.1055, observed 286.1058.

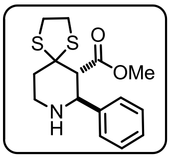
Methyl 2-(furan-2-yl)-4-oxopiperidine-3-carboxylate (19j)

Pale yellow oil (72%); R_f = 0.37 EtOAc (100); IR (neat) cm^{-1}: 2963, 1711, 1618, 1514, 1373, 1255, 1172, 759; δ_H(400 MHz, DMSO-d_6) 7.58 (d, *J* = 1.6 Hz 1H), 6.40 (q, *J* =2, 3.2 Hz, 1H), 6.25 (d, *J* = 3.6 Hz, 1H), 4.25 (d, *J* = 10 Hz, 1H), 3.74 (d, *J* = 10 Hz, 1H), 3.57 (s, 3H), 3.27-3.21 (m, 1H), 2.86 (dt, *J* = 3.6, 12 Hz, 1H), 2.57-2.52 (m, 1H), 2.31-2.26 (m, 1H); δ_C(100 MHz, DMSO-d_6) 204.1, 168.8, 153.9, 142.4, 110.4, 106.4, 62.1, 57.1, 51.7, 44.6, 41.8; MALDI TOF/TOF m/z Calcd for $C_{11}H_{13}NO_4$ $[M + K]^+$ 262.0482, observed 262.0493.

General experimental procedure for the domino strategy to synthesise piperidones using BF_3·Et_2O

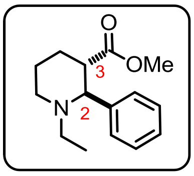
To a mixture of Knoevenagel compound (18a–18f) (1 mmol) and activated 4 Å molecular sieves in DCM (15 mL) was added BF_3·Et_2O (5 mmol) added drop-wise at room temperature and stirred for 1-2 h. After completion of the reaction (1-2 h) DCM was evaporated, and the residue was dissolved in ethyl acetate (30 mL), and it was washed with water (3 x 25 mL), brine solution (2 x 20 mL), the collective organic layer was dried over anhydrous sodium sulphate. The solution was rotary evaporated to afford crude material which was purified by flash chromatography by using neutral alumina pet. Ether/EtOAc (50:50 to 0:100) to afford 2, 3-disubstituted piperidone (free amine). The free amine was further treated with trifluoro acetic acid to afford stable 2, 3-disubstituted piperidone TFA salt (19a-19f).

Methyl 7-phenyl-1,4-dithia-8-azaspiro[4.5]decane-6-carboxylate (20) (1, 4 dithiane protection)



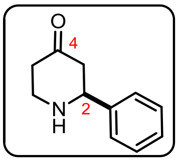
To the cooled mixture of 2-phenyl piperidone (19aA) (0.400 g, 1.71 mmol) in anhydrous dichloromethane (DCM) (50 mL) at 0 °C under inert atmosphere added 1, 2-ethanedithiol (0.7 mL, 8.6 mmol) drop wise. Then BF_3·Et_2O was added over 5 min to the reaction mixture at 0 °C. The reaction mixture was allowed to stir for 5 min at the same temp then warmed to room temperature gradually. After stirring for 8 h, the reaction mixture was quenched with NaOH solution (2N, 25 mL), after which it was extracted with dichloromethane (DCM) (2 x 20 mL), collected organic layers were washed with water (2 x 30 mL), brine solution (2 x 35 mL), and dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to furnish the crude compound. The compound (7) was purified by flash column chromatography over neutral alumina by eluting with pet. Ether/EtOAc (70: 30 to 20: 80) to furnish pure compound **20 (**0.385 g, 72.6%); The compound (20) was crystallized from pet. ether and ethyl Acetate. Molecular structure of the compound was confirmed by X-ray analysis. R_f = 0.41 Pet. Ether/EtOAc (50:50); IR (KBr) cm^{-1}: IR (KBr) cm^{-1}: 3334, 2930, 1733, 1581, 1439, 1343, 1142, 1030, 803, 747, 698; δ_H (400 MHz, $CDCl_3$) 7.38-7.35 (m, 2H), 7.31-7.22 (m, 3H), 4.03 (d, *J* = 10 Hz, 1H), 3.32 (s, 3H), 3.29-3.19 (m, 5H), 3.10-3.06 (m, 2H), 2.31 (dt, *J* = 4 Hz, 13.2 Hz, 1H), 2.23-2.18 (m, 1H); δ_C (100 MHz, $CDCl_3$) 170.7, 141.2, 128.5, 128.1, 127.9, 68, 64.1, 61.1, 51.3, 46.1, 45.4, 39.7, 38.5; HRMS (ESI TOF) m/z Calcd for $C_{15}H_{19}NO_2S_2$ $[M + H]^+$ 310.0935, observed 310.0939.

Methyl 1-ethyl-2-phenylpiperidine-3-carboxylate (21)



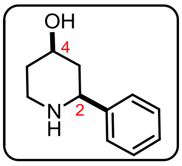
To a stirred solution of 20 (0.2 g) in absolute ethanol (7 mL) was added Raney Ni (0.2 g) and the reaction mixture was refluxed for 7 h. After which the reaction mixture was allowed to cool to room temp and then it was filtered through Celite bed. The filtrate was rotary evaporated to furnish crude compound which was purified by flash column chromatography over neutral alumina Pet. Ether/EtOAc (60:40) to afford the compound 21, as pale yellow oil (0.067 g, 42%). R_f = 0.37 Pet. Ether/EtOAc (70:30); IR (neat) cm^{-1}: 2944, 2796, 1735, 1477, 1367, 1314, 1261, 1158, 758, 700; δ_H (400 MHz, $CDCl_3$) 7.32-7.20 (m, 5H), 3.33 (s, 3H), 3.29 (d, *J* = 12 Hz, 1H), 3.15-3.11 (m, 1H), 2.67-2.60 (m, 1H), 2.53-2.44 (m, 1H), 2.20 (dt, *J* = 2.8 Hz, 12.6 Hz, 1H), 2.10-1.97 (m, 1H), 1.85-1.58 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 174.7, 141.6, 128.4, 128.3, 127.5 (two signals lost due to overlap), 69.3, 52.0, 51.8, 51.4, 48.6, 28.8, 24.9, 10.7; MALDI TOF/TOF m/z Calcd For $C_{15}H_{21}NO_2$ $[M + K]^+$ 286.1209, observed 286.1204.

2-phenylpiperidin-4-one (23)



To a stirred solution of methyl 2-benzylidene-5-(tert-butoxy carbonylamino)-3-oxopentanoate (Knoevenagel product) (18b) (4.2 g, 10.3 mmol) in anhydrous dichloromethane (DCM) (20 mL) at 0 ^oC, added trifluoroacetic acid (TFA) (15 mL, 205 mmol) drop-wise and the reaction was allowed to stir for 1.5 h. After completion of the reaction, the excess of TFA was rotary evaporated to furnish light yellow residue. Further the residue was dissolved in anhydrous THF (100 mL) under inert atmosphere condition and stirred with TEA (7.14 mL, 51.3 mmol) at room temperature. After 15 min the reaction mixture was concentrated to dryness under reduced pressure to get light yellow residue, which was dissolved in ethyl acetate (50 mL), washed with distilled water (3 x 30 mL), brine (2 x 30 mL), then the collective organic layer was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to afford 2-phenyl 3-carboxyethyl piperidine 4-one (19bA) as yellow residue which was subjected for beta-keto decarboxylation without any purification. To a stirred solution of Pd/C (0.700 g) in anhydrous MeOH (40 mL) was added 2-phenyl 3-carboxyethyl piperidine 4-one (19bA) and the reaction mixture was heated at 40 ^{o}C for 24 hour under hydrogen atmosphere. Upon which the reaction mixture was filtered through Celite bed and the filtrate was concentrated under reduced pressure to afford a crude product which was purified by flash chromatography using neutral alumina by eluting with pet. Ether/EtOAc (100: 0 to 0: 100) affording 23 as light yellow viscous oil (1.12 g, 62.2% over the two steps); R_f = 0.5 EtOAc; δ_H (400 MHz, $CDCl_3$) 7.38-7.15 (m, 5H), 3.94 (t, *J* = 7.6 Hz, 1H), 3.48 (ddd, *J* = 2.4, 6.8 Hz, 1H), 3.03 (td, *J* = 3.8, 11.8 Hz, 1H), 2.67-2.38 (m, 3H), 2.47-2.40 (m, 1H), 1.91 (bs, 1H); δ_C (100 MHz, $CDCl_3$) 208.9, 142.6, 128.9, 127.9, 126.5 (two signals lost due to_overlap), 62.1, 50.8, 45.9, 42.3; MALDI TOF/TOF m/z Calcd for $C_{11}H_{13}NO$ $[M + K]^+$ 214.0634, observed 214.0640.

2-phenylpiperidin-4-ol (24)



To a stirred solution of 2-phenylpiperidin-4-one (23) (0.130 g, 0.74 mmol) in anhydrous THF (10 mL) under inert atmosphere was added lithium tri-*tert*-butoxyaluminum hydride (0.37 g, 1.48 mmol) at -78 ^{o}C. The reaction mixture was stirred for 5 h at the maintaining at -78 ^{o}C. After which the reaction mixture was quenched with water (2 mL). Then the solution was filtered through sintered glass funnel and filtrate was concentrated to afford crude product which was purified by column chromatography over neutral alumina DCM/MeOH (96:4) to give 24 (0.110 g, 84%); R_f = 0.45 DCM/MeOH (95:5); IR (neat) cm^{-1}: 3377, 2927, 2855, 1649, 1451, 1137,1066, 974, 755, 696; δ_H (400 MHz, $CDCl_3$) 7.35-7.22 (m, 5H), 3.80-3.73 (m, 1H), 3.61 (dd, *J* = 2 Hz, 11.6 Hz, 1H), 3.24-3.19 (m, 1H), 2.77 (dt, *J* = 2.4 Hz, 12.4 Hz, 1H), 2.14-2.08 (m, 1H), 2.03-1.97 (m, 1H), 1.54-1.43 (m, 2H); δ_C (100 MHz, $CDCl_3$) 143.9, 128.7, 127.5, 126.8 (two signals lost due to overlap), 69.9, 60.4, 45.2, 44.1, 35.6; MALDI TOF/TOF m/z Calcd for $C_{11}H_{15}NO$ $[M + K]^+$ 216.0791, observed 216.0788.

1.5 Appendix I: ^{1}H and ^{13}C spectral data of representative compounds

compound No.	Fig AI.X	data	page No.
13	Fig AI.1 and AI.2	1H-13C	41
***E*-18a**	Fig AI.3 and AI.4	1H-13C	42
***Z*-18a**	Fig AI.5 and AI.6	1H-13C	43
19aA	Fig AI.7 and AI.8	1H-13C	44
19a	Fig AI.9 and AI.10	1H-13C	45
19d	Fig AI.11 and AI.12	1H-13C	46
24	Fig AI.13 and AI.14	1H-13C	47
21	Fig AI.15 and AI.16	1H-13C	48

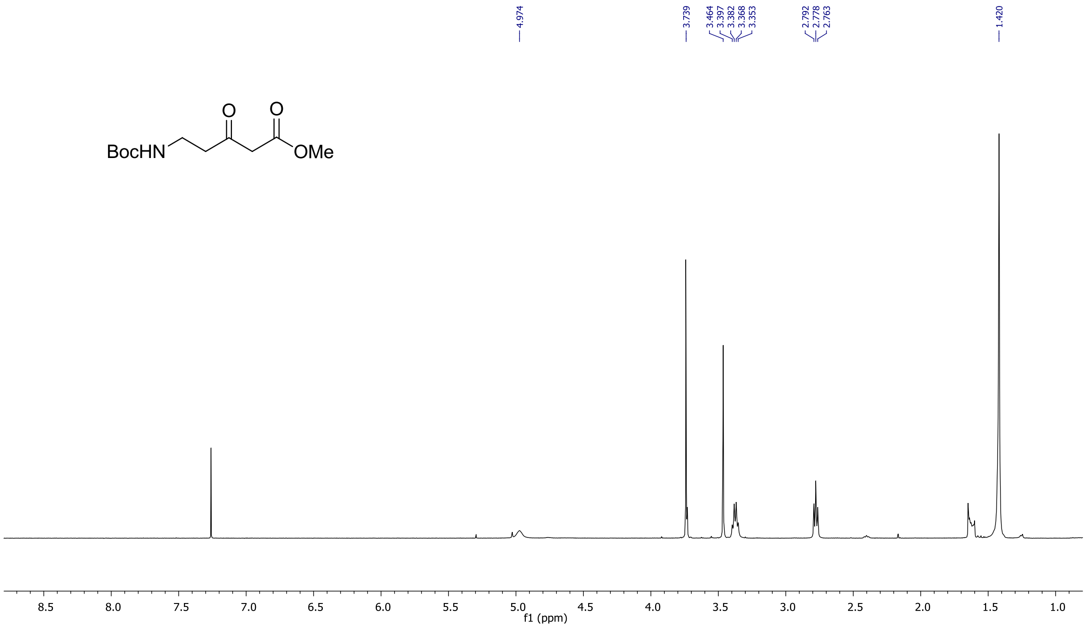


Fig AI.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **13**

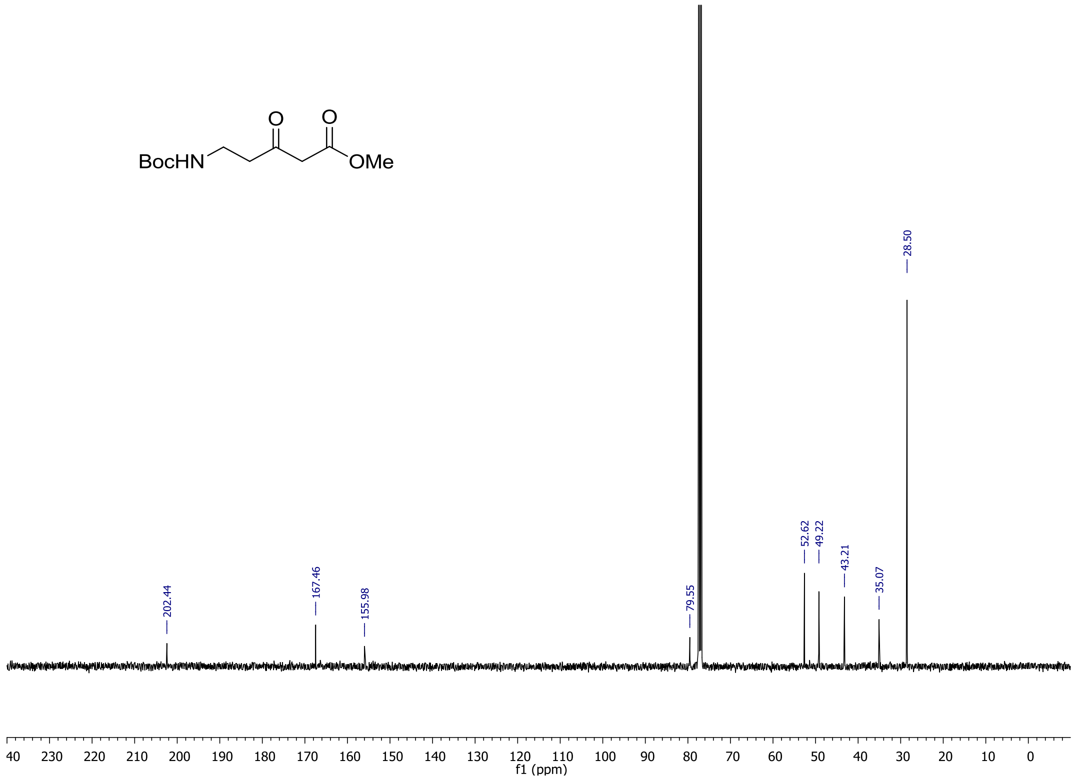


Fig AI.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **13**

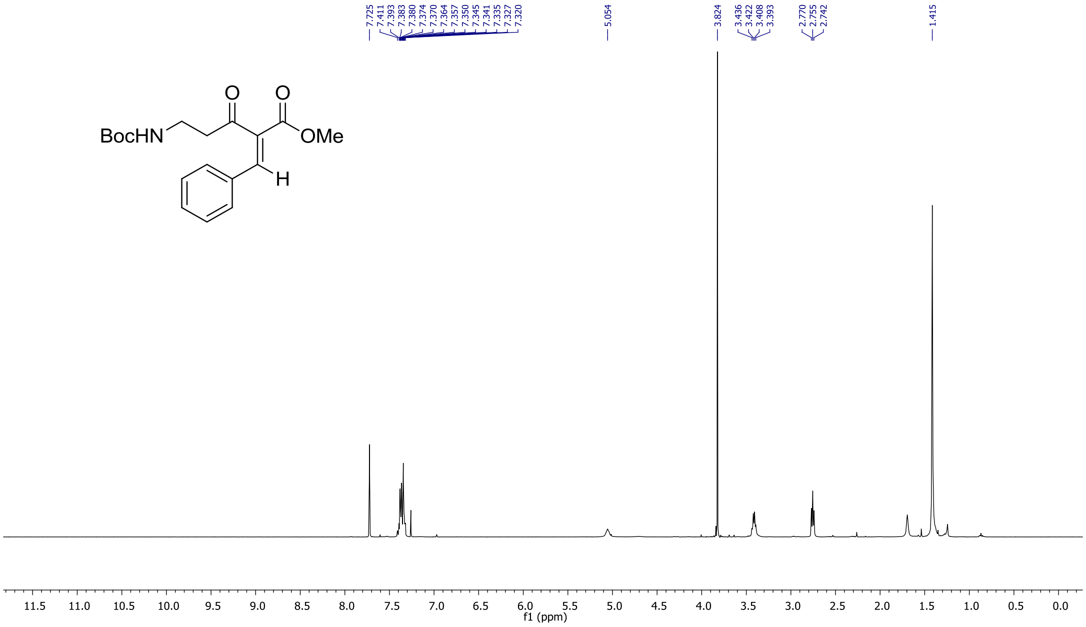


Fig AI.5: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound ***E*-18a**

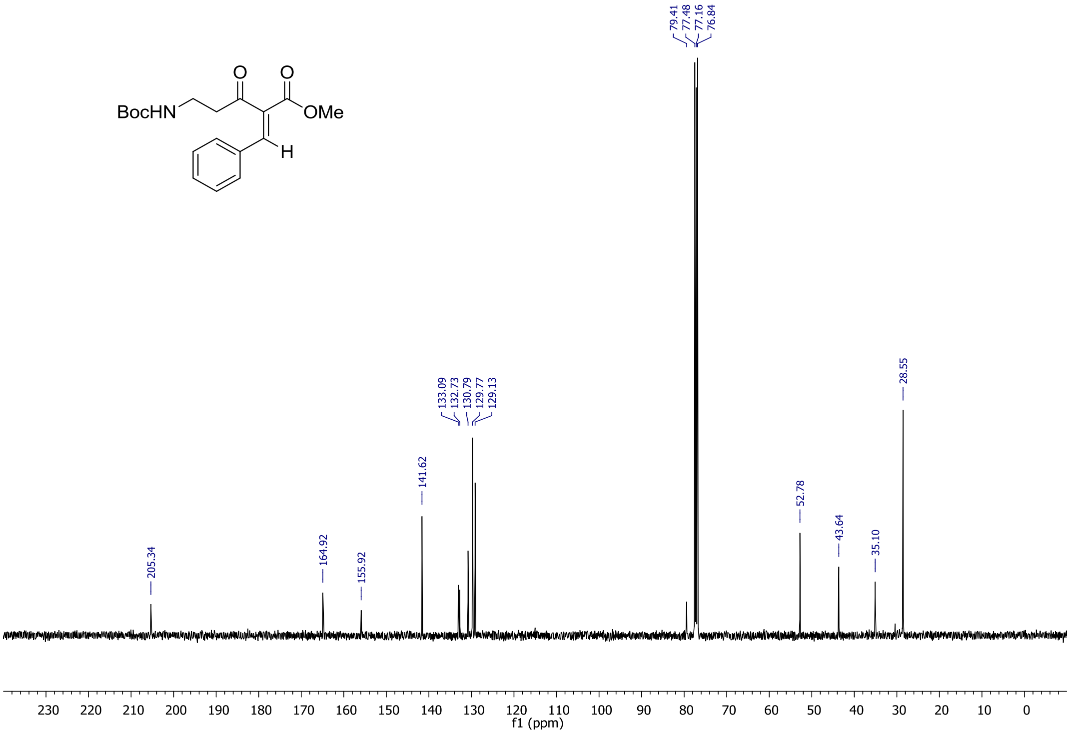


Fig AI.6: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound ***E*-18a**

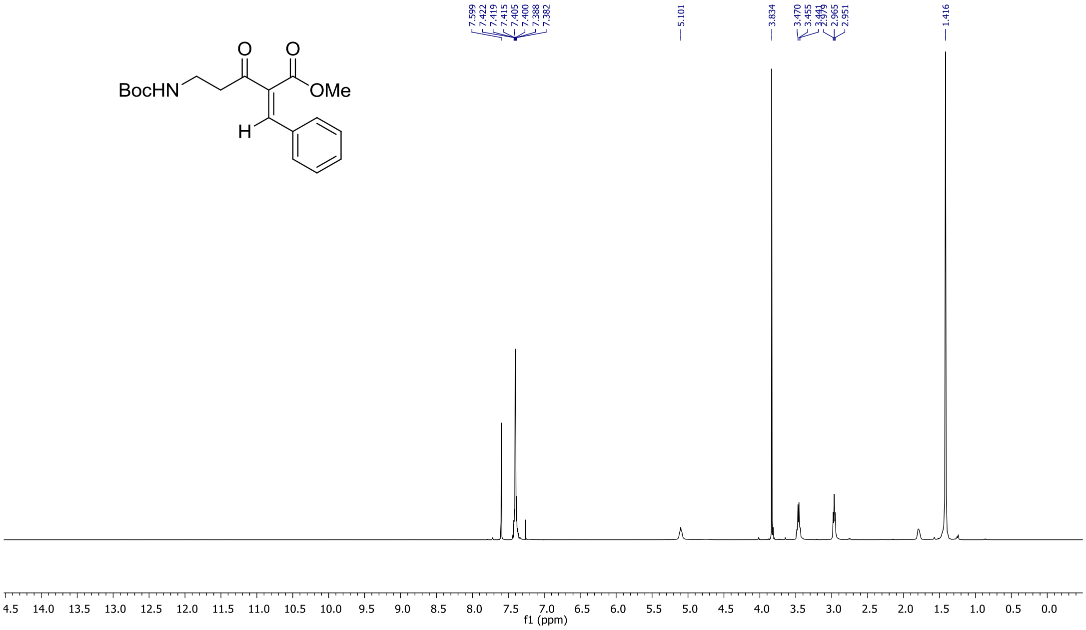


Fig AI.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound ***Z*-18a**

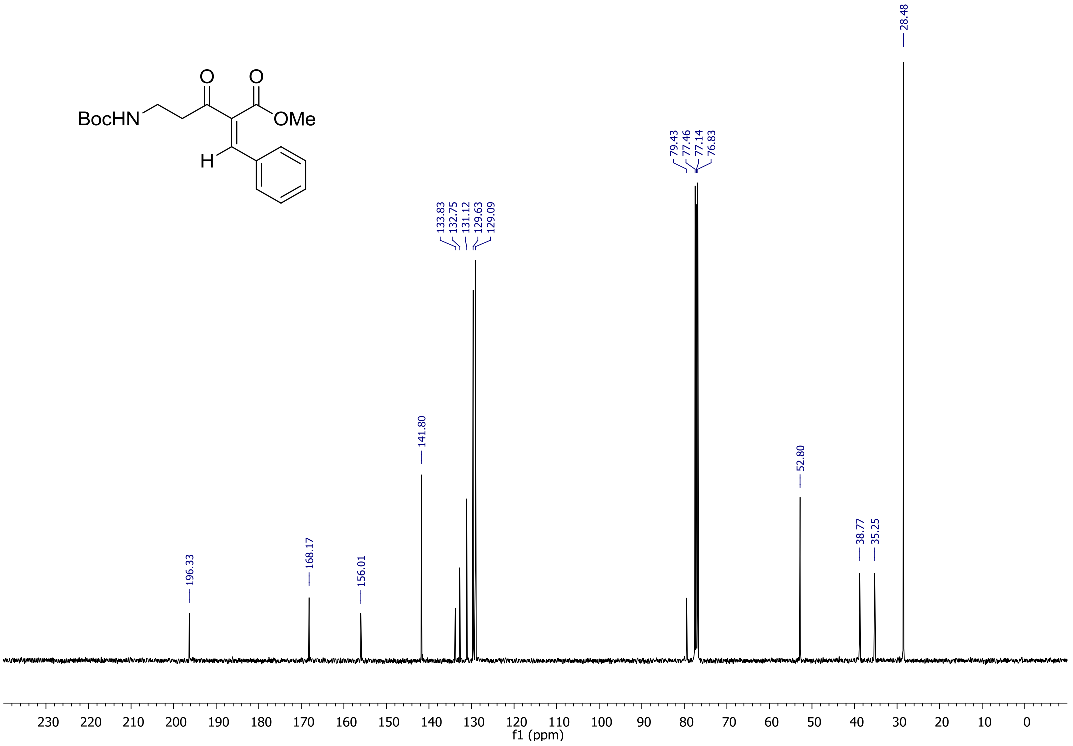


Fig AI.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound ***Z*-18a**

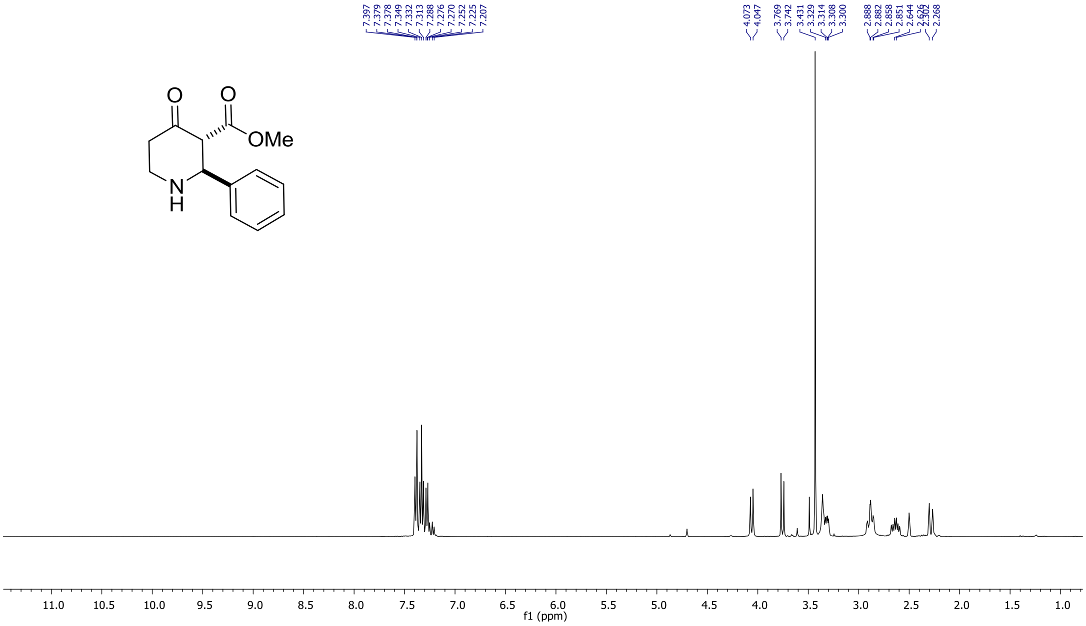


Fig AI.9: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **19aA**

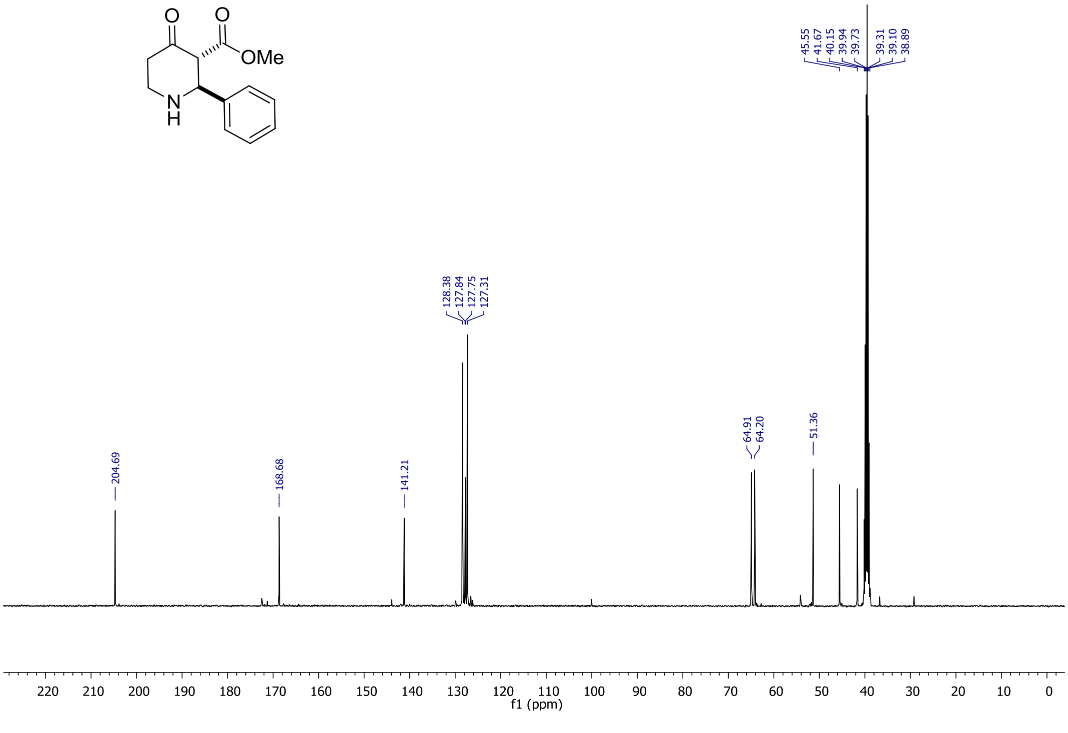


Fig AI.10: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **19aA**

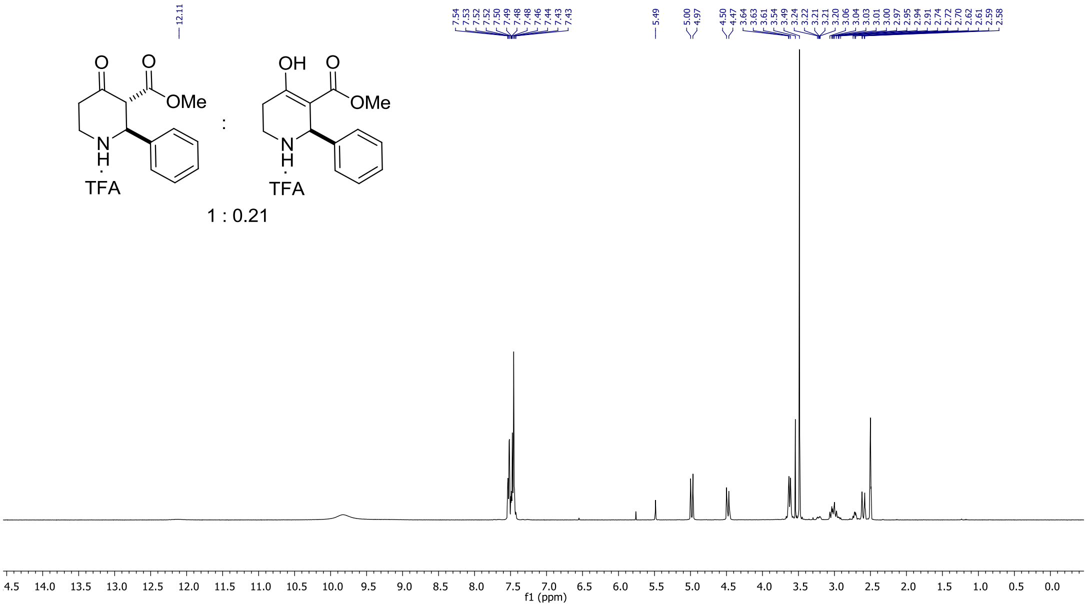


Fig AI.11: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **19a**

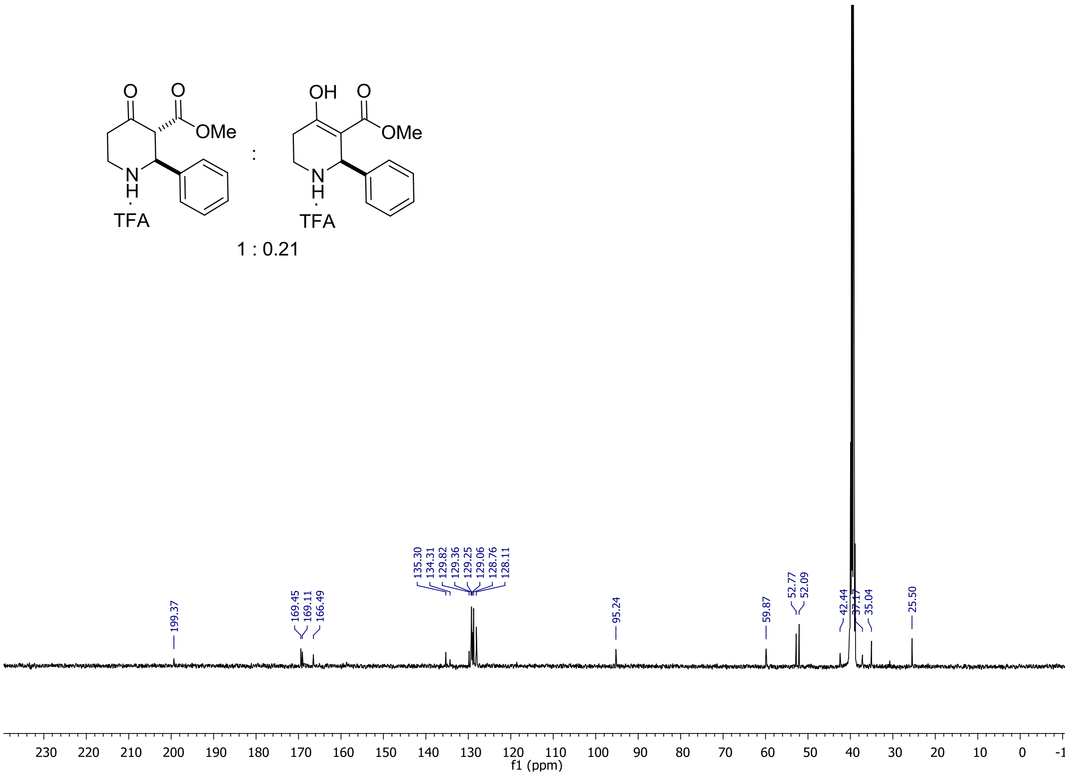


Fig AI.12: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **19a**

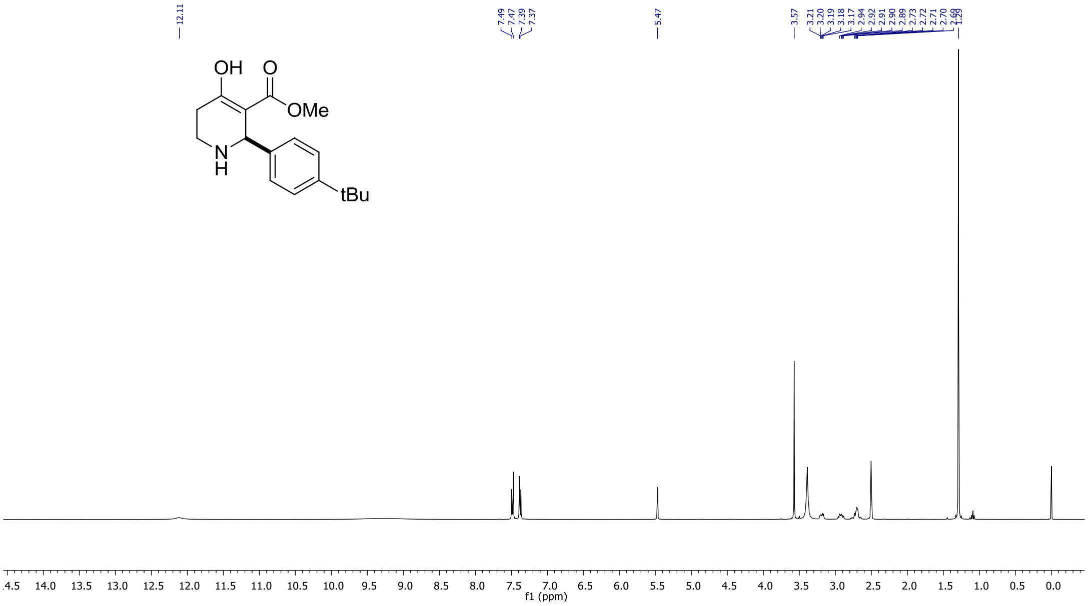


Fig AI.13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19d**

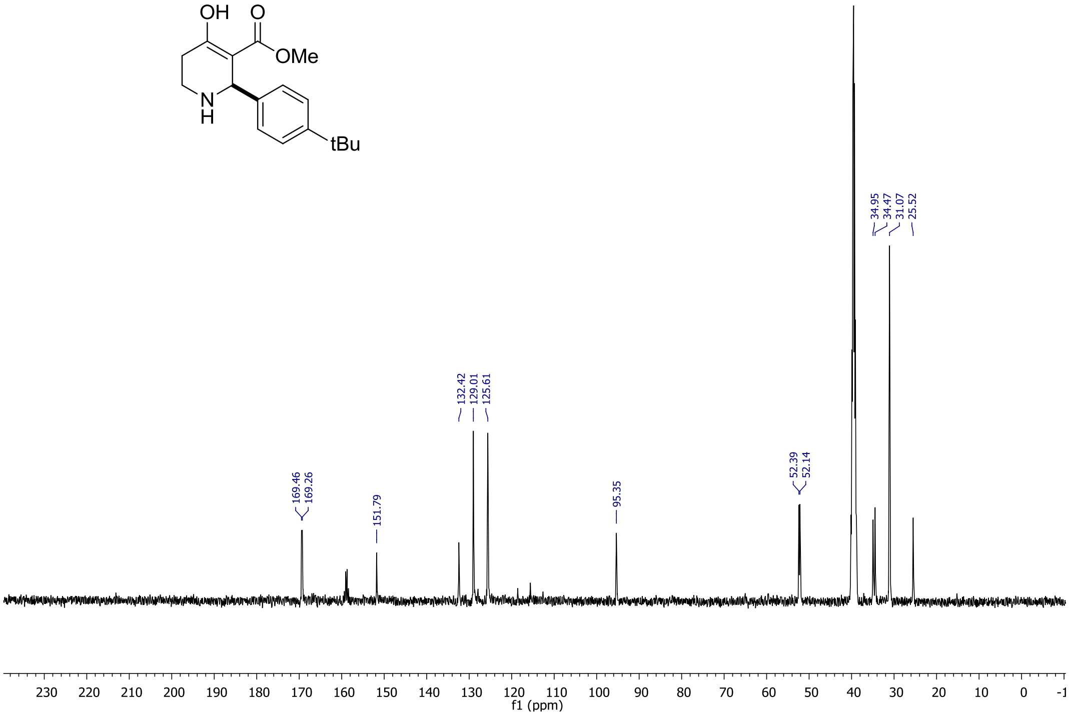


Fig AI.14: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **19d**

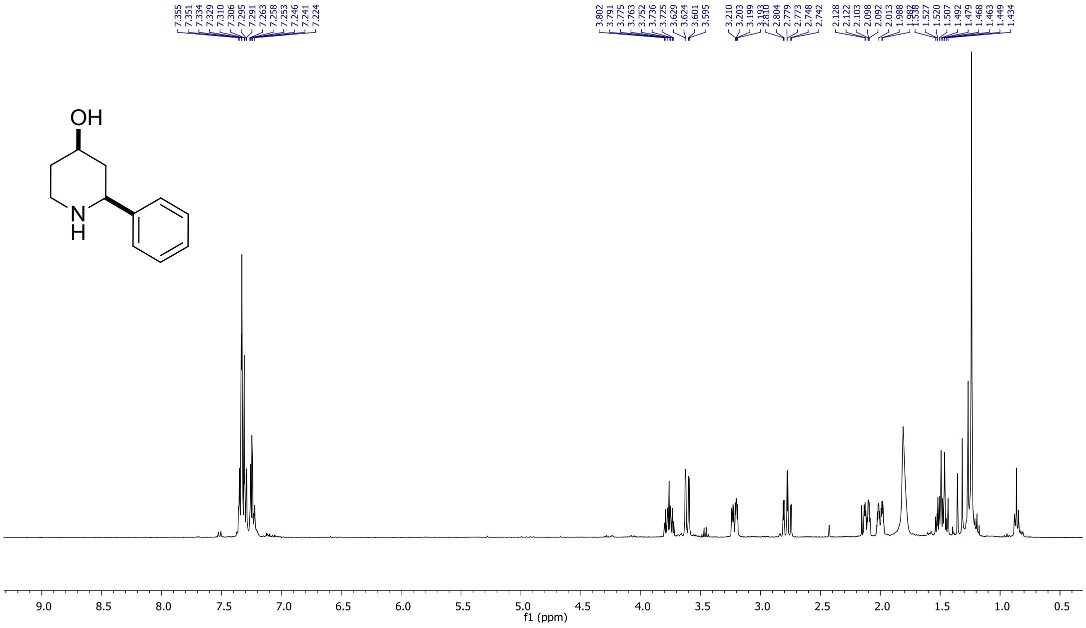


Fig AI.15: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **24**

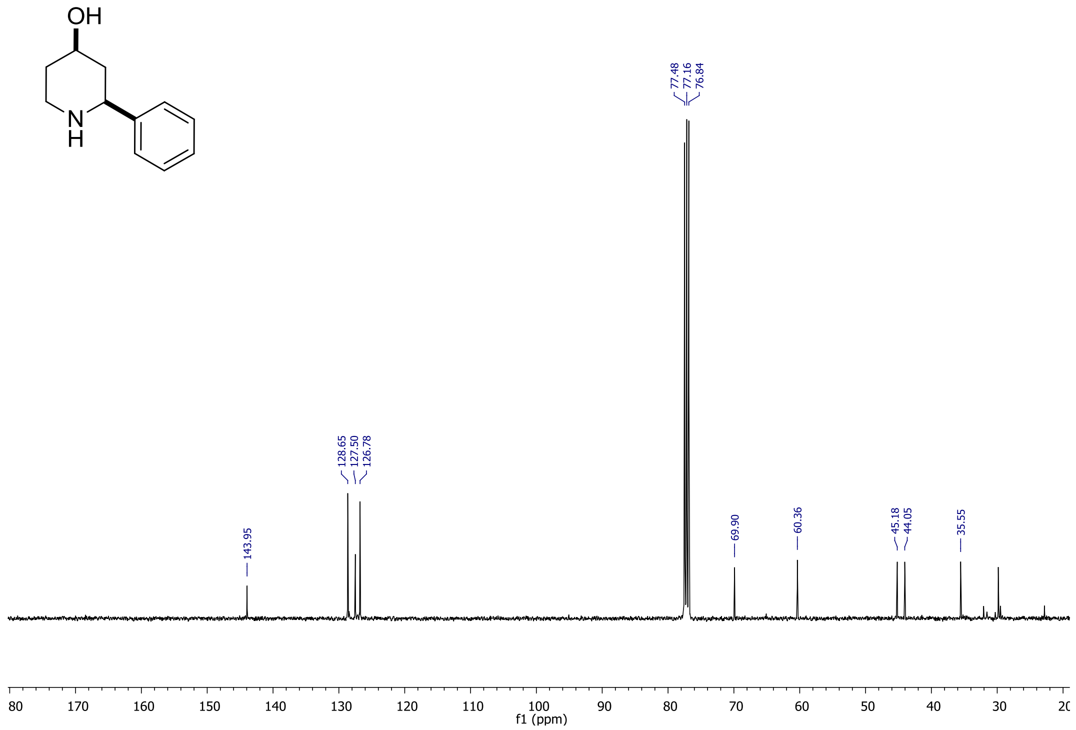


Fig AI.16: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **24**

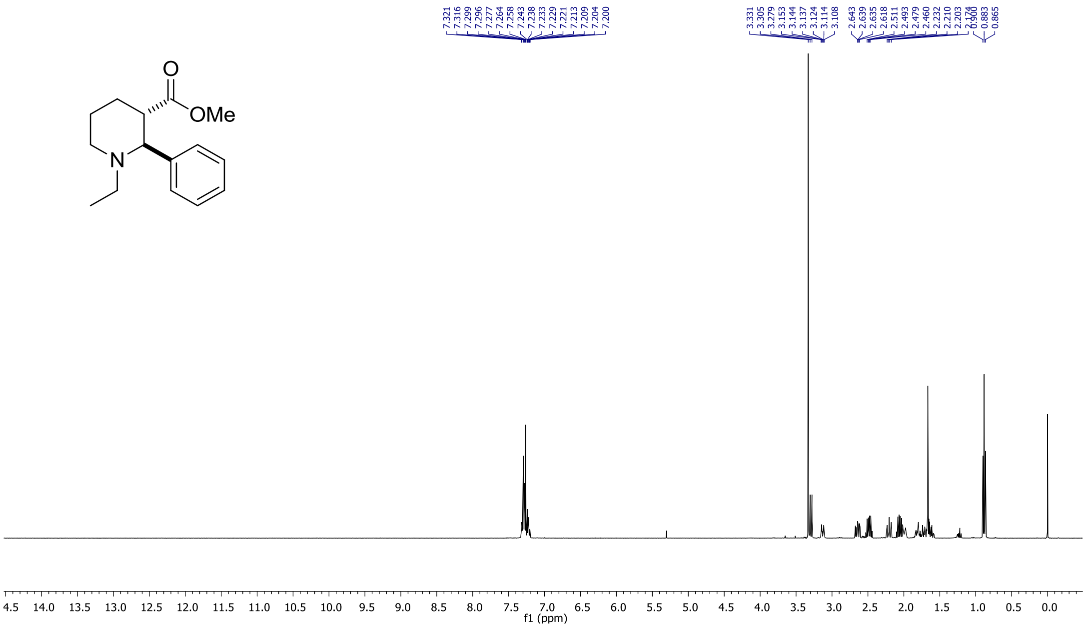


Fig AI.17: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **21**

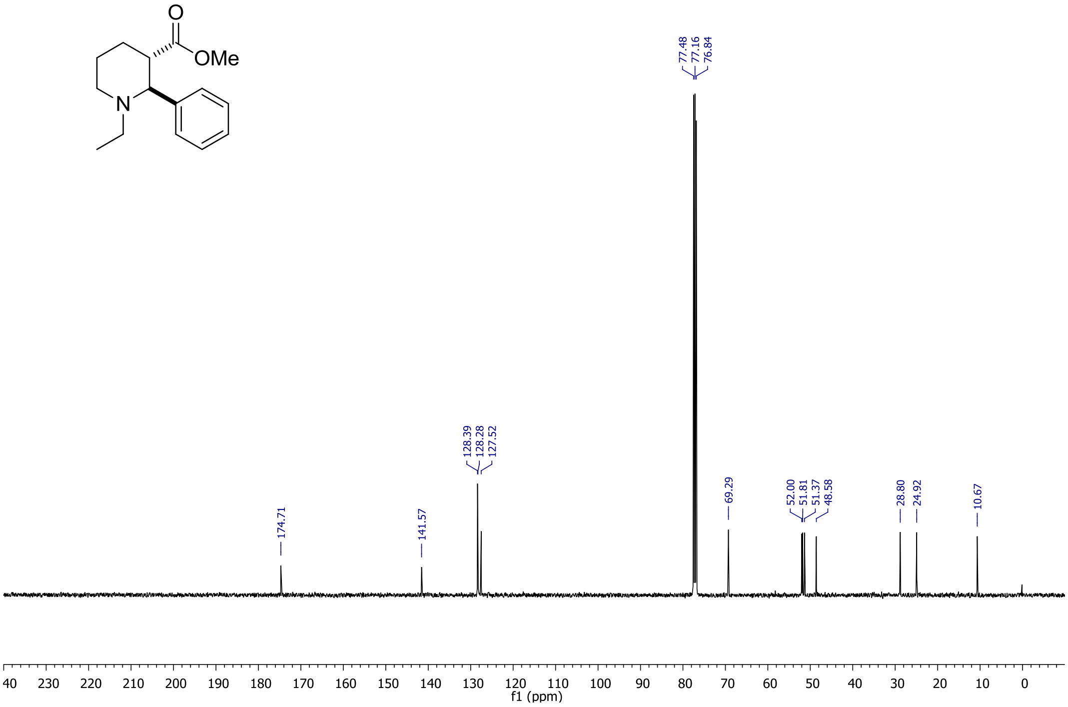


Fig AI.18: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **21**

1.6 References

[1] T. Reynolds, *Phytochemistry* **2005**, *66*, 1399–1406.

[2] J. M. Finefield, D. H. Sherman, M. Kreitman, R. M. Williams, *Angew. Chem., Int. Ed.* **2012**, *51*, 4802–4836.

[3] J. L. Arbiser, T. Kau, M. Konar, K. Narra, R. Ramchandran, S. A. Summers, C. J. Vlahos, K. Q. Ye, B. N. Perry, W. Matter, A. Fischl, J. Cook, P. A. Silver, J. Bain, P. Cohen, D. Whitmire, S. Furness, B. Govindarajan, J. P. Bowen, *Blood* **2007**, *109*, 560–565.

[4] G. David, (*The tree of Life online project, Retrived 2008-10-13*) 1**995** *http://tolweb.org/Dendrobatidae/16956/1995.01.01*

[5] V. Gilman, *Chem. Eng. News* **2005**, *83*, 108-108.

[6] A. Badolo, E. Ilboudo-Sanogo, A. P. Ouedraogo, C. Costantini, *Trop. Med. Int. Health* **2004**, *9*, 330–334.

[7] a) A. I. Meyers, G. P. Brengel, *Chem. Commun.* **1997**, 1–8; b) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.* **1998**, 633–640; c) K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588; d) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781–1813; e) F. X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712.

[8] P. S. Watson, B. Jiang, B. Scott, *Org. Lett.* **2000**, *2*, 3679–3681.

[9] a) H. Poerwono, K. Higashiyama, T. Yamauchi, H. Kubo, S. Ohmiya, H. Takahashi, *Tetrahedron* **1998**, *54*, 13955–13970; b) C. Agami, S. Comesse, C. Kadouri-Pichot, *J. Org. Chem.* **2000**, *65*, 4435–4439; c) D. Enders, C. Thiebes, *Pure Appl. Chem.* **2001**, *73*, 573–578; d) C. Agami, S. Comesse, C. Kadouri-Puchot, *J. Org. Chem.* **2002**, *67*, 2424–2428; e) M. Amat, N. Llor, J. Hidalgo, C. Escolano, J. Bosch, *J. Org. Chem.* **2003**, *68*, 1919–1928.

[10] a) P. Sulmon, N. De kimpe, N. Schamp, *Tetrahedron* **1989**, *45*, 3907–3922; b) G. E. Keck, A. Palani, *Tetrahedron Lett.* **1993**, *34*, 3223-3224; c) K. T. Kang, E. H. Kim, W. J. Kim, N. S. Song, J. K. Shin, B. Y. Cho, *Synlett* **1998**, 921–923; d) G. Verniest, R. Surmont, E. Van Hende, A. Deweweire, F. Deroose, J. W. Thuring, N. De Kimpe, *J. Org. Chem.* **2008**, *73*, 5458–5461.

[11] U. Kazmaier, R. Grandel, *Eur. J. Org. Chem.* **1998**, 1833–1840.

[12] a) D. M. Ryckman, R. V. Stevens, *J. Org. Chem.* **1987**, *52*, 4274–4279; b) H. M. Peltier, J. A. Ellman, *J. Org. Chem.* **2005**, *70*, 7342–7345; c) H. P. Kokatla, R. Lahiri, P. K. Kancharla, V. R. Doddi, Y. D. Vankar, *J. Org. Chem.* **2010**, *75*, 4608–4611.

[13] a) W. Van Brabandt, R. Van Landeghem, N. De Kimpe, *Org. Lett.* **2006**, *8*, 1105–1108; b) E. Leemans, M. D'hooghe, Y. Dejaegher, K. W. Toemroos, N. De Kimpe, *J. Org. Chem.* **2008**, *73*, 1422–1428.

[14] a) C. Schneider, C. Borner, A. Schuffenhauer, *Eur. J. Org. Chem.* **1999**, 3353–3362; b) I. Abrunhosa-Thomas, O. Roy, M. Barra, T. Besset, P. Chalard, Y. Troin, *Synlett* **2007**, 1613–1615; c) E. L. Wynne, G. J. Clarkson, M. Shipman, *Tetrahedron Lett.* **2008**, *49*, 250–252.

[15] a) B. M. Trost, A. B. Pinkerton, D. Kremzow, *J. Am. Chem. Soc.* **2000**, *122*, 12007-12008; b) O. V. Singh, H. Han, *Org. Lett.* **2004**, *6*, 3067–3070; c) A. P. Dobbs, S. J. J. Guesne, *Synlett* **2005**, 2101–2103; d) T. Kobayashi, M. Nakashima, T. Hakogi, K. Tanaka, S. Katsumura, *Org. Lett.* **2006**, *8*, 3809–3812; e) M. Z. Chen, G. C. Micalizio, *Org. Lett.* **2009**, *11*, 4982–4985; f) S. M. Hande, N. Kawai, J. Uenishi, *J. Org. Chem.* **2009**, *74*, 244–253; g) T. P. Lebold, A. B. Leduc, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3770–3772.

[16] a) S. Carbonnel, C. Fayet, J. Gelas, Y. Troin, *Tetrahedron Lett.* **2000**, *41*, 8293–8296; b) A. Bariau, W. B. Jatoi, P. Calinaud, Y. Troin, J. L. Canet, *Eur. J. Org. Chem.* **2006**, 3421–3433.

[17] a) D. J. Wallace, J. M. Goodman, D. J. Kennedy, A. J. Davies, C. J. Cowden, M. S. Ashwood, I. F. Cottrell, U. H. Dolling, P. J. Reider, *Org. Lett.* **2001**, *3*, 671–674; b) S. J. Dolman, E. S. Sattely, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **2002**, *124*, 6991–6997; c) G. A. Cortez, R. R. Schrock, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2007**, *46*, 4534–4538; d) J. C. Gonzalez-Gomez, F. Foubelo, M. Yus, *Synlett* **2008**, 2777–2780.

[18] a) V. Baliah, R. Jeyaraman, L. Chandrasekaran, *Chem. Rev.* **1983**, *83*, 379–423; b) P. A. Clarke, A. V. Zaytzev, A. C. Whtwoo, *Tetrahedron Lett.* **2007**, *48*, 5209–5212; c) G. Aridoss, S. Amirthaganesan, N. A. Kumar, J. T. Kim, K. T. Lim, S. Kabilan, Y. T. Jeong, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6542–6548; d) A. T. Khan, T. Parvin, L. H. Choudhury, *J. Org. Chem.* **2008**, *73*, 8398–8402.

[19] M. Ahari, A. Perez, C. Menant, J. L. Vasse, J. Szymoniak, *Org. Lett.* **2008**, *10*, 2473–2476.

[20] D. Hernandez, L. Nielsen, K. B. Lindsay, M. A. Lopez-Garcia, K. Bjerglund, T. Skrydstrup, *Org. Lett.* **2010**, *12*, 3528–3531.

[21] L. Cui, C. Q. Li, L. M. Zhang, *Angew. Chem., Int. Ed.* **2010**, *49*, 9178–9181.

[22] A. G. Jamieson, A. Sutherland, *Org. Lett.* **2007**, *9*, 1609–1611.

[23] C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966-8967.

[24] M. K. Ghorai, S. Halder, R. K. Das, *J. Org. Chem.* **2010**, *75*, 7061–7072.

[25] S. Fustero, D. Jimenez, J. Moscardo, S. Catalan, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283–5286.

[26] S. Benetti, R. Romagnoli, C. Derisi, G. Spalluto, V. Zanirato, *Chem. Rev.* **1995**, *95*, 1065–1114.

[27] a) R. Couffignal, J. L. Moreau, *J. Organomet. Chem.* **1977**, *127*, C65–C68; b) B. D. Harris, K. L. Bhat, M. M. Joullie, *Tetrahedron Lett.* **1987**, *28*, 2837–2840; c) M. Birch, S. Challenger, J. P. Crochard, D. Fradet, H. Jackman, A. Luan, E. Madigan, N. McDowall, K. Meldrum, C. M. Gordon, M. Widegren, S. Yeo, *Org. Process Res. Dev.* **2011**, *15*, 1172–1177.

[28] D. Kralj, M. Friedrich, U. Groselj, S. Kiraly-Potpara, A. Meden, J. Wagger, G. Dahmann, B. Stanovnik, J. Svete, *Tetrahedron* **2009**, *65*, 7151–7162.

[29] E. M. Arnett, S. G. Maroldo, S. L. Schilling, J. A. Harrelson, *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.

[30] J. D. Butler, K. C. Coffman, K. T. Ziebart, M. D. Toney, M. J. Kurth, *Chem.—Eur. J.* **2010**, *16*, 9002–9005.

[31] J. Marin, C. Didierjean, A. Aubry, J. R. Casimir, J. P. Briand, G. Guichard, *J. Org. Chem.* **2004**, *69*, 130–141.

[32] a) T. Conroy, J. T. Guo, N. H. Hunt, R. J. Payne, *Org. Lett.* **2010**, *12*, 5576–5579; b) A. D. Cuiper, M. Brzostowska, J. K. Gawronski, W. J. J. Smeets, A. L. Spek, H. Hiemstra, R. M. Kellogg, B. L. Feringa, *J. Org. Chem.* **1999**, *64*, 2567–2570.

[33] J. A. Robl, L. A. Duncan, J. Pluscec, D. S. Karanewsky, E. M. Gordon, C. P. Ciosek, L. C. Rich, V. C. Dehmel, D. A. Slusarchyk, T. W. Harrity, K. A. Obrien, *J. Med. Chem.* **1991**, *34*, 2804–2815.

[34] E. F. Evans, N. J. Lewis, I. Kapfer, G. Macdonald, R. J. K. Taylor, *Synth. Commun.* **1997**, *27*, 1819–1825.

[35] J. W. Muskopf, R. M. Coates, *Organic Synthesis* **1990**, *Coll. Vol. 7*, 393.

[36] C. Reichardt, *Solvents and Solvent Effects in Organic chemsitry*, **2004**.

[37] J. L. G. Ruano, A. Parra, J. Aleman, F. Yuste, V. M. Mastranzo, *Chem. Commun.* **2009**, 404–406.

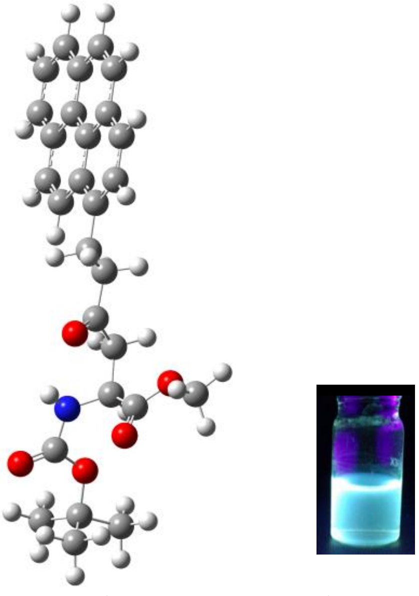
[38] M. Haddad, M. Larcheveque, *Tetrahedron Asymm.* **1999**, *10*, 4231-4237.

[39] F. A. Davis, T. N. Fang, B. Chao, D. M. Burns, *Synthesis* **2000**, 2106-2112.

[40] O. G. Mancheno, R. G. Arrayas, J. C. Carretero, *J. Am. Chem. Soc.* **2004**, *126*, 456-457.

Chapter Two

Synthesis of side chain modified oxo-α-amino acids and *cis*-5-alkyl prolines



Energy minimized structure and Fluorescence of Pyrene derivative of Oxo-α-amino acid

T w o

Chapter 2

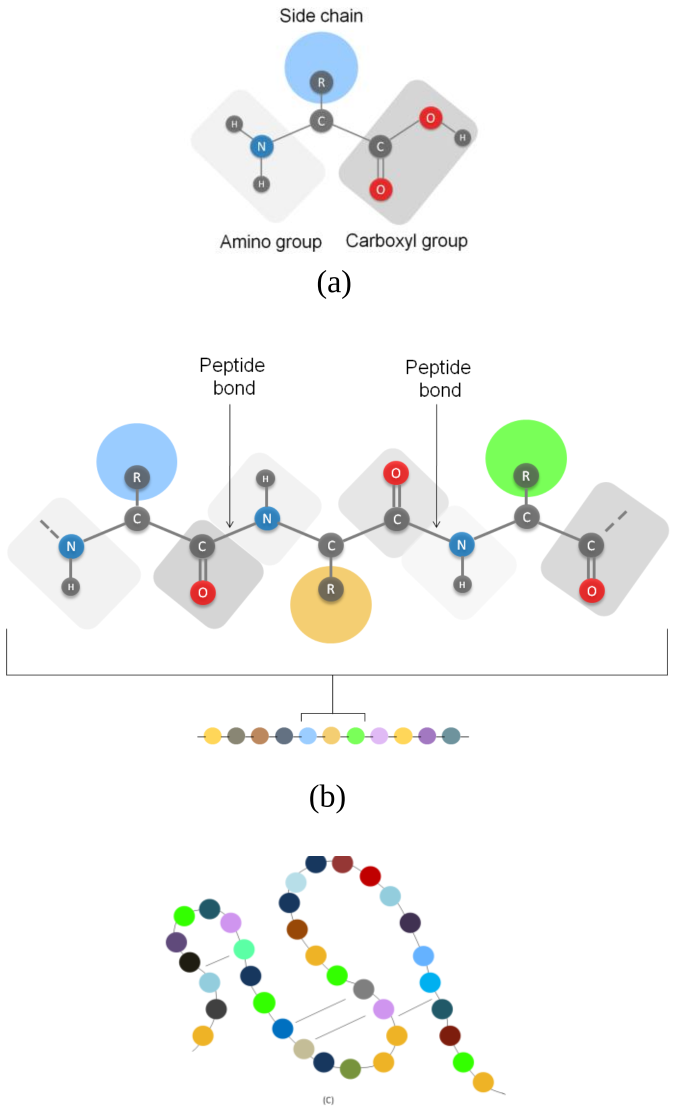
In this chapter a short and concise synthesis of enantiopure side chain-modified α-amino acids such as 4-oxo-L-norvaline, 6-oxo-L-homonorleucine, and 5-cis-alkyl prolines is described. Meldrum's acid has been employed for the preparation of aminocarboxylate-derived β-ketoesters. Knoevenagel condensation of L-aminocarboxylate-derived β-ketoesters with aldehydes followed by reductive decarboxylation afforded unnatural α-amino acids. Application of the method has been illustrated by the synthesis of a fluorescent amino acid.

2.1 Introduction

Naturally occurring and chemically synthesized non-natural amino acids are gaining significance as useful and important tools for modern drug discovery research. Unnatural amino acids are used as chiral building blocks and molecular scaffolds for constructing molecular libraries due to their structural diversity and functional versatility.[1] Some of these unnatural amino acids play a vital role in pharmaceuticals and lead development in drug discovery.[2] Non-genetically coded amino acids, particularly non-natural α-amino acids, have contributed strongly in the area of peptide research.[3] Side chain conformational restrictions deliver a practical approach in peptidomimetics to understand the interactions of peptides with proteins, nucleic acids, lipids, and sugars in biological systems. These amino acids play a significant role in peptide analogs to limit conformational flexibility, to enhance enzymatic stability, and to improve pharmacodynamics and bioavailability.

2.1.1 Non-Proteinogenic Oxo-α-Amino Acids

Most of the organisms are encoded with 20 common natural α-amino acids and in very rare cases they are encoded with proteinogenic amino acids such as selenocysteine[4] and pyrrolysine[5] and they are considered as 21st and 22nd natural α-amino acids, respectively. Natural α-amino acids can be differentiated based on their side chain functionality. They can be broadly classified in to basic, acidic and neutral amino acids. Hence, this leads to fascinating chemistry of amino acids. These amino acids play a significant role in peptide conformation and polar amino acids facilitate hydrogen bonds in peptides (Fig **2.1**). Also, charged amino acids are capable of forming ionic bonds. These weak bonds are non-covalent in nature.



(a)

(b)

(c)

Fig 2.1: (a) Amino acid with side chain represented in colored circles (b) Amino acid units in the polypeptide (c) Polypeptide folds in specific conformation depending upon side chain interactions

The chemistry of amino acid side chains is critical to protein structure. These side chain interactions are mostly non-covalent in nature. Due to these side chain interactions, the sequence and location of amino acids in a particular protein/polypeptide influences where the bends and folds occur in that peptide (Fig **2.1**). These weak interactions play a key role in protein structure and interactions. There are significant efforts have been carried out to understand these interactions. One such effort has been directed towards the synthesis and utility of the side chain modified unnatural α-amino acid for such studies. The keto group is ubiquitous in organic compounds. Keto group can easily be explored for simple chemical transformation to form other functional moieties.

It has been observed that reaction between ε-amino group of lysine present in the protein and ketone is reversible.[6] Keto acid such keto glutaric acid is the precursor of amino acid such glutamic acid during the biosynthesis. There are few examples in which keto α-amino acids have been successfully introduced in the proteins. For example unnatural amino acid 4-oxo-L-norvaline (**1**, Fig **2.2**) has been selectively introduced in the T4 lysozyme by process of unnatural amino acid mutagenesis.[6]

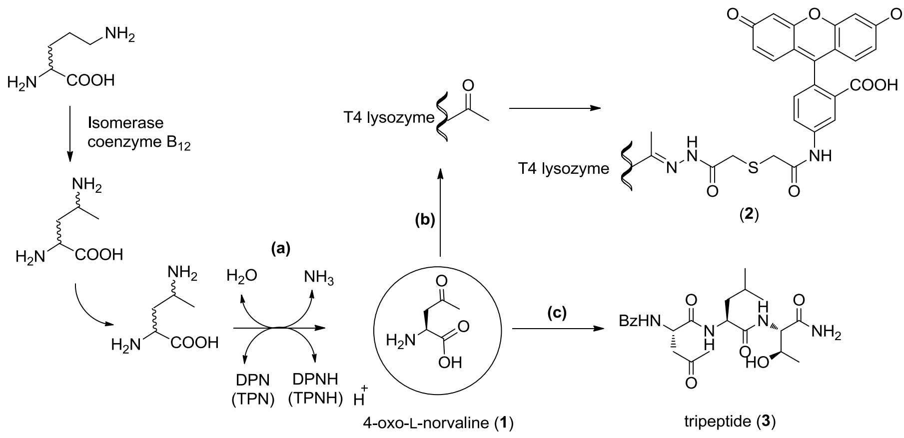


Fig 2.2: (a) Proposed initial pathway of ornithine catabolism by *Clostridium sticklandi* (b) Ketone handle in T4 Lysozyme, labelling using fluorescent tag (c) tripeptide containing 4-oxo-L-norvaline

The keto group containing side chain was utilized for labelling, by the reaction of keto group with flouresenscent hydrazine dye to afford labelled protein **2**. In another example, 4-oxo-L-norvaline **1** is a part of tripeptide **3** known to inhibit oligosaccharyltransferase.[7]

(+)-Hygrine **4** (Fig **2.3**) is a pyrrolidine alkaloid isolated from coca leaves and has been explored for its biological and pharmacological studies.[8] Hygrine is also a precursor of few tropane alkaloids like (−)-hyoscyamine, (−)-scopolamine and (–)-cocaine. Synthesis of (+)-Hygrine is a great challenge, as it is known to racemize in basic as well as neutral conditions. Nevertheless, this alkaloid has been efficiently synthesized[9] starting from protected 4-oxo-L-norvaline in its enantiomeric form.

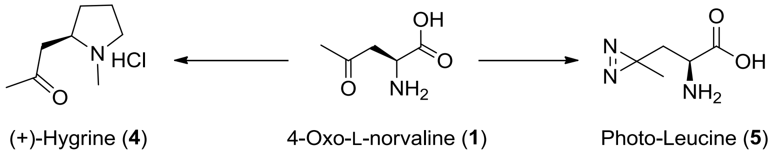


Fig 2.3: 4-Oxo-L-norvaline as precursor of (+)-Hygrine

Photo-leucine **5** (Fig **2.3**) is a photoreactive unnatural α-amino acid containing photoreactive diazirine group. Under exposure of specific UV wavelength, amino acid **5** liberates nitrogen along with the formation of highly reactive carbene species that can be trapped by protein by covalently binding to it. This photoreactive α-amino acid has been efficiently synthesized[10] starting from 4-oxo-L-norvaline in only two steps. Similar properties have been shown by photo-methionine that in turn has been synthesized starting from 4-oxo-L-homonorvaline.

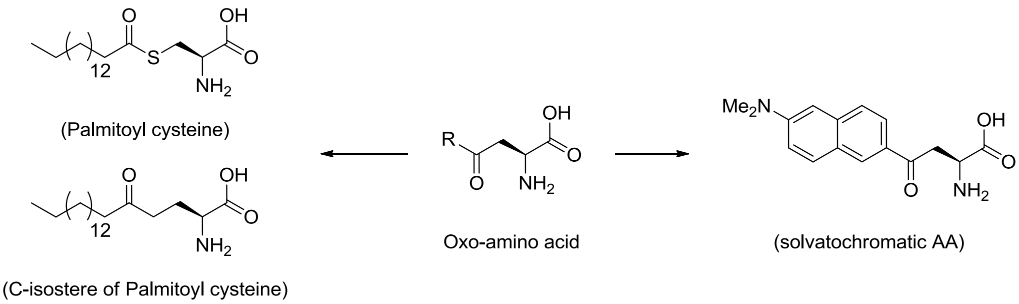
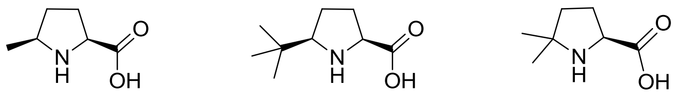


Fig 2.4: Examples of 4-Oxo-α-Amino acids

Environmentally sensitive fluorescent oxo-α-amino acids (Fig **2.4**) have been synthesized and incorporated into the proteins.[11] Palmitoyl cysteine[12] contains thioamide in its side chain and its C-isostere is typical example of δ-oxo-α-amino acid. Oxo-α-amino acids have been utilized as a precursor for the synthesis different unnatural amino acids. The ‘thiol’ of palmitoyl cysteine has been replaced by ‘methylene’ moiety and successfully introduced into H-Ras heptapeptide 180–186 sequence, forming highly lipidated peptide.

2.1.2 Non-Proteinogenic Prolines

Occurrence of non-proteinogenic prolines in natural and synthetic bioactive natural products makes them very important target compounds. Some of these proline derivatives are critical precursors of conformationally rigid bioactive peptides.[13] Further, proline has contributed in the field of asymmetric catalysis.[14] Various analogues of proline derivatives have been employed for catalyzing different enantioselective organic transformations. D-proline has been established as a turn inducer in peptides. Properties of proline derivatives can be manipulated by steric or electronic means depending upon the substitutions on the ring. There are few reports in the literature for the synthesis of 5-substituted prolines[15] and their subsequent utility in constructing the conformationally constrained peptidomimetics.[16] The 5-substituted prolines have been used as scaffold in drug discovery,[17] this structural motif is also present in natural product (+)-RP-66803.[18] 5-substituted proline has been used as a key precursor for synthesizing indolizidine alkaloids[19] and nicotine analogs.[20] Prolyl *cis*/*trans* isomerism is present in *N*-terminal of amide bond in the proline and this isomerism may disturb the weak interactions in peptides and thus interrupting stability of proteins. In order to overcome this difficulty 5-substituted-alkyl-proline surrogates have been effectively synthesized (Fig **2.5**).[21] The 5-*tert*-butylproline[22] provides a rigid amide bond those results in conformational rigidity.



5-*cis*-Methylproline 5-*tert*-butylproline 5,5-dimethylproline

Fig 2.5: Examples of 5-substituted proline derivative

The nonnatural amino acid such as 5,5-dimethylproline was incorporated into *ribonuclease A*, and that led to acceleration of protein folding and enhancement of conformational stability.[23] 5,5-dimethylproline provided a new insight into protein folding pathways.

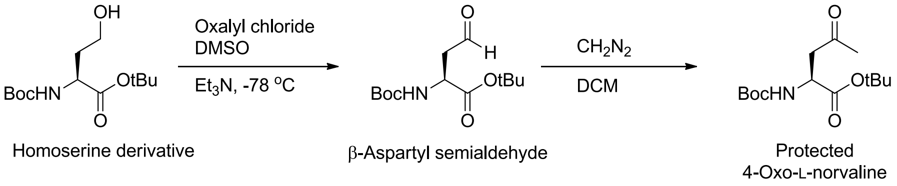
2.2 Methods for Synthesis of Oxo-α-Amino Acids

Oxo-α-amino acids have been synthesized from different routes. These unnatural amino acids have been synthesized from acylation of *N*-(Phenylfluorenyl)glutamate enolate followed by hydrolytic-decarboxylation,[24] or by the reaction between zinc reagent prepared from β-iodoalanine and acid chlorides/aryl iodides.[25] Enolate of glycine derivative has been treated with the epoxides to give γ-hydroxy-α-amino acid, which on oxidation afforded γ-oxo-α-amino acids.[26] Few other methods such as reversible Mannich type reaction,[27] oxidation of γ-nitro-α-amino acid[28] and organocatalytic Mannich reaction[29] have been successfully employed for the preparation of oxo-α-amino acids. Some of the methods have been discussed in detail below.

2.2.1 Diazomethane homologation

Davis and co-workers used diazomethane homologation[30] strategy for the synthesis of 4-oxo-L-norvaline starting from protected serine derivative (Scheme **2.1**). Diazomethane homologation of β-aspartyl semialdehyde afforded 4-oxo-L-norvaline.

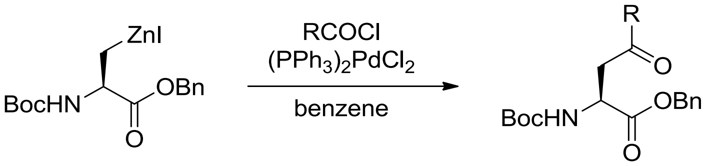
Similarly, trimethylsilyldiazomethane ($TMSCHN_2$) has been used in the synthesis of 4-oxo-L-norvaline in low yield (28%). The protecting groups have been found to be very crucial for the synthesis of 4-oxo-L-norvaline in enantiomeric form. This methodology has been further extended for the synthesis of β-ketoesters.



Scheme 2.1

2.2.2 Organozinc reagent

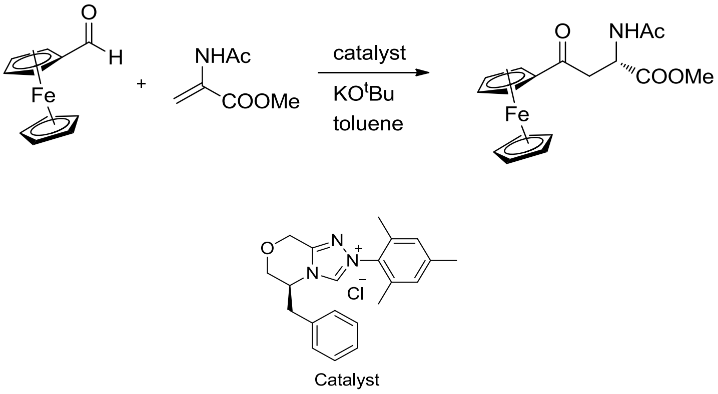
Jackson and co-workers showed an elegant method for the synthesis of oxo-α-amino acids by coupling acyl chloride and organozinc reagent derived from L-iodoserine derivative in presence of Pd catalyst (Scheme **2.2**).[31]



Scheme 2.2

2.2.3 Stetter reaction

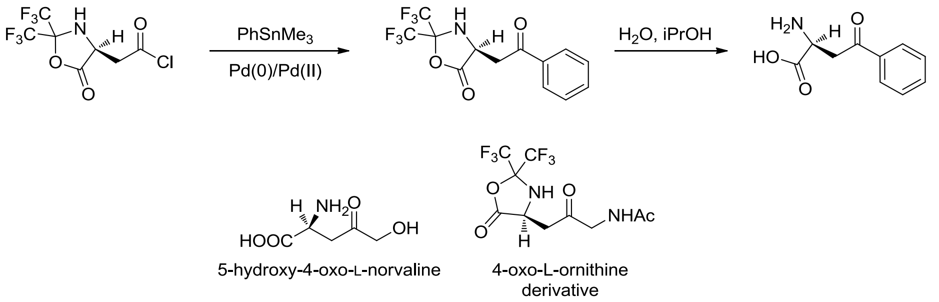
Enantioselective intramolecular Stetter reaction has been effectively employed for the synthesis of oxo-α-amino acid derivatives. Reaction of ferrocene aldehyde and α,β-unsaturated aminoester (dehydro serine ester) in presence of chiral *N*-heterocyclic carbene (NHC) catalyst afforded enantiopure oxo amino acids (>99% ee) in good yields (Scheme **2.3**).[32]



Scheme 2.3

2.2.4 Stille cross coupling

Stille cross coupling of hexafluoroacetone protected L-aspartic acid chloride with organotin reagent followed by the subsequent hydrolysis afforded the corresponding oxo-α-amino acids (Scheme **2.4**).[33] Using this strategy synthesis of 5-hydroxy-4-oxo-L-norvaline and 4-oxo-L-ornithine derivatives has been described.



Scheme 2.4

It has been indisputably demonstrated in the literature that side chain conformational restrictions deliver a practical approach in peptidomimetics to understand the interactions of peptides with proteins, nucleic acids, lipids, and sugars in biological systems. Since reactions utilizing these modified α-amino acids as organocatalysts and/or scaffolds for building of peptidomimetics are gaining importance, there is a need to synthesize such scaffolds in a novel way. It is still a challenge for synthetic organic chemists to develop a cost effective and efficient protocol for the synthesis of such unnatural α-amino acids. Herein, in this chapter we describe a new method for the synthesis of enantiopure oxo-α-amino acids starting from commercially available amino acids and Meldrum's acid. Application of this method has been explored in synthesizing fluorescent amino acid.

2.3 Results and Discussion

In chapter 1, we described the synthesis of β-ketoesters starting from β-alanine exploring the use of Meldrum's acid. It is very well known in the literature that under suitable reaction conditions β-ketoesters undergo facile decarboxylation to afford the keto derivatives. Also, as β-ketoesters contain electrophilic and nucleophilic sites they have been used as precursors in the organic synthesis for variety of reactions.

2.3.1 General strategy

After gleaning through the literature, we presumed that β-ketoesters derived from acidic α-amino acids (having carboxylic group in the side chain) may serve as effective precursors of oxo-α-amino acids. We believed that commercially available and less expensive aspartic acid and glutamic acid can be employed for the study. Hence we planned for the preparation of benzyl β-ketoesters for the easy access of oxo-α-amino acids. As benzyl β-ketoesters undergo facile hydrogenolysis, we presumed that simultaneous debenzylation and β-keto decarboxylation would afford keto group in the side chain of amino acids (Fig **2.6**).

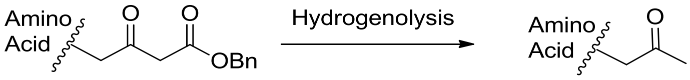
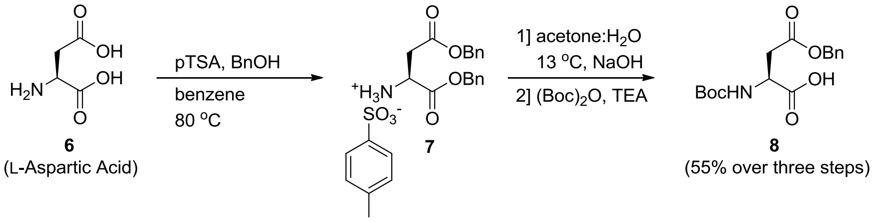


Fig 2.6: Easy access to oxo-amino acids

2.3.2 Preparation of amino acid derivatives with side chain free carboxyl group

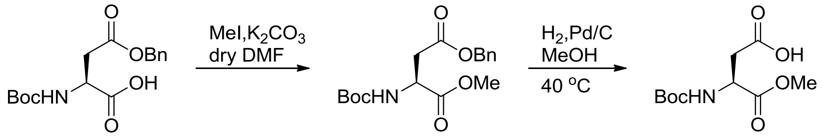
L-Aspartic acid **6** (Scheme **2.5**) under refluxing conditions in benzyl alcohol/benzene using catalytic amount of *p*-toluene sulfonic acid (*p*TSA) using Dean-Stark apparatus afforded the corresponding dibenzyl ester of α-amino acid salt **7**. Both the benzyl esters in **7** are chemically distinct from each other. The α-ester group of **7** is slightly more prone for hydrolysis than β-ester group due to −I effect of nitrogen and possible hydrogen bonding between the oxygen of α-ester and NH hydrogen. Also, α-ester of **7** is more sterically crowded than β-ester. Under the careful optimization of hydrolysis condition one can hydrolyse α-ester more rapidly than the β-ester.



Scheme 2.5

Compound **7** under optimized reaction conditions[34] [Acetone/H_2O (1:3), 2N NaOH at 13 °C for 30 min], underwent facile hydrolysis of α-ester. Resultant reaction mixture was immediately treated with di-*tert*-butyl dicarbonate (Boc_2O) and triethyl amine (TEA) to afford compound **8** in an overall yield of 55%. Further, esterification of α-carboxylic group of **8** was carried out using iodomethane and K_2CO_3 to give the corresponding diester **9** (Scheme **2.6**).[35] Further, we exploited the orthogonal relation of two different esters and selectively deprotected the benzyl group by using $Pd/C/H_2$

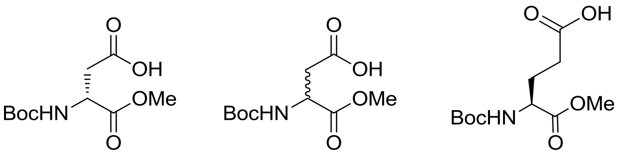
under hydrogenolysis conditions to afford the required substrate, *N*-Boc-L-aspartic acid 1-methyl ester **10**.



8 **9** (95%) **10** (99%)

Scheme 2.6

Following the similar approach (Scheme **2.5** and **2.6**), further we synthesized compounds **11**, **12** and **13** starting from D-aspartic acid, *rac*-aspartic acid and L-glutamic acid respectively (Fig **2.7**). Importantly, all these amino acid derivatives were synthesized on a gram scale. These amino acid derivatives (**10–13**) were further employed for the preparation of β-keto esters and these in turn can be employed for the synthesis of oxo-amino acids as shown in the design strategy (Fig **2.6)**.

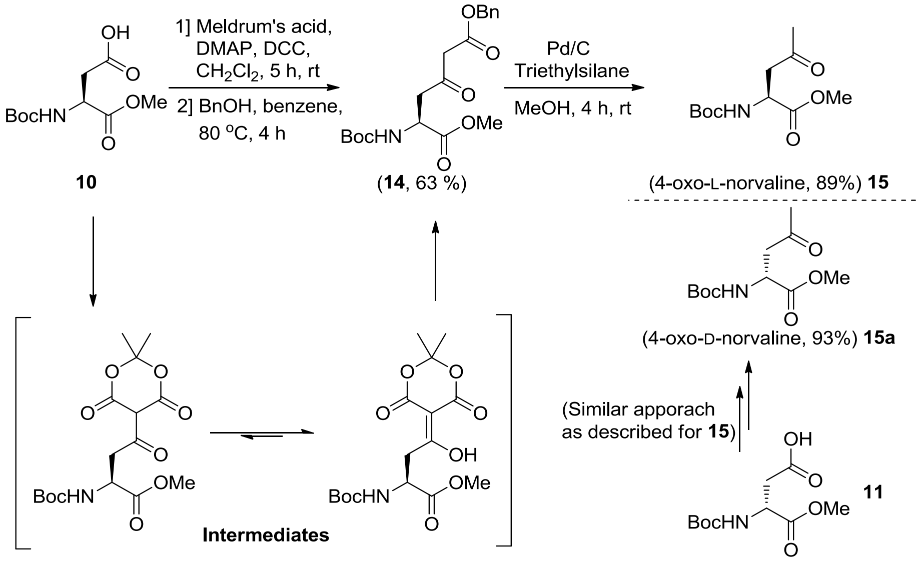


(**11**, 43%) (**12**, 44%) (**13**, 55%)

Fig 2.7: Protected derivatives of L-Aspartic acid, *rac*-Aspartic acid and L-Glutamic acid

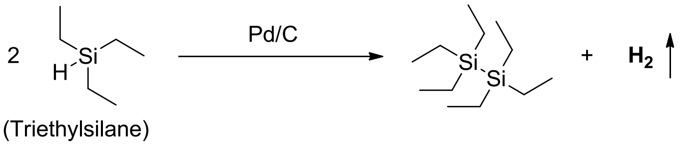
2.3.3 Synthesis of 4-Oxo-L-Norvaline

Coupling of *N*-Boc-L-aspartic acid 1-methyl ester **10** with Meldrum's acid in presence of DCC and DMAP furnished the corresponding acyl Meldrum's acid as an intermediate, which on subsequent treatment with benzyl alcohol afforded β-ketoester **14** in 63% yield (Scheme **2.8**) in one pot using a procedure reported for similar compounds.[36] We opted for the synthesis of benzyl β-ketoester owing to ease with which it undergoes facile hydrogenolysis to afford β-ketoacid followed by the instantaneous decarboxylation. Compound **14** under hydrogenolysis conditions using Pd/C and triethylsilane (TES) in methanol gave the corresponding protected 4-oxo-L-norvaline **15** in 89% yields in 4 hours.



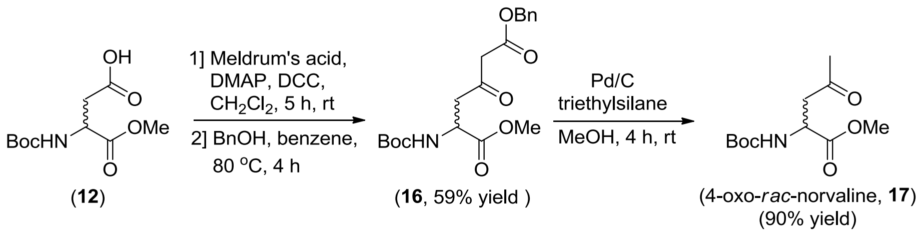
Scheme 2.8

Hydrogen gas was generated in-situ instantaneously by the treatment of TES with of Pd/C (Scheme **2.9**). We observed that the process was very convenient and avoided the external use of potentially hazardous hydrogen gas.[37]



Scheme 2.9

It is very important to note that TES known to reduce ketones,[38] however, we did not observe even the trace amount of reduced product. The transformation from **14** to **15** was selective and neat. No side products were formed during the reaction or work up. By similar approach mentioned above D-isomer **15a** was synthesized starting from **11** in good yield (93%, Scheme **2.8**). In order to confirm the enantiopurity of compounds **15** and **15a**, racemic compound **17** was synthesized for the control experiment (Scheme **2.10**). All the compounds were characterized by the spectroscopic studies.



Scheme 2.10

Spectroscopic data for compound **15** was in a close agreement with reported values.[39]

2.3.4 High Performance Liquid Chromatography (HPLC)

More accurate and sensitive HPLC analyses have been carried out to confirm the degree of optical purity of compounds **15** and **15a**. Analytical NP-HPLC was performed using a chiralpak IA column using n-hexane/isopropanol (90:10) as eluent. Chromatogram of racemic compound **17** was compared for the purity of products **15** and **15a** (Fig **2.7**).

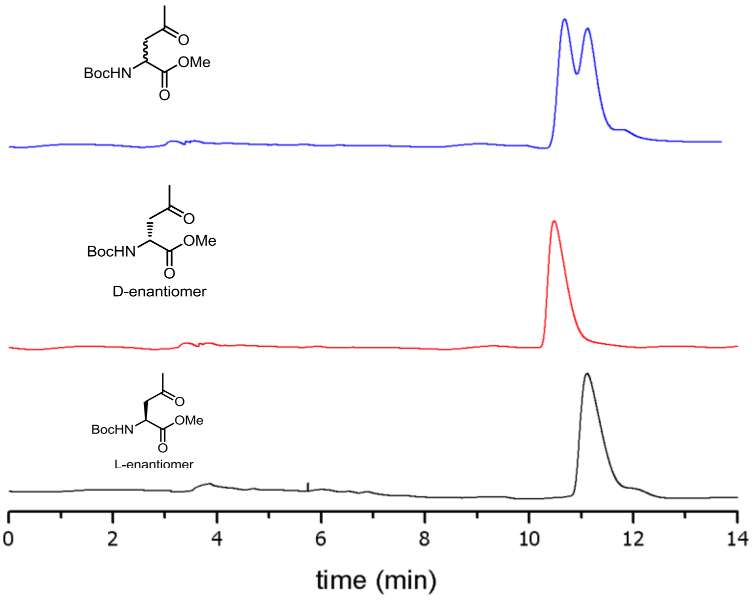


Fig 2.7: HPLC[*] chromatograms of compound **15**, **15a** and **17**

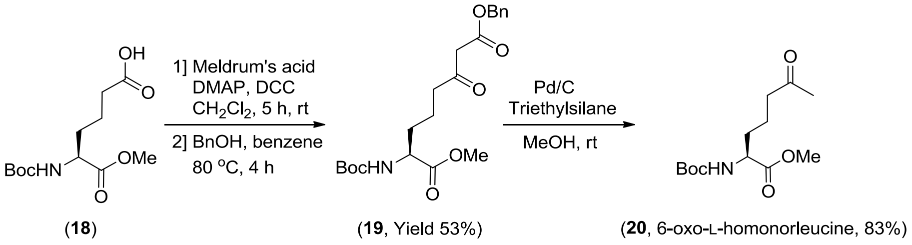
Chromatograms of compound **15** and **15a** clearly indicated that compounds were indeed optically pure and, importantly no trace of racemization could be detected.

---

[*] Conditions used for the HPLC: column—Chiralpack IA (normal phase NP; solvent system—hexane/isopropanol (90:10); wavelength—220 nm; program—isocratic.

Further, optical purity of the compounds **15** and **15a** was supported by the specific optical rotations *S*-enantiomer $[\alpha]_D^{22}$ +32.2 (*c* 1, $CHCl_3$); lit. $[\alpha]_D^{22}$ +32.7 (*c* 1, $CHCl_3$)[39] and *R*-enantiomer $[\alpha]_D^{22}$ −31.6 (*c* 1, $CHCl_3$). These evidences supported the optical integrity during the transformations.

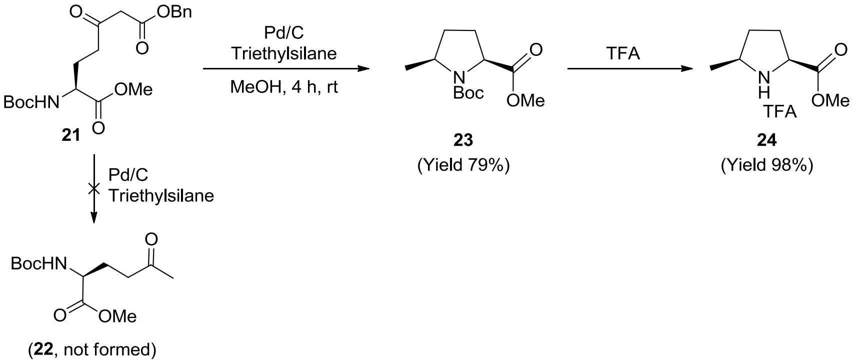
Similarly, *N*-Boc-6-oxo-L-homonorleucine methyl ester **20** was prepared starting from, *N*-Boc-L-homoglutamic acid 1-methyl ester **18** in one pot in 83% yield (Scheme **2.11**). Interesting to note that earlier synthesis of a protected L-homonorleucine (6-oxo-α-amino acid) was achieved from protected aspartic acid in four steps.[40]



Scheme 2.11

2.3.5 Synthesis of 5-*cis*-Methylproline

However, the L-glutamic acid derived β-ketoester **21** on treatment with Pd/C and triethylsilane did not afford the anticipated protected 5-oxo-L-norleucine **22**, instead we obtained 5-methyl-*N*-Boc-L-proline methyl ester **23** exclusively in 79% yield. Compound **23** on treatment with trifluoroacetic acid gave salt of methyl 5-methylproline ester **24** in 98% yield (Scheme **2.12**).



Scheme 2.12

Compound **24** was characterized by the usual spectroscopic methods such as FT-IR, NMR and HRMS. The optical and spectroscopic data of compound **23** was in a close agreement with reported data.[41] HMQC and DEPT spectral data of **24** revealed presence of number of methylene and methine carbon atoms and the presence of methyl group at position C-5.

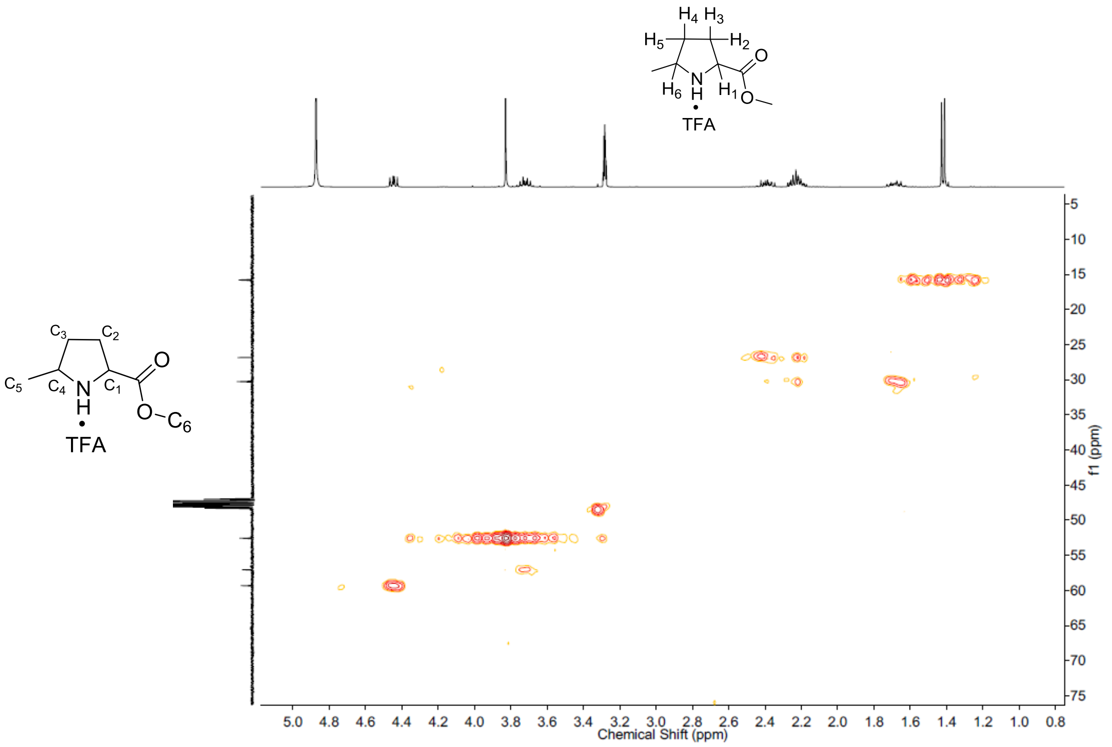


Fig 2.8: HMQC spectra of **24**

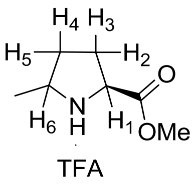
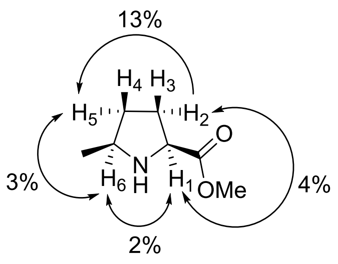


Fig 2.9: Structure obtained from ^{1}H, ^{13}C, DEPT and HMQC analysis of **24**

Further we carried out nOe studies of compound **24**, by irradiating each proton and observed the corresponding nOe enhancement. When, proton H_1 was irradiated, we observed nOe enhancement for protons H_2, H_3 and H_6. Stereochemical arrangements were confirmed from the nOe enhancement values given in the Fig **2.10**. The *cis* relation of H_1 and H_6 proved the *cis* relation of substituents at C-2 and C-5.

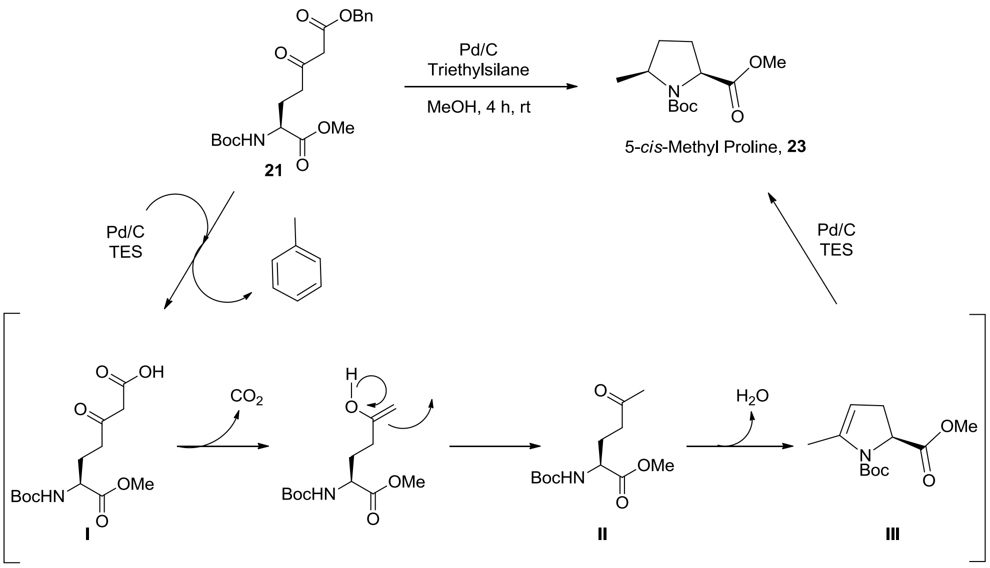


List of nOe observed
H_1-H_2-H_1 = 4%
H_1-H_6-H_1 = 2%
H_2-H_3 = 13%
H_2-H_5 = 13%
H_4-H_3 = 17%
H_4-H_5 = 17%
H_5-H_2 = 5%
H_5-H_4 = 10%
H_5-H_6-H_5 = 3%

Fig 2.10: nOe values for compound **24** (TFA was omitted for clarity)

It is important to note that, we synthesized *N*-Boc-5-*cis*-methylproline methyl ester **23** in one pot starting from *N*-Boc-L-glutamic acid β-ketoester **21** under relatively mild conditions unlike the harsh conditions and longer routes used earlier.[41] It is also interesting that, the Boc-protected amine reacted easily with a β-ketoester, which is generally expected to exist largely in the enolic form.

A plausible mechanism involves the β-keto decarboxylation of compound **21** under hydrogenolysis conditions (Pd/C, TES) affording keto intermediate **II**, which cyclizes to **23** *via* enamine intermediate **III** (Scheme **2.13**).



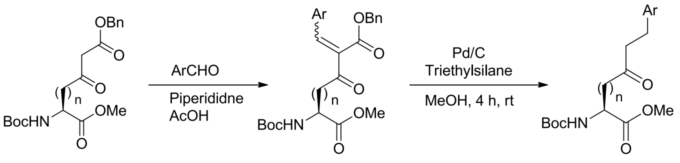
Scheme 2.13

Brimble[42] and Sutherland[43] have earlier reported the formation of a similar, but six-membered enamine intermediate in their syntheses of pipecolic acid derivatives by the intramolecular condensation of homoglutamic acid ε-semialdehyde with a protected amine. The synthetic strategy that we employed for the synthesis of **15** and **23** were short, and practical with mild reaction conditions, unlike the previous reports which relied on explosive hazards such as diazomethane, ozonolysis, and the used of expensive starting materials unlike.[6, 24, 25b, 30, 44]

2.3.6 Synthesis of side chain modified AAs

Encouraged by this initial success, we next employed this strategy to synthesize additional oxo-amino acids based on aspartic and glutamic acids (Table **2.1**). Earlier in chapter 1 we described the use of aminocarboxylate-derived β-ketoesters in the synthesis of piperidine derivatives.[45] We now planned to explore the reactivity of active methylene in aminodicarboxylate-derived β-ketoesters **14** and **21** for Knoevenagel condensation with different aldehydes to synthesize various oxo-amino acids.

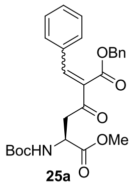
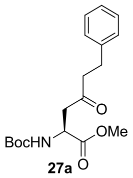
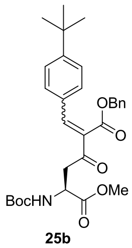
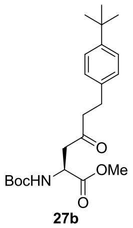
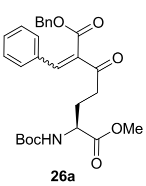
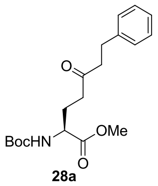
Table 2.1: Side chain modified AAs via Knoevenagel condensation



(n = 1, 2)

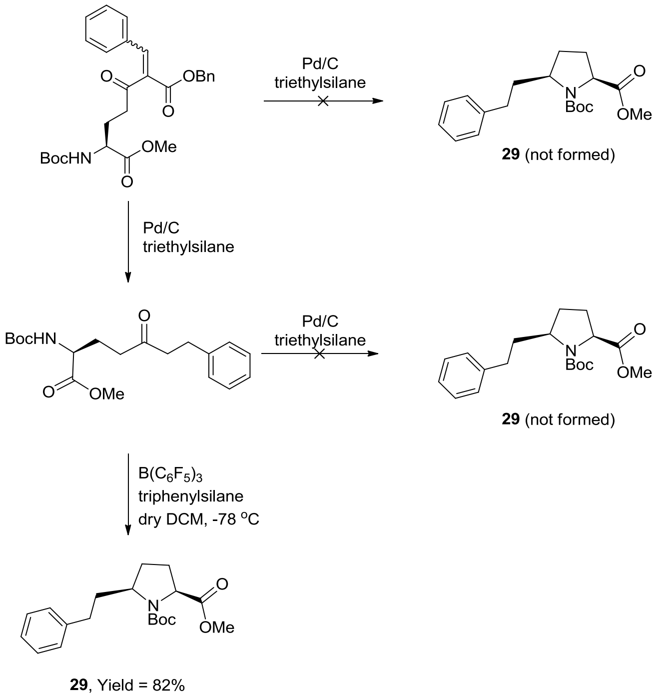
n = 1 (**25**)
2 (**26**)

n = 1 (**27**)
2 (**28**)

unsaturated β-ketoester	yield %	oxo-α–amino-acid	yield %
 **25a**	(74%)	 **27a**	(77%)
 **25b**	(73%)	 **27b**	(72%)
 **26a**	(77%)	 **28a**	(77%)

Aldehydes were condensed with β-ketoesters **14** and **21** to afford the corresponding unsaturated β-ketoesters **25a**, **25b** and **26a (**Table **2.1**). These compounds (**25a**, **25b**, **26a**) on treatment with Pd/C and triethylsilane gave the novel oxo α-amino acids **27a**, **27b** and **28a** respectively.

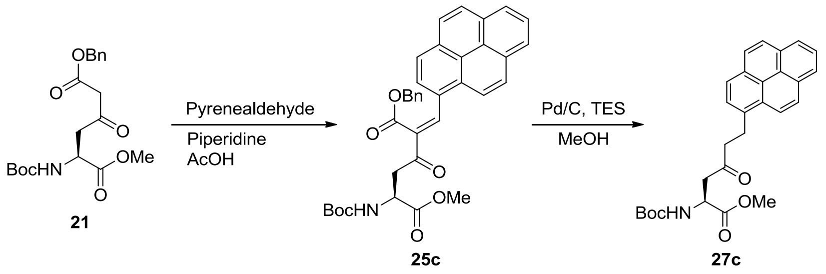
Interestingly, compound **28a** when subjected to hydrogenolysis conditions did not give the expected proline derivative. Nevertheless, compound **28a** on treatment with $B(C_6F_5)_3$ and triphenylsilane afforded the expected 2,5-*cis*-disubstituted proline derivative **29** in 82% yield (Scheme **2.14**).



Scheme 2.14

2.3.7 Synthesis of fluorescent amino acid

Fluorescent amino acids are widely applied for labelling of proteins. These fluorescent amino acids are valuable in combinatorial chemistry as well in chemical biology. Thus, attention has been directed for the design and development of non-natural α-amino acids that have a fluorophore in their side chain.[11, 46] In this regard, we embarked on the synthesis of fluorescent amino acid to illustrate the application of this method. To demonstrate the utility, pyrene aldehyde was condensed with β-ketoester **21** to afford the corresponding unsaturated β-ketoester **25c.** The **25c** under hydrogenolysis conditions led to the formation of pyrene-derived α-oxo amino acid **27c** in moderate yield 54% (Scheme **2.15**).



Scheme 2.15

The absorption and fluorescence properties of compound **27c** in dichloromethane resembled those of pyrene **(**Fig **2.11**). Using this protocol any fluorescent aldehyde may easily be condensed with aminodicarboxylate-derived β-ketoesters and series of different fluorescent non-natural amino acids can be synthesized according to need. This result is encouraging because compound **27c** and similar fluorescent amino acids can be inserted into peptides to be excited at long wavelength without excitation of tryptophan, tyrosine, or phenylalanine.

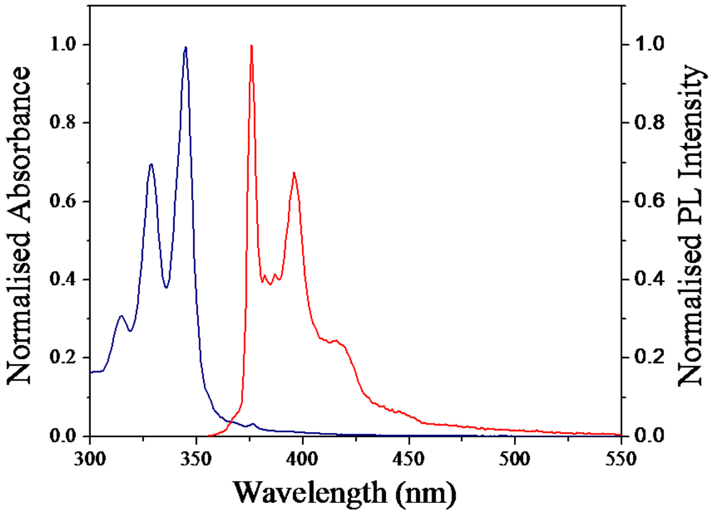


Fig 2.11: Normalized absorption (blue) and fluorescence (red) spectrum of **27c**

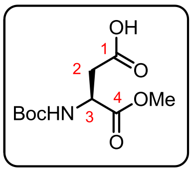
2.4 Conclusions

We have developed a general and efficient approach for the preparation of protected γ(*δ*)-keto(oxo)-α-amino acids. In addition, a concise synthesis of 5-*cis*-alkylproline derivatives is described. The protocol described in here can be employed for the synthesis of different oxo-α-amino acids, since the approach is general, useful, and simple. The application of the method is further exemplified by the synthesis of new fluorescent α-amino acid. The penultimate step affords protected unsaturated β-ketoester that has high potential for incorporation into peptides and proteins.

2.5 Experimental Section

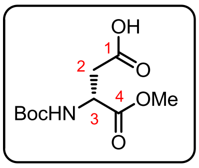
General: Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and MeOH-d_4. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, J values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and MeOH-d_4. ^{13}C-NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF and MALDI TOF/TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride or KBr discs and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Enantioselectivities were determined by HPLC analysis and enantiomeric excess was determined using Chiralpak IA column with *n*-hexane and 2-propanol as eluent.

(*S*)-3-(*tert*-butoxycarbonylamino)-4-methoxy-4-oxobutanoic acid (10)



White solid (12.2 g, 45% yield); mp = 88-90 °C; R_f = 0.2 DCM/ MeOH (90:10); IR (KBr) cm^{-1}: 3310, 1711, 1735; δ_H (400 MHz, $CDCl_3$) 9.12 (bs, 1H), 5.55 (d, J = 8 Hz, 1H), 4.59 (t, J = 4 Hz, 1H), 3.75 (s, 3H), 3.08-3.03 (m, 1H), 2.89-2.84 (m, 1H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 176.3, 171.6, 155.6, 80.6, 52.9, 49.8, 36.7, 28.4; $[\alpha]_D^{22}$ −19.2 (*c* 1, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{10}H_{17}NO_6Na$ $[M + Na]^+$ 270.0954, found 270.0957.

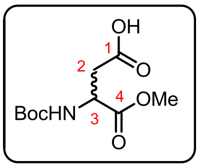
(*R*)-3-(*tert*-butoxycarbonylamino)-4-methoxy-4-oxobutanoic acid (11)



White solid (8.2 g, 43% yield); mp = 88–91 °C; R_f = 0.2 DCM/ MeOH (90:10); IR (neat) cm^{-1}: 3300, 1705, 1740; δ_H (400 MHz, $CDCl_3$) 9.1 (bs, 1H), 5.55 (d, J = 8 Hz, 1H), 4.60 (quintet, J = 4 Hz, 1H), 3.75 (s, 3H), 3.08-3.02 (m, 1H), 2.89-2.83 (m, 1H), 1.44

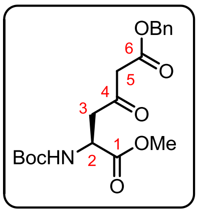
(s, 9H); δ_C (100 MHz, $CDCl_3$) 176.3, 171.6, 155.6, 80.6, 52.9, 49.8, 36.7, 28.4; $[\alpha]_D^{23}$ +18.3 (*c* 1, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{10}H_{17}NO_6Na$ $[M + Na]^+$ 270.0954, found 270.0955.

(*R*,*S*)-3-(*tert*-butoxycarbonylamino)-4-methoxy-4-oxobutanoic acid (12)



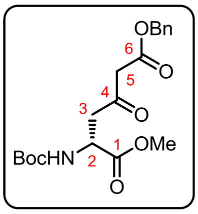
White solid (4.3 g, 44% yield); mp = 88 °C; R_f = 0.2 DCM/MeOH (90:10); IR (KBr) cm^{-1}: 3318, 1713, 1739, 685; δ_H (400 MHz, $CDCl_3$) 9.11 (bs, 1H), 5.55 (d, *J* = 8 Hz, 1H), 4.59 (t, *J* = 4 Hz, 1H), 3.75 (s, 3H), 3.08-3.03 (m, 1H), 2.89-2.83 (m, 1H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 176.3, 171.6, 155.6, 80.6, 52.9, 49.7, 36.7, 28.4; HRMS (ESI TOF) *m/z* calcd for $C_{10}H_{17}NO_6Na$ $[M + Na]^+$ 270.0954, found 270.0962.

(*S*)-6-Benzyl 1-methyl 2-((*tert*-butoxycarbonyl)amino)-4-oxohexanedioate (14)



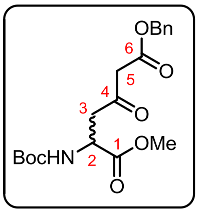
To a well stirred mixture of (*S*)-3-((*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoic acid 10 (2.5 g, 10 mmol), Meldrum's acid (1.5 g, 10 mmol), DMAP (1.6 g, 13 mmol) in anhydrous dichloromethane (40 mL) at 0 °C was added portion-wise dicyclohexyl carbodiimide (DCC) (2.7 g, 13 mmol) over 10 min at 0 °C. Then reaction mixture was allowed to warm to room temperature and stirred 5 h. The precipitate formed was removed by filtration through sintered glass funnel. Filtrate was washed with aq 1M $KHSO_4$ solution (2 x 70 mL) then brine (2 x 75 mL), dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The yellowish residue was dissolved in dry benzene (30 mL), benzyl alcohol (1.5 mL, 13 mmol) added, then refluxed 4 h and solvent was removed under reduced pressure to give crude product, purified by column chromatography over silica gel eluting with Pet. Ether/EtOAc (97:5 to 90:30) to give 14 as a light yellow oil (2.3 g, 63% yield); R_f = 0.4 Pet. Ether:EtOAc (50:50); IR (Neat) cm^{-1}: 1739, 1711, 1156; δ_H (400 MHz, $CDCl_3$) 7.38-7.34 (m, 5H), 5.45 (d, *J* = 8 Hz, 1H), 5.17 (s, 2H), 4.52 (quintet, *J* = 4 Hz, 1H), 3.71 (s, 3H), 3.51 (s, 2H), 3.29-3.23 (m, 1H), 3.11-3.05 (m, 1H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 200.8, 171.6, 166.5, 155.6, 135.2, 128.8, 128.7, 128.6, 80.3, 67.5, 52.9, 49.5, 49.2, 45, 28.4; $[\alpha]_D^{25}$ −12.3 (*c* 0.33, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{25}NO_7Na$ $[M + Na]^+$ 402.1529, found 402.1537.

(*R*)-6-Benzyl 1-methyl 2-((*tert*-butoxycarbonyl) amino)-4-oxohexanedioate (14a)



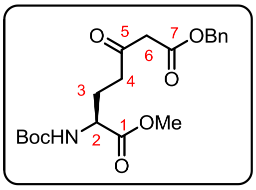
Compound 14a was prepared from (*R*)-3-((*tert*-butoxycarbonyl)-amino)-4-methoxy-4-oxobutanoic acid (D-aspartic acid derivative) 11, following the experimental procedure described for 14 above afforded light yellow oil (1.3 g, 53% yield). R_f = 0.4 Pet. Ether/EtOAc (50:50); IR (Neat) cm^{-1}: 1742, 1721, 1150, 962; δ_H (400 MHz, $CDCl_3$) 7.37-7.30 (m, 5H), 5.44 (d, *J* = 8 Hz, 1H), 5.15 (s, 2H), 4.52 (quintet, *J* = 4 Hz, 1H), 3.68 (s, 3H), 3.49 (s, 2H), 3.26-3.20 (m, 1H), 3.09-3.03 (m, 1H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 200.8, 171.6, 166.5, 155.5, 135.2, 128.7, 128.6, 128.5, 80.3, 67.4, 52.8, 49.4, 49.1, 44.9, 28.4; $[\alpha]_D^{25}$ +12.9 (*c* 0.33, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{25}NO_7Na$ $[M + Na]^+$ 402.1529, found 402.1525.

(*R*,*S*)-6-Benzyl 1-methyl 2-((*tert*-butoxycarbonyl) amino)-4-oxohexanedioate (16)



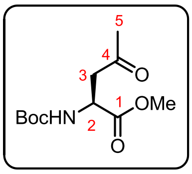
Compound 16 was prepared from racemic-(*RS*)-3-((*tert*-butoxy-carbonyl)amino)-4-methoxy-4-oxobutanoic acid (DL-aspartic acid derivative) 12 using a similar experimental procedure to that described for 14 afforded light yellow oil (1.45 g, 59% yield); R_f = 0.4 Pet. Ether/EtOAc (50:50); IR (Neat) cm^{-1}: 1738, 1712, 1149; δ_H (400 MHz, $CDCl_3$) 7.38-7.33 (m, 5H), 5.46 (d, *J* = 8 Hz, 1H), 5.16 (s, 2H), 4.54 (quintet, *J* = 4 Hz, 1H), 3.69 (s, 3H), 3.50 (s, 2H), 3.27-3.22 (m, 1H), 3.10-3.04 (m, 1H), 1.43 (s, 9H); δ_C (100 MHz, $CDCl_3$) 200.8, 171.6, 166.5, 155.6, 135.2, 128.8, 128.7, 128.5, 80.3, 67.4, 52.8, 49.4, 49.1, 45, 28.4; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{25}NO_7Na$ $[M + Na]^+$ 402.1529, found 402.1532.

(*S*)-7-Benzyl 1-methyl 2-((*tert*-butoxycarbonyl)amino)-5-oxoheptanedioate (19)



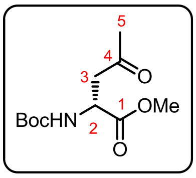
Experimental procedure similar as described for (14). Light yellow oil (1.7 g, 53% yield); R_f = 0.5 Pet. Ether/EtOAc (50:50); IR (Neat) cm^{-1}: 2960, 2874, 1723, 1456, 1285; δ_H (400 MHz, $CDCl_3$): 7.37-7.34 (m, 5H), 5.17 (s, 2H), 5.08 (d, *J* = 8 Hz, 1H), 4.26 (d, *J* = 4 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 2H), 2.72-2.56 (m, 2H), 2.18-2.13 (m, 1H), 1.92-1.83 (m, 1H), 1.43 (s, 9H); δ_C (100 MHz, $CDCl_3$) 201.5, 172.8, 166.9, 155.6, 135.4, 128.8, 128.6, 128.5, 80.2, 67.3, 52.7, 52.6, 49.4, 38.9, 28.4, 26.2; $[\alpha]_D^{25}$ −7.1 (*c* 1, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{20}H_{27}NO_7Na$ $[M + Na]^+$ 416.1685, found 416.1681.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-4-oxopentanoate (15)



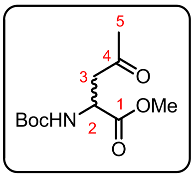
To the stirred mixture of 14 (1 g, 2.64 mmol) and 10% Pd/C (10% w/w, 0.100 g) in dry MeOH (35 mL) at room temperature was added triethylsilane (TES) (4.2 mL, 26 mmol). The progress of the reaction was monitored by TLC. After completion of reaction (4-5 h), the solution was filtered through a Celite bed, the filtrate evaporated under reduced pressure, and the residue purified over silica gel eluting with Pet. Ether/EtOAc (98:1 to 93:7) affording 15 as a colourless oil (0.575 g, 89% yield); R_f = 0.2 Pet. Ether/EtOAc (80:20); $[\alpha]_D^{22}$ +32.2 (*c* 1, $CHCl_3$); IR (Neat) cm^{-1}: 1708, 1499, 1157; δ_H (400 MHz, $CDCl_3$) 5.50 (d, *J* = 4 Hz, 1H), 4.51 (quintet, *J* = 4 Hz, 1H), 3.73 (s, 3H), 3.20-3.16 (m, 1H), 2.98-2.94 (m, 1H), 2.17 (s, 3H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 206.6, 171.8, 155.5, 79.9, 52.6, 49.4, 45.3, 29.8, 28.2; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{19}NO_5Na$ $[M + Na]^+$ 268.1161, found 268.1161.

(*R*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-4-oxopentanoate (15a)



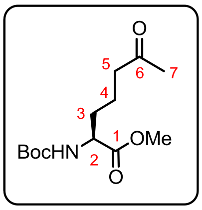
Compound 15a was prepared starting from **(***R***)**-6-benzyl 1-methyl 2-((*tert*-butoxycarbonyl) amino)-4-oxohexanedioate 14a, following similar experimental procedure described for **15** (0.153 g, 93% yield); $[\alpha]_D^{22}$ −31.6 (*c* 1, $CHCl_3$); R_f = 0.2 Pet. Ether/EtOAc (80:20); IR (Neat) cm^{-1}: 1712, 1485, 1151, 679; δ_H (400 MHz, $CDCl_3$) 5.48 (d, *J* = 4 Hz, 1H), 4.47 (t, *J* = 4 Hz, 1H), 3.70 (s, 3H), 3.18-3.14 (m, 1H), 2.96-2.90 (m, 1H), 2.14 (s, 3H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 206.7, 171.9, 155.62, 80.2, 52.7, 49.5, 45.5, 30, 28.4; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{19}NO_5Na$ $[M + Na]^+$ 268.1161, found 268.1169.

(*R*,*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-4-oxopentanoate (17)



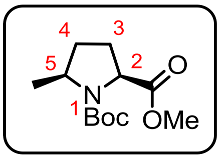
Compound 17 was prepared starting from racemic **(***RS***)**-6-benzyl 1-methyl 2-((*tert*-butoxycarbonyl) amino)-4-oxohexanedioate 16, following similar experimental procedure described for 15 above colorless oil (0.150 g, 90% yield); R_f = 0.2 Pet. Ether/EtOAc (80:20); IR (Neat) cm^{-1}: 1709, 1478, 1148, 684; δ_H (400 MHz, $CDCl_3$) 5.48 (d, *J* = 4 Hz, 1H), 4.47 (t, *J* = 4 Hz, 1H), 3.69 (s, 3H), 3.18-3.13 (m, 1H), 2.96-2.90 (m, 1H), 2.13 (s, 3H), 1.41 (s, 9H); δ_C (100 MHz, $CDCl_3$) 206.7, 171.9, 155.6, 80.1, 52.7, 49.5, 45.5, 30, 28.4; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{19}NO_5Na$ $[M + Na]^+$ 268.1161, found 268.1165.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-6-oxoheptanoate (20)



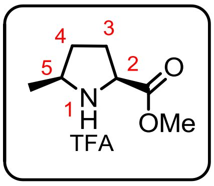
Experimental procedure similar as described for (15) resulted colorless oil (0.062 g, 83% yield); R_f = 0.3 Pet. Ether/EtOAc (65:35); IR (Neat) cm^{-1}: 2954, 2360, 1746, 1715, 1517, 1163; δ_H (400 MHz, $CDCl_3$) 5.11(d, *J* = 8 Hz, 1H), 4.30 (q, *J* = 8 and 4 Hz, 1H), 3.74 (s, 3H), 2.61-2.45 (m, 2H), 2.14(s, 3H), 1.81-1.78 (m, 1H), 1.68-1.60 (m, 3H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.4, 173.3, 155.5, 80.1, 53.2, 52.5, 42.9, 32.1, 30.1, 28.4, 19.4; $[\alpha]_D^{23}$ +8.2 (*c* 1, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{23}NO_5K$ $[M + K]^+$ 312.1213, found 312.1219.

(2*S*,5*S*)-1-*tert*-Butyl 2-methyl 5-methylpyrrolidine-1,2-dicarboxylate (23)



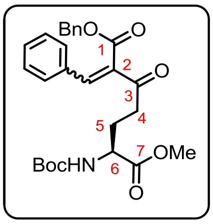
To a stirred mixture of 19 (0.650 g, 1.65 mmol) and Pd/C (10% w/w, 0.065 g) in dry MeOH (20 mL) at rt was added triethylsilane (TES) (2.64 mL, 16.52 mmol) and after 1 h an additional amount of TES (1.32 mL) was added. After completion of reaction (4 h) methanol was evaporated under vacuum and the residue purified over silica gel eluting with Pet. Ether/EtOAc (100:0 to 90:10) affording 23 as a colorless oil (0.280 g, 79% yield); R_f = 0.4 Pet. Ether:EtOAc (80:20); $[\alpha]_D^{25}$ −28.4 (*c* 1, MeOH); IR (neat) cm^{-1}: 1750, 1693, 1387, 1364, 1164; (rotamers) δ_H (400 MHz, $CDCl_3$) 4.35-4.33 (m, 1H), 4.22-4.19 (m, 1H), 4.01 (bs, 1H), 3.91 (bs, 1H), 3.73 (s, 6H), 2.19-2.16 (m, 2H), 2.05-2 (m, 4H), 1.63 (m, 2H), 1.47 (s, 9H), 1.41 (s, 9H), 1.27 (d, *J* = 6 Hz, 6H); (showed a mixture of carbamate isomers) δ_C (100 MHz, $CDCl_3$) 174.2, 173.9, 155.5, 154.4, 79.9, 60.3, 59.9, 54.2, 52.1, 32.6, 31.8, 28.9, 28.4, 20.7, 19.9; $[\alpha]_D^{25}$ −28.4 (*c* 1, MeOH); HRMS (MALDI TOF/TOF) *m/z* calcd for $C_{12}H_{21}NO_4Na$ $[M + Na]^+$ 266.1368, found 266.1369.

(2*S*,5*S*)-Methyl 5-methylpyrrolidine-2-carboxylate (24)



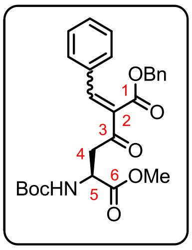
To a stirred solution of 23 (0.2 g, 0.82 mmol) in dry DCM (3 mL) at 0 °C was added acetic acid (TFA) (1.3 mL, 16 mmol) and gradually the reaction mixture was warmed to rt. After completion of reaction (1.5 h) DCM was evaporated under vacuum and the residue precipitated with diethyl ether to give 24 as a white solid (0.115 g, 98% yield); mp = 114-116 °C; IR (KBr) cm^{-1}: 1742, 1676, 1438, 1205, 1143; δ_H (400 MHz, MeOH-d$_4$): 4.47 (t, J = 8 Hz, 1H), 3.85 (s, 3H), 3.77-3.72 (m, 1H), 2.45-2.37 (m, 2H), 1.75-1.68 (m, 1H), 1.45 (d, J = 4 Hz, 3H); δ_C (100 MHz, MeOH-d$_4$) 170.5, 60.7, 58.4, 53.9, 31.6, 28.2, 17.5; $[\alpha]_D^{25}$ −4.3 (*c* 0.3, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_7H_{14}NO_2$ $[M + H]^+$ 144.1025, found 144.1027.

(*S*)-(*E*,*Z*)-1-Benzyl 7-methyl 2-benzylidene-6-((*tert*-butoxycarbonyl)amino)-3-oxoheptanedioate (26a)



To a stirred mixture of 21 (0.5 g, 1.27 mmol) and benzaldehyde (0.1 mL, 1.27 mmol) in benzene (65 mL), was added piperidine (0.013 mL, 0.127 mmol) and acetic acid (0.015 mL, 0.24 mmol). The reaction mixture was refluxed using Dean-Stark apparatus to remove the water. After completion of reaction (2.5-3 h) benzene was evaporated under vacuum and the residue purified by flash chromatography over silica gel eluting with Pet. Ether/EtOAc (98:2 to 70:30) giving 26a as a light yellow oil (0.480 g, 77% yield). (*E:Z* = 0.96:1); R_f = 0.6 Pet. Ether: EtOAc (50:50); IR (Neat) cm^{-1}: 1700, 1497, 1158; (mixture of *E* and *Z* isomers) δ_H (400 MHz, CDCl$_3$) 7.74 (s, 1H), 7.60 (s, 1H), 7.39-7.25 (m, 20H), 5.30-5.29 (m, 4H), 5.1 (bs, 1H), 4.94 (bs, 1H), 4.34 (bs, 1H), 4.21 (bs, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.84-2.82 (m, 2H), 2.66-2.62 (m, 2H), 2.05-1.96 (m, 2H), 1.94-1.91 (m, 2H), 1.44 (s, 9H), 1.40 (s, 9H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, CDCl$_3$) 204.3, 95.8, 172.8, 167.6, 164.3, 155.5, 141.8, 141.5, 135.5, 133.3, 132.9, 130.8, 129.8, 129.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 80.2, 79.9, 67.8, 67.4, 53.6, 52.6, 52.5, 39.7, 34.9, 28.4, 26.9, 26.6; $[\alpha]_D^{25}$ −4.2 (*c* 1, MeOH); HRMS (MALDI TOF/TOF) *m/z* calcd for $C_{27}H_{31}NO_7Na$ $[M + Na]^+$ 504.1998, found 504.2009.

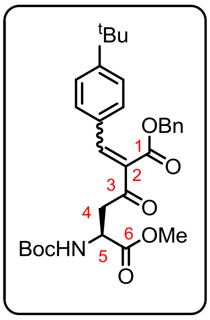
(*S*)-(*E*,*Z*)-1-Benzyl 6-methyl 2-benzylidene-5-((*tert*-butoxycarbonyl)amino)-3-oxohexanedioate (25a)



Experimental procedure similar as described for (26a), 25a was obtained as a pale yellow oil (0.210 g, 74% yield); (*E:Z* = 0.71:1); IR (neat) cm^{-1}:1714, 1477, 1165; (mixture of *E* and *Z* isomers) δ_H 400 MHz, CDCl$_3$) 7.77 (s, 1H, *E*), 7.61 (s, 1H, *Z*), 7.41-7.23 (m, 20H), 5.55-5.48 (m, 2H), 5.29-5.26 (m, 4H), 4.62 (quintet, J = 4

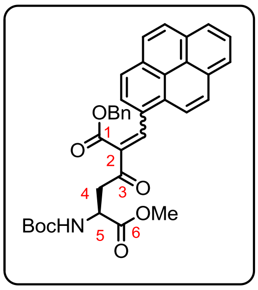
Hz, 1H), 4.51 (quintet, *J* = 4 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.51 (m, 1H), 3.35-3.25 (m, 2H), 3.16 (m, 1H), 1.45 (d, *J* = 8 Hz, 18H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, $CDCl_3$) 202.9, 194.6, 171.8, 171.7, 167.1, 164.1, 155.6, 142.7, 135.4, 134.6, 133.3, 132.6, 132.1, 131.1, 130.9, 130.1, 129.8, 129.2, 129, 128.9, 128.8, 128.7, 128.6, 128.4, 80.2, 80.1, 67.9, 67.4, 52.8, 52.6, 49.5, 49.1, 45.6, 41.2, 28.5, 28.4; $[\alpha]_D^{25}$ −3.8 (*c* 0.8, MeOH); HRMS (MALDI TOF/TOF) *m/z* calcd for $C_{26}H_{29}NO_7Na$ $[M + Na]^+$ 490.1841, found 490.1844.

(*S*)-(*E*,*Z*)-1-Benzyl-6-methyl5-((*tert*-butoxycarbonyl)amino)-2-(4-(*tert*-butyl)benzylidene)-3-oxohexanedioate (25b)



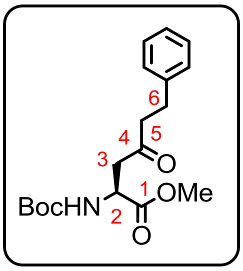
The experimental procedure is similar as described for 26a. Product 25b was obtained as light yellow oil (0.335 g, 73% yield). (*E:Z* = 0.64:1); IR (Neat) cm^{-1}: 2977, 1718, 1498, 1167; (mixture of *E* and *Z* isomers) δ_H (400 MHz, $CDCl_3$) 7.71 (s, 1H, *E*), 7.58 (s, 1H, *Z*), 7.38-7.31 (m, 14H), 7.26-7.25 (m, 4H), 5.55-5.50 (m, 2H), 5.30-5.26 (m, 4H), 4.62-4.56 (m, 2H), 3.73 (s, 3H), 3.66 (s, 3H), 3.50-3.19 (m, 4H), 1.43 (d, *J* = 4 Hz, 18H), 1.30 (d, *J* = 8 Hz, 18H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, $CDCl_3$) 203, 194.6, 171.9, 167.4, 155, 148.3, 142.7, 135.6, 134.8, 130.9, 130.3, 129.9, 129.7, 129.3, 128.8, 128.74, 128.7, 128.6, 128.55, 128.4, 126.1, 126, 125.7, 80.2, 67.8, 67.4, 52.8, 52.6, 45.6, 41.1, 35.1, 31.5, 31.22, 31.19, 28.53, 28.47; $[\alpha]_D^{25}$ −4.4 (*c* 0.9, MeOH); HRMS (MALDI TOF/TOF) *m/z* calcd for $C_{30}H_{37}NO_7Na$ $[M + Na]^+$ 546.2468, found 546.2479.

(*S*)-(*E*, *Z*)-1-Benzyl 6-methyl-5-((*tert*-butoxycarbonyl)amino)-3-oxo-2-(pyren-1-ylmethylene)hexanedioate (25c)



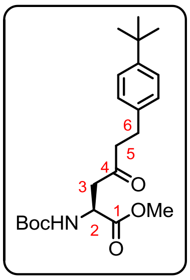
The experimental procedure was similar to that described for 26a and gave product 25c as light yellow oil (0.180 g, 69% yield) (*E:Z* = 1:0.86); IR (Neat) cm^{-1}: 1715, 2927, 1593, 1498, 1366, 1209, 1165, 848; (mixture of *E* and *Z* isomers) δ_H (400 MHz, $CDCl_3$): 8.83 (s, 1H, *E*), 8.73 (s, 1H, *Z*), 8.28-7.99 (m, 16H), 7.87-7.82 (m, 3H), 7.47-7.37 (m, 5H), 7.14 (m, 1H), 7.03-6.90 (m, 3H), 5.64 (d, *J* = 8 Hz, 1H), 5.41-5.34 (m, 3H), 5.13 (s, 2H), 4.71 (quintet, *J* = 4 Hz, 1H), 4.39 (quintet, *J* = 4 Hz, 1H), 3.80 (s, 3H), 3.69-3.63 (m, 1H), 3.48-3.41 (m, 4H), 3.20-3.14 (m, 1H), 3.01-2.95 (m, 1H), 1.48 (s, 9H), 1.37 (s, 9H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, $CDCl_3$) 202.5, 194.4, 171.9, 171.6, 164.2, 155.7, 155.5, 142.2, 141.6, 135.5, 135.1, 134.5, 134.2, 133.1, 131.3, 130.8, 130, 129.9, 129.13, 129.1, 129.05, 128.9, 128.7, 128.6, 128.4, 128.35, 127.4, 127.3, 127, 126.6, 126.56, 126.5, 126.43, 126.4, 126.36, 125.9, 124.8, 124.7, 124.5, 123.1, 123, 80.3, 80, 67.6, 67.5, 52.9, 52.5, 45.9, 41.9, 28.5, 28.4; $[\alpha]_D^{25}$ −5.9 (*c* 1, MeOH); HRMS (MALDI TOF/TOF) *m/z* calcd for $C_{36}H_{33}NO_7Na$ $[M + Na]^+$ 614.2155, found 614.2157.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-4-oxo-6-phenylhexanoate (27a)



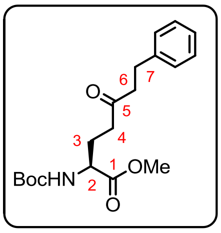
Experimental procedure as for (15), product 27a obtained as a white solid (0.116 g, 77% yield); mp = 62-63 °C; IR (KBr) cm^{-1}: 2962, 1715, 1492, 1391, 1161; δ_H (400 MHz, $CDCl_3$) 7.29-7.26 (m, 2H), 7.21-7.15 (M, 3H), 5.49 (d, *J* = 8 Hz, 1H), 4.49 (quintet, *J* = 4 Hz, 1H), 3.71 (s, 1H), 3.12 (m, 1H), 2.94-2.86 (m, 3H), 2.77-2.72 (m, 2H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.1, 171.9, 155.6, 140.6, 128.6, 128.4, 126.3, 80.2, 52.8, 49.5, 44.8, 44.3, 29.6, 28.4; $[\alpha]_D^{25}$ −12.8 (*c* 1, MeOH); HRMS (MALDI TOF/TOF) *m/z* calcd for $C_{18}H_{25}NO_5Na$ $[M + Na]^+$ 358.1630, found 358.1614.

(*S*)-Methyl-2-((*tert*-butoxycarbonyl)amino)-6-(4-(*tert*-butyl)phenyl)-4-xohexanoate (27b)



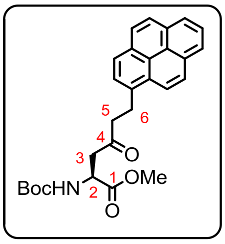
Experimental procedure as for (15), product 27b obtained as a colorless oil (0.192 g, 72% yield); R_f = 0.5 Pet. Ether/EtOAc (50:50); IR (Neat) cm^{-1}: 2963, 1716, 1499, 1392, 1165; δ_H (400 MHz, $CDCl_3$) 7.31 (d, *J* = 8 Hz, 2H), 7.1 (d, *J* = 12 Hz, 2H), 5.51 (d, *J* = 12 Hz, 1H), 4.50 (quintet, *J* = 4 Hz, 1H), 3.71 (s, 3H), 3.18-3.12 (m, 1H), 2.96-2.71 (m, 5H), 1.44 (s, 9H), 1.30 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.8, 172.6, 155.1, 149.8, 138.2, 128.6, 126.2, 80.8, 53.4, 50.2, 45.3, 44.9, 35.1, 32.1, 29.6, 29.1; $[\alpha]_D^{25}$ −8.6 (*c* 1, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{22}H_{33}NO_5Na$ $[M + Na]^+$ 414.2256, found 414.2251.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-5-oxo-7-phenylheptanoate (28a)



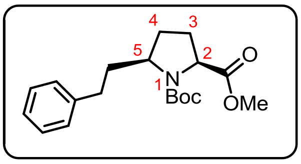
Experimental procedure as described for (15), product 28a obtained as a colorless oil (0.268 g, 77% yield); R_f = 0.5 Pet. Ether/EtOAc (50:50); IR (Neat) cm^{-1}: 1742, 1705, 1158; δ_H (400 MHz, $CDCl_3$) 7.30-7.26 (m, 2H), 7.21-7.16 (m, 3H), 5.10 (d, J = 8 Hz, 1H), 4.29 (q, J = 8 and 4 Hz, 1H), 3.73 (s, 3H), 3.90 (t, J = 8 Hz, 2H), 2.73 (t, J = 8 Hz, 2H), 2.55-2.42 (m, 2H), 2.15-2.10 (m, 1H), 1.19-1.84 (m, 1H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.8, 172.9, 155.6, 141, 128.6, 128.4, 126.3, 80.1, 52.9, 52.5, 44.5, 38.8, 29.8, 28.4, 26.6; $[\alpha]_D^{25}$ −12.6 (*c* 1, MeOH); HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{27}NO_5Na$ $[M + Na]^+$ 372.1787, found 372.1787.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-4-oxo-6-(pyren-1-yl)hexanoate (27c)



Experimental procedure as described for (15), product 27c obtained as a pale yellow oil (0.075 g, 54% yield); R_f = 0.2 Pet. Ether/ EtOAc (80:20); IR (Neat) cm^{-1}: 1732, 1708; δ_H (500 MHz, $CDCl_3$) 8.22-8.10 (m, 5H), 8.03-8.00 (m, 3H), 7.86 (d, J = 8 Hz, 1H), 5.53 (d, J = 8 Hz, 1H), 4.52 (t, J = 4 Hz, 1H), 3.72 (s, 3H), 3.62 (t, J = 8 Hz, 2H), 3.19-3.13 (m, 1H), 3.00-2.93 (m, 3H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.1, 172.1, 155.7, 134.7, 131.5, 130.3, 128.6, 127.8, 127.6, 127.2, 127, 126.1, 125, 125.1, 122.9, 80.3, 52.8, 49.6, 44.9, 44.4, 28.4, 27.2; $[\alpha]_D^{25}$ −4.1 (*c* 1, MeOH); HRMS (MALDI TOF/TOF) *m/z* calcd for $C_{28}H_{29}NO_5Na$ $[M + Na]^+$ 482.1943, found 482.1937.

(2*S*,5*S*)-1-*tert*-Butyl 2-methyl 5-phenethylpyrrolidine-1, 2-dicarboxylate (29)



To a stirred mixture of 28a (0.558 g, 1.46 mmol) and $B(C_6F_5)_3$ (0.075 g) in dry DCM (10 mL) was added triphenylsilane (1.14 g) in dry DCM (3 mL) at -78 ^{o}C and the reaction mixture allowed to warm to rt. After completion of reaction (2 h) DCM was evaporated and the residue purified by flash chromatography over silica gel eluting with Pet. Ether/EtOAc (100:0 to 90:10) to give 29 as a colorless oil (0.339 g, 82% yield). R_f = 0.5 Pet. Ether/EtOAc (80:20); IR (Neat) cm^{-1}: 2973, 1751, 1697, 1392, 1169; (showed a mixture of carbamate isomers) δ_H (400 MHz, $CDCl_3$) 7.26-7.15 (m, 10H), 4.36 (t, J = 8

Hz, 1H), 4.22 (t, *J* = 8 Hz, 1H), 3.98 (bs, 1H), 3.83 (bs, 1H), 3.71 (s, 6H), 2.67-2.65 (m, 4H), 2.20-2.16 (m, 4H), 2.0-1.92 (m, 4H), 1.76-1.72 (m, 4H), 1.43 (s, 9H), 1.40 (s, 9H); (rotational isomers) δ_C (100 MHz, $CDCl_3$) 174.1, 153.8, 142.4, 142.1, 128.5, 128.4, 125.9, 125.8, 80.11, 80.02, 60.2, 59.8, 58.5, 58.2, 52.3, 52.11, 36.6, 36.2, 33.2, 33.1, 30.3, 29.6, 29.1, 28.6, 28.4, 28.3; $[\alpha]_D^{25}$ −4.4 (*c* 0.29, MeOH); HRMS (ESI) *m/z* calcd for $C_{19}H_{27}NO_4Na$ $[M + Na]^+$ 356.1838, found 356.1831.

2.6 Appendix II: ^{1}H and ^{13}C spectral data of representative compounds

compound No.	Fig AII.X	data	page No.
14	Fig AII.1-AII.2	1H-13C	34
15	Fig AII.3-AII.4	1H-13C	35
24	Fig AII.5-AII.6	1H-13C	36

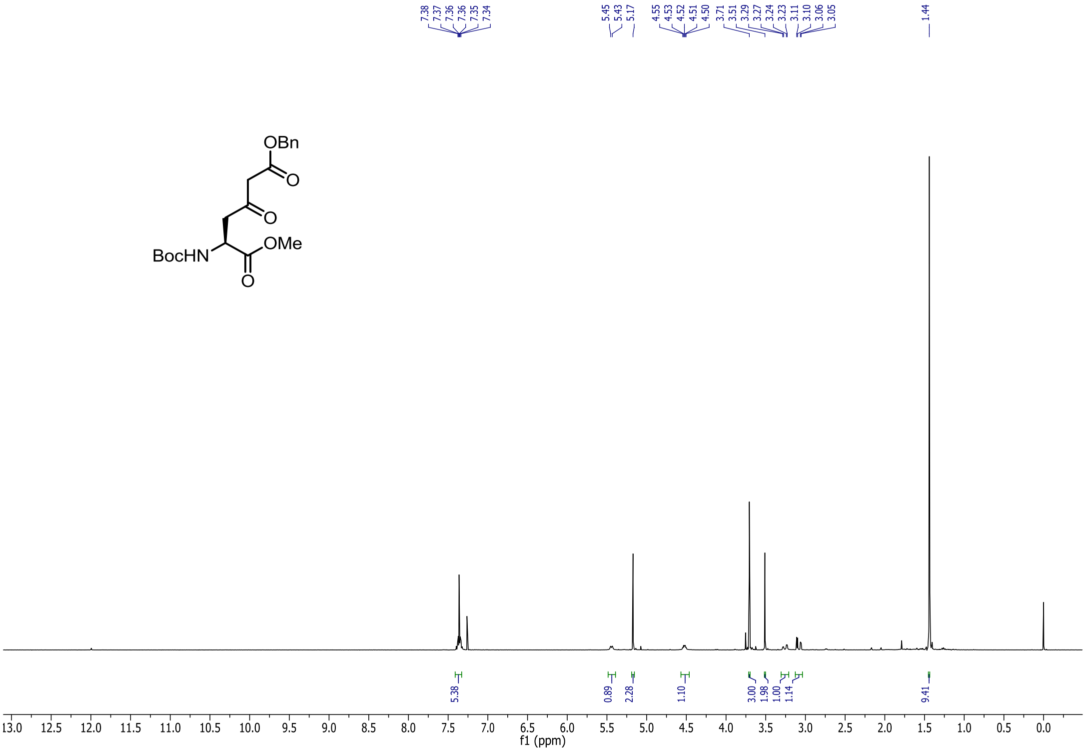


Fig AII.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **14**

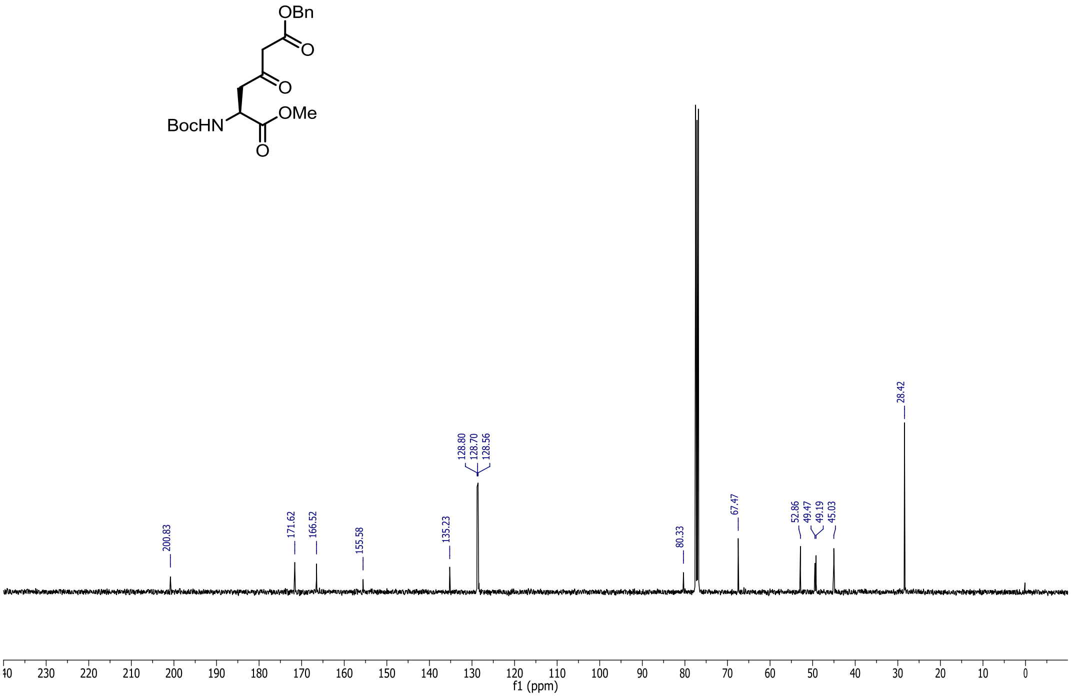


Fig AII.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **14**

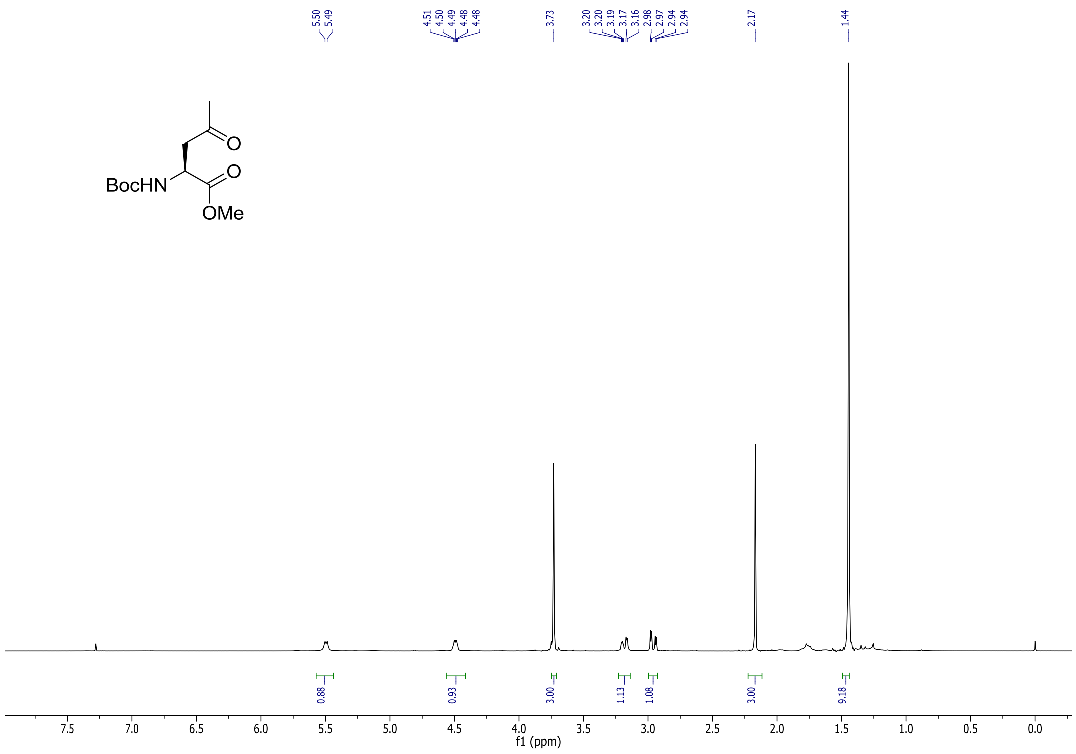


Fig AII.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **15**

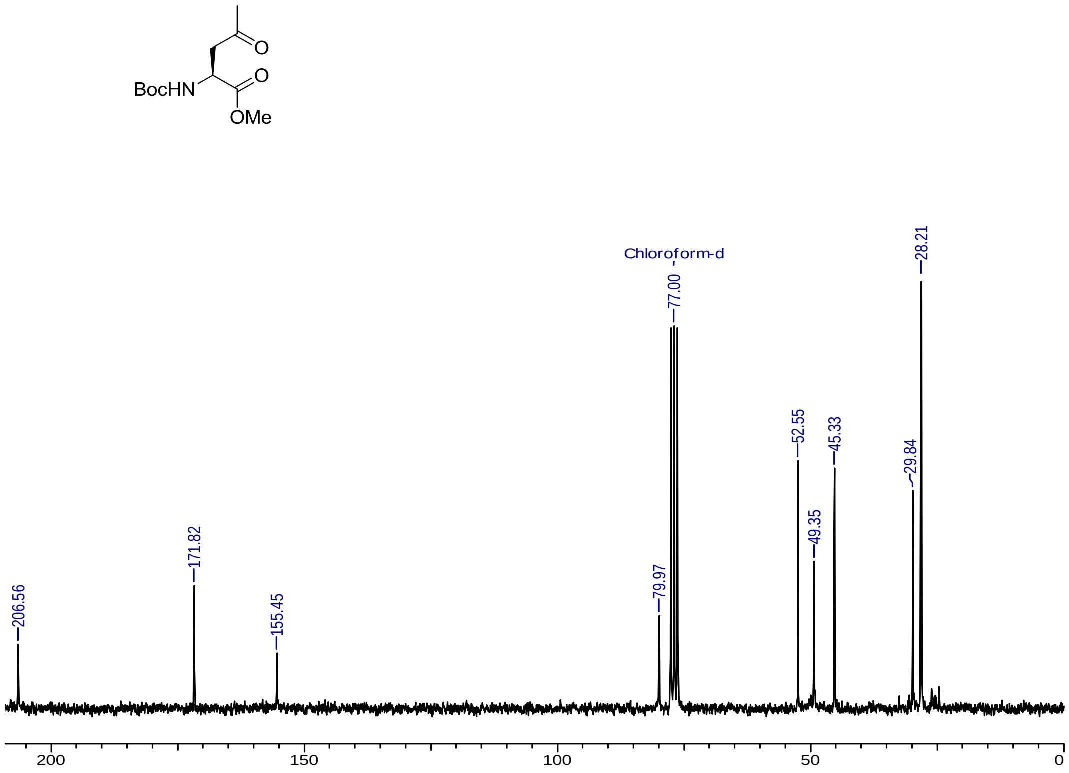


Fig AII.4: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **15**

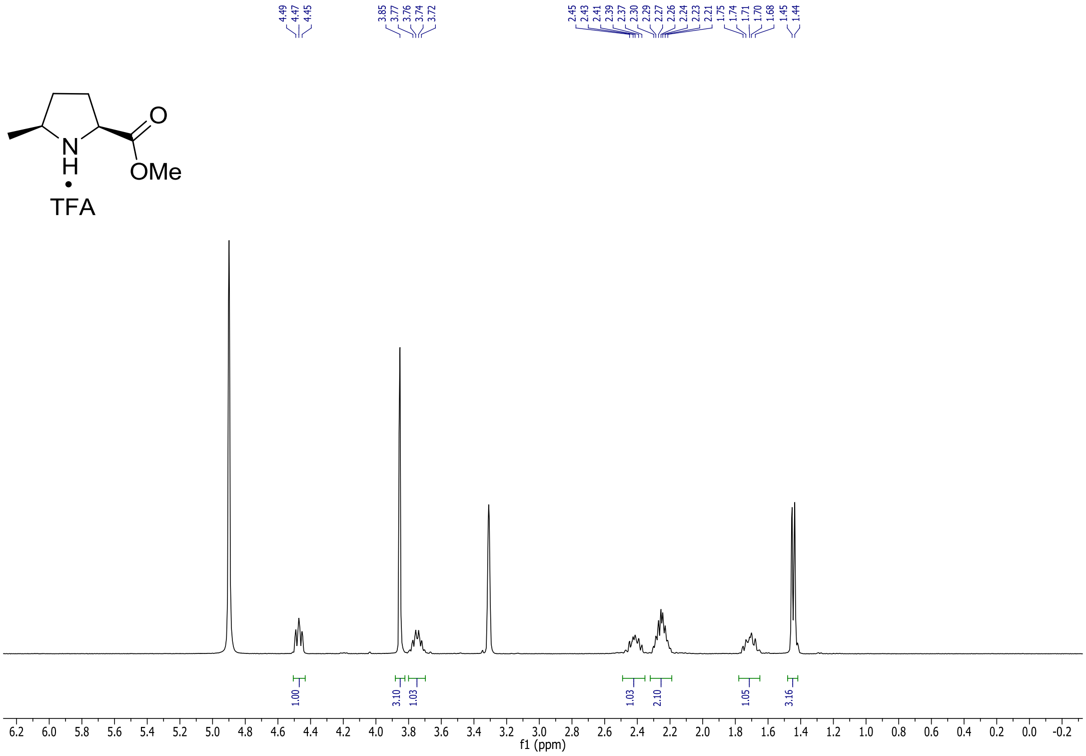


Fig AII.5: ^{1}H NMR (400 MHz, MeOH-d$_4$) spectrum of compound **24**

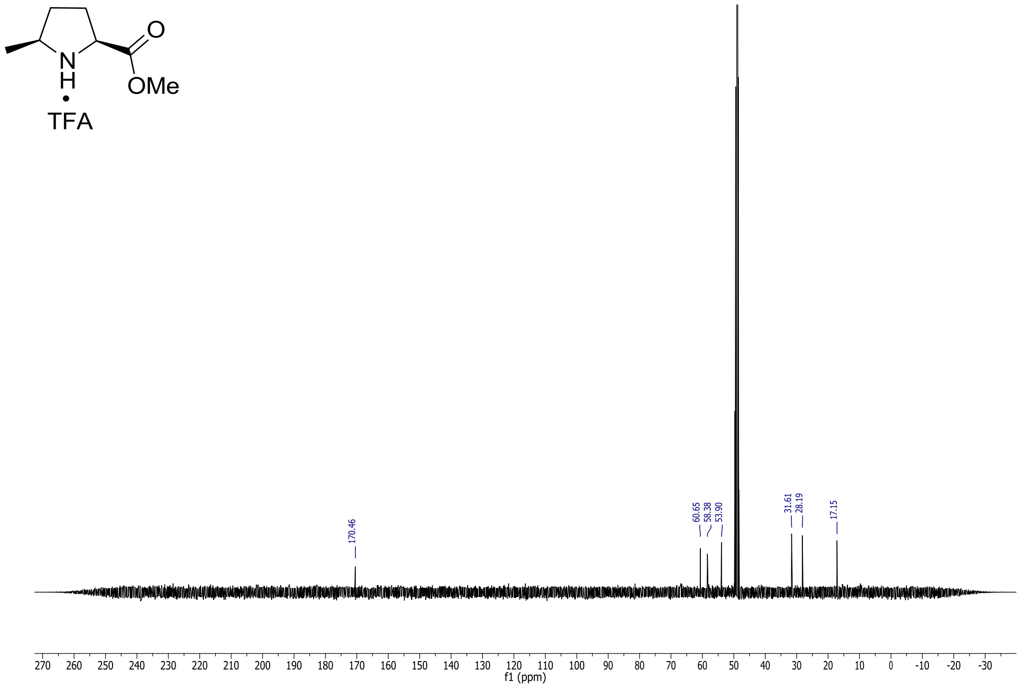


Fig AII.6: ^{13}C NMR (100 MHz, MeOH-d$_4$) spectrum of compound **24**

2.7 References

[1] F. A. Davis, B.-C. Chen, *Chem. Soc. Rev.* **1998**, *27*, 13–18.

[2] D. J. Seebach, A. Schmidt, J. Maetzke, *Chimia* **1989**, *43*, 314–317.

[3] a) A. G. Beck-Sickinger, *Methods Mol. Biol.* **1997**, *73*, 61-63; b) M. Goodman, H. Shao, *Pure Appl. Chem.* **1996**, *68*, 1303–1308; c) G. Lubec, G. A. Rosenthal, *Amino Acids: Chemistry, Biology, and Medicine*, ESCOM Science Publishers, **1990**.

[4] IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN) and Nomenclature Committee of IUBMB (NC-IUBMB), *Eur. J. Biochem.* **1999**, *264*, 607-609.

[5] G. Srinivasan, C. M. James, J. A. Krzycki, *Science* **2002**, *296*, 1459–1462.

[6] V. W. Cornish, K. M. Hahn, P. G. Schultz, *J. Am. Chem. Soc.* **1996**, *118*, 8150-8151.

[7] T. Xu, R. M. Werner, K. C. Lee, J. C. Fettinger, J. T. Davis, J. K. Coward, *J. Org. Chem.* **1998**, *63*, 4767–4778.

[8] E. B. Arevalo-Garcia, J. C. Q. Colmenares, *Tetrahedron Lett.* **2008**, *49*, 3995-3996.

[9] J. H. Lee, B. S. Jeong, J. M. Ku, S. S. Jew, H. G. Park, *J. Org. Chem.* **2006**, *71*, 6690-6692.

[10] M. Suchanek, A. Radzikowska, C. Thiele, *Nat. Methods* **2005**, *2*, 261–267.

[11] B. E. Cohen, T. B. McAnaney, E. S. Park, Y. N. Jan, S. G. Boxer, L. Y. Jan, *Science* **2002**, *296*, 1700–1703.

[12] E. Cini, L. R. Lampariello, M. Rodriduez, M. Taddei, *Tetrahedron* **2009**, *65*, 844–848.

[13] S. K. Panday, *Tetrahedron Asymmetry* **2011**, *22*, 1817–1847.

[14] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

[15] a) P. W. R. Harris, M. A. Brimble, P. D. Gluckman, *Org. Lett.* **2003**, *5*, 1847–1850; b) B. C. J. van Esseveldt, P. W. H. Vervoort, F. L. van Delft, F. P. J. T. Rutjes, *J. Org. Chem.* **2005**, *70*, 1791–1795.

[16] a) T. A. Godina, W. D. Lubell, *J. Org. Chem.* **2011**, *76*, 5846–5849; b) S. Surprenant, W. D. Lubell, *Org. Lett.* **2006**, *8*, 2851–2854.

[17] Z. H. Pei, X. F. Li, K. Longenecker, T. W. von Geldern, P. E. Wiedeman, T. H. Lubben, B. A. Zinker, K. Stewart, S. J. Ballaron, M. A. Stashko, A. K. Mika, D. W. A. Beno, M. Long, H. Wells, A. J. Kempf-Grote, D. J. Madar, T. S. McDermott, L. Bhagavatula, M. G. Fickes, D. Pireh, L. R. Solomon, M. R. Lake, R. Edalji, E. H. Fry, H. L. Sham, J. M. Trevillyan, *J. Med. Chem.* **2006**, *49*, 3520–3535.

[18] B. Lygo, C. Beynon, M. C. McLeod, C. E. Roy, C. E. Wade, *Tetrahedron* **2010**, *66*, 8832–8836.

[19] A. J. Mota, A. Chiaroni, N. Langlois, *Eur. J. Org. Chem.* **2003**, 4187–4198.

[20] S. C. Turner, H. B. Zhai, H. Rapoport, *J. Org. Chem.* **2000**, *65*, 861–870.

[21] a) I. Rodriguez, M. I. Calaza, C. Cativiela, *Eur. J. Org. Chem.* **2013**, 1093–1099; b) Y. Che, G. R. Marshall, *Biopolymers* **2006**, *81*, 392–406.

[22] a) E. Beausoleil, B. LArcheveque, L. Belec, M. Atfani, W. D. Lubell, *J. Org. Chem.* **1996**, *61*, 9447–9454; b) L. Halab, W. D. Lubell, *J. Am. Chem. Soc.* **2002**, *124*, 2474–2484.

[23] U. Arnold, M. P. Hinderaker, J. Koditz, R. Golbik, R. Ulbrich-Hofmann, R. T. Raines, *J. Am. Chem. Soc.* **2003**, *125*, 7500-7501.

[24] H. H. Ibrahim, W. D. Lubell, *J. Org. Chem.* **1993**, *58*, 6438–6441.

[25] a) R. F. W. Jackson, K. James, M. J. Wythes, A. Wood, *J. Chem. Soc., Chem. Comm.* **1989**, 644-645; b) R. F. W. Jackson, N. Wishart, A. Wood, K. James, M. J. Wythes, *J. Org. Chem.* **1992**, *57*, 3397–3404; c) R. F. W. Jackson, J. L. Fraser, N. Wishart, B. Porter, M. J. Wythes, *J. Chem. Soc. Perk.Trans.1* **1998**, 1903–1912.

[26] A. F. Zahoor, U. Kazmaier, *Synthesis* **2011**, 3020–3026.

[27] S. B. Tsogoeva, S. Wei, M. Freund, M. Mauksch, *Angew. Chem., Int. Ed.* **2009**, *48*, 590–594.

[28] M. J. Crossley, Y. M. Fung, E. Kyriakopoulos, J. J. Potter, *J. Chem. Soc. Perk.Trans.1* **1998**, 1123–1130.

[29] M. Hosseini, N. Stiasni, V. Barbieri, C. O. Kappe, *J. Org. Chem.* **2007**, *72*, 1417–1424.

[30] R. M. Werner, O. Shokek, J. T. Davis, *J. Org. Chem.* **1997**, *62*, 8243–8246.

[31] H. J. C. Deboves, C. A. G. N. Montalbetti, R. F. W. Jackson, *J. Chem. Soc. Perk.Trans.1* **2001**, 1876–1884.

[32] T. Jousseaume, N. E. Wurz, F. Glorius, *Angew. Chem., Int. Ed.* **2011**, *50*, 1410–1414.

[33] A. S. Golubev, N. Sewald, K. Burger, *Tetrahedron* **1996**, *52*, 14757–14776.

[34] S. Sato, M. Tetsuhashi, K. Sekine, H. Miyachi, M. Naito, Y. Hashimoto, H. Aoyama, *Bioorg. Med. Chem.* **2008**, *16*, 4685–4698.

[35] A. J. Potter, S. Ray, L. Gueritz, C. L. Nunns, C. J. Bryant, S. F. Scrace, N. Matassova, L. Baker, P. Dokurno, D. A. Robinson, A. E. Surgenor, B. Davis, J. B. Murray, C. M. Richardson, J. D. Moore, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 586–590.

[36] F. Venturi, C. Venturi, F. Liguori, M. Cacciarini, M. Montalbano, C. Nativi, *J. Org. Chem.* **2004**, *69*, 6153-6155.

[37] R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, *Chem. Rev.* **1985**, *85*, 129–170.

[38] M. F. Semmelhack, R. N. Misra, *J. Org. Chem.* **1982**, *47*, 2469–2471.

[39] M. A. D. Estiarte, A.; Rubiralta, M.; Jackson, R. F. W., *Tetrahedron* **2001**, *57*, 157–161.

[40] S. C. Bergmeier, A. A. Cobas, H. Rapoport, *J. Org. Chem.* **1993**, *58*, 2369–2376.

[41] T. L. Ho, B. Gopalan, J. J. Nestor, *J. Org. Chem.* **1986**, *51*, 2405–2408.

[42] K. Y. Hung, P. W. R. Harris, M. A. Brimble, *J. Org. Chem.* **2010**, *75*, 8728–8731.

[43] K. N. Fanning, A. Sutherland, *Tetrahedron Lett.* **2007**, *48*, 8479–8481.

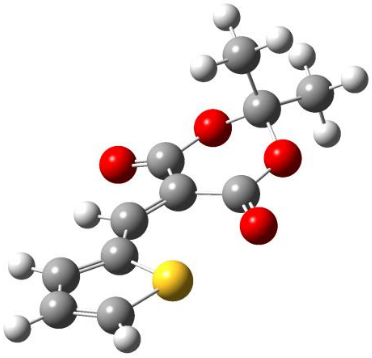
[44] a) P. K. Chang, L. J. Sciarini, Handschu.Re, *J. Med. Chem.* **1973**, *16*, 1277–1280; b) K. Burger, M. Rudolph, H. Neuhauser, M. Gold, *Synthesis* **1992**, 1150–1156.

[45] A. R. Mohite, P. R. Sultane, R. G. Bhat, *Tetrahedron Lett.* **2012**, *53*, 30–35.

[46] M. Sameiro, T. Goncalves, *Chem. Rev*. **2009**, *109*, 190–212.

Chapter Three

$FeCl_3 \cdot 6H_2O$ catalyzed novel and expedient synthesis of α,β-unsaturated carboxylic acids/esters from alkylidene meldrum's acids



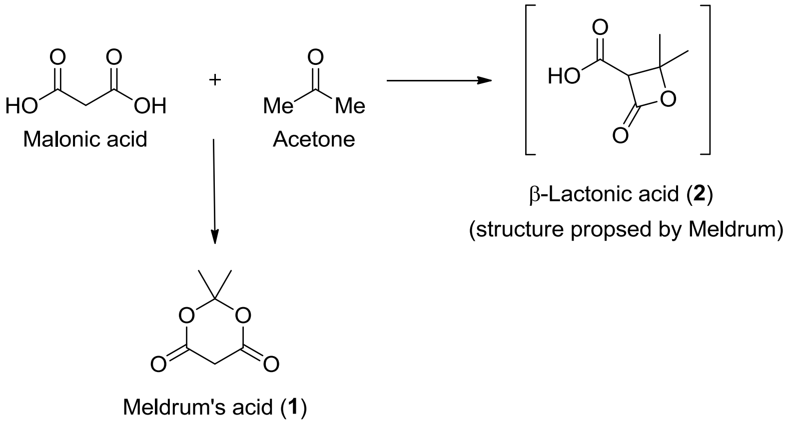
Energy minimized structure
of thiophene alkylidene Meldrum's acid

Chapter 3

In this chapter novel and expedient syntheses of α,β-unsaturated carboxylic acids/esters has been described by exploring the reactivity of alkylidene Meldrum's acids with water/alcohols in presence of $FeCl_3{\cdot}6H_2O$*. Section A presents the synthetic study of α,β-unsaturated carboxylic acids. Application of this method has been extended to biomass derived aldehydes. Similarly, Section B presents the rapid synthesis of α,β-unsaturated esters and their application in the synthesis of sunscreen filters.*

3.1 Introduction

In the year 1908, A. N. Meldrum reported a reaction of malonic acid and acetone in presence of catalytic amount of sulphuric acid. He proposed the structure of the product as β-lactonic acid **2** in the absence of any spectroscopic methods for structure determination (Scheme **3.1**).[1] However, 40 years later Davidson and Bernhard reassigned[2] the structure of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) to **1**. Later on, A. N. Meldrum's name was coined to the compound **1**.[3] Hence, development of reactions involving Meldrum's acid **1** was impeded by the original incorrect assignment of its structure by Meldrum. The Meldrum's acid has a very unusual acidity (Fig **3.1**). The acidity of Meldrum's acid (pKa = 7.3 in DMSO[4]) is quite higher than dimedone (pKa = 11.2 in DMSO). This is surprising because generally diketone loses proton more easily than diesters, hence acidity of Meldrum's acid should have been lower than dimedone **3**, but it was not observed. Also, an open chain analogue of Meldrum's acid, the malonate derivatives (**6**, **7**) are also less acidic.



Scheme 3.1: First report of synthesis of Meldrum’s acid

The high acidity of Meldrum’s acid was reasoned in several articles. Arnett *et al.* reported the anomalous acidity[5] of Meldrum’s acid is due to geometrical constraint of (*E*)-conformation of the two ester groups, which is not seen in less acidic, large-ring-sized bislactone or open-chain diesters. *Ab initio* calculations were also applied to this system to understand the acidic properties.[6]

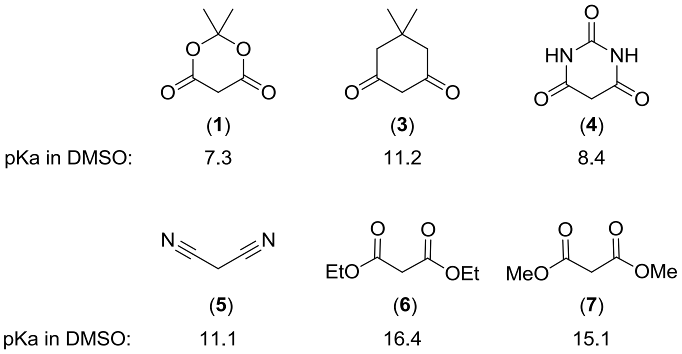


Fig 3.1: Comparison of acidity of Meldrum’s acid with different analogs

High acidity of Meldrum’s acid and its unusual reactivity with electrophiles (which does not disturb six membered ring of Meldrum’s acid) has been explored for synthesizing diverse number of compounds (Fig **3.2**). Meldrum’s acid derivatives find a great utility in organic synthesis as important class of reagents. Acyl derivatives of Meldrum’s acid **8** have been explored in the synthesis of dicarbonyl compounds[7] like β-ketoesters,[8] β-ketoacids and β-ketoamides.[9] 5,5-disubstituted compounds **9** have been utilized in mild α-bromination of aldehydes and ketones.[10] The 5-thioxo derivative **10** has been used as dienophile.[11] Compounds **11** and **12** have been employed in the heterocyclization reactions.[12] Photolysis of diazo compound **14** is known to generate corresponding Meldrum's acid carbene[13] that can be trapped by soft nucleophiles. Meldrum's acid containing cyclopropane ring **15** has shown to be highly reactive and reacted very rapidly with nucleophiles to form lactams and lactones.[14] Betaine **16**, has been prepared as a stable source for methylene[15] Meldrum's acid.

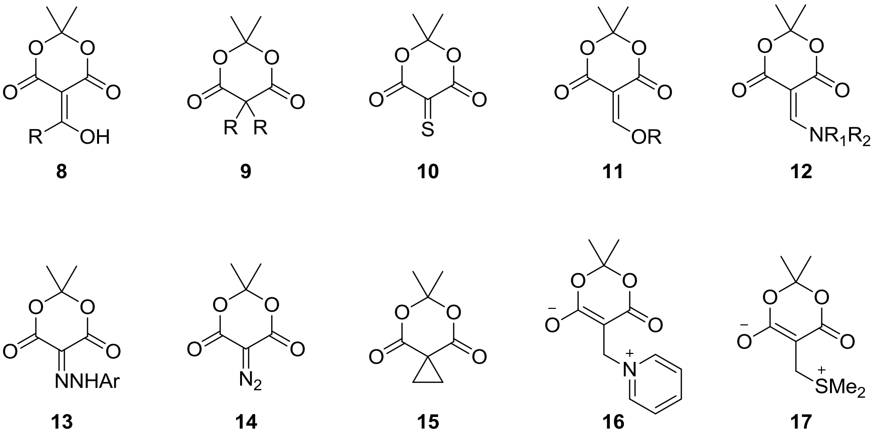
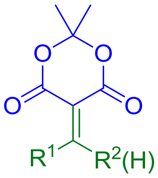


Fig 3.2: 5,5-disubstituted derivatives of Meldrum's acid

3.1.1 Alkylidene Meldrum's acid

Compound of general structure **18** (Fig **3.3**) is an important class of Meldrum's acid derivatives which find miscellaneous applications in organic synthesis. Starting from the very first synthesis of alkylidene Meldrum's acid,[16] properties of these derivatives have attracted the interests of organic chemists. Alkylidene Meldrum's acid derivatives mostly exist in crystalline solid form, and can easily be purified and they are air/moisture stable. These properties make them important reagents in organic synthesis. X-ray analysis gave an insight on boat type structures of such derivatives.[17] Crystallographic data revealed the perfect overlap of π electron cloud of carbonyl and unsaturated double bond. Hence, these derivatives are known to be excellent dienophiles. Alkylidene Meldrum's acids are biselectrophilic species[18] used in the variety of organic reactions and in the natural product synthesis as precursors.

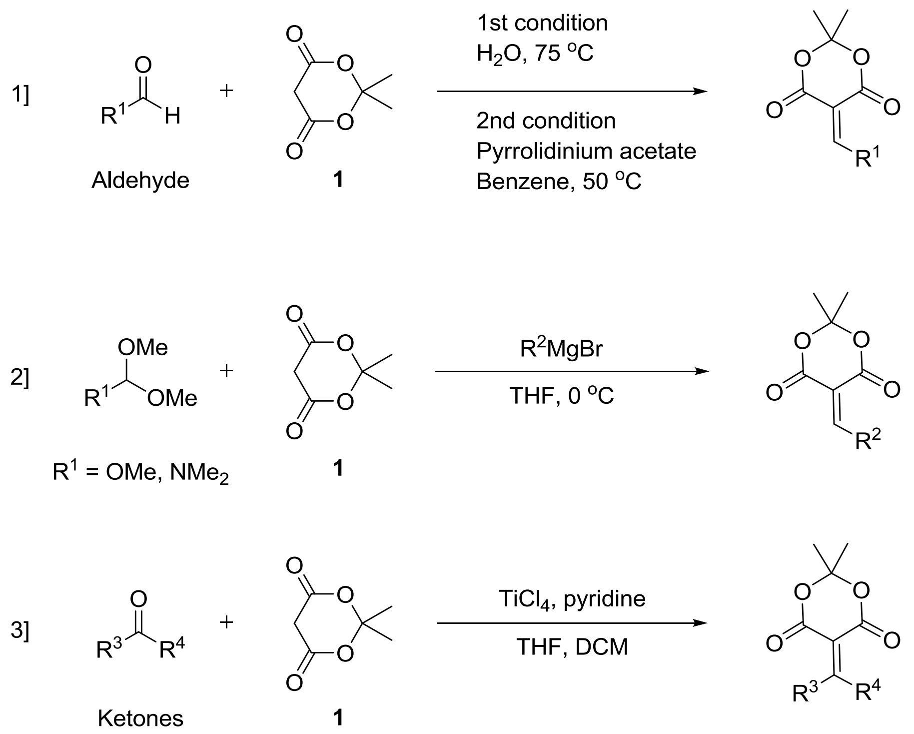


18

Fig 3.3: Structure of alkylidene Meldrum's acid

3.1.2 Preparation of Alkylidene Meldrum's acid

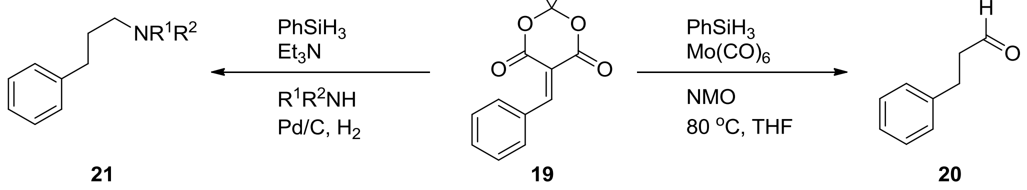
Usually, alkylidene Meldrum's acids are prepared from Knoevenagel condensation of aldehydes with Meldrum's acid. Recently, Bigi and co-workers[19] reported the Knoevenagel condensation in water at 75 °C (Scheme **3.2**, eq 1, 1st condition). This protocol has been extensively utilized for the synthesis of alkylidene Meldrum's acid derivatives. Fillion and co-workers reported another reliable method for the preparation of alkylidene Meldrum's acid using pyrrolidinium acetate as a catalyst for the Knoevenagel condensation at much lower temperature (50 °C) (Scheme **3.2**, eq 1, 2nd condition).[20] Problems associated with the condensation of aldehydes during Knoevenagel condensation has led to the development of alternative procedures for the synthesis of monosubstituted alkylidenes. One method that avoids the use of aldehydes altogether is the preparation of the dimethylaminomethylene Meldrum's acid by reaction of Meldrum's acid with dimethylformamide dimethylacetal (Scheme **3.2**, eq 2).[21] Mostly, $TiCl_4$ has been used as a catalyst for the synthesis of ketone derived alkylidene Meldrum's acid derivatives (Scheme **3.2**, eq 3).[22]



Scheme 3.2: Preparation of Alkylidene Meldrum's acids

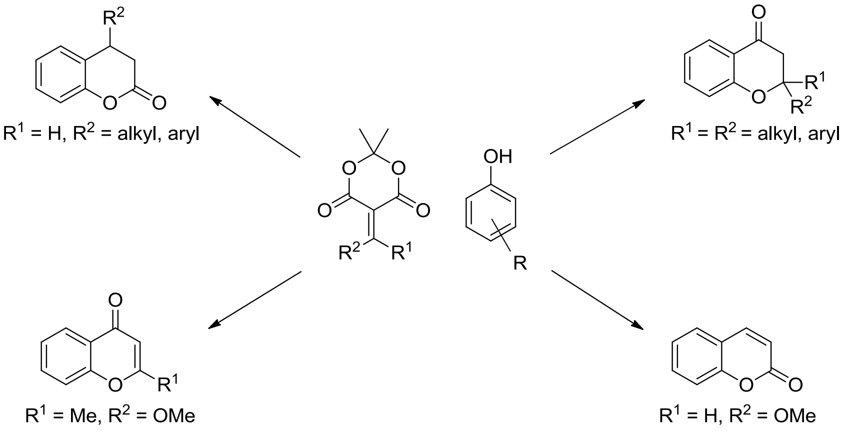
3.1.3 Alkylidene Meldrum's acid in organic synthesis

Alkylidene Meldrum's acid derivatives have been explored as reagents in organic synthesis for several transformations due to its interesting chemical and physical properties. They are also very important chemical entities in some of the natural product synthesis. Frost and co-workers[23] have reported the synthesis of two carbon homologated aldehydes **20** via the molybdenum catalyzed hydrosilylation of the alkylidene Meldrum's acid derivatives **19** (Scheme **3.3**). Alkylidene Meldrum's acid derivatives **19** have been utilized in the synthesis of saturated two carbon homologated amine derivatives **21** by Lewis base promoted hydrosilylation.[24]



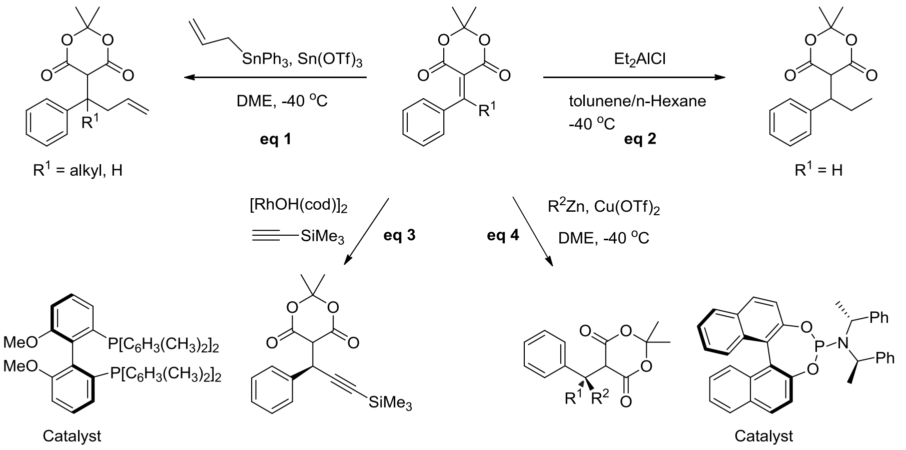
Scheme 3.3: Two carbon homologated aldehydes and amines

Coumarin derivatives are found in many natural products and are also important tagging reagents in chemical biology due to its fluorescent property. Chromones structurally similar to coumarins are also important motifs of bioactive natural products. Fillion and co-workers have extensively worked on divergent applications of alkylidene Meldrum's acid derivatives.[18] Their group has successfully explored the biselectrophilic nature of alkylidene Meldrum's acids for the synthesis of coumarin and chromones (Scheme **3.4**). The reaction of phenols (nucleophiles) with alkylidene Meldrum's acids led to coumarin and chromone analogs.



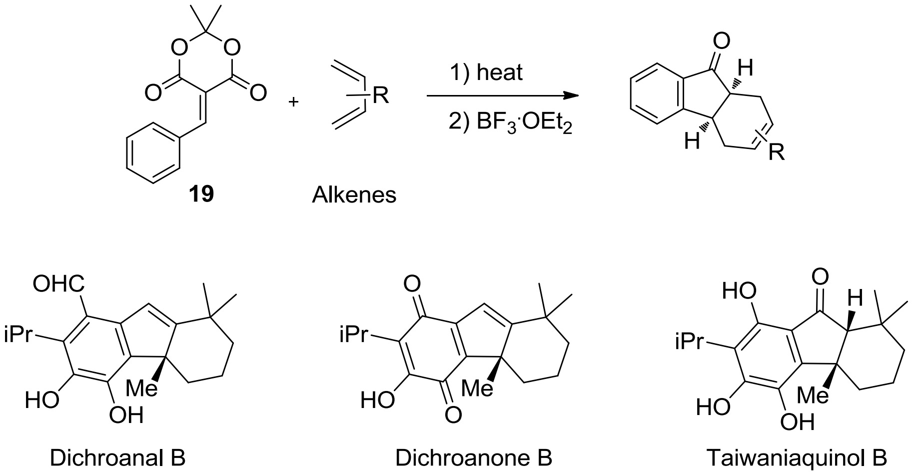
Scheme 3.4: Synthesis of coumarin and chromone derivatives

Alkylidene Meldrum's acids have also been explored in conjugate additions. Dumas *et al.* described an elegant method for the conjugate addition of allyltin[25] compounds on alkylidene Meldrum's acids using $Sc(OTf)_3$ as Lewis acid catalyst (Scheme **3.5**, eq 1). Fillion *et al.* have reported the Cu-catalyzed enantioselective conjugate addition[26] of dialkylzinc reagents (Scheme **3.5**, eq 4) on alkylidene Meldrum's acids. This method gave a direct access to the enantiomerically pure quaternary carbon centre. Dialkylaluminum chlorides (Scheme **3.5**, eq 2) have also been used for the conjugate addition.[27] Alkylidene Meldrum's acids have also been explored for the asymmetric alkenylation.[28] Further, resulted products have been converted in to chiral functionalized compounds. Rhodium catalyzed conjugate addition of sensitive silylated alkynes (Scheme **3.5**, eq 3) has been described using alkylidene Meldrum's acids.[29]



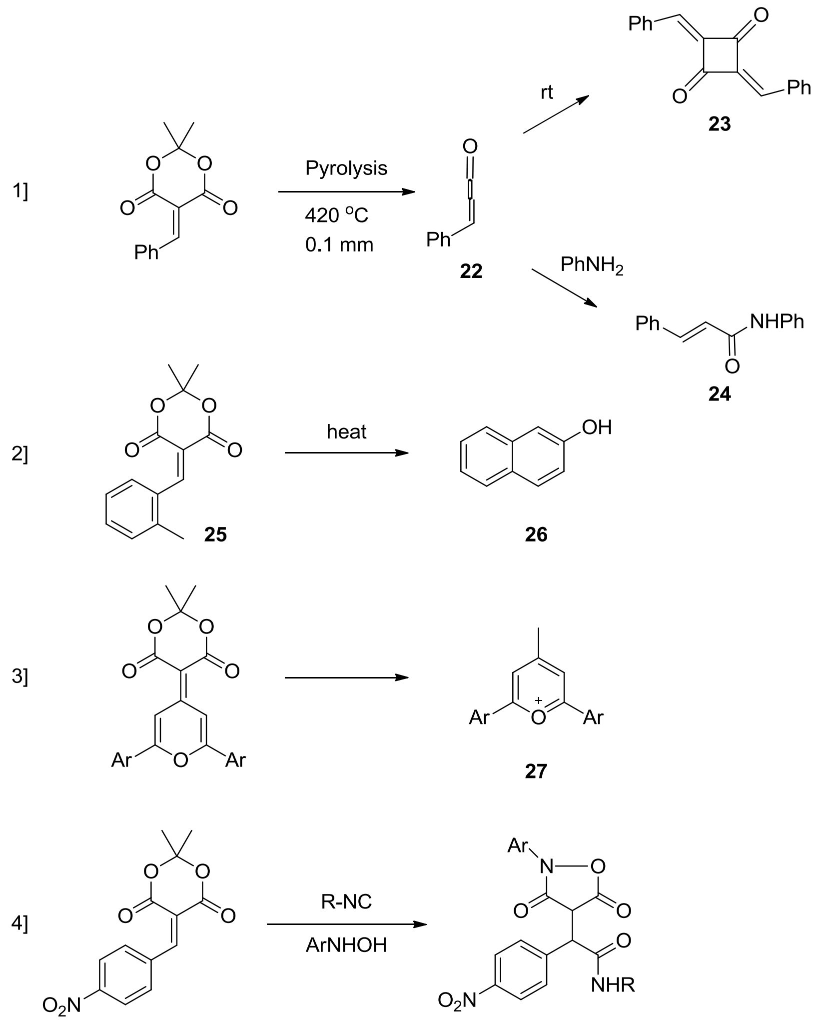
Scheme 3.5: Addition reactions on alkylidene Meldrum's acids by various carbon nucleophiles

The exceptional dienophilic property of alkylidene Meldrum's acids have been explored for the synthesis of 6-5-6 tricyclic structural motifs (tetrahydrofluorenones) found in norditerpenoid natural products (Scheme **3.6**), One-pot $BF_3{\cdot}OEt_2$ mediated thermal Diels-Alder reaction[30] followed by the Friedel-Crafts acylation furnished tricyclic core in high stereoselectivity.



Scheme 3.6: Synthesis of tetrahydrofluorenone derivatives

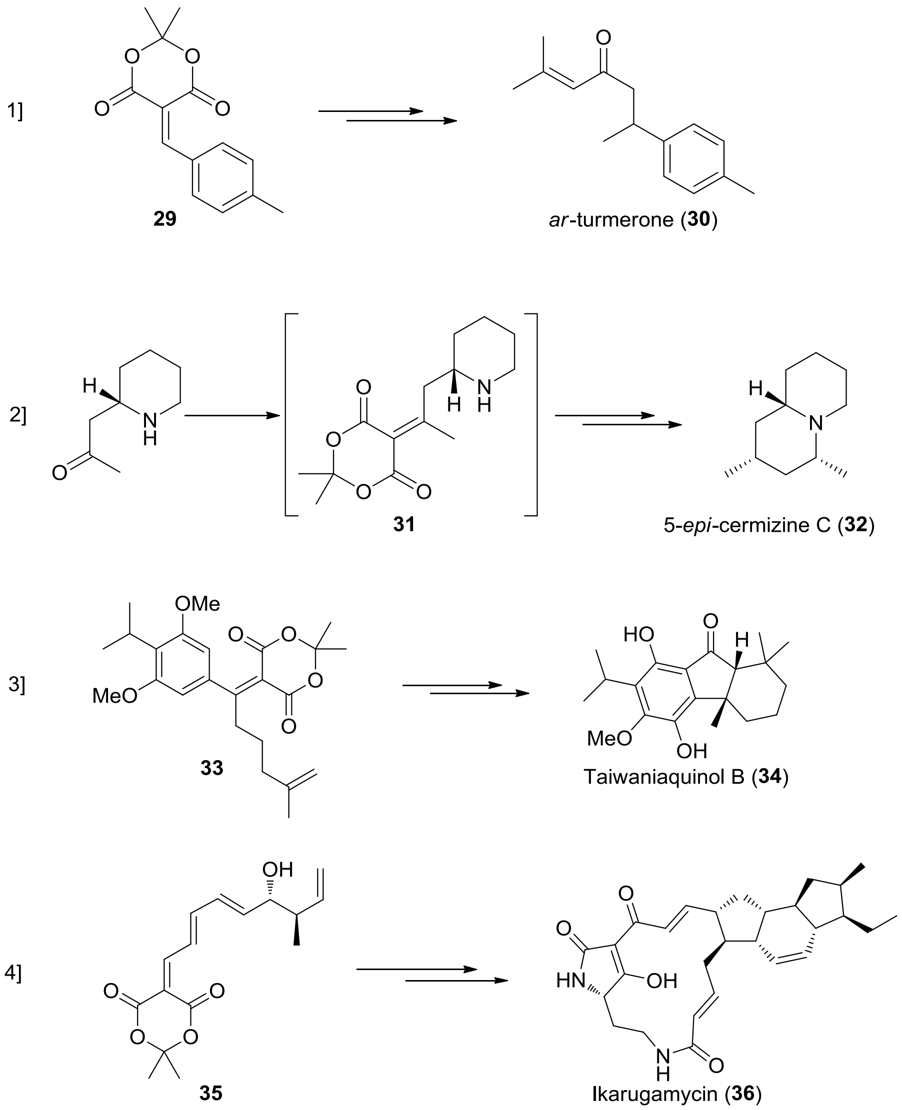
Alkylidene Meldrum's acids are known to afford very reactive phenylmethylene ketene **22** under pyrolysis conditions **(**Scheme **3.7**, eq 1) The formation of intermediate **22** was further supported by its dimerization to afford cyclobutanedione[3] product **23**. The ketene intermediate **22** was reacted with phenyl amine to afford unsaturated amide **24**. Further, alkylidene Meldrum's acid derivative **25** has been used for the synthesis of naphthol **26** via ketene trapping by the substrate itself (Scheme **3.7**, eq 2). Similarly, by trapping ketene intermediate pyrylium salt **27** (Scheme **3.7**, eq 3) has been synthesized. Isoxazolinediones[31] has been synthesized by the reaction of isocyanides and alkylidene Meldrum's acid derivative in presence of arylhydroxylamine **28** (Scheme **3.7**, eq. 4).



Scheme 3.7: Various applications of alkylidene Meldrum's acid derivatives

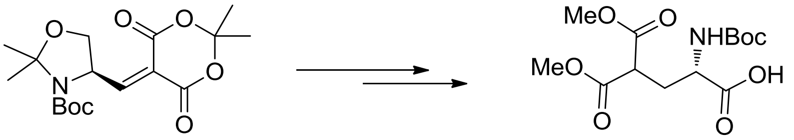
Alkylidene Meldrum's acids have been extensively utilized in the various natural product syntheses. The various alkylidene Meldrum's acids have been successfully employed at various stages for the synthesis of several natural products. Some of the selected examples have been listed here (Scheme **3.8**). Natural products such as *ar*-turmerone **30**, 5-*epi*-cermizine C **32**, Taiwaniaquinol B **34** and Ikarugamycin

36 have been synthesized effectively utilizing different alkylidene Meldrum's acids **29**, **31**, **33** and **35** respectively (Scheme **3.8**).



Scheme 3.8

Similarly, the γ-carboxyl-L-glutamic acid **38** (Scheme **3.9**) is an important component of prothrombin, a vitamin K dependent blood clotting factor.[32] This amino acid is also used as a building block in the total synthesis of quinocarcin[33] and related natural products. Alkylidene Meldrum's acid **37** obtained from the condensation of Garner's aldehyde and Meldrum's acid has been utilized in synthesizing γ-carboxyl-L-glutamic acid (**38**).[34]



Scheme 3.9: Synthesis of γ-carboxyl-L-glutamic acid

In this chapter we have synthesized various alkylidene Meldrum's acids and explored the controlled monoelectrophilic reactivity of alkylidene Meldrum's acids in synthesizing very useful α,β-unsaturated carboxylic acids and corresponding esters. Synthetic studies are presented in detail in section A and Section B.

Section A: Synthesis of α,β-unsaturated Carboxylic Acids

3.2 Introduction

The α,β-unsaturated acids are very important and useful reagents in organic synthesis. They are significant structural motifs in many natural products (viz. the secretion of the queen honey bee,[35] caffeic acid[36]), pheromones,[37] and bioactive compounds.[38] Owing to their wide ranging applications, the α,β-unsaturated carboxylic acids are synthesized on commercial scale.

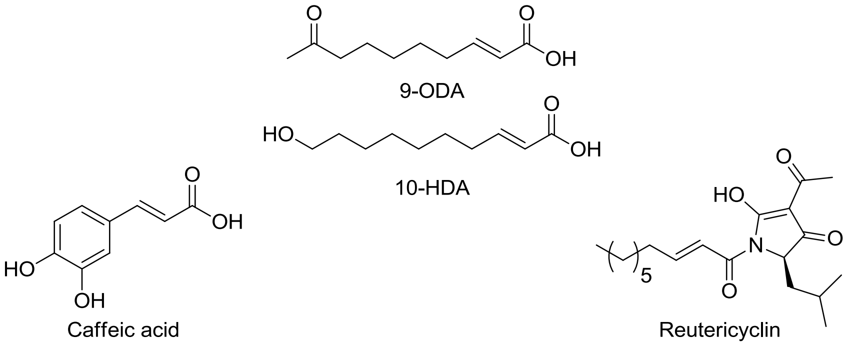
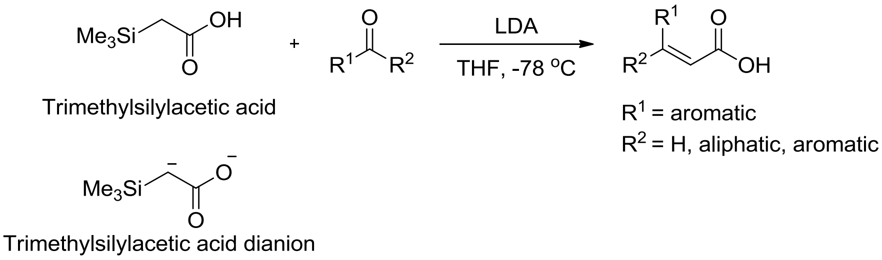


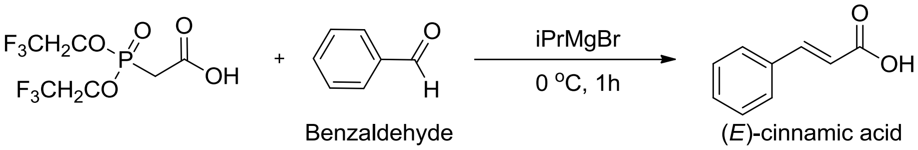
Fig 3.4: Natural products containing α,β-unsaturated carboxylic acid motifs

Undeniably, the Doebner-Knoevenagel reaction has been one of the most extensively used protocols for the preparation of α,β-unsaturated carboxylic acids but most often they need severe refluxing conditions and use of excess base.[39] Grieco *et al.* reported[40] an elegant method for the synthesis of α,β-unsaturated carboxylic acids from trimethylsilyl acetic acid dianion and carbonyl compounds (aldehydes and ketones, Scheme **3.10**). Though α,β-unsaturated acids have been obtained in very good yields but with very poor/variable stereoselectivity (*E/Z* ratio 1:1).



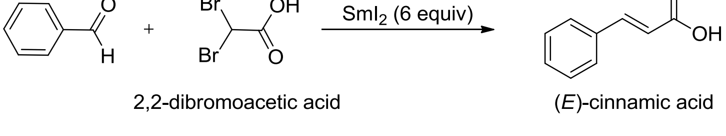
Scheme 3.10: Trimethylsilylacetic acid dianion

Horner-Wadsworth-Emmons (HWE) reaction[41] was utilized for the synthesis of α,β-unsaturated acids. Bis-(2,2,2-trifluoroethyl) phosphono acetic acid, a modified phosphano reagent[42] has been employed for the HWE reaction with various aldehydes to synthesize α,β-unsaturated acids in good yields (Scheme **3.11**).



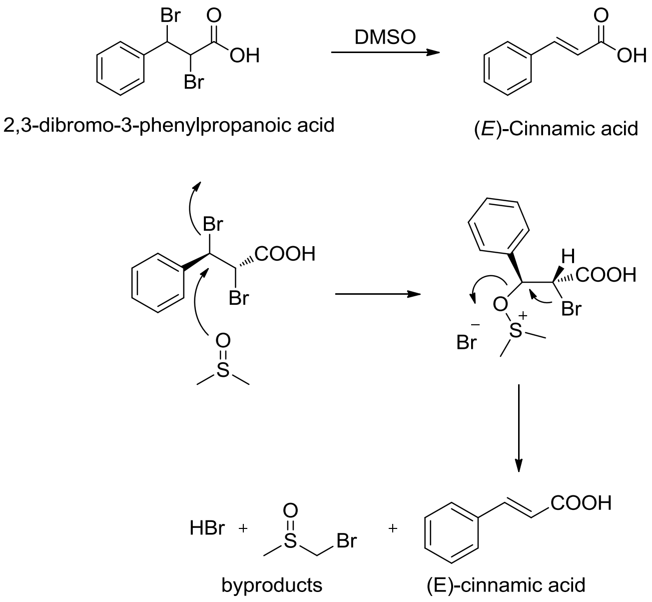
Scheme 3.11: Horner-Wadsworth-Emmons reaction

Concellon[43] and co-workers have described a method for the synthesis of (*E*)-α,β-unsaturated carboxylic acids by employing dibromoacetic acid and SmI_2 (Scheme **3.12**). Though, the reaction was highly stereoselective but it required an excess amount of SmI_2.



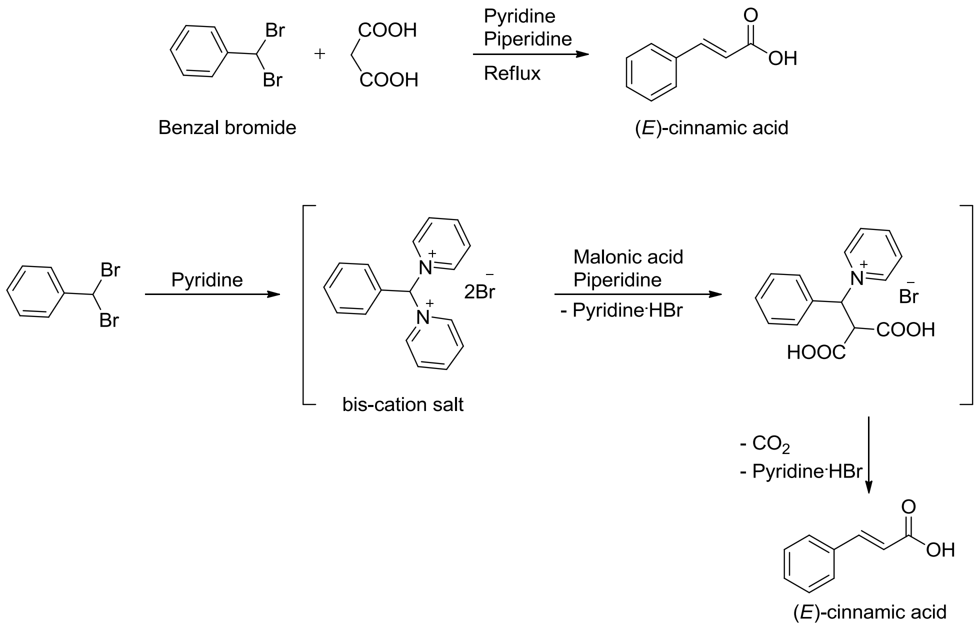
Scheme 3.12: Samarium diiodide promoted synthesis of (*E*)-α,β-unsaturated carboxylic acid

Li-We *et al*. reported[44] the synthesis of (*E*)-α,β-unsaturated carboxylic acids via reductive elimination of 3-aryl 2,3-dibromopropanoates using dimethyl sulfoxide (DMSO) (Scheme **3.13**). Although, reaction showed a vast substrate scope, but in some cases it suffered from poor stereoselectivity. It is interesting to note that starting material 3-aryl 2,3-dibromopropanoates are generally prepared from the corresponding unsaturated acids and appropriate bromine source.



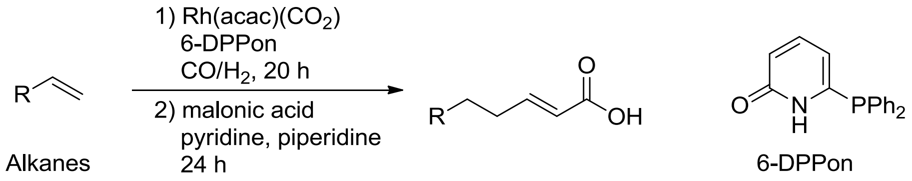
Scheme 3.13: DMSO mediated reductive elimination in dibromo compounds and its mechanism

Knoevenagel-Doebner reaction has been extensively documented for synthesis of α,β-unsaturated acid derivatives. Augustine[39f] and co-workers demonstrated the use of benzal bromide derivatives in the synthesis of (*E*)-α,β-unsaturated carboxylic acids (Scheme **3.14**). Knoevenagel-Doebner reaction of benzal bromide and malonic acid in the presence of excess pyridine/piperidine as base afforded (*E*)-α,β-unsaturated acids. Salt intermediate generated by the reaction of bis-cation salt and malonic acid undergoes a tandem decarboxylation followed by the elimination of pyridine to yield cinnamic acid derivative.



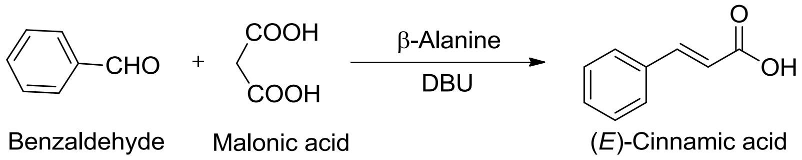
Scheme 3.14: Knoevenagel-Doebner reactions employing benzal bromide

Though, many reports for the synthesis of α,β-unsaturated carboxylic acids have been described in the literature, to our knowledge, there is no efficient catalytic method for the preparation of α,β-unsaturated acids other than the catalytic method reported by Breit[45] and co-workers. They showed an effective method for the synthesis of atom economical C3 homologated α,β-unsaturated carboxylic acids starting from readily available terminal alkenes (Scheme **3.15**). Method involved hydroformylation of alkenes followed by the decarboxylative Knoevenagel condensation with malonic acid using organic base.



Scheme 3.15: C3 homologation of alkenes to α,β-unsaturated carboxylic acids

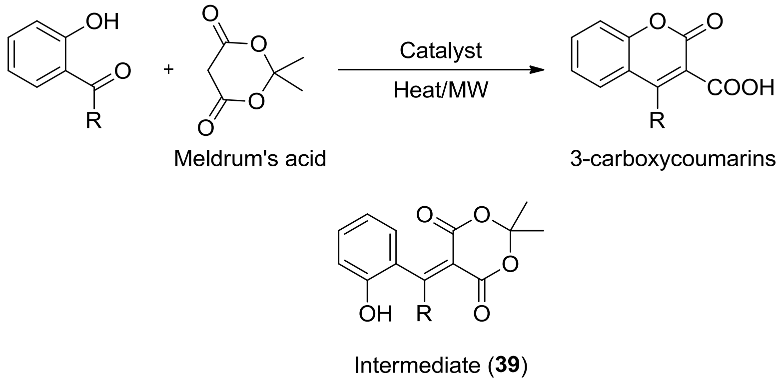
Zhu *et al.* used β-alanine/DBU (as organocatalyst) for synthesis of (*E*)-α,β-unsaturated acids[46] for the modified Knoevenagel-Doebner reaction. Stereoselective transformation has been achieved with good yields (Scheme **3.16**).



Scheme 3.16: Organocatalysts in Knoevenagel-Doebner reaction

3.3 Results and Discussion

Earlier literature precedence reveals that intramolecular reaction of an intermediate **39** (containing alkylidene Meldrum's acid as well as phenolic group) afforded 3-carboxycoumarin[47] derivative under heating condition (Scheme **3.17**). The Phenolic –OH group attacked the electron deficient carbonyl of alkylidene Meldrum's acid to afford 3-carboxycoumarins. Where in instantaneous decarboxylation was found to be very tedious due to the presence of a double bond in conjugation with the carboxylic group. Similarly, the synthesis of dihydrocoumarins has been reported starting from phloroglucinols and alkylidene Meldrum's acid under alkaline conditions.[48]



Scheme 3.17: One-pot procedure for synthesis of 3-carboxycoumarins and structure of intermediate formed

3.3.1 Strategy

These earlier results encouraged us to believe that alkylidene Meldrum's acid derivatives would afford the corresponding α,β-unsaturated carboxylic acid on treatment with appropriate Lewis acid catalyst and H_2O as a nucleophile. Reactivity of alkylidene Meldrum's acids towards nucleophiles is very interesting and it has always been a subject of investigation. Lewis acid activates the carbonyl group of alkylidene Meldrum's acid (Fig **3.5**, a) and facilitates two possible competing reactions, viz. 1,4 addition (Fig **3.5**, b, Michael addition) and 1,2 addition (Fig **3.5**, c, nucleophilic addition to carbonyl carbon). It's very challenging to control Michael addition, as unsaturation is activated by cyclic diester. In such case, it is very difficult to avoid intermolecular Michael addition of nucleophiles (for Michael addition examples see Scheme **3.4** and **3.5**). Carbon nucleophiles are known to undergo conjugate Michael addition on alkylidene Meldrum's acids.

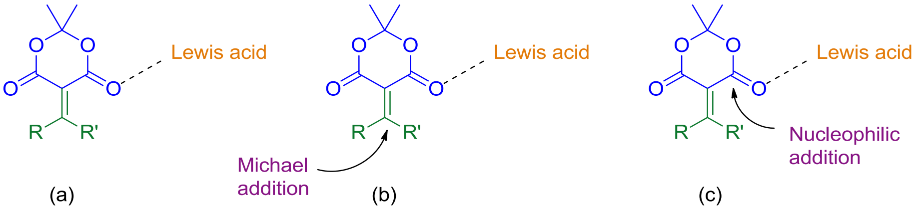


Fig 3.5: (a) Activation of carbonyl group of alkylidene Meldrum's acid; (b) Michael addition on alkylidene Meldrum's acid, (c) Nucleophilic addition on alkylidene Meldrum's acid

In our retrosynthetic analysis (Fig **3.6)**, we envisaged that α,β-unsaturated carboxylic acids can be constructed by the selective decarboxylation of alkylidene Meldrum's acid **18**. This in turn can be synthesized by condensing aldehyde with Meldrum's acid **1**.

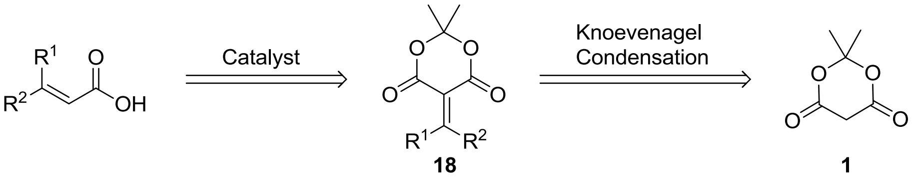
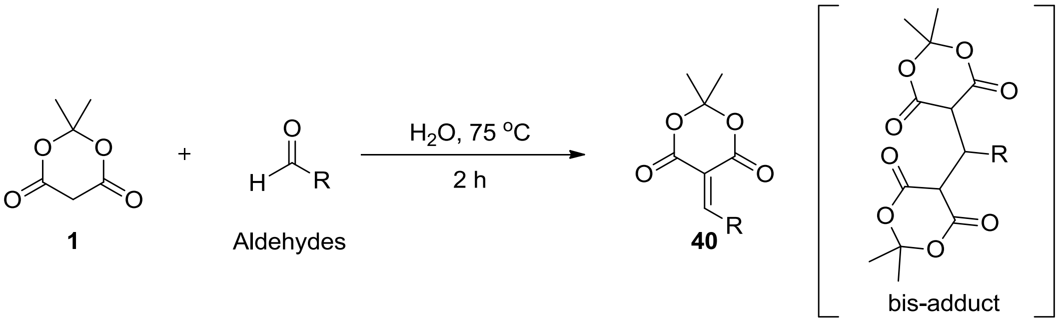


Fig 3.6: Reterosynthetic analysis of α,β-unsaturated carboxylic acids

3.3.2 Synthesis of alkylidene Meldrum's acid

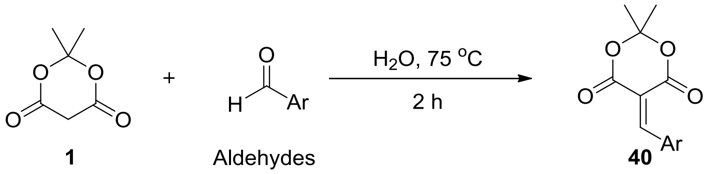
In order to verify this, we prepared various methylene tethered Meldrum's acid derivatives by condensing different aldehydes with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in water following the reported procedure.[19] This reaction conditions are suitable for synthesis of alkylidene Meldrum's acid derivatives as it avoids the formation of bis-Meldrum's acid adduct (Scheme **3.18**). The bis-adduct[49] is usually formed due to the Michael addition of second molecule of Meldrum's acid (**1**) with alkylidene Meldrum's acid (**40**).

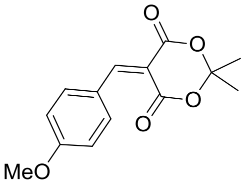
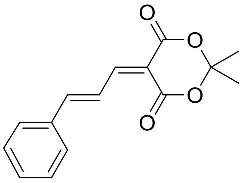
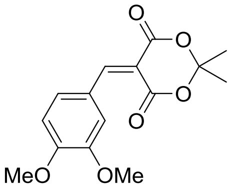
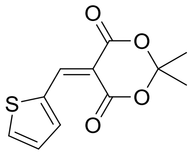
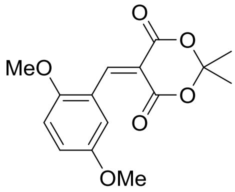
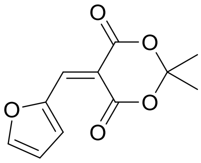
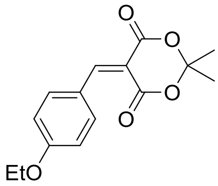
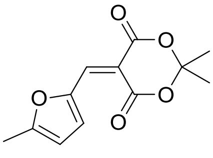
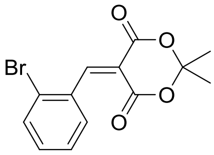
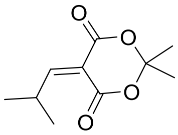
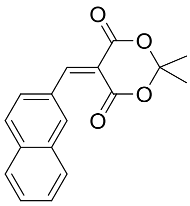


Scheme 3.18: Condensation of various aldehydes in water

Different alkylidene Meldrum's acid derivatives (**40a**–**40k**, Table **3.1**) were synthesized in good yields (up to 96%) by condensing different aldehydes with Meldrum's acid **1** in water at 75 °C for 2 h. Aromatic, heteroaromatic, aliphatic and unsaturated aldehydes underwent facile condensation and were found to be compatible under the reaction conditions (Table **3.1**, **40a**–**f**, **40h**–**j**, **40k** and **40g**).

Table 3.1: Substrate scope for uncatalyzed condensation

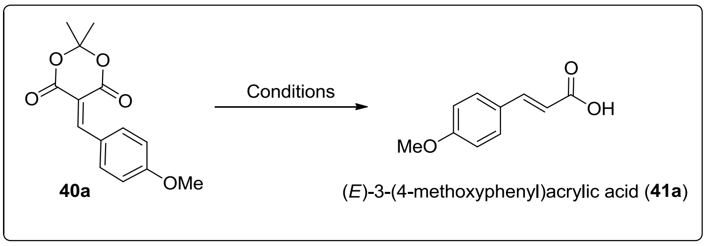


substarte	**yield (%)**	**substarte**	**yield (%)**
	(**40a**, 92%)		(**40g**, 96%)
	(**40b**, 81%)		(**40h**, 65%)
	(**40c,** 84%)		(**40i**, 94%)
	(**40d**, 90%)		(**40j**, 83%)
	(**40e**, 74%)		(**40k**, 35%)
	(**40f**, 45%)		

3.3.3 Decarboxylation of alkylidene Meldrum’s acid

Having obtained the alkylidene Meldrum’s acid derivatives, we selected *p*-methoxybenzylidene derivative of Meldrum’s acid (**40a**) as a model substrate and screened various Lewis acids as catalyst at different reaction conditions in order to achieve the efficient catalytic decarboxylation for the one pot synthesis of α,β-unsaturated carboxylic acid (Table **3.2**).

Table 3.2



40a

(*E*)-3-(4-methoxyphenyl)acrylic acid (**41a**)

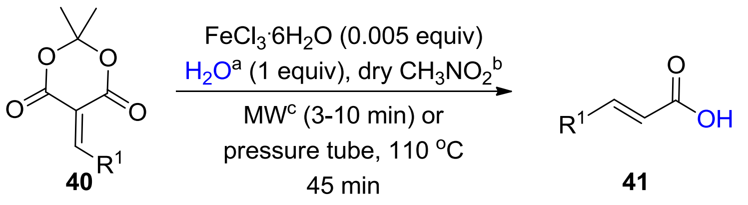
Entry	Catalyst (mmol %)	Solvent[a]	T ($^\circ$C)/t (h)	Y[b] (%)	MW[c] (%)
1	$CeCl_3{\cdot}7H_2O$ (0.03)	CH_3NO_2	110/3	0	0
2	$MgSO_4$ (0.023)	CH_3NO_2	110/3	0	0
3	LiBr (0.015)	CH_3NO_2	110/3	0	0
4	$FeCl_3{\cdot}6H_2O$ (0.0063)	CH_3NO_2	110/3	5	6
5	$FeCl_3{\cdot}6H_2O$ (0.0063)	H_2O	100/2	dec[d]	dec[d]
6	$FeCl_3{\cdot}6H_2O$ (0.0063)	CH_3NO_2[e]	110/45 m	87	86
7	$FeCl_3{\cdot}6H_2O$ (0.0063)	EtOAc	77/2	0	0
8	$FeCl_3{\cdot}6H_2O$ (0.0063)	MeOH	65/2	0	0
9	$FeCl_3{\cdot}6H_2O$ (0.0063)	CH_3CN[e]	82/2	0	0
10	$FeCl_3{\cdot}6H_2O$ (0.0038)	CH_3NO_2[e]	110/45 m	87	88
11	$B(C_6F_5)_3$ (0.0076)	CH_3NO_2[e]	110/3	39	39
12	$SnCl_2$(0.0076)	CH_3NO_2[e]	110/3	0	0
13	$CeCl_3{\cdot}7H_2O$/NaI (0.0076)	CH_3NO_2[e]	110/3	65	65
14	No catalyst	CH_3NO_2[e]	110/3	0	0
15	$FeCl_3{\cdot}6H_2O$ (0.0063)	THF[e]/THF	68/3	0	0
16	$FeCl_3$ (0.0063)	THF[e]/THF	68/3	0	0

[a]anhydrous solvents were used, [b]isolated yield, [c]microwaved for 3-10 min (2.5 GHz, 250 W), [d]decomposition, [e]1 equiv H_2O used, T-temperature, t-time in hours (h) or min (m), Y-Yield in %, reactions were carried out using 0.2 g of **40a**.

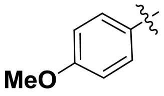
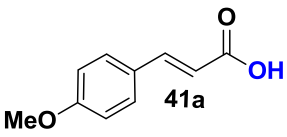
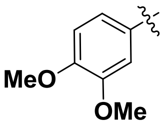
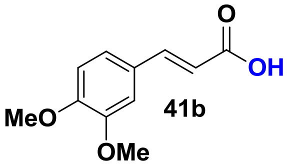
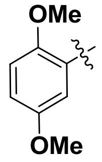
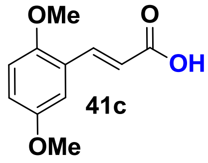
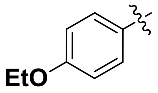
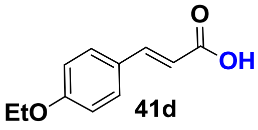
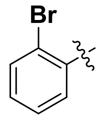
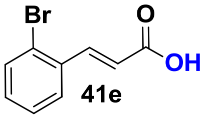
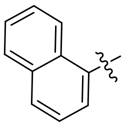
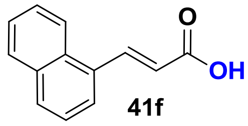
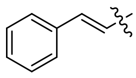
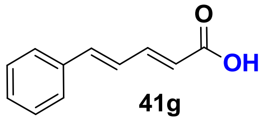
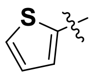
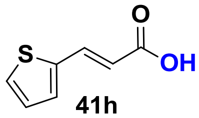
The reactions were screened under both conventional heating conditions and microwave irradiation (2.5 GHz) in pressure tube. We did not observe any trace amount of the expected product even after prolonged reaction time (entry 1-3, Table **3.2**). However, when reaction was carried out in nitromethane using $FeCl_3 \cdot 6H_2O$ (0.0063 mmol %) we obtained the *p*-methoxycinnamic acid **41a** in very poor yields (5-6%). We surmised that trace amount of water present in the nitromethane might have facilitated the reaction. Interestingly, we observed that under both the conditions $FeCl_3 \cdot 6H_2O$ (0.0063 mmol %) and H_2O (1 equiv) in nitromethane catalyst system worked efficiently in relatively short time. Heating condition afforded **41a** in 87% yield in 45 min (entry 6), similarly compound **41a** was obtained in 86% yield in very short time (4 min) under microwave irradiation (entry 6). Different solvents were also screened as described in Table **3.1** and we observed that nitromethane and water (1 equiv) proved to be very crucial to bring about the desired transformation.[50] Interestingly, when water alone was used as solvent the reaction led to decomposition (entry 5). It is very significant to mention that reaction worked very efficiently with 0.0038 mmol % (0.005 equiv) of $FeCl_3 \cdot 6H_2O$ as catalyst, under both microwave and heating conditions (TON 176, TOF 44/min, microwave and TON 174, TOF 3.9/min for heating) (entry 10). This catalytic conversion was accompanied by volatile by-products such as CO_2 and acetone.

Encouraged by this initial success we explored this catalytic protocol using $FeCl_3 \cdot 6H_2O$ (0.005 equiv)-H_2O (1 equiv) in CH_3NO_2 under optimized reaction conditions for synthesizing various α,β-unsaturated carboxylic acids (**41a**–**41h**) in good yields (67-90%, Table **3.3**). Notably, we observed that (*E*)-stereoisomers were formed as major products (>99%) using this protocol, however, compound **41h** was obtained in an *E/Z* = 87:13 ratio. *E*-stereochemistry of the C=C double bond of α,β-unsaturated carboxylic acid was assigned on the basis of ^1H NMR coupling constants. However, compound **40k** under reaction conditions led to non-isolable mixture of products.

Table 3.3: Substrate scope for α,β-unsaturated carboxylic acids



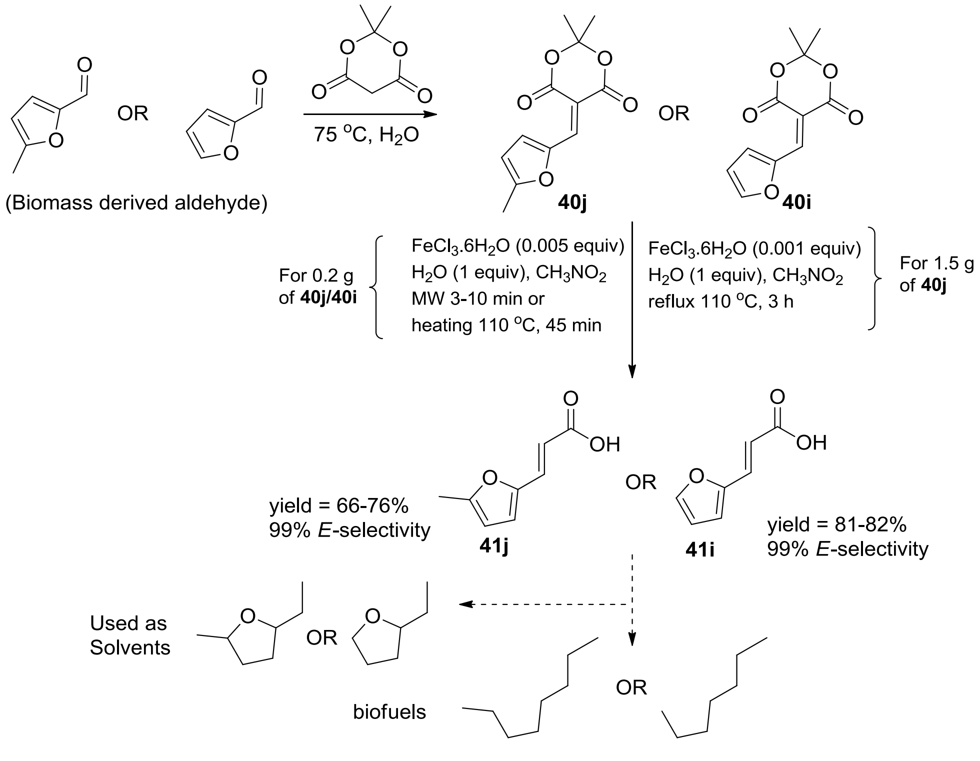
> 99% *E*-selectivity[d]

entry	R^1	R	41	MW yield (%)	heating yield (%)
1		H	 **41a**	88	87
2		H	 **41b**	67	77
3		H	 **41c**	84	87
4		H	 **41d**	90	87
5		H	 **41e**	90	87
6		H	 **41f**	76	83
7		H	 **41g**	79	87
8		H	 **41h**	84	87

[a] equiv of H_2O. [b] CH_3NO_2 as solvent. [c] Microwave irradiation (2.5GHz, 250W). [d] We observed more than 99% *E*-selectivity in (41a-41g); however 41h gave an *E*/*Z* = 87:13 ratio.

3.3.4 Utility of biomass derived aldehydes in gram scale

There is huge demand to develop methods that can be utilized for the conversion of biomass derived molecules into more useful and renewable products. A practical C-C bonding approach to make mildly oxygenated hydrocarbons (C_8-C_{15}) from biomass derived molecules would be very useful in generating gasoline and diesel fuels.[51] Biomass derived molecules such as furfural, 5-hydroxy methyl furfural (HMF) have been converted into useful molecules such as α,β-unsaturated carboxylic acids for potential use in fuels.[52] To date, there is a thrust on converting biomass into useful chemical building blocks that may also be pivotal to chemical manufacturing. It is known that some of α,β-unsaturated carboxylic acid derivatives obtained from biomass derived aldehydes are subsequently converted into fuel additives in the gasoline range C_8-C_9. Owing to this importance, we demonstrated the utility of biomass derived aldehydes such as furfural and 5-methyl furfural for efficient preparation of corresponding unsaturated carboxylic acids (**41i** and **41j**) in good yields (81-82%, TON 164, TOF 40.5/min and 66-76%, TON 132, TOF 26.4/min) with high *E*-stereoselectivity (>99%) using the optimized protocol under both microwave and conventional heating conditions (Scheme **3.19**).

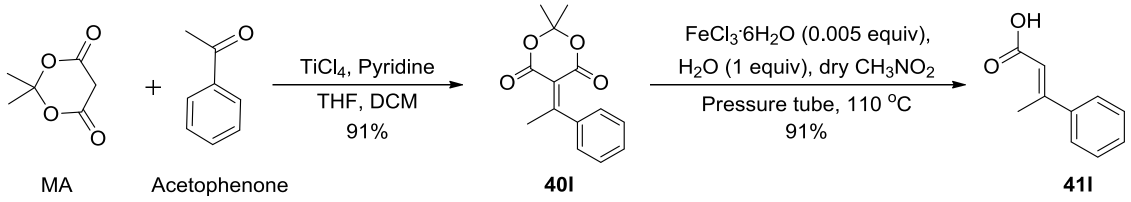


Scheme 3.19: Utility of biomass derived aldehydes for synthesis of α,β-unsaturated carboxylic acids

In order to have wider application synthesis of α,β-unsaturated carboxylic acid **41j** (85%) was demonstrated on a gram scale (53 g) starting from **40j** using $FeCl_3{\cdot}6H_2O$ (0.1 mol%) and H_2O (1 equiv) in dry nitromethane under conventional refluxing condition (110 °C, 3 h) at ambient pressure. It is significant to note that catalytic load was further reduced to 0.001 equiv. at large scale reaction.

3.3.5 Ketone derived alkylidene Meldrum's acid

Moreover, to study the reactivity of ketone derived cyclic 1,3-diester towards the catalyst system we prepared the alkylidene derivative **40l** from the corresponding acetophenone using $TiCl_4$ and pyridine in THF[22, 26] (Scheme **3.20**). When subjected to the optimized reaction condition using $FeCl_3{\cdot}6H_2O$ (0.005 equiv)-H_2O (1 equiv) in dry CH_3NO_2 under microwave irradiation the alkylidene Meldrum's acid derivative **40l** furnished the corresponding α,β-unsaturated carboxylic acid **41l** in just 3 minutes in very good yield (91%). However, reaction under heating conditions at 110 ^oC using optimized catalytic protocol afforded **41l** 87% in 45 min. To our knowledge for the first time synthesis of α,β-unsaturated carboxylic acids starting from corresponding ketone has been successfully demonstrated. The catalytic system also showed good functional group compatibility as many functional moieties were tolerated under these reaction conditions.



Scheme 3.20: Trisubstituted α,β-unsaturated carboxylic acids

3.3.6 TGA study

Thermo gravimetric analysis in which the mass of a substance is monitored as a function of temperature or time as the sample compound is subjected to a controlled temperature program in a controlled atmosphere. In order to confirm liberation of CO_2 and acetone during the course of the reaction and to understand the reaction pathway, few compounds were screened for TGA study (Fig **3.7**). With the increase in temperature, we observed the descending TGA thermal curves and this clearly indicated the weight loss of compounds with increase in temperature. The compound **40d** showed highest thermal stability, while aliphatic **40k** compound showed lowest thermal stability. Calculated percentage weight loss for compounds **40a**, **40c**, **40d** and **40e** from these curves were nearly 40%. This indicated that starting material had lost 40% of its original weight. This value was found to be constant for all these derivatives. We surmised that possibly same molecules might have liberated during this thermal process of all the substrates. Liberated molecules were accounted for acetone and CO_2 (theoretical percentage weight loss, 37%) from the respective starting compounds based on descending TGA curves. However, TGA curves showed the complete decomposition of compounds **40k** and **40i** below 225 °C.

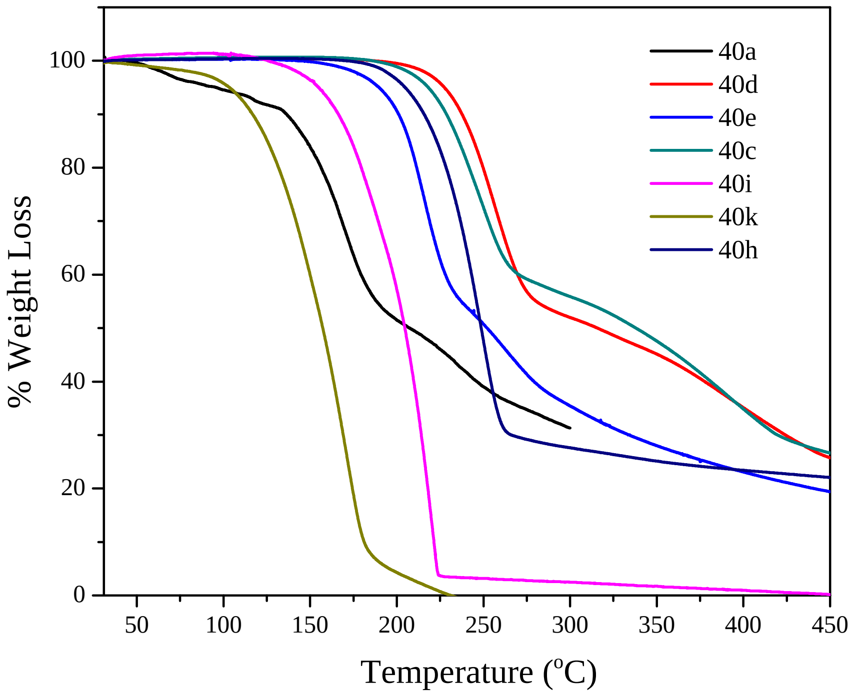


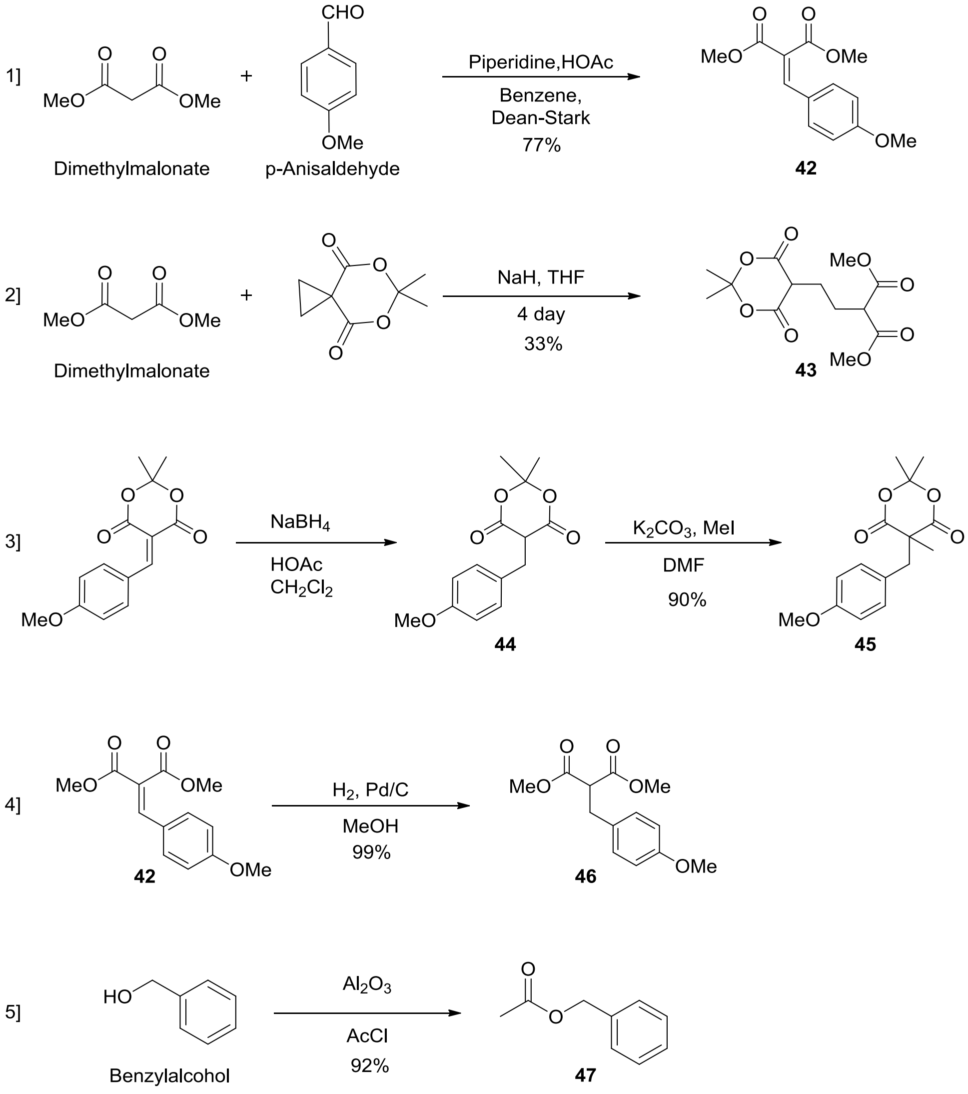
Fig 3.7: TGA curves for compounds

3.3.7 Competitive experiments

In order to verify the efficiency of this protocol, we further embarked on the study of selective decarboxylation of various substituted cyclic 1,3-diesters with varied substrates. For this purpose compounds **42, 43** and **45–47** were synthesized**.**

3.3.8 Synthesis of staring materials for competitive experiments

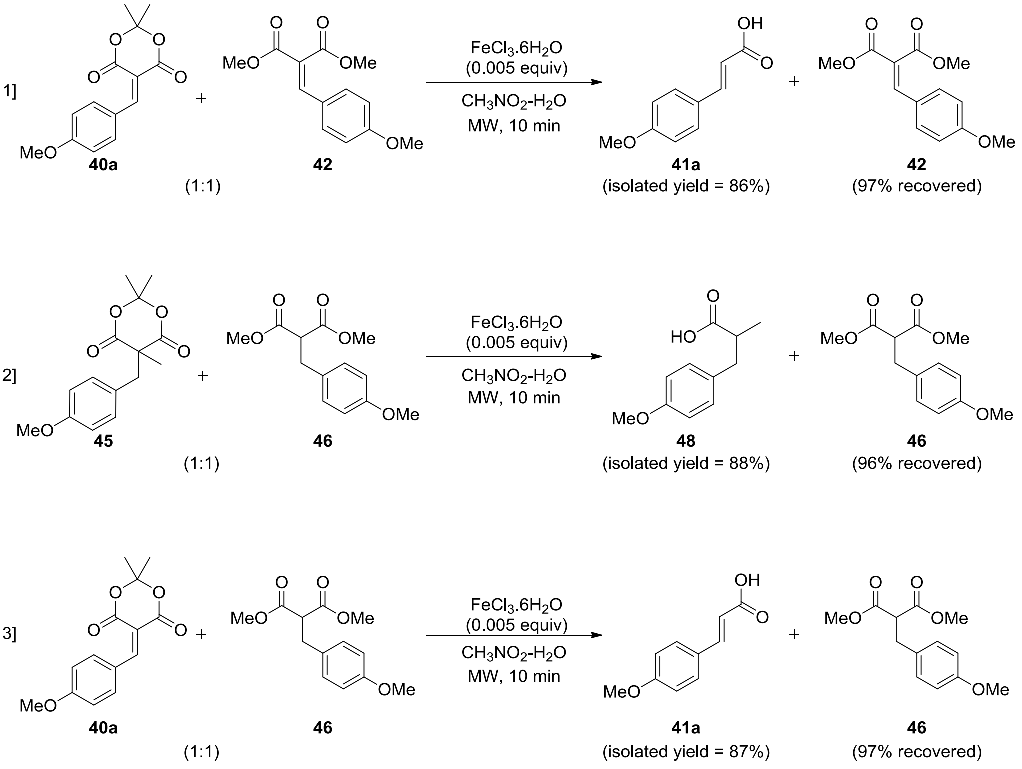
Acyclic alkylidene 1,3-diester **42** was synthesized by classical Knoevenagel condensation[8] between dimethylmalonate and anisaldehyde in good yield (84%, eq 1 Scheme **3.21**).

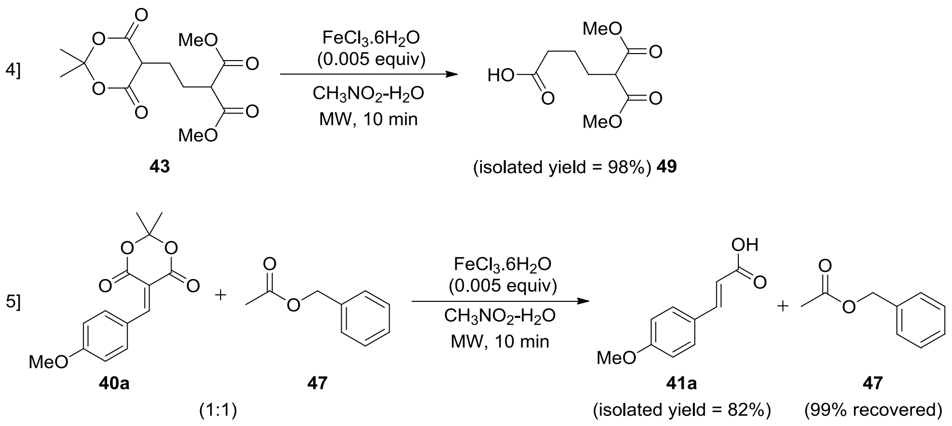


Scheme 3.21: Substrates for competitive experiments by various reactions

The compound **43** was synthesized by following the literature procedure[53] for similar compounds, in which enolate of malonate was generated which attacks on cyclopropane ring to afford **43** (eq 2). Methylation of hydrogenated alkylidene derivative **54** furnished the corresponding cyclic ester **45**. The acyclic alkylidene derivative **42** was hydrogenated to afford **46**. Similarly, the reaction of acetyl chloride and benzyl alcohol gave **47**.

Competition experiments were carried out with alkylidene acyclic 1,3-diesters (Scheme **3.22**, eq 1), substituted acyclic 1,3-diester (eq 2, 3 and 4) and an ester (eq 5) under optimized reaction condition to demonstrate the selectivity of the catalyst system towards cyclic 1,3-diesters. Initially for the competitive experiments we subjected derivatives of acyclic 1,3-diesters (**42** and **46**), and cyclic 1,3-diesters (**40a** and **45**) using the optimized catalytic protocol $FeCl_3 \cdot 6H_2O$ (0.005 equiv)-H_2O (1 equiv) in dry nitromethane under microwave irradiation for 3-10 min (eq 1–3). It is quite remarkable that catalyst system reacted exclusively with substituted cyclic 1,3-diesters (**40a** and **45**) and competitive substrates were significantly unreactive towards the catalyst. Unreacted substrates were recovered in almost quantitative yields (eq. 1–3).





Scheme 3.22: Competitive experiments

Also, when compound **43** containing both cyclic and acyclic 1,3-diester moieties (eq 4) was treated with the catalyst system, cyclic 1,3-diester part underwent selective decarboxylation to afford compound **49** in 98% yield. Unlike previously reported protocols this one pot catalytic approach is certainly very convenient, practical, cost effective and environmental friendly. Moreover, this method proved to be reproducible on gram scale (53 g), as exemplified by the synthesis of compound **51a**.

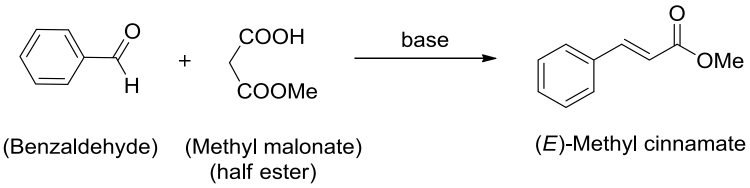
3.4 Conclusions

A methodology to achieve α,β-unsaturated carboxylic acids from derivatives of cyclic 1,3-diesters using an efficient catalytic protocol containing an inexpensive $FeCl_3 \cdot 6H_2O$ has been described. This method proved to be very rapid reliably selective with volatile by-products formation. Selective decarboxylation and esterification route enabled gram-scale synthesis, using very low catalyst loading (0.001 equiv). Simple approach gave an easy access to variety of α,β-unsaturated acids in good to excellent yields. This approach opens an avenue for a whole range of new chemical entities and molecules of high industrial value. Also, method effectively augments the biomass derived aldehydes into precursors for fuel additives.

Section B: Synthesis of α,β-unsaturated esters

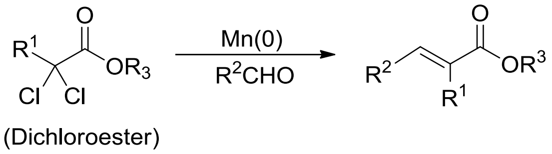
3.5 Introduction

The, α,β-unsaturated esters have been used as reagents and precursors of many compounds in organic synthesis. Unsaturated esters have been utilized as starting materials for 1,4-addition[54] reactions. *p*-Methoxycinnamates are commonly used as sunscreen chemical filters in industry and octyl methoxycinnamate (Octinoxate, OMC) is a common ingredient in most of the sunscreen lotions.[55] This molecule of commercial significance has been undoubtedly the subject of synthesis by various routes. List and co-workers recently reported[56] a method for the synthesis of (*E*)-α,β-unsaturated esters from malonate half esters and aldehydes (Scheme **3.23**), using Doebner-Knoevenagel condensation. The malonate half ester was condensed with aldehyde and the resulting Knoevenagel product on treatment with catalytic DMAP afforded α,β-unsaturated ester via decarboxylation. However, octinoxate was synthesized by the traditional transesterification of α,β-unsaturated esters, formed by this method. Another strategy was used for synthesis of α,β-unsaturated esters, in which decarboxylative Knoevenagel condensation was carried out between aldehydes and malonate half esters using bifunctional polymer catalyst.[57]



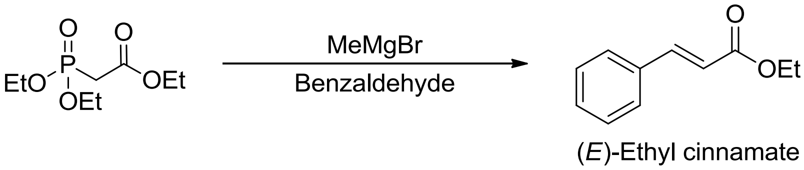
Scheme 3.23: The decarboxylative Knoevenagel-type reaction of malonate half esters with aldehyde

Less explored, active manganese has been successfully utilized for the synthesis of α,β-unsaturated esters.[58] The efficiency of Mn(0) as a catalyst has been demonstrated by the reaction α,α-dichloroesters with aldehydes to afford complete *E*-stereoselective α,β-unsaturated esters (Scheme **3.24**). The disubstituted and trisubstituted α,β-unsaturated esters have also been synthesized. Similarly, carbohydrate derived (*E*)-α,β-unsaturated esters have been synthesized by using chromium catalyst[59] using dichloroesters.



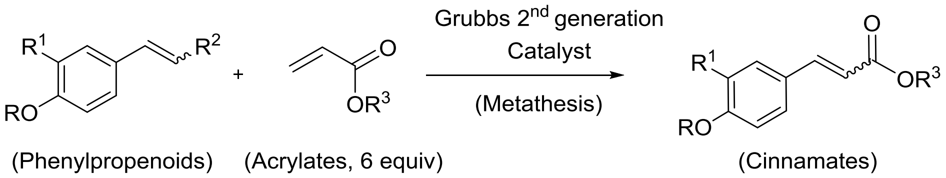
Scheme 3.24: Active Mn(0) in synthesis of α,β-unsaturated esters

Davies[60] and co-workers reported an elegant method for synthesis of α,β-unsaturated esters using Wadsworth-Emmons reaction. They described the MeMgBr promoted highly stereoselective synthesis of (*E*)-α,β-unsaturated esters (Scheme **3.25**). Results showed that the stereoselectivity can be heavily influenced by the nature of the metal counterion such as magnesium.



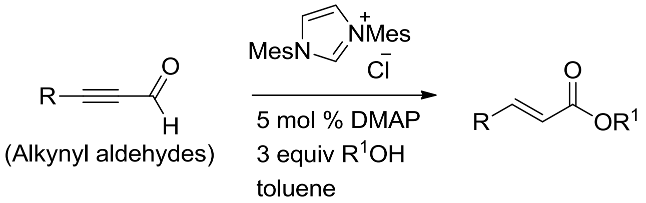
Scheme 3.25: Wadsworth-Emmons reaction promoted by MeMgBr

Olefin metathesis has been one of the most celebrated reactions in organic chemistry for constructing C=C double bonds. Naturally occurring phenylpropenoids from essential-oils[61] have been elegantly used in constructing building blocks of fine chemicals. To increase complexity of such materials cross-metathesis has been carried out between acrylates and phenylpropenoids to afford the corresponding cinnamates in good yields with excellent *E*-stereoselectivity (Scheme **3.26**).



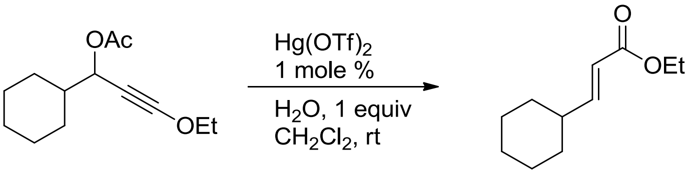
Scheme 3.26: Olefin metathesis of phenylpropenoids

Zeitler[62] developed a novel method for synthesis of α,β-unsaturated esters starting from alkynyl aldehydes catalyzed by *N*-heterocyclic carbene (NHC) (Scheme **3.27**). However, products were formed in variable stereoselectivity (*E:Z* varied from 80:20 to 95:5).



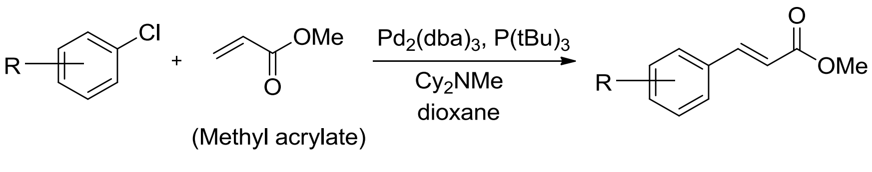
Scheme 3.27: Carbene catalyzed redox esterification

Nishizawa *et al*. reported[63] the reaction of alkylsubstituted *sec*-ethoxyalkynyl acetates with water catalyzed by $Hg(OTf)_2$ to afford α,β-unsaturated esters (Scheme **3.28**). This transformation was highly (*E*)-stereoselective with moderate yields. High catalytic turnover was observed in this transformation, but use of mercuric salt has been a major environmental concern.



Scheme 3.28: Hydration of *sec*-ethoxyalkynyl acetate

Fu and co-workers reported an improved catalyst system for the Heck coupling[64] of the unactivated aryl chlorides with acrylates to afford α,β-unsaturated esters (Scheme **3.29)**. Although, this reaction has a wide substrate scope and high stereoselectivity, different alkyl acrylates would be required in order to give a variety of cinnamate esters.

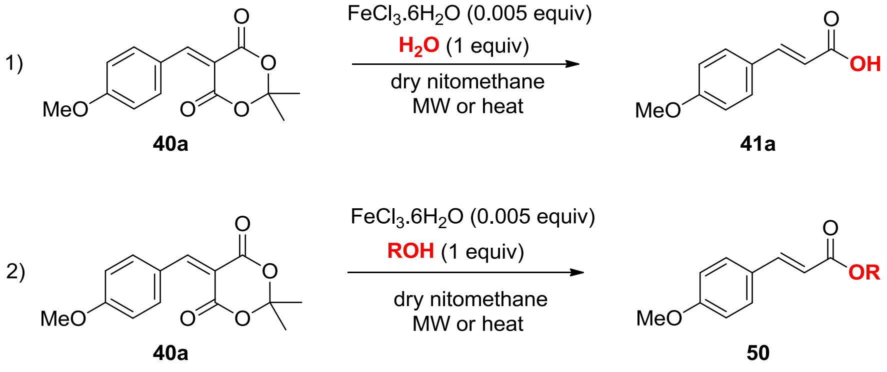


Scheme 3.29: Heck coupling for unsaturated esters

In spite of these available methods, there is a challenge to develop a cost-effective catalytic route for the synthesis of α,β-unsaturated esters. In this section, we have presented a convenient and economical novel synthetic procedure for the stereoselective synthesis of α,β-unsaturated esters from alkylidene Meldrum's acids and alcohols in presence of catalyst: $FeCl_3{\cdot}6H_2O$.

3.6 Results and Discussion

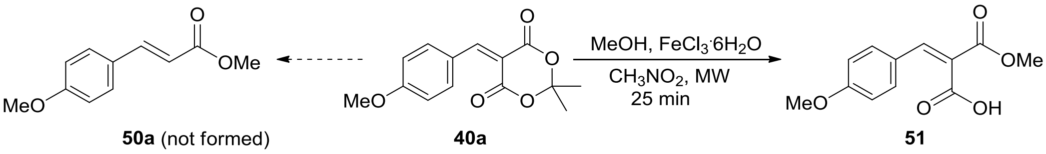
In earlier section (3.3 Section A) we described the novel approach for the synthesis of α,β-unsaturated acids.[65] Wherein, alkylidene Meldrum's acids (**40a–40j**, **40l**) on treatment with one equivalent of water in presence of catalytic amount of $FeCl_3{\cdot}6H_2O$ afforded the corresponding (*E*)-α,β-unsaturated acids (**41a–41j**, **41l**). This catalytic transformation suggested that water acted as a nucleophile by attacking cyclic 1,3-diester and thus facilitating the hydrolysis, and instantaneous of decarboxylation simultaneously with the aid of Lewis acid: $FeCl_3{\cdot}6H_2O$ (Scheme **3.30**, eq 1). We anticipated that similarly, the reaction of alkylidene Meldrum's acid (MA) with alcohols in the presence of catalytic $FeCl_3{\cdot}6H_2O$ would yield α,β-unsaturated esters. We believed that alcohol would react as a nucleophile under similar reaction conditions used for the synthesis of (*E*)-α,β-unsaturated acids (Scheme **3.30**, eq 2).



Scheme 3.30: Rationale for synthesis of α,β-unsaturated ester

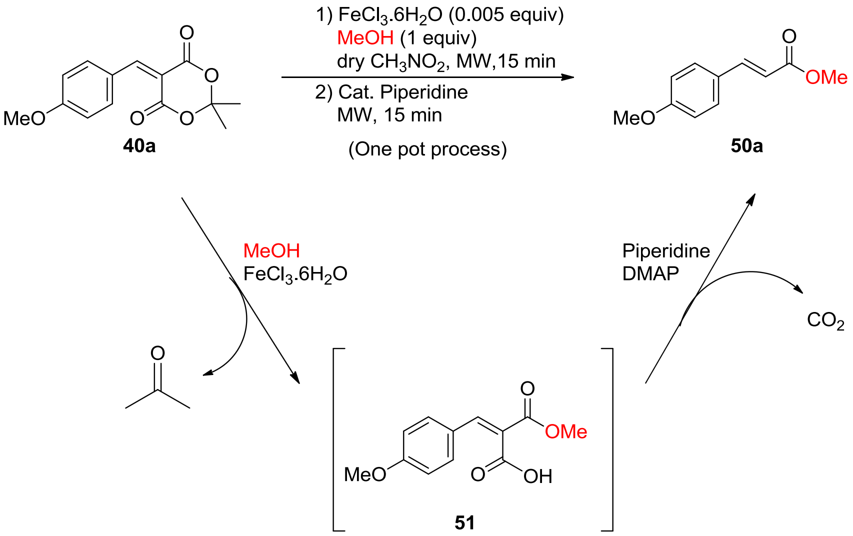
Earlier the bis-electrophilic nature of alkylidene Meldrum's acids (MA) has been explored for the synthesis of coumarins and chromones from phenols by Fillion's group (Scheme **3.4**). However, we believed that it would be a challenge to explore the controlled monoelectrophilic reactivity of alkylidene Meldrum's acids with alcohols.

In order to verify our hypothesis, we first examined the model reaction of *p*-methoxybenzylidene derivative of MA (**40a**) with MeOH (1 equiv) in presence of 0.005 equiv (0.5 mol %) $FeCl_3 \cdot 6H_2O$ in dry nitromethane under microwave irradiation (2.5 GHz, 15-25 min, Scheme **3.31**). However, instead of the expected methyl *p*-methoxycinnamate **50a**, we obtained the alkylidene malonate half-ester **51** as a product. The starting material **40a** was completely consumed and afforded **51**. Even, the prolonged microwave irradiation (2 h) of the reaction mixture did not facilitate decarboxylation of this half-ester **51.**



Scheme 3.31: Anticipated synthesis of α,β-unsaturated ester

We anticipated that ‘base’ may facilitate the facile decarboxylation by abstracting the proton from acid **51** thus leading to expected unsaturated ester (Scheme **3.32**). As expected, interestingly, alkylidene malonic acid half-ester **51** underwent facile decarboxylation on treatment with piperidine in dry CH_3NO_2 under microwave irradiation (15 min) to afford methyl *p*-methoxycinnamate **50a** in excellent yield (92%).



Scheme 3.32: Synthesis of *p*-methoxycinnamate

Encouraged by this initial success, we next carried out a one-pot, two-step synthesis of methyl *p*-methoxycinnamate **50a** starting from **40a** and MeOH (**52a**, 1 equiv). The reaction was carried out under microwave irradiation (15 min) in the presence of $FeCl_3{\cdot}6H_2O$ (0.005 equiv) in CH_3NO_2, followed by addition of piperidine and subsequent microwave irradiation (15 min). This reaction afforded **50a** in 94% yield (entry 1, Table **3.4**). Compound **50a** was characterized and it was found to be almost exclusively (*E*)-methyl cinnamate by ^{1}H-NMR (Fig. **3.8**).

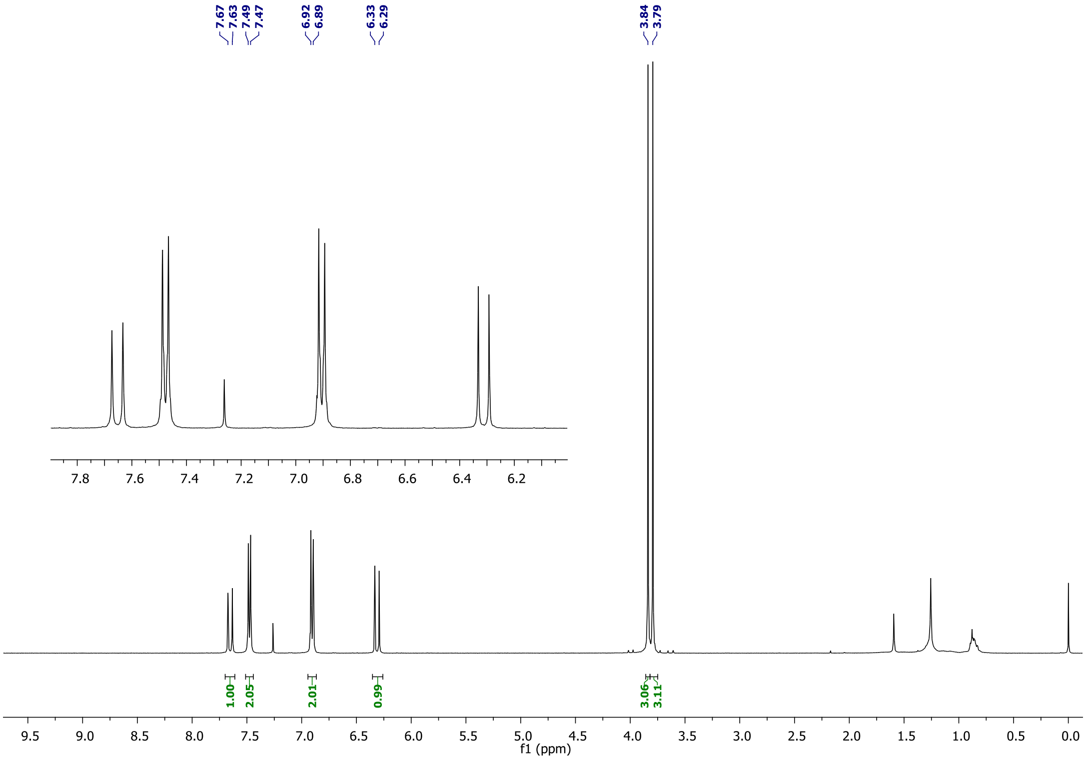
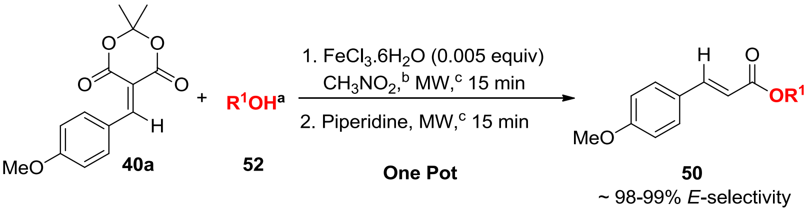
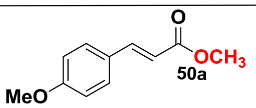
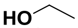
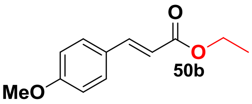
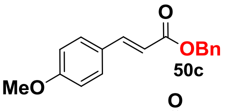
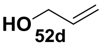
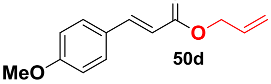
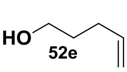
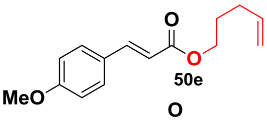
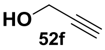
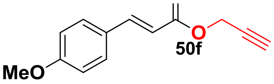
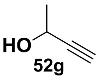
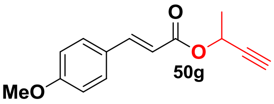
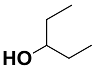
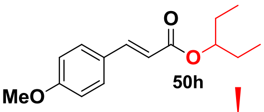
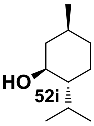
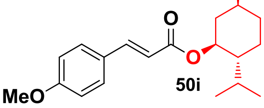
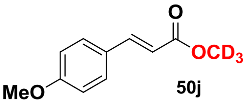
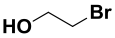
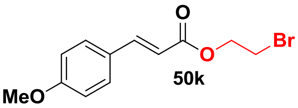
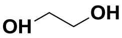
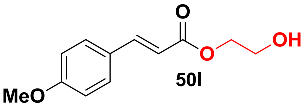


Fig **3.8**: ^{1}H NMR spectrum of compound **50a**

The catalytic conversion was neat and led to only volatile by-products. In a controlled blank experiment, reaction did not proceed in the absence of a catalyst ($FeCl_3{\cdot}6H_2O$) even after a prolonged reaction time (1 h). In order to expand the scope of this methodology, a range of primary alcohols, including alkenyl and alkynyl alcohols were treated with *p*-methoxybenzylidene derivative of MA (**40a**) under optimized conditions (Table **3.4**).

Table 3.4: Synthesis of various α,β-unsaturated esters

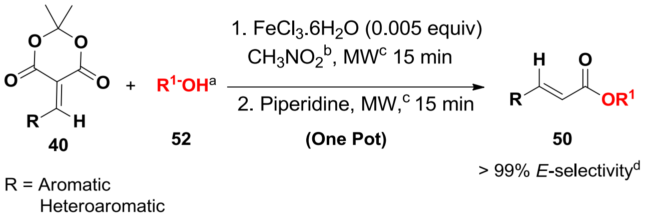


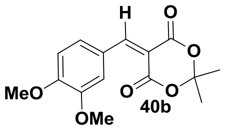
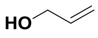
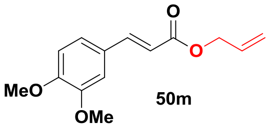
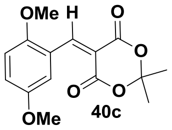
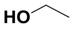
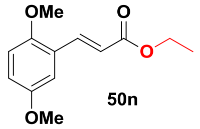
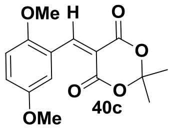
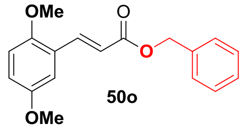
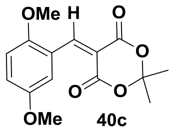
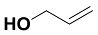
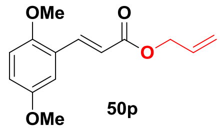
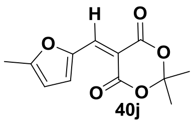
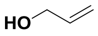
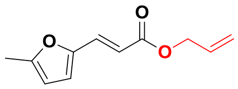
entry	substrate **40a**	alcohol (**R^{1}OH**) **52**	*p*-methoxycinnamate esters **50**	yield (%)
1	**40a**	**$HOCH_3$** **52a**	 **50a**	94
2	**40a**	 **52b**	 **50b**	96
3	**40a**	**BnOH** **52c**	 **50c**	79
4	**40a**	 **52d**	 **50d**	89
5	**40a**	 **52e**	 **50e**	96
6	**40a**	 **52f**	 **50f**	91
7	**40a**	 **52g**	 **50g**	74
8	**40a**	 **52h**	 **50h**	96
9	**40a**	 **52i**	 **50i**	71
10	**40a**	**$HOCD_3$** **52j**	 **50j**	94
11	**40a**	 **52k**	 **50k**	57
12	**40a**	 **52l**	 **50l**	71

[a]1 equiv Alcohol (R^1-OH), [b]anhydrous CH_3NO_2 as solvent, [c]Microwave irradiation (2.5 GHz,100 W), [d]99% *E*-selectivity observed for (50a, 50b, 50e, 50g, 50h, 50i, 50k, 50l); ~98% E-selectivity for 50d, 50j; however 50c, 50f gave an *E/Z* = 94:6 ratio (NMR analysis)

The corresponding α,β-unsaturated esters (**50b–50f**) were produced in one pot in moderate to excellent yields (79 to 96%). Interestingly, secondary alcohols **52g** and **52h** (entries 7 & 8, Table **3.4**) also reacted smoothly with **40a** to furnish the corresponding unsaturated esters (**50g**, **50h**). We next explored the procedure using a chiral alcohol (+)-menthol (**52i**) to afford the corresponding chiral ester **50i** in 71% yield (entry 9, Table **3.4**). The compatibility of the methodology with a bromine-substituted alcohol was also investigated and the corresponding unsaturated ester **50k** was obtained in 57% yield (entry 11, Table **3.4**). Notably, we observed that (*E*)-stereoisomers were formed as major products (~98-99%) using this protocol, however, compounds **50c** and **50f** were obtained in an *E/Z* = 94:6 ratio. *E*-stereochemistry was assigned on the basis on ^{1}H-NMR coupling constants. In order to establish the generality and efficiency of this protocol different alkylidene MA derivatives were prepared (Table **3.5**).

Table 3.5: Substrate scope

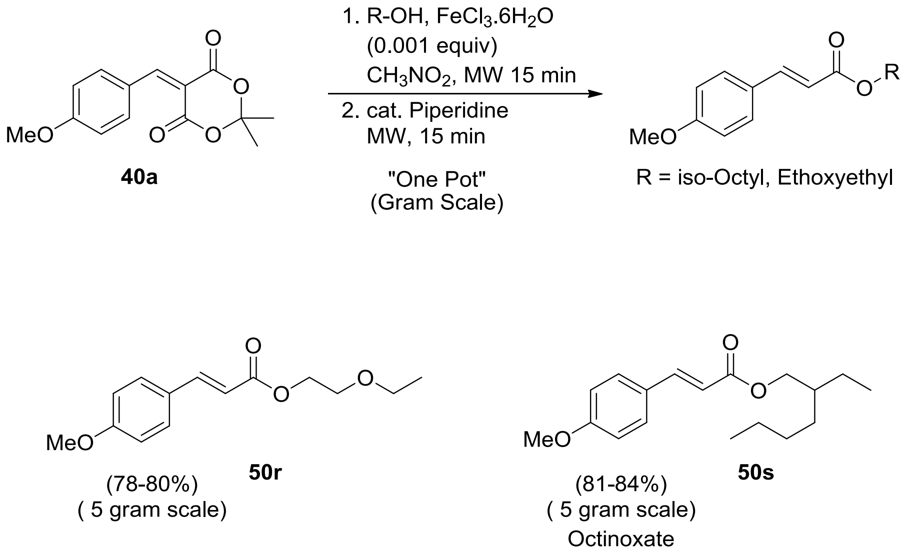


entry	substrate	alcohol (R^{1}OH) **52**	α,β-unsaturated esters **50**	yield (%)
1	 **40b**	 **52d**	 **50m**	74
2	 **40c**	 **52b**	 **50n**	84
3	 **40c**	BnOH **52c**	 **50o**	63
4	 **40c**	 **52d**	 **50p**	83
5	 **40j**	 **52d**	 **50q**	69

[a] 1 equiv alcohol, [b] anhydrous CH_3NO_2 as solvent, [c] Microwave irradiation (2.5 GHz, 100 W), [d] >99% *E*-selectivity observed in 50m-50q

Compounds **40b**, **40c** and **40j** when treated with alcohols (**52b**, **52c** and **52d**) in the presence of 0.005 equiv $FeCl_3 \cdot 6H_2O$ afforded the corresponding α,β-unsaturated esters (**50m–50q**) in good yields (Table **3.5**). Aromatic as well as heteroaromatic substrates reacted efficiently. Moreover, different functional groups and substituents did not affect the rate or yield of reactions. Using this novel protocol various α,β-unsaturated esters were synthesized efficiently in good *E*-stereoselectivity.[66]

To make this approach of wider applicability, we planned to synthesize some of the well known sun screen filters (**50r**, **50s**) (Scheme **3.33**). Treatment of compound **40a** with 2-ethoxyethanol or 2-ethyl-1-hexanol under optimized catalytic conditions afforded expected compounds **50r**, **50s** in excellent yields (78%, 81%) in relatively quick time (15 min). In order to make this approach more practical on gram scale we treated compound **40a** (5 gram) under similar reaction conditions to furnish the corresponding (**50r**, **50s**)[67] in very good yields (80, 84%). It is noteworthy to mention that catalyst loading was reduced from 0.005 equiv to 0.001 equiv (0.5 to 0.1 mol %), when reaction was carried out on a larger scale.



Scheme 3.33: Synthesis of Sunscreen filters

3.7 Conclusions

In conclusion, we have described an efficient procedure to generate α,β-unsaturated esters from alkylidene Meldrum's Acids using an inexpensive catalyst. Microwave assisted one-pot, two-step synthesis of α,β-unsaturated esters is relatively rapid, high yielding and reliably selective. Reactions are neat and by-products formed are volatile. The novel protocol described for the selective esterification and decarboxylation uses very low catalyst loading (0.001–0.005 equiv; 0.1–0.5 mol %). This methodology provides an easy access to a range of α,β-unsaturated esters, including compounds of high industrial value, and on a gram scale.

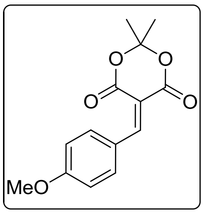
3.8 Experimental section

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C-NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF. IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. All microwave irradiation experiments were performed using CEM Discover Labmate. All reactions were carried out in dried glassware. Absolute nitromethane was used for the reaction. All purchased chemicals were used without further purification. Column chromatography was carried out using silica gel.

Section A

General procedure A: alkylidene Meldrum's acids

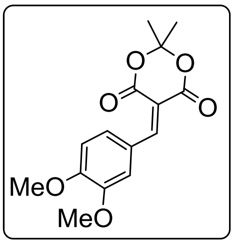
5-(4-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (40a)



The stirred mixture of Meldrum's acid (0.5 g, 3.47 mmol) and anisaldehyde (0.42 mL, 3.47 mmol) in water (15 mL) was heated at 75 °C for 2 h. Then the reaction mixture was cooled to room temperature. The solid formed was filtered and washed with water (2 X 30 mL) and residue was further purified by re-crystallization from hot methanol to afford 40a as a yellow solid (0.83 g, 91% yield): mp = 124-125 °C; R_f = 0.5 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1712, 1553, 1261, 1162, 1013; δ_H (400 MHz, $CDCl_3$) 8.38 (s, 1H), 8.24 (d, *J* = 8 Hz, 2H), 7 (d, *J* = 8 Hz, 2H), 3.91 (s, 3H), 1.79 (s, 6H); δ_C (100 MHz, $CDCl_3$) 164.6, 164.1, 160.5, 157.9, 137.6, 124.7, 114.4, 110.8, 104.2, 55.7, 27.5; HRMS (ESI TOF) *m/z* calcd. for $C_{14}H_{14}O_5Na$ [M + Na]$^+$ 285.0739, found 285.0739.

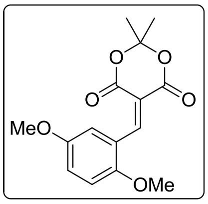
5-(3,4-Dimethoxybenzylidene)-2,2-dimethyl-1, 3-dioxane-4, 6-dione (40b)

The compound 40b was synthesized following the general procedure A described for 40a; The compound 40b was obtained as a yellow solid (0.82 g, 81% yield): mp = 156-



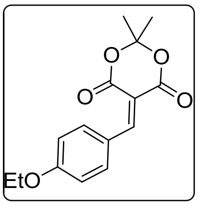
157 °C; R_f = 0.3 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1714, 1556, 1510, 1268, 1149; δ_H (400 MHz, $CDCl_3$) 8.37 (s, 1H), 8.31 (d, *J* = 4 Hz, 1H), 7.66 (q, *J* = 8 Hz, 1H), 6.97 (d, *J* = 8 Hz, 1H), 4 (s, 3H), 3.96 (s, 3H), 1.80 (s, 6H); δ_C (100 MHz, $CDCl_3$) 164.2, 160.7, 158.3, 154.7, 148.7, 132.7, 125.1, 115.6, 110.6, 110.5, 104.2, 56.2, 56, 27.5; HRMS (ESI TOF) *m/z* calcd. for $C_{15}H_{16}O_6Na$ [M + Na]$^+$ 315.0845, found 315.0841.

5-(2,5-Dimethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (40c)



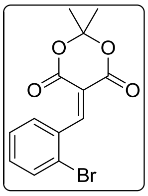
The compound 40c was was synthesized following the general procedure A described for 40a; The compound 40c was obtained as a orange solid (0.85 g, 84% yield): mp = 124-126 °C; R_f = 0.4 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1724, 1577, 1493, 1430, 1181; δ_H (400 MHz, $CDCl_3$) 8.73 (s, 1H), 7.69 (d, *J* = 4 Hz, 1H), 7.11 (q, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 1.81 (s, 6H); δ_C (100 MHz, $CDCl_3$) 163.3, 160.1, 154.4, 152.8, 152.4, 122.1, 121.4, 116, 115, 112, 104.4, 56.1, 55.9, 27.5; HRMS (ESI TOF) *m/z* calcd. for $C_{15}H_{16}O_6Na$ [M + Na]$^+$ 315.0845, found 315.0843.

5-(4-Ethoxybenzylidene)-2, 2-dimethyl-1,3-dioxane-4,6-dione (40d)



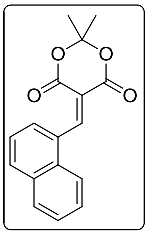
The compound 40d was synthesized following the general procedure A described for 40a; The compound 40d was obtained as a yellow solid (0.86 g, 90% yield): mp = 119-120 °C; R_f = 0.5 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1718, 1554, 1261, 1163; δ_H (400 MHz, $CDCl_3$) 8.35 (s, 1H), 8.21 (d, *J* = 8 Hz, 2H), 6.95 (d, *J* = 8 Hz, 2H), 4.15 (q, *J* = 8 Hz, 2H), 1.77 (s, 6H), 1.46 (t, *J* = 8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 164.1, 160.5, 158, 137.7, 124.5, 114.8, 110.5, 104.1, 64.1, 27.5, 14.6; HRMS (ESI TOF) *m/z* calcd. for $C_{15}H_{16}O_5Na$ [M + Na]$^+$ 299.0895, found 299.0896.

5-(2-Bromobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (40e)



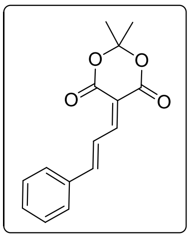
The compound 40e was synthesized following the general procedure A described for 40a; The compound 40e was obtained as a white solid (0.8 g, 74% yield): mp = 132-134 °C; R_f = 0.65 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1732, 1618, 1277, 1194; δ_H (400 MHz, $CDCl_3$) 8.61 (s, 1H), 7.76-7.74 (m, 1H), 7.68-7.65 (m, 1H), 7.41-7.32 (m, 2H), 1.83 (s, 6H); δ_C (100 MHz, $CDCl_3$) 162.1, 158.9, 156.6, 132.8, 132.81, 131.7, 127, 124.9, 117.8, 105, 27.8; HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{11}BrO_4Na$ $[M + Na]^+$ 332.9738, found 332.9741.

2,2-dimethyl-5-(naphthalen-1-ylmethylene)-1,3-dioxane-4,6-dione (40f)



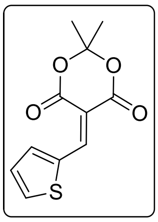
The compound 40f was synthesized following the general procedure A described for 40a; The compound 40f was obtained as a yellow solid (0.44 g, 45% yield): mp = 126-127 °C; R_f = 0.6 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1728, 1603, 1285, 1201; δ_H (400 MHz, $CDCl_3$) 9.22 (s, 1H), 8.03-7.91 (m, 3H), 7.64-7.52 (m, 4H), 1.86 (s, 6H); δ_C (100 MHz, $CDCl_3$) 162.8, 159.4, 156.5, 136.7, 135.3, 133.2, 129.9, 129.1, 129, 127.8, 126.7, 124.9, 123.6, 116.9, 104.8, 27.8; HRMS (ESI TOF) *m/z* calcd. for $C_{17}H_{14}O_4Na$ $[M + Na]^+$ 305.0790, found 305.0795.

(*E*)-2,2-Dimethyl-5-(3-phenylallylidene)-1,3-dioxane-4,6-dione (40g)



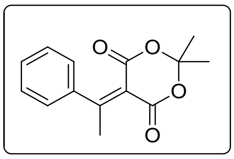
The compound 40g was synthesized following the general procedure A described for 40a; The compound 40g was obtained as a yellow solid (0.87 g, 97% yield): mp = 110-112 °C; R_f = 0.6 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1714, 1566, 1371, 1275, 1161; δ_H (400 MHz, $CDCl_3$) 8.36-8.17 (m, 2H), 7.68-7.66 (m, 2H), 7.45 (m, 4H), 1.77 (s, 6H); δ_C (100 MHz, $CDCl_3$) 162.9, 160.7, 158, 154.4, 134.9, 131.8, 129.2, 129.1, 124.5, 111.4, 104.7, 27.7; HRMS (ESI TOF) *m/z* calcd. for $C_{15}H_{14}O_4Na$ $[M + Na]^+$ 281.0790, found 281.0788.

2,2-Dimethyl-5-(thiophen-2-ylmethylene)-1,3-dioxane-4,6-dione (40h)



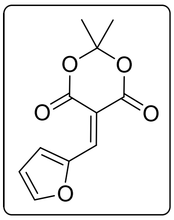
The compound 40h was synthesized following the general procedure A described for 40a; The compound 40h was obtained as a white solid (0.54 g, 65% yield): mp = 196-197 °C; R_f = 0.6 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 3093, 1710, 1614, 1554, 1387, 1325, 1186; δ_H (400 MHz, $CDCl_3$) 8.67 (s, 1H), 8.03 (d, J = 4 Hz, 1H), 7.91 (d, J = 4 Hz, 1H), 7.29-7.26 (m, 1H), 1.78 (s, 6H); δ_C (100 MHz, $CDCl_3$) 163.5, 161.1, 149.1, 144.9, 141.8, 136.4, 128.3, 107, 104.6, 27.5; HRMS (ESI TOF) *m/z* calcd. for $C_{11}H_{10}O_4SNa$ $[M + Na]^+$ 261.0197, found 261.0193.

2,2-Dimethyl-5-(1-phenylethylidene)-1, 3-dioxane-4,6-dione (40l)



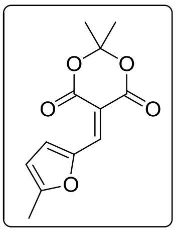
The compound 40k was prepared following the literature procedure; White solid (0.55 g, 47% yield): mp = 108-109 °C; R_f = 0.66 Pet. Ether/EtOAc (50:50); IR (neat) cm^{-1}: 2999, 2943, 1726, 1595, 1274, 1202; δ_H (400 MHz, $CDCl_3$) 7.38 (m, 3H), 7.19-7.16 (m, 2H), 2.71 (s, 3H), 1.82 (s, 6H); δ_C (100 MHz, $CDCl_3$) 173.3, 161.3, 160.5, 141.9, 129.6, 128.7, 126, 117, 104, 27.5, 26.5; HRMS (ESI TOF) *m/z* calcd. for $C_{14}H_{14}O_4Na$ $[M + Na]^+$ 269.0790, found 269.0786.

5-(Furan-2-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (40i)



The compound 40i was synthesized following the general procedure A described for 40a; The compound 40i was obtained as a yellow solid (0.73 g, 94% yield): mp = 93-95 °C; R_f = 0.55 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1713, 1583, 1457, 1274; δ_H (400 MHz, $CDCl_3$) 8.47 (d, *J* = 4 Hz, 1H), 8.36 (s, 1H), 7.85 (s, 1H), 6.76 (d, *J* = 4 Hz, 1H), 1.77 (s, 6H); δ_C (100 MHz, $CDCl_3$) 163.2, 160.2, 150.4, 150.2, 141.2, 128.1, 115.2, 107.5, 104.5, 27.5; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{10}O_5Na$ $[M + Na]^+$ 245.0426, found 245.0422.

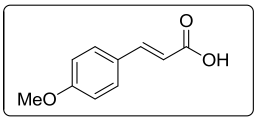
2,2-Dimethyl-5-((5-methylfuran-2-yl)methylene)-1,3-dioxane-4,6-dione (40j)



The compound 1k was synthesized following the general procedure A described for 1a; The compound 1k was obtained as a yellow solid (0.68 g, 83% yield): mp = 112-114 °C; R_f = 0.6 Pet. Ether/EtOAc (65:35); IR (neat) cm^{-1}: 1712, 1588, 1556, 1500, 1278, 1232, 1194; δ_H (400 MHz, $CDCl_3$) 8.47 (d, *J* = 4 Hz, 1H), 8.29 (s, 1H), 6.44 (d, *J* = 4 Hz, 1H), 2.48 (s, 3H), 1.76 (s, 6H); δ_C (100 MHz, $CDCl_3$) 163.7, 163.1, 160.6, 149.4, 140.7, 131, 113.1, 104.8, 104.2, 27.5, 14.6; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{12}O_5Na$ $[M + Na]^+$ 259.0582, found 259.0582.

General procedure B: Conventional Heating

(*E*)-3-(4-methoxyphenyl)acrylic acid (41a)

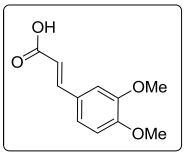


A sealed (capped) pressure tube (Ace) containing a mixture of 40a (0.2 g, 0.76 mmol), catalyst $FeCl_3.6H_2O$ (1 mg, 0.0038 mmol) and H_2O (14 µL, 0.76 mmol) in anhydrous nitromethane (2 mL), was heated at 110 °C for 45 min, after which the reaction mixture was allowed cool to room temperature. Then, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography Pet. Ether:EtOAc (50:50 to 10: 90) to afford 41a as white solid (87% yield).

General procedure C: Microwave Heating

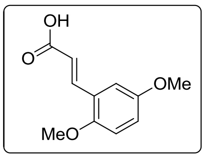
A sealed (capped) pressure tube (Ace) containing a mixture of 40a (0.2 g, 0.76 mmol), catalyst- $FeCl_3.6H_2O$ (1 mg, 0.0038 mmol) and H_2O (14 µL, 0.76 mmol) in anhydrous nitromethane (2 mL), was placed in a microwave reactor (2.5 GHz, 250 W). The reaction mixture was microwaved for 3-5 min. Completion of the reaction was monitored by thin layer chromatography. Then, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography Pet. Ether/EtOAc (50:50 to 10: 90) to afford 41a as white solid. (0.12 g, 88% yield): mp = 176-177 °C; R_f = 0.4 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 2928, 2842, 1679, 1625, 1511, 1254; δ_H (400 MHz, $CDCl_3$) 7.76 (d, *J* = 16 Hz, 1H), 7.52 (d, *J* = 8 Hz, 2H), 6.93 (d, *J* = 8 Hz, 2H), 6.34 (d, *J* = 16 Hz, 1H), 3.85 (s, 3H); δ_C (100 MHz, $CDCl_3$) 172.5, 161.9, 146.9, 130.3, 126.9, 114.8, 114.5, 55.6; HRMS (ESI TOF) *m/z* calcd for $C_{10}H_{10}O_3Na$ $[M + Na]^+$ 201.0528, found 201.0526.

(*E*)-3-(3,4-dimethoxyphenyl)acrylic acid (41b)



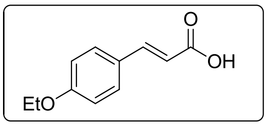
The compound 41b was synthesized following both general procedures B and C described for 41a. The compound 41b was obtained as a white solid (109 mg, 77%; 95 mg, 67% yield): R_f = 0.12 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 3045, 1682, 1620; δ_H (400 MHz, $CDCl_3$) 7.75 (d, *J* = 16 Hz, 1H), 7.15-7.07 (m, 2H), 6.9 (d, *J* = 8 Hz, 1H), 6.34 (d, *J* = 16 Hz, 1H), 3.93 (s, 6H).

(*E*)-3-(2,5-dimethoxyphenyl)acrylic acid (41c)



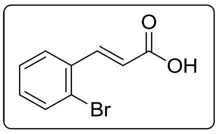
The compound 41c was synthesized following both general procedures B and C described for 41a. The compound 41c was obtained as a white solid (124 mg, 87% yiled; 120 mg, 84% yield): R_f = 0.15 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 3040, 1690, 1620; δ_H (400 MHz, $CDCl_3$) 8.09 (d, *J* = 16 Hz, 1H), 7.07 (d, *J* = 4 Hz, 1H), 6.96-6.95 (m, 1H), 6.88-6.85 (m, 1H), 6.54 (d, *J* = 16 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H); δ_C (100 MHz, $CDCl_3$) 172.5, 153.5, 153.1, 142.4, 123.5, 117.9, 117.8, 113.5, 112.6, 56.1, 55.9; HRMS (ESI TOF) *m/z* calcd. for $C_{11}H_{13}O_4$ $[M + H]^+$ 209.0814, found 209.0811.

(*E*)-3-(4-ethoxyphenyl) acrylic acid (41)



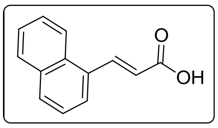
The compound 41d was synthesized following both general procedures B and C described for 41a. The compound 41d was obtained as a white solid (122 mg, 87% yield; 126 mg, 90% yield): mp = 192-194 °C; R_f = 0.4 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 2976, 2926, 1673, 1600, 1213, 1175; δ_H (200 MHz, $CDCl_3$) 7.78 (d, J = 16 Hz, 1H), 7.52 (d, J = 10 Hz, 2H), 6.93 (d, J = 10 Hz, 2H), 6.35 (d, J = 16 Hz, 1H), 4.13 (q, J = 8 Hz, 2H), 1.44 (t, J = 8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 172.3, 161.3, 146.9, 130.3, 126.7, 115, 114.5, 63.8, 14.9; HRMS (ESI TOF) *m/z* calcd. for $C_{11}H_{13}O_3$ $[M + H]^+$ 193.0865, found 193.0860.

(*E*)-3-(2-bromophenyl)acrylic acid (41e)



The compound 41e was synthesized following both general procedures B and C described for 41a. The compound 41e was obtained as a white solid (128 mg, 87% yield; 132 mg, 90% yield): mp = 224-225 °C; R_f = 0.2 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 2925, 1686, 1331; δ_H (400 MHz, DMSO-d_6) 7.91-7.72 (m, 2H), 7.70 (d, J = 4 Hz, 1H), 7.45-7.33 (m, 2H), 6.59 (d, J = 16 Hz, 1H); δ_C (100 MHz, DMSO-d_6) 167.1, 141.4, 133.5, 133.2, 131.9, 128.4, 128.3, 124.5, 122.4; HRMS (ESI TOF) *m/z* calcd. for $C_9H_8O_2Br$ $[M + H]^+$ 226.9708, found 226.9708.

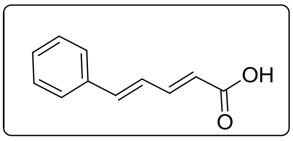
(*E*)-3-(naphthalen-1-yl)acrylic acid (41f)



The compound 41f was synthesized following both general procedures B and C described for 41a. The compound 41f was obtained as a white solid (117 mg, 83% yield; 107 mg, 76 % yield): mp = 215-217 °C; R_f = 0.2 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 3048, 2924, 1682, 1619; δ_H (200 MHz, $CDCl_3$) 8.71 (d, J = 16 Hz, 1H), 7.96 (d, J = 8 Hz, 1H) 7.89-7.80 (m, 3H), 7.62-7.52 (m, 3H), 6.62 (d, J = 16 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 171.4, 144.2, 133.4, 131.4, 131.2, 129.3, 128.9, 127.2, 126.5, 125.6, 125.5, 123.4, 119.7; HRMS (ESI TOF) *m/z* calcd. for $C_{13}H_{10}O_2Na$ $[M + Na]^+$ 221.0578, found 221.0574.

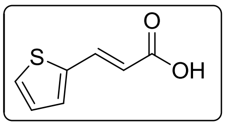
(2*E*, 4*E*)-5-phenylpenta-2,4-dienoic acid (41g)

The compound 41g was synthesized following both general procedures B and C described for 41a. The compound 41g was obtained as a white solid (116 mg, 87%



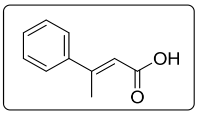
yield; 106 mg, 79% yield): mp = 163-164 °C; R_f = 0.35 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 3045, 1695, 1612; δ_H (400 MHz, $CDCl_3$) 7.58-7.47 (m, 3H), 7.40-7.33 (m, 3H), 6.99-6.87 (m, 2H), 6.03 (d, J = 16 Hz, 1H); HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{11}O_2$ [M + H]$^+$ 175.0759, found 175.0759.

(*E*)-3-(thiophen-2-yl)acrylic acid (41h)



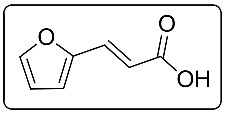
The compound 41h was synthesized following both general procedures B and C described for 41a. The compound 41h was obtained as a white solid (114 mg, 87% yield; 110 mg, 84% yield): mp = 148-150 °C; R_f = 0.3 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 2927, 2572, 1675, 1613; δ_H (200 MHz, $CDCl_3$) 7.93 (d, J = 16 Hz, 1H), 7.58-7.42 (m, 1H), 7.32-7.18 (m, 1H), 7.10-7.06 (m, 1H), 6.28 (d, J = 16 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 172.2, 139.5, 131.8, 129.5, 128.4, 126.8, 116; HRMS (ESI TOF) *m/z* calcd. for $C_7H_7O_2S$ [M + H]$^+$ 155.0167, found 155.0163.

(*E*)-3-phenylbut-2-enoic acid (41k)



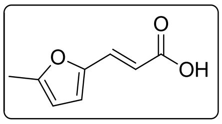
The compound 41k was synthesized following both general procedures B and C described for 41a. The compound 41k was obtained as a white solid (115 mg, 87% yield; 120 mg, 91% yield): mp = 98-100 °C; R_f = 0.44 Pet. Ether/EtOAc/AcOH (5:5:1); IR (neat) cm^{-1}: 3071, 1680, 1622; δ_H (400 MHz, $CDCl_3$) 7.51-7.48 (m, 2H), 7.41-7.39 (m, 3H), 6.17 (d, J = 1.4 Hz, 1H), 2.60 (d, J = 1.4 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 171.8, 158.7, 142.1, 129.5, 128.7, 126.6, 116.4, 18.5; HRMS (ESI TOF) *m/z* calcd for $C_{10}H_{11}O_2$ [M + H]$^+$ 163.0759, found 163.0760.

(*E*)-3-(furan-2-yl)acrylic acid (41i)



The compound 41i was synthesized following both general procedures B and C described for 41a. The compound 41i was obtained as a white solid (101 mg, 81% yield; 102 mg, 82% yield): mp = 148-149 °C; R_f = 0.3 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 2923, 2854, 1693, 1627, 1311, 1270, 1227; δ_H (400 MHz, $CDCl_3$) 7.75-7.51 (m, 2H), 6.68 (d, J = 4 Hz, 1H), 6.50-6.49 (m, 1H), 6.34 (d, J = 16 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 172.7, 150.8, 145.5, 133.2, 116, 115, 112.6; HRMS (ESI TOF) *m/z* calcd. for $C_7H_8O_3$ [M + H]$^+$ 139.0395, found 139.0402.

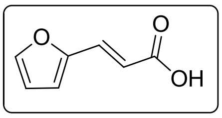
(*E*)-3-(5-methylfuran-2-yl) acrylic acid (41j)



The compound 41j was synthesized following both general procedures B and C described for 40a; The compound 41j was obtained as a white solid (94 mg, 76% yield; 84 mg, 66% yield): mp = 154-156 °C; R_f = 0.35 Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 2930, 1680, 1630; δ_H (400 MHz, $CDCl_3$) 7.46 (d, *J* = 16 Hz, 1H), 6.57 (d, *J* = 4 Hz, 1H), 6.24 (d, *J* = 16 Hz, 1H), 6.11-6.10 (m, 1H), 2.36 (s, 3H); δ_C (100 MHz, $CDCl_3$) 172.7, 156.4, 149.4, 133.2, 117.8, 113, 109.2, 14.1; HRMS (ESI TOF) *m/z* calcd. for $C_8H_8O_3Na$ $[M + Na]^+$ 175.0371, found 175.0347.

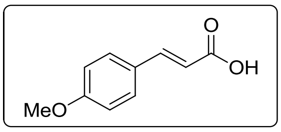
Refluxing Condition: Gram scale Synthesis

(*E*)-3-(furan-2-yl)acrylic acid (41i)



A mixture of 40i (1.5 g, 6.75 mmol), catalyst $FeCl_3.6H_2O$ (1.8 mg, 0.00675 mmol, 0.001 equiv.) and H_2O (122 μL, 6.75 mmol, 1 equiv.) in dry nitromethane (15 mL), was refluxed in a round bottomed flask at 110 ^oC for 3 h with a guard tube on the top. After which the reaction mixture was allowed cool to room temperature. Then, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography Pet. Ether/EtOAc (50:50 to 10: 90) to afford 41i in 85% yield.

Procedure for Gram Scale Synthesis of 41a: (*E*)-3-(4-methoxyphenyl)acrylic acid



A mixture of 40a (53 g, 202 mmol), catalyst $FeCl_3.6H_2O$ (35 mg, 0.2 mmol, 0.0006 equiv) and H_2O (3.6 mL, 0.2 mmol, 1 equiv) in dry nitromethane (350 mL), was refluxed in a round bottomed flask at 110 ^oC for 6.5 h with a guard on the top. After which the reaction mixture was allowed cool to room temperature. Expected product crystallized out slowly upon cooling. Then, the solvent was removed under reduced pressure and then the residue was dissolved in sodium bicarbonate solution and extracted with ethyl acetate (60 ml x 3). Then the water layer was acidified by dil. HCl (till solution turns acidic pH 2-3). Then the aqueous layer was extracted with ethyl acetate (60 mL X 5). The organic layer was evaporated under pressure to afford compound 41a in 80% yield (29 g). The compound 41a was quite pure and did not require further purification.

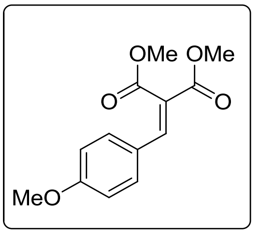
Note:

(a) The amount of catalyst (**(**$FeCl_3.6H_2O$) was lowered to 0.0006 equiv in the large scale

(b) In order to avoid side product formation and to improve the yield we optimized the procedure by adding the required amount of water in portion wise (500 μL for 1 h) over a period of 6 h and monitored the reaction till the complete conversion, instead of adding required amount of water at the beginning.

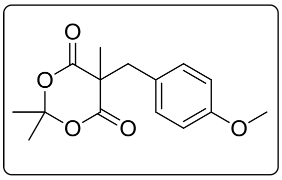
Substrates for Competitive Experiments

Dimethyl 2-(4-methoxybenzylidene)malonate (42)



To a stirred mixture of dimethyl malonate (2 g, 15.14 mmol) and 4-anisaldehyde (1.84 mL, 15.14 mmol) in benzene (50 mL), piperidine (15 μL, 0.15 mmol) and acetic acid (17 μL, 0.3 mmol) were added. The reaction mixture was refluxed using Dean-Stark apparatus to remove water formed during the course of the reaction. After completion of reaction (4 h), benzene was evaporated under vacuum and the residue was purified by flash chromatography over silica gel by eluting with Pet. Ether/EtOAc (95:5 to 70:30) to afford 42 as a white solid (2.9 g, 77% yield). $R_f = 0.7$ Pet. Ether:EtOAc (50:50); mp = 61-62 °C; IR (neat) cm^{-1}: 3004, 2953, 2842, 1721, 1598, 831; δ_H (400 MHz, $CDCl_3$) 7.71 (s, 1H), 7.40 (d, J = 8 Hz, 2H), 6.91 (d, J = 8 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 6H); δ_C (100 MHz, $CDCl_3$) 167.8, 165, 161.8, 142.8, 131.7, 125.4, 122.8, 114.5, 55.5, 52.8, 52.7; HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{14}O_5$ [M + Na]$^+$ 273.0739, found 273.0747.

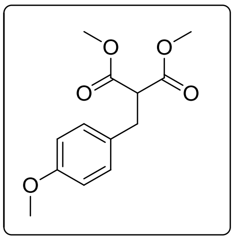
5-(4-Methoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (45)



The compound 45 was prepared by following the literature procedure (Ref. 6); Compound 45 was obtained as a white solid (1 g, 90% yield): mp = 100-102 °C; $R_f = 0.8$ Pet. Ether/EtOAc (50:50); IR (neat) cm^{-1}: 2997, 2939, 2839, 1738, 1512, 1275, 1247; δ_H (400 MHz, $CDCl_3$) 7.08 (d, J = 8 Hz, 2H), 6.78 (d, J = 8 Hz, 2H), 3.73 (s, 3H), 3.25 (s, 2H), 1.7 (s, 3H), 1.58 (s, 3H), 0.95 (s, 3H); δ_C (100 MHz, $CDCl_3$) 170.1, 159.3, 131.3, 127.5, 114.2, 105.4, 55.4, 52.5, 44.3, 29.5, 28.6, 25.8; HRMS (ESI TOF) *m/z* calcd. for $C_{15}H_{18}O_5$ [M + Na]$^+$ 301.1052, found 301.1053.

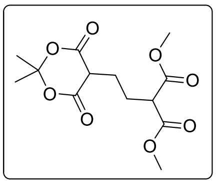
Dimethyl 2-(4-methoxybenzyl)malonate (46)

The mixture of 46 (1 g) and 10% Pd/C (10 % w/w, 100 mg) in MeOH (10 mL) were stirred at room temperature in hydrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of reaction 1 h, the solution was filtered through a



Celite bed and the filtrate was evaporated under reduced pressure. Then the residue was purified over silica gel by eluting with Pet. Ether/EtOAc (95:5 to 75:25) to afford 46 as a colorless oil (1 g, 99% yield). R_f = 0.75 Pet. Ether/EtOAc (50:50); IR (neat) cm^{-1}: 3004, 2954, 2842, 1736, 1512, 1242, 1147, 1027; δ_H (400 MHz, $CDCl_3$) 7.06 (d, *J* = 8Hz, 2H), 6.77 (d, *J* = 8Hz, 2H), 3.70 (s, 3H), 3.63-3.57 (m, 7H), 3.12 (d, *J* = 8Hz, 2H); δ_C (100 MHz, $CDCl_3$) 169.2, 158.4, 129.7, 129.6, 113.9, 55.1, 53.8, 52.4, 33.9; HRMS (ESI TOF) *m/z* calcd. for $C_{13}H_{16}O_5$ $[M + Na]^+$ 275.0895, found 275.0899.

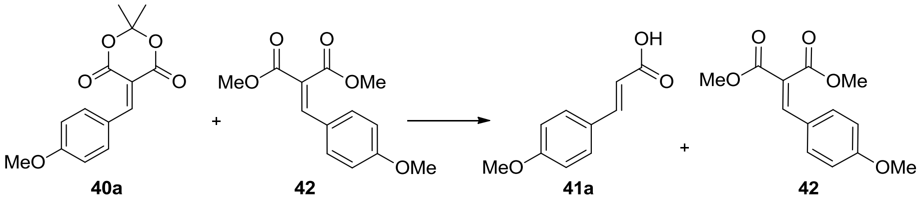
Dimethyl 2-(2-(2, 2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl)malonate (43)



The compound 43 was prepared by following the literature procedure of similar compound (Ref. 7); The compound 43 was obtained as a white solid (500 mg, 33% yield): mp = 84-85 °C; R_f = 0.3 Pet. Ether/EtOAc (50:50); IR (neat) cm^{-1}: 3003, 2955, 2882, 1734, 1200; δ_H (400 MHz, $CDCl_3$) 3.75 (s, 6H), 3.62 (t, *J* = 4 Hz, 1H), 3.45 (t, *J* = 7 Hz, 1H), 2.16-2.11 (m, 4H), 1.81 (s, 3H), 1.77 (s, 3H); δ_C (100 MHz, $CDCl_3$) 169.5, 165.1, 105.2, 52.8, 51.6, 46.1, 28.6, 26.7, 25.9, 23.8; HRMS (ESI TOF) *m/z* calcd. for $C_{13}H_{18}O_8Na$ $[M + Na]^+$ 325.0899, found 325.0904.

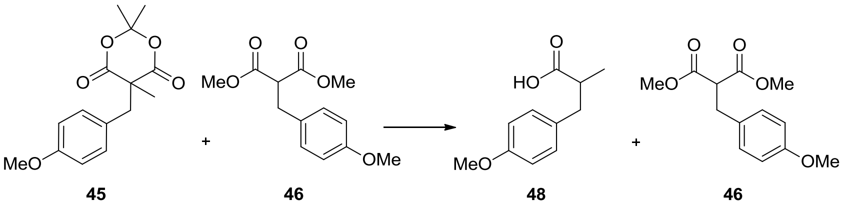
Competitive Experiments for Selective Decarboxylation:

Equation 1



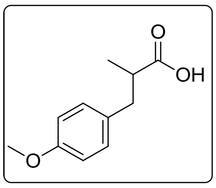
To the mixture of compound 40a (0.2 g) and 42 (0.19 g) dissolved in anhydrous CH_3NO_2 (4 mL), were added catalyst $FeCl_3.6H_2O$ (1 mg, 0.005 equiv) and H_2O (14 μL 1 equiv). The reaction mixture was microwave irradiated for 5 minutes. After which the reaction was cooled to room temperature. Then the reaction was concentrated under reduced pressure. The residue was purified over silica gel by flash column chromatography to afford 40a (0.117 g, 86%). The compound 42 was recovered in (0.185 g, 97% yield).

Equation 2



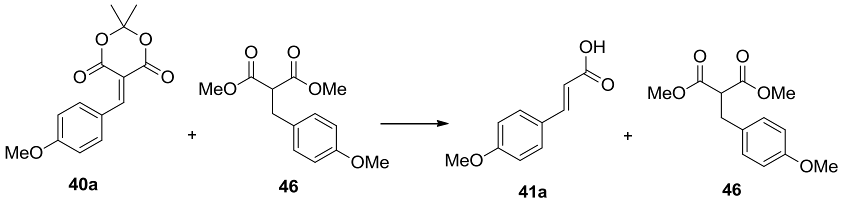
To the mixture of compound 45 (0.2 g) and 46 (0.181 g) dissolved in anhydrous CH_3NO_2 (4 mL), were added catalyst $FeCl_3.6H_2O$ (1 mg, 0.005 equiv corresponds to 45) and H_2O (14 µL 1 equiv corresponds to 45). The reaction mixture was microwave irradiated for 5 minutes. After which the reaction was cooled to room temperature. Then the reaction was concentrated under reduced pressure. The residue was purified over silica gel by flash column chromatography to afford 48 (0.123 g, 88%). The compound 46 was recovered in (0.175 g, 97% yield).

3-(4-methoxyphenyl)-2-methylpropanoic acid (48)



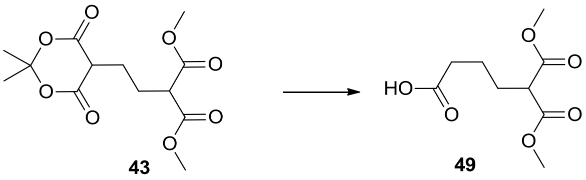
The compound 48 was obtained as a colorless oil (123 mg, 88% yield): $R_f = 0.2$ Pet. Ether/EtOAc/AcOH (5:5:0.1); IR (neat) cm^{-1}: 2928, 2860, 1705, 1612, 1512, 1246; δ_H (400 MHz, $CDCl_3$) 7.09 (d, J = 8 Hz, 2H), 6.82 (d, J = 8 Hz, 2H), 3.77 (s, 3H), 3.02-2.97 (m, 1H), 2.73-2.58 (m, 2H), 1.16 (d, J = 7 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 181.6, 158.3, 130.1,113.9, 55.4, 41.5, 38.6, 16.6; HRMS (ESI TOF) *m/z* calcd. for $C_{11}H_{13}O_3$ $[M - H]^-$ 193.0864, found 193.0857.

Equation 3



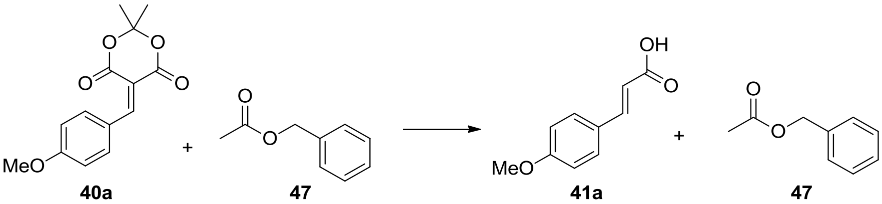
To the mixture of compound 40a (0.2 g) and 46 (0.193 g) dissolved in anhydrous CH_3NO_2 (4 mL), were added catalyst $FeCl_3.6H_2O$ (1 mg, 0.005 equiv corresponds to 40a) and H_2O (14 µL 1 equiv corresponds to 40a). The reaction mixture was microwave irradiated for 5 minutes. After which the reaction was cooled to room temperature. Then the reaction was concentrated under reduced pressure. The residue was purified over silica gel by flash column chromatography to afford 41a (0.118 g, 87%). The compound 46 was recovered in (0.190 g, 98% yield).

Equation 4



The compound 43 (0.2 g) was dissolved in anhydrous CH_3NO_2 (2 mL). To this solution catalyst $FeCl_3.6H_2O$ (0.9 mg, 0.005 equiv) and H_2O (14 μL 1 equiv) were added. Then the reaction mixture was microwave irradiated for 5 minutes. After which the reaction was cooled to room temperature. Then the reaction was concentrated under reduced pressure. The residue was purified over silica gel by flash column chromatography to afford 49 (0.141 g, 98%). The compound 49 (Methoxy-5-(methoxycarbonyl)-6-oxohexanoic acid) was obtained as a colorless oil (141 mg, 98% yield): R_f = 0.3 Pet. Ether/EtOAc (50:50); IR (neat) cm^{-1}: 2955, 2926, 2856, 1726, 1438, 1201, 1150; δ_H (400 MHz, $CDCl_3$) 3.75 (s, 6H), 3.39 (t, J = 8 Hz, 1H), 2.40 (t, J = 8 Hz, 2H), 1.99-1.71 (m, 2H), 1.71-1.65 (m, 2H); δ_C (100 MHz, $CDCl_3$) 178.6, 169.7, 52.7, 51.5, 33.5, 28.2, 22.5; HRMS (ESI TOF) *m/z* calcd for $C_9H_{14}O_6Na$ $[M + Na]^+$ 241.0688, found 241.0429.

Equation 5

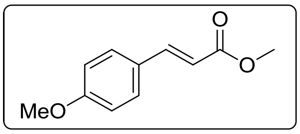


To the mixture of compound 40a (0.2 g) and 47 (0.115 g) dissolved in anhydrous CH_3NO_2 (4 mL), were added catalyst $FeCl_3.6H_2O$ (1 mg, 0.005 equiv corresponds to 40a) and H_2O (14 μL 1 equiv corresponds to 40a). The reaction mixture was microwave irradiated for 5 minutes. After which the reaction was cooled to room temperature. Then the reaction was concentrated under reduced pressure. The residue was purified over silica gel by flash column chromatography to afford 41a (0.112 g, 82%). The compound 47 was recovered in (0.114 g, 97% yield).

Section B

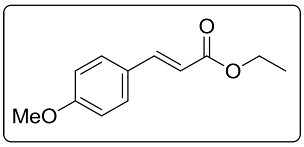
General Procedure D: Synthesis of α,β-Unsaturated esters

(*E*)-Methyl 3-(4-methoxyphenyl)acrylate (50a)



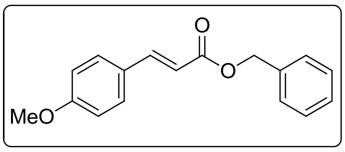
In a seal tube containing a mixture of 40a (200 mg, 0.76 mmol), catalyst $FeCl_3.6H_2O$ (1 mg, 0.0037 mmol) and MeOH (52a) (31 μL, 0.76 mmol) in dry nitromethane (2 mL), was microwave irradiated for 15 min. In the same reaction flask piperidine (5 μL, 0.05 mmol) was added and microwaved again for 15 min. The reaction mixture was cooled to room temperature, concentrated under reduced pressure. The residue was purified on silica gel flash column chromatography to furnish compound 50a as a white solid (138 mg, 94% yield): mp = 89-90 °C; R_f = 0.6 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2933, 2841, 1708, 1632, 1602, 1573; δ_H (400 MHz, $CDCl_3$) 7.67 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8Hz, 2H), 6.33 (d, *J* = 16 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167.9, 161.5, 144.7, 129.9, 127.2, 115.4, 114.5, 55.5, 51.7; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{12}O_3Na$ $[M + Na]^+$ 215.0684, found 215.0690.

(*E*)-ethyl 3-(4-methoxyphenyl)acrylate (50b)



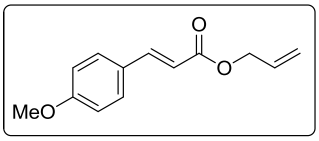
The compound 50b was synthesized starting from 40a and 52b following the general procedure D described for 50a; The compound 50b was obtained as a colourless oil (151 mg, 96% yield): R_f = 0.64 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2935, 2860, 1705, 1631, 1604, 1574; δ_H (400 MHz, $CDCl_3$) 7.66 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.33 (d, *J* = 16 Hz, 1H), 4.28 (q, *J* = 4 Hz and 8 Hz, 2H), 3.84 (s, 3H), 1.33 (t, *J* = 7 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 167.5, 161.4, 144.4, 129.8, 127.3, 115.9, 114.4, 60.5, 55.5, 14.5; HRMS (ESI TOF) *m/z* calcd. for $C_{12}H_{14}O_3Na$ $[M + Na]^+$ 229.0841, found 229.0850.

(*E*)-benzyl 3-(4-methoxyphenyl)acrylate (50c)



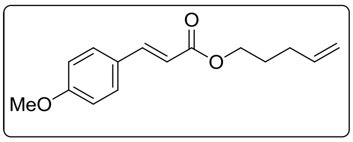
The compound 50c was synthesized starting from 40a and 52c following the general procedure D. The compound 50c was obtained as a light yellow oil (162 mg, 79% yield): R_f = 0.52 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2932, 1709, 1633, 1603, 1511, 1252, 1160, 828; δ_H (400 MHz, $CDCl_3$) 7.71 (d, *J* = 16 Hz, 1H), 7.48-7.39 (m, 7H), 6.91 (d, *J* = 8 Hz, 2H), 6.38 (d, *J* = 16 Hz, 1H), 5.24 (s, 2H), 3.83 (s, 3H); δ$_C$ (100 MHz, CDCl$_3$) 167.3, 161.6, 145, 136.3, 129.9, 128.7, 128.4, 128.3, 127.2, 115.4, 114.5, 66.4, 55.5; HRMS (ESI TOF) *m/z* calcd. for $C_{17}H_{16}O_3Na$ $[M + Na]^+$ 291.0997, found 291.1002.

(*E*)-allyl 3-(4-methoxyphenyl)acrylate (50d)



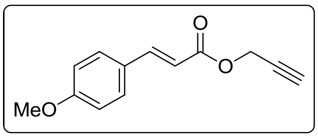
The compound 50d was synthesized starting from 40a and 52d following the general procedure D. The compound 50d was obtained as a light yellow oil (148 mg, 89% yield): *R$_f$* = 0.64 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2935, 2840, 1708, 1633, 1602, 1574, 1250, 1160, 828; δ$_H$ (400 MHz, CDCl$_3$) 7.69 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.36 (d, *J* = 16 Hz, 1H), 6.03 (m, 1H), 5.39-5.26 (m, 2H), 4.72-4.70 (m, 2H), 3.84 (s, 3H); δ$_C$ (100 MHz, CDCl$_3$) 167.1, 161.5, 144.9, 132.5, 129.9, 127.2, 118.3, 115.4, 114.5, 65.2, 55.5; HRMS (ESI TOF) *m/z* calcd. for $C_{13}H_{14}O_3Na$ $[M + Na]^+$ 241.0841, found 241.0847.

(*E*)-pent-4-en-1-yl 3-(4-methoxyphenyl)acrylate (50e)



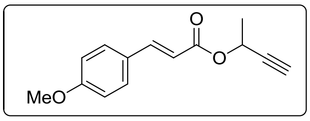
The compound 50e was synthesized starting from 40a and 52e following the general procedure D. The compound 50e was obtained as a light yellow oil (180 mg, 96% yield): *R$_f$* = 0.58 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2950, 2842, 1705, 1634, 1602, 1574, 1249, 1158, 827; δ$_H$ (400 MHz, CDCl$_3$) 7.66 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.33 (d, *J* = 16 Hz, 1H), 5.87-5.81 (m, 1H), 5.09-4.99 (m, 2H), 4.21 (t, *J* = 8 Hz, 2H), 3.84 (s, 3H), 2.21-2.15 (m, 2H), 1.83-1.77 (m, 2H); δ$_C$ (100 MHz, CDCl$_3$) 167.5, 161.5, 144.5, 137.7, 129.8, 127.3, 115.8, 115.4, 114.4, 63.9, 55.5, 30.3, 28.1; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{18}O_3Na$ $[M + Na]^+$ 269.1154, found 269.1161.

(*E*)-prop-2-yn-1-yl 3-(4-methoxyphenyl)acrylate (50f)



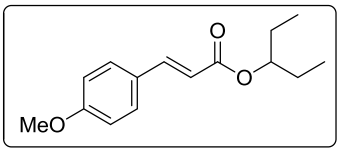
The compound 50f was synthesized starting from 40a and 52f following the general procedure D. The compound 50f was obtained as a light yellow oil (150 mg, 91% yield): *R$_f$* = 0.66 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 3289, 2932, 2843, 1709, 1631, 1600, 1510, 1247, 1148, 825; δ$_H$ (400 MHz, CDCl$_3$) 7.72 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.35 (d, *J* = 16 Hz, 1H), 4.81 (d, *J* = 4 Hz, 2H), 3.84 (s, 3H), 2.50 (t, *J* = 4 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 166.5, 161.7, 145.8, 130, 127, 115.1, 144.5, 78.1, 74.9, 55.5, 52; HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{12}O_3Na$ $[M + Na]^+$ 239.0684, found 239.0687.

(*E*)-but-3-yn-2-yl 3-(4-methoxyphenyl)acrylate (50g)



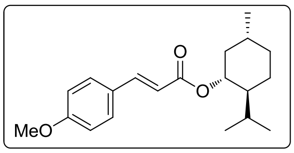
The compound 50g was synthesized starting from 40a and 50g following the general procedure D. The compound 50g was obtained as a light yellow solid (130 mg, 74% yield): R_f = 0.6 Pet. Ether/EtOAc (80:20); mp = 67-70 °C; IR (neat) cm^{-1}: 3248, 2959, 1701, 1572, 1512, 1252; δ_H (400 MHz, $CDCl_3$) 7.69 (d, *J* = 16 Hz, 1H), 7.50 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.35 (d, *J* = 16 Hz, 1H), 4.31 (t, *J* = 8 Hz, 2H), 3.84 (s, 3H), 2.63 (dt, *J* = 4 Hz, 2H), 2.03 (t, *J* = 4 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 167.2, 161.6, 145.1, 130, 127.2, 115.2, 114.5, 80.4, 70, 62.2, 55.5, 19.3; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{15}O_3$ $[M + H]^+$ 231.1021, found 231.1026.

(*E*)-pentan-3-yl 3-(4-methoxyphenyl)acrylate (50h)



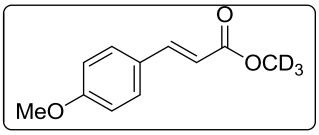
The compound 50h was synthesized starting from 40a and 52h following the general procedure D. The compound 50h was obtained as a light yellow oil (182 mg, 96% yield): R_f = 0.7 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2968, 2936, 2879, 1705, 1633, 1604, 1552, 1291, 1169, 865; δ_H (400 MHz, $CDCl_3$) 7.66 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8 Hz, 2H), 6.35 (d, *J* = 16 Hz, 1H), 4.91 (d, *J* = 8 Hz, 1H), 3.80 (s, 3H), 1.64 (bs, 4H), 0.93 (t, *J* = 8 Hz, 6H); δ_C (100 MHz, $CDCl_3$) 167.4, 161.4, 144.1, 129.8, 127.4, 116.3, 114.4, 55.5, 26.7, 9.8; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{20}O_3Na$ $[M + Na]^+$ 271.1310, found 271.1316.

(*E*)-(1*R*,5*R*)-2-isopropyl-5-methylcyclohexyl 3-(4-methoxyphenyl)acrylate (50i)



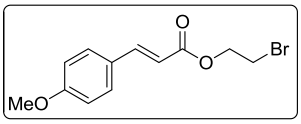
The compound 50i was synthesized starting from 40a and 52i following the general procedure D. The compound 50i was obtained as a pale yellow oil (170 mg, 71% yield): R_f = 0.6 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2982, 2836, 1705, 1604, 1560; δ_H (400 MHz, $CDCl_3$) 7.65 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8 Hz, 2H), 6.32 (d, *J* = 16 Hz, 1H), 4.85 (m, 1H), 3.86 (s, 3H), 2.08-2.03 (m, 1H), 1.93-1.91 (m, 1H), 1.72-1.65 (m, 2H), 1.53-1.48 (m, 2H), 1.14-0.99 (m, 2H), 0.93 (q, *J* = 4 Hz, 7H), 0.8 (d, *J* = 8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 167, 161.4, 144.1, 129.8, 127.4, 116.3, 114.4, 74.1, 55.5, 47.4, 41.2, 34.5, 31.6, 26.5, 23.7, 22.2, 20.9, 16.6; HRMS (ESI TOF) *m/z* calcd for $C_{20}H_{28}O_3Na$ [M + Na]$^+$ 339.1936, found 339.1852.

(*E*)-d3-3-(4-methoxyphenyl)acrylate (50j)



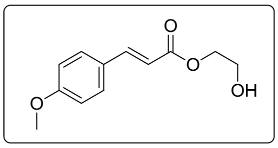
The compound 50j was synthesized starting from 40a and 52j following the general procedure D. The compound 50j was obtained as a yellowish solid (140 mg, 94% yield): mp = 95-96 °C; R_f = 0.6 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2933, 2842, 1708, 1633, 1602; δ_H (400 MHz, $CDCl_3$) 7.67 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.33 (d, *J* = 16 Hz, 1H), 3.84 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167.9, 161.5, 144.7, 129.9, 127.2, 115.4, 114.5, 55.5; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{10}O_3D_3$ [M + H]$^+$ 196.1053, found 196.1049.

(*E*)-2-bromoethyl 3-(4-methoxyphenyl)acrylate (50k)



The compound 50k was synthesized starting from 40a and 52k following the general procedure D. The compound 50k was obtained as a light yellow oil (125 mg, 57% yield): R_f = 0.63 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2959, 1716, 1632, 1512, 1423, 1253, 827; δ_H (400 MHz, $CDCl_3$) 7.70 (d, *J* = 16 Hz, 1H), 7.50 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.35 (d, *J* = 16 Hz, 1H), 4.50 (t, *J* = 8 Hz, 2H), 3.84 (s, 3H), 3.58 (t, *J* = 8 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 166.8, 161.7, 145.5, 131.9, 130, 129.8, 127, 114.8, 114.6, 114.4, 63.8, 55.5, 29; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{15}BrO_3$ [M + H]$^+$ 285.0126, found 285.0129.

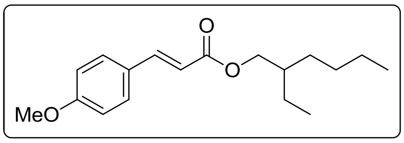
(*E*)-2-hydroxyethyl 3-(4-methoxyphenyl)acrylate (50l)



The compound 50l was synthesized starting from 40a and 52l following the general procedure D. The compound 50l was obtained as a light yellow oil (120 mg, 71% yield): R_f = 0.1 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 3484, 2954, 1705, 1631, 1604, 1442; δ_H (400 MHz, $CDCl_3$) 7.70 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.36 (d, *J* = 16 Hz, 1H), 4.34 (t, *J* = 8 Hz, 2H), 3.90 (t, *J* = 8 Hz, 2H), 3.84 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167.8, 161.6, 145.3, 130.0, 127.1, 115.0, 114.5, 66.2, 61.5, 55.5; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{14}O_4Na$ [M + Na]$^+$ 245.0790, found 245.0794.

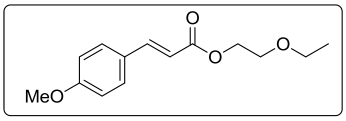
Gram Scale preparation

(*E*)-2-ethylhexyl 3-(4-methoxyphenyl)acrylate (50s)



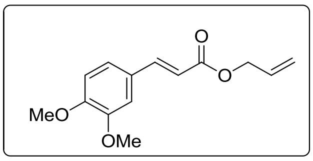
In a pressure tube (capped) mixture of 40a (5 g, 19 mmol), catalyst $FeCl_3.6H_2O$ (5.1 mg, 0.019 mmol) and 2-ethylhexan-1-ol (2.98 mL, 19 mmol) in dry nitromethane (15 mL), was microwave irradiated for 15 min. Afterwhich, to the same reaction flask, piperidine (20 μL, 0.2 mmol) was added and microwaved again for 15 min. The reaction mixture was cooled to room temperature, concentrated under reduced pressure. The residue was purified on silica gel column flash chromatography to furnish compound 50s as light yellow oil (4.65 g, 84% yield): R_f = 0.6 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2940, 1705, 1633, 1602, 1512; δ_H (400 MHz, $CDCl_3$) 7.65 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8 Hz, 2H), 6.34 (d, *J* = 16 Hz, 1H), 4.12 (q, *J* = 4 Hz, 2H), 3.84 (s, 3H), 1.66-1.58 (m, 1H), 1.47-1.25 (m, 8H), 0.92-0.89 (m, 7H); δ_C (100 MHz, $CDCl_3$) 167.7, 161.4, 144.3, 129.8, 127.4, 116, 114.4, 67, 55.5, 39, 30.6, 29.1, 24, 23.1, 14.2, 11.2; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{26}O_3Na$ $[M + Na]^+$ 313.1780, found 313.1807.

(*E*)-2-ethoxyethyl 3-(4-methoxyphenyl)acrylate (50r)



The compound 50r was synthesized starting from 40a and ethoxyethanol following the procedure described for 50s. The catalyst loading of $FeCl_3.6H_2O$ was reduced to 0.1 mol% (0.001 equiv). The compound 50r was obtained as a light yellow oil (3.85 g, 80% yield): R_f = 0.36 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2970, 2860, 1708, 1637, 1601; δ_H (400 MHz, $CDCl_3$) 7.69 (d, *J* = 16 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8 Hz, 2H), 6.38 (d, *J* = 16 Hz, 1H), 4.36 (q, *J* = 4 Hz, 2H), 3.84 (s, 3H), 3.72 (q, *J* = 4 Hz, 2H), 3.60 (q, *J* = 4 Hz, 2H), 1.26 (t, *J* = 8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 167.5, 161.5, 144.8, 129.9, 127.3, 115.5, 114.4, 68.6, 66.8, 63.8, 55.5, 15.3; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{18}O_4Na$ $[M + Na]^+$ 273.1103, found 273.1103.

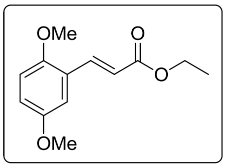
(*E*)-allyl 3-(3,4-dimethoxyphenyl)acrylate (50m)



The compound 50m was synthesized starting from 40b and 52d following the general procedure D. The compound 50m was obtained as a light yellow oil (125 mg, 74% yield): R_f = 0.55 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2937, 1709, 1631, 1510, 1261; δ_H (400 MHz, $CDCl_3$) 7.68 (d, *J* = 16 Hz, 1H), 7.12-7.05 (m, 2H), 6.88 (d, *J* = 4 Hz, 1H), 6.36

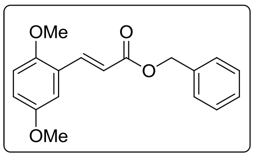
(d, *J* = 16 Hz, 1H), 6.03-5.96 (m, 1H), 5.40-5.26 (m, 2H), 4.72-4.70 (m, 2H), 3.91 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167, 151.3, 149.3, 145.1, 132.5, 127.5, 122.8, 118.3, 115.6, 111.1, 109.7, 65.2, 56.1, 56; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{16}O_4Na$ $[M + Na]^+$ 271.0946, found 271.0935.

(*E*)-ethyl 3-(2,5-dimethoxyphenyl)acrylate (50n)



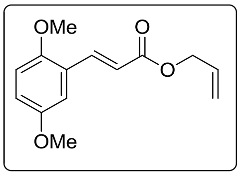
The compound 50n was synthesized starting from 40c and 52b following the general procedure D. The compound 50n was obtained as a light yellow oil (135 mg, 84% yield): R_f = 0.6 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2948, 1705, 1631, 1496, 1429, 861; δ_H (400 MHz, $CDCl_3$) 7.69 (d, *J* = 16 Hz, 1H), 7.03 (d, *J* = 4 Hz, 1H), 6.90-6.87 (m, 1H), 6.83-6.81 (m, 1H), 6.49 (d, *J* = 16 Hz, 1H), 4.25 (q, *J* = 8 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 1.32 (t, *J* = 8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 167.5, 153.6, 152.9, 139.9, 124.1, 119.1, 117.2, 113.3, 112.5, 60.5, 56.2, 55.9, 14.5; HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0946, found 259.0956.

(*E*)-benzyl 3-(2,5-dimethoxyphenyl)acrylate (50o)



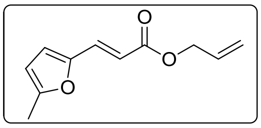
The compound 50o was synthesized starting from 40c and 52c following the general procedure D. The compound 50o was obtained as a light yellow oil (130 mg, 63% yield): R_f = 0.7 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2945, 1712, 1628, 1496, 1463; δ_H (400 MHz, $CDCl_3$) 8.03 (d, *J* = 16 Hz, 1H), 7.41-7.36 (m, 5H), 7.03 (d, *J* = 3 Hz, 1H), 6.92-6.83 (m, 2H), 6.57 (d, *J* = 16 Hz, 1H), 5.25 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167.3, 153.6, 153, 140.6, 136.3, 128.7, 128.4, 128.3, 123.9, 118.7, 117.4, 113.4, 112.5, 66.4, 56.4, 55.9; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{18}O_4Na$ $[M + Na]^+$ 321.1103, found 321.1106.

(*E*)-allyl 3-(2,5-dimethoxyphenyl)acrylate (50p)



The compound 50p was synthesized starting from 40c and 52d following the general procedure D. The compound 50p was obtained as a light yellow oil (140 mg, 83% yield): R_f = 0.6 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2944, 1712, 1628, 1495, 710; δ_H (400 MHz, $CDCl_3$) 8.02 (d, *J* = 16 Hz, 1H), 7.05 (d, *J* = 4 Hz, 1H), 6.91-6.84 (m, 2H), 6.55 (d, *J* = 16 Hz, 1H), 6 (m, 1H), 5.40-5.29 (m, 2H), 4.73-4.71 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167.1, 153.6, 153, 140.4, 132.6, 124, 118.7, 118.3, 117.3, 113.4, 112.6, 65.3, 56.2, 55.9; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{16}O_4Na$ [M + Na]$^+$ 271.0946, found 271.0948.

(*E*)-allyl 3-(5-methylfuran-2-yl)acrylate (50q)



The compound 50q was synthesized starting from 40d and 52d following the general procedure D. The compound 50q was obtained as a light yellow oil (112 mg, 69% yield): R_f = 0.48 Pet. Ether/EtOAc (80:20); IR (neat) cm^{-1}: 2947, 1580, 1366, 1258; δ_H (400 MHz, $CDCl_3$) 7.40 (d, *J* = 16 Hz, 1H), 6.52 (d, *J* = 4 Hz, 1H), 6.27 (d, *J* = 16 Hz, 1H), 6.08 (m, 1H), 5.94 (m, 1H), 5.38-5.33 (m, 1H), 5.27-5.23 (m, 1H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167.1, 155.7, 149.6, 132.6, 131.6, 118.1, 116.8, 113.7, 109, 65.1, 14; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{12}O_3Na$ [M + Na]$^+$ 215.0684, found 215.0687.

3.9 Appendix III: ^{1}H and ^{13}C NMR spectra of representative compounds

compound No.	Fig AIII.X	data	page No.
40a	Fig AIII.1 and AIII.2	1H-13C	57
41e	Fig AIII.3 and AIII.4	1H-13C	58
41h	Fig AIII.5 and AIII.6	1H-13C	59
50s	Fig AIII.7 and AIII.8	1H-13C	60

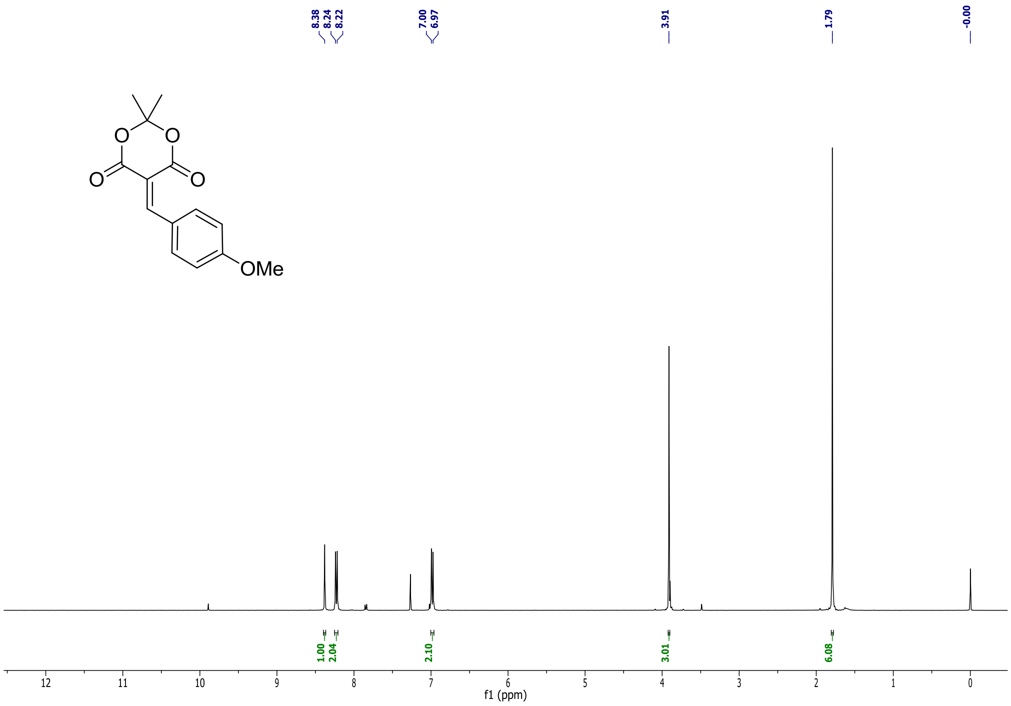


Fig AIII.1: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **40a**

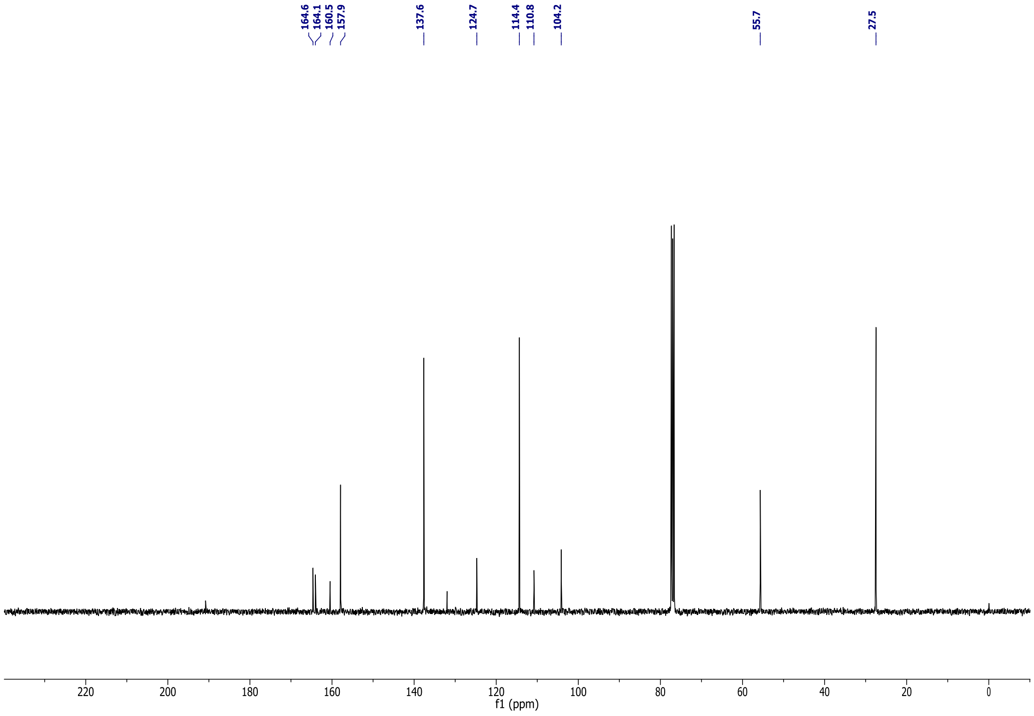


Fig AIII.2: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **40a**

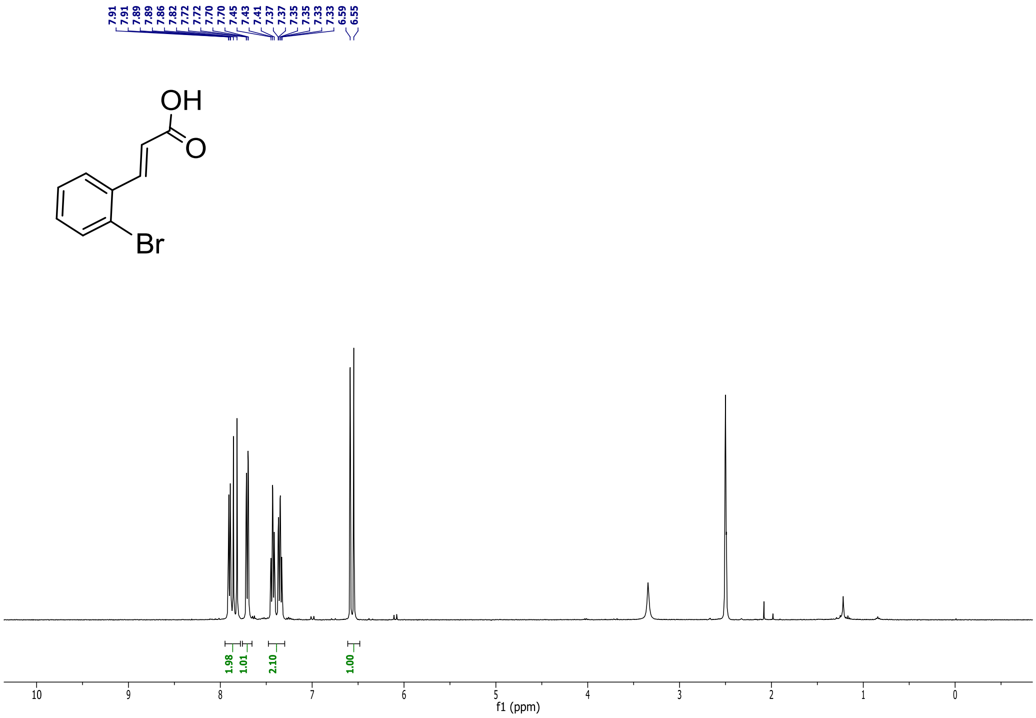


Fig AIII.3: ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **41e**

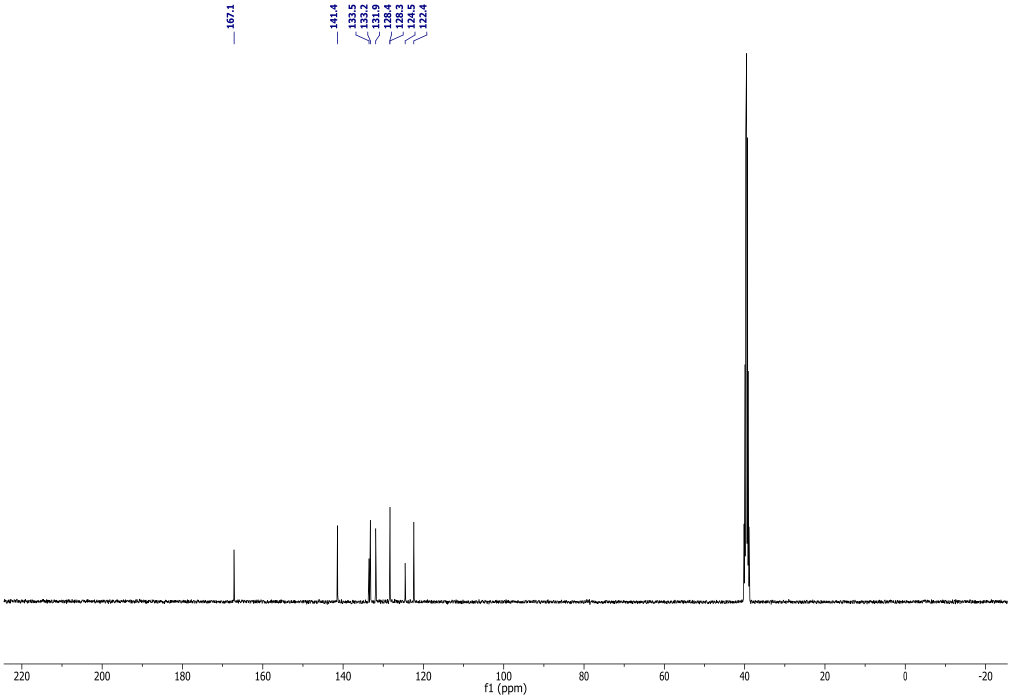


Fig AIII.4: ^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound **41e**

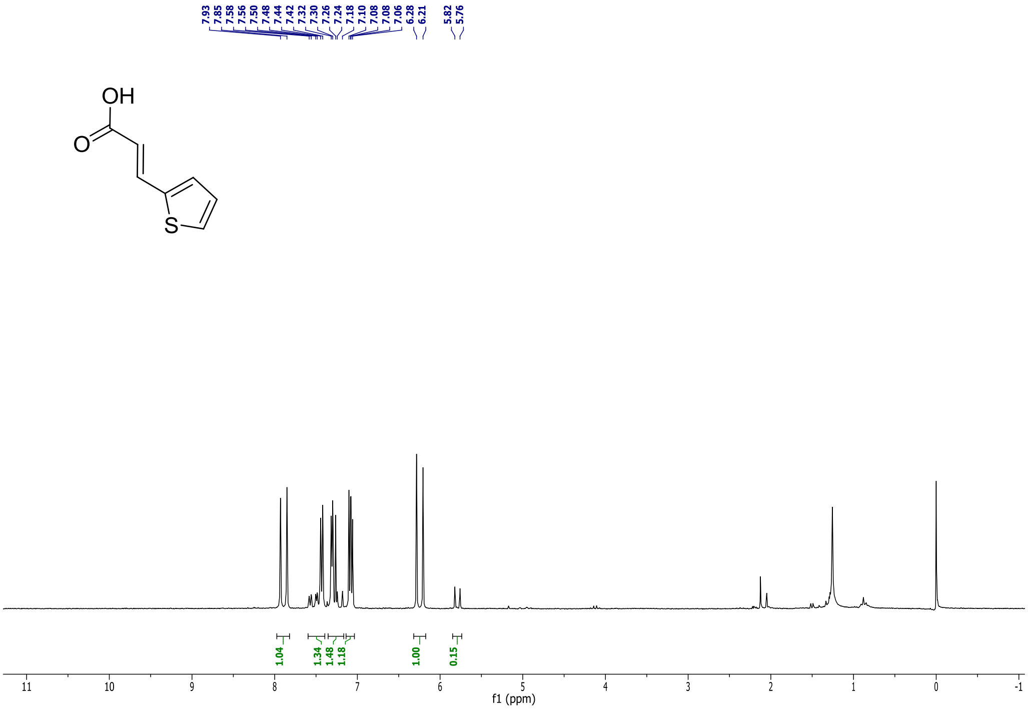


Fig AIII.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **41h**

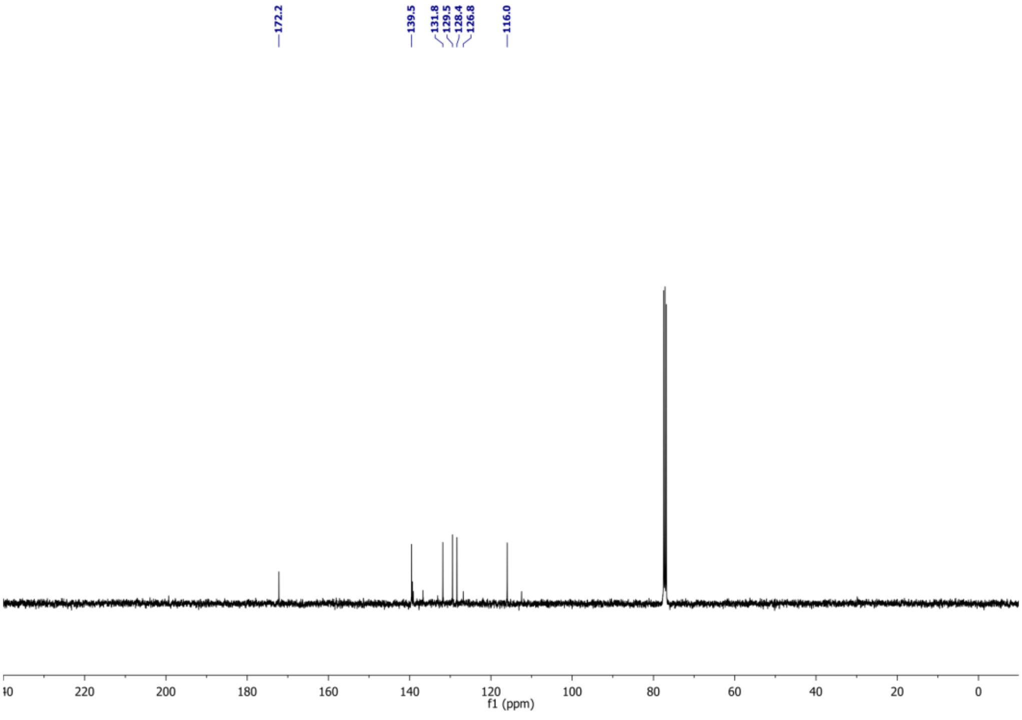


Fig AIII.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **41h**

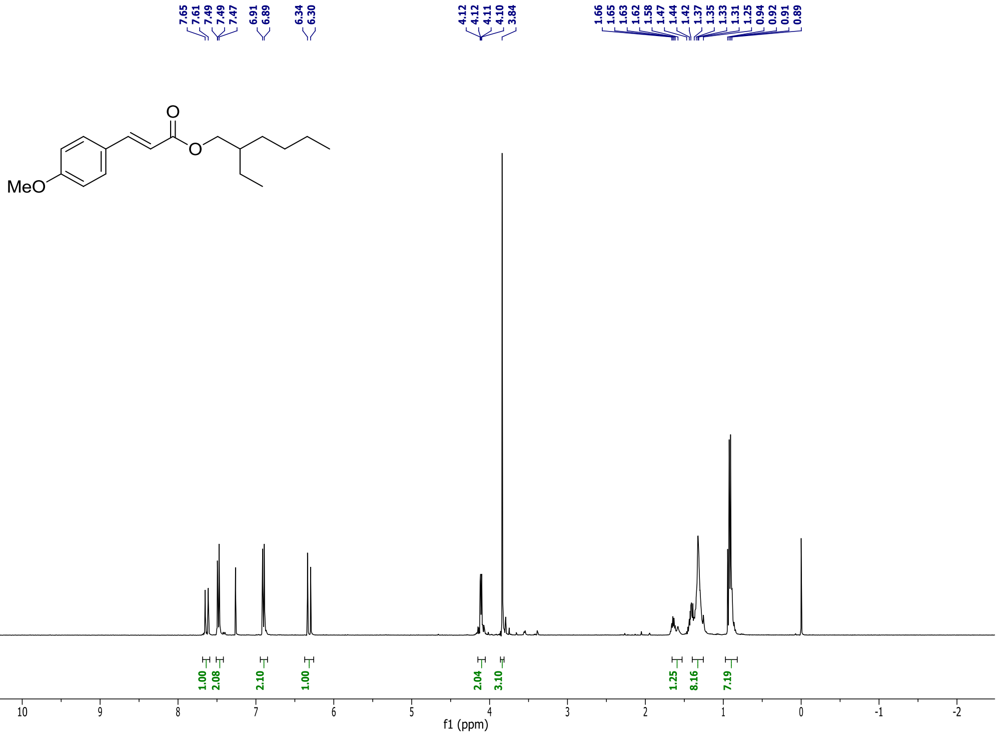


Fig AIII.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **50s**

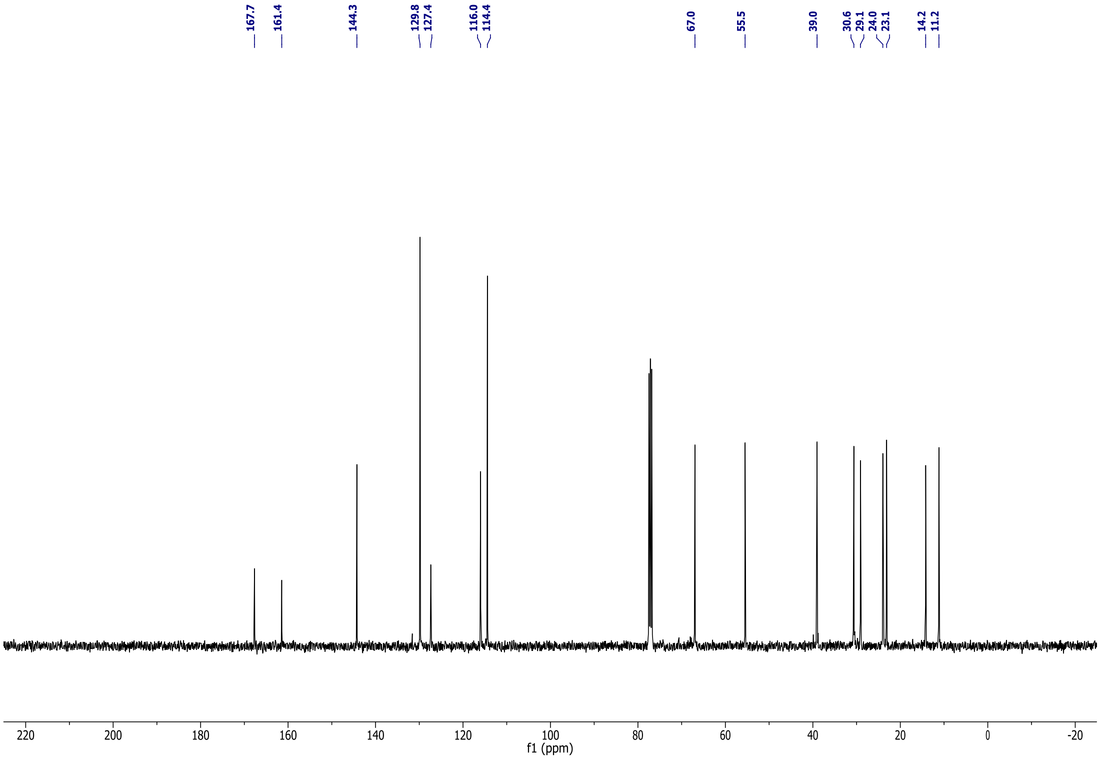


Fig AIII.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **50s**

3.10 References

[1] A. N. Meldrum, *J. Chem. Soc., Trans.* **1908**, *93*, 598–601.

[2] D. Davidson, S. A. Bernhard, *J. Am. Chem. Soc.* **1948**, *70*, 3426–3428.

[3] H. McNab, *Chem. Soc. Rev.* **1978**, *7*, 345.

[4] E. M. Arnett, S. G. Maroldo, S. L. Schilling, J. A. Harrelson, *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.

[5] E. M. Arnett, J. A. J. Harrelson, *J. Am. Chem. Soc.* **1987**, *109*, 809–812.

[6] a) K. Byun, Y. Mo, J. Gao, *J. Am. Chem. Soc.* **2001**, *123*, 3974-3979; b) K. B. Wiberg, K. E. Laidig, *J. Am. Chem. Soc.* **1988**, *110*, 1872–1874.

[7] Y. Oikawa, K. Sugano, O. Yonemitsu, *J. Org. Chem.* **1978**, *43*, 2087-2088.

[8] A. R. Mohite, P. R. Sultane, R. G. Bhat, *Tetrahedron Lett.* **2012**, *53*, 30–35.

[9] H. Zhang, D. E. Ryono, P. Devasthale, W. Wang, K. O'Malley, D. Farrelly, L. Q. Gu, T. Harrity, M. Cap, C. X. Chu, K. Locke, L. T. Zhang, J. Lippy, L. Kunselman, N. Morgan, N. Flynn, L. Moore, V. Hosagrahara, L. Zhang, P. Kadiyala, C. Xu, A. M. Doweyko, A. Bell, C. Y. Chang, J. Muckelbauer, R. Zahler, N. Hariharan, P. T. W. Cheng, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1451–1456.

[10] R. Bloch, *Synthesis* **1978**, *2*, 140–142.

[11] S. Perreault, C. Spino, *Org. Lett.* **2006**, *8*, 4385–4388.

[12] B.-C. Chen, *Heterocycles* **1991**, *32*, 529–358.

[13] E. Roberts, J. P. Sancon, J. B. Sweeney, J. A. Workman, *Org. Lett.* **2003**, *5*, 4775-4777.

[14] a) S. Danishefsky, R. K. Singh, *J. Org. Chem.* **1975**, *40*, 3807-3808; b) S. Danishefsky, *Acc. chem. Res.* **1979**, *12*, 66–72.

[15] M. Zia-Ebrahimi, G. W. Huffman, *Synthesis* **1996**, *2*, 215–218.

[16] J. Swoboda, J. Derkosch, F. Wessely, *Monatsh. Chem.* **1960**, *91*, 188–201.

[17] a) A. Wilsily, E. Fillion, *J. Org. Chem.* **2009**, *74*, 8583–8594; b) D. Chopra, V. V. Zhurov, E. A. Zhurova, A. A. Pinkerton, *J. Org. Chem.* **2009**, *74*, 2389–2395.

[18] E. Fillion, A. M. Dumas, B. A. Kuropatwa, N. R. Malhotra, T. C. Sitler, *J. Org. Chem.* **2006**, *71*, 409–412.

[19] F. Bigi, S. Carloni, L. Ferrari, R. Maggi, A. Mazzacani, G. Sartori, *Tetrahedron Lett.* **2001**, *42*, 5203.

[20] A. M. Dumas, A. Seed, A. K. Zorzitto, E. Fillion, *Tetrahedron Lett.* **2007**, *48*, 7072–7074.

[21] F. E. Zieglera, T. Guenthera, R. V. Nelsona, *Synth. Commun.* **1980**, *10*, 661–665.

[22] G. Baxter, R. Brown, *Aust. J. Chem.* **1975**, *28*, 1551–1557.

[23] C. G. Frost, B. C. Hartley, *Org. Lett.* **2007**, *9*, 4259–4261.

[24] C. G. Frost, B. C. Hartley, *J. Org. Chem.* **2009**, *74*, 3599–3602.

[25] A. M. Dumas, E. Fillion, *Org. Lett.* **2009**, *11*, 1919–1922.

[26] E. Fillion, A. Wilsily, *J. Am. Chem. Soc.* **2006**, *128*, 2774-2775.

[27] S. Maas, *Synthesis* **1999**, *10*, 1792–1798.

[28] T. F. Knöpfel, P. Zarotti, T. Ichikawa, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682-9683.

[29] E. Fillion, A. K. Zorzitto, *J. Am. Chem. Soc.* **2009**, *131*, 14608-14609.

[30] E. Fillion, A. M. Dumas, S. A. Hogg, *J. Org. Chem.* **2006**, *71*, 9899–9902.

[31] A. Habibi, L. Mousavifar, I. Yavari, M. R. Yazdanbakhsh, *Monatsh. Chem.* **2007**, *138*, 603–606.

[32] a) G. L. Nelsestuen, T. H. Zytkovicz, J. B. Howard, *J. biol. chem.* **1974**, *249*; b) T. H. Zytkovicz, G. L. Nelsestuen, *J. biol. chem.* **1975**, *250*, 2968–2972.

[33] J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669–1730.

[34] J. Zhu, C. Couturier, M. Liron, T. Schlama, *Synlett* **2005**, 0851–0853.

[35] a) R. K. Callow, N. C. Johnston, *Bee World* **1960**, *41*, 152-153; b) A. Brockmann, D. Dietz, J. Spaethe, *J. Chem. Ecol.* **2006**, *32*, 657–667.

[36] H. Cho, M. Ueda, M. Tamaoka, M. Hamaguchi, K. Aisaka, Y. Kiso, T. Inoue, R. Ogino, T. Tatsuoka, *J. Med. Chem.* **1991**, *34*, 1503–1505.

[37] S. Hilz, *Topics in current chemistry, Springer, Velag, Heidelberg, Berlin* **2004**, 154.

[38] a) U. Marquardt, D. Schmid, G. Jung, *Synlett* **2000**, *8*, 1131-1132; b) J. Song, M. Hesse, *Tetrahedron* **1993**, *49*, 6797–6808.

[39] a) E. Knoevenagel, *Chem Ber.* **1894**, *27*, 2345; b) O. Doebner, *Chem Ber.* **1900**, *33*, 2140; c) C. A. Kingsbury, G. Max, *J. Org. Chem.* **1978**, *43*, 3131–3139; d) R. H. Wiley, N. R. Smith, *Org. Synth.* **1953**, *33*, 62; e) P. J. Jessup, C. B. Petty, J. Roos, L. E. Overman, *Org. Synth.* **1979**, *59*, 1; f) J. K. Augustine, Y. A. Naik, A. B. Mandal, N. Chowdappa, V. B. Praveen, *J.Org. Chem.* **2007**, *72*, 9854–9856.

[40] P. A. Grieco, C.-L. J. Wang, S. D. Burke, *J. Chem. Soc., Chem. Commun.* **1975**, 537.

[41] P. Helquist, D. Schauer, *Synthesis* **2006**, *2006*, 3654–3660.

[42] S. Sano, Y. Takemoto, Y. Nagao, *ARKIVOC* **2003**, *viii*, 93–101.

[43] J. M. Concellón, C. Concellón, *J. Org. Chem.* **2006**, *71*, 1728–1731.

[44] W. Li, J. Li, M. Lin, S. Wacharasindhu, K. Tabei, T. S. Mansour, *J. Org. Chem.* **2007**, *72*, 6016–6021.

[45] a) S. T. Kemme, T. Smejkal, B. Breit, *Chem.—Eur.J* **2010**, *16*, 3423–3433; b) S. T. Kemme, T. Šmejkal, B. Breit, *Adv. Synth. Catal.* **2008**, *350*, 989–994.

[46] L. Zhu, N. Lei, Z. Miao, C. Sheng, C. Zhuang, J. Yao, W. Zhang, *Chin. J. Chem.* **2012**, *30*, 139–143.

[47] a) B. P. Bandgar, L. S. Uppalla, D. S. Kurule, *Green Chem.* **1999**, *1*, 243–245; b) A. Song, X. Wang, K. S. Lam, *Tetrahedron Lett.* **2003**, *44*, 1755–1758; c) V. Armstronga, O. Sotoa, J. A. Valderramaa, *Synth. Commun.* **1988**, *18*, 717–725.

[48] a) V. Naira, *Synth. Commun.* **1987**, *17*, 723–727; b) A. Kumar, B. K. Singh, R. Tyagi, S. K. Jain, S. K. Sharma, A. K. Prasad, H. G. Raj, R. C. Rastogi, A. C. Watterson, V. S. Parmar, *Bioorg. Med. Chem.* **2005**, *13*, 4300–4305.

[49] J. A. Hedge, C. W. Kruse, H. R. Snyder, *J. Org. Chem.* **1961**, *26*, 3166–3170.

[50] A. M. Dumas, E. Fillion, *Acc. Chem. Res.* **2010**, *43*, 440–454.

[51] a) A. V. Dr. Subrahmanyam, S. Prof. Thayumanavan, G. W. Prof. Huber, *ChemSusChem* **2010**, *3*, 1158-1161; b) Y.-B. Huang, Z. Yang, J.-J. Dai, Q.-X. Guo, Y. Fu, *RSC Adv.* **2012**, *2*, 11211–11214.

[52] A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411–2502.

[53] G. Guazzelli, S. De Grazia, K. D. Collins, H. Matsubara, M. Spain, D. J. Procter, *J. Am. Chem. Soc.* **2009**, *131*, 7214-7215.

[54] a) D. J. Chen, L. Guo, J. Y. Liu, S. Kirtane, J. F. Cannon, G. G. Li, *Org. Lett.* **2005**, *7*, 921–924; b) F. Lopez, S. R. Harutyunyan, A. Meetsma, A. J. Minnaard, B. L. Feringa, *Angew. Chem., Int. Ed.* **2005**, *44*, 2752–2756; c) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844.

[55] W. F. Ringk, K. Othmer, *Encyclopedia of Chemical Technology 3rd Ed.; John Wiley and Sons: New York* **1981**, *6*, 143–149.

[56] B. List, A. Doehring, M. T. H. Fonseca, A. Job, R. R. Torres, *Tetrahedron* **2006**, *62*, 476–482.

[57] J. N. Lu, P. H. Toy, *Synlett* **2011**, 1723–1726.

[58] J. M. Concellon, H. Rodriguez-Solla, P. Diaz, R. Llavona, *J. Org. Chem.* **2007**, *72*, 4396–4400.

[59] H. Rodriguez-Solla, C. Concellon, E. G. Blanco, J. I. Sarmiento, P. Diaz, R. G. Soengas, *J. Org. Chem.* **2011**, *76*, 5461–5465.

[60] T. D. W. Claridge, S. G. Davies, J. A. Lee, R. L. Nicholson, P. M. Roberts, A. J. Russell, A. D. Smith, S. M. Toms, *Org. Lett.* **2008**, *10*, 5437–5440.

[61] J. A. M. Lummiss, K. C. Oliveira, A. M. T. Pranckevicius, A. G. Santos, E. N. dos Santos, D. E. Fogg, *J. Am. Chem. Soc.* **2012**, *134*, 18889–18891.

[62] K. Zeitler, *Org. Lett.* **2006**, *8*, 637–640.

[63] M. Nishizawa, H. Hirakawa, Y. Nakagawa, H. Yamamoto, K. Namba, H. Imagawa, *Org. Lett.* **2007**, *9*, 5577–5580.

[64] A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.

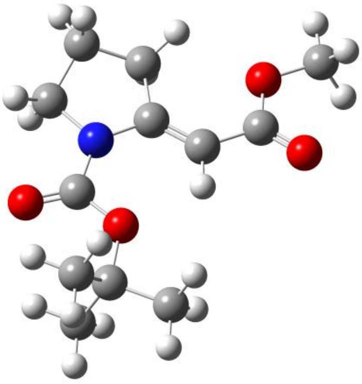
[65] A. R. Mohite, R. G. Bhat, *Org. Lett.* **2013**, *15*, 4564–4567.

[66] Unlike, the well known Horner-Wadsworth-Emmons reaction, our reaction conditions were very mild and avoids the use of strong bases. The reactions were neat and by-products formed are volatile.

[67] A. R. Mohite, R. G. Bhat, *Provisional Patent filed in India, App No.: 2437/MUM/2013.* **2013**.

Chapter Four

Lewis acid catalyzed one pot Synthesis of heterocyclic β-enamino esters from amino acid β-ketoesters



Energy minimized structure of
β-enamino Ester

Chapter 4

In this chapter initial synthetic study of 5-membered heterocyclic β-enamino esters has been established using catalytic amount of $B(C_6F_5)_3$*. Few 5-membered heterocyclic β-enamino esters have synthesized by optimizing the reaction conditions. This procedure gives an easy access to the chiral and non-chiral 5-membered heterocyclic β-enamino esters in good yields under mild reaction condition.*

4.1 Introduction

Heterocyclic enamines are very useful intermediates for the synthesis of heterocyclic compounds and natural products. The chemistry of heterocyclic β-enamino esters was initially explored by Eschenmoser during synthetic study of Corrin systems.[1] One of the most interesting features of β-enamino esters is their ambident bisnucleophilicity.[2] Nucleophilic reaction can be carried out at the site of enaminic carbon and/or the secondary amino nitrogen (Fig **4.1**). This unique property led to the synthetic study of piperidines, pyrrolidines and several other natural products. Several groups have utilized β-enamino esters as precursors for the synthesis of natural products (saxitoxin,[3] camptothecin[4] and mitomycins[5]).

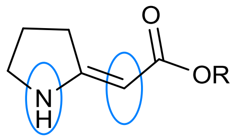


Fig 4.1: General structure of β-enamino ester. (Blue colored circles showing nucleophilic centres)

Heterocyclic β-enamino ester has been utilized in the synthesis of antibiotic (5*R*)carbapenem-3-carboxylic acid,[6] homoproline derivatives,[7] 2,5-disubstituted pyrrolidines,[8] pyrrol derivatives,[9] pyrrolizidine and indolizidine alkaloids[10] (Fig **4.2**).

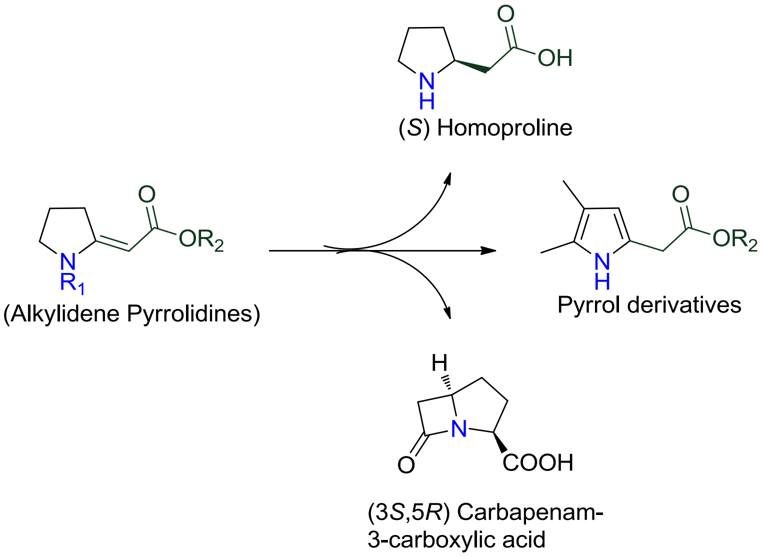


Fig 4.2: Alkylidene pyrrolidines

Generally, 5-membered heterocyclic β-enamino esters have been used for the synthesis of pyrrolidine and pyrrole derivatives. Similarly 6-membered heterocyclic β-enamino esters have been employed for the synthesis of 6-membered alkaloids: pipecolate[7] and sedridine derivatives (Fig **4.3**).

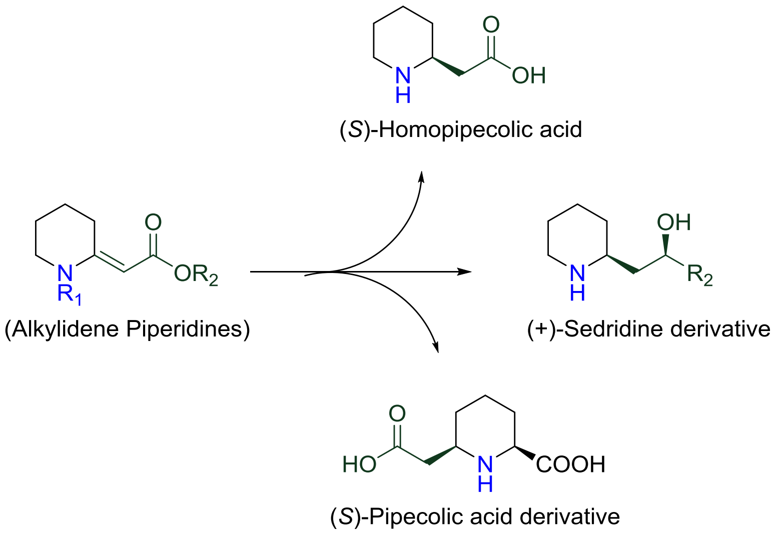
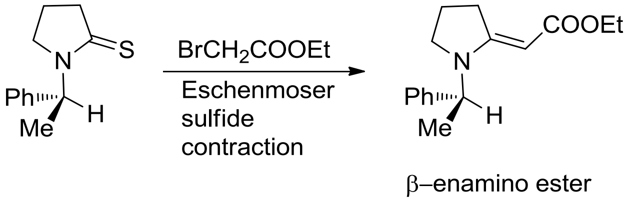


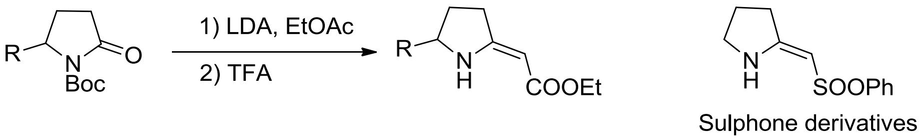
Fig 4.3: Alkylidene piperidines

Eschenmoser and co-workers first reported the method for the synthesis of β-heterocyclic pyrrolidines. This method has been used successfully for many years and applicable till date for the synthesis of β-enamino ester derivatives. The reaction of thioamide with bromoacetoacetate via the transformation termed as Eschenmoser sulfide contraction is known to afford β-enamino esters (Scheme **4.1**).[11]



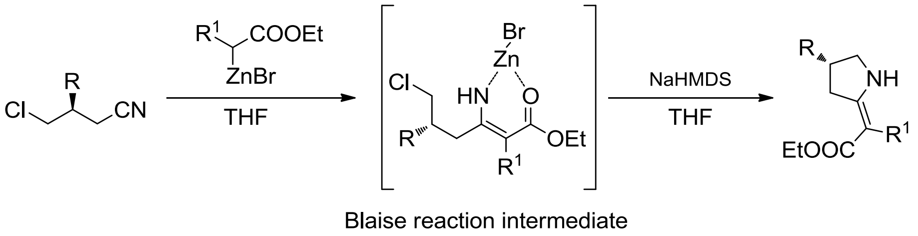
Scheme 4.1 Eschenmoser thioamide contraction

Elliott and co-workers reported an efficient method for the synthesis of β-heterocyclic pyrrolidine derivatives. The reaction between enolate of ester/ketone and the lactone afforded the corresponding β-ketoesters, which on addition of TFA gave the corresponding β-heterocyclic pyrrolidines in-situ (Scheme **4.2**).[12] This method has been further extended for synthesis of alkylidene sulfone derivatives.



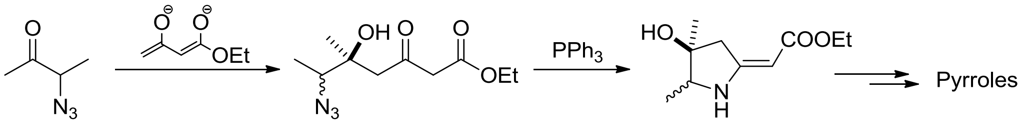
Scheme 4.2

Kim *et al.* reported an elegant method for the synthesis of 4-substituted β-enamino esters by exploring the use of Blaise reaction intermediate.[13] They synthesized Blaise reaction intermediate by treating Reformatsky reagent with nitriles. Resulting reaction mixture was further treated with NaHMDS to afford 4-substituted β-enamino esters (Scheme **4.3**). Further, the 4-substituted β-enamino esters have been used for the synthesis of *N*-heterocyclic compounds.



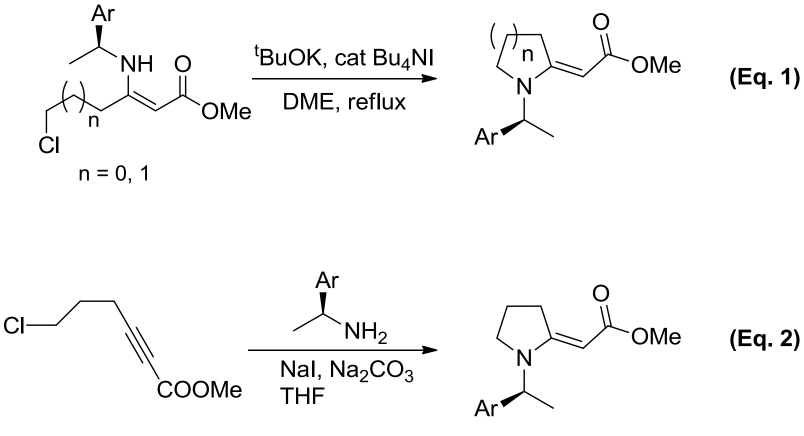
Scheme 4.3

Two types of enolates can be selectively generated from of β-keto esters, the mono enolate and dienolate by using specific reaction conditions. The Langer *et al.*[9, 14] generated the dianion of ethylacetoacetate, which upon reaction with α-diazo ketone gave aldol product. This under aza-Wittig reaction conditions afforded β-enamino esters (Scheme **4.4**). Further substituted pyrrole derivatives have been synthesized starting from these β-enamino esters.



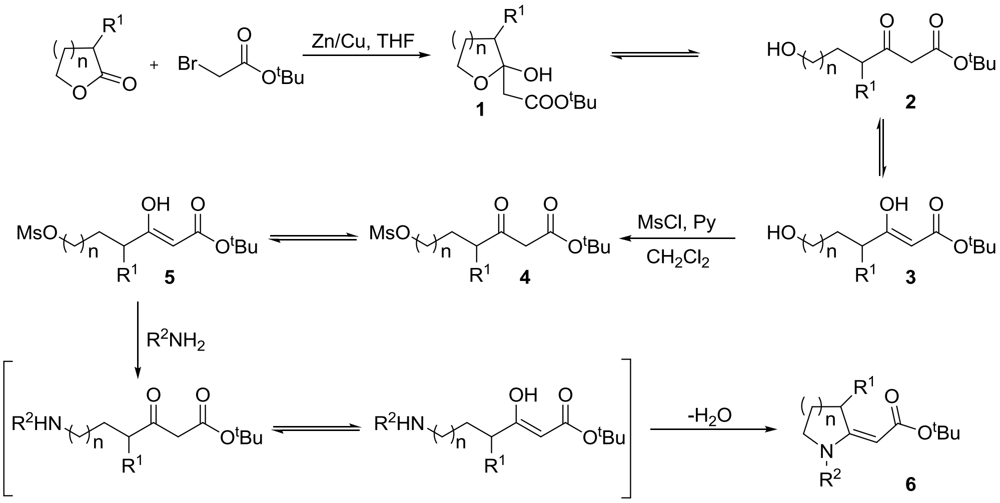
Scheme 4.4

Hashimoto and co-workers[7] demonstrated the synthesis of heterocyclic β-enamino esters starting from chloro derivative of acyclic β-enamino esters in presence of of ^{t}BuOK and catalytic amount tetrabutyl ammonium iodide (Bu_4NI)(Scheme **4.5**, eq 1). These β-enamino esters have been further explored in the synthesis of (*R*)-homopipecolinic acid and (*R*)-homoproline esters. David *et al.* reported[15] an elegant synthesis of *exo*-cyclic enamino esters from 6-chlorohexynoate (Scheme **4.5**, eq 2). The reaction of (*S*)-1-phenylethanamine and 6-chlorohexynoate in presence of NaI and sodium carbonate gave the corresponding *exo*-cyclic enamino ester in good yield.



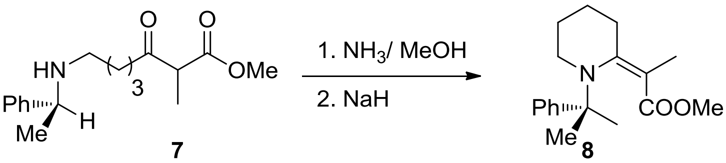
Scheme 4.5

The ring-chain tautomerism of lactone[16] was explored by Wang and co-workers for synthesizing heterocyclic β-enamino esters (Scheme **4.6**). The Reformatsky reaction of lactones with *tert*-butylacetate gave **1**, which equilibrated with the open chain hydroxy β-ketoester **2** and corresponding enol form of open chain hydroxy β-ketoester **3**. Further, the enol **3** was mesylated with MsCl to form compound **4**. Enol derivative **5** on treatment with primary amine furnished the heterocyclic β-enamino ester **6**.



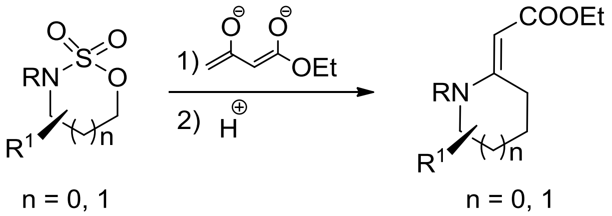
Scheme 4.6

The methods described above furnished for *E*-isomer of β-enamino ester as a major product in almost all cases. However, Lhommet and co-workers successfully developed a method[17] for β-enamino ester with tetrasubstituted *exo*-cyclic double bond with *Z*-configuration (Scheme **4.7**). The chiral amino β-ketoester methylated at active methylene **7** was used as a starting material. This on treatment with ammonia/NaH afforded the β-enamino ester **8**.



Scheme 4.7

Utility of cyclic sulfamidates has been explored for the synthesis of pyrrolidines and piperidines by Bower *et al.* (Scheme **4.8**).[18] Reaction of chiral cyclic sulfamidates with dienolate of ethyl acetoacetate directly afforded the heterocyclic exocyclic piperidines and pyrrolidines. These substrates further reduced to substituted piperidines and pyrrolidines.



Scheme 4.8

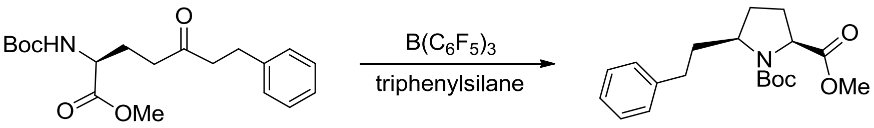
Though many syntheses of cyclic β-enamino esters have been reported, most of them use strong alkaline conditions.

Earlier, we have successfully explored the use of Meldrum’s acid and β-keto esters in the synthesis of piperidones and oxo-amino acids. As ongoing research work, we believed that it would be interesting to develop a cost effective method for β-enamino esters starting from amino acid β-keto esters. In this chapter we have demonstrated the initial study on Lewis acid catalyzed novel protocol for the synthesis of cyclic β-enamino esters.

4.2 Results and Discussion

In chapter 2, we described the synthesis of side chain modified α-amino acids starting from amino acid β-keto esters. Utility of amino acid β-keto esters has been further employed in the synthesis of synthetically challenging 5-*cis*-alkyl prolines by using strong Lewis acid such as $B(C_6F_5)_3$ and triethylsilane (Scheme **4.9**).

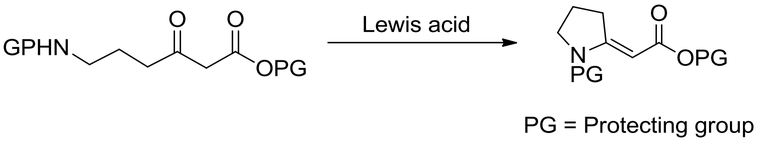
We learnt from our earlier experiments that $B(C_6F_5)_3$ has a great affinity for the hydride of triethylsilane. This reactivity led to the reductive carbamoylation under Martin's conditions[19] to afford 5-*cis*-phenethyl proline.



Scheme 4.9

4.2.1 Strategy

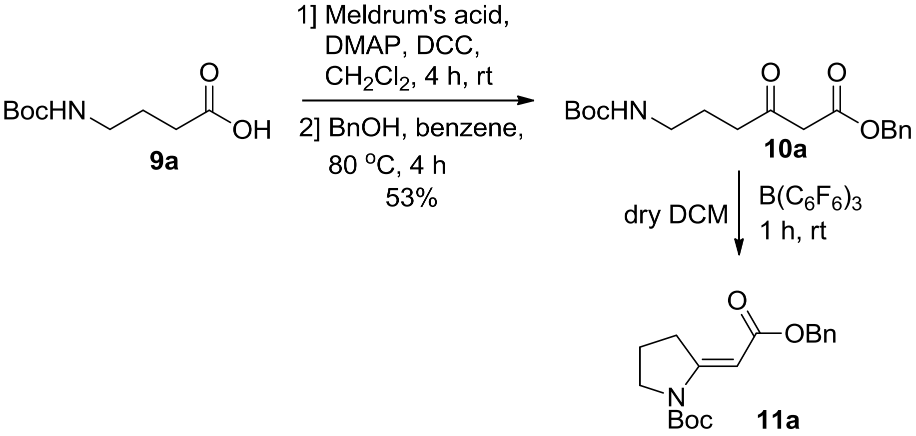
From this observation, we presumed that in the absence of any hydride source, oxo-amino acids in presence of $B(C_6F_5)_3$, possibly would furnish of β-enamino esters (Scheme **4.10**). It is known that Lewis acids can coordinate with carbonyl oxygen, thereby activating the carbonyl carbon for the facile nucleophilic attack.



Scheme 4.10

4.2.2 Model Reaction

In order to verify the strategy, we first synthesized the β-ketoester **10a** starting from the corresponding 4-*N*-^{t}Bocaminobutyric acid **9a**. Compound **10a** was treated with Meldrum's acid and coupling agent DCC in presence of DMAP in dichloromethane at room temperature 4 h. Then benzyl alcohol was added and was refluxed in benzene using a Dean-Stark apparatus to afford the expected β-ketoester **10a**.[20] Having obtained compound **10a**, we then turned our attention towards the Lewis acid catalyzed synthesis of β-enamino ester derivative (Scheme **4.11**).



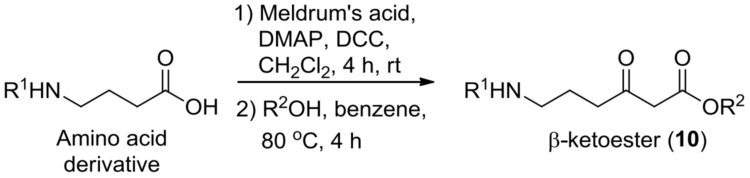
Scheme 4.11

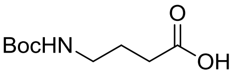
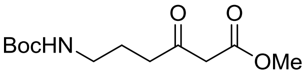
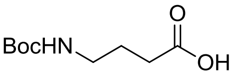
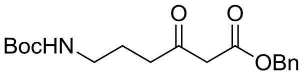
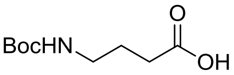
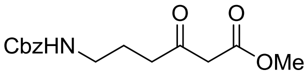
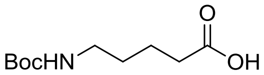
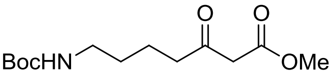
Compound **10a** was treated with the catalytic amount of $B(C_6F_5)_3$ (0.06 mmol, 10 mol%) in DCM. The reaction mixture was monitored over TLC. To our delight, we observed that compound **10a** gave the corresponding β-enamino ester ((*E*)-*tert*-butyl 2-(2-(benzyloxy)-2-oxoethylidene)pyrrolidine-1-carboxylate) **11a** in 95% in just 1h. However, during our experiment, we noticed that very trace amount of starting material was not consumed (based on the TLC). We concluded that either water eliminated during the course of the reaction may have slowed down the conversion or more catalytic amount of $B(C_6F_5)_3$ may be needed for the complete conversion. Hence, in the second trail reaction, we added 0.18 mmol amount of $B(C_6F_5)_3$ and 4 Å MS and stirred for 3 h. However, we observed that trace amount of starting material **10a** was not consumed (as per TLC). We carried out a gram scale reaction to isolate the unreacted starting material to calculate the percentage of conversion. Based on the reaction we observed that just 1% of compound **10a** was not consumed. Based on this, the isolated product **11a** was obtained in 97%. *E*-stereochemistry was confirmed by ^{1}H NMR.

4.2.3 Synthesis of β-ketoesters

Encouraged by this initial result, we planned to explore this methodology for the synthesis of few other heterocyclic β-enamino esters. In order to generalize this method and to check the protecting group compatibility few different β-ketoesters starting from the corresponding amino acids using the similar method as described in Scheme **4.1** as an initial study. Different β-ketoesters **10b–10d**, were synthesized in one pot from respective protected starting materials **9b–9d** (Table **4.1**).

Table 4.1: Synthesis of β-ketoester derivatives



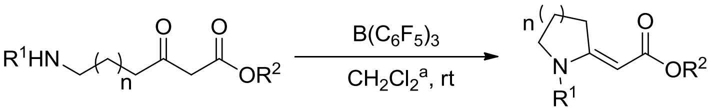
protected amino acid[a]	R^2OH[a]	β-ketoester	yield[b] %
 **9a**	MeOH	 **10a**	53%
 **9b**	BnOH	 **10b**	49%
 **9c**	MeOH	 **10c**	57%
 **9d**	MeOH	 **10d**	43%

[a] anhydrus solvent was used
[b] isolated yield

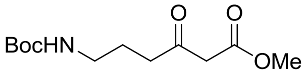
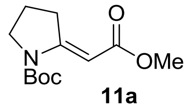
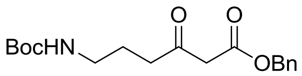
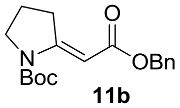
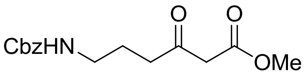
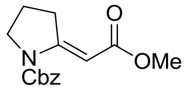
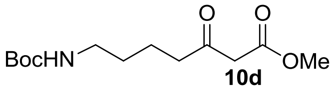
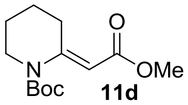
4.2.4 Synthesis of heterocyclic β-enamino esters

Amino acid β-ketoesters (**10b, 10c**), when subjected to the optimized reaction conditions $B(C_6F_5)_3$ (10 mol%) in dry DCM at room temperature afforded the corresponding β-enamino esters (**11b, 11c**) in excellent yields (up to 97%) (Table **4.2**). These β-enamino esters were well characterized by spectroscopic methods.

Table 4.2: Synthesis of β-enamino esters



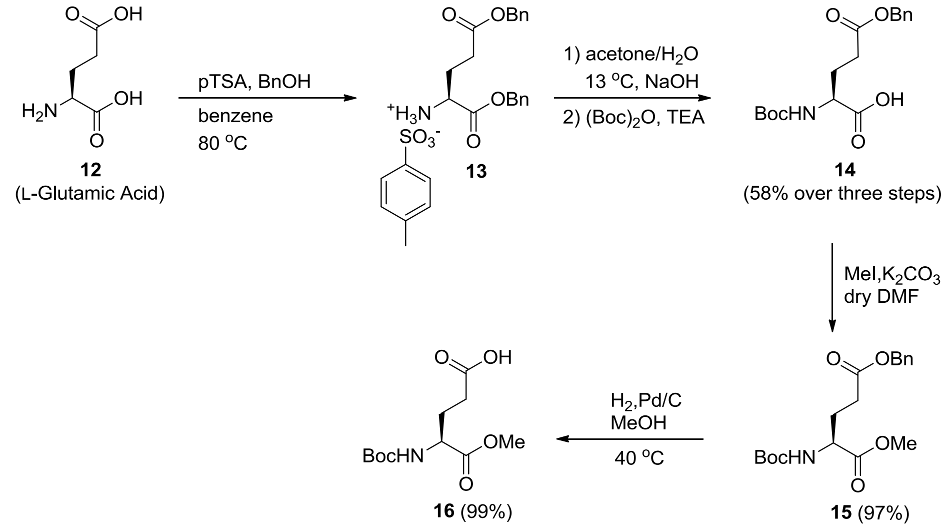
10 n = 1, 2 (**11**)

entry	β-ketoester	β-enamino esters	yield^a %
1	 **10a**	 **11a**	97%
2	 **10b**	 **11b**	95%
3	 **10c**	 **11c**	95%
4	 **10d**	 **11d**	No reaction

^{a}dry solvent was used
^{b}isolated yield

However, compound **10d** under optimized reaction conditions did not yield the expected 6-membered β-enamino ester **11d** in spite of the prolonged reaction time and more catalytic amount of $B(C_6F_5)_3$ (1 equiv). Even, the reaction under reflux conditions did not afford the expected product **11d**. Then we turned our attention towards the synthesis of chiral 5-membered β-enamino ester.

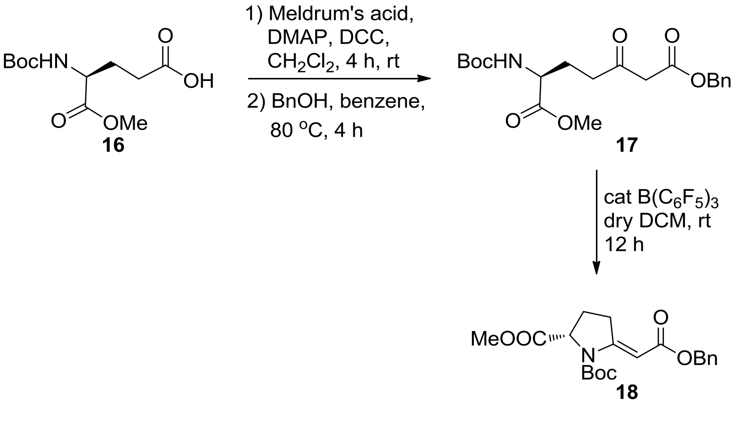
In order to synthesize chiral 5-membered β-enamino ester, synthesis of chiral amino acid β-ketoester as a precursor was planned. Thus, L-aspartic acid **12** (Scheme **4.12**) under refluxing conditions in benzyl alcohol/benzene using catalytic amount of *p*-toluene sulfonic acid (*p*TSA) afforded the corresponding dibenzyl ester **13.** Compound **13** under optimized reaction condition [acetone/H_2O (1:3), 2 N NaOH at 13 °C for 30 min], underwent facile hydrolysis of α-este.The resultant reaction mixture was immediately treated with di-*tert*-butyl dicarbonate (Boc_2O) and triethyl amine (TEA) to afford compound **14** in an overall yield of 46%. Further, esterification of α-carboxylic group of **14** was carried out using iodomethane/K_2CO_3 to give the corresponding diester **15.** Then, selective deprotection of the benzyl group using Pd/C/H_2 under hydrogenolysis conditions afforded the required substrate, *N*-Boc-L-glutamic acid 1-methyl ester **16**.



Scheme 4.12

L-Glutamic acid derivative **16** was converted to the corresponding benzyl β-ketoester **17** using the method as described in Scheme **4.11**.

The β-ketoester **17** under optimized reaction conditions:$B(C_6F_5)_3$ (10 mol %) in dry DCM at room temperature afforded **18** in 94% yield (Scheme **4.13**). Compound **18** was characterized by spectroscopic methods.



Scheme 4.13

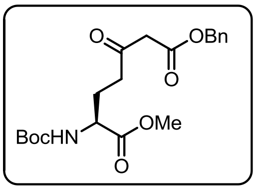
4.3 Conclusions

A novel method for the synthesis of 5-membered heterocyclic β-enamino esters have been established using catalytic amount of $B(C_6F_5)_3$. We also described an easy access to the chiral and non-chiral 5-membered heterocyclic β-enamino esters in good yields with mild reaction condition and easy purification. Our initial study on the synthesis of β-enamino esters proved to be efficient and rapid. More detailed study is currently under progress.

4.4 Experimental section

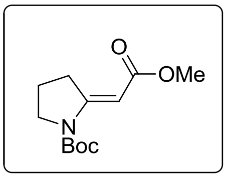
General: Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C-NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride reported in cm^{-1}. Optical rotations were measured on a polarimeter.

(*S*)-7-Benzyl 1-methyl 2-((*tert*-butoxycarbonyl)amino)-5-oxoheptanedioate (17)



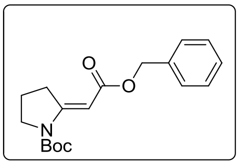
To a well stirred mixture of (*S*)-4-((*tert*-butoxycarbonyl) amino)-5-methoxy-5-oxopentanoic acid (2.5 g, 10 mmol), Meldrum's acid (1.5 g, 10 mmol), DMAP (1.6 g, 13 mmol) in anhydrous dichloromethane (40 mL) at 0 °C was added portion-wise dicyclohexyl carbodiimide (DCC) (2.7 g, 13 mmol) over 10 min at 0 °C. Then reaction mixture was allowed to warm to rt and stirred for 5 h. The precipitate formed was removed by filtration through sintered glass funnel. Filtrate was washed with aq 1M $KHSO_4$ solution (2 x 70 mL), then brine (2 x 75 mL), dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The yellowish residue was dissolved in dry benzene (30 mL), benzyl alcohol (1.5 mL, 13 mmol) added, then refluxed for 4 h. The solvent was removed under reduced pressure to give crude product, which was purified by column chromatography over silica gel eluting with Pet.Ether/EtOAc (97:5 to 90:30) to give a aight yellow oil **17** (1.7 g, 53% yield); R_f = 0.5 Pet. Ether: EtOAc (50:50); $[\alpha]^{25}_D$ -7.1 (*c* 1, MeOH); IR (Neat) cm^{-1}: 2960, 2874, 1723, 1456, 1285; δ_H (400 MHz, $CDCl_3$) 7.37-7.34 (m, 5H), 5.17 (s, 2H), 5.08 (d, *J* = 8 Hz, 1H), 4.26 (d, *J* = 4 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 2H), 2.72-2.56 (m, 2H), 2.18-2.13 (m, 1H), 1.92-1.83 (m, 1H), 1.43 (s, 9H); δ_C (100 MHz, $CDCl_3$) 201.5, 172.8, 166.9, 155.6, 135.4, 128.8, 128.6, 128.5, 80.2, 67.3, 52.7, 52.6, 49.4, 38.9, 28.4, 26.2; HRMS (ESI TOF) *m/z* calcd for $C_{20}H_{27}NO_7Na$ [M + Na]$^+$ 416.1685, found 416.1681.

(*E*)-*tert*-butyl 2-(2-methoxy-2-oxoethylidene)pyrrolidine-1-carboxylate (11a)



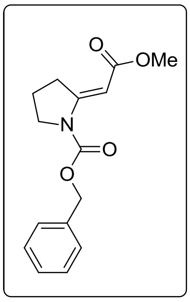
To the stirred mixture of **10a** (200 mg, 0.6 mmol) and dry dichloromethane was added $B(C_6F_5)_3$ (34 mg, 0.06 mmol) at room temperature and reaction progress was monitored by TLC. After completion of reaction (1 h) dichloromethane was evaporated under reduced pressure and residue was purified by silica column chromatography to afford white solid **10a** (0.180 g, 97% yield). R_f = 0.65 Pet. Ether/EtOAc (50:50); δ_H (400 MHz, $CDCl_3$) 6.39 (s, 1H), 3.62-3.59 (m, 5H), 3.11 (t, 2H), 1.81 (quintet, *J* = 8 Hz, 2H), 1.45 (s, 9H); δ_C (100 MHz, $CDCl_3$) 169.5, 157.9, 152.2, 95.7, 82.2, 50.8, 49.9, 32, 28.3, 21; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{19}NO_4K$ [M + K]$^+$ 280.0951, found 280.0029.

(*E*)-*tert*-butyl 2-(2-(benzyloxy)-2-oxoethylidene)pyrrolidine-1-carboxylate (11b)



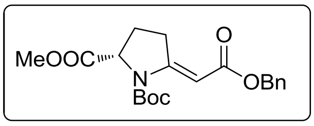
Similar experimental procedure was followed as described for (**11a**); product **11b** was obtained as a white solid (0.150 g, 95% yield). R_f = 0.7 Pet. Ether/EtOAc (50:50); δ_H (400 MHz, $CDCl_3$) 7.62-7.28 (m, 5H), 6.55 (s, 1H), 5.12 (s, 2H), 3.67 (t, *J* = 8 Hz, 2H), 3.19 (dt, *J* = 4 Hz, 2H), 1.88 (quintet, *J* = 8 Hz, 2H), 1.51 (s, 9H); HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{23}NO_4K$ [M + K]$^+$ 356.1264, found 356.0318.

(*E*)-benzyl 2-(2-methoxy-2-oxoethylidene)pyrrolidine-1-carboxylate (11c)



Similar experimental procedure was followed as described for (**11a**); product **11c** was obtained as a white solid (0.140 g, 95% yield). R_f = 0.7 Pet. Ether/EtOAc (50:50); δ_H (400 MHz, $CDCl_3$) 7.32-7.29 (m, 5H), 6.51 (s, 1H), 5.16 (s, 2H), 3.69 (t, *J* = 8 Hz, 2H), 3.60 (s, 3H), 3.12 (dt, *J* = 8 Hz, 2H), 1.84 (quintet, *J* = 8 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 169.4, 157.5, 152.9, 135.8, 128.8, 128.7, 128.6, 128.3, 96.7, 67.9, 50.9, 49.7, 31.8, 21.3; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{17}NO_4Na$ [M + Na]$^+$ 298.1055, found 298.1238.

***S*,*E*)-1-*tert*-butyl 2-methyl 5-(2-(benzyloxy)-2-oxoethylidene)pyrrolidine-1,2-dicarboxylate (18)**



Similar experimental procedure was followed as described for (**11a**); product **18** was obtained as a White solid (0.180 g, 94% yield). R_f = 0.6 Pet. Ether/EtOAc (50:50); δ_H (400 MHz, $CDCl_3$) 7.35 (m, 5H), 6.6 (s, 1H), 5.13 (d, *J* = 4 Hz, 2H), 4.61 (dd, *J* = 4 Hz), 3.75 (s, 3H), 3.40-3.38 (m, 1H), 3.07-3.03 (m, 1H), 2.23-2.18 (m, 1H), 1.47 (s, 9H); δ_C (100 MHz, $CDCl_3$) 172.3, 168.6, 157.2, 151.2, 136.9, 128.5, 127.9, 127.8, 96.6, 83, 65.3, 62.2, 52.4, 30.3, 28, 25.5; HRMS (ESI TOF) *m/z* calcd for $C_{20}H_{25}NO_6K$ $[M + K]^+$ 414.1319, found 414.0352.

4.5 Appendix IV: ^{1}H and ^{13}C spectroscopic data for representative compounds

compound No.	Fig AIV.X	data	page No.
17	Fig AIV.1 and AIV.2	1H-13C	19
18	Fig AIV.3 and AIV.4	1H-13C	20
11c	Fig AIV.5 and AIV.6	1H-13C	21

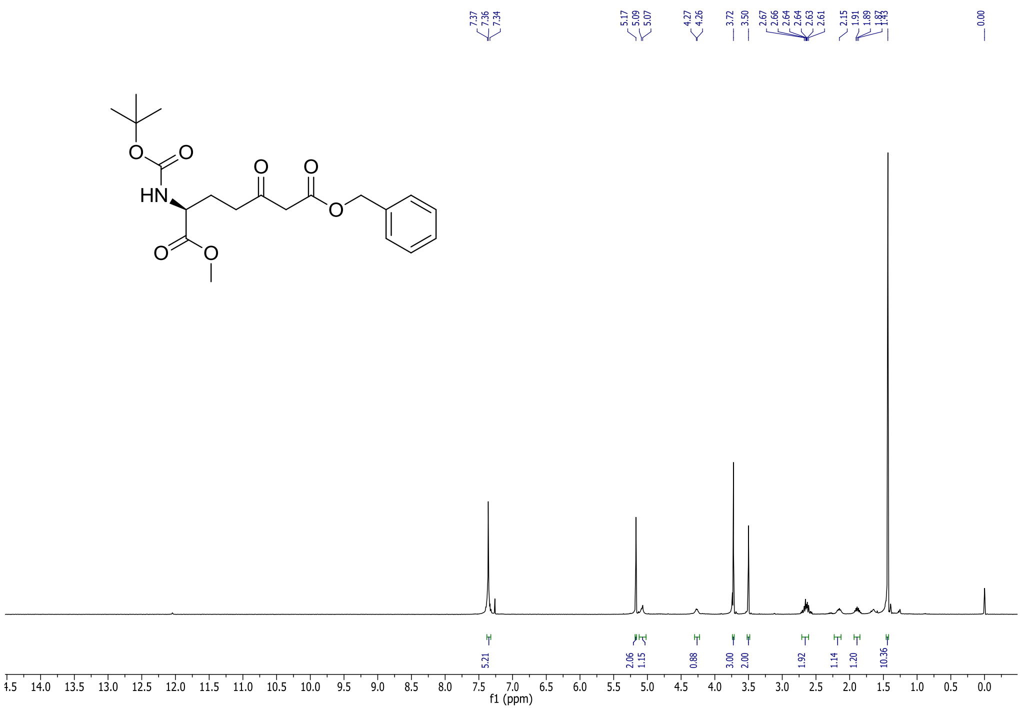


Fig AIV.1: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **17**

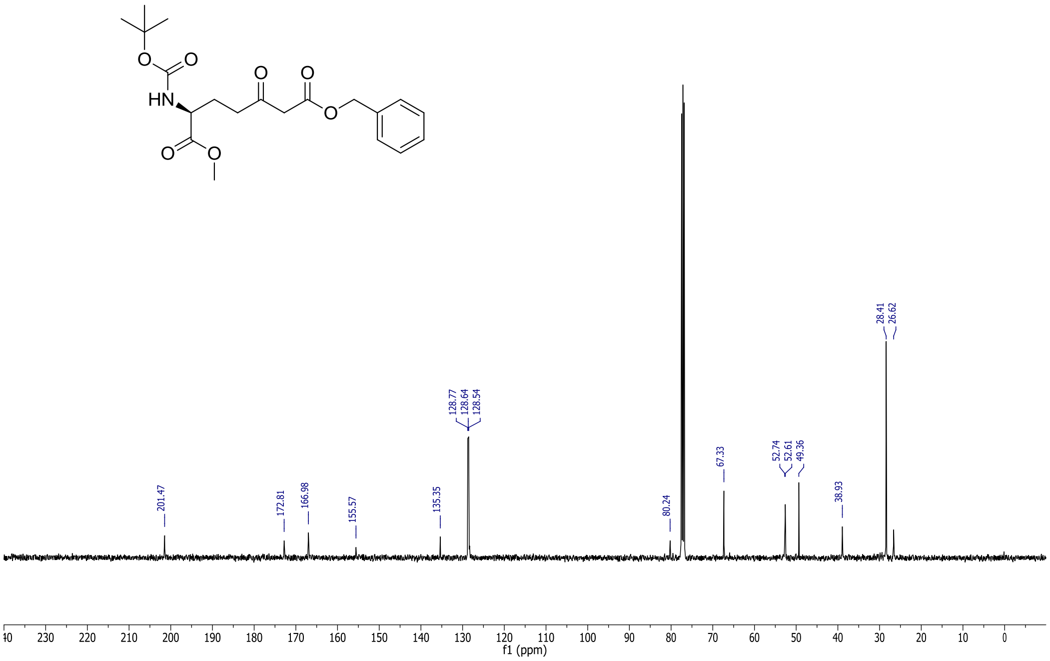


Fig AIV.2: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **17**

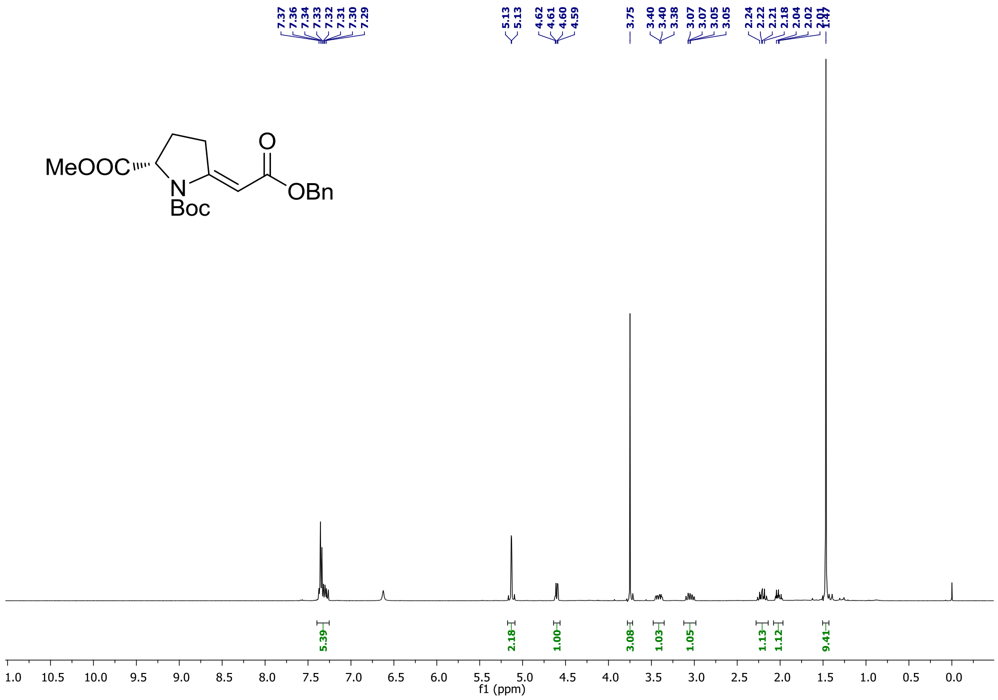


Fig AIV.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **18**

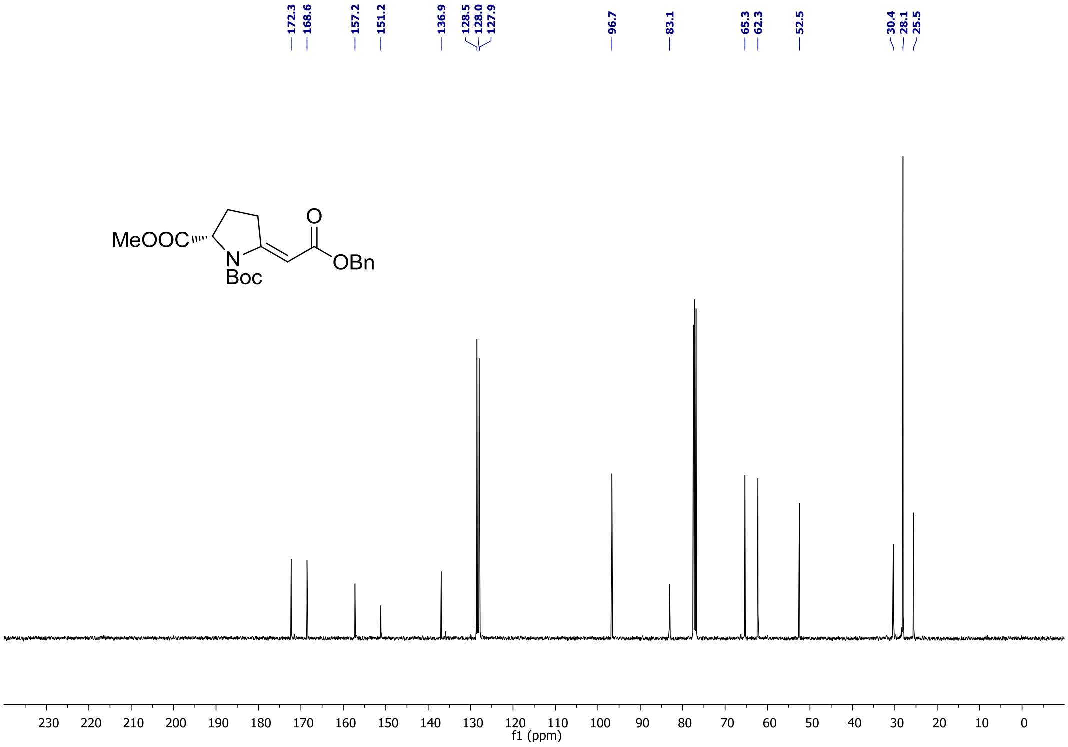


Fig AIV.4: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **18**

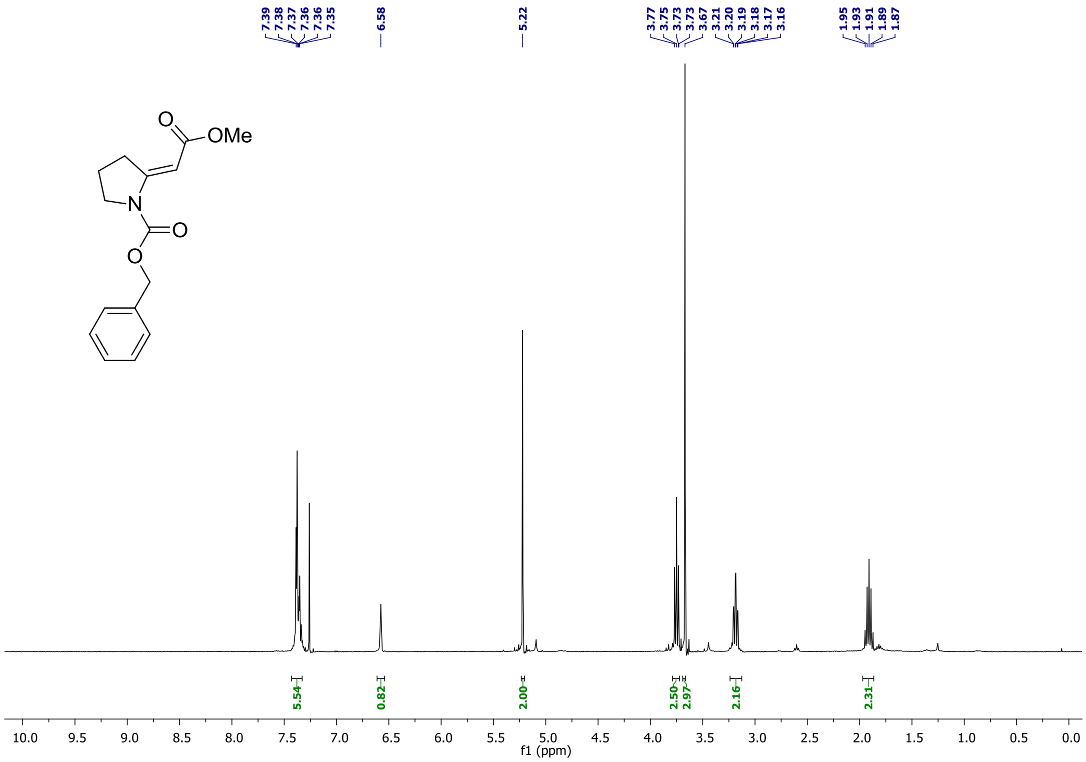


Fig AIV.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **11c**

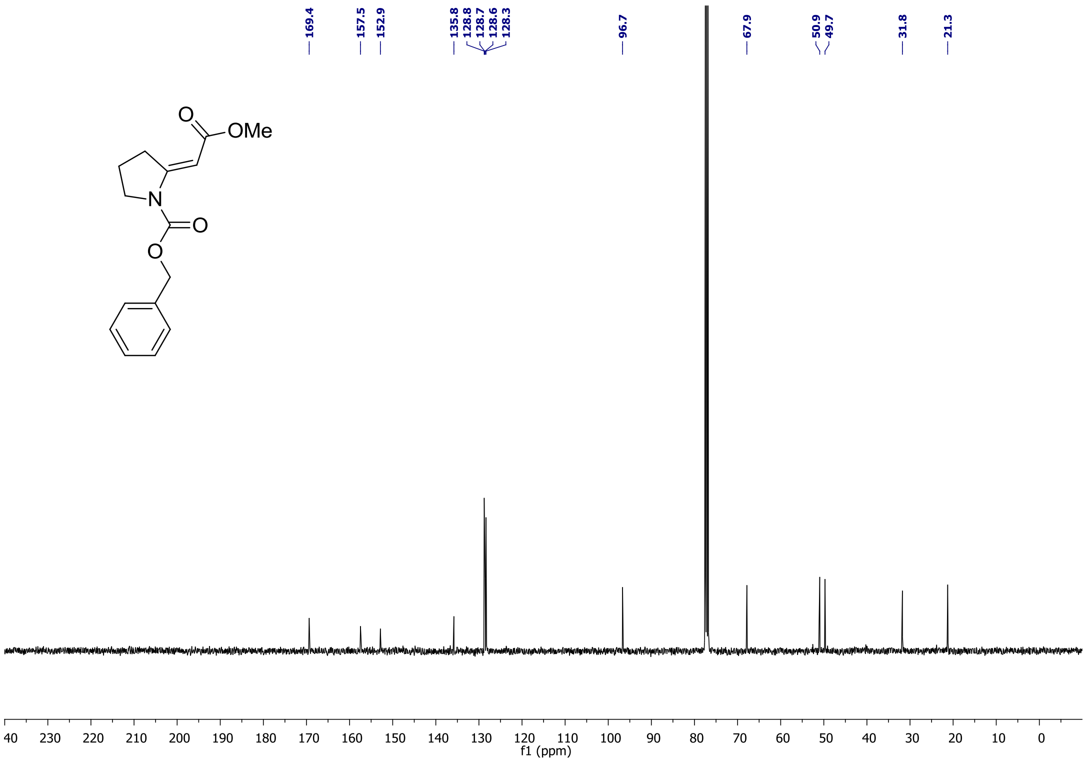


Fig AIV.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **11c**

4.6 References

[1] H. B. Dr. E. Bertele, Prof. Dr. J. D. Dunitz, Dr. F. Elsinger, Prof. Dr. A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, Dr. E. F. Meyer, D. M. Pesaro, D. R. Scheffold, *Angew. Chem., Int. Ed.* **1964**, *3*, 490–496.

[2] Y. Cheng, H. B. Yang, M. X. Wang, D. J. Williams, *Tetrahedron* **2002**, *58*, 2821–2829.

[3] H. Taguchi, H. Yazawa, J.F. Arnett, Y. Kishi, *Tetrahedron Lett.* **1977**, *18*, 627–630.

[4] a) S. J. Danishefsky, S. J. Etheredg, *J. Org. Chem.* **1974**, *39*, 3430–3432; b) S. Wang, C. A. Coburn, W. G. Bornmann, S. J. Danishefsky, *J. Org. Chem.* **1993**, *58*, 611–617.

[5] J. R. Luly, H. Rapoport, *J. Am. Chem. Soc.* **1983**, *105*, 2859–2866.

[6] A. Stapon, R. F. Li, C. A. Townsend, *J. Am. Chem. Soc.* **2003**, *125*, 15746-15747.

[7] N. Hashimoto, T. Funatomi, T. Misaki, Y. Tanabe, *Tetrahedron* **2006**, *62*, 2214–2223.

[8] S. R. Hussaini, M. G. Moloney, *Org. Biomol. Chem.* **2006**, *4*, 2600–2615.

[9] P. Langer, I. Freifeld, *Chem. Commun.* **2002**, 2668-2669.

[10] O. David, J. Blot, C. Bellec, M. C. Fargeau-Bellassoued, G. Haviari, J. P. Celerier, G. Lhommet, J. C. Gramain, D. Gardette, *J. Org. Chem.* **1999**, *64*, 3122–3131.

[11] M. Roth, P. Dubs, E. Götschi, A. Eschenmoser, *Helv. Chim. Acta* **1971**, *54*, 710–734.

[12] M. C. Elliott, S. V. Wordingham, *Synthesis* **2006**, 1162–1170.

[13] J. H. Kim, H. Shin, S. G. Lee, *J. Org. Chem.* **2012**, *77*, 1560–1565.

[14] P. H. Lambert, M. Vaultier, R. Carrie, *J. Org. Chem.* **1985**, *50*, 5352–5356.

[15] O. David, M. C. Fargeau-Bellassoued, G. Lhommet, *Tetrahedron Lett.* **2002**, *43*, 3471–3474.

[16] M. X. Wang, Y. Liu, H. Y. Gao, Y. Zhang, C. Y. Yu, Z. T. Huang, G. W. J. Fleet, *J. Org. Chem.* **2003**, *68*, 3281–3286.

[17] S. Calvet-Vitale, C. Vanucci-Bacque, M. C. Fargeau-Bellassoued, G. Lhommet, *J. Org. Chem.* **2006**, *71*, 2071–2077.

[18] J. F. Bower, P. Szeto, T. Gallagher, *Org. Lett.* **2007**, *9*, 4909–4912.

[19] J. B. Brenneman, R. Machauer, S. F. Martin, *Tetrahedron* **2004**, *60*, 7301–7314.

[20] A. R. Mohite, P. R. Sultane, R. G. Bhat, *Tetrahedron Lett.* **2012**, *53*, 30–35.