NUCLEOPHILIC REACTIONS OF CYCLIC ANHYDRIDES AND THEIR DERIVATIVES: FACILE SYNTHESIS OF BIOACTIVE NATURAL AND UNNATURAL COMPOUNDS

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IN

CHEMISTRY

BY

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Dedicated to my Parents….

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Nucleophilic Reactions of Cyclic Anhydrides and their Derivatives: Facile Synthesis of Bioactive Natural and Unnatural Compounds''*** which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Md. Merajuddin Baag*** 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.

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Candidate's Declaration

I hereby declare that the thesis entitled "***Nucleophilic Reactions of Cyclic Anhydrides and their Derivatives: Facile Synthesis of Bioactive Natural and Unnatural Compounds***" submitted by me for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune*** is the record of work carried out by me during the period of July, 2002 to November, 2007 and has not been submitted by me for a degree to any other University or Institution. This work was carried out at the Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune, India.

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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 and (silica gel, 60-120 mesh/100-200 mesh/230-400 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol) and bromocresol green (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (conc. 1 μM) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), MSL 300 and ACF 300 (300 MHz for ^{1}H NMR and 75 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 recorded on Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.
- Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser. Elemental analyses observed for all the newly synthesized compounds were within the limits of accuracy (± 0.3%).
- All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
- All the compounds previously known in the literature were characterized by comparison of their R_f values on TLC, IR and NMR spectra as well as melting point 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.
- During the thermal condensation reactions with α,β-unsaturated aldehydes, always some polymeric material forms which also makes difficult the purification of products.
- **Independent referencing and numbering of compounds, schemes, tables & figures have been employed for each Section.**

ABBREVIATIONS

AIBN	2,2'-Azobisisobutyronitrile
Aq.	Aqueous
Bn	Benzyl
Boc	*t*-Butoxy carbonyl
Cat.	Catalytic
CCDC	Cambridge crystallographic data centre
CSA	10-Camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBP	Dibenzoyl peroxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarization Transfer
DHP	Dihydropyran
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulphoxide

DMPU	N'N'-Dimethyl-N'N'-propylene urea
EDCI	*N*-Ethyl-*N'*-(3-dimethylaminopropyl) carbodiimide hydrochloride
dr	Diastereomeric ratio
ee	Enantiomeric excess
equiv.	Equivalent(s)
h	Hour(s)
HIV	Human immunodeficiency virus
HMPA	Hexamethylphosphoramide
HOBT	1-Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IBX	Iodoxybenzoic acid
IR	Infra Red
KHMDS	Potassium 1,1,1,3,3,3-hexamethydisilazane
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LiHMDS	Litium hexamethyldisilazide
m-CPBA	*m*-Chloroperbenzoic acid
min.	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
Mp	Melting point
MS 4Å	Molecular sieves (4Å)
MS	Mass Spectrum
NBS	*N*-Bromosuccinimide

NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
ORTEP	Orthogonal Thermal Ellipsoid Plots
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PPA	Polyphosphoric acid
p-TSA	*p*-Toluenesulfonic acid
p-TsCl	*p*-Toluenesulfonyl chloride
Py	Pyridine
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS / TBS	*t*-Butyldimethylsilyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
Tlc/TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Trimethylchlorosilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPAP	Tetrapropylammonium perruthenate
TPP	Triphenylphosphine

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Abstract

The present dissertation is divided into two chapters. The first chapter presents a short

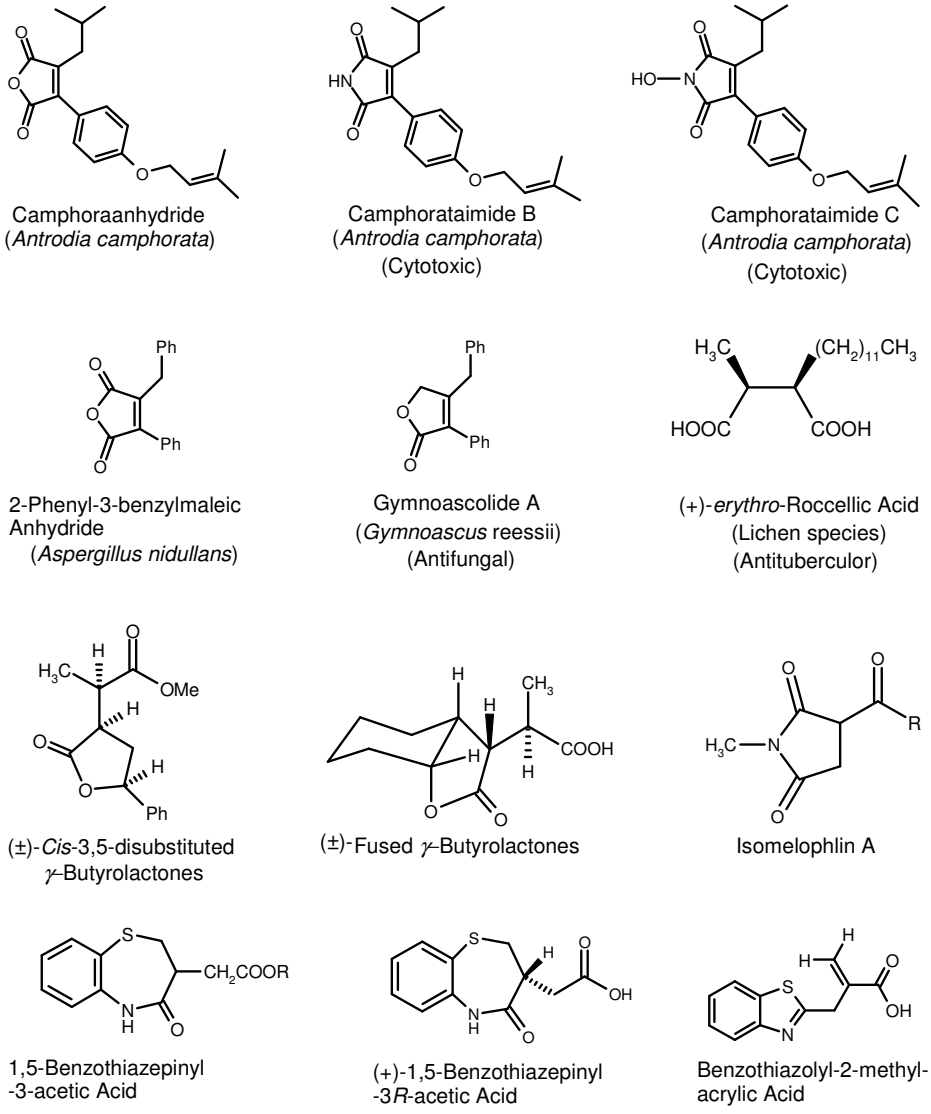


Figure 1. Natural Products and Unnatural Compounds Synthesized

overview of the chemistry of itaconic acid and derivatives followed by description of our efforts towards the chemo-, regio- and stereoselective reactions of *o*-aminothiophenol and *o*-aminophenyl disulphide with itaconic anhydride and (−)-dimenthyl itaconate, simple synthesis of enantiomerically pure 1,5-benzothiazepines, synthesis of unnatural isomelophilin A and studies towards the synthesis of natural melophilin A. In the second chapter, concise account on the chemistry of dialkyl bromomethylfumarate precede a description of our studies towards the synthesis of dimethyl bromomethylfumarate and development of new methodology for *Z*- to *E*- alkene isomerization using *N*-bromosuccinimide-dibenzoyl peroxide/azobisisobutyronitrile, synthesis of gymnoascolide A, camphorataanhydride, camphorataimides B & C, (+)-*erythro*-roccellic acid, diastereoselective synthesis of *cis*-3,5-disubstituted *γ*-butyrolactones and fused *γ*-butyrolactones.

Chapter One: A Concise Account on the Chemistry of Itaconic Acid and Derivatives and their Uses in the Synthesis of Heterocycles and Tetramic Acid Derivatives

This chapter is divided into three sections. The first section provides a short overview on the chemistry of itaconic acid and derivatives while the second section describes our effort in using itaconic anhydride for the synthesis of enantiomerically pure 1,5-benzothiazepines and the third section summarizes our studies in using itaconimide for the synthesis of unnatural isomelophilin A and studies towards the synthesis of natural melophilin A. Subsequently, the detailed experimental procedures, analytical and spectral data and some selected spectra have been illustrated. Independent scheme numbers, structure numbers and references have been given for each section.

Section A: A Concise Account on the Chemistry of Itaconic Acid and Derivatives

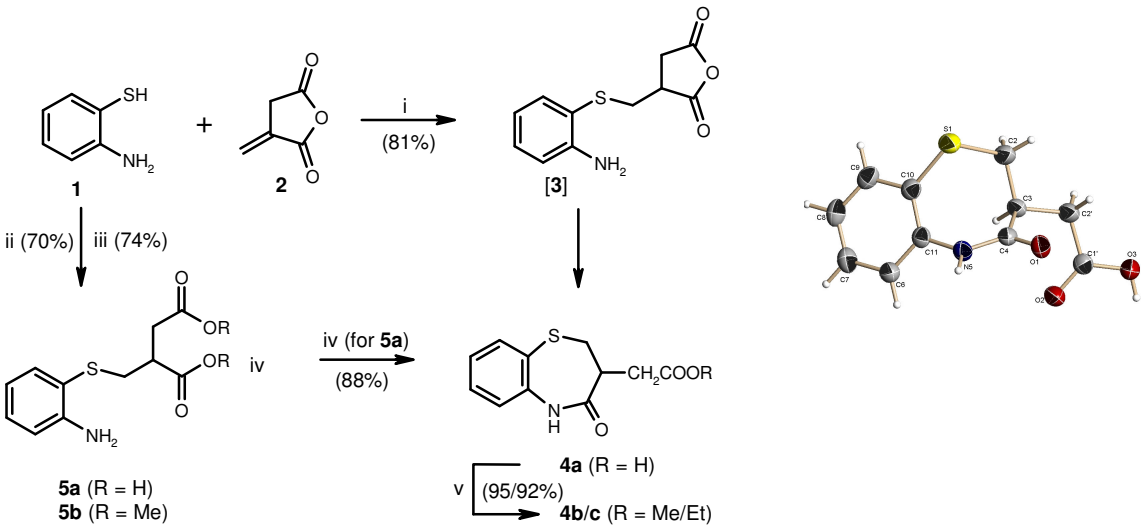
Itaconic acid, itaconic anhydride, itaconates and itaconimides are the multifunctional entity and hence have been extensively used for the construction of variety of heterocyclic structures in past century. Itaconic acid and derivatives are practically used in the synthesis of variety of key intermediates employed in the heavy and fine chemical industries and as such these compounds have been often used to model (i) compounds highlighting regiochemical dichotomy, (ii) heterocyclic skeletons, (iii) natural products and their precursors, (iv) bioactive molecules and (v) series of polymers with tailored material

characteristics. This chapter portrays a concise account on synthesis and use of these itaconic acid derivatives for the synthesis of bioactive natural products and heterocycles, followed by references.

<u>Section B</u>: Chemo-, Regio- and Stereoselective Reactions of *o*-Aminothiophenol and *o*-Aminophenyl Disulfide with Itaconic Anhydride and (–)-Dimenthyl Itaconate: Simple and Efficient Access to Enantiomerically Pure 1,5-Benzothiazepines

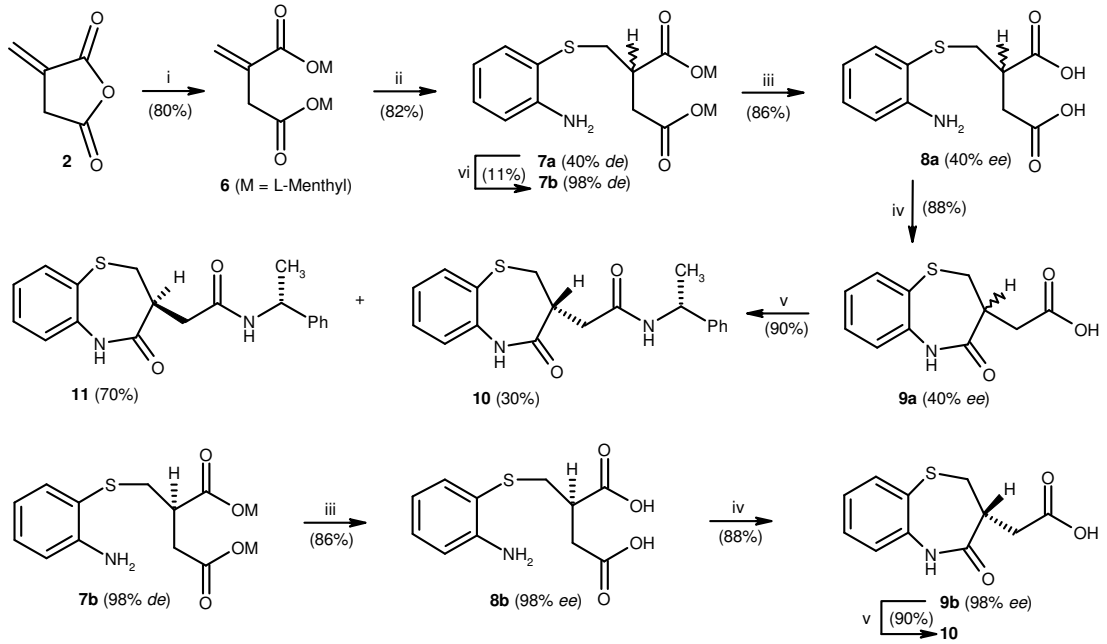
Heterocycles play a pivotal role in pharmaceutical and agrochemical industries. The 1,5-benzothiazepines are known to have antimitochondrial, antiinflammatory, anticancer, and anti-HIV activities. Development of new facile routes to these seven-membered 1,5-benzothiazepines is a challenging task of current interest.

In this section we report the short and simple synthesis of enantiomerically pure 1,5-benzothiazepine. We felt that, with a proper combination of reactivity and selectivity, the itaconic anhydride (**2**) and *o*-aminothiophenol (**1**) could be used as potential building blocks to synthesize higher-membered heterocycles. Reaction of anhydride **2** with *o*-ATP in THF at room temperature furnished 7-membered benzothiazepine **4a** in 81% yield (Scheme 1). The formation of the 7-membered benzothiazepine **4a** was confirmed by X-ray crystallographic data.



Scheme 1. *Reagents, conditions and yields*: (i) THF, rt, 12 h (81%); (ii) Itaconic acid, THF, rt, 36 h (70%); (iii) Dimethyl itaconate, THF, rt, 24 h (74%); (iv) *N*-Ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide hydrochloride, DMAP (cat.), THF, rt, 4 h (88%); (v) CH_3OH/C_2H_5OH, H^+/H_2SO_4, 50 °C, 2 h (95/92%).

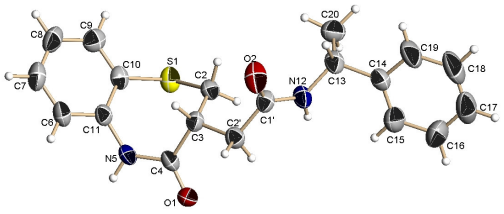
The stereoselective reaction of *o*-ATP with the chiral diester dimenthyl itaconate **6** in dry acetic acid at room temperature furnished the desired adduct **7a** with 82% yield. The ^{1}H NMR data of product **7a** revealed that the reaction was moderately stereoselective and the mixture of two diastereomers was formed in nearly 7:3 ratio (Scheme 2). The adduct **7a** on acid catalyzed hydrolysis gave the diacid **8a** in 86% yield. As expected, the carbodiimide induced regioselective ring closure of **8a** yielded the 1,5-benzothiazepinyl-1,3-acetic acid (**9a**) in 88% yield. Finally, for the separation of the two enantiomers of **9a** and their stereochemical assignments, we transformed **9a** into two diastereomers **10** and **11** in 90% yield, by reacting **9a** with (+)-(*R*)-phenylethylamine. The mixture of diastereomers **10** and **11** was easily separated by flash column chromatography to obtain pure **10** and **11** with quantitative recovery (**10**:**11** = 30:70). The mixture of diastereomers in **7a** was semi-



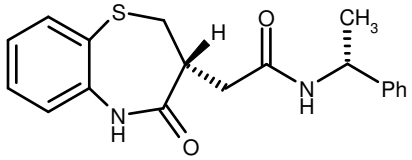
Scheme 2. *Reagents, conditions and yields*: (i) Itaconic anhydride, L-menthol, *p*-TSA, toluene, reflux, 36 h (80%); (ii) *o*-Aminothiophenol, dry AcOH, rt, 36 h (82%); (iii) (a) AcOH:HCl (3:1), reflux, 12 h, (b) 10% Aq. $NaHCO_3$, (c) AcOH (86%); (iv) *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride, DMAP (cat.), THF, rt, 4 h (88%); (v) (*R*)-(+)-1-Phenylethylamine, *N*-ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide hydrochloride, DMAP (cat.), THF, rt, 4 h (10:11 = 3:7, 90%); (vi) Three recrystalisations from petroleum ether (11%).

solid in nature and after three successive recrystalisations from petroleum ether (60-80), gave the minor diastereomer **7b** as a fine amorphous powder with only 11% recrystalisation yield, but with 98% *de*. This observation indicates that the major isomer has higher solubility in petroleum ether. Due to the amorphous nature of **7b**, we were

unable to get the X-ray crystallographic data to fix the stereochemistry of the newly generated chiral centre. The single isomer **7b** on hydrolysis followed by ring closure gave the desired enantiomerically pure 1,5-benzothiazepinylacetic acid (**9b**) in 76% yield. The reaction of **9b** with (+)-(*R*)-phenylethylamine gave compound **10** in 90% yield. On the basis of X-ray crystallographic data of diastereomer **10**, we could assign the (*R*)-configuration to the newly generated chiral centre in **7b** & **10** and hence consequently, the (*S*)-configuration to the chiral centre in **11**.

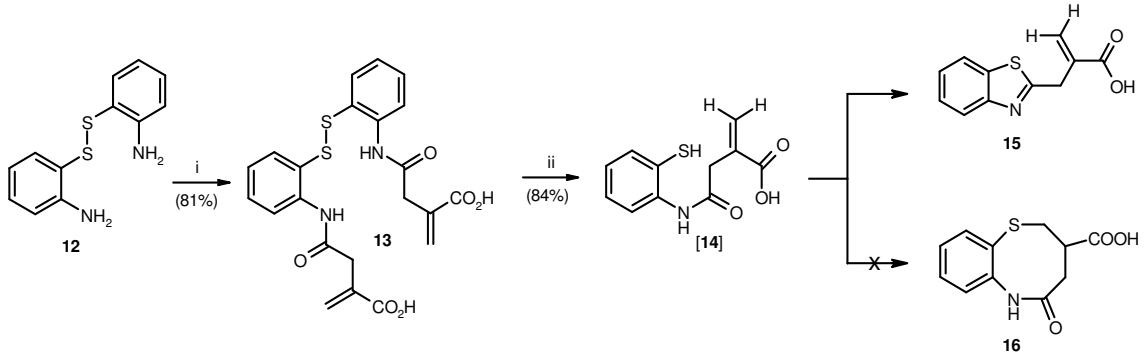


ORTEP Diagram of **10.**



10 (30%)

As the activation of α,β-unsaturated double bond by the carboxylic acid unit in itaconic acid is sufficient for Michael type addition of thiol unit from *o*-ATP, we felt that the *o*-mercapto-α-methylenesuccinanilic acid (**14**) would be a potential precursor for the synthesis of benzothioazocine **16**. Hence to obtain the acid **14**, we performed the reaction of 2-aminophenyl disulfide (**12**) with 2.20-equivalents of itaconic anhydride in THF at room temperature and obtained the dicarboxylic acid **13** in 81% yield (Scheme 3). The triphenylphosphine induced reductive cleavage of sulfur-sulfur bond in diacid **13** formed the expected but inisolable intermediate acid **14**, which on an in situ intramolecular-dehydrative cyclization furnished the 2-benzothiazo-2-ylmethylacrylic acid (**15**) in 84% yield and not the expected benzothioazocine **16**, indicating the relative reluctance in **14** for the intramolecular Michael type addition of thiol to form the eight-membered heterocycle.



Scheme 3. *Reagents, conditions and yields*: (i) Itaconic anhydride, THF, rt, 8 h (81%); (ii) PPh_3, 1,4-dioxane:water (4:1), H^+/HCl, rt, 2 h (84%).

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

<u>Section C</u>: Synthesis of Isomelophlin A and Studies Towards the Synthesis of Melophlin A

Compounds which reverse the transformed phenotype caused by *ras* have high potential as a new type of anti-cancer agents. Recently, two novel tetramic acids having such activity, melophlin A & B, were isolated from the Indonesian marine sponge *Melophlus sarassinorum*. One synthesis of melophlin A is reported. In this section we describe the synthesis of unnatural isomelophlin A (**2**) and our studies towards the synthesis of natural melophlin A (**1**).

The synthesis of isomelophlin A (**2**), an unnatural compound starts with the Wittig coupling of hexadecanal with *N*-methyl maleimide (**3**) to give the imide **4**, dihydroxylation of imide **4** provided dihydroxy compound **5**. The diol **5** when refluxed in acetic anhydride for dehydration, we got the diacetoxy compound **6**. However, when the diol **5** was subjected to dehydration using H_2SO_4 adsorbed on silica gel furnished isomelophlin A (**2**) in 3 steps and 55% overall yield (Scheme 1).

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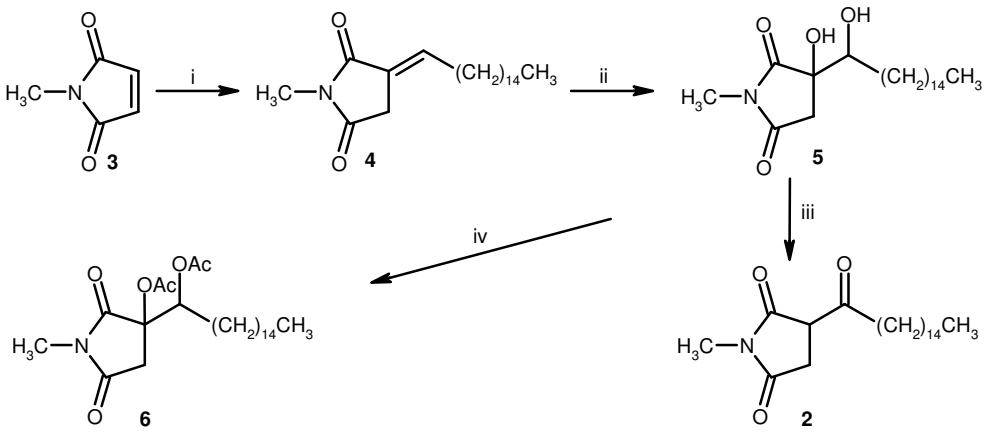
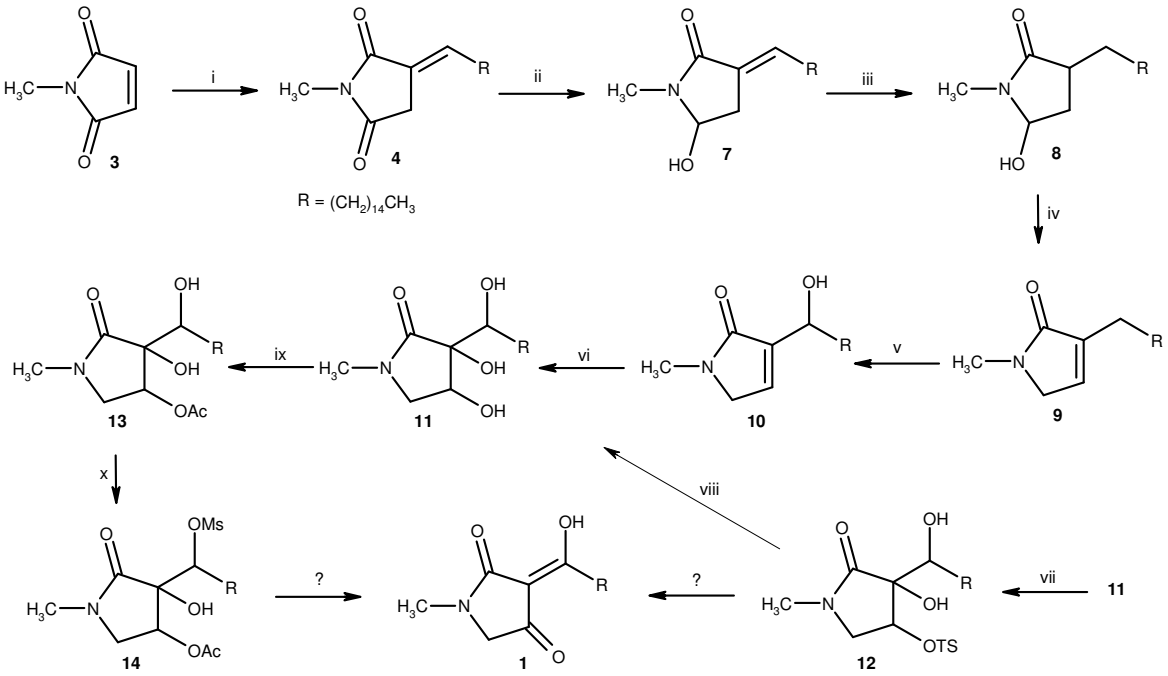


Scheme 1. *Reagents, conditions and yields*: (i) PPh_3, hexadecanal, THF, reflux, 8 h (96%); (ii) OsO_4, NMO, *t*-BuOH, rt, 36 h (88%); (iii) Conc. H_2SO_4 on silica-gel (0.5 mL in 5 g), toluene, reflux, 24 h (60%); (iv) Ac_2O, reflux, 5 h (80%).

Our studies towards the synthesis of melophilin A start with the Wittig coupling of hexadecanal with *N*-methyl maleimide (**3**) to give the imide **4**, which was regioselectively reduced to afford the hydroxyl lactam **7**, which on further reduction using Pd-C and

hydrogen gave hydroxylactam **8**. Dehydration followed by SeO_2 induced selective allylic oxidation gave lactam **10**, which on OsO_4 oxidation gave triol **11**. Triol **11** on tosylation gave the monotosylated lactam **12**. Lactam **12** when treated with NaH gave back the unprotected triol **11** but not the expected epoxide. Futher triol **11** was converted to monoacetate lactam **13** by treating with acetic anhydride in pyridine. Monoacetate lactam **13** on reaction with MsCl in presence of Et_3N gave the mesyl and acetate protected lactam **14** in 80% yield. We are in search of suitable reaction conditions to get meliphilin A from the triol **18** and the work is under active progress in our laboratory (Scheme 2).



Scheme 2. *Reagents, conditions and yields*: (i) PPh_3, hexadecanal, THF, reflux, 8 h (96%); (ii) $NaBH_4$, THF-H_2O (10:1), rt, 12 h (95%); (iii) H_2, Pd-C, MeOH, rt, 4 h (90%); (iv) Amberlyst, CH_3CN, reflux, 6 h (85%); (v) SeO_2, EtOH, reflux, 10 h (75%); (vi) OsO_4, NMO, *t*-BuOH, rt, 36 h (88%); (vii) *p*-TSCl, Et_3N, DMAP, CH_2Cl_2, rt, 6 h (90%); (viii) NaH, THF, rt 4 h (90%); (ix) Ac_2O, pyridine, CH_2Cl_2, rt, 12 h (95%); (x) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 10 h (80%).

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

Chapter Two: A Concise Account on the Chemistry of Dialkyl Bromomethylfumarates and their Uses in the Synthesis of Natural and Unnatural Compounds

This Chapter is divided into three sections. The first section portrays a short account on the chemistry of dialkyl bromomethylfumarate and also a report on their applications in organic synthesis. While the second section describes our studies towards the synthesis of dimethyl bromomethylfumarate, development of new methodology for *Z*- to *E*- alkene isomerization using *N*-bromosuccinimide-dibenzoyl peroxide/azobisisobutyronitrile and Grignard coupling reaction for the synthesis of gymnoascolide A, camphorataanhydride, camphorataimides B & C and (+)-*erythro*-roccellic acid, and the third section portrays our studies towards the use of dimethyl bromomethylfumarate for the diastereoselective synthesis of *cis*-3,5-disubstituted *γ*-butyrolactones and fused *γ*-butyrolactones. Subsequently, the detailed experimental procedures, analytical and spectral data and some selected spectra have been illustrated. Independent scheme numbers, structure numbers and references have been given for each section.

Section A: A Concise Account on the Chemistry of Dialkyl Bromomethylfumarates

Dialkyl bromomethylfumarates are a useful synthons in organic synthesis. Dialkyl bromomethylfumarates are multifunctional entity and hence have been extensively used for the construction of variety of heterocyclic structures. S_N2'-coupling reactions of different Grignard reagents, Wittig reagents and the Diels-Alder reactions with dialkyl bromomethylfumarates have been extensively used for the synthesis of several bioactive natural products and unnatural compounds. This section portrays a concise account on synthesis, use of dialkyl bromomethylfumarate for the synthesis of bioactive natural products and heterocycles.

Section B: Synthesis and S_N2' Grignard Coupling Reactions with Dialkyl Bromomethylfumarate

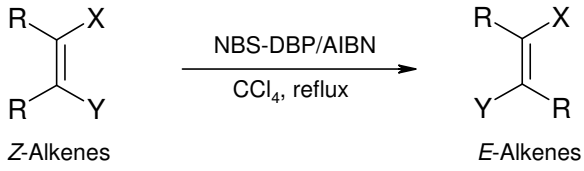
This section describes our approach towards the synthesis of dimethyl bromomethylfumarate, development of new methodology for *Z*- to *E*- alkene isomerization using *N*-bromosuccinimide-dibenzoyl peroxide/azobisisobutyronitrile and Grignard coupling reactions for the synthesis of 2-phenyl-3-benzylmaleic anhydride,

gymnoascolide A, camphorataanhydride, camphorataimides B & C and (+)-*erythro*-roccellic acid.

N-Bromosuccinimide-Dibenzoyl Peroxide/Azobisisobutyronitrile: A Reagent for *Z*- to *E*-Alkene Isomerization

In our on going studies towards the synthesis of several recently isolated bioactive natural products, we carried out the reaction of dimethyl methylmaleate with NBS-AIBN and obtained dimethyl bromomethylfumarate in 85% yield. Both allylic bromination and isomerization of the carbon-carbon double bond took place in one-pot via an in situ addition-elimination of the bromine radical, which was further confirmed by obtaining the same product from dimethyl methylfumarate. This section describes our studies on the NBS-DBP/AIBN induced *Z*- to *E*-carbon-carbon double bond isomerization of olefins having variety of substituents (Scheme 1).

Scheme 1

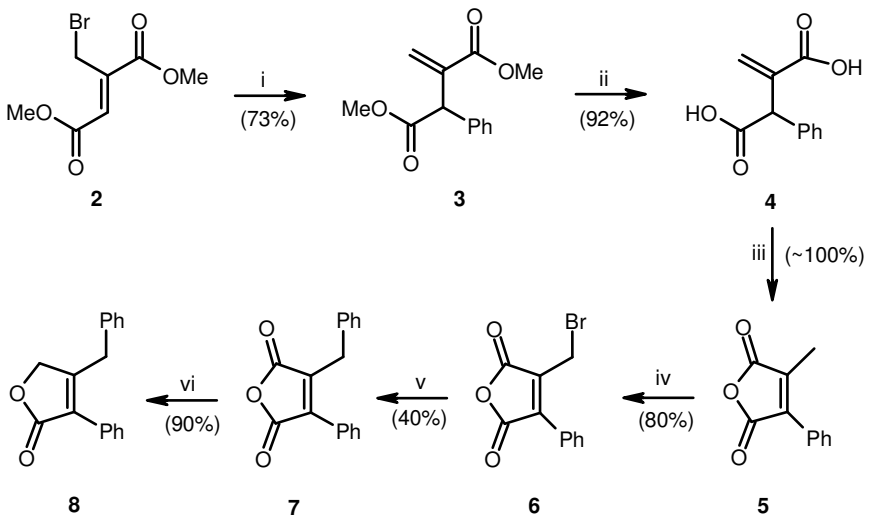


R = H, CO_2H, CO_2Me; X/Y = H, Me, Alkyl, CH_2Br, $CHBr_2$, Ph, Aryl, CO_2Me, CONHAr

Synthetic of Natural Antifungal Gymnoascolide A

Gymnoascolide A was isolated from the Australian soil ascomycete *Gymnoascus* reessii, while 2-phenyl-3-benzylmaleic anhydride was isolated from terrestrial fungi *Aspergillus nidullans*. Gymnoascolide A possesses moderate, selective activity against the pathogenic plant fungus *Septoria nodorum*. Till date, no synthesis of gymnoascolide A has been reported. We envisaged dimethyl bromomethylfumarate (**2**) as a potential starting material for the stepwise construction of natural product Gymnoascolide A (**8**). The chemoselective S_N2' coupling reaction of phenylmagnesium bromide with **2** exclusively gave the desired arylalkylidenesuccinic diester **3** in 73% yield. The base catalyzed hydrolysis of diester **3** to diacid **4** followed by acetic anhydride induced ring closure gave the expected phenylmethylmaleic anhydride (**5**) in nearly 100% yield. The NBS-bromination of the allylic carbon in the anhydride **5** furnished the required bromoanhydride **6** in 80% yield. The chemoselective allylic substitution of bromo atom in anhydride **6** with

phenylmagnesium bromide gave the natural product 2-phenyl-3-benzylmaleic anhydride (**7**), which on N-selectride induced regioselective reduction, exclusively provided the natural product Gymnoascolide A (Scheme 2).

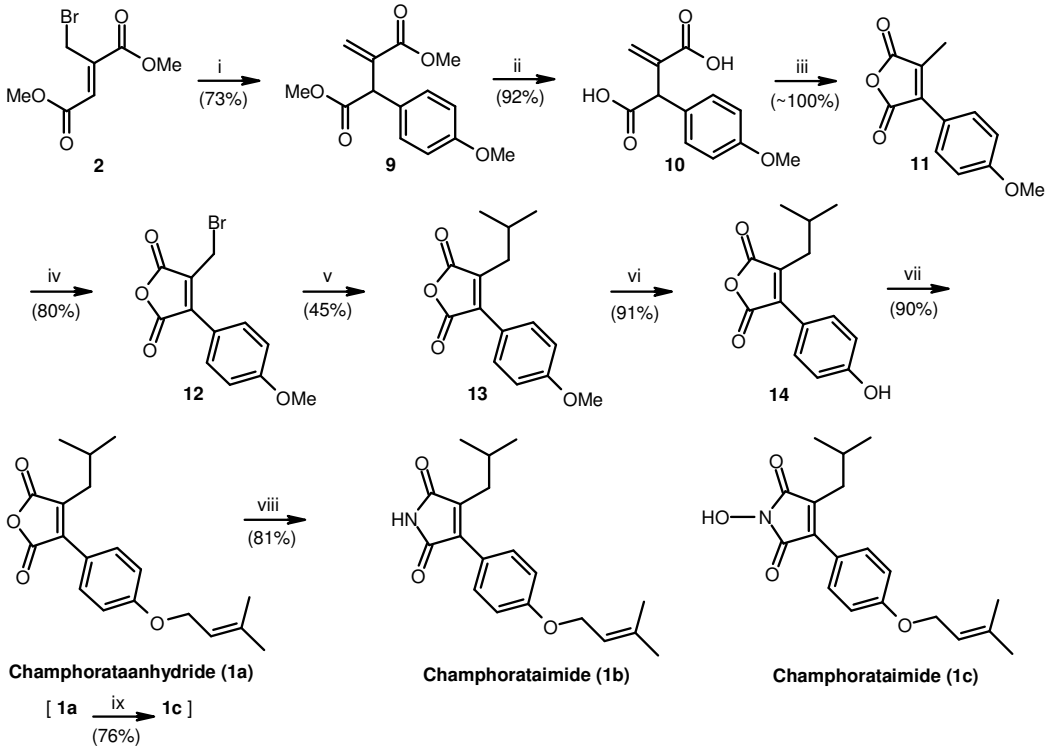


Scheme 2. *Reagents, conditions and yields*: (i) C_6H_5MgBr (1.5 equiv.), THF, HMPA, –20 ºC, 0.5 h (73%); (ii) (a) LiOH (10.0 equiv.), THF + H_2O (3:1), rt, 18 h, (b) H^+/HCl (92%); (iii) Ac_2O, reflux, 1.5 h (~100%); (iv) NBS (1.5 equiv.), DBP (10 mol%), CCl_4, reflux, 12 h (80%); (v) C_6H_5MgBr (5.0 equiv.), THF, HMPA, CuI, 0 ºC, 8 h (40%); (vi) N-Selectride, THF, -78 ºC, 2 h (90%).

Synthesis of Natural Cytotoxic Camphorataimides B & C

Recently camphorataanhydride/imides were isolated from the mycelium of *Antrodia camphorata* and the imides **1b**,**c** showed appreciable cytotoxic effects on LLC tumor cells. Recently one synthesis of these natural products is reported. We envisaged dimethyl bromomethylfumarate (**2**) as a potential starting material for the stepwise construction of natural products **1a**-**c** and their various analogs. The chemoselective S_N2' coupling reaction of *p*-methoxyphenylmagnesium bromide with **2** exclusively gave the desired arylalkylidenesuccinic diester **9** in 73% yield. The base catalyzed hydrolysis of diester **9** to diacid **10** followed by acetic anhydride induced ring closure gave the expected anhydride **11** in nearly 100% yield. The NBS-bromination of the allylic carbon in the anhydride **11** furnished the required bromoanhydride **12** in 80% yield. The chemoselective allylic substitution of bromo atom in anhydride **12** with isopropylmagnesium bromide gave the 2-(*p*-methoxyphenyl)-3-isobutylmaleic anhydride (**13**) in 45% yield. Boron tribromide induced demethylation of **13** provided the corresponding 2-(*p*-hydroxyphenyl)-3-isobutylmaleic anhydride (**14**) in 91% yield. Allylation of anhydride **14** with 3,3-

dimethylallyl bromide in the presence of K_2CO_3 furnished the naturally occurring camphorataanhydride A (**1a**) in 90% yield. The anhydride **1a** was heated with urea at 130 ºC for one hour to obtain the natural bioactive camphorataimide B (**1b**) in 81% yield. Treatment of anhydride **1a** with hydroxylamine hydrochloride in refluxing pyridine gave the desired third bioactive natural product camphorataimide C (**1c**) in 76% yield (Scheme 3).

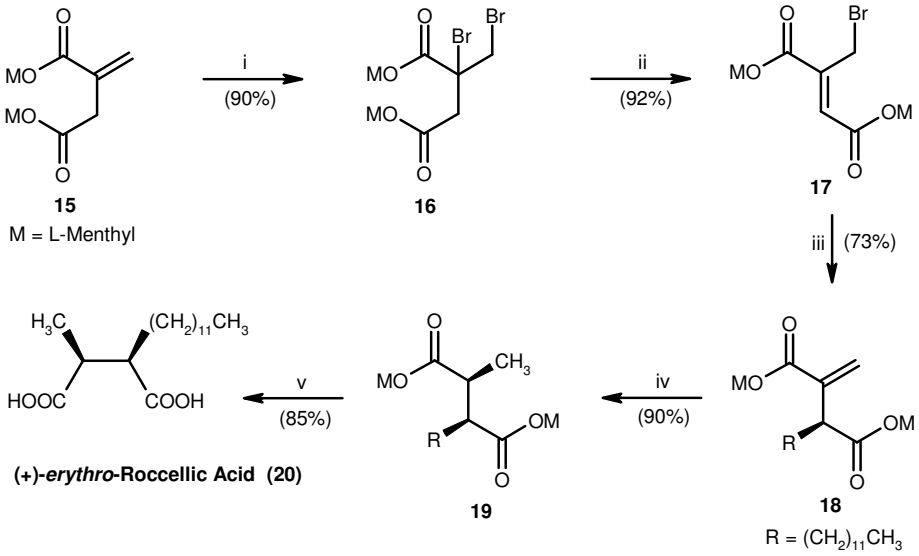


Scheme 3. *Reagents, conditions and yields*: (i) *p*-CH_3O-C_6H_4MgBr (1.5 equiv.), THF, HMPA, –20 ºC, 0.5 h (73%); (ii) (a) LiOH (10.0 equiv.), THF + H_2O (3:1), rt, 18 h, (b) H^+/HCl (92%); (iii) Ac_2O, reflux, 1.5 h (~100%); (iv) NBS (1.5 equiv.), DBP (10 mol%), CCl_4, reflux, 12 h (80%); (v) C_3H_7MgBr (5.0 equiv.), CuI (0.1 equiv.), THF, HMPA, –5 to 0 ºC, 8 h (45%); (vi) BBr_3 (5 equiv.), DCM, –78 to 0 ºC, 12 h (91%); (vii) 3,3-Dimethylallyl bromide (1.2 equiv.), K_2CO_3 (10 equiv.), acetone, reflux, 2 h (90%); (viii) Urea (1.1 equiv.), 130 ºC , 1 h (81%); (ix) $NH_2OH.HCl$, pyridine, reflux, 2 h (76%).

Synthesis of (+)-*erythro*-Roccellic Acid

Roccellic acid has been isolated from variety of naturally occurring lichen species and it is well known for antituberculor activity. Its absolute configuration has been proved to be (2*R*, 3*S*)-2- dodecyl-3-methylbutanedioic acid. Till date, three racemic synthesis of roccellic acid, of which the most recent one is from our group and one asymmetric synthesis have been reported. Dimenthyl itaconate **15** on bromination and dehydrobromination gave dimenthyl bromomethylfumarate **17**. The chemoselective S_N2'

coupling reaction of **17** with dodecylmagnesium bromide gave the itaconate derivative **18** with the desired C_{12} substituent, which on catalytic hydrogenation followed by hydrolysis furnished the natural product (+)-*erythro*-Roccellic (**20**) with only 33% de (Scheme 4). Further work is under progress in our laboratory to improve the diastereomeric excess using different chiral auxiliaries derived from camphor.



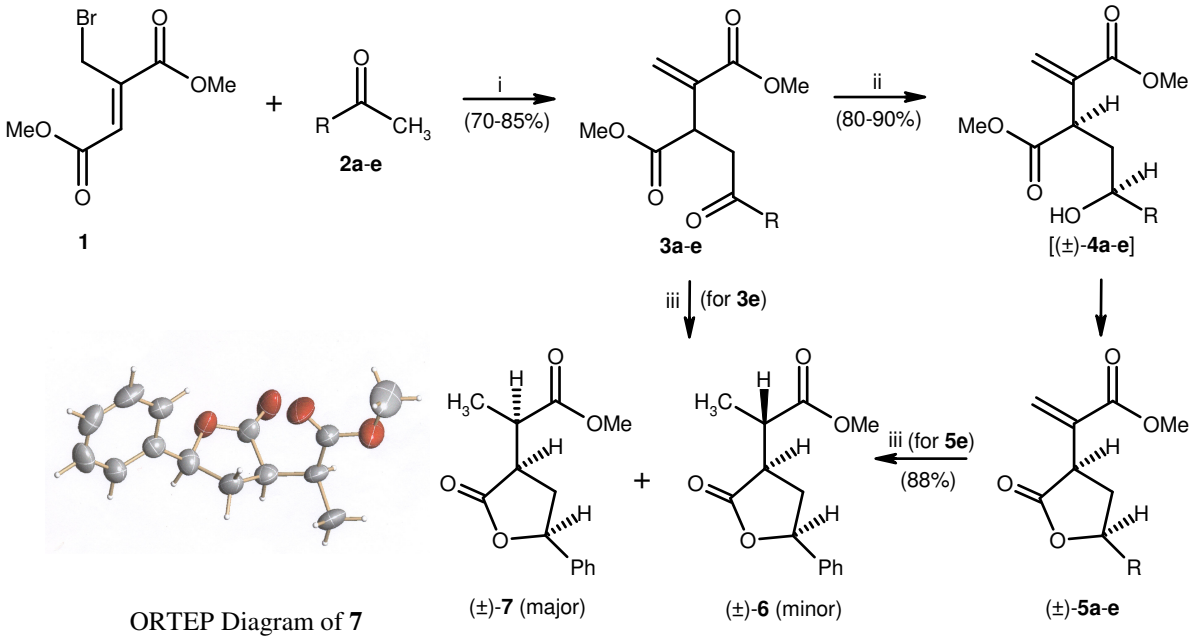
Scheme 4. *Reagents, conditions and yields*: (i) Br_2, CCl_4, rt, 12 h (90%); (ii) Et_3N, CCl_4, rt, 6 h (92%); (iii) $C_{12}H_{25}MgBr$ (1.5 equiv.), THF, HMPA, 0 ºC, 0.5 h (73%) (33% *de*); (iv) H_2, Pd-C, MeOH, rt, 4 h (90%) (33% *de*); (v) AcOH:HCl (3:1), reflux, 10 h (85%) (33% *ee*).

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

<u>Section C</u>: A Facile Chemo-, Regio- and Diastereoselective Synthesis of *cis*-3,5-Disubstituted *γ*-Butyrolactones and Fused *γ*-Butyrolactones

The natural and unnatural *γ*-butyrolactones are an important class of compounds that find major applications in organic, medicinal and polymer chemistry. A very large number of such *γ*-butyrolactones have been synthesized during the past century using several elegant synthetic strategies. This section illustrates our approach for the synthesis of these *γ*-butyrolactones using S_N2'-coupling reactions of alkyl methyl ketones with dimethyl bromomethylfumarate followed by a reductive regioselective cyclization to constitute a simple two-step approach to 3,5-disubstituted *γ*-butyrolactones via the [3 + 2] annulation

pathway. The chemoselective S_N2'-coupling reaction of primary enolates of alkyl methyl ketones **2a**-**e** with dimethyl bromomethylfumarate (**1**) at -78 °C furnished ketodiester **3a**-**e** in 70-85% yields. Upon treatment of the ketodiesters **3a**-**e** with $NaBH_4$ (1.50 equiv) in methanol at room temperature, a highly diastereoselective reduction of the ketone carbonyl group took place with the attack of hydride ion from the less hindered side (Cram addition) to generate the unisolable pair of enantiomers of hydroxydiesters (±)-**4a**-**e**, which on an in situ regioselective lactonization with the more reactive non-conjugated ester moiety furnished the *cis*-3,5-disubstituted lactones (±)-**5a**-**e** in 80-90% yields (Scheme 1).



ORTEP Diagram of **7**

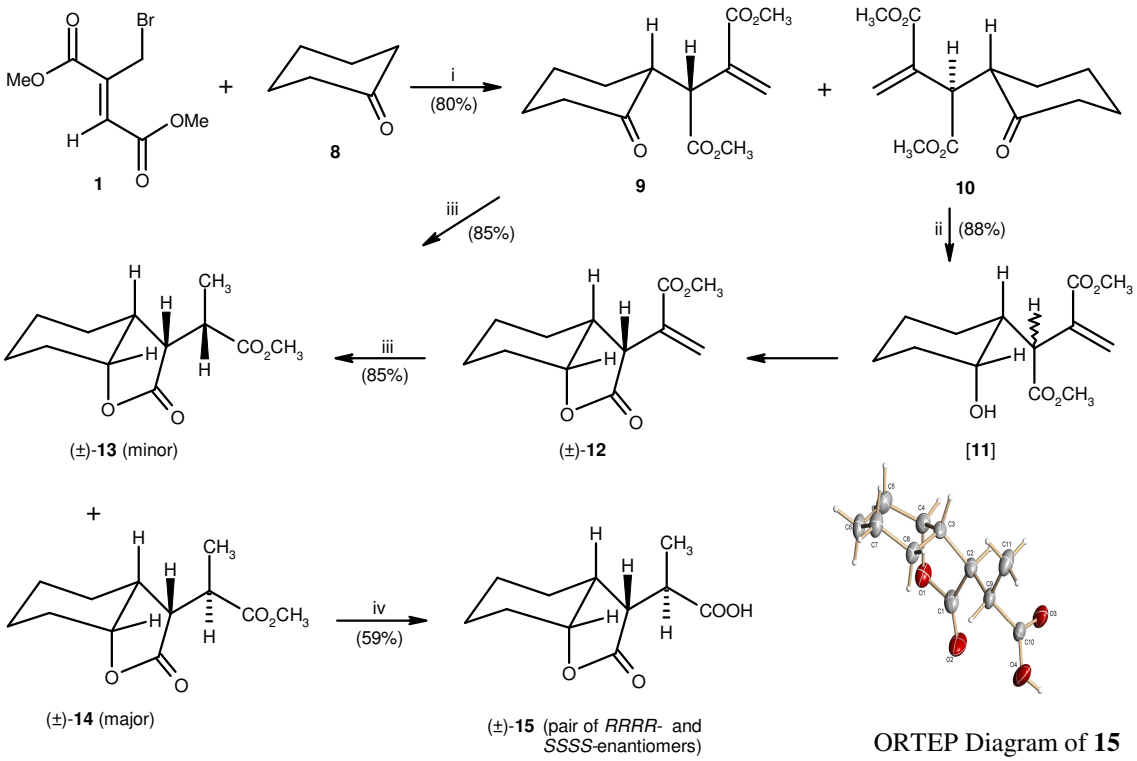
a, R = CH_2CH_3; **b**, R = $CH_2(CH_2)_2CH_3$; **c**, R = $CH_2(CH_2)_5CH_3$; **d**, R = $CH_2(CH_2)_8CH_3$; **e**, R = Ph.

Scheme 1. *Reagents, conditions and yields*: (i) LDA, THF, –78 ºC, 20 min (**3a**, 80%; **3b**, 78%; **3c**, 72%; **3d**, 70%; **3e**, 85%); (ii) $NaBH_4$ (1.5 equiv.), MeOH, rt, 15 min (**5a**, 88%; **5b**, 85%; **5c**, 82%; **5d**, 80%; **5e**, 90%); (iii) $NaBH_4$ (3.0 equiv.), MeOH, rt, 1 h (88%, **6**:**7** = 1:9).

The ^{1}H NMR data of these lactones **5a**-**e** revealed that they are formed with ~100% diastereoselectivity. Treatment of the lactonylacrylate **5e** with $NaBH_4$ in methanol at room temperature for 1 hour facilitated the reduction of the carbon-carbon double bond with a Michael type addition of the hydride ion followed by a highly diastereoselective acquisition of a proton from the less hindered side leading to the formation of a mixture of diastereomers (±)-**6** and (±)-**7** in a 1:9 ratio (by ^{1}H NMR) with 88% yield. Similarly (±)-**3e** too, on treatment with an excess of $NaBH_4$, directly furnished the mixture of (±)-**6** and (±)-

7 in nearly the same ratio and yield. The mixture of **6** and **7** on recrystallization from dichloromethane provided analytically pure (±)-**7** with 69% recrystallization yield. The structure of (±)-**7** thus obtained was established on the basis of analytical and spectral data and it was unambiguously confirmed on the basis of X-ray crystallographic data.

Next, we prepared a plan to synthesize the fused γ-butyrolactones using the present S_N2'-coupling reaction. Towards this, we performed the S_N2' coupling of cyclohexanone enolate with **1** at -78 °C and obtained the coupling product in 80% yield. The ^1H and ^{13}C NMR spectrum of the coupled product showed two sets of signals with nearly equal intensities, suggesting that a column inseparable mixture of diastereomers is formed in nearly equal proportions. However, the S_N2' coupling of **1** and the cyclohexanone enolate, with an attack of the expected axial carbanion, was partly diastereoselective at -100 °C, resulting in mixture of diasteriomers **9** and **10** in a nearly 8:2 ratio. The observed face selective coupling could be ascribed to the steric interactions between **1** and axial carbanionic species of **8** and/or the thermodynamic stability of the formed major diastereomer **9**. Interestingly, the mixture of diastereomers **9** and **10** (1:1/8:2) underwent a very stereospecific $NaBH_4$ reduction of ketone group at room temperature with a less hindered equatorial approach of the hydride ion to generate the axial alcohols, which, upon in situ cyclization, exclusively furnished the octahydrobenzofuran (±)-**12** (pair of *RRR*- and *SSS*-lactones) in 88% yield (Scheme 2). Finally, further reduction of the carbon-carbon double bond in (±)-**12** with $NaBH_4$ was also diastereoselective (70% *de*) with abstraction of proton occurring predominantly from the less hindered site giving rise to a mixture of (±)-**13** (minor) and (±)-**14** (major, pair of *RRRR*- and *SSSS*-isomers) as a thick oil in 85% yield. Acid catalyzed ester hydrolysis furnished a diastereomeric mixture of corresponding carboxylic acids in 92% yield. Recrystallization of the above diastereomeric mixture of acids in ethyl acetate gave the analytically pure single diastereomer with 64% recrystallization yield. The X-ray crystallographic data of the analytically pure diastereomer revealed that a (±)-lactone **15** is formed. Finally, on the basis of X-ray data we could postulate the complete mechanistic and stereochemical aspects of the present conversion of **1** plus **8** to (±)-**15** as indicated in Scheme 2.



Scheme 2. *Reagents, conditions and yields*: (i) LDA, THF, –78 ºC, 20 min (**9**/**10** = 8:2, 80%); (ii) $NaBH_4$ (1.5 equiv.), MeOH, rt, 15 min (88%); (iii) $NaBH_4$ (3.0 equiv.), MeOH, rt, 1 h (85%, **13**:**14** = 15:85); (iv) (a) AcOH:HCl (3:1), reflux, 6 h (92%), (b) Recrystallisation from EtOAc (64%).

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

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

Chapter 1

A Concise Account on the Chemistry of Itaconic Acid and Derivatives and their Uses in the Synthesis of Heterocycles and Tetramic Acid Derivatives

This chapter features the following sections:

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1B	*Section B*	48
1C	*Section C*	82

1A. Section A

A Concise Account on the Chemistry of Itaconic Acid and Derivatives

This section features the following topics:

1A.1	*Introduction to Chemistry of Itaconic Acid*	1
1A.1.1	*Synthetic Utility of Itaconic Acid*	1
1A.2	*Introduction to the Chemistry of Dialkyl Itaconates*	10
1A.2.1	*Synthetic Utility of Dialkyl Itaconate*	11
1A.3	*Introduction to Chemistry of Itaconic Anhydride*	21
1A.3.1	*Synthetic Utility of Itaconic Anhydride*	21
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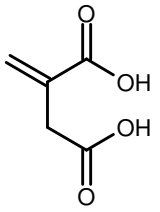
1A. Section A: A Concise Account on the Chemistry of Itaconic Acid and Derivatives

1A. 1: Introduction to Chemistry of Itaconic Acid

Itaconic acid was prepared in 1836 from the pyrolysis of citric acid.[1] Itaconic acid was also isolated as a metabolite of fungi such as *Aspergillus itaconicus*,[2a] *Helicobasi diummompa*,[2b] *Ustilago zeae*,[2c] *U. maydis*[2d] and some yeasts belonging to the genus *Candida*.[2e] Itaconic acid has been produced by the fermentation of market refuse, the apple and banana by using the strain *Aspergillus terreus* SKR10.[3] It has also been produced by the fermentation of glucose using *Aspergillus terreus* immobilized in polyacrylimide gels.[4]



Itaconic Acid (**1**)

Itaconic acid was synthesized by the reaction of propargyl chloride with excess of carbon monoxide and water in presence of $Ni(CO)_4$ as catalyst.[5] Itaconic acid has also been prepared by carbonylation of propargyl alcohol in MeOH or benzene containing aqueous HI in the presence of Pd black or $Co_2(CO)_8$ as catalyst.[6] Thermolysis of 7-phenyl-2,3,7-triazabicyclo[3.3.0]oct-2-ene-6,8-dione in boiling xylene at 138 °C, produces itaconic acid.[7] Itaconic acid undergoes copolymerization with butyl acrylate in dioxane in the presence of azobisisobutyronitrile as the initiator at 65 °C.[8]

1A.1.1: Synthetic Utility of Itaconic Acid

Itaconic acid has been used for asymmetric hydrogenation, synthesis of several natural and unnatural products. This section provides a short overview on the application of Itaconic acid for the asymmetric hydrogenation and synthesis of several useful natural and unnatural products, however we have tried our best to summarize and present the information here, but no pretension of completeness is claimed.

1A. 1.1.1: Asymmetric hydrogenation:

Itaconic acid has been extensively used as a prochiral substrate for asymmetric hydrogenation employing variety of chiral ligands (Table 1). Zhang and co-workers[9a] have used phosphine-phosphoramidite ligand and $Rh(COD)_2BF_4$ as a catalyst and reported the

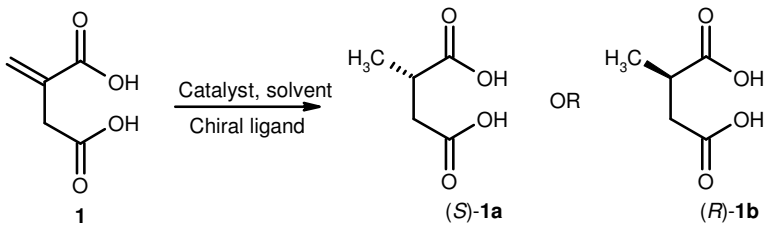


Table 1. Asymmetric hydrogenation of itaconic acid

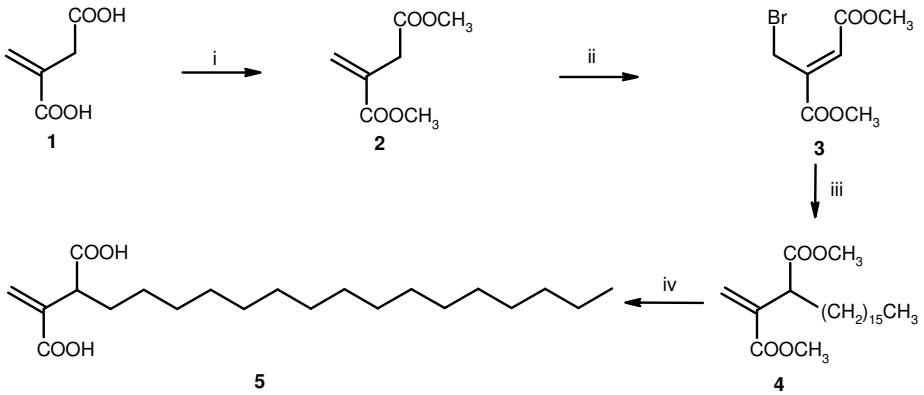
Entry	Catalyst	Chiral ligand	Solvent	Product (*ee* %)	Reference
1	$Rh(COD)_2BF_4$	Phosphine-Phosphoramidite	TFE	**1b** (99.6)	9a
			MEK	**1a** (71.2)	9a
2	$[Rh(cod)_2]BARF$	(*R*,*S*)-3-H^2F^6 BINAPHOS	H_2O	**1a** (83.6)	9b
3	$Rh(COD)BF_4$	UlluPHOS	MeOH	**1a** (48.0)	9c
4	$Rh(COD)BF_4$	*BoPhoz*	MeOH	**1b** (97.6)	9d
5	$Rh(COD)_2OTf$	Spiro monodentate	CH_2Cl_2	**1a** (97.9)	9e
6	$Rh(nbd)_2BF_4$	Phosphoramidite ddppm	MeOH	**1a** (64.0)	9f
7	$Rh(COD)_2BF_4$	Ferrocenyl diphosphine	MeOH	**1b** (99.5)	9g
8	$Rh(COD)_2PF_6$ $Rh(COD)_2BF_4$	Mono- and bidentate phosphinanes	*i*PrOH	**1a** (96.0)	9h
9	$Rh(COD)_2BF_4$	MonoPhos	CH_2Cl_2	**1a** (96.6)	9i

formation of both the isomers. Litner and co-workers[9b] have used the inverted supercritical CO_2/aqueous biphasic catalytic system for highly enantioselective hydrogenation of polar water-soluble substrates. Sannicoló and co-workers[9c] have synthesized 2,5-dimethyl-3,4-bis[(2*R*,5*R*)-2,5-dimethylphospholano]thiophene (UlluPHOS) and employed as ligand of rhodium and ruthenium in hydrogenation reactions of prostereogenic functionalized carbon-carbon and carbon-oxygen double bonds. Boaz *et al*[9d] have prepared phosphinoferrocenylaminophosphines, known as *BoPhoz* ligands. The rhodium complexes of these ligands show high enantioselectivities (>95% *ee*) for the asymmetric hydrogenation of itaconic acid derivatives. Zhang and co-workers[9e] have also prepared a new spiro monodentate phosphoramidite ligand and used for the Rh-catalyzed asymmetric hydrogenation of itaconic acid with excellent enantioselectivities (>99% *ee*). Dervisi and co-workers[9f] have synthesized the novel C_2-symmetric diphosphine 1,4:3,6-dianhydro-2,5-

bis(diphenylphosphino)-*D*-mannitol (ddppm) from *D*-isomannide and used as a ligand for the Rh-catalyzed asymmetric hydrogenation of itaconic acid. Zhang and co-workers[9g] have also prepared a new chiral ferrocenyl diphosphine ligand from *D*-mannitol. Rh-complex with this ligand showed high enantioselectivity in the asymmetric hydrogenation of itaconic acid derivatives. Prie and co-workers[9h] have synthesized mono- and bidentate phosphinanes and employed for the Rh-catalysed asymmetric hydrogenation of itaconic acid. Feringa and co-workers[9i] have used monodentate phosphoramidite chiral ligand for the rhodium catalyzed asymmetric hydrogenation of itaconic acid with 99% enantioselectivity.

1A.1.1.2: Synthesis of ceriporic acid B (Enoki et al)

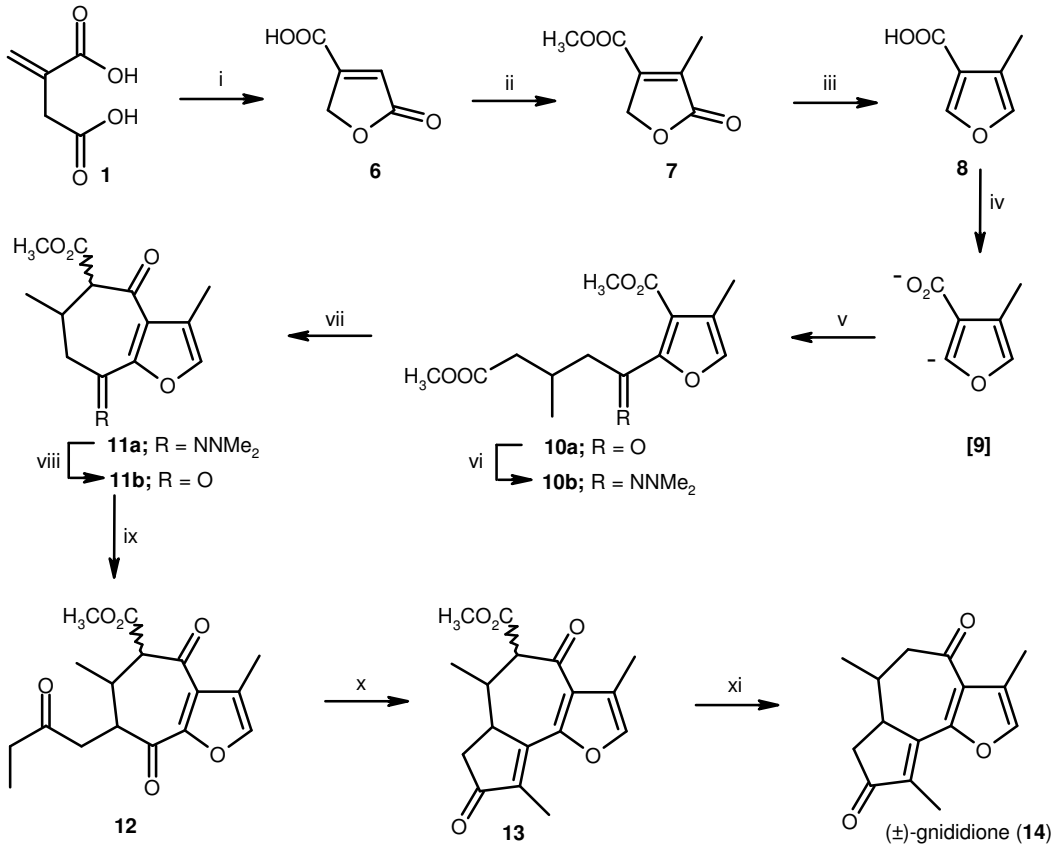
Ceriporic acid B has been isolated from white rot basidiomycete, *Ceriporiopsis subvermisrpora*.[10] Ceriporic acid B is protective against the depolymerization of cellulose by the Fenton reaction.[11] Enoki *et al*[12] have synthesized ceriporic acid B from itaconic acid by bromination, the Grignard reaction and acidolysis. Itaconic acid (**1**) on esterification gave diester **2**, which on bromination and dehydrobromination gave dimethyl bromomethylfumarate (**3**). Introduction of a hexadecyl group into the itaconate core was carried out with 1-hexadecylmagnesium bromide and $LiCuBr_2$ at -3 °C to furnish itaconate ester **4**. Further criporic acid (**5**) was prepared by acidolysis of **4** with formic acid and sulfuric acid in the presence of hydroquinone as a polymerization inhibitor (Scheme 1). The chemistry of dimethyl bromomethylfumarate (**3**) has been discussed in detail in chapter 2.



Scheme 1. *Reagents, conditions and yields*: (i) MeOH, H_2SO_4; (ii) (a) Br_2, (b) NEt_3; (iii) LiCuBr, $CH_3(CH_2)_{15}MgBr$, THF, -3 °C, (35%, 3-steps); (iv) 0.5 M H_2SO_4, HCOOH, 120 °C, 4 h (64%).

1A.1.1.3: Synthesis of the (±)-gnididione (Knight and co-worker)

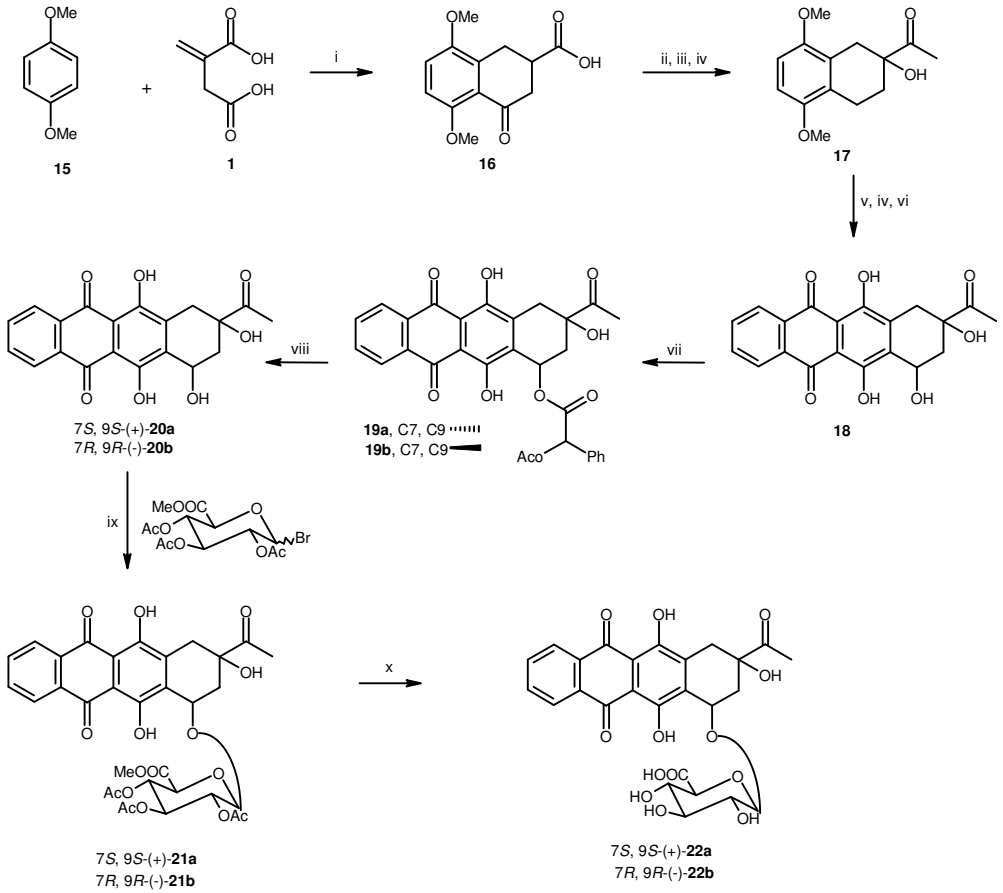
Gnididione was isolated by Kupchan *et al*[13] from the antileukaemic fraction of the plant *Gnidia latifolia* Gilg. Knight and co-workers[14] have synthesized the (±)-gnididione (**14**) by the condensation of dianion **9** with 3-methylglutaric anhydride. Protection of the derived keto-diester **10a** as the *N*,*N*-dimethylhydrazone **10b** and Dieckmann cyclization gave them the diketo-ester **11b** after deprotection (Scheme 2). Stereospecific incorporation of the appropriate butanone side chain by double deprotonation of ester **11b** and alkylation using 1-bromobutane-2-one gave dione **12**, which was subjected to intramolecular aldol ring closure using potassium *t*-butoxide as base. Saponification and decarboxylation of the aldol product **13** then gave (±)-gnididione (**14**).



Scheme 2. *Reagent, conditions and yields*: (i) Br_2, Na_2CO_3, HCl (44%); (ii) (a) CH_2N_2, (b) xylene, 140 °C (80%); (iii) (a) DIBALH, THF (90%), (b) KOH, rt, 8 h, HCL (90%); (iv) LDA, THF, - 78 °C, 30 min; (v) (a) 3-Methylglutaric anhydride, (b) AcCl, MeOH, reflux, 15 h (56%); (vi) 1,1-Dimethylhydrazene, EtOH, AcOH, reflux, 6.5 h (84%); (vii) Sodium *bis*-(timethylsilyl)amide, Et_2O, reflux, 2.5 h (62%); (viii) MeI, EtOH, reflux, 8 h (65%); (ix) 1-Bromobutan-2-one, LDA, THF, HMPA, -78 °C, 3 h (55%); (x) KO^{t}Bu, THF, ^{t}BuOH, 1.5 h (67%); (xi) 1 M Aq. K_2CO_3, MeOH, 4 h, HCl (80%).

1A.1.1.4: Syntheses of idarubicinone-7-b-D-glucuronide (Yoo and co-worker)

Anthracycline antibiotics are well-known antitumor agents. Yoo and co-worker[15] have reported the regiospecific syntheses of anthracycline antibiotics idarubicinone coupled with *D*-glucuronic acid (Scheme 3). Cyclization of dimethoxybenzene with itaconic acid in polyphosphoric acid (PPA) in one step afforded the naphthalenone **16**, which was transformed into the cis form of (±)-idarubicinone (**18**) as a major product. Esterification of (±)-**18** with (*S*)-(+)-*o*-acetylmandelic acid followed by subsequent separation and deprotection gave (+)-**20a** and (-)-**20b**. Novel glycosides **22a** and **22b** containing glucuronic acid moiety were readily prepared via glycosylation of (+)-idarubicinone (**20a**)

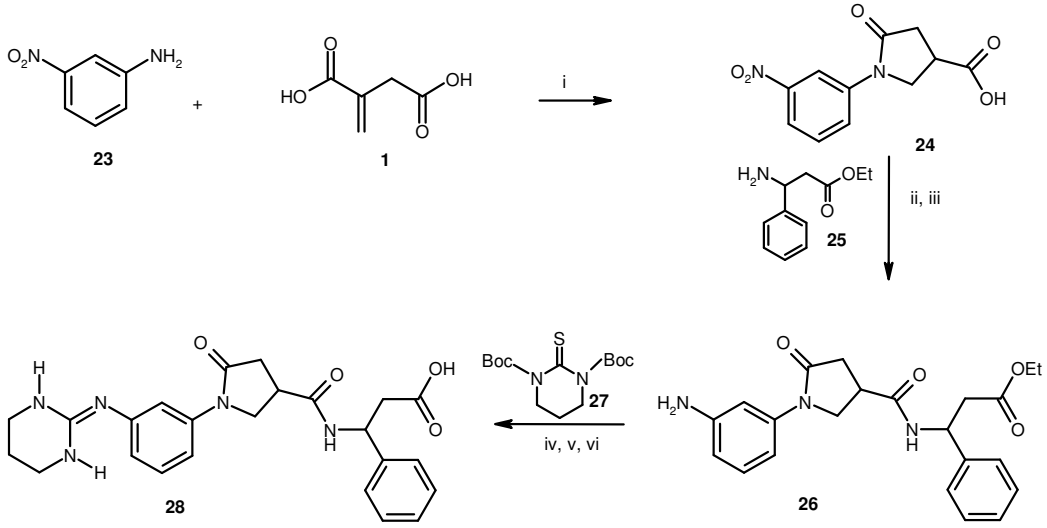


Scheme 3. *Reagents, conditions and yields*: (i) $AlCl_3$, CH_2Cl_2 or PPA (66%); (ii) Et_3SiH/CF_3CO_2H (90%); (iii) MeLi/THF, 0 °C (81%); (iv) O_2, *t*-BuOK, $P(OEt)_3$/DMF, -15 °C (85%); (v) C_6H_4-1,2-$(COCl)_2$, $AlCl_3/PhNO_2$, 80–100 °C (87%); (vi) (a) $HOCH_2CH_2OH$, *p*-TsOH/PhH, reflux, (b) NBS, AIBN/CCl_4, reflux, SiO_2/wet THF:HCl/dioxane (74%); (vii) (*S*)-(+)-*O*-Acetylmandelic acid, DCC, DMAP/CH_2Cl_2 (**19a** = 47%, **19b** = 40%); (viii) Satd. NaOH solution (5 drops) (**20a** = 86%, **20b** = 85%); (ix) $ZnBr_2$, 4Å molecular sieves/CH_2Cl_2 (**21a** = 56%, **21b** = 53%); (x) LiOH, Amberite resin/MeOH, THF (**22a** = 84%, **22b** = 82%).

and (-)-idarubicinone (**20b**) with acetobromo-α-*D*-glucuronic acid methyl ester using $ZnBr_2$, followed by hydrolysis with lithium hydroxide and amberite cation exchange resin.

1A.1.1.5: Synthesis of N-aryl-γ-lactams (Domingueza and co-workers)

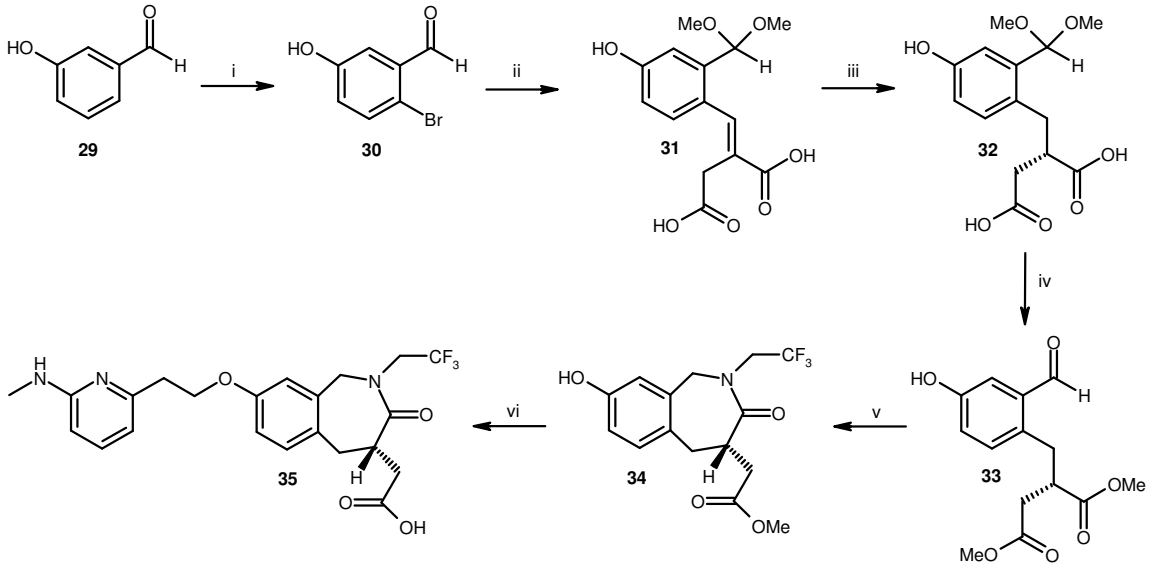
Integrins are a family of cell surface receptors that function in cell–substrate recognition and cell–cell communication. $\alpha_v\beta_3$ Antagonists could provide novel therapeutic strategies for the treatment of pathological conditions involving abnormal cell adhesion and neovascularization, such as cancer, restenosis, angiogenic ocular disorders and osteoporosis.[16] Domingueza and co-workers[17] have synthesized various *N*-aryl-*γ*-lactam as $\alpha_v\beta_3$ antagonists. The *γ*-lactam **24** was obtained from the condensation of 3-nitroaniline (**23**) with itaconic acid (Scheme 4). Compound **24** was then coupled with *β*-amino ester **25** in the presence of EDCI to afford ester which on reduction of the nitro group under acidic conditions led to aniline derivative **26**. Guanidine analogue **28** was prepared by the treatment of aniline derivative **26** with thiourea **27** to give protected guanidine. Removal of the Boc-groups and basic hydrolysis led to acid **28**. Six-membered homologue **28** showed higher binding affinity towards integrins.



Scheme 4. *Reagents, conditions and yields*: (i) Neat, 110 °C, 8 h (70%); (ii) **25**, EDCI, HOBt, Et_3N, DMF, rt, 8 h (90%); (iii) Zn, AcOH, THF/H_2O (80%); (iv) **27**, cat. $HgCl_2$, DMF, 16 h (80%); (v) 1:1 TFA in CH_2Cl_2, rt, 30 min (100%); (vi) Aq NaOH, THF/MeOH; H^+ (95%).

1A.1.1.6: Synthesis of the vitronectin receptor antagonist SB-273005 (Wallave et al)

The integrin family of transmembrane glycoproteins that acts as cell adhesion receptors and signal transducers include the vitronectin receptor $\alpha_v\beta_3$.[18] The vitronectin receptor, $\alpha_v\beta_3$, is known to assist a wide variety of biological processes. As a consequence of this broad activity, it was anticipated that suitably designed antagonists would be useful in the treatment of inflammation,[19a] cardiovascular disorders,[19b] cancer[19c] and osteoporosis.[19d] Wallave *et al* have developed the multi-kiloscale enantioselective synthesis of a vitronectin receptor antagonist SB-273005 (**35**).[20] The synthesis starts with the bromination of 3-hydroxybenzaldehyde **29** to get bromoaldehyde **30**. Heck reaction between bromoaldehyde **30** and itaconic acid gave diacid derivative **31**, which on asymmetric hydrogenation gave **32**. The diesterification of diacid acetal **32** furnished diester-aldehyde **33**. The conversion of diester aldehyde **33** to the desired benzazepinone **34** was carried out by a reductive amination cyclization sequence. Finally benzazepinone **34** was coupled to the 2-methylamino-6-ethanol pyridine using Mitsunobu reaction conditions to complete the synthesis of SB-273005 (**35**) (Scheme 5).

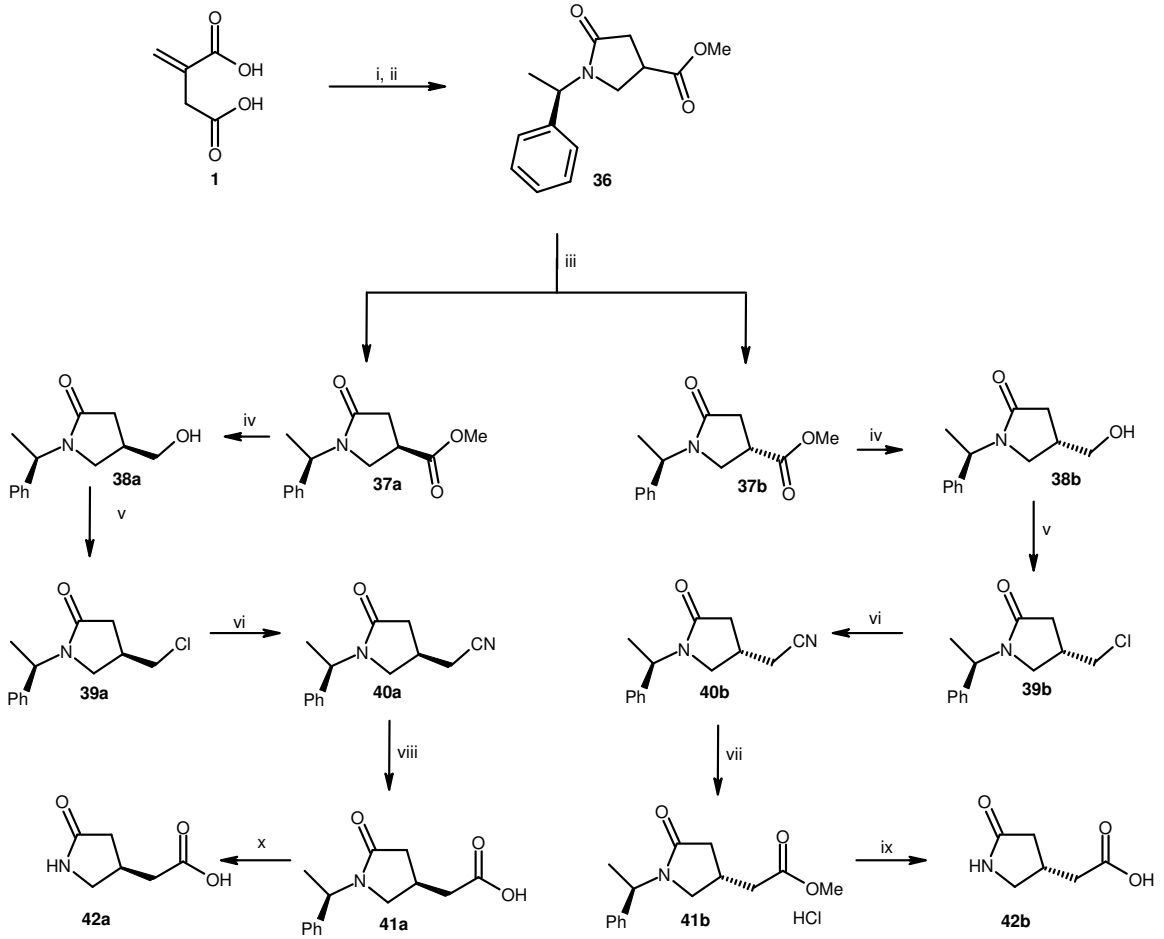


29 **30** **31** **32** **33** **34** **35**

Scheme 5. *Reagents, conditions and yields*: (i) Br_2, CH_2Cl_2, reflux (65%); (ii) (a) MeOH, HCl, rt, (b) itaconic acid, Et_3N, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Bu_4NBr, CH_3CN (80%); (iii) DCA, $[RuCl_2(R\text{-}BINAP)]_2$-$Et_3N$, 60 psi of H_2, 60 °C, MeOH/H_2O (84%); (iv) H_2SO_4, MeOH, reflux (86%); (v) (a) Trifluoroethylamine-HCl, $ZnCl_2$, CH_3CN, reflux, (b) $NaBH(OAc)_3$, DMA, (c) TFA, toluene, reflux (72%); (vi) (a) PPh_3, DIAD, 6-methylamino-2-pyridineethanol, TBME, (b) LiOH, H_2O, THF/H_2O, 50 °C (66%).

1A.1.1.7: Synthesis of (R)-(-)- and (S)-(+)-homo-β-proline (Nielsen et al)

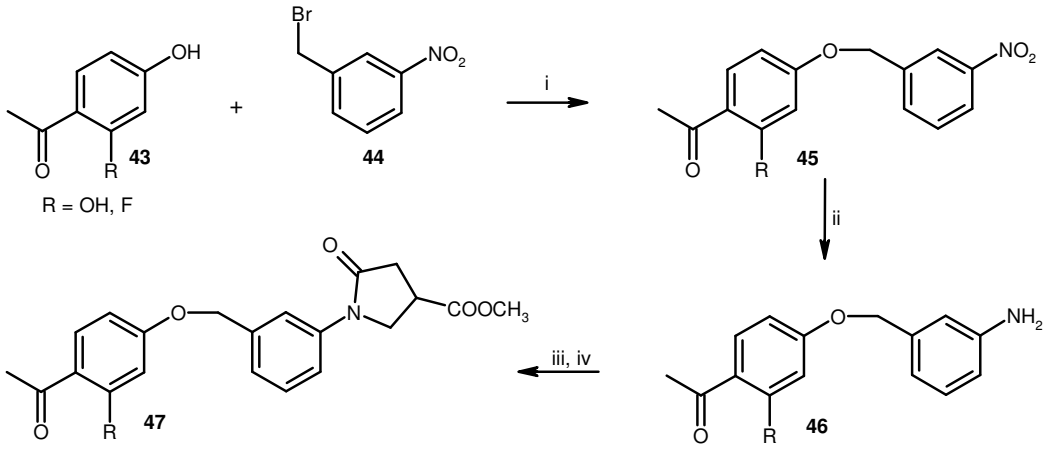
4-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the mammalian central nervous system (CNS).[21] Nielsen *et al* have synthesized (*R*)-(-)- and (*S*)-(+)-homo-*β*-proline as inhibitor of GABA receptor (Scheme 6).[22] Conjugate addition of (*R*)-(+)-1-phenylethylamine to itaconic acid (**1**) and subsequent cyclization gave a diastereomeric mixture of carboxylic acids, which were converted into methyl esters **36** and then separated by preparative HPLC to give **37a** and **37b**. The LAH reduction of **37a** and **37b** gave **38a** and **38b** respectively. The compounds **38a** and **38b** were converted in two steps into their corresponding amino nitriles **40a** and **40b** respectively. Two different synthetic routes were used to convert these intermediates into (*S*)-(+)-homo-*β*-proline (**42a**) and (*R*)-(-)-homo-*β*-proline (**42b**) as described in scheme.



Scheme 6. *Reagents, conditions and yields*: (i) (*R*)-(+)-1-Phenylethylamine, heat, 160 °C, 4 h (97%); (ii) AcCl/MeOH, reflux, 2 h (76%); (iii) Preparative HPLC (**37a** = 43%, **37b** = 45%); (iv) $LiAlH_4$, Et_2O, 3.5 h (85%); (v) $SOCl_2$, $CHCl_3$, reflux, 2 h (92%); (vi) NaCN, H_2O, reflux, 48 h (67%); (vii) MeOH/AcCl, 1 h (50%); (viii) Conc. HCl, IRA-400 (50%); (ix) H_2/Pd-C, IRA-400 (62%); (x) H_2/Pd-C (62%).

1A.1.1.8: Synthesis of 4-carbomethoxypyrrolidinones (Kees et al)

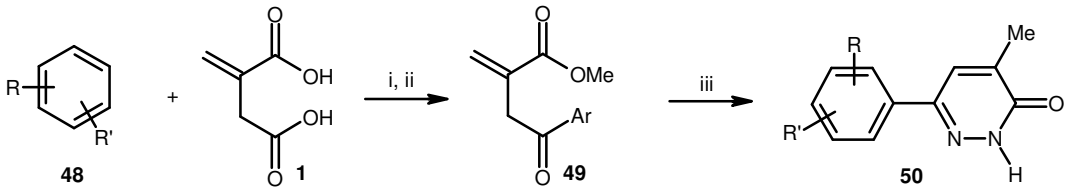
5-Lipoxygenase inhibitors have shown antiallergic activity. 5-LO Inhibitors are related by the presence of a bis-aryl system, a feature also common to many of the known cyclooxygenase inhibitors.[23] Kees *et al*[24] have synthesized 4-carbomethoxypyrrolidinones **47** and tested for 5-Lipoxygenase inhibitory activity. Alkylation of the 2,4-dihydroxyacetophenone **43** with 3-nitrobenzyl bromide (**44**) and potassium carbonate/cesium carbonate mixture in acetone gave the bis-aryl system **45**. Reduction of the nitro group with iron powder in ethanol saturated with anhydrous HCI gave the aniline derivative **46**. The 4-carbomethoxypyrrolidinones **47** were prepared in a one-pot procedure from itaconic acid and the corresponding aniline derivative **46** at 180 °C (1 h neat), followed by dilution with methanol and refluxing the reaction mixture overnight in the presence of *p*-TSA (Scheme 7).



Scheme 7. *Reagents and conditions*: (i) K_2CO_3, Cs_2CO_3 (cat), acetone, reflux, 3 d (56%); (ii) Fe/HCl, ethanol, rt, 15 h (81%); (iii) Itaconic acid, fuse, 180 °C, 1 h; (iv) MeOH, *p*-TSA, reflux, 12 h (29%).

1A.1.1.9: Synthesis of 6-(substituted aryl)-4-methyl-2,3-dihydropyridazin-3-ones (Wani and co-workers)

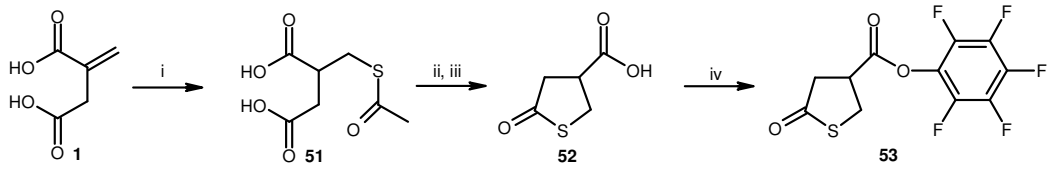
Wani and co-workers[25] have synthesized 6-aryl-4-methyl-2,3-dihydropyridazin-3-ones (**50**). The reaction of substituted benzene **48** with itaconic acid in presence of $AlCl_3$ followed by esterification gave *β*-aroyl-2-methylene propionate (**49**), cyclization of *β*-aroyl-2-methylene propionate (**49**) with hydrazine hydrate in the presence of sodium acetate gave 6-aryl-4-methyl-2,3-dihydropyridazin-3-ones (**50**) (Scheme 8). These compounds have shown significant hypotensive activity.



Scheme 8. *Reagents, conditions and yields*: (i) $AlCl_3$, benzene , reflux, 4 h, (74%); (ii) Me_2SO_4, K_2CO_3, MeCN, reflux 4 h, (79%); (iii) N_2H_4, NaOAc, MeOH, Reflux, 8 h (65%).

1A.1.1.10: Synthesis of carboxythiolactones (Garbiras et al)

The design of peptidyl immunogen construction requires the incorporation of several entities, to form an ensemble that generates antibodies. Activated carboxythiolactones, provide such a system, two acyl sites susceptible to nucleophilic attack at disparate rates and a liberated thiol susceptible to electrophilic alkylation can act as immune stimulator. Garbiras *et al*[26] have synthesized carboxylthiolactones **52** from itaconic acid. Itaconic acid on Michael addition of thiolacetic acid, followed by acyl deprotection and cyclization furnished 5-oxotetrahydrothiophene-3-carboxylic acid (**52**). This was converted to **53** by the reaction of perfluorophenol in the presence of dicyclohexylcarbodiimide (Scheme 9).



Scheme 9. *Reagents*, *conditions and yields*: (i) AcSH, H_2O, reflux (91%); (ii) 6 M HCl, reflux; (iii) TFA, reflux (100%); (iv) Perflurophenol, DCC, EtOAc, 0 °C (91%).

1A. 2: Introduction to the Chemistry of Dialkyl Itaconates

Dialkyl itaconates have been synthesized by Tsuge *et al*[27] from the corresponding dialkyl fumarate. The reaction of dialkyl fumarate with *N*-(trimethylsilylmethyl)pyridinium triflate in the presence of cesium fluoride in refluxing DME gave the corresponding diakyl itaconates. Kovaleva *et al*[28] have reported the formation of dimethyl itaconate as a minor product in the reaction of aq. NaN_3 with dimethyl bromomethylfumarate. Gabriele *et al*[29] have reported the formation of dimethyl itaconate as minor product in the palladium-catalysed carbonylation of propynyl alcohol. Ram *et al*[30] have reported a simple method for the preparation of monomethyl esters of dicarboxylic acids by selective esterification of the nonconjugated carboxyl group in the presence of an aromatic or conjugated carboxyl

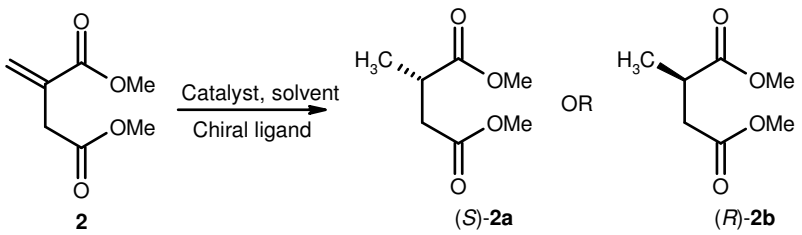
group. Loh *et al* have reported the formation of dimethyl itaconate as a side product in the indium-mediated allylation of dimethyl bromomethylfumarate with hexanal in water.[31]

1A.2.1: Synthetic Utility of Dialkyl Itaconate

Dialkyl itaconates have been used for asymmetric hydrogenation, synthesis of several natural and unnatural products. This section provides a short overview on application of dialkyl itaconates for the asymmetric hydrogenation and synthesis of several natural and unnatural products.

1A. 2.1.1: Asymmetric hydrogenation:

Dialkyl itaconates have been extensively used as a prochiral substrate for asymmetric hydrogenation employing variety of chiral ligands (Table 2). Reek and co-workers[32a] have introduced a new class of supramolecular bidentate phosphite ligands and successfully employed them for the rhodium catalyzed asymmetric hydrogenation of dimethyl itaconate. Ding and co-workers have demonstrated that hydrogen bonding makes a difference in the rhodium-catalyzed enantioselective hydrogenation of dimethyl itaconate using monodentate phosphoramidites.[32b] Zhang and co-workers[32c] have synthesized a new family of air-stable and moisture-stable phosphine-phosphoramidite ligands (PEAPhos) from commercially available (*S*)-*α*-phenylethylamine and applied in the rhodium-catalyzed enantioselective hydrogenations of dialkyl itaconates. Breit and co-workers have prepared self-assembly of chiral monodentate to chiral bidentate ligands through complementary hydrogen-bonding on the basis of an A-T base pair analogue for combinatorial rhodium-catalyzed hydrogenation of variety of prochiral substrates.[32d] Reetz *et al*[32e] have used chiral diphosphites and diphosphoramidites derived from BINOL or diphenylprolinol as ligands for the asymmetric Rh-catalyzed olefin hydrogenation of dimethyl itaconate. Monti *et al* have prepared a library of chiral tropos phosphorus ligands, based on a flexible (tropos) biphenol unit and a chiral phosphorus bound alcohol or secondary amine. These ligands were screened, individually and as a combination of two, in the rhodium-catalyzed asymmetric hydrogenation of dehydro-*α*-amino acids, dehydro-*β*-amino acids, enamides and dimethyl itaconate.[32f] Reetz *et al*[32g] have also reported that Rh-catalyzed olefin-hydrogenation mixtures, comprising a BINOL-derived phosphorus ligand in combination with an achiral phosphorus compound, or a BINOL-derived phosphorus ligand in



2 (*S*)-**2a** (*R*)-**2b**

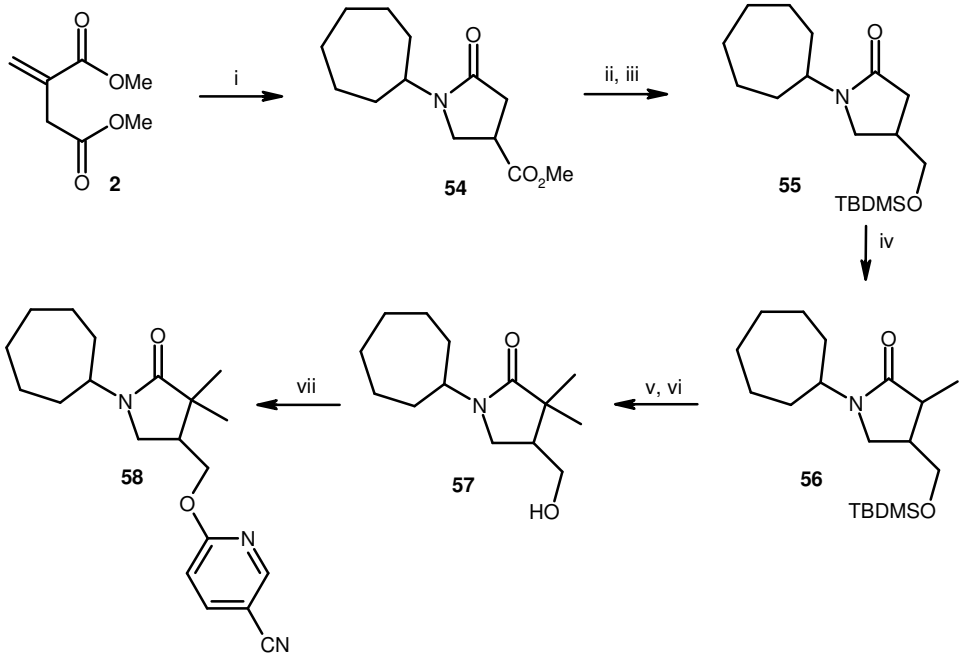
Table 2. Asymmetric hydrogenation of dimethyl itaconate

Entry	Catalyst	Chiral ligand	Solvent	Product (*ee* %)	Reference
1	$Rh(COD)BF_4$	UREA-phos	CH_2Cl_2	**2a** (95.8)	32a
2	$Rh(COD)_2BF_4$	Monophosphorus	CH_2Cl_2	**2b** (94.0)	32b
3	$Rh(COD)_2BF_4$	PEAPhos	CH_2Cl_2	**2b** (99.9)	32c
4	$Rh(COD)_2BF_4$	Self-assembly of monodentate-bidentate	CH_2Cl_2	**2a** (94.0)	32d
5	$[Rh(cod)_2]BF_4$	BINOL-derived	CH_2Cl_2	**2b** (92.0)	32e
6	$[Rh(cod)_2]BF_4$	Tropos	CH_2Cl_2	**2a** (75.0)	32f
7	$[Rh(cod)_2]BF_4$	BINOL-derived + biphenol-derived	CH_2Cl_2	**2b** (94.0)	32g
8	$[Rh(cod)_2]BF_4$	DpenPhos	CH_2Cl_2	**2a** (98.4)	32h
9	$Rh(COD)_2BF_4$	PipPhos and MorfPhos	CH_2Cl_2	**2a** (99.0)	32i

combination with a chiral but configurationally fluxional biphenol-derived phosphite can result in high enantioselectivity. Ding and co-workers have developed a new class of monodentate phosphoramidite ligands (DpenPhos), based on a modular concept for Rh(I)-catalyzed asymmetric hydrogenations of a variety of olefin derivatives, affording the corresponding optically active compounds in excellent yields and enantioselectivities.[32h] Bernsmann *et al*[32i] have prepared a library of monodentate phosphoramidite ligands and applied in rhodium catalyzed asymmetric hydrogenation. This resulted in the identification of two ligands, PipPhos and MorfPhos, that afforded excellent and in several cases unprecedented enantioselectivities in the hydrogenation of *N*-acyldehydroamino acid esters, dimethyl itaconate, acyclic *N*-acylenamides, and cyclic *N*-acylenamides.

1A.2.1.2: Synthesis of butyrolactam 11β-HSD1 inhibitors (Yeh et al)

Metabolic syndrome is a cluster of factors associated with an increased risk of atherosclerotic cardiovascular disease and diabetes. The current hypothesis presumes a small molecule that inhibits 11β-HSD1 can be a viable therapeutic strategy for the treatment of metabolic syndrome. Yeh *et al*[33] have synthesized a series of metabolically stable butyrolactam 11β-HSD1 inhibitors. Tandem Michael addition and cyclization between cycloheptylamine and dimethyl itaconate gave lactam **54** which was reduced and protected as silylether **55**. Position 3 of the lactam was then sequentially alkylated, and after removal of silyl group, a pyridyl group was appended on the hydroxymethylene of **57** to give **58** (Scheme 10). Lactam **58** showed good potency and excellent selectivity for the enzyme 11β-HSD1.

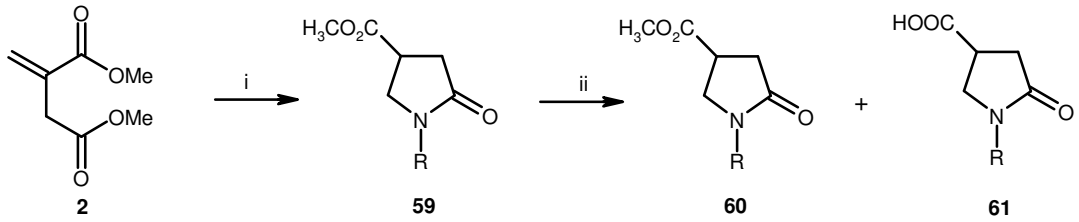


Scheme 10. *Reagents, conditions and yields*: (i) Cycloheptylamine, MeOH, reflux, 5 h (90%); (ii) $LiAlH_4$, THF, 0 °C, 1 h (85%); (iii) TBDMSCl, imidazole, THF, rt (99%); (iv) (a) LiHMDS, THF, -78 °C, 30 min, (b) MeI, 1 h (80%); (v) $LiNEt_2$, THF, 0 °C, 30 min, MeI, DMPU, 0 °C to rt, 4 h (75%); (vi) HCl, THF, rt, 3 h (100%); (vii) 6-Chloronicotinonitrile, NaH, DMF, 0 °C to rt, (89%).

1A.2.1.3: Synthesis of enantiopure 1-alkyl-5-oxo-3-pyrrolidinecarboxylic acids (Valentin and co-workers)

Number of compounds containing the γ-lactam (2-pyrrolidinone) moiety exhibit interesting biological and pharmacological activities. Valentin and co-workers[34] have reported the synthesis of enantiopure 1-alkyl-5-oxo-3-pyrrolidinecarboxylic acids (**61**) by the enzymatic

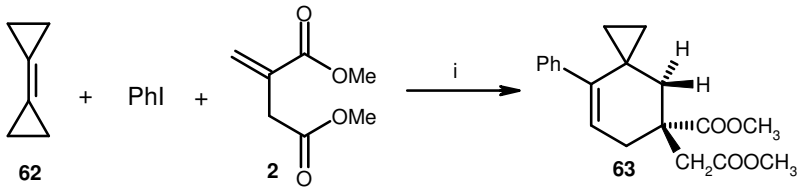
resolution of the corresponding racemic mixtures. The 5-oxo-3- pyrrolidinecarboxylic acid methyl ester **59** was easily prepared by the conjugate Michael addition of the appropriate primary amine to dimethyl itaconate (**2**), resulting in spontaneous cyclization and leading to the desired heterocyclic ring **59**, which on enzymatic resolution gave the corresponding enantiomerically pure ester **60** and acid **61** (Scheme 11).



Scheme 11. *Reagents and conditions*: (i) RNH_2, NH_4Cl, Et_3N; (ii) Hydrolytic enzyme α-CT, phosphate buffer, rt [*R*-(-)-**60** = 36% yield, 99% *ee*; *S*-(+)-**61** = 30% yield, 85% *ee*].

1A.2.1.4: Synthesis of spiro[2.5]oct-4-ene derivatives (de Meijere and coworkers)

Three-component domino Heck-Diels-Alder reaction with bicyclopropylidene (**62**) have been reported by de Meijere and co-workers.[35] The three components bicyclopropylidene (**62**), phenyl iodide and dimethyl itaconate, were mixed with the palladium catalyst in acetonitrile and the mixture was heated in a Pyrex bottle, to give the corresponding spiro[2.5]octenes **63**. Here the tetrasubstituted alkene **62** is more rapidly carbopalladated than even methyl acrylate, which is known to be a particularly good substrate in Heck coupling reactions (Scheme 12).



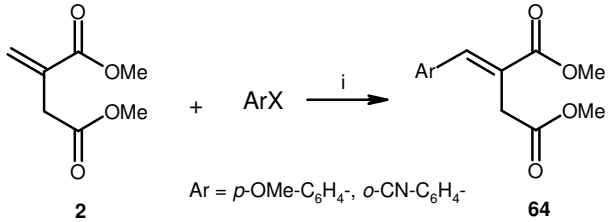
Scheme 12. *Reagents, conditions and yields*: (i) $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), K_2CO_3, Et_4NCl, MeCN, 80 °C (47%).

1A.2.1.5: Heck coupling reactions

[A] *Buchwald's approach*

The palladium-catalyzed reaction of organic halides with alkenes[36] has become a well established synthetic method for carbon-carbon bond formation.[37] Buchwald and co-

workers[38] have described general, phosphane-free, reaction conditions for the Heck type coupling of aryl iodides and aryl bromides with dialkyl itaconates (Scheme 13).



Scheme 13. *Reagents, conditions and yield*: (i) 1-4 mol % $Pd(OAc)_2$, Et_4NCl, Cy_2NMe, dimethylacetamide, 95-100 °C, 16 h (72-74%).

[B] *Nájera's approach*

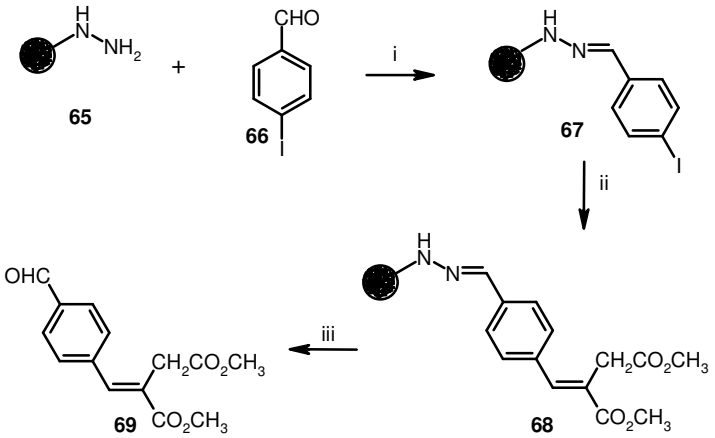
Nájera and co-workers[39] have optimized the reaction conditions for the mono-arylation of dimethyl itaconate in aqueous media catalyzed either by a *p*-hydroxyacetophenone oxime-derived palladacycle or by palladium(II) acetate under phosphine-free conditions and in the presence of (dicyclohexyl)-methylamine as base.

[C] *Correia's approach*

Correia and co-workers[40] have reported the Heck arylation of dialkyl itaconate using several arenediazonium tetrafluoroborates. Arylations were carried out under aerobic, ligand-free conditions to provide the corresponding substituted acrylates in moderate to high isolated yields.

[D] *Wessjohann's approach*

Wessjohann and co-workers[41] have synthesized polymer-supported benzylhydrazines using poly(ethyleneglycol) acrylamide (PEGA) resin. They can be used to scavenge electrophiles reactive with hydrazine. Especially aromatic aldehydes can be captured selectively, monoprotected and reversibly linked in the presence of other functional groups. Various reactions can be performed on these protectively linked aldehydes. As an example, a Heck coupling was performed with polymer-supported substrate **65**. The polymer bound aldehyde **67** reacted with dimethyl itaconate to give the coupling product **68**. By using the established cleavage method, the final coupling product **69** was obtained in 46% overall isolated yield (Scheme 14).

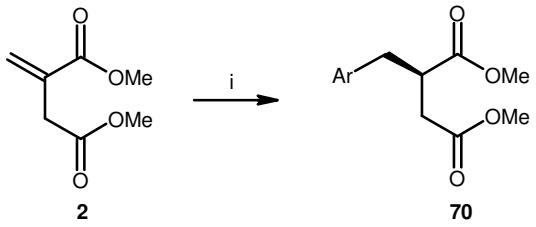


Scheme 14. *Reagents, conditions and yields*: (i) MeOH, 1% AcOH, rt, 24 h; (ii) Dimethyl itaconate, $Pd(OAc)_2$, Bu_4NCl, NaOAc, DMA, 100 °C, 24 h; (iii) Acetone:THF:conc. HCl = 1:2:0.03, rt, 30 min (45% overall yield).

1A.2.1.6: Enantioselective 1,4-addition reactions

[A] *Frost's approach*

The rhodium catalysed asymmetric addition of aryl and alkenyl organoboron reagents to activated alkenes has emerged as fundamental methodology for organic synthesis.[42] Frost and co-workers[43] have reported the enantioselective synthesis of 2-substituted succinic esters by a tandem rhodium catalyzed conjugate addition and enantioselective protonation (Scheme 15, Table 3).



Scheme 15. *Reagents, conditions and yields*: (i) $ArylBF_3K$, $[Rh(cod)_2]PF_6$ (3 mol%), BINAP (6.6 mol%), benzene/H_2O (20:1), 110 °C (56% yield, 82% *ee*).

Table 3. Scope of rhodium catalysed conjugate addition-protonation

Entry	Aryl	Ligand	Yield %	*Ee* %
1	1-Naphthyl	(*R*)-BINAP	56	82 (*R*)
2	Ph	(*R*)-BINAP	51	68 (*R*)
3	2-OMe-C_6H_4-	(*R*)-BINAP	Trace	N.d.
4	4-OMe-C_6H_4-	(*R*)-BINAP	89	62 (*R*)
		(*S*)-BINAP	93	56 (*S*)
5	4-Ac-C_6H_4-	(*R*)-BINAP	75	48 (*R*)
		(*S*)-BINAP	96	46 (*S*)
6	3-Br-C_6H_4-	(*R*)-BINAP	80	60 (*R*)
		(*S*)-BINAP	93	54 (*S*)
7	4-Br-C_6H_4-	(*R*)-BINAP	85	58 (*R*)
		(*S*)-BINAP	95	62 (*S*)
8	4-Cl-C_6H_4-	(*R*)-BINAP	89	60 (*R*)
		(*S*)-BINAP	96	60 (*S*)

[B] *Sibi's approach*

Sibi *et al*[44] have reported that the chiral Lewis acid mediated conjugate radical addition to dimethyl itaconate followed by enantioselective hydrogen-atom transfer proceeds with moderate selectivity in the formation of 2-substituted succinic esters.

[C] *Marinetti's approach*

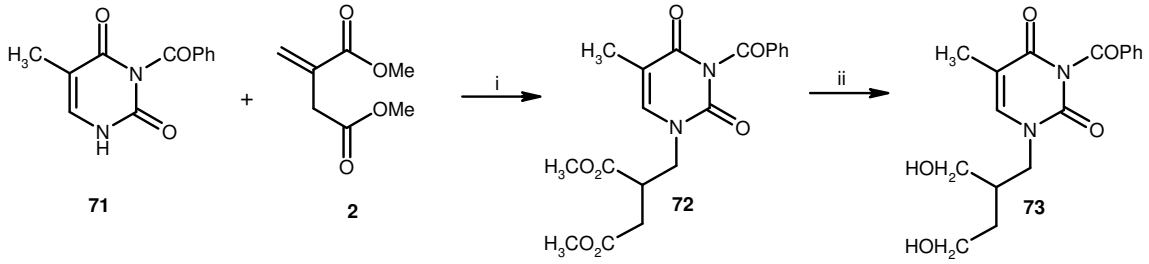
Marinetti and co-workers[45] have prepared the new heterotopic atropisomeric diphosphine (*R*)-5,6-benzo-2,20-bis(diphenylphosphino)-4´,5´,6´-trimethylbiphenyl and used it for the rhodium catalysed 1,4-additions of boronic acids to dimethyl itaconate.

[D] *Frost's approach*

Frost and co-workers[46] have reported the cationic rhodium complex [Rh(cod)2][BF_4] catalysed 1,4-addition of organotrialkoxysilanes to dimethyl itaconate.

1A.2.1.7: Synthesis of acyclic nucleosides (Huet and co-workers)

Interest in acyclic nucleosides[47] started in 1970 when acyclovir (ACV, 'Zovirax') was reported as a potent anti-viral agent.[48a] Huet and co-workers[48b] have synthesized several acyclic nucleosides by a short route involving a Michael addition as the key step. Addition of protected adenine, cytosine, thymine and guanine to dimethyl itaconate (**2**), in basic conditions, gave corresponding acyclic nucleosides **72** which on reduction and deprotection gave the corresponding penciclovir analogs **73** (Scheme 16).

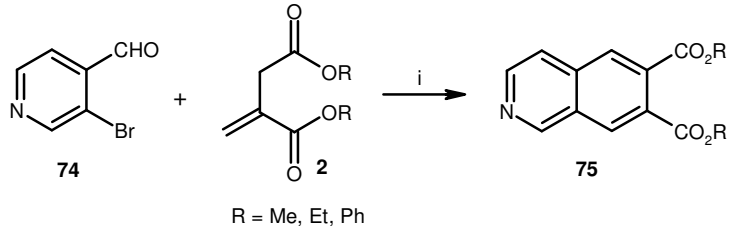


Scheme 16. *Reagents, conditions and yields*: (i) DBU, CH_3CN (64%); (ii) (a) $Ca(BH_4)_2$, THF, (b) NH_3/MeOH (53%).

1A.2.1.8: Tandem Heck and aldol reactions

[A] *Cho's approach*

Isoquinoline containing compounds are found as naturally occurring alkaloids. Cho *et al*[49] have reported a new route for the synthesis of isoquinolines. 3-Bromopyridine-4-carbaldehyde (**74**) is treated with dialkyl itaconate via Heck coupling followed by aldol reaction in dioxane at 150 °C under a catalytic system of $Pd(OAc)_2/PPh_3$/NaOAc to afford the corresponding isoquinolines **75** in good yields (Scheme 17).



Scheme 17. *Reagents, conditions and yields*: (i) $Pd(OAc)_2$, PPh_3, NaOAc, Dioxane, 150 °C, 24 h (50-78 %).

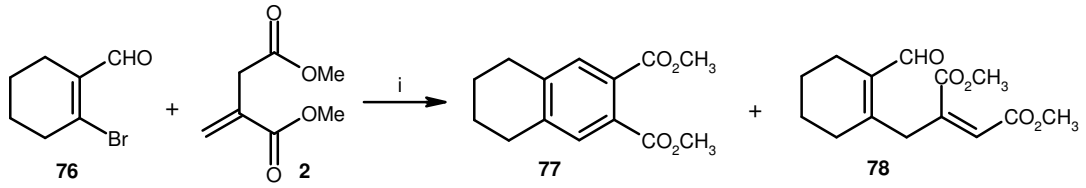
[B] *Cho's approach*

Cho *et al*[50] have also reported a new route for the synthesis of functionalized naphthalenes. 2-Bromobenzaldehydes were treated with dialkyl itaconate via Heck coupling followed by

aldol reaction in dioxane at 150 °C under a catalytic system of $Pd(OAc)_2/PPh_3/NaOAc$ to afford the corresponding naphthalenes in good yields.

1A.2.1.9: Aromatization of β-bromovinyl aldehydes (Cho et al)

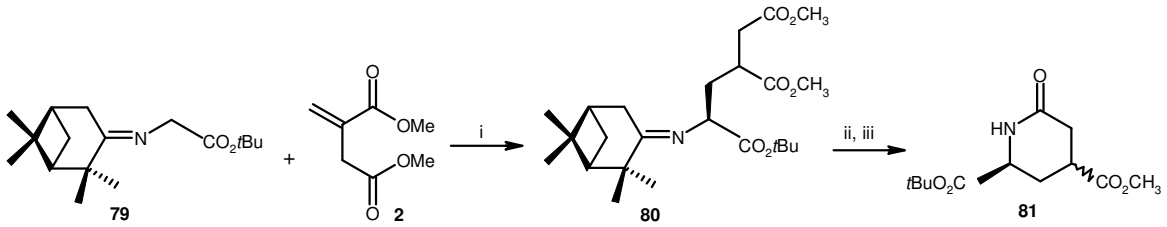
Palladium-catalyzed annulation technology has been widely introduced as a useful synthetic tool to obtain carbocycles and heterocycles, which play an important role as a basic unit for the design of many pharmacologically and biologically active compounds.[51] Cho *et al* have reported the palladium catalyzed aromatization of *β*-bromovinyl aldehydes with alkenes via intrinsic tandem Heck and aldol reactions. The reactions of various *β*-bromovinyl aldehydes **76** with dialkyl itaconate **2** in the presence of a catalytic amount of a palladium catalyst along with a base afforded corresponding dialkyl 5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylates (**77**) with concomitant formation of corresponding dialkyl 2-(2-formylcyclohex-1-enylmethyl)maleate (**78**) (Scheme 18).[52]



Scheme 18. *Reagents, conditions and yields*: (i) $Pd(OAc)_2$, PPh_3, NaOAc, THF, 120 °C, 20 h (**77** = 45-60%, **78** = 19%).

1A.2.1.10: Enantioselective synthesis of 4-substituted glutamic acid derivatives (Rolland and co-workers)

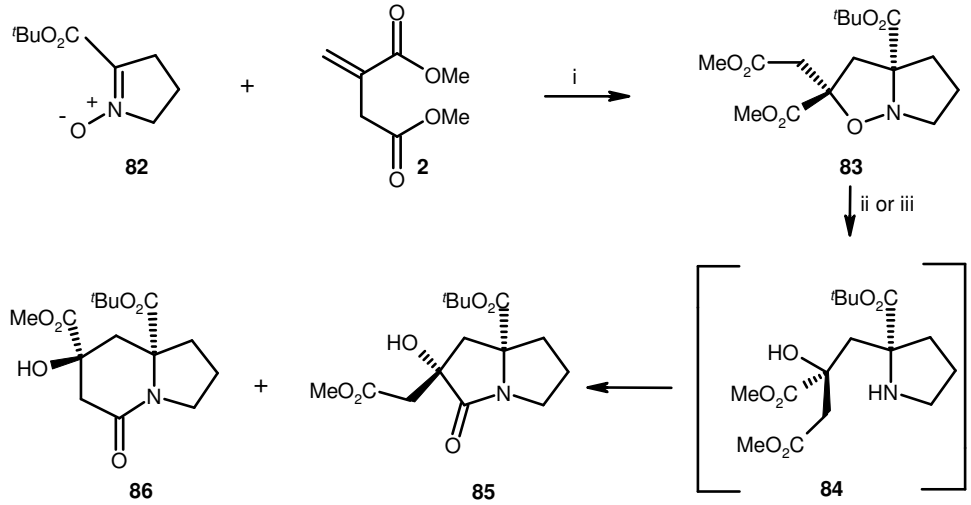
(*S*)-Glutamic acid is the main excitatory neurotransmitter in the mammalian central nervous system. Rolland and co-workers have synthesized 4-substituted glutamic acid derivatives. Schiff base **79** prepared from the commercially available chiral auxiliary (2*R*,3*R*,5*R*)-2-hydroxypinan-3-one.[53] Schiff base **79** on reaction with dimethyl itaconate, in DBU as base at -20°C in THF gave **80** in 64% yield as a mixture of two diastereomers (d.r. = 55/45). Acid treatment of **80** with 15% citric acid in THF at room temperature followed by neutralization with Na_2CO_3 gave six membered glutamic acid derivatives **81** (Scheme 19).[54]



Scheme 19. *Reagents, conditions and yields*: (i) DBU, THF, - 20 °C (64%); (ii) 15% Citric acid, 4 days, rt; (iii) Na_2CO_3 (74%).

1A.2.1.11: Synthesis of pyrrolizidinone and indolizidinone (Cordero and co-workers)

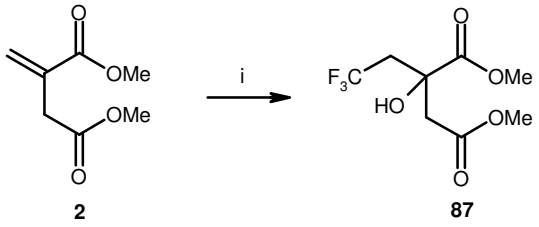
Severely constrained dipeptides able to induce a folding in peptide chains are useful building blocks for synthesizing peptides with a reduced conformational freedom.[55] Cordero and co-workers have synthesized several pyrrolizidinones by the 1,3-dipolar cycloaddition reaction. The cycloadditions of nitrone **82**[56] with dimethyl itaconate was completely regio- and diastereoselective affording one single cycloadduct **83**. The cycloaducct **83** on $Pd(OH)_2$ catalyzed hydrogenation in the presence of 10 mol equiv. of AcOH gave a ca 1.5:1 mixture of pyrrolizidinone **85** and indolizidinone **86** through the competitive 5- and 6-exo-trig cyclizations, respectively, of the inisolable intermediate amino diester **84**. In the absence of AcOH it was found that the 5-exo-trig pathway becomes more important, in this case a ca. 4.5:1 mixture of **85** and **86** were obtained (Scheme 20).[57]



Scheme 20. *Reagents, conditions and yields*: (i) Neat, 42 °C, 2.5 h (73%); (ii) $Pd(OH)_2/C$ (cat), H_2, AcOH (10 mol equiv), MeOH (**85** = 38%, **86** = 26%); (iii) $Pd(OH)_2/C$ (cat), H_2, MeOH (**85** = 73%, **86** = 16%).

1A.2.1.12: Hydroxyalkylation of α,β-unsaturated esters (Nagano and co-workers)

Radical additions have become a very useful synthetic tool and much attention has been paid to the development of efficient carbon–carbon bond-forming reactions.[58] Nagano and co-workers have developed a new method of radical hydroxyalkylation of *α,β*-unsaturated esters using alkyl iodides and trialkylborane in the presence of KF and H_2O. Dimethyl itaconate (**2**) reacted with CF_3 radical to give corresponding hydroxytrifluoromethylated product **87** (Scheme 21).[59]



2 **87**

Scheme 21. *Reagents, conditions and yields*: (i) CF_3I, Et_3B, THF, - 30 °C, rt, 6 h (54%).

1A. 3: Introduction to Chemistry of Itaconic Anhydride

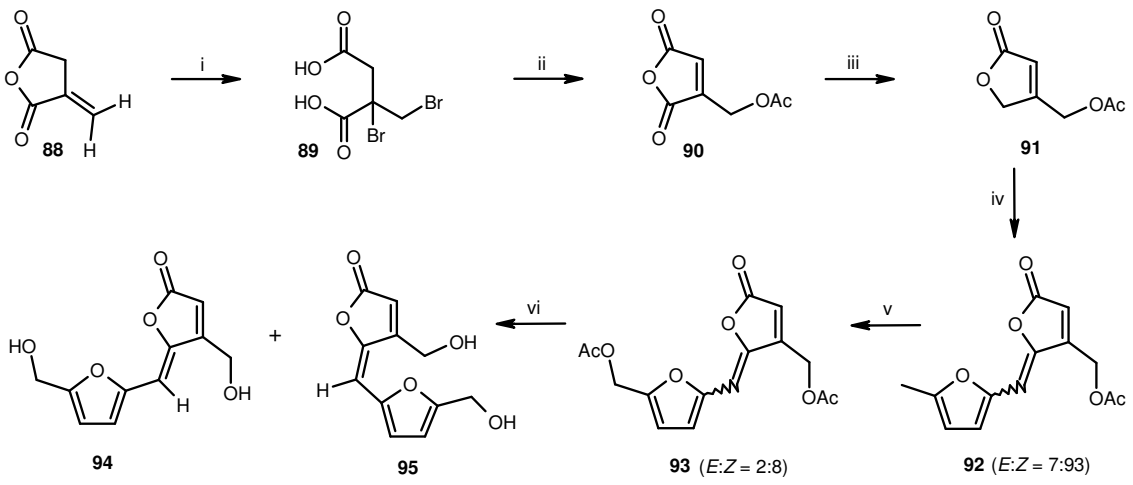
Itaconic anhydride has been synthesised by Gusev *et al* using the carbonilation of propargyl alcohol in MeOH or C_6H_6 containing aq. HI and either Pd black or $Co_2(CO)_8$ as a catalyst.[60] McCabe *et al* have synthesized itaconic anhydride by the reaction of itaconic acid with Al_3^+-montmorillonite in refluxing toluene by the intramolecular cyclocondensation.[61] Kita *et al* have used (trimethylsilyl)ethoxyacetylene as an excellent dehydrating agent for the synthesis of itaconic anhydride from itaconic acid.[62] Liang *et al* have synthesized itaconic anhydride and citraconic anhydride by the double dehydrative decarboxylation of citric acid.[63] Dinand *et al* have observed the formation of itaconic anhydride by the decarboxylation, double bond isomerization, and hydrolysis reactions of *cis*-aconityl anhydride during the amine addition to *cis*-aconityl anhydride.[64] Filimoshkin *et al* have reported the formation of itaconic anhydride by the hydrochlorination and prototropic tautomerism of (chloromethyl)succinic anhydride.[65]

1A.3.1: Synthetic Utility of Itaconic Anhydride

Itaconic anhydride has been used for the synthesis of several natural and unnatural products and this section provides an account of application of itaconic anhydride for the same.

1A.3.1.1: Synthesis of naturally occurring cytotoxic ellipsoidone A and ellipsoidone B

Ellipsoidones A (**94**) and B (**95**) have been isolated by Nomura et al in collaboration with group of researchers from China from the tubers of *Hemsleya ellipsoidea*.[66] The synthesis of ellipsoidones A and B has been reported from our group[67] by using itaconic anhydride. The bromination of itaconic anhydride (**88**) furnished the dibromodiacid **89** in 98% yield. The diacid **89** on treatment with Ac_2O/NaOAc mixture at room temperature for 6 h gave the acetoxymethylmaleic anhydride (**90**). Regioselective reduction of acetoxymethylmaleic anhydride (**90**) gave lactone **91** which on Knoevenagel condensation with 5-methylfurfural gave the monoacetoxymethylbutenolide **92**, selenium dioxide induced allylic hydroxylation of butenolide **92** gave the diacetoxybutenolide **93**. Amano PS catalyzed double deacylation of **93** at pH 7 gave the mixture of natural products **94** and **95**, which upon HPLC separation gave pure **94** and **95** with quantitative recovery (Scheme 22).

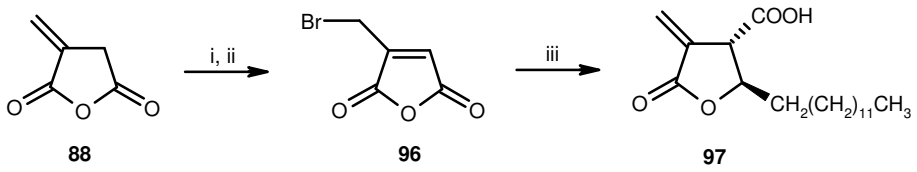


Scheme 22. *Reagents, conditions and yields*: (i) Br_2, CCl_4, rt, 24 h (98%); (ii) Ac_2O, AcONa, rt, 6 h; (iii) (a) $NaBH_4$, THF, 0 °C, 2 h, (b) H^+/HCl (2-steps, 37%); (iv) 5-Methylfurfural, piperidine, rt, 15 h (75%); (v) SeO_2, AcOH (anhydrous), reflux, 6 h (92%); (vi) Amano PS, hexane/benzene (2:1), phosphate buffer pH 7.0, rt, 40 h (95%, **94**:**95** = 86:14).

1A.3.1.2: Synthesis of protolichesterinic acid (Nokami et al)

Protolichesterinic acid (**97**) is a naturally occurring fungal metabolite which shows antibiotic activity.[68] Nokami *et al* have synthesized protolichesterinic acid (**97**) using itaconic anhydride. Itaconic anhydride on bromination and dehydrobromination gave the bromomethylmaleic anhydride (**96**), which on reaction with tetradecenal in the presence of

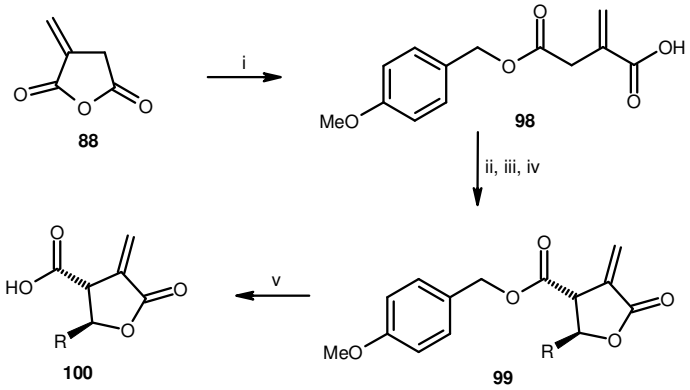
metallic tin gave the natural product protolichesterinic acid (**97**) but only in 25% yield (Scheme 23).[69]



Scheme 23. *Reagents, conditions and yields*: (i) Br_2, CCl_4, rt, 24 h; (ii) Et_3N, CCl_4, -20 °C, 3 h (70%); (iii) $CH_3(CH_2)_{12}CHO$, Sn, DME, 40 °C, 10 h (25%).

1A.3.1.3: Synthesis of α-methylene-γ-butyrolactones (Biel et al)

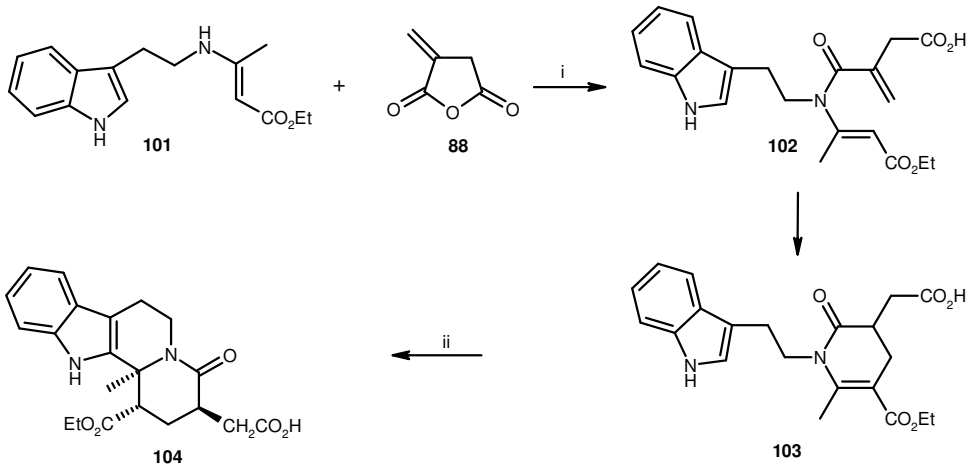
Histone proteins are basic components of the eukaryotic chromatin.[70] The small molecule inhibitors of HATs may open up new possibilities for treatment of pathological diseases like cancer.[71,72] The γ-butyrolactone scaffold is a recurrent structural motif in many natural products.[73] Biel *et al* have descried the synthesis and biological evaluation of a small-molecule inhibitor of the histone acetyltransferase Gcn5. The synthesis of the γ-butyrolactones **100**[74] started with the regioselective ring-opening of itaconic anhydride (**88**) with 4-methoxybenzyl alcohol gave compound **98**. Treatment with lithium bis(trimethylsilyl)amide converted **98** into the corresponding ester enolate, which reacted with an aliphatic aldehyde to give the unisolable hydroxycarboxlic acid**.** The ring-closing reaction was performed in a mixture of chloroform and ethanol to give lactone **99**. The cleavage of the 4-methoxybenzyl ester by heating with acetic acid in molten phenol gave the γ-butyrolactones **100** (Scheme 24).[75]



Scheme 24. *Reagents, conditions and yields*: (i) 4-Methoxybenzylic alcohol, *n*-hexane, toluene, 60 °C, 36 h (88%); (ii) LiHMDS, THF, -78 °C, 1 h; (iii) RCHO, THF, -78 °C, 12 h; (iv) $CHCl_3$, EtOH, rt, 72 h; (v) Phenol, AcOH, 60 °C, 3 h.

1A.3.1.4: Synthesis of natural products like pyrrolinone (Abelman et al)

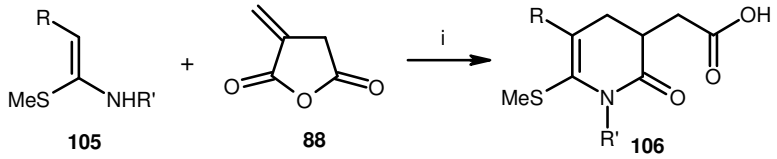
The *N*-acyliminium ion cyclization protocol to prepare alkaloid natural products has been utilized with great effect over the past 30 years.[76] Abelman *et al*[77] have synthesized natural product like heterocyclic scaffolds and templates using the *N*-acyliminium ion as a key intermediate. *β*-Enamino ester was combined with itaconic anhydride the addition occurs regiospecifically to form a pyrrolinone **103** bearing an acetic acid residue which on cyclization gave the natural product like heterocyclic scaffold **104** (Scheme 25). Authors have not mentioned any reason for the reversal in regioselectivity in the condensation of enamine **101** with anhydride **88**.



Scheme 25. *Reagents, conditions and yields*: (i) Heat, 50-60 °C, 4 h; (ii) 1,4-Dioxane, HCl, 40 °C, 1 h (100%).

1A.3.1.5: Synthesis of novel functionalized 1,2,3,4-tetrahydro-2-pyridones and related azabicycles (Junjappa and co-workers)

Substituted six-membered lactams, 2-pyridones, and their dihydro/tetrahydro-derivatives have attracted considerable attention from synthetic organic chemists since these scaffolds are found in a wide variety of naturally occurring alkaloids[78] and compounds with these structural motifs have been shown to exhibit significant pharmacological properties.[79] Junjappa and co-workers have described the synthesis of novel highly functionalized 2-oxo-(1,2,3,4-tetrahydropyridin-3-yl)acetic acids (**106**) via aza-annulation of both acyclic and cyclic *α*-oxo- and *α*-nitro-*N*,*S* and -*N*,*N*-ketene acetals with itaconic anhydride (Scheme 26, Table 4).[80]



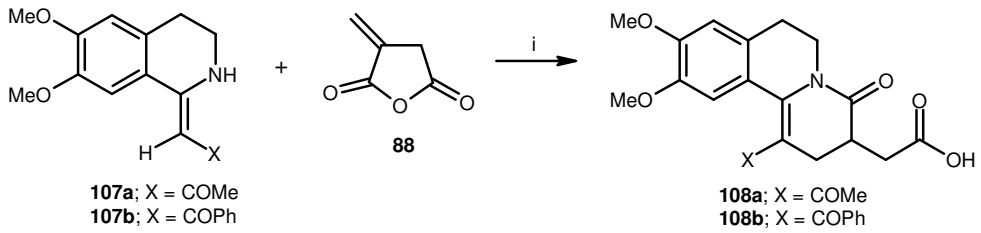
Scheme 26. *Reagents, conditions and yields*: (i) MeCN, reflux, 6-8 h (60-85%).

Table 4. Synthesis of functionalized 2-oxo-(1,2,3,4-tetrahydropyridin-3-yl)acetic acids **106a**-**f**

Product	R	R^1	Yield %
106a	COPh	$PhCH_2$	70
106b	COPh	4-$OMeC_6H_4CH_2$	68
106c	COPh	c-C_6H_{11}	65
106d	COPh	*n*-Bu	55
106e	COPh	Ph	66
106f	COMe	4-$OMeC_6H_4CH_2$	46
106g	NO_2	$PhCH_2CH_2$	80
106f	NO_2	*n*-Bu	55

1A.3.1.6: Synthesis of functionalized benzo[a]quinolizin-4-ones (Junjappa and co-workers)

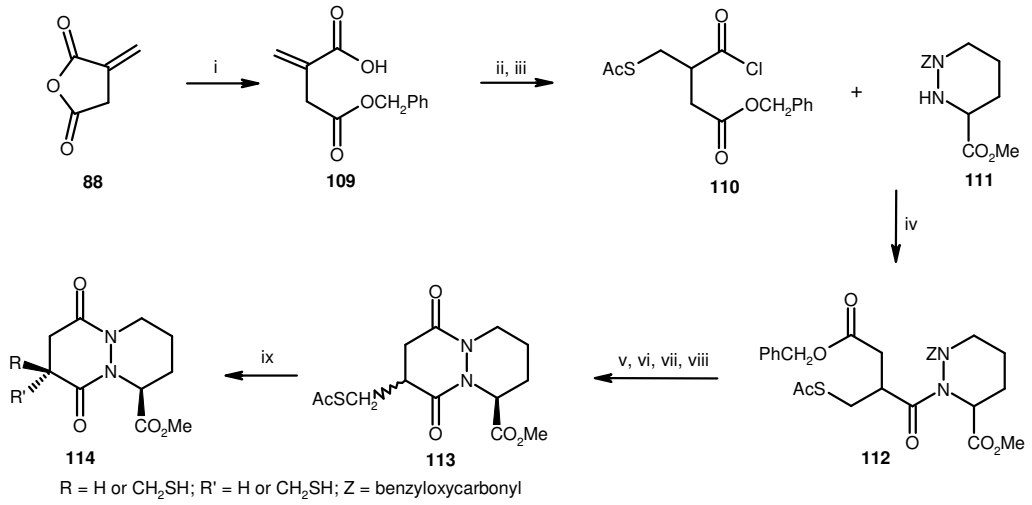
The benzo[*a*]quinolizinone[81,82] derivatives such as Ro 41-3696 have been identified as promising nonsedative hypnotics. Junjappa and co-workers[83] have employed the aza-annulation reactions with various 1,3-biselectrophiles for the synthesis of novel functionalized benzo[*a*]quinolizin-4-ones. Enaminones **107a**,**b**[84] reacted smoothly with itaconic anhydride in refluxing acetonitrile to furnish the corresponding benzo[*a*]quinolizinone-3-acetic acid derivatives **108a**,**b** in excellent yields (Scheme 27).



Scheme 27. *Reagents, conditions and yields*: (i) MeCN, reflux, 6-7 h (**108a** = 81%; **108b** = 85%).

1A.3.1.7: Synthesis of new triazolo, pyrazolo-, and pyridazo-pyridazine derivatives as inhibitors of angiotensin converting enzyme (Hassall et al)

Angiotensin converting enzyme inhibitors have been used as antihypertensive drug. Clinical efficacy has been demonstrated for the nonapeptide SQ 20 88,[85] the orally active agents captopril [86,87] and enalapril.[88a] Hassall *et al* have described the synthesis of bicyclic octahydropyridazo[1,2-*a*]-pyridazinediones memitric of captopril. The bicyclic pyridazo[1,2-*a*]pyridazines were prepared by using itaconic anhydride. Alcoholysis of the anhydride occurs regiospecifically[88b] and the resulting monobenzyl itaconate (**109**) was treated in succession with thioacetic acid (conjugate addition) and phosphorus pentachloride. Acylation of (*Z*)-piperazic acid methyl ester **111**[89] with the acid chloride **110** gave the expected compound **112** which was separated into individual diastereoisomers. The less polar diastereoisomer was debenzylated and then cyclized to give the bicyclic compound **113** which on deacylation gave octahydropyridazo[1,2-*a*]-pyridazinediones **114** (Scheme 28).[90]

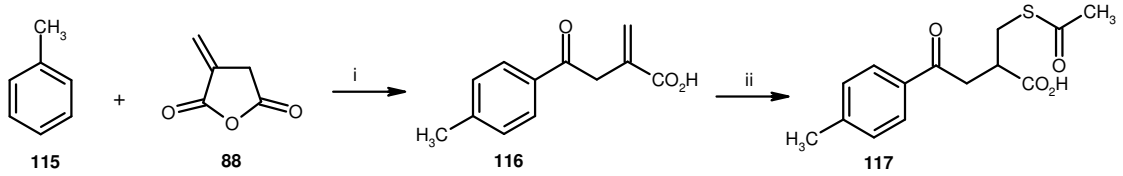


Scheme 28. *Reagents, conditions and yields*: (i) $PhCH_2OH$, reflux, 2 h; (ii) AcSH, reflux, 3 h; (iii) PCl_5, rt (94%); (iv) Aq. NaOH, CH_2Cl_2, rt, 4 h; (v) Separation of diastereoisomers; (vi) HBr, AcOH, rt 1.5 h; (vii) PCl_5, DMF 0 °C – rt, 2.5 h; (viii) Pyridine, rt, 2 h (11%); (ix) Aq. NaOH, MeOH, rt (41%).

1A.3.1.8: Synthesis of esonarimod (Noguchi et al)

Esonarimod, (*R*,*S*)-2-acetylthiomethyl-4-(4-methylphenyl)-4-oxobutanoic acid (**117**) has shown antirheumatic activity.[91-93] Noguchi *et al* have reported an efficient large-scale synthesis of esonarimod. 2-Methylene-4-(4-methylphenyl)-4-oxobutanoic acid (**116**) was obtained by Friedel–Crafts acylation of toluene with commercially available itaconic

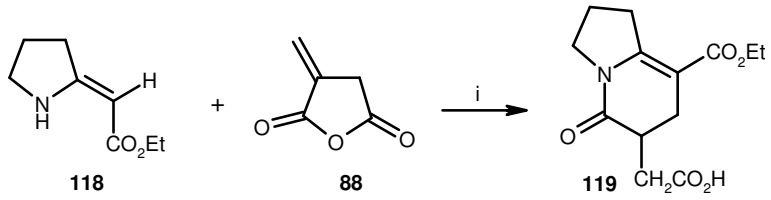
anhydride (**88**) in the presence of aluminum trichloride ($AlCl_3$) in nitrobenzene. Compound **117** was obtained by the Michael addition of thioacetic acid to **116** in the presence of triethylamine and toluene (Scheme 29).[94]



Scheme 29. *Reagents, conditions and yields*: (i) $AlCl_3$, nitrobenzene, 50 °C, 40 min (63%); (ii) Et_3N, toluene, 60 °C, 4 h (74%).

1A.3.1.9: Synthesis of 5-oxoindolizine derivatives (Nagasaka et al)

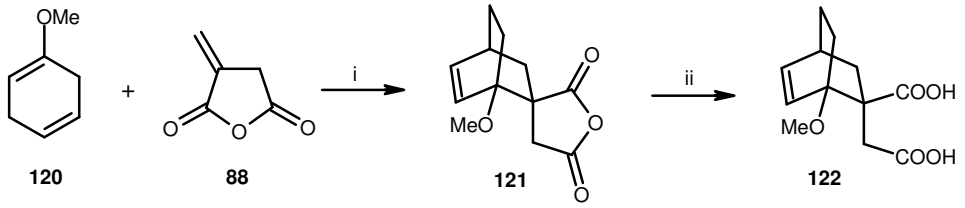
Enamine ketones[95] and enamine esters[96] are versatile intermediates in organic synthesis. Enamine ester ethyl pyrrolidin-2-ylideneacetate (**118**) has been shown to be promising starting material for the synthesis of fused heterocyclic compounds.[97,98] Nagasaka *et al* have reported the synthesis of 5-oxoindolizine derivatives **119** by the anellation reaction of **118** with itaconic anhydride (Scheme 30)[99]



Scheme 30. *Reagent, condition and yield*: (i) C_6H_6, reflux, 1 h (92%).

1A.3.1.10: Synthesis of macrophomate synthase inhibitors (Oikawa et al)

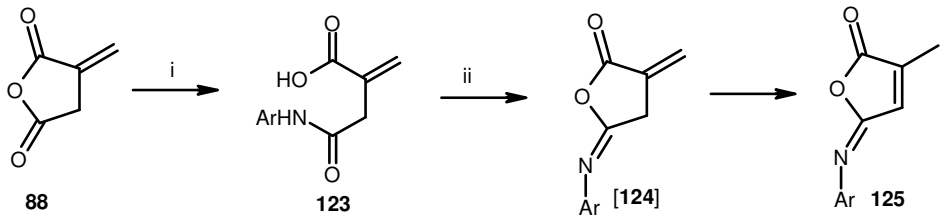
Macrophomate synthase catalyzes an extraordinary three steps transformation involving decarboxylation, C-C bond formation and dehydration. Oikawa *et al* have synthesized several reaction intermediate analogs inhibitor of macrophomate synthase by using itaconic anhydride. Diels Alder reaction of 1-methoxy-1,4-cyclohexadine (**120**) with itaconic anhydride gave the anhydrides **121**. Acidic hydrolysis of anhydride **121** provided the most potent macrophomate synthase **122** (Scheme 31).[100]



Scheme 31. *Reagents, conditions and yields*: (i) Neat, 60 °C (63%); (ii) TFA, THF-H_2O, heat (88%).

1A.3.1.11: Synthesis of α-methylisomaleimide

A large number of maleic anhydrides and maleimides have been extensively used in the synthesis of natural and unnatural bioactive heterocyclic compounds.[101] Synthesis of α-methylisomaleimide has been reported from our group.[102] The regioselective ring opening of itaconic anhydride (**88**) with *p*-toluidine gave the α-methylenesuccinanilic acid **123** in 98% yield. The treatment of acid **123** with cyanuric chloride in the presence of triethylamine gave α-methylisomaleimide **125** in 90% yield via the intermediate α-methyleneisosuccinimide **124** (Scheme 32).



Scheme 32. *Reagents, conditions and yields*: (i) Et_2O, $ArNH_2$, rt, 1 h (98%); (ii) Cyanuric chloride, NEt_3, DCM, 0 °C to rt, 8 h (90%).

1A.4: Introduction to Chemistry of Substituted Itaconimide

Itaconimide has been synthesized by Tsuge *et al*[103] using the reaction between *N*-(trimethylsilylmethyl)pyridinium triflate with *N*-(*p*-tolyl)-malimide in presence of cesium floride. Akiyama *et al*[104] have reported the synthesis of *N*-hydroxyitaconimide by the dehydration of *N*-hydroxyitaconamic acid with dicyclohexylcarbodi-imide (DCC). Majchrzak *et al*[105] have prepared *N*-phenylitaconimide by the thermolysis of 7-phenyl-2,3,7-triazabicyclo[3.3.0]oct-2-ene-6,8-dione in boiling xylene. *N*-(*p*-Tolyl)-itaconimide has been synthesized in our group[106] by the Wittig reactions of maleimide and paraformaldehyde. Hirata and co-workers[107] have synthesized itaconimide by the reaction of itaconic anhydride and amines by heating upto 120 °C under high pressure. Several

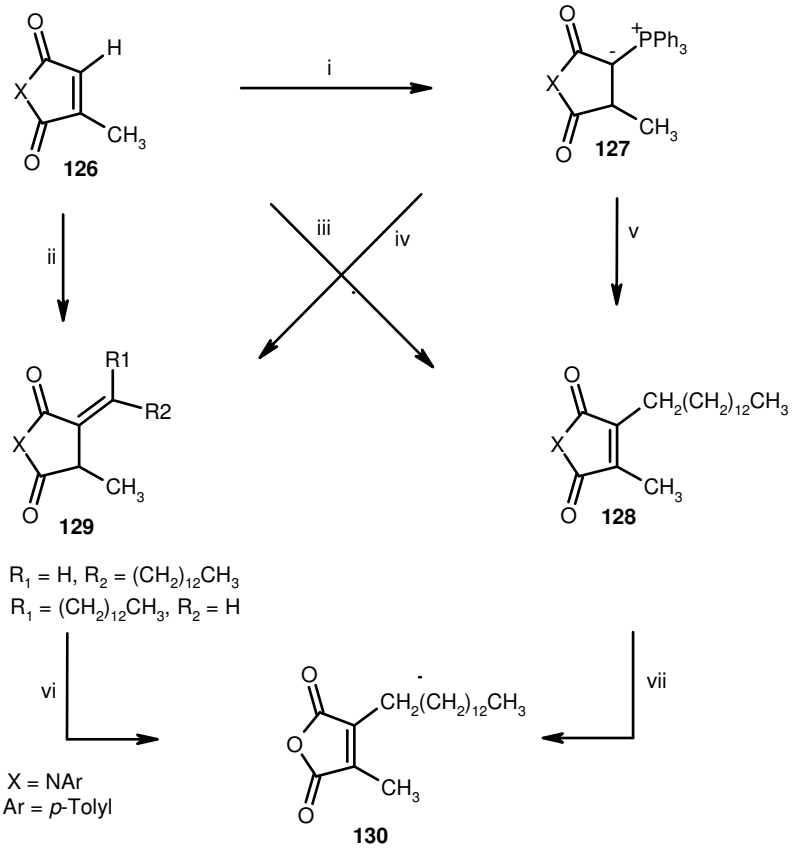
substituted itaconimides have also been synthesized in our group[108] by the Wittig reactions of maleimide and different aldehydes.

1A.4.1: Synthetic Utility of Substituted Itaconimide

Itaconimides have been used for the synthesis of several natural and unnatural products. This section provides application of substituted itacomimides for the synthesis of natural and unnatural products.

1A.4.1.1: Synthesis of chaetomellic anhydride A

Chaetomellic anhydride A and B have been recently isolated[109] from *Chaetomella acutiseta*, and their dianionic forms are potent and highly specific inhibitors of ras farnesyl-protein transferase. Chaetomellic anhydride A has been synthesized in our group[110] by utilizing citraconimide-TPP adduct coupling reaction with tetradecanal. The



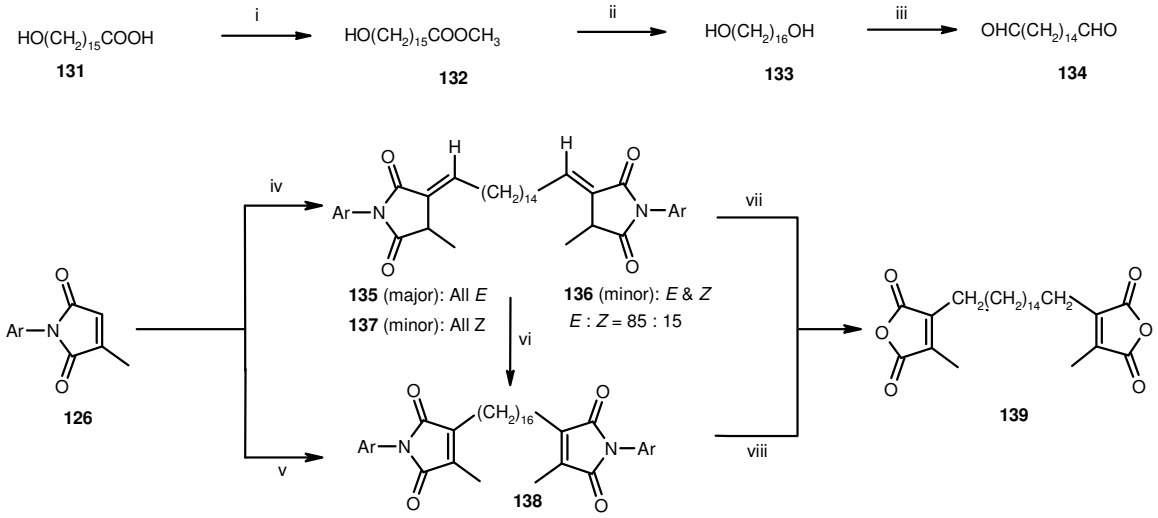
R_1 = H, R_2 = $(CH_2)_{12}CH_3$
R_1 = $(CH_2)_{12}CH_3$, R_2 = H

Scheme 33. *Reagents, conditions and yields*: (i) PPh_3, AcOH, reflux, 2 h; (ii) PPh_3, AcOH, $CH_3(CH_2)_{12}CHO$, reflux, 18 h (71%); (iii) (a) Condition ii, (b) reflux, 140-150 °C, 30 min. (iv) AcOH, $CH_3(CH_2)_{12}CHO$, reflux, 18 h; (v) (a) Condition iv, (b) Reflux, 140-150 °C, 30 min (91%); (vi) (a) CH_3ONa/CH_3OH, reflux, 2 h, (b) H^+/HCl (62%); (vii) (a) $KOH/H_2O/CH_3OH/THF$, reflux, 2 h, (b) H^+/HCl (98%).

first step in this synthetic strategy involves the formation of an ylide methyl-*N*-*p*-tolyl(triphenylphosphoranylidene)succinimide (**127**) obtained from citraconic anhydride which smoothly condensed with the tetradecanal in refluxing glacial acetic acid to yield mixture of geometric isomers **129** in 71% yield, which on thermal isomerisation of double bond (exo to endo) in the same pot directly furnished maleimide derivative **128**. The alkaline hydrolysis of maleimide derivative followed by acidification furnished the chaetomellic anhydride A (**130**) in 98% yield (Scheme 33). The exo-isomers on hydrolysis and acidification also furnished the target molecule but in less yield as compared to maleimide derivative. Amongst the all existing syntheses this approach is most efficient and practical.

1A.4.1.2: Synthesis of tyromycin A

Tyromycin A has been isolated from mycelial cultures of basidiomycete *Tyromyces lacteus* (Fr.) Murr. Tyromycin A was found to inhibit the leucine and cysteine aminopeptidases bound to the outer surface of HeLa S3 cells and it also exhibits cytostatic activity.[111] Tyromycin A has been synthesized in our group[112] by utilizing citraconimide-TPP adduct coupling reaction with aliphatic dialdehyde. The reaction of dialdehyde (**134**) with an excess of citraconimide-TPP adduct in refluxing glacial acetic acid followed by removal of acetic acid in vacuo furnished a mixture of *bis*-condensed exo Wittig products **135** (*E*,*E*

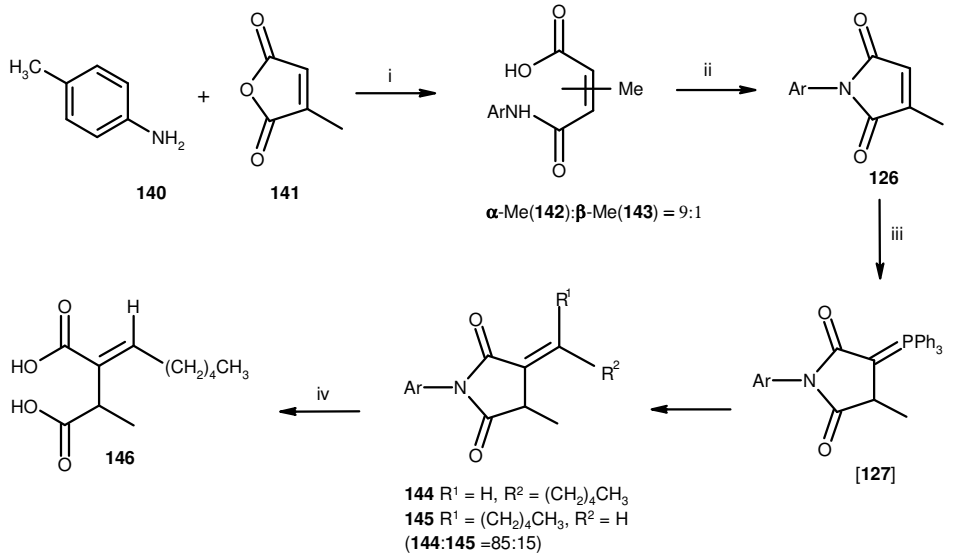


Scheme 34. *Reagents, conditions and yields*: (i) CH_2N_2, Et_2O, 0 ^oC, 2 h (95%); (ii) LAH, Et_2O, rt, 2 h (98%); (iii) PCC, CH_2Cl_2, rt, 10 h (77%); (iv) TPP, AcOH, **134**, reflux, 10 h (70%); (v) (a) TPP, AcOH, **134**, reflux, 10 h, (b) reflux, 140-150 ^oC, 30 min (72%); (vi) Tetralin, reflux, 1 h (98-100%); (vii) (a) CH_3ONa, CH_3OH, reflux, 2 h, (b) H^+/HCl (60%); (viii) (a) KOH, H_2O, THF, CH_3OH, reflux, 2 h, (b) H^+/HCl (98%).

major), **136** (*E*,*Z* minor) and **137** (*Z*,*Z* minor) in 70% yield with an 85:15 ratio of *E*:*Z* geometry of the carbon-carbon double bond, whereas the removal of acetic acid under normal atmospheric pressure and heating the residue for 30 min. at 140-150 °C, the reaction directly furnished the endo bisimide **138** in 72% yield. The mixture of **135** + **136** + **137** in refluxing tetraline underwent *exo* to *endo* isomeristaion to yield bismaleimide derivative **138** in quantitative yield which on treatment with alkali followed by acidification furnished tyromycin A (**139**). The mixture of *exo* isomers (**135, 136** and **137)** on treatment with sodium methoxide in methanol followed by acidification also gave tyromycin A (**139)** in 60% yield (Scheme 34).

1A.4.1.3: Synthesis of (±)-piliformic acid

Piliformic acid (2-hexylidene-3-methylsuccinic acid, **146**) was identified[113] in 1985 as a metabolite of several closely related fungi of the Xylariaceous genera. Piliformic acid has been synthesized in our group[114] by utilizing citraconimide-TPP adduct coupling reaction with hexanal. The reaction of *p*-toluidine (**140**) with citraconic anhydride (**141**) furnished the mixture of methylmaleanilic acids (α-methyl:β-methyl = 9:1) in 95% yield. This mixture of regioisomers **142** and **143** on treatment with acetic anhydride-sodium acetate gave citraconiimide **126**. Imide **126** on Wittig reaction with hexanal and triphenylphosphine in glacial acetic acid yielded a combination of geometric isomers **144**

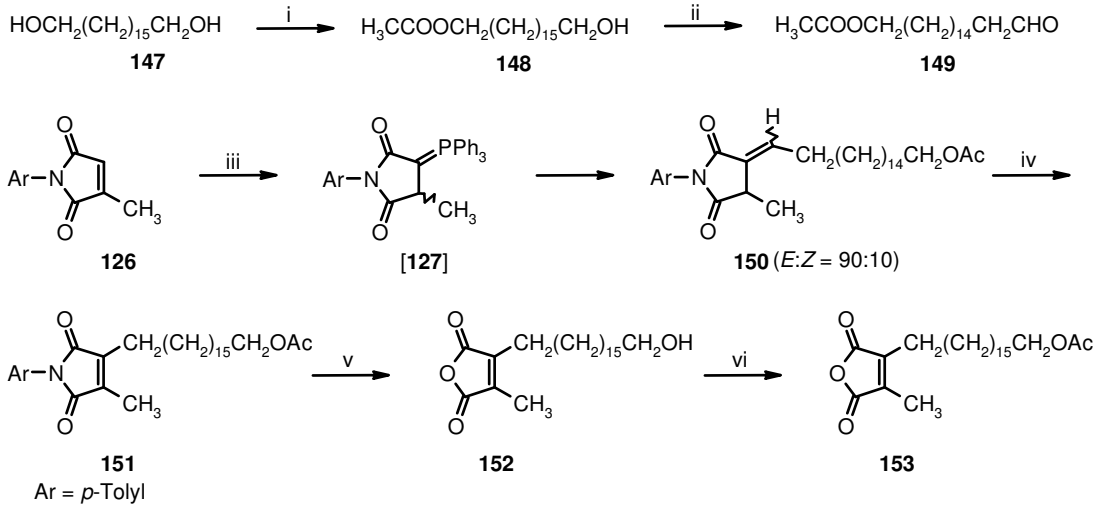


Scheme 35. *Reagents, conditions and yields*: (i) Et_2O, rt, 1 h (95%); (ii) Ac_2O/NaOAc, 60 °C, 1 h (90%); (iii) PPh_3, AcOH, hexanal, reflux, 10 h (83%); (iv) (a) AcOH, Conc. HCl, reflux, 60 h (98%); (b) Recrystalization from excess of hot water, (*E*)-isomer (70%).

and **145** as a thick-oil with 83% yield, *via* an adduct **127**. The mixture of isomers **144** and **145** on refluxing with concentrated hydrochloric acid and glacial acetic acid (1:1) furnished only the mixture of (*E*)- and (*Z*)-piliformic acids in 98% yield without the migration of carbon-carbon double bond. Recrystallisation of this mixture from excess of hot water gave the desired pure (*E*)-isomer in more than 70% yield (Scheme 35).

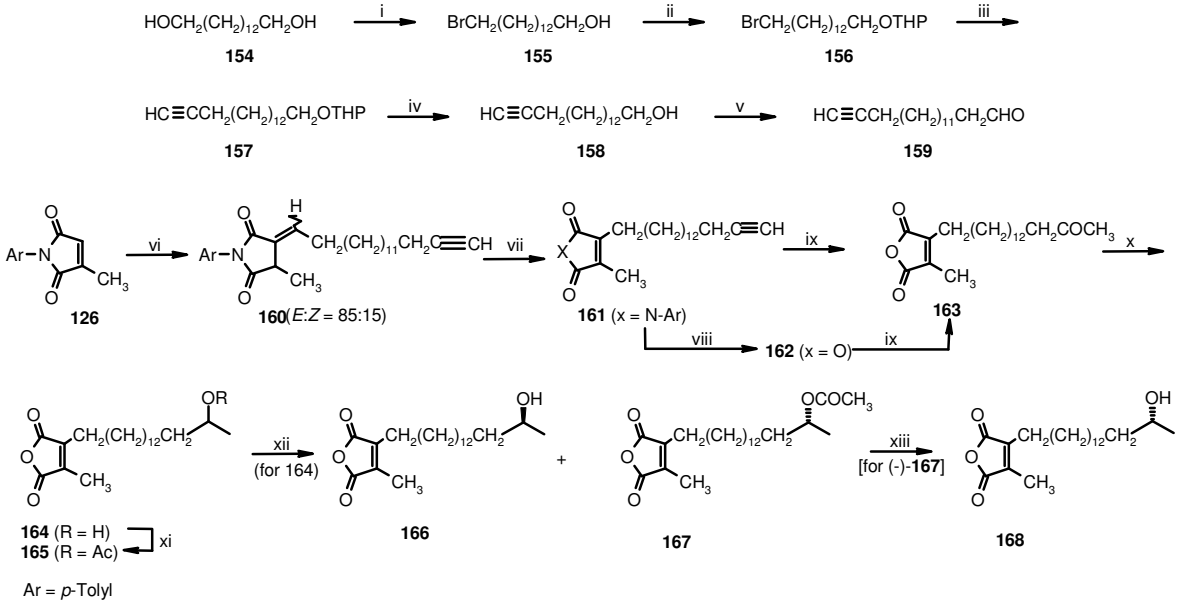
1A.4.1.4: Synthesis of aspergillus acids A-D

Aspergillus acids A-D have been isolated by Assante *et al*, in 1979, from the mould *Aspergillus wentii*.[115] Aspergillus acids A-D have been synthesized in our group by utilizing citraconimide-TPP adduct coupling reaction with corresponding remotely functionalised aldehydes. The triphenylphosphine induced Wittig olefination of citraconimide **126** with acetoxyaldehyde **149** in refluxing acetic acid gave the corresponding *exo*-alkylidene succinimide **150** (*E*:*Z* = 90:10, by ^{1}H NMR) in 70% yield. Trisubstituted exocyclic to tetrasubstituted endocyclic carbon-carbon double bond migration using triethylamine as a base furnished the desired maleimide **151** in 92% yield. The base catalyzed hydrolysis of maleimide **151** furnished the 2-(17-hydroxytetradecyl)-3-methylmaleic anhydride (**152**) in 94% yield. Acetic anhydride mediated acylation of anhydride **152** gave the naturally occurring aspergillus acid A (**153**) in 89% yield (Scheme 36). [116]



Scheme 36. *Reagents, conditions and yields*: (i) Ac_2O (0.98 equiv.), Py, rt, 6 h (79%); (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, – 60 °C, 90 min (89%); (iii) Ph_3P, AcOH, 4, reflux, 18 h (70%); (iv) Et_3N, THF, reflux, 48 h (92%); (v) (a) KOH (30% aq.), THF-MeOH (1:2), reflux, 12 h, (b) H^+/HCl (94%); (vi) Ac_2O, Py, rt, 8 h (89%).

The synthesis of aspergillus acids B-D was accomplished by the Wittig condensation of aldehyde **159** with the imide/TPP adduct generated in situ from citraconimide **126** to gave the *exo*-imide **160** (*E*:*Z* = 85:15, by ^{1}H NMR) in 78% yield with the carbon-carbon triple bond intact. Subsequently, triethylamine induced isomerization of the exocyclic trisubstituted carbon-carbon double bond in *exo*-alkylidene succinimide **160** afforded the tetrasubstituted endocyclic maleimide **161** in 93% yield. Imide **161** on treatment with a mixture of acetic acid and 6 M sulfuric acid (2:1) at 100 °C furnished the natural product **163**. The intermediate acetylinic anhydride **162** on acid catalyzed hydration gave the desired aspergillus acid B (**163**) in 90% yield (Scheme 37). A chemoselective reduction of the ketone carbonyl in **163** was obtained by carrying out sodium borohydride reduction of the corresponding di-sodium salt of **163** followed by quenching the reaction with dilute HCl to exclusively afford the natural product **164** in 81% yield. Hydroxy anhydride **164** upon acetylation with acetic anhydride-pyridine furnished the fourth metabolite in the series **165** with 91% yield. The overall yield of aspergillus acid C in 4-steps was 53% and

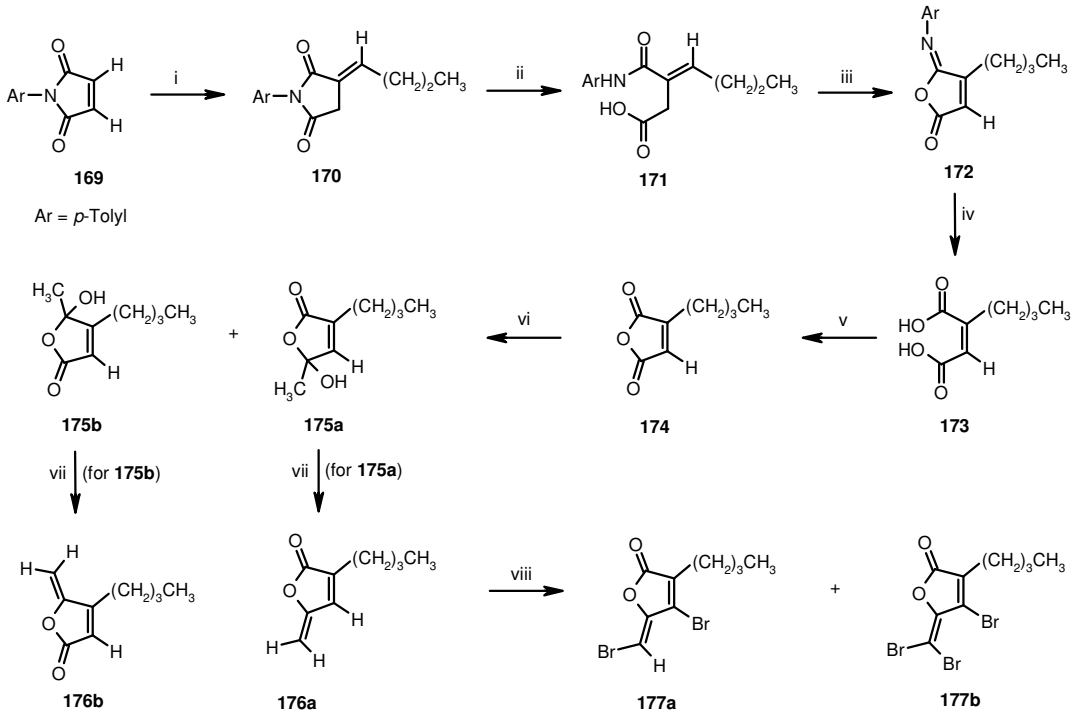


Scheme 37. *Reagents, conditions and yields*: (i) HBr (47% aq.), toluene, reflux, 96 h (85%); (ii) DHP, PPTS (cat.), CH_2Cl_2, rt, 4 h (93%); (iii) NaC≡CH, THF, HMPA, – 78 °C to rt, 40 h (85%); (iv) *p*-TSA, MeOH, rt, 2 h (95%); (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, – 60 °C, 90 min (85%); (vi) Ph_3P, AcOH, **159**, reflux, 24 h (78%); (vii) Et_3N, THF, reflux, 48 h (93%); (viii) (a) KOH (30% aq.), THF-MeOH (1:2), reflux, 12 h, (b) H^+/HCl (95%); (ix) 6 M H_2SO_4-AcOH (1:2), 100 °C, 8 h (90%); (x) (a) Aq. NaOH, THF, 50 ºC, 2 h, (b) $NaBH_4$, 0 ºC to rt, 3 h, (c) H^+/HCl (81%); (xi) Ac_2O, Py, rt, 12 h (91%). (xii) Amano PS, vinyl acetate, hexane-benzene (2:1), 45 ºC, 72 h (**166**, 45%; **167**, 43%); (xiii) (a) Aq. NaOH, THF, 50 ºC, 4 h, (b) H^+/HCl (90%).

that of aspergillus acid D in 5-steps was 48%. Amano PS catalyzed acylation of (±)-**164** in hexane-benzene mixture (2:1) at 45 °C furnished the acids (+)-**166** (45%) and (−)-**167** (43%), after the column chromatographic separation. The base catalyzed hydrolysis of (−)-aspergillus acid D (**167**) furnished (−)-aspergillus acid C (**168**) in 90% yield.

1A.4.1.5: Synthesis of natural fimbrolides

Fimbrolides have been isolated from the red marine algae *Delisea fimbriata* and are bromobutenolides with interesting antifungal and antimicrobial properties.[117a-d] Fimbrolides have been synthesized in our group[118] by utilizing maleimide-TPP adduct coupling reaction with butanal. Wittig olefination of maleimide **169** with butanal in refluxing THF gave the corresponding succinimide **170** which on hydrolysis followed by reaction with cynuric chloride furnished the *n*-butylisomaleimide **172**. The acid-catalyzed hydrolysis of the isomaleimide **172** followed by the acetic anhydride-induced dehydrative cyclization of the formed *n*-butylmaleic acid **173** gave the anhydride **174** in 90% yield. The

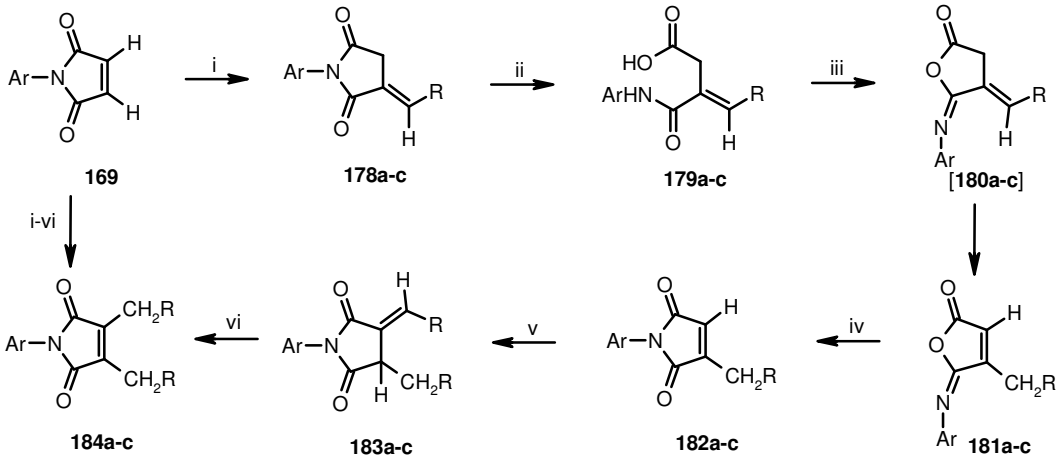


Scheme 38. *Reagents*, *conditions and yields*: (i) PPh_3 (1.00 equiv.), THF, $CH_3(CH_2)_2CHO$ (1.50 equiv.), reflux, 10 h (90%); (ii) Aq. 2 N LiOH, THF, 0 ^oC to rt, 5 h (93%); (iii) Cyanuric chloride (1.10 equiv.), NEt_3 (3.00 equiv.), DCM, 0 ^oC to rt, 8 h (85%); (iv) HCl:AcOH (1:1), reflux, 66 h (96%); (v) Acetic anhydride, 60 ^oC, 3 h (90%); (vi) CH_3MgI (1.10 equiv.), Et_2O, −20 ^oC, 2 h (**175a**: 62%, **175b**: 9%); (vii) P_2O_5, benzene, reflux, 5 h (**176a**: 90%, **176b**: 87%); (viii) (a) Br_2 (2.20/3.30 equiv.), CCl_4, 0 ^oC to rt, 10 h, (b) NEt_3 (2.20/3.30 equiv.), $CHCl_3$, 0 ^oC to rt, 5 h (**177a**: 37/15%, **177b**: 18/41%).

regioselective reaction of methylmagesium iodide with anhydride **174** at –20 ^{o}C produced a mixture of lactols **175a** and **175b** in ~ 85:15 ratio with 71% yield. Silica-gel column-chromatographic separation of **175a** and **175b** followed by P_4O_{10}-induced dehydration gave the butenolides **176a** and **176b** in 90% and 87% yields respectively. Bromination followed by dehydrobromination of **176a** with the use of 2.20 equivalents of bromine gave, **177a** as the major product, while **177b** was formed as the major product with the use of 3.30 equivalents of bromine. The mixture of **177a** and **177b** was separated by HPLC (Scheme 38).

1A.4.1.6: Synthesis of alkyl and dialkyl substituted maleimides

A large number of maleic anhydrides and maleimides have been extensively used in the synthesis of natural and unnatural bioactive heterocyclic compounds.[101] Alkyl and dialkyl substituted maleimides have been synthesized in our group[102] by utilizing maleimide-TPP adduct coupling reaction with several aliphatic aldehydes. Wittig olefination of maleimide **169** with aliphatic aldehydes in refluxing THF gave the corresponding (*E*)-alkylidenesuccinimides **178a-c** in 89-91% yield. The highly regioselective aqueous lithium hydroxide induced hydrolysis of **178a-c** exclusively furnished the *β*-alkylidenesuccinanilic acids **179a-c** in 95-98% yields. The treatment of acids **179a-c** with cyanuric chloride in the presence of triethyl amine as a base furnished the kinetically controlled alkylisomaleimides



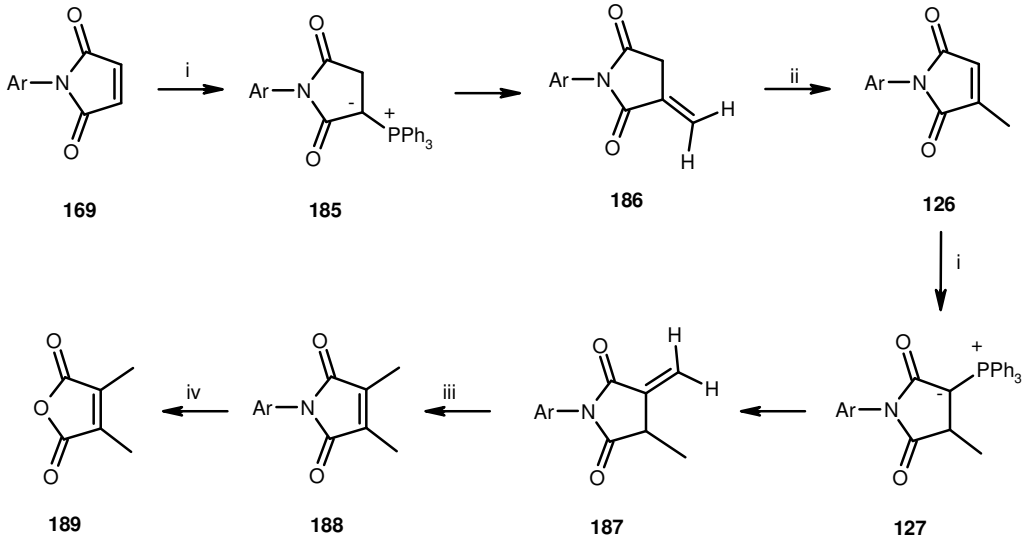
Ar = *p*-Tolyl; **a**, R = -$CH_2(CH_2)_3CH_3$; **b**, R = -$CH_2(CH_2)_7CH_3$; **c**, R = -$CH_2(CH_2)_{11}CH_3$

Scheme 39. *Reagents, conditions and yields*: (i) PPh_3, THF, RCHO, reflux, 10 h (89-91%); (ii) Aq. 2 N LiOH, THF, 0 ^{o}C to rt, 5 h, (95-98%); (iii) Cyanuric chloride, NEt_3, DCM, 0 ^{o}C to rt, 8 h (78-80%); (iv) AcOH, reflux, 5 h (98%); (v) PPh_3, AcOH, RCHO, reflux,18 h (77-80%); (vi) NEt_3 + THF (1:1), reflux, 48 h (95-96%).

181a-c in 78-80% yields. The alkylisomaleimides **181a-c** on refluxing in glacial acetic acid gave the corresponding thermodynamically more stable alkylmaleimides **182a-c** in 98% yield. Finally, the alkylmaleimides on triphenylphosphine induced Wittig condensation with aliphatic aldehydes in refluxing acetic acid furnished the imides **184a-c** via the intermediates **183a-c** in 77-80% yield (Scheme 39).

1A.4.1.7: Synthesis of dimethylmaleic anhydride

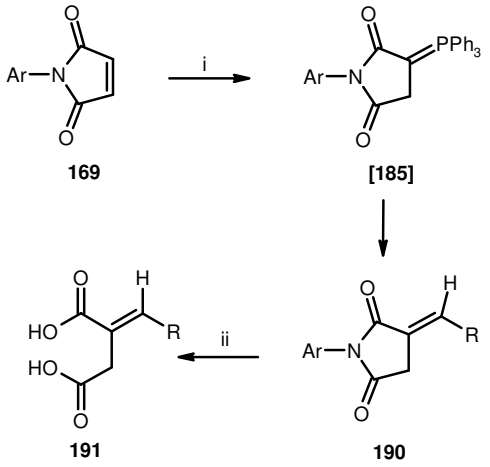
The utilities of methyl and dimethylmaleic anhydrides/imides have been well-proved in practice.[119,120] Dimethylmaleic anhydride/imides have been used as a potential building blocks for the synthesis of adriamycin, daunorubicin derivatives,[121] the naturally occuring cyclopentene 1,3-diones, calythrone,[122] chaetomellic acid A[123] and 2,3-disubstituted maleic anhydride segment of tautomycin.[124] Dimethylmaleic anhydride has been synthesized in our group[106] by utilizing maleimide-TPP adduct coupling reaction with paraformaldehyde. The reaction of maleimide **169** with TPP and paraformaldehyde in glacial acetic acid yielded the corresponding methylmaleimide **126** in 85% yield. The methylmaleimide **126** on further reaction with same reagents and reaction conditions furnished the dimethylmaleimide **188.** The conversion of **169** to **188** was also carried out in one pot in a stepwise fashion without the isolation of **126** with 68% yield. The dimethylmaleimide **188** on alkaline hydrolysis in refluxing aqueous methanol followed by acidification yielded the dimethylmaleic anhydride (**189**) (Scheme 40).



Scheme 40. *Reagents, conditions and yields*: (i) PPh_3, $(CH_2O)n$, AcOH, reflux, 1 h (92%); (ii) Et_3N, THF, reflux, 3 h (93%); (iii) 50 °C, 3 h (98%); (iv) Aq. MeOH, KOH, reflux, 2 h, (b) H^+/HCl (97%).

1A.4.1.8: Synthesis of (E)-alkylidenesuccinic acids

Alkyl and alkylidenesuccinic anhydrides have been used as a potential precursors for synthesis of many bioactive natural and unnatural products.[125a-j] (*E*)-Alkylidenesuccinic acids has been synthesized in our group[108] by utilizing maleimide-TPP adduct coupling reaction with several aliphatic aldehydes. The reaction of maleimide **169** with triphenylphosphine (TPP) formed the intermediate Wittig adduct **185**, which in situ condensed very smoothly with aliphatic aldehydes to yield the alkylidenesuccinimides **190** in excellent yields. The alkylidenesuccinimides **190a**-**e** on hydrolysis under reflux with concentrated hydrochloric acid and glacial acetic acid (1:1) mixture gave the corresponding desired (*E*)-alkylidenesuccinic acids **191a**-**e** in quantitative yields (Scheme 41).

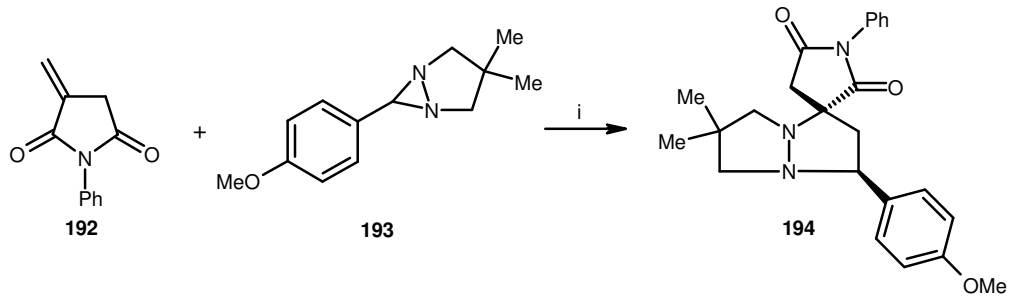


Ar = *p*-Tolyl, **a**, R = $(CH_2)_2CH_3$; **b**, R = $(CH_2)_4CH_3$; **c**, R = $(CH_2)_8CH_3$; **d**, R = $(CH_2)_{10}CH_3$; **e**, R = $(CH_2)_{12}CH_3$

Scheme 41. *Reagents, conditions and yields*: (i) PPh_3, RCHO, THF, reflux, 10 h (85-90%); (ii) Conc.HCl, AcOH, reflux, 60 h (96-98%).

1A.4.1.9: Addition of itaconimide to 6-aryl-1,5-diazabicyclo[3.1.0]hexane (Molchanov et al)

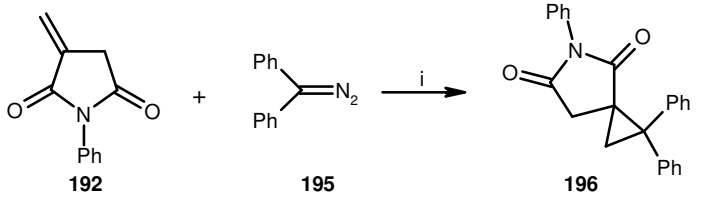
Molchanov *et al* have reported that the thermolysis of 6-aryl-1,5-diazabicyclo[3.1.0]hexane (**193**) in the presence of itaconimide **192** gave the corresponding 1,3-dipolar cycloaddition product **194**. The reaction was regioselective and only one regioisomer was obtained (Scheme 42).[126]



Scheme 42. *Reagents, conditions and yield*: (i) Toluene, 110 °C, 2 h (34%).

1A.4.1.10: Synthesis of 1-pyrazoline derivatives (Molchanov et al)

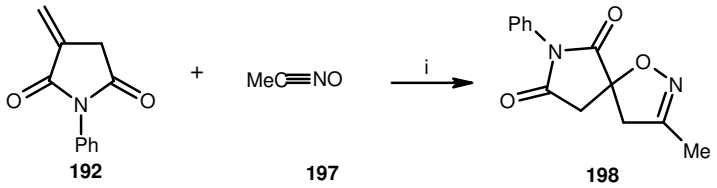
Pyrazoline derivatieves were synthesized by the reactions of aliphatic diazo compounds with itaconimide. Molchanov *et al* have reported the reaction between *N*-arylsubstituted itaconimide **192** with the diphenyldiazomethane **195** to furnish 5-aryl-4,6-dioxo-1,1-diphenyl-5-azaspiro[2.4]heptane (**196**) (Scheme 43).[127]



Scheme 43. *Reagents, conditions and yield*: (i) CH_2Cl_2, rt, 48 h (64%).

1A.4.1.11: Cycloadditions of Nitrile Oxides to Itaconimides (Jan et al) [128]

New spiro heterocycle, 1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-dione (**198**), has been synthesized by Jan *et al* by the reaction of itaconimide with nitrile oxide **197** (Scheme 44).[128]

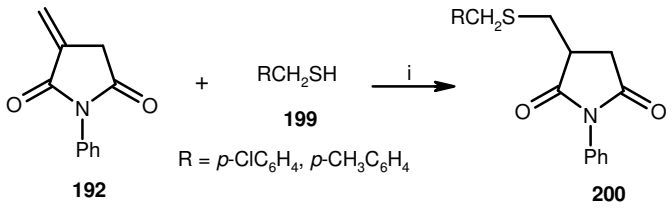


Scheme 44. *Reagents, conditions and yields*: (i) Et_3N, CH_2Cl_2 (73%).

1A.4.1.12: Nucleophilic addition of thiols and amine to N-arylitaconimide

[A] *White's approach*

Nucleophilic addition of thiols **199** to *N*-phenylitaconimide (**192**) has been reported by White *et al* to give Michael adducts **200** in good yields (Scheme 45).[129]



Scheme 45. *Reagents, conditions and yields*: (i) Et_3N, CH_3CN (72-17%).

[B] *Veverka's approach*

Veverka M[130] has reported that the addition of amines to *N*-arylitaconimides provide arylsuccinimides in 33-78% yield. While treatment of *N*-arylitaconimides with amine in the presence of pyridine afford arylcitraconimides.

1A.4.1.13: Utility of itaconimide in polymer synthesis

Mohamed and co-workers[131] have investigated several *N*-(substituted phenyl)itaconimide derivatives as organic photo-stabilizers for poly(vinyl chloride) (PVC) plasticized with dioctyl phthalate (DOP). Anand *et al*[132] have reported the synthesis, characterization, and thermal behavior of copolymers of Me methacrylate (MMA) and *N*-(p-tolyl)itaconimide (PTI)/*N*-phenylitaconimide. Solanki *et al*[133] have reported the synthesis and characterization of bisitaconimides on the basis of 4,4'-diaminodiphenyl ether, 2,2'-bis[4-(4-aminophenoxy)phenyl]propane, 1,3-bis(4-aminophenoxy)benzene, and 1,4-bis (4-aminophenoxy)benzene. Yamazaki, *et al*[134] have reported the effects of the *N*-substituents on the polymerisation. rates, propagation rate constants, cross-propagation rate constants and termination rate constants.

1A.5. Summary

In summary, in the present section we have described the results on reactions of itaconic acid, dialkyl itaconates, itaconic anhydrides and itaconimides. Several types of reactions with carbon, nitrogen, oxygen and sulfur nucleophiles have been performed on these potential precursors to design natural and unnatural compounds in good yields via the regioselective reactions with carbonyl carbon and/or Micheal addition to the activated carbon-carbon double bond. The reported asymmetric hydrogenations on these substrates are also noteworthy. We belive that all these starting materials have broad scope to design several desired organic target molecules with a concise and efficient routes.

1A.6. References

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1B. Section B

Chemo-, Regio- and Stereoselective Reactions of o-Aminothiophenol and o-Aminophenyl Disulfide with Itaconic Anhydride and (−)-Dimenthyl Itaconate: Simple Access to Enantiomerically Pure 1,5-Benzothiazepines and Benzothiazolyl-2-methylacrylic Acid

This section features the following topics:

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1B. Section B: Chemo-, Regio- and Stereoselective Reactions of *o*-Aminothiophenol and *o*-Aminophenyl Disulfide with Itaconic Anhydride and (–)-Dimenthyl Itaconate: Simple Access to Enantiomerically Pure 1,5-Benzothiazepines and Benzothiazolyl-2-methylacrylic Acid

1B.1. Background

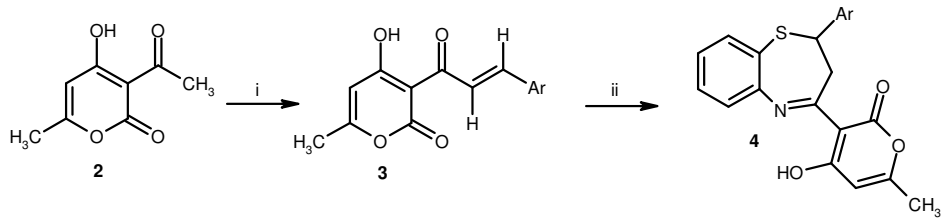
Heterocycles play a pivotal role in pharmaceutical and agrochemical industries.[1] The 1,5-benzothiazepines are famous for their antimitochondrial sodium-calcium exchanger (mNCE),[2a] angiotensin converting enzyme inhibitor,[2b] antiinflammatory,[2c] anticancer,[2d] vasodilating,[2e] antihypertensive,[2f] platelet aggregation inhibitory,[2g] antisycotic,[2h] antidiabetic,[2i] cardioprotective,[2j] antifungal,[2k] antibacterial[2l] and anti-HIV[2m] activities. 1,5-Benzothiozepines behave as effective chiral solvating agents (CSA) for NMR enantiomeric excess (ee) determination of different classes of compounds such as α-arylalkanoic acids, *α*-hydroxy acids, alkanesulfonic acids, alcohols and 1,5-benzothiazepines.[2n] Several synthetic stratergies are known in literature for the synthesis of variety of seven-membered 1,5- and 1,4-benzothiazepines owing to there biological activities.

1B.1.1: Synthetic approaches towards 1,4- and 1,5-benzothiazepines

The biological activities associated with 1,4- and 1,5-benzothiazepines led to great interest in the developing new synthetic routes. Before discussing our results, the reported synthetic approaches towards 1,4- and 1,5-benzothiazepines are illustrated in brief in the following part.

[A] *Prakash's approach*[3a]

Prakash *et al* have reported the synthesis of several substituted dihydro-1,5-benzothia-zepines **4** by the reaction of *o*-aminothiophenol (**1**) with chalcone analogs of dehydroacetic acid **3**, which was prepared by the condensation of dehydroacetic acid (**2**) with benzaldehydes or their heterocyclic analogs in chloroform in the presence of piperidine (Scheme 1).

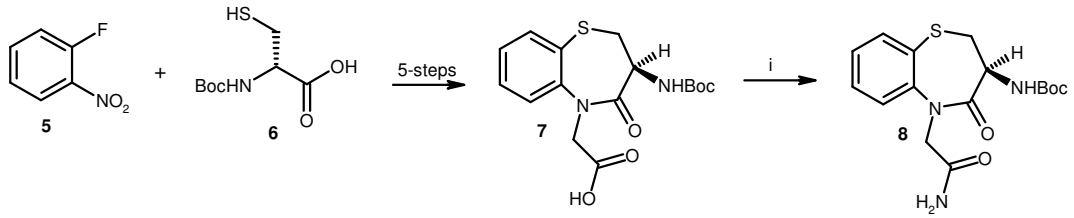


Ar = C_6H_5, 4-Cl-C_6H_4, 4-CH_3-C_6H_4, 2-OH-C_6H_4, 4-OH-C_6H_4, 4-OCH_3-C_6H_4, 4-$N(CH_3)_2$-C_6H_4
2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2-thienyl, 4-pyridyl.

Scheme 1. *Reagents, conditions and yields*: (1) ArCHO, $CHCl_3$, piperidine (43-85); (ii) *o*-Aminothiophenol (**1**), piperidine, EtOH, reflux, 15 min (76-86%).

[B] *Amblard's approach*[3b]

Amblard *et al* have reported the synthesis of Boc-DBT-NH_2 (**8**) [DBT = *S*-[amino]-5-carbethoxymethyl-2,3-dihydro-1,5-benzothiazepine-4(5H)-one] and showed that this constrained dipeptide mimetic adopts a type II´ β-turn in the solid state. IR and NMR studies indicated that the folded conformation is retained in solution. Boc-DBT-OH (**7**) was obtained by a five-step procedure starting from the nucleophilic aromatic substitution by a thiol unit of Boc-$_D$-Cys-OH (**6**) on 1-fluoro-2-nitrobenzene (**5**).[4] Condensation of Boc-DBT-OH with NH_4OH was carried out through activation with isobutyl chloroformate in the presence of *N*-methylmorpholine to afford Boc-DBT-NH_2 (**8**) in quantitative yield (Scheme 2).

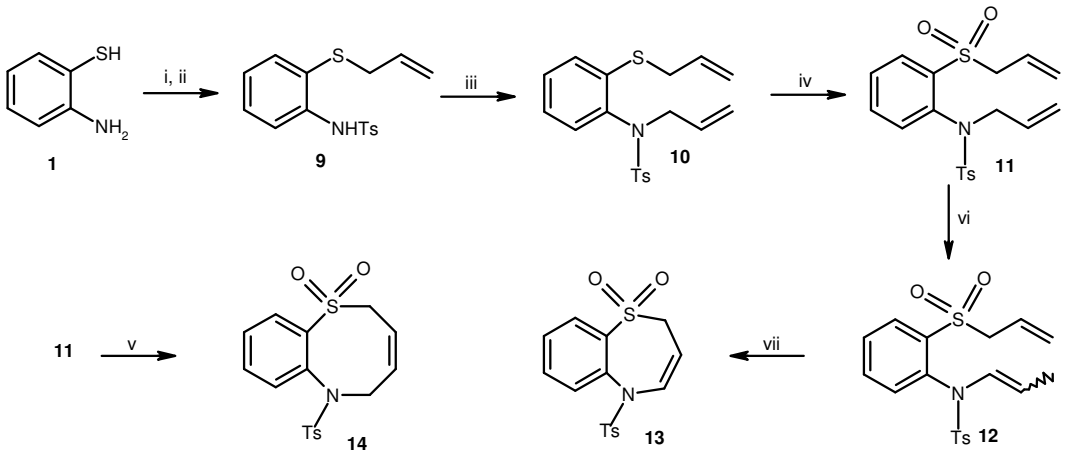


Scheme 2. *Reagents and conditions*: (i) IBCF, NMM, NH_4OH.

[C] *van Otterlo's approach*[3c]

van Otterlo *et al* have reporetd the synthesis of 7-membered ring system, 2,5-dihydro-1,5-benzothiazepine 1,1-dioxide by isomerization and ring-closing metathesis. *o*-Aminothiophenol (**1**) was monoalkylated with allyl bromide and the amine subsequently protected with a tosyl group to afford compound **9**. Furthermore, the allylation readily afforded compound **10**. Compound **10** was oxidized to the corresponding sulfone **11** and the RCM successfully afforded the product **14** in good yield. Finally, the sequential isomerization of compound **11** furnished compound **12** in which only the *N*-allyl group

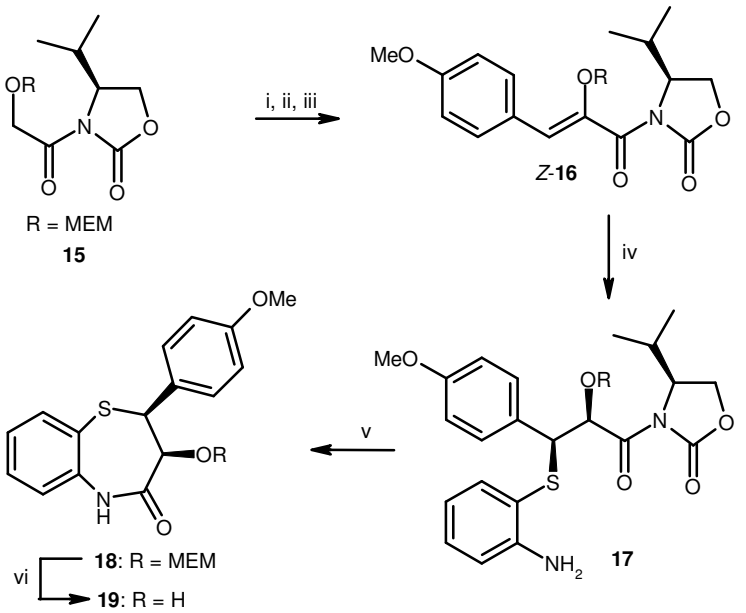
was isomerized. Subsequently, the RCM of **12** gave the 7-membered 1,5-benzothiazepine **13** (Scheme 3).



Scheme 3. *Reagents, conditions and yields*: (i) Allyl bromide, MeOH, NaOH, H_2O, rt, 2 h (71%); (ii) *p*-TSCl, pyridine, CH_2Cl_2, 45 °C, N_2, 24 h (97%); (iii) K_2CO_3, allyl bromide, acetone, rt, 24 h (99%); (iv) *m*-CPBA (2.2 equiv), CH_2Cl_2, -5 °C, 48 h (71%); (v) 5% Grubb's catalyst, $CHCl_3$, rt, 24 h, then 45 °C, 24 h (95%); (vi) 10% $[RuClH(CO)(PPh_3)_3]$, toluene, 105 °C, 24 h (84%); (vii) 5% Grubb's catalyst, toluene, 50 °C, 24 h, then further 5% Grubb's catalyst, 80 °C, 24 h, **13** (41%) and **12** (59%).

[D] *Naito's approach*[3d]

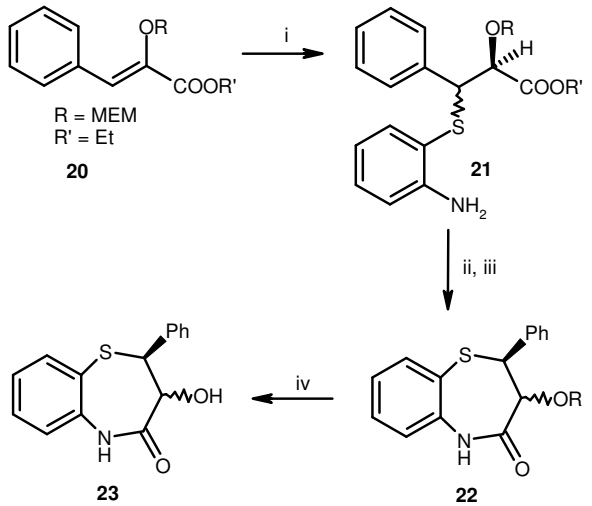
Naito and co-worker have reported that the diastereoface differentiating nucleophilic addition of thiophenol to olefins delivers a new concomitant asymmetric construction of two contiguous stereogenic centers and has been successfully applied to the asymmetric synthesis of (+)-diltiazem. Aldol condensation of the imide **15** and anisaldehyde followed by the dehydration gave a 4:l mixture of the *Z*- and *E*-olefins **16** which was readily separated by column chromatography. Addition reaction of *o*-aminothiophenol to the *Z*-isomer of **16** proceeded smoothly and furnished (2*S*,3*S*)-adduct **17** with high diastereoselectivity (threo:erythro = 82:18) in 97% yield (Scheme 4). The adduct **17** was also obtained with the almost same diastereoselectivity from the corresponding *E*-isomer of **16** under the same reaction conditions. The adduct **17** on treatment with trimethylaluminum in refluxing methylene dichloride give the optically pure lactam **18** in 78% yield along with the efficient recovery of the valuable auxiliary. Removal of a methoxyethoxymethyl group in **18** with titanium tetrachloride afforded the hydroxylactam **19**, conversion of **19** into (+)-diltiazem hydrochloride is known in letrature.[5]



Scheme 4. *Reagents, conditions and yields*: (i) LDA, anisaldehyde; (ii) MsCl, Et_3N; (iii) DBU (61%); (iv) Litium salt of *o*-ATP. *o*-ATP, - 40 °C (97%); (v) $AlMe_3$, CH_2Cl_2, reflux (78%); (vi) $TiCl_4$ (83%).

[E] *Ninomiya's approach*[3e]

Ninomiya and co-workers have reported a stereocontrolled synthesis of (±)-diltiazem analog by applying nucleophilic addition of 2-aminothiophenol to *α*-alkoxycinnamic acid derivatives. Michael additions of 2-aminothiophenol to cinnamates **20**[6] with an *a*-MEM-protected group gave the mixture of *threo*-**21** and *erythro*-**21** in good yield and moderate selectivity (Scheme 5). The mixture of *threo*-**21** and *erythro*-**21** was hydrolyzed by the

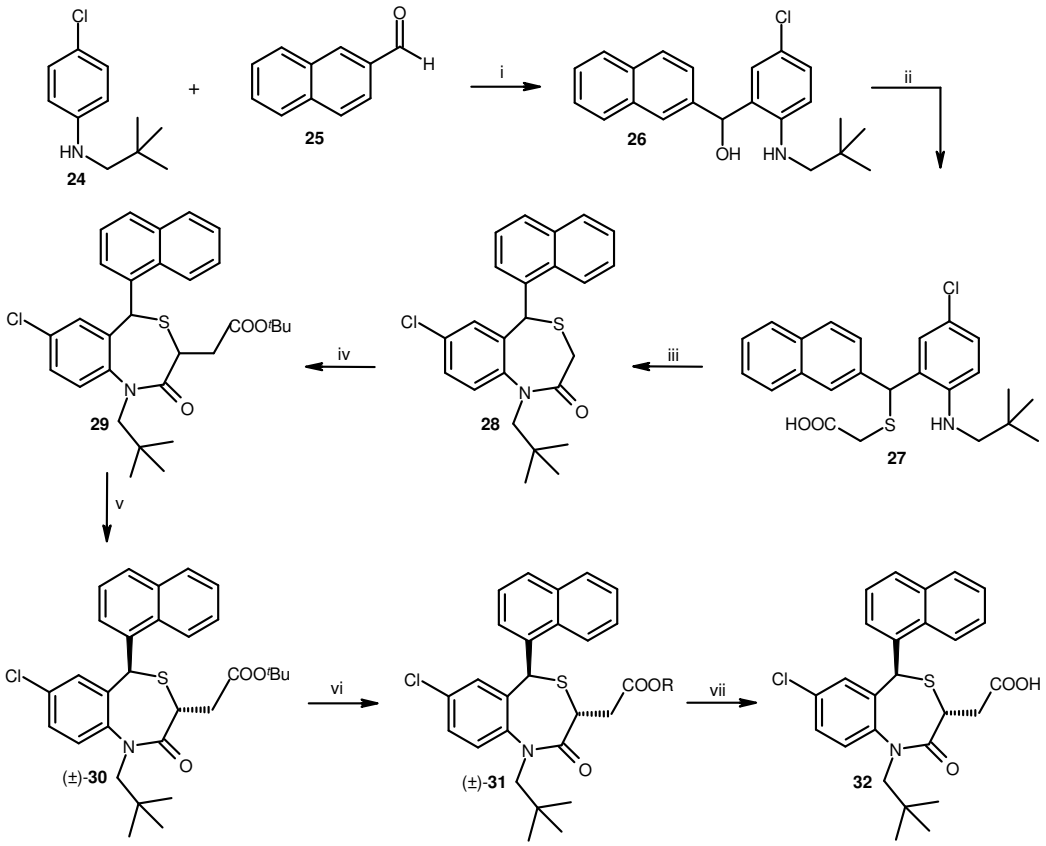


Scheme 5. *Reagents, conditions and yields*: (i) Litium salt of *o*-ATP, *o*-ATP, -40 °C (97% *threo*-**21**: *erythro*-**21** = 74:26); (ii) 5% NaOH; (iii) MS-4Å, xylene, reflux (2,3-*cis*-**22**:2,3-*trans*-**22** = 30:13%); (iv) $TiCl_4$, CH_2Cl_2, 0 °C (83%).

treatment with 5% sodium hydroxide to give the aminocarboxylic acids which were heated in the presence of MS-4Å under reflux in xylene to give a mixture of two lactams, 2,3-*cis*-**22** and 2,3-*trans*-**22** in 30 and 13% yields, respectively. Removal of the MEM group of **22** with titanium tetrachloride afforded the hydroxylactum **23**. Conversion of **23** into (±)-diltiazem analog is known in letrature.[7]

[F] *Liu's approach*[3f]

Liu and co-workers have reported the synthesis of 1,4-benzothiazepine skeleton, useful for the synthesis of potent squalene synthetase inhibitors, via enzymatic resolution providing excellent yield and enantiomeric purity. The synthesis started with the Friedel–Crafts hydroxyalkylation of 4-chlorophenyl-2,2-dimethylpropyl amine (**24**) with 1-naphthaldehyde (**25**) gave compound **26**. The compound **26** was treated with



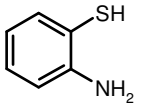
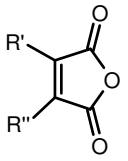
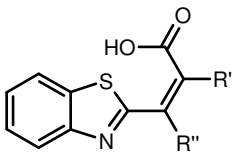
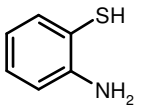
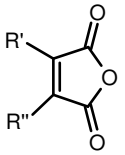
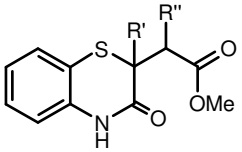
Scheme 6. *Reagents, conditions and yields*: (i) BCl_3, CH_2Cl_2, benzene, Et_3N (80%); (ii) Mercaptoacetic acid, 6N HCl, 100°C (90%); (iii) Morpho-CDI, CH_2Cl_2 (75%); (iv) LDA, THF, *t*-butyl bromoacetate (85%); (v) K_2CO_3, MeOH, 65°C (80%); (vi) (a) CF_3COOH, CH_2Cl_2 (95%), (b) H^+, ROH, (80–95%); (vii) enzyme, 10% DMF, pH 7 phosphate buffer, H_2O (lipase FAP-15, 45%, 98% *ee*; lipase from rhizopus arrhizus, 36%, 99.5% *ee*).

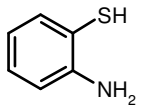
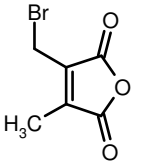
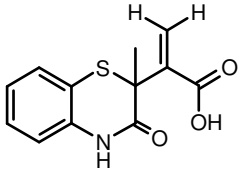
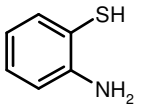
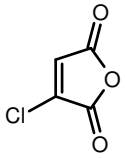
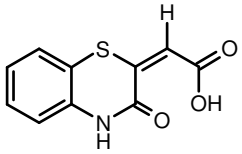
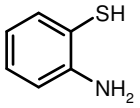
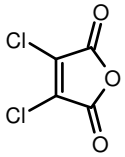
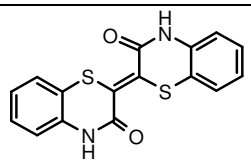
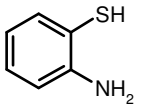
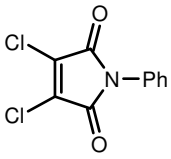
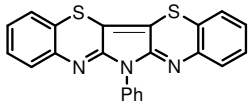
mercaptoacetic acid to produce the corresponding thiacarboxylic acid **27**. Subsequently, carbodiimide (morpho-CDI) was employed for the intramolecular amidation to provide the 1,4-benzothiazepine derivative **28**. Compound **28** was then reacted with *t*-butyl bromoacetate to yield the alkylated product **29** (Scheme 6). The pure *trans*-isomer **30**, was obtained after recrystallization. To prepare the enantiomerically pure **32**, compound **30** was trans esterified to variety of esters **31**, to further investigate their enzymatic resolution. Two lipases, rhizopus arrhizus and FAP-15, provided promising results when the chloromethyl ester was used as the substrate. When lipase FAP-15 was used 45% yield (90% theoretical yield) and 98% *ee* of **32** was obtained while 36% yield (72% theoretical yield) and 99.3% *ee* of **32** was obtained with the lipase from rhizopus arrhizus.

1B.1.2: Synthesis of five and six- membered thioaza-heterocyclic systems

The nucleophilic reactions of a variety of cyclic anhydrides/imides with *ortho*-aminothiophenol (*o*-ATP) have been used to design structurally interesting and biologically important five and six membered thioaza-heterocyclic systems via the intramolecular Michael addition, condensation and dehydration pathway. The representative examples of above mentioned class of reactions are summarized in the following table.

Table: Heterocycles Derived from *ortho*-Aminothiophenol and Cyclic Anhydrides/Imides

Sr. No	*ortho*-Aminothio-phenol	Cyclic anhydrides/ imides	Reaction conditions (% Yield)	Product	Ref.
1		 R' = H R" = OH, OMe	(i) Acetone, reflux or (ii) Pyridine, reflux (75%)		8a
2		 R' = H, Me	(i) Et_2O, rt (R'/R'' = H) (98%) (ii) AcOH, reflux (R'/R'' = Me) (90%) (iii) PhCl, reflux (R' = H, R'' = Ph)		8b, 8c

		R" = H, Me, Ph	(87%)		
3			(i) $CHCl_3$, -15 °C to rt, 3 h (90%)		8d
4			(i) Acetone, rt (60%)		8e
5			(i) Acetic acid, reflux (60%)		8f
6			(i) Acetic acid, reflux (60%)		8f

The various examples mentioned in the above table reveal that the nucleophilic reactions of symmetrical and unsymmetrical cyclic anhydrides have provided several interesting and important heterocyclic systems.

1B.2. Present Work Results and Discussion

In continuation of our studies[9] on cyclic anhydride chemistry to design bioactive natural and unnatural heterocyclic compounds, we felt that, with a proper combination of reactivity and selectivity, the itaconic anhydride (**33**) and *o*-ATP (**1**) could be used as potential building blocks to synthesize higher-membered heterocycles. The Michael-type additions of aromatic thiols to activated carbon-carbon double bonds and nucleophilic ring opening of cyclic anhydrides with primary aromatic amines are well known in the litrature.[10] We envisaged that in the reaction of itaconic anhydride (**33**) with *o*-ATP, the Michael type addition of thiol to a highly activated carbon-carbon double bond in itaconic anhydride followed by an intramolecular nucleophilic ring opening of an adjacent anhydride carbonyl with an amine moiety would provide benzothiazepinylacetic acid **35a**, while the first nucleophilic regioselective ring opening of anhydride **33** at the unconjugated carbonyl with primary amine moiety followed by intramolecular dehydrative

condensation/Michael type addition of thiol unit would provide an easy access to benzothiazole/benzothioazocine system **47** (Figure 1).

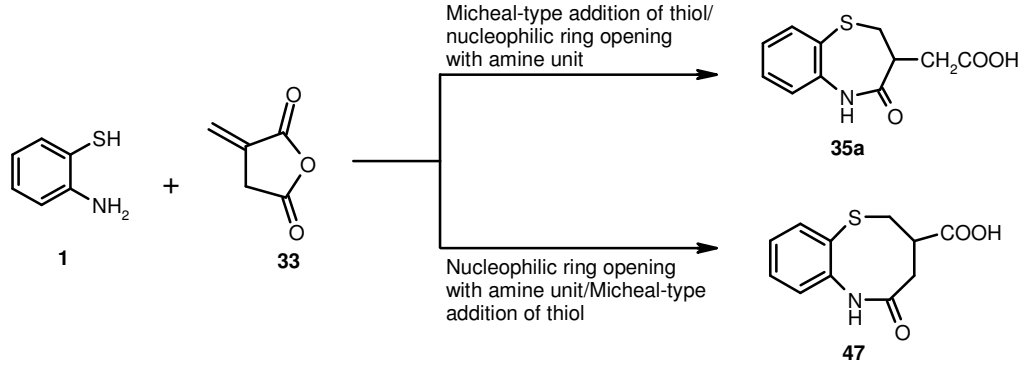
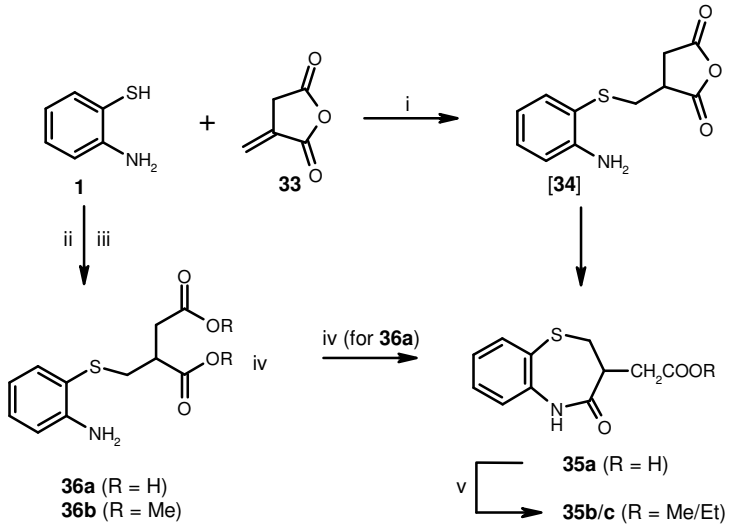


Figure 1. Michael type addition *o*-aminothiophemol to itaconic anhydride

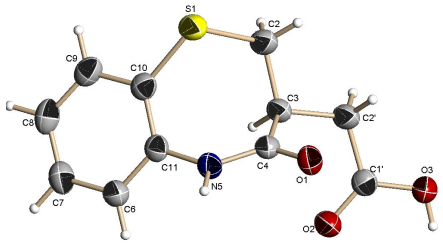
Hence, we performed the reaction of anhydride **33** with *o*-ATP in THF at room temperature and obtained a single product in 81% yield (Scheme 7).

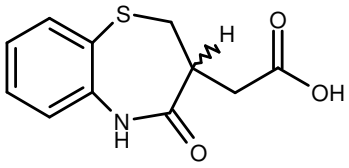


Scheme 7. *Reagents, conditions and yields*: (i) THF, rt, 12 h (81%); (ii) Itaconic acid, THF, rt, 36 h (70%); (iii) Dimethyl itaconate, THF, rt, 24 h (74%); (iv) *N*-Ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide hydrochloride, DMAP (cat.), THF, rt, 4 h (88%); (v) CH_3OH/C_2H_5OH, H^+/H_2SO_4, 50 °C, 2 h (95/92%).

The ^1H and ^{13}C NMR data of the product revealed a very clean formation of Michael type addition-condensation/condensation-Michael type addition product, ruling out the formation of thiazole **46**. It was difficult to conclusively assign the structure **35a** or **47** to the formed product on the basis of NMR data and hence we carried out the reaction of

itaconic acid with *o*-ATP at room temperature and obtained the Michael adduct **36a** in 70% yield. Similarly the reaction of dimethyl itaconate with *o*-ATP also furnished the desired adduct **36b** in 74% yield. The water soluble carbodimide (EDCI) induced regioselective intramolecular dehydrative cyclization of diacid **36a** again exclusively furnished the same product in 88% yield, which was earlier obtained from the reaction of **1** and **33**. Since the formation of 7-membered rings are preferred over the formation of 8-membered rings,[11] we proposed the formation of benzothiazepinylacetic acid **35a**. The benzothiazepinylacetic acid **35a** was further characterized as its methyl and ethyl esters **35b/c** respectively. Finally, we confirmed the formation of 7-membered benzothiazepine **35a** by X-ray





35a

Figure 2. ORTEP Diagram of **35a**.

crystallographic data (Figure 2)[13] and completely ruled out the possibility of formation of 8-membered compound benzothioazocine **47**. The X-ray crystallographic data of **35a** also revealed the formation of very nice supramolecular assemblies of **35a** molecules with the set-patterned intramolecular hydrogen bonding (Figure 3).

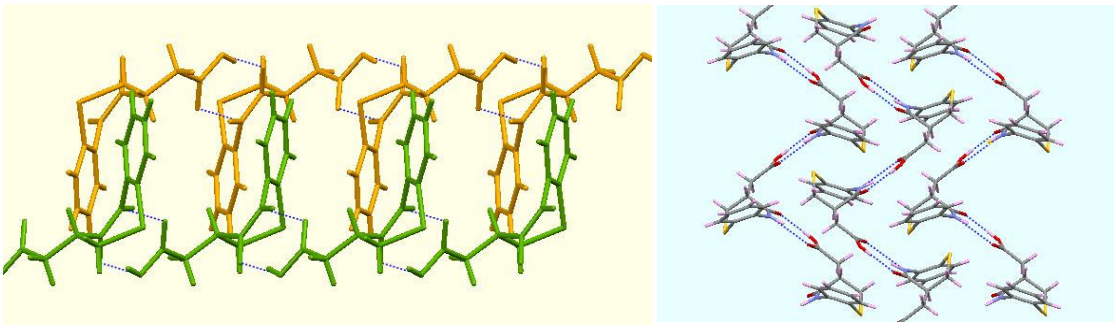
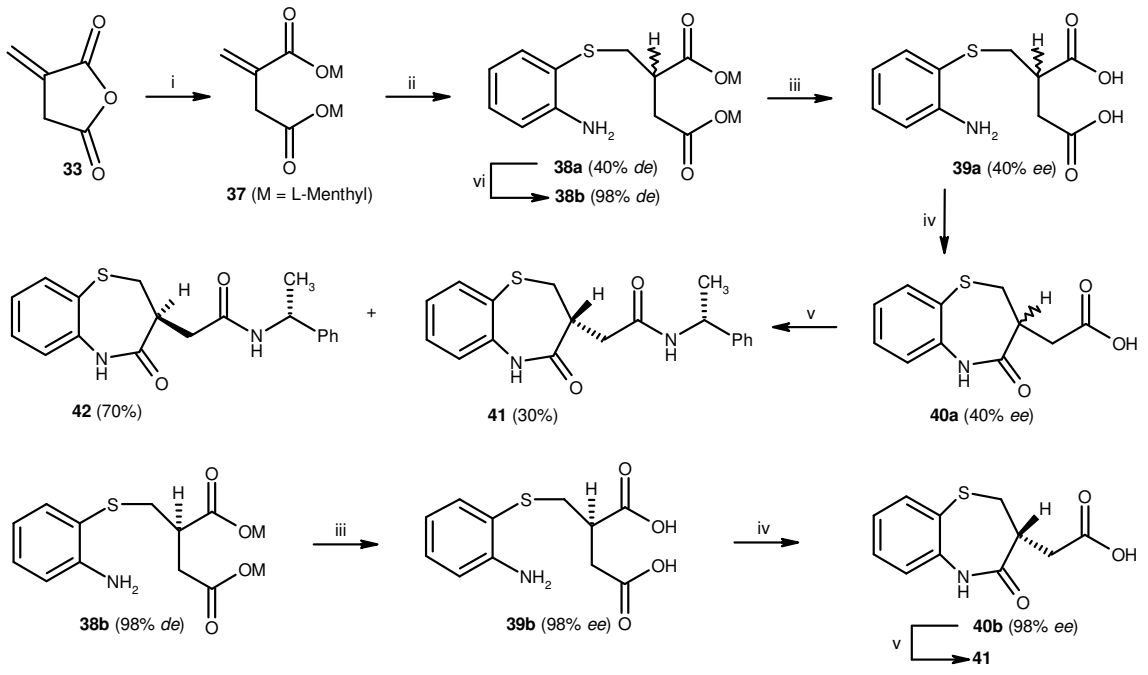


Figure 3. Supramolecular assemblies of **35a** molecules

These observations revealed that in the reaction of itaconic anhydride (**33**) with *o*-ATP, chemoselective Michael type addition of thiol takes place first to form the inisolable intermediate **34**, the amine moiety of which condenses in an intramolecular fashion with the adjacent anhydride carbonyl to furnish the benzothiazepine **35a**. We feel that, herein an

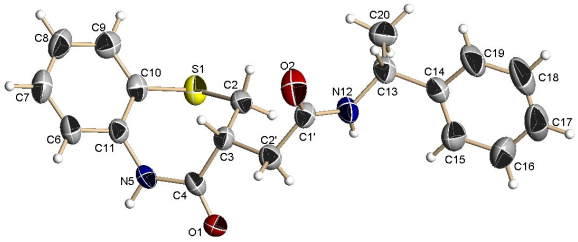
exclusive addition of thiol to the carbon-carbon double bond on an anhydride system before the anhydride ring opening with an internal amine moiety is worth mentioning and is an example of delicately balanced selectivity.

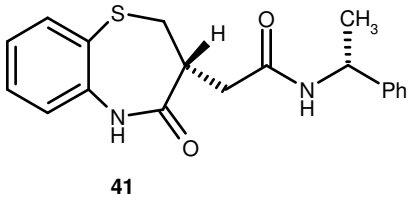
Next, we planed to study the stereoselective addition of thiol from *o*-ATP to itaconate system and prepared the (−)-dimenthyl itaconate (**37**) from the reaction of itaconic anhydride (**33**) with natural (−)-menthol in 80% yield (Scheme 8). In our hands the reaction of *o*-ATP with dimenthyl ester **37** in THF at room temperature and also under reflux condition was not successful and the TLC of the reaction mixture indicated the clear presence of both the starting materials along with slight formation of the corresponding disulfide **43**. The stereoselective reaction of *o*-ATP with the chiral diester **37** in dry acetic acid at room temperature furnished the desired adduct **38a** with 82% yield in 36 hours time. The ^{1}H NMR data of product **38a** revealed that the reaction was moderately stereoselective and the mixture of two diastereomers was formed in nearly 7:3 ratio (from the comparison of the relative integrations of one of the α-methyl protons). The TLC of the



Scheme 8. *Reagents, conditions and yields*: (i) Itaconic anhydride, L-menthol, *p*-TSA, toluene, reflux, 36 h (80%); (ii) *o*-Aminothiophenol, dry AcOH, rt, 36 h (82%); (iii) (a) AcOH:HCl (3:1), reflux, 12 h, (b) 10% Aq. $NaHCO_3$, (c) AcOH (86%); (iv) *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride, DMAP (cat.), THF, rt, 4 h (88%); (v) (*R*)-(+)-1-Phenylethylamine, *N*-ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide hydrochloride, DMAP (cat.), THF, rt, 4 h (10:11 = 3:7, 90%); (vi) Three recrystalisations from petroleum ether (11%).

mixture of diastereomers in **38a** did not show any resolution and separation of these two diastereomers by flash column chromatography was also not successful in our hands. The adduct **38a** on acid catalyzed hydrolysis gave the diacid **39a** in 86% yield. As expected, the carbodiimide induced regioselective ring closure of **39a** yielded the 1,5-benzothiazepinyl-1,3-acetic acid (**40a**) in 88% yield. Finally, for the separation of the two enantiomers of **40a** and their stereochemical assignments, we transformed **40a** into two diastereomers **41** and **42** in 90% yield, by reacting **40a** with (+)-(*R*)-phenylethylamine. The mixture of diastereomers **41** and **42** was easily separated by flash column chromatography to obtain pure **41** and **42** with quantitative recovery (**41**:**42** = 30:70). The mixture of diastereomers in **38a** was semi-solid in nature and after three successive recrystalisations from petroleum ether (60-80), gave the minor diastereomer **38b** as a fine amorphous powder with only 11% recrystalisation yield, but with 98% de. This observation indicates that the major isomer has higher solubility in petroleum ether. Due to the amorphous nature of **38b**, we were unable to get the X-ray crystallographic data to fix the stereochemistry of the newly generated chiral centre. The single isomer **38b** on hydrolysis followed by ring closure gave the desired enantiomerically pure 1,5-benzothiazepinylacetic acid (**40b**) in 76% yield. The reaction of **40b** with (+)-(*R*)-phenylethylamine gave compound **41** in 90% yield. On the basis of X-ray crystallographic data of diastereomer **41** (Figure 4)[13],





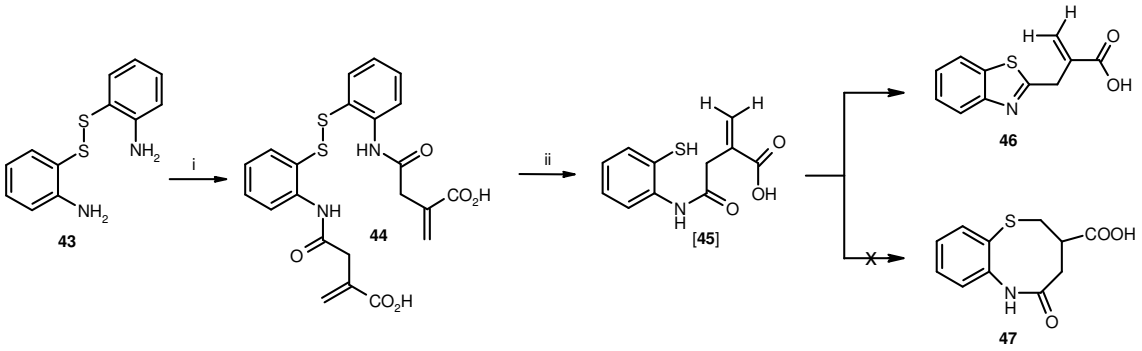
41

Figure 4. ORTEP Diagram of **41.**

we could assign the (*R*)-configuration to the newly generated chiral centre in **38b** & **41** and hence consequently, the (*S*)-configuration to the chiral centre in **42**.

As the activation of α,β-unsaturated double bond by the carboxylic acid unit in itaconic acid is sufficient for Michael type addition of thiol unit from *o*-ATP (Scheme 7, **1** → **36a**), we felt that the *o*-mercapto-α-methylenesuccinanilic acid (**45**) would be a potential precursor for the synthesis of benzothioazocine **47**. Hence to obtain the acid **45**, we

performed the reaction of 2-aminophenyl disulfide (**43**) with 2.20-equivalents of itaconic anhydride in THF at room temperature and obtained the dicarboxylic acid **44** in 81% yield (Scheme 9). The triphenylphosphine induced reductive cleavage of sulfur-sulfur bond in diacid **44** formed the expected but inisolable intermediate acid **45**, which on an in situ intramolecular-dehydrative cyclization furnished the 2-benzothiazo-2-ylmethylacrylic acid



Scheme 9. *Reagents, conditions and yields*: (i) Itaconic anhydride, THF, rt, 8 h (81%); (ii) PPh_3, 1,4-dioxane:water (4:1), H^+/HCl, rt, 2 h (84%).

(**46**) in 84% yield and not the expected benzothioazocine **47**, indicating the relative reluctance in **45** for the intramolecular Michael type addition of thiol to form the eight-membered heterocycle.

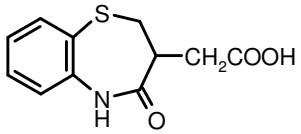
1B.3. Summary

In summary, in this section we have presented the essence of methods employed in the literature to design the 1,5-benzothiazepines derivatives both in racemic and enantiomerically pure form. A brief account of reactions of various symmetrical and unsymmetrical anhydrides with *o*-aminothiophenol has been also described. *ortho*-Aminothiophenol (*o*-ATP) reacts chemo-, regio- and stereoselectively with itaconic anhydride and (−)-dimenthyl itaconate to obtain the corresponding racemic and enantiomerically pure 1,5-benzothiazepines in very good yields. The remarkably selective addition of thiol unit from *o*-ATP to the activated carbon-carbon double bond in itaconic anhydride in the presence of an internal amine unit is note-worthy. We also feel that our present simple approach to 1,5-benzothiazepines is general in nature and will be useful to design large number of its congeners for biological screening. All our attempts to obtain the benzothioazocine met with failure and instead we obtained the corresponding benzothiazole.[12]

1B.4. Experimental Section

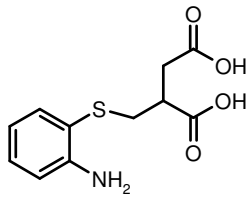
Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60-120 mesh). Commercially available itaconic anhydride, itaconic acid, dimethyl itaconate, *o*-aminothiophenol, 2-aminophenyldisulphide, L-menthol, (*R*)-(+)-1-phenylethylamine, *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and triphenylphosphine were used.

(4-Oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]thiazepin-3-yl)acetic acid (35a). Method A: To a solution of itaconic anhydride (**33**, 1.00 g, 8.92 mmol) in THF (25 mL) was added *o*-aminothiophenol (**1**, 1.05 mL, 10.70 mmol) and the reaction mixture was stirred under argon atmosphere for 8 h at room temperature. A white precipitate was obtained, which was then filtered, washed with diethyl ether and dried in vacuo to give **35a** (white solid): 1.71 g (81% yield). Analytically pure **35a** was obtained by recrystalisation from methanol. Method B: To a solution of **36a** (300 mg, 1.18 mmol) and DMAP (5 mg) in THF (10 mL) was added *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (248 mg, 1.29 mmol) in THF (5 mL) and the reaction mixture was stirred under argon atmosphere for 4 h at room temperature. The reaction mixture was concentrated in vacuo, dried over Na_2SO_4 and acidified with 2 N HCl (10 mL). The precipitate was filtered, washed with water and dried in vacuo to give **35a** (white solid): 245 mg (88% yield).

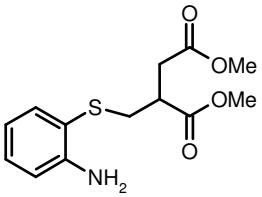
 **35a** **$C_{11}H_{11}NO_3S$ (237)**	**Mp** 234-235 °C. **IR** (Nujol) ν_{max} 3171, 2725-2500, 1703, 1639, 1630, 1462, 1454 cm^{-1}. **^{1}H NMR** (DMSO-d_6, 500 MHz) δ 2.29 (dd, J = 20 & 5 Hz, 1H), 2.68 (dd, J = 18 & 10 Hz, 1H), 2.82-2.92 (m, 1H), 2.96 (dd, J = 10 & 8 Hz, 1H), 3.47 (dd, J = 10 & 5 Hz, 1H), 7.12 (d, J = 10 Hz, 1H), 7.17 (dt, J = 10 & 2 Hz, 1H), 7.41 (dt, J = 10 & 2 Hz, 1H), 7.56 (d, J = 10 Hz, 1H). **^{13}C NMR** (DMSO-d_6, 125 MHz) δ 34.9, 38.1, 38.8, 123.6, 125.8, 126.2, 130.0, 134.8, 142.4, 172.7, 173.4. **Anal. Calcd** for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.55; H, 4.49; N, 6.02; S, 13.47.

2-(2-Amino-phenylsulfanylmethyl)succinic acid (36a). To a solution of itaconic acid (500 mg, 3.84 mmol) in THF (15 mL) was added *o*-aminothiophenol (0.50 mL, 4.61 mmol) and the reaction mixture was stirred under argon atmosphere for 36 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was

dissolved in 10% aqueous $NaHCO_3$ solution. The resulting solution was washed with ethyl acetate (10 mL x 3) acidified with glacial acetic acid and extracted with ethyl acetate containing 5% methanol (25 mL x 4). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give **36a**. Analytically pure **36a** was obtained by recrystalization from methanol (yellow solid): 686 mg (70% yield).

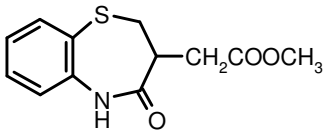
 **36a** **$C_{11}H_{13}NO_4S$ (255)**	**Mp** 146 °C. **IR** (Nujol) ν_{max} 3356, 3285, 2725, 1697, 1462, 1377 cm^{-1}. **^{1}H NMR** (CD_3OD, 500 MHz) δ 2.69 (t, J = 5 Hz, 2H), 2.87 (q, J = 5 Hz, 2H), 3.14 (q, J = 5 Hz, 1H), 6.61 (t, J = 10 Hz, 1H), 6.76 (d, J = 10 Hz, 1H), 7.07 (t, J = 10 Hz, 1H), 7.33 (d, J = 10 Hz, 1H). **^{13}C NMR** (DMSO-d_6, 125 MHz) δ 35.0, 35.6, 41.4, 114.8, 115.5, 116.9, 129.8, 135.3, 149.6, 173.0, 174.6. **Anal. Calcd** for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.88; H, 5.26; N, 5.37; S, 12.66.

2-(2-Amino-phenylsulfanylmethyl)succinic acid dimethyl ester (36b). To a solution of dimethyl itaconate (500 mg, 3.16 mmol) in THF (15 mL) was added *o*-aminothiophenol (0.40 mL, 3.79 mmol) and the reaction mixture was stirred under argon atmosphere for 24 h at room temperature. The reaction mixture was concentrated in vacuo and the crude residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to furnish **36b** (yellow thick oil): 662 mg (74 % yield).

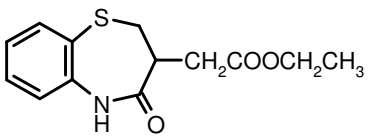
 **36b** **$C_{13}H_{17}NO_4S$ (283)**	Thick oil. **IR** (Neat) ν_{max} 3460, 3364, 2847, 1740, 1726, 1611, 1479, 1439 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 2.71 (dd, J = 15 & 5 Hz, 1H), 2.83 (dd, J = 15 & 5 Hz, 1H), 2.95 (dd, J = 10 & 5 Hz, 1H), 3.02 (quintet, J = 5 Hz, 1H), 3.13 (dd, J = 10 & 5 Hz, 1H), 3.65 (s, 3H), 3.66 (s, 3H), 4.04 (bs, 2H), 6.69 (t, J = 10 Hz, 1H), 6.73 (d, J = 10 Hz, 1H), 7.13 (t, J = 10 Hz, 1H), 7.37 (d, J = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 34.5, 35.6, 41.2, 51.7, 51.9, 114.9, 116.1, 118.3, 130.0, 135.9, 148.3, 171.7, 173.3. **Anal. Calcd** for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; S, 11.32. Found: C, 54.99; H, 6.11; N, 5.07; S, 11.17.

(4-Oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]thiazepin-3-yl)acetic acid methyl ester (35b). To a solution of **35a** (500 mg, 2.10 mmol) in methanol (15 mL), two drops of conc. H_2SO_4

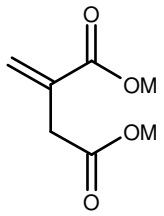
were added and the reaction mixture was heated at 50 °C for 2 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (25 mL). The resulting solution was washed successively with 5% aqueous $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (7:3) to furnish **35b** (white solid): 503 mg (95% yield).

 **35b** **$C_{12}H_{13}NO_3S$ (251)**	**Mp** 168 °C. **IR** (Nujol) ν_{max} 3179, 1734, 1666, 1462, 1439 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 2.35 (dd, *J* = 18 & 6 Hz, 1H), 2.93-3.06 (m, 2H), 3.10-3.23 (m, 1H), 3.52 (dd, *J* = 10 & 5 Hz, 1H), 3.63 (s, 3H), 7.16 (d, *J* = 6 Hz, 1H), 7.19 (t, *J* = 9 Hz, 1H), 7.38 (t, *J* = 9 Hz, 1H), 7.60 (d, *J* = 6 Hz, 1H), 7.80-8.20 (bs, 1H). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 2.38 (dd, *J* = 18 & 6 Hz, 1H), 2.74 (dd, *J* = 15 & 9 Hz, 1H), 2.58-3.05 (m, 2H), 3.44-3.51 (m, 1H), 3.52 (s, 3H), 7.05-7.20 (m, 2H), 7.42 (t, *J* = 9 Hz, 1H), 7.57 (d, *J* = 9 Hz, 1H), 9.93 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 34.7, 38.1, 39.1, 51.7, 123.6, 126.4, 126.8, 129.9, 135.0, 141.0, 171.8, 174.4. **^{13}C NMR** (DMSO-d_6, 125 MHz) δ 34.4, 38.1, 38.6, 51.6, 123.6, 125.9, 126.1, 130.1, 134.9, 142.3, 171.9, 173.2. **Anal. Calcd** for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.58; S, 12.76. Found: C, 57.22; H, 5.29; N, 5.43; S, 12.63.

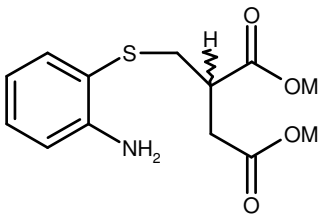
(4-Oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]thiazepin-3-yl)acetic acid ethyl ester (35c). Repetition of the above reaction in ethanol furnished the corresponding ethyl ester. **35c** (white solid): 514 mg (92% yield).

 **35c** **$C_{13}H_{15}NO_3S$ (265)**	**Mp** 146 °C. **IR** (Nujol) ν_{max} 3296, 1713, 1688, 1587, 1468 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.20 (t, *J* = 8 Hz, 3H), 2.33 (dd, *J* = 16 & 4 Hz, 1H), 2.85-3.25 (m, 3H), 3.51 (dd, *J* = 10 & 6 Hz, 1H), 4.08 (q, *J* = 8 Hz, 2H), 7.10-7.45 (m, 3H), 7.60 (d, *J* = 6 Hz, 1H), 8.05-8.30 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 14.0, 34.9, 38.1, 39.0, 60.6, 123.5, 126.3, 126.8, 129.9, 135.0, 141.1, 171.3, 174.5. **Anal. Calcd** for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; S, 12.10. Found: C, 59.02; H, 5.84; N, 5.13; S, 12.25.

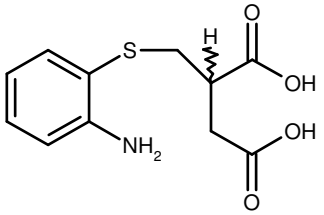
2-Methylene-succinic acid bis-(2-isopropyl-5-methyl-cyclohexyl)ester (37). To a solution of itaconic anhydride (5.20 g, 40 mmol) in toluene (70 mL) was added L-menthol (12.48 g, 80 mmol) and *p*-TSA (100 mg, 40 mmol) and the reaction mixture was refluxed under argon atmosphere for 36 h using Dean and Stark apparatus. The reaction mixture was allowed to cool to ambient temperature and concentrated in vacuo and the residue was dissolved in ethyl acetate (150 mL) and washed successively with 5% aqueous $NaHCO_3$ solution, brine and dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to give **37** (thick oil): 13.12 g (80% yield).

 **37** (M = L-Menthyl) **$C_{25}H_{42}O_4$ (406)**	Thick oil. $[\alpha]_D^{25} = -85.12$ (*c* 1.77, $CHCl_3$) . **IR** (Neat) ν_{max} 1734, 1719, 1641, 1456, 1200 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.77 (d, *J* = 8 Hz, 6H), 0.90 (d, *J* = 6 Hz, 12H), 0.75-1.25 (m, 6H), 1.30-1.55 (m, 4H), 1.55-1.75 (m, 4H), 1.80-2.10 (m, 4H), 3.31 (s, 2H), 4.60-4.85 (m, 2H), 5.65 (s, 1H), 6.29 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 16.2, 20.6, 21.9, 23.3, 23.4, 26.0, 26.1, 31.2, 34.1, 37.9, 40.5, 40.6, 46.8, 46.9, 74.4, 74.6, 127.5, 134.4, 165.4, 170.0 (three carbon atoms from the two menthol units did not show splitting). **Anal. Calcd** for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 74.01; H, 10.33.

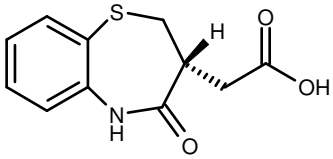
2-(2-Amino-phenylsulfanylmethyl)-succinic acid bis-(2-isopropyl-5-methyl-cyclohexyl)ester (38a). To a solution of diester **37** (6.57 g, 15 mmol) in dry acetic acid (25 mL) was added *o*-aminothiophenol (1.63 mL, 15 mmol) and the reaction mixture was stirred under argon atmosphere for 36 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (70 mL) and washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give **38a** (thick oil/semi solid): 6.92 g (82% yield). The compound **38a** (1.00 g, 40% *de*) on three recrystalisations from petroleum ether (60-80) furnished compound **38b** (white solid, minor isomer): 110 mg (98% *de*).

 **38b** (98% *de*) **$C_{31}H_{49}NO_4S$ (531)**	**Mp** 104 °C. $[\alpha]_D^{25} = -85.71$ (*c* 0.50, $CHCl_3$). **IR** (Nujol) ν_{max} 3468, 3371, 1724, 1607, 1215 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.74 (d, *J* = 4 Hz, 3H), 0.77 (d, *J* = 4 Hz, 3H), 0.80-0.95 (m, 12H), 0.95-1.10 (m, 6H), 1.25-1.53 (m, 4H), 1.62-1.72 (m, 4H), 1.77-1.87 (m, 1H), 1.90-2.05 (m, 3H), 2.63 (dd, *J* = 16 & 8 Hz, 1H), 2.76 (dd, *J* = 16 & 8 Hz, 1H), 2.89 (dd, *J* = 12 & 8 Hz, 1H), 2.98 (q, *J* = 8Hz, 1H), 3.11 (dd, *J* = 12 & 8 Hz, 1H), 4.38 (bs, 2H), 4.67 (dt, *J* = 8 & 4 Hz, 1H), 4.71 (dt, *J* = 8 & 4 Hz, 1H), 6.69 (t, *J* = 8 Hz, 1H), 6.72 (d, *J* = 8 Hz, 1H), 7.13 (t, *J* = 8 Hz, 1H), 7.38 (d, *J* = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 16.0, 16.3, 20.8, 22.0, 23.1, 23.4, 26.0, 26.2, 31.3, 34.2, 34.3, 35.6, 36.1, 40.6, 40.7, 42.0, 46.8, 46.9, 74.6, 75.0, 115.0, 116.8, 118.5, 130.1, 136.1, 148.4, 170.7, 172.6 (one of the carbon atom from the two menthol units did not show splitting). **Anal. Calcd** for $C_{31}H_{49}NO_4S$: C, 70.01; H, 9.29; N, 2.63; S, 6.03. Found: C, 69.93; H, 9.27; N, 2.55; S, 6.12.

2-(2-Amino-phenylsulfanylmethyl)succinic acid (39a). A solution of **38a** (5.63 g, 10 mmol) in AcOH:HCl (3:1) (30 mL) was refluxed for 12 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo and the residue was dissolved in 10% aqueous $NaHCO_3$ solution. The resulting solution was washed with ethyl acetate (10 mL x 3), acidified with glacial acetic acid and extracted with ethyl acetate containing 5% methanol (25 mL x 4). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give **39a** (yellow solid): 2.19 g (86% yield). Similarly compound **38b** furnished compound **39b** (yellow solid). Analytical and spectral data obtained for **39a/b** were identical with (±)-**36a**.

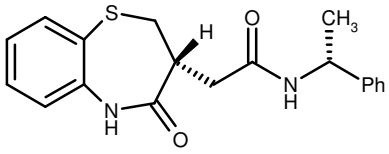
 **39b** (98% *ee*) **$C_{11}H_{13}NO_4S$ (255)**	**Mp** 146 °C. $[\alpha]_D^{25} = +20.83$ (*c* 0.24, methanol) Analytical and spectral data obtained for **39a/b** were identical with (±)-**36a**.

(4-Oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]thiazepin-3-yl)acetic acid (40a). To a solution of **39a** (1.28 g, 5 mmol) and DMAP (20 mg) in THF (20 mL) was added *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.06 g, 5.50 mmol) in THF (5 mL) and the reaction mixture was stirred under argon atmosphere for 4 h at room temperature. The reaction mixture was concentrated in vacuo, dried and acidified with 2 N HCl (20 mL). The precipitate was filtered, washed with water and dried in vacuo to give **40a** (white solid): 1.04 g (88% yield). Similarly compound **39b** furnished compound **40b** (white solid).

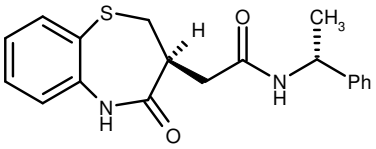
 **40b** (98% *ee*) **$C_{11}H_{11}NO_3S$ (237)**	**Mp** 234-235 °C. $[\alpha]_D^{25}$ = + 178.30 (*c* 0.19, methanol). Analytical and spectral data obtained for **40a/b** were identical with (±)-**35a**.

2-(4-Oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]thiazepin-3-yl-*N*-(1-phenylethyl)-acetamide (41 & 42). To a solution of **40a** (474 mg, 2 mmol), (*R*)-(+)-1-phenylethylamine (290 mg, 2.40 mmol) and DMAP (10 mg) in THF (10 mL) was added a solution of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (422 mg, 2.20 mmol) in THF (5 mL) and the reaction mixture was stirred under argon atmosphere for 4 h at room temperature. The reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (50 mL) washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give a mixture of diastereomers 612 mg (90% yield) which was separated by flash column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to give major isomer **42** (white solid): 428 mg (70%) and minor isomer **41** (white solid): 183 mg (30%).

2-(4-Oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]thiazepin-3*R*-yl-*N*-(1*R*-phenylethyl)-acetamide (**41**, minor isomer).

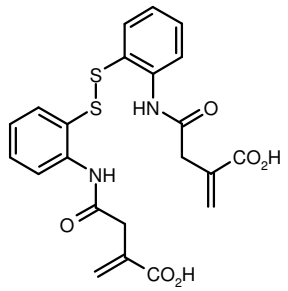
 **41** (30%) **$C_{19}H_{20}N_2O_2S$ (340)**	**Mp** 198 °C. $[\alpha]_D^{25}$ = + 45.45 (*c* 0.08, $CHCl_3$). **IR** (Nujol) ν_{max} 3287, 3190, 1665, 1632, 1551, 1466, 1377 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.44 (d, *J* = 6 Hz, 3H), 2.24 (dd, *J* = 14 & 4 Hz, 1H), 2.80 (dd, *J* = 24 & 14 Hz, 1H), 2.99 (d, *J* = 10 Hz, 1H), 3.05-3.30 (m, 1H), 3.53 (dd, *J* = 10 & 6 Hz, 1H), 5.01 (q, *J* = 8 Hz, 1H), 6.49 (bs, 1H), 7.00 (d, *J* = 8 Hz, 1H), 7.14 (d, *J* = 8 Hz, 1H), 7.20-7.40 (m, 6H), 7.57 (dd, *J* = 8 & 2 Hz, 1H), 8.15 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 22.0, 37.2, 39.1, 39.7, 48.8, 123.7, 126.0, 126.7, 127.0, 127.1, 128.5, 130.0, 135.2, 140.6, 143.2, 169.5, 175.0. **Anal. Calcd** for $C_{19}H_{20}N_2O_2S$: C, 67.02; H, 5.92; N, 8.22; S, 9.42. Found: C, 67.20; H, 6.04; N, 8.13; S, 9.36.

2-(4-Oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]thiazepin-3*S*-yl-*N*-(1*R*-phenylethyl)-acetamide (42, major isomer**).**

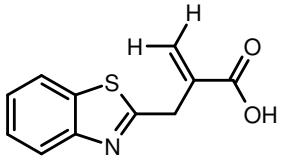
 **42** (70%) **$C_{19}H_{20}N_2O_2S$ (340)**	**Mp** 104 °C. **IR** (Nujol) ν_{max} 3296, 3192, 1663, 1635, 1535, 1475 cm^{-1}. $[\alpha]_D^{25}$ = + 172.83 (*c* 0.08, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.40 (d, *J* = 8 Hz, 3H), 2.21 (dd, *J* = 14 & 2 Hz, 1H), 2.77 (dd, *J* = 24 & 12 Hz, 1H), 2.94 (d, *J* = 12 Hz, 1H), 3.10-3.30 (m, 1H), 3.45 (dd, *J* = 12 & 6 Hz, 1H), 4.99 (q, *J* = 8 Hz, 1H), 6.68 (bs, 1H), 7.00-7.40 (m, 8H), 7.56 (d, *J* = 6 Hz, 1H), 8.74 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 21.8, 36.8, 38.7, 39.5, 48.8, 123.7, 126.0, 126.6, 126.8, 127.1, 128.4, 129.9, 135.1, 140.7, 143.3, 169.6, 175.5. **Anal. Calcd** for $C_{19}H_{20}N_2O_2S$: C, 67.02; H, 5.92; N, 8.22; S, 9.42. Found: C, 66.97; H, 5.85; N, 8.30; S, 9.50.

2-({2-[2-(3-Carboxy-but-3-enoylamino)-phenyldisulfanyl]phenylcarbamoyl}-methyl)acrylic acid (44). To a solution of itaconic anhydride (695 mg, 6.20 mmol) in THF (15 mL) was added a solution of 2-aminophenyl disulphide (**43**, 700 mg, 2.81 mmol) in dry THF (15 mL) and the reaction mixture was stirred under argon atmosphere for 8 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was stirred with diethyl ether (30 mL) for 1 h. The precipitate was filtered and washed with

diethyl ether to obtain **44**. Analytically pure **44** was obtained by recrystalisation from methanol. **44** (yellow solid): 1.08 g (81% yield).

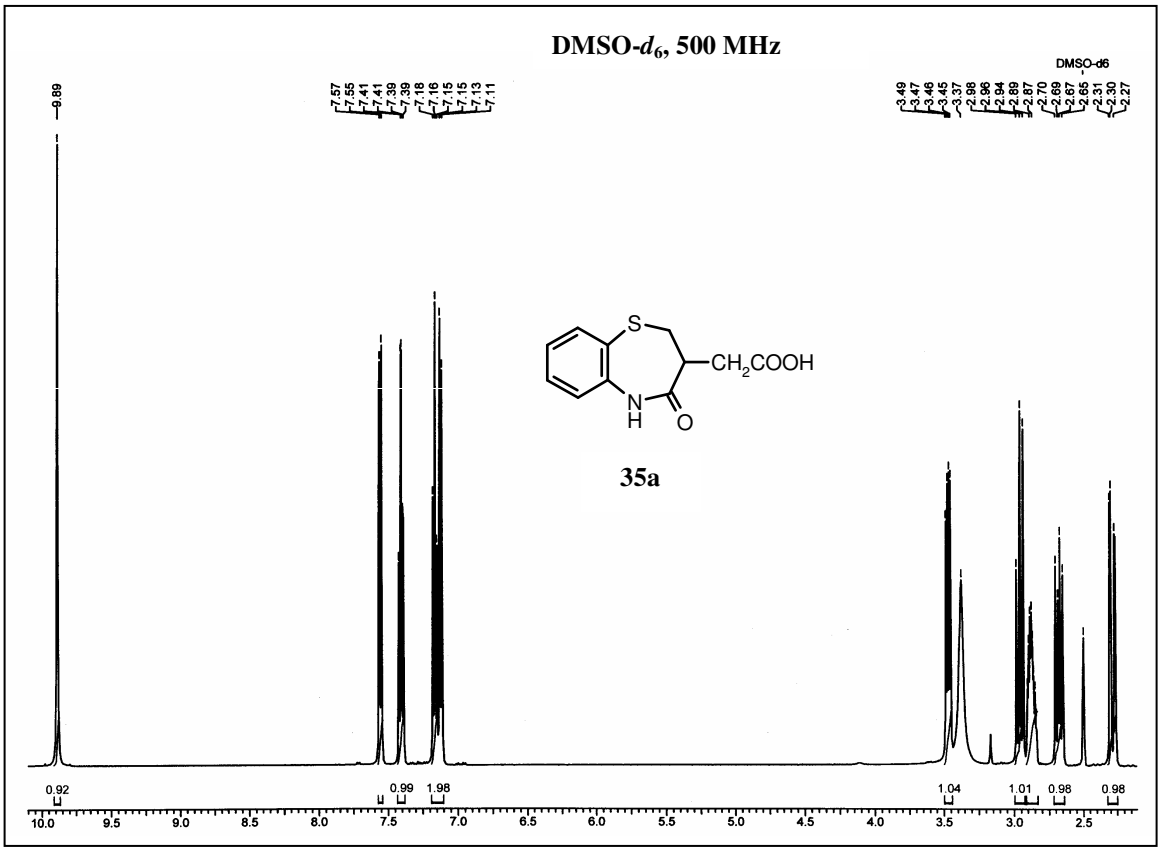
 **44** **$C_{22}H_{20}N_2O_6S_2$ (472)**	**Mp** 192-193 °C. **IR** (Nujol) ν_{max} 3242, 2725, 2633, 1697, 1659, 1634, 1578, 1535 cm^{-1}. **^{1}H NMR** (CD_3OD, 200 MHz) δ 3.38 (bs, 4H), 5.88 (bs, 2H), 6.35 (s, 2H), 7.11 (t, *J* = 8 Hz, 2H), 7.31 (t, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 7.68 (d, *J* = 8 Hz, 2H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 39.3, 126.3, 127.0, 128.2, 128.5, 129.2, 131.8, 136.0, 136.3, 168.0, 169.5. **Anal. Calcd** for $C_{22}H_{20}N_2O_6S_2$: C, 55.92; H, 4.27; N, 5.93; S, 13.57. Found: C, 56.09; H, 4.13; N, 6.02; S, 13.72.

2-Benzothiazol-2-ylmethylacrylic acid (46). To a solution of **44** (500 mg, 1.06 mmol) in 4:1 dioxane-water (15 mL), was added triphenylphospine (278 mg, 1.06 mmol) and two drops of conc. HCl and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo and the resulting mixture was extracted with ethyl acetate (25 mL x 4). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated in vacuo and the residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (7:3) to furnish **46** (white solid): 390 mg (84% yield).

 **46** **$C_{11}H_9NO_2S$ (219)**	Mp 139-142 °C (ethyl acetate). **IR** (Nujol) ν_{max} 2700-2500, 1701, 1690, 1630, 1462, 1456 cm^{-1}. **^{1}H NMR** (CD_3OD, 200 MHz) δ 4.12 (s, 2H), 5.92 (s, 1H), 6.41 (s, 1H), 7.30-7.55 (m, 2H), 7.80-8.00 (m, 2H). **^{13}C NMR** (CD_3OD, 50 MHz) δ 37.4, 122.8, 123.0, 126.2, 127.3, 129.7, 136.3, 138.3, 153.8, 169.0, 172.0. **Anal. Calcd** for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39; S, 14.63. Found: C, 60.28; H, 4.09; N, 6.51; S, 14.54.

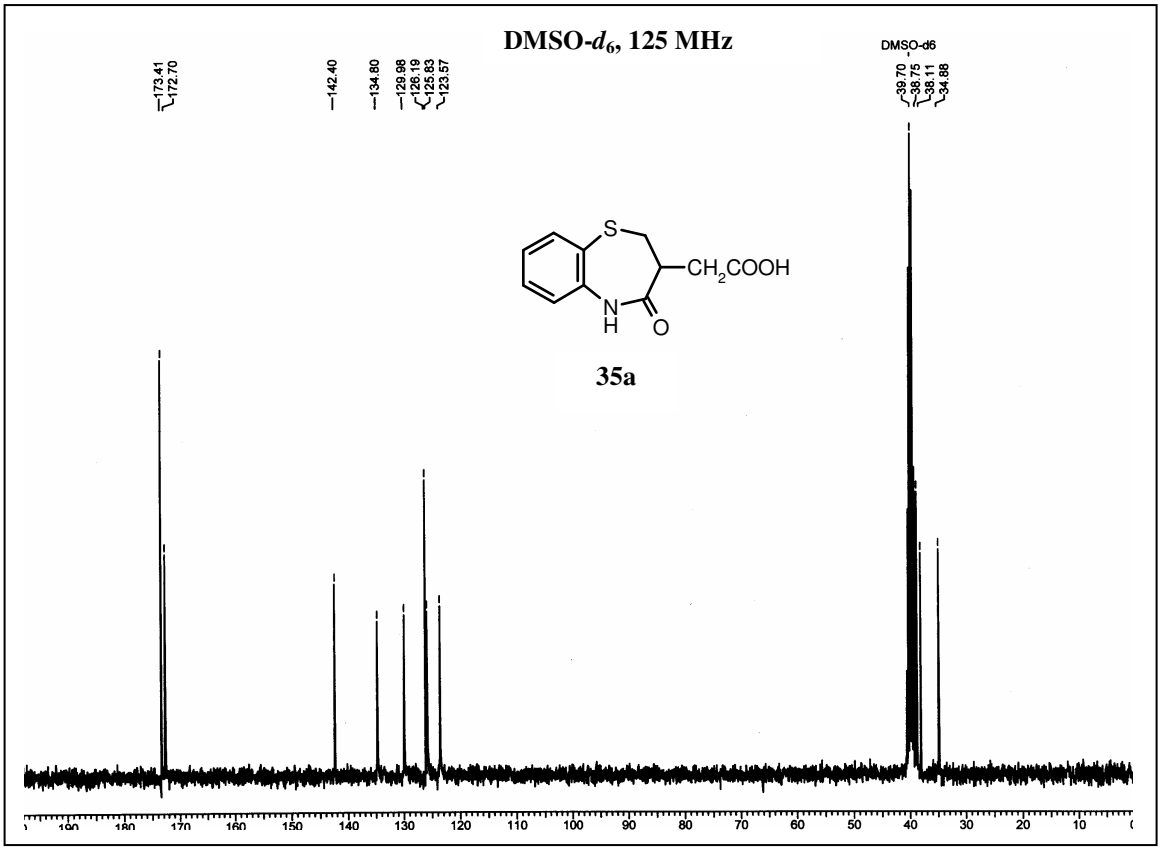
1B.5 Selected Spectra

DMSO-d_6, 500 MHz

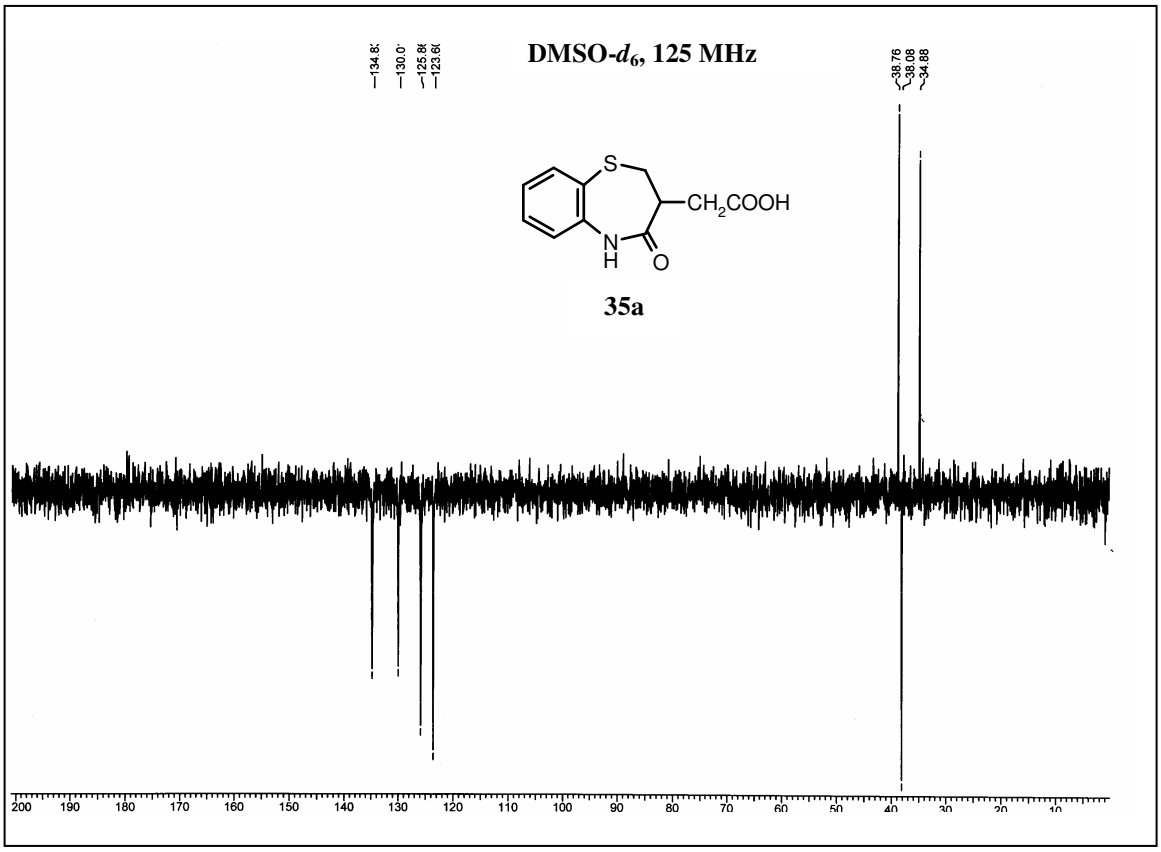


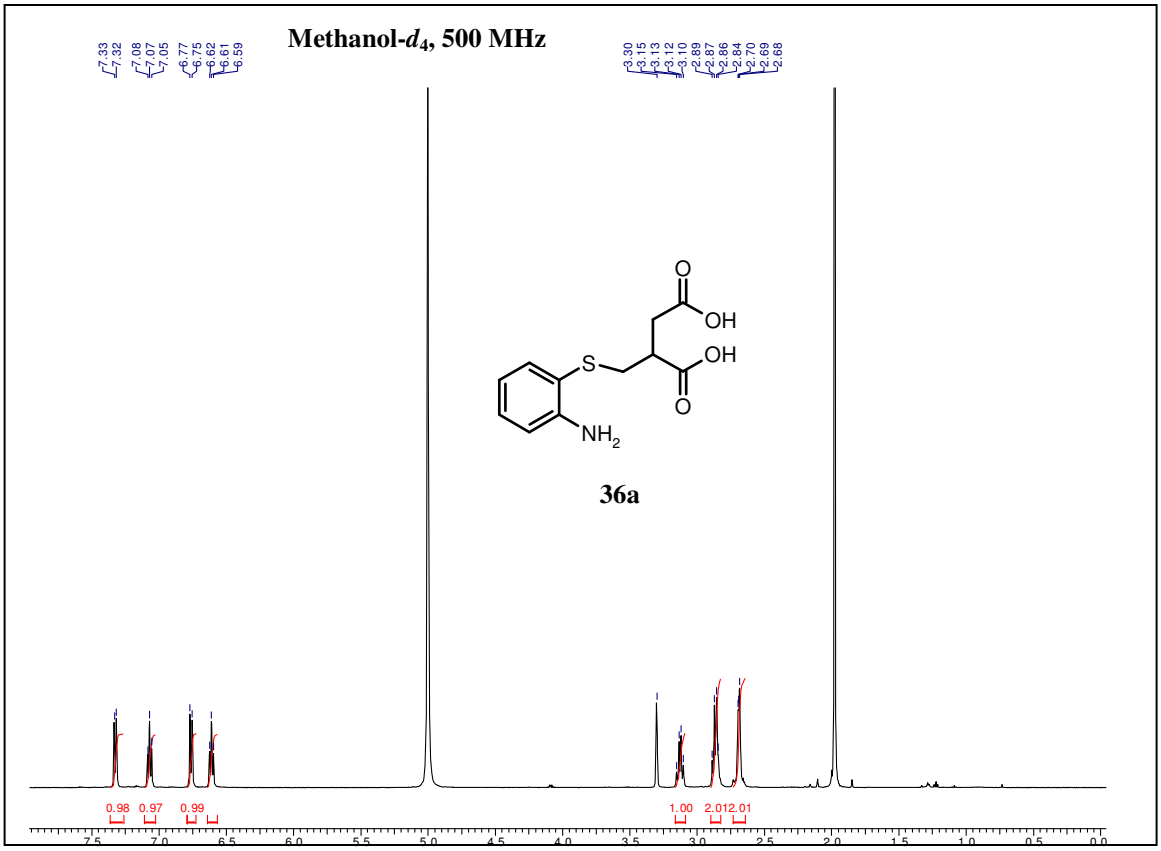
35a

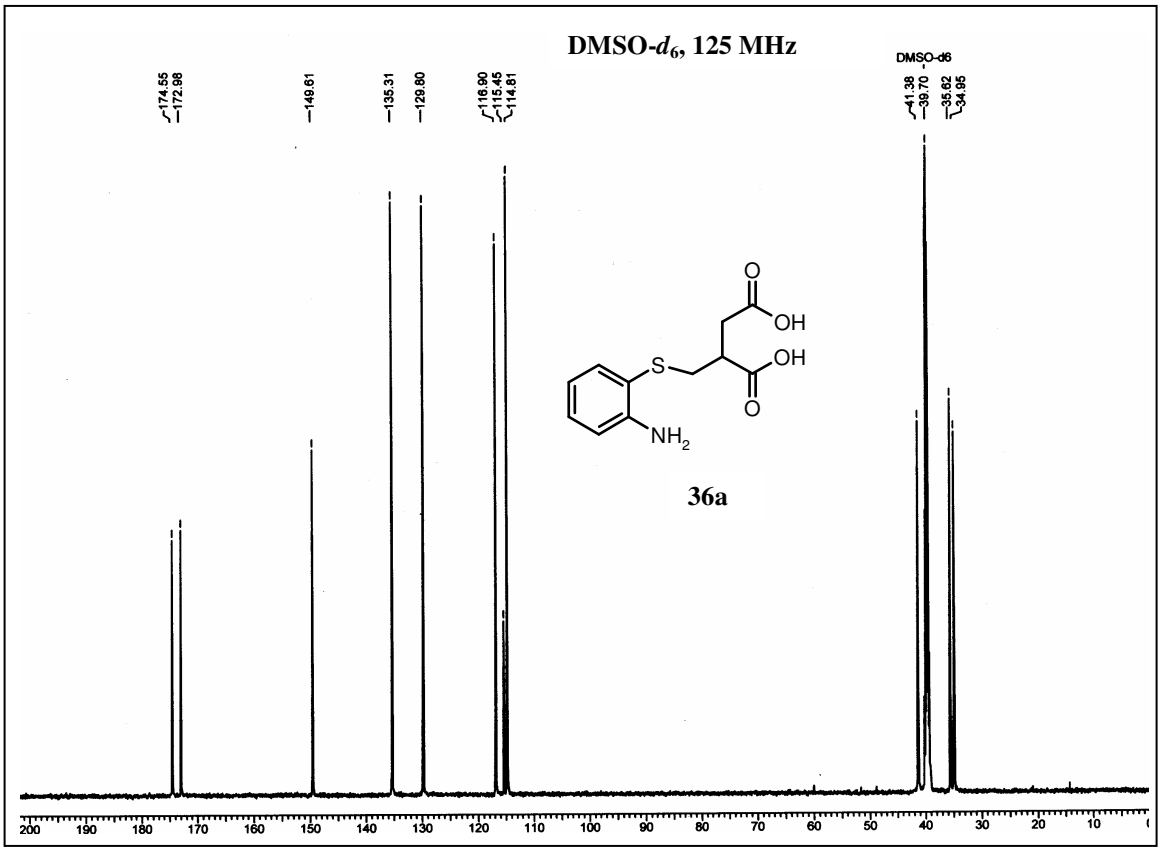
DMSO-d_6, 125 MHz

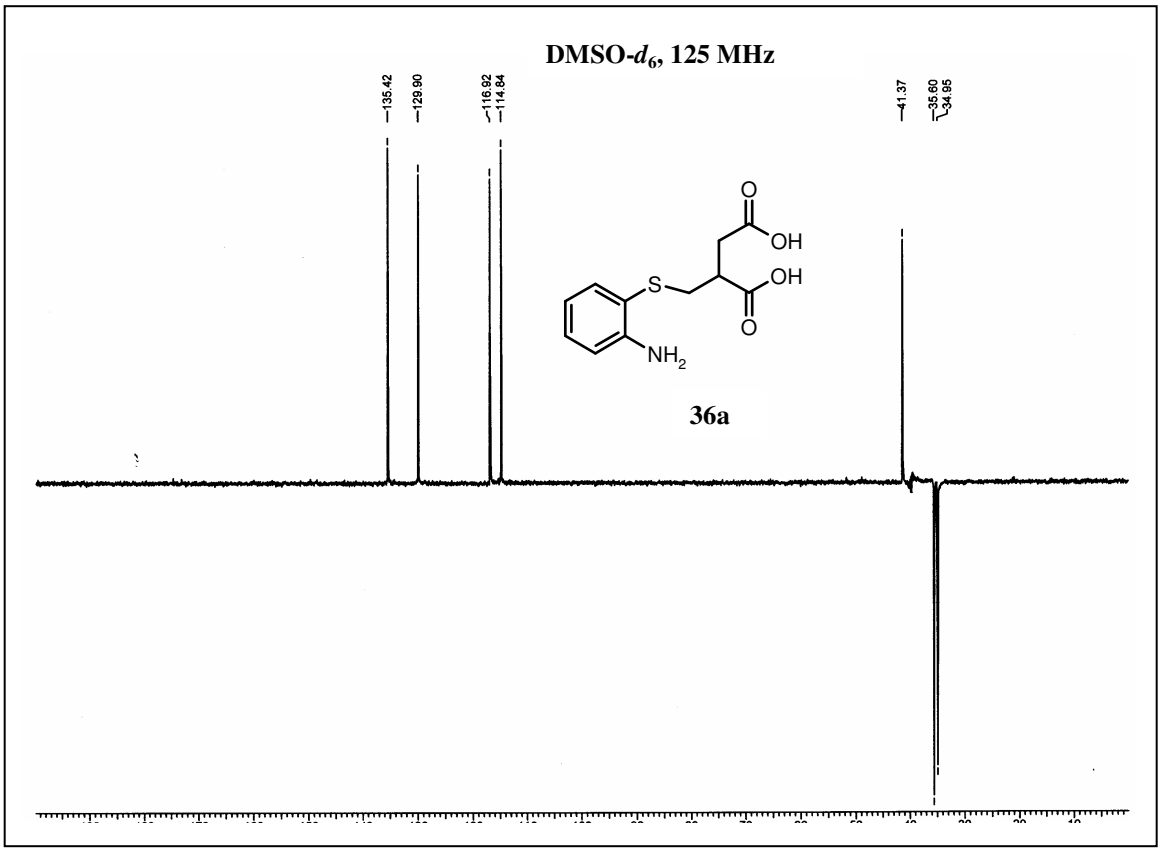


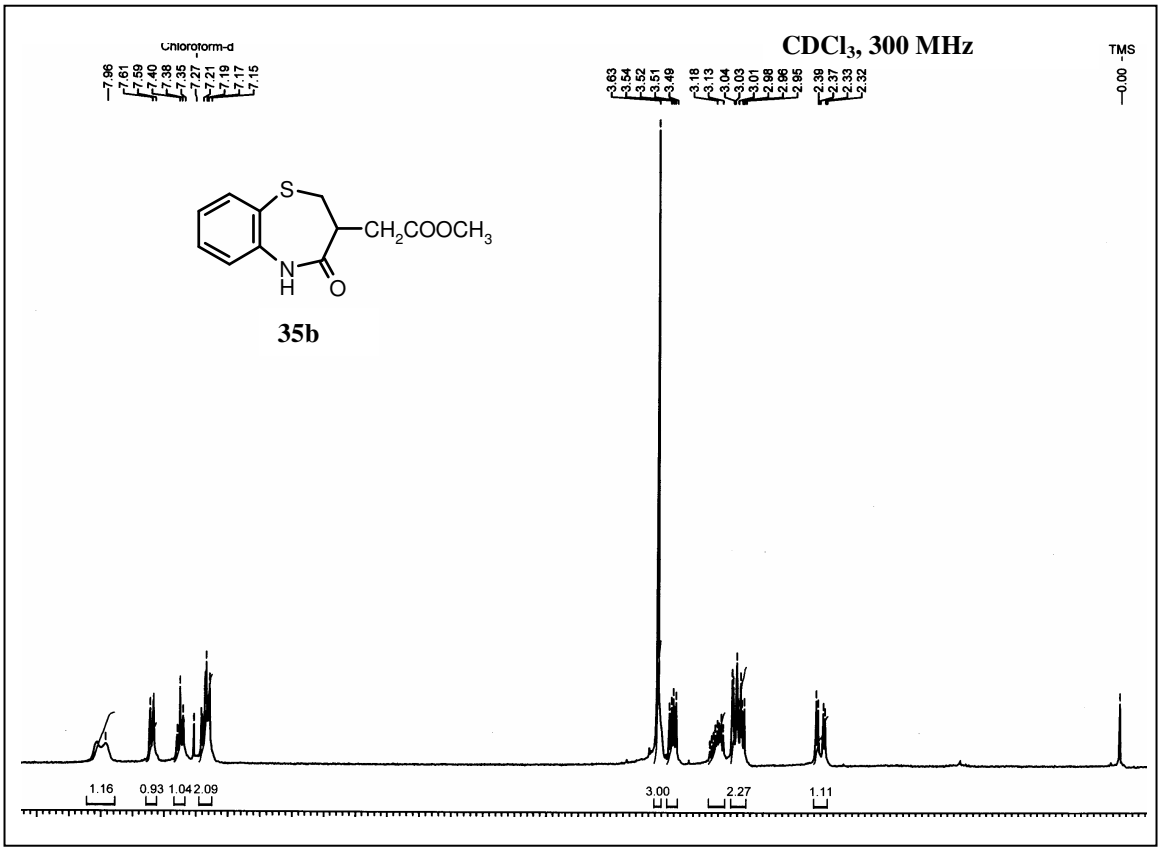
35a

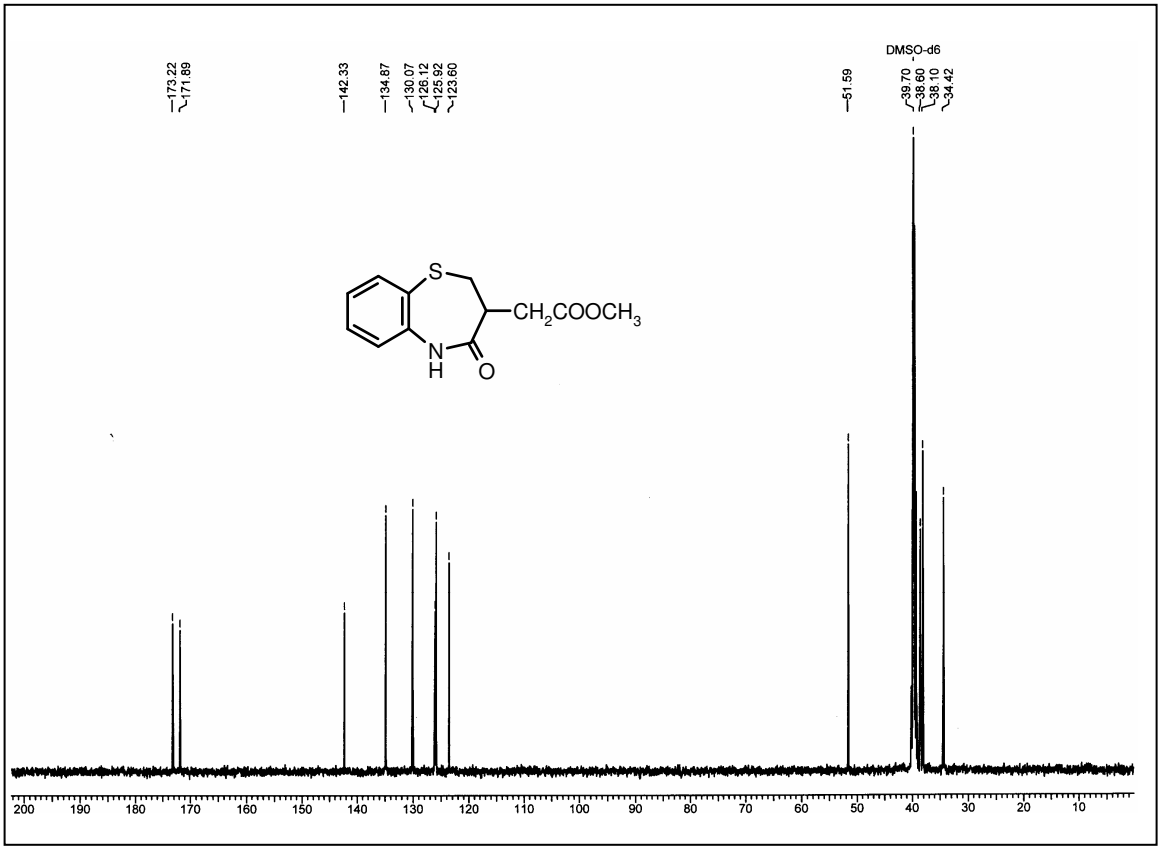

DMSO-d_6, 125 MHz
S
CH2COOH
N
H
O
35a

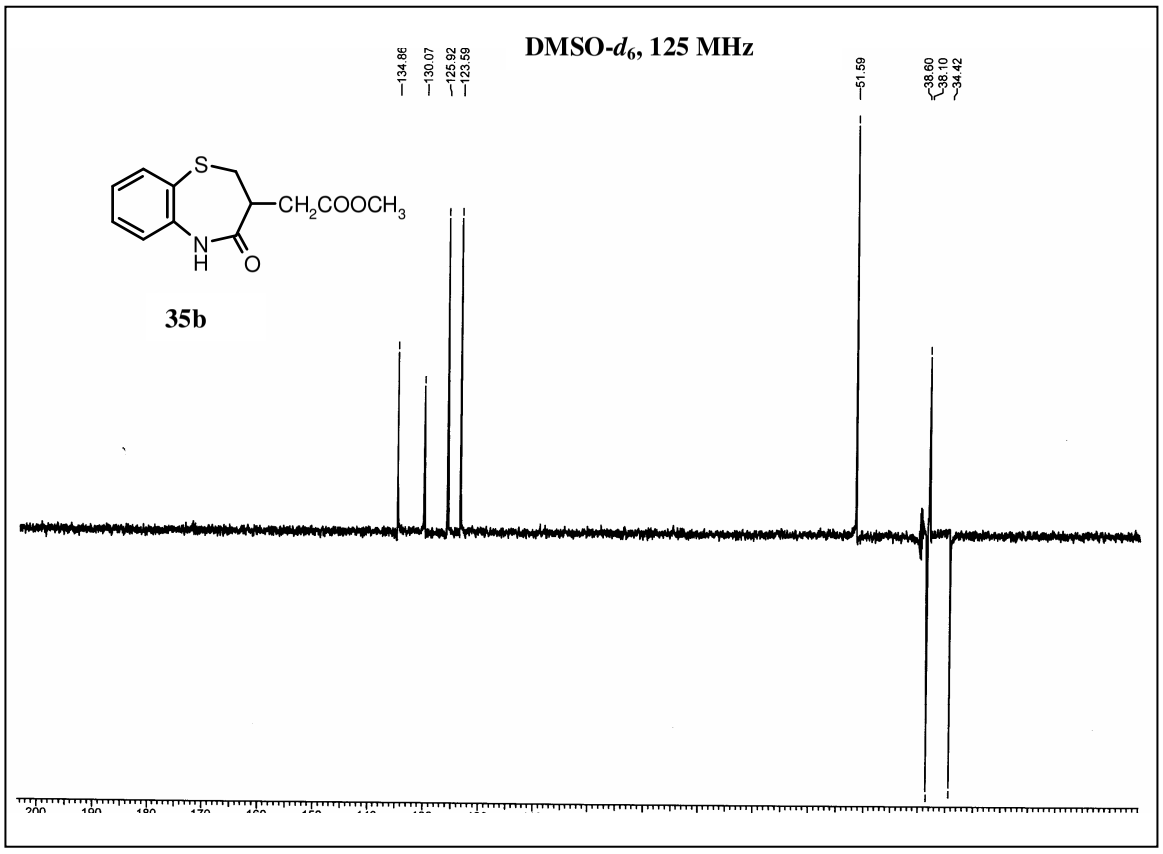

Methanol-d_4, 500 MHz
OH
OH
O
O
S
NH2
36a

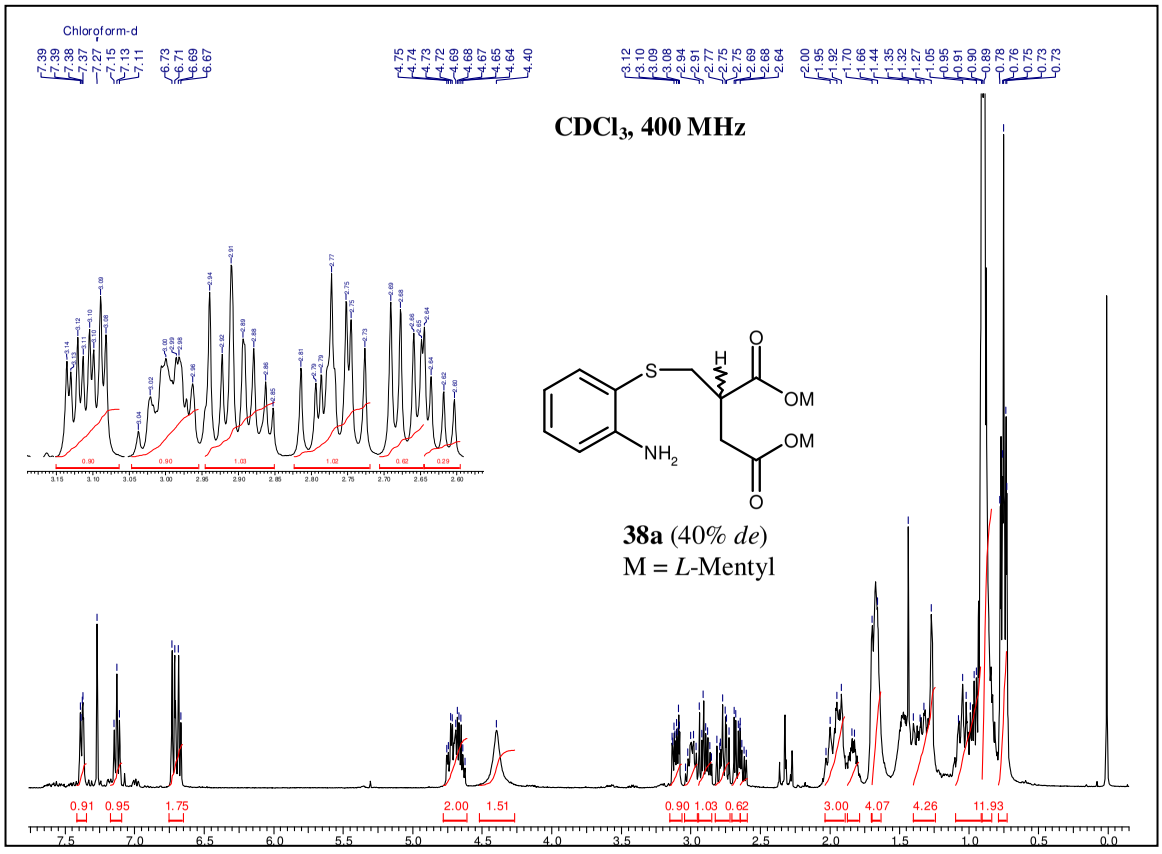

DMSO-d_6, 125 MHz
DMSO-d6
174.55
172.98
149.61
135.31
129.80
116.90
115.45
114.81
41.38
39.70
35.62
34.95
OH
OH
O
O
S
NH2
36a

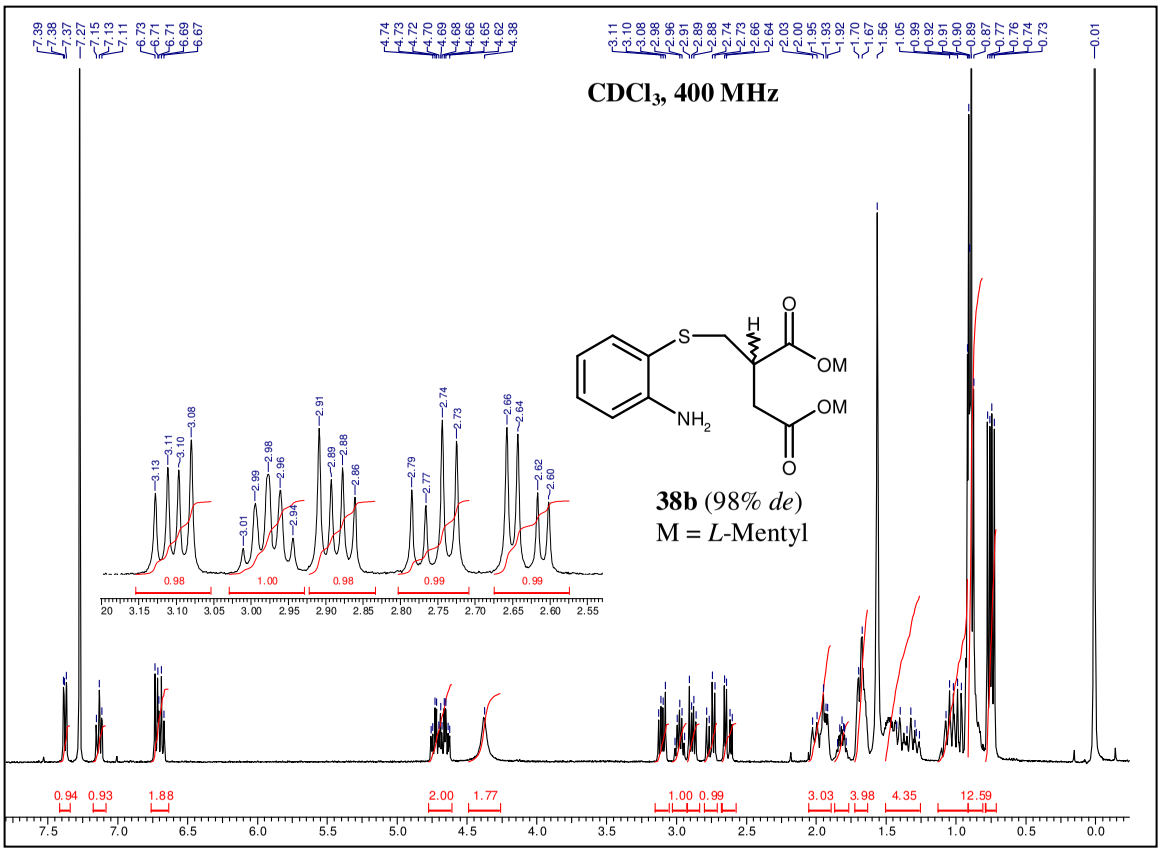

DMSO-d_6, 125 MHz
135.42
129.90
116.92
114.84
41.37
35.60
34.95
OH
OH
O
O
S
NH2
36a

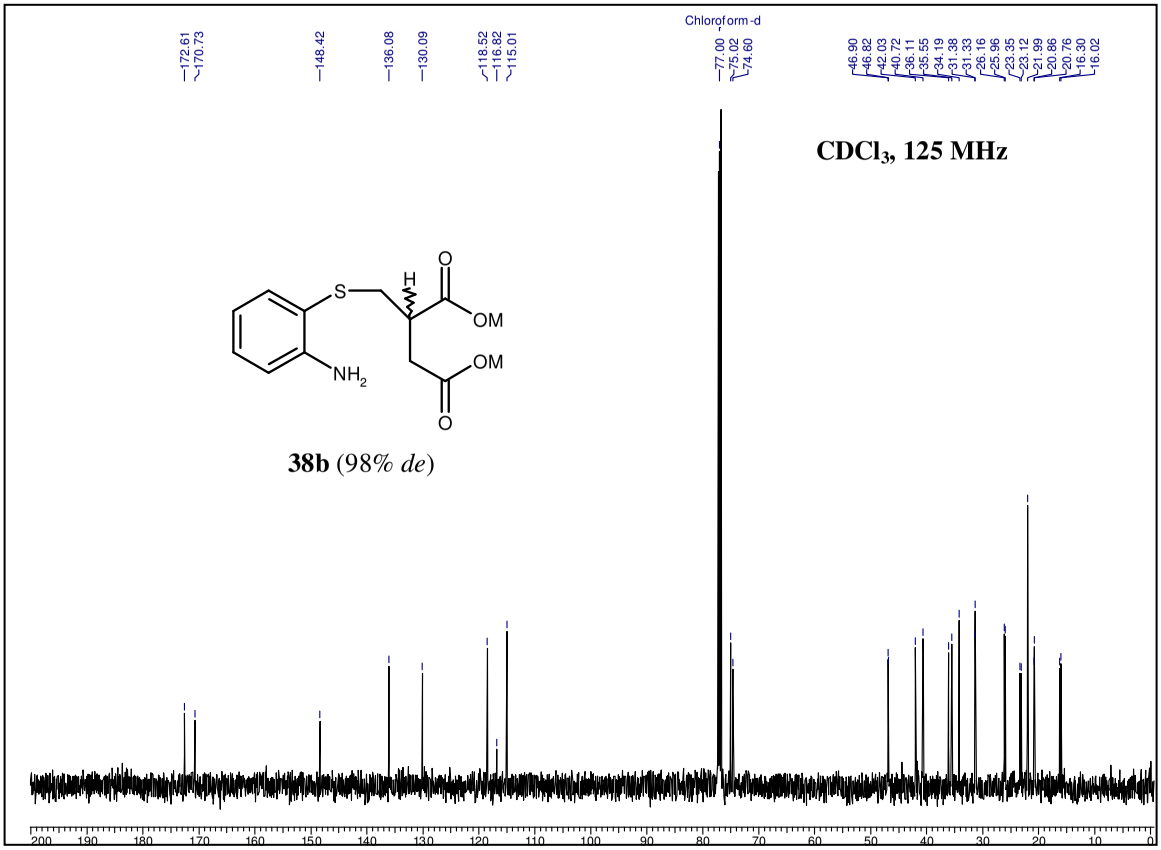

CDCl3, 300 MHz
Chloroform-d
TMS
7.96
7.61
7.59
7.40
7.38
7.35
7.27
7.21
7.19
7.17
7.15
3.63
3.54
3.52
3.51
3.49
3.18
3.13
3.04
3.03
3.01
2.98
2.96
2.95
2.39
2.37
2.33
2.32
0.00
S
CH2COOCH3
N
H
O
35b
1.16
0.93
1.04
2.09
3.00
2.27
1.11

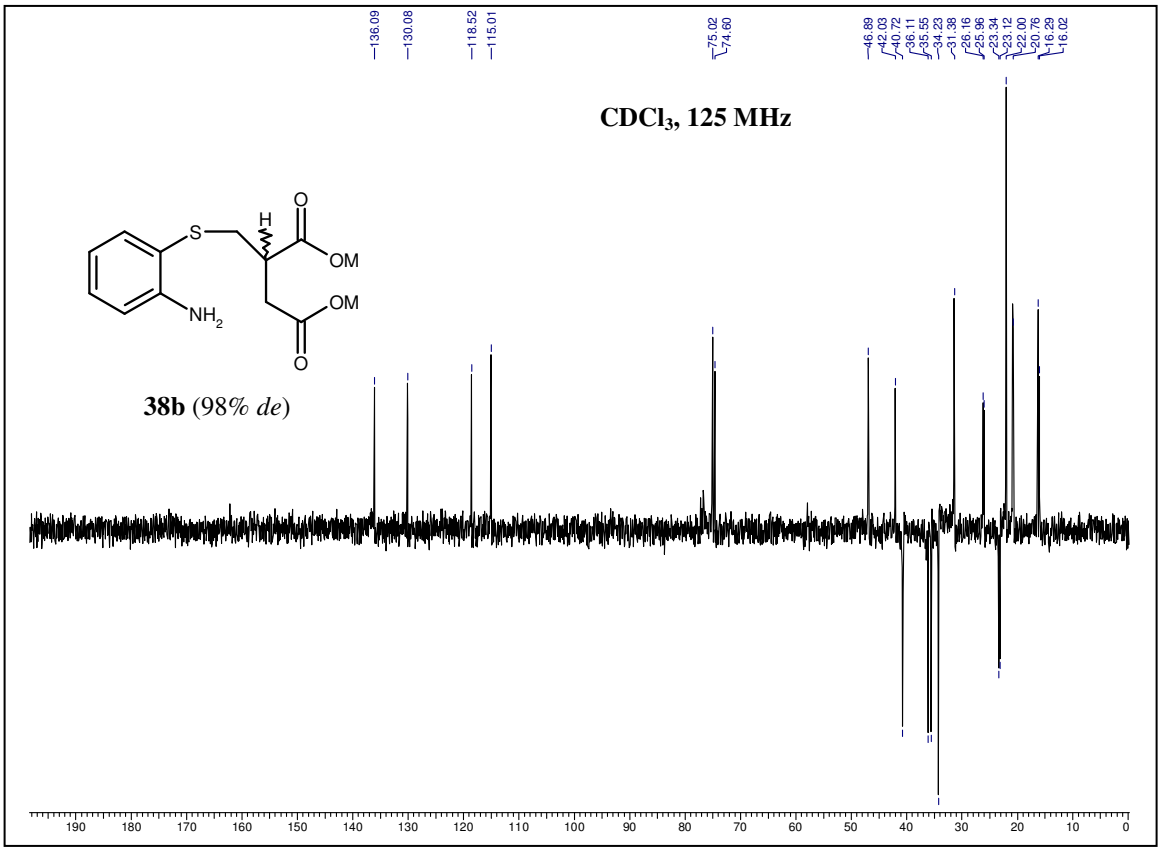

DMSO-d6
173.22
171.89
142.33
134.87
130.07
126.12
125.92
123.60
51.59
39.70
38.60
38.10
34.42
S
CH2COOCH3
N
H
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

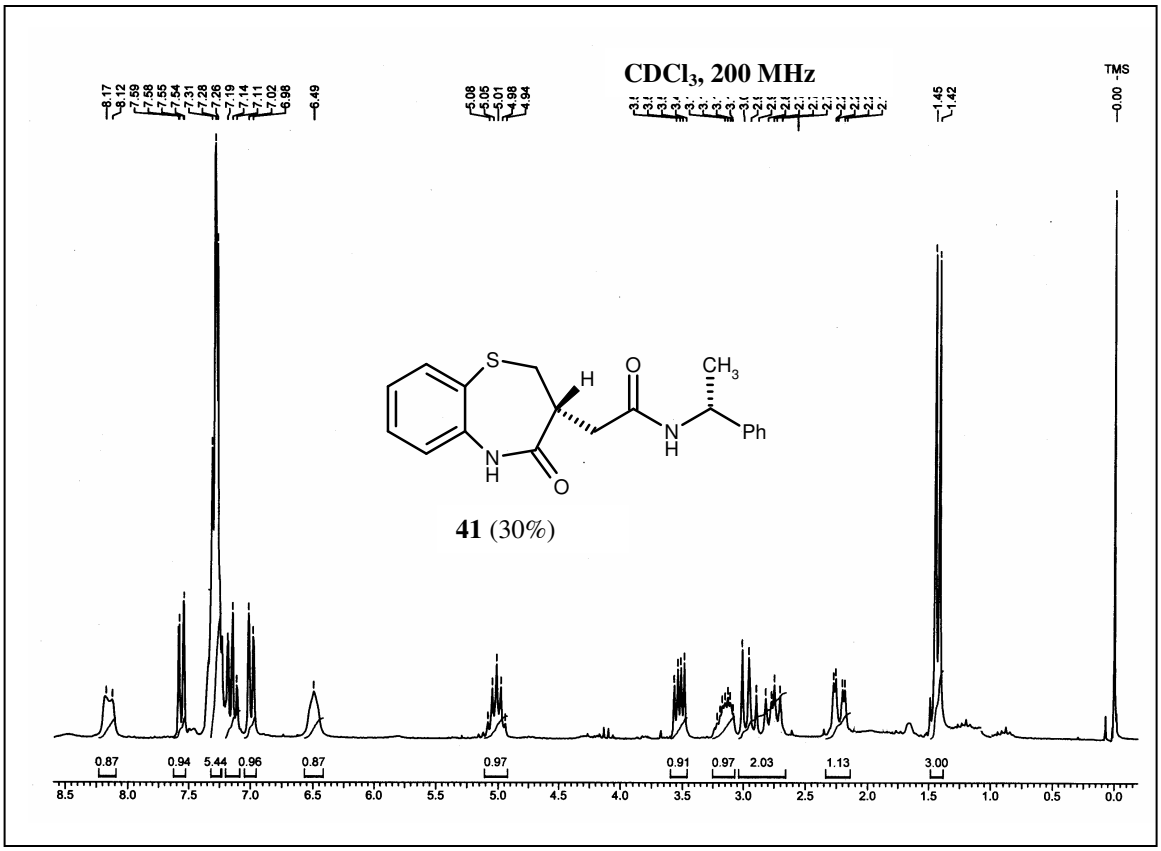

DMSO-d_6, 125 MHz
134.86
130.07
125.92
123.59
51.59
38.60
38.10
34.42
S
CH2COOCH3
N
H
O
35b

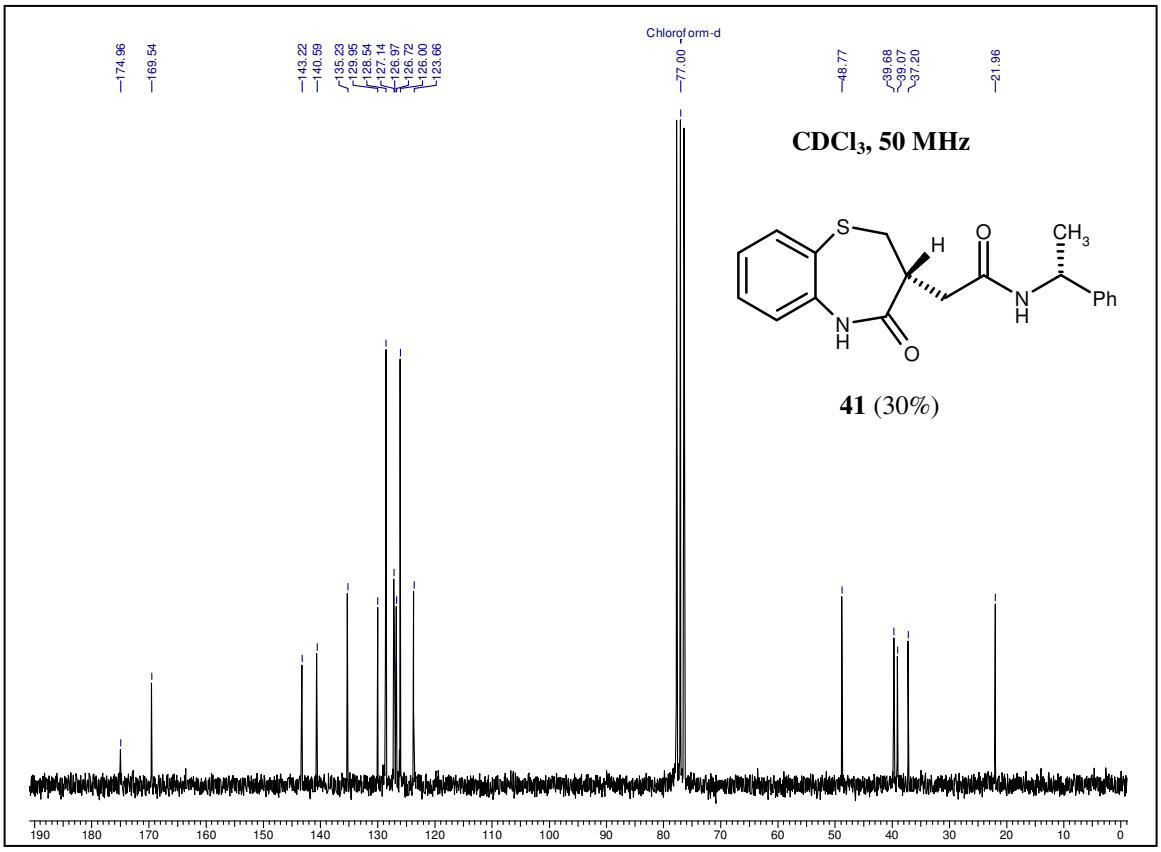

Chloroform-d
CDCl3, 400 MHz
S
H
O
OM
OM
NH2
O
38a (40% de)
M = L-Mentyl
0.91 0.95 1.75 2.00 1.51 0.90 1.03 0.62 3.00 4.07 4.26 11.93

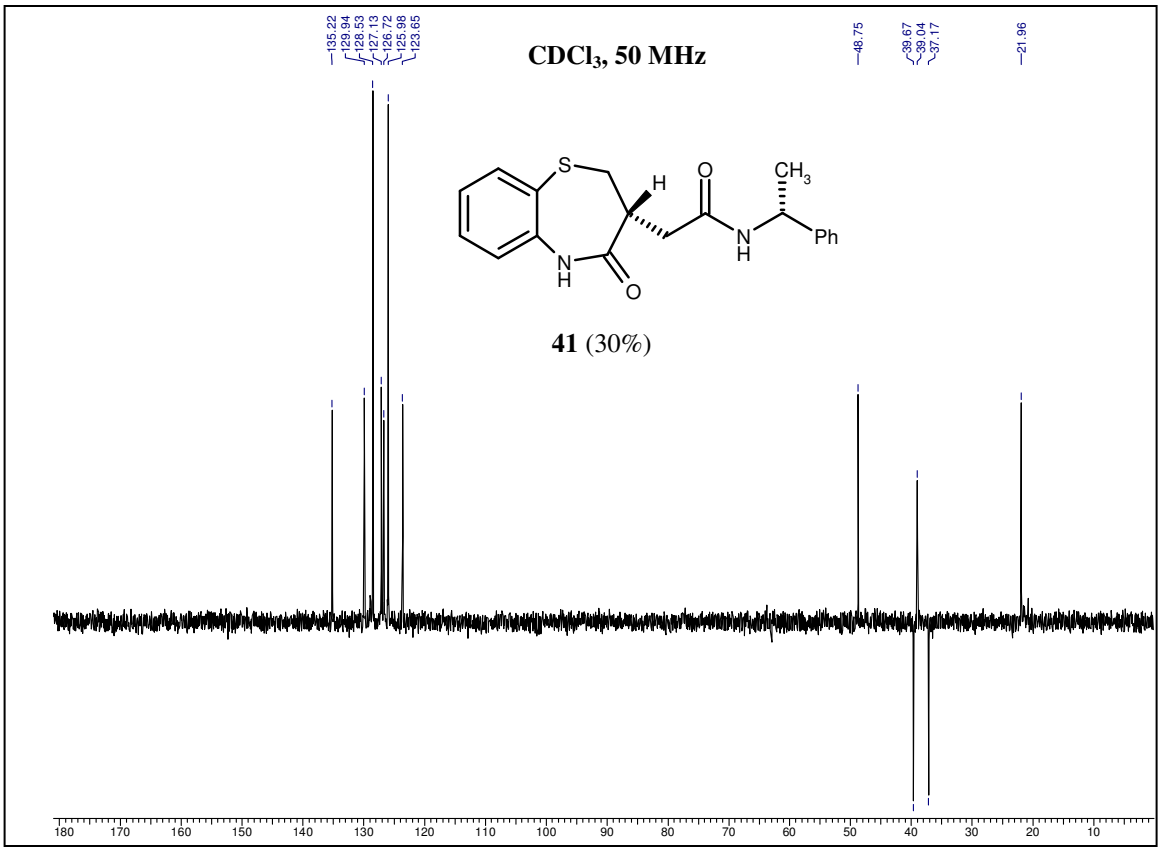

CDCl3, 400 MHz
38b (98% de)
M = L-Mentyl

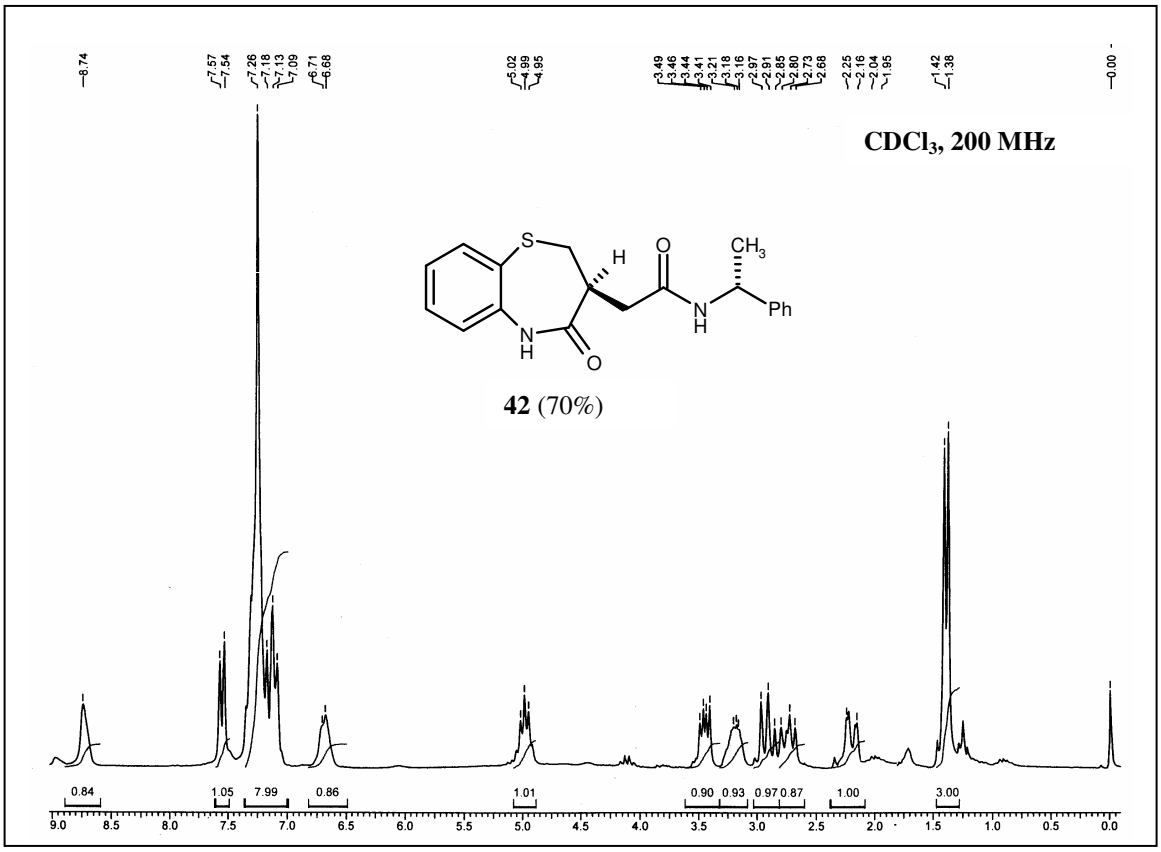

CDCl3, 125 MHz
38b (98% de)

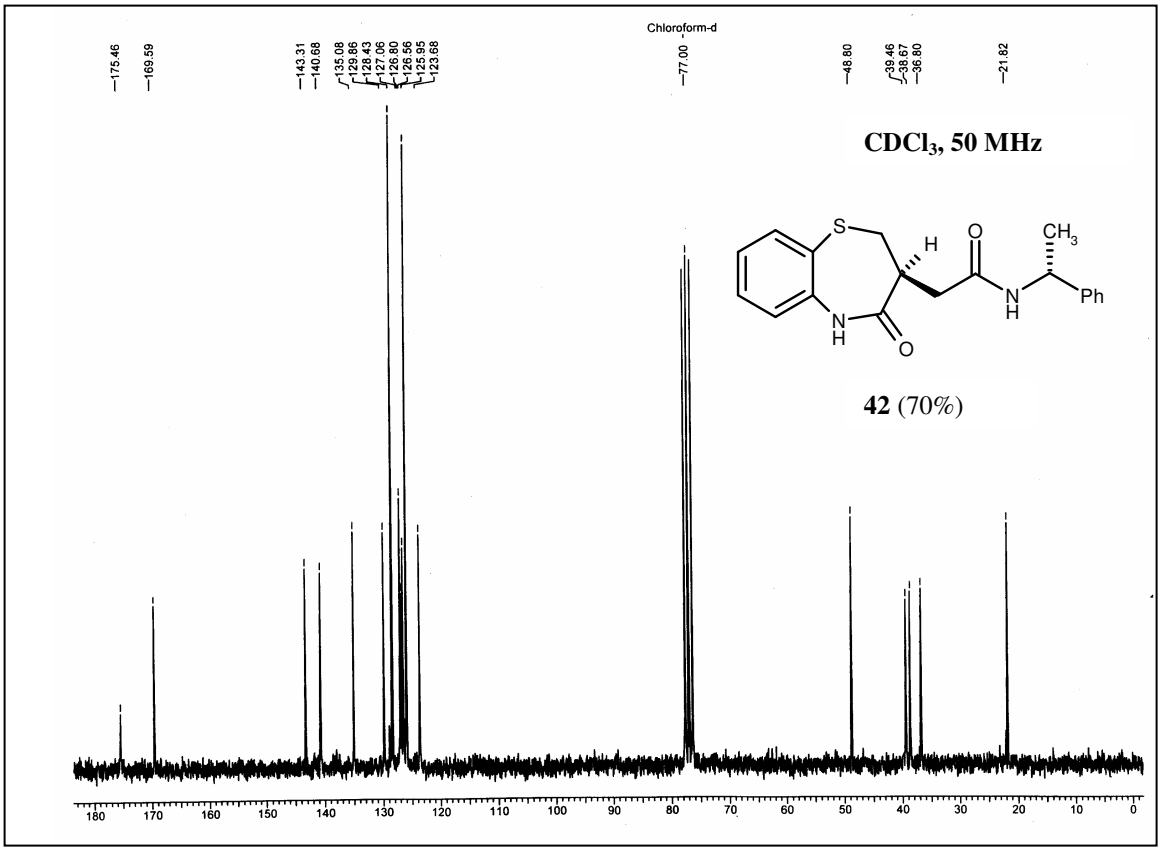

CDCl3, 125 MHz
38b (98% de)

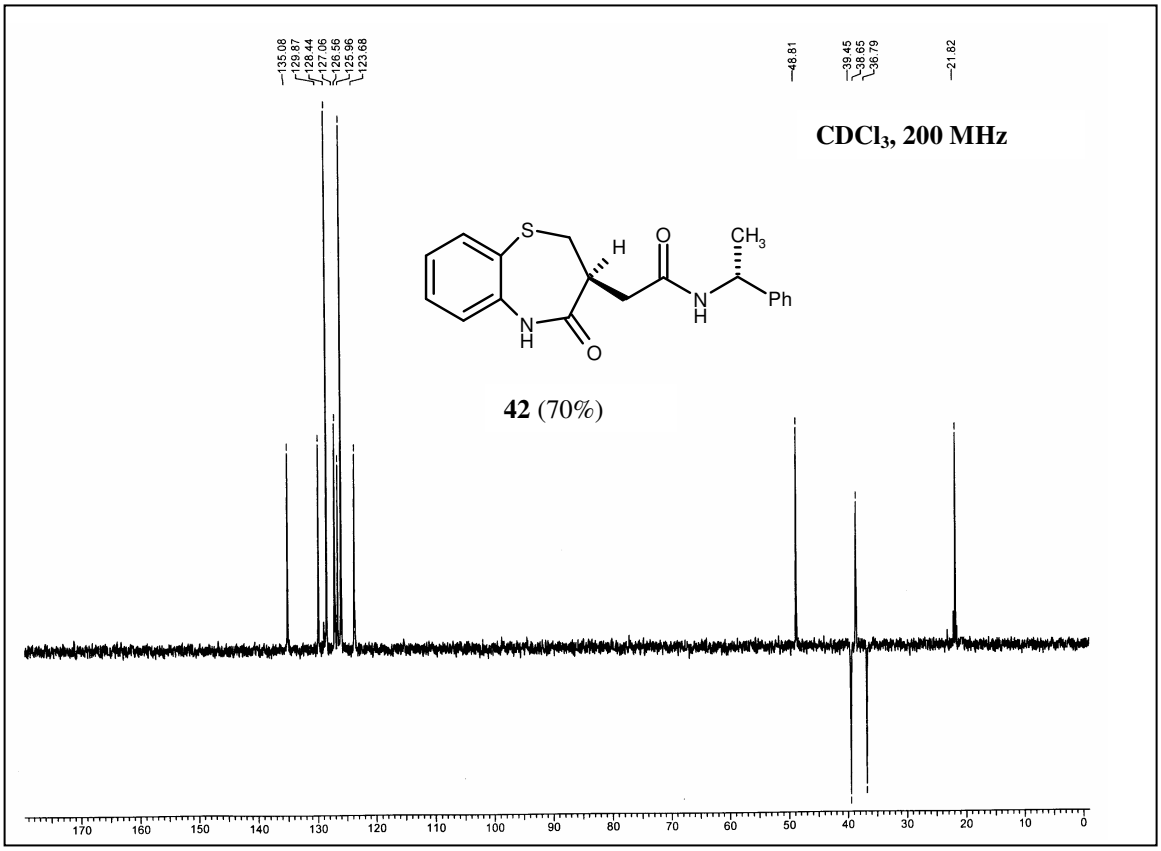

CDCl3, 200 MHz
41 (30%)

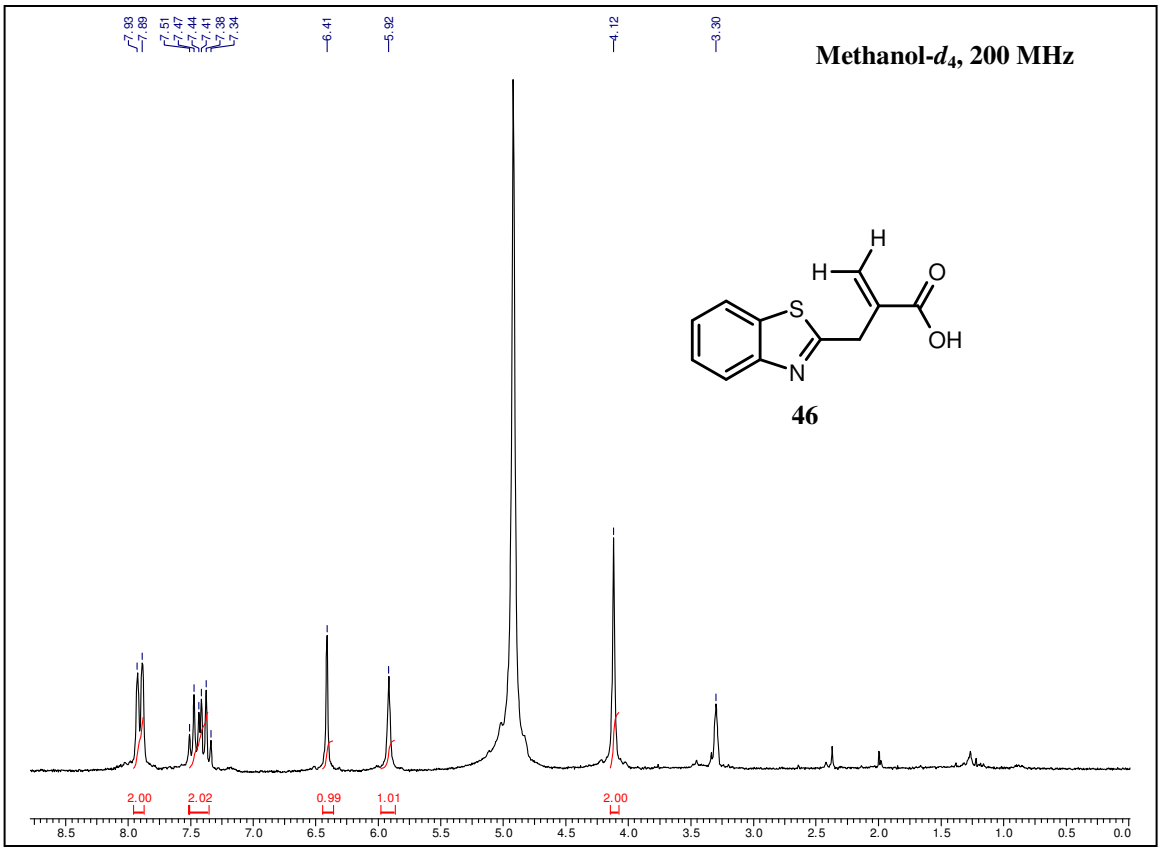

Chloroform-d
174.96
169.54
143.22
140.59
135.23
129.95
128.54
127.14
126.97
126.72
126.00
123.66
77.00
48.77
39.68
39.07
37.20
21.96
CDCl3, 50 MHz
S
H
O
CH3
N
H
Ph
N
H
O
41 (30%)

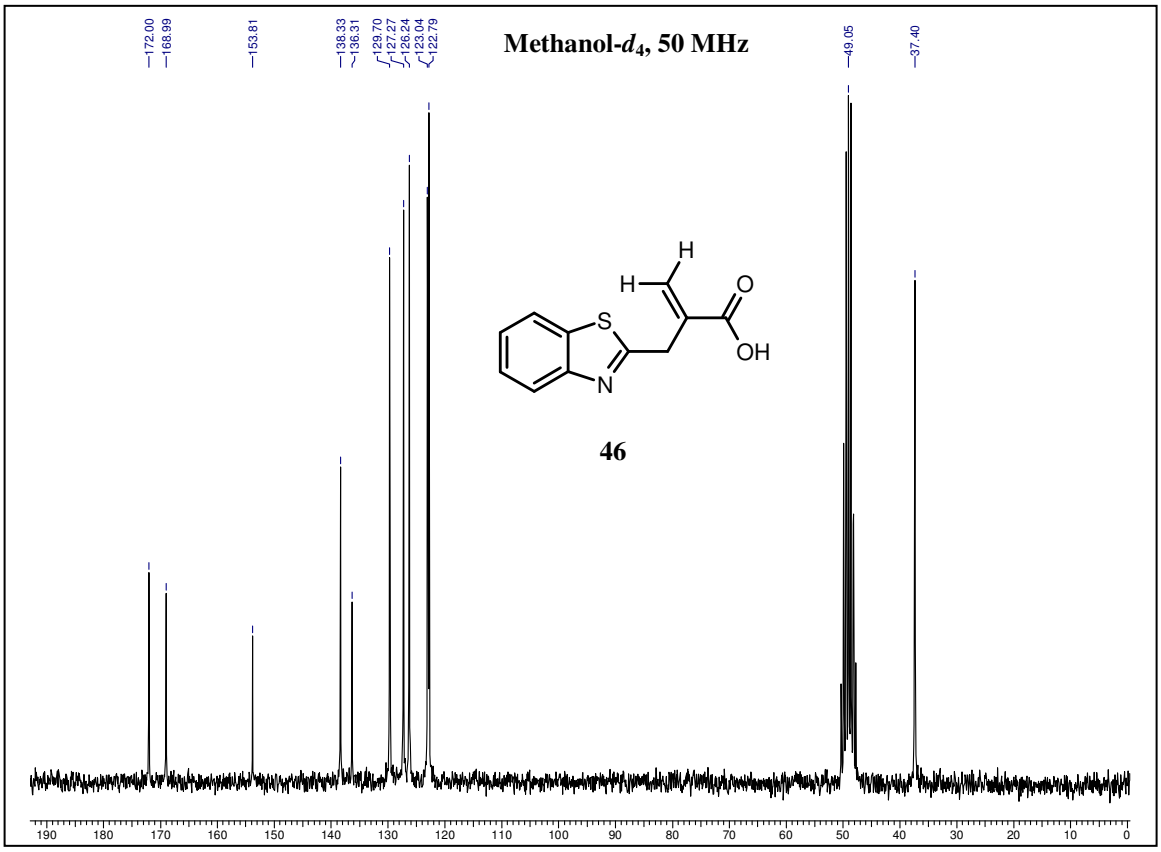

135.22
129.94
128.53
127.13
126.72
125.98
123.65
48.75
39.67
39.14
37.17
21.96
CDCl3, 50 MHz
S
H
O
CH3
N
H
Ph
N
H
O
41 (30%)

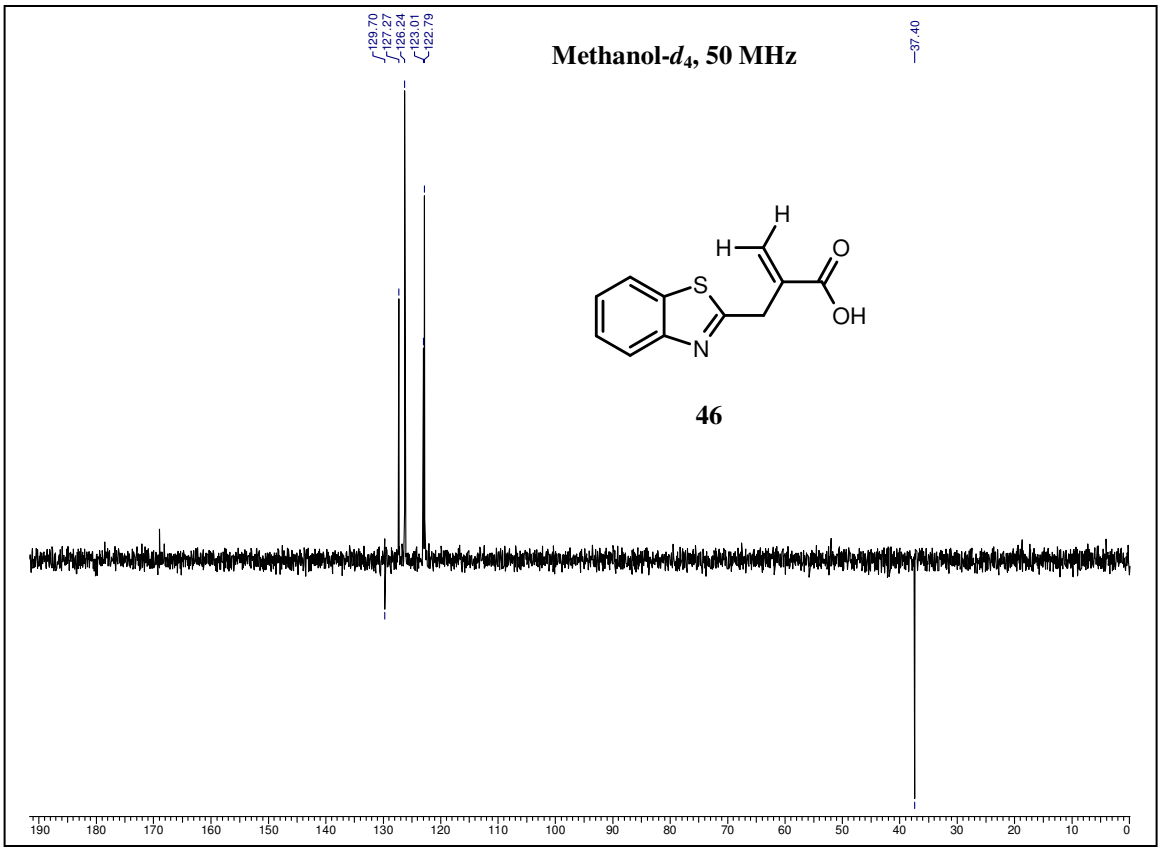

CDCl3, 200 MHz
42 (70%)


Chloroform-d
CDCl3, 50 MHz
42 (70%)


135.08
129.87
128.44
127.06
126.56
125.96
123.68
48.81
39.45
38.65
36.79
21.82
CDCl3, 200 MHz
S
H
O
CH3
N
H
Ph
N
H
O
42 (70%)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


7.93
7.89
7.51
7.47
7.44
7.41
7.38
7.34
6.41
5.92
4.12
3.30
Methanol-d4, 200 MHz
H
H
O
S
OH
N
46
2.00
2.02
0.99
1.01
2.00
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


Methanol-d_4, 50 MHz
172.00
168.99
153.81
138.33
136.31
129.70
127.27
126.24
123.04
122.79
49.05
37.40
H
H
O
S
OH
N
46


Methanol-d_4, 50 MHz
129.70
127.27
126.24
123.01
122.79
37.40
H
H
O
S
OH
N
46

1B.6. References

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(13) Crystallographic data (excluding structure factors) for the structures **35a** and **41** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 600537 and 600538 respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

1C. Section C

Synthesis of Isomelophlin A and Studies Towards the Synthesis of Melophlin A

This section features the following topics:

1C.1	*Background*	82
1C.2	*Present Work Results and Discussion*	83
1C.3	*Summary*	87
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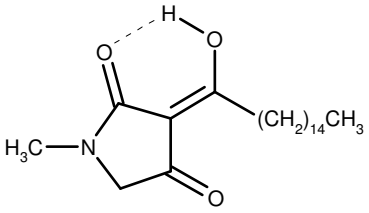
1C.6	*References*	107

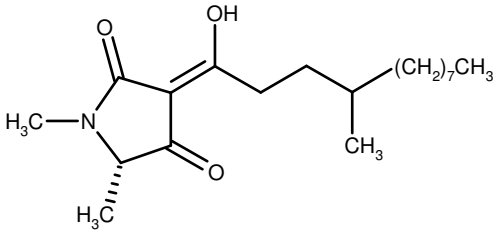
1C. Section C: Synthesis of Isomelophlin A and Studies Towards the Synthesis of Melophlin A

1C.1. Background

Ras oncogenes have an important role in cell growth and differentiation,[1] and so a substance, which reverses the transformed phenotype caused by *ras* oncogene, has high potential as a new type of anti-cancer agent. Kobayashi and co-workers[2] have isolated two novel tetramic acids named melophlins A (**1**) and B (**2**) from the marine sponge *Melophlus sarassinorum,* and the absolute stereo-structures were elucidated on the basis of chemical and physicochemical evidence. Melophlins A (**1**) and B (**2**) induced reversion of the tumorous phenotype of *ras*-transformed NIH3T3 cells to normal at the concentration of 5 $\mu g\ mL^{-1}$.



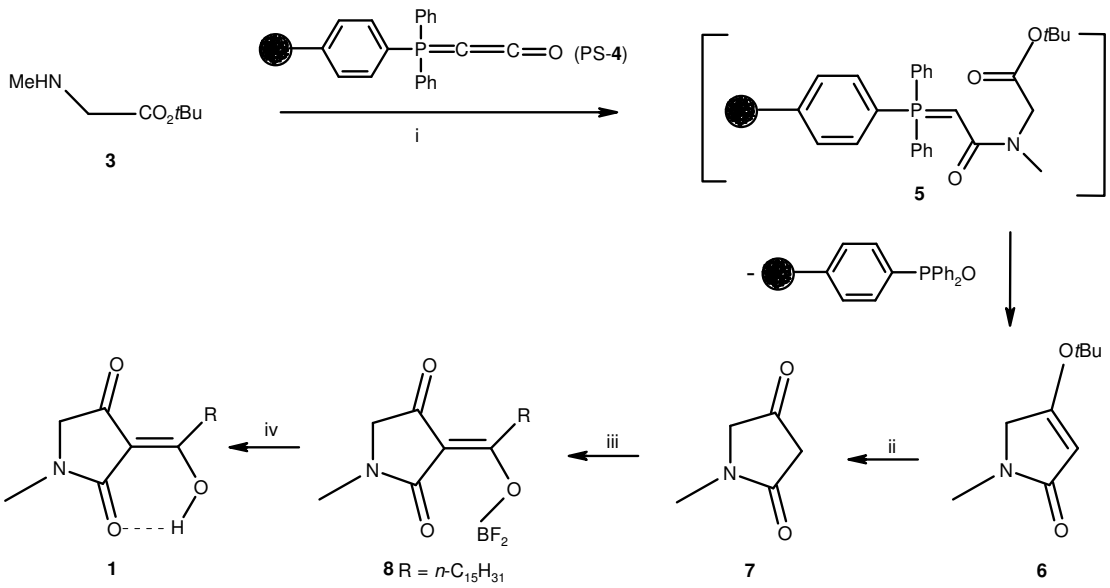
Melophlin A (**1**)



Melophlin B (**2**)

1C.1.1: *Schobert's approach towards melophlins A*

Schobert *et al*[3] have synthesized 3-acyltetramic acids of the melophlin family from *α*-aminoesters and immobilized (triphenylphosphoranylidene)ketene (Ph_3PCCO). Melophlin A was synthesized in four steps from sarcosine *t*-butyl ester **3**. Ester **3** on treatment with Ph_3PCCO (**4**),[4] immobilized by attachment to a polystyrene (PS) resin, gave the *N*-methyl-4-*t*-butoxypyrrolin-2-one (**6**) as product of a domino addition-intramolecular Wittig alkenation sequence. Cleavage of *t*-butyl group in **6** with TFA quantitatively yielded *N*-methylpyrrolidine-2,4-dione **7**. Acylation of **7** with palmitoyl chloride in presence of BF_3-diethyl ether under microwave irradiation furnished the BF_2-chelates **8** which on heating with methanol furnished melophlin A (**1**) in 40% overall yield (Scheme 1).

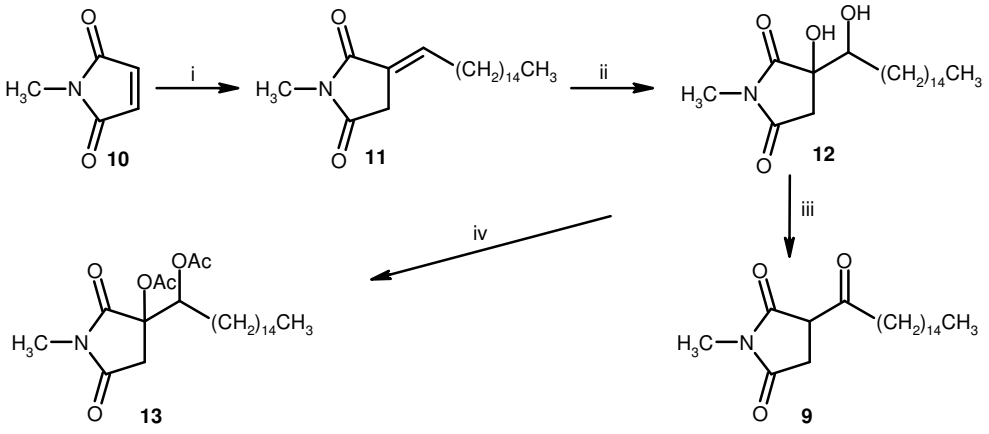


Scheme 1. *Reagents, conditions and yields*: (i) **4**, THF, 60 °C, 10 h, or Microwave, 120 °C, 30 min; (ii) TFA, rt, 3 h (99%); (iii) n-$C_{15}H_{31}COCl$, $BF_3{\cdot}Et_2O$, microwave, 100 °C, 45 min (47%); (iv) MeOH, reflux, 2 h (91%).

1C.2. Present Work Results and Discussion

1C.2.1: *Synthesis of isomelophlin A*

The synthesis of isomelophlin A (**9**), an unnatural analog of melophilin A was completed by employing Wittig condensation strategy[5] developed in our laboratory. Wittig coupling of hexadecanal, prepared from the potassium palmitate via acidification, esterification using $MeOH/H_2SO_4$, $LiAlH_4$-reduction and PCC-oxidation, with *N*-methyl maleimide (**10**) gave the itaconimide derivative **11**. Osmium tetraoxide induced dihydroxylation of the

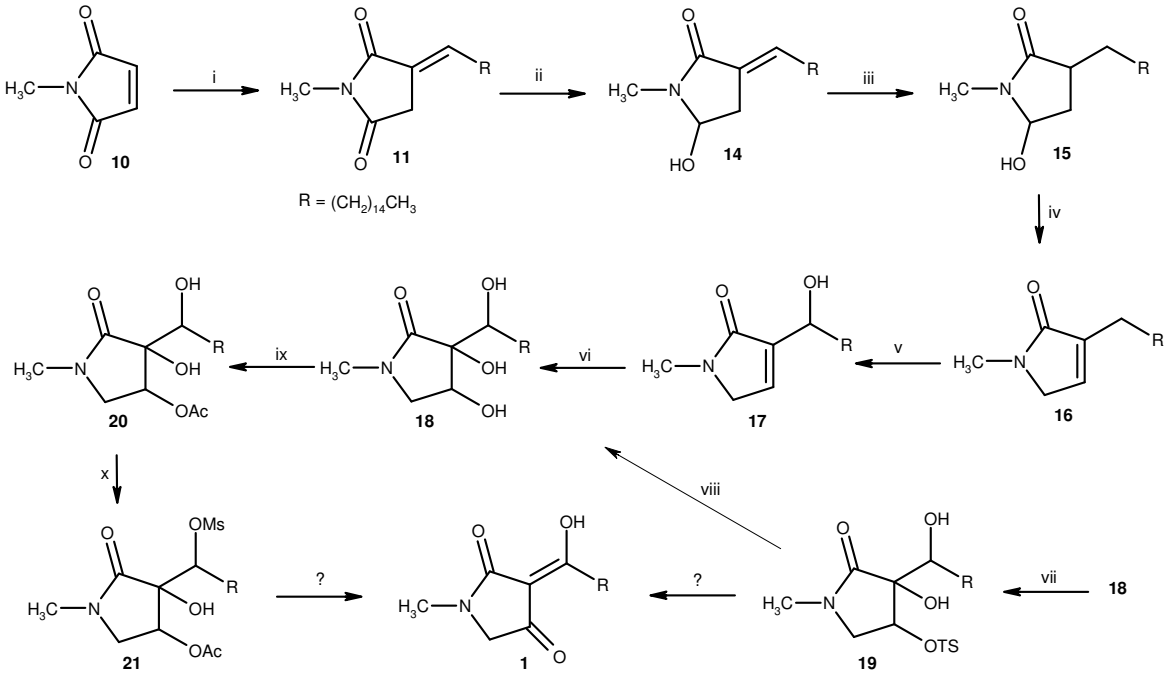


Scheme 2. *Reagents, conditions and yields*: (i) PPh_3, hexadecanal, THF, reflux, 8 h (96%); (ii) OsO_4, NMO, *t*-BuOH, rt, 36 h (88%); (iii) Conc. H_2SO_4 on silica-gel (0.5 mL in 5 g), toluene, reflux, 24 h (60%); (iv) Ac_2O, reflux, 5 h (80%).

imide **11** furnished the diol **12**. The diol **12** when refluxed in acetic anhydride for dehydration, we got the corresponding diacetoxy compound **13**. However, when the diol **12** was subjected to dehydration using H_2SO_4 adsorbed on silica gel furnished isomelophlin A (**9**) in 3 steps and 50% overall yield (Scheme 2). The ^1H and ^{13}C NMR data of compound **9** revealed that in solution it prefers to stay as a dicarbonyl system exclusively.

1C.2.2: *Studies towards the synthesis of melophilin A*

Our studies towards the synthesis of melophilin A started with the Wittig coupling of hexadecanal with *N*-methyl maleimide (**10**) to give the itaconimide derivative **11**, which was regioselectively reduced using $NaBH_4$ in THF:H_2O mixture (9:1) to afford the hydroxyl lactam **14**. Further reduction of hydroxyl lactam using Pd-C and hydrogen gave saturated hydroxylactam **15**. Dehydration of hydroxylactam **15** using Amberlyst resin in refluxing CH_3CN furnished the lactam **16** in 85% yield. We surmise that the



Scheme 3. *Reagents, conditions and yields*: (i) PPh_3, hexadecanal, THF, reflux, 8 h (96%); (ii) $NaBH_4$, THF-H_2O (10:1), rt, 12 h (95%); (iii) H_2, Pd-C, MeOH, rt, 4 h (90%); (iv) Amberlyst, CH_3CN, reflux, 6 h (85%); (v) SeO_2, EtOH, reflux, 10 h (75%); (vi) OsO_4, NMO, *t*-BuOH, rt, 36 h (88%); (vii) *p*-TSCl, Et_3N, DMAP, CH_2Cl_2, rt, 6 h (90%); (viii) NaH, THF, rt 4 h (90%); (ix) Ac_2O, pyridine, CH_2Cl_2, rt, 12 h (95%); (x) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 10 h (80%).

lone pair on nitrogen atom participates in the elimination process, which is followed by two prototropic shifts. SeO_2 induced allylic oxidation of lactam **16** regioselectively furnished the *β*-hydroxy lactam **17** in 75% yield (Scheme 3). The *β*-hydroxyl lactam **17** was subjected to oxidation using variety of oxidizing agents and conditions (Table 1).

Table 1. Reaction conditions tried for oxidation of *β*-hydroxyl lactam **17**

Sr. No	Reagents and conditions	Result
1	PCC, CH_2Cl_2	No reaction
2	Swern oxidation	No reaction
3	$BH_3 \cdot Me_2S$, THF, PCC, CH_2Cl_2	No reaction
4	Jones oxidation	No reaction
5	*m*-CPBA, CH_2Cl_2	No reaction
6	OsO_4, Oxone, DMF	No reaction

All these reaction conditions unfortunately met with failure and we were unable to oxidize *β*-hydroxyl lactam **17** and this may be due to strong hydrogen bonding with the lactam carbonyl group. Then we planed to convert *β*-hydroxyl lactam **17** to triol **18**. Osmium tetraoxide induced dihydroxylation of *β*-hydroxyl lactam **17** in presence of NMO in *t*-BuOH furnished the triol **18** in 88% yield. Variety of oxidizing and dehydrating agents were used to convert triol in the natural product melophilin A (**1**) as shown in table 2 and 3.

Table 2. Reaction conditions tried for oxidation of triol **18**

Sr. No	Reagents and conditions	Result
1	PCC, CH_2Cl_2	No reaction
2	Swern oxidation	No reaction
3	Jones oxidation	No reaction
4	DMP, CH_2Cl_2	Decomposition
5	DDQ, benzene	Complex reaction mixture
6	Oxone, NaCl, EtOAc	No reaction
7	TEMPO, $NaClO_2$, CH_2Cl_2	No reaction
8	IBX, EtOAc	Complex reaction mixture

Table 3. Reaction conditions tried for dehydration of triol **18**

Sr. No	Reagents and conditions	Result
1	H_2SO_4 on silica gel, toluene, reflux	Decomposition
2	Amberlyst CH_3CN, reflux	No reaction
3	Et_3SiH, $BF_3{\cdot}Et_2O$	No reaction
4	I_2, PPh_3, CH_2Cl_2	No reaction
5	Silica chloride, $CHCl_3$, reflux	Decomposition
6	$SOCl_2$, pyridine, CH_2Cl_2, rt	Complex reaction mixture
7	P_2O_5, benzene, reflux	Complex reaction mixture

Unfortunately all our attempt to either oxidize or dehydrate the triol **18** met will failure. Triol **18** on tosylation with TsCl, Et_3N and DMAP gave the monotosylated lactam **19** in 90% yield. Lactam **19** when treated with NaH gave back the unprotected triol **18** but not the expected epoxide. Further triol **18** was converted to monoacetate lactam **20** in 95% yield by treating with acetic anhydride in pyridine. Variety of oxidizing and dehydrating agents were used to convert monoacetate lactam **20** to the acetate protected natural product melophilin A as shown in table 4.

Table 4. Reaction conditions tried for oxidation (Sr. No. 1-4) and dehydration (Sr. No. 5-8) of monoacetate lactam **20**

Sr. No	Reagents and conditions	Result
1	SeO_2, EtOH, reflux	No reaction
2	Jones oxidation	No reaction
3	$SOCl_2$, Pyridine CH_2Cl_2	Complex reaction mixture
4	Tf_2O, DMSO, *t*-BuOH	No reaction
5	*p*-NO_2-$C_6H_4CH_2Cl$, reflux	Decomposition
6	*p*-NO_2-$C_6H_4CH_2Cl$, Et_3N, THF	No reaction
7	TFA, NaOAc, reflux	Decomposition
8	Neat, 150 °C	Decomposition

Unfortunately all our attempt to either oxidize or dehydrate monoacetate lactam **20** met with failure. Monoacetate lactam **20** on reaction with MsCl in presence of Et_3N gave the mesyl and acetate protected lactam **21** in 80% yield. We are in search of suitable reaction conditions to get melophlin A from the triol **18** and the work is under active progress in our laboratory.

1C.3. Summary

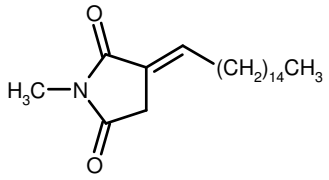
In summary, in this section we have described the first solid support synthesis of naturally occurring melophlin A. Our results on synthesis of isomelophlin A and an attempted synthesis of melophlin A have been described. We have designed the melophlin A skeleton and the condition to perform the last dehydrative oxidation step to reach the target compound is still elusive for us.

In conclusion, in the present three sections chapter we have described the relevant literature and our results with experimental and spectral data. Itaconic acid and its derivatives are the multifunctional entity and have been extensively used for different reactions at all the reactive sites on the 5-carbon itaconic acid, for the construction of variety of heterocyclic structures in past century. Itaconic acid and derivatives are practically used in the synthesis of variety of key intermediates employed in the heavy and fine chemical industries and as such these compounds have been often used to model (i) compounds highlighting regiochemical dichotomy, (ii) heterocyclic skeletons, (iii) natural products and their precursors, (iv) bioactive molecules and (v) series of polymers with tailored material characteristics. We used these starting materials for the synthesis of 1,5-benzothiazapines, benzothiazoles and isomelophlin A. We feel that with a choice of an appropriate chiral auxiliary, it will be possible to synthesize the 1,5-benzothiazapines with high yield and enantiomeric excess. We also feel that a reduction of an amide carbonyl in the substrate will pave the way to benzothiazacines. The synthesis of isomelophlin A was very straight forward job for us but however, the carbonyl transposition to naturally occurring melophlin A by employing several reaction conditions and strategies has still kept us away from the goal. We are hopeful about the transformation of isomelophlin A to melophlin A.

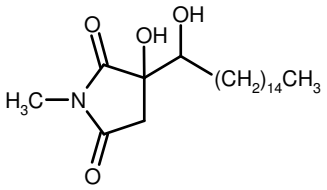
1C.4. Experimental Section

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60-120 mesh). Commercially available maleic anhydride, $NaBH_4$, OsO_4, PPh_3, Amberlyst, SeO_2, TsCl, MsCl and DMAP were used.

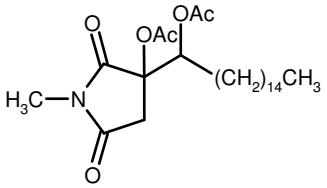
3-Hexadecylidene-1-methylpyrrolidine-2,5-dione (11). To the solution of *N*-methyl maleimide (**10**, 2.00 g, 18.01 mmol) and PPh_3 (4.72 g, 18.01 mmol) in THF (70 mL) was added the solution of hexadecanal (6.483 g, 27.01 mmol) in THF (30 mL) and the reaction mixture was refluxed for 8 h. The reaction was allowed to come to room temperature and solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to give **11** (white solid): 5.79 g (96% yield).

 **11** **$C_{21}H_{37}NO_2$ (335)**	**Mp** 76 °C. **IR** (Nujol) ν_{max} 1769, 1711, 1672, 1462, 1435, 1377 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.86 (t, *J* = 6 Hz, 3H), 1.20-1.35 (m, 24H), 1.40-1.60 (m, 2H), 2.17 (q, *J* = 8 Hz, 2H), 3.03 (s, 3H), 3.19 (s, 2H), 6.79 (t, *J* = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 13.8, 22.4, 24.2, 27.9, 29.1-29.4 (12 carbons), 31.5, 125.4, 138.2, 169.6, 173.8. **Anal. Calcd** for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.11; N, 4.17. Found: C, 75.06; H, 11.15; N, 4.10.

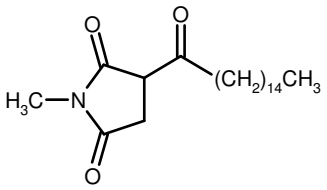
3-Hydroxy-3-(1-hydroxyhexadecyl)-1-metylpyrrolidine-2,5-dione (12). To the solution of imide **11** (2.00 g, 5.97 mmol) in *t*-BuOH (30 mL) was added 60% aqueous solution of NMO (15 mL) and OsO_4 (24 mg, 0.012 mmol) in *t*-BuOH (0.6 mL) and the reaction mixture was stirred for 36 h. The reaction was quenched by adding sodium sulphite and stirred for 1 h, filtered through celite, washed with ethyl acetate and filtrate was evaporated in vacuo. The residue was dissolved in water and extracted with ethyl acetate containing 5% MeOH (30 mL x 4) washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (6:4) to provide **12** (white solid): 1.94 g (88% yield).

 **12** **$C_{21}H_{39}NO_4$ (369)**	**Mp** 88 °C. **IR** ($CHCl_3$) ν_{max} 3474, 3396, 1786, 1703, 1446, 1408, 1385 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.87 (t, *J* = 8 Hz, 3H), 1.20-1.70 (m, 28H), 2.75 (q, *J* = 18 Hz, 2H), 3.00 (s, 3H), 3.43 (bs, 2H), 3.80 (bd, *J* = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 14.1, 22.6, 24.8, 25.9, 29.3-29.4 (9 carbons), 29.6, 30.2, 31.9, 38.3, 74.3, 76.9, 174.4, 179.6. **Anal. Calcd** for $C_{21}H_{39}NO_4$: C, 68.25; H, 10.64; N, 3.79. Found: C, 68.34; H, 10.57; N, 3.88.

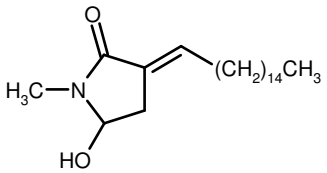
3-Actoxy-3-(1-acetoxyhexadecyl)-1-metylpyrrolidine-2,5-dione (13). A solution of **12** (500 mg, 1.35 mmol) in acetic anhydride (15 mL) was gently refluxed for 5 h and the reaction mixture was concentrated in vacuo at 50 °C. The residue was diluted with ethyl acetate (40 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give **13** (white solid): 491 mg (80% yield).

 **13** **$C_{25}H_{43}NO_6$ (453)**	**Mp** 62-63 °C. **IR** ($CHCl_3$) ν_{max} 1792, 1749, 1720, 1439, 1373 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.87 (t, *J* = 6 Hz, 3H), 1.20-1.45 (m, 26H), 1.50-1.70 (m, 2H), 2.08 (s, 3H), 2.11 (s, 3H), 2.89 (d, *J* = 10 Hz, 2H), 3.03 (s, 3H), 5.30 (dd, *J* = 10 & 4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) 14.1, 20.7 (2 carbons), 22.6, 25.0, 25.5, 28.4, 29.1-29.4 (9 carbons), 29.6, 31.9, 37.5, 74.0, 79.9, 169.9, 170.1, 172.8, 173.4. **Anal. Calcd** for $C_{25}H_{43}NO_6$: C, 66.19; H, 9.55; N, 3.09. Found: C, 65.98; H, 9.43; N, 3.00.

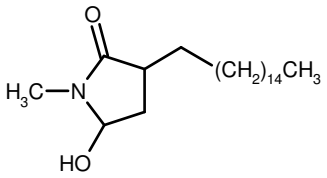
1-Methyl-3-palmitoylpyrrolidine-2,5-dione (9). To the solution of diol **12** (1.00 g, 2.71 mmol) in toluene (20 mL) was added conc. H_2SO_4 on silica-gel (5 g, 0.5 mL in 5 g) and the reaction mixture was refluxed for 24 h. The reaction was allowed to reach room temperature and solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give **9** (white solid): 570 mg (60% yield).

 **9** **$C_{21}H_{37}NO_3$ (351)**	**Mp** 69 °C. **IR** ($CHCl_3$) ν_{max} 1778, 1709, 1439, 1383 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.88 (t, *J* = 6 Hz, 3H), 1.20-1.40 (m, 24H), 1.50-1.75 (m, 2H), 2.55-2.75 (m, 2H), 3.01 (s, 3H), 3.05-3.40 (m, 2H), 3.85-4.05 (m, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 13.9, 22.4, 23.0, 24.9, 28.7, 29.1-29.2 (8 carbons), 29.4, 29.7, 31.7, 42.9, 52.8, 172.6, 175.6, 201.7. **Anal. Calcd** for $C_{21}H_{37}NO_3$: C, 71.75; H, 10.61; N, 3.98. Found: C, 71.66; H, 10.72; N, 3.95.

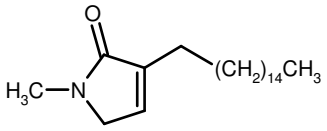
3-Hexadecylidene-5-hydroxy-1-methylpyrrolidin-2-one (14). To the solution of imide **11** (3.00 g, 8.95 mmol) in THF:H_2O (9:1, 40 mL) was added $NaBH_4$ (1.02 g, 26.86 mmol) and the reaction mixture was stirred for 12 h. The reaction was quenched by adding water (10 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (6:4) to give **14** (white solid): 2.87 g (95% yield).

 **14** **$C_{21}H_{39}NO_2$ (337)**	**Mp** 60 °C. **IR** (Nujol) ν_{max} 3315, 1655, 1462, 1377 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.87 (t, *J* = 6 Hz, 3H), 1.20-1.45 (m, 26H), 2.00-2.20 (m, 2H), 2.48 (d, *J* = 16 Hz, 1H), 2.86 (d, *J* = 14 Hz, 1H), 2.89 (s, 3H), 5.10 (t, *J* = 8 Hz, 1H), 6.35-6.50 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) 14.1, 22.6, 27.1, 28.5, 29.3-29.7 (11 carbons), 31.9, 33.0, 82.1, 129.2, 134.3, 168.1. **Anal. Calcd** for $C_{21}H_{39}NO_2$: C, 74.72; H, 11.65; N, 4.15. Found: C, 74.69; H, 11.53; N, 4.08.

3-Hexadecyl-5-hydroxy-1-methylpyrrolidin-2-one (15). To the stirred solution of **14** (2.50 g, 7.42 mmol) in MeOH (40 mL) was added Pd-C (80 mg) and the reaction mixture was stirred for 4 h at room temperature under the Hydrogen pressure (50 psi). The reaction mixture was diluted with ethyl acetate (30 mL) and filtered through celite and washed with ethyl acetate, the filtrate was then evaporated in vacuo to give **15** (white solid): 2.27 g (90% yield).

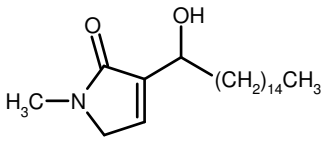
 **15** **$C_{21}H_{41}NO_2$ (339)**	**Mp** 65 °C. **IR** ($CHCl_3$) ν_{max} 3315, 1666, 1468, 1246 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.88 (t, *J* = 6 Hz, 3H), 1.20-1.45 (m, 28H), 1.80-2.00 (m, 2H), 2.05-2.20 (m, 1H), 2.25-2.45 (m, 1H), 2.60-2.70 (m, 1H), 2.87 (s, 3H), 4.85-5.10 (m, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 14.0, 22.6, 26.9, 27.0, 27.3, 29.3, 29.5-29.6 (6 carbons), 31.4, 31.9, 32.1, 34.8, 35.1, 39.5, 41.0, 83.4, 177.2. **Anal. Calcd** for $C_{21}H_{41}NO_2$: C, 74.28; H, 12.17; N, 4.13. Found: C, 74.11; H, 12.04; N, 4.05.

3-Hexadecyl-1-methyl-1*H*-pyrrol-2(5*H*)-one (16). To the solution of **15** (2.00 g, 5.90 mmol) in CH_3CN (30 mL) was added Amberlyst resin (500 mg) and the reaction mixture was refluxed for 6 h. The reaction was allowed to reach to room temperature, filtered through celite, washed with ethyl acetate and filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate (50 mL) washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (7:3) to give **16** (white solid): 1.61 g (85% yield).

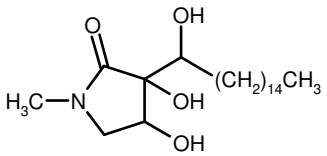
 **16** **$C_{21}H_{39}NO$ (321)**	**Mp** 70 °C. **IR** ($CHCl_3$) ν_{max} 1701, 1647, 1466, 1437, 1215 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.86 (t, *J* = 6 Hz, 3H), 1.20-1.40 (m, 26H), 1.45-1.65 (m, 2H), 2.25 (dt, *J* = 8 & 2 Hz, 2H), 3.02 (s, 3H), 3.80 (d, *J* = 2Hz, 2H), 6.58 (dt, *J* = 4 & 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 14.0, 22.6, 25.9, 27.5, 29.2-29.3 (11 carbons), 29.6, 31.9, 52.6, 133.5, 140.6, 171.8. **Anal. Calcd** for $C_{21}H_{39}NO$: C, 78.44; H, 12.22; N, 4.36. Found: C, 78.32; H, 12.17; N, 4.29.

3-(1-Hydroxyhexadecyl)-1-methyl-1*H*-pyrrol-2(5*H*)-one (17). To the solution of **16** (1.50 g, 4.67 mmol) in EtOH (30 mL) was added SeO_2 (1.56 g, 14.02 mmol) and the reaction mixture was refluxed for 10 h. The reaction was allowed to reach to room temperature, filtered through celite, washed with ethyl acetate and filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel

column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give **17** (yellow solid): 1.18 g (75% yield).

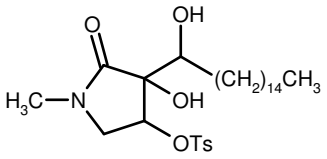
 **17** **$C_{21}H_{39}O_2N$ (337)**	**Mp** 37 °C **IR** ($CHCl_3$) ν_{max} 3421, 1705, 1637, 1466, 1445 1246 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200MHz) 0.88 (t, *J* = 6 Hz, 3H), 1.20-1.40 (m, 24H), 1.45-1.65 (m, 2H), 2.28 (dt, *J* = 8 & 2 Hz, 2H), 2.93 (s, 3H), 3.31 (q, *J* = 8 Hz, 2H), 5.18 (bs, 1H), 6.44 (t, *J* = 2Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 14.1, 22.7, 25.5, 26.4, 27.4, 29.3-29.7 (10 carbons), 31.9, 58.5, 87.8, 135.0, 143.2, 170.2. **Anal. Calcd** for $C_{21}H_{39}O_2N$: C, 74.72; H, 11.65; N, 4.15. Found: C, 74.53; H, 11.79; N, 4.02.

3,4-Dihydroxy-3-(1-hydroxyhexadecyl)-1-methylpyrrolidin-2-one (18). To the solution of compound **17** (500 mg, 1.48 mmol) in *t*-BuOH (10 mL) was added 60% aqueous solution of NMO (7 mL) and OsO_4 (6 mg, 0.003 mmol) in *t*-BuOH (0.15 mL) and the reaction mixture was stirred for 36 h. The reaction was quenched by adding sodium sulphite and stirred for 1 h, filtered through celite, washed with ethyl acetate and filtrate was evaporated in vacuo. The residue was dissolved in water and extracted with ethyl acetate containing 5% MeOH (30 mL x 4) washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (6:4) to give **18** (white solid): 486 mg (88% yield).

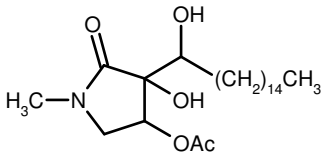
 **18** **$C_{21}H_{41}NO_4$ (371)**	**Mp** 57 °C. **IR** ($CHCl_3$) ν_{max} 3429, 3342, 1686, 1468 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.88 (t, *J* = 6 Hz, 3H), 1.20-1.40 (m, 26H), 1.60-1.85 (m, 2H), 2.91 (s, 3H), 3.33 (bs, 1H), 3.60-3.80 (m, 2H), 3.83 (s, 1H), 3.95 (bs, 1H), 4.51 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) 14.0, 22.6, 22.8, 28.3, 29.3, 29.6-29.8 (10 carbons), 31.9, 36.5, 64.6, 76.0, 94.9, 175.4. **Anal. Calcd** for $C_{21}H_{42}NO_4$: C, 67.70; H, 11.36; N, 3.76. Found: C, 67.56; H, 11.43; N, 3.41.

4-Hydroxy-4-(1-hydroxyhexadecyl)-1-metyl-5-oxopyrrolidin-3-yl- 4-metylbenzenesulfonate (19). To the solution of **18** (100 mg, 0.27 mmol) in CH_2Cl_2 (20 mL) was added *p*-TSCl (52.00 mg, 0.27 mmol), DMAP (5 mg) and Et_3N (0.37 mL, 0.27

mmol) and the reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give **19** (thick oil): 127 mg (90% yield).

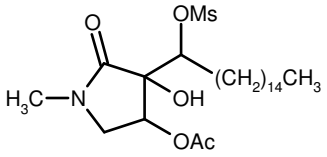
 **19** **$C_{28}H_{47}NO_6S$ (525)**	**IR** (Neat) ν_{max} 3398, 1738, 1726, 1713, 1466, 1371, 1242, 1178 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.88 (t, J = 6 Hz, 3H), 1.10-1.35 (m, 26H), 1.50-1.80 (m, 2H), 2.47 (s, 3H), 2.89 (s, 3H), 3.60-3.75 (m, 2H), 4.47 (s, 1H), 4.76 (s, 1H), 7.38 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 2H). **Anal. Calcd** for $C_{28}H_{47}NO_6S$: C, 63.97; H, 9.01; N, 2.66; S, 6.09. Found: C, 64.03; H, 9.12; N, 2.60; S, 6.00.

4-Hydroxy-4-(1-hydroxyhexadecyl)-1-metyl-5-oxopyrrolidin-3-yl 4-acetate (20). To the solution of **18** (200 mg, 0.54 mmol) in CH_2Cl_2 (20 mL) was added Ac_2O (0.6 mL, 0.54 mmol), and pyridine (0.44 mL, 0.54 mmol) and the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated in vacuo. The reaction was quenched with water and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give **20** (white solid): 211 mg (95% yield).

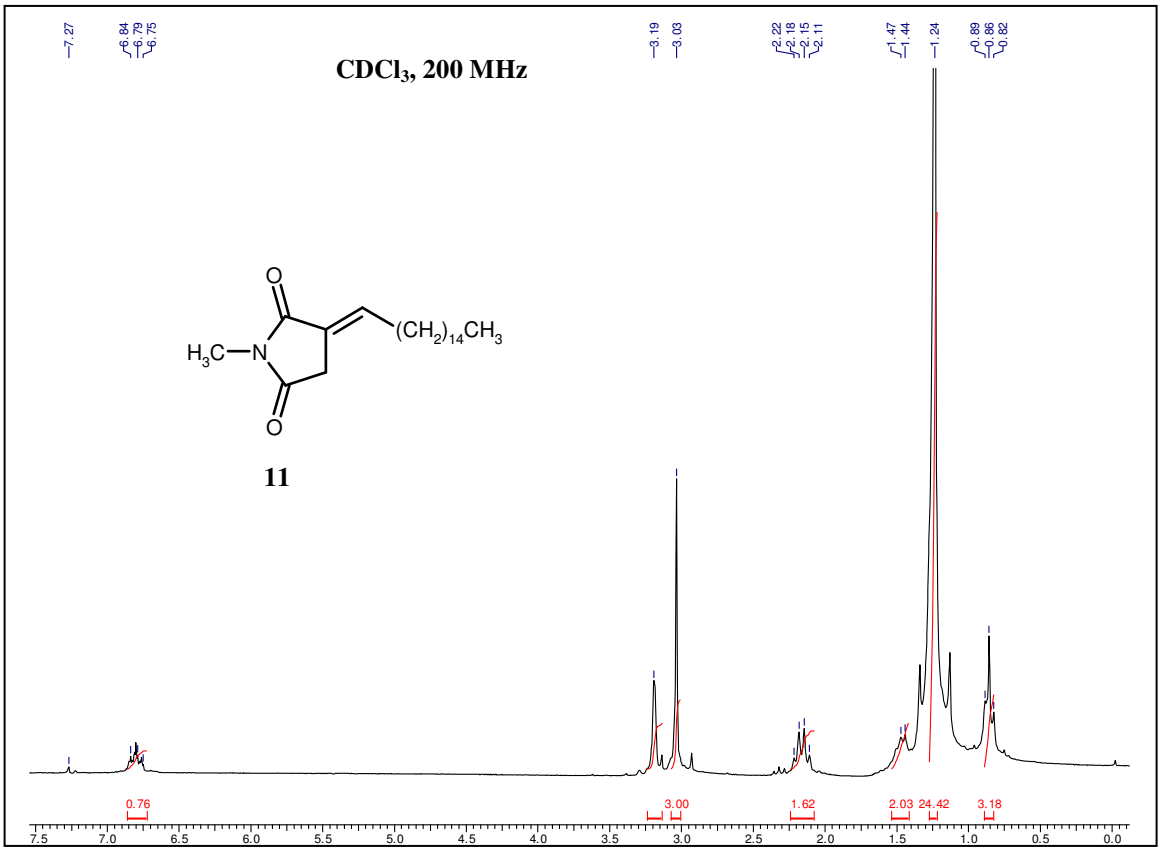
 **20** **$C_{23}H_{43}NO_5$ (413)**	**Mp** 59 °C. **IR** ($CHCl_3$) ν_{max} 3391, 1744, 1709, 1466, 1375, 1215 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.87 (t, J = 6 Hz, 3H), 1.20-1.35 (m, 24H), 1.40-1.60 (m, 2H), 1.65-1.85 (m, 2H), 2.12 (s, 3H), 2.91 (s, 3H), 3.55-3.85 (m, 2H), 4.51 (s, 1H), 4.95 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 14.1, 20.8, 22.7, 28.2, 29.3, 29.4-29.7 (10 carbons), 31.9, 36.9, 64.7, 73.6, 75.4, 92.2, 170.0, 175.0. **Anal. Calcd** for $C_{23}H_{43}NO_5$: C, 66.79; H, 10.48; N, 3.39. Found: C, 66.67; H, 10.37; N, 3.42.

4-Hydroxy-1-methyl-4-[1-(methylsulfonyloxy)hexadecyl]-5-oxopyrrolidin-3-yl-acetate (21). To the solution of **20** (50 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) was added MsCl (41.22

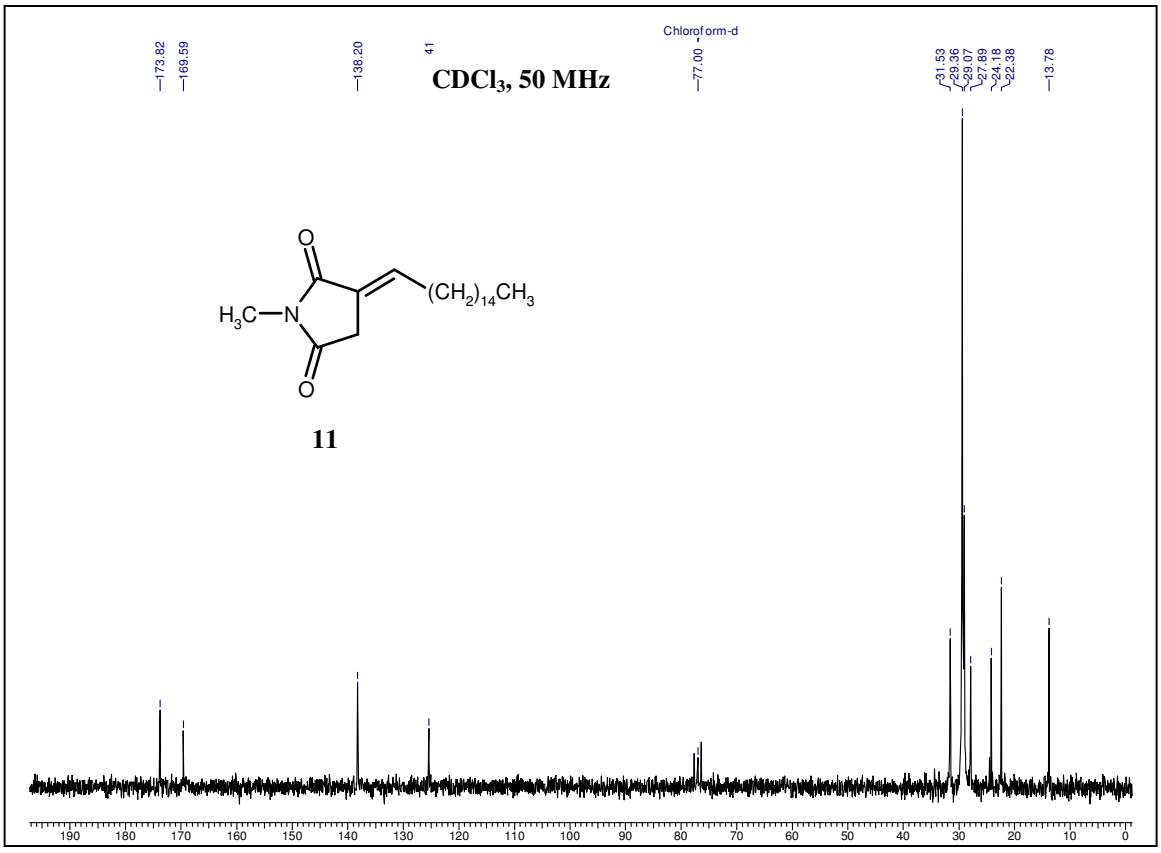
g, 0.36 mL, 0.36 mmol), DMAP (5 mg) and Et_3N (0.36 mL, 0.36 mmol) and the reaction mixture was stirred at room temperature for 10 h. The solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (8:2) to give **21** (thick oil): 48 mg (80% yield).

 **21** **$C_{24}H_{45}NO_7S$ (491)**	**IR** ($CHCl_3$) ν_{max} 1749, 1718, 1466, 1362, 1215 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.87 (t, J = 6 Hz, 3H), 1.20-1.45 (m, 26H), 1.90-2.10 (m, 2H), 2.22 (s, 3H), 2.91 (s, 3H), 3.21 (s, 3H), 3.55-3.75 (m, 2H), 4.72 (s, 1H), 4.98 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 14.1, 20.8, 22.7, 27.9, 29.3, 29.6-29.7 (10 carbons), 31.5, 31.9, 37.2, 41.2, 72.7, 87.2, 92.7, 168.3, 170.1. **Anal. Calcd** for $C_{24}H_{45}NO_7S$: C, 58.62; H, 9.22; N, 2.85; S, 6.52. Found: C, 58.74; H, 9.13; N, 2.90; S, 6.41.

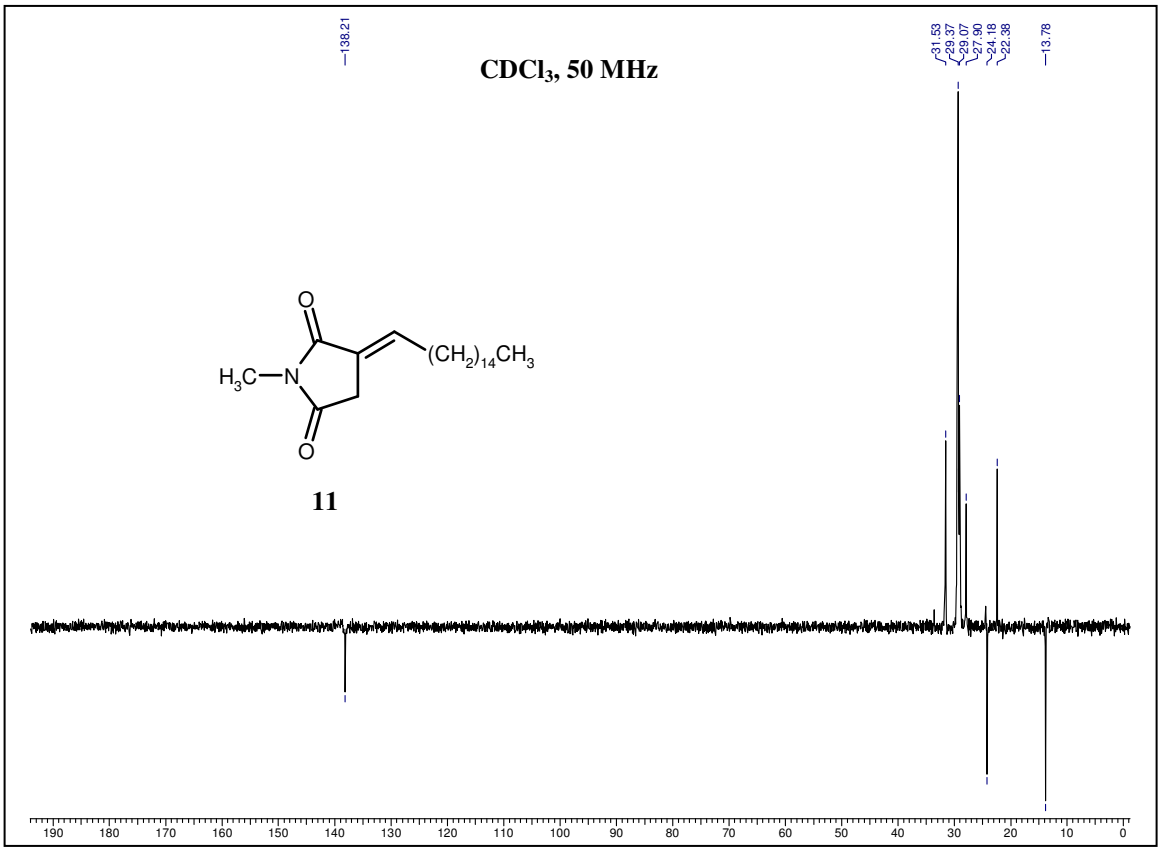
1C.5 Selected Spectra

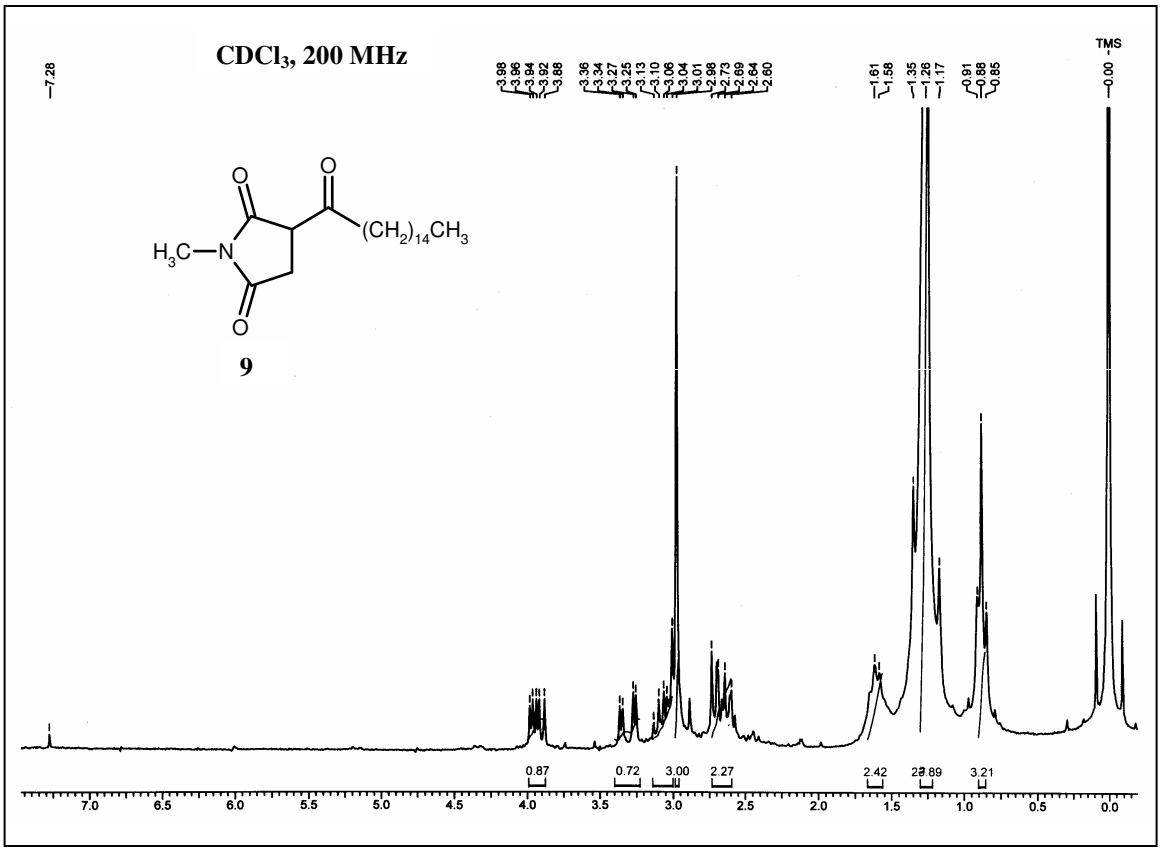

CDCl3, 200 MHz
7.27
6.84
6.79
6.75
3.19
3.03
2.22
2.18
2.15
2.11
1.47
1.44
1.24
0.89
0.86
0.82
O
H3C—N
O
(CH2)14CH3
0.76
3.00
1.62
2.03
24.42
3.18
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

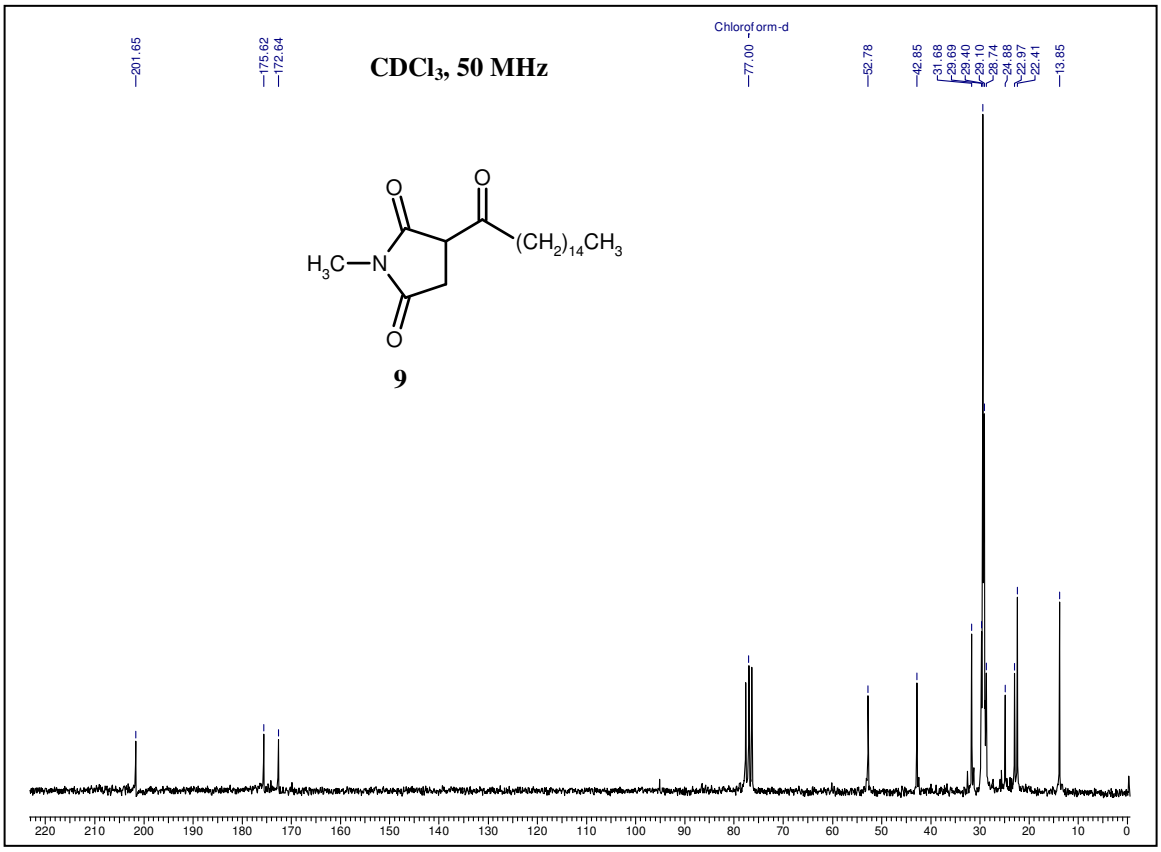
11

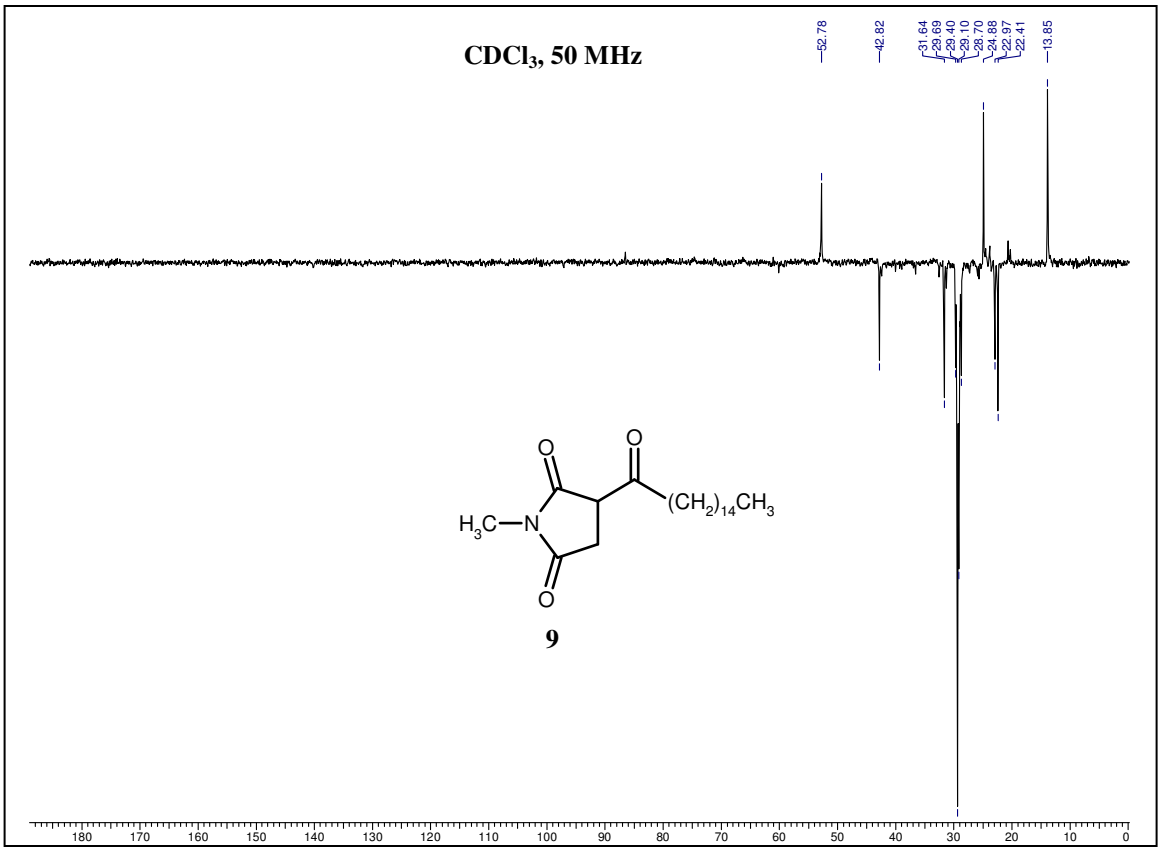

CDCl3, 50 MHz
Chloroform-d
173.82
169.59
138.20
41
77.00
31.53
29.36
29.07
27.89
24.18
22.38
13.78
O
H3C—N
O
(CH2)14CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

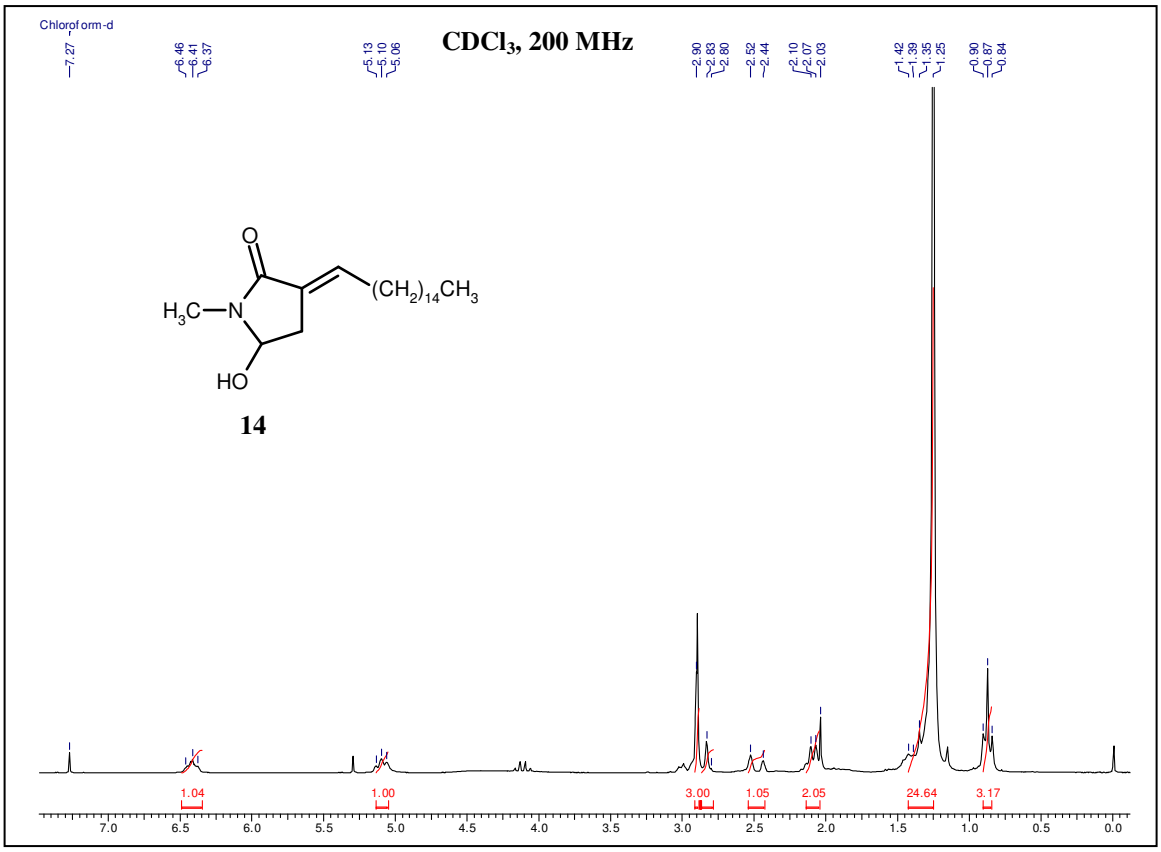
11

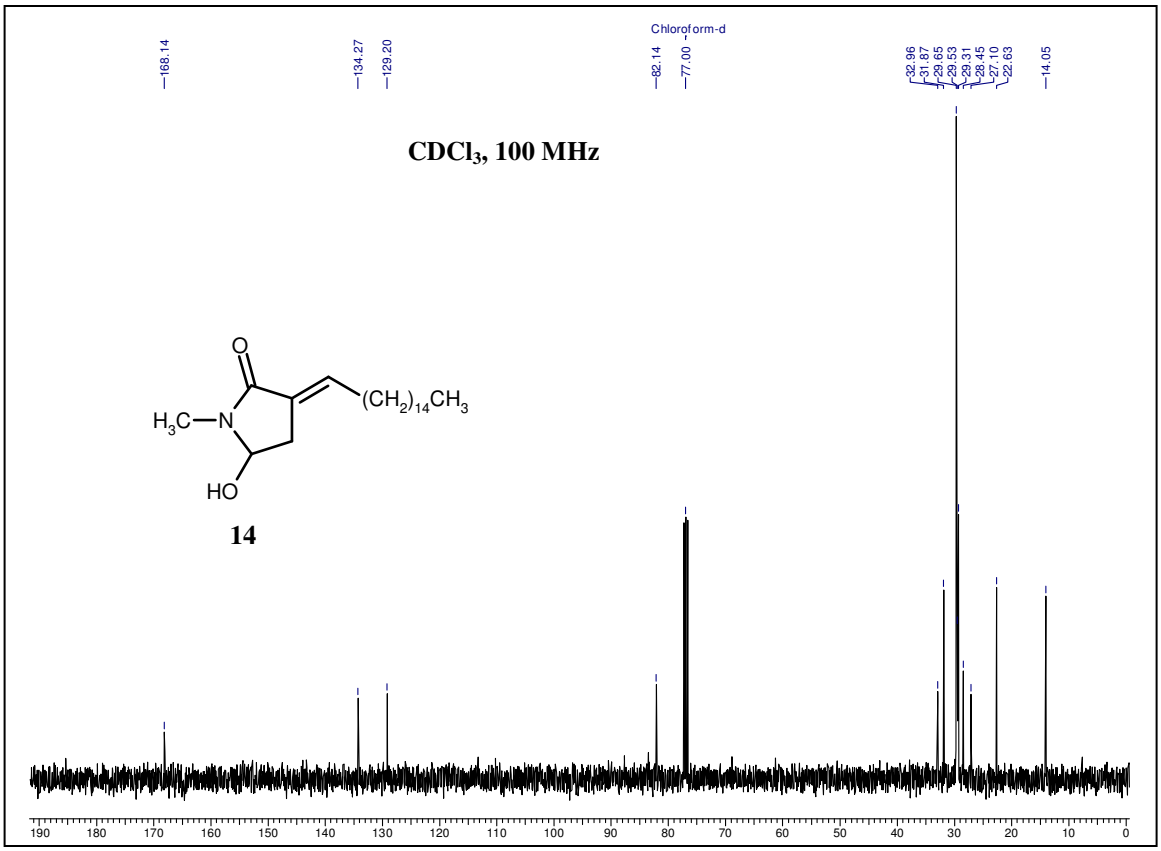

CDCl3, 50 MHz
138.21
31.53
29.37
29.07
27.90
24.18
22.38
13.78
H3C–N
(CH2)14CH3
11

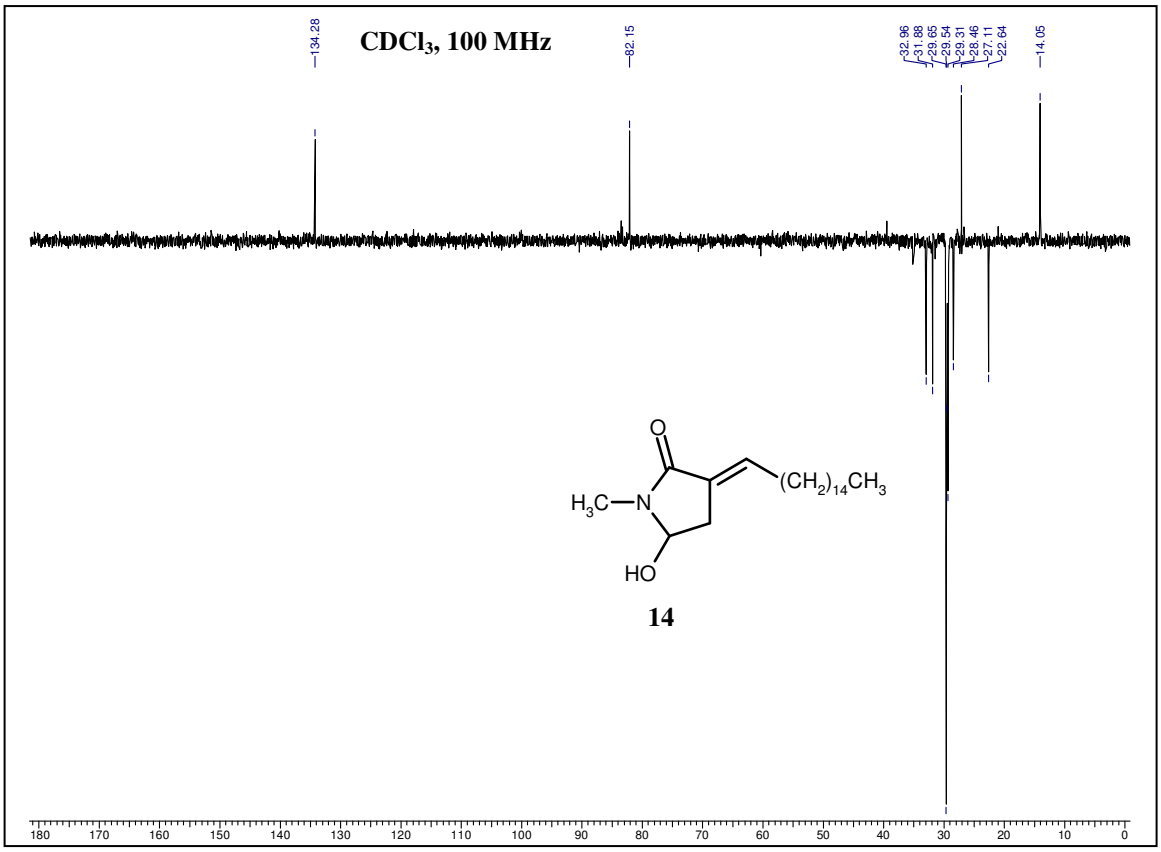

CDCl3, 200 MHz
7.28
3.98
3.96
3.94
3.92
3.88
3.36
3.34
3.27
3.25
3.13
3.10
3.06
3.04
3.01
2.98
2.73
2.69
2.64
2.60
1.61
1.58
1.35
1.26
1.17
0.91
0.88
0.85
TMS
0.00
H3C–N
(CH2)14CH3
9
0.87
0.72
3.00
2.27
2.42
3.89
3.21

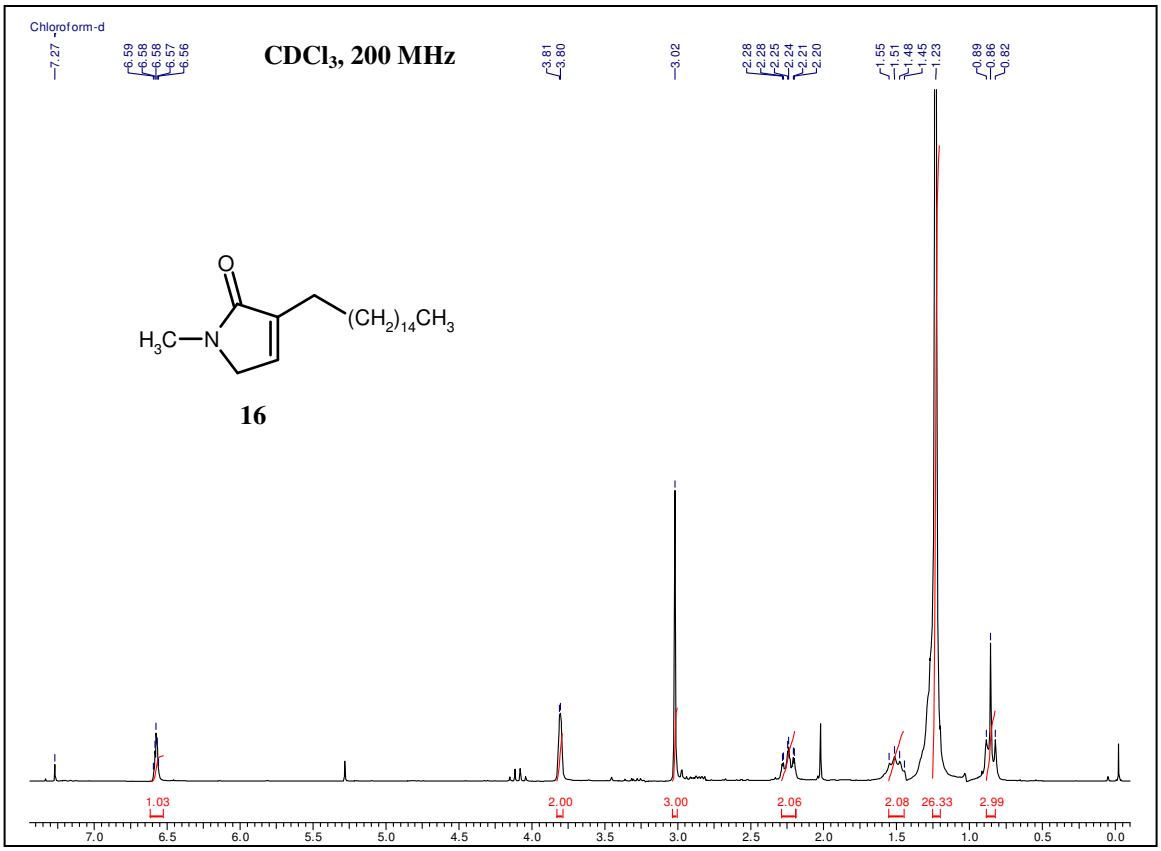

CDCl3, 50 MHz
Chloroform-d
201.65
175.62
172.64
77.00
52.78
42.85
31.68
29.69
29.40
29.10
28.74
24.88
22.97
22.41
13.85
O
O
H3C—N
(CH2)14CH3
O
9

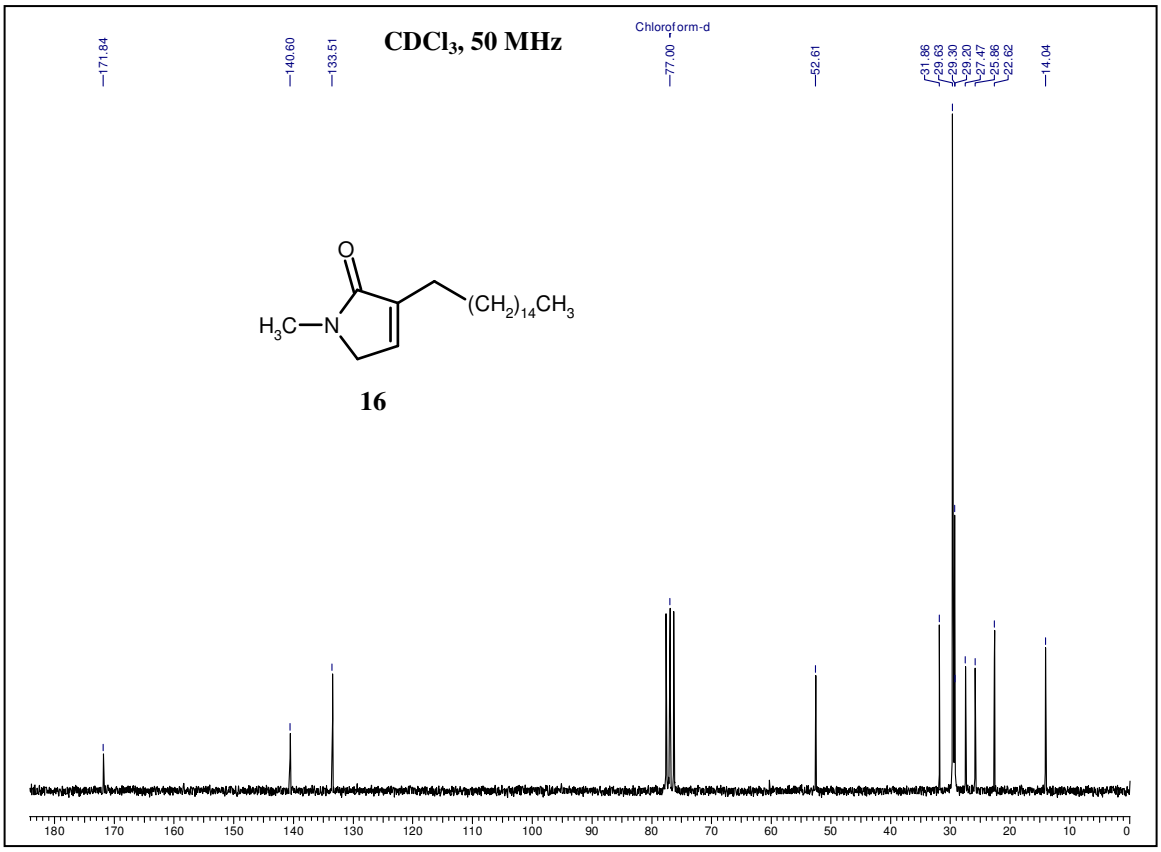

CDCl3, 50 MHz
52.78
42.82
31.64
29.69
29.40
29.10
28.70
24.88
22.97
22.41
13.85
O
O
H3C—N
(CH2)14CH3
O
9

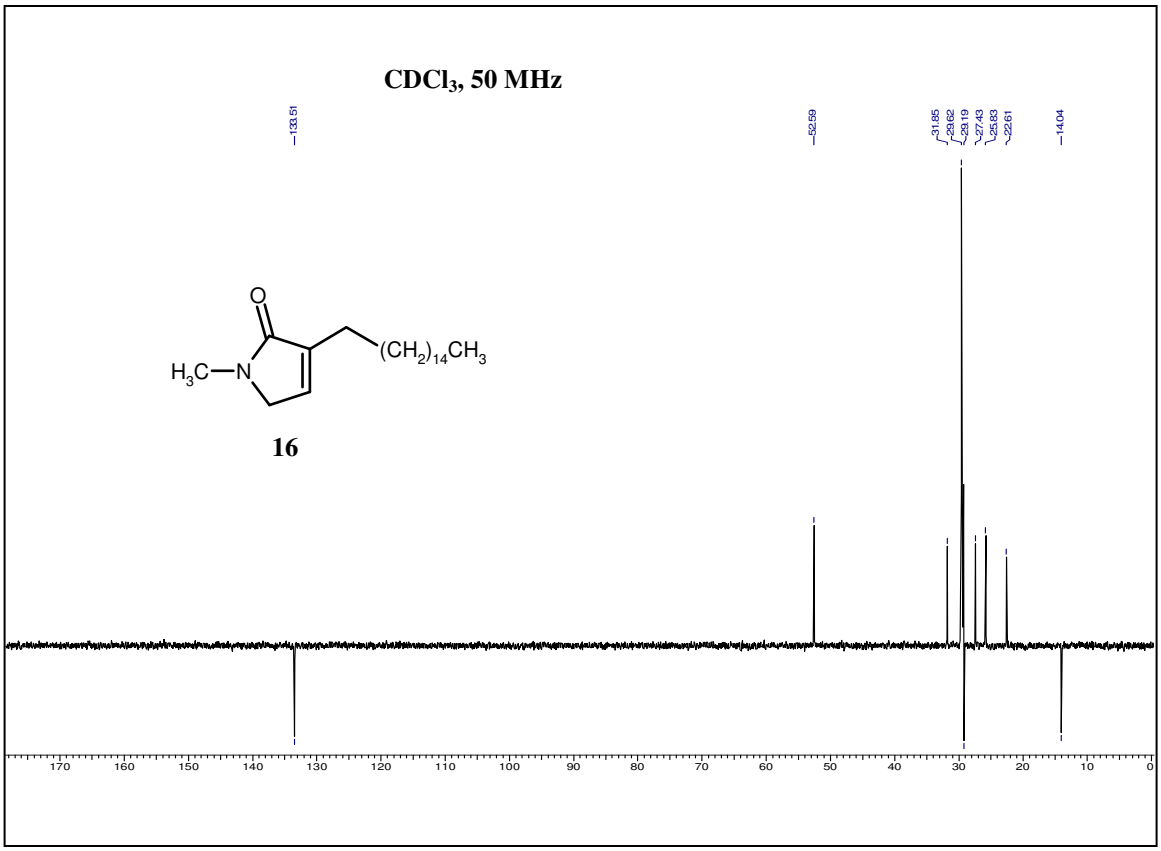

CDCl3, 200 MHz
Chloroform-d
7.27
6.46
6.41
6.37
5.13
5.10
5.06
2.90
2.83
2.80
2.52
2.44
2.10
2.07
2.03
1.42
1.39
1.35
1.25
0.90
0.87
0.84
O
H3C—N
HO
(CH2)14CH3
14
1.04
1.00
3.00
1.05
2.05
24.64
3.17
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

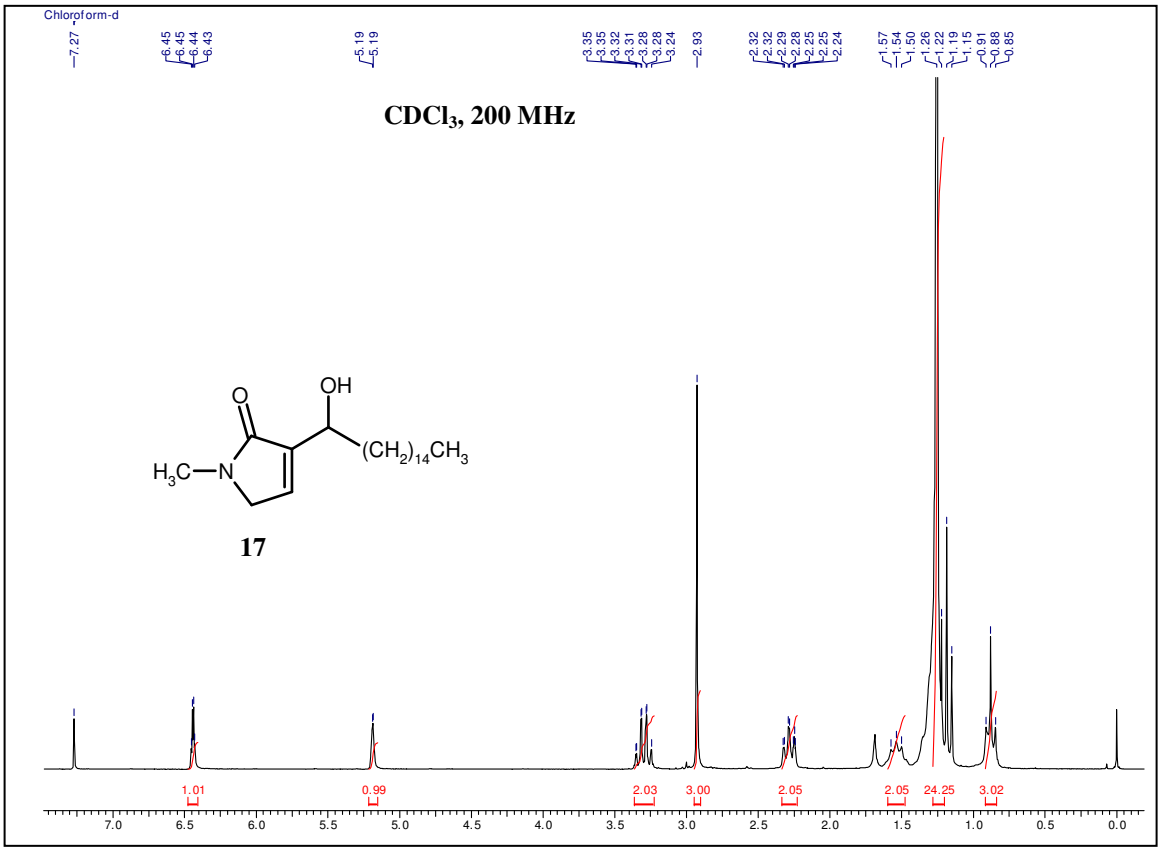

CDCl3, 100 MHz
Chloroform-d
168.14
134.27
129.20
82.14
77.00
32.96
31.87
29.65
29.53
29.31
28.45
27.10
22.63
14.05
O
H3C—N
HO
(CH2)14CH3
14
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

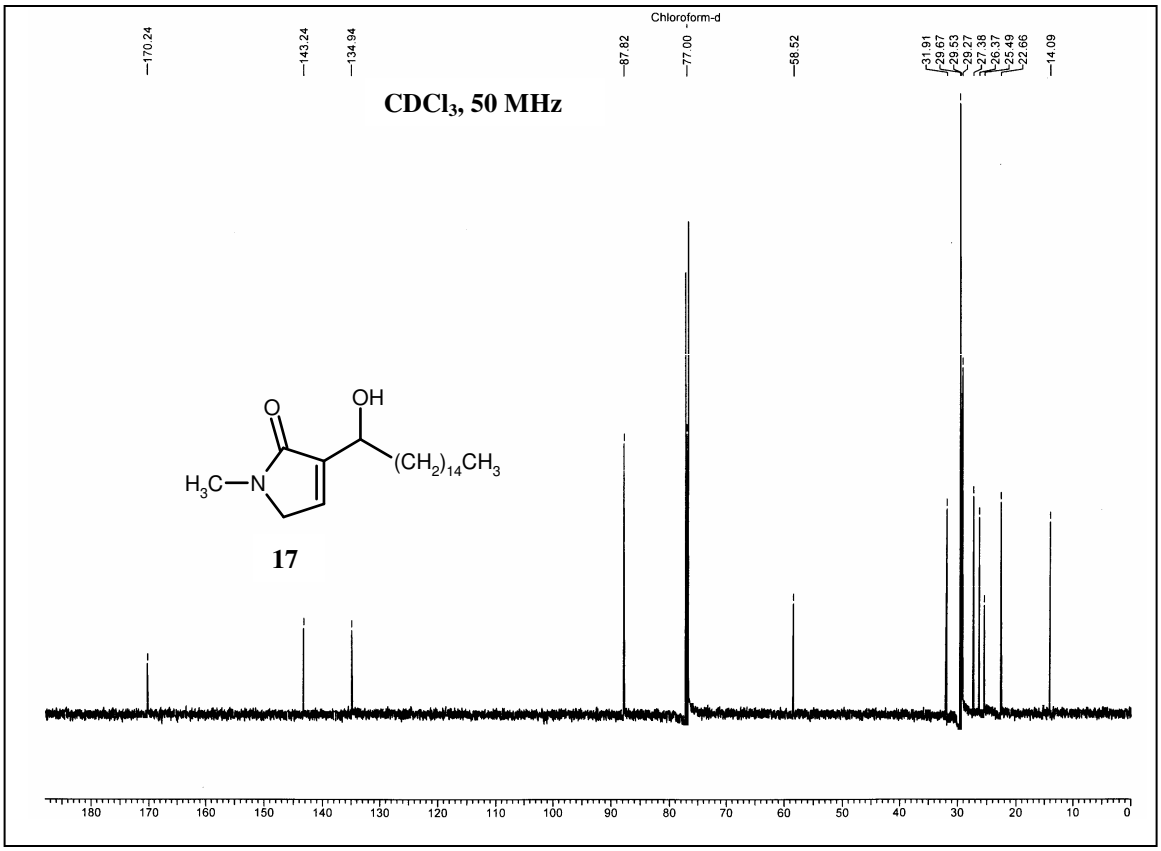

CDCl3, 100 MHz
134.28
82.15
32.96
31.88
29.65
29.54
29.31
28.46
27.11
22.64
14.05
O
H3C—N
HO
(CH2)14CH3
14

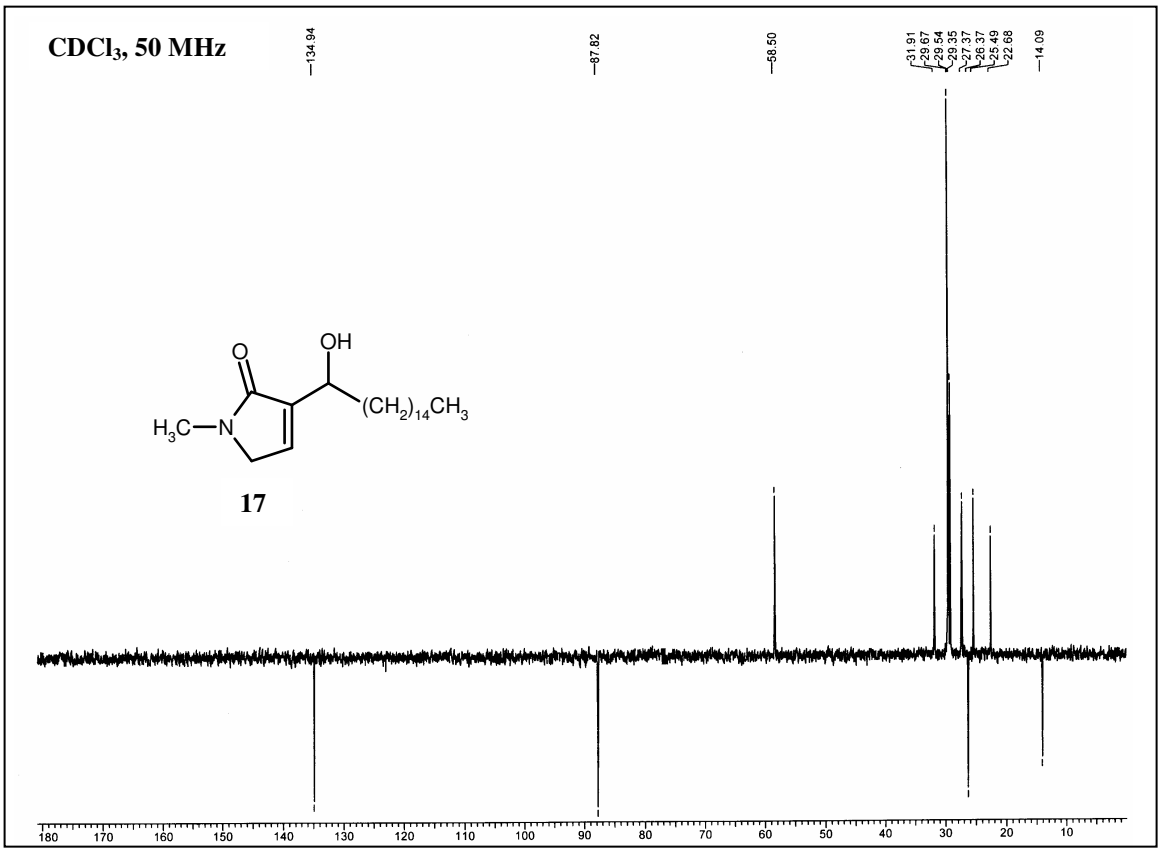

Chloroform-d
CDCl3, 200 MHz
7.27
6.59
6.58
6.58
6.57
6.56
3.81
3.80
3.02
2.28
2.28
2.25
2.24
2.21
2.20
1.55
1.51
1.48
1.45
1.23
0.89
0.86
0.82
O
H3C—N
(CH2)14CH3
16
1.03
2.00
3.00
2.06
2.08
26.33
2.99

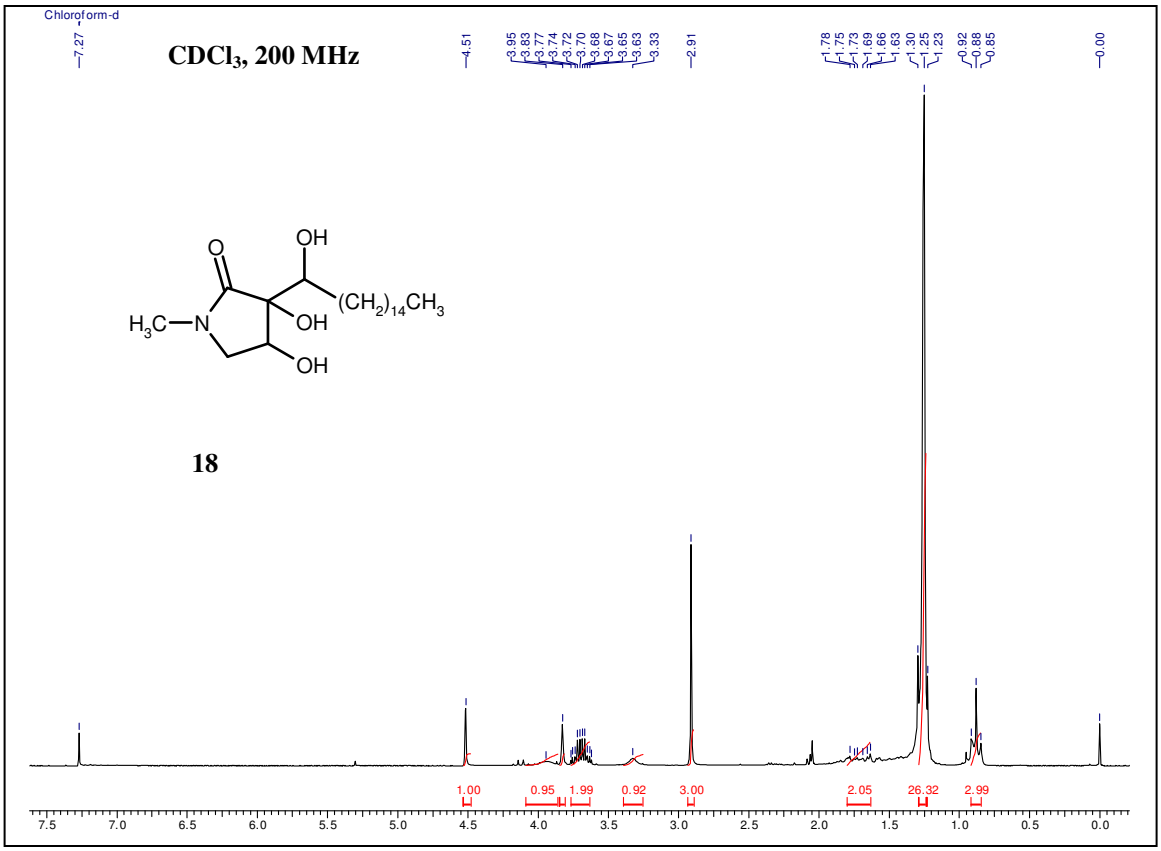

CDCl3, 50 MHz
Chloroform-d
171.84
140.60
133.51
77.00
52.61
31.86
29.63
29.30
29.20
27.47
25.86
22.62
14.04
O
H3C—N
(CH2)14CH3
16

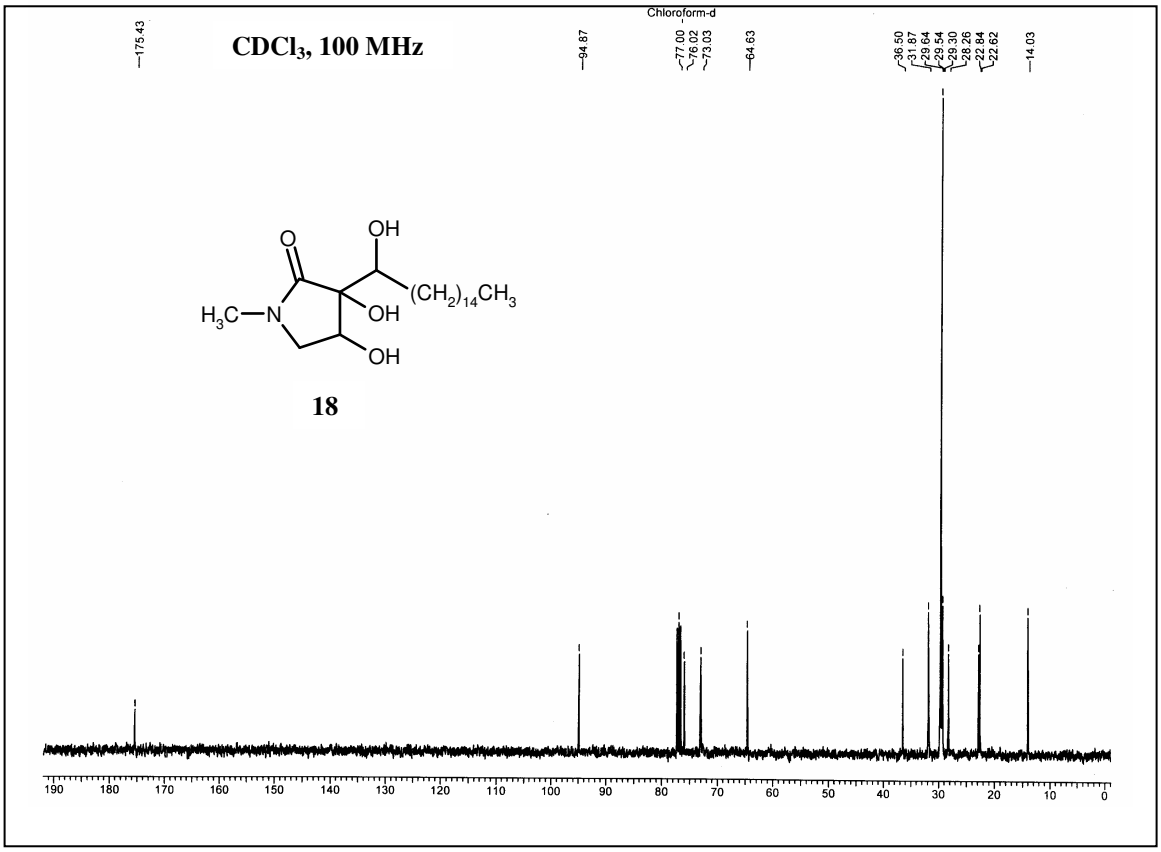

CDCl3, 50 MHz
133.51
52.59
31.85
29.62
29.19
27.43
25.83
22.61
14.04
O
H3C—N
(CH2)14CH3
16


Chloroform-d
7.27
6.45
6.45
6.44
6.43
5.19
5.19
3.35
3.35
3.32
3.31
3.28
3.28
3.24
2.93
2.32
2.32
2.29
2.28
2.25
2.25
2.24
1.57
1.54
1.50
1.26
1.22
1.19
1.15
0.91
0.88
0.85
CDCl3, 200 MHz
O
OH
H3C—N
(CH2)14CH3
17
1.01
0.99
2.03
3.00
2.05
2.05
24.25
3.02
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
170.24
143.24
134.94
87.82
77.00
58.52
31.91
29.67
29.53
29.27
27.38
26.37
25.49
22.66
14.09
CDCl3, 50 MHz
O
OH
H3C—N
(CH2)14CH3
17
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


CDCl3, 50 MHz
134.94
87.82
58.50
31.91
29.67
29.54
29.35
27.37
26.37
25.49
22.68
14.09
O
OH
H3C—N
(CH2)14CH3
17
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


Chloroform-d
7.27
CDCl3, 200 MHz
4.51
3.95
3.83
3.77
3.74
3.72
3.70
3.68
3.67
3.65
3.63
3.33
2.91
1.78
1.75
1.73
1.69
1.66
1.63
1.30
1.25
1.23
0.92
0.88
0.85
0.00
O
OH
H3C—N
(CH2)14CH3
OH
OH
18
1.00
0.95
1.99
0.92
3.00
2.05
26.32
2.99
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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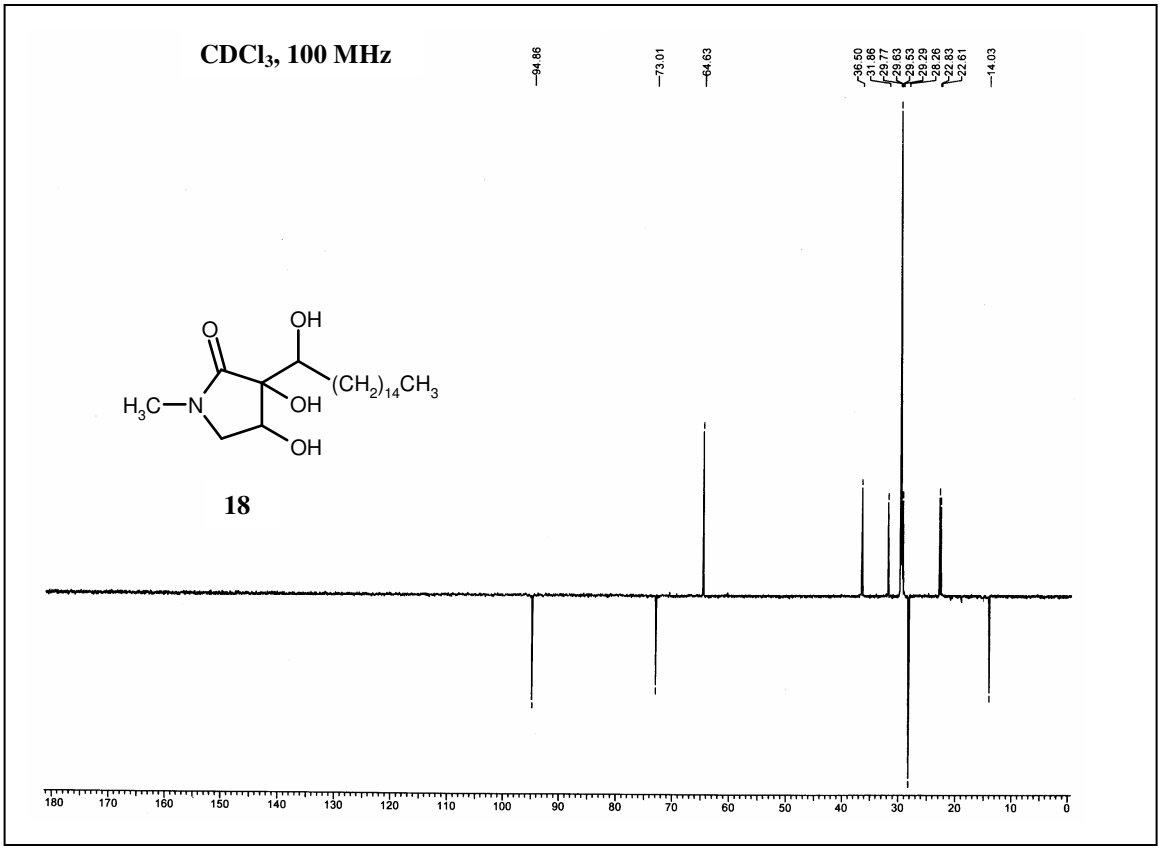
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H3C—N
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OH
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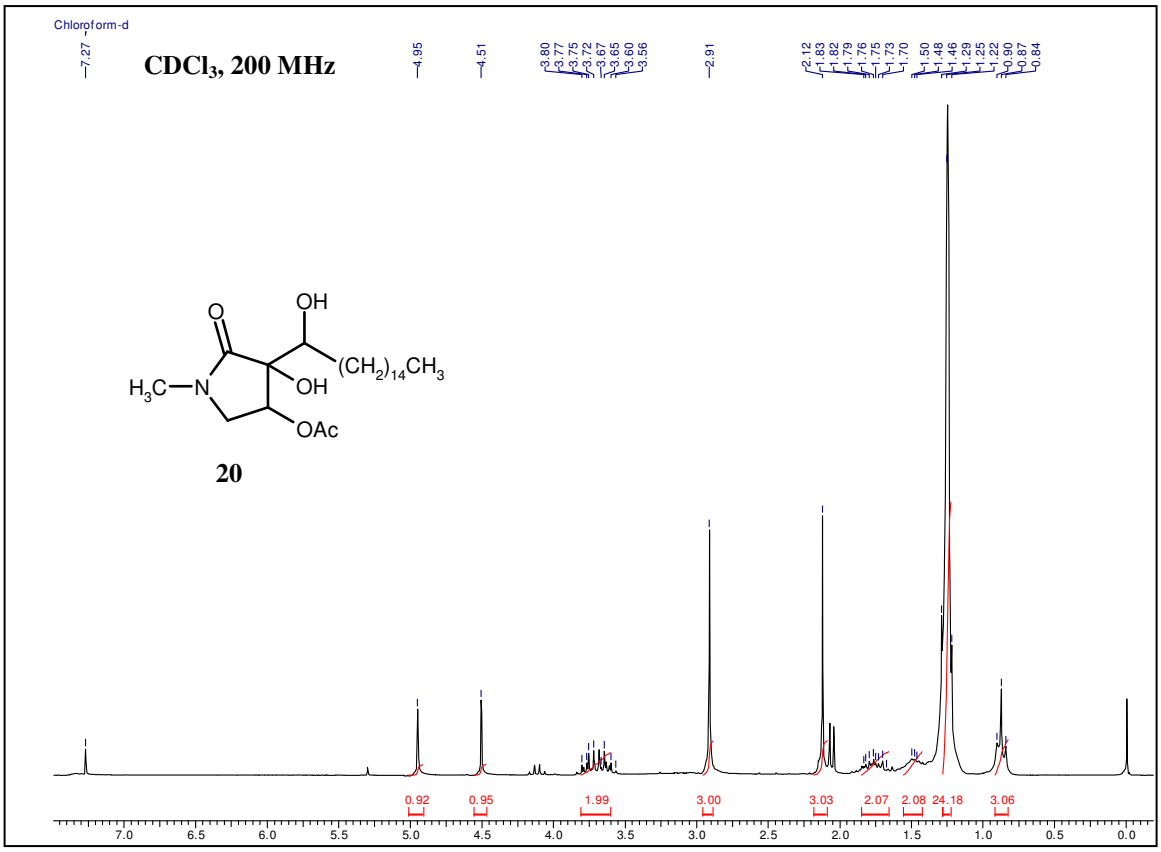
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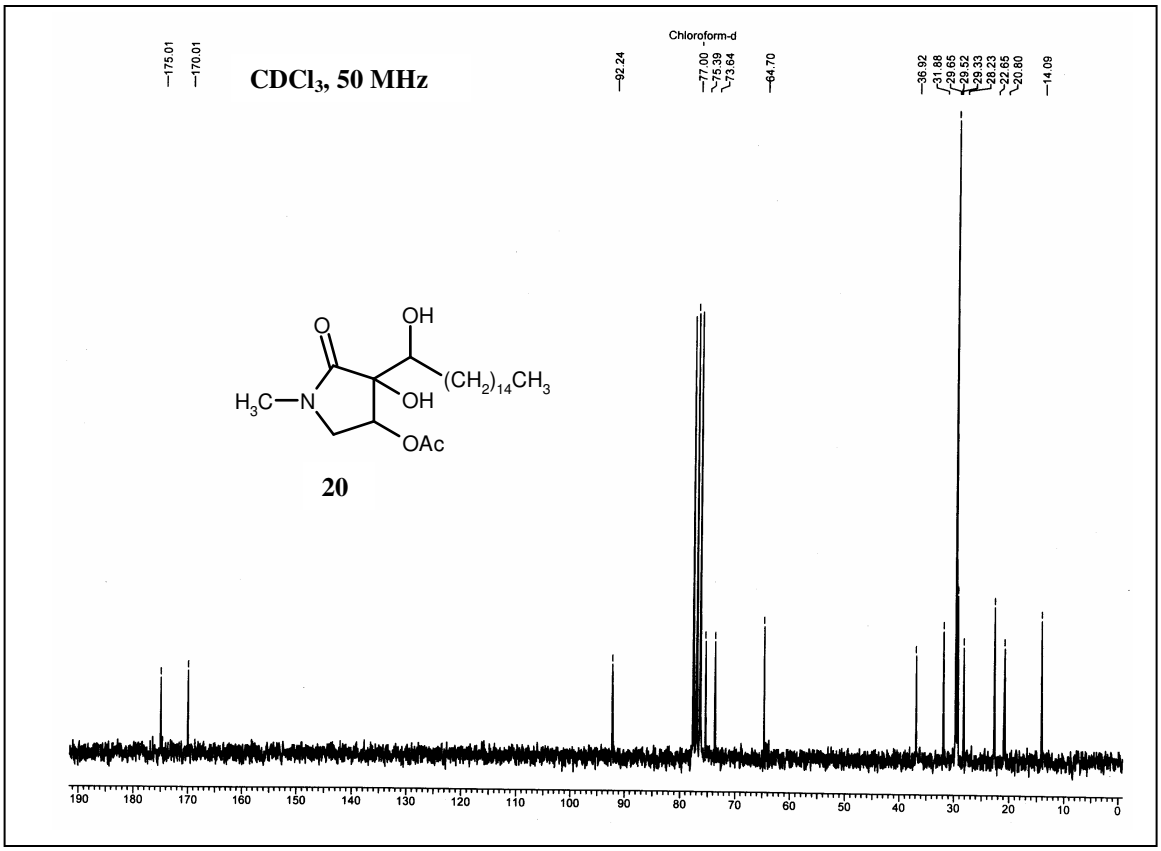
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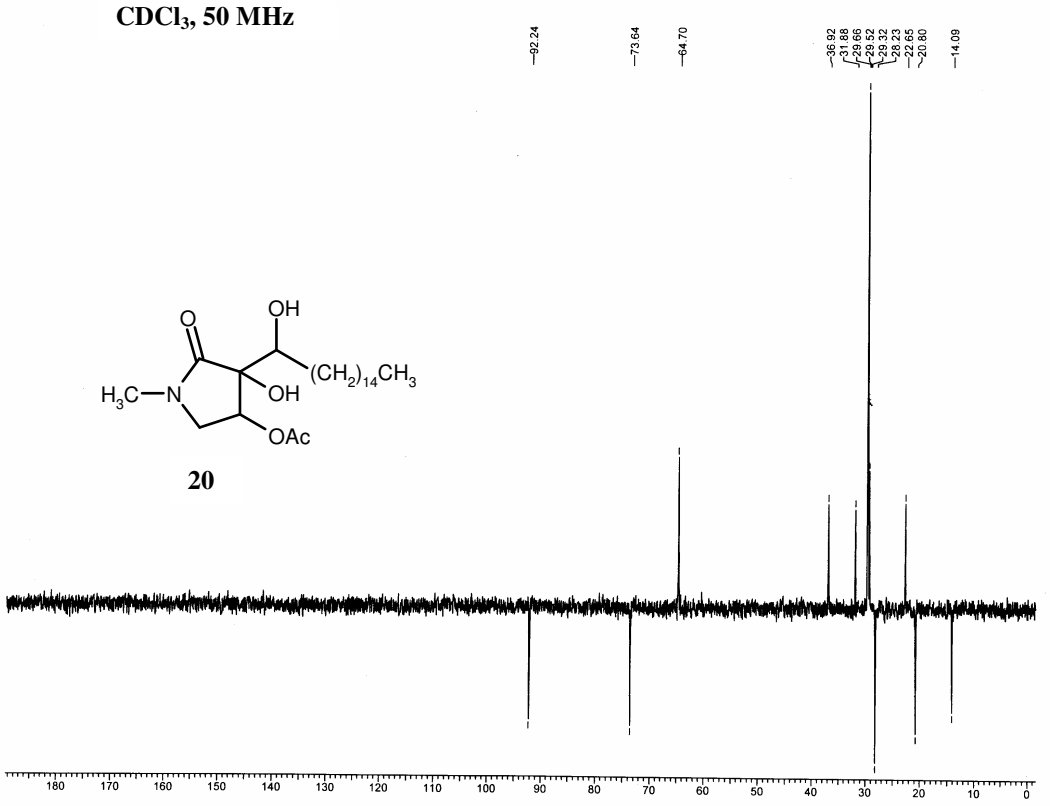

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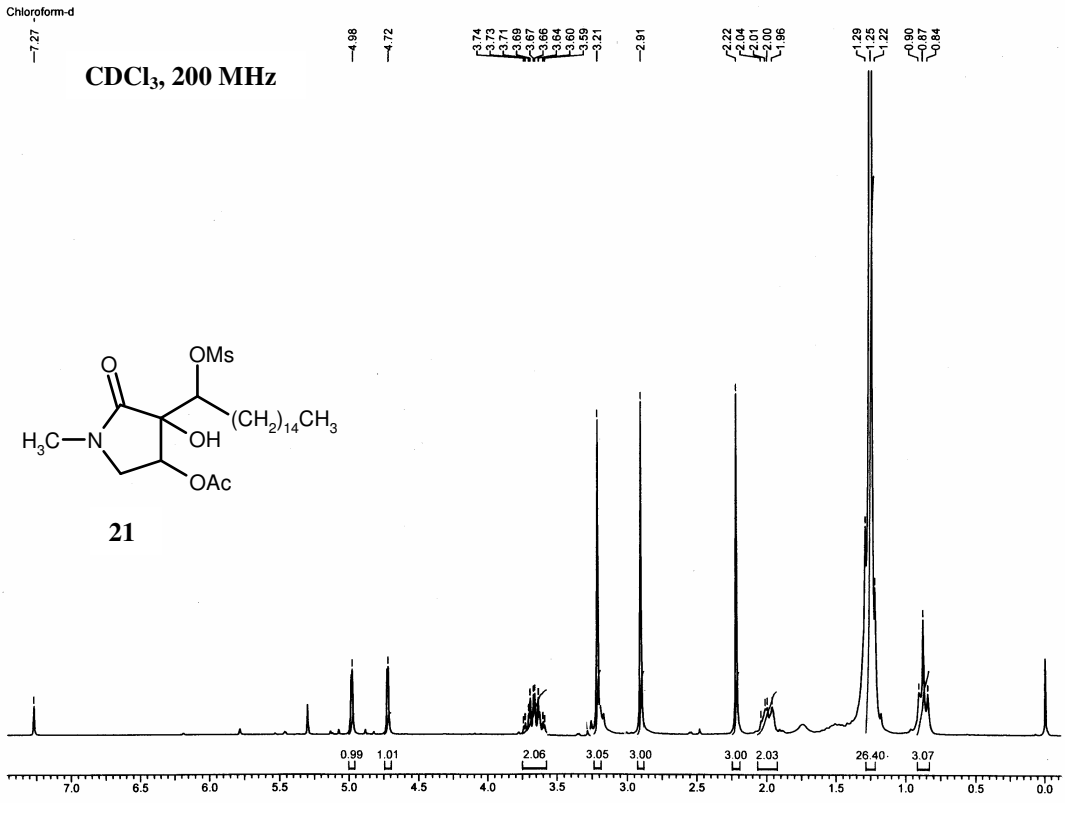

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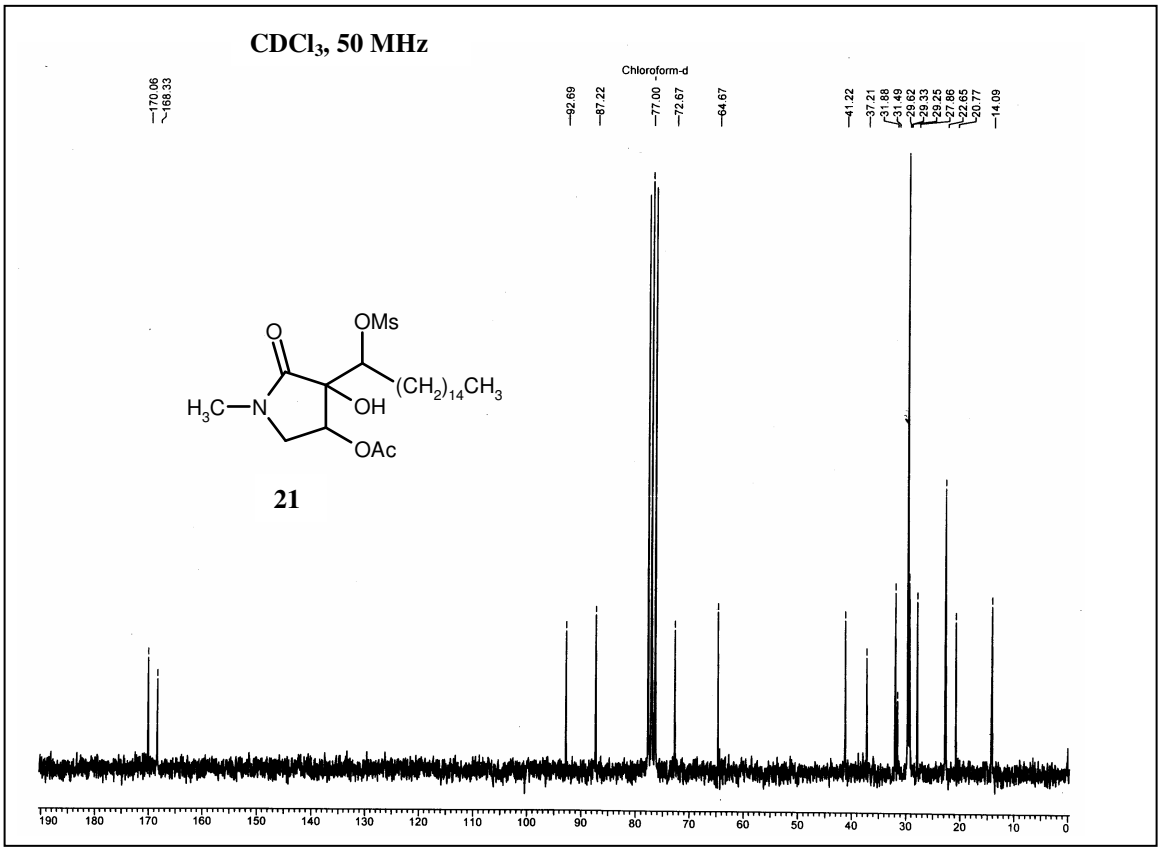
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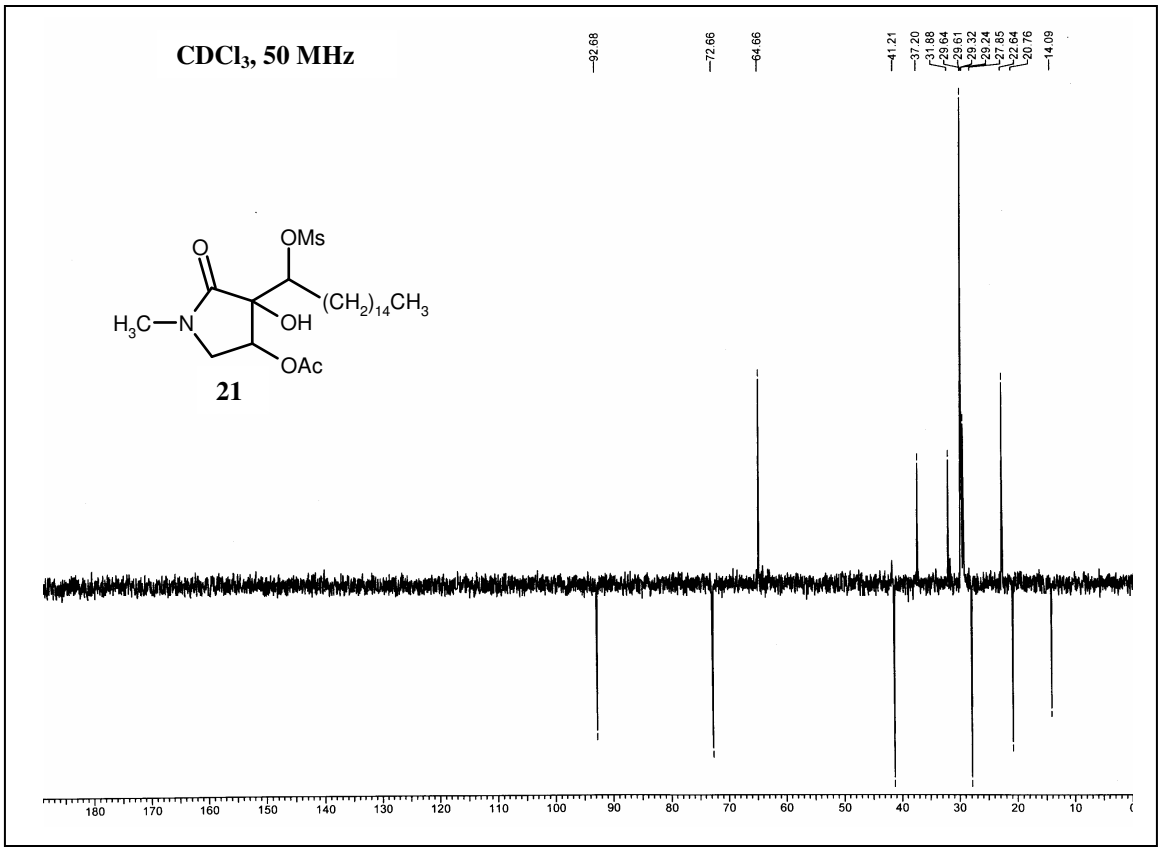
OAc
21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OMs
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H3C—N
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OAc
21

1C.6. References

(1) Duesberg, P. H. *Science* **1985**, *228*, 669.

(2) Aoki, S.; Higuchi, K.; Ye, Y.; Satari, R.; Kobayashi, M. *Tetrahedron* **2000**, *56*, 1833.

(3) Schobert, R.; Jagusch, C. *Tetrahedron* **2005**, *61*, 2301.

(4) Schobert, R.; Gordon, G. J. In Padwa, A., Ed.; Science of Synthesis; Houben-Weyl Methods of Molecular Transformations; Thieme: Stuttgart, **2004**; Vol. 27; p 1047.

(5) Desai, S. B.; Argade, N. P. *J. Org. Chem*. **1997**, *62*, 4862.

Chapter 2

A Concise Account on the Chemistry of Dialkyl Bromomethylfumarates and their Uses in the Synthesis of Natural and Unnatural Compounds

This chapter features the following sections:

1A	*Section A*	108
1B	*Section B*	142
1C	*Section C*	194

2A. Section A

A Concise Account on the Chemistry of Dialkyl Bromomethylfumarate

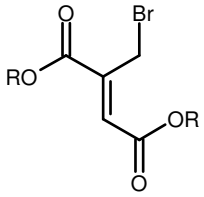
This section features the following topics:

2A.1	*Introduction*	108
2A.1.1	*Synthetic utility of dialkyl bromomethylfumarate*	108
2A.2	*Summary*	137
2A.3	*References*	138

2A. Section A: A Concise Account on the Chemistry of Dialkyl Bromomethylfumarate

2A. 1: Introduction

Diethyl bromomethylfumarate has been prepared by Campbel *et al*[1] in 1947 via bromination of the methyl group of diethyl methylfumarate by using *N*-bromosuccinimide and dibenzoyl peroxide. Laursen *et al*[2] have reported the synthesis of di-*t*-butyl bromomethylfumarate by bromination of di-*t*-butyl methylfumarate prepared by the action of NaO*t*-Bu on the acid chloride and then *N*-bromosuccinimide. Loh *et al*[3] have synthesized dimethyl bromomethylfumarate by the Baylis–Hillman reaction involving the



Dialkyl bromomethylfumarate

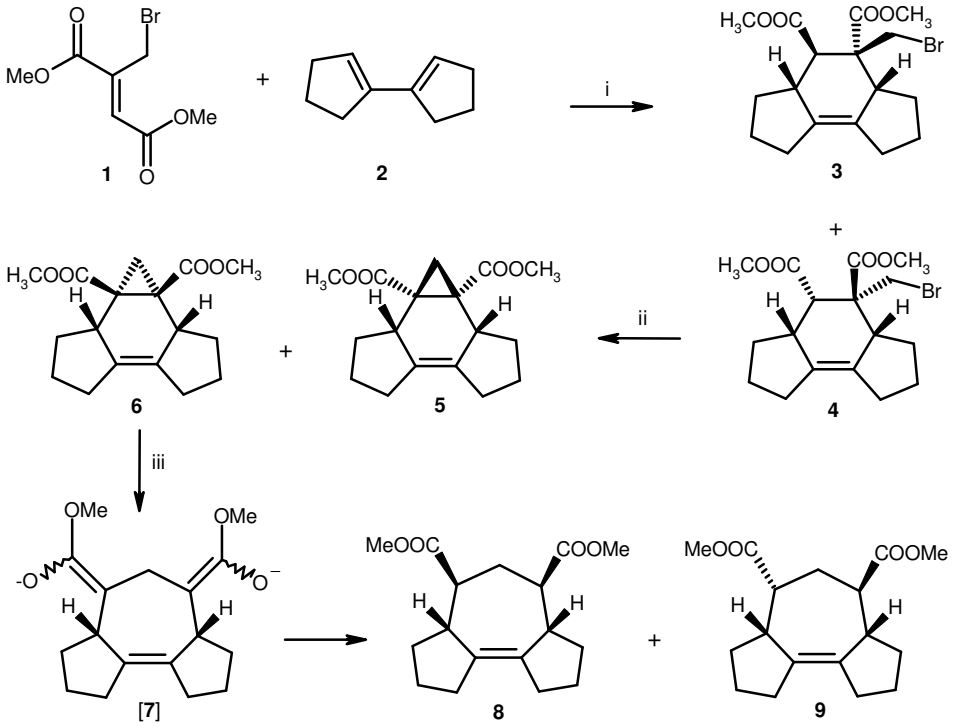
coupling of methyl glyoxylate with methyl acrylate in dioxane and subsequent bromination with PBr_3 in ether. Abarhat *et al*[4] have synthesized labeled di-*t*-butyl bromomethylfumarate and bromo methylfumaric acid by the reaction of di-*t*-butyl acetylenedicarboxylate with $Li(^{13}CH_3)_2Cu$ followed by isomarization and bromination. Amri and co-workers[5] have synthesized dimethyl bromomethylfumarate by the bromination of dimethyl itaconate and dehydrobromination with triethylamine.

2A.1.1: *Synthetic utility of dialkyl bromomethylfumarate*

The introduction of bromo atom at the allylic position to form **1**, opens to more sites for nucleophilic reactions viz, allylic substitutions and S_N2' coupling reactions. Dialkyl bromomethylfumarate has been used for the synthesis of natural and unnatural products. This section provides application of dialkyl bromomethylfumarate for the synthesis of natural and unnatural products, however we have tried our best to summarize and present the information here, but no pretension of completeness is claimed.

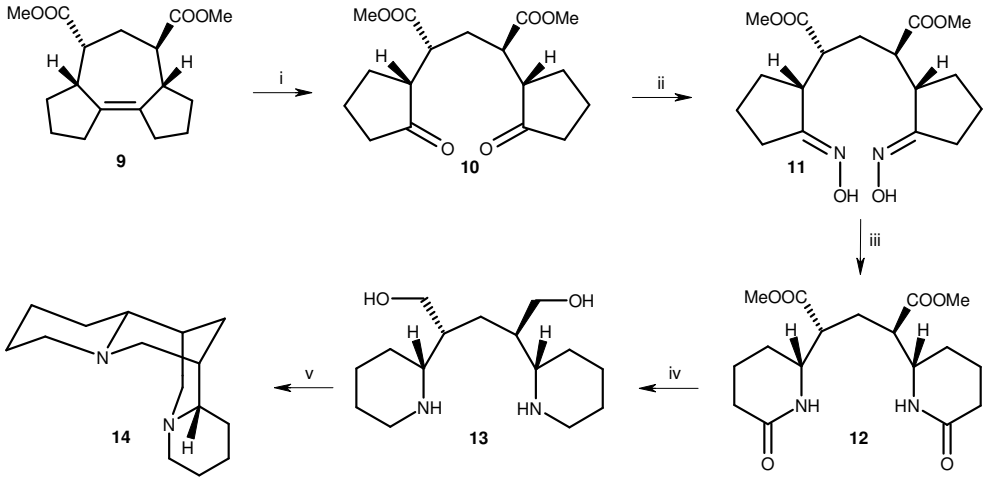
2A.1.1.1: *Synthesis of (±)-sparteine (Fleming and co-workers)*

(-)-Sparteine **14**, has been used to induce absolute stereocontrol in a number of lithiations,[6a,b] but is readily available only in one enantiomeric series. Fleming and co-workers[7a,b] have reported the recemic synthesis of sparteine by using Diels–Alder reaction between dimethyl bromomethylfumarate and dicyclopentenyl **2**. Diels–Alder cycloaddition between dimethyl bromomethylfumarate (**1**) and the diene **2** gave the mixture of adducts **3** and **4** which on reaction with sodium methoxide gave the *meso* cyclopropane intermediates **5** and **6**. Lithium in liquid ammonia induced reductive cleavage of mixture of **5** and **6** gave the bisenolate **7** which on quenching with ammonium chloride gave the mixture of esters **8** and **9** (**8**:**9** = 30:70) while quenching with methanol gave (**8**:**9** = 24:76), which are separated by crystallization and chromatography of the mother liquor (Scheme 1).



Scheme 1. *Reagents, conditions and yields*: (i) Me_2AlCl, CH_2Cl_2, -78 °C to rt, 12 h (95% yield, **3**:**4** = 75:25); (ii) NaOMe, toluene, reflux 12 h (90%, **5**:**6** = 75:25); (iii) Li, NH_3, isoprene, NH_4Cl (90% yield, **8**:**9** = 30:70) and MeOH (90% yield, **8**:**9** = 24:76).

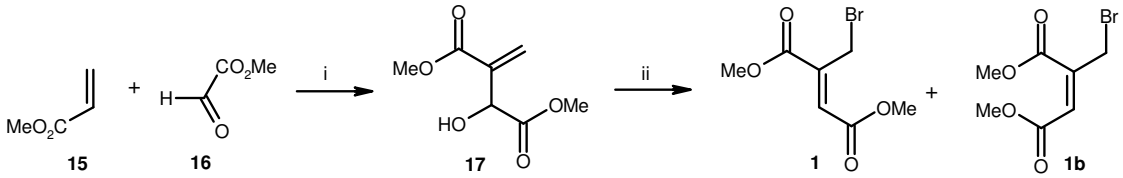
The ester **9** on ozonolysis in acetone and quenching with acetaldehyde furnished the diketone **10** which on reaction with hydroxylamine hydrochloride gave bis-oxime **11**. Beckmann rearrangement of bisoxime **11** gave the bis-lactam **12** which on reduction gave bis-piperidine diol **13**. (±)-Sparteine **14** was obtained by treating **13** with carbon tetrachloride and triphenylphosphine (Scheme 2).



Scheme 2. *Reagents, conditions and yields*: (i) O_3, acetone, -78 °C to rt, MeCHO, PPh_3, rt, 12 h (98%); (ii) $NH_2OH.HCl$, pyridine, EtOH, 0 °C, 2 d (53%); (iii) (a) $MeSO_2Cl$, Et_3N, CH_2Cl_2, -20 °C, 0.5 h, (b) THF, H_2O, 60 °C, 24 h (52%); (iv) $LiAlH_4$, THF, reflux, 12 h (90%); (v) PPh_3, CCl_4, Et_3N, MeCN, rt, 18 h (53%).

2A.1.1.2: *Synthesis of (±)-methylenolactocin (Loh et al)*

α-Methylene-*β*-butyrolactone is an integral building block of many bioactive natural products.[8] Among them, methylenolactocin **28** has attracted the major attention because of its interesting anti-tumour activity and its unusual structure with high functionality and stereochemistry.[9] (±)-Methylenolactocin **28** and (±)-phaseolinic acid **29**, have been isolated from the fungus *Macrophomina phaseolina*.[10] Loh *et al*[11] have reported the synthesis of (±)-methylenolactocin by using an indium-mediated allylation reaction as the key step. Baylis–Hillman reaction involving the coupling of methyl glyoxylate (**16**) with methyl acrylate (**15**) in dioxane gave alcohol **17** in 52% yield. Subsequent bromination of **17** with PBr_3 in ether proceeded smoothly to afford both dimethyl bromometylfumarate (**1**) and dimethyl bromomethylmaleate (**1b**) in 90% overall yield (Scheme 3).



Scheme 3. *Reagents, conditions and yields*: (i) DABCO, dioxane, rt, 72 h (52%); (ii) PBr_3, ether, 0 °C, 0.5 h (90%, *Z*-**1**: *E*-**1b** = 95:5).

Indium-mediated allylation reaction of dimethyl bromomethylfumarate (**1**) with hexanal has been investigated. The results are shown in Table 1.

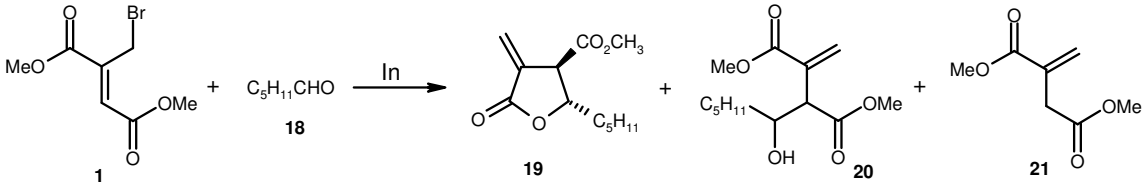


Table 1. Optimization of allylation reaction of dimethyl bromomethylfumarate (**1**) with hexanal

Entry	Conditions[a]	% Yields (**19** + **20**)[b] (**19**:**20**:**21**)[c]
1	H_2O	**21** (major)
2	THF: H_2O (1:1)	8 (20:20:60)
3	THF: H_2O: buffer pH 7.0 (1:1:2)	60 (36:36:28)
4	Dry THF	60 (40:40:20)
5	Neat	85 (40:45:15)

[a] All reactions were performed at room temperature for 3 days.
[b] Overall purified yield for **19** and **20**.
[c] Product ratios (**19**:**20**:**21**) were determined based on ^{1}H NMR analysis.

With these optimized conditions, the reactions of dimethyl bromomethylfumarate (**1**) with four other different aldehydes were investigated. The results are shown in Table 2.

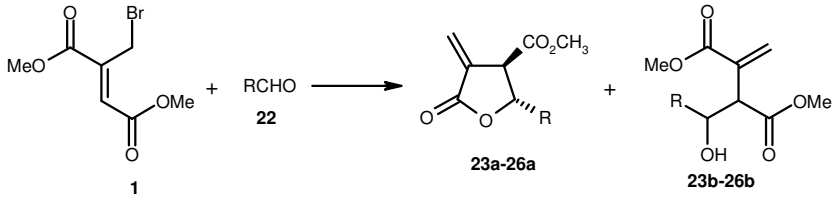


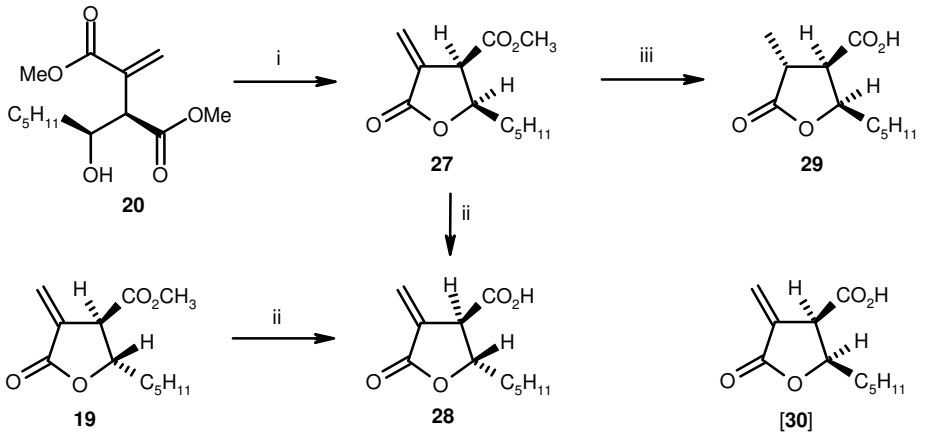
Table 2. Allylation reaction with four different aldehydes

Entry	Aldehyde[a]	Ratio (a:b)[b]	Total yield (a + b%)[c]
1	Nonyl aldehyde	(**23a**:**23b**) (53:47)	34[d]
2	Cyclohexanecarboxyaldehyde	(**24a**:**24b**) (64:36)	95
3	Benzaldehyde	(**25a**:**25b**) (35:65)	77
4	3-Methoxybenzaldehyde	(**26a**:**26b**) (15:85)	60

[a] All reactions were performed under neat conditions at room temperature for 3 days.
[b] Product ratios (**a**:**b**) were determined based on isolated yields.
[c] Overall purified yield for **a** and **b**.
[d] Reaction not optimized.

Both the isomers, **19** and **20**, have been separated by them through flash column chromatography and converted to (±)-methylenolactocin **28**. In the presence of TFA, **20** was cyclized to the *cis*-β,γ-substituted lactone **27** in 79% yield. Acid hydrolysis of **27** and

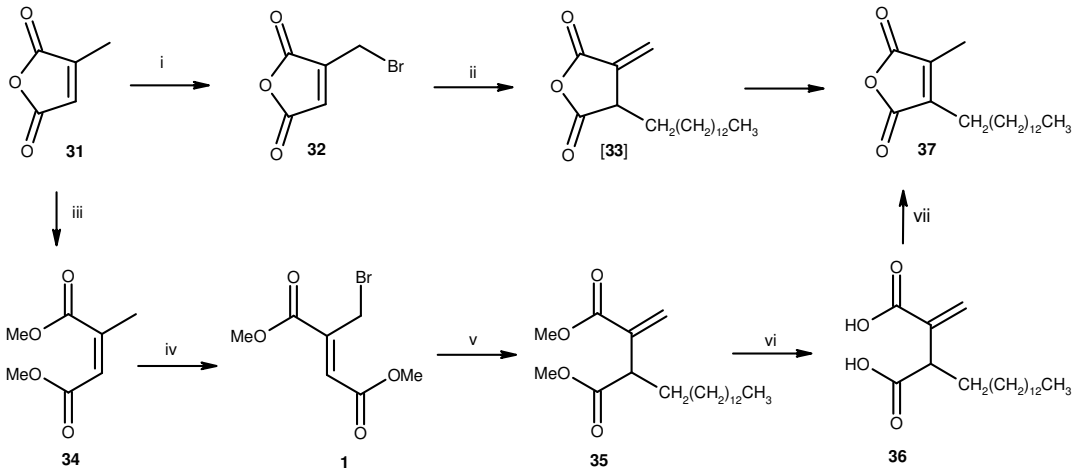
19 with 6 N HCl afforded **28** in 70% yield, **27** undergoes epimerization via the intermediate acid **30** to give **28** (Scheme 4). Compound **27** can lead to a formal synthesis of (±)-phaseolinic acid (**29**) via a stereoselective hydrogenation using thiophenol, followed by the removal of the sulfide group with Na–Hg.[12]



Scheme 4. *Reagents, conditions and yields*: (i) TFA, CH_2Cl_2, rt, 24 h (79%); (ii) 6 N HCL, butanone reflux, 2 h (70%); (iii) (a) PhSH, Et_3N, THF, rt (88%), (b) Na-Hg, NaH_2PO_4, MeOH, -20 °C (75%) (ref 12).

2A.1.1.3: *Synthesis of chaetomellic acid A*

Chaetomellic acid A has been isolated from *Chaetomella acutiseta*[13] and its dianionic form is a potent and highly specific inhibitor of rasfernesyl-protein transferase. Chaetomellic acid A (**37**) has been synthesized in our group[14] via S_N2' Grignard coupling reaction of

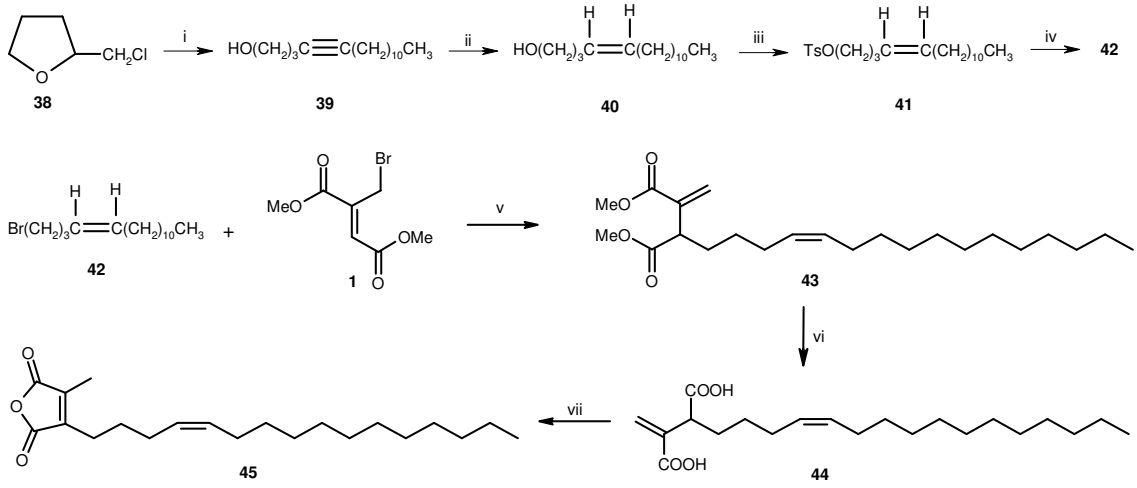


Scheme 5. *Reagents, conditions and yields*: (i) NBS, DBP, CCl_4, reflux, 8 h (55%); (ii) $C_{14}H_{29}MgBr$, Et_2O, rt, 8 h (8-10%); (iii) CH_3OH, H^+/H_2SO_4, reflux, 12 h (75%); (iv) NBS, AIBN, CCl_4, reflux, 12 h (85%); (v) $C_{14}H_{29}MgBr$, Et_2O, HMPA, rt, 8 h (60%); (vi) AcOH + HCl (7:3), reflux, 2 h (98%); (vii) Ac_2O, reflux, 2 h (~100%).

tetradecylmagnesium bromide with dimethyl bromomethylfumarate (**1**) followed by hydrolysis of the diester **35** to diacid **36** accompanied by ring closure and simultaneous exocyclic to endocyclic carbon-carbon double bond isomerization with 58% overall yield in 3-steps (Scheme 5).

2A.1.1.4: *Synthesis of 1,7(Z)-nonadecadiene-2,3-dicarboxylic acid*

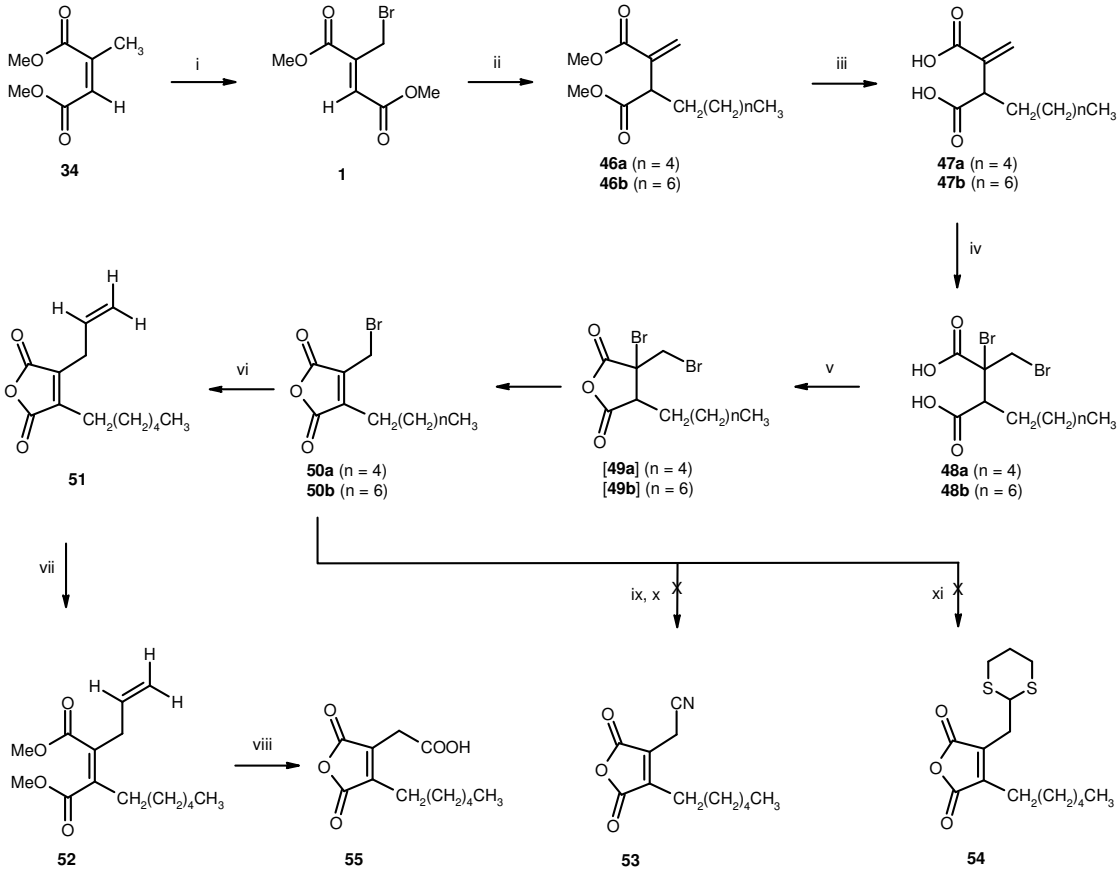
This novel dicarboxylic acid **44** was isolated from cultures of a white-rot fungus *Ceriporiopsis subvermispora*.[15] The compound has one chiral centre but the absolute configuration has not yet been established. 1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic acid has been synthesized in our group[14] by using the chemoselective S_N2' Grignard coupling reaction of dimethyl bromomethylfumarate (**1**) with (*Z*)-hexadeca-4-enyl bromide (**42**) which was prepared from tetrahydrofurfuryl chloride (**38**). Tetrahydrofurfuryl chloride (**38**) on reaction with $C_{11}H_{23}Br$ in presence of $LiNH_2/NH_3$ give alcohol **39** which on hydrogenation followed by tosylation gave compound **41**, which on reaction with LiBr gave (*Z*)-hexadeca-4-enyl bromide (**42**). The Grignard coupling of **42** with **1** followed by hydrolysis of the diester **43** gave the natural product 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**44**). The diacid **44** in refluxing acetic anhydride furnished the isochaetomellic acid B (**45**) (Scheme 6).



Scheme 6. *Reagents, conditions and yields*: (i) $LiNH_2/NH_3$, $C_{11}H_{23}Br$, – 78 °C to – 33 °C to rt, 4 h (80%); (ii) H_2, Lindlar Pd, quinoline, hexane, rt, 30 min (99%); (iii) *p*-TsCl, TEA, DMAP, CH_2Cl_2, rt, 6 h (86%); (iv) LiBr, $NaHCO_3$, acetone, rt, 15 h (85%); (v) $CH_3(CH_2)_{10}CH{=}CH(CH_2)_3MgBr$, Et_2O, HMPA, rt, 8 h (62%); (vi) LiOH, THF + H_2O (2:1), rt, 18 h (98%); (vii) Ac_2O, reflux, 2 h (~100%).

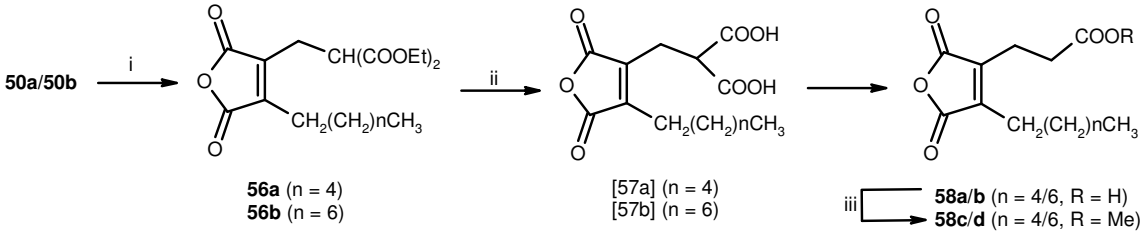
2A.1.1.5: *Synthesis of natural and unnatural disubstituted maleic anhydrides*

During the past decade several structurally interesting compounds with dialkylsubstituted maleic anhydride moieties have been isolated as bioactive natural products and synthesized in view of their promising bioactivities.[16-18] The 2-carboxymethyl-3-hexylmaleic anhydride (**55**) has been isolated as a novel metabolite from the *Aspergillus* FH-X-213 from an apple.[19] In 1994, Soda *et al*[20] reported the biotransformation of stearic acid with a microbial strain isolated from soil, *Pseudomonas cepacica* A-1419, to produce two new maleic anhydride derivatives 2-(*β*-carboxyethyl)-3-hexylmaleic anhydride (**58a**) and 2-(*β*-carboxyethyl) -3-octylmaleic anhydride (**58b**).



Scheme 7. *Reagents, conditions and yields:* (i) NBS (1.5 equiv.), AIBN, CCl_4, reflux, 12 h (85%); (ii) $CH_3(CH_2)_nCH_2MgBr$ (1.5 equiv., n = 4/6), Et_2O, HMPA, – 20 ºC, 0.5 h (64-65%); (iii) LiOH (10 equiv.), THF + H_2O (3:1), rt, 18 h (90-92%); (iv) Br_2 (1.5 equiv.), CCl_4, rt, 6 h (~100%); (v) Ac_2O, reflux, 1.5 h (~100%); (vi) C_2H_3MgBr (5 equiv.), CuI (0.1 equiv.), Et_2O, HMPA, – 5 to 0 ºC (55%); (vii) CH_2N_2, Et_2O, 0 ºC, 3 h (95%); (viii) O_3, $(CH_3)_2CO$, – 78 ºC, 3 min then $Na_2Cr_2O_7.H_2O$, H_2SO_4, H_2O, Et_2O, 0 ºC, 3 h then 1 M aq. NaOH then 1 M aq. HCl, (42%); (ix) NaCN (1.1 equiv.), MeOH, rt, 2 h (0%); (x) CuCN (5 equiv.), MeOH, reflux, 8 h (0%); (xi) 1,3-Dithiane (1.1 equiv.), *n*-BuLi (1.2 equiv.), THF, HMPA, 6 h (0%).

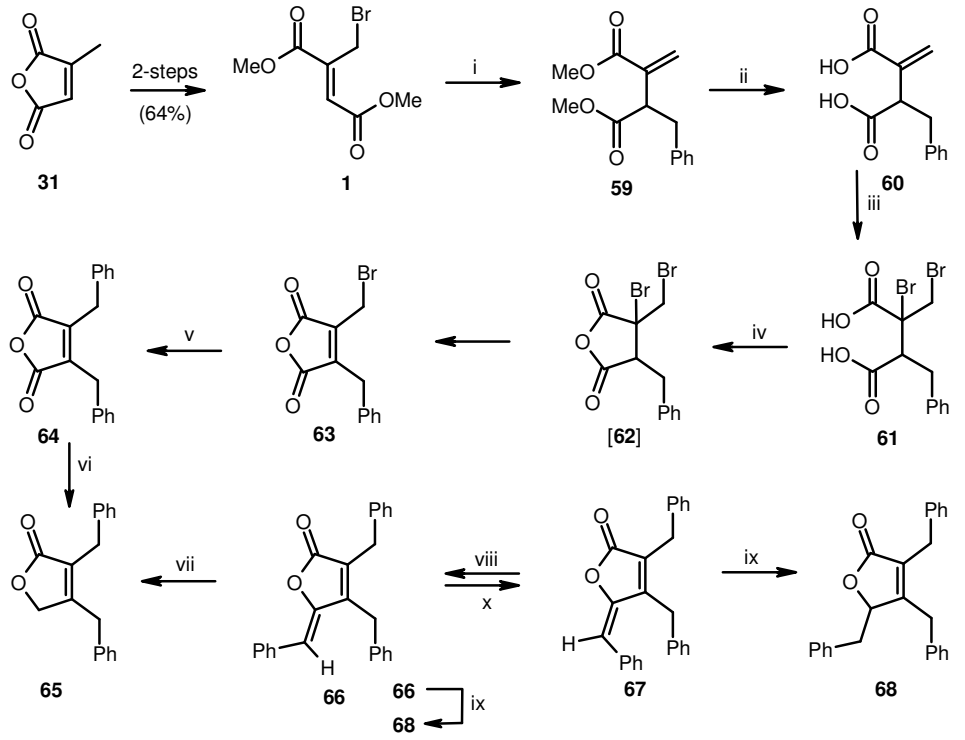
These natural products have been synthesized in our group[21] via the potential building blocks 2-bromomethyl-3-alkylmaleic anhydrides **50a/b**. These compounds **50a/b** were synthesized starting from dimethyl citraconate (**34**) via NBS-bromination, S_N2' Grignard coupling reactions, hydrolysis, molecular bromine addition and dehydrative ring closure reaction pathway with 49-51% overall yield in 5-steps. Chemoselective allylic substitution of bromoatom in **50a** with Grignard reagents gave the unsymmetrical maleic anhydride **51** in 55% yield. The naturally occurring 2-carboxymethyl-3-hexylmaleic anhydride (**55**) was synthesized from **51** via esterification, ozonolysis and oxidation route. The synthesis of two naturally occurring 2-(*β*-carboxyethyl)-3-alkylmaleic anhydrides **58a/b** have been completed via a chemoselective diethylmalonate coupling reaction followed by acid induced hydrolysis (Schemes 7 & 8)



Scheme 8. *Reagents, conditions and yields*: (i) (a) Diethyl malonate (1.1 equiv.), NaH (1.1 equiv.), C_6H_6, rt, 8 h, (b) H^+/HCl (72-74%); (ii) AcOH + HCl (1:1), reflux, 12 h (95-96%); (iii) CH_2N_2, Et_2O, 0 ºC, 3 h (95%).

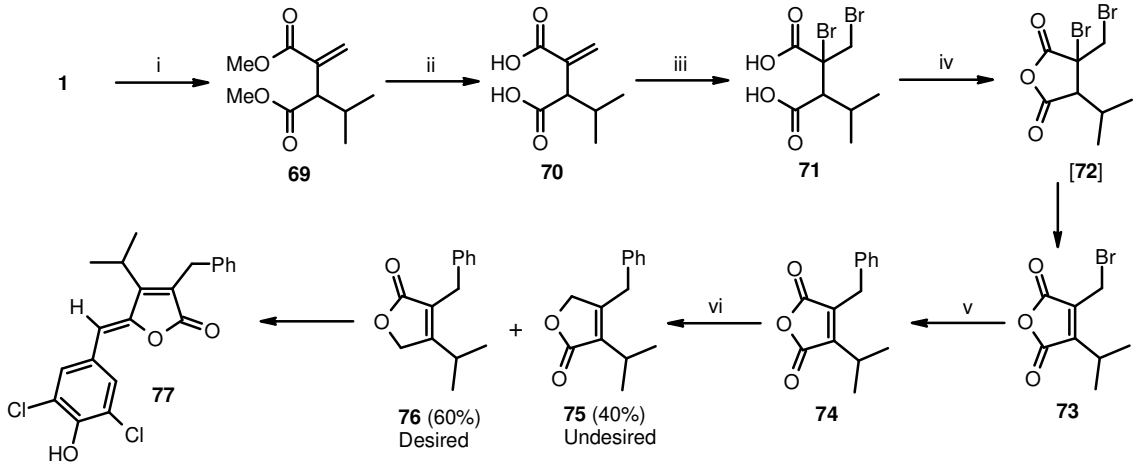
2A.1.1.6: *Synthesis of naturally occurring bioactive butyrolactones: maculalactones A-C and nostoclide I*

Maculalactones A-C have been isolated from the epilithic-encrusting cyanobacterium *Kyrtuthrix maculans* from Hong Kong island and they possess marine anti-fouling activity.[22] The natural (+)-maculalactone A has been assigned *S*-configuration. Nostoclide I (**77**) has been isolated from the culture of a symbiotic blue-green alga, *Nostoc* sp., from the lichen *Peltigera canina* and possesses cytotoxic activity.[23] These naturally occurring butyrolactones maculalactone A (**68**), maculalactone B (**66**) maculalactone C (**67**) and nostoclide I (**77**) have been synthesized in our group[24] starting from citraconic anhydride (**31**) with good overall yields via dibenzylmaleic anhydride (**64**) and benzylisopropylmaleic anhydride (**74**). The two anhydrides **64** and **74** were prepared by



Scheme 9. *Reagents, conditions and yields:* (i) $PhCH_2MgBr$ (1.5 equiv.), THF, HMPA, – 20 ºC, 0.5 h (70%); (ii) (a) LiOH (10 equiv.), THF + H_2O (3:1), rt, 18 h, (b) H^+/HCl (92%); (iii) Br_2 (1.5 equiv.), CCl_4, rt, 6 h (~100%); (iv) Ac_2O, reflux, 1.5 h (~100%); (v) C_6H_5MgBr (5 equiv.), CuI (0.1 equiv.), Et_2O, HMPA, – 5 to 0 ºC (45%); (vi) $NaBH_4$ (2.5 equiv.), THF, 0 ºC, 2 h (91%); (vii) Piperidine (0.7 equiv.), PhCHO (1 equiv.), MeOH, rt, 16 h (77%); (viii) $CHCl_3$, rt, 8 days (50%); (ix) H_2, Pd/C, EtOAc, 12 h (75%); (x) Δ, 200 ºC, 3 h (100%).

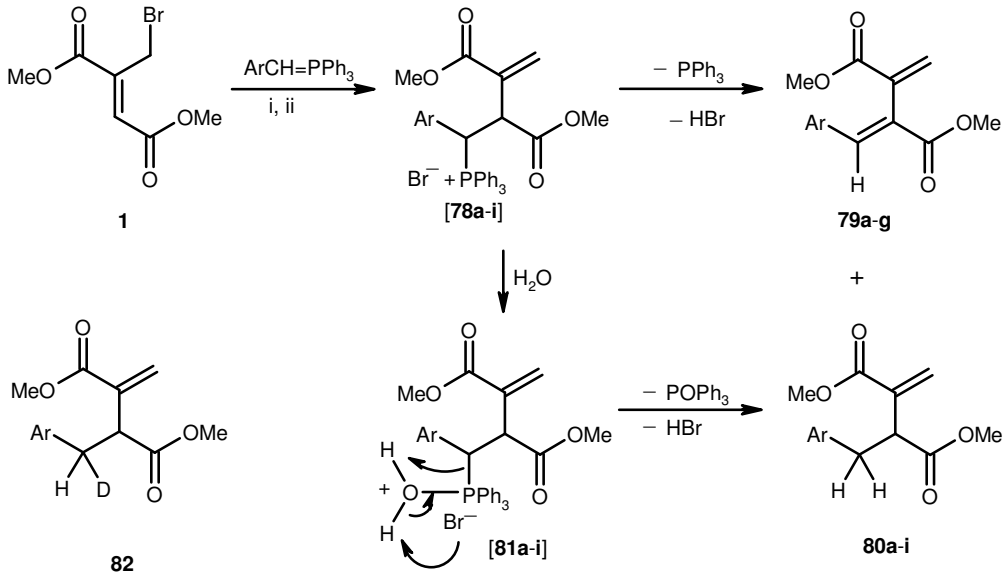
coupling reactions of appropriate Grignard reagents with dimethyl bromomethylfumarate (**1**), LiOH-induced hydrolysis of esters to acids, bromination of carbon-carbon double bond, in situ dehydration followed by dehydro-bromination and chemoselective allylic substitution of bromoatom in disubstituted anhydrides **63** and **73** with appropriate Grignard reagents. The $NaBH_4$ reduction of these anhydrides **64** and **74** furnished the desired lactones **65** and **76** respectively. The lactone **65** on Knoevenagel condensation with benzaldehyde furnished maculalactone B (**66**), which on carbon-carbon double bond isomerization gave maculalactone C (**67**), while **66** on selective catalytic hydrogenation gave maculalactone A (**68**) (Scheme 9 & 10). The conversion of lactone **76** to nostoclide I (**77**) is known in the literature.[25]



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

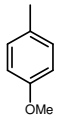
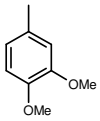
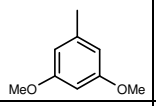
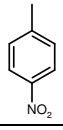
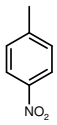
2A.1.1.7: Synthesis of enes, dienes and related natural products

Enes and dienes are an important class of compounds and they find applications in preparation of dyes, UV screens, drugs, in Diels-Alder reactions and also for the synthesis of complex natural and unnatural products.[26] These Enes and dienes have been synthesized in our group[27] by employing the S_N2' coupling reactions of Wittig reagents



Scheme 11. *Reagents, conditions and yields*: (i) Wittig reagent, –100 °C to rt, 3 h [**79a-g / 80a-i** : (60-66%) / (8-85%)]; (ii) Wittig reagent, –100 °C, 3 h, then H_2O at –100 °C [**79a-g / 80a-i** : (15-20%) / (50-85%)].

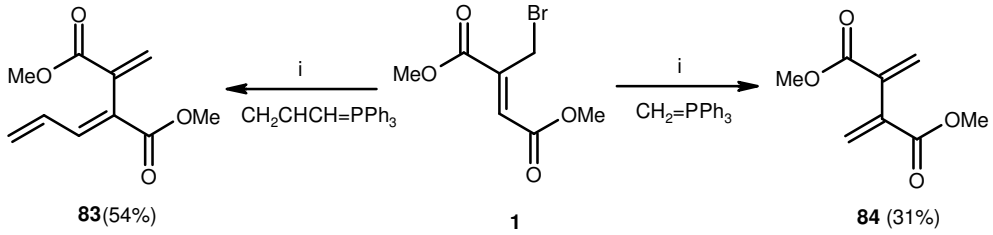
Table 3. Synthesis of variety of enes **80** and dienes **79** from dimethyl bromomethylfumarate (**1**)

Entry	Ar-	Products **79** & **80** Condition (i)		Products **79** & **80** Condition (ii)	
		79a-i (yield %)[a]	**80a-i** (yield %)[a]	**79a-i** (yield %)[a]	**80a-i** (yield %)[a]
1		**79a** (60)	**80a** (8)	**79a** (18)	**80a** (50)
2		**79b** (64)	**80b** (11)	**79b** (20)	**80b** (55)
3		**79c** (65)	**80c** (10)	**79c** (15)	**80c** (60)
4		**79d** (64)	**80d** (11)	**79d** (64)	**80d** (11)
5		**79e** (66)	**80e** (12)	**79e** (18)	**80e** (60)
6		**79f** (62)	**80f** (13)	**79f** (20)	**80f** (55)
7		**79g** (60)	**80g** (10)	**79g** (18)	**80g** (52)
8		**79h** (00)	**80h** (85)	**79h** (00)	**80h** (85)
9		**79i** (00)	**80i** (85)	**79i** (00)	**80i** (85)

Conditions: (i) Wittig reagent, −100 °C to rt; (ii) Wittig reagent, −100 °C, H_2O. [a] The obtained mixtures of enes and dienes were separated by silica-gel column chromatography and the isolated yields have been indicated in the parenthesis.

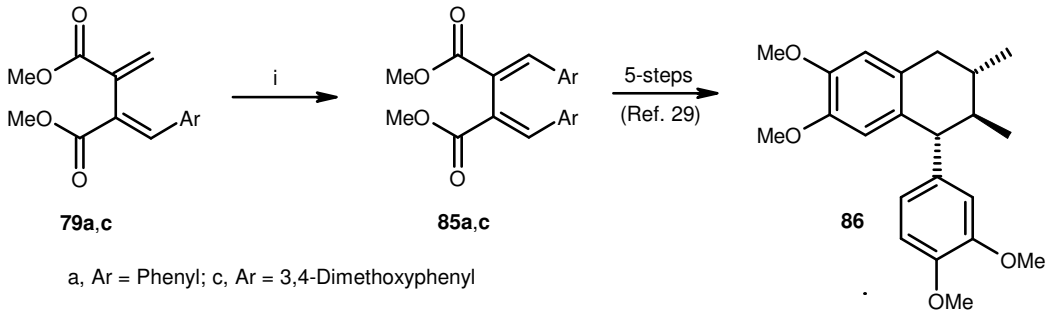
with dimethyl bromomethylfumarate. Wittig reagents were prepared using variety of aryl bromide and triphenylphosphene and the ylide was prepared using *n*-BuLi as a base. S_N2'

Coupling reactions of these ylides with dimethyl bromomethylfumarate (**1**) gave the corresponding column separable mixture of ene **80a**-**i** and diene **79a**-**i** (Scheme 11, Table 3). S_N2' coupling reactions of relatively more reactive phosphoranes generated from phosphonium salts of methyl iodide and allyl bromide, with **1** exclusively furnished the corresponding diene **83** and dimethyl ester of fulgenic acid (**84**)[28] respectively (Scheme 12).



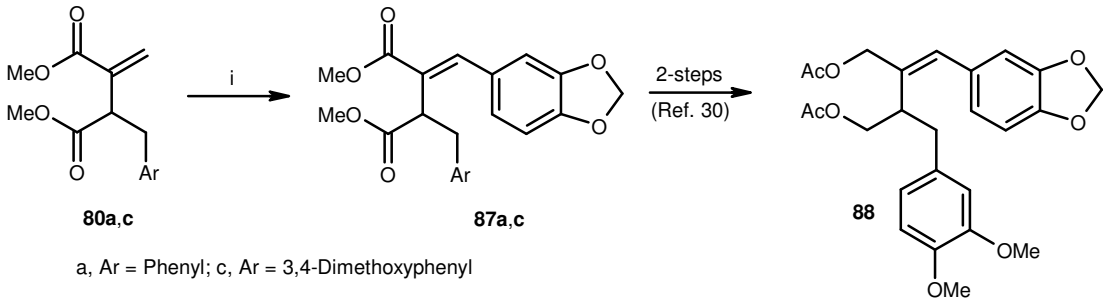
Scheme 12. *Reagents, conditions and yields*: (i) Wittig reagent, –100 °C to rt, 3 h.

The dienes **79a**,**c** on a Heck coupling reactions with an appropriate halides gave the (*E*,*E*)-dienes **85a**,**c**. The 5-step conversion of diene **85c** to natural product (±)-gulbulin (**86**) is known in the literature[29] (Scheme 13).



Scheme 13. *Reagents, conditions and yields*: (i) ArI, $Pd(OAc)_2$, Cy_2NH, H_2O, 120 °C, 24 h (*E*:*Z* = 94:6, 86%).

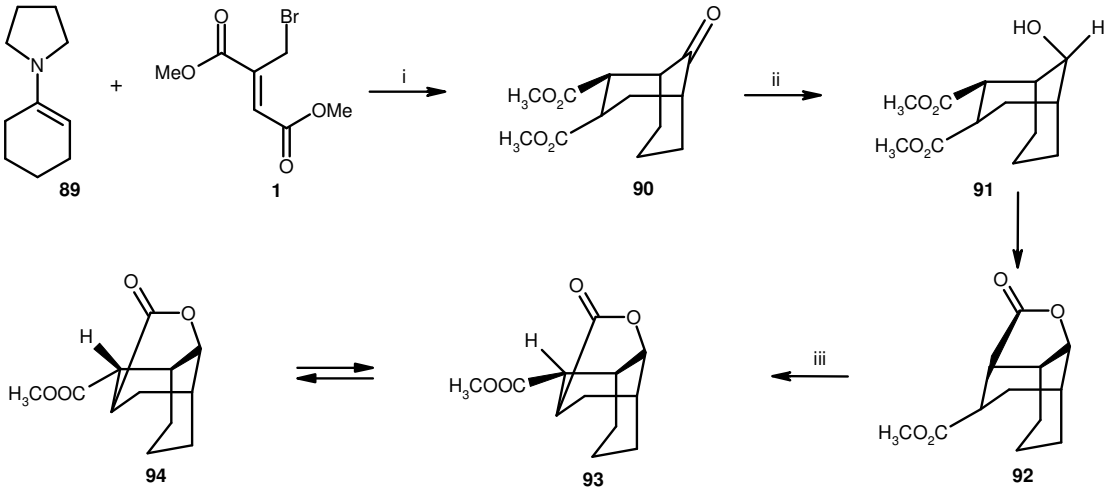
Similarly, Heck coupling reactions of enes **80a**,**c** with appropriate halides gave the corresponding diesters **87a**,**c**. The reduction of two ester groups in ene **87c** followed by an in situ acylation of the formed intermediate 1,4-diol provided the natural product (±)-prasanthaline (**88**)[30] (Scheme 14).



Scheme 14. *Reagents, conditions and yields*: (i) ArI, $Pd(OAc)_2$, Cy_2NH, H_2O, 120 ^oC, 24 h (*E*:*Z* = 82:18, 88%).

2A.1.1.8: *Synthesis of bicyclo[3.3.1]nonanone derivatives (Lawton and co-workers)*

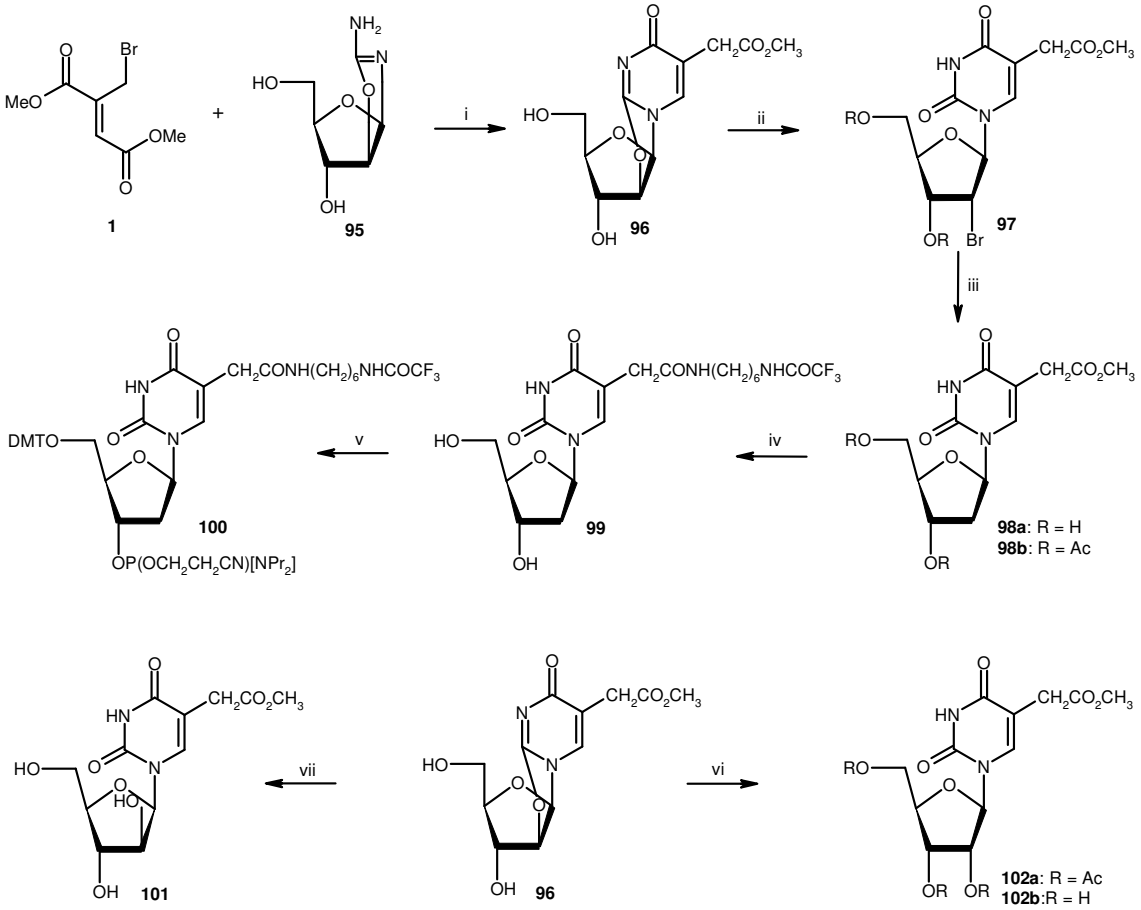
3-Aza-bicyclo-[3.3.1]nonane derivatives has been synthesized by dekkers *et al*[31] by using the reaction of dimethyl bromomethylfumarate with *N*-tosylpipredone enamine. Lawton and co-workers[32] have reported the synthesis of bicyclo[3.3.1]nonan-9-one derivatives by the reaction of enamines of substituted cyclohexanones with dimethyl bromomethylfumarate. Condensation of dimethyl bromomethylfumarate (**1**) with cyclohexanone enamine (**89**) furnished bicyclononanone diester **90**. Sodium borohydride reduction of **90** yielded a hydroxy diester **91,** which did not undergo complete γ-lactone formation until heated to 170 °C for 2 hr. Further, sodium methoxide-methanol converted the γ-lactone **92** into a 4:1 mixture of δ-lactone esters **93** and **94** (Scheme 15). Via the C-3 ester epimerization, opening of the γ-lactone, conformational inversion to a boat form and condensation to & lactone **93**, which is then epimerized at the C-2 ester to an equilibrium mixture of **93** and **94**.



Scheme 15. *Reagents, conditions and yields*: (i) CH_3CN, reflux, 5 h (76%); (ii) (a) $NaBH_4$, MeOH, rt, 1 h, (b) neat, 170 °C, 4h (37%); (iii) NaOMe, MeOH, rt, 12 h (70%).

2A.1.1.9: *Synthesis of 5-substituted uracil nucleosides (Sawai et al)*

Uridine and related pyrimidine nucleosides substituted with various functional groups at the C-5 position have found a wide variety of applications as antiviral agents[33] and as constituent of modified nucleic acids.[34] Sawai *et al*[35] have reported the synthesis of 5-substituted uracil nucleosides useful for the attachment of linker arm to nucleic acids by the reaction of arabinoaminooxazoline and dimethyl bromomethylfumarate. Dimethyl bromomethylfumarate (**1**) was reacted with arabinoaminooxazoline **95**[36] in the presence of triethylamine to obtain compound **96** in 50% yield. Bromination of **96** with HBr in CF_3CO_2H at 40 °C give 5-methoxycarbonylmethyl-2′-bromo-2′-deoxyuridine (**97**) in 74% yield. The 2'-bromo nucleoside was converted to 5-methoxycarbonylmethyl-2′-deoxyuridine **98a** in 73% yield by hydrogenation on Pd-black catalyst in the presence of



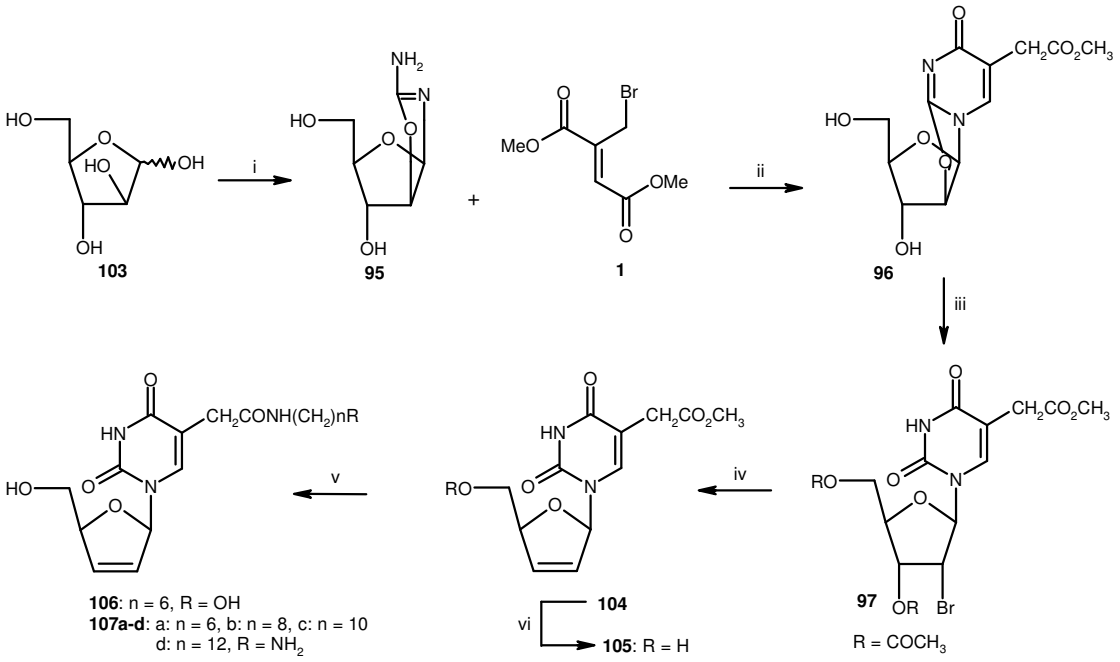
Scheme 16. *Reagents, conditions and yields*: (i) Et_3N, MeOH, reflux, 2 h (50%); (ii) (a) HBr, CF_3CO_2H, 40 °C, 12 h (74%) or (b) AcBr, MeCN, NaOAc reflux 1 h (37% from **95**); (iii) (a) H_2-Pd-black, NaOAc, MeOH, rt, 4 h (73%) or (b) Bu_3SnH-AIBN, C_6H_6, reflux, 1 h (79%); (iv) $H_2N(CH_2)_6NH_2$, DMAP, MeOH, 50 °C, 12 h, then CF_3CO_2Et, MeOH (90%); (v) DMTCI, DMAP, pyridine, rt then $ClP(OCH_2CH_2CN)$ $[NPr_2]$, CH_2Cl_2, rt (77%); (vi) AcOH, Ac_2O then MeOH-NH_3 (62%); (vii) MeOH-NH_3 (90%).

sodium acetate in aqueous methanol. Reduction of the 2′-bromo derivative with Bu_3SnH-AIBN in benzene under reflux for 1 h also furnished 3′,5′-0-diacetyl-5-methoxycarbonylmethy1-2′-deoxyuridine **98b** in 79% yield. The reaction of **98b** with 1,6-hexanediamine in methanol in the presence of dimethylaminopyridine at 50 °C overnight gave 5-[*N*-(6-aminohexyl)carbamoylmethyl]-2′-deoxyuridine**,** the terminal amino group of which was protected with trifluoroacetyl group by reaction with ethyl trifluoroacetate in methanol, to afford *5-[N-(6-* trifluoroacetylamidohexyl)carbamoylmethyl]-2′-deoxyuridine **99** in 90% yield (Scheme 16). The reaction of **99** with dimethyoxytrityl chloride (DMTCl) in the presence of dimethylaminopyridine in pyridine at room temperature afforded the 5′-DMT protected nucleoside, which was phosphitylated with diisopropylamino-*P*-cyanoethoxychlorophosphine in dichloromethane at room temperature to give the 5′-DMT nucleoside phosphoramidite **100** in 77% yield. Hydrolysis of **96** with methanolic ammonia at room temperature led to the corresponding arabinosyl nucleoside **101** in high yield. Compound **96** was converted to 2′,3′,5′-tri-O-acetyl-5-methoxycarbonylmethyluridine **102a** in 62% yield by heating in acetic anhydride. Hydrolysis of **102a** with methanolic ammonia at room temperature for 2 h yielded quantitatively 5-methoxycarbonylmethyluridine **102b,** one of the modified nucleosides of transfer RNA.

2A.1.1.10: *Synthesis of C-5 substituted β-D- and β-L-d4T analogues (Ladurée and co-workers)*

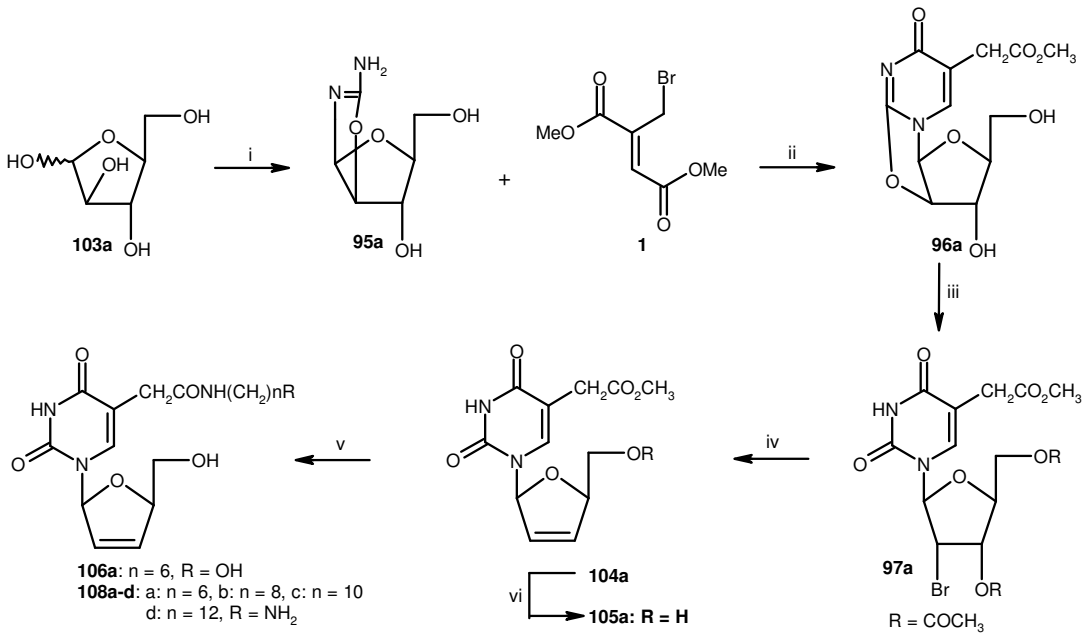
Intensive efforts in the search of effective therapies for treatment of human immunodeficiency virus (HIV) infection have led to the discovery of 2′,3′-didehydro- 2′,3′-dideoxynucleosides(d4N) including 2',3'-didehydro-2',3'-dideoxythymidine (d4T) which has been already approved for the treatment of HIV infections.[37] Ladurée and co-workers[38] have synthesized a series of d4T analogues and evaluated *in vitro* for anti-HIV-1 activity in various cells. *D*-arabinose (**103**) on reaction with cyanamide in the presence of $NaHCO_3$ in DMF afforded the 2-amino-*β-D*-arabinofurano[1′,2′:4,5]oxazoline (**95**). Subsequent treatment of **95** with dimethyl bromomethylfumarate (**1**) in the presence of triethylamine in methanol yielded the 2,2′-anhydro-nucleoside **96**. Reaction of **96** with acetyl bromide in anhydrous acetonitrile afforded the 1-(3′,5′-di-O-acetyl-2′-bromo-2′-deoxy-,*β*-D-ribofuranosy1)-5-(methoxycarbony1 methyl)-uracil (**97**) in 63% yield. The reductive *β*-elimination of this acetoxy-bromo intermediate with freshly activated zinc powder gave 5′-

O-acetyl-*β*-D-d4T analogue **104**. The 2′,3′-didehydro-2′,3′-dideoxy-nucleosides **106** and **107a-d** bearing a linker at C-5 position were prepared by reaction of **104** with either 6-aminohexan-1-ol or 1,6- 1,8- 1,l0 and 1,12-alkyldiamines in the presence of dimethylaminopyridine via amide linkages by ester-amide exchange reactions of 5-carbonylmethyl esters. Finally, removal of the C-5′-O-acetyl protecting group of **104** with sodium cyanide in methanol afforded the *5*-(methoxycarbonylmethyl)-d4T **105** in 85% yield (Scheme 17).



Scheme 17. *Reagents, conditions and yields*: (i) H_2NCN, $NaHCO_3$, DMF (80%); (ii) Et_3N, MeOH (61%); (iii) CH_3COBr, CH_3CN (63%); (iv) Zinc dust, EtOH (54%); (v) 6-Aminohexan-1-ol or 1,n-diaminoalkane, DMAP, CH_3OH; (vi) NaCN, MeOH (85%).

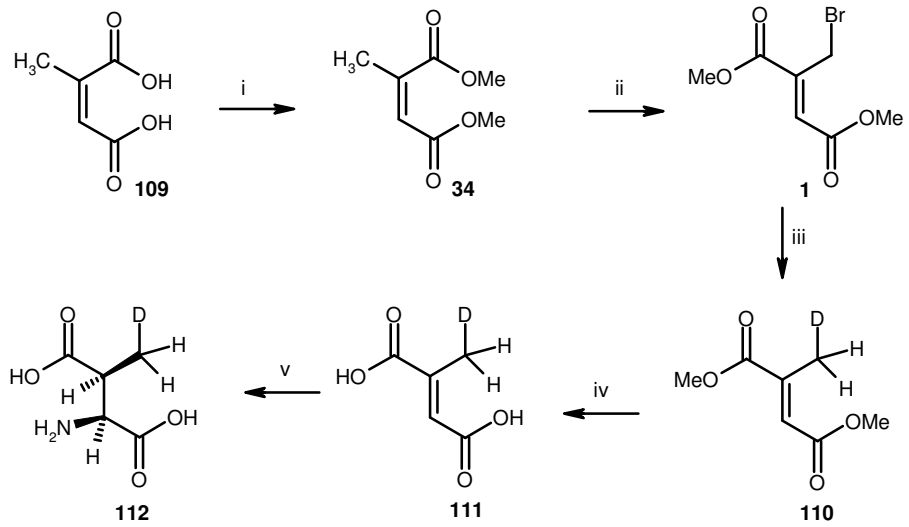
The corresponding 5-[*N*-(hexan-6-ol)carbamoylmethyl]- and 5-[*N*-(aminoalkyl)carbamoylmethyl]-,*β*-L-d4T analogues **106a** and **108a-d** (n = 6, 8**,** 10 and 12) were prepared by a similar synthetic approach as summarized in Scheme 17. Removal of the C-5′-O-acetyl group of **104a** was carried out using methanolic sodium methoxide yielding the 5-(methoxycarbonyl methyl)-,*β*-L-d4T analogue **105a** (Scheme 18).



Scheme 18. *Reagents, conditions and yields*: (i) H_2NCN, NH_4OH, MeOH (80%); (ii) Et_3N, MeOH (61%); (iii) CH_3COBr, CH_3CN (63%); (iv) Zinc dust, EtOH (54%); (v) 6-Aminohexan-1-ol or 1,n-diaminoalkane, DMAP, CH_3OH; (vi) NaOMe, MeOH (85%).

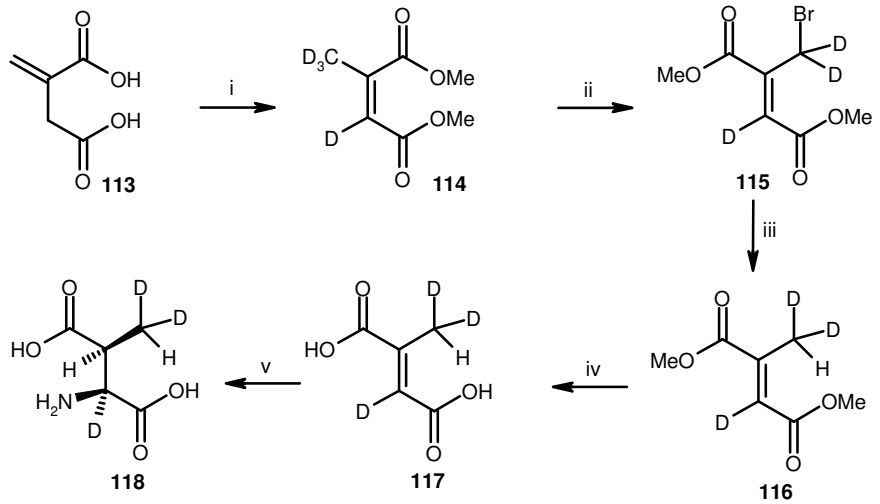
2A.1.1.11: *Synthesis of mono- and di-deuterated (2S,3S)-3-methylaspartic acids (Marsh and co-workers)*

Isotope effects provide an extremely powerful tool to probe the mechanisms of chemical reactions and have proved particularly useful for investigating enzyme mechanisms.[39] Marsh and co-workers[40] have synthesized mono- and di-deuterated (*2S*,*3S*)-3-



Scheme 19. *Reagents, conditions and yields*: (i) H_2SO_4, MeOH, reflux, 12 h (80%); (ii) NBS, AIBN, CCl_4, reflux, 12 h (78%); (iii) Bu_3SnD, AIBN, C_6H_6, 55 °C, 1 h (50%); (iv) LiOH, H_2O/THF (1:2), rt, 8 h (64%); (v) NH_4Cl, *β*-methylaspartate, 15 h (50%).

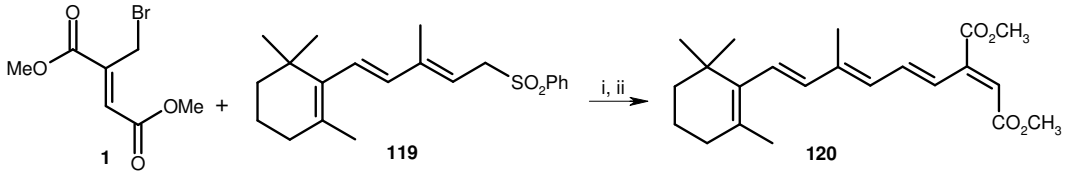
methylaspartic acids and used for the mechanistic investigations of the adenosyl cobalamin-dependent enzyme, glutamate mutase. Methylmaleic acid **109** was converted into its dimethyl ester **34** which was brominatated using *N*-bromosuccinimide and a catalytic amount (10%) of AIBN as a radical initiator to give dimethyl bromomethylfumarate (**1**). Introduction of deuterium was accomplished by reductive debromination using tributyltin deuteride in dry benzene at 55 °C with 10% AIBN as a radical initiator. This gave the mono-deuterated dimethyl methylfumarate **110** in 50% yield. Further, the ester was hydrolyzed using lithium hydroxide to yield after acidification mono-deuterated methylfumaric acid **111** in 64% yield. Which is enzymatically converted to the mono-deuterated (2*S*,3*S*)-3-methylaspartic acids **112** (Scheme 19). Mesaconic acid incorporating two deuterium atoms in the methyl group was synthesized by an analogous strategy starting with itaconic acid. Itaconic acid **113** was dissolved in 40% NaOD/D_2O and heating at 120 °C for 90 min. The resulting d_4-mesaconic acid was converted to dimethyl ester **114**, and then to deuterated dimethyl bromomethylfumarate (**115**) as described above. Reduction with tributyl-tin hydride yielded the dimethyl ester of mesaconate **116**, containing two deuterium atoms in the methyl group, which was then hydrolyzed to give (2-$^2H_1$,methyl-$^2H_2$)-mesaconic acid **117**. Which is enzymatically converted to the dideuterated (2*S*,3*S*)-3-methylaspartic acids **118** (Scheme 20).



Scheme 20. *Reagents, conditions and yields*: (i) (a) 40% NaOD, D_2O, 120 °C, 90 min, (b) H_2SO_4, MeOH, reflux, 12 h (80%); (ii) NBS, AIBN, CCl_4, reflux, 12 h (78%); (iii) Bu_3SnH, AIBN, C_6H_6, 55 °C, 1 h (50%); (iv) LiOH, H_2O/THF (1:2), rt, 8 h (64%); (v) NH_4Cl, *β*-methylaspartate, 15 h (50%).

2A.1.1.12: *Synthesis of C-13-substituted retinoic acid analogues (Welch et al)*

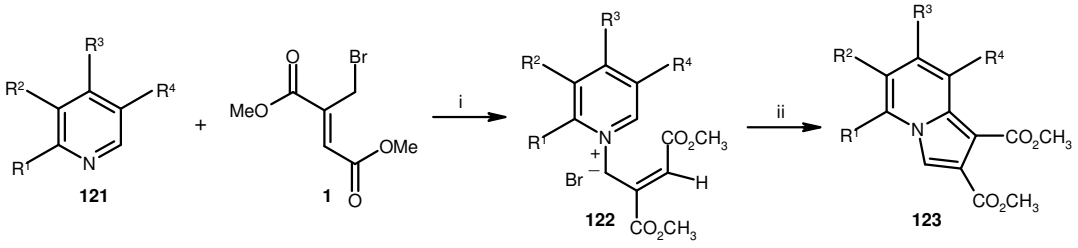
Retinoic acid (vitamin A acid) and its analogues have received considerable attention for their importance in controlling the normal growth, development, and differentiation of epithelial cells.[41] Welch *et al*[42] have synthesized retinoic acid anolog by the deprotonation of sulfone **119**[43,44] with alkyl lithium reagent (*n*-BuLi or MeLi) or lithium diisopropylamide (LDA) followed by addition of bromide **1** effects alkylation. Elimination of benzenesulfonic acid to give retinoid **120** is most conveniently accomplished by direct treatment with sodium methoxide (Scheme 21).



Scheme 21. *Reagents, conditions and yields*: (i) LDA, THF, -78 °C; (ii) NaOMe (17%).

2A.1.1.13: *Synthesis of substituted indolizines (Sasaki et al)*

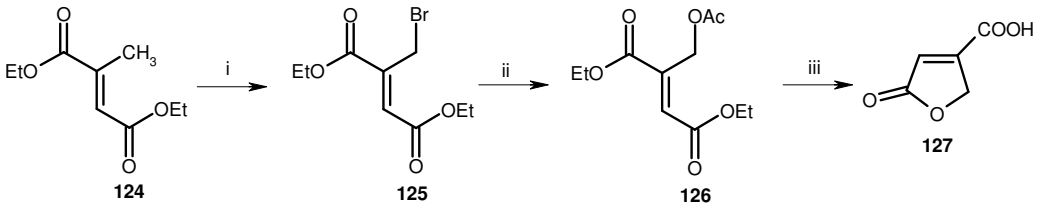
Sasaki *et al*[45] have reported the synthesis of pyridinium allylides and used it for the synthesis indolizine derivatives. The starting material pyridine derivatives **121** and dimethyl bromomethylfumarate (**1**) were mixed in benzene at room temperature, the corresponding pyridinium salts **122** were obtained in quantitative yield. The pyridinium salts were treated with an excess of potassium carbonate in benzene at room temperature, they underwent intramolecular 1,5- dipolar cyclisation followed by dehydrogenation to give the corresponding l,2-bismethoxycarbonylindolizine derivatives **123** (Scheme 22).



Scheme 22. *Reagents, conditions and yields*: (i) C_6H_6, rt, 1-2 days; (ii) K_2CO_3, C_6H_6, rt, 1 day (20-45%).

2A.1.1.14: *Synthesis of aconic acid (Campbel et al)*

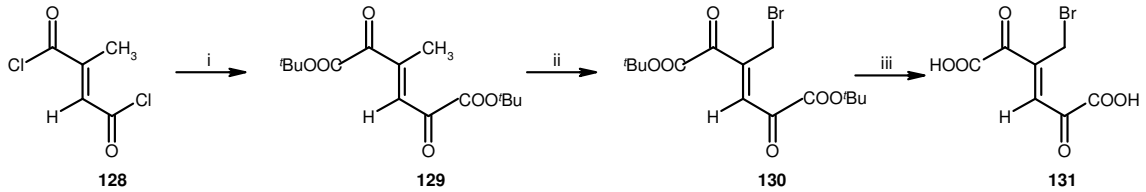
Aconic acid (127) has been synthesized by Campbel *et al*[1] by the bromination of the methyl group of diethyl mesaconate (**124**) by using *N*-bromosuccinimide, dibenzoyl peroxide, replacement of the bromine by an acetoxy group under mild conditions, hydrolysis with barium hydroxide, and cyclisation by warming with water (Scheme 23).



Scheme 23. *Reagents, conditions and yields*: (i) NBS, DBP, CCl_4, reflux, 1 h (72%); (ii) KOAc, EtOH, reflux, 1 h (78%); (iii) (a) $Ba(OH)_2$, H_2O, reflux 1.5 h (b) 5 N H_2SO_4, 70 °C, 0.5 h (30%).

2A.1.1.15: *Synthesis of bromomesaconic acid (Laursen et al)*

Bromomesaconic acid and its substrate analogs are potent active site specific irreversible inhibitor of fumarase.[46] Laursen *et al*[2] have prepared bromomesaconic acid **131** by the bromination of di-*t*-butyl methylfumarate **129,** prepared by the action of *t*-BuONa on the acid chloride **128** using *N*-bromosuccinimide, produced the bromo ester **130**. Hydrolysis of **130** in CF_3CO_2H gave bromomesaconic acid **131** (Scheme 24).

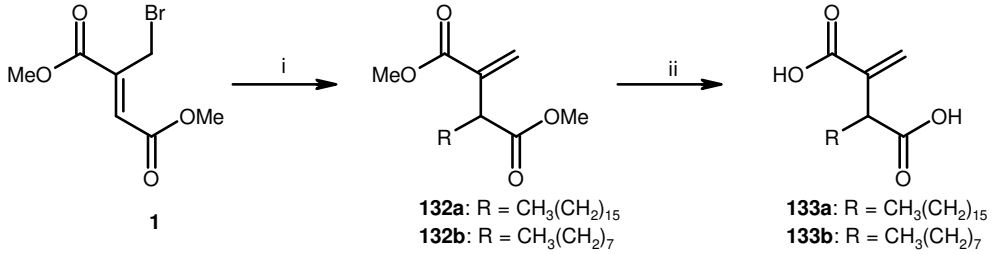


Scheme 24. *Reagents, conditions and yields*: (i) *t*-BuONa, reflux, 1.5 h (69%); (ii) NBS, DBP, MgO, $CHCl_3$ reflux, 1 h (85%); (iii) CF_3COOH, C_6H_6, reflux, 5 h (50%).

2A.1.1.16: *Synthesis of alkylitaconic acids (Watanabe and co-workers)*

Watanabe and co-workers[47] have synthesized alkylitaconic acid from dimethyl bromomethylfumarate and analyzed the physicochemical and redox properties of these alkylitaconic acids. Dimethyl bromomethylfumatrate on Grignard reaction with alkylmagnesium bromide gave the corresponding itaconates **132a**,**b** which on

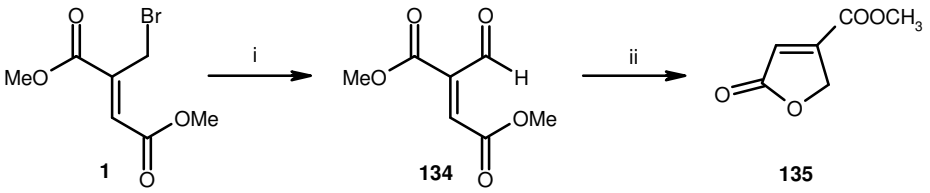
demethylation using formic acid, hydroquinone as polymerization inhibitor and sulfuric acid gave the corresponding alkylitaconic acids **133a**,**b** (Scheme 25).



Scheme 25. *Reagents, conditions and yields*: (i) RMgBr, $LiCuBr_2$, THF, rt (35-49%); (ii) HCOOH, hydroquinone, H_2SO_4, 100 °C, 3 h (48-51%).

2A.1.1.17: *Synthesis of 4-methoxycarbonyl-2(5H)-furanone (Amri and co-workers)*

Amri and co-workers[48] have reported the synthesis of 4-methoxycarbonyl-2(*5H*)-furanone (**135**) by the formylation of dimethyl bromomethylfumarate (**1**), followed by acid catalysed transesterification in methanol to give the corresponding substituted furanone in 67% overall yield (Scheme 26).



Scheme 26. *Reagents, conditions and yields*: (i) TEAF, CH_3CN, rt, 20 h (80%); (ii) Conc. HCl, MeOH, rt, 3 h (84%).

2A.1.1.18: *Synthesis of α-alkylidene-γ-lactams (Amri and co-workers)*

2,3-Dimethoxycarbonylbutadienes are useful intermediates in organic synthesis.[49] Amri and co-workers[50] have reported the synthesis of functional 1,3-butadienes and their conversion into heterocyclic compounds such as γ-lactams. Dimethyl bromomethylfumarate (**1**) reacts with nitroalkanes in the presence of base to furnish (*E*)-1-alkyl-2,3-dimethoxycarbonyl butadienes **137** in good yields (Scheme 27, Table 4).

Scheme 27

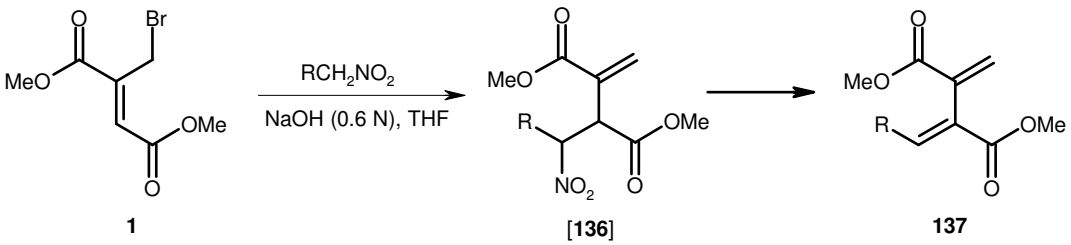


Table 4. Preparation of difunctional buta-1,3-dienes **137a**,**b**-(*E*)

1,3-Butadiene **137**	Time (h)	Yield (%)
137a, R = CH_3	4	70
137b, R = C_2H_5	1	96

α-Alkylidene-γ-lactams show cytotoxicity, anti-tumor and anti-inflammation activities.[51] The reaction of **137a**,**b** with primary amines takes place via conjugate addition followed by an intermolecular cyclization and displacement reaction leading to the formation of the corresponding α-alkylidene-γ-lactams **139** in good yields (Scheme 28, Table 5).

Scheme 28

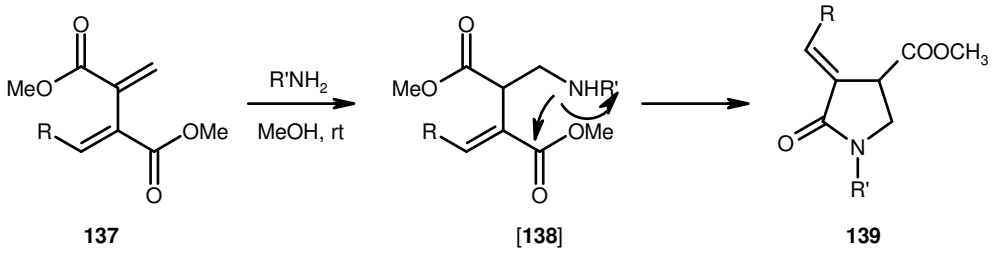


Table 5. Synthesis of the α-alkylidene-γ-lactams (*E*)-**139a-h**

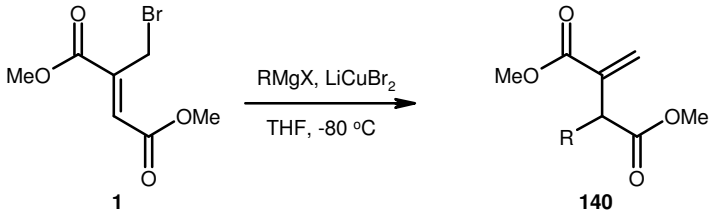
R	R'	Time (h)	γ-Lactam **139**	Yields (%)[a]
Me	$PhCH_2$	16	**139a**	63
Me	^{n}Bu	16	**139b**	75
Me	^{n}Pr	16	**139c**	80
Me	^{i}Pr	16	**139d**	72
Et	$PhCH_2$	8	**139e**	80
Et	^{n}Bu	5	**139f**	64
Et	^{n}Pr	4	**139g**	87
Et	^{i}Pr	12	**139h**	70

All reactions were carried out in 10 mmol scale of conjugated diene **137**.
[a] Yield of isolated γ-lactam **139** after silica gel chromatography (AcOEt:hexane = 1:1).

2A.1.1.19: *Synthesis of dimethyl 3-alkyl itaconates and 2-alkyl 3-carbomethoxy-γ-lactams (Amri and co-workers)*

Amri and co-workers[52] have reported the synthesis of β-alkylated itaconates **140** (Scheme 26) and α-alkyl-β-carbomethoxy-γ-butyrolactams **142**. Alkylmagnesium halide in the presence of a catalytic amount of $LiCuBr_2$, reacts spontaneously and regioselectively to give the corresponding 3-substituted dimethyl itaconates **140** with satisfactory yields as indicated in (Scheme 29, Table 6).

Scheme 29



1 **140**

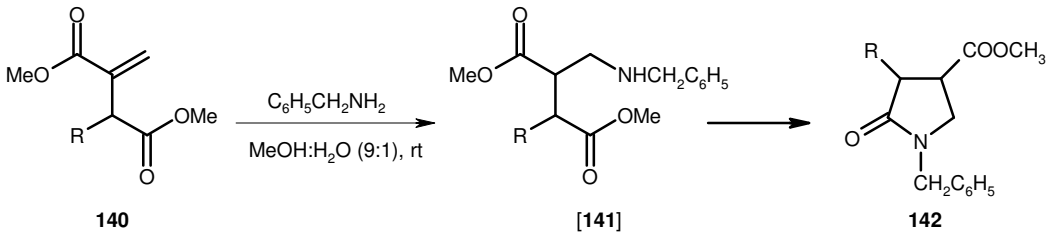
Table 6. Synthesis of 3-substituted dimethyl itaconates **140a**-**j**[a]

Entry	Reagents (equiv.) RMgX + 5% cu (I)*	Adducts **140a**-**j**	Yield (%)
1	CH_3MgI (1.2)	**140a**	60
2	C_2H_5MgBr (1.2)	**140b**	73
3	*n*-C_3H_7MgCl (1.3)	**140c**	78
4	*i*-C_3H_7MgCl (1.3)	**140d**	79
5	*i*-C_3H_5MgCl (1.7)	**140e**	43
6	*n*-C_4H_9MgCl (1.2)	**140f**	80
7	*t*-C_4H_9MgCl (1.4)	**140g**	75
8	C_6H_5MgCl (1.2)	**140h**	53
9	$C_6H_5CH_2MgCl$ (1.4)	**140i**	74
10	*o*-$C_6H_{11}MgCl$ (1.3)	**140j**	63

All reactions were carried out in 10 mmol scale of allylic bromide **1**. *Solution of $LiCuBr_2$ (I M) in THF was used. [a] Products **140a**-**i** were isolated as yellow liquids after column chromatography (10% AcOEt in hexane) except **140j** which was distilled.

The reaction of primary amines with 3-alkylated itaconic esters **140** proceeds through a conjugate addition/lactamization sequence leading to the diastereoselective formation of α-alkyl-β-carbomethoxy γ-lactams **142** (Scheme 30) with moderate to good yields (Table 7).

Scheme 30



140 [**141**] **142**

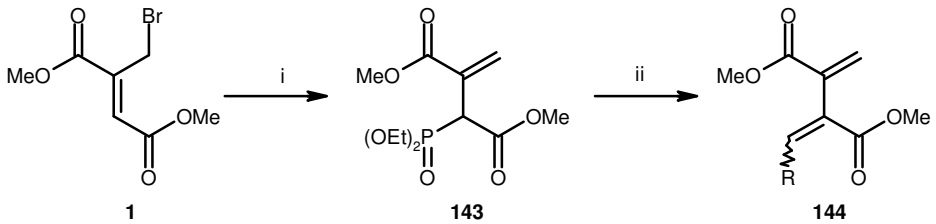
Table 7. Synthesis of α-alkyl-β-methoxycarbonyl-γ-lactams **142b-j**

3-Alkylated itaconates **140**	R	γ-Lactams **142b-j**	% Cis/trans	Yield (%)*
140b	C_2H_5	**142b**	23/77	60
140c	*n*-C_3H_7	**142c**	13/87	54
140e	*i*-C_3H_5	**142e**	0/100	37
140f	*n*-C_4H_9	**142f**	22/78	83
140g	*t*-C_4H_9	**142g**	47/53	50[a]
140i	$C_6H_5CH_2$	**142i**	19/81	77
140j	*o*-C_6H_{11}	**142j**	28/72	55

All reactions were carried out in 10 mmol scale of 3-alkyl itaconate **140**. * Yield of isolated lactams **142** after silica gel chromatography (30% AcOEt in hexane), [a]The lactamization of **142g** was carried out in bromobenzene at reflux.

2A.1.1.20: *Synthesis of (E/Z)-1-alkyl-2,3,dimethoxycarbonyl-1,3-butadienes (Amri and co-workers)*

Amri and co-workers[53] have reported the synthesis of 1-alkyl-2,3-dimethoxycarbonyl-1,3-butadienes by using Wittig-Horner reaction. Dimethyl bromomethylfumarate (**1**) on reaction with diethyl phosphite anion exclusively furnished the phosphonate **143** in excellent yield. The Wittig-Horner reaction of **143** with aldehydes using an aqueous potassium carbonate solution as base leads to the functional 1,3-butadienes **144a-f** with good stereoselectivities (Scheme 31, Table 8).



1 **143** **144**

Scheme 31. *Reagents, conditions and yields*: (i) $NaPO(OEt)_2$, THF, -78 °C (80%); (ii) RCHO, K_2CO_3, THF, reflux (60-71%).

Table 8. Synthesis of (*E*/*Z*)-1-alkyl-2,3,dimethoxycarbonyl-1,3-butadienes **144a–f**

1,3-Dienes[c] **144**	R	% *E*/*Z*[a]	Yield (%)[b]
144a	H	-	71
144b	CH_3	78/22	66
144c	C_2H_5	82/18	62
144d	nC_3H_7	80/20	67
144e	iC_4H_9	70/30	67
144f	nC_5H_{11}	75/25	68

[a]The *E* and *Z* configuration are assigned on the basis of ^{1}H NMR chemical-shift data. The isomer ratio for a given reaction was initially deduced from NMR on the crude reaction mixture and C.P G analysis.
[b]Yields of isolated 1,3-dienes **144** after silica gel chromatography (30% EtOAc in Hexane).
[c]All the products gave satisfactory spectral analysis IR, ^{1}H, ^{13}C NMR, and mass data.

2A.1.1.21: *Synthesis of functionalized allylamines (Amri and co-workers)*

Allylamines constitute an important class of compounds not only for their utility in organic synthesis but also for their biological activities.[54] Amri and co-workers[55] have reported the synthesis of a new functional allylamines via an effective coupling of secondary amines and dimethyl bromomethylfumarate (**1**). The reaction of **1** with excess secondary amine leads to the corresponding secondary allylamino substrates **146k-l** or S_N2'-type products **145a-j** that contain terminal methylene group in very high yields (Scheme 32, Table 9). Authors have not mentioned any specific reason for the formation of **145** and **146**.

Scheme 32

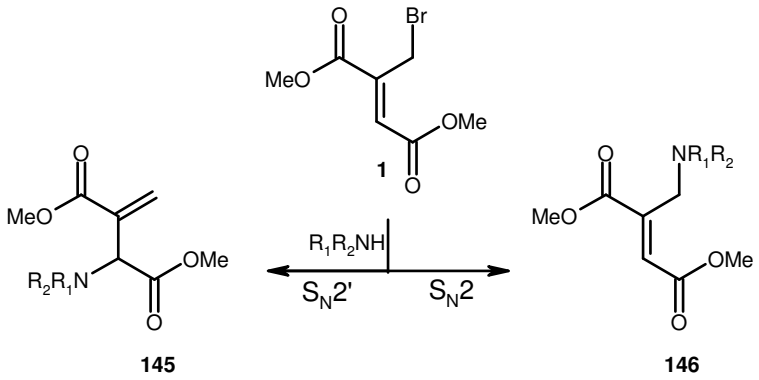


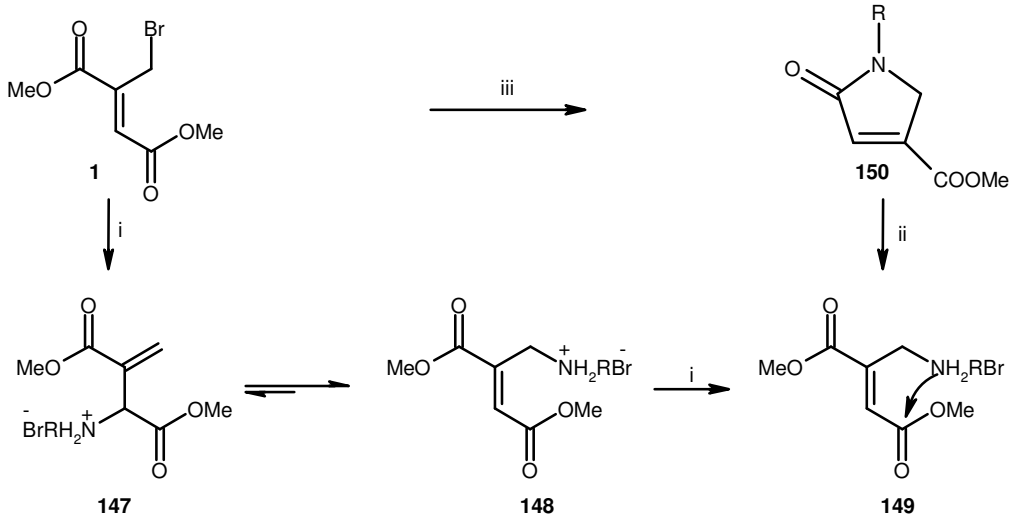
Table 9. Synthesis of α-(alkylamino) acrylic and fumaric esters **145a-j** and **146k-I**

Product	R_1	R_2	Time (h)	Temp °C	Yield (%)
145a	*i*-Pr	*i*-Pr	12	25	86[a]
145b	*n*-Pr	*n*-Pr	24	25	93[b]
145c	*c*-C_6H_{11}	*c*-C_6H_{11}	36	25	90[a]
145d	*i*-Pr	*c*-C_6H_{11}	28	25	90[c]
145e	Me	CH_2Ph	2	25	87[b]
145f	*i*-Pr	CH_2Ph	24	25	90[b]
145g	-$CHMe(CH_2)_3CH_2$-	-	25	25	71[b]
145h	- $CHMe(CH_2)_3CHMe$-	-	2	-70	69[b,d]
145i	-$(CH_2)_2$-O-$(CH_2)_2$-	-	2	-70	79[b,d]
145j	Et	Et	12	25	82[a]
146k	Me	Ph	48	25	87[b]
146l	-$CMe_2(CH_2)_3CMe_2$-	-	2	150	60[a,c]

Excess of amine *is* used: [a] 4 Eqniv.; [b] 2 Eqniv. ; [c] 3 Equiv. [d,e] Reactions were carried out respectively at -70 °C and in boiling benzene bromide.

2A.1.1.22: *Synthesis of pyrrolin-2-ones (Amri and co-workers)*

Pyrrolin-2-ones are potentially useful intermediates for the synthesis of biologically active compounds like aza-sarkomycin[56] and porphirins.[57] Amri and co-workers[5] have reported



Scheme 33. *Reagents, conditions and yields*: (i) C_6H_5Br, reflux, RNH_2 (1 equiv.); (ii) C_6H_5Br, reflux; (iii) RNH_2 (2 equiv.), C_6H_5Br, reflux.

the synthesis of pyrrolin-2-ones by using the addition of primary amines to dimethyl bromomethylfumarate (**1**). Addition of 1 equiv. of primary amine to dimethyl bromomethylfumarate gave a mixture of S_N2' allylic substituted compound **147** and the pyrorolin-2-ones in moderate yield. While the addition of second equivalent of amine to this mixture furnished pyrrolin-2-ones **150a-g** good yield (Scheme 33, Table 10).

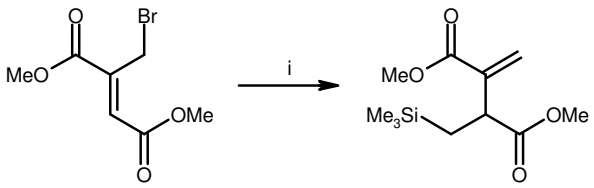
Table 10. 4-Methoxycabonyl-1-Δ^3-pyrrolin-2-ones **150a**-**g**

Compound	R	Yields (%)[a]
150a	*n*-Pr	66
150b	*i*-Pr	50
150c	*n*-C_4H_9	90
150d	C_6H_{11}	52
150e	$PhCH_2$	70
150f	*p*-$ClC_6H_4CH_2$	80
150g	EtO_2CCH_2	74

[a] Yield of isolated crystalline products **150a**-**g** based on **1**.

2A.1.1.23: *Synthesis of functionalized homoallylsilanes (Amri and co-workers)*

Amri and co-workers[58] have synthesized functionalized homoallylsilane compound **151** via a nucleophilic Michael addition of silylcuprate to dimethyl bromomethylfumarate (Scheme 34).

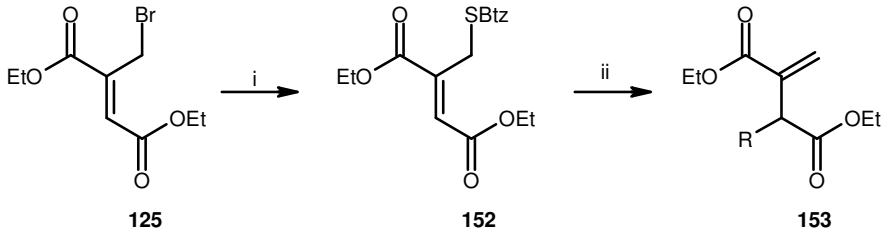


1 **151**

Scheme 34. *Reagents, conditions and yields*: (i) Me_3SiCH_2MgCl, $LiCuBr_2$, THF, -45 °C (66%).

2A.1.1.24: *Synthesis of β,β-disubstituted acrylates (Caló et al)*

Caló et al[59] have reported the synthesis of *β,β*-disubstituted acrylates. Diethyl bromomethylfumarate on reaction with benzothiazole in presence of potassium carbonate gave the corresponding allylic sulphide **152** which on reaction with organomagnesium compound in presence of CuBr or CuI gave the *β,β*-disubstituted acrylate **153** (Scheme 35).

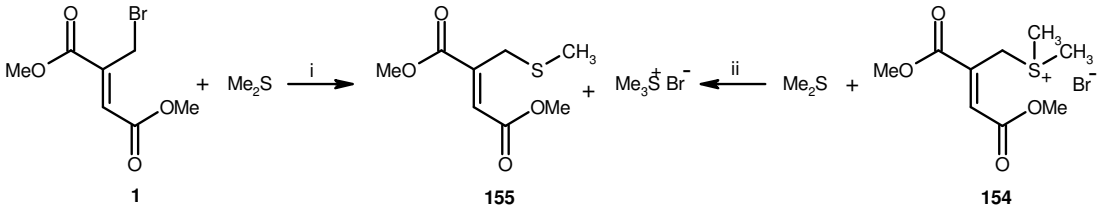


125 **152** **153**

Scheme 35. *Reagents, conditions and yields*: (i) Btz-SH, K_2CO_3; (ii) *n*-C_4H_9MgBr, CuBr, THF, -25 °C, 24 h (95%).

2A.1.1.25: *Synthesis of symmetrical and unsymmetrical organic sulphides (Schneider and co-workers)*

Schneider and co-workers[60] have reported the synthesis of a variety of unsymmetrical methyl and ethyl sulphides, by the treatment of appropriate organic halides or the corresponding sulphonium salts with an excess of dimethyl or diethyl sulphides. Dimethyl bromomethylfumarate (**1**) on treatment with excess of dimethyl sulphide gave allylic sulphide (**155**). However, **155** has been synthesized in quantitative yield under non-basic conditions by heating the corresponding dimethylsulphonium salt (**154**) with an excess of dimethyl sulphide in Me_2SO (Scheme 36).



1 **155** **154**

Scheme 36. Reagents, conditions and yields: (i) Excess Me_2S, 60 °C, 12 h (79%); (ii) Me_2SO, 60 °C (100%).

2A.2. Summary

In summary, the dimethyl bromomethylfumarate has six alternate sites available for nucleophilic reactions, viz (i) two ester carbonyls for 1,2-additions (ii) two sites for Michael addition (iii) allylic bromo atom for nucleophilic substitution reaction (iv) one site for S_N2' coupling reaction. All the reactive sites have been extensively used for the construction of variety of heterocyclic structures. The nucleophilic substitution of bromine, S_N2'-coupling reactions of different Grignard reagents, Wittig reagents, different nucleophiles and the Diels-Alder reactions with dialkyl bromomethylfumarates have been extensively used for the synthesis of several bioactive natural products and unnatural compounds. The concise account on the reactions of dialkyl bromomethylfumarate clearly demonstrate an impression about its synthetic utility and further scope in synthetic organic chemistry.

2A.3. References

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2B. Section B

Synthesis and S_N2' Grignard Coupling Reactions with Dialkyl Bromomethylfumarate

This section features the following topics:

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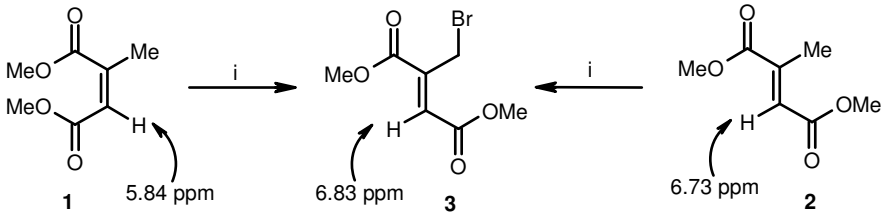
2B. Section B: Synthesis and S_N2' Grignard Coupling Reactions with Dialkyl Bromomethylfumarate

2B.1. Synthesis of Dimethyl Bromomethylfumarate

The reaction of citraconic anhydride with methanol/H_2SO_4 under reflux gave the desired diester **1** in 75% yield.[1] The diester **1** on treatment with NBS/AIBN in refluxing carbon tetrachloride underwent smooth allylic bromination to yield bromodiester **3** in 85% yield.[2] The high difference in vinylic proton signal in product **3** and starting material **1** (vinylic proton signal appears at 6.83 and 5.84 for **3** and **1** respectively) forced us to investigate whether an in situ isomerization accompanied the allylic bromination. The process of isomerization of (*Z*)-isomer to (*E*)-isomer along with allylic bromination was confirmed by obtaining the same product **3** from the corresponding dimethyl methylfumarate (**2**) under the same set of reaction conditions (Scheme 1). (vinylic proton signal appeared at 6.83 and 6.79 ppm, when the ^{1}H NMR of **3** was recorded in $CDCl_3$ and CCl_4 respectively for compounds obtained from both the starting materials). In Section 2B.2 we have described in detail the NBS-DBP/AIBN induced *Z*- to *E*- carbon-carbon double bond isomerization with several types of olefins having a variety of substituents.



Scheme 1. *Reagent, condition and yield*: (i) NBS, AIBN, CCl_4, reflux 12 h (85%).

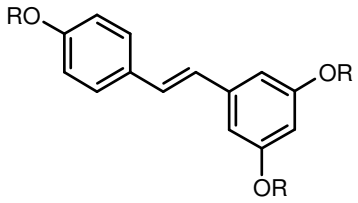
2B.2. *N*-Bromosuccinimide-Dibenzoyl Peroxide/ Azobis-isobutyronitrile: A Reagent for *Z*- to *E*-Alkene Isomerization

2B.2.1. Background

The generation of carbon-carbon double bonds in geometrically pure form is one of the most important reactions in synthetic organic chemistry[3] and many elegant methods are known in the literature for achieving the same.[4] However, in many of these reactions, such as Wittig reaction or olifine metathesis, mixtures of *Z*- and *E*-alkenes are also formed[4,5]

and radical[6] or photochemical[7] reactions have been used to transform the *Z*-isomers to the corresponding *E*-isomers. Photochemical methods for these isomerizations, with or without sensitization, are often not satisfactory as the reactions are very slow and give rise to undesired product. Several methods involving catalysis by diaryl disulfide,[6b,c] iodine,[7a] R_3SnH-Et_3B (R = Ph or *n*-Bu)[6d] are reported in the literature. Amongst them the former two got widespread applicability over a range of substrates. Isomerization of (*Z*)-stilbene to the *E*-isomer and dimethyl maleate to dimethyl fumarate are usually catalyzed by bromine via the reversible addition of a bromine radical to the double bond.[8] Spencer *et al*. have demonstrated[9] a facile palladium(II)-catalyzed isomerization of *Z*-arylalkenes to *E*-arylalkenes, and have used this methodology in the synthesis of trimethoxy resveratrol[10] (Figure 1) to demonstrate its synthetic utility. The high biological importance of resveratrol

Figure 1



R = Me; Trimethoxy resveratrol (**4**)
R = H; Resveratrol (**5**)

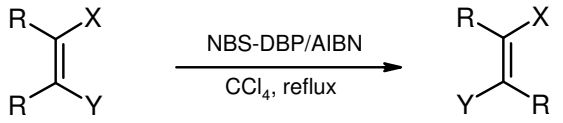
prompted them to synthesize it as a single geometrical isomer and they achieved it by first synthesizing it via Wittig reaction in 92% yield (1:1 mixture of *Z*- and *E*-isomers) followed by isomerization of the obtained mixture to *E*-isomer in 94% yield. Recently, Pemak and co-workers[11] have reported the isomerization of (*Z*)- to (*E*)-alkene in protic, imidazolium ionic liquids. While, Jung and co-workers[12] have reported a efficient synthetic method for producing geometrically pure (*E*)-alkenes from (*Z*)-alkenes using palladium acetate, tributyltin hydride, and triethylamine.

The provision of a new method for isomerization of *Z*-olefins to *E*-olefins is a task of current interest and in this context; we herein present our studies on an easy access to several types of geometrically pure *E*-olefins using *N*-bromosuccinimide-dibenzoyl peroxide/azobisisobutyronitrile (NBS-DBP/AIBN) as a reagent for *Z* to *E* isomerization.

2B.2.2. Present Work Results and Discussion

In our on going studies on the synthesis of recently isolated bioactive natural products, we carried out the reaction of dimethyl methylmaleate (**1**) with NBS-AIBN and obtained dimethyl bromomethylfumarate (**3**) in 85% yield. Both allylic bromination and isomerization of the carbon-carbon double bond took place in one-pot via an in situ addition-elimination of the bromine radical, which was further confirmed by obtaining the same product from dimethyl methylfumarate (**2**) (Table 1, Entry 3). On the basis of this observation, we prepared a systematic plan to study the NBS-DBP/AIBN induced *Z*- to *E*-carbon-carbon double bond isomerization with several types of olefins having variety of substituents. The results are presented in Scheme 1 and Table 1. Maleic acid (**4**), on treatment with NBS-DBP in refluxing acetic acid, gave fumaric acid (**5**) in 90% yield, while dimethyl maleate (**6**), on treatment with NBS-AIBN in refluxing CCl_4 gave dimethyl fumarate (**7**) in 98% yield (Entries 1 and 2). The process of carbon-carbon

Scheme 1



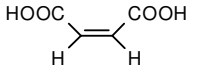
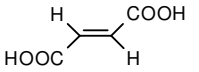
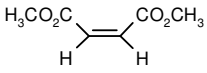
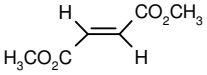
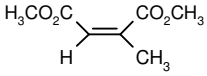
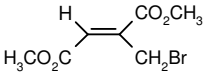
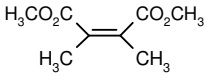
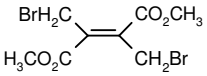
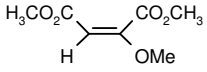
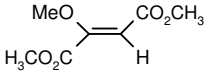
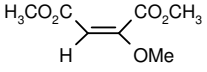
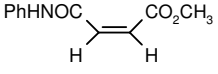
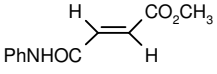
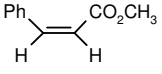
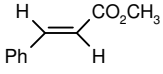
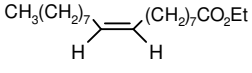
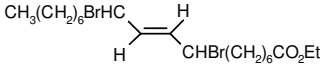
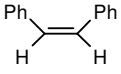
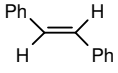
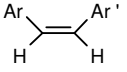
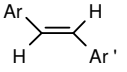
Z-Alkenes *E*-Alkenes

R = H, CO_2H, CO_2Me; X/Y = H, Me, Alkyl, CH_2Br, $CHBr_2$, Ph, Aryl, CO_2Me, CONHAr

double bond isomerization was found to be slow in tetrasubstituted dimethyl dimethylmaleate (**8**) using 1.1 equivalents of NBS while the use of 2.5 equivalent of NBS gave a 1:1 mixture of dimethyl dibromomethylmaleate and dimethyl dibromomethylfumarate (**9**) in 96% yield (Entry 4). Interestingly, dimethyl methoxymaleate (**10**), on treatment with NBS-DBP in refluxing CCl_4, did not show any reaction. On the contrary, the corresponding dimethyl methoxyfumarate (**11**) underwent very smooth carbon-carbon double bond isomerization to yield dimethyl methoxymaleate (**10**) in 92% yield, revealing that the *E*-isomer is thermodynamically more stable than the *Z*-isomer, probably due to the presence of the extended conjugation involving the lone pairs of electrons on oxygen atom in the -OMe group of the *E*-isomer (Entries 5 and 6). Methyl maleanilate (**12**) and methyl *Z*-cinnamate (**14**) under similar reaction conditions gave the corresponding *E*-products in 90% and 96% yields respectively (Entries 7 and 8).

As expected, methyl *Z*-oleate (**16**) on treatment with NBS-DBP in refluxing CCl_4 gave the methyl *E*-dibromooleate (**17**) in 95% yield, while under the same set of reaction conditions

Table 1. NBS-DBP/AIBN Induced carbon-carbon double bond isomerizations

Sr. No.	Starting Material[a]	Reaction Conditions	Product	% Yield
1	 **4**	NBS (2.0 eqv.), DBP, AcOH, reflux, 6 h	 **5**	90
2	 **6**	NBS (1.1 eqv.), AIBN, CCl_4, reflux, 1 h	 **7**	98
3	 **1**	NBS (1.5 eqv.), AIBN, CCl_4, reflux, 12 h	 **3**	85
4	 **8**	NBS (2.5 eqv.), DBP, CCl_4, reflux, 2 h	 **9**	46[b]
5	 **10**	NBS (2.0 eqv.), DBP, CCl_4, reflux, 8 h	No Reaction	0
6	 **11**	NBS (2.0 eqv.), DBP, AcOH, reflux, 8 h	 **10**	92
7	 **12**	NBS (4.0 eqv.), DBP, CCl_4, reflux, 10 h	 **13**	90
8	 **14**	NBS (1.1 eqv.), AIBN, CCl_4, reflux, 2 h	 **15**	96
9	 **16**	NBS (2.5 eqv.), DBP, CCl_4, reflux, 4 h	 **17**	95
10	 **18**	NBS (2.0 eqv.), DBP, CCl_4, reflux, 3 h	 **19**	~ 100
11	 **20**	NBS (1.1 eqv.), DBP, CCl_4, reflux, 2 h	 **21**	60[c]

[a] The *Z*-alkenes and geometric mixtures of alkenes were prepared by using known literature procedures.[70,75] [b] 50% Dimethyl dibromomethylmaleate was also formed. [c] 10-15% Mixture of ring brominated products was also obtained. Ar = 3,5-dimethoxyphenyl; Ar ′ = *p*-methoxyphenyl.

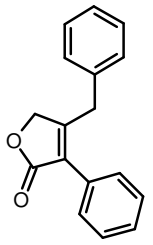
Z-stilbene (**18**) was transformed into *E*-stilbene (**19**) in ~100% yield (Entries 9 and 10). *Z*-Trimethoxystilbene (**20**), on treatment with NBS (1.1 equiv.) and DBP (catalytic) in refluxing CCl_4 gave the trimethoxy derivative of bioactive resveratrol (**21**)[10] in 60% yield

and due to the mesomeric effect of the methoxy groups, formation of mixtures of ring brominated *E*-trimethoxystilbene derivatives was also observed in 10-15% yield (Entry 11). As indicated in Table 3, we could isomerize different types of olefins with a variety of substituent patterns from *Z*- to *E*- forms using NBS-DBP/AIBN and the present method is simple and efficient.

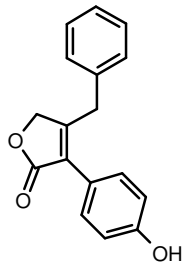
2B.3. Synthesis of Gymnoascolide A

2B.3.1. Background

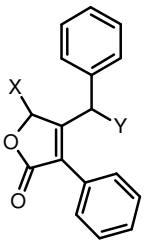
Recently gymnoascolides A-C (**22**, **23a/23b**) were isolated from the Australian soil ascomycete *Gymnoascus reessii*[13] and *Malbranchea filamentosa* IFM41300.[14] The 2-phenyl-3-benzylmaleic anhydride was isolated from *Aspergillus nidulans*.[15] Gymnoascolides A-C possess moderate activity against the pathogenic plant fungus *Septoria nodorum*.[13] Gymnoascolide A also possesses vasodilatory activity and it inhibits Ca^{2+} induced vasocintraction in aortic rings pretreated with high K^+ or norepinephrine.[14] The 2-phenyl-3-benzylmaleic anhydride possesses plant growth regulatory activity and it effectively accelerates the root elongation of radish seedlings.[15] The gymnoascolides possess possess a rare structural motif, only a few examples are known in the literature



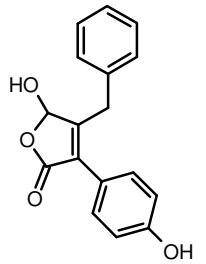
Gymnoascolide A (**22**)[13]



Eutypoid A (**24**)[16]



Gymnoascolide B (**23a**, X = *β*-OMe, Y = OH)[13]
Gymnoascolide C (**23b**, X = *α*-OMe, Y = OH)[13]



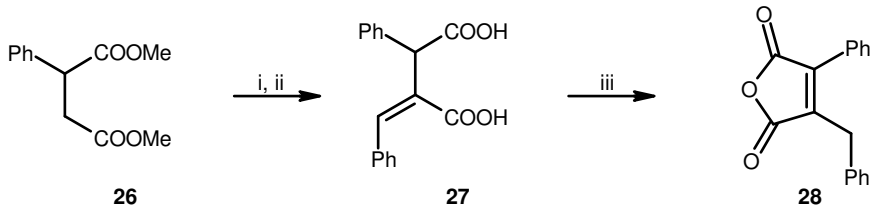
Microperfuranone (**25**)[17]

Figure 2. Naturally occurring bioactive butenolactones **22**-**25**

such as eutypoid A (**24**), isolated from a south China sea marine fungus of the genus *Eutypa*[16] and microperfuranone (**25**), isolated from terrestrial fungi *Anixiella micropertusa*[17] (Figure 2).

2B.3.1.1: Momose's approach towards 2-phenyl-3-benzylmaleic anhydride

Momose and co-workers[18] have reported the synthesis of 2-phenyl-3-benzylmaleic anhydride. The stobe condensation of dimethyl phenylsuccinate (**26**)[19] with benzaldehyde followed by hydrolysis with potassium hydroxide in aqueous ethanol gave the corresponding dicarboxylic acid **27**, which on heating in acetic anhydride gave 2-phenyl-3-benzylmaleic anhydride (**28**) in 23% overall yield (Scheme 2).



26 **27** **28**

Scheme 2. *Reagents and conditions and yields*: (i) PhCHO, *t*-BuOK; (ii) KOH, EtOH; (iii) Ac_2O, reflux (23%).

In order to study the structure-activity relationship of these types of natural and unnatural small size molecules, a flexible synthetic approach that will allow mono/dialkyl/allyl/benzyl/aryl functionalization of both the vinylic carbons, with the presence of several types of heteroatoms in five membered ring needs to be developed.

2B.3.2. Present Work Results and Discussion

The dimethyl bromomethylfumarate (**3**) has six alternate sites available for nucleophilic reactions, viz (i) two ester carbonyls for 1,2-additions (ii) two sites for Michael addition (iii) allylic bromo atom for nucleophilic substitution reaction (iv) one site for S_N2' coupling reaction (Figure 3).

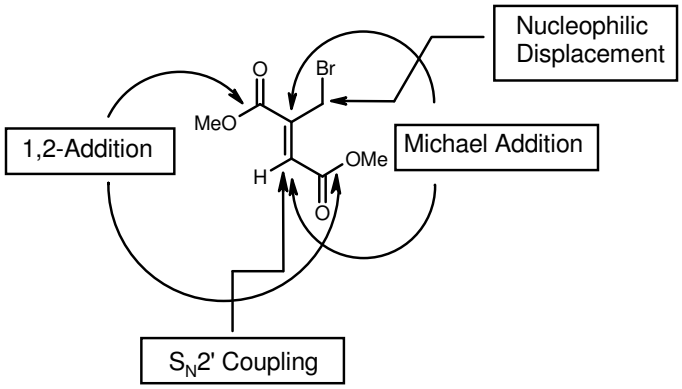
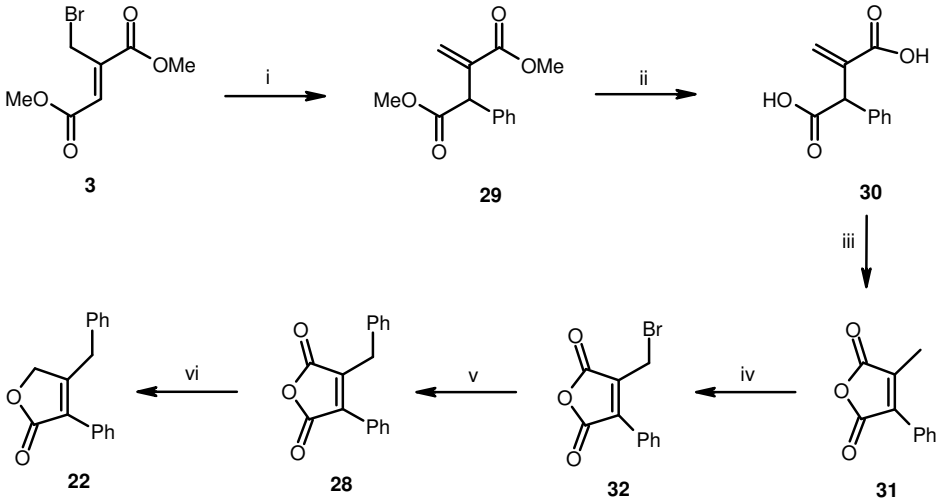


Figure 3

We envisaged the use of S_N2' coupling reaction on dimethyl bromomethylfumarate (**3**) as a key step for the stepwise construction of natural product gymnoascolides. The chemoselective S_N2' coupling reaction of phenylmagnesium bromide with **3** exclusively gave the desired arylalkylidenesuccinic acid diester **29** in 73% yield (Scheme 3). The base catalyzed hydrolysis of diester **29** to diacid **30** (92%) followed by acetic anhydride induced ring closure gave the expected anhydride **31** in nearly 100% yield. In this reaction, both the formation of succinic anhydride intermediate and carbon-carbon double bond migration took place in one-pot. The NBS-bromination of the allylic carbon in the anhydride **31** furnished the required bromoanhydride **32** in 80% yield. We did not observe any phenyl ring bromination under our reaction conditions. The chemoselective allylic substitution of the bromo atom in anhydride **32** with phenylmagnesium bromide gave the 2-phenyl-3-benzylmaleic anhydride (**28**) in 45% yield. In anhydride **28**, one of the carbonyl groups is in conjugation with the phenyl ring, while the other one is sterically hindered because of an adjacent phenyl ring. Hence the regeioselective reduction of one of the carbonyls to obtain **22** is a challenging task. In our hands the sodium borohydride reduction of anhydride **28** was not selective and we obtained an inseparable mixture of both the regioisomers in 74% yield (desired:undesired = 1:2, by ^{1}H NMR). Fortunately, N-selectride regioselectively reduced the unhindered carbonyl in anhydride **28** at -78 °C and exclusively furnished the natural product gymnoascolide A (**22**) in 90% yield. The analytical and spectral data obtained for these natural products **28** and **22** ware in complete agreement with the reported data.[13-15,18]

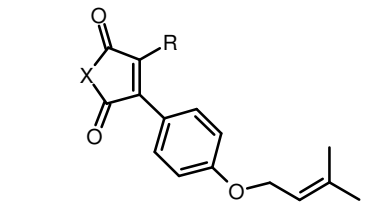


Scheme 3. *Reagents, conditions and yields*: (i) C_6H_5MgBr (1.50 equiv.), THF, HMPA, 0 ºC, 0.5 h (73%); (ii) (a) LiOH (10.00 equiv.), THF + H_2O (3:1), rt, 18 h, (b) H^+/HCl (92%); (iii) Ac_2O, reflux, 1.5 h (~100%); (iv) NBS (1.50 equiv.), dibenzoyl peroxide (10 mol%), CCl_4, reflux, 12 h (80%); (v) C_6H_5MgBr (5.00 equiv.), THF, HMPA, CuI, 0 ºC, 8 h (45%); (vi) N-Selectride (3.00 equiv.), THF, –78 ºC, 1 h (90%).

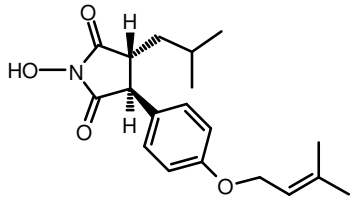
2B.4. Synthesis of Natural Cytotoxic Camphorataimides B and C

2B.4.1. Background

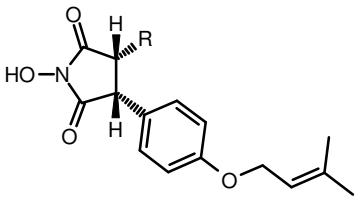
Recently camphorataanhydride/imides were isolated from the mycelium of *Antrodia camphorata* and the imides **33b**,**c** showed appreciable cytotoxic effects on LLC tumor cells.[20] The analogous himanimides A-D possessing antimicrobial and antifungal activities



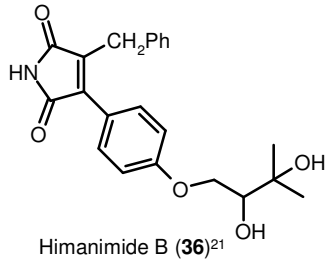
Camphorataanhydride A [**33a**, X = O, R = $CH_2CH(CH_3)_2$][20]
Camphorataimide B [**33b**, X = NH, R = $CH_2CH(CH_3)_2$][20]
Camphorataimide C [**33c**, X = NOH, R = $CH_2CH(CH_3)_2$][20]
Himanimide A [**33d**, X = NH, R = CH_2Ph][21]
Himanimide C [**33e**, X = NOH, R = CH_2Ph][21]



Camphorataimide E (**35**)[20]



Camphorataimide D [**34a**, R = $CH_2CH(CH_3)_2$][20]
Himanimide D [**34b**, R = CH_2Ph][21]



Himanimide B (**36**)[21]

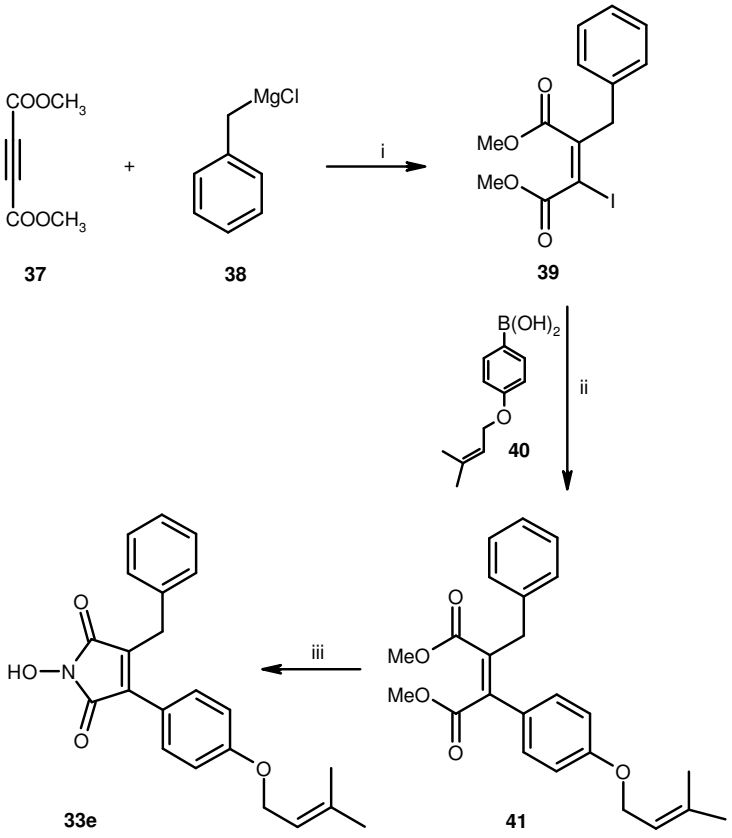
Figure 4. Naturally occurring bioactive camphorata/himan-anhydride/imides **33**-**36**

were recently isolated from basidomycete culture of *Serpata himantoides*[21] (Figure 4). The biological screening studies of these naturally occurring anhydrides/imides **33**-**36** revealed that their activity is linked to the *N*-hydroxylated maleimide moiety.[20,21]

2B.4.1.1: Synthetic approachs towards himanimide C and camphorataanhydride/imides

[A] *Selles's approach towards himanimide C*

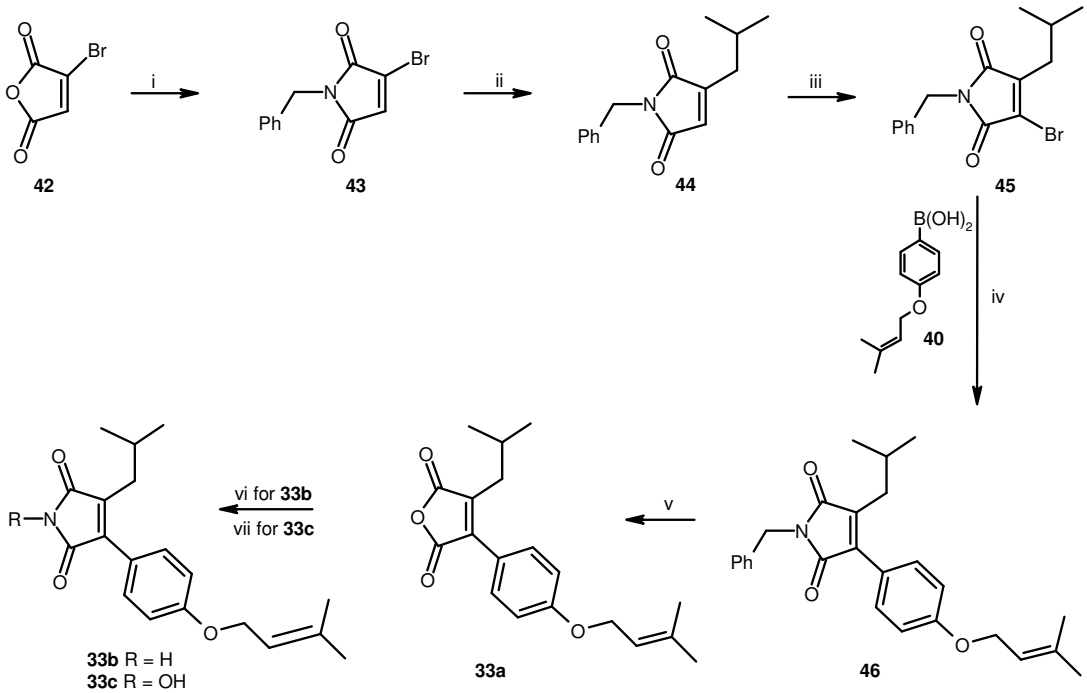
Patrice Selles has reported[22] a flexible approach to the himanimide scaffold using a copper mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate (DMAD) as a key step.[23,24] The reaction of benzyl magnesium chloride (**38**) with DMAD (**37**) in the presence of $CuBr{\cdot}Me_2S$ followed by iodine addition gave the tetrasubstituted vinyl iodide **39** as a single isomer in 50% yield. The compound **39** on Suzuki cross coupling reaction[25] with boronic acid **40** furnished the diester **41**, which was readily transformed by the complete saponification-cyclization-imide formation sequence into the himanimide C **33e** (Scheme 4).



Scheme 4. *Reagents, conditions and yields*: (i) $CuBr{\cdot}Me_2S$, THF, - 40 °C, 2 h, I_2, - 40 °C to rt (50%); (ii) $Pd(PPh_3)_4$ (2.5 mol%), toluene/EtOH/Na_2CO_3 (2 M in H_2O): 3/1/1, reflux, 2 h (72%); (iii) (a) 2 N NaOH, reflux, 4 h, (b) 1 N HCl, rt, (c) Hydroxylamine phosphate, H_2O, reflux, 7 h (25%).

[B] *Stewart's approach towards camphorataanhydride/imides*

Recently Stewart *et al*[26] have reported the synthesis of camphorataanhydride/imides by using the Negishi and Suzuki cross coupling reactions. Bromomaleic anhydride (**42**) was converted to the *N*-benzyl derivative **43**. The corresponding metal mediated conjugate substitution reaction using the Negishi[27] protocol gave alkyl maleimide **44** in 49% yield. Bromination of **44** using bromine and a catalytic amount of aluminium tribromide afforded vinyl bromide **45**. Suzuki cross coupling reaction[28] of **45** with boronic acid **40** furnished disubstituted imide **46**, which on hydrolysis and cyclization gave the natural product camphorataanhydride A (**33a**). The synthesis of the natural product camphorataimide B (**33b**) was completed by treatment of anhydride **33a** with urea to afford **33b** in 60% yield. Similarly, the treatment of **33a** with *N*-hydroxylamine hydrochloride gave camphorataimide C (**33c**) in 79% yield (Scheme 5).



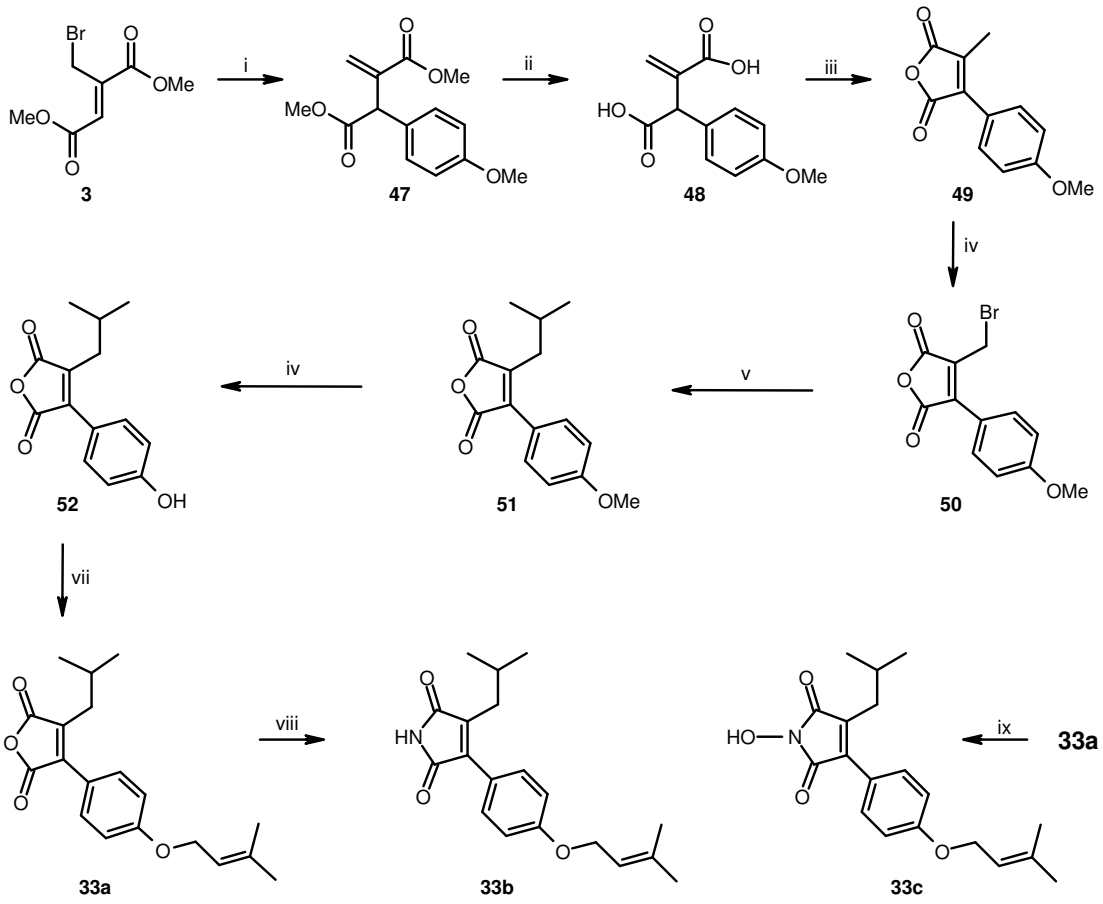
Scheme 5. *Reagents, conditions and yields*: (i) $BnNH_2$, AcOH, 50 °C, 16 h (83%); (ii) $Ni(PPh_3)_2Cl_2$, *t*-BuZnBr, THF, 20 °C, 4 h (49%); (iii) Br_2, $AlBr_2$, CH_2Cl_2, 0-20 °C, 1 h (55%); (iv) **8**, $Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$, Cy_2NMe, dioxane, 20 °C, 3 h (56%); (v) (a) KOH, THF/MeOH (1:2), 78 °C, 12 h, (b) 2 N HCl, 20 °C (63%); (vi) Urea, 140 °C, 4 h (60%); (vii) $NH_2OH{\cdot}HCl$, pyridine, 100 °C, 12 h (79%).

We feel that these simple natural products **33**-**36** are of interest as new leads. To study the structure-activity relationship of these type of natural and unnatural molecules, a flexible

synthetic approach that will allow mono/di-alkyl/allyl/benzyl/aryl functionalization of both the available carbons with several types of heteroatoms in five membered ring is essential.

2B.4.2. Present Work Results and Discussion

We envisaged dimethyl bromomethylfumarate (**3**) as a potential starting material for the stepwise construction of natural products **33a**-**c** and their various analogs. The chemoselective S_N2' coupling reaction of *p*-methoxyphenylmagnesium bromide with **3** exclusively gave the desired arylalkylidenesuccinic diester **47** in 73% yield (Scheme 6). The base catalyzed hydrolysis of diester **47** to diacid **48** followed by acetic anhydride



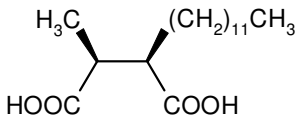
Scheme 6. *Reagents, conditions and yields*: (i) *p*-CH_3O-C_6H_4MgBr (1.50 equiv.), THF, HMPA, –20 ºC, 0.5 h (73%); (ii) (a) LiOH (10 equiv.), THF + H_2O (3:1), rt, 18 h, (b) H^+/HCl (92%); (iii) Ac_2O, reflux, 1.5 h (~100%); (iv) NBS (1.50 equiv.), DBP (10 mol%), CCl_4, reflux, 12 h (80%); (v) C_3H_7MgBr (5 equiv.), CuI (0.10 equiv.), THF, HMPA, –5 to 0 ºC, 8 h (45%); (vi) BBr_3 (5 equiv.), DCM, –78 to 0 ºC, 12 h (91%); (vii) 3,3-Dimethylallyl bromide (1.20 equiv.), K_2CO_3 (10 equiv.), acetone, reflux, 2 h (90%); (viii) Urea (1.20 equiv.), 130 ºC , 1 h (81%); (ix) $NH_2OH.HCl$, pyridine, reflux, 2 h (76%).

induced ring closure gave the expected anhydride **49** in nearly 100% yield. In this reaction, both the formation of succinic anhydride intermediate and carbon-carbon double bond migration took place in one-pot. The NBS-bromination of the allylic carbon in the anhydride **49** furnished the required bromoanhydride **50** in 80% yield. We did not observeany ring bromination or demethylation of methoxy group in **49/50** under our reaction conditions. The chemoselective allylic substitution of bromo atom in anhydride **50** with isopropylmagnesium bromide gave the 2-(*p*-methoxyphenyl)-3-isobutylmaleic anhydride (**51**) in 45% yield. Boron tribromide induced demethylation of **51** provided the corresponding 2-(*p*-hydroxyphenyl)-3-isobutylmaleic anhydride (**52**) in 91% yield. Allylation of anhydride **52** with 3,3-dimethylallyl bromide in the presence of K_2CO_3 furnished the naturally occurring camphorataanhydride A (**33a**) in 90% yield. The anhydride **33a** was heated with urea at 130 ºC for one hour to obtain the natural bioactive camphorataimide B (**33b**) in 81% yield. Treatment of anhydride **33a** with hydroxylamine hydrochloride in refluxing pyridine gave the desired third bioactive natural product camphorataimide C (**33c**) in 76% yield. The analytical and spectral data obtained for these three natural products **33a-c** were in complete agreement with the reported data.[20]

2B.5. Synthesis of (+)-*erythro*-Roccellic Acid

2B.5.1. Background

(+)-Roccellic acid [(2*R*, 3*S*)-2-dodecyl-3-methylbutanedioic acid, **53**] occurs in lichens[29,30] and it was first isolated in 1898. In the past century it has been isolated from the following several lichen species: *Roccella Capensis,*[31] *R. fuciformis,*[32,33] *R. hypomecha,*[34] *R. gayana,*[35] *R. fucoides,*[35,36] *R. condensata,*[37] *R. montagnei*,[38,39] *Dirinaria aegialita,*[40] *D. applanata,*[40] *D. confusa saxicola,*[40] *D. consimilis,*[40] *D. leopoldii,*[40] *Pyxine berteriana,*[40] *P. caesiopruinosa,*[40] *P. pungens,*[40] *Lobodirina cerebriformes,*[41] *L. mahuiana,*[42] *Acarospora chlorophana,*[43] *Lecanora riparia,*[44] *L. rupicola,*[45,46] *L. sordida,*[47,48] *Lepraria latebrarum,*[49] *L. aeruginosa,*[50] *Dirina lutosa,*[51] *Crocynea membranacea*[52,53] and more recently from *Haematomma nemetzii*[54] and *Tornabena. Scutellifera*[54] with a major contribution from Siegfried Huneck's group. The structural assignment of roccellic acid **53** has been done on the basis of analytical and spectral data.[45,47,52,54]



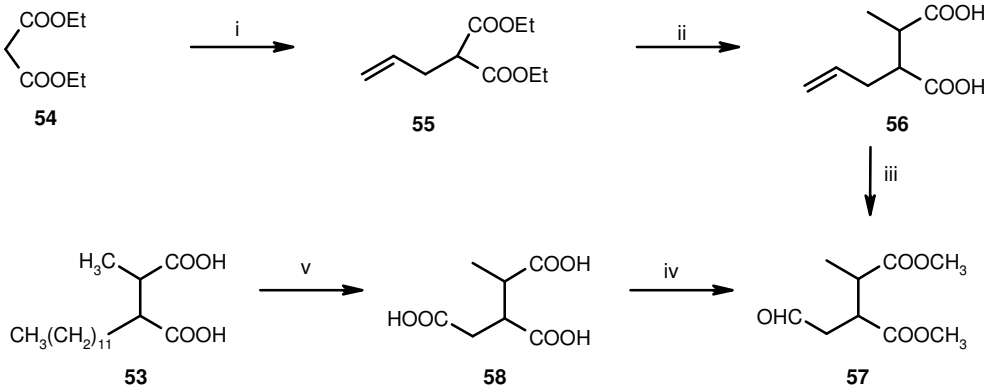
(2*R*, 3*S*)-2-Dodecyl-3-methylbutanedioic acid (**53**)

Its absolute configuration has been established by Åkermark by degrading **53** to its two isomeric monomethyl esters.[52,55] roccellic acid **53** possesses antitubercular activity[56-58] and concentration dependent plant growth promotor[59-61]/inhibitor[61,62] activity. It is also used for (i) synthesis of structural analogues of the antibiotic actinonin,[63] (ii) precipitation of human serum albumin[64] and (iii) preparation of colored metal complexes.[65]

2B.5.1.1: Synthetic Approaches Towards (±)-erythro-Roccellic acid (71) and (+)-erythro-Roccellic acid (71a)

[A] *Åkermark's approach*

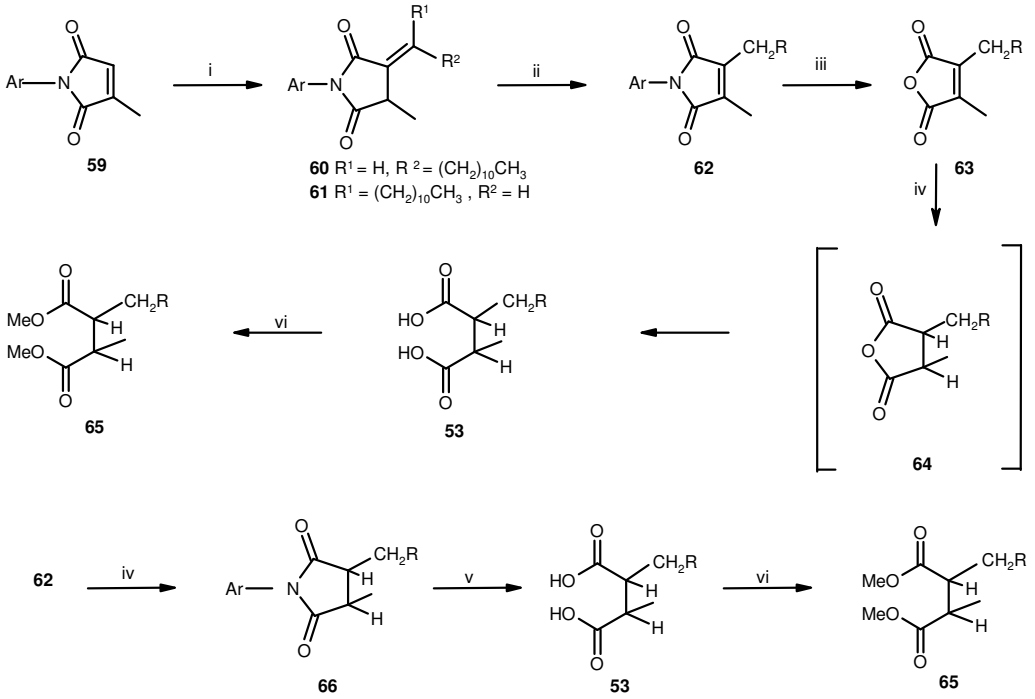
The first synthesis of unnatural *threo*-(±)-roccellic acid was completed by Åkermark and co-workers[66,67] starting from diethylmalonate (**54**). Diethylmalonate on allyalation gave dieater **55** which on reaction with *α*-bromoethyl propionate followed by hydrolysis furnished diacid **56**. Esterification and ozonolysis of **56** gave aldehyde **57** which on oxidation and hydrolysis furnished tricarboxylic acid **58**. Tricarboxylic acid **58** on electrolytic anodic coupling with dodecanoic acid gave (±)-*erythro*-roccellic acid (**53**) in 0.026% overall yield (Scheme 7) .



Scheme 7. *Reagents, conditions and yields*: (i) Allyl bromide, NaOEt, EtOH; (ii) (a) *α*-Bromo ethylpropeonate, NaH, dioxane, (b) NaOH, H_2O, (c) Neat, 160 °C; (iii) (a) CH_2N_2, Zn, ether, 0 °C, (b) O_3, EtOAc, -80 °C; (iv) (a) H^+/H_2O, (b) $KMnO_4$, EtOAc; (v) (a) Electrolytic anodic coupling $CH_3(CH_2)_{10}COOH$, (b) Four recrystallisations from EtOAc.

[B] *Approach from our group*

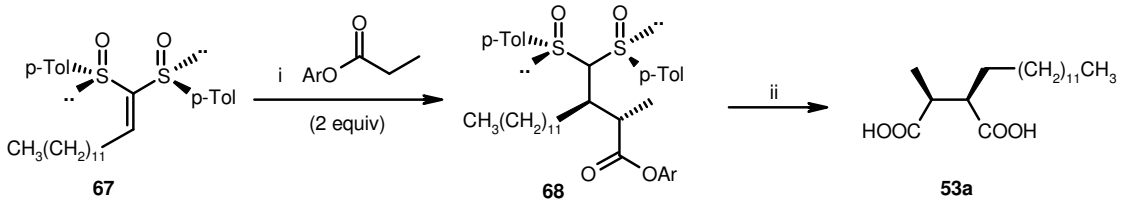
(±)-*Erythro*-roccellic acid **53** has been synthesized in our group[68] by employing the Wittig condensation of methyl(triphenylphosphoranylidene)succinimide with aliphatic aldehydes. The mixture of citraconimide **59**, TPP and dodecanal in refluxing glacial acetic acid gave a combination of geometric isomers **60** and **61** in 82% yield via Wittig reaction. The mixture of exo-isomers **60** and **61** on refluxing with triethylamine and THF mixture (1:1) furnished dodecylmethylmaleimide **62** in 98% yield. The maleimide **62** on alkaline hydrolysis followed by acidification gave the desired dodecylmethylmaleic anhydride (**63**) which on hydrogenation in presence of Adam's catalyst gave the desired (±)-*erythro*-roccellic acid **53** in 60% yield. The maleimide **62** on hydrogenation in presence of Adam's catalyst exclusively furnished the desired *cis*-succinimide derivative **66** in 95% yield. The *cis*-succinimide derivative **66** on hydrolysis furnished the (±)-*erythro*-roccellic acid **53** in 98% yield which was further characterised as its dimethyl ester **65** (Scheme 8).



Scheme 8. *Reagents, conditions and yields*: (i) TPP, AcOH, dodecanal, reflux, 10 h (82%); (ii) TEA, THF, reflux, 48 h (98%); (iii) (a) KOH, THF, MeOH, H_2O, reflux, 2 h; (b) H^+/HCl (98%); (iv) Adam's catalyst, petroleum ether, H_2, rt, 10 h (**53**: 60%; **66**: 95%); (v) CF_3COOH, conc. HCl, reflux, 48 h (98%); (vi) CH_2N_2, Et_2O, rt, 2 h, (98%).

[C] *Fensterbank's asymmetric synthesis*

Recently, Fensterbank and coworkers[69] have completed the first asymmetric synthesis of (+)-*erythro*-roccellic acid **53a**, by employing a highly diasteroselective addition of a lithium ester enolate to a bisulfinyl acceptor as a key step. The synthesis involves the addition of lithium enolate of Heathcock's ester to alkylidene acceptor **67** to give adduct **68** (major diasteromer, 79% yield) accompanied by the minor diastereomer (10% yield). The major diastereomer **68** on Pummerer rearrangement followed by double saponification furnished (+)-*erythro*-roccellic acid **53a** (Scheme 9) .

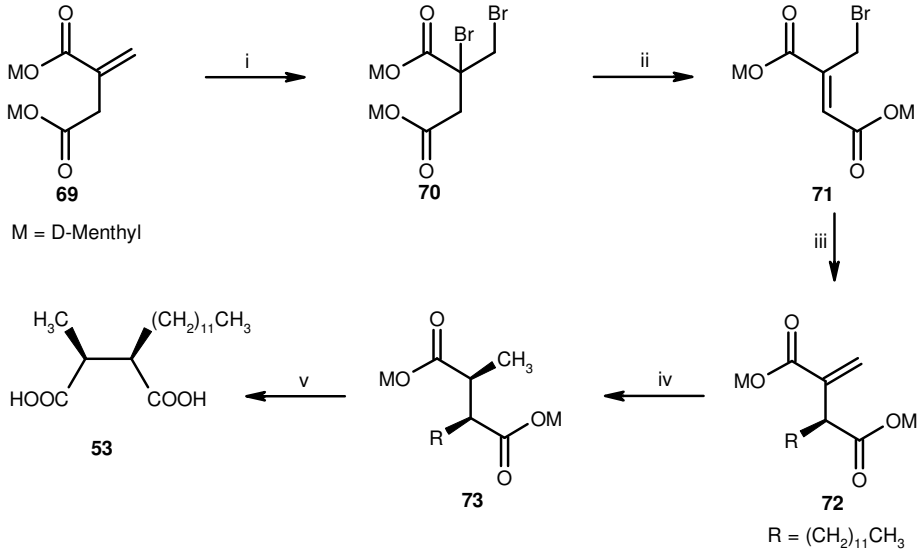


Scheme 9. *Reagents, conditions and yields*: (i) LDA, THF, -78 °C (79%); (ii) (a) CF_3COOH, pyridine, (b) LiOH, H_2O_2 (50%).

2B.5.2: Present Work: Results and Discussion

We envisaged D-menthol can be used as chiral auxillary to induce chirality in the S_N2' coupling reaction of dodecylmagnesium bromide with dimenthyl bromomethylfumarate. (+)-Dimenthyl itaconate **69** was prepared by the reaction of itaconic anhydride with (+)-menthol in 80% yield. Bromination of diester **69** using Br_2 in CCl_4 gave the dibromoester **70** in 90% yield. Dehydrobromination of dibromoester **70** with triethylamine in CCl_4 furnished dimenthyl bromomethylfumarate **71** in 92% yield. The stereoselective S_N2' coupling reaction of dodecylmagnesium bromide with **71** gave the itaconate derivative **72** with the desired C_{12} substituent. The ^1H NMR data of product **72** revealed that the reaction was moderately stereoselective and the mixture of two diastereomers was formed in nearly 6.5:3.5 ratio (from the comparison of the relative integrations of the olefinic protons). The TLC of the mixture of diastereomers in **72** did not show any resolution and separation of these two diastereomers by flash column chromatography was also not successful in our hands. The catalytic hydrogenation of the itaconate derivative **72** using Pd/C in MeOH furnished the dimenthyl ester of roccellic acid **73** in 90% yield. The hydrolysis of dimenthyl ester in refluxing mixture of AcOH/HCl (3:1) furnished the natural product (+)-

erythro-roccellic acid **53** with 85% yield and 33% *de* (from the comparison of specific rotation with the reported natural product)[29] (Scheme 10). Further work is under progress in our laboratory to improve the diastereomeric excess using chiral auxiliaries derived from camphor.



Scheme 10. *Reagents, conditions and yields*: (i) Br_2, CCl_4, rt, 12 h (90%); (ii) Et_3N, CCl_4, rt, 6 h (92%); (iii) $C_{12}H_{25}MgBr$ (1.5 equiv.), THF, HMPA, 0 ºC, 0.5 h (73%) (33% *de*); (iv) H_2, Pd-C, MeOH, rt, 4 h (90%); (v) AcOH:HCl (3:1), reflux, 10 h (85%) (33% *ee*).

2B.6. Summary

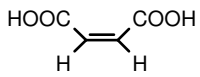
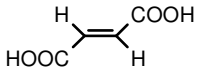
In summary, in this section we have described the synthetic strategies for the synthesis of naturally occurring 2-phenyl-3-benzylmaleic anhydride, camphorataanhydride, camphorataimides B & C and (+)-*erythro*-roccellic acid in recemic and enantiomerically pure form. We have also presented the essence of methods employed in the literature for the *Z*- to *E*- carbon-carbon double bond isomerization. We have demonstrated that the reagent NBS-DBP brings about both allylic bromination and *Z*- to *E*- carbon-carbon double bond isomerization. The *Z*-alkenes without allylic hydrogens in pure form or mixtures of geometric isomers can be easily transformed into the corresponding *E*-alkenes using NBS-DBP/AIBN in quantitative yields.[70] The present studies also provide a useful caution mark to the chemists attempting allylic bromination of *Z*-alkenes. We have demonstrated the synthesis of natural 2-phenyl-3-benzylmaleic anhydride (5-steps, 24%) and the first synthetic approach to bioactive natural product gymnoascolide A (6-steps, 22%). In the present synthesis, the selective Grignard reagent coupling reactions and N-

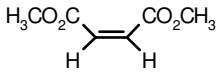
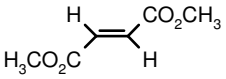
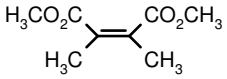
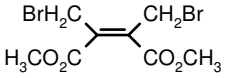
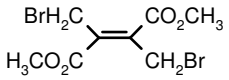
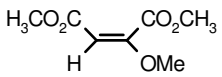
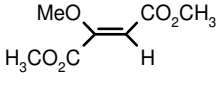
selectride reduction are noteworthy.[71] We have also demonstrated the first synthetic approach to natural camphorataanhydride (7-steps, 20%) and bioactive camphorataimides B & C (8-steps, 16% and 15% respectively). In our present approach the stepwise functionalization and generation of anhydride moiety with a variety of alkyl/allyl/benzyl/aryl groups and conversion of anhydride to a variety of *N*-substituted maleimides is possible. Hence, we feel that our present approach is general in nature and will be useful to design congeners of camphorataimides in search of new lead molecules with better activity.[72] We have also completed the synthesis of (+)-*erythro*-roccellic acid (5 steps, 46% yields) in 33% *ee* by using *D*-menthol as chiral auxillary. Further work is under progress in our laboratory to improve the diastereomeric excess using the suitable chiral auxiliaries derived from camphor.

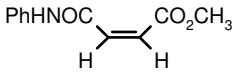
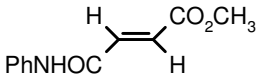
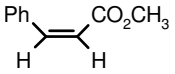
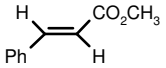
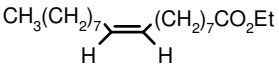
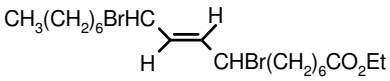
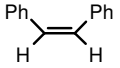
2B.7. Experimental section

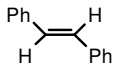
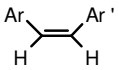
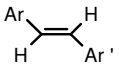
Melting points are uncorrected. The ^{1}H NMR spectra were recorded on Bruker AC 200 NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on either Bruker AC 200 NMR spectrometer (50 MHz), Bruker AC 300 NMR spectrometer (75 MHz) or Bruker AC 500 NMR spectrometer (125 MHz). The FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. Column chromatographic separations were carried out on silica gel (60-120 mesh). Commercially available citraconic anhydride, bromobenzene, magnesium turnings, HMPA, *N*-bromosuccinimide, dibenzoyl peroxide, acetic anhydride and N-selectride, 4-bromoanisole, 2-bromopropane, CuI, BBr_3, 3,3-dimethylallyl bromide, urea, hydroxylamine hydrochloride, *D*-menthol, *p*-TSA, Br_2 and dodecyl bromide were used.

General procedure for the isomerization of *Z*-alkenes to *E*-alkenes. A mixture of *Z*-alkene, *N*-bromosuccinimide and catalytic amount of DBP/AIBN (10 mol %) in carbon tetrachloride (5-10 mL per mmol of substrate) was gently refluxed (see Table 1). The mixture was allowed to cool to room temperature and then filtered. The residue was washed with CCl_4 and the combined organic layer was washed with water, 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 obtain the desired *E*-alkene.

 **4** **$C_4H_4O_4$ (116)**	**Mp**:143°C. **IR** (Nujol): ν_{max} 2700-2500, 1707, 1636, 1587, 1568, 1460, 1435, 1263, 1221, 862, 608 cm^{-1}. **^{1}H NMR** (Acetone-d_6, 200 MHz): δ 6.43 (s, 2H), 9.60 (bs, 2H).
 **5** **$C_4H_4O_4$ (116)**	**Mp**: 298-300 °C (sublimes). **IR** (Nujol): ν_{max} 2700-2500, 1703, 1462, 1377, 1277, 928, 721, 644 cm^{-1}. **^{1}H NMR** (Acetone-d_6, 200 MHz): δ 6.80 (s, 2H), 9.89 (bs, 2H).

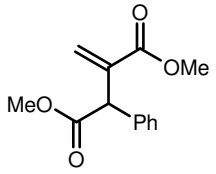
 **6** **$C_6H_8O_4$ (144)**	Thick oil. **IR** (Neat): ν_{max} 1734, 1645, 1439, 1391, 1223, 1165, 1007, 864, 822 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.74 (s, 6H), 6.23 (s, 2H).
 **7** **$C_6H_8O_4$ (144)**	**Mp**: 100–101 °C. **IR** (Nujol): ν_{max} 1726, 1645, 1439, 1310, 1215, 1161, 1034, 980, 758, 669 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.82 (s, 6H), 6.88 (s, 2H).
 **8** **$C_8H_{12}O_4$ (172)**	Thickoil. **IR** (Neat): ν_{max} 1724, 1649, 1437, 1271, 1198, 1167, 1101, 932, 762 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.96 (s, 6H), 3.77 (s, 6H).
 **8a** **$C_8H_{10}O_4Br_2$ (330)**	Thick oil. **IR** (Neat): ν_{max} 1728, 1634, 1435, 1321, 1277, 1217, 1155, 1074, 957 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.85 (s, 6H), 4.25 (s, 4H).
 **9** **$C_8H_{10}O_4Br_2$ (330)**	Thick oil. **IR** (Neat): ν_{max} 1726, 1628, 1435, 1269, 1217, 1161, 1103, 1007, 847, 785 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.92 (s, 6H), 4.50 (s, 4H).
 **10** **$C_7H_{10}O_5$ (174)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1753, 1720, 1630, 1439, 1371 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.71 (s, 3H), 3.75 (s, 3H), 3.89 (s, 3H), 5.21 (s, 1H).
 **11** **$C_7H_{10}O_5$ (174)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1745, 1726, 1641, 1437, 1269 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.75 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 6.18 (s, 1H).

 **12** **$C_{11}H_{11}O_3N$ (205)**	**Mp**: 76-77°C. **IR** (Nujol): ν_{max} 3252, 1732, 1668, 1632, 1597 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.85 (s, 3H), 6.22 (d, *J* = 12 Hz, 1H), 6.45 (d, *J* = 12 Hz, 1H), 7.13 (t, *J* = 8 Hz, 1H), 7.35 (t, *J* = 8 Hz, 2H), 7.67 (d, *J* = 8 Hz, 2H), 10.85 (bs, 1H).
 **13** **$C_{11}H_{11}O_3N$ (205)**	**Mp**: 164-165 °C. **IR** ($CHCl_3$): ν_{max} 3325, 1717, 1684, 1659 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.83 (s, 3H), 6.85-7.65 (m, 7H), 7.90-8.20 (m, 1H).
 **14** **$C_{10}H_{10}O_2$ (162)**	Thick oil. **IR** (Neat): ν_{max} 1724, 1628, 1271, 1200, 1169 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.73 (s, 3H), 5.98 (d, *J* = 12 Hz, 1H), 6.98 (d, *J* = 12 Hz, 1H), 7.20-7.70 (m, 5H).
 **15** **$C_{10}H_{10}O_2$ (162)**	**Mp**: 36-38 °C. **IR** ($CHCl_3$): ν_{max} 1717, 1638, 1281, 1204, 1173 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.82 (s, 3H), 6.46 (d, *J* = 16 Hz, 1H), 7.30-7.60 (m, 5H), 7.71 (d, *J* = 16 Hz, 1H).
 **16** **$C_{20}H_{38}O_2$ (310)**	Thick oil. **IR** (Neat): ν_{max} 1740, 1464, 1373, 1180, 1036, 723 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.86 (t, *J* = 6 Hz, 3H), 1.27 (bs, 25H), 1.60 (m, 2H), 2.00 (m, 2H), 2.27 (t, *J* = 8 Hz, 2H), 4.11 (q, *J* = 8 Hz, 2H), 5.33 (t, *J* = 6 Hz, 2H).
 **17** **$C_{20}H_{36}O_2Br_2$ (468)**	Thick oil. **IR** (Neat): ν_{max} 1730, 1462, 1373, 1180, 1034, 962 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6 Hz, 3H), 1.26 (m, 21H), 1.50-2.00 (m, 4H), 2.29 (t, *J* = 8 Hz, 2H), 4.13 (q, *J* = 8 Hz, 2H), 4.40-4.90 (m, 2H), 5.70-6.00 (m, 2H).
 **18** **$C_{14}H_{12}$ (180)**	Thick oil. **IR** (Neat): ν_{max} 1601, 1493, 1447, 924, 779, 698 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 6.60 (s, 2H), 7.05-7.35 (m, 10H).

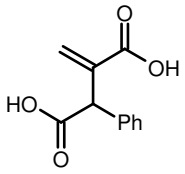
 **19** **$C_{14}H_{12}$ (180)**	**Mp**: 122-123 °C. **IR** ($CHCl_3$): ν_{max} 1599, 1495, 1452, 1217, 962, 762, 692 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 7.12 (s, 2H), 7.15-7.60 (m, 10H).
 **20** Ar = 3,5-dimethoxyphenyl; Ar ′ = *p*-methoxyphenyl **$C_{17}H_{18}O_3$ (270)**	Thick oil. **IR** (Neat): ν_{max} 1600, 1591, 1510, 1250, 1155 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.69 (s, 6H), 3.80 (s, 3H), 6.30-6.40 (m, 1H), 6.44-6.51 (m, 2H), 6.46 (d, *J* = 12 Hz, 1H), 6.56 (d, *J* = 12 Hz, 1H), 6.80 (d, *J* = 10 Hz, 2H), 7.25 (d, *J* = 10 Hz, 2H).
 **21** Ar = 3,5-dimethoxyphenyl; Ar ′ = *p*-methoxyphenyl **$C_{17}H_{18}O_3$ (270)**	**Mp**: 78 °C. **IR** ($CHCl_3$): ν_{max} 1612, 1589, 1510, 1252, 756 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.83 (s, 9H), 6.32-6.44 (m, 1H), 6.60-6.70 (m, 2H), 6.86-6.94 (d, *J* = 16 Hz, 1H), 6.88-6.92 (d, *J* = 8 Hz, 2H), 7.06 (d, *J* = 16 Hz, 1H), 7.46 (d, *J* = 8 Hz, 2H).

2-Phenyl-3-methylenesuccinic acid dimethyl ester (29). A fresh solution of phenylmagnesium bromide in THF was prepared as follows. A solution of bromobenzene (3.76 g, 24.00 mmol) in dry THF (30 mL) was added at room temperature to magnesium turnings (1.73 g, 72.00 mmol) in THF (10 mL) under argon atmosphere with constant stirring in three equal portions at an interval of 10 minutes. The reaction mixture was further stirred at room temperature for 4 h. This freshly generated Grignard reagent was added drop-wise to a solution of **3** (3.79 g, 16.00 mmol) and HMPA (14.34 g, 80.00 mmol) in anhydrous THF (30 mL) under argon atmosphere at 0 ºC and the reaction mixture was further stirred at the same temperature for 30 min. The reaction was quenched by the addition of a saturated ammonium chloride solution (30 mL). Ethyl acetate (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (20 mL X 3). The combined ethyl acetate extract was washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. The obtained residue

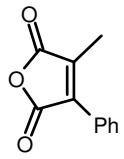
was chromatographed over silica gel using petroleum ether-ethyl acetate mixture (9:1) to give **29** as thick oil; 2.73 g (73%).

 **29** **$C_{13}H_{14}O_4$ (234)**	**IR** (neat): ν_{max} 1738, 1724, 1634, 1448, 1250 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 3.71 (s, 3H), 3.78 (s, 3H), 4.84 (s, 1H), 5.40 (s, 1H), 6.41 (s, 1H), 7.20-7.45 (m, 5H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ = 52.2, 52.4, 53.0, 127.8, 128.1, 128.8, 129.0, 135.7, 138.8, 166.7, 172.2. **Anal. Calcd** for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.49; H, 5.88.

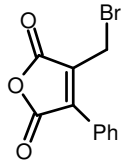
2-Phenyl-3-methylenesuccinic acid (30). A solution of lithium hydroxide (2.40 g) in water (20 mL) was added to a solution of **29** (2.34 g, 10.00 mmol) in THF (30 mL) at room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was concentrated in vacuo and ethyl acetate (50 mL) was added to the reaction mixture and then it was acidified to pH 2 with 2 N hydrochloric acid. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was chromatographed over silica gel using petroleum ether-ethyl acetate mixture (6:4) to give **30** as a white solid; 1.89 g (92%).

 **30** **$C_{11}H_{10}O_4$ (206)**	**Mp**: 145 ^oC. **IR** (nujol): ν_{max} 2700-2500, 1713, 1693, 1634, 1463, 1304 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 4.78 (s, 1H), 5.36 (s, 1H), 6.54 (s, 1H), 7.25-7.50 (m, 5H), 11.12 (bs, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ = 53.4, 128.2, 129.1, 129.2, 130.8, 134.4, 138.6, 172.2, 178.5. **Anal. Calcd** for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.92; H, 5.02.

3-Phenyl-4-methylfuran-2,5-dione (31). A solution of **30** (1.65 g, 8.00 mmol) in acetic anhydride (15 mL) was gently refluxed for 1.5 h and the reaction mixture was concentrated under vacuo at 50 °C. The residue was diluted with ethyl acetate (40 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo to obtain **31** as a yellow solid; 1.50 g (~100%).

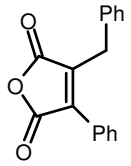
 **31** **$C_{11}H_8O_3$ (188)**	**Mp**: 100 °C (lit.[73] 94.5 °C). **IR** (nujol): ν_{max} 1774, 1759, 1643, 1460, 1377 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 2.33 (s, 3H), 7.50-7.58 (m, 3H), 7.62-7.71 (m, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ = 10.8, 127.4, 129.0, 129.4, 131.0, 138.7, 139.9, 164.8, 166.2. **Anal. Calcd** for $C_{11}H_8O_3$: C, 70.21; H, 4.28. Found: C, 70.10; H, 4.37.

3-Bromomethyl-4-phenylfuran-2,5-dione (32). A mixture of **31** (940 mg, 5.00 mmol), *N*-bromosuccinimide (1.34 g, 7.50 mmol) and catalytic amount of DBP (122 mg, 10 mol%) in carbon tetrachloride (50 mL) was gently refluxed for 12 h. The reaction mixture was left overnight at room temperature and then filtered. The residue was washed with CCl_4 (25 mL) and the combined organic layer was washed with water, brine and then dried over Na_2SO_4 and concentrated in vacuo to furnish the crude compound which was purified by silica gel column chromatography using petroleum ether-ethyl acetate mixture (9:1) to give desired compound **32** as a yellow solid; 1.07 g (80%).

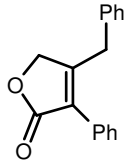
 **32** **$C_{11}H_7O_3Br$ (267)**	**Mp**: 72 °C. **IR** (nujol): ν_{max} 1761, 1636, 1601, 1512, 1460 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 4.35 (s, 2H), 7.50-7.70 (m, 3H), 7.75-7.90 (m, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ = 17.9, 126.6, 129.4, 129.7, 132.1, 136.2, 141.2, 163.9 (2 carbons). **Anal. Calcd** for $C_{11}H_7O_3Br$: C, 49.47; H, 2.64. Found: C, 49.39; H, 2.55.

3-Benzyl-4-phenylfuran-2,5-dione (28). A fresh solution of phenylmagnesium bromide in THF was prepared as follows. A solution of bromobenzene (785 mg, 5.00 mmol) in dry THF (20 mL) was added at room temperature to magnesium turnings (600 mg, 25.00 mmol) in THF (5 mL) under argon atmosphere with constant stirring in three equal portions in an interval of 10 minutes. The reaction mixture was further stirred at room temperature for 4 h. This freshly generated Grignard reagent was added drop wise to the solution of **32** (267 mg, 1.00 mmol) and copper(I) iodide (19 mg, 0.10 mmol) in THF (10 mL) and HMPA (1 mL) under argon atmosphere at 0 °C over 15 to 20 minutes under stirring. The reaction mixture was allowed to reach room temperature and further stirred for 8 h. The reaction mixture was diluted with ethyl acetate (10 mL) and acidified with 4 N

H_2SO_4 (20 mL) and the aqueous layer was further extracted with ethyl acetate (30 mL X 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was chromatographed over silica gel using petroleum ether-ethyl acetate mixture (9.5:0.5) to give **28** as a white solid; 118 mg (45%).

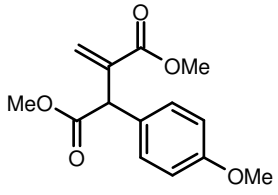
 **28** **$C_{17}H_{12}O_3$ (264)**	**Mp**: 65 °C (lit.[18] 67-68 °C). **IR** ($CHCl_3$): ν_{max} 1769, 1656, 1508, 1215, 758 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 4.04 (s, 2H), 7.15-7.35 (m, 5H), 7.45-7.70 (m, 5H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ = 30.4, 127.1, 127.3, 128.4, 129.0, 129.1, 129.3, 131.2, 135.4, 140.6, 141.1, 164.8, 165.8. **Anal. Calcd** for $C_{17}H_{12}O_3$: C, 77.26; H, 4.57. Found: C, 77.13; H, 4.44.

4-Benzyl-3-phenylfuran-2(*5H*)-one (gymnoascolide A, **22).** To a stirred solution of **28** (50 mg, 0.19 mmol) in dry THF (10 mL) at –78 ºC, was added a solution of N-selectride in THF (1 M, 0.60 mL, 0.60 mmol) over a period of 10 min. The reaction mixture further kept at same temperature for 1 h. The reaction was quenched with water (5 mL) at –78 ºC and allowed to reach to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic layer was washed with water, brine and 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 (9:1) to give gymnoascolide A (**22**) as a thick oil; 42 mg (90%).

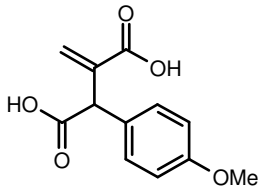
 **22** **$C_{17}H_{14}O_2$ (250)**	**IR** ($CHCl_3$): ν_{max} 1751, 1655, 1522, 1215, 768 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 3.97 (s, 2H), 4.70 (s, 2H), 7.10-7.20 (m, 2H), 7.25-7.35 (m, 3H), 7.40-7.60 (m, 5H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ = 34.0, 71.1, 127.4, 127.6, 128.5, 128.7, 128.8, 128.9, 129.2, 129.6, 136.1, 159.7, 173.3. **Anal. Calcd** for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.62; H, 5.49.

2-(4-Methoxyphenyl)-3-methylenesuccinic acid dimethyl ester (47). A fresh solution of 4-methoxyphenylmagnesium bromide in THF was prepared as follows. A solution of 4-bromoanisole (4.49 g, 24 mmol) in dry THF (30 mL) was added at room temperature to magnesium turnings (1.73 g, 72 mmol) in THF (10 mL) under argon atmosphere with constant stirring in three equal portions at an interval of 10 minutes. The reaction mixture

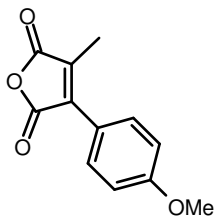
was further stirred at room temperature for 4 h. This freshly generated Grignard reagent was added drop wise to a solution of HMPA (14.34 g, 80 mmol) and **3** (3.79 g, 16 mmol) in anhydrous THF (30 mL) under argon atmosphere at 0 ºC and the reaction mixture was further stirred at the same temperature for 30 min. The reaction was quenched by the addition of a saturated ammonium chloride solution (30 mL). Ethyl acetate (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (40 mL X 3). The combined ethyl acetate extract was washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. The obtained residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9:1) to give **47** as a thick oil; yield: 3.07 g (73%).

 **47** **$C_{14}H_{16}O_5$ (264)**	**IR** (neat): ν_{max} 1736, 1720, 1632, 1611 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 3.71 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.77 (s, 1H), 5.43 (s, 1H), 6.39 (s, 1H), 6.89 (d, J = 10 Hz, 2H), 7.19 (d, J = 10 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ = 52.1 (2 carbons), 52.3, 55.2, 114.2, 127.6, 127.8, 130.0, 139.1, 159.1, 166.8, 172.5. **Anal. Calcd** for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.78; H, 6.18.

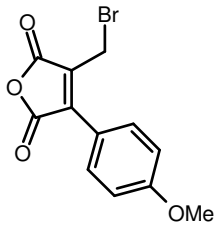
2-(4-Methoxyphenyl)-3-methylenesuccinic acid (48). A solution of lithium hydroxide (2.40 g) in water (20 mL) was added to a solution of **47** (2.64 g, 10 mmol) in THF (30 mL) at room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was concentrated in vacuo and ethyl acetate (50 mL) was added to the reaction mixture and then it was acidified to pH 2 with 2 N hydrochloric acid. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (25 mL X 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was chromatographed over silica gel using petroleum ether/ethyl acetate (6:4) to give **48** as a white solid; yield: 2.17 g (92%).

 **48** **$C_{12}H_{12}O_5$ (236)**	**Mp**: 158 °C. **IR** (nujol): ν_{max} 2700-2500, 1713, 1693, 1634, 1611 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 3.82 (s, 3H), 4.73 (s, 1H), 5.42 (s, 1H), 6.54 (s, 1H), 6.92 (d, *J* = 8 Hz, 2H), 7.24 (d, *J* = 8 Hz, 2H). **^{13}C NMR** (acetone-d_6, 75 MHz): δ = 52.8, 55.5, 114.8, 127.3, 129.3, 131.0, 141.4, 160.0, 167.8, 173.4. **Anal. Calcd** for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.88; H, 5.19.

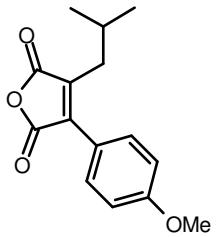
3-(4-Methoxyphenyl)-4-methylfuran-2,5-dione (49). A solution of **48** (1.89 g, 8 mmol) in acetic anhydride (15 mL) was gently refluxed for 1.5 h and the reaction mixture was concentrated under vacuo at 50 °C. The residue was diluted with ethyl acetate (40 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo to obtain **49** as a yellow solid; yield: 1.74 g (~100%).

 **49** **$C_{12}H_{10}O_4$ (218)**	**Mp**: 112 °C. **IR** (nujol): ν_{max} 1840, 1811, 1759, 1726, 1635, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 2.32 (s, 3H), 3.89 (s, 3H), 7.04 (d, *J* = 8 Hz, 2H), 7.70 (d, *J* = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ = 10.8, 55.4, 114.5, 120.1, 131.3, 135.8, 139.2, 161.8, 165.2, 166.5. **Anal. Calcd** for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.92; H, 4.80.

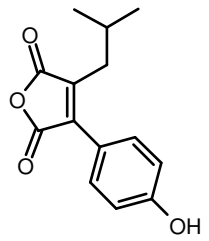
3-Bromomethyl-4-(4-methoxyphenyl)furan-2,5-dione (50). A mixture of **49** (1.09 g, 5 mmol), *N*-bromosuccinimide (1.34 g, 7.5 mmol) and catalytic amount of DBP (122 mg, 10 mol%) in carbon tetrachloride (50 mL) was gently refluxed for 12 h. The reaction mixture was left overnight at room temperature and then filtered. The residue was washed with CCl_4 (25mL), the combined organic layer was washed with water, brine and then dried over Na_2SO_4 and concentrated in vacuo to furnish the crude compound which was purified by silica gel column chromatography using petroleum ether/ethyl acetate (9:1) to give desired compound **50** as a yellow solid; yield: 1.18 g (80%).

 **50** **$C_{12}H_9O_4Br$ (297)**	**Mp**: 78 ^oC. **IR** (nujol): ν_{max} 1840, 1811, 1761, 1725, 1636, 1601 cm^{-1}. **^1H NMR** ($CDCl_3$, 200 MHz): δ = 3.91 (s, 3H), 4.36 (s, 2H), 7.09 (d, J = 8 Hz, 2H), 7.86 (d, J = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ = 18.7, 55.6, 115.0, 119.2, 130.1, 132.0, 132.8, 140.5, 162.7, 164.3. **Anal. Calcd** for $C_{12}H_9O_4Br$: C, 48.51; H, 3.05. Found: C, 48.65; H, 3.16.

3-(4-Methoxyphenyl)-4-isobutylfuran-2,5-dione (51). A fresh solution of isopropylmagnesium bromide in THF was prepared as follows. A solution of 2-bromopropane (1.23 g, 10 mmol) in dry THF (20 mL) was added at room temperature to magnesium turnings (1.20 g, 50 mmol) in THF (5 mL) under argon atmosphere with constant stirring in three equal portions at an interval of 10 minutes. The reaction mixture was further stirred at room temperature for 4 h. This freshly generated Grignard reagent was added drop-wise to the solution of **50** (594 mg, 2 mmol) and copper (I) iodide (38 mg, 0.2 mmol) in THF (10 mL) and HMPA (2 mL) under argon atmosphere at – 5 to 0 °C over 15 to 20 minutes under stirring. The reaction mixture was allowed to reach room temperature and further stirred for 8 h. The reaction mixture was diluted with ethyl acetate (10 mL) and acidified with 4 N H_2SO_4 (20 mL) and the aqueous layer was further extracted with ethyl acetate (30 mL X 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **51** as a thick oil; yield: 234 mg (45%).

 **51** **$C_{15}H_{16}O_4$ (260)**	**IR** ($CHCl_3$): ν_{max} 1844, 1825, 1763, 1736, 1607 cm^{-1}. **^1H NMR** ($CDCl_3$, 200 MHz): δ = 0.95 (d, J = 6 Hz, 6H), 2.13 (septet, J = 6 Hz, 1H), 2.60 (d, J = 8 Hz, 2H), 3.88 (s, 3H), 7.02 (d, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ = 22.6, 27.9, 33.6, 55.4, 114.5, 120.1, 131.1, 140.0, 140.2, 161.7, 165.4, 166.3. **Anal. Calcd** for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.20; H, 6.13.

3-(4-Hydroxyphenyl)-4-isobutylfuran-2,5-dione (52). To a stirred solution of **51** (160 mg, 0.62 mmol) in dry CH_2Cl_2 (10 mL) at –78 ºC, was added a solution of BBr_3 in CH_2Cl_2 (1 M, 3.10 mL, 3.10 mmol) over a period of 15 min. The reaction mixture then allowed to warm up to room temperature and stirred for further 12 h. The reaction was quenched with water (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic layer was washed with water, brine and 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 (8:2) to give **52** as a thick oil; yield: 138 mg (91%).

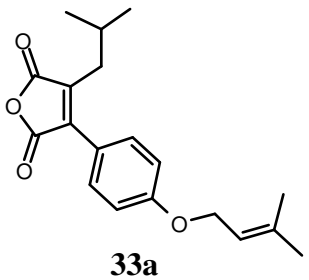


52

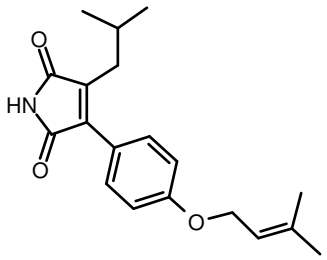
$C_{14}H_{14}O_4$ (246)

IR ($CHCl_3$): ν_{max} 3391, 1832, 1765, 1719, 1709, 1609 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.95 (d, J = 6 Hz, 6H), 2.12 (septet, J = 6 Hz, 1H), 2.60 (d, J = 8 Hz, 2H), 6.98 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.6, 27.9, 33.6, 116.1, 120.0, 131.3, 140.1, 140.3, 158.1, 165.5, 166.5.
Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.33; H, 5.89.

3-[4-(3-Methyl-but-2-enyloxy)phenyl]-4-isobutylfuran-2,5-dione (Camphorataanhydride A, 33a). A solution of **52** (100 mg, 0.41 mmol) in acetone (10 mL) was added 3,3-dimethylallyl bromide (73.3 mg, 0.49 mmol) and potassium carbonate (566 mg, 4.10 mmol) and the mixture was refluxed for 2 h. The reaction mixture was concentrated in vacuo and diluted with water (5 mL). The aqueous layer was extracted with ethyl acetate (15 mL x 3) and the combined organic layer was washed with brine and 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 (9.5:0.5) to give camphorataanhydride A **(33a)** as a thick yellow oil; yield: 115 mg (90%).

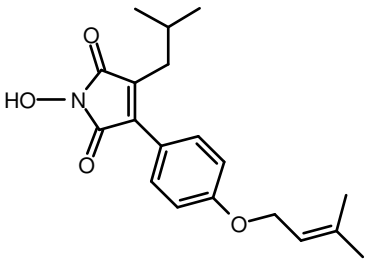
 **33a** **$C_{19}H_{22}O_4$ (314)**	**IR** (neat): ν_{max} 1836, 1825, 1763, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 0.95 (d, *J* = 8 Hz, 6H), 1.77 (s, 3H), 1.82 (s, 3H), 2.13 (septet, *J* = 6 Hz, 1H), 2.61 (d, *J* = 6 Hz, 2H), 4.59 (d, *J* = 6 Hz, 2H), 5.50 (brt, *J* = 6 Hz, 1H), 7.03 (d, *J* = 10 Hz, 2H), 7.63 (d, *J* = 10 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ = 18.2, 22.7, 25.8, 27.9, 33.6, 65.0, 115.1, 118.9, 119.9, 131.1, 139.0, 139.8, 140.2, 160.9, 165.4, 166.4. **Anal. Calcd** for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.66; H, 7.10.

3-[4-(3-Methyl-but-2-enyloxy)phenyl]-4-isobutylpyrrole-2,5-dione (Camphorataimide B, 33b). A mixture of **33a** (40 mg, 0.13 mmol) and urea (9 mg, 0.15 mmol) was heated to 130-135 ºC for 1 h. The reaction mixture was allowed to cool to room temperature then water (10 mL) was added and the aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic layer was washed with brine and 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 (8.5:1.5) to give camphorataimide B **(33b)** as a yellow solid; yield: 32 mg (81%).

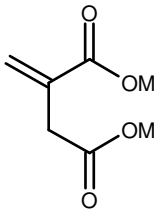
 **33b** **$C_{19}H_{23}NO_3$ (313)**	**Mp**: 110 ^oC. **IR** ($CHCl_3$): ν_{max} 3435, 1773, 1717, 1715, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 0.91 (d, *J* = 8 Hz, 6H), 1.77 (s, 3H), 1.82 (s, 3H), 2.06 (septet, *J* = 6 Hz, 1H), 2.52 (d, *J* = 6 Hz, 2H), 4.57 (d, *J* = 6 Hz, 2H), 5.51 (brt, *J* = 6 Hz, 1H), 7.00 (d, *J* = 8 Hz, 2H), 7.32 (bs, 1H), 7.52 (d, *J* = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ = 18.2, 22.7, 25.8, 28.1, 32.8, 64.9, 114.8, 119.2, 121.1, 130.9, 138.7, 138.8, 139.1, 160.1, 171.0, 171.7. **Anal. Calcd** for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.72; H, 7.51; N, 4.53.

3-[4-(3-Methyl-but-2-enyloxy)phenyl]-4-isobutyl-*N*-hydroxypyrrole-2,5-dione (Camphorataimide C, 33c). A mixture of **33a** (40 mg, 0.13 mmol) and hydroxylamine hydrochloride (18 mg, 0.26 mmol) was refluxed in pyridine (5 mL) for 2 h. The reaction mixture was allowed to cool to room temperature, pyridine was removed in vacuo and then water (5 mL) was added to reaction mixture and the aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic layer was washed with brine and 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 (8:2) to give camphorataimide C **(33c)** as a yellow oil; yield: 32 mg (76%).

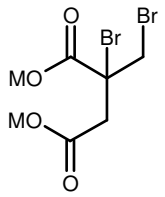
 **33c** **$C_{19}H_{23}NO_4$ (329)**	**IR** (neat): ν_{max} 3306, 1782, 1722, 1713, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 0.89 (d, *J* = 8 Hz, 6H), 1.76 (s, 3H), 1.81 (s, 3H), 2.06 (septet, *J* = 6 Hz, 1H), 2.51 (d, *J* = 8 Hz, 2H), 4.56 (d, *J* = 6 Hz, 2H), 5.51 (brt, *J* = 6 Hz, 1H), 6.98 (d, *J* = 8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ = 18.2, 22.7, 25.8, 28.1, 33.0, 64.9, 114.9, 119.1, 120.7, 131.0, 135.9, 136.0, 138.8, 160.2, 168.0, 168.7. **Anal. Calcd** for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.39; H, 6.92; N, 4.37.

2-Methylene-succinic acid bis-(2-isopropyl-5-methyl-cyclohexyl)ester (69). To a solution of itaconic anhydride (5.20 g, 40 mmol) in toluene (70 mL) was added *D*-menthol (12.48 g, 80 mmol) and *p*-TSA (100 mg, 40 mmol) and the reaction mixture was refluxed under argon atmosphere for 36 h using Dean and Stark apparatus. The reaction mixture was allowed to cool to ambient temperature and concentrated in vacuo and the residue was dissolved in ethyl acetate (150 mL) and washed successively with 5% aqueous $NaHCO_3$ solution, brine and dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to give **69** (thick oil): 13.12 g (80% yield).

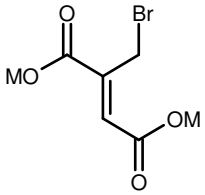
 **69** (M = *D*-Menthyl) **$C_{25}H_{42}O_4$ (406)**	Thick oil. **$[\alpha]_D^{25}$** = + 78.16 (*c* 1.47, $CHCl_3$) . **IR** (Neat) ν_{max} 1734, 1719, 1641, 1456, 1200 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.77 (d, *J* = 8 Hz, 6H), 0.90 (d, *J* = 6 Hz, 12H), 0.75-1.25 (m, 6H), 1.30-1.55 (m, 4H), 1.55-1.75 (m, 4H), 1.80-2.10 (m, 4H), 3.31 (s, 2H), 4.60-4.85 (m, 2H), 5.65 (s, 1H), 6.29 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 16.2, 20.6, 21.9, 23.3, 23.4, 26.0, 26.1, 31.2, 34.1, 37.9, 40.5, 40.6, 46.8, 46.9, 74.4, 74.6, 127.5, 134.4, 165.4, 170.0 (three carbon atoms from the two menthol units did not show splitting). **Anal. Calcd** for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 74.01; H, 10.33.

Bis(2-isopropyl-5-methylcyclohexyl) 2-bromo-2-bromomethyl)succinate (70). To the stirring solution of dimentyl itaconate (**69**, 5.00g, 12.32 mmol) in CCl_4 (50 mL) was added Br_2 (4.10 g, 1.31 mL, 25.62 mmol) and the reaction mixture was stirred for 12 h at room

temperature. The solvent was then evaporated in vacuo. The residue was dissolved in ethyl acetate (100 mL) and washed successively with saturated Na_2HSO_3, water, brine and dried over Na_2SO_4 and concentrated in vacuo to gave compound **70** (thick oil): 6.27 g (90% yield).

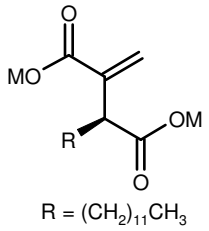
 **70** (M = *D*-Menthyl) **$C_{25}H_{42}O_4Br_2$ (566)**	$[\alpha]_D^{25}$ = + 50.67 (*c* 0.81, $CHCl_3$) . **IR** (Neat) ν_{max} 1738, 1732, 1454, 1420, 1286 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.76 (d, *J* = 6 Hz, 6H), 0.80-1.10 (m, 18H) 1.30-1.55 (m, 4H), 1.60-1.80 (m, 4H), 1.85-2.10 (m, 4H), 3.40 (d, *J* = 4 Hz, 2H), 4.20-4.45 (m, 2H), 4.60-4.85 (m, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 15.9, 16.2, 16.3, 20.8, 22.0, 23.1, 23.4, 25.9, 26.2, 31.4, 34.1, 36.5, 36.7, 39.8, 39.9, 40.7, 40.8, 41.1, 41.2, 46.9, 47.0, 55.7, 56.0, 75.2, 77.2, 167.2, 168.4 (Two carbons show diastereomeric splitting). **Anal. Calcd** for $C_{25}H_{42}O_4Br_2$: C, 53.01; H, 7.47. Found: C, 52.75; H, 7.58.

Bis(2-isopropyl-5-methylcyclohexyl) 2-(bromomethyl)maleate (71). To the stirring solution of dibromo diester **70** (5.00g, 8.83 mmol) in CCl_4 (50 mL) was added triethyl amine (1.26g, 1.74 mL, 12.48 mmol) and the reaction mixture was stirred for 10 h at room temperature. The solid formed was filtered through celite and washed with CCl_4 and filtrate was then evaporated in vacuo. The residue was dissolved in ethyl acetate (100 mL) and washed successively with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (9:1) to give **71** (thick oil): 3.94 g (92% yield).

 **71** (M = *D*-Menthyl) **$C_{25}H_{41}O_4Br$ (485)**	$[\alpha]_D^{25}$ = + 62.09 (*c* 0.31, $CHCl_3$) . **IR** (Neat) ν_{max} 1722, 1717, 1647, 1456, 1273 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.78 (d, *J* = 6 Hz, 6H), 0.80-1.00 (m, 16H), 1.05-1.20 (m, 2H), 1.40-1.60 (m, 4H), 1.65-1.80 (m, 4H), 1.85-2.10 (m, 4H), 4.65-4.80 (m, 2H), 4.80- 4.95 (m, 2H), 6.77 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 16.1, 20.8, 22.0, 22.8, 23.3, 26.1, 26.2, 31.4, 34.1, 40.6, 40.8, 47.0, 75.5, 76.4, 128.8, 142.8, 164.4, 168.5 (Some of the carbon from two different menthol unit did not show splitting). **Anal. Calcd** for $C_{25}H_{41}O_4Br$: C, 61.85; H, 8.51. Found: C, 62.00; H, 8.34.

Bis(2-isopropyl-5-methylcyclohexyl) 2-dodecyl-3-methylenesuccinate (72).

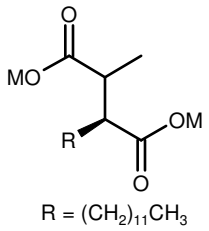
A fresh solution of dodecylmagnesium bromide in THF was prepared as follows. A solution of dodecylbromide (1.50 g, 6 mmol) in dry THF (20 mL) was added at room temperature to magnesium turnings (720 mg, 30 mmol) in THF (5 mL) under argon atmosphere with constant stirring in three equal portions at an interval of 10 minutes. The reaction mixture was further stirred at room temperature for 4 h. This freshly generated Grignard reagent was added drop wise to a solution of HMPA (5.37 g, 30 mmol) and **71** (1.94 g, 4 mmol) in anhydrous THF (20 mL) under argon atmosphere at 0 ºC and the reaction mixture was further stirred at the same temperature for 30 min. The reaction was quenched by the addition of a saturated ammonium chloride solution (15 mL). Ethyl acetate (40 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (30 mL X 3). The combined organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. The obtained residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9:1) to give **72** as a thick oil; yield: 1.68 g (73%).

 R = $(CH_2)_{11}CH_3$ **72** (M = *D*-Menthyl) **$C_{37}H_{66}O_4$ (574)**	**$[\alpha]_D^{25}$** = + 58.22 (*c* 0.79, $CHCl_3$) . **IR** (Neat) ν_{max} 1730, 1718, 1630, 1456, 1178 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz) 0.69-0.78 (m, 9H), 0.85-0.92 (m, 14H), 0.95-1.10 (m, 4H), 1.20-1.31 (m, 20H), 1.42-1.50 (m, 4H), 1.63-1.72 (m, 6H), 1.80-1.90 (m, 2H), 1.97-2.02 (m, 2H), 3.45-3.55 (m, 1H), 4.60-4.70 (m, 1H), 4.70-4.80 (m, 1H), 5.69-5.71 (s, 1H), 6.30-6.31 (s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) 14.0, 15.9, 16.3, 20.7, 21.9, 22.6, 23.2, 25.8, 26.2, 27.4, 29.3, 29.6, 31.3, 31.8, 34.2, 40.7, 46.5, 46.8, 46.9, 47.0, 64.5, 74.3, 74.7, 125.2, 125.6, 139.3, 165.6, 172.7 (Some of the carbon from two different menthol unit did not show splitting). **Anal. Calcd** for $C_{37}H_{66}O_4$: C, 77.30; H, 11.57. Found: C, 77.11; H, 11.42.

Bis(2-isopropyl-5-methylcyclohexyl) 2-dodecyl-3-methisuccinate (73).

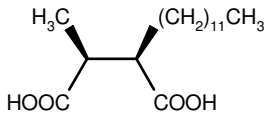
To the stirring solution of **72** (1.5 g, 2.61mmol) in MeOH (50 mL) was added Pd-C (50 mg) and the reaction mixture was stirred for 6 h at room temperature under the Hydrogen atmosphere (pressure, 50 psi). The reaction mixture was diluted with ethyl acetate (30 mL) and filtered through celite and washed with ethyl acetate the filtrate was then evaporated in

vacuo. The residue obtained was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (9:1) to give **73** (thick oil): 1.35 g (90% yield).

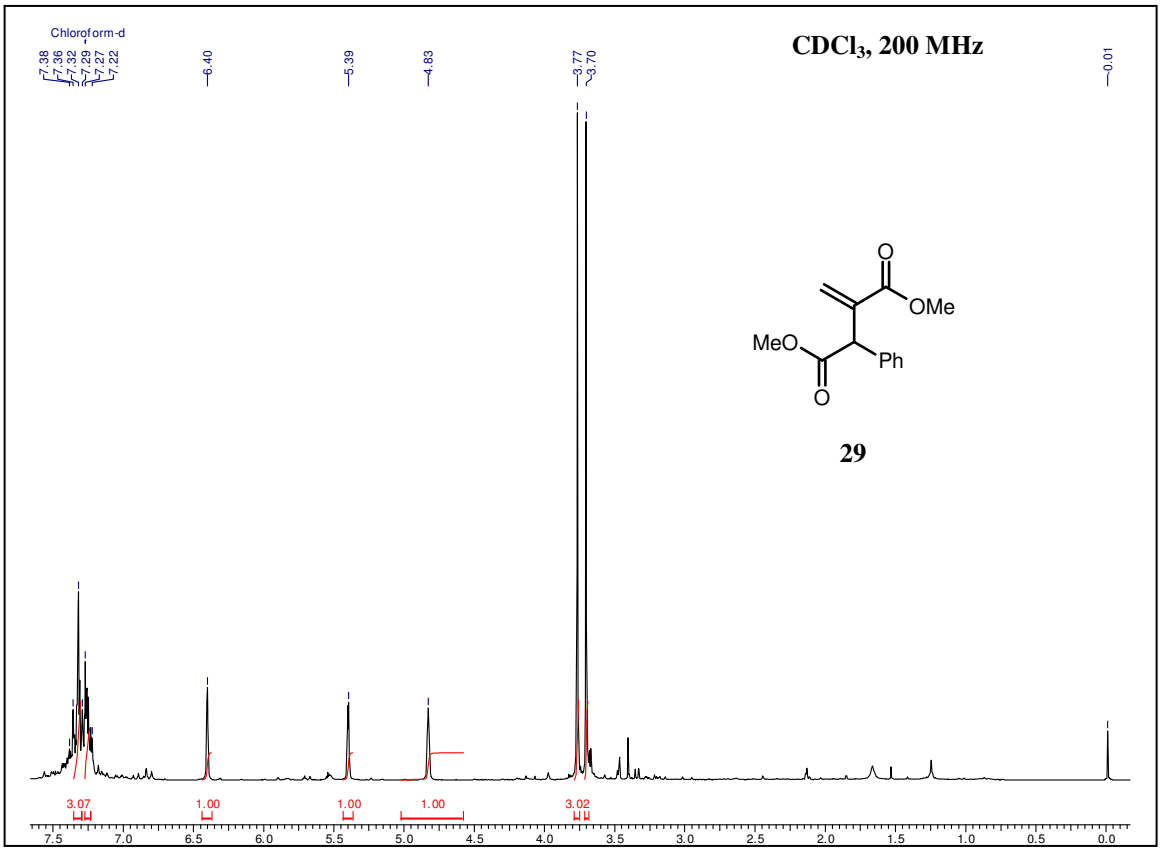
 **73** (M = *D*-Menthyl) **$C_{37}H_{68}O_4$ (576)**	**$[\alpha]_D^{25}$** = + 41.80 (*c* 0.91, $CHCl_3$) . **IR** (Neat) ν_{max} 1728, 1456, 1369, 1252, 1163 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) 0.70-0.80 (m, 9H), 0.85-0.95 (m, 18H), 1.05-1.15 (m, 4H), 1.20-1.30 (m, 23H), 1.40-1.50 (m, 4H), 1.60-1.75 (m, 4H), 1.85-2.00 (m, 2H), 2.50-2.75 (m, 2H), 4.55-4.80 (m, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) 14.1, 15.7, 16.0, 20.8, 22.0, 22.6, 22.9, 25.8, 26.1, 29.3, 29.4, 29.6, 31.3, 31.9, 34.2, 40.8, 42.9, 46.9, 49.7, 60.3, 74.3, 173.8, 174.5 (Some of the carbon from two different menthol unit did not show splitting). **Anal. Calcd** for $C_{37}H_{68}O_4$: C, 77.03; H, 11.88. Found: C, 76.84; H, 11.97.

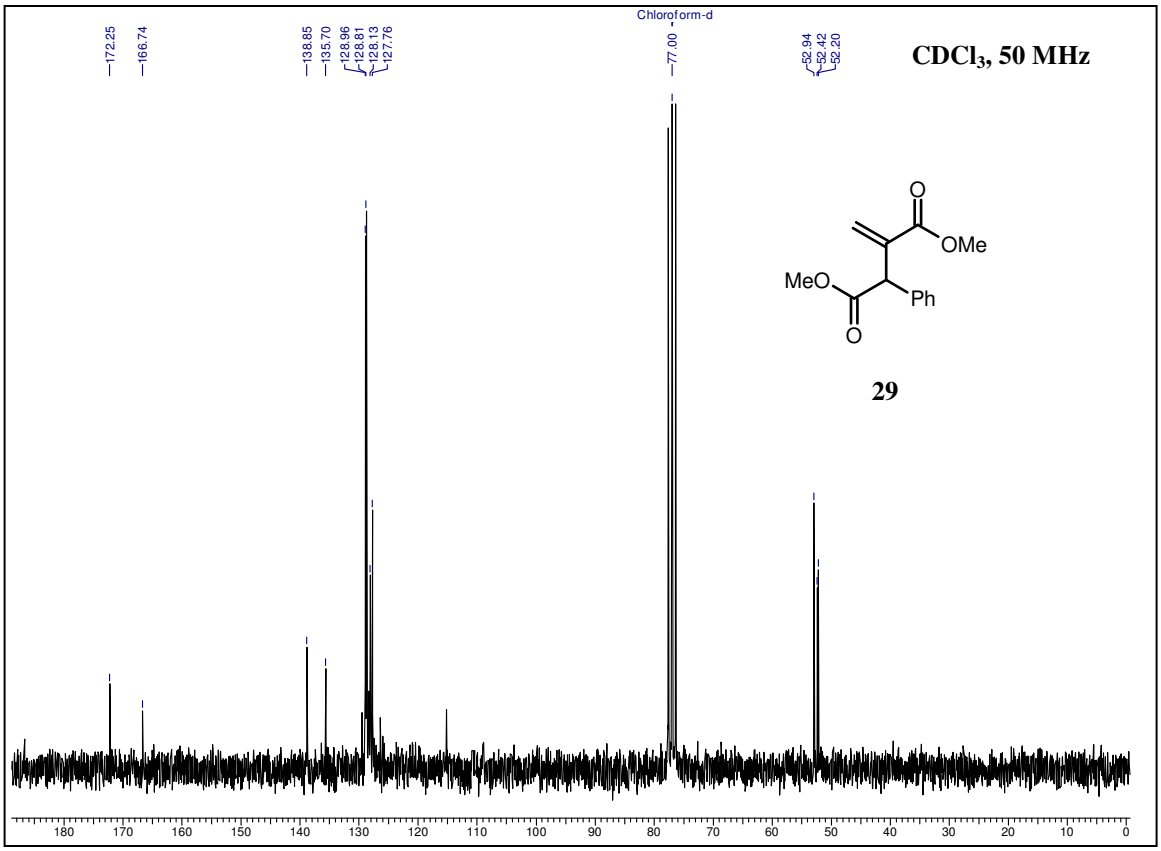
2-Dodecyl-3-methylsuccinic acid (roccellic acid 53)

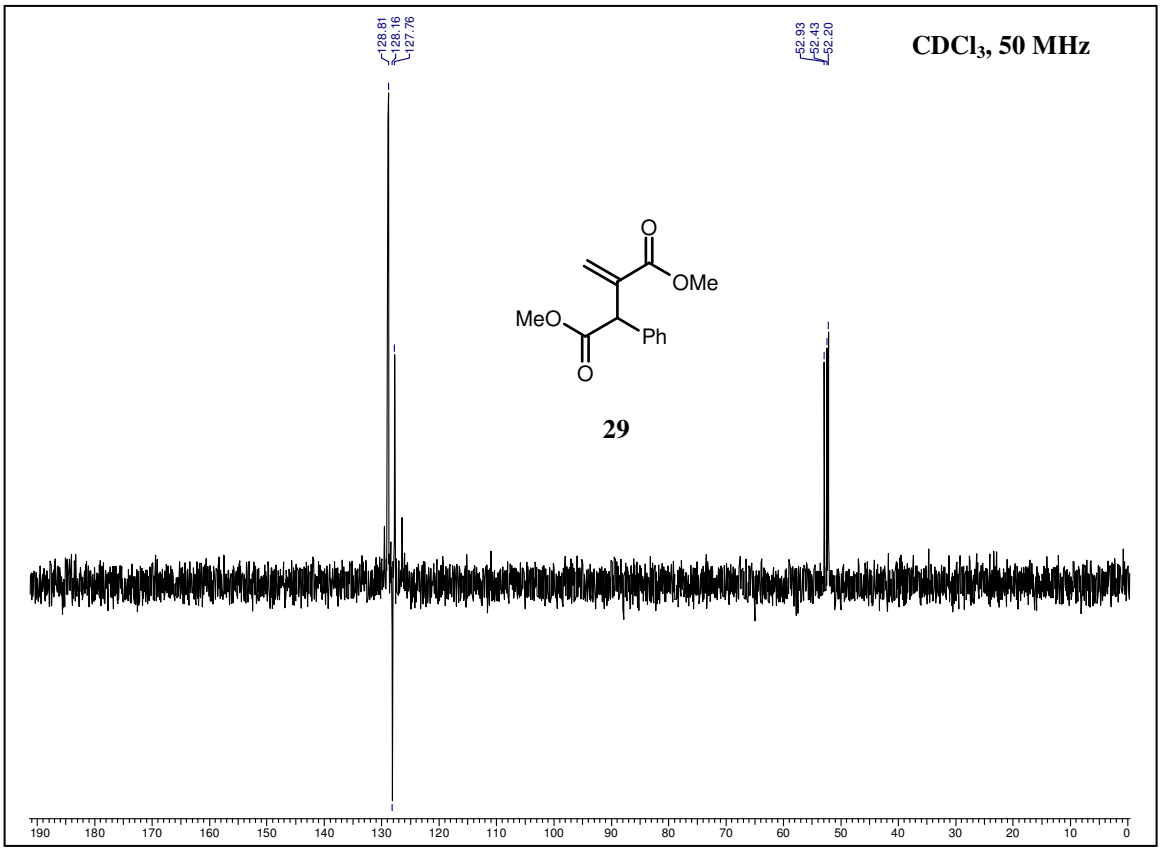
A solution of **73** (1.00g, 1.74 mmol) in the mixture of AcOH:HCl (3:2) (20 mL) was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo and the residue was dissolved in 10% aqueous $NaHCO_3$ solution. The resulting solution was washed with ethyl acetate (10 mL x 3), acidified with 1 N HCl and extracted with ethyl acetate containing 5% methanol (25 mL x 4). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give **53** (white solid): 443 g (85% yield).

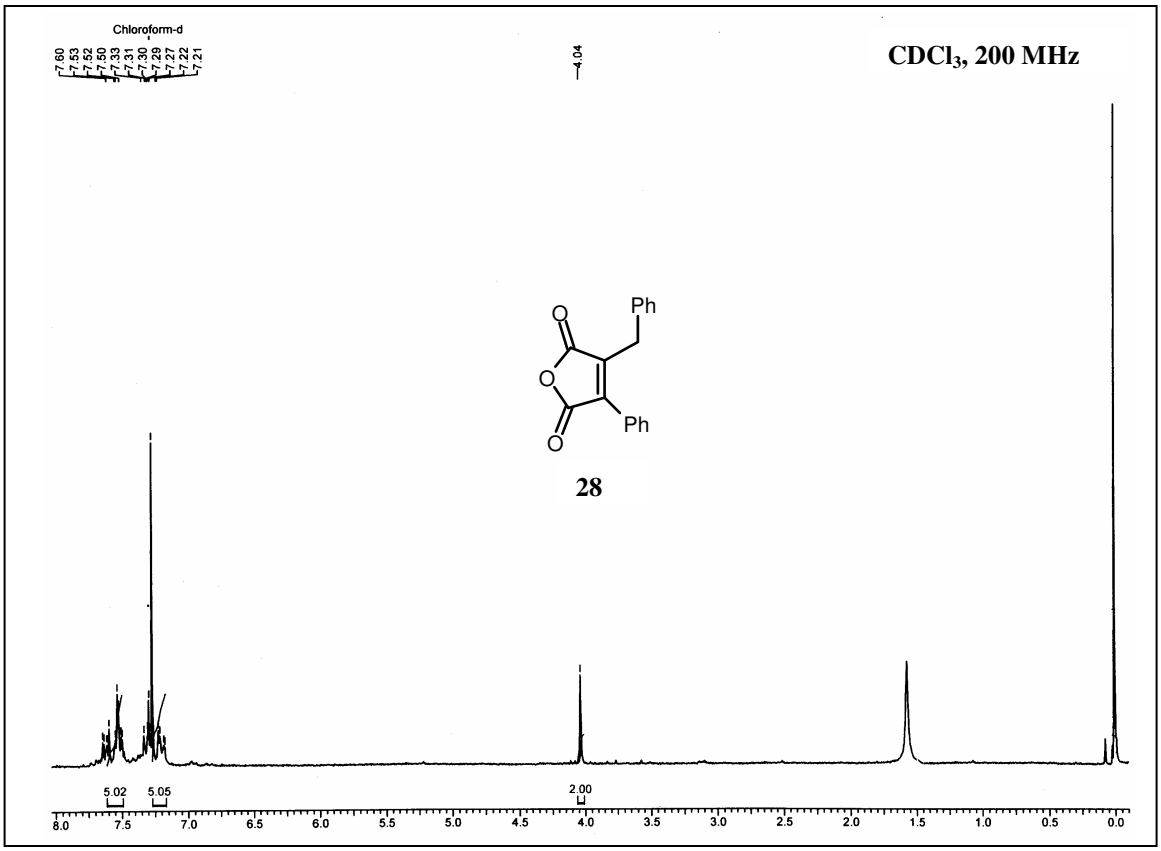
 **53** **$C_{17}H_{32}O_4$ (300)**	**$[\alpha]_D^{25}$** = + 6.66 (*c* 0.76, MeOH) . **Mp** 125 °C (Lit 130 °C) **IR** (Neat) ν_{max} 2700-2500, 1691, 1464, 1420, 1215 cm^{-1}. **^{1}H NMR** (Pyridine-d_5, 200 MHz) 0.86 (t, *J* = 4 Hz, 3H), 1.10-1.50 (m, 20H), 1.63 (d, *J* = 4 Hz, 3H), 1.90-2.05 (m, 1H), 2.10-2.25 (m, 1H), 3.26 (bs, 2H). **^{13}C NMR** (Pyridine-d_5, 50 MHz) 14.2, 16.2, 22.9, 28.2, 29.5, 29.8, 31.7, 32.0, 43.3, 50.0, 176.8, 177.7; **Anal. Calcd** for $C_{17}H_{32}O_4$: C, 67.96; H, 10.73. Found: C, 68.13; H, 10.55.

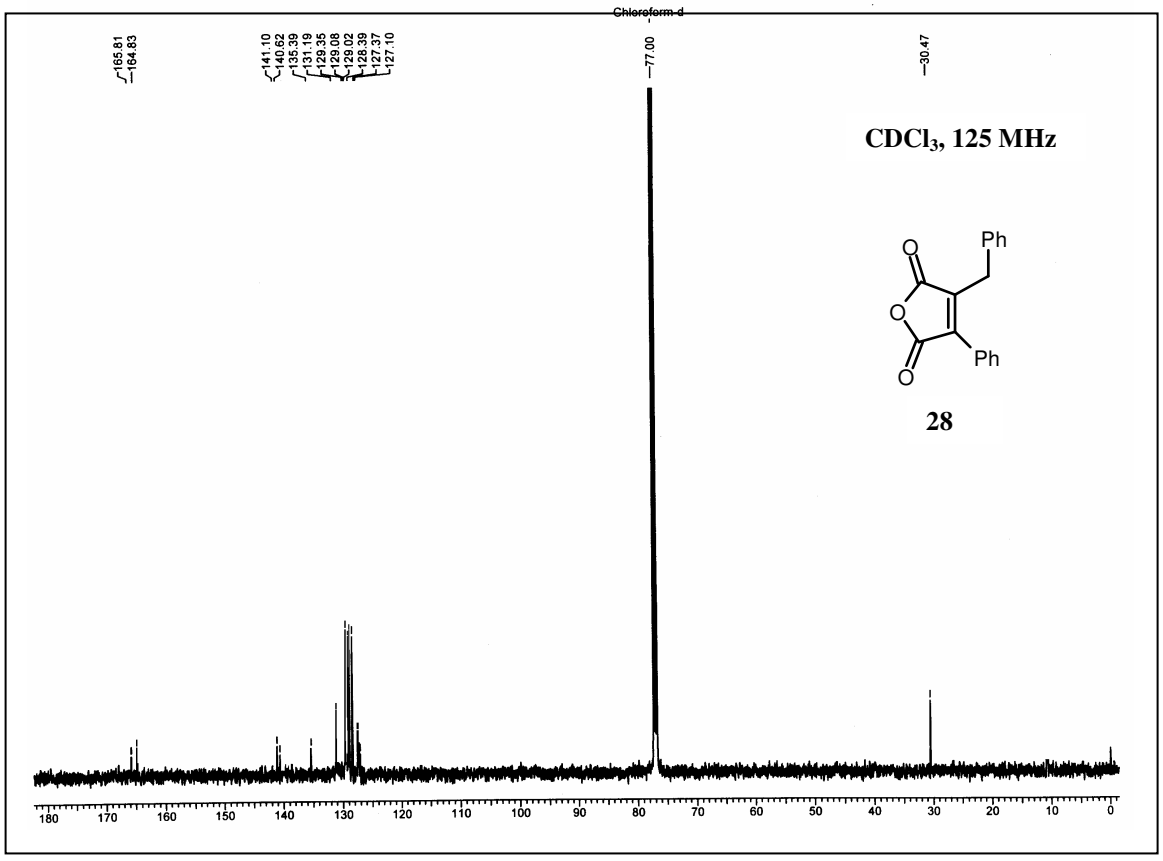
2B.8 Selected Spectra

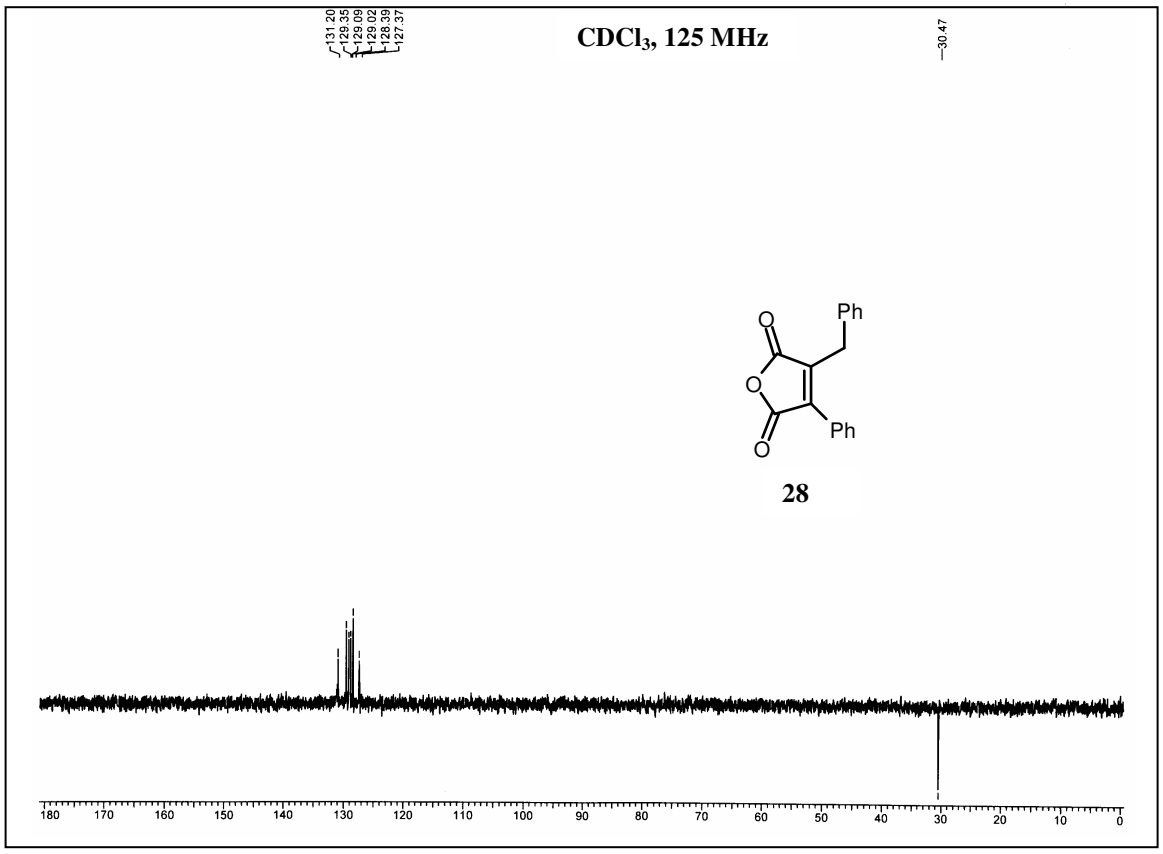

CDCl3, 200 MHz
Chloroform-d
7.38
7.36
7.32
7.29
7.27
7.22
6.40
5.39
4.83
3.77
3.70
0.01
O
OMe
MeO
Ph
O
29
3.07
1.00
1.00
1.00
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

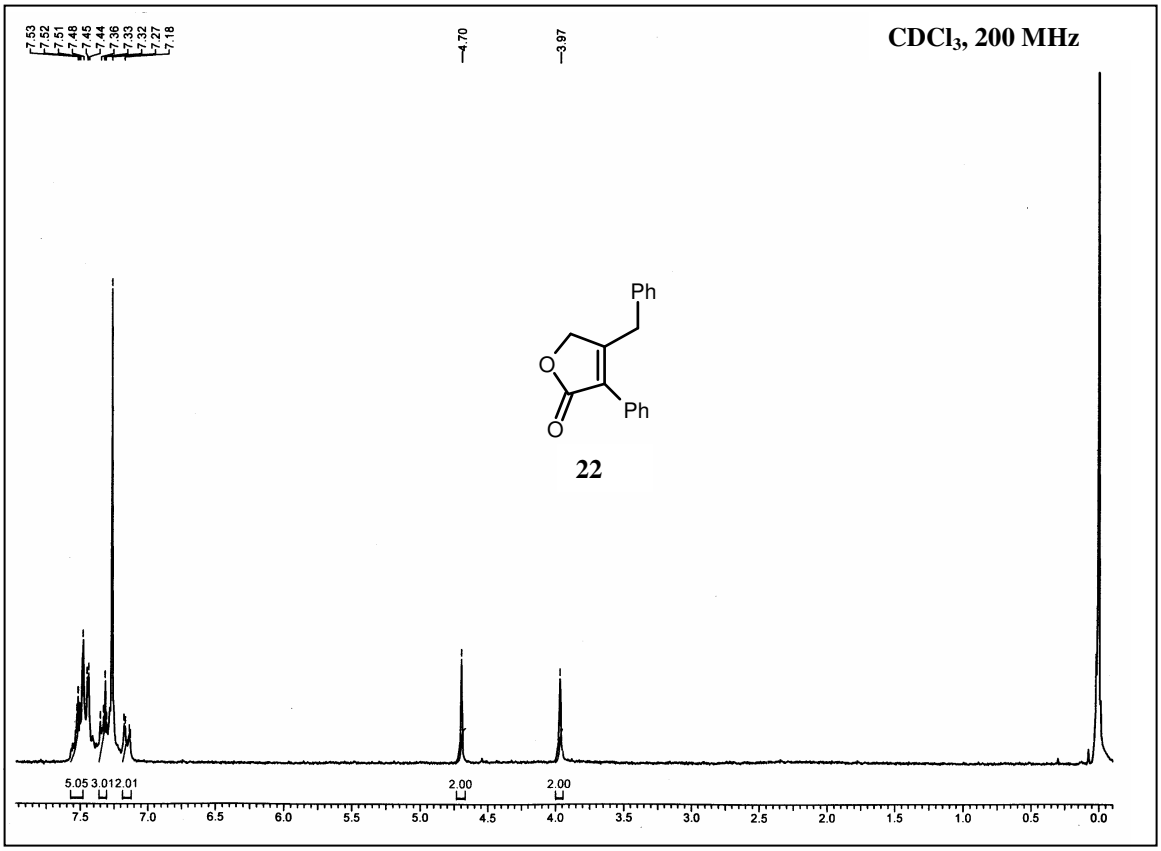

CDCl3, 50 MHz
172.25
166.74
138.85
135.70
128.96
128.81
128.13
127.76
Chloroform-d
77.00
52.94
52.42
52.20
O
OMe
MeO
Ph
O
29
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

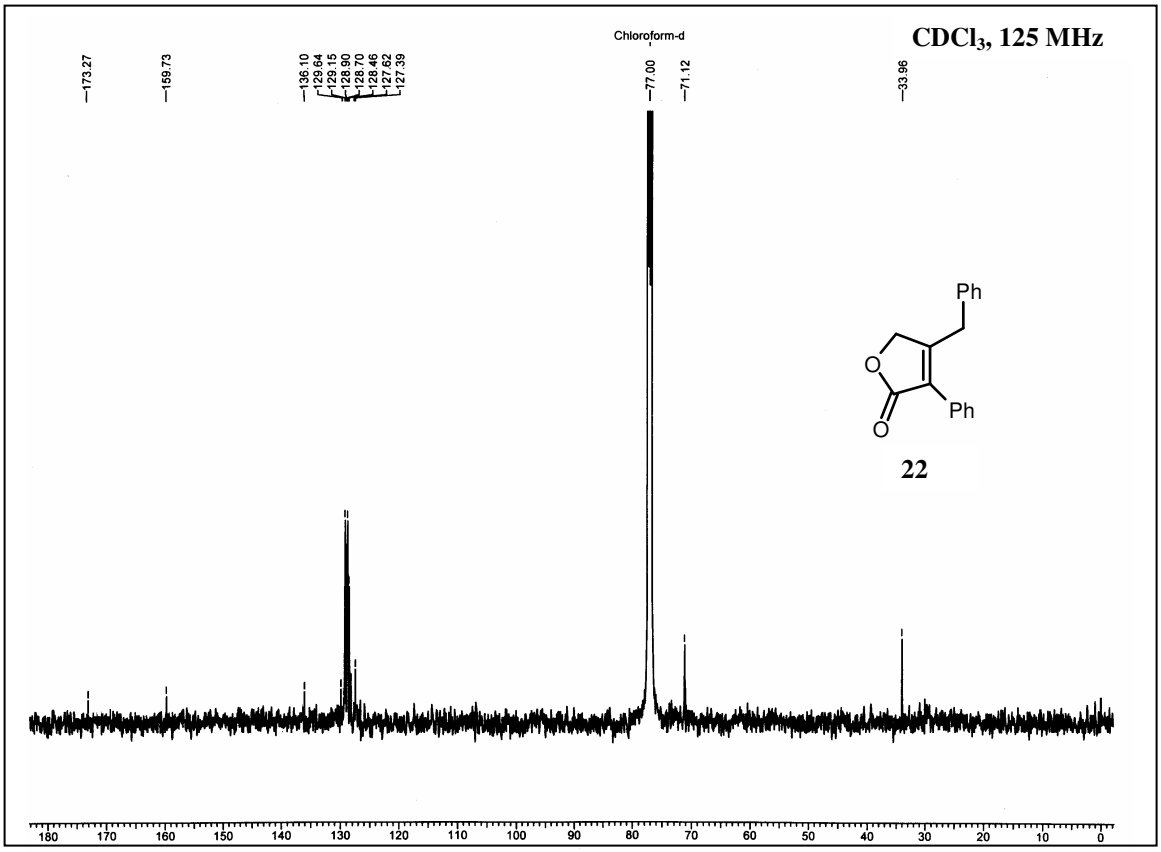

128.81
128.16
127.76
52.93
52.43
52.20
CDCl3, 50 MHz
O
OMe
MeO
Ph
O
29
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

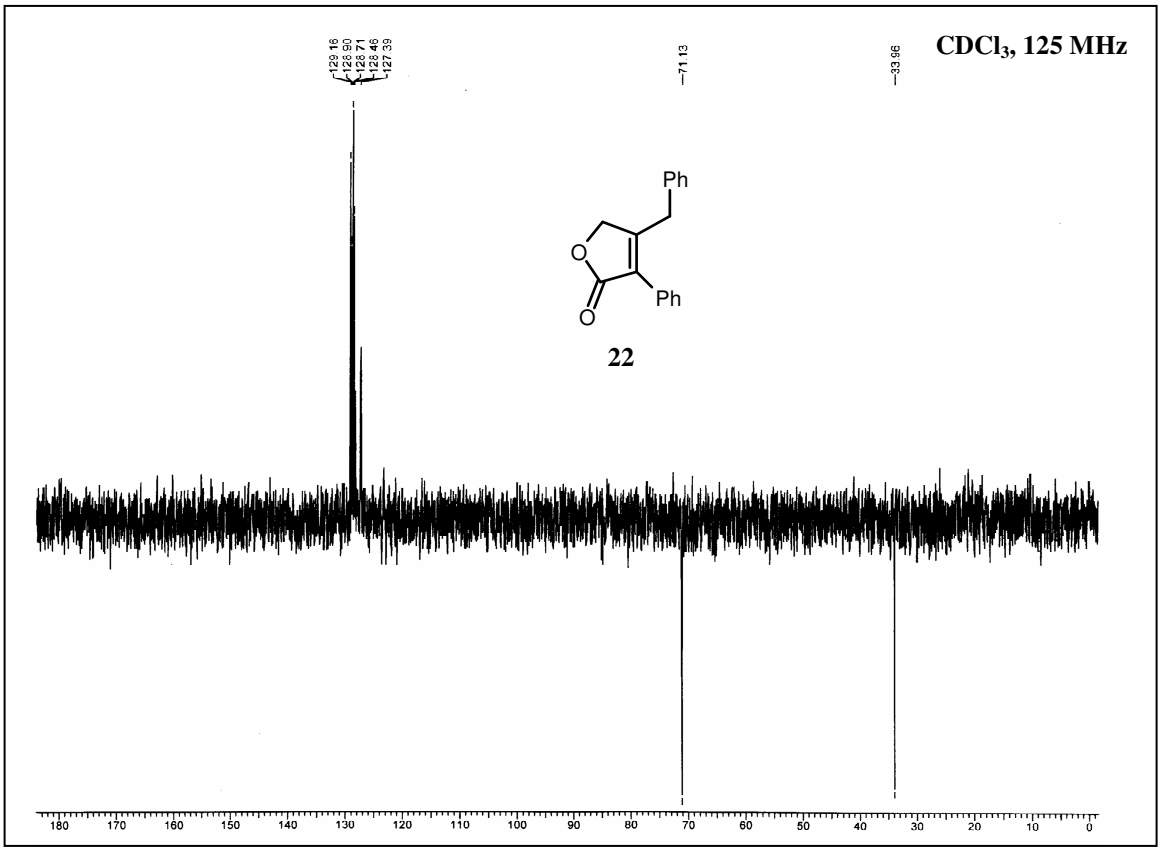

Chloroform-d
7.60
7.53
7.52
7.50
7.33
7.31
7.30
7.29
7.27
7.22
7.21
4.04
CDCl3, 200 MHz
Ph
O
O
Ph
O
28
5.02
5.05
2.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

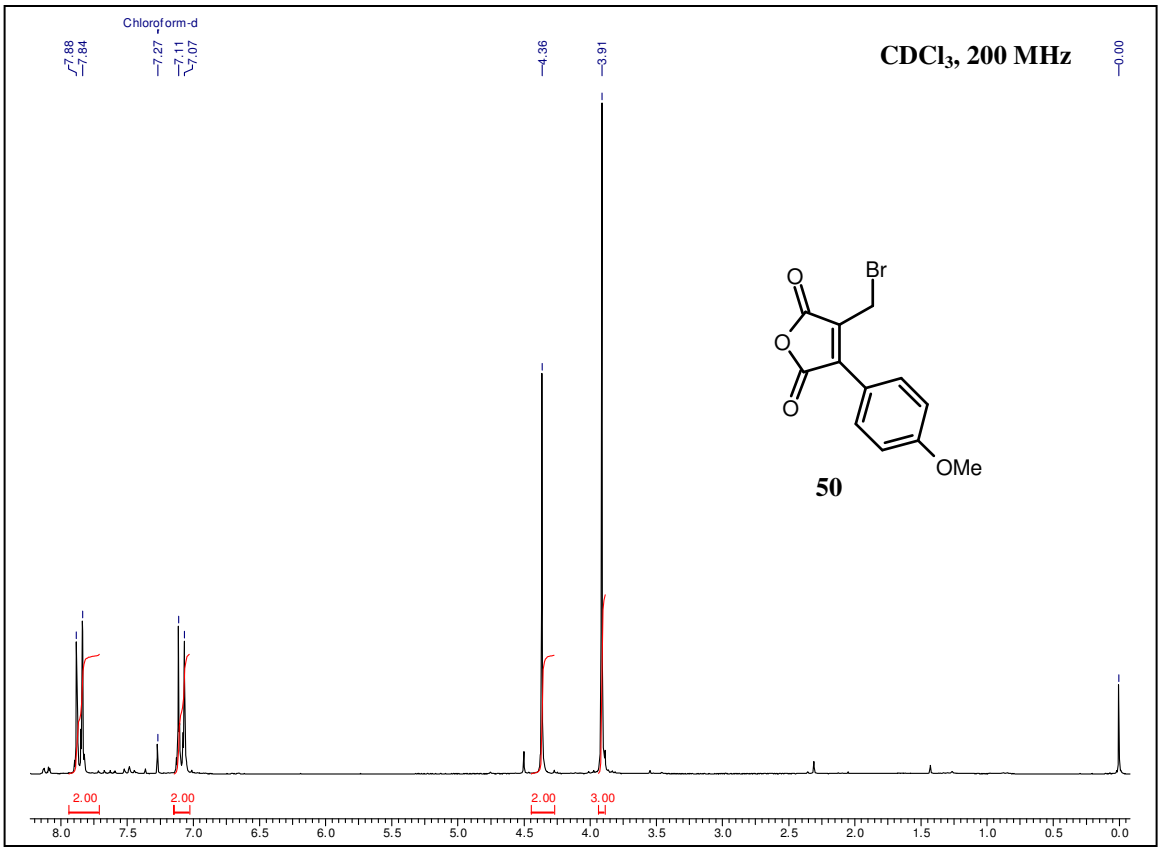

Chloroform-d
165.81
164.83
141.10
140.62
135.39
131.19
129.35
129.08
129.02
128.39
127.37
127.10
77.00
30.47
CDCl3, 125 MHz
Ph
O
O
Ph
O
28
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

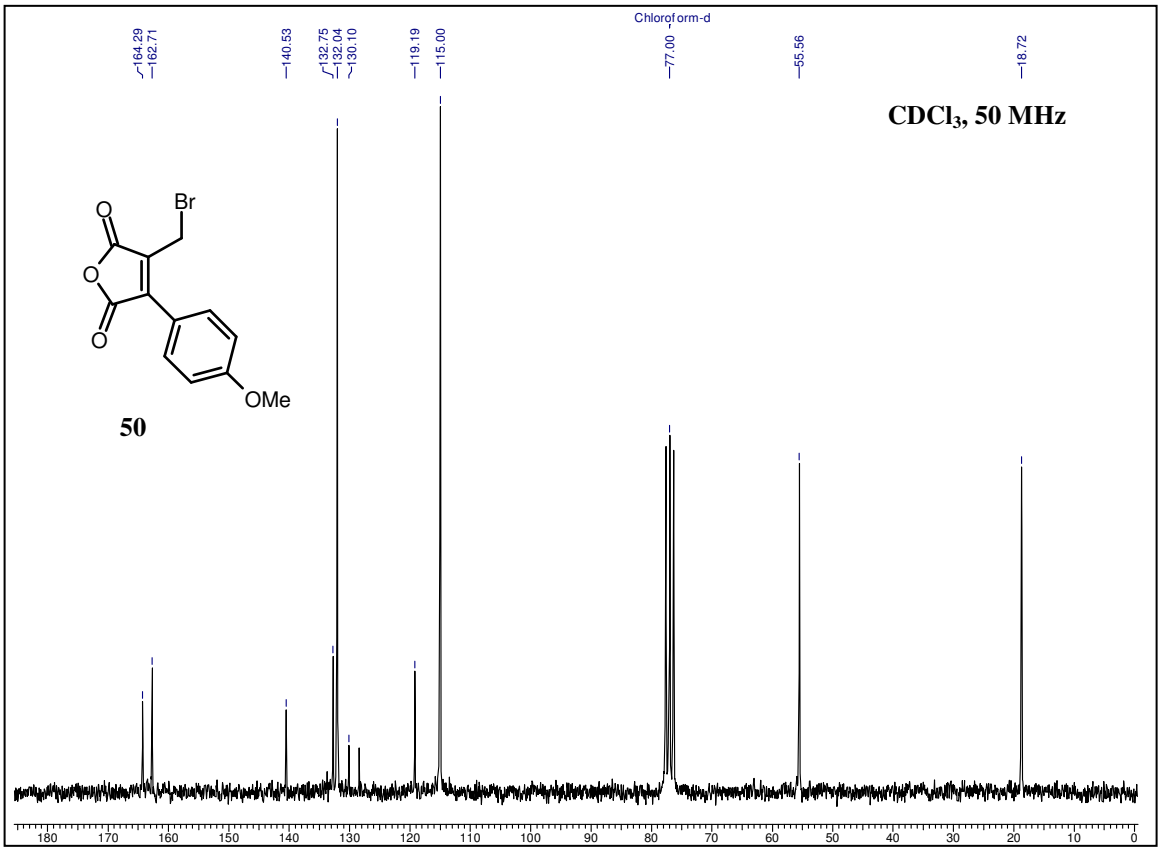

131.20
129.35
129.09
129.02
128.39
127.37
30.47
CDCl3, 125 MHz
Ph
O
O
Ph
O
28
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

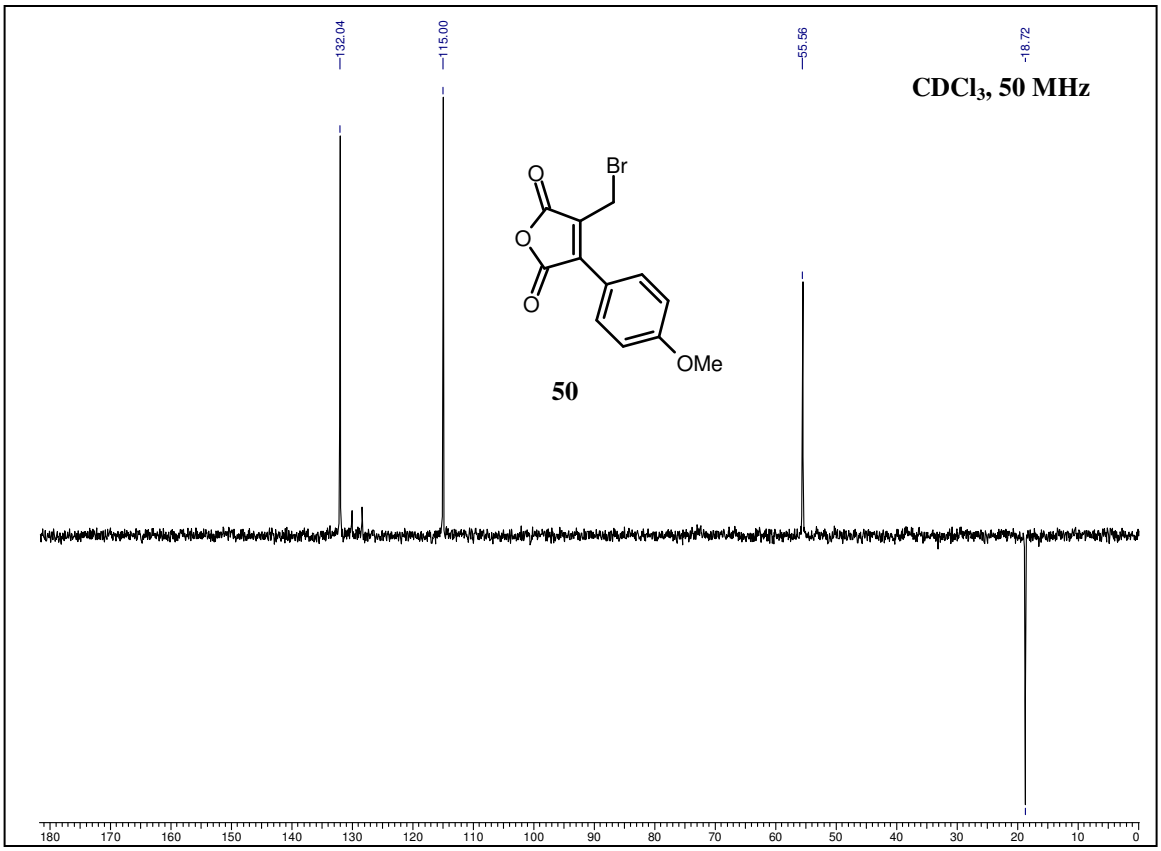

CDCl3, 200 MHz
7.53
7.52
7.51
7.48
7.45
7.44
7.36
7.33
7.32
7.27
7.18
4.70
3.97
Ph
O
O
Ph
22
5.05 3.01 2.01
2.00
2.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

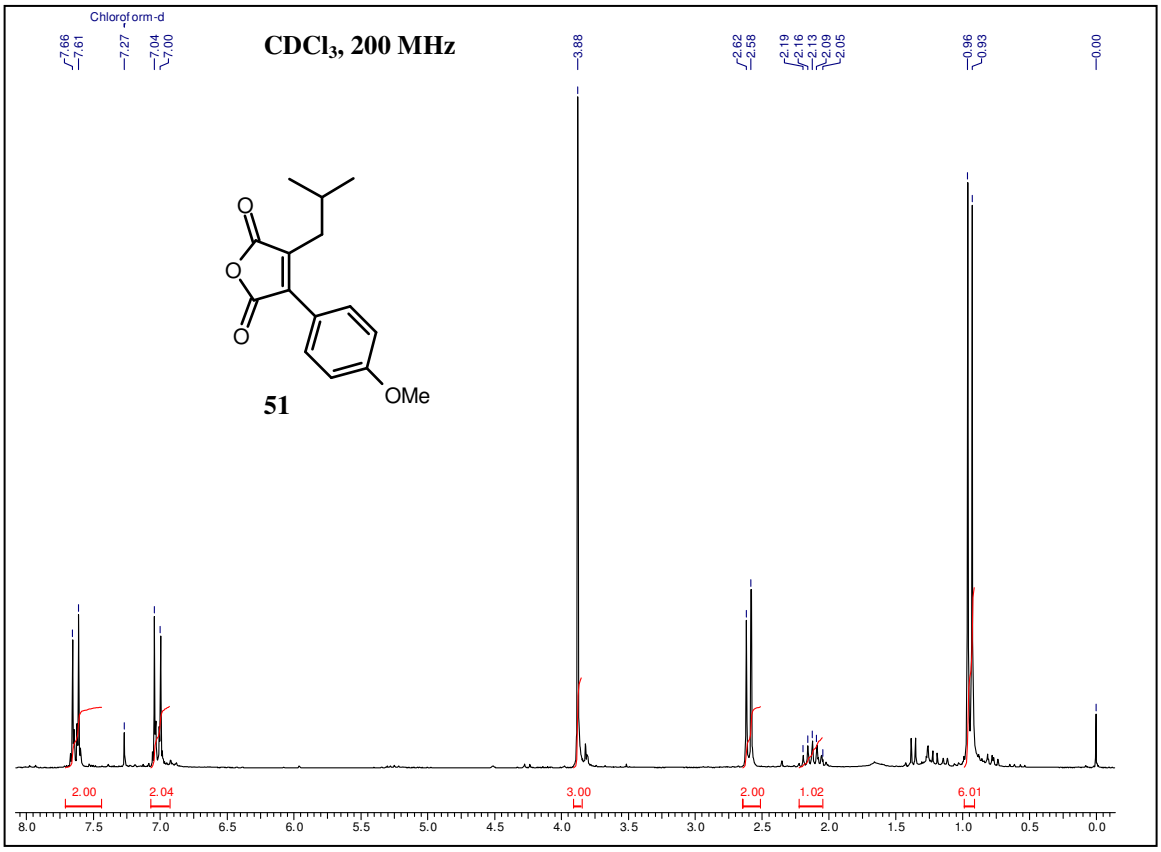

CDCl3, 125 MHz
Chloroform-d
173.27
159.73
136.10
129.64
129.15
128.90
128.70
128.46
127.62
127.39
77.00
71.12
33.96
Ph
O
O
Ph
22
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

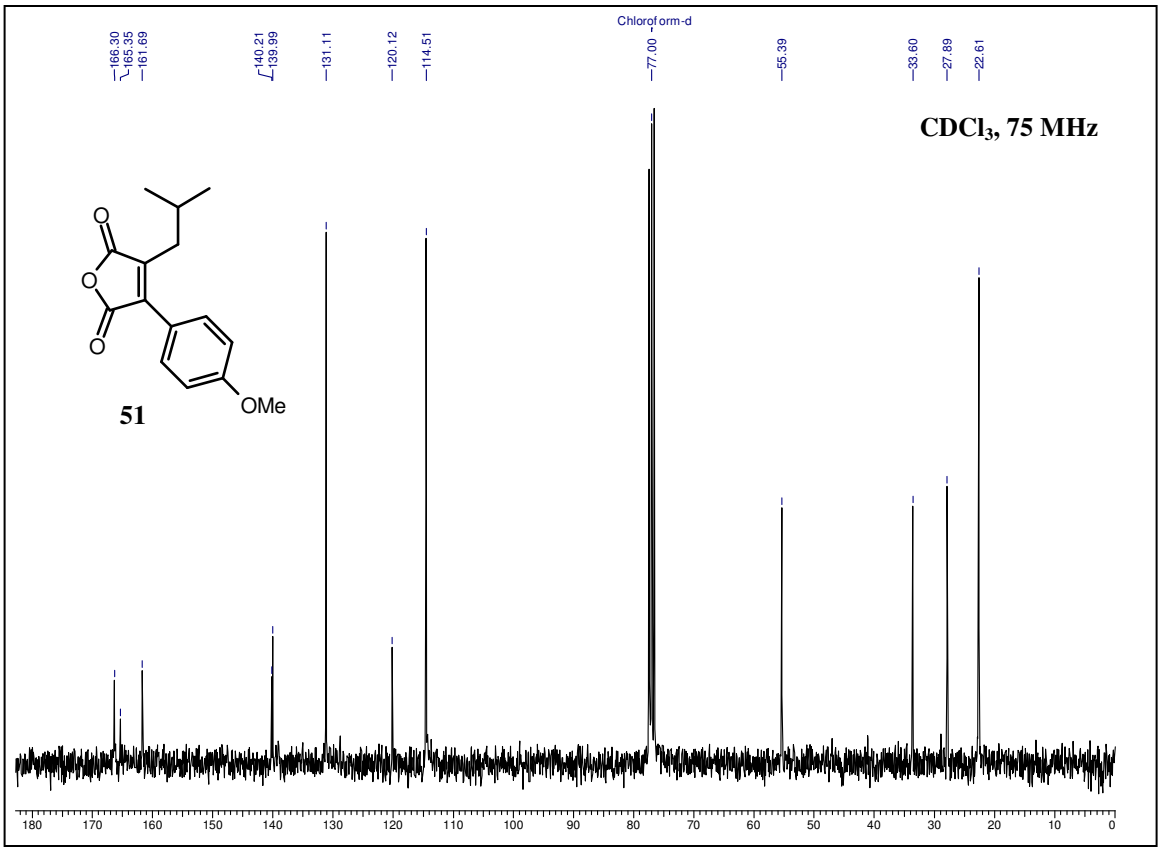

CDCl3, 125 MHz
Ph
O
Ph
O
22

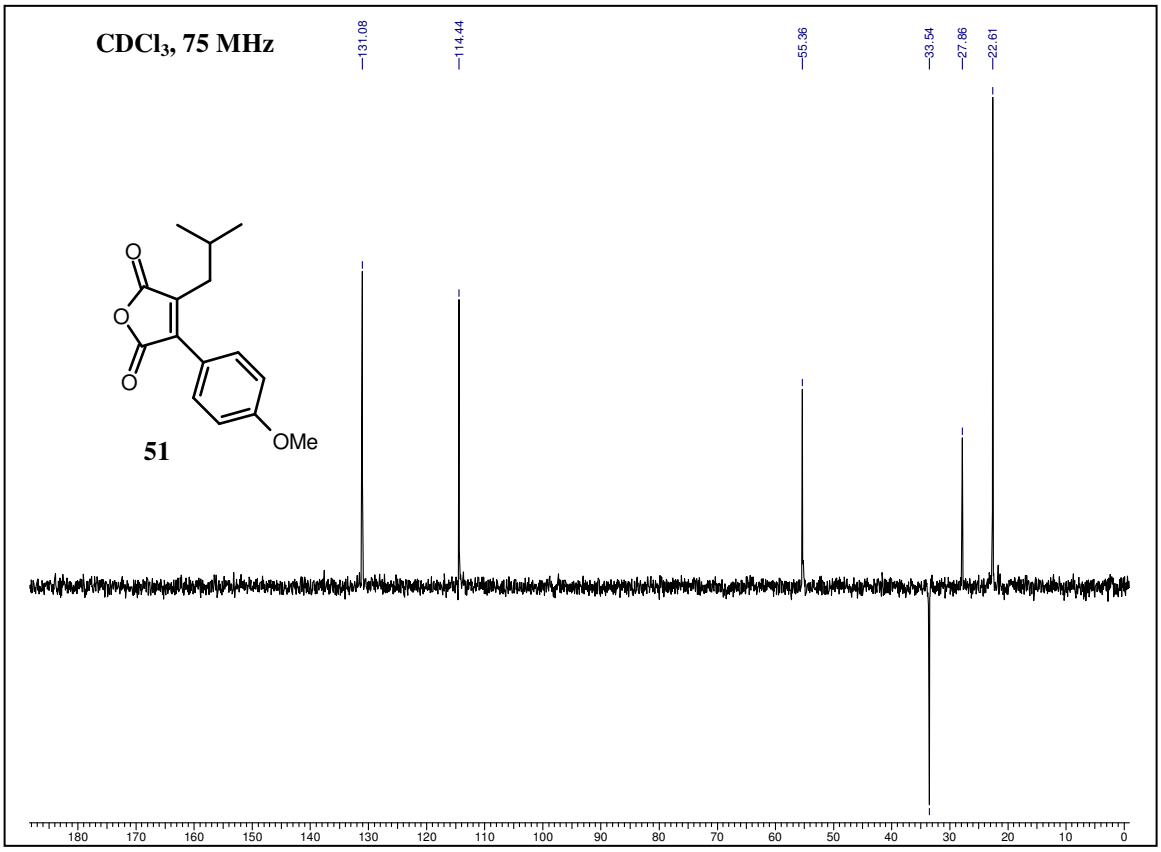

Chloroform-d
CDCl3, 200 MHz
Br
O
O
O
OMe
50

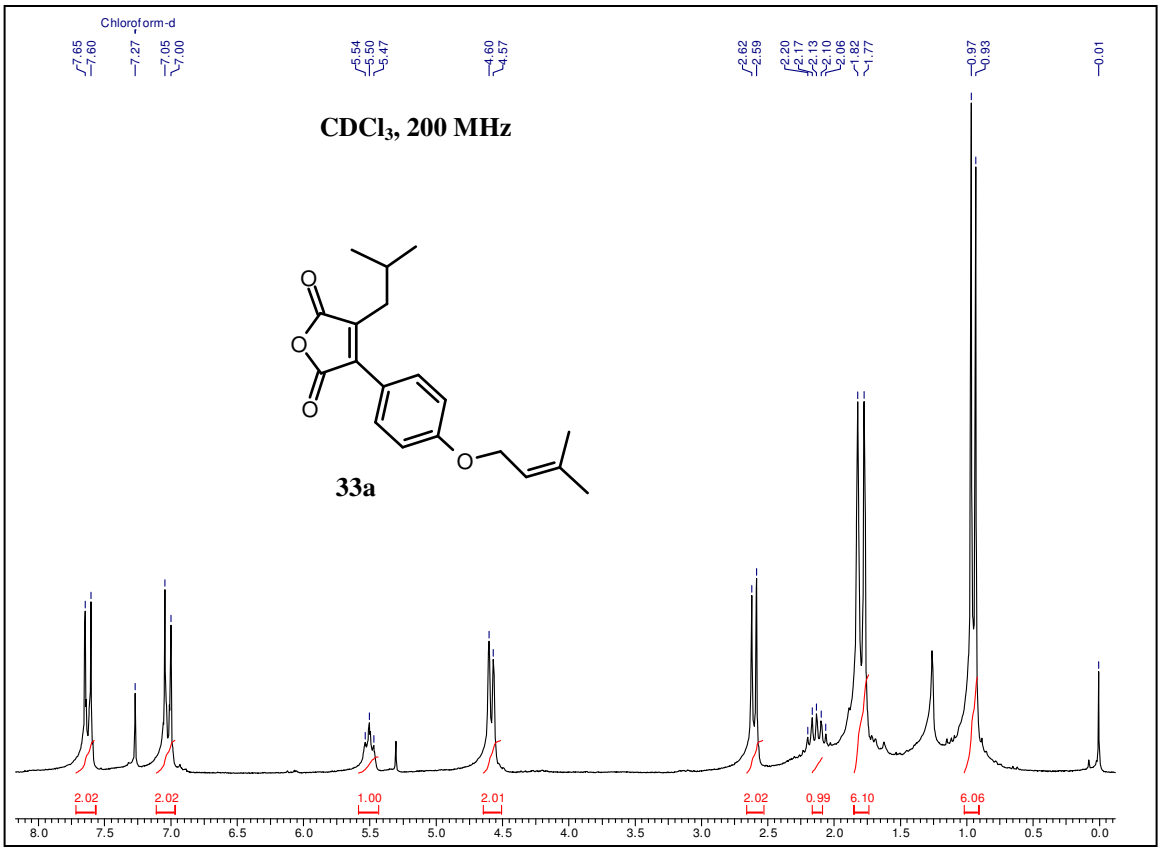

Chloroform-d
164.29
162.71
140.53
132.75
132.04
130.10
119.19
115.00
77.00
55.56
18.72
CDCl3, 50 MHz
Br
O
O
O
OMe
50

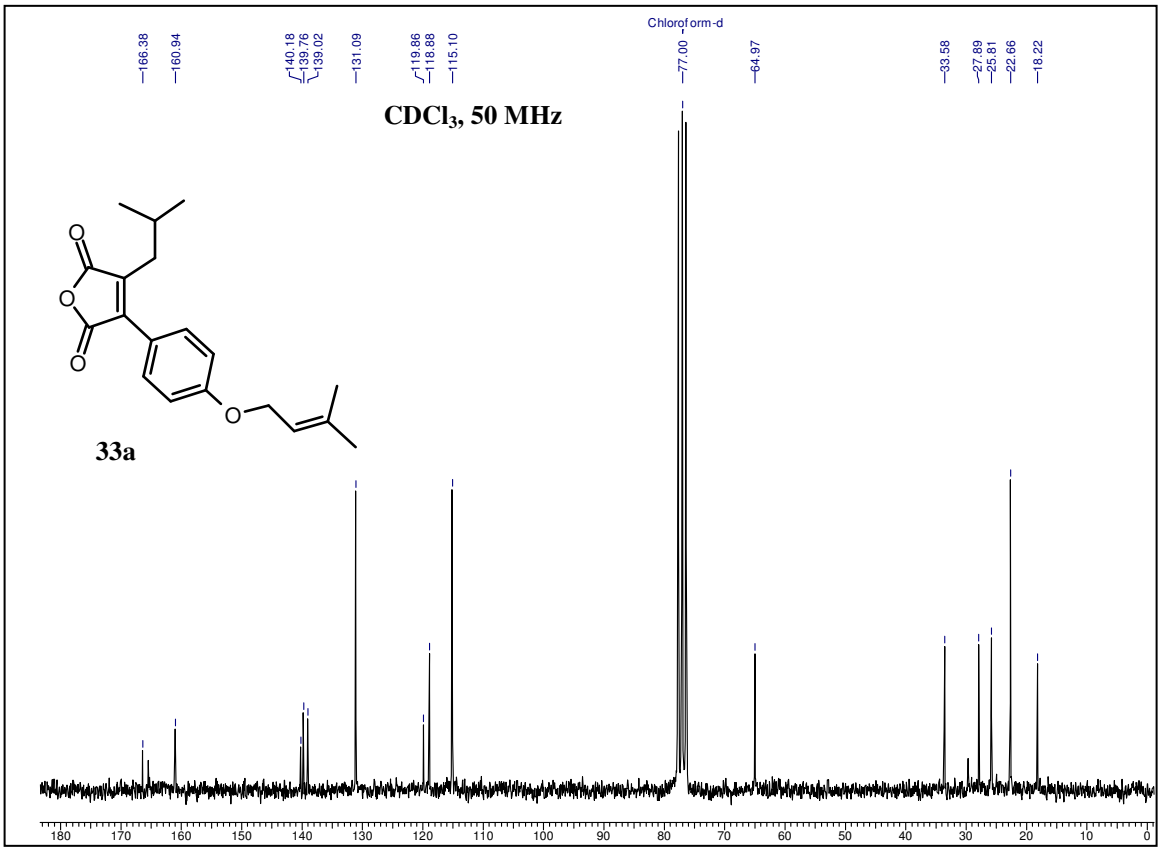

132.04
115.00
55.56
18.72
CDCl3, 50 MHz
Br
O
O
O
OMe
50

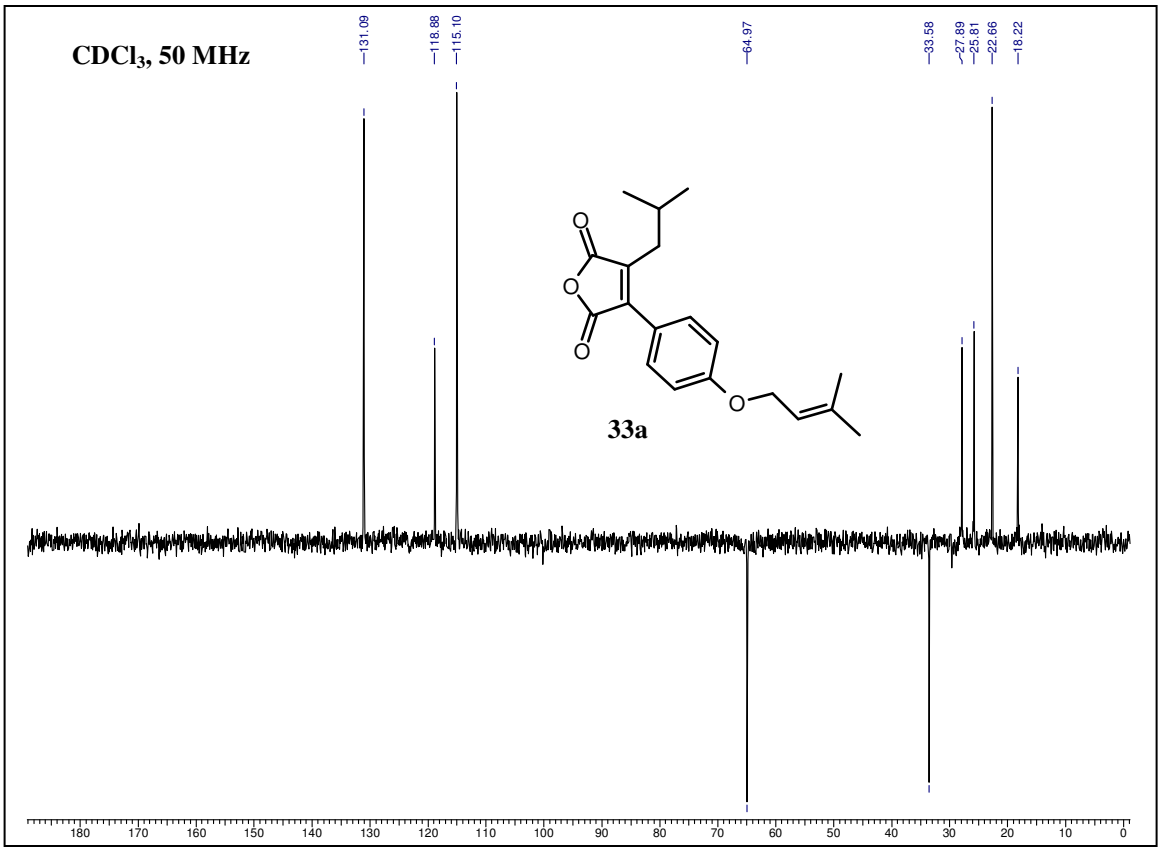

Chloroform-d
CDCl3, 200 MHz
7.66
7.61
7.27
7.04
7.00
3.88
2.62
2.58
2.19
2.16
2.13
2.09
2.05
0.96
0.93
0.00
O
O
O
OMe
51
2.00
2.04
3.00
2.00
1.02
6.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

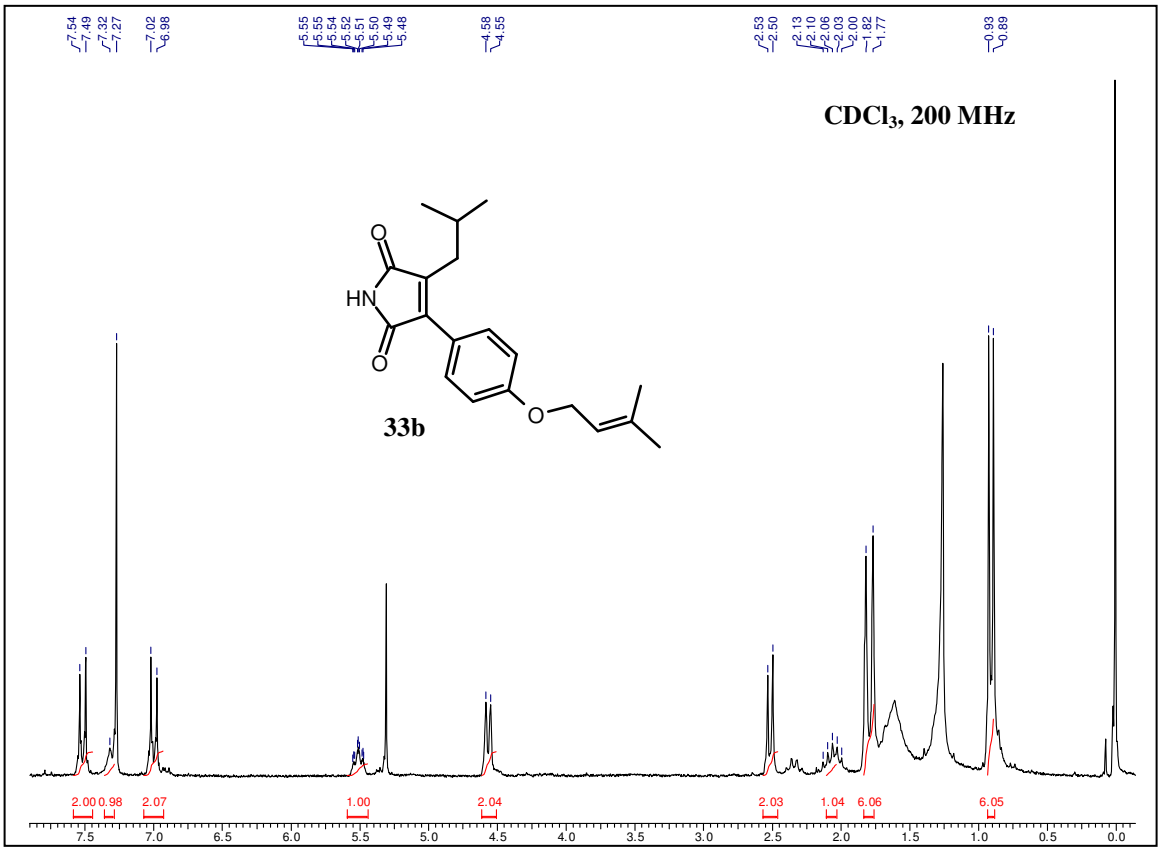

Chloroform-d
166.30
165.35
161.69
140.21
139.99
131.11
120.12
114.51
77.00
55.39
33.60
27.89
22.61
CDCl3, 75 MHz
O
O
O
OMe
51
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

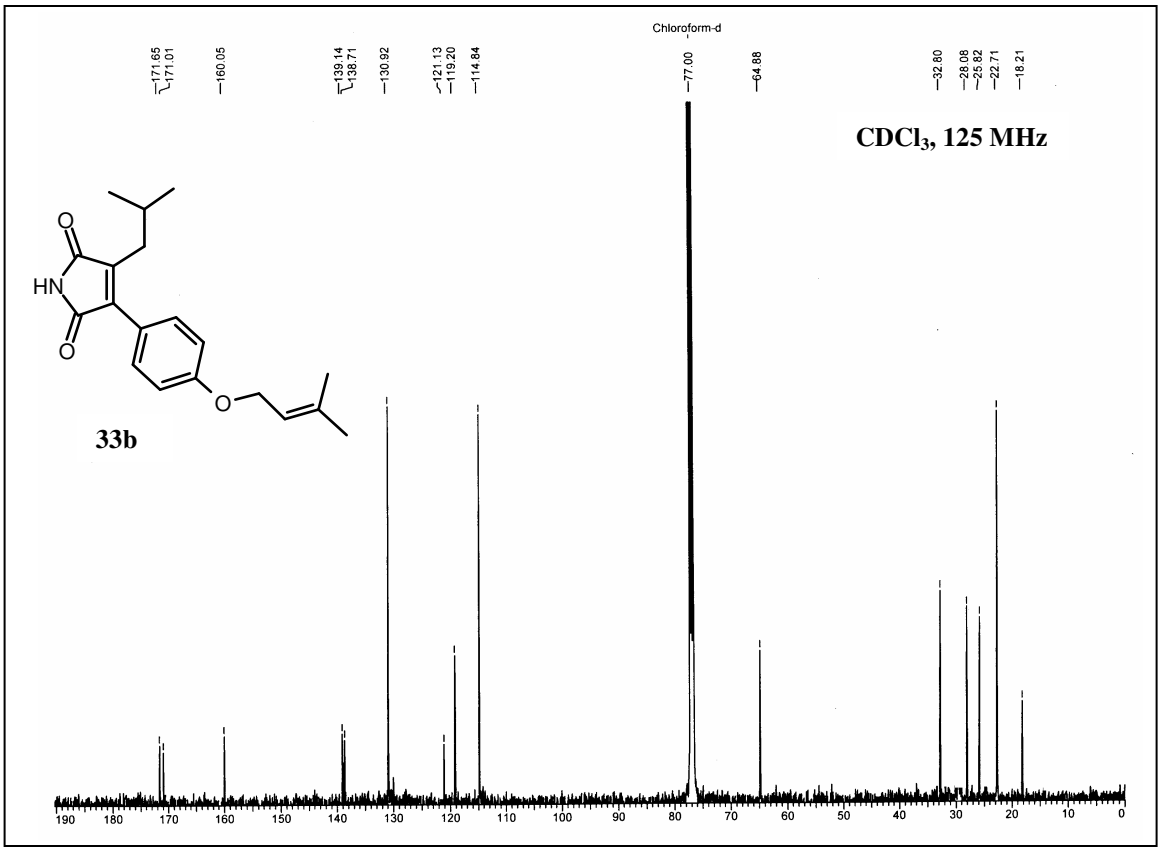

CDCl3, 75 MHz
131.08
114.44
55.36
33.54
27.86
22.61
OMe
51

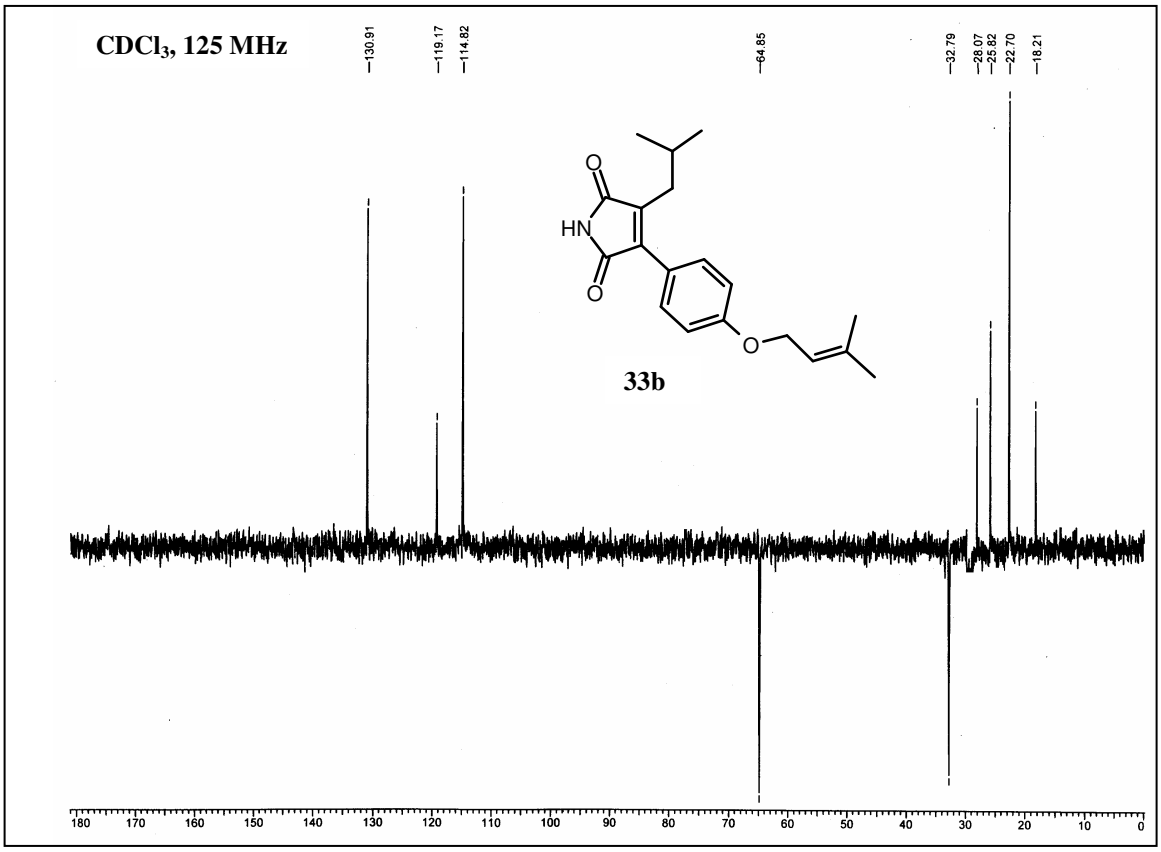

Chloroform-d
7.65
7.60
7.27
7.05
7.00
5.54
5.50
5.47
4.60
4.57
2.62
2.59
2.20
2.17
2.13
2.10
2.06
1.82
1.77
0.97
0.93
0.01
CDCl3, 200 MHz
33a
2.02
2.02
1.00
2.01
2.02
0.99
6.10
6.06

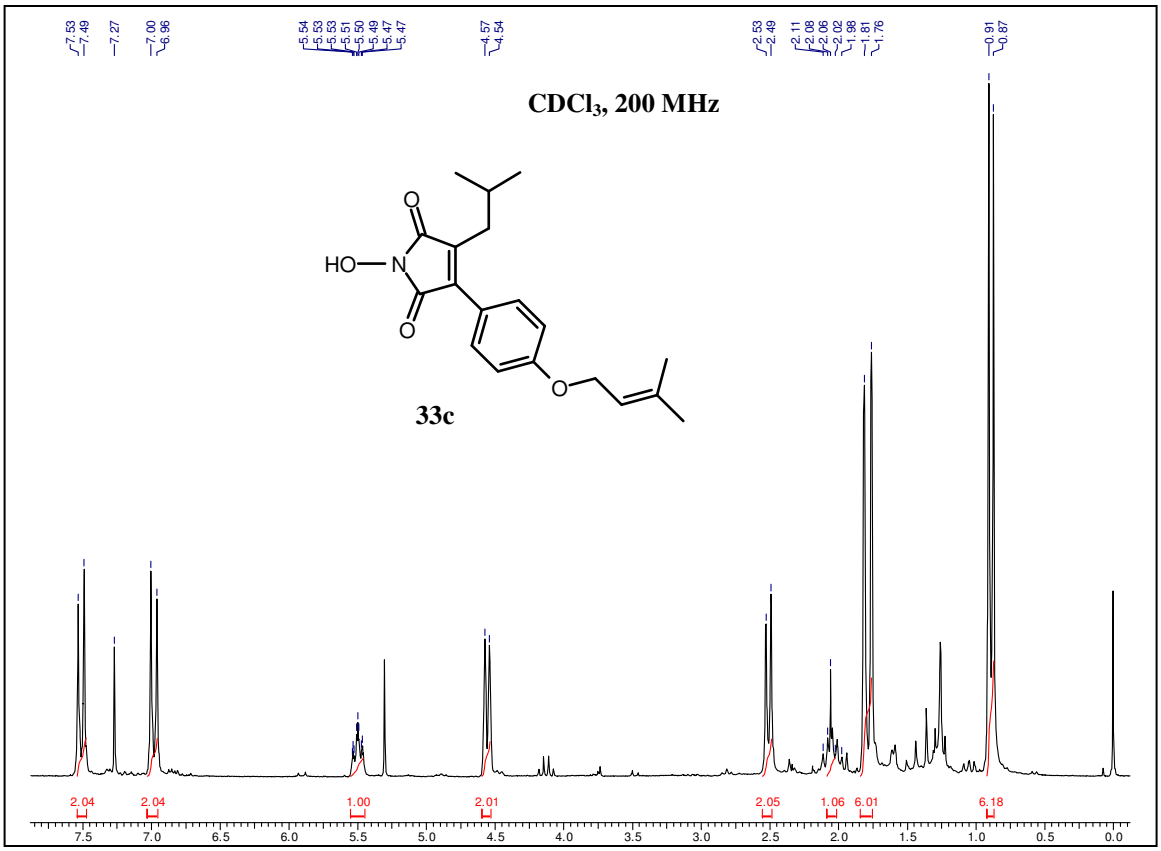

Chloroform-d
166.38
160.94
140.18
139.76
139.02
131.09
119.86
118.88
115.10
77.00
64.97
33.58
27.89
25.81
22.66
18.22
CDCl3, 50 MHz
33a

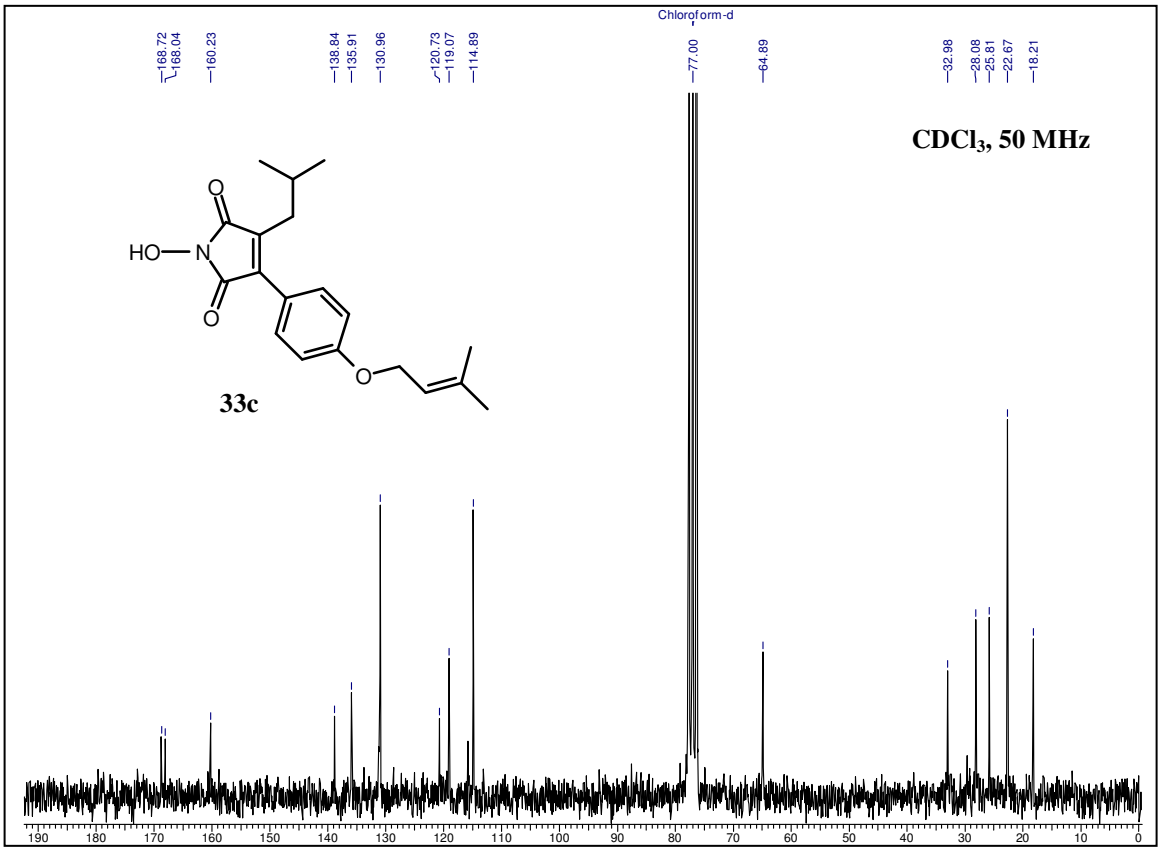

CDCl3, 50 MHz
131.09
118.88
115.10
64.97
33.58
27.89
25.81
22.66
18.22
33a

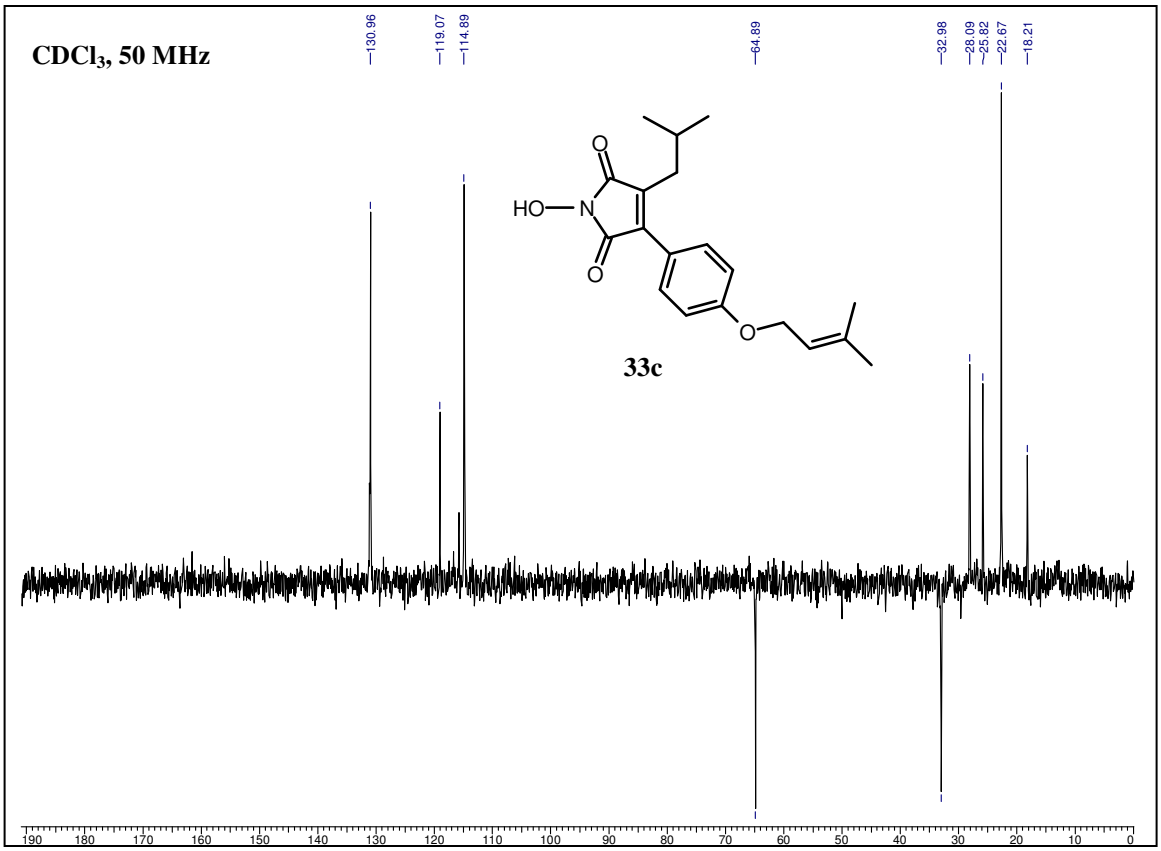

CDCl3, 200 MHz
33b

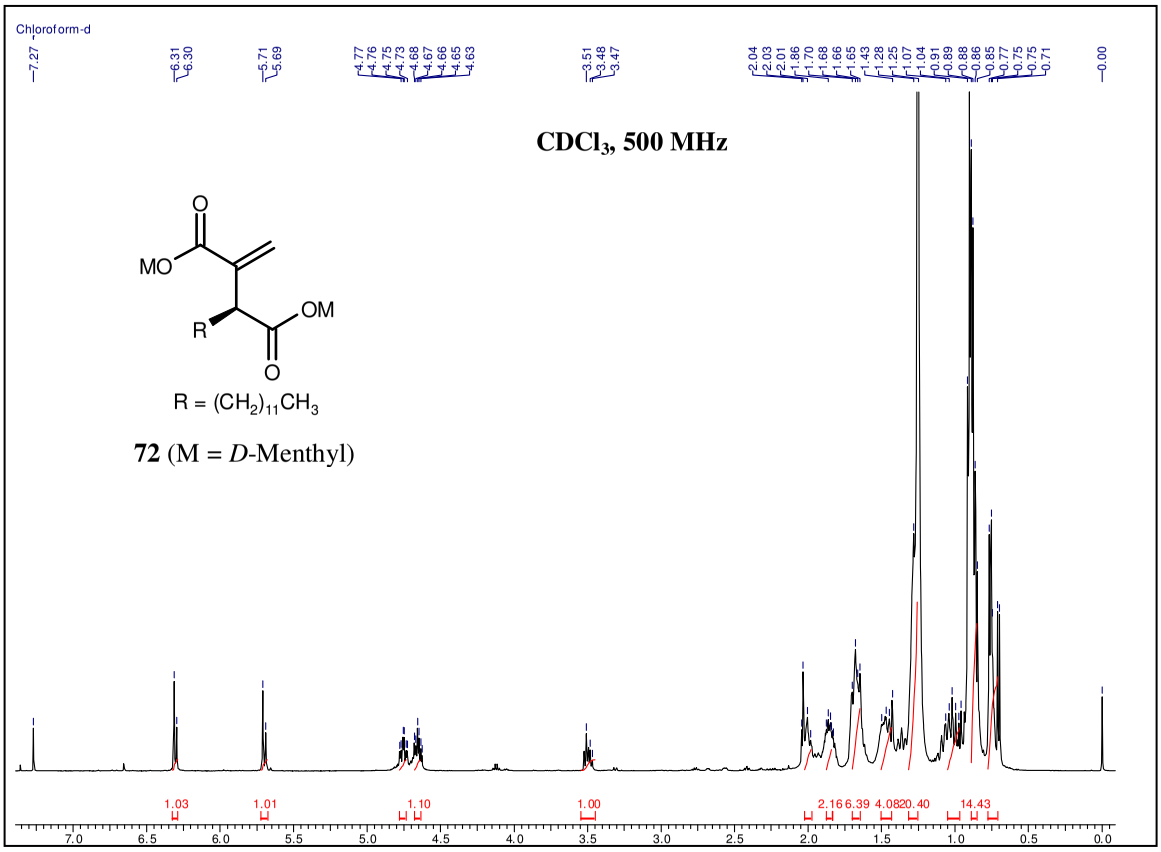

CDCl3, 125 MHz
Chloroform-d
33b

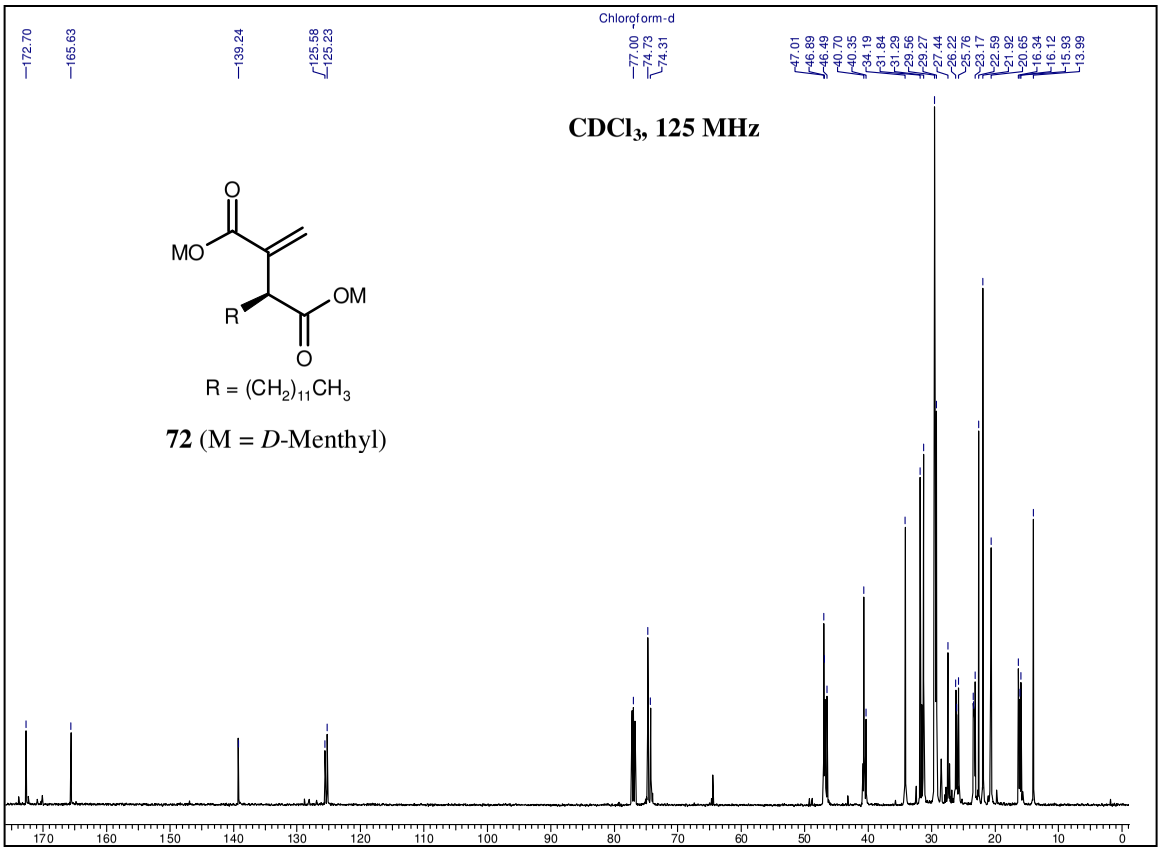

CDCl3, 125 MHz
130.91
119.17
114.82
64.85
32.79
28.07
25.82
22.70
18.21
HN
O
O
O
33b

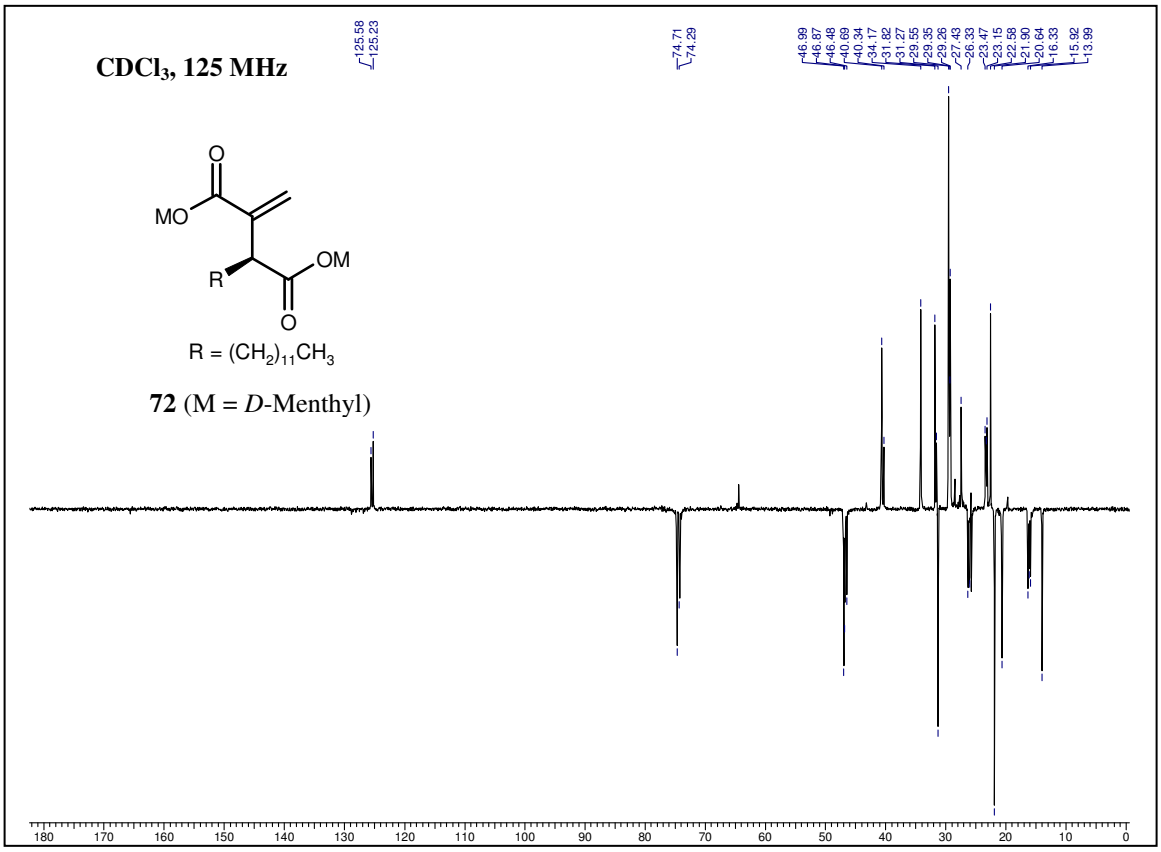

CDCl3, 200 MHz
HO—N
O
O
O
33c
2.04
2.04
1.00
2.01
2.05
1.06
6.01
6.18

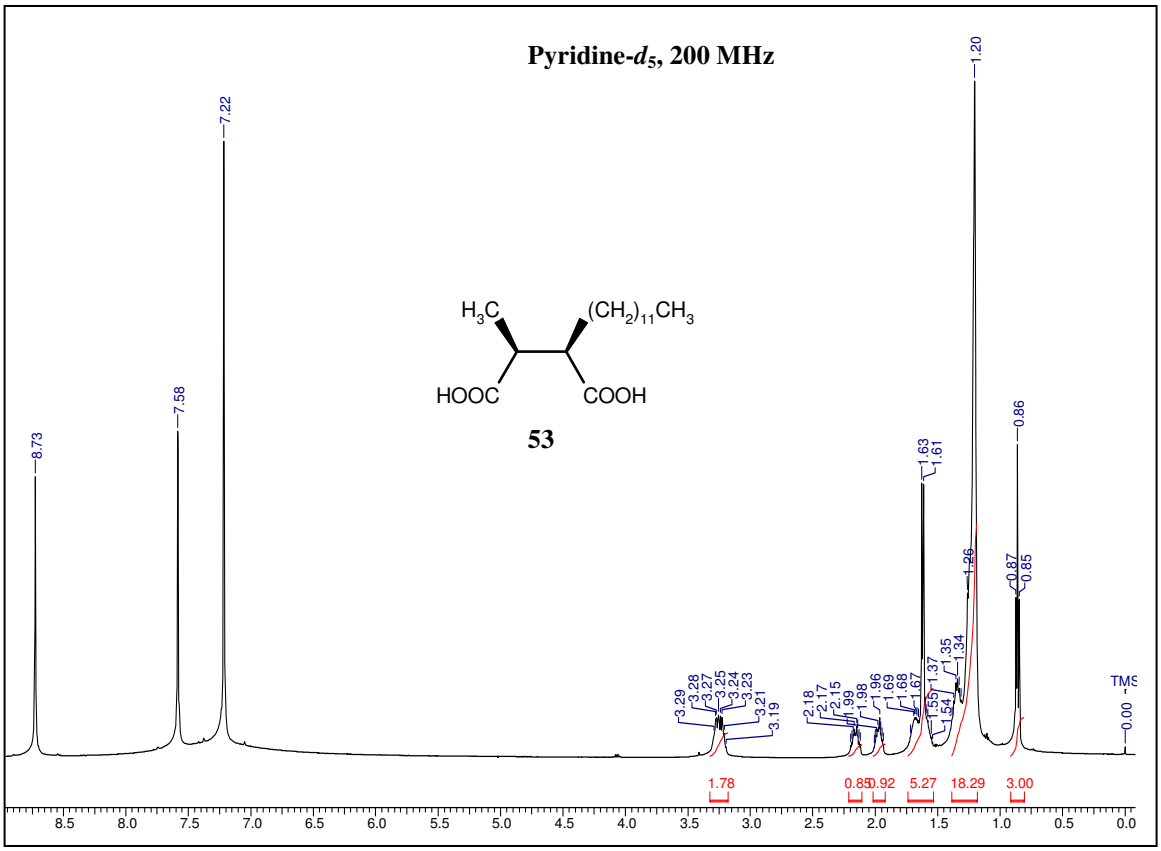

Chloroform-d
168.72
168.04
160.23
138.84
135.91
130.96
120.73
119.07
114.89
77.00
64.89
32.98
28.08
25.81
22.67
18.21
CDCl3, 50 MHz
HO
N
O
O
O
33c

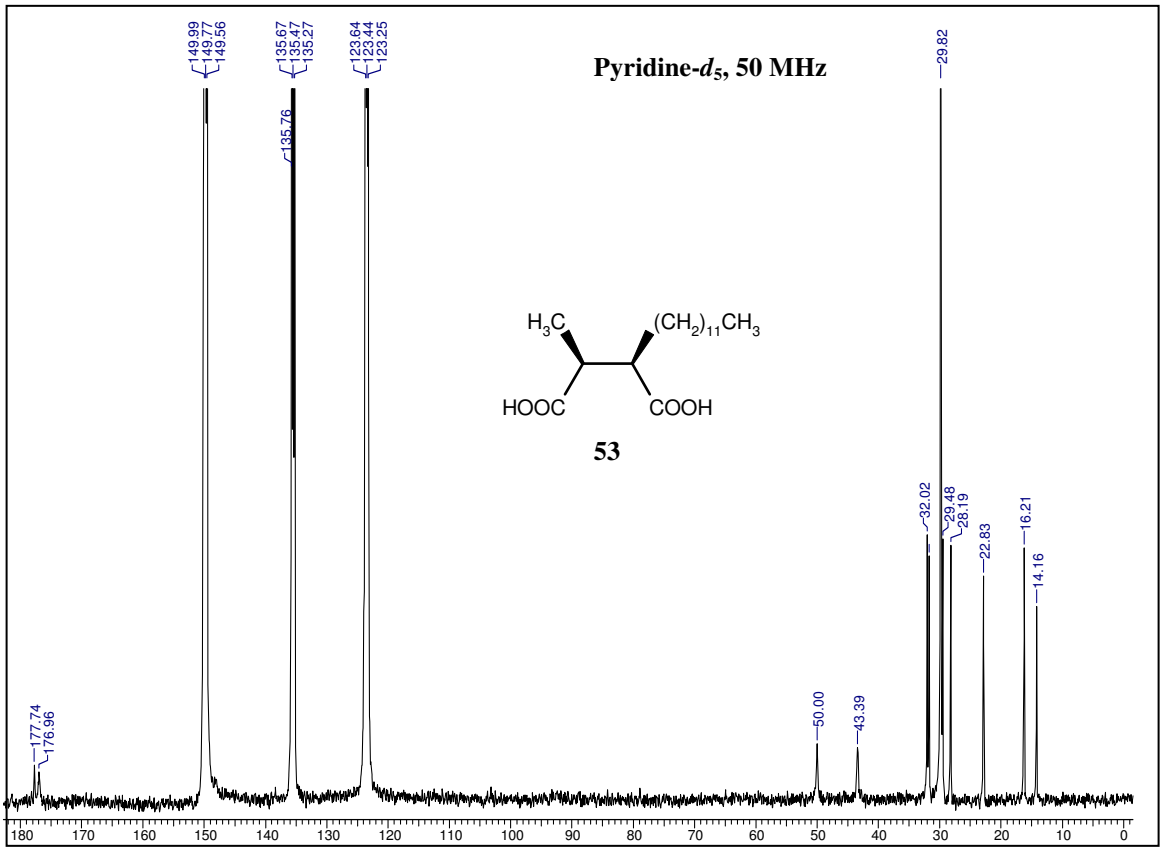

CDCl3, 50 MHz
130.96
119.07
114.89
64.89
32.98
28.09
25.82
22.67
18.21
HO
N
O
O
O
33c

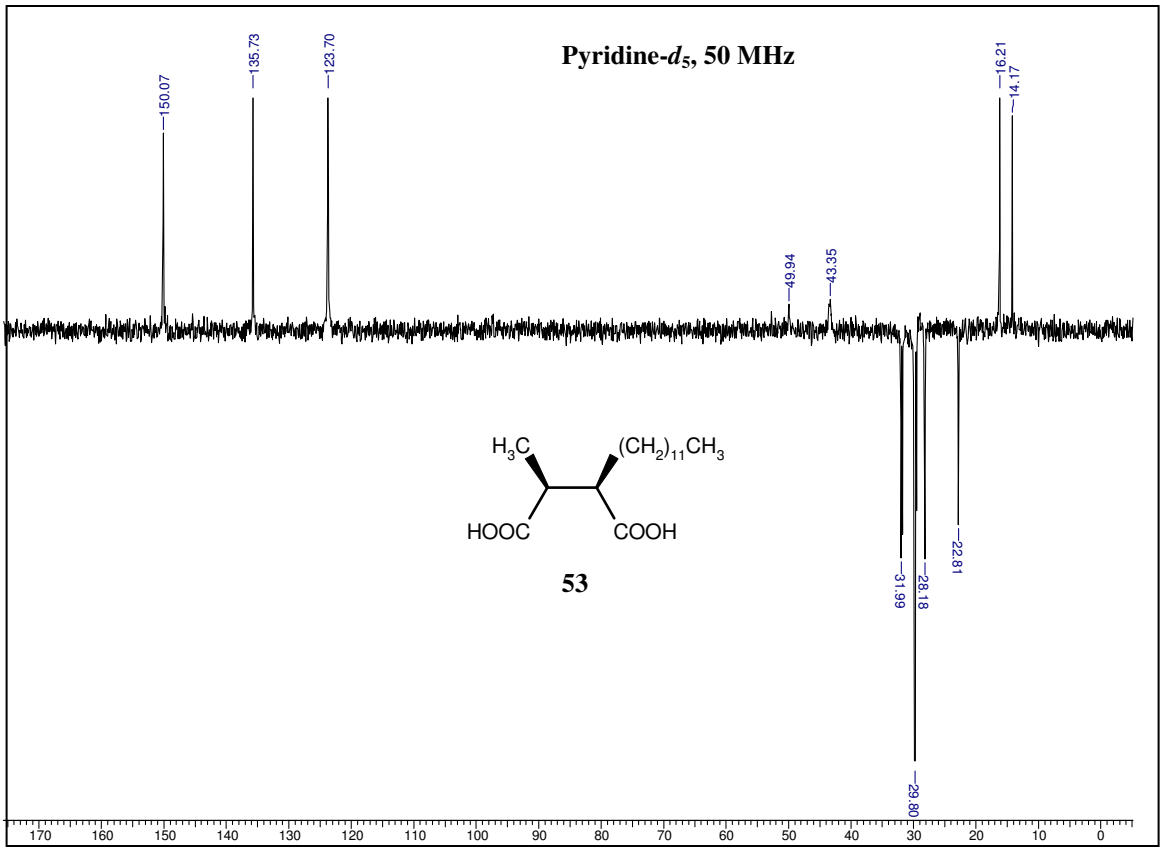

Chloroform-d
CDCl3, 500 MHz
MO
OM
R
O
R = (CH2)11CH3
72 (M = D-Menthyl)


Chloroform-d
CDCl3, 125 MHz
MO
OM
R
O
R = (CH2)11CH3
72 (M = D-Menthyl)


CDCl3, 125 MHz
MO
OM
R
O
R = (CH2)11CH3
72 (M = D-Menthyl)


Pyridine-d5, 200 MHz
H3C
(CH2)11CH3
HOOC
COOH
53


Pyridine-d_5, 50 MHz
149.99
149.77
149.56
135.67
135.47
135.27
135.76
123.64
123.44
123.25
29.82
177.74
176.96
50.00
43.39
32.02
29.48
28.19
22.83
16.21
14.16
H_3C
$(CH_2)_{11}CH_3$
HOOC
COOH
53


Pyridine-d_5, 50 MHz
150.07
135.73
123.70
16.21
14.17
49.94
43.35
31.66
28.18
22.81
29.80
H_3C
$(CH_2)_{11}CH_3$
HOOC
COOH
53

2B.9. References

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2C. Section C

A Facile Chemo-, Regio- and Diastereoselective Approach to Cis-3,5-Disubstituted γ-Butyrolactones and Fused γ-Butyrolactones

This section features the following topics:

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2C. Section C: A Facile Chemo-, Regio- and Diastereoselective Approach to *Cis*-3,5-Disubstituted γ-Butyrolactones and Fused γ-Butyrolactones

2C.1. Background

The natural and unnatural γ-butyrolactones are an important class of compounds that find major applications in organic, medicinal and polymer chemistry.[1] A broad range of biological properties have been conferred on them that include strong antibiotic, antihelmitic, antifungal, antitumor, antiviral, anti-inflammatory, cytostatic, antiallergenic, histone acetyltransferase Gcn5 inhibitor and anti-HIV activities.[1-4] From the bioactivity point of view, among all types of butyrolactones, the α-methylene-γ-butyrolactones are of special interest as alkylating agents via Michael-type acceptor of biological cellular nucleophiles or cysteine residues of functional proteins.[4] A very large number of such γ-butyrolactones have been synthesized during the past century using several elegant synthetic strategies.

2C.1.1: Synthetic approaches towards γ-butyrolactones

The diverse range of γ-butyrolactone skeletons have been designed by employing new C-O bond construction reactions and metal catalyzed C-C bond formations via the carbocyclization of enynes. Before discussing our results, the reported synthetic approaches towards γ-butyrolactone are illustrated in brief in the following part.

[A] *Zhang's approach*

The α-methylene-γ-butyrolactone unit is an important motif of many natural products, such as (+)-pilocarpine, (+)-isopilocarpine, and (+)-isopilosine.[5] The exocyclic double bond is considered not only to be responsible for the interesting biological properties of γ-lactones but also to serve as a functional group for further manipulations in organic synthesis.[6] Zhang and co-workers[7] have reported the synthesis of α-methylene-γ-butyrolactone by Rh(I)-catalyzed intramolecular Alder ene reaction. The asymmetric Rh-catalyzed Alder ene reactions were carried out in the presence of $[Rh(COD)Cl]_2$, (*R*)- or (*S*)-BINAP, and $AgSbF_6$ at room temperature. Extraordinarily high enantioselectivity (>99% ee) and high yields (90-98%) were obtained for a wide range of substituents (Scheme 1, Table 1).

Scheme 1

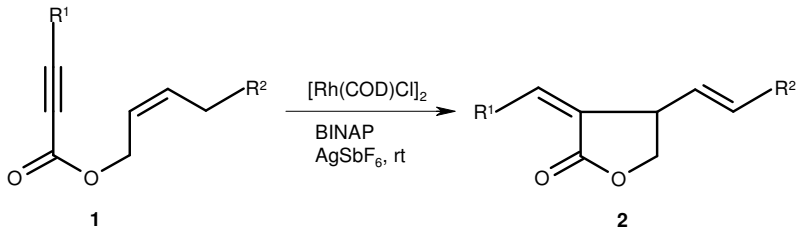


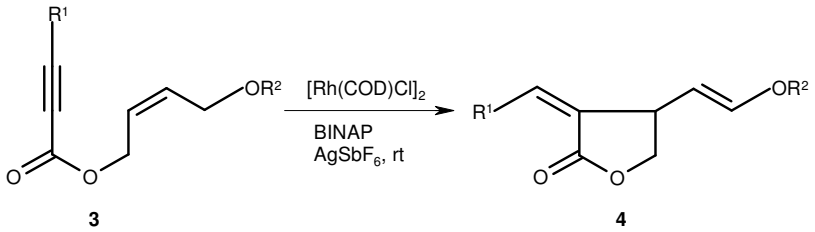
Table 1. Asymmetric Rh(I)-catalyzed intramolecular Alder ene reaction[a]

	Substrate				Product		
Entry	**1**	R^1	R^2	BINAP	**2**[d]	Yield (%)[b]	*Ee* (%)[c]
1	**1a**	Ph	Et	*S*-BINAP	(*S*)-(+)-**2a**	93	>99
2	**1b**	Ph	H	*R*-BINAP	(*R*)-(-)-**2b**	94	>99
3	**1c**	Ph	Me	*R*-BINAP	(*R*)-(-)-**2c**	92	>99
4	**1c**	Ph	Me	*S*-BINAP	(*S*)-(+)-**2c**	93	>99
5	**1d**	Me	H	*R*-BINAP	(*R*)-(-)-**2d**	92	>99
6	**1e**	Me	Me	*R*-BINAP	(*R*)-(-)-**2e**	98	>99
7	**1f**	*n*-C_5H_{11}	H	*S*-BINAP	(*S*)-(+)-**2f**	90	>99
8	**1g**	*n*-C_5H_{11}	Me	*S*-BINAP	(*S*)-(+)-**2g**	95	>99

[a]All the reactions were carried out in 2 mL of $ClCH_2CH_2Cl$ in 0.2 mmol scale. The ratio of substrate/$[Rh(COD)Cl]_2$/BINAP/$AgSbF_6$ was 1:0.05:0.11:0.20. This reaction finished within 2-10 min. [b] Isolated yield. [c] Ee value was determined by GC or HPLC. [d] Stereochemical assignments -(*R*) and -(*S*) are based on comparison with known compound **6a**.

Vinyl acetate and vinyl ether-substituted γ-lactone were formed in high yields (91-98%) with excellent enantioselectivities (>99%) (Scheme 2, Table 2).

Scheme 2



3 4

Table 2. Asymmetric Rh(I)-catalyzed Alder ene reactions of **3** to form functionalized lactones[a]

	Substrate				Product		
Entry	**3**	R^1	R^2	BINAP	**4**[d]	Yield (%)[b]	*Ee* (%)[c]
1	**3a**	Ph	Ac	*R*-BINAP	(*R*)-(-)-**4a**	96	>99
2	**3b**	Ph	Me	*S*-BINAP	(*S*)-(+)-**4b**	96	>99
3	**3c**	Ph	Bn	*S*-BINAP	(*S*)-(+)-**4c**	92	>99
4	**3d**	Me	AC	*R*-BINAP	(*R*)-(-)-**4d**	93	>99
5	**3d**	Me	Ac	*S*-BINAP	(*S*)-(+)-**4d**	98	>99
6	**3e**	Me	Me	*S*-BINAP	(*S*)-(-)-**4e**	95	>99
7	**3f**	Me	Bn	*S*-BINAP	(*S*)-(+)-**4f**	91	>99
8	**3g**	*n*-C_5H_{11}	Ac	*S*-BINAP	(*S*)-(-)-**4g**	97	>99
9	**3h**	*n*-C_5H_{11}	Me	*S*-BINAP	(*S*)-(-)-**4h**	96	>99
10	**3i**	*n*-C_5H_{11}	Bn	*R*-BINAP	(*R*)-(+)-**4i**	91	>99
11	**3i**	*n*-C_5H_{11}	Bn	*S*-BINAP	(*S*)-(+)-**4i**	92	>99

[a]All the reactions were carried out in 2 mL of $ClCH_2CH_2Cl$ in 0.2 mmol scale. The ratio of substrate/$[Rh(COD)Cl]_2$/BINAP/$AgSbF_6$ was 1: 0.05: 0.11:0.20. This reaction finished within 2-10 min. [b] Isolated yield. [c] *Ee* value was determined by GC or HPLC. [d] Stereochemical assignments -(*R*) and -(*S*) are based on comparison with known compound **6a**.

When the substrates with alcohol at allylic position **5** were used, the resulting products **6** contained an aldehyde. Again, high yields (91-99%) and enantioselectivities (>99%) were obtained (Scheme 3, Table 3). (+)-Pilocarpine can be prepared in two additional steps from (*R*)-(+)-**6a** according to the literature method.[8]

Scheme 3

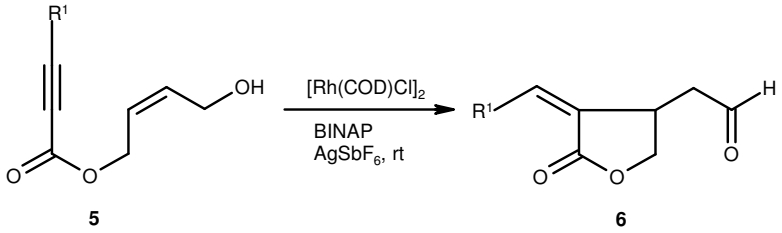


Table 3. Asymmetric Rh(I)-catalyzed Alder ene reactions of **5** to form aldehyde substituted lactones[a]

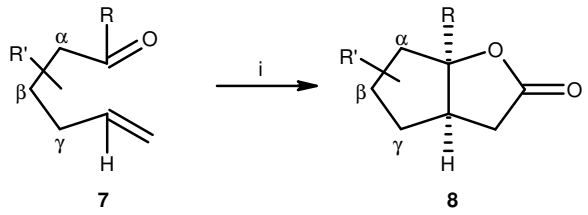
Entry	R	**5**	BINAP	**6**[d]	Yield (%)[b]	*Ee* (%)[c]
1	Me	**5a**	*R*-BINAP	(*R*)-(+)-**6a**	99	>99
2	Me	**5a**	*S*-BINAP	(*S*)-(-)-**6a**	98	>99
3	*n*-C_5H_{11}	**5b**	*S*-BINAP	(*S*)-(-)-**6b**	95	>99
4	Ph	**5c**	*R*-BINAP	(*R*)-(+)-**6c**	92	>99
5	Ph	**5c**	*S*-BINAP	(*S*)-(-)-**6c**	91	>99

[a] All the reactions were carried out in 2 mL of $ClCH_2CH_2Cl$ in 0.2 mmol scale. The ratio of substrates/$[Rh(COD)Cl]_2$/BINAP/$AgSbF_6$ was 1: 0.05: 0.11:0.20. This reaction finished within 2-10 min. [b] Isolated yield. [c] Ee value was determined by GC. [d] Stereochemical assignments -(*R*) and -(*S*)are based on comparison with known compound **6a**.

[B] *Crowe's approach*

The butyrolactone ring is an integral building block of many natural products.[9] Crowe and co-workers[10] have reported a general catalytic cyclocarbonylation of enals and enones using a chiral titanocene catalyst that also affords the asymmetric version of this reaction. In a typical experiment a mixture of substrate and ansa-metallocene (EBTHI)$Ti(CO)_2$ catalyst[11] in toluene was heated at 100 °C, under CO pressure, in the presence of excess

PMe_3. The catalyst system worked well both for enal and enone substrates forming fused γ-butyrolactones in very good to excellent yield (Scheme 4, Table 4 and 5).



7 **8**

Scheme 4. *Reagents, conditions and yield*: (i) 10-20 mol % Catalyst, 30-80 mol% PMe_3, 50 psi CO, toluene, 100 °C, 36-40 h (73-92%).

Table 4. Catalytic cyclocarbonylation diastereoselective reactions

Reactant	R	R'	Product	Yield (%)
7a	H	β-Me	**8a**	92
7b	H	β-Ph	**8b**	89
7c	Me	β-Ph	**8c**	73
7d	Ph	β-Ph	**8d**	76
7e	H	α-Me	**8e**	79
7f	H	γ-Me	**8f**	80

Table 5. Catalytic cyclocarbonylation enantioselective reactions

Reactant	R	R'	Product	Yield (%)	Catalyst	*Ee* (%)
7g	H	-	**8g**	84	(*S*,*S*)	0
7h	H	α-$(Me)_2$	**8h**	91	(*S*,*S*)	0
7i	H	β-$(Me)_2$	**8i**	87	(*S*,*S*)	58
					(*R*,*R*)	60
7j	H	γ-$(Me)_2$	**8j**	86	(*S*,*S*)	89
7k	Me	-	**8k**	80	(*S*,*S*)	90
					(*R*,*R*)	89
7l	Me	γ-$(Me)_2$	**8l**	88	(*S*,*S*)	90
7m	Me	β-$(Me)_2$	**8m**	93	(*S*,*S*)	58

[C] *Bode's approach*

Bode and co-workers[12a] and also Glorius and co-workers[12b] have reported the catalytic generation of homoenolates from α,*β*-unsaturated aldehydes and their application to the stereoselective synthesis of *γ*-butyrolactones (Scheme 5). A variety of enals with extended conjugation serve as efficient nucleophiles in direct annulations (Table 6).

Scheme 5

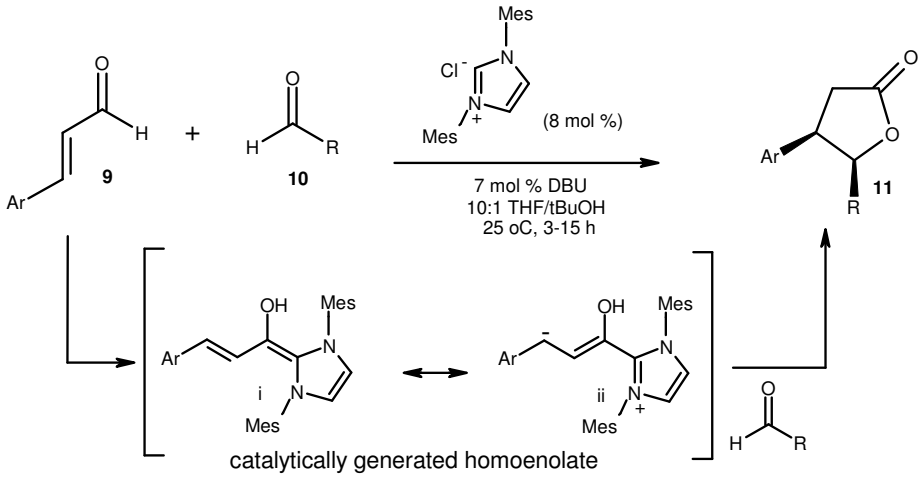


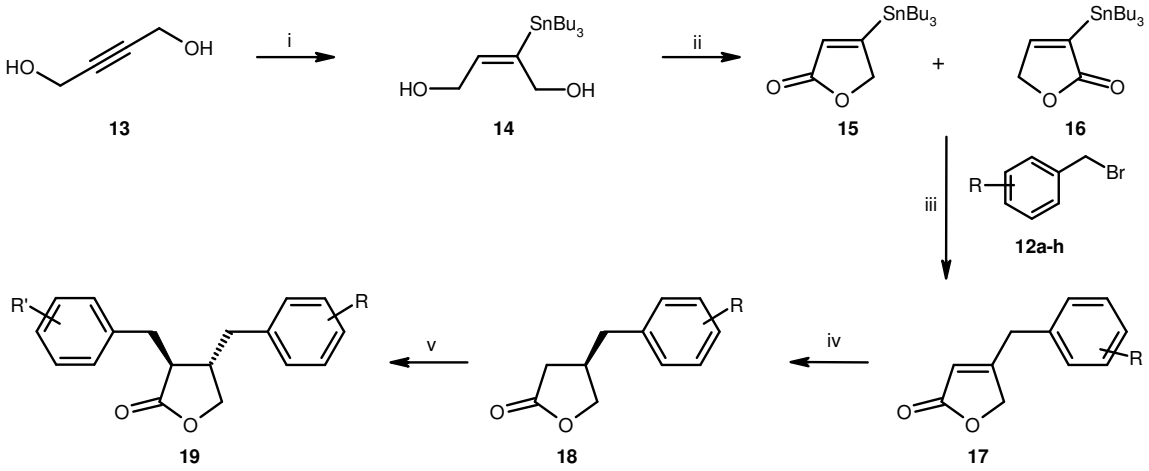
Table 6. Direct, catalytic annulations of aldehydes and enals

Entry	Ar	R	Product	*Dr* ratio	Yield (%)
1	Ph	4-Br-C_6H_4	**11a**	4:1	79
2	Ph	4-MeO-OCC_6H_4	**11b**	5:1	87
3	4-MeO-C_6H_4	4-Br-C_6H_4	**11c**	4:1	76
4	4-MeO-C_6H_4	Ph	**11e**	4:1	65
5	1-Naph	-	**11f**	5:1	67

[D] *Peter's approach*

Lignans, dimers of phenylpropenes, are ubiquitous secondary plant metabolites.[13] They exhibit notable biological activities, in particular antiviral,[14a] cytotoxic[14b] and canceroprotective[14c] properties. Peter and co-workers[15] have reported the synthesis of biologically active lignan analogs by using transition metal catalysed reactions. The palladium catalysed *cis*-selective addition of tributylstannane to butynediol **13** gave diol **14**. Treatment of diol **14** with NMO and 7.5 mol% TPAP at -78 °C to rt afforded the lactones **15** and **16** in 47 % yield (25:1 ratio). Lactones **15** and **16** were subjected to Stille coupling with benzyl bromides **12a**–**h** to furnish the coupling products **17a**–**h**. In analogy,

only lactone **15** reacted with benzyl bromides **12a–h** to furnished the coupling products **17a–h** (Table 7). Hydrogenation of lactones **17a–h** to lactones **18a–h** were achieved by means of 10% Pd on charcoal or Ra-Ni T4 (Table 8). Alkylation of lactones **18** with benzyl halides using LDA as base and DMPU as cosolvent provides lactone lignans **19** (Scheme 6 and Table 7).



Scheme 6. *Reagents, conditions and yields*: (i) Bu_3SnH, cat. $Pd(PPh_3)_4$ (92%); (ii) NMO, 7.5 mol% TPAP at -78 °C to rt, 62 h (47%); (iii) **12a**-**h**, Cat. Pd_2dba_3 (24-80%); (iv) H_2, cat. Ra-Ni or Pd/C (70-98%); (v) LiHMDS, DMPU, **12d**,**f**-**h**, -78 °C (18-43%).

Table 7. Benzyl bromides **12a–h** employed for the Stille coupling and yields of the reaction products **17a–h**

Entry	R	Bromide	Lactone	Yield(%)
1	4-Mesyl-3-methoxy	**12a**	**17a**	80
2	3,4,5-Trimethoxy	**12b**	**17b**	56
3	4-Methyl	**12c**	**17c**	76
4	H	**12d**	**17d**	70
5	4-Nitro	**12e**	**17e**	24
6	2,4,6-Trimethyl	**12f**	**17f**	77
7	3-Methoxy	**12g**	**17g**	59
8	3,4-Methylinedioxy	**12h**	**17h**	45

Table 8. Hydrogenation of the unsaturated lactones **17a–h** using different catalysts

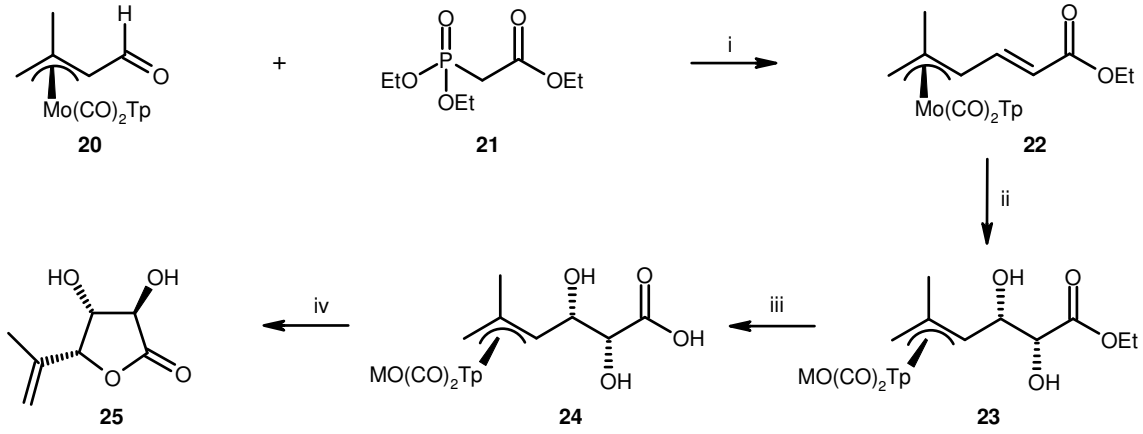
Entry	Unsat. lactone	Product	Catalyst	Pressure (bar)	Time (h)	Yield (%)
1	**17a**	**18a**	Pd/C	0.1	14	93
2	**17a**	**18a**	Ra-Ni T4	0.1	2	98
3	**17b**	**18b**	Pd/C	0.1	14	0
4	**17b**	**18b**	Ra-Ni T4	0.1	2	70
5	**17c**	**18c**	Pd/C	0.1	24	98
6	**17d**	**18d**	Pd/C	50	48	97
7	**17e**	**18e**	Pd/C	0.1	14	0
8	**17f**	**18f**	Pd/C	0.1	14	0
9	**17f**	**18f**	Pd/C	100	72	88
10	**17f**	**18f**	Ra-Ni T4	0.1	2	98
11	**17g**	**18g**	Pd/C	100	14	92
12	**17h**	**18h**	$Pd(OH)_2$	100	16	0
13	**17h**	**18h**	Ra-Ni T4	0.1	2	70

Table 9. Alkylation of lactones **18d**,**f–h** to the symmetrically and unsymmetrically substituted lignan analogues **19**

Entry	Lactone	Bromide	Residue (R')	Lignan	Yield (%)
1	**18d**	**12d**	H	**19d**	30
2	**18f**	**12f**	2,4,6-Trimethyl	**19f**	43
3	**18f**	**12h**	3,4-Metrhylenedioxy	**19fb**	25
4	**18g**	**12g**	3-Methoxy	**19g**	18
5	**18h**	**12h**	3,4-Metrhylenedioxy	**19h**	35

[E] *Pearson's approach*

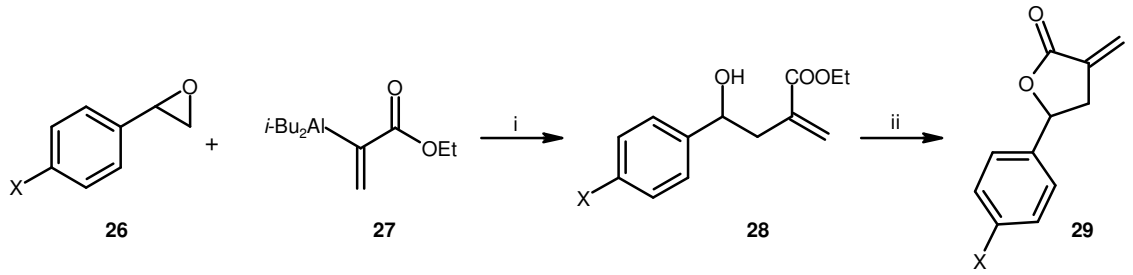
Pearson *et al*[16] have reported a novel methodology for the construction of hydroxylated *γ*-butyrolactones, via a diastereoselective osmylation reaction of organometallic species having an α,*β*-unsaturated ester lateral to a *π*-allyl molybdenum system. Aldehyde **20**[17] on a Horner-Wadsworth-Emmons reaction, with phosphonate **21** afforded the α,*β*-unsaturated ester **22** as a single isomer. The ester **22** on treatment with osmium tetroxide in THF, in the presence of tetramethylethylenediamine (TMEDA) the diol **23** in 94% yield. The hydrolysis of **23** with KOH, followed by neutralization with HCl at 0 °C furnished crude acid **24** which on treatment with $NOBF_4$ at 0 °C, followed by addition of Et_3N and subsequent exposure to air at room temperature, afforded lactone **25** as a single diastereoisomer (Scheme 7).



Scheme 7. *Reagents, conditions and yields*: (i) BuLi, THF, -78 °C (*E*: *Z* = 98: 2, 92%); (ii) (a) OsO_4, TMEDA, THF, -78 °C; (b) H_2S, MeOH, -78 °C-rt (94%, dr > 98:2); (iii) KOH, MeOH; (iv) (a) $NOBF_4$, MeCN, 0 °C; (b) Et_3N (64% from 13, dr > 98:2).

[F] *Ramchandran's approach*

Ramchandran *et al*[18] have reported the synthesis of the *α*-alkylidene-*γ*-aryl-*γ*-butyrolactones via the alkenylalumination of oxiranes. The reaction of [*α*-(ethoxycarbonyl)vinyl]diisobutylaluminum (**27**), prepared via the hydroalumination of ethyl propiolate with Dibal-H-NMO complex[19] and substituted styrene oxide **26** gave the correspondinghydroxy ester **28** which on lactonisation furnished the corresponding *γ*-butyrolactone **29** in good yield (Scheme 8, Table 10).

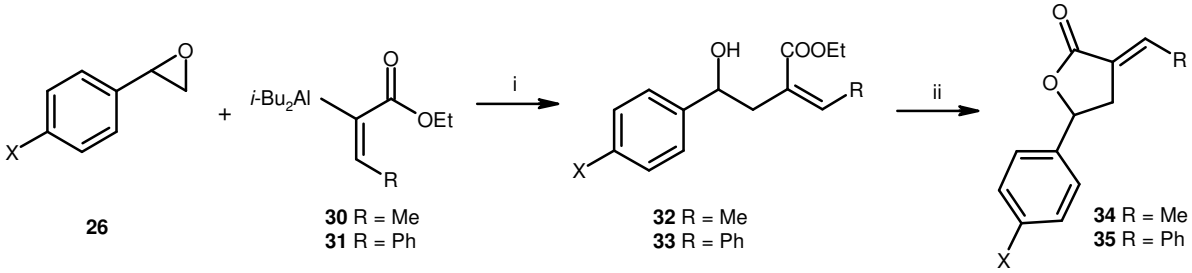


Scheme 8. *Reagents, conditions and yields*: (i) $BF_3{\cdot}Et_2O$, 0 °C, H^+, 8 h (77-84%); (ii) CF_3COOH, CH_2Cl_2, rt, 2-10 h (83-93%).

Table 10. Vinylalumination and lactonization of substituted styrene oxides

Entry	Styrene oxide		Homoallyl alcohol		γ-Butyrolactone	
	No.	X	No	Yield (%)	No	Yield (%)
1	**26a**	H	**28a**	82	**29a**	88
2	**26b**	Cl	**28b**	84	**29b**	93
3	**26c**	F	**28c**	77	**29c**	91
4	**26d**	Br	**28d**	81	**29d**	83

(*Z*)-[*α*-(Ethoxycarbonyl)-*β*-methylvinyl]diisobutylaluminum (**30**) and [*α*-(ethoxycarbonyl)-*β*-phenylvinyl]diisobutylaluminum (**31**)[19] when reacted with styrene oxides **26a**-**d** gave homoallylic alcohols **32a**-**d** and **33a**-**d** which on lactonisation furnished the corresponding *γ*-butyrolactone **34a**-**d** and **35a**-**d** in good yield. The reaction of (*Z*)-**32** with LDA, followed by treatment with BHT, provided the isomerized product (*E*)-**32** in good yield. Lactonization of (*Z*)-**32a**, provided (*E*)-**34a** in good yield (Scheme 9, Table 11).



Scheme 9. *Reagents, conditions and yields*: (i) $BF_3{\cdot}Et_2O$, 0 °C, H^+, 8 h (77-84%); (ii) CF_3COOH, CH_2Cl_2, rt, 2-10 h (83-93%).

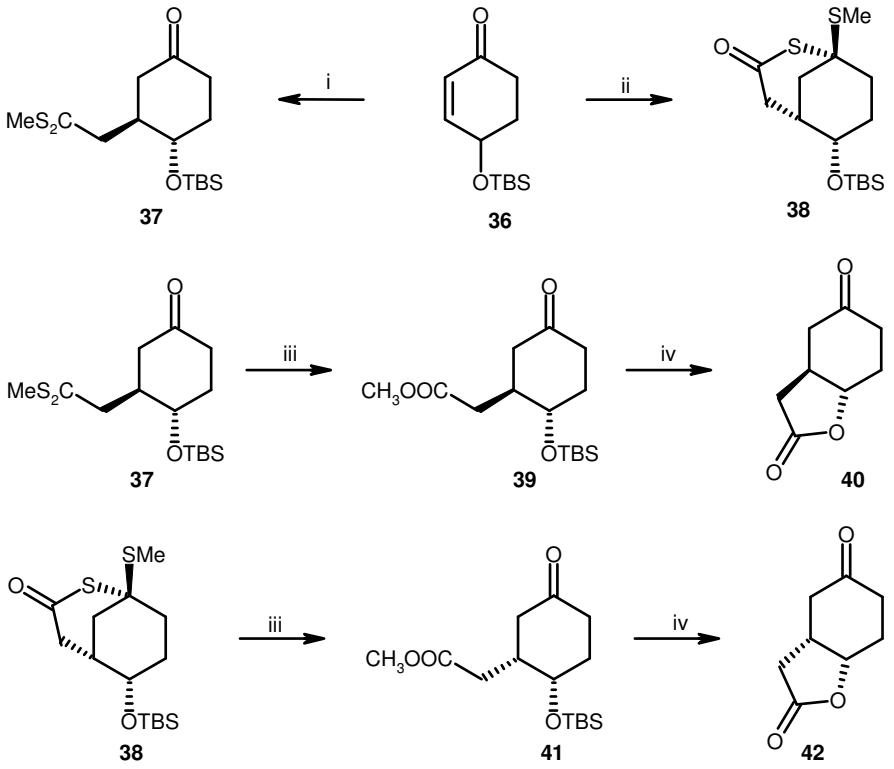
Table 11. Alkenylalumination and lactonization of substituted styrene oxides

Entry	Reagents	Styrene oxide	Homoallyl alcohol		γ-Butyrolactone	
			No	Yield (%)	No	Yield (%)
1	**30**	**26a**	(*Z*)-**32a**	76	(*Z*)-**34a**	82
2	**30**	**26b**	(*Z*)-**32b**	77	(*Z*)-**34b**	85
3	**30**	**26c**	(*Z*)-**32c**	81	(*Z*)-**34c**	84
4	**30**	**26d**	(*Z*)-**32d**	82	(*Z*)-**34d**	77
5	**30**[a]	**26a**	(*E*)-**32a**	72	(*E*)-**34a**	80
6	**30**[a]	**26b**	(*E*)-**32b**	73	(*E*)-**34b**	85
7	**30**[a]	**26c**	(*E*)-**32c**	77	(*E*)-**34c**	85
8	**30**[a]	**26d**	(*E*)-**32d**	78	(*E*)-**34d**	78
9	**31**	**26a**	(*Z*)-**33a**	74	(*Z*)-**35a**	79
10	**31**	**26b**	(*Z*)-**33b**	72	(*Z*)-**35b**	79
11	**31**	**26c**	(*Z*)-**33c**	76	(*Z*)-**35c**	70
12	**31**	**26d**	(*Z*)-**33d**	75	(*Z*)-**35d**	74

[a] Reaction conditions: alcohol **30** (3.0 mmol) added to LDA (12.0 mmol) in THF at -78 °C for 12 h. BHT (12 mmol) in THF added at -78 °C and warmed to rt.

[G] *Spivey's approach*

Spivey *et al*[20] have reported the synthesis of *trans* and *cis* bicyclic ketolactones. 1,4-Addition of the lithium enolate of methyldithioacetate (LMDTA) to (±)-4-O-TBS-2-cyclohexenone (**36**) gave two isomeric products **37** and **38** exclusively depending on whether the reactions were quenched at -78 °C or after warming to room temperature, respectively. HgO-mediated conversion of **37** and **38** to the isomeric methyl esters **39** and **41** followed by acid mediated TBS deprotection/lactonization gave ketolactone **40** and **42** respectively (Scheme 10).

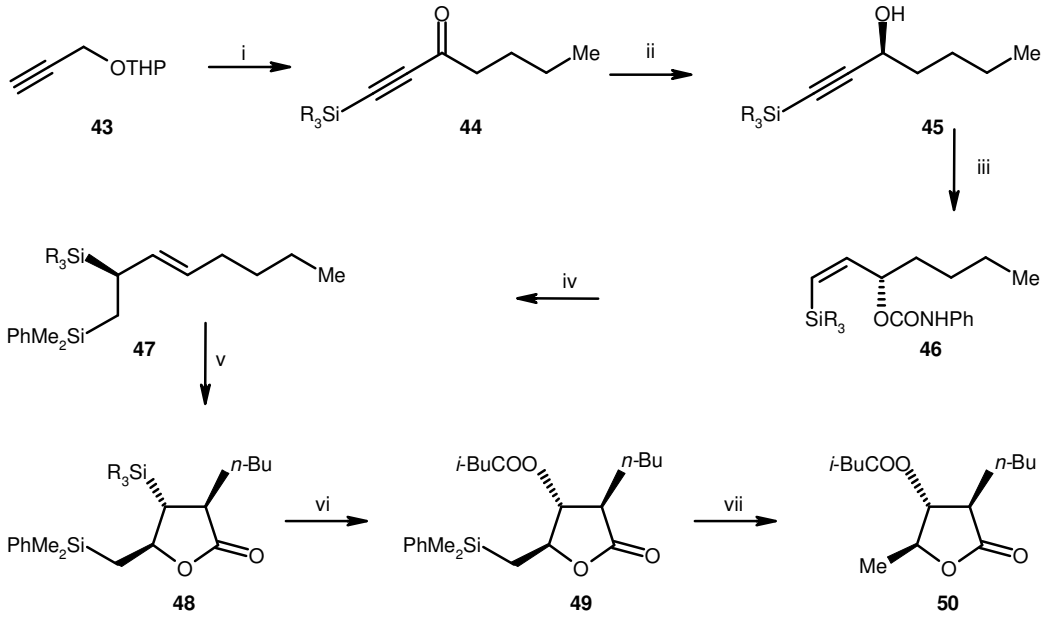


Scheme 10. *Reagents, conditions and yields*: (i) (a) $MeCS_2Me$, LHMDS, THF, -78 °C, (b) aq. NH_4Cl (77%); (ii) (a) $MeCS_2Me$, LHMDS, THF, -78 °C, rt, (b) aq. NH_4Cl (53%); (iii) HgO-BF_3, MeOH (88%); (iv) Conc. HCl, MeCN, H_2O (73%).

[H] *Woerpel's approach*

Woerpel and co-workers[21] have report a method for the stereoselective construction of the *γ*-butyrolactone subunit by the [3 + 2] annulation reaction of substituted allylic silanes with *N*-chlorosulfonyl isocyanate ($ClSO_2NCO$) and used it for the enantioselective synthesis of the polyketide metabolite (+)-blastmycinone (**50**). Silylation of **43** with benzhydryldimethylsilyl chloride followed by deprotection and oxidation of the resultant alcohol afforded an aldehyde, which was then treated with *n*-butyllithium and oxidized to give the acetylenic ketone **44**. Asymmetric transfer hydrogenation on **44** afforded the chiral alcohol (*R*)-**45** with high enantioselectivity (97.4% *ee*). The chiral alcohol **45** was then protected as the THP ether. Hydroboration, protonolysis, and deprotection afforded the (*Z*)-allylic alcohol, which was then treated with phenyl isocyanate to give the carbamate **46**. A copper-mediated S_N2' reaction provided chiral allylic silane **47** with high (*E*)-selectivity and enantioselectivity (95% *ee*). The key [3 + 2] annulation of **47** with

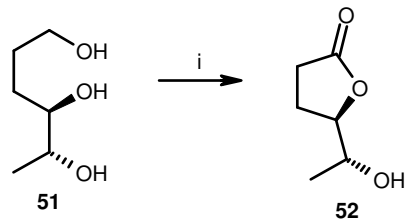
$ClSO_2NCO$ proceeded with a C=O/C=N annulation ratio of 20:1 as determined by ^1H NMR spectroscopic analysis. After hydrolysis with aqueous HCl in THF, γ-lactone **48** was obtained in 72% yield with a diastereomeric ratio of 97:3 and an *ee* of 94%. The oxidation of the benzhydryldimethylsilyl group with CsF/H_2O_2 yielded the corresponding alcohol without epimerization. The resultant alcohol was then acylated with isovaleroyl chloride to afford **49**. Finally, oxidation of the terminal dimethylphenylsilyl group with KBr-AcOOH, followed by bromination and reduction of the resultant bromide, furnished (+)-blastmycinone **50** (Scheme 11).



Scheme 11. *Reagents, conditions and yields*: (i) (a) BuLi, $(Ph_2Ch)Me_2SiCl$, *p*-TsOH (94%), (b) PCC, BuLi (71%), (c) PDC (91%); (ii) Ru-catalyst (3 mol%), *i*-PrOH (99%, 97.4% *ee*); (iii) (a) DHP, CSA (96%), (b) Cy_2BH, AcOH, *p*-TsOH (90%), (c) PhNCO (96%); (iv) BuLi, CuI·2LiCl, $PhMe_2SiCH_2MgCl$ (*E*:*Z* = 98:2, 88%, 95% *ee*); (v) CSI, CH_2Cl_2, HCl, THF-H_2O (72%); (vi) (a) CsF, H_2O_2 (81%), (b) Me_2CHCH_2COCl, Et_3N, DMAP (89%); (vii) (a) KBr, AcOOH (73%), (b) CBr_4, PPh_3, Bu_3SnH, AIBN (79%).

[I] *Ikariya's approch*

Ikariya and co-workers[22] have reported the synthesis of γ-butyrolactones by an efficient oxidative lactonization of 1,4-diols in acetone by the well-defined ruthenium catalyst, whose bifunctional nature underlies the high efficiency as well as unique chemo- and regioselectivity of the reaction. 1,4-Diols **51** was rapidly converted to the γ-butyrolactone **52** in acetone (0.5 M) containing Ru-Catalyst (Scheme 12).

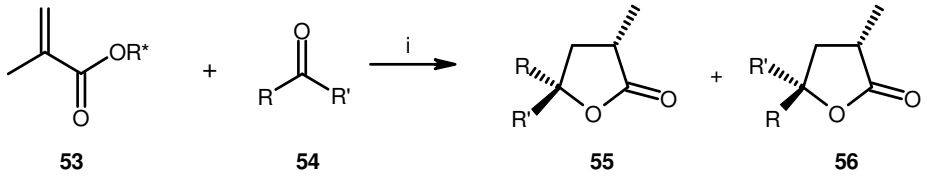


51 52

Scheme 12. *Reagents, conditions and yields*: (i) Cp*RuCl[$Ph_2P(CH_2)_2NH_2$-k_2-*P*,*N*] (1 mol%), KO*t*-Bu (1 mol%), acetone, 30 °C, 1-2h (>99%).

[J] *Lin's approach*

Lin and co-workers[23] have reported the synthesis of highly optically active *α*,*γ*-substituted *γ*-butyrolactones by using a carbohydrate-derived amide as both a chiral auxiliary and a proton source. The wedge-shaped isosorbide derived methacrylate **53** and ketone **54** in THF at -78 °C was treated with 2 equiv of SmI_2, the reaction proceeded smoothly in the absence of any other proton source, and the diastereomeric *trans*- and *cis*- *γ*-butyrolactone **55** and **56** were obtained in good yield and enantioseletivity (Scheme 13, Table 12).



53 **54** **55** **56**

R* = Chiral auxillary

Scheme 13. *Reagents, conditions and yields*: (i) SmI_2, THF, -78 to -10 °C (36-91%).

Table 12. Enantioselective synthesis active *α*,*γ*-substituted *γ*-butyrolactones using different Ketones

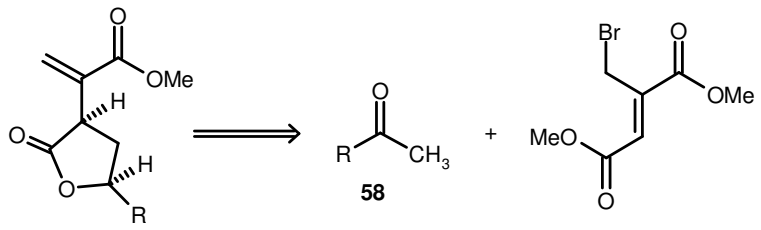
Ketones	R	R'	*Trans*-**55** (*ee* %)	*Cis*-**56** (*ee* %)	Yield (%)
54a	Me	CH_3O-C_6H_5	95	29	57
54b	Me	Ph	94	20	60
54c	Me	2-Naphthyl	96	99	44
54d	Me	3,4-Methylenedioxy-phenyl	77	87	91
54e	Me	*p*-Br-C_6H_4	99	81	36
54f		1,2,3,4-Tetrahydro-naphthalen-1-yl	71	79	82
54g	Et	Ph	90	99	59
54h	Ph	Ph	85	99	57

All these studies reveal that *γ*-butyrolactones are present in several biologically important natural products and unnatural compounds. The development of new potential routes to *γ*-butyrolactones is still a challenging task of current interest.

2C.2. Present Work Results and Discussion

The S_N2'-coupling reaction is a very important tool to form new carbon-carbon bonds in synthetic organic chemistry. Retrosynthetically, the S_N2'-coupling reactions of alkyl methyl ketones with dimethyl bromomethylfumarate followed by a reductive regioselective cyclization would constitute a simple two-step approach to 3,5-disubstituted *γ*-butyrolactones via the [3 + 2] annulation pathway (Figure 1).

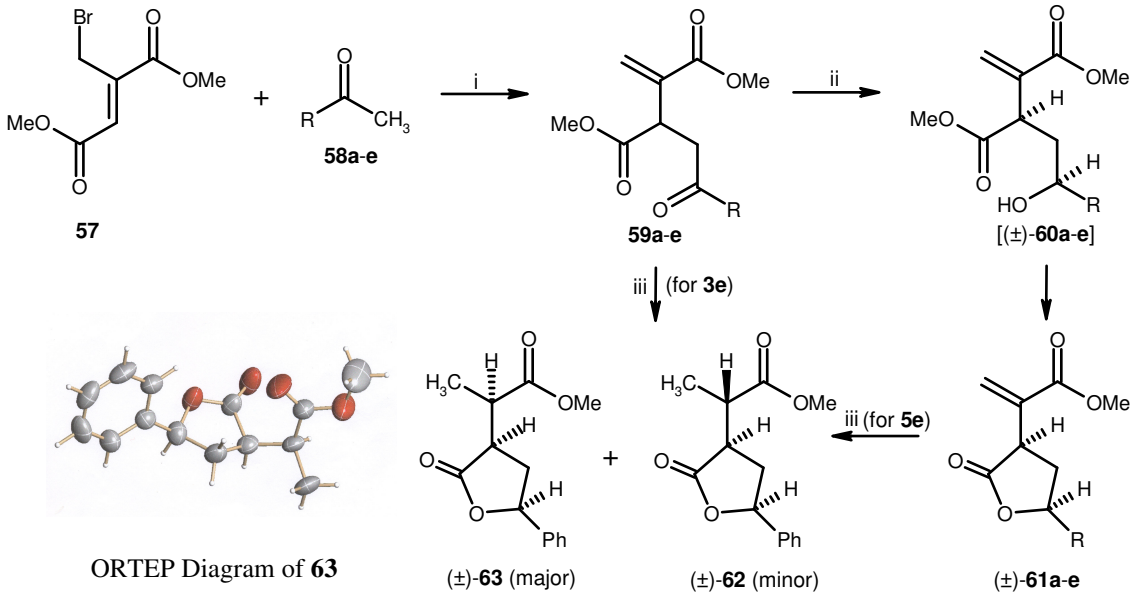
Figure 1



In continuation of our studies[24] on cyclic anhydrides to bioactive natural products, we recently synthesized dimethyl bromomethylfumarate (**57**) starting from citraconic anhydride in two steps.[25] We could perform a very chemoselective S_N2' coupling reaction of primary enolates of alkyl methyl ketones **58a**-**e** with **57** at -78 °C in 70-85% yields (Scheme 14). In the present S_N2' coupling of **57** with ketone enolates, the migration of the stable trisubstituted carbon-carbon double bond with the sole formation of the relatively less stable *gem*-disubstituted carbon-carbon double bond takes place as a result of excellent Michael acceptor capacity of the substrate **57** and a better leaving group ability of the bromide group.

The spectral characterization of these newly formed ketodiesters (±)-**59a**-**e** was easily possible on the basis of the appearance of two vinylic proton singlets for one hydrogen each in the ^{1}H NMR spectra of **59a**-**e** at ca. *ä* 5.27 and ca. *ä* 6.28. Upon treatment of the ketodiesters **59a**-**e** with $NaBH_4$ (1.50 equiv) in methanol at room temperature, a highly diastereoselective reduction of the ketone carbonyl group took place with the attack of the hydride ion from the less hindered side (Cram addition) to generate the unisolable pair of enantiomers of hydroxydiesters (±)-**60a**-**e**, which on an in situ regioselective lactonization with the more reactive non-conjugated ester moiety furnished the *cis*-3,5-disubstituted lactones (±)-**61a**-**e** in 80-90% yields. The ^{1}H NMR data of these lactones **61a**-**e** revealed that they are formed with ~100% diastereoselectivity. Treatment of the lactonylacrylate **61e** with $NaBH_4$ in methanol at room temperature for 1 h facilitated the reduction of the carbon carbon double bond with a Michael-type addition of the hydride ion followed by a highly diastereoselective acquisition of a proton from the less hindered side leading to the formation of a mixture of diastereomers (±)-**62** and (±)-**63** in a 1:9 ratio (by ^{1}H NMR) with 88% yield. Similarly, (±)-**59e** too, on treatment with an excess of $NaBH_4$, directly furnished the mixture of (±)-**62** and (±)-**63** in nearly the same ratio and yield. The mixture of **62** and **63** on recrystallization from dichloromethane provided analytically pure (±)-**63**

with 69% recrystallization yield. The structure of (±)-**63** thus obtained was established on the basis of analytical and spectral data, and it was unambiguously confirmed on the basis of X-ray crystallographic data.[27]

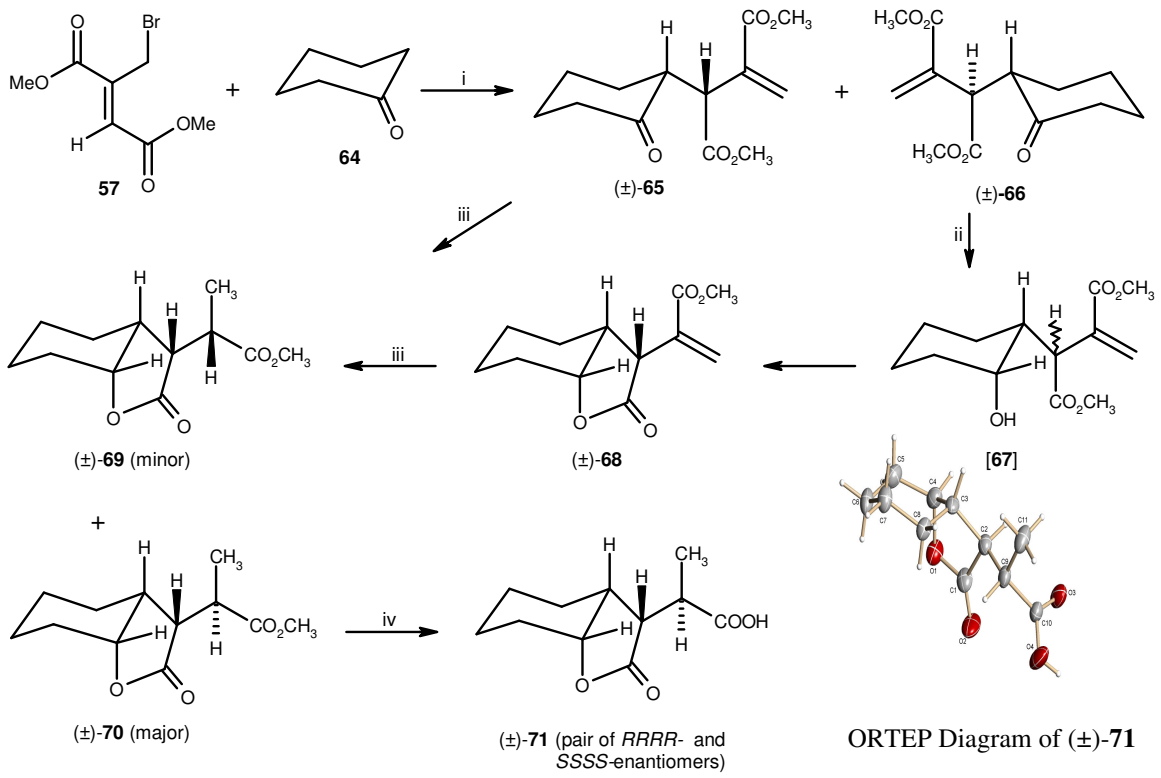


ORTEP Diagram of **63**

a, R = CH_2CH_3; **b**, R = $CH_2(CH_2)_2CH_3$; **c**, R = $CH_2(CH_2)_5CH_3$; **d**, R = $CH_2(CH_2)_8CH_3$; **e**, R = Ph.

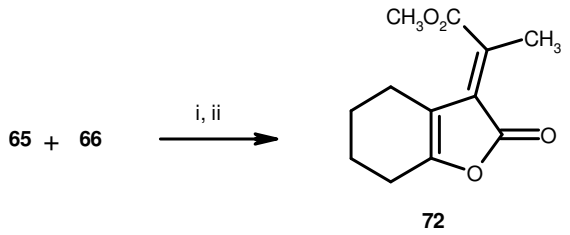
Scheme 14. *Reagents, conditions and yields*: (i) LDA, THF, –78 ºC, 20 min (**59a**, 80%; **59b**, 78%; **59c**, 72%; **59d**, 70%; **59e**, 85%); (ii) $NaBH_4$ (1.50 equiv.), MeOH, rt, 15 min (**61a**, 88%; **61b**, 85%; **61c**, 82%; **61d**, 80%; **61e**, 90%); (iii) $NaBH_4$ (3.00 equiv.), MeOH, rt, 1 h (88%, **62**:**63** = 1:9).

Next, we prepared a plan to synthesize the fused γ-butyrolactones using the present S_N2' coupling reaction. Toward this, we performed the S_N2' coupling of cyclohexanone enolate with **57** at -78 °C and obtained the coupling product in 80% yield (Scheme 15). The ^1H and ^{13}C NMR spectrum of the previously coupled product showed two sets of signals with nearly equal intensities, suggesting that a column inseparable mixture of diastereomers is formed in nearly equal proportions. However, the S_N2' coupling of **57** and the cyclohexanone enolate, with an attack of the expected axial carbanion, was partly diastereoselective at -100 °C, resulting in a mixture of diastereomers **65** and **66** in a nearly 8:2 ratio. The observed face selective coupling could be ascribed to the steric interactions between **57** and axial carbanionic species of **64** and/or the thermodynamic stability of the formed major diastereomer **65**. It was not possible for us to still lower the temperature of



Scheme 15. *Reagents, conditions and yields*: (i) LDA, THF, -100 °C, 20 min (**65/66** = 8:2, 80%); (ii) $NaBH_4$ (1.50 equiv), MeOH, rt, 15 min (88%); (iii) $NaBH_4$ (3.00 equiv), MeOH, rt, 1 h (85%, **69/70** = 15:85); (iv) (a) AcOH/HCl (3:1), reflux, 6 h (92%), (b) recrystallization from EtOAc (64%).

the reaction mixture to obtain the complete diastereoselectivity, as the THF solution began solidifying below -105 to -110 °C. Interestingly, the mixture of diastereomers **65** and **66** (1:1/8:2) underwent a very stereospecific $NaBH_4$ reduction of the ketone group at room temperature with a less hindered equatorial approach of the hydride ion to generate the axial alcohols, which, upon in situ cyclization, exclusively furnished the octahydrobenzofuran (±)-**68** (pair of *RRR*- and *SSS*-lactones) in 88% yield. Herein, we surmise that during the course of the reaction, the formed lactone from (±)-**66** undergoes an instantaneous epimerization at an allylic carbon, with the catalytic amount of sodium methoxide generated in situ from $NaBH_4$ and methanol, thus providing the single diastereomer (±)-**68** in 88% yield. However, the mixture of **65** plus **66** on treatment with equimolar amounts of sodium methoxide in methanol at room temperature directly furnished the lactone **72** in 87% yield, via the enolization, cyclization, and isomerization of the carbon-carbon double bond (Scheme 16).



Scheme 16. *Reagents, conditions and yields*: (i) NaOMe, MeOH, rt, I h; (ii) H^+/HCl (87%).

Finally, further reduction of the carbon-carbon double bond in (±)-**68** with $NaBH_4$ was also diastereoselective (70% de, by ^1H NMR) with abstraction of the proton occurring predominantly from the less hindered site giving rise to a mixture of (±)-**69** (minor) and (±)-**70** (major, pair of *RRRR*- and *SSSS*- isomers) as a thick oil in 85% yield. Acid-catalyzed ester hydrolysis of **69** plus **70** furnished a diastereomeric mixture of corresponding carboxylic acids in 92% yield. Recrystallization of the previous diastereomeric mixture of acids in ethyl acetate gave the analytically pure single diastereomer with 64% recrystallization yield. The X-ray crystallographic data[27] of the analytically pure diastereomer revealed that a (±)-lactone **71** is formed. Finally, on the basis of X-ray data, we could postulate the complete mechanistic and stereochemical aspects of the present conversion of **57** plus **64** to (±)-**71** as indicated in Scheme 15.

2C.3. Summary

In summary, in this section we have presented the essence of methods employed in the literature to design the *γ*-butyrolactones derivatives both in racemic and enantiomerically pure form. We have demonstrated a simple, efficient as well as highly chemo-, regio- and diastereoselective approach to *cis*- 3,5-disubstituted *γ*-butyrolactones for the first time by employing the S_N2'-coupling reactions of ketones with dimethyl bromomethylfumarate (**57**) followed by reductive cyclization pathway. In the present approach, the face selective condensation of primary enolate of cyclohexanone with **57** and the diastereoselective reduction of the ketone moiety are noteworthy.[26] We feel that our present approach is general in nature and the natural stereochemical outcome in the present approach to obtain *γ*-butyrolactones, which is interesting, would be useful to design a large number of desired substituted and bicyclic/fused structurally complex *γ*-butyrolactones. We also feel that the independent acrylate moiety at the 3-position in **61a**-**e** and **68** will be useful for further synthetic structural elaborations and their Michael acceptor capacity might be an added advantage from the bioactivity point of view.

In conclusion, in the present three sections chapter we have described the relevant literature and our results with experimental and spectral data. Dialkyl bromomethylfumarates are the multifunctional entity and have been extensively used for different reactions at all the reactive sites for the construction of variety of bioactive natural products and unnatural compounds in past century. We used dialkyl bromomethylfumarate for the synthesis of natural products 2-phenyl-3-benzylmaleic anhydride, gymnoascolide A, camphorataanhydride, camphorataimides B & C and (+)-erythro-roccellic acid in 33% ee by using D-menthol as chiral auxillary. We feel that with a choice of an appropriate chiral auxiliary, it will be possible to synthesize the (+)-erythro-roccellic with high yield and enantiomeric excess. We have also described a simple, efficient as well as highly chemo-, regio- and diastereoselective approach to cis-3,5-disubstituted γ-butyrolactones. We have also demonstrated that the reagent NBS-DBP brings about both allylic bromination and Z- to E- carbon-carbon double bond isomerization. The present studies also provide a useful caution mark to the chemists attempting allylic bromination of Z-alkenes.

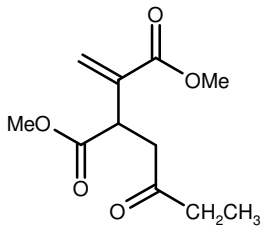
2C.4 Dissertation Conclusions and Perspectives

A look at the literature reveals that the itaconic acid derivatives and dialkyl bromomethylfumarate are the more common and widely used synthons for the synthesis of natural products and unnatural compounds. These studies also provided us a nice opportunity for learning a lot of new chemistry not just from our work but also from the vast literature in this field, covering practically all aspects in synthetic organic chemistry. Although several references have been cited from our group we feel that they are relevant to the subject. In the introduction part of both the chapters, we have initially discussed the synthesis of natural and unnatural compounds, which is followed by the important methodologies. Thus, overall, in the present dissertation, we have seen and proved the utility of itaconic acid and derivatives for the synthesis of important heterocycles, natural products and unnatural compounds. We now with our experience foresee that the naturally occurring 5-carbon itaconic acid with several active sites may be a part structure of ample number of structurally interesting and biologically important complex carbocycles, alkaloids and oxygen heterocycles. The above discipline has enjoyed a glorious past and holds a great deal of significance in the present day world of chemistry (& medicine). It can be said with assurance that, this interesting discipline will spread wings wider over the field of organic and pharmaceutical chemistry in the future.

2C.5. Experimental section

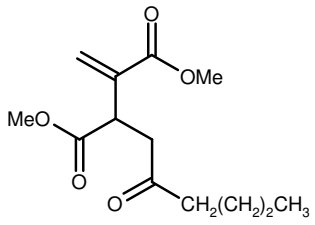
Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on either 200 NMR spectrometer (50 MHz) or 400 NMR spectrometer (100 MHz). The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60-120 mesh). Commercially available citraconic anhydride, 2-butanone, 2-hexanone, 2-nonanone, 2-dodecanone, acetophenone, cyclohexanone, *n*-BuLi, $NaBH_4$ and *N*-bromosuccinimide were used.

(±)-Dimethyl 2-methylene-3-(2-oxobutyl)succinate (59a). To a stirred solution of 2-butanone (144 mg, 2.00 mmol) in THF (5 mL) at –78 °C was added freshly prepared LDA (214 mg, 2.00 mmol) in THF (5 mL) in a dropwise fashion under argon atmosphere. The reaction mixture was stirred at –78 °C temperature for 1 h and the above reaction mixture was added to a stirred solution of dimethyl bromomethylfumarate (**57**, 474 mg, 2.00 mmol) at –78 °C under argon atmosphere in a dropwise fashion. Stirring was continued for a further 10 minutes at the same temperature. The reaction was then quenched with a saturated solution of NH_4Cl. The reaction mixture was extracted with ethyl acetate (30 mL x 4) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (2:8) as an eluant gave **59a** as a thick oil (365 mg, 80%).

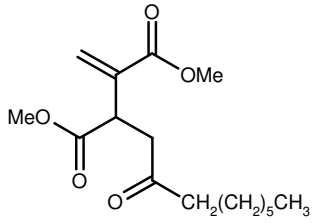
 **59a** **$C_{11}H_{16}O_5$ (228)**	**IR** (Neat) ν_{max} 1740, 1730, 1717, 1630, 1437, 1231 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.00 (t, J = 8 Hz, 3H), 2.25-2.50 (m, 2H), 2.56 (dd, J = 18 & 4 Hz, 1H), 3.14 (dd, J = 18 & 10 Hz, 1H), 3.62 (s, 3H), 3.71 (s, 3H), 4.03 (dd, J = 10 & 4 Hz, 1H), 5.68 (s, 1H), 6.25 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 7.4, 35.8, 42.5, 43.4, 51.9, 52.1, 127.5, 137.8, 165.9, 172.6, 208.2. **Anal. Calcd** for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.69; H, 7.18.

The compounds **59b**-**e**, **65** and **66** were prepared similarly using the above procedure.

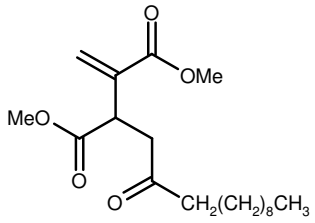
(±)-Dimethyl 2-methylene-3-(2-oxohexyl)succinate (59b). Starting from **57** (474 mg, 2.00 mmol) and 2-hexanone (200 mg, 2.00 mmol) the compound **59b** was obtained as a thick oil (400 mg, 78%).

 **59b** **$C_{13}H_{20}O_5$ (256)**	**IR** (Neat) ν_{max} 1742, 1728, 1715, 1632, 1439, 1232 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.86 (t, J = 8 Hz, 3H), 1.27 (sextet, J = 8 Hz, 2H), 1.53 (quintet, J = 8 Hz, 2H), 2.30-2.50 (m, 2H), 2.58 (dd, J = 18 & 6 Hz, 1H), 3.16 (dd, J = 18 & 8 Hz, 1H), 3.63 (s, 3H), 3.73 (s, 3H), 4.04 (dd, J = 8 & 4 Hz, 1H), 5.70 (s, 1H), 6.26 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 13.7, 22.1, 25.6, 42.5 (2 carbons), 43.9, 52.0, 52.2, 127.7, 137.8, 166.0, 172.6, 208.0. **Anal. Calcd** for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 61.13; H, 7.77.

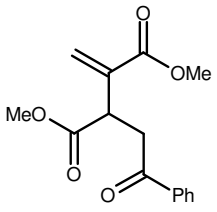
(±)-Dimethyl 2-methylene-3-(2-oxononyl)succinate (59c). Starting from **57** (474 mg, 2.00 mmol) and 2-nonanone (284 mg, 2.00 mmol) the compound **59c** was obtained as a thick oil (430 mg, 72%).

 **59c** **$C_{16}H_{26}O_5$ (298)**	**IR** (Neat) ν_{max} 1740, 1720, 1630, 1437, 1231 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 8 Hz, 3H), 1.26 (bs, 8H), 1.57 (quintet, J = 8 Hz, 2H), 2.35-2.50 (m, 2H), 2.61 (dd, J = 18 & 6 Hz, 1H), 3.19 (dd, J = 18 & 8 Hz, 1H), 3.67 (s, 3H), 3.76 (s, 3H), 4.07 (dd, J = 10 & 4 Hz, 1H), 5.73 (s, 1H), 6.30 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 23.7, 29.0, 29.1, 31.6, 42.6, 42.9, 44.0, 52.3 (2 carbons), 127.8, 137.9, 166.1, 172.8, 208.2. **Anal. Calcd** for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.32; H, 8.59.

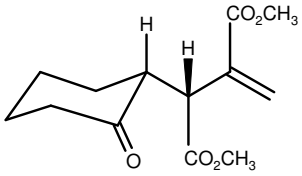
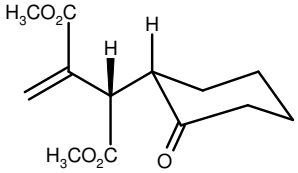
(±)-Dimethyl 2-methylene-3-(2-oxododecyl)succinate (59d). Starting from **57** (474 mg, 2.00 mmol) and 2-dodecanone (360 mg, 2.00 mmol) the compound **59d** was obtained as a thick oil (476 mg, 70%).

 **59d** **$C_{19}H_{32}O_5$ (340)**	**IR** (Neat) ν_{max} 1740, 1720, 1630, 1462, 1437, 1232 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.84 (t, J = 8 Hz, 3H), 1.22 (bs, 14H), 1.53 (quintet, J = 8 Hz, 2H), 2.30-2.50 (m, 2H), 2.58 (dd, J = 18 & 6 Hz, 1H), 3.16 (dd, J = 18 & 8 Hz, 1H), 3.64 (s, 3H), 3.73 (s, 3H), 4.04 (dd, J = 8 & 4 Hz, 1H), 5.70 (s, 1H), 6.27 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 23.6, 29.1, 29.2, 29.3, 29.4, 29.5, 31.8, 42.6, 42.9, 43.9, 52.2 (2 carbons), 127.7, 137.9, 166.1, 172.7, 208.1. **Anal. Calcd** for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.95; H, 9.58.

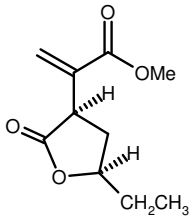
(±)-Dimethyl 2-methylene-3-(2-oxo-2-phenylethyl)succinate (59e). Starting from **57** (474 mg, 2.00 mmol) and acetophenone (240 mg, 2.00 mmol) the compound **59e** was obtained as a thick oil (470 mg, 85%).

 **59e** **$C_{15}H_{16}O_5$ (276)**	**IR** (Neat) ν_{max} 1736, 1720, 1686, 1630, 1448, 1437, 1260 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.24 (dd, J = 18 & 4 Hz, 1H), 3.69 (s, 3H), 3.76 (s, 3H), 3.77 (dd, J = 18 & 8 Hz, 1H), 4.27 (dd, J = 8 & 6 Hz, 1H), 5.81 (s, 1H), 6.34 (s, 1H), 7.35-7.60 (m, 3H), 7.90-8.00 (m, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 40.2, 42.6, 52.2 (2 carbons), 127.9, 128.0, 128.5, 133.1, 136.3, 137.8, 166.0, 172.7, 197.1. **Anal. Calcd** for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.19; H, 5.90.

(±)-Dimethyl 2-methylene-3-(2-oxocyclohexyl)succinate (65 & 66). Starting from **57** (474 mg, 2.00 mmol) and cyclohexanone (196 mg, 2.00 mmol) the mixture of compounds **65** and **66** was obtained as a thick oil (mixture of diastereomers in the ratio of 1:1, 406 mg, 80%).

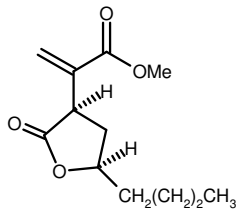
 **65** +  **66** **$C_{13}H_{18}O_5$ (254)**	**IR** (Neat) ν_{max} 1734, 1713, 1628, 1437 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.50-2.50 (m, 16H), 2.80-3.15 (m, 2H), 3.64 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.89 (d, J = 10 Hz, 1H), 4.06 (d, J = 8 Hz, 1H), 5.66 (s, 1H), 5.79 (s, 1H), 6.30 (s, 1H), 6.37 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 24.9, 25.3, 27.4, 28.2, 30.6, 31.4, 42.0, 42.1, 45.2, 45.8, 52.0, 52.1, 52.2 (2 carbons), 52.6, 52.8, 126.5, 128.4, 136.7, 137.3, 166.4, 166.6, 172.8, 172.9, 210.0, 211.1. **Anal. Calcd** for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13. Found: C, 61.33; H, 7.25.

(±)-Methyl 2-(5-ethyl-2-oxo-tetrahydrofuran-3-yl)acrylate (61a). To a solution of **59a** (228 mg, 1.00 mmol) in methanol (15 mL) was added $NaBH_4$ (60 mg, 1.50 mmol) at 0 °C and the reaction mixture was stirred for 15 minutes. The reaction was then quenched with water. The reaction mixture was extracted with ethyl acetate (25 mL x 4) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (3:7) as an eluant gave **61a** as a thick oil (174 mg, 88%).

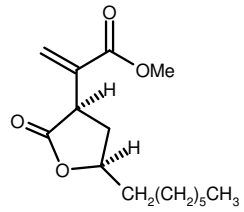
 **61a** **$C_{10}H_{14}O_4$ (198)**	**IR** (Neat) ν_{max} 1771, 1720, 1634, 1439 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.01 (t, J = 8 Hz, 3H), 1.55-2.10 (m, 3H), 2.53 (ddd, J = 12, 10 & 6 Hz, 1H), 3.66 (dd, J = 12 & 8 Hz, 1H), 3.77 (s, 3H), 4.25-4.50 (m, 1H), 5.84 (s, 1H), 6.40 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 9.3, 28.2, 35.0, 44.9, 52.1, 80.0, 129.2, 136.1, 165.7, 175.8. **Anal. Calcd** for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.76; H, 7.03.

The compounds **61b-e** and **68** were prepared similarly using the above procedure.

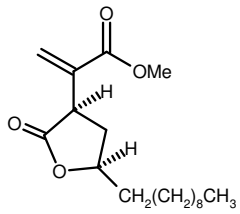
(±)-Methyl 2-(5-butyl-2-oxo-tetrahydrofuran-3-yl)acrylate (61b). Starting from **59b** (256 mg, 1.00 mmol) and $NaBH_4$ (60 mg, 1.50 mmol) the compound **61b** was obtained as a thick oil (192 mg, 85%).

 **61b** **$C_{12}H_{18}O_4$ (226)**	**IR** (Neat) ν_{max} 1771, 1720, 1634, 1439 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 8 Hz, 3H), 1.15-1.50 (m, 4H), 1.50-1.85 (m, 2H), 1.85-2.07 (m, 1H), 2.53 (ddd, J = 13, 8 & 6 Hz, 1H), 3.55-3.75 (m, 1H), 3.75 (s, 3H), 4.30-4.50 (m, 1H), 5.83 (s, 1H), 6.38 (s,1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.8, 22.3, 27.2, 35.0, 35.4, 44.9, 52.0, 78.8, 129.1, 136.0, 165.6, 175.8. **Anal. Calcd** for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.61; H, 7.92.

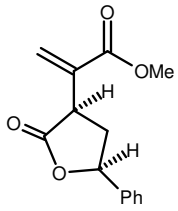
(±)-Methyl 2-(5-heptyl-2-oxo-tetrahydrofuran-3-yl)acrylate (61c). Starting from **59c** (298 mg, 1.00 mmol) and $NaBH_4$ (60 mg, 1.50 mmol) the compound **61c** was obtained as a thick oil (220 mg, 82%).

 **61c** **$C_{15}H_{24}O_4$ (268)**	**IR** (Neat) ν_{max} 1771, 1720, 1632, 1439 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.27 (bs, 10H), 1.40-1.85 (m, 2H), 1.85-2.10 (m, 1H), 2.54 (ddd, J = 12, 10 & 6 Hz, 1H), 3.66 (dd, J = 12 & 8 Hz, 1H), 3.78 (s, 3H), 4.30-4.50 (m, 1H), 5.85 (s, 1H), 6.41(s,1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 25.2, 29.1, 29.2, 31.7, 35.4, 35.6, 44.9, 52.1, 78.9, 129.2, 136.1, 165.7, 175.8. **Anal. Calcd** for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.98; H, 8.93.

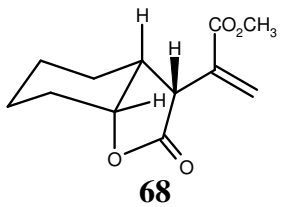
(±)-Methyl 2-(5-decyl-2-oxo-tetrahydrofuran-3-yl)acrylate (61d). Starting from **59d** (340 mg, 1.00 mmol) and $NaBH_4$ (60 mg, 1.50 mmol) the compound **61d** was obtained as a thick oil (248 mg, 80%).

 **61d** **$C_{18}H_{30}O_4$ (310)**	**IR** (Neat) ν_{max} 1774, 1734, 1634, 1439 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.25 (bs, 16H), 1.40-1.85 (m, 2H), 1.85-2.10 (m, 1H), 2.54 (ddd, J = 12, 10 & 6 Hz, 1H), 3.55-3.75 (m, 1H), 3.78 (s, 3H), 4.30-4.50 (m, 1H), 5.85 (s, 1H), 6.41 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 25.2, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 35.4, 35.6, 44.9, 52.1, 78.9, 129.1, 136.1, 165.7, 175.8. **Anal. Calcd** for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.57; H, 9.88.

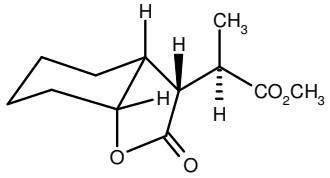
(±)-Methyl 2-(2-oxo-5-phenyl-tetrahydrofuran-3-yl)acrylate (61e). Starting from **59e** (200 mg, 0.72 mmol) and $NaBH_4$ (45 mg, 1.10 mmol) the compound **61e** was obtained as a white solid (160 mg, 90%).

 **61e** **$C_{14}H_{14}O_4$ (246)**	**Mp** 127-128°C. **IR** (Neat) ν_{max} 1771, 1728, 1632, 1439 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.30-2.50 (m, 1H), 2.83 (ddd, J = 12, 10 & 6 Hz, 1H), 3.65-3.75 (m, 1H), 3.80 (s, 3H), 5.42 (dd, J = 10 & 6 Hz, 1H), 5.91 (s, 1H), 6.45 (s, 1H), 7.30-7.50 (m, 5H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 38.1, 45.6, 52.2, 79.7, 125.9, 128.6, 128.7, 129.7, 135.7, 138.8, 165.5, 175.5. **Anal. Calcd** for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.22; H, 5.71.

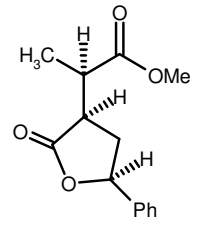
(±)-Methyl 2-(2-oxo-octahydrobenzofuran-3-yl)acrylate (68). Starting from a mixture of **65** & **66** (150 mg, 0.60 mmol) and $NaBH_4$ (36 mg, 0.90 mmol), the compound **68** was obtained as a thick oil (116 mg, 88 %).

 **68** **$C_{12}H_{16}O_4$ (224)**	**IR** (Neat) ν_{max} 1769, 1732, 1632, 1445 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.15-1.65 (m, 4H), 1.75-2.35 (m, 4H), 3.36 (d, J = 14 Hz, 1H), 3.65-3.90 (m, 2H), 3.79 (s, 3H), 5.77 (s, 1H), 6.46 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 24.0, 25.1, 27.4, 30.1, 50.1, 50.3, 52.2, 83.0, 129.2, 134.9, 166.0, 175.5. **Anal. Calcd** for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.23.

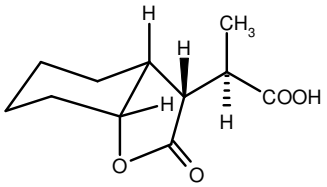
Methyl 2-(2-oxo-octahydrobenzofuran-3-yl)propanoate (69 & 70). To a solution of a mixture of **65** & **66** (150 mg, 0.60 mmol) in methanol (15 mL) was added $NaBH_4$ (72 mg, 1.80 mmol) at 0 °C and the reaction mixture was stirred for 1 hour. The reaction was then quenched with water. The reaction mixture was extracted with ethyl acetate (25 mL x 4) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (3:7) as an eluant gave the mixture of **69** & **70** as a thick oil (the mixture of diastereoisomers was formed in the ratio of **69**:**70** = 15:85, 113 mg, 85%). Major isomer (±)-**70**.

 **70** **$C_{12}H_{18}O_4$ (226)**	**IR** (Neat) ν_{max} 1778, 1734, 1450, 1254 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.19 (d, J = 6 Hz, 3H), 1.20-2.00 (m, 8H), 2.15-2.30 (m, 1H), 2.85 (dd, J = 14 & 4 Hz, 1H), 2.90-3.10 (m, 1H), 3.70 (s, 3H), 3.70-3.83 (m,1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 12.8, 23.9, 25.1, 28.0, 30.0, 37.3, 45.8, 48.6, 51.9, 82.7, 174.8, 176.7. **Anal. Calcd** for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.65; H, 8.14.

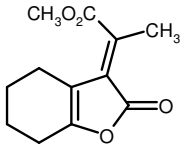
Methyl 2-(2-oxo-5-phenyl-tetrahydrofuran-3-yl)propanoate (62 & 63). Starting from **59e** (200 mg, 0.72 mmol) and $NaBH_4$ (90 mg, 2.20 mmol) the mixture of **62** & **63** was obtained as a white solid (the mixture of diastereoisomers was formed in the ratio of **62**:**63** = 10:90, 158 mg, 88%). Recrystallization from dichloromethane furnished the analytically pure major isomer (±)-**63**.

 **63** **$C_{14}H_{16}O_4$ (248)**	**Mp** 79-80°C. **IR** (Neat) ν_{max} 1774, 1732, 1458 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.35 (d, J = 6 Hz, 3H), 2.08-2.30 (m, 1H), 2.68 (ddd, J = 12, 8 & 6 Hz, 1H), 2.85-3.20 (m, 2H), 3.69 (s, 3H), 5.37 (dd, J = 12 & 6 Hz, 1H), 7.30-7.45 (m, 5H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 15.1, 34.5, 38.6, 44.1, 51.9, 79.5, 125.7, 128.5, 128.6, 139.1, 173.9, 176.8. **Anal. Calcd** for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.89; H, 6.47.

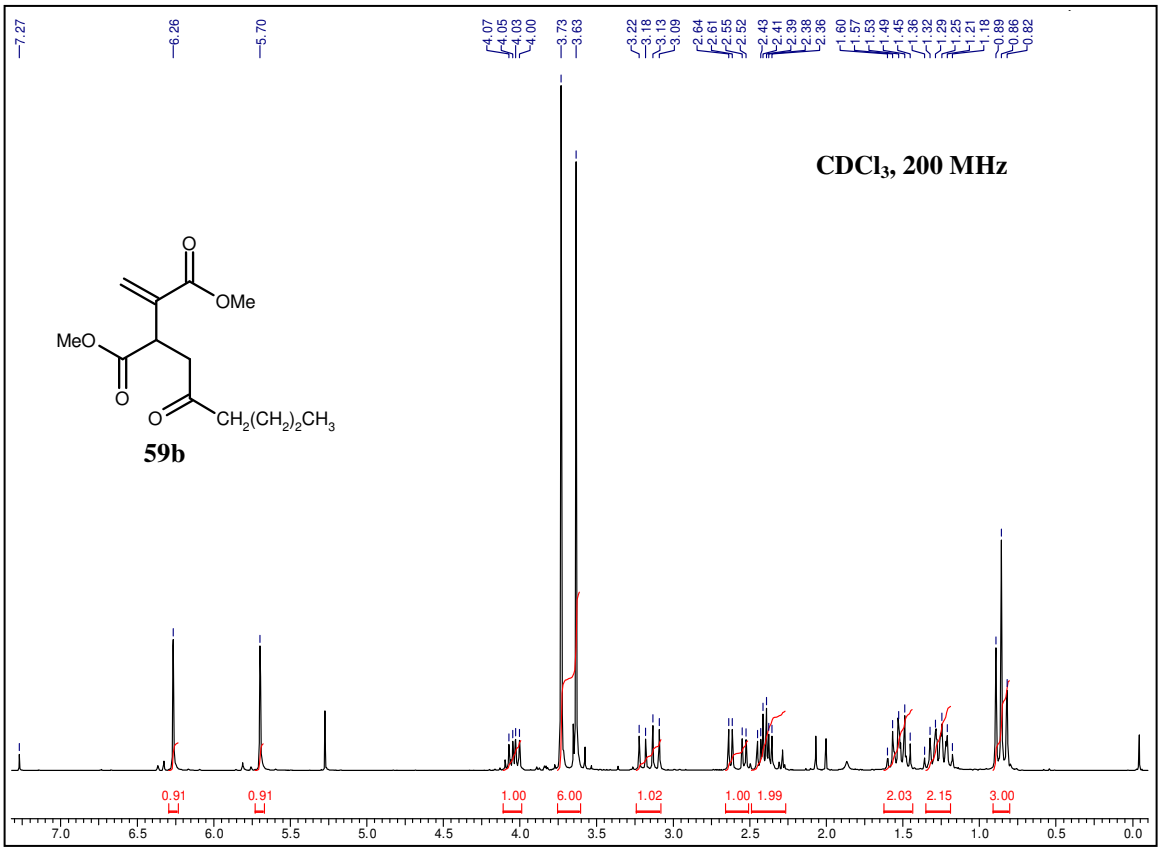
(±)-2-(2-Oxo-octahydrobenzofuran-3-yl)propanoic acid (71). A solution of the mixture of **69** & **70** (70 mg, 0.30 mmol) in AcOH:HCl (3:1) (10 mL) was refluxed for 6 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo and the resulting solution was washed with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give a mixture of diastereomers as a white solid (60 mg, 92%). Recrystalization from ethyl acetate furnished the analytically pure major isomer **71**.

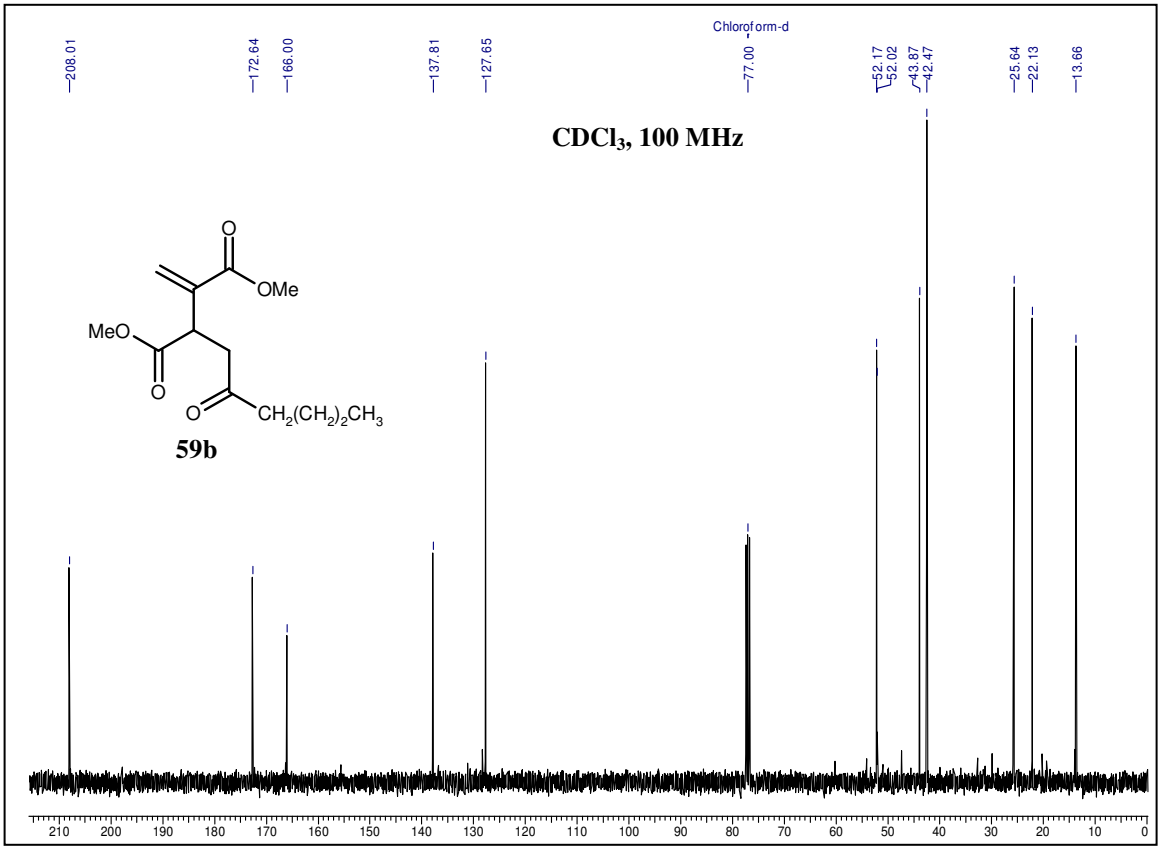
 **71** **$C_{11}H_{16}O_4$ (212)**	**Mp** 215-216 °C. **IR** (Neat) ν_{max} 2700-2500, 1757, 1697, 1464, 1377 cm^{-1} **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.00-1.30 (m, 2H), 1.29 (d, J = 6 Hz, 3H), 1.35-1.85 (m, 4H), 2.20-2.45 (m, 2H), 2.55-2.75 (m, 1H), 3.00-3.15 (m, 2H), 4.45-4.55 (m, 1H). **^{13}C NMR** (Acetone-d_6, 100 MHz) δ 16.9, 20.4, 23.0, 23.7, 28.0, 36.5, 38.0, 51.3, 78.1, 176.9, 177.6. **Anal. Calcd** for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.37; H, 7.56.

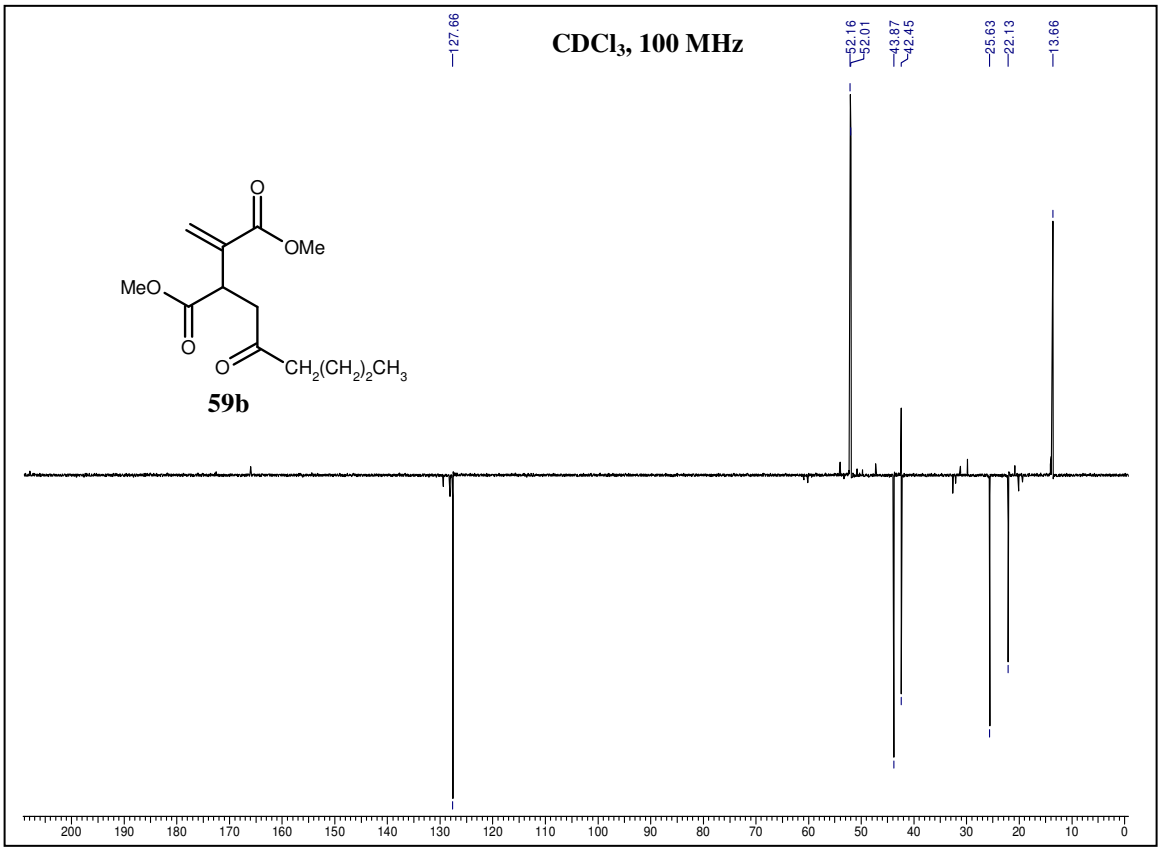
(*E*)-Methyl 2-(2-Oxo-4,5,6,7-tetrahydrobenzofuran-3(2*H*)-ylidene)propanoate (72). To a solution of a mixture of **65** and **66** (125 mg, 0.50 mmol) in methanol (5 mL) was added NaOMe (27 mg, 0.50 mmol) at room temperature, and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate (15 mL), and acidified with 2 N HCl. The aqueous layer was extracted with ethyl acetate (10 mL x 2), and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (2:8) as an eluant gave **72** as a white solid (95 mg, 87%).

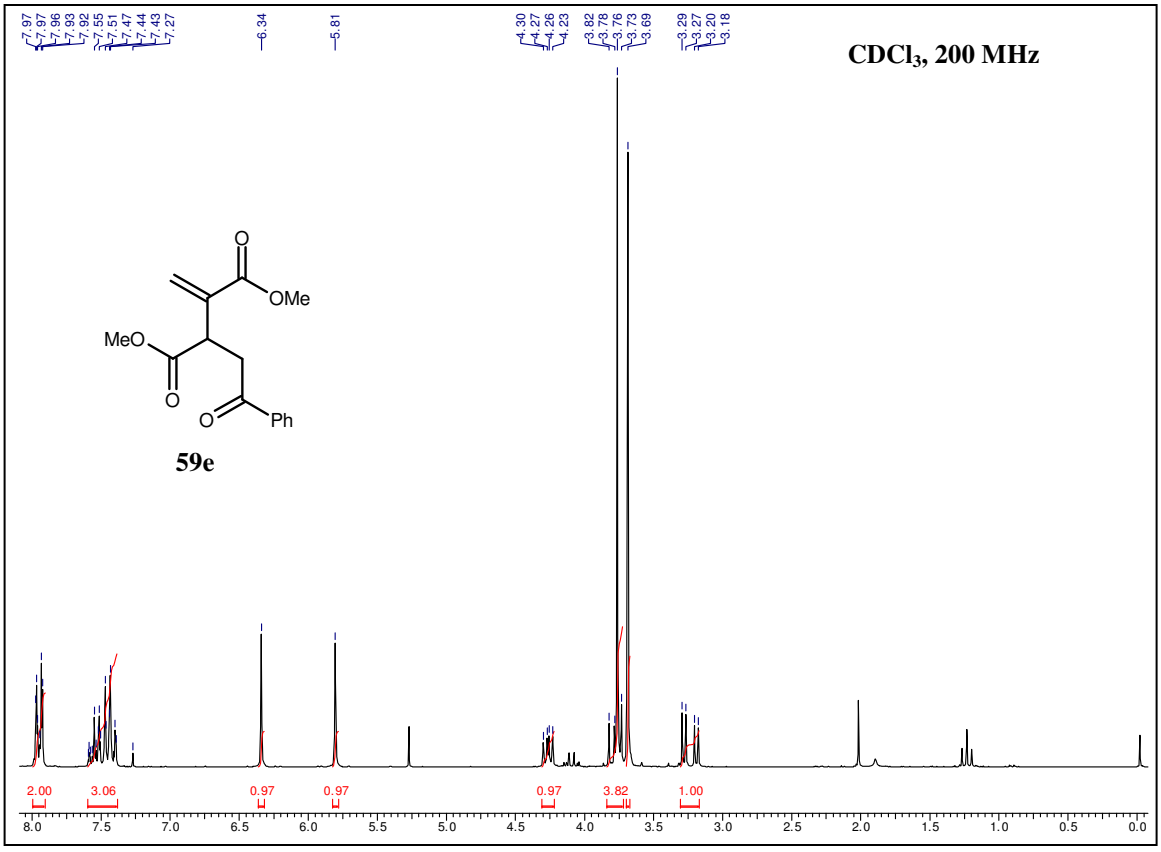
 **72** **$C_{12}H_{14}O_4$ (222)**	**Mp** 88-89 °C. **IR** ($CHCl_3$) ν_{max} 1736, 1719, 1647 cm-1. **^{1}H NMR** (CDCl3, 200 MHz) δ 1.55-1.90 (m, 4H), 2.03 (s, 3H), 2.29 (t, J = 6 Hz, 2H), 2.53 (t, J = 6 Hz, 2H), 3.91 (s, 3H). **^{13}C NMR** (CDCl3, 50 MHz) δ 13.8, 21.4, 21.8, 23.4, 27.3, 52.5, 109.1, 119.6, 145.4, 157.7, 163.3, 166.4. **Anal.Calcd** for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.03; H, 6.52.

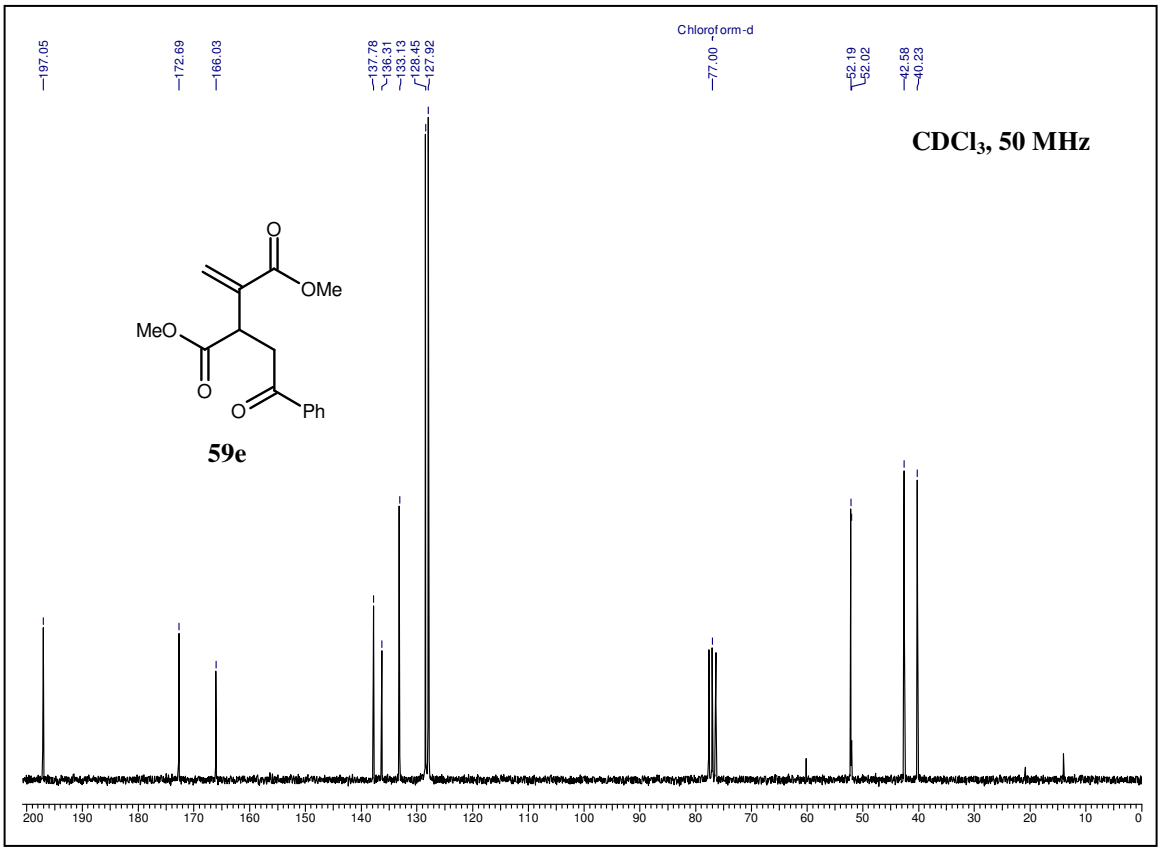
2C.5 Selected Spectra

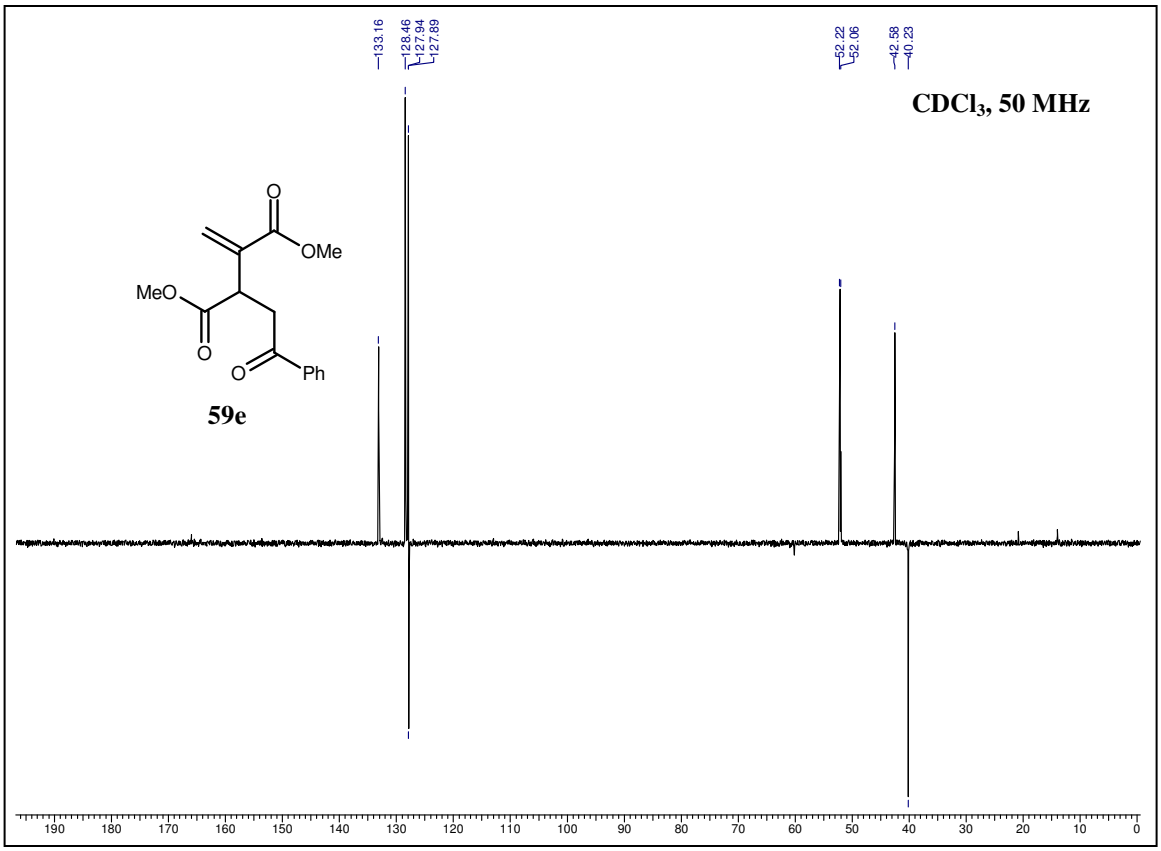

CDCl3, 200 MHz
59b

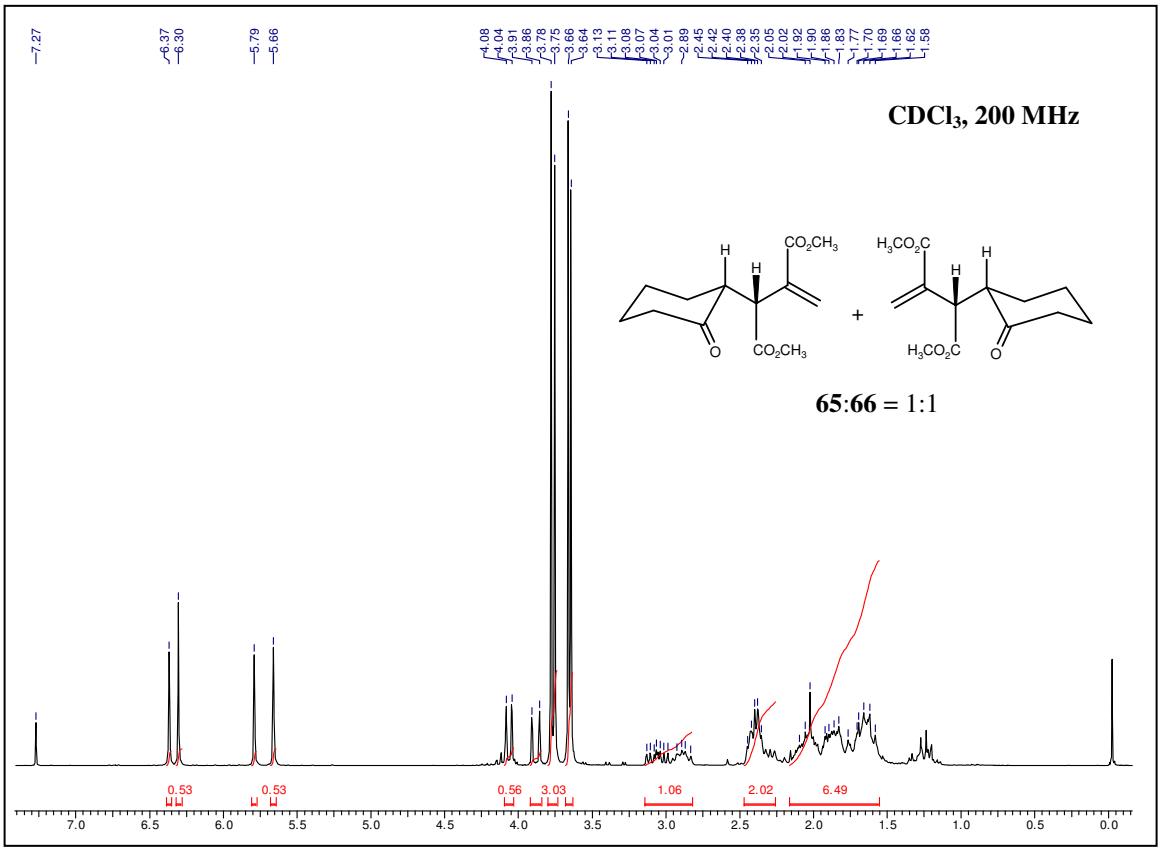

Chloroform-d
CDCl3, 100 MHz
59b

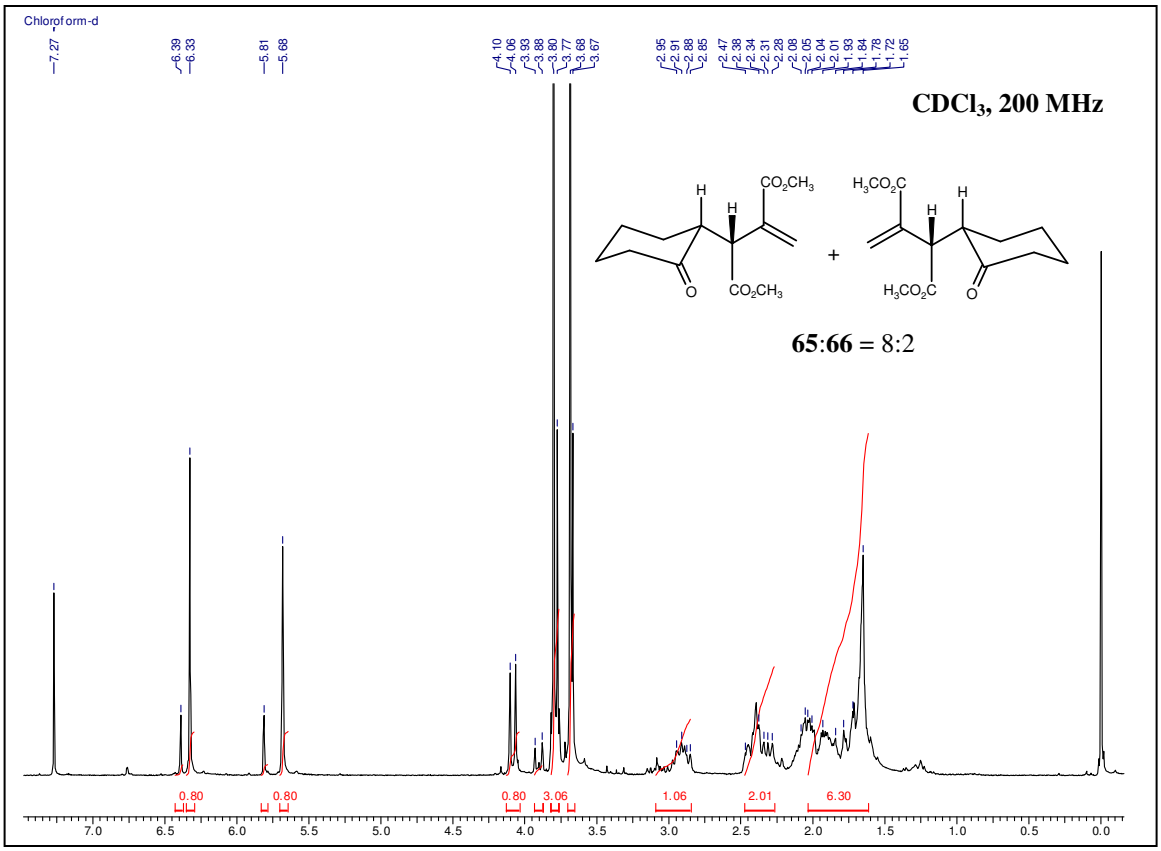

CDCl3, 100 MHz
127.66
52.16
52.01
43.87
42.45
25.63
22.13
13.66
OMe
MeO
O
CH2(CH2)2CH3
59b

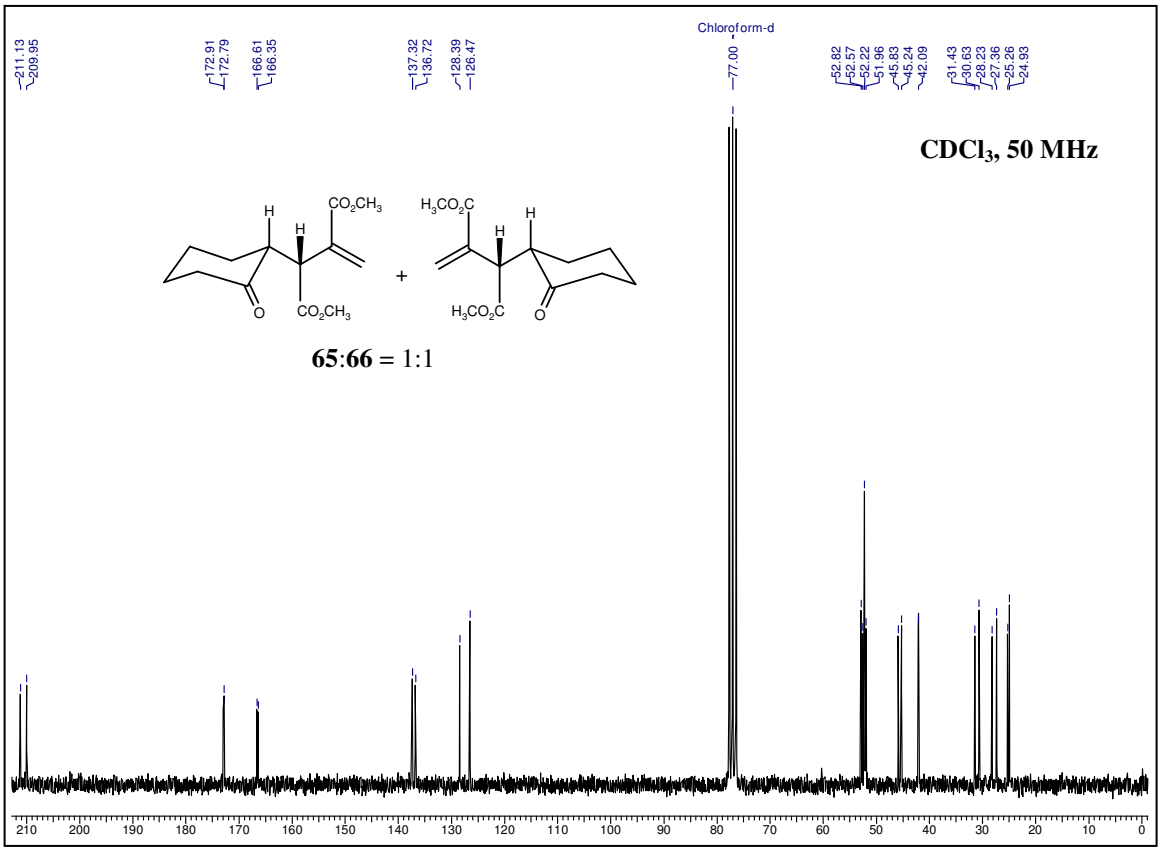

CDCl3, 200 MHz
7.97
7.97
7.96
7.93
7.92
7.55
7.51
7.47
7.44
7.43
7.27
6.34
5.81
4.30
4.27
4.26
4.23
3.82
3.78
3.76
3.73
3.69
3.29
3.27
3.20
3.18
OMe
MeO
Ph
59e
2.00
3.06
0.97
0.97
0.97
3.82
1.00

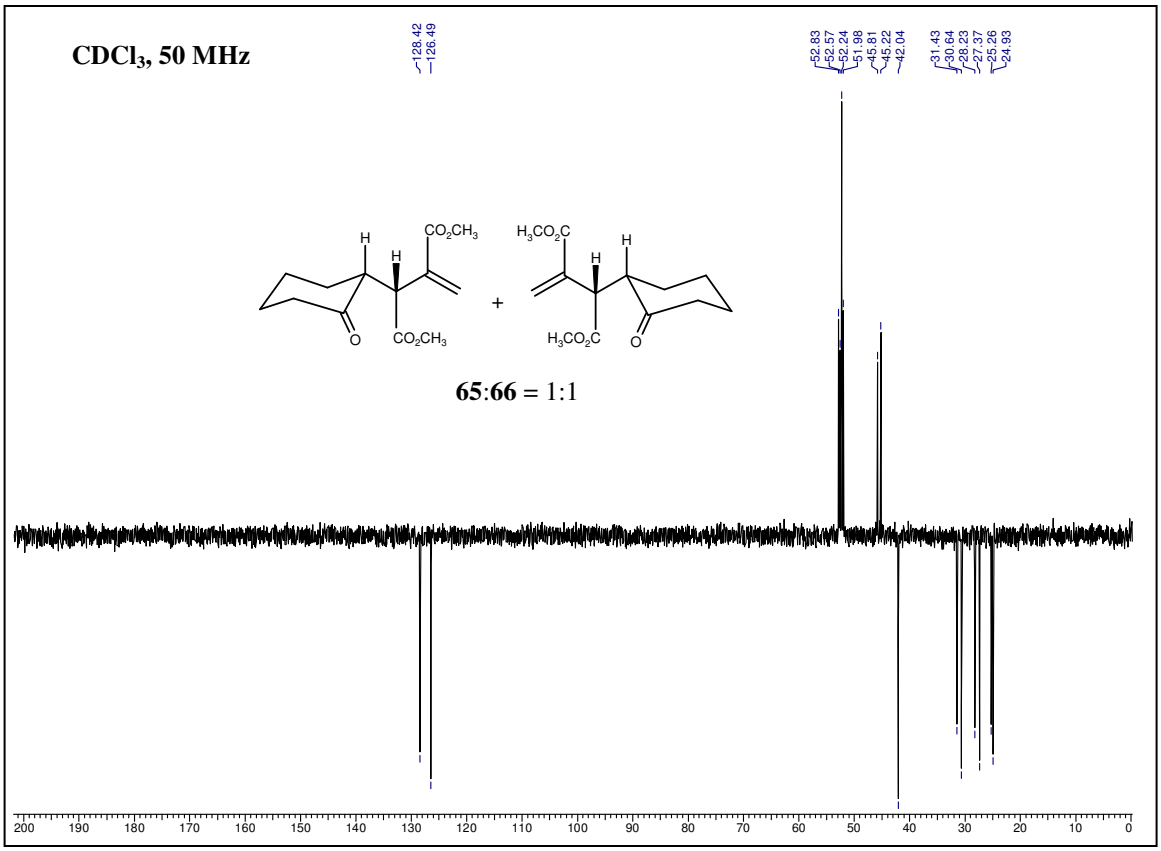

Chloroform-d
197.05
172.69
166.03
137.78
136.31
133.13
128.45
127.92
77.00
52.19
52.02
42.58
40.23
CDCl3, 50 MHz
O
OMe
MeO
O
O
Ph
59e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

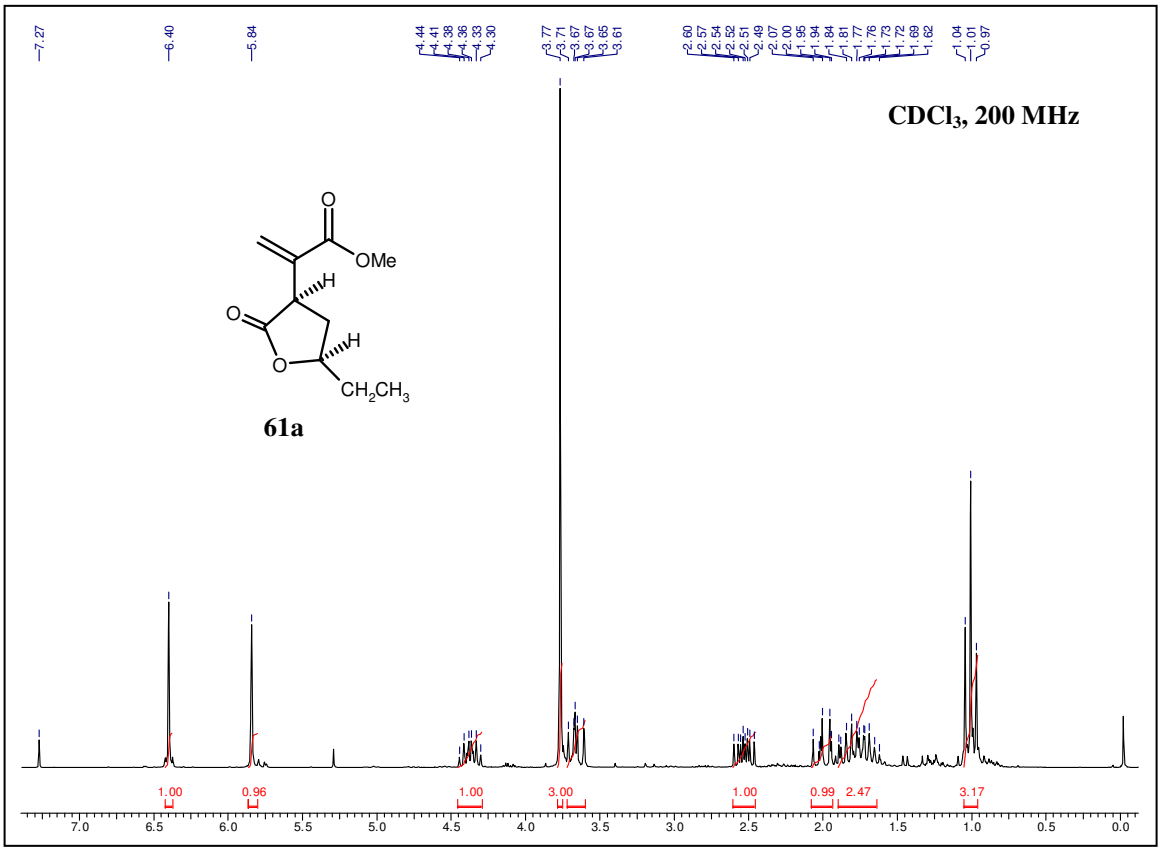

133.16
128.46
127.94
127.89
52.22
52.06
42.58
40.23
CDCl3, 50 MHz
O
OMe
MeO
O
O
Ph
59e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

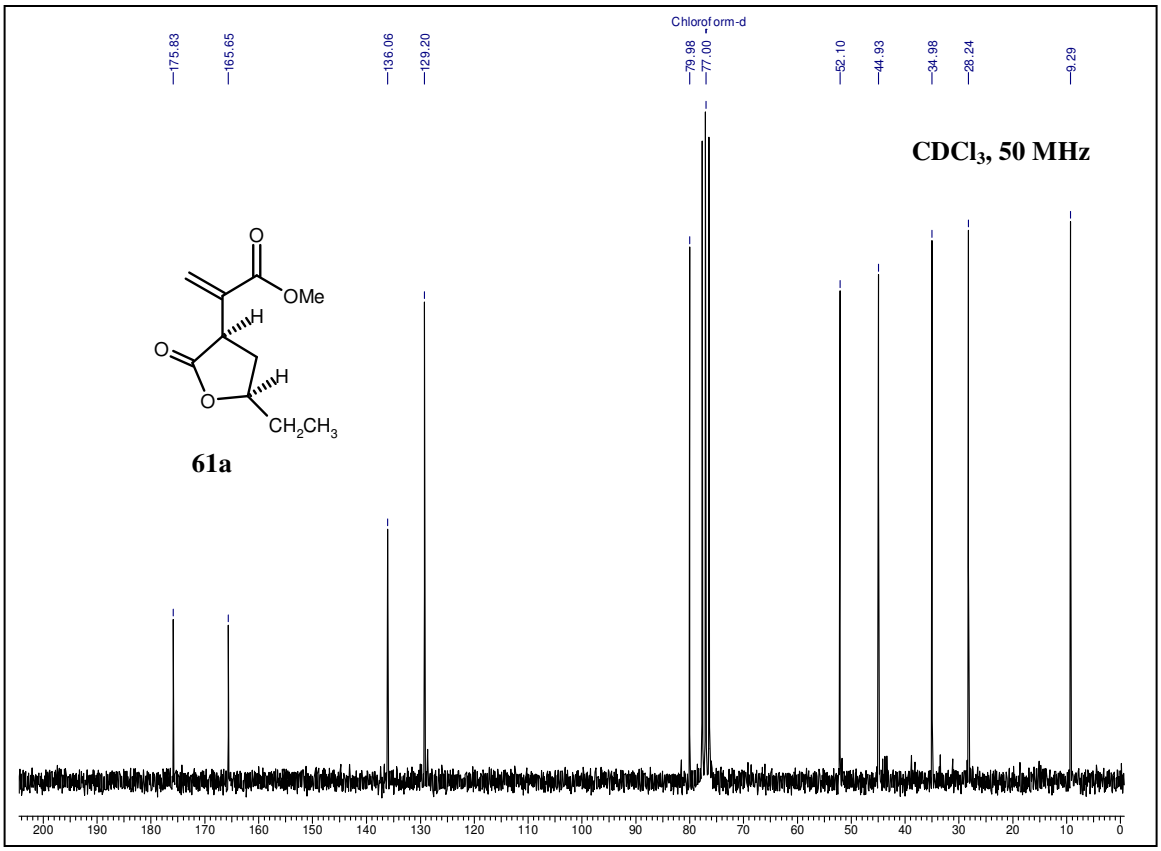

CDCl3, 200 MHz
65:66 = 1:1

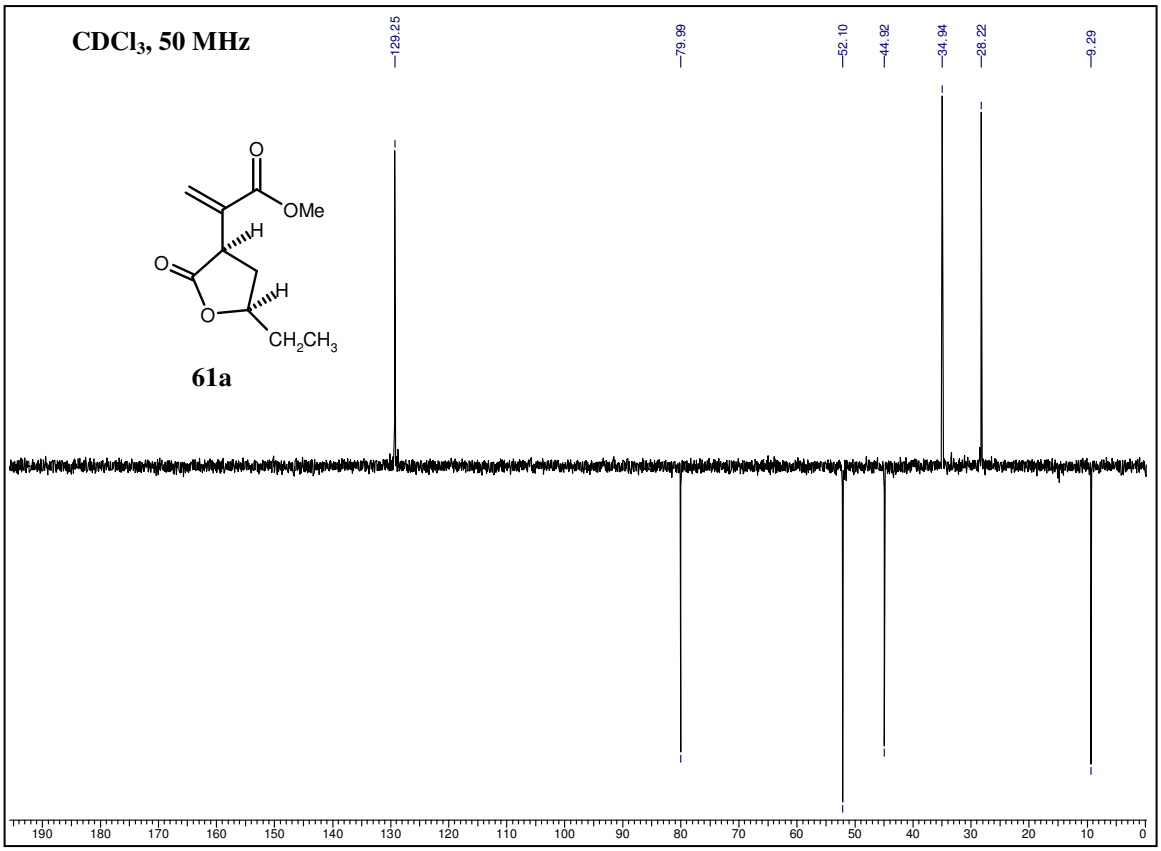

Chloroform-d
CDCl3, 200 MHz
65:66 = 8:2

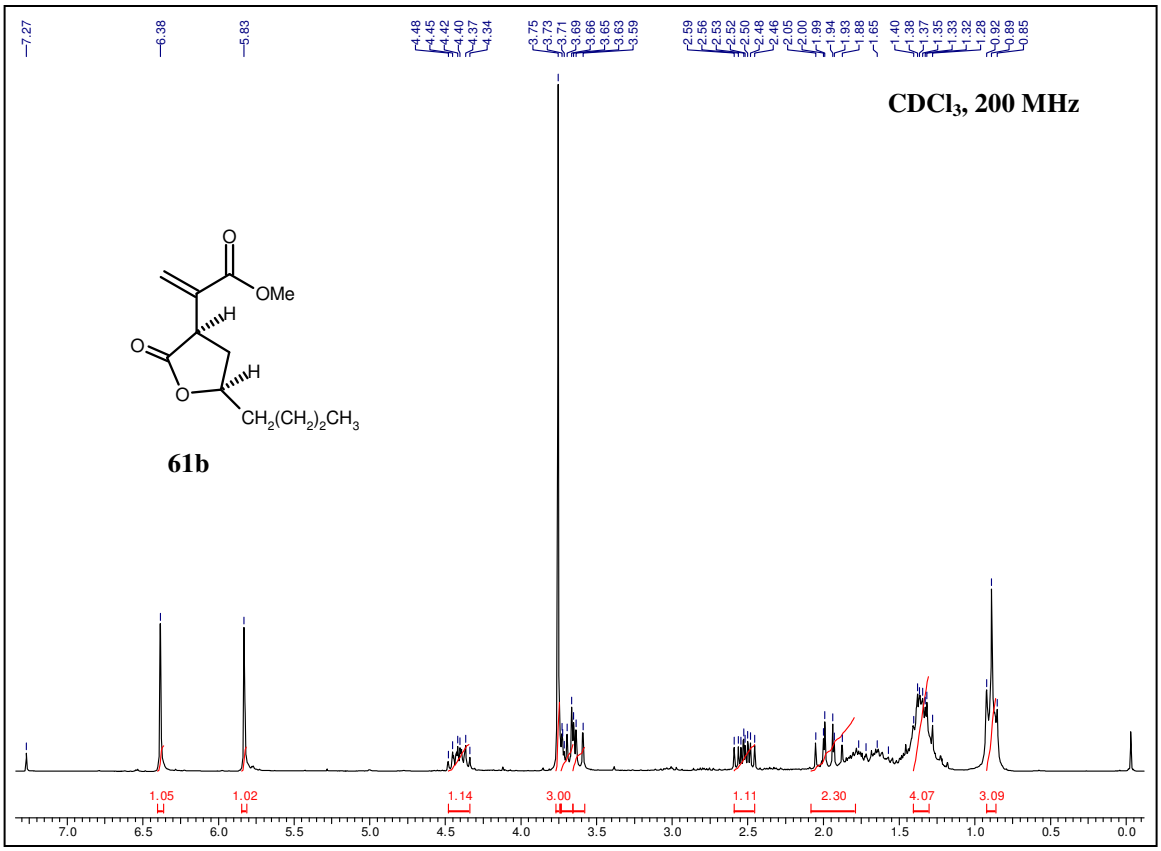

211.13
209.95
172.91
172.79
166.61
166.35
137.32
136.72
128.39
126.47
Chloroform-d
77.00
52.82
52.57
52.22
51.96
45.83
45.24
42.09
31.43
30.63
28.23
27.36
25.26
24.93
CDCl3, 50 MHz
65:66 = 1:1

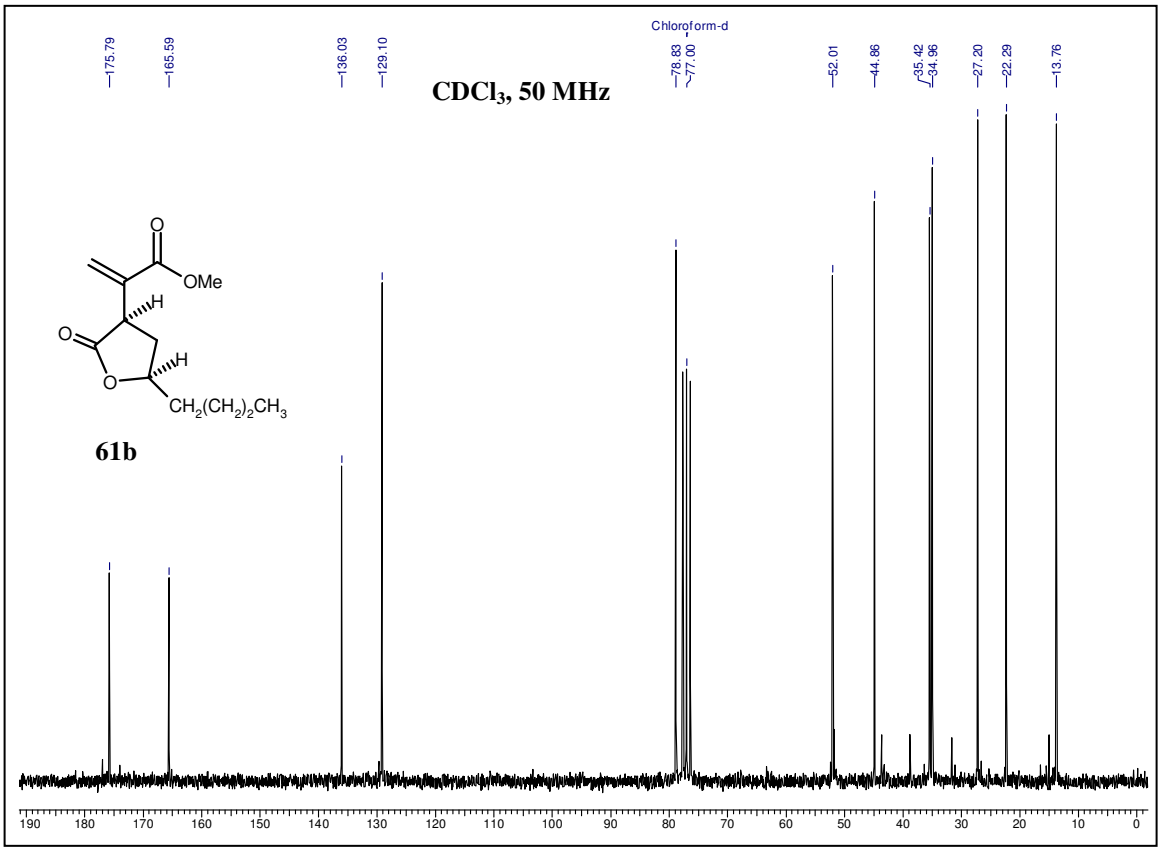

CDCl3, 50 MHz
128.42
126.49
52.83
52.57
52.24
51.98
45.81
45.22
42.04
31.43
30.64
28.23
27.37
25.26
24.93
65:66 = 1:1

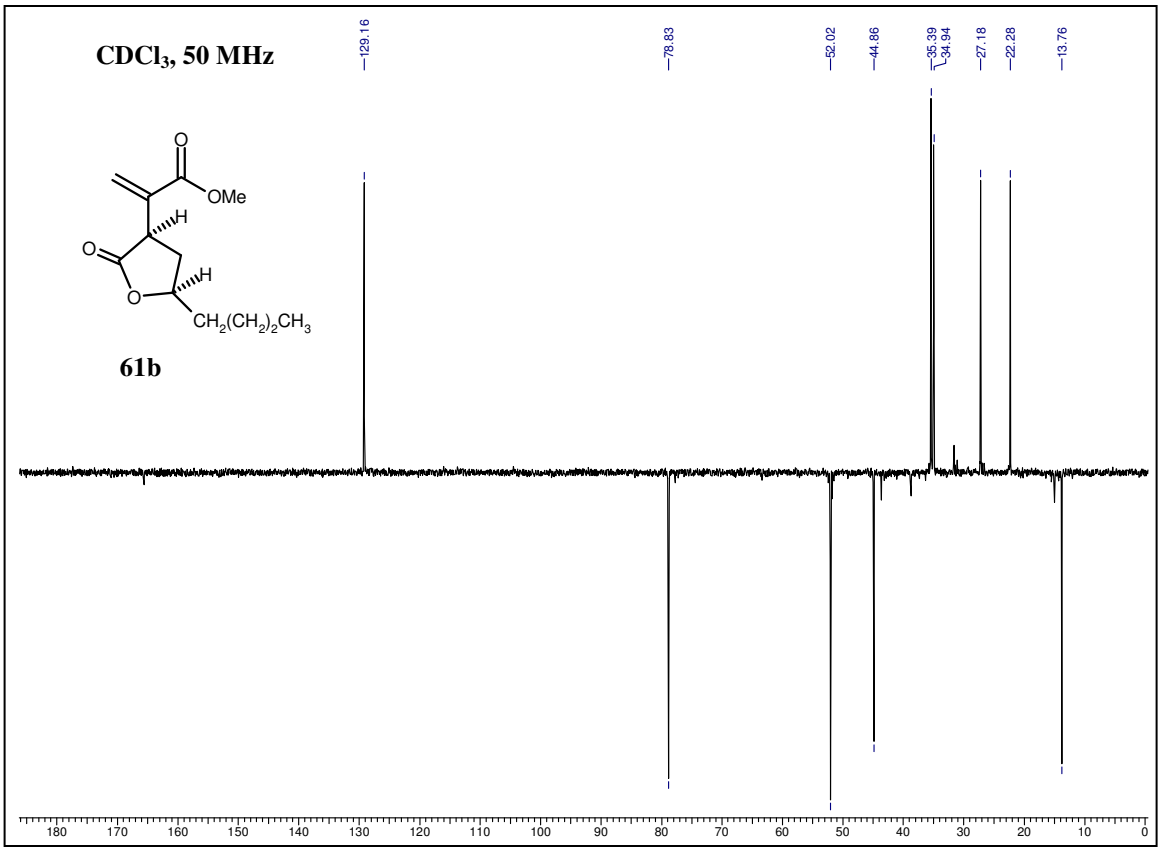

CDCl3, 200 MHz
OMe
H
O
O
H
O
CH2CH3
61a

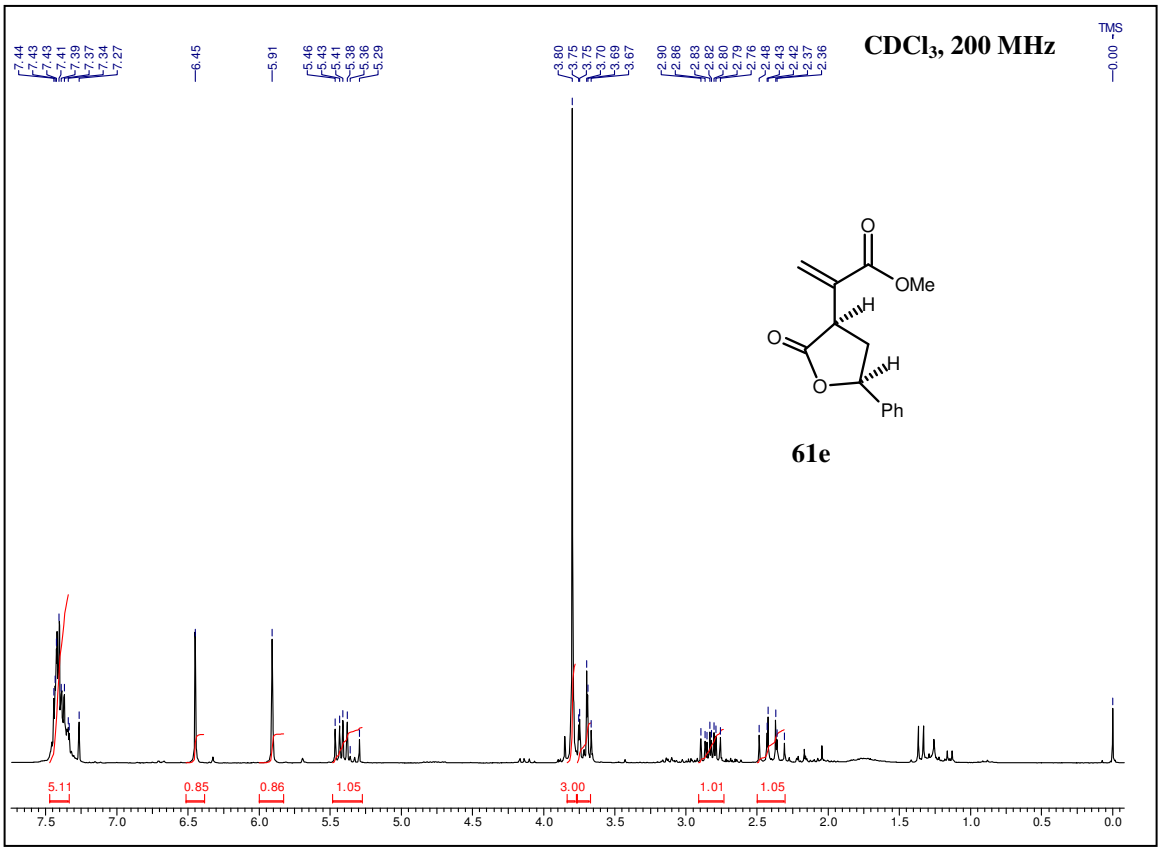

Chloroform-d
CDCl3, 50 MHz
OMe
H
O
O
H
O
CH2CH3
61a

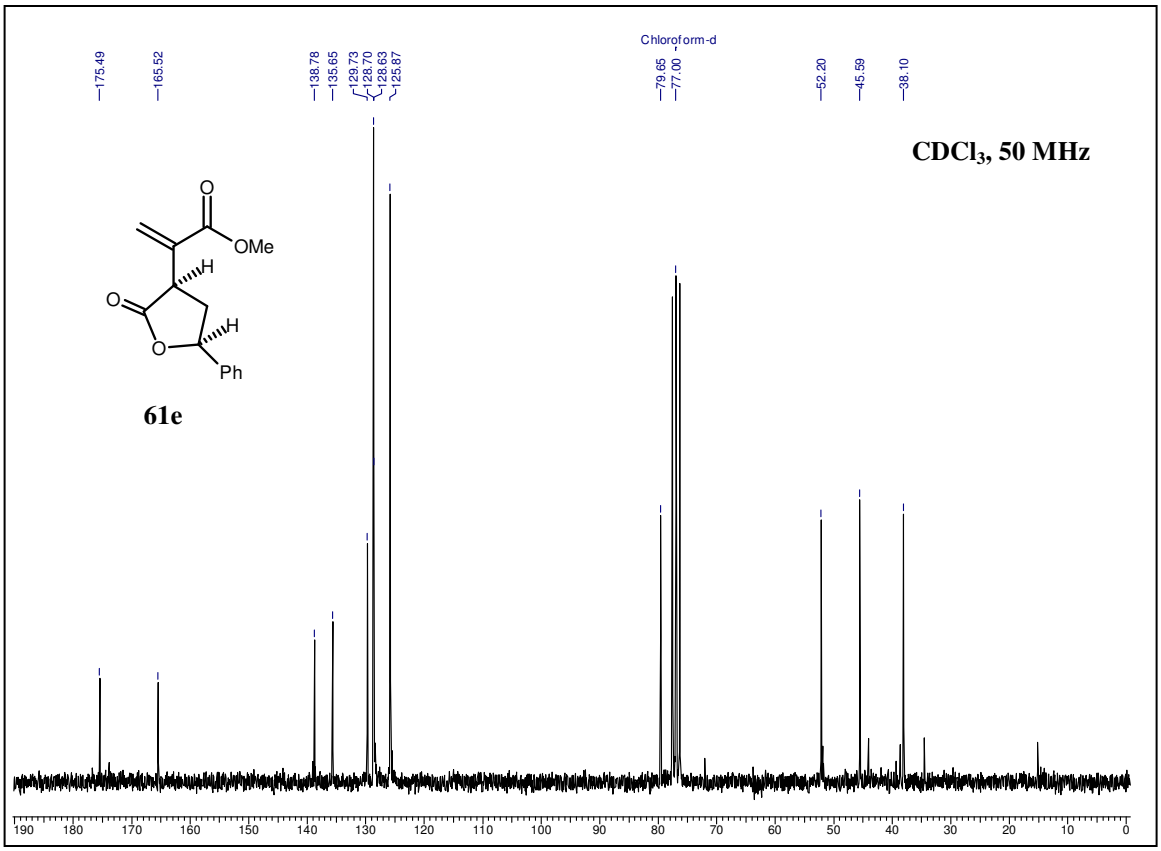

CDCl3, 50 MHz
129.25
79.99
52.10
44.92
34.94
28.22
9.29
OMe
H
O
H
O
CH2CH3
61a

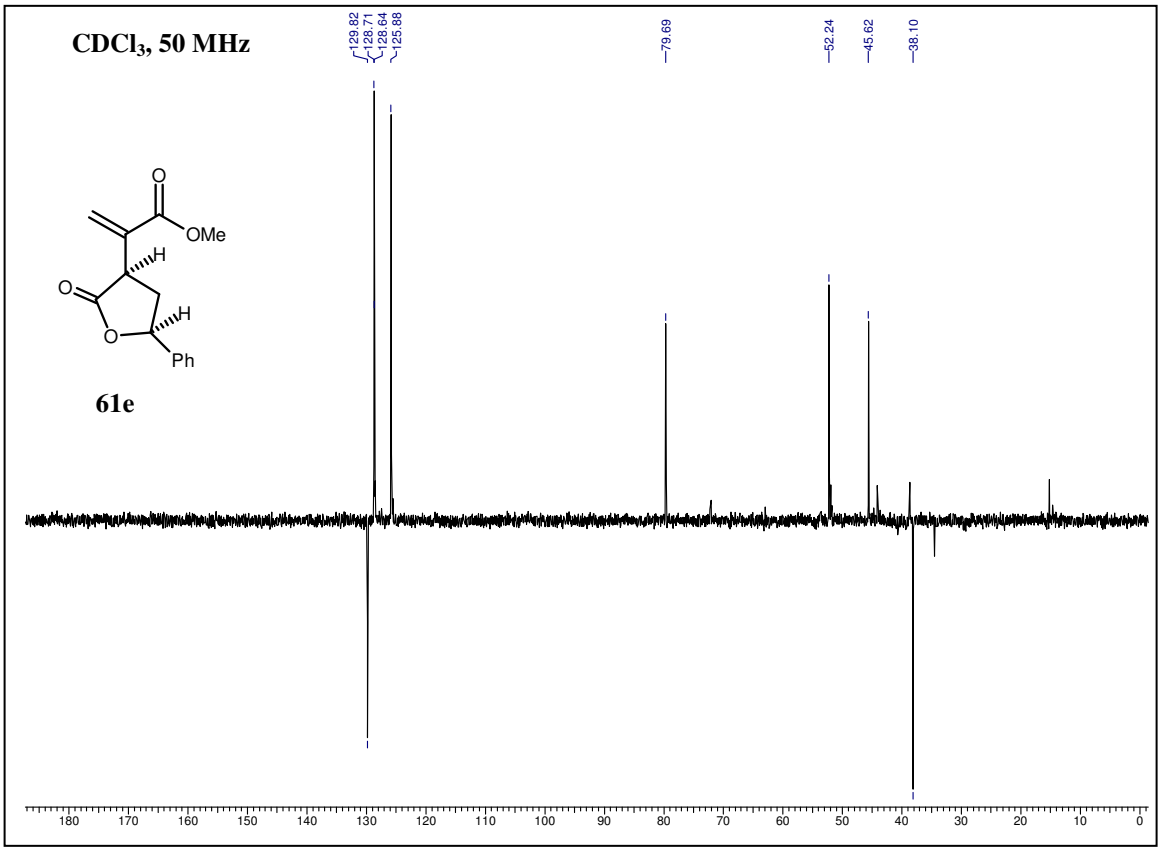

7.27
6.38
5.83
CDCl3, 200 MHz
OMe
H
O
H
O
CH2(CH2)2CH3
61b
1.05
1.02
1.14
3.00
1.11
2.30
4.07
3.09

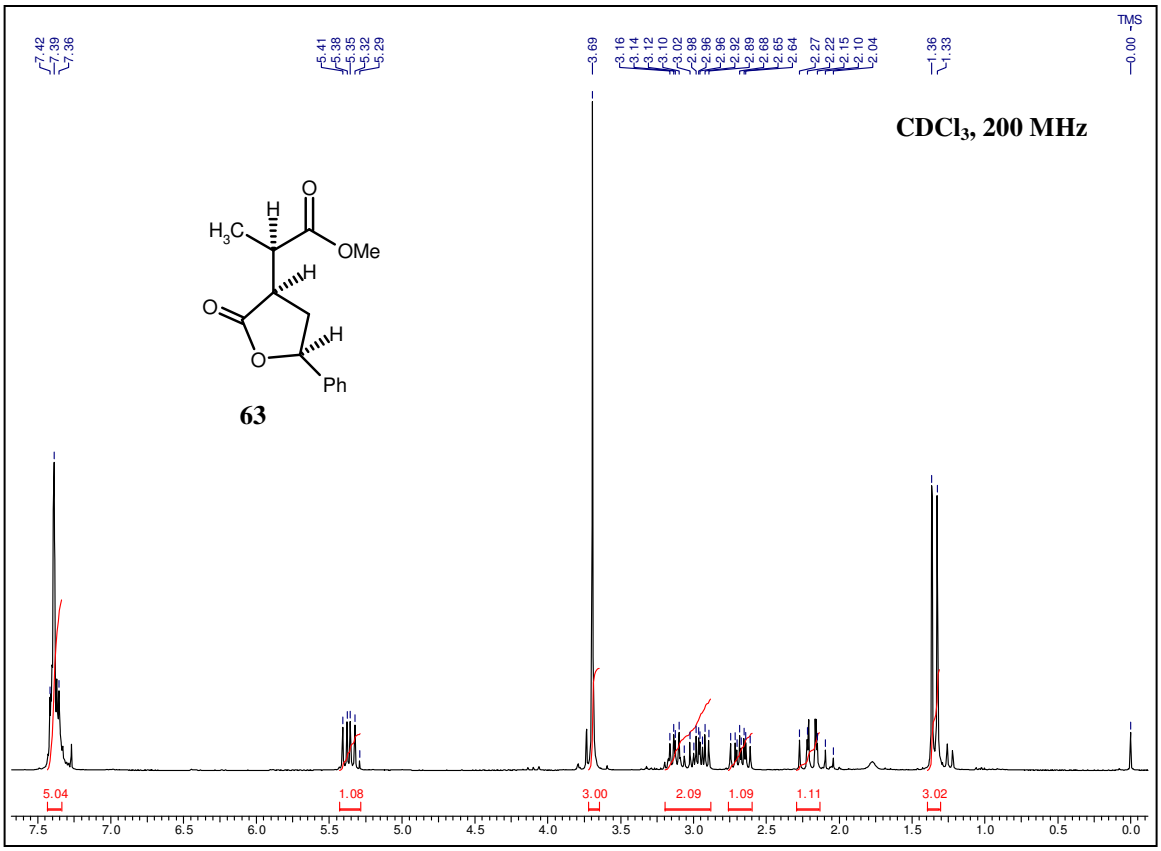

Chloroform-d
175.79
165.59
136.03
129.10
78.83
77.00
52.01
44.86
35.42
34.96
27.20
22.29
13.76
CDCl3, 50 MHz
O
OMe
H
O
H
O
CH2(CH2)2CH3
61b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

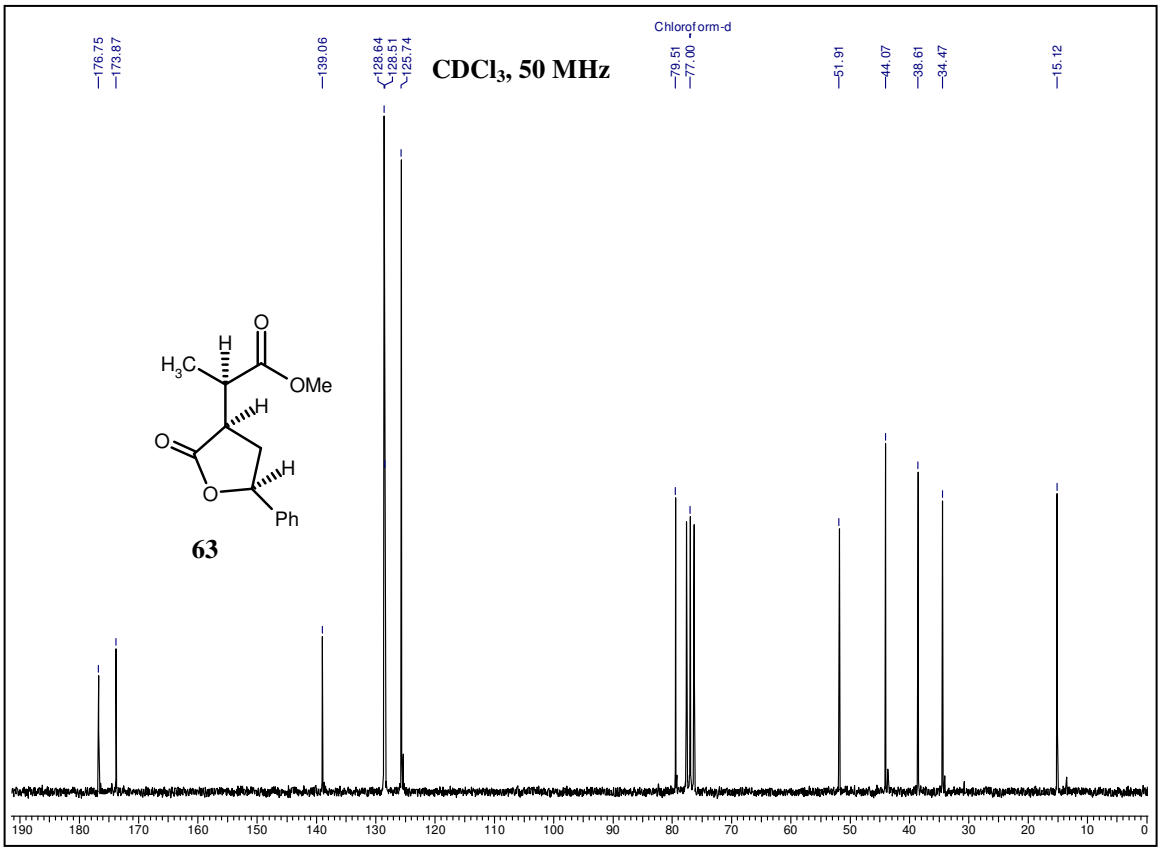

CDCl3, 50 MHz
129.16
78.83
52.02
44.86
35.39
34.94
27.18
22.28
13.76
O
OMe
H
O
H
O
CH2(CH2)2CH3
61b
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

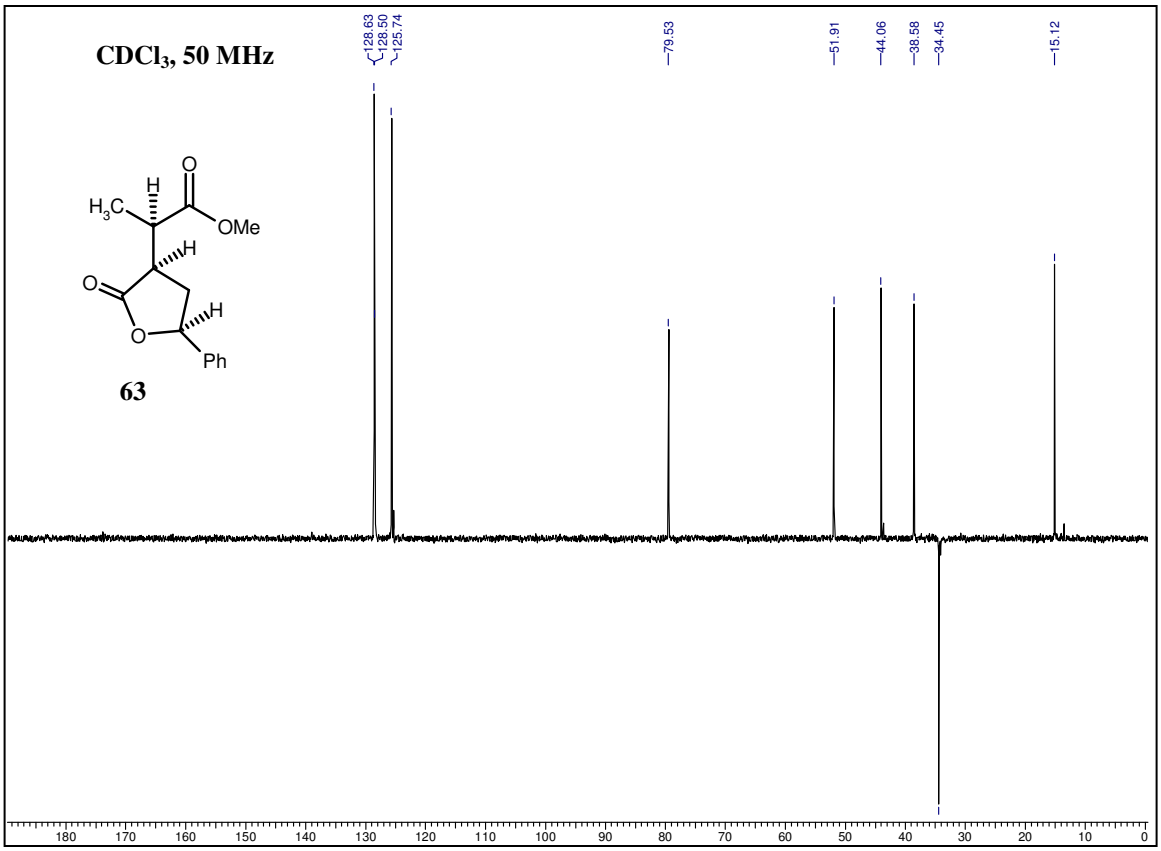

CDCl3, 200 MHz
TMS
7.44
7.43
7.43
7.41
7.39
7.37
7.34
7.27
6.45
5.91
5.46
5.43
5.41
5.38
5.36
5.29
3.80
3.75
3.75
3.70
3.69
3.67
2.90
2.86
2.83
2.82
2.80
2.79
2.76
2.48
2.43
2.42
2.37
2.36
0.00
5.11
0.85
0.86
1.05
3.00
1.01
1.05
O
OMe
H
O
H
O
Ph
61e

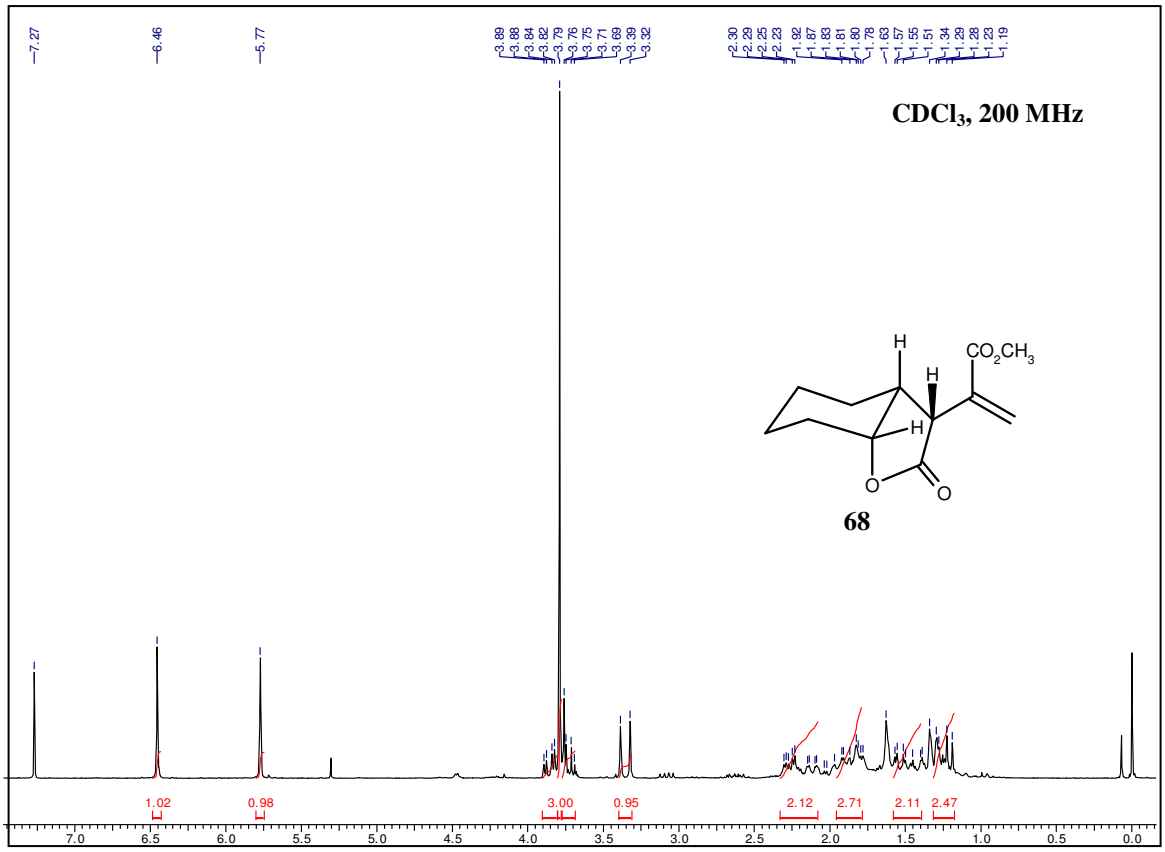

CDCl3, 50 MHz
Chloroform-d
175.49
165.52
138.78
135.65
129.73
128.70
128.63
125.87
79.65
77.00
52.20
45.59
38.10
O
OMe
H
O
H
O
Ph
61e

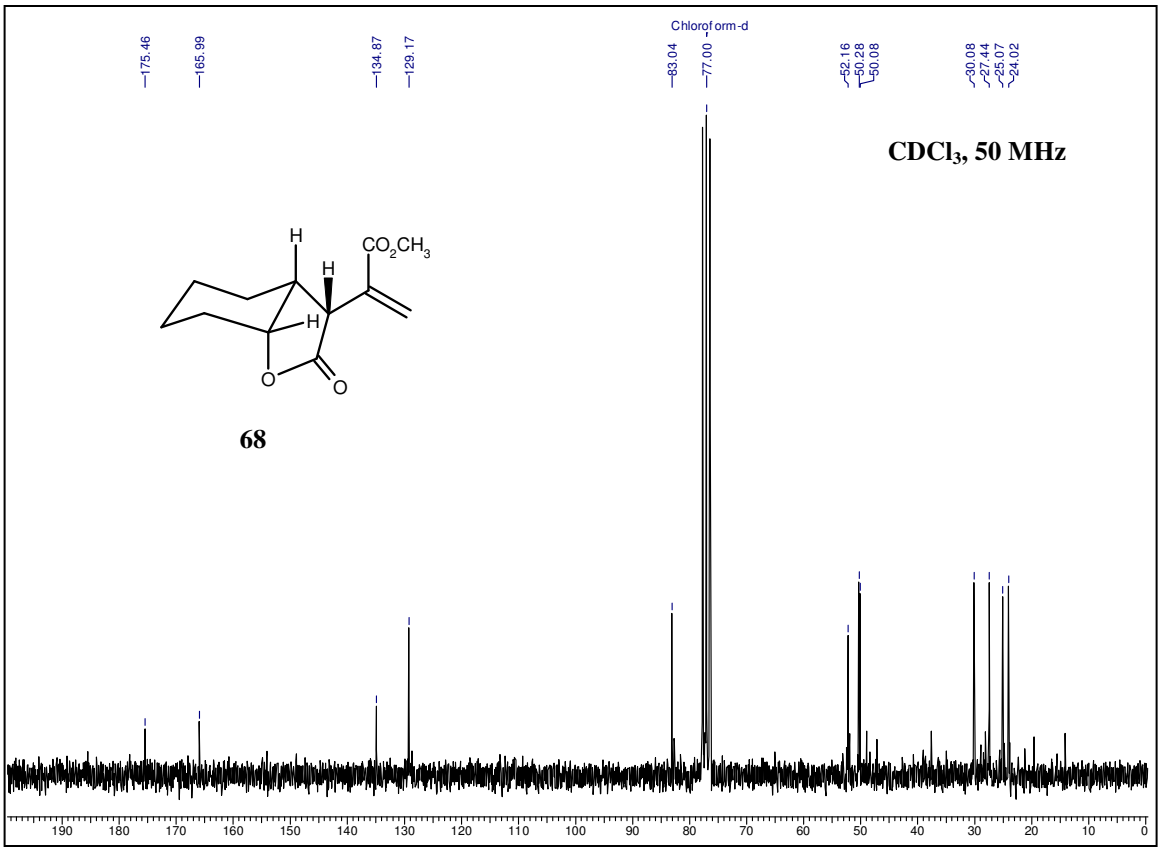

CDCl3, 50 MHz
129.82
128.71
128.64
125.88
79.69
52.24
45.62
38.10
O
OMe
H
O
H
O
Ph
61e

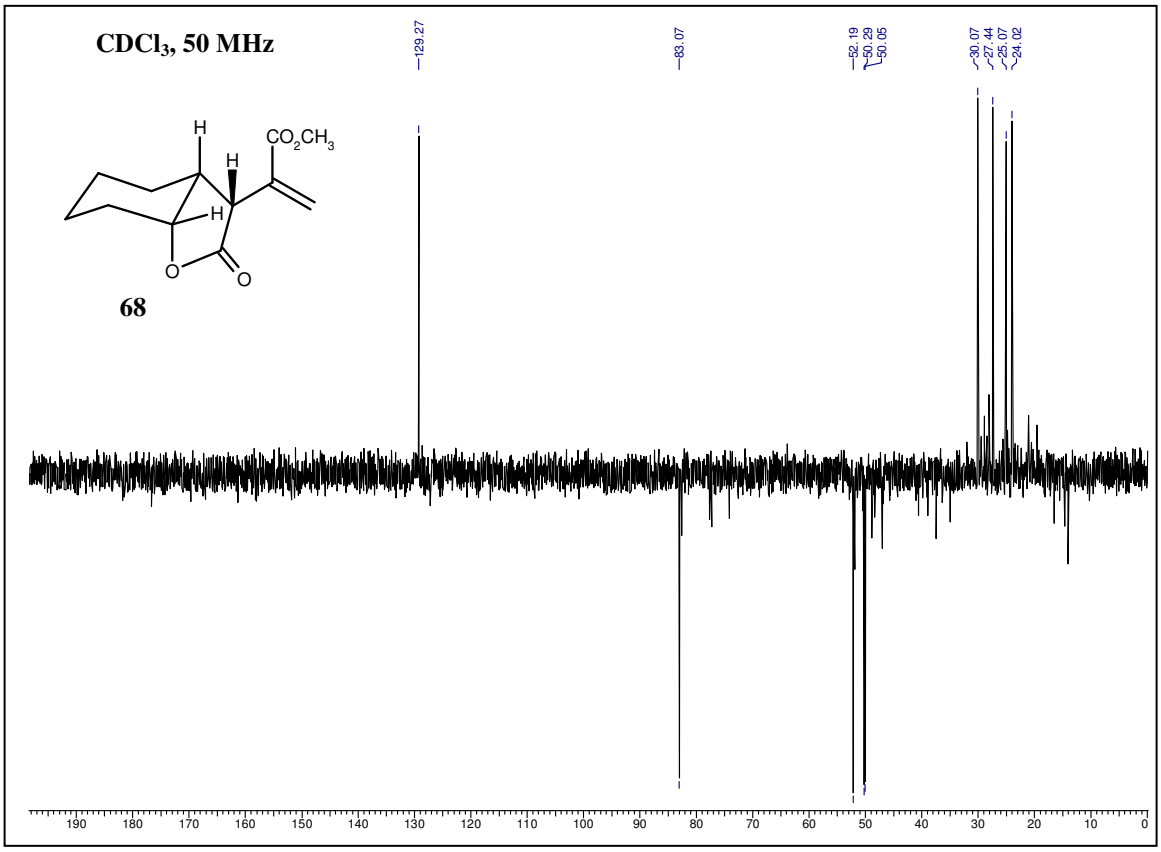

TMS
7.42
7.39
7.36
5.41
5.38
5.35
5.32
5.29
3.69
3.16
3.14
3.12
3.10
3.02
2.98
2.96
2.96
2.92
2.89
2.68
2.65
2.64
2.27
2.22
2.15
2.10
2.04
1.36
1.33
0.00
CDCl3, 200 MHz
O
H
H3C
OMe
H
O
H
O
Ph
63
5.04
1.08
3.00
2.09
1.09
1.11
3.02

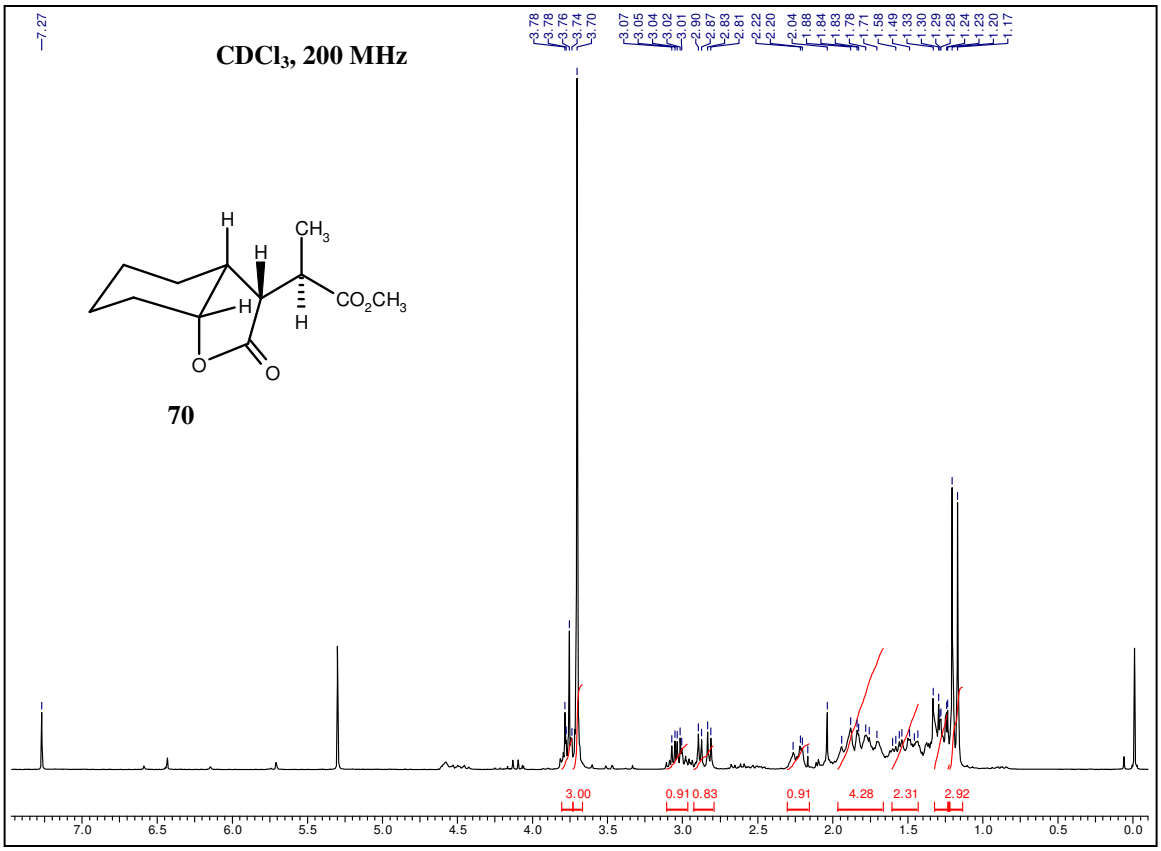

CDCl3, 50 MHz
Chloroform-d
176.75
173.87
139.06
128.64
128.51
125.74
79.51
77.00
51.91
44.07
38.61
34.47
15.12
O
H
H3C
OMe
H
O
H
O
Ph
63

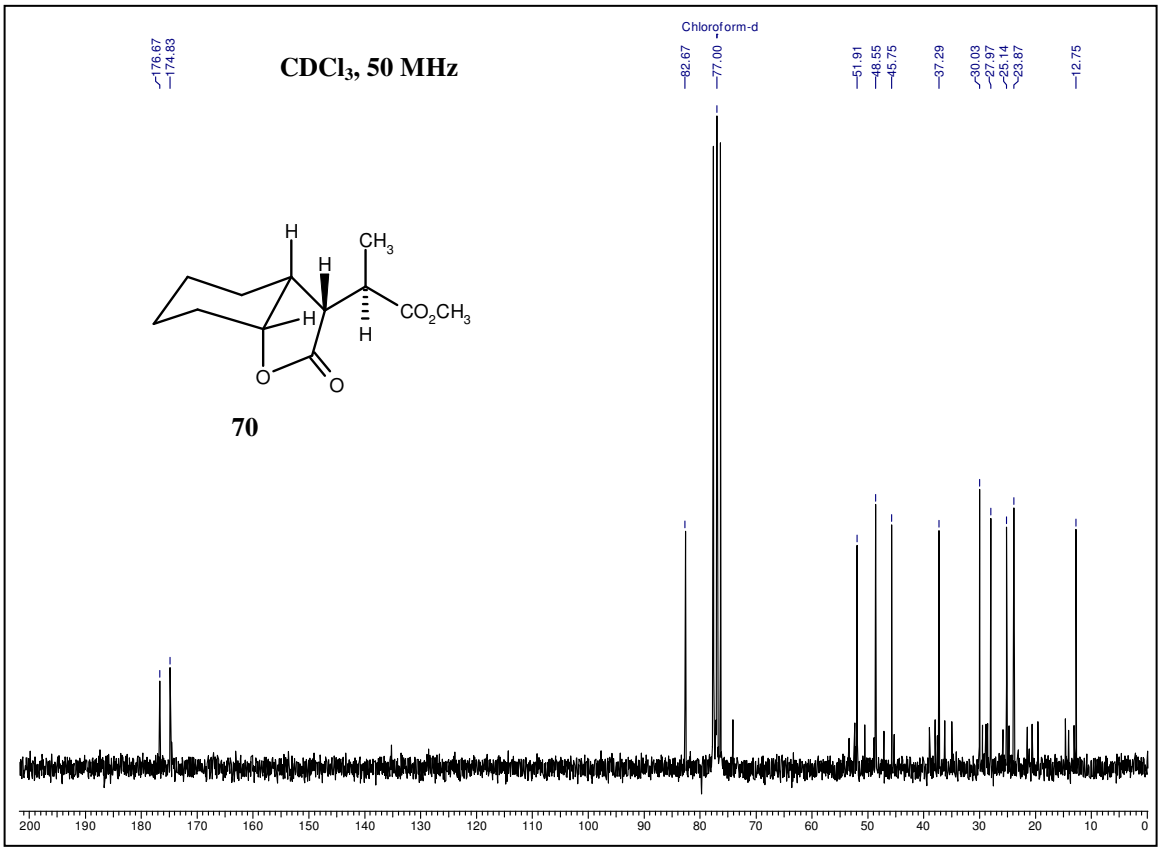

CDCl3, 50 MHz
128.63
128.50
125.74
79.53
51.91
44.06
38.58
34.45
15.12
O
H
H3C
OMe
H
O
H
O
Ph
63

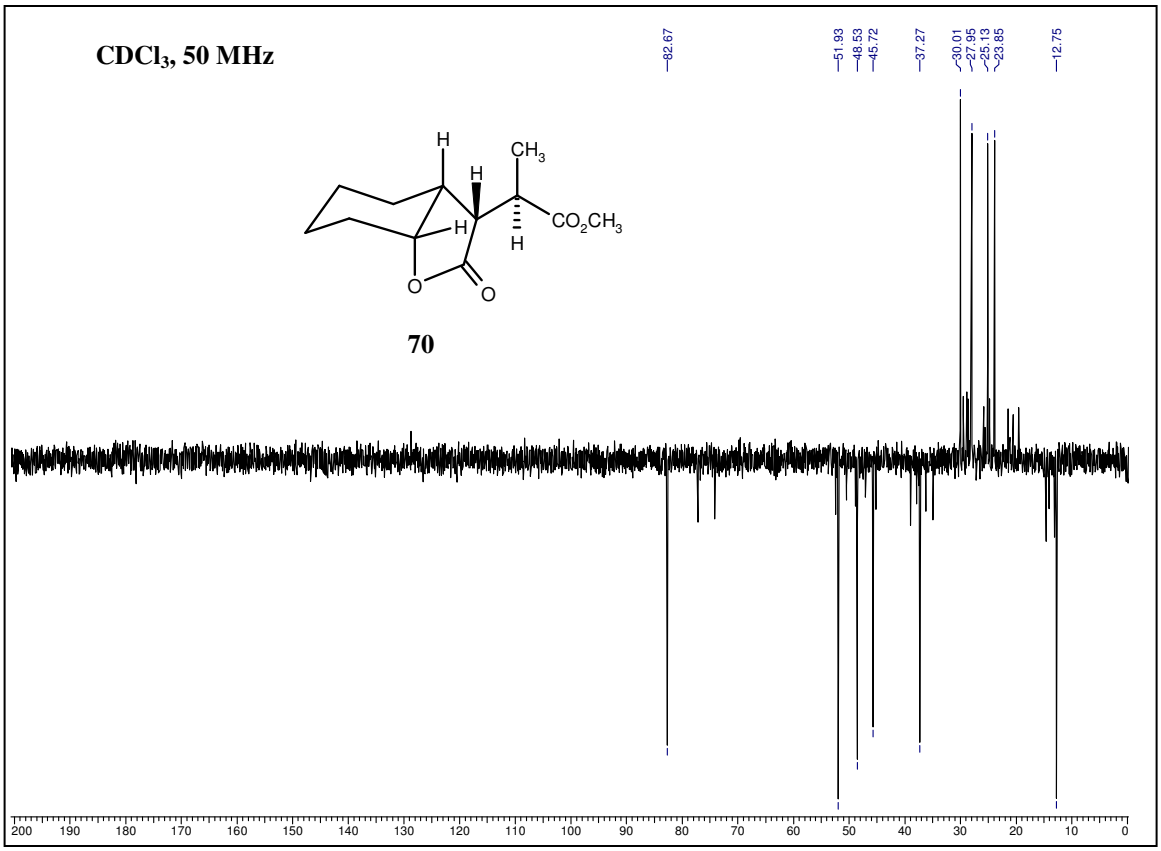

CDCl3, 200 MHz
H
CO2CH3
H
H
O
O
68

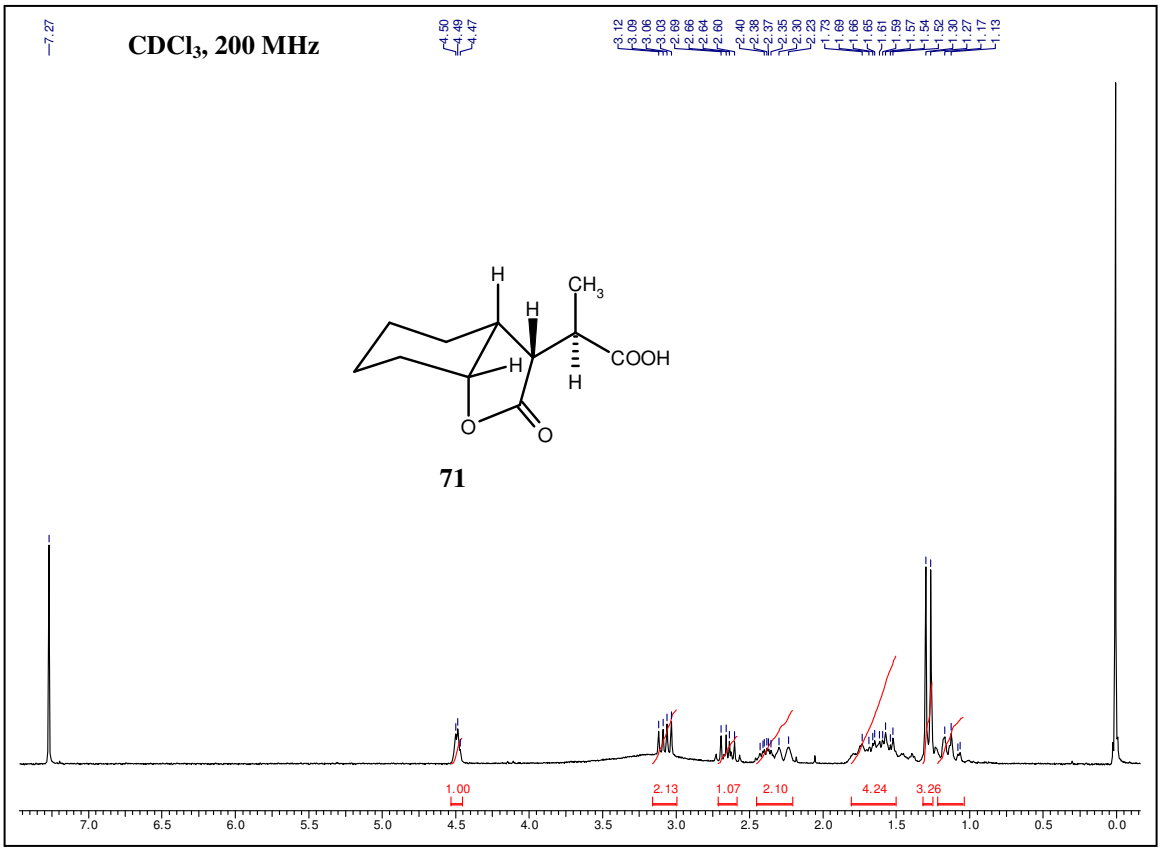

Chloroform-d
CDCl3, 50 MHz
H
CO2CH3
H
H
O
O
68

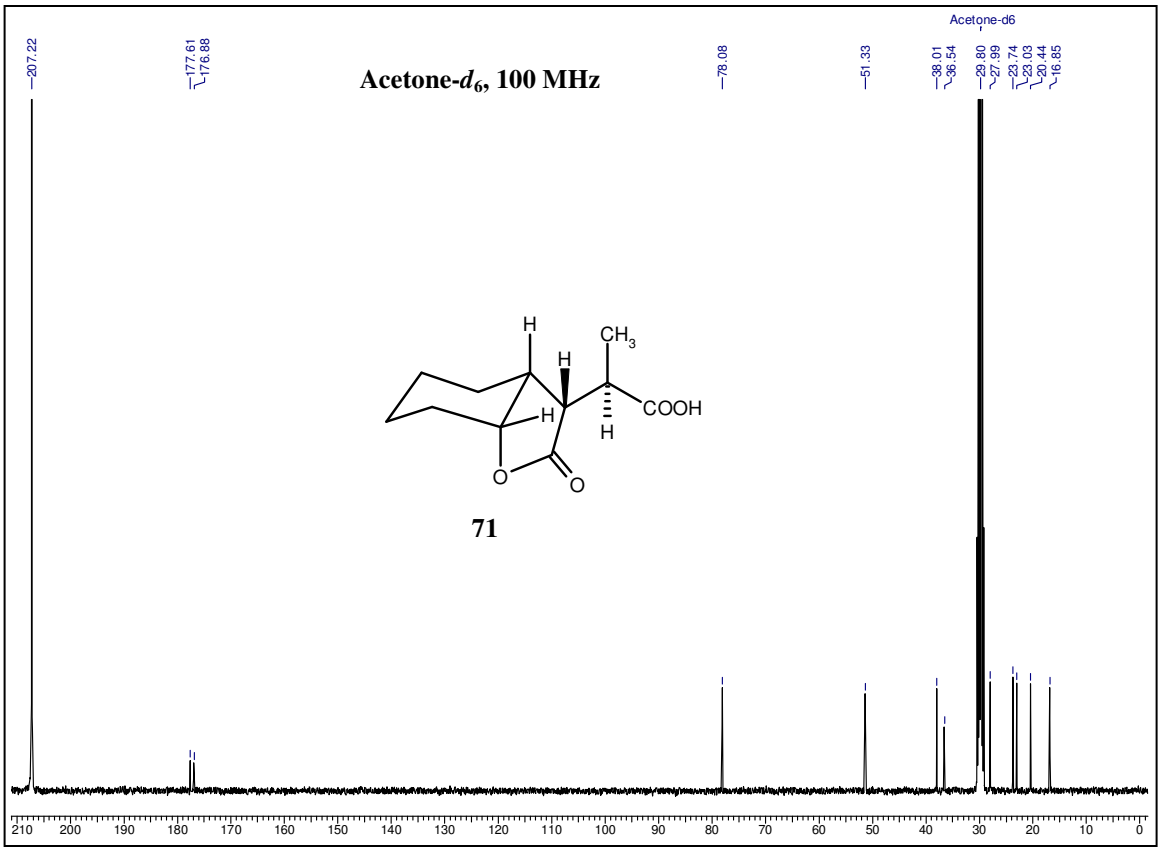

CDCl3, 50 MHz
129.27
83.07
52.19
50.29
50.05
30.07
27.44
25.07
24.02
H
CO2CH3
H
H
O
O
68


CDCl3, 200 MHz
7.27
3.78
3.78
3.76
3.74
3.70
3.07
3.05
3.04
3.02
3.01
2.90
2.87
2.83
2.81
2.22
2.20
2.04
1.88
1.84
1.83
1.78
1.71
1.58
1.49
1.33
1.30
1.29
1.28
1.24
1.23
1.20
1.17
H
CH3
H
CO2CH3
H
H
O
O
70
3.00
0.91
0.83
0.91
4.28
2.31
2.92

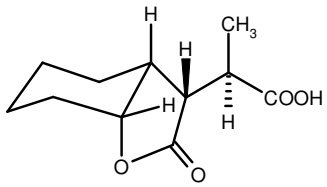

CDCl3, 50 MHz
Chloroform-d
176.67
174.83
82.67
77.00
51.91
48.55
45.75
37.29
30.03
27.97
25.14
23.87
12.75
H
CH3
H
H
CO2CH3
H
O
O
70


CDCl3, 50 MHz
82.67
51.93
48.53
45.72
37.27
30.01
27.95
25.13
23.85
12.75
H
CH3
H
H
CO2CH3
H
O
O
70


CDCl3, 200 MHz
7.27
4.50
4.49
4.47
3.12
3.09
3.06
3.03
2.69
2.66
2.64
2.60
2.40
2.38
2.37
2.35
2.30
2.23
1.73
1.69
1.66
1.65
1.61
1.59
1.57
1.54
1.52
1.30
1.27
1.17
1.13
H
H
CH3
H
COOH
H
O
O
71
1.00
2.13
1.07
2.10
4.24
3.26
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

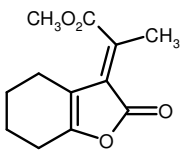

Acetone-d6
207.22
177.61
176.88
Acetone-d6, 100 MHz
78.08
51.33
38.01
36.54
29.80
27.99
23.74
23.03
20.44
16.85
H
H
CH3
H
COOH
H
O
O
71
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Acetone-d_6, 100 MHz

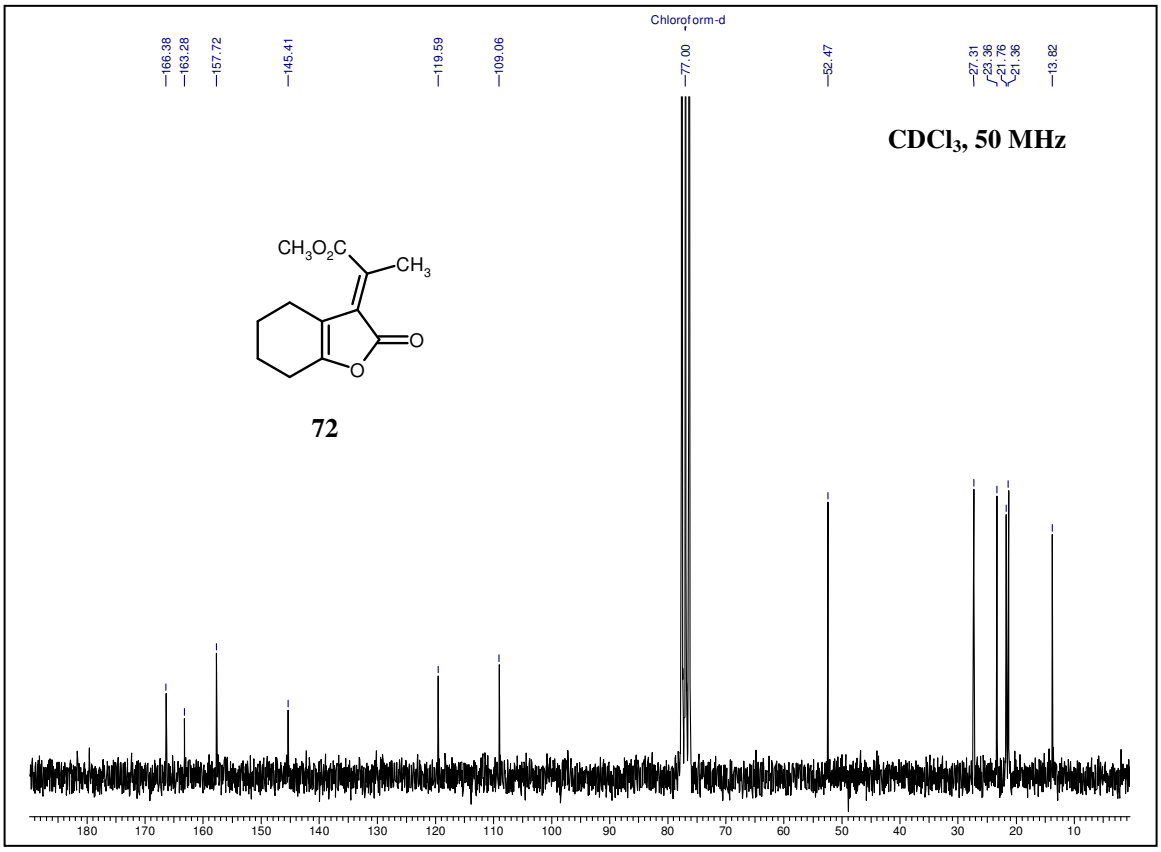


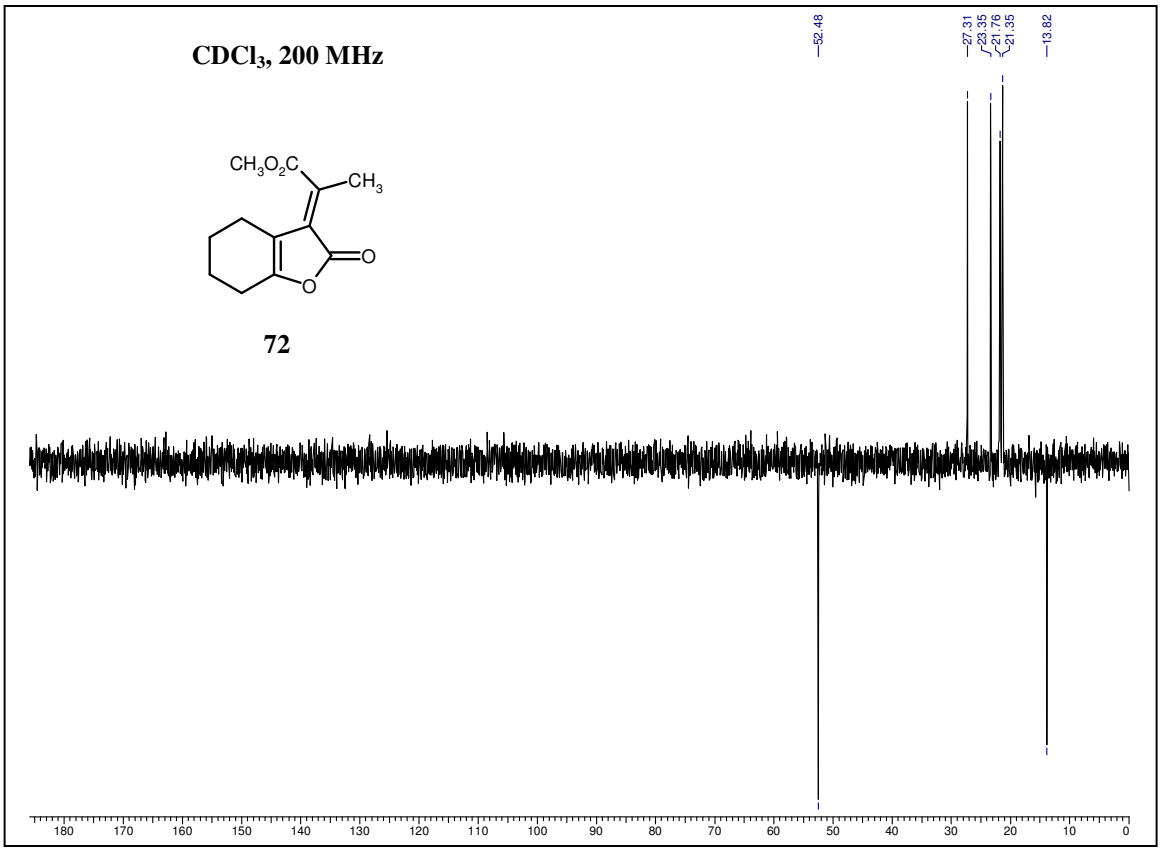
71

$CDCl_3$, 200 MHz



72


Chloroform-d
166.38
163.28
157.72
145.41
119.59
109.06
77.00
52.47
27.31
23.36
21.76
21.36
13.82
CDCl3, 50 MHz
CH3O2C
CH3
O
O
72
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


52.48
27.31
23.35
21.76
21.35
13.82
CDCl3, 200 MHz
CH3O2C
CH3
O
O
72
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

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(27) Crystallographic data (excluding structure factors) for the structures **63** and **71** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 620210 and 620211 respectively. Copies of the data can

be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

LIST OF PUBLICATIONS

1. N-Bromosuccinimide-dibenzoyl peroxide/azabisisobutyronitrile: a reagent for Z- to E alkene isomerization
   Md. Merajuddin Baag, Anirban Kar and Narshinha P. Argade *Tetrahedron* **2003**, 59, 6489.

2. Synthesis of natural cytotoxic camphorataimides B and C
   Md. Merajuddin Baag and Narshinha P. Argade *Synthesis* **2006**, 1005.

3. Reactions of *o*-aminothiophenol and *o*-aminophenyl disulfide with itaconic anhydride and (–)-dimenthyl itaconate: access to enantiomerically pure 1,5-benzothiazepines and benzothiazolyl-2-methylacrylic Acid
   Md. Merajuddin Baag and Narshinha P. Argade *Synthesis* **2007**, 457.

4. Facile chemo-, regio-, and diastereoselective approach to *cis*-3,5-disubstituted *γ*-butyrolactones and fused *γ*-butyrolactones
   Md. Merajuddin Baag, V. G. Puranik and N. P. Argade *J. Org. Chem*. **2007**, *72*, 1009.

5. Synthesis of gymnoascolide A
   Md. Merajuddin Baag and Narshinha P. Argade *Synthesis* **2008**, 26.

6. Synthesis of isomelophlin A and natural melophlin A
   Md. Merajuddin Baag and Narshinha P. Argade
   Unpublished Results

7. Diastereoselective synthesis of (+)-*erythro*-roccellic acid
   Md. Merajuddin Baag and Narshinha P. Argade
   Unpublished Results

Erratum