SELECTIVE CARBON–CARBON BOND FORMING REACTIONS WITH MALEIC ANHYDRIDES AND MALEIMIDES: FACILE SYNTHESIS OF BIOACTIVE NATURAL AND UNNATURAL PRODUCTS

THESIS

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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 "***Selective Carbon–Carbon Bond Forming Reactions With Maleic Anhydrides and Maleimides: Facile Synthesis of Bioactive Natural and Unnatural Products***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Prashant S. Deore*** 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.

December 2013
Pune

Dr. N. P. Argade
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Candidate's Declaration

I hereby declare that the research work incorporated in the thesis entitled "***Selective Carbon–Carbon Bond Forming Reactions With Maleic Anhydrides and Maleimides: Facile Synthesis of Bioactive Natural and Unnatural Products***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune***, has been carried out by me at the Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune, India, from January 2008 to December 2013 under the supervision of Dr. Narshinha P. Argade. This work has not been submitted in part or full by me for a degree or diploma to this or any other University or Institution.

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Let me take this opportunity to express my genuine gratitude and homage to my research supervisor Dr. N. P. Argade who introduced me into this fascinating empire of chemistry. His principles, discipline, simplicity, support, caring attitude and provision of fearless work environment will be cherished in all walks of my life. I am very much grateful to him for his valuable guidance, everlasting encouragement, supporting my attendance at various conferences, engaging me in new ideas, and demanding a high quality of work in all my endeavors. I am certain that his ethics and moral values which I learnt from him will go a long way in making me a better human being.

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I wish to express my gratitude towards "god-almighty", who gave me the strength and courage to fulfil my dream and has showered upon me his choicest blessings.

Prashant

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General Remarks

- All the solvents used were purified using the known literature procedures.
- Petroleum ether used in the experiments was of 60–80 °C boiling range.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether–ethyl acetate mixture, unless otherwise mentioned (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), bromocresol green (in ethanol) and phosphomolybdic acid (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (concentration 0.05 to 10%) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker and Jeol ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), ACF 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethyl silane.
- Mass spectra were taken on MS-TOF mass spectrometer.
- HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer.
- Microanalysis data were obtained using Flash EA 1112 series and Elementar Vario EL analyser.
- 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 IR and NMR spectra as well as melting point 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.

Abbreviations

Å	Angstrom
Ac	Acetyl
Aq.	Aqueous
AIBN	2,2'-Azobisisobutyronitrile
BINAP	2,2'-Bis(diphenylphosphino)1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
cat.	Catalytic
CDI	1,1'-Carbonyldiimidazole
DBP	Dibenzoyl peroxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEIPS	Diethylisopropylsilyl
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropyl ethyl amine
DMA	*N*,*N*-Dimethylacetamide
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMDO	3,3-Dimethyldioxirane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMMA	Dimethylmaleic anhydride
DMP	Dess-Martin periodinane
DMPM	3,4-Dimethoxybenzyl
DMSO	Dimethyl sulphoxide
dr	Diastereomeric ratio
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride
ee	Enantiomeric excess
ESI	Electro spray ionization
EI	Electron impact
equiv	Equivalent
h	Hour(s)
HMDS	1,1,1,3,3,3-hexamethydisilazane
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectra
HPLC	High performance liquid chromatography
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IC	Inhibitory concentration
Im	Imidazole

IR	Infra Red
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m-CPBA	*m*-Chloroperbenzoic acid
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
Morph.HCl	Morpholine hydrochloride
Mp	Melting point
MS	Mass Spectrum
Ms	Methanesulfonyl (mesyl)
MsCl	Methanesulfonyl chloride (mesyl chloride)
MS-TOF	Time-of-flight mass spectrometry
MW	Microwave
NaH	Sodium hydride
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NBSH	2-Nitrobenzenesulfonylhydrazide
NCS	*N*-Chlorosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
PAF	Platelet-activating factor
PCC	Pyridinium chlorochromate
PCy_3	Tricyclohexylphosphine
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
PE	Petroleum ether
p-TSA/*p*-TSOH	*p*-Toluenesulfonic acid
p-TsCl	*p*-Toluenesulfonyl chloride
Py	Pyridine
RFTase	Ras farnesyl-protein transferase
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide (*t*-BuOOH)
TES	Triethylsilyl
TESOTf	Triethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPP	Triphenylphosphine (PPh_3)
UV	Ultraviolet

Abstract

The maleic anhydride is an important functionality in chemistry from both basic and applied point of view. Large number of structurally fascinating maleic anhydride based architectures with wide range of biological properties has been known in the literature and a few have been depicted in Figure 1. In the present dissertation work we selected some of the target compounds and synthesized them by performing highly selective carbon–carbon bond forming reactions (Figure 2).

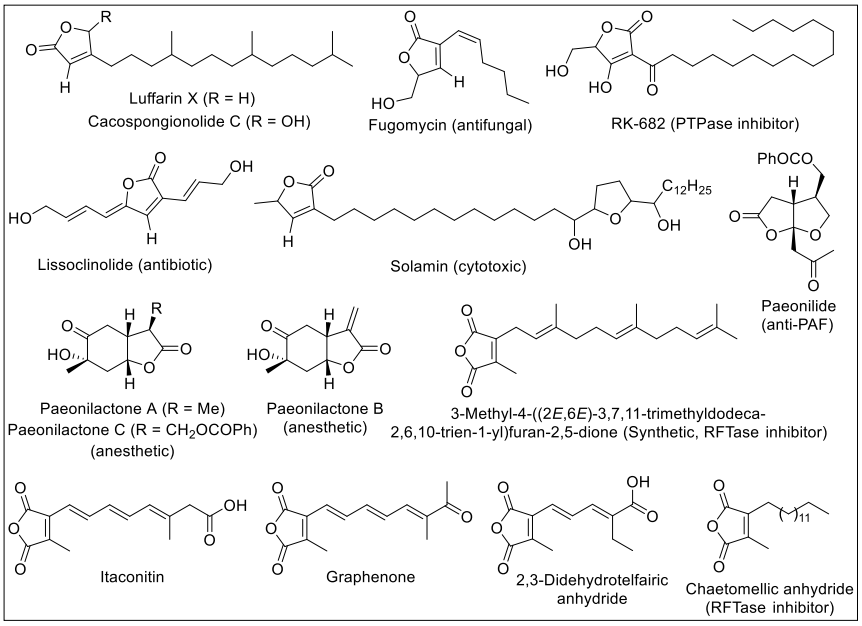


Figure 1. Naturally occurring bioactive compounds.

The present dissertation work is divided into three chapters, wherein applications of cyclic anhydrides and derivatives for the synthesis of structurally interesting and biologically important natural and unnatural products have been presented in details. The section A of first chapter presents a concise literature account on the metal catalyzed cross coupling reactions of halomaleic anhydrides and imides. Our contribution on the Sonogashira coupling reactions of halomaleimides and their applications in natural product synthesis has been presented in section B. The section A of second chapter presents a concise literature account on isolation, characterization, activity and reported syntheses of natural product paeonilide. The section B presents our diastereoselective total synthesis of paeonilide. The section A of third chapter presents a concise literature account on the synthesis of structurally related bioactive

alkyl(methyl)maleic anhydrides. The present dissertation work on total synthesis of natural product 2,3-didehydrotelfairic anhydride and unnatural conjugative alkenyl(methyl)maleic anhydrides have been presented in section B.

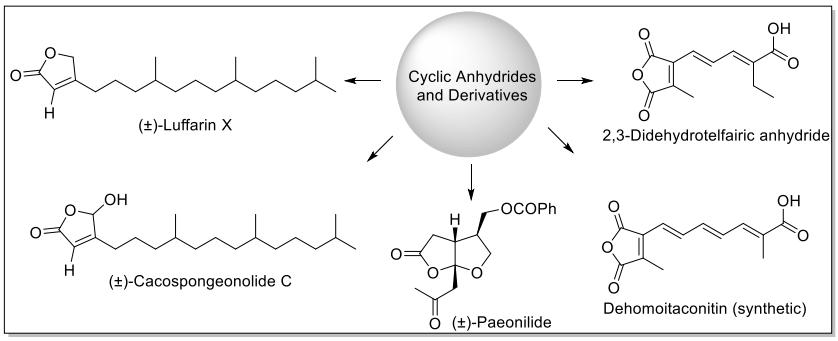


Figure 2. Natural and unnatural bioactive compounds synthesized.

Notes: (i) An independent figure, table, scheme, structure and reference numbers have been used for the each section of all chapters, (ii) complete experimental procedures and tabulated analytical and spectral data have been presented at the end of section B of each chapter and (iii) selected ^{1}H and ^{13}C NMR spectra have been included at the end of each chapter.

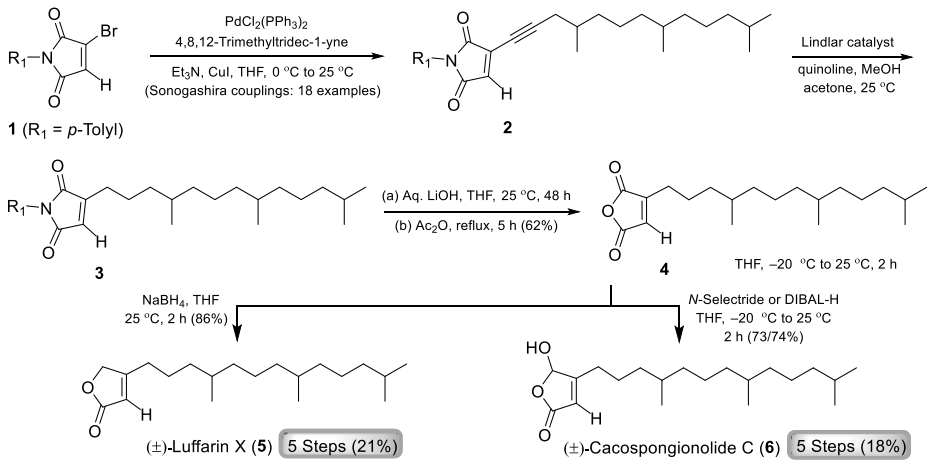
<u>Chapter One</u>: Metal Catalyzed Cross Coupling Reactions of Halomaleimides: Synthesis of Bioactive Natural and Unnatural Products

<u>Section A</u>: A brief review on metal catalyzed cross coupling reactions of halogen substituted maleic anhydrides and maleimides

A concise summary of literature account on metal-catalyzed cross coupling reactions of halogen substituted maleic anhydrides and imides has been presented.

<u>Section B</u>: Sonogashira coupling reactions of halomaleimides: route to alkyne/(*cis*)-alkene/alkyl maleimides: total synthesis of luffarin X and cacospongionolide C

Palladium-catalyzed Sonogashira coupling reaction of bromomaleimides and iodomaleimides with diverse range of terminal alkynes has been demonstrated to furnish the corresponding alkynylmaleimides in very good yields. The coupling reaction followed by selective reduction of carbon–carbon triple bond to single bond have been utilized as the decisive steps to accomplish the first total synthesis of two structurally similar natural products. The regioselective $NaBH_4$ and DIBAL reduction of alkylmaleic anhydride **4** respectively furnished (±)-luffarin X and (±)-cacospongionolide C (Scheme 1).



Scheme 1. Sonogashira Coupling Reactions of Bromomaleimides: Synthesis of Luffarin X and Cacospongionolide C

Overall, we have demonstrated a new general approach to alkyne/alkene/alkyl substituted maleimides/anhydrides by performing the palladium-catalyzed Sonogashira coupling reactions on the multifunctional bromomaleimides with a variety of terminal alkynes using CuI as the co-catalyst. The present Sonogashira coupling reactions of bromomaleimides and the chemo- and regioselective reductions are of general interest.

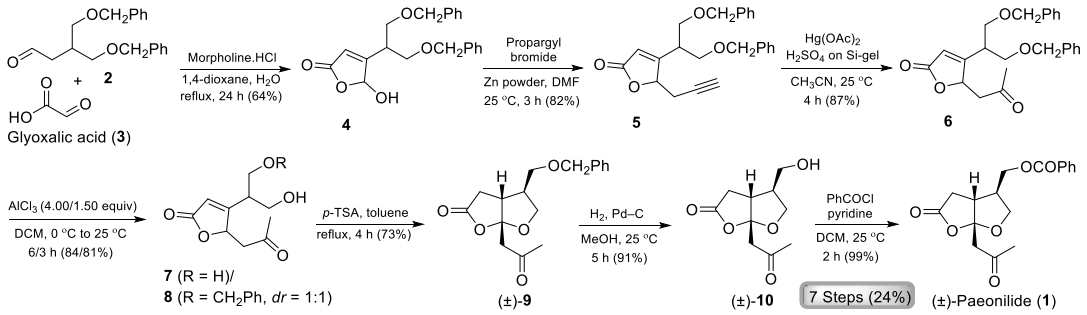
Chapter Two: Diastereoselective Total Synthesis of Paeonilide

Section A: A concise literature account of paeonilide

To date, two racemic and two stereoselective total synthesis of naturally occurring paeonilide have been reported in the literature by employing new carbon–carbon/oxygen bond forming strategies. A concise schematic summary of all four syntheses has been presented.

Section B: Reactivity umpolung in intramolecular ring closure of 3,4-disubstituted butenolides: diastereoselective total synthesis of paeonilide

Remarkable reactivity reversal stratagem in 3,4-disubstituted butenolides under acidic conditions is described. Design of suitably substituted multifunctional butenolide followed by an acid catalyzed chemo- and diastereoselective intramolecular ring closure via the reactivity umpolung has been demonstrated to accomplish a concise total synthesis of paeonilide (Scheme 1). The present protocol involves one-pot reduction of α,β-unsaturated carbon–carbon double bond and intramolecular nucleophilic insertion of oxygen function at the electron rich γ-position of butenolide.



Scheme 1. A Concise Diastereoselective Total Synthesis of (±)-Paeonilide via Reactivity Umpolung

Overall, we have demonstrated a novel reactivity umpolung in 3,4-disubstituted butenolides and accomplished the diastereoselctive total synthesis of paeonilide via an unusual carbon–carbon double bond isomerization and formation of oxocarbenium intermediate. The observed chemo- and diastereoselctivity in the intramolecular cyclization leading to a paeonilide is noteworthy from basic chemistry point of view. The reactivity umpolung process involves insertion of oxygen function at the electron rich γ-carbon and reduction of internal unsaturated carbon–carbon double bond in absence of metal-hydrogen/metal hydride. The involved mechanistic aspects have been also discussed in brief. We feel that the enzymatic *meso*-desymmetrization will also provide an access to the corresponding enantiomerically pure forms of paeonilide and the present convergent access to fused furofuran systems has a broad scope. We believe that our present redox protocol will also work equally well to plan the corresponding furopyran based structural architectures. Finally, the present reactivity umpolung opens a new avenue in the significant field of butenolide chemistry.

<u>Chapter Three</u>: Synthesis of Natural and Unnatural Conjugative Alkenyl(methyl)maleic Anhydrides

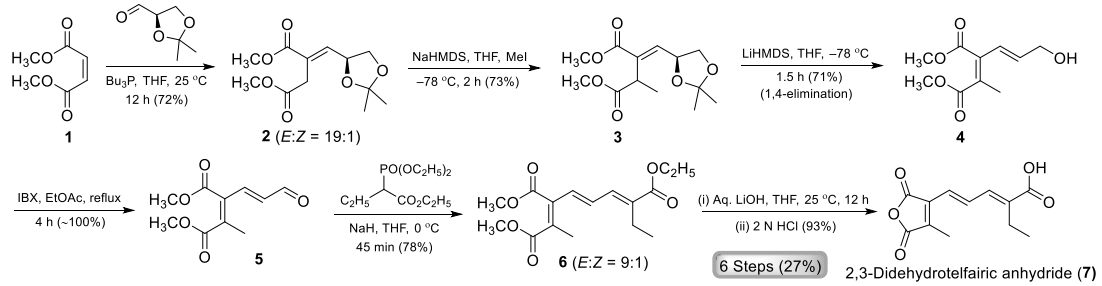
<u>Section A</u>: A concise literature account on the reported syntheses of naturally occurring alkyl(methyl)maleic anhydrides

Till date several new approaches to imperious dialkyl substituted maleic anhydrides/imides have been reported in the contemporary literature. A concise literature account of the same has been presented in schematic and tabular form.

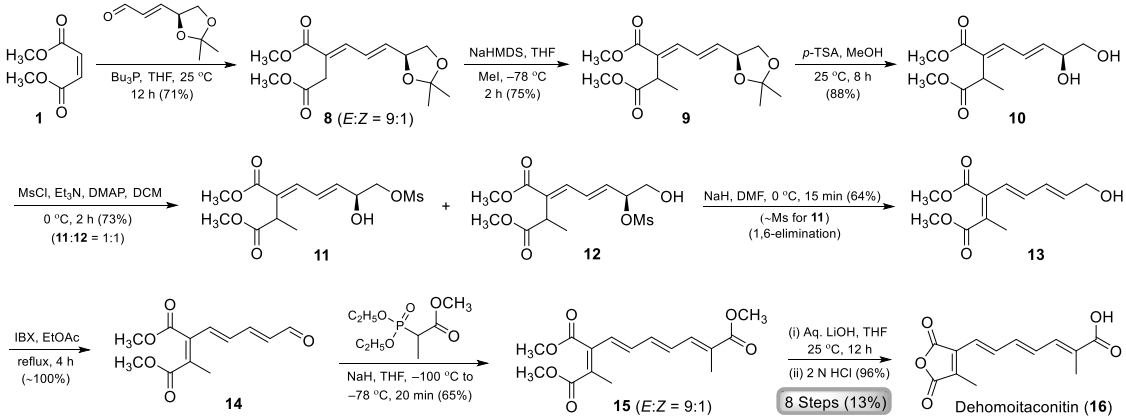
<u>Section B</u>: Base stimulated novel 1,4- and 1,6-eliminations in alkylidenesuccinates: stereoselective total synthesis of natural and unnatural conjugative alkenyl(methyl)maleic anhydrides

Starting from dimethyl maleate, facile synthesis of sensitive natural and unnatural conjugative alkenyl(methyl)maleic anhydrides have been described in search of effective RFTase inhibitors

(Schemes 1 and 2). The involved key reactions were base endorsed 1,4- and 1,6-eliminations in the corresponding alkylidenesuccinate derivatives. The characteristic 1,4- and 1,6-elimination reactions with respective release of acetone and mesylate furnished the unsaturated alcohols. The obtained alcohols were transformed into conjugative alkenyl(methyl)maleic anhydrides via HWE reactions pathway, utilizing their corresponding unsaturated aldehydes as the building blocks.



Scheme 1. Synthesis of Naturally Occurring 2,3-Didehydrotelfairic Anhydride and Unnatural Dehomoitaconitin



Scheme 2. Base Induced 1,6-Elimination: Synthesis of Dehomoitaconitin

We have demonstrated distinguishing conjugative 1,4- and 1,6-elimination progressions in alkylidenesuccinates to design first unique approach to naturally occurring 2,3-didehydrotelfairic anhydride and unnatural dehomoitaconitin. The described base promoted 1,4-elimination of acetone with the cleavage of a cyclic ketal moiety and the well-ordered 1,6-elimination of distantly placed mesylate are noteworthy from basic chemistry point of view. The anti-migration of formed carbanionic species in α,β-unsaturated and $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl systems in 1,4- and 1,6-elimination processes are momentous and thermodynamically favourable for stability reasons. The involved mechanistic aspects in these imperative elimination reactions have been also described in brief. We feel that these esteemed pigments will find several potential applications in the field of science.

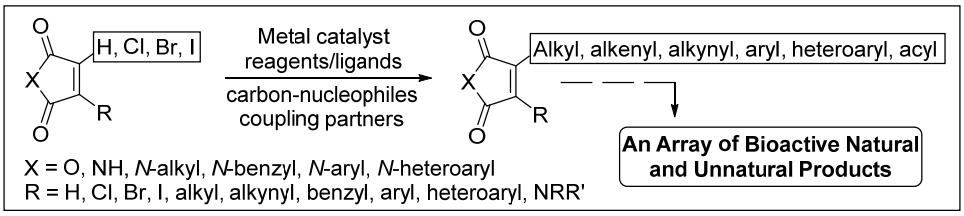
CHAPTER 1

Metal Catalyzed Cross-Coupling Reactions of Halomaleimides: Synthesis of Bioactive Natural and Unnatural Products

This chapter features the following topics:

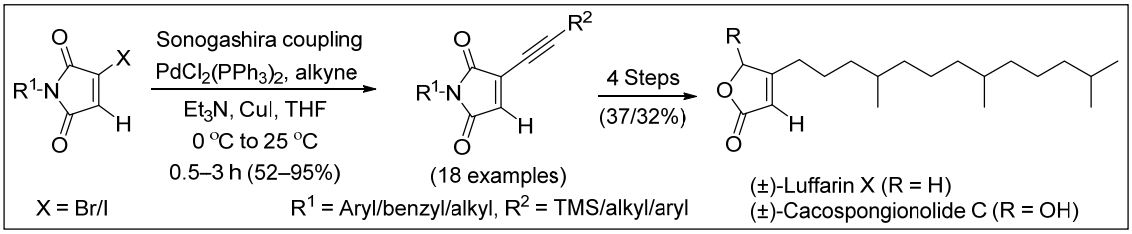
Notes: (i) An independent figure, table, scheme, structure and reference numbers have been used for the each section, (ii) detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end part of section B.

This chapter is divided into two sections. The section A presents a concise literature account on the metal catalyzed cross-coupling reactions of halomaleic anhydrides and haloimides. The overall summary of metal catalyzed exchange of vinylic leaving group by carbon-nucleophiles or coupling partner has been portrayed in Scheme 1.



Scheme 1. Cross-Coupling Reactions of Halomaleic Anhydrides/Imides Leading to Bioactive Natural Products

The section B describes our contribution on the Sonogashira coupling reactions of halomaleimides and their applications in natural product synthesis. Palladium-catalyzed Sonogashira coupling reaction of bromomaleimides with a diverse range of terminal alkynes has been demonstrated to furnish the corresponding alkynylmaleimides in very good yields. This coupling reaction followed by selective reduction of the triple bond to single bond have been utilized as the decisive steps to accomplish the first total synthesis of natural products (±)-luffarin X and (±)-cacospongionolide C (Scheme 2).



Scheme 2. Sonogashira Reactions of Halomaleimides: Synthesis of Luffarin X and Cacospongionolide C

CHAPTER 1: SECTION A

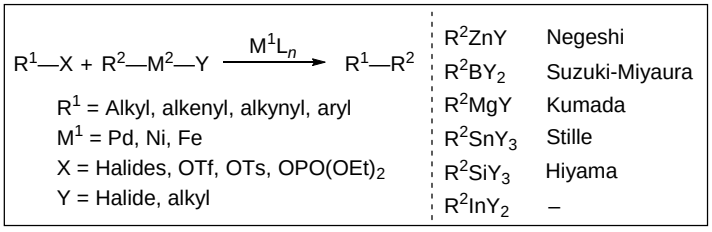
A Brief Review on Metal Catalyzed Cross-Coupling Reactions of Halogen Substituted Maleic Anhydrides and Maleimides

This section A of chapter 1 features the following topics:

1A.1 Introduction

Maleic anhydrides, maleimides and their derivatives are the potential building blocks and their nucleophilic reactions belong to the foundations of organic chemistry. In the past few decades, cyclic anhydrides and derivatives chemistry has experienced a revitalization not only due to its occurrence in molecules in the frontiers of organic chemistry such as medicinal chemistry, material sciences and polymer chemistry, but also as building blocks and versatile intermediates for the total synthesis of a vast array of structurally interesting bioactive natural and unnatural compounds.[1] The selective insertion of carbon nucleophiles at one of the four possible sites in maleic anhydrides/imides and more specifically the S_NV reactions are imperative from basic and applied point of view. The boost to maleic anhydride/imide chemistry has been stimulated mainly by the development of new synthetic methodologies based on transition metal catalysis, a field where palladium always occupies a central position.

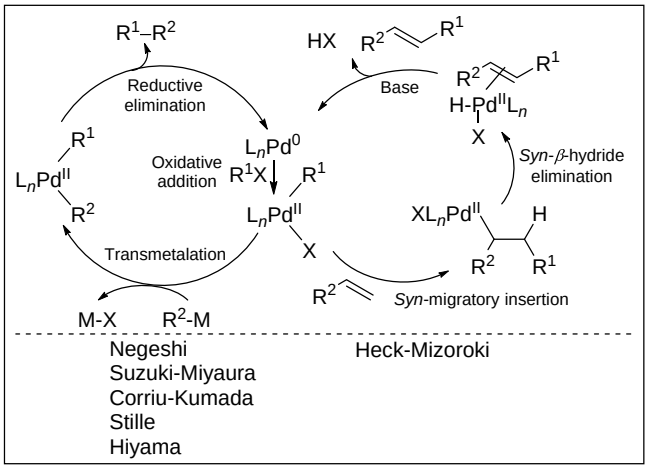
The 2010 Nobel Prize in Chemistry for Pd-catalyzed cross-coupling reactions was one of the most highly anticipated awards within the synthetic organic and organometallic chemist's community.[2] The substitution of an aryl, vinyl, alkyl halides and pseudohalides by a nucleophile that takes place with catalysis by forming transition-metal complex is generally referred as a cross-coupling reaction following the mechanistic course of oxidative addition, transmetalation and reductive elimination. Many types of cross-coupling reactions have been known for past several decades and the advances in recent years have greatly increased their scope and practicality (Scheme 1).[3] This progress has a significant impact on both academic and industrial research. Cross-coupling reactions are now widely employed in a variety of synthetic venues from total synthesis of natural products to the preparation of new materials for bioorganic chemistry.[4] Thus the cross-coupling reactions have shown remarkable impact on pharmaceuticals, agrochemicals and polymers industries.



Scheme 1. General Representation of Named Metal Catalyzed Cross-Coupling Reactions

Selection of an appropriate ligand plays a vital role and now these palladium and other transition metal-catalyzed processes have become part of the everyday repertoire of the

synthetic chemist's. One common group of these processes utilizes carbon-based nucleophiles, such as aryl, vinyl and alkyl derivatives of magnesium (Kumada-Corriu), boron (Suzuki-Miyaura), tin (Stille-Migita), zinc (Negishi) and silicon (Hiyama). In another very important cross-coupling process, a terminal alkyne serves as a pronucleophile in the presence (Sonogashira) or absence (Heck alkynylation) of a copper co-catalyst. In both sets of cross-couplings, the catalysts that are utilized most frequently have been palladium-based. Only recently the electrophilic component of these processes has been extended to alkyl halides and pseudohalides. These substrates can now be coupled with aryl, vinyl and alkynyl nucleophiles. Moreover, a great deal of progress has been made in the area of palladium- and copper-catalyzed carbon–carbon/heteroatom bond forming reactions. Furthermore, a tremendous upsurge in the development of new ligands has contributed substantially to the recent advances, specifically in the reaction conditions and yields.



Scheme 2. Catalytic Cycles for Pd-Catalyzed Cross-Coupling Reactions

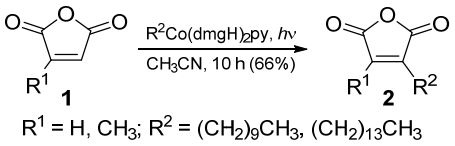
The general mechanistic progressions for these palladium-catalyzed cross-coupling reactions have been depicted in Scheme 2.[5] The common step for both types of coupling reactions is the oxidative addition of aryl halide (or pseudohalide) to the catalytically active L_nPd^0 species which initiates the catalytic cycle. At this stage the processes diverge. In Mizoroki-Heck coupling, the reaction progresses by co-ordination of an alkene to the Pd^{II} species, followed by its *syn* migratory insertion. The regioselectivity of this insertion depends on the nature of alkene, catalyst and reaction conditions employed. The newly generated organopalladium species then undergo *syn* β-hydride elimination to form the alkene product. For steric reasons, the bulky group tends to eclipse the smallest group on an adjacent carbon during the course of elimination process, predominantly forming to a *trans* product. Subsequently, base-assisted

elimination of H–X from [$L_nPd(H)(X)$] occurs to regenerate the L_nPd^0 catalyst (typically n = 2). Alternatively, in the Negishi and Suzuki-Miyaura reactions and in the related Corriu-Kumada, Stille, and Hiyama coupling processes, the oxidative addition is followed by transmetalation of an organometallic species to generate a Pd^{II} intermediate bearing the two organic coupling partner fragments. Subsequent reductive elimination results in carbon–carbon bond formation with the regeneration of Pd^0 species to re-enter into the catalytic cycle. The issue of selectivity in cross-coupling reactions is of decisive significance, since a number of possible side reactions viz. homocoupling, isomerization, β-hydride elimination and functional group interferences need to be addressed to develop a general practical method for significant applications in organic synthesis.

1A.2 Recent Methodologies for the Transition Metal Catalyzed Cross-Coupling Reactions of Maleic Anhydrides and Maleimides

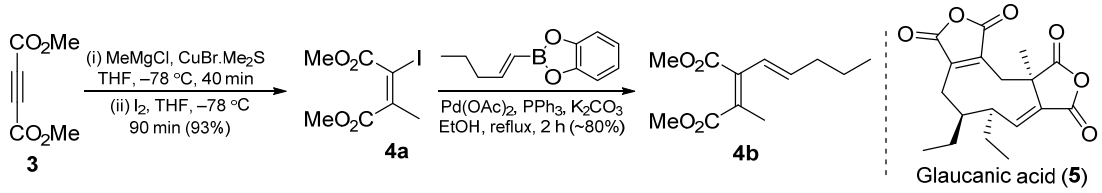
The maleic anhydrides and corresponding imides are sensitive functionalities and performing the chemo-, regio- and stereoselective organometallic coupling reactions on them with an intact preservation of both the carbonyl groups is a challenging task. In the present section, we have described a concise literature account on transition metal catalyzed cross-coupling reactions of halogenated maleic anhydrides and maleimides with an emphasis on new synthetic routes and strategies. Related representative examples have been chosen for this purpose. Since large amount of relevant data is available in the literature, no pretension of completeness has been claimed.

Branchaud and co-workers in their basic studies on photochemical cross-coupling of alkyl cobaloximes with maleic anhydrides and PhSSPh observed stereoselective addition of an alkyl moiety and a -SPh moiety across the carbon–carbon double bond.[6a] The *m*-CPBA oxidation of sulfide to a sulfoxide followed by elimination of phenylsulfenic acid provided corresponding substituted maleic anhydrides. Alternatively, they coupled the alkyl cobaloximes with maleic anhydrides **1** in the absence of PhSSPh to directly yield the substituted maleic anhydrides **2**. This radical approach was applied to accomplish short and efficient synthesis of the naturally occurring potent ras-farnesyl protein transferase inhibitor chaetomellic anhydride A[6b] and also in preparations of *C*-glycosyl maleic anhydrides (Scheme 3). The yields of these reactions were highly solvent dependant.



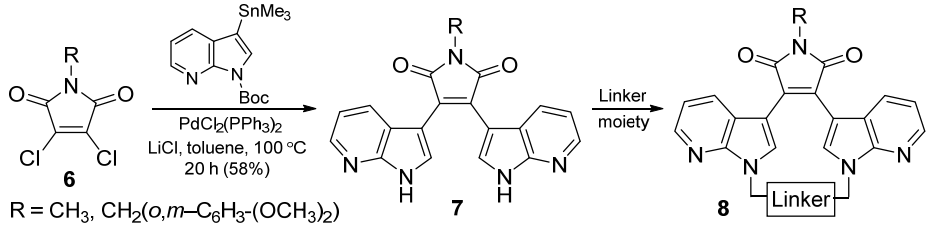
Scheme 3. Cross-Coupling Reactions of Alkyl Cobaloximes with Maleic Anhydrides

Baldwin's research group prepared the glaucanic acid analogue precursor **4b**. Reaction of an alkyl Grignard reagent with DMAD (**3**) in the presence of CuBr.Me_2S followed by an in situ quenching with iodine in THF at –78 °C stereoselectively formed the tetrasubstituted *cis*-iodoalkene **4a**. It was then successfully transformed into the desired product **4b** by using Suzuki cross-coupling reaction with (*E*)-pent-1-enyl benzodioxaborole (Scheme 4).[7]



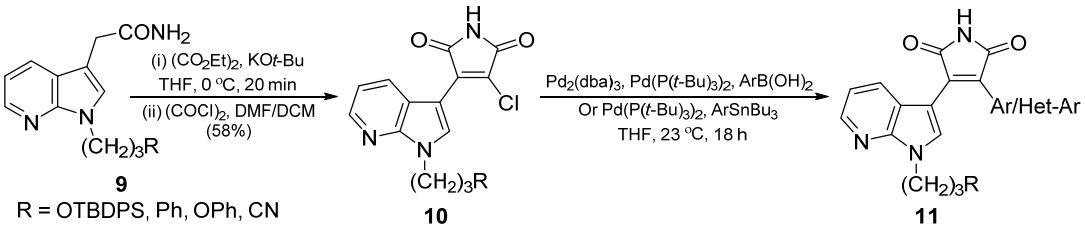
Scheme 4. Synthesis of Glaucanic Acid Precursor via Suzuki Coupling Reaction

Kuo and co-workers utilized the Pd-catalyzed cross-coupling reaction of dichloromaleimide **6** with *t*-butyl 3-(trimethylstannyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate to prepare a multifunctional key intermediate **7** for the synthesis of novel series of macrocyclic bis-7-azaindolylmaleimides **8** (Scheme 5).[8]



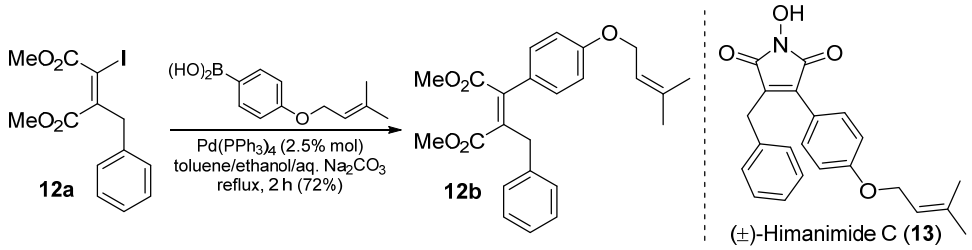
Scheme 5. Synthesis of Macrocyclic Bis-7-azaindolylmaleimides with Stille Coupling Reaction

Kuo and co-workers also developed two more approaches to synthesize the novel 7-azaindolyl-heteroarylmaleimides **11**.[9] As shown in Scheme 6, the first approach was based upon the Pd-catalyzed Suzuki cross-couplings or Stille cross-couplings of chloromaleimide **10** with various arylboronic acids or arylstannanes to obtain compounds **11** in moderate to good yields. The second approach was based upon the condensation of ethyl 7-azaindolyl-3-glyoxylate with various acetamides. Many synthesized compounds demonstrated a high potency at GSK-3b, good GS activity in HEK293 cells and good to excellent metabolic stability in human liver microsomes.



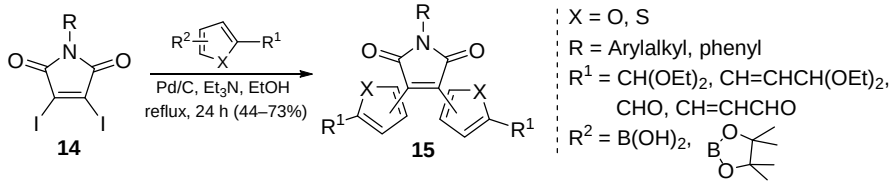
Scheme 6. Synthesis of 7-Azaindolylheteroaryl Maleimides Employing Two Different Cross-Coupling Reactions

Patrice Sellès has investigated Suzuki cross-coupling reactions of various aryl boronic acids with tetrasubstituted iodoalkenes. The obtained product **12b** from iodoalkene **12a** has been further utilized for the synthesis of natural product himanimide C (**13**) via the saponification–cyclization–amide formation sequence (Scheme 7).[10]



Scheme 7. Suzuki Cross-Coupling Reactions of Tetrasubstituted Iodoalkene Diester

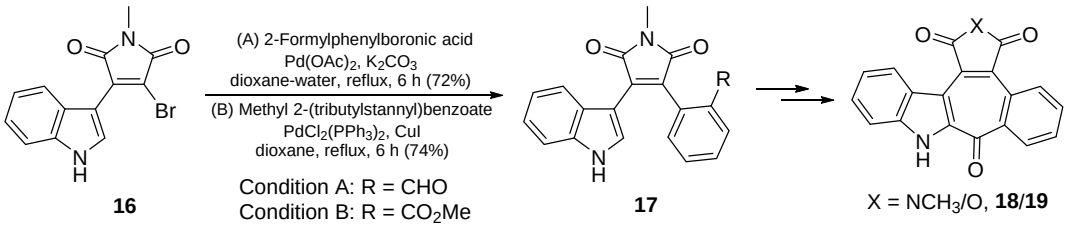
Viaud-Massuard and co-workers have developed a new method based on Suzuki cross-coupling reactions between various organoboron derivatives and the diiodomaleimides **14** to synthesize broad range of symmetrically and unsymmetrically substituted bis(fur-2-yl), bis(fur-3-yl) and bis(thien-2-yl) maleimides **15** having potential antidiabetic properties (Scheme 8).[11]



Scheme 8. Synthesis of Substituted Bis(heteroaryl)maleimides by Suzuki Coupling Reaction

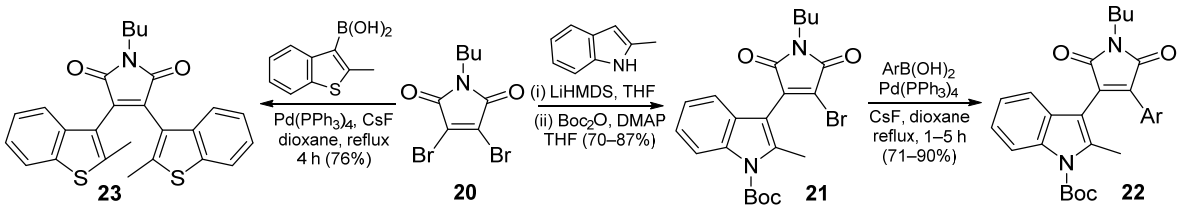
Routier and co-workers have described two different ways for the synthesis of oxophenylarcyriaflavins.[12] As demonstrated in Scheme 9, the key steps involved were Pd-catalyzed cross-coupling between the 3-bromo-4-(1*H*-indol-3-yl)1-methylpyrrole-2,5-dione (**16**) and the 2-formylphenylboronic acid or a methyl 2-trialkylstannylbenzoate. It was followed by an intramolecular acylation at *C*-2 indolic position to form the heterocyclic systems. Suzuki reaction led to imide **18** in 52% overall yield whereas the Stille reaction afforded anhydride **19**

in 51% global yield. It is noteworthy that the sequence was carried out without any indolic protective group.



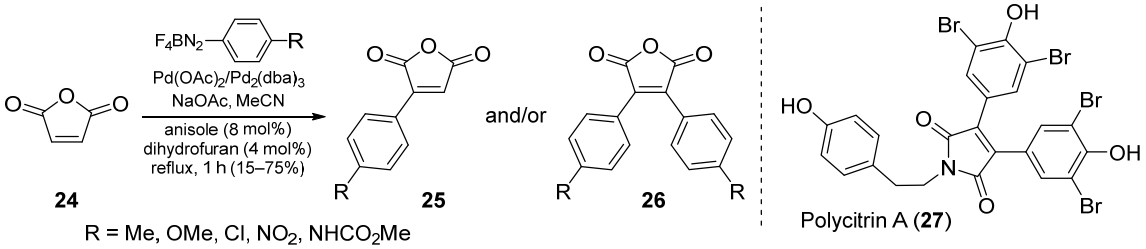
Scheme 9. Synthesis of Oxophenyl-Arcyriaflavin Analogs Using Two Organometallic Coupling Reactions

Krayushkin, Irie and co-workers reported a nice approach for the synthesis of 3,4-diaryl(or hetaryl)maleimides **22** and **23** by using Suzuki cross-coupling of *N*-butyl 3,4-dibromomaleimide (**20**) with aryl(hetaryl)boronic acids in the presence of $Pd(Ph_3P)_4$ and CsF (Scheme 10).[13] The unsymmetrically substituted maleimides and maleic anhydrides having an indole fragment were also synthesized in high yield.



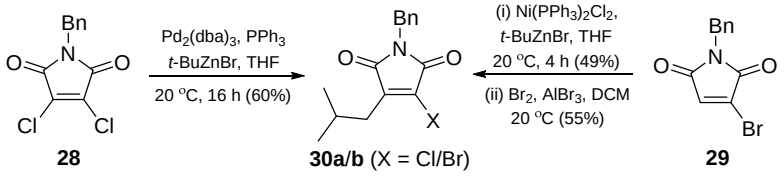
Scheme 10. Synthesis of 3,4-Diaryl(hetaryl) Substituted Maleimides via Suzuki Cross-Coupling Reactions

Correia and co-workers demonstrated the Heck arylation of maleic anhydride (**24**) using arenediazonium tetrafluoroborates for the synthesis of symmetrical and unsymmetrical arylmaleic anhydrides and their derivatives (Scheme 11). The method was successfully applied for the total synthesis of marine alkaloid polycitrin A.[14]

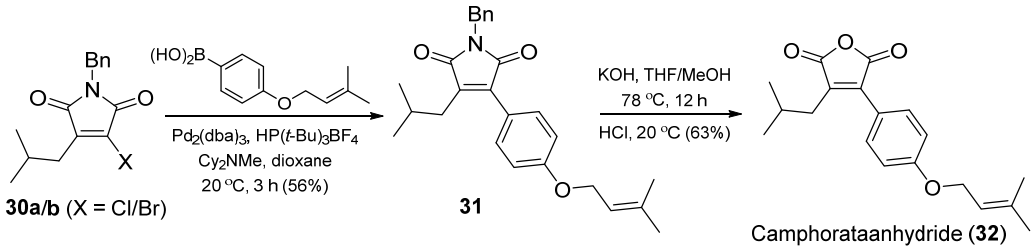


Scheme 11. Heck Arylation of Maleic Anhydrides Using Arenediazonium Tetrafluoroborates

Stewart et al described applications of Negishi and Suzuki reactions as the key steps for synthesis of camphorataanhydride (**32**) and related maleimide based natural products from the mushroom *Antrodia camphorata* (Schemes 12 and 13).[15] The present approach provides concise and efficient access to these bioactive natural products.

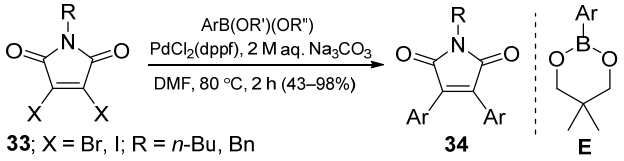


Scheme 12. Negishi Cross-Coupling of Halomaleimides



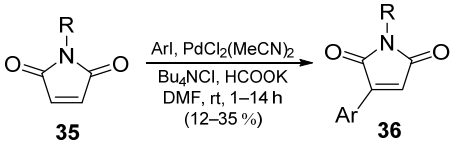
Scheme 13. Application of Suzuki Cross-Coupling in Natural Product Synthesis

Heynderickx and co-workers developed a method for the synthesis of symmetrical or unsymmetrical bis(heteroaryl)maleimides by using a one-pot approach involving Suzuki-Miyaura cross-coupling sequence.[16] The reaction of halomaleimides **33** with a large number of commercial boronic acids and esters using $PdCl_2$(dppf) as catalyst provided the corresponding bis(heteroaryl)maleimides **34** in very good yields (Scheme 14). The reaction success was highly dependent on the protection of unstable boronic acids in the form of cyclic boronate esters **E**.



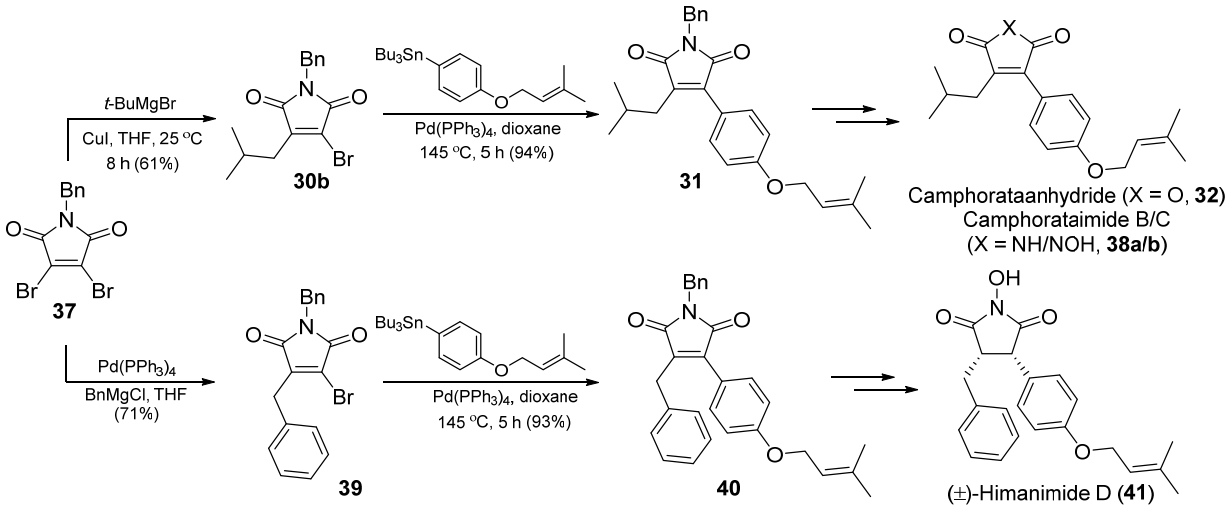
Scheme 14. Suzuki-Miyaura Cross-Coupling of Dihalomaleimides and Arylboronic Acid/Ester

Roshchin and Polunin performed the Heck reaction of maleimides **35** with aryl iodides in the presence of $PdCl_2(MeCN)_2$, Bu_4NCl and HCOOK to afford the corresponding 2-arylmaleimides **36** in moderate yields (Scheme 15).[17] This organometallic approach provides simple and efficient one-step access to a variety of arylmaleimides.



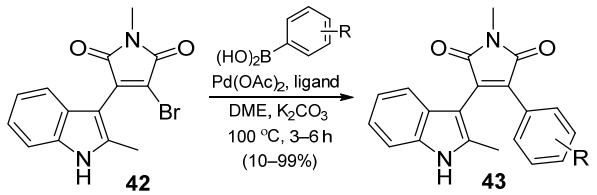
Scheme 15. Heck Arylation of Maleimides

Lee and co-workers have verified the usefulness of the Stille coupling reaction and Zn/AcOH mediated stereoselective reduction reaction for synthesis of (±)-*cis*-himanimide D (**41**).[18] The *cis* orientation of an aryl and benzyl groups in product is remarkable from stability and structural point of view. This protocol was also nicely extended for the total synthesis of natural products from *Antrodia camphorata*, camphorataanhydride (**32**) and camphorataimide B, C (**38a**,**b)** (Scheme 16).



Scheme 16. Total Synthesis of Camphorataanhydride/Imides and (±)-Himanimide D Using Stille Coupling

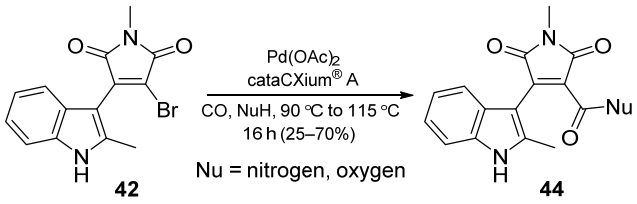
Beller and co-workers carried out Pd-catalyzed Suzuki coupling of 3-bromo-1-methyl-4-(2-methylindolyl)maleimide (**42**) with various arylboronic acids for the synthesis of 3-aryl-4-indolylmaleimides **43** (Scheme 17).[19] The coupling of both aryl- and heteroarylboronic acids proceeded smoothly in good to excellent yields at low catalyst loading and without any protection–deprotection steps.



Scheme 17. Suzuki Coupling for Synthesis of 3-Aryl-4-indolylmaleimides

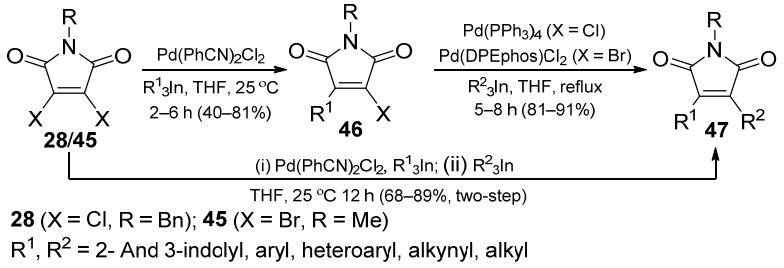
Beller and co-workers have also demonstrated that 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide (**42**) can be successfully carbonylated by using carbon monoxide with amines or alcohols in the presence of $Pd(OAc)_2$/di-1-adamantyl-*n*-butylphosphane (cata*CX*ium® A).[20] The resulting 3-aminocarbonyl-4-indolylmaleimides and 3-alkoxycarbonyl-

4-indolylmaleimides **44** were obtained in 25–70% yields (Scheme 18). This approach provides nice scope to build new heterocyclic systems for SAR studies.



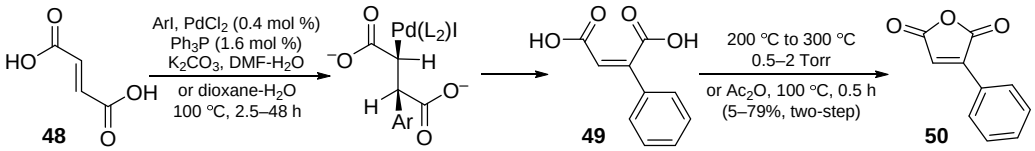
Scheme 18. Pd-Catalyzed Carbonylation of Bromomaleimide with Amines and Alcohols.

Sarandeses and co-workers developed a new method for the synthesis of 3,4-disubstituted maleimides using Pd-catalyzed cross-coupling reactions with various triorganoindium reagents.[21] The synthesis was performed by selective stepwise or sequential one-pot procedures starting from *N*-benzyl 3,4-dichloromaleimides (**28**) or *N*-methyl 3,4-dibromomaleimide (**45**). This method was used to prepare a wide range of symmetrically and unsymmetrically 3,4-disubstituted maleimides possessing alkyl, aryl, heteroaryl and alkynyl substituents in good yields with high selectivity and atom economy (Scheme 19).



Scheme 19. Pd-Catalyzed Cross-Coupling Reactions of Indium Organometallics

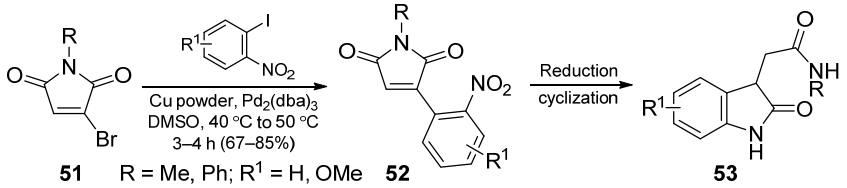
Roshchin, Kuznetsov and Polunin also found out that the Pd-catalyzed arylation of fumaric acid with aryl iodides to be a very simple, economic and scalable approach for the synthesis of arylmaleic anhydrides **50** (Scheme 20).[22] The reaction is facilitated by presence of electron donating groups on the aryl fragment and as expected the strong electron withdrawing groups retard the same.



Scheme 20. Synthesis of Arylmaleic Anhydrides via Heck Arylation of Fumaric Acid

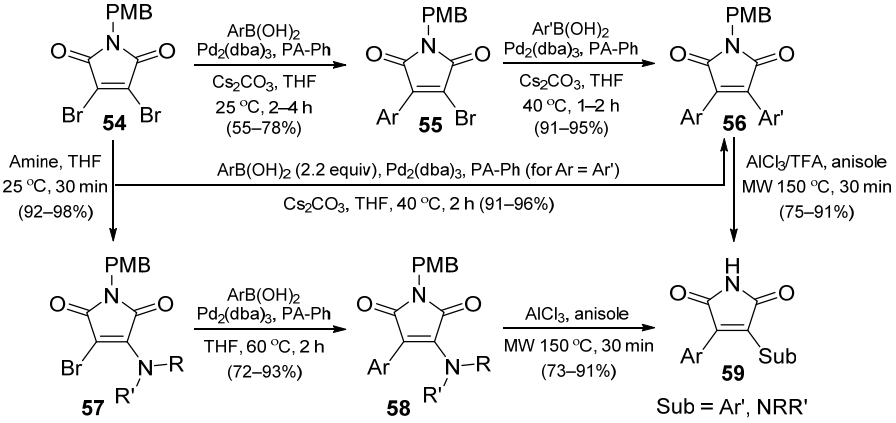
Banwell et al reported a new method for the synthesis of *C*-3 mono-alkylated oxindoles **53** by using the Pd-catalyzed Ullmann cross-coupling of *o*-nitrohaloarenes with various

bromomaleimides **51** followed by reductive intramolecular cyclization pathway, plausibly via the corresponding *o*-aminosuccinimide intermediate (Scheme 21).[23] The applicability of present protocol with lactams and lactones has been also described in details.

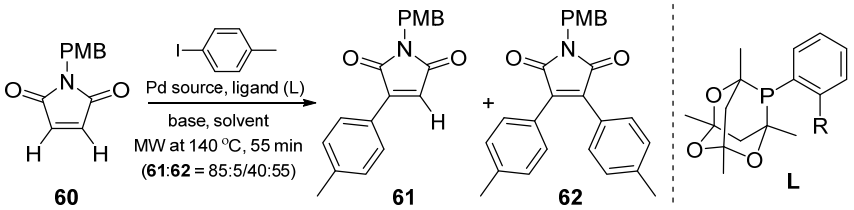


Scheme 21. Pd-Catalyzed Ullmann Cross-Coupling of *o*-Nitrohaloarenes

Awuah and Capretta described Pd-catalyzed cross-coupling and conjugate addition/elimination reactions for the facile synthesis of bisaryl-maleimides, anilinoaryl-maleimides and bisanilino-maleimides allowing to keep the control over the formation of symmetrical or unsymmetrical derivatives (Schemes 22 and 23).[24] Similarly, the synthesis of bisaryl substituted *α,β*-unsaturated-*γ*-butyrolactams with the scope and limitations of these approaches have been also presented in brief.



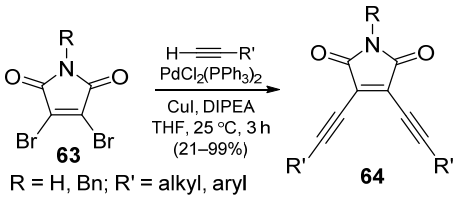
Scheme 22. Suzuki Coupling Reactions Leading to Bisaryl and 3-Amino-4-aryl Substituted Maleimides



Scheme 23. Heck Arylation of Maleimide

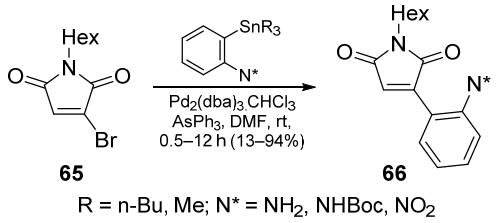
We developed Pd-catalyzed Sonogashira coupling reaction of bromomaleimides with a diverse range of terminal alkynes to furnish the corresponding alkynylmaleimides in very good yields.[25] Soon after, Viaud-Massuard and co-workers elaborated the scope of Sonogashira

coupling reaction for the double alkynylation of maleimides.[26] The dibrominated maleimides **63** were dialkynylated with various terminal alkynes using $PdCl_2(PPh_3)_2$ as catalyst (5 mol %) in the presence of CuI as co-catalyst (10 mol %) and diisopropylethylamine (DIPEA) as base in THF at room temperature to provide alkynylated maleimides **64** in 21% to 99% yields (Scheme 24). We feel that these dialkynylated products will be interesting precursors to study the intramolecular photocyclization reactions directing to substituted aromatic compounds.



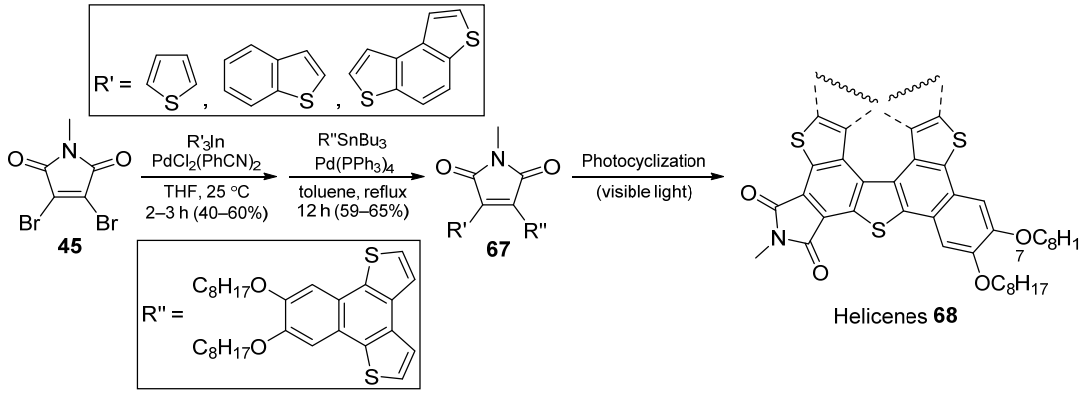
Scheme 24. Double Sonogashira Cross-Coupling Reactions of Dibromomaleimides

Izgu and Hoye prepared air stable *o*-anilinostannane reagents and coupled them with *N*-hexyl bromomaleimide (**65**) via Migita-Kosugi-Stille cross-coupling reaction. The transmetallation rate was observed in order of NH_2 > NHBoc > NO_2 (Scheme 25).[27] The studies with a series of other arylhalides and triflate are also reported.



Scheme 25. Migita-Kosugi-Stille cross-coupling reactions of *o*-anilinostannanes with *N*-hexyl bromomaleimide

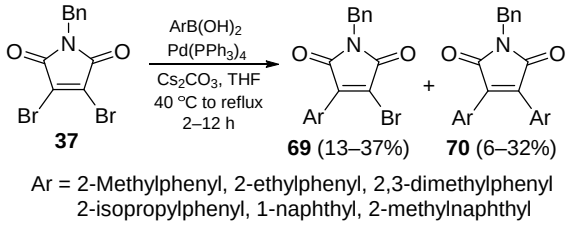
Waghray and Dehaen carried out the synthesis of [5]-, [6]-, [7]-, [9]- and [11]thiahelicenes, employing Pd-catalyzed coupling reactions.[28] Triorganoindium derivatives were selectively mono-cross-coupled with *N*-methyl-3,4-dibromomaleimide (**45**) followed by Stille coupling



Scheme 26. Synthesis of Thia[*n*]helicenes via Two Stepwise Cross-Coupling Reactions

with the readily available naphthodithiophene building block to provide the intermediate **67** (Scheme 26). Oxidative photocyclization of the conjugated precursors **67** using the visible light was utilized to synthesize a series of interesting thia[*n*]helicene architectures **68**.

Mazzanti and co-workers synthesized 4-aryl-3-bromo-*N*-benzylmaleimides **69** and 3,4-biaryl-*N*-benzylmaleimides **70** from 3,4-dibromo-*N*-benzylmaleimide (**37)** by using Suzuki cross-coupling reaction (Scheme 27).[29] The conformational studies by dynamic NMR and DFT



Scheme 27. Suzuki Cross-Coupling Reaction of 3,4-Dibromo-*N*-benzylmaleimide

calculations showed that the interconversion barrier between the two available skewed conformations is under steric control. When the aryl group was a 2-methylnaphthyl, thermally stable atropisomers were isolated by chiral HPLC and their absolute configurations were assigned by TD-DFT simulations of the ECD spectra.

1A.3 Summary

In summary, we have presented a concise literature account of various synthetic methodologies on the transition metal catalyzed cross-coupling reactions of maleic anhydrides, maleimides and their derivatives. Emphasis has been placed on recent developments of synthetic methodologies for transition metal catalyzed cross-coupling reactions of maleic anhydrides, maleimides and their derivatives, including palladium- and nickel-catalyzed selective mono- and di-coupling reactions. Number of research groups has reported variety of short and efficient synthetic approaches to biologically active natural and synthetic products from halomaleic anhydrides and haloimides using cross-coupling reactions as the key steps. All the information collected and presented here has been well supported by the provision of references from various monographs and international journals. We also foresee the huge amount of imperative information available about this scaffold in the literature. Synthesis of -OMs and -OTf substituted maleic anhydrides and maleimides followed by their metal catalyzed cross-coupling reactions are the next challenges for the synthesis of corresponding compounds. An especially exciting development on the use of other transition metal catalysts, organometallics and ligands to obtain high efficiency with practical, economical and greener approach will be the next promising wave in this important field. Our synthetic studies towards the development of new methodology for the metal catalyzed cross-coupling reaction of halomaleimides have been discussed in details in the section B of the present chapter.

1A.4 References

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CHAPTER 1: SECTION B

Sonogashira Coupling Reactions of Halomaleimides: Route to Alkyne/(*cis*)-Alkene/Alkyl Maleimides: Total Synthesis of Luffarin X and Cacospongionolide C

This section B of chapter 1 features the following topics:

1B.1 Rationale of the Present Work

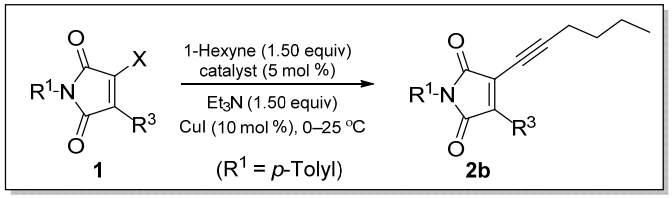
A large number of alkyl and dialkyl substituted maleic anhydrides, maleimides, the corresponding lactols and γ-lactones (butenolides), have been isolated as the natural products with an array of promising bioactivities.[1] Many new routes have been devised in recent times to synthesize the essential dialkyl-substituted maleic anhydrides[2] and butenolides.[3] To the best of our knowledge, only a few practical routes have been known for the synthesis of alkylmaleic anhydrides.[4–7] They have been based on condensation of glyoxylic acid with aldehydes/esters bearing the active α-hydrogens[4] and also Heck reaction using palladium-catalyzed dicarbonylation of terminal acetylenes with carbon monoxide.[5] Our own recent approach based on imide chemistry involves more synthetic steps (maleimides − alkeledenesuccinimide − alkeledeneisosuccinimide intermediate − isomaleimide − alkylmaleimide − alkylmaleic anhydride).[6]

It is evident from the discussion in section A that the cross-coupling reactions, and thus the Sonogashira coupling is one of the most important carbon–carbon bond-forming reactions for the introduction of an alkyne segment.[7] The synthetic utility of this reaction has been demonstrated on a broad assortment of vinylic, aromatic, and heteroaromatic substrates to accomplish the effective synthesis of many exotic bioactive natural and unnatural products.[8] Although the Sonogashira coupling with halomaleimides was not been previously described, several palladium-catalyzed cross-coupling reactions with them have been reported and discussed in section A of the present chapter. In continuation of our studies on carbon–carbon and carbon–heteroatom coupling reactions, we realized that Sonogashira coupling of bromomaleic anhydrides/bromomaleimides would be useful to develop a new general route to alkyne/alkene/alkyl-substituted maleic anhydrides and several analogous natural products. This coupling reaction followed by selective reduction of the triple bond to single bond have been utilized as the decisive steps to accomplish the first total synthesis of natural products (±)-luffarin X and (±)-cacospongionolide C.

1B.2 Results and Discussion

The initially attempted Sonogashira coupling reaction of reactive bromomaleic anhydride with 1-hexyne resulted in decomposition. Relatively more stable corresponding multifunctional halomaleimides **1**[9] were therefore preferred as the potential precursors for our systematic

studies on Sonogashira coupling reactions. As depicted in Table 1, the reaction between bromomaleimide and 1-hexyne was performed employing three different palladium catalysts in THF. Two of these catalysts selectively furnished the desired coupled product **2b** in ~90% yields (entries 2 and 4). However, the bromomethylmaleimide and dibromomaleimide under similar set of reaction conditions failed to deliver the corresponding desired mono/double coupling products, leading to decomposition (entries 5–8). The corresponding chloromaleimide and dichloromaleimide also failed to deliver the coupling products and remained unreacted at room temperature, while slowly undergoing decomposition under the reflux conditions (entries 9 and 10).



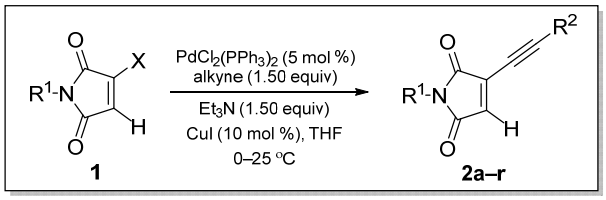
entry	X	R^3	catalyst	solvent	time (h)	% yield
1	Br	H	$Pd(PPh_3)_4$	THF	6.0	NR[a]
2	Br	H	$PdCl_2(PPh_3)_2$	THF	1.0	90
3	Br	H	$PdCl_2(PPh_3)_2$	DMF	1.0	67
4	Br	H	$PdCl_2(CH_3CN)_2$	THF	1.0	89
5	Br	Me	$PdCl_2(PPh_3)_2$	THF	6.0	NR[a]
6	Br	Me	$PdCl_2(CH_3CN)_2$	THF	6.0	NR[a]
7	Br	Br	$PdCl_2(PPh_3)_2$	THF	6.0	NR[a]
8	Br	Br	$PdCl_2(CH_3CN)_2$	THF	6.0	NR[a]
9	Cl	H	$PdCl_2(PPh_3)_2$	THF	6.0	NR[b]
10	Cl	Cl	$PdCl_2(PPh_3)_2$	THF	6.0	NR[b]

[a] No reaction, decomposition after 24 hours. [b] No reaction from 25 °C to 65 °C.

Table 1. Sonogashira Coupling Reactions of Bromomaleimides and Chloromaleimides

As described in Table 2, the reactions of bromomaleimides with several aliphatic and aromatic alkynes were performed in the presence of $PdCl_2(PPh_3)_2$/CuI in THF, and the desired products **2a**–**r** were obtained in very good yields (entries 1–18). We also obtained the coupling products **2b**, **2k** and **2n** from the corresponding iodomaleimide in similar yields (Table 2, entries 19–21). In these multifunctional maleimides **2a–r**, a variety of chemoselective transformations would be possible on carbon–carbon triple bond to obtain the corresponding alkenyl/alkyl/acyl/1,2-

dicarbonyl-substituted maleimides/maleic anhydrides as potential building blocks.[10,11] As indicated in Table 3, chemoselective and controlled hydrogenation of carbon–carbon triple bond in product **2b** was performed employing several catalysts. The reduction of imide **2b** in the presence of Wilkinson catalyst and Pearlman catalyst were futile. While the former reaction

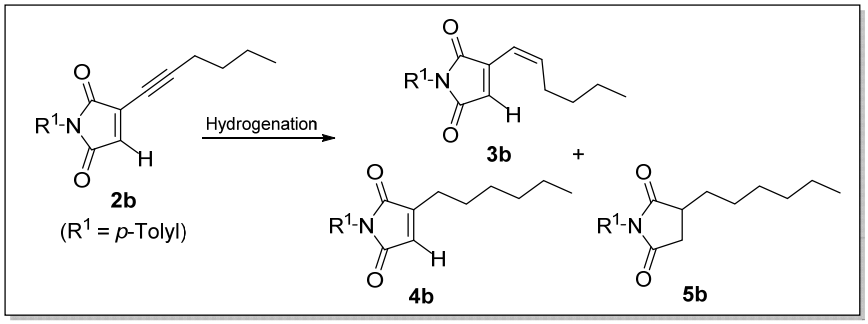


entry	X	R^1	R^2	time (h)	2 (% yield)
1	Br	*p*-C_6H_4-CH_3	$Si(Me)_3$	3.0	**2a** (52)
2	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_2CH_3$	1.0	**2b** (90)
3	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_4CH_3$	1.0	**2c** (90)
4	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_6CH_3$	1.0	**2d** (93)
5	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_{11}CH_3$	0.5	**2e** (93)
6	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_{12}CH_3$	0.5	**2f** (95)
7	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_{13}CH_3$	0.5	**2g** (95)
8[a]	Br	*p*-C_6H_4-CH_3	$C_{14}H_{29}$	1.0	**2h** (56)
9	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_7CH_2OH$	2.0	**2i** (67)
10	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_7COOH$	2.0	**2j** (63)
11	Br	*p*-C_6H_4-CH_3	C_6H_5	1.0	**2k** (75)
12	Br	*p*-C_6H_4-CH_3	*p*-C_6H_4-CH_3	1.0	**2l** (78)
13	Br	*p*-C_6H_4-CH_3	*o*-C_6H_4-OCH_3	1.5	**2m** (67)
14	Br	*p*-C_6H_4-CH_3	*p*-C_6H_4-OCH_3	1.0	**2n** (72)
15	Br	C_6H_5	$CH_2(CH_2)_2CH_3$	1.0	**2o** (91)
16	Br	$CH_2C_6H_5$	$CH_2(CH_2)_2CH_3$	1.0	**2p** (86)
17	Br	CH_3	C_6H_5	1.0	**2q** (81)
18	Br	$(CH_2)_2CO_2CH_3$	$CH_2(CH_2)_2CH_3$	1.5	**2r** (74)
19	I	*p*-C_6H_4-CH_3	$CH_2(CH_2)_2CH_3$	1.0	**2b** (86)
20	I	*p*-C_6H_4-CH_3	C_6H_5	1.0	**2k** (77)
21	I	*p*-C_6H_4-CH_3	*p*-C_6H_4-OCH_3	1.0	**2n** (69)

[a] $C_{14}H_{29}$: $CH_2CHCH_3(CH_2)_3CHCH_3(CH_2)_3CH(CH_3)_2$ (diastereomeric mixture).

Table 2. Sonogashira Couplings of Bromomaleimides and Iodomaleimides: Synthesis of Alkynylmaleimides

did not proceed at all, the latter resulted in decomposition (entries 1 and 3). As shown in entry 4, the transfer hydrogenation conditions also resulted in decomposition. The selective reduction of imide **2b** in the presence of Lindlar catalyst was feasible, and it was dependent on both the solvent used and the presence/absence of quinoline.[11] As described in entry 2, the acetylene segment of imide **2b** in the presence of Lindlar catalyst in ethyl acetate did not undergo reduction and remained unreacted. The reaction of **2b** in the presence of Lindlar catalyst in methanol reduced both the triple bond and internal double bond to provide alkylsuccinimide **5b** in 74% yield (entry 6). However the same reaction in methanol–acetone (1:1) in the presence of quinoline (1.00 equiv) selectively reduced only the carbon–carbon triple bond to the single bond furnishing the alkylmaleimide **4b** in 68% yield (entry 8). The reaction of **2b** in the



entry	catalyst	reaction conditions	% yield		
			3b	4b	5b
1	Wilkinson	H_2, DCM, reflux, 5 h	——NR[a]——		
2	Lindlar	H_2, quinoline, EtOAc, 25 °C, 24 h	——NR[a]——		
3	Pearlman	H_2, MeOH, 25 °C, 5 h	——D[b]——		
4	–	$TsNHNH_2$, DME aq. NaOAc, reflux, 5 h	——D[b]——		
5	Pd–C	H_2, EtOAc, 25 °C, 1 h	–	–	78
6	Lindlar	H_2, MeOH, 25 °C, 5 h	–	–	74
7	Pd–C	H_2, quinoline, MeOH, 25 °C, 1.5 h	–	63	–
8	Lindlar	H_2, quinoline MeOH + acetone (1:1), 25 °C, 6 h	–	68	–
9	Lindlar	H_2, quinoline, CH_3CN, 25 °C, 5 h	56	6	–
10	Lindlar	H_2, quinoline, acetone, 25 °C, 5 h	57	6	–

[a] No reaction. [b] Decomposition.

Table 3. Selective Hydrogenation of Alkynylmaleimides

presence of Lindlar catalyst in solvent acetonitrile/acetone and quinoline (1.50 equiv) yielded the desired monoreduction product *cis*-alkenylmaleimide **3b** in 56/57% yields along with the ~6% of **4b** (entries 9 and 10). The reaction of imide **2b** in the presence of Pd–C in ethyl acetate provided completely reduced product **5b** in 78% yield (entry 5). The same reaction in methanol in the presence of quinoline (1.50 equiv) was also selective and gave the alkylmaleimide **4b** in 63% yield (entry 7). The *cis*-geometry of the products **3** was confirmed on the basis of NOE studies and the comparison with reported data[1e] (Figure 1).

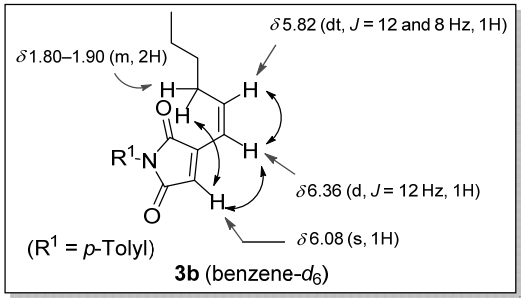
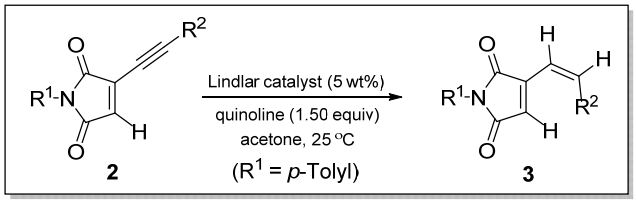


Figure 1. NOESY interactions in *cis*-hexenylmaleimide

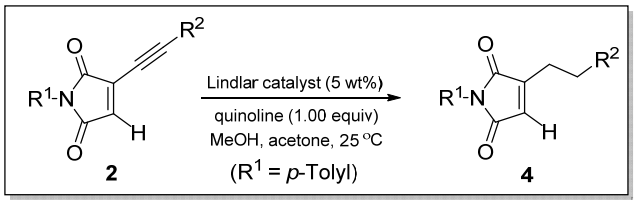
Finally, as depicted in Tables 4 and 5, the aliphatic alkyne-substituted maleimides were selectively reduced to the corresponding *cis*-alkenylmaleimides in 61–66% yields and alkylmaleimides in 68–75% yields. However the alkyne-substituted maleimides with aromatic rings led to decomposition under present reduction conditions (Tables 4 and 5, entry 5).



entry	R^2	time (h)	3 (% yield)
1	$CH_2(CH_2)_2CH_3$	5.0	**3b** (63)[a]
2	$CH_2(CH_2)_6CH_3$	5.0	**3d** (61)[a]
3	$CH_2(CH_2)_{12}CH_3$	5.0	**3f** (65)
4[b]	$C_{14}H_{29}$	5.0	**3h** (66)
5	C_6H_5	12.0	**3k** D[c]

[a] The products were contaminated with traces of over reduced products **4b** and **4d**.
[b] $C_{14}H_{29}$: $CH_2CHCH_3(CH_2)_3CHCH_3(CH_2)_3CH(CH_3)_2$. [c] Decomposition.

Table 4. Stereoselective Reduction of Alkynylmaleimides



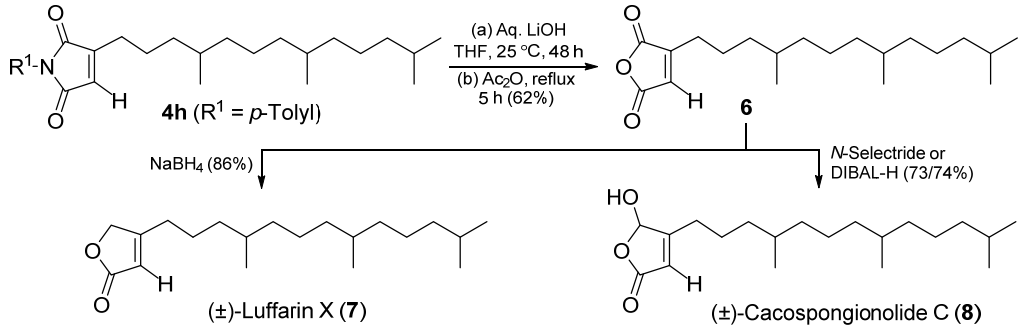
entry	R^2	time (h)	4 (% yield)
1	$CH_2(CH_2)_2CH_3$	6.0	**4b** (68)
2	$CH_2(CH_2)_6CH_3$	5.0	**4d** (70)
3	$CH_2(CH_2)_{12}CH_3$	6.5	**4f** (75)
4[a]	$C_{14}H_{29}$	6.5	**4h** (70)
5	C_6H_5	12.0	**4k** D[b]

[a] $C_{14}H_{29}$: $CH_2CHCH_3(CH_2)_3CHCH_3(CH_2)_3CH(CH_3)_2$. [b] Decomposition.

Table 5. Synthesis of Alkylmaleimides

Thus, the present protocol provides a facile new route to both the alkylmaleimides and the alkylmaleic anhydrides. Further conversion of alkylmaleimides to the corresponding dialkylmaleic anhydrides has been recently reported from our group.[6]

The terpenoids luffarin X and cacospongionolide C have been isolated, respectively, from the marine sponge *Luffariella geometrica*[12] and *Fasciospongia cavernosa*.[13] To date, no synthesis of these natural products has been reported in the literature. The present protocol was extended for the first synthesis of the above-mentioned natural products. The appropriate precursor **4h** on base-promoted hydrolysis followed by the acetic anhydride induced ring-closure provided the corresponding alkylmaleic anhydride **6** in 62% yield[9] (Scheme 1).



Scheme 1. Synthesis of Luffarin X and Cacospongionolide C

The regioselective reduction of anhydride **6** was studied using the five different reducing agents.[14] In the sodium borohydride reduction of unsymmetrical anhydride **6**, boron atom complexes with the unhindered carbonyl group and delivers the hydride to the hindered

carbonyl group to exclusively yield the desired butenolide (±)-luffarin X (**7**) in 86% yield. The reduction reactions of anhydride **6** with $NaBH(OAc)_3$ and $Li(t\text{-}BuO)_3AlH$ were less selective and provided the column chromatographically separable mixture of products **7** and **8** in 81/70% yields (**7**:**8** = ~1:3). The reduction reactions of anhydride **6** with the $NaB[CH(CH_3)C_2H_5]_3H$ and DIBAL-H at −78 °C were also completely regioselective and reduced the hindered carbonyl group to the corresponding lactol to provide yet another desired natural product (±)-cacospongionolide C (**8**) in 73/74% yields, respectively. Such compounds containing hemiketal/lactol/lactamol unit display the ring–chain tautomerism and are prone to racemize.[15] The analytical and spectral data obtained for both the natural products **7** and **8** were in complete agreement with reported data.[12,13] Thus, starting from imide **1** the natural products **7** and **8** were obtained in five linear steps with 21% and 18% overall yields, respectively.

1B.3 Summary

In summary, we have demonstrated a new general approach to alkyne/alkene/alkyl substituted maleimides/anhydrides by performing the palladium-catalyzed Sonogashira coupling reactions on the multifunctional bromomaleimides with a variety of terminal alkynes using CuI as the cocatalyst. The present protocol has been utilized to accomplish the total synthesis of natural products luffarin X and cacospongionolide C. The present Sonogashira coupling reactions of bromomaleimides and the chemo- and regioselective reductions are of general interest. We foresee their usefulness to obtain several complex bioactive natural and unnatural products for SAR studies.

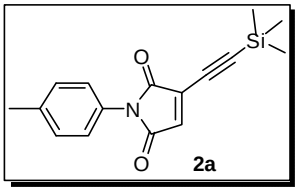
1B.4 Experimental Section

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz, and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 (50 MHz), 400 (100 MHz), and 500 (125 MHz) NMR spectrometer. Mass spectra were taken on an MS-TOF mass spectrometer. HRMS were taken on ESI mass spectrometer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 and 200–400 mesh). Commercially available $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(CH_3CN)_2$, CuI, alkynes, Lindlar catalyst (5 wt %), Pd on charcoal (10 wt %), synthetic quinoline, $NaBH_4$, $NaBH(OAc)_3$, DIBAL-H, *N*-Selectride, Super-Hydride were used. The halomaleimides and required alkynes were prepared by using known procedure.[9,16]

General Procedure for Sonogashira Coupling Reaction of 3-Bromo-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (1).

A round-bottom flask was charged with $PdCl_2(PPh_3)_2$ (13 mg, 5 mol %) and bromomaleimide (100 mg, 0.37 mmol) in THF (7 mL). The alkyne (0.55 mmol), triethyl amine (0.077 mL, 0.55 mmol), and CuI (0.70 mg, 10 mol %) were added successively at 0 ^{o}C, and reaction mixture was stirred at 25 ^{o}C under argon atmosphere. After completion of the reaction (by TLC), ethyl acetate (10 mL) and water (5 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined 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–ethyl acetate as an eluent to furnish the desired coupling product 2. Alternatively, the reaction mixture was filtered through a Celite, concentrated under vacuum, and then directly subjected to silica gel column chromatographic purification. All the reactions were performed using bromomaleimides (100 mg) to obtain the desired products **2a**–**g**,**i**–**r**. For the preparation of natural products precursor **2h**, the reaction was performed on a 1 g scale of 3-bromo-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione.

1-(*p*-Tolyl)-3-((trimethylsilyl)ethynyl)-1*H*-pyrrole-2,5-dione (2a).

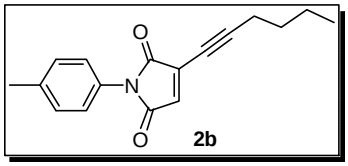


2a

Yellow solid (55 mg, 52%). Mp 89–92 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.30 (s, 9H), 2.39 (s, 3H), 6.79 (s, 1H), 7.15–7.32 (m, 4H); ^{13}C

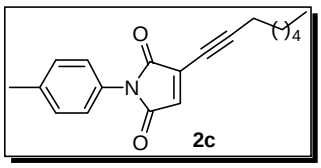
NMR ($CDCl_3$, 50 MHz) δ 0.7, 21.1, 92.9, 115.2, 125.9, 128.5, 129.8, 130.4, 132.3, 138.1, 166.1, 169.0; ESIMS (*m*/*z*) 306 $[M+Na]^+$, 322 $[M+K]^+$; HRMS (ESI) calcd for $C_{16}H_{18}NO_2Si$ $[M+H]^+$ 284.1107, found 284.1110; IR ($CHCl_3$) ν_{max} 2311, 1713, 1393 cm^{-1}.

3-(Hex-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2b).



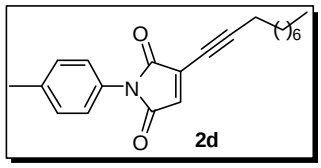
Yellow solid (90 mg, 90%). Mp 93–94 ºC; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (t, J = 8 Hz, 3H), 1.35–1.70 (m, 4H), 2.38 (s, 3H), 2.54 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.15–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.5, 19.9, 21.1, 22.0, 30.0, 70.9, 110.3, 125.9, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (*m*/*z*) 290 $[M+Na]^+$, 306 $[M+K]^+$; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$ 268.1338, found 268.1339; IR ($CHCl_3$) ν_{max} 2230, 1721, 1715 cm^{-1}.

3-(Oct-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2c).



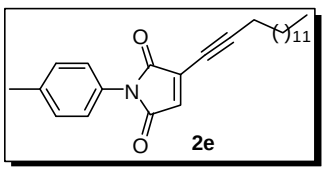
Yellow solid (100 mg, 90%). Mp 74–75 ºC; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 6 Hz, 3H), 1.20–1.52 (m, 6H), 1.60 (quintet, J = 8 Hz, 2H), 2.37 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.10–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 20.2, 21.1, 22.4, 27.9, 28.5, 31.2, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (*m*/*z*) 366 $[M+K+MeOH]^+$; HRMS (ESI) calcd for $C_{19}H_{22}NO_2$ $[M+H]^+$ 296.1651, found 296.1649; IR ($CHCl_3$) ν_{max} 2224, 1723, 1715 cm^{-1}.

3-(Dec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2d).



Yellow solid (113 mg, 93%). Mp 52–53 ºC; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.28 (br s, 8H), 1.35–1.53 (m, 2H), 1.64 (quintet, J = 6 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.13–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.6, 27.9, 28.9, 29.0, 29.1, 31.8, 70.9, 110.4, 125.9, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (*m*/*z*) 394 $[M+K+MeOH]^+$; HRMS (ESI) calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$ 324.1964, found 324.1975; IR ($CHCl_3$) ν_{max} 2225, 1724, 1715 cm^{-1}.

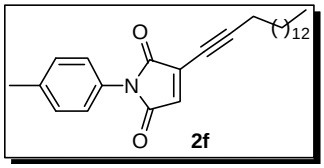
3-(Pentadec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2e).



Yellow solid (137 mg, 93%). Mp 59–60 ºC; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.25 (br s, 18H), 1.30–1.50 (m, 2H),

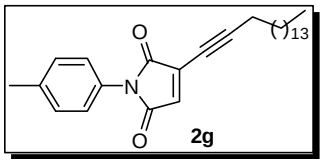
1.64 (quintet, J = 8 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.13–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.7, 28.0, 28.9, 29.0, 29.3, 29.4, 29.57, 29.61 (3 carbons), 31.9, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.5; ESIMS (m/z) 426 $[M+H+MeOH]^+$; HRMS (ESI) calcd for $C_{26}H_{36}NO_2$ $[M+H]^+$ 394.2746, found 394.2737; IR ($CHCl_3$) ν_{max} 2218, 1721, 1713 cm^{-1}.

3-(Hexadec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2f).



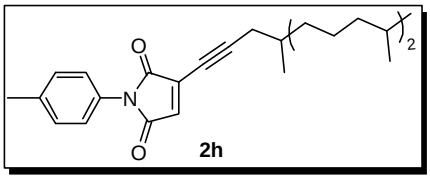
Yellow solid (145 mg, 95%). Mp 61–62 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 8 Hz, 3H), 1.26 (br s, 20H), 1.35–1.55 (m, 2H), 1.64 (quintet, J = 8 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.66 (s, 1H), 7.15–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.7, 28.0, 28.9, 29.0, 29.3, 29.4, 29.6 (5 carbons), 31.9, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.5; ESIMS (m/z) 440 $[M+H+MeOH]^+$; HRMS (ESI) calcd for $C_{27}H_{38}NO_2$ $[M+H]^+$ 408.2903, found 408.2899; IR ($CHCl_3$) ν_{max} 2224, 1718, 1608 cm^{-1}.

3-(Heptadec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2g).



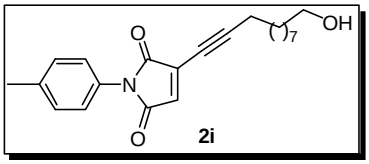
Yellow solid (150 mg, 95%). Mp 65–66 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (br s, 22H), 1.30–1.52 (m, 2H), 1.64 (quintet, J = 8 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.66 (s, 1H), 7.15–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.7, 28.0, 28.9, 29.0, 29.3, 29.4, 29.57, 29.63, 29.7 (4 carbons), 31.9, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (m/z) 444 $[M+Na]^+$; HRMS (ESI) calcd for $C_{28}H_{40}NO_2$ $[M+H]^+$ 422.3059, found 422.3078; IR ($CHCl_3$) ν_{max} 2361, 1717 cm^{-1}.

1-(*p*-Tolyl)-3-(4,8,12-trimethyltridec-1-yn-1-yl)-1*H*-pyrrole-2,5-dione (2h, Diastereomeric Mixture).



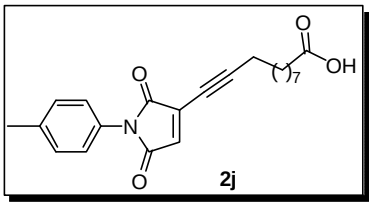
Thick oil (86 mg, 56%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.75–1.60 (m, 26H), 1.70–1.92 (m, 1H), 2.25–2.65 (m, 2H), 2.39 (s, 3H), 6.67 (s, 1H), 7.15–7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.5, 19.6, 21.1, 22.6, 22.7, 24.4, 24.7, 27.5, 27.6, 27.9, 32.5, 32.7, 36.5, 37.1, 37.2, 37.3, 39.3, 71.8, 109.5, 125.9, 128.6, 129.7, 130.3, 131.5, 137.9, 166.6, 169.4; ESIMS (m/z) 430 $[M+Na]^+$; HRMS (ESI) calcd for $C_{27}H_{38}NO_2$ $[M+H]^+$ 408.2903, found 408.2903; IR ($CHCl_3$) ν_{max} 2220, 1721, 1606 cm^{-1}.

3-(11-Hydroxyundec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2i).



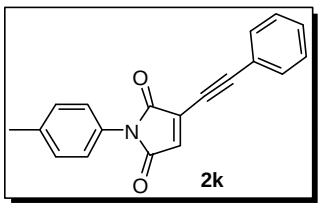
Yellow solid (89 mg, 67%). Mp 70–72 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.75 (m, 14H), 2.38 (s, 3H), 2.54 (t, J = 8 Hz, 2H), 3.64 (t, J = 6 Hz, 2H), 6.68 (s, 1H), 7.15–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.2, 21.1, 25.6, 27.9, 28.8, 28.9, 29.28, 29.33, 32.7, 63.0, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.5; ESIMS (*m*/*z*) 376 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$ 354.2069, found 354.2066; IR ($CHCl_3$) ν_{max} 2359, 1721, 1715, 1697 cm^{-1}.

11-(2,5-Dioxo-1-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrol-3-yl)undec-10-ynoic Acid (2j).



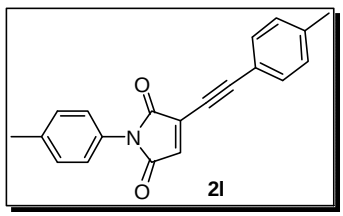
Yellow solid (87 mg, 63%). Mp 114–116 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.75 (m, 12H), 2.35 (t, J = 8 Hz, 2H), 2.37 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.12–7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.2, 21.1, 24.6, 27.9, 28.7, 28.8, 28.9, 29.0, 33.9, 70.9, 110.3, 126.0, 128.6, 129.8, 130.6, 131.5, 138.0, 166.7, 169.5, 179.7; ESIMS (*m*/*z*) 390 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 2359, 1721, 1715, 1697 cm^{-1}; Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.09; H, 6.77; N, 4.30.

3-(Phenylethynyl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2k).



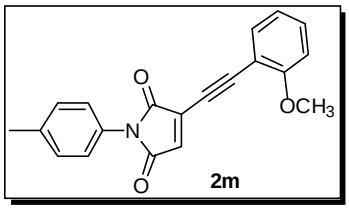
Yellow solid (81 mg, 75%). Mp 138–139 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H), 6.82 (s, 1H), 7.15–7.33 (m, 4H), 7.33–7.52 (m, 3H), 7.62 (d, J = 6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 79.0, 106.8, 121.0, 126.0, 128.6, 129.8, 130.4, 130.7, 130.8, 132.4, 138.1, 166.3, 169.1; ESIMS (*m*/*z*) 342 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1025, found 288.1028; IR ($CHCl_3$) ν_{max} 2212, 1717 cm^{-1}.

1-(*p*-Tolyl)-3-(*p*-tolylethynyl)-1*H*-pyrrole-2,5-dione (2l).



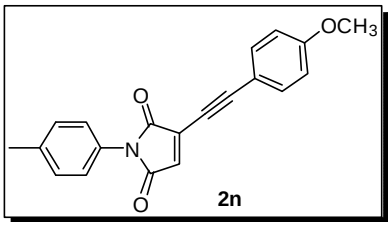
Yellow solid (88 mg, 78%). Mp 133–134 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 6H), 6.78 (s, 1H), 7.15–7.32 (m, 6H), 7.51 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 21.7, 78.8, 107.4, 117.9, 125.9, 128.6, 129.4, 129.7, 130.2, 130.8, 132.4, 138.0, 141.1, 166.4, 169.2; ESIMS (*m*/*z*) 356 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_2$ $[M+H]^+$ 302.1181, found 302.1181; IR ($CHCl_3$) ν_{max} 2212, 1721, 1715 cm^{-1}.

3-((2-Methoxyphenyl)ethynyl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2m).



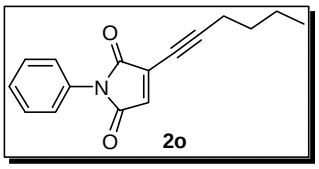
Yellow solid (80 mg, 67%). Mp 127–129 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40 (s, 3H), 3.94 (s, 3H), 6.82 (s, 1H), 6.94 (d, J = 8 Hz, 1H), 6.99 (dt, J = 8 and 2 Hz, 1H), 7.20–7.32 (m, 4H), 7.43 (dt, J = 8 and 2 Hz, 1H), 7.57 (dd, J = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 55.9, 83.1, 103.9, 110.3, 110.8, 120.6, 126.0, 128.6, 129.7, 130.1, 130.9, 132.2, 134.3, 138.0, 160.7, 166.4, 169.3; ESIMS (m/z) 372 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_3$ $[M+H]^+$ 318.1130, found 318.1119; IR ($CHCl_3$) ν_{max} 2359, 1717 cm^{-1}.

3-((4-Methoxyphenyl)ethynyl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2n).



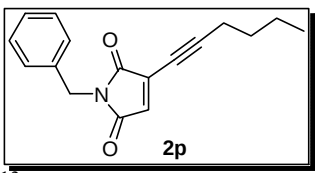
Yellow solid (86 mg, 72%). Mp 140–141 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H), 3.85 (s, 3H), 6.75 (s, 1H), 6.87–6.95 (m, 2H), 7.17–7.32 (m, 4H), 7.50–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 55.4, 78.8, 107.8, 113.0, 114.3, 126.0, 128.7, 129.4, 129.7, 131.0, 134.3, 138.0, 161.3, 166.5, 169.4; ESIMS (m/z) 372 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_3$ $[M+H]^+$ 318.1130, found 318.1131; IR ($CHCl_3$) ν_{max} 2212, 1721, 1715 cm^{-1}.

3-(Hex-1-yn-1-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (2o).



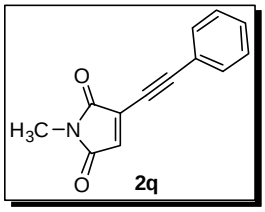
Yellow solid (91 mg, 91%). Mp 67−68 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, J = 8 Hz, 3H), 1.37−1.73 (m, 4H), 2.55 (t, J = 8 Hz, 2H), 6.68 (s, 1H), 7.30−7.53 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.5, 19.9, 22.0, 29.9, 70.8, 110.5, 126.0, 127.9, 129.1, 130.5, 131.3, 131.5, 166.5, 169.3; HRMS (ESI) calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.1181, found 254.1182; IR (CHCl3) ν_{max} 2231, 1719 cm^{-1}.

1-Benzyl-3-(hex-1-yn-1-yl)-1*H*-pyrrole-2,5-dione (2p).



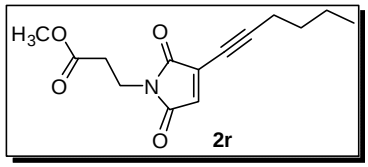
Thick oil (86 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 8 Hz, 3H), 1.45 (sextet, J = 8 Hz, 2H), 1.60 (quintet, J = 8 Hz, 2H), 2.50 (t, J = 8 Hz, 2H), 4.67 (s, 2H), 6.53 (s, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 19.8, 21.9, 29.9, 41.8, 70.9, 109.8, 127.8, 128.4, 128.6, 130.6, 131.4, 136.0, 167.4, 170.1; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$ 268.1338, found 268.1328; IR ($CHCl_3$) ν_{max} 2228, 1773, 1714 cm^{-1}.

1-Methyl-3-(phenylethynyl)-1*H*-pyrrole-2,5-dione (2q).



Yellow solid (90 mg, 81%). Mp 74−75 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.07 (s, 3H), 6.70 (s, 1H), 7.35−7.48 (m, 3H), 7.59 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 79.0, 106.3, 121.1, 128.6, 130.3, 130.8, 131.0, 132.4, 167.5, 170.3; HRMS (ESI) calcd for $C_{13}H_{10}NO_2$ $[M+H]^+$ 212.0712, found 212.0711; IR (CHCl3) ν_{max} 2200, 1775, 1713 cm^{-1}.

Methyl 3-(3-(hex-1-yn-1-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoate (2r).

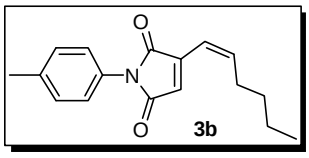


Thick oil (74 mg, 74%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (t, J = 8 Hz, 3H), 1.35−1.75 (m, 4H), 2.52 (t, J = 8 Hz, 2H), 2.64 (t, J = 8 Hz, 2H), 3.68 (s, 3H), 3.84 (t, J = 8 Hz, 2H), 6.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 19.9, 22.0, 30.0, 32.6, 34.0, 51.9, 70.8, 110.0, 130.6, 131.6, 167.3, 170.0, 171.0; HRMS (ESI) calcd for $C_{14}H_{18}NO_4$ $[M+H]^+$ 264.1236, found 264.1238; IR ($CHCl_3$) ν_{max} 2220, 1775, 1734, 1716 cm^{-1}.

General Procedure for Hydrogenation of Alkynylmaleimides (2b,d,f,h) to Alkenylmaleimides (3b,d,f,h).

To a solution of alkynylmaleimide **2** (0.10 mmol) in CH_3CN or acetone (2 mL) were added quinoline (19.4 mg, 0.15 mmol) and Lindlar catalyst (10 mg, 5 wt %). The reaction mixture was then stirred at 25 ^{o}C under balloon pressure hydrogen atmosphere for 5 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and obtained residue was purified by silica gel flash column chromatography using petroleum ether–ethyl acetate as an eluent to yield the desired (*Z*)-alkene **3**. All the reactions were performed using alkynylmaleimides **2b**,**d**,**f**,**h** (0.10 mmol) to obtain the desired products **3b**,**d**,**f**,**h**.

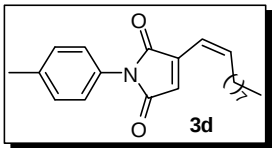
(*Z*)-3-(Hex-1-en-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (3b).



Yellow solid (17 mg, 63%). Mp 81–83 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (t, J = 8 Hz, 3H), 1.25–1.75 (m, 4H), 2.40 (s, 3H), 2.40 (t, J = 8 Hz, 2H), 6.30–6.50 (m, 2H), 6.57 (s, 1H), 7.17–7.35 (m, 4H); ^{1}H NMR (benzene-d_6, 400 MHz) δ 0.80 (t, J = 8 Hz, 3H), 1.05–1.20 (m, 4H), 1.80–1.90 (m, 2H), 2.05 (s, 3H), 5.82 (dt, J = 12 and 8 Hz, 1H), 6.08 (s, 1H), 6.36 (d, J = 12 Hz, 1H), 6.98 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 21.1, 22.5, 30.5,

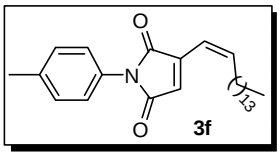
30.9, 115.5, 123.9, 125.9, 128.8, 129.7, 137.7, 140.7, 147.5, 170.4, 170.5; ^{13}C NMR (benzene-d_6, 125 MHz) δ 14.0, 20.9, 22.5, 30.4, 31.0, 115.9, 124.1, 125.9, 129.6, 130.0, 137.1, 140.3, 146.4, 169.8, 170.3; ESIMS (*m*/*z*) 292 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$ 270.1494, found 270.1507; IR ($CHCl_3$) ν_{max} 1777, 1714, 1620 cm^{-1}.

(*Z*)-3-(Dec-1-en-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (3d).



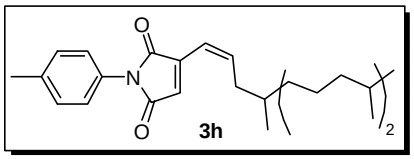
Yellow solid (20 mg, 61%). Mp 77–78 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.82 (t, J = 8 Hz, 3H), 1.21 (br s, 10H), 1.40–1.60 (m, 2H), 2.20–2.40 (m, 2H), 2.31 (s, 3H), 6.20–6.40 (m, 2H), 6.48 (s, 1H), 7.10–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.6, 28.8, 29.2, 29.36, 29.42, 30.9, 31.8, 115.5, 124.0, 125.9, 128.8, 129.7, 137.8, 140.8, 147.6, 170.49, 170.54; ESIMS (*m*/*z*) 380 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$ 326.2120, found 326.2121; IR ($CHCl_3$) ν_{max} 1709, 1621 cm^{-1}.

(*Z*)-3-(Hexadec-1-en-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (3f).



Yellow solid (27 mg, 65%). Mp 76–77 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (br s, 22H), 1.45–1.65 (m, 2H), 2.30–2.45 (m, 2H), 2.38 (s, 3H), 6.27–6.45 (m, 2H), 6.55 (s, 1H), 7.17–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 21.1, 22.7, 28.8, 29.3, 29.4, 29.5, 29.6, 29.7 (5 carbons), 30.9, 31.9, 115.5, 124.0, 125.9, 128.8, 129.7, 137.8, 140.8, 147.6, 170.5, 170.6; ESIMS (*m*/*z*) 464 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{27}H_{40}NO_2$ $[M+H]^+$ 410.3059, found 410.3052; IR ($CHCl_3$) ν_{max} 1712, 1625 cm^{-1}.

(*Z*)-1-(*p*-Tolyl)-3-(4,8,12-trimethyltridec-1-en-1-yl)-1*H*-pyrrole-2,5-dione (3h, Diastereomeric Mixture).



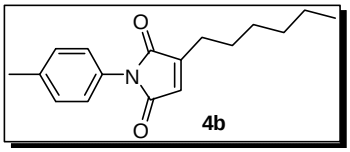
Thick oil (27 mg, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75–1.45 (m, 24H), 1.45–1.60 (m, 1H), 1.65–1.75 (m, 1H), 2.15–2.30 (m, 1H), 2.30–2.40 (m, 2H), 2.38 (s, 3H), 6.35–6.48 (m, 2H), 6.57 (s, 1H), 7.20–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 19.6, 19.7, 19.8, 21.1, 22.6, 22.7, 24.5, 24.8, 28.0, 29.4, 29.7, 31.9, 32.7, 33.3, 37.2, 37.4, 38.2, 38.3, 39.3, 116.1, 124.0, 125.9, 128.9, 129.7, 137.8, 140.8, 146.6, 170.5, 170.6; ESIMS (*m*/*z*) 464 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{27}H_{40}NO_2$ $[M+H]^+$ 410.3059, found 410.3061; IR ($CHCl_3$) ν_{max} 1712, 1604 cm^{-1}.

General Procedure for Hydrogenation of Alkynylmaleimides (2b,d,f,h) to Alkylmaleimides (4b,d,f,h).

Method A. To a solution of alkynylmaleimide **2** (0.10 mmol) in methanol (2 mL) were added quinoline (19.4 mg, 0.15 mmol) and palladium on activated charcoal (5 mg, 10 wt %). The reaction mixture was then stirred at 25 ^{o}C under balloon pressure hydrogen atmosphere for 1.5 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether–ethyl acetate as an eluent to yield the desired monoalkyl-substituted maleimide **4**.

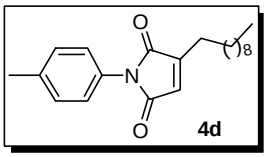
Method B. To a solution of alkynylmaleimide **2** (0.10 mmol) in methanol (2 mL) plus acetone (2 mL) were added quinoline (13 mg, 0.10 mmol) and Lindlar catalyst (10 mg, 5 wt %). The reaction mixture was then stirred at 25 ^{o}C under balloon pressure hydrogen atmosphere for 6 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether–ethyl acetate as an eluent to yield the desired monoalkyl-substituted maleimide **4**. All of the reactions were performed using alkynylmaleimides **2b**,**d**,**f** (0.10 mmol) to obtain the desired products **4b**,**d**,**f**. For the preparation of natural product precursor **4h** the reaction was performed using a 1.00 mmol scale of **2h**.

3-Hexyl-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (4b).[6a]



Yellow solid (19 mg, 68%). Mp 70–72 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 6 Hz, 3H), 1.25–1.52 (m, 6H), 1.65 (quintet, J = 6 Hz, 2H), 2.38 (s, 3H), 2.51 (dt, J = 8 and 2 Hz, 2H), 6.41 (t, J = 2 Hz, 1H), 7.15–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 21.1, 22.5, 25.5, 27.0, 28.9, 31.4, 125.9, 126.2, 128.9, 129.7, 137.7, 150.3, 169.9, 170.6; ESIMS (*m*/*z*) 294 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1713, 1637 cm^{-1}.

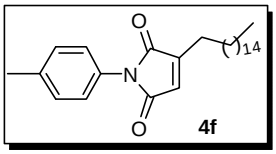
3-Decyl-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (4d).[6a]



Yellow solid (23 mg, 70%). Mp 60–61 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.26 (br s, 14H), 1.63 (quintet, J = 8 Hz, 2H), 2.36 (s, 3H), 2.49 (dt, J = 8 and 2 Hz, 2H), 6.40 (t, J = 2 Hz, 1H), 7.10–

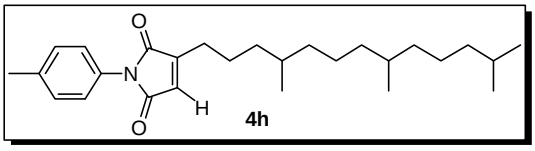
7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 25.5, 27.1, 29.21, 29.24, 29.27, 29.46, 29.54, 31.9, 125.9, 126.3, 129.0, 129.7, 137.7, 150.3, 169.9, 170.6; ESIMS (*m*/*z*) 350 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1713, 1675 cm^{-1}.

3-Hexadecyl-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (4f).



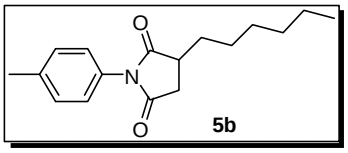
Yellow solid (31 mg, 75%). Mp 66–67 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 8 Hz, 3H), 1.25 (br s, 26H), 1.63 (quintet, J = 8 Hz, 2H), 2.36 (s, 3H), 2.49 (dt, J = 8 and 2 Hz, 2H), 6.39 (t, J = 2 Hz, 1H), 7.15–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 25.5, 27.1, 29.3, 29.4, 29.5, 29.7 (8 carbons), 31.9, 125.9, 126.3, 128.9, 129.7, 137.7, 150.3, 170.0, 170.5; ESIMS (*m*/*z*) 444 $[M+H+MeOH]^+$; HRMS (ESI) calcd for $C_{27}H_{42}NO_2$ $[M+H]^+$ 412.3216, found 412.3213; IR ($CHCl_3$) ν_{max} 1713, 1635 cm^{-1}.

1-(*p*-Tolyl)-3-(4,8,12-trimethyltridecyl)-1*H*-pyrrole-2,5-dione (4h, Diastereomeric Mixture).



Thick oil (290 mg, 70%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80–0.93 (m, 12H), 0.95–1.75 (m, 19H), 2.36 (s, 3H), 2.48 (dt, J = 8 and 2 Hz, 2H), 6.40 (t, J = 2 Hz, 1H), 7.15–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.5, 19.55, 19.64, 19.7, 21.1, 22.6, 22.7, 24.4, 24.7, 24.8, 25.8, 28.0, 32.5, 32.8, 36.55, 36.64, 37.2, 37.4, 39.3, 125.9, 126.3, 128.9, 129.7, 137.6, 150.3, 169.9, 170.6; ESIMS (*m*/*z*) 434 $[M+Na]^+$; HRMS (ESI) calcd for $C_{27}H_{42}NO_2$ $[M+H]^+$ 412.3216, found 412.3216; IR ($CHCl_3$) ν_{max} 1710, 1635 cm^{-1}.

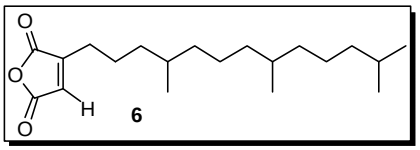
3-Hexyl-1-(*p*-tolyl)pyrrolidine-2,5-dione (5b).



Method A. To a solution of alkynylmaleimide **2b** (27 mg, 0.10 mmol) in ethyl acetate (2 mL) was added palladium on activated charcoal (5 mg, 10 wt %). The reaction mixture was stirred at 25 ^oC under balloon pressure hydrogen atmosphere for 1 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether–ethyl acetate (85:15) as an eluent to yield **5b**[17] as a white solid (21 mg, 78% yield).

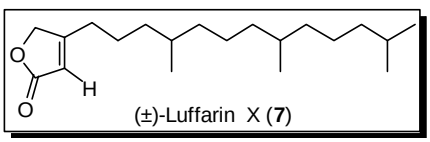
Method B. To a solution of alkynylmaleimide **2b** (27 mg, 0.10 mmol) in methanol (2 mL) was added Lindlar catalyst (10 mg, 5 wt %). The reaction mixture was stirred at 25 °C under balloon pressure hydrogen atmosphere for 5 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether–ethyl acetate (85:15) as an eluent to yield **5b** as a white solid (20 mg, 74% yield). Mp 74–76 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 6 Hz, 3H), 1.20–1.55 (m, 8H), 1.55–1.75 (m, 1H), 1.90–2.10 (m, 1H), 2.39 (s, 3H), 2.45–2.72 (m, 1H), 2.87–3.10 (m, 2H), 7.16 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 21.1, 22.5, 26.5, 28.9, 31.4, 31.5, 34.4, 39.9, 126.2, 129.2, 129.7, 138.5, 175.8, 179.1; ESIMS (m/z) 296 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1705 cm^{-1}.

3-(4,8,12-Trimethyltridecyl)furan-2,5-dione (6, Diastereomeric Mixture).



To a stirred solution of monoalkylmaleimide **4h** (1.20 g, 2.92 mmol) in THF (6 mL) was added 5% aq. LiOH (3 mL) solution in a dropwise manner. The reaction mixture was stirred at 25 °C for 48 h. The reaction mixture was acidified with 10% aq HCl (3 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue without any further purification was heated at 100 °C in acetic anhydride (10 mL) for 5 h. The acetic anhydride was distilled off in vacuo, and obtained residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (9:1) as an eluent to yield the desired anhydride **6** as thick liquid (580 mg, 62% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80–0.93 (m, 12H), 1.00–1.80 (m, 19H), 2.51 (dt, J = 8 and 2 Hz, 2H), 6.60 (t, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 19.5, 19.6, 19.7, 22.6, 22.7, 24.4, 24.5, 24.8, 26.2, 28.0, 32.5, 32.7, 36.4, 36.5, 37.1, 37.15, 37.24, 37.29, 37.33, 39.3, 128.4, 153.8, 164.0, 165.9; ESIMS (m/z) 377 $[M+Na+MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{35}O_3$ $[M+H]^+$ 323.2586, found 323.2585; IR ($CHCl_3$) ν_{max} 1842, 1777, 1707, 1642 cm^{-1}.

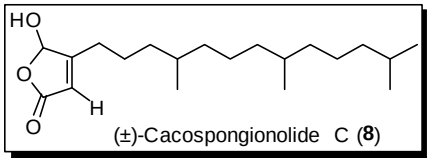
4-(4,8,12-Trimethyltridecyl)furan-2(5*H*)-one (Luffarin X, 7, Diastereomeric Mixture).



To a stirred solution of alkylmaleic anhydride **6** (50 mg, 0.15 mmol) in dry THF (3 mL) at 0 °C was added $NaBH_4$ (6.84 mg, 0.18 mmol) in a three equal portion over a period of 10

min. The reaction mixture was allowed to reach room temperature (25 ^{o}C) and further stirred for 2 h. It was then quenched with dilute HCl (2 N, 3 mL) and extracted with ethyl acetate (5 mL × 3). The combined 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–ethyl acetate (9:1) as an eluent to yield the desired product **7**[12] as thick oil (41 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80–0.95 (m, 12H), 1.00–1.75 (m, 19H), 2.40 (t, J = 8 Hz, 2H), 4.75 (d, J = 2 Hz, 2H), 5.85 (t, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 19.5, 19.6, 19.7, 22.6, 22.7, 24.4, 24.7, 27.9, 28.8, 32.5, 32.7, 36.5, 36.6, 37.1, 37.16, 37.19, 37.25, 37.29, 39.3, 73.0, 115.3, 170.6, 174.1; ESIMS (*m*/*z*) 331 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1782, 1751, 1640 cm^{-1}.

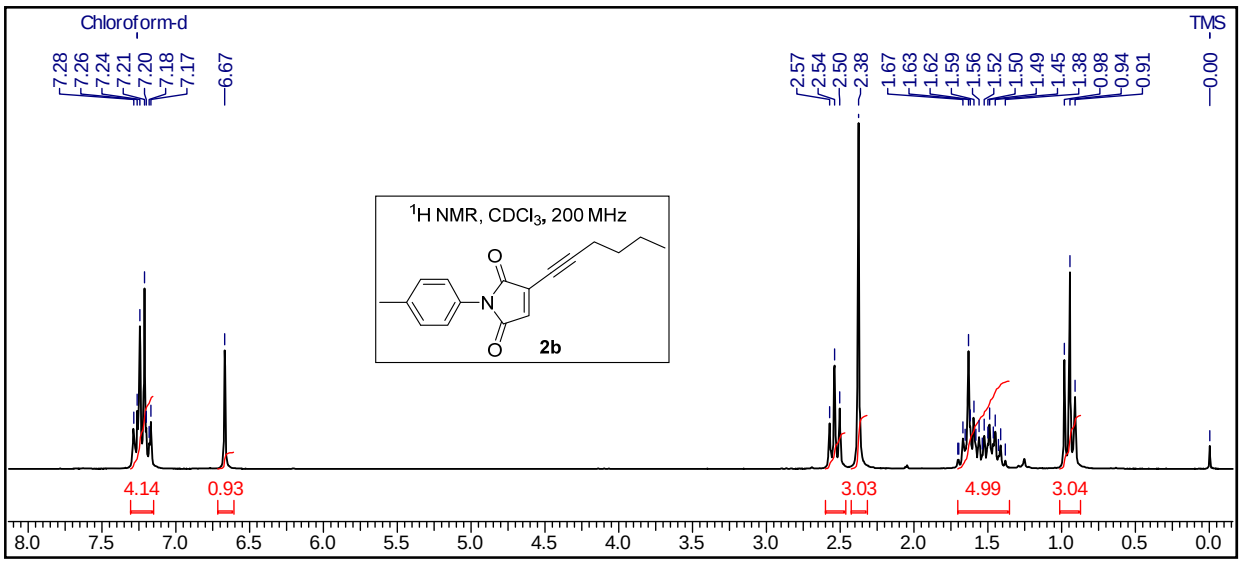
5-Hydroxy-4-(4,8,12-trimethyltridecyl)furan-2(5*H*)-one (Cacospongionolide C, 8, Diastereomeric Mixture).

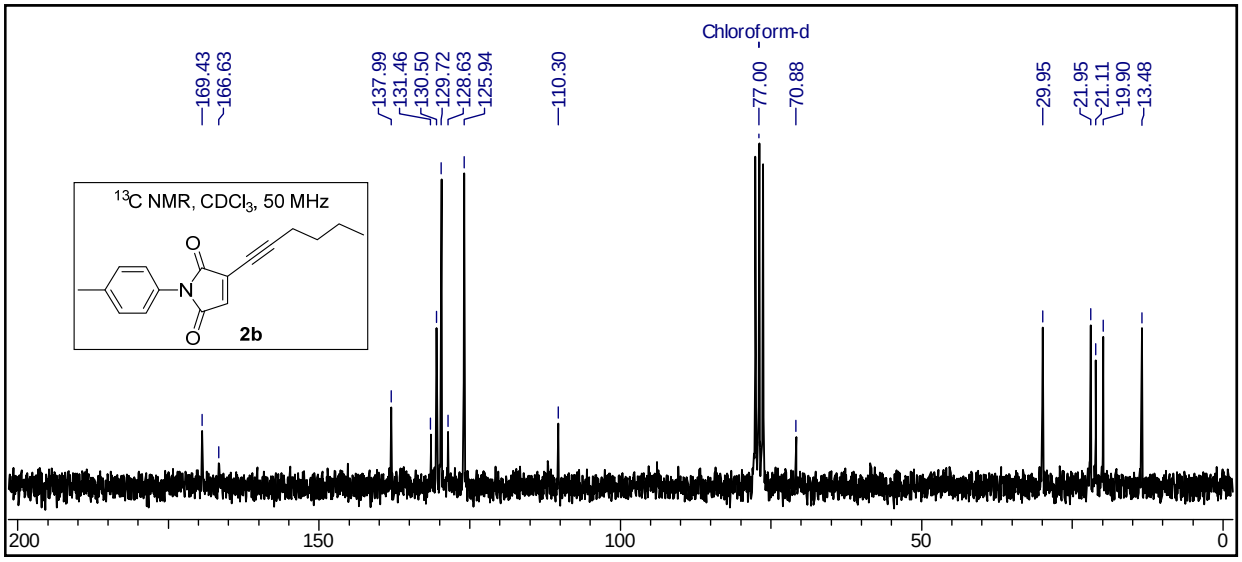


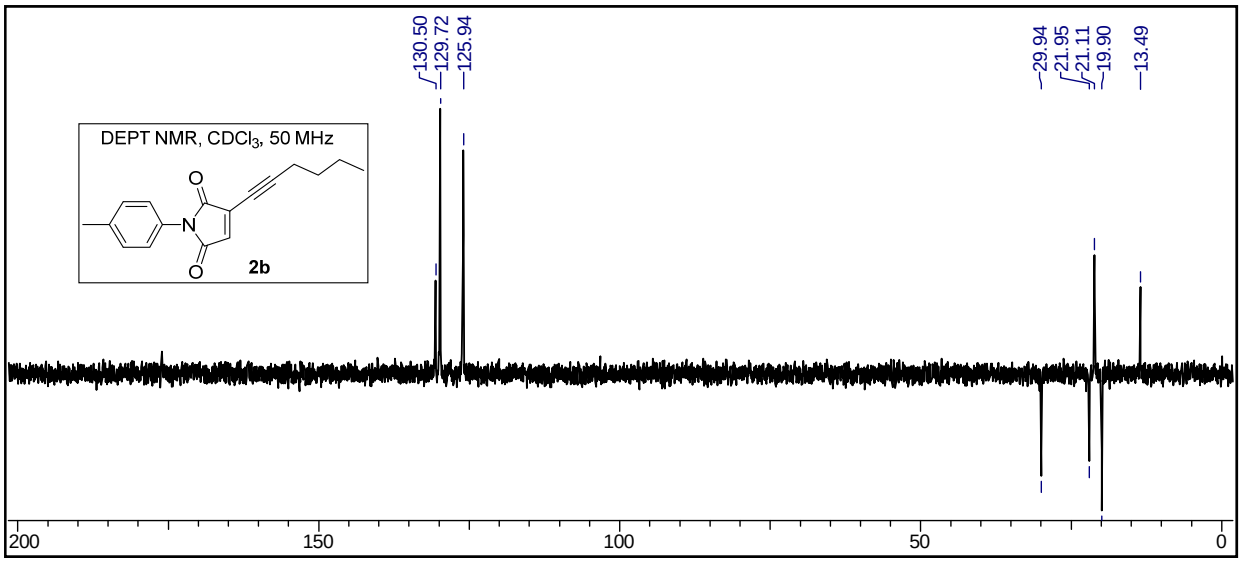
(±)-Cacospongionolide C (**8**)

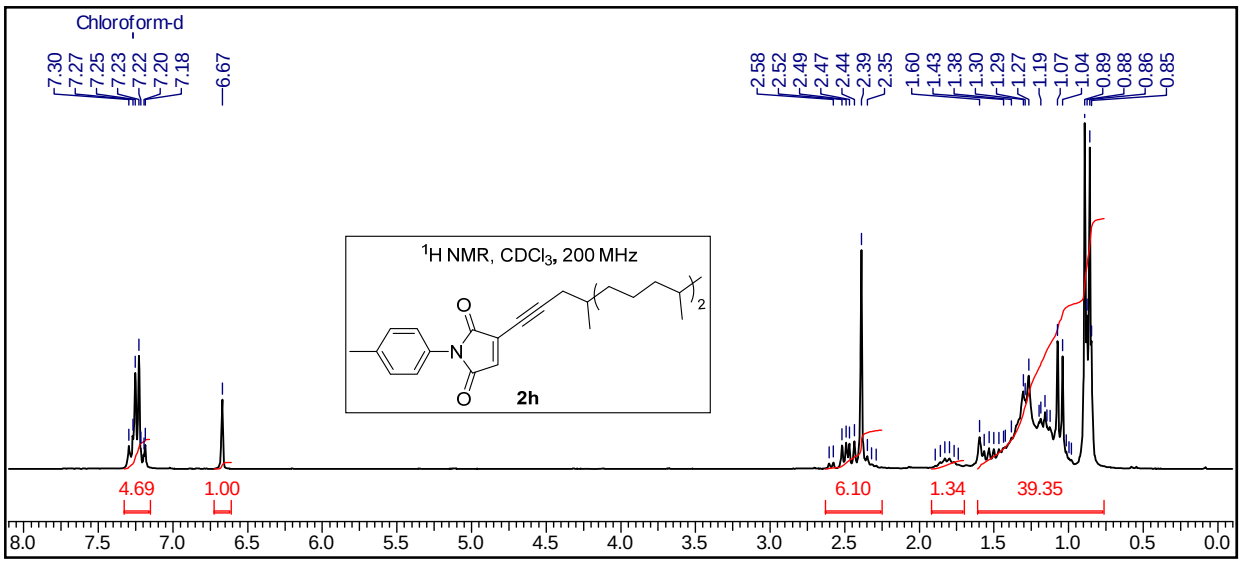
To a stirred solution of alkylmaleic anhydride **6** (50 mg, 0.15 mmol) in dry THF (3 mL) at −20 ^{o}C was added DIBAL-H or *N*-Selectride (1 M in THF, 0.18 mL, 0.18 mmol) in a dropwise manner over 10 min. The reaction mixture was stirred at –20 ^{o}C for 1 h and then at 25 ^{o}C for 1 h. It was then quenched with water (3 mL) and extracted with ethyl acetate (5 mL × 3). The combined 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–ethyl acetate (8:2) to give desired product **8**[13] as a thick oil (37 mg, 74% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80–0.93 (m, 12H), 0.95–1.75 (m, 19H), 2.20–2.60 (m, 2H), 5.39 (br s, 1H), 5.83 (s, 1H), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.44, 19.50, 19.53, 19.6, 19.7, 22.6, 22.7, 24.2, 24.4, 24.8, 27.9, 28.0, 32.5, 32.8, 36.6, 36.7, 37.3, 37.4, 39.3, 99.2, 117.2, 170.4, 172.0; ESIMS (*m*/*z*) 347 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3363, 1759, 1747, 1652 cm^{-1}.

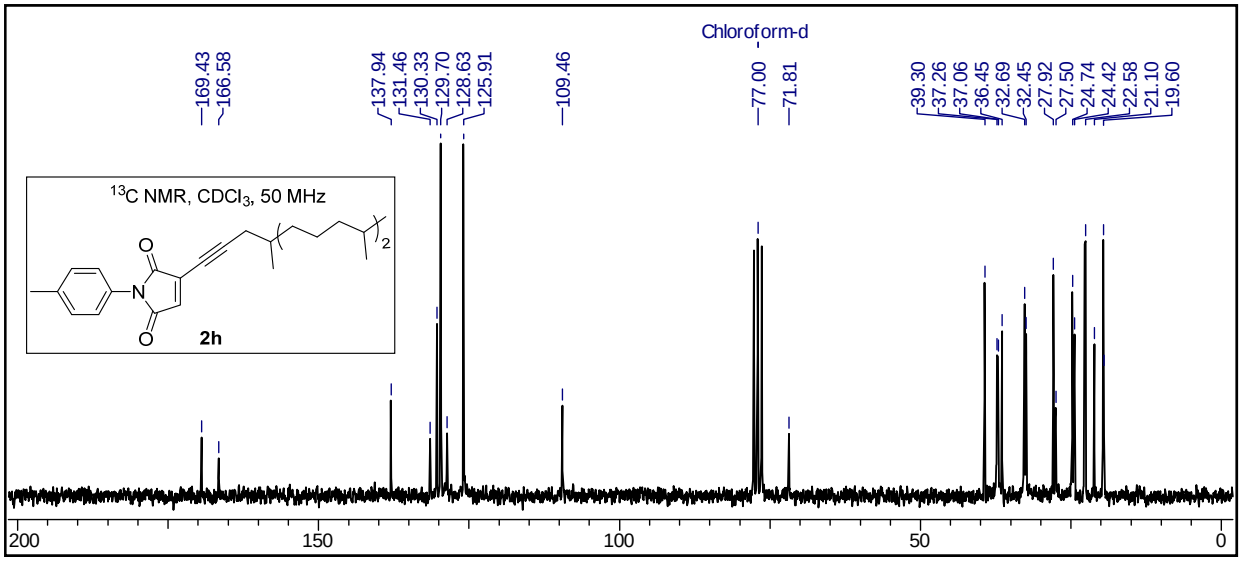
1B.5 Selected Spectra

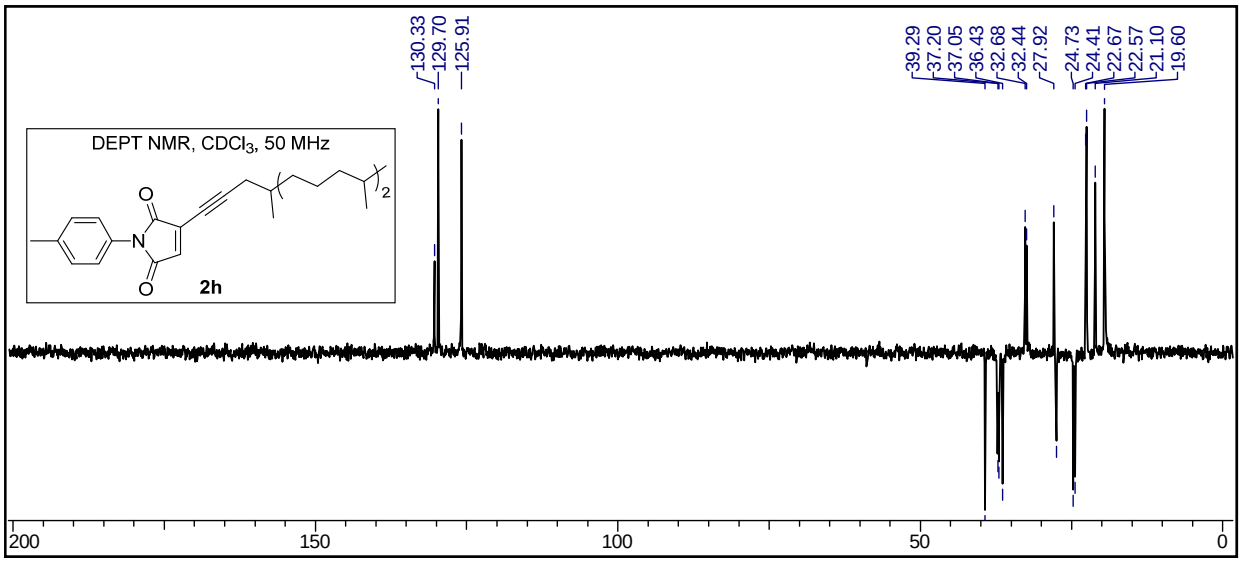

Chloroform-d
TMS
7.28
7.26
7.24
7.21
7.20
7.18
7.17
6.67
2.57
2.54
2.50
2.38
1.67
1.63
1.62
1.59
1.56
1.52
1.50
1.49
1.45
1.38
0.98
0.94
0.91
0.00
^{1}H NMR, $CDCl_3$, 200 MHz
2b
4.14
0.93
3.03
4.99
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

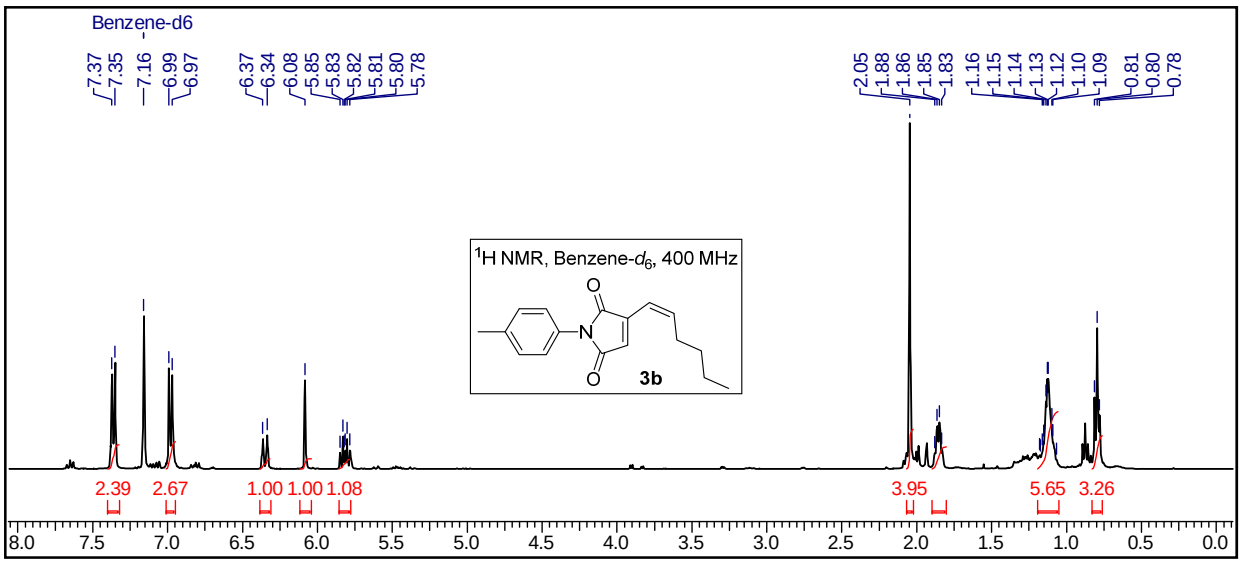

Chloroform-d
169.43
166.63
137.99
131.46
130.50
129.72
128.63
125.94
110.30
77.00
70.88
29.95
21.95
21.11
19.90
13.48
^{13}C NMR, $CDCl_3$, 50 MHz
2b
200
150
100
50
0

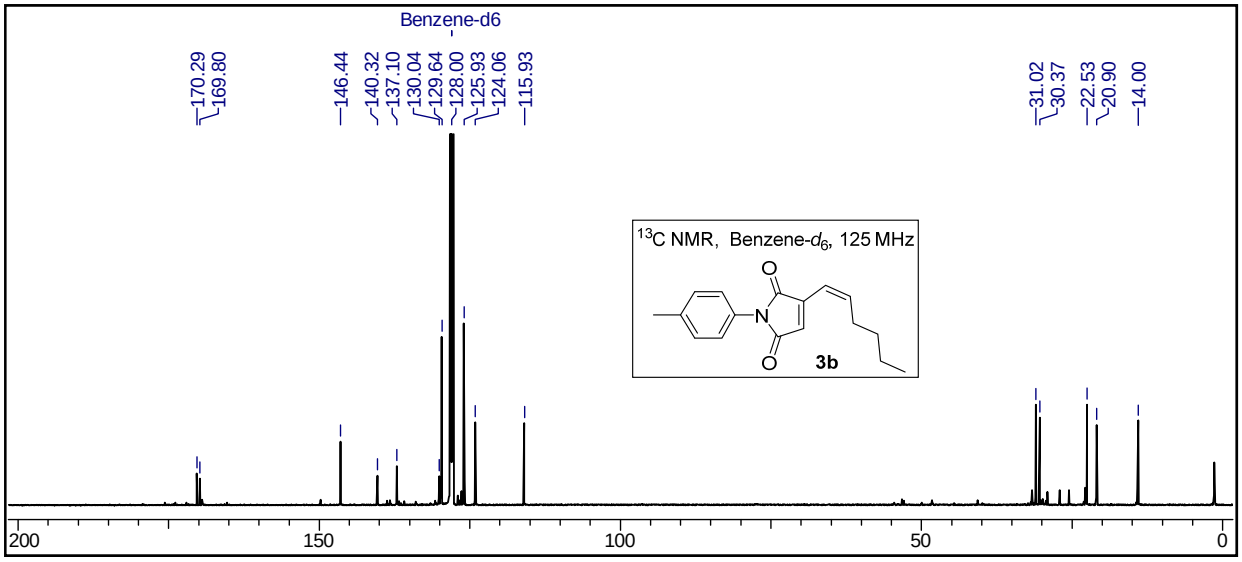

130.50
129.72
125.94
29.94
21.95
21.11
19.90
13.49
DEPT NMR, $CDCl_3$, 50 MHz
2b
200
150
100
50
0

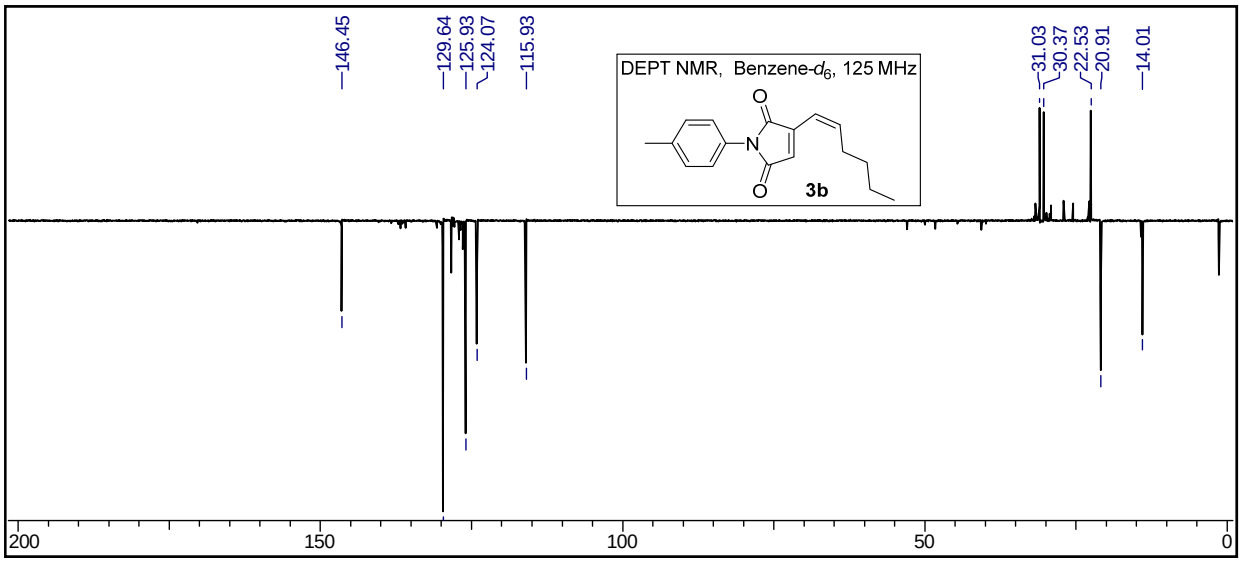

Chloroform-d
7.30
7.27
7.25
7.23
7.22
7.20
7.18
6.67
2.58
2.52
2.49
2.47
2.44
2.39
2.35
1.60
1.43
1.38
1.30
1.29
1.27
1.19
1.07
1.04
0.89
0.88
0.86
0.85
^{1}H NMR, $CDCl_3$, 200 MHz
2h
4.69
1.00
6.10
1.34
39.35
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

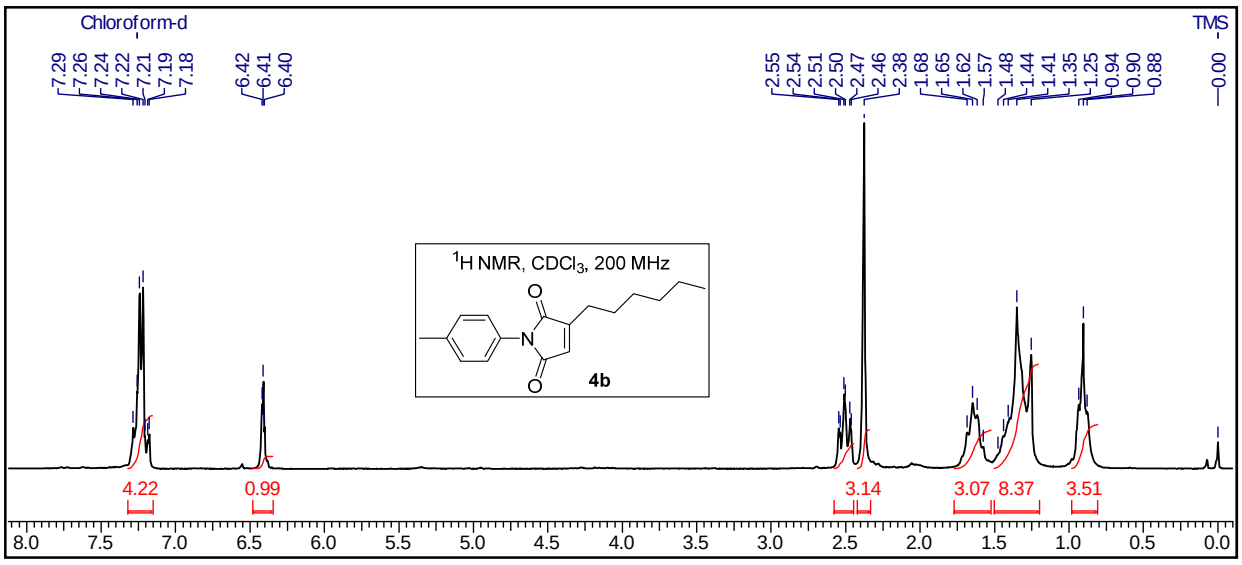

Chloroform-d
169.43
166.58
137.94
131.46
130.33
129.70
128.63
125.91
109.46
77.00
71.81
39.30
37.26
37.06
36.45
32.69
32.45
27.92
27.50
24.74
24.42
22.58
21.10
19.60
^{13}C NMR, $CDCl_3$, 50 MHz
2h
200
150
100
50
0

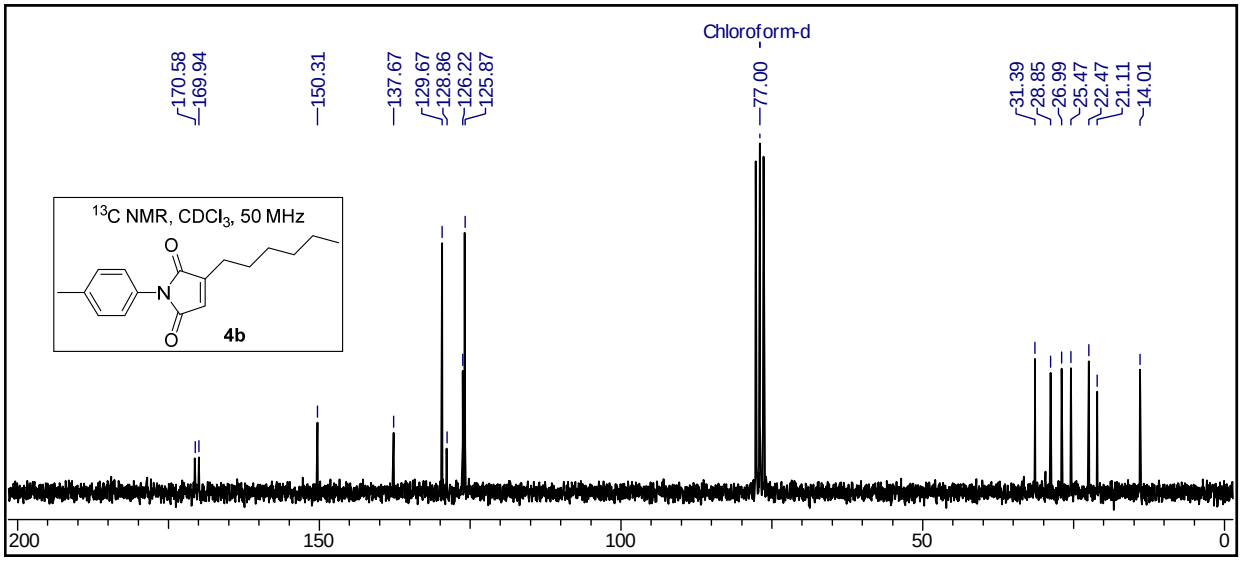

130.33
129.70
125.91
39.29
37.20
37.05
36.43
32.68
32.44
27.92
24.73
24.41
22.67
22.57
21.10
19.60
DEPT NMR, $CDCl_3$, 50 MHz
2h
200
150
100
50
0

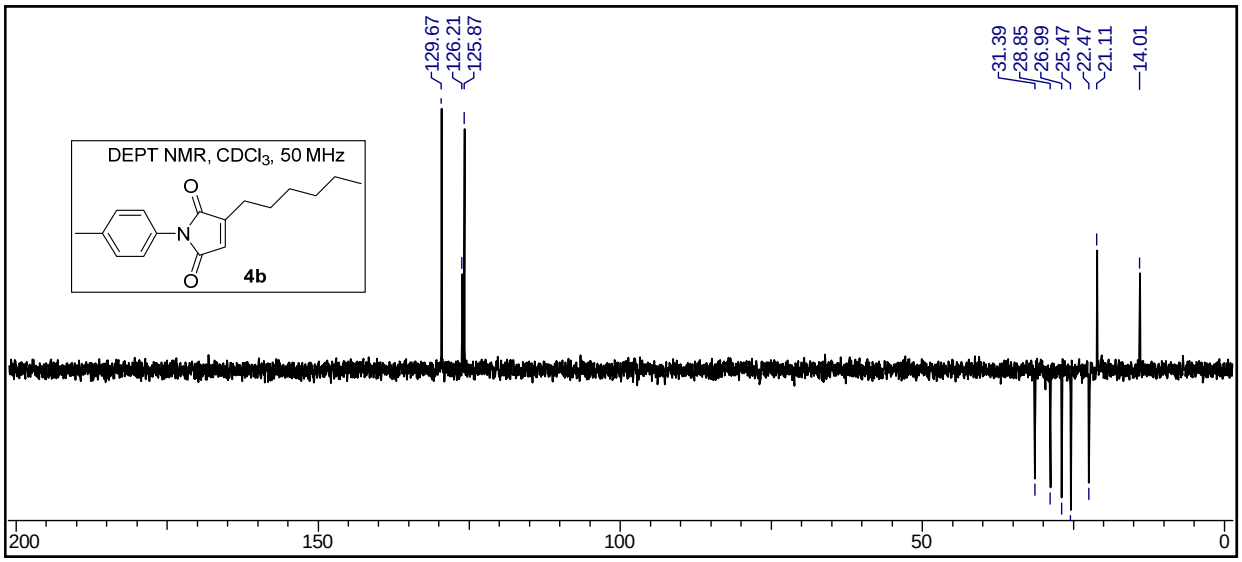

Benzene-d6
7.37
7.35
7.16
6.99
6.97
6.37
6.34
6.08
5.85
5.83
5.82
5.81
5.80
5.78
2.05
1.88
1.86
1.85
1.83
1.16
1.15
1.14
1.13
1.12
1.10
1.09
0.81
0.80
0.78
^{1}H NMR, Benzene-d_6, 400 MHz
3b
2.39
2.67
1.00
1.00
1.08
3.95
5.65
3.26
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

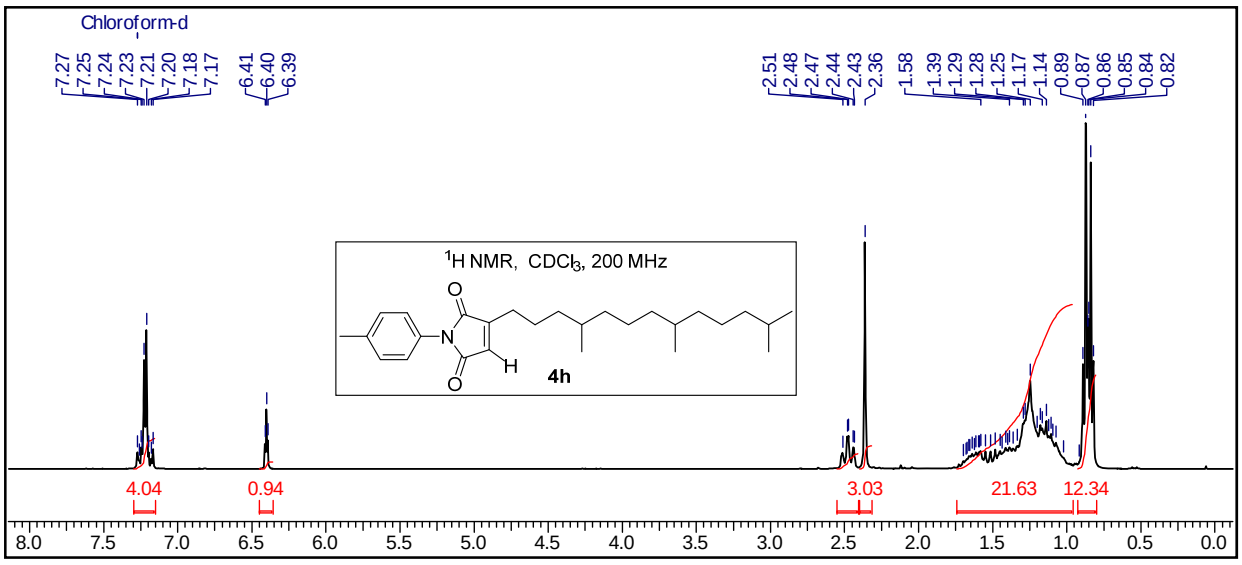

Benzene-d6
170.29
169.80
146.44
140.32
137.10
130.04
129.64
128.00
125.93
124.06
115.93
31.02
30.37
22.53
20.90
14.00
^{13}C NMR, Benzene-d_6, 125 MHz
3b
200
150
100
50
0

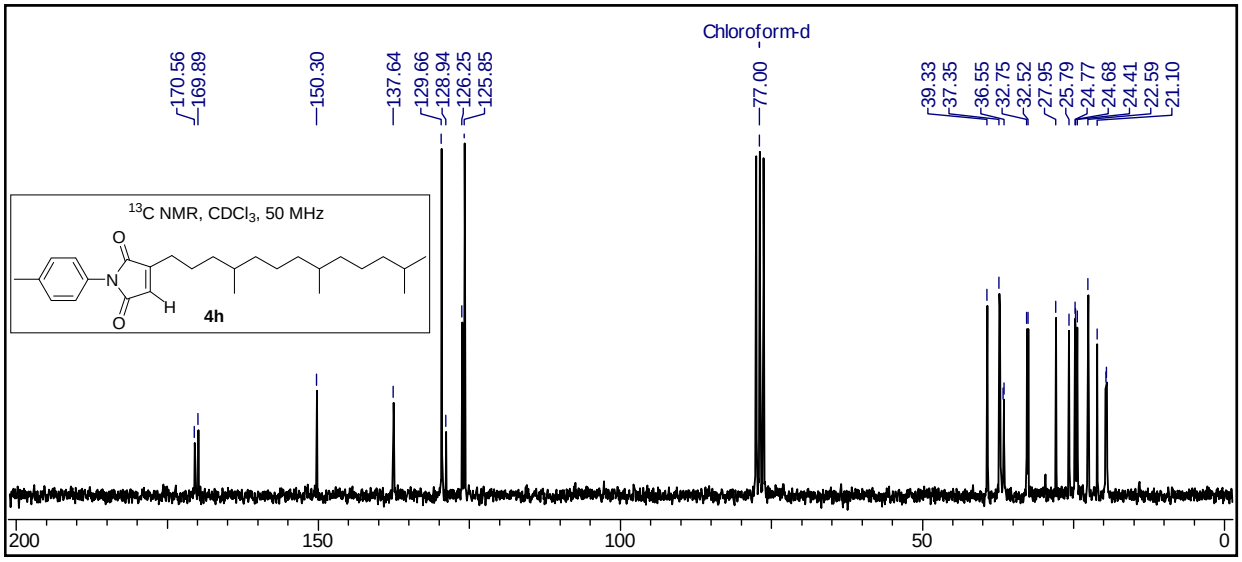

146.45
129.64
125.93
124.07
115.93
31.03
30.37
22.53
20.91
14.01
DEPT NMR, Benzene-d_6, 125 MHz
3b
200
150
100
50
0

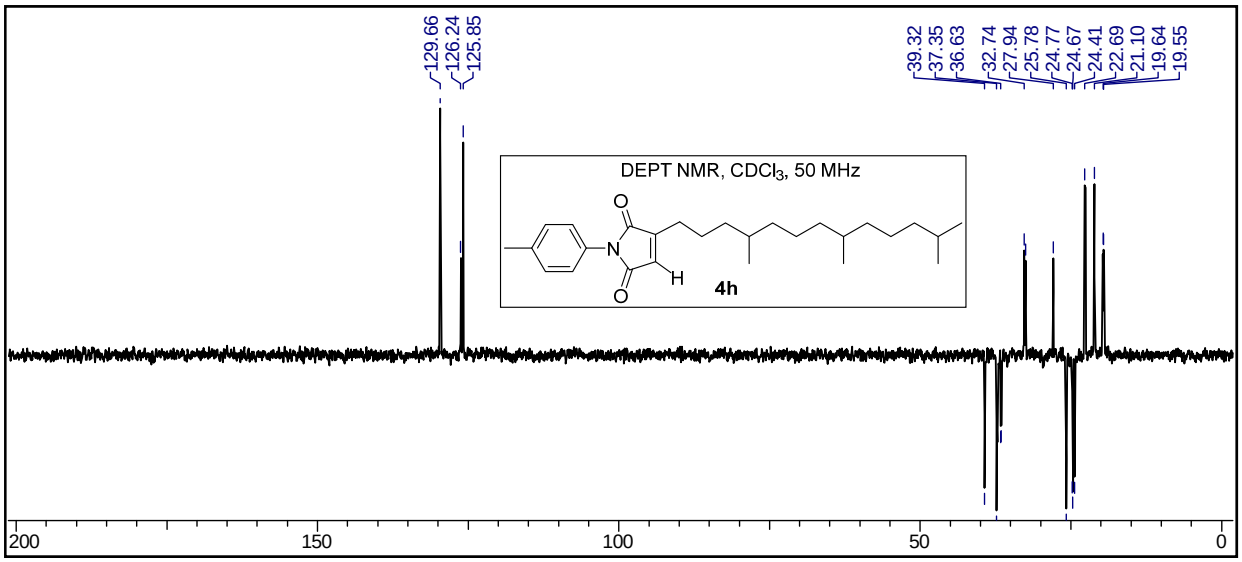

Chloroform-d
TMS
7.29
7.26
7.24
7.22
7.21
7.19
7.18
6.42
6.41
6.40
2.55
2.54
2.51
2.50
2.47
2.46
2.38
1.68
1.65
1.62
1.57
1.48
1.44
1.41
1.35
1.25
0.94
0.90
0.88
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
4b
4.22
0.99
3.14
3.07
8.37
3.51
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

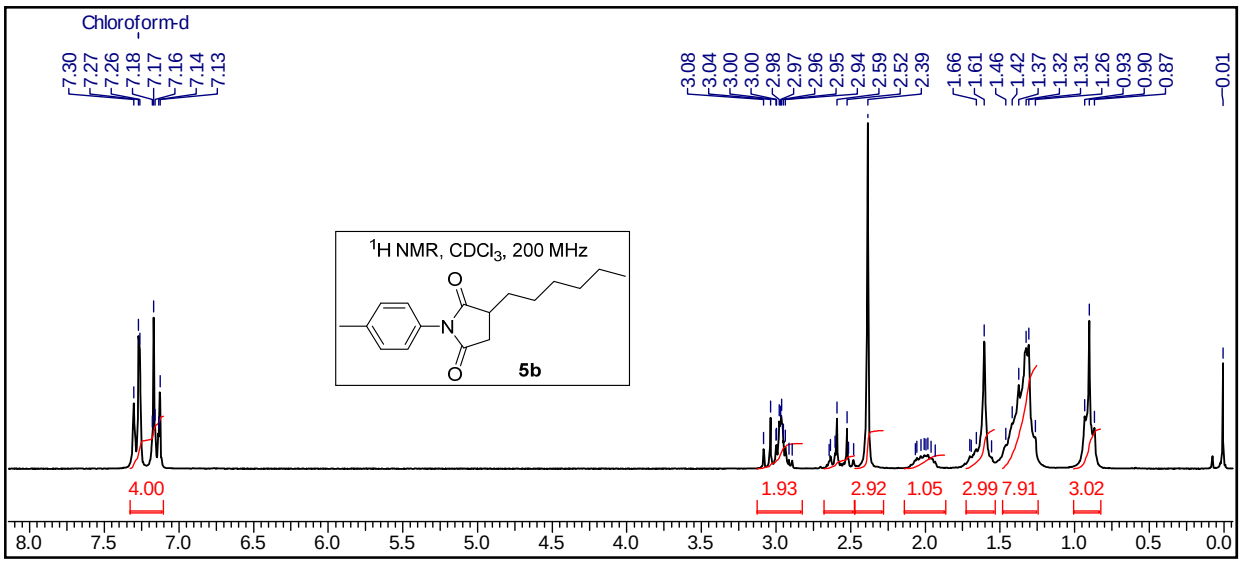

Chloroform-d
170.58
169.94
150.31
137.67
129.67
128.86
126.22
125.87
77.00
31.39
28.85
26.99
25.47
22.47
21.11
14.01
^{13}C NMR, CDCl$_3$, 50 MHz
4b
200
150
100
50
0

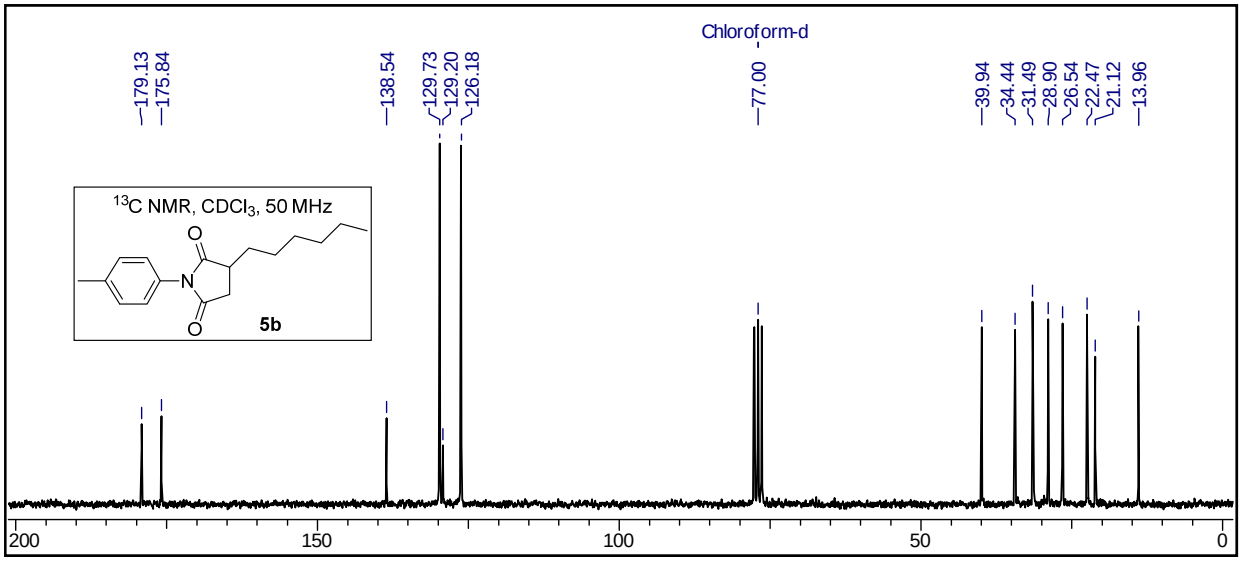

129.67
126.21
125.87
31.39
28.85
26.99
25.47
22.47
21.11
14.01
DEPT NMR, CDCl$_3$, 50 MHz
4b
200
150
100
50
0

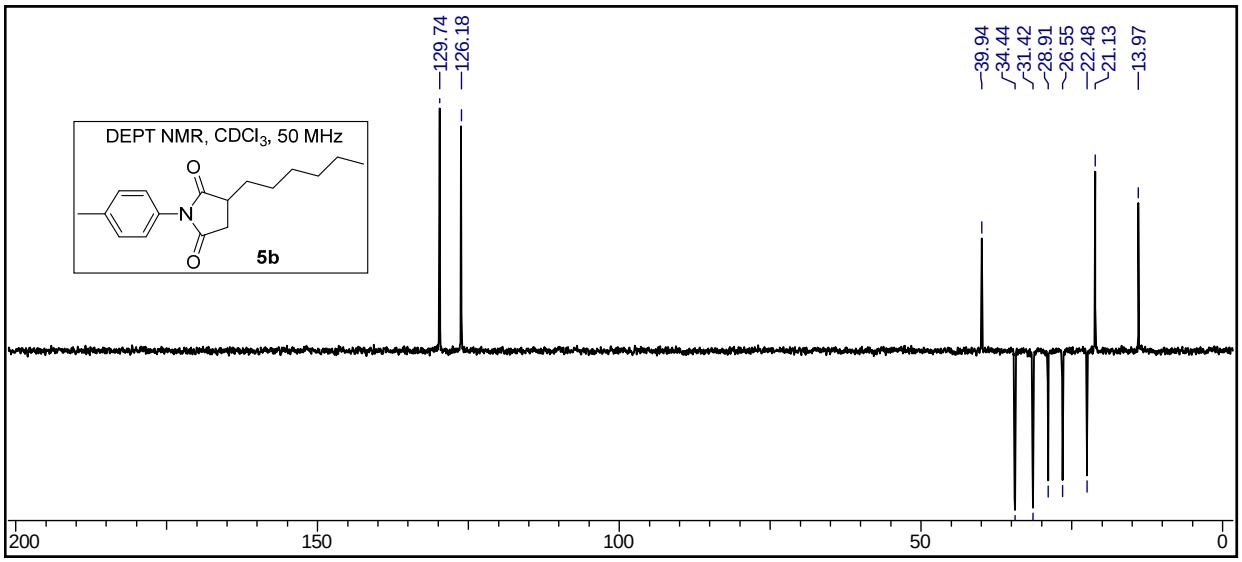

Chloroform-d
7.27
7.25
7.24
7.23
7.21
7.20
7.18
7.17
6.41
6.40
6.39
2.51
2.48
2.47
2.44
2.43
2.36
1.58
1.39
1.29
1.28
1.25
1.17
1.14
0.89
0.87
0.86
0.85
0.84
0.82
^{1}H NMR, CDCl$_3$, 200 MHz
4h
4.04
0.94
3.03
21.63
12.34
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

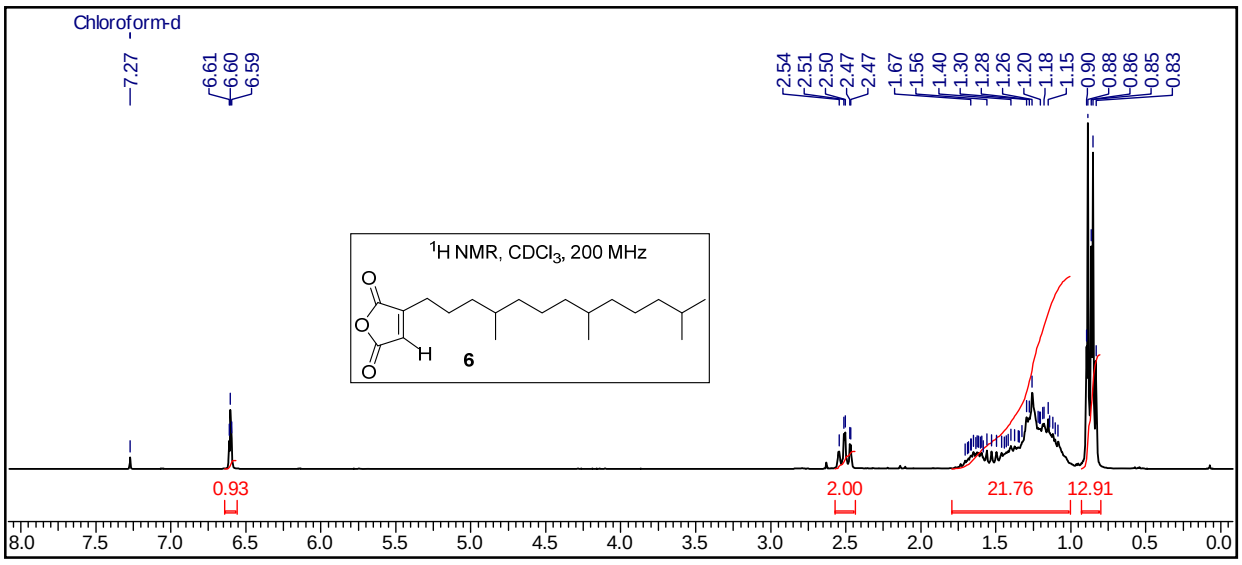

Chloroform-d
170.56
169.89
150.30
137.64
129.66
128.94
126.25
125.85
77.00
39.33
37.35
36.55
32.75
32.52
27.95
25.79
24.77
24.68
24.41
22.59
21.10
^{13}C NMR, CDCl$_3$, 50 MHz
4h
200
150
100
50
0

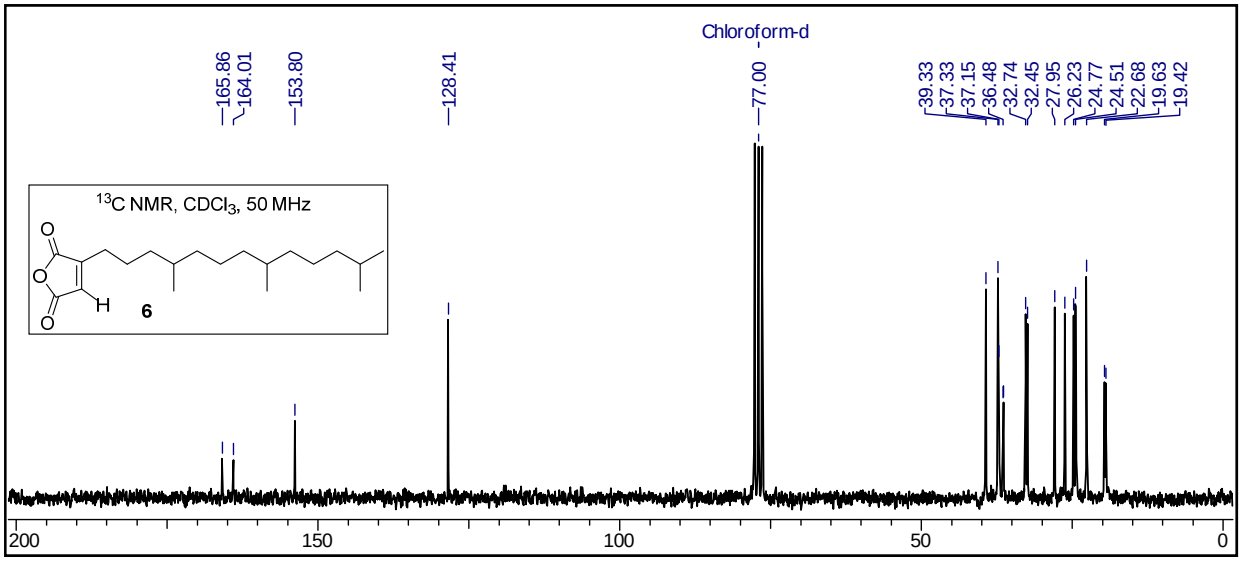

129.66
126.24
125.85
39.32
37.35
36.63
32.74
27.94
25.78
24.77
24.67
24.41
22.69
21.10
19.64
19.55
DEPT NMR, CDCl$_3$, 50 MHz
4h
200
150
100
50
0

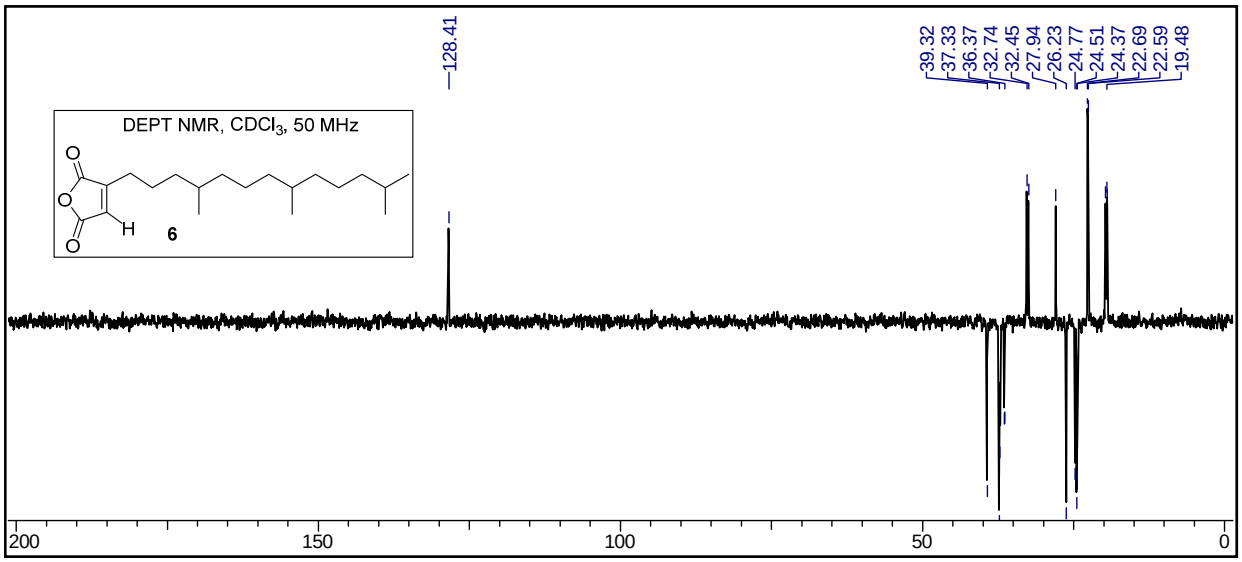

Chloroform-d
7.30
7.27
7.26
7.18
7.17
7.16
7.14
7.13
3.08
3.04
3.00
3.00
2.98
2.97
2.96
2.95
2.94
2.59
2.52
2.39
1.66
1.61
1.46
1.42
1.37
1.32
1.31
1.26
0.93
0.90
0.87
0.01
^{1}H NMR, CDCl$_3$, 200 MHz
5b
4.00
1.93
2.92
1.05
2.99
7.91
3.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

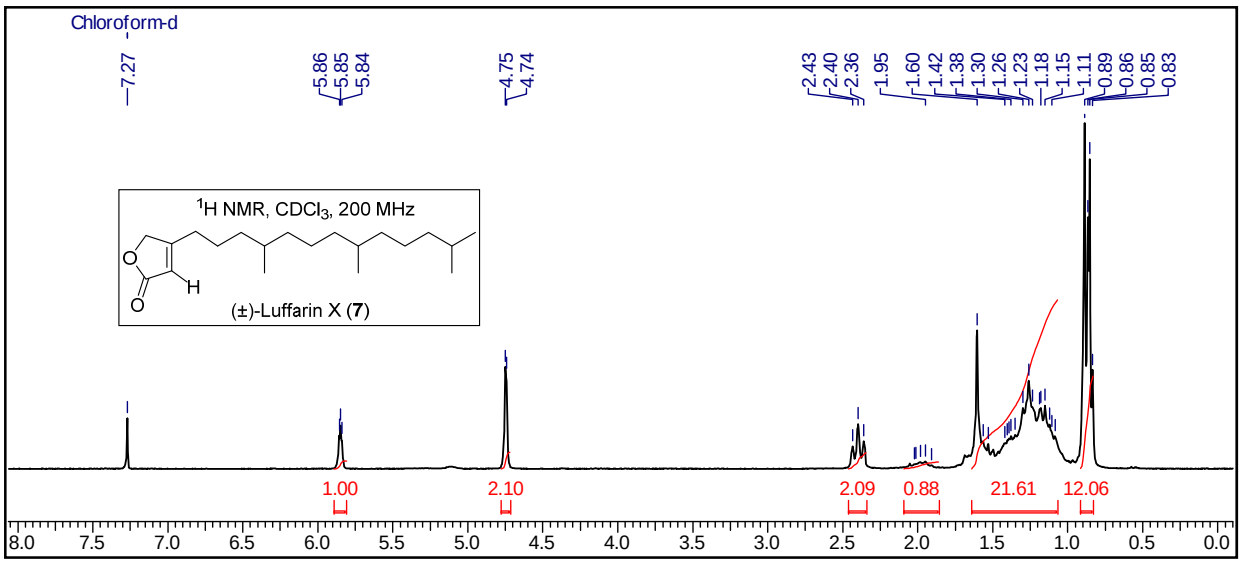

Chloroform-d
179.13
175.84
138.54
129.73
129.20
126.18
77.00
39.94
34.44
31.49
28.90
26.54
22.47
21.12
13.96
^{13}C NMR, CDCl$_3$, 50 MHz
5b
200
150
100
50
0

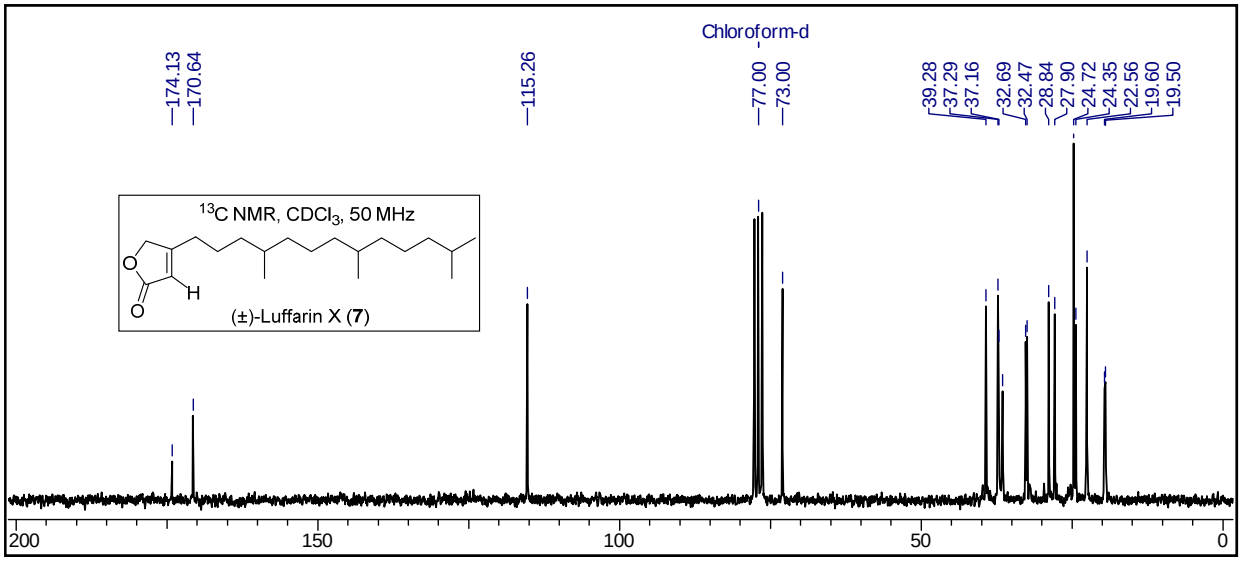

129.74
126.18
39.94
34.44
31.42
28.91
26.55
22.48
21.13
13.97
DEPT NMR, CDCl$_3$, 50 MHz
5b
200
150
100
50
0

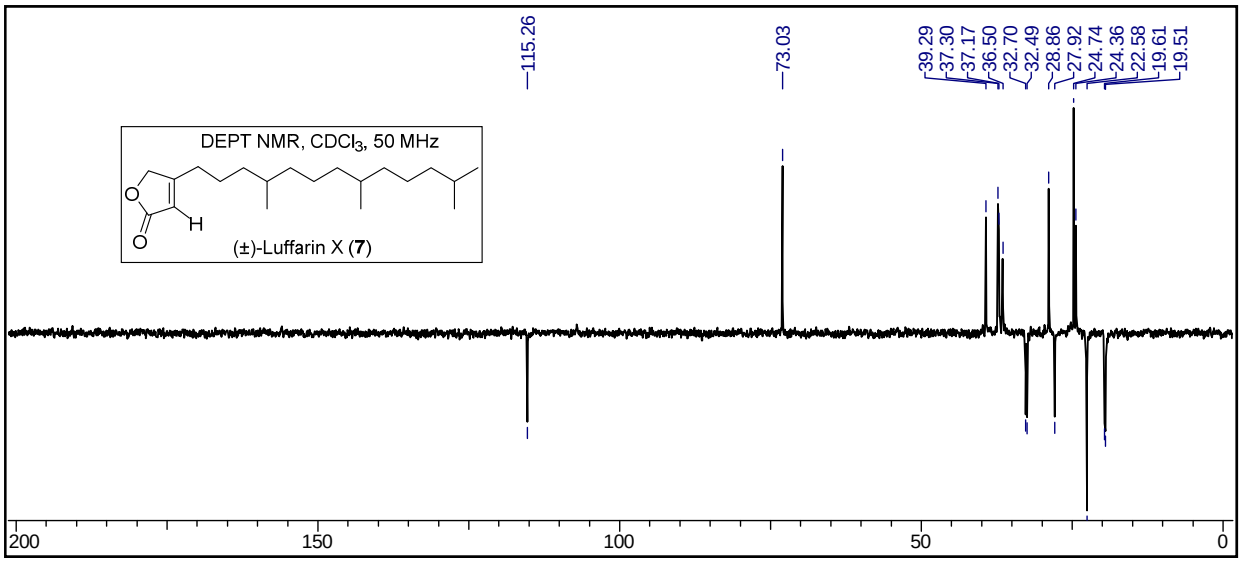

Chloroform-d
7.27
6.61
6.60
6.59
2.54
2.51
2.50
2.47
2.47
1.67
1.56
1.40
1.30
1.28
1.26
1.20
1.18
1.15
0.90
0.88
0.86
0.85
0.83
^{1}H NMR, CDCl$_3$, 200 MHz
6
0.93
2.00
21.76
12.91
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

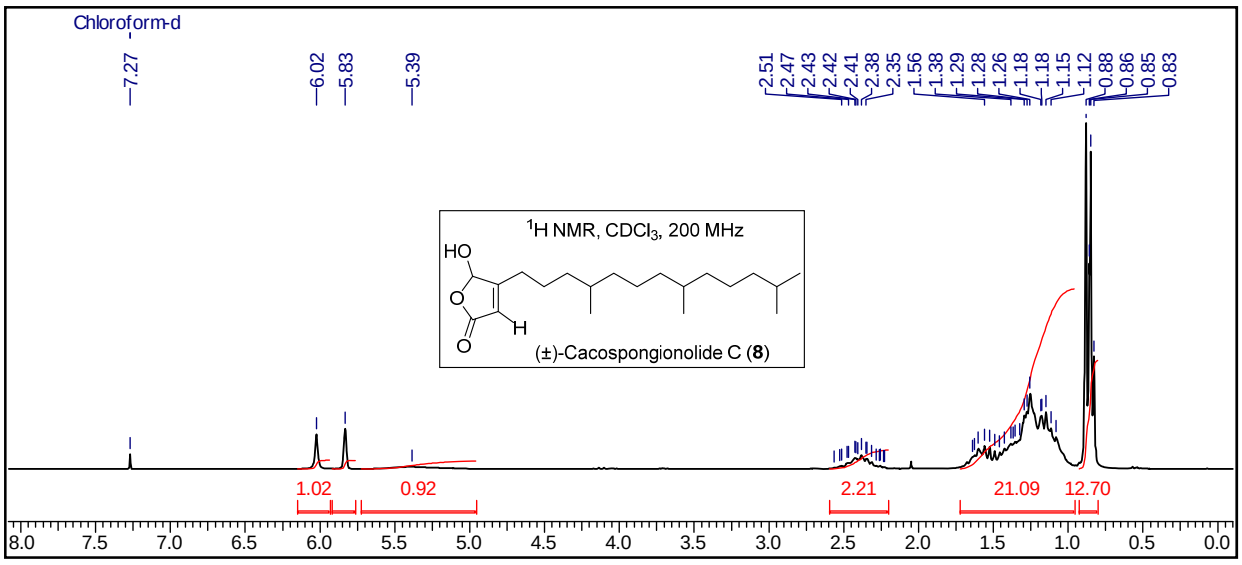

Chloroform-d
165.86
164.01
153.80
128.41
77.00
39.33
37.33
37.15
36.48
32.74
32.45
27.95
26.23
24.77
24.51
22.68
19.63
19.42
^{13}C NMR, CDCl$_3$, 50 MHz
6
200
150
100
50
0

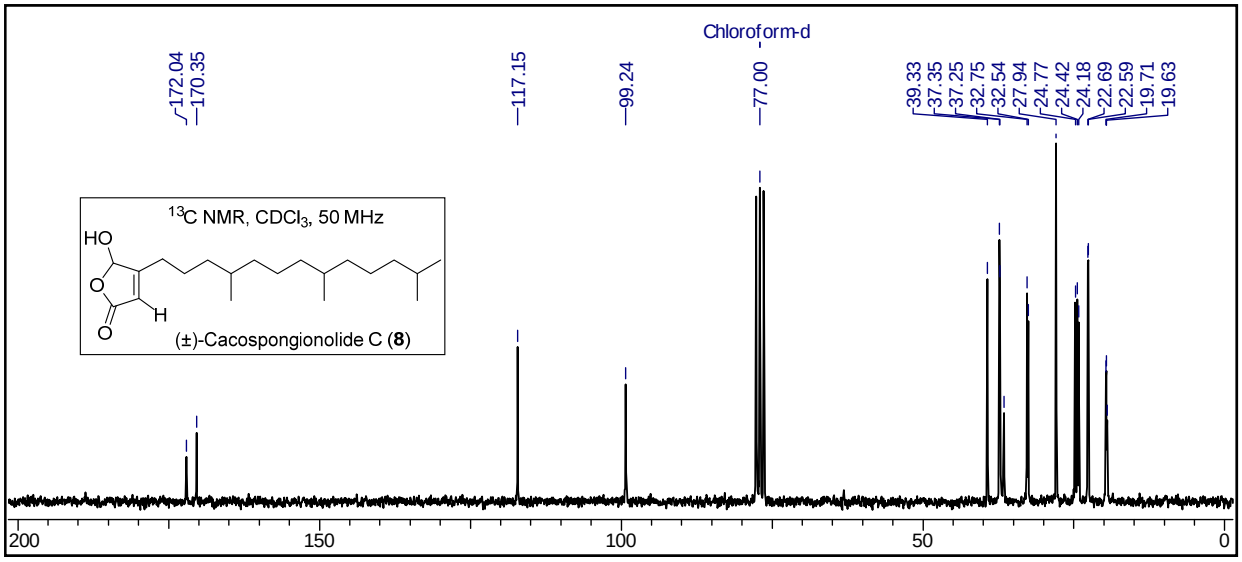

128.41
39.32
37.33
36.37
32.74
32.45
27.94
26.23
24.77
24.51
24.37
22.69
22.59
19.48
DEPT NMR, CDCl$_3$, 50 MHz
6
200
150
100
50
0

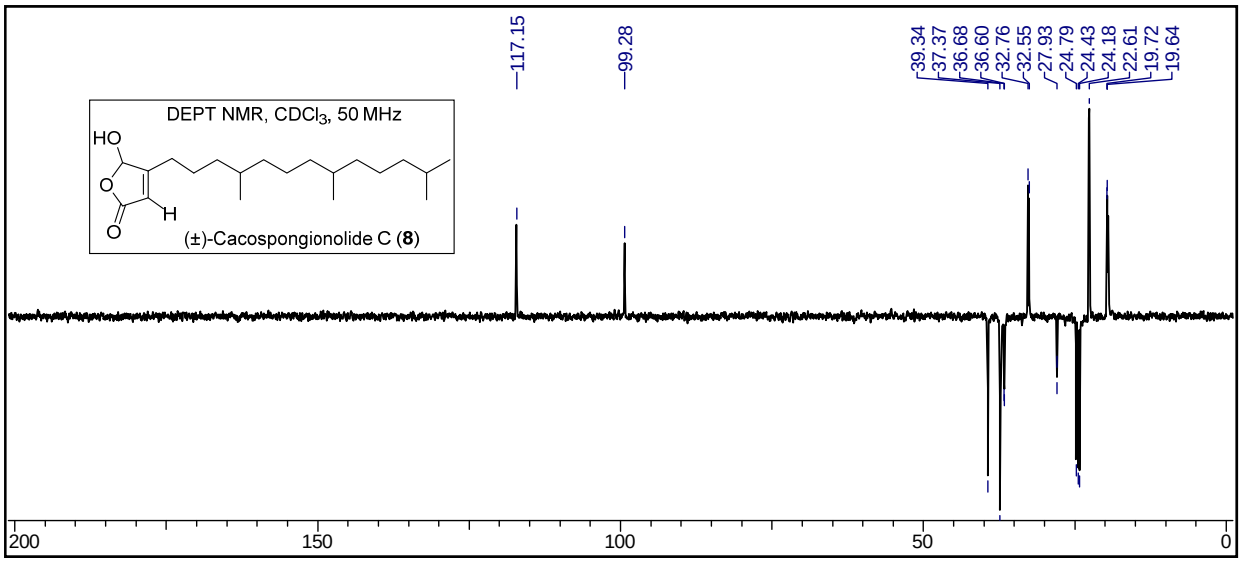

Chloroform-d
7.27
5.86
5.85
5.84
4.75
4.74
2.43
2.40
2.36
1.95
1.60
1.42
1.38
1.30
1.26
1.23
1.18
1.15
1.11
0.89
0.86
0.85
0.83
^{1}H NMR, CDCl$_3$, 200 MHz
(±)-Luffarin X (7)
1.00
2.10
2.09
0.88
21.61
12.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
174.13
170.64
115.26
77.00
73.00
39.28
37.29
37.16
32.69
32.47
28.84
27.90
24.72
24.35
22.56
19.60
19.50
^{13}C NMR, CDCl$_3$, 50 MHz
(±)-Luffarin X (7)
200
150
100
50
0


115.26
73.03
39.29
37.30
37.17
36.50
32.70
32.49
28.86
27.92
24.74
24.36
22.58
19.61
19.51
DEPT NMR, CDCl$_3$, 50 MHz
(±)-Luffarin X (7)
200
150
100
50
0


Chloroform-d
7.27
6.02
5.83
5.39
2.51
2.47
2.43
2.42
2.41
2.38
2.35
1.56
1.38
1.29
1.28
1.26
1.18
1.18
1.15
1.12
0.88
0.86
0.85
0.83
^{1}H NMR, CDCl$_3$, 200 MHz
HO
O
H
O
(±)-Cacospongionolide C (**8**)
1.02
0.92
2.21
21.09
12.70
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


Chloroform-d
172.04
170.35
117.15
99.24
77.00
39.33
37.35
37.25
32.75
32.54
27.94
24.77
24.42
24.18
22.69
22.59
19.71
19.63
^{13}C NMR, CDCl$_3$, 50 MHz
HO
O
H
O
(±)-Cacospongionolide C (**8**)
200
150
100
50
0


117.15
99.28
39.34
37.37
36.68
36.60
32.76
32.55
27.93
24.79
24.43
24.18
22.61
19.72
19.64
DEPT NMR, CDCl$_3$, 50 MHz
HO
O
H
O
(±)-Cacospongionolide C (**8**)
200
150
100
50
0

1B.6 References

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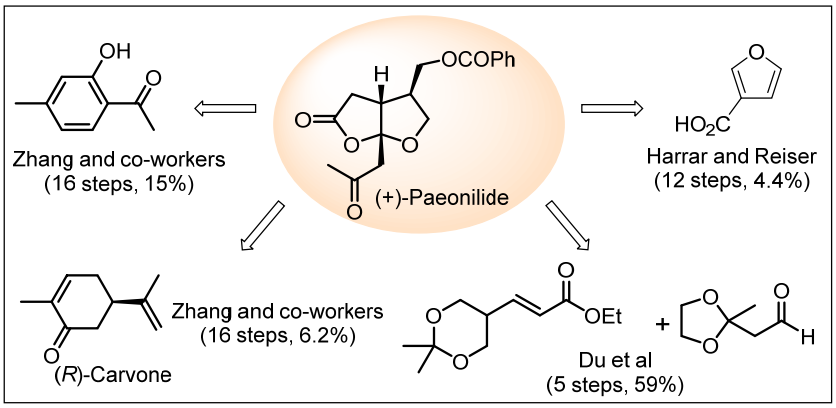
CHAPTER 2

Diastereoselective Total Synthesis of Paeonilide

This chapter features the following topics:

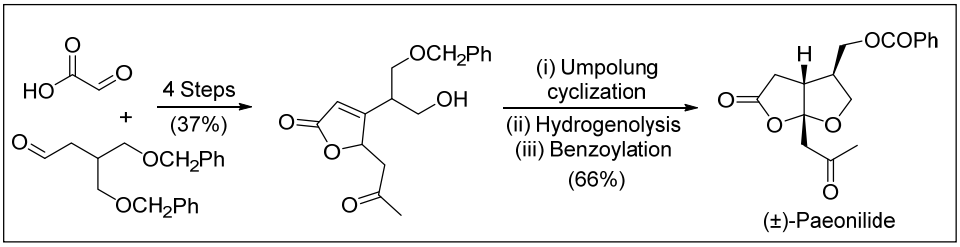
Notes: (i) An independent figure, table, scheme, structure and reference numbers have been used for the each section, (ii) detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end part of section B.

This chapter is divided into two sections. The section A presents a concise literature account on isolation, structure, activity and schematic summary of all syntheses of naturally occurring paeonilide. To date, four well-designed approaches for the synthesis of paeonilide have been reported in the literature. A concise representation on these elegant literature approaches has been exemplified in brief (Scheme 1).



Scheme 1. Fundamental Literature Approaches for the Total Synthesis of (±)/(+)/(–)-Paeonilides

The section B describes our contribution on the remarkable reactivity reversal stratagem in 3,4-disubstituted butenolides under acidic conditions and its application in diastereoselective total synthesis of paeonilide. Design of suitably substituted multifunctional butenolide followed by an acid catalyzed chemo- and diastereoselective intramolecular ring closure via the reactivity umpolung has been demonstrated to accomplish a concise total synthesis of paeonilide (Scheme 2).



Scheme 2. Concise Diastereoselective Total Synthesis of (±)-Paeonilide via Reactivity Umpolung

Overall the protocol involves one-pot reduction of an α,β-unsaturated carbon−carbon double bond and intramolecular nucleophilic insertion of oxygen function at the electron rich γ-position of butenolide. The involved mechanistic aspects have also been discussed.

CHAPTER 2: SECTION A

A Concise Literature Account of Paeonilide

This section A of chapter 2 features the following topics:

2A.1 Introduction

The use of plants as medicines predates written human history. The use of herbs to treat disease is almost universal among non-industrialized societies and is often more affordable than purchasing pharmaceuticals. Ethnobotany[1] (the study of traditional human uses of plants) is recognized as an effective way to discover future medicines (reverse pharmacology). Paeonia root bark, "mu-dan-pi" or "dan-pi" in Chinese, is one of the most important herbal drugs used in China, Japan and Korea to alleviate the syndromes of blood stasis and in an analgesic relieve for soothing muscle pain.[2] Since Paeony roots are under chemical and pharmacological investigation for many years, several new componants have been isolated, characterized and pharmacologically examined (Figure 1).[3]

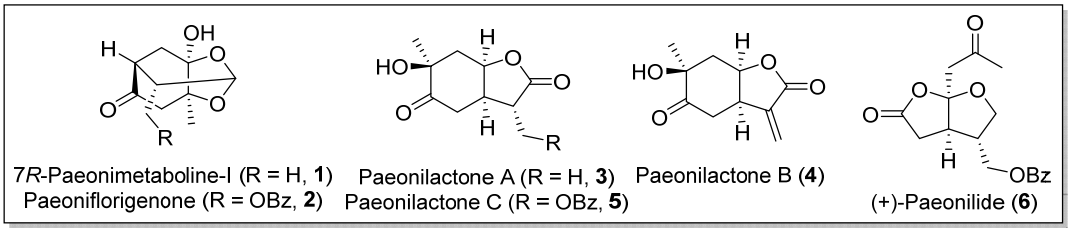
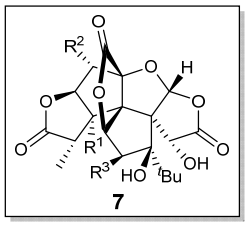


Figure 1. Natural products isolated from paeony roots

A metabolite, 7*R*-paeonimetaboline-I (**1**) isolated from bacterial digestion of paeony extracts,[4] inhibits penetetraxole- and pentylenetetrazole-induced convulsions in rats.[2] The monoterpenoids, paeoniflorigenone (**2**) has a blocking effect on the neuromuscular junction in phrenic nerve diaphragm preparations of mice.[2d,5] Paeonilactone C (**5**) suppresses both directly and indirectly stimulated muscle twitching of sciatic nerve-sartorius muscle from frogs.[2e,6]

(+)-Paeonilide (**6**), a highly oxygenated irregular monoterpenoid-derived metabolite has been isolated by Liu and co-workers from roots of *Paeonia delavayi* in 2000.[7] Approximately, 1.13 kg of *Paeonia delavayi* roots provided 8 mg of pure (+)-paeonilide. Its structure was established by the combination of spectroscopic and crystallographic study. Paeonilide bears a partial ring structure of the privileged class of ginkgolides **7** from *Ginkgo biloba* which is a living fossil dating back 270 million years ago (Figure 2).[8] Ginkgolides are known to inhibit the human platelet aggregation by inhibition of the binding of (3*H*)-PAF-acether to its membrane platelet receptor.[9] The pharmacological properties are, inter alia, antagonism on PAF induced thrombosis, lung anaphylaxis, cardiac anaphylaxis and inhibition of transplant rejection.[10]

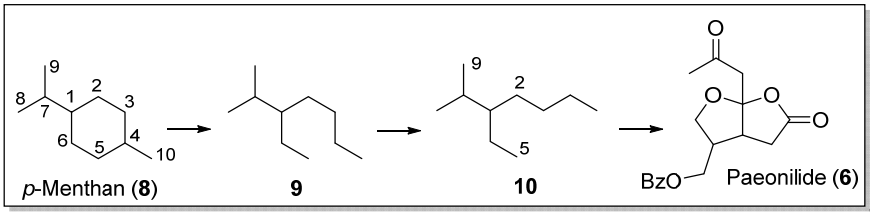


Ginkgolide	R^1	R^2	R^3
A	OH	H	H
B	OH	OH	H
C	OH	OH	OH
J	OH	H	OH
M	H	OH	OH

Figure 2. Naturally occurring bioactive ginkgolides

The inspiration from structural similarity with ginkgolides and in search of new lead, (+)-paeonilide was screened for bioassays.[7] The results confirmed a selective inhibition of the platelet aggregation induced by the platelet activating factor (PAF) with an IC_{50} value of 8 μg/mL (25 μM), importantly, without inhibitory effect on adenoside diphosphate (ADP) or arachidonic acid (AA)-induced platelet aggregation. The platelet-activating factor receptor is a G-protein coupled receptor which shows structural characteristics of the rhodopsin gene family and binds PAF. [11] The PAF is a phospholipid (1-0-alkyl-2-acetyl-sn-glycero-3-phosphorylcholine) which is implicated as a mediator in many pathologic processes like allergy, asthma, septic shock, arterial thrombosis and inflammation.[12]

The probable biogenesis of paeonilide may arise from re-arrangements of the isoprene units by cleavage of the cyclic monoterpenoid *p*-menthan (**8**). A subsequent oxidation and ring formation between *C*-2, *C*-5 and *C*-9 carbon atoms would generate the core structure of Paeonilide (Scheme 1).[7]



Scheme 1. Proposed Biosynthetic Pathway to Paeonilide

2A.2 Synthetic Approaches Towards Paeonilide

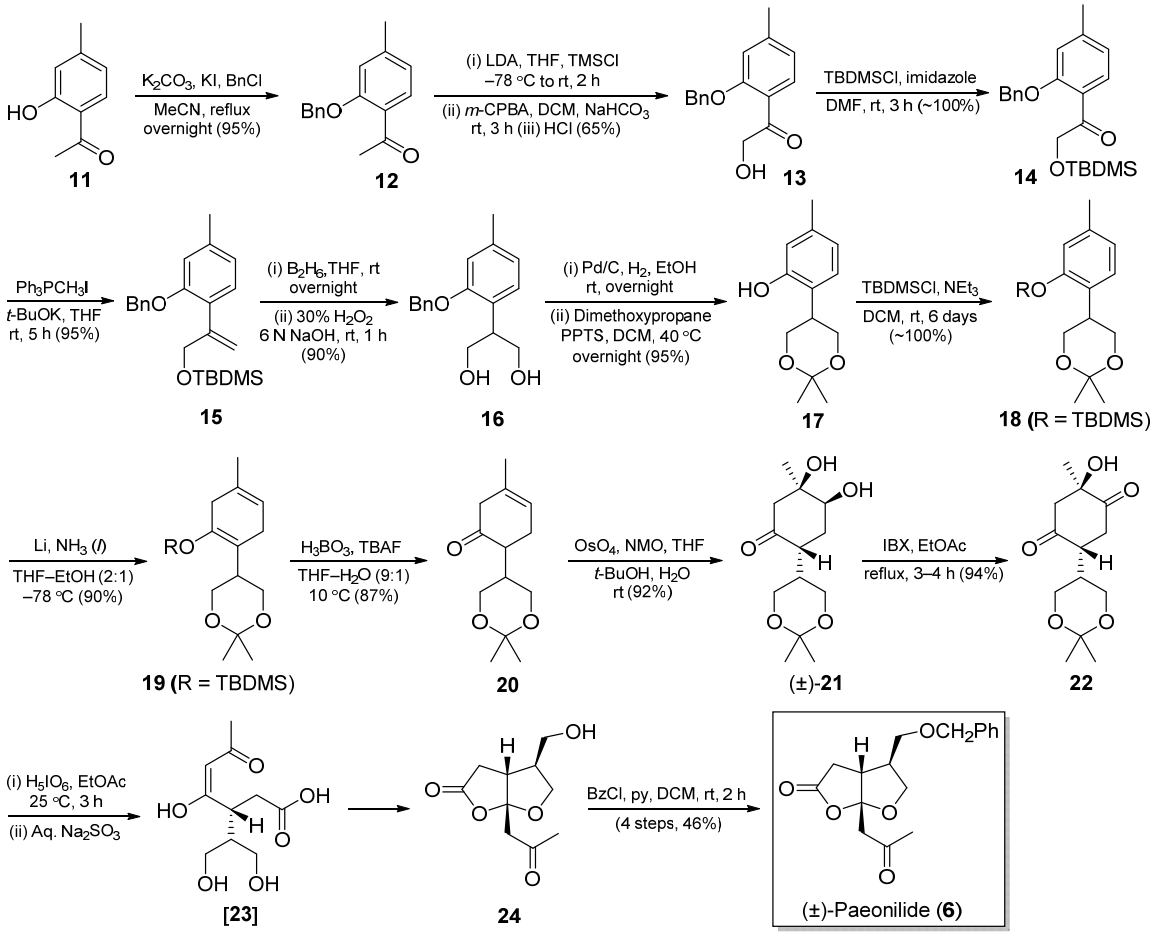
In a very short time paeonilide became a challenging synthetic target for many organic chemists. This is due to the combination of its interesting biological activity and the uncommonly densely oxygenated monoterpenoid attributed with an acetonyl moiety attached to the ketal function with contiguous three stereocenters on the tetrahydrofurofuran framework. In the total synthesis of paeonilide, generation of three contiguous chiral centres in an enantioselective or diastreoselective fashion is the challenging task. To date, two racemic and

two stereoselective well-organized total synthesis of paeonilide have been reported in the literature by employing new carbon−carbon/oxygen bond forming strategies. Herein a concise schematic summary on these elegant literature approaches has been presented (Schemes 2–5).

2A.2.1 Zhang's Approach Towards Total Synthesis of (±)-Paeonilide

Zhang and co-workers[13] achieved the total synthesis (±)-paeonilide in 16 steps with an overall yield of 15%. As described in Scheme 2, the synthesis started from commercially available 2-hydroxy-4-methylacetophenone (**11**).

Benzyl protection followed by Rubottom oxidation and TBDMS protection of resulting alcohol provided the *α*-hydroxy ketone compound **14**. Further, one carbon Wittig olefination followed by hydroboration of the resulting olefin gave the diol **16** in 86% yield. Benzyl group was deprotected using hydrogenolysis, 1,3-diol was protected to form the corresponding acetonate and phenolic hydroxyl group was protected with TBDMS chloride to afford compound **18**. The compound **18** was subjected to a Birch reduction followed by desilylation of resulting enol ether provided the desired nonconjugated enone **20** in 78% yields over two-step.

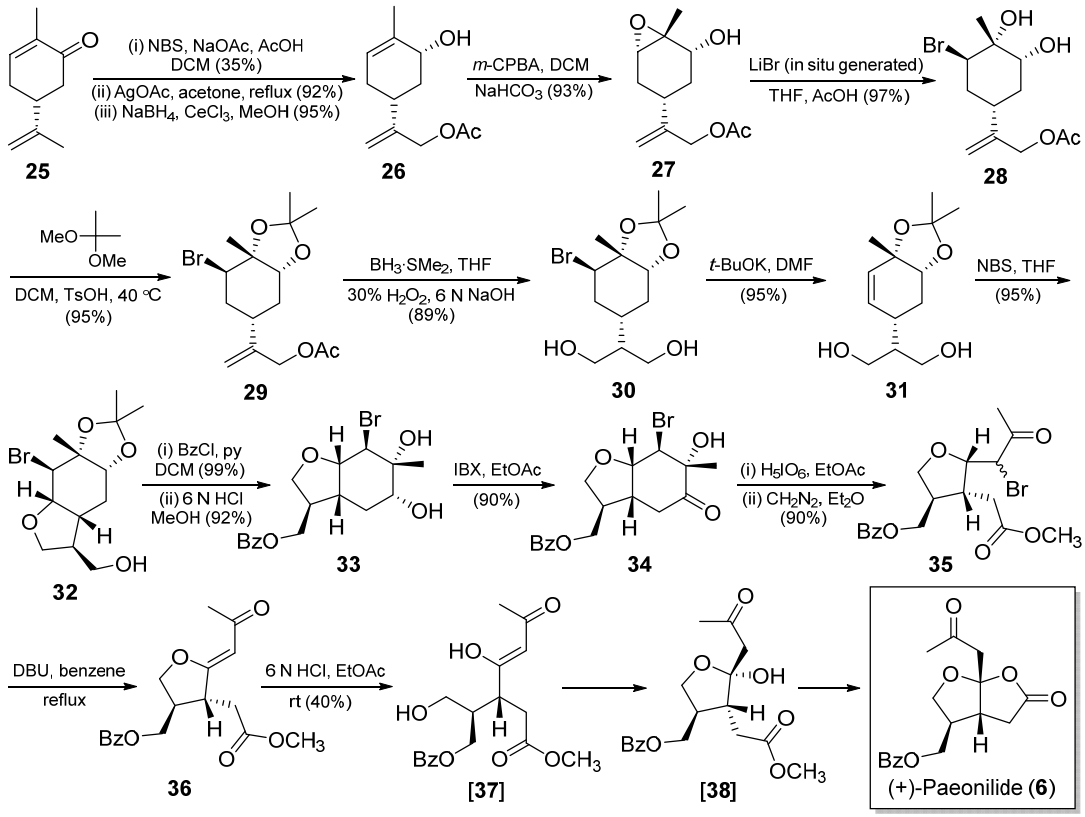


Scheme 2. Zhang's Total Synthesis of (±)-Paeonilide

The *cis*-dihydroxylation of *β,γ*-olefin using osmium tetroxide selectively produced (±)-**21** in 92% yield. The cause of diastereoselectivity is back side shielding by the acetonide ring. The selective IBX oxidation of secondary hydroxyl and oxidative cleavage with periodic acid generated the inisolable key intermediate **23**. The constitutionally similar but topologically different hydroxyl group in intermediate **23** underwent stereoselective intramolecular cyclization to deliver the desired alcohol **24**. Finally, benzoylation of free hydroxyl group provided racemic (±)-paeonilide (**6**). In the present synthesis use of an appropriate aromatic precursor to create all the desired functionalities in paeonilide is noteworthy.

2A.2.2 Zhang's Approach Towards Stereoselective Synthesis of (+)-Paeonilide

Zhang and co-workers also ascertained the stereoselective synthesis of (+)-paeonilide. Starting from (*R*)-carvone, paeonilide was obtained in 16 steps and 6.2% overall yield (Scheme 3).[14]



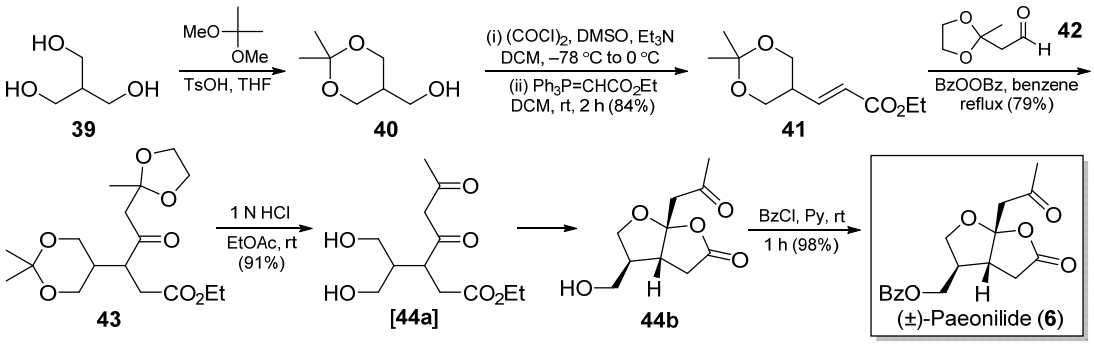
Scheme 3. Zhang's Total Synthesis of (+)-Paeonilide

Carvone (**25**) was selectively transformed into epoxide **27** via the allylic bromination, acetoxylation, Luche-reduction and hydroxyl directed chemo- and stereoselective epoxidation sequence. Regioselective epoxide opening with an *in situ* generated LiBr (acetyl bromide + *n*-BuLi) followed by ketal protection of the resulting vicinal diol **28** gave compound **29** in 92%

yields (2 steps). It was then subjected for hydroboration and the dehydrobromination was performed using *t*-BuOK to obtain the product **31**. The intramolecular diastereoselective bromoetherification using NBS lead to furan derivative **32**. Benzoylation of primary alcohol followed by deketalization under acidic conditions generated diol **33** in 91% yield. The IBX oxidation to ketone **34** and subsequent oxidative cleavage using periodic acid and trapping the free acid with diazomethane afforded diastereomeric mixture of compound **35**. Dehydrobromination by using DBU selectively yielded the key intermediate **36**. Finally, acid promoted furan opening and diastereoselective intramolecular cyclizations provided (+)-paeonilide (**6**) in 40% yield. The absolute configuration assigned for the natural paeonilide was confirmed on basis of this chiral pool synthesis.

2A.2.3 Du's Approach Towards Facile Synthesis of (±)-Paeonilide

The shortest five steps synthesis of paeonilide was published from Du's research group[15] with an overall yield of 59% starting from commercially available tris(hydroxymethyl)methane (**39**). As depicted in Scheme 4, the compound **39** was protected as the corresponding acetal **40** and subjected for a one-pot Swern oxidation and Wittig olefination to furnish the desired (*E*)-ester **41** in 84% yield. Benzoyl peroxide promoted Michael type radical addition of aldehyde **42** to ester **41** afforded the critical ketone-ester **43** in 79% yield. Acid promoted *in situ* deacetalization, hemiacetal formation and lactonization followed by benzoylation provided (±)-paeonilide (**6**) in 89% yield. Herein the selective ring closure in intermediate **44a** exclusively forming the paeonilide framework is remarkable.

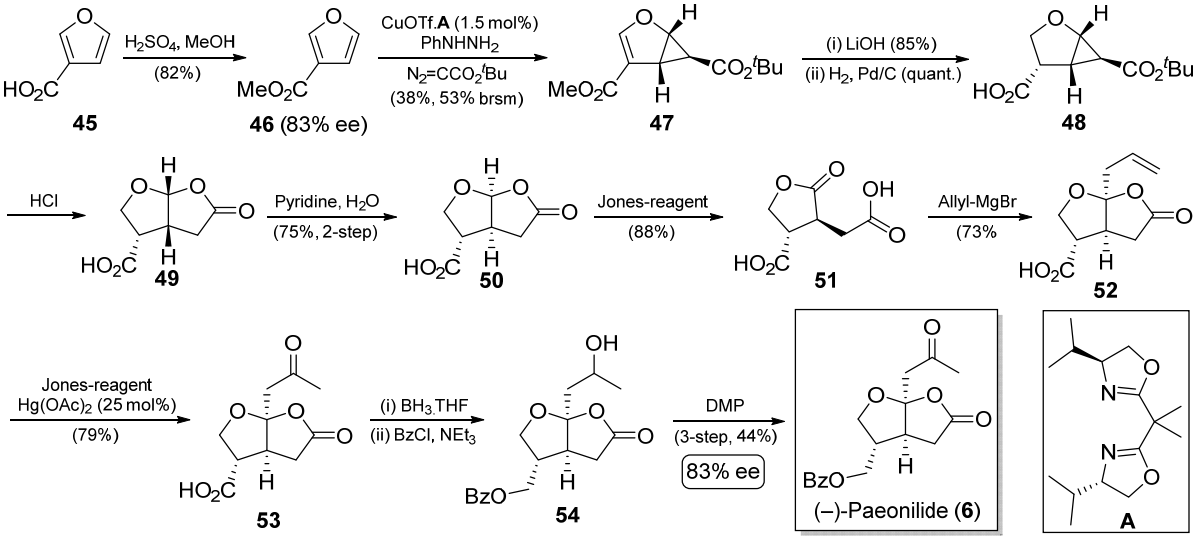


Scheme 4. Du's Total Synthesis of (±)-Paeonilide

2A.2.4 Reiser's Approach Towards Enantioselective Synthesis of (–)-Paeonilide

Very recently, Harrar and Reiser[16] reported the enantioselective synthesis of (–)-paeonilide in 12 steps with 4.4% overall yield via an asymmetric cyclopropanation-lactonization cascade and

a stereoselective side chain insertion reactions. As portrayed in Scheme 5, The enantioselective cyclopropanation of the furan **46** with *t*-butyl diazoacetate using copper(I)-bis(oxazoline) CuOTf.**A** complex resulted in formation of compound **47** in 38% yield with 83% ee. Selective hydrolysis of methyl ester in compound **47** followed by reduction of carbon–carbon double bond provided compound **48**. Acid induced cyclopropane ring-opening and lactonization proceeded smoothly to generate the paeonilide core structure **49**. It was converted to relatively more stable bicyclo[3.3.0] frameworks **50** with larger groups on convex face, with the epimerization of stereocenters on the ring junctions. Simultaneous lactone opening and oxidation of the formed hemi-acetal using Jones reagent afforded dicarboxy-γ-lactone **51** in 88% yield.



Scheme 5. Reiser's Synthesis of (–)-Paeonilide

Stereoselective installation of allyl group was achieved using addition of allylmagnesium bromide to obtain compound **52**. The combination of Jones reagent with catalytic amounts of mercury(II)-acetate led to compound **53** in 79% yield. Finally, a reduction using BH_3.THF, benzoylation of primary alcohol and reoxidation of the secondary alcohol with Dess–Martin periodinane (DMP) provided (–)-paeonilide (**6**) in three-step with 44% yield (83% ee). Unnatural (–)-paeonilide was found inactive against the PAF receptor.

2A.3 Summary

In summary, we have presented a concise literature account on the isolation, bioactivity and syntheses of paeonilide. The key reactions that were employed to efficiently accomplish the four syntheses of paeonilide were Rubottom oxidation, Birch reduction, hydroboration, stereoselective epoxidtion, bromoetherification, benzoyl peroxide mediated radical addition, topologically favored diastereoselective cyclizations, asymmetric cyclopropanation and lactonization. Overall, remarkable approaches coupled with development of novel methodologies for the synthesis of this target compound have been known in the literature. Our synthetic studies towards the synthesis of (±)-paeonilide along with development of a concept of reactivity umpolung in butenolides have been discussed in details in the section B of the present chapter.

2A.4 References

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CHAPTER 2: SECTION B

Reactivity Umpolung in Intramolecular Ring Closure of 3,4-Disubstituted Butenolides: Diastereoselective Total Synthesis of Paeonilide

This section B of chapter 2 features the following topics:

2B.1 Rationale of the Present Work

In standard organic reactions, the "normal" mode of reactivity is the formation of new bonds between atoms of opposite polarity. Whereas, reactivity umpolung or polarity inversion in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group. This alteration allows otherwise forbidden, secondary reactions of this functional group. The concept was introduced by D. Seebach and E. J. Corey (in German *umpolung* means reversal of polarity).[1] For example, the use of cyanide in benzoin condensation impelled into the development of famous Corey–Seebach umpolung, Stork umpolung, Stetter reaction and, Hünig/Stork reaction. Very recently this concept has gained much consideration due to the modern development in the field of *N*-heterocyclic carbene (NHC) chemistry.[2] The use of thiamine pyrophosphate, 3-membered rings, dithiane, oxidative couplings and organometallic reagents are the accustomed epitomes.[3]

A large number of the ginkgolide class of natural and unnatural hydrofurofuran systems have been known in the literature and have attributed a wide range of biological activities.[4] More specifically, the fused tetrahydrofurofurans and hexahydrofurofurans bearing common acetal/ketal carbon atom have been imperative targets for stability reasons and well-ordered synthetic routes have been known in the literature (Figure 1).[5,6]

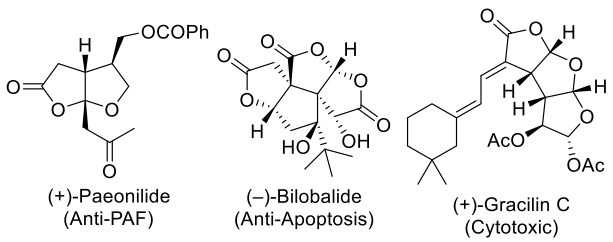
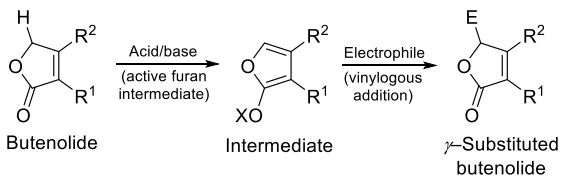


Figure 1. Furofuran based bioactive natural products

We have been using cyclic anhydrides and their derivatives as the potential precursors for total synthesis of structurally interesting and biologically important natural products for almost the past two decades.[7]

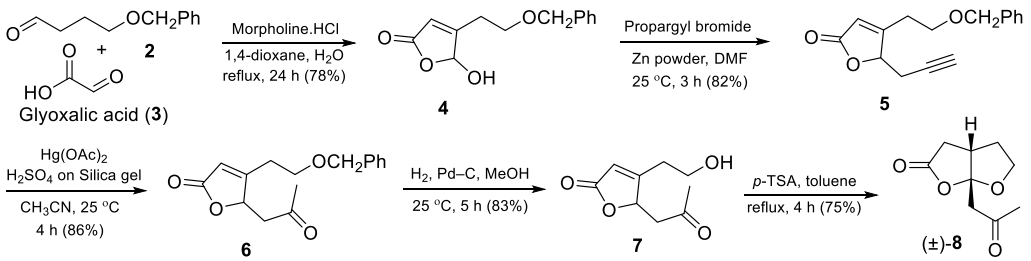


Scheme 1. γ-Butenolides as the Nucleophiles in Vinylogous Addition Reactions (Reported Work)

During the course of our studies on intramolecular oxa-Michael addition reaction of suitably 3,4-disubstituted butenolide, we serendipitously witnessed an unusual isomerization of carbon–carbon double bond followed by nucleophilic insertion of oxygen function at the *γ*-position. The normal reactivity at *γ*-position of butenolides is nucleophilic and they undergo facile reactions with an array of electrophiles (Scheme 1).[8] In this context, we herein report an interesting instance of reactivity umpolung and its application for the total synthesis of (±)-paeonilide (**1**) (Schemes 2–7).

2B.2 Results and Discussion

Initially, we selected the bioactive natural product buergerinin from *Scrophularia buergeriana*[9] as a target compound and started the synthesis of requisite advanced butenolide intermediate (Scheme 2). Aldol condensation of *O*-benzyl protected aldehyde **2**[10] with relatively more reactive glyoxalic acid (**3**) in the presence of morpholine-hydrochloride directly furnished the corresponding maleic anhydride derivative **4** in 78% yield via a stereoselective dehydrative cyclization pathway.[11] Barbier reaction[12] of propargyl bromide with lactol **4** (masked aldehyde) provided the corresponding acetylenic derivative **5** in 82% yield following a ring-opening and ring-closing pathway. Compound **5** upon treatment with sulfuric acid adsorbed on silica gel underwent smooth hydrolytic acetylene to ketone transformation and formed the required product **6** in 86% yield. Chemoselective debenzylation of compound **6** with H_2/Pd–C yielded the essential precursor 3,4-disubstituted butenolide **7** in 83% yield. The protection-free multifunctional compound **7** bearing free ketone and alcohol units at appropriate positions can theoretically form two different intramolecular cyclization products under acidic conditions (Figure 2). Namely, (i) intramolecular cyclization to the corresponding hemiketal **9** followed by a dehydration to form furooxepine **10** and (ii) generation of hemiketal intermediate **9** followed by a concomitant diastereoselective intramolecular oxa-Michael addition to the *α*,*β*-unsaturated carbon–carbon double bond leading to (±)-buergerinin G (**11**). Surprisingly, the reaction of compound **7** with *p*-TSA in refluxing benzene/toluene followed an alternative novel intramolecular cyclization pathway in a highly chemo- and diastereoselective fashion and exclusively delivered the exotic furofuran system (±)-**8** in 75% yield.



Scheme 2. Diastereoselective Synthesis of Furofuran Framework of Paeonilide via Reactivity Reversal

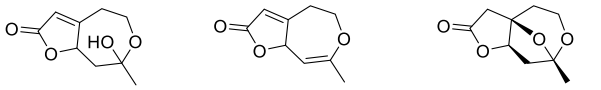
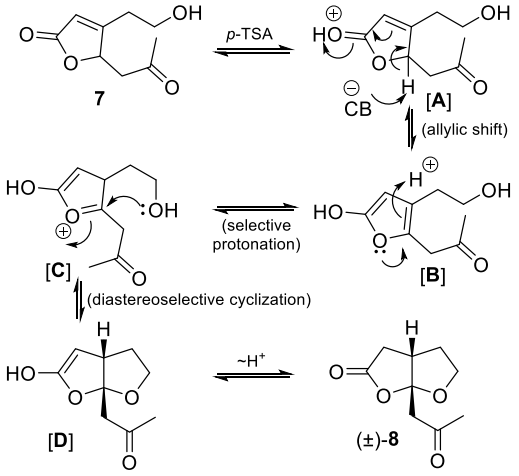


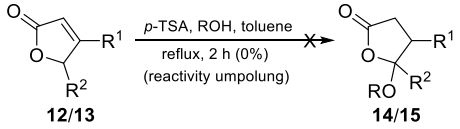
Figure 2. Plausible products from intramolecular cyclization of butenolide **7**

The observed addition of oxygen function at the electron rich γ-position of butenolide is exceptional. Mechanistically, the present fact can be attributed to an acid-catalyzed structural rearrangement encompassing reactivity umpolung depicted in Scheme 3. The butenolide **7** on protonation of lactone carbonyl followed by a conjugate base induced allylic prototropic shift results in an unusual olefin isomerization[13] to form the labile hydroxyfuran intermediate **B**. The possible driving forces for the present allylic shift are, (i) generation of tetrasubstituted carbon–carbon double bond between the β- and γ-positions of butenolide and (ii) formation of an aromatic furan intermediate **B**. Intermediate **B** under acidic conditions selectively transforms into oxocarbenium ion **C** using relatively more reactive double bond in furan ring. The synchronized intramolecular nucleophilic addition of primary alcohol forms a unique product **8**. In transformation of intermediates **A** to **D**, an oxygen function adds to the electron rich γ-carbon and a proton to the electron deficient β-carbon of starting butenolide. Hence, the overall reaction process becomes viable due to reactivity umpolung[14] at the γ-position of 3,4-disubstituted butenolide **7**.



Scheme 3. Plausible Mechanism for the Reactivity Umpolung

As shown in Scheme 4, the intermolecular reactions of 3,4-disubstituted butenolide **12/13** with methanol/ethanol/isopropanol in the presence of *p*-TSA in refluxing toluene were unsuccessful to provide the corresponding desired product **14**/**15**. In all cases, the starting butenolide was isolated back in quantitative amount. The above fact clearly reveals that the transformation of butenolide **7** into the bicyclic product **8** follows a stepwise pathway and it is a both enthalpically (formation of new carbon–oxygen bond) and entropically (formation of five-membered ring) favoured process.



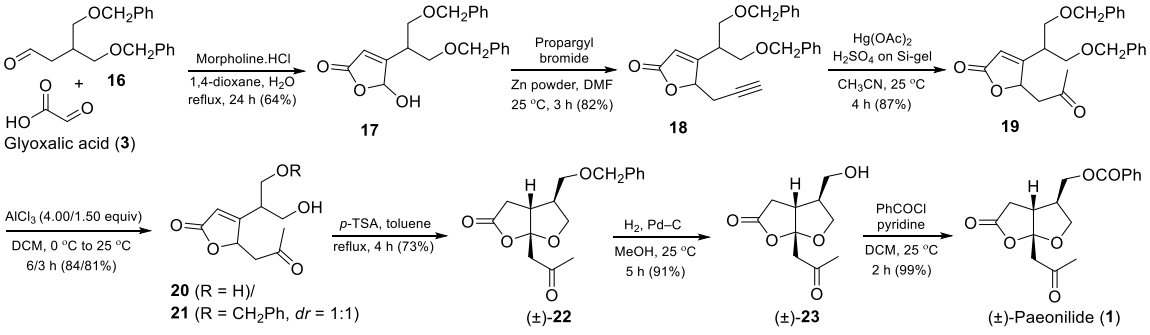
12/14: R = Me/Et/*i*-Pr, R^1 = R^2 = Me
13/15: R = Me/Et/*i*-Pr, R^1 = *i*-Pr, R^2 = CH_2COCH_3

Scheme 4. Attempted Intermolecular Nucleophilic Oxygen Insertions

In the next part of our study, we planned to authenticate the feasibility of reactivity umpolung conception to design a diastereoselctive total synthesis of (±)-paeonilide (**1**). The isolation, biological activity and synthetic approaches from various research groups have been already described in section A of present chapter.[5a,15]

As described in Scheme 5, our synthesis of paeonilide began with morpholine-hydrochloride promoted condensation of appropriately double *O*-benzyl protected aldehyde **16**[16] with glyoxalic acid (**3**). The above stated stereoselective condensation directly furnished the expected maleic anhydride derivative **17** in 64% yield following a dehydrative cyclization pathway. Barbier reaction of propargyl bromide with a masked aldehyde **17** in presence of

activated zinc powder provided the corresponding acetylenic derivative **18** in 82% yield, which on acidic hydrolysis transformed into the desired ketone **19** in 87% yield. We systematically studied the selective mono-benzyl and di-benzyl deprotections in compound **19** under various reaction conditions. The reactions of compound **19** with H_2/Pd–C in MeOH, HCOOH/Pd–C in MeOH, LiCl in DMF, BCl_3 in DCM and BBr_3 in DCM resulted in isolation of staring material and/or decomposition of reaction mixture. Fortunately, both benzyl groups in compound **19** were smoothly deprotected in the presence of excess of aluminum chloride[17] in DCM plus *m*-xylene mixture at room temperature and delivered the essential 3,4-disubstituted butenolide **20** in 84% yield. However, the reaction of compound **20** with *p*-TSA in refluxing benzene/toluene furnished a complex mixture of products. We reasoned that the cause for such decomposition could be a presence of multiple oxygen-functions in the starting material **20** (C:O = 2:1 ratio). The controlled reaction of compound **19** with a use of precise amount of $AlCl_3$ (1.50 equiv) in DCM plus *m*-xylene mixture at room temperature was selective and formed the expected mono-deprotected pair of diastereomers **21** in 81% yield with nearly 1:1 ratio (by ^{1}H NMR). An attempted flash silica gel column chromatographic separation of the diastereomeric **21** resulted in their ~9:1 and ~1:4 mixtures (by ^{1}H NMR), which were used as such for the cyclizations. Gratifyingly, the reactions of 1:1 mixture of diasteromers of compound **21** and their partially purified forms with *p*-TSA in refluxing toluene were highly chemo- and diastereoselective resulting in the same desired product (±)-**22** in 73% yield via structural rearrangement following an intramolecular cyclization pathway with reactivity umpolung.

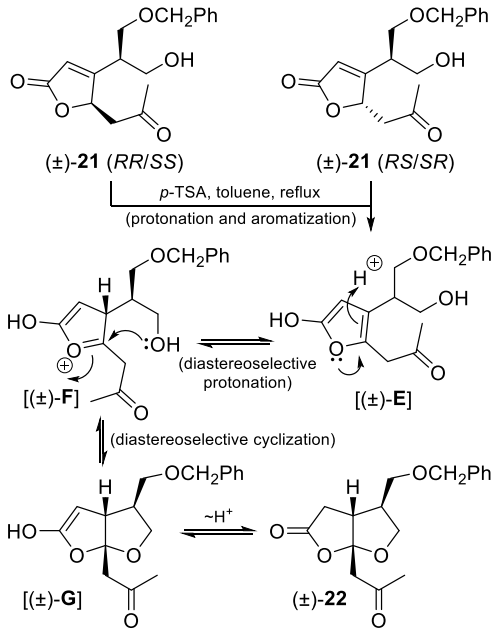


Scheme 5. A Concise Diastereoselective Total Synthesis of (±)-Paeonilide via Reactivity Umpolung

The plausible mechanism for involved diastereoselectivity and reactivity umpolung in the formation of preferred product (±)-**22** is represented in Scheme 6. As described therein, the cause for diastereoselectivity is formation of the labile hydroxyfuran intermediate (±)-**E**, tentatively nullifying the chirality at *γ*-position of both diastereomers of butenolide **21** to

generate a pair of enantiomers. The cause for reactivity umpolung is generation of oxocarbenium ion intermediate (±)-**F** with a highly diastereoselective in situ protonation. The intermediate **F** undergoes further instantaneous diastereoselective intramolecular ring closure to yield the desired product **22** as a racemic mixture.

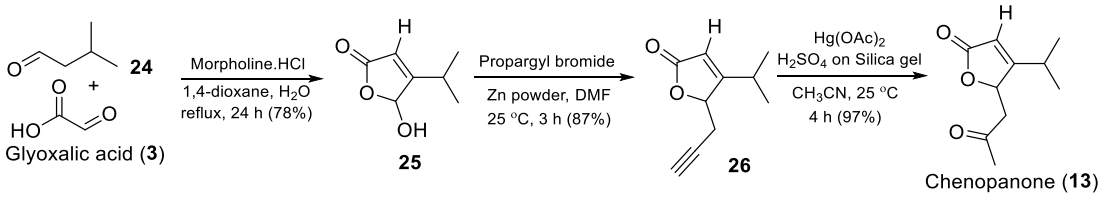
Finally, *O*-benzyl group in compound (±)-**22** was deprotected under H_2/Pd–C conditions to form the known ultimate stage intermediate alcohol (±)-**23** in 91% yield. Primary alcohol **23** on treatment with benzoyl chloride/pyridine in DCM furnished the desired natural product (±)-paeonilide (**1**) in 99% yield. The analytical and spectral data obtained for paeonilide (**1**) was in complete agreement with the reported data[5,15] and starting from glyoxalic acid it was obtained in seven steps with 24% overall yield.



Scheme 6. Plausible Mechanism for the Diastereoselective Ring Closure

Herein we also describe the synthesis of starting material **13** from Scheme 4. Compound **13** is a natural product chenopanone which was isolated in the year 2000 from an Egyptian collection of aerial parts of *C. ambrosioides* L. (Chenopodiaceae) extract.[18] The genus *Chenopodium* consists of 120 plus species which are imperative due to their wide range of medicinal properties.[19] The crude extract of *C. ambrosioides* is known to possess antifungal acitity.[20] The structure of chenopanone was established as 4-isopropyl-5-(2-oxopropyl)furan-2(5*H*)-one (**13**) on the basis of MS and NMR spectroscopic data.

We reasoned that isopropylmaleic anhydride or its equivalent would be a potential precursor for the synthesis of chenopanone and completed the first synthesis of this simple target molecule (Scheme 7).



Scheme 7. Synthesis of Chenopanone

For a simplicity reasons, we decided to start our synthesis from readily available glyoxalic acid to design the requisite hydroxylactone.[11] The morpholinum hydrochloride induced reaction of glyoxalic acid with 3-methylbutanal (isovaleraldehyde) exclusively furnished the desired lactol **25** in 78% yield via a selective dehydrative intermolecular condensation and intramolecular cyclization pathway. The selective zinc promoted Barbier reaction of propargyl bromide with a masked aldehyde **25** gave the required acetylenic γ-lactone **26** in 87% yield with overall substitution of hydroxy group in the lactol by a propargyl group. The structure of product **26** was confirmed on the basis of analytical and spectral data. Finally, the hydration of an acetylenic unit in product **26** to the corresponding ketone unit provided the desired chenopanone (**13**) in 97% yield. The analytical and spectral data obtained for synthetic **13** were in complete agreement with the reported data.[18] The natural product **13** was obtained in three steps with 66% overall yield.

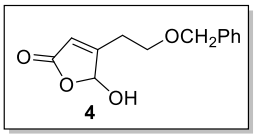
2B.3 Summary

In summary, we have demonstrated a novel reactivity umpolung in 3,4-disubstituted butenolides and accomplished the diastereoselctive total synthesis of paeonilide. The observed chemo- and diastereoselctivity in the intramolecular cyclization leading to a paeonilide is noteworthy from a basic chemistry point of view. The overall reactivity umpolung process involves insertion of oxygen function at the electron rich γ-carbon. The enzymatic meso-desymmetrization of the corresponding diacetate derivative will also provide access to the corresponding enantiomerically pure forms of paeonilide. The present convergent access to fused furofuran systems has a broad scope and it will be useful to design several focused minilibraries of their natural and unnatural analogues and congeners for SAR studies. We believe that our present redox protocol will also work equally well to plan the corresponding furopyran based structural architectures. Finally, the present reactivity umpolung opens a new avenue in the significant field of butenolide chemistry.

2B.4 Experimental Section

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR spectrometer, 400 MHz NMR spectrometer and 500 MHz NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz) and 500 NMR spectrometer (125 MHz). Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 and 200–400 mesh). Commercially available glyoxalic acid monohydrate, propargyl bromide (80% solution in toluene), Zn power, $Hg(OAc)_2$, Pd on charcoal (10 wt%), *p*-TSA, anhydrous $AlCl_3$ and benzoyl chloride were used. The starting aldehydes **2** and **16** were prepared by using known procedures.[10,16]

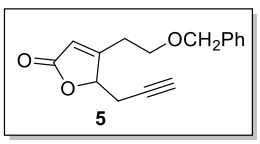
4-(2-(Benzyloxy)ethyl)-5-hydroxyfuran-2(5*H*)-one (4).



4

To a stirred homogeneous suspension of glyoxalic acid monohydrate (194 mg, 2.10 mmol) and powdered morpholinium hydrochloride (260 mg, 2.10 mmol) in 1,4-dioxane (4 mL) plus water (60 μL) mixture was added aldehyde **2** (356 mg, 2.00 mmol). The reaction mixture was stirred at 25 ^{o}C for 1 h and refluxed for 24 h. Solvent was evaporated under vacuo and water (10 mL) was added to the reaction mixture. It was extracted with ethyl acetate (15 mL × 3), 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 mixture (3:2) as an eluent to yield the pure product **4** as thick oil (364 mg 78% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55–2.83 (m, 2H), 3.71 (t, J = 6 Hz, 2H), 4.52 (s, 2H), 5.47 (br s, 1H), 5.91 (q, J = 2 Hz, 1H), 5.97 (d, J = 2 Hz, 1H), 7.23–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.8, 66.9, 73.1, 99.4, 118.4, 127.8, 127.9, 128.4, 137.2, 166.9, 171.8; ESIMS (*m*/*z*) 257 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{14}O_4Na$ 257.0784, found 257.0784; IR ($CHCl_3$) ν_{max} 3350, 1758, 1649 cm^{-1}.

4-(2-(Benzyloxy)ethyl)-5-(prop-2-yn-1-yl)furan-2(5*H*)-one (5).

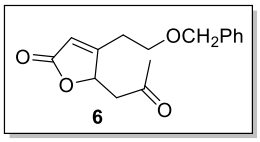


5

To a stirred solution of compound **4** (360 mg, 0.154 mmol) in dimethylformamide (4 mL) at 0 ºC was added propargyl bromide (174 μL, 80 wt% in toluene, 1.84 mmol) and zinc power (300 mg, 4.60 mmol). The reaction mixture was stirred at 25 ^{o}C for 3 h and quenched with saturated aqueous NH_4Cl

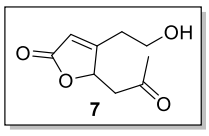
solution (2 mL). After 0.5 h the reaction mixture was diluted with ethyl acetate (20 mL) and filtered to remove the zinc residues. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (4:1) as an eluent to yield the pure product **5** as thick oil (322 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.00 (t, J = 4 Hz, 1H), 2.50–2.90 (m, 4H), 3.55–3.80 (m, 2H), 4.53 (s, 2H), 5.02 (dt, J = 6 and 2 Hz, 1H), 5.95 (s, 1H), 7.20–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.1, 28.5, 66.9, 71.9, 73.0, 76.6, 80.8, 117.6, 127.5, 127.7, 128.3, 137.4, 168.5, 172.3; ESIMS (m/z) 279 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{16}O_3Na$ 279.0992, found 279.0992; IR ($CHCl_3$) ν_{max} 2100, 1756, 1641 cm^{-1}.

4-(2-(Benzyloxy)ethyl)-5-(2-oxopropyl)furan-2(5*H*)-one (6).



To a stirred solution of compound **5** (320 mg, 1.26 mmol) in acetonitrile (4 mL) plus water (0.20 mL) mixture at 25 ^{o}C was added con H_2SO_4 impregnated on a silica gel (40 mg, 10 wt%) and mercury(II) acetate (40 mg, 0.12 mmol). The reaction mixture was stirred for 4 h and diluted with ethyl acetate (15 mL). The filtered organic layer was dried over Na_2SO_4 and concentrated in vacuo. The silica gel column chromatographic purification of the resulting residue using petroleum ether and ethyl acetate mixture (7:3) as an eluent afforded the pure product **6** as a thick oil (306 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H), 2.45–2.68 (m, 2H), 2.67 (dd, J = 18 and 8 Hz, 1H), 2.89 (dd, J = 16 and 4 Hz, 1H), 3.56–3.77 (m, 2H), 4.51 (s, 2H), 5.39 (ddd, J = 8, 4 and 2 Hz, 1H), 5.90 (d, J = 2 Hz, 1H), 7.23–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.5, 30.3, 45.1, 67.0, 73.1, 79.8, 116.8, 127.6, 127.7, 128.3, 137.3, 169.9, 172.3, 203.9; ESIMS (m/z) 297 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{18}O_4Na$ 297.1097, found 297.1100; IR ($CHCl_3$) ν_{max} 1756, 1722, 1638 cm^{-1}.

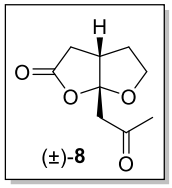
4-(2-Hydroxyethyl)-5-(2-oxopropyl)furan-2(5*H*)-one (7).



To a stirred solution of compound **6** (280 mg, 1.02 mmol) in methanol (4 mL) under the balloon pressure hydrogen atmosphere was added activated Pd–C (40 mg, 10 wt%). The reaction mixture was stirred at 25 ^{o}C for 5 h, filtered to remove Pd–C and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (1:4) as an eluent provided the pure product **7** as a thick oil (156 mg, 83% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60–1.95

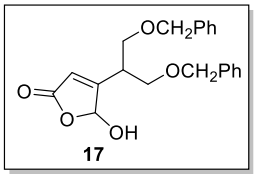
(br s, 1H), 2.25 (s, 3H), 2.43–2.87 (m, 2H), 2.76 (dd, *J* = 18 and 8 Hz, 1H), 2.96 (dd, *J* = 18 and 6 Hz, 1H), 3.78–4.02 (m, 2H), 5.44 (ddd, *J* = 7, 5 and 2 Hz, 1H), 5.96 (d, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.8, 31.0, 45.1, 59.8, 80.1, 117.1, 170.3, 172.8, 204.6; ESIMS (*m*/*z*) 207 $[M+Na]^+$; HRMS (ESI) calcd for $C_9H_{12}O_4Na$ 207.0628, found 207.0621; IR ($CHCl_3$) ν_{max} 3433, 1769, 1716 cm^{-1}.

(±)-6a-(2-Oxopropyl)tetrahydrofuro[2,3-b]furan-2(3*H*)-one (8).



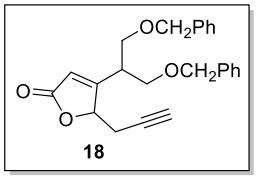
To a stirred solution of compound **7** (120 mg, 0.66 mmol) in dry toluene (4 mL) under argon atmosphere was added anhydrous *p*-TsOH (22 mg, 0.14 mmol). The reaction mixture was refluxed for 4 h and concentrated in vacuo. The direct silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (7:3) as an eluent gave the pure product **8** as a thick oil (90 mg, 75% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.77 (ddd, *J* = 12, 6 and 2 Hz, 1H), 2.05–2.35 (m, 1H), 2.19 (s, 3H), 2.43 (dd, *J* = 16 and 2 Hz, 1H), 2.97 (d, *J* = 18 Hz, 1H), 3.03–3.28 (m, 2H), 3.29 (d, *J* = 16 Hz, 1H), 3.85 (ddd, *J* = 12, 10 and 6 Hz, 1H), 4.05 (dt, *J* = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.0, 33.5, 36.7, 41.0, 49.2, 66.5, 115.3, 175.1, 204.5; ESIMS (*m*/*z*) 207 $[M+Na]^+$; HRMS (ESI) calcd for $C_9H_{12}O_4Na$ 207.0628, found 207.0627; IR ($CHCl_3$) ν_{max} 1775, 1721 cm^{-1}.

4-(1,3-Bis(benzyloxy)propan-2-yl)-5-hydroxyfuran-2(5*H*)-one (17).



It was obtained from glyoxalic acid monohydrate (97 mg, 1.05 mmol), morpholinium hydrochloride (130 mg, 1.05 mmol) and aldehyde **16** (314 mg, 1.00 mmol) using the same procedure as described for compound **4**, as a thick oil (226 mg, 64%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.14 (quintet, *J* = 6 Hz, 1H), 3.60–3.80 (m, 4H), 4.49 (s, 2H), 4.51 (s, 2H), 4.96 (d, *J* = 8 Hz, 1H), 5.99 (s, 1H), 6.00 (d, *J* = 8 Hz, 1H), 7.20–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.2, 69.0, 73.3, 99.1, 119.4, 127.6, 127.8, 128.4, 137.2, 167.6, 171.1; ESIMS (*m*/*z*) 377 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{22}O_5Na$ 377.1359, found 377.1358; IR ($CHCl_3$) ν_{max} 3394, 1760, 1648 cm^{-1}.

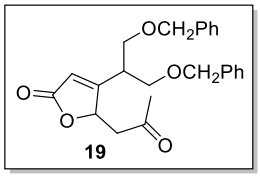
4-(1,3-Bis(benzyloxy)propan-2-yl)-5-(prop-2-yn-1-yl)furan-2(5*H*)-one (18).



It was obtained from compound **17** (190 mg, 0.54 mmol), propargyl bromide (83 μL, 80 wt% in toluene, 0.64 mmol) and zinc power (105 mg,

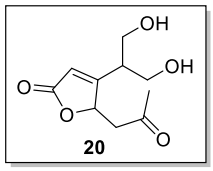
1.61 mmol) using the same procedure as described for compound **5**, as a thick oil (165 mg, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.96 (t, J = 2 Hz, 1H), 2.75 (ddq, J = 18, 4 and 2 Hz, 2H), 2.94 (quintet, J = 6 Hz, 1H), 3.56 (t, J = 8 Hz, 1H), 3.60–3.80 (m, 3H), 4.48 (s, 2H), 4.51 (s, 2H), 5.11 (dt, J = 4 and 2 Hz, 1H), 5.97 (s, 1H), 7.18–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.4, 39.7, 68.6, 70.1, 72.1, 73.4, 76.9, 81.1, 117.9, 127.7, 128.0, 128.5, 137.5, 170.0, 172.4; ESIMS (m/z) 399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{24}O_4Na$ 399.1567, found 399.1568; IR ($CHCl_3$) ν_{max} 2100, 1760, 1722, 1635 cm^{-1}.

4-(1,3-Bis(benzyloxy)propan-2-yl)-5-(2-oxopropyl)furan-2(5*H*)-one (19).



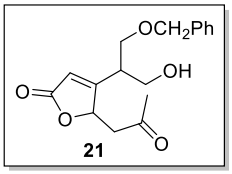
It was obtained from compound **18** (160 mg, 0.43 mmol), con H_2SO_4–Si (20 mg, 10 wt%) and mercury(II) acetate (14 mg, 0.04 mmol) using the same procedure as described for compound **6**, as a thick oil (146 mg, 87%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.09 (s, 3H), 2.58 (dd, J = 18 and 8 Hz, 1H), 2.85 (quintet, J = 6 Hz, 1H), 2.91 (dd, J = 18 and 4 Hz, 1H), 3.53 (dd, J = 9 and 7 Hz, 1H), 3.60–3.77 (m, 3H), 4.47 (s, 2H), 4.49 (s, 2H), 5.45 (ddd, J = 8, 4 and 2 Hz, 1H), 5.90 (s, 1H), 7.20–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.4, 39.8, 45.3, 69.3, 69.8, 73.4, 80.0, 116.9, 127.8, 127.9, 128.5, 137.3, 171.6, 172.4, 204.0; ESIMS (m/z) 395 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{26}O_5Na$ 417.1672, found 417.1672; IR ($CHCl_3$) ν_{max} 3450, 1784, 1715 cm^{-1}.

4-(1,3-Dihydroxypropan-2-yl)-5-(2-oxopropyl)furan-2(5*H*)-one (20).



To a stirred solution of compound **19** (60 mg, 0.16 mmol) in dry dichloromethane (4 mL) at 0 ^{o}C under argon atmosphere was added anhydrous aluminium chloride (80 mg, 0.62 mmol). The reaction mixture was allowed to warm gradually to 25 ^{o}C and stirred for 6 h. Reaction was quenched with water (1 mL) and it was extracted with dichloromethane (10 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using ethyl acetate as an eluent furnished the pure product **20** as a thick oil (28 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.00–2.25 (br s, 2H), 2.25 (s, 3H), 2.72 (quintet, J = 5 Hz, 1H), 2.80 (dd, J = 15 and 5 Hz, 1H), 3.05 (dd, J = 15 and 5 Hz, 1H), 3.88 (dd, J = 5 and 5 Hz, 2H), 3.96 (dd, J = 5 and 5 Hz, 2H), 5.47 (ddd, J = 8, 4 and 2 Hz, 1H), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.2, 42.9, 44.9, 62.8, 63.5, 79.9, 117.7, 170.4, 172.1, 204.8; ESIMS (m/z) 237 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_{14}O_5Na$ 237.0733, found 237.0733; IR ($CHCl_3$) ν_{max} 3300, 1738, 1722, 1667 cm^{-1}.

4-(1-(Benzyloxy)-3-hydroxypropan-2-yl)-5-(2-oxopropyl)furan-2(5*H*)-one (21).

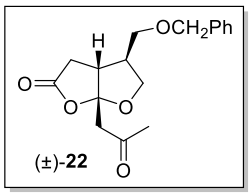


To a stirred solution of compound **19** (100 mg, 0.25 mmol) in dry dichloromethane (5 mL) at 0 ^{o}C under argon atmosphere was added anhydrous aluminium chloride (51 mg, 0.38 mmol). The reaction mixture was allowed to warm gradually to 25 ^{o}C and stirred for 3 h. It was quenched with water (1 mL) and extracted with dichloromethane (15 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to obtain mixture of diastereomers of (±)-**21** as a thick oil in 1:1 ratio (63 mg, 81% yield). The silica gel flash column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (2:3) as an eluent yielded the mixture of two diastereomers of **21** in 9:1 and 1:4 ratios as thick oils.

***Data for major isomer from 9:1 mixture*:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 3H), 2.72 (dd, *J* = 18 and 8 Hz, 1H), 2.79 (quintet, *J* = 5 Hz, 1H), 2.95 (dd, *J* = 15 and 5 Hz, 1H), 3.74 (dd, *J* = 5 and 2 Hz, 2H), 3.83 (quintet, *J* = 5 Hz, 2H), 4.54 (s, 2H), 5.48 (ddd, *J* = 10, 5 and 2 Hz, 1H), 5.94 (s, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.8, 41.5, 45.2, 63.2, 69.9, 73.7, 79.8, 117.4, 127.9, 128.1, 128.6, 137.2, 171.0, 172.4, 204.6; ESIMS (*m*/*z*) 327 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ 327.1203, found 327.1202; IR ($CHCl_3$) ν_{max} 3600, 1733, 1632 cm^{-1}.

***Data for major isomer from 1:4 mixture*:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3H), 2.71 (dd, *J* = 18 and 8 Hz, 1H), 2.78 (quintet, *J* = 5 Hz, 1H), 3.00 (dd, *J* = 15 and 5 Hz, 1H), 3.61 (dd, *J* = 10 and 5 Hz, 1H), 3.69 (dd, *J* = 10 and 5 Hz, 1H), 3.91 (t, *J* = 10 Hz, 2H), 4.50 (s, 2H), 5.41 (ddd, *J* = 10, 5 and 2 Hz, 1H), 5.98 (s, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.9, 41.4, 44.9, 62.5, 70.3, 73.6, 80.1, 117.2, 127.8, 128.1, 128.6, 137.1, 171.0, 172.4, 204.5; ESIMS (*m*/*z*) 327 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ $[M+Na]^+$ 327.1203, found 327.1202; IR ($CHCl_3$) ν_{max} 3600, 1732, 1633 cm^{-1}.

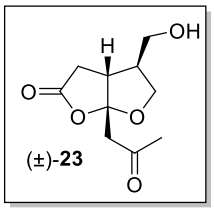
(±)-4-((Benzyloxy)methyl)-6a-(2-oxopropyl)tetrahydrofuro[2,3-b]furan-2(3*H*)-one (22).



It was obtained from compound **21** (50 mg, 0.17 mmol) and anhydrous *p*-TsOH (6 mg, 0.03 mmol) using the same procedure as described for compound **8**, as a thick oil (36 mg, 73%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15 (s, 3H), 2.23–2.38 (m, 1H), 2.47 (dd, *J* = 18 and 2 Hz, 1H), 2.76 (d, *J* = 18 Hz, 1H), 2.89 (td, *J* = 10 and 2 Hz, 1H), 3.22 (d, *J* = 6 Hz, 1H), 3.24–3.42 (m, 3H), 3.89 (dd, *J* = 10 and 2 Hz, 1H), 3.97 (dd, *J* = 10 and 4 Hz, 1H), 4.46 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* =

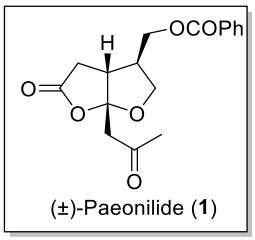
12 Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.9, 36.7, 44.2, 47.5, 49.5, 68.5, 70.7, 73.2, 115.2, 127.8, 127.9, 128.5, 137.7, 174.9, 204.4; ESIMS (*m*/*z*) 327 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ 327.1203, found 327.1201; IR ($CHCl_3$) ν_{max} 1754, 1719, 1629 cm^{-1}.

(±)-4-(Hydroxymethyl)-6a-(2-oxopropyl)tetrahydrofuro[2,3-b]furan-2(3*H*)-one (23).



To a stirred solution of compound **22** (30 mg, 0.10 mmol) in methanol (2 mL) was added activated Pd–C (5 mg, 10 wt%) under the balloon pressure hydrogen atmosphere. The reaction mixture was stirred at 25 ^{o}C for 5 h, filtered to remove Pd–C and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (3:1) as an eluent gave the pure product (±)-**23** as a thick oil (19 mg, 91% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76 (br s, 1H), 2.20 (s, 3H), 2.20–2.28 (m, 1H), 2.52 (dd, *J* = 16 and 4 Hz, 1H), 2.93–2.98 (m, 1H), 2.97 (d, *J* = 16 Hz, 1H), 3.29 (dd, *J* = 20 and 12 Hz, 1H), 3.32 (d, *J* = 16 Hz, 1H), 3.58 (d, *J* = 8 Hz, 2H), 3.95 (dd, *J* = 8 and 2 Hz, 1H), 4.01 (dd, *J* = 10 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.0, 36.8, 44.0, 49.3, 49.5, 63.8, 68.4, 115.4, 174.8, 204.6; ESIMS (*m*/*z*) 237 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_{14}O_5Na$ 237.0733, found 237.0734; IR ($CHCl_3$) ν_{max} 3435, 1762, 1715 cm^{-1}.

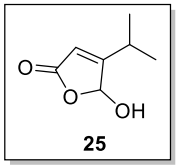
(±)-(5-Oxo-6a-(2-oxopropyl)hexahydrofuro[2,3-b]furan-3-yl)methyl Benzoate (Paeonilide, 1).



To a stirred solution of compound **23** (15 mg, 0.07 mmol) in dry dichloromethane (1 mL) at 0 ^{o}C under argon atmosphere was added pyridine (0.10 mL) and benzoyl chloride (10 μL, 0.08 mmol). The reaction mixture was stirred at 25 ^{o}C for 2 h and diluted with dichloromethane (10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (7:3) as an eluent furnished the pure product (±)-**1** as white needles (22 mg, 99% yield). MP 165–166 ^{o}C (lit. 144–145 ^{o}C);[5a] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H), 2.52–2.56 (m, 1H), 2.55 (dd, *J* = 20 and 2 Hz, 1H), 2.93–3.00 (m, 1H), 2.96 (d, *J* = 20 Hz, 1H), 3.35 (dd, *J* = 20 and 10 Hz, 1H), 3.42 (d, *J* = 15 Hz, 1H), 4.00–4.07 (m, 2H), 4.19 (dd, *J* = 10 and 10 Hz, 1H), 4.30 (dd, *J* = 10 and 5 Hz, 1H), 7.47 (t, *J* = 10 Hz, 2H), 7.60 (t, *J* = 10 Hz, 1H), 8.02

(d, J = 10 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.9, 36.6, 44.4, 46.7, 49.5, 64.9, 67.9, 115.0, 128.6, 129.5, 129.6, 133.4, 166.4, 174.5, 204.4; ESIMS (m/z) 341 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{18}O_6Na$ 341.0996, found 341.0995; IR ($CHCl_3$) ν_{max} 1775, 1711 cm^{-1}.

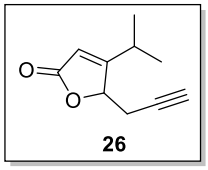
5-Hydroxy-4-isopropylfuran-2(5*H*)-one (25).



25

It was obtained from glyoxalic acid monohydrate (920 mg, 10 mmol), morpholinium hydrochloride (1.36 g, 11.00 mmol) and isobutyraldehyde (860 mg, 10.00 mmol) using the same procedure as described for compound **4**, as a white solid (1.11 g, 78% yield).[11] Mp. 77–80 ^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, J = 6 Hz, 3H), 1.24 (d, J = 8 Hz, 3H), 2.77 (doublet of septet, J = 8 and 2 Hz, 1H), 5.37 (br s, 1H), 5.81 (s, 1H), 6.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.9, 20.9, 27.3, 98.8, 115.7, 172.5, 175.9; ESIMS: (m/z) 143 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3368, 1745, 1642 cm^{-1}.

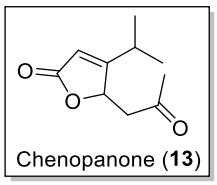
4-Isopropyl-5-(prop-2-ynyl)furan-2(5*H*)-one (26).



26

It was obtained from compound **25** (710 mg, 5.00 mmol), propargyl bromide (0.84 mL, 80 wt% in toluene, 7.50 mmol) and zinc power (975 mg, 15.00 mmol) using the same procedure as described for compound **5**, as a thick oil (710 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (d, J = 6 Hz, 3H), 1.26 (d, J = 8 Hz, 3H), 2.02 (t, J = 2 Hz, 1H), 2.50–2.90 (m, 3H), 5.06 (t, J = 6 Hz, 1H), 5.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.3, 21.7, 22.5, 27.5, 72.0, 76.5, 79.7, 115.0, 172.5, 177.0; ESIMS: (m/z) 187 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_{13}O_2$ 165.0910, found 165.0910; IR ($CHCl_3$) ν_{max} 2121, 1752, 1635 cm^{-1}.

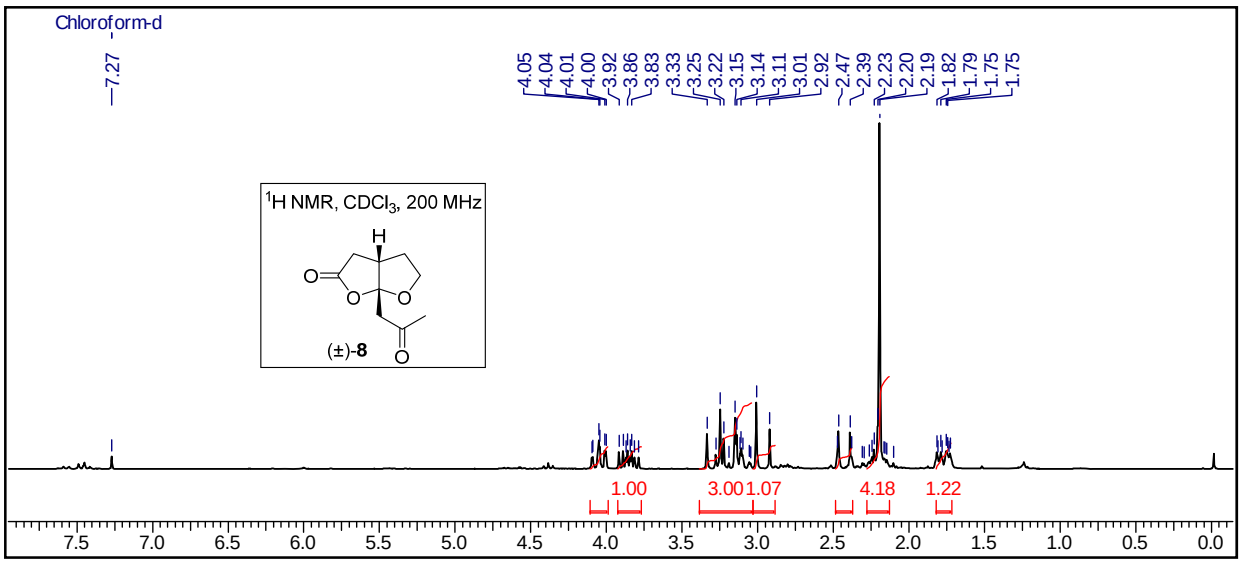
4-Isopropyl-5-(2-oxopropyl)furan-2(5*H*)-one (Chenopanone, 13).

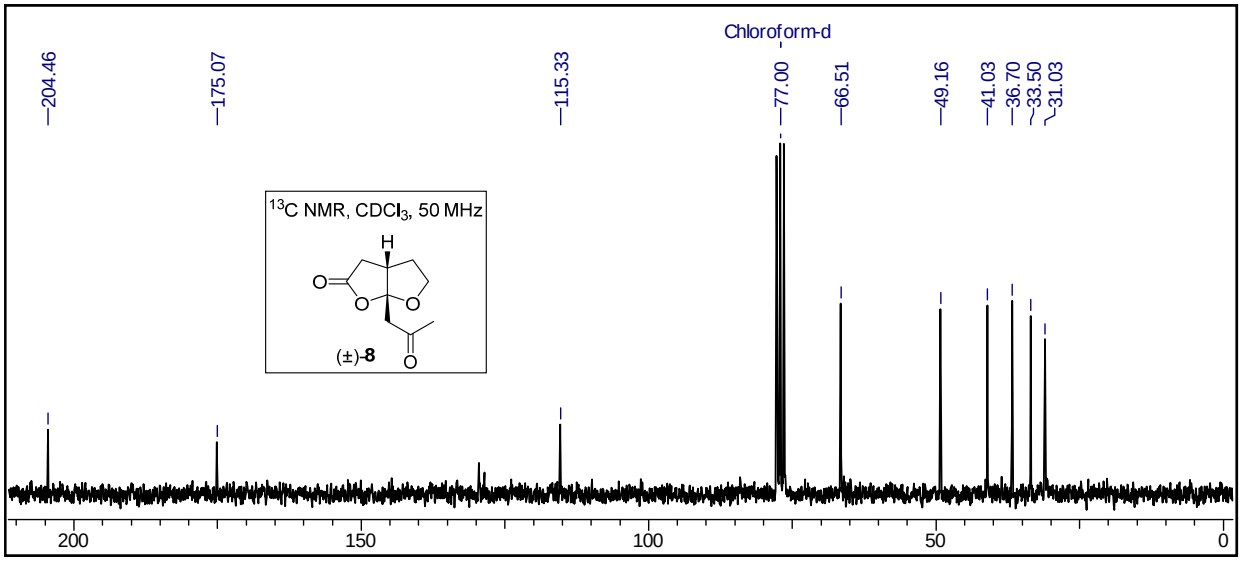


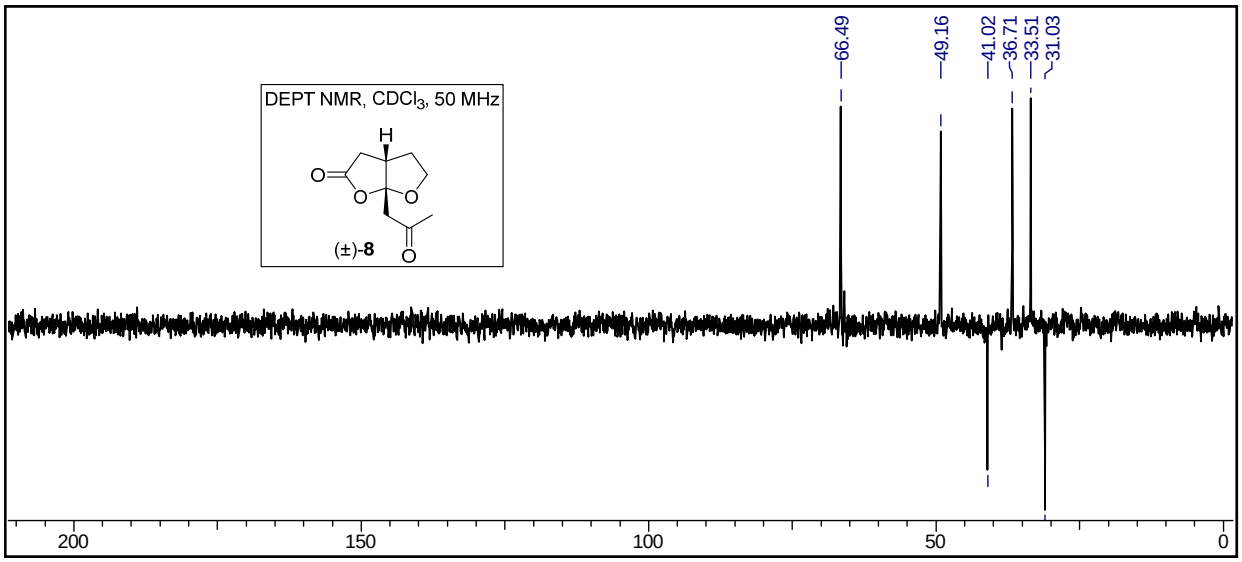
Chenopanone (**13**)

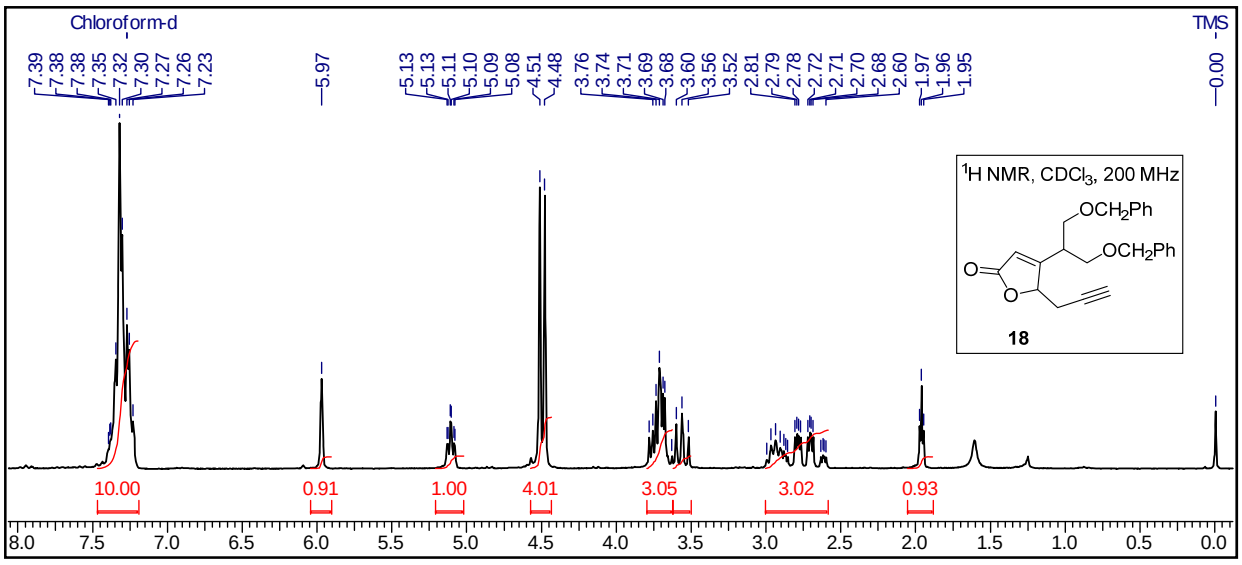
It was obtained from compound **26** (500 mg, 5.00 mmol), con H_2SO_4–Si (100 mg, 10 wt%) and mercury(II) acetate (150 mg, 0.5 mmol) using the same procedure as described for compound **6**, as a thick oil (538 mg, 97% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.17 (d, J = 6 Hz, 3H), 1.24 (d, J = 8 Hz, 3H), 2.25 (s, 3H), 2.49 (septet, J = 8 Hz, 1H), 2.68 (dd, J = 16 and 8 Hz, 1H), 2.84 (dd, J = 16 and 4 Hz, 1H), 5.43 (ddd, J = 8, 4 and 2 Hz, 1H), 5.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.2, 21.4, 27.3, 30.6, 45.2, 78.6, 114.1, 172.4, 178.3, 203.8; ESIMS: (m/z) 205 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1756, 1728, 1634 cm^{-1}.

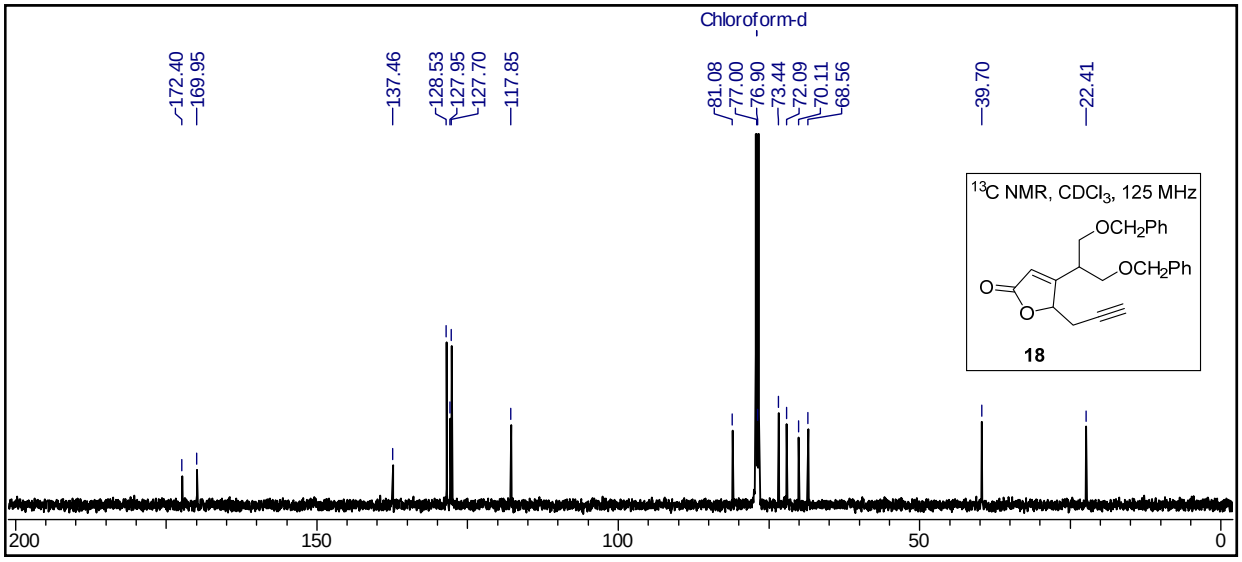
2B.5 Selected Spectra

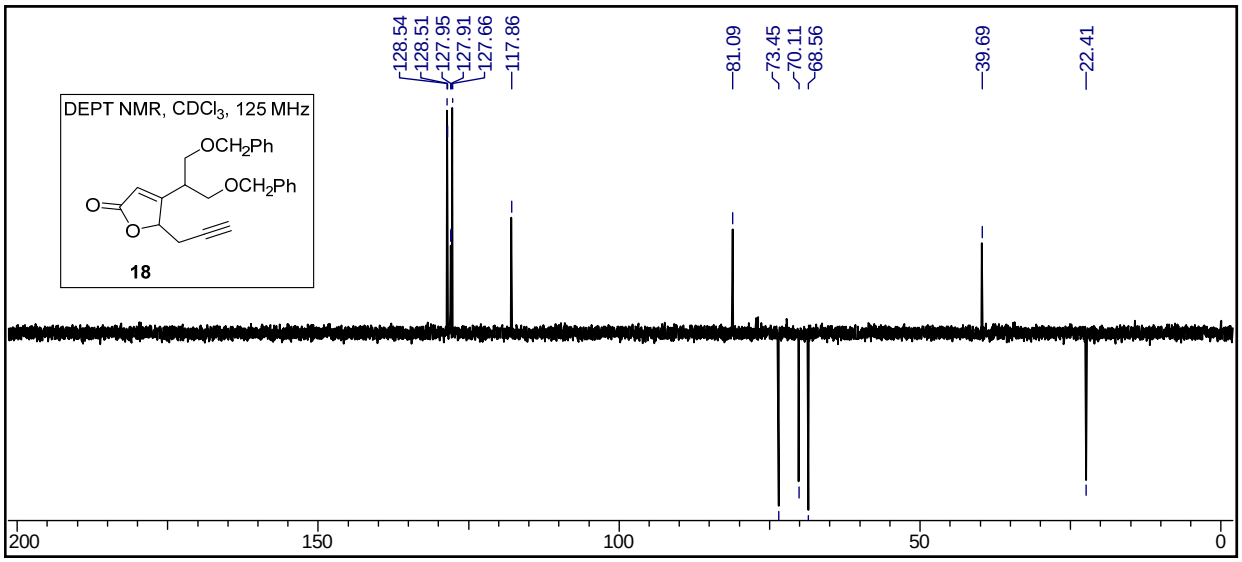

Chloroform-d
7.27
4.05
4.04
4.01
4.00
3.92
3.86
3.83
3.33
3.25
3.22
3.15
3.14
3.11
3.01
2.92
2.47
2.39
2.23
2.20
2.19
1.82
1.79
1.75
1.75
^{1}H NMR, CDCl$_3$, 200 MHz
(±)-8
1.00
3.00
1.07
4.18
1.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

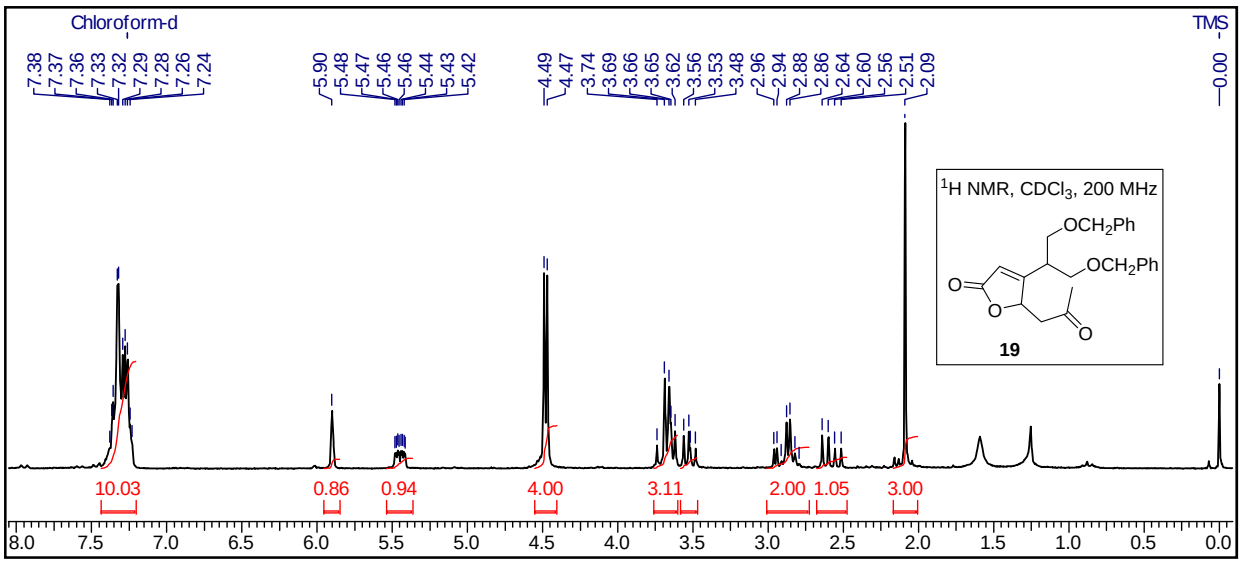

Chloroform-d
204.46
175.07
115.33
77.00
66.51
49.16
41.03
36.70
33.50
31.03
^{13}C NMR, CDCl$_3$, 50 MHz
(±)-8
200
150
100
50
0

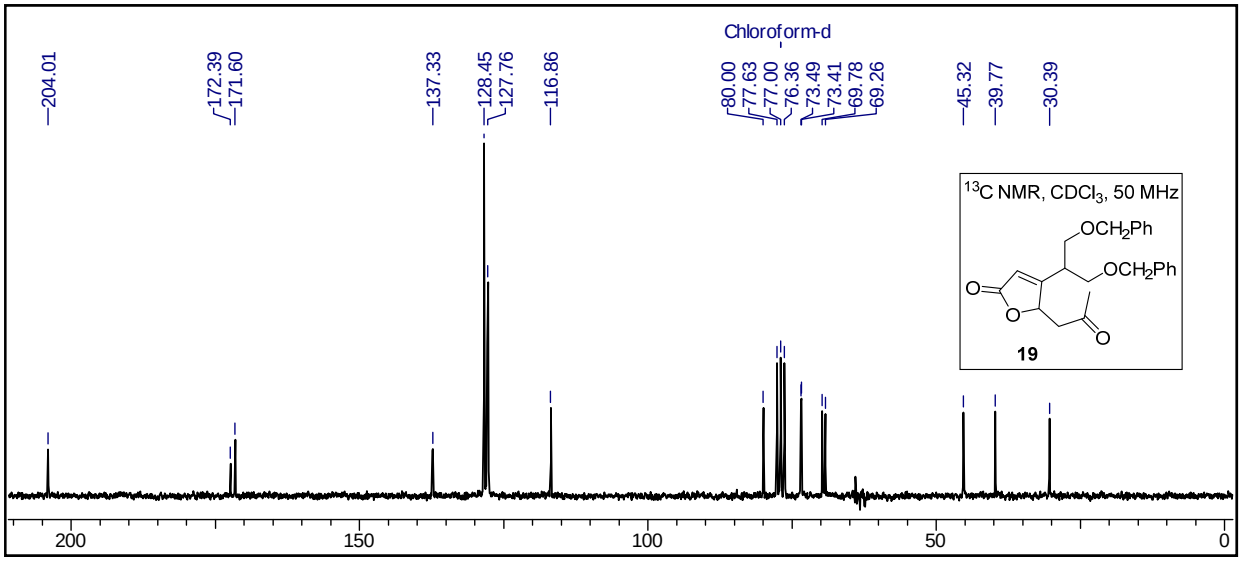

66.49
49.16
41.02
36.71
33.51
31.03
DEPT NMR, CDCl$_3$, 50 MHz
(±)-8
200
150
100
50
0

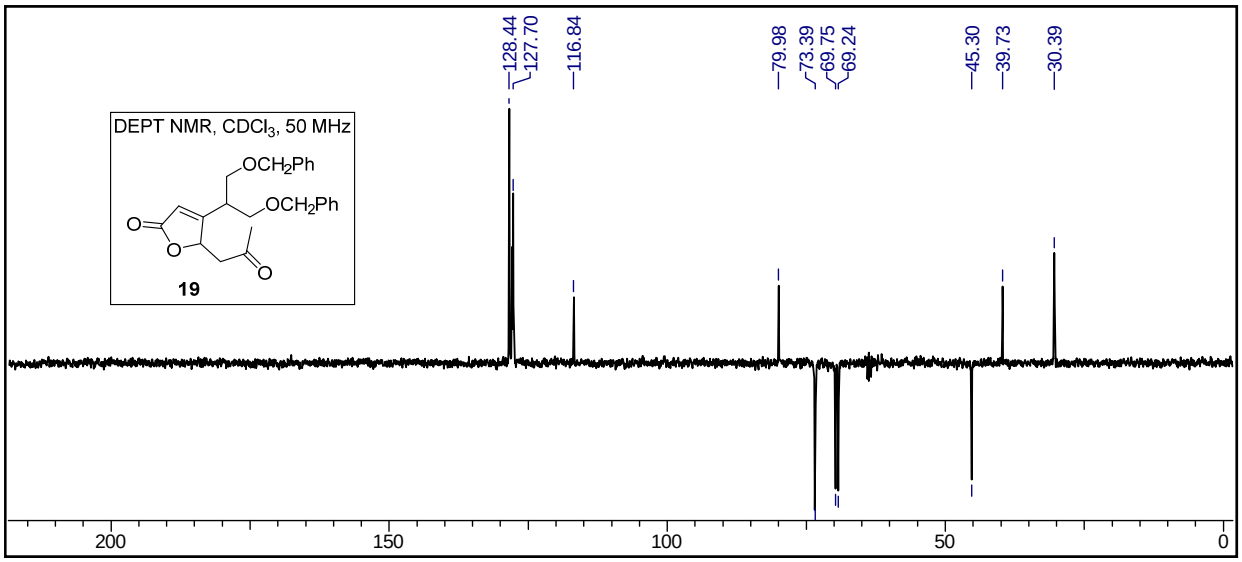

Chloroform-d
TMS
7.39
7.38
7.38
7.35
7.32
7.30
7.27
7.26
7.23
5.97
5.13
5.13
5.11
5.10
5.09
5.08
4.51
4.48
3.76
3.74
3.71
3.69
3.68
3.60
3.56
3.52
2.81
2.79
2.78
2.72
2.71
2.70
2.68
2.60
1.97
1.96
1.95
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
OCH$_2$Ph
OCH$_2$Ph
O
O
18
10.00
0.91
1.00
4.01
3.05
3.02
0.93
8.0
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

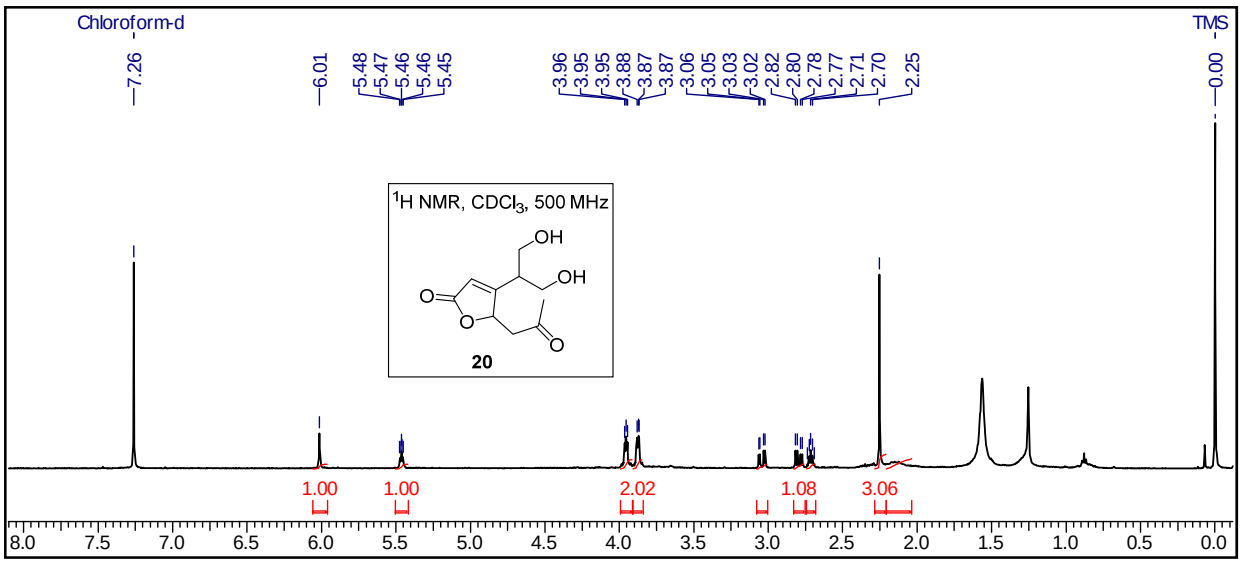

Chloroform-d
172.40
169.95
137.46
128.53
127.95
127.70
117.85
81.08
77.00
76.90
73.44
72.09
70.11
68.56
39.70
22.41
^{13}C NMR, CDCl$_3$, 125 MHz
OCH$_2$Ph
OCH$_2$Ph
O
O
18
200
150
100
50
0

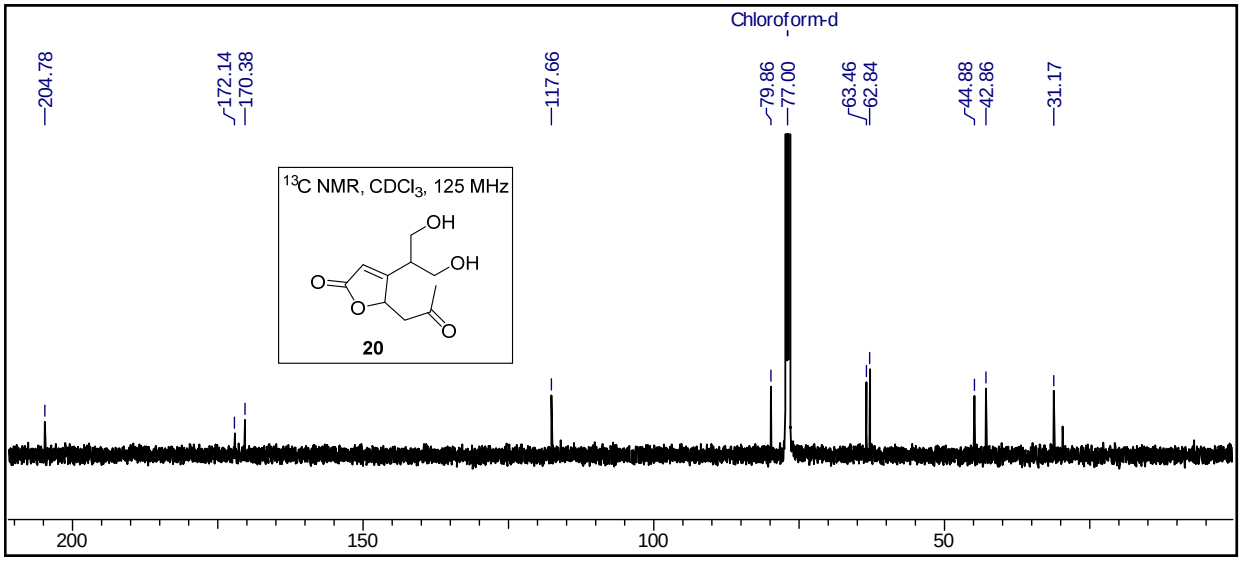

128.54
128.51
127.95
127.91
127.66
117.86
81.09
73.45
70.11
68.56
39.69
22.41
DEPT NMR, CDCl$_3$, 125 MHz
OCH$_2$Ph
OCH$_2$Ph
O
O
18
200
150
100
50
0

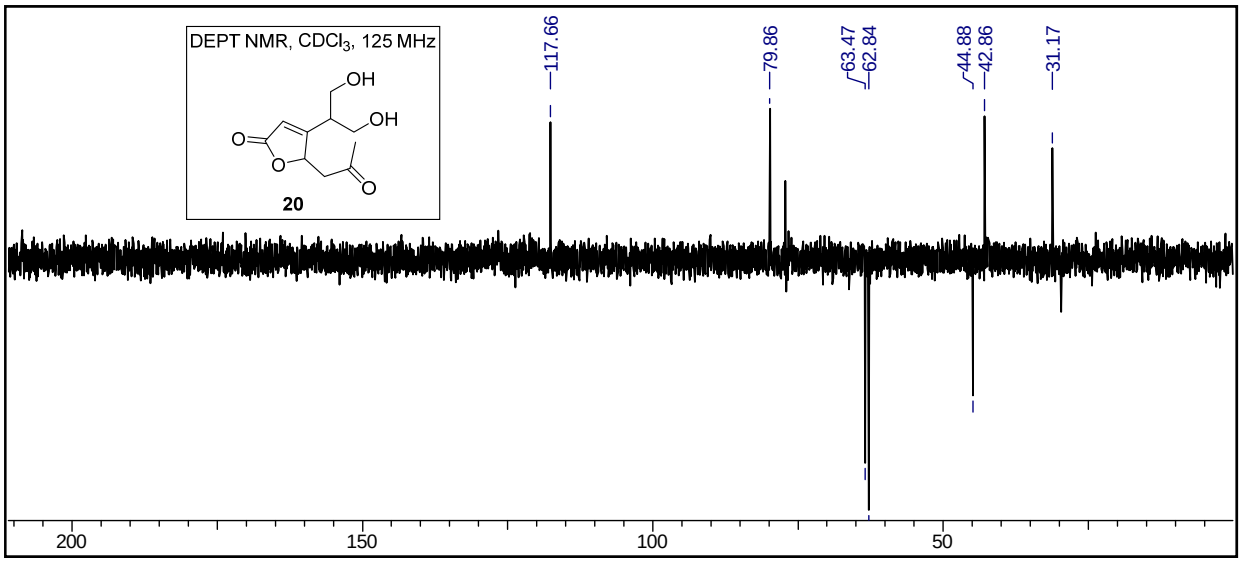

Chloroform-d
TMS
7.38
7.37
7.36
7.33
7.32
7.29
7.28
7.26
7.24
5.90
5.48
5.47
5.46
5.46
5.44
5.43
5.42
4.49
4.47
3.74
3.69
3.66
3.65
3.62
3.56
3.53
3.48
2.96
2.94
2.88
2.86
2.64
2.60
2.56
2.51
2.09
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
OCH$_2$Ph
OCH$_2$Ph
O
O
O
19
10.03
0.86
0.94
4.00
3.11
2.00
1.05
3.00
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

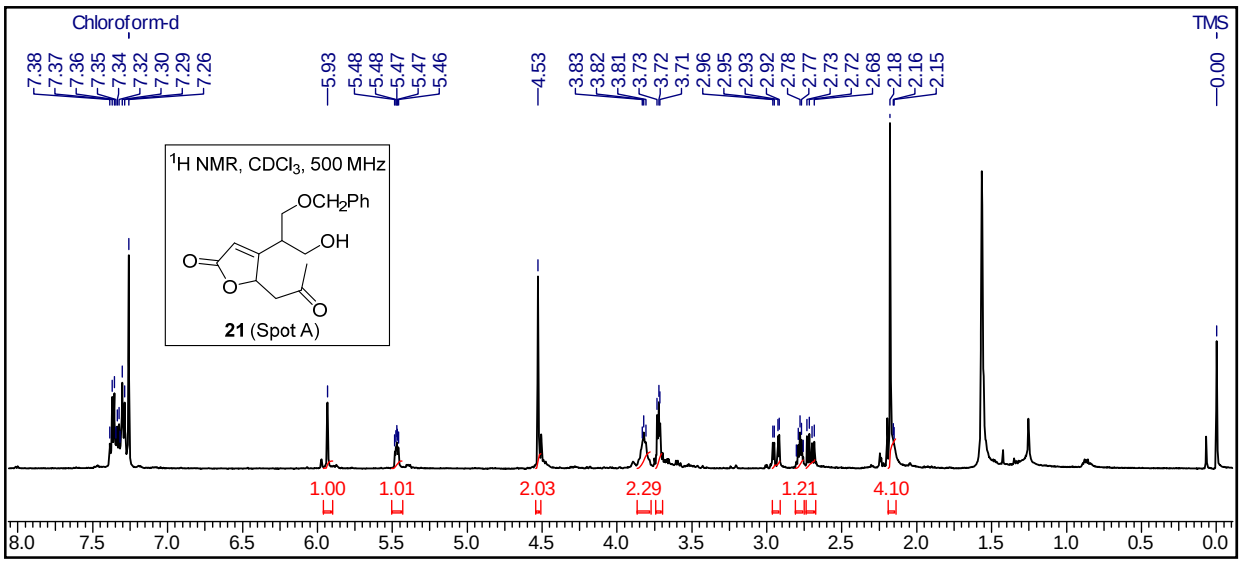

Chloroform-d
204.01
172.39
171.60
137.33
128.45
127.76
116.86
80.00
77.63
77.00
76.36
73.49
73.41
69.78
69.26
45.32
39.77
30.39
^{13}C NMR, CDCl$_3$, 50 MHz
OCH$_2$Ph
OCH$_2$Ph
O
O
O
19
200
150
100
50
0

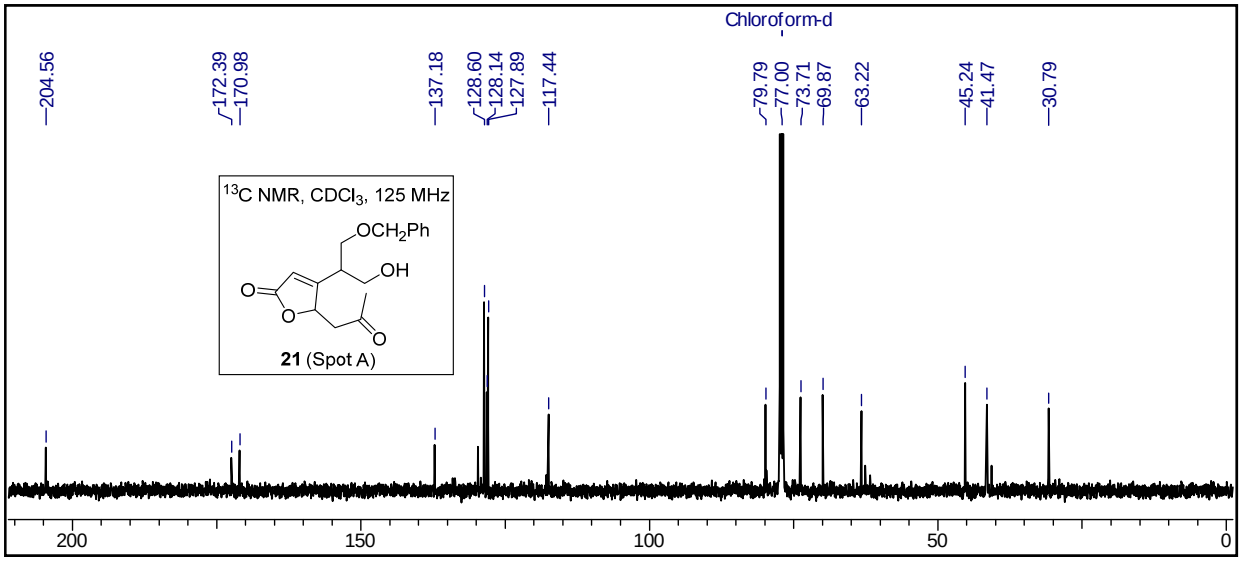

128.44
127.70
116.84
79.98
73.39
69.75
69.24
45.30
39.73
30.39
DEPT NMR, CDCl$_3$, 50 MHz
OCH$_2$Ph
OCH$_2$Ph
O
O
O
19
200
150
100
50
0

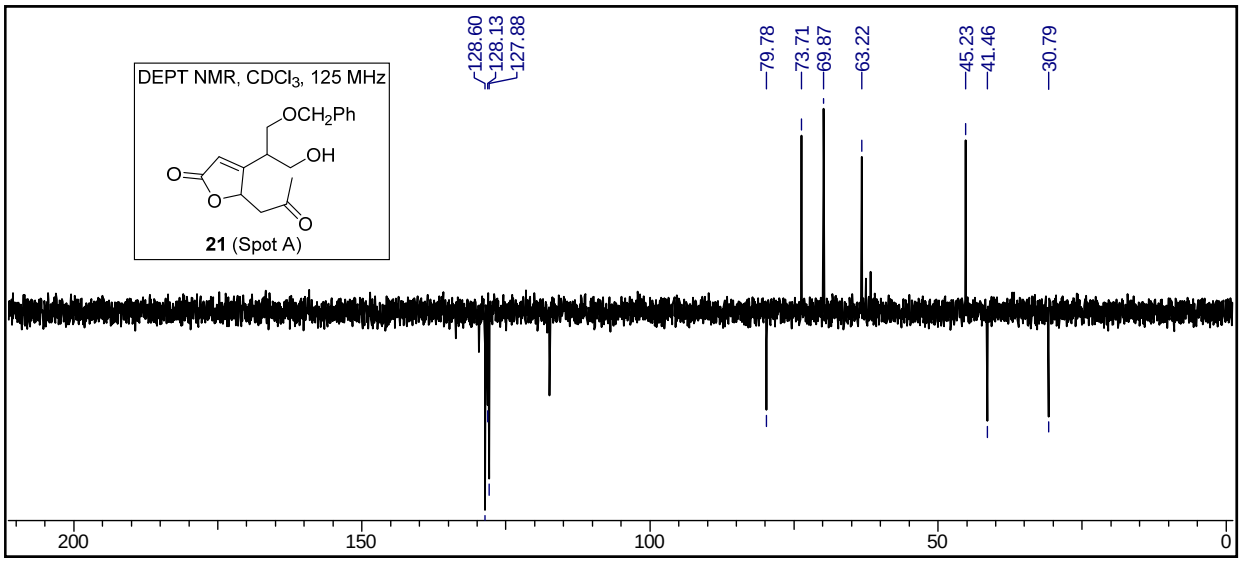

Chloroform-d
TMS
7.26
6.01
5.48
5.47
5.46
5.46
5.45
3.96
3.95
3.95
3.88
3.87
3.87
3.06
3.05
3.03
3.02
2.82
2.80
2.78
2.77
2.71
2.70
2.25
0.00
1H NMR, CDCl3, 500 MHz
OH
OH
O
O
O
20
1.00
1.00
2.02
1.08
3.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

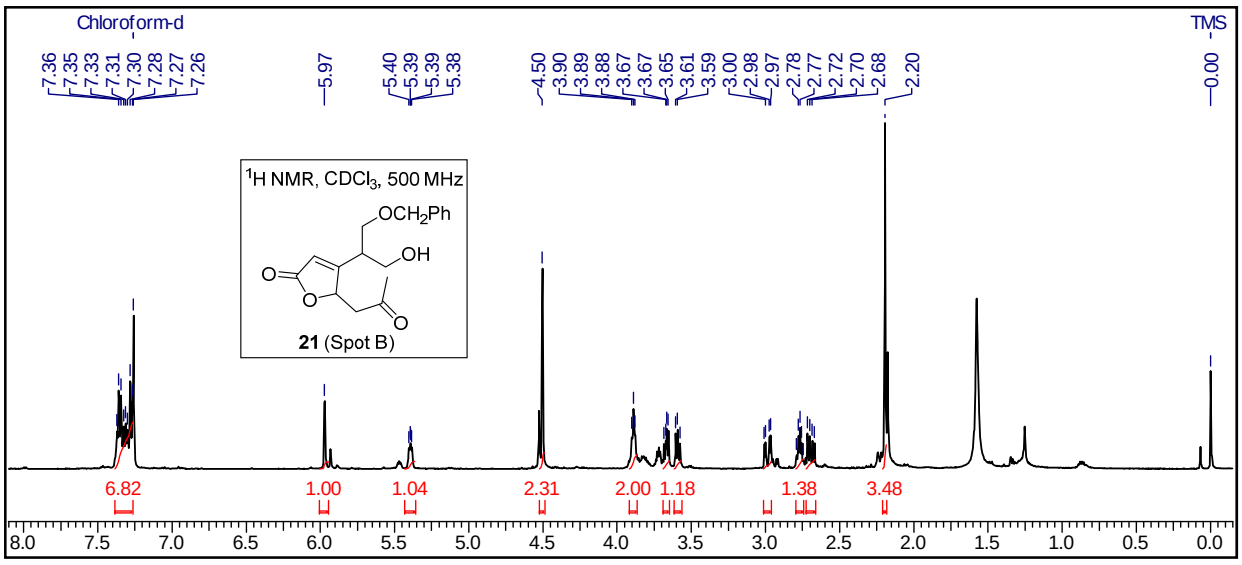

Chloroform-d
204.78
172.14
170.38
117.66
79.86
77.00
63.46
62.84
44.88
42.86
31.17
13C NMR, CDCl3, 125 MHz
OH
OH
O
O
O
20
200
150
100
50

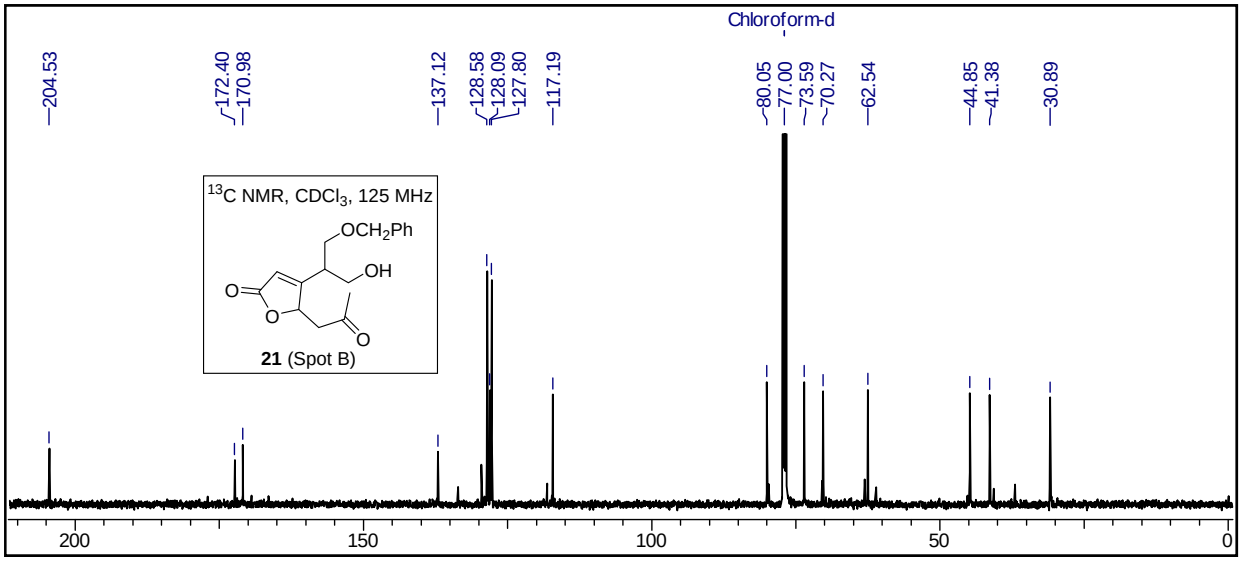

DEPT NMR, CDCl3, 125 MHz
OH
OH
O
O
O
20
117.66
79.86
63.47
62.84
44.88
42.86
31.17
200
150
100
50

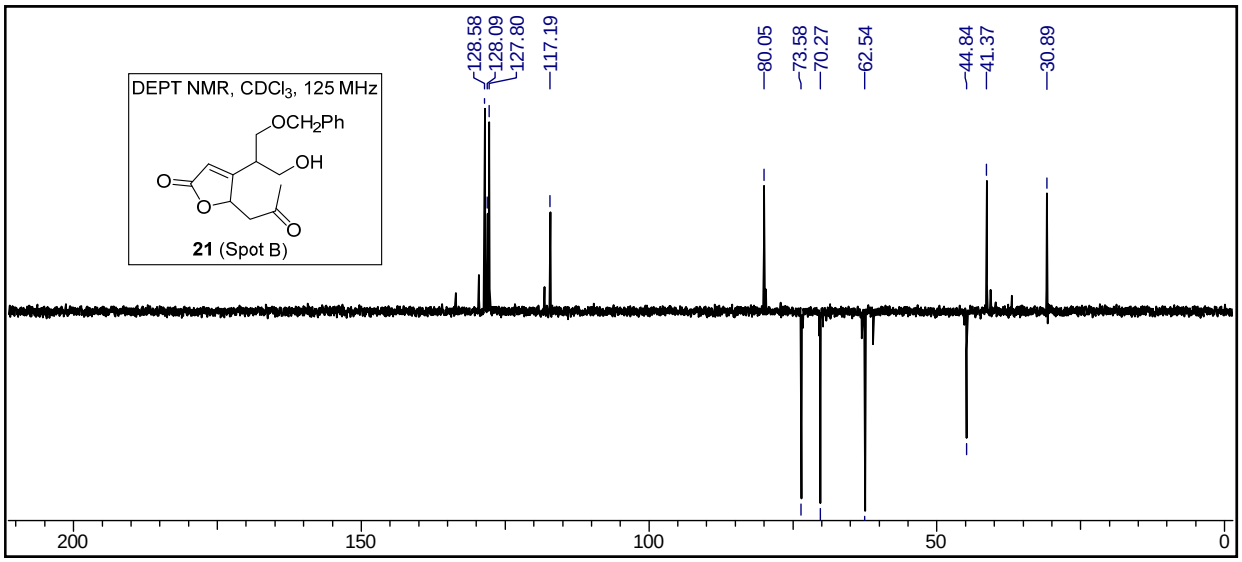

Chloroform-d
TMS
7.38
7.37
7.36
7.35
7.34
7.32
7.30
7.29
7.26
5.93
5.48
5.48
5.47
5.47
5.46
4.53
3.83
3.82
3.81
3.73
3.72
3.71
2.96
2.95
2.93
2.92
2.78
2.77
2.73
2.72
2.68
2.18
2.16
2.15
0.00
^{1}H NMR, $CDCl_3$, 500 MHz
OCH_2Ph
OH
O
O
O
21 (Spot A)
1.00
1.01
2.03
2.29
1.21
4.10
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

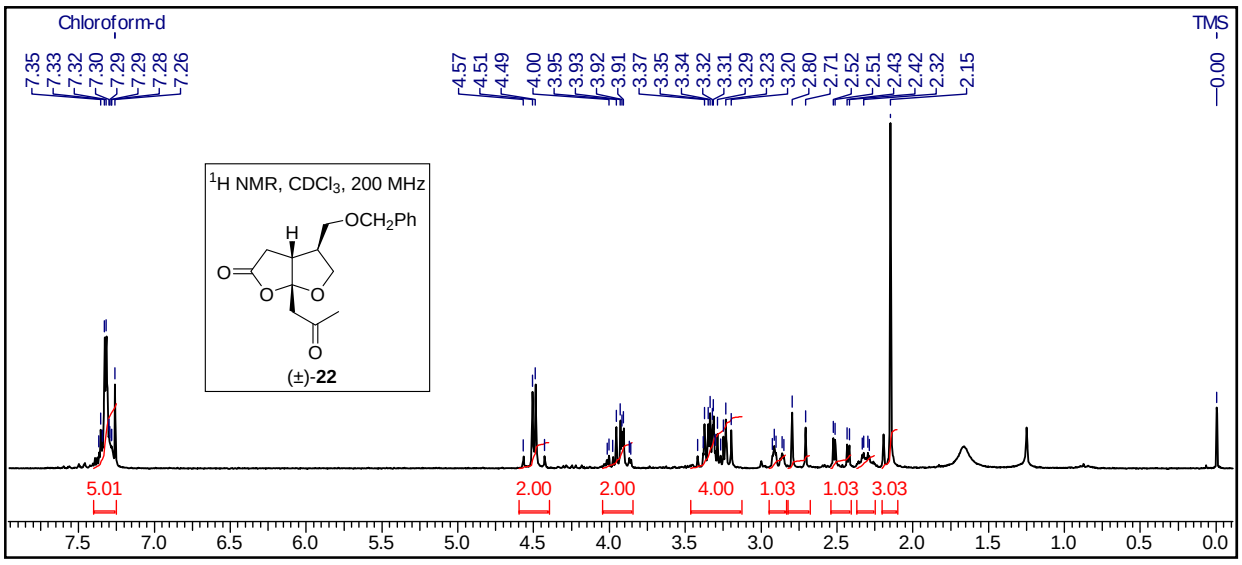

Chloroform-d
204.56
172.39
170.98
137.18
128.60
128.14
127.89
117.44
79.79
77.00
73.71
69.87
63.22
45.24
41.47
30.79
^{13}C NMR, $CDCl_3$, 125 MHz
OCH_2Ph
OH
O
O
O
21 (Spot A)
200
150
100
50
0

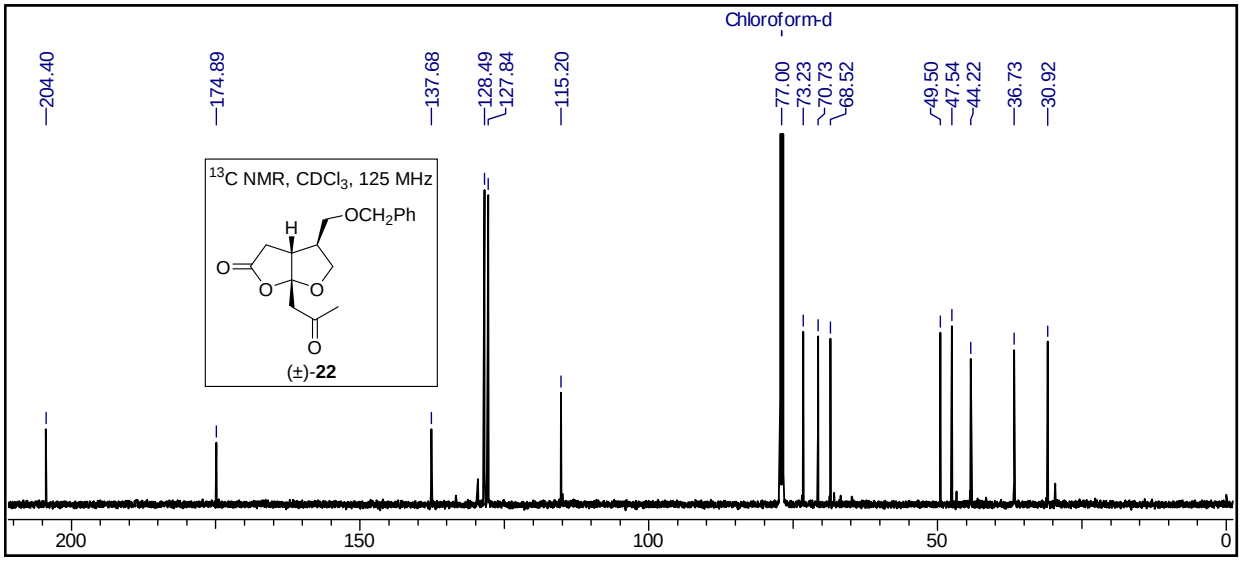

128.60
128.13
127.88
79.78
73.71
69.87
63.22
45.23
41.46
30.79
DEPT NMR, $CDCl_3$, 125 MHz
OCH_2Ph
OH
O
O
O
21 (Spot A)
200
150
100
50
0

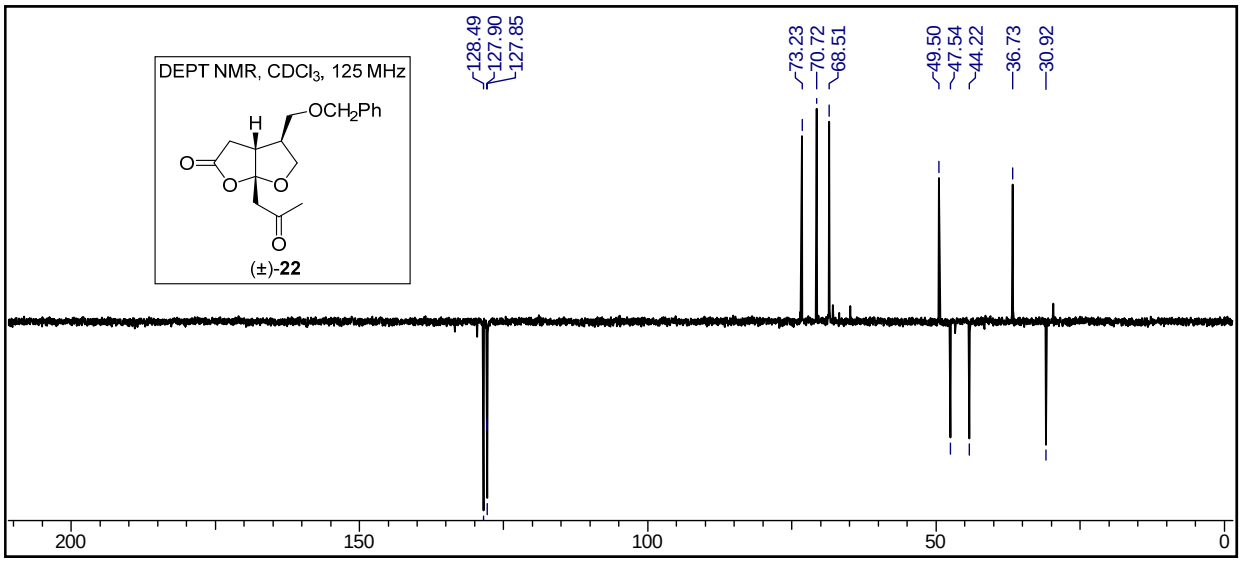

Chloroform-d
TMS
7.36
7.35
7.33
7.31
7.30
7.28
7.27
7.26
5.97
5.40
5.39
5.39
5.38
4.50
3.90
3.89
3.88
3.67
3.67
3.65
3.61
3.59
3.00
2.98
2.97
2.78
2.77
2.72
2.70
2.68
2.20
0.00
^{1}H NMR, CDCl$_3$, 500 MHz
OCH$_2$Ph
OH
O
O
O
21 (Spot B)
6.82
1.00
1.04
2.31
2.00
1.18
1.38
3.48
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

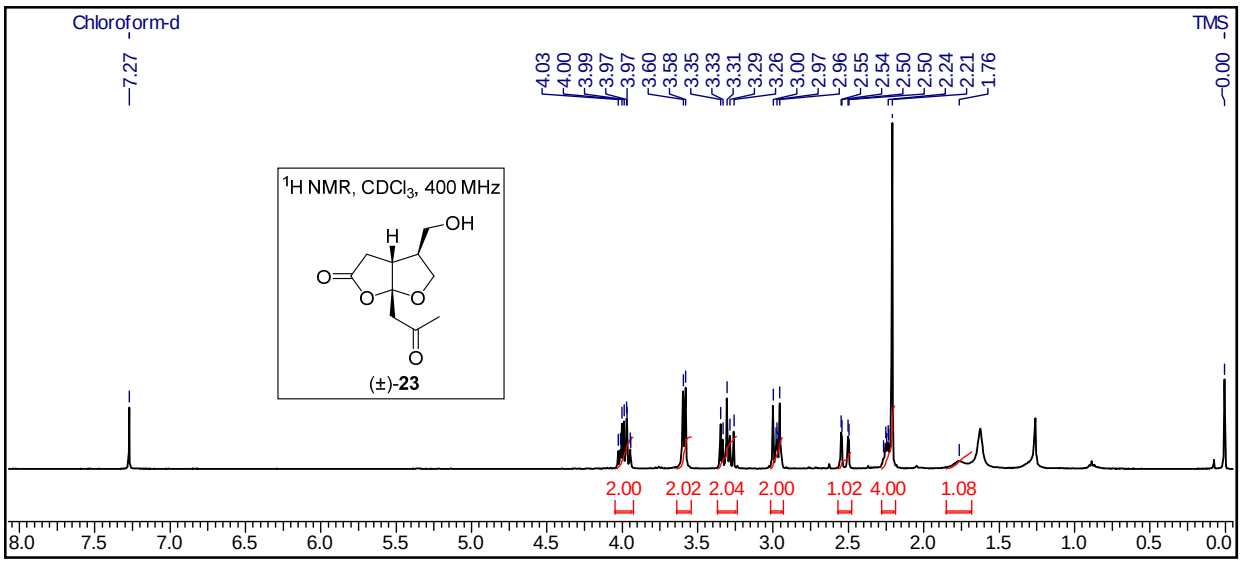

Chloroform-d
204.53
172.40
170.98
137.12
128.58
128.09
127.80
117.19
80.05
77.00
73.59
70.27
62.54
44.85
41.38
30.89
^{13}C NMR, CDCl$_3$, 125 MHz
OCH$_2$Ph
OH
O
O
O
21 (Spot B)
200
150
100
50
0

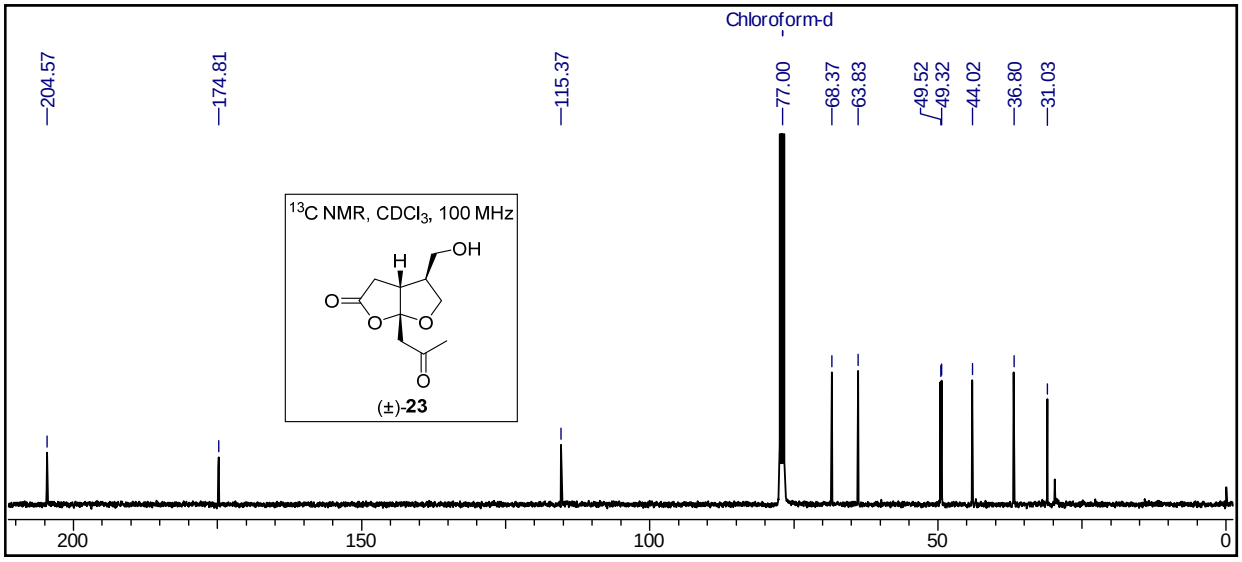

128.58
128.09
127.80
117.19
80.05
73.58
70.27
62.54
44.84
41.37
30.89
DEPT NMR, CDCl$_3$, 125 MHz
OCH$_2$Ph
OH
O
O
O
21 (Spot B)
200
150
100
50
0

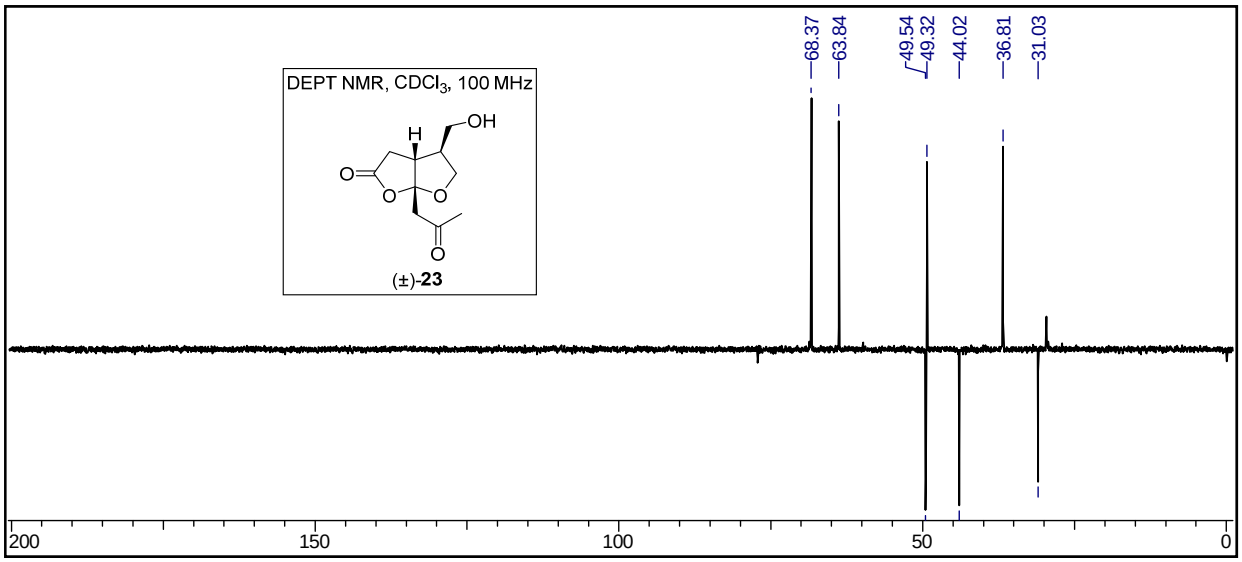

Chloroform-d
TMS
7.35
7.33
7.32
7.30
7.29
7.29
7.28
7.26
4.57
4.51
4.49
4.00
3.95
3.93
3.92
3.91
3.37
3.35
3.34
3.32
3.31
3.29
3.23
3.20
2.80
2.71
2.52
2.51
2.43
2.42
2.32
2.15
0.00
^{1}H NMR, $CDCl_3$, 200 MHz
OCH_2Ph
(±)-**22**
5.01
2.00
2.00
4.00
1.03
1.03
3.03

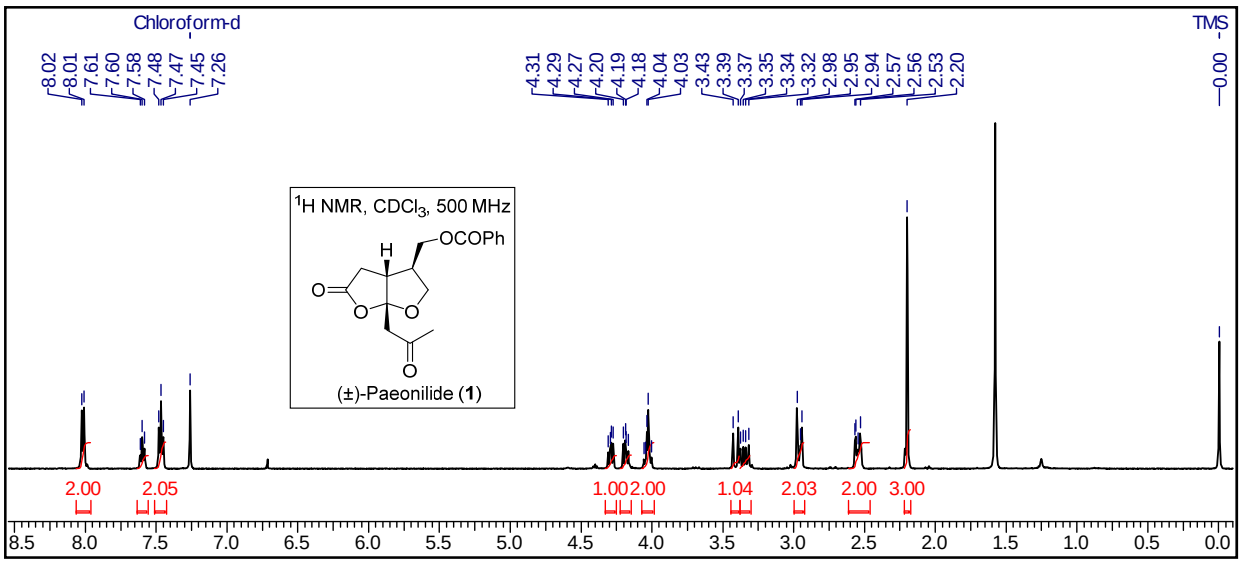

Chloroform-d
204.40
174.89
137.68
128.49
127.84
115.20
77.00
73.23
70.73
68.52
49.50
47.54
44.22
36.73
30.92
^{13}C NMR, $CDCl_3$, 125 MHz
OCH_2Ph
(±)-**22**

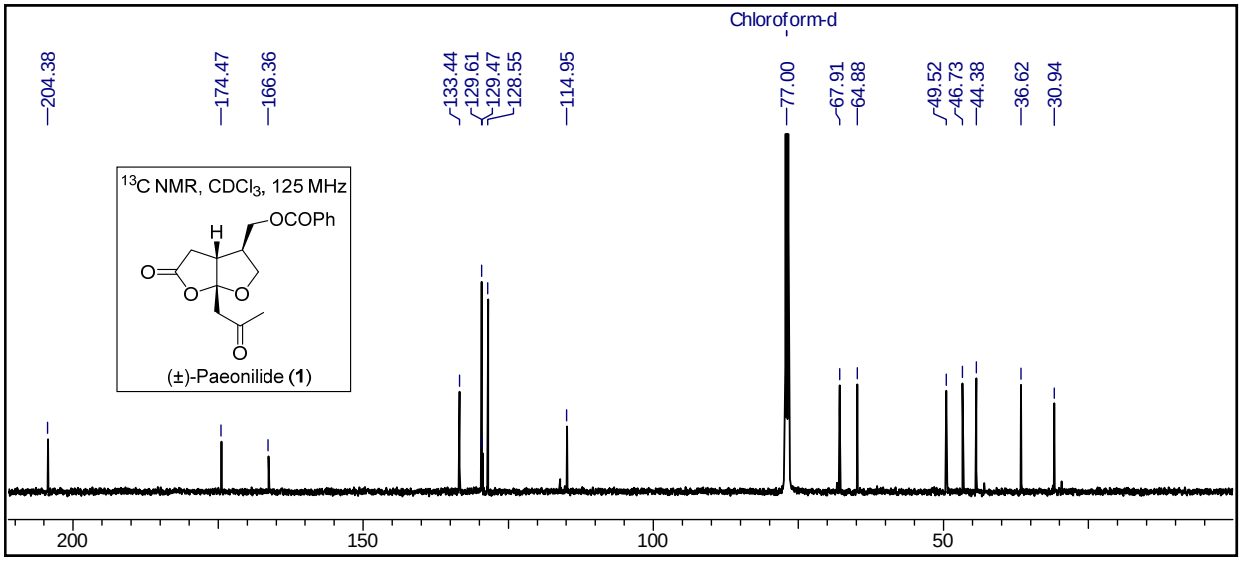

128.49
127.90
127.85
73.23
70.72
68.51
49.50
47.54
44.22
36.73
30.92
DEPT NMR, $CDCl_3$, 125 MHz
OCH_2Ph
(±)-**22**

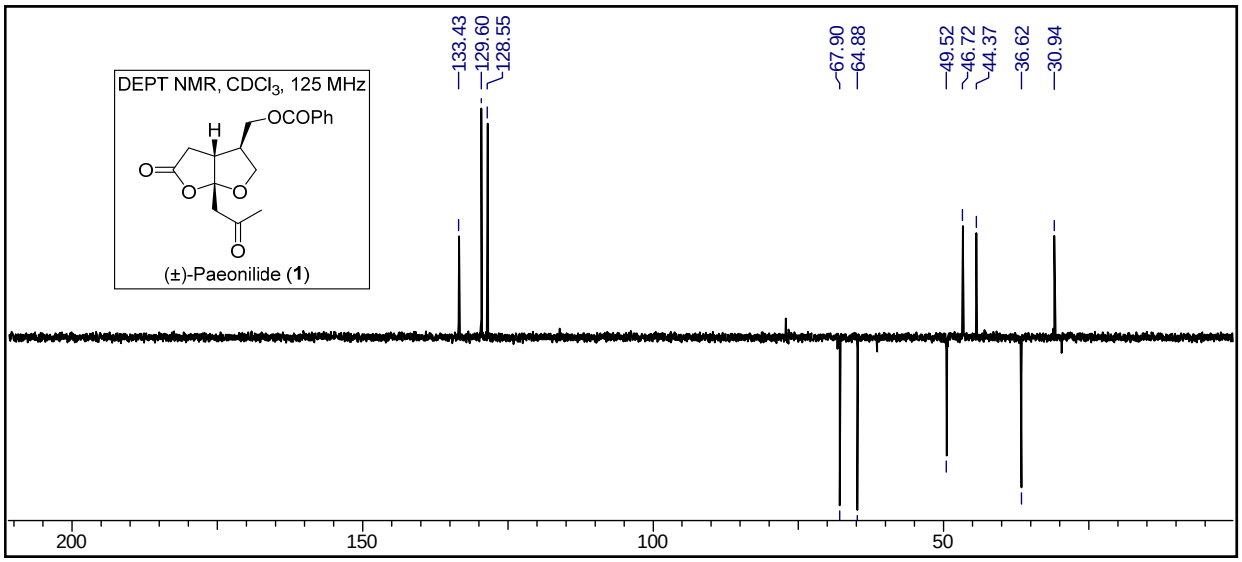

Chloroform-d
TMS
7.27
4.03
4.00
3.99
3.97
3.97
3.60
3.58
3.35
3.33
3.31
3.29
3.26
3.00
2.97
2.96
2.55
2.54
2.50
2.50
2.24
2.21
1.76
0.00
^{1}H NMR, $CDCl_3$, 400 MHz
OH
H
O
O
O
O
(±)-23
2.00
2.02
2.04
2.00
1.02
4.00
1.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

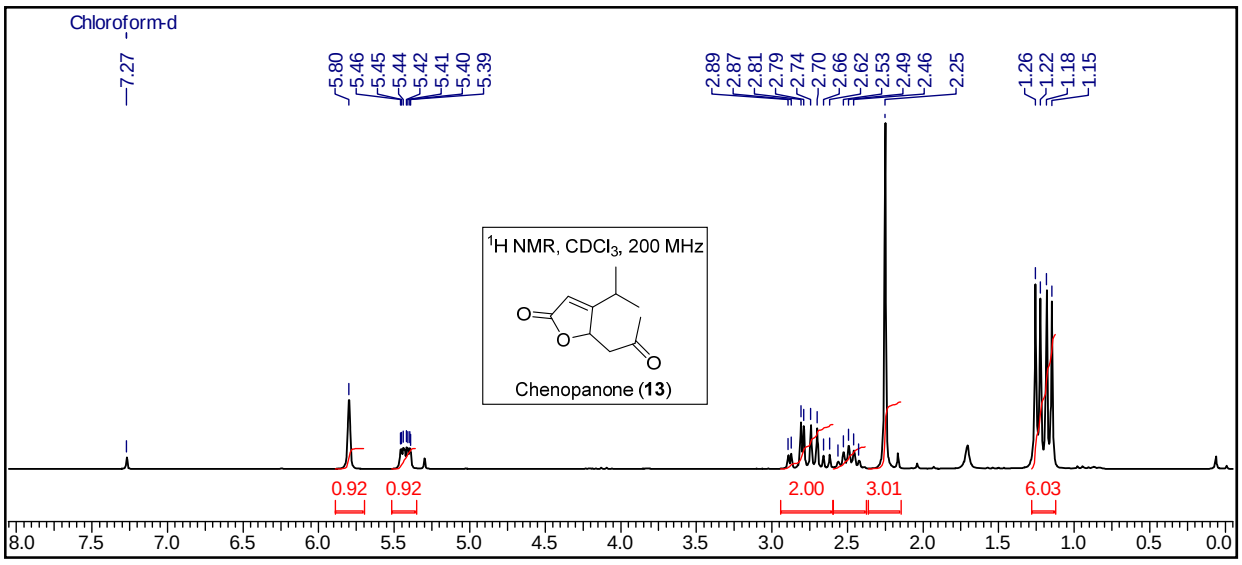

Chloroform-d
204.57
174.81
115.37
77.00
68.37
63.83
49.52
49.32
44.02
36.80
31.03
^{13}C NMR, $CDCl_3$, 100 MHz
OH
H
O
O
O
O
(±)-23
200
150
100
50
0

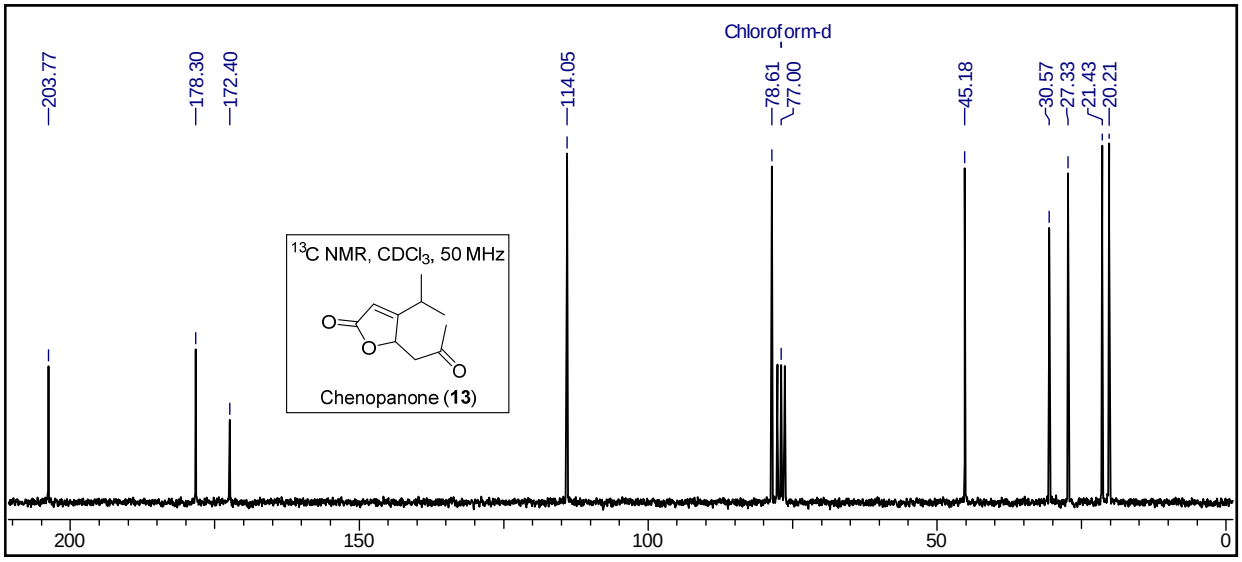

68.37
63.84
49.54
49.32
44.02
36.81
31.03
DEPT NMR, $CDCl_3$, 100 MHz
OH
H
O
O
O
O
(±)-23
200
150
100
50
0

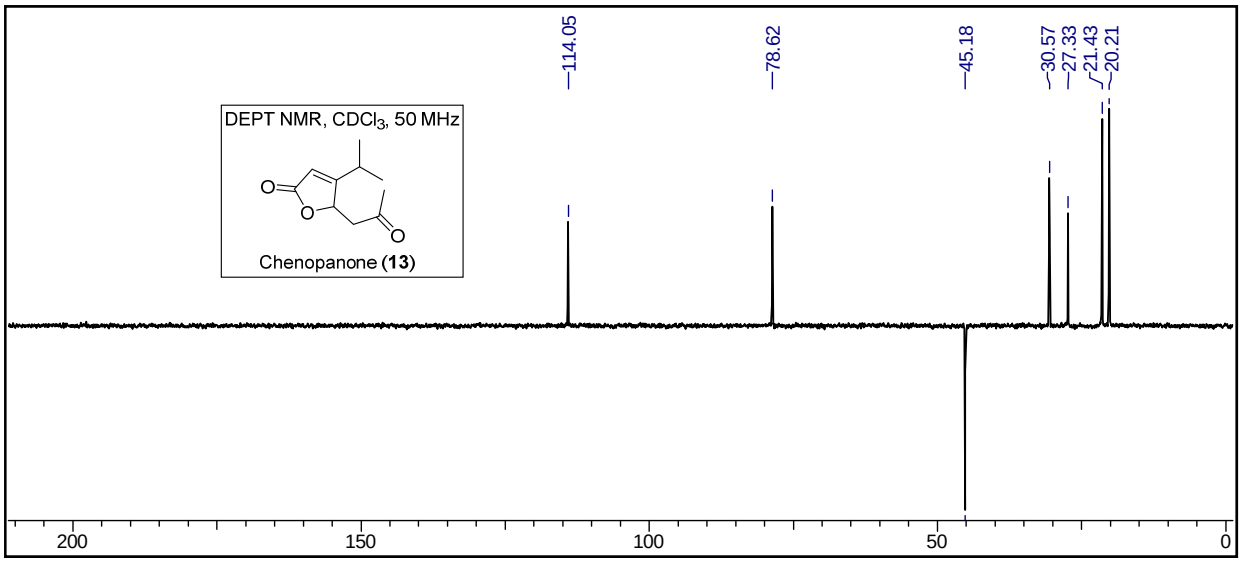

Chloroform-d
TMS
8.02
8.01
7.61
7.60
7.58
7.48
7.47
7.45
7.26
4.31
4.29
4.27
4.20
4.19
4.18
4.04
4.03
3.43
3.39
3.37
3.35
3.34
3.32
2.98
2.95
2.94
2.57
2.56
2.53
2.20
0.00
^{1}H NMR, $CDCl_3$, 500 MHz
OCOPh
H
O
O
O
O
(±)-Paeonilide (**1**)
2.00
2.05
1.00
2.00
1.04
2.03
2.00
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
204.38
174.47
166.36
133.44
129.61
129.47
128.55
114.95
77.00
67.91
64.88
49.52
46.73
44.38
36.62
30.94
^{13}C NMR, $CDCl_3$, 125 MHz
OCOPh
H
O
O
O
O
(±)-Paeonilide (**1**)
200
150
100
50

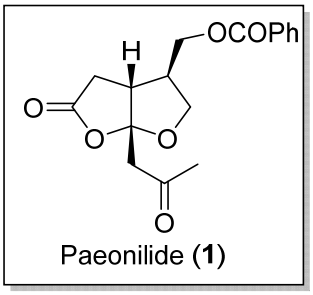

133.43
129.60
128.55
67.90
64.88
49.52
46.72
44.37
36.62
30.94
DEPT NMR, $CDCl_3$, 125 MHz
OCOPh
H
O
O
O
O
(±)-Paeonilide (**1**)
200
150
100
50


Chloroform-d
7.27
5.80
5.46
5.45
5.44
5.42
5.41
5.40
5.39
2.89
2.87
2.81
2.79
2.74
2.70
2.66
2.62
2.53
2.49
2.46
2.25
1.26
1.22
1.18
1.15
^{1}H NMR, CDCl$_3$, 200 MHz
Chenopanone (13)
0.92
0.92
2.00
3.01
6.03
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


Chloroform-d
203.77
178.30
172.40
114.05
78.61
77.00
45.18
30.57
27.33
21.43
20.21
^{13}C NMR, CDCl$_3$, 50 MHz
Chenopanone (13)
200
150
100
50
0


114.05
78.62
45.18
30.57
27.33
21.43
20.21
DEPT NMR, CDCl$_3$, 50 MHz
Chenopanone (13)
200
150
100
50
0

Comparison of ^{1}H and ^{13}C NMR Data between Natural and Synthetic Paeonilide in Tabular Form



Paeonilide (**1**)

^{1}H NMR ($CDCl_3$, 500 MHz)	
Natural	**Synthetic**
2.20 (s, 3H)	2.20 (s, 3H)
2.54 (m, 1H)	2.52–2.56 (m, 1H)
2.55 (dd, *J* = 18.5 and 2.8 Hz, 1H)[#]	2.55 (dd, *J* = 20 and 2 Hz, 1H)
2.96 (d, *J* = 17.8 Hz, 1H)	2.96 (d, *J* = 20 Hz, 1H)
2.97 (m, 1H)	2.93–3.00 (m, 1H)
3.34 (dd, *J* = 18.5 and 10.5 Hz, 1H) [#]	3.35 (dd, *J* = 20 and 10Hz, 1H)
3.40 (d, *J* = 17.8 Hz, 1H)	3.42 (d, *J* = 15 Hz, 1H)
4.03 (m, 2H)	4.00–4.07 (m, 2H)
4.19 (dd, *J* = 11 and 8 Hz, 1H)	4.19 (dd, *J* = 10 and 10 Hz, 1H)
4.30 (dd, *J* = 11 and 7.3 Hz, 1H)	4.30 (dd, *J* =10 and 5 Hz, 1H)
7.47 (t, *J* = 8.5 Hz, 2H)	7.47 (t, *J* = 10 Hz, 2H)
7.60 (br t, 1H)	7.60 (t, *J* = 10 Hz, 1H)
8.02 (dd, *J* = 8.5 and 1.2 Hz, 2H)	8.02 (d, *J* = 10 Hz, 2H)

[#]The corrected proton assignments has been included (see references 15a and 15c).

^{13}C NMR ($CDCl_3$, 125 MHz)	
Natural	**Synthetic**
30.9	30.9
36.6	36.6
44.4	44.4
46.7	46.7
49.5	49.5
64.9	64.9
67.9	67.9
114.9	115.0
128.5	128.6
129.6	129.5
129.6	129.6
133.4	133.4
166.3	166.4
174.4	174.5
207.1	204.4

2B.6 References

(1) (a) Seebach, D. *Angew*. *Chem*. *Int*. *Ed*. **1979**, *18*, 239. (b) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357. (c) Seebach, D.; Corey, E. J. *J*. *Org*. *Chem*. **1975**, *40*, 231.

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CHAPTER 3

Synthesis of Natural and Unnatural Conjugative Alkenyl(methyl)maleic Anhydrides

This chapter features the following topics:

Notes: (i) An independent figure, table, scheme, structure and reference numbers have been used for the each section, (ii) detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end part of section B.

This chapter is divided into two sections. The section A presents a concise literature account on the synthesis of structurally related bioactive alkyl(methyl)maleic anhydrides. Several inventive approaches to imperious alkyl(methyl)maleic anhydrides have been accounted in the contemporary literature. The list of these disubstituted maleic anhydrides is very vast and few of them are represented below (Figure 1).

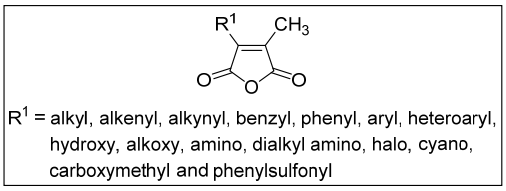
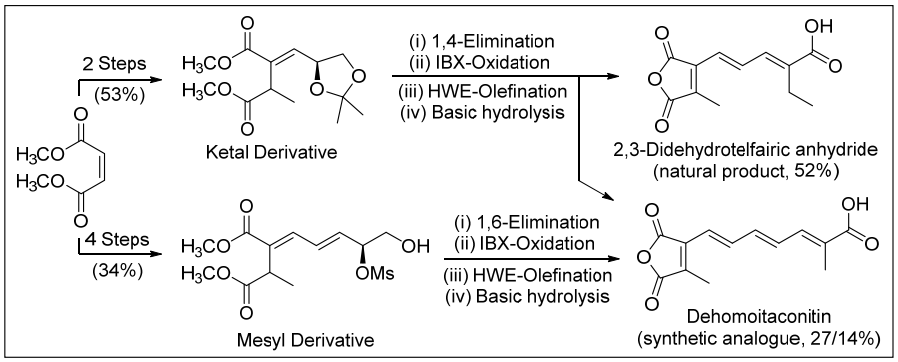


Figure 1. Natural and unnatural substituted maleic anhydrides

The section B describes our contribution on total synthesis of natural product 2,3-didehydrotelfairic anhydride and unnatural conjugative alkenyl(methyl)maleic anhydrides (Scheme 1).



Scheme 1. Base Induced 1,4- and 1,6-Eliminations in Alkylidenesuccinates: Application in Stereoselective Total Synthesis of Natural and Unnatural Conjugative Alkenyl(methyl)maleic Anhydrides

Starting from dimethyl maleate, facile stereoselective syntheses of natural and unnatural conjugative alkenyl(methyl)maleic anhydrides have been described in search of effective RFTase inhibitors. The key reactions were base endorsed 1,2-, 1,4- and 1,6-eliminations in the corresponding alkylidenesuccinate derivatives. The 1,2-eliminations in cyclic carbonate and sulfite by regioselective abstraction of methine protons with release of CO_2 and SO_2 provided a conjugated ketone product. The characteristic 1,4- and 1,6-elimination reactions with respective release of acetone and mesylate furnished the unsaturated alcohols, which were transformed into conjugative alkenyl(methyl)maleic anhydrides via oxidation followed by HWE reactions pathway. The involved mechanistic aspects in these imperative elimination reactions have also been discussed in brief.

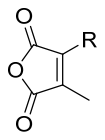
CHAPTER 3: SECTION A

A Concise Literature Account on the Reported Syntheses of Naturally Occurring Alkyl(methyl)maleic Anhydrides

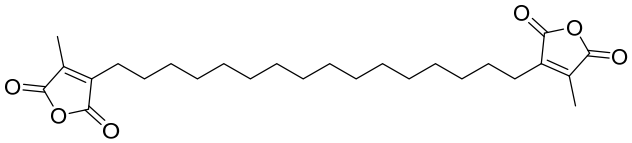
This section A of chapter 3 features the following topics:

3A.1 Introduction

Cyclic anhydrides, especially maleic anhydrides are fascinating molecules for two main reasons: (i) they are endowed with tremendous biological potential and are prominent class of natural products,[1] and (ii) their applications as potential building blocks or versatile intermediates for the synthesis of a vast array of structurally interesting bioactive compounds.[2] Maleic anhydride (2,5-furandione) was prepared for the first time two centuries ago by the catalytic oxidation of benzene over vanadium pentoxide.[3] Large number of naturally occurring maleic anhydrides and their derivatives has been identified, most of them have been biologically active and display wide range of pharmacological properties.[4] Methylmaleic anhydride (citraconic anhydride) is the most widely used derivative of monoalkyl substituted maleic anhydride. Only few synthetic approaches for methylmaleic anhydride are known in the literature.[5] Hitherto, monoalkyl substituted maleic anhydrides have not been much explored as compared to methyl maleic anhydride.[6] A large number of alkyl(methyl)maleic anhydrides have been isolated as natural products and they exhibit broad range of biological activities as summarized in Table 1. Due to the significant biological activities, those natural products received the immediate attention from several research groups with development of elegant synthetic approaches. Many synthetic structural analogs of these natural anhydrides have been also synthesized and biologically examined during past two decades. Recently one comprehensive review dedicated to this artistic class of natural products has been published in the literature.[1b] On the basis of past two decades research work in field of cyclic anhydrides and their derivatives chemistry, many new interesting results in the synthesis of these natural products using selective carbon–carbon/heteroatom bond forming reactions have been published from our group.[7] Preceding syntheses and our approach to the natural and unnatural products with maleic anhydride backbone have been described in the earlier Ph. D. dissertation.[8]



Alkyl(methyl)maleic anhydride



Tyromycin A (*Tyromyces lacteus*, aminopeptidase inhibitor)

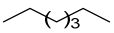
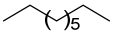
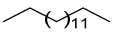
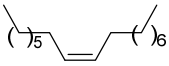
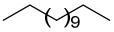
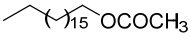
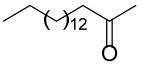
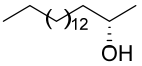
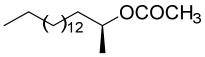
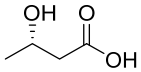
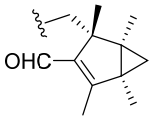
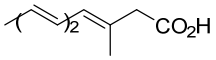
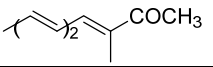
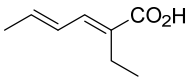
sr. no.	—R	name	isolation source	activity	ref.
1		ethyl(methyl)maleic anhydride	*Paederia foetida L.* and *Sambucus nigra L.*	flavoring agent	9
2		hexyl(methyl)maleic anhydride	*Agropyrum repens*	flavoring agent	10
3		octyl(methyl)maleic anhydride	*Pseudomonas cepacia* A-1419	flavoring agent	11
4		chaetomellic acid A anhydride	*Chaetomella acutiseta* (fermentation extract)	RFTase inhibitor	12 13
5		chaetomellic acid B anhydride		RFTase inhibitor	
6		chaetomellic acid C anhydride		RFTase inhibitor	
7		aspergillus acid A	*Aspergillus wentii* (mould)	unknown	14
8		aspergillus acid B		unknown	
9		(*S*)-aspergillus acid C		unknown	
10		(*S*)-aspergillus acid D		unknown	
11		maleic anhydride segment of tautomycin and tautomycetin	*Streptomyces spirovertivillatus* *Streptomyces griseochromogenes*	antifungal and antibiotic	15
12		lindenanolide E	*Lindera chunii* MERR	HIV-1 integrase inhibitor	16
13		itaconitin	*Aspergillus itaconicus*	unknown	17
14		graphenone	*Graphis scripta* (lichen mycobiont)	unknown	18
15		2,3-didehydrotelfairic anhydride	*Xylaria telfairii* berk	unknown	19

Table 1. Naturally Occurring Diversely Substituted Bioactive Methylmaleic Anhydrides

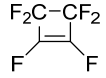
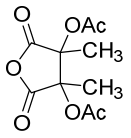
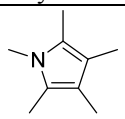
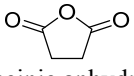
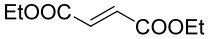
[Note: Ample synthetic utilities of methyl, monoalkyl substituted, dialkyl substituted, complex dialkyl substituted maleic anhydrides and their derivatives are known in the earlier and recent literature]

3A.2 Recent Synthetic Strategies Towards the Natural and Unnatural Alkyl(methyl)maleic Anhydrides

In the present section we have collected and discussed the widespread knowledge regarding natural and unnatural alkyl substituted methylmaleic anhydrides. Furthermore, an emphasis has been put on the newly developed synthetic routes and strategies. Some medicinal, biological, or pharmacological data and uses of corresponding maleic anhydrides and derivatives have been mentioned as available. Since large amount of data is available in the literature, no pretension of completeness has been claimed.

3A.2.1 Dimethylmaleic Anhydride

Dimethylmaleic anhydride (DMMA) is the most simple and widely used derivative of alkyl(methyl)maleic anhydride. More than 20 synthetic approaches to dimethyl maleic anhydride using variety of strategies are known in literature. The chemistry involved in those approaches is summarized in a tabular format (Table 2). However, only four of them provide the desired dimethylmaleic anhydride in 60% plus overall yields.

sr. no.	starting material	reagents and reaction conditions	% yield	ref.
1	CH_3COCH_2COOEt Ethyl acetoacetate	(i) NaH, MeBr; (ii) $NaCN/H_2O$; (iii) H_2SO_4	13	20
2	 Perfluro cyclobutene	(i) CH_3Li, Et_2O, 45 ^oC; (ii) H^+/H_2O; (iii) 30% Aq. H_2O_2	23	21
3	$HOOCCH_2CH_2COOH$ Succinic acid	$CH_3COCOOH$, pyridine, 150 ^oC, 1.5 h	40	22
4	 Dimethyldiacetyl tartaric anhydride	(i) Pyrolysis, 440 ^oC; (ii) pyrolysis of formed 2-methyl-2-acetoxyitaconic anhydride at 545 ^oC	Low yield	23
5	 Pentamethyl pyrrole	(i) 70% H_2O_2; (ii) pyrolysis, 155 ^oC	Low yield	24
6	 Succinic anhydride	(i) (a) Pyridine, 125 ^oC, 0.5 h, (b) MeCOCOOH, 125 ^oC; (ii) steam distillation	40	25
7	 Diethyl fumarate	(i) Methyl acrylate, $P(Cy)_3$, dioxane; (ii) H^+/H_2O; (iii) H_2, Pd/C; (iv) thermal decomposition	27	26
8	 2,3-Dimethyl-1,3-butadiene	Air oxidation over a catalyst at 400 ^oC	21	27

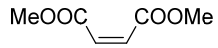
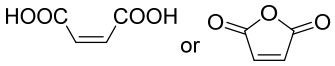
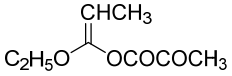
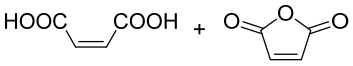
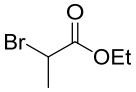
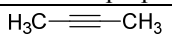
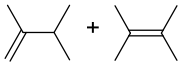
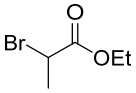
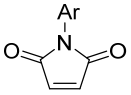
9	 Dimethyl maleate	(i) Methyl acrylate, $P(Cy)_3$, dioxane; (ii) $NaOH/H_2O$; (iii) heating at 220–230 ^oC	40	28
10	 2,3-Dimethyl but-2-ene	Air oxidation over vanadium and phosphorus catalyst at 300–500 ^oC	35	29
11	 Maleic acid or Maleic anhydride	(i) 2-Aminopyridine, AcOH, reflux; (ii) 4 N H_2SO_4	50/75	30
12	 1-Ethoxy-1-propenyl pyruvate	Pyrolysis	35	23
13	 Maleic acid and maleic anhydride	(i) 2-(Methylamino)thiazole, 150 ^oC, 0.5 h; (ii) 4 N H_2SO_4	57	31
14	$CH_3COCOOEt$ Ethyl pyruvate	(i) $CH_3CH[PO(OEt)_2]COOEt$ NaH, 1,2-diethoxyethane; (ii) H^+/H_2O	46	32
15	 Ethyl 2-bromopropionate	Self coupling in liq. NH_3 using calcium napthalenide	40	33
16	 But-2-yne	(i) $Ir(CO)_3Br$, THF; (ii) 4 N HNO_3	Not reported	34
17	 2,3-Dimethyl but-1-ene and 2,3-dimethyl but-2-ene (73:27)	V_2O_5-MoO_3-P_2O_5-TiO_2 (9.8:19.4:0.8:70), air, 400 ^oC	67	35
18	 Ethyl 2-bromopropionate	(i) $Ca(NH_2)_2$ and liq. NH_3; (ii) H^+, H_2O	36	36
19	 But-2-yne	$(bipy)Ni(CO)_2$, O_2, THF, 20 ^oC, 24 h	63	37
20	 *N*-(*p*-Tolyl)maleimide	PPh_3, *p*-formaldehyde, AcOH, reflux	74	38

Table 2. Reported Methods for the Synthesis of Dimethylmaleic Anhydride

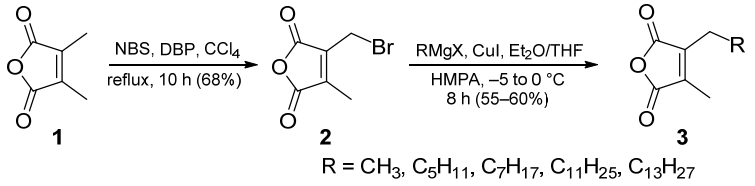
The utilities of methyl and dimethylmaleic anhydrides have been well proved in laboratory as well as in industrial practices.[39] Methyl and dimethylmaleic anhydrides have also been used for the synthesis of important heterocyclic systems[40] and as a potential dienophiles in the Diels-Alder reactions.[41] A large number of natural products have been synthesized from them.[42]

3A.2.2 Ethyl/hexyl/octyl(methyl)maleic Anhydrides

2-Ethyl-3-methylmaleic anhydride[9] was isolated from *Paederia foetida L*. (from volatile oil) and *Sambucus nigra L*. (fruit) whereas 2-hexyl-3-methylmaleic anhydride[10] and 2-octyl-3-

methylmaleic anhydride[11] were isolated from *Agropyrum repens* (rhizome) and *Pseudomonas cepacia* A-1419 respectively (Table 1, entries 1–3). Structurally related oxygenated hexylitaconates from a marine sponge-derived fungus have been also isolated and were evaluated for cytotoxic and anti-inflammatory activity.[43]

In our laboratory we have synthesized these natural products using chemoselective carbon–carbon coupling reaction of bromomethyl(methyl)maleic anhydride (**2**) with organocuprates.[44] The Alkyl(methyl)maleic anhydrides **3** were obtained in 55–60% yield (Scheme 1). It is remarkable that the present coupling reactions take place with the intact preservation of cyclic anhydride moiety.



Scheme 1. Synthesis of Ethyl/hexyl/octyl/dodecyl/tetradecyl(methyl)maleic Anhydrides

3A.2.3 Chaetomellic Anhydride A, B and C

Chaetomellic acid A, chaetomellic acid B and chaetomellic acid C have been isolated from fermentation extract of the coleomycete *Chaetomella acutiseta* by a group of scientists at Merck, USA in 1993 (Table 1, entries 4–6).[12,13] The structural assignment of chaetomellic anhydride A and B has been done on the basis of analytical and spectral data. The position and geometry of the carbon–carbon double bond in chaetomellic acid B side chain was established by MS analysis of monoepoxide prepared by reacting it with *m*-CPBA in DCM. Chaetomellic acid A and B have been identified as potent inhibitors of Ras farnesyl-protein transferase (FPTase), with an IC_{50} value of 55 and 185 nM, respectively.[45] Chaetomellic acid A is three times more potent than chaetomellic acid B and became the main attraction of synthetic efforts because of its potent FPTase inhibitory activity for the treatment of cancer; in contrast, chaetomellic acid C is 10-times less active against human FPTase.[46] FPTase is an enzyme catalyzing a post-translational modification of Ras. Mutated form of ras oncogens are found in about 25% of the human tumors and believed to play a key role in their growth. Due to the presence of both essential hydrophilic and hydrophobic units, chaetomellic acid A appropriately binds and deactivates the responsible enzyme.[47] Owing the propensity to present

in the cyclized form, these natural products were isolated as their anhydrides (Figure 1). However, they actually exhibit their FPTase inhibitory activity in their dianionic form.

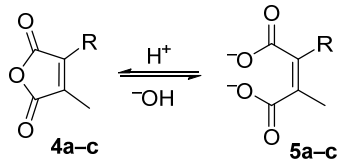
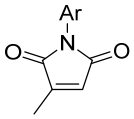


Figure 1. Chaetomellic acid anhydrides A, B and C (R = $C_{14}H_{29}$, $C_{16}H_{31}\Delta$ and $C_{12}H_{25}$)

Recently, the dianionic form of chaetomellic acid A has found application in characterizing the FPP (fernesyl diphospahte) binding site in rubber transferase.[48] Since the isolation of chaetomellic acids in 1993, several syntheses of them have been reported in past two decades. The chemistry involved in all earlier syntheses is summarized in Table 3.

sr. no.	starting material	reagents and conditions	% yield	ref.
1	$CH_3(CH_2)_{14}COOMe$ Methyl palmitate	(i) Methyl pyruvate, LDA, THF, −78 °C to −10 °C; (ii) 2,6-Di-*t*-butyl-4-methyl pyridine, *p*-tolunesulphonic anhydride, pyridine, DCM; (iii) DBU, toluene, reflux; (iv) (a) NaOH-CH_3OH-THF-H_2O; (b) 4 N HCl	18%	48 49
2	$CH_3(CH_2)_{12}CH_2Br$ Tetradecyl bromide	(i) $CoCl_2$, pyridine, $NaBH_4$, NaOH, CH_3OH; (ii) PhSSPh, *hv*; (iii) *m*-CPBA, pH 7.4, phosphate buffer, DCM	64%	50
3	$MeOOCCH_2COOMe$ 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	**4a** (83%) **4b** (80%)	51
4	MeOOC—≡—COOMe Dimethyl acetylenedicarboxylate	(i) (a) $C_{14}H_{29}MgBr$, $CuBr.Me_2S$, (b) MeI, THF-HMPA, (c) aq. NH_4Cl; (ii) (a) $LiOH/H_2O$, (b) H^+/HCl	78%	52
5	$CH_3(CH_2)_{12}CH(Br)COCl$ 2-Bromopalmitoyl chloride	(i) 2-Aminopyridine, Et_3N, Et_2O, rt; (ii) *t*-BuOH, reflux; (iii) maleic anhydride, NaOAc, reflux	62%	53
6	 *N*-(*p*-Tolyl)methyl maleimide	(i) (a) PPh_3, $CH_3(CH_2)_{12}CHO$, AcOH, reflux, 18 h; (b) Δ, 140–150 °C, 0.5 h; (ii) (a) $KOH/H_2O/CH_3OH$/THF, reflux, 2 h, (b) H^+/HCl	89%	54
7	$CH_3(CH_2)_{13}COOH$ Pentadecanoic acid $C_{16}H_{31}COOH$ (*Z*)-8-Heptadecanoic acid	(i) (a) DCC, 2-mercaptopyridine *N*-oxide, DCM, 2 h, (b) citraconic anhydride, *hv* (500 W), 10–15 °C, 0.5 h	**4a** (70%) **4b** (60%)	55

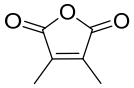
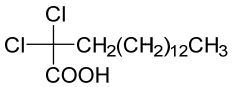
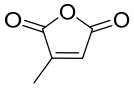
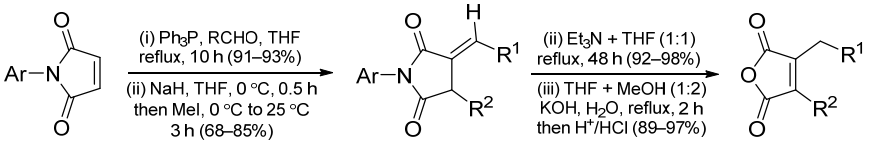
8	 Dimethylmaleic anhydride	(i) NBS, DBP, CCl_4, reflux, 10 h; (ii) $CH_3(CH_2)_{13}MgX$, CuI, HMPA, Et_2O/THF, –5 to 0 °C	38%	44
9	 2,2-Dichloropalmitic acid	(i) (a) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h, (b) *N*-Benzyl-3-chloro-2-propylamine, pyridine, 23 °C, 1 h; (ii) CuCl/TMEDA, MeCN–CH_2Cl_2, 60 °C, 20 h; (iii) (a) Na, MeOH-Et_2O, 25 °C, 20 h, (b) H^+/H_2O; (iv) (a) KOH, MeOH–THF, reflux, 2 h, (b) H^+/H_2O	55%	56
10	 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	37%	57
11	$CH_3(CH_2)_{13}CHO$ Pentadecanal	(i) Trimethylsilylacetylide, THF, –78 to –10 °C; (ii) DIAD, PPh_3, NBSH, THF, –15 °C to rt; (iii) CO_2, $Ni(cod)_2$, DBU, Me_2Zn, THF, 25 °C, 19 h; (iv) Ac_2O, 2 h	57%	58

Table 3. Reported Methods for the Synthesis of Chaetomellic Anhydride A and Chaetomellic Anhydride B

Apart from the above mentioned syntheses, some more recent approaches for synthesis of chaetomellic anhydride and/or their analogs have been presented in schematic format and are discussed below.

The recent synthetic approach reported from our group involves the generation of a carbanion on an alkylidenesuccinimide unit and its condensation with various alkyl halides as the key reaction for synthesis of a wide range of dialkylmaleic anhydrides **8** (Scheme 2).[59] Trisubstituted exocyclic to tetrasubstituted endocyclic carbon–carbon double bond isomerization followed by basic hydrolysis and acidification furnished the desired maleic anhydrides in good yields.



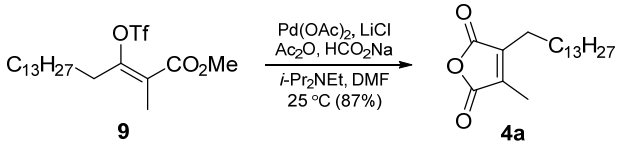
6 **7** **8**

Ar = *p*-Tolyl; R^1 = $(CH_2)_4Me$, $(CH_2)_{12}Me$, Ph; R^2 = Me, *i*-Pr, Bn, CH_2CO_2Me/CH_2CO_2H, $CH_2CH_2CO_2Me/CH_2CH_2CO_2H$

Scheme 2. Reactions of Carbanion with Alkyl Halides: Synthesis of Disubstituted Maleic Anhydrides

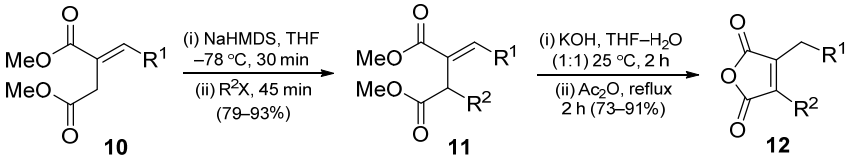
Tanaka and co-workers reported synthesis of chaetomellic anhydride A (**4a**) via Pd-catalyzed carbonylation under Cacchi conditions. They efficiently incorporated *in situ* generated carbon monoxide from acetic anhydride and sodium formate, into the *β*-carbomethoxyalkenyl triflate providing maleic anhydride motif in 61% yield over 4 steps from propionate (Scheme 3).[60] Remarkably, the carbonylation takes place at room temperature, although the fact is that

some Pd-catalyzed carbonylation reactions demand higher temperature. The scope of the method has been also well illustrated.



Scheme 3. Synthesis of Chaetomellic Anhydride A via *in situ* Generated CO Insertion

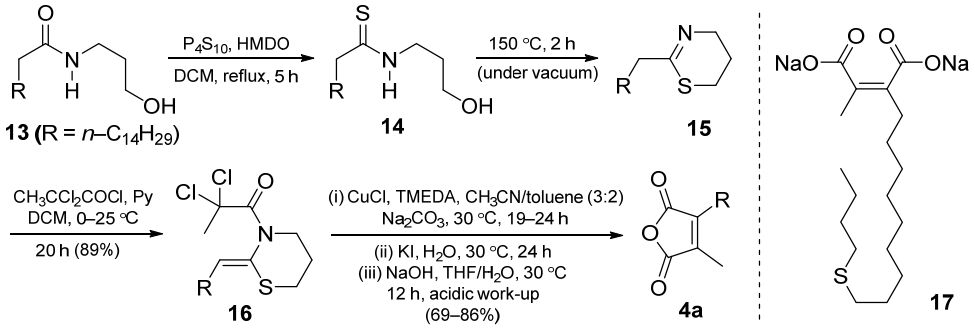
Very recently, in our laboratory chaetomellic anhydride and other natural and unnatural dialkylmaleic anhydrides were readily prepared by sodium hexamethyldisilazide-induced selective monoalkylation of dimethyl alkylidenesuccinates **10**.[61] The basic hydrolysis of formed product **11** followed by dehydrative cyclization delivered the corresponding disubstituted maleic anhydrides **12** in excellent yields (Scheme 4).



R^1 = $(CH_2)_4Me$, $(CH_2)_{12}Me$, $(CH_2)_3OPMB$, Ph; R^2 = Me, Bn, CH_2CO_2Me/CH_2CO_2H

Scheme 4. Base Induced Monoalkylation of Dimethyl Alkylidenesuccinates

The most recent approach described by Ghelfi's group is based on the copper catalyzed radical cyclization of (*Z*)-3-(2,2-dichloropropanoyl)-2-pentadecylidene-1,3-thiazinane (**16**) (Scheme 5).[62] This method offers a versatile approach for the preparation of chaetomellic acid A (**4a**) and analogs through the synthesis of an intermediate maleic anhydride with a vinylic group at the end of the aliphatic chain. It was then further transformed through a thiol-ene coupling to the desired product **17**. Molecular docking study revealed that, sulfurated analog of chaetomellic acid A, the disodium salt of 2-(9-(butylthio)nonyl)-3-methylmaleic acid (**17**) is more competent FTase inhibitor than chaetomellic acid A itself.

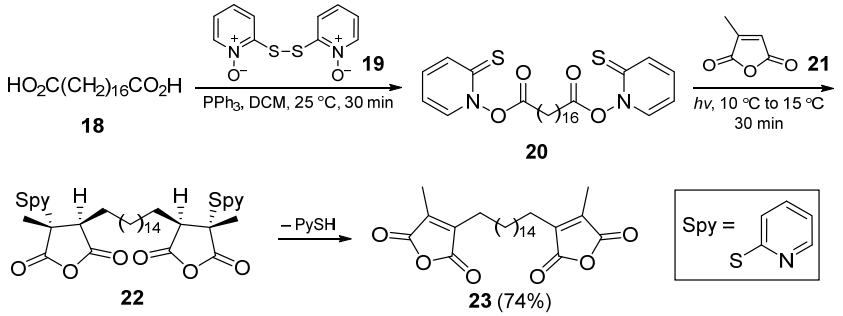


Scheme 5. Copper Catalyzed Radical Cyclization Leading to Chaetomellic Acid A Anhydride

3A.2.4 Tyromycin A

Tyromycin A has been isolated from mycelial cultures of basidomycete *Tyromyces lacteus* (Fr.) Murr,[63] 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. Among the enzymes bound to surfaces of mammalian cells, amino peptidases have been recognized as a potential target for the immunomodulating drugs. Tyromycin A 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 more specifically it 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 being devoid of inhibitory activity on the cell-bound amino peptidases of HeLa cells. Tyromycin A 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 pyruvic acid.

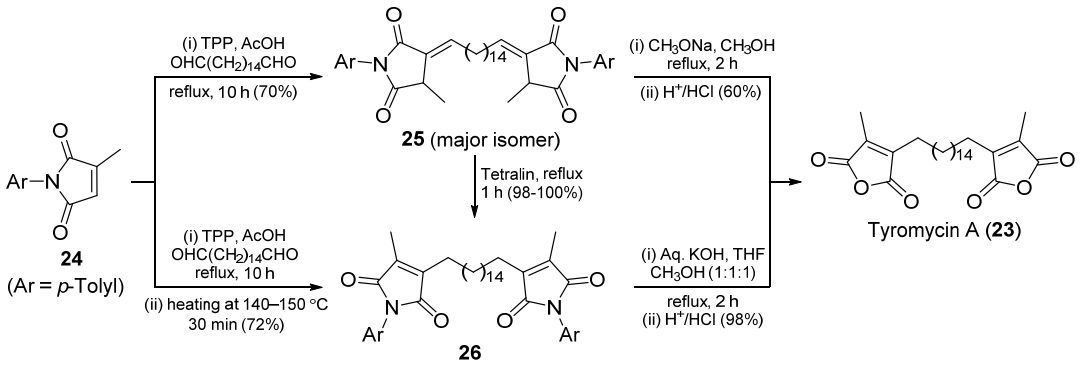
The first synthesis of tyromycin A has been completed by Samadi and co-workers employing the decarboxylative Barton-radical coupling reaction.[64] The starting compound 1,18-octadecanedioic acid (**18**) was converted to corresponding thiohydroxamic diester **20** using PPh_3/2,2′ dithiobis(pyridine *N*-oxide) (**19**). The formed diester **20** *in situ* reacts with citraconic anhydride (**21**) in presence of tungsten light (500 W) to furnish the intermediate addition product **22**, which upon silica gel column chromatographic purification afforded the eliminated product tyromycin A (**23**) (Scheme 6). The lower homologs were also synthesized by them in good overall yields.



Scheme 6. Synthesis of Tyromycin A via Decarboxylative Barton Radical Coupling Reaction

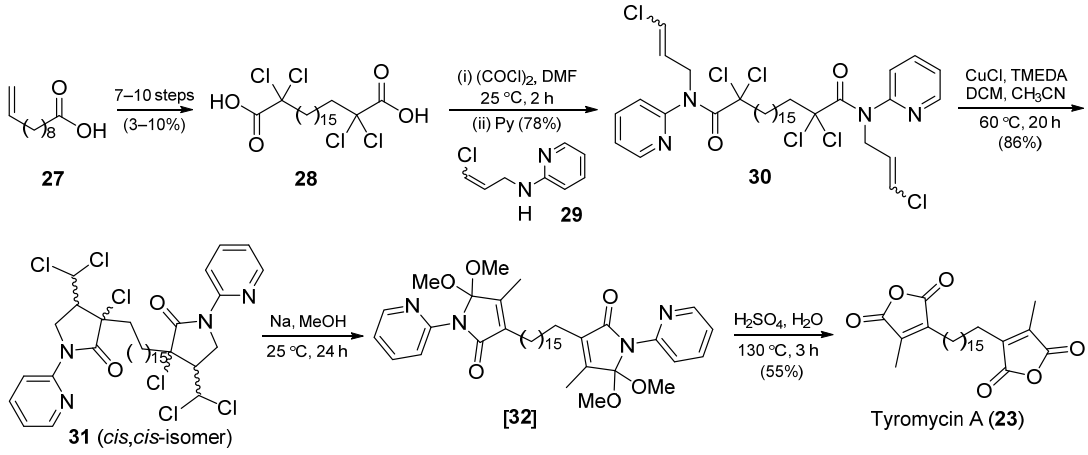
In our laboratory, we have also synthesized tyromycin A by employing double Wittig reaction of citraconimide-TPP adduct with 1,16-hexadecanedial.[65] The desired starting 1,16-

hexadecanedial was prepared from 1,16-hexadecanediol in 72% overall yield. Wittig reaction of a citraconimide-TPP adducts with 1,16-hexadecanedial furnished geometric mixture of products with **25** as a major isomer in very good yield. The geometric mixture of products in refluxing tetralin underwent a smooth trisubstituted exocyclic to tetrasubstituted endocyclic double bond isomerization to exclusively yield the bismaleimide derivative **26** in quantitative yield. The bisimide **26** upon treatment with KOH in H_2O + THF + MeOH (1:1:1) followed by acidification gave tyromycin A (**23**) in 98% yield (Scheme 7).



Scheme 7. Double Wittig Reaction Protocol for Synthesis of Tyromycin A

Most recently, Roncaglia et al described the synthesis of tyromycin A (**23**) and its unnatural lower homologs. The pivotal intermediates to these target compounds, $\alpha,\alpha,\alpha',\alpha'$-tetrachlorodicarboxylic acids **28**, were obtained from a castor oil renewable resource, the undecylenic acid (**27**). Further transformation of this polyhalogenated carboxylic acid **28** into the tyromycin A (**23**) was carried out by using a transition metal catalyzed atom transfer radical cyclization and a functional rearrangement reaction as the key steps (Scheme 8).[66] It has been also proposed that the transformation of compound **31** to the desired product **23** takes place via the inisolable intermediate **32**.

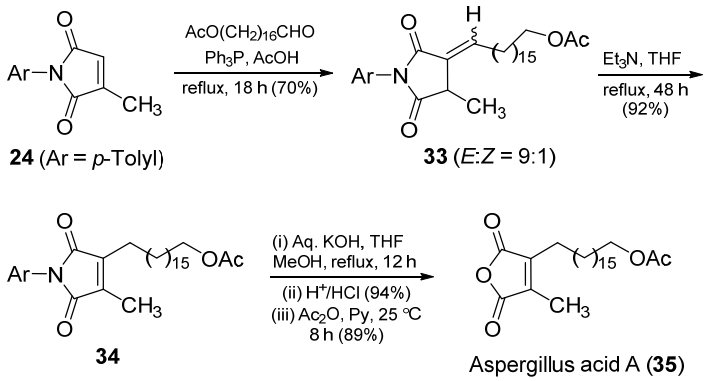


Scheme 8. Synthesis of Tyromycin A via Atom Transfer Radical Cyclization Route

3A.2.5 Aspergillus Acids A–D

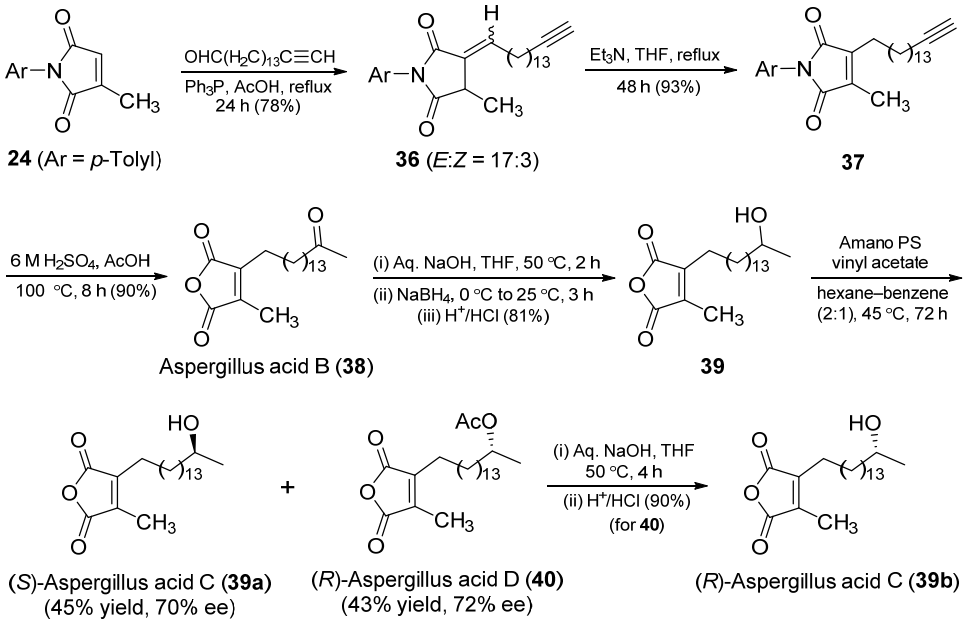
Assante *et al* in 1979, isolated four new secondary metabolites aspergillus acids A–D produced by the mould *Aspergillus wentii* when grown on yeast-glucose medium (Table 1, entries 7–10).[14] On the basis of Horeau method, the chiral centre in acids C and D has been assigned the (*S*)-configuration.

The first synthesis of these naturally occurring acids have been carried out in our laboratory comprising introduction of the remote functional groups and a lipase-catalyzed resolution as the key steps.[67] The triphenylphosphine induced Wittig olefination of citraconimide **24** with acetoxyaldehyde in refluxing acetic acid gave the corresponding *exo*-alkylidene succinimide **33** (*E*:*Z* = 9:1, by ^{1}H NMR) in 70% yield. Trisubstituted exocyclic to tetrasubstituted endocyclic carbon–carbon double bond isomerization using triethylamine furnished the desired maleimide **34** in 92% yields. The basic hydrolysis of maleimide **34** furnished the 2-(17-hydroxytetradecyl)-3-methylmaleic anhydride in 94% yield. Acylation of the free hydroxyl group using acetic anhydride gave the naturally occurring aspergillus acid A (**35**) in 89% yield (Scheme 9).



Scheme 9. Wittig Reaction Based Approach for the Synthesis of Aspergillus Acid A

The synthesis of aspergillus acids B–D were accomplished by the Wittig condensation of citraconimide-TPP adduct with the corresponding alkynyl aldehyde to give the *exo*-imide **36** (*E*:*Z* = 17:3, by ^{1}H NMR) in 78% yield. Trisubstituted to tetrasubstituted carbon–carbon double bond migration furnished the desired maleimide **37** in 93% yields. Maleimide **37** on treatment with a mixture of acetic acid and 6 M sulfuric acid (2:1) at 100 °C directly furnished the aspergillus acid B (**38**) in 90% yield via the acid catalyzed hydration of acetylinic unit followed by hydrolysis pathway (Scheme 10).



Scheme 10. Chemoenzymatic Synthesis of Aspergillus Acids

A chemoselective $NaBH_4$ reduction of the ketone carbonyl in **38** under the basic conditions exclusively furnished the racemic natural product **39** in 81% yields. Amano PS catalyzed acylation of (±)-**39** in hexane–benzene mixture (2:1) at 45 °C furnished the (*S*)-aspergillus acid C [(+)-**39a**] with 45% yield (70% ee) and (*R*)-aspergillus acid D [(–)-**40**] with 43% yield (72% ee). The basic hydrolysis of (–)-aspergillus acid D (**40**) furnished (–)-aspergillus acid C (**39b**) in 90% yield.

3A.2.6 Tautomycin and Tautomycetin

Isono and co-workers in 1987 reported the isolation and structural elucidation of tautomycin (**41**) from a strain of *Streptomyces spiroverticillatus* as a new antibiotic (Figure 2).[15,68] It exhibits a strong antifungal activity against *Sclerotinia sclerotiorum*. The structural elucidation of tautomycin was done on the basis of chemical degradation and spectroscopic evidence. It contains maleic anhydride and spiroketal moieties with 13 chiral centers. Few photoaffinity probes on the 2-position of tautomycin, were prepared in order to prove the details of binding site to PP1.[69] These photoaffinity probes were designed on the basis of the structure–activity relationship; thus, the diacid moiety is indispensable. The selective introduction of photolabeling units on the 2-position of tautomycin was achieved through the 2-oxime of tautomycin diacid.[70] The structure activity relationship has been also studied for this compound.[71]

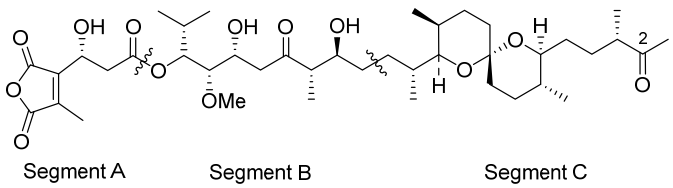


Figure 2. Antifungal antibiotic tautomycin (TTM, **41**)

Tautomycetin (**42**) has been isolated from *Streptomyces griseochromogenes* (Figure 3).[15] Tautomycetin 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 and it possesses a strong immunosuppressive activity.[72] Biosynthesis of tautomycetin (**42**) has been done by Kiyoshi and co-workers by feeding experiments with ^{13}C labeled precursors.[73] The biosynthetic gene cluster for tautomycetin (TTN) has recently been cloned and sequenced. To elucidate the biosynthetic machinery associated with TTN production, the *ttn* biosynthetic gene cluster from *S. griseochromogenes* was isolated, characterized and its involvement in TTN biosynthesis was confirmed by gene inactivation and complementation experiments.[74] The left half segment 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.

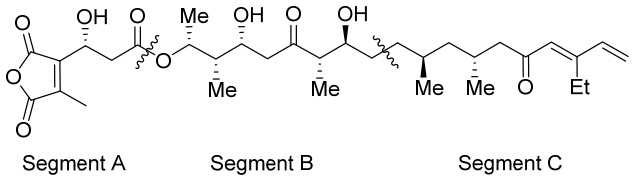


Figure 3. Strong immunosuppressive tautomycetin (TTN, **42**)

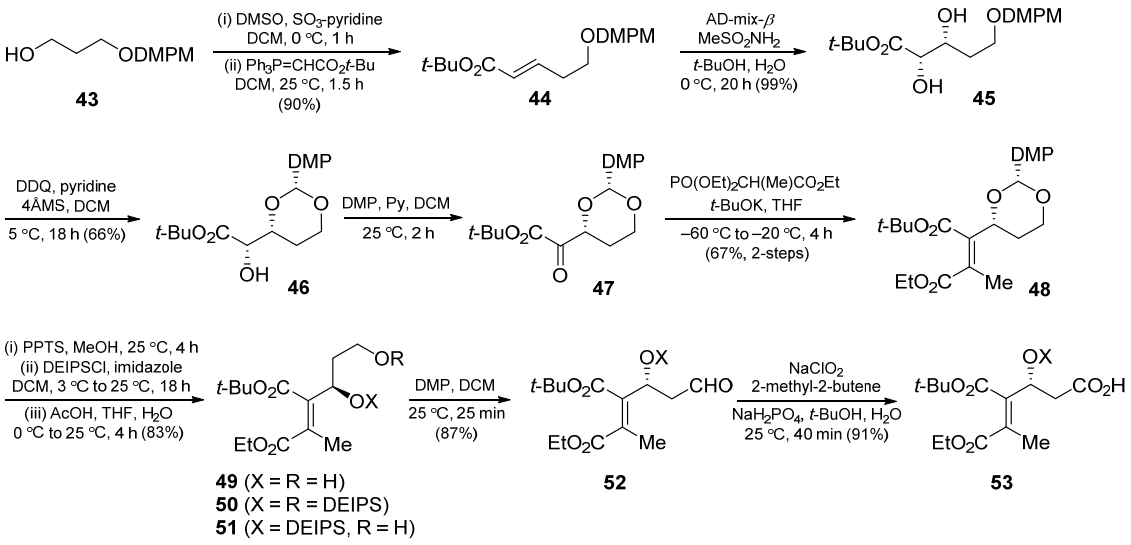
Tautomycin (**41**) and tautomycetin (**42**) both exhibit good biological activities, including antimicrobial activity and Ser/Thr/Tyr protein phosphatase inhibitory activity. Besides antifungal activities, they were found to induce morphological changes (bleb formation) in human leukemia cells K562.[75] The structural complexity and unique biological activity has stimulated many research groups to select them as synthetic targets.

Disubstituted Maleic Anhydride Segment of Tautomycin and Tautomycetin

As shown in Figures 2 and 3, the broad retrosynthetic analysis of tautomycin and tautomycetin afforded segments A, B and C. Total synthesis of these molecules involves the synthesis of three segments followed by stepwise coupling of these building blocks.[76] Both of them possess a unique 2,3-disubstituted maleic anhydride ring system at the left terminal of the molecule,

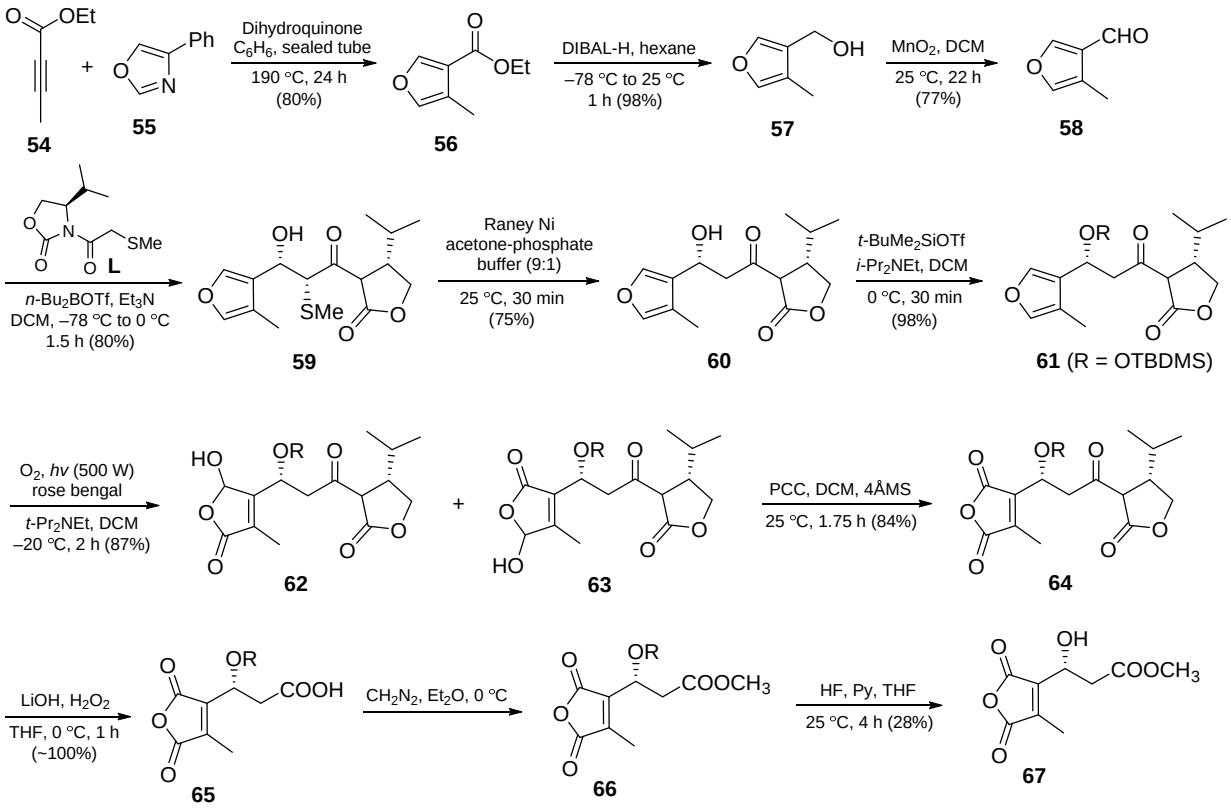
which is known as segment A (Table 1, entry 11). Segment A is a highly oxygenated molecule with three carboxylic groups and one hydroxy group. According to Chamberlin and co-workers, the greatest challenge in the synthesis of tautomycin (**41**) lies in the construction of the simple looking 2,3-disubstituted maleic anhydride segment A.[77] The anhydride moiety in tautomycin/tautomycetin shows an interesting chemical behavior in aqueous media, i.e. they exist in equilibrium between anhydride and diacid form. So far, five multi-step synthesis of segment A have been known in the literature employing various elegant strategies.

In the total synthesis of tautomcin, Ichihara and coworkers developed an admirable approach for the synthesis of segment A (Scheme 11).[78] The alcohol **43** was oxidized under Parikh-Doering conditions and transformed to afford *trans*-olefin **44**. Subsequent Sharpless asymmetric dihydroxylation using AD-mix-β in the presence of methanesulfonamide, provided diol **45**, with a high enantioselectivity. Oxidative acetalization by DDQ in nonaqueous media regio- and stereoselectively achieved effective protection of the C1′ and C3′ hydroxyl groups as 3,4-dimethoxybenzylidene acetal. The remaining free hydroxyl group in **46** was then oxidized by Dess-Martin periodinane. The obtained keto-ester **47** was subjected to the HWE-reaction producing the desired dialkyl maleate **48** in 67% yield over two-step. The acetal protecting group was removed by pyridinium *p*-toluenesulfonate (PPTS) in methanol. The diethylisopropylsilyl (DEIPS) group, a slightly more acid-sensitive protecting group than the TBDMS, was employed for final protection of the C3′ hydroxyl, and thus the diol **49** was bis-silylated. Selective primary silyl ether deprotection yielded C3′ DEIPS ether **51**, which was successively converted to requisite segment **53** via aldehyde **52**.



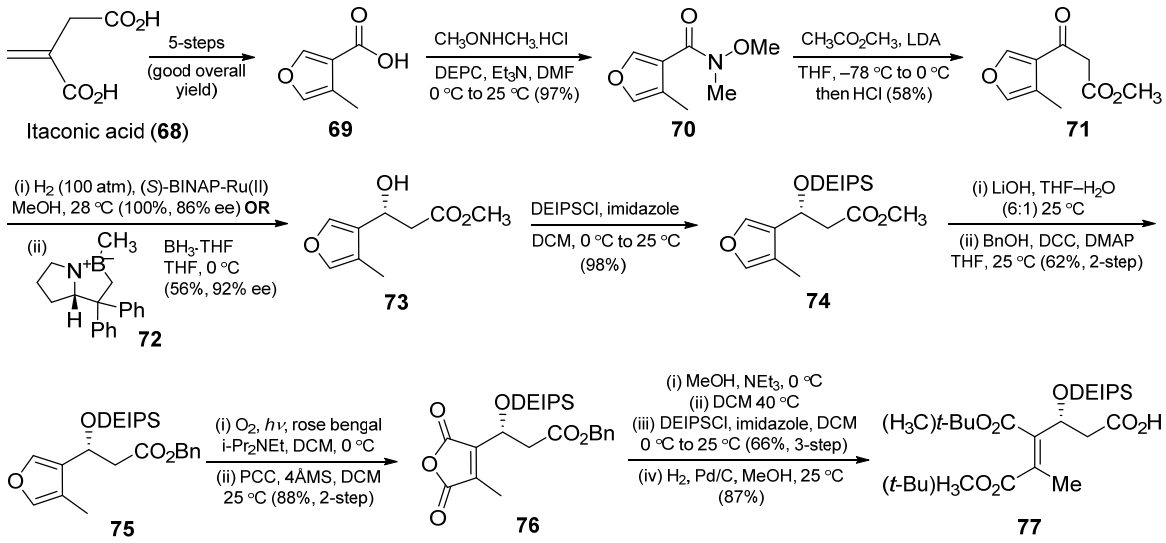
Scheme 11. Ichihara's Approach for the Synthesis of Maleic Anhydride Segment of Tautomcin

Isobe and co-workers synthesized the 2,3-disubstituted maleic anhydride segment of tautomycin in enantiomerically pure form. Singlet oxygen induced oxidation of 3,4-disubstituted furan followed by esterification were the key steps (Scheme 12).[79] Diels-Alder addition of ethyl tetrolate **54** with 4-phenyloxazole **55** and spontaneous retro Diels-Alder reaction with the elimination of benzonitrile furnished a 3,4-disubstituted furan **56**. Reduction of the ester **56** with diisobutylaluminium hydride and subsequent oxidation with an activated manganese (IV) oxide gave the aldehyde **58**. Asymmetric condensation of chiral oxazolidinone boron enolate of chiral *N*-acetloxazolidinone **L** with the aldehyde **58** exclusively provided the adduct **59**. Desulfurization of **59** using Raney nickel afforded a mixture of compound **60** and the corresponding *β*-elimination product. The formatiom of side product was avoided by employing a mixture of acetone and phosphate buffer (pH 7) as the reaction media. Finally in this reaction the product **60** was obtained in 75% yield. Protection of the hydroxyl group as *t*-butyldimethylsilyl ether gave compound **61** in quantitative yield. Photosensitized oxidation of the furan **61** 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 **62** and **63**, which upon PCC oxidation furnished the requisite maleic anhydride **64**. Removal of the auxiliary with lithium hydroperoxide gave the acid **65** which was in turn esterified using diazomethane in ether to provide the corresponding monomethyl ester **66**. Finally, *t*-butyldimethylsilyl group was removed with pyridinium poly(hydrogen fluoride) complex to furnish the desired 2,3-disubstituted maleic anhydride segment **67**.



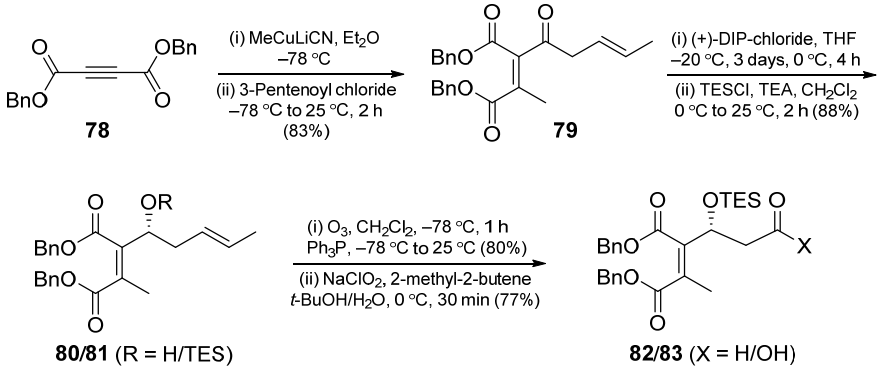
Scheme 12. Isobe's Approach for Maleic Anhydride Segment of Tautomycin

Shibasaki and co-workers carried out the synthesis of fragment A **77** by using an asymmetric reduction of *β*-keto ester as a key step (Scheme 13).[80] A commercially available itaconic acid (**68**) was transformed to the carboxylic acid **69** in a five-step reactions sequence by using the literature procedures. The carboxylic acid **69** was converted to the Weinreb amide **70**, which was treated with the lithium enolate of methyl acetate to yield the *β*-keto ester **71**. Asymmetric reduction of ketone was carried out using BH_3.THF and oxazaborolidine catalyst developed by Corey to obtain an alcohol **73** with 56% yield. The resulting alcohol **73** was protected as DEIPS ether **74**, which upon hydrolysis followed by re-esterification furnished compound **75**. It was then converted to the required fragment **76** by light induced oxidation. It was further used for condensation with fragment B in the total synthesis of tautomycin.



Scheme 13. Shibasaki's Approach for Maleic Anhydride Segment Precursor

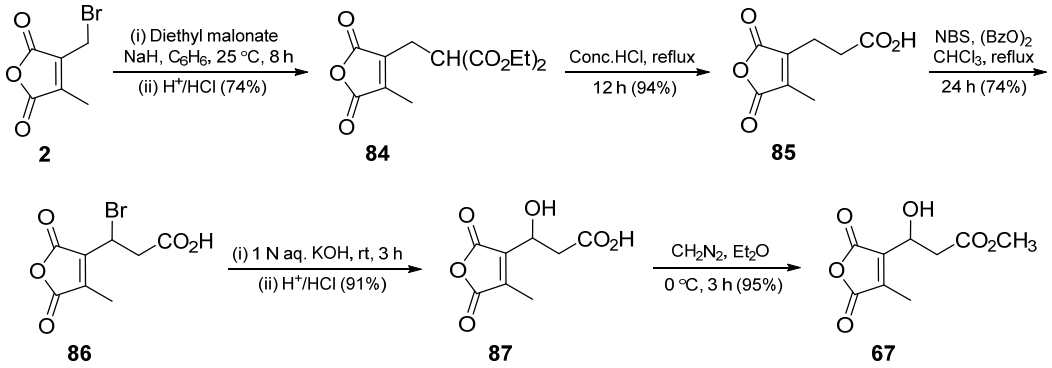
Chamberlin and co-workers carried out the total synthesis of tautomycin. The addition of a mixed methyl cuprate to a symmetrical acetylenedicarboxylic ester **78**, followed by trapping of the intermediate with an electrophile, the malonic acid equivalent 3-pentenoyl chloride ultimately gave the unstable enone **79** as a mixture of geometrical isomers (Scheme 14).[77] Reducing enone **79** with (+)-DIP-chloride afforded the alcohol (+)-**80**. Protection of the hydroxyl substituent as TES-ether **81**, ozonolytic cleavage of the disubstituted alkene and subsequent oxidation of the aldehyde to a carboxylic acid gave (±)-**83** in 72% yield.



Scheme 14. Chamberlin's Approach for Maleic Anhydride Segment Precursor

In our laboratory, we have synthesized 2,3-disubstituted maleic anhydride segment of tautomycin **67** employing chemoselective condensation of diethyl malonate with bromomethyl(methyl)maleic anhydride (**2**). Acidic hydrolysis and decarboxylation of diester **84** followed by regioselective NBS bromination gave the bromoacid **86** in 70% yield over two-step. The bromoacid **86** on treatment with 1 N aqueous KOH followed by acidification and then

esterification by using diazomethane yielded the desired tautomycin segment A **67** in 87% overall yield (Scheme 15).[81]



Scheme 15. Bromomethyl(methyl)maleic Anhydride to Tautomycin Segment A

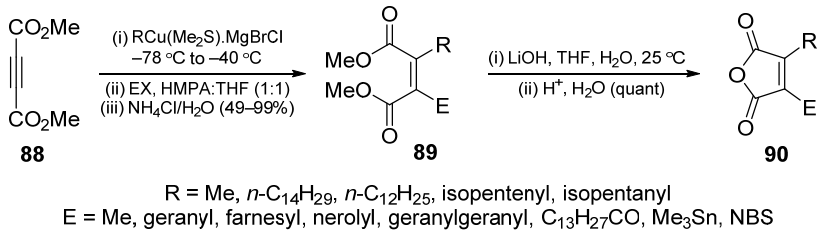
3A.2.7 Lindenanolide E, Itaconitin, Graphenone and 2,3-Didehydrotelfairic Anhydride

Lindenanolide E has been isolated from the species *Lindera chunni* Merr and it possesses HIV-1 integrase inhibiting activity and to date its synthesis has not been reported (Table 1, entry 12).[16] Itaconitin was first isolated by Kinoshita in 1950 from the culture filtrate of *Aspergillus itaconicus* and later its structure was established by Nakajima (Table 1, entry 13).[17] Graphenone was isolated by Hamada et al in 1993 from the seven month old cultured mycobiont *Graphis scripta* (Table 1, entry 14).[18] 2,3-Didehydrotelfairic anhydride was isolated by Edwards et al in 1996 from the culture medium of fungus *Xylaria telfairii* Berk (Table 1, entry 15).[19] The biological screening of these natural products has not been done and synthesis of these three imperative targets are not reported. We strongly believe that these conjugative alkenyl(methyl)maleic anhydrides will also show potency towards RFTase inhibition. The challenge in total synthesis of these delicate compounds is the conservation of the double bond stereochemistry throughout the total synthesis. As a part of this dissertation work, in section B of present chapter, first total synthesis for 2,3-didehydrotelfairic anhydride and some structural analogs of itaconitin and graphenone have been described in detailed.

3A.2.8 Synthetic Analogs of Alkyl(methyl)maleic anhydrides

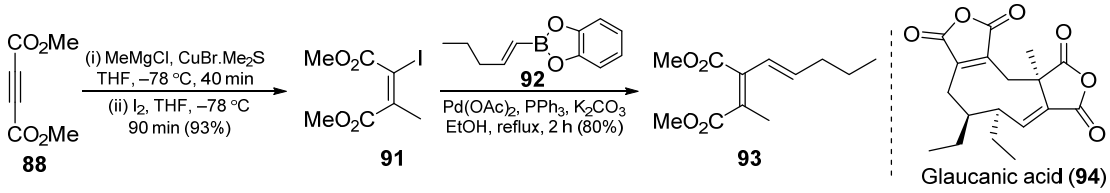
Vederas and co-workers reasoned and synthesized the unnatural farnesyl(methyl)maleic anhydride, which exhibited 7-fold enhancement in RFTase inhibition compared to chaetomelic acid A (Scheme 16).[52,82] Addition of organocuprates derived from corresponding Grignard reagents to dimethyl acetylenedicarboxylate (DMAD, **88**) in tetrahydrofuran containing

hexamethylphosphoramide was followed by capture of the resulting copper enolates with a variety of electrophiles to give dimethyl maleate derivatives **89**. The formed vinylic carbanion was trapped with an appropriate electrophile at lower temperature to gain the stereoselectivity. Hydrolysis of diester **89** with lithium hydroxide generated the corresponding lithium carboxylates, which upon acid treatment readily ring closed to 2,3-disubstituted maleic anhydrides **90**.



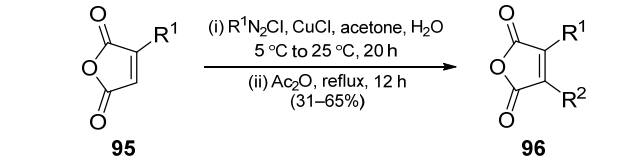
Scheme 16. Synthesis of Chaetomellic Acid A Analogs via Conjugate Addition to DMAD

Baldwin et al synthesized the glaucanic acid precursor **93**. Reaction of an alkyl Grignard reagent with DMAD (**88**) in the presence of CuBr.Me_2S followed by an in situ quenching with iodine at –78 °C stereoselectively formed the tetrasubstituted *cis*-iodoalkene **91**. It was then successfully transformed into the desired product **93** by using Suzuki cross-coupling reaction with (*E*)-pent-1-enyl benzodioxaborole (**92**) (Scheme 17).[83]



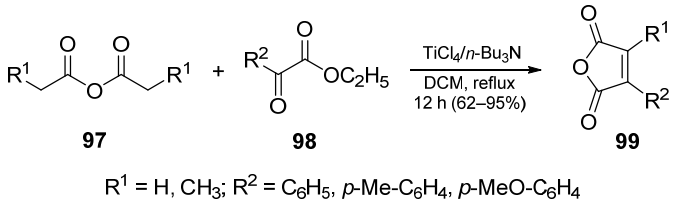
Scheme 17. Synthesis of Glaucanic Acid Precursor via Suzuki Coupling Reaction

Nikitin and Andryukhova demonstrated synthesis of a library of 5-alkoxy-1-aralkyl-3-aryl-4-methyl-2,5-dihydro-2-pyrrolones and the corresponding alkylthio derivatives through the intermediate formation of unsymmetrical maleimides and maleic anhydrides (Scheme 18).[84] The unsymmetrical anhydrides **96** were obtained by the Meerwein reaction of arenediazonium chloride with monosubstituted anhydrides **95** in acetone with copper salts as the catalyst. The formed intermediate 3-aryl-4-chloro-4-methylsuccinic anhydrides were directly subjected for elimination of HCl in refluxing acetic anhydride.



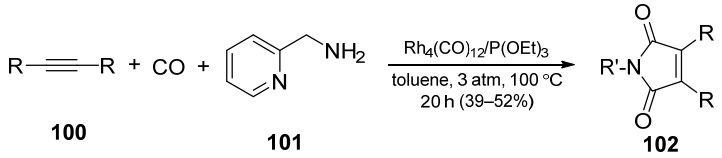
Scheme 18. Meerwein Reaction of Arenediazonium Chloride with Monosubstituted Maleic Anhydrides

Kishorebabu and Periasamy reported the reaction of alkanoic acid anhydrides **97** with *α*-keto esters **98** by using the $TiCl_4$/*n*-Bu_3N reagent system to provide the corresponding disubstituted maleic anhydrides **99** in 62–95% yields (Scheme 19).[85]



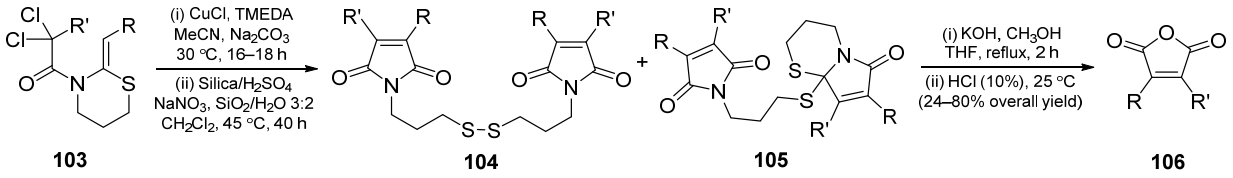
Scheme 19. $TiCl_4$/*n*-Bu_3N Induced Condensation of Alkanoic Acid Anhydrides with *α*-Keto-Esters

Chatani and co-workers described the reaction of alkynes **100** with CO and pyridin-2-ylmethylamine (**101**) in the presence of $Rh_4(CO)_{12}$/$P(OEt)_3$ to furnish the disubstituted maleimide derivatives **102** in 39–52% yields (Scheme 20).[86] The maleimide derivatives can be easily further transformed into the corresponding maleic anhydride derivatives.



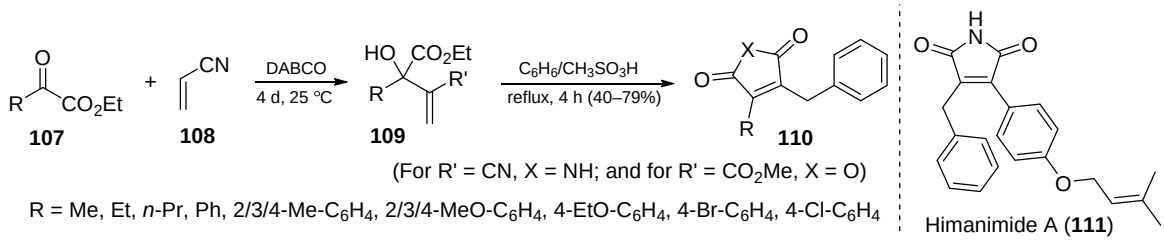
Scheme 20. Synthesis of Maleimides via Dicarbonylation of Alkynes

Ghelfi and co-workers studied the copper-catalyzed radical cyclization of *N*-*α*-perchloroacyl cyclic ketene-*N*(*N*R/*O*/*S*)acetals (Scheme 21).[87] Invariably the catalytic cycle begins with the formation of a carbamoyl methyl radical. The formed radical leads to a cascade of reactions, including a radical polar crossover step, which results in the formation of maleimide nucleus, or its precursors. The products **104** and **105** obtained from the radical cyclization of the hexa-atomic cyclic ketene-*N*,*S*-acetals, were efficiently transformed into disubstituted maleic anhydrides **106**.



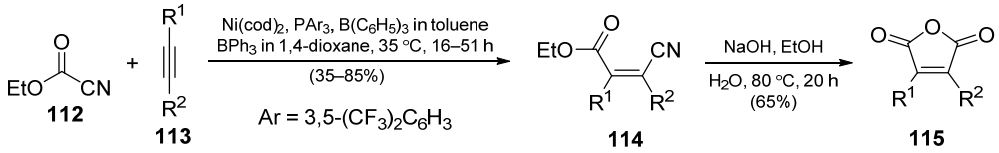
Scheme 21. Copper-Catalyzed Radical Cyclization: Synthesis of Disubstituted Maleic Anhydrides

Basavaiah et al developed a one-pot procedure for the synthesis of unsymmetrical 3,4-disubstituted maleimide and maleic anhydride derivatives **110** using Baylis-Hillman Adducts **109** derived from α-keto esters **107** as the electrophiles (Scheme 22).[88] This strategy has been successfully employed for the synthesis of important bioactive natural product himanimide A (**111**).



Scheme 22. Application of Baylis-Hillman Reaction for Synthesis of Unsymmetrical Disubstituted Maleimides and Maleic Anhydrides

Hiyama and co-workers reported that cyanoformates and cyanoformamides add across alkynes via the nickel/Lewis acid (LA) co-operative catalysis to provide cyano-substituted acrylates **114** and acrylamides respectively, in highly stereoselective and regioselective manners.[89] The resulting adducts were demonstrated to serve as versatile synthetic building blocks through chemoselective transformations of the ester, amide, and cyano groups for the synthesis of typical structures of -cyano ester, -amino nitrile, *γ*-lactam, disubstituted maleic anhydride **115** (Scheme 23), and *γ*-aminobutyric acid.



R^1 = Me, $SiMe_3$, Hex, *i*-Bu, geranyl, $(CH_2)_3OSiMe_2t$-Bu, $(CH_2)_3CO_2Me$, $(CH_2)_3NPhth$; R^2 = $SiMe_3$, *i*-Pr, *t*-Bu

Scheme 23. Nickel/Lewis Acid-Catalyzed Cyanoesterification and Cyanocarbamoylation of Alkynes

Apart from these practical synthetic approaches and significant biological activities, a vast degree of synthetic applications are also attributed to these fundamental classes of compounds, alkyl(methyl)maleic anhydrides. We believe that most of the protocols described herein for the

synthesis of alkyl(methyl)maleic anhydrides will work equally well for the synthesis of array of corresponding symmetrical and unsymmetrical dialkyl substituted maleic anhydrides (for synthesis of corresponding dialkyl substituted maleic anhydrides, see reference 90).

3A.3 Summary

In summary, we have presented a concise literature account on the chemistry and synthesis of alkyl(methyl)maleic anhydrides with their isolation and bioactivity data. Various synthetic methodologies to the substituted alkyl(methyl)maleic anhydrides and related derivatives reported by different research groups have been presented.

More than 20 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. Large number of alkyl(methyl)maleic anhydrides are known as the natural products and quite a few well-designed routes for their synthesis have been accounted in the contemporary literature. The most promising bioactive anticancer agent, chaetomellic anhydride A, has been synthesized by many research groups having their own advantages. In short, maleic anhydrides and their derivatives are potential building blocks to design several desired complex bioactive natural and unnatural products. All the information presented here has been well supported by the provision of more than 175 references from various monographs and international journals. We also foresee the huge amount of imperative information available about this scaffold in the literature.

We strongly believe that the broad field of alkyl(methyl)maleic anhydrides will be of continuing interest to both the synthetic and medicinal chemists and positively there will be interminable promising advancements in the knowledge. In this context, as part of present dissertation, we have synthesized few conjugative alkenyl(methyl)maleic anhydrides. Our studies towards the synthesis of these natural/unnatural products will be discussed in details in the section B of present chapter.

3A.4 References

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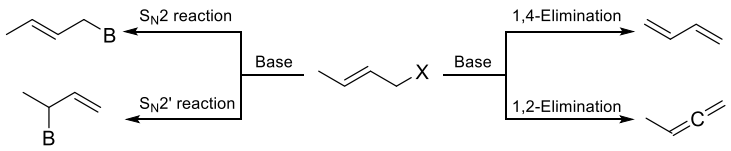
CHAPTER 3: SECTION B

Base Stimulated Novel 1,4- and 1,6-Eliminations in Alkylidenesuccinates: Stereoselective Total Synthesis of Natural and Unnatural Conjugative Alkenyl(methyl)maleic Anhydrides

This section B of chapter 3 features the following topics:

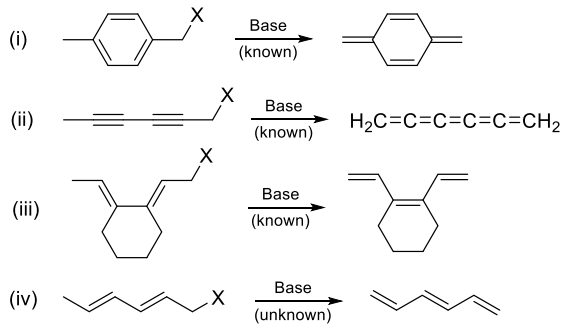
3B.1 Rationale of the Present Work

Stereoselective introduction of carbon–carbon double bond is an important and challenging task in organic chemistry. The elimination reaction, with its rich synthetic diversity, is recognized as one of the keystone reactions in basic as well as in modern organic chemistry. This reaction has undergone intensive development and has become strength of organic synthesis and is the frequently used key step for the construction of complex biologically active natural and unnatural products.[1] The conjugative elimination reactions are one of the most anticipated reactions in the field of organic chemistry for the synthesis of bioactive molecules. Nevertheless, conjugative elimination reactions have significant applications in synthetic organic chemistry and play an important role in certain biological processes. The base-induced 1,2-elimination plays a key role in organic chemistry and are described in all major textbooks. However, closely related to 1,2-elimination reactions, base-induced 1,4-eliminations and 1,6-eliminations have received some attention and studies on these reactions have been carried out by a few research groups. A special challenge in practical studies on 1,4-elimination reactions[2] is the many possibilities of competing side reactions, namely, vinylic 1,2-elimination, nucleophilic displacement and allylic substitution (Scheme 1).[3]



Scheme 1. 1,4-Elimination Reaction Processes and Other Possibilities

As displayed in Scheme 2, the most important "π spacer units" involved in 1,6-elimination reactions are being aromatic and heteroaromatic rings, triple bonds and double bonds.[4–6] Major number of such reactions have been reported with aryl rings and few with triple bonds, as the separating units involving obvious well-ordered transition states.[4,5] Only handful of reactions with double bonds as spacer units in substrates bearing cyclic backbones are known in the literature.[6] Otera et al proposed 1,6-elimination reaction with double bonds as spacer units in open chain system and according to them the possibility of stepwise double elimination processes also exists.[7] To the best of our knowledge, such 1,6-eliminations with double bonds as spacer units in open chain systems are not known in the literature. The necessary requirements for such type of 1,6-elimination reactions are namely, (i) the formed carbanion needs to sense the remotely placed leaving group in the presence of possible middle carbon–carbon single bond rotation, and (ii) the compatibility of formed carbanion to delocalize through π-cloud with the departing ability of leaving group.



Scheme 2. General Representation of Known 1,6-Elimination Reactions

It is evident from the discussion in section A, the maleic anhydride is a vital functionality in chemistry from both basic and applied point of view.[8] A large number of alkyl(methyl)maleic anhydrides has been isolated as natural products and reported to exhibit broad range of biological activities. More specifically, the dianionic form of tetradecyl(methyl)maleic anhydride (chaetomellic acid A) is a potent ras farnesyl-protein transferase (RFTase) inhibitor as it contains both the essential hydrophilic and hydrophobic units to appropriately bind and deactivate the responsible enzyme.[9] Vederas and co-workers reasoned and synthesized the unnatural farnesyl(methyl)maleic anhydride, which exhibited 7-fold enhancement in RFTase inhibition compared to chaetomelic acid A.[10] A cursory literature search in this context revealed that three yellow crystalline conjugative alkenyl(methyl)maleic anhydrides have also been isolated as the natural products (Figure 1). The itaconitin,[11] graphenone[12] and 2,3-didehydrotelfairic anhydride[13] were respectively isolated from the cultures *Aspergillus itaconicus*, mycobiont *Graphis scripta* and *Xylaria telfairii* Berk.

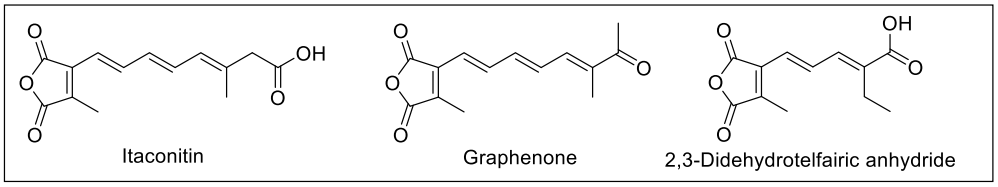


Figure 1. Naturally occuring conjugative alkenyl(methyl)maleic anhydrides

Retro-biogenetically, Nature might be designing these novel multifunctional architectures from pyruvic acid in a step wise fashion. To date, synthesis of those naturally occurring alkenyl(methyl)maleic anhydrides have not been reported. However the itaconitin side chain is known to undergo an intramolecular cyclization to form the aryl ring.[11] Accordingly, these conjugative alkenyl(methyl)maleic anhydrides are anticipated to be acid, base, metal ions, temperature and light sensitive. Hence, the real challenge in total synthesis of these delicate targets is in creating geometrically pure conjugative alkenyl chains and conserving their integrity throughout the total synthesis. In the present section, Starting from dimethyl maleate, the first total synthesis of natural product 2,3-didehydrotelfairic anhydride along with

analogous unnatural conjugative alkenyl(methyl)maleic anhydrides via conceptually new and novel 1,2-/1,4-/1,6-elimination reactions in alkylidenesuccinates have been described in search of effective RFTase inhibitors (Schemes 3–9).

3B.2 Results and Discussion

Retrosynthetically, the unknown unsaturated aldehydes portrayed in Figure 2 would be potential building blocks for the target compounds from Figure 1. Amongst these, dimethyl formylmethylmaleate is still elusive for stability reasons. Synthesis of the other two requisite unsaturated aldehydes were planned from readily available dimethyl maleate via Wittig reaction, allylic α-methylation, ketal-deprotection, 1,4-/1,6-elimination and oxidation route.

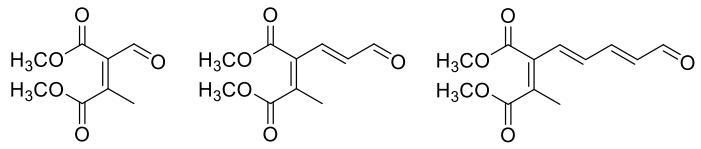
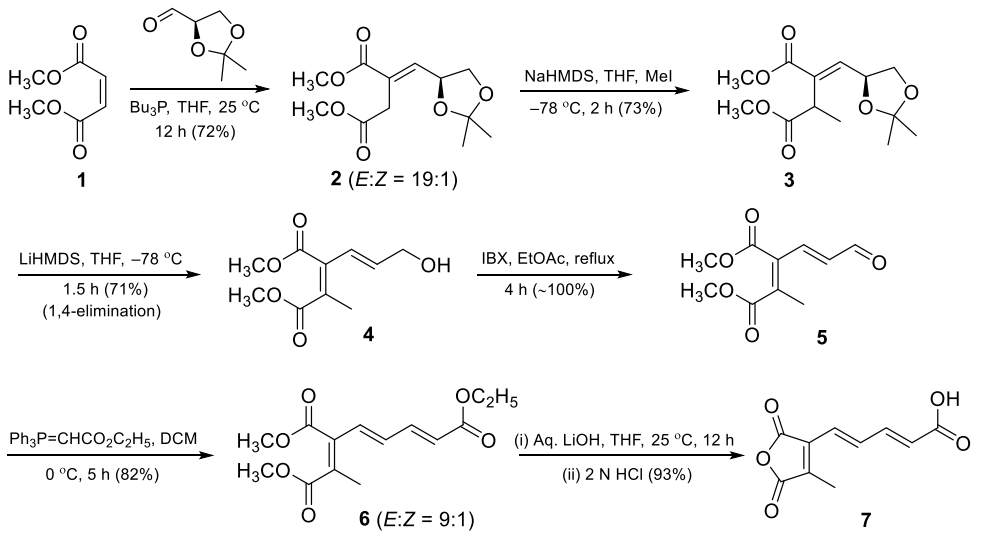


Figure 2. Potential precursors for the synthesis of natural and unnatural conjugative alkenyl(methyl)maleic anhydrides

The reaction of an in situ generated Wittig reagent from tributylphosphine and dimethyl maleate (**1**)[14] with commercially available (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde in THF at room temperature furnished the required coupling product **2** in 72% yield (*E*:*Z* = 19:1, by ^{1}H NMR) (Scheme 3). The (*E*)-geometry of carbon–carbon double bond in major product **2** was confirmed on the basis of ^{1}H NMR data (δ 6.89, peri interaction of ester carbonyl group with vinylic proton). Base induced α-methylation of compound **2** was performed using NaHMDS and methyl iodide at –78 °C to obtain the geometrically pure product **3** in 73% yield. In the course of above mentioned methylation studies, we serendipitously witnessed the formation of a small amount of an unexpected product **4** at slightly higher reaction temprature (nearly 5%). We initially characterized the obtained product **4** on the basis of spectral data and then systematically studied the above mentioned unusual conversion of compound **3** into desired product **4**. The results obtained by employing various bases are summarized in Table 1. Rewardingly, LiHMDS was most effective at –78 °C and provided the aimed E2'-elimination product **4** in 71% yield (Table 1, entry 7). The base NaHMDS was found to be relatively less effective for the Na^+ ion size and its complexing ability issues (Table 1, entry 9, 42% yield).



Scheme 3. Base Promoted Unusual Cleavage of Ketal with 1,4-Elimination of Acetone Leading to Alkenyl(methyl)maleic Anhydride

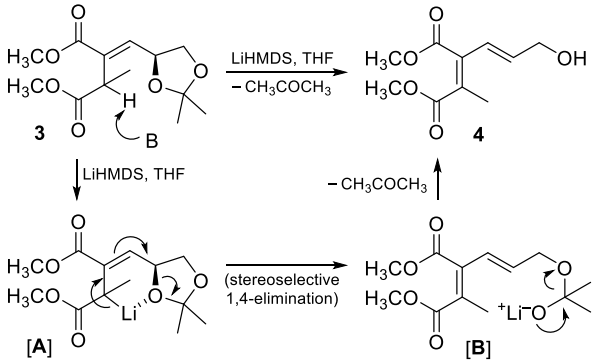
entry	base (equiv)	temp	time	% yield
1	Et_3N (3.00)	reflux	12 h	NR[a]
2	DBU (3.00)	reflux	12 h	CM[b]
3	NaH (2.00)	25 °C	5 h	5
4	*n*-BuLi (2.00)	–78 °C	1.5 h	CM[b]
5	*t*-BuLi (2.00)	–78 °C	1.5 h	CM[b]
6	LDA (2.00)	–78 °C	1.5 h	CM[b]
7	LiHMDS (2.00)	–78 °C	1.5 h	71
8	LiHMDS (1.50)	–78 °C	1.5 h	67
9	NaHMDS (2.00)	–50 °C	1.5 h	42
10	KHMDS (2.00)	–78 °C	1.5 h	CM[b]

[a] No reaction, [b] complex mixture (by tlc).

Table 1. Base Induced 1,4-Elimination Studies in Cyclic Ketal

The plausible mechanism for present ketal to allylic alcohol reaction has been described in Scheme 4. The LiHMDS regioselectively abstracts an acidic methine proton at the α-position of ester moiety and forms cyclic six-membered lithium complex **A**.[15] Thus formed, an allylic carbanion in intermediate **A** delocalizes and the system undergoes concerted E2'-1,4-elimination process to yield intermediate **B**, which releases acetone as a leaving group generating α,β-unsaturated alcohol **4**. In this transformation, the carbanion stereoselectively delocalizes in an anti-direction to gain the extension of conjugation along with generation of more stable tetrasubstituted carbon–carbon double bond. To the best of our knowledge, this is first example of an exceptional cleavage of a ketal moiety under the basic conditions with a release of acetone as a leaving group leading to the corresponding allylic alcohol. The present one-pot transformation of ketal to allylic alcohol is characteristic as it beneficially covers the otherwise essential; ketal deprotection, selective primary alcohol protection, transformation of secondary alcohol to good leaving group, requisite 1,4-elimination progression and the final

deprotection of primary alcohol, steps. The observed base stimulated intramolecular cleavage of ketal moiety via the cyclic transition state would be feasible in several other structurally related systems and can be meticulously used for concise and efficient synthesis of many other complex target compounds. However, such type of ketal cleavage is known on the sulfone system.[2e]

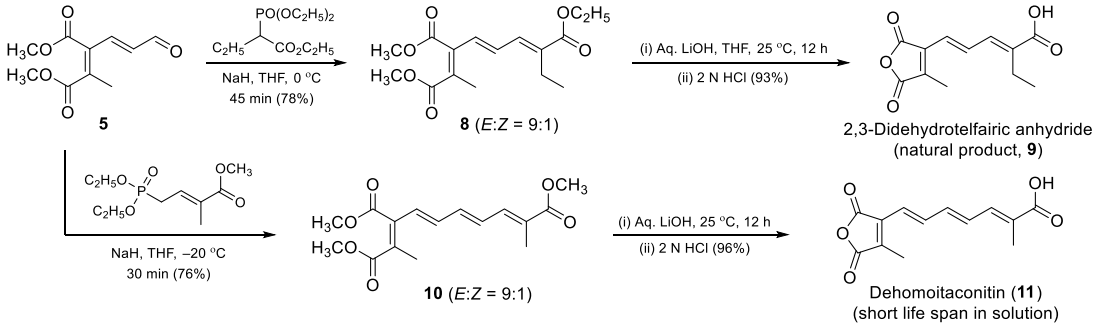


Scheme 4. Plausible Mechanism for LiHMDS Induced Cleavage of Ketal

The allylic alcohol **4** on IBX oxidation formed a requisite building block, the *α,β*-unsaturated aldehyde **5** in almost quantitative yield. We initially studied the reactions of two different unstabilized Wittig reagents generated from the corresponding alkyl halides with unsaturated aldehyde **5** and noticed the complete decomposition of reaction mixtures even at –78 °C. Providentially, Wittig reaction of the stabilized ylide ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate with aldehyde **5** was very clean and provided the essential triester **6** in 82% yield (*E*:*Z* = 9:1, by ^{1}H NMR). Basic hydrolysis of the triester **6** followed by acidification and immediate solvent extraction exclusively delivered the model compound **7** in 93% yield. In the hydrolysis reaction, the minor *Z*-isomer also rearranged into the thermodynamically more stable *E*-isomer. The dialkyl substituted maleic anhydrides are known to stay in ring closed form under neutral and acidic conditions.[8a]

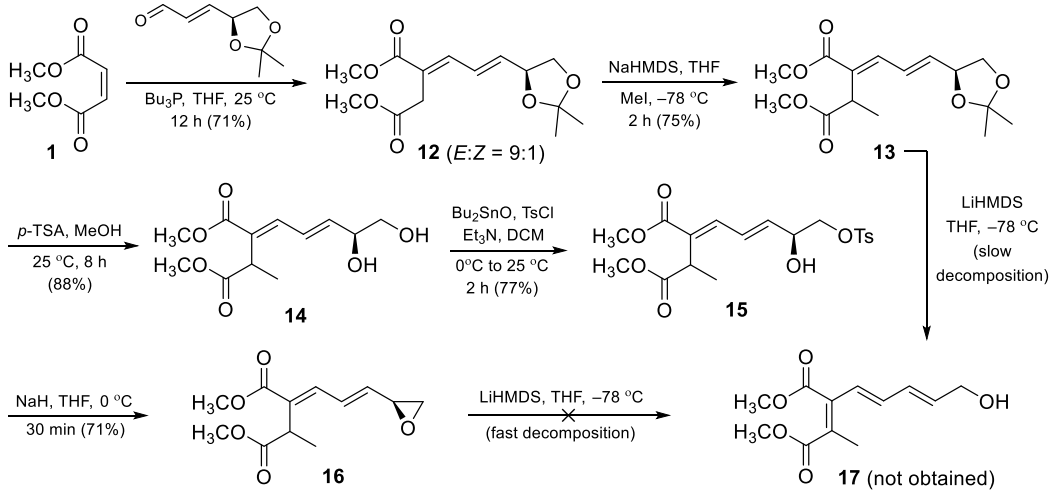
Further applications of aldehyde **5** for the synthesis of natural product 2,3-didehydrotelfairic anhydride and dehomoitaconitin have been represented in Scheme 5. An appropriate HWE reaction of ethyl 2-(diethoxyphosphoryl)butanoate with aldehyde **5** followed by hydrolysis of the resulting triester **8** furnished geometrically pure natural product 2,3-didehydrotelfairic anhydride (**9**) in 73% yield (Scheme 5). The analytical and spectral data obtained for natural product **9** was in complete agreement with the reported data[13] and starting from dimethyl maleate it was obtained in six steps with 27% overall yield. Yet another suitable HWE reaction of aldehyde **5** with appropriate conjugated stabilized ylide followed by the hydrolysis of formed triester **10** offered unnatural dehomoitaconitin (**11**) in 73% yield over two-step. Fortunately, the

model compund **7** and the natural product **9** were found to be fairly stable, though as surmised the compound **11** with an additional carbon–carbon double bond in conjugation was not stable in acetone for longer time. The immediately scanned ^{1}H NMR spectrum of compound **11** in acetone was very clean, however the ^{1}H NMR spectrum of the same sample scanned after 2 h indicated the initiation of formation of other rearranged products.



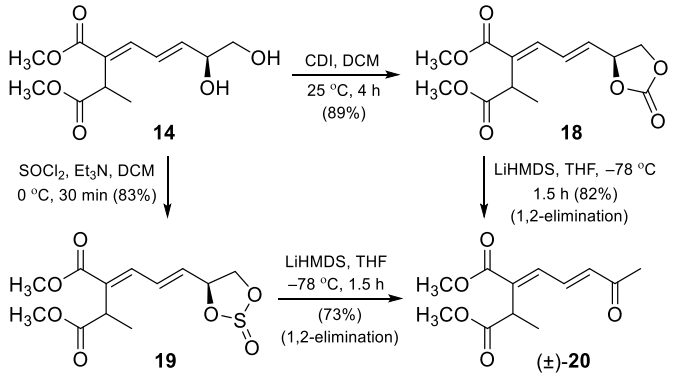
Scheme 5. Synthesis of Naturally Occurring 2,3-Didehydrotelfairic Anhydride and Dehomoitaconitin

In next part of the study, we planned to synthesize another building block from Figure 2, dimethyl 2-methyl-3-((1*E*,3*E*)-5-oxopenta-1,3-dien-1-yl)maleate via corresponding 1,6-elimination approach. The tributylphosphine induced Wittig reaction of dimethyl maleate (**1**) with (*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylaldehyde[16] gave the coupling product **12** in 71% yield (*E*:*Z* = 9:1, by ^{1}H NMR) (Scheme 6). The compound **12** has been also prepared earlier via catalytic carbenoid insertion into the olefinic C–H bond of allylic ylide.[17] The *α*-methylation of compound **12** was performed by using NaHMDS and methyl iodide to obtain product **13** in 75% yield. Unfortunately, the reaction of ketal **13** with LiHMDS at –78 °C underwent slow decomposition and failed to deliver the anticipated product **17** via possible 1,6-elimination pathway. In this case the formation of stable cyclic lithium complex is forbidden because of ring size and the geometry issues. Ketal **13** on usual *p*-TSA deprotection provided the diol **14** in 88% yield. The diol **14** was transformed to epoxide **16** via the corresponding primary mono-tosylate **15** (55% over two steps). Oxirane **16** also underwent an excessive decomposition on treatment with LiHMDS.



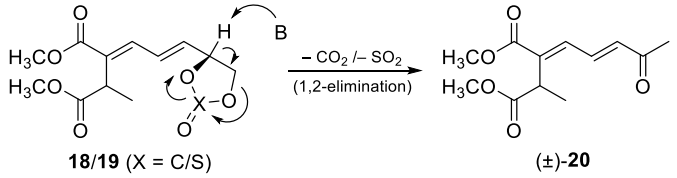
Scheme 6. Synthesis and an Attempted Base Promoted 1,6-Eliminative Cleavages of Ketal and Oxirane Units

As illustrated in Scheme 7, diol **14** was converted into the corresponding cyclic carbonate **18** and sulfite **19** in 89% and 83% yields respectively. The compounds **18** and **19** on treatment with LiHMDS also failed to deliver a required product **17** via 1,6-elimination sequence. Instead, both the reactions exclusively provided the same unsaturated ketone product **20** in 82% and 73% yields respectively.



Scheme 7. Remarkable Base Promoted Cleavages of Cyclic Carbonate and Sulfite

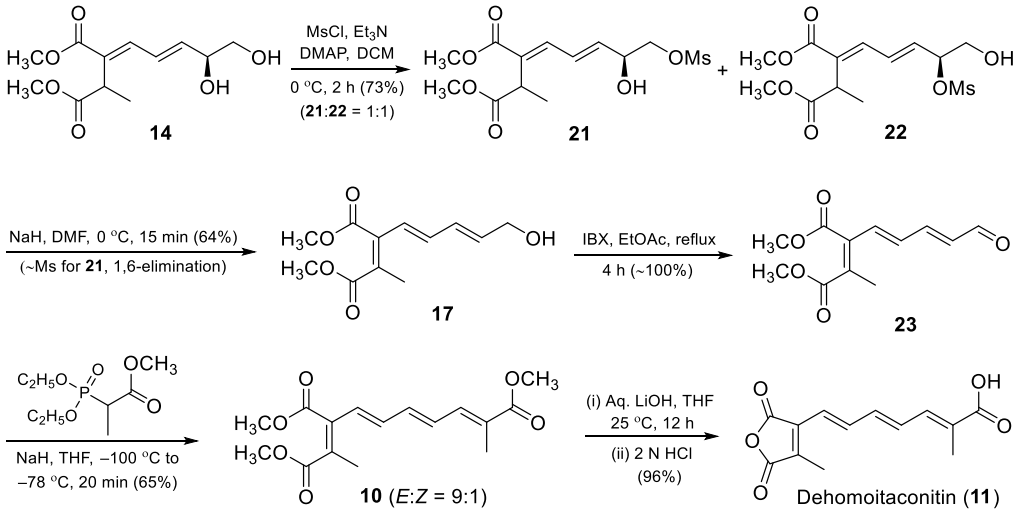
Mechanistically, LiHMDS regioselectively abstracts the acidic methine protons present on cyclic carbonate and sulfite moities, which on concurrent 1,2-eliminations respectively release CO_2 and SO_2 to form the product **20** (Scheme 8). The present selective 1,2-elimination reactions are also significant from basic chemistry point of view.



Scheme 8. Proposed Mechanism for the Unusual Cleavages of Cyclic Carbonate and Sulfite

Finally, in search of a suitable substrate to enforce the 1,6-elimination reaction, we decided to transform diol **14** into the corresponding mesylate derivative (Scheme 9). Diol **14** on treatment

with methanesulfonyl chloride gave ~1:1 mixture of corresponding primary and secondary mesylates **21** and **22** in 73% yield. We presume that initially primary alcohol forms the corresponding mesylate **21** and an in situ partial intramolecular migration results in secondary mesylate **22** for stability reasons. Such type of an in situ intramolecular vicinal migration is in accordance with the literature precedence.[18] The mixture of primary and secondary mesylates **21** and **22** was separated by using silica gel column chromatography for characterization purpose and their structures were established with the help of NMR data obtained for diol **14** and tosylate **15**. Rewardingly, the mixture of mesylates **21** and **22** on treatment with sodium hydride underwent a smooth 1,6-elimination process and delivered the desired unsaturated alcohol **17** in 64% yield. In the above reaction primary mesylate **21** transforms into secondary mesylate **22** under basic conditions and then the combined product undergoes requisite 1,6-elimination process. We believe that it is the first full-proof 1,6-elimination reaction in flexible acyclic system involving carbon–carbon double bond spacer. Alcohol **17** on IBX oxidation produced yet another building block, the unsaturated aldehyde **23** also in ~100% yield. We studied the HWE reaction of ylide, methyl 2-(diethoxyphosphoryl)propanoate with aldehyde **23** at –78 °C and noticed partial decomposition of reaction mixture. However, the same Wittig reaction of highly reactive aldehyde **23** at –100 °C was successful and furnished triester **10** in 65% yield (*E*:*Z* = 9:1, by ^{1}H NMR), which was again transformed into dehomoitaconitin (**11**) in 96% yield.



Scheme 9. Base Induced 1,6-Elimination: Synthesis of Conjugative Alkenyl(methyl)maleic Anhydride

Present study clearly reveals that the dimethyl 2-methyl-3-(*E*)-3-oxoprop-1-en-1-yl)maleate from Figure 2 is the most appropriate building block to synthesize such type of conjugative alkenyl(methyl)maleic anhydrides.

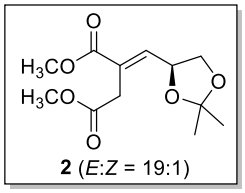
3B.3 Summary

In summary, we have demonstrated the distinguishing conjugative 1,2-, 1,4- and 1,6-elimination progressions in alkylidenesuccinates to design first unique approach to natural and unnatural alkenyl(methyl)maleic anhydrides. The described base promoted 1,4-elimination of acetone with the cleavage of a cyclic ketal moiety and the well-ordered 1,6-elimination of distantly placed mesylate are noteworthy from basic chemistry point of view. The anti-migration of formed carbanionic species in α,β-unsaturated and α,β,γ,δ-unsaturated carbonyl systems in 1,4- and 1,6-elimination processes are momentous and thermodynamically favourable for stability reasons. We deeply believe that these alkenyl(methyl)maleic anhydrides will exhibit potential RFTase inhibitory activity. We also believe that our present protocol will provide practical approach to analogues and congeners of target compounds for focused biological screenings.

3B.4 Experimental Section

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR spectrometer, 400 MHz NMR spectrometer and 500 MHz NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz) and 500 NMR spectrometer (125 MHz). Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 and 200–400 mesh). Commercially available dimethyl maleate, tributylphosphine, (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde, NaHMDS, LiHMDS, *p*-TSA, *p*-toluenesulfonyl chloride, carbonyldiimidazole, thionyl chloride, methanesulfonyl chloride, IBX, NaH (60% dispersion in mineral oil) were used. The known starting materials, (*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylaldehyde,[16] methyl 2-(diethoxyphosphoryl)propanoate,[19] ethyl 2-(diethoxyphosphoryl)butanoate[20] and methyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate were prepared by using literature procedures.[21]

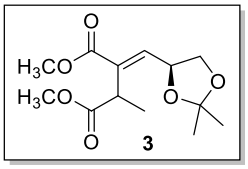
Dimethyl (*S*,*E*)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)succinate (2).



2 (*E*:*Z* = 19:1)

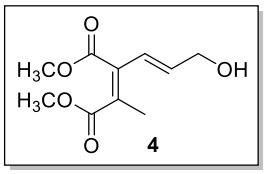
To a stirred solution of dimethyl maleate (1.44 g, 10.00 mmol) and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (1.60 g, 12.00 mmol) in THF (10 mL) was added *n*-Bu_3P (3.73 mL, 15.00 mmol) in a drop wise fashion at 25 ^{o}C under argon atmosphere. The reaction mixture was stirred for 12 h and concentrated in vacuo. The obtained residue was directly subjected for silica gel column chromatographic purification using petroleum ether and ethyl acetate mixture (9:1) as an eluent to give pure alkylidenesuccinate **2** as thick oil (1.86 g, 72% yield). $[\alpha]^{25}_{D}$ –19.3 (c 0.1, $CHCl_3$); *E*-isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (s, 3H), 1.45 (s, 3H), 3.35 (d, *J* = 16 Hz, 1H), 3.53 (d, *J* = 16 Hz, 1H), 3.68 (s, 3H), 3.70 (dd, *J* = 8 and 8 Hz, 1H), 3.76 (s, 3H), 4.16 (dd, *J* = 8 and 8 Hz, 1H), 4.78 (q, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.7, 26.5, 32.4, 52.2, 52.3, 68.7, 72.6, 110.1, 127.7, 141.8, 166.7, 170.7; ESIMS (*m*/*z*) 281 $[M+Na]^{+}$; HRMS (ESI) calcd for $C_{12}H_{18}O_6Na$ 281.0996, found 281.0984; IR ($CHCl_3$) ν_{max} 1742, 1720, 1657 cm^{-1}.

Dimethyl (*E*)-2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-3-methylsuccinate (3, diastereomeric mixture).



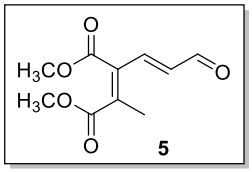
To a stirred solution of alkylidenesuccinate **2** (516 mg, 2.00 mmol) in THF (7 mL) was added solution of NaHMDS in THF (1 M, 2.60 mL, 2.60 mmol) in a drop wise manner at –78 °C under argon atmosphere. The reaction mixture was stirred at same temperature for 30 minutes and then MeI (0.15 mL, 2.40 mmol) was added. It was further stirred at –78 °C for 1.5 h and quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and residue was dissolved in EtOAc (30 mL). The organic layer was washed with water, brine and dried over sodium sulfate. Concentration of organic layer in vacuo followed by the silica gel column chromatographic purification of the obtained residue by using petroleum ether and ethyl acetate mixture (9:1) as an eluent provided pure methyl alkylidenesuccinate **3** as a thick oil (397 mg, 73% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30–1.50 (m, 6H), 1.41 (s, 3H), 3.55–3.80 (m, 2H), 3.67 (s, 3H), 3.75 (br s, 3H), 4.07–4.23 (m, 1H), 4.83 (q, J = 8 Hz, 1H), 6.78 (dd, J = 8 and 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 16.6, 25.7, 26.5, 26.6, 38.0, 38.4, 52.0, 52.1, 68.8, 68.9, 72.3, 110.1, 110.2, 134.6, 134.7, 140.0, 140.1, 166.2, 173.4; ESIMS (m/z) 295 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_6Na$ 295.1152, found 295.1137; IR ($CHCl_3$) ν_{max} 1745, 1720, 1654 cm^{-1}.

Dimethyl 2-((*E*)-3-hydroxyprop-1-en-1-yl)-3-methylmaleate (4).



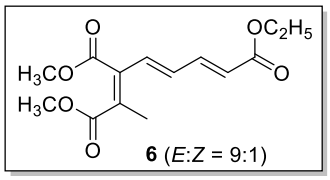
To a stirred solution of methyl alkylidenesuccinate **3** (380 mg, 1.40 mmol) in THF (5 mL) was added solution of LiHMDS in THF (1 M, 2.80 mL, 2.80 mmol) in a drop wise mode at –78 °C under argon atmosphere. The reaction mixture was stirred at same temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl and solvent was removed under vacuum. The residue was dissolved in EtOAc (25 mL) and the organic layer was washed with water, brine and dried over sodium sulfate. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using petroleum ether and ethyl acetate mixture (2:1) as an eluent yielded pure alcohol **4** as a thick oil (212 mg, 71% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.01 (s, 3H), 2.10–2.40 (br s, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 4.29 (d, J = 4 Hz, 2H), 6.03 (td, J = 16 and 4 Hz, 1H), 6.61 (td, J = 16 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 52.3, 52.4, 62.7, 122.6, 126.1, 138.4, 140.4, 167.5, 169.3; ESIMS (m/z) 237 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_{14}O_5Na$ 237.0733, found 237.0725; IR ($CHCl_3$) ν_{max} 3445, 1744, 1716, 1634, 1603 cm^{-1}.

Dimethyl 2-methyl-3-((*E*)-3-oxoprop-1-en-1-yl)maleate (5).



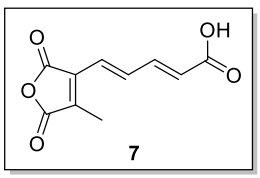
To a stirred solution of alcohol **4** (210 mg, 0.98 mmol) in ethyl acetate (4 mL) was added IBX (329 mg, 1.18 mmol) and it was refluxed for 4 h. The reaction mixture was allowed to cool to 25 ^{o}C, filtered through pad of Celite and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (3:1) as an eluent to furnish pure aldehyde **5** as a pale yellow solid (208 mg, ~100% yield). Mp 60–61 ^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 6.34 (dd, J = 16 and 8 Hz, 1H), 7.39 (d, J = 16 Hz, 1H), 9.70 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.8, 52.66, 52.73, 134.4, 136.2, 137.0, 142.2, 166.8, 167.2, 192.7; ESIMS (m/z) 235 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_{12}O_5Na$ 235.0577, found 235.0577; IR ($CHCl_3$) ν_{max} 2850, 1745, 1725, 1691, 1616 cm^{-1}.

1-Ethyl 5,6-dimethyl (1*E*,3*E*,5*Z*)-hepta-1,3,5-triene-1,5,6-tricarboxylate (6).



To a stirred solution of aldehyde **5** (64 mg, 0.30 mmol) in DCM (3 mL) was added ethyl 2-(triphenyl-l5-phosphanylidene)acetate (138 mg, 0.36 mmol) at 0 ^{o}C. The reaction mixture was stirred for 5 h and concentrated under vacuum. The obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (4:1) as an eluent to afford pure triester **6** as a yellow solid (40 mg, 82% yield). Mp 50–51 ^{o}C; *EE*-isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, J = 8 Hz, 3H), 2.08 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 4.22 (q, J = 8 Hz, 2H), 6.04 (d, J = 8 Hz, 1H), 6.47 (dd, J = 16 and 10 Hz, 1H), 6.81 (d, J = 16 Hz, 1H), 7.35 (dd, J = 16 and 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 14.2, 52.5, 52.6, 60.6, 125.1, 129.6, 131.9, 134.1, 140.0, 142.8, 166.4, 167.1, 168.5; ESIMS (m/z) 305 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{18}O_6Na$ 305.0996, found 305.0994; IR ($CHCl_3$) ν_{max} 1738, 1729, 1710, 1618 cm^{-1}.

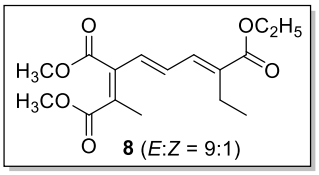
(2*E*,4*E*)-5-(4-Methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)penta-2,4-dienoic acid (7).



To a stirred solution of triester **6** (56 mg, 0.20 mmol) in THF (1 mL) was added 5% aqueous LiOH (1 mL) at 25 ^{o}C. The reaction mixture was stirred for 12 h and acidified by using 2 N HCl. The solvent was removed in vacuo and the obtained residue was dissolved in EtOAc (15 mL). The organic layer was washed with water, brine and dried over sodium sulfate. It was concentrated in vacuo and the obtained crude yellow solid was recrystallized from ethyl acetate to get pale yellow needles of

anhydride **7** (38 mg, 93% yield). Mp 191–192 °C; ^{1}H NMR (acetone–d_6, 500 MHz) δ 2.25 (s, 3H), 6.36 (d, J = 15 Hz, 1H), 7.08 (d, J = 15 Hz, 1H), 7.46 (dd, J = 15 and 10 Hz, 1H), 7.64 (dd, J = 15 and 10 Hz, 1H); ^{13}C NMR (acetone–d_6, 50 MHz) δ 9.7, 126.5, 127.8, 136.5, 138.5, 141.2, 144.0, 165.3, 166.7, 167.1; ESIMS (m/z) 231 $[M+Na]^+$; HRMS (ESI) calcd for $C_{10}H_8O_5Na$ 231.0264, found 231.0264; IR (nujol) ν_{max} 2700–2500, 1768, 1755, 1716 cm^{-1}.

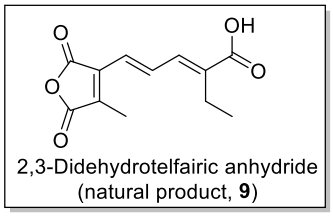
7-Ethyl 2,3-dimethyl (2*Z*,4*E*,6*E*)-nona-2,4,6-triene-2,3,7-tricarboxylate (8).



8 (*E*:*Z* = 9:1)

To a stirred slurry of NaH (60% dispersion in mineral oil; 16 mg, 0.39 mmol) in THF (2 mL) was added ethyl 2-(diethoxyphosphoryl)butanoate (80 mg, 0.36 mmol) in THF (2 mL) in a drop wise manner at 0 °C under argon atmosphere. After ceasing of hydrogen evolution, the mixture was warmed to 25 °C and stirred for 5 minutes. The resulting mixture was cooled to 0 °C and a solution of aldehyde **5** (64 mg, 0.30 mmol) in THF (2 mL) was added drop wise. The reaction mixture was stirred at 0 °C for 45 minutes and then quenched with saturated aqueous NH_4Cl. The solvent was removed under vacuum and residue was dissolved in EtOAc (20 mL). The organic layer was washed with water, brine and dried over sodium sulfate. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained reside using petroleum ether and ethyl acetate mixture (4:1) as an eluent afforded pure triester **8** as a yellow solid (73 mg, 78% yield). Mp 56–57 °C; *EE*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, J = 8 Hz, 3H), 1.31 (t, J = 8 Hz, 3H), 2.07 (s, 3H), 2.43 (q, J = 8 Hz, 2H), 3.77 (s, 3H), 3.88 (s, 3H), 4.23 (q, J = 8 Hz, 2H), 6.66 (dd, J = 16 and 8 Hz, 1H), 6.78 (d, J = 16 Hz, 1H), 7.21 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 14.2, 14.3, 20.7, 52.45, 52.47, 60.8, 128.5, 130.8, 131.5, 136.2, 137.9, 140.6, 167.2, 167.4, 168.7; ESIMS (m/z) 333 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{22}O_6Na$ 333.1309, found 333.1304; IR ($CHCl_3$) ν_{max} 1736, 1709, 1616 cm^{-1}.

(2*E*,4*E*)-2-Ethyl-5-(4-methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)penta-2,4-dienoic acid (2,3-Didehydrotelfairic anhydride, 9).

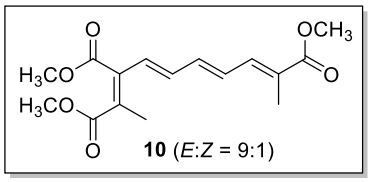


2,3-Didehydrotelfairic anhydride
(natural product, **9**)

It was obtained from triester **8** (62 mg, 0.20 mmol) and 5% aqueous LiOH (1 mL) using the same procedure as described for compound **7**. The product was recrystallized from ethyl acetate to provide pale yellow needles of natural product **9** (44 mg, 93% yield). Mp 199–201 °C (lit. 203–205 °C);[13] ^{1}H NMR (acetone–d_6, 400 MHz) δ 1.11 (t, J = 8 Hz, 3H), 2.25 (s,

3H), 2.57 (q, *J* = 8 Hz, 2H), 7.03 (d, *J* = 16 Hz, 1H), 7.34 (d, *J* = 12 Hz, 1H), 7.85 (dd, *J* = 12 and 16 Hz, 1H); ^{13}C NMR (acetone–d_6, 100 MHz) δ 9.6 14.7, 21.4, 125.6, 135.8, 136.9, 137.2, 140.3, 140.7, 165.5, 166.8, 168.4; ESIMS (*m*/*z*) 259 $[M+Na]^+$; IR (nujol) ν_{max} 2700–2500, 1768, 1756, 1713 cm^{-1}.

Trimethyl (2*Z*,4*E*,6*E*,8*E*)-deca-2,4,6,8-tetraene-2,3,9-tricarboxylate (10).



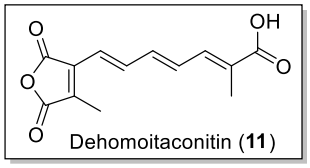
10 (*E*:*Z* = 9:1)

Method A: To a stirred slurry of NaH (60% dispersion in mineral oil; 16 mg, 0.39 mmol) in THF (2 mL) was added methyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (79 mg, 0.36 mmol) in THF (2 mL) in a drop wise mode at –20 °C under argon atmosphere. After the evolution of hydrogen was ceased, the reaction mixture was warmed to 0 °C and stirred for 5 minutes. The resulting mixture was cooled to –20 °C and a solution of aldehyde **5** (64 mg, 0.30 mmol) in THF (2 mL) was added drop wise. The reaction mixture was stirred for 30 minutes and quenched with saturated aqueous NH_4Cl. The solvent was removed in vacuo and residue was dissolved in EtOAc (20 mL). The organic layer was washed with water, brine and dried over sodium sulfate. It was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (6:1) as an eluent to yield pure triester **10** as a yellow solid (71 mg, 76% yield).

Method B: To a stirred slurry of NaH (60% dispersion in mineral oil; 11 mg, 0.27 mmol) in THF (2 mL) was added ethyl 2-(diethoxyphosphoryl)propanoate (57 mg, 0.25 mmol) in THF (2 mL) in a drop wise mode at –20 °C under argon atmosphere. After the evolution of hydrogen was ceased, the reaction mixture was warmed to 0 °C and stirred for 5 minutes. The resulting mixture was cooled to –100 °C and a solution of aldehyde **23** (50 mg, 0.21 mmol) in THF (2 mL) was added drop wise. The reaction mixture was stirred for 20 minutes and quenched with saturated aqueous NH_4Cl at –78 °C. The above specified workup followed by purification gave pure product **10** (42 mg, 65% yield).

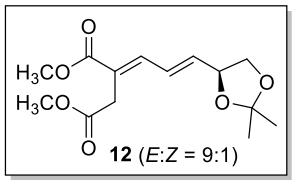
Mp 98–100 ^{o}C; *EEE*-isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.00 (s, 3H), 2.07 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 6.35–6.80 (m, 4H), 7.25 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.0, 13.8, 52.0, 52.4, 52.6, 126.9, 127.8, 129.4, 132.1, 136.8, 137.4, 137.9, 141.3, 167.2, 168.5, 169.1; ESIMS (*m*/*z*) 331 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{20}O_6Na$ 331.1152, found 331.1150; IR ($CHCl_3$) ν_{max} 1740, 1732, 1709, 1617 cm^{-1}.

(2*E*,4*E*,6*E*)-2-Methyl-7-(4-methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)hepta-2,4,6-trienoic acid (Dehomoitaconitin, 11).



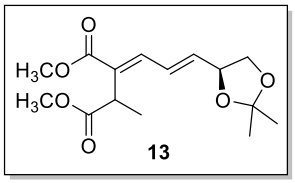
It was obtained from triester **10** (60 mg, 0.20 mmol) and 5% aqueous LiOH (1 mL) using the same procedure as described for compound **7**. The crude product was recrystallized from ethyl acetate to furnish pale yellow needles of anhydride **11** (46 mg, 96% yield). Mp 220–222 ^{o}C; ^{1}H NMR (acetone–d_6, 500 MHz) δ 2.04 (s, 3H), 2.20 (s, 3H), 6.79 (d, J = 15 Hz, 1H), 6.86 (dd, J = 15 and 15 Hz, 1H), 7.13 (t, J = 15 Hz, 1H), 7.31 (d, J = 10 Hz, 1H), 7.69 (dd, J = 15 and 10 Hz, 1H); ^{13}C NMR (acetone–d_6, 125 MHz) δ 9.8, 13.3, 122.5, 131.9, 135.4, 137.5, 138.1, 138.5, 139.3, 141.6, 165.8, 167.1, 169.2; ESIMS (*m*/*z*) 271 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{12}O_5Na$ 271.0577, found 271.0574; IR (nujol) ν_{max} 2700–2500, 1767, 1754, 1715 cm^{-1}.

Dimethyl (*E*)-2-((*E*)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allylidene)succinate (12).



It was obtained from dimethyl maleate (432 mg, 3.00 mmol), (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (562 mg, 3.60 mmol) and *n*-Bu_3P (1.12 mL, 4.50 mmol) in THF (3 mL) using the same procedure as described for compound **2** as a thick oil (605 mg, 71% yield). $[\alpha]^{25}_{D}$ +3.4 (c 0.1, $CHCl_3$); *EE*-isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.45 (s, 3H), 3.47 (s, 2H), 3.58–3.73 (m, 1H), 3.69 (s, 3H), 3.78 (s, 3H), 4.16 (dd, J = 8 and 6 Hz, 1H), 4.65 (q, J = 6 Hz, 1H), 6.12 (dd, J = 16 and 8 Hz, 1H), 6.56 (dd, J = 14 and 12 Hz, 1H), 7.35 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.7, 26.5, 32.3, 52.11, 52.14, 69.2, 76.1, 109.9, 125.0, 126.6, 139.7, 140.1, 167.4, 170.8; ESIMS (*m*/*z*) 307 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{20}O_6Na$ 307.1152, found 307.1143; IR ($CHCl_3$) ν_{max} 1739, 1715, 1646, 1615 cm^{-1}.

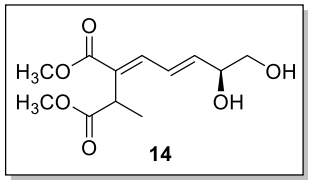
Dimethyl (*E*)-2-((*E*)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allylidene)-3-methylsuccinate (13, diastereomeric mixture).



It was obtained from alkylidenesuccinate **12** (570 mg, 2.00 mmol), NaHMDS in THF (1 M, 2.60 mL, 2.60 mmol) and MeI (0.15 mL, 2.40 mmol) using the same procedure as described for compound **3** as a thick oil (448 mg, 75% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (d, J = 8 Hz, 3H), 1.41 (s, 3H), 1.45 (s, 3H), 3.58–3.80 (m, 2H), 3.66 (s, 3H), 3.75 (s, 3H), 4.17 (dd, J = 10 and 8 Hz, 1H), 4.65 (q, J = 6 Hz, 1H), 6.11 (dd, J = 16 and 8 Hz, 1H), 6.59 (dd, J = 16 and 12 Hz, 1H), 7.25 (d, J = 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1, 25.7, 26.5,

37.9, 51.9, 52.0, 69.2, 76.0, 76.1, 109.9, 126.1, 126.2, 131.8, 131.9, 138.07, 138.14, 140.0, 140.1, 166.91, 166.94, 173.7; ESIMS (*m*/*z*) 321 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{22}O_6Na$ 321.1309, found 321.1309; IR ($CHCl_3$) ν_{max} 1729, 1716, 1651 cm^{-1}.

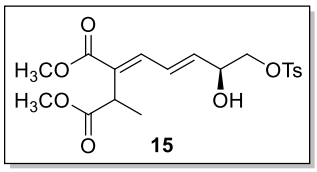
Dimethyl (*E*)-2-((*S*,*E*)-4,5-dihydroxypent-2-en-1-ylidene)-3-methylsuccinate (14, diastereomeric mixture).



14

To a stirred solution of compound **13** (400 mg, 1.34 mmol) in MeOH (8 mL) was added *p*-TSA monohydrate (26 mg, 10 mol %) at 25 °C. The reaction mixture was stirred for 8 h and solvent was removed under vacuum. The residue was dissolved in EtOAc (30 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$, water and brine. It was dried over sodium sulfate and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (1:1) as an eluent to give pure diol **14** as thick oil (305 mg, 88% yield). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.35 (d, J = 8 Hz, 3H), 3.43–3.60 (m, 1H), 3.60–3.83 (m, 2H), 3.65 (s, 3H), 3.74 (s, 3H), 4.30–4.45 (m, 1H), 6.14 (dd, J = 15 and 6 Hz, 1H), 6.64 (dd, J = 14 and 12 Hz, 1H), 7.24 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 37.9, 52.0, 52.1, 66.0, 72.4, 125.1, 131.2, 138.6, 141.5, 167.1, 174.2; ESIMS (*m*/*z*) 281 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{18}O_6Na$ 281.0996, found 281.0990; IR ($CHCl_3$) ν_{max} 3453, 1733, 1715, 1654 cm^{-1}.

Dimethyl (*E*)-2-((*S*,*E*)-4-hydroxy-5-(tosyloxy)pent-2-en-1-ylidene)-3-methylsuccinate (15, diastereomeric mixture).

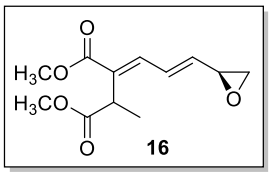


15

To a solution of compound **14** (50 mg, 0.19 mmol) in DCM (5 mL) was added dibutyltin oxide (10 mg, 20 mol %) at 0 °C under argon atmosphere and the reaction mixture was stirred for 30 minutes. To the above reaction mixture was added triethylamine (0.026 mL, 0.19 mmol) followed by tosyl chloride (36 mg, 0.19 mmol) and it was stirred at 25 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and solvent was removed under vacuum. The residue was dissolved in EtOAc (15 mL) and the organic layer was washed with water, brine and dried over sodium sulfate. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (2:1) as an eluent furnished pure product **15** as a thick oil (80 mg, 77% yield). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.36 (d, J = 8 Hz, 3H), 2.47 (s, 3H), 3.66 (s, 3H), 3.68–3.80 (m, 1H), 3.76

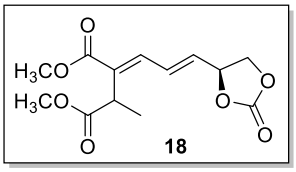
(s, 3H), 3.95 (ddd, *J* = 10, 6 and 2 Hz, 1H), 4.11 (dd, *J* = 10 and 4 Hz, 1H), 4.50–4.63 (m, 1H), 6.00 (dd, *J* = 14 and 6 Hz, 1H), 6.65 (dd, *J* = 14 and 12 Hz, 1H), 7.19 (d, *J* = 10 Hz, 1H), 7.37 (d, *J* = 8 Hz, 2H), 7.81 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 21.6, 37.8, 51.9, 52.1, 69.4, 72.4, 126.1, 127.9, 129.9, 131.9, 132.3, 138.0, 138.7, 145.2, 166.9, 173.8; ESIMS (*m*/*z*) 435 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{25}O_8S$ 413.1265, found 413.1280; IR ($CHCl_3$) ν_{max} 3436, 1733, 1711, 1598 cm^{-1}.

Dimethyl (*E*)-2-methyl-3-((*E*)-3-((*S*)-oxiran-2-yl)allylidene)succinate (16, diastereomeric mixture).



To a stirred slurry of NaH (60% dispersion in mineral oil; 8 mg, 0.20 mmol) in THF (1 mL) was added compound **15** (70 mg, 0.17 mmol) in THF (2 mL) in a drop wise manner at 0 °C under argon atmosphere. After being stirred for 30 minutes the reaction was quenched with saturated aqueous NH_4Cl and solvent was removed in vacuo. The residue was dissolved in EtOAc (20 mL) and the organic layer was washed with water, brine and dried over sodium sulfate. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (4:1) as an eluent yielded epoxide **16** as a thick oil (41 mg, 71% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, *J* = 8 Hz, 3H), 2.73 (dd, *J* = 6 and 4 Hz, 1H), 3.07 (t, *J* = 6 Hz, 1H), 3.40–3.51 (m, 1H), 3.67 (s, 3H), 3.70–3.85 (m, 1H), 3.76 (s, 3H), 5.85 (ddd, *J* = 14, 8 and 4 Hz, 1H), 6.71 (dd, *J* = 16 and 12 Hz, 1H), 7.25 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 16.2, 37.91, 37.93, 49.5, 51.55, 51.63, 52.0, 52.1, 127.6, 127.8, 131.69, 131.72, 137.75, 137.78, 140.0, 140.1, 167.0, 173.8; ESIMS (*m*/*z*) 263 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{17}O_5$ 241.1071, found 241.1070; IR ($CHCl_3$) ν_{max} 1733, 1714, 1622 cm^{-1}.

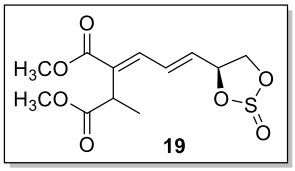
Dimethyl (*E*)-2-methyl-3-((*E*)-3-((*S*)-2-oxo-1,3-dioxolan-4-yl)allylidene)succinate (18, diastereomeric mixture).



To a stirred solution of compound **14** (50 mg, 0.19 mmol) in DCM (2 mL) was added carbonyldiimiazole (37 mg, 0.23 mmol) at 25 ^{o}C under argon atmosphere. The reaction mixture was stirred for 4 h and solvent was removed in vacuo. The residue was dissolved in EtOAc (15 mL) and the organic layer was washed with water, brine and dried over sodium sulfate. The organic layer was concentrated in vacuo and the obtained residue was purified by silica gel column

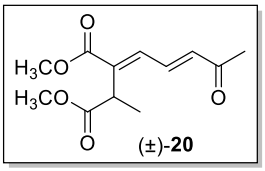
chromatography using petroleum ether and ethyl acetate mixture (2:1) as an eluent to provide carbonate **18** as thick oil (49 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (dd, J = 6 and 2 Hz, 3H), 3.67 (s, 3H), 3.68–3.82 (m, 1H), 3.78 (s, 3H), 4.20 (dd, J = 8 and 8 Hz, 1H), 4.66 (t, J = 8 Hz, 1H), 5.28 (q, J = 8 Hz, 1H), 6.11 (dd, J = 16 and 6 Hz, 1H), 6.71 (dd, J = 14 and 12 Hz, 1H), 7.24 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 16.2, 37.97, 38.03, 52.19, 52.22, 68.9, 76.1, 76.3, 128.9, 129.1, 134.2, 134.5, 134.6, 136.3, 136.4, 154.3, 166.49, 166.52, 173.29, 173.34; ESIMS (*m*/*z*) 307 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O_7$ 285.0969, found 285.0967; IR ($CHCl_3$) ν_{max} 1805, 1733, 1646, 1610 cm^{-1}.

Dimethyl (*E*)-2-methyl-3-((*E*)-3-((4*S*)-2-oxido-1,3,2-dioxathiolan-4-yl)allylidene)succinate (19, diastereomeric mixture).



To a stirred solution of compound **14** (50 mg, 0.19 mmol) in DCM (2 mL) was added triethylamine (0.053 mL, 0.38 mmol) followed by thionyl chloride (0.017 mL, 0.28 mmol) at 0 ^{o}C under argon atmosphere. The reaction mixture was stirred for 30 minutes and solvent was removed under vacuum.The residue was dissolved in EtOAc (15 mL) and the organic layer was washed with water, brine and dried over sodium sulfate. Concentration of organic layer in vacuo and silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (2:1) gave pure sulfite **19** as a thick oil (49 mg, 83% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, J = 6 Hz, 3H), 3.67 (s, 3H), 3.68–3.80 (m, 1H), 3.77 (s, 3H), 4.08 (dd, J = 10 and 6 Hz, 0.50H), 4.42 (t, J = 10 Hz, 0.50H), 4.62 (dd, J = 10 and 6 Hz, 0.50H), 4.81 (dd, J = 8 and 6 Hz, 0.50H), 5.03 (q, J = 8 Hz, 0.50H), 5.51 (q, J = 6 Hz, 0.50H), 6.02 (dd, J = 16 and 8 Hz, 0.50H), 6.20 (dd, J = 16 and 8 Hz, 0.50H), 6.69 (dd, J = 16 and 12 Hz, 1H), 7.24 (dd, J = 12 and 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1, 37.96, 37.99, 52.1, 69.5, 71.2, 79.3, 79.4, 82.9, 83.0, 129.1, 129.3, 129.88, 129.93, 133.6, 133.9, 133.98, 134.04, 134.1, 134.8, 134.9, 136.6, 136.65, 136.69, 166.6, 173.3, 173.39, 173.43; ESIMS (*m*/*z*) 327 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{16}O_7NaS$ 327.0509, found 327.0507; IR ($CHCl_3$) ν_{max} 1714, 1646 cm^{-1}.

Dimethyl (*E*)-2-methyl-3-((*E*)-4-oxopent-2-en-1-ylidene)succinate (20).

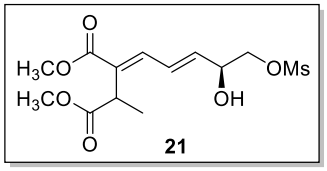


To a stirred solution of compound **18**/**19** (40/40 mg, 0.14/0.13 mmol) in THF (4 mL) was added solution of LiHMDS in THF (1 M, 0.28/0.26 mL, 0.28/0.26 mmol) in a drop wise fashion at –78 °C under argon

atmosphere. The reaction mixture was stirred at same temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl and solvent was removed in vacuo. The residue was dissolved in EtOAc (15 mL) and the organic layer was washed with water, brine and dried over sodium sulfate. The concentration of organic layer followed by silica gel column chromatography of the resulting residue using petroleum ether and ethyl acetate mixture (4:1) as an eluent furnished pure ketone **20** as a thick oil (28/23 mg, 82/73% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (d, J = 6 Hz, 3H), 2.34 (s, 3H), 3.68 (s, 3H), 3.80 (s, 3H), 3.86 (q, J = 8 Hz, 1H), 6.48 (d, J = 14 Hz, 1H), 7.20–7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3, 28.2, 38.3, 52.2, 52.3, 134.9, 136.2, 136.5, 138.7, 166.2, 173.1, 197.7; ESIMS (m/z) 263 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{17}O_5$ 241.1071, found 241.1072; IR ($CHCl_3$) ν_{max} 1740, 1720, 1674, 1625 cm^{-1}.

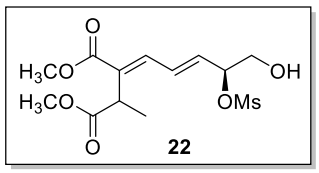
Dimethyl (*E*)-2-((*S*,*E*)-4-hydroxy-5-((methylsulfonyl)oxy)pent-2-en-1-ylidene)-3-methylsuccinate (21, diastereomeric mixture).

To a stirred solution of compound **14** (180 mg, 0.70 mmol) in DCM (10 mL) was added triethylamine (0.127 mL, 0.91 mmol) followed by mesyl chloride (0.065 mL, 0.84 mmol) and DMAP (4 mg, 5 mol %) at 0 ^{o}C under argon atmosphere. The reaction mixture was stirred for 2 h and quenched with saturated aqueous NH_4Cl. Solvent was removed in vacuo and the residue was dissolved in EtOAc (25 mL). The organic layer was washed with water, brine and dried over sodium sulfate. Concentration of organic layer in vacuo gave mixture of mesylates **21** and **22** in 1:1 ratio. The obtained mixture of primary and secondary mesylates was separated by silica gel column chromatography using petroleum ether and ethyl acetate mixture (7:3) as an eluent to afford pure products as thick oils (85/86 mg, 73% yield).



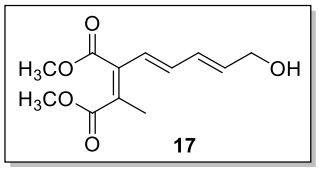
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38 (d, J = 8 Hz, 3H), 2.02 (br s, 1H), 3.09 (s, 3H), 3.67 (s, 3H), 3.70–3.85 (m, 1H), 3.76 (s, 3H), 4.16 (dd, J = 12 and 8 Hz, 1H), 4.32 (dd, J = 12 and 4 Hz, 1H), (4.57–4.70 m, 1H), 6.11 (dd, J = 16 and 6 Hz, 1H), 6.72 (dd, J = 12 and 12 Hz, 1H), 7.25 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1, 37.7, 37.9, 52.0, 52.2, 69.8, 72.0, 126.5, 132.4, 137.8, 138.3, 166.9, 173.8; ESIMS (m/z) 359 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_8NaS$ 359.0771, found 359.0768; IR ($CHCl_3$) ν_{max} 3445, 1728 cm^{-1}.

Dimethyl (*E*)-2-((*S*,*E*)-5-hydroxy-4-((methylsulfonyl)oxy)pent-2-en-1-ylidene)-3-methylsuccinate (22, diastereomeric mixture).



^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, J = 6 Hz, 3H), 1.77 (br s, 1H), 3.09 (s, 3H), 3.67 (s, 3H), 3.70–3.80 (m, 1H), 3.77 (s, 3H), 4.30–4.47 (m, 2H), 4.73 (q, J = 8 Hz, 1H), 6.11 (dd, J = 14 and 8 Hz, 1H), 6.67 (dd, J = 16 and 12 Hz, 1H), 7.23 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 31.5, 37.9, 38.0, 52.1, 52.2, 56.99, 57.02, 70.27, 70.33, 128.88, 128.91, 133.9, 134.0, 135.8, 136.8, 166.6, 173.5; ESIMS (*m*/*z*) 359 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_8NaS$ 359.0771, found 359.0768; IR ($CHCl_3$) ν_{max} 3440, 1729 cm^{-1}.

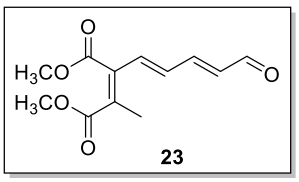
Dimethyl 2-((1*E*,3*E*)-5-hydroxypenta-1,3-dien-1-yl)-3-methylmaleate (17).



To a stirred slurry of NaH (60% dispersion oil; 27 mg, 0.68 mmol) in DMF (2 mL) was added mixture of compound **21** and **22** (150 mg, 0.45 mmol) in DMF (2 mL) in a drop wise mode at 0 °C under argon atmosphere. After stirring for 15 minutes, the reaction was quenched with saturated aqueous NH_4Cl and solvent was removed under vacuum. The residue was dissolved in EtOAc (25 mL) and the organic layer was washed with water, brine and dried over sodium sulfate. The organic layer was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (2:1) as an eluent to provide alcohol **17** as thick oil (69 mg, 64% yield).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85 (br s, 1H), 2.02 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.25 (d, J = 6 Hz, 2H), 5.95–6.10 (m, 1H), 6.30–6.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 52.3, 52.4, 62.8, 125.2, 125.6, 129.8, 136.8, 137.6, 141.5, 167.3, 169.3; ESIMS (*m*/*z*) 263 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{17}O_5$ 241.1071, found 241.1070; IR ($CHCl_3$) ν_{max} 3502, 1756, 1722, 1634 cm^{-1}.

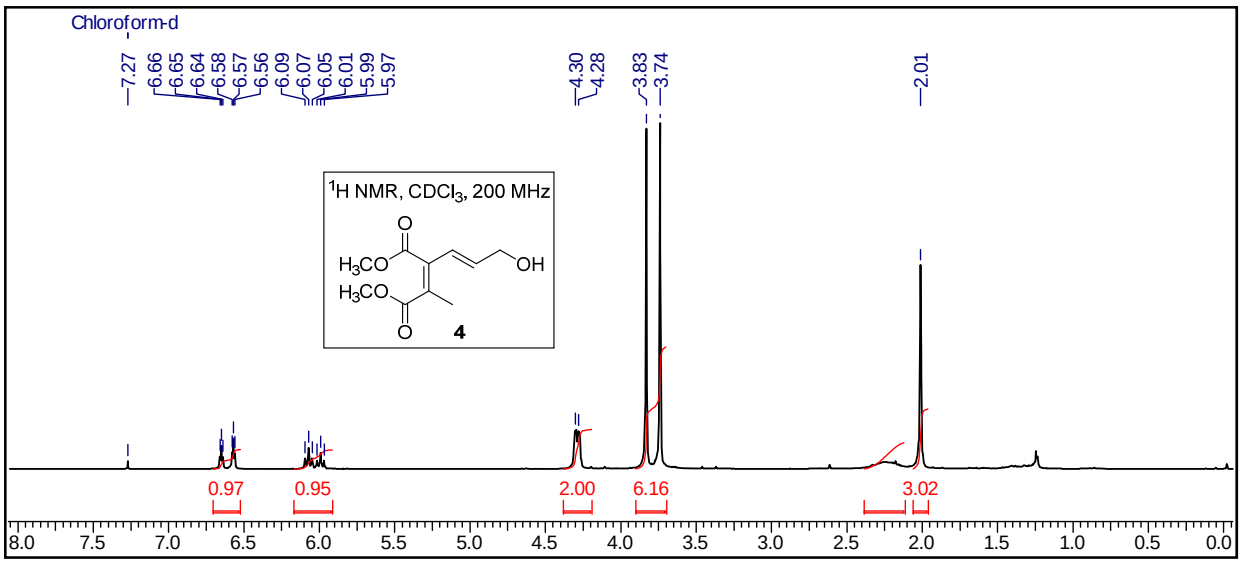
Dimethyl 2-methyl-3-((1*E*,3*E*)-5-oxopenta-1,3-dien-1-yl)maleate (23).

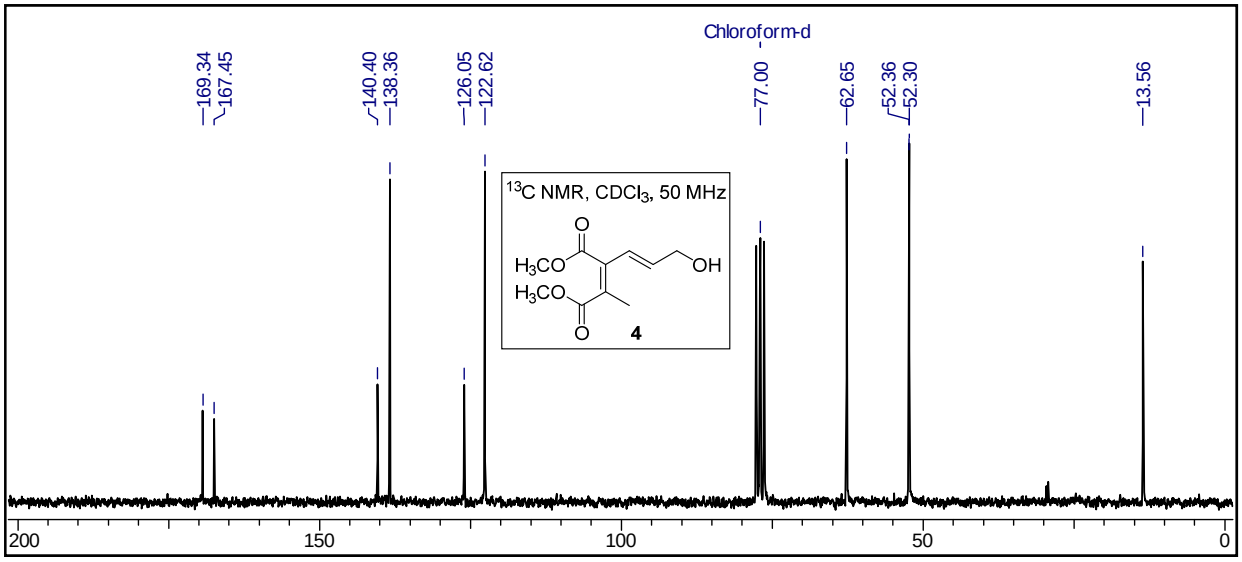


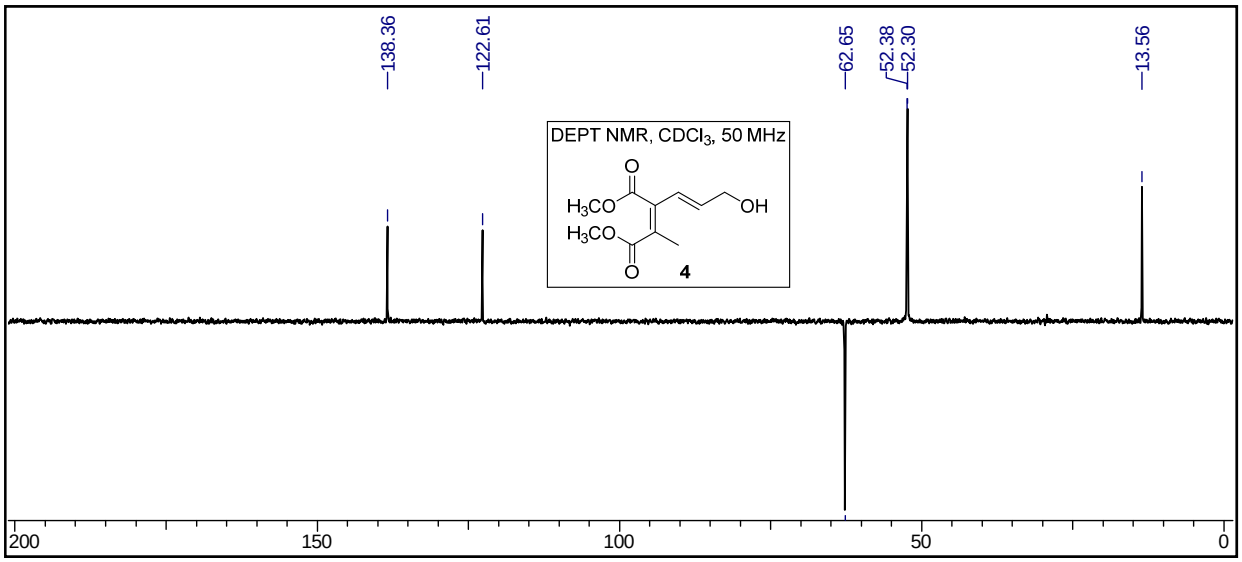
It was obtained from alcohol **17** (60 mg, 0.25 mmol) and IBX (84 mg, 0.30 mmol) as a thick oil using the same procedure as described for compound **5** (59 mg, ~100% yield). Mp 89–91 ^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 6.29 (dd, J = 14 and 8 Hz, 1H), 6.61 (dd, J = 16 and 10 Hz, 1H), 6.94 (d, J = 16 Hz, 1H), 7.21 (dd, J = 16 and 10 Hz, 1H), 9.64 (d, J = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 52.6, 52.7, 131.2, 133.5, 133.8, 134.2, 139.5, 149.6, 167.0, 168.2, 193.1; ESIMS (*m*/*z*) 261 $[M+Na]^+$; HRMS

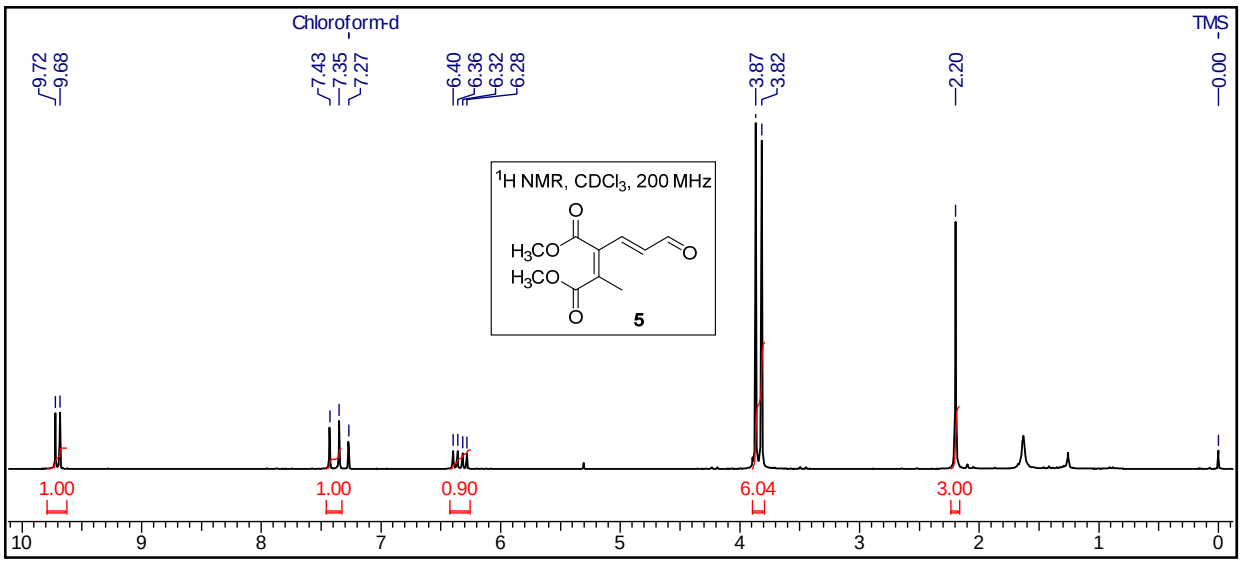
(ESI) calcd for $C_{12}H_{14}O_5Na$ 261.0733, found 261.0731; IR ($CHCl_3$) ν_{max} 3445, 2854, 1734, 1674, 1627 cm^{-1}.

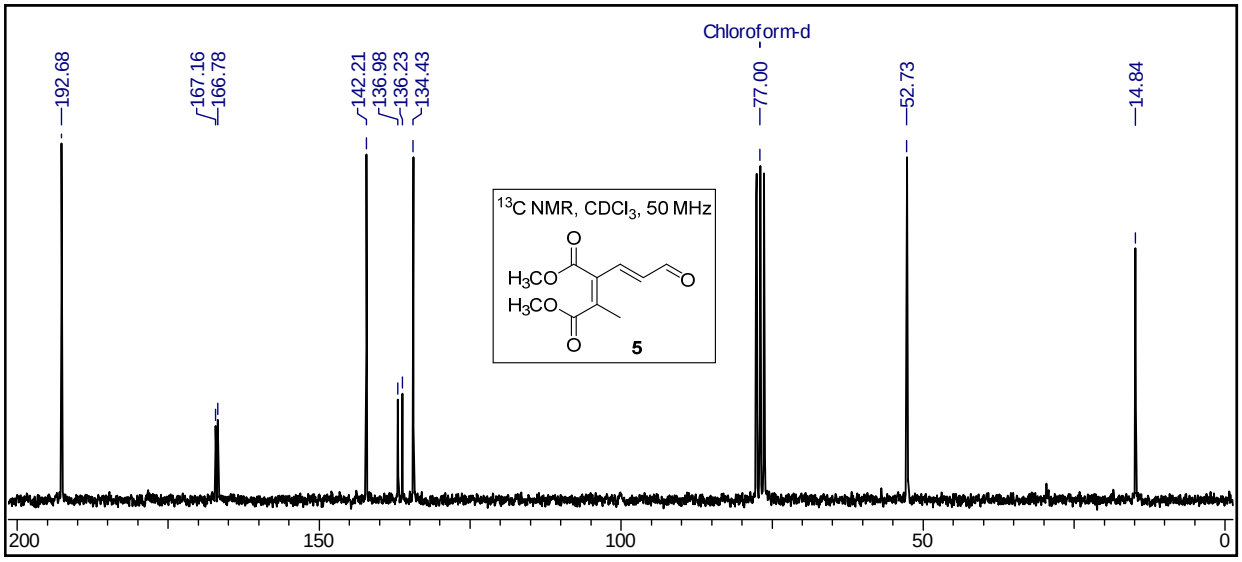
3B.5 Selected Spectra

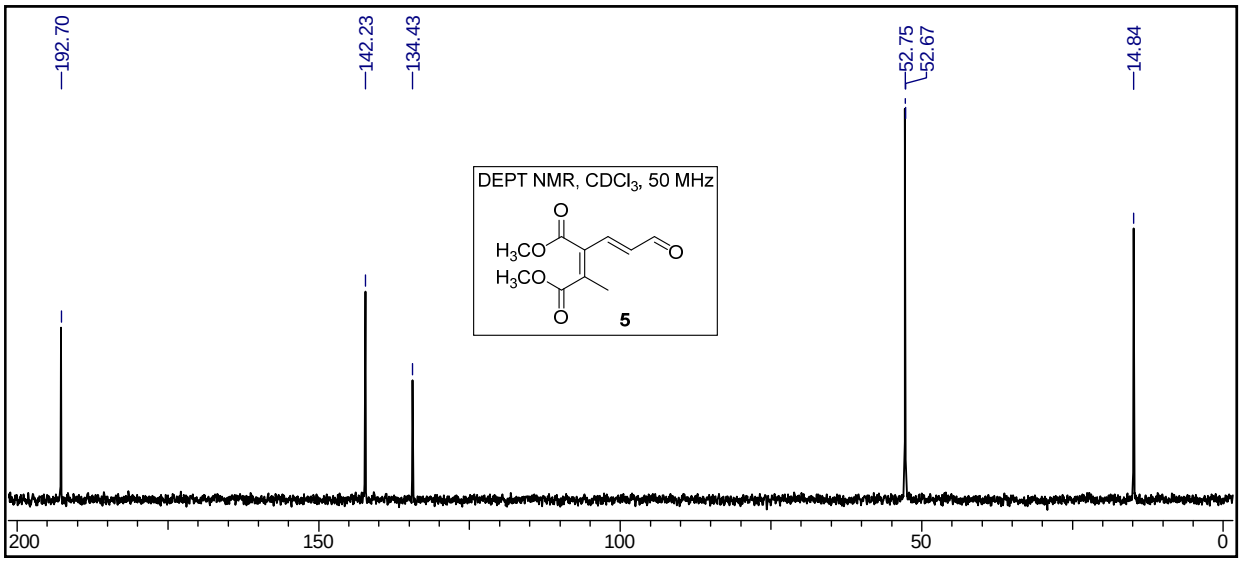

Chloroform-d
7.27
6.66
6.65
6.64
6.58
6.57
6.56
6.09
6.07
6.05
6.01
5.99
5.97
4.30
4.28
3.83
3.74
2.01
^{1}H NMR, CDCl$_3$, 200 MHz
H$_3$CO
H$_3$CO
OH
O
4
0.97
0.95
2.00
6.16
3.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

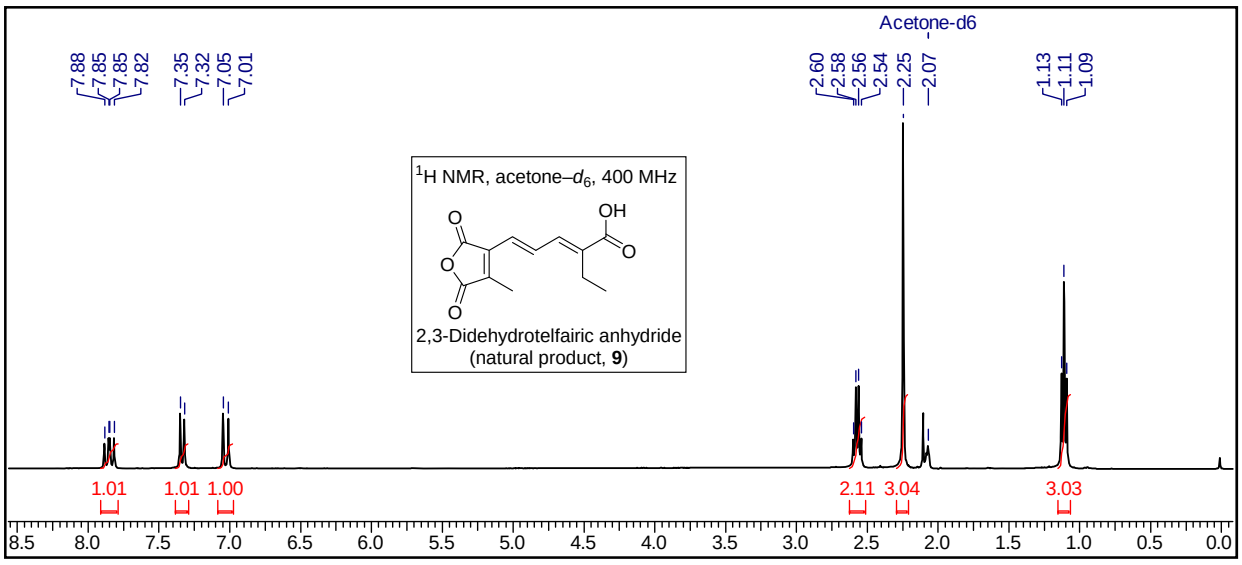

Chloroform-d
169.34
167.45
140.40
138.36
126.05
122.62
77.00
62.65
52.36
52.30
13.56
^{13}C NMR, CDCl$_3$, 50 MHz
H$_3$CO
H$_3$CO
OH
O
4
200
150
100
50
0

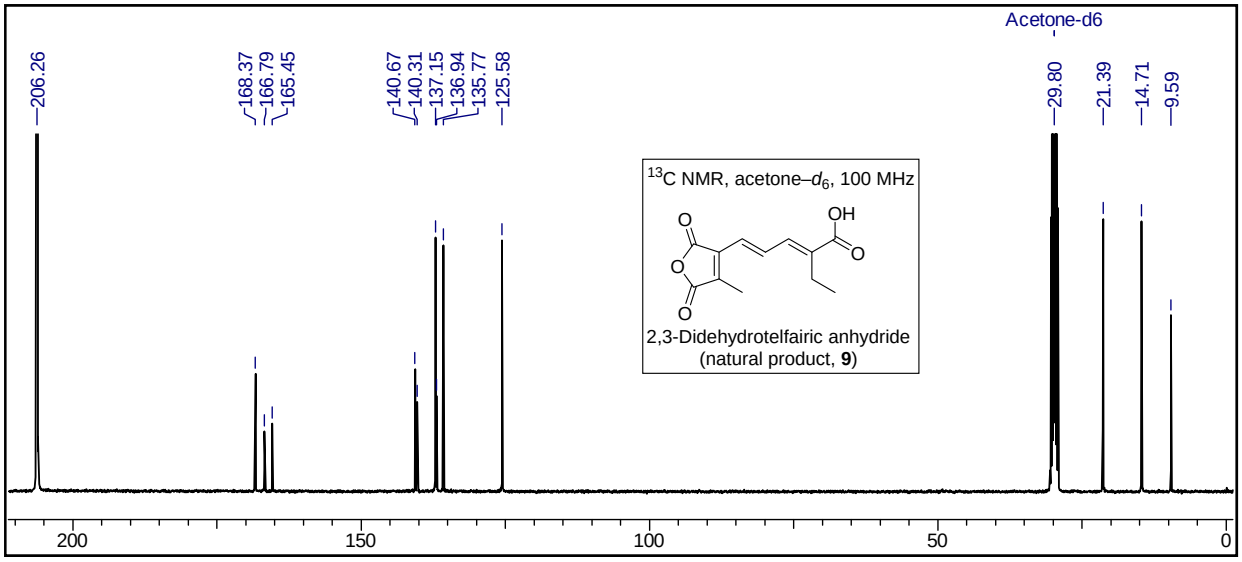

138.36
122.61
62.65
52.38
52.30
13.56
DEPT NMR, CDCl$_3$, 50 MHz
H$_3$CO
H$_3$CO
OH
O
4
200
150
100
50
0

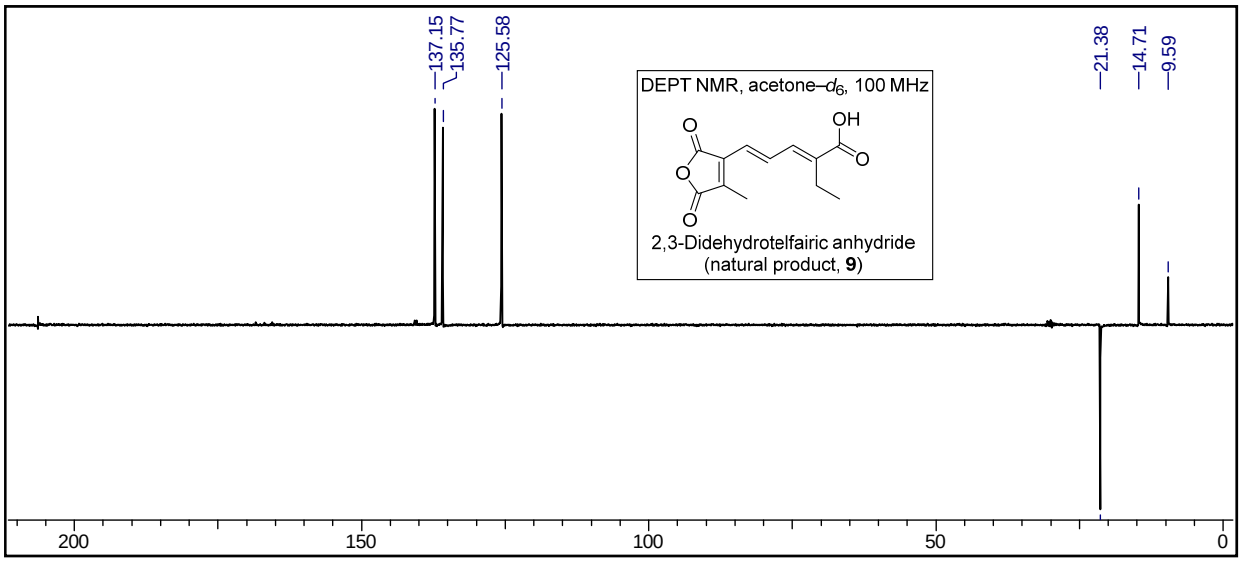

Chloroform-d
TMS
9.72
9.68
7.43
7.35
7.27
6.40
6.36
6.32
6.28
3.87
3.82
2.20
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
H$_3$CO
H$_3$CO
O
O
O
5
1.00
1.00
0.90
6.04
3.00
10
9
8
7
6
5
4
3
2
1
0

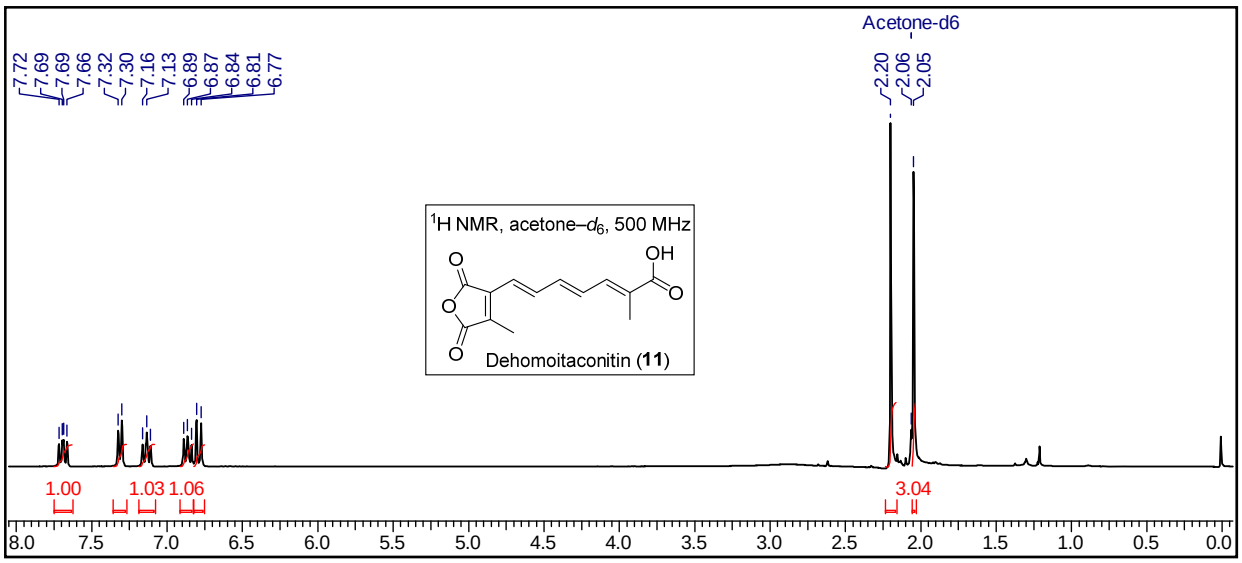

Chloroform-d
192.68
167.16
166.78
142.21
136.98
136.23
134.43
77.00
52.73
14.84
^{13}C NMR, CDCl$_3$, 50 MHz
H$_3$CO
H$_3$CO
O
O
O
5
200
150
100
50
0

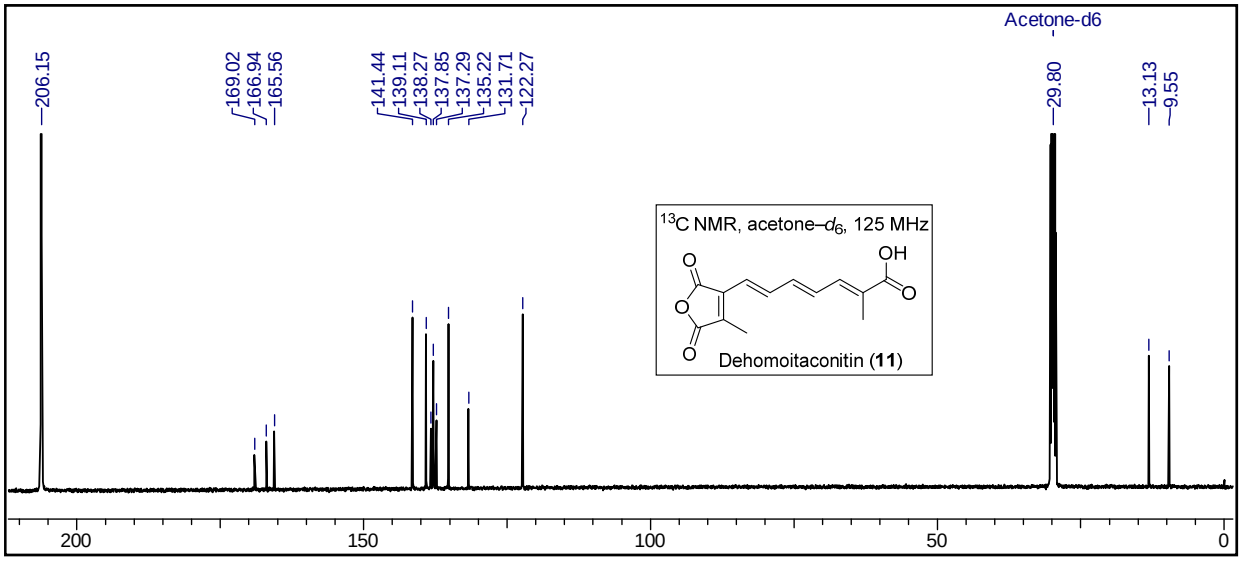

192.70
142.23
134.43
52.75
52.67
14.84
DEPT NMR, CDCl$_3$, 50 MHz
H$_3$CO
H$_3$CO
O
O
O
5
200
150
100
50
0

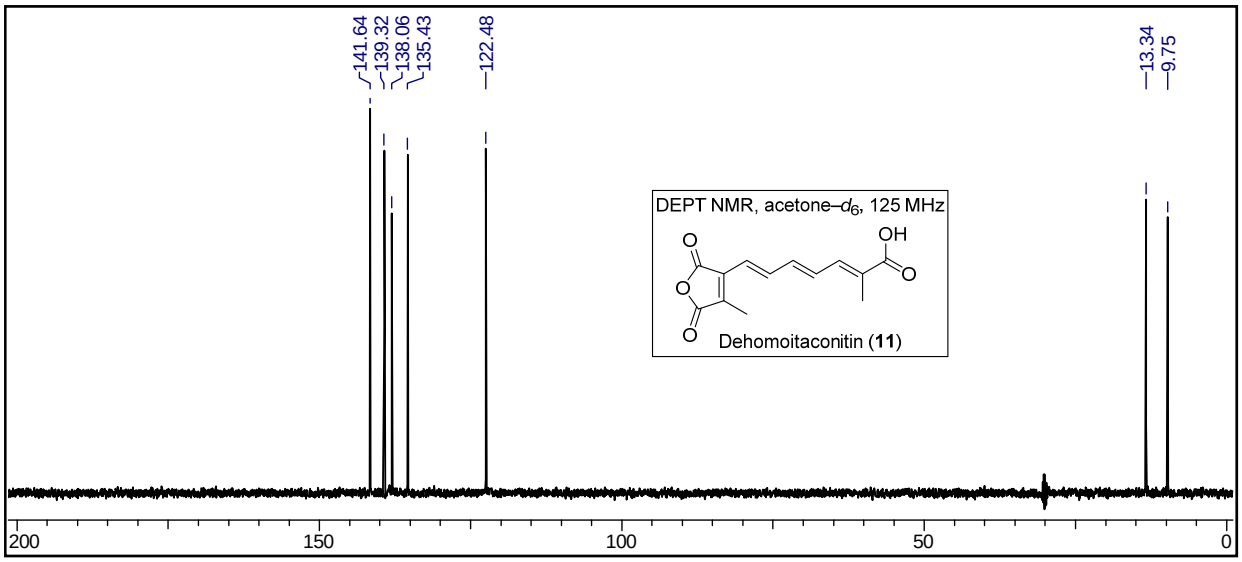

Acetone-d6
7.88
7.85
7.85
7.82
7.35
7.32
7.05
7.01
2.60
2.58
2.56
2.54
2.25
2.07
1.13
1.11
1.09
^{1}H NMR, acetone–d_6, 400 MHz
OH
O
O
O
2,3-Didehydrotelfairic anhydride
(natural product, **9**)
1.01
1.01
1.00
2.11
3.04
3.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

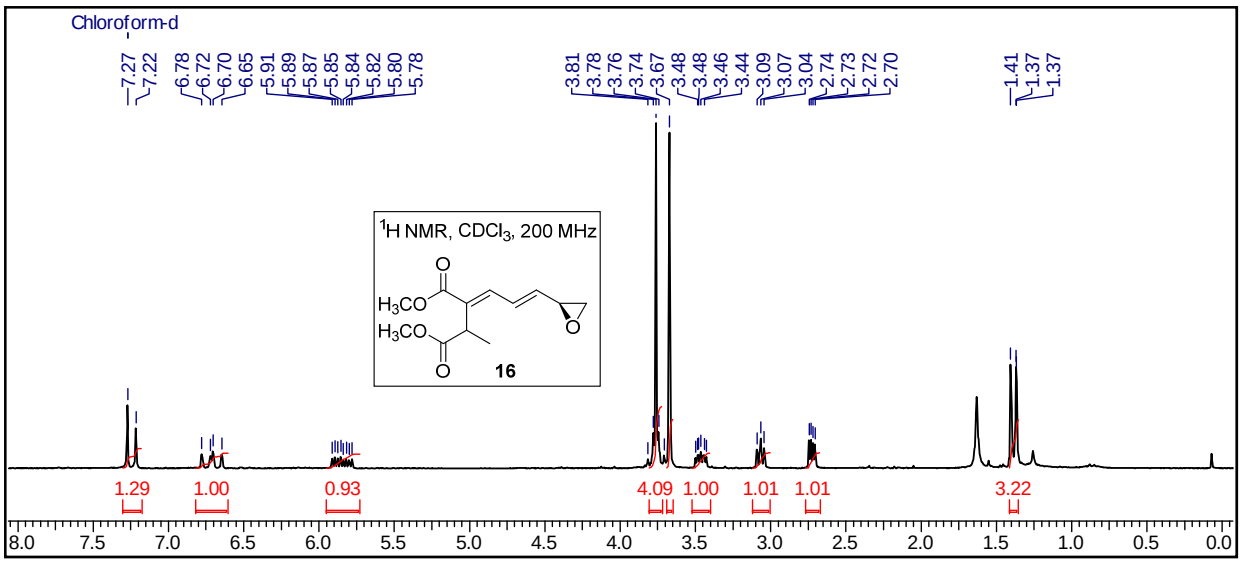

Acetone-d6
206.26
168.37
166.79
165.45
140.67
140.31
137.15
136.94
135.77
125.58
29.80
21.39
14.71
9.59
^{13}C NMR, acetone–d_6, 100 MHz
OH
O
O
O
2,3-Didehydrotelfairic anhydride
(natural product, **9**)
200
150
100
50
0

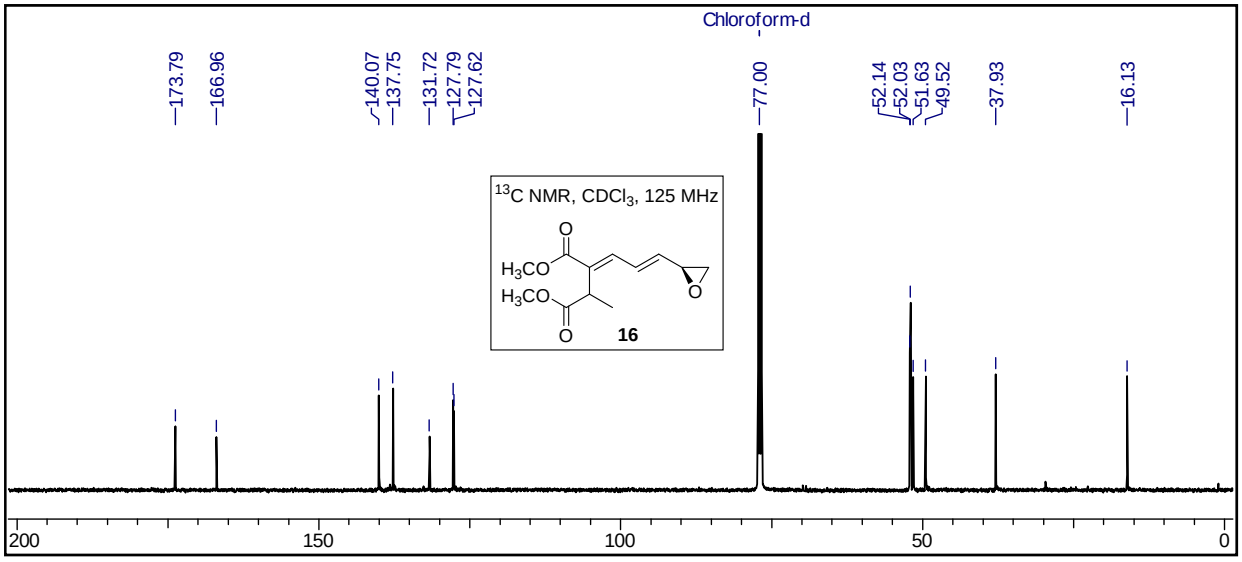

137.15
135.77
125.58
21.38
14.71
9.59
DEPT NMR, acetone–d_6, 100 MHz
OH
O
O
O
2,3-Didehydrotelfairic anhydride
(natural product, **9**)
200
150
100
50
0

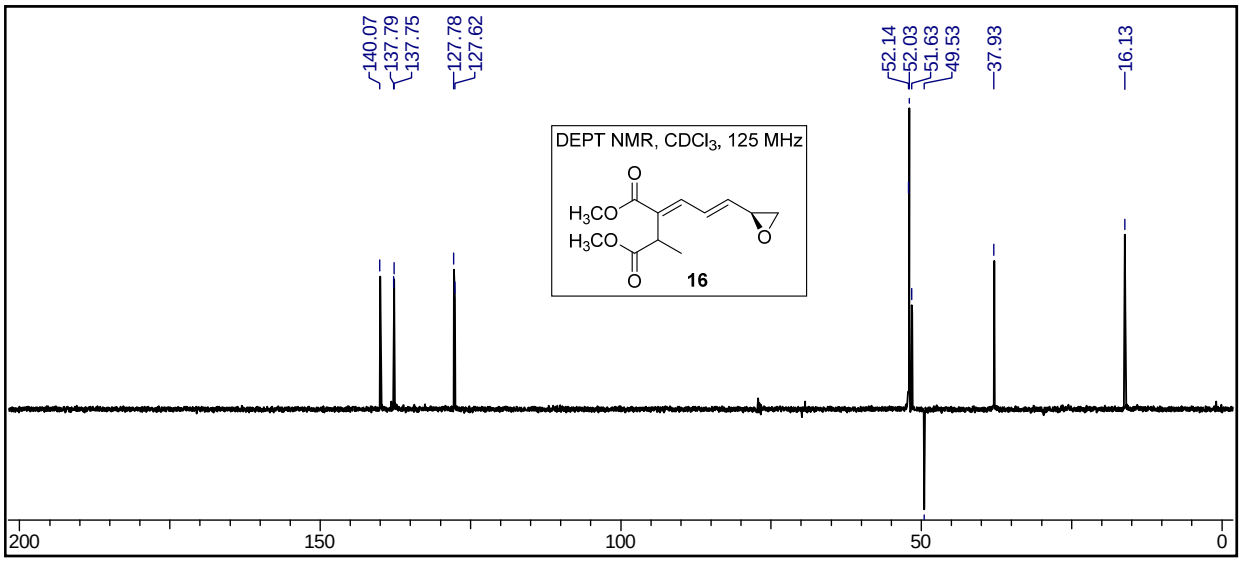

Acetone-d6
7.72
7.69
7.69
7.66
7.32
7.30
7.16
7.13
6.89
6.87
6.84
6.81
6.77
2.20
2.06
2.05
^{1}H NMR, acetone–d_6, 500 MHz
OH
O
O
O
Dehomoitaconitin (**11**)
1.00
1.03
1.06
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

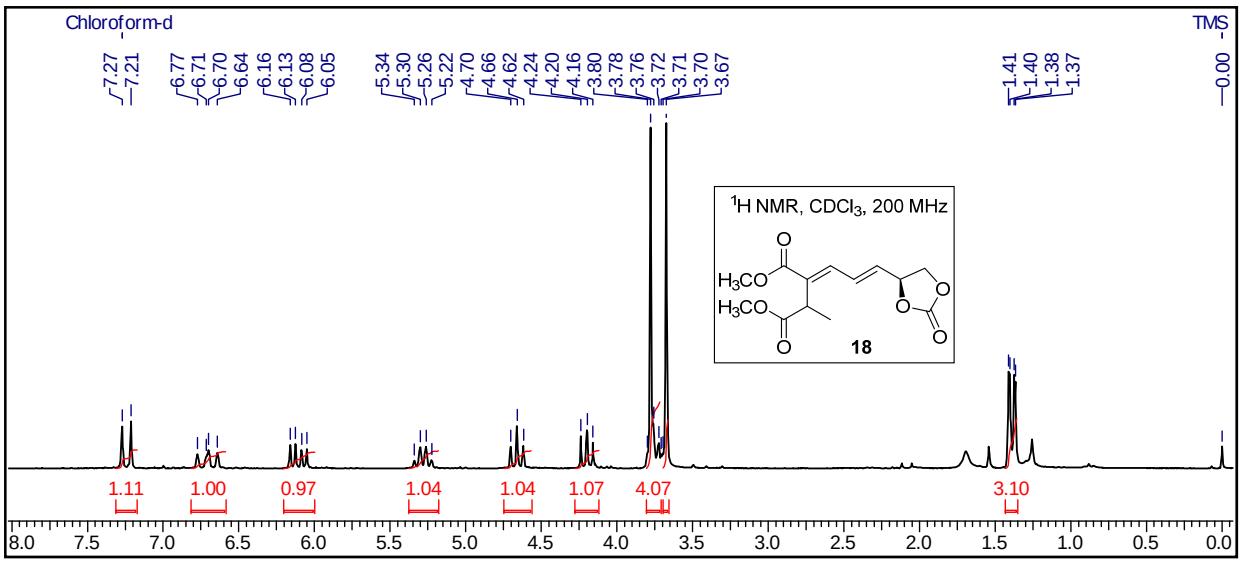

Acetone-d6
206.15
169.02
166.94
165.56
141.44
139.11
138.27
137.85
137.29
135.22
131.71
122.27
29.80
13.13
9.55
^{13}C NMR, acetone–d_6, 125 MHz
OH
O
O
O
Dehomoitaconitin (**11**)
200
150
100
50
0

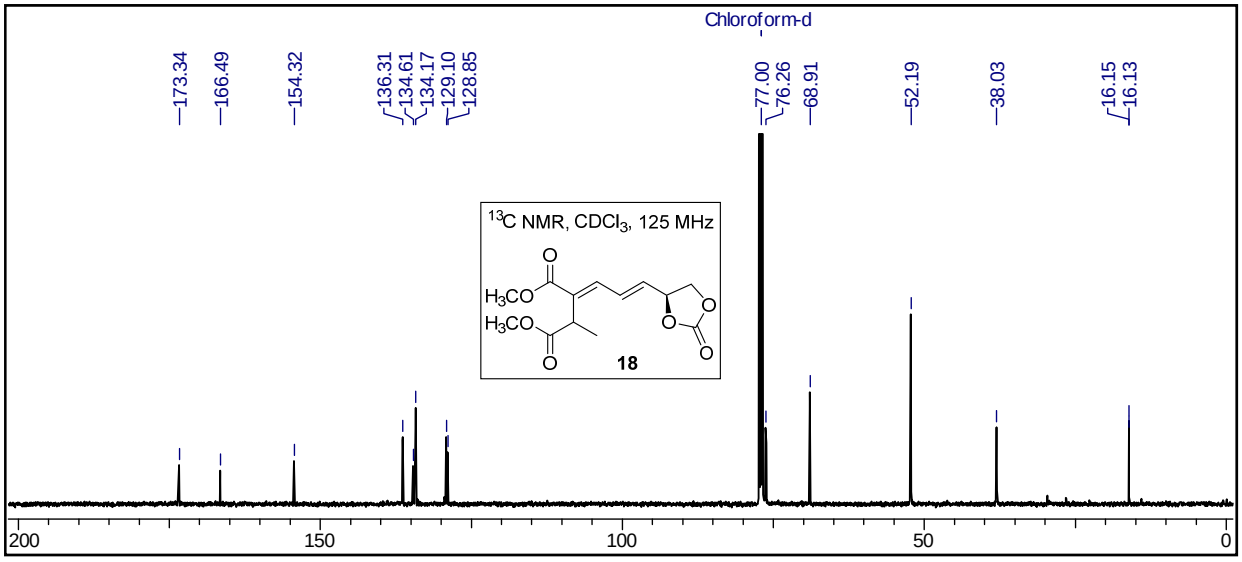

141.64
139.32
138.06
135.43
122.48
13.34
9.75
DEPT NMR, acetone–d_6, 125 MHz
OH
O
O
O
Dehomoitaconitin (**11**)
200
150
100
50
0

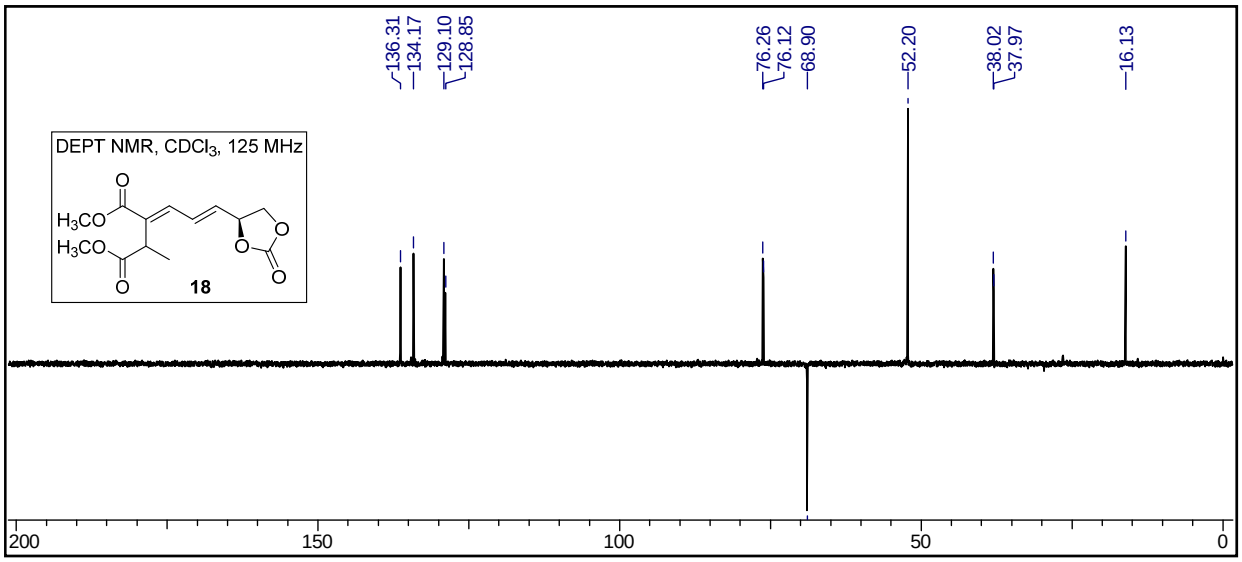

Chloroform-d
7.27
7.22
6.78
6.72
6.70
6.65
5.91
5.89
5.87
5.85
5.84
5.82
5.80
5.78
3.81
3.78
3.76
3.74
3.67
3.48
3.46
3.44
3.09
3.07
3.04
2.74
2.73
2.72
2.70
1.41
1.37
1.37
^{1}H NMR, CDCl$_3$, 200 MHz
H$_3$CO
H$_3$CO
O
O
O
16
1.29
1.00
0.93
4.09
1.00
1.01
1.01
3.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

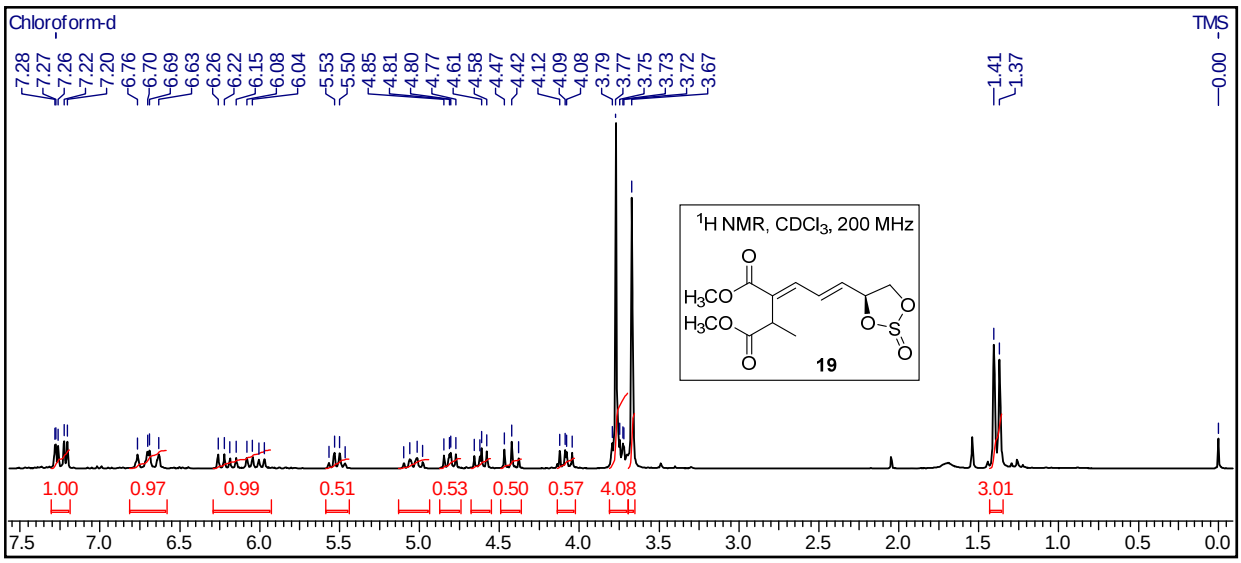

Chloroform-d
173.79
166.96
140.07
137.75
131.72
127.79
127.62
77.00
52.14
52.03
51.63
49.52
37.93
16.13
^{13}C NMR, CDCl$_3$, 125 MHz
H$_3$CO
H$_3$CO
O
O
O
16
200
150
100
50
0


140.07
137.79
137.75
127.78
127.62
52.14
52.03
51.63
49.53
37.93
16.13
DEPT NMR, CDCl$_3$, 125 MHz
H$_3$CO
H$_3$CO
O
O
O
16
200
150
100
50
0


Chloroform-d
TMS
7.27
7.21
6.77
6.71
6.70
6.64
6.16
6.13
6.08
6.05
5.34
5.30
5.26
5.22
4.70
4.66
4.62
4.24
4.20
4.16
3.80
3.78
3.76
3.72
3.71
3.70
3.67
1.41
1.40
1.38
1.37
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
18
1.11
1.00
0.97
1.04
1.04
1.07
4.07
3.10
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


Chloroform-d
173.34
166.49
154.32
136.31
134.61
134.17
129.10
128.85
77.00
76.26
68.91
52.19
38.03
16.15
16.13
^{13}C NMR, CDCl$_3$, 125 MHz
18
200
150
100
50
0


136.31
134.17
129.10
128.85
76.26
76.12
68.90
52.20
38.02
37.97
16.13
DEPT NMR, CDCl$_3$, 125 MHz
18
200
150
100
50
0


Chloroform-d
TMS
7.28
7.27
7.26
7.22
7.20
6.76
6.70
6.69
6.63
6.26
6.22
6.15
6.08
6.04
5.53
5.50
4.85
4.81
4.80
4.77
4.61
4.58
4.47
4.42
4.12
4.09
4.08
3.79
3.77
3.75
3.73
3.72
3.67
1.41
1.37
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
19
1.00
0.97
0.99
0.51
0.53
0.50
0.57
4.08
3.01
7.5
7.0
6.5
6.0
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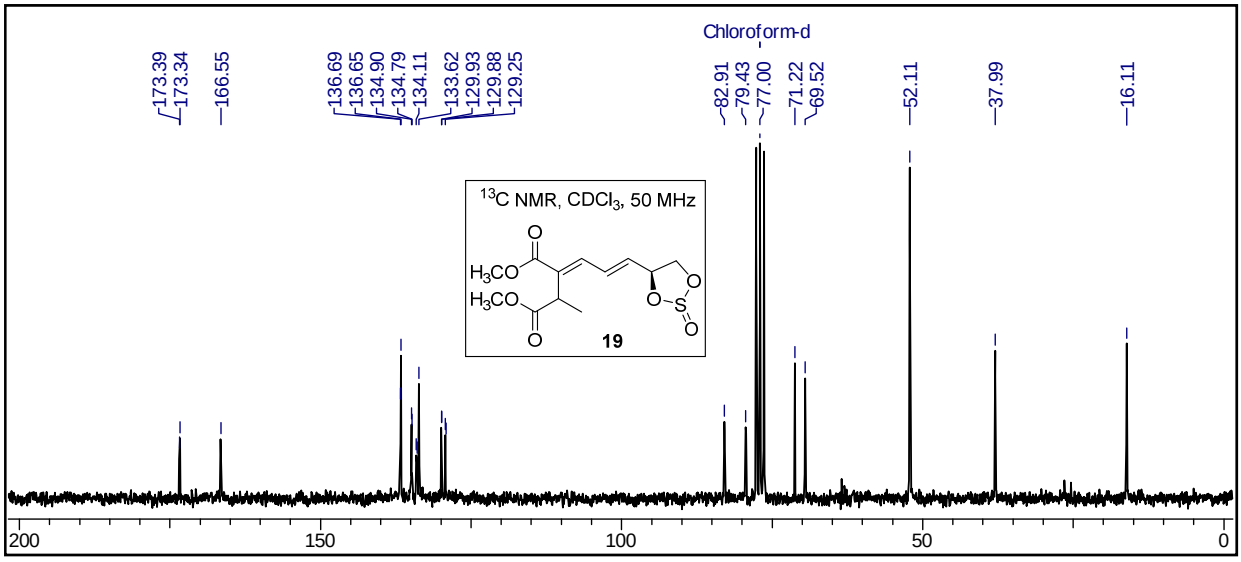
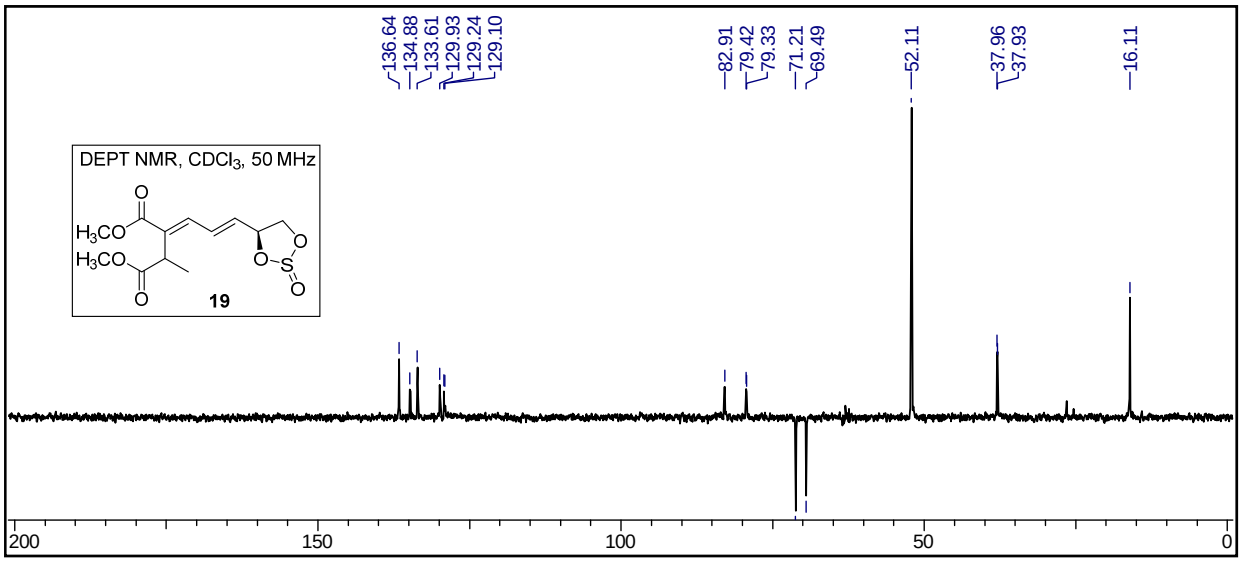

Chloroform-d
173.39
173.34
166.55
136.69
136.65
134.90
134.79
134.11
133.62
129.93
129.88
129.25
82.91
79.43
77.00
71.22
69.52
52.11
37.99
16.11
^{13}C NMR, CDCl$_3$, 50 MHz
19
200
150
100
50
0


136.64
134.88
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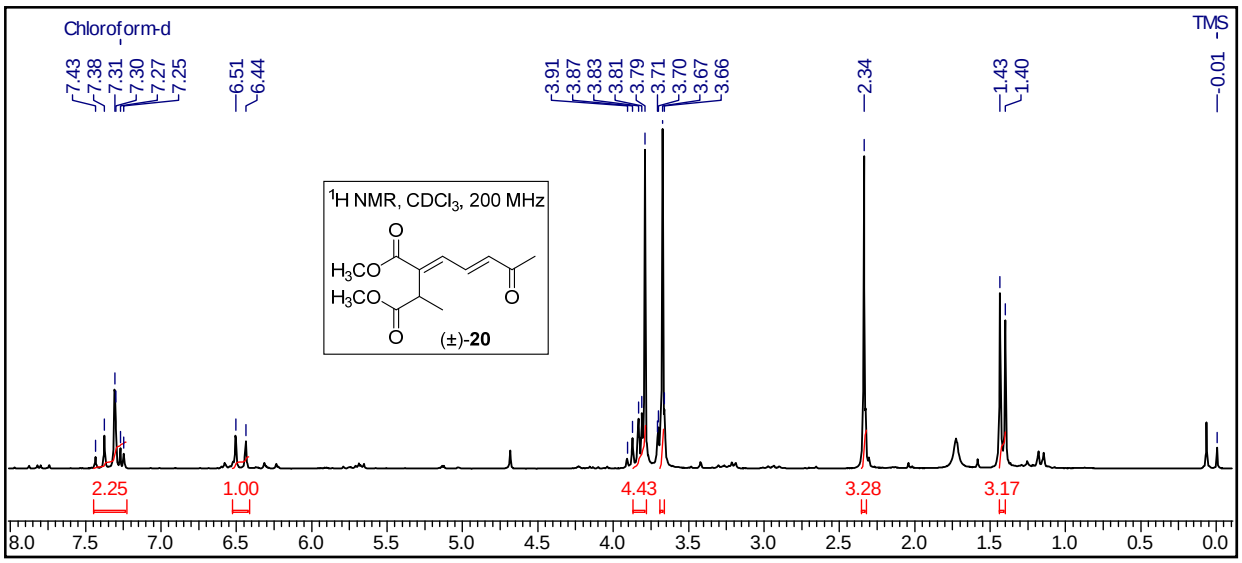
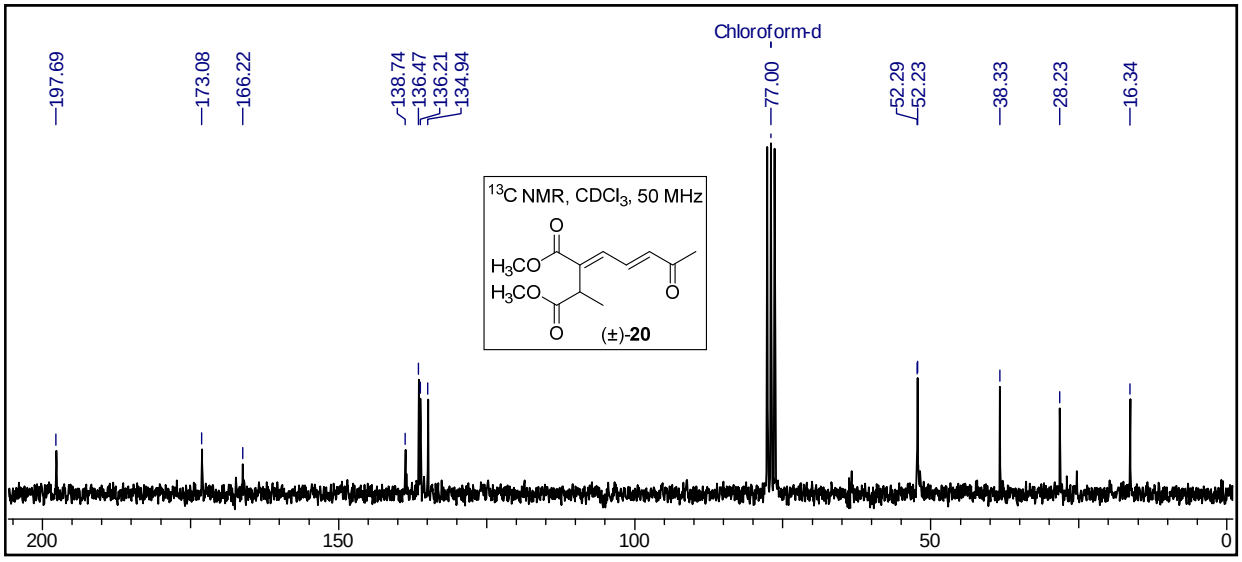
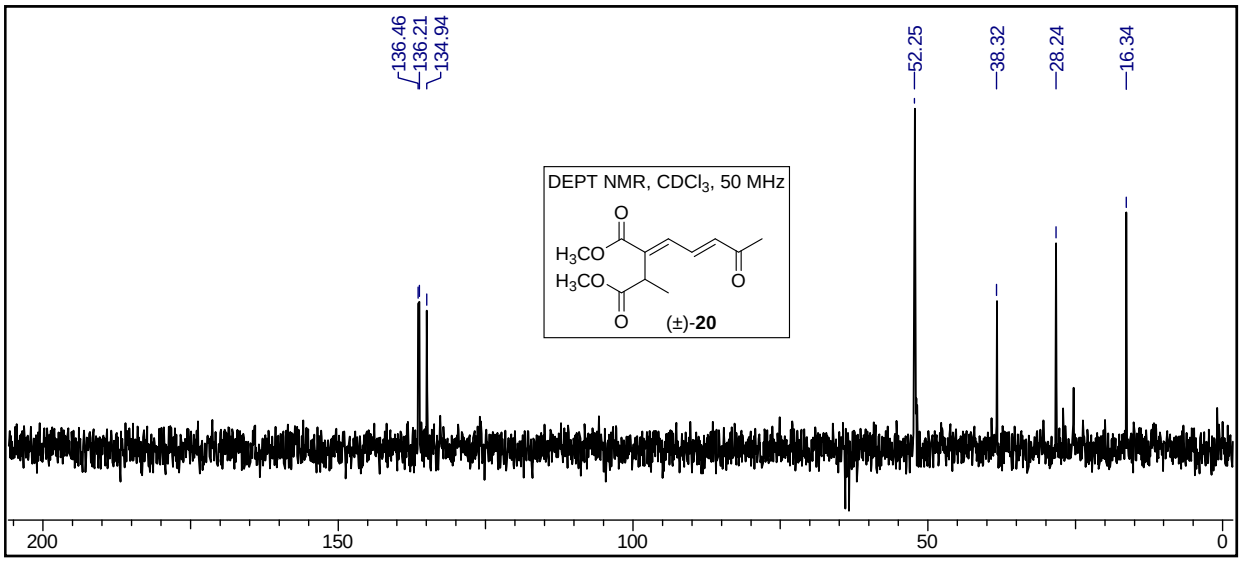
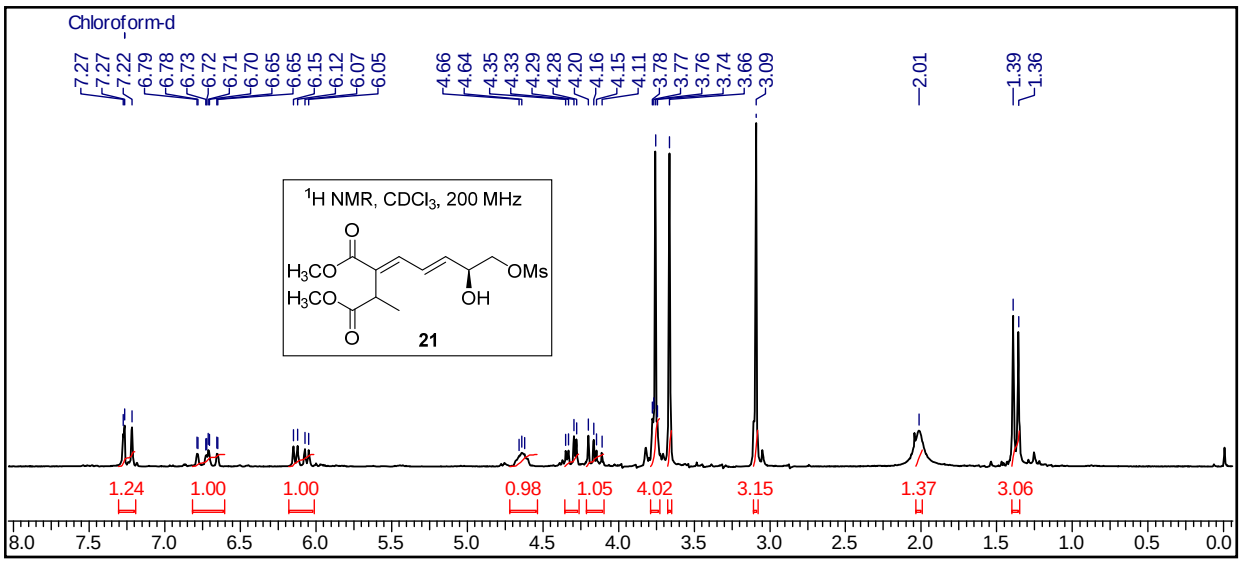
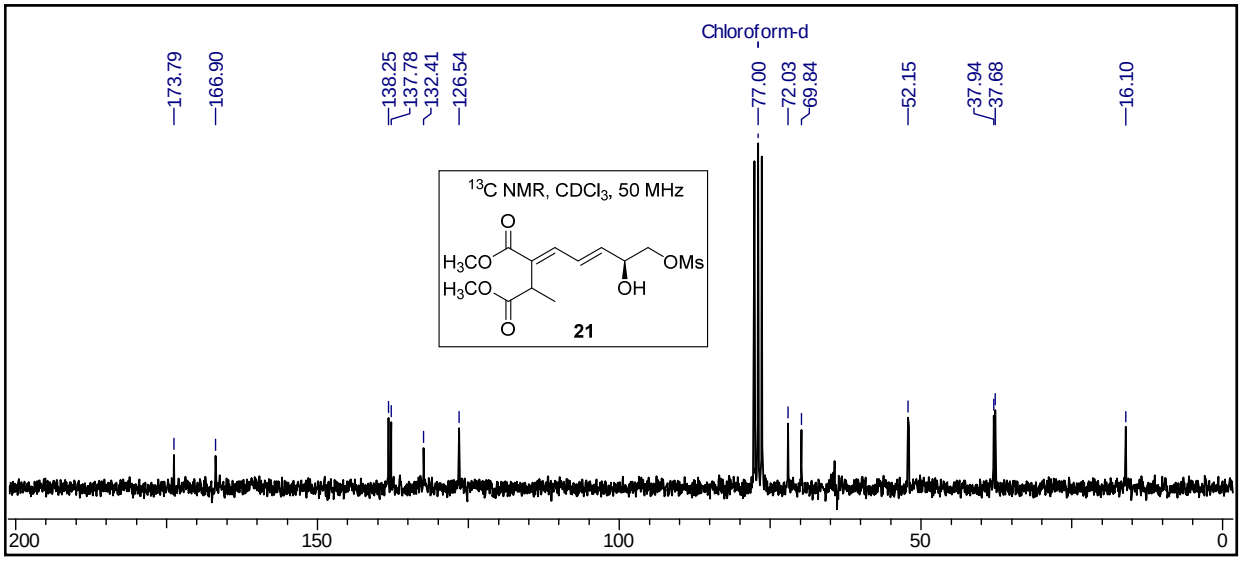
129.93
129.24
129.10
82.91
79.42
79.33
71.21
69.49
52.11
37.96
37.93
16.11
DEPT NMR, CDCl$_3$, 50 MHz
19
200
150
100
50
0

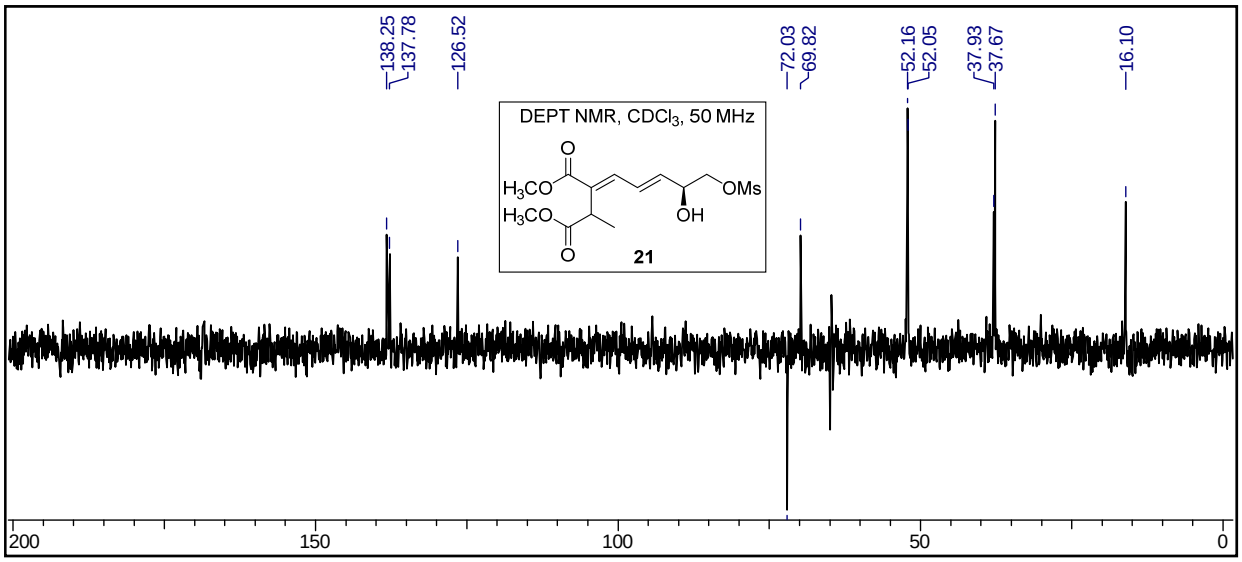

Chloroform-d
TMS
7.43
7.38
7.31
7.30
7.27
7.25
6.51
6.44
3.91
3.87
3.83
3.81
3.79
3.71
3.70
3.67
3.66
2.34
1.43
1.40
0.01
^{1}H NMR, $CDCl_3$, 200 MHz
(±)-20
2.25
1.00
4.43
3.28
3.17
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

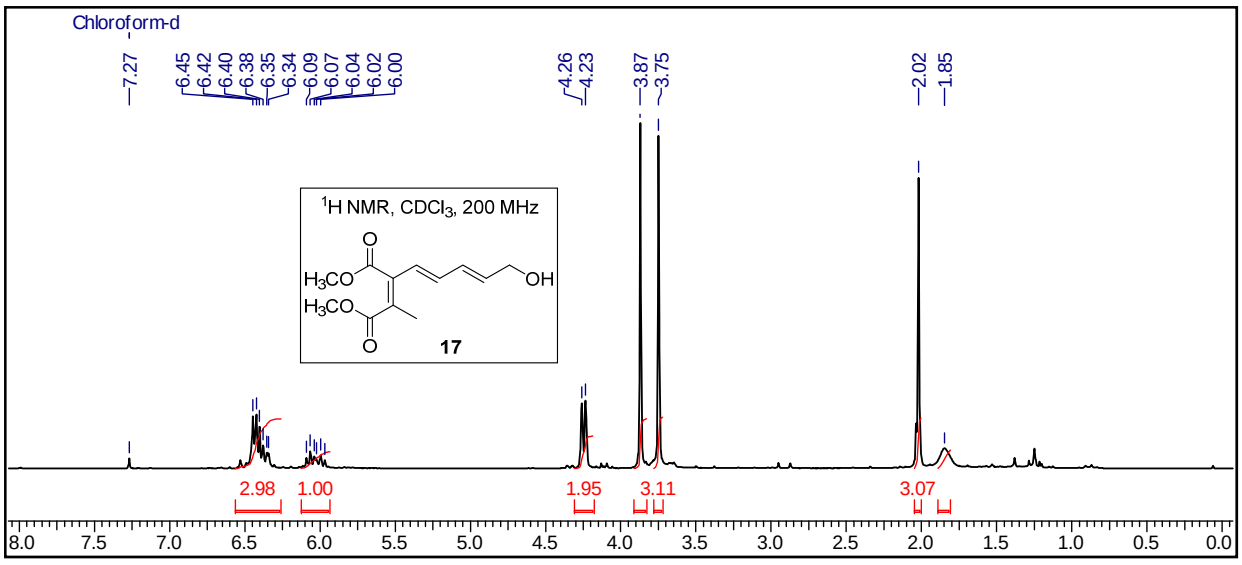

Chloroform-d
197.69
173.08
166.22
138.74
136.47
136.21
134.94
77.00
52.29
52.23
38.33
28.23
16.34
^{13}C NMR, $CDCl_3$, 50 MHz
(±)-20
200
150
100
50
0

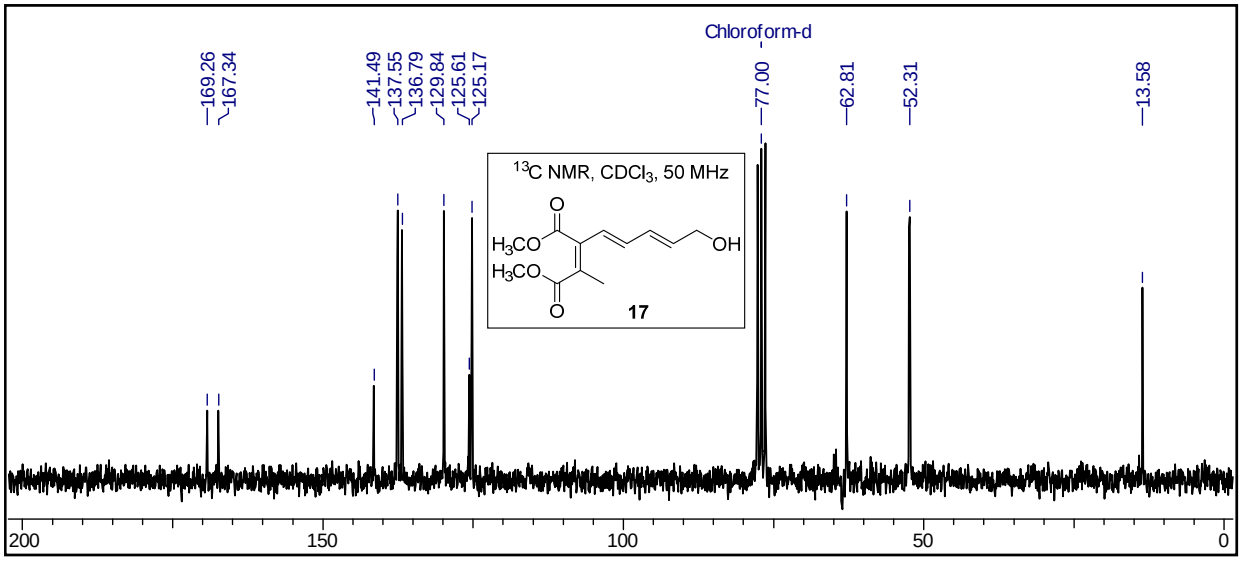

136.46
136.21
134.94
52.25
38.32
28.24
16.34
DEPT NMR, $CDCl_3$, 50 MHz
(±)-20
200
150
100
50
0

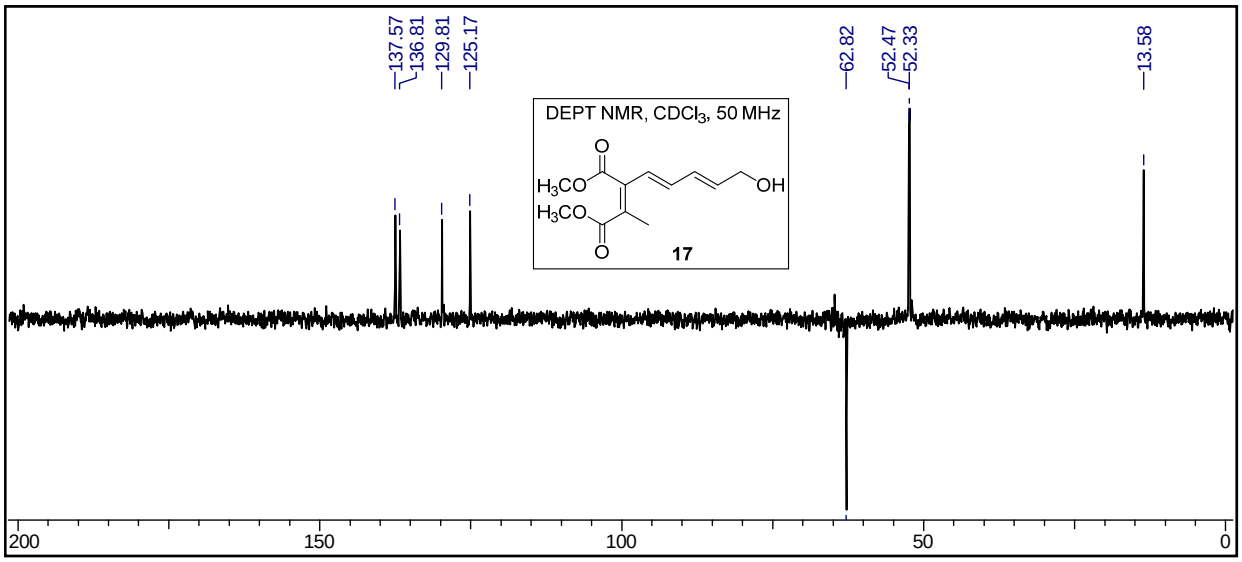

Chloroform-d
7.27
7.27
7.22
6.79
6.78
6.73
6.72
6.71
6.70
6.65
6.65
6.15
6.12
6.07
6.05
4.66
4.64
4.35
4.33
4.29
4.28
4.20
4.16
4.15
4.11
3.78
3.77
3.76
3.74
3.66
3.09
2.01
1.39
1.36
1H NMR, CDCl3, 200 MHz
H3CO
H3CO
OMs
OH
21
1.24
1.00
1.00
0.98
1.05
4.02
3.15
1.37
3.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

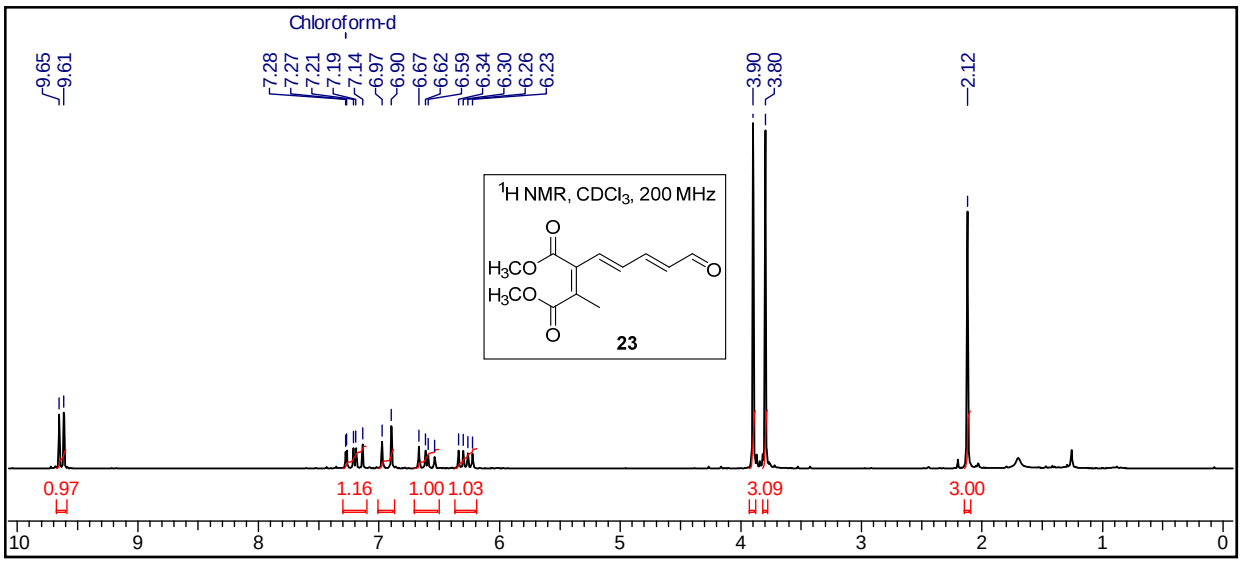

Chloroform-d
173.79
166.90
138.25
137.78
132.41
126.54
77.00
72.03
69.84
52.15
37.94
37.68
16.10
13C NMR, CDCl3, 50 MHz
H3CO
H3CO
OMs
OH
21
200
150
100
50
0

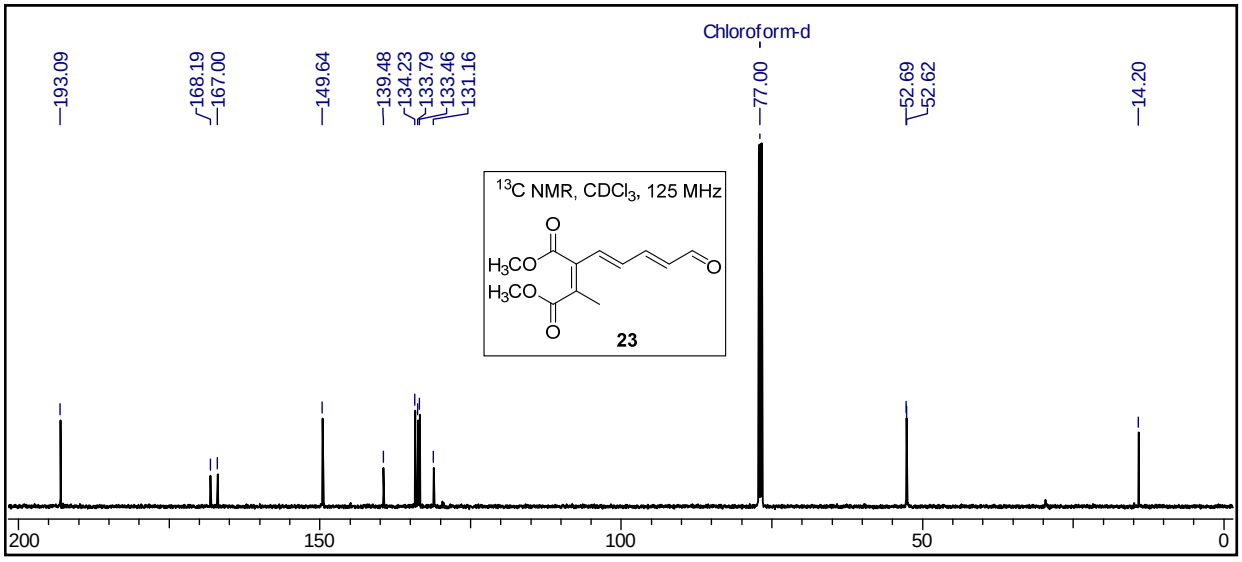

138.25
137.78
126.52
72.03
69.82
52.16
52.05
37.93
37.67
16.10
DEPT NMR, CDCl3, 50 MHz
H3CO
H3CO
OMs
OH
21
200
150
100
50
0

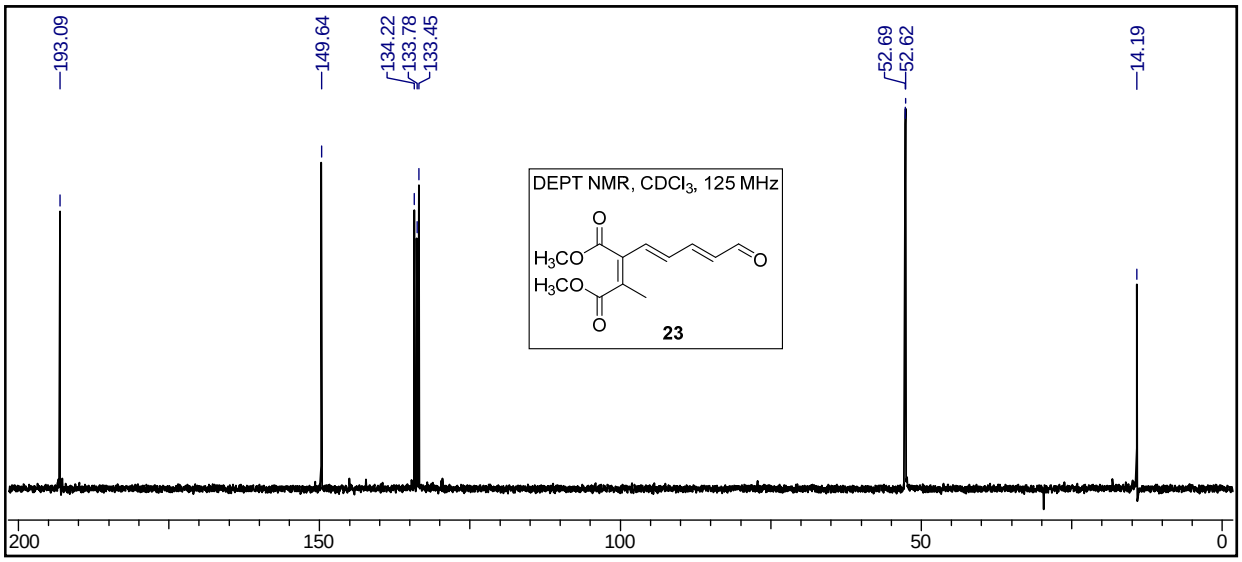

Chloroform-d
7.27
6.45
6.42
6.40
6.38
6.35
6.34
6.09
6.07
6.04
6.02
6.00
4.26
4.23
3.87
3.75
2.02
1.85
^{1}H NMR, $CDCl_3$, 200 MHz
17
2.98
1.00
1.95
3.11
3.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
169.26
167.34
141.49
137.55
136.79
129.84
125.61
125.17
77.00
62.81
52.31
13.58
^{13}C NMR, $CDCl_3$, 50 MHz
17
200
150
100
50
0

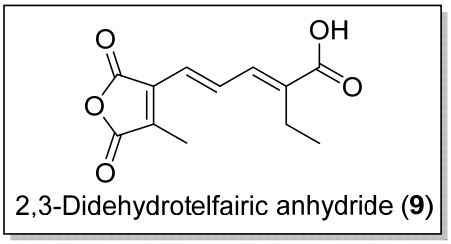

137.57
136.81
129.81
125.17
62.82
52.47
52.33
13.58
DEPT NMR, $CDCl_3$, 50 MHz
17
200
150
100
50
0


Chloroform-d
9.65
9.61
7.28
7.27
7.21
7.19
7.14
6.97
6.90
6.67
6.62
6.59
6.34
6.30
6.26
6.23
3.90
3.80
2.12
^{1}H NMR, CDCl$_3$, 200 MHz
23
0.97
1.16
1.00
1.03
3.09
3.00


Chloroform-d
193.09
168.19
167.00
149.64
139.48
134.23
133.79
133.46
131.16
77.00
52.69
52.62
14.20
^{13}C NMR, CDCl$_3$, 125 MHz
23


193.09
149.64
134.22
133.78
133.45
52.69
52.62
14.19
DEPT NMR, CDCl$_3$, 125 MHz
23

Comparison of ^{1}H and ^{13}C NMR Data between Natural and Synthetic 2,3-Didehydrotelfairic Anhydride in Tabular Form:



2,3-Didehydrotelfairic anhydride (**9**)

^{1}H NMR (acetone–d_6)	
Natural(270 MHz)	**Synthetic**(400 MHz)
1.09 (t, *J* = 7.5 Hz, 3H)	1.11 (t, *J* = 8 Hz, 3H)
2.23 (s, 3H)	2.25 (s, 3H)
2.56 (q, *J* = 7.5 Hz, 2H)	2.57 (q, *J* = 8 Hz, 2H)
6.99 (d, *J* = 15.4 Hz, 1H)	7.03 (d, *J* = 16 Hz, 1H)
7.32 (d, *J* = 11.9 Hz, 1H)	7.34 (d, *J* = 12 Hz, 1H)
7.84 (dd, *J* = 11.9 and 15.4 Hz, 1H)	7.85 (dd, *J* = 12 and 16 Hz, 1H)

^{13}C NMR (acetone–d_6)	
Natural (67.8 MHz)	**Synthetic** (100 MHz)
9.62	9.6
14.74	14.7
21.42	21.4
125.63	125.6
135.80	135.8
136.97	136.9
137.19	137.2
140.35	140.3
140.65	140.7
165.49	165.5
166.82	166.8
168.30	168.4

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Overall Conclusion and Perspective

Present dissertation describes our concise and efficient approaches for the synthesis of various bioactive maleic anhydrides and their derivatives based natural and unnatural products implementing novel synthetic strategies along with the concise account of the relevant contemporary literature. Maleic anhydrides, maleimides and butenolides containing natural products bear the fascinating structures and their remarkable bioactivity has incited a lot of activity in the organic chemist's community towards their isolation, characterization, total synthesis and biological screening. Metal catalyzed cross-coupling reactions have gained nobel attention in recent years. A brief re-materialization of the concise literature account on the metal catalyzed cross-coupling reactions of halomaleic anhydrides and halomaleimides leading to bioactive natural and unnatural products has been portrayed. (+)-Paeonilide is most promising anti-PAF agent and a schematic summary of previously reported four elegant synthetic approaches for this eminent natural product has been described in detail. A large number of alkyl(methyl)maleic anhydrides with a broad range of bioactivities have been isolated as the natural products since 1950. Novel synthetic approaches to biologically active natural/synthetic maleic anhydrides have been reported by various research groups. A composed literature report on the various synthetic approaches for alkyl(methyl)maleic anhydrides along with their promising biological activities has been presented.

In the present dissertation work, we have demonstrated an efficient approach to the various monoalkyl substituted maleimides, maleic anhydrides and butenolides for the first time by employing Sonogashira cross-coupling reaction on halomaleimides. The present general approach has been successfully utilized for the synthesis of several alkynyl, alkenyl and alkyl substituted maleimides involving the chemo-, regio-, and stereoselective reduction reactions. This protocol has been further extended to accomplish the first total synthesis of two natural butenolides namely, luffarin X and cacospongionolide C. The serendipitously witnessed intramolecular nucleophilic oxygen insertion at the γ-position of 3,4-disubstituted butenolide with unusual double bond isomerisation led us the new reactivity in butenolides. The redox-neutral protocol with the insertion of oxygen at the electron rich position in butenolide coupled with reduction of internal carbon–carbon double bond provided the paeonilide skeleton in highly diastereoselective fashion. We have successfully explored this newly

developed reactivity umpolung conception to accomplish simple and efficient total synthesis of (±)-paeonilide with a very good overall yield. We have also presented the first total synthesis of natural 2,3-didehydrotelfairic anhydride and unnatural alkenyl(methyl)maleic anhydrides starting from simple substrate, the dimethyl maleate. The Wittig reaction, methylation followed by innovative 1,2-, 1,4- and 1,6-elimination reactions and HWE-reaction strategy were the key points in accessing this intriguing class of compounds. The 1,2-eliminations in cyclic carbonate/sulfite by regioselective abstraction of methine proton with release of CO_2/SO_2 provided a conjugated ketone product. The characteristic 1,4-elimination in cyclic ketal with release of acetone and the 1,6-elimination of remotely placed mesylate in open chain system lead to the corresponding allylic alcohols. Both the allylic alcohols were systematically transformed into conjugative alkenyl(methyl)maleic anhydrides via oxidation followed by HWE reactions pathway. Although the biological screening of these fascinating structures have been not reported yet, we feel that the conjugative alkenyl(methyl)maleic anhydrides will exhibit strong RFTase inhibitory activity.

All above specified studies provided us an excellent opportunity for learning lot of new basic and applied chemistry not just from our research work point of view but also from the vast literature in this field. We also feel that the approaches which we have developed are quite general and biogenetic in nature and would be useful in designing several structurally similar important natural products and natural product hybrids for structure activity relationship studies. A look at the recent literature also revealed that the histogram of the maleic anhydride, maleimide and butenolide chemistry is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed maleic anhydride/imides and butenolides would maintain the high positive slope in the present day world of medicinal and synthetic chemistry. In our opinion, a combination of natural and hybrid anhydrides and their derivatives would serve as a launching pad to fight against new generation diseases. Finally, on the basis of exposure to the literature of anhydride chemistry and our contribution to the same, it can be said with assurance that, in future, this significant discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry.

List of Publications

1. Sonogashira Coupling Reactions of Halomaleimides: Route to Alkyne/(*cis*)-Alkene/Alkyl Maleimides: Total Synthesis of Luffarin X and Cacospongionolide C
   Prashant S. Deore and Narshinha P. Argade*
   J. Org. Chem. **2012**, *77*, 739.

2. Reactivity Umpolung in Intramolecular Ring Closure of 3,4-Disubstituted Butenolides: Diastereoselective Total Synthesis of Paeonilide
   Prashant S. Deore and Narshinha P. Argade*
   Org. Lett. **2013**, *15*, 5826.

3. Metal Catalyzed Cross-Coupling Reactions of Halomaleic Anhydrides and Halomaleimides: Synthesis of Structurally Interesting and Biologically Important Natural and Unnatural Products (**Short Review**)
   Prashant S. Deore* and Narshinha P. Argade*
   Synthesis (*In Press*), December 2013.

4. Synthesis of Chenopanone
   Prashant S. Deore and Narshinha P. Argade*
   Manuscript Communicated (*Indian J. Chem. Sec. B*), October 2013.

5. Base Stimulated Novel 1,2-, 1,4- and 1,6-Eliminations in Alkylidenesuccinates: Stereoselective Total Synthesis of Natural and Unnatural Conjugated Alkenyl(methyl)maleic Anhydrides
   Prashant S. Deore and Narshinha P. Argade*
   Manuscript Under Preparation.

6. A Concise Account on Chemistry of Imperative Alkyl(methyl)maleic Anhydrides (**Review**)
   Prashant S. Deore, Kishan P. Haval, Smita R. Gadre and Narshinha P. Argade*
   Manuscript Under Preparation.