STUDIES ON SYNTHESIS OF BIOACTIVE NATURAL PRODUCTS: TYROMYCIN A, PILIFORMIC ACID, ROCCELLIC ACID, BYSSOCHLAMIC ACID & ISOLINDERANOLIDE B

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

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PUNE - 411 008

DEDICATED TO MY PARENTS

For Their Warmth, Humor And Ethics

CONTENTS

ACKNOWLEDGEMENTS

I wish to express my wholehearted gratitude to my research supervisor Dr. N. P. Argade for his masterly guidance, invaluable suggestions and perceptive criticism while carrying out the present work. His untiring enthusiasm, moral support, kind care and help out of the way led me to overcome all the difficulties I encountered during this endeavor.

It is my privilege to thank Dr. K. N. Ganesh, Head OCS Division, for his constant encouragement and keen interest shown during the progress of the work. Thanks are due to the Director, NCL for providing the infrastructure and necessary facilities. I take this opportunity to thank Dr. Suresh Iyer and Dr. S. S. Bhosale for their help and encouragement during this work.

The work would not have been complete without the help provided by the analytical groups. My sincere thanks to Dr. Rajmohananan, Dr. Bhalerao, Mrs. U. D. Phalgune and Mr. V. T. Sathe for providing NMR training as well as for recording the spectra. I would like to thank Mrs. Shantakumari, Mrs. Kale, Mrs. Joshi for their help in recording the Mass and IR spectra and all the library staff for providing documentation.

My special thanks to lab-friends Dr. Vallabh, Dr. Anil, Santosh, Anirban, Easwar, Mukulesh, Manoj, Mehrajuddin, Sunil, Sanjib and Kishan for their cheerful co-operation and help in every aspect throughout this work.

My heartfelt thanks are due to my friends Drs. C. Ramesh, Vinay, Murugan, Thiagu, Kicha, Selvaraj, Saravanan, Anbu, Karups, Sanki, Suresh and Debasis for their friendly suggestions and timely help, making my stay at NCL a very comfortable and memorable one. I would like to extend my thanks to Subbu, Santhanam uncle, Jayanthi, Pashu, Sankar, Malli, Selvakannan, Vijayraj, Ramesh, KT, Ilan, Protein, Devaraj, Nagendra, Mandar, Siddharth, Vishal, Girish, Sanjay, Prabal, Dumbre, Bala, Dilip, Vidyesh, Bidhan and my other colleagues. I thank Mr. P. Pawar for his help and Mr. T. Patil and Mr. Chavan for their assistance.

I sincerely acknowledge CSIR, New Delhi for the award of a research fellowship.

Finally, no words can express the feelings towards my parents and family members, who have contributed and sacrificed a lot for me to reach this stage and will always remain a sole source of inspiration in my life.

S. Mangaleswaran

GENERAL REMARKS

- All the solvents used were purified according to the literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned and silica gel (60-120 mesh/100-200 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, phosphomolybdic acid (in ethanol), bromocresol green (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (conc. 1 μM) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), MSL 300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethyl silane.
- Mass spectra were recorded on Finning-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.
- Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser. Elemental analyses observed for all the newly synthesized compounds were within the limits of accuracy (± 0.3%).
- All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
- All the compounds previously known in the literature were characterized by comparison of their R_f values on TLC, IR and NMR spectra as well as melting point (in case of solid) with authentic samples.
- All the new experiments were repeated two or more times.
- Starting materials were obtained from commercial sources or prepared using known procedures.

LIST OF PUBLICATIONS

1. An Efficient Synthesis of (±)-Piliformic Acid
   S. Mangaleswaran and N. P. Argade
   J. Chem. Soc., Perkin Trans. 1, **2000**, 3290.
2. A Facile Synthesis of Naturally Occurring Aminopeptidase Inhibitor Tyromycin A
   S. Mangaleswaran and N. P. Argade
   J. Org. Chem. **2001**, *66*, 5259.
3. First Efficient Synthesis of (±)-*erythro*-Roccellic acid
   S. Mangaleswaran and N. P. Argade
   J. Chem. Soc., Perkin Trans. 1, **2001**, 1764.
4. An Efficient Synthesis of Dimethylmaleic Anhydride
   S. Mangaleswaran and N. P. Argade
   Synthesis **2002**, 865.
5. An Easy Access to (*E*)-Alkylidenesuccinic Acids
   S. Mangaleswaran and N. P. Argade
   Synthesis **2003**, 343.

6 A Facile Synthesis of CD45 Protein Tyrosine Phosphatase Inhibitor Marine Natural Product Pulchellalactam
S. Mangaleswaran and N. P. Argade (Manuscript Communicated to *Tetrahedron Letters*)

ABBREVIATIONS

AIBN	α,α'-Azobisisobutyronitrile
Aq.	Aqueous
ATP	Adenosine triphosphate
BINAP	Binaphthyl
CAN	Ceric ammonium nitrate
CMR	Carbon magnetic resonance
m-CPBA	*meta*-Chloroperbenzoic acid
DBP	Dibenzoyl peroxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMMA	Dimethylmaleic anhydride
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulphoxide
EIA	Enzyme immuno assay
equiv	Equivalent
Fig.	Figure
FPP	Farnesylpyrophosphate
FPTase	Farnesyl-protein transferase
h	Hour(s)
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
Hz	Hertz

o-IBX	*ortho*-Iodoxybenzoic acid
IC	Inhibitory concentration
IR	Infra red
IMDA	Intramolecular Diels Alder
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
MA	Maleic anhydride
mmol	Millimolar
min.	Minute(s)
mL	Millilitre
MOM	Methoxymethyl
MS	Mass spectrum
NBS	*N*-Bromosuccinimide
PCC	Pyridinium chlorochromate
PCy_3	Tricyclohexylphosphine
PMB	*p*-Methoxybenzyl
PMR	Proton magnetic resonance
PPs	Protein phosphtase
PPA	Polyphosphoric acid
PLE	Porcine liver esterase
PPL	Pig pancreatic lipase
PPM	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
rt	Room temperature
SAR	Structure activity relationship
SPOS	Solid phase organic synthesis

TEA	Triethylamine
TEP	Triethylphosphite
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
TsCl	*p*-Toluenesulfonyl chloride
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPP	Triphenylphosphine
UV	Ultraviolet

ABSTRACT

The present dissertation is divided into three chapters. First chapter reports a concise account on chemistry of monoalkylsubstituted, dialkylsubstituted and complex dialkylsubstituted maleic anhydrides where as the second chapter describes in detail our contribution towards the synthesis of potential building block dimethylmaleic anhydride, aminopeptidase inhibitor Tyromycin A, cytotoxic Piliformic acid and antituberculor Roccellic acid. This chapter also describes a facile synthesis of CD45 protein tyrosine phosphatase inhibitor (*Z*)-Pulchellalactam and our ongoing studies on synthesis of bioactive natural products Isolinderanolide B and Byssochlamic acid (**Figure 1**). Third chapter presents the experimental procedures, spectral and analytical data of the compounds synthesized.

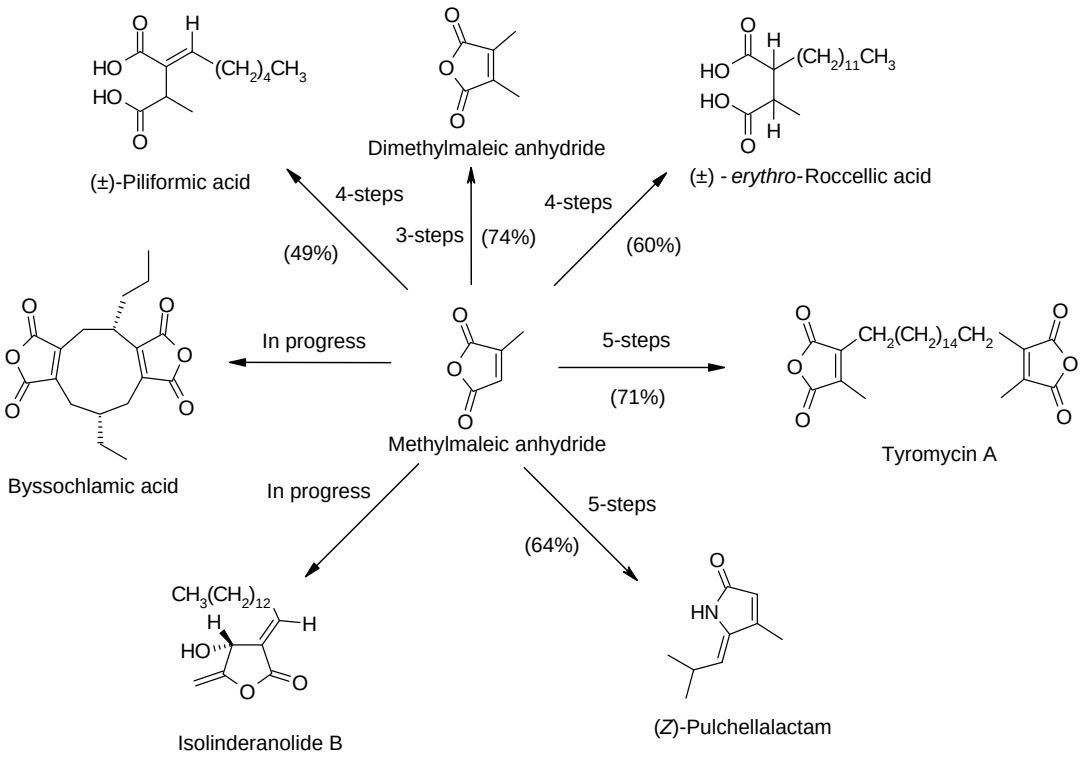


Figure 1: Methylmaleic anhydride to dimethylmaleic anhydride and bioactive natural products

CHAPTER ONE: Concise Account on Chemistry of Monoalkylsubstituted, Dialkylsubstituted and Complex Dialkylsubstituted Maleic Anhydrides

Recently, several alkylmethylmaleic anhydrides and acyclic/cyclic compounds containing two maleic anhydride moieties have been isolated as bioactive natural products. This chapter portrays a concise account on isolation, bioactivity and syntheses of these bioactive natural products. This chapter is divided into three sections. The first section gives a brief summary about monoalkylsubstituted maleic anhydrides. The second section presents a concise account on dilakylsubstituted maleic anhydrides and the final section summarizes the recent developments in the area of complex dialkylsubstituted maleic anhydrides and nonadrides.

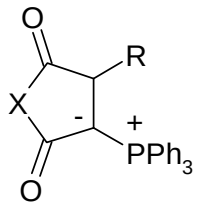
CHAPTER TWO: Synthesis of Dimethylmaleic Anhydride and Bioactive Natural Products

This chapter is divided into four sections. The first section presents a brief introduction about the phosphorous ylides generated from maleimide and maleic anhydride. The second section describes an efficient synthesis of a potential building block dimethylmaleic anhydride and synthesis of aminopeptidase inhibitor Tyromycin A. The third section summarizes an efficient synthesis of cytotoxic Piliformic acid and antituberculor *erythro*-Roccellic acid, while the fourth section describes a facile synthesis of (*Z*)-Pulchellalactam and our ongoing studies on synthesis of bioactive natural products Isolinderanolide B, and Byssochlamic acid.

SECTION A: An Introduction to Phosphorous Ylides Derived from Maleimides and Maleic Anhydrides

This section presents an introduction about the preparation of phosphorous ylides from maleimides and maleic anhydrides and their reported reactions. A number

of stable phosphorous ylides are easily prepared by reacting slight excess of triphenylphosphine with maleimide/citraconic anhydride in glacial acetic acid.



R = H, X = O
R = H, X = NH
R = H, X = NPh
R = Me, X = O
R = Me, X = NPh

The succinimide ylides were found to react with a variety of aldehydes giving the corresponding (*E*)-alkylidene derivatives in high yields. Recently, we have developed a reaction condition in our laboratory for the condensation of methylmaleimide-TPP adduct with aliphatic aldehydes and employed it for the synthesis of anticancer agent Chaetomellic Acid A.

SECTION B: I. An Efficient Synthesis of Methyl and Dimethylmaleimides/ Anhydrides

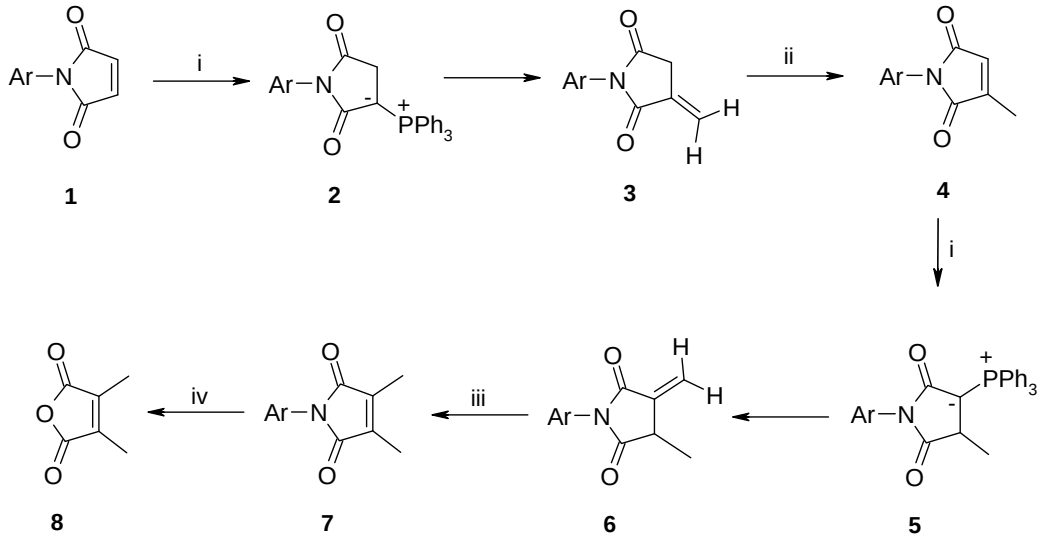
The utilities of methyl and dimethylmaleimides/anhydrides have been well proven in practice. They have been used as potential building blocks for the synthesis of many natural products, as monomers in polymer chemistry and some of their derivatives possess herbicidal, fungicidal and defoliant activities.

Several synthetic approaches to dimethylmaleic anhydride (**8**) using a variety of synthetic strategies are known in the literature. Only few methods are known with an overall yield in excess of 50%. Hence, there is a need to develop simple and efficient methods for the synthesis of alkylmaleimides/anhydrides and symmetrical/unsymmetrical dialkylmaleimides/anhydrides. We herein present yet another new approach employing the condensation reactions of maleimide-TPP adduct with a series of aldehydes.

This section describes a facile three-step synthesis of dimethylmaleic anhydride (**8**) with 74% overall yield starting from maleimide **1**, via methylmaleimde **4**, using two Wittig reactions with paraformaldehyde followed by alkaline hydrolysis (**Scheme 1**).

All attempts to transform higher analogues of **3** to **4** by using thermal (heat, tetralin reflux), base catalysed (pyridine, TEA, DBU, NaH, *t*-BuOK, *t*-BuLi) and transition metal induced [$RuCl_3$, $HRuCl(PPh_3)_3$, $RhCl_3$, $HRhCl(PPh_3)_3$] trisubstituted exocyclic to trisubstituted endocyclic carbon-carbon double bond isomerization proved futile.

Scheme 1



Ar = *p*-Tolyl

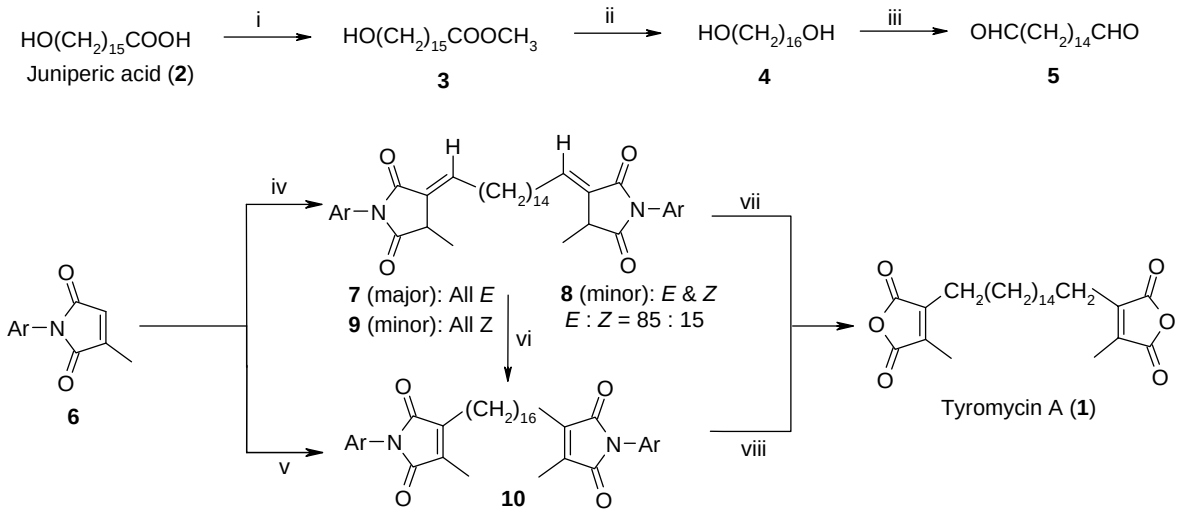
Reagents, conditions and yields: (i) PPh_3, $(CH_2O)_n$, AcOH, reflux, 1 h (92%); (ii) TEA, THF, reflux, 3 h (93%); (iii) 50 °C, 3 h (98%); (iv) (a) aq. MeOH, KOH, reflux, 2 h; (b) H^+/HCl (97%).

SECTION B: II. A Facile Synthesis of Naturally Occuring Aminopeptidase Inhibitor Tyromycin A

Aminopeptidases are the enzymes that are bound to the surfaces of mammalian cells and have been recognized as a target for immunomodulating drugs. Tyromycin A (**1**) is one of the two aminopeptidase inhibitors known in the literature. The first synthesis of **1** has been completed by using the well-known decarboxylative Barton-radical coupling reaction. Development of a new facile synthetic route to this bioactive natural product **1** is imperative. This section describes a two-step synthesis of bioactive natural product Tyromycin A (**1**) in 71% yield employing the condensation of methylmaleimide-TPP adduct with 1,16-hexadecanedial (**5**) as the key step and this method also offers an easy

access to Tyromycin congeners for structure-activity relationship studies. The desired dialdehyde **5** was prepared from naturally occurring Juniperic acid (**2**) in 3-steps with 72% overall yield (**Scheme 2**).

Scheme 2



Ar = *p*-Tolyl

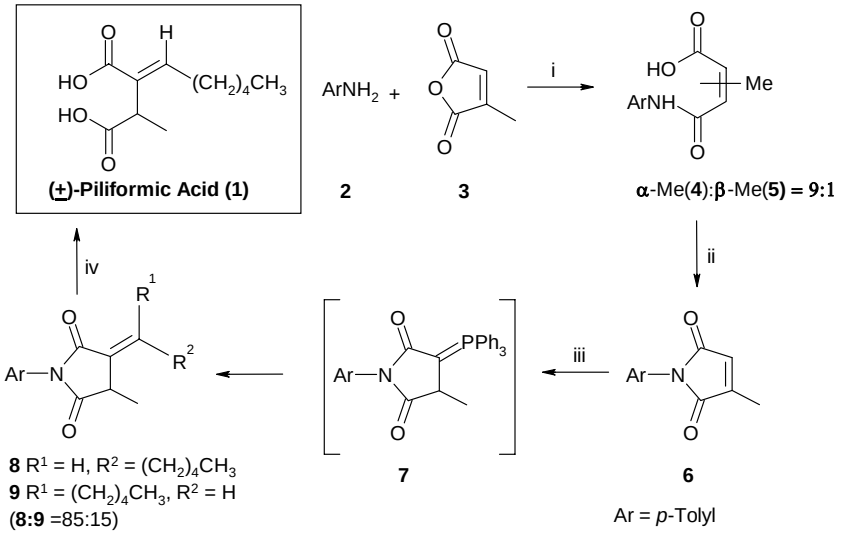
Reagents, conditions and yields: (i) CH_2N_2, Et_2O, 0 ^oC, 2 h (95%); (ii) LAH, Et_2O, rt, 2 h (98%); (iii) PCC, CH_2Cl_2, rt, 10 h (77%); (iv) TPP, AcOH, **5**, reflux, 10 h (70%); (v) (a) TPP, AcOH, **5**, reflux, 10 h; (b) △, 140-150 ^oC, 30 min (72%); (vi) Tetralin, reflux, 1 h (98-100%); (vii) (a) CH_3ONa, CH_3OH, reflux, 2 h; (b) H^+/HCl (60%); (viii) (a) KOH, H_2O, THF, CH_3OH, reflux, 2 h; (b) H^+/HCl (98%).

SECTION C: I. An Efficient Synthesis of (±)-Piliformic Acid

Piliformic acid (2-hexylidene-3-methylsuccinic acid, **1**) was identified in 1985 as a metabolite of several closely related fungi of the Xylariaceous genera. In nature, Piliformic acid (**1**) exists in *levo*, *dextro* and *racemic* form, although the absolute stereochemistry has not been determined. Till date only one four-step synthesis of this natural product **1** is known starting from Meldrum's acid with 1.75% overall yield. Recently the biosynthesis of Piliformic acid (**1**) has been studied and the provision of a simple synthetic approach to this natural product is a challenging task of current interest. This section describes an easy four-step access to naturally occurring (±)-(*E*)-2-

hexylidene-3-methylsuccinic acid (Piliformic acid, **1**) with 49% overall yield via Wittig reaction of methyltriphenylphosphoranylidenesuccinimide **7** with hexanal followed by an acid induced hydrolysis of the formed succinimide derivatives (*E)*-**8** plus (*Z)*-**9**. The hydrolysis furnished only the mixture of (*E*)- and (*Z*)-Piliformic acids (85:15) in 98% yield without migration of the carbon–carbon double bond. Recrystallization of this mixture from excess of hot water gave the desired pure (*E*)-isomer **1** in more than 70% yield (**Scheme 3**).

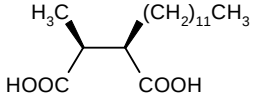
Scheme 3



Reagents, conditions and yields: (i) Et_2O, rt, 1 h, (95%); (ii) Ac_2O/NaOAc, water bath, 60-65 ºC, 1 h (90%); (iii) TPP, AcOH, hexanal, reflux, 10 h (83%); (iv) (a) AcOH, con. HCl, reflux, reflux, 60 h (98%); (b) Recrystallization from excess of hot water, (*E*)-isomer (97%).

SECTION C: II. First Efficient Synthesis of (±)-*erythro*-Roccellic Acid

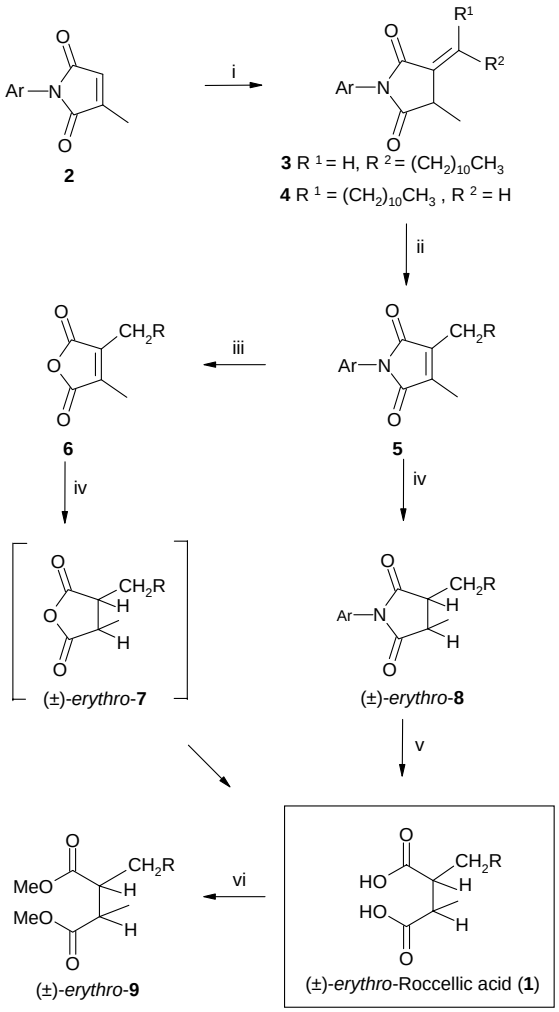
(+)-Roccellic acid [(2*R*, 3*S*)-2-dodecyl-3-methylbutanedioic acid, **1a**] occurs in lichens and was isolated in 1898. In the past century it has been isolated from several lichen species with a major contribution from Siegfried Huneck's group.



(2*R*, 3*S*)-2-Dodecyl-3-methylbutanedioic acid (**1a**)

Its absolute configuration has been established by Åkermark by degrading **1** to its two isomeric monomethyl esters. Roccellic acid possesses antituberculosis activity and

Scheme 4



Ar = *p*-Tolyl, R = $(CH_2)_{10}CH_3$

Reagents, conditions and yields: (i) TPP, AcOH, dodecanal, reflux, 10 h (82%); (ii) TEA, THF, reflux, 48 h (98%); (iii) (a) KOH, THF, MeOH, H_2O, reflux, 2 h; (b) H^+/HCl (98%); (iv) Adam's catalyst, petroleum ether, H_2, rt, 10 h (**1**: 60%; **8**: 95%); (v) CF_3COOH, con. HCl, reflux, 48 h (98%); (vi) CH_2N_2, Et_2O, rt, 2 h, (98%).

concentration dependent plant growth promoter/inhibitor activity. To date, one synthesis of unnatural (±)-*threo*-Roccellic acid is known starting from diethylmalonate and during these studies small amount of (25 mg) (±)-*erythro*-Roccellic acid has been obtained via 8-step synthesis with 0.026% overall yield. Recently, Fensterbank and coworkers have completed the first asymmetric synthesis of (+)-*erythro*-roccellic acid (**1a**), by employing a highly diasteroselective addition of a lithium ester enolate to a bisulfinyl acceptor as a key step.

The provision of a facile synthetic approach to this bioactive natural product roccellic acid is essential. This section presents the first efficient synthesis of (±)-*erythro*-Roccellic acid (**1**) starting from citraconimide **2** via *cis*-reduction of maleimide **5** to succinimide **8** employing catalytic hydrogenation reaction with Adam's catalyst (**Scheme 4**). The reaction of maleimide **5** to succinimide **8** was much more clean and efficient as compared to the conversion of **6** to **1** via **7**. The *cis*-succinimide derivative **8** on hydrolysis in a refluxing mixture of trifluoroacetic acid and conc. hydrochloric acid (1:1) gave a mixture of desired *erythro* and undesired *threo* isomers (93:7, by ^{1}H NMR, from integral values of methine protons) in 48 h with 98% yield. Recrystallization of above mixture of *erythro* and *threo* isomers (93:7) from acetone gave the desired (±)-*erythro*-Roccellic acid (**1**) in 80% yield.

In our hands, the asymmetric hydrogenation of maleimide **5** and related substrates using Ru-BINAP complexes to synthesize enantiomerically pure (+)-Roccellic acid [(2*R*, 3*S*)-2-dodecyl-3-methylbutanedioic acid, **1a**] met with failure.

SECTION D: I. Synthetic Studies on Isolinderanolide B

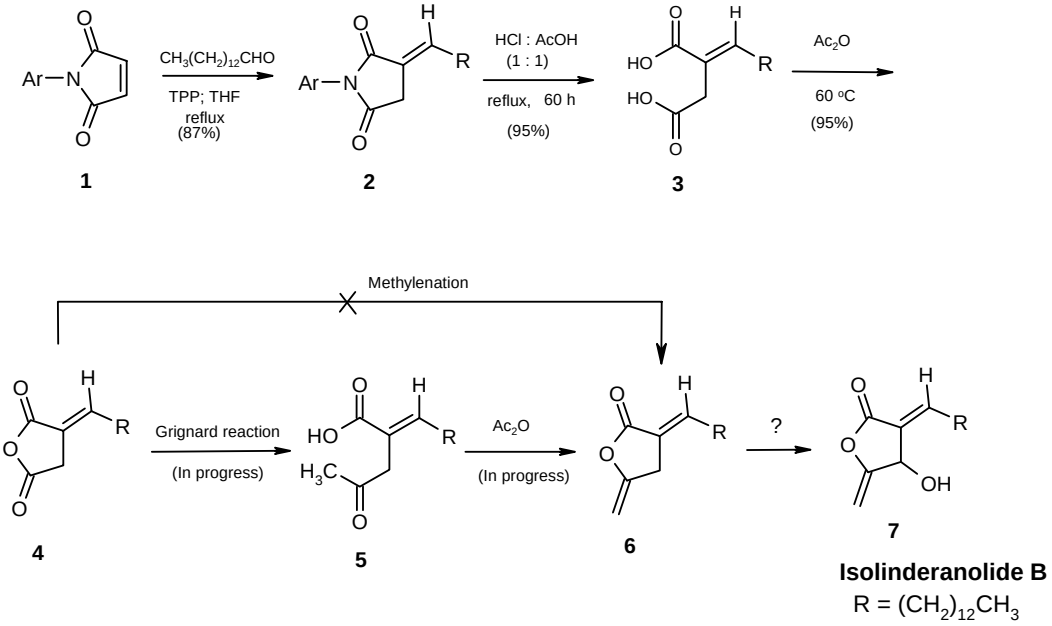
Isolinderanolides with cytotoxic activity have been isolated from the leaves of several members of the species *Lauraceae*. Two syntheses are known for the construction of α-alkylidene-β-hydroxy-γ-methylene butyrolactone structural framework. The first synthesis involves the use of α-phenylselenenyl esters, which on aldol reaction with propargyl aldehyde followed by oxidation to the selenoxide and elimination provides the final compound. In the second synthesis, the butyrolactone was prepared via steroselective aldol reaction of α,β-unsaturated carboxylate α-anion equivalent, derived from optically active α-(arylsulfinyl)carboxylate and

bromomagnesium diisopropylamide, with propargyl aldehyde as a key step. Development of a new facile synthetic route to this bioactive natural product is imperative.

This section describes the synthetic studies on Isolinderanolide B starting from maleimide **1.** The in situ generated maleimide-TPP adduct condensed efficiently with tetradecyl aldehyde to give tetradecylidenesuccinimide **2**. The compound **2** on hydrolysis and dehydrative cyclisation provided exoalkylidenesuccinic anhydride **4**. In our hands, the carbonyl olefination of **4** using Wittig and Petasis methods to synthesize the enol lactone **6** met with failure. The synthesis of enol lactone **6** would be possible by Grignard reaction followed by treatment with acetic anhydride as depicted in the Scheme 5. Further efforts to design **7** are in progress (**Scheme 5**).

During these studies, using Chemspeed Parrallel Synthesizer, a general method has been developed for the synthesis of exoalkylidenesuccinic acids by condensing maleimide-TPP adduct with various aliphatic aldehydes.

Scheme 5

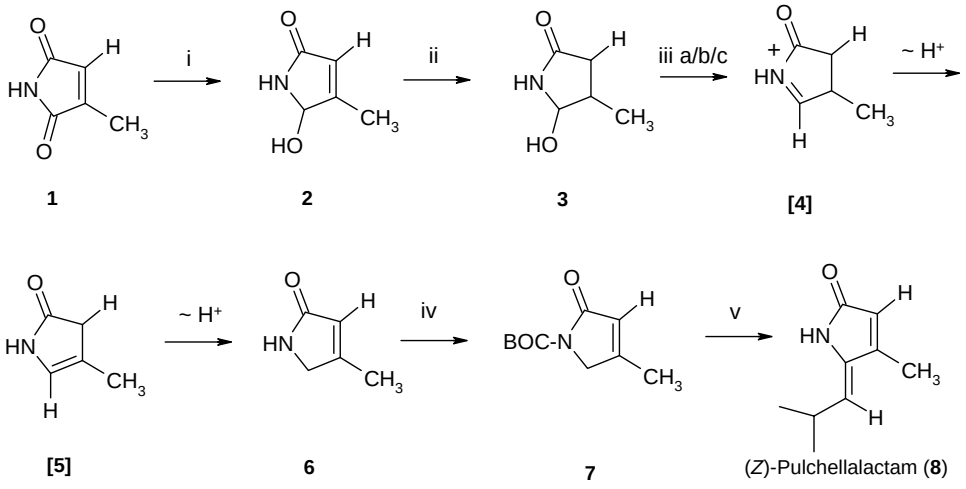


SECTION D: II. Synthetic Studies on (*Z*)-Pulchellalactam

A potent CD45 protein tyrosine phosphatase inhibitor, (*Z*)-Pulchellalactam (**8**) was isolated from marine fungus *Corollospora pulchella*. Till date, two syntheses are known and the first synthesis has been completed by Li and co-workers from BOC-protected glycine in 6-steps with 32% overall yield and the geometry of double bond has been proved to be *Z*.

We have completed a facile synthesis of (*Z*)-pulchellalactam (**8**) from citraconimde (**1**) by employing a double reductive dehydration strategy as the key step to synthesize the potential intermediate **6** which on BOC protection and condensation with isobutyraldehyde furnished **8** in 5-steps with 64% overall yield. (**Scheme 6**).

Scheme 6



Reagents, conditions and yields: (i) $NaBH_4$, EtOH, - 40 ºC, 1 h (~100%); (ii) Pd/C, H_2, MeOH, rt, 2 h (~100%); (iii) (a) *p*-TSA, benzene, reflux, 3 h (25-30%); (b) AcOH, 80 ºC, 1 h (50-55%); (c) Amberlyst, CH_3CN, reflux, 2 h (92%); (iv) $(BOC)_2O$, DMAP, CH_3CN, rt, 3 h (85%); (v) NaH, THF, isobutyraldehyde, rt, 5 min. (82%).

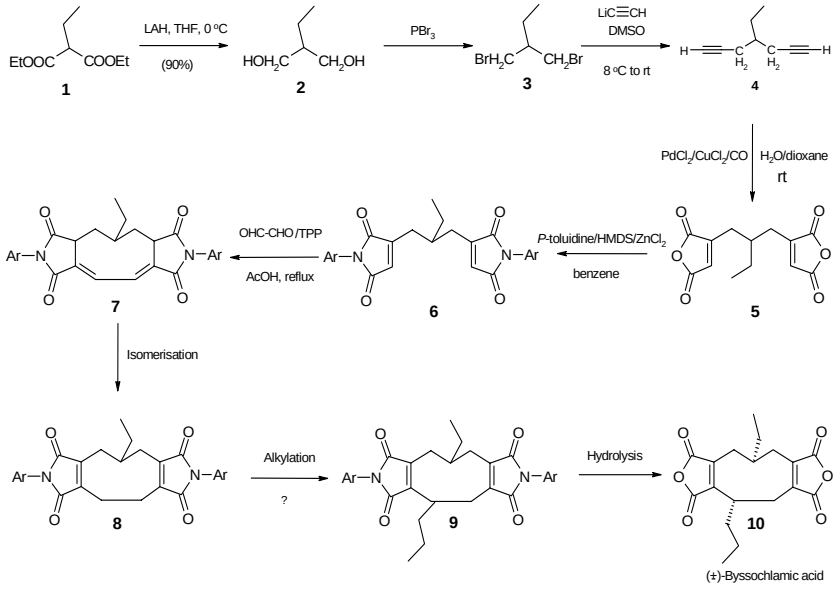
Our earlier synthetic efforts starting from *N*-PMB imide, *N*-Benzyl imide and *N*-Aryl imide failed to give the desired compound.

SECTION D: III. Synthetic Studies on Byssochalmic Acid

Byssochlamic acid, a metabolite first isolated from ascomycete *Byssochlamys fulva*, is a member of the small but structurally unique class of natural products known as

nonadrides. The absolute configuration of byssochlamic acid was determined by degradative experiments, which caused fission of the nine-membered ring and gave products with known stereochemistry. One enantiospecific and two racemic syntheses have been reported by James D. White and Gilbert Stork starting from bromomaleic anhydride and suitably substituted tetralone derivative via diolide and bis-hydroquinone dimethyl ether respectively. Our plan to synthesize Byssochlamic acid starting from diethyl ethylmalonate (**1**) including synthesis of diacetylenic compound **4** via bis-anhydride system **5** followed by double Wittig reaction using glyoxal is depicted in Scheme 7. The sequence of reactions described in Scheme 7 would provide a rapid access to this desired bioactive natural product and very recently, we have initiated work towards the same (**Scheme 7**).

Scheme 7



CHAPTER THREE: Experimental Procedures and Data

This chapter presents the experimental procedures, spectra of important molecules, tabulated analytical and spectral data of the compounds synthesized.

Note: Compound numbers in the abstract are different from those in the thesis.

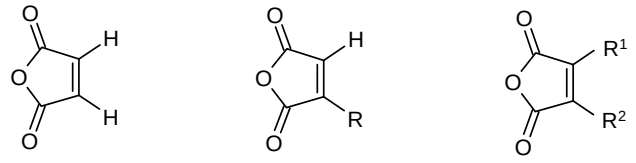
CHAPTER ONE

CONCISE ACCOUNT ON CHEMISTRY OF MONOALKYLSUBSTITUTED, DIALKYLSUBSTITUTED AND COMPLEX DIALKYLSUBSTITUTED MALEIC ANHYDRIDES

1.1 INTRODUCTION

1.1.1 Maleic Anhydrides and their Applications

Maleic anhydride (2,5-furandione) was prepared for the first time two centuries ago and became commercially available a century later by the catalytic oxidation of benzene using vanadium pentoxide.[1] Being a multifunctional entity, it finds applications in nearly every field of both laboratory and industrial chemistry. The utmost interest has been centred in the use of maleic anhydride as a building block in organic synthesis. It is a versatile synthon wherein all the sites are amenable for a variety of reactions and possesses exceptionally selective reactivity towards several nucleophiles. A vast array of nucleophilic reactions undergone by maleic anhydrides confer a high synthetic potential on them.[2] In the past century, several symmetrically and unsymmetrically substituted maleic anhydride derivatives have been prepared. The list of mono and disubstituted maleic anhydrides is very vast and a few of them are represented below.



1 **2** **3**

$R/R^1/R^2$ = alkyl, benzyl, phenyl, aryl, hydroxy, alkoxy, halo, carboxymethyl, phenylsulphonyl and cyano

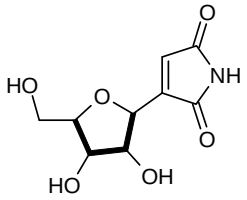
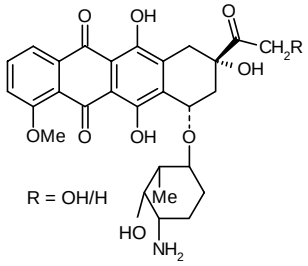
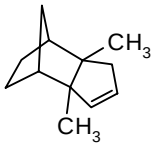
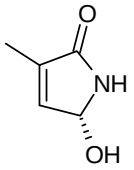
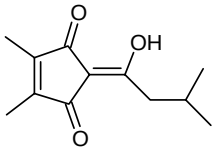
Maleic anhydride and its derivatives are used extensively in the synthesis of a wide array of key intermediates employed in the heavy and fine chemical industries[2] and as such these compounds have often been used to model

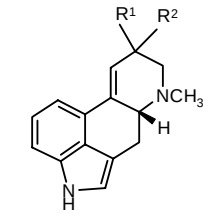
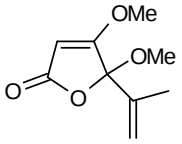
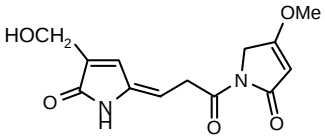
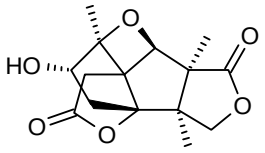
- Compounds highlighting regiochemical dichotomy
- Heterocyclic skeletons
- Natural products and their precursors
- Bioactive molecules such as drugs and agrochemicals
- Series of polymers with tailored material characteristics

1.1.2 Synthetic Utility of Methyl, Dimethyl and Substituted Maleic Anhydrides

The utilities of methyl and dimethylmaleic anhydrides have been well proved in laboratory as well as in industrial practice.[3] Methyl and dimethylmaleic anhydrides have also been used for the synthesis of important heterocyclic systems[4] and as a potential dienophile in the Diels-Alder reaction.[5] Interestingly some of their derivatives possess herbicidal, fungicidal, insecticidal and defoliant activities.[6] A few representative examples of the above mentioned applications are listed in Table 1. The synthesis of antibiotics showdomycin and *epi*-showdomycin via the reaction of maleimide-triphenylphosphine (TPP) adduct with D-ribose and subsequent cyclization using phenylselenyl chloride followed by oxidative elimination using hydrogen peroxide is very elegant and practical,[7] whereas the conversion of dimethylmaleic anhydride to antibiotic adriamycin and daunorubicin are of commercial interest.[8] The exo Diels-Alder adduct of dimethylmaleic anhydride and cyclopentadiene has been used in the total synthesis of natural product (±)-albene.[9] Jatropham, an alkaloid isolated in 1973 by Cole et al, has been synthesized[10] in three steps from citraconic anhydride via a highly regioselective reduction of the corresponding citraconimide as the key step. Substituted maleic anhydrides have been used for the synthesis of pulvinic acid and pulvinone analogues via 2(5*H*)-one phosphonate derivatives by employing Wadsworth-Emmons olefination.[11] The use of dimethylmaleic anhydride in the synthesis of claythrone and related cyclopentene-1,3-dione through 4-ylidenebutenolide has been reported by Pattenden and co-workers.[12] Phosphorous ylide of maleate ester has been employed as a starting material for the total synthesis of (±)-lysergic acid[13] whereas methoxymaleic anhydride has been used as a building block for the synthesis of penicillic acid.[14] Pattenden and co-workers have reported an elegant synthesis of pukelimide employing methylmaleic anhydride as the starting material,[15] while, recently, Danishefsky et al have started with dimethylmaleic anhydride to complete the total synthesis of the neurotrophic agent (±)-merrilactone A in an elegant fashion.[16]

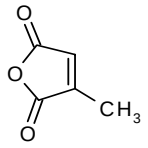
Table 1: Important Synthetic Applications of Symmetrically and Unsymmetrically Substituted Maleic Anhydrides

No.	Compound Synthesized	Source and Activity	Characterization	Ref.
1	 Showdomycin	*Streptomyces showdoensis* Antibiotic	IR, PMR, CMR, Mass	7
2	 Adriamycin/Daunorubicin	*Streptomyces peucetius* Antibiotic, anticancer, and immunomodulator	IR, PMR, CMR, Mass	8
3	 (±)-Albene	*Petasites albus* Not known	IR, PMR, CMR, Mass	9
4	 Jatropham	*Jatropha macrohiza* Antitumor	IR, PMR, CMR, Mass	10
5	 Claythrone	*Claythrix tetragona* Not known	IR, PMR, CMR, Mass	12

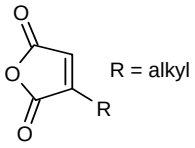
6	 R^1 = COOH, R^2 = H (±)-Lysergic acid	*Claviseps paspali* *Claviseps purpurea* (ergot fungus) Hallucinogenic and anti-serotonin	IR, UV, PMR, Mass	13
7	 Penicillic acid	*Lyngbya majuscula* (marine blue-green algae) Antimicrobial and antitumor	IR, PMR, CMR, Mass	14
8	 Pukelimide	*Lyngbya majuscula* (marine blue-green algae) Not known	IR, UV, PMR, Mass	15
9	 (±)-Merrilactone	*Illicium merrillianum* Neurotropic agent	IR, UV, PMR, Mass	16

1.2 MONOALKYLSUBSTITUTED MALEIC ANHYDRIDES

This section describes the synthetic approaches reported in the literature towards the synthesis of methylmaleic anhydride (**4**) and alkylmaleic anhydrides **12**.



4



12

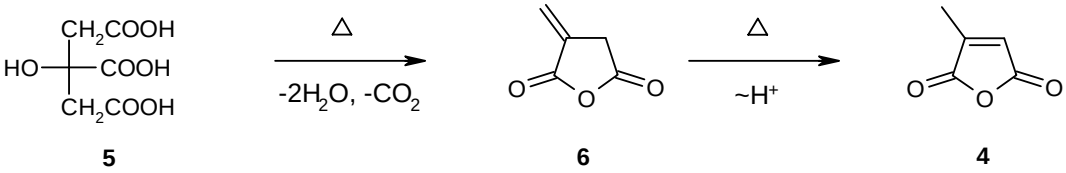
1.2.1 Methylmaleic Anhydride

The most simple and widely used derivative of monoalkylsubstituted maleic anhydride is methylmaleic anhydride (citraconic anhydride, **4**). Three synthetic approaches to **4** are known in the literature. The synthetic utilities of methylmaleic anhydride (**4**) have been described in the earlier section.

I. Roll's Approach

Methylmaleic anhydride (citraconic anhydride, **4**) was prepared by Roll et al from citric acid (**5**) in two-steps with 34% overall yield (**Scheme 1**).[17] Citric acid (**5**) was heated over a free flame and the fraction which distills around 175-190 °C was collected. On heating, **5** undergoes double dehydrative decarboxylation to furnish itaconic anhydride (**6**) which on further heating isomerizes and distills out around 210-215 °C as methylmaleic anhydride (**4**).

Scheme 1

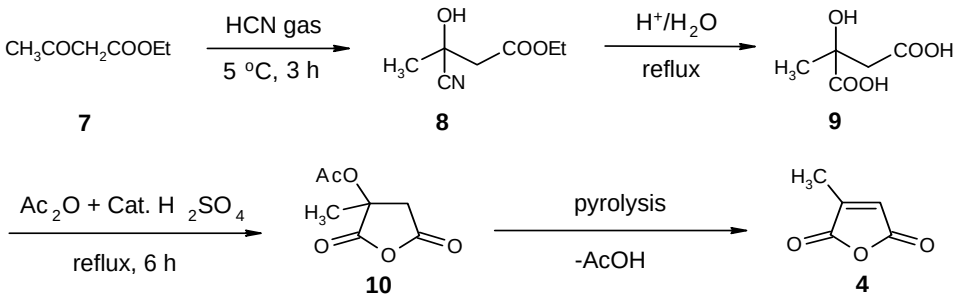


5 **6** **4**

II. Tanaka's Approach

In this approach, ethyl acetoacetate (**7**) was quantitatively converted into the corresponding cyanohydrin **8**, which on acid catalyzed hydrolysis followed by dehydrative cyclization and pyrolysis furnished methylmaleic anhydride (**4**) with 46% overall yield in 4-steps (**Scheme 2**).[18]

Scheme 2

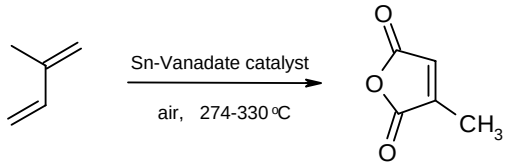


7 **8** **9** **10** **4**

III. Pichler's Approach

The gas phase oxidation of isoprene (**11**) in presence of air using Sn-Vanadate catalyst at the temperature range of 274-330 °C is known to furnish methylmaleic anhydride (**4**) with 21% yield (**Scheme 3**).[19]

Scheme 3



11 **4**

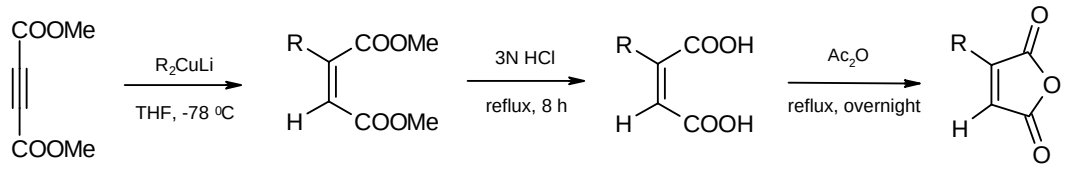
1.2.2 Alkylmaleic Anhydrides

Only a few approaches are known for the synthesis of alkylmaleic anhydrides **12** in the literature. The first approach involves the conjugate addition of organocuprates to dimethyl acetylenedicarboxylate (**13**) as a key reaction. Recently, two synthetic approaches have been reported for compound **12** by palladium-catalyzed dicarbonylation of terminal acetylenes **16**. The synthetic utilities of alkylmaleic anhydrides **12** are yet to be explored.

I. Bates' Approach

Alkylmaleic anhydrides **12** have been prepared starting from dimethyl acetylenedicarboxylate (**13**) in three steps with 52% overall yield (**Scheme 4**).[20] The first step is the conjugate addition of dialkyl cuprate to dimethyl acetylenedicarboxylate (**13**) to form alkylsubstituted dimethyl maleate **14** with some amount of *trans* isomer. The formed diester **14** on acid catalyzed hydrolysis followed by dehydrative cyclization provided them the alkylmaleic anhydride **12** with 52% overall yield in 3-steps.

Scheme 4

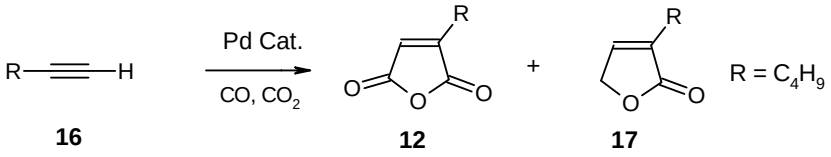


13 **14** **15** R = C_5H_{11} **12**

II. Gabriele's Approach

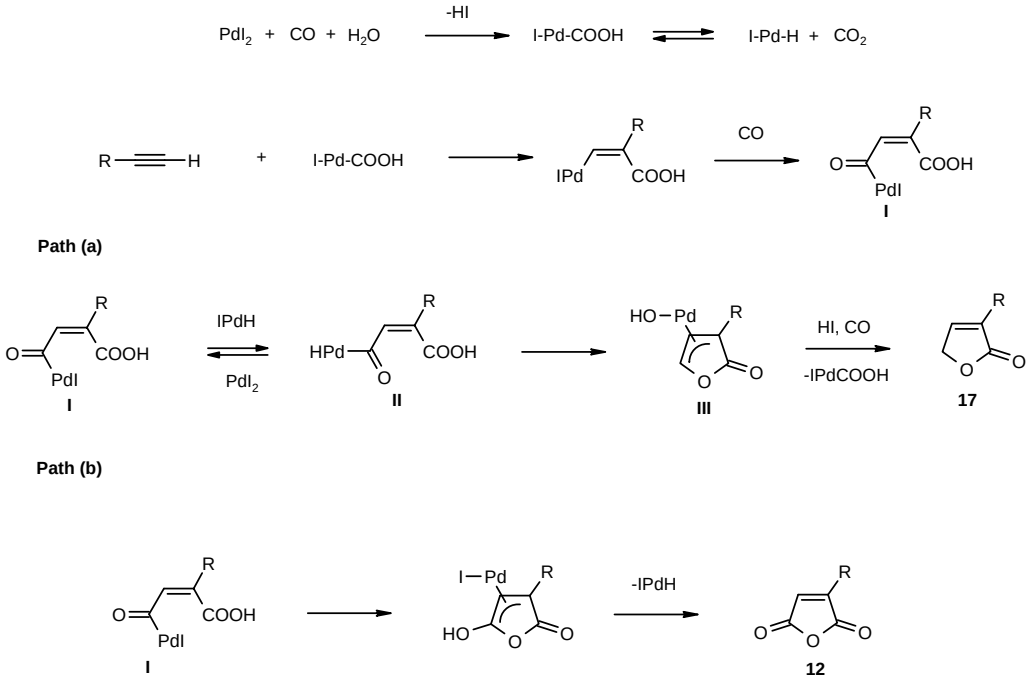
Recent synthesis of alkylmaleic anhydrides **12** involves palladium catalysed reductive carbonylation of terminal acetylenes **16** in presence of CO and excess CO_2 furnishing 5:3 mixture of alkylmaleic anhydride **12** and the furan–2(5*H*)-ones **17** with 80% combined yield (**Scheme 5**).[21] The present reaction is the first example in which CO and CO_2 are used together for the catalytic formation of unsaturated cyclic anhydrides. The one-step approach employed and the atom economy are the advantages of the present method.

Scheme 5



The following mechanism explains the product formation and the effect of CO_2 in the product distribution (**Scheme 6**).[21] An I-Pd-COOH species, stabilized by iodide ligands, is first generated from PdI_2, CO & H_2O and then inserts the alkyne **16** and CO to give intermediate **I**. At this point two pathways are possible. Formation of furanones **17** requires the intervention of palladium hydride species, which must be derived from decarboxylation of I-Pd-COOH as shown in Scheme 6. Hydride exchange on complex **I** by H-Pd-I followed by reductive cyclization of intermediate **II** leads to allylpalladium complex **III** which on treatment with HI affords **17** with regeneration of the catalytically active species [path (a)]. On the other hand, anhydrides can be formed via tautomerization of acylpalladium intermediate **I** followed by elimination of Pd^0 and HI or H-Pd-I [path (b)]. The tautomerization reaction of **I** is stoichiometric and reoxidation is needed to start a new cycle. However, in the presence of excess CO_2, H-Pd-I can be converted into a catalytically active form. Moreover, in the presence of added CO_2, the decarboxylation equilibrium is shifted to the left and the anhydride cycle becomes competitive with the reduction pathway leading to furanones **17**.

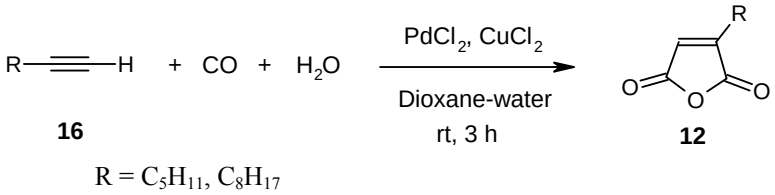
Scheme 6



III. Chen's Approach

The most recent synthetic approach involves a $PdCl_2$ catalyzed dicarbonylation of terminal acetylenes **16** in presence of CO to yield monoalkylmaleic anhydride **12** with 80-90% yield (**Scheme 7**).[22] Use of $CuCl_2$ as reoxidant increased the rate of the reaction as well as the yield of **12**. This synthetic approach is the most efficient and general method known in the literature for the synthesis of **12**. The mechanistic aspects of the reaction are yet to be studied.

Scheme 7



R = C_5H_{11}, C_8H_{17}

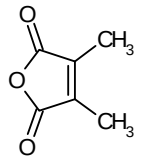
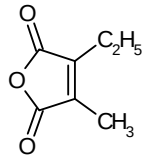
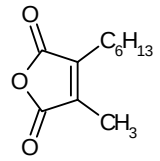
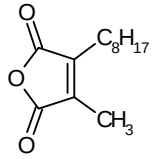
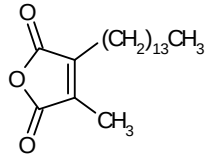
To date, three methods are known for the synthesis of methylmaleic anhydride. In our laboratory, we have developed a method for methylmaleimide, which can be

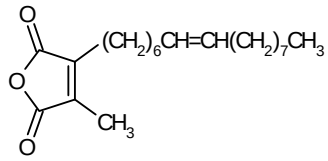
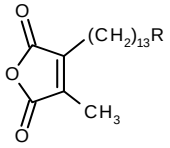
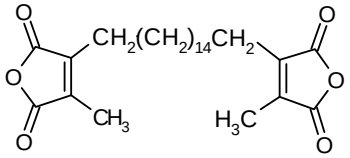
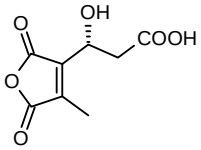
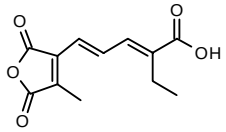
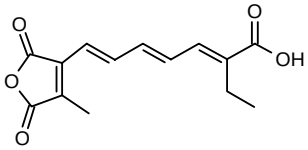
transformed to methylmaleic anhydride. This will be discussed in detail in chapter two. The synthetic utilities of methylmaleic anhydride have already been discussed earlier. Three methods are known for the synthesis monoalkylmaleic anhydrides and have been summarized in the earlier section. In our laboratory, all attempts at synthesizing the monoalkylmaleic anhydrides via the corresponding exoalkylidenesuccinimides met with failure. The synthetic utilities of monoalkylmaleic anhydrides have not been much explored, nevertheless, these compounds could serve as potential building blocks for the synthesis of many natural products.

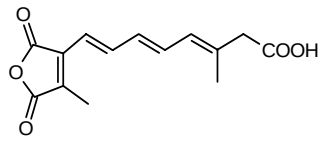
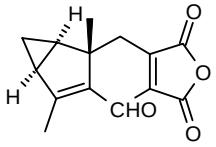
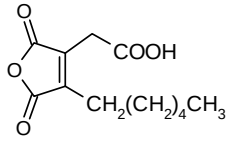
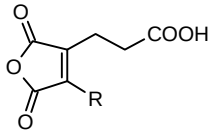
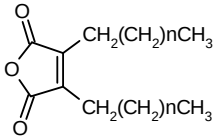
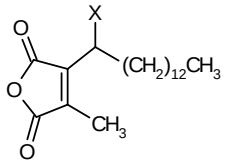
1.3 DIALKYLSUBSTITUTED MALEIC ANHYDRIDES

Recently, several structurally interesting and biologically important dialkylsubstituted maleic anhydrides have been isolated as bioactive natural products and these compounds as well as a few synthetic dialkylsubstituted derivatives are listed in Table 2. The structural features of these molecules reveal that they might have been designed in nature by the combination of pyruvic acid and the respective long chain carboxylic acids. These target molecules received immediate attention from several elegant schools of synthetic organic chemistry for the synthesis of the natural product itself and also of its analogues for structure activity relationship studies. For example, during the past ten years, nine synthesis of Ras farnesyl-protein transferase inhibitor chaetomellic anhydride A (**30**) have been reported and some of the Ras farnesyl protein transferase inhibitors are currently in human clinical trials.[23] The complete details concerning the synthetic efforts on all of these natural products and unnatural dialkylsubstituted maleic anhydride derivatives are summarized in the following section.

Table 2: Natural and Unnatural Dialkylsubstituted Maleic Anhydrides

No.	Compound Structure	Source and Bioactivity	Characterization	Ref.
1	 Dimethylmaleic anhydride	Synthetic derivative	PMR, CMR, Mass, C, H analysis	24
2	 2-Ethyl-3-methylmaleic anhydride	*Paederia foetida L.*(from volatile oil) *Sambucus nigra L*. (fruit) Flavouring agent	PMR, CMR, Mass, C, H analysis	25
3	 2-Hexyl-3-methylmaleic anhydride	*Agropyrum repens* (Rhizome) Flavoring agent	PMR, CMR, Mass, C, H analysis	26
4	 2-Octyl-3-methylmaleic anhydride	*Pseudomonas cepacia* A-1419 Flavoring agent	PMR, CMR, Mass, C, H analysis	27
5	 Chaetomellic anhydride A	*Chaetomella acutiseta* Ras farnesyl-protein transferase inhibitor (Anticancer)	PMR, CMR, Mass, C, H analysis	28

6	 (*Z*)-Chaetomellic anhydride B	*Chaetomella acutiseta* Ras farnesyl-protein transferase inhibitor (Anticancer)	PMR, CMR, Mass, C, H analysis	28
7	 R = $COCH_3$, $CH(OCOCH_3)CH_3$, $CH(OH)CH_3$, $(CH_2)_3OCOCH_3$ Fungal metabolites	*Aspergillus wentii* Not known	IR, PMR, CMR, Mass	29
8	 Tyromycin A	*Tyromyces lacteus* Aminopeptidase inhibitor, potential cytostatic activity	IR, PMR, CMR, Mass	30
9	 Maleic anhydride segment of Tautomycin/Tautomycetin	*Streptomyces spirovertivillatus* *Streptomyces griseochromogenes* Antifungal, antibiotic	IR, PMR, CMR, Mass	31, 32
10	 Telfairic anhydride	*Xylaria telfairi* Not known	PMR, CMR, Mass, C, H analysis	33
11	 Graphenone	*Graphis scripta* (Lichen mycobiont) Not known	IR, PMR, CMR, Mass	34

12	 Itaconitin	*Aspergillus itaconicus* Not known	IR, PMR, Mass	35a
13	 Lindenanolide E	*Lindera chunii* MERR. HIV-1 Integrase inhibitor	IR, PMR, CMR, Mass	35b
14	 2-Carboxymethyl-3-hexylmaleic anhydride	*Aspergillus niger* Antibiotic	IR, PMR, CMR, Mass	36
15	 R = C_6H_{13}, C_8H_{17} 2-(β-Carboxyethyl)-3-alkylmaleic anhydrides	*Pseudomonas cepacica* A-1419 *Paecilomyces varotii* Not known	IR, PMR, CMR, Mass	37, 38
16	 Dialkylmaleic anhydride n = 0, 4 and 6	Synthetic derivative	IR, PMR, CMR, Mass	39, 40a, b
17	 X = Br, OH, OAc Functionalized chaetomellic anhydride A	Synthetic derivative	IR, PMR, CMR, Mass	40c

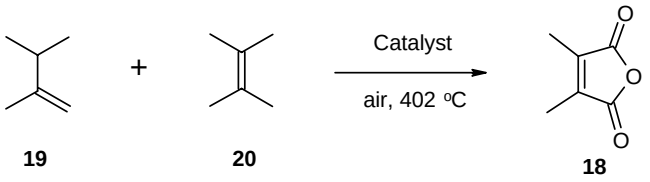
1.3.1 Synthetic Approaches Towards Dimethylmaleic Anhydride

The most simple and widely used derivative of dialkylsubstituted maleic anhydride is dimethylmaleic anhydride (DMMA, **18**). More than 20 synthetic approaches to dimethylmaleic anhydride (**18**) using a variety of strategies are known in literature.[24] The list of approaches to **18** with an overall yield of greater than 60% includes (i) oxidation of but-2-ene in the presence of a metal catalyst with 68% yield[41] (ii) self condensation of ethyl α-bromopropionates with 67% yield[42] (iii) oxidation of but-2-yne in 2-steps with 63% overall yield[43] and (iv) an elegant one-pot approach employing maleic anhydride and 2-aminopyridine with 75% yield.[44c] The chemistry involved in these approaches is discussed briefly in the following schemes.

I. **Pichler's Approach**

Dimethylmaleic anhydride (**18**) has been prepared by the air oxidation of a mixture of 2,3-dimethyl but-2-ene (**19**) and 2,3-dimethyl but-1-ene (**20**) (73:27) at 402 ^{o}C over a catalyst (consisting of 9.8:19.4:0.8:70 V_2O_5-MoO_3-P_2O_5-TiO_2) with 67% yield. A little amount of citraconic anhydride (**4**) has also been formed as a side product (**Scheme 8**).[41]

Scheme 8

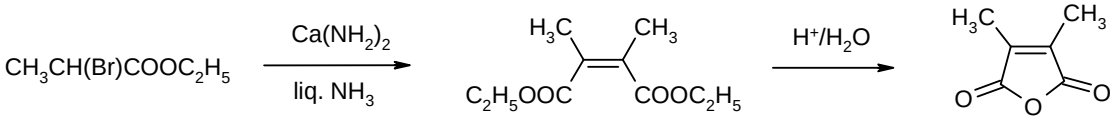


19 **20** **18**

II. **Kreiser's Approach**

2-Bromopropionate (**21**), on reaction with $Ca(NH_2)_2$ in liq.NH_3, is known to furnish dimethyl maleic ester **22** with 80% yield along with some amount of undesired 2-bromo propionamide (**Scheme 9**). The formed diester **22** on acid catalyzed hydrolysis provided dimethylmaleic anhydride (**18**) with 67% overall yield.[42]

Scheme 9

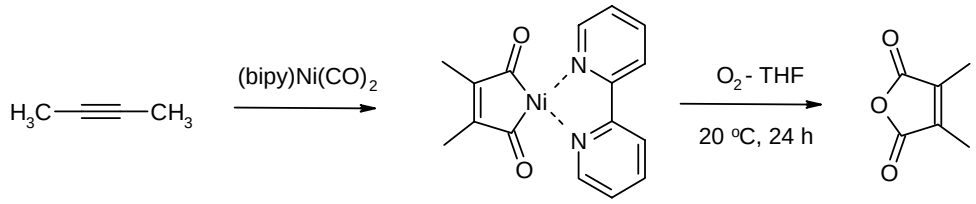


21 **22** **18**

III. Hoberg's Approach

The third synthesis has been completed using dimethyl acetylene (**23**) as starting material (**Scheme 10**).[43] The acetylenic compound **23** was treated with nickel (bipyridyl) carbonyl complex to form nickel diacyl complex **24** which on reaction with oxygen in THF furnished dimethylmaleic anhydride (**18**) with 63% overall yield.

Scheme 10

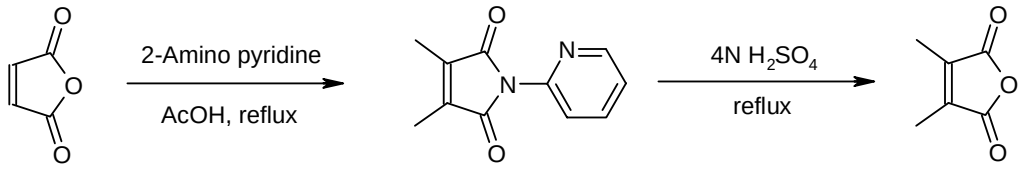


23 **24** **18**

IV. Baumann's Approach

An elegant one-pot approach towards **18** starting with 2-aminopyridine and two equivalents of maleic anhydride (**1**) via formation of disubstituted maleimide **25** with 75% overall yield has been reported by Baumann and coworkers (**Scheme 11**).[44c] The reaction has been used several times in our laboratory to prepare dimethylmaleic anhydride (**18**) in large amounts.

Scheme 11

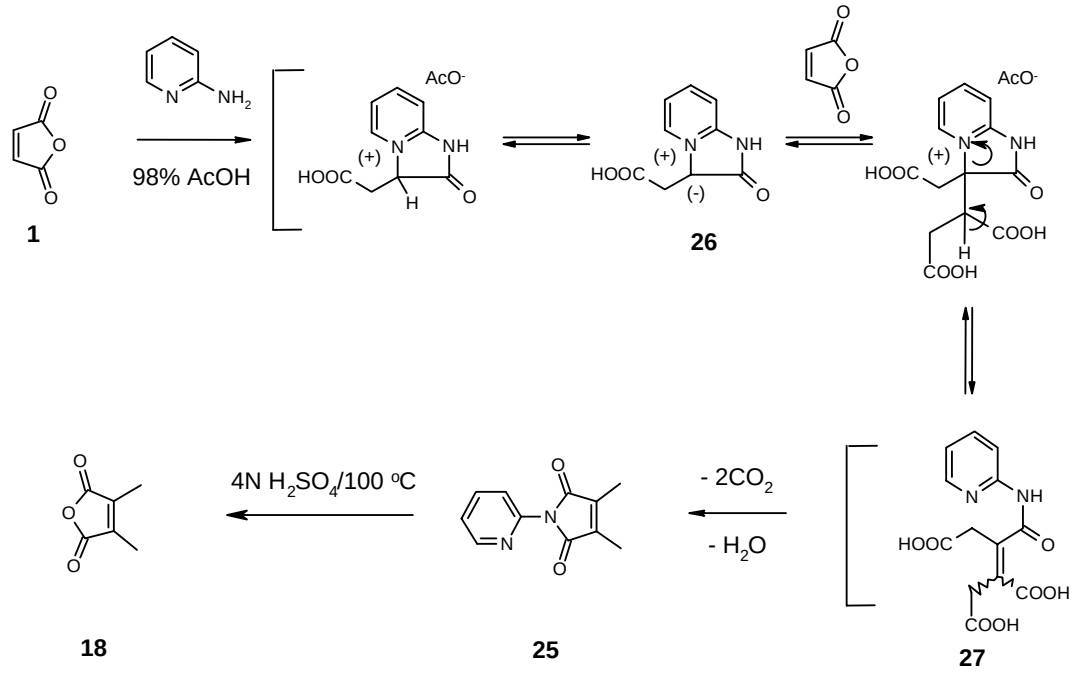


1 **25** **18**

The mechanism of decarboxylative dimerization of maleic anhydride (**1**) to dimethylmaleic anhydride (**18**) was investigated by Baumann and coworkers (**Scheme 12**).[44a,b] The first step is the reaction of maleic anhydride (**1**) with 2-amino pyridine to form imidazo [1,2,-α]pyridine **26** as an intermediate which Michael adds to maleic anydride (**1**) yielding a tricarboxylic acid intermediate **27** which undergoes instantaneous dehydrative decarboxylation leading to disubstituted maleimide **25**. The

compound **25** on acid catalyzed hydrolysis furnished dimethylmaleic anhydride (**18**) with 75% overall yield.

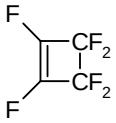
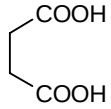
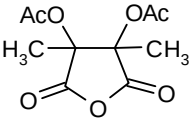
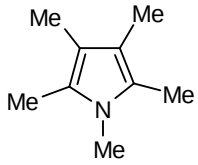
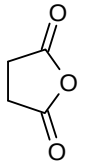
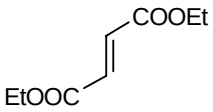
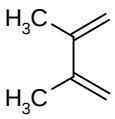
Scheme 12

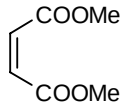
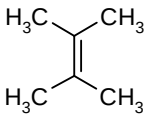
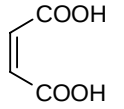
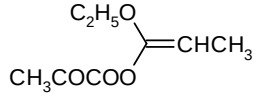
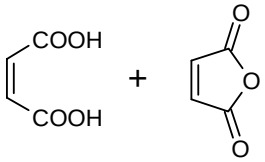
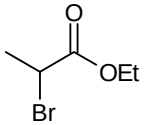


Most Recent Approach: The most recent approach towards dimethylmaleic anhydride (**18**) has been developed in our laboratory and it will be discussed in section B of chapter two as a part of this dissertation.[24] All other low yielding approaches (less than 50% overall yield) to **18** have been summarized in Table 3.

Table 3: Known Approaches for the Synthesis of Dimethylmaleic Anhydride (**18**)

No.	Starting Compound	Reagents and Conditions	Product	Overall Yield (%)	Ref.
1	CH_3COCH_2COOEt Ethyl acetoacetate	(i) NaH, MeBr; (ii) $NaCN/H_2O$; (iii) H_2SO_4.	Dimethylmaleic anhydride (DMMA)	13	45

2	 Perfluoro cyclobutene	(i) CH_3Li, Et_2O, 45 ^oC; (ii) H^+/H_2O; (iii) aq. H_2O_2 (30-35%).	DMMA	23	46
3	 Succinic acid	$CH_3COCOOH$, pyridine, 150 ^oC, 1.5 h.	DMMA	40	47
4	 Dimethyldiacetyl tartaric anhydride	(i) Pyrolysis, 440 ^oC; (ii) pyrolysis of formed 2-methyl-2-acetoxy itaconic anhydride 545 ^oC.	DMMA	Low yield	48
5	 Pentamethyl pyrrole	(i) 70% H_2O_2; (ii) pyrolysis, 155 ^oC.	DMMA	Low yield	49
6	 Succinic anhydride	(i) (a) Pyridine, 125 ^oC, 0.5 h; (b) MeCOCOOH, 125 ^oC; (ii) steam distillation.	DMMA	40	50
7	 Diethyl fumarate	(i) Methyl acrylate, PCy_3, dioxane; (ii) H^+/H_2O; (iii) H_2, Pd/C; (iv) thermal decomposition.	DMMA	27	51
8	 2,3-Dimethyl-1,3-butadiene	Oxidation in air over a catalyst at 400 ^oC.	DMMA	21	52

9	 Dimethyl maleate	(i) Methyl acrylate, PCy_3, dioxane; (ii) $NaOH/H_2O$; (iii) heating 220-230 ^oC.	DMMA	40	53
10	 2,3-Dimethyl but-2-ene	Oxidation in air over vanadium and phosphorus catalyst at 300-500 ^oC.	DMMA	35	54
11	 Maleic acid	(i) 2-Amino pyridine, AcOH, reflux; (ii) 4N H_2SO_4.	DMMA	50	55
12	 1-Ethoxy-1-propenyl pyruvate	Pyrolysis	DMMA	35	56
13	 Maleic Acid + Maleic anhydride	(i) 2-(Methylamino)thiazole, 150 ^oC, 0.5 h; (ii) 4N H_2SO_4.	DMMA	57	57
14	$CH_3COCOOEt$ Ethyl pyruvate	(i) $CH_3CH[PO(OEt)_2]COOEt$ NaH, 1,2 diethoxy ethane; (ii) H^+/H_2O.	DMMA	46	58
15	 2-Bromo propionate	Self coupling in liq. NH_3 using calcium napthalenide	DMMA	40	59
16	 But-2-yne	(i) $Ir(CO)_3Br$, THF, inert atmosphere; (ii) 4N HNO_3.	DMMA	Not reported	60

1.3.2 Tetradecylmethylmaleic Anhydride: Chaetomellic Anhydride A

The dicarboxylic acids chaetomellic acid A (**28**) and chaetomellic acid B (**29**) were isolated from fermentation extract of the coleomycete *Chaetomella acutiseta* (**Fig. 1**), by a group of scientists[28] at Merck, USA in 1993. The structural assignment of chaetomellic anhydride A (**30**) and chaetomellic anhydride B (**31**) has been done on the basis of analytical and spectral data. The position and geometry of the double bond in chaetomellic acid B was established by MS analysis of monoepoxide (prepared by reacting **31** with *meta*-chloroperbenzoic acid in dichloromethane). The biogenesis of these compounds[28] may be occurring through an aldol condensation of palmitate or *cis*-oleate with pyruvate followed by dehydration pathway.

Fig. 1

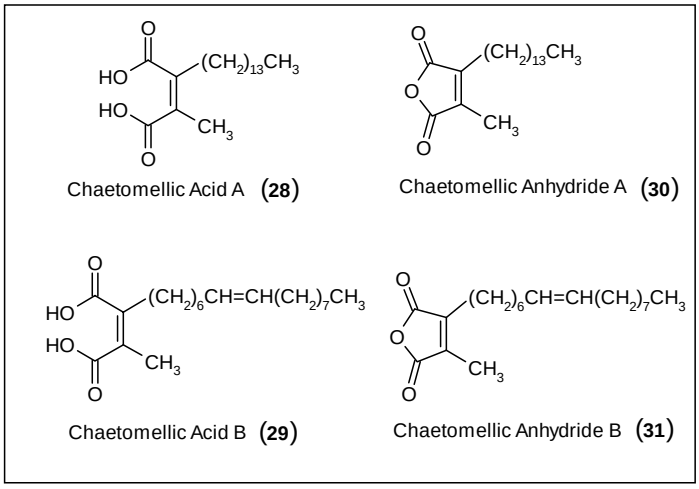
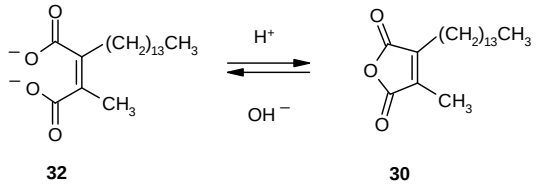


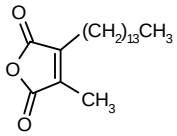
Fig. 2

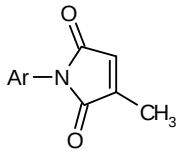
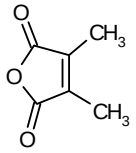
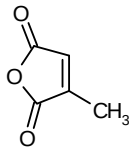


Chaetomellic acid A and B have been identified as potent inhibitors of Ras farnesyl-protein transferase[28,61] (FPTase), an enzyme catalyzing a post-translational modification of Ras. Mutated form of Ras oncogens are found in about 25% of the human tumors[62] and are believed to play a key role in their growth. Molecular modeling studies reveal that these acids structurally resemble FPP. These classes of natural products have propensity to cyclize as shown in Fig. 2 and all members of this family were isolated in the anhydride form. However, they actually exhibit their FPTase inhibitory activity in the dianionic form as shown below in compound **32**. Chaetomellic acid A (**28**) is 3 times more potent than chaetomellic acid B (**29**) and became the main attraction of

synthetic efforts because of its potent FPTase inhibibitory activity for the treatment of cancer. After its isolation in 1993, the past ten years have seen nine syntheses being accomplished including four from our group. The chemistry of all nine syntheses [63-71] of **30** is summarized in Table 4.

Table 4: Reported Syntheses of Chaetomellic Anhydride A (30)

No.	Starting Compound	Reagents and Conditions	Product	Overall Yield (%)	Ref.
1	$CH_3(CH_2)_{14}COOMe$ Methyl palmitate	(i) Methyl pyruvate, LDA, THF, −78 °C to −10 °C; (ii) 2,6-Di-^{t}butyl-4-methyl pyridine, *p*-tolunesulphonic anhydride, pyridine, DCM; (iii) DBU, toluene, reflux; (iv) (a) NaOH-CH_3OH-THF-H_2O; (b) 4N HCl.	 Chaetomellic anhydride A	18	63
2	$CH_3(CH_2)_{12}CH_2Br$ Tetradecyl bromide	(i) $CoCl_2$, $dmgH_2$, pyridine, $NaBH_4$, NaOH, CH_3OH; (ii) PhSSPh, *hv*; (iii) *m*-CPBA, pH 7.4 phosphate buffer, DCM.	Chaetomellic anhydride A	64	64
3	$MeOOCCH_2COOMe$ Dimethyl malonate	(i) NaH, $C_{14}H_{29}Br$, THF-DMF, reflux, 1.5 h; (ii) $BrCH(CH_3)COOMe$, NaH, THF-DMF, reflux, 1.5 h; (iii) (a) ethanolic KOH; (b) H^+/H_2O, reflux; (iv) N-methylmorpholine, methylchloroformate; (v) Et_3N, TMSOTf, C_6H_6, reflux, 2 h; (vi) Br_2, Bu_4NBr.	Chaetomellic anhydride A	83	65
4	MeOOC—≡—COOMe Dimethyl acetylenedicarboxylate	(i) (a) $C_{14}H_{29}Cu(Me_2S)MgBr$; (b) MeI, THF-HMPA; (c) aq. NH_4Cl; (ii) (a) $LiOH/H_2O$; (b) acidification.	Chaetomellic anhydride A	78	66

5	$CH_3(CH_2)_{12}CH(Br)COCl$ 2-Bromopalmitoyl chloride	(i) 2-Amino pyridine, Et_3N, Et_2O, rt; (ii) ^tBuOH, reflux; (iii) maleic anhydride, NaOAc, reflux.	Chaetomellic anhydride A	62	67
6	 Ar = *p*-Tolyl *N*-*p*-Tolylmethylmaleimide	(i) (a) PPh_3, AcOH, reflux, 2h; (b) $CH_3(CH_2)_{12}CHO$, reflux, 18 h; (c) Δ, 140-150 ^oC, 0.5 h; (ii) (a) $KOH/H_2O/CH_3OH/THF$, reflux, 2 h; (b) acidification.	Chaetomellic anhydride A	89	68
7	$CH_3(CH_2)_{13}COOH$ Pentadecanoic acid	(i) (a) DCC, 2-mercaptopyridine *N*-oxide, DCM, 2 h; (b) citraconic anhydride, *hv* (500 W), 10-15 ^oC, 0.5 h.	Chaetomellic anhydride A	70	69
8	 Dimethylmaleic anhydride	(i) NBS, DBP, CCl_4, reflux, 10 h; (ii) $CH_3(CH_2)_{13}MgX$, Et_2O/THF, HMPA, CuI, −5 to 0 ^oC.	Chaetomellic anhydride A	60	70
9	 Methylmaleic anhydride	(i) $MeOH/H_2SO_4$ (9:1), 24 h; (ii) NBS, AIBN, CCl_4, 16 h; (iii) $CH_3(CH_2)_{13}MgBr$, HMPA, Et_2O, rt, 8 h; (iv) AcOH/HCl (6:4), 5 h; (v) Ac_2O, reflux.	Chaetomellic anhydride A	56	71

A few secondary metabolites have been isolated[29] from the mycelium species *Aspergillus wentii* and characterized as long chain derivatives of citraconic anhydride and may be called as remotely functionalized derivatives of chaetomellic anhydride A (entry 7, **Table 2**). The structural elucidation of fungal metabolites has been done with the help of spectral data.[29] The biosynthesis of these metabolites may proceed via condensation of C_{18} polyketide derived from fatty acid unit with oxaloacetic acid, followed by decarboxylation and dehydration. The synthesis of these derivatives has not been reported to date and efforts towards this are in active progress in our laboratory.

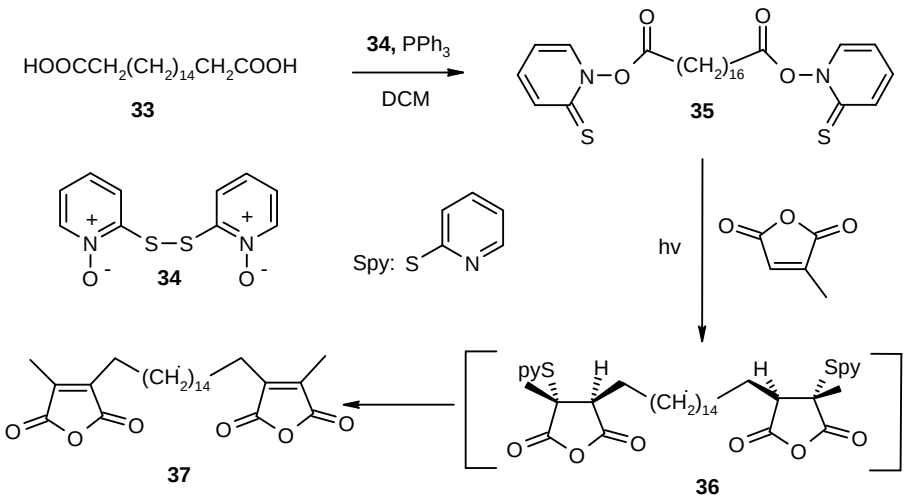
1.3.3 Synthetic Approaches Towards Tyromycin A

Tyromycin A (entry 8, **Table 2**) has been recently isolated from mycelial cultures of basidomycete *Tyromyces lacteus* (Fr.) Murr[30], and its structure was established as 1,16-*bis*-(4-methyl-2,5-dioxo-3-furyl)hexadecane by using spectral and analytical techniques and by transformation into the corresponding tetramethyl ester and diimide derivatives.[30] Among the enzymes bound to surfaces of mammalian cells, amino peptidases have been recognized as a potential target for the immunomodulating drugs.[30,72] Tyromycin A (**37**) was found to inhibit the leucine and cysteine amino peptidases bound to the outer surface of HeLa S3 cells and it also exhibits cytostatic activity[72] and is one of the two amino peptidase inhibitors known in the literature. The enzyme inhibiting activity is dependent on the two maleic anhydride moieties, the stable imide of tyromycin A (**37**) being devoid of inhibitory activity on the cell-bound amino peptidases of HeLa cells. Tyromycin A (**37**) is the first bioactive natural product with two citraconic anhydride units, which suggests a biosynthesis by condensation of an activated eicosanedioic acid with two molecules of oxaloacetate.

I. First Synthesis of Tyromycin A

The first synthesis of tyromycin A (**37**) has been completed by Samadi and co-workers employing the well-known decarboxylative Barton-radical coupling reaction (**Scheme 13**).[73] The starting compound 1,18-octadecanedioic acid (**33**) was converted to corresponding thiohydroxamic diester **35** using PPh_3/2,2'-dithiobis(pyridine *N*-oxide) (**34**) and the formed **35** reacts in situ with citraconic anhydride in presence of tungsten light (500 W) to furnish the intermediate addition products **36**, which upon purification on silica gel afforded the eliminated product tyromycin A (**37**) (**Scheme 13**).

Scheme 13

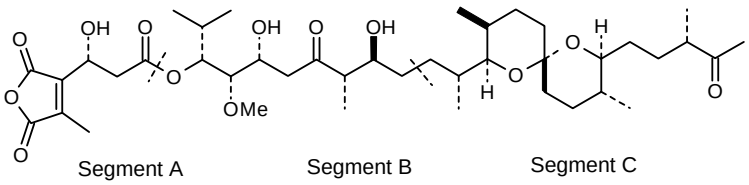


II. Second Synthesis: Recently, we have completed an efficient synthesis of tyromycin A (**37**) employing a one-pot double Wittig reaction involving methylmaleimide-TPP adduct and aliphatic dialdehyde as a key step and the work will be discussed as a part of this dissertation in section B of Chapter two.[74]

1.3.4 2,3-Disubstituted Maleic Anhydride Segment of Tautomycin

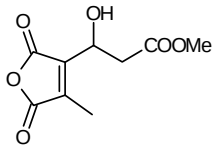
Recently, in 1987 Isono and co-workers[31] reported the isolation of tautomycin (**38,** entry 9, **Table 2**) from a strain of *Streptomyces spiroverticillatus* as a new antibiotic with strong antifungal activity against *Sclerotinia sclerotiorum*. The same group elucidated the structure of tautomycin on the basis of chemical degradation and spectroscopic evidence.[31] 2D INADEQUATE spectroscopy of tautomycin labeled with [1,2-^{13}C] acetate permitted the complete assignment of ^{13}C and ^{1}H signals and established the total structure. In 1993 the absolute configuration of **38** with 13 chiral centers was determined by the same research group,[75] using chemical transformations, spectroscopic data and conformational calculations. The absolute configuration by X-ray analysis was not possible because of its non-crystalline nature. Apart from its antifungal activity, the antibiotic was found to induce morphological changes (bleb formation) in human leukemia cells K562, which is correlated with protein

phosphorylation and also inhibited spreading of human myeloid leukemia cells HL60.[76a] It has also been identified as a future drug candidate.[76b]

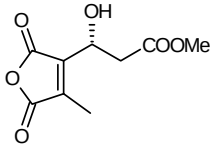


Tautomycin (38)

The important biological activity and interesting structural features made the total synthesis of tautomycin a challenging task of current interest and attracted many chemists to put in their efforts towards this goal. The broad retrosynthetic analysis of tautomycin afforded segment A, B, and C as shown in structure **38**. Total synthesis of this molecule involves the synthesis of three segments followed by stepwise coupling of these building blocks.[77] To date, five total synthesis have been accomplished by different groups.[78] It has a unique 2,3-disubstituted maleic anhydride ring at the left



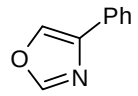
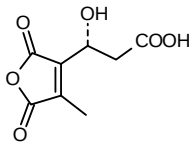
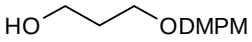
39a

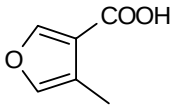
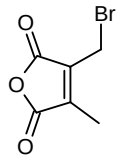


39b

terminal of the molecule, which is known as segment A **39**.[79] Segment A is a highly oxygenated molecule with three carboxylic groups and one hydroxy group. According to Chamberlin et al[80] the greatest challenge in the synthesis of tautomycin lies in the construction of the simple looking 2,3-disubstituted maleic anhydride segment A **39**. The anhydride moiety of tautomycin shows an interesting chemical behavior in aqueous media, i.e. tautomycin exists in an equilibrium between anhydride and diacid.[79] To date, five multi-step synthesis of segment A **39**, including the most recent synthesis developed in our laboratory, have been accomplished using various elegant strategies. All the reported syntheses of **39** have been summarized in Table 5. The synthesis reported from our laboratory looks simple but provides a racemic mixture **39a**.

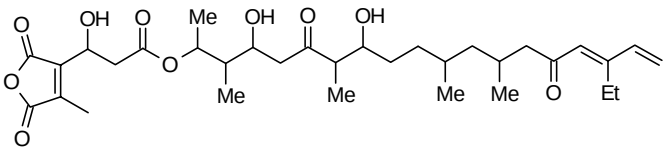
Table 5: Reported Syntheses of 2,3-Disubstituted Maleic Anhydride Segment of Tautomycin (39a & 39b)

No.	Starting Material	Reagents and Conditions	Product	Overall Yield (%)	Ref.
1	 4-Phenyloxazole	(i) Ethyl tetrolate, C_6H_6, 190 °C, sealed tube; (ii) DIBAL, −78 °C; (iii) MnO_2; (iv) Chiral *N*-acetyloxazolidinone, *n*-Bu_2BOTf, Et_3N, DCM, −78 to 0 °C; (v) Raney nickel (W-4) acetone-phosphate buffer (9:1); (vi) ^{t}BuMe$_2$SiOTf, ^{i}Pr$_2$Net; (vii) O_2, $h\nu$, rose Bengal, ^{i}Pr$_2$NEt, DCM, 0 °C; (viii) PCC, MS 4Å, DCM, rt; (ix) LiOH/H_2O; (x) (a) CH_2N_2, Et_2O; (b) HF-Py.	 (*S*)-Isomer **39b**	18	81
2	 Monoprotected 1,3-propane diol	(i) (a) DMSO, SO_3.pyridine, DCM, 0 °C; (b) Ph_3P=CHCOO^{t}Bu, DCM, 25 °C; (iii) AD-mix-β, $MeSO_2NH_2$, ^{t}BuOH-H_2O, 0 °C; (iii) DDQ, pyridine, MS 4Å, DCM, 5 °C; (iv) DMP, pyridine, DCM, 25 °C; (v) $(EtO)_2P(O)CH(Me)COOEt$, ^{t}BuOK, THF, −60 °C to −20 °C; (vi) (a) PPTS, methanol, 25 °C; (b) DEIPSCl, imidazole, DCM, 3 to 25 °C; (c) AcOH, THF-H_2O, 0 to 25 °C; (vii) DMP, DCM, 25 °C; (viii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^{t}BuOH, H_2O, 25 °C.	(*S*)-Isomer **39b**	83	82

3	 4-Methyl-3-furan carboxylic acid	(i) $CH_3ONHCH_3.HCl$, DEPC, Et_3N, DMF, 0 °C to rt; (ii) CH_3COOCH_3, LDA, THF, −78 to 0 °C then HCl, 0 °C to rt; (iii) H_2, 100 atm., cat. (*S*)-(BINAP)Ru(II), CH_3OH, 28 °C; (iv) DEIPSCl, imidazole, DCM, 0 °C to rt; (v) (a) LiOH, THF-H_2O (6:1), rt; (b) BnOH, DCC, DMAP, THF, rt; (vi) (a) O_2, $h\nu$, rose bengal, $^iPr_2NEt$, DCM, 0 °C; (b) PCC, MS 4Å, DCM, rt.	(*S*)-Isomer **39b**	31	83
4	BnOOC-≡-COOBn Dibenzyl acetylene dicarboxylate	(i) MeCuLiCN, Et_2O, −78 °C, then 3-pentenoyl chloride, −78 to 0 °C; (ii) (a) (−)-DIP chloride, THF, -20 °C, 3 days; (b) TESCl, TEA, DCM, 0 °C; (iii) O_3, DCM, −78 °C then PPh_3, −78 °C to rt; (iv) $NaClO_2$, 2-methyl-2-butene, $^tBuOH/H_2O$, 0 °C.	(*S*)-Isomer **39b**	78	80
5	 (Bromomethyl)methyl maleic anhydride	(i) (a) Diethyl malonate, NaH, C_6H_6, rt, 8 h; (b) H^+/HCl; (ii) con. HCl, reflux, 12 h; (iii) NBS, benzoyl peroxide, $CHCl_3$, reflux, 24 h; (iii) (a) 1N aq. KOH, rt, 3 h; (b) H^+/HCl; (v) CH_2N_2, Et_2O, 0 °C, 3 h.	(±)-Segment A **39a**	44	84

1.3.5 2,3-Disubstituted Maleic Anhydride Segment of Tautomycetin

Recently, a new antibiotic tautomycetin (**40**, entry 9, **Table 2**) has been obtained from a strain of *Streptomyces griseochromogenes* and the chemical structure of



Tautomycetin (40)

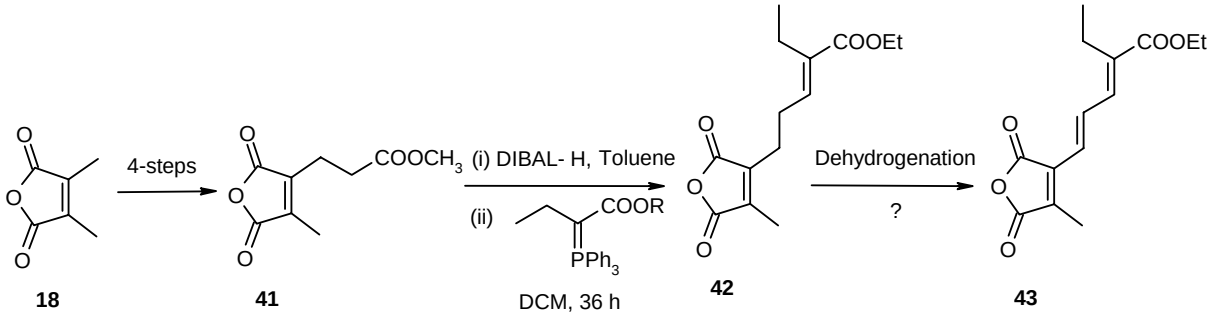
was determined by chemical degradation and spectroscopic evidence.[32] Tautomycetin (**40**) exists in methanol-buffer solution (1% Et_2NH-HCOOH, pH 7.3) as an equilibrium mixture of 2,3-dialkylmaleic anhydride and its dicarboxylic acid. Biosynthesis of tautomycetin (**40**) has been done by Kiyoshi and coworkers using feeding experiments with ^{13}C labeled precursors.[85] The left half of tautomycetin is synthesized from a propionate and a C-5 unit wherein the C-5 unit is formed from three acetate units through decarboxylation. The right half of tautomycetin (**40**) is formed via a polyketide pathway which starts with acetate followed by introduction of three acetate units, four propionate units and one butyrate unit.

1.3.6 Telfairic Anhydride

A new methylmaleic anhydride metabolite has been isolated in 1996 by Edward and his co-workers[33a] from the culture medium of the fungus *Xylaria telfairii* Berk and was named as 2,3-didehydrotelfairic anhydride (entry 10, **Table 2**). The structural assignment of telfairic anhydride has been done on the basis of analytical and spectral data.[33a] The biosynthesis of telfairic anhydride presumably originates from a process involving a condensation of an acetate malonate-derived acid with oxaloacetate. Till date, a biological role for such a structure does not appear to have been established.

In our laboratory, the synthetic efforts are in active progress towards first synthesis of telfairic anhydride (**Scheme 14**).[33b] The synthetic strategy utilizes the ester **41** as a starting material which on chemoselective DIBAL-H reduction followed by Wittig reaction with phosphorane obtained from methyl-2-bromobutyrate gave the dihydrotelfairic ester **42**. The studies on dehydrogenation of ester **42** to yield ethyl ester of telfairic anhydride (**43**) is in progress.

Scheme 14



1.3.7 Graphenone, Itaconitin and Lindenanolide E

Two other structurally similar natural products graphenone[34] (entry 11, **Table 2**) and itaconitin[35] (entry 12, **Table 2**) have been reported in the literature. Graphenone, a new pigment, has been isolated from the cultures of spore derived mycobionts of the lichens *Graphis scripta* and the structure was established using spectral and X-ray diffraction analysis. Tetraenoic anhydride, itaconitin, has been isolated as a secondary fungal metabolite from the species *Aspergillus itaconicus* and *Aspergillus gorakhpurensis*. The parent acids related to both of these anhydrides are currently unknown as natural products.[33] Very recently, lindenanolide E has been isolated from the species *Lindera chunii* Merr with HIV-1 integrase inhibiting activity. Till date, no syntheses have been reported for graphenone, itaconitin and lindenanolide E.

1.3.8 2-Carboxymethyl-3-hexylmaleic anhydride and 2-(*β*-Carboxyethyl)-3-alkylmaleic Anhydride

The first title compound has been isolated as a novel metabolite of the *Aspergillus* FH-X-213 from an apple (2-carboxymethyl-3-hexylmaleic anhydride, **46**, entry 13, **Table 2**).[36] The structural assignment of the molecule has been done on the basis of analytical and spectral data. The compound shows a weak *in vitro* activity against grampositive bacteria.[36]

Very recently, Soda and coworkers reported the biotransformations of stearic acid with a microbial strain isolated from the soil, *Pseudomonas cepacica* A-1419, to produce two new maleic anhydride derivatives with different alkyl substitents[37,38] (2-(*β*-carboxy ethyl)-3-alkylmaleic anhydrides, **49**, entry 14, **Table 2**). Bioactivities of these compounds are unknown till date.[37,38]

1.3.8.1 Synthetic Approaches Toward 2-Carboxymethyl-3-hexylmaleic anhydride (46) and 2-(*β*-carboxyethyl)-3-Alkylmaleic anhydride (49)

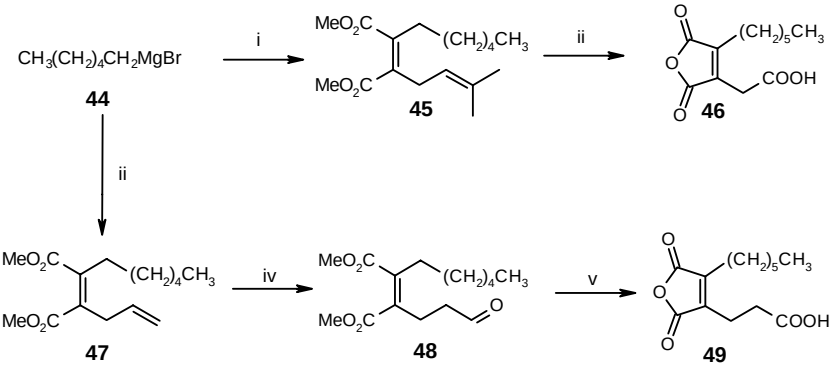
Two general synthetic routes to these diverse dialkylsubstituted maleic anhydrides have been reported in the literature. First general synthetic route has been developed by Baldwin and coworkers employing the versatile copper mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate as a key reaction.[86] The most recent approach has been developed in our laboratory via the chemoselective S_N2'/S_N2 coupling of Grignard reagents/diethylmalonate with dimethyl bromomethylfumarate (**49**)/2-bromomethyl-3-alkylmaleic anhydrides **54 a**/**b**.[40]

I. First Synthetic Approach

The first step of the synthesis of **46** was the conjugate addition of hexylcopper species derived from Grignard reagents **44** (hexylmagnesium bromide and $CuBr.Me_2S$) to dimethyl acetylenedicarboxylate followed by quenching of the copper enolate with prenyl bromide at −78 °C to furnish dialkyl maleic ester **45** which on ozonolysis followed by Jones oxidation, basic hydrolysis and acidic work up provided **46** with 33% overall yield (**Scheme 15**).[86]

The second compound **49** has been prepared starting from dimethyl acetylenedicarboxylate with 29% overall yield (**Scheme 15**). The first step is the same as described above except that the copper enolate (generated) was quenched with allylbromide. The allylic double bond of the formed diester **47** was selectively hydroborated with disiamylborane. Subsequent oxidation, ester hydrolysis and acidic workup furnished **49**.

Scheme 15



Reagents, conditions and yields: (i) (a) $CuBr.SMe_2$, THF, –40 °C then dimethyl acetylenedicarboxylate, THF, –78 °C, 1 h; (b) DMPU, THF, –78 °C; (c) $Me_2C{=}CHCH_2Br$, THF, –78 °C to rt, 16 h (73%); (ii) (a) O_3, acetone, –78 °C, 3 min then $Na_2Cr_2O_7.2H_2O$, H_2O, Et_2O, 0 °C, 3 h; (b) 1 M aq. NaOH then 1 M aq. HCl (45%); (iii) (a) $CuBr.SMe_2$, THF, –40 °C; (b) dimethyl acetylenedicarboxylate, THF, –78 °C, 1 h; (c) DMPU, THF, –78 °C; (d) $CH_2{=}CHCH_2Br$, THF, –78 °C to rt, 16 h (79%) (iv) (a) Sia_2BH, Et_2O, 0 °C, 2 h; (b) PCC (8 equiv), MS 4Å, DCM, reflux, 2 h (50%) (v) (a) $Na_2Cr_2O_7.2H_2O$, H_2SO_4, H_2O, Et_2O, 0 °C, 2.5 h; (b) 1 M aq. NaOH, rt, 16 h; (c) 1 M aq. HCl (74%).

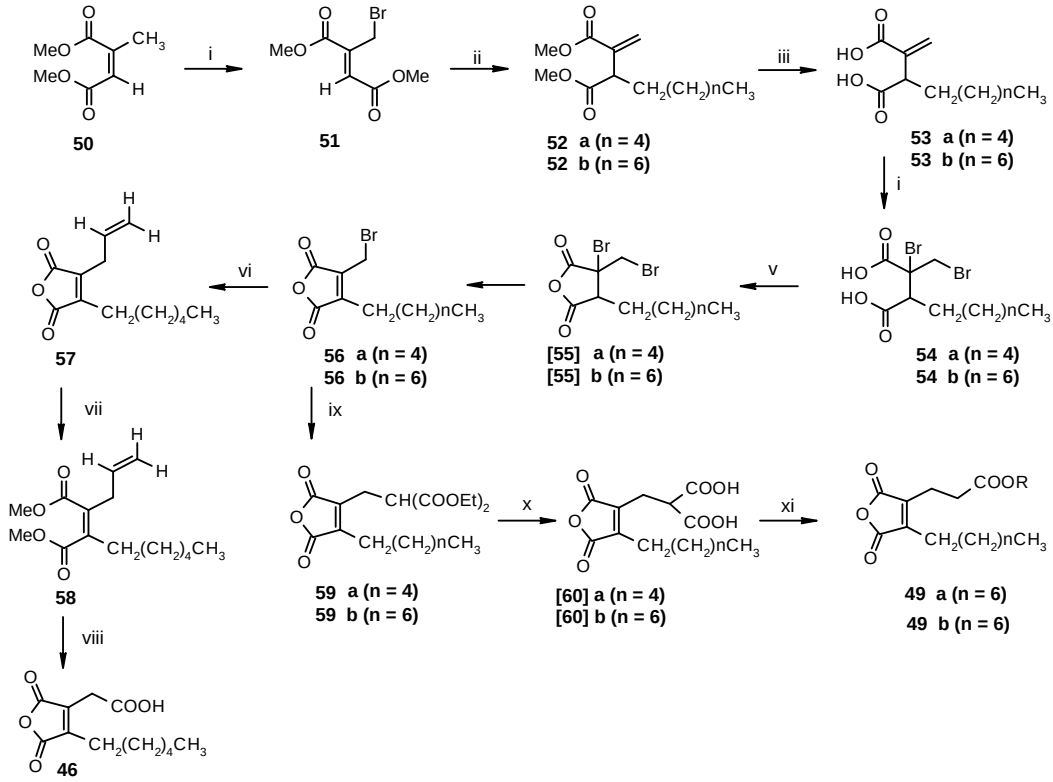
II. Second Synthetic Approach

2-(Bromomethyl)-3-alkylmaleic anhydrides **57a/b** have been used as starting material for the synthesis of these two natural products. Freshly prepared hexyl/octylmagnesium bromide was chemoselectively coupled with **52** in an S_N2' fashion to yield the diesters **53a/b** which on LiOH induced hydrolysis, followed by bromination and treatment with acetic anhydride furnished the desired **57a/b**. Highly chemoselective S_N2 displacement of allylic bromo atom in **57a** with vinylmagnesium bromide in the presence of HMPA and a copper catalyst gave the anhydride **58** which on treatment with diazomethane furnished diester **59**. The diester **59** on ozonolysis followed by an in situ oxidation and hydrolysis provided the natural product 2-carboxymethyl-3-hexylmaleic anhydride in 11% overall yield (**45**) (**Scheme 16**).[40]

The synthesis of 2-(*β*-carboxyethyl)-3-alkylmaleic anhydride (**46**) has been accomplished starting from **57a**/**b** in three steps with 34-36% overall yield (**Scheme 16**). The first step was a chemoselective diethylmalonate coupling with **57a**/**b** to furnish

anhydride derivatives **60a/b** which on acid catalyzed hydrolysis and an in situ decarboxylation of the intermediate gem-dicarboxylic acids gave the natural products **46** .[40]

Scheme 16



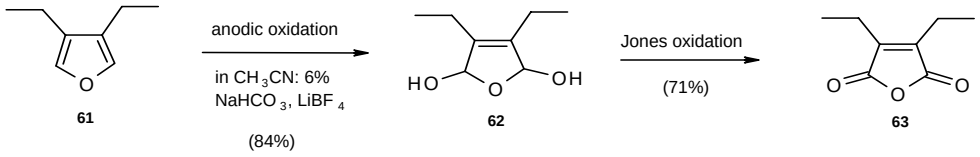
Reagents, conditions and yields: (i) NBS (1.5 equiv.), AIBN, CCl_4, reflux, 12 h (85%) (ii) $CH_3(CH_2)_nCH_2MgBr$ (1.5 equiv., n = 4/6), Et_2O, HMPA, –20 °C, 0.5 h (64-65%) (iii) LiOH (10 equiv.), THF + H_2O (3:1), rt, 18 h (90-92%) (iv) Br_2 (1.5 equiv.), CCl_4, rt, 6 h (~100%) (v) Ac_2O, reflux, 1.5 h (~100%) (vi) C_2H_3MgBr (5 equiv.), CuI (0.1 equiv.), Et_2O, HMPA, –5 to 0 °C (55%) (vii) CH_2N_2, Et_2O, MeOH, 0 °C, 3 h (95%) (viii) (a) O_3, acetone, –78 °C, 3 min.; (b) $Na_2Cr_2O_7.H_2O$, H_2SO_4, H_2O, Et_2O, 0 °C, 3 h; (c) 1 M aq. NaOH; (d) 1 M aq. HCl (42%) (ix) (a) diethyl malonate (1.1 equiv.), NaH (1.1 equiv.), C_6H_6, rt, 8 h; (b) H^+/HCl (72-74%) (x) AcOH + HCl (1:1), reflux, 12 h (95-96%) (xi) CH_2N_2, Et_2O, 0 °C, 3 h (95%).

1.3.9 Dialkylmaleic Anhydrides

Many synthetic approaches are known for the foremost member of dialkylmaleic anhydride family namely dimethylmaleic anhydride (**18**) and it has been discussed in Section 1.3.1. The next member of this family, diethylmaleic anhydride (**63**) has been

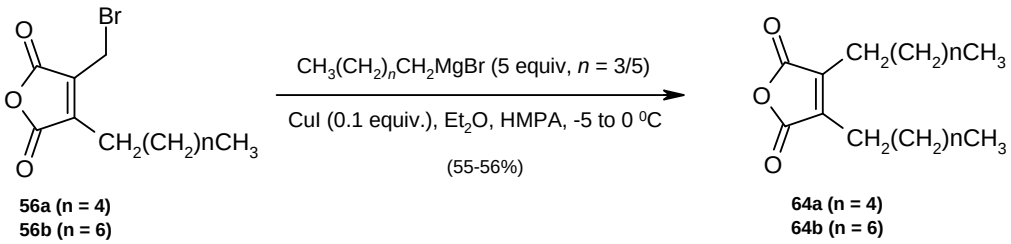
prepared from 3,4-diethyl furan (**61**) with 60% overall yield (**Scheme 17**). The starting compound **61** was converted into 3,4-diethyl-2,5-dihydroxy-2,5-dihydrofuran (**62**) which on Jones oxidation furnished diethylmaleic anhydride (**63**) .[39]

Scheme 17



Recently, in our laboratory, we have developed a new facile synthetic route to symmetrical and unsymmetrical dialkylsubstituted maleic anhydrides (**Scheme 18**).[40] The synthesis involves coupling of freshly prepared pentylmagnesium bromide with **56a** (the preparation of starting compounds **56a/b** has been described in **Scheme 16**) and heptylmagnesium bromide with **56b** in the presence of HMPA and a copper catalyst gave the desired dihexylmaleic anhydride (**64a**) and dioctylmaleic anhydride (**64b**) in 55-56% yield .

Scheme 18



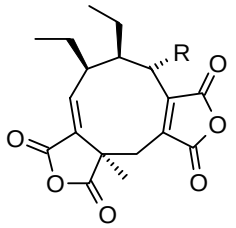
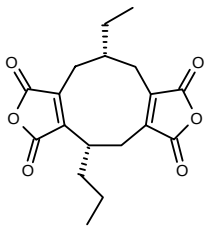
Several approaches for the synthesis of dimethylmaleic anhydride are known. These methods and the synthetic utilities of dimethylmaleic anhydride have already been discussed. Our approach towards dimethylmaleic anhydride will be discussed in chapter two. Many methods are also known for the synthesis of alkylmethylmaleic anhydrides. Several natural products bearing the same nucleus are known, some of which have been synthesized in our laboratory. Only a few methods are known for the

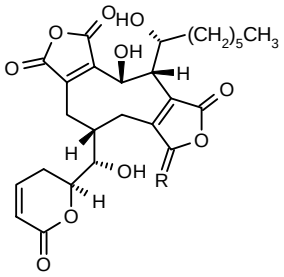
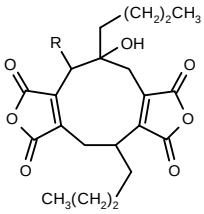
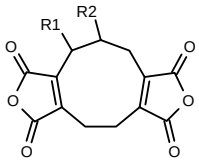
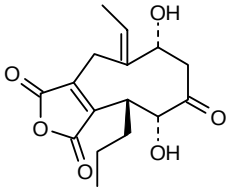
synthesis of dialkylmaleic anhydride, including recent synthesis from our laboratory. The synthetic utilities of these compounds have not been much explored

1.4 COMPLEX DIALKYLSUBSTITUTED MALEIC ANHYDRIDES OR NONADRIDES

The natural products known collectively as nonadride comprises a small structural class in which the core unit is a nine membered ring.[87] Two five-membered cyclic anhydrides or an anhydride and a lactol are fused to the core, which also bears a pair of *n*-alkyl chains and in some cases, one or more hydroxyl substitutents. Glaucanic and glauconic acids were the first members of the class to be discovered[88] and soon thereafter byssochlamic acid,[89] was isolated from ascomycete *Byssochlamys fulva* and some of the naturally occurring nonadrides have been listed in Table 6.

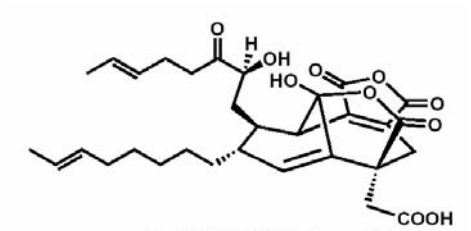
Table 6: Naturally Occurring Bioactive Nonadride Molecules

No.	Compound Structure	Source and Bioactivity	Characterization	Ref.
1	 Glaucanic Acid R = H Glauconic Acid R = O	*Pencillium purpurogenum* Not known	IR, PMR, CMR, Mass	88
2	 Byssochlamic Acid	*Byssochlamys fulva* Not Known	IR, PMR, CMR, Mass	89

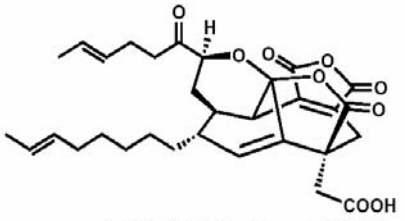
3	 Rubratoxin A R = H, OH Rubratoxin B R = O	*Penicillium rubrum* Hepatotoxic activity	IR, PMR, CMR, Mass	90
4	 Scytalidin R = H Castaneolide R = OH	*Macrophoma castaneicola* Not known	IR, PMR, CMR, Mass	91
5	 Heveadride R1 = *n*-C_3H_7 R2 = *n*-C_2H_5 Homoheveadride R1 = *n*-C_5H_{11} R2 = *n*-C_4H_9	Helminthosporium heveae Cladonia polycarpoides Not known	IR, PMR, CMR, Mass	92
6	 Cornexistin	*Paecilomyces variotii* Herbicidal activity	IR, PMR, CMR, Mass	93

The latest examples of this structural family are phomoidrides A and B (CP-225,917 and CP-263,114), two metabolites isolated by a research group at Pfizer from an unidentified fungus which also produces zaragozic acid.[94] These nonadrides attracted the attention of the researchers due to their powerful inhibition of Ras farnesyl

transferase [94]. CP molecules exemplify architectures of unprecedented molecular connectivities and complexities and possess intriguing biological activity.

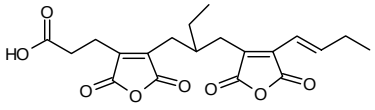


65a

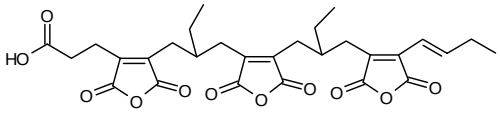


65b

Very recently two unique anhydrides namely cordyanhydrides A and B bearing two and three maleic anhydride moieties in the linear acid chain respectively have been isolated from the insect pathogenic fungus *Cordyceps pseudomilitaris* BCC 1620 and they belong to the nonadride family.[95] Most of the previously reported nonadrides contain either one or two C_9 units [C_9 unit is represented as 2-(1-butenyl)-3-methylmaleic anhydride], where these units are connected by head to head or head to tail coupling to furnish a nine membered ring. In these compounds, these two and three C_9-units are linearly connected in compounds A and B, a novel structure for the nonadride family.



Cordyanhydride A



Cordyanhydride B

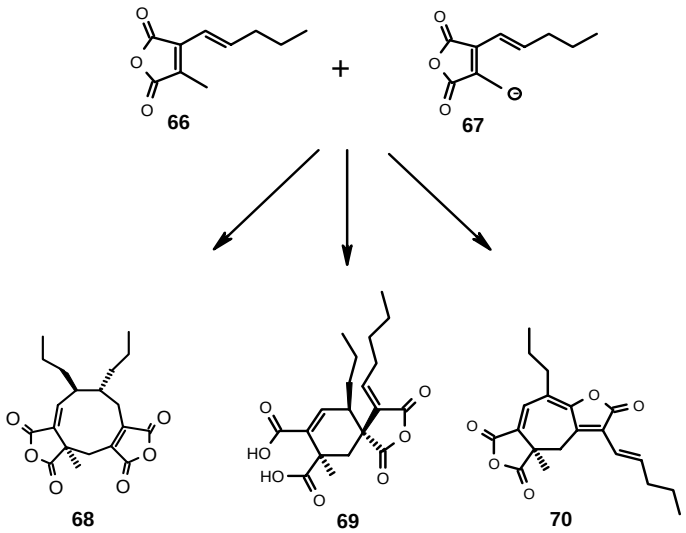
1.4.1 Biomimetic Approach to Nonadrides

The unusual core structures of the phomoidrides **65a & 65b** (CP molecules) attracted many scientists to study their biosynthesis. Understanding and development of a biosynthetic route to glauconic acids could prove extremely beneficial in deducing how these complicated natural products are formed and could be imperative in designing a short biomimetic route to the CP molecules **65a & 65b**. With its challenging structure and significant biological activity, the CP molecules **65a & 65b**

spurred scientists the world over to investigate the biosynthesis of related nonadride compounds which could provide a hint to its synthesis.

Much before the CP molecules **65a & 65b** were isolated, Sutherland and co-workers proposed that glauconic acid (entry 1, **Table 6**) and iso-glaucanic acid (entry 1, **Table 6**) are produced in nature by the head to head dimerization of the anhydride derivative **66**, although he was only successful in isolating iso-glaucanic acid through what he proposed to be a concerted [6π + 4π] cyclodimerisation.[96] More recently, Baldwin and co-workers been investigating the glaucanic acid derivative biosynthesis with a view to establish a one-pot biomimetic protocol for the nine-membered ring core of the CP molecules (**Scheme 19**). Initially, they showed that the base catalyzed dimerization of anhydride **66** afforded the bis-anhydride **68** along with dimerization products **69** and **70**, the desired **68** being obtained in 8.5% overall yield. The formation of the undesired products suggested a stepwise dimerization process via successive Michael additions .[97]

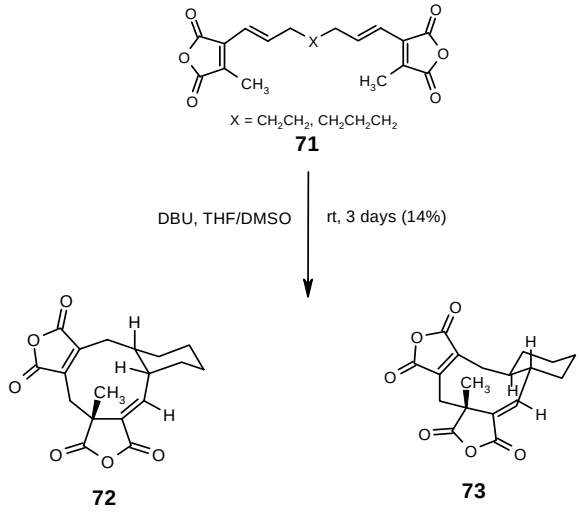
Scheme 19



In further studies, Baldwin and co-workers synthesized the anhydride tethered systems **71** and attempted the cyclization of these so as to focus on the effect that the tethering of the anhydride subunits would have on the Michael addition selectivity.

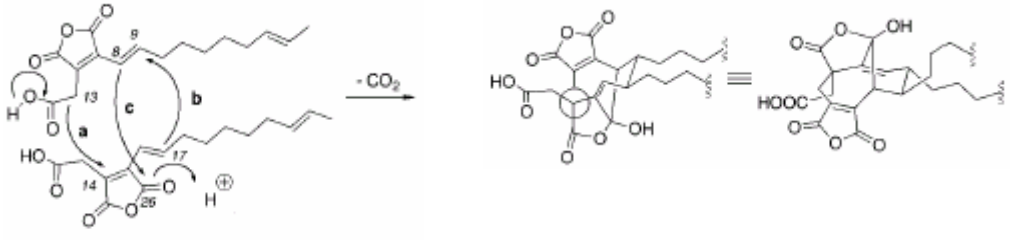
Their studies demonstrated that incorporating linkers might bring the anhydride terminii together, similar to nature wherein enzyme bring the two anhydride monomers before cyclization. Intramolecular cyclizations of dimeric bis-anhydride compounds **71**, afforded two bicyclic products **72** and **73** in a 3:2 ratio in a reasonable yield (**Scheme 20**).[98]

Scheme 20



Studies on biosynthesis of CP molecules **65** has been carried out by Sulikowski and co-workers (**Scheme 21**).[99] They have proved that the core structure common to phomoidride A and phomoidride B (**65**) is assembled by the decarboxylative homodimerization of a 16-carbon unsaturated anhydride **74**. In this remarkable dimerization, loss of carbon dioxide is accompanied by the steroselective formation of three carbon-carbon bonds (a, b, and c).

Scheme 21



1.4.2 Synthetic Approaches Toward Nonadrides

The intriguing structural features and promising biological activity of the nonadrides inspired several synthetic chemists to embark on a journey toward the total synthesis of the natural products falling in this rather unique league. Much of the attention, not surprisingly, has been captured by the phomoidrides which with their fascinating yet complex structures and potential activity prove to be an alluring yet challenging target. Amongst the other nonadrides, only byssochamic acid and phomoidrides have been successfully synthesized while not much attention has been focused on the other members of the nonadride family. Discussed briefly below are the two synthetic approaches reported for byssochlamic acid and an overview of the approaches towards the CP molecules.

1.4.2.1 Synthetic Approaches Toward Byssochlamic Acid:

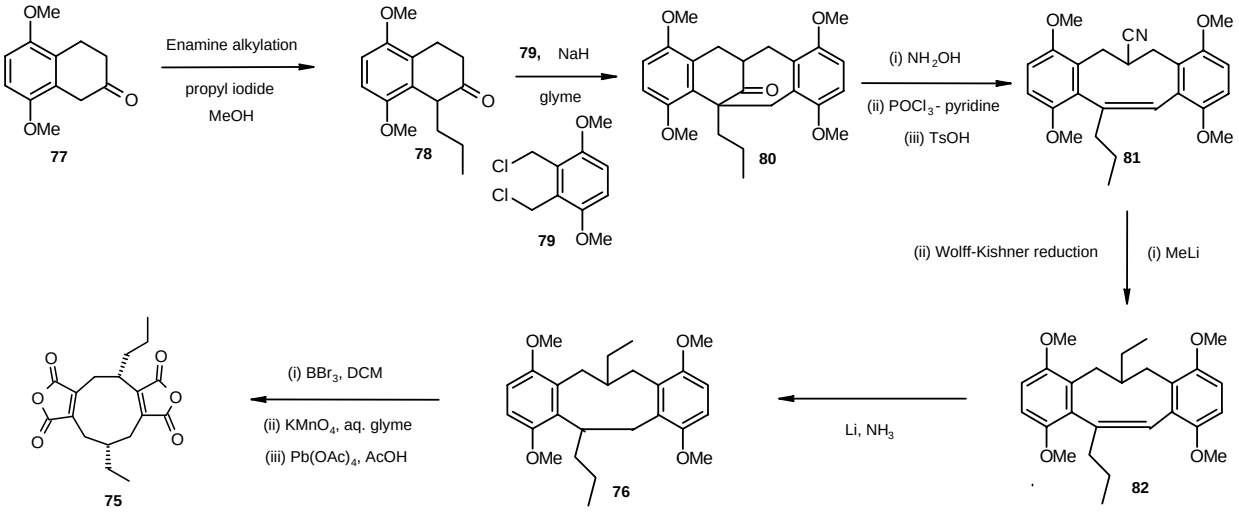
I. Gilbert Stork Synthesis

In 1972, much before the isolation of the phomoidrides, Stork et al presented a very elegant synthesis of byssochlamic acid (**75**) (**Scheme 22**).[100] The bishydroquinone dimethylether **76** was envisaged as an intermediate target, which the author proposed would serve not only as latent anhydride systems but also play an important role in establishing the two *cis* alkyl substituents.[100] The synthesis started with 5,8-dimethoxy-2-tetralone (**77**), which on enamine alkylation as the pyrrolidine enamine with propyl iodide produced **78** in ~80% yield. Dichloro compound **79**, with which the authors desired to bring about the elaboration of the ring system, was prepared by LAH reduction of the diethyl ester derived from 3,6-dimethoxyphthalic anhydride and subsequent treatment of the diol with concentrated HCl at 0 °C.

Cycloalkylation of **78** and **79** using NaH yielded tetracyclic skeleton **80** which was transformed to the substituted 9-membered ring system by oxime formation followed by fragmenation with phosphorous oxy chloride-Py. The cyano group of **81** thus obtained was converted to the required ethyl substitutent by MeLi treatment and subsequent reduction thus leading to **82**. Li-liqNH_3 was employed for reducing **82** as its tub shape and projecting methoxy groups rendered the C=C unapproachable for

catalytic hydrogenation. The dihydro derivative **76** thus obtained was transformed to the natural product **75** by first cleavage of the OMe groups followed by oxidation, first with $KMnO_4$ and then with $Pb(OAc)_4$. The *cis* geometry of the two alkyl chains was established at the precursor stage itself by single crystal X-ray structure determination of the Li-NH_3 reduction product **76**.

Scheme 22



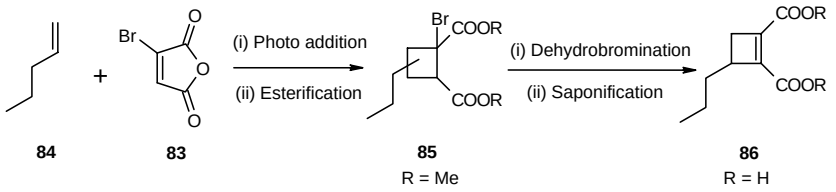
II. James D. White Synthesis

A. Racemic Synthesis of Byssochlamic Acid

The second total synthesis of byssochlamic acid (**75**) was accomplished by White et al[101] in 1992. Before going about the synthesis, the authors confirmed by experimentation the prediction (from theory) that natural *cis* alkyl chains (as present in byssochlamic acid) are more stable than the *trans* orientation. The synthesis starts with bromomaleic anhydride (**83**)**,** which on irradiation in the presence of 1-pentene (**84**) afforded photoadducts isolated as the corresponding diacids and characterized as the corresponding dimethyl esters **85**. Dehydrobromination of **85** followed by saponification of the formed cyclobutene yielded the dicarboxylic acid **86** (**Scheme 23**). The second component required for the synthesis, diol **89**, was synthesized starting from 4-ethylcyclohexanone (**87**). Carboxylation of **87** afforded β-keto ester which was

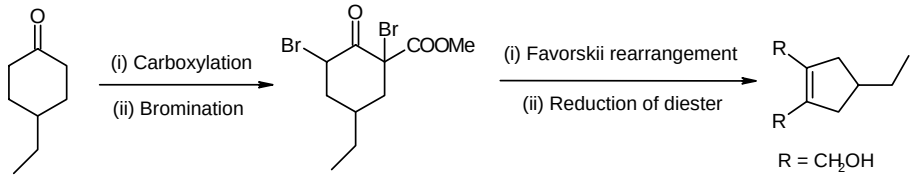
brominated to give **88**. Favorskii rearrangement of **88** followed by reduction of the formed diester yielded the desired diol **89** (**Scheme 24**).

Scheme 23



84 **83** **85** R = Me **86** R = H

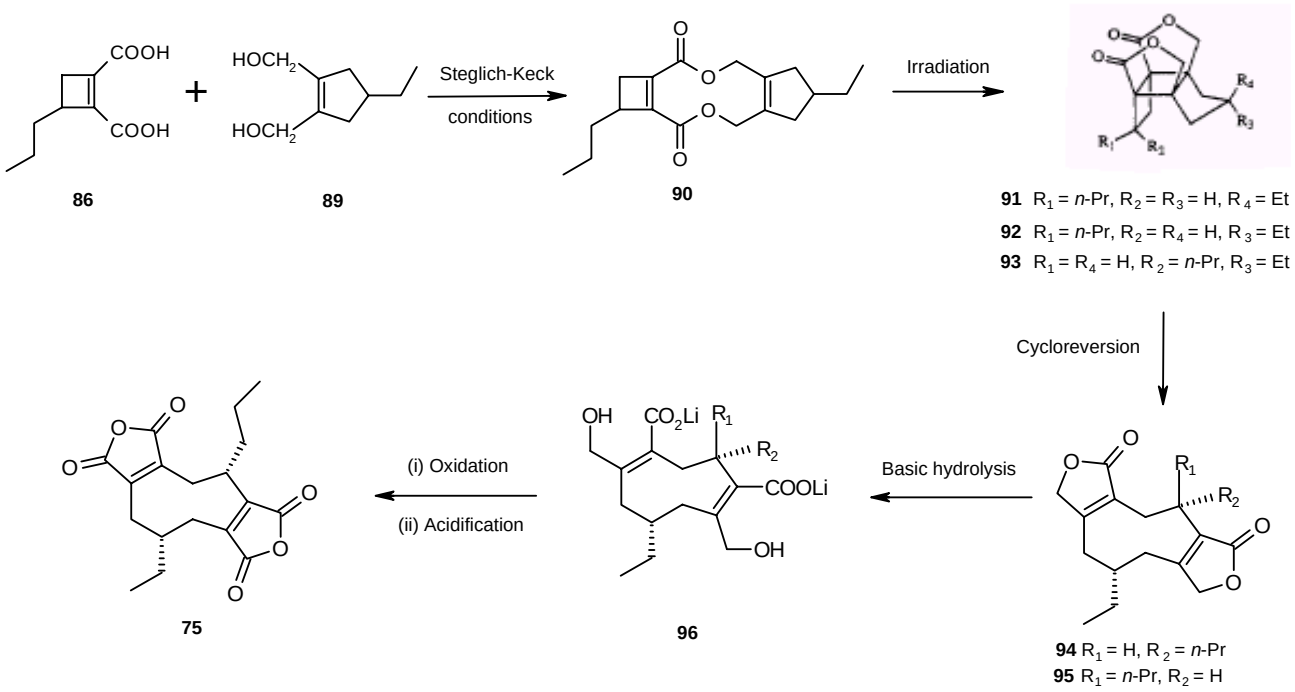
Scheme 24



87 **88** **89**

Treatment of a mixture of **86** and **89** under Steglich-Keck conditions was adopted for obtaining diolide **90** (**Scheme 25**). The diolide **90**, which was obtained as a mixture of *cis* and *trans* isomers, was irradiated to yield the intramloecular products **91**, **92**, and **93** as exo-exo, exo-endo and endo-endo stereoisomers (with respect to ethyl and propyl side chain). Cycloreversion of this mixture in refluxing toluene produced 2:1 mixture of *cis* and *trans* cyclononadienes **94** and **95** (the former originating proposedly from **91** and **93** and the latter from **92**). Basic hydrolysis of a mixture of **94** and **95** followed by oxidation of the carboxylates **96** with permanganate and subsequent acidification afforded **75** exclusively. The authors explained herein that epimerization of the propyl side chain occurs during oxidation yielding exclusively the more stable *cis* isomer **75**.

Scheme 25



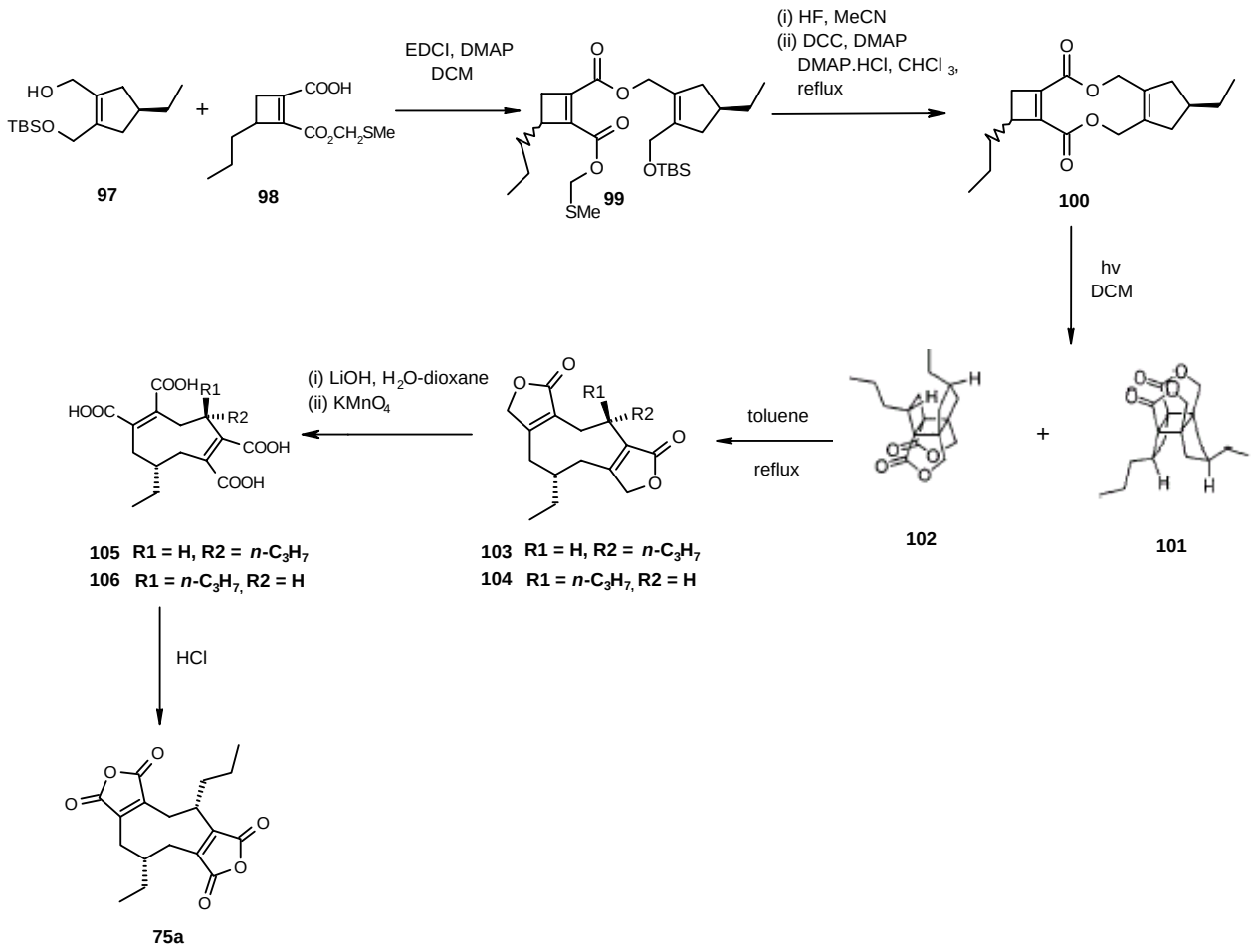
B. Asymmetric Synthesis of Byssochlamic Acid

James D. White et al, recently, extended the photo addition-cycloreversion approach that they utilized for the synthesis of (±)-byssochlamic acid to embrace an asymmetric variant of the plan shown in racemic synthesis (**Scheme 23, 24** and **25**) which leads to both enantiomers of the natural product (**Scheme 26**).[102]

A photoaddition-cycloreversion strategy applicable to enantiospecific synthesis of natural byssochlamic acid and its enantiomer was developed by James D. White et al in which porcine liver esterase (PLE) catalyzed hydrolysis of **89** followed by sequence of reactions furnished monoprotected diol **97**. The diacid **86** was converted into corresponding bismethylthiomethyl ester which on porcine liver esterase (PLE) catalyzed hydrolysis provided the desired monocarboxylic acid **98**. Stepwise coupling of (±)-**98** and (*R*)-**97**, afforded diolide **100**, which upon irradiation gave exo,exo and exo,endo [2 + 2] photoadducts **103** and **104**, respectively. The photoadducts underwent thermal cycloreversion to produce nine-membered bislactones **103** and **104**. Conversion of these lactones via 1,5-cyclononadienes **105** and **106** to naturally occurring (+)-byssochlamic acid (**75a**) was accompanied by acid-catalyzed epimerization of the *n*-

propyl substitutent. The same sequence of reactions using the (*S*)-isomer of **97** furnished the unnatural byssochlamic acid.

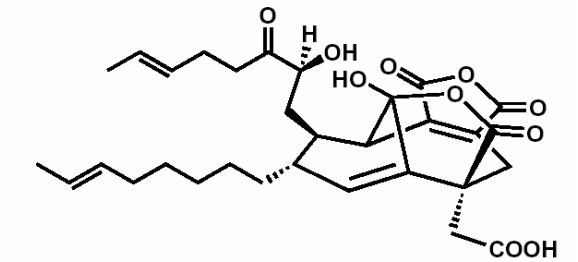
Scheme 26



1.4.2.2 Synthetic Approaches Toward Phomoidrides A and B (CP-225,917 and CP-263,114):

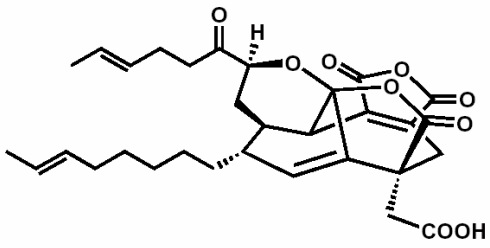
The Herculean efforts of the synthetic community toward the total syntheses of phomoidrides A and B have culminated in four completed total syntheses and at least 18 advanced synthetic approaches have been developed in recent years. Recently, the chemistry of phomoidrides A and B has been reviewed by John L. Wood and coworkers.[103] Only the highlights of the syntheses have been described in the following section in the order in which they were published. The multiplicity of synthetic

obstacles posed by phomoidrides A and B can be divided into four main structural challenges. These are the carbocyclic core including the C15-C16 bridgehead olefin, the maleic anhydride moiety, the γ-hydroxy lactone containing the quaternary center at C14, and the stereocenter at C7.



(+)-CP-225,917 (phomoidride A)

65a



(–)-CP-263,114 (phomoidride B)

65b

I. K. C. Nicolaou Synthesis

The first of these was achieved by Nicolaou and co-workers at Scripps and incorporates as its key step an Intramolecular Diels-Alder reaction (type II IMDA) to form the phomoidrides bicyclo[4.3.1]decene core.[104] Other noteworthy aspects of the approach include a unique tandem sequence to form the maleic anhydride, as well as an Arndt-Eistert homologation to elaborate the C14 quaternary center. Nicolaou's synthesis also gave rise to a number of novel chemical methods, which include two new one-carbon homologation methods and a range of new applications for iodine(V)-mediated oxidation chemistry.

The Nicolaou group determined the absolute configuration of the natural product by comparing an indoline intermediate with an analogous indoline intermediate derived from natural phomoidride B. The synthetic compound possessed the opposite optical rotation to the fungal material.

II. Tohru Fukuyama Synthesis

Professor Tohru Fukuyama and co-workers at the University of Tokyo completed the second total synthesis of the phomoidrides,[105] which also represented the second asymmetric route to these molecules. Like Nicolaou, Fukuyama chose to employ a type II intramolecular Diels-Alder strategy for the construction of the phomoidrides

bicyclo[4.3.1]decene core. They were then able to exploit exquisitely chemoselective chemistry for the facile completion of the total synthesis.

III. Matthew Shair Synthesis

The third phomoidride total synthesis was accomplished by Professor Matthew Shair and co-workers at Harvard University.[106] This route involves as its key step a "triple-domino" cyclization reaction, which proceeds in a single convergent operation to provide a highly functionalized bicyclo[4.3.1]decene core structure. To complete the quaternary center, Shair and co-workers employed the Arndt-Eistert homologation, also utilized by Nicolaou and Fukuyama. The maleic anhydride moiety was prepared by employing the Pd(0)-$P(OMe)_3$-catalyzed carbonylation reaction.

IV. Samuel Danishefsky Synthesis

The most recently completed total synthesis of the phomoidrides is that of Professor Samuel Danishefsky and co-workers.[107] Key aspects of this synthesis include: sequential aldol reaction-intramolecular Heck ring closure sequence, a diasteroselective sulfur-mediated cleavage of a spirocyclobutanone and a late stage C7 epimerization strategy to provide phomoidrides A and B (**65a** and **65b**).

1.5 SUMMARY

Maleic anhydride and its derivatives have been used as potential starting materials for the elegant synthesis of biologically active natural products, heterocycles, drugs, drug intermediates and a variety of polymers. Methylmaleic anhydride has been used to design several natural products and it is an important building block. The synthetic utilities of monoalkylmaleic anhydrides are yet to be explored. In our laboratory, we have developed an efficient method for the synthesis of potential building block dimethylmaleic anhydride. Nature offers a diverse menu of dialkylsubstituted maleic anhydrides with well established and new promising bioactivities. A number of natural products with an alkylmethylmaleic anhydride moiety are known and have been synthesized, the most important being chaetomellic anhydride A which is a promising anticancer agent. The past ten years have seen nine

syntheses being accomplished including four from our laboratory. The synthesis of maleic anhydride segment of antifungal tautomycin has been completed in our laboratory using dimethylmaleic anhydride without employing any protection/deprotection chemistry. Two syntheses are known for amino peptidase inhibitor tyromycin A including the recent synthesis from our laboratory. Only few synthetic methods are known for the synthesis of symmetrical/unsymmetrical dialkylmaleic anhydrides which includes the recent method developed from our laboratory employing Grignard reaction as a key step. Recently, nonadrides have been isolated as bioactive natural products and these molecules have attracted the attention of researchers due to their powerful inhibition of Ras farnesyl transferase and anticholestemic activity. The important members of this family are byssochlamic acid and the CP molecules (phomoidrides A and B). Two synthesis of byssochlamic acid have been completed, the first one by Gilbert Stork, while James D. White *et al* have accomplished the more recent synthesis. The latest examples of the nonadrides are CP molecules (phomoidrides A and B) and the Herculean efforts of the synthetic community toward the total syntheses of phomoidrides A and B have culminated in four completed total syntheses and at least 18 advanced synthetic approaches have been developed in recent years.

The chemistry of cyclic anhydrides is highly useful from both basic and applied point of view. Monoalkylmaleic anhydrides which promise to be versatile synthons, commends a lot of new synthetic endeavors. The recent synthesis of furan derivatives starting from maleic anhydrides represents a new paradigm in the synthesis of butenolides and variety of heterocycles. The tremendous bioactivity of dialkylsubstituted maleic anydride natural products has provided the impetus for newer synthetic approaches in spite of many earlier syntheses. The fascinating structure and remarkable bioactivity of nonadrides has spurred a lot of activity in synthetic community towards their total synthesis which paves the way for breakthroughs in medicinal chemistry and drug design.

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CHAPTER TWO

SYNTHESIS OF DIMETHYLMALEIC ANHYDRIDE AND BIOACTIVE NATURAL PRODUCTS

This chapter is divided into four sections. The first section presents a brief introduction about the phosphorous ylides generated from maleimide and maleic anhydride and some of its selected synthetic applications. The second section describes an efficient synthesis of a potential building block dimethylmaleic anhydride and synthesis of aminopeptidase inhibitor Tyromycin A. The third section summarizes an efficient synthesis of cytotoxic Piliformic acid and antituberculor *erythro*-Roccellic acid, while the fourth section describes a facile synthesis of CD45 protein tyrosine phosphatase inhibitor (*Z*)-Pulchellalactam and our ongoing studies on synthesis of bioactive natural products Isolinderanolide B and Byssochlamic acid (**Figure 1**).

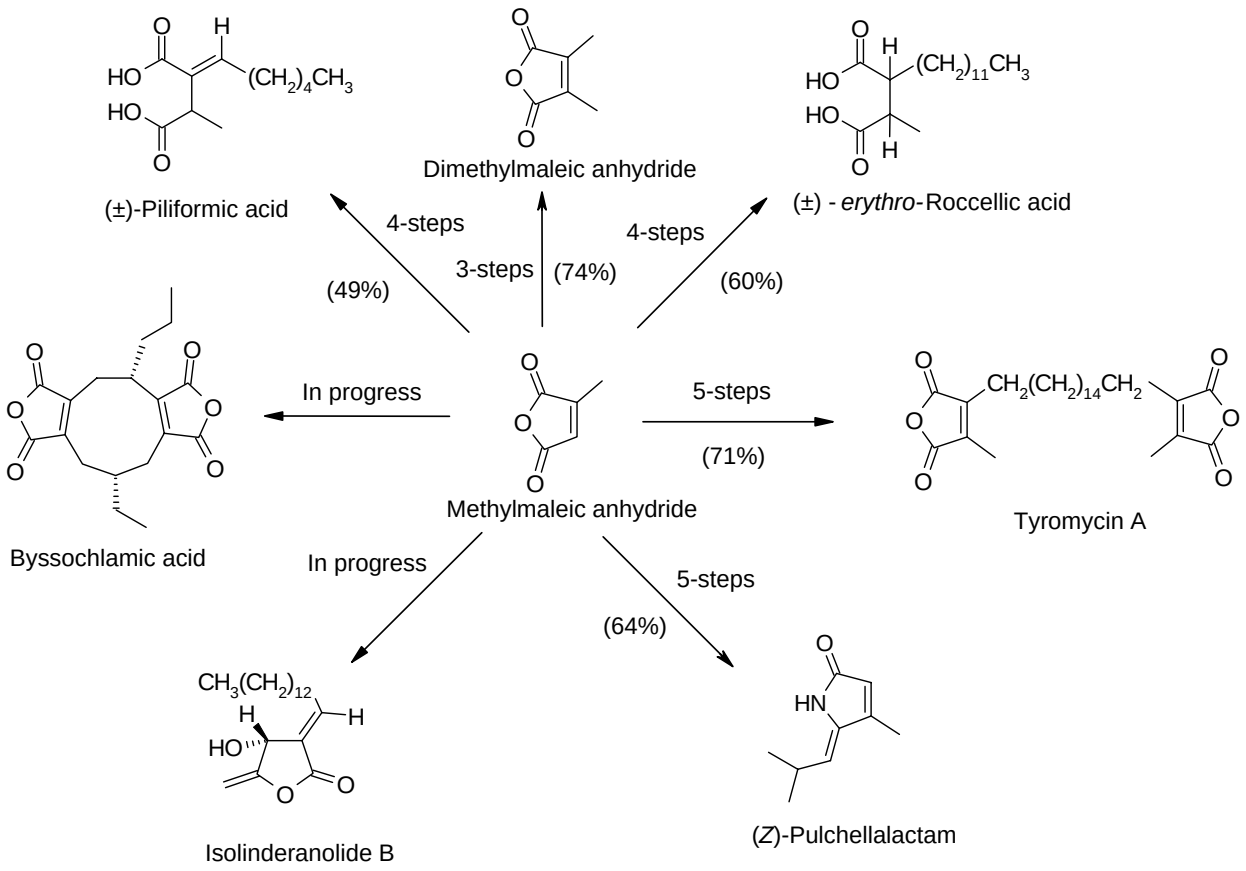


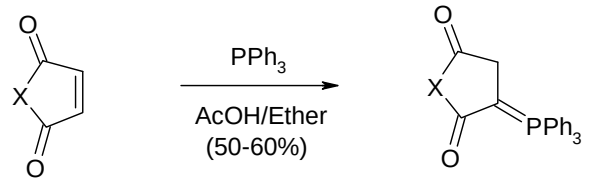
Figure 1: Methylmaleic anhydride to dimethylmaleic anhydride and bioactive natural products

2.1 SECTION A: AN INTRODUCTION OF PHOSPHOROUS YLIDES DERIVED FROM MALEIMIDES AND MALEIC ANHYDRIDES

2.1.1 Preparation of Phosphorous Ylides from Maleimides and Maleic Anhydrides

A number of stable phosphorous ylides **2a-c** are easily prepared by reacting a slight excess of triphenylphosphine with maleic anhydride/imides **1a-c** in glacial acetic acid/ether (**Scheme 1**).[1-6]

Scheme 1

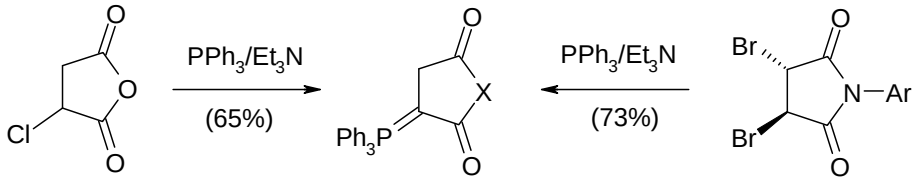


1a: X = O; **b**: X = *N*-Ar; **c**: X = *N*-H

2a: X = O; **b**: X = *N*-Ar; **c**: X = *N*-H

These phosphoranes **2a,b** were alternately obtained from the reaction of TPP with chlorosuccinic anhydride (**3**)[2,3] and dibromosuccinimide **4**[7] in presence of triethylamine. In the latter case, TPP-induced debromination[8] is followed by Michael-type addition to generate **2b** (**Scheme 2**).[9]

Scheme 2



3 **2a**: X = O; **b**: X = *N*-Ar **4**

The reactions of triethylphosphite (TEP) with cyclic anhydrides and imides follow a different course. The reaction of triethylphosphite with maleic anhydride furnishes a mixture of mono and diphosphorous heterocycles **9** and **10**[9] (**Scheme 3** and **Table 1**), whereas its reaction with maleimide is reported to yield an Arbuzov-type

product **8**.[10] This variation in the reaction course of TEP with cyclic anhydrides and imides would appear to arise from the difference in olefinic activation in maleic anhydrides and maleimides. Diphenylmaleic anhydride undergoes deoxygenative dimerization with TEP generating bifurandione **5**.[11-13] All these results are summarized in Scheme 3 and Table 1.

Scheme 3

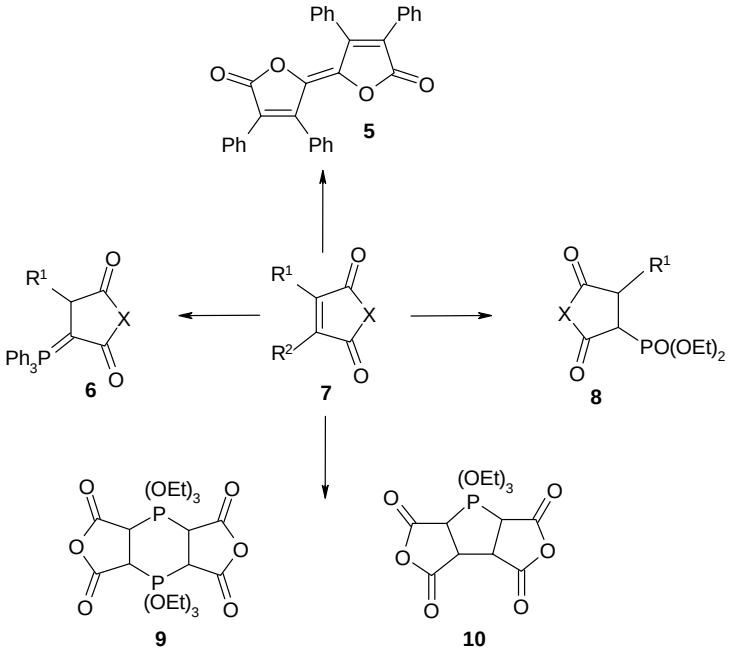


Table 1: Reactions of Triphenylphosphine/Triethylphosphite with Maleic Anhydrides/Imides

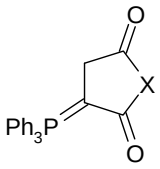
X	R^1	R^2	Reagent	Reaction conditions	Product (% yield)	Ref.
O	H	H	PPh_3	Ether, rt	**6** (90)	1-6
O	H	H	$P(OEt)_3$	NR*	**9** + **10** (NR)	9
N-Ar	H	H	PPh_3	AcOH, steam bath, 0.5 h	**6** (66)	5, 14-15
N-Ar	H	H	$P(OEt)_3$	NR	**8** (NR)	10
O	Ph	Ph	$P(OEt)_3$	Reflux, 6 h	**5** (50)	11-13
O	Me	H	PPh_3	AcOH, steam bath, 0.5 h	**6** (52)	5

* NR => Not Reported

More definitive studies to examine these reactions will be rewarding and no generalization regarding the course of the reaction of trivalent and pentavalent phosphorous reagents with cyclic anhydrides and imides can be advanced at this stage.

2.1.2 Reactions of Phosphorous Ylides derived from Maleic Anhydride/Imide and Triphenylphosphine

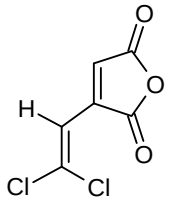
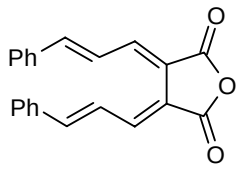
The phosphorous ylides **2a-c** from maleic anhydride and TPP, maleimide and TPP show a remarkable difference in their reactivities and have been used for a variety of chemical conversions; for example, the reaction of maleic anhydride-TPP adduct **2a** with cinnamaldehyde (1 mole or 2 moles) always furnished fulgide (entry 2**, Table 2**). In contrast, the reaction of maleimide-TPP adduct **2b** with cinnamaldehyde stops with the formation of a monosubstituted imide (entry 3**, Table 2**).

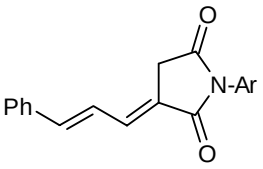
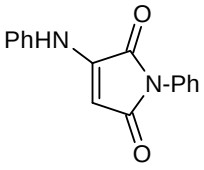
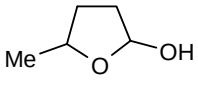
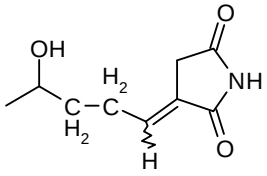


2

2a: X = O; **b**: X = *N*-Ar;
c: X = *N*H

Table 2: Reactions of Phosphoranes Derived from Maleic Anhydrides and Imides

No.	X	Reaction conditions	Product	Yield (%)	Ref.
1	O	CCl_3CHO, DCM/Acetone		25	3
2	O	2 PhCH=CHCHO, AcOH, Δ, 60 °C		85	5

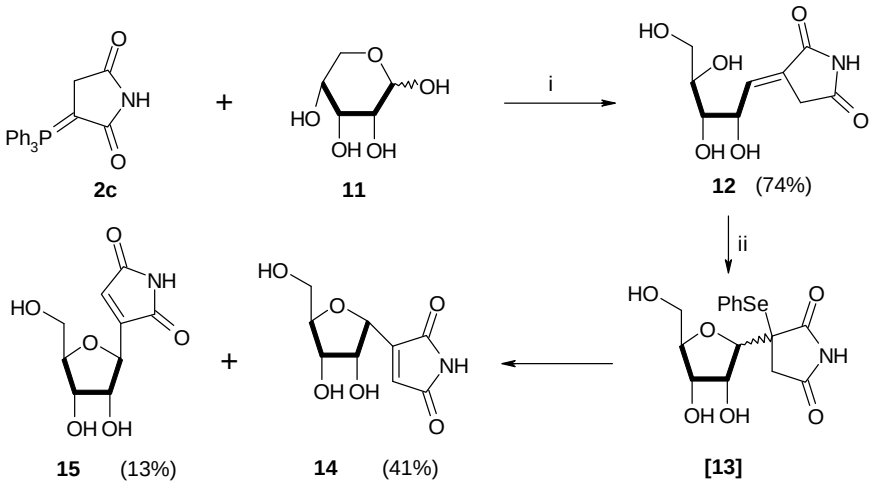
3	N-Ar	PhCH=CHCHO, rt, 0.5 h		85	16
4	N-Ph	PhNO, CH_3OH, Δ, 50 °C, 0.5 h		99	5, 16
5	NH	 AcOH, rt		68-83	14, 15

2.1.3 Synthetic Utilities of Phosphorous Ylides of Maleimides/Anhydrides

I. Synthesis of Showdomycin and *epi*-Showdomycin

Synthesis of naturally occurring antitumor, antibiotic showdomycins has been achieved using the condensation reaction of maleimide-TPP adduct **2c** with D-ribose (**11**) as a key step (**Scheme 4**).[14,15] This was followed by selenation-selenoxide elimination sequence to give showdomycin (**15**) and *epi*-showdomycin (**14**).

Scheme 4

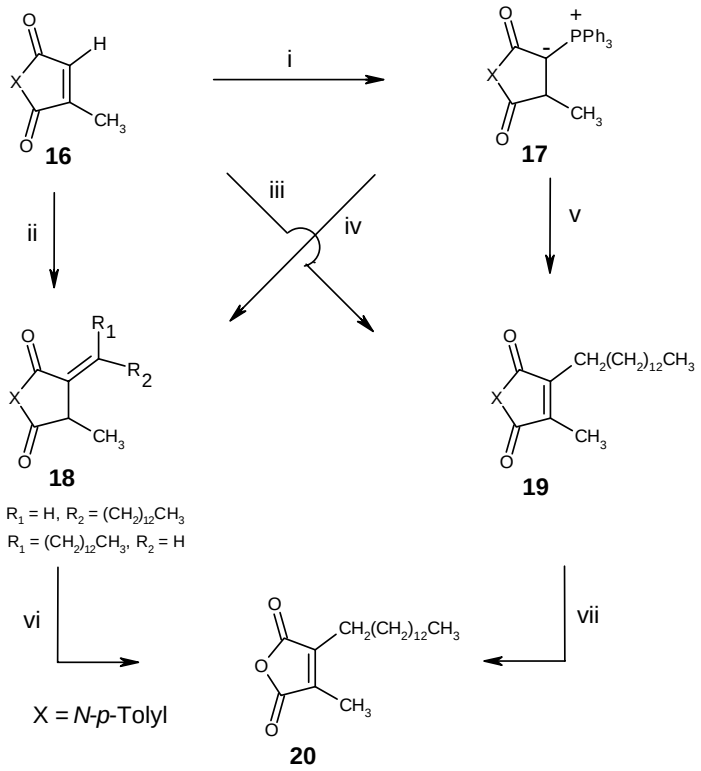


Reagents and conditions: (i) THF, reflux, 192 h; (ii) (a) PhSeCl, CH_3CN, 65 °C, 29 h; (b) H_2O_2.

II. Synthesis of Chaetomellic Acid A

Recently, we have developed in our laboratory the first reaction condition for the condensation of methylmaleimide-TPP adduct **17** with aliphatic aldehydes and employed it for the synthesis of anticancer agent chaetomellic acid A (**20**) (**Scheme 5**).[17]

Scheme 5



Reagents, conditions and yields: (i) PPh_3, AcOH, reflux, 2 h; (ii) AcOH, $CH_3(CH_2)_{12}CHO$, reflux, 18 h (71%); (iii) (a) condition ii, (b) Δ, 140-150 °C, 0.5 h (91%); (iv) AcOH, $CH_3(CH_2)_{12}CHO$, reflux, 18 h; (v) (a) condition iv, (b) Δ, 140-150 °C, 0.5 h; (vi) (a) CH_3ONa/CH_3OH, reflux, 2 h (61%), (b) H^+/HCl; (vii) (a) $KOH/H_2O/CH_3OH/THF$, reflux, 2 h, (b) H^+/HCl (98%).

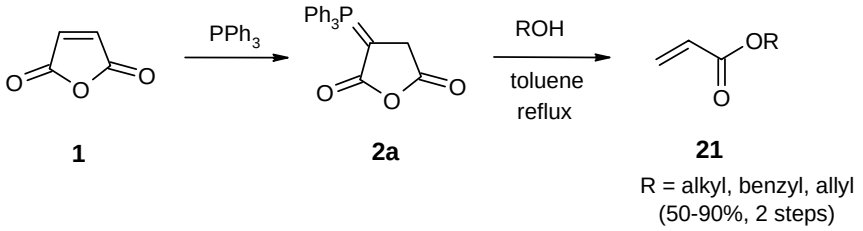
The first step in this strategy involves the formation of an ylide methyl-*N*-*p*-tolyl (triphenylphosphoranylidene)succinimide (**17**) from citraconimde **16** which smoothly condenses with tetradecanal in refluxing glacial acetic acid to yield a mixture of geometric isomers **18** in 71% yield. The exo double bond in **18** isomerizes thermally in the same pot furnishing directly the maleimide derivative **19**. The alkaline hydrolysis of

the maleimide derivative **19** followed by acidification furnished chaetomellic acid A (**20**) in 91% yield. The exo-isomers **18**, on hydrolysis and acidification, also afforded the target molecule **20** but in a lower yield as compared to the maleimide derivative **19**. Amongst all the existing syntheses, this approach appears to be the most efficient and practical one.

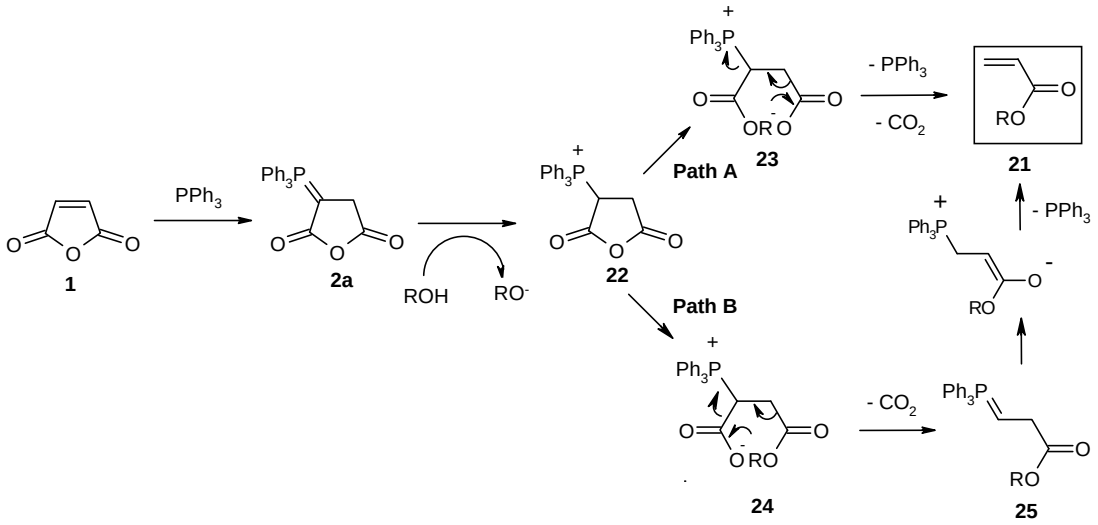
III. Triphenylphosphine-Catalyzed Conversion of Maleic Anhydride into Acrylate Esters

Recently, Jonathan and coworkers have developed an unusual triphenylphosphine catalyzed process for the conversion of maleic anhydride (**1**) into acrylate esters **21** with the loss of one carbon atom as carbon dioxide (**Scheme 6**).[18]

Scheme 6



Scheme 7



Two possible mechanisms for acrylate formation are shown in Scheme 7. Protonation of ylide **2a** would lead to the phosphonium salt **22** which could undergo ring opening to provide phosphonium carboxylates **23** and/or **24** via path A and/or path B. Decomposition of these carboxylates would lead to the observed acrylate product **21** liberating the phosphine catalyst. Experiments have shown that non-phosphine nucleophiles would be less able to support the formation of an ylide, suggesting the formation of an intermediate ylide in the phosphine catalyzed reaction which indicates that path B is preferred over path A. The regiochemistry observed in the reactions involving monosubstituted anhydrides is consistent with the intermediate similar to **24**, again suggesting that path B is preferred.

In summary, the preparation of ylides as well as the Wittig reactions are facile and high yielding. The Stobbe condensation with aldehydes generally gives relatively low yields of ylidene derivatives and a number of byproducts because of the highly basic reaction medium hence the reaction of phosphorous ylides with aldehydes may find applications which formerly would involve the Stobbe condensation. Imines, ketenes, azides and epoxides may act as potential reactants like aldehydes in reactions with these resonance stabilized ylides although an exhaustive survey is not available for the same.

2.2A SECTION B: I. AN EFFICIENT SYNTHESIS OF METHYL AND DIMETHYLMALEIMIDES/ANHYDRIDES

2.2A.1 BACKGROUND

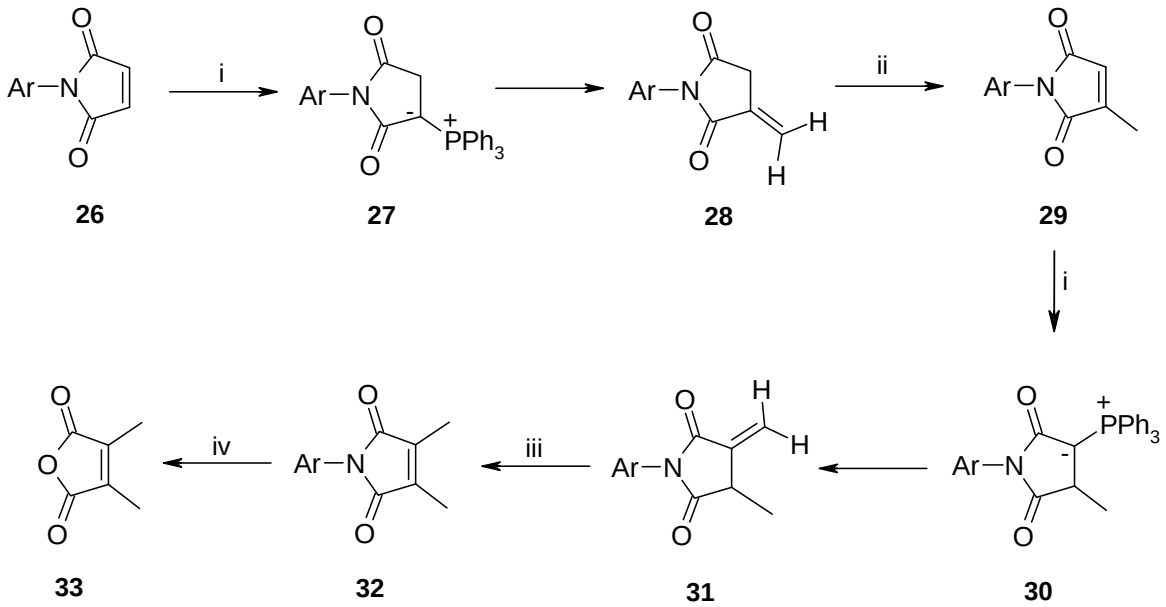
The utilities of methyl and dimethylmaleic anhydrides/imides have been well-proven in practice.[19,20] Methylmaleic anhydride/imides have been used for the synthesis of bioactive natural products chaetomellic acid A,[17,21,22] and pukelimide A.[23] Dimethylmaleic anhydride/imides have been used as potential building blocks for the synthesis of adriamycin, daunorubicin derivatives,[24] naturally occuring cyclopentene 1,3-diones,[25] calythrone,[25] chaetomellic acid A[26a] and 2,3-disubstituted maleic anhydride segment of tautomycin.[26b] Methyl and dimethylmaleic anhydrides/imides have also been used as starting materials for the synthesis of important heterocyclic systems,[27] potential dienophiles in Diels-Alder reactions,[28] well-known monomers in polymer chemistry[29] and some of their derivatives possess herbicidal, fungicidal, insecticidal and defoliant activities.[30,31] As such, methylmaleic anhydride has been obtained via oxidation of isoprene with 21% yield,[32] cyanohydration of ethyl acetoacetate with 47% overall yield[33] in 4-steps and double dehydrative decarboxylation of citric acid in 2-steps with 34% overall yield (these approaches have been discussed in the first chapter).[34] Several synthetic approaches to dimethylmaleic anhydride (**33**) using a variety of synthetic strategies are known in the literature.[35] The list of approaches to **33** with overall yield exceeding 40% include (i) oxidation of 2-butene in presence of a metal catalyst with 68% yield[36] (ii) oxidation of dimethylacetylene in 2-steps with 59% overall yield[37] (iii) self condensation of ethyl α-bromopropionates with 67% yield[38] and (iv) an elegant one-pot approach employing 2-aminopyridine with 75% yield (all the four approaches have been discussed in the first chapter).[35c] Encouraged by our recent success in the synthesis of bioactive natural products,[17,26] we planned to develop a simple and efficient method for the synthesis of alkylmaleimides/anhydrides and symmetrical/unsymmetrical dialkylmaleimides/anhydrides employing the condensation reaction of maleimide-triphenylphosphine adduct with a series of aldehydes.

2.2A.2 PRESENT WORK: RESULTS AND DISCUSSION

The formation of ylide adducts **27** and **30**, respectively from the reactions of maleimides and methylmaleimides with triphenylphosphine (TPP) in AcOH has been well established.[5,39] Acetic acid was the solvent of choice for both the generation of reactive formaldehyde monomer from paraformaldehyde under reflux conditions and condensation. The first Wittig reaction was standardized by varying the stoichiometric equivalents of paraformaldehyde and maleimide-TPP adduct **27**, the optimum condition being the reaction of paraformaldehyde (5 mmol) with maleimide-TPP adduct **27** (1 mmol) in refluxing glacial acetic acid. The reaction of maleimide **26** (1 equiv.) with TPP (1 equiv.) and paraformaldehyde (5 equiv.) in refluxing glacial acetic acid followed by removal of AcOH in vacuo at 70-75 °C and silica-gel column chromatographic purification of the residue yielded the corresponding methylmaleimide **29** in 84% yield, thus offering a new simple method for the synthesis of **29**.[40] The same reactions with a 40% aqueous solution of formaldehyde and glyoxalic acid also gave the corresponding imide **29**, but with a lower yield (30-40%).[40] The methylmaleimide **29** on further reaction with the same reagents under similar conditions furnished the dimethylmaleimide **32** in 91% yield, thus providing a facile approach to **32**.[40] In both the above mentioned conversions, the formation of ylide adducts **27** and **30**, Wittig reaction and exocyclic to endocyclic double bond isomerization takes place in one pot. In the transformation of **26** to **29** it was possible to isolate the corresponding exo-isomer **28** with 86% yield by distilling off the AcOH under high vacuum at rt, as the disubstituted exocyclic to trisubstituted endocyclic double bond isomerisation process was slow. The conversion of **28** to **29** was accomplished in refluxing THF/triethylamine (1:1) mixture with 93% yield. In the transformation of **29** to **32**, the isolation of corresponding exo-isomer **31** in pure form was difficult as the disubstituted exocyclic to tetrasubstituted endocyclic double bond isomerization was relatively fast. The ^{1}H NMR spectrum revealed that the isolated product is a mixture of **31** and **32** in 7:3 proportion. The conversion of **31** to **32** was quantitatively accomplished by heating the neat mixture at 50 °C for 3 h. The conversion of **26** to **32** was also carried out in one pot in a stepwise fashion without the isolation of **29** in 68% yield, while the direct use of two equivalents of TPP ended up with the formation of a phosphorous containing complex heterocyclic

system. The dimethylmaleimide **32** on alkaline hydrolysis in refluxing aqueous methanol followed by acidification yielded the dimethylmaleic anhydride (**33**) in 97% yield (**Scheme 8**).[40]

Scheme 8



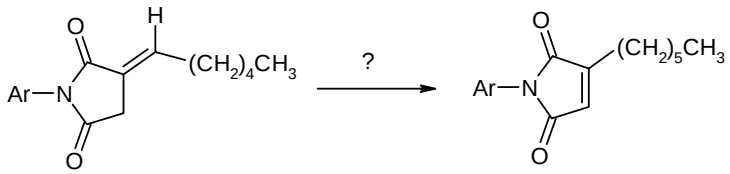
Ar = *p*-Tolyl

Reagents, conditions and yields: (i) PPh_3, $(CH_2O)_n$, AcOH, reflux, 1 h (92%); (ii) TEA, THF, reflux, 3 h (93%); (iii) 50 °C, 3 h (98%); (iv) (a) aq. MeOH, KOH, reflux, 2 h; (b) H^+/HCl (97%).

After the completion of an efficient synthesis of potential building block dimethylmaleic anhydride (**33**), we planned to extrapolate the same strategy for the synthesis of higher alkyl substituted maleimides/anhydrides and higher symmetrically/unsymmetrically dialkylsubstituted maleimides/anhydrides. We have employed 3-hexylidene-*N*-*p*-tolylsuccinimide (**34**) as the starting compound which was prepared by condensing maleimide-TPP adduct with hexanal in THF with 85% yield. All attempts at transforming the alkylidene succinimide **34** to alkylmaleimde **35** (**Scheme 9**) by using thermal (heat, tetralin reflux), base catalyzed (pyridine, TEA, DBU, NaH, *t*-BuOK, *t*-BuLi) and transition metal induced [$RuCl_3$, $HRuCl(PPh_3)_3$, $RhCl_3$, $HRhCl(PPh_3)_3$] conditions to isomerize the trisubstituted exocyclic to

trisubstituted endocyclic carbon-carbon double bond met with failure (**Scheme 9**). All our studies have been summarized in Table 3, 4, and 5.

Scheme 9



34 **35**

Table 3: Attempted Base Catalyzed Isomerizations of 34 to 35

Imide	Reagent	Reaction conditions	Conclusion
3-Hexylidene-*N*-*p*-tolylsuccinimide (**34**)	Et_3N (equiv.)	Et_3N, reflux	No reaction
	Pyridine (equiv.)	Pyridine, reflux	No reaction
	NaH (cat.)	Benzene, rt	No reaction
	t-BuO^-K^+ (cat.)	Benzene, rt	No reaction
	t-BuLi (cat.)	THF, - 78 °C to rt, 2 h	No reaction
	DBU (cat.)	THF, reflux	No reaction
		Benzene, reflux	No reaction
	DBU (equiv.)	THF, rt	No reaction

Table 4: Attempted Thermal Isomerizations of 34 to 35

Imide	Solvent	Reaction conditions	Conclusion
3-Hexylidene-*N*-*p*-tolylsuccinimide (**34**)	Neat heating	130 ^oC, 6 h	No reaction
	Tetralin	210 ^oC, 6 h	No reaction

Table 5: Attempted Transition Metal Catalyzed Isomerization of 34 to 35

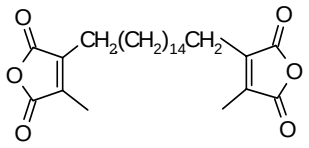
Imide	Catalyst	Reaction conditions	Conclusion
3-Hexylidene-*N*-*p*-tolylsuccinimide (**34**)	$RuCl_3$	EtOH, reflux, 8 h	No reaction
	$HRuCl(PPh_3)_3$	Toluene, reflux, 8 h	No reaction
	$RhCl_3.3H_2O$	EtOH, reflux, 8 h	No reaction
	$HRhCl(PPh_3)_3$	EtOH, reflux, 8 h	No reaction

In summary, we have demonstrated a simple and efficient approach to methyl and dimethyl substituted maleimides/anhydrides. Studies on synthesis of higher alkyl substituted maleimides/anhydrides and higher symmetrically/unsymmetrically dialkylsubstituted maleimides/anhydrides are in progress in our laboratories and we are in search of suitable conditions for the isomerization of the trisubstituted exocyclic double bond to the trisubstituted endo cyclic double bond so as to convert alkylidene succinimides to the corresponding alkylmaleimides. All our efforts in these systems reveal that the exocyclic trisubstituted compounds are theromodynamically more satble than the corresponding endocyclic compounds.

2.2B SECTION B: II. A FACILE SYNTHESIS OF NATURALLY OCCURRING AMINOPEPTIDASE INHIBITOR TYROMYCIN A

2.2B.1 BACKGROUND

Tyromycin A has been recently isolated from mycelial cultures of basidiomycete *Tyromyces lacteus* (Fr.) Murr[41] and its structure was established as 1,16-*bis*-[4-methyl-2,5-dioxo-3-furanyl]hexadecane (**36**) by using spectral and analytical data and by transformation into corresponding tetramethyl ester and diimide derivatives.[41]Among the enzymes bound to surfaces of mammalian cells, aminopeptidases have been recognized as potential targets for the immunomodulating drugs.[42] Tyromycin A was found to inhibit the leucine and cysteine aminopeptidases bound to the outer surface of HeLa S3 cells and it also exhibits cytostatic activity.[41] The first synthesis of tyromycin A (**36**) has been completed by Samadi and coworkers employing the decarboxylative Barton-radical coupling reaction (discussed in the first chapter).[43] Development of a new facile synthetic route to this bioactive natural product, **36** is a task of current interest. We planned to complete a practical synthesis of tyromycin A by employing a double Wittig reaction of citraconimide-TPP adduct with 1,16-hexadecanedial as a key step followed by hydrolysis pathway.



Tyromycin A (**36**)

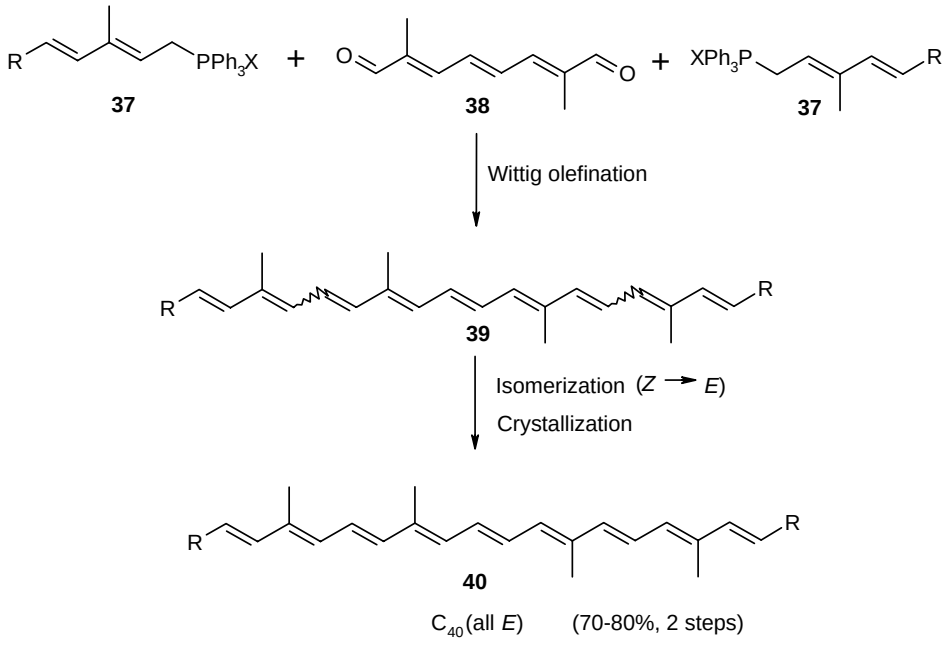
2.2B.1.1 Applications of Double Wittig Reaction in Organic Synthesis

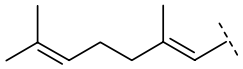
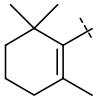
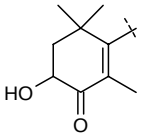
I. Industrial Synthesis of Symmetrical Carotenoids and Retenoids

Symmetrical carotenoids are synthesized by double Wittig condensation of a symmetrical C_{10}-dialdehyde 38 which serves as the central C_{10} building block, with two equivalents of an appropriate C_{15}-phosphonium salt 37 (Scheme 10).[44] The productivity of this convergent synthetic strategy has been demonstrated in numerous symmetrical carotenoids. It is used industrially in production processes for lycopene, β-carotene and astaxanthin. The double Wittig olefination of 38 affords a highly efficient method capable of diverse application in the final stage of the industrial synthesis of

carotenoids. These carotenoids are used as animal feed additives, in particular, in poultry farming and in aquaculture. β-Carotene is used for the direct coloring of foods and lycopene is employed as nutritional supplements (Scheme 10).

Scheme 10



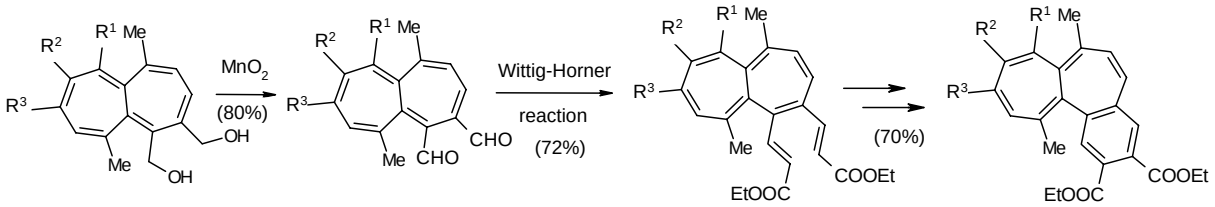
R	Carotenoid
	Lycopene
	β-Carotene
	Astaxanthin

II. Synthesis of Benzo[*a*]heptalenes

Double Wittig-Horner reaction has been used for the synthesis of the key intermediate diester **43** which on 6 π-electrocyclic ring closure-aromatization sequence

is known to furnish the functionalized benzo[*a*]heptalenes **44** with very good yield (**Scheme 11**).[45]

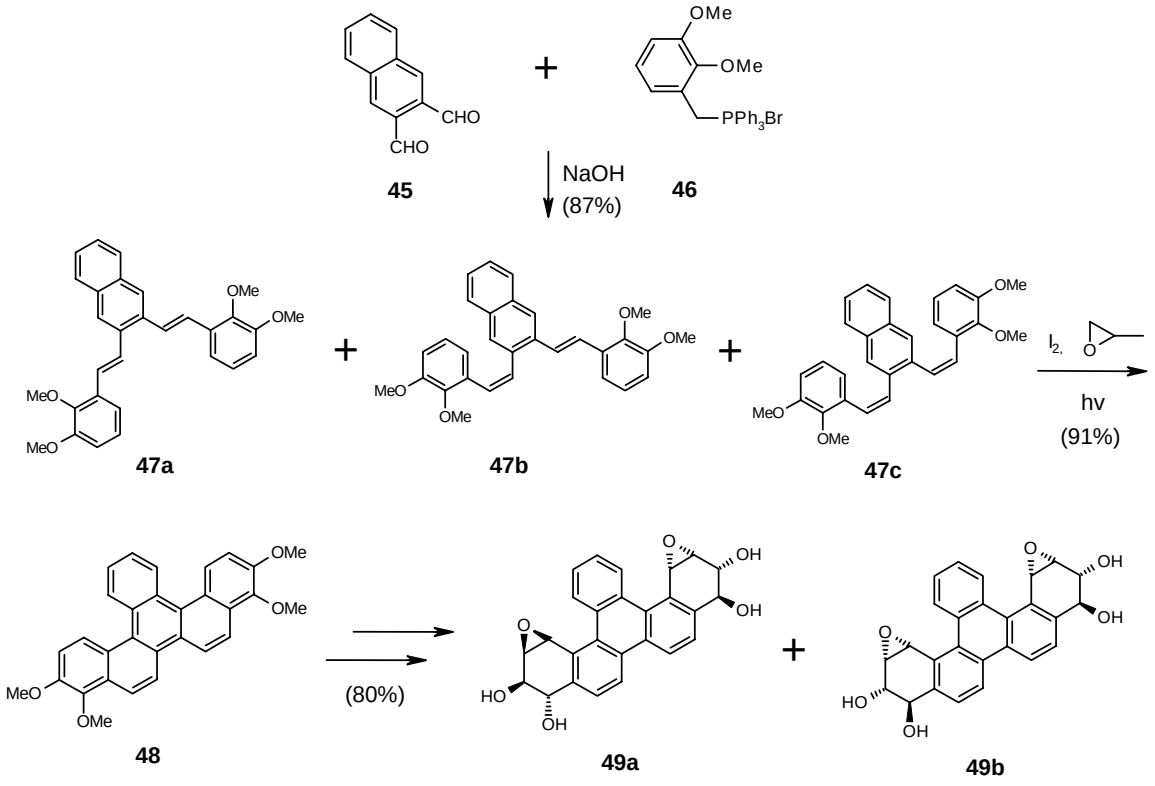
Scheme 11



III. Syntheses of Bis-dihydrodiol and Bis-anti-diol epoxide Metabolites of Benzo[*s*]picene

Bis-dihydrodiol and bis-anti-diol epoxide metabolites of benzo[*s*]picene (**49a,b**) are suspected proximate and ultimate carcinogenic metabolites and synthesis of these compounds involves the double oxidative photocyclization of a tetramethoxy-2,3-distyrylnapthalene **47a-c** as a key step (**Scheme 12**).[46]

Scheme 12

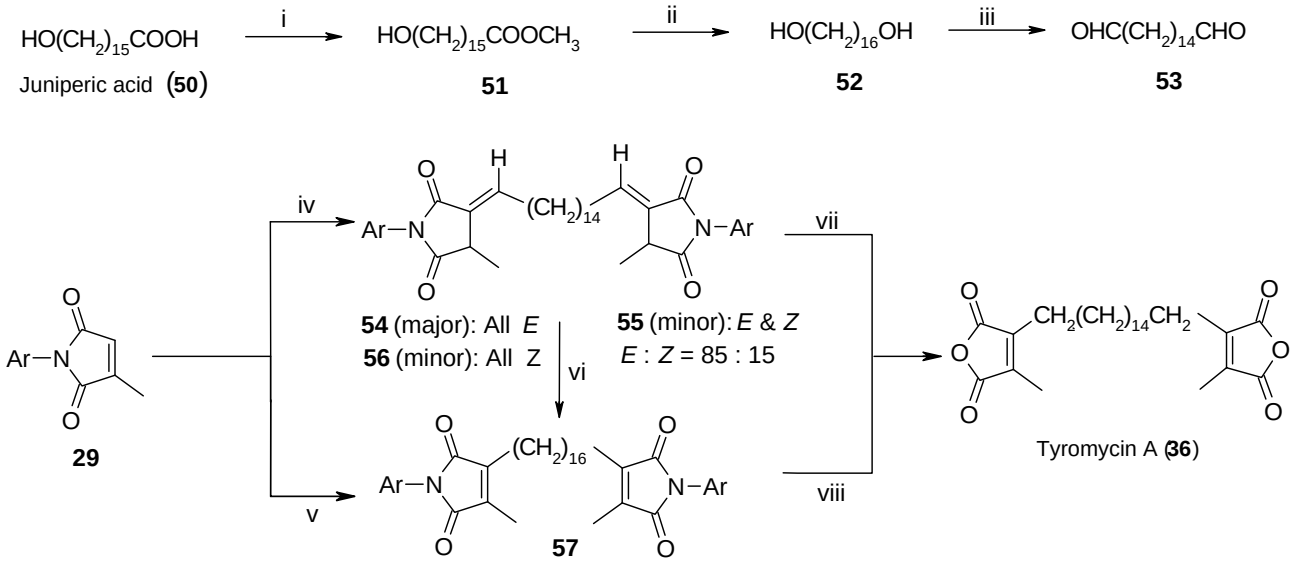


These compounds **47a-c** (mixture with equal proportions) were obtained by double Wittig reaction between naphthalene-2,3-dialdehyde (**45**) and 2,3-dimethoxybenzyl triphenylphosphonium bromide (**46**).

2.2B.2 PRESENT WORK: RESULTS AND DISCUSSION

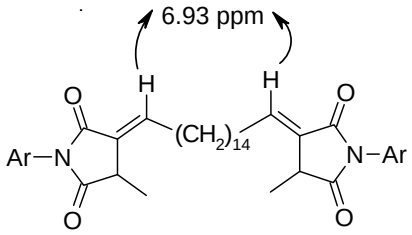
The key step in our synthesis of tyromycin A involved the double Wittig condensation of citraconimide-TPP adduct **30** with 1,16-hexadecanedial (**53**). Dialdehyde **53** was synthesized starting from commercially available juniperic acid (**50**). This hydroxy acid **50** was converted to methyl ester **51** quantitatively using diazomethane in diethyl ether. The formed methyl ester **51** was then reduced to 1,16-hexadecanediol[47] (**52**) using LAH in ether at rt with very good yield. PCC oxidation[48] of the 1,16-hexadecanediol (**52**) gave the desired 1,16-hexadecanedial[49] (**53**) with 72% overall yield (**Scheme 13**).[50]

Scheme 13

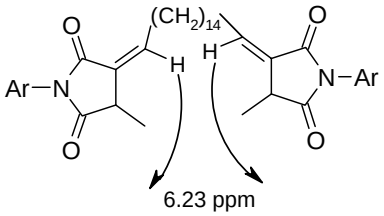


Reagents, conditions and yields: (i) CH_2N_2, Et_2O, 0 ^oC, 2 h (95%); (ii) LAH, Et_2O, rt, 2 h (98%); (iii) PCC, CH_2Cl_2, rt, 10 h (77%); (iv) TPP, AcOH, **53**, reflux, 10 h (70%); (v) (a) TPP, AcOH, **53**, reflux, 10 h; (b) △, 140-150 ^oC, 30 min (72%); (vi) Tetralin, reflux, 1 h (98-100%); (vii) (a) CH_3ONa, CH_3OH, reflux, 2 h; (b) H^+/HCl (60%); (viii) (a) KOH, H_2O, THF, CH_3OH, reflux, 2 h; (b) H^+/HCl (98%).

After the efficient synthesis of desired dialdehyde **53**, we planned for the double Wittig reaction of this aldehyde with citraconimide-TPP adduct **30**. In accordance with this idea, the double Wittig reaction was performed and we could get the condensed product with very good yield. The optimum molar ratio of dialdehyde **53** and citraconimide-TPP adduct **30** was found to be 1:3. The reaction mixture was refluxed for 10 h which was followed by removal of acetic acid in vacuo and a mixture of bis-condensed exo Wittig products **54** (*E, E* - major), **55** (*E, Z* - minor) and **56** (*Z, Z* - minor) in 70% yield with 85:15 ratio of *E*:*Z* geometry of the carbon-carbon double bond were obtained. The geometrical isomers were inseparable by silica-gel column chromatography and the ratio of *E*:*Z* geometry of the carbon-carbon double bond was determined from ^{1}H spectrum of mixture of exo adducts **54-56**. The vinylic proton in the *E*-isomer appears at lower field resonance than the *Z*-isomer because of the formers close proximity to the carbonyl.



54 (*E, E* - major)



56 (*Z, Z* - minor)

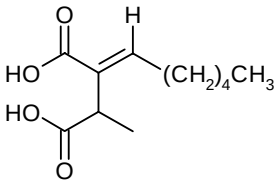
In the above reaction, when the acetic acid was distilled off under normal atmospheric pressure and the residue was heated at 140 - 150 ^{o}C for 30 min. and the reaction directly furnished the endo bisimide **58** in 72% yield. Mixture of **54-56** in refluxing tetralin underwent a smooth trisubstituted exocyclic to tetrasubstituted endocyclic double bond isomerization to yield the bismaleimide derivative **58** in quantitative yield. The mixture of exo-isomers **54-56** upon treatment with sodium methoxide in methanol followed by acidification gave tyromycin A (**36**) in 60% yield. The bisimide **57** upon treatment with KOH in water + THF + CH_3OH (1:1:1) followed by acidification, ethyl acetate extraction and silica gel column chromatographic purification gave tyromycin A (**36**) in 98% yield (**Scheme 13**).[50] In the first synthesis

report,[43] it has been mentioned that tyromycin A (**36**) during silica gel column chromatographic purification undergoes ring opening to form the corresponding di- and tetracarboxylic acids. To prove the stability of tyromycin A during silica gel column chromatographic conditions, we chromatographed 100 mg of pure tyromycin A over a silica gel column (60-120 mesh) using petroleum ether (60-80 fraction)-ethylacetate mixture (9:1) and obtained more than 98 mg of tyromycin A which proved that it is fairly stable to silica gel column purification conditions. The disubstituted maleic anhydrides under neutral and acidic conditions stay in a ring closed form, while in basic medium they exist in dianionic form.[51] To our knowledge, the condition to obtain them in *cis*-dicarboxylic acid form is still elusive. The spectral and analytical data obtained for tyromycin A (**36**) were in agreement with reported data.[41,43]

In summary, we have demonstrated yet another application of our recently reported citraconimide-TPP adduct coupling reaction with aliphatic aldehydes to complete the practical two-step synthesis of bioactive natural product tyromycin A in 71% overall yield and our method also offers potentially easy access to tyromycin congeners for structure-activity relationship studies.

2.3A SECTION C: I. AN EFFICIENT SYNTHESIS OF (±)-PILIFORMIC ACID

2.3A.1 BACKGROUND



(±)-Piliformic Acid (58)

Piliformic acid (2-hexylidene-3-methylsuccinic acid, **58**) was identified[52] in 1985 as a metabolite of several closely related fungi of the Xylariaceous genera. It was isolated in small quantities from *Hypoxylon deustum*, while it was obtained in substantial quantities as the major metabolite of the dung *Poronia piliformis* and also from four members of the morphologically related *Xylaria* genus, *X. polymorpha*, *X. longipes*, *X. mali* and *X. hypoxylon*, which grow on dead and decaying wood. Very recently, it has been isolated from culture broth of the marine fungus *Halorosellinia oceanica* BCC 5149 and proven to be cytotoxic against KB and BC-1 cell lines with IC_{50} values of 1-13 μg/mL.[53] In nature, piliformic acid (**58**) exists in *levo*, *dextro* and *racemic* form, although the absolute stereochemistry has not been determined. The structural assignment of piliformic acid (**58**) has been done on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.[52,53,54] On the basis of ^{1}H NMR data the carbon-carbon double bond in **58** has been assigned the (*E*)-geometry and this has been further confirmed by comparison with synthetic sample.

2.3A.1.1 Synthetic and Biosynthetic Approaches Towards (±)-Piliformic acid (58)

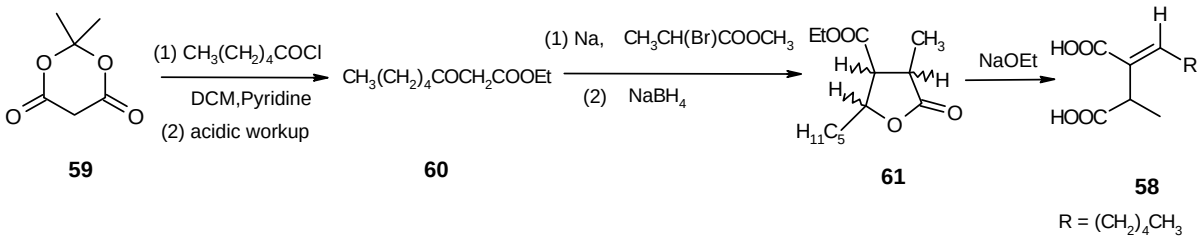
I. Edward's Synthetic Approach

The first synthesis has been completed by Edwards and coworkers starting from Meldrum's acid (**59**) via condensation of ethyl 3-oxo-octanoate (**60**) with ethyl 2-bromopropionate to obtain diethyl 2-hexanoyl-3-methylsuccinate, followed by its sodium borohydride reduction to give ethyl ester of paraconic acid **61**, which on treatment with sodium ethoxide followed by alkaline hydrolysis furnishes **58** with 1.75% overall yield (**Scheme 14**).[52]

They have examined a number of possible routes for the synthesis of diacid **58**. They report that the attempts to condense hexanal with diethyl methylsuccinate using

potassium *tert*-butoxide or sodium hydride as base and the reaction of 1, 2-*bis*(ethoxycarbonyl)propylidene(triphenyl)phosphorane with hexanal in refluxing benzene met with failure (**Scheme 14**).[52]

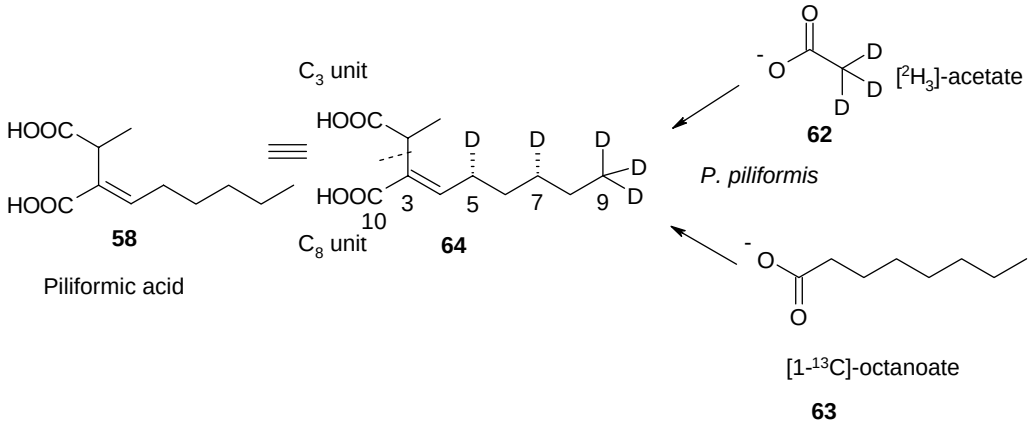
Scheme 14



II. David O'Hagan's Biosynthetic Studies

A recent biosynthetic investigation by David O'Hagan and coworkers in both *P. piliformis* and *X. mali* has shown that piliformic acid (**58**) is constructed from a C_3 unit, derived from the citric acid cycle intermediate oxaloacetate, and from a C_8 octanoic acid moiety as shown in Scheme 15.[54,55] Sodium [1-^{13}C]-octanoate (**63**) was incorporated predominately as an intact unit with isotope enrichment at C-10. Additionally the stereochemical configuration of the resultant deuterium atoms at C-5 and C-7 after incorporation of sodium [$^2H_3$]-acetate (**62**) was consistent with operation of an enoyl reductase from a fungal fatty acid synthase (FAS), rather than that from a polyketide synthase (PKS). This study therefore established the operation of a fungal FAS and not a PKS operating during piliformic acid biosynthesis (**Scheme 15**).

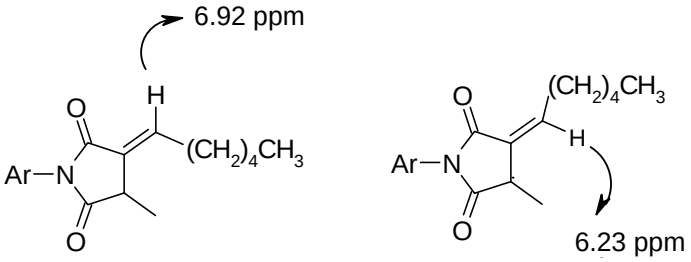
Scheme 15



With its cytotoxic activity, piliformic acid presents itself as an attractive synthetic challenge for organic chemists and we planned to complete a practical synthesis of this bioactive natural product employing the condensation of methyl(triphenylphosphoranylidene)succinimde with hexanal.

2.3A.2 PRESENT WORK: RESULTS AND DISCUSSION

The reaction of *p*-toluidine (**67**) with citraconic anhydride (**68**)[34] in ether at room temperature furnished a mixture[56] of methylmaleanilic acids **69** & **70** (α-methyl:β-methyl = 9:1) in 95% yield. This mixture of regioisomers **69** plus **70** on treatment with acetic anhydride-sodium acetate gave citraconimide **29** in 90% yield. A mixture of equimolar amounts of imide **29** and triphenylphosphine on refluxing with 1.5 equivalents of hexanal in glacial acetic acid for 10 hours yielded a combination of geometric isomers **65** and **66** as a thick-oil with 83% yield, via an adduct **30**. The integral values for vinylic protons in ^{1}H NMR spectrum of this mixture of geometric isomers (*E*)-**65** and (*Z*)-**66** revealed that they are formed in 85:15 ratio (**Scheme 16**).



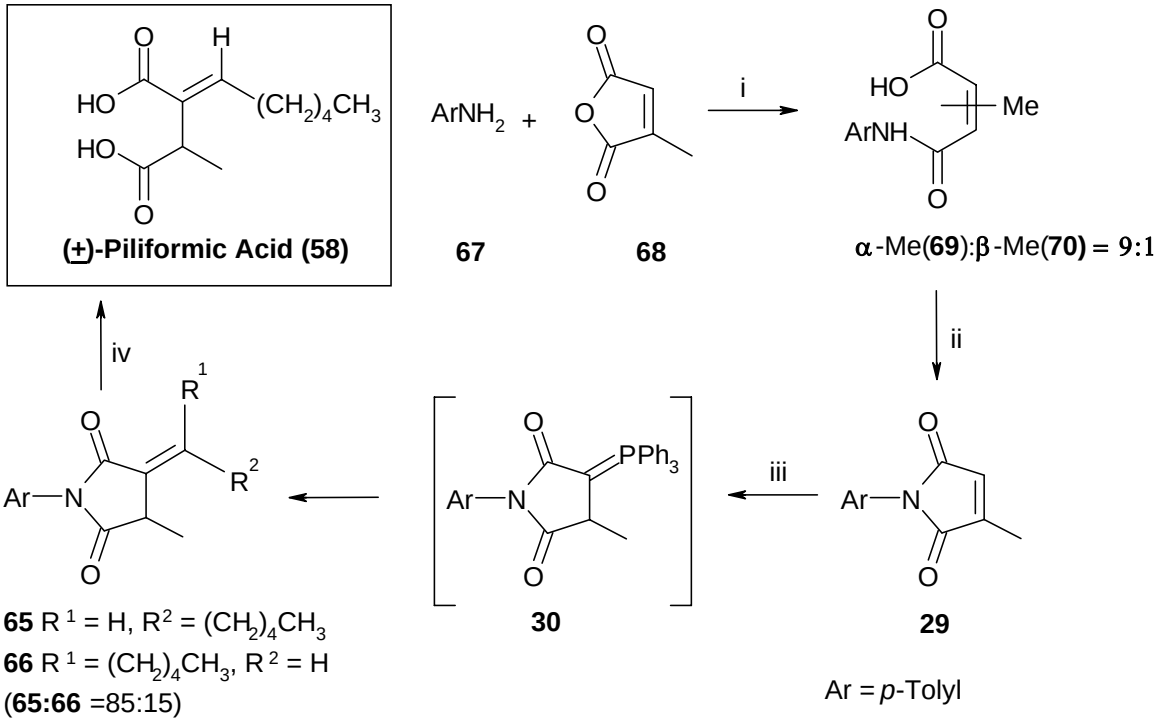
65 **66**

Several reaction conditions were tried for hydrolysis of **65** plus **66** to obtain (*E*)- plus (*Z*)-Piliformic acids, without the isomerization of trisubstituted exocyclic to tetrasubstituted endocyclic double bond in **65** plus **66** mixture and the best results were obtained with a combination of acetic acid and concentrated hydrochloric acid. The mixture of isomers **65** plus **66** on refluxing with concentrated hydrochloric acid and glacial acetic acid (1:1) for 60 hours furnished only the mixture of (*E*)- and (*Z*)-piliformic acids in 98% yield in the same ratio and without the migration of carbon-carbon double bond (**Scheme 16**).[57]

Our endeavors to obtain the desired (*E*)-isomer from the mixture of *E* + *Z* piliformic acids finally met with success when the pure (*E*)-isomer crystallized out from

hot water in more than 70% yield (**Scheme 16**).[57] The analytical and spectral data obtained for **58** were in agreement with the reported data.[52,53]

Scheme 16



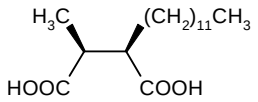
Reagents, conditions and yields: (i) Et_2O, rt, 1 h, (95%); (ii) Ac_2O/NaOAc, water bath, 60-65 ºC, 1 h (90%); (iii) TPP, AcOH, hexanal, reflux, 10 h (83%); (iv) (a) AcOH, con. HCl, reflux, reflux, 60 h (98%); (b) Recrystallization from excess of hot water, (*E*)-isomer (97%).

In summary, we have demonstrated an efficient 4-step synthesis of naturally occurring cytotoxic (±)-piliformic acid (**58**) starting from citraconic anhydride with 49% overall yield. Ours is the first efficient synthesis of this natural product and has got scale up potential. The present strategy will also be useful as a general method to obtain a series of 2-alkylidene-3-alkyl succinic acid derivatives.

2.3B SECTION C: II. FIRST EFFICIENT SYNTHESIS OF (±)-*erythro*-ROCCELLIC ACID

2.3B.1 BACKGROUND

(+)-Roccellic acid [(2*R*, 3*S*)-2-dodecyl-3-methylbutanedioic acid, **71a**] occurs in lichens[58,59] and it was first isolated in 1898. In the past century it has been isolated from the following several lichen species: *Roccella Capensis,*[60] *R. fuciformis,*[61,62] *R. hypomecha,*[63] *R. gayana,*[64] *R. fucoides,*[64,65] *R. condensata,*[66] *R. montagnei*,[67,68] *Dirinaria aegialita,*[69] *D. applanata,*[69] *D. confusa saxicola,*[69] *D. consimilis,*[69] *D. leopoldii,*[69] *Pyxine berteriana,*[69] *P. caesiopruinosa,*[69] *P. pungens,*[69] *Lobodirina cerebriformes,*[70] *L. mahuiana,*[71] *Acarospora chlorophana,*[72] *Lecanora riparia,*[73] *L. rupicola,*[74,75] *L. sordida,*[76,77] *Lepraria latebrarum,*[78] *L. aeruginosa,*[79] *Dirina lutosa,*[80] *Crocynea membranacea*[81,82] and more recently from *Haematomma nemetzii*[83] and *Tornabena. Scutellifera*[83] with a major contribution from Siegfried Huneck's group. The structural assignment of roccellic acid **71a** has been done on the basis of analytical and spectral data.[74,76,81,83]



(2*R*, 3*S*)-2-Dodecyl-3-methylbutanedioic acid (**71a**)

Its absolute configuration has been established by Åkermark by degrading **71a** to its two isomeric monomethyl esters.[81,84] Roccellic acid **71a** possesses antitubercular activity[85-87] and concentration dependent plant growth promotor[88-90]/inhibitor[90,91] activity. It is also used for (i) synthesis of structural analogues of the antibiotic actinonin[92] (ii) precipitation of human serum albumin[93] and (iii) preparation of colored metal complexes.[94, 95]

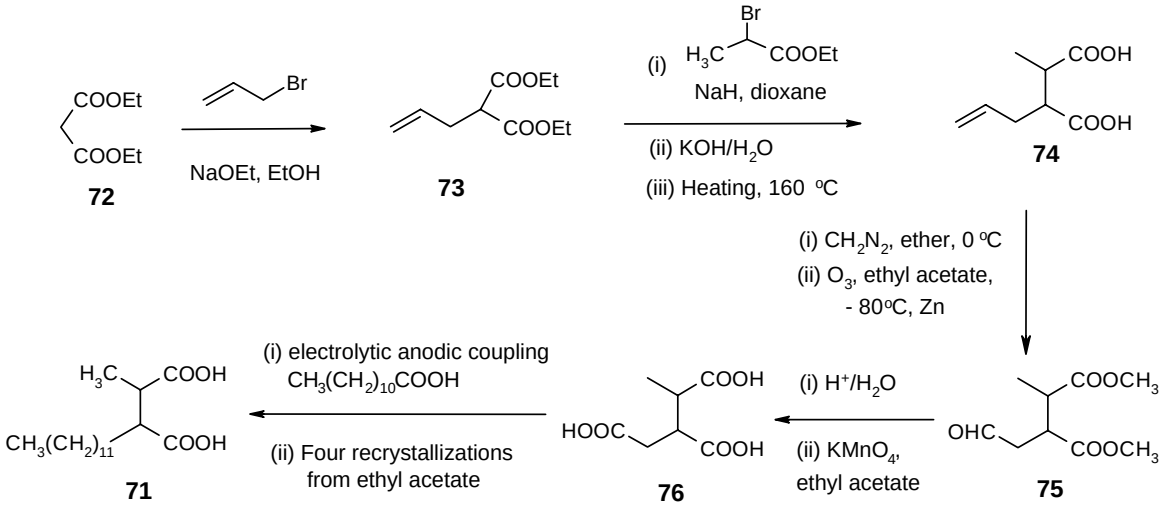
2.3B.1.1 Synthetic Approaches Towards (±)-*erythro*-Roccellic acid (71) and (+)-*erythro*- Roccellic acid (71a)

I. Åkermark's Synthetic Approach

The first synthesis of unnatural *threo*-(±)-roccellic acid was completed by Åkermark and co-workers[96] starting from diethylmalonate (**72**) as shown in Scheme 17 and during

these studies a small amount (25 mg) of (±)-*erythro*-roccellic acid (**71**) was obtained by an 8-step synthesis with 0.026% overall yield (**Scheme 17**).

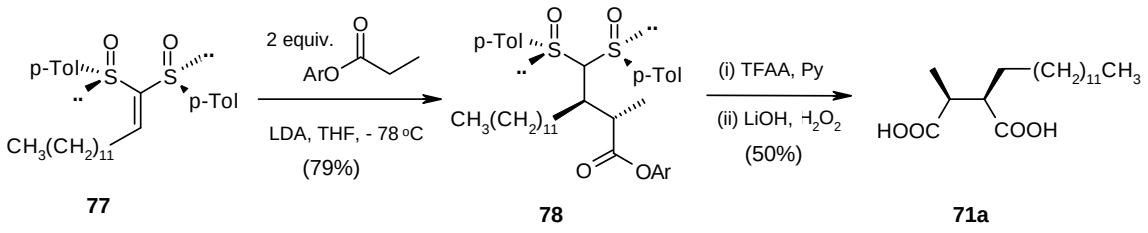
Scheme 17



II. Fensterbank's Asymmetric Synthesis

Recently, Fensterbank and coworkers have completed the first asymmetric synthesis of (+)-*erythro*-roccellic acid (**71a**), by employing a highly diasteroselective addition of a lithium ester enolate to a bisulfinyl acceptor as a key step (**Scheme 18**).[97] The synthesis involves the addition of lithium enolate of Heathcock's ester to alkylidene acceptor **77** to give adduct **78** (major diasteromer, 79% yield) accompanied by the minor diasteromer (10% yield). The major diasteromer **78** on Pummerer rearrangement followed by double saponification furnished (+)-*erythro*-roccellic acid (**71a**) (**Scheme 18**).

Scheme 18



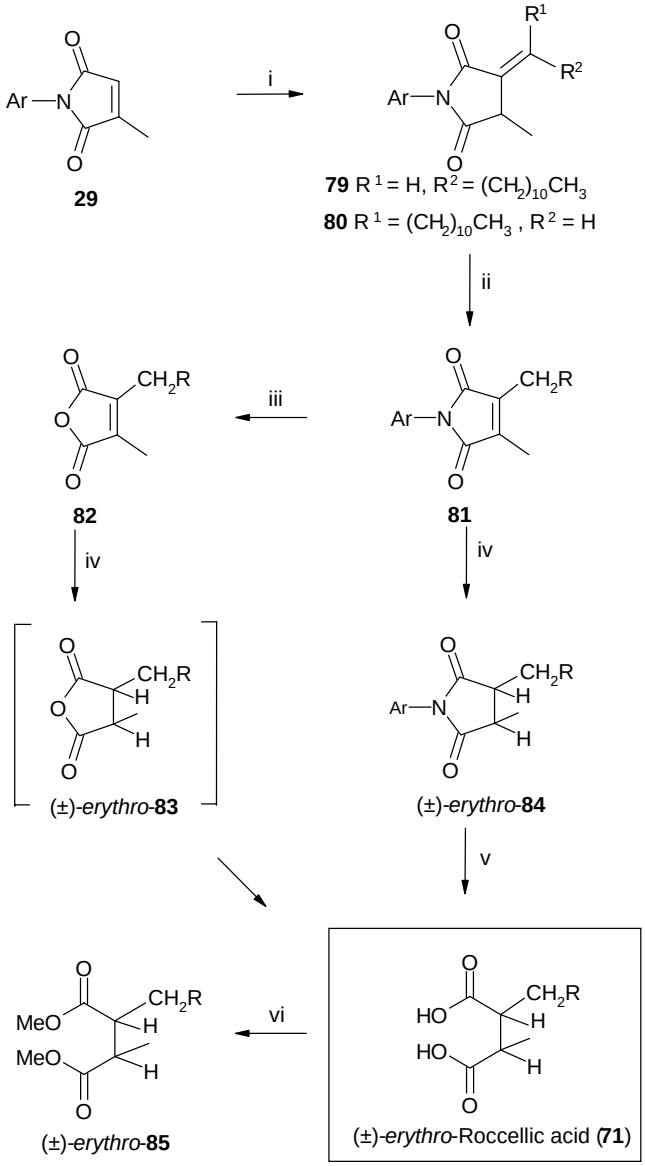
The conditions developed in our group for the condensation of methyl(triphenylphosphoranylidene)succinimide with aliphatic aldehydes[17] fuelled our interest to synthesize this antitubercular natural product by employing the afore-mentioned condensation and catalytic hydrogenation pathway as a key pathway.

2.3B.2 PRESENT WORK: RESULTS AND DISCUSSION

A mixture of equimolar amounts of citraconimide **29** and TPP on refluxing with 1.5 equivalents of dodecanal in glacial acetic acid for 10 h yielded a combination of geometric isomers **79** and **80** in 82% yield via Wittig reaction. The integral values for vinylic protons in the ^{1}H NMR spectrum of this mixture of geometric isomers (*E*)-**79** and (*Z*)-**80** revealed that they are formed in 85:15 ratio. The mixture of exo-isomers **79** and **80** on refluxing with triethylamine plus THF mixture (1:1) for 48 h, underwent a smooth exocyclic to endocyclic carbon-carbon double bond isomerization to yield dodecylmethylmaleimide **81** in 98% yield. The maleimide **81** on alkaline hydrolysis followed by acidification gave the desired dodecylmethylmaleic anhydride **82** in 98% yield. We systematically studied the catalytic *cis*-hydrogenation reactions of maleimide **81** and disubstitued maleic anhydride **82** to obtain succinimide derivative **84** and succinic anhydride derivative **83** respectively. In our hands, the anhydride **82** and imide **81** when subjected to catalytic hydrogenation with palladium on charcoal as catalyst in methanol remained completely unreacted for 12 h at 50-psi pressure of hydrogen. The anhydride **82** in petroleum ether on treatment with Adam's platinum dioxide catalyst at 50-psi pressure of hydrogen for 10 h followed by filtration, concentration and recrystallization with acetone gave the desired (±)-*erythro*-roccellic acid **71** in 60% yield.[98] We were unable to isolate the intermediate anhydride **83** under the above mentioned reaction conditions. The maleimide **81** underwent a very smooth *cis*-catalytic hydrogenation at rt in petroleum ether with Adam's platinum dioxide catalyst at 50-psi hydrogen pressure in 10 h to yield exclusively the desired *cis*-succinimide derivative **84** in 95% yield. The conversion of maleimide **81** to succinimide **84** was more efficient as against that of **82** to **71** via **83**. The *cis*-succinimide derivative **84** on hydrolysis using refluxing a mixture of acetic acid and conc. hydrochloric acid (1:1) gave a mixture of *erythro* and *threo* isomers of roccellic acid, in 2:1 ratio (by ^{1}H NMR, from integral

values of methine protons) in 48 h with 98% yield. The *cis*-succinimide derivative **84** on hydrolysis in a refluxing mixture of trifluoroacetic acid and conc. hydrochloric acid (1:1) gave the mixture of desired *erythro* and undesired *threo* isomers in a more favourable proportion of the *erythro*-isomer (93:7, by ^{1}H NMR, from integral values of methine protons) in 48 h with 98% yield (**Scheme 19**).[98]

Scheme 19

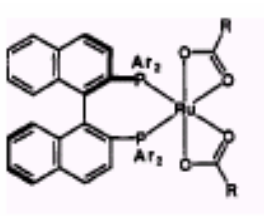


Reagents, conditions and yields: (i) TPP, AcOH, dodecanal, reflux, 10 h (82%); (ii) TEA, THF, reflux, 48 h (98%); (iii) (a) KOH, THF, MeOH, H_2O, reflux, 2 h; (b) H^+/HCl (98%); (iv) Adam's catalyst, petroleum ether, H_2, rt, 10 h (**71**: 60%; **84**: 95%); (v) CF_3COOH, con. HCl, reflux, 48 h (98%); (vi) CH_2N_2, Et_2O, rt, 2 h, (98%).

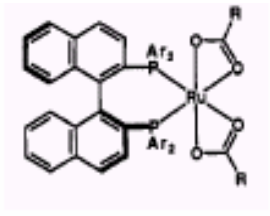
Recrystallization of the above mixture of *erythro* and *threo* isomers (93:7) from acetone gave the desired (±)-*erythro*-roccellic acid **71** in 80% yield. The formed acid **71** was further characterised as its dimethyl ester **85**. The analytical and spectral data obtained for (±)-*erythro*-roccellic acid **71** and its corresponding dimethyl ester **85** were in complete agreement with reported data.[59,74,95]

2.3B.2.1. Synthetic Studies Towards (+)-*erythro*-Roccellic Acid (71a)

Encouraged by our success in synthesizing the racemic natural product, we were driven towards attempts at obtaining the natural product in the enantiomerically pure form. We planned to achieve this through asymmetric hydrogenation of dodecylmaleimide **81** and related substrates using Noyori's Ru-BINAP catalyst **87** and **88a**.



88a R = CH_3 Ru$(OAc)_2$(*R*-BINAP)

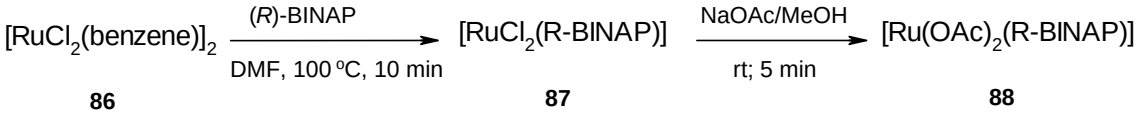


88b R = CH_3 Ru$(OAc)_2$(*S*-BINAP)

We prepared the following two BINAP-Ru(II) complexes[99] to carry out the proposed asymmetric hydrogenation $RuCl_2$(*R*-BINAP) **87** and Ru$(OAc)_2$(*R*-BINAP) (Noyoris catalyst, **88a**). BINAP-Ru(II) dicarboxylate complexes serve as excellent catalyst precursors for highly enatioselective hydrogenation of a wide range of prochiral functionlaized olefins. Ru$(OAc)_2$(*R*-BINAP) (Noyori's catalyst, **88a**) was prepared according to the literature procedure.[100] The catalyst **88a** was synthesized starting from the known complex $RuCl_2$(benzene)$_2$. A mixture of $RuCl_2$(benzene)$_2$[101] and (*R*)-BINAP (Ru:BINAP = 1.05:1) was heated in DMF at 100 ºC for 10 min., the exchange of the neutral ligands occurred efficiently to give $RuCl_2$-BINAP complexes. The chloride ligands were then displaced by acetates by treatment of the DMF solution with 20-fold excess of sodium acetate in methanol at room temperature for 5 min. Extractive workup followed by concentration afforded the crude Ru$(OCOCH_3)_2$(*R*-BINAP) which on

recrystallization from a toluene-hexane mixture gave an analytically pure sample in 85% overall yield (**Scheme 20**).[100]

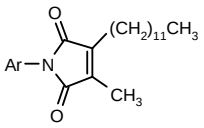
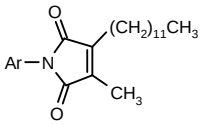
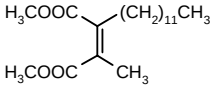
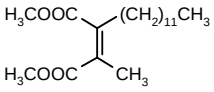
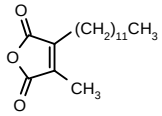
Scheme 20

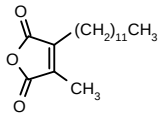


86 **87** **88**

We attempted several asymmetric hydrogenation reactions employing these two complexes on maleimide **81** and related substrates (**82a** was prepared from **82** by reacting with diazomethane in methanol and the procedure has been given in the Chapter–III) under various conditions and the results are summarized in Table 6. Unfortunately, the asymmetric hydrogenation of these substrates using Ruthenium-BINAP catalysts met with failure at our hands.

Table 6: Attempted Asymmetric Hydrogenation Reactions

No.	Compound	Catalyst	Reaction conditions	Conclusion
1	 **81**	Ru(OAc)$_2$(*R*-BINAP)	MeOH, 400 Psi, 25 °C, 4 h MeOH, 600 Psi, 25 °C, 4 h MeOH, 800 Psi, 40 °C, 4 h	No reaction
2	 **81**	Ru(Cl)$_2$(*R*-BINAP)	MeOH, 400 Psi, 40 °C, 10 h MeOH 800 Psi, 80 °C, 10 h	No reaction
3	 **82a**	Ru(Cl)$_2$(*R*-BINAP)	MeOH, 400 Psi, 40 °C, 10 h MeOH, 800 Psi, 80 °C, 10 h	No reaction
4	 **82a**	Ru(OAc)$_2$(*R*-BINAP)	MeOH, 400 Psi, 40 °C, 10 h MeOH, 800 Psi, 80 °C, 10 h	No reaction
5	 **82**	Ru(Cl)$_2$(*R*-BINAP)	MeOH, 400 Psi, 40 °C, 10 h MeOH, 800 Psi, 80 °C, 10 h	No reaction

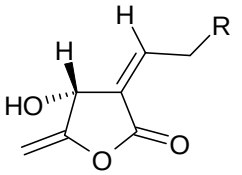
6	 **82**	$Ru(OAc)_2$(*R*-BINAP)	MeOH, 400 Psi, 40 °C, 10 h MeOH, 800 Psi, 80 °C, 10 h	No reaction

In summary, we have demonstrated an efficient four-step synthesis of (±)-*erythro*-roccellic acid with 60% overall yield which is also the first total synthesis of the natural product, starting from citraconimide via catalytic *cis*-hydrogenation pathway. The present strategy will also be useful to obtain several 2,3-dialkylsubstituted succinic acid derivatives. Efforts are on for the asymmetric hydrogenation of these substrates using more active transition metal catalysts to obtain the natural product in its enantiopure form.[102, 103]

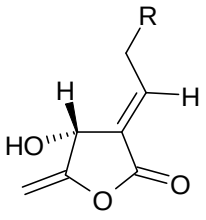
2.4A SECTION D: I. SYNTHETIC STUDIES ON ISOLINDERANOLIDE B

2.4A.1 BACKGROUND

Linderanolides **89A-E** and isolinderanolides **90A-E**, geometrical isomers with cytotoxic activity, have been isolated from the leaves of several members of the plant *Lauraceae*.[104] They all contain the *α*-alkylidene-*β*-hydroxy-*γ*-methylene butyrolactone structural unit and this core may be responsible for its activity.[105] The density of functional groups on the *γ*-lactone ring of the *Lauraceae* lactones makes many of the methods available for the synthesis of *α*-methylene lactones unsuitable.[106] The synthetic problems put forth by these structurally intriguing molecule make it an attractive and challenging target for organic chemists worldwide.[106]



89A-E



90A-E

R = -$(CH_2)_8CH{=}CHCH_2Me$ (A)
R = -$(CH_2)_{11}Me$ (B)
R = -$(CH_2)_4CH{=}CHCH_2CCH{=}CH(CH_2)_4Me$ (C)
R = - $(CH_2)_4CH{=}CH(CH_2)_7Me$ (D)
R = - $(CH_2)_{13}Me$ (E)

2.4A.1.1 Synthetic Approaches Toward Racemic and Chiral Lauraceae Lactones

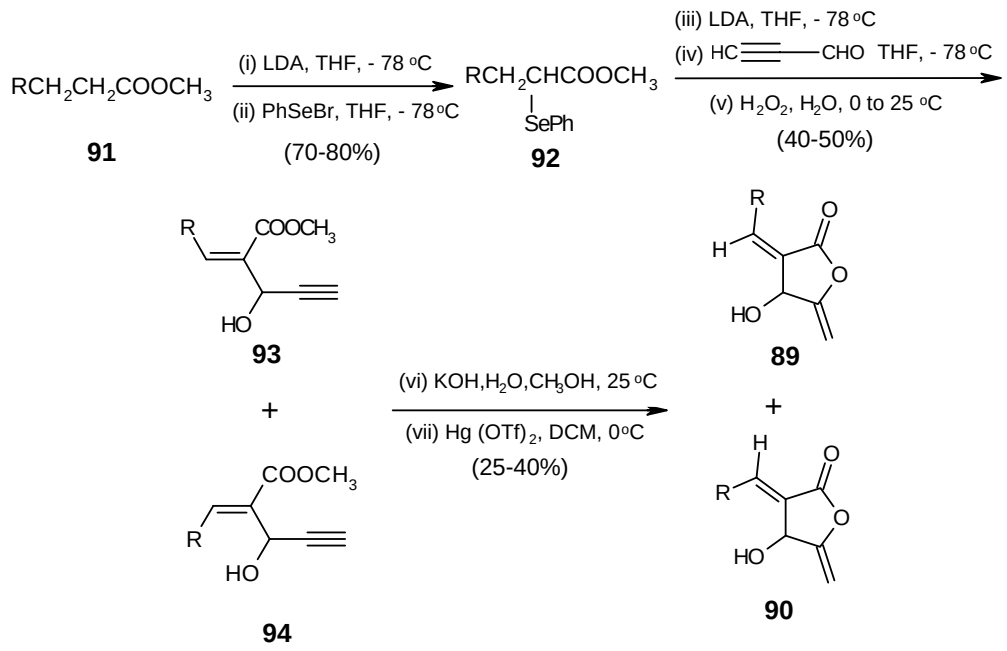
One racemic and stereoselective synthesis of *α*-alkylidene-*β*-hydroxy-*γ*-methylene butyrolactone (*Lauraceae* lactones) has been reported in the literature.[106,107]

I. Katzenellenbogen's Racemic Synthesis

Katzenellenbogen and coworkers have completed the first racemic synthesis of the *α*-alkylidene-*β*-hydroxy-*γ*-methylene butyrolactone frame work by employing the aldol addition reaction of *α*-phenylselenenyl ester and propargyl aldehyde as a key step (**Scheme 21**).[106] The first step of the synthesis involves the preparation of appropriately substituted *α*-phenylselenenyl ester **92** which on aldol addition with propargyl aldehyde followed by selenoxide elimination to give isomeric acetylenic esters **93** and **94**. The acetylenic esters **93** and **94** on saponification, followed by bicarbonate catalyzed

lactonization furnished α-alkylidene-β-hydroxy-γ-methylene butyrolactones **89** and **90** (**Scheme 21**).

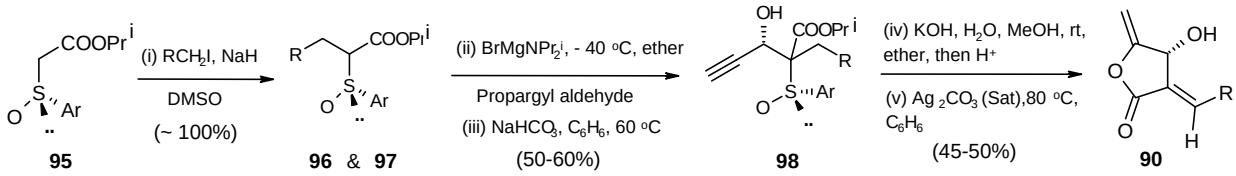
Scheme 21



II. Nokami's Asymmetric Synthesis

Nokami and coworkers have completed the first asymmetric synthesis of optically active *Lauraceae* lactones by employing the steroselective aldol reaction of α, β-unsaturated carboxylic α-anion equivalent with propargyl aldehyde as a key step (**Scheme 22**).[107] Diasteromeric mixtures of optically active isopropyl(*S*)-α(*p*-tolylsulfinyl)carboxylates (**96** and **97**) were prepared by alkylation of isopropyl(*S*)-(*p*-tolylsulfinyl)acetate (**95**) with sodium hydride and alkyl halide in DMSO. The less polar diasteromer **96** on aldol reaction with propargyl alehyde in the presence of bromomagnesium diisopropylamide furnished the aldol product which on treatment with bicarbonate in benzene afforded the (*S*)-(*E*)-α-alkylidene-β-hydroxy ester **98** (along with some amount of *Z*-isomer). The ester **98** on basic hydrolysis followed by lactonization using catalytic silver carbonate furnished the optically active α-alkylidene-β-hydroxy-γ-methylene butyrolactones **90** with 70-85% ee (**Scheme 22**).

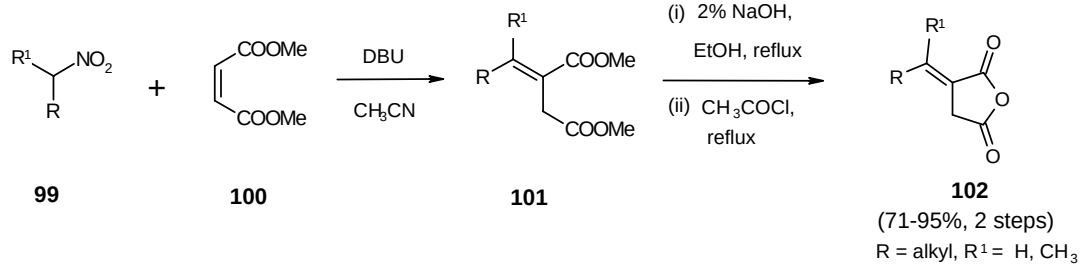
Scheme 22



Only few synthetic approaches are known in the literature for these *Lauraceae* lactones and development of a new synthetic route to linderanolides **89** and isolinderanolides **90** is imperative. We planned to develop a general synthetic route to isolinderanolides starting from maleimide via (*E*)-alkylidenesuccinic anhydride followed by anhydride carbonyl methylenation and allylic hydroxylation reaction (**Scheme 25**).

We envisaged that (*E*)-alkylidenesuccinic anhydride could be used as a potential starting material for the synthesis of isolinderanolide B. Literature survey on the chemistry of alkyl and alkylidenesuccinic anhydrides/acids revealed that they have been used as potential building blocks for the synthesis of many natural and synthetic products.[108-114] Several methods are known for its synthesis.[110-119] Recently, Ballini and coworkers have demonstrated an elegant DBU induced coupling of nitroalkanes with dimethylmaleate (**99**) to obtain (*E*)-alkylidenesuccinic acids/anhydrides with 71-95% overall yield (**Scheme 23**).[120]

Scheme 23



Development of a new, general and cost-effective synthetic route to (*E*)-alkylidenesuccinic acids/anhydrides is imperative. We planned to develop a new

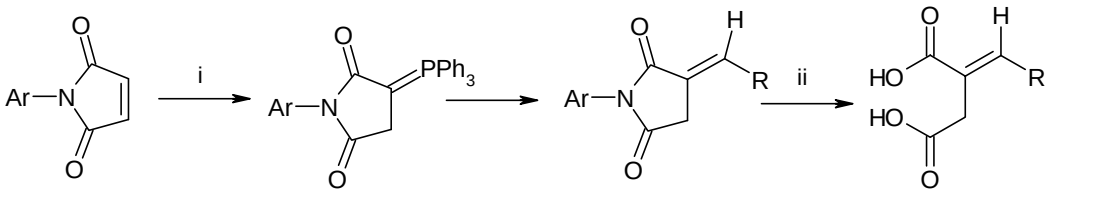
synthetic route to (*E*)-alkylidenesuccinic acids/anhydrides by employing the Wittig reaction of maleimide-TPP adduct with aliphatic aldehydes as a key step.

2.4A.2 PRESENT WORK: RESULTS AND DISCUSSION

2.4A.2.1 An Easy Access to (*E*)-Alkylidenesuccinic Acids

The condensation of maleimide-TPP adduct with several aromatic aldehydes is well established[5] while the condensation with aliphatic aldehydes have not been explored intensely. We systematically investigated the Wittig reaction of maleimide-TPP adduct with aliphatic aldehydes. The reaction of maleimide **26** with triphenylphosphine (TPP) furnished the intermediate Wittig product **27**, which in situ condensed very smoothly with aliphatic aldehydes to afford the alkylidenesuccinimides **103a-e** in excellent yields. The ^{1}H NMR spectra of **103a-e** revealed that the Wittig reaction under study exclusively furnishes the thermodynamically more stable (*E*)-isomers of **103a-e**.[121,122] We carried out all the Wittig reactions in Automated Synthesizer Workstation 2000P which resulted in significant reduction of time and effort involved. The (*E*)-alkylidenesuccinimides **103a-e** on hydrolysis under reflux with a mixture of concentrated hydrochloric acid and glacial acetic acid (1:1) mixture gave the desired (*E*)-alkylidenesuccinic acids **104a-e** in quantitative yields (**Scheme 24**, **Table 7**).[122] In both alkylidenesuccinimides **103a-e** as well as alkylidenesuccinic acids **104a-e,** the trisubstituted double bond was assigned the *E*-configuration on the basis of the lower field ^{1}H NMR resonance at δ 6.95 (approx) for the vinylic proton in close proximity to the carbonyl and this was further confirmed by comparing with similar known compounds.[120,121] The analytical and spectral data obtained for **104a-e** were in complete agreement with reported data.[110-120] The reduction of alkylidenesuccinic acids **104a-e** to alkylsuccinic acids using palladium-charcoal and ring closure of both the alkyl and alkylidenesuccinic acids to the corresponding alkyl and alkylidenesuccinic anhydrides using acetyl chloride as a dehydrating agent are well established.[120]

Scheme 24



Ar = *p*-Tolyl, **a**: R = $(CH_2)_2CH_3$; **b**: R = $(CH_2)_4CH_3$; **c**: R = $(CH_2)_8CH_3$; **d**: R = $(CH_2)_{10}CH_3$; **e**: R = $(CH_2)_{12}CH_3$

Reagents, conditions and yields: (i) PPh_3, RCHO, THF, reflux, 10 h (85-90%); (ii) con. HCl, AcOH, reflux, 60 h (96-98%).

Table 7: Data for products **103a-e** and **104a-e**

No.	Aliphatic aldehydes	Alkylidenesuccinimides (103a-e)		Alkylidenesuccinic acids (104a-e)	
		Product No.	% Yield	Product No.	% Yield
1	*n*-Butanal	**103a**	85	**104a**	96
2	*n*-Hexanal	**103b**	90	**104b**	96
3	*n*-Decanal	**103c**	90	**104c**	97
4	*n*-Dodecanal	**103d**	86	**104d**	98
5	*n*-Tetradecanal	**103e**	87	**104e**	98

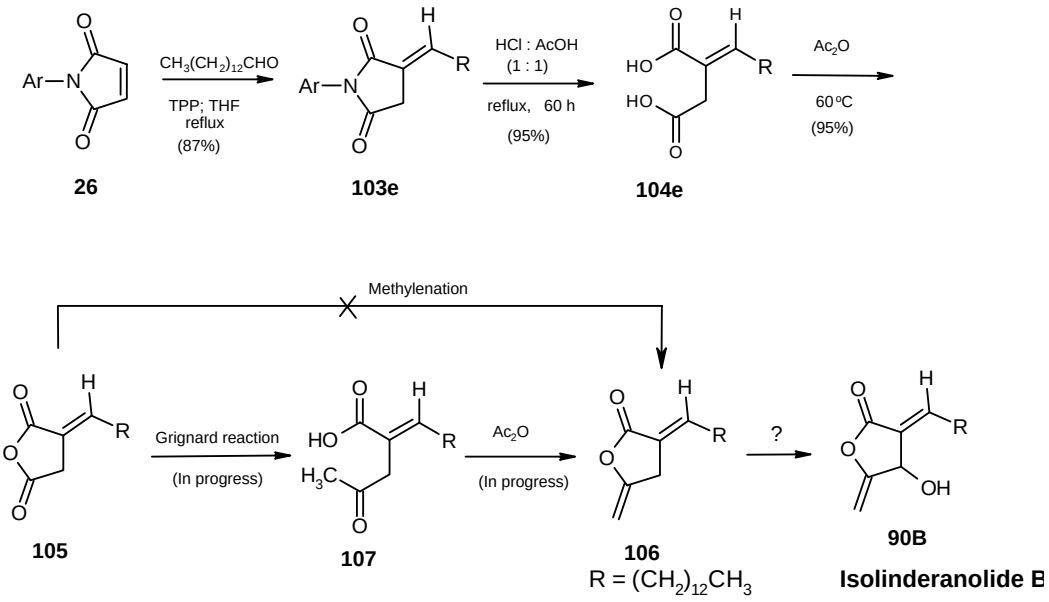
2.4A.2.2 Synthetic Studies on Isolinderanolide B

Our strategy towards isolinderanolide B involves the synthesis of (*E*)-tetradecylidenesuccinic anhydride (**105**) which on anhydride carbonyl olefination followed by allylic hydroxylation would provide the target compound (**Scheme 25**).

The reaction of maleimide **26** with triphenylphosphine (TPP) furnished the intermediate Wittig product **27**, which in situ condensed very smoothly with tetradecyl aldehyde in THF under argon atmosphere to afford the (*E*)-tetradecylidenesuccinimide **103e** in 87% yield.[122] The ^{1}H NMR spectrum of **103e** revealed that the Wittig reaction exclusively furnished the thermodynamically more stable (*E*)-isomer of **103e**. The formed Wittig product **103e** was then hydrolyzed to

the corresponding (*E*)-alkylidenesuccinic acid **104e** in 60 h under reflux in a mixture of glacial acetic acid and con. HCl.[122] On keeping the reaction mixture overnight at rt, the (*E*)-alkylidenesuccinic acid **104e** precipitated out as crystals. Filtration afforded crystals and further purification was not required. We tried a few experiments for the conversion of (*E*)-alkylidenesuccinic acid **104e** to the corresponding anhydride **105** and succeeded using acetic anhydride as the dehydrating agent to effect the conversion smoothly (**Scheme 25**).

Scheme 25



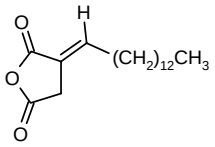
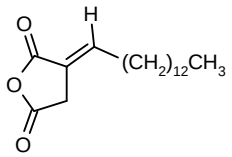
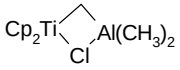
After the efficient synthesis of (*E*)-alkylidenesuccinic anhydride **105**, we planned for the anhydride carbonyl olefination of **105** to the desired enol lactone **106** using Wittig, Tebbe[123] and Petasis reagents.[124]

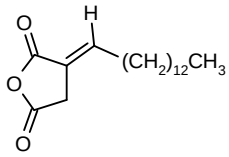
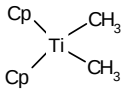
The Wittig reaction of anhydride **105** and the non-stabilized phosphorous ylide PPh_3CH_2 (generated in situ using the corresponding Wittig salt and a strong base i.e BuLi, $NaNH_2$) in THF at – 80 ºC lead to decomposition of starting material. It has been observed that direct carbonyl olefination of cyclic anhydrides/imides have been successful only in cases utilizing stabilized ylides (i.e substituted with electron withdrawing groups).[125] Hence, the failure of the reaction was not a surprise and it prompted us to focus our attention towards titanium mediated methylene transfer

agents such as Tebbe reagent (**108**) and Petasis reagent (**109**). Methylenation reaction of anhydride **105** using Tebbe reagent (**108**) failed to give the desired product **106** which we reasoned could be because of its Lewis acid behavior. Petasis reagent (Dimethyl titanocene, **109**), being aluminium free, was envisioned to be a better reagent for the conversion as it was already well known for the methylenation of heteroatom substituted carbonyl compounds including: silylethers, anhydrides, carbamates, amides, imides, and thioesters.

We prepared the Petasis reagent (dimethyl titanocene, **109**) by methylating commercially available dichloro titanocene using methyl lithium.[126] The formed dimethyl titanocene (**109**) was stored as a 0.5 M solution in toluene at a temperature around 4 ºC (the compound is light sensitive and it should be protected from exposure to light). Methylenation reactions were tried using Petasis reagent under different conditions but failed to give the desired product. All the results of methylenation reactions are summarized in Table 8. Presently we are working on the conversion of anhydride **105** to enol lactone **106** by a Grignard reaction followed by reaction with acetic anhydride which might furnish the desired product as shown in Scheme 25.

Table 8: Attempted Methylenation Reactions of (*E*)-alkylidenesuccinic Anhydride 105

No.	Compound	Reagent	Reaction conditions	Conclusion
1		$[CH_2PPh_3]$	CH_3PPh_3I, BuLi, THF, - 80 ºC, 4 h CH_3PPh_3I, $NaNH_2$, THF, -80 ºC, 4 h	Decomposition of starting compound Decomposition of starting compound
2		 Tebbe reagent **108**	Tebbe reagent, THF, rt, 4 h Tebbe reagent, THF, 65 ºC, 4 h	No reaction Decomposition of starting compound

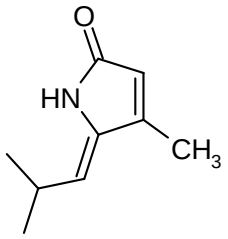
3		 Petasis reagent **109**	Petasis reagent, THF, dark, 65 ^{o}C, 4 h Petasis reagent, Toluene, dark, 65 ^{o}C, 4 h	Complex reaction mixture Complex reaction mixture

In summary, we have demonstrated an efficient two-step approach to (*E*)-alkylidenesuccinic acids and feel that our method, besides being cost effective and general, has a good scale-up potential and hence will be of interest to a large number of organic chemists from a practical point of view. Efforts are on for the synthesis of isolinderanolide B in our laboratory.

2.4B SECTION D: II. A FACILE SYNTHESIS OF CD45 PROTEIN TYROSINE PHOSPHATASE INHIBITOR MARINE NATURAL PRODUCT PULCHELLALACTAM

2.4B.1 BACKGROUND

Recently, a receptor-like transmembrane protein tyrosine phosphatase, CD45,[127] has been shown to play a crucial role in activation of both B and T cells.[128] CD45 therefore represents a therapeutic target for various autoimmune and chronic anti-inflammatory diseases.[129] As a part of efforts to find enzyme inhibitors from microbial sources, Alvi and coworkers[130] identified the marine fungus *Corollospora pulchella* extract with very potent CD45 activity and a novel active component (*Z*)-pulchellalactam (**110**) was isolated from the crude extract. The structural assignment of (*Z*)-pulchellalactam (**110**) has been done on the basis of analytical and spectral data.[130,131]



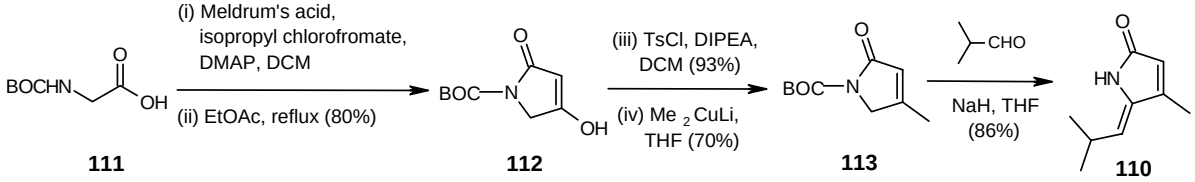
(*Z*)-Pulchellalactam
(**110**)

2.4B.1.1 Synthetic Approaches Toward (*Z*)-Pulchellalactam

I. First Synthesis

The first synthesis of (*Z*)-pulchellalactam has been completed by Li and coworkers in 6-steps with 32% overall yield from BOC-glycine (**111**, **Scheme 26**).[131] The key step of the sequence involves addition and elimination of an enolic lactam **112** in a single step employing an organocuprate reagent and the resulting *α,β*-unsaturated lactam **113** on condensation with isobutyraldehyde furnishes (*Z*)-pulchellalacatm (**Scheme 26**).[131]

Scheme 26

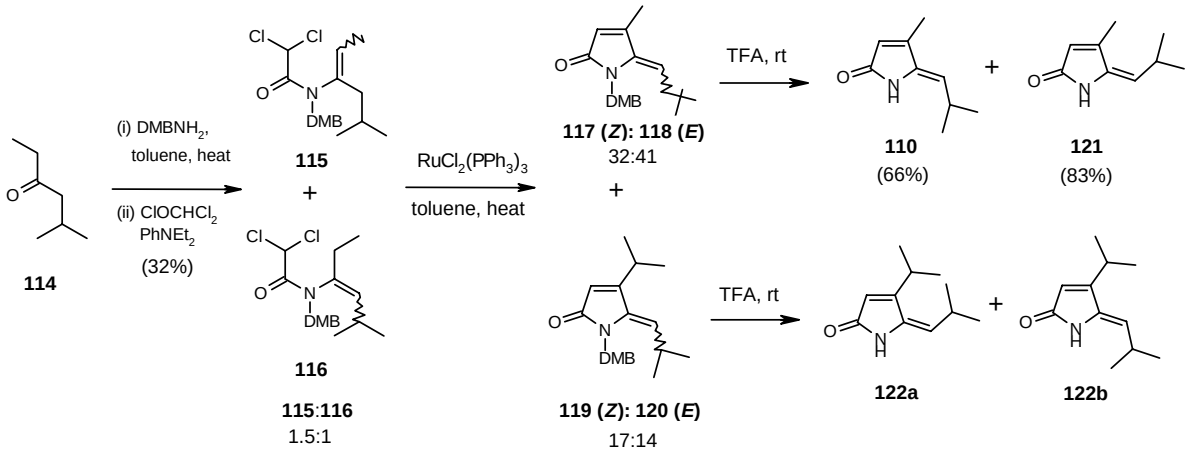


111 **112** **113** **110**

II. Second Synthesis

Recently, Parsons and coworkers have completed the second synthesis of (*Z*)-pulchellalactam (**110**) with 10% overall yield starting from 2-methyl-hexan-3-one (**114**) via metal catalyzed radical cyclization strategy (**Scheme 27**).[132] The synthesis involves the condensation of 2,4-dimethoxybenzylamine with a ketone **114** followed by reaction with dichloroacetyl chloride to produce an inseparable 1.5:1 mixture of the enamide regioisomers **115** and **116** respectively in 32% yield. On heating the mixture of **115** and **116** with $RuCl_2(PPh_3)_3$ in toluene, enamide **115** gave the desired dienones **117** and **118** in 32 and 41% yield while the alternate enamide **116** gave **119** and **120** in 17 and 14% yield. Dienones **117** and **118** were separated on column chromatography. Stirring **117** in neat TFA at rt resulted in clean *N*-deprotection and the formation of (*Z*)-pulchellalactam (**110**) in 66% yield. The other compound **118** similarly gave (*E*)-pulchellalactam (**121**) in 83% yield (**Scheme 27**).

Scheme 27



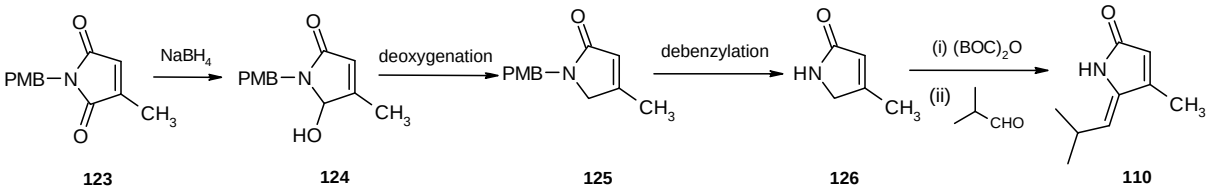
Development of new efficient synthetic routes to **110** for the realistic supply of the natural product is a challenging task of current interest.[131,132] In our continuing interest[26b,50,57,98,133] to provide new synthetic routes to bioactive natural products using cyclic anhydrides as potential precursors, we planned to complete a facile synthesis of (*Z*)-pulchellalactam (**110**) starting from citraconimide (**123**). We envisaged the use of regioselective reduction of maleimides for an efficient synthesis of potential

intermediate lactam **126**[134] which on reaction with BOC-anhydride followed by condensation with isobutyraldehyde would furnish **110** (**Scheme 28**).

2.4B.2 PRESENT WORK: RESULTS AND DISCUSSION

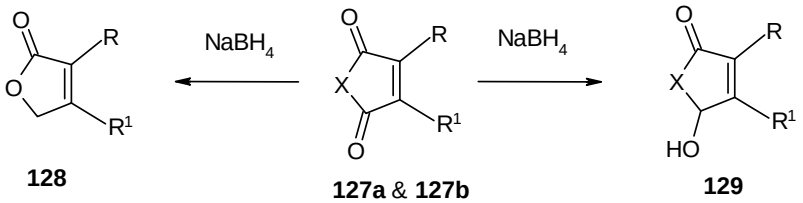
Our initial strategy towards the target molecule was to synthesize it by condensation of isobutyraldehyde and the lactam **113** which we envisioned could be synthesized in a short and efficient fashion starting from *N*-*p*-methoxybenzyl citraconimide (**123**) (**Scheme 28**).

Scheme 28



Alkyl and dialkyl substituted maleic anhydrides **127a** are known[135] to undergo highly regioselective $NaBH_4$ reductions at the hindered/relatively more hindered carbonyl group to directly form the corresponding butyrolactones **128**. Maleimides **127b** also follow the same regioselectivity but the reduction stops with the formation of corresponding 5-hydroxylactams **129** (**Scheme 29**).[136] The regioselectivity can be explained by steric factors, the incoming hydride anion approaches from the less hindered carbonyl and attacks the more hindered carbonyl to furnish the 5-hydroxy lactam as a major regioisomer (**Scheme 29**).[136a]

Scheme 29



a: X = O; **b**: X = *N*H, *N*-Bz, *N*-Ar

R = H/CH_3 ; R^1 = alkyl

Such type of tight regiocontrol during the $NaBH_4$ reduction has not been observed[137] with the corresponding alkyl and vicinal dialkylsubstituted succinimides. We planned to take advantage of such regioselectivity in synthesizing lactam **126**.

Thus, starting compound **123** on sodium borohydride reduction furnished the 5-hydroxylactam **124** as the major regioisomer with 97% yield (regiosomeric ratio was 93:7, by ^1H NMR). All our efforts to convert hydroxylactam **124** into the desired *N*-PMB lactam **125** through a deoxygenation process using a variety of conditions (TFA/Et_3SiH, TFA/$NaBH_3CN$, $LiClO_4$/Et_3SiH, $BF_3.OEt_2$/Et_3SiH, Barton-McCombie deoxygenation) met with failure (**Scheme 30**).

The hydroxylactam **124** was then converted into the thioether compound **130.** Desulferisation of **130** was tried under different conditions (deactivated Raney nickel, nickel boride, Bu_3SnH/AIBN) to synthesize the *N*-PMB lactam **125** but instead gave rise to a saturated lactam **131** (**Scheme 30**).

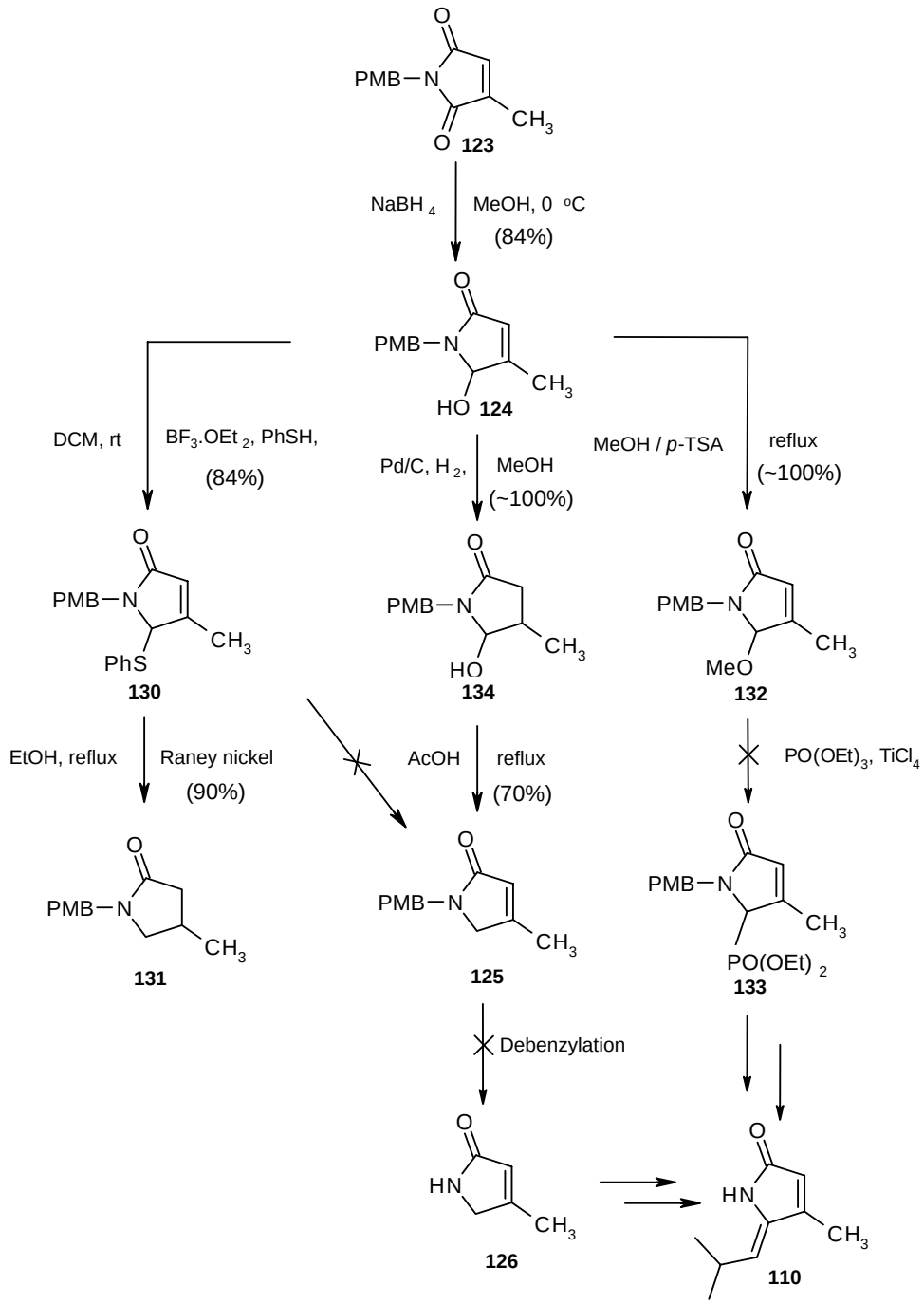
Failure of our attempts at synthesizing **125** led us towards a different strategy wherein we planned to convert the hydroxylactam **124** to a diethyl phosphono compound **133** which would serve as a reactant for a proposed Wittig reaction[138] via methoxy compound **132**. The methoxy compound **132** was prepared by reacting hydroxylactam **124** with dry methanol in presence of a catalytic amount of *p*-TSA. But the reaction of methoxylactam **132** with triethylphosphite in presence of $TiCl_4$ failed to give the desired diethyl phosphono compound **133** (**Scheme 30**).

At this stage, we felt that the deoxygenation would be easier in a saturated hydroxylactam rather than an unsaturated hydroxylactam, and hence decided to hydrogenate the unsaturated hydroxylactam **124** to the corresponding saturated hydroxylactam **134**. This was achieved, after a few trial experiments, using Pd/C as a catalyst.

Dehydration of **134** was systematically studied under different acidic conditions and to our delight, **134** on refluxing in dry acetic acid furnished the desired lactam **125** with 70% yield. That left us with just the task of debenzylating **125** to obtain the required lactam **126** but to our surprise, oxidative deprotection using CAN[138] under a variety of conditions was unsuccessful and gave rise to complex reaction mixtures.

Deprotection using TFA, TFA/anisole,[138] DDQ also failed to give the desired NH-lactam **126** (**Scheme 30**).

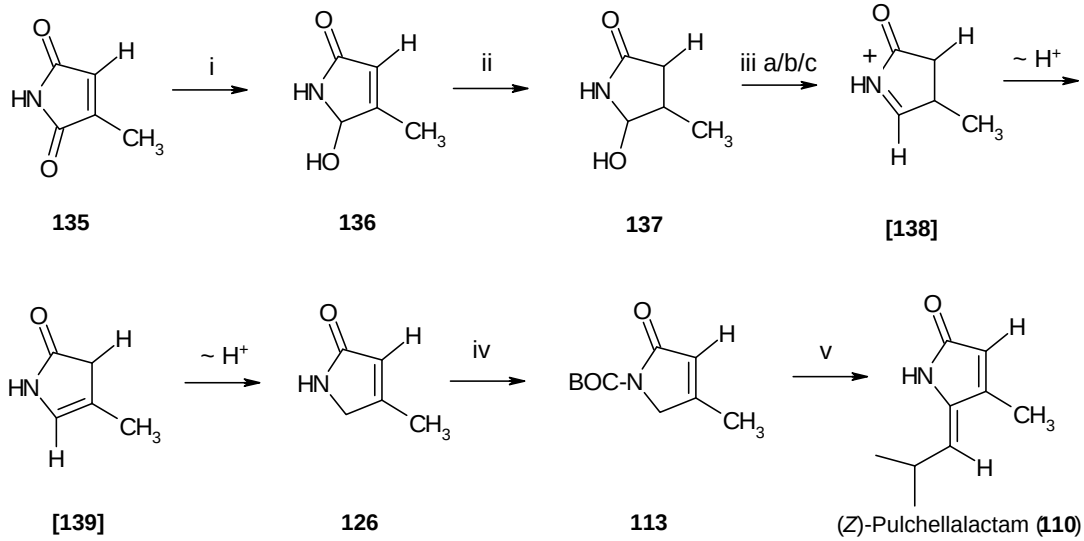
Scheme 30



Failure of debenzylation of **125** to the desired lactam **126** for the synthesis of (Z)-pulchellalactam (**110**) led us to explore the option of starting with citraconimde (**135**) and repeating the saturated hydroxylactam pathway (**Scheme 31**).

Citracoinimide (**135**) underwent a highly regioselective $NaBH_4$-reduction to exclusively give the corresponding hydroxylactam **136** in ~ 100% yield.[136b] The palladium on charcoal catalyzed hydrogenation of **136** furnished a mixture of the stereoisomers of **137** in ~ 100% yield, with 1:2 ratio (by ^1H NMR spectrum). Such types of hydroxylactams on treatment with *p*-TSA are known to under go polymerization reactions.[139] We systematically studied the dehydration of **137** under the acidic conditions. The hydroxylactam **137** on treatment with *p*-TSA in refluxing benzene gave the desired product **126** only in 25-30% yields. The lactam **137** on heating in glacial acetic acid at 80 ºC for one hour furnished **126** with 50-55% yields. Finally, we could effect an efficient conversion of **137** to **126** using the strong acidic resin Amberlyst. The resin-catalyzed dehydration of **137** in refluxing acetonitrile gave the desired 4-methyl-3-pyrrolin-2-one (**126**) in 92% yield. We surmise that the above dehydration process of **137** to **126** takes place via intermediate **139** and a very facile in situ prototopic shift. The lactam **126** on reaction with BOC-anhydride in acetonitrile at room temperature gave the BOC-protected lactam **113** in 85% yield which under Li et al conditions[131] (NaH, THF, isobutyroaldehyde, rt) exclusively furnished the bioactive natural product (*Z*)-pulchellalactam (**110**) in 82% yield (**Scheme 31**).[140]

Scheme 31



Reagents, conditions and yields: (i) $NaBH_4$, EtOH, - 40 ºC, 1 h (~100%); (ii) Pd/C, H_2, MeOH, rt, 2 h (~100%); (iii) (a) *p*-TSA, benzene, reflux, 3 h (25-30%); (b) AcOH, 80 ºC, 1 h (50-55%); (c) Amberlyst, CH_3CN, reflux, 2 h (92%); (iv) $(BOC)_2O$, DMAP, CH_3CN, rt, 3 h (85%); (v) NaH, THF, isobutyraldehyde, rt, 5 min. (82%).

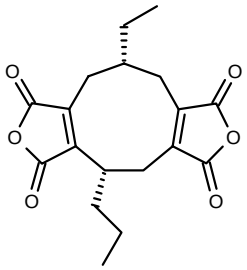
Little is known about this type of condensation reaction in the literature and it is assumed that allylic deprotanation of compound **113** and subsequent condensation with isobutyraldehyde might have led to (*Z*)-pulchellalactam (**110**) through an E1cB mechanism via *tert*-butoxy-carbonyl group (Boc) migration reaction.[131] The analytical and spectral data obtained for **110** were in complete agreement with the reported data.[130-132] Starting from citraconimide (**135**), pulchellalactam (**110**) was obtained in 5-steps with 64% overall yield (**Scheme 31**).[140]

After trying several experiments using *N*-PMB citraconimide as starting compound, we could synthesize (*Z*)-pulchellalactam (**110**) from citraconimde (**135**) by employing a double reductive dehydration strategy as the key step to synthesize the potential intermediate **126** followed by BOC protection and condensation with isobutyraldehyde which furnished **110** in 5-steps with 64% overall yield. We feel that the present approach is general and can be used to design the synthetic library of pulchellalactam analogues.

2.4C SECTION D: III. SYNTHETIC STUDIES ON BYSSOCHLAMIC ACID

2.4C.1 BACKGROUND

Byssochlamic acid, a metabolite first isolated from ascomycete *Byssochlamys fulva*, is a member of the small but structurally unique class of natural products known as nonadrides.[141] The absolute configuration of byssochlamic acid was determined by degradative experiments, which caused fission of the nine-membered ring and gave products with known stereochemistry.[142] Sodium byssochlamate inhibits germination of mustard seed and elongation of the seedlings.[143] The intriguing structural features and promising biological activity of the nonadrides inspired several synthetic chemists to embark on a journey toward the total synthesis of the natural products falling in this rather unique league. One enantiospecific[144] and two racemic syntheses[145,146] have been reported by James D. White and Gilbert Stork starting from bromomaleic anhydride and suitably substituted tetralone derivative via diolide and *bis*-hydroquinone dimethyl ether respectively (discussed in the first chapter).

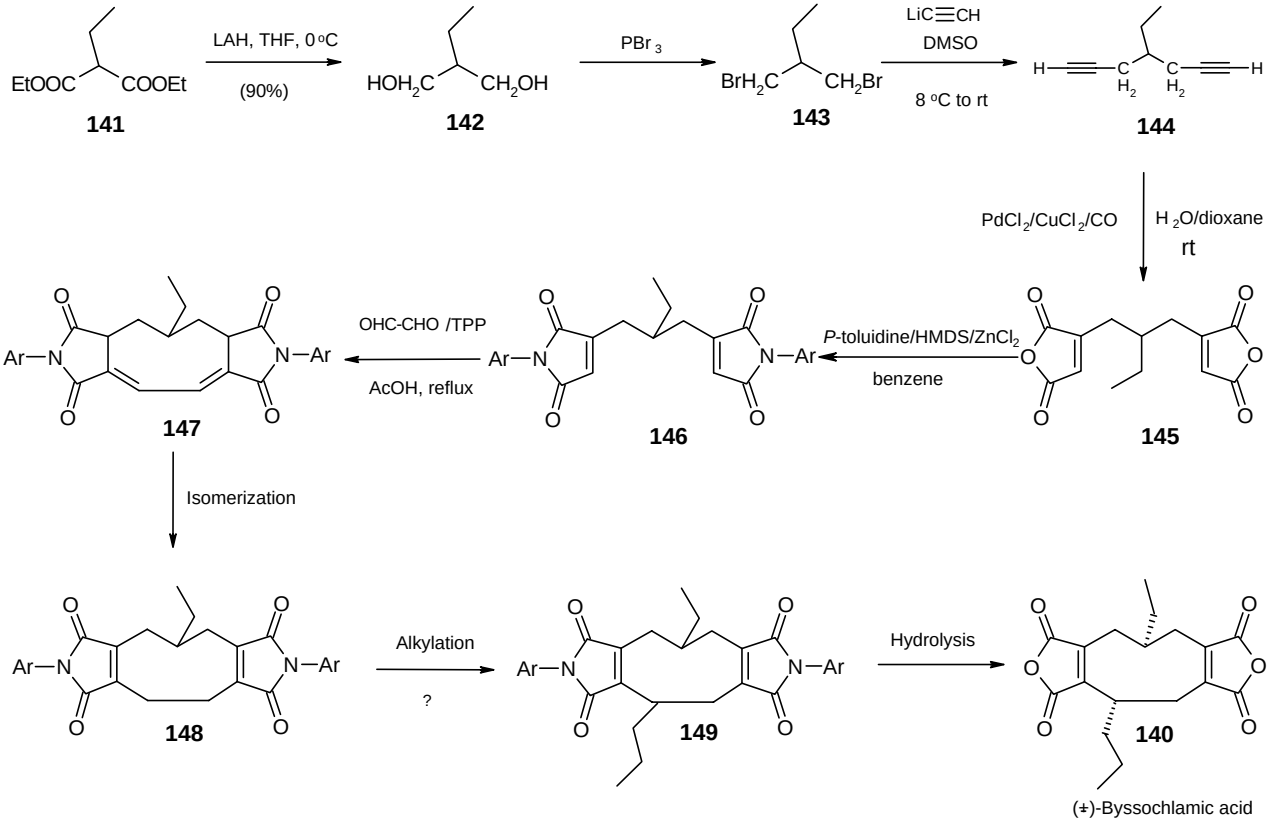


(±)-Byssochlamic acid (**140**)

2.4C.2 PRESENT WORK: RESULTS AND DISCUSSION

Our plan to synthesize (±)-byssochlamic acid starting from diethyl ethylmalonate (**141**) including synthesis of diacetylenic compound **144** via bisanhydride system **145** followed by double Wittig reaction using glyoxal is depicted in Scheme 32. The sequence of reactions described in Scheme 32 would provide a rapid access to this desired bioactive natural product and very recently, we have initiated work towards the same (**Scheme 32**).

Scheme 32 (In Progress)



2.5 SUMMARY

In summary, We have developed a simple and efficient approach to methyl and dimethyl substituted maleimides/anhydrides by employing the reaction of maleimide-TPP adduct with paraformaldehyde as a key step followed by alkaline hydrolysis with good yield. An efficient synthesis of aminopeptidase inhibitor tyromycin A has been achieved by a double Wittig condensation of citraconimide-TPP adduct with 1,16-hexadecanedial in two steps with 71% overall yield and this method also offers an easy access to tyromycin A congeners for structure-activity relationship studies. We have completed an efficient synthesis of cytotoxic piliformic acid by employing the Wittig reaction of methylmaleimide-TPP adduct with hexanal as a key step with 49% overall yield. This method has got the potential to be scaled up and will also be useful as a general method to obtain 2-alkylidene-3-alkylsuccinic acid derivatives. An efficient synthesis of antituberculor (±)-*erythro*-roccellic acid has been demonstrated, starting from citraconimide via catalytic *cis*-hydrogenation pathway in four-steps with 60% overall yield. The present strategy will also be useful to obtain several 2,3-dialkylsubstituted succinic acid derivatives. An efficient two-step approach has been developed for (*E*)-alkylidenesuccinic acids utilizing the condensation of maleimide-TPP adduct with aldehydes as a key step and this method too has a good scale up potential which promises to be cost effective. A facile synthesis of CD45 protein tyrosine phosphates inhibitor (*Z*)-pulchellalactam has been completed starting from citraconimide by employing a double dehydrative strategy as a key pathway with very good yield.

Efforts are on for the methylenation of exoalkylidene succinic anhydride to obtain the corresponding enol lactone and subsequent allylic hydroxylation to complete the synthesis of isolinderanolide B. Asymmetric hydrogenation of dodecylmethyl maleimide and related substrates to obtain roccellic acid in its enantiopure form continues to be a challenge in our synthetic endeavors. Very recently, we have started the synthesis of byssochlamic acid and plan to complete its synthesis starting from ethyl diethylmalonate.

In our laboratory, starting from cyclic anhydrides, we have designed several bioactive natural products using variety of new synthetic strategies. We feel that with

proper control on chemo-, regio- and stereoselectivities, the cyclic anhydrides can be used as potential precursors for the total syntheses of several complex bioactive natural and unnatural compounds without using any protection-deprotection steps. A wide range of synthetically useful reactions would be possible on the maleic anhydrides/imides systems, for example, development of new reaction conditions for Baylis-Hillman reaction would provide a useful applications of these molecules in the near future. In short, maleic anhydride and their derivatives have a very rich history and very bright present to their credit in the field of chemistry and a highly useful future is assured.

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CHAPTER THREE

EXPERIMENTAL PROCEDURES, TABULATED ANALYTICAL DATA, SPECTRAL DATA AND SELECTED ^{1}H NMR & ^{13}C NMR SPECTRA

EXPERIMENTAL PROCEDURES

***N*-*p*-Tolylmethylenesuccinimide (28):** A mixture of *N*-*p*-tolylmaleimide (**26**, 11.22 g, 60.00 mmol) and triphenylphosphine (15.72 g, 60.00 mmol) in glacial acetic acid (150 mL) was stirred at rt for 30 min. Paraformaldehyde (9.00 g, 300.00 mmol) was added to the reaction mixture and it was refluxed for 1 h. Acetic acid was distilled off in vacuo at rt and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (4:1) gave **29**: 102 mg (0.85% yield) and **28**: 11.04 g (92% yield) respectively.

***N*-*p*-Tolylmethylmaleimide (29):** The imide **29** was prepared using the same procedure as described for the preparation of **28** plus **29**, except that the acetic acid was distilled off slowly over a period of 15-20 min. at 70-75 ^{o}C and the oily residue was further heated with stirring for 30 min. at the same temperature. The residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column purification of the residue using a mixture of petroleum ether and ethyl acetate (9:1) gave **29**: 10.10 g (84% yield).

Isomerization of *N*-*p*-Tolylmethylenesuccinimide (28) to *N*-*p*-Tolylmethylmaleimide (**29**)**:** To a stirred solution of *N*-*p*-tolylmethylenesuccinimide (**28**, 11.04 g, 55.00 mmol) in THF (70 mL) was added triethylamine (70 mL) and the reaction mixture was refluxed for 3 h and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (9:1) gave **29**: 10.24 g (93% yield).

***N*-*p*-Tolyl-2-methylene-3-methylsuccinimide (31):** A mixture of *N*-*p*-tolylmethylmaleimide (**29**, 1.01 g, 5.00 mmol), triphenylphosphine (1.31 g, 5.00 mmol) in glacial acetic acid (25 mL) was stirred at rt for 30 min. Paraformaldehyde (750 mg, 25.00 mmol) was added to the mixture and refluxed for 30 min. The reaction was stopped after 30 min. in order to isolate **31,** further refluxing resulted in complete conversion of formed **31** to **32**. Acetic acid was distilled off in vacuo at rt and the residue was dissolved in ethyl acetate (25 mL) and the organic layer was washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column purification of the residue using a mixture of petroleum ether and ethyl acetate (4:1) gave the mixture of dimethylmaleimide **32** and *N*-*p*-tolyl-2-methylene-3-methylsuccinimide (**31**) (**31**:**32**=7:3): 335 mg (31% yield) respectively.

***N*-*p*-Tolyldimethylmaleimide (32):** A mixture of *N*-*p*-tolylmethylmaleimide (**29**, 10.24 g, 50.94 mmol), triphenylphosphine (13.35 g, 50.94 mmol) in glacial acetic acid (150 mL) was stirred at rt for 30 min. Paraformaldehyde (7.64 g, 254.70 mmol) was added to the reaction mixture and then it was refluxed for 2 h. Acetic acid was distilled off slowly over a period of 15 min at 50-60 ^{o}C and the oily residue was further heated with stirring for 30 min. at the same temperature. Silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (9:1) gave **32**: 9.90 g (91% yield).

Isomerization of *N*-*p*-tolyl-2-methylene-3-methylsuccinimide (31) to *N*-*p*-tolyldimethylmaleimide (32): A mixture of **31** + **32** (100 mg) was heated neat at 50-60 ^{o}C for 3 h. The molten thick oily residue was cooled to rt to obtain *N*-*p*-tolyldimethylmaleimide (**32**) in quantitative yield. The exo compound **31** from **31** + **32** mixture also gets completely transformed to **32** at room temperature in 3 days time.

One pot synthesis of *N*-*p*-tolyldimethylmaleimide (32): To a stirred solution of maleimide **26** (3.74 g, 20.00 mmol) in acetic acid (75 mL) was added triphenylphosphine (5.24 g, 20.00 mmol) and the reaction mixture was stirred at rt for

15 min. To this mixture was added paraformaldehyde (3.00 g, 100.00 mmol) and the reaction mixture was refluxed for 1 h. Acetic acid was distilled off slowly over a period of 15-20 min. at 70-75 ^{o}C and the oily residue was further heated with stirring for 30 min. at the same temperature. After allowing the reaction mixture to reach rt, the residue was redissolved in acetic acid (75 mL). Triphenylphosphine (5.24 g, 20.00 mmol) and paraformaldehyde (3.00 g, 100.00 mmol) were added to the reaction mixture and it was refluxed for 1 h. The acetic acid was distilled off in vacuo at 50-60 ^{o}C to obtain a thick oily residue. Silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (9:1) gave pure **32**: 2.92 g (68% yield).

Dimethylmaleic Anhydride (33): To the solution of imide **32** (9.30 g, 43.26 mmol) in methanol (100 mL) was added a solution of KOH (12.10 g) in water (25 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated in vacuo, the obtained residue was acidified with dil. HCl and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo gave **33**: 5.26 g (97% yield).

Methyl ester of juniperic acid (**51**)**:** A solution of acid **50** (2.72 g, 10.00 mmol) in ether (30 mL) was treated with a solution of diazomethane in ether at 0 ^{o}C until the starting material was completely consumed (2 h, by tlc). Excess diazomethane was quenched at rt with acetic acid and the reaction mixture was concentrated in vacuo. Silica gel column purification of the residue using petroleum ether and ethyl acetate mixture (8:2) gave pure **51**: 2.71 g (95% yield).

1,16-Hexadecanediol (**52**)**:** A solution of **51** (2.29 g, 8.00 mmol) in ether (25 mL) was added dropwise to a suspension of lithium aluminium hydride (379 mg, 10.00 mmol) in ether (20 mL) at rt over a period of 10 min. The reaction mixture was stirred at rt for 2 h and excess reagent was quenched by cautious addition of moist ether (30 mL) and stirring for 30 min. The reaction mixture was acidified with dilute HCl (20 mL) and

then it was extracted with ether (3 × 25 mL). The organic layer was washed with brine (15 mL), dried over Na_2SO_4, concentrated and dried in vacuo. Silica gel column chromatographic purification of the residue using petroleum ether-ethyl acetate (1:1) gave pure **52**: 2.02 g (98% yield).

1,16-Hexadecanedial (**53**)**:** To a stirred suspension of PCC (3.24 g, 15.00 mmol) in CH_2Cl_2 (35 mL) at 0 ^oC was added a solution of 1,16-hexadecanediol (1.29 g, 5.00 mmol) in CH_2Cl_2 (15 mL) over a period of 20 min. and the reaction mixture was further stirred for 10 h at rt. The reaction mixture was diluted with anhydrous ether (40 mL) and then stirred vigorously for 30 min. The supernatant of the reaction mixture was filtered through a small pad of silica gel and concentrated in vacuo. The silica gel column purification of the residue using petroleum ether and ethyl acetate mixture (9:1) gave pure **53**: 978 mg (77% yield).

(*E*/*Z*)-1,16-*Bis*[4-methyl-2,5-dioxo-1-*p*-tolyl-pyrrolidin-3-yl]–1,15-hexadecadiene (54/55/56): A mixture of citraconimide **29** (3.01 g, 15.00 mmol), triphenylphosphine (3.93 g, 15.00 mmol) and 1,16-hexadecanedial (762 mg, 3.00 mmol) in glacial acetic acid (40 mL) was refluxed with stirring for 10 h. Acetic acid was distilled off in vacuo at 45-50 ^oC and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (15 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of the organic layer followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (85:15) gave a mixture of **54**, **55** and **56** (*E:Z* = 85:15 respectively by ^1H NMR): 1.31 g (70% yield).

1,16-*Bis*[4-methyl-2,5-dioxo-1-*p*-tolyl-pyrrol-3-yl]hexadecane (57): The imide **57** was prepared using the same procedure as described for the preparation of **54** + **55** + **56** except that the acetic acid was distilled off slowly over a period of 15 min. at 140-150 ^oC and the oily residue was further heated with stirring for 30 min. at the same temperature to obtain **57**: 1.34 g (72% yield).

Isomerization of exo-isomers (54 + 55 + 56) to endo-isomer (57): A solution of **54**, **55**, and **56** mixture (500 mg) in tetralin (10 mL) was refluxed for 1 h with stirring. The reaction mixture was then cooled to rt and silica gel column purification of the reaction mixture using petroleum ether and ethyl acetate mixture (9:1) gave pure **57**: 490 mg (98% yield).

1,16-*Bis*-[4-methyl-2,5-dioxo-3-furanyl]hexadecane (Tyromycin A, 36): (a) A mixture of **54** + **55** + **56** (500 mg) in a solution of sodium methoxide (500 mg) in methanol (20 mL) was refluxed for 2 h with stirring and then the methanol was distilled off in vacuo. The residue was acidified with dilute HCl, extracted with ether (2 × 30 mL) and the organic layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue furnished pure **36**: 214 mg (60% yield). (b) To the solution of imide **57** (500 mg) in THF-methanol mixture (12 mL, THF:MeOH = 1:1) was added a solution of KOH (1.20 g) in water (6 mL) and the reaction mixture was refluxed for 2 h with stirring. The solvent mixture was removed in vacuo, and the residue was acidified with dilute HCl. Repetition of the above work up procedure followed by silica gel column chromatographic purification furnished pure **36**: 350 mg (98% yield).

***p*-Methylmaleanilic acids[1] (69 + 70):** To a stirred solution of citraconic anhydride (3.92 g, 3.50 mmol) in ether (25 mL) at rt was added a solution of *p*-toluidine (3.75 g, 3.50 mmol) in ether (25 mL) with constant stirring in a dropwise fashion over a period of 10 min. The reaction mixture was stirred at rt for 50 min and the precipitated product was filtered, washed with ether (2 x 10 mL) dried under vacuum to obtain a mixture of α- and β-isomers in a ratio of 9:1 (7.29 g, 95%) respectively; mp 195-199 ^{o}C. The above mixture of acids (1.00 g) on recrystallization from methanol (10 mL) gave exclusively the α-isomer **69**: 800 mg (80% yield).[1]

***N*-*p*-Tolylmethylmaleimide (29):** A mixture of the methylmaleanilic acids **69** plus **70** (2.20 g, 10.00 mmol) in Ac_2O (15 mL) and fused NaOAc (100 mg) was heated in a

water-bath at 60–65 ^{o}C for 1 h. The reaction mixture was allowed to reach rt and was poured into ice-cold water (200 mL). The formed precipitate was filtered off, washed with excess of water, and vacuum dried to give **29**: 1.82 g (90% yield).

(±)-(*E/Z*)-2-Hexylidene-3-methyl-*N*-*p*-tolylsuccinimides (65 + 66): A mixture of citraconimide **29** (1.51 g, 7.50 mmol), triphenylphosphine (1.97 g, 7.50 mmol) and hexanal (1.13 g, 11.25 mmol) in glacial acetic acid (20 mL) was refluxed with stirring for 10 h. Acetic acid was distilled off in vacuo at 50 ^{o}C and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (9:1) gave **65** plus **66** (**65:66** = 85:15, by ^{1}H NMR) as a thick oil: 1.78 g (83% yield).

(±)-(*E*)-Piliformic acid (58): A mixture of **65** plus **66** (1.10 g, 3.86 mmol) in glacial acetic acid plus concentrated hydrochloric acid (1:1, 100 mL) was refluxed for 48 h. Additional amount of conc. HCl (25 mL) was added to the reaction mixture and further refluxed for 12 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in 5% aq. bicarbonate solution (25 mL). The aqueous layer was washed with ethyl acetate (2 × 15 mL) and acidified with dil. HCl. The acidified aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the organic layer was washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo gave a mixture of (*E*)-plus (*Z*)-piliformic acids (810 mg, 98%). The above mixture of acids was recrystallized from excess of hot water (120 mL) to obtain pure (*E*)-piliformic acid (**58**): 570 mg, (70% yield).

(±)-(*E/Z*)-2-Dodecylidene-3-methyl-*N*-*p*-tolylsuccinimides (79 + 80): A mixture of citraconimide **29** (3.01 g, 15.00 mmol), TPP (3.93 g, 15.00 mmol) and dodecylaldehyde (4.14 g, 22.50 mmol) in glacial acetic acid (50 mL) was refluxed with stirring for 10 h. Acetic acid was distilled off in vacuo at 50 ^{o}C and the residue was dissolved in ethyl acetate (60 mL). The organic layer was washed successively with water (30 mL), brine

(20 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column purification of the residue using a mixture of petroleum ether and ethyl acetate (9:1) gave a mixture of **79** plus **80** (**79**:**80** = 85:15, by ^{1}H NMR): 4.54 g, (82% yield).

2-Dodecyl-3-methyl-*N*-*p*-tolylmaleimide (81): A solution of **79** and **80** mixture (3.30 g) in THF (15 mL) and triethylamine (15 mL) was refluxed for 48 h with stirring. The reaction mixture was then allowed to reach rt, concentrated in vacuo and silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (9:1) gave pure **81**: 3.23 g (98% yield).

2-Dodecyl-3-methylmaleic anhydride (**82):** To the solution of imide **81** (1.11 g, 3.00 mmol) in a THF-methanol mixture (1:2, 18 mL) was added 30% aqueous KOH solution (10 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated in vacuo and the residue was acidified with dilute HCl, extracted with diethyl ether (3 × 50 mL) and the organic layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (9:1) furnished pure **82** as a thick oil: 820 mg (98% yield).

2-Dodecyl-3-methyl-dimethylmaleate (82a): A solution of dodecylmethylmaleic anhydride (**82**, 560 mg, 2.00 mmol) in methanol (10 mL) was treated with a solution of diazomethane in ether at 0 ºC until the starting material was completely consumed (3 h, by tlc). Excess diazomethane was quenched with acetic acid and the reaction mixture was concentrated in vacuo to give a residue. Silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (9:1) furnished dimethyl ester **82a**: 620 mg (95% yield).

(±)-*erythro*-2-Dodecyl-3-methyl-*N*-*p*-tolylsuccinimide (84): A mixture of maleimide **81** (1.10 g, 3.00 mmol) and Adams catalyst (25 mg) in petroleum ether (50 mL) was

subjected to hydrogenation at 50-psi hydrogen pressure for 10 h at rt. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. Silica gel column purification of the residue using petroleum ether and ethyl acetate (9:1) gave succinimide **84**: 1.05 g (95% yield).

(±)-*erythro*-Roccellic acid (71): Succinimide **84** (740 mg, 2.00 mmol) was dissolved in trifluoroacetic acid plus conc. hydrochloric acid mixture (1:1, 15 mL) and the reaction mixture was refluxed for 48 h. The reaction mixture was kept aside at rt for 12 h and the white precipitate of roccellic acid was filtered in vacuo to obtain **71**: 590 mg (98% yield, *erythro*:*threo* = 93:7 respectively proved by ^{1}H NMR). The mixture of *erythro*- and *threo*-roccellic acid (500 mg, 93:7) was recrystallized from acetone (30 mL) to obtain pure (±)-*erythro*-roccellic acid **71**: 400 mg (80% yield).

Dimethylester of (±)-*erythro*-roccellic acid (85): A solution of (±)-*erythro*-roccellic acid (**71**, 300 mg, 1.00 mmol) in ether (10 mL) was treated with a solution of diazomethane in ether at 0 ^{o}C, till the complete consumption of the starting material (2 h, by tlc). Excess diazomethane was quenched with acetic acid and the reaction mixture was concentrated in vacuo. Silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (9:1) gave pure **85** as a thick oil: 320 mg, (98% yield).

General procedure for the synthesis of *N*-*p*-tolyl-3(*E*)-alkylidenesuccinimides 103a-e: A mixture of *N*-*p*-tolylmaleimide (**27**, 9.35 g, 50.00 mmol) and Ph_3P (13.11 g, 50.00 mmol) in distilled THF (125 mL) was stirred at rt for 30 min. Aliphatic aldehyde (75.00 mmol) was added to the reaction mixture and it was refluxed for 10 h. THF was distilled off in vacuo at 50 ^{o}C and silica-gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (9:1) gave *N*-*p*-tolyl-3(*E*)-alkylidenesuccinimides **103a-e** with very good yields (85-90%).

General procedure for the hydrolysis of *N*-*p*-tolyl-3(*E*)-alkylidenesuccinimides 103a-e to (*E*)- alkylidenesuccinic acids 104a-e: A mixture of succinimides (**103a-e**,

40 mmol) glacial acetic acid and concentrated hydrochloric acid was refluxed for 60 h. The reaction mixture was allowed to reach room temperature, concentrated in vacuo and the obtained residue was dissolved in 5% aq. sodium bicarbonate (60 mL). The aqueous layer was washed with ethyl acetate (3 × 50 mL) and acidified with dil. HCl. The acidified aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layer was washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo gave pure (*E*)-alkylidenesuccinic acids **104a-e**. Analytically pure compounds were obtained by recrystallization with ethyl acetate.

(*E*)-Tetradecylidenesuccinic anhydride (105): A solution of (*E*)-tetradecylidenesuccinic acid (**104e**, 1.00 g, 3.21 mmol) in acetic anhydride (15 mL) was heated at 60 ºC for 3 h. The reaction mixture was concentrated under vacuum to give a residue. The residue on silica gel column chromatographic purification using petroleum ether and ethyl acetate mixture (9:1) as eluent afforded anhydride **105** as a thick oil: 895 mg (95% yield).

***N*-*p*-Methoxybenzylmethylmaleimide[2] (123):** To a solution of citraconic anhydride (2.24 g, 20.00 mmol) in dry benzene (20 mL) was added a solution of *p*-methoxybenzylamine (2.74 g, 20.00 mmol) in dry benzene and stirred at rt for 4 h. Precipitated maleamic acid was separated by decanting the solvent and washed with dry ether. To a suspension of the amic acid in dry benzene (50 mL) was added $ZnCl_2$ (2.73 g, 20.00 mmol) and the mixture was heated at 80 ºC. To this was added a solution of HMDS (6.29 mL, 30 mmol) in dry benzene (20 mL) slowly over a period of 30 min, and then the mixture was refluxed for an additional hour. The reaction mixture was cooled to rt and poured into 0.5 N HCl (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed successively with $NaHCO_3$ (30 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum to leave the residue, which was purified by silica gel column chromatographic purification using petroleum ether and ethyl acetate mixture (8:2) to give pure **123**: 4.16 g (90% yield).[2]

***N*-*p*-Methoxybenzyl-5-hydroxy-4-methyl-3-pyrrolin-2-one**[3] (**124**) **and *N*-*p*-Methoxybenzyl-5-hydroxy-3-methyl-3-pyrrolin-2-one (124a):** To a solution of imide **123** (2.31 g, 10.00 mmol) in methanol (20 mL) at 0 ºC was added sodium borohydride (380 mg, 10.00 mmol) portionwise, and stirred for 1 h. The reaction mixture was quenched with ice water (2 mL), and methanol was removed under reduced pressure. The residue was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum to give a crude product. The purification of the residue by silica gel column chromatography using petroleum ether and ethyl acetate mixture (8:2) gave a pure white solid **124**: 1.95 g (84% yield) and **124a**: 160 mg (7% yield) respectively.[3]

***N*-*p*-Methoxybenzyl-5-hydroxy-3-methyl-2-pyrrolidinone (134):** A mixture of hydroxylactam **124** (1.17 g, 5.00 mmol) and Pd/C catalyst (50 mg) in methanol (20 mL) was subjected to hydrogenation at hydrogen balloon pressure for 3 h at rt. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to give saturated hydroxylactam as a thick oil **134**: 1.17 g (~ 100% yield).

***N*-*p*-Methoxybenzyl-4-methyl-3-pyrrolin-2-one (125):** A solution of saturated hydroxylactam **134** (700 mg, 3.00 mmol) in dry acetic acid (10 mL) was refluxed with stirring for 1 h. The reaction mixture was allowed to reach rt and acetic acid was removed under vacuum to give a residue. The residue on silica gel column chromatographic purification using petroleum ether and ethyl acetate mixture (1:1) gave a thick oil **125**: 460 mg (70% yield).

***N*-*p*-Methoxybenzyl-5-thiophenyl-3-methyl-3-pyrrolin-2-one (130):** To a mixture of hydroxylactam **124** (700 mg, 3.00 mmol) and thiophenol (0.53 mL, 3.90 mmol) in dry DCM at 0 ºC was added $BF_3.OEt_2$ (0.43 mL, 3.30 mmol) drop wise over 5 min. After being stirred under an atmosphere of nitrogen at rt for 6 h, the mixture was diluted by the addition of diethyl ether (20 mL). This diluted mixture was then washed with $NaHCO_3$ (2 × 15 mL), brine (10 mL) and dried over anhydrous Na_2SO_4 and

concentrated under vacuum to give a residue. The residue on silica gel column chromatographic purification using petroleum ether and ethyl acetate mixture (7:3) gave a thick oil **130**: 820 mg (84% yield).

***N-p*-Methoxybenzyl-3-methyl-2-pyrrolidinone (131):** A solution of thio compound **130** (650 mg, 2.00 mmol) in absolute ethanol (15 mL) was added dropwise to a stirred mixture of Raney nickel (3.55 g) in absolute ethanol (20 mL) and the reaction mixture was refluxed for 3 h. The reaction mixture was allowed to reach rt and it was filtered through celite. The celite was washed with absolute ethanol (50 mL) and the combined ethanol solution was evaporated under vacuum to give a residue. The residue on silica gel column chromatographic purification using petroleum ether and ethyl acetate mixture (1:1) gave a thick oil **131**: 380 mg (90% yield).

Citraconimide[4] (135): A mixture of predried ammonium acetate (35.00 g, 454.00 mmol) and citraconic anhydride (25 mL, 179.00 mmol) were added acetic acid (50 mL) and heated under reflux for 3 h. The reaction mixture was allowed to reach rt and then the reaction mixture was concentrated to give a syrupy residue. Ice water (200 mL) was added to the residue which was followed by extraction with ethyl acetate (8 × 30 mL) and DCM (2 × 25 mL). The combined organic extracts were concentrated to give a yellow solid, which was further purified by distillation using Kugelrohr apparatus. The fraction obtained at 120-130 ºC (0.1 mm) was collected as a colorless solid **135**: 10.90 g (55% yield).[4]

5-Hydroxy-4-methyl-3-pyrrolin-2-one[5] (136): Sodium borohydride (1.60 g, 40.00 mmol) was added at – 30 ºC to a solution of citraconimide (**135**, 4.44 g, 40.00 mmol) in absolute ethanol (60 mL). After the reaction mixture was stirred at – 30 to – 40 ºC for 50 min., the excess $NaBH_4$ was quenched at – 40 ºC by dropwise addition of 10% aqueous AcOH till pH 7 over a 45 min. period. The solvent was evaporated under reduced pressure at rt and the residue was extracted with acetone. After filtration, evaporation of the extracted portion afforded a white solid **136**: 4.52 g (~ 100% yield).[5]

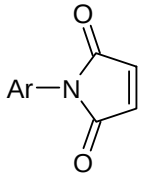
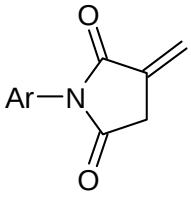
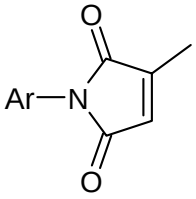
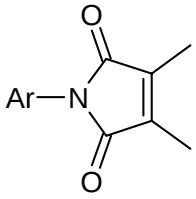
5-Hydroxy-4-methyl-2-pyrrolidinone (137): A mixture of hydroxylactam **136** (1.13 g, 10.00 mmol) and Pd/C catalyst (30 mg) in methanol (15 mL) was subjected to hydrogenation at hydrogen balloon pressure for 2 h at rt. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to give saturated hydroxylactam as a thick oil **137**: 1.15 g (~ 100% yield).

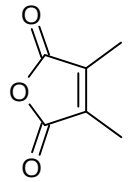
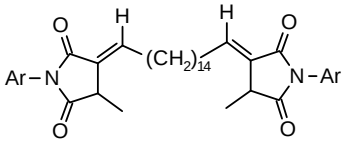
4-Methyl-3-pyrrolin-2-one (126): To a solution of saturated hydroxylactam **137** (575 mg, 5.00 mmol) in dry acetonitrile (10 mL) was added Amberlyst resin (100 mg) and the reaction mixture was refluxed under argon atmosphere for 2 h. The reaction mixture was allowed to reach rt and then it was concentrated under reduced pressure to give a residue. The residue on silica gel column chromatographic purification using ethyl acetate and methanol (98:2) gave pure lactam **127** as a white solid: 446 mg (92% yield).

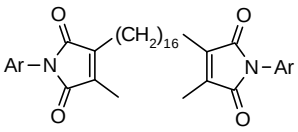
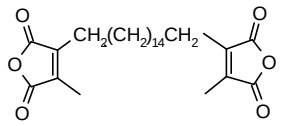
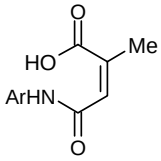
***N*-*tert*-Butoxycarbonyl-4-methyl-3-pyrrolin-2-one (113):** A solution of DMAP (31 mg, 0.25 mmol) in dry acetonitrile (3 mL) was added dropwise to a mixed solution of lactam **126** (243 mg, 2.50 mmol) and di-*t*-butyl carbonate (818 mg, 3.75 mmol) in dry acetonitrile (12 mL) at rt under nitrogen atmosphere and the mixture stirred for 3 h. The reaction mixture was concentrated under vacuum at rt to give a residue. The residue on silica gel column chromatographic purification using petroleum ether and ethyl acetate (7:3) gave a thick oil **113**: 420 mg (85% yield).

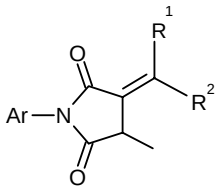
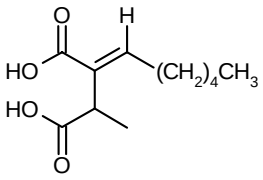
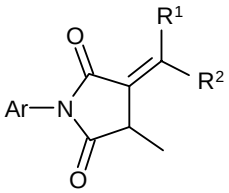
5(*Z*)-Isobutylidene-4-methyl-1,5-dihydropyrrol-2-one[6] (110): A solution of *N*-BOC lactam **113** (197 mg, 1.00 mmol) in dry THF (5 mL) was treated with 60% NaH (62 mg, 1.52 mmol) at rt and stirred for 5 min. Isobutyraldehyde (0.28 mL, 3.00 mmol) was added to the mixture and stirred for 5 more min. The reaction mixture was concentrated in vacuo at rt to give a residue. The residue was dissolved in DCM (30 mL), which was then washed with 5% HCl (10 mL), aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried on sodium sulfate, filtered and concentrated in vacuo. Silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (7:3) afforded (*Z*)-pulchellalactam (**110**) as a thick oil: 124 mg (82% yield).[6]

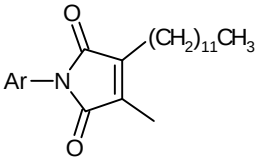
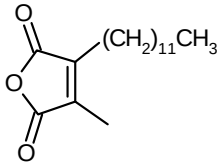
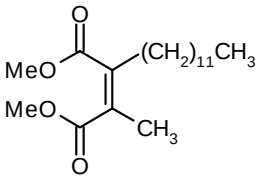
ANALYTICAL AND SPECTRAL DATA FOR COMPOUNDS IN SECTION A TO D

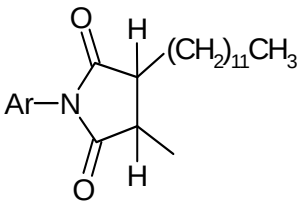
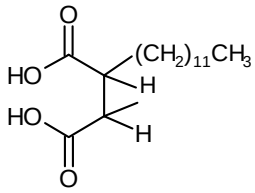
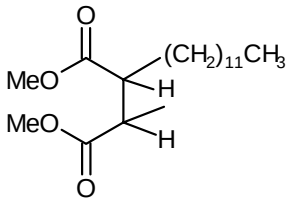
No.	Structure & Text Number Mol. Formula (Mol.Wt.).	IR (cm^{-1}), ^1H NMR (δ), ^{13}C NMR (δ) and Mass Spectral Data.
1	 **26** Ar = *p*-Tolyl **$C_{11}H_9NO_2$** (187)	**Mp** 110-111 ^oC (ethanol). **IR ($CHCl_3$)** ν_{max} 1760, 1702, 1654 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 2.38 (s, 3H), 6.84 (s, 2H), 7.20 (d, *J* = 6 Hz, 2H), 7.28 (d, *J* = 6 Hz, 2H). **MS (*m/e*)** 187, 172, 158, 143, 130, 117, 104, 91, 82, 77, 65, 54.
2	 **28** Ar = *p*-Tolyl **$C_{12}H_{11}NO_2$** (201)	**Mp** 112-114 ^oC. **IR ($CHCl_3$)** ν_{max} 1763, 1702, 1658 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 2.39 (s, 3H), 3.51 (t, *J* = 3 Hz, 2H), 5.74 (t, *J* = 2 Hz, 1H), 6.47 (t, *J* = 2 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H). **MS (*m/e*)** 201, 186, 173, 158, 144, 132, 120, 104, 91, 86, 77, 68, 57.
3	 **29** Ar = *p*-Tolyl **$C_{12}H_{11}NO_2$** (201)	**Mp** 115-116 ^oC. **IR (Nujol)** ν_{max} 1710, 1685 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 2.18 (d, *J* = 2 Hz, 3H), 2.38 (s, 3H), 6.47 (q, *J* = 2 Hz, 1H), 7.20 (d, *J* = 10 Hz, 2H), 7.27 (d, *J* = 10 Hz, 2H). **MS (*m/e*)** 201, 186, 172, 157, 144, 132, 117, 104, 91, 86, 77, 68, 57.
4	 **32** Ar = *p*-Tolyl **$C_{13}H_{13}NO_2$** (215)	**Mp** 109-110 ^oC. **IR (Nujol)** ν_{max} 1701, 1507, 1388, 1085 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 2.06 (s, 6H), 2.38 (s, 3H), 7.21 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H). **MS (*m/e*)** 215, 200, 186, 172, 156, 144, 132, 117, 104, 91, 77, 65, 54.

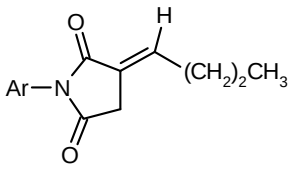
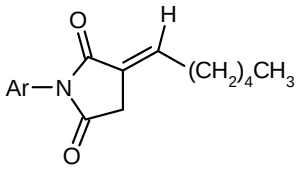
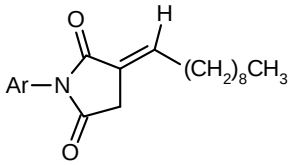
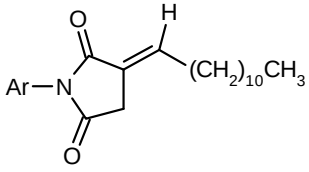
5	 **33** **$C_6H_6O_3$** (126)	**Mp** 94-96 ^oC. **IR (Nujol)** ν_{max} 1748 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 2.08 (s, 6H). **MS (*m*/*e*)** 126, 82, 67, 54.
6	$HO(CH_2)_{15}COOCH_3$ **51** **$C_{17}H_{34}O_3$** (286)	**Mp** 60-62 ^oC. **IR ($CHCl_3$)** ν_{max} 3400, 1712 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 1.28 (bs, 22H), 1.45-1.75 (bm, 5H), 2.35 (t, J = 8 Hz, 2H), 3.65 (t, J = 8 Hz, 2H), 3.68 (s, 3H). **MS (*m*/*e*)** 286, 268, 256, 236, 199, 143, 112, 98, 87, 74, 69, 55.
7	$HO(CH_2)_{16}OH$ **52** **$C_{16}H_{34}O_2$** (258)	**Mp** 91-92 ^oC. **IR (Nujol)** ν_{max} 3415, 3356, 1462 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 1.30 (bs, 24H), 1.58 (q, J = 6 Hz, 4H), 3.65 (t, J = 6 Hz, 4H). **MS (*m*/*e*)** 258, 240, 228, 222, 210, 194, 180, 166, 152, 137, 123, 109, 95, 82, 67, 54.
8	$OHC(CH_2)_{14}CHO$ **53** **$C_{16}H_{30}O_2$** (254)	**Mp** 52-53 ^oC. **IR (Nujol)** ν_{max} 2748, 1713 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 1.26 (bs, 24H), 1.63 (quintet, J = 6 Hz, 4H), 2.43 (dt, J = 6 and 2 Hz, 4H), 9.77 (s, 2H). **MS (*m*/*e*)** 254, 236, 192, 136, 108, 95, 81, 68, 57.
9	 **54 + 55 + 56** **54** (major) All *E* **55** (minor) All *E* & *Z*	**Mp** 96-100 ^oC. **IR (Nujol)** ν_{max} 1770, 1710, 1672 cm^{-1}. **^1H NMR ($CDCl_3$, 200 MHz)** δ 1.29 (bs, 20H), 1.48 (d, J = 8 Hz, 0.9H) (*Z*-isomer), 1.53 (d, J = 8 Hz, 5.1H), 1.40-1.60 (m, 4H), 2.00-2.40 (m, 3.4H), 2.39 (S, 6H), 2.70-2.90 (m, 0.6H) (*Z*-isomer), 3.35 (q, J = 8 Hz, 0.3H) (*Z*-isomer), 3.46 (q, J = 8 Hz, 1.7H), 6.23 (dt, J = 8 and 2 Hz, 0.3H) (*Z*-isomer), 6.93

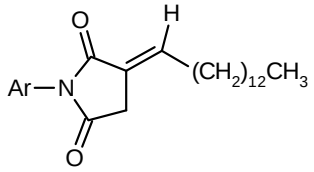
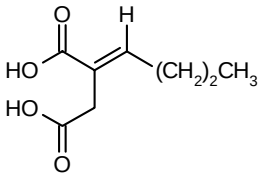
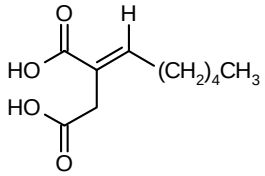
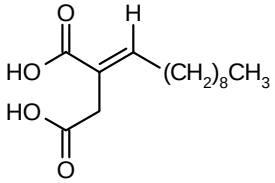
	56 (minor) All *Z* Ar = *p*-Tolyl **$C_{40}H_{52}N_2O_4$** (624)	(dt, *J* = 8 and 2 Hz, 1.7H), 7.21 (d, *J* = 8 Hz, 4H), 7.29 (d, *J* = 8 Hz, 4H). **MS (*m*/*e*)** 624, 518, 423, 396, 312, 242, 228, 215, 202, 186, 133, 118, 107, 95, 81, 68, 55.
10	 **57** Ar = *p*-Tolyl **$C_{40}H_{52}N_2O_4$** (624)	**Mp** 96-98 ^{o}C. **IR (Nujol)** ν_{max} 1770, 1713 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 1.29 (bs, 20H), 1.35 (bs, 4H), 1.60 (quintet, *J* = 4 Hz, 4H), 2.07 (s, 6H), 2.40 (s, 6H), 2.48 (t, *J* = 6 Hz, 4H), 7.24 (d, *J* = 6 Hz, 4H), 7.28 (d, *J* = 6 Hz, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 8.2, 20.5, 23.2, 27.6, 28.7, 29.1 (5 × CH_2), 125.1 (2-carbons) 129.0 (2-carbons), 136.5, 140.7, 170.2, 170.5. **MS (*m*/*e*)** 624, 438, 242, 228, 215, 202, 154, 136, 120, 106, 91, 81, 55.
11	 **36** **$C_{26}H_{38}O_6$** (446)	**Mp** 60 ^{o}C. **IR (Nujol)** ν_{max} 1855, 1767, 1670 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 1.23 (bs, 24H), 1.55 (quintet, *J* = 8 Hz, 4H), 2.05 (s, 6H), 2.43 (t, *J* = 8 Hz, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 9.5, 24.4, 27.5, 29.2, 29.4, 29.6 (4 × CH_2), 140.4, 144.7, 165.8, 166.2. **MS (*m*/*e*)** 446, 428, 400, 373, 210, 196, 149, 126, 98, 55.
12	 **69** Ar = *p*-Tolyl **$C_{12}H_{13}NO_3$** (219)	**Mp** 201 ^{o}C (methanol). **IR (Nujol)** ν_{max} 3400, 1715, 1660, 1620 cm^{-1}.

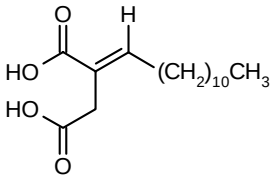
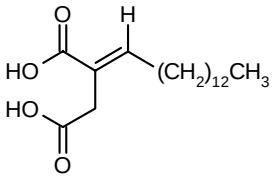
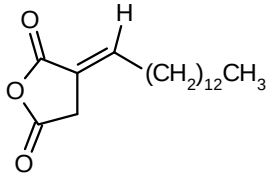
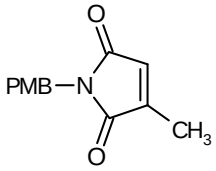
13	 **65 + 66** **65** R^1 = H, R^2 = $(CH_2)_4CH_3$ **66** R^1 = $(CH_2)_4CH_3$, R^2 = H (**65**: **66** = 85:15) Ar = *p*-Tolyl **$C_{18}H_{23}NO_2$** (285)	**Mp** 112-116 ^oC. **IR (Neat)** ν_{max} 1771, 1710, 1672 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.92 (t, *J* = 6 Hz, 3H), 1.25-1.45 (m, 4H), 1.45-1.70 (m, 2H), 1.48 (d, *J* = 6 Hz, 0.45H, *Z*-isomer), 1.53 (d, *J* = 6 Hz, 2.55H), 2.20-2.38 (m, 1.70H), 2.39 (s, 3H), 2.75-2.95 (m, 0.3H) (*Z*-isomer), 3.30-3.55 (m, 1H), 6.23 (dt, *J* = 8 and 3 Hz, 0.15H) (*Z*-isomer), 6.92 (dt, *J* = 8 and 3 Hz, 0.85H), 7.21 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H). **MS (*m/e*)** 286, 230, 147, 106, 91, 81, 77, 73, 55.
14	 **58** **$C_{11}H_{18}O_4$** (214)	**Mp** 155 ^oC (water). **IR (Nujol)** ν_{max} 1717, 1678, 1637 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.90 (t, *J* = 6 Hz, 3H), 1.15-1.47 (m, 7H), 1.47-1.65 (m, 2H), 2.05-2.40 (m, 2H), 3.58 (q, *J* = 8 Hz, 1H), 7.03 (t, *J* = 8 Hz, 1H), 11.00-12.50 (bs, 2H) [In (*E*+*Z*)-isomer mixture, the signals for vinylic proton and allylic-methylene protons from *Z*-isomer appeared at δ 6.23 and δ 2.63 respectively]. **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 13.9, 15.3, 22.4, 28.1, 28.7, 31.4, 37.6, 131.4, 147.1, 172.4, 180.7. **MS (*m/e*)** 214, 196, 168, 139, 125, 112, 99, 95, 91, 81, 67, 55.
15	 **79 + 80** **79**: R^1 = H, R^2 = $(CH_2)_{10}CH_3$ **80**: R^1 = $(CH_2)_{10}CH_3$, R^2 = H (**79**: **80** = 85:15) Ar = *p*-Tolyl	**Mp** 49-52 ^oC. **IR (Nujol)** ν_{max} 1717, 1458 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.88 (t, *J* = 6 Hz, 3H), 1.27 (bs, 16H), 1.45-1.60 (m, 2H), 1.48 (d, *J* = 6 Hz, 0.45H) (*Z*-isomer), 1.52 (d, *J* = 6 Hz, 2.55H), 2.20-2.36 (m, 1.7H), 2.38 (s, 3H), 2.74-2.92 (m, 0.3H) (*Z*-isomer), 3.34-3.59 (m, 1H), 6.23 (dt, *J* = 8 and 3 Hz, 0.15H) (*Z*-isomer), 6.92 (dt, *J* = 8 Hz and 3 Hz, 0.85H), 7.20 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H).

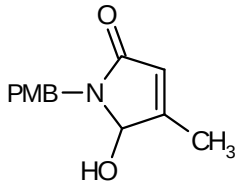
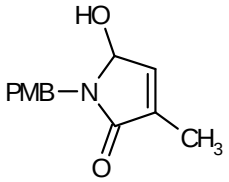
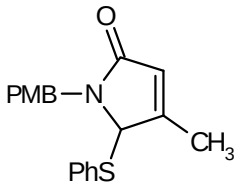
	$C_{24}H_{35}NO_2$ (369)	**MS (*m/e*)** 369, 354, 340, 270, 256, 242, 229, 216, 203, 186, 170, 157, 144, 132, 118, 107, 95, 91, 81, 68, 55.
16	 **81** Ar = *p*-Tolyl **$C_{24}H_{35}NO_2$** (369)	**Mp** 68-69 ^{o}C. **IR (Nujol)** ν_{max} 1710, 1690, 1650 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.89 (t, J = 8 Hz, 3H), 1.27 (bs, 18H), 1.50-1.75 (m, 2H), 2.05 (s, 3H), 2.38 (s, 3H), 2.46 (t, J = 8 Hz, 2H), 7.10-7.40 (m, 4H). **^{13}C NMR ($CDCl_3$, 50 MHz)** δ 8.7, 14.0, 21.0, 22.6, 23.8, 28.1, 29.3, 29.6 (6 × CH_2), 31.9, 125.6, 129.5, 137.1, 137.2, 141.4, 159.7, 170.7, 171.1. **MS (*m/e*)** 369, 256, 228, 215, 203, 107, 91, 81, 67, 55.
17	 **82** **$C_{17}H_{28}O_3$** (280)	Thick oil. **IR (Nujol)** ν_{max} 1823, 1767, 1674, 1466 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.45-1.70 (m, 2H), 2.07 (s, 3H), 2.46 (t, J = 6 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50 MHz)** δ 9.2, 13.9, 22.5, 24.3, 27.4, 29.3, 29.5 (6 × CH_2), 31.8, 140.3, 144.6, 165.7, 166.1. **MS (*m/e*)** 281, 262, 252, 235, 207, 196, 178, 168, 150, 139, 126, 109, 98, 81, 67.
18	 **82a** **$C_{19}H_{34}O_4$** (326)	Thick oil. **IR (Neat)** ν_{max} 1726, 1460, 1435, 1265 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 20H), 1.94 (s, 3H), 2.33 (t, J = 6 Hz, 2H), 3.75 (s, 3H), 3.76 (s, 3H). **^{13}C NMR ($CDCl_3$, 50 MHz)** δ 13.7, 14.6, 22.4, 27.4, 29.1 (7 × CH_2), 29.3, 31.6, 51.6 (2 × OCH_3), 131.2, 139.4, 168.6, 169.2.

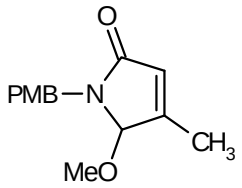
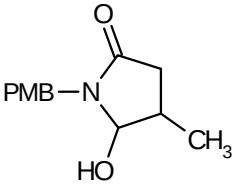
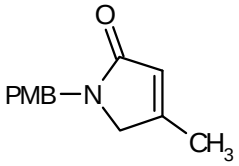
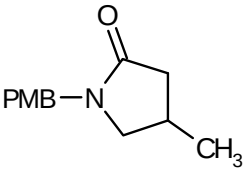
19	 **84** Ar = *p*-Tolyl **$C_{24}H_{37}NO_2$** (371)	**Mp** 67-68 ^{o}C (methanol). **IR (Nujol)** ν_{max} 1774, 1709, 1516, 1470 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.91 (t, J = 6 Hz, 3H), 1.29 (bs, 20H), 1.35 (d, J = 6 Hz, 3H), 1.60-1.95 (m, 2H), 2.39 (s, 3H), 2.85-3.20 (m, 2H), 7.16 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50 MHz)** δ 11.6, 13.9, 21.0, 22.6, 26.5, 27.6, 29.3, 29.5 (6 × CH_2), 31.8, 38.6, 43.8, 126.1, 129.6, 138.2, 138.4, 178.4, 179.3. **MS (*m/e*)** 371, 265, 216, 203, 175, 134, 107, 91, 69.
20	 **71** **$C_{17}H_{32}O_4$** (300)	**Mp** 141-142 ^{o}C (acetone). **IR (Nujol)** ν_{max} 1693, 1464, 1271, 1202 cm^{-1}. **^{1}H NMR (Pyridine-d_5, 500 MHz)** δ 0.86 (t, J = 5 Hz, 3H), 1.20 (bs, 16H), 1.30-1.45 (m, 2H), 1.62 (d, J = 10 Hz, 3H), 1.53-1.75 (m, 2H), 1.92-2.03 (m, 1H), 2.10-2.23 (m, 1H), 3.17-3.33 (m, 2H). **^{13}C NMR (Pyridine-d_5, 125 MHz)** δ 14.2, 16.2, 22.8, 28.2, 29.5, 29.8 (6 × CH_2), 31.7, 32.0, 43.4, 50.0, 177.0, 177.7. **MS (*m/e*)** 282, 254, 227, 209, 170, 156, 132, 97, 83, 69.
21	 **85** **$C_{19}H_{36}O_4$** (328)	Thick oil. **IR (Neat)** ν_{max} 1740, 1464, 1435, 1195 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.87 (t, J = 6 Hz, 3H), 1.13 (d, J = 6 Hz, 3H), 1.23 (bs, 18H), 1.30-1.50 (m, 2H), 1.50-1.75 (m, 2H), 2.58-2.78 (m, 2H), 3.68 (s, 3H), 3.69 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 14.0, 15.1, 22.7, 27.5, 29.4, 29.6 (6 × CH_2), 30.7, 31.9, 42.1, 48.6, 51.4, 51.7, 174.6, 175.3. **MS (*m/e*)** 328, 298, 267, 242, 184, 170, 160, 128, 111, 101, 91, 81, 69, 55.

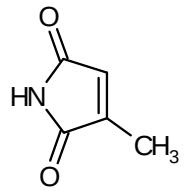
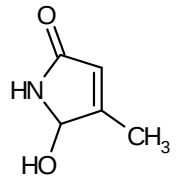
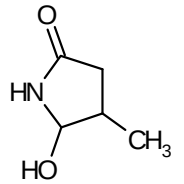
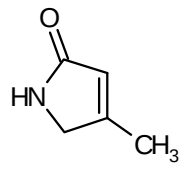
22	 **103a** Ar = *p*-Tolyl **$C_{15}H_{17}NO_2$** (243)	**Mp** 90-92 ^{o}C. **IR (Nujol)** ν_{max} 1773, 1709, 1676 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.99 (t, J = 8 Hz, 3H), 1.58 (sextet, J = 8 Hz, 2H), 2.23 (q, J = 8 Hz, 2H), 2.39 (s, 3H), 3.39 (s, 2H), 6.95 (t, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H). **MS (*m/e*)** 243, 228, 214, 133, 95, 67, 53.
23	 **103b** Ar = *p*-Tolyl **$C_{17}H_{21}NO_2$** (271)	**Mp** 112-113 ^{o}C. **IR (Nujol)** ν_{max} 1771, 1749, 1712, 1691, 1676 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.90 (t, J = 6 Hz, 3H), 1.20-1.45 (m, 4H), 1.55 (quintet, J = 6 Hz, 2H), 2.25 (q, J = 6 Hz, 2H), 2.38 (s, 3H), 3.38 (s, 2H), 6.94 (t, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H). **MS (*m/e*)** 271, 242, 228, 214, 200, 189, 172, 133, 107, 95, 81, 67, 53.
24	 **103c** Ar = *p*-Tolyl **$C_{21}H_{29}NO_2$** (327)	**Mp** 106-108 ^{o}C. **IR (Nujol)** ν_{max} 1771, 1709, 1676, 1466 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.90 (t, J = 6 Hz, 3H), 1.29 (bs, 12H), 1.54 (quintet, J = 6 Hz, 2H), 2.25 (q, J = 8 Hz, 2H), 2.40 (s, 3H), 3.40 (s, 2H), 6.96 (t, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H). **MS (*m/e*)** 327, 275, 228, 202, 155, 129, 107, 83, 73, 55, 43.
25	 **103d** Ar = *p*-Tolyl **$C_{23}H_{33}NO_2$** (355)	**Mp** 109-111 ^{o}C. **IR (Nujol)** ν_{max} 1771, 1711, 1674, 1466 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.88 (t, J = 6 Hz, 3H), 1.27 (bs, 16H), 1.45-1.60 (m, 2H), 2.24 (q, J = 8 Hz, 2H), 2.39 (s, 3H), 3.39 (s, 2H), 6.94 (t, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H). **MS (*m/e*)** 355, 228, 202, 189, 149, 133, 107, 73, 55, 43.
26		**Mp** 58-60 ^{o}C.

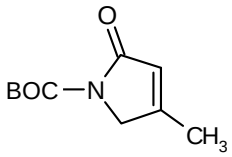
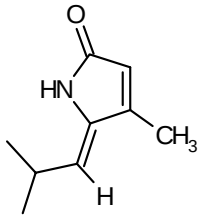
	 **103e** Ar = *p*-Tolyl **$C_{25}H_{37}NO_2$** (383)	**IR (Nujol)** ν_{max} 1785, 1720, 1695, 1470 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.88 (t, J = 6 Hz, 3H), 1.25 (bs, 20H), 1.55 (quintet, J = 6 Hz, 2H), 2.25 (q, J = 8 Hz, 2H), 2.39 (s, 3H), 3.38 (s, 2H), 6.95 (t, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 13.7, 20.8, 22.3, 27.9, 29.1, 29.2, 29.3 (9 × CH_2), 29.5, 31.8, 125.4, 125.9, 129.2, 129.5, 137.8, 139.1, 168.5, 172.6. **MS (*m/e*)** 383, 355, 257, 228, 215, 202, 189, 172, 108, 95, 81.
27	 **104a** **$C_8H_{12}O_4$** (172)	**Mp** 169-170 ^oC. **IR (Nujol)** ν_{max} 2800-2500, 1705, 1693, 1640 cm^{-1}. **^{1}H NMR (Acetone-d_6, 200 MHz)** δ 0.94 (t, J = 8 Hz, 3H), 1.50 (sextet, J = 8 Hz, 2H), 2.23 (q, J = 8 Hz, 2H), 3.37 (s, 2H), 6.97 (t, J = 8 Hz, 1H). **MS (*m/e*)** 173, 154, 126, 111, 81, 53, 41.
28	 **104b** **$C_{10}H_{16}O_4$** (200)	**Mp** 149-150 ^oC. **IR (Nujol)** ν_{max} 2800-2500, 1704, 1692, 1643 cm^{-1}. **^{1}H NMR (Acetone-d_6, 200 MHz)** δ 0.88 (t, J = 6 Hz, 3H), 1.20-1.40 (m, 4H), 1.49 (quintet, J = 6 Hz, 2H), 2.24 (q, J = 6 Hz, 2H), 3.35 (s, 2H), 6.96 (t, J = 8 Hz, 1H). **MS (*m/e*)** 182, 154, 139, 109, 98, 55, 67, 41.
29	 **104c** **$C_{14}H_{24}O_4$** (256)	**Mp** 147-148 ^oC. **IR (Nujol)** ν_{max} 2800-2500, 1703, 1693, 1643 cm^{-1}. **^{1}H NMR (Acetone-d_6, 200 MHz)** δ 0.88 (t, J = 6 Hz, 3H), 1.29 (bs, 12H), 1.49 (quintet, J = 6 Hz, 2H), 2.26 (q, J = 6 Hz, 2H), 3.36 (s, 2H), 6.97 (t, J = 8 Hz, 1H). **MS (*m/e*)** 238, 211, 178, 166, 148, 123, 113, 69, 55, 41.

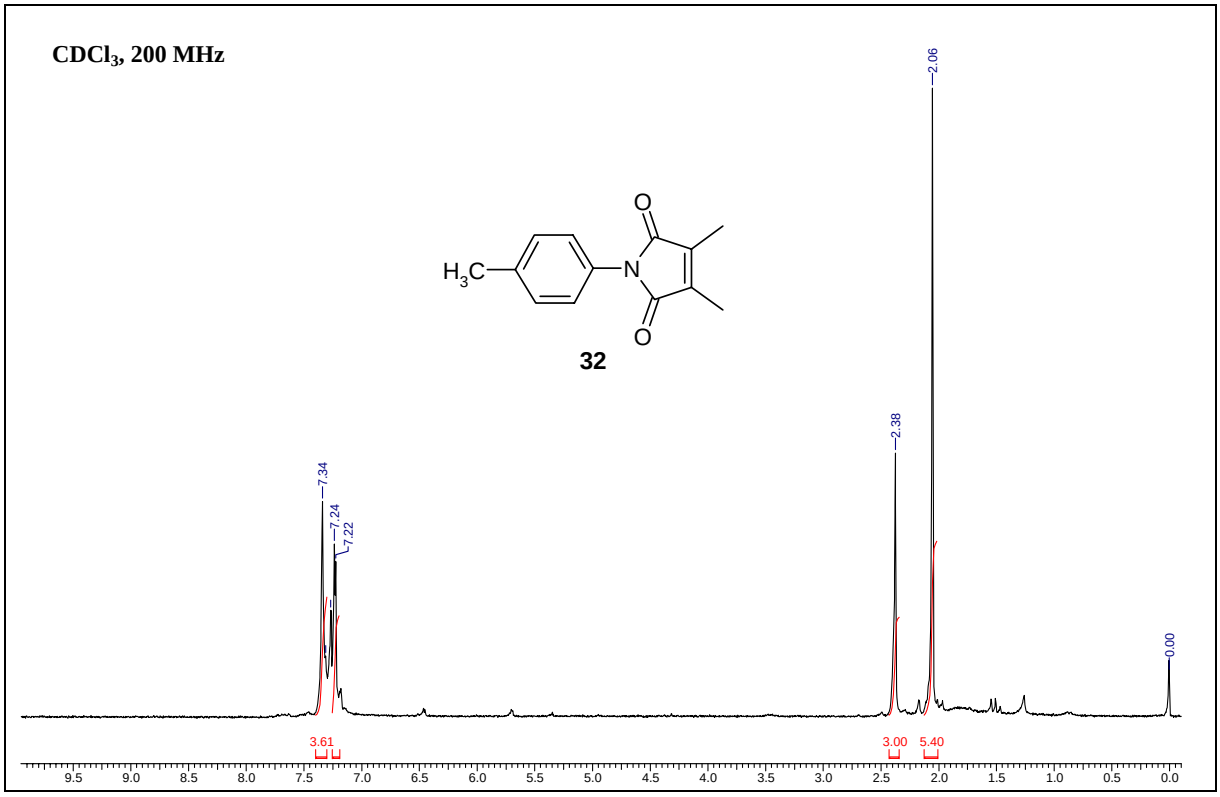
30	 **104d** **$C_{16}H_{28}O_4$** (284)	**Mp** 146-147 ^{o}C. **IR (Nujol)** ν_{max} 2800-2500, 1702, 1692, 1641 cm^{-1}. **^{1}H NMR (Acetone-d_6, 200 MHz)** δ 0.87 (t, J = 6 Hz, 3H), 1.28 (bs, 16H), 1.40-1.60 (m, 2H), 2.25 (q, J = 6 Hz, 2H), 3.35 (s, 2H), 6.95 (t, J = 8 Hz, 1H). **MS (*m/e*)** 266, 238, 174, 137, 123, 113, 95, 81, 69, 55, 43.
31	 **104e** **$C_{18}H_{32}O_4$** (312)	**Mp** 148 ^{o}C. **IR (Nujol)** ν_{max} 2800-2500, 1705, 1699, 1647 cm^{-1}. **^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz)** δ 0.70 (t, J = 6 Hz, 3H), 1.08 (bs, 20H), 1.20-1.35 (m, 2H), 2.01 (q, J = 8 Hz, 2H), 3.13 (s, 2H), 6.78 (t, J = 8 Hz, 1H). **^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz)** δ 12.6, 21.0, 27.0, 27.3, 27.6, 27.7, 28.0 (6 × CH_2), 30.2, 30.8, 125.3, 143.0, 167.1, 170.8. **MS (*m/e*)** 312, 294, 276, 266, 206, 192, 178, 139, 126, 113, 95, 81, 67, 55.
32	 **105** **$C_{18}H_{30}O_3$** (294)	Thick oil. **IR (Nujol)** ν_{max} 1842, 1788, 1680, 1470, 1230 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 20H), 1.40-1.65 (m, 2H), 2.23 (q, J = 6 Hz, 2H), 3.49 (d, J = 4 Hz, 2H), 7.06 (tt, J = 8 and 2 Hz, 1H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 13.9, 22.5, 27.7, 29.2, 29.3 (6 × CH_2), 29.5, 30.6, 31.7, 31.8, 122.6, 145.8, 164.8, 168.4. **MS (*m/e*)** 294, 276, 266, 249, 192, 177, 168, 137, 123, 95, 81, 67, 55.
33	 **123** PMB = *p*-Methoxybenzyl	**Mp** 85-86 ^{o}C. **IR (Nujol)** ν_{max} 1695, 1612, 1461 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 2.06 (s, 3H), 3.77 (s, 3H), 4.58 (s, 2H), 6.30 (s, 1H), 6.83 (d, J = 10 Hz, 2H), 7.29 (d, J = 10 Hz, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 10.7, 40.8, 55.0, 113.9,

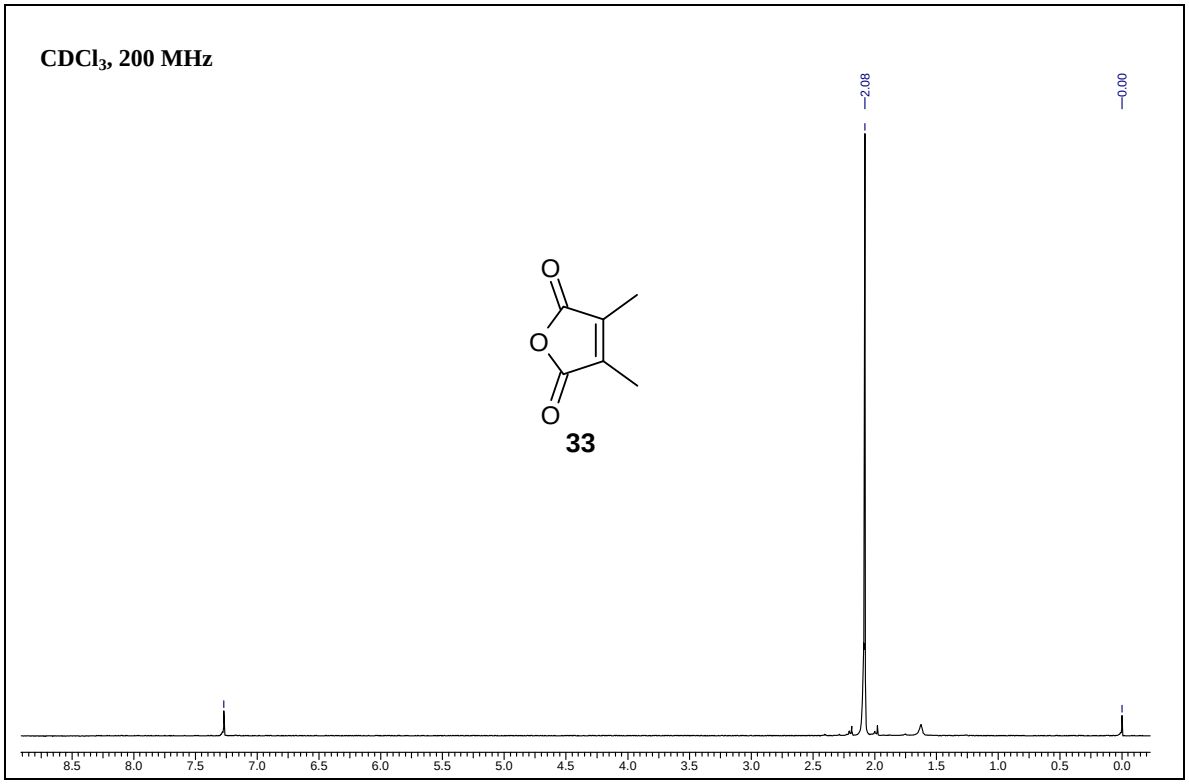
	$C_{13}H_{13}NO_3$ (231)	127.2, 128.7, 129.7, 145.5, 159.1, 170.3, 171.4.
34	 **124** PMB = *p*-Methoxybenzyl **$C_{13}H_{15}NO_3$** (233)	**Mp** 165-167 ^{o}C. **IR (Nujol)** ν_{max} 3130, 2923, 1664, 1629, 1311, 1248 cm^{-1}. **^{1}H NMR (DMSO-d_6, 500 MHz)** δ 1.88 (s, 3H), 3.67 (s, 3H), 4.03 (d, *J* = 15 Hz, 1H), 4.60 (d, *J* = 15 Hz, 1H), 4.92 (d, *J* = 10 Hz, 1H), 5.75 (s, 1H), 6.34 (d, *J* = 10 Hz, 1H), 6.82 (d, *J* = 10 Hz, 2H), 7.11 (d, *J* = 10 Hz, 2H). **^{13}C NMR (DMSO-d_6, 125 MHz)** δ 13.1, 41.1, 54.9, 82.9, 113.7, 121.2, 128.8, 131.0, 158.2, 158.7, 168.8.
35	 **124a** PMB = *p*-Methoxybenzyl **$C_{13}H_{15}NO_3$** (233)	**Mp** 128-130 ^{o}C. **IR (Nujol)** ν_{max} 3219, 2923, 1664, 1634, 1310, 1244 cm^{-1}. **^{1}H NMR (CD_3OD, 500 MHz)** δ 1.90 (s, 3H), 3.78 (s, 3H), 4.21 (d, *J* = 15 Hz, 1H), 4.84 (d, *J* = 15 Hz, 1H), 5.14 (s, 1H), 6.64 (s, 1H), 6.88 (d, *J* = 10 Hz, 2H), 7.21 (d, *J* = 10 Hz, 2H). **^{13}C NMR (CD_3OD, 125 MHz)** δ 10.9, 43.2, 55.8, 81.9, 115.2, 130.5, 131.0, 137.1, 141.1, 160.7, 172.3.
36	 **130** PMB = *p*-Methoxybenzyl **$C_{19}H_{19}NO_2S$** (325)	Thick oil. **IR (Nujol)** ν_{max} 3013, 1690, 1612, 1512, 1400, 1248 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 2.07 (s, 3H), 3.80 (s, 3H), 4.35 (d, *J* = 15 Hz, 1H), 4.81 (s, 1H), 5.23 (d, *J* = 15 Hz, 1H), 5.68 (s, 1H), 6.87 (d, *J* = 5 Hz, 2H), 7.22 (d, *J* = 5 Hz, 2H), 7.35-7.25 (m, 5H). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 14.4, 42.4, 55.1, 69.9, 114.0, 123.4, 128.9, 129.0, 129.2, 129.5, 130.0, 134.4, 155.8, 159.0, 169.8.

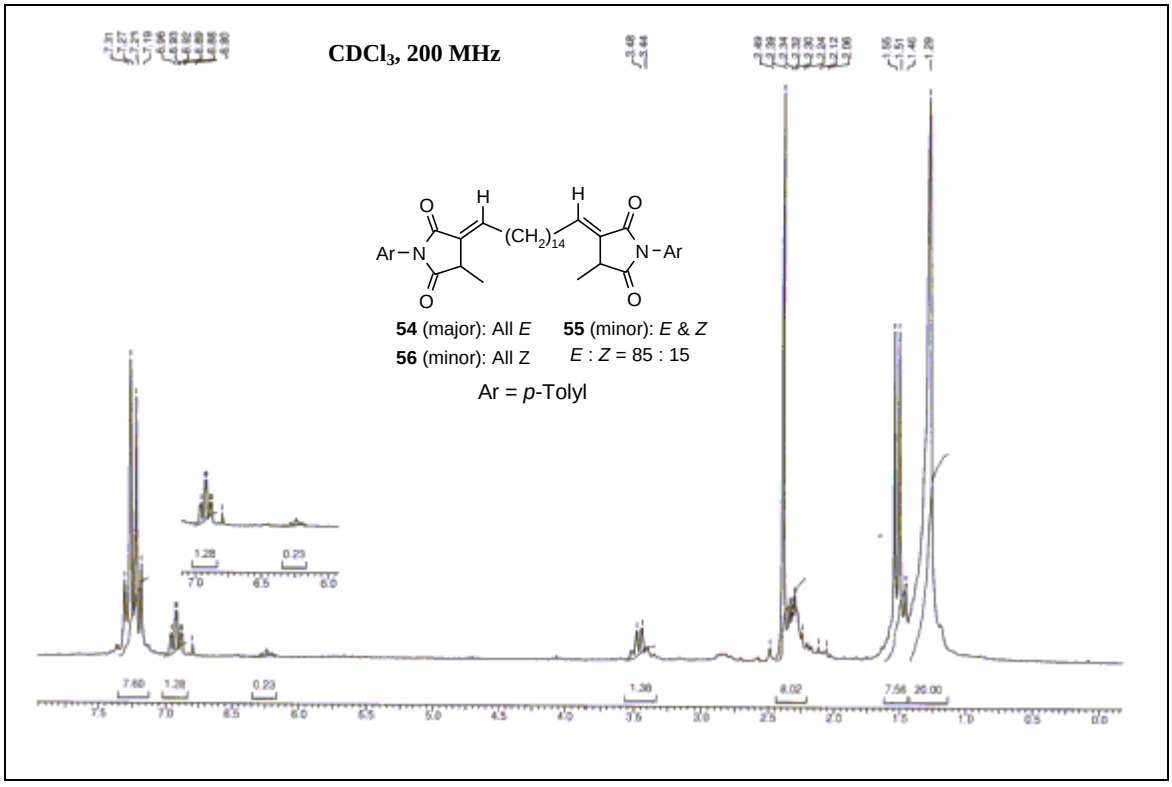
37	 **132** PMB = *p*-Methoxybenzyl **$C_{14}H_{17}NO_3$** (247)	Thick oil. **IR (Neat)** ν_{max} 2933, 1703, 1512, 1410, 1248 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 1.94 (s, 3H), 2.98 (s, 3H), 3.79 (s, 3H), 3.98 (d, *J* = 10 Hz, 1H), 4.90 (d, *J* = 10 Hz, 1H), 5.02 (s, 1H), 5.95 (s, 1H), 6.85 (d, *J* = 6 Hz, 2H), 7.23 (d, *J* = 6 Hz, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 13.5, 42.5, 49.2, 55.2, 88.6, 114.0, 124.9, 129.4, 129.8, 154.9, 159.1, 169.9.
38	 **134** PMB = *p*-Methoxybenzyl **$C_{13}H_{17}NO_3$** (235)	Thick oil. **IR (Neat)** ν_{max} 2924, 1649, 1462, 1377, 1250 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 1.02 (d, *J* = 8 Hz, 1.2H), 1.09 (d, *J* = 6 Hz, 1.8H), 1.95-2.80 (complex m, 3H), 3.79 (s, 3H), 4.05 (d, *J* = 14 Hz, 1H), 4.55 (d, *J* = 4 Hz, 0.40H), 4.78 (d, *J* = 6 Hz, 0.60H), 4.83 (d, *J* = 14 Hz, 1H), 6.90 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H).
39	 **125** PMB = *p*-Methoxybenzyl **$C_{13}H_{15}NO_2$** (217)	Thick oil. **IR (Neat)** ν_{max} 2916, 1672, 1512, 1454, 1248 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 2.00 (s, 3H), 3.70 (s, 2H), 3.79 (s, 3H), 4.52 (s, 2H), 5.86 (s, 1H), 6.85 (d, *J* = 10 Hz, 2H), 7.17 (d, *J* = 10 Hz, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 15.2, 45.2, 54.9, 55.2, 114.1, 122.8, 129.3, 129.6, 155.1, 159.0, 172.0.
40	 **131** PMB = *p*-Methoxybenzyl **$C_{13}H_{17}NO_2$** (219)	Thick oil. **IR (Neat)** ν_{max} 2974, 1695, 1400, 1169 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 1.04 (d, *J* = 5 Hz, 3H), 2.04 (dd, *J* = 15 and 10 Hz, 1H), 2.30-2.40 (m, 1H), 2.56 (dd, *J* = 15 and 10 Hz, 1H), 2.78 (dd, *J* = 15 and 10 Hz, 1H), 3.32 (t, *J* = 10 Hz, 1H), 3.77 (s, 3H), 4.35 (s, 2H), 6.83 (d, *J* = 10 Hz, 2H), 7.14 (d, *J* = 10 Hz, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 19.7, 26.3, 39.5, 45.9, 53.8,

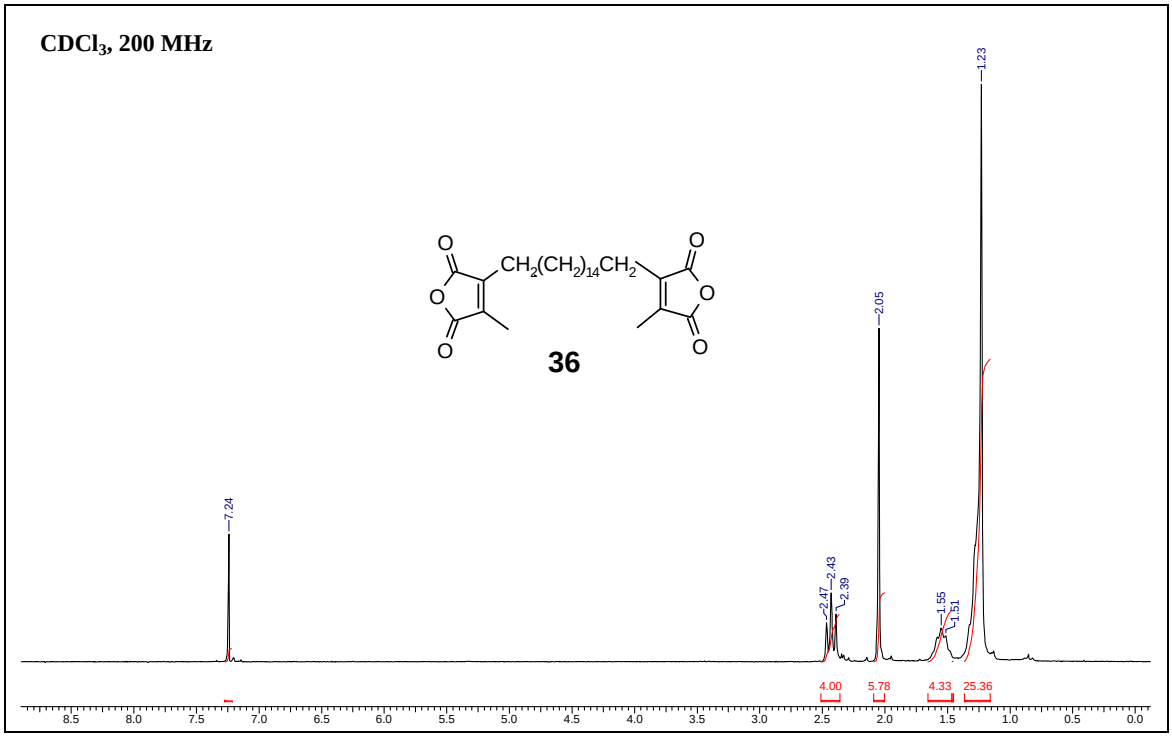
		55.2, 114.0, 128.7, 129.4, 159.1, 174.3.
41	 **135** **$C_5H_5NO_2$** (111)	**Mp** 110-111 °C. **IR (Nujol)** ν_{max} 3267, 1773, 1709, 1634, 1460 cm^{-1}. **^{1}H NMR (DMSO-d_6, 500 MHz)** δ 1.94 (s, 3H), 6.48 (s, 1H), 10.69 (bs, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz)** δ 10.1, 128.0, 145.9, 172.1, 173.0. **MS (*m/e*)** 111, 68, 40, 38.
42	 **136** **$C_5H_7NO_2$** (113)	**Mp** 163-164 °C. **IR (Nujol)** ν_{max} 3202, 1711, 1665, 1645, 1460 cm^{-1}. **^{1}H NMR (CD_3OD, 500 MHz)** δ 2.05 (s, 3H), 5.36 (s, 1H), 5.74 (s, 1H). **^{13}C NMR (CD_3OD, 125 MHz)** δ 13.5, 83.5, 122.4, 163.5, 175.5. **MS (*m/e*)** 113, 98, 85, 69, 39.
43	 **137** **$C_5H_9NO_2$** (115)	Thick oil. **IR ($CHCl_3$)** ν_{max} 3261, 1672, 1460 cm^{-1}. **^{1}H NMR (CD_3OD, 200 MHz)** δ 1.05 (d, J = 6 Hz, 2H), 1.07 (d, J = 8 Hz, 1H), 1.57-2.75 (complex m, 3H), 4.77 (d, J = 2 Hz, 0.33H), 5.01 (d, J = 6 Hz, 0.67H). **MS (*m/e*)** 115, 98, 70, 57, 46.
44	 **126** **C_5H_7NO** (97)	**Mp** 110-111 °C. **IR ($CHCl_3$)** ν_{max} 3460, 1717, 1688, 1261, 1215 cm^{-1}. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 2.06 (s, 3H), 3.90 (s, 2H), 5.83 (s, 1H). **^{13}C NMR ($CDCl_3$, 50 MHz)** δ 15.3, 51.7, 122.3, 158.5, 176.0. **MS (*m/e*)** 97, 82, 60, 58, 42.

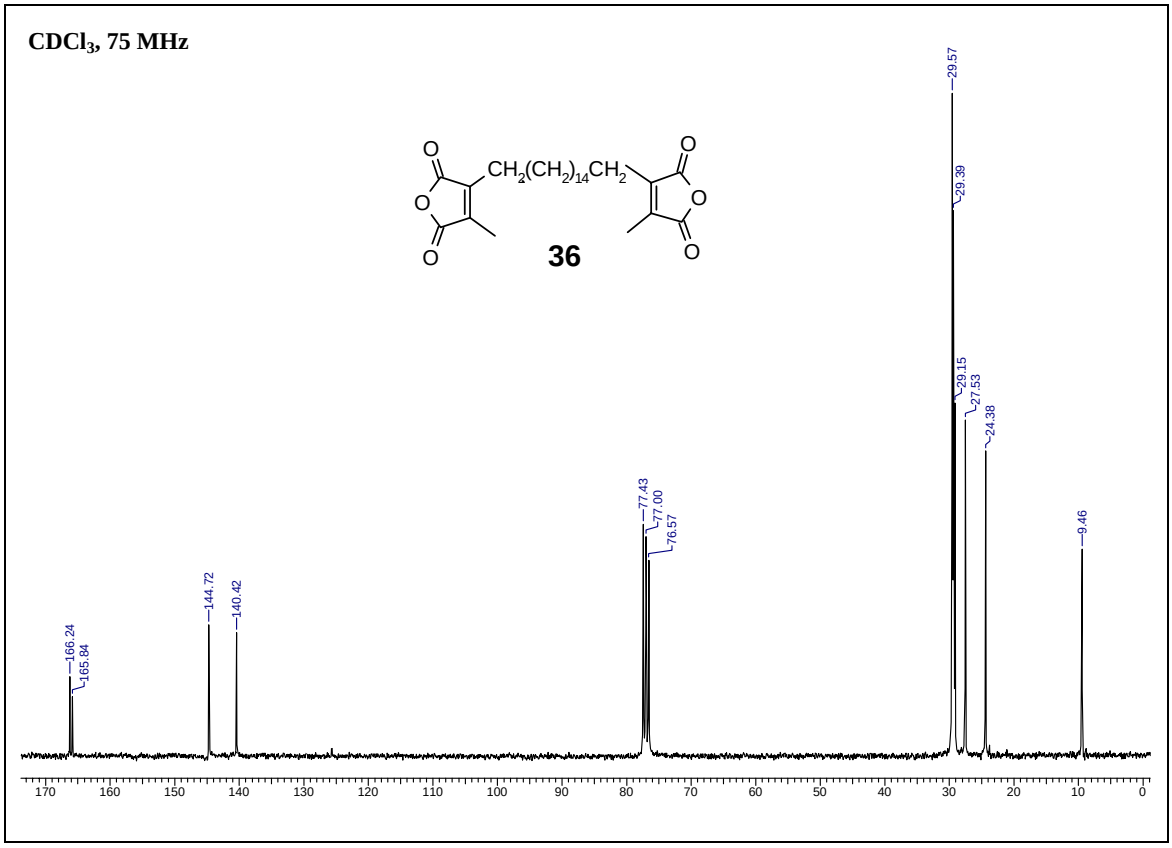
45	 **113** **$C_{10}H_{15}NO_3$** (197)	Thick oil. **IR ($CHCl_3$)** ν_{max} 1774, 1724, 1643, 1445 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz)** δ 1.51 (s, 9H), 2.06 (d, J = 2 Hz, 3H), 4.18 (s, 2H), 5.82 (bs, 1H). **^{13}C NMR ($CDCl_3$, 50 MHz)** δ 15.5, 28.0, 54.3, 82.6, 122.8, 149.4, 158.1, 169.7.
46	 **110** **$C_9H_{13}NO$** (151)	Thick oil. **IR ($CHCl_3$)** ν_{max} 3209, 1682, 1464, 1215 cm^{-1}. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 1.11 (d, J = 6 Hz, 6H), 2.08 (s, 3H), 2.55-2.90 (m, 1H), 5.12 (d, J = 8 Hz, 1H), 5.86 (s, 1H), 8.81 (bs, 1H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 11.8, 22.9, 27.6, 120.0, 121.1, 137.5, 148.8, 171.5.

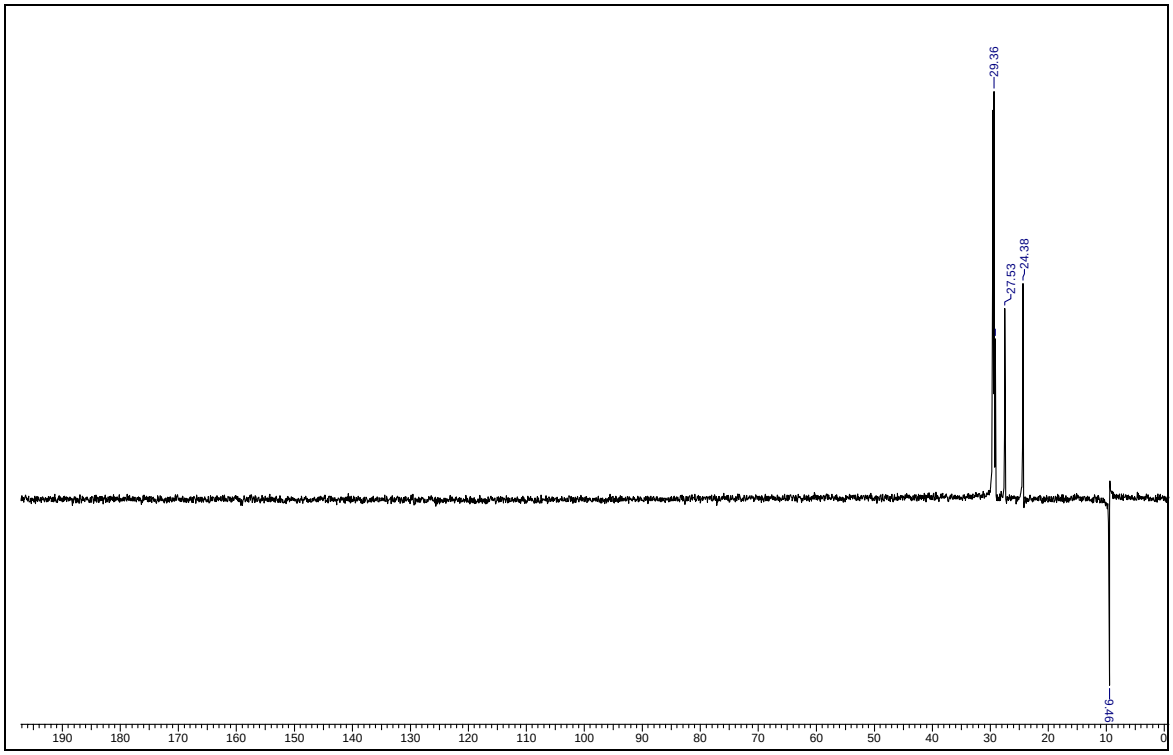

CDCl3, 200 MHz
O
H3C
N
O
32
2.06
2.38
7.34
7.24
7.22
0.00
3.61
3.00
5.40
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


CDCl3, 200 MHz
O
O
O
33
2.08
0.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

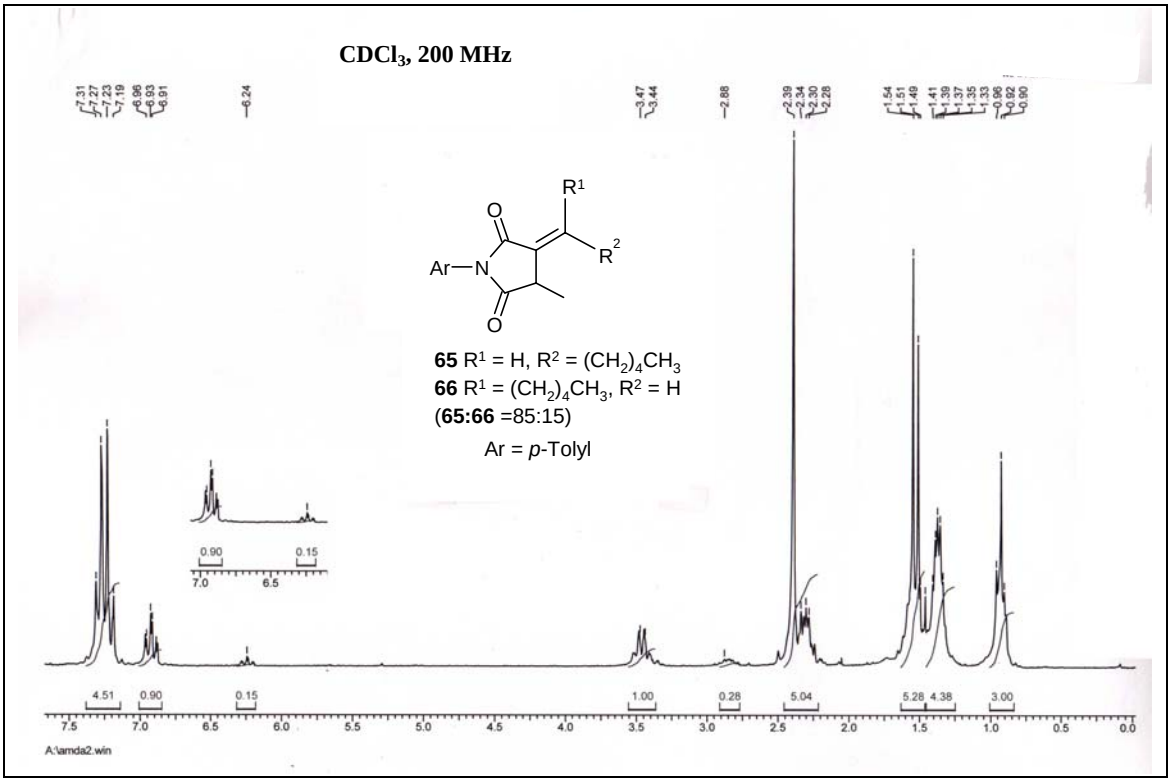

CDCl3, 200 MHz
Ar–N
(CH2)14
N–Ar
54 (major): All E
55 (minor): E & Z
56 (minor): All Z
E : Z = 85 : 15
Ar = p-Tolyl


CDCl3, 200 MHz
CH2(CH2)14CH2
36
7.24
2.47
2.43
2.39
2.05
1.55
1.51
1.23
4.00
5.78
4.33
25.36


CDCl3, 75 MHz
CH2(CH2)14CH2
36
29.57
29.39
29.15
27.53
24.38
77.43
77.00
76.57
9.46
166.24
165.84
144.72
140.42

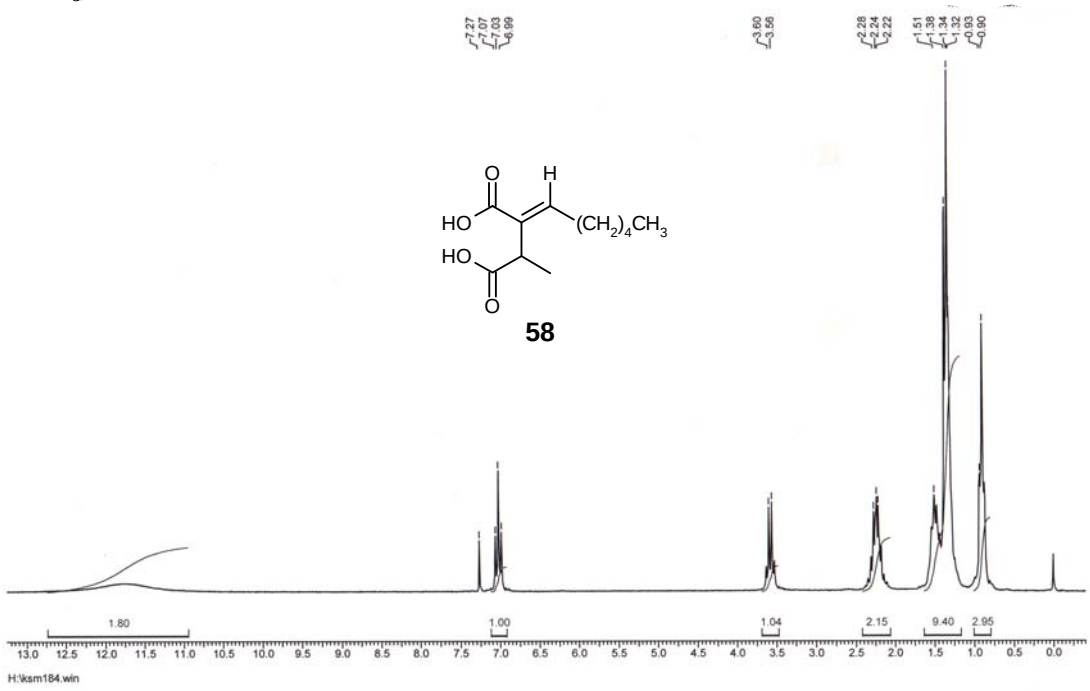

29.36
27.53
24.38
9.46

$CDCl_3$, 200 MHz



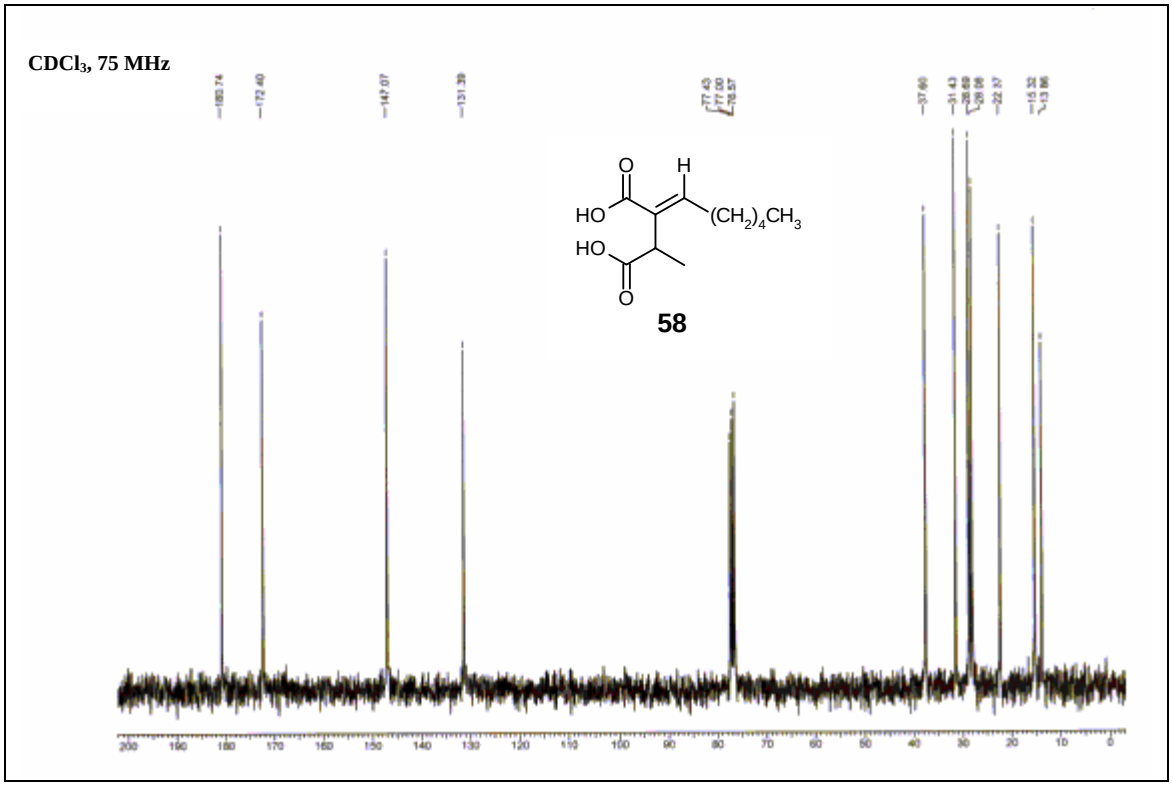
65 R^1 = H, R^2 = $(CH_2)_4CH_3$
66 R^1 = $(CH_2)_4CH_3$, R^2 = H
(**65:66** =85:15)
Ar = *p*-Tolyl

$CDCl_3$, 200 MHz

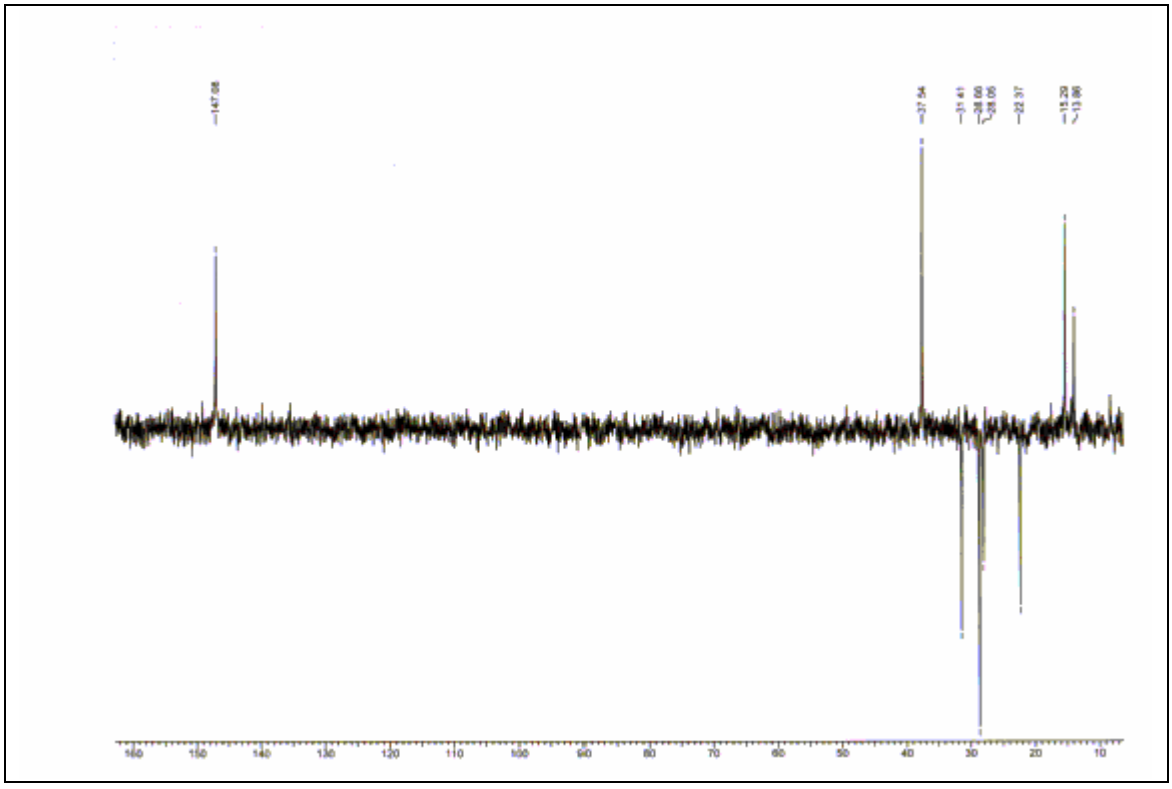


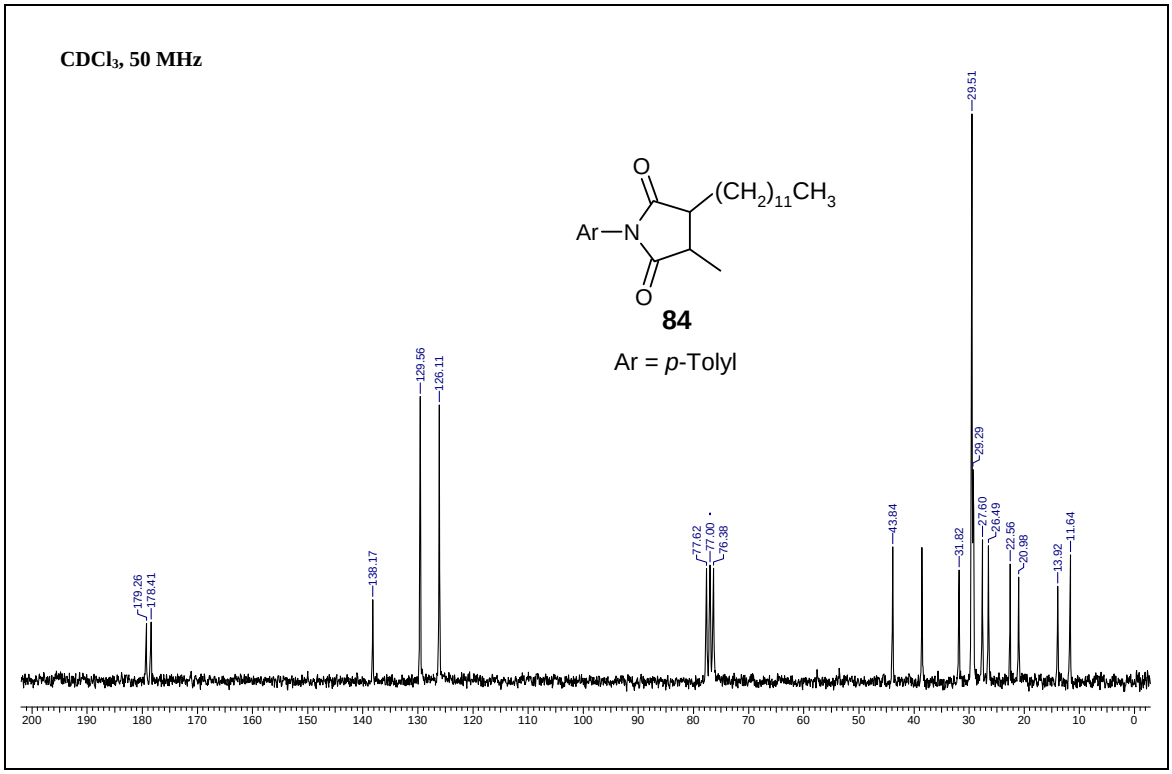
58

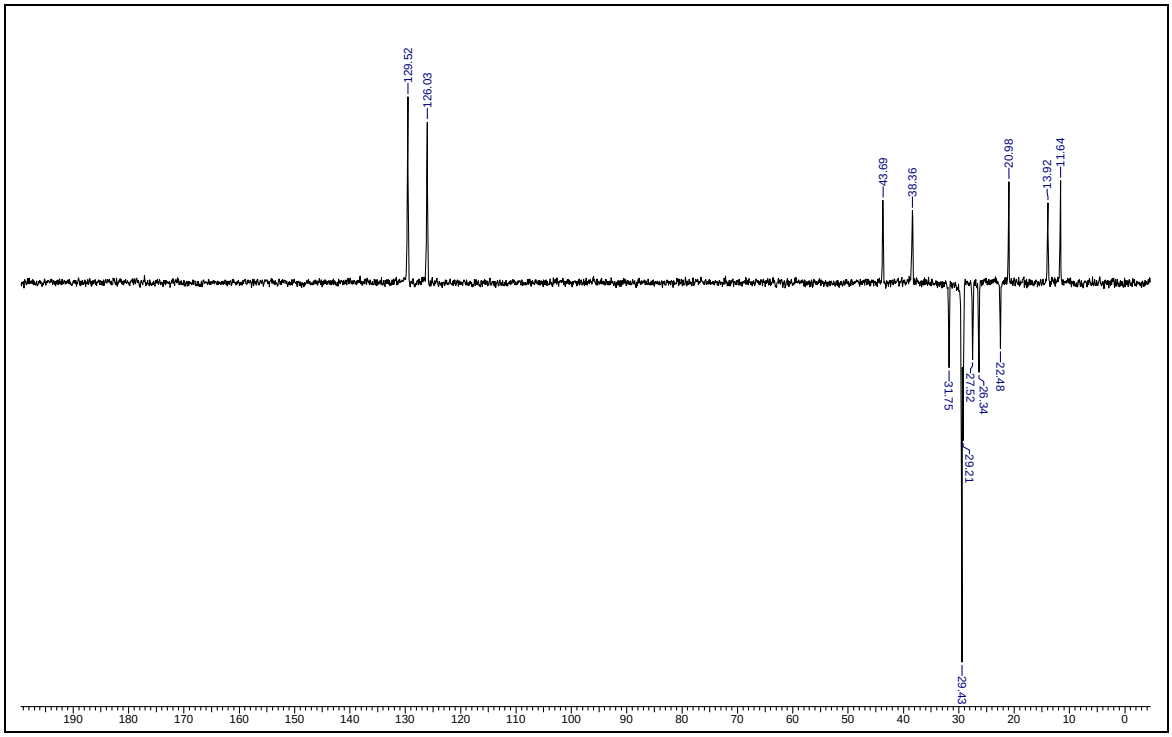
$CDCl_3$, 75 MHz

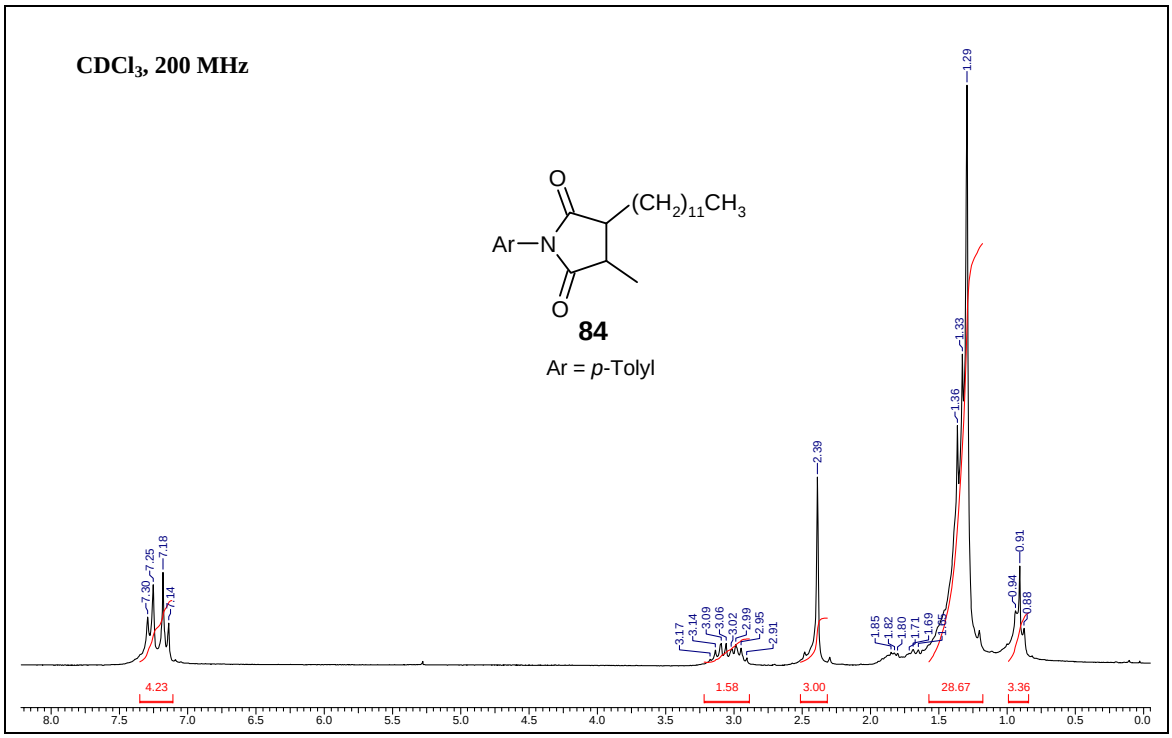


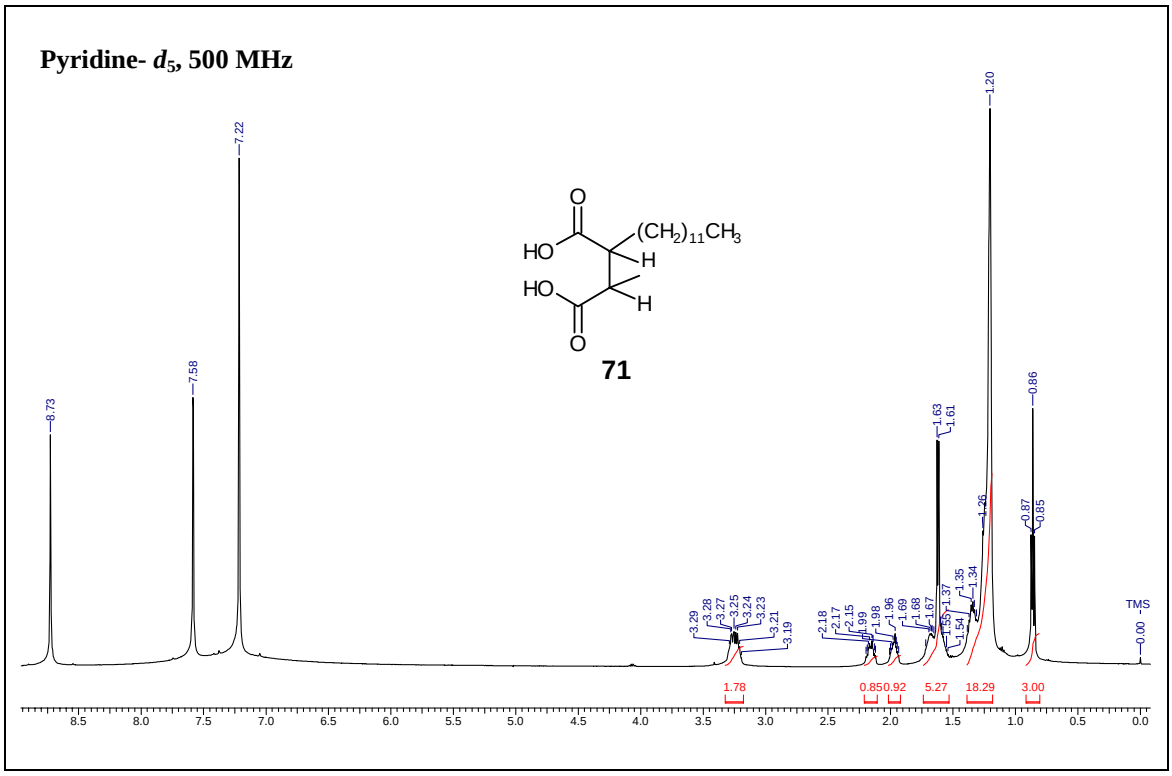
58

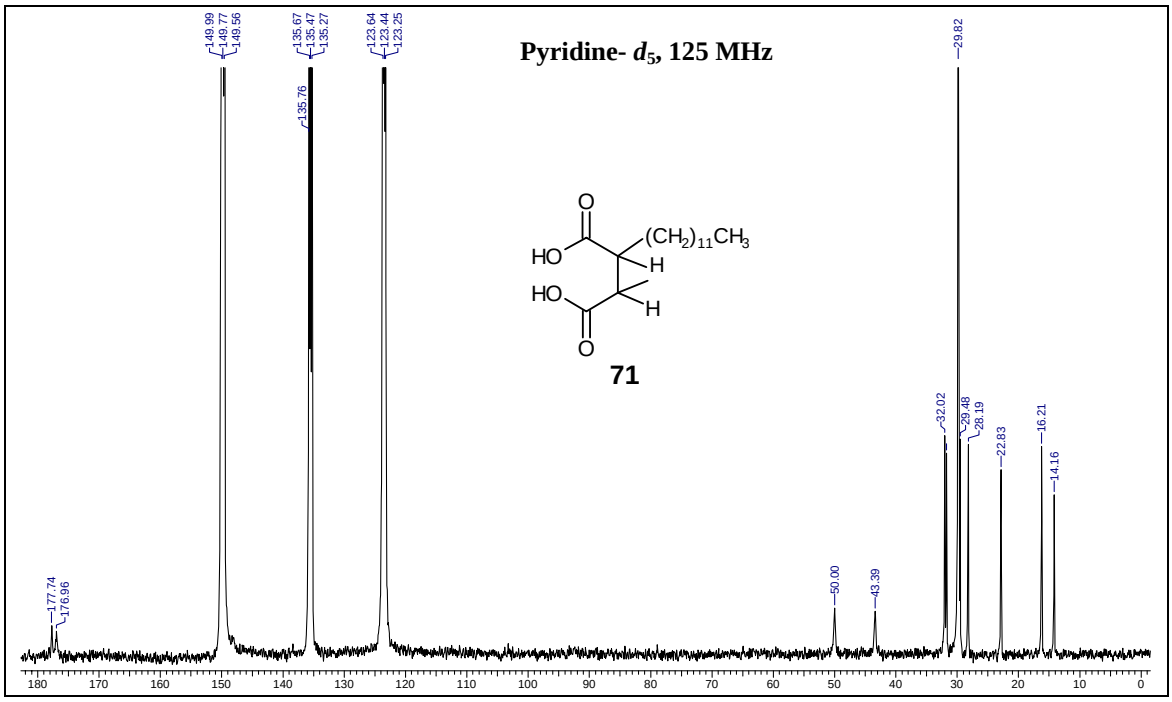


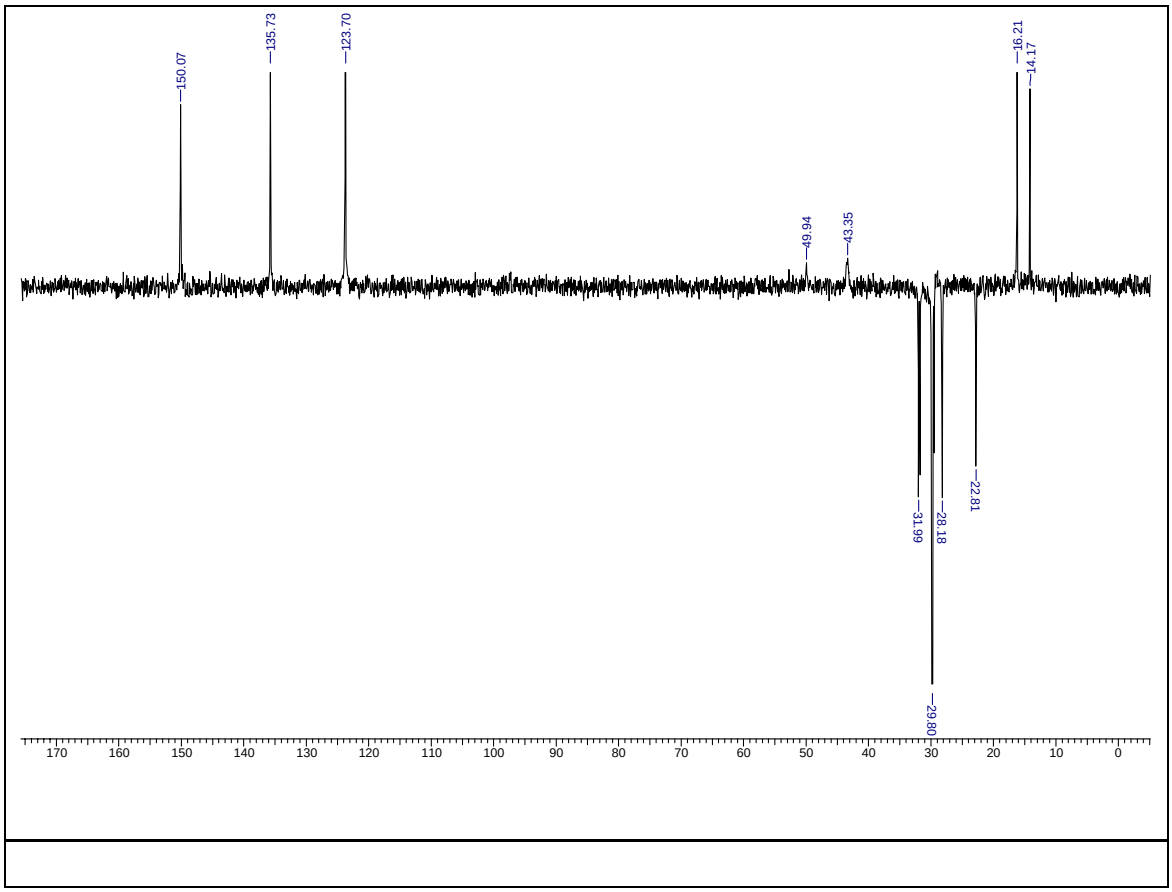

CDCl3, 50 MHz
O
(CH2)11CH3
Ar—N
O
84
Ar = p-Tolyl
179.26
178.41
138.17
129.56
126.11
77.62
77.00
76.38
43.84
31.82
29.51
29.29
27.60
26.49
22.56
20.98
13.92
11.64

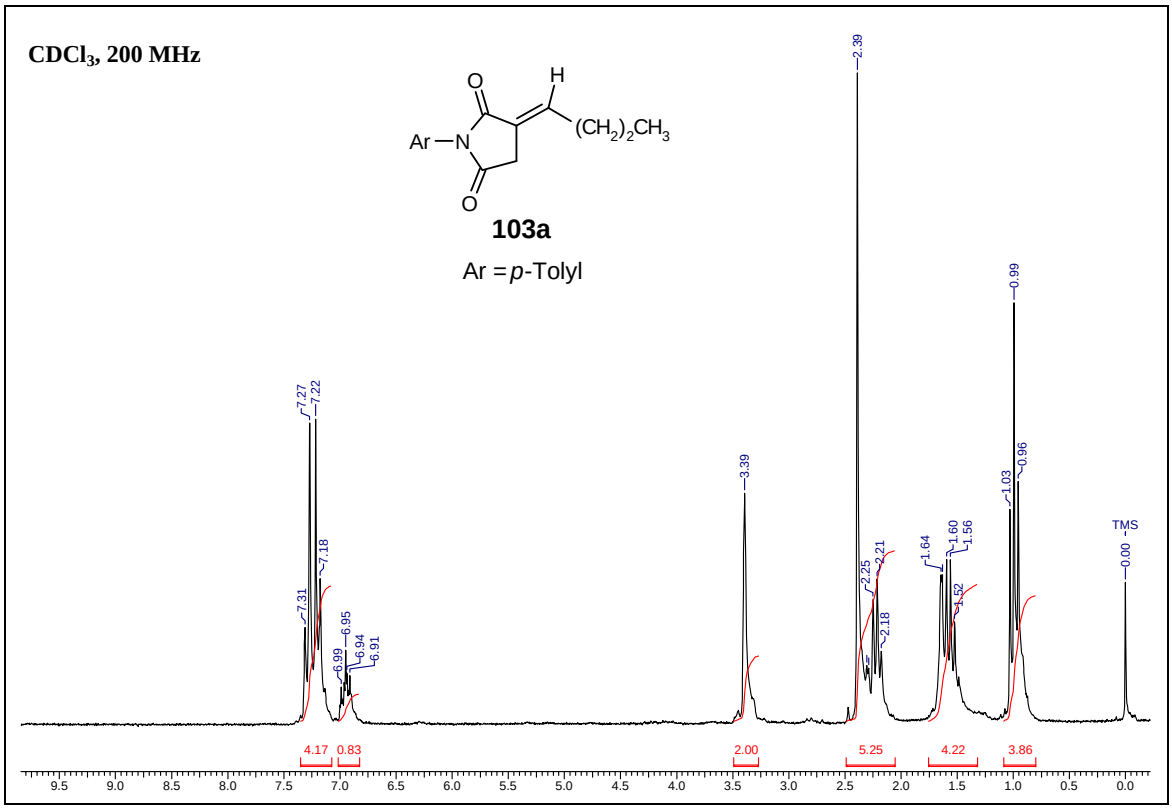

129.52
126.03
43.69
38.36
20.98
13.92
11.64
31.75
27.62
26.34
22.48
29.71
29.43

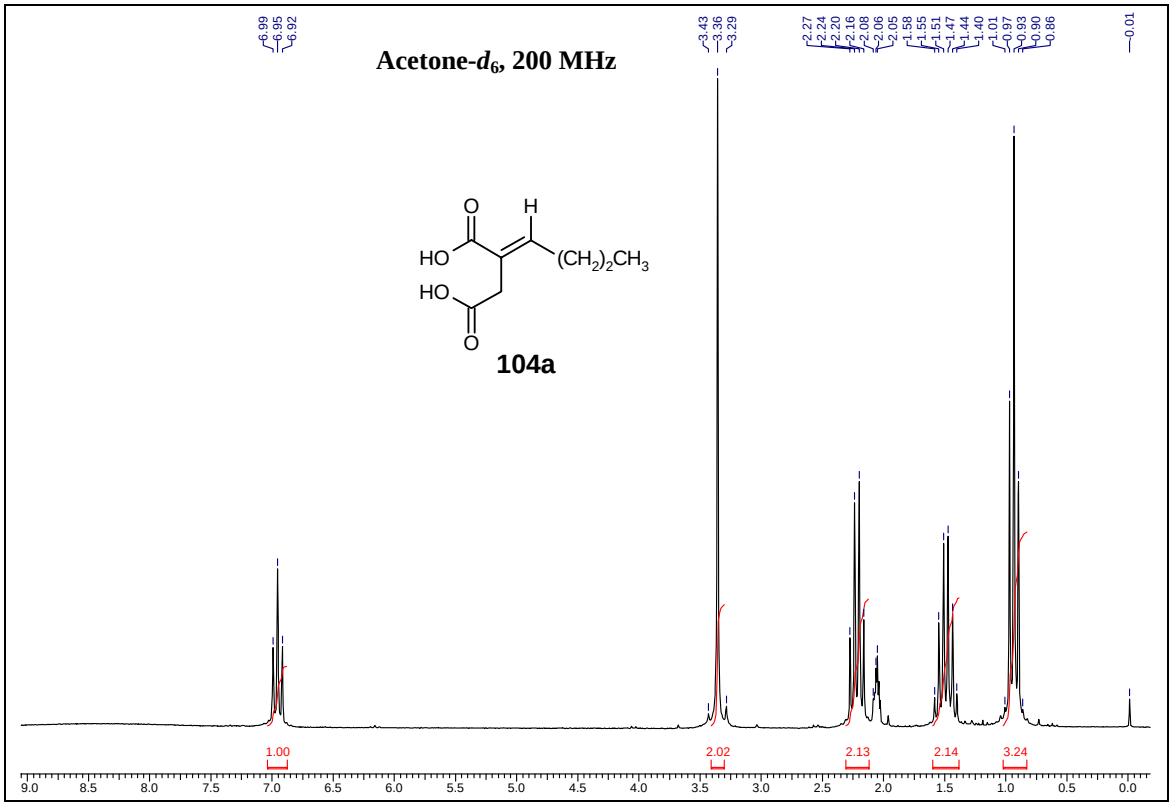

CDCl3, 200 MHz
O
(CH2)11CH3
Ar—N
O
84
Ar = p-Tolyl
1.29
1.33
1.36
2.39
0.91
0.94
0.88
7.30
7.25
7.18
7.14
3.17
3.14
3.09
3.06
3.02
2.99
2.95
2.91
1.85
1.82
1.80
1.71
1.69
1.65
4.23
1.58
3.00
28.67
3.36
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Pyridine- d5, 500 MHz
HO
HO
O
O
(CH2)11CH3
H
H
71
1.20
7.22
7.58
8.73
1.63
1.61
0.86
1.26
0.87
0.85
1.35
1.34
1.37
TMS
0.00
3.29
3.28
3.27
3.25
3.24
3.23
3.21
3.19
2.18
2.17
2.15
1.99
1.98
1.96
1.69
1.68
1.67
1.55
1.54
1.78
0.85
0.92
5.27
18.29
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Pyridine- d_5, 125 MHz
149.99
149.77
149.56
135.67
135.47
135.27
135.76
123.64
123.44
123.25
29.82
177.74
176.96
50.00
43.39
32.02
29.48
28.19
22.83
16.21
14.16
HO
HO
O
O
$(CH_2)_{11}CH_3$
H
H
71


150.07
135.73
123.70
49.94
43.35
16.21
14.17
31.96
28.18
28.80
22.81

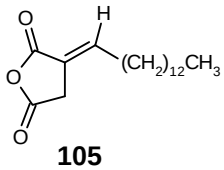

CDCl3, 200 MHz
O
H
Ar—N
(CH2)2CH3
O
103a
Ar = p-Tolyl
7.27
7.22
7.31
7.18
6.99
6.95
6.94
6.91
3.39
2.39
2.25
2.21
2.18
1.64
1.60
1.56
1.52
1.03
0.99
0.96
TMS
0.00
4.17
0.83
2.00
5.25
4.22
3.86


Acetone-d6, 200 MHz
6.99
6.95
6.92
3.43
3.36
3.29
2.27
2.24
2.20
2.16
2.08
2.06
2.05
1.58
1.55
1.51
1.47
1.44
1.40
1.01
0.97
0.93
0.90
0.86
0.01
O
H
HO
(CH2)2CH3
HO
O
104a
1.00
2.02
2.13
2.14
3.24

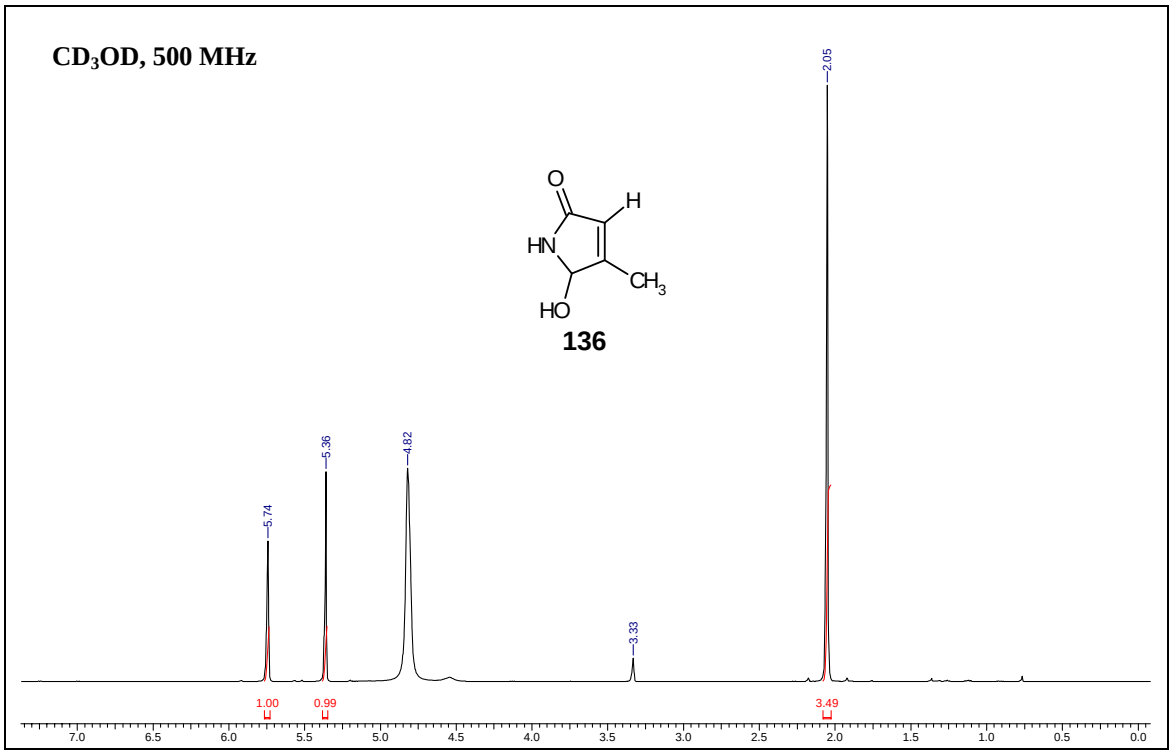
$CDCl_3$ + DMSO-d_6, 200 MHz

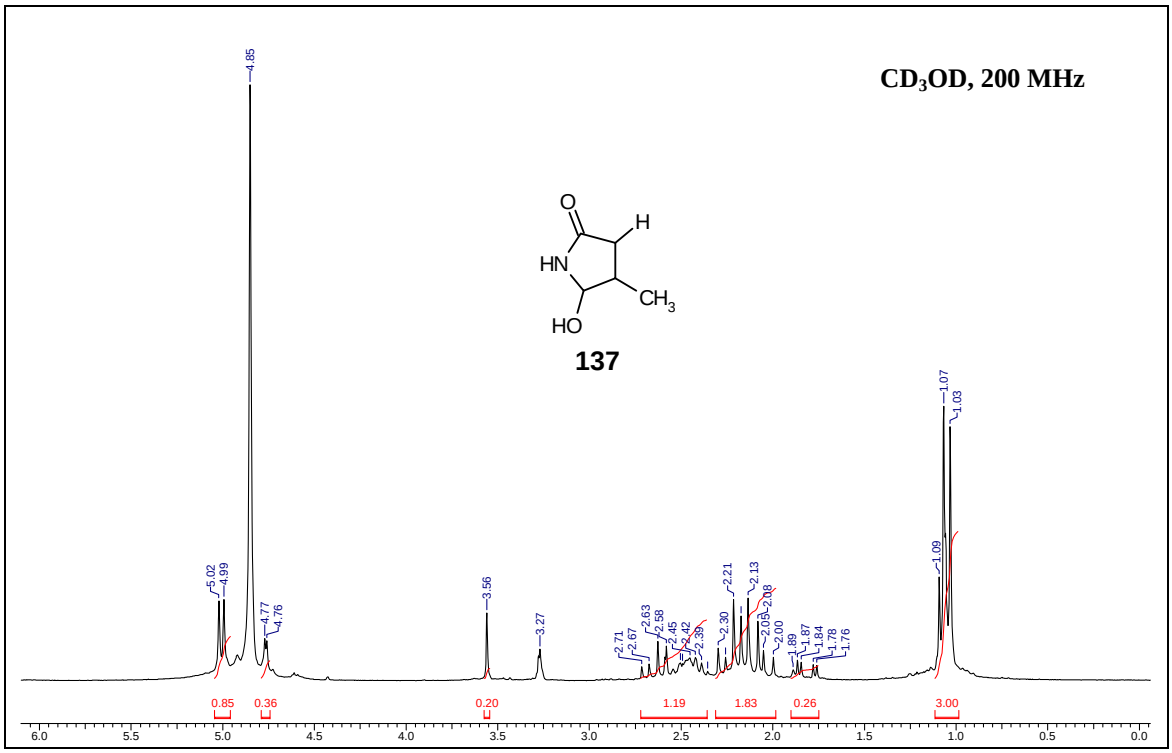
104e

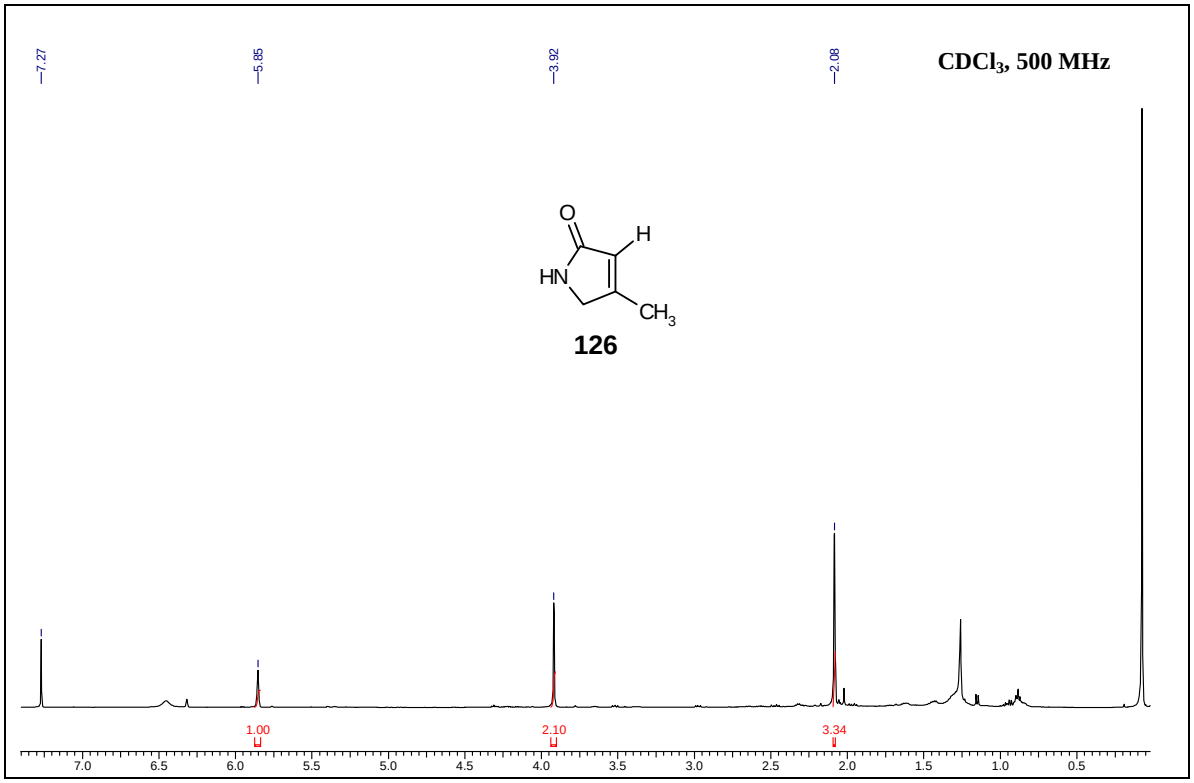
$CDCl_3$, 200 MHz

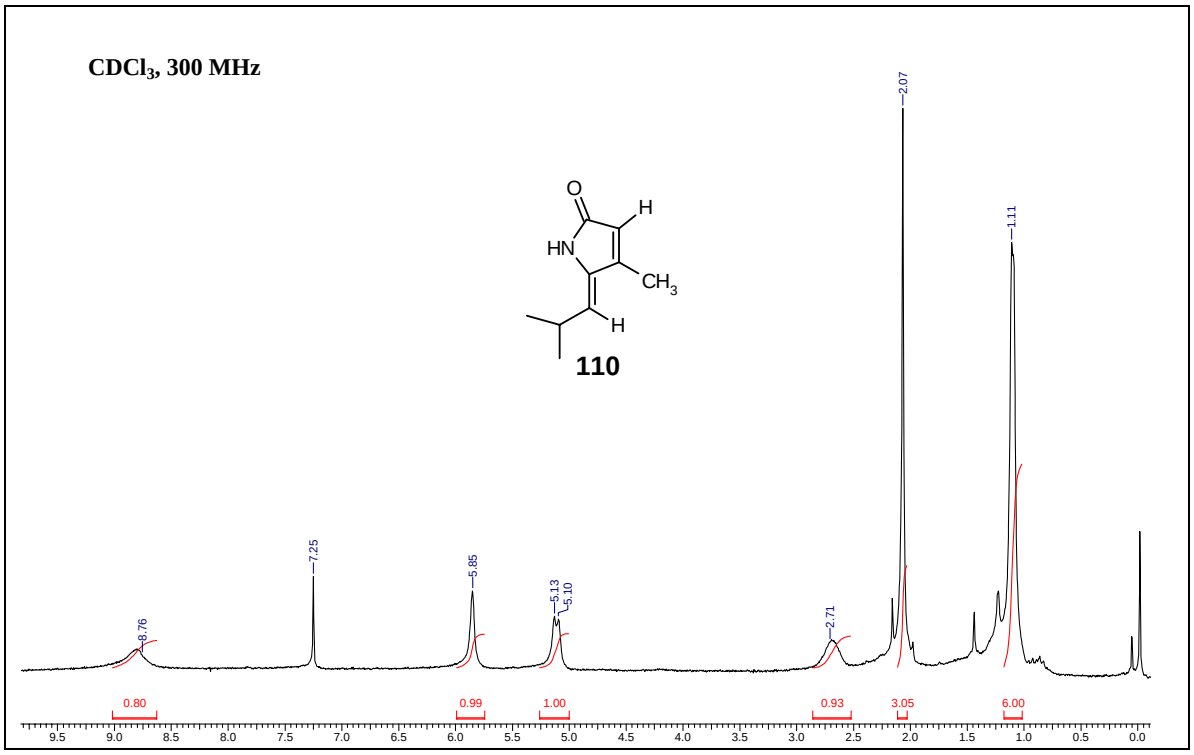


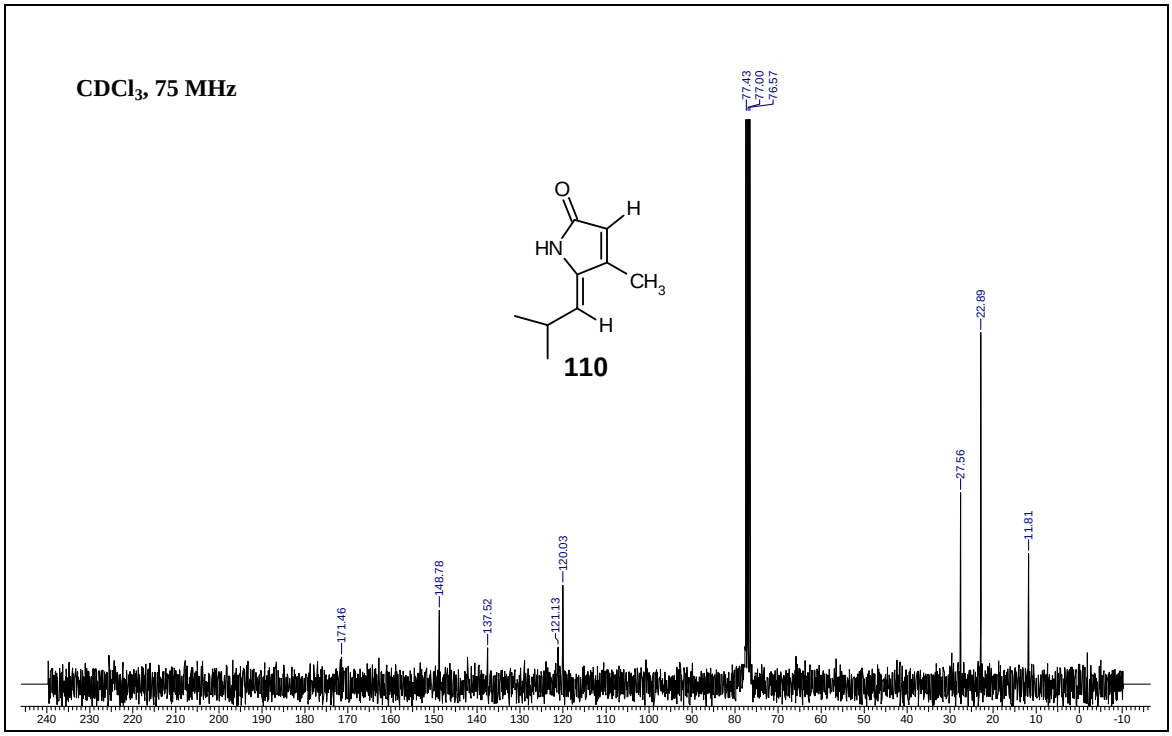
105

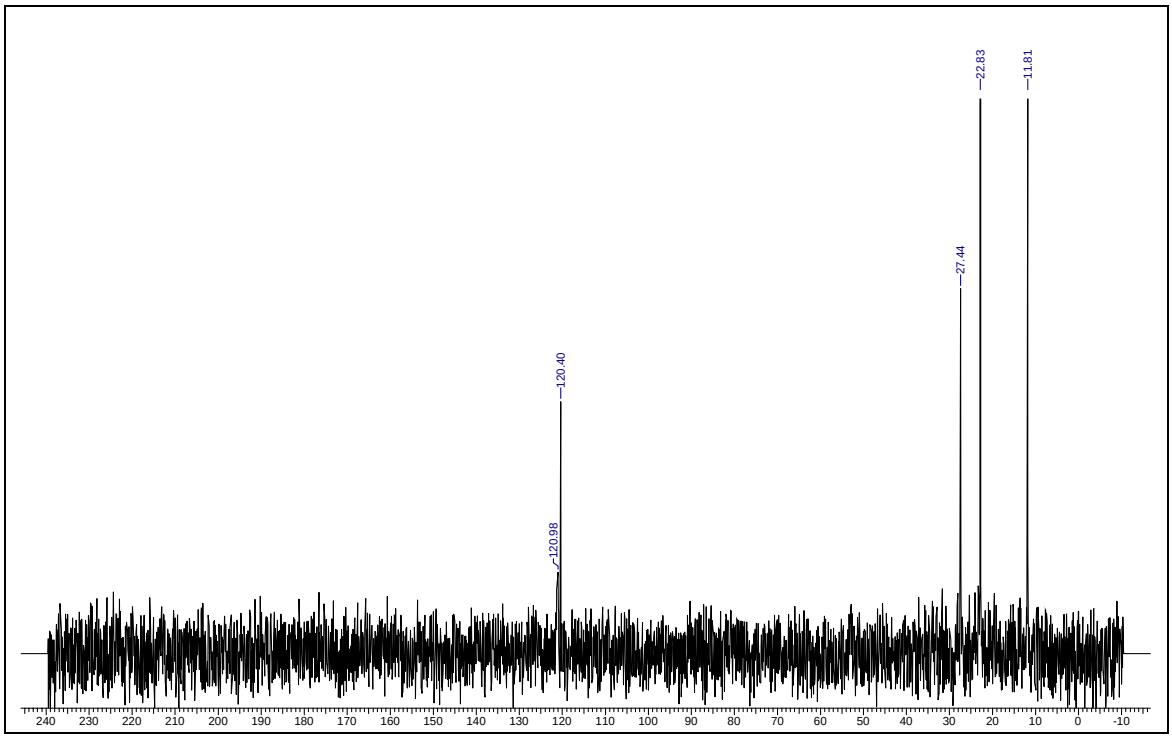

CD3OD, 500 MHz
O
H
HN
CH3
HO
136
2.05
5.74
5.36
4.82
3.33
1.00
0.99
3.49
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


CD3OD, 200 MHz
O
H
HN
CH3
HO
137
4.85
5.02
4.99
4.77
4.76
3.56
3.27
2.71
2.67
2.63
2.58
2.45
2.42
2.39
2.30
2.21
2.13
2.08
2.05
2.00
1.89
1.87
1.84
1.78
1.76
1.09
1.07
1.03
0.85
0.36
0.20
1.19
1.83
0.26
3.00
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


CDCl3, 500 MHz
7.27
5.85
3.92
2.08
O
H
HN
CH3
126
1.00
2.10
3.34


CDCl3, 300 MHz
2.07
1.11
O
H
HN
CH3
H
110
7.25
5.85
5.13
5.10
8.76
2.71
0.80
0.99
1.00
0.93
3.05
6.00


CDCl3, 75 MHz
O
H
HN
CH3
H
110
77.43
77.00
76.57
171.46
148.78
137.52
121.13
120.03
27.56
22.89
11.81
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


22.83
11.81
27.44
120.40
120.98
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

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