# SYNTHESIS OF NATURAL AND UNNATURAL DIALKYL SUBSTITUTED MALEIC ANHYDRIDES AND RELATED NATURAL PRODUCTS

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**NOVEMBER 2008**

# SYNTHESIS OF NATURAL AND UNNATURAL DIALKYL SUBSTITUTED MALEIC UNHYDRIDES AND RELATED NATURAL PRODUCTS

**THESIS**

*SUBMITTED TO THE*

**UNIVERSITY OF PUNE**

*FOR THE DEGREE OF*

**DOCTOR OF PHILOSOPHY**

*IN*

**CHEMISTRY**

*BY*

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**Dedicated to my parents….**

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## CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Synthesis of Natural and Unnatural Dialkyl Substituted Maleic Anhydrides and Related Natural Products***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Kishan P. Haval*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

**November 2008**

**Pune**

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# Candidate's Declaration

I hereby declare that the thesis entitled "***Synthesis of Natural and Unnatural Dialkyl Substituted Maleic Anhydrides and Related Natural Products***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune*** has not been submitted by me for a degree to any other University or Institution. This work was carried out at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India.

**November 2008**

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# *Acknowledgements*

*It gives me great pleasure to express my heartfelt gratitude to my research supervisor Dr. N. P. Argade for his astute guidance, invaluable suggestions and keen criticism while carrying out the present work. His enduring passion, moral support and help out of the way led me to overcome all the difficulties I encountered during this endeavor. I am certain that the guidance and training provided by him laid a foundation for future success.*

*I thank our Head, Division of Organic Chemistry and Director NCL for providing infrastructure facilities. CSIR, New Delhi is acknowledged for financial assistance. I am also thankful to Prof. D. D. Dhavale, Dr. N. N. Joshi, Dr. S. P. Chavan, Dr. P. P. Wadgaonkar, Dr. M. K. Dongare, Dr. A. R. A. S. Deshmukh and Dr. S. S. Bhosale. I thank all DOC students, staff members for their timely help through out. Help rendered by the members of IR, microanalysis, mass spectroscopy, NMR group and library staff members is also acknowledged.*

*I am thankful to my mentors at my School, College and University for their inspirational teaching, ethics and discipline.*

*I was blessed with an opportunity to work in a most united, homogeneous and clean lab. I enjoyed the cheerful co-operation and accompany of my seniors Anil, Mangaleswaran, Santosh, Sunil, Anirban, Easwar, Mukul, Manoj, Mehraj, Sanjib who made me felt like a member of this family right from the day one in the lab. My special thanks to lab-friends Umesh, Ramesh, Prasad, Mandeep, Prashant and Chavan mama for their co-operation and maintaining amazing atmosphere with humor in the lab. The warm memories of my days in Lab-195 will haunt me forever.*

*I am also thankful to my close friends Sudhir, Anil, Kiran, and Ravi for their continuous encouragement, help and whose companionship always kept my mood cheerful and with whom I shared golden moments.*

*My warm thanks are due to my seniors and friends Shriram, Amol, Nagendra, Kulbhushan, Bapu, Namdev, Giri, Arun, Pandu, Ganesh, Deepak, Ankush, Jayanti, Arif, Ajay, Nilesh, Pinak, Panchami, Arup, Gouri, Roshana, Ramesh, Sangram, Madhuri, Bharat, Geetali, Manmat and Ravi for their help whenever I needed. I would like to extend my thanks to Abasaheb, Lalya, Kishor, Nilesh, Mak, Ravi, Bala, Nishant, Amrut, Deepak, Ganesh, Sulake, Vinod and Suleman for their help whenever I needed.*

*I owe my deepest gratitude and affection to Mahesh, Sandeep, Sager, Sachin, Esak, Amol and Shankar who provided me a home away from my home with their affection.*

*No word would be sufficient to express my gratitude and love to my parents and all family members who have contributed and sacrificed a lot for me to reach this stage and will always remain a sole source of inspire in my life to achieve higher goals.*

*Finally, my acknowledgement would not be completed without thanking the God, for giving me the strength and the determination to overcome the hardship faced in my life.*

*Kishan*

# CONTENTS

# 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/230-400 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, *p*-anisaldehyde (in ethanol) and 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/chloroform solution 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 ($\delta$) reported are referred to internal reference tetramethyl silane.
- Mass spectra were recorded on Finnigan-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.
- ***Independent referencing and numbering of compounds, schemes, tables & figures have been employed for Chapter I, all Sections of Chapter II and Chapter III***

# Abbreviations

| | |
|---|---|
| AIBN | 2,2′-Azobisisobutyronitrile |
| Aq. | Aqueous |
| Ar | *p*-Tolyl |
| Cat. | Catalytic |
| 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 |
| DEAD | Diethyl azodicarboxylate |
| DEIPS | Diethylisopropylsilyl |
| DEPT | Distortionless Enhancement by Polarization Transfer |
| DHF | Dihydrofuran |
| DHP | Dihydropyran |
| DIAD | Diisopropyl azodicarboxylate |
| DIBAL-H | Diisobutylaluminium hydride |
| DMAP | 4-(Dimethylamino)pyridine |
| DMF | Dimethylformamide |
| DMMA | Dimethylmaleic anhydride |
| DMP | Dess-Martin Periodinane |
| DMPU | 1,3-Dimethyl-3, 4, 5, 6-tetrahydro-2(1*H*)-pyrimidinone |
| DMSO | Dimethyl sulphoxide |
| EDC/EDCI | 1-Ethyl-3-(3-(dimethylaminopropyl)carbodiimide/1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride |
| ee | Enantiomeric excess |

| | |
|---|---|
| equiv. | Equivalent(s) |
| GC | Gas Chromatography |
| h | Hour(s) |
| HMDS | Hexamethyldisilazane |
| HMPA | Hexamethylphosphoramide |
| HMBC | Heteronuclear Multiple Bond Correlation |
| HMQC | Heteronuclear Multiple Quantum Coherence |
| HPLC | High Performance Liquid Chromatography |
| Hz | Hertz |
| IC | Inhibitory concentration |
| IR | Infra Red |
| LAH | Lithium aluminum hydride |
| LDA | Lithium diisopropylamide |
| *m*-CPBA | *m*-Chloroperbenzoic acid |
| min. | Minute(s) |
| mL | Millilitre(s) |
| mmol | Millimole(s) |
| Mp | Melting point |
| MS | Mass Spectrum |
| MsCl | Methanesulfonyl chloride |
| MTPA | $\alpha$-Methoxy-$\alpha$-trifluoromethylphenylacetic acid (Mosher's acid) |
| NBS | *N*-Bromosuccinimide |
| NBSH | *o*-Nitrobenzenesulfonylhydrazine |
| NMO | *N*-Methylmorpholine-*N*-oxide |
| NMP | *N*-Methyl pyrollidone |

| | |
|---|---|
| NMR | Nuclear Magnetic Resonance |
| PCC | Pyridinium chlorochromate |
| PLE | Porcine Liver Esterase |
| PMB | *p*-Methoxybenzyl |
| PPTS | Pyridinium *p*-toluenesulfonate |
| *p*-TSA | *p*-Toluenesulfonic acid |
| *p*-TsCl | *p*-Toluenesulfonyl chloride |
| Py | Pyridine |
| rt | Room temperature |
| TBAF | Tetrabutylammonium fluoride |
| TBDMS / TBS | *t*-Butyldimethylsilyl |
| TEA | Triethylamine |
| TESCl | Triethylsilyl chloride |
| THF | Tetrahydrofuran |
| THP | Tetrahydropyranyl |
| TIPS | Triisopropylsilyl |
| TMEDA | *N*, *N*, *N*', *N*'-Tetramethylethylenediamine |
| TMSCl | Trimethylchlorosilane |
| TMSOTf | Trimethylsilyl trifluoromethanesulfonate |
| TPP | Triphenylphosphine |
| UV | Ultraviolet |

| | |
|---|---|
| **Research Student** | Kishan P. Haval |
| **Research Guide** | Dr. N. P. Argade |
| **Title of the thesis** | *Synthesis of Natural and Unnatural Dialkyl Substituted Maleic Anhydrides and Related Natural Products* |
| **Registration No.** | EI/171/Ph.D/2006 Dated July 5, 2006 |
| **Date of Registration** | 24.12.2004 |
| **Place of work** | Division of Organic Chemistry, National Chemical Laboratory, Pune 411 008 |

## Abstract

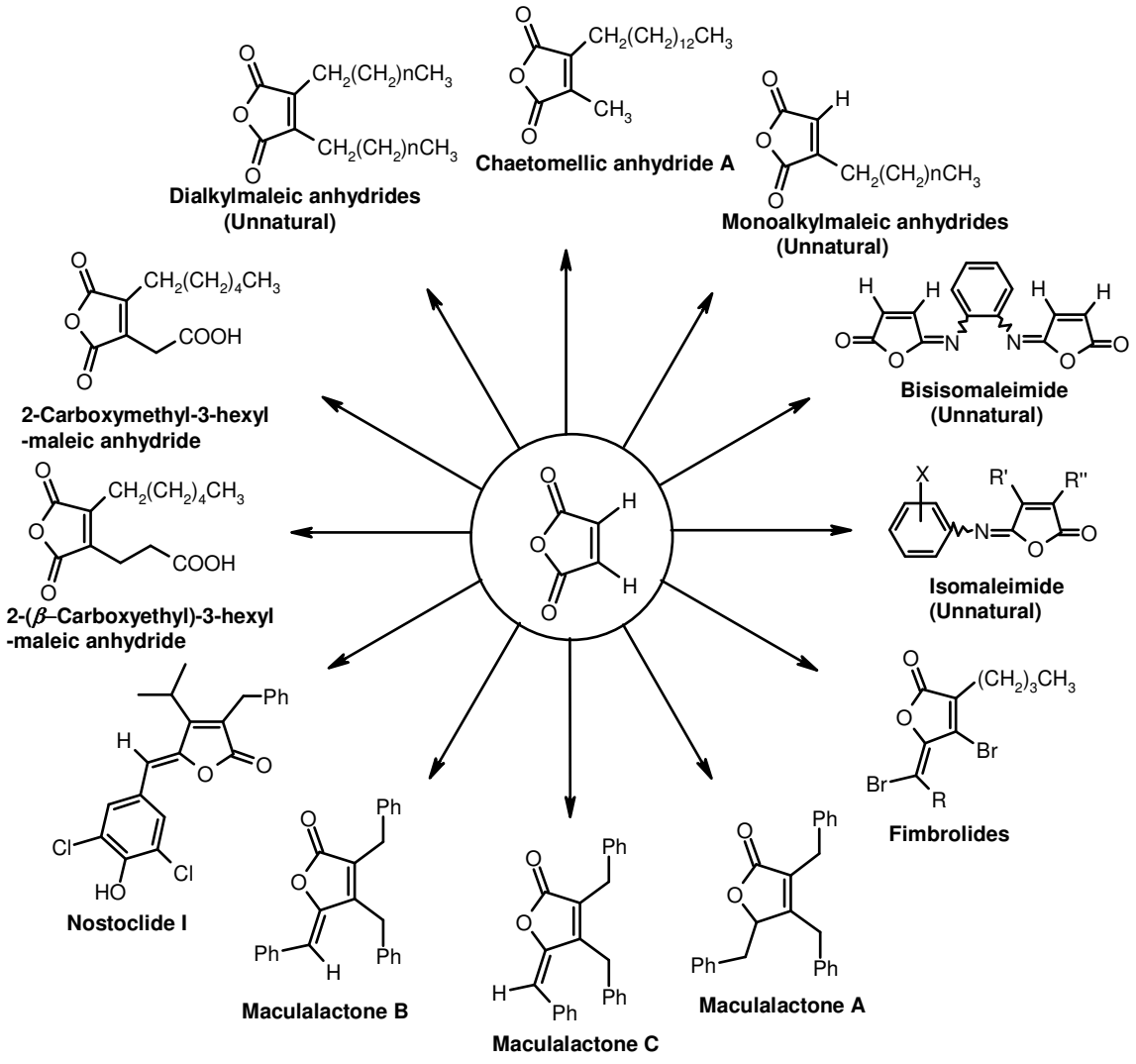



**Figure 1.** Natural and Unnatural Products Synthesized from Maleic Anhydride

The present dissertation is divided into three chapters. The first chapter presents a concise account on chemistry of monoalkyl substituted, dialkyl substituted and complex dialkyl substituted maleic anhydrides. In the second chapter, a facile general approach to kinetically controlled isomaleimides followed by a simple and efficient approach to alkyl and dialkyl substituted maleimides have been described via the new contrathermodynamic rearrangement of (*E*)-alkylidenesuccinimides to alkylmaleimides. Also, synthesis of two natural fimbrolides has been reported via the synthesis of requisite butylmaleic anhydride, its regioselective Grignard coupling reaction, and a bromination-dehydrobromination pathway. Third chapter describes a general approach for synthesis of bioactive natural products chaetomellic anhydride A, 2-carboxymethyl-3-hexylmaleic anhydride, 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride, maculalactones A-C, nostoclide I and unnatural dialkyl substituted maleic anhydrides followed Wittig reaction of maleimide/citraconimide and triphenylphosphine adduct with dihdrofuran/dihydropyran. Finally, our on going study towards the synthesis of natural product byssochlamic acid has been described. For the purpose of simplification, independent numbering system is used for each section (e.g. scheme, table, figure, compound and reference numbers).

**Chapter One: A Concise Account on the Chemistry of Monoalkyl Substituted, Dialkyl Substituted and Complex Dialkyl Substituted Maleic Anhydrides**

This chapter is divided into four sections.

**1.1 Introduction**

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. This section portrays a concise account on maleic anhydrides and synthetic utility of methyl, dimethyl and substituted maleic anhydrides.

**1.2 Monoalkyl Substituted Maleic Anhydrides**

This section describes the synthetic approaches reported in the literature towards the synthesis of methylmaleic anhydride and alkylmaleic anhydrides.

**1.3 Dialkyl Substituted Maleic Anhydrides**

This section summarizes complete details concerning the synthetic efforts towards dialkyl substituted natural and unnatural maleic anhydride derivatives.

**1.4 Complex Dialkyl Substituted 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. 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 substituents. Isolation, biological activity and synthesis of some of these naturally occurring nonadrides have been described in this section.

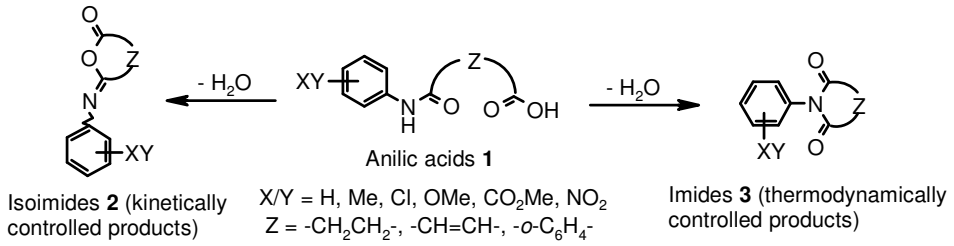
**Chapter Two: Synthesis of Isomaleimides, Alkyl and Dialkyl Substituted Maleimides and Natural Fimbrolides**

This Chapter is divided into three sections.

**Section A: Cyanuric Chloride: Decent Dehydrating Agent for an Exclusive and Efficient Synthesis of Kinetically Controlled Isomaleimides**

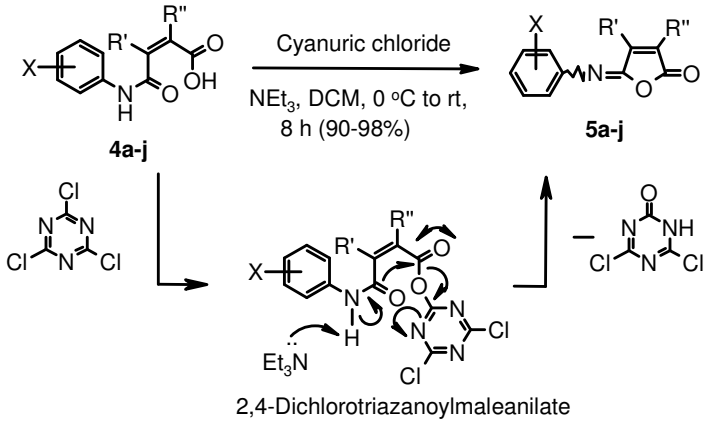
Anilic acids on dehydration under kinetically controlled conditions form isoimides while under thermodynamically controlled conditions they furnish the corresponding imides (Scheme 1).

**Scheme 1**




We performed the reaction of *N*-phenylmaleanilic acid (**4a**) in DCM with cyanuric chloride (1.1 equiv.) in the presence of triethylamine (3.0 equiv.) at room temperature and exclusively obtained the corresponding *N*-phenylisomaleimide (**5a**) in 90% yield (Scheme 2). To establish the generality of this new set of reaction conditions, we prepared several maleanilic acids **4b**-**j** and all of them on treatment with cyanuric chloride furnished exclusively the corresponding desired *N*-arylisomaleimides **5b**-**j** in 90-98% yields.

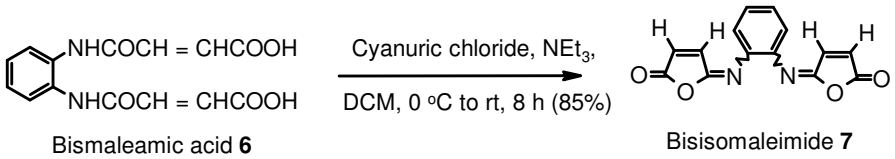
**Scheme 2**



| Sr. No. | Acid | X | R' | R'' | Product (%) |
|---|---|---|---|---|---|
| 1. | **4a** | H | H | H | **5a** (90) |
| 2. | **4b** | *o*-$CH_3$ | H | H | **5b** (98) |
| 3. | **4c** | *p*-$CH_3$ | H | H | **5c** (93) |
| 4. | **4d** | *o*-$OCH_3$ | H | H | **5d** (90) |
| 5. | **4e** | *p*-$OCH_3$ | H | H | **5e** (91) |
| 6. | **4f** | *p*-Cl | H | H | **5f** (93) |
| 7. | **4g** | *o*-$CO_2CH_3$ | H | H | **5g** (94) |
| 8. | **4h** | H | H | $CH_3$ | **5h** (97) |
| 9. | **4i** | *p*-$CH_3$ | H | $CH_3$ | **5i** (90) |
| 10. | **4j** | *p*-$CH_3$ | Ph | H | **5j** (95) |

The diacid **6** on treatment with cyanuric chloride (2.2 equiv.) also smoothly furnished the bis-isomaleimide **7** in 85% yield (Scheme 3).

**Scheme 3**




Bismaleamic acid **6** Bisisomaleimide **7**

The treatment of *o*-nitromaleanilic acid with cyanuric chloride exclusively gave the corresponding *o*-nitroisomaleimide in 94% yield, while *m*-nitromaleanilic acid and *p*-nitromaleanilic acid under the same set of reaction conditions gave only the corresponding nitromaleimides in quantitative yields. The reaction of cyanuric chloride with maleamic acids also gave the corresponding *N*-alkylisomaleimides in 85-96% yields indicating that the present kinetic dehydration condition works equally well with maleamic acids to design *N*-alkylisomaleimides in very good yields. We studied the dehydration reactions of phthalanilic acid and succinanilic acid using cyanuric chloride as a dehydrating agent under the same set of reaction conditions. The phthalianilic acid furnished the desired isophthalimide in 91% yield, while the succianilic acid gave exclusively the corresponding succinimide in 92% yield.

This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

**<u>Section B</u>: Contrathermodynamic Rearrangement of Alkylidenesuccinimides to Alkylmaleimides via the Corresponding Isoimides: A General Approach to Alkyl and Dialkyl Substituted Maleimides**

The formation of maleimide-triphenylphosphine adduct is well known (Figure 1) and we felt that the stepwise activation of two vinylic protons in maleimide as Wittig adducts would provide an efficient approach to alkylmaleimides and dialkylmaleimides. The conversion of alkylidenesuccinimdes to alkylmaleimides is a difficult process due extra stability of carbon-carbon double bond with (*E*)-geometry. We planned with reason and decided to alter the imide dicarbonyl symmetry of alkylidenesuccinimide for such type of double bond migrations. A simple and efficient access to alkyl and dialkyl substituted maleimides has been demonstrated via the new contrathermodynamic rearrangement of (*E*)-alkylidenesuccinimides to alkylmaleimides. The (*E*)-alkylidenesuccinimides obtained from the Wittig-condensation of *N*-arylmaleimide with aliphatic aldehydes on regioselective hydrolysis furnished the corresponding (*E*)-alkylidenesuccinanilic acids in 95-98% yields. The $\beta$-alkylidenesuccinanilic acids on treatment with cyanuric chloride in the presence of triethylamine gave the corresponding $\beta$-alkylisomaleimides in 78-80% yields via the $\beta$-alkylideneisosuccinimides with the exocyclic to endocyclic carbon-carbon double bond migration.

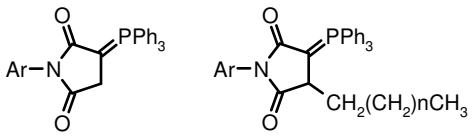
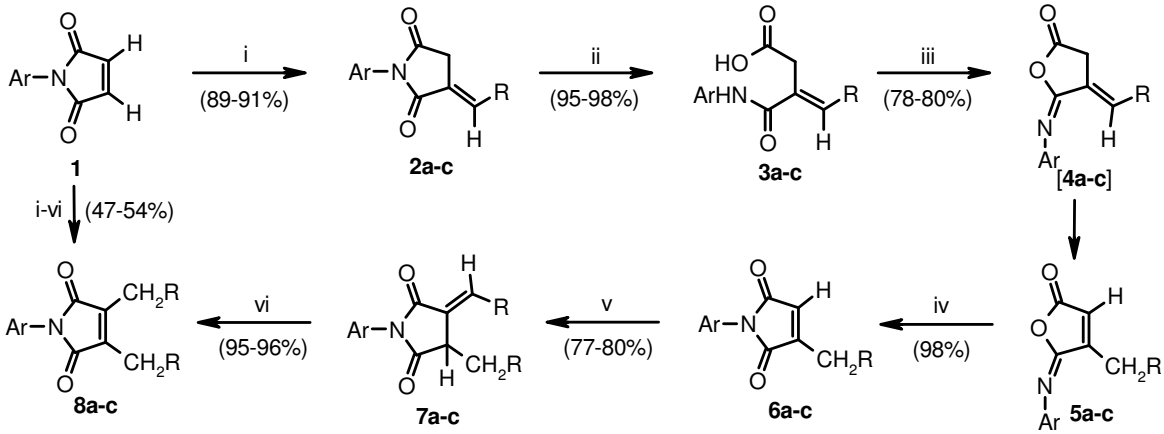



**Figure 1.** Triphenylphosphine and maleimide adducts (Wittig adducts)

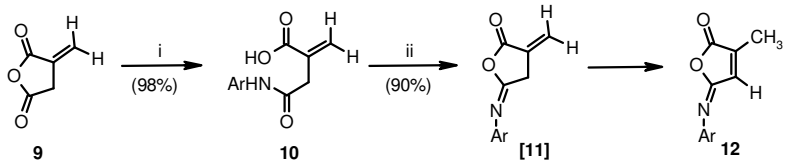



Ar = *p*-Tolyl; **a**, R = -$CH_2(CH_2)_3CH_3$; **b**, R = -$CH_2(CH_2)_7CH_3$; **c**, R = -$CH_2(CH_2)_{11}CH_3$

**Scheme 1.** *Reagents, conditions and yields*: (i) $PPh_3$, THF, RCHO, reflux, 10 h (89-91%); (ii) Aq. 2 N LiOH, THF, 0 $^oC$ to rt, 5 h, (95-98%); (iii) Cyanuric chloride, $NEt_3$, DCM, 0 $^oC$ to rt, 8 h (78-80%); (iv) AcOH, reflux, 5 h (98%); (v) $PPh_3$, AcOH, RCHO, reflux, 18 h (77-80%); (vi) $NEt_3$ + THF (1:1), reflux, 48 h (95-96%).

| Comp. No. | **2a** | **2b** | **2c** | **3a** | **3b** | **3c** | **5a** | **5b** | **5c** | **6a** | **6b** | **6c** | **7a** | **7b** | **7c** | **8a** | **8b** | **8c** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % Yield | 91 | 89 | 89 | 98 | 96 | 95 | 80 | 78 | 78 | 98 | 98 | 98 | 80 | 78 | 77 | 96 | 95 | 95 |

The kinetically controlled products alkylisomaleimides in refluxing acetic acid furnished the thermodynamically controlled alkylmaleimides in 98% yield. The second Wittig condensation of alkyl substituted isomaleimides/maleimides with aliphatic aldehydes gave the desired dialkyl substituted maleimides in high yields (Scheme 1).



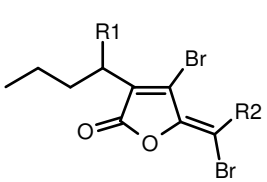

**Scheme 2.** *Reagents, conditions and yields*: (i) $Et_2O$, $ArNH_2$, rt, 1 h (98%); (ii) Cyanuric chloride, $NEt_3$, DCM, 0 $^oC$ to rt, 8 h (90%).

In the present strategy, we have proved that the $\alpha$-protons on the unisolable intermediate alkylideneisosuccinimides **4** are accessible for such type of rearrangements. We planned to verify the accessibility of the corresponding $\beta$-protons in $\alpha$-alkylideneisosuccinimides. The treatment of acid **10** with cyanuric chloride in the presence of triethylamine also gave $\alpha$-methylisomaleimide **12** in 90% yield, proving that $\beta$-methylene protons in intermediate **11** can also be abstracted in a similar fashion for such type of exo-endo framework rearrangements (Scheme 2).

This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

## Section C: Synthesis of Natural Fimbrolides

Fimbrolides (**1**) have been isolated from the red marine algae *Delisea fimbriata* and are bromobutenolides with interesting antifungal and antimicrobial properties. Pulchralides (**2**) appear to be the [2+2] cycloadducts of the fimbrolides (**1**) and they have been isolated from *Antarctic macroalgae* (Figure 1).

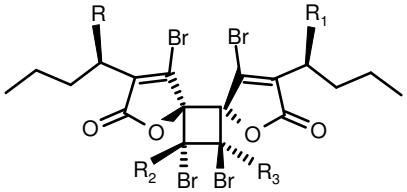


Fimbrolide (**1a**): $R_1 = R_2 = H$

Fimbrolide (**1b**): $R_1 = H$, $R_2 = Br$

Acetoxyfimbrolide (**1c**): $R_1 = OAc$, $R_2 = H$

Hydroxyfimbrolide (**1d**): $R_1 = OH$, $R_2 = H$



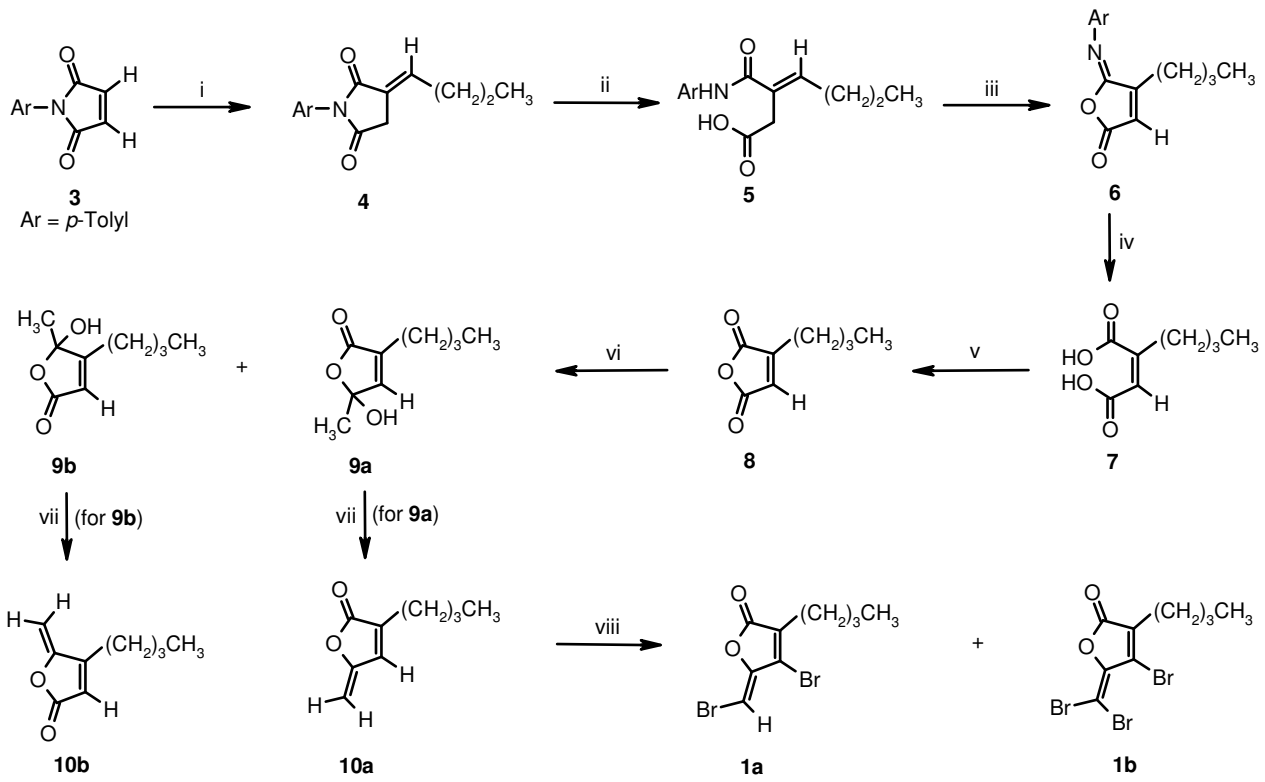
Pulchralide A (**2a**): $R = R_1 = OAc$, $R_2 = R_3 = H$

Pulchralide B (**2b**): $R = R_1 = R_2 = R_3 = H$

Pulchralide C (**2c**): $R = OAc$, $R_1 = R_2 = R_3 = H$

**Figure 1.** Fimbrolides and Pulchralides

Starting from *N*-(4-tolyl)maleimide, an eight-step synthesis of two natural fimbrolides have been reported in good yields via the synthesis of requisite butylmaleic anhydride, its regioselective Grignard coupling reaction and a bromination-dehydrobromination pathway (Scheme 1).




**Scheme 1.** *Reagents*, *conditions and yields*: (i) $PPh_3$ (1.00 equiv.), THF, $CH_3(CH_2)_2CHO$ (1.50 equiv.), reflux, 10 h (90%); (ii) Aq. 2 N LiOH, THF, 0 $^oC$ to rt, 5 h (93%); (iii) Cyanuric chloride (1.10 equiv.), $NEt_3$ (3.00 equiv.), DCM, 0 $^oC$ to rt, 8 h (85%); (iv) HCl:AcOH (1:1), reflux, 66 h (96%); (v) Acetic anhydride, 60 $^oC$, 3 h (90%); (vi) $CH_3MgI$ (1.10 equiv.), $Et_2O$, –20 $^oC$, 2 h (**9a**: 62%, **9b**: 9%); (vii) $P_2O_5$, benzene, reflux, 5 h (**10a**: 90%, **10b**: 87%); (viii) (a) $Br_2$ (2.20/3.30 equiv.), $CCl_4$, 0 $^oC$ to rt, 10 h, (b) $NEt_3$ (2.20/3.30 equiv.), $CHCl_3$, 0 $^oC$ to rt, 5 h (**1a**: 37/15%, **1b**: 15/41%).

This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

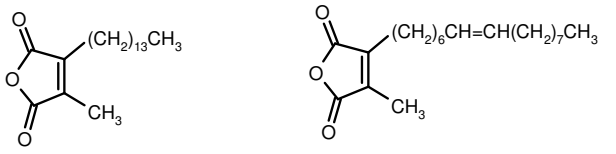
## <u>Chapter Three</u>: A General Approach to Natural and Unnatural Dialkyl Substituted Maleic Anhydrides and Related Natural Products

This Chapter is divided into four sections.

### <u>Section A</u>: Synthesis of Bioactive Natural Product Chaetomellic Anhydride A

Chaetomellic anhydride A (**1**) and chaetomellic anhydride B (**2**) have been isolated from fermentation extract of the coleomycete *Chaetomella acutiseta* (Figure 1). They have been

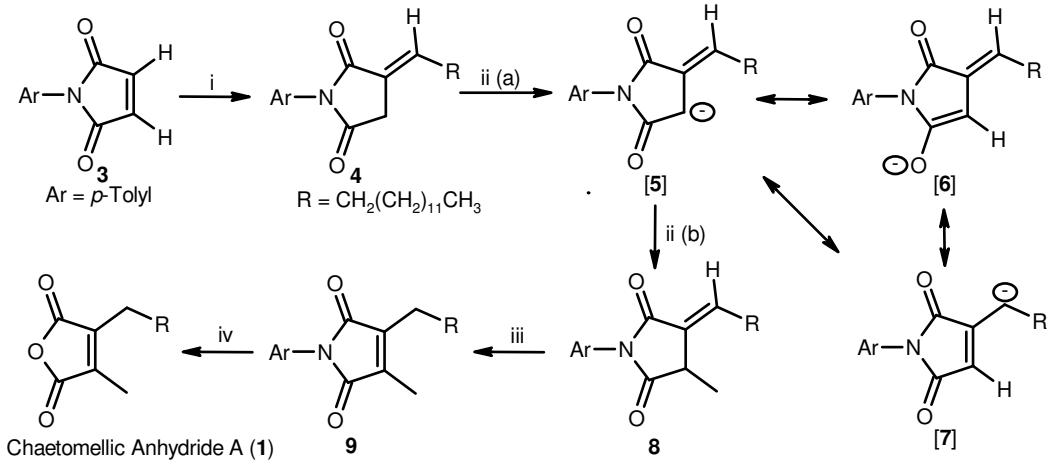
identified as potent inhibitors of ras farnesyl-protein transferase. After its isolation in 1993, in the past fifteen years eleven syntheses have been reported.



Chaetomellic Anhydride A (**1**) Chaetomellic Anhydride B (**2**)

**Figure 1**

Wittig reaction of *N*-*p*-tolylmaleimide (**3**) and triphenylphosphine adduct with tetradecylaldehyde furnished (*E*)-tetrdecylidenesuccinimide (**4**) in 89% yield. (*E*)-Tetrdecylidenesuccinimide (**4**) on treatment with an equivalent amount of sodium hydride in THF at 0 $^{o}$C turned into a deep red colored solution, indicating the formation of the carbanion. The reaction of the above carbanionic solution with methyl iodide at 0 $^{o}$C, exclusively furnished the desired ring mono-alkylated product **8** in 65% yield. With the introduction of methyl substituent on **4** to form **8**, the trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond isomerzation became feasible on treatment of **8** with triethylamine to obtain **9** in 90% yield. The dialkyl substituted maleimide **9** on base catalyzed hydrolysis followed by acidification, furnished chaetomellic anhydride A (**1**) in 91% yield (Scheme 1).

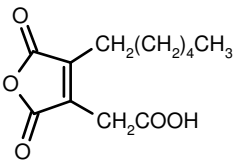


**Scheme 1**. *Reagents*, *conditions and yields*: (i) $Ph_3P$ (1.00 equiv.), $CH_3(CH_2)_{12}CHO$ (1.50 equiv.), THF, reflux, 10 h (89%); (ii) (a) NaH (1.00 equiv.), THF, 0 °C, 0.5 h, (b) $CH_3I$ (1.00 equiv.), 0 °C – rt, 3 h (65%); (iii) $Et_3N$ + THF (1:1), reflux, 48 h (90%); (iv) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (91%).

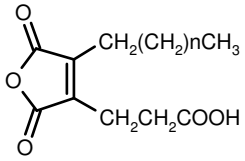
This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

**<u>Section B</u>: A General Approach to Bioactive Natural Products 2-Carboxymethyl-3-hexylmaleic Anhydride and 2-(*β*-Carboxyethyl)-3-hexylmaleic Anhydride**

2-Carboxymethyl-3-hexylmaleic anhydride (**1**) has been isolated as a novel metabolite of the *Aspergillus* FH-X-213 from an apple (Figure 1). It has been reported to show a weak in vitro activity against grampositive bacteria. The biotransformation of stearic acid with a microbial strain isolated from soil, *Pseudomonas cepacica* A-1419, produced two new maleic anhydride derivatives 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride (**2a**) and 2-(*β*-carboxyethyl)-3-octylmaleic anhydride (**2b**). The biological role of these compounds has not been examined. Three synthetic approaches towards these tricarboxylic acid anhydrides have been reported in the literature.



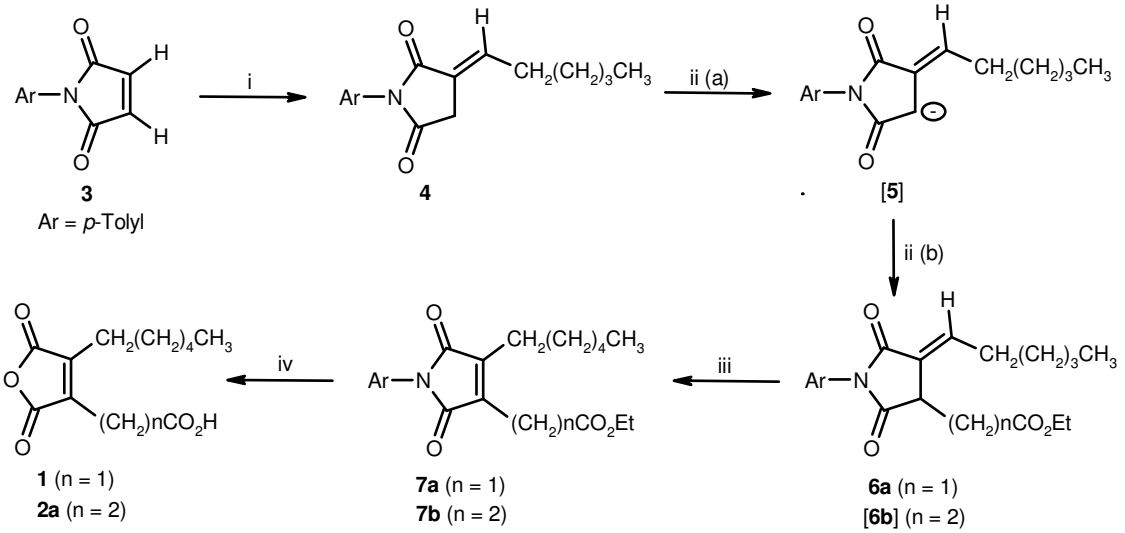

2-Carboxymethyl-3-hexyl-maleic anhydride (**1**)




2-(*β*-Carboxyethyl)-3-alkylmaleic anhydrides (**2a**/**b**, n = 4/6)

**Figure 1**

We planned the synthesis of these bioactive natural products by employing Wittig reaction *N*-*p*-tolylmaleimide (**3**) and triphenylphosphine adduct with caproaldehyde (hexanal) to furnish the (*E*)-hexylidenesuccinimide **4** in 89% yield. The (*E*)-hexylidenesuccinimide **4** was treated with an equivalent amount of sodium hydride in THF at 0 °C and to it was added activated alkyl halides at 0 °C, which exclusively furnished corresponding desired ring mono-alkylated product **6a** in 70% yield. It was difficult to obtain pure product **6b** as both the starting material **4** and the product **6b** were having the same $R_f$ value. With the introduction of alkyl substituents on **4** to form **6a** and **6b**, the trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond isomerization became feasible on treatment of **6a** and **6b** with triethylamine to obtain **7a** (92% yield) and **7b** (70% yield), respectively. The dialkyl substituted maleimide **7a** and **7b** on base catalyzed hydrolysis followed by acidification, furnished the bioactive natural products 2-carboxymethyl-3-hexylmaleic anhydride (**1**, 88% yield) and 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride (**2a**, 85% yield), respectively (Scheme 1).




**Scheme 1**. *Reagents*, *conditions and yields*: (i) $Ph_3P$ (1.00 equiv.), $CH_3(CH_2)_4CHO$ (1.50 equiv.), THF, reflux, 10 h (91%); (ii) (a) NaH (1.00 equiv.), THF, 0 °C, 0.5 h, (b) $EtO_2C(CH_2)_nBr$ (1.00 equiv.), 0 °C – rt, 3 h (70%); (iii) $Et_3N$ + THF (1:1), reflux, 48 h (70-92%); (iv) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (85-88%).

This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

## Section C: Formal Synthesis of Bioactive Natural Products Maculalactones A-C and Nostoclide I

Maculalactones A-C (**1-3**) (Figure 1) were isolated from cyanobacterium *Kyrtuthrix maculans* from Hong Kong island and they possess marine anti-fouling activity. Nostoclide I (**4**) and nostoclide II (**5**) was isolated from the lichen *Peltigera canina* and they possess cytotoxic activity. These butyrolactones were previously synthesized via Stobbe condensation, conversion of furan to the required lactone, Stille coupling reaction, and $S_N2'$ Grignard coupling reactions.

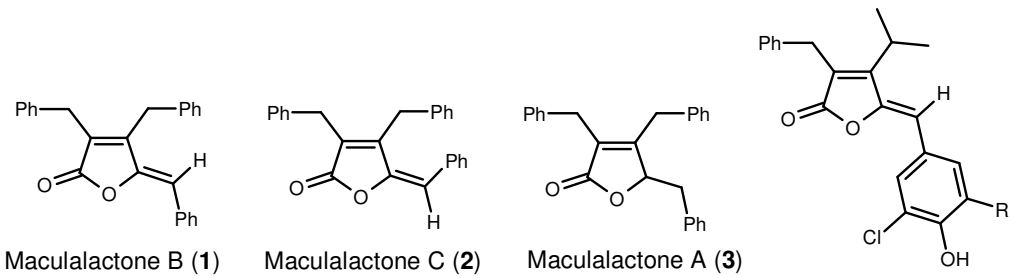
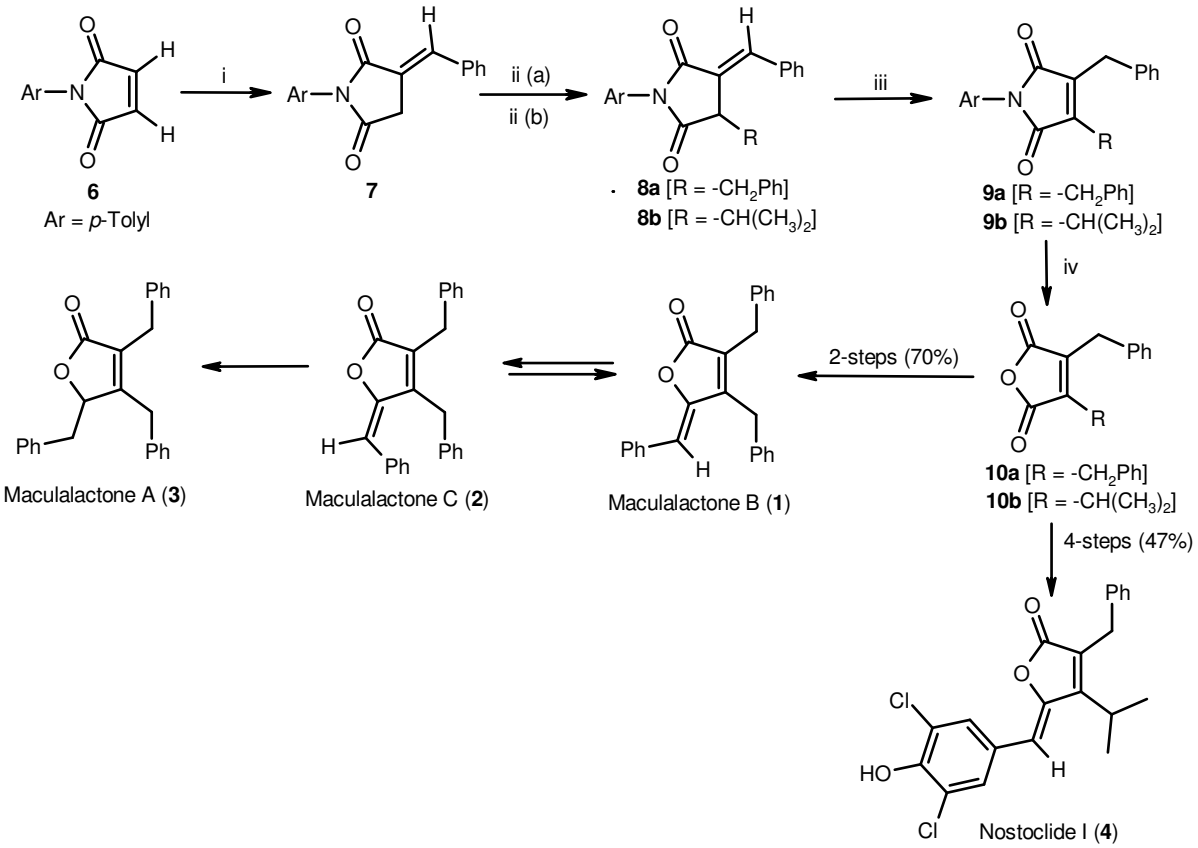



**Figure 1**

The Wittig reaction of *N*-*p*-tolylmaleimide (**6**) and triphenylphosphine adduct with benzaldehyde gave (*E*)-benzylidenesuccinimide **7** in 93% yield. The (*E*)-benzylidenesuccinimide **7** on treatment with an equivalent amount of sodium hydride in THF at 0 $^{o}$C and added benzyl bromide/isopropyl iodide at 0 $^{o}$C, exclusively furnished the desired ring mono-benzylated/alkylated products **8a** (87% yield) and **8b** (92% yield), respectively. Trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond isomerization of **8a** and **8b** was carried out by using triethylamine to obtain dibenzyl substituted maleimide **9a** (94% yield) and benzylisopropyl substituted maleimide **9b** (98% yield), respectively. The dibenzyl substituted maleimide **9a** and benzylisopropyl substituted maleimide **9b** on base catalyzed hydrolysis followed by acidification, furnished the desired dibenzylmaleic anhydride **10a** (97% yield) and benzylisopropylmaleic anhydride **10b** (94% yield), respectively (Scheme 1). The formal synthesis of naturally occurring maculactones A-C (**1**-**3**) from dibenzylmaleic anhydride **10a** and nostoclide I (**4**) from isopropylbenzylmaleic anhydride **10b** is known in literature.



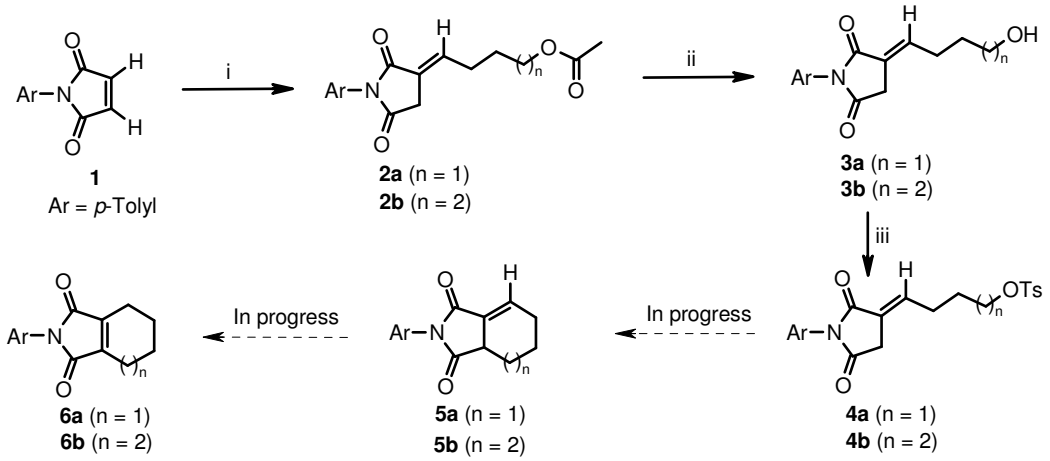

**Scheme 1**. *Reagents*, *conditions and yields*: (i) $Ph_3P$ (1.00 equiv.), $C_6H_5CHO$ (1.50 equiv.), THF, reflux, 10 h (93%); (ii) (a) NaH (1.00 equiv.), THF, 0 °C, 0.5 h, (b) RX (1.00 equiv.), 0 °C – rt, 3 h (87-92%); (iii) $Et_3N$ + THF (1:1), reflux, 48 h (94-98%); (iv) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (97-94%).

This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

## Section D: Wittig Reaction of Maleimide and Triphenylphosphine Adduct with Dihydrofuran/Dihydropyran and Studies Towards the Synthesis of Byssochlamic Acid

### 3D.1 Wittig Reaction of Maleimide and Triphenylphosphine Adduct with Dihydrofuran/Dihydropyran

In our on going studies towards the synthesis of bioactive natural products, we were in search of suitable reagent to introduce side chain functionality without protection-deprotection chemistry. We thought that dihydrofuran/dihydropyran might act as sources of four/five carbon aldehydes. In this context, we carried out the Wittig reaction of *N*-*p*-tolylmaleimide (**1**) and triphenylphosphine adduct with dihydrofuran/dihydropyran and obtained (*E*)-alkylidenesuccinimides **2a/b** in 97/98% yields. Acid catalyzed deprotection under acidic conditions furnished alcohols **3a/b** in 92/93% yields. Alcohols **3a/b** were converted into corresponding tosylates **4a/b** in 87/89% yields. Our studies on intramolecular cyclization using sodium hydride as base followed by base catalyzed isomerization of carbon-carbon double bond to obtain carbocycles **6a/b** are in active progress (Scheme 1).



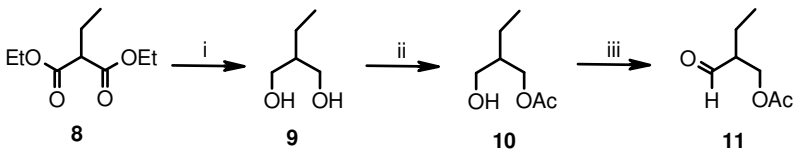

**Scheme 1.** *Reagents, Conditions and yields*: (i) $Ph_3P$, DHF/DHP, AcOH, reflux, 10 h (97/98%); (ii) 2 N HCl, EtOAc + MeOH (1:1), rt, 8 h (92/93%); (iii) $Et_3N$, DMAP, *p*-TSCl, DCM, 0 $^oC$ to rt, 10 h (87/89%).

### 3D.2 Studies Towards the Synthesis of Byssochlamic Acid

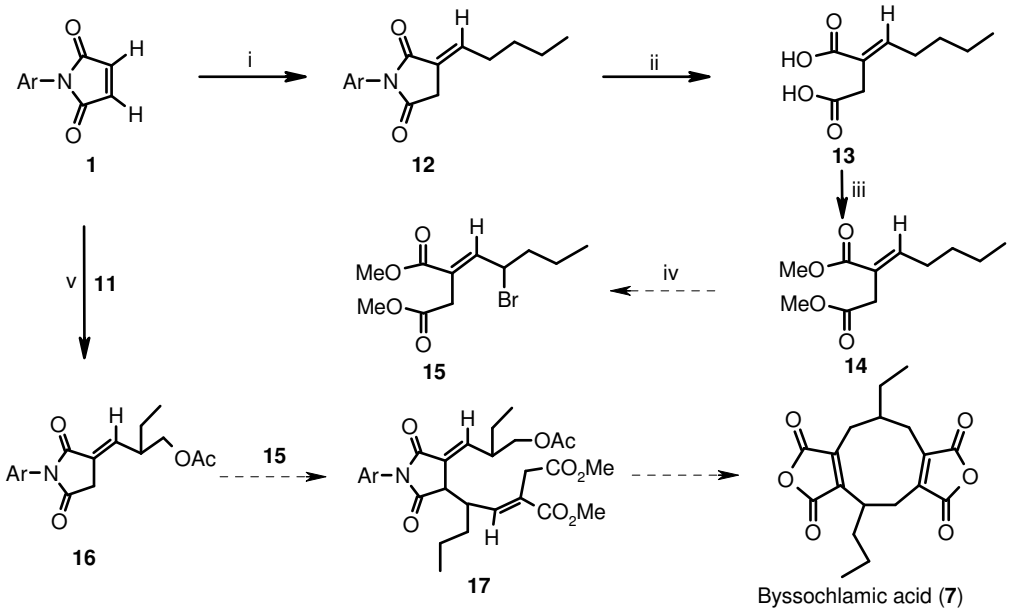
Byssochlamic acid, a metabolite first isolated from ascomycete *Byssochlamys fulva* is a member of the small but structurally unique class of natural products known as nonadrides. Sodium salt of

byssochlamic acid inhibits germination of mustard seed and elongation of the seedlings. To date, three syntheses of byssochlamic acid have been reported in the literature.

We started synthesis of byssochlamic acid from diethyl ethylmalonate (**8**). Lithium aluminum hydride induced reduction of diethyl ethylmalonate (**8**) furnished diol **9** in 90% yield. Diol **9** was monoprotected using acetic anhydride to obtain acetoxy-alcohol **10** in 65% yield. PCC oxidation of **10** furnished aldehyde **11** in 85% yield (Scheme 2).




**Scheme 2.** *Reagents*, *conditions and yields*: (i) LAH (2.00 equiv.), THF, 0 $^{o}$C to rt, 12 h (90%); (ii) $Ac_2O$ (1.00 equiv.), pyridine (1.00 equiv.), DCM, 0 $^{o}$C to rt, 12 h (65%); (iii) PCC (1.00 equiv.), DCM, 0 $^{o}$C to rt, 3 h (85%).




**Scheme 3.** *Reagents*, *conditions and yields*: (i) $PPh_3$ (1.00 equiv.), THF, $CH_3(CH_2)_3CHO$ (1.50 equiv.), reflux, 10 h (94%); (ii) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (85%); (iii) MeOH, $H^+/H_2SO_4$, reflux, 12 h (80%); (iv) In progress; (v) $PPh_3$ (1.00 equiv.), THF, **11** (1.50 equiv.), reflux, 10 h (91%).

Triphenylphosphine induced Wittig reaction of *N*-*p*-tolylmaleimide (**1**) with valeraldehyde exclusively furnished the corresponding (*E*)-alkylidenesuccinimide **12** in 94% yield. Base catalyzed hydrolysis of (*E*)-alkylidenesuccinimide **12** followed by acidification, furnished the desired diacid **13** in 85% yield. Esterification of diacid **13** using methanol/$H_2SO_4$ furnished diester **14** in 80%

yield. Regioselective bromination of diester **14** would furnish bromodiester **15**. Wittig reaction of *N*-*p*-tolylmaleimide (**1**) and triphenylphosphine adduct with aldehyde **11** furnished (*E*)-alkylidenesuccinimide **16** in 91% yield. Then, alkylation of alkylidenesuccinimide **16** can be performed by using sodium hydride and bromodiester **15** to obtain exo-diester **17**. Our work towards this goal is in active progress (Scheme 3).

This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

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

# Chapter 1

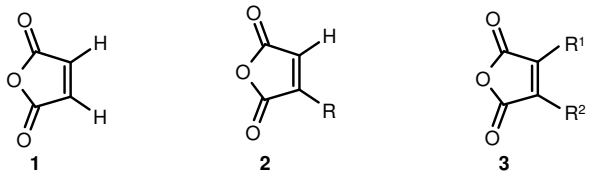
## *A Concise Account on the Chemistry of Monoalkyl Substituted, Dialkyl Substituted and Complex Dialkyl Substituted Maleic Anhydrides*

This chapter features the following sections:

## 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 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. It has been used as potential 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.




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

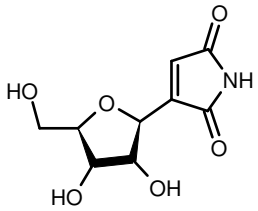
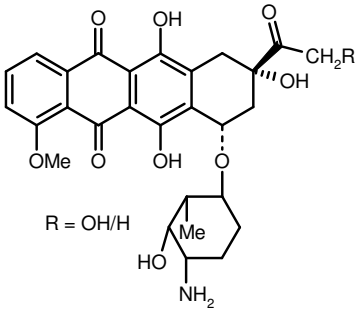
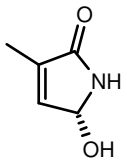
Maleic anhydride and its derivatives are used extensively in the synthesis of a wide array of key intermediates employed in the heavy and fine chemical industries[2] and as such these compounds have often been used to model

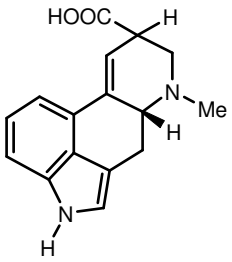
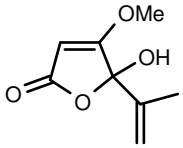
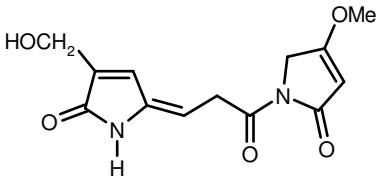
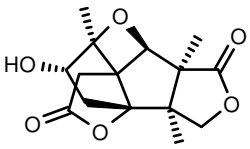
- Compounds highlighting regiochemical dichotomy
- Heterocyclic skeletons
- Natural products and their precursors
- Bioactive molecules such as drugs and agrochemicals
- Series of polymers with tailored material characteristics

### 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 practices.[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 synthesis of pukelimide employing methylmaleic anhydride as the starting material,[15] while recently, Danishefsky and co-workers have started with dimethylmaleic anhydride to complete the total synthesis of the neurotrophic agent (±)-merrilactone A.[16]

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

| No. | Compound | Source | Activity | Ref. |
|---|---|---|---|---|
| 1 |  Showdomycin | *Streptomyces showdoensis* | Antibiotic | 7 |
| 2 |  Adriamycin/Daunorubicin | *Streptomyces peucetius* | Antibiotic, anticancer, immunomodulator | 8 |
| 3 |  (±)-Albene | *Petasites albus* | Not known | 9 |
| 4 |  Jatropham | *Jatropha macrohiza* | Antitumor | 10 |

| | | | | |
|---|---|---|---|---|
| 5 |  <br>(±)-Lysergic acid | *Claviseps paspali*<br>*Claviseps purpurea*<br>(ergot fungus) | Hallucinogenic and anti-serotonin | 13 |
| 6 |  <br>Penicillic acid | *Lyngbya majuscula*<br>(marine blue-green algae) | Antimicrobial and antitumor | 14 |
| 7 |  <br>Pukelimide | *Lyngbya majuscula*<br>(marine blue-green algae) | Not known | 15 |
| 8 |  <br>(±)-Merrilactone | *Illicium merrillianum* | Neurotropic agent | 16 |

## 1.2 Monoalkyl Substituted Maleic Anhydrides

This section describes the synthetic approaches reported in the literature towards the synthesis of methylmaleic anhydride and alkylmaleic anhydrides.

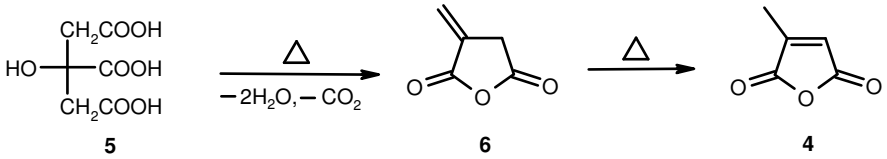
### 1.2.1 Methylmaleic Anhydride

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. Some of the synthetic utilities of methylmaleic anhydride (**4**) have been described in the earlier section.

**I. Roll's Approach**

Roll and co-workers,[17] reported an efficient approach to methylmaleic anhydride starting from citric acid in two-steps with 34% overall yield (Scheme 1). Citric acid (**5**) was heated over a free flame and the fraction which distills around 175-190 °C was collected. First formation of itaconic anhydride (**6**) takes place, which on heating isomerises to methylmaleic anhydride (**4**).

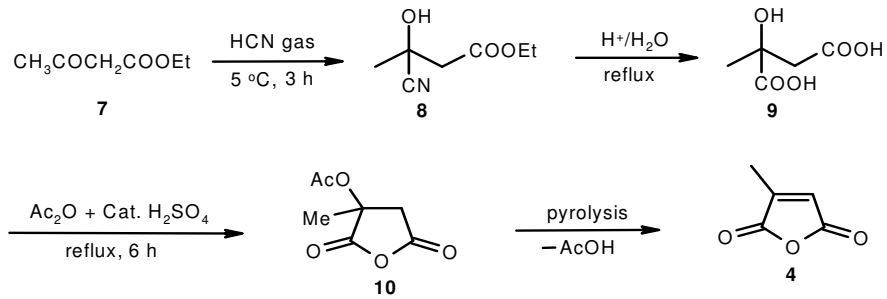
**Scheme 1**




**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]

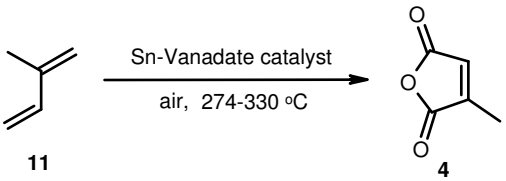
**Scheme 2**



**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 $^{o}$C is known to furnish methylmaleic anhydride (**4**) with 21% yield (Scheme 3).[19]

**Scheme 3**



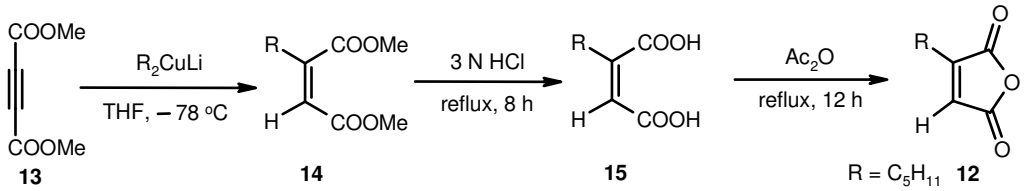

### 1.2.2 Alkylmaleic Anhydrides

A large number of substituted maleic anhydrides exihibit a range of biological activities.[20] However, only a few general methods are available for the synthesis of substituted maleic anhydrides.

**I. Bates's Approach**

Conjugate addition of dialkyl cuprate to dimethyl acetylenedicarboxylate takes place to form alkylsubstituted dimethyl maleate **14** with some amount of *trans* isomer. Diester **14** on acid catalyzed hydrolysis followed by dehydrative cyclisation furnished alkylmaleic anhydride **12** in 3-steps with 52% overall yield (Scheme 4).[21]

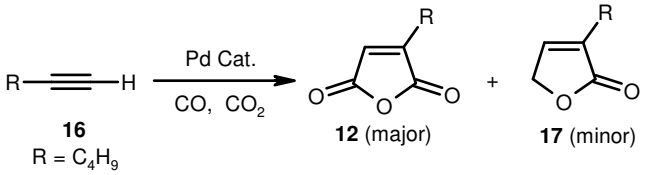
**Scheme 4**




**II. Gabriele's Approach**

Palladium catalyzed reductive carbonylation of terminal acetylenes **16** in presence of CO and excess $CO_2$ furnished mixture of alkylmaleic anhydride **12** and the furan-2(5*H*)-ones **17** with 80% combined yield (Scheme 5).[22] The present reaction is the first example in which CO and $CO_2$ are used together for the catalytic formation of unsaturated cyclic anhydrides.

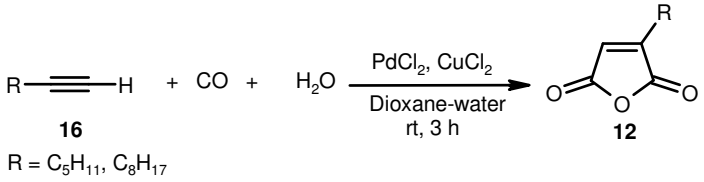
**Scheme 5**




**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 alkylmaleic anhydride **12** with 80-90% yield (Scheme 6).[23] 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**.

**Scheme 6**




In summary, three methods are known for the synthesis of monoalkylmaleic anhydrides. The synthetic utilities of monoalkylmaleic anhydrides have not been much explored, neverthless, these compounds could serve as potential building blocks for the synthesis of many natural products.

## 1.3 Dialkyl Substituted Maleic Anhydrides

Several structurally interesting and biologically important dialkyl substituted maleic anhydrides are known in the literature. These target molecules received immediate attention from several schools of synthetic organic chemistry for the synthesis of the natural product itself and also of its analogues for structure activity relationship studies. In this section, the complete details concerning the synthetic efforts on all of these natural and unnatural dialkyl substituted maleic anhydride derivatives have been described.

### 1.3.1 Dimethylmaleic Anhydride

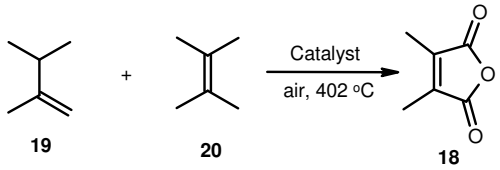
Dimethylmaleic anhydride (DMMA, **18**) is the most simple and widely used derivative of dialkyl substituted maleic anhydride. More than 21 synthetic approaches to

dimethyl maleic anhydride using variety of strategies are known in literature. The chemistry involved in these approaches is discussed below.

**I. Pichler's Approach**

Dimethylmaleic anhydride (**18**) has been prepared by the air oxidation of a mixture of 2,3-dimethyl but-1-ene (**19**) and 2,3-dimethyl but-2-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 7).[24]

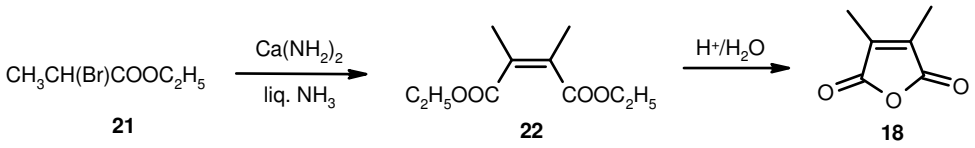
**Scheme 7**




**II**. **Kreiser's Approach**

Self condensation reaction of ethyl 2-bromopropionate (**21**) in the presence of $Ca(NH_2)_2$ and liq. $NH_3$ furnished ester **22** (major isomer) with 53% yield. The formed diester **22** on acid catalyzed hydrolysis gave dimethylmaleic anhydride (**18**) with 67% overall yield (Scheme 8).[25]

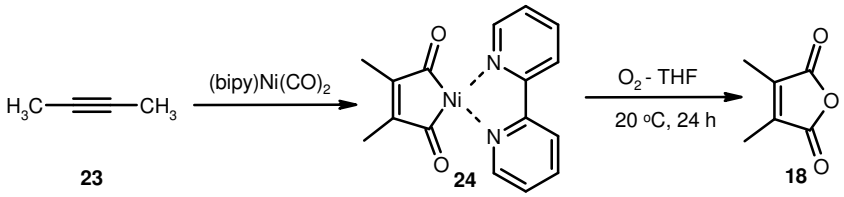
**Scheme 8**




**III**. **Hoberg's Approach**

Dimethyl acetylene (**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 9).[26]

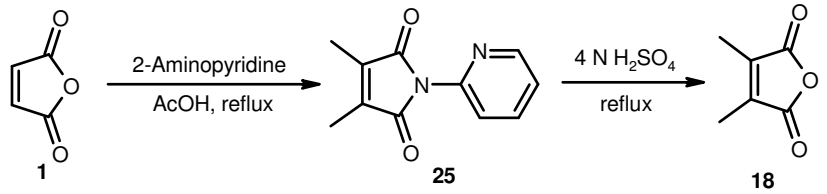
**Scheme 9**



## IV. Baumann's Approach

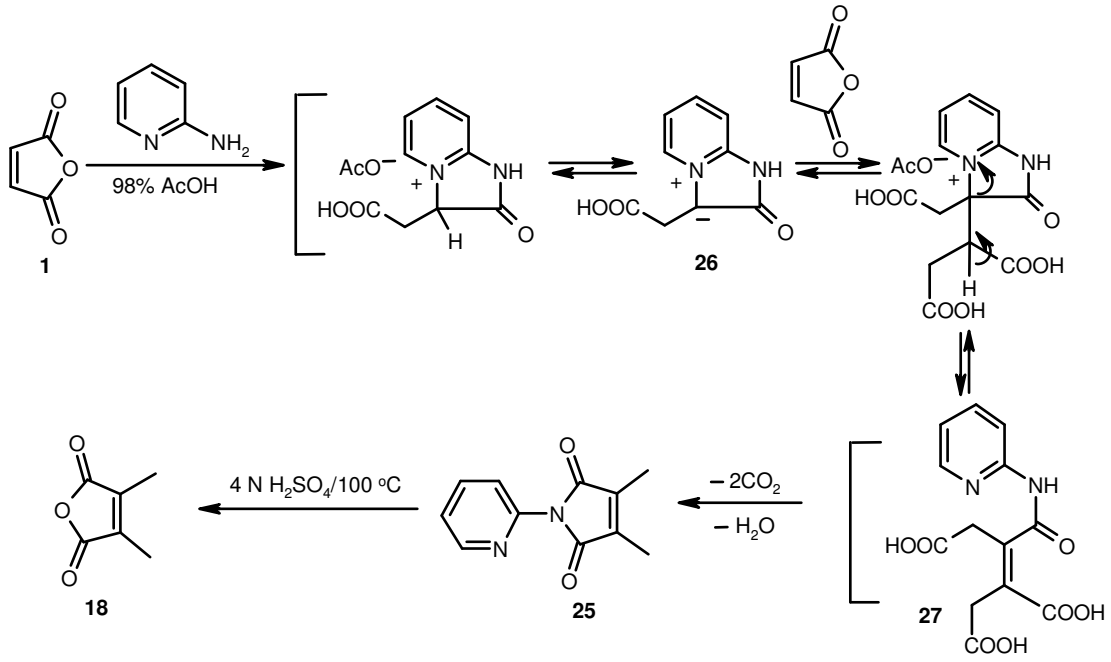
Baumann *et al*, have reported an elegant approach to dimethylmaleic anhydride (**18**) starting from 2-aminopyridine and two equivalents of maleic anhydride (**1**) via the formation of disubstituted maleimide **25** with 75% overall yield (Scheme 10).[27a]

**Scheme 10**



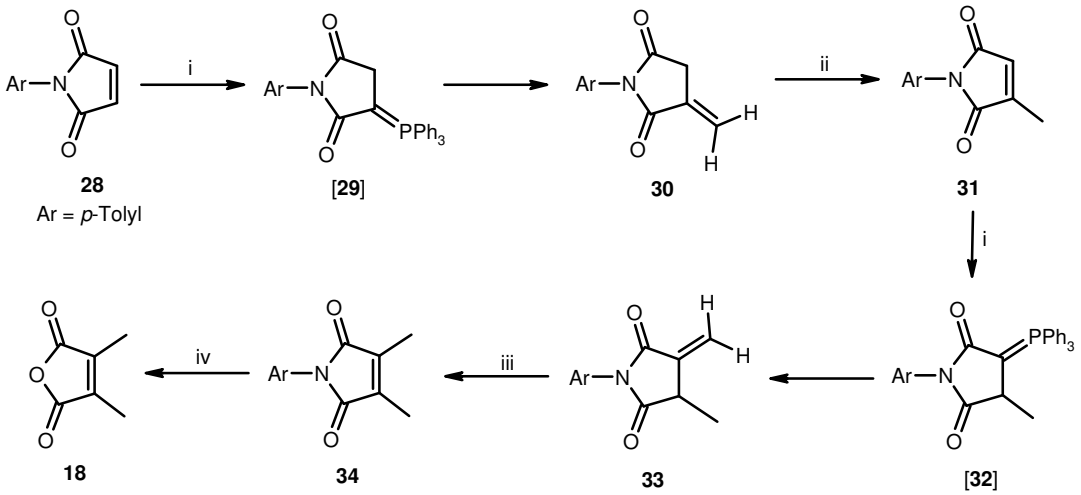

The mechanism of decarboxylative dimerization of maleic anhydride (**1**) to dimethylmaleic anhydride (**18**) was investigated by Baumann *et al* (Scheme 11).[27b,c] Reaction of maleic anhydride (**1**) with 2-aminopyridine gave imidazo [1,2,-$\alpha$]pyridine **26** as an intermediate which on Michael addition to maleic anydride (**1**) furnished a tricarboxylic acid intermediate **27**, which undergoes instantaneous dehydrative decarboxylation leading to disubstituted maleimide **25**. The compound **25** on acid catalysed hydrolysis furnished dimethylmaleic anhydride (**18**) with 75% overall yield.

**Scheme 11**



## V. Argade's Approach

The most recent approach towards dimethylmaleic anhydride (**18**) has been developed in our laboratory. The reaction of maleimide **28** (1 equiv.) with triphenylphosphine (1 equiv.) and paraformaldehyde (5 equiv.) in refluxing acetic acid furnished methylmaleimide **31** in 84% yield. The methylmaleimide **31** on further reaction with the same reagents under similar reaction conditions furnished the dimethylmaleimide **34** in 91% yield.

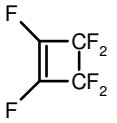
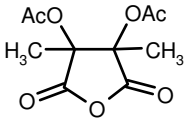
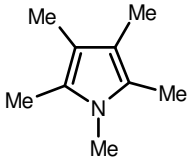
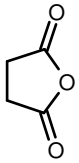
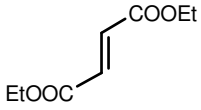
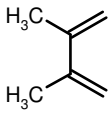
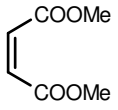


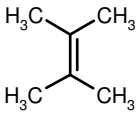
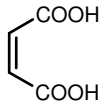
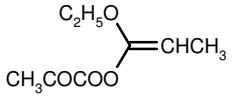
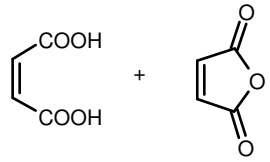
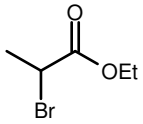
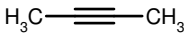

**Scheme 12.** ***Reagents, conditions and yields*****:** (i) $PPh_3$, $(CH_2O)_n$, AcOH, reflux, 1 h (92%); (ii) TEA, THF, reflux, 3 h (93%); (iii) 50 °C, 3 h (98%); (iv) (a) Aq. MeOH, KOH, reflux, 2 h, (b) $H^+$/HCl (97%).

The dimethylmaleimide **34** on alkaline hydrolysis followed by acidification furnished the dimethylmaleic anhydride (**18**) in 97% yield (Scheme 12).[28] All other approaches to **18** have been summarized in Table 2.

**Table 2. Synthetic Approaches to Dimethylmaleic Anhydride (18)**

| No. | Starting Material | Reagents and Conditions | Overall Yield (%) | Ref. |
|---|---|---|---|---|
| 1 | $CH_3COCH_2COOEt$<br>Ethyl acetoacetate | (i) NaH, MeBr; (ii) $NaCN/H_2O$;<br>(iii) $H_2SO_4$. | 13 | 29 |

| | | | | |
|---|---|---|---|---|
| 2 |  Perfluro cyclobutene | (i) $CH_3Li$, $Et_2O$, 45 $^oC$; (ii) $H^+/H_2O$; (iii) Aq. $H_2O_2$ (30-35%). | 23 | 30 |
| 3 | $HOOCCH_2CH_2COOH$ Succinic acid | $CH_3COCOOH$, pyridine, 150 $^oC$, 1.5 h. | 40 | 31 |
| 4 |  Dimethyldiacetyl tartaric anhydride | (i) Pyrolysis, 440 $^oC$; (ii) pyrolysis of formed 2-methyl-2-acetoxyitaconic anhydride at 545 $^oC$. | Low yield | 32 |
| 5 |  Pentamethyl pyrrole | (i) 70% $H_2O_2$; (ii) pyrolysis, 155 $^oC$. | Low yield | 33 |
| 6 |  Succinic anhydride | (i) (a) Pyridine, 125 $^oC$, 0.5 h, (b) MeCOCOOH, 125 $^oC$; (ii) steam distillation. | 40 | 34 |
| 7 |  Diethyl fumarate | (i) Methyl acrylate, tricyclohexylphosphine, dioxane; (ii) $H^+/H_2O$; (iii) $H_2$, Pd/C; (iv) thermal decomposition. | 27 | 35 |
| 8 |  2,3-Dimethyl-1,3-butadiene | Oxidation in air over a catalyst at 400 $^oC$. | 21 | 36 |
| 9 |  Dimethyl maleate | (i) Methyl acrylate, tricyclohexylphosphine, dioxane; (ii) $NaOH/H_2O$; (iii) $\Delta$, 220-230 $^oC$. | 40 | 37 |

| | | | | |
|---|---|---|---|---|
| 10 |  <br>2,3-Dimethyl but-2-ene | Oxidation in air over vanadium and phosphorus catalyst at 300-500 $^{o}$C. | 35 | 38 |
| 11 |  <br>Maleic acid | (i) 2-Aminopyridine, AcOH, reflux; (ii) 4 N $H_2SO_4$. | 50 | 39 |
| 12 |  <br>1-Ethoxy-1-propenyl pyruvate | Pyrolysis | 35 | 32 |
| 13 |  <br>Maleic Acid  Maleic anhydride | (i) 2-(Methylamino)thiazole, 150 $^{o}$C, 0.5 h; (ii) 4 N $H_2SO_4$. | 57 | 40 |
| 14 | $CH_3COCOOEt$<br>Ethyl pyruvate | (i) $CH_3CH[PO(OEt)_2]COOEt$ NaH, 1,2-diethoxyethane; (ii) $H^+/H_2O$. | 46 | 41 |
| 15 |  <br>Ethyl 2-bromopropionate | Self coupling in liq. $NH_3$ using calcium napthalenide | 40 | 42 |
| 16 |  <br>But-2-yne | (i) $Ir(CO)_3Br$, THF, inert atmosphere; (ii) 4 N $HNO_3$. | Not reported | 43 |

In conclusion, very high amount of utilities of dimethylmaleic anhydride (**18**) in organic and bioorganic chemistry keep the scope open for the development of new practical routes to this important molecule.

### 1.3.2 Dialkyl Substituted Maleimides/Maleic Anhydrides

During the past decade several structurally interesting compounds with dialkyl substituted maleic anhydride moieties have been isolated as bioactive natural products and synthesized in view of their promising bioactivities.[44-54] Some of them are listed below (Figure 1). However, only a very few general methods are reported for the synthesis of dialkyl substituted maleimides/maleic anhydrides as compared to dimethyl maleic anhydrides.

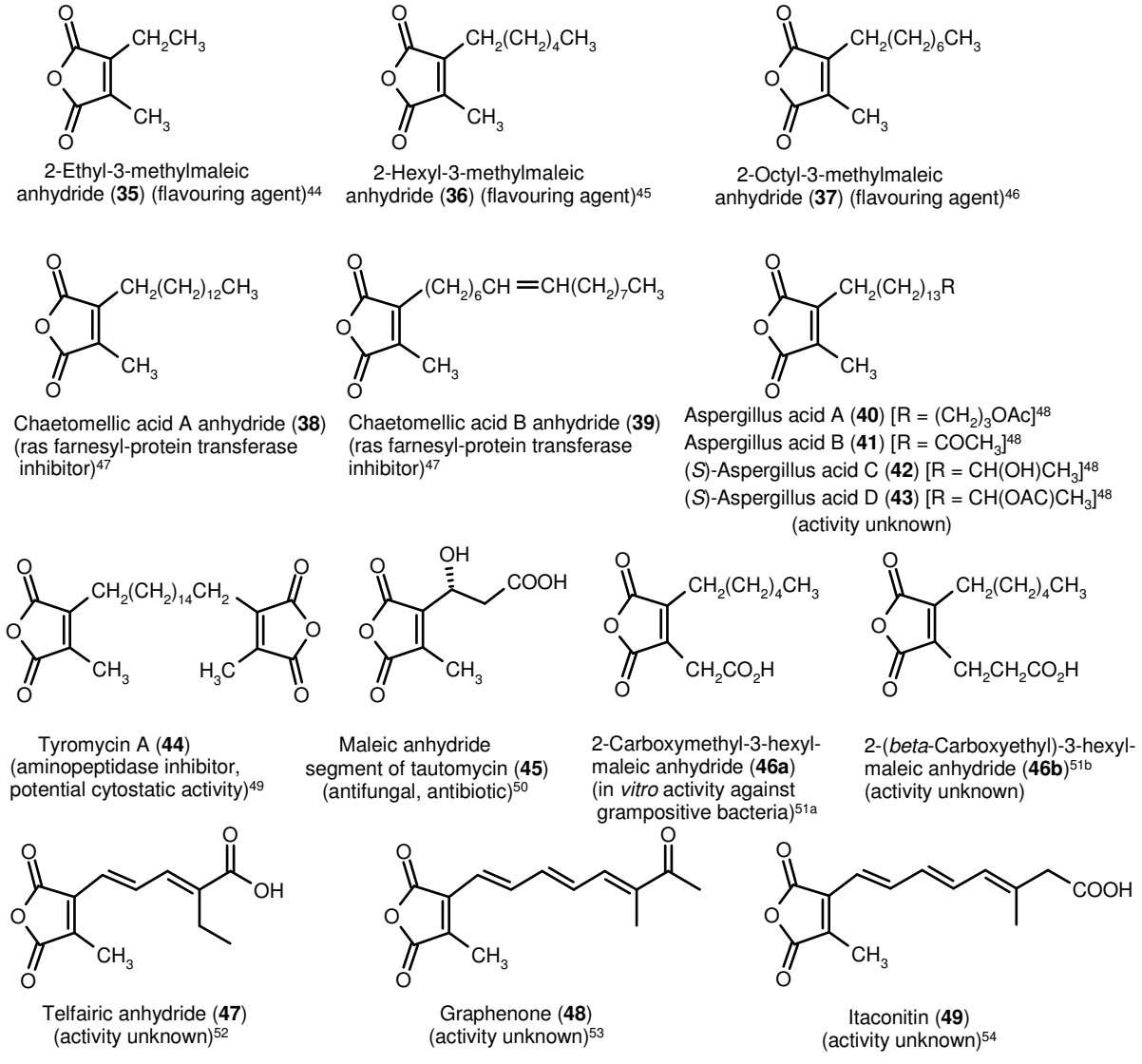


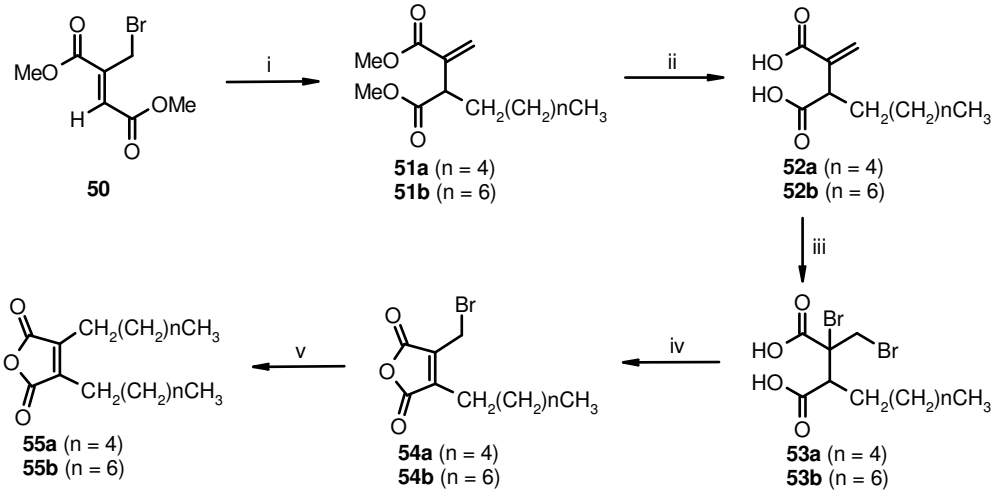

**Figure 1.** Naturally occurring dialkyl substituted maleic anhydrides

2-Ethyl-3-methylmaleic anhydride (**35**)[44] was isolated from *Paederia foetida L.* (from volatile oil) and *Sambucus nigra L.* (fruit) whereas 2-hexyl-3-methylmaleic anhydride (**36**)[45] and 2-octyl-3-methylmaleic anhydride (**37**)[46a] were isolated from *Agropyrum repens* (rhizome) and *Pseudomonas cepacia* A-1419 respectively. In our laboratory, we have synthesized these natural products using chemoselective carbon-carbon coupling of organocuprates with (bromomethyl)methylmaleic anhydride.[46b] Chaetomellic acid A and B have been identified as potent inhibitors of Ras farnesyl-protein transferase[47] (FPTase), an enzyme catalyzing a post-translational modification of Ras. Isolation, earlier syntheses and our approach to chaetomellic anhydride A (**38**) have been described in chapter three (section A). 2-Carboxymethyl-3-hexylmaleic anhydride (**46a**) has been isolated as a novel metabolite of the *Aspergillus* FH-X-213 from an apple.[51a] Recently, Soda and co-workers[51b] reported the biotransformations of stearic acid with a microbial strain isolated from the soil *Pseudomonas cepacica* A-1419 to produce new maleic anhydride derivative 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride (**46b**). Earlier syntheses and our approach to these natural products have been described in chapter three (section B). A new methylmaleic anhydride metabolite has been isolated in 1996 by Edward and his co-workers[52] from the culture medium of the fungus *Xylaria telfairii* berk and was named as telfairic anhydride (**47**). Two other structurally similar natural products, graphenone (**48**)[53] and itaconitin (**49**)[54] have been isolated from the cultures of spore derived mycobionts of the lichens *Graphis scripta* and from the species *Aspergillus itaconicus* and *Aspergillus gorakhpurensis* respectively. Biological role for such a structure does not appear to have been established yet. Till date, no synthesis has been reported for telfairic anhydride (**47**), graphenone (**48**) and itaconitin (**49**). Earlier approaches to dialkyl substituted maleic anhydrides/maleimides have been described below.

**I**. **Argade's Approach**

Chemoselective $S_N2'$ coupling reaction of Grignard reagents with dimethyl bromomethylfumrate (**50**) gave the corresponding diesters **51a/b** in 64-65% yields. The LiOH induced hydrolysis of diesters **51a/b** followed by bromination of diacids **52a/b** furnished the corresponding dibromodiacids **53a/b** in ~100% yield. The dibromodiacids **53a/b** in refluxing acetic anhydride yielded the desired (bromomethyl)alkylmaleic anhydrides **54a/b** in quantitative yield. The chemoselective coupling of freshly prepared

pentylmagnesium bromide with **54a** and heptylmagnesium bromide with **54b** in the presence of HMPA and a copper catalyst gave the desired dihexylmaleic anhydride (**55a**) and dioctylmaleic anhydride (**55b**) in 55-56% yields (Scheme 13).[55]

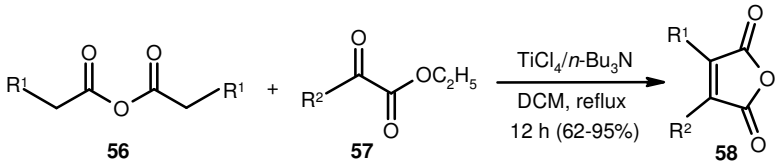



**Scheme 13.** ***Reagents*, *conditions and yields*:** (i) $CH_3(CH_2)_nCH_2MgBr$ (1.2 equiv., n = 4/6), $Et_2O$, HMPA, –20 $^oC$, 0.5 h (64-65%); (ii) LiOH (10 equiv.), THF + $H_2O$ (3:1), rt, 18 h (90-92%); (iii) $Br_2$ (1.5 equiv.), $CCl_4$, rt, 6 h (~100%); (iv) $Ac_2O$, reflux, 1.5 h (~100%); (v) $CH_3(CH_2)_nCH_2MgBr$ (5 equiv., n = 3/5), CuI (0.1 equiv.), $Et_2O$, HMPA, –5 to 0 $^oC$ (55-56%).

## II. Periasamy's Approach

Reaction of alkanoic acid anhydrides **56** with $\alpha$-keto esters **57** using the $TiCl_4/n\text{-}Bu_3N$ reagent system gives the corresponding maleic anhydrides **58** in 62-95% yields (Scheme 14).[56]

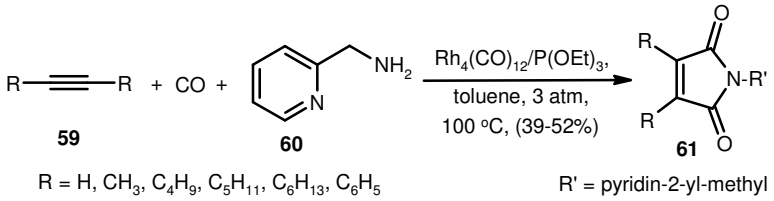
**Scheme 14**




## III. Chatani's Approach

The reaction of alkynes **59** with CO and pyridin-2-ylmethylamine (**60**) in the presence of $Rh_4(CO)_{12}/P(OEt)_3$ furnished maleimide derivatives **61** in 39-52% yields (Scheme 15).[57]

**Scheme 15**




**Our Approach:** Our approach to monoalkyl and dialkyl substituted maleimides and maleic anhydrides have been discussed in chapter two (section B) and chapter three respectively as a part of this dissertation work.

### 1.3.3 Tyromycin A

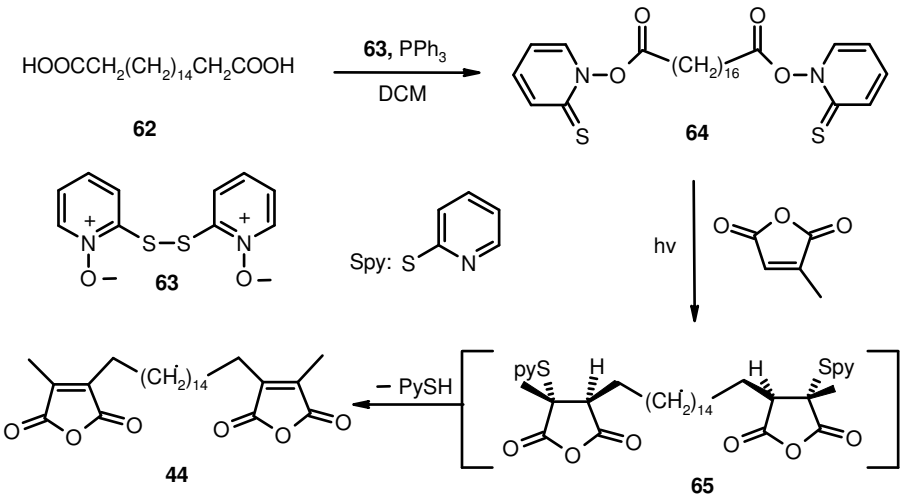
Tyromycin A (**44**) has been recently isolated from mycelial cultures of basidomycete *Tyromyces lacteus* (Fr.) Murr[49], and its structure was established as 1,16-bis-(4-methyl-2,5-dioxo-3-furyl)hexadecane by using spectral and analytical techniques and by transformation into the corresponding tetramethyl ester and diimide derivatives.[49] Among the enzymes bound to surfaces of mammalian cells, amino peptidases have been recognized as a potential target for the immunomodulating drugs.[49] Tyromycin A (**44**) 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 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 (**44**) being devoid of inhibitory activity on the cell-bound amino peptidases of HeLa cells. Tyromycin A (**44**) 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. Samadi's Approach**

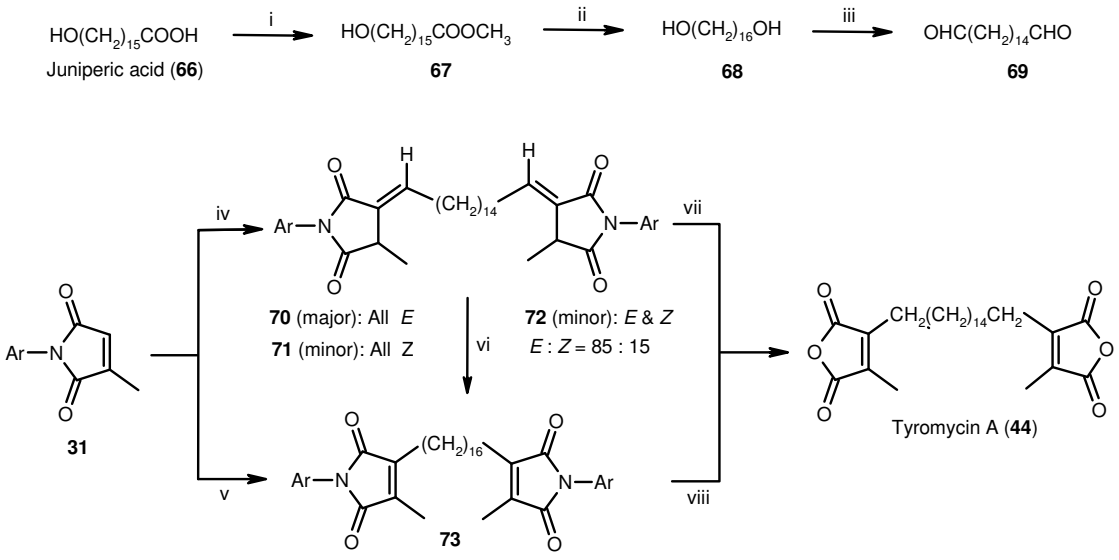
The first synthesis of tyromycin A (**44**) has been completed by Samadi and co-workers employing the decarboxylative Barton-radical coupling reaction (Scheme 16).[58] The starting compound 1,18-octadecanedioic acid (**62**) was converted to corresponding thiohydroxamic diester **64** using $PPh_3$/2,2′ dithiobis(pyridine *N*-oxide) (**63**) and the formed diester **64** reacts in situ with citraconic anhydride in presence of tungsten light

(500 W) to furnish the intermediate addition products **65**, which upon purification on silica gel afforded the eliminated product tyromycin A (**44**).

**Scheme 16**




## II. Argade's Approach

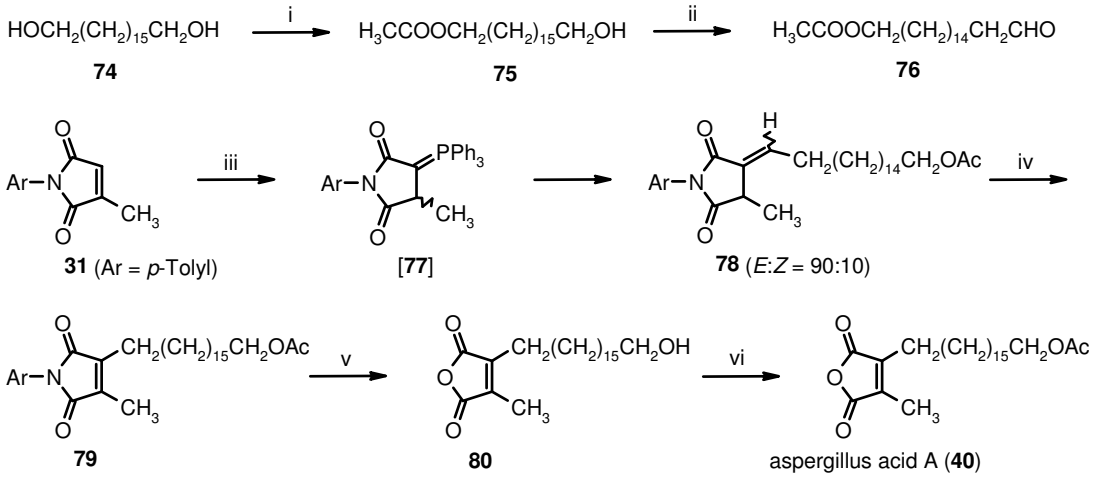



**Scheme 17.** ***Reagents*, *conditions and yields*:** (i) $CH_2N_2$, $Et_2O$, 0 $^oC$, 2 h (95%); (ii) LAH, $Et_2O$, rt, 2 h (98%); (iii) PCC, $CH_2Cl_2$, rt, 10 h (77%); (iv) TPP, AcOH, **69**, reflux, 10 h (70%); (v) (a) TPP, AcOH, **69**, reflux, 10 h, (b) Δ, 140-150 $^oC$, 30 min (72%); (vi) Tetralin, reflux, 1 h (98-100%); (vii) (a) $CH_3ONa$, $CH_3OH$, reflux, 2 h, (b) $H^+$/HCl (60%); (viii) (a) Aq. KOH + THF + $CH_3OH$ (1:1:1), reflux, 2 h, (b) $H^+$/HCl (98%).

Recently, in our laboratory, we have synthesized tyromycin A (**44**) employing double Wittig condensation of citraconimide-TPP adduct with 1,16-hexadecanedial (**69**). The desired 1,16-hexadecanedial (**69**) was prepared starting from 1,16-hexadecanediol with 72% overall yield (Scheme 17). Wittig reaction of citraconimide-TPP adduct with dialdehyde **69** furnished condensed product with very good yield. The mixture of **70**, **71** and **72** in refluxing tetralin underwent a smooth trisubstituted exocyclic to tetrasubstituted endocyclic double bond isomerization to yield the bismaleimide derivative **73** in quantitative yield. The bisimide **73** upon treatment with KOH in $H_2O$ + THF + MeOH (1:1:1) followed by acidification gave tyromycin A (**44**) in 98% yield (Scheme 17).[59]

### 1.3.4 Aspergillus Aicds A-D

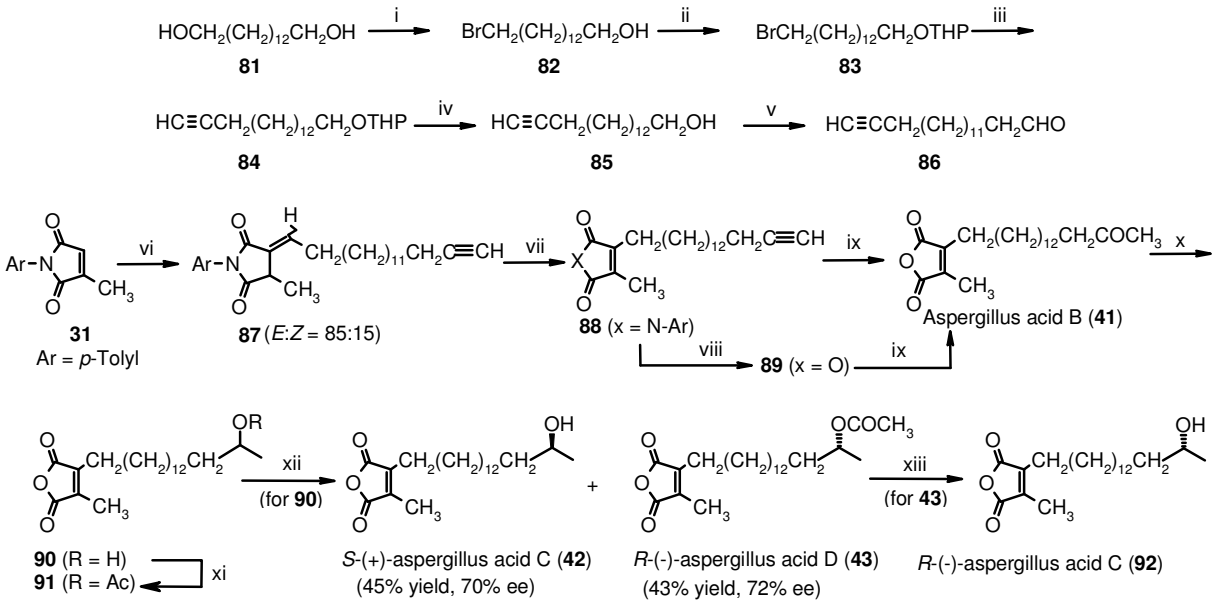
Assante *et al*,[48] isolated four new secondary metabolites aspergillus acids A-D (**40**-**43**) produced by the mould *Aspergillus wentii* when grown on yeast-glucose medium.




**Scheme 18.** *Reagents, conditions and yields*: (i) $Ac_2O$ (0.98 equiv.), Py, rt, 6 h (79%); (ii) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −60 °C, 90 min (89%); (iii) $Ph_3P$, AcOH, 4, reflux, 18 h (70%); (iv) $Et_3N$, THF, reflux, 48 h (92%); (v) (a) KOH (30% aq.), THF-MeOH (1:2), reflux, 12 h, (b) $H^+$/HCl (94%); (vi) $Ac_2O$, Py, rt, 8 h (89%).

The first synthesis of these naturally occurring acids **40**-**43** have been carried out in our laboratory comprising introduction of the remote functional groups and a lipase-catalyzed resolution.[60] The triphenylphosphine induced Wittig olefination of citraconimide **31** with acetoxyaldehyde **76** in refluxing acetic acid gave the

corresponding *exo*-alkylidene succinimide **78** (*E*:*Z* = 90:10, by $^1$H NMR) in 70% yield. Trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond migration using triethylamine as a base furnished the desired maleimide **79** in 92% yield. The base catalyzed hydrolysis of maleimide **79** furnished the 2-(17-hydroxytetradecyl)-3-methylmaleic anhydride (**80**) in 94% yield. Acetic anhydride mediated acylation of anhydride **80** gave the naturally occurring aspergillus acid A (**40**) in 89% yield (Scheme 18).



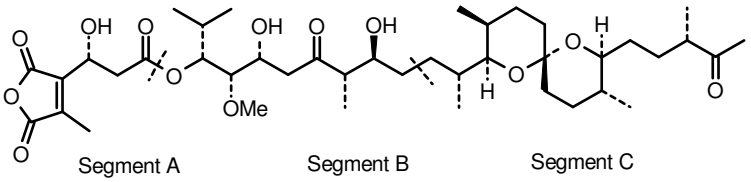

**Scheme 19.** *Reagents, conditions and yields*: (i) HBr (47% aq.), toluene, reflux, 96 h (85%); (ii) DHP, PPTS (cat.), $CH_2Cl_2$, rt, 4 h (93%); (iii) NaC≡CH, THF, HMPA, –78 °C to rt, 40 h (85%); (iv) *p*-TSA, MeOH, rt, 2 h (95%); (v) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, –60 °C, 90 min (85%); (vi) $Ph_3P$, AcOH, **86**, reflux, 24 h (78%); (vii) $Et_3N$, THF, reflux, 48 h (93%); (viii) (a) KOH (30% aq.), THF-MeOH (1:2), reflux, 12 h, (b) $H^+$/HCl (95%); (ix) 6 M $H_2SO_4$-AcOH (1:2), 100 °C, 8 h (90%); (x) (a) Aq. NaOH, THF, 50 ºC, 2 h, (b) $NaBH_4$, 0 ºC to rt, 3 h, (c) $H^+$/HCl (81%); (xi) $Ac_2O$, Py, rt, 12 h (91%); (xii) Amano PS, vinyl acetate, hexane-benzene (2:1), 45 ºC, 72 h (**42**, 45%; **43**, 43%); (xiii) (a) Aq. NaOH, THF, 50 ºC, 4 h, (b) $H^+$/HCl (90%).

The synthesis of aspergillus acids B-D was accomplished by the Wittig condensation of citraconimide-TPP adduct with the aldehyde **86** to give the *exo*-imide **87** (*E*:*Z* = 85:15, by $^1$H NMR) in 78% yield. Trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond migration using triethylamine as a base furnished the desired maleimide **88** in 93% yield. Maleimide **88** on treatment with a mixture of acetic acid and

6 M sulfuric acid (2:1) at 100 °C furnished the natural product **41**. The intermediate acetylinic anhydride **89** on acid catalyzed hydration gave the desired aspergillus acid B (**41**) in 90% yield (Scheme 19). A chemoselective reduction of the ketone carbonyl in **41** exclusively furnished the natural product **90** in 81% yield. Hydroxyanhydride **90** upon acetylation with acetic anhydride-pyridine furnished the fourth metabolite in the series **91** with 91% yield. Amano PS catalyzed acylation of (±)-**90** in hexane-benzene mixture (2:1) at 45 °C furnished the (*S*)-aspergillus acid C [(+)-**42**] with 45% yield (70% ee) and (*R*)-aspergillus acid [(−)-**43**] with 43% yield (72% ee). The base catalyzed hydrolysis of (−)-aspergillus acid D (**43**) furnished (−)-aspergillus acid C (**92**) in 90% yield.

### 1.3.5 Tautomycin and Tautomycetin

Tautomycin (**93**) and tautomycetin (**94**) have been isolated from *Streptomyces spiroverticillatus*[50a] and *Streptomyces griseochromogenes*[50c] respectively. Tautomycin (**93**) and tautomycetin (**94**) both exhibit good biological activities, including antimicrobial activity and Ser/Thr protein phosphatase inhibitory activity. Besides antifungal activities, they were found to induce morphological changes (bleb formation) of human leukemia cells K562. Tautumycetin (**94**) also exhibits immunosuppressive activity.[61] The structure of **93** contains spiroketal and maleic anhydride moieties and 13 chiral centers. The structural complexity and unique biological activity has stimulated many research groups to carry out synthetic studies of **93** and **94**.

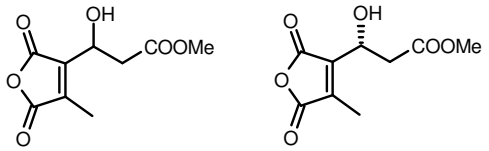


Tautomycin (**93**)

### I. 2,3-Disubstituted Maleic Anhydride Segment of Tautomycin

The broad retrosynthetic analysis of tautomycin afforded segment A, B and C as shown in structure **93**. Total synthesis of this molecule involves the synthesis of three segments followed by stepwise coupling of these building blocks.[62] It has a unique 2,3-disubstituted maleic anhydride ring at the left terminal of the molecule, which is known

as segment A **95**.[63] Segment A is a highly oxygenated molecule with three carboxylic groups and one hydroxy group. According to Chamberlin and co-workers,[64] the greatest challenge in the synthesis of tautomycin (**93**) lies in the construction of the simple looking 2,3-disubstituted maleic anhydride segment A **95**. The anhydride moiety of tautomycin shows an interesting chemical behavior in aqueous media, i.e. tautomycin (**93**) exists in an equilibrium between anhydride and diacid.[63] To date, five multi-step synthesis of segment A **95**, including the most recent synthesis developed in our laboratory, have been accomplished using various elegant strategies.

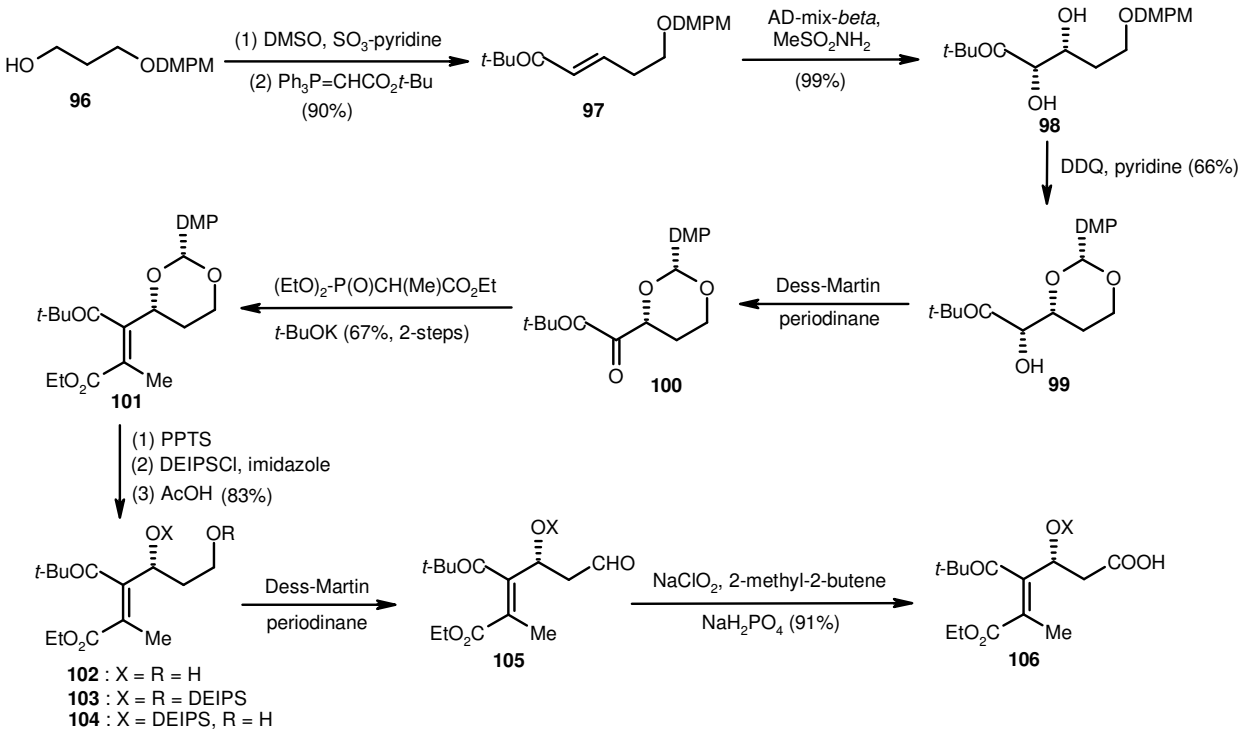



**95a** **95b**

**(a) Ichihara's Approach**

The alcohol **96** was oxidized under Parikh-Doering conditions and olefinated to afford *trans*-olefin **97**. Subsequent asymmetric dihydroxylation using AD-mix-$\beta$ in the presence of methanesulfonamide, successfully developed by Sharpless, functioned with high enantioselectivity to provide diol **98**. Oxidative acetalization by DDQ in nonaqueous media achieved effective protection of the C1′ and C3′ hydroxyl groups as 3,4-dimethoxybenzylidene acetal regio- and stereoselectively. The remaining free hydroxyl group in **99** was then oxidized by Dess-Martin periodinane. Then, keto ester **100** was subjected to the Horner-Wadsworth-Emmons reaction producing the desired dialkyl maleate **101**. The acetal protecting group was removed by the action of pyridinium *p*-toluenesulfonate (PPTS) in methanol. The diethylisopropylsilyl (DEIPS) group, a slightly more acid-sensitive protecting group than TBDMS, was employed for final protection of the C3′ hydroxyl, and thus the diol **102** was bis-silylated. Selective primary silyl ether deprotection yielded C3′ DEIPS ether **104**, which was successively converted to DMS segment **106** via aldehyde **105** (Scheme 20).[65]

**Scheme 20**

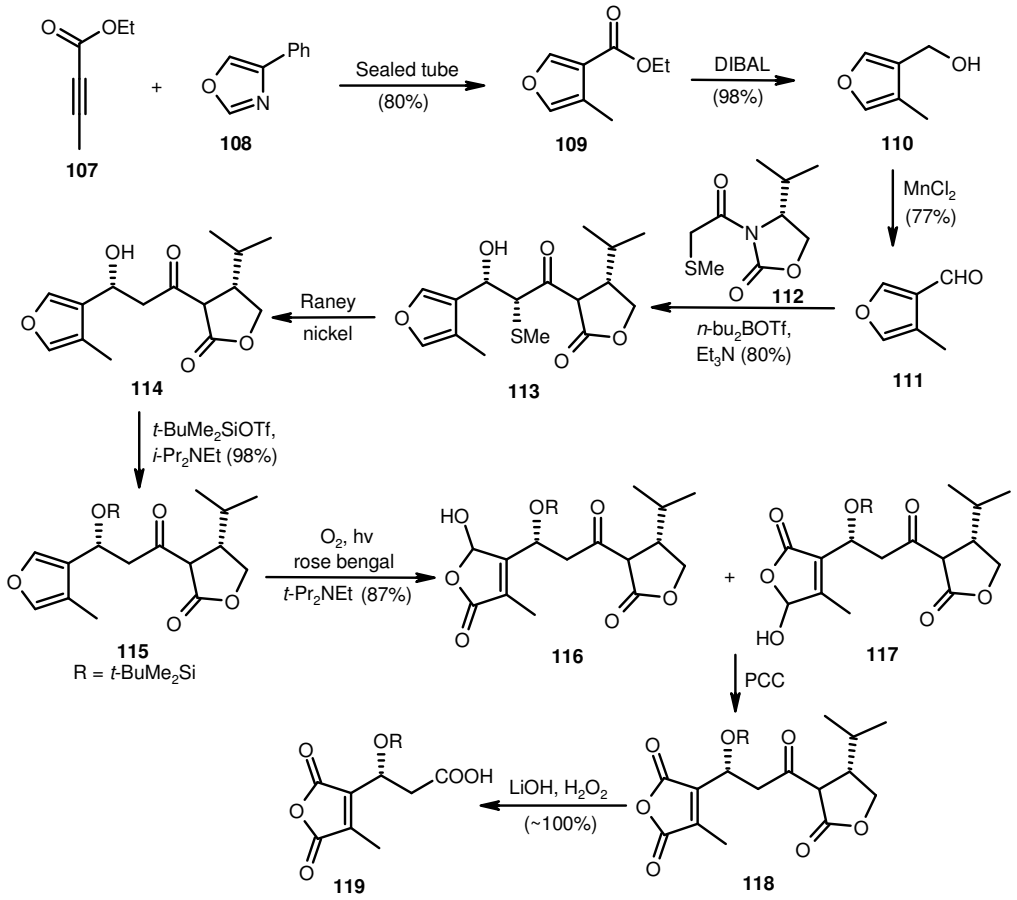



## (b) Isobe's Approach

Diels-Alder addition of ethyl tetrolate **107** with 4-phenyloxazole **108** and spontaneous retro Diels-Alder reaction with elimination of benzonitrile furnished the 3,4-disubstituted furan **109** (Scheme 21). Reduction of the ester **109** with diisobutylaluminium hydride and subsequent oxidation with activated manganese (IV) oxide gave the aldehyde **111**. Asymmetric aldol condensation involving chiral oxazolidinone boron enolate was chosen in the synthesis. Accordingly, the aldol reduction between boron enolate of chiral *N*-acetloxazolidinone **112** and the aldehyde **111** exclusively provided the aldol adduct **113**. Desulfurization of **113** using Raney nickel afforded a mixture of **114** and *β*-elimination product. The formatiom of side product was avoided by employing a mixture of acetone and pH 7 phosphate buffer as the reaction media, in which only **114** was obtained in 75% yield. Protection of the hydroxy group as *t*-butyldimethylsilyl ether gave **115** quantitatively. Photosensitized oxidation of the furan **115** by a 500W tungsten incandescent lamp under oxygen atmosphere in the presence of rose bengal and diisopropylethylamine gave a regioisomeric mixture of 2,3-disubstituted-4-hydroxy-

butenolides **116** and **117**, which upon PCC oxidation in the presence of powdered and activated molecular sieves 4 Å furnished the maleic anhydride **118**. Removal of the auxiliary with lithium hydroperoxide gave the acid **119**. [66]

**Scheme 21**

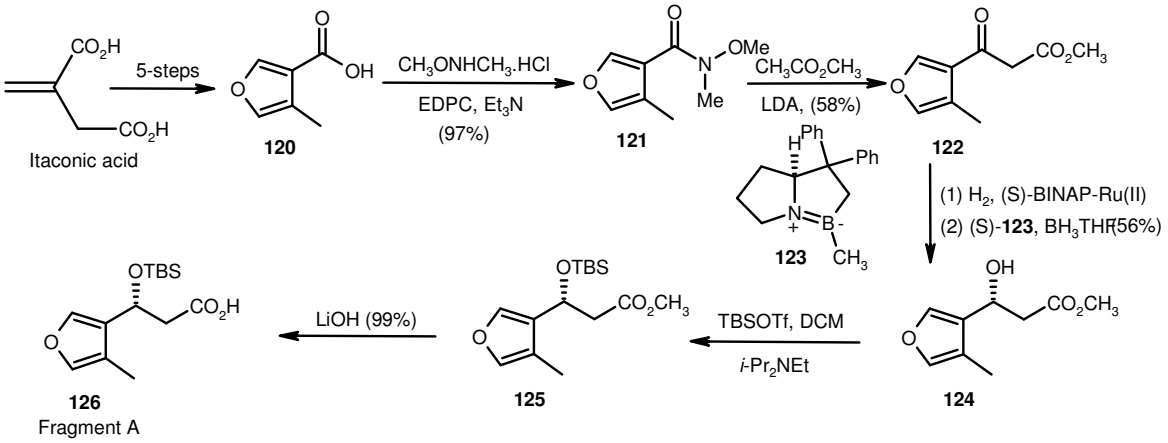



**(c) Shibasaki's Approach**

The fragment A **126** was synthesized by using an asymmetric reduction of *β*-keto ester as a key step (Scheme 22). By using the literature procedure itaconic acid, a commercially available starting material, was transformed to the carboxylic acid **120** in a five-step sequence of reactions. Using EDPC as a condensing reagent the carboxylic acid **120** was converted to the amide **121**, which was treated with the lithium enolate of methyl acetate to yield the *β*-keto ester **122**. Asymmetric reduction was carried out using $BH_3$.THF and oxazoboroliding catalyst **123** developed by Corey. The resulting alcohol

**124** was protected as TBS ester **125**, which upon hydrolysis followed by acidification furnished compound **126**.[67] Compound **126** was further condensed with fragment B.

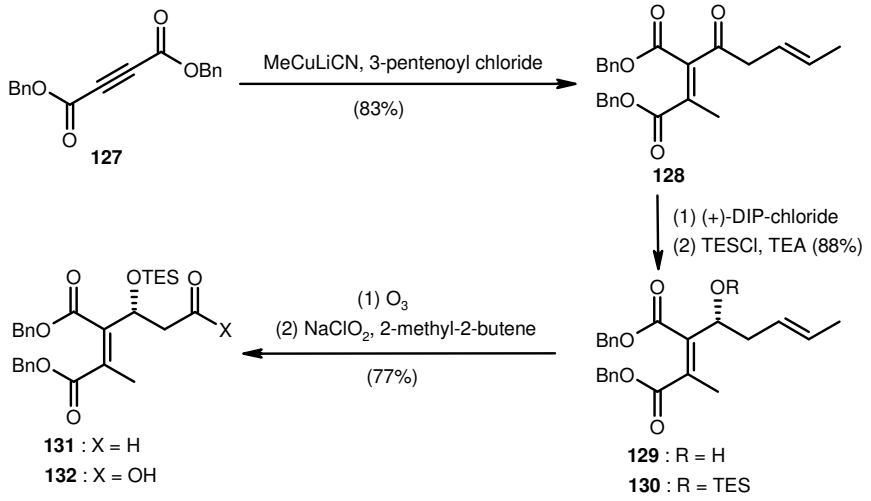
**Scheme 22**




**(d) Chamberlin's Approach**

The synthesis was performed with the addition of a mixed methyl cuprate to a symmetrical acetylenedicarboxylic ester **127**, followed by trapping of the intermediate with an electrophile (Scheme 23). The use of malonic acid equivalent 3-pentenoyl chloride ultimately gave the unstable enone **128** as a mixture of geometrical isomers. Reducing enone **128** with (+)-DIP-chloride afforded the alcohol (+)-**129**. Protection of the hydroxyl substituent as TES ether **130**, ozonolytic cleavage of the disubstituted alkene, and subsequent oxidation of the aldehyde to a carboxylic acid gave (±)-**132**.[64]

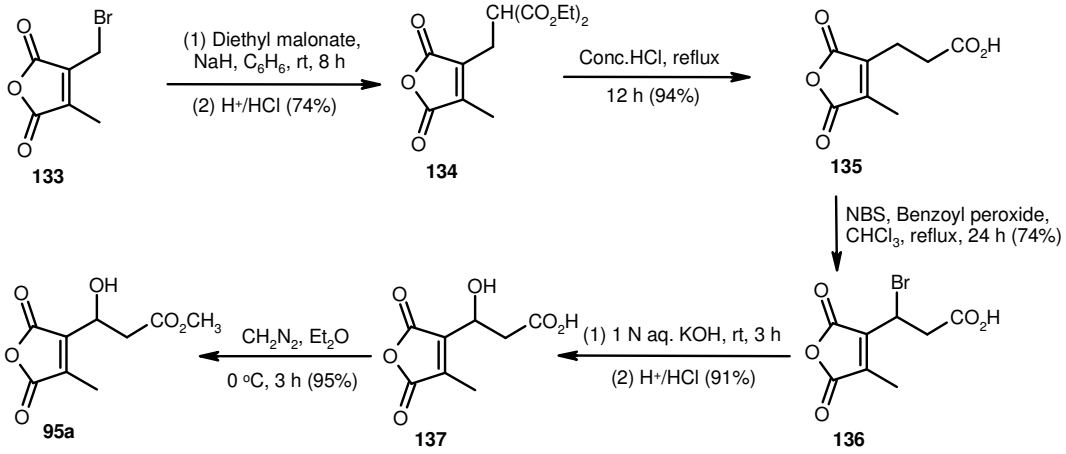
**Scheme 23**



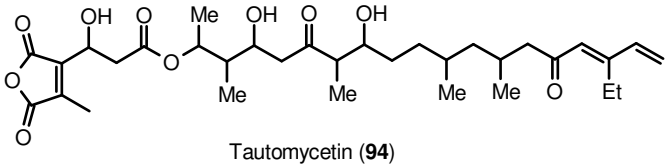
**(e) Argade's Approach**

In our laboratory, we have synthesized 2,3-disubstituted maleic anhydride segment of tautomycin **95a** employing chemoselective condensation of diethyl malonate with (bromomethyl)methylmaleic anhydride (**133**). Acid catalyzed hydrolysis and decarboxylation of diester **134** followed by regioselective NBS bromination gave the bromoacid **136**. The bromoacid **136** on treatment with 1 N aqueous KOH followed by acidification and esterification yielded the desired segment of tautomycin **95a** (Scheme 24).[68]

**Scheme 24**




## II. 2,3-Disubstituted Maleic Anhydride Segment of Tautomycetin




Tautomycetin (**94**)

Tautomycetin (**94**) exists in methanol-buffer solution (1% $Et_2NH$-$HCO_2H$, pH 7.3) as an equilibrium mixture of 2,3-dialkylmaleic anhydride and its dicarboxylic acid. Biosynthesis of tautomycetin (**94**) has been done by Kiyoshi and co-workers using feeding experiments with $^{13}C$ labelled precursors.[50c, 69] 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 (**94**) is formed via a

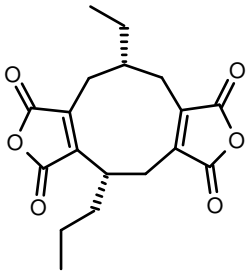
polyketide pathway, which starts with acetate followed by introduction of three acetate units, four propionate units and one butyrate unit.

## 1.4 Complex Dialkyl Substituted Maleic Anhydrides or Nonadrides

The word "nonadrides", meant the substances such as glaucanic acid, glauconic acid and byssochlamic acid were biosynthesized by two $C_9$ units.[70] Later, the name nonadride has evolved to mean the compounds that own the core structure of nonadrides, a $C_9$ ring with an affixed anhydride.[61] 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. 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 other nanadrides.

### 1.4.1 Byssochlamic acid

Byssochlamic acid was isolated from ascomycete *Byssochlamys fulva*.[71] Till date, two racemic and one asymmetric syntheses of byssochlamic acid have been reported in literature.[72-74]



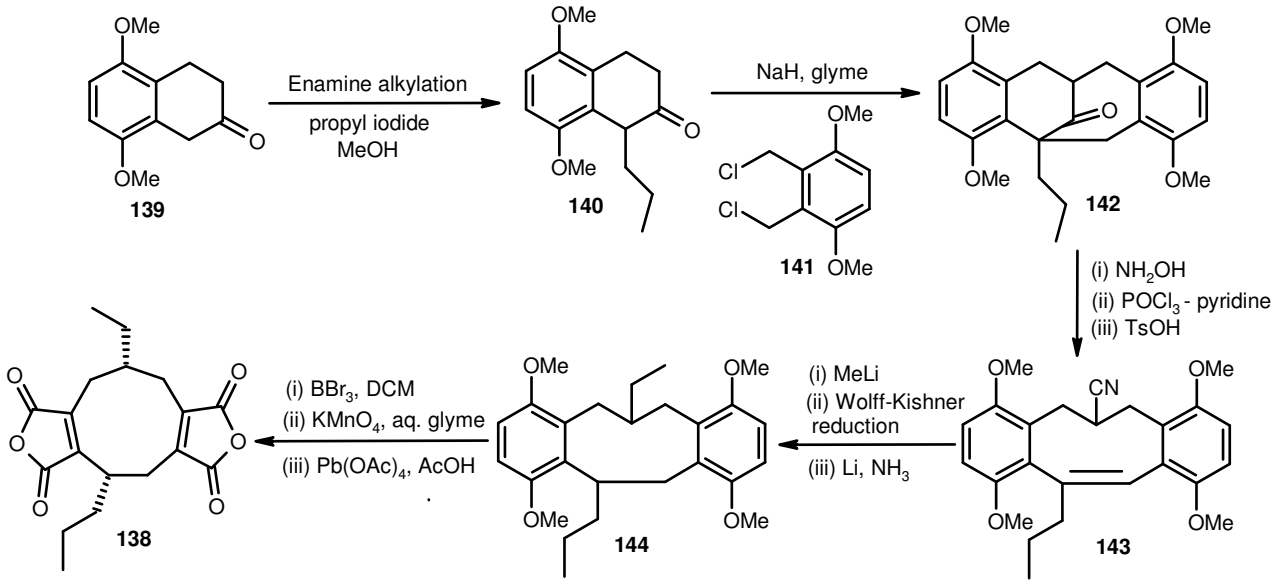
Byssochlamic acid (**138**)

**I. Gilbert Stork's Approach**

In 1972, much before the isolation of the phomoidrides, Stork *et al* presented a very elegant synthesis of byssochlamic acid (**138**).[72] The synthesis started with 5,8-dimethoxy-2-tetralone (**139**), which on enamine alkylation as the pyrrolidine enamine with propyl iodide produced **140** in ~80% yield. Cycloalkylation of **140** with **141** using NaH yielded tetracyclic skeleton **142** which was transformed to the substituted 9-

membered ring system by oxime formation followed by fragmenation with phosphorous oxychloride-py. The cyano group of **143** thus obtained was converted to the required ethyl substitutent by MeLi treatment and subsequent reductions thus leading to bishydroquinone dimethylether **144**. The dihydro derivative **144** thus obtained was transformed to the natural product **138** by first cleavage of the -OMe groups followed by oxidation (Scheme 25).

**Scheme 25**

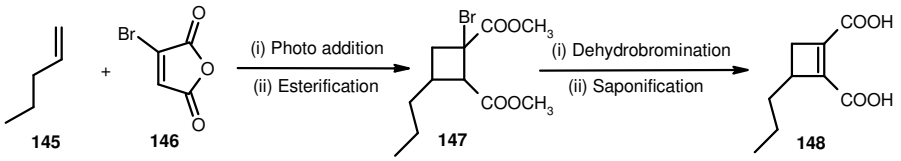



## II. James D. White's Approach

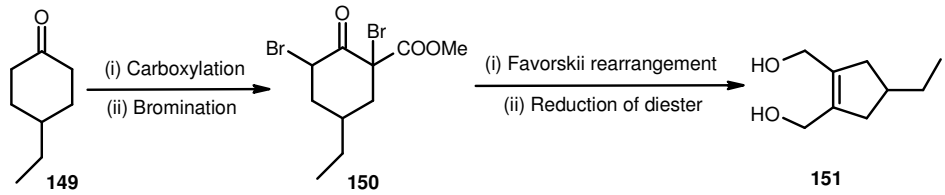
### (a) Racemic Synthesis of Byssochlamic acid

The second total synthesis of byssochlamic acid (**138**) was accomplished by White *et al* in 1992. Bromomaleic anhydride (**146**) on irradiation in the presence of 1-pentene (**145**) followed by esterification furnished diester **147**. Dehydrobromination of **147** followed by saponification of the formed cyclobutene yielded the dicarboxylic acid **148** (Scheme 26). Carboxylation of **149** afforded *β*-keto ester which was brominated to give **150**. Favorskii rearrangement of **150** followed by reduction of the formed diester yielded the desired diol **151** (Scheme 27).[73]

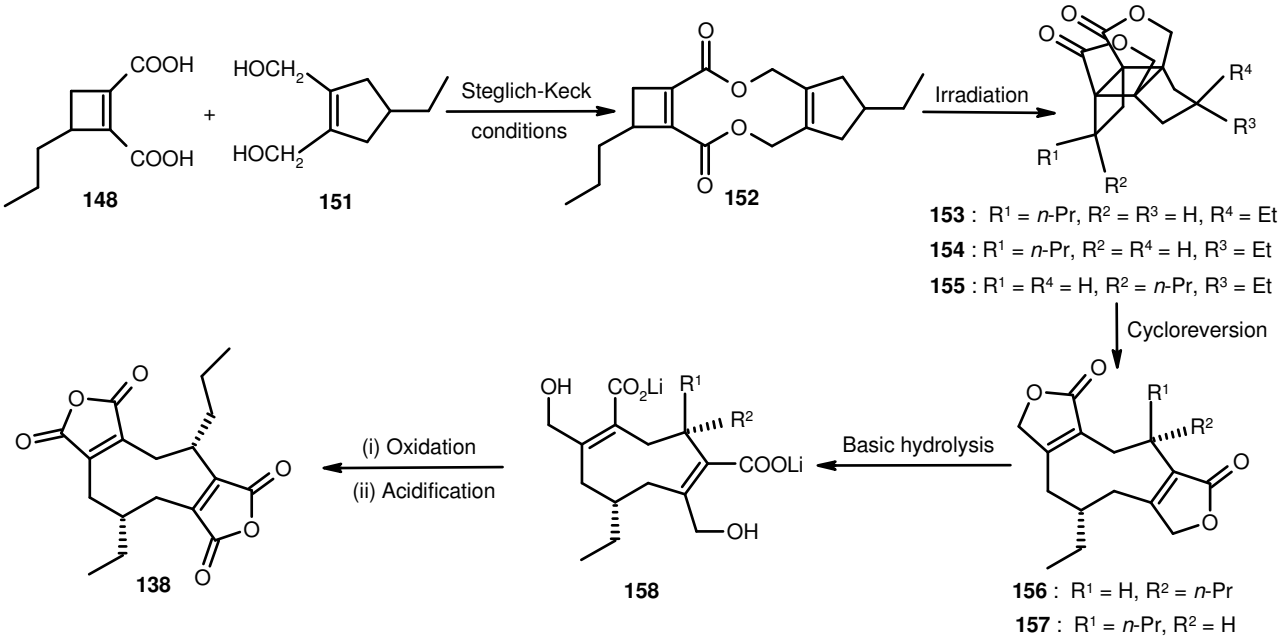
**Scheme 26**




**Scheme 27**




**Scheme 28**



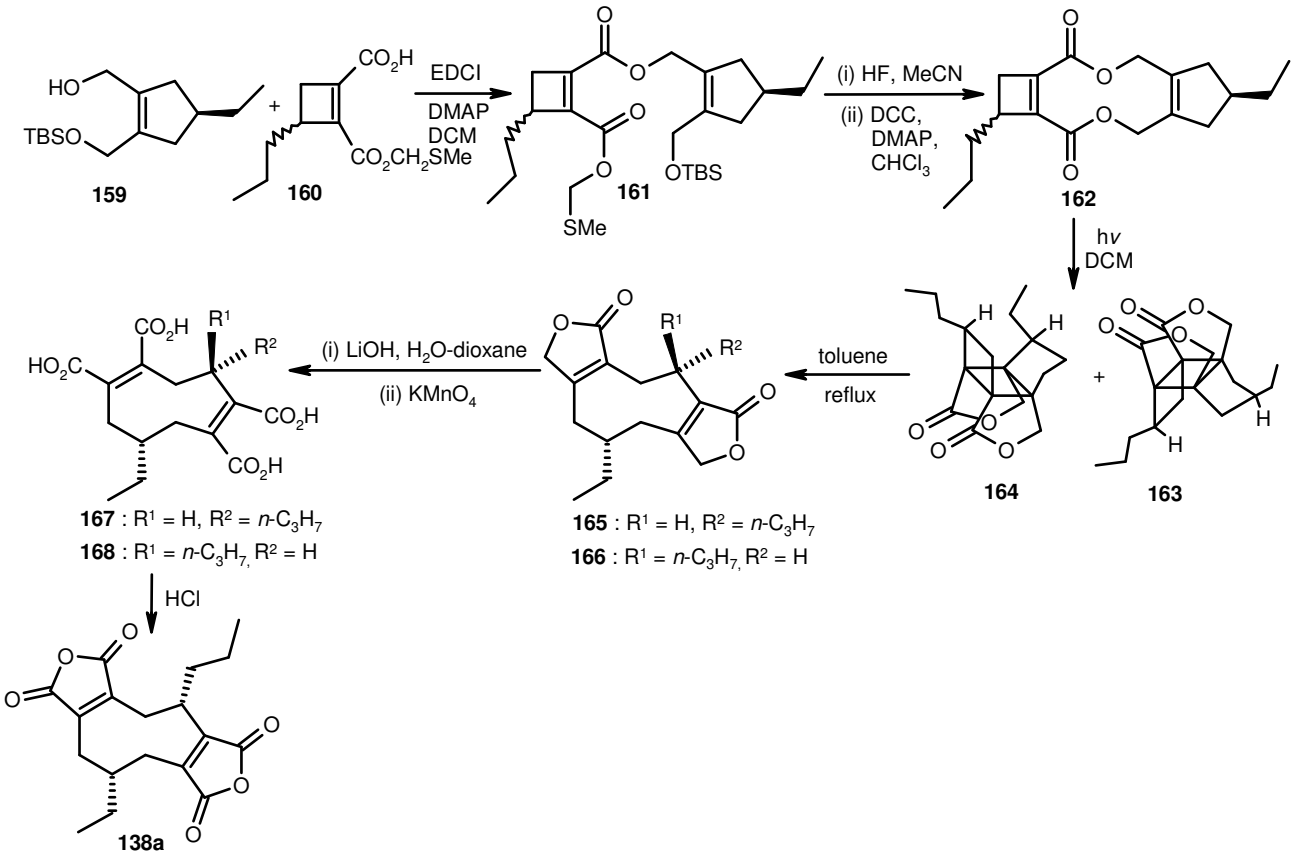

Treatment of a mixture of **148** and **151** under Steglich-Keck conditions was adopted for obtaining diolide **152** (Scheme 28). The diolide **152**, which was obtained as a mixture of *cis* and *trans* isomers, was irradiated to yield the intramloecular products **153**, **154** and **155** as *exo-exo*, *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 **156** and **157**. Basic hydrolysis of a mixture of **156** and **157** followed by oxidation of the carboxylates **158** with permanganate and subsequent acidification afforded **138** exclusively. The authors explained herein that epimerisation of the propyl side chain occurs during oxidation yielding exclusively the more stable *cis* isomer **138**.[73]

**(b) Asymmetric Synthesis of Byssochlamic acid**

James D. White *et al*, extended the photo addition-cycloreversion approach which they utilized for the synthesis of (±)-byssochlamic acid to embrace an asymmetric variant of the plan shown in racemic synthesis (Scheme 26, 27 and 28) which leads to both enantiomers of the natural product (Scheme 29).[74]

**Scheme 29**

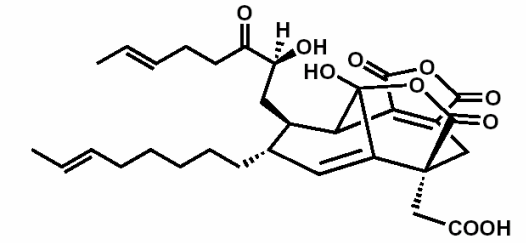



A photoaddition-cycloreversion strategy applicable to enatiospecific synthesis of natural byssochlamic acid and its enantiomer was developed by James D. White *et al*. Methylthiomethyl ester **161** was obtained by coupling (–)-**159** with (±)-monocarboxylic

acid **160**. Removal of both the silyl and methylthiomethyl groups was carried out using HF. The hydroxy acid generated in this reaction was not isolated but was subjected directly to Keck-Steglich lactonization conditions to produce diester **162**, which upon irradiation gave *exo*,*exo* and *exo*,*endo* [2 + 2] photoadducts **163** and **164**, respectively. The photoadducts underwent thermal cycloreversion to produce nine-membered bislactones **165** and **166**. Conversion of these lactones via 1,5-cyclononadienes **167** and **169** to naturally occurring (+)-byssochlamic acid (**138a**) was accompanied by acid-catalyzed epimerization of the *n*-propyl substitutent. The same sequence of reactions using the (*S*)-isomer of **159** furnished the unnatural byssochlamic acid.

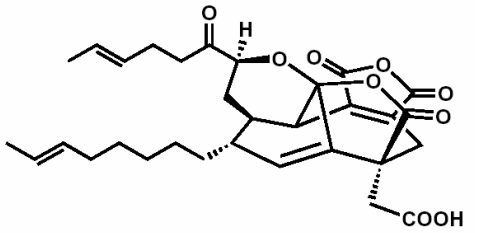
### 1.4.2 Phomoidrides

Phomoidrides have been isolated from *Phoma* species. They have been shown in vitro to inhibit the enzymes SQS and Ras farnesyl transferase.[75-77] Therefore, **169a** and **169b** are thought to be attractive lead structures for the development of cholesterol-lowering or anticancer agents. Because of their biological activities and wide array of intriguing structural features, five total syntheses have been developed in recent years.[78-82]




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

**169a**

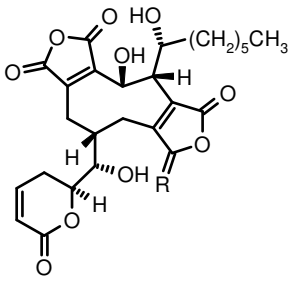
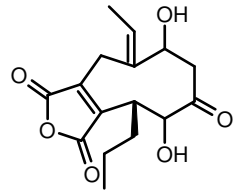
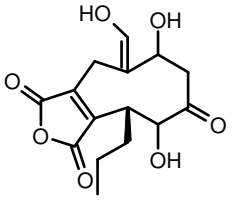
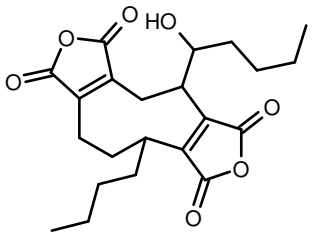


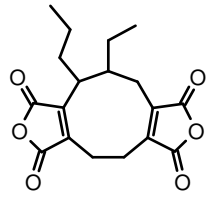
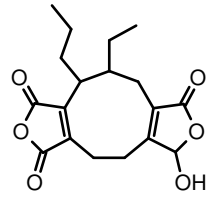
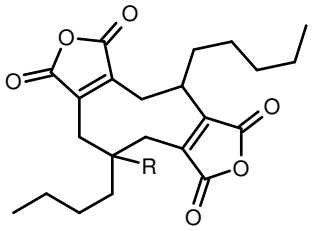
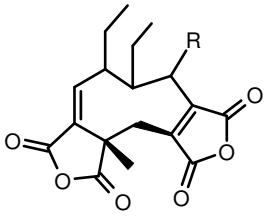

(–)-CP-263,114 (phomoidride B)

**169b**

Isolation and biological activity of all other naturally occurring bioactive nonadrides have been summarized in Table 3.

**Table 3. Isolation and Biological Activity of Naturally Occurring Nonadrides**

| No. | Compound Struture | Source | Activity | Refs. |
|---|---|---|---|---|
| 1 |  Rubratoxin A (R = H, OH) Rubratoxin B (R = O) | *Penicillium rubrum* | Antimicrobial and antitumor | 83, 84, 85 |
| 2 |  Cornexistin  Hydroxycornexistin | *Paecilomyces variotii* SANK 21086 | Herbicidal | 86, 87, 88 |
| 3 |  Zopfiellin | *Zopfiella curvata* | Fungicidal and antibacterial | 89, 90 |

| | | | | |
|---|---|---|---|---|
| 4 |  <br>Heveadride | *Helminthosporium heveae* | Antifungal | 91, 93 |
| 5 |  <br>Dihydroepiheveadride | *Bipolaris heveae* | Antifungal | 92, 93 |
| 6 |  <br>Scytalidin (R = OH)<br>Deoxyscytalidin (R = H) | *Scytalidium* | Fungicidal | 94, 95 |
| 7 |  <br>Glauconic acid (R = OH)<br>Glaucanic acid (R = H) | *Penicillium glaucum* and *Penicillium purpurogenum* | Not known | 71, 96 |

In conclusion, because of the structural complexity and unique biological activity, all above nonadrides appear to be good target molecules to carry out the total synthesis.

## 1.5 Summary

In this chapter we have described a concise account on the chemistry of monoalkyl substituted, dialkyl substituted and complex dialkyl substituted maleic anhydrides. Maleic anhydride and its derivative are an important building block and they have been used to design several natural products. Methylmaleic anhydride (citraconic anhydride) is the most widely used derivative of monoalkyl substituted maleic anhydride. Only three synthetic approaches to methylmaleic anhydride are known in the literature. Monoalkyl substituted maleic anhydrides have not been much explored as compared to methylmaleic anhydride. Few general methods are reported for the synthesis of monoalkyl substituted maleic anhydrides. First approach involves conjugate addition of dialkyl cuprate to dimethyl acetylenedicarboxylate. Recently, Chen and co-workers reported a palladium catalyzed dicarbonylation of terminal acetylenes in the presence of carbon monoxide. Nature offers a diverse menu of dialkyl substituted maleic anhydrides with well established and promising bioactivities. More than 21 synthetic approaches to dimethyl maleic anhydride using variety of strategies are known in the literature. The most elegant approach to dimethyl maleic anhydride has been reported by Baumann using 2-aminopyridine and two equivalents of maleic anhydride via the formation of disubstituted maleimide. Many alkylmethylmaleic anhydrides are known as natural products and have been synthesized. The most important being chaetomellic anhydride A, which is a promising anticancer agent. After its isolation, in the past fifteen years several syntheses have been reported. Novel chemistry has been involved in these approaches and each synthesis having its own advantages. Nonadrides have been isolated as bioactive natural products and these molecules have attracted attention of researchers due to their powerful inhibition of ras farnesyl transferase. Three syntheses of byssochlamic acid have been reported, the first one by Gilbert Stork, while James D. White has accomplished the most recent syntheses. In short, maleic anhydrides and their derivatives are potential building blocks to design several desired complex bioactive natural and unnatural products. We feel that development of new elegant approaches to symmetrical and unsymmetrical maleic anhydrides is challenging task of current interest.

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# Chapter 2

## *Synthesis of Isomaleimides, Alkyl and Dialkyl Substituted Maleimides and Natural Fimbrolides*

This chapter features the following sections:

# 2A. Section A

## *Cyanuric Chloride: Decent Dehydrating Agent for an Exclusive and Efficient Synthesis of Kinetically Controlled Isomaleimides*

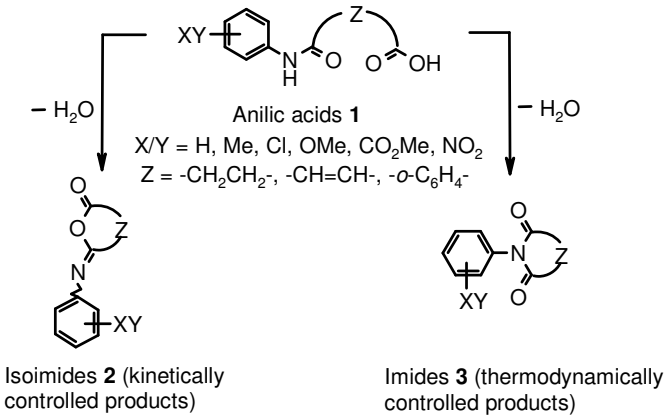
This section features the following topics:

## 2A Section A: Cyanuric Chloride: Decent Dehydrating Agent for an Exclusive and Efficient Synthesis of Kinetically Controlled Isomaleimides

### 2A.1 Background

Anilic acids on dehydration under kinetically controlled conditions form isoimides while under thermodynamically controlled conditions they furnish the corresponding imides (Scheme 1).[1,2]

**Scheme 1**




A large number of applications of imides are known and plenty of methods to design them are well established.[2] The first isomaleimide synthesis was reported in 1955 by Tsou *et al*[1a] using trifluroacetic anhydride as a dehydrating agent and to the best of our knowledge a natural product with an isoimide moiety is not known. In comparison with imide, the isoimide chemistry is less explored and only limited isoimide chemistry is known, as a general and efficient method to exclusively design isoimides is still elusive. Presently isomaleimides have been synthesized from the corresponding maleamic acids by using (i) $COCl_2/Et_3N$,[3] (ii) DCC,[4] (iii) $Ac_2O/NaOAc$,[5] (iv) $CH_3COCl/Et_3N$,[6] (v) $EtOCOCl/Et_3N$,[6] (vi) $(CF_3CO)_2O/Et_3N$,[7] (vii) ketenes[8] and (viii) 2-chloro-1,3-dimethylimidazolinium chloride[9] in pyridine as dehydrating agents. In the synthesis of isomaleimides,[3-9] the use of above mentioned dehydrating reagents have the following limitations (a) excess amount of reagent is required, (b) tedious workup and purification procedures are involved, (c) low yields of isoimides with decomposition of anilic acids, (d) formation of inseparable mixtures of imides and isoimides in varying proportions, (e)

addition of liberated hydrochloric acid to the carbon-carbon double bond and (f) [2+2] cycloaddition reactions of formed imine with ketenes, chlorosulfonylisocyanates, chloroacetyl or 2-chlorophenoxyacetyl chlorides.[10] Recently isoimides have found wide range of applications in preparation of surfmers,[11] novel polyimides,[12] novel polyisoimides,[5d,13] agro-chemicals,[9a] pharmaceuticals,[9a] spiro $\beta$-lactams,[6,10a,b] resins,[14] polyhydrazides,[15] herbicidal anti-dotes,[16] membranes,[13b] adhesives,[13b] diagnosis and cancer treatment and in vivo photodynamic therapy.[4d,17] Isoimides are useful in the detection and measurement of biological materials such as bacteria, enzymes and hormones.[7b] To focus on the unique butiminolide functional moiety and to explore the chemistry of this important functional group, a search for readily available, cheap, efficient and general quantized reagent is a task of significant challenge.[1-9] Cyanuric chloride has been used earlier as dehydrating agent on several type of organic compounds. Trichloro-1,3,5-triazine (cyanuric chloride) has been known since 1827. It has occupied an important place in organic synthesis because of its easy availability, low cost and clean selective reactions.[18] It is commercially available and can also be conveniently synthesized by trimerization of cyanogens chloride.[19] The reactivity of cyanuric chloride with amines, alcohols, thiols and phenols has been widely put to use[20] in the synthesis of dyes, herbicides, insecticides, fungicides, pesticides, drugs and in the preparation of immobilized enzymes, a new class of polypode ligands and chiral stationary phases for GC and HPLC. It has been also used for the synthesis of *N*-protected chiral $\alpha$-aminonitriles,[21] as a mild reducing agent for carboxylic acids to alcohols,[22] in the synthesis of 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM),[23] dendrimers,[24] macrocyclic scaffolds,[25] as a mild and efficient alternative to the classical Swern oxidation,[26] in the preparation of acyl azides,[27] acyl chlorides[28] and chiral monochloro-s-triazine reagents for the liquid chromatographic separation of amino acid enantiomers.[29] 2,4,6-Trisubstituted triazines have been used as antimalarial and antibacterial agents.[30] Recently, cyanuric chloride has been used for the synthesis of cyanuric acid-bridged porphyrin-porphyrin dyads,[31] calixarenes[32] and benzoxazinones.[33] Cyanuric chloride is a highly effective catalyst for the organocatalytic Beckmann rearrangement under reflux in acetonitrile or nitromethane.[34] The predominance of deprotonation of the amide groups or conversion of

carboxylic hydroxyl group into good leaving groups results in predominant formation of the imides or isoimides respectively.[35] In this context, we reasoned that in comparison with acid anhydrides, acid chlorides, ketenes and carbodiimides, the optimum reactive chloroimines will be soft and the best dehydrating agents to obtain these kinetically controlled isomaleimide products. We chose cyanuric chloride with three inherently present chloro-imine units for this kinetic dehydrative cyclization purpose.

### 2A.2 Present Work: Results and Discussion

In our research group we have been using cyclic anhydrides as potential precursors for the synthesis of recently isolated bioactive natural and unnatural products[36] and the reactions of cyclic anhydrides with a variety of aromatic and aliphatic amines are known to furnish the corresponding anilic and amic acids in high yields.[36f] In accordance with our aim, we performed the reaction of *N*-phenylmaleanilic acid (**4a**) in DCM with cyanuric chloride (1.1 equiv.) in the presence of triethylamine (3.0 equiv.) at room temperature and exclusively obtained the corresponding *N*-phenylisomaleimide (**5a**) in 90% yield (Scheme 2). We believe that the present kinetic dehydration must be proceeding via the formation of intermediate 2,4-dichlorotriazinoylmaleanilate and both the leaving group ability of 2,4-dichlorotrazine-2-ol and the stability of the formed 4,6-dichlorotriazin-2-one must be responsible for this quantitative and exclusive formation of isoimide. In the same conversion, use of half an equivalent of cyanuric chloride also furnished the isoimide **5a** but in less than 50% yield, revealing that 1.1 equivalent of cyanuric chloride is necessary for the quantitative conversion of maleanilic acid to the corresponding isoimide, indicating that the in situ generated 4,6-dichlorotriazin-2-one does not further act as a dehydrating agent with same reactivity. To establish the generality of this new set of reaction conditions, we prepared several maleanilic acids **4b**-**g** and all of them on treatment with cyanuric chloride furnished exclusively the corresponding desired *N*-arylisomaleimides **5b**-**g** in 90-98% yields (Table 1). The structures of these butiminolides **5a**-**g** were established from the characteristic lactone carbonyl and imine double bond stretching frequencies in Infra-red spectra, presence of two doublet peaks for the vinylic protons in $^{1}$H NMR spectra and $^{13}$C NMR data. The presence of *syn* and *anti* isomerism was observed in $^{1}$H NMR spectra of some

of the isoimides. We prepared the mono-substituted methyl and phenyl maleanilic acids **4i** and **4j** from the reactions of *p*-toluidine with methylmaleic and phenylmaleic anhydrides respectively.[37] These acids **4h**-**j** on treatment with cyanuric chloride also gave the corresponding mono-substituted isomaleimides **5h**-**j** in 90-97% yields.

**Scheme 2**

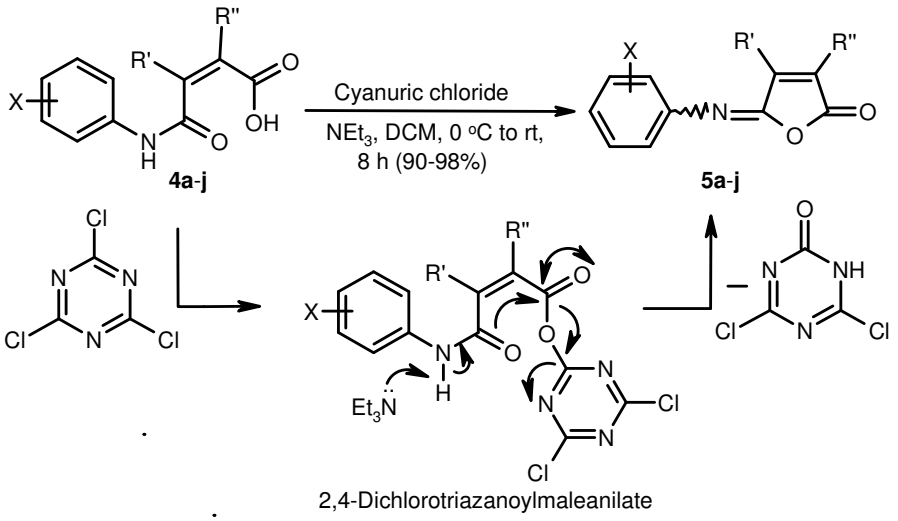
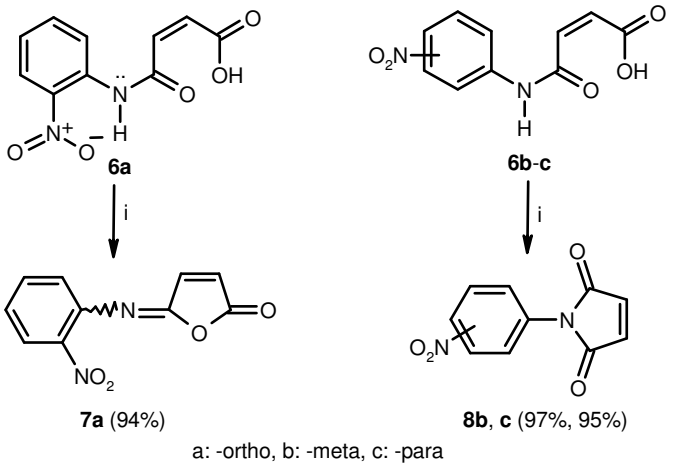



**Table 1**

| No. | Acid | X | R’ | R’’ | Product (%) |
|---|---|---|---|---|---|
| 1. | **4a** | H | H | H | **5a** (90) |
| 2. | **4b** | *o*-$CH_3$ | H | H | **5b** (98) |
| 3. | **4c** | *p*-$CH_3$ | H | H | **5c** (93) |
| 4. | **4d** | *o*-$OCH_3$ | H | H | **5d** (90) |
| 5. | **4e** | *p*-$OCH_3$ | H | H | **5e** (91) |
| 6. | **4f** | *p*-Cl | H | H | **5f** (93) |
| 7. | **4g** | *o*-$CO_2CH_3$ | H | H | **5g** (94) |
| 8. | **4h** | H | H | $CH_3$ | **5h** (97) |
| 9. | **4i** | *p*-$CH_3$ | H | $CH_3$ | **5i** (90) |
| 10. | **4j** | *p*-$CH_3$ | Ph | H | **5j** (95) |

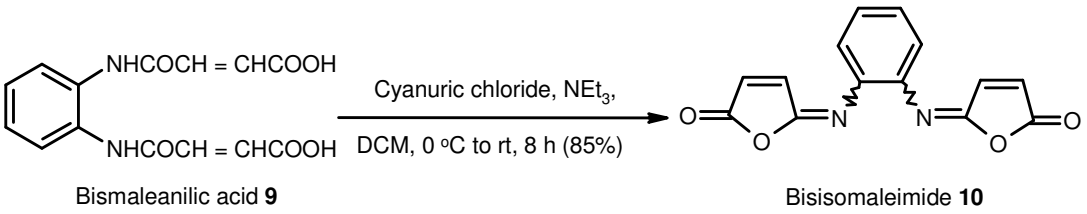



**Scheme 3.** *Reagents and conditions*: (i) Cyanuric chloride, $NEt_3$, DCM, 0 $^oC$ to rt, 8 h.

Generally, the isomaleimides with a nitro group on aromatic ring are prepared directly from the corresponding diacidchlorides and nitro anilines.[38] We planned to study the effect of electron withdrawing *ortho-/meta-/para*-nitro groups on these cyanuric chloride induced dehydration reactions and prepared the corresponding *o-/m-/p*-nitromaleanilic acids **6a**-**c**. The treatment of *o*-nitromaleanilic acid (**6a**) with cyanuric acid chloride exclusively gave the corresponding *o*-nitroisomaleimide **7a** in 94% yield, while *m*-nitromaleanilic acid (**6b**) and *p*-nitromaleanilic acid (**6c**) under the same set of reaction conditions gave only the corresponding nitromaleimides **8b**,**c** in quantitative yields (Scheme 3). Herein we were unable to obtain the corresponding isomaleimides from acids **6b**,**c** even after carrying out the addition of cyanuric chloride at –20 $^oC$ or –78 $^oC$ and we always ended-up with formation of maleimides **8b**,**c**. We reason that the *o*-nitromaleanilic acid **6a** exclusively provides isoimide **7a** due to the intramolecular hydrogen bonding of –NH proton with the *o*-nitro group forming a stable six-membered cyclic structure. This makes the –NH proton less accessible to the base and isoimide formation takes place via the participation of lone pair of electrons on the nitrogen atom.

The diacid **9** on treatment with cyanuric chloride (2.2 equiv.) also smoothly furnished the bis-isomaleimide **10** in 85% yield (Scheme 4). It appears that the bisisoimide **10** will be a potential substrate to attempt novel [2+2] intramolecular cycloaddition reaction.

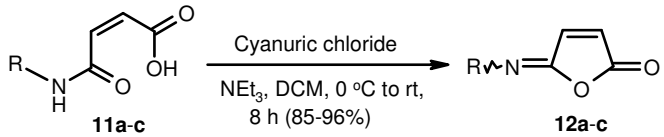
**Scheme 4**




Bismaleanilic acid **9** — Bisisomaleimide **10**

The reaction of cyanuric chloride with maleamic acids **11a-c** also gave the corresponding *N*-alkylisomaleimides **12a-c** in 85-96% yields (Scheme 5, Table 2) indicating that the present kinetic dehydration condition works equally well with maleamic acids to design *N*-alkylisomaleimides in very good yields.

**Scheme 5**



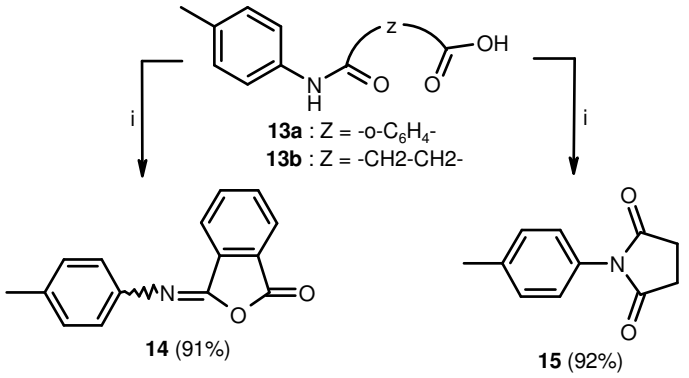

**11a-c** **12a-c**

**Table 2**

| No. | Acid | R | Product (%) |
|---|---|---|---|
| 1. | **11a** | $CH_3$ | **12a** (87) |
| 2. | **11b** | *p*-$H_3CO$-$C_6H_4$-$CH_2$ | **12b** (85) |
| 3. | **11c** | (*R*)-PhCH($CH_3$)$CH_2$ | **12c** (96) |

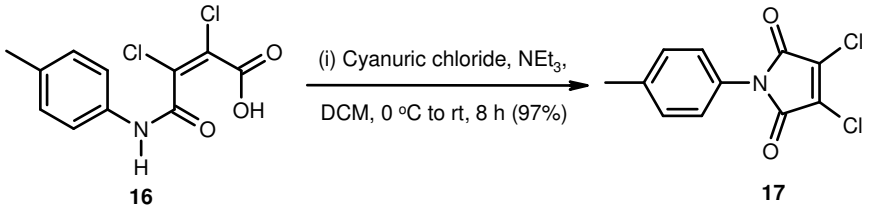
We studied the dehydration reactions of phthalanilic acid **13a** and succinanilic acid **13b** using cyanuric chloride as a dehydrating agent under the same set of reaction conditions. The acid **13a** furnished the desired isophthalimide **14** in 91% yield, while the acid **13b** gave exclusively the corresponding succinimide **15** in 92% yield (Scheme 6). Here we surmise that for isolation of these kinetically controlled butiminolides, a strong carbon-carbon double bond support to the backbone is essential. Alternatively, the formed relatively less stable isosuccinimide might be undergoing an in situ isomerization to the corresponding succinimide. In our hands reaction of dichloromaleanilic acid **16** with cyanuric chloride also gave the corresponding dichloromaleimide **17** in 97% yield[39]

(Scheme 7). We feel that the present imide formation could be due to the extra thermodynamic stability of disubstitued maleimides, indicating that the present conditions are also useful to design the corresponding succinimides and disubstituted maleimides.[40] The conversion of kinetically controlled isoimides to the corresponding thermodynamically more stable imides is known in the literature.[41]




**Scheme 6.** *Reagents and conditions*: (i) Cyanuric chloride, $NEt_3$, DCM, 0 $^oC$ to rt, 8 h.

**Scheme 7**




## 2A.3 Summary

In summary, we have described an elegant general approach to exclusively design kinetically controlled *N*-aryl/*N*-alkyl isomaleimides and isophthalimides using readily available cyanuric chloride as a dehydrating agent and the present approach has several advantages over earlier approaches. We feel that the present new clean and efficient route to isoimides will be highly useful to further explore the important field of isoimide chemistry as they are dissymmetric in nature, nucleophilic ring openings under neutral conditions are feasible and both carbonyl and imine functionalities will be accessible.

## 2A.4 Experimental

Commercially available cyclic anhydrides and aromatic/aliphatic amines were used. Freshly recrystallized cyanuric chloride ($CCl_4$) was used. The amic/anilic acids were obtained by adding solution of aliphatic/aromatic amines in ether to the solution of corresponding anhydrides in ether at room temperature. The reaction of MMA with amines in general was not regioselective; a mixture of isomeric maleanilic acids (85:15) was obtained, which upon recrystalization gave pure major isomer. However, the reaction of PMA with amines was regioselective; only single isomer of maleanilic was obtained.

**General procedure for the preparation of isoimides.** To a slurry of amic acid (10 mmol) in DCM (30 mL) was added $Et_3N$ (30 mmol) in a drop-wise fashion with constant stirring at 0 $^oC$. To the resulting reaction mixture was added a solution of cyanuric chloride (11 mmol) in DCM (20 mL) and the reaction mixture was further stirred for 8 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water, 5% aqueous bicarbonate, brine and dried over $Na_2SO_4$. The organic layer was concentrated in vacuo and the obtained product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to obtain pure isoimide (85-98% yields). Satisfactory IR, $^1H$ NMR and $^{13}C$ NMR and elemental analysis data were obtained for all the newly synthesized compounds.

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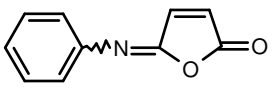
|  <br>**5a (173)** | **MP**: 65-67 $^oC$.<br>**IR** (nujol) $\nu_{max}$ 1819, 1798, 1724, 1678 $cm^{-1}$.<br>**$^1H$ NMR** ($CDCl_3$, 200 MHz) $\delta$ 6.70 (d, $J$ = 8 Hz, 0.95H), 6.80 (d, $J$ = 8 Hz, 0.05H), 7.20-7.60 (m, 6H).<br>**Anal. Calcd for $C_{10}H_7NO_2$**: C, 69.36; H, 4.08; N, 8.09. Found: C, 69.29; H, 3.97; N, 8.11. |

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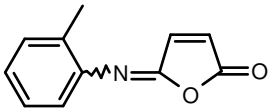
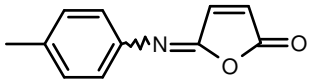
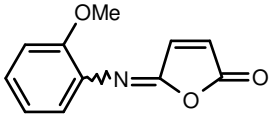
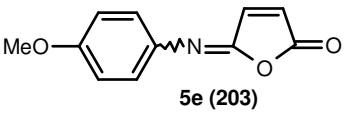
|---|---|
|  **5b (187)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1801, 1794, 1688 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.31 (s, 3H), 6.71 (d, *J* = 6 Hz, 0.96H), 6.83 (d, *J* = 6 Hz, 0.04H), 7.05-7.44 (m, 4H), 7.44 (d, *J* = 6 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 17.7, 121.7, 125.9, 126.2, 128.0, 130.2, 132.0, 142.3, 142.6, 149.7, 166.9.<br>**Anal. Calcd for $C_{11}H_9NO_2$**: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.42; H, 4.81; N, 7.53. |
|  **5c (187)** | **MP**: 76-78 $^oC$.<br>**IR** (nujol) $\nu_{max}$ 1796, 1763, 1676 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 300 MHz) $\delta$ 2.37 (s, 3H), 6.66 (d, *J* = 6 Hz, 0.9H), 6.74 (d, *J* = 6 Hz, 0.1H), 7.20 (d, *J* = 6 Hz, 2H), 7.35-7.40 (m, 3H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.0, 125.5, 127.2, 129.5, 137.6, 140.7, 143.1, 149.4, 167.2.<br>**Anal. Calcd for $C_{11}H_9NO_2$**: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.43; H, 4.92; N, 7.36. |
|  **5d (203)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1807, 1794, 1690 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 3.87 (s, 3H), 6.66 (d, *J* = 6 Hz, 1H), 6.90-7.00 (m, 2H), 7.19 (dd, *J* = 8 & 2 Hz, 1H), 7.33 (dd, *J* = 8 & 2 Hz, 1H), 7.47 (d, *J* = 6 Hz, 1H).<br>**Anal. Calcd for $C_{11}H_9NO_3$**: C, 65.01; H, 4.46; N, 6.89. Found: C, 64.94; H, 4.51; N, 6.92. |
|  **5e (203)** | **MP**: 75-77 $^oC$.<br>**IR** (nujol) $\nu_{max}$ 1796, 1665 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 3.84 (s, 3H), 6.62 (d, *J* = 6 Hz, 0.96H), 6.74 (d, *J* = 6 Hz, 0.04H), 6.92 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 6 Hz, 1H), 7.56 (d, *J* = 8 Hz, 2H).<br>**Anal. Calcd for $C_{11}H_9NO_3$**: C, 65.01; H, 4.46; N, 6.89. Found: C, 64.92; H, 4.32; N, 6.97. |

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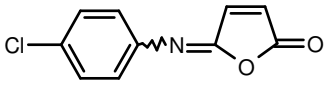
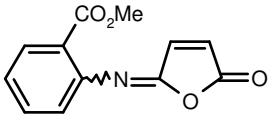
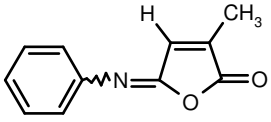
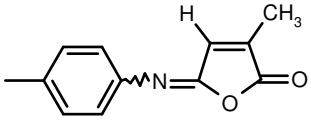
|  <br>**5f (207)** | **MP**: 100-102 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1825, 1801, 1759, 1678 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 6.71 (d, $J$ = 6 Hz, 0.94H), 6.78 (d, $J$ = 6 Hz, 0.06H), 7.37 (s, 4H), 7.40 (d, $J$ = 6 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 126.7, 128.0, 129.2, 133.2, 141.9, 143.2, 150.4, 166.8.<br>**Anal. Calcd for $C_{10}H_6NO_2Cl$**: C, 57.85; H, 2.91; N, 6.75. Found: C, 58.01; H, 3.01; N, 6.66. |
|  <br>**5g (231)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1801, 1720, 1713 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 3.83 (s, 3H), 6.73 (d, $J$ = 6 Hz, 1H), 7.02 (d, $J$ = 8 Hz, 1H), 7.24 (t, $J$ = 8 Hz, 1H), 7.44-7.57 (m, 2H), 7.98 (d, $J$ = 8 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 51.8, 121.3, 121.7, 124.8, 129.2, 130.5, 132.5, 141.7, 145.3, 151.3, 165.7, 166.1.<br>**Anal. Calcd for $C_{12}H_9NO_4$**: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.43; H, 3.81; N, 5.97. |
|  <br>**5h (187)** | **MP**: 110-112 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1780, 1674 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 300 MHz) $\delta$ 2.16 (s, 3H), 7.04 (s, 1H), 7.15-7.45 (m, 5H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 10.9, 124.5, 126.7, 128.8, 136.4, 139.3, 143.8, 149.6, 168.6.<br>**Anal. Calcd for $C_{11}H_9NO_2$**: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.43; H, 4.66; N, 7.59. |
|  <br>**5i (201)** | **MP**: 115-116 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1778, 1674 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 300 MHz) $\delta$ 2.15 (s, 3H), 2.36 (s, 3H), 7.02 (s, 1H), 7.19 (d, $J$ = 9 Hz, 2H), 7.32 (d, $J$ = 9 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 10.7, 20.9, 125.0, 129.4, 136.5, 136.9, 138.7, 141.2, 148.9, 168.7.<br>**Anal. Calcd for $C_{12}H_{11}NO_2$**: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.70; H, 5.63; N, 7.07. |

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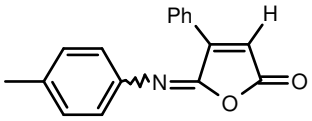
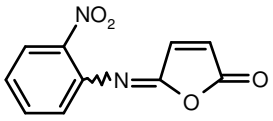
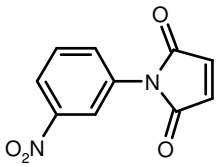
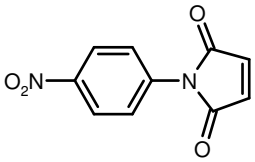
|  <br>**5j (263)** | **MP**: 174-176 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1771, 1657 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.37 (s, 3H), 7.15-7.30 (m, 2H), 7.35-7.55 (m, 6H), 7.85-8.05 (m, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.2, 125.6, 127.9, 128.1, 129.0, 129.6, 130.9, 133.0, 137.5, 137.8, 141.3, 148.7, 166.7.<br>**Anal. Calcd for $C_{17}H_{13}NO_2$**: C, 75.55; H, 4.98; N, 5.32. Found: C, 75.71; H, 5.06; N, 5.38. |
|  <br>**7a (218)** | **MP**: 113-115 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1817, 1801, 1702, 1527, 1377 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 6.80 (d, $J$ = 6 Hz, 1H), 7.17 (d, $J$ = 8 Hz, 1H), 7.34 (t, $J$ = 8 Hz, 1H), 7.50 (d, $J$ = 6 Hz, 1H), 7.62 (t, $J$ = 8 Hz, 1H), 8.06 (d, $J$ = 8 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 123.4, 124.9, 125.8, 129.9, 133.7, 139.3, 141.4, 141.8, 152.8, 165.6.<br>**Anal. Calcd for $C_{10}H_6N_2O_4$**: C, 55.05; H, 2.77; N, 12.84. Found: C, 54.97; H, 2.88; N, 12.97. |
|  <br>**8b (218)** | **MP**: 132-134 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1724, 1533, 1346 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 6.94 (s, 2H), 7.66 (t, $J$ = 8 Hz, 1H), 7.80 (d, $J$ = 8 Hz, 1H), 8.24 (d, $J$ = 8 Hz, 1H), 8.34 (t, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_{10}H_6N_2O_4$**: C, 55.05; H, 2.77; N, 12.84. Found: C, 55.09; H, 2.82; N, 12.90. |
|  <br>**8c (218)** | **MP**: 173-175$^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1780, 1715, 1521, 1348 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 6.94 (s, 2H), 7.68 (d, $J$ = 10 Hz, 2H), 8.33 (d, $J$ = 10 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 124.4, 125.4, 134.6, 137.1, 146.2, 168.5.<br>**Anal. Calcd for $C_{10}H_6N_2O_4$**: C, 55.05; H, 2.77; N, 12.84. Found: C, 55.17; H, 2.87; N, 12.92. |

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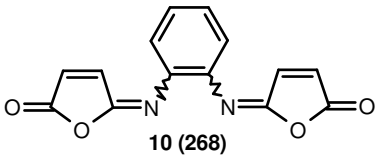
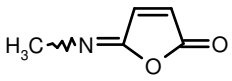
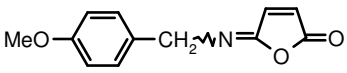
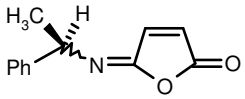
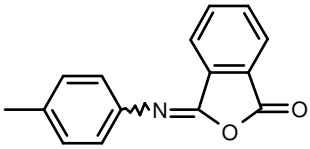
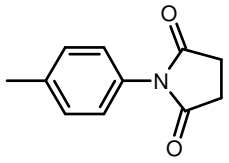
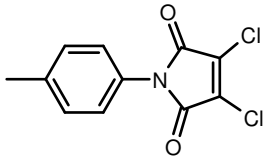
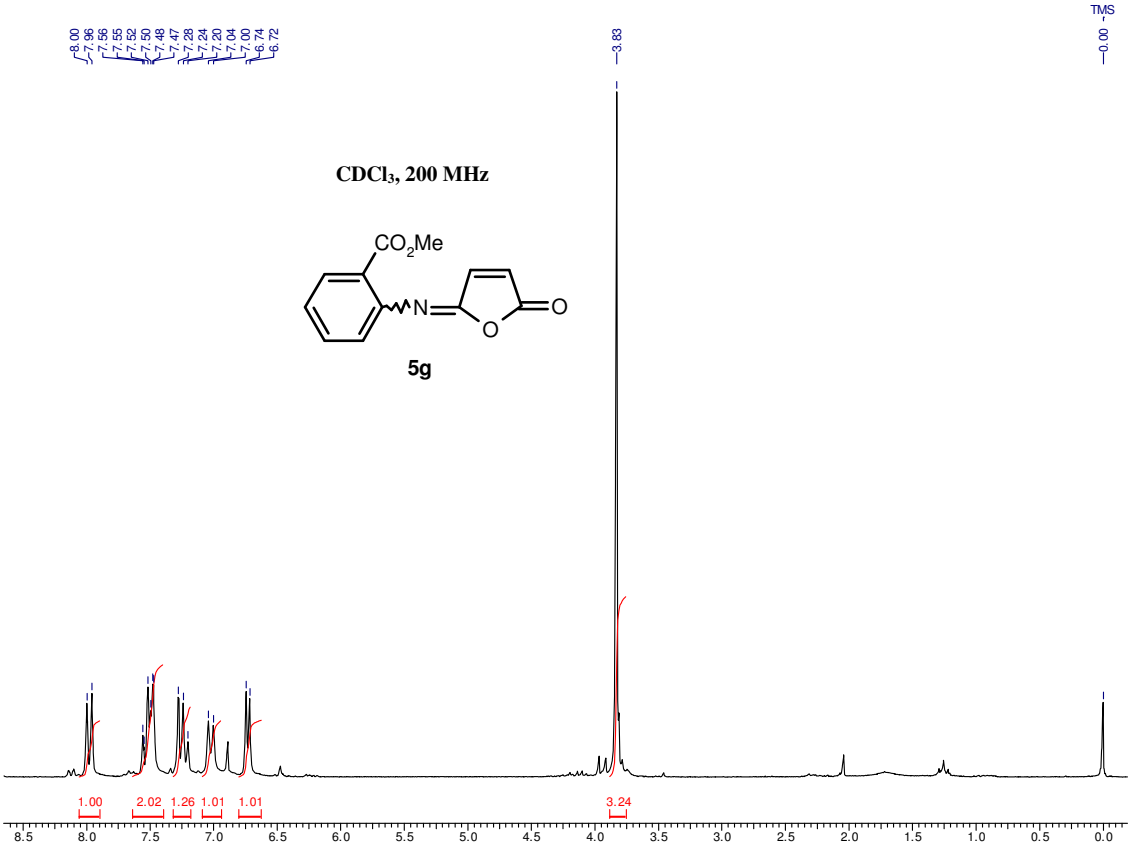
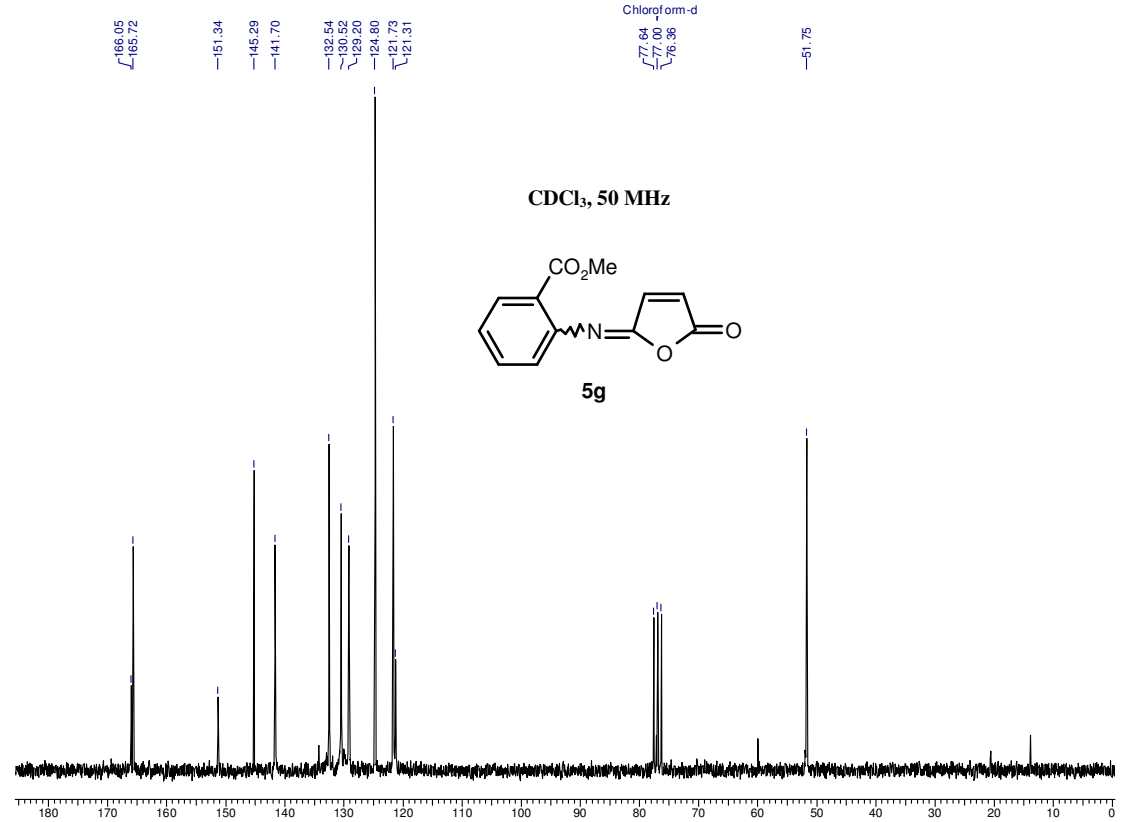
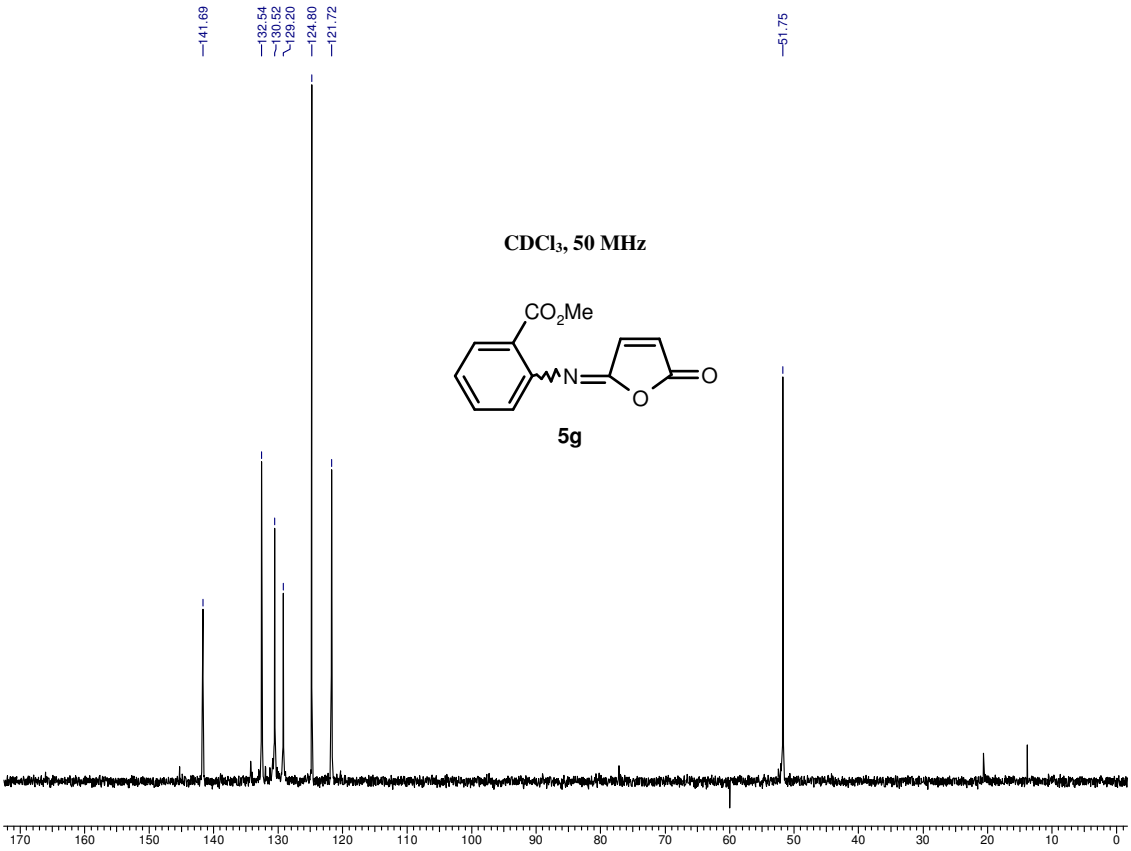
|  <br>**10 (268)** | **MP**: 143-145 $^{o}$C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1813, 1796, 1720, 1686, 1678 $cm^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 6.70 (d, $J$ = 8 Hz, 1.92H), 6.80 (d, $J$ = 8 Hz, 0.08H), 7.10-7.55 (m, 6H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 121.8, 127.0, 128.5, 137.2, 142.5, 151.4, 166.6.<br>**MS** (*m*/*e*) 268, 207, 170, 142, 115, 102, 90, 82, 64, 54.<br>**Anal. Calcd for $C_{14}H_8N_2O_4$**: C, 62.69; H, 3.00; N, 10.44. Found: C, 62.82; H, 3.11; N, 10.57. |
|  <br>**12a (111)** | Thick oil.<br>**IR** (nujol) $\nu_{max}$ 1711, 1618 $cm^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.88 (s, 3H), 6.21 (d, $J$ = 12 Hz, 1H), 7.01 (d, $J$ = 12 Hz, 1H).<br>**Anal. Calcd for $C_5H_5NO_2$**: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.11; H, 4.60; N, 12.49. |
|  <br>**12b (217)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1709, 1630 $cm^{-1.}$<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 3.80 (s, 3H), 4.76 (s, 2H), 6.64 (d, $J$ = 6 Hz, 1H), 6.90 (d, $J$ = 8 Hz, 2H), 7.15-7.35 (m, 3H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 52.7, 55.0, 113.8, 128.4, 129.0, 130.1, 142.1, 151.9, 158.6, 166.5.<br>**Anal. Calcd for $C_{12}H_{11}NO_3$**: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.24; H, 5.09; N, 6.42. |
|  <br>**12c (201)** | Thick oil.<br>**IR** (nujol) $\nu_{max}$ 1711, 1634 $cm^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.55 (d, $J$ = 6 Hz, 3H), 5.19 (q, $J$ = 6 Hz, 1H), 6.62 (d, $J$ = 6 Hz, 0.95H), 6.73 (d, $J$ = 6 Hz, 0.05H), 7.15-7.60 (m, 6H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 24.0, 58.4, 126.5, 127.2, 128.5, 128.8, 142.5, 143.7, 150.9, 166.7.<br>**Anal. Calcd for $C_{12}H_{11}NO_2$**: C, 71.62; H, 5.11; N, 6.96. Found: C, 71.77; H, 5.03; N, 7.06. |

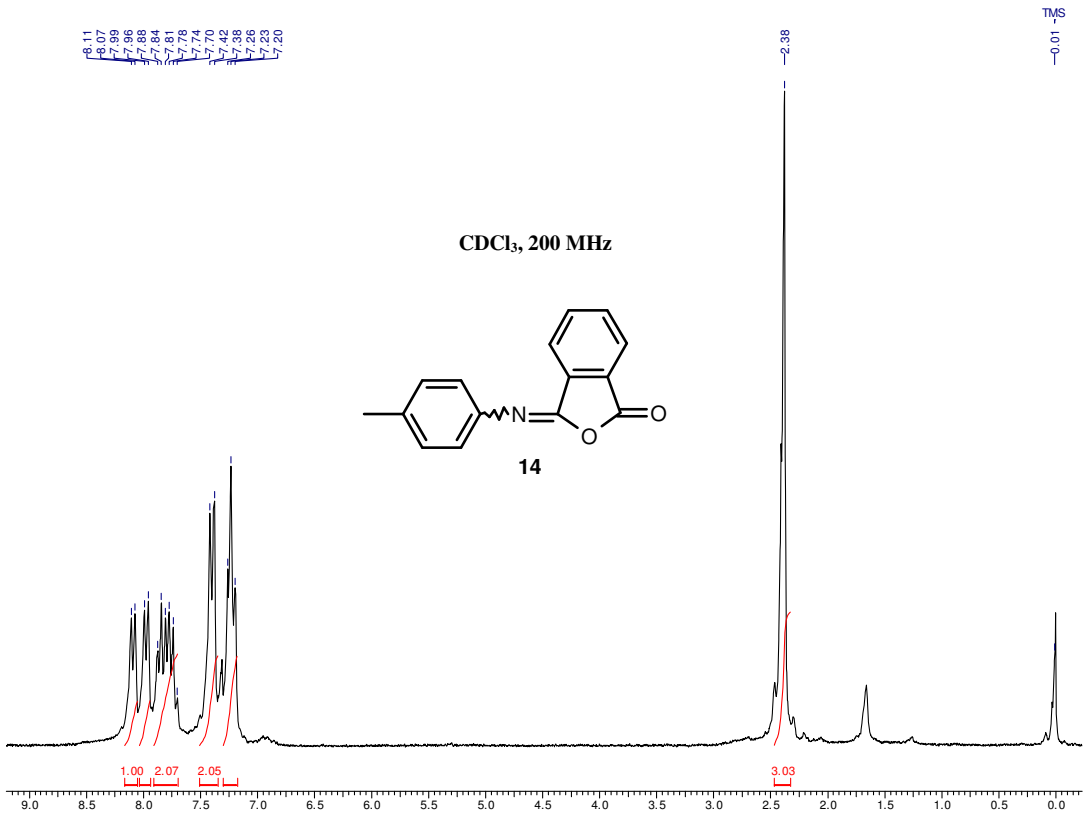
| | |
|---|---|
|  <br>**14 (237)** | **MP**: 125-127 °C.<br>**IR** (nujol) $\nu_{max}$ 1811, 1792, 1705 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.39 (s, 3H), 7.23 (d, *J* = 8 Hz, 2H), 7.41 (d, *J* = 8 Hz, 2H), 7.79 (t, *J* = 8 Hz, 1H), 7.85 (t, *J* = 6 Hz, 1H), 7.99 (d, *J* = 6 Hz, 1H), 8.10 (d, *J* = 8 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.0, 123.4, 124.9, 125.1, 127.4, 129.4, 132.7, 135.2, 136.4, 137.1, 140.9, 146.1, 164.9.<br>**Anal. Calcd for $C_{15}H_{11}NO_2$**: C, 75.93; H, 4.67; N, 5.90. Found: C, 76.06; H, 4.71; N, 5.85. |
|  <br>**15 (189)** | **MP**: 158-160 °C.<br>**IR** (nujol) $\nu_{max}$ 1770, 1705, 1600 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.38 (s, 3H), 2.88 (s, 4H), 7.16 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H).<br>**Anal. Calcd for $C_{11}H_{11}NO_2$**: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.99; H, 5.72; N, 7.33. |
|  <br>**17 (256)** | **MP**: 152-154 °C.<br>**IR** (nujol) $\nu_{max}$ 1730 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.40 (s, 3H), 7.22 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 21.2, 125.9, 127.8, 130.0, 133.5, 138.6, 162.1.<br>**Anal. Calcd for $C_{11}H_7NO_2Cl_2$**: C, 51.59; H, 2.76; N, 5.47. Found: C, 51.62; H, 2.81; N, 5.55. |

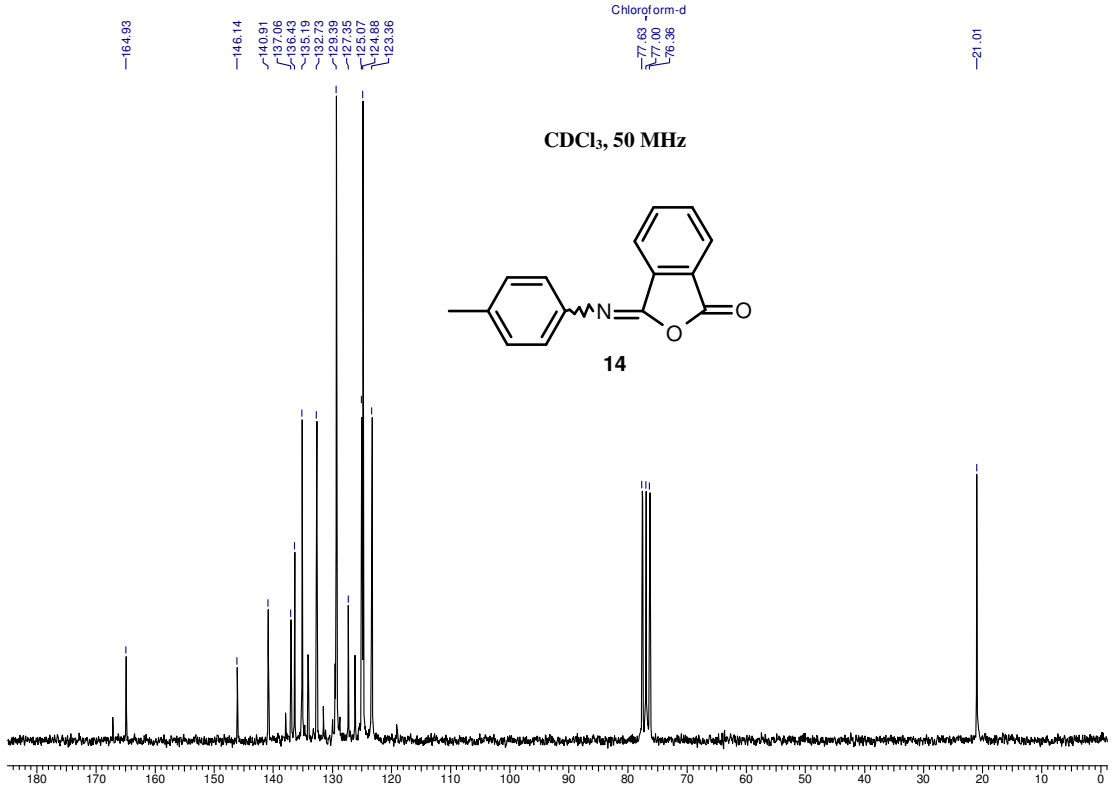
# 2A.5 Selected Spectra


8.00
7.96
7.56
7.55
7.52
7.50
7.48
7.47
7.28
7.24
7.20
7.04
7.00
6.74
6.72
3.83
TMS
0.00
CDCl3, 200 MHz
CO2Me
N
O
O
5g
1.00
2.02
1.26
1.01
1.01
3.24


166.05
165.72
151.34
145.29
141.70
132.54
130.52
129.20
124.80
121.73
121.31
Chloroform-d
77.64
77.00
76.36
51.75
CDCl3, 50 MHz
CO2Me
N
O
O
5g


141.69
132.54
130.52
129.20
124.80
121.72
51.75
CDCl3, 50 MHz
CO2Me
N
O
O
5g
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

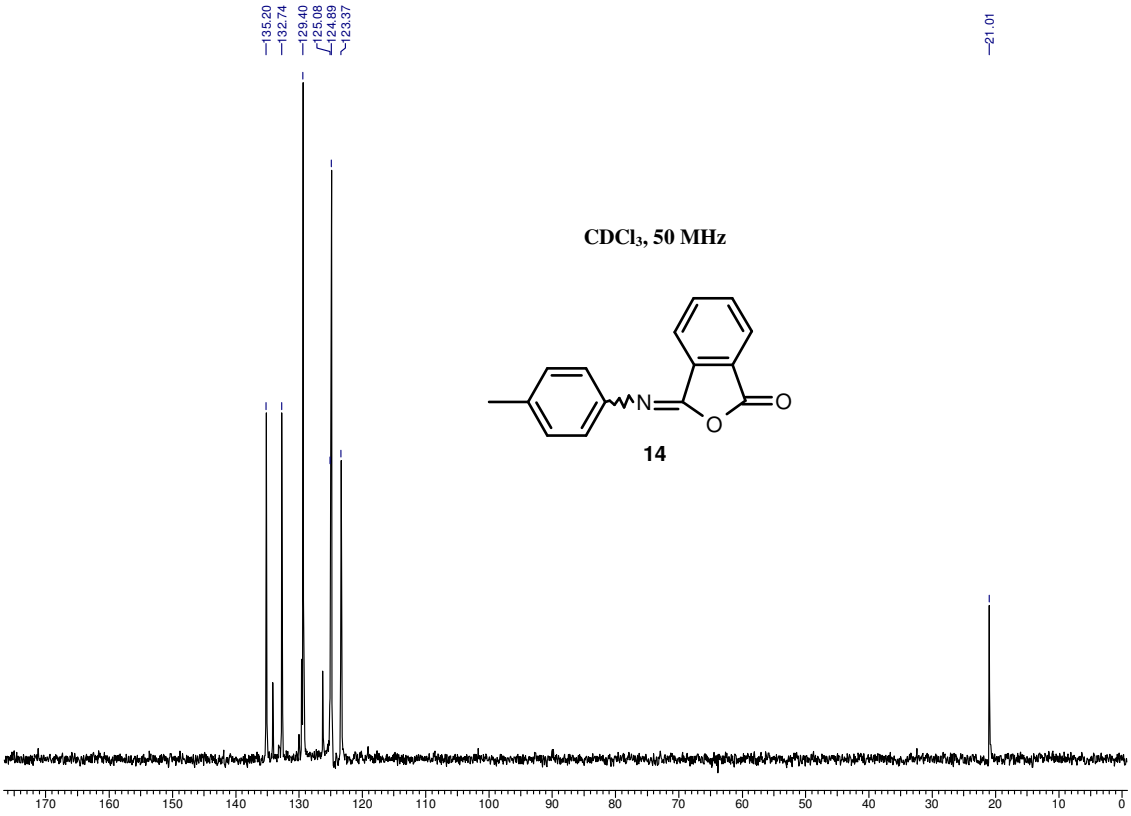

8.11
8.07
7.99
7.96
7.88
7.84
7.81
7.78
7.74
7.70
7.42
7.38
7.26
7.23
7.20
2.38
TMS
0.01
CDCl3, 200 MHz
N
O
O
14
1.00
2.07
2.05
3.03
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0




**$CDCl_3$, 50 MHz**



**14**




**$CDCl_3$, 50 MHz**



**14**

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# 2B. Section B

## *Contrathermodynamic Rearrangement of Alkylidenesuccinimides to Alkylmaleimides via the Corresponding Isoimides: A General Approach to Alkyl and Dialkyl Substituted Maleimides*

This section features the following topics:

## 2B Section B: Contrathermodynamic Rearrangement of Alkylidenesuccinimides to Alkylmaleimides via the Corresponding Isoimides: A General Approach to Alkyl and Dialkyl Substituted Maleimides

### 2B.1 Background

The cyclic anhydrides and imides are the compounds of choice for all chemists from both the basic and applied point of view for multiple purposes. The vast array of nucleophilic reactions undergone by symmetrical and unsymmetrical maleic anhydrides and maleimides confer on them a high synthetic potential.[1-3] Maleic anhydrides and maleimides bearing both hydrophilic groups and hydrophobic parts are very important for their bioactivities and material properties[4] (Figure 1). Several alkylmethyl substituted maleic anhydrides such as chaetomellic acids A and B, aspergillus acids A-D, maleic anhydride segment of tautomycin and tyromycin A are known in the literature[5,6] as bioactive natural products and one can surmise that nature might be designing them by employing the condensation of pyruvic acid with the other respective carboxylic acids. Several elegant routes to alkylmethylmaleic anhydrides have been reported in the past decade.[6] To the best of our knowledge, to date no natural product with a simple monoalkyl or dialkyl substituted maleic anhydride moiety is known in the literature. Earlier approaches to monoalkyl[7] and dialkyl[8] substituted maleic anhydrides and maleimides have been described in chapter one. The use of poisonous carbon monoxide, low temperature reactions, lower reactivities of *cis*-enolates at that temperature and contamination of *trans*-enolates are the limitations of these approaches. Hence, development of a new practical approach to the alkyl and dialkyl substituted maleic anhydrides and maleimides is still a useful and challenging task of current interest.

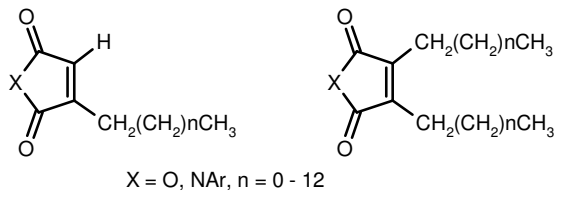



**Figure 1.** Alkyl and dialkyl substituted maleic anhydrides and imides.

## 2B.2 Present Work: Results and Discussion

The formation of maleimide-triphenylphosphine adduct is well known[9] (Figure 2) and we felt that the stepwise activation of two vinylic protons in maleimide as Wittig adducts would provide an efficient approach to alkylmaleimides and dialkylmaleimides.

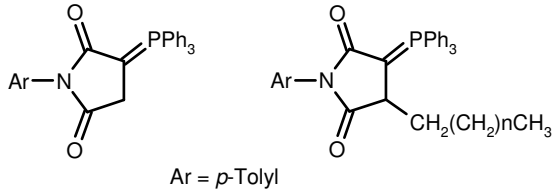
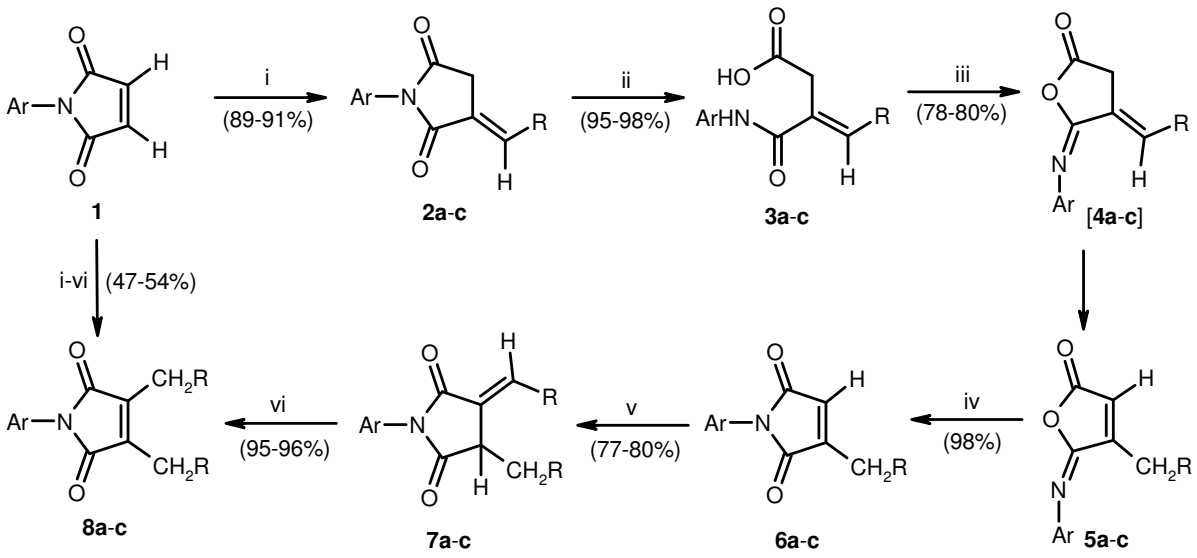



**Figure 2**. Triphenylphosphine and maleimide adducts (Wittig adducts).

In this context, starting from *N*-*p*-tolylmaleimide (**1**), we prepared the (*E*)-alkylidenesuccinimides **2a-c** in 89-91% yields[10] (Scheme 1). We thought that trisubstituted exocyclic carbon-carbon double bond in compounds **2** will migrate easily to form the trisubstituted endocyclic compounds **6** for the two reasons, *viz* (i) exocyclic to endocyclic carbon-carbon double bond migrations are generally more easy and (ii) the endocyclic trisubstituted carbon-carbon double bond will be in conjugation with two imide carbonyls.[11] We tried several reagents and reaction conditions for the conversion of **2** to **6**, but all our attempts met with failure. The conversion of **2** to **6** under basic conditions ($Et_3N$, Pyridine, DBU, NaH, *t*-BuOK, *t*-BuLi), under the thermal conditions (heat 150-200 $^oC$, tetralin reflux) and under the transition metal catalyzed isomerization conditions [$RuCl_3$, $HRuCl(PPh_3)_3$, $RhCl_3$, $HRhCl(PPh_3)_3$] were fruitless. We learnt from these experiments that such type of (*E*)-alkylidenesuccinimides **2** to alkylmaleimides **6** conversion is a difficult process. The compounds **2a-c** could be thermodynamically more stable due to the extra stability of carbon-carbon double bond with (*E*)-geometry, than the corresponding compounds **6a-c**. We planned with reason and decided to alter the imide dicarbonyl symmetry of **2** for such type of double bond migrations. The amic/anilic acids under kinetically controlled dehydration conditions are known to furnish the corresponding isoimides.[12] We felt that preparation of isoimides would be helpful for such a carbon-carbon double bond migration as the isomaleimides are expected to be more stable than the corresponding alkylidineisosuccinimides due to the extension of $\pi$-cloud conjugation from the aryl ring to the butyroiminolide carbonyl group. The highly

regioselective aqueous lithium hydroxide induced hydrolysis of **2** exclusively furnished the *β*-alkylidenesuccinanilic acids **3** in 95-98% yields.




Ar = *p*-Tolyl; **a**, R = -$CH_2(CH_2)_3CH_3$; **b**, R = -$CH_2(CH_2)_7CH_3$; **c**, R = -$CH_2(CH_2)_{11}CH_3$

**Scheme 1.** *Reagents, conditions and yields*: (i) $PPh_3$, THF, RCHO, reflux, 10 h (89-91%); (ii) Aq. 2 N LiOH, THF, 0 $^oC$ to rt, 5 h, (95-98%); (iii) Cyanuric chloride, $NEt_3$, DCM, 0 $^oC$ to rt, 8 h (78-80%); (iv) AcOH, reflux, 5 h (98%); (v) $PPh_3$, AcOH, RCHO, reflux, 18 h (77-80%); (vi) $NEt_3$ + THF (1:1), reflux, 48 h (95-96%).

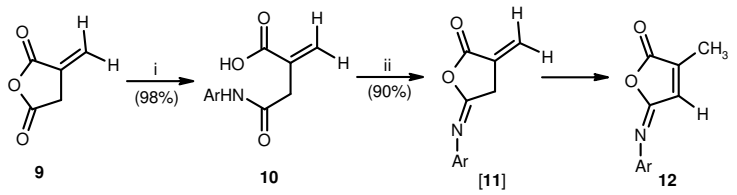
| Comp. No. | **2a** | **2b** | **2c** | **3a** | **3b** | **3c** | **5a** | **5b** | **5c** | **6a** | **6b** | **6c** | **7a** | **7b** | **7c** | **8a** | **8b** | **8c** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % Yield | 91 | 89 | 89 | 98 | 96 | 95 | 80 | 78 | 78 | 98 | 98 | 98 | 80 | 78 | 77 | 96 | 95 | 95 |

Cyanuric chloride is a decent dehydrating agent for such type of kinetic dehydrations[12] and the treatment of acids **3** with cyanuric chloride in the presence of triethylamine as a base at room temperature directly furnished the expected *anti-β*-alkylisomaleimides **5** in 78-80% yields. Both the dehydrative cyclizations of acids **3** to form the intermediates *β*-alkylideneisosuccinimides **4** (which could not be isolated) and the abstraction of the *α*-methylene proton on intermediate **4** to form the *β*-alkyl isomaleimides **5** took place in one-pot. Our hypothesis turned out to be correct and to the best of our knowledge this is the first example of carbanion generation on an isoimide skeleton, though in situ, and its application for the facile carbon framework

rearrangement. The structures of isomaleimides **5a-c** were unambiguously established on the basis of lactone carbonyl (1794-1798 $cm^{-1}$) and imine (1676-1678 $cm^{-1}$) stretching frequencies in IR-spectra, appropriate $^{1}H$ NMR data and the presence of imine carbon atom ($\delta$ 140.9-141.0) in $^{13}C$ NMR spectra. We could very easily convert these kinetically controlled alkylisomaleimides **5a-c** to the desired corresponding thermodynamically more stable alkylmaleimides **6a-c** in 98% yield, by just refluxing them in glacial acetic acid for five hours. Both the opening of iminobutenolides **5** with acetic acid to form the mix anhydride intermediates and the intramolecular cyclization via the amide nitrogen lone pair to form the compounds **6** took place in one-pot. We feel that these monoalkyl substituted maleimides **6** will be potential precursors for several bioactive natural products containing butenolide/butyrolactone and butyrolactam core with fatty alkyl chain substituents.[13] Both the alkylisomaleimides **5** and alkylmaleimides **6** on treatment with refluxing acetic acid-sodium acetate mixture or on treatment with triethylamine in THF reverted to the more stable (*E*)-alkylidenesuccinimides **2** in quantitative yield, proving that in these systems the endocyclic to exocyclic carbon-carbon double bond migrations are more facile. These observations revealed and confirmed that the order of thermodynamic stability for these imides and isoimides is **2 > 6 > 5 > 4** and what we have accomplished was the contrathermodynamic rearrangement of exoimides **2** to endoimides **6** via the isoimides **4** and **5**. Finally, with the application of our earlier developed synthetic protocol[6f] for the synthesis of chaetomellic acid A, we could very easily transform the alkyl substituted maleimides to the symmetrically dialkyl substituted maleimides **8** via the intermediates **7** in very good yields. As expected the alkylisomaleimides on triphenylphosphine induced Wittig condensation with aliphatic aldehydes in refluxing acetic acid also furnished the imides **8** via the intermediates **6** and **7** in 77-80% yields. In the present 4-step approach the alkylmaleimides were obtained in 65-70% overall yields, while in the 5-step approach, the dialkylsubstituted maleimides were obtained in 48-55% overall yields. In the present synthetic sequence, the stepwise use of two different aliphatic aldehydes would provide a way to the unsymmetrically dialkylsubstituted maleimides. The hydrolysis of alkylsubstituted maleimides **6** under acidic conditions followed by the dehydration to the corresponding alkylmaleic

anhydrides and the hydrolysis of dialkylmaleimides to the corresponding dialkylmaleic anhydrides is well known in the literature.[6f,7]

In the present strategy, we have proved that the $\alpha$-protons on the unisolable intermediate alkylideneisosuccinimides **4** are accessable for such type of rearrangements. We planned to verify the accessability of the corresponding $\beta$-protons in $\alpha$-alkylideneisosuccinimides. In this context, we performed the regioselective ring opening of itaconic anhydride (**9**) with *p*-toluidine and obtained the $\alpha$-methylenesuccinanilic acid **10** in 98% yield (Scheme 2). The treatment of acid **10** with cyanuric chloride in the presence of triethylamine also gave $\alpha$-methylisomaleimide **12** in 90% yield via the intermediate $\alpha$-methyleneisosuccinimide **11**, proving that $\beta$-methylene protons can also be abstracted in a similar fashion for such type of exo-endo framework rearrangements.[14]




**Scheme 2.** *Reagents, conditions and yields*: (i) $Et_2O$, $ArNH_2$, rt, 1 h (98%); (ii) Cyanuric chloride, $NEt_3$, DCM, 0 $^oC$ to rt, 8 h (90%).

### 2B.3 Summary

In this section, we have described a simple and efficient approach to alkylmaleimides and dialkylmaleimides via the two Wittig coupling reactions, taking advantage for the first time of kinetically controlled isoimides as intermediates to enforce the difficult migration of exocyclic carbon-carbon double bonds to the endocyclic position. We have also demonstrated that in the present strategy, both the $\alpha$- and $\beta$-methylene protons on isosuccinimide skeleton are accessable for such type of exocyclic to endocyclic carbon-carbon double bond migrations. The present practical approach with scale up potential is general in nature and it will be useful to design a large number of analogs and congeners of alkylmaleimides and dialkylmaleimides of interest, to a large section of the chemist's community. The present results will also be of interest to chemists studying such type of exo-endo carbon-carbon double bond isomerization reactions.

## 2B.4 Experimental

Commercially available cyclic anhydrides and aromatic/aliphatic amines were used. Freshly recrystallized cyanuric chloride ($CCl_4$) was used.

**General procedure for *N*-*p*-tolyl-3(*E*)-alkylidenesuccinimides 2a-c**. A solution of *N*-*p*-tolylmaleimide (**1**, 50 mmol) and triphenylphosphine (50 mmol) in THF (125 mL) was stirred at room temperature for 30 min. Alipahtic aldehyde (75 mmol) was added to the reaction mixture and refluxed for 10 h. The THF was distilled off in vacuo at 50 $^{o}$C and the residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to obtain the alkylidenesuccinimides **2a/b/c** in 89-91% yields.

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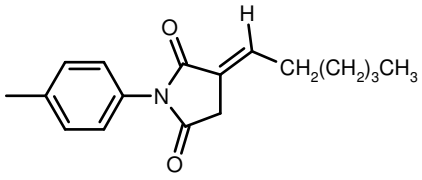
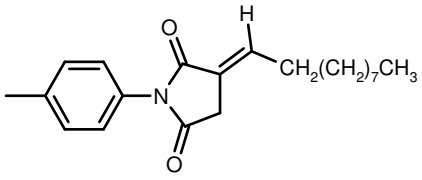
|  <br>**2a (271)** | **MP**: 112-113 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1771, 1749, 1712, 1691, 1676 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, $J$ = 6 Hz, 3H), 1.22-1.45 (m, 4H), 1.53 (quintet, $J$ = 6 Hz, 2H), 2.23 (q, $J$ = 6 Hz, 2H), 2.37 (s, 3H), 3.37 (d, $J$ = 2 Hz, 2H), 6.93 (tt, $J$ = 8 & 2 Hz, 1H), 7.18 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.7, 20.9, 22.2, 27.5, 29.6, 31.2, 31.8, 125.1, 126.0, 129.2, 129.4, 138.1, 139.6, 168.7, 173.0.<br>**MS** (*m/e*) 271, 242, 228, 214, 200, 189, 172, 133, 107, 95, 81, 67, 53.<br>**Anal. Calcd for $C_{17}H_{21}NO_2$**: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.11; H, 7.92; N, 5.07. |
|  <br>**2b (327)** | **MP**: 106-108 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1771, 1709, 1676, 1466 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, $J$ = 6 Hz, 3H), 1.27 (bs, 12H), 1.52 (quintet, $J$ = 6 Hz, 2H), 2.23 (q, $J$ = 6 Hz, 2H), 2.37 (s, 3H), 3.37 (d, $J$ = 2 Hz, 2H), 6.93 (tt, $J$ = 8 & 2 Hz, 1H), 7.18 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.0, 21.1, 22.6, 28.0, 29.18, 29.24, 29.31, 29.37, 29.9, 31.8, 32.0, 125.2, 126.2, 129.3, 129.7, 138.4, 140.0, 169.0, 173.2.<br>**Anal. Calcd for $C_{21}H_{29}NO_2$**: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.89; H, 9.02; N, 4.16. |

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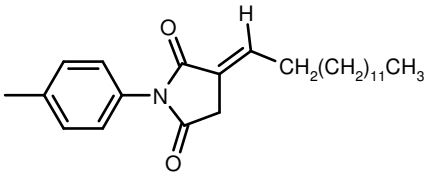
|  <br>**2c (383)** | **MP**: 58-60 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1785, 1720, 1695, 1470 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, *J* = 6 Hz, 3H), 1.25 (bs, 20H), 1.55 (quintet, *J* = 6 Hz, 2H), 2.25 (q, *J* = 6 Hz, 2H), 2.39 (s, 3H), 3.38 (d, *J* = 2 Hz, 2H), 6.95 (tt, *J* = 8 & 2 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H).<br>**MS** (*m*/*e*) 383, 355, 257, 228, 215, 202, 189, 172, 108, 95, 81.<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 13.7, 20.8, 22.3, 27.9, 29.1, 29.2, 29.3 (7 x $CH_2$), 29.5, 31.8, 125.4, 125.9, 129.2, 129.5, 137.8, 139.1, 168.5, 172.6.<br>**Anal. Calcd for $C_{25}H_{37}NO_2$**: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.19; H, 9.64; N, 3.60. |

**General procedure for *N*-*p*-tolyl-3(*E*)-alkylidenesuccinanilic acids 3a-c**. To a solution of alkylidenesuccinimides (**2a-c**, 40 mmol) in THF (50 mL) was added 2 N aqueous LiOH (50 mL) in a dropwise fashion at 0 $^{o}$C and the reaction mixture was stirred for 5 h at room temperature. THF was distilled off in vacuo and the aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water, brine and dried over $Na_2SO_4$. Concentration of the organic layer in vacuo gave the desired alkylidenesuccinanilic acids **3a-c** in 95-98% yields.

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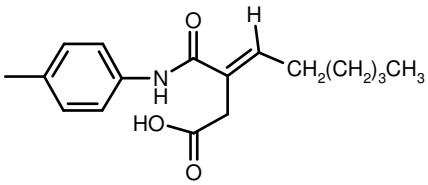
|  <br>**3a (289)** | **MP**: 143-145 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 2383, 2700-2500, 1682, 1657, 1597 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, *J* = 6 Hz, 3H), 1.20-1.40 (m, 4H), 1.47 (quintet, *J* = 6 Hz, 2H), 2.27 (s, 3H), 2.37 (q, *J* = 6 Hz, 2H), 3.38 (s, 2H), 7.06 (d, *J* = 8 Hz, 2H), 7.16 (t, *J* = 6 Hz, 1H), 7.33 (d, *J* = 8 Hz, 2H), 8.01 (bs, 1H).<br>**$^{13}$C NMR** (DMSO-$d_6$, 50 MHz) $\delta$ 14.0, 20.6, 22.1, 28.0, 28.5, 31.1, 34.1, 119.0, 119.1, 129.2, 131.9, 137.0, 137.1, 168.3, 168.4.<br>**Anal. Calcd for $C_{17}H_{23}NO_3$**: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.43; H, 7.96; N, 4.85. |

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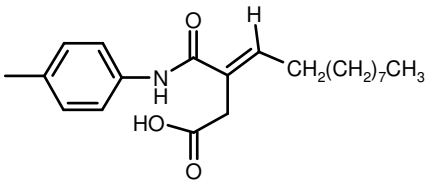
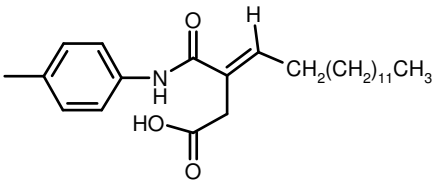
|  <br>**3b (345)** | **MP**: 138-140 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 3420, 2700-2500, 1682, 1661, 1597 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 3H), 1.24 (bs, 12H), 1.47 (quintet, $J$ = 6 Hz, 2H), 2.28 (s, 3H), 2.39 (q, $J$ = 6 Hz, 2H), 3.38 (s, 2H), 7.07 (d, $J$ = 8 Hz, 2H), 7.18 (t, $J$ = 6 Hz, 1H), 7.34 (d, $J$ = 8 Hz, 2H), 7.96 (bs, 1H).<br>**$^{13}$C NMR** (DMSO-$d_6$, 50 MHz) $\delta$ 14.2, 20.6, 22.3, 28.3, 28.5, 28.6, 28.7, 28.9, 29.1, 29.2, 31.5, 119.0, 119.1, 129.2, 131.9, 137.0, 137.1, 168.4, 168.5.<br>**Anal. Calcd for $C_{21}H_{31}NO_3$**: C, 73.00; H, 9.04; N, 4.05. Found: C, 73.12; H, 9.13; N, 4.16. |
|  <br>**3c (401)** | **MP**: 126-128 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 3411, 2700-2500, 1688, 1660, 1599 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 3H), 1.24 (bs, 20H), 1.47 (quintet, $J$ = 6 Hz, 2H), 2.28 (s, 3H), 2.38 (q, $J$ = 6 Hz, 2H), 3.38 (s, 2H), 7.07 (d, $J$ = 8 Hz, 2H), 7.17 (t, $J$ = 6 Hz, 1H), 7.33 (d, $J$ = 8 Hz, 2H), 7.94 (bs, 1H).<br>**$^{13}$C NMR** ($CDCl_3$ + DMSO-$d_6$, 50 MHz) $\delta$ 12.6, 19.2, 20.9, 27.0, 27.3, 27.5, 27.6, 27.7, 27.9 (5 x $CH_2$), 30.2, 33.1, 117.8, 125.4, 127.5, 130.7, 135.2, 143.6, 167.0, 167.4.<br>**Anal. Calcd for $C_{25}H_{39}NO_3$**: C, 74.77; H, 9.79; N, 3.49. Found: C, 74.69; H, 9.82; N, 3.51. |

**General procedure for *N*-*p*-tolylalkylisomaleimides 5a-c**. To a slurry of alkylidenesuccinanilic acids (**3a-c**, 30 mmol) in DCM (50 mL) was added triethylamine (90 mmol) in a dropwise fashion with constant stirring at 0 $^{o}$C. To the resulting reaction mixture was added a solution of cyanuric chloride (33 mmol) in DCM (50 mL) and the reaction mixture was further stirred under argon atmosphere for 8 h at room temperature. The reaction mixture was concentrated in vacuo and residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water, 5% aqueous sodium bicarbonate, brine and dried over $Na_2SO_4$. The ethyl acetate layer was concentrated in vacuo and the crude product was purified by silica gel column chromatography using a

mixture of petroleum ether and ethyl acetate (9:1) to obtain pure *N-p*-tolylalkylisomaleimides **5a-c** in 78-80% yields.

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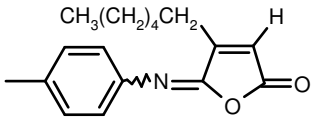
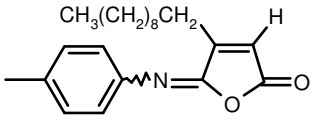
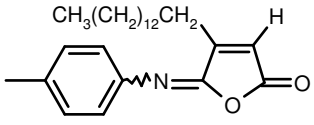
|  **5a (271)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1798, 1678, 1622, 1506 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, $J$ = 6 Hz, 3H), 1.35 (bs, 6H), 1.69 (quintet, $J$ = 6 Hz, 2H), 2.35 (s, 3H), 2.64 (t, $J$ = 6 Hz, 2H), 6.29 (s, 1H), 7.17 (d, $J$ = 8 Hz, 2H), 7.33 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.9, 21.0, 22.4, 26.2, 27.3, 28.8, 31.3, 121.0, 125.3, 129.4, 137.1, 140.9, 150.1, 159.7, 167.1.<br>**Anal. Calcd for $C_{17}H_{21}NO_2$**: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.12; H, 7.93; N, 5.02. |
|  **5b (327)** | **MP**: 53-55 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1798, 1678, 1622, 1506 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 3H), 1.25 (bs, 14H), 1.68 (quintet, $J$ = 6 Hz, 2H), 2.35 (s, 3H), 2.64 (t, $J$ = 6 Hz, 2H), 6.29 (s, 1H), 7.17 (d, $J$ = 8 Hz, 2H), 7.33 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.1, 21.1, 22.7, 26.3, 27.4, 29.1, 29.2, 29.3, 29.4, 29.6, 31.9, 121.1, 125.4, 129.5, 137.1, 141.0, 150.2, 159.8, 167.2.<br>**Anal. Calcd for $C_{21}H_{29}NO_2$**: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.11; H, 9.04; N, 4.33. |
|  **5c (383)** | **MP**: 58-60 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1794, 1676, 1620, 1506 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 3H), 1.25 (bs, 22H), 1.68 (quintet, $J$ = 6 Hz, 2H), 2.35 (s, 3H), 2.64 (t, $J$ = 6 Hz, 2H), 6.29 (s, 1H), 7.17 (d, $J$ = 8 Hz, 2H), 7.33 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.1, 21.1, 22.7, 26.3, 27.4, 29.1, 29.2, 29.3, 29.4, 29.6 (5 x $CH_2$), 31.9, 121.1, 125.4, 129.5, 137.1, 141.0, 150.2, 159.8, 167.2.<br>**Anal. Calcd for $C_{25}H_{37}NO_2$**: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.33; H, 9.59; N, 3.60. |

**General procedure for *N-p*-tolylalkylmaleimides 6a-c**. A solution of *N-p*-tolylalkylisomaleimides (**5a-c**, 20 mmol) in glacial acetic acid (50 mL) was refluxed for 5

h. Acetic acid was distilled off in vacuo at 50 °C and the residue was dissolved in ethyl acetate. The organic layer was washed with water, aqueous sodium bicarbonate, brine and dried over $Na_2SO_4$. The organic layer was concentrated in vacuo and the obtained residue on silica gel column chromatographic purification using petroleum ether and ethyl acetate (9.5:0.5), gave *N*-*p*-tolylalkylmaleimides **6a-c** in 98% yield.

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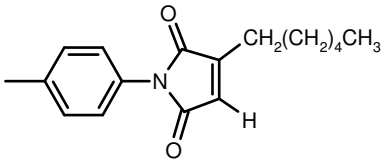
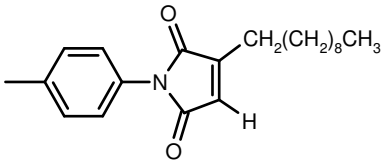
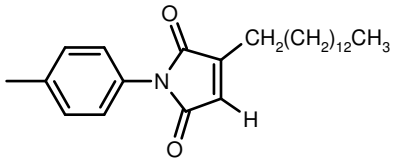
|  <br>**6a (271)** | **MP**: 70-72 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1713, 1638, 1516 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.89 (t, $J$ = 6 Hz, 3H), 1.15-1.50 (m, 6H), 1.64 (quintet, $J$ = 6 Hz, 2H), 2.36 (s, 3H), 2.50 (dt, $J$ = 6 & 2 Hz, 2H), 6.40 (t, $J$ = 2 Hz, 1H), 7.10-7.30 (m, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.0, 21.1, 22.4, 25.4, 27.0, 28.8, 31.4, 125.8, 126.2, 128.9, 129.6, 137.6, 150.3, 169.9, 170.5.<br>**Anal. Calcd for $C_{17}H_{21}NO_2$**: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.20; H, 7.73; N, 5.11. |
|  <br>**6b (327)** | **MP**: 58-60 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1713, 1638, 1516 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 3H), 1.26 (bs, 14H), 1.64 (quintet, $J$ = 6 Hz, 2H), 2.36 (s, 3H), 2.50 (dt, $J$ = 6 & 2 Hz, 2H), 6.40 (t, $J$ = 2 Hz, 1H), 7.10-7.30 (m, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.1, 21.1, 22.6, 25.5, 27.0, 29.2, 29.3, 29.4, 29.5, 30.1, 31.9, 125.8, 126.2, 128.9, 129.7, 137.6, 150.3, 170.0, 170.6.<br>**Anal. Calcd for $C_{21}H_{29}NO_2$**: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.95; H, 8.88; N, 4.21. |
|  <br>**6c (383)** | **MP**: 72-74 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1713, 1638, 1516 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 3H), 1.25 (bs, 22H), 1.64 (quintet, $J$ = 6 Hz, 2H), 2.36 (s, 3H), 2.50 (dt, $J$ = 6 & 2 Hz, 2H), 6.40 (t, $J$ = 2 Hz, 1H), 7.10-7.30 (m, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.1, 21.1, 22.7, 25.5, 27.1, 29.2, 29.3, 29.5, 29.6 (6 x $CH_2$), 31.9, 125.9, 126.2, 128.9, 129.7, 137.7, 150.3, 169.9, 170.6.<br>**Anal. Calcd for $C_{25}H_{37}NO_2$**: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.22; H, 9.81; N, 3.54. |

**General procedure for *N-p*-tolyl-2-alkylidene-3-alkylsuccinimides 7a-c**. A solution of *N-p*-tolylalkylmaleimides (**6a-c**, 10 mmol), triphenylphosphine (10 mmol) and aliphatic aldehyde (15 mmol) in glacial acetic acid (30 mL) was refluxed for 18 h with constant stirring. Acetic acid was distilled off in vacuo at 50 $^{o}$C and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water, brine 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 (9:1) gave *N-p*-tolyl-2-alkylidene-3-alkylsuccinimides **7a-c** in 77-80% yields.

The above compounds were also obtained from *N-p*-tolylalkylisomaleimides **5a-c** using the same procedure.

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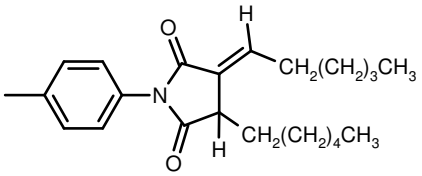
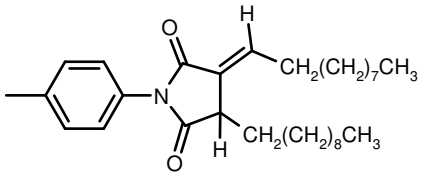
|  <br>**7a (355)** | **MP**: 69-70 $^{o}$C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1767, 1709, 1670, 1516 cm$^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.86 (t, $J$ = 6 Hz, 3H), 0.91 (t, $J$ = 6 Hz, 3H), 1.15-1.45 (m, 12H), 1.53 (quintet, $J$ = 6 Hz, 2H), 1.75-1.98 (m, 1H), 1.98-2.15 (m, 1H), 2.28 (q, $J$ = 8 Hz, 2H), 2.38 (s, 3H), 3.51 (t, $J$ = 4 Hz, 1H), 6.93 (dt, $J$ = 8 & 2 Hz, 1H), 7.17 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.9, 14.0, 21.2, 22.4, 22.5, 24.6, 28.1, 29.2, 29.3, 30.7, 31.5, 31.6, 42.5, 126.2, 129.0, 129.3, 129.7, 138.4, 140.3, 169.3, 176.9.<br>**Anal. Calcd for $C_{23}H_{33}NO_2$**: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.79; H, 9.43; N, 3.72. |
|  <br>**7b (467)** | **MP**: 71-73 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1769, 1719, 1670, 1516 cm$^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 6H), 1.25 (bs, 28H), 1.40-1.60 (m, 2H), 1.75-2.15 (m, 2H), 2.27 (q, $J$ = 8 Hz, 2H), 2.37 (s, 3H), 3.50 (t, $J$ = 4 Hz, 1H), 6.92 (dt, $J$ = 8 & 2 Hz, 1H), 7.17 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.1, 21.2, 22.6, 24.7, 28.5, 29.3, 29.4, 29.5 (11 x $CH_2$), 30.7, 31.9, 42.5, 126.2, 129.0, 129.4, 129.7, 138.4, 140.3, 169.2, 176.8.<br>**Anal. Calcd for $C_{31}H_{49}NO_2$**: C, 79.60; H, 10.56; N, 2.99. Found: C, 79.52; H, 10.44; N, 3.07. |

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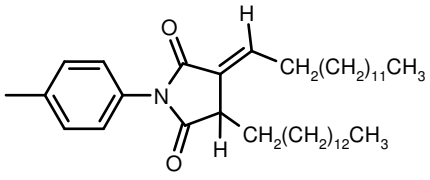
|  <br>**7c (579)** | **MP**: 73-75 $^{o}$C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1769, 1705, 1670, 1518 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 500 MHz) $\delta$ 0.80-0.90 (m, 6H), 1.10-1.40 (m, 44H), 1.45-1.55 (m, 2H), 1.80-1.95 (m, 1H), 1.95-2.10 (m, 1H), 2.20-2.33 (m, 2H), 2.37 (s, 3H), 3.50 (t, $J$ = 4 Hz, 1H), 6.91 (dt, $J$ = 8 & 2 Hz, 1H), 7.17 (d, $J$ = 10 Hz, 2H), 7.26 (d, $J$ = 10 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 125 MHz) $\delta$ 14.1, 21.2, 22.7, 24.7, 28.5, 29.3-29.6 (21 x $CH_2$), 30.8, 31.9, 42.5, 126.2, 129.1, 129.4, 129.7, 138.5, 140.4, 169.3, 176.9.<br>**Anal. Calcd for $C_{39}H_{65}NO_2$**: C, 80.77; H, 11.30; N, 2.42. Found: C, 80.67; H, 11.16; N, 2.53. |

**General procedure for *N-p*-tolyldialkylmaleimides 8a-c**. To a stirred solution of *N-p*-tolyl-2-alkylidene-3-alkylsuccinimides (**7a-c**, 5 mmol) in THF (20 mL) was added triethylamine (20 mL) and the reaction mixture was refluxed for 48 h and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine 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 (9.5:0.5) gave *N-p*-tolyldialkylmaleimides **8a-c** in 95-96% yields.

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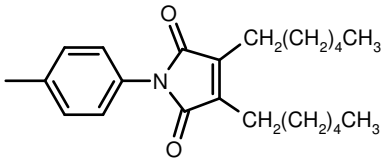
|  <br>**8a (355)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1707, 1516, 1395 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.89 (t, $J$ = 6 Hz, 6H), 1.15-1.45 (m, 12H), 1.57 (quintet, $J$ = 6 Hz, 4H), 2.36 (s, 3H), 2.44 (t, $J$ = 8 Hz, 4H), 7.22 (s, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.0, 21.1, 22.5, 23.9, 28.6, 29.3, 31.4, 125.7, 129.3, 129.5, 137.2, 141.1, 170.9.<br>**Anal. Calcd for $C_{23}H_{33}NO_2$** : C, 77.70; H, 9.36; N, 3.94. Found: C, 77.79; H, 9.45; N, 3.99. |

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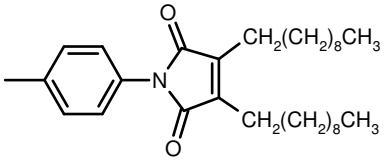
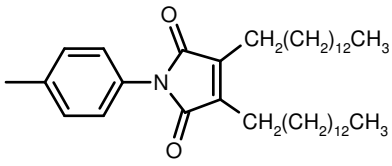
|  <br>**8b (467)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1711, 1516, 1389 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 6H), 1.25 (bs, 28H), 1.57 (quintet, $J$ = 6 Hz, 4H), 2.36 (s, 3H), 2.44 (t, $J$ = 6 Hz, 4H), 7.22 (s, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 14.0, 21.0, 22.6, 23.9, 28.6, 29.3, 29.5, 29.6 (3 x $CH_2$), 31.9, 125.7, 129.3, 129.5, 137.1, 141.1, 170.9.<br>**Anal. Calcd for $C_{31}H_{49}NO_2$**: C, 79.60; H, 10.56; N, 2.99. Found: C, 79.66; H, 10.47; N, 3.03. |
|  <br>**8c (579)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1707, 1516, 1394 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.87 (t, $J$ = 6 Hz, 6H), 1.25 (bs, 44H), 1.57 (quintet, $J$ = 6 Hz, 4H), 2.36 (s, 3H), 2.44 (t, $J$ = 6 Hz, 4H), 7.22 (s, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.1, 21.1, 22.7, 23.9, 28.6, 29.3, 29.5, 29.6 (7 x $CH_2$), 31.9, 125.7, 129.3, 129.5, 137.2, 141.1, 170.9.<br>**Anal. Calcd for $C_{39}H_{65}NO_2$**: C, 80.77; H, 11.30; N, 2.42. Found: C, 80.81; H, 11.42; N, 2.37. |

**2-Methylene-*N*-*p*-tolyl-succinamic acid (10)**. To a stirred solution of itaconic anhydride (2.00 g, 17.8 mmol) in ether (10 mL) at room temperature was added a solution of *p*-toluidine (1.90 g, 17.8 mmol) in ether (10 mL) in a dropwise fashion over a period of 10 min. The reaction mixture was stirred at room temperature for 50 min. and the precipitated product was filtered, washed with ether (2 x 10 mL) and dried under vacuum to obtain 2-methylene-*N*-*p*-tolyl-succinamic acid **10** (4.00 g, 98% yield).

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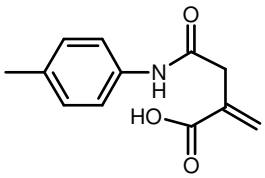
|  <br>**10 (219)** | **MP**: 188-190 $^oC$.<br>**IR** (nujol) $\nu_{max}$ 3292, 2700-2500, 1676, 1655, 1630, 1462 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$ + DMSO-$d_6$, 200 MHz) $\delta$ 2.20 (s, 3H), 3.28 (s, 2H), 5.69 (s, 1H) 6.21 (s, 1H), 6.98 (d, $J$ = 8 Hz, 2H), 7.39 (d, $J$ = 8 Hz, 2H), 9.48 (bs, 1H).<br>**$^{13}$C NMR** (DMSO-$d_6$, 50 MHz) $\delta$ 20.7, 39.8, 119.3, 127.8, 129.4, 132.2, 136.2, 137.1, 168.0, 168.6.<br>**Anal. Calcd for $C_{12}H_{13}NO_3$**: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.62; H, 6.05; N, 6.24. |

**3-Methyl-5-*p*-tolylimino-5*H*-furan-2-one (12).** This compound was obtained in 90% yield by using the same procedure as used for the synthesis of compounds **5a-c**.

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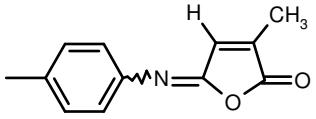
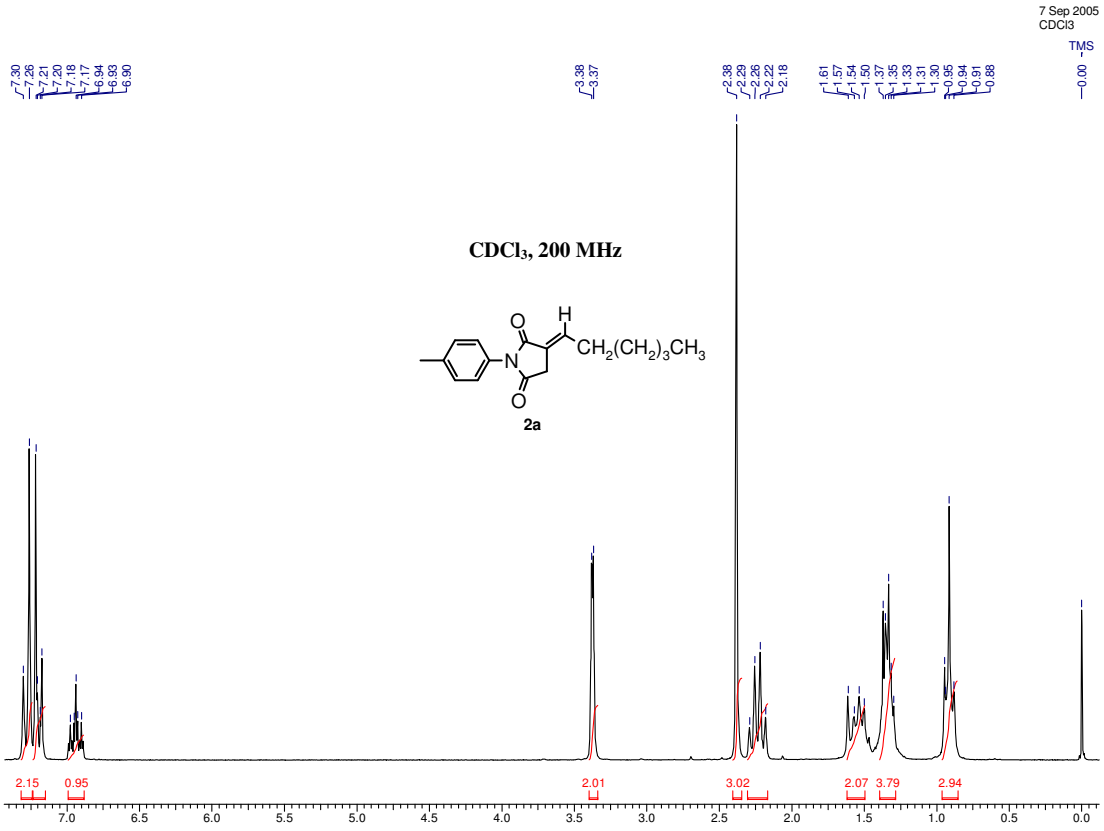
|   **12 (201)** | **MP**: 115-116 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1778, 1674, 1599, 1462 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 300 MHz) $\delta$ 2.15 (s, 3H), 2.36 (s, 3H), 7.02 (s, 1H), 7.19 (d, $J$ = 9 Hz, 2H), 7.32 (d, $J$ = 9Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 10.7, 21.0, 125.0, 129.4, 136.5, 136.9, 138.7, 141.2, 148.9, 168.7.<br>**Anal. Calcd for $C_{12}H_{11}NO_2$**: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.77; H, 5.48; N, 6.93. |

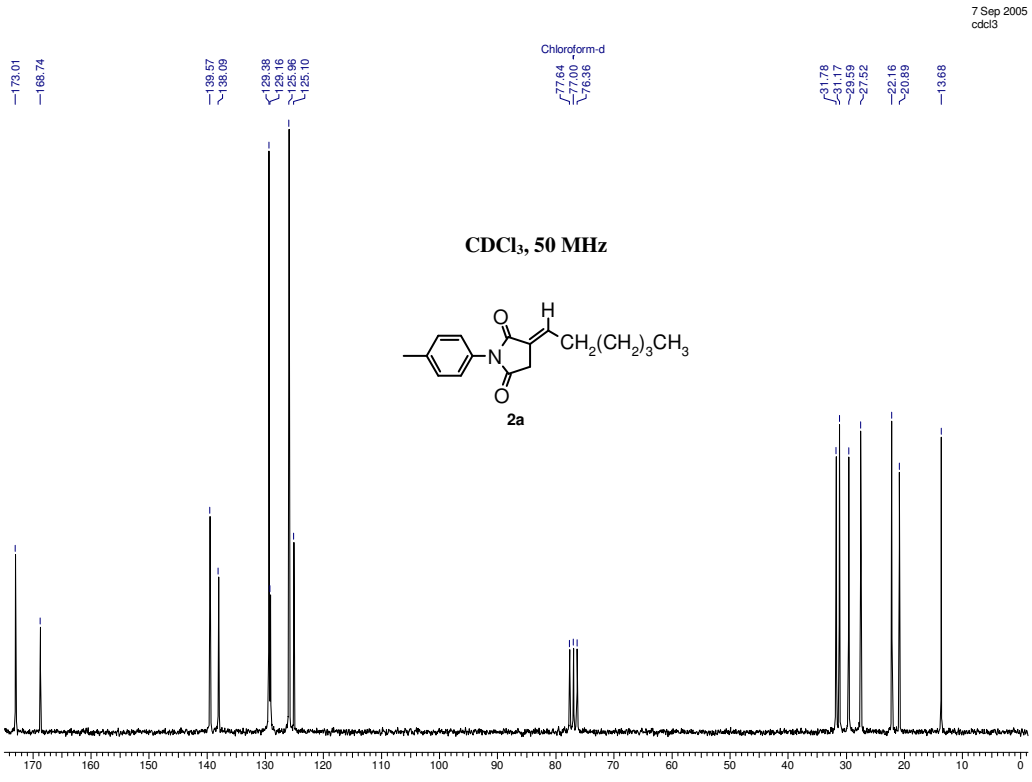
# 2B.5 Selected Spectra




**$CDCl_3$, 200 MHz**



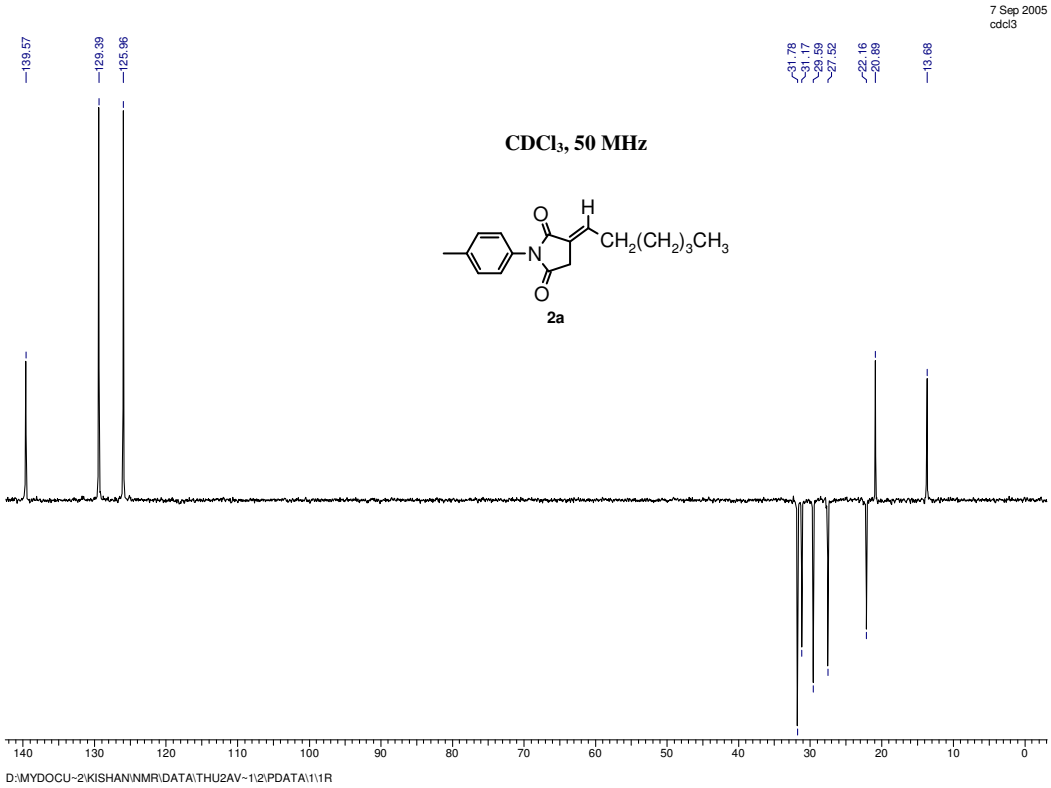
**2a**




**$CDCl_3$, 50 MHz**



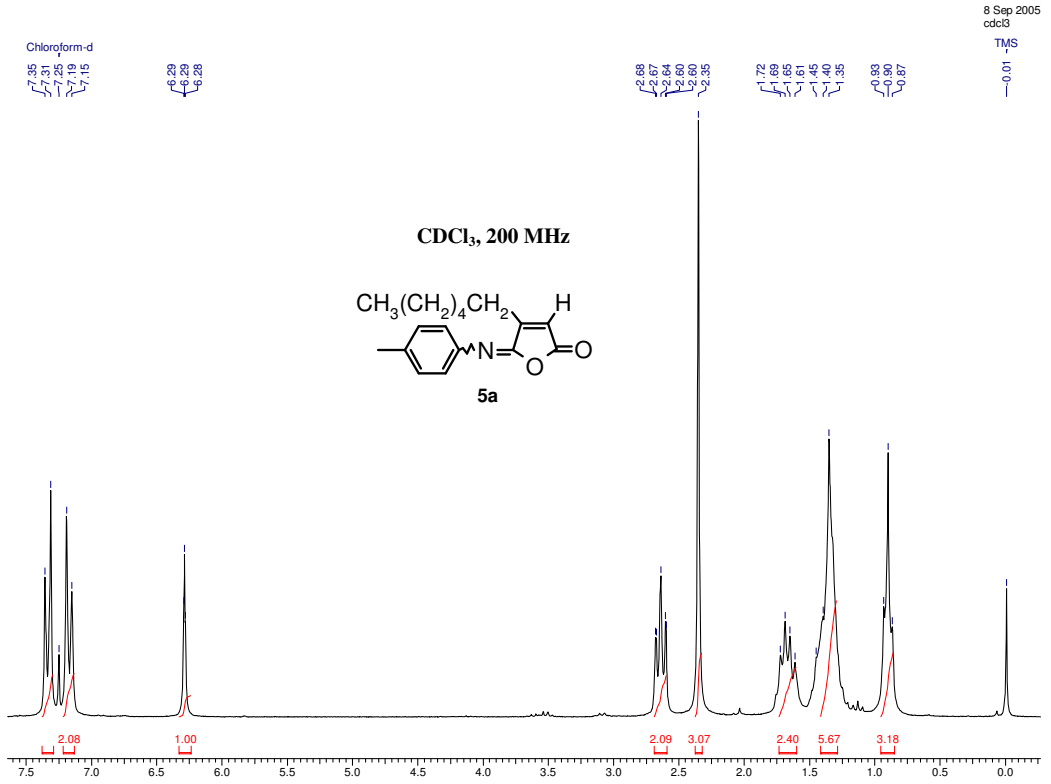
**2a**




**$CDCl_3$, 50 MHz**



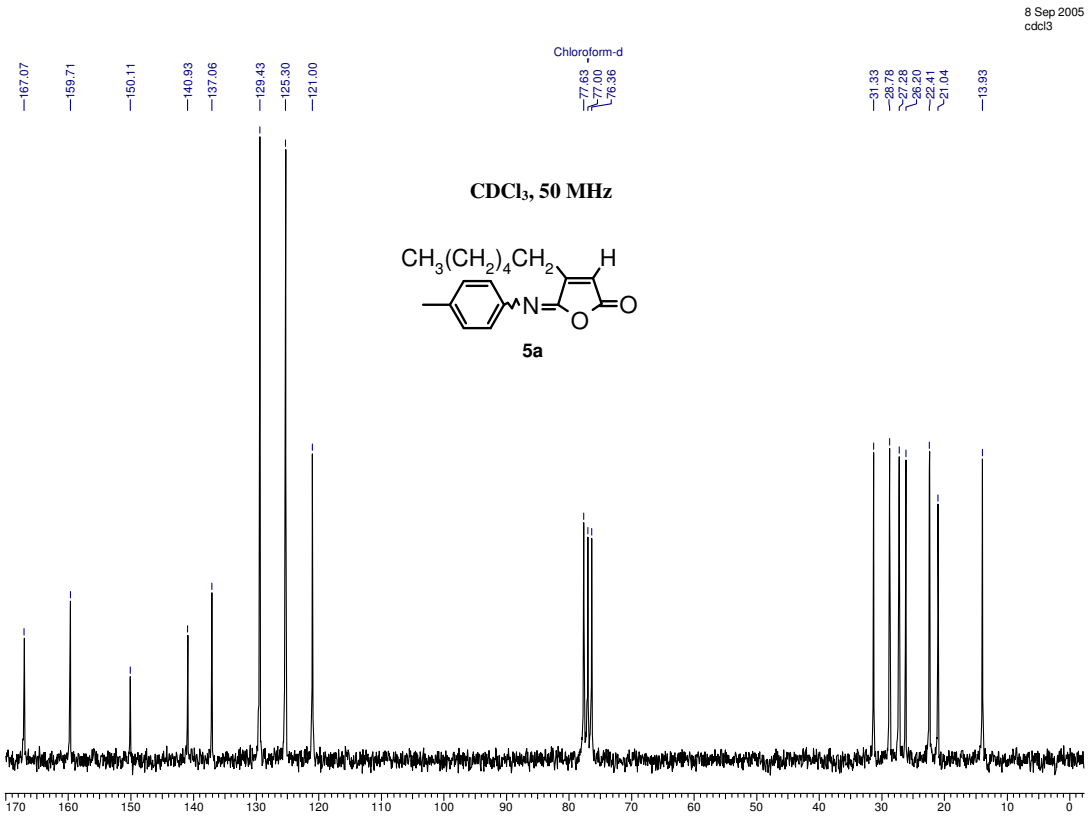

**2a**

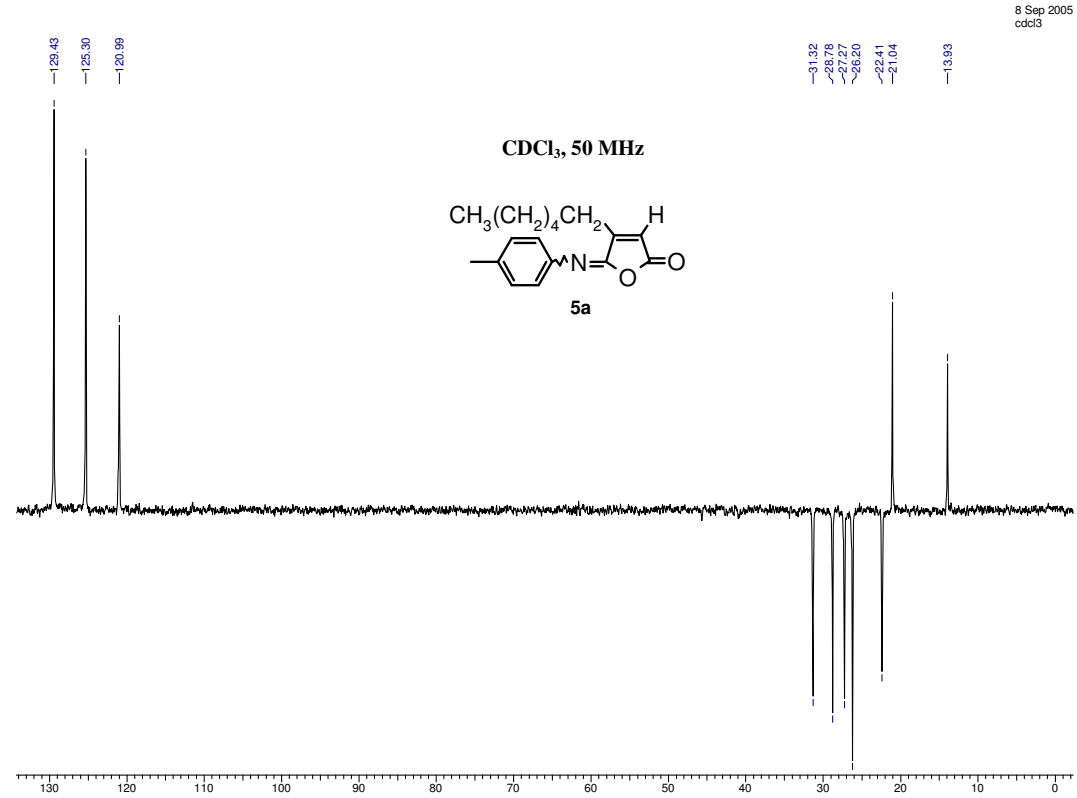


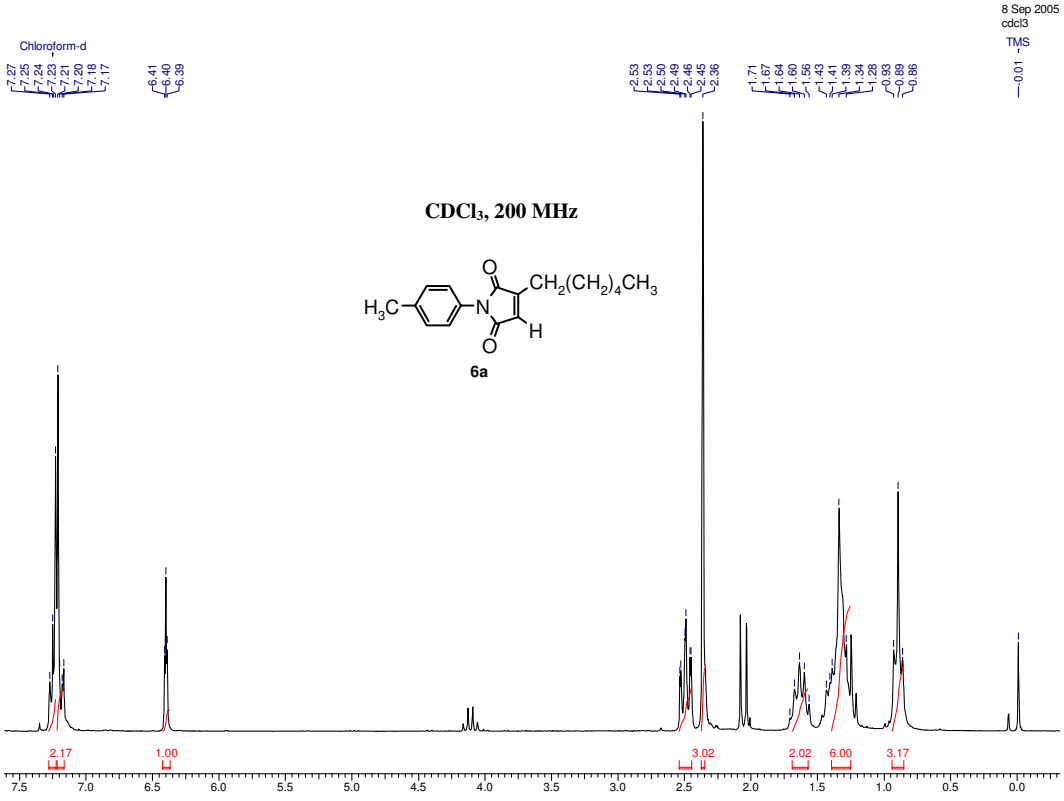

**$CDCl_3$, 200 MHz**

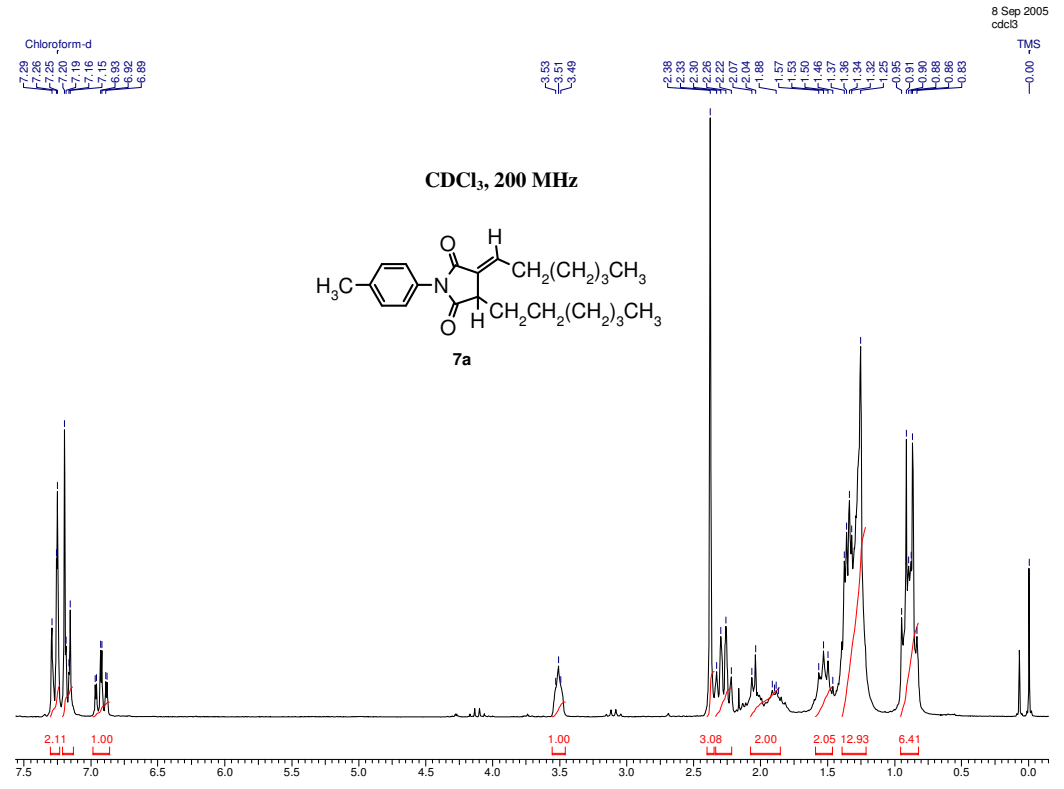


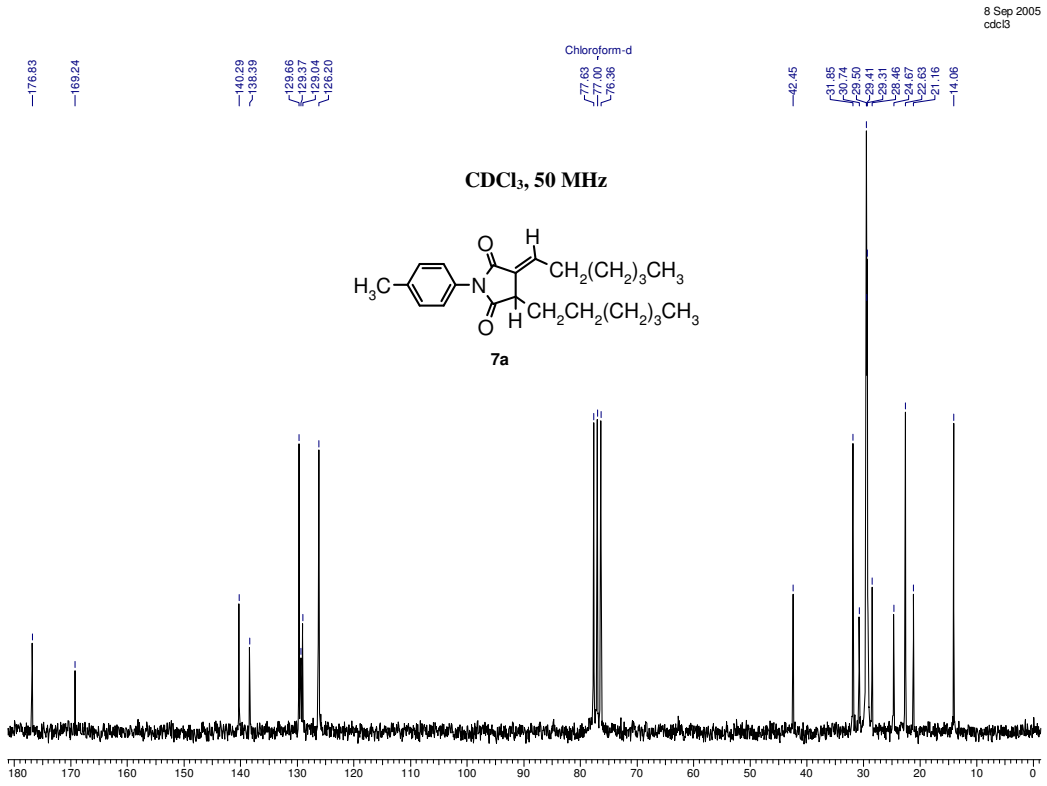

**5a**

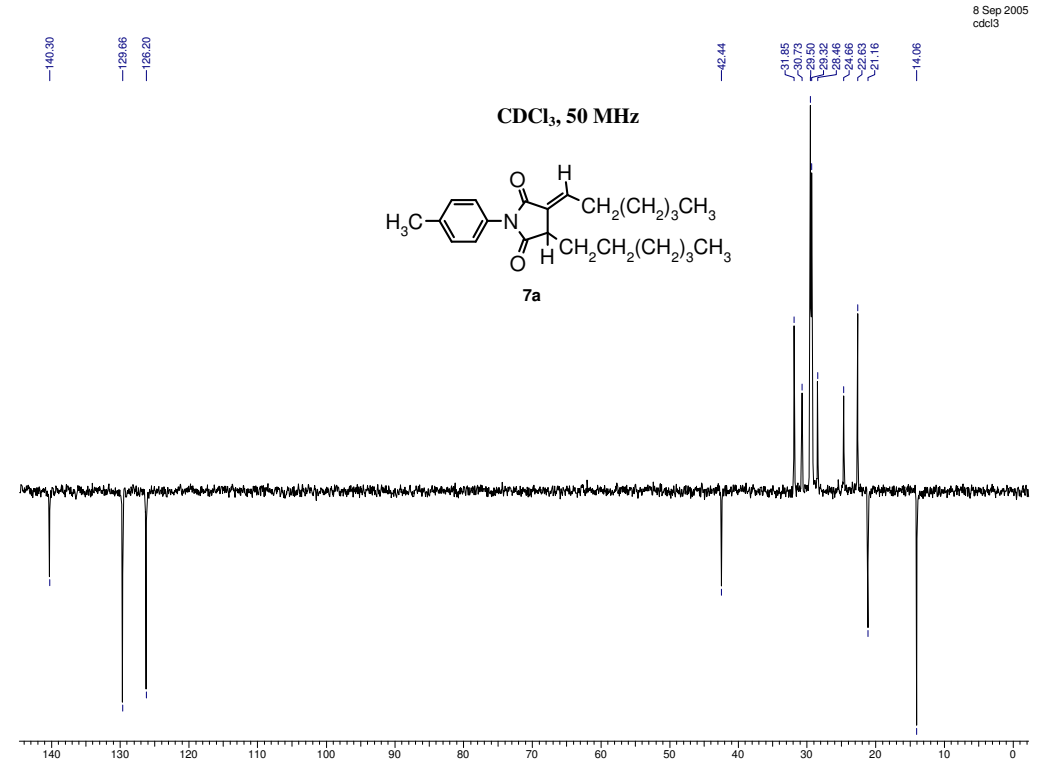

8 Sep 2005
cdcl3
Chloroform-d
167.07
159.71
150.11
140.93
137.06
129.43
125.30
121.00
77.63
77.00
76.36
31.33
28.78
27.28
26.20
22.41
21.04
13.93
CDCl3, 50 MHz
CH3(CH2)4CH2
H
N
O
O
5a
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

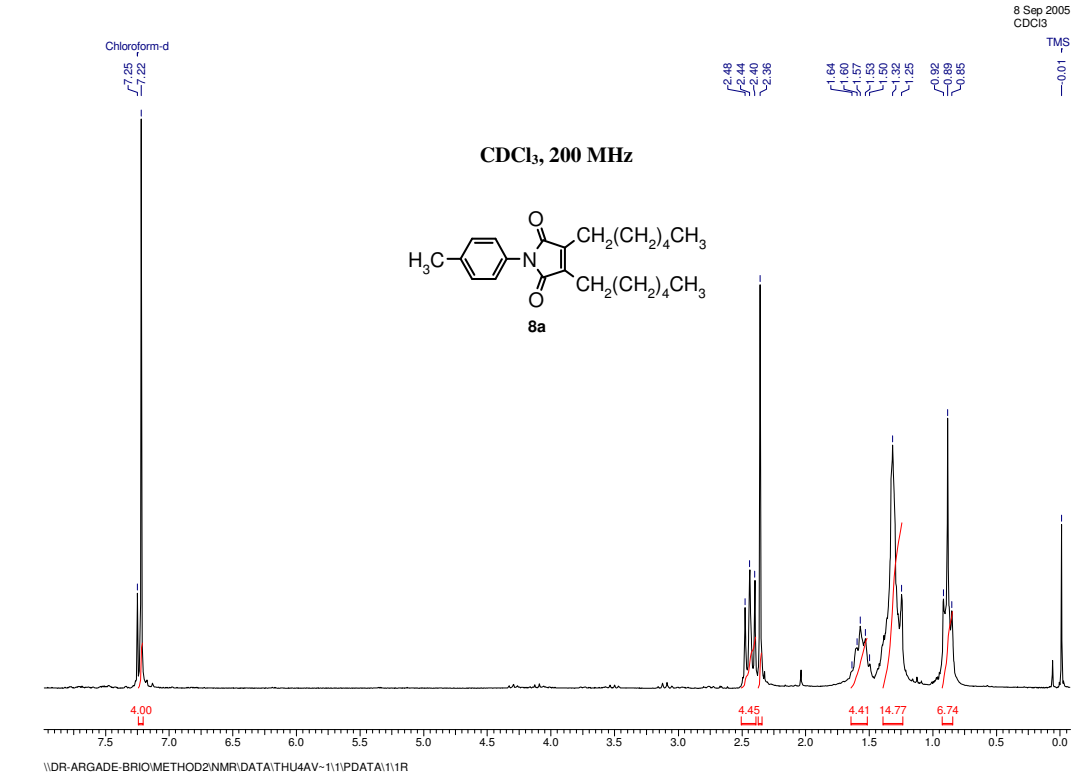

8 Sep 2005
cdcl3
129.43
125.30
120.99
31.32
28.78
27.27
26.20
22.41
21.04
13.93
CDCl3, 50 MHz
CH3(CH2)4CH2
H
N
O
O
5a
130 120 110 100 90 80 70 60 50 40 30 20 10 0


8 Sep 2005
cdcl3
TMS
Chloroform-d
CDCl3, 200 MHz
CH2(CH2)4CH3
H3C
N
O
H
6a
2.17
1.00
3.02
2.02
6.00
3.17


8 Sep 2005
cdcl3
TMS
Chloroform-d
CDCl3, 200 MHz
CH2(CH2)3CH3
CH2CH2(CH2)3CH3
H3C
N
O
H
7a
2.11
1.00
1.00
3.08
2.00
2.05
12.93
6.41


8 Sep 2005
cdcl3
Chloroform-d
176.83
169.24
140.29
138.39
129.66
129.37
129.04
126.20
77.63
77.00
76.36
42.45
31.85
30.74
29.50
29.41
29.31
28.46
24.67
22.63
21.16
14.06
CDCl3, 50 MHz
7a


8 Sep 2005
cdcl3
140.30
129.66
126.20
42.44
31.85
30.73
29.50
29.32
28.46
24.66
22.63
21.16
14.06
CDCl3, 50 MHz
7a


8 Sep 2005
CDCl3
Chloroform-d
TMS
7.25
7.22
2.48
2.44
2.40
2.36
1.64
1.60
1.57
1.53
1.50
1.32
1.25
0.92
0.89
0.85
0.01
CDCl3, 200 MHz
H3C
N
CH2(CH2)4CH3
CH2(CH2)4CH3
8a
4.00
4.45
4.41
14.77
6.74
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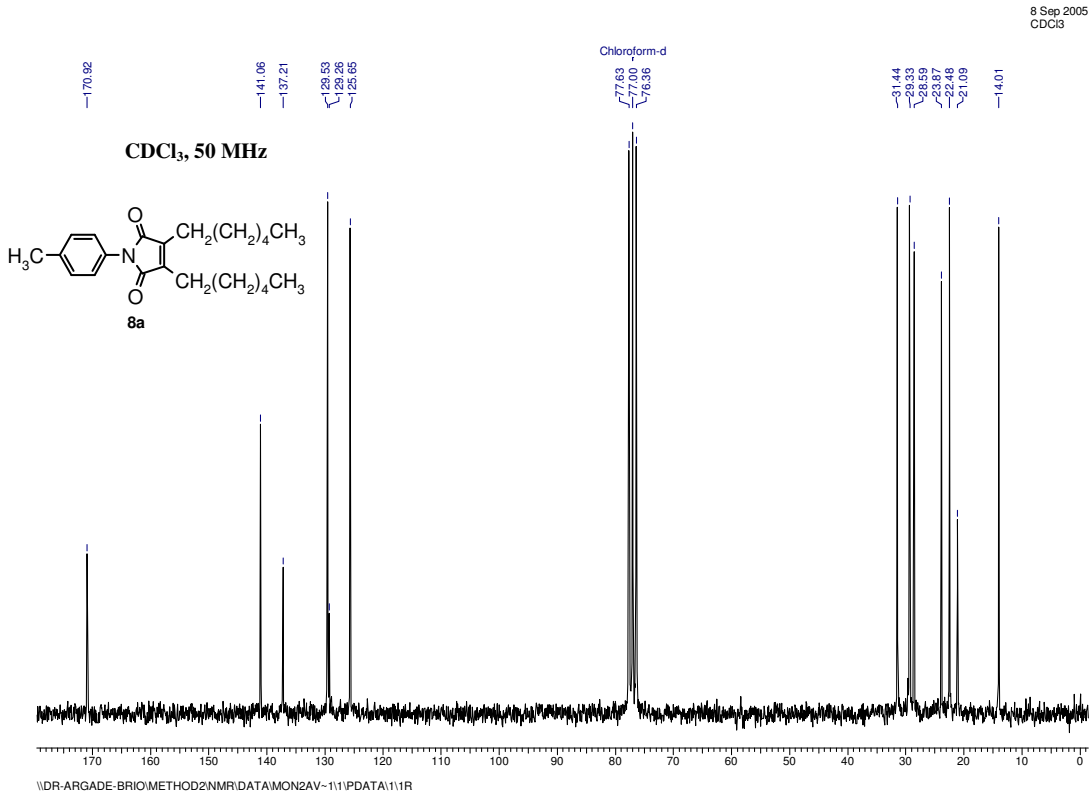
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Chloroform-d
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141.06
137.21
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129.26
125.65
77.63
77.00
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29.33
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23.87
22.48
21.09
14.01
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8a
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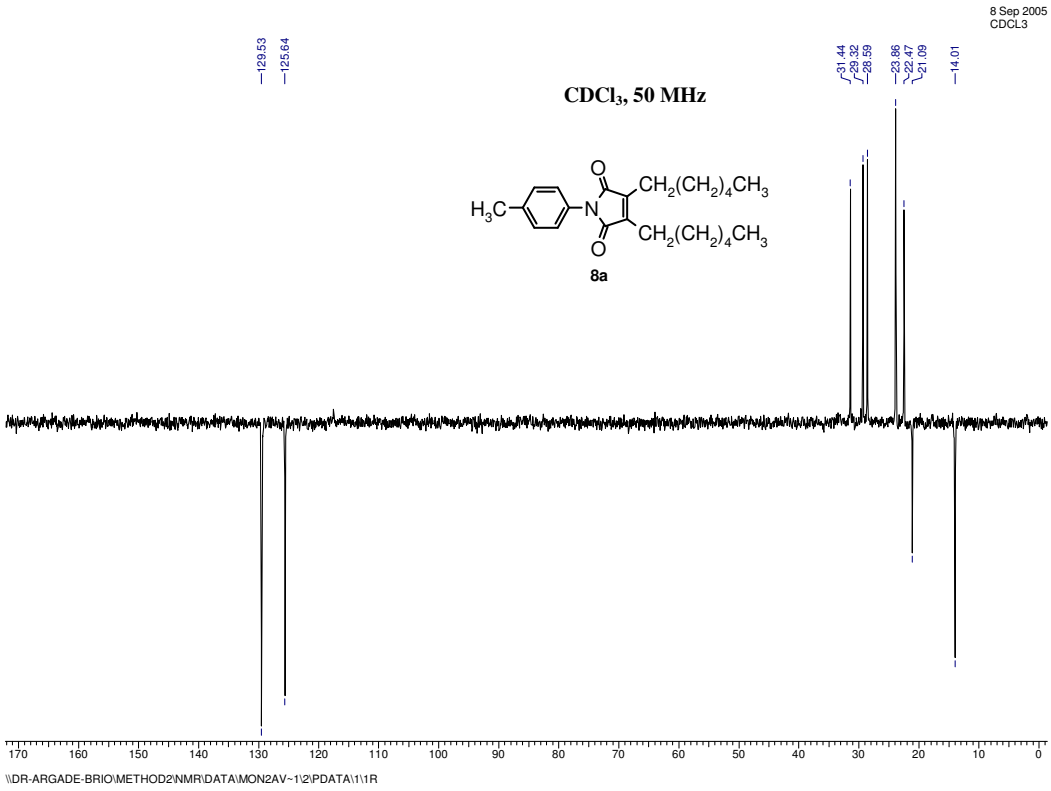
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21.09
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O
O
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CH2(CH2)4CH3
8a
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\\DR-ARGADE-BRIO\METHOD2\NMR\DATA\MON2AV~1\2\PDATA\1\1R

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# 2C.Section C

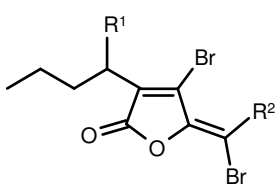
## *Synthesis of Natural Fimbrolides*

This section features the following topics:

## 2C Section C: Synthesis of Natural Fimbrolides

### 2C.1 Background

Fimbrolides (**1**) have been isolated from the red marine algae *Delisea fimbriata* and are bromobutenolides with interesting antifungal and antimicrobial properties.[1] Pulchralides (**2**) appear to be the [2+2] cycloadducts of the fimbrolides (**1**) and they have been isolated from Antarctic macroalgae[2] (Figure 1). The natural fimbrolides (**1**) are limited in availability and till date three syntheses of **1** are described in the literature.[3-6]

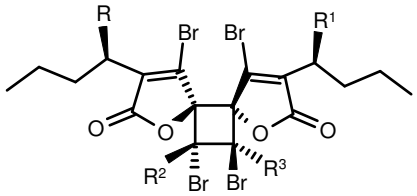



Fimbrolide (**1a**) : $R^1 = R^2 = H$

Fimbrolide (**1b**) : $R^1 = H$, $R^2 = Br$

Acetoxyfimbrolide (**1c**) : $R^1 = OAc$, $R^2 = H$

Hydroxyfimbrolide (**1d**) : $R^1 = OH$, $R^2 = H$




Pulchralide A (**2a**) : $R = R^1 = OAc$, $R^2 = R^3 = H$

Pulchralide B (**2b**) : $R = R^1 = R^2 = R^3 = H$

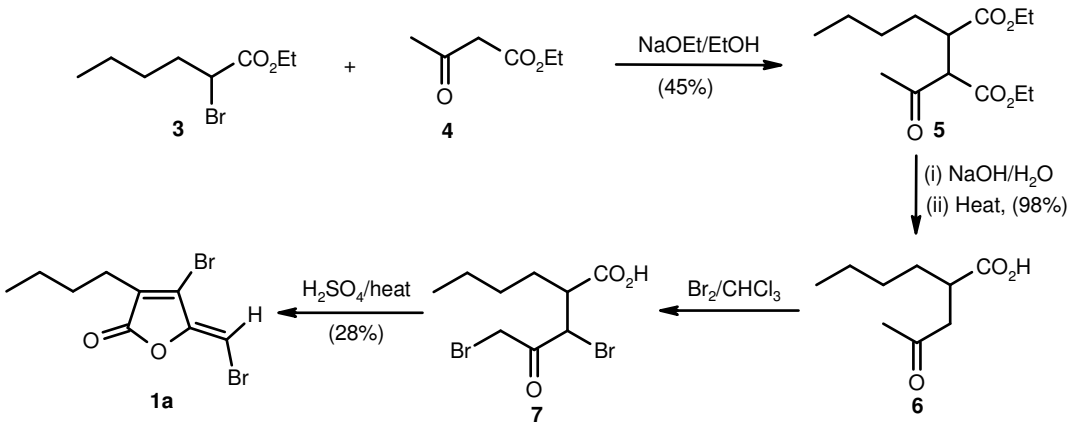
Pulchralide C (**2c**) : $R = OAc$, $R^1 = R^2 = R^3 = H$

**Figure 1.** Fimbrolides and Pulchralides

### I. Sims's Approach

Sims and Beechan[3] reported the first total synthesis of fimbrolides via oxidation/dehydration of dibrominated 2-butyllevulinic acid **7** using sulfuric acid (Scheme 1). Further, Read and co-workers[4] reinvestigated the sulfuric acid-catalyzed cyclisation of brominated 2-alkyllevulinic acid.

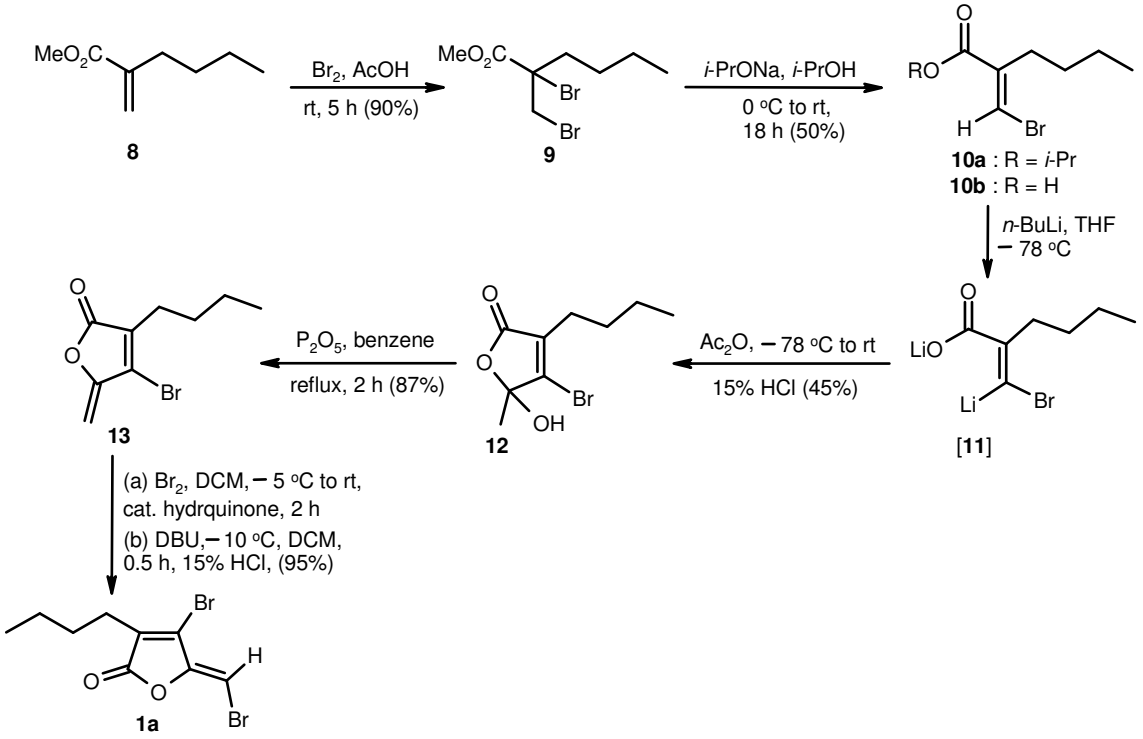
**Scheme 1**



## II. Caine's Approach

Bromination of methyl 2-*n*-butylpropenoate (**8**) gave *α*,*β*-dibromo derivative **9**, which was converted into the (*E*)-bromo ester **10a** by dehydrobromination and transesterification with sodium isopropoxide in isopropyl alcohol (Scheme 2).[5] Treatment of bromo acid **10b** with *n*-butyllithium in THF at −78 °C provided the *β*-lithio carboxylate [**11**] which upon reaction with acetic anhydride yielded *γ*-hydroxybutenolide **12** in 50% yield. Conversion of compound **12** into **1a** was accomplished by known procedure.[7]

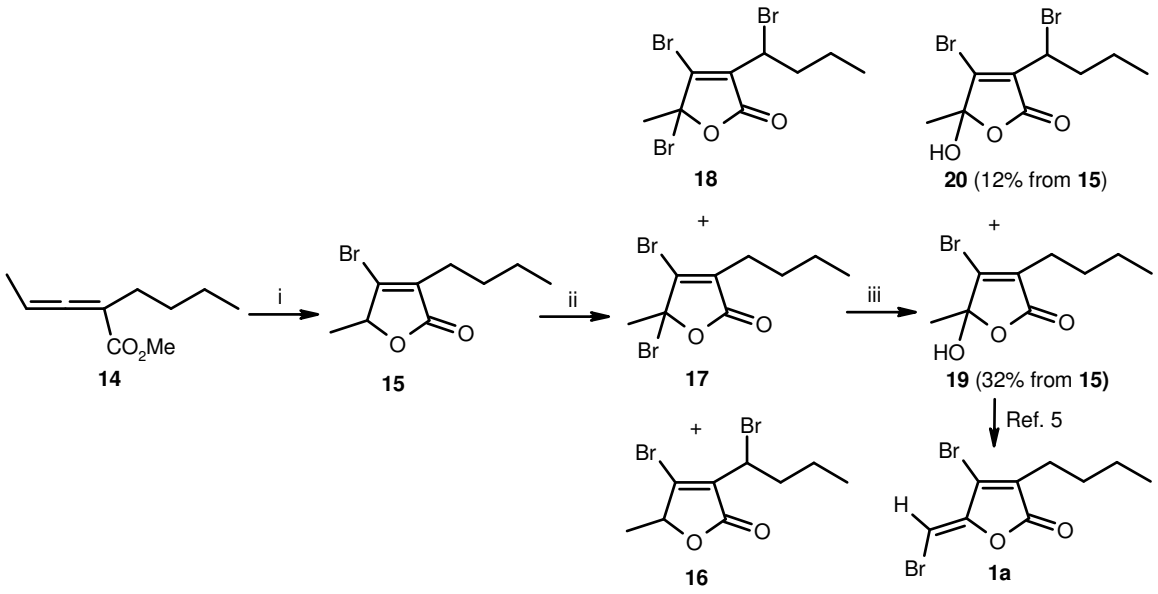
**Scheme 2**




## III. March's Approach

Methyl 2-butyl-2,3-pentadienoate (**14**) was treated with NBS in water to obtain bromolactone **15**. The photochemical allylic bromination of bromolactone **15** gave mixture of dibromolactones **16**, **17** and tribromolactone **18**. The crude mixture was subjected to hydrolysis to obtain mixture of pseudoacids **19** and **20** (Scheme 3).[6] The pseudoacid **19** was converted to fimbrolide (**1a**) using known procedure.[5]

**Scheme 3**



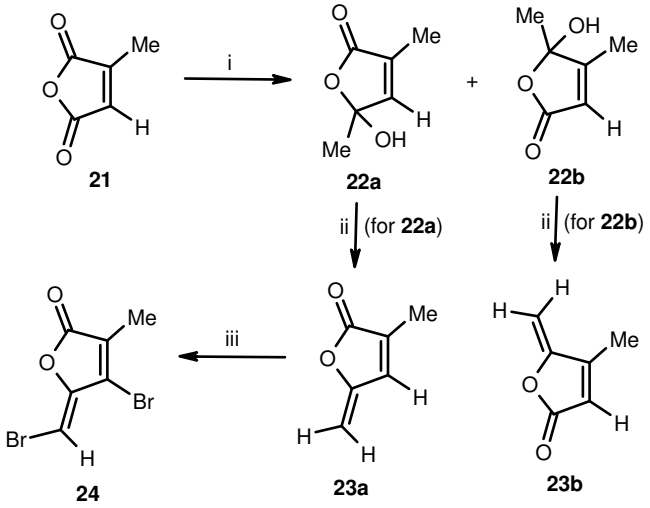

**Scheme 3.** *Reagents*, *conditions and yields*: (i) NBS, water (79%); (ii) 1 equiv. NBS, $CCl_4$, hν; (iii) THF, Water.

### 2C.2 Present Work: Results and Discussion

We decided to use *n*-butylmaleic anhydride as precursor for the synthesis of fimbrolides. To confirm the feasibility of our proposal, we initially used the readily available citraconic anhydride (**21**) for model studies (Scheme 4). The regioselective nucleophilic addition of methylmagnesium iodide to citraconic anhydride (**21**) at –20 $^{o}$C furnished a mixture of lactols **22a** and **22b** in ~ 88:12 ratio with 76% yield. The silica gel column chromatographic separation of **22a** and **22b** followed by the $P_4O_{10}$-induced dehydration gave the butenolides **23a** and **23b** in 88% and 85% yields, respectively. Reaction of compound **23a** with 2.20-equivalents of bromine at 0 $^{o}$C followed by the treatment with triethylamine, yielded exclusively the dibromobutenolide **24** in 68% yield, via the addition of two bromine molecules to two different carbon-carbon double bonds, followed by the double dehydrobromination pathway.

We prepared the *n*-butylmaleic anhydride (**30**) using our own method.[8] The *n*-butylisomaleimide **28** was obtained from the maleimide **25** in three-steps (Scheme 5).

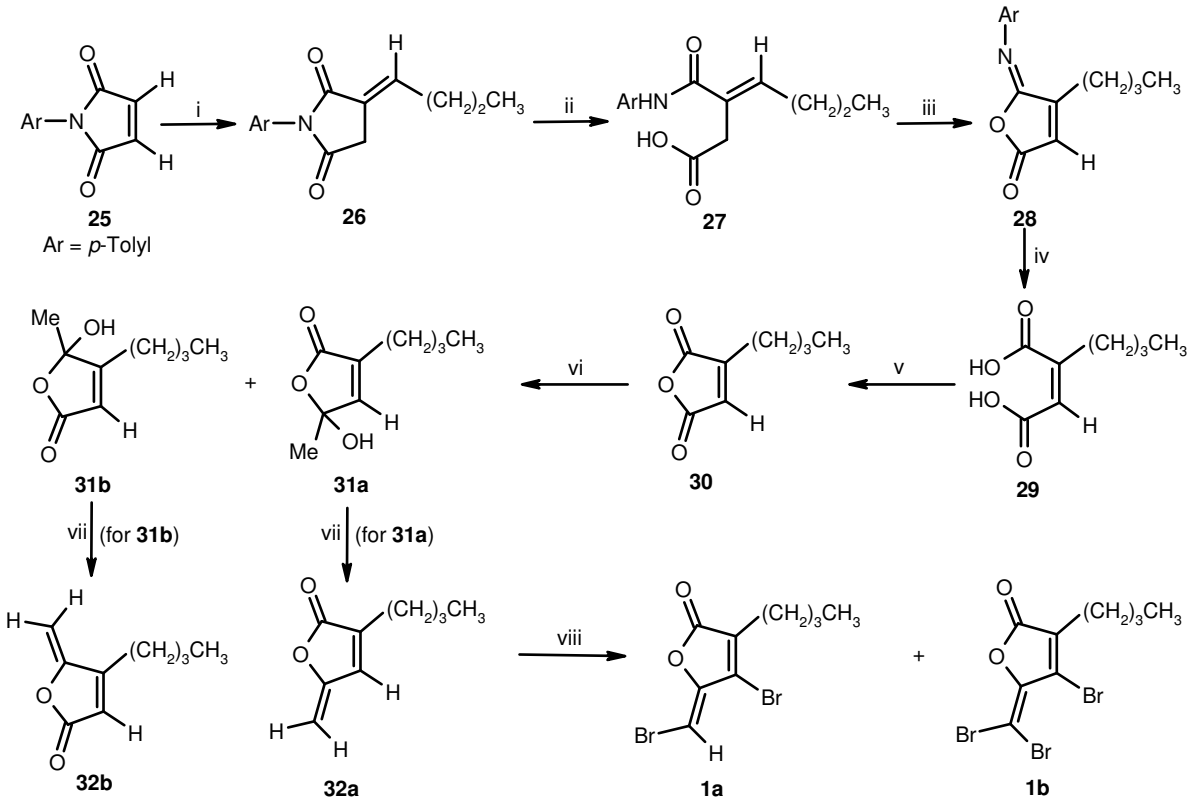
The acid catalyzed hydrolysis of the isomaleimide **28** followed by the acetic anhydride-induced dehydrative cyclization of the formed *n*-butylmaleic acid **29** gave the anhydride




**Scheme 4.** *Reagents*, *conditions and yields*: (i) $CH_3MgI$ (1.10 equiv.), $Et_2O$, −20 °C, 2 h (**22a**: 68%, **22b**: 8%); (ii) $P_2O_5$, benzene, reflux, 5 h (**23a**: 88%, **23b**: 85%); (iii) (a) $Br_2$ (2.20 equiv.), $CCl_4$, 0 °C to rt, 10 h, (b) $NEt_3$ (2.20 equiv.), $CHCl_3$, 0 °C to rt, 5 h (68%).

**30** in 90% yield. The regioselective reaction of methylmagesium iodide with anhydride **30** at –20 °C again produced a mixture of lactols **31a** and **31b** in ~ 85:15 ratio with 71% yield. Herein, as expected, the nucleophilic addition of the Grignard reagent majorly took place at the unhindered carbonyl carbon, thus providing **31a** as the major product. It was difficult for us to lower the temperature in order to get a higher regioselectivity because the anhydride **30** started separating out as a sticky solid below –20 °C. Silica gel column chromatographic separation of **31a** and **31b** followed by $P_4O_{10}$-induced dehydration gave the expected butenolides **32a** and **32b** in 90% and 87% yields, respectively. During the isolation of **32a** and **32b**, we noticed that the butenolides **32a** and **32b** are quite stable in organic solvents, but they have a propensity to undergo polymerization during the course of isolation and also in the neat form. The structural assignment of **32a** and **32b** was done on the basis of NMR spectral data and as expected the $\beta$-hydrogen in **32a** was more deshielded ($\delta$ = 7.03) than the $\alpha$-hydrogen in **32b** ($\delta$ = 5.99). At this stage, to obtain the fimbrolides, we systematically studied the bromination reactions of **32a** at 0 °C with 2.20 and 3.30 equivalents of bromine in $CCl_4$. In these reactions, we always ended up with the

formation of a mixture of the fimbrolides **1a** and **1b** via the addition-elimination pathway along with the formation of some amount of gummy-material. With the use of 2.20 equivalents of bromine, **1a** was formed as the major product, while **1b** was formed as the major product with the use of 3.30 equivalents of bromine. In these reactions, both the addition of bromine to the carbon-carbon double bonds and the elimination of hydrogen bromide were quite instantaneous, but to ensure a complete dehydrobromination, the use of triethylamine was necessary. Herein, all our attempts to exclusively obtain **1a** and **1b** met with failure and forced conditions resulted in the formation of polymeric gum. Thus, the obtained mixture of **1a**, **1b**, and polymeric gum was initially filtered through a silica gel column for the removal of impurities and then the remaining mixture of **1a** and **1b**




**Scheme 5.** *Reagents*, *conditions and yields*: (i) $PPh_3$ (1.00 equiv.), THF, $CH_3(CH_2)_2CHO$ (1.50 equiv.), reflux, 10 h (90%); (ii) Aq. 2 N LiOH, THF, 0 $^oC$ to rt, 5 h (93%); (iii) Cyanuric chloride (1.10 equiv.), $NEt_3$ (3.00 equiv.), DCM, 0 $^oC$ to rt, 8 h (85%); (iv) HCl:AcOH (1:1), reflux, 66 h (96%); (v) Acetic anhydride, 60 $^oC$, 3 h (90%); (vi) $CH_3MgI$ (1.10 equiv.), $Et_2O$, −20 $^oC$, 2 h (**31a**: 62%, **31b**: 9%); (vii) $P_2O_5$, benzene, reflux, 5 h (**32a**: 90%, **32b**: 87%); (viii) (a) $Br_2$ (2.20/3.30 equiv.), $CCl_4$, 0 $^oC$ to rt, 10 h, (b) $NEt_3$ (2.20/3.30 equiv.), $CHCl_3$, 0 $^oC$ to rt, 5 h (**1a**: 37/15%, **1b**: 15/41%).

was separated by HPLC using the known procedure.[1c] The analytical and spectral data obtained for **1a** and **1b** were in complete agreement with the reported data.[3-6] Starting from maleimide **25**, the fimbrolides **1a** and **1b** were obtained in eight steps with 13% and 14% overall yields, respectively.[9] An attempted photochemical conversion of fimbrolide to pulchralide has been reported unsuccessful, supporting their biotic genesis.[2]

### 2C.3 Summary

In summary, we have demonstrated a facile synthesis of two natural fimbrolides, starting from *n*-butylmaleic anhydride, taking the advantage of a regioselective Grignard coupling reaction and an instantaneous bromination-dehydrobromination process. We feel that our present approach is general in nature and will be useful for the synthesis of several other suitably substituted butyrolactone congeners for structure-activity relationship studies.

*In conclusion, in the present three sections chapter we have described the relevant literature and our results with experimental and spectral data. In the present chapter, we have demonstrated an elegant general approach to exclusively design kinetically controlled N-aryl/N-alkyl isomaleimides and isophthalimides using readily available cyanuric chloride as a dehydrating agent and the present approach has several advantages over earlier approaches. We have developed a simple and efficient approach to alkylmaleimides and dialkylmaleimides via the two Wittig coupling reactions, taking the advantage for the first time of kinetically controlled isoimides as intermediates to enforce the difficult migration of exocyclic carbon-carbon double bonds to the endocyclic position. We have also completed a facile synthesis two natural fimbrolides, starting from butylmaleic anhydride, taking the advantage of a regioselective Grignard coupling reaction and an instantaneous bromination-dehydrobromonation process.*

### 2C.4 Experimental

Commercially available citrconic anhydride, *p*-toluidine, phosphorus pentaoxide, *n*-butyraldehyde, acetic anhydride, iodomethane, bromine and triphenylphosphine were used. Freshly recrystallized cyanuric chloride (from $CCl_4$) was used.

**5-Hydroxy-3,5-dimethylfuran-2(5*H*)-one (22a) and 5-hydroxy-4,5-dimethylfuran-2(5*H*)-one (22b).** A fresh solution of methylmagnesium iodide in diethyl ether was prepared as follows: A solution of iodomethane (1.40 g, 9.82 mmol) in anhydrous diethyl ether (30 mL) was added at 0 ºC to magnesium turnings (1.18 g, 49.10 mmol) in anhydrous diethyl ether (10 mL) under argon atmosphere with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was further stirred at 0 ºC for 30 min. This freshly generated Grignard reagent was added in a dropwise fashion to a solution of citraconic anhydride (**21**, 1.00 g, 8.92 mmol) in anhydrous diethyl ether (15 mL) under argon atmosphere at –20 ºC and the reaction mixture was further stirred at the same temperature for 2 h. The reaction was quenched by the addition of a saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (50 mL) was added to the reaction mixture. The separated organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate (9:1) to give **22a** (780 mg, 68% yield) and **22b** (90 mg, 8% yield).

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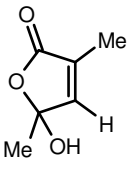
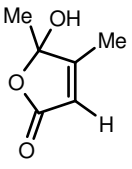
|---|---|
|  <br>**22a (128)** | **MP**: 98-99 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 3385, 1767, 1751, 1709 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.63 (s, 3H), 1.85 (d, $J$ = 2 Hz, 3H), 5.01 (bs, 1H), 6.84 (q, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_6H_8O_3$**: C, 56.25; H, 6.29. Found: C, 56.31; H, 6.13. |
|  <br>**22b (128)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 3354, 1744, 1670, 1647 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.64 (s, 3H), 2.09 (d, $J$ = 2 Hz, 3H), 4.96 (bs, 1H), 5.74 (q, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_6H_8O_3$**: C, 56.25; H, 6.29. Found: C, 56.09; H, 6.22. |

**3-Methyl-5-methylenefuran-2(5*H*)-one (23a).** A suspension of 5-hydroxy-3,5-dimethylfuran-2(5*H*)-one (**22a**, 700 mg, 5.47 mmol) and phosphorus pentoxide (2.33 g, 16.41 mmol) in benzene (20 mL) was refluxed for 5 h. The reaction mixture was filtered

through celite and the residue was washed with benzene (2 x 20 mL). The organic layer was concentrated in vacuo and the obtained crude product was purified by silica gel column chromatography using petroleum ether and ethyl acetate (9:1) to give **23a** (530 mg, 88% yield).

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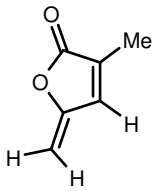
|  <br>**23a (110)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1771, 1653 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.03 (d, $J$ = 2 Hz, 3H), 4.77 (d, $J$ = 4 Hz, 1H), 5.11 (t, $J$ = 2 Hz, 1H), 7.06 (d, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_6H_6O_2$**: C, 65.45; H, 5.49. Found: C, 65.32; H, 5.55. |

**4-Methyl-5-methylenefuran-2(5*H*)-one (23b).** This compound was obtained in 85% yield by using same procedure as described for the synthesis of compound **23a**.

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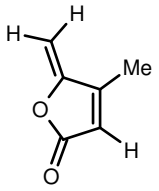
|  <br>**23b (110)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1767, 1655 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.18 (d, $J$ = 2 Hz, 3H), 4.91 (dd, $J$ = 4 & 1 Hz, 1H), 5.15 (dd, $J$ = 4 & 2 Hz, 1H), 6.00 (sextet, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_6H_6O_2$**: C, 65.45; H, 5.49. Found: C, 65.51; H, 5.53. |

**(*Z*)-4-Bromo-5-(bromomethylene)-3-methylfuran-2(5*H*)-one (24).** A solution of bromine (0.21 mL, 3.99 mmol) in $CCl_4$ (5 mL) was added to the solution of 3-methyl-5-methylenefuran-2(5*H*)-one (**23a**, 200 mg, 1.82 mmol) in $CCl_4$ (10 mL) at 0 $^oC$. The reaction mixture was stirred at room temperature for 10 h and then the solvent was removed in vacuo. The obtained residue was dissolved in chloroform and triethylamine (0.56 mL, 3.99 mmol) was added at 0 $^oC$. The reaction mixture was further stirred at room temperature for 5 h. The solvent was removed in vacuo and the obtained crude product was purified by silica gel column chromatography using petroleum ether and ethyl acetate to give pure **24** (330 mg, 68% yield).

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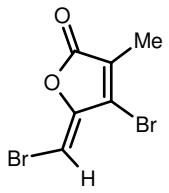
|  <br>**24 (267)** | **MP**: 69-70 $^{o}$C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1786, 1638, 1609 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.16 (s, 3H), 6.22 (s, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 11.6, 90.6, 112.2, 149.5, 152.0, 163.5.<br>**Anal. Calcd for $C_6H_4Br_2O_2$**: C, 26.90; H, 1.50; Br, 59.65. Found: C, 27.10; H, 1.44; Br, 59.67. |

**3-Butylidene-1-*p*-tolylpyrrolidine-2,5-dione (26).** A solution of *N*-*p*-tolylmaleimide (**25**, 2.00 g, 10.70 mmol) and triphenylphosphine (2.80 g, 10.70 mmol) in THF (50 mL) was stirred at room temperature for 30 min. To the reaction mixture was added *n*-butyraldehyde (1.16 g, 16.04 mmol) and it was gently refluxed for 10 h. The THF was removed in vacuo at 50 $^{o}$C and the residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate (9:1) to obtain **26** (2.34 g, 90% yield).

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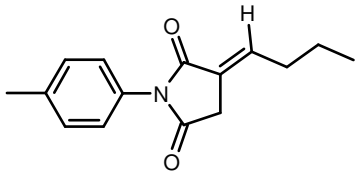
|  <br>**26 (243)** | **MP**: 90-92 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 1773, 1709, 1676 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.99 (t, $J$ = 8 Hz, 3H), 1.58 (sextet, $J$ = 8 Hz, 2H), 2.23 (q, $J$ = 8 Hz, 2H), 2.39 (s, 3H), 3.39 (s, 2H), 6.95 (t, $J$ = 8 Hz, 1H), 7.20 (d, $J$ = 8 Hz, 2H), 7.29 (d, $J$ = 8 Hz, 2H).<br>**MS** (*m*/*e*) 243, 228, 214, 133, 95, 67, 53.<br>**Anal. Calcd for $C_{15}H_{17}NO_2$**: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.92; H, 7.15; N, 5.69. |

**3-(*p*-Tolylcarbamoyl)hept-3-enoic acid (27).** To a solution of 3-butylidene-1-*p*-tolylpyrrolidine-2,5-dione (**26**, 2.00 g, 8.23 mmol) in THF (25 mL) was added 2 N aqueous LiOH (4 mL) in a dropwise fashion at 0 $^{o}$C and the reaction mixture was stirred for 5 h at room temperature. THF was removed in vacuo and the aqueous layer was acidified with aqueous 2 N HCl till pH 4 and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water, brine and dried over $Na_2SO_4$. Concentration of the organic layer in vacuo gave the desired compound compound **27** (1.99 g, 93% yield).

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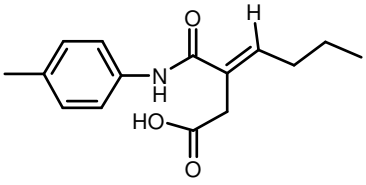
|  **27 (261)** | **MP**: 140-142 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 3283, 1682, 1657, 1597 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.94 (t, $J$ = 6 Hz, 3H), 1.50 (sextet, $J$ = 8 Hz, 2H), 2.31 (s, 3H), 2.15-2.40 (m, 2H), 3.39 (s, 2H), 6.46 (t, $J$ = 6 Hz, 1H), 7.13 (d, $J$ = 8 Hz, 2H), 7.40 (d, $J$ = 8 Hz, 2H), 8.07 (bs, 1H).<br>**Anal. Calcd for $C_{15}H_{19}NO_3$**: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.89; H, 7.40; N, 5.28. |

**4-*n*-Butyl-5-(*p*-tolylimino)furan-2(5*H*)-one (28).** To a slurry of 3-(*p*-tolylcarbamoyl)hept-3-enoic acid (**27**, 1.50 g, 5.75 mmol) in dichloromethane (25 mL) was added triethylamine (2.40 mL, 17.24 mmol) in a dropwise fashion with constant stirring at 0 $^{o}$C. To the resulting reaction mixture was added a solution of cyanuric chloride (1.16 g, 6.22 mmol) in dichloromethane (25 mL) and the reaction mixture was further stirred under argon atmosphere for 8 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water, 5% aqueous sodium bicarbonate, brine and dried over $Na_2SO_4$. The ethyl acetate layer was concentrated in vacuo and the crude product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to obtain pure **28** (1.19 g, 85% yield).

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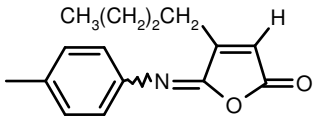
|  **28 (243)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1798, 1682, 1622 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.99 (t, $J$ = 8 Hz, 3H), 1.46 (sextet, $J$ = 8 Hz, 2H), 1.70 (quintet, $J$ = 8 Hz, 2H), 2.37 (s, 3H), 2.67 (dt, $J$ = 8 & 2 Hz, 2H), 6.31 (t, $J$ = 2 Hz, 1H), 7.19 (d, $J$ = 8 Hz, 2H), 7.35 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 125 MHz) $\delta$ 13.6, 20.9, 22.2, 25.8, 29.3, 120.9, 125.2, 129.3, 137.0, 140.9, 150.0, 159.6, 167.0.<br>**Anal. Calcd for $C_{15}H_{17}NO_2$**: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.88; H, 7.15; N, 5.67. |

**2-*n*-Butylmaleic acid (29).** A solution of 4-*n*-butyl-5-(*p*-tolylimino)furan-2(5*H*)-one (**28**, 1.00 g, 4.12 mmol) in glacial acetic acid and concentrated hydrochloric acid (1:1, 20

mL) was refluxed for 66 h. The reaction mixture was allowed to reach room temperature, concentrated in vacuo, and the obtained residue was dissolved in 5% aqueous sodium bicarbonate (40 mL). The aqueous layer was washed with ethyl acetate (2 x 50 mL). The aqueous layer was acidified with aqueous 2 N HCl till pH 4 and then extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water, brine and dried over $Na_2SO_4$. Concentration of the organic layer in vacuo gave **29** (680 mg, 96% yield).

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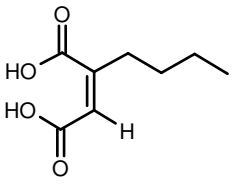
|  <br>**29 (172)** | **MP**: 163-164 $^{o}$C.<br>**IR** (nujol) $\nu_{max}$ 2700-2500, 1690, 1647 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$ + DMSO-$d_6$, 200 MHz) $\delta$ 0.94 (t, $J$ = 8 Hz, 3H), 1.48 (sextet, $J$ = 8 Hz, 2H), 2.17 (q, $J$ = 8 Hz, 2H), 2.56-2.63 (m, 2H), 6.90 (t, $J$ = 8 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$ + DMSO-$d_6$, 125 MHz) $\delta$ 12.6, 20.5, 29.5, 31.0, 125.5, 143.4, 167.5, 171.4.<br>**Anal. Calcd for $C_8H_{12}O_4$**: C, 55.81; H, 7.02. Found: C, 55.74; H, 7.13. |

**3-*n*-Butylfuran-2,5-dione (30).** A solution of 2-*n*-butylmaleic acid (**29**, 600 mg, 3.49 mmol) in acetic anhydride (15 mL) was heated at 60 $^{o}$C for 3 h. The reaction mixture was concentrated under vacuum to give a crude residue, which on careful silica gel column chromatographic purification by using petroleum ether and ethyl acetate (9:1) gave pure **30** (480 mg, 90% yield).

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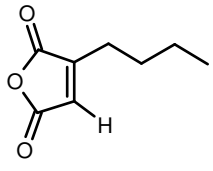
|  <br>**30 (154)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1844, 1773, 1638 cm$^{-1}$.<br>**$^{1}$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.96 (t, $J$ = 8 Hz, 3H), 1.42 (sextet, $J$ = 8 Hz, 2H), 1.64 (quintet, $J$ = 8 Hz, 2H), 2.54 (dt, $J$ = 8 & 2 Hz, 2H), 6.60 (t, $J$ = 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 125 MHz) $\delta$ 13.6, 22.2, 25.6, 28.9, 128.4, 153.8, 164.0, 165.9.<br>**Anal. Calcd for $C_8H_{10}O_3$**: C, 62.33; H, 6.54. Found: C, 62.40; H, 6.47. |

**3-*n*-Butyl-5-hydroxy-5-methylfuran-2(5*H*)-one (31a) and 4-*n*-butyl-5-hydroxy-5-methylfuran-2(5*H*)-one (31b).** These compounds were obtained by using the same procedure as described for the synthesis of compounds **22a** and **22b** in 62% and 9% yields, respectively.

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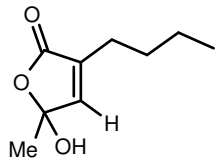
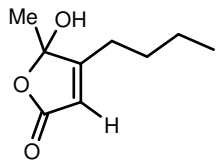
|  <br>**31a (170)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 3462, 1755, 1609 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.94 (t, $J$ = 8 Hz, 3H), 1.28-1.60 (m, 4H), 1.70 (s, 3H), 2.28 (dt, $J$ = 8 & 2 Hz, 2H), 3.26 (bs, 1H), 6.82 (t, $J$ = 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 13.7, 22.3, 24.6, 24.9, 29.3, 104.1, 136.4, 146.5, 171.2.<br>**Anal. Calcd for $C_9H_{14}O_3$**: C, 63.51; H, 8.29. Found: C, 63.61; H, 8.32. |
|  <br>**31b (170)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 3381, 1744, 1670 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.94 (t, $J$ = 8 Hz, 3H), 1.30-1.50 (m, 2H), 1.50-1.70 (m, 2H), 1.63 (s, 3H), 2.20-2.45 (m, 2H), 5.71 (t, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_9H_{14}O_3$**: C, 63.51; H, 8.29. Found: C, 63.56; H, 8.07. |

**3-*n*-Butyl-5-methylenefuran-2(5*H*)-one (32a).** This compound was obtained in 90% yield by using the same procedure as described for the synthesis of compound **23a**.

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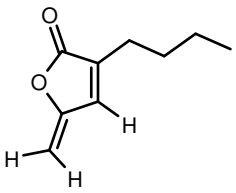
|  <br>**32a (152)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1655 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.94 (t, $J$ = 8 Hz, 3H), 1.37 (sextet, $J$ = 8 Hz, 2H), 1.50-1.66 (m, 2H), 2.38 (t, $J$ = 8 Hz, 2H), 4.77 (d, $J$ = 2 Hz, 1H), 5.11 (d, $J$ = 2 Hz, 1H), 7.03 (t, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_9H_{12}O_2$**: C, 71.03; H, 7.94. Found: C, 70.92; H, 7.89. |

**4-*n*-Butyl-5-methylenefuran-2(5*H*)-one (32b).** This compound was obtained in 87% yield by using the same procedure as used for the synthesis of compound **23a**.

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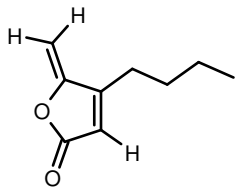
|  **32b (152)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1657 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.96 (t, $J$ = 8 Hz, 3H), 1.42 (sextet, $J$ = 8 Hz, 2H), 1.63 (quintet, $J$ = 8 Hz, 2H), 2.49 (dt, $J$ = 8 & 2 Hz, 2H), 4.93 (dd, $J$ = 3 & 2 Hz, 1H), 5.16 (dd, $J$ = 2 & 2 Hz, 1H), 5.99 (t, $J$ = 2 Hz, 1H).<br>**Anal. Calcd for $C_9H_{12}O_2$**: C, 71.03; H, 7.94. Found: C, 70.91; H, 7.88. |

**(*Z*)-4-Bromo-5-(bromomethylene)-3-*n*-butylfuran-2(5*H*)-one (1a) and 4-bromo-3-*n*-butyl-5-(dibromomethylene)furan-2(5*H*)-one (1b).** As per the procedure for the preparation of compound **24**, the bromination of **32a** (70 mg, 0.46 mmol) with bromine (162 mg, 1.01 mmol), followed by silica gel column chromatographic filtration, and followed by HPLC separation[1c] furnished **1a** (53 mg, 37%) and **1b** (32 mg, 18%). Similarly, the use of 3.30 equivalents of bromine furnished **1a** (21 mg, 15%) and **1b** (73 mg, 41%).

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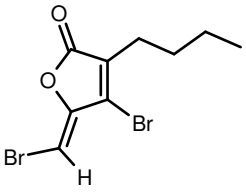
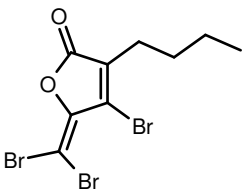
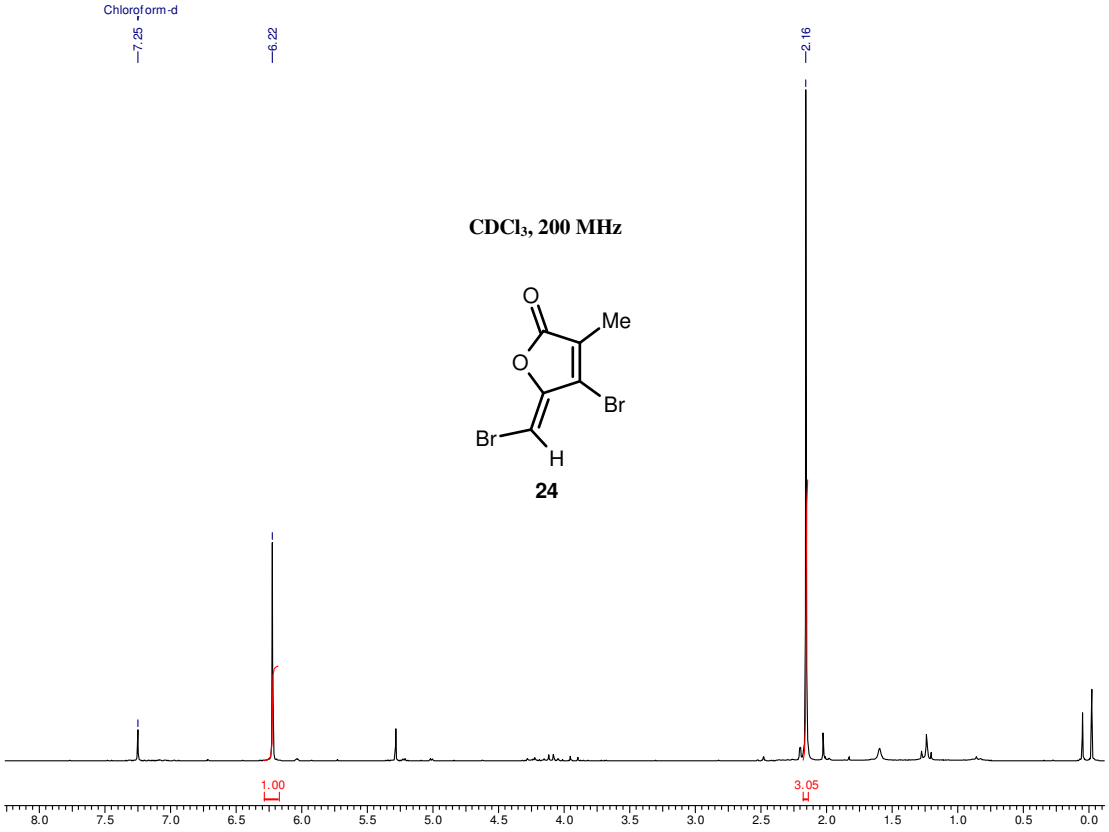
|  **1a (309)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1790, 1621 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.92 (t, $J$ = 7 Hz, 3H), 1.26-1.42 (m, 2H), 1.49-1.65 (m, 2H), 2.39 (t, $J$ = 7 Hz, 2H), 6.25 (s, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.5, 22.4, 29.2, 25.1, 91.0, 149.9, 130.1, 133.9, 166.2.<br>**Anal. Calcd for $C_9H_{10}Br_2O_2$**: C, 34.87; H, 3.25; Br, 51.55. Found: C, 34.72; H, 3.19; Br, 51.42. |
|  **1b (388)** | Thick oil.<br>**IR** (neat): 1780, 1622 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.93 (t, $J$ = 7 Hz, 3H), 1.29-1.45 (m, 2H), 1.50-1.64 (m, 2H), 2.40 (t, $J$ = 7 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.6, 22.2, 25.9, 28.8, 81.5, 128.3, 138.1, 144.7, 164.9.<br>**Anal. Calcd for $C_9H_9Br_3O_2$**: C, 27.80; H, 2.33; Br, 61.64. Found: C, 27.73; H, 2.41; Br, 61.50. |

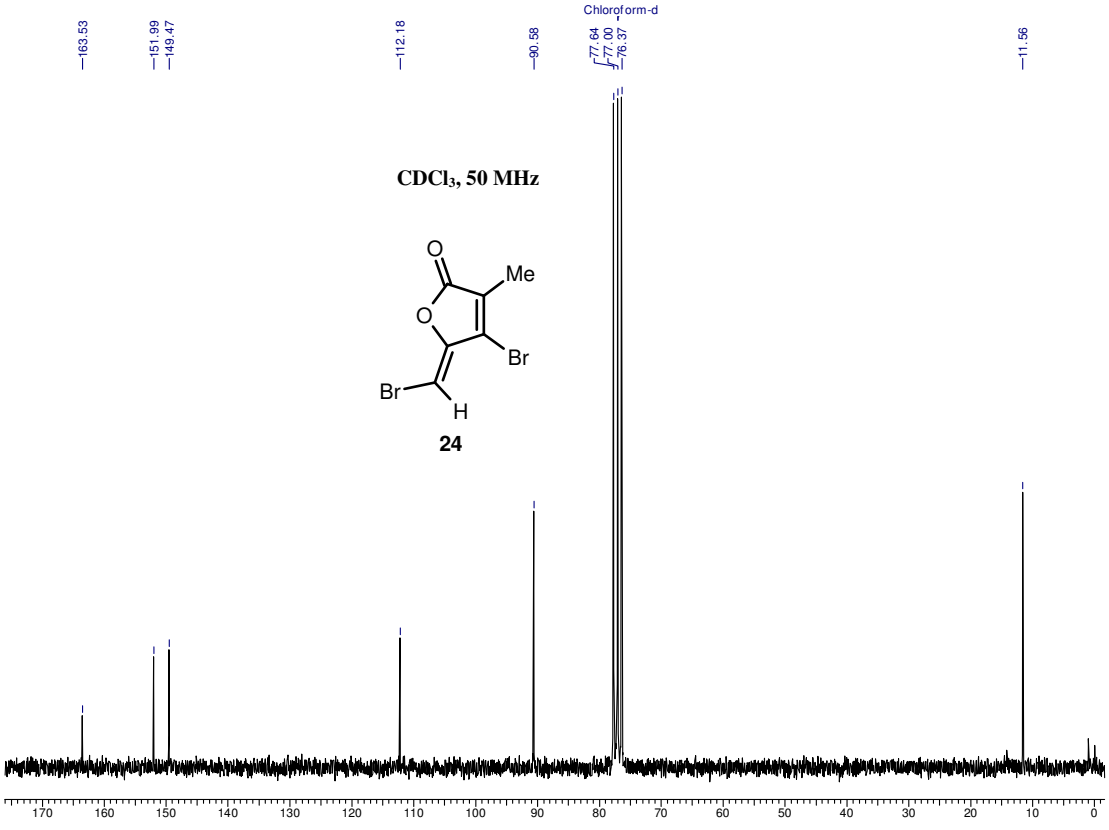
# 2C.5 Selected Spectra




**$CDCl_3$, 200 MHz**



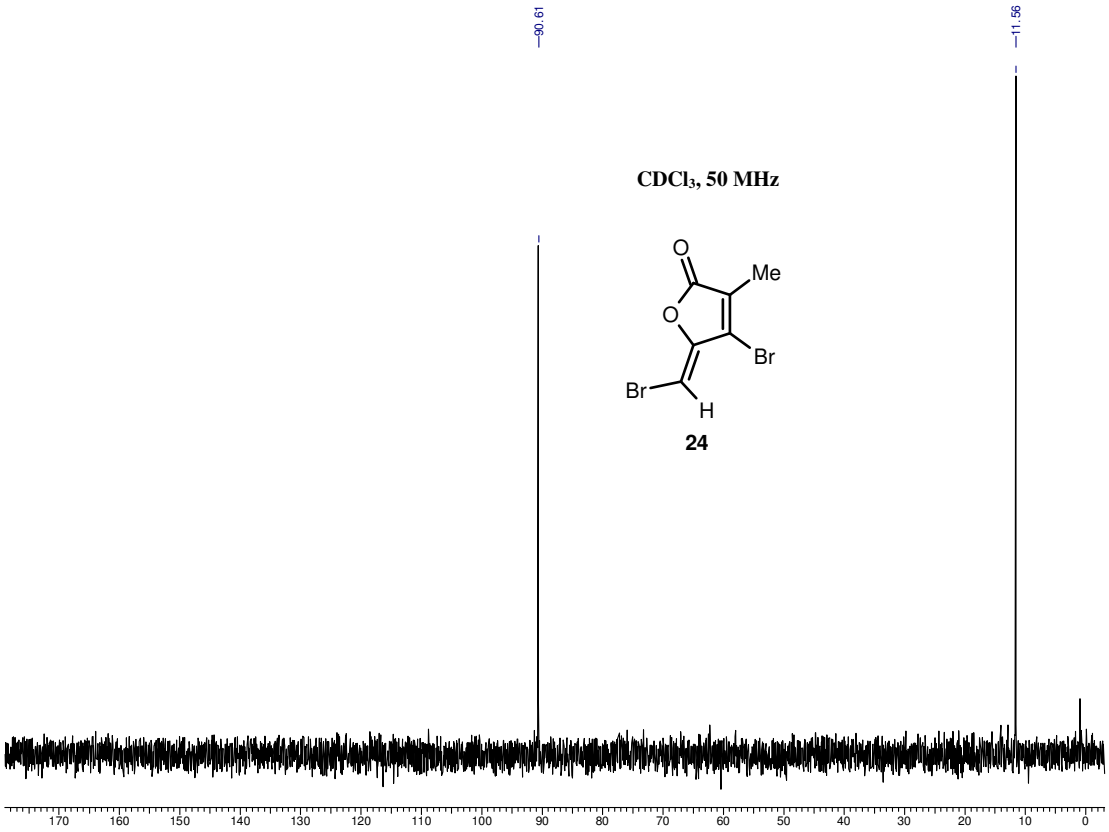

**24**




**$CDCl_3$, 50 MHz**




**24**


90.61
11.56
CDCl3, 50 MHz
O
Me
O
Br
Br
H
24
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

## 2C.6 References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# Chapter 3

## *A General Approach to Natural and Unnatural Dialkyl Substituted Maleic Anhydrides and Related Natural Products*

This chapter features the following sections:

# 3A. Section A

*Synthesis of Bioactive Natural Product*

*Chaetomellic Anhydride A*

This section features the following topics:

# 3A Section A: Synthesis of Bioactive Natural Product Chaetomellic Anhydride A

## 3A.1 Background

Chaetomellic acid A (**3**) and chaetomellic acid B (**4**) have been isolated[1] from fermentation extract of the coleomycete *Chaetomella acutiseta* (Figure 1) by a group of scientists at Merck, USA in 1993. Chaetomellic acid A and B have been identified as potent inhibitors of ras farnesyl-protein transferase[1,2] (FPTase), an enzyme catalyzing a post-translational modification of ras. Mutated form of ras oncogens found in about 25% of the human tumors[3] and believed to play a key role in their growth.

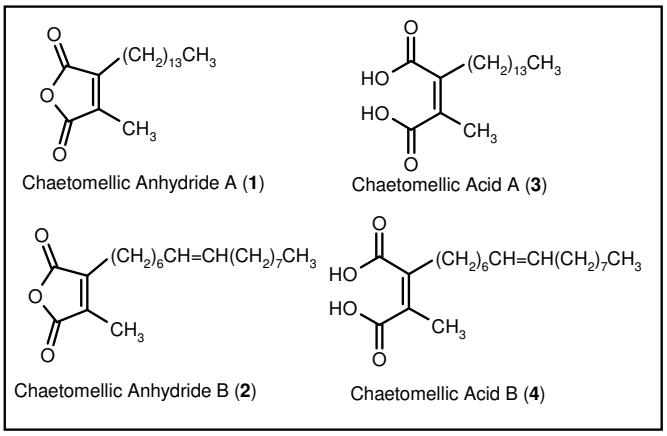



**Figure 1**

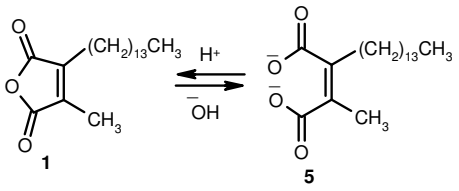
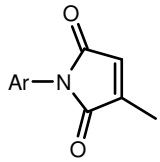
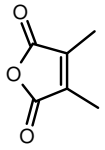
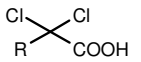
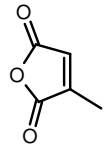



**Figure 2**

These classes of natural products have propensity to cyclize as shown in Figure 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 above in compound **5**. Chaetomellic acid A (**3**) is three times more potent than chaetomellic acid B (**4**) and became the main attraction of synthetic efforts because of its potent FPTase inhibitory activity for the treatment of cancer. Recently, the dianion of chaetomellic acid A (**5**) has found application in characterizing the FPP (fernesyl diphospahte) bonding site in rubber transferase.[4] After its isolation in 1993, in the past fifteen years several syntheses[5-15] have been reported. The chemistry of all earlier syntheses of **1** and **2** is summarized in Table 1.

**Table 1.** Syntheses of chaetomellic anhydride A (**1**) and chaetomellic anhydride B (**2**)

| No. | Starting Material | Reagents and Conditions | Product | Yield | Ref. |
|---|---|---|---|---|---|
| 1 | $CH_3(CH_2)_{14}COOMe$<br>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) 4 N HCl. | **1** | 18% | 5 |
| 2 | $CH_3(CH_2)_{12}CH_2Br$<br>Tetradecyl bromide | (i) $CoCl_2$, pyridine, $NaBH_4$, NaOH, $CH_3OH$; (ii) PhSSPh, *hv*; (iii) *m*-CPBA, pH 7.4, DCM. | **1** | 64% | 6 |
| 3 | $MeOOCCH_2COOMe$<br>Dimethyl malonate | (i) NaH, $C_{14}H_{29}Br$ or $C_{16}H_{29}Br$, 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, methyl chloroformate; (v) $Et_3N$, TMSOTf, $C_6H_6$, reflux, 2 h; (vi) $Br_2$, $Bu_4NBr$. | **1 or 2** | **1** (83%)<br>**2** (80%) | 7 |
| 4 |  <br>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) $H^+/HCl$. | **1** | 78% | 8 |
| 5 | $CH_3(CH_2)_{12}CH(Br)COCl$<br>2-Bromopalmitoyl chloride | (i) 2-Amino pyridine, $Et_3N$, $Et_2O$, rt; (ii) *t*-BuOH, reflux; (iii) maleic anhydride, NaOAc, reflux. | **1** | 62% | 9 |
| 6 |  <br>(Ar = *p*-Tolyl)<br>*N*-*p*-Tolyl Methylmaleimide | (i) (a) $PPh_3$, AcOH, reflux, 2 h, (b) $CH_3(CH_2)_{12}CHO$, reflux, 18 h; (c) Δ, 140-150 °C, 0.5 h; (ii) (a) $KOH/H_2O/CH_3OH$/THF, reflux, 2 h, (b) $H^+/HCl$. | **1** | 89% | 10 |

| | | | | | |
|---|---|---|---|---|---|
| 7 | RCOOH<br>R = $C_{14}H_{29}$<br>Pentadecanoic acid<br>R = $C_{16}H_{31}$ (*Z*)-8-<br>Heptadecanoic acid | (i) (a) DCC, 2-mercaptopyridine *N*-oxide, DCM, 2 h, (b) citraconic anhydride, *hv* (500 W), 10-15 $^{o}$C, 0.5 h. | **1 or 2** | **1** (70%)<br>**2** (60%) | 11 |
| 8 |  <br>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 $^{o}$C. | **1** | 38% | 12 |
| 9 |  <br>R = $CH_2(CH_2)_{12}CH_3$<br>2,2-Dichloropalmitic acid | (i) (a) $(COCl)_2$, $CH_2Cl_2$, DMF, 23 $^{o}$C, 2 h, (b) *N*-Benzyl-3-chloro-2-propylamine, pyridine, 23 $^{o}$C, 1 h; (ii) CuCl/TMEDA, MeCN-$CH_2Cl_2$, 60 $^{o}$C, 20 h; (iii) (a) Na, MeOH-$Et_2O$, 25 $^{o}$C, 20 h, (b) $H^+/H_2O$; (iv) (a) KOH, MeOH-THF, reflux, 2 h, (b) $H^+/H_2O$. | **1** | 55% | 13 |
| 10 |  <br>Methylmaleic anhydride | (i) MeOH, $H^+/H_2SO_4$, reflux, 12 h; (ii) NBS, AIBN, $CCl_4$, reflux, 12 h; (iii) $C_{14}H_{29}MgBr$, $Et_2O$, HMPA, rt, 8 h; (iv) AcOH + HCl (7:3), reflux, 2 h; (v) $Ac_2O$, reflux, 2 h. | **1** | 37% | 14 |
| 11 | $CH_3(CH_2)_{13}CHO$<br>Pentadecanal | (i) Trimethylsilylacetylide, THF, −78 to −10 $^{o}$C; (ii) DIAD, $PPh_3$, NBSH, THF, −15 $^{o}$C to rt; (iii) $CO_2$, $Ni(cod)_2$, DBU, $Me_2Zn$, THF, rt, 19 h; (iv) $Ac_2O$, 2 h. | **1** | 57% | 15 |

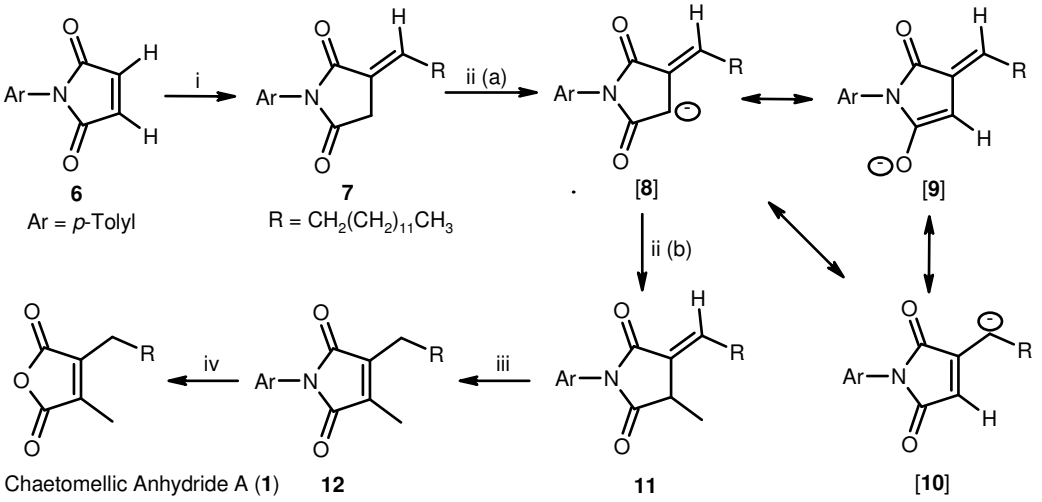
Studies of structure-activity relationship and pharmacological tests have stimulated the development of chemical synthesis for the production of larger quantities of chaetomellic anhydride A (**1**) than that available from natural sources.

### 3A.2 Present Work: Results and Discussion

To date, several alkylmethylmaleic anhydrides have been isolated as potent bioactive natural products[16,17] and many product specific syntheses with some limitations are known in the literature.[18,19] Hence, we decided to develop a general strategy for the synthesis of wide range of natural and unnatural dialkylmaleic anhydrides.

It is well established that maleimides couple with triphenylphosphine to generate an in situ Wittig reagent, which on reaction with variety of aldehydes provide the corresponding thermodynamically more stable (*E*)-alkylidenesuccinimides in decent yields.[20] The exclusive formation of (*E*)-isomer in product **7** was established on the basis of the lower field $^{1}$H NMR resonance for the vinylic proton in close proximity to the carbonyl and was further confirmed by comparing with similar known compounds.[10] Recently, we have proved that the alkylidenesuccinimides are thermodynamically more stable than the corresponding alkylmaleimides, hence the direct prototropic shift with an exocyclic to endocyclic double bond migration is impossible (Chapter 2, Section B).[21] We reasoned and planned to take the advantage of this observation by studying the feasibility of generation of allylic carbanion on alkylidenesuccinimide nucleus and further explore its condensation reactions with variety of alkyl halides to develop new general approach to dialkyl maleimides and maleic anhydrides. In this context, starting from *N*-*p*-tolylmaleimide (**6**), we prepared the (*E*)-tetrdecylidenesuccinimide (**7**) in 89% yield. In (*E*)-tetrdecylidenesuccinimide (**7**) the methylene proton is acidic because of the adjacent imide carbonyl group and their allylic nature. As per our hypothesis, the (*E*)-tetrdecylidenesuccinimide (**7**) on treatment with an equivalent amount of sodium hydride in THF at 0 $^{o}$C turned into a deep red colored solution, indicating the formation of the carbanion. The reaction of the above carbanionic solution with methyl iodide at 0 $^{o}$C, exclusively furnished the desired ring mono-alkylated product **11** in 65% yield. These observations clearly revealed that the tetradecylidenesuccinimidoyl carbanionic species **8** can be in resonance with intermediates **9** and tetradecylmaleidoyl carbanionic species **10**. We feel that the resonance hybrid prefer to react with methyl iodide via the relatively more contributing carbanionic species **8** rather than the carbanionic species **10** to form the product **11**. With the introduction of methyl substituent on **7** to form **11**, the trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond

isomerzation became feasible on treatment of **11** with triethylamine to obtain **12** in 90% yield. The dialkyl substituted maleimide **12** on base catalyzed hydrolysis followed by acidification, furnished chaetomellic anhydride A (**1**) in 91% yield (Scheme 1).[22]




**Scheme 1**. *Reagents*, *conditions and yields*: (i) $Ph_3P$ (1.00 equiv.), $CH_3(CH_2)_{12}CHO$ (1.50 equiv.), THF, reflux, 10 h (89%); (ii) (a) NaH (1.00 equiv.), THF, 0 °C, 0.5 h, (b) $CH_3I$ (1.00 equiv.), 0 °C – rt, 3 h (65%); (iii) $Et_3N$ + THF (1:1), reflux, 48 h (90%); (iv) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (91%).

### 3A.3 Summary

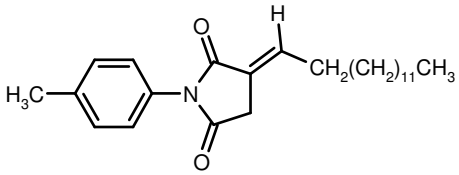
In summary, we have described a facile synthesis of potent ras fernesyl-protein transferase inhibitor cheatomellic anhydride A via the generation of a carbanion on the tetradecylidenesuccinimide core. We feel that our present general approach can be used to design the synthetic library of chaetomellic anhydride A, B and their analogues/congeners for structure-activity relationship studies.

### 3A.4 Experimental

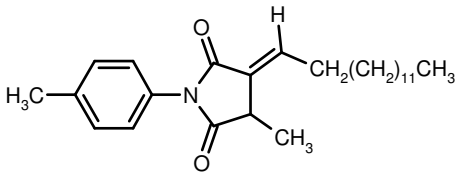
Commercially available maleic anhydride, *p*-toluidine, triphenylphosphine, sodium hydride and methyl iodide were used. Tetradecyl aldehyde was synthesized from tetradecyl alcohol by PCC oxidation.

**(*E*)-3-Tetradecylidene-1-*p*-tolylpyrrolidene-2,5-dione (7).** A solution of *N*-*p*-tolylmaleimide (**6**, 1.87 g, 10.00 mmol) and triphenylphosphine (2.62 g, 10.00 mmol) in THF (100 mL) was stirred at room temperature for 30 min. To the reaction mixture was

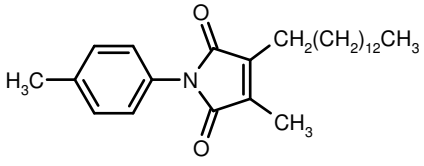
added the tetradecyl aldehyde (3.18 g, 15.00 mmol) and the reaction mixture was refluxed for 10 h. The THF was distilled off in vacuo at 50 °C and the obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to obtain **7** (3.41 g, 89% yield).

| | |
|---|---|
|  **7 (383)** | **MP**: 58-60 °C.<br>**IR** (nujol) $\nu_{max}$ 1785, 1720, 1695, 1470 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, *J* = 6 Hz, 3H), 1.25 (bs, 20H), 1.55 (quintet, *J* = 6 Hz, 2H), 2.25 (q, *J* = 6 Hz, 2H), 2.39 (s, 3H), 3.38 (d, *J* = 2 Hz, 2H), 6.95 (tt, *J* = 8 & 2 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 13.7, 20.8, 22.3, 27.9, 29.1, 29.2, 29.3 (7 x $CH_2$), 29.5, 31.8, 125.4, 125.9, 129.2, 129.5, 137.8, 139.1, 168.5, 172.6.<br>**MS** (*m*/*e*) 383, 355, 257, 228, 215, 202, 189, 172, 108, 95, 81.<br>**Anal. Calcd for $C_{25}H_{37}NO_2$**: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.19; H, 9.64; N, 3.60. |

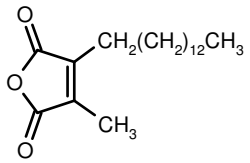
**(*E*)-3-Methyl-4-tetradecylidene-1-*p*-tolylpyrrolidine-2,5-dione (11).** A solution of **7** (613 mg, 1.60 mmol) in THF (20 mL) was added to the slurry of sodium hydride (77 mg, 1.60 mmol) in THF (10 mL) at 0 °C and the reaction mixture was stirred for 30 min. Then, the methyl iodide (227 mg, 1.60 mmol) was added to the reaction mixture at 0 °C and it was stirred for 3 h. The reaction mixture was acidified by 2 N HCl and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine and dried over $Na_2SO_4$. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of residue using petroleum ether and ethyl acetate furnished **11** (412 mg, 65% yield).

| | |
|---|---|
|  <br>**11 (397)** | **MP**: 53-57 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1705, 1655 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, *J* = 8 Hz, 3H), 1.30 (bs, 20H), 1.45-1.60 (m, 2H), 1.53 (d, *J* = 10 Hz, 3H), 2.20-2.35 (m, 2H), 2.40 (s, 3H), 3.30-3.55 (m, 1H), 6.93 (dt, *J* = 10 & 4 Hz, 1H), 7.20 (d, *J* = 13 Hz, 2H), 7.30 (d, *J* = 13 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.1, 16.4, 21.6, 22.7, 28.4-29.7 (10 x $CH_2$), 32.0, 37.5, 126.2 (2-carbons), 129.6, 130.8, 138.2, 140.3, 168.7, 177.2.<br>**MS** (m/e) 397, 242, 229, 216, 203, 133, 118, 107, 95, 92, 81, 67, 55.<br>**Anal. Calcd for $C_{26}H_{39}NO_2$**: C, 78.54; H, 9.89; N, 3.52. Found: C, 78.49; H, 10.02; N, 3.48. |

**3-Methyl-4-tetradecyl-1-*p*-tolyl-1*H*-pyrrole-2,5-dione (12).** To a stirred solution of **11** (318 mg, 0.80 mmol) in THF (10 mL) was added triethylamine (10 mL) and the reaction mixture was refluxed for 48 h and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine 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 furnished **12** (285 mg, 90% yield).

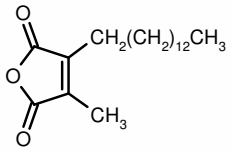
| | |
|---|---|
|  <br>**12 (397)** | **MP**: 74-76 °C.<br>**IR** (nujol) $\nu_{max}$ 1710, 1690, 1650 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, *J* = 7 Hz, 3H), 1.30 (bs, 22H), 1.60 (m, 2H), 2.06 (s, 3H), 2.38 (s, 3H), 2.47 (t, *J* = 7 Hz, 2H), 7.24 (bs, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 9.0, 14.3, 21.3, 22.9, 24.0, 28.4, 29.5-29.9 (9 x $CH_2$), 32.1, 125.9 (2-carbons), 129.8, 137.3, 137.4, 141.5, 171.0, 171.3.<br>**MS** (*m*/*e*) 397, 382, 294, 228, 215, 203, 183, 149, 107, 91, 81, 67, 57.<br>**Anal. Calcd for $C_{26}H_{39}NO_2$**: C, 78.54; H, 9.87; N, 3.52. Found: C, 78.69; H, 9.75; N, 3.62. |

**3-Methyl-4-tetradecylfuran-2,5-dione (Chaetomellic acid A anhydride, 1).** To a stirred solution of **12** (198 mg, 0.50 mmol) in a THF-methanol mixture (1:2, 6 mL) was added 20% aqueous KOH solution (4 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated in vacuo. The obtained residue was dissolved in diethyl ether and acidified with 2 N HCl, extracted with diethyl ether (3 x 20 mL) and the organic layer was washed with water, brine 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 furnished chaetomellic anhydride A (**1**, 139 mg, 91% yield).

| | |
|---|---|
|  **1 (308)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1770, 1680 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, $J$ = 7 Hz, 3H), 1.15-1.45 (bs, 22H), 1.46-1.69 (m, 2H), 2.07 (s, 3H), 2.45 (t, $J$ = 7 Hz, 2H).<br>**$^{13}$C NMR** (CDCl3, 50MHz) $\delta$ 9.6, 14.3, 22.9, 24.6, 27.7, 29.0-31.0 (9 x $CH_2$), 32.1, 140.6, 144.9, 166.0, 166.4.<br>**MS** (*m/e*) 308, 290, 191, 150, 126, 91, 81, 69.<br>**Anal. Calcd for $C_{19}H_{32}O_3$**: C, 73.98; H, 10.46. Found: C, 74.00; H, 10.51. |

# 3A.5 Selected Spectra

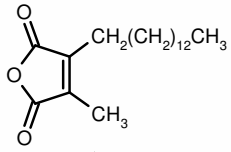
**$CDCl_3$, 200 MHz**



**1**



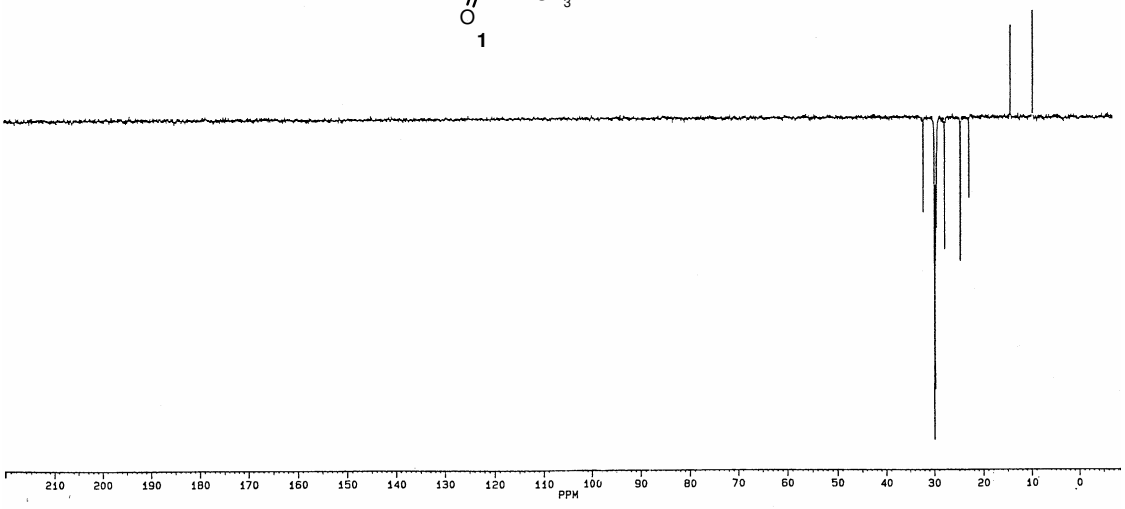
**$CDCl_3$, 50 MHz**



**1**

**$CDCl_3$, 50 MHz**


**1**



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# 3B. Section B

*A General Approach to Bioactive Natural Products 2-Carboxymethyl-3-hexylmaleic Anhydride and 2-(β-Carboxyethyl)-3-hexylmaleic Anhydride*

This section features the following topics:

## 3B Section B: A General Approach to Bioactive Natural Products 2-Carboxymethyl-3-hexylmaleic Anhydride and 2-(*β*-Carboxyethyl)-3-hexylmaleic Anhydride

### 3B.1 Background

A number of natural products containing a substituted maleic anhydride unit have been reported in the literature.[1] They exhibit a range of biological activities, including antibacterial activity,[2] immunomodulating,[3] and plant growth promoting.[4]

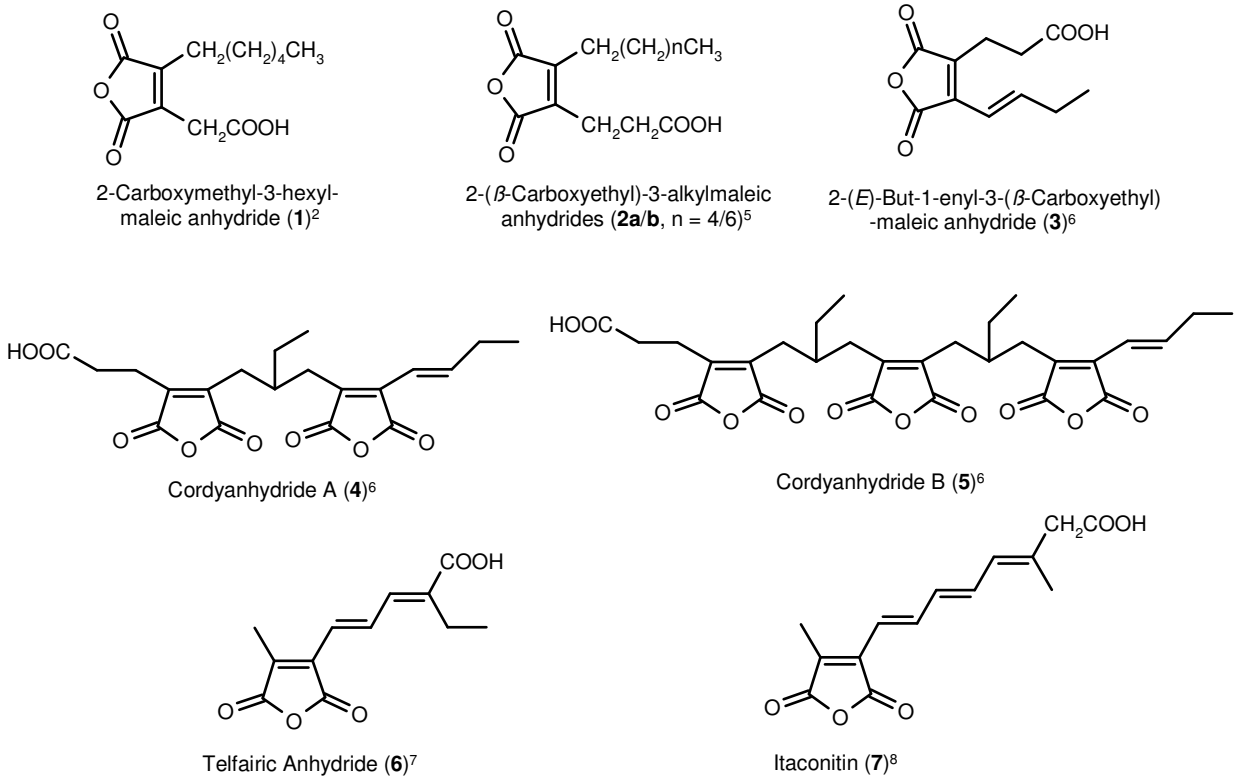



**Figure 1.** Dialkyl substituted maleic anhydrides with a free carboxylic group

Recently isolated bioactive naturally occurring dialkyl substituted maleic anhydrides with free carboxylic group are shown in Figure 1. A new methylmaleic anhydride metabolite has been isolated in 1996 by Edward and his co-workers[7] from the culture medium of the fungus *Xylaria telfairii* Berk and was named as telfairic anhydride (**6**). Itaconitin (**7**) has been isolated from the species *Aspergillus itaconicus*.[8] Till date, no synthesis has been reported for telfairic anhydride (**6**) and itaconitin (**7**). The two rather unique anhydrides namely cordyanhydrides A (**4**) and B (**5**) bearing two and three maleic

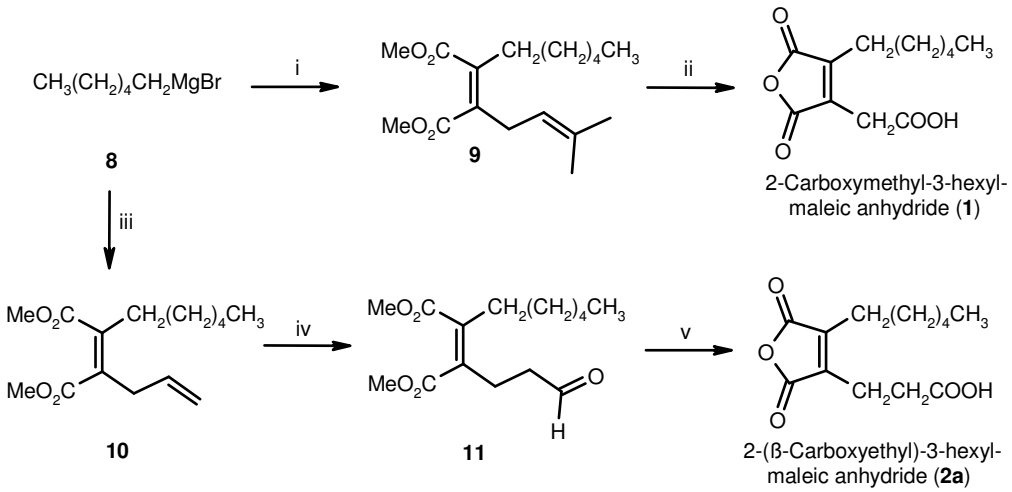
anhydride moieties in the linear acid chain respectively have been isolated from the insect pathogenic fungus *Cordyceps psedomilitaris* BCC 1620 and they belong to the nonadride family.[6] Most of the previously reported nonadrides contain either one or two $C_9$ units [$C_9$ unit is represented as 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. Till date no synthetic route to these natural products has been reported.

The anhydride **1** has been isolated[2] as a novel metabolite of the *Aspergillus* FH-X-213 from an apple. In 1994, Soda *et al* reported the biotransformation of stearic acid with a microbial strain isolated from soil, *Pseudomonas cepacica* A-1419, to produce two new maleic anhydride derivatives **2a** and **2b**.[5] The structural assignment of these molecules has been done on the basis of analytical and spectral data. 2-Carboxymethyl-3-hexylmaleic anhydride (**1**) has been reported to show a weak in vitro activity against grampositive bacteria,[2] whereas the biological role of 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride (**2a**) and 2-(*β*-carboxyethyl)-3-octylmaleic anhydride (**2b**) have not been examined. The synthetic approaches towards these tricarboxylic acid anhydrides have been described below.

**I. Baldwin's Approach**

The first synthetic route to these diverse dialkylsubstituted maleic anhydride analogs was demonstrated by Baldwin *et al*,[9] using a versatile copper mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate. The first step of synthesis of **1** was the conjugate addition of hexylcopper species derived from Grignard reagent **8** (hexylmagnesium bromide and CuBr-$Me_2S$) to dimethyl acetylenedicarboxylate followed by quenching of the copper enolate with prenyl bromide at −78 $^oC$ to furnish dialkylmaleic ester **9**, which on ozonolysis followed by Jones oxidation, basic hydrolysis and acidic work up provided **1** with 33% overall yield (Scheme 1). The second compound **2a** has been also prepared starting from dimethyl acetylenedicarboxylate with 29% overall yield. The first step is the same as described above except that the copper enolate (in situ generated) was quenched with allylbromide. The carbon-carbon double bond in

the formed diester **10** was selectively hydroborated with disiamyl borane. Subsequent oxidation, ester hydrolysis and acidic workup furnished **2a**.

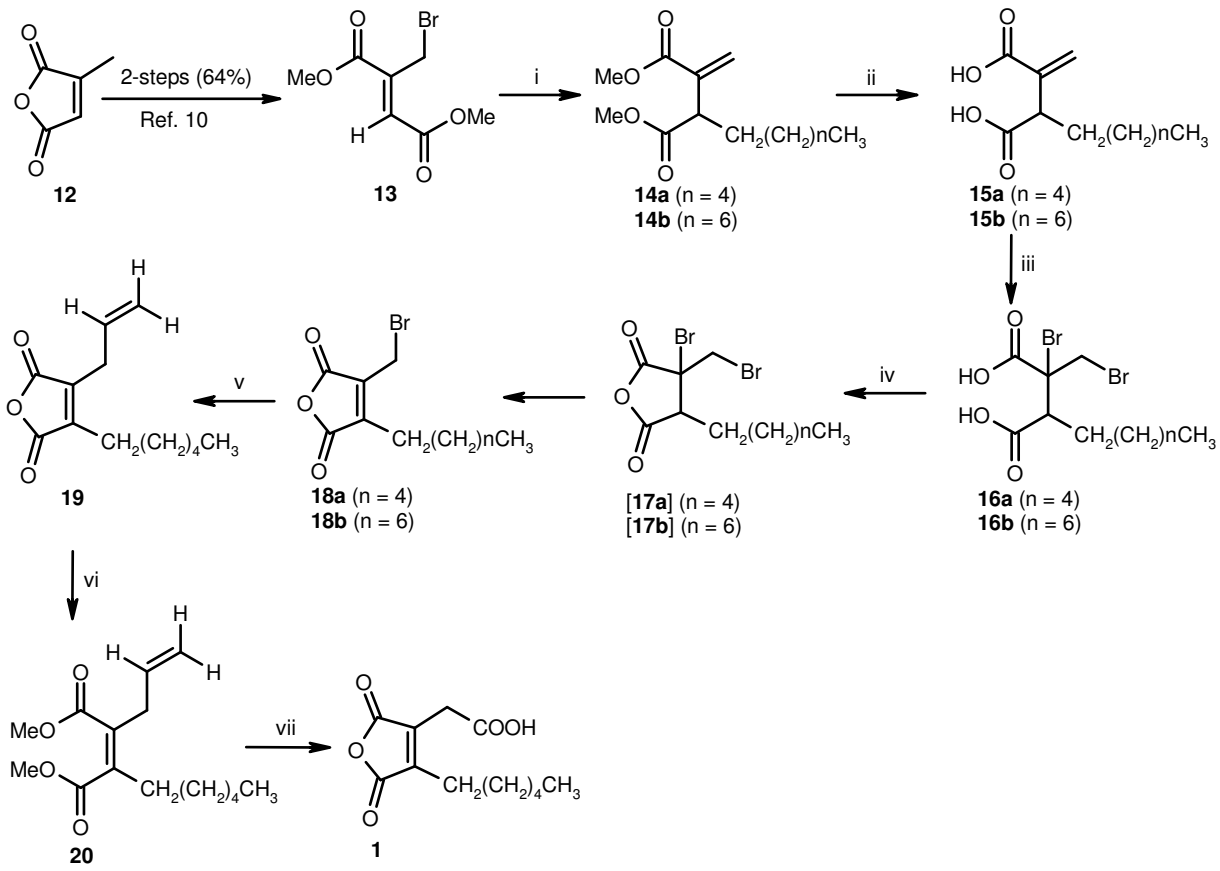



**Scheme 1.** *Reagents*, *conditions and yields*: (i) (a) $CuBr.SMe_2$, THF, −40 °C then dimethyl acetylenedicarboxylate, THF, −78 °C, 1 h, (b) DMPU, THF, −78 °C, (c) $Me_2C{=}CHCH_2Br$, THF, −78 °C to rt, 16 h (73%); (ii) (a) $O_3$, acetone, −78 °C, 3 min then $Na_2Cr_2O_7.2H_2O$, $H_2O$, $Et_2O$, 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. Argade's Approach

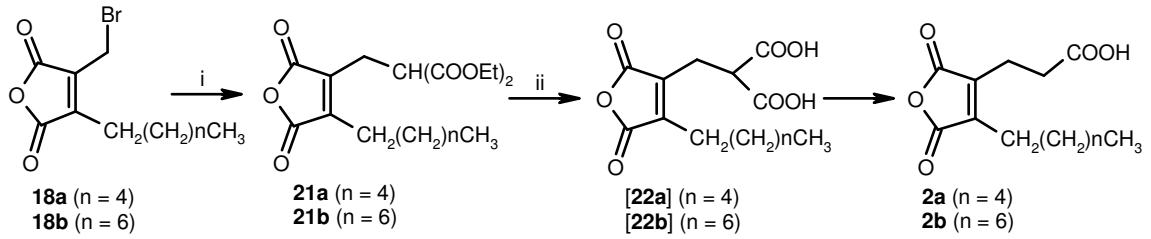
In our laboratory, we have synthesized 2-carboxymethyl-3-hexylmaleic anhydride (**1**) and 2-(*β*-carboxyethyl)-3-alkylmaleic anhydride (**2a/b**) employing the chemoselective $S_N2/S_N2'$ coupling reactions. Dimethyl bromomethylfumarate (**13**) was prepared from citraconic anhydride (**12**) in two steps with 64% overall yield.[10] The freshly prepared hexylmagnesium bromide was chemoselectively coupled with **13** in an $S_N2'$ fashion to yield the diester **14a** in 64% yield. The LiOH induced hydrolysis of **14a** followed by bromination of the diacid **15a** with molecular bromine gave a mixture of all four possible stereoisomers of **16a** in nearly equal proportions with ~100% yield. The diacid **16a** in refluxing acetic anhydride yielded the desired (bromomethyl)hexylmaleic anhydride (**18a**) in quantitative yield and both the dehydrative ring closure of diacid **16a** to succinic

anhydride derivative **17a** and the dehydrobromination took place in one pot. Similarly, the coupling reaction of **13** with octylmagnesium bromide followed by repetition of above sequence of reactions furnished **18b**. Highly chemoselective $S_N2$ displacement of allylic bromoatom in **18a** with vinylmagnesium bromide in the presence of HMPA and a copper catalyst gave the desired anhydride **19** in 55% yield.[11] The anhydride **19** on treatment with diazomethane gave the diester **20** in 95% yield, which on selective ozonolysis followed by in situ oxidation and hydrolysis gave[9] the natural product 2-carboxymethyl-3-hexylmaleic anhydride (**1**) in 42% yield.




**Scheme 2.** *Reagents, conditions and yields*: (i) $CH_3(CH_2)_nCH_2MgBr$ (1.5 equiv., n = 4/6), $Et_2O$, HMPA, –20 ºC, 0.5 h (64-65%); (ii) LiOH (10 equiv.), THF + $H_2O$ (3:1), rt, 18 h (90-92%); (iii) $Br_2$ (1.5 equiv.), $CCl_4$, rt, 6 h (~100%); (iv) $Ac_2O$, reflux, 1.5 h (~100%); (v) $C_2H_3MgBr$ (5 equiv.), CuI (0.1 equiv.), $Et_2O$, HMPA, –5 to 0 ºC (55%); (vi) $CH_2N_2$, $Et_2O$, MeOH, 0 ºC, 3 h (95%); (vii) $O_3$, $(CH_3)_2CO$, –78 ºC, 3 min then $Na_2Cr_2O_7.H_2O$, $H_2SO_4$, $H_2O$, $Et_2O$, 0 ºC, 3 h then 1 M aq. NaOH then 1 M aq. HCl, (42%).

The highly chemoselective coupling of diethyl malonate with **18a/b** in benzene using sodium hydride as base furnished the anhydride derivatives **21a/b** in 72-74% yields (Scheme 3).[12] Acid catalysed hydrolysis of these diesters **21a/b** and in situ decarboxylation of the intermediate *gem*-dicarboxylic acids **22a/b** gave the natural products **2a/b** in 95-96% yields.

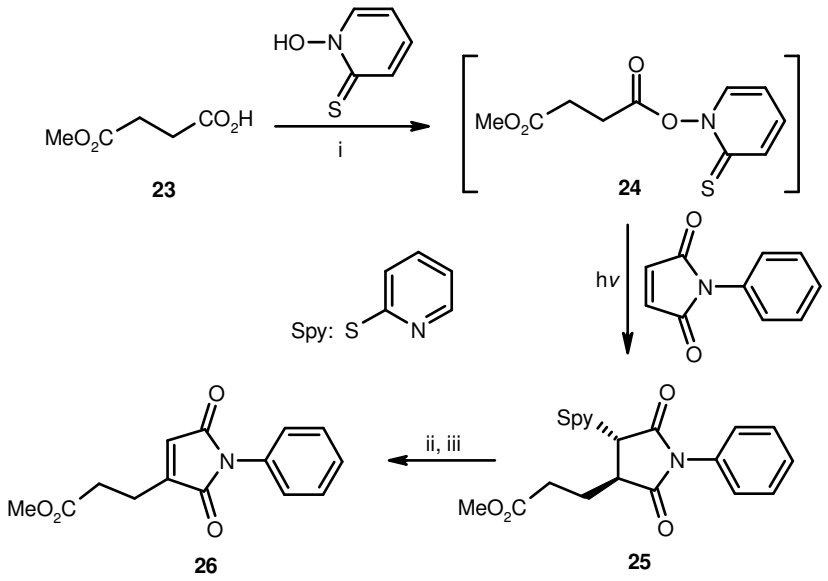



**Scheme 3.** *Reagents, conditions and yields*: (i) (a) diethyl malonate (1.1 equiv.), NaH (1.1 equiv.), $C_6H_6$, rt, 8 h, (b) $H^+$/HCl (72-74%); (ii) AcOH + HCl (1:1), reflux, 12 h (95-96%).

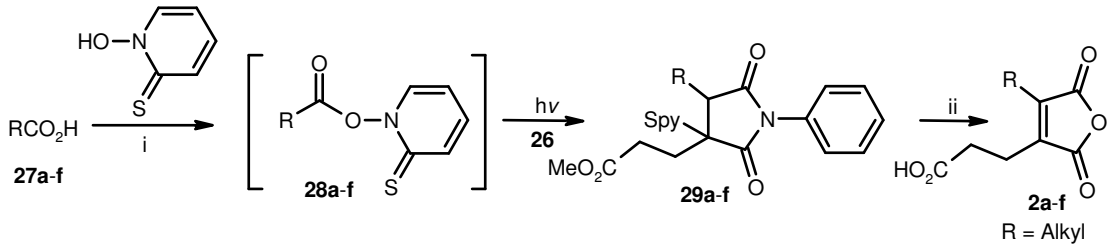
### III. Samadi's Approach

Samadi and co-workers,[13] reported a facile approach to natural and unnatural substituted maleic anhydrides using Barton radical decarboxylation. The strategy for the synthesis **2** is based on a two-step radical addition to phenyl maleimide. In the first step, the readily available succinic acid monomethyl ester **23**, by the DCC coupling method in the presence of 1-hydroxypyridine-2(1*H*)-thione. Irradiation in situ with a tungsten light (500 W) of **24**, in the presence of phenyl maleimide (5 equiv.) gave the intermediate addition product **25** in 82% yield. The oxidation of **25** with *m*-CPBA, followed by the elimination of the resulting sulfoxide produced compound **26** in 90% yield. The *syn* elimination of the 2-pyridylthio group of the intermediate **25** established the *trans* stereochemical relationship of the 2-pyridylthio group and the alkyl substituents, which is the result of a *trans* addition of the radical to phenyl maleimide (Scheme 4).[14]

Having compound **26** in hand, it was subjected as the olefin trap to a second step radical reaction. Thus, acids **27a**-**f** were converted to their thiohydroxamic esters **28a**-**f** as described for **24**, and irradiation in situ with tungsten light (500 W) in the presence of olefin **26** (5 equiv.), produced the intermediate addition products **29a**-**f** as a mixture of isomers,[15] which were further treated with KOH in MeOH-THF to furnish the desired dialkylsubstituted maleic anhydrides **2a**-**f** in 42-48% yield (Scheme 5).




**Scheme 4.** *Reagents, conditions and yields*: (i) DCC, DCM, rt, 2 h, then phenyl maleimide (5 equiv.) hν, 15 $^{o}$C, 30 min. (82%); (ii) *m*-CPBA, DCM, 0 $^{o}$C, 1 h; (iii) toluene, 110 $^{o}$C, 1 h (90% from **25**).

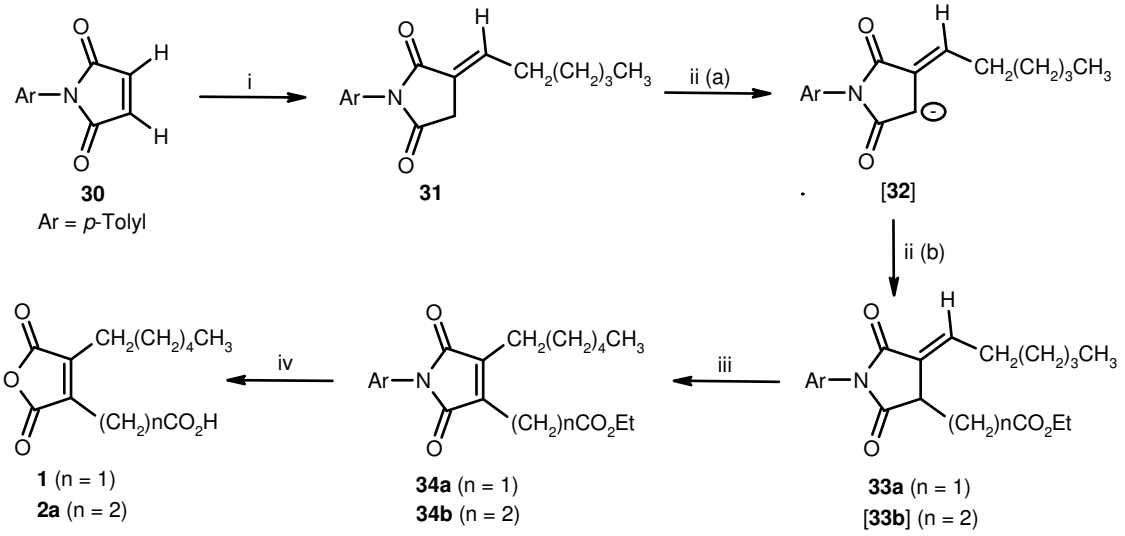



**Scheme 5.** *Reagents, conditions and yields*: (i) DCC, DCM, rt, 2 h, then 5 equiv. of **26**, hν, 15 $^{o}$C, 30 min.; (ii) KOH, THF-MeOH, reflux, 3h.

### 3B.2 Present Work: Results and Discussion

We planned the synthesis of these bioactive natural products by employing Wittig reaction *N*-*p*-tolylmaleimide (**30**) and triphenylphosphine adduct with caproaldehyde (hexanal) to furnish the (*E*)-hexylidenesuccinimide **31** in 89% yield. The (*E*)-hexylidenesuccinimide **31** was treated with an equivalent amount of sodium hydride in THF at 0 °C and to it was added activated alkyl halides at 0 °C, which exclusively furnished corresponding desired ring mono-alkylated product **33a** in 70% yield. It was difficult to obtain pure product **33b** as both the starting material **31** and the product **33b**

were having the same $R_f$ value. With the introduction of alkyl substituents on **31** to form **33a** and **33b**, the trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond isomerization became feasible on treatment of **33a** and **33b** with triethylamine to obtain **34a** (92% yield) and **34b** (70% yield), respectively. The dialkyl substituted maleimide **34a** and **34b** on base catalyzed hydrolysis followed by acidification, furnished the bioactive natural products 2-carboxymethyl-3-hexylmaleic anhydride (**1**, 88% yield) and 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride (**2a**, 85% yield), respectively (Scheme 6).[16]




**Scheme 6**. *Reagents*, *conditions and yields*: (i) $Ph_3P$ (1.00 equiv.), $CH_3(CH_2)_4CHO$ (1.50 equiv.), THF, reflux, 10 h (91%); (ii) (a) NaH (1.00 equiv.), THF, 0 °C, 0.5 h, (b) $EtO_2C(CH_2)_nBr$ (1.00 equiv.), 0 °C – rt, 3 h (70%); (iii) $Et_3N$ + THF (1:1), reflux, 48 h (70-92%); (iv) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (85-88%).

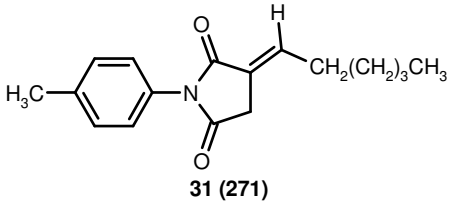
### 3B.3 Summary

In summary, we have described a general approach to bioactive natural products 2-carboxymethyl-3-hexylmaleic anhydride and 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride. In the present approach, the key reaction is the generation of carbanion on hexylidenesuccinimide core. We feel that our present approach can be useful to design diverse dialkyl substituted maleic anhydrides with free carboxylic group for the structure-activity relationship studies.

### 3B.4 Experimental

Commercially available maleic anhydride, *p*-toluidine, triphenylphosphine, hexanaldehyde, sodium hydride and alkyl halides were used.

**(*E*)-3-Hexylidene-1-*p*-tolylpyrrolidene-2,5-dione (31).** A solution of *N*-*p*-tolylmaleimide (**30**, 1.87 g, 10.00 mmol) and triphenylphosphine (2.62 g, 10.00 mmol) in THF (100 mL) was stirred at room temperature for 30 min. To the reaction mixture was added the hexanaldehyde (1.62 g, 15.00 mmol) and the reaction mixture was refluxed for 10 h. The THF was distilled off in vacuo at 50 °C and the residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to obtain **31** (2.47 g, 91% yield).



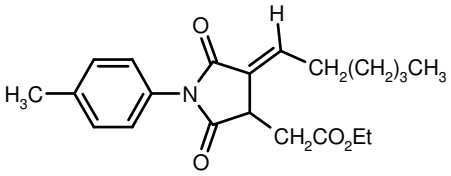

**31 (271)**

**MP**: 112-113 °C.
**IR** (nujol) $\nu_{max}$ 1771, 1749, 1712, 1691, 1676 $cm^{-1}$.
**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, $J$ = 6 Hz, 3H), 1.22-1.45 (m, 4H), 1.53 (quintet, $J$ = 6 Hz, 2H), 2.23 (q, $J$ = 6 Hz, 2H), 2.37 (s, 3H), 3.37 (d, $J$ = 2 Hz, 2H), 6.93 (tt, $J$ = 8 & 2 Hz, 1H), 7.18 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H).
**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.7, 20.9, 22.2, 27.5, 29.6, 31.2, 31.8, 125.1, 126.0, 129.2, 129.4, 138.1, 139.6, 168.7, 173.0.
**MS** (*m*/*e*) 271, 242, 228, 214, 200, 189, 172, 133, 107, 95, 81, 67, 53.
**Anal. Calcd for $C_{17}H_{21}NO_2$**: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.11; H, 7.92; N, 5.07.

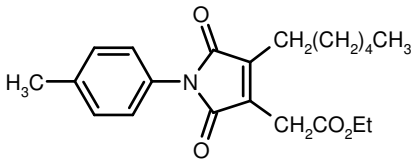
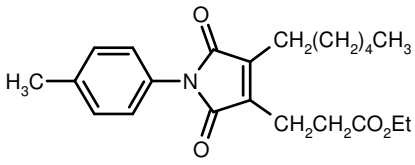
**General procedure for synthesis of 33a/b.** A solution of **31** (1.60 mmol,) in THF (20 mL) was added to the slurry of sodium hydride (1.60 mmol) in THF (10 mL) at 0 °C and the reaction mixture was stirred for 30 min. Then, the corresponding alkyl halide (1.60 mmol) was added to the reaction mixture at 0 °C and it was stirred for 3 h. The reaction mixture was acidified by 2 N HCl and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine and dried over $Na_2SO_4$. Concentration of the organic layer in vacuo followed by silica gel

column chromatographic purification of residue using petroleum ether and ethyl acetate furnished **33a** (79% yield) and **33b**.

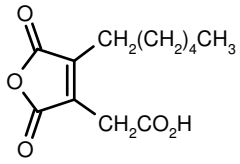
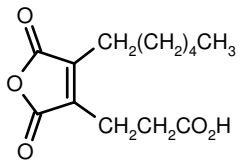
**Note:** We were unable to purify **33b** using the silica gel column chromatography as both starting material **31** and product **33b** were having the same $R_f$ value, however exocyclic to endocyclic carbon-carbon double bond isomerization followed by purification of **34b** by using silica gel column chromatography was possible.

| | |
|---|---|
|  **33a (357)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1771, 1732, 1713, 1672 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.92 (t, $J$ = 8 Hz, 3H), 1.21 (t, $J$ = 8 Hz, 3H), 1.27-1.43 (m, 4H), 1.53 (quintet, $J$ = 6 Hz, 2H), 2.29 (q, $J$ = 6 Hz, 2H), 2.39 (s, 3H), 3.01 (dd, $J$ = 17 & 6 Hz, 1H), 3.26 (dd, $J$ = 17 & 4 Hz, 1H), 3.57-3.68 (m, 1H), 4.12 (q, $J$ = 8 Hz, 2H), 6.94 (dt, $J$ = 7 & 2 Hz, 1H), 7.20-7.33 (m, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.9, 14.1, 21.2, 22.4, 28.2, 29.3, 31.5, 34.5, 38.8, 61.2, 126.3, 128.1, 129.5, 129.7, 138.5, 140.6, 169.2, 170.0, 176.1.<br>**Anal. Calcd for $C_{21}H_{27}NO_4$**: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.44; H, 7.80; N, 3.99. |

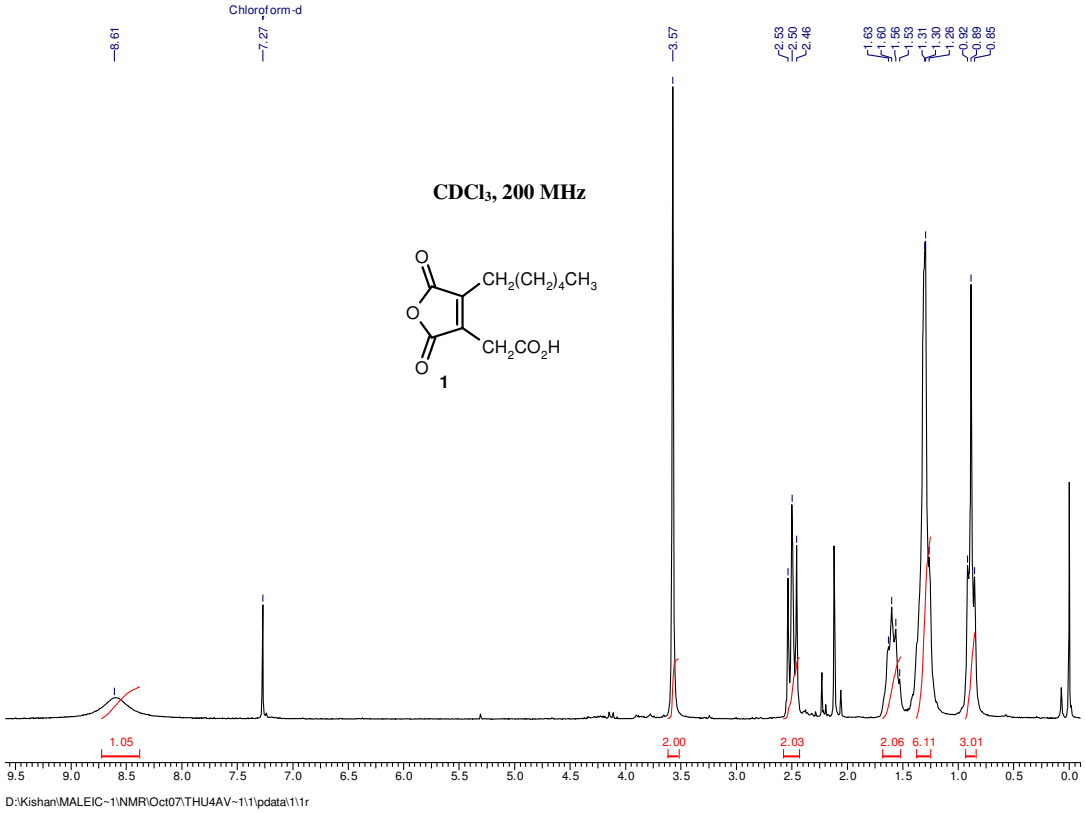
**General procedure for synthesis of 34a/b.** To a stirred solution of **33a/b** (0.80 mmol) in THF (10 mL) was added triethylamine (10 mL) and the reaction mixture was refluxed for 48 h and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine 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 furnished **34a/b** in 92/70% yields respectively.

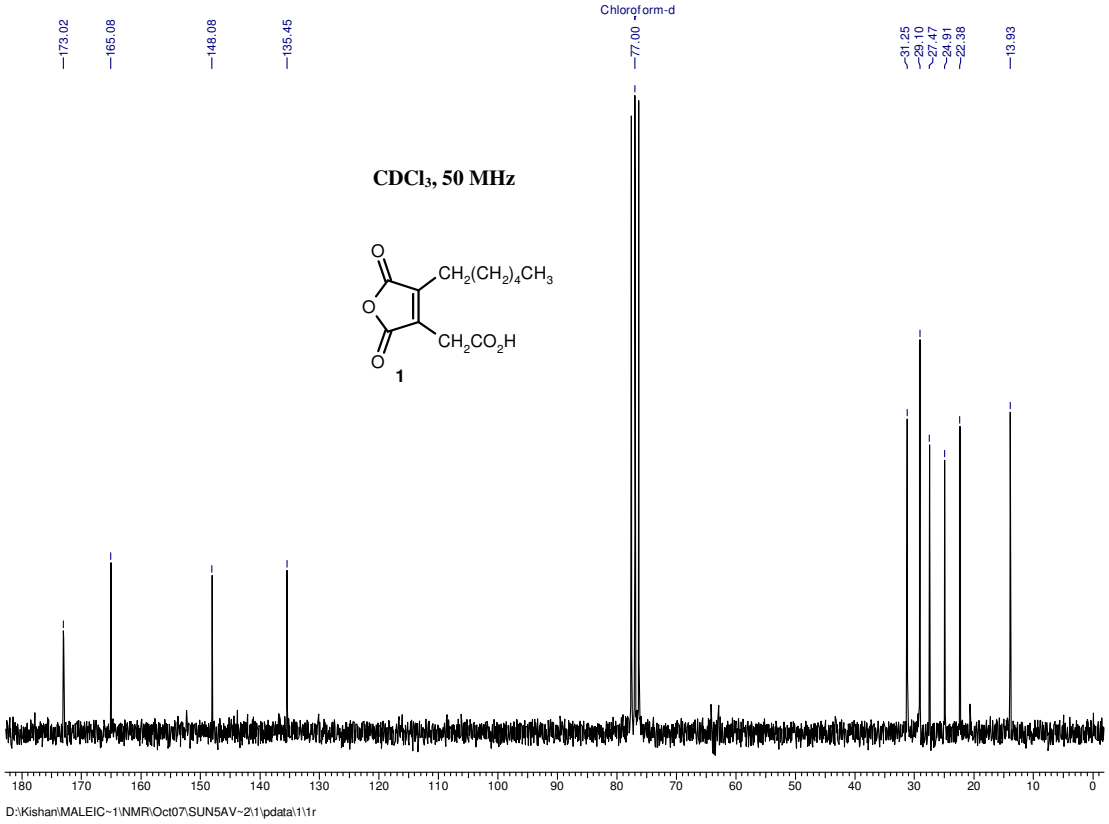
| | |
|---|---|
|  <br>**34a (357)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1772, 1740, 1713, 1616 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, $J$ = 8 Hz, 3H), 1.29 (t, $J$ = 6 Hz, 3H), 1.20-1.45 (m, 6H), 1.61 (quintet, $J$ = 8 Hz, 2H), 2.38 (s, 3H), 2.50 (t, $J$ = 8 Hz, 2H), 3.52, (s, 2H), 4.21 (q, $J$ = 8 Hz, 2H), 7.15-7.30 (m, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.9, 14.0, 21.0, 22.4, 24.2, 28.0, 29.0, 29.2, 31.3, 61.5, 125.6, 129.0, 129.5, 133.0, 137.4, 144.1, 168.5, 169.9, 170.2.<br>**Anal. Calcd for $C_{21}H_{27}NO_4$**: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.63; H, 7.72; N, 4.01. |
|  <br>**34b (371)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1740, 1707 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 0.90 (t, $J$ = 8 Hz, 3H), 1.20-1.45 (m, 9H), 1.58 (quintet, $J$ = 8 Hz, 2H), 2.38 (s, 3H), 2.51 (t, $J$ = 8 Hz, 2H), 2.67 (t, $J$ = 8 Hz, 2H), 2.80 (t, $J$ = 8 Hz, 2H), 4.16 (q, $J$ = 8 Hz, 2H), 7.22 (d, $J$ = 8 Hz, 2H), 7.25 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 14.0, 14.2, 19.5, 21.1, 22.5, 23.9, 28.6, 29.4, 31.5, 32.3, 60.8, 125.7, 129.1, 129.6, 137.4, 138.6, 142.6, 170.5, 170.6, 172.1.<br>**Anal. Calcd for $C_{22}H_{29}NO_4$**: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.29; H, 7.64; N, 3.82. |

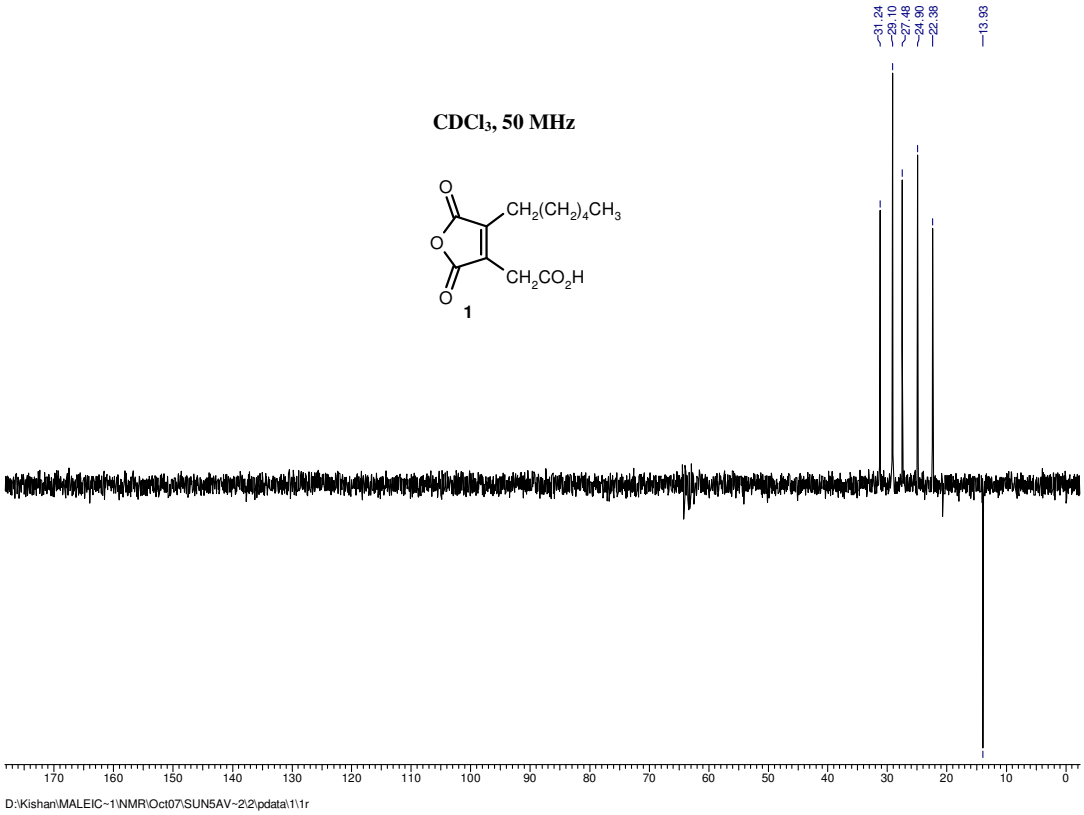
**General procedure for synthesis of 1/2a.** To a stirred solution of **34a/b** (0.50 mmol) in a THF-methanol mixture (1:2, 6 mL) was added 20% aqueous KOH solution (4 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated and the residue was acidified with 2 N HCl, extracted with diethyl ether (3 x 20 mL) and the organic layer was washed with water, brine 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 furnished **1/2a** in 85/97% yields respectively.

| | |
|---|---|
|  <br>**1 (240)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1820, 1771, 1718, 1216, 925, 670 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.89 (t, $J$ = 8 Hz, 3H), 1.15-1.45 (m, 6H), 1.60 (quintet, $J$ = 8 Hz, 2H), 2.50 (t, $J$ = 8 Hz, 2H), 3.57 (s, 2H), 8.60 (bs, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.9, 22.4, 24.9, 27.5, 29.1 (2-carbons), 31.3, 135.5, 148.1, 165.1(2-carbons), 173.0.<br>**Anal. Calcd for $C_{12}H_{16}O_5$**: C, 59.99; H, 6.71. Found: C, 60.12; H, 6.65. |
|  <br>**2a (254)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 2700-2500, 1840, 1765, 1713, 1437, 1273 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, $J$ = 6 Hz, 3H), 1.28 (m, 6H), 1.57 (quintet, $J$ = 6 Hz, 2H), 2.49 (t, $J$ = 8 Hz, 2H), 2.76 (s, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.9, 19.6, 22.4, 24.6, 27.8, 29.2, 31.0, 31.3, 141.5, 146.3, 165.4, 165.6, 177.4.<br>**MS** (*m*/*e*) 254, 236, 208, 162, 148, 91, 60.<br>**Anal. Calcd for $C_{13}H_{18}O_5$**: C, 61.40; H, 7.13. Found: C, 61.33; H, 7.17. |

# 3B.5 Selected Spectra


Chloroform-d
8.61
7.27
3.57
2.53
2.50
2.46
1.63
1.60
1.56
1.53
1.31
1.30
1.26
0.92
0.89
0.85
CDCl3, 200 MHz
CH2(CH2)4CH3
CH2CO2H
1
1.05
2.00
2.03
2.06
6.11
3.01
D:\Kishan\MALEIC~1\NMR\Oct07\THU4AV~1\1\pdata\1\1r


Chloroform-d
173.02
165.08
148.08
135.45
77.00
31.25
29.10
27.47
24.91
22.38
13.93
CDCl3, 50 MHz
CH2(CH2)4CH3
CH2CO2H
1
D:\Kishan\MALEIC~1\NMR\Oct07\SUN5AV~2\1\pdata\1\1r


31.24
29.10
27.48
24.90
22.38
13.93
CDCl3, 50 MHz
O
O
O
CH2(CH2)4CH3
CH2CO2H
1
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
D:\Kishan\MALEIC~1\NMR\Oct07\SUN5AV~2\2\pdata\1\1r

**3B.6 References**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(6) (a) Isaka, M.; Tanticharoen, M.; Thebtaranonth, Y. *Tetrahedron Lett.* **2000**, *41*, 1657. (b) Yamanishi, R.; Okada, K.; Tamugi, N.; Iwashima, M.; Iguchi, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2087. (c) Aldridge, D. C.; Carman, R. M.; Moore, R. B. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2134.

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(12) (a) Kar, A.; Argade, N. P. *Tetrahedron Lett*. **2002**, *43*, 6563. (b) Kar, A.; Argade, N. P. *Tetrahedron* **2003**, *59*, 2991.

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# 3C. Section C

## *Formal Synthesis of Bioactive Natural Products Maculalactones A-C and Nostoclide I*

This section features the following topics:

## 3C Section C: Formal Synthesis of Bioactive Natural Products Maculalactones A-C and Nostoclide I

### 3C.1 Background

Maculalactones A-C (**1-3**) (Figure 1) were isolated from cyanobacterium *Kyrtuthrix maculans* from Hong Kong island and they possess marine anti-fouling activity.[1] The structures of maculalactones A-C (**1**-**3**) were determined by analytical and spectral data[1] and the natural (+)-maculalactone A (**3**) was assigned *S*-configuration.[2] Clardy and co-workers isolated nostoclide I (**4**) and nostoclide II (**5**) from the lichen *Peltigera canina* and they possess cytotoxic activity.[3] Structures of Nostoclide I (**4**) and II (**5**) were determined by spectroscopic data and X-ray diffraction study.[3] These butyrolactones were previously synthesized via Stobbe condensation,[2] conversion of furan to the required lactone,[4a] Stille coupling reaction,[4b] and $S_N2'$ Grignard coupling reactions[5] which are discussed briefly below.

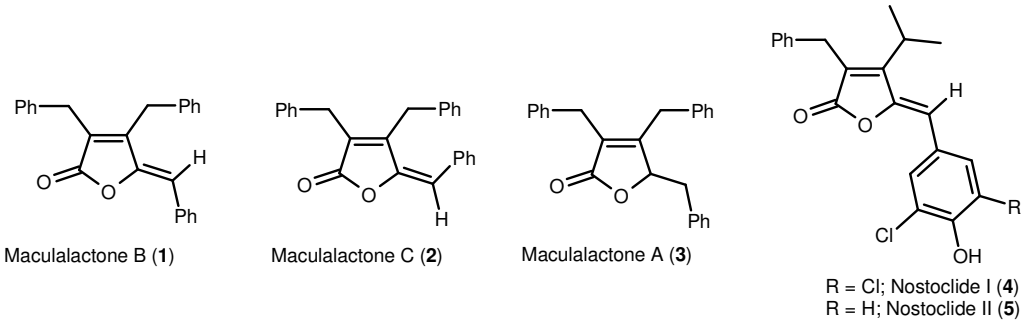



**Figure 1.** Maculalactones A-C and Nostoclide I & II

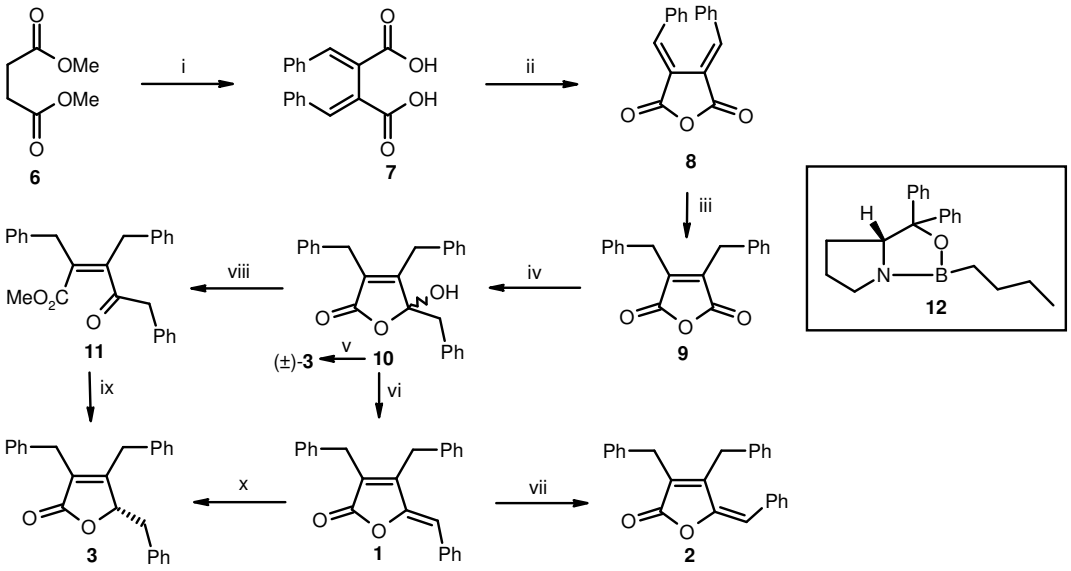
#### 3C.1.1 Earlier Approaches Towards Maculalactones A-C

Prior to our work two syntheses of Maculalactones A-C (**1**-**3**) were reported in the literature including one from our group.[2,5]

**[A] Brown's Approach**

Brown *et al*, reported the first general synthetic route to these butyrolactones and also completed an asymmetric synthesis of (+)-maculalactone A (Scheme 1).[2] They completed the synthesis of (±)-maculalactone A (**3**), starting from dibenzylidinesuccinic acid (**7**), which was obtained by Stobbe condensation of dimethylsuccinate (**6**) with benzaldehyde, via acetyl chloride mediated ring closing to anhydride **8**, 1,4-hydrogenation of anhydride

to dibenzylmaleic anhydride (**9**), addition of benzylmagnesium bromide followed by reduction of the lactol **10**. The overall yield of maculalactone A (**3**) in four steps was 36%. Dehydration of **10** in the presence of sulfuric acid gave maculalactone B (**1**, 82%). Maculalactone B (**1**) was converted to maculalactone C (**2**) by irradiation with UV light in 79% yield. They also assigned the (+) and (−)-enantiomers of maculalactone A (**3**) to be the *S*- and *R*-configurations respectively on the basis of the chiral selectivity expected for catecholborane reduction of an unsymmetrical ketone **11** in the presence of Corey's oxaborolidine catalyst **12**.[6]

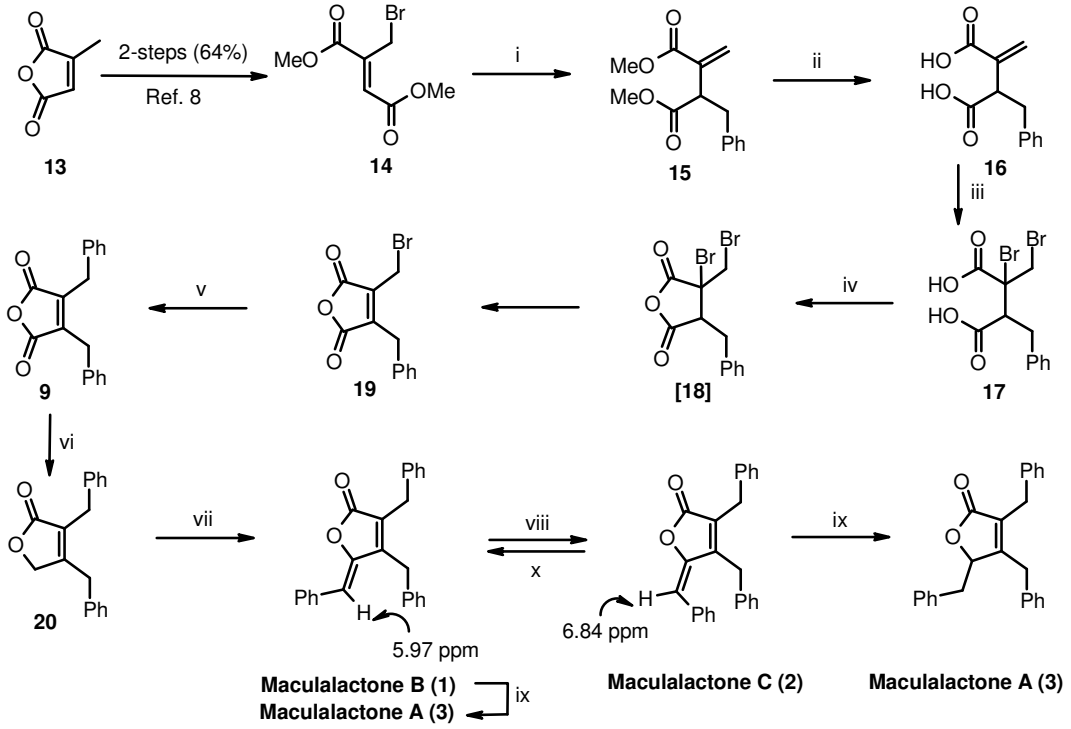



**Scheme 1.** *Reagents, conditions and yields*: (i) Na, benzaldehyde, $Et_2O$, 0 °C to rt, 12 h (19%); (ii) Acetyl chloride, reflux, 2 h (84%); (iii) Pd/C, EtOAc, $H_2$, rt, 18 h (74%); (iv) BnMgBr, $Et_2O$, 0 °C, 30 min (59%); (v) $NaBH_4$, THF/$H_2O$ (24:1), 0 °C, 2 h (99%); (vi) $H_2SO_4$ absorbed on silica gel, toluene, reflux, 5 h (82%); (vii) UV light, $C_6H_6$, rt, 1 h (79%); (viii) $CH_2N_2$, $Et_2O$, rt, 4 h (92%); (ix) (*R*)-**12**, catecholborane, toluene, −78 °C for 6 h then −18 °C for 15 h (88%, *S*-isomer, 81.4% *ee*); (x) Pd/C, EtOAc, $H_2$, rt, 18 h (79%).

**[B] Argade's Approach**

Recently, our group reported the second synthesis of maculalactones A-C using chemoselective $S_N2'$ Grignard coupling reactions. The $S_N2'$ coupling reaction of benzylmagnesium bromide with **14** furnished the diester **15** in 70% yield.[7] Hydrolysis of diester **15** followed by acidification gave the desired dicarboxylic acid **16** in 92% yield. Bromination of **16** gave a mixture of isomers of dibromodicarboxylic acid **17** in ~100%

yield. The dibromodicarboxylic acid **17** in situ dehydration followed by dehydrobromination reaction gave (bromomethyl)benzylmaleic anhydride (**19**) in ~100% yield. The allylic substitution of **19** with phenylmagnesium bromide furnished dibenzylmaleic anhydride (**9**) in 45% yield. Sodium borohydride reduction of dibenzylmaleic anhydride (**9**) gave the desired lactone **20** in 91% yield. The Knoevenagel condensation of lactone **20** furnished maculalactone B (**1**) in 77% yield (Scheme 2).[5]




**Scheme 2.** *Reagents, conditions and yields*: (i) $PhCH_2MgBr$ (1.5 equiv.), THF, HMPA, –20 ºC, 0.5 h (70%); (ii) (a) LiOH (10 equiv.), THF + $H_2O$ (3:1), rt, 18 h, (b) $H^+$/HCl (92%); (iii) $Br_2$ (1.5 equiv.), $CCl_4$, rt, 6 h (~100%); (iv) $Ac_2O$, reflux, 1.5 h (~100%); (v) $C_6H_5MgBr$ (5 equiv.), CuI (0.1 equiv.), $Et_2O$, HMPA, −5 to 0 ºC (45%); (vi) $NaBH_4$ (2.5 equiv.), THF, 0 ºC, 2 h (91%); (vii) Piperidine (0.7 equiv.), PhCHO (1 equiv.), MeOH, rt, 16 h (77%); (viii) $CHCl_3$, rt, 8 days (50%); (ix) $H_2$, Pd/C, EtOAc, 12 h (75%); (x) Δ, 200 ºC, 3 h (100%).

The maculalactone B (**1**) on hydrogenation gave (±)-maculalactone A (**3**) in 75% yield. Maculalactone B (**1**) is thermodynamically more stable than maculalactone C (**2**), but due to the presence of associated $\pi$-stacking interaction between the two phenyl groups[1] it slowly transforms to maculalactone C (**2**). Maculalactone B (**1**) in chloroform at room temperature underwent nearly 50% conversion to maculalactone C (**2**) in 8-days

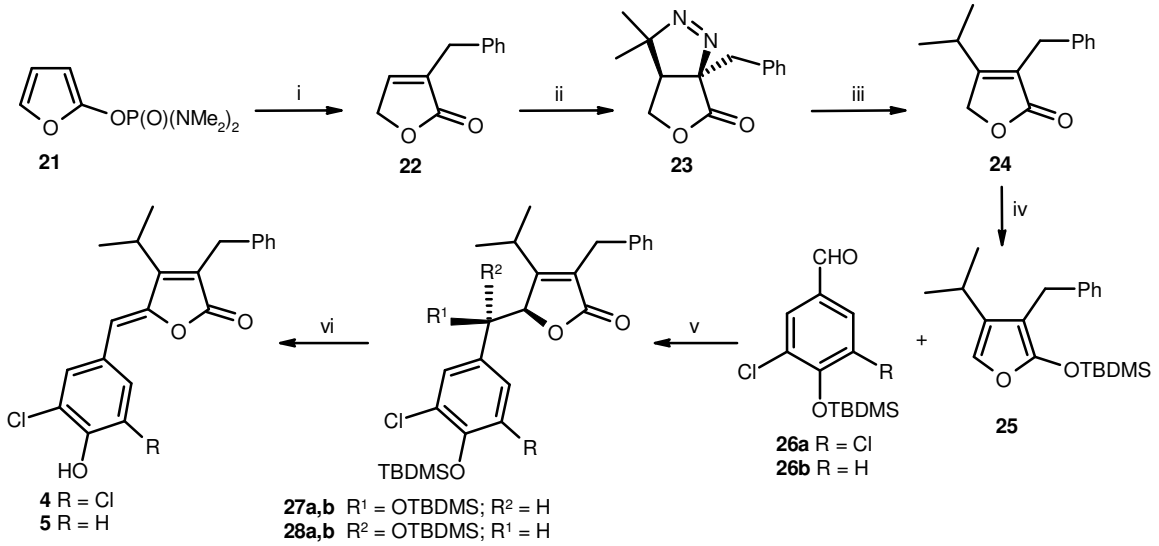
span (by $^1$H NMR). They isolated and heated the above neat 50:50 mixture of maculalactones B and C at 200 ºC for and obtained exclusively maculalactone B (**1**).

### 3C.1.2 Earlier Approaches Towards Nostoclide I and II

Prior to our work only one total synthesis and two formal synthesis of nostoclide I and II (**4** & **5**) were reported in the literature.[4,5]

**[A] Boukouvalas's Approach**

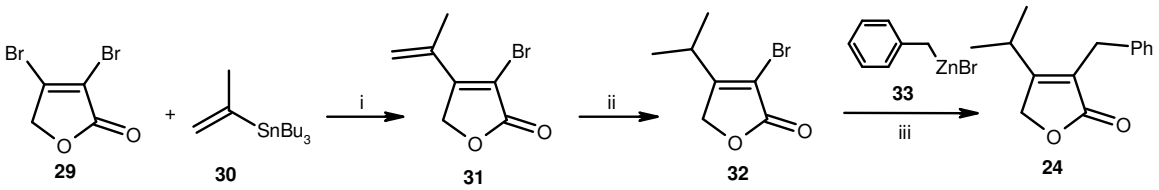
Boukouvalas *et al*, reported the first synthesis of nostoclide I and II using 2-furanolates as the key intermediate in 6-steps with 29-32% overall yield (Scheme 3).[4a] They prepared furan **25** starting from 2-furyl-*N*,*N*,*N*′,*N*′-tetramethyldiamidophosphate (**21**), via directed *ortho*-alkylation, introduction of an isopropyl group by 1,3-dipolar cycloaddition of formed butyrolactone **22** with 2-diazopropane and thermolysis, followed by the silylation of the resulting disubstituted butyrolactone **24**. Aldol condensation of **25** with the required aldehydes (**26a** and **26b**) and subsequent DBU induced *cis*-selective E1cb elimination of the resulting mixture of diastereomers **27a**,**b** and **28a**,**b** followed by acidification furnished **4** and **5**.




**Scheme 3.** *Reagents, conditions and yields*: (i) *n*-BuLi, THF, −78 °C, $PhCH_2Br$, $HCO_2H$ (72%); (ii) $(Me)_2CN_2$, $Et_2O$, 0 °C, 24 h; (iii) $C_6H_6$, reflux, 1 h (56%, 2-steps); (iv) TBDMSOTf, $Et_3N$, $CH_2Cl_2$, 0-25 °C, 24 h (88%); (v) TBDMSOTf, $CH_2Cl_2$, −78 °C, 2 h (**27a**/**28a** = 93%, **27b**/**28b** = 91%); (vi) (a) DBU, $CHCl_3$, reflux, 18-24 h, (b) Aq. 3 M HCl, 25 °C (**4** = 96%, **5** = 90%).

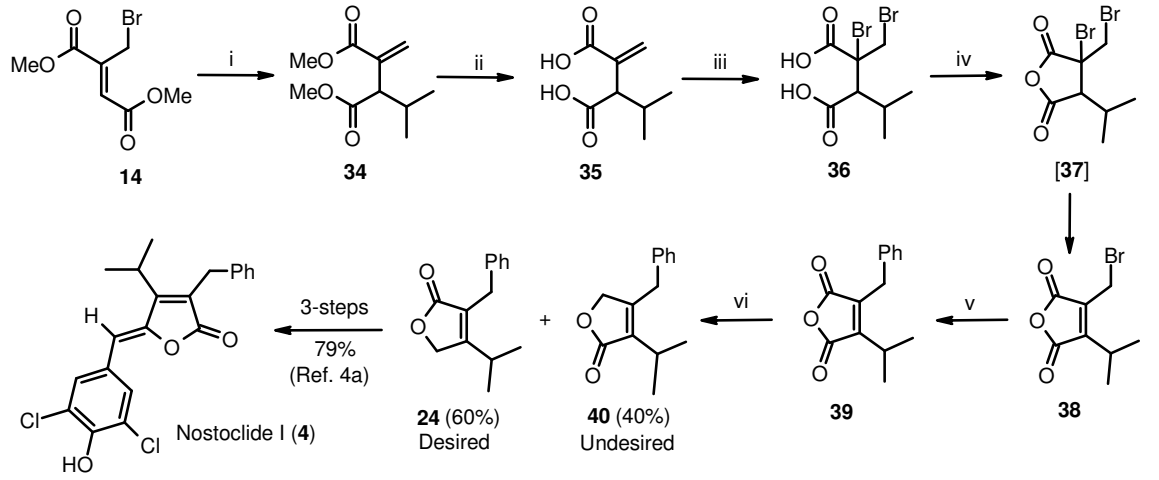
**[B] Bellina's Approach**

Recently Bellina *et al*, reported the synthesis 3-benzyl-4-isopropyl-2(5*H*)-furanone (**24**), which is a precursor of nostoclides, starting from 3,4-dibromo-2(5*H*)-furanone (**29**) in three steps with 27% overall yield (Scheme 4).[4b] They synthesized butyrolactone **24** by Stille coupling of one equivalent of isopropenyltributyl tin with dibromobutenolide **29**, which on Rh (I) catalyzed regioselective hydrogenation followed by Pd-catalyzed cross coupling reaction with benzylzinc bromide gave **24**.




**Scheme 4.** *Reagents, conditions and yields*: (i) $PdCl_2(PhCN)_2$, $Ph_3As$, NMP, rt, 5 days (78%); (ii) $RhCl(Ph_3P)_3$, $H_2$, benzene, rt (95%); (iii) **33**, DMF/THF (1:1), $PdCl_2[(o\text{-Tolyl})_3P]_2$, 60 °C, 5 h (36%).

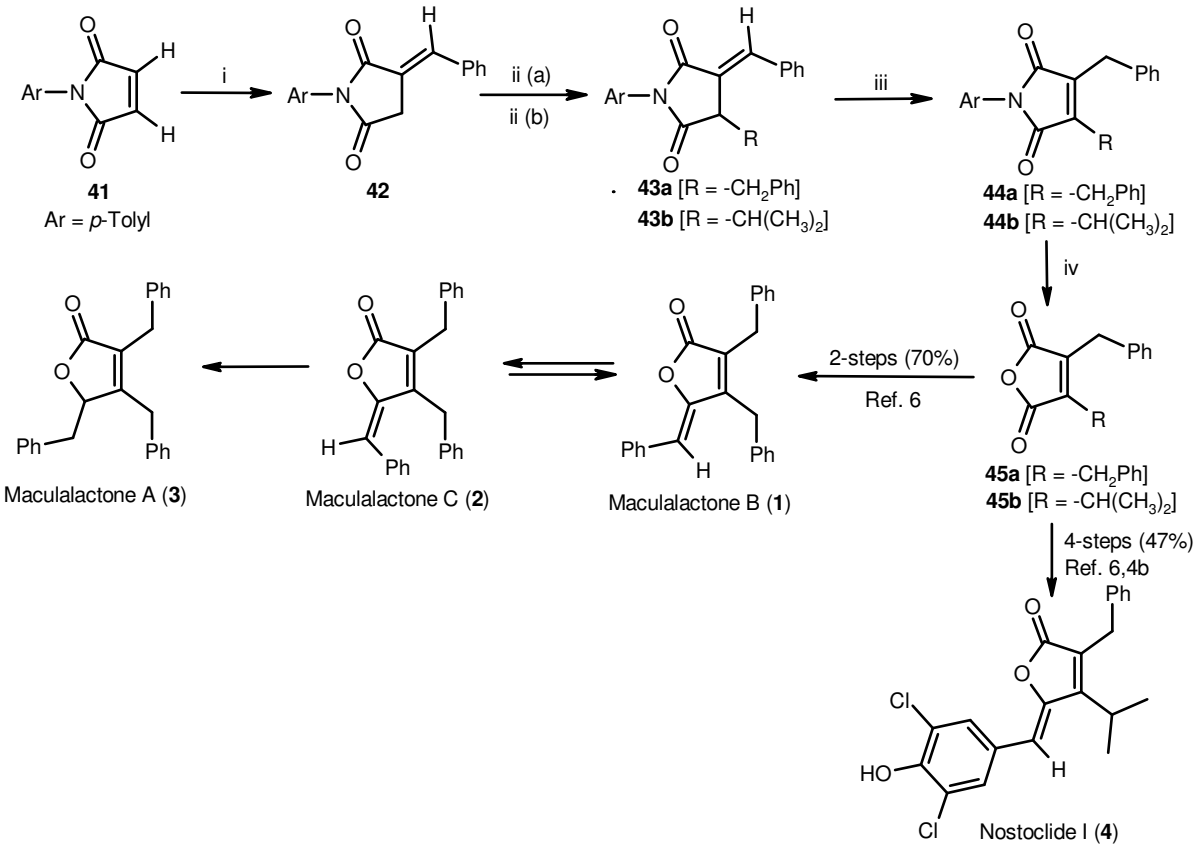
**[C] Argade's Approach**




**Scheme 5.** *Reagents, conditions and yields*: (i) $C_3H_7MgBr$ (1.5 equiv.), THF, HMPA, –20 ºC, 0.5 h (79%); (ii) (a) LiOH (10 equiv.), THF + $H_2O$ (3:1), rt, 18 h, (b) $H^+$/HCl (91%); (iii) $Br_2$ (1.5 equiv.), $CCl_4$, rt, 6 h (~100%); (iv) $Ac_2O$, reflux, 1.5 h (~100%); (v) $C_6H_5MgBr$ (5 equiv.), CuI (0.1 equiv.), $Et_2O$, HMPA, –5 to 0 ºC (43%); (vi) $NaBH_4$ (2.5 equiv.), THF, 0 ºC, 4 h (70%).

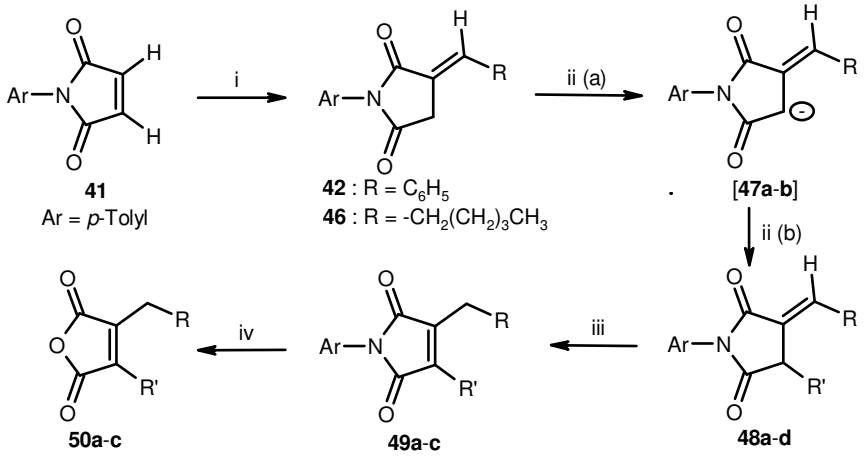
Recently, our group reported formal synthesis of nostoclide I starting from diester **14**. They prepared the benzylisopropylmaleic anhydride (**39**) in 5-steps with 31% overall yield via $S_N2'$ Grignard coupling, hydrolysis, bromination, in situ dehydration followed by dehydrobromination and allylic substitution pathway (Scheme 5).[5] The sodium borohydride induced regioselective reduction[8] at the relatively more hindered carbonyl group of unsymmetrical maleic anhydride **39** in THF at 0 ºC gave the silica-gel column separable mixture of desired and undesired lactones **24** and **40** with 70% yield in 3:2 ratio respectively. The three-step conversion of lactone **24** to nostoclide I (**4**) is known in the literature.[4a]

### 3C.2 Present Work: Results and Discussion




**Scheme 6**. *Reagents*, *conditions and yields*: (i) $Ph_3P$ (1.00 equiv.), $C_6H_5CHO$ (1.50 equiv.), THF, reflux, 10 h (93%); (ii) (a) NaH (1.00 equiv.), THF, 0 °C, 0.5 h, (b) RX (1.00 equiv.), 0 °C – rt, 3 h (87-92%); (iii) $Et_3N$ + THF (1:1), reflux, 48 h (94-98%); (iv) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (97-94%).

The Wittig reaction of *N*-*p*-tolylmaleimide (**41**) and triphenylphosphine adduct with benzaldehyde gave (*E*)-benzylidenesuccinimide **42** in 93% yield. The (*E*)-benzylidenesuccinimide **42** on treatment with an equivalent amount of sodium hydride in THF at 0 $^{o}$C and added benzyl bromide/isopropyl iodide at 0 $^{o}$C, exclusively furnished the desired ring mono-benzylated/alkylated products **43a** (87% yield) and **43b** (92% yield), respectively. Trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond isomerization of **43a** and **43b** was carried out by using triethylamine to obtain dibenzyl substituted maleimide **44a** (94% yield) and benzylisopropyl substituted maleimide **44b** (98% yield), respectively. The dibenzyl substituted maleimide **44a** and benzylisopropyl substituted maleimide **44b** on base catalyzed hydrolysis followed by acidification, furnished the desired dibenzylmaleic anhydride **45a** (97% yield) and benzylisopropylmaleic anhydride **45b** (94% yield), respectively (Scheme 6).[9] The formal syntheses of naturally occurring maculactones A-C (**1**-**3**) from dibenzylmaleic anhydride **45a** and nostoclide I (**4**) from isopropylbenzylmaleic anhydride **45b** are known in literature.[5,4a]



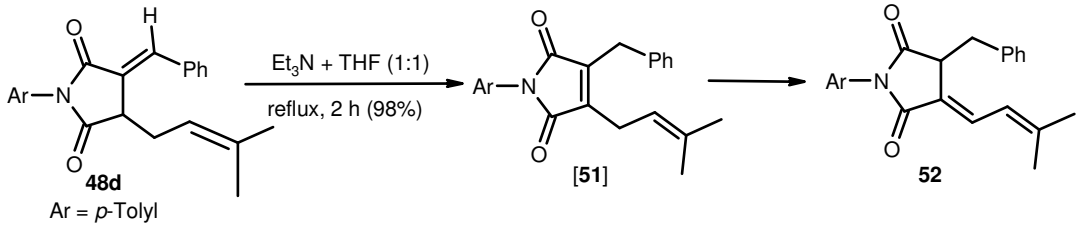

**Scheme 7**. *Reagents*, *conditions and yields*: (i) $Ph_3P$ (1.00 equiv.), RCHO (1.50 equiv.), THF, reflux, 10 h (91-93%); (ii) (a) NaH (1.00 equiv.), THF, 0 °C, 0.5 h, (b) R'X (1.00 equiv.), 0 °C – rt, 3 h (68-85%); (iii) $Et_3N$ + THF (1:1), reflux, 48 h (92-98%); (iv) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (89-97%).

**Table 1. Synthesis of Unnatural Dialkylmaleic Anhydrides**

| Entry | RCHO | Product-42/46 (% yield) | R'X | Product-48 (% yield) | Product-49 (% yield) | Product-50 (% yield) |
|---|---|---|---|---|---|---|
| 1 | $CH_3(CH_2)_4CHO$ | **46** (91) | $CH_3(CH_2)_4CH_2Br$ | **48a** (72) | **49a** (98) | **50a** (90) |
| 2 | $CH_3(CH_2)_4CHO$ | **46** (91) | $PhCH_2Br$ | **48b** (80) | **49b** (93) | **50b** (97) |
| 3 | PhCHO | **42** (93) | $CH_3$ | **48c** (68) | **49c** (92) | **50c** (89) |
| 4 | PhCHO | **42** (93) | $(CH_3)_2C{=}CHCH_2Br$ | **48d** (85) | -- | -- |

After completion of syntheses of above bioactive natural products we utilized this new robust approach to synthesize potentially useful unnatural dialkylmaleic anhydrides via the generation of a carbanion on the alkylidenesuccinimide core (Scheme 7). The obtained results have been tabulated in the Table 1. Interestingly, the alkylidenesuccinimide **48d** on treatment with triethylamine underwent two successive prototropic shifts to obtain the thermodynamically more stable alkylidenesuccinimide **52** via the unisolable dialkyl maleimide intermediate **51** (Scheme 8).

**Scheme 8**




## 3C.3 Summary

In this section, we have described formal synthesis of maculalactones A-C and nostoclide I. We feel that our present approach is general in nature and can be useful to design diverse dialkyl substituted maleic anhydrides and butyrolactone skeletons for the structure-activity relationship studies.

### 3C.4 Experimental

Commercially available maleic anhydride, *p*-toluidine, triphenylphosphine, aldehydes, sodium hydride and alkyl halides were used.

**General procedure for synthesis of 42/46.** A solution of *N*-*p*-tolylmaleimide (**41**, 10.00 mmol) and triphenylphosphine (10.00 mmol) in THF (100 mL) was stirred at room temperature for 30 min. To the reaction mixture was added the corresponding aldehyde (15.00 mmol) and the reaction mixture was refluxed for 10 h. The THF was distilled off in vacuo at 50 °C and the residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to obtain **42/46** in 93/91% yields respectively.

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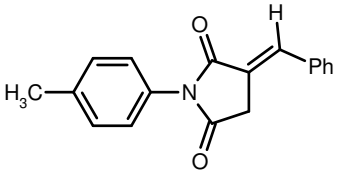
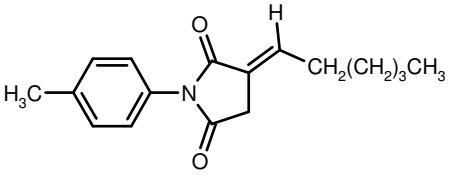
|  <br>**42 (277)** | **MP**: 192-194 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1771, 1709, 1659 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.40 (s, 3H), 3.77 (d, *J* = 2 Hz, 2H), 7.25 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.43-7.59 (m, 5H), 7.74 (t, *J* = 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.2, 34.1, 123.1, 126.2, 129.1, 129.2, 129.7, 130.2 (2-carbons), 134.0, 135.1, 138.6, 170.1, 173.1.<br>**Anal. Calcd for $C_{18}H_{15}NO_2$**: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.11; H, 5.54; N, 5.09. |
|  <br>**46 (271)** | **MP**: 112-113 °C.<br>**IR** (nujol) $\nu_{max}$ 1771, 1749, 1712, 1691, 1676 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, *J* = 6 Hz, 3H), 1.22-1.45 (m, 4H), 1.53 (quintet, *J* = 6 Hz, 2H), 2.23 (q, *J* = 6 Hz, 2H), 2.37 (s, 3H), 3.37 (d, *J* = 2 Hz, 2H), 6.93 (tt, *J* = 8 & 2 Hz, 1H), 7.18 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.7, 20.9, 22.2, 27.5, 29.6, 31.2, 31.8, 125.1, 126.0, 129.2, 129.4, 138.1, 139.6, 168.7, 173.0.<br>**MS** (*m*/*e*) 271, 242, 228, 214, 200, 189, 172, 133, 107, 95, 81, 67, 53.<br>**Anal. Calcd for $C_{17}H_{21}NO_2$**: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.11; H, 7.92; N, 5.07. |

**General procedure for synthesis of 43a,b/48a-d.** A solution of **42/46** (1.60 mmol) in THF (20 mL) was added to the slurry of sodium hydride (1.60 mmol) in THF (10 mL) at 0 °C and the reaction mixture was stirred for 30 min. Then, the corresponding alkyl halide (1.60 mmol) was added to the reaction mixture at 0 °C and it was stirred for 3 h. The reaction mixture was acidified by 2 N HCl and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine and dried over $Na_2SO_4$. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of residue using petroleum ether and ethyl acetate furnished **43a**,**b/48a-d** in 87-92/68-85% yields respectively.

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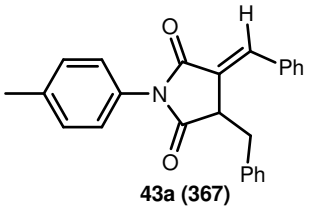
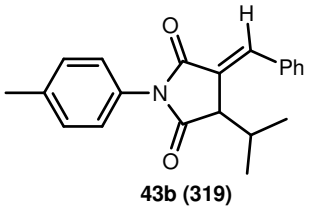
|  <br>**43a (367)** | **MP**: 103-104 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1709, 1655 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.36 (s, 3H), 3.36, (dq, *J* = 14 & 6 Hz, 2H), 4.31 (dt, *J* = 6 & 2 Hz, 1H), 6.82 (d, *J* = 8 Hz, 2H), 6.90-7.00 (m, 2H), 7.15-7.25 (m, 5H), 7.47-7.61 (m, 3H), 7.62-7.71 (m, 2H), 7.79 (d, *J* = 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.2, 33.4, 44.6, 126.2, 127.2, 127.3, 128.2, 129.0, 129.2, 129.6, 129.7, 130.1, 130.2, 133.7, 135.1, 135.7, 138.6, 169.6, 175.9.<br>**Anal. Calcd for $C_{25}H_{21}NO_2$**: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.51; H, 5.80; N, 3.77. |
|  <br>**43b (319)** | **MP**: 107-109 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1767, 1707, 1647 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.89 (d, *J* = 8 Hz, 3H), 1.34 (d, *J* = 8 Hz, 3H), 2.35-2.50 (m, 1H), 2.41 (s, 3H), 3.92 (t, *J* = 4 Hz, 1H), 7.23 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.40-7.59 (m, 5H), 7.74 (d, *J* = 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 16.9, 20.9, 21.2, 29.7, 48.7, 126.2, 128.6, 129.0, 129.2, 129.7, 129.9, 130.1, 133.7, 134.9, 138.5, 170.1, 175.4.<br>**Anal. Calcd for $C_{21}H_{21}NO_2$**: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.87; H, 6.66; N, 4.25. |

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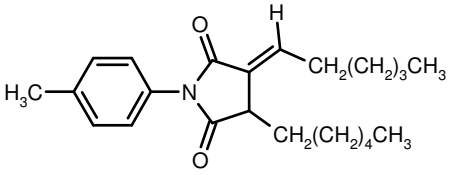
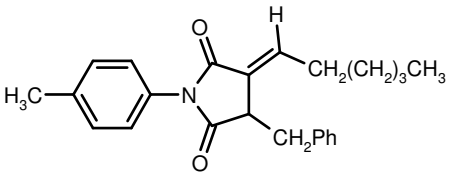
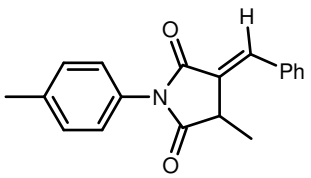
|  <br>**48a (355)** | **MP**: 69-70 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1767, 1709, 1670, 1516 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.86 (t, $J$ = 6 Hz, 3H), 0.91 (t, $J$ = 6 Hz, 3H), 1.15-1.45 (m, 12H), 1.53 (quintet, $J$ = 6 Hz, 2H), 1.75-1.98 (m, 1H), 1.98-2.15 (m, 1H), 2.28 (q, $J$ = 8 Hz, 2H), 2.38 (s, 3H), 3.51 (bs, 1H), 6.93 (dt, $J$ = 8 & 2 Hz, 1H), 7.17 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.9, 14.0, 21.2, 22.4, 22.5, 24.6, 28.1, 29.2, 29.3, 30.7, 31.5, 31.6, 42.5, 126.2, 129.0, 129.3, 129.7, 138.4, 140.3, 169.3, 176.9.<br>**Anal. Calcd for $C_{23}H_{33}NO_2$**: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.79; H, 9.43; N, 3.72. |
|  <br>**48b (361)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1709 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.94 (t, $J$ = 8 Hz, 3H), 1.26 (bs, 4H), 1.30-1.45 (m, 2H), 2.20-2.45 (m, 2H), 2.34 (s, 3H), 3.21 (dd, $J$ = 13 & 6 Hz, 1H), 3.36 (dd, $J$ = 13 & 6 Hz, 1H), 3.78 (bt, $J$ = 6 Hz, 1H), 6.78 (d, $J$ = 8 Hz, 2H), 6.94 (dt, $J$ = 8 & 2 Hz, 1H), 7.08-7.26 (m, 7H).<br>**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 13.9, 21.2, 22.5, 28.1, 29.5, 31.6, 36.5, 44.2, 126.3, 127.3, 128.5, 128.7, 129.1, 129.6, 129.7, 135.5, 138.5, 140.6, 175.8 (2-carbons).<br>**Anal. Calcd for $C_{24}H_{27}NO_2$**: C, 79.74; H, 7.53; N, 3.88. Found: C, 80.00; H, 7.42; N, 3.91. |
|  <br>**48c (291)** | **MP**: 116-118 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1769, 1709, 1649 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.51 (d, $J$ = 6 Hz, 3H), 2.40 (s, 3H), 3.95 (dq, $J$ = 8 & 4 Hz, 1H), 7.21-7.35 (m, 4H), 7.36-7.58 (m, 5H), 7.74 (d, $J$ = 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.4, 21.1, 38.2, 126.1, 128.9, 129.3, 129.4, 129.7, 130.0, 130.1, 133.4, 135.5, 138.5, 169.7, 177.4.<br>**Anal. Calcd for $C_{19}H_{17}NO_2$**: C, 78.32; H, 5.88; N, 4.81. Found: C, 78.47; H, 5.69; N, 4.73. |

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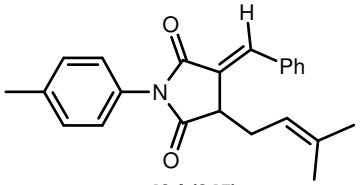
|  <br>**48d (345)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1769, 1711, 1651 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.40 (s, 3H), 1.61 (s, 3H), 2.40 (s, 3H), 2.60-2.92 (m, 2H), 4.06 (dt, $J$ = 6 & 2 Hz, 1H), 4.92-5.06 (m, 1H), 7.18 (d, $J$ = 8 Hz, 2H), 7.30 (d, $J$ = 8 Hz, 2H), 7.40-7.61 (m, 5H), 7.75 (d, $J$ = 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 17.8, 21.2, 25.9, 27.1, 43.4, 117.1, 126.2, 127.9, 129.0, 129.4, 129.8, 130.0, 130.1, 133.7, 135.4, 136.9, 138.6, 170.2, 176.7.<br>**Anal. Calcd for $C_{23}H_{23}NO_2$**: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.08; H, 6.90; N, 4.15. |

**General procedure for synthesis of 44a,b/49a-c/52.** To a stirred solution of **43a**,**b/48a**-**d** (0.80 mmol) in THF (10 mL) was added triethylamine (10 mL) and the reaction mixture was refluxed for 48 h and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine 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 furnished **44a**,**b/49a**-**c/52** in 94-98/92-98% yields respectively.

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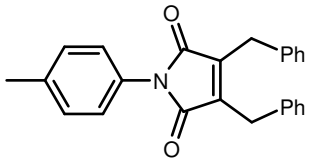
|  <br>**44a (367)** | **MP**: 107-108 $^oC$.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1713, 1601 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.37 (s, 3H), 3.84 (s, 4H), 7.17-7.36 (m, 14H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.0, 29.6, 125.5, 126.9, 128.8, 128.9, 129.0, 129.5, 136.5, 137.3, 139.7, 170.6.<br>**Anal. Calcd for $C_{25}H_{21}NO_2$**: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.69; H, 5.89; N, 3.78. |

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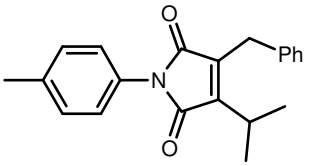
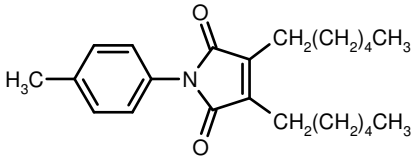
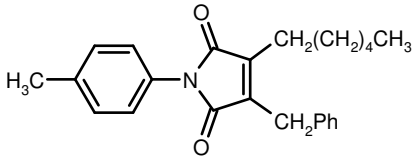
|  <br>**44b (319)** | **MP**: 78-80 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1742, 1713, 1657 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.31 (d, $J$ = 6 Hz, 6H), 2.36 (s, 3H), 3.11 (septet, $J$ = 6 Hz, 1H), 3.83 (s, 2H), 7.15-7.35 (m, 9H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 20.5, 21.0, 26.2, 29.1, 125.6, 126.6, 128.6, 128.7, 129.0, 129.4, 137.1, 137.2, 137.7, 145.5, 169.8, 170.5.<br>**Anal. Calcd for $C_{21}H_{21}NO_2$**: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.11; H, 6.52; N, 4.22. |
|  <br>**49a (355)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1707, 1516, 1395 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.89 (t, $J$ = 6 Hz, 6H), 1.15-1.45 (m, 12H), 1.57 (quintet, $J$ = 6 Hz, 4H), 2.36 (s, 3H), 2.44 (t, $J$ = 8 Hz, 4H), 7.22 (s, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.0, 21.1, 22.5, 23.9, 28.6, 29.3, 31.4, 125.7, 129.3, 129.5, 137.2, 141.1, 170.9.<br>**Anal. Calcd for $C_{23}H_{33}NO_2$**: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.79; H, 9.45; N, 3.99. |
|  <br>**49b (361)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1713 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, $J$ = 6 Hz, 3H), 1.15-1.40 (m, 6H), 1.50 (quintet, $J$ = 8 Hz, 2H), 2.36 (s, 3H), 2.46 (t, $J$ = 8 Hz, 2H), 3.81 (s, 2H), 7.15-7.35 (m, 9H).<br>**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 14.0, 21.1, 22.5, 24.2, 28.3, 29.4, 29.6, 31.4, 125.6, 126.8, 128.8, 128.9, 129.1, 129.6, 137.0, 137.3, 138.9, 142.0, 170.7, 170.8.<br>**Anal. Calcd for $C_{24}H_{27}NO_2$**: C, 79.74; H, 7.53; N, 3.88. Found: C, 79.66; H, 7.61; N, 3.79. |

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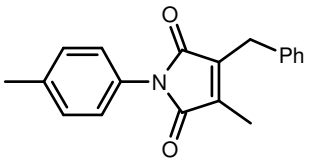
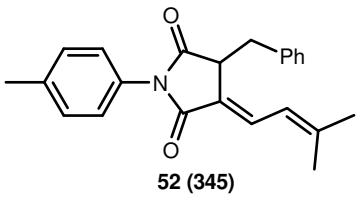
|  <br>**49c (291)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1709 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.06 (s, 3H), 2.36 (s, 3H), 3.81 (s, 2H), 7.10-7.40 (m, 9H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 9.1, 21.1, 29.7, 125.6, 126.9, 128.9 (2-carbons), 129.1, 129.6, 136.8, 137.4, 137.8, 139.2, 170.6, 171.0.<br>**Anal. Calcd for $C_{19}H_{17}NO_2$**: C, 78.32; H, 5.88; N, 4.81. Found: C, 78.44; H, 5.60; N, 4.71. |
|  <br>**52 (345)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1765, 1705, 1634 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.99 (s, 3H), 2.01 (s, 3H), 2.35 (s, 3H), 3.22-3.44 (m, 2H), 3.84 (t, $J$ = 4 Hz, 1H), 6.05 (td, $J$ = 12 & 2 Hz, 1H), 6.81 (d, $J$ = 10 Hz, 2H), 7.05-7.32 (m, 7H), 7.56 (dd, $J$ = 14 & 2 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 19.1, 21.2, 27.2, 36.5, 44.5, 120.4, 124.4, 126.3, 127.2, 128.3, 129.2, 129.6, 129.8, 131.6, 135.4, 138.4, 150.2, 169.8, 176.0.<br>**Anal. Calcd for $C_{23}H_{23}NO_2$**: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.06; H, 6.83; N, 4.02. |

**General procedure for synthesis of 45a,b/50a-c.** To a stirred solution of **44a**,**b/49a-c** (0.50 mmol) in a THF-methanol mixture (1:2, 6 mL) was added 20% aqueous KOH solution (4 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated and the residue was acidified with 2 N HCl, extracted with diethyl ether (3 x 20 mL) and the organic layer was washed with water, brine 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 furnished **45a**,**b/50a-c** in 85-97/89-97% yields respectively.

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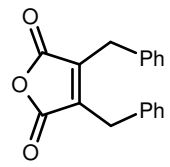
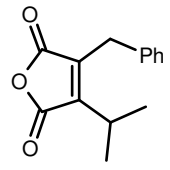
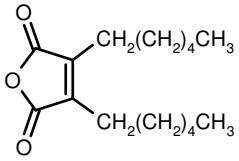
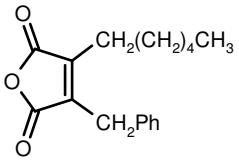
|  <br>**45a (278)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1769 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 3.78 (s, 4H), 7.05-7.20 (m, 4H), 7.20-7.35 (m, 6H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 29.9, 127.1, 128.6, 128.8, 134.9, 142.7, 165.6.<br>**Anal. Calcd for $C_{18}H_{14}O_3$**: C, 77.68; H, 5.07. Found: C, 77.78; H, 5.00. |
|  <br>**45b (230)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1773, 1703, 1605 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 300 MHz) $\delta$ 1.28 (d, $J$ = 9 Hz, 6H), 3.06 (sept, $J$ = 9 Hz, 1H), 3.81 (s, 2H), 7.15-7.45 (m, 5H).<br>**$^{13}$C NMR** ($CDCl_3$, 75 MHz) $\delta$ 20.0, 26.4, 29.8, 126.2, 127.3, 127.9, 128.6, 129.0, 135.7, 141.2, 149.1, 164.4, 165.8.<br>**Anal. Calcd for $C_{14}H_{14}O_3$**: C, 73.03; H, 6.13. Found: C, 73.21; H, 6.03. |
|  <br>**50a (266)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1765 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.89 (t, $J$ = 8 Hz, 6H), 1.15-1.45 (m, 12H), 1.57 (quintet, $J$ = 6 Hz, 4H), 2.44 (t, $J$ = 8 Hz, 4H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.0, 22.5, 24.5, 28.0, 29.2, 31.4, 144.5, 166.0.<br>**Anal. Calcd for $C_{16}H_{26}O_3$**: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.99. |
|  <br>**50b (272)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1767 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, $J$ = 6 Hz, 3H), 1.26 (bs, 6H), 1.49 (quintet, $J$ = 8 Hz, 2H), 2.44 (t, $J$ = 8 Hz, 2H), 3.80 (s, 2H), 7.15-7.40 (m, 5H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 14.0, 22.4, 24.7, 27.7, 29.2, 30.2, 31.3, 127.4, 128.7, 129.0, 135.4, 142.2, 145.2, 165.8, 165.9.<br>**Anal. Calcd for $C_{17}H_{20}O_3$**: C, 74.97; H, 7.40. Found: C, 74.82; H, 7.53. |

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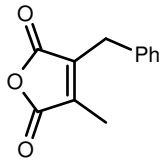
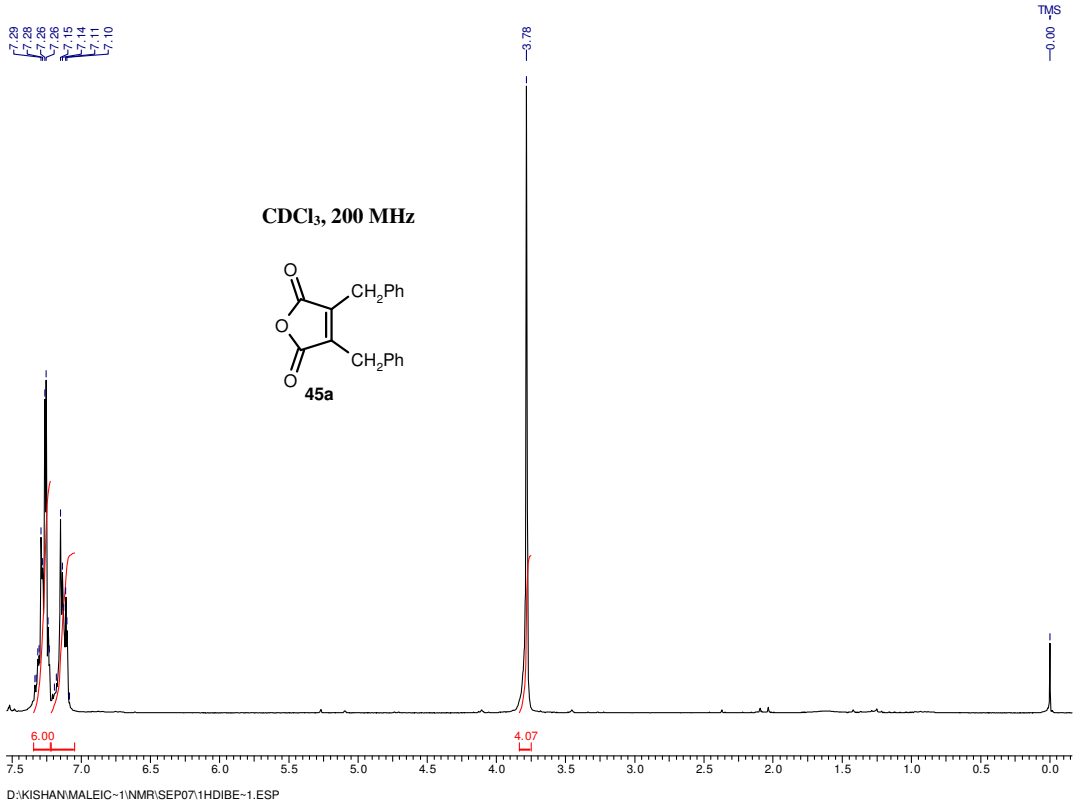
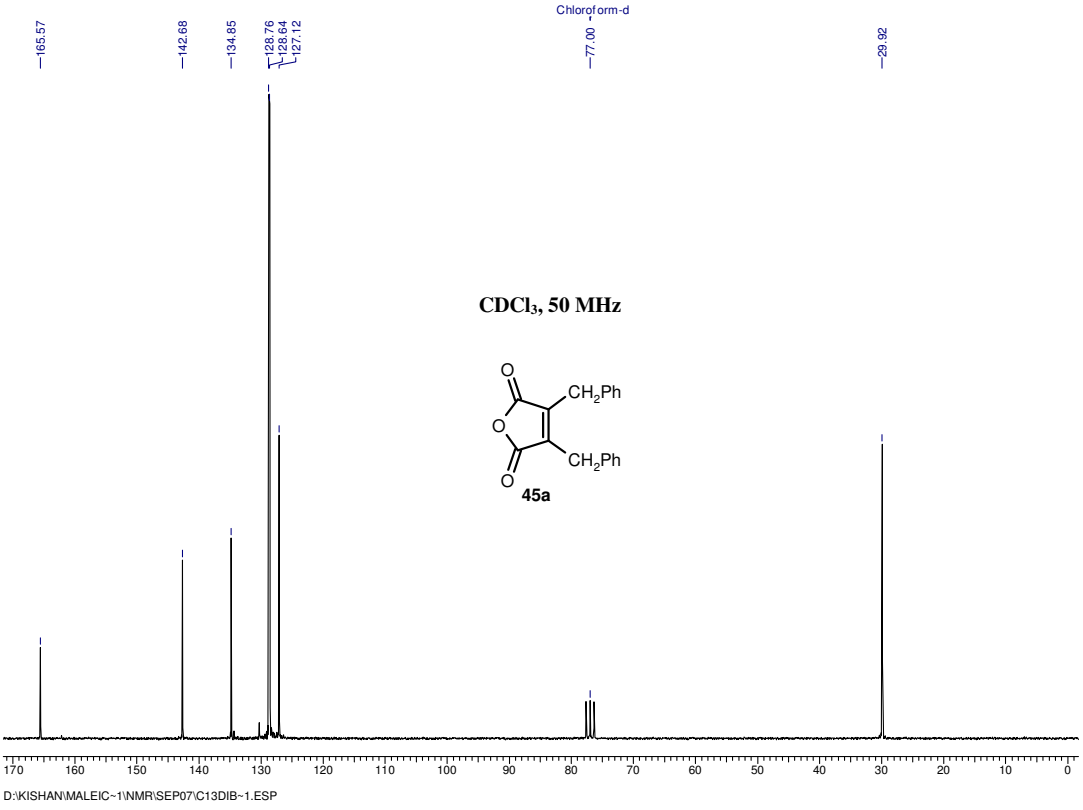
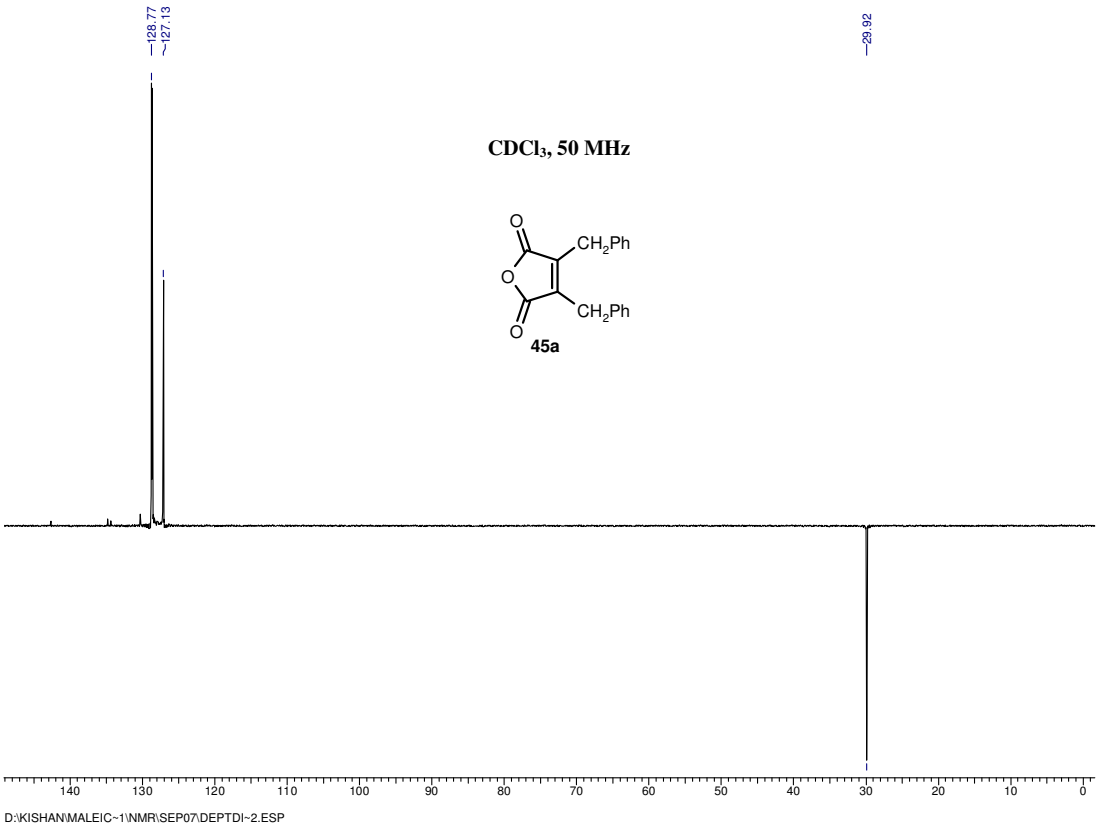
|  <br>**50c (202)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1825, 1765, 1674 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 2.05 (s, 3H), 3.79 (s, 2H), 7.15-7.40 (m, 5H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 9.6, 30.2, 127.3, 128.7, 129.0, 135.1, 141.0, 142.5, 165.7, 166.1.<br>**Anal. Calcd for $C_{12}H_{10}O_3$**: C, 71.28; H, 4.99. Found: C, 71.19; H, 5.04. |

# 3C.5 Selected Spectra


7.29
7.28
7.26
7.25
7.15
7.14
7.11
7.10
3.78
TMS
0.00
CDCl3, 200 MHz
O
CH2Ph
O
CH2Ph
O
45a
6.00
4.07
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
D:\KISHAN\MALEIC~1\NMR\SEP07\1HDIBE~1.ESP


165.57
142.68
134.85
128.76
128.64
127.12
Chloroform-d
77.00
29.92
CDCl3, 50 MHz
O
CH2Ph
O
CH2Ph
O
45a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
D:\KISHAN\MALEIC~1\NMR\SEP07\C13DIB~1.ESP


128.77
127.13
29.92
CDCl3, 50 MHz
O
O
O
CH2Ph
CH2Ph
45a
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
D:\KISHAN\MALEIC~1\NMR\SEP07\DEPTDI~2.ESP

### 3C.6 References


(1) (a) Tsui, W.-Y.; Williams, G. A.; Brown, G. D. *Phytochemistry* **1996**, *43*, 1083. (b) Lee, S.-C.; Brown, G. D. *J. Nat. Prod.* **1998**, *61*, 29.

(2) Brown, G. D.; Wong, H.-F. *Tetrahedron* **2004**, *60*, 5439.

(3) Yang, X.; Shimizu, Y.; Steiner, J. R.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 761.

(4) (a) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897. (b) Bellina, F.; Rossi, R. *Synthesis* **2002**, 2729.

(5) Kar, A.; Gogoi, S.; Argade, N. P. *Tetrahedron* **2005**, *61*, 5297.

(6) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.

(7) Kar, A.; Argade, N. P. *J. Org. Chem.* **2002**, *67*, 7131.

(8) (a) Assante, G.; Camarda, L.; Merlini, L.; Nasini, G. *Gazzetta Chimica Italiana* **1979**, *109*, 151. (b) Kayser, M. M.; Breau, L.; Eliev, S.; Morand, P. *Can. J. Chem.* **1986**, *64*, 104.

(9) Haval, K. P.; Argade, N. P. *J. Org. Chem.* **2008**, *73*, 6936.

# 3D. Section D

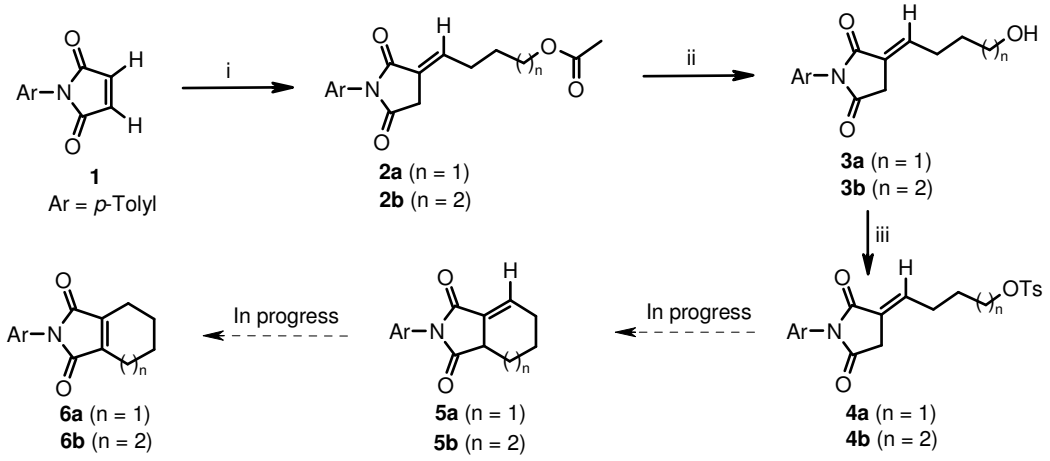
## *Wittig Reaction of Maleimide and Triphenylphosphine Adduct with Dihydrofuran/Dihydropyran and Studies Towards the Synthesis of Byssochlamic Acid*

This section features the following topics:

## 3D Section D: Wittig Reaction of Maleimide and Triphenylphosphine Adduct with Dihydrofuran/Dihydropyran and Studies Towards the Synthesis of Byssochlamic Acid

### 3D.1 Wittig Reaction of Maleimide and Triphenylphosphine Adduct with Dihydrofuran/Dihydropyran

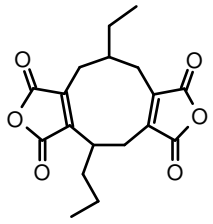
Recently, several structurally interesting and biologically important natural products containing maleic anhydride unit have been isolated.[1] They show a wide range of biological activities.[2-4] In our on going studies towards the synthesis of bioactive natural products,[5] we were in search of suitable reagent to introduce side chain functionality without protection-deprotection chemistry. We thought that dihydrofuran/dihydropyran might act as sources of four/five carbon aldehydes. In this context, we carried out the Wittig reaction of *N*-*p*-tolylmaleimide (**1**) and triphenylphosphine adduct with dihydrofuran/dihydropyran and obtained (*E*)-alkylidenesuccinimides **2a/b** in 97/98% yields. Acid catalyzed deprotection under acidic conditions furnished alcohols **3a/b** in 92/93% yields. Alcohols **3a/b** were converted into corresponding tosylates **4a/b** in 87/89% yields. Our studies on intramolecular cyclization using sodium hydride as base followed by base catalyzed isomerization of carbon-carbon double bond to obtain carbocycles **6a/b** are in active progress (Scheme 1).




**Scheme 1.** *Reagents, Conditions and yields*: (i) $Ph_3P$, DHF/DHP, AcOH, reflux, 10 h (97/98%); (ii) 2 N HCl, EtOAc + MeOH (1:1), rt, 8 h (92/93%); (iii) $Et_3N$, DMAP, *p*-TSCl, DCM, 0 $^oC$ to rt, 10 h (87/89%).

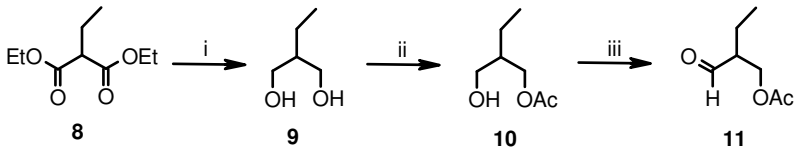
### 3D.2 Studies Towards the Synthesis of Byssochlamic Acid

Byssochlamic acid, a metabolite first isolated from ascomycete *Byssochlamys fulva*[6] 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.[7] Sodium salt of byssochlamic acid inhibits germination of mustard seed and elongation of the seedlings.[8] One enantiospecific[9] and two racemic syntheses[10,11] 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).

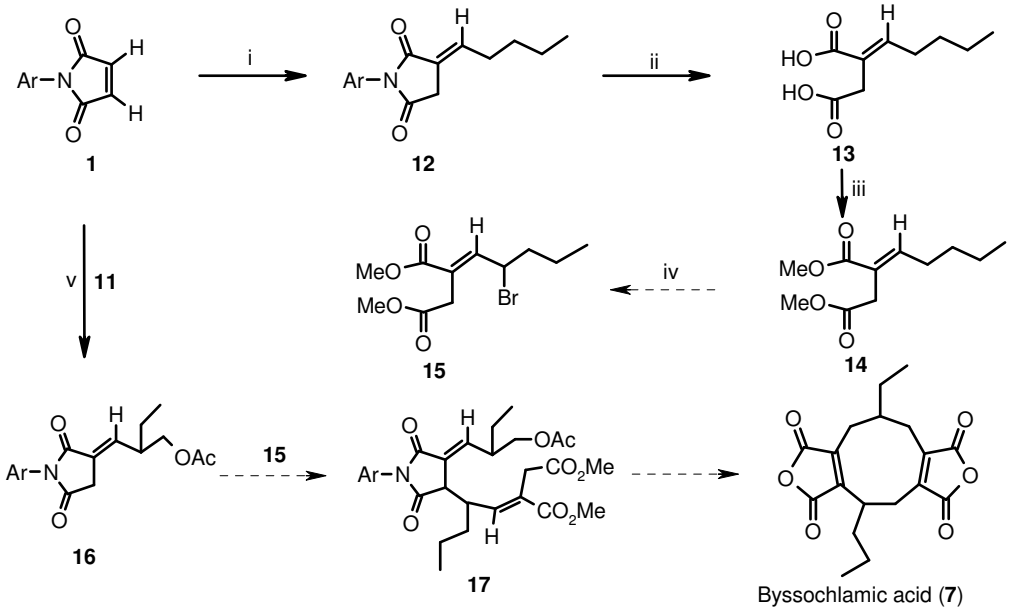


Byssochlamic acid (**7**)

We started synthesis of byssochlamic acid from diethyl ethylmalonate (**8**). Lithium aluminum hydride induced reduction of diethyl ethylmalonate (**8**) furnished diol **9** in 90% yield. Diol **9** was monoprotected using acetic anhydride to obtain acetoxy-alcohol **10** in 65% yield. PCC oxidation of **10** furnished aldehyde **11** in 85% yield (Scheme 2). Triphenylphosphine induced Wittig reaction of *N*-*p*-tolylmaleimide (**1**) with valeraldehyde exclusively furnished the corresponding (*E*)-alkylidenesuccinimide **12** in 94% yield. Base catalyzed hydrolysis of (*E*)-alkylidenesuccinimide **12** followed by acidification, furnished the desired diacid **13** in 85% yield. Esterification of diacid **13** using methanol/$H_2SO_4$ furnished diester **14** in 80% yield. Regioselective bromination of diester **14** would furnish bromodiester **15**. Wittig reaction of *N*-*p*-tolylmaleimide (**1**) and triphenylphosphine adduct with aldehyde **11** furnished (*E*)-alkylidenesuccinimide **16** in 91% yield. Then, alkylation of alkylidenesuccinimide **16** can be performed by using sodium hydride and bromodiester **15** to obtain exo-diester **17**. Our work towards this goal is in active progress (Scheme 3).



**Scheme 2.** *Reagents*, *conditions and yields*: (i) LAH (2.00 equiv.), THF, 0 $^{o}$C to rt, 12 h (90%); (ii) $Ac_2O$ (1.00 equiv.), pyridine (1.00 equiv.), DCM, 0 $^{o}$C to rt, 12 h (65%); (iii) PCC (1.00 equiv.), DCM, 0 $^{o}$C to rt, 3 h (85%).



**Scheme 3.** *Reagents*, *conditions and yields*: (i) $PPh_3$ (1.00 equiv.), THF, $CH_3(CH_2)_3CHO$ (1.50 equiv.), reflux, 10 h (94%); (ii) (a) THF + MeOH (1:2), KOH, $H_2O$, reflux, 2 h, (b) $H^+$/HCl (85%); (iii) MeOH, $H^+/H_2SO_4$, reflux, 12 h (80%); (iv) In progress; (v) $PPh_3$ (1.00 equiv.), THF, **11** (1.50 equiv.), reflux, 10 h (91%).

### 3D.3 Summary

In this section, we have described Wittig reaction of maleimide and triphenylphosphine adduct with dihydrofuran/dihydropyran. Our studies on intramolecular cyclization followed by isomerization of carbon-carbon double bond to obtain carbocycles are in active progress. We have also described our studies towards the total synthesis of byssochlamic acid.

*In conclusion, in the present four sections chapter we have described the relevant literature and our results with experimental and spectral data. In the present chapter we described a new general approach to potentially useful natural and unnatural dialkylmaleic anhydrides via the generation of a carbanion on the alkylidenesuccinimide core. We have utilized this methodology in the total synthesis of bioactive natural products chaetomellic anhydride A, 2-carboxymethyl-3-hexylmaleic anhydride, 2-(ß-carboxyethyl)-3-hexylmaleic anhydride and formal synthesis of butyrolactones maculacatones A-C and nostoclide I. We have described Wittig reaction of maleimide and triphenylphosphine adduct with dihydrofuran/dihydropyran. We have also described our studies towards the synthesis of bioactive natural product byssochlamic acid.*

### 3D.4 Experimental

Commercially available diethyl ethylmalonate, lithium aluminum hydride, pyridinium chlorochromate, maleic anhydride, *p*-toluidine, triphenylphosphine, dihydrofuran, dihydropyran and *p*-tolylsulfonyl chloride were used.

**General procedure for synthesis of 2a/b.** A solution of *N*-*p*-tolylmaleimide (**1**, 10.00 mmol) and triphenylphosphine (10.00 mmol) in acetic acid (100 mL) was stirred at room temperature for 30 min. To the reaction mixture was added the dihydrofuran/dihydropyran (10.00 mmol) and the reaction mixture was refluxed for 10 h. Then, the acetic acid was distilled off in vacuo and the obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to obtain **2a/b** in 97/98% yields respectively.

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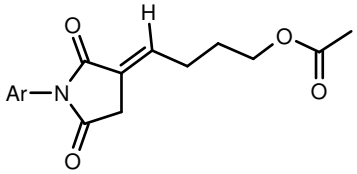
|  <br>**2a (301)**<br>Ar = *p*-Tolyl | **MP**: 112-114 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1772, 1733, 1714, 1676 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.89 (quintet, $J$ = 6 Hz, 2H), 2.08 (s, 3H), 2.34 (q, $J$ = 6 Hz, 2H), 2.39 (s, 3H), 3.40 (d, $J$ = 2 Hz, 2H), 4.13 (t, $J$ = 6 Hz, 2H), 6.91 (tt, $J$ = 8 & 2 Hz, 1H), 7.20 (d, $J$ = 8 Hz, 2H), 7.29 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 125 MHz) $\delta$ 20.6, 20.9, 26.2, 26.9, 31.7, 63.1, 126.0, 126.1, 129.1, 129.4, 137.8, 138.3, 168.6, 170.6, 172.8.<br>**Anal. Calcd for $C_{17}H_{19}NO_4$**: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.70; H, 6.43; N, 4.42. |

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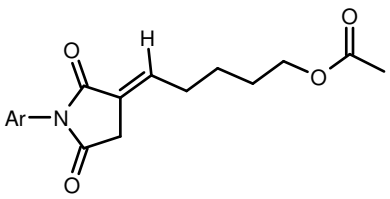
|  <br>**2b (315)**<br>Ar = *p*-Tolyl | **MP**: 93-95 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1715, 1676 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.57-1.75 (m, 4H), 2.07 (s, 3H), 2.30 (q, *J* = 6 Hz, 2H), 2.39 (s, 3H), 3.39 (d, *J* = 2 Hz, 2H), 4.10 (t, *J* = 6 Hz, 2H), 6.92 (tt, *J* = 8 & 2 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 20.8, 21.1, 24.5, 28.2, 29.4, 32.0, 63.7, 125.8, 126.1, 129.2, 129.6, 138.5, 138.8, 168.8, 171.0, 173.0.<br>**Anal. Calcd for $C_{18}H_{21}NO_4$**: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.59; H, 6.82; N, 4.52. |

**General procedure for synthesis of 3a/b.** To a solution of **2a/b** (8.00 mmol) in ethyl acetate (20 mL) and methanol (20 mL) was added 2 N HCl (10 mL) in a dropwise fashion with continuous stirring. The reaction mixture was stirred for 8 h at room temperature. Then the solvent was evaporated in vacuo. The obtained residue was dissolved in ethyl acetate, washed with water, brine, dried over $Na_2SO_4$ and concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to furnish **3a/b** in 92/93% yields respectively.

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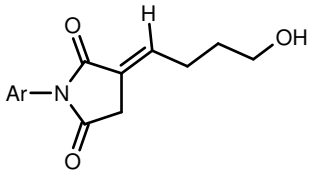
|  <br>**3a (259)**<br>Ar = *p*-Tolyl | **MP**: 109-111 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 3450, 1771, 1713, 1674 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.79 (quintet, *J* = 6 Hz, 2H), 2.38 (q, *J* = 6 Hz, 2H), 2.39 (s, 3H), 3.42 (d, *J* = 2 Hz, 2H), 3.70 (t, *J* = 6 Hz, 2H), 6.94 (tt, *J* = 8 & 2 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** (DMSO-$d_6$, 50 MHz) $\delta$ 21.0, 26.2, 31.1, 32.2, 60.3, 127.0, 127.1, 129.5, 130.2, 138.0 (2-carbons), 169.1, 173.8.<br>**Anal. Calcd for $C_{15}H_{17}NO_3$**: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.53; H, 6.58; N, 5.56. |

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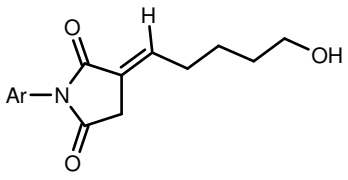
|  <br>**3b (273)**<br>Ar = *p*-Tolyl | **MP**: 130-132 °C.<br>**IR** (nujol) $\nu_{max}$ 3373, 1769, 1705, 1674 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.59-1.69 (m, 4H), 2.29 (q, *J* = 6 Hz, 2H), 2.39 (s, 3H), 3.39 (d, *J* = 2 Hz, 2H), 3.69 (t, *J* = 6 Hz, 2H), 6.94 (tt, *J* = 8 & 2 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.1, 24.4, 29.6, 32.0 (2-carbons), 62.2, 125.5, 126.2, 129.2, 129.7, 138.5, 139.5, 169.0, 173.2.<br>**Anal. Calcd for $C_{16}H_{19}NO_3$**: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.19; H, 6.95; N, 5.04. |

**General procedure for synthesis of 4a/b.** To a solution of **3a/b** (6.00 mmol) in DCM was added *p*-TSCl (6.00 mmol), DMAP (5 mg) and triethylamine (6.00 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 10 h. The solvent was evaporated in vacuo. The obtained residue was dissolved in ethyl acetate, washed with water, brine, dried over $Na_2SO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to furnish **4a/b** in 87/89% yields respectively.

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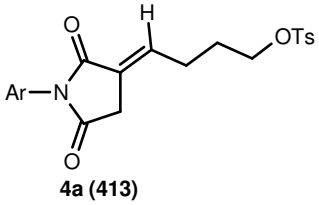
|  <br>**4a (413)**<br>Ar = *p*-Tolyl | **MP**: 97-99 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1719, 1678 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.90 (quintet, *J* = 6 Hz, 2H), 2.33 (q, *J* = 6 Hz, 2H), 2.39 (s, 3H), 2.45 (s, 3H), 3.34 (d, *J* = 2 Hz, 2H), 4.09 (t, *J* = 6 Hz, 2H), 6.78 (tt, *J* = 8 & 2 Hz, 1H), 7.19 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.81 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.1, 21.5, 25.7, 27.3, 31.8, 69.0, 126.1, 126.8, 127.7, 129.2, 129.6, 129.9, 132.8, 136.9, 138.5, 145.0, 168.6, 172.8.<br>**Anal. Calcd for $C_{22}H_{23}NSO_5$**: C, 63.90; H, 5.61; N, 3.39; S, 7.76. Found: C, 64.01; H, 5.72; N, 3.45; S, 7.81. |

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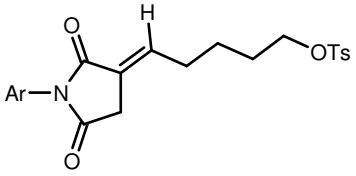
|  <br>**4b (427)**<br>Ar = *p*-Tolyl | **MP**: 120-122 °C.<br>**IR** (nujol) $\nu_{max}$ 1701, 1670 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 1.50-1.80 (m, 4H), 2.23 (q, *J* = 6 Hz, 2H), 2.39 (s, 3H), 2.46 (s, 3H), 3.35 (d, *J* = 2 Hz, 2H), 4.06 (t, *J* = 6 Hz, 2H), 6.84 (tt, *J* = 8 & 2 Hz, 1H), 7.19 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.80 (d, *J* = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 21.1, 21.5, 24.0, 28.3, 29.0, 31.9, 69.7, 126.0, 126.1, 127.7, 129.2, 129.7, 129.8, 132.9, 138.3, 138.5, 144.8, 168.8, 173.0.<br>**Anal. Calcd for $C_{23}H_{25}NSO_5$**: C, 64.62; H, 5.89; N, 3.28; S, 7.50. Found: C, 64.73; H, 6.00; N, 3.32; S, 7.42. |

**2-Ethylpropane-1,3-diol (9).** To a slurry of lithium aluminum hydride (760 mg, 20.00 mmol) in THF (50 mL) was added a solution of diethyl ethylmalonate (**8**, 1.88 g, 10.00 mmol) in THF (50 mL) in a dropwise fashion at 0 °C over a period of 30 min. with continuous stirring. The reaction mixture was stirred at room temperature for 12 h. Then it was quenched with 5% aqueous $NH_4Cl$ solution and further stirred for 30 min. The solvent was evaporated in vacuo. The obtained residue was dissolved in ethyl acetate and filtered through celite, dried over $Na_2SO_4$ and concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to obtain **9** (936 mg, 90% yield).

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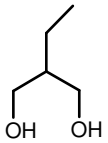
|  <br>**9 (104)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 3366, 1043 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.91 (t, *J* = 6 Hz, 3H), 1.26 (quintet, *J* = 6 Hz, 2H), 1.55-1.75 (m, 1H), 3.06 (bs, 2H), 3.62 (dd, *J* = 13 & 6 Hz, 2H), 3.79 (dd, *J* = 11 & 4 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 11.5, 20.5, 43.7, 64.7.<br>**Anal. Calcd for $C_5H_{12}O_2$**: C, 57.67; H, 11.61. Found: C, 57.49; H, 11.72. |

**2-(Hydroxymethyl)butyl acetate (10).** To a solution of **9** (832 mg, 8.00 mmol) in DCM (20 mL) was added acetic anhydride (0.76 mL, 8.00 mmol) and pyridine (0.65 mL, 8.00 mmol) at 0 °C and the reaction mixture was stirred for 12 h at room temperature.

The reaction was quenched with water and extracted with ethyl acetate (3 X 30 mL). The combined organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to obtain **10** (759 mg, 65% yield).

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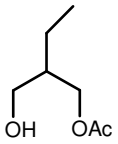
|  **10 (146)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 3433, 1740, 1720, 1043 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.96 (t, *J* = 8 Hz, 3H), 1.20-1.50 (m, 2H), 1.60-1.82 (m, 1H), 2.08 (s, 3H), 2.30 (bs, 1H), 3.53 (dd, *J* = 12 & 6 Hz, 1H), 3.62 (dd, *J* = 12 & 6 Hz, 1H), 4.10 (dd, *J* = 12 & 6 Hz, 1H), 4.21 (dd, *J* = 12 & 6 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 11.3, 20.6, 20.8, 41.9, 62.1, 64.3, 171.6.<br>**Anal. Calcd for $C_7H_{14}O_3$**: C, 57.51; H, 9.65. Found: C, 57.63; H, 9.71. |

**2-Formylbutyl acetate (11).** A solution of **10** (730 mg, 5.00 mmol) in DCM (20 mL) was added to the mixture containing PCC (1.08 g, 5.00 mmol) and 4 Å molecular sieves (1.00 g) in DCM (20 mL) at 0 $^oC$. The reaction mixture was stirred for 3 h at room temperature. Then it was diluted with diethyl ether (50 mL) and stirred for next 30 min. The reaction mixture was then filtered through a bed of celite and silica gel, washed with diethyl ether (100 mL) and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate to gave **11** (612 mg, 85% yield).

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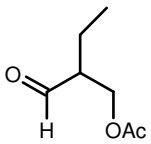
|  **11 (144)** | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 2731, 1736, 1724, 1719 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.95 (t, *J* = 6 Hz, 3H), 1.40-1.85 (m, 2H), 2.01 (s, 3H), 2.43-2.61 (m, 1H), 4.23 (dd, *J* = 8 & 4 Hz, 1H), 4.15-4.35 (m, 2H).<br>**Anal. Calcd for $C_7H_{12}O_3$**: C, 58.32; H, 8.39. Found: C, 58.44; H, 8.44. |

**(*E*)-3-Pentylidene-1-*p*-tolylpyrrolidine-2,5-dione (12).** It was obtained using the same procedure used for the synthesis of **2a/b**, but in THF instead of acetic acid.

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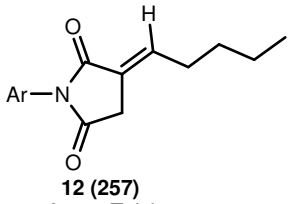
|  <br>**12 (257)**<br>Ar = *p*-Tolyl | **MP**: 108-110 °C.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1771, 1713, 1682 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.95 (t, $J$ = 6 Hz, 3H), 1.25-1.62 (m, 4H), 2.26 (q, $J$ = 6 Hz, 2H), 2.39 (s, 3H), 3.39 (d, $J$ = 2 Hz, 2H), 6.95 (tt, $J$ = 8 & 2 Hz, 1H), 7.20 (d, $J$ = 8 Hz, 2H), 7.29 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.7, 21.1, 22.3, 29.5, 30.1, 32.0, 125.2, 126.1, 129.3, 129.6, 138.4, 139.9, 168.9, 173.2.<br>**Anal. Calcd for $C_{16}H_{19}NO_2$**: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.74; H, 7.57; N, 5.39. |

**(*E*)-2-Pentylidenesuccinic acid (13)**. To a stirred solution of **12** (2.06 g, 8.00 mmol) in a THF-methanol mixture (1:2, 20 mL) was added 20% aqueous KOH solution (10 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated in vacuo. Then the obtained residue was dissolved in diethyl ether and acidified with 2 N HCl. It was extracted with diethyl ether (3 x 50 mL) and the organic layer was washed with water, brine 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 furnished **13** (1.26 g, 85% yield).

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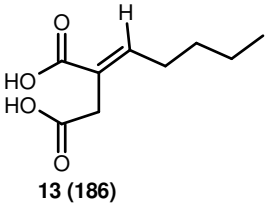
|  <br>**13 (186)** | **MP**: 128-130 °C.<br>**IR** (nujol) $\nu_{max}$ 1709, 1695, 1682, 1643 $cm^{-1}$.<br>**$^1$H NMR** (DMSO-$d_6$, 200 MHz) $\delta$ 0.86 (t, $J$ = 6 Hz, 3H), 1.15-1.45 (m, 4H), 2.13 (q, $J$ = 6 Hz, 2H), 3.19 (s, 2H), 6.77 (t, $J$ = 8 Hz, 1H).<br>**$^{13}$C NMR** (DMSO-$d_6$, 50 MHz) $\delta$ 14.1, 22.3, 28.3, 30.6, 32.4, 127.2, 144.5, 168.6, 172.5.<br>**Anal. Calcd for $C_9H_{14}O_4$**: C, 58.05; H, 7.58. Found: C, 58.01; H, 7.63. |

**(*E*)-Dimethyl 2-pentylidenesuccinate (14)**. To a stirred solution of **13** (930 mg, 5.00 mmol) in methanol (20 mL), two drops of conc. $H_2SO_4$ were added and the reaction mixture was refluxed for 12 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate. The resulting solution was washed successively

with 5% aqueous $NaHCO_3$ solution, brine, dried over $Na_2SO_4$ and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate to furnish **14** (856 mg, 80% yield).

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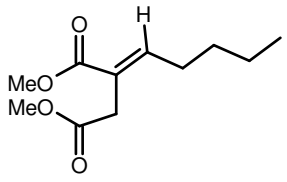
|  <br>**14 (214)** | Thick oil.<br>**IR** (neat) $\nu_{max}$ 1744, 1713 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.90 (t, $J$ = 6 Hz, 3H), 1.20-1.55 (m, 4H), 2.19 (q, $J$ = 6 Hz, 2H), 3.36 (s, 2H), 3.68 (s, 3H), 3.74 (s, 3H), 6.97 (t, $J$ = 6 Hz, 1H).<br>**$^{13}$C NMR** ($CDCl_3$, 50 MHz) $\delta$ 13.5, 22.1, 28.4, 30.3, 31.8, 51.6, 51.7, 125.1, 145.9, 167.1, 171.0.<br>**Anal. Calcd for $C_{11}H_{18}O_4$**: C, 61.66; H, 8.47 Found: C, 61.50; H, 8.52. |

**(*E*)-2-((-Dioxo-1-*p*-tolylpyrrolidin-3-ylidene)methyl)butyl acetate (16).** It was obtained using the same procedure used for the synthesis of **2a/b**, but in THF instead of acetic acid.

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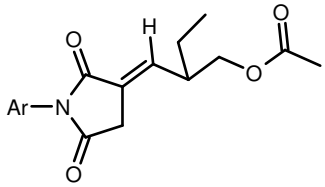
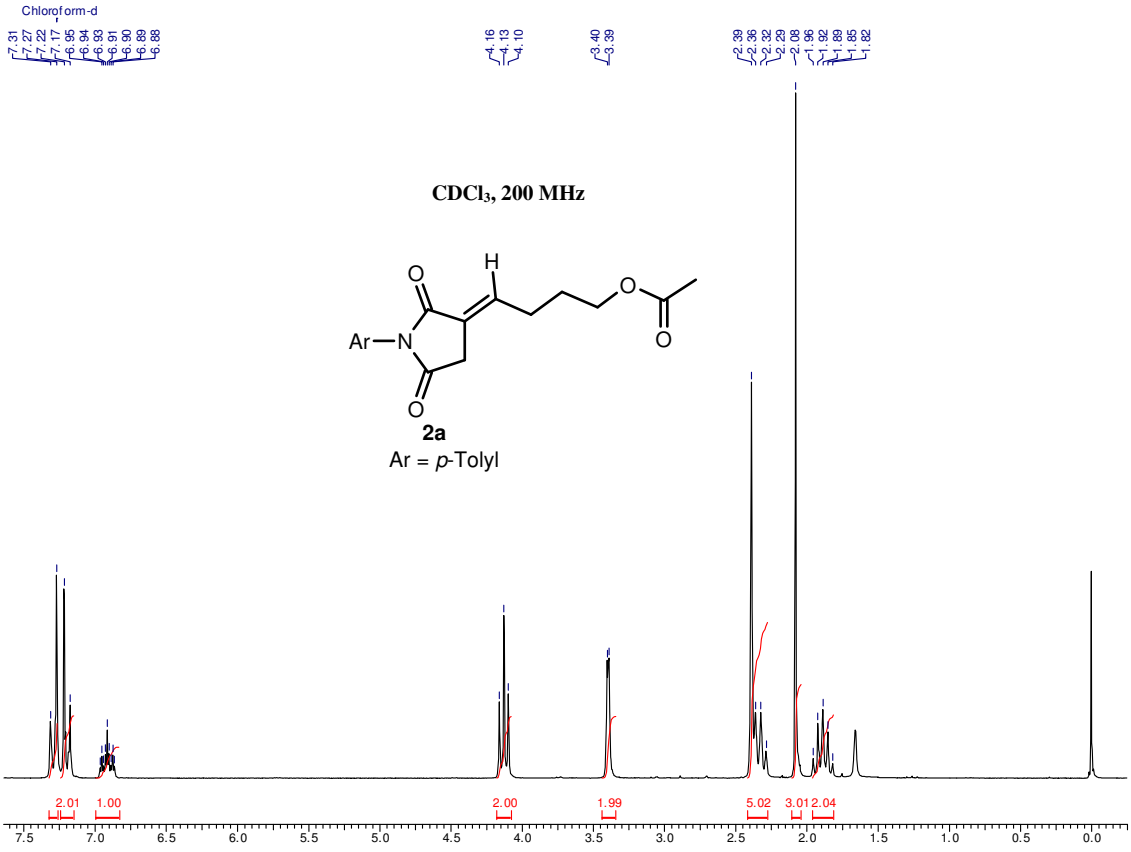
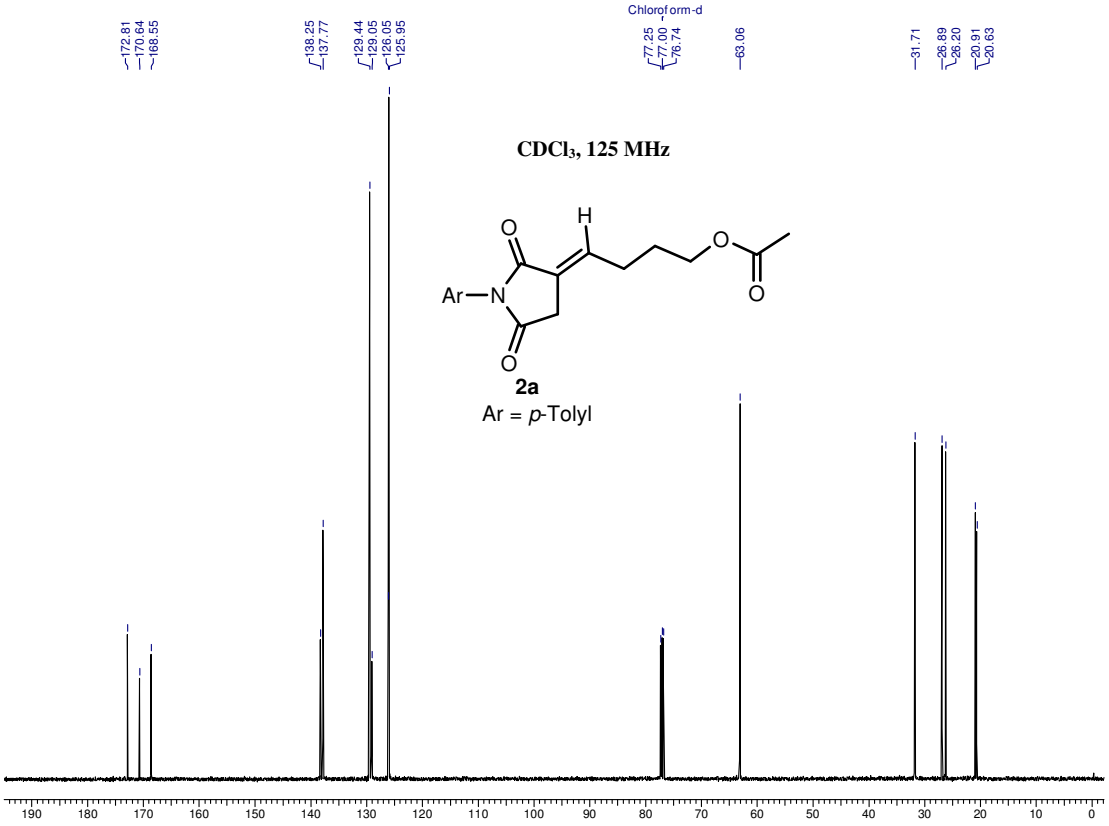
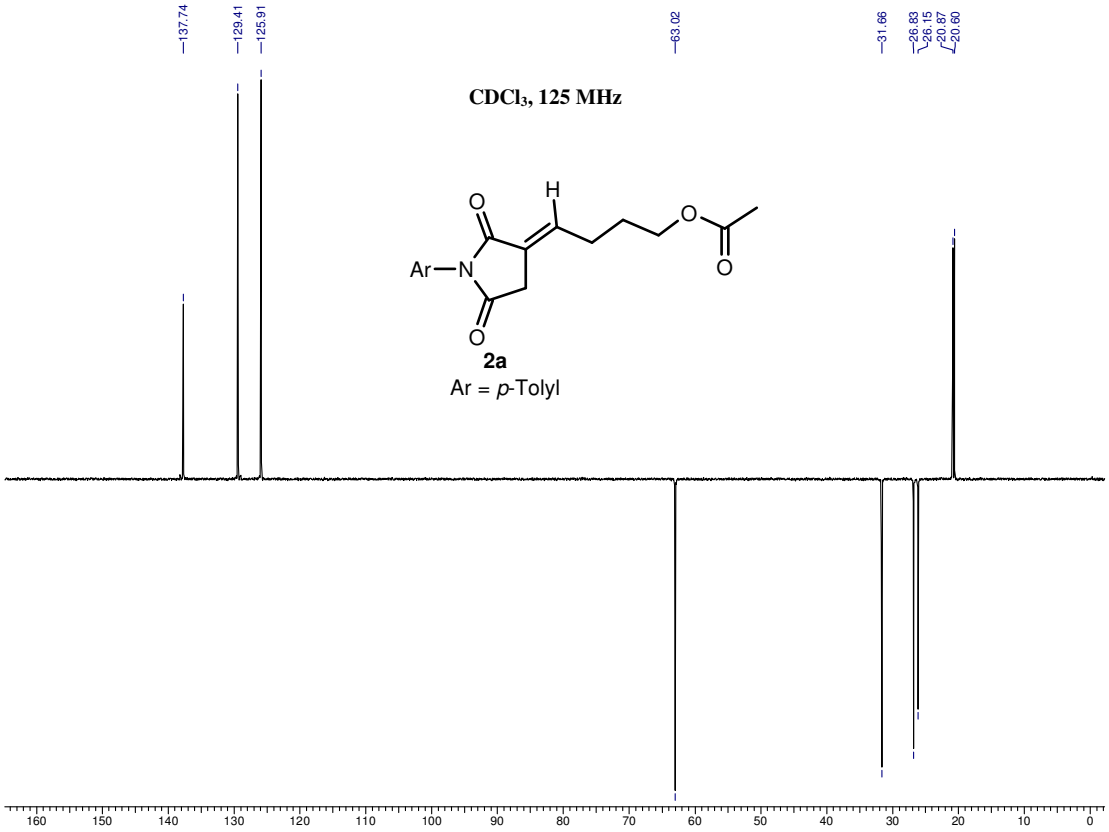
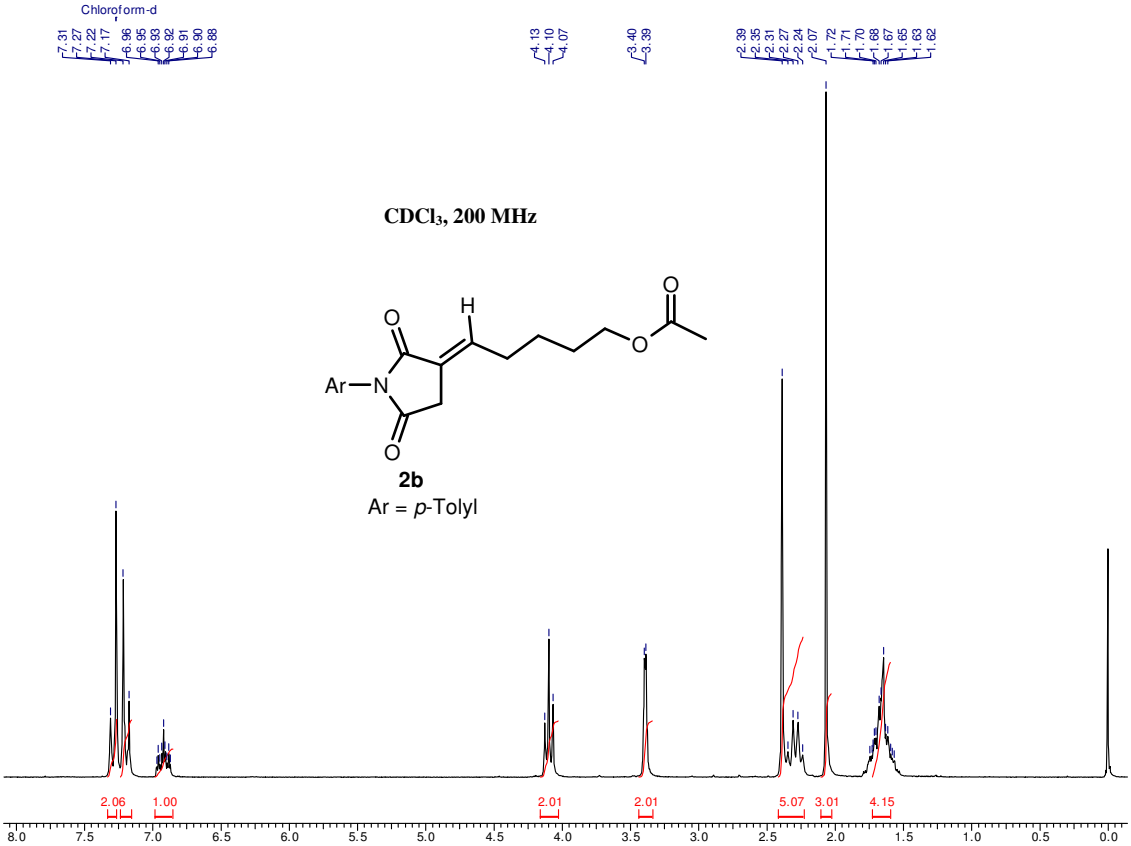
|  <br>**16 (315)**<br>Ar = *p*-Tolyl | Thick oil.<br>**IR** ($CHCl_3$) $\nu_{max}$ 1773, 1716, 1681 $cm^{-1}$.<br>**$^1$H NMR** ($CDCl_3$, 200 MHz) $\delta$ 0.95 (t, $J$ = 6 Hz, 3H), 1.30-1.80 (m, 2H), 2.06 (s, 3H), 2.39 (s, 3H), 2.45-2.70 (m, 1H), 3.43 (dd, $J$ = 2 & 2 Hz, 2H), 4.03 (dd, $J$ = 12 & 8 Hz, 1H), 4.16 (dd, $J$ = 11 & 6 Hz, 1H), 6.74 (dt, $J$ = 10 & 2 Hz, 1H), 7.21 (d, $J$ = 8 Hz, 2H), 7.30 (d, $J$ = 8 Hz, 2H).<br>**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 11.6, 20.8, 21.1, 24.0, 32.2, 41.5, 66.1, 126.1, 127.3, 129.1, 129.7, 138.6, 139.5, 168.7, 170.8, 173.0.<br>**Anal. Calcd for $C_{18}H_{21}NO_4$**: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.52; H, 6.76; N, 4.50. |

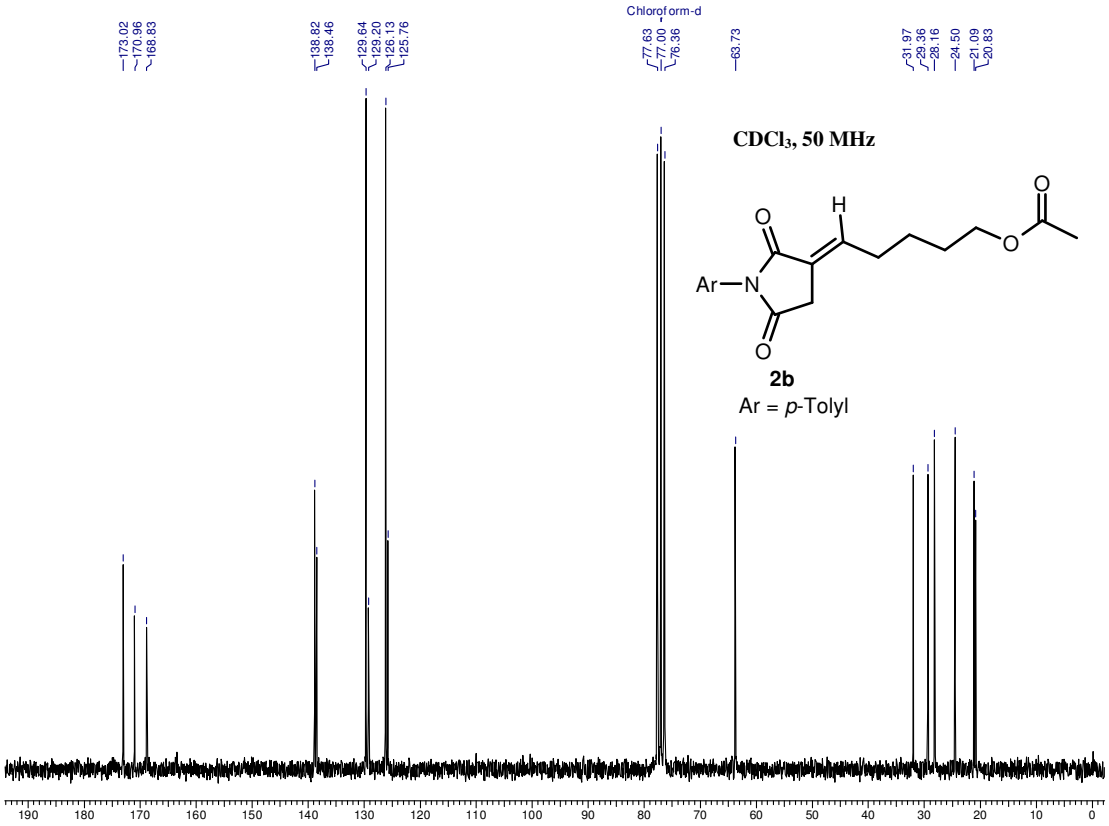
# 3D.5 Selected Spectra

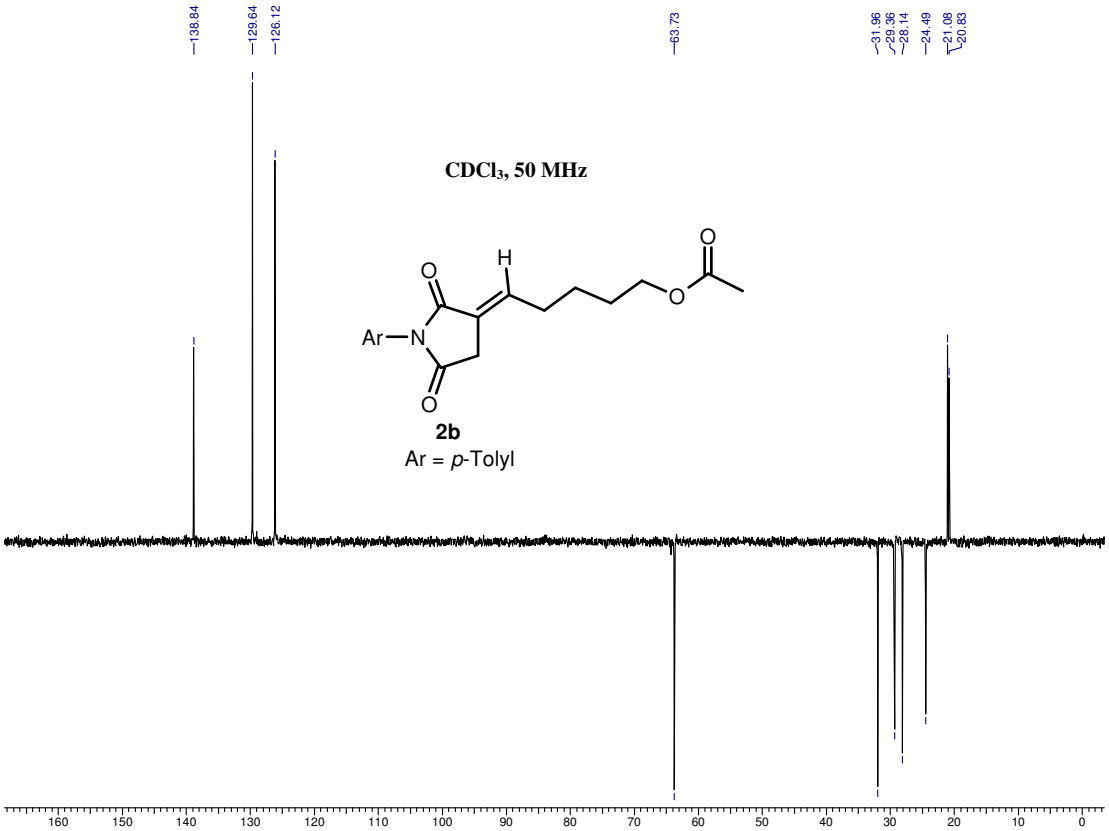

Chloroform-d
7.31
7.27
7.22
7.17
6.95
6.94
6.93
6.91
6.90
6.89
6.88
4.16
4.13
4.10
3.40
3.39
2.39
2.36
2.32
2.29
2.08
1.95
1.92
1.89
1.85
1.82
CDCl3, 200 MHz
H
O
O
Ar—N
O
O
2a
Ar = p-Tolyl
2.01
1.00
2.00
1.99
5.02
3.01
2.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

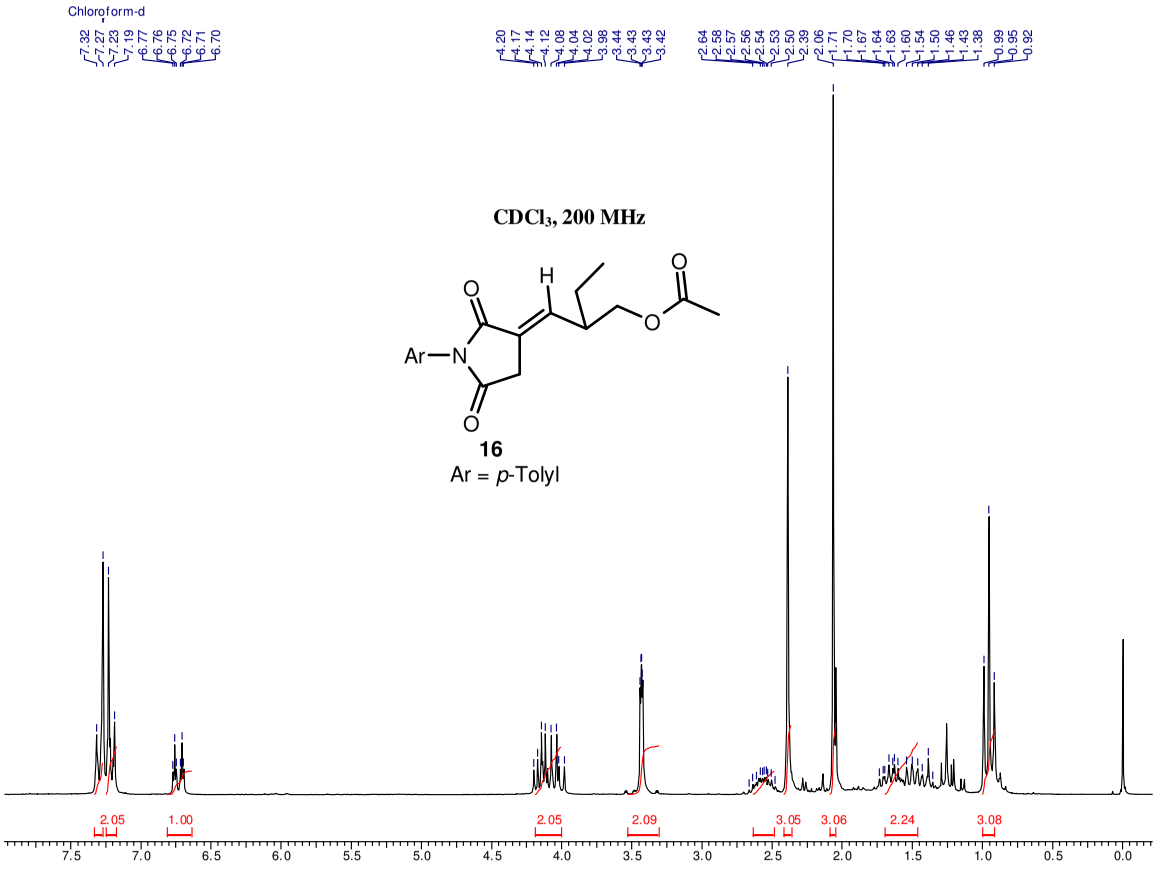

172.81
170.64
168.55
138.25
137.77
129.44
129.05
126.05
125.95
Chloroform-d
77.25
77.00
76.74
63.06
31.71
26.89
26.20
20.91
20.63
CDCl3, 125 MHz
H
O
O
Ar—N
O
O
2a
Ar = p-Tolyl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

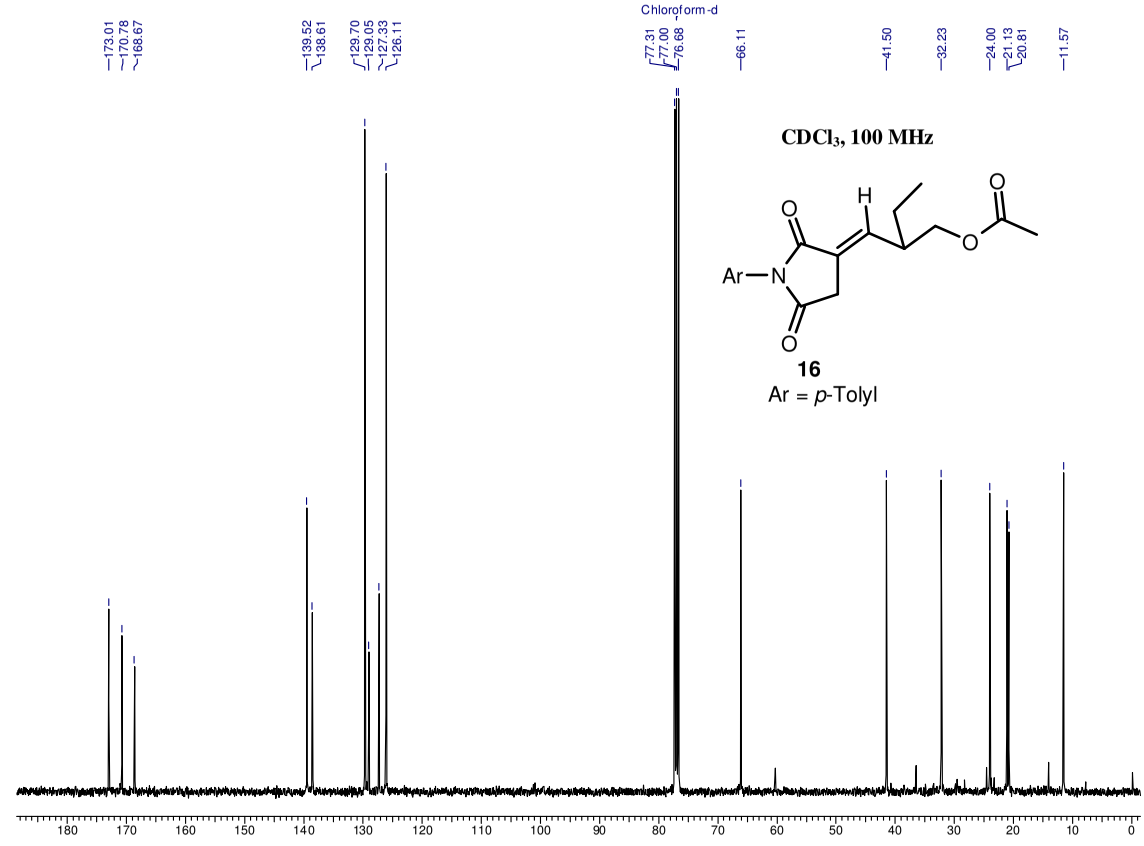

137.74
129.41
125.91
63.02
31.66
26.83
26.15
20.87
20.60
CDCl3, 125 MHz
Ar—N
O
H
O
O
O
2a
Ar = p-Tolyl

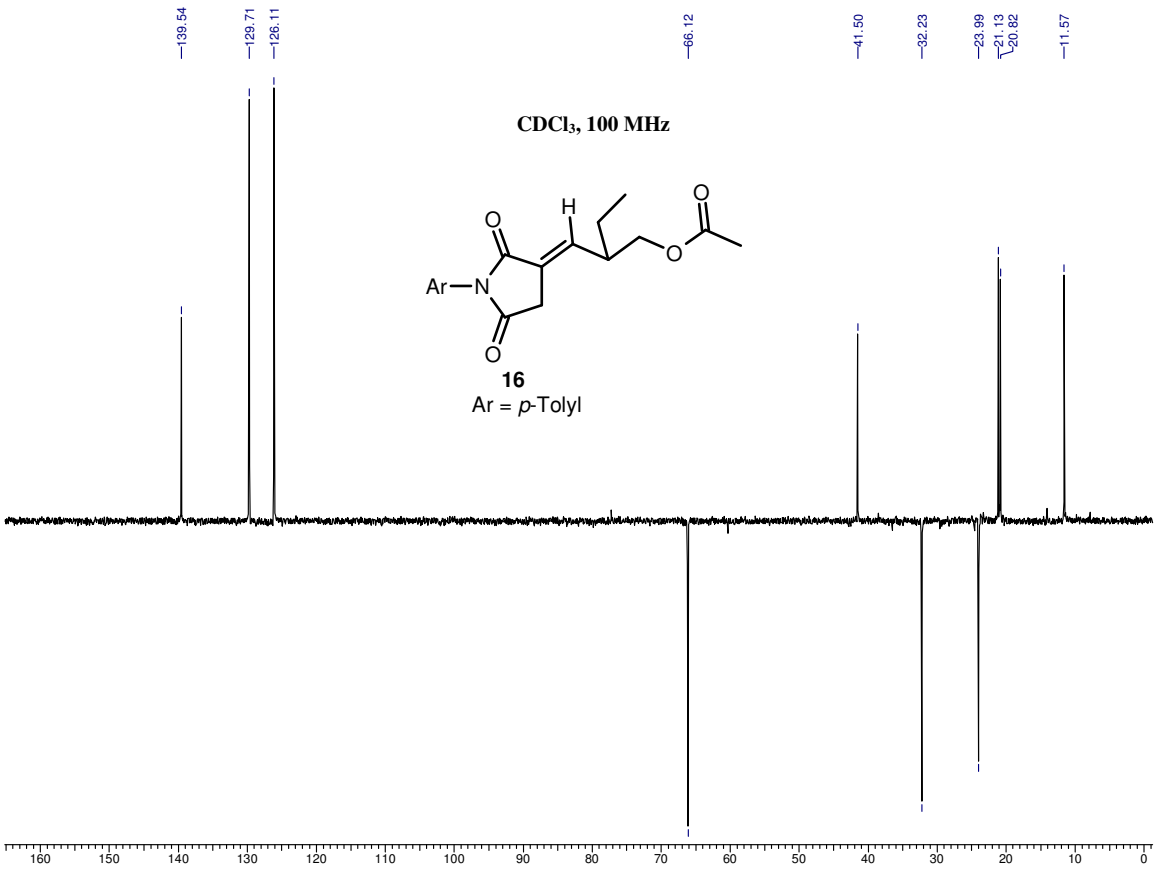

Chloroform-d
7.31
7.27
7.22
7.17
6.96
6.95
6.93
6.92
6.91
6.90
6.88
4.13
4.10
4.07
3.40
3.39
2.39
2.35
2.31
2.27
2.24
2.07
1.72
1.71
1.70
1.68
1.67
1.65
1.63
1.62
CDCl3, 200 MHz
Ar—N
O
H
O
O
O
2b
Ar = p-Tolyl
2.06
1.00
2.01
2.01
5.07
3.01
4.15


Chloroform-d
173.02
170.96
166.83
138.82
138.46
129.64
129.20
126.13
125.76
77.63
77.00
76.36
63.73
31.97
29.36
28.16
24.50
21.09
20.83
CDCl3, 50 MHz
Ar
N
O
H
2b
Ar = p-Tolyl


138.84
129.64
126.12
63.73
31.96
29.36
28.14
24.49
21.08
20.83
CDCl3, 50 MHz
Ar
N
O
H
2b
Ar = p-Tolyl


Chloroform-d
7.32
7.27
7.23
7.19
6.77
6.76
6.75
6.72
6.71
6.70
4.20
4.17
4.14
4.12
4.08
4.04
4.02
3.98
3.44
3.43
3.43
3.42
2.64
2.58
2.57
2.56
2.54
2.53
2.50
2.39
2.06
1.71
1.70
1.67
1.64
1.63
1.60
1.54
1.50
1.46
1.43
1.38
0.99
0.95
0.92
CDCl3, 200 MHz
H
O
O
Ar—N
O
O
16
Ar = p-Tolyl
2.05
1.00
2.05
2.09
3.05
3.06
2.24
3.08
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


173.01
170.78
168.67
139.52
138.61
129.70
129.05
127.33
126.11
Chloroform-d
77.31
77.00
76.68
66.11
41.50
32.23
24.00
21.13
20.81
11.57
CDCl3, 100 MHz
H
O
O
Ar—N
O
O
16
Ar = p-Tolyl
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


139.54
129.71
126.11
66.12
41.50
32.23
23.99
21.13
20.82
11.57
CDCl3, 100 MHz
Ar
N
O
H
O
O
O
16
Ar = p-Tolyl
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

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## 3E Section E: Overall Conclusions and Perspectives

*The present dissertation describes our studies on the synthesis of natural and unnatural dialkyl substituted maleic anhydrides and related natural products along with a concise account on the chemistry of monoalkyl substituted, dialkyl substituted and complex dialkyl substituted maleic anhydrides (nonadrides).*

*Isoimide has found wide range of applications in organic chemistry and pharmaceuticals. It is dissymmetric in nature and nucleophilic ring openings under neutral conditions are feasible. To explore the important field of isoimide, we developed a practical approach to exclusively design kinetically controlled N-aryl/N-alkyl isomaleimides and isophthalimides using readily available cyanuric chloride as a dehydrating agent. A number of alkylmethyl substituted maleic anhydrides such as chaetomellic anhydride A and B, aspergillus acids A-D, maleic anhydride segment of tautomycin and tyromycin A are known in the literature as bioactive natural products and several approaches to these natural products have been reported in the past decade. Very few methods are reported to synthesize dialkyl substituted maleic anhydrides compared to alkylmethyl substituted maleic anhydrides. We have described a general approach to alkylmaleimides and dialkylmaleimides via the two Wittig coupling reactions, taking the advantage for the first time of kinetically controlled isoimides as intermediates to enforce the difficult migration of exocyclic carbon-carbon double bonds to the endocyclic position. The present results will be of interest to chemists studying such type of exo-endo carbon-carbon double bond isomerization reactions. We have utilized this contrathermodynamic rearrangement in the synthesis of bioactive natural fimbrolides. Earlier approaches to bioactive natural products containing dialkyl substituted maleic anhydride unit are target oriented with some limitations. We have developed a general approach to natural and unnatural dialkylmaleic anhydrides also via the generation of a carbanion on the alkylidenesuccinmide core. We have explored this strategy in the total synthesis of bioactive natural products chaetomellic anhydride A, 2-carboxymethyl-3-hexylmaleic anhydride, 2-(ß-carboxyethyl)-3-hexylmaleic anhydride and formal synthesis of maculalactones A-C and nostoclide I. We have also described Wittig reaction of maleimide and triphenylphosphine adduct with*

*dihydrofuran/dihydropyran and our studies towards the synthesis of bioactive natural product byssochlamic acid.*

*In short, the chemistry of maleic anhydrides is highly useful from both basic and applied point of view. Monoalkylmaleic anhydrides, which promise to be versatile synthons, commend a lot of new synthetic endeavors. The tremendous bioactivity of dialkyl substituted maleic anhydride natural products has provided the impetus for newer synthetic approaches in spite of many earlier syntheses. The fascinating structure and remarkable bioactivity of nanadrides has spurred a lot of activity in synthetic community towards their total synthesis. It can be said with assurance that, this interesting field of maleic anhydride will spread wings wide over the organic and pharmaceutical chemistry with the bright future.*

## LIST OF PUBLICATIONS

1. Cyanuric chloride: decent dehydrating agent for an exclusive and efficient synthesis of kinetically controlled isomaleimides
   **Kishan P. Haval**, Santosh B. Mhaske and Narshinha P. Argade *Tetrahedron* **2006**, *62*, 937.
2. Haval-Argade contrathermodynamic rearrangement of alkylidenesuccinimide to alkylmaleimides via the corresponding isoimides: a general approach to alkyl and dialkyl substituted maleimides
   **Kishan P. Haval** and Narshinha P. Argade *Tetrahedron* **2006**, *62*, 3557.
3. Cyanuric chloride: Trichloro-1, 3, 5-triazine
   **Kishan P. Haval** *Synlett* **2006**, 2156.
4. Synthesis of natural fimbrolides
   **Kishan P. Haval** and Narshinha P. Argade *Synthesis* **2007**, 2198.
5. General strategy for the synthesis of natural and unnatural dialkylmaleic anhydrides
   **Kishan P. Haval** and Narshinha P. Argade *J. Org. Chem.* **2008**, *73*, 6936.

# Erratum