STUDIES ON TOTAL SYNTHESIS OF BIOACTIVE NATURAL BUTYROLACTONES

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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 "***Studies on Total Synthesis of Bioactive Natural Butyrolactones***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Sanjib Gogoi*** 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.

March 2008

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Candidate's Declaration

I hereby declare that the thesis entitled "***Studies on Total Synthesis of Bioactive Natural Butyrolactones***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune*** has not been submitted by me for a degree to any other University or Institution. This work was carried out at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India.

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Sanjib

CONTENTS

General Remarks

- All the solvents used were purified according to the literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned and silica gel (60-120 mesh/100-200 mesh/230-400 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol) and bromocresol green (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (conc. 1 μM) and neat/chloroform solution in case of liquid compounds.
- NMR spectra were recorded on Brucker ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), MSL 300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (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 (in case of solid) with authentic samples.
- All the new experiments were repeated two or more times.
- Starting materials were obtained from commercial sources or prepared using known procedures.
- ***Independent referencing and numbering of compounds, schemes, tables & figures have been employed for Chapter I, all Sections of Chapter II and Chapter III***

Abbreviations

AIBN	2,2′-Azobisisobutyronitrile
Aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bz	Benzoyl
Boc	*t*-Butoxycarbonyl
Cat.	Catalytic
Conv.	Conversion
Cp	Cyclopentadienyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DHP	Dihydropyran
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulphoxide
DTAD	Di-*tert*-butyl azodicarboxylate
ee	Enantiomeric excess
equiv.	Equivalent(s)

h	Hour(s)
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IC	Inhibitory concentration
IR	Infra Red
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
m-CPBA	*m*-Chloroperbenzoic acid
min.	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
Mp	Melting point
MS	Mass Spectrum
MsCl	Methanesulfonyl chloride
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid)
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methyl pyrollidone
PCC	Pyridinium chlorochromate
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate

p-TSA	*p*-Toluenesulfonic acid
p-TsCl	*p*-Toluenesulfonyl chloride
Py	Pyridine
RCM	Ring closing metathesis
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
TBDMS / TBS	*t*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIPS	Triisopropylsilyl
TMSCl	Trimethylchlorosilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Troc	*β*,*β*,*β*-Trichloroethoxycarbonyl

Lipase Abbreviations

Amano AY	Commercially available preparation of lipase from *Candida rugosa*
Amano PS	Commercially available preparation of lipase from *Burkholderia cepacia*
Amano PS-D	Lipase from *Pseudomonas cepacia* immobilized on diatomite
CAL-A	Lipase from *Candida antartica* (A)
CAL-B	Lipase from *Candida antartica* (B)
CCL	Lipase from *Candida cylindracea*
LIP-300	Lipase from *Pseudomonas aeruginosa*
Lipase AK	Commercially available preparation of lipase from *Pseudomonas fluorescens*
Lipase Godo E-1	Lipase from *Pseudomonas sp.*
Lipase MY	Lipase from *Candida rugosa*
Lipase PL-266	Lipase from *Alcaligenes sp.*
Lipase PS-C	Lipase from *Pseudomonas cepacia* immobilized on ceramic particles
Lipozyme	Lipase from *Mucor miehei*
Novozym 435	Lipase from *Candida antarctica*
PCL = PSL	Lipase from *Burkholderia cepacia*

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Abstract

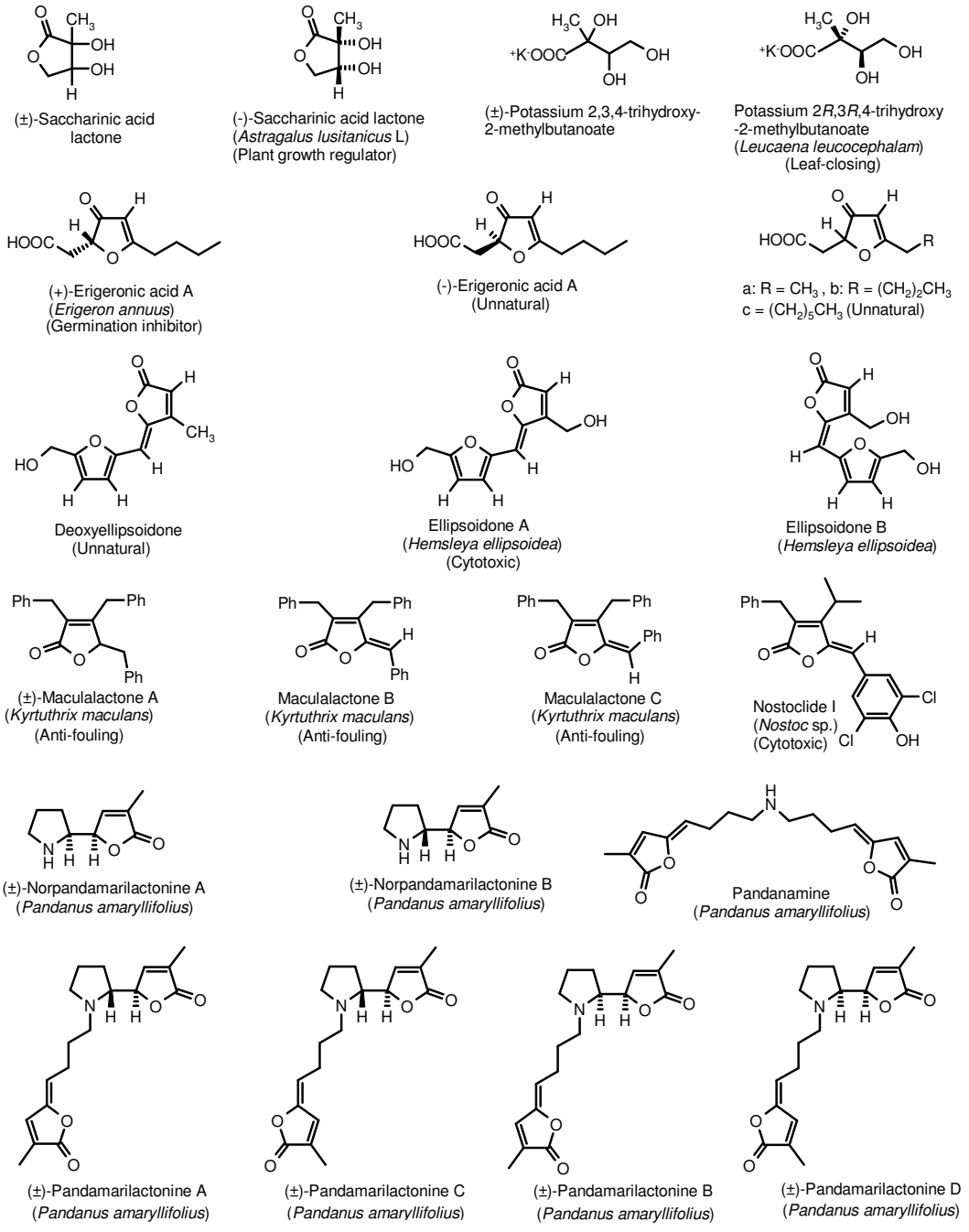


Figure 1. Natural Products and Unnatural Compounds Synthesized

The present dissertation is divided into three chapters. The first chapter presents a short overview on the chemistry of recently isolated bioactive *γ*-butyrolactone containing natural products. In the second chapter, our contribution towards the total synthesis of bioactive natural products containing *γ*-alkylidenebutyrolactone moiety, marine anti-fouling agents maculalactones A-C, cytotoxic nostoclide I, (±)-pandamarilactonines A-D and pandanamine has been elaborated in details (Figure 1). In the third chapter, a concise account of the use of lipases in organic synthesis followed by our contribution towards the total synthesis of plant growth regulator (–)-saccharinic acid lactone, leaf closing compound potassium 2*R*,3*R*,4-trihydroxy-2-methylbutanoate, cytotoxic ellipsoidone A, ellipsoidone B and germination inhibitor (+)-erigeronic acid using the lipases for the resolution of key intermediate or in significant transformation has been described. In the present dissertation we used citraconic anhydride, itaconic anhydride and (*R*/*S*)-acetoxysuccinic anhydride as the starting materials, a brief account of their preparations, reactions and uses are also included at appropriate places. For the purpose of simplification independent numbering system (e.g. compound numbers, reference numbers) is used for each section.

Chapter One: A Concise Account on the Chemistry of Recently Isolated Bioactive *γ*-Butyrolactone Containing Natural Products

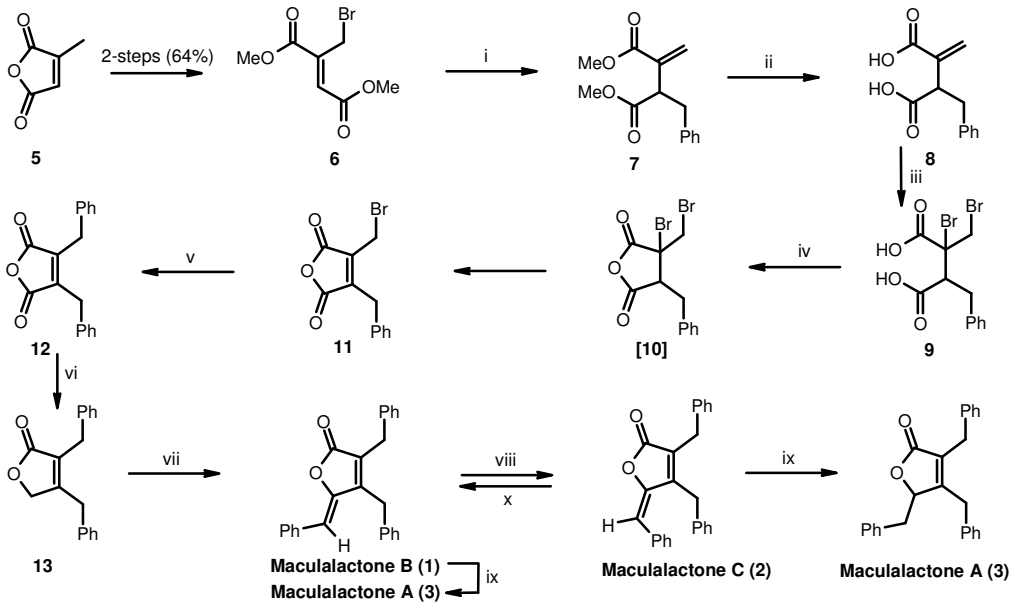
γ–Butyrolactone is a very common structural element in organic compounds, present in about 10% of all natural products. Natural products containing the butyrolactone skeleton attracted considerable attention due to their interesting biological activities. This chapter portrays a short overview on isolation, bioactivity and synthesis of recently isolated important bioactive *γ*-butyrolactones and *γ*-alkylidenebutenolides containing natural products with an emphasis on new synthetic routes and strategies. A concise account of butyrolactones is presented here and in view of large amount of literature on chemistry of butyrolactones, no pretension of completeness is claimed.

Chapter Two: Facile Synthesis of Maculalactones, Nostoclide I and Pandamarilactonines

This chapter is divided into two sections. The first section presents an elegant access to marine anti-fouling agents maculalactones A-C and cytotoxic nostoclide I, while the second section describes a facile synthesis of (±)-norpandamarilactonines A-B, (±)-pandamarilactonines A-D and pandanamine.

Section A: Synthesis of Naturally Occurring Bioactive Butyrolactones: Maculalactones A-C and Nostoclide I

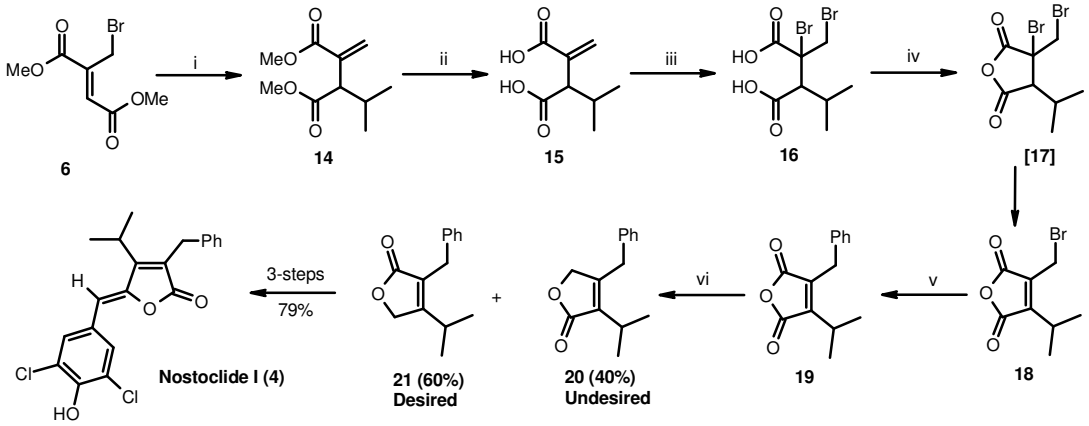
Maculalactones A-C have been isolated from the epilithic-encrusting cyanobacterium *Kyrtuthrix maculans* from Hong-Kong island and they possess marine anti-fouling activity. The natural (+)-maculalactone A has been assigned *S*-configuration. Till date, only one synthesis of each of these butyrolactones **1**-**3** has been reported in the literature.



Scheme 1. *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%).

Nostoclide I (**4**) has been isolated from the culture of a symbiotic blue-green alga, *Nostoc* sp., from the lichen *Peltigera canina* and possesses cytotoxic activity. Till date, two syntheses of **4** are known in the literature.

This section describes a simple multistep synthesis of naturally occurring butyrolactones maculalactone A (**3**), maculalactone B (**1**), maculalactone C (**2**) and nostoclide I (**4**) starting from citraconic anhydride (**5**) with good overall yields via dibenzylmaleic anhydride (**12**) and benzylisopropylmaleic anhydride (**19**) (Scheme 1). The two anhydrides **12** and **19** were prepared by S_N2' coupling reactions of appropriate Grignard reagents with



Scheme 2. *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%).

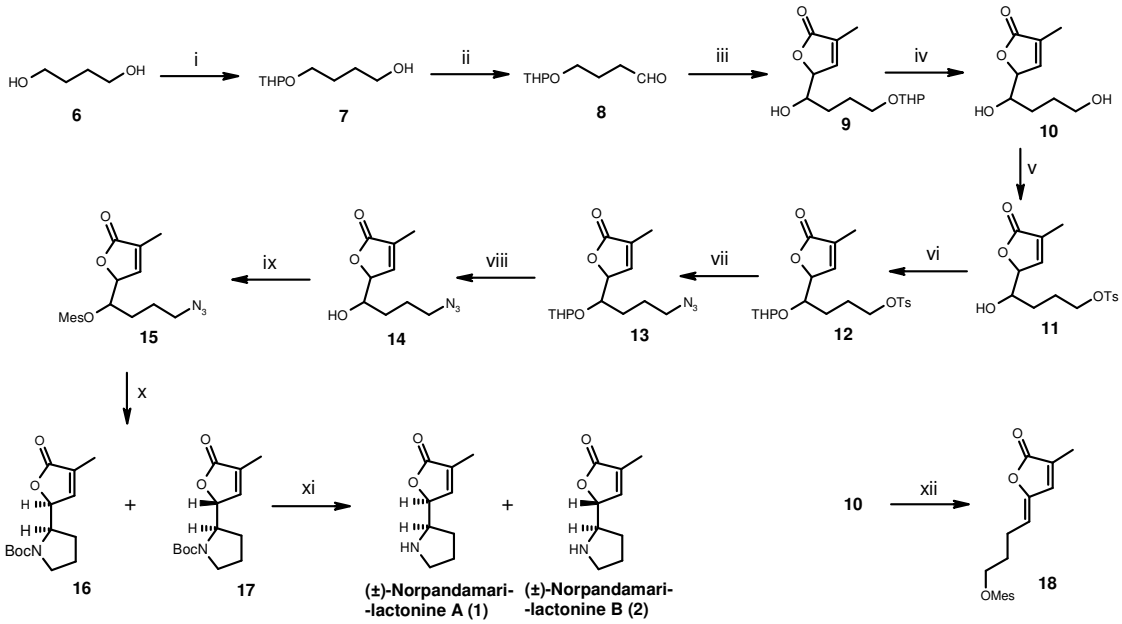
dimethyl bromomethylfumarate (**6**), LiOH-induced hydrolysis of esters to acids, bromination of carbon-carbon double bond, in situ dehydration followed by dehydro-bromination and chemoselective allylic substitution of bromo atom in disubstituted anhydrides **11** and **18** with appropriate Grignard reagents (29% overall yield in 5-steps for **12** and 31% overall yield in 5-steps for **19**). The $NaBH_4$ reduction of these anhydrides **12** and **19** furnished the desired lactones **13** (91%) and **21** (60%) respectively. The lactone **13** on Knoevenagel condensation with benzaldehyde furnished maculalactone B (**1**) in 77% yield, which on carbon-carbon double bond isomerization gave maculalactone C (**2**) in 50% yield, while **1** on regio-selective catalytic hydrogenation gave maculalactone A (**3**) in 75% yield (Scheme 2). The conversion of lactone **21** to nostoclide I (**4**) is known in the literature.

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

<u>Section B</u>: Synthesis of (±)-Norpandamarilactonines, (±)-Pandamarilactonines and Pandanamine

The genus *Pandanus* belonging to the family Pandanaceae with nearly 600 species are widely spread in tropical and subtropical regions. Several *Pandanus* species have been identified as medicinal plants and are used as a remedy for toothache, rheumatism, diuretic, cardio tonic and the hypoglycemia. Takayama *et al.* have isolated the natural products

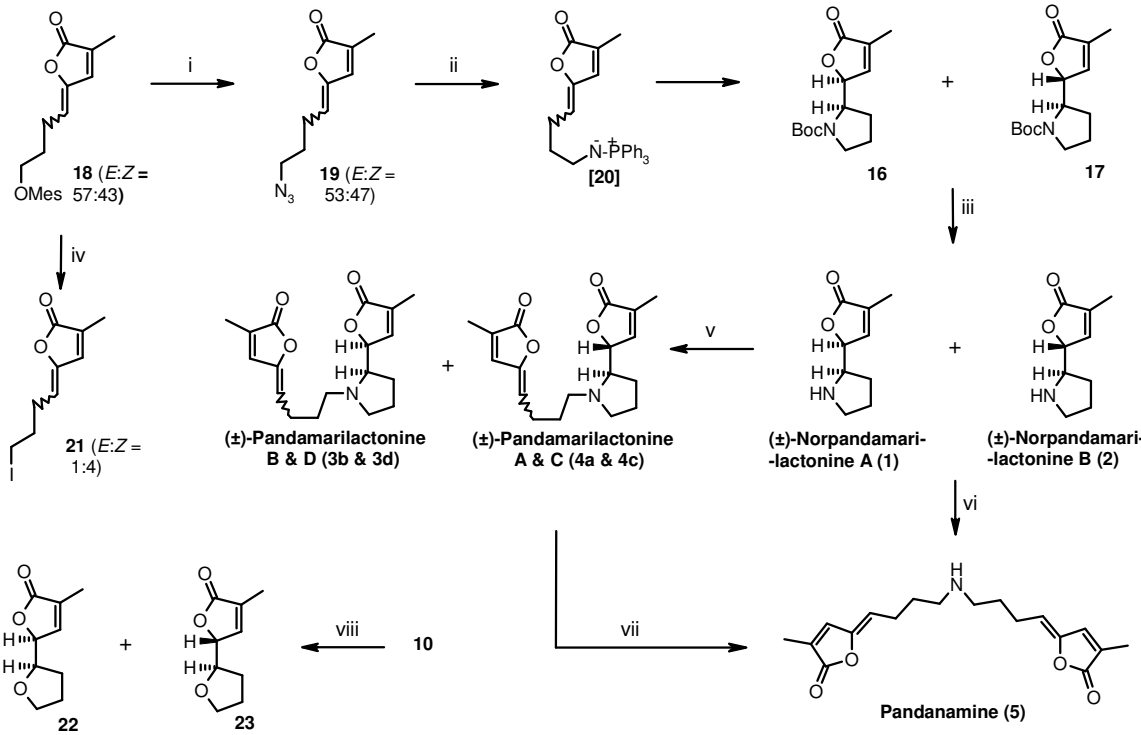
norpandamarilactonines A & B, pandamarilactonines A-D and pandanamine from *Pandanus amaryllifolius* species. Several syntheses of these natural products are known in the literature using variety of synthetic strategies. This section describes our synthetic efforts towards the simple and efficient synthesis of these natural amines starting from 3-methyl-2(5*H*)-furanone (Scheme 1). We envisaged the formation of **1** and **2** from



Scheme 1. *Reagents, conditions and yields*: (i) 3,4-Dihydro-2*H*-pyran, H^+/HCl, rt, 4 h (76%); (ii) Pyridinium chlorochromate, NaOAc, CH_2Cl_2, rt, 1 h (79%); (iii) 3-Methyl-2(5*H*)-furanone, LDA, THF, –78 ^oC to rt, 2 h (76%); (iv) PPTS, C_2H_5OH, 56 ^oC, 24 h (91%); (v) *p*-TsCl, Et_3N, DMAP, DCM, 0 ^oC to rt, 1.5 h (85%); (vi) 3,4-Dihydro-2*H*-pyran, PPTS, DCM, rt, 12 h (91%); (vii) NaN_3, DMF, rt, 12 h (88%); (viii) PTSA, CH_3OH, rt, 1.5 h (95%); (ix) CH_3SO_2Cl, Et_3N, DCM, -10 ^oC, 2.5 h (91%); (x) (a) PPh_3, THF, rt, 0.5 h, (b) H_2O, rt, 12 h, (c) Boc_2O, DCM, Et_3N, 16 h (**16**:**17** = 3:7, 31%); (xi) TMSOTf, DCM, –20 ^oC to –5 ^oC, 2.5 h (**1**:**2** = 1:1, 99%); (xii) CH_3SO_2Cl, Et_3N, DCM, rt, 24 h (77%).

mesylazide **15,** which on chemoselective reduction followed by cyclization would furnish **1** and **2**. The mesylazide **15** was synthesized starting from 3-methyl-2(5*H*)-furanone, which on base catalyzed condensation with the aldehyde **8**, obtained from 1,4-butanediol (**6**) via the selective mono –OTHP protection and oxidation sequence followed by the –OTHP deprotection furnished lactone-diol **10** in 69% overall yield in 2-steps. Regioselective tosylation of the primary hydroxy group followed by -OTHP protection of the secondary hydroxy group, chemoselective substitution of tosyl group by azide group, -OTHP deprotection and conversion of hydroxyl group to mesylate gave mesylazide **15** in 59% overall yield in 5-steps. The reduction of mesylazide **15** to amine and in situ cyclization

gave amines **1** and **2** which were separated from the crude reaction mixture by converting them to Boc-derivatives **16** and **17**. The Boc-deprotection of **16** and **17** afforded directly



Scheme 2. *Reagents, conditions and yields*: (i) NaN_3, DMF, rt, 16 h (87%); (ii) (a) PPh_3, THF, 42 ^oC, 0.5 h, (b) H_2O, 42 ^oC, 12 h, (c) Boc_2O, DCM, Et_3N, 16 h (**16**:**17** = 3:7, 77%); (iii) TMSOTf, DCM, –20 ^oC to –5 ^oC, 2.5 h (**1**:**2** = 1:1, 99%); (iv) LiI, THF, rt, 4 h (78%); (v) **21**, Ag_2CO_3, CH_3CN, rt, 24 h (**3b**:**3d**:**4a**:**4c** = 4:1:4:1, 64%); (vi) **21**, Ag_2CO_3, CH_3CN, rt, 48 h (66%); (vii) SiO_2, CH_2Cl_2, rt, 1 h (63%); (viii) P_2O_5, toluene, reflux, 1 h (**22** = 42%, **23** = 46%).

1 and **2** but with low yield of 30% (2-steps) only. Therefore we altered our strategy and decided to start the synthesis of **1** and **2** from mesylbutenolide **18**.

The diol **10** on treatment with methylsulfonyl chloride gave the desired mesylbutenolide **18**, which on chemo-selective substitution reaction with sodium azide followed by triphenylphosphine induced reductive regioselective intramolecular aza-Michael type addition to the exocyclic activated carbon-carbon double bond yielded the desired mixture of lactones **1** and **2** (Scheme 2). The mixture of **1** and **2** was separated from the crude product by preparing Boc-derivatives, which on subsequent deprotection furnished pure **1** and **2** (1:1) in 51% overall yield in 4-steps. The mesylbutenolide **18** (*E*:*Z* = 57:43) on reaction with lithium iodide gave the iodobutenolide **21** (*E*:*Z* = 1:4) in 78% yield. The intermolecular coupling reaction of **21** (*E*:*Z* = 1:4) with **1**+**2** (1:1) in the presence of Ag_2CO_3 as a coupling reagent in 24 hours reaction time gave the desired mixture of natural

products pandamarilactonines A-D in 64% yield in a 4:4:1:1 ratio respectively and pandanamine (**5**), in 48 hours reaction time. The pandamarilactonines A-D mixture also on treatment with silica gel in CH_2Cl_2 at room temperature exclusively yielded the pandanamine (**5**) in 63% yield.

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

Chapter Three: Chemoenzymatic Synthesis of Potassium (2*R*,3*R*)-2,3,4-Trihydroxy-2-methylbutanoate, Ellipsoidones and (+)-Erigeronic Acid

This chapter is divided into four sections. The first section presents a concise account of the applications of lipases in the synthetic organic chemistry. Earlier two Ph. D. dissertations from our group described details about the use of lipases, so to avoid repetition selected data are presented here. The second section summarizes our studies in employing lipases for the resolution of key intermediate (±)-saccharinic acid lactone and synthesis of potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate. The third section portrays an efficient and 6-steps first total synthesis of natural cytotoxic ellipsoidone A and ellipsoidone B. The fourth section describes the synthesis of (+)-erigeronic acid using lipase in significant transformation.

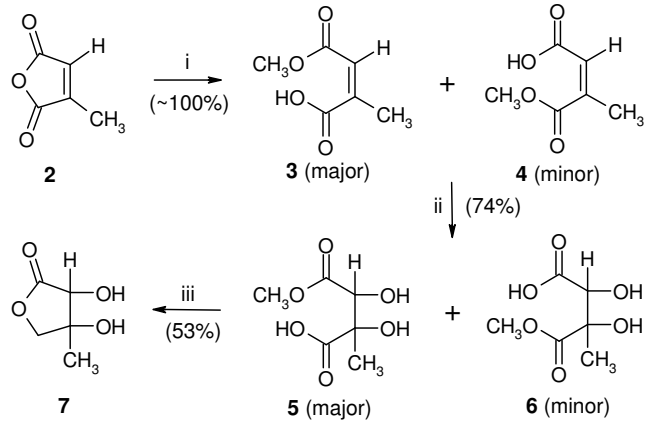
Section A: The Use of Lipases in Organic Synthesis

In recent years, enzymes have emerged as powerful tools in organic synthesis for bringing about kinetic resolution of racemates as they are extremely specific in their action and offer a high degree of chemo-, regio- and stereoselectivity, which is of huge importance in organic synthesis. Amongst all enzymes, lipases are the most popular given their tremendous versatility in applications. This section gives a brief introduction about enzymes in general and a concise account of the applications of lipases in synthetic organic chemistry followed by references.

Section B: An Efficient Amano PS-Catalyzed Chemo-, Regio- and Enantioselective Hydrolysis of (±)-2,3-Di-*O*-acetyl-2-*C*-methyl-D-erythrono-1,4-lactone: A Facile Preparation of Bioactive Natural Products (–)-Saccharinic Acid Lactone and Potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate

Most leguminosae plants close their leaves in the evening and open them in the morning. This circadian rhythmic movement of the leaves is called nyctinasty and has been controlled by their biological clocks. These leaf movements of the plants is dependent on

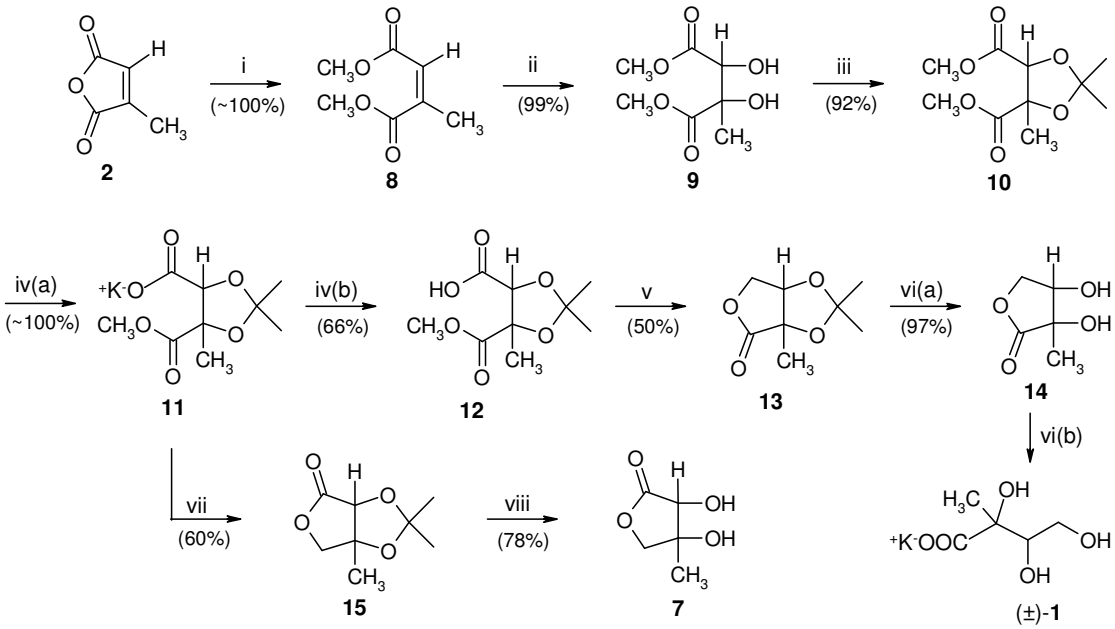
the interaction between leaf-opening and leaf-closing substances and are essential for the survival of legumes. Very recently, potassium 2*R*,3*R*,4-trihydroxy-2-methylbutanoate (**1a**) was isolated as a leaf-closing substance of *Leucaena leucocephalam*. The saccharinic acid lactone [(2*R*,3*R*)-2,3-dihydroxy-2-methyl-γ-butyrolactone] is a potential precursor of leaf-closing substance **1a** and it has also been isolated earlier as a natural product from *Astragalus lusitanicus* L. and *Cicer arietinum* L. In the recent years a number of natural products have been isolated which contain the saccharinic acid lactone [(–)-**14**] unit, such as 3-*O*-caffeoyl-2-*C*-methyl-D-erythrono-1,4-lactone [(–)-**24**], isolated from the leaves of *Bidens pilosa*. The natural lactone (–)-**14** was thought to be a plant growth regulator involved in feedback inhibition in biosynthesis of valine and three syntheses are reported for this lactone in the literature. This section reports a facile 6-step synthesis of leaf closing substance (±)-*erythro* potassium 2,3,4-trihydroxy-2-methyl-butanoate (**1**) starting from citraconic anhydride (**2**) with 29% overall yield. In this section we also describe our studies on enantioselective Amano PS-catalyzed hydrolysis of diacetyl lactone (±)-**16** to obtain the enantiomerically pure lactones (+)-**14** and (–)-**14** in 45% yield (99% ee) (2-steps) and 46% yield (99% ee) respectively followed by our studies on synthesis of natural products **1a** and (–)-**24** (Schemes 1-5).



Scheme 1. *Reagents, conditions and yields*: (i) CH_3OH, 0 ºC, 60 h (~100%, **3**:**4** = 86:14); (ii) OsO_4, NMO, *t*-BuOH, CH_3COCH_3, rt, 72 h (74%, **5**:**6** = 85:15), (two recrystalisations of **5** plus **6** mixture with ethyl acetate furnished pure **5** in 50% yield); (iii) $NaBH_4$, CH_3OH, reflux, 12 h, (53%).

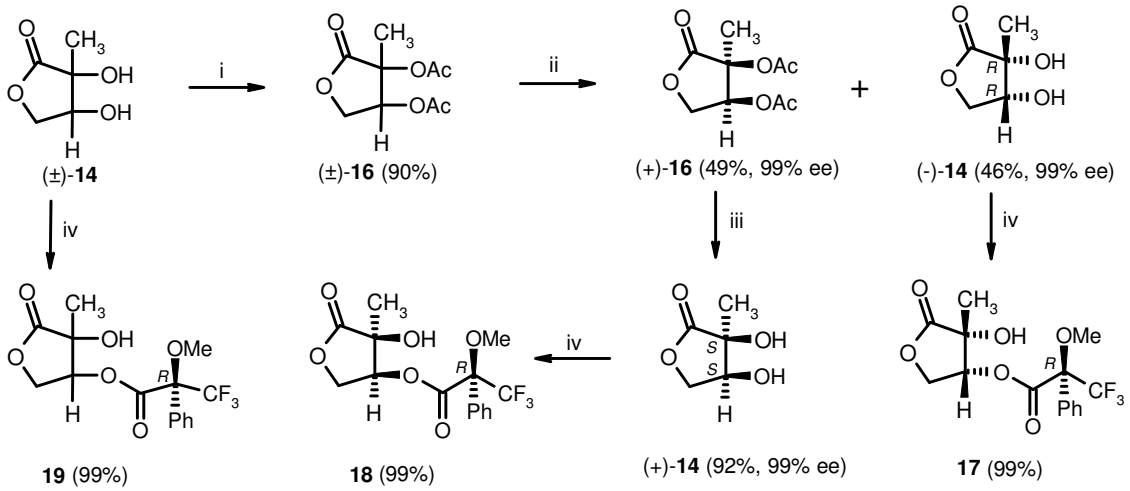
The reaction of citraconic anhydride (**2**) with methanol at 0 ^oC furnished the mixture of regioisomers of esters **3** and **4** in 86:14 ratio (Scheme 1) which on OsO_4-induced *cis*-dihydroxylation again furnished the mixture of diols **5** and **6** in 85:15 ratio in 74% overall yield in two steps. Two recrystalisations of mixture of diols **5** plus **6** with ethyl acetate

gave the pure diol **5** in 50% yield. Surprisingly, the $NaBH_4$-reduction of mixture of **5** plus **6** or pure **5** in methanol, exclusively furnished the undesired lactone **7** in 53% yield. Thus our first straightforward approach to obtain **1** met with failure and then we planned for the synthesis of **1** using a different synthetic route as depicted in scheme 2. The citraconic anhydride (**2**) on treatment with methanol and catalytic amount of conc. H_2SO_4 furnished the diester **8**, which on OsO_4-induced *cis*-dihydroxylation, followed by protection of



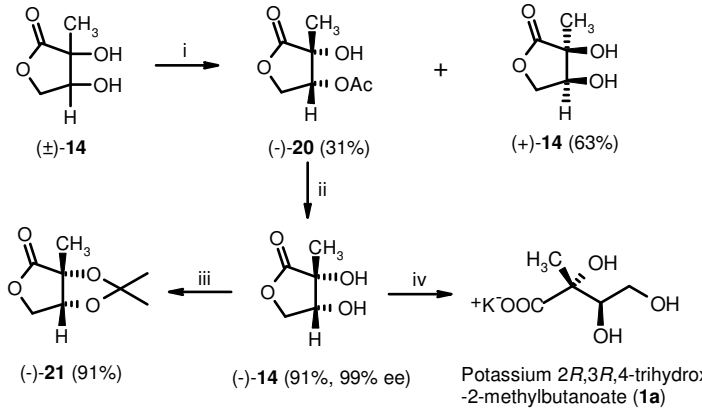
Scheme 2. *Reagents, conditions and yields:* (i) CH_3OH, H_2SO_4, reflux, 12 h (~100%); (ii) OsO_4, NMO, *t*-BuOH, CH_3COCH_3, rt, 60 h (99%); (iii) $(CH_3)_2C(OCH_3)_2$, *p*-TSA, benzene, reflux, 3 h (92%); (iv) (a) KOH, CH_3OH, rt, 2 h (~100%); (iv) (b) 2N HCl, (66%); (v) $BH_3(CH_3)_2S$, THF, -8 ^oC to rt, 36 h (50%); (vi) (a) CF_3COOH, H_2O, 0 ^oC to rt, 24 h (97%); (vi) (b) KOH, rt, 10 min.; (vii) (a) $LiBH_4$, THF, 0 ^oC to rt, 6 h; (b) dil. HCl (60%); (viii) CF_3COOH, THF, H_2O, 0 ^oC to rt, 3 h (78%).

cis-diol moiety as acetonide, regioselective hydrolysis of unhindered ester moiety, borane-dimethylsulfide complex induced chemoselective reduction of carboxylic group and acetonide deprotection gave lactone **14** in 29% yield over 6-steps. The lactone on treatment with aqueous KOH gave the desired leaf-closing compound (±)-**1** in quantitative yield. As expected the $LiBH_4$-reduction of compound **11** gave the undesired diol-protected lactone **15**, which on acetonide deprotection gave the undesired lactone **7** in 47% yield over 2-steps. The lactone (±)-**14** on acetylation gave diacetyl lactone (±)-**16** (Scheme 3), which on



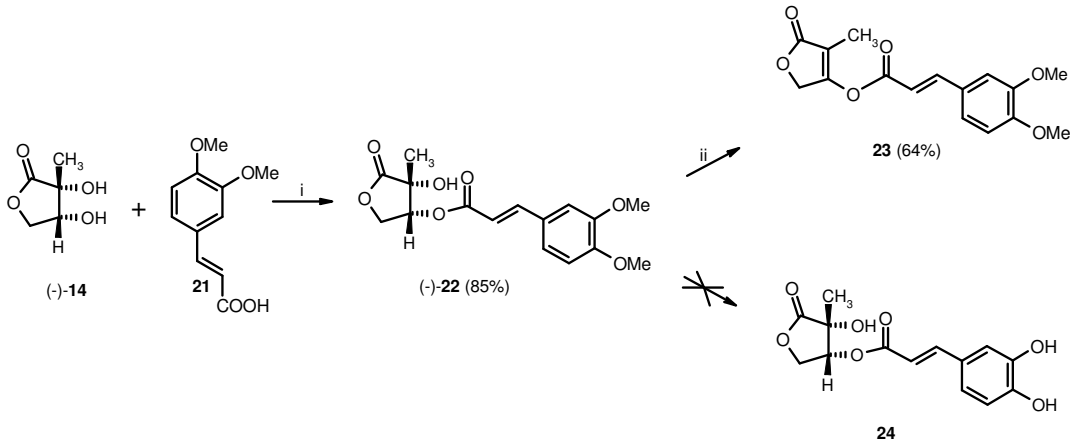
Scheme 3: *Reagents, conditions and yields*: (i) Ac_2O, pyridine, rt, 12 h (90%); (ii) Amano PS, petroleum ether/benzene (2:1), sodium phosphate buffer (0.1 M, pH 7.0), 45 ^oC, 36 h, (+)-**16** (49%) and (–)-**14** (46%); (iii) K_2CO_3, CH_3OH, 0 ^oC to rt, 3 h (92%); (iv) (*R*)-Mosher's acid, DCC, DMAP, CH_2Cl_2, 0 ^oC to rt, 8 h.

enzyme Amano PS-catalyzed biphasic hydrolysis at 45 ^oC directly furnished nearly 1:1 mixture of the dihydroxy lactone (–)-**14** and the unrecognized diacetyl lactone (+)-**16** in 36 hours reaction time in 86% yield over 2-steps. The diacetyl lactone (+)-**16** on base catalyzed methanolysis gave (+)-**14** in 92% yield. The ^1H NMR spectrum of Mosher's esters of lactones (±)-**14**, (+)-**14** and (–)-**14** revealed that both of the isomers (+)-**14** and (-)-**14** possess plus 99% ee. Next we performed the Amano PS-catalyzed regio- and enantioselective acylation of dihydroxy lactone (±)-**14** using vinyl acetate as an acyl donor at 45 °C and obtained the monoacetyl lactone (–)-**20** in 31% yield and the dihydroxy



Scheme 4: *Reagents, conditions and yields*: (i) Amano PS, vinyl acetate, *n*-hexane/benzene (2:1), 45 ^oC, 96 h, (+)-**14** (63%) and (–)-**20** (31%); (ii) K_2CO_3, CH_3OH, 0 ^oC to rt, 3 h (91%); (iii) $(CH_3)_2C(OCH_3)_2$, *p*-TSA, rt, 10 h, (91%); (iv) Aq. KOH (1 equiv.), rt, 10 min (~100%).

lactone (+)-**14** in 63% yield (Scheme 4). This monoacetyl lactone (–)-**20** on base catalyzed methanolysis furnished the dihydroxy lactone (–)-**14** (91% yield, 99% ee), which on treatment with aqueous KOH at room temperature gave the enantiomerically pure naturally



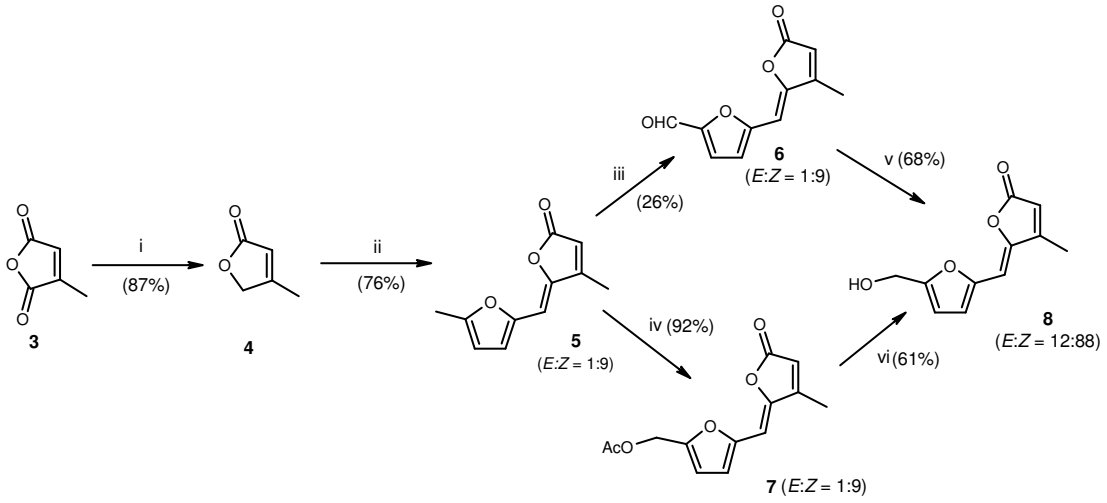
Scheme 5: *Reagents, conditions and yields*: (i) DCC, DMAP, CH_2Cl_2, rt, 10 h (85%); (ii) BBr_3, CH_2Cl_2, -78 ^oC, 0.5 h (64%).

occurring leaf-closing compound, the potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate (**1a)** in quantitative yield. We then planned to synthesize natural product (–)-**24** starting from lactone (–)-**14**. The lactone (–)-**14** on treatment with 3,4-dimethoxycinnamic acid (**21**) in the presence of DCC furnished the desired ester (–)-**22** in 85% yield (Scheme 5). Unfortunately, BBr_3-induced demethylation at –78 °C furnished the dehydrated product **23**.

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 Chemoenzymatic Approach to Natural Cytotoxic Ellipsoidone A and Natural Ellipsoidone B

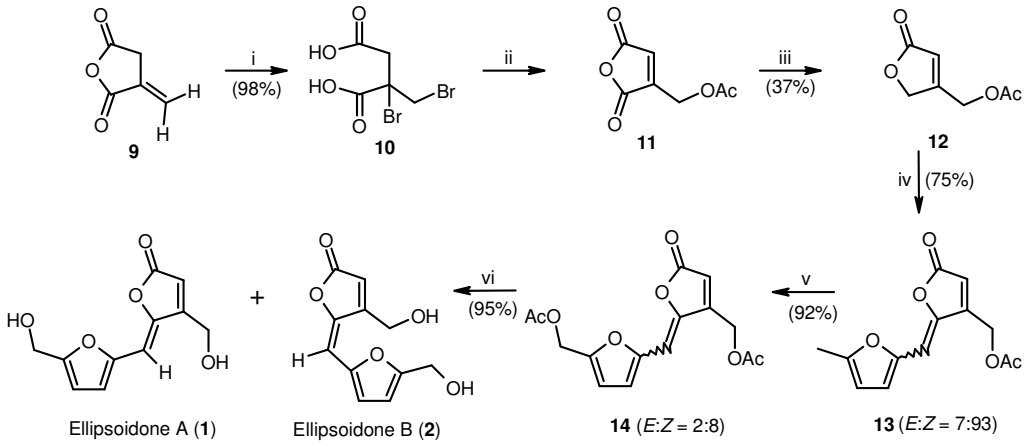
Ellipsoidones A (**1**) and B (**2**) were isolated from the tubers of *Hemsleya ellipsoidea.* These two new acetogenins **1** and **2** are geometric stereoisomers of each other and ellipsoidone A (**1**) possesses cytotoxic activity against P-388 cells [IC_{50} 47 mg/mL]. Synthesis of these two geometric isomers **1** and **2** with two hydroxymethyl moities is a challenging task as Nature derives them from the sugar, siphonodin 6-*O*-*β*-D-glycopyranoside. This section reports a facile 4-step synthesis of deoxyellipsoidone **8** with 37% overall yield (Scheme 1) and an elegant 6-step facile chemoenzymatic first synthesis



Scheme 1. *Reagents, conditions and yields*: (i) (a) $NaBH_4$, THF, 0 °C, 2 h, (b) H^+/HCl (87%); (ii) 5-Methylfurfural, piperidine, CH_3OH, rt, 15 h (76%); (iii) SeO_2, CH_3COOH, reflux, 2 h (26%); (iv) SeO_2, CH_3COOH (anhydrous), reflux, 1.5 h (92%); (v) (a) $NaBH_4$, C_2H_5OH, rt, 1 h, (b) H^+/HCl (68%); (vi) K_2CO_3, CH_3OH, 0 °C to rt, 2 h (61%).

of naturally occurring cytotoxic ellipsoidone A (**1**) and ellipsoidone B (**2**). We felt that the butenolide **5** would be a potential starting material for the synthesis of ellipsoidones A (**1**) and B (**2**) and selenium dioxide oxidation of both the allylic methyl groups in **5** would provide a simple and efficient access to these natural products. To prepare **5**, we performed the regioselective reduction of citraconic anhydride (**3**) with sodium borohydride and obtained butyrolactone **4,** which on piperidine catalyzed Knoevenagel condensation, with 5-methylfurfural gave the desired butenolide **5** in 66% overall yield in 2-steps (*E*:*Z* = 1:9). The SeO_2 oxidation of **5** in 98% acetic acid directly furnished the aldehyde **6**, but only in 26% yield, whereas the SeO_2 oxidation of **5** in a freshly dried anhydrous acetic acid gave the monoacetoxymethylbutenolide **7**, which on base catalyzed deacylation gave the deoxyellipsoidone **8** in 56% overall yield in 2-steps (*E*:*Z* = 12:88). The aldehyde **6** on $NaBH_4$ reduction also gave the deoxyellipsoidone **8** (*E*:*Z* = 12:88) in 61% yield. All our attempts to oxidize the allylic methyl group of the lactone moiety in **5** met with failure. Therefore we altered our strategy and decided to start the synthesis of **1** and **2** from acetoxymethylbutenolide **12**.

We envisaged the preparation of acetoxymethyllactone **12** from itaconic anhydride (**9**). The bromination of itaconic anhydride (**9**) furnished the dibromodiacid **10,** which on



Scheme 2. *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%, **1**:**2** = 86:14).

treatment with Ac_2O/NaOAc followed by regioselective reduction of the obtained acetoxymethylmaleic anhydride (**11**) gave lactone **12** in 36% overall yield in 3-steps (Scheme 2). The Knoevenagel condensation of lactone **12** with 5-methylfurfural followed by SeO_2 oxidation gave diacetoxymethylbutenolide **14** (*E*:*Z* = 1:4) in 69% overall yield in 2-steps. The deacylation of **14** under both acidic and basic condition gave a complex mixture of products. Finally, we carried out the Amano PS catalyzed double deacylation of **14** at pH 7 and obtained the mixture of desired products **1** and **2** (**1**:**2** = 86:14) in 95% yield which were separated by HPLC to obtained pure **1** and **2** with quantitative recovery.

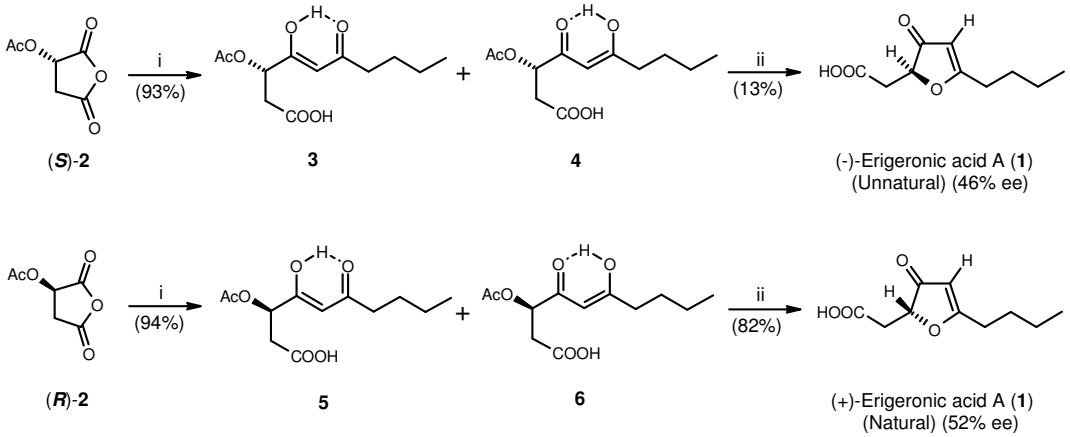
This section also provides the detailed experimental procedures, tabulated analytical and spectral data along with some selected spectra followed by references.

<u>Section D</u>: An Elegant Two-step Chemoenzymatic Access to Natural Germination Inhibitor (+)-Erigeronic Acid

Plants are known to produce secondary metabolites which affect the germination and growth of other plants. 5-Butyl-3-oxo-2, 3-dihydrofuran-2-yl-acetic acid [Erigeronic acid A, **1**] was isolated from the flowers of *Erigeron annuus* and it possesses strong lettuce seed germination inhibitory activity [IC_{50} (mM) 2.13]. The structure of acid **1** was unambiguously deduced by analysis of 2D NMR spectroscopic data (COSY, HMQC and HMBC) but the configuration at the C-2 centre was not determined. This section reports a facile 2-step synthesis of natural germination inhibitor (+)-Erigeronic acid A (**1**), which

can be a agriculturally useful product. We envisaged (*S*)-acetoxysuccinic anhydride (**2**) as a potential starting material for the stepwise construction of natural product **1**.

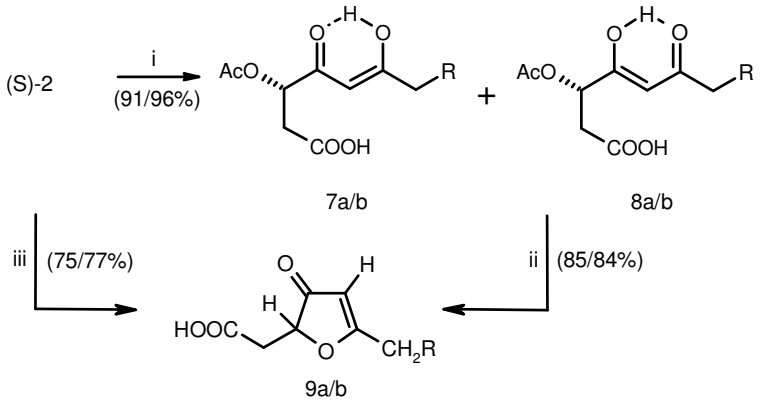
The highly regioselective ring opening of (*S*)-acetoxysuccinic anhydride with the primary enolate of butyl methyl ketone using LDA as a base exclusively provided the intermediate diketo compound in 93% yield which was transformed in situ to a mixture



Scheme 1. *Reagents, conditions and yields:* (i) (a) $CH_3COCH_2(CH_2)_2CH_3$, LDA, THF, –78 °C, 90 min, (b) H^+/HCl (3:4/5:6 = 8:2); (ii) Amano PS, pet. ether/benzene (2:1), rt, 40 h, phosphate buffer pH 7.0.

of enantiomerically pure enols **3** and **4** in the ratio 80:20 (Scheme 1). Under both basic and acid catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture furnished erigeronic acid and its ester respectively, via the intramolecular dehydrative cyclization pathway, but in a racemic form. Hence we planned for an enzymatic hydrolysis of **3** plus **4** mixture under neutral conditions at pH 7. The Amano PS catalyzed hydrolysis of **3** plus **4** mixture was very slow and gave the unnatural (–)-erigeronic acid only in 13% yield (46% ee). With the hope that the enzyme Amano PS will better recognize opposite isomer, we similarly obtained the mixture of **5** plus **6** from the corresponding (*R*)-acetoxysuccinic anhydride, which on Amano PS catalyzed hydrolysis at pH 7 furnished the desired natural (+)-erigeronic acid A in 77% overall yield in 2-steps (52% ee). Using the present chiral pool and chemoenzymatic strategy we could assign the (*R*)-configuration to C-2 chiral centre in the natural acid. The present approach to 5-alkyl-3-oxo-dihydrofuranyl-2-acetic acids is general in nature and starting from **2** and ethyl methyl ketone/heptyl methyl ketone, we could synthesize **9a/b** in very good yields both in one pot and a stepwise fashion (Scheme 2). In the one pot synthesis, we quenched the anhydride **2** and ketone condensation

reactions with 10% aqueous lithium hydroxide and then acidified the reaction mixture with hydrochloric acid to obtain **9a/b** in 75-77% yield.



Scheme 2. *Reagents, conditions and yields*: (i) (a) $CH_3COCH_2CH_3/CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, –78 °C, 90 min, (b) H^+/HCl (**a**: 91%, **b**: 96%; **7a/b**:**8a/b** = 8:2); (ii) (a) K_2CO_3, MeOH, 6 h, (b) H^+/HCl(**a**: 85%, **b**: 84%); (iii) (a) $CH_3COCH_2CH_3/CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, –78 °C, 90 min, (b) 10% aq. LiOH, rt, 8 h, (c) H^+/HCl (**a**: 75%, **b**: 77%).

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 Recently Isolated Bioactive γ-Butyrolactone Containing Natural Products

This chapter features the following topics:

1.1 Introduction

A lactone is a cyclic ester formed by the intramolecular condensation of an alcoholic group with a carboxylic acid group. γ-Butyrolactones are those cyclic esters, which are hydrolyzed under basic conditions, for example in a sodium hydroxide solution into sodium γ-hydroxybutyrate, the sodium salt of γ-hydroxybutyric acid. γ-Butyrolactone can be synthesized from γ-hydroxybutyric acid by removal of water. It may also be obtained via oxidation of THF. One such process, which affords γ-butyrolactones in yields of up to 80%, utilizes bromine generated in situ from an aqueous solution of sodium bromate and potassium hydrogen sulfate.[1] γ-Butyrolactones are a very common structural element in organic compounds, present in about 10% of all natural products.[2] A wide variety of naturally occurring mono-, di- and tri-substituted monocyclic γ-butyrolactones are known. They are also found as a part of more complex frameworks, especially in bicyclic and tricyclic ring systems. They display a broad biological profile including strong antibiotic, anti-helmitic, anti-fungal, anti-tumor, anti-viral, anti-inflammatory and cytostatic properties, which makes them interesting lead structures for new drugs. The lactone unit itself represents a reactive functionality, being a possible target for nucleophilic and electrophilic centers of biomolecules. In many cases, an α-methylene group in the lactone ring, being potentially able to bind the nucleophilic sites of biomolecules by conjugate addition, manifests their biological activity. Although such Michael acceptors are generally avoided as a structural element in a potential drug because of the toxicity caused by unspecific binding, it does offer the possibility of generating adducts that can act as a prodrug with improved pharmacological properties. For example, the dimethylamino adduct of arglabin, currently in clinical phase I trials because of its promising activity against various cancer types, shows improved water solubility compared with the natural product itself, and can therefore be applied as an oral drug.[3]

Enantiomerically pure γ-butyrolactones have attracted much attention owing to their presence in a large variety of biologically active compounds and their use as important intermediates for fine chemicals and pharmaceuticals.[4] For instance, they have been reported as building blocks for the synthesis of many natural products such as alkaloids,[5] antibiotics,[6] pheromones[7] and flavor components.[8]

There are several reports on the synthesis of, especially, monocyclic γ-butyrolactones, but only relatively few general synthetic strategies are known that readily allow the

stereocontrolled synthesis of monocyclic as well as polycyclic frameworks in a structurally diverse way. Most of these approaches are target driven, aiming at a particular class of *γ*-butyrolactone natural products and therefore generally enabling access to only one framework with a *γ*-butyrolactone unit at a time. The great structural variety, especially of polycyclic *γ*-butyrolactone frameworks, found in nature makes them attractive scaffolds for combinatorial synthesis. However, only in recent years, mainly through the developments in transition metal catalysis, have developed syntheses of broadly functionalized as well as stereochemically diverse *γ*-butyrolactones.

This chapter portrays a short overview on isolation, bioactivity and synthesis of recently isolated important bioactive *γ*-butyrolactones and *γ*-alkylidenebutenolides containing natural products with an emphasis on new general synthetic routes and strategies. A concise account of butyrolactones is presented here and in view of large amount of literature on chemistry of *γ*-butyrolactones, no pretension of completeness is claimed. In order to simplify and understand the chemistry of *γ*-butyrolactons, they have been divided according to their structures. Each group contains information about the natural products in tabular form (Table 1-5), which shows the natural product's structure, name, bioactivity, name of the species from which it was isolated, references pertaining to its isolation and synthesis. The tables are followed by general synthetic strategies for *γ*-butyrolactones and the synthesis of *γ*-alkylidenebutenolides using different substrates and catalysts. In the last part of this chapter summary and references have been listed.

1.2 Monocyclic γ-butyrolactones

Some representative examples of mono-, di- and tri-substituted monocyclic γ-butyrolactones are shown in Table 1-3 with structure, name, source, activity and references pertaining to their isolation and synthesis.

Table 1: Mono-substituted monocyclic γ-butyrolactones

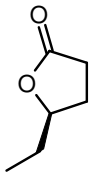
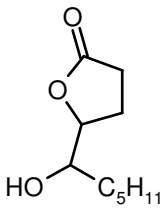
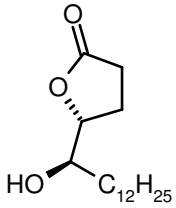
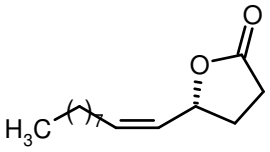
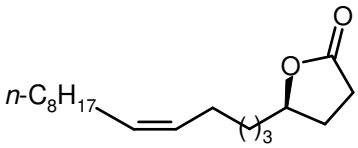
No.	Mono-substituted γ-butyrolactones	Source	Activity	Ref.
1	 (+)-4-Hexanolide	*Trogoderma glabrum*	Not known	9, 10
2	 L-Factor	*Streptomyces griseus*	Not known	11, 12
3	 (-)-Muricatacin	*Annona muricata* L.	Anti-tumor	13, 14
4	 Japonilur	*Popillia japonica*	Sex pheromone	15, 16
5	 (4*R*,9*Z*)-9-Octadecane-4-olide	*Janus integer*	Sex pheromone	16,17

Table 2: Di-substituted monocyclic γ-butyrolactones

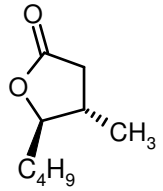
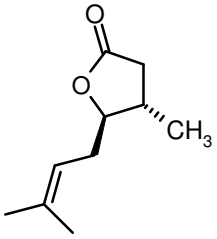
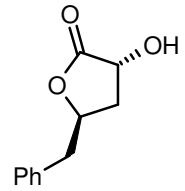
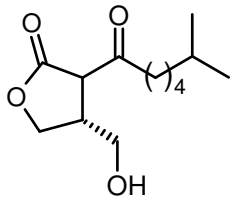
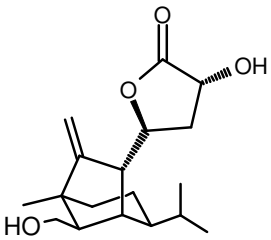
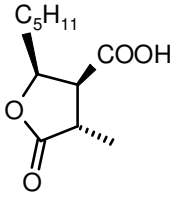
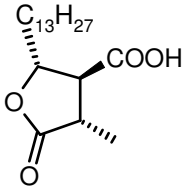
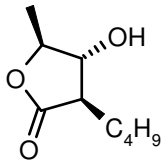
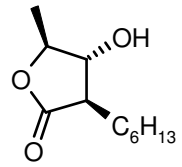
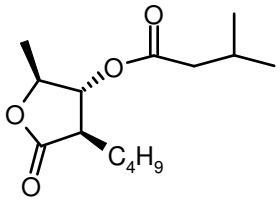
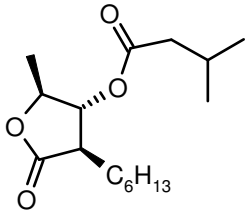
No.	Di-substituted γ-butyrolactones	Source	Activity	Ref.
1	 (+)-Whisky lactone	*Quercus mongolica*	Flavoring agent	18, 19
2	 (+)-Eldanolide	*Eldana sacharina*	Pheromone (Sex attractant)	20, 21
3	 (+)-Harzialactone A	*Trichoderma harianium* OUPS-N115	Anti-tumor	22, 23
4	 A-Factor	*Streptomyces griseus*	Regulatory factor that induces antibiotic production	24, 25
5	 (+)-Sorokinianin	*Bipolaris sorokiniana* OB-25-1	Germination inhibitor	26, 27

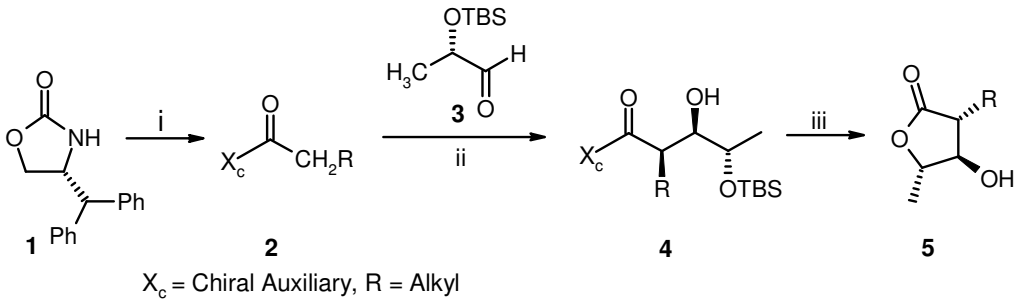
Table 3: Tri-substituted monocyclic *γ*-butyrolactones

No.	Tri-substituted *γ*-butyrolactones	Source	Activity	Ref.
1	 (+)-Phaseolinic acid	*Macrophomzna phaseolzna*	Antibiotic and Anti-tumor	28, 29
2	 (+)-Roccellaric acid	*Roceellaria mollis*	Antibiotic and Anti-tumor	30, 31
3	 (+)-Blastmycinolactol	*Streptomyces* (Degraded product of antimycin A[9])	Not known	32, 33
4	 NFX-2	*Streptomyces* (Degraded product of antimycin A)	Not known	33, 34
5	 (+)-Blastmycinone	*Streptomyces* (Degraded product of antimycin A)	Not known	33, 35
6	 (+)-Antimycinone	*Streptomyces* (Degraded product of antimycin A)	Antibiotic	33, 36

1.2.1 General synthetic approaches to monocyclic *γ*-butyrolactones

A facile and stereocontrolled construction of functionalized *γ*-butyrolactone skeletons has attracted considerable attention. Consequently, number of stereoselective syntheses have been developed leading to a variety of *γ*-butyrolactone in racemic or in enantiopure form, using starting materials from the chiral pool, chiral auxiliaries or applying catalytic asymmetric methodology. Moreover, number of strategies leading to *γ*-butyrolactone in a non-stereoselective way have also been reported.

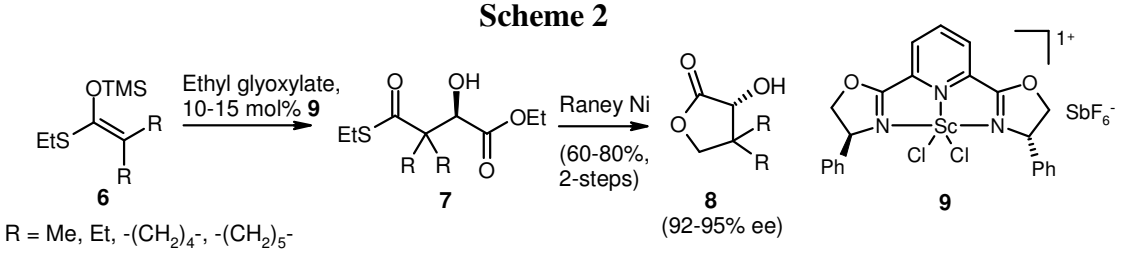
The Aldol reaction was used by Sibi and co-workers[33b] for the preparation of biologically active *γ*-butyrolactone containing natural products. The generality of the method allows for the preparation of a variety of *γ*-butyrolactone containing natural products such as blastmycinolactol,[33] NFX-2, NFX-4,[34] blastmycinone,[35] antimycinone[36] and their analogs by a simple change in the starting materials. They started with the attachment of the required side chain to (*R*)-4-(diphenylmethyl)-2-oxazolidinone (**1**) by treatment with *n*-BuLi and appropriate acid chlorides (Scheme 1). Treatment of the acyloxazolidinone **2** with freshly prepared dibutylboron triflate followed by Et_3N and lactaldehyde **3** furnished *syn* products **4**, which on hydroxy deprotection gave directly *γ*-butyrolactones **5**.



Scheme 1. *Reagents, conditions and yields*: (i) *n*-BuLi, -78 °C, 10 min., RCH_2COCl, 15 min. (95-98%); (ii) (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) **3**, -78 °C to 0 °C, 24 h; (iii) AcOH/THF/H_2O (3:1:1), 60-65 °C, 48 h (81-89%, 2-steps).

The asymmetric synthesis of pantolactone[37] and its derivatives continue to be of interest to organic chemists as a consequence of their biological activity and utility as a secondary alcohol derived chiral auxiliary. Evans *et al*[38] reported an efficient enantioselective synthesis of *β,β*-dialkyl-*γ*-substituted pantolactones, utilizing the [Sc{(*S,S*)-R-pybox}]$(Cl)_2^+SbF_6^-$ complex (**9**, where R = Ph) catalyzed aldol reaction of enolsilane **6** nucleophiles with ethyl glyoxylate as the key step to give **7** (Scheme 2). Raney nickel reduction of thioester **7** afforded pantolactones **8**.

Scheme 2



6 R = Me, Et, -$(CH_2)_4$-, -$(CH_2)_5$-

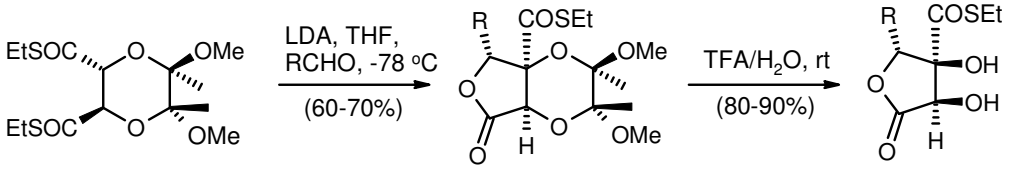
7

8 (92-95% ee)

9

Maycock and co-workers[39] reported a simple procedure for the synthesis of highly substituted γ-butyrolactones based on aldol reactions between the enolate of dioxanes derived from tartaric acid and aldehydes. Dioxane **10**[40] derived from tartaric acid was treated with 2.2 equiv. of LDA (Scheme 3). Quenching with various aldehydes, formed exclusively one of the possible diastereomeric lactones **11**, which on removal of the dioxane acetal gave diol lactones **12** in good yields (80-90%).

Scheme 3



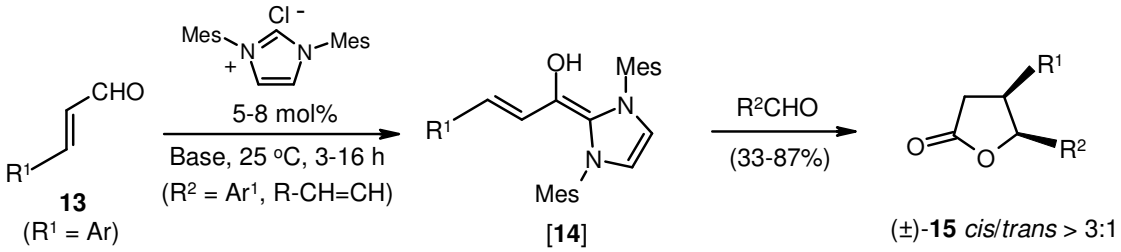
10

11 R = Alkyl, aryl

12 R = Alkyl, aryl

With the advent of nucleophilic carbenes as organocatalysts, the generation of homoenolates **14** from α,β-unsaturated aldehydes **13** and their subsequent reaction with aldehydes was recently realized in racemic form by Glorious and co-workers[41] with moderate diastereocontrol to yield predominantly 4,5-*cis* disubstituted lactones (±)-**15** (Scheme 4).

Scheme 4



13 (R^1 = Ar)

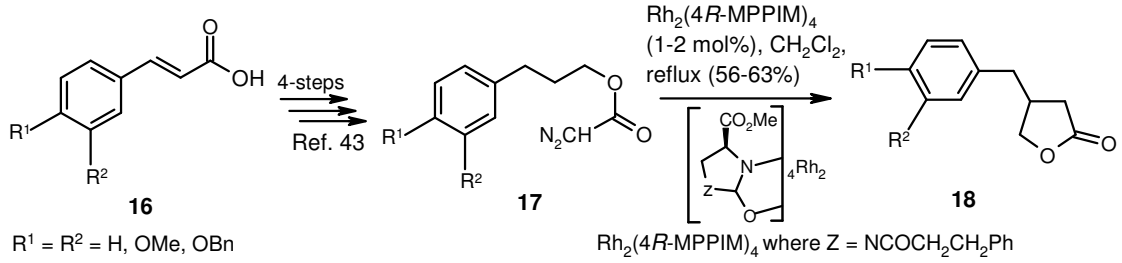
[**14**]

(±)-**15** *cis*/*trans* > 3:1

Catalytic C,H-insertions[42] are rapidly growing into a reliable synthetic tool for organic synthesis. In particular, rhodium-catalyzed decomposition of diazo acetates **17** reported by Doyle and co-workers[43] offers a facile entry to γ-butyrolactones because intramolecular C,H-insertion readily occurs with a strong preference for five-membered ring closure. This

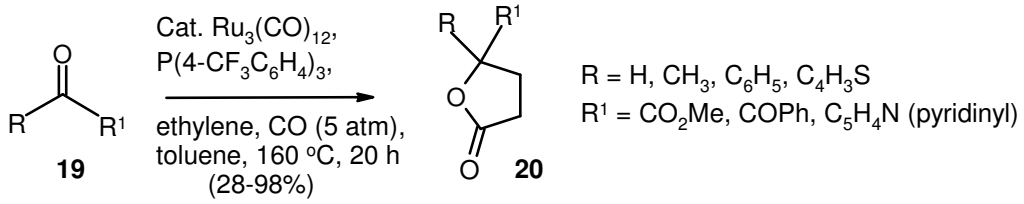
methodology has been applied for the total synthesis of dibenzylbutyrolactone lignans[44,45] (+)- and (–)-enterolactone, (+)- and (–)-hinokinin, (+)-arctigenin and aryltetralin lignan (+)-isodeoxypodophyllotoxin.[44,45] The diazoacetates **17** were synthesized from the corresponding cinnamic acids **16**.[43] These diazoacetates **17** on refluxing in CH_2Cl_2 with the catalyst $Rh_2(4R\text{-MPPIM})_4$ furnished the lactones **18** with high ee (91-96.5%) (Scheme 5).

Scheme 5



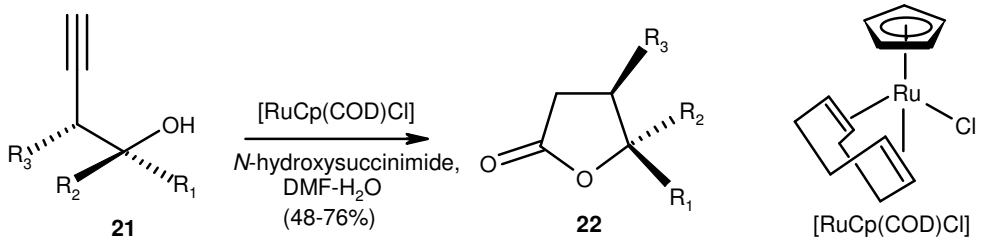
Murai and coworkers[46] reported the first example of the catalytic intermolecular [2+2+1] cyclocoupling of ketones (or aldehydes), olefins and CO leading to functionalized 5,5′-disubstituted γ-butyrolactones in presence of $Ru_3(CO)_{12}$ as a catalyst (Scheme 6). A variety of ketones containing a carbonyl group at the α-position were examined.

Scheme 6

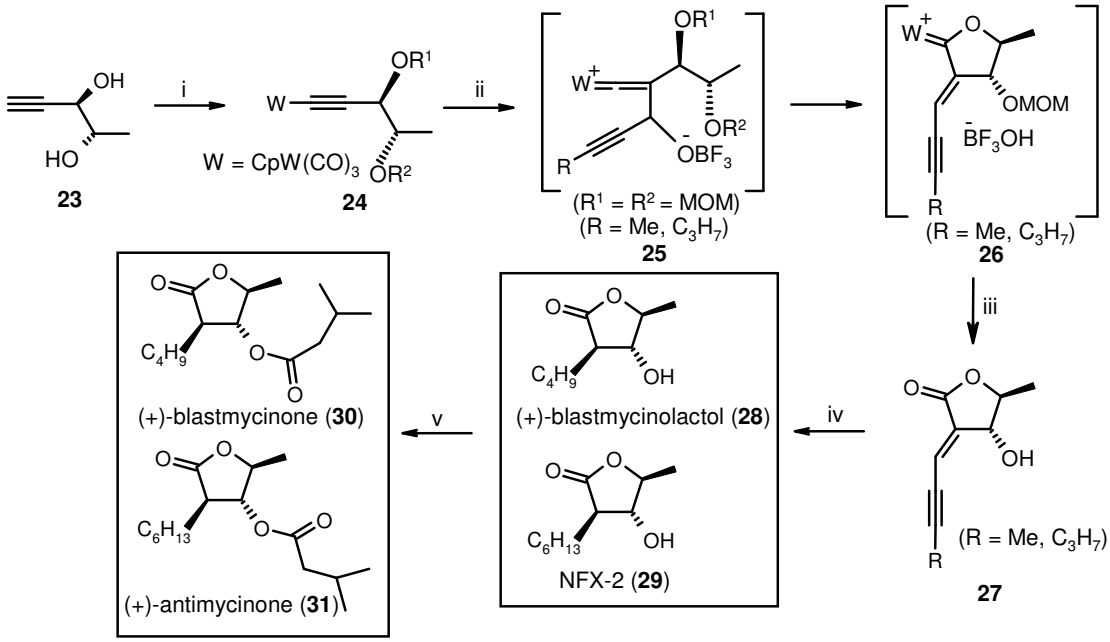


Transition metal catalyzed ring closing strategies have been widely developed for the synthesis of γ-butyrolactones. Trost *et al*[47] demonstrated that homopropargyl alcohols **21** could be directly converted to γ-butyrolactones by a ruthenium-catalyzed cycloisomerization-oxidation sequence (Scheme 7). Because **21** is readily available (e.g. by epoxide opening with lithium acetylide or addition of alkyne magnesiumbromide to ketones or aldehydes), a broad variety of γ-butyrolactones are accessible by this route. Besides alkyl or aryl substituted derivatives **22**, also polycyclic derivatives with various annulation patterns can be obtained, thereby greatly expanding the diversity of the structures available.

Scheme 7



Another strategy which is related to this strategy is the oxidative cyclization of alkyl tungsten complexes, reported by Liu and co-workers.[33a] The key step in this approach involves the cycloalkenation of hydroxyl protected tungsten-η^1-(3*R*,4*S*)-pent-1-yne-3,4-diol **24** with aldehydes to give tungstenoxacarbenium salts **26**, further leading to 3-

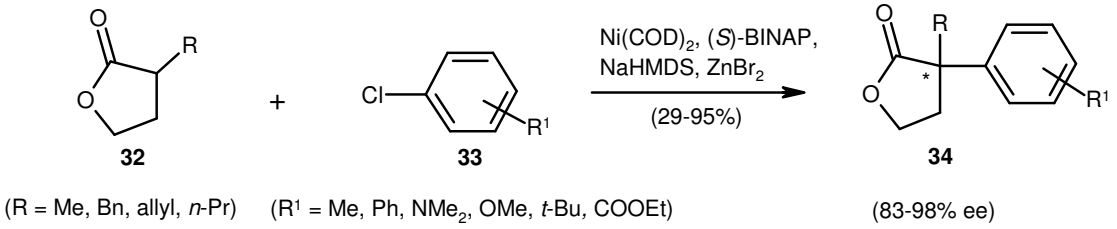


Scheme 8. *Reagents, conditions and yields*: (i) $CpW(CO)_3Cl$, Et_2NH, CuI, 4 h then MOMCl, 3 h (64%); (ii) (a) $BF_3.Et_2O$, alkynyl aldehydes (R = Me, C_3H_7); (iii) (a) Me_3NO, CH_2Cl_2, rt, 0.5 h (55% when R = Me, 57% when R = C_3H_4, two-steps), (b) HCl/MeOH, 60 ^oC, 0.5 h (90-91%); (iv) H_2/Pd, MeOH, rt, 24 h (**28** = 95%, **29** = 96%); (v) Valeryl chloride, DMAP, CH_2Cl_2, rt, 24 h (**30** = 88%, **31** = 86%).

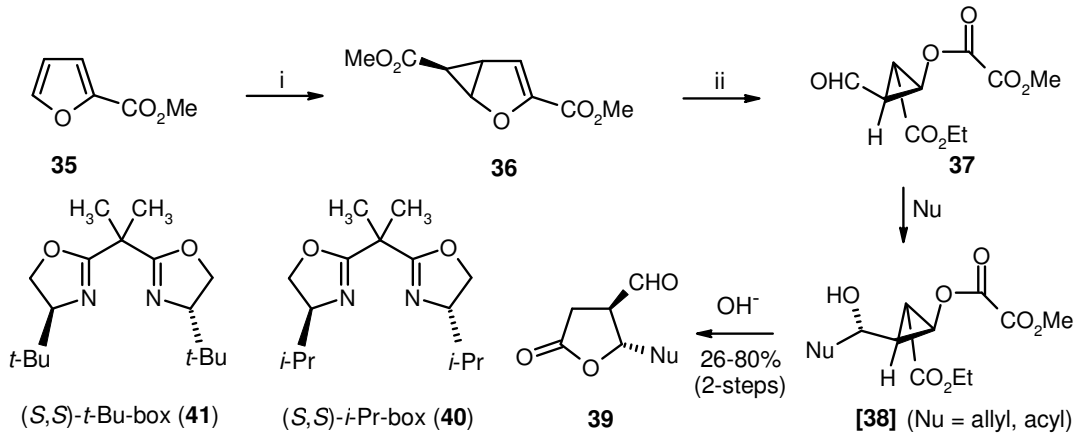
alkylidene-4-hydroxy-5-methyl-γ-lactones **27** upon demetalation (Scheme 8). The resulting γ-butyrolactone products were transformed into natural trisubstituted butyrolactones including (+)-blastmycinolactol (**28**), NFX-2 (**29**), (+)-blastmycinone (**30**), and (+)-antimycinone (**31**). This synthetic approach was also applicable for the synthesis of natural α-alkylidene-γ-butyrolactone such as (+)-isodihydromahubanolide A.[48]

The functionalization of γ-butyrolactones at the α-position to the carbonyl group is easily accessible via conventional enolate chemistry, and even enantioselective methods for building up a quaterny stereo center at this position have been recently reported by Buchwald and co-workers.[49] They used a Ni(0)-BINAP catalytic system for the highly enantioselective α-arylation of α-substituted γ-butyrolactones **32** with aryl chlorides and bromides **33** in presence of a base (Scheme 9).

Scheme 9



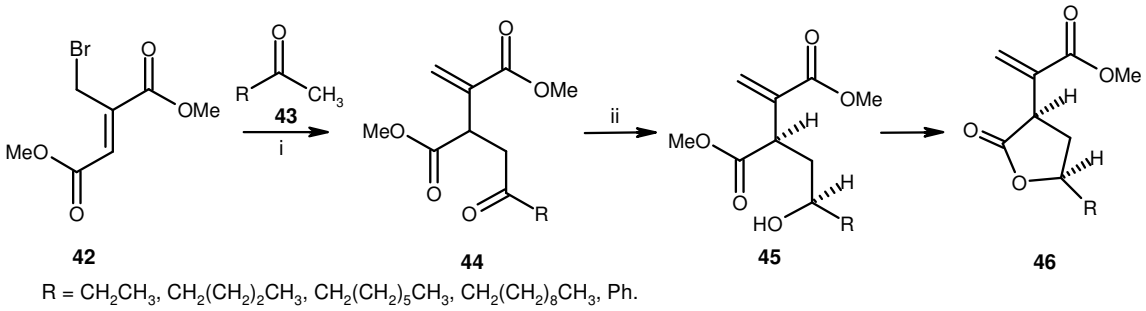
Reiser and co-workers[50] developed a general route to disubstituted γ-butyrolactones **39** (Nu = allyl, acyl) starting with the asymmetric copper (I)-catalyzed cyclopropanation of **35** with (*S*,*S*)-*i*-Pr-box (**40**) or (*S*,*S*)-*t*-Bu-box (**41**) as chiral ligands (Scheme 10). Starting from methyl 2-furoate (**35**) they synthesized trisubstituted cyclopropane **36** using



Scheme 10. *Reagents, conditions and yields*: (i) Ethyl diazoacetate, $Cu(OTf)_2$, (*S*,*S*)-*i*-Pr-box, $PhNHNH_2$, CH_2Cl_2 (38%); (ii) (a) O_3, CH_2Cl_2, -78 ^oC, (b) DMS (94%).

the catalyst **40**. Ozonolysis of **36** followed by reductive work up gave aldehyde **37**, which underwent highly diastereoselective additions with nucleophiles to **38** followed by a retroaldol/lactonization cascade furnished γ-butyrolactones **39**.

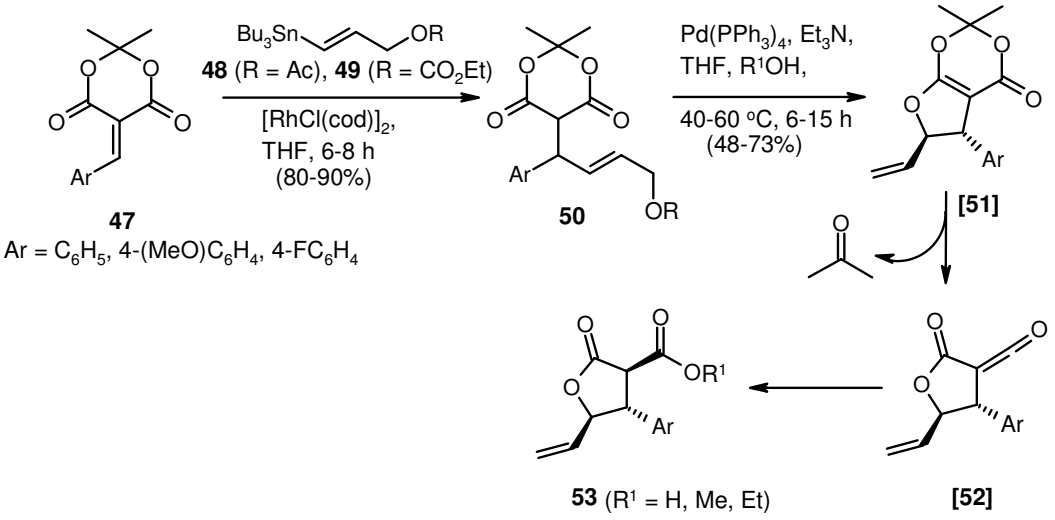
Recently, a method has been developed in our group[51] by using S_N2'-coupling reactions of alkyl methyl ketones **43** with dimethyl bromomethylfumarate (**42**) followed by a reductive regioselective cyclization, which afforded chemo-, regio- and diastereoselectively *cis*-3,5-disubstituted *γ*-butyrolactones **46** (Scheme 11).



Scheme 11. *Reagents, conditions and yields*: (i) LDA, THF, –78 ºC, 20 min (70-85%); (ii) $NaBH_4$, MeOH, rt, 15 min. (80-90%).

Very recently, Fillon *et al*[52] reported addition of (*E*/*Z*)-3-(tributylstannyl)allyl acetate (**48**) and ethyl carbonate (**49**) under mild reaction conditions to 5-(arylmethylene) Meldrum's acids (**47**) in presence of Rh (I) catalyst followed by Pd-catalyzed transformation of the resulting Meldrum's acids **50** in presence of alcohol directly gave polysubstituted *γ*-butyrolactones **53** (Scheme 12).

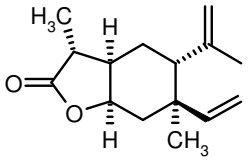
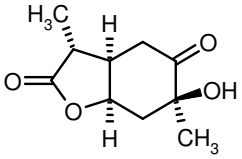
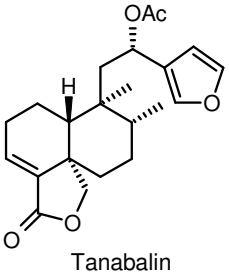
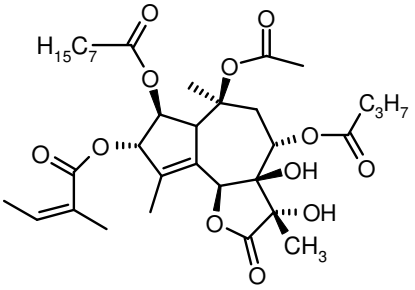
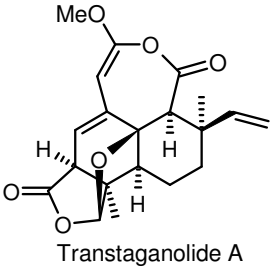
Scheme 12



1.3 Bi- and polycyclic *γ*-butyrolactones

Some representative examples of bi- and polycyclic *γ*-butyrolactones are shown in Table 4 with structure, name, source, activity and references pertaining to their isolation and synthesis.

Table 4: Bi- and polycyclic *γ*-butyrolactones

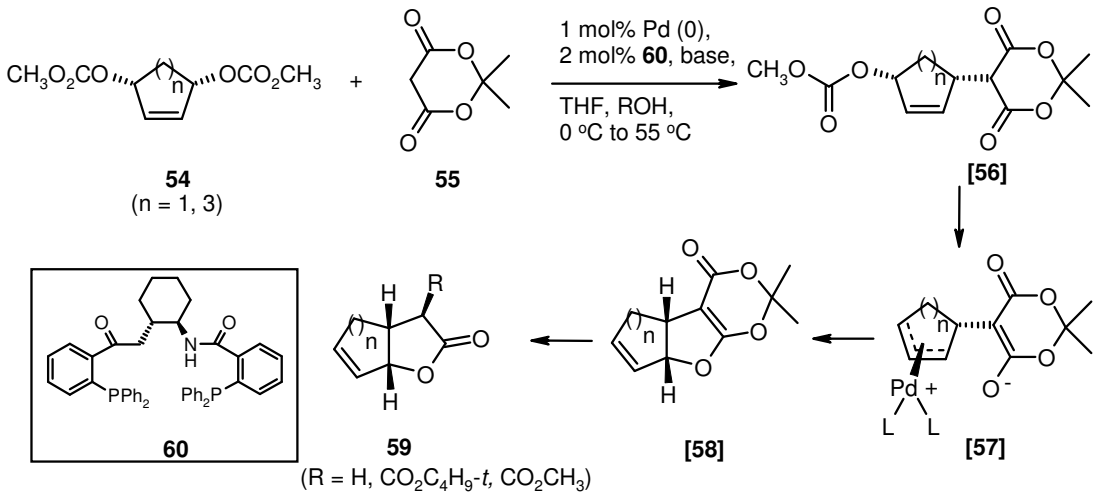
No.	Bi- and polycyclic *γ*-butyrolactones	Source	Activity	Ref.
1	 Callitrin	*Cupressaceae*	Anti-inflammatory	53
2	 Paeonilactone A	*Paeoniae Radix*	Not known	54, 55
3	 Tanabalin	*Tanacetum balsamita*	Insect antifeedant	56, 57
4	 Thapsigargin (TG)	*Thapsia garganica* L.	Microsomal SERCA-ATPase inhibitor	58, 59
5	 Transtaganolide A	*Thapsia garganica* L.	Not known	60, 61

1.3.1 General synthetic approaches to bi- and polycyclic *γ*-butyrolactones

Despite several reports on the synthesis of monocyclic *γ*-butyrolactones, there are few general synthetic strategies known, which readily allow the stereocontrolled synthesis of polycyclic frameworks containing *γ*-butyrolactones.

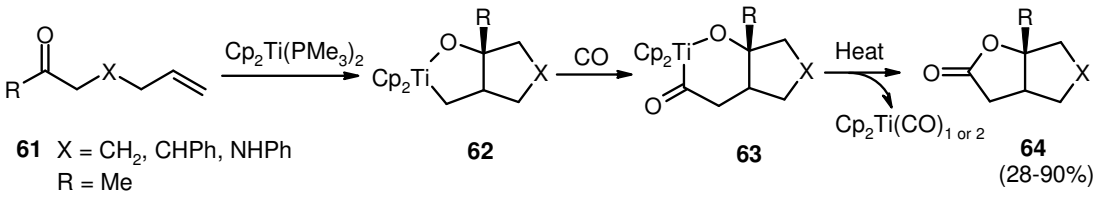
Lactone annulations are usually multi-step processes. Trost and co-workers[62] developed one pot Pd catalyzed asymmetric lactone annulation reaction in which they treated dicarbonates **54** with Meldrum's acid (**55**) (as the pronucleophile) in presence of $[\eta^3\text{-}C_3H_5PdCl]_2$, phosphine catalyst **60**, base and alcohol in THF at 0 ^oC followed by heating afforded γ-butyrolactones **59** (Scheme 13).

Scheme 13



α,ω-Enones such as **61** being readily available with good diversity by several methods, can undergo by concurrent carbonylation a [2+2+1]-cycloaddition to yield polycyclic γ-butyrolactones. Buchwald and co-workers[63] reported a heteroatom variant of the intramolecular Pauson-Khand reaction[64] mediated by $Cp_2Ti(PMe_3)_2$ in which either the alkyne or the alkene can be replaced by a carbonyl, which results in the diastereoselective formation of γ-butyrolactones.

Scheme 14

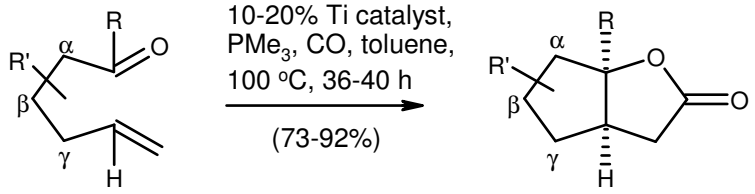


In this reaction, first $Cp_2Ti(PMe_3)_2$ reacts with enones to form bicyclic oxametallacycles[65] **62**, which on CO insertion into the Ti-C bond followed by thermolysis of the resulting metallacycle **63** gave γ-butyrolactones **64** (Scheme 14).

Crowe and co-workers[66] have reported a general catalytic cyclocarbonylation of enals and enones using a chiral titanocene {ansa-metallocene $(EBTHI)Ti(CO)_2$}[67] catalyst that also affords the asymmetric version of this reaction. The catalyst system worked well both

for enal and enone substrates forming fused γ-butyrolactones **66** in very good to excellent yield (Scheme 15).

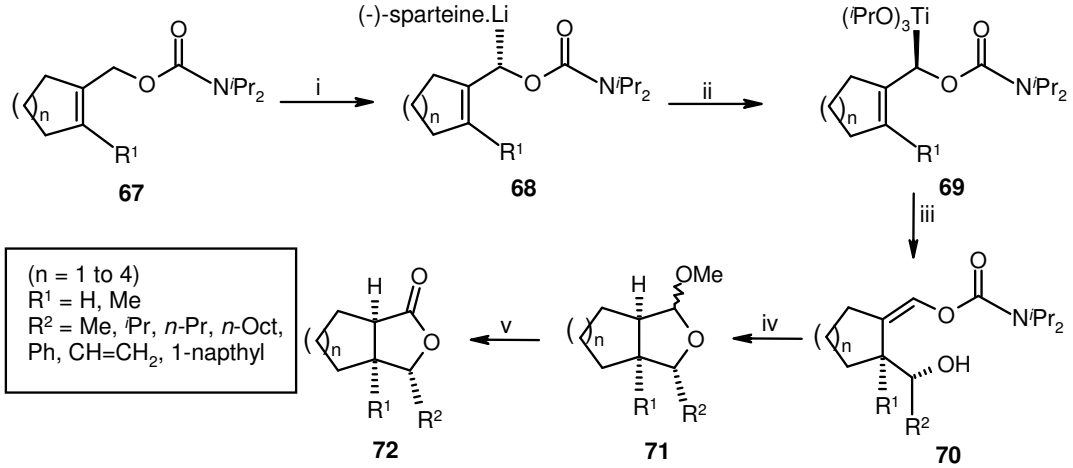
Scheme 15



65 **66**

(R = H, Me, Ph) (R^1 = β-Me, α-Me, β-Ph)

Hoppe and co-workers[68] utilized homoaldol reaction to synthesize γ-butyrolactones. Stereoselective addition of aldehydes to metallated 1-(-1-cycloalkenyl)methyl-*N*,*N*-diisopropylcarbamates **69** gave cyclic homoaldol adducts **70**. By applying the (-)-sparteine method,[69] enantiomerically enriched products **70** were obtained, which on oxidative cyclization gave diastereomerically pure γ-butyrolactones **72** via the γ-lactol ether **71** (Scheme 16).



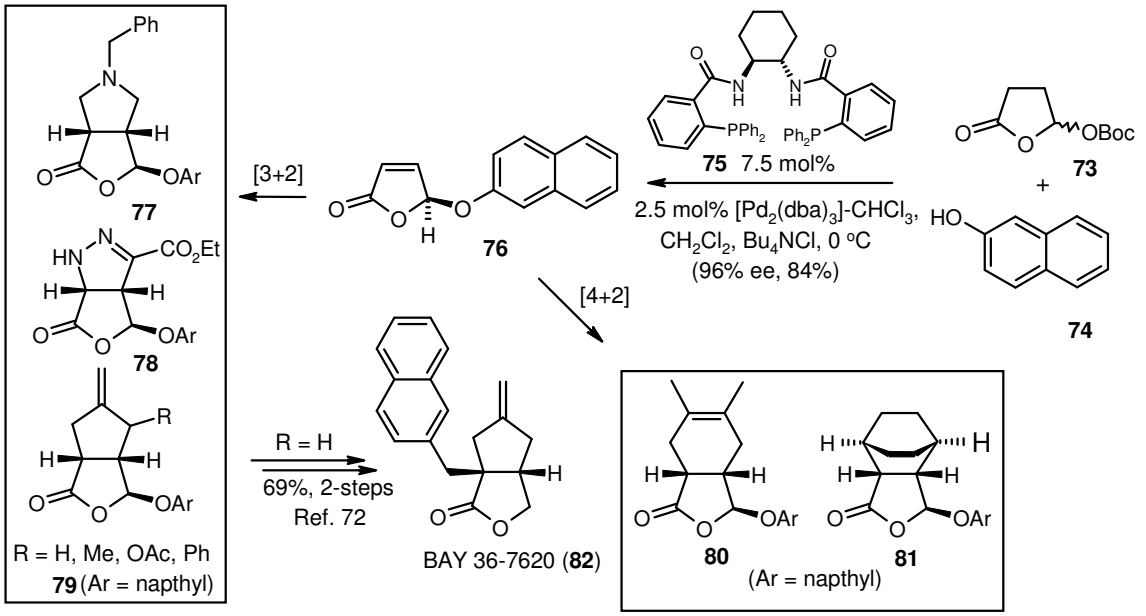
67 **68** **69** **70** **71** **72**

Scheme 16. *Reagents, conditions and yields*: (i) *n*-BuLi, (-)-sparteine, toluene, -78 °C, 10 min. to 2 h; (ii) $ClTi(O^iPr)_3$, 1 h, -78 °C; (iii) (a) R^2CHO, 1 h, -78 °C, (b) 2 N HCl (21-88%, 3-steps); (iv) $Hg(OAc)_2$, $MeSO_3H$, MeOH, 0 °C, 15 h; (v) *m*-CPBA, $BF_3.OEt_2$, CH_2Cl_2, rt, 15 h (45-83%).

Butenolides are natural products themselves, but they are also versatile building blocks for monocyclic and polycyclic γ-butyrolactones due to the highly reactive α,β-double bond for conjugate and cycloadditions. Consequently, many approaches towards butenolide natural products are also useful for the synthesis of γ-butyrolactones.[70] Recently, Trost *et*

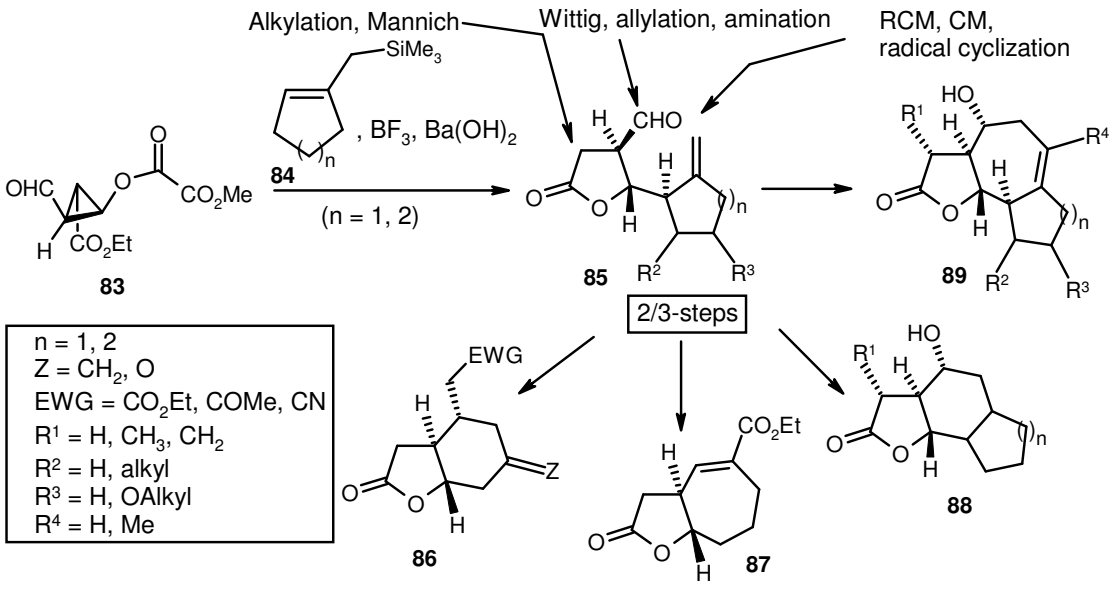
al[71] disclosed butenolide **76**, being available by an asymmetric palladium-catalyzed allylic alkylation between lactone (±)-**73** and *β*-naphthol **74** with high enantiomeric purity (Scheme 17). Butenolide **76** readily undergoes cycloadditions, giving rise to a broad variety of bicyclic and tricyclic lactones, which can be transformed into natural products and drugs, as exemplified with the synthesis of meabotropic glutamate receptorantagonist BAY 36-7620 (**82**).[72]

Scheme 17



Reiser and co-workers[73] developed a flexible strategy that allows the diastereoselective and enantioselective construction of bi- and tricyclic *γ*-butyrolactone cores found in many sesquiterpene lactones. Using allylsilane as nucleophile they synthesized lactones **85** from cyclopropane **83**. In the resulting lactones **85** the aldehyde functionality can be readily transformed by alkenylation, allylation or amination reactions, while the exo olefin group can be used in cross-metathesis (CM) and ringclosing metathesis (RCM) or radical cyclization reactions. Thereby, a variety of bi- (5.6 or 5.7) and tricyclic (5.6.5, 5.6.6, 5.7.5 or 5.7.6) scaffolds **86**-**89**, being commonly found in eudesmanolides,[74] xanthanolides[75]or guaianolides[76] become accessible in only a few steps (Scheme 18).

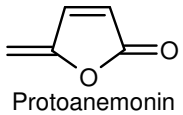
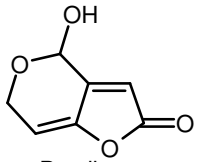
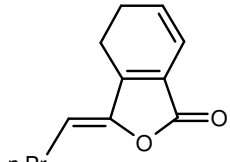
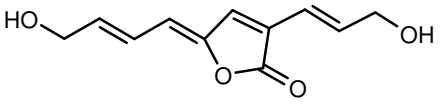
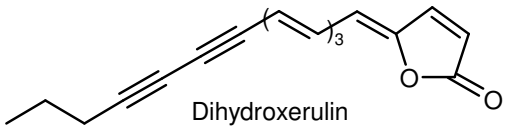
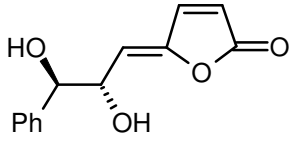
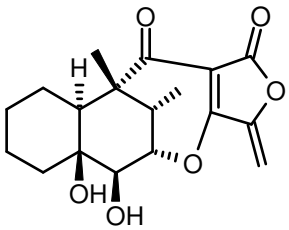
Scheme 18



1.4 *γ*-Alkylidenebutenolides

Butenolides[77] are *γ*–butyrolactones with a $C^{\alpha}=C^{\beta}$ bond. They represent a large number of natural products and the *γ*-methylene/alkylidene butenolides are of interest from both synthetic as well as from medicinal point of view.[78] Over the past few decades, an increasing number of stereodefined *γ*-alkylidenebutenolides have been isolated from natural sources and many of them have been shown to display a wide range of biological activities. They are important subunits present in a large variety of natural products and biologically active compounds such as alkaloids,[79] lignan lactones[77] and sex attractant insect pheromones.[78] Many of these compounds exhibit a variety of properties including anti-cancer and anti-fungal, insecticidal, anti-bacterial, phytotoxic, or anti-inflammatory activities; some of them are antibiotics, cyclooxygenase or phospholipase A2 inhibitors. Some representative *γ*-alkylidenebutenolides are shown in Table 5.

Table 5: Natural products containing *γ*-methylene/alkylidene butenolide moiety

No.	*γ*-Methylene/alkylidenebutenolide containing natural products	Source	Activity	Ref.
1	 Protoanemonin	*Anemone Pulsatilla*	Antibiotic	80a, 80b
2	 Patulin	*Penicillium Aspergillus*	Antibiotic	81a, 81b
3	 Ligustilide	*Ligusticum*	Anticholinergic, Antispasmodic	82a, 82b
4	 Tetrenolin	*Micropolyspora venezuelensis*	Antibiotic	83a, 83b
5	 Dihydroxerulin	*Xerula melanotricha*	Inhibitors of the biosynthesis of cholesterol	84a, 84b
6	 Goniobutenolide A	*Goniothalamus giganteus*	Antitumor	85a, 85b
7	 Tetrodecamycin	*Streptomyces nashvillensis*	Antibiotic	86, 87

It is noted that the majority of the compounds shown in Table 5 contain a (*Z*)-*γ*-alkylidene moiety, and it does appear that, for steric and electronic reasons, the *Z*- isomers

are, in general, thermodynamically favored. Most of the synthetic methods developed earlier produce *E* and *Z* mixtures. Moreover, steps generating the γ-alkylidene moiety often occur late in the synthetic schemes, rendering such syntheses rather unattractive. Mainly during the past ten years, several organometallic methods, some of which are highly selective, have been reported. In particular, palladium-catalyzed lactonization of alkynoic acids appears to be highly promising. It also provides procedures that are applicable to the stereoselective synthesis of either *Z*- or *E*-stereoisomers.

1.4.1 Synthesis of γ-alkylidenebutenolides

For the synthesis of γ-alkylidenebutenolides, different methods are documented in the literature which are summarized below. These methods are classified according to the type of substrates and reagents used for their synthesis.

Synthesis of γ-alkylidenebutenolides from

1.4.1.1: γ-Ketoacids

1.4.1.2: γ-Hydroxyacids

1.4.1.3: Five membered heterocycles

1.4.1.4: Bis-silyl enolethers

Synthesis of γ-alkylidenebutenolides using catalytic methods

1.4.1.5: Cobalt carbonyl catalyzed lactonization

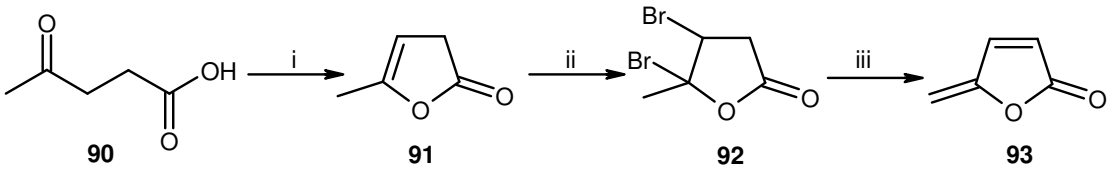
1.4.1.6: Chromium carbonyl catalyzed lactonization

1.4.1.7: Ag and Hg-catalyzed lactonization

1.4.1.8: Pd or Rh-catalyzed lactonization

1.4.1.1 Synthesis of γ-alkylidenebutenolides from γ-ketoacids

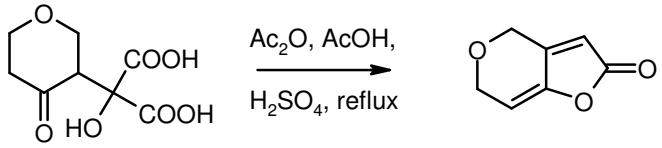
Lactonization of γ-ketoacids is one of the oldest routes for the synthesis of γ-alkylidenebutenolides. Synthesis of protoanemonin (**93**),[88] an antibiotic isolated from *Anemone Pulsatilla* and synthesized from levulinic acid (**90**), is the simplest example of lactonization of γ-ketoacids (Scheme 19). Lactonization of levulinic acid (**90**) gave α-angelica lactone (**91**) followed by its bromination and dehydrobromination to form protoanemonin (**93**).



Scheme 19. *Reagents, conditions and yields*: (i) Ac_2O, H_2SO_4, reflux (90%); (ii) Br_2, CS_2, -20 ºC; (iii) NEt_3, -20 ºC to rt (44%, 2-steps).

Similarly synthesis of deoxy-patulin (**95**)[81a] involved treatment of γ-ketoacid **94** with warm acetic anhydride and sulphuric acid in acetic acid as shown in scheme 20.

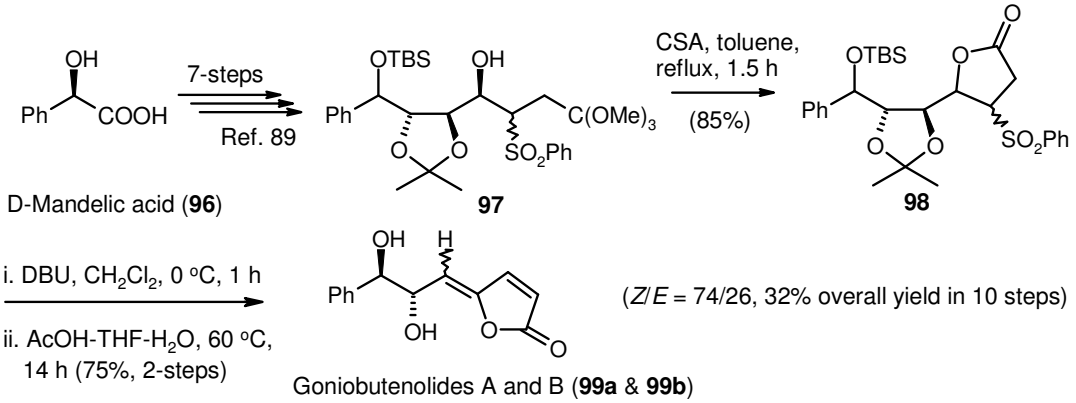
Scheme 20



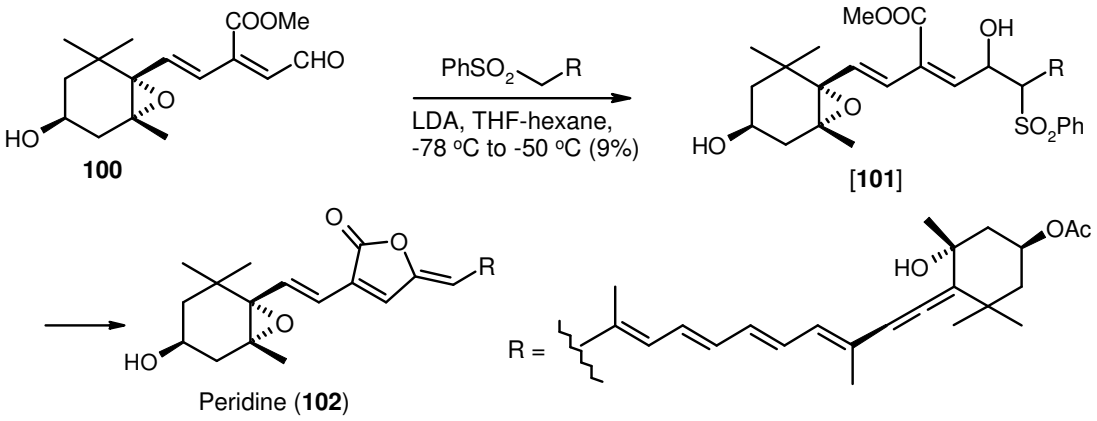
1.4.1.2 Synthesis of γ-alkylidenebutenolides from γ-hydroxyacids

It is well known that γ-hydroxyacids readily cyclize to give γ-lactones. In cases where such γ-lactones contain a suitable functional group, such as an allyl, alkenyl, halogen, oxygen, or sulfur group that can participate in elimination reactions, γ-alkylidenebutenolides can be obtained as demonstrated by the synthesis of goniobutenolides A and B (**99a** & **99b**)[89] (Scheme 21) and peridine (**102**)[90] (Scheme 22).

Scheme 21



Scheme 22



1.4.1.3 Synthesis of γ-alkylidenebutenolides from five membered heterocycles

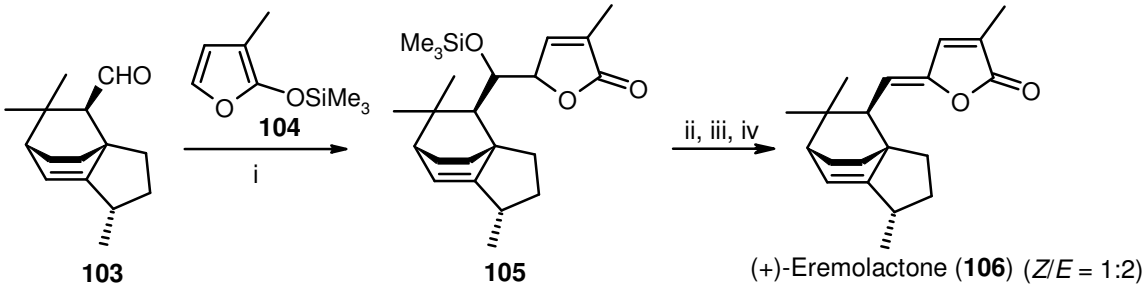
This method involved the synthesis of γ-alkylidenebutenolides from 2-oxyfurans,[91] γ-lactones[92,93] or maleic anhydride derivatives.[94] Oxyfurans and γ-lactones have been used mainly as nucleophiles, while maleic anhydrides have served as electrophiles. Synthesis of γ-alkylidenebutenolides by this method is nonstereoselective but due to the steric and electronic reasons, formation of *Z*-isomer is dominated as it is thermodynamically preferred.

1.4.1.3a: Synthesis from 2-oxyfurans

Many natural and unnatural compounds were synthesized from substituted 2-oxyfurans involving β-elimination pathway to obtain γ-alkylidenebutenolides. Two representative examples of the synthesis of γ-alkylidenebutenolides from 2-oxyfurans are given below.

Eremolactone (**106**) is a γ-alkylidenebutenolide, which was isolated from *Eremophila*

Scheme 23

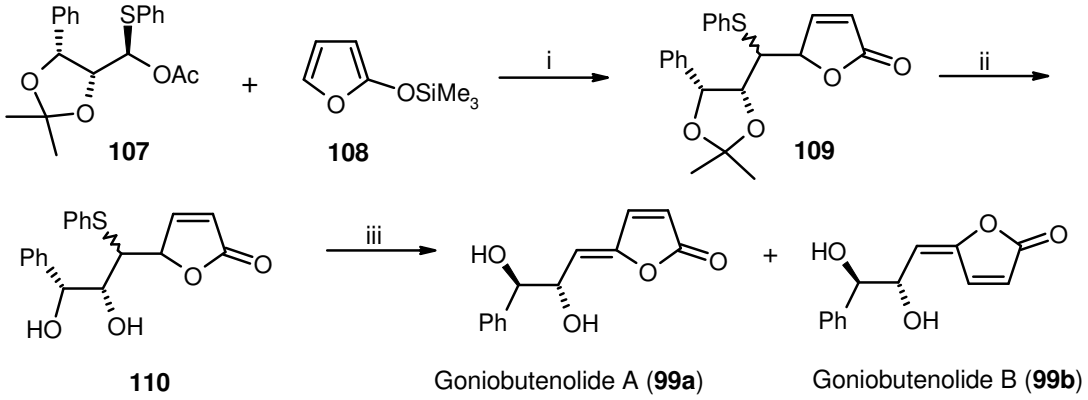


Scheme 23. *Reagents, conditions and yields*: (i) $SnCl_4$, DCM, -78 °C (99%); (ii) TBAF, AcOH, THF; (iii) CH_3SO_2Cl, DCM; (iv) NEt_3, DCM, rt (88%, 3-steps).

fraseri and it was synthesized by Ramage *et al* from substituted 2-trimethylsilyloxyfuran **104** by treating it with aldehyde **103** in presence of $SnCl_4$ to obtain **105**, followed by desilylation, conversion of secondary hydroxyl to mesylate and *β*-elimination (Scheme 23)[95] pathway.

Ko *et al*[85a] reported synthesis of cytotoxic Goniobutenolides A (**99a**) and B (**99b**) (**99a**:**99b** = 1.6:1), starting from 2-trimethylsilyloxyfuran **108** via Mukaiyama coupling with acetal **107** in presence of Lewis acid $SnCl_4$ to obtain **109**, which on acetonide deprotection followed by *β*-elimination of thiophenol gave **99a** and **99b** (Scheme 24).

Scheme 24

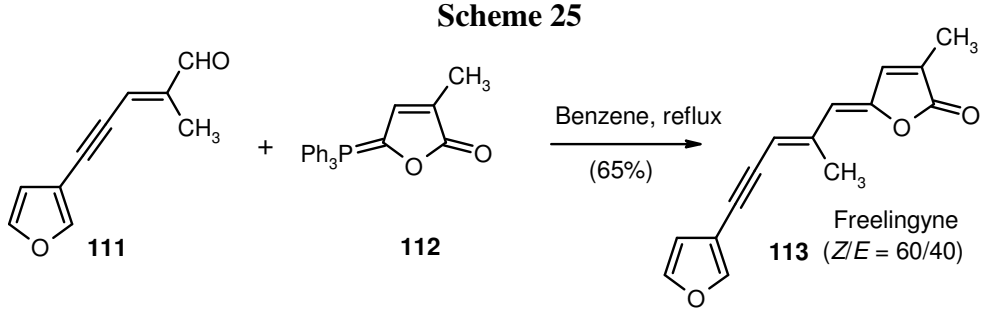


Scheme 24. *Reagents, conditions and yields*: (i) $SnCl_4$, DCM, -78 °C (65%); (ii) 90% Aq. TFA (84%); (iii) AgF, pyridine (68%).

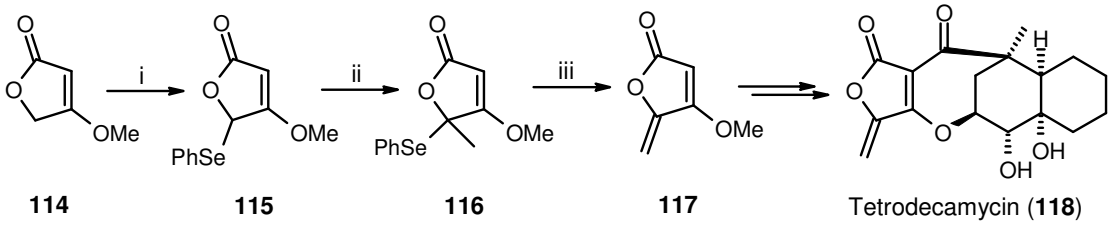
1.4.1.3b: Synthesis of *γ*-alkylidenebutenolides from *γ*-lactones

γ-Butyrolactones could be converted to *γ*-alkylidenebutenolide by Wittig olefination reaction. One example is synthesis of sesquiterpene freelingyne (**113**)[96] isolated from *Eremophila freelngyne*, which was synthesized by the application of Wittig reaction of 3-methyl-5-triphenyl phosphoranylidene-(5*H*)-furan-2-one (**112**) with (*E*)-5-(3-Furyl)-2-methylpent-2-en-4-ynal (**111**) depicted in scheme 25.

Scheme 25



Paintner *et al* reported formal synthesis of tetrodecamycin (**118**), having unique ring skeleton bearing exo-methylene moiety.[97] 4-Methoxy-5-phenylseleno-2(5*H*)-furanone (**115**) prepared by selenation of commercially available 4-methoxy-2(5*H*)-furanone (**114**), was alkylated followed by oxidative elimination of phenyl selenium group using *m*-CPBA afforded the *γ*-alkylidene derivative **117** (Scheme 26), which is an intermediate for the synthesis of tetrodecamycin (**118**).

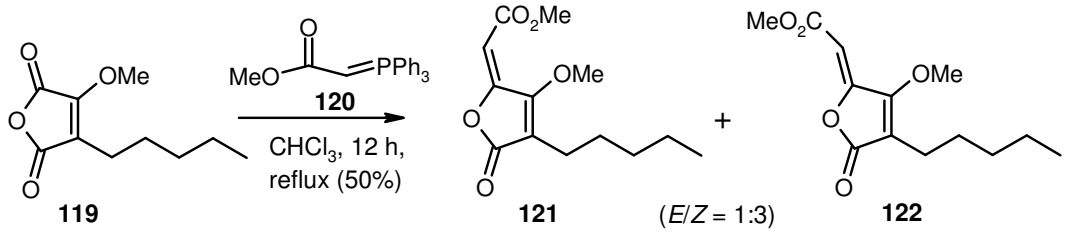


Scheme 26. *Reagents, conditions and yields*: (i) (a) *n*-BuLi, THF, -78 °C; (b) PhSeCl, -78 °C (90%); (ii) (a) *t*-BuLi, THF, -78 °C; (b) CH_3I, -78 °C to rt (82%); (iii) *m*-CPBA, CH_2Cl_2, 0 °C (92%).

***1.4.1.3c*: Synthesis of *γ*-alkylidenebutenolides from maleic anhydride derivatives**

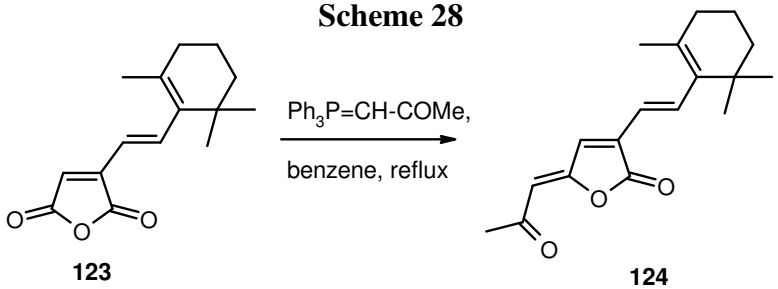
Pattenden and co-workers reported the synthesis of methyl *O*-methylmulticolanate[94] by the reaction between the anhydride **119** and the phosphorane **120**, which gave a 1:3 mixture of (*E*)- and (*Z*)-isomers (**121**) and (**122**), respectively, of methyl *O*-methylmulticolanate (Scheme 27).

Scheme 27



In the synthesis of retinoids, Ito *et al* used Wittig olefination reaction to convert maleic anhydride derivative **123** into *γ*-alkylidenefuranones **124** in one step as shown in scheme 28.[98,99]

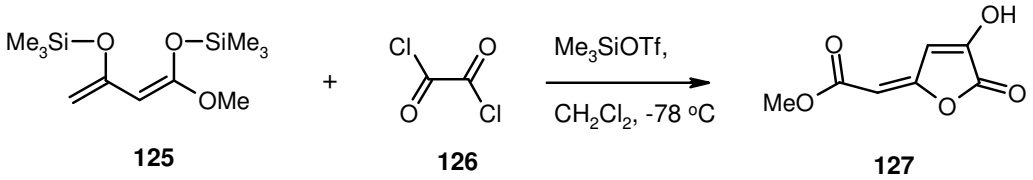
Scheme 28



1.4.1.4 Synthesis of substituted γ-alkylidenebutenolides from 1,3 bis-silyl enol ethers

Langer reported[100] simple and efficient method for the synthesis of γ-alkylidenebutenolide **127** involving Lewis acid Me_3SiOTf-catalyzed cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadiene (**125)** with oxalyl chloride (**126)** (Scheme 29). A great variety of γ-alkylidenebutenolides were efficiently prepared.

Scheme 29

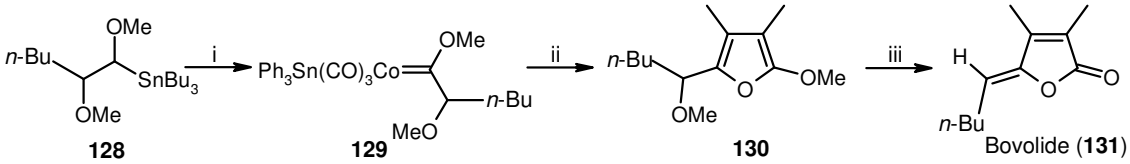


Synthesis of γ-alkylidenebutenolides using catalytic methods

γ-Alkylidenebutenolides derivatives were also synthesized by using different types of metal complexes. These methods either involved metal catalyzed carbonylation or intermolecular or intramolecular reactions of alkynes, alkenes or organic halides using Co, Cr, Ag, Hg and Pd complexes.

1.4.1.5 Cobalt carbonyl catalyzed lactonization

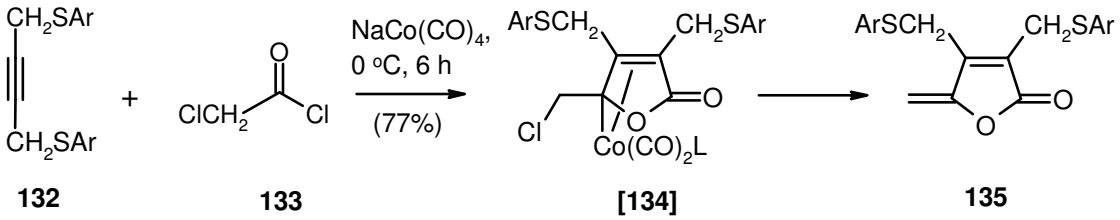
Wulff *et al* reported the synthesis of naturally occurring bovolide (**131**) using cobalt complex as shown in scheme 30.[101] The methoxycobalt carbonyl complex **129**, which was prepared from stannyl ether **128** and triphenyltincobalttetracarbonyl was heated with 2-butyne in benzene under inert atmosphere. The crude reaction mixture was then treated with trimethylsilyl iodide to give bovolide (**131**) in 48% yield (Scheme 30).



Scheme 30. *Reagents, conditions and yields*: (i) *n*-BuLi, $Ph_3SnCo(CO)_4$, $Me_3O^+.BF_4^-$, THF (45%); (ii) 2-Butyne, benzene, 50 ºC; (iii) Me_3SiI, CH_2Cl_2, 25 °C (48%, 2-steps).

Acyl cobalt carbonyl compounds, substituted at the α-position with a leaving group react with internal alkyne to give rise to substituted butenolides in good yields.[102] For example, Krafft *et al*. synthesized butenolide **135**, using cobalt complex as shown in scheme 31.[102] 1,4-(Bis-4-ethylphenylthio)-2-butyne (**132**) on treatment with chloroacetyl chloride (**133**) in presence of sodium cobalt carbonyl complex [$NaCo(CO)_4$] at 0 °C provided **135** in 77% yield.

Scheme 31

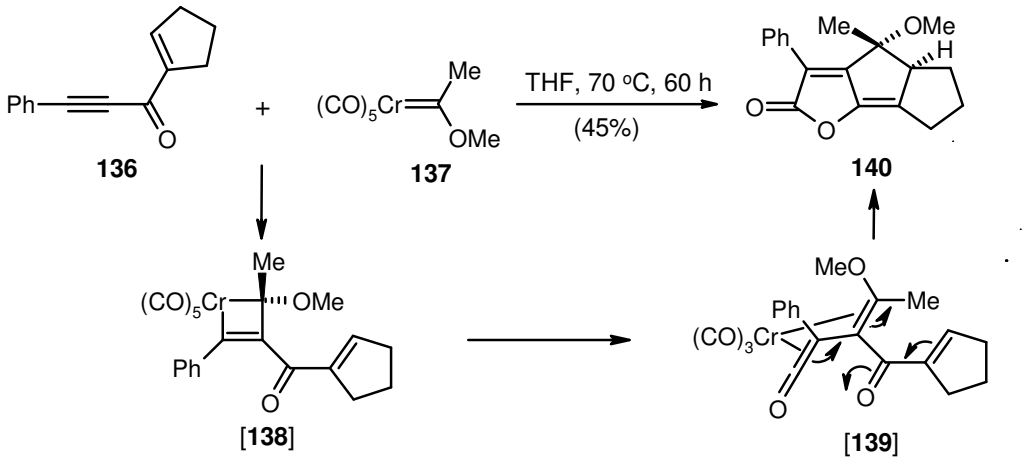


132 **133** **[134]** **135**

1.4.1.6 Chromium carbonyl catalyzed lactonization

Wulff and co-workers synthesized tricyclic lactone **140**,[103] which contains *γ*-alkylidenebutenolide moiety, heating a mixture of alkylchromium carbene complex **137** and ketoalkyne **136** as depicted in scheme 32. In the synthesis of **140**, the carbene-Cr complex presumably undergoes cyclic carbometallation to produce a metallacyclobutene **138,** which is converted via carbonylation to the ene-ketene-metal complex **139** and then to *γ*-alkylidenebutenolides **140**, as shown in scheme 32.

Scheme 32



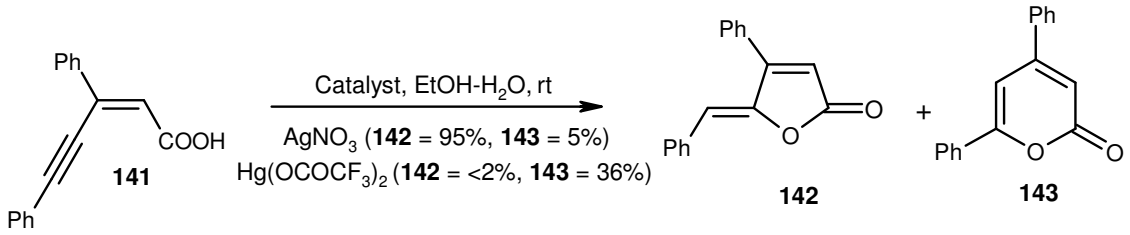
136 **137** **140** [**138**] [**139**]

1.4.1.7 Ag and Hg-catalyzed lactonization of 4-alkynoic acids

Silver catalysed lactonization of 4-alkynoic acid[104] was found to be very fast and cleaner as compared to other methods, such as thermal cyclization processes. Various silver reagents eg. $AgNO_3$, $AgClO_4$, Ag_2CO_3, AgI, AgO and Ag were used for lactonization of 4-alkynoic acid. These reactions proceeded cleanly in ethanol-water at room temperature to provide stereoselectively *γ*-alkylidenebutenolide **142** with *Z*-geometry (Scheme 33). 4-Alkynoic acids have also been lactonized in presence of catalytic amounts of Hg compounds such as HgO and $Hg(OAc)_2$. Terminal alkynes lactonize readily. For the

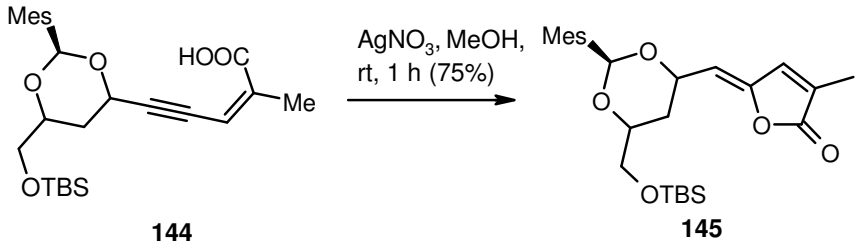
reaction shown in scheme **33**, Hg catalyst gave poor yield of butenolide **142** and pyrone derivatives **143** as the exclusive side product.

Scheme 33



Recently, Sulikowski *et al* synthesized butenolide **145**, which is a synthetic intermediate of diterpene natural product bielschowskysin, using $AgNO_3$ as catalyst from alkyne **144** (Scheme 34).[105]

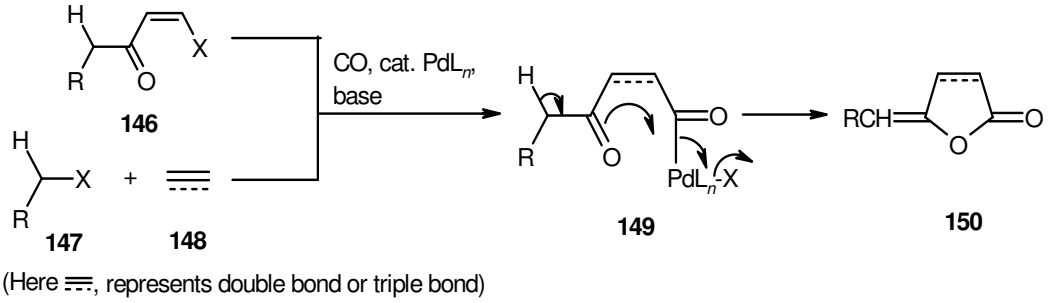
Scheme 34



1.4.1.8 Pd-catalyzed lactonization of 4-alkynoic acids

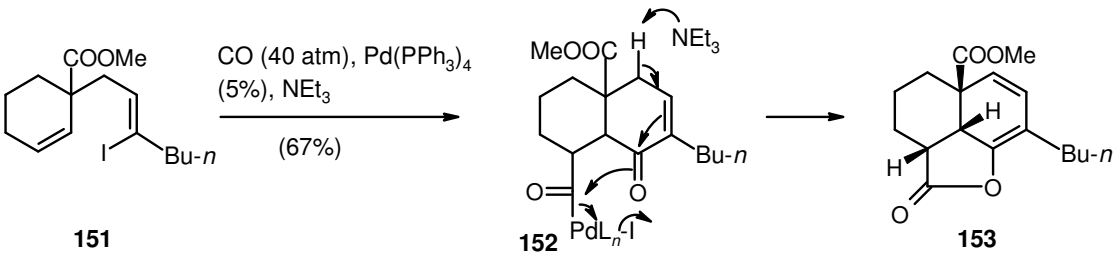
Palladium catalyzed carbonylation is most widely used for the synthesis of *γ*-alkylidenebutenolides. Stereoselectivity of this method is better than other methods but it varies with substitution pattern of the substituents. Negishi and co-workers developed a new and potentially general route to *γ*-alkylidenebutenolides via *γ*-ketoacylpalladium complexes **149** (Scheme 35).[106] The requisite *γ*-ketoacylpalladium **149** derivatives can be generated by Pd-catalyzed carbonylation of either (*Z*)-*β*-halo-*α*,*β*-unsaturated ketones **146** or an intramolecular or intermolecular combination of alkynes or alkenes (**148**) and organic halides (**147**) capable of undergoing oxidative addition with Pd, such as alkenyl, allyl, benzyl, and acyl halides. In the presence of a suitable base *γ*-ketoacylpalladium **149** intermediates can be converted to the desired *γ*-alkylidenebutenolides **150**.

Scheme 35

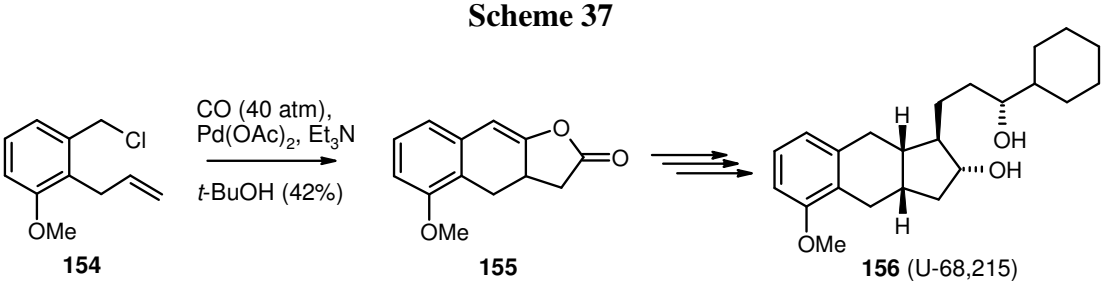


Negishi and co-workers converted iodo compound **151** to tricyclic lactone **153**[107] (Scheme 36) and chloro compound **154** to **155**, which provided an efficient route to a promising antiulcer agent U-68,215[108] (Scheme 37).

Scheme 36

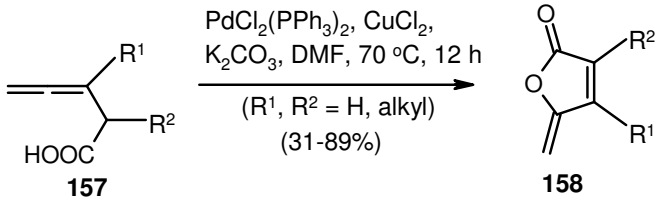


Scheme 37



Shengming *et al* have described a convenient method for the preparation of the *γ*-methylene-2(5*H*)-furanones by Pd-catalyzed cyclization of 3,4-allenoic acids in high yield[109] (Scheme 38).

Scheme 38



1.5 Summary

In this chapter we have presented a concise account of naturally occurring γ-butyrolactones and γ-alkylidenebutenolides and various synthetic approaches towards them. The combination of unique features, extensive functionalization and high biological activity found in γ-butyrolactones and γ-alkylidenebutenolides containing natural products, have presented an elegant challenge to the synthetic chemists. Transition metal catalyst made it convenient not only the efficient introduction of broad variety of functional groups but also the flexible construction of various monocyclic and polycyclic butyrolactones and butenolides from the same common precursors. Although most of the reported approaches are target driven aiming at a specific class of γ-butyrolactone natural products, many of the reported strategies clearly demonstrate their broad scope, which should make them attractive in the future for combinatorial library synthesis.

All the butyrolactones have been classified as monocyclic, bicyclic and polycyclic according to their structural variations. The informations about the isolation, activity and synthesis have been summarized in 5 tables. Various synthetic approaches to these γ-butyrolactones and γ-alkylidenebutenolides have been described by providing 38 schemes. All the information collected and provided here has been well supported by providing more than 140 references from monographs and international journals.

We believe that from both synthetic and pharmaceutical point of view, the γ-butyrolactone chemistry is of high importance. To build these useful γ-butyrolactone and γ-alkylidenebutenolides skeletons in highly stereoselective fashion, high amount of synthetic efforts have been studied, employing variety of new elegant strategies and efforts are still in progress to invent newer methods, which will definitely develop lot of new and useful chemistry. In this context, as a part of this present dissertation, we have synthesized some naturally occurring bioactive γ-butyrolactones and γ-alkylidenebutenolides and their derivatives using variety of synthetic strategies. Our synthetic strategies towards the syntheses of all these natural and unnatural butyrolactone containing natural products will be discussed in details in the second and third chapter of present dissertation.

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Chapter 2

Facile Synthesis of Maculalactones, Nostoclide I and Pandamarilactonines

This chapter features the following sections:

2A. Section A

Synthesis of Naturally Occurring Bioactive Butyrolactones: Maculalactones A-C and Nostoclide I

This section features the following topics:

2A Section A: Synthesis of Naturally Occurring Bioactive Butyrolactones: Maculalactones A-C and Nostoclide I

2A.1 Background

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

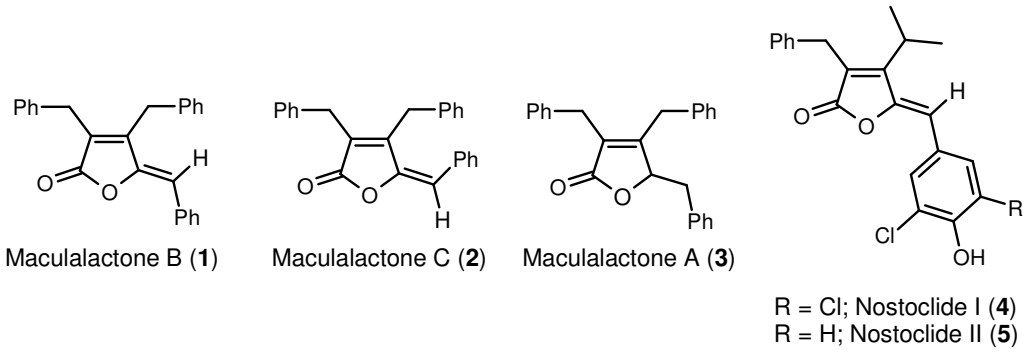
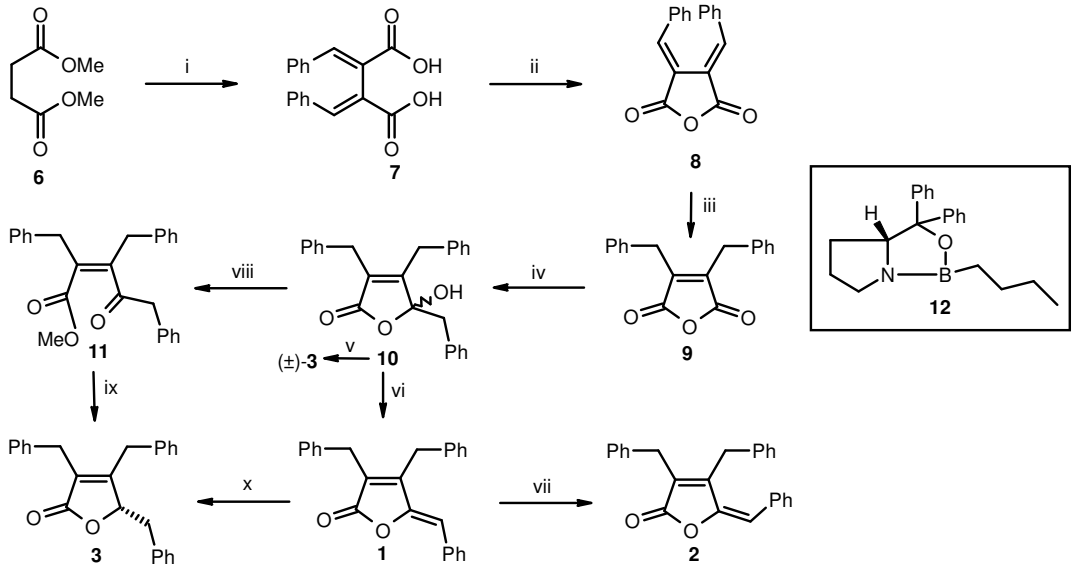


Figure 1. Maculalactones A-C and Nostoclide I & II

2A.1.1 First Synthetic Approach Towards Maculalactones A-C

Recently Brown et al. reported the first general synthetic route to these butyrolactones and also completed an asymmetric synthesis of (+)-maculalactone A (Scheme 1).[2] They completed the synthesis of (±)-maculalactone A (**3**), starting from dibenzylidinesuccinic acid (**7**), which was obtained by Stobbe condensation of dimethylsuccinate (**6**) with benzaldehyde, via acetyl chloride mediated ring closing to anhydride **8**, 1,4-hydrogenation of anhydride to tetrasubsituted alkene **9**, addition of benzylmagnesium bromide followed by reduction of the lactol **10**. The overall yield of maculalactone A (**3**) in four steps was 36% (Scheme 1). Dehydration of **10** in the presence of sulfuric acid gave maculalactone B

(**1**, 82%). Maculalactone B (**1**) was converted to maculalactone C (**2**) by irradiation with UV light in 79% yield. They also assigned the (+) and (−)-enantiomers of maculalactone A (**3**) to be the *S*- and *R*- configurations respectively on the basis of the chiral selectivity



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

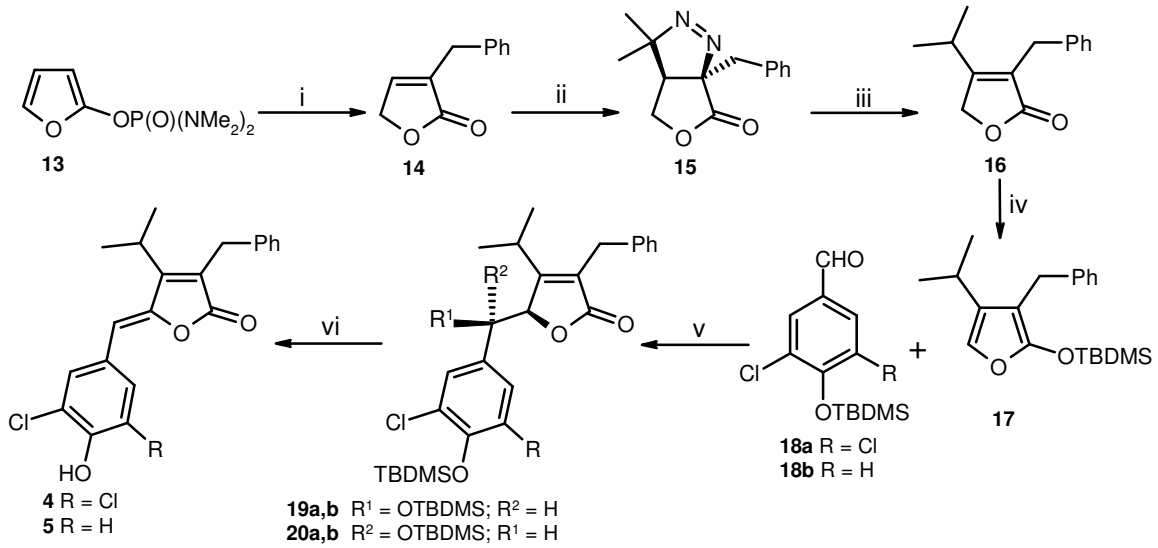
expected for catecholborane reduction of an unsymmetrical ketone **11** in the presence of Corey's oxaborolidine catalyst **12**.[5]

2A.1.2 Synthetic Approaches Towards Nostoclide I and II

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

[A] Boukouvalas's Synthetic Approach

Boukouvalas et al. reported the first synthesis of nostoclide I and II in a fully regio- and stereocontrolled manner using 2-furanolates as key intermediate in 6-steps with 29-32% overall yield (Scheme 2).[4a] They prepared furan **17** starting from 2-furyl-*N*,*N*,*N*′,*N*′-tetramethyldiamidophosphate (**13**), via directed *ortho*-alkylation, introduction of an isopropyl group by 1,3-dipolar cycloaddition of formed butyrolactone **14** with 2-diazopropane and themolysis, followed by the silylation of the resulting disubstituted

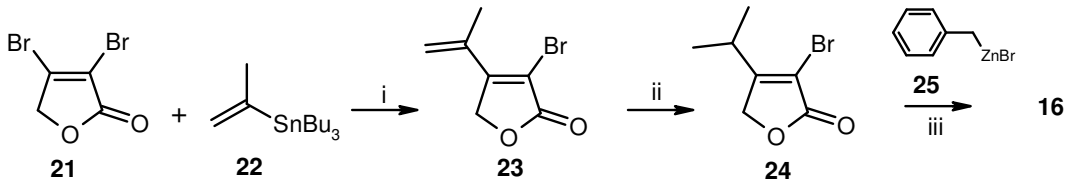


Scheme 2. *Reagents, conditions and yields*: (i) *n*-BuLi, THF, -78 °C, $PhCH_2Br$, HCOOH (72%); (ii) $(Me)_2CN_2$, Et_2O, 0 °C, 24 h; (iii) C_6H_6, reflux, 1 h (56%, 2-steps); (iv) TBDMSOTf, Et_3N, CH_2Cl_2, 0-25 °C, 24 h (88%); (v) TBDMSOTf, CH_2Cl_2, -78 °C, 2 h (**19a/20a** = 93%, **19b/20b** = 91%); (vi) (a) DBU, $CHCl_3$, reflux, 18-24 h, (b) Aq. 3 M HCl, 25 °C (**4** = 96%, **5** = 90%).

butyrolactone **16**. Aldol condensation of **17** with the required aldehydes (**18a** and **18b**) and subsequent DBU induced *cis*-selective E1cb elimination of the resulting mixture of diastereomers **19a,b** and **20a,b**, followed by acidification furnished **4** and **5**.

[B] Bellina's Synthetic Approach

Recently, Bellina et al. reported the synthesis 3-benzyl-4-isopropyl-2(5*H*)-furanone (**16**), which is a precursor of nostoclides, starting from 3,4-dibromo-2(5*H*)-furanone (**21**) in three steps with 27% overall yield (Scheme 3).[4b] They synthesized butyrolactone **16** by Stille coupling of one equivalent of isopropenyltributyl tin with dibromobutenolide **21**,



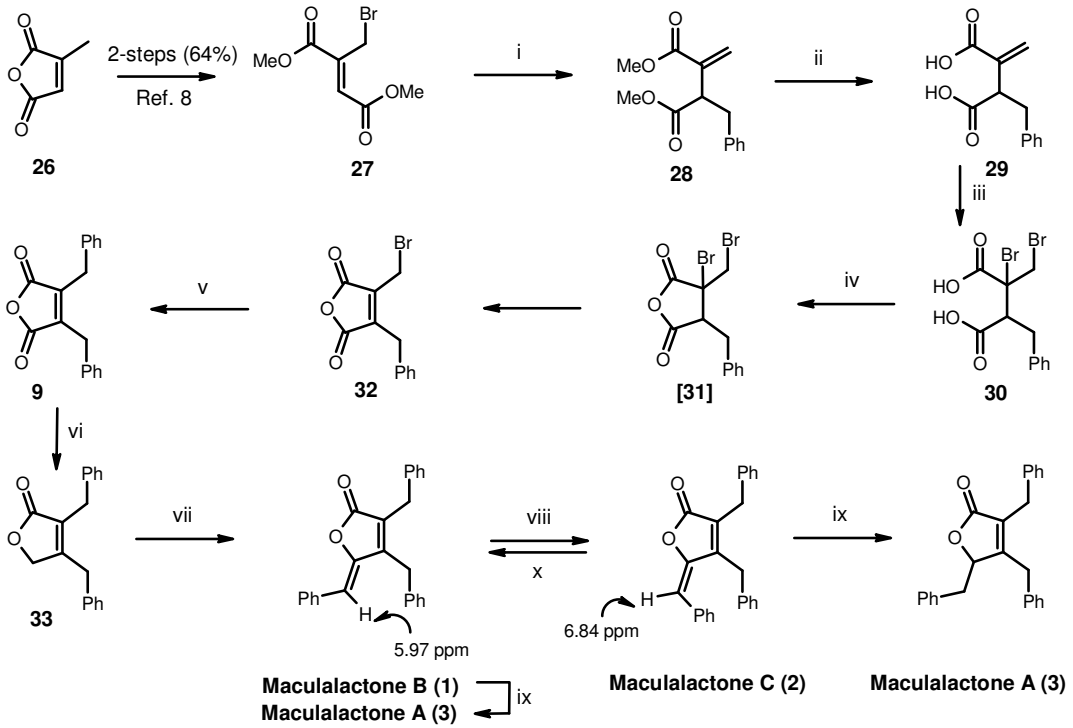
Scheme 3. *Reagents, conditions and yields*: (i) $PdCl_2(PhCN)_2$, Ph_3As, NMP, rt, 5 days (78%); (ii) $RhCl(Ph_3P)_3$, H_2, benzene, rt (95%); (iii) **25**, DMF/THF (1:1), $PdCl_2[(o\text{-Tolyl})_3P]_2$, 60 °C, 5 h (36%).

which on Rh (I) catalyzed regioselective hydrogenation followed by Pd-catalyzed cross coupling reaction with benzylzinc bromide gave precursor of nostoclides **16**.

We envisaged that the synthesis of suitably disubstituted maleic anhydrides followed by their reductive conversion to the respective lactones and then the Knoevenagel condensation with different aldehydes would provide an easy access to these novel butenolide skeletons (Scheme 4 and 5).[6]

2A.2 Present Work: Results and Discussion

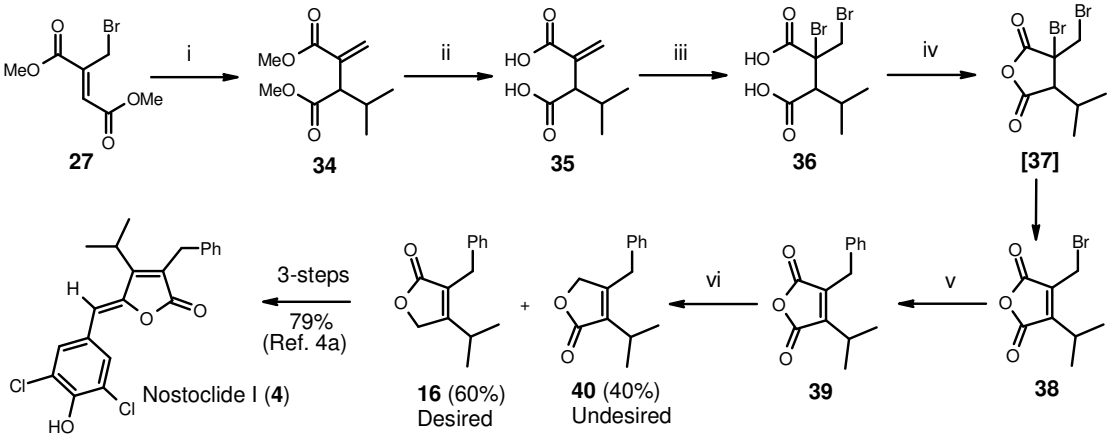
Recently, our group studied the NBS-allylic bromination of dimethyl methylmaleate,[7] chemoselective S_N2' coupling reactions of Grignard reagents prepared from primary alkyl halides with dimethyl bromomethylfumarate (**27**) in absence of CuI[8,9] and chemoselective allylic S_N2' substitution of bromoatom in (bromomethyl)methylmaleic anhydride with Grignard reagents prepared from primary alkyl halides in presence of CuI,[10] to design the bioactive natural products. We planned to study the above two coupling reactions with Grignard reagents from secondary alkyl halides, benzyl halides and aryl halides to design the desired substituted maleic anhydrides **9** and **39**. The S_N2' coupling reaction of benzylmagnesium bromide with **27**[8] furnished the diester **28** in 70% yield, with *exo*-type carbon-carbon double bond. Lithium hydroxide induced hydrolysis of diester **28** at room temperature followed by acidification gave the desired dicarboxylic acid **29** in 92% yield, without isomerization of carbon-carbon double bond. The addition of molecular bromine to the carbon-carbon double bond in **29** gave a mixture of all possible isomers of dibromodicarboxylic acid **30** in ~100% yield. The dibromodicarboxylic acid **30** underwent a smooth in situ dehydration followed by dehydrobromination reaction in presence of refluxing acetic anhydride to give unsymmetrical (bromomethyl)benzylmaleic anhydride (**32**) in ~100% yield via the unisolable intermediate dibromosuccinic anhydride **31**. The chemoselective allylic substitution of bromoatom in anhydride **32** with phenylmagnesium bromide furnished dibenzylmaleic anhydride (**9**) in 45% yield. Sodium borohydride reduction of dibenzylmaleic anhydride (**9**) in THF at room temperature gave the desired lactone **33** in 91% yield. The Knoevenagel condensation of lactone **33** with benzaldehyde furnished the naturally occurring maculalactone B (**1**) in 77% yield (Scheme 4).[6] The maculalactone B (**1**) on palladium-charcoal catalyzed chemoselective hydrogenation gave (±)-maculalactone A (**3**) in 75% yield. The photochemical conversion of maculalactone B (**1**) to maculalactone C (**2**) is known with 80% yield.[2] Maculalactone B (**1**) is thermodynamically more stable than maculalactone C (**2**), but due to the presence of



Scheme 4. *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%).

associated π-stacking interaction between the two phenyl groups[1] it slowly transforms to maculalactone C (**2**). Maculalactone B (**1**) in chloroform at room temperature underwent nearly 50% conversion to maculalactone C (**2**) in 8-days span (by ^{1}H NMR). In maculalactone B, the vinylic proton is shielded (δ = 5.97 in ^{1}H NMR spectra) because it lies in the shielding region of the adjacent benzyl group; whereas, in maculalactone C, the vinylic proton points out from the adjacent benzyl group and has a normal value for a vinylic proton involved in conjugation (δ = 6.84 in ^{1}H NMR spectra). We isolated and heated the above neat 50:50 mixture of maculalactones B and C at 200 ºC for three hours and obtained exclusively maculalactone B (**1**), thus proving that it is thermodynamically more stable than maculalactone C (**2**). Maculalactones B plus C mixture on catalytic hydrogenation also gave maculalactone A (**3**) in identical 75% yield. The analytical and spectral data obtained for maculalactones A-C were in complete agreement with reported data.[1,2]

Our next plan was to design the bioactive natural product nostoclide I (**4**). Starting from diester **27**, we similarly prepared the benzylisopropylmaleic anhydride (**39**) in 5-steps with 31% overall yield via S_N2' Grignard coupling, hydrolysis, bromination, in situ dehydration followed by dehydrobromination and allylic substitution pathway (Scheme 5).[6] The



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

sodium borohydride induced regioselective reduction[11] at the relatively more hindered carbonyl group of unsymmetrical maleic anhydride **39** in THF at 0 ºC gave the silica-gel column separable mixture of desired and undesired lactones **16** and **40** with 70% yield in 3:2 ratio respectively. The analytical and spectral data obtained for lactone **16** was in complete agreement with the reported data. The three step conversion of lactone **16** to nostoclide I (**4**) via silylation followed by aldol condensation and *cis*-selective elimination with 79% overall yield is well known in the literature.[4a] In the present approach, starting from dimethyl bromomethylfumarate (**27**) we have completed the multi-step synthesis of novel bioactive natural products maculalactone A (**3**, 8-steps, 15%), maculalactone B (**1**, 7-steps, 20%), maculalactone C (**2**, 8-steps, 11%). Similarly, we have also completed the formal synthesis of bioactive natural product nostoclide I (**4**), the desired precursor **16** was obtained in 6-steps with 22% overall yield.

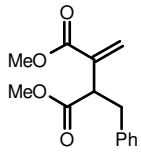
2A.3 Summary

In this section we have demonstrated a novel route to natural bioactive butyrolactones. In the present approach, the key intermediate bromomethyl alkylmaleic anhydrides were synthesized using highly chemo and regioselective S_N2' Grignard coupling reactions, hydrolysis, molecular bromine addition and dehydrative ring closure reactions pathway. These bromoanhydrides were then converted into butyrolactones by chemoselective allylic substitution reactions with appropriate Grignard reagents to obtain maleic anhydride derivatives followed by reduction to lactone and Knoevenagel condensation reactions. It is to be noted that in our hand the allylic substitution reactions with bromomethyl alkylmaleic anhydrides used in the present approach gave only moderate yields (43-45%) of the desired products with different types of Grignard reagents (alkyl and phenyl). Improvement in these reaction conditions to increase the conversion efficiency will be helpful, as it will directly increase the overall yield of these natural products and will also be useful for general purpose. We feel that our present approach is general in nature and can be used to design diverse dialkylsubstituted maleic anhydride and butyrolactone skeletons for the structure-activity relationship studies.

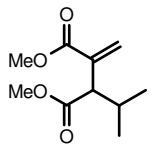
2A.4 Experimental

Commercially available citraconic anhydride, benzyl bromide, 2-bromopropane, bromobenzene, magnesium turnings, HMPA, CuI, diethyl malonate, NaH, lithium hydroxide, piperidine, acetic anhydride, $NaBH_4$ and benzaldehyde were used.

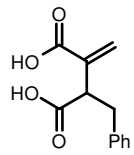
Dimethyl 1-buten-4-phenyl-2,3-dicarboxylate (28). A fresh solution of benzylmagnesium bromide in ether was prepared as follows. A solution of benzyl bromide (4.10 g, 24 mmol) in LAH–dried ether (20 mL) was added at room temperature to magnesium turnings (1.73 g, 72 mmol) in ether (20 mL) under argon with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was stirred at room temperature for a further 4 h. This freshly generated Grignard reagent was added drop wise to a solution of HMPA (14.34 g, 80 mmol) and **27** (3.79 g, 16 mmol) in anhydrous ether (40 mL) under argon at –20 ^{o}C and the reaction mixture was stirred at the same temperature for a further 30 min. The reaction was quenched by the addition of a saturated ammonium chloride solution (50 mL). An additional quantity of ether (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ether (30 mL x 3), the combined ether extract was washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether-ethyl acetate (9.5:0.5) to give **28**: 2.78 g (70% yield).

 **28** **$C_{14}H_{16}O_4$ (248)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1730, 1725, 1630 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.96 (dd, J = 14 & 6 Hz, 1H), 3.25 (dd, J = 14 & 8 Hz, 1H), 3.63 (s, 3H), 3.76 (s, 3H), 3.75-3.90 (m, 1H), 5.67 (s, 1H), 6.31 (s, 1H), 7.10-7.40 (m, 5H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 37.3, 48.6, 51.9, 52.0, 126.3, 127.3, 128.2, 128.8, 137.5, 138.6, 166.2, 172.8. **Anal. Calcd for $C_{14}H_{16}O_4$**: C, 67.73; H, 6.50. Found: C, 67.81; H, 6.44.

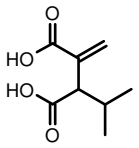
Dimethyl 1-penten-4-methyl-2,3-dicarboxylate (34). Repetition of the same procedure described above using 2-propylmagnesium bromide [prepared from 2-bromopropane (2.95 g, 24 mmol) and magnesium (1.73 g, 72 mmol)] and **27** (3.79 g, 16 mmol) gave the corresponding diester **34**: 2.53 g (79% yield).

 **34** **$C_{10}H_{16}O_4$ (200)**	Thick oil. **IR** (Neat): ν_{max} 2961, 1736, 1726, 1626 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.87 (d, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 2.10-2.50 (m, 1H), 3.41 (d, J = 10 Hz, 1H), 3.66 (s, 3H), 3.76 (s, 3H), 5.92 (s, 1H), 6.41 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 19.8, 20.7, 31.2, 51.4, 51.9, 52.3, 127.0, 137.6, 166.8, 173.3. **Anal. Calcd for $C_{10}H_{16}O_4$**: C, 59.98; H, 8.06. Found: C, 59.93; H, 8.11.

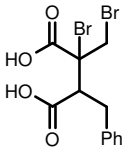
1-Buten-4-phenyl-2,3-dicarboxylic acid (29). A solution of lithium hydroxide (2.40 g in 18 mL water) was added to a solution of **28** (2.48 g, 10 mmol) in tetrahydrofuran (54 mL) at room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was then concentrated in vacuo. To the residue was added ethyl acetate (100 mL) and then acidified to pH 2 with 2 M hydrochloric acid. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether-ethyl acetate (6:4) to give **29**: 2.02 g (92% yield).

 **29** **$C_{12}H_{12}O_4$ (220)**	Thick oil. **IR** (Nujol): ν_{max} 2700-2500, 1709, 1705, 1628 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.03 (dd, J = 14 & 10 Hz, 1H), 3.38 (dd, J = 14 & 6 Hz, 1H), 3.60-3.75 (m, 1H), 5.61 (s, 1H), 6.42 (s, 1H), 7.00-7.40 (m, 5H), 10.6 (bs, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 36.6, 48.8, 126.6, 128.5, 128.9, 131.0, 136.4, 138.3, 171.7, 179.0. **Anal. Calcd for $C_{12}H_{12}O_4$**: C, 65.45; H, 5.49. Found: C, 65.52; H, 5.43.

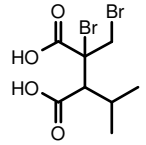
1-Penten-4-methyl-2,3-dicarboxylic acid (37). It was prepared similarly from **34** (2.00 g, 10 mmol) and aqueous lithium hydroxide solution (2.40 g in 18 mL water) as described above to obtain the corresponding dicarboxylic acid **35**: 1.57 g (91% yield).

 **35** **$C_8H_{12}O_4$ (172)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3020, 2968, 2700-2500, 1703, 1701, 1624 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.92 (d, J = 6 Hz, 3H), 1.06 (d, J = 6 Hz, 3H), 2.05-2.35 (m, 1H), 3.40 (d, J = 10 Hz, 1H), 6.07 (s, 1H), 6.62 (s, 1H), 10.16 (bs, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 19.9, 20.8, 31.1, 52.3, 130.3, 136.7, 172.0, 179.3. **Anal. Calcd for $C_8H_{12}O_4$**: C, 55.81; H, 7.02. Found: C, 55.73; H, 7.00.

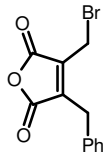
1,2-Dibromobutan-4-phenyl-2,3-dicarboxylic acid (30). A solution of bromine (1.92 g, 12 mmol) in CCl_4 (20 mL) was added dropwise to a solution of **29** (1.76 g, 8 mmol) in CCl_4 (30 mL) at room temperature and the reaction mixture was stirred for 6 h. The reaction mixture was then concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with saturated sodium metabisulphite, water and brine, dried over Na_2SO_4 and concentrated in vacuo, to obtain **30**: 3.03 g (~100% yield).

 **30** **$C_{12}H_{12}Br_2O_4$ (380)**	Thick oil. **IR** (Nujol): ν_{max} 2700-2500, 1757, 1713, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.00-3.40 (m, 2H), 3.64 (t, J = 6 Hz, 1H), 3.85-4.25 (m, 2H), 7.00-7.60 (m, 5H), 11.01 (bs, 2H). **Anal. Calcd for $C_{12}H_{12}Br_2O_4$**: C, 37.93; H, 3.18. Found: C, 37.97; H, 3.11.

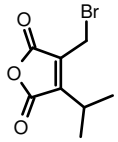
1,2-Dibromopentan-4-methyl-2,3-dicarboxylic acid (36). It was prepared similarly from **35** (1.38 g, 8 mmol) and bromine (1.92 g, 12 mmol) as described above to obtain the corresponding diacid **36**: 2.65 g (~ 100% yield).

 **36** **$C_8H_{12}Br_2O_4$ (332)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1714, 1711 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.80-1.40 (m, 6H), 2.00-2.45 (m, 1H), 3.30-3.55 (m, 1H), 3.80-4.50 (m, 2H), 8.76 (bs, 2H). **Anal. Calcd for $C_8H_{12}Br_2O_4$**: C, 28.94; H, 3.64. Found: C, 29.01; H, 3.66.

2-Bromomethyl-3-benzylmaleic anhydride (32). A solution of **30** (3.03 g, 8 mmol) in acetic anhydride (20 mL) was gently heated at reflux for 1.5 h and the reaction mixture was concentrated under vacuo at 50 ^{o}C. The residue was diluted with ethyl acetate (40 mL) and the organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo to obatin **32**: 2.24 g (~100% yield).

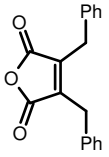
 **32** **$C_{12}H_9BrO_3$ (281)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1828, 1773, 1705, 1638 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.91 (s, 2H), 4.05 (s, 2H), 7.15-7.50 (m, 5H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 15.9, 30.7, 127.6, 128.9, 129.1, 133.6, 139.0, 144.7, 163.6, 164.6. **Anal. Calcd for $C_{12}H_9BrO_3$**: C, 51.27; H, 3.23. Found: C, 51.33; H, 3.18.

2-Bromomethyl-3-isopropylmaleic anhydride (38). It was prepared similarly from **36** (2.65 g, 8 mmol) and acetic anhydride (20 mL) as described above to obtain the corresponding anhydride **38**: 1.86 g (~ 100% yield).

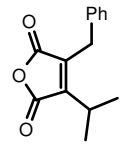
 **38** **$C_8H_9BrO_3$ (233)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1850, 1832, 1773, 1707, 1655 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 1.36 (d, J = 9 Hz, 6H), 3.09 (sept, J = 9 Hz, 1H), 4.21(s, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 15.8, 19.5, 26.7, 137.7, 151.2, 163.6, 163.7. **Anal. Calcd for $C_8H_9BrO_3$**: C, 41.23; H, 3.89. Found: C, 41.17; H, 3.85.

2,3-Dibenzylmaleic anhydride (9). A fresh solution of phenylmagnesium bromide in ether was prepared as follows. A solution of bromobenzene (3.93 g, 25 mmol) in LAH–dried ether (20 mL) was added at room temperature to magnesium turnings (1.80 g, 75 mmol) in ether (20 mL) under argon with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was stirred at room temperature for a further 4 h. This freshly generated Grignard reagent was added dropwise to a solution of **32** (1.41 g, 5 mmol) and copper (I) iodide (95 mg, 0.5 mmol) in ether (30 mL) and HMPA (10 mL) under argon at –5 to 0 ^{o}C over 15–20 min. with stirring. The reaction mixture was allowed to reach room temperature and stirred for a further 8 h. It was diluted with ether (30 mL) and acidified with 4 M H_2SO_4 (30 mL), and the aqueous layer was further extracted with

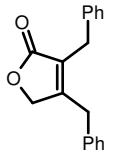
ether (30 mL x 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether-ethyl acetate (9.5:0.5) to give **9**: 626 mg (45% yield).

 **9** **$C_{18}H_{14}O_3$ (278)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1769 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.78 (s, 4H), 7.05-7.20 (m, 4H), 7.20-7.35 (m, 6H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 29.9, 127.1, 128.6, 128.8, 134.9, 142.7, 165.6. **Anal. Calcd for $C_{18}H_{14}O_3$**: C, 77.68; H, 5.07. Found: C, 77.75; H, 5.14.

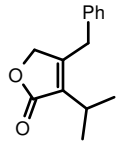
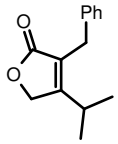
2-Benzyl-3-isopropylmaleic anhydride (39). Repetition of the same procedure described above using phenylmagnesium bromide [prepared from bromobenzene (3.93 g, 25 mmol) and magnesium (1.80 g, 75 mmol)], **38** (1.17 g, 5 mmol), copper (I) iodide (95 mg, 0.5 mmol) and HMPA (10 mL) gave the corresponding anhydride **39**: 495 mg (43% yield).

 **39** **$C_{14}H_{14}O_3$ (230)**	Thick oil. **IR** (Neat): ν_{max} 1773, 1703, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 1.28 (d, J = 9 Hz, 6H), 3.06 (sept, J = 9 Hz, 1H), 3.81 (s, 2H), 7.15-7.45 (m, 5H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 20.0, 26.4, 29.8, 126.2, 127.3, 127.9, 128.6, 129.0, 135.7, 141.2, 149.1, 164.4, 165.8. **Anal. Calcd for $C_{14}H_{14}O_3$**: C, 73.03; H, 6.13. Found: C, 72.96; H, 6.07.

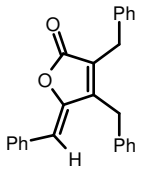
3,4-Dibenzyl-5*H*-furan-2-one (33). To a stirred solution of **9** (300 mg, 1.08 mmol) in THF, $NaBH_4$ (102 mg, 2.70 mmol) was added at 0 ºC. The reaction mixture was further stirred at 0 ºC for 2 h and then quenched with water and acidified with dilute HCl and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (20 mL), dried with Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate-petroleum ether (1:4) to furnish **33**: 259 mg (91% yield).

 **33** **$C_{18}H_{16}O_2$ (264)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1755, 1672, 1601 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.72 (s, 2H), 3.74 (s, 2H), 4.53 (s, 2H), 6.95-7.10 (m, 2H), 7.15-7.50 (m, 8H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 29.6, 33.5, 71.2, 126.6, 126.8, 127.2, 128.6, 128.7, 129.0, 130.1, 135.8, 138.0, 159.7, 174.6. **Anal. Calcd for $C_{18}H_{16}O_2$**: C, 81.79; H, 6.10. Found: C, 81.83; H, 6.05.

3-Isopropyl-4-benzyl-5*H*-furan-2-one (40) and 3-Benzyl-4-isopropyl-5*H*-furan-2-one (16). Repetition of above procedure using **39** (248 mg, 1.08 mmol) and $NaBH_4$ (102 mg, 2.70 mmol) gave the mixture of both the corresponding lactones (**40**:**16** = 40:60): 163 mg (70% yield). The mixture was separated by flash column chromatography using a mixture of ethyl acetate and petroleum ether (1:17) to furnish **40** (65 mg) and **16** (98 mg).

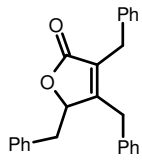
 **40** **$C_{14}H_{16}O_2$ (216)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1746, 1665, 1603 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 1.30 (d, J = 9 Hz, 6H), 2.97 (sept, J = 9 Hz, 1H), 3.77 (s, 2H), 4.49 (s, 2H), 7.15 (dd, J = 9 & 3 Hz, 2H), 7.25-7.45 (m, 3H). **Anal. Calcd for $C_{14}H_{16}O_2$**: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.52.
 **16** **$C_{14}H_{16}O_2$ (216)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1753, 1666, 1603 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 1.11 (d, J = 9 Hz, 6H), 3.08 (sept, J = 9 Hz, 1H), 3.63 (s, 2H), 4.73 (s, 2H), 7.10-7.40 (m, 5H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 20.9, 27.3, 29.4, 68.7, 124.5, 126.5, 128.4, 128.6, 138.2, 166.9, 175.1. **Anal. Calcd for $C_{14}H_{16}O_2$**: C, 77.75; H, 7.46. Found: C, 77.81; H, 7.53.

3,4-Dibenzyl-5*Z*-benzylidine-5*H*-furan-2-one (Maculalactone B, 1). To a stirred solution of lactone **33** (200 mg, 0.76 mmol) in methanol, piperidine (0.05 mL, 0.53 mmol) and benzaldehyde (0.08 mL, 0.76 mmol) were added at room temperature and the reaction mixture was stirred for another 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) furnished **1**: 206 mg (77% yield).

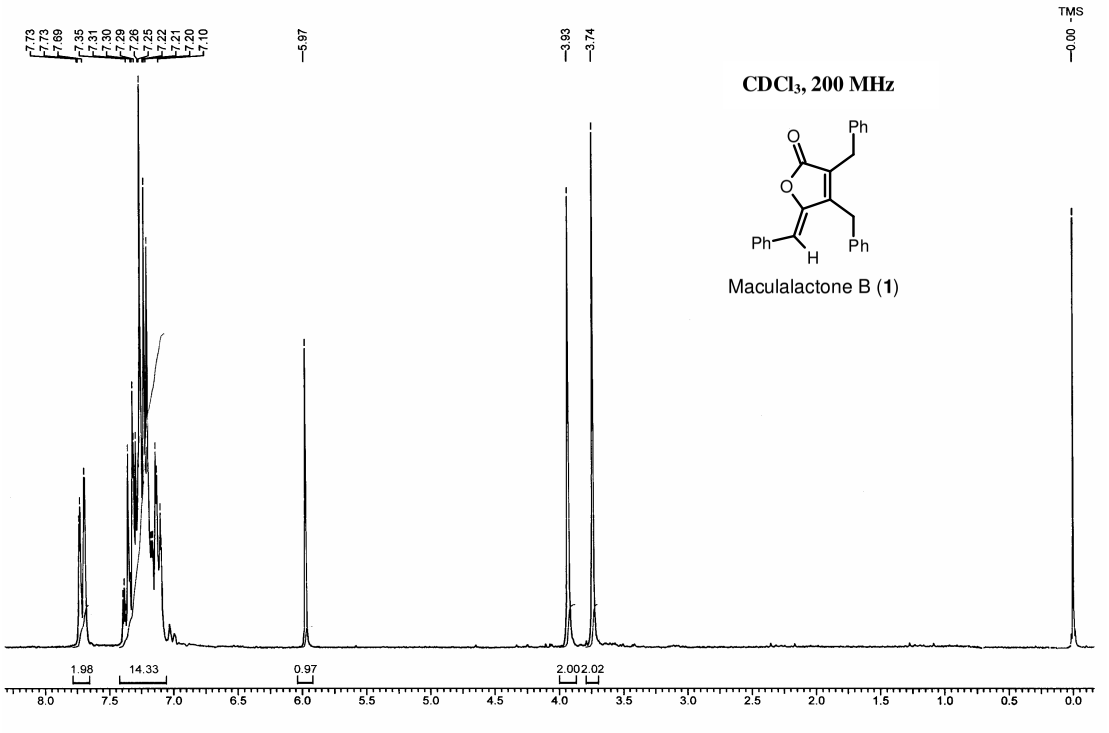
 **Maculalactone B (1)** **$C_{25}H_{20}O_2$ (352)**	**Mp**: 102-103 °C. **IR** ($CHCl_3$): ν_{max} 1755, 1649, 1603 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.74 (s, 2H), 3.93 (s, 2H), 5.97 (s, 1H), 7.05-7.40 (m, 13H), 7.71 (dd, *J* = 6 & 2 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 29.8, 30.6, 110.4, 126.7, 127.0, 127.7, 127.9, 128.2, 128.4, 128.6, 128.7, 128.8, 128.9, 129.3, 130.5, 133.1, 136.6, 137.5, 148.3, 150.7, 170.2. **Anal. Calcd for $C_{25}H_{20}O_2$**: C, 85.20; H, 5.72. Found: C, 85.27; H, 5.66.

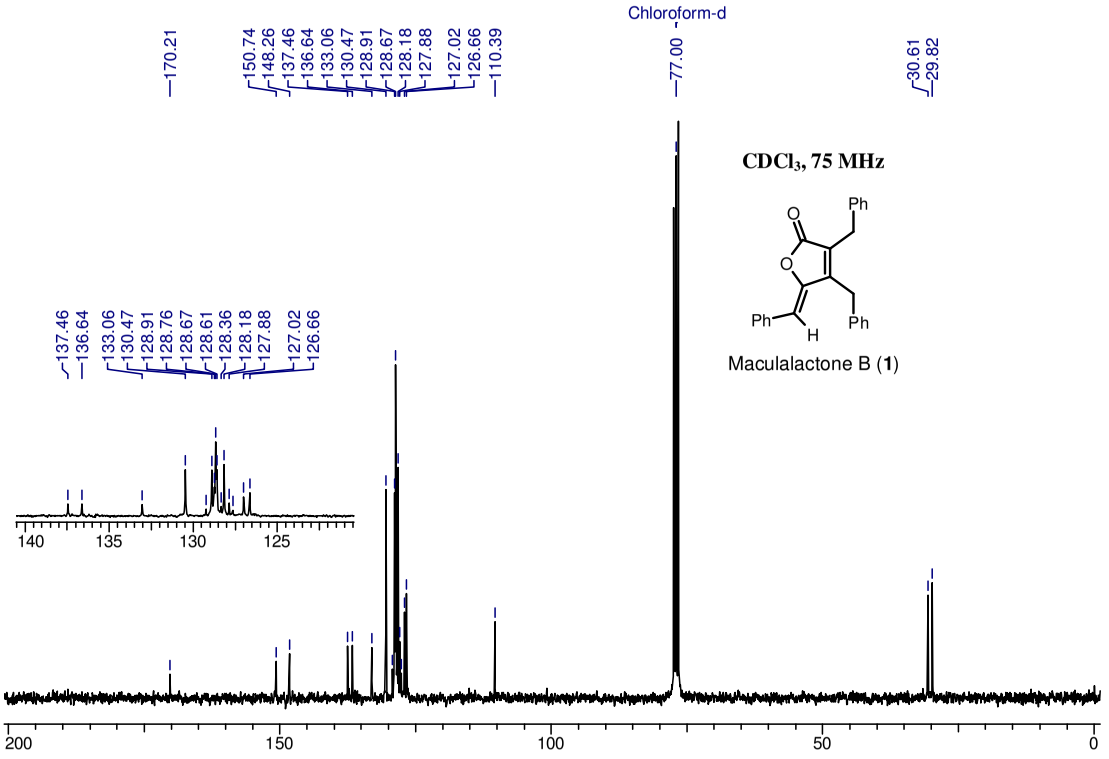
3,4-Dibenzyl-5*E*-benzylidine-5*H*-furan-2-one (Maculalactone C, 2). A solution of **1** (100 mg) in $CHCl_3$ (10 mL) was kept at room temperature for 8 days. Concentration of above $CHCl_3$ solution in vacuo furnished 100 mg of 50:50 mixture of **1** and **2**. In ^{1}H NMR ($CDCl_3$), the vinylic proton in **2** appeared at δ 6.84. The preparative HPLC separation of mixture of **1** and **2** is known.[2]

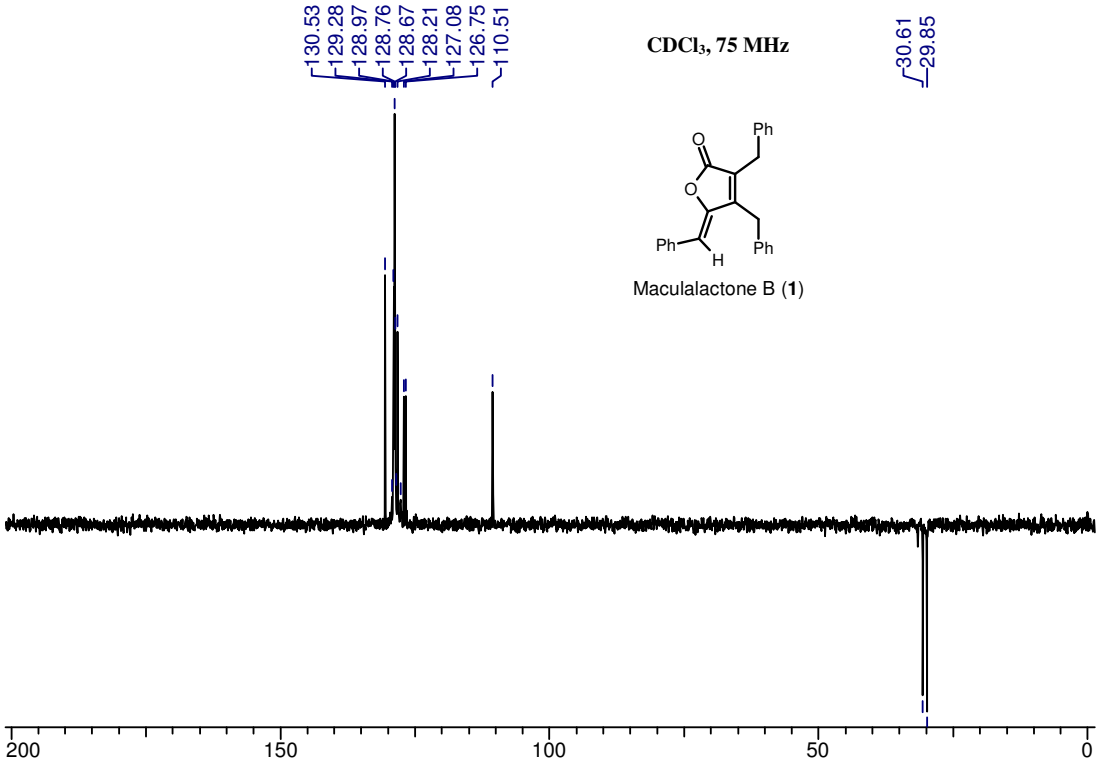
3,4,5-Tribenzyl-5*H*-furan-2-one (Maculalactone A, 3). A mixture of **1** (100 mg, 0.28 mmol) and catalytic amount of Pd/C in ethyl acetate (8 mL) was subjected to hydrogenation at 65-psi hydrogen pressure for 16 h at room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **3**: 75 mg (75% yield).

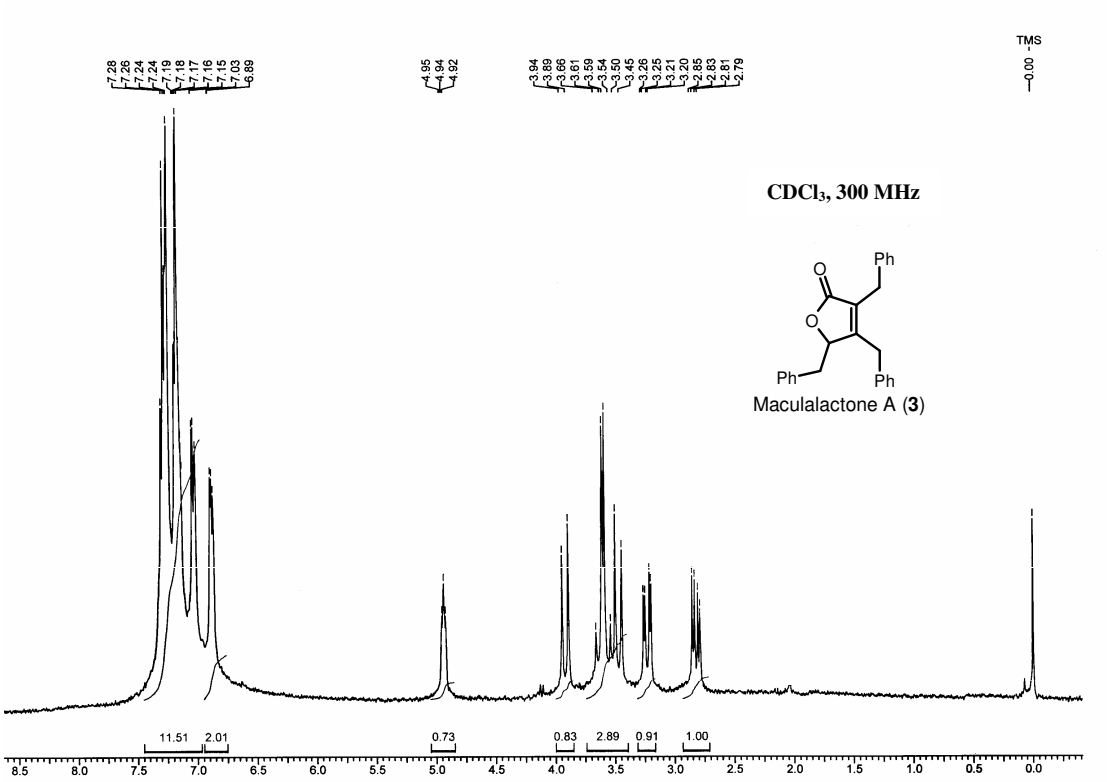
 **Maculalactone A (3)** **$C_{25}H_{22}O_2$ (354)**	Thick oil. **IR** (Neat): ν_{max} 1755, 1668, 1603 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 2.82 (dd, *J* = 12 & 6 Hz, 1H), 3.23 (dd, *J* = 12 & 3 Hz, 1H), 3.48 (d, *J* = 15 Hz, 1H), 3.57 (d, *J* = 15 Hz, 1H), 3.64 (d, *J* = 15 Hz, 1H), 3.92 (d, *J* = 15 Hz, 1H), 4.94 (dd, *J* = 6 & 3 Hz, 1H), 6.88 (m, 2H), 7.02 (m, 2H), 7.05-7.40 (m, 11H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 29.3, 33.1, 37.9, 81.5, 126.3, 127.1, 127.3, 128.1, 128.5 (3-carbons), 128.6, 129.0, 129.4, 134.8, 135.9, 137.6, 161.7, 173.5. **Anal. Calcd for $C_{25}H_{22}O_2$**: C, 84.72; H, 6.25. Found: C, 84.85; H, 6.12.

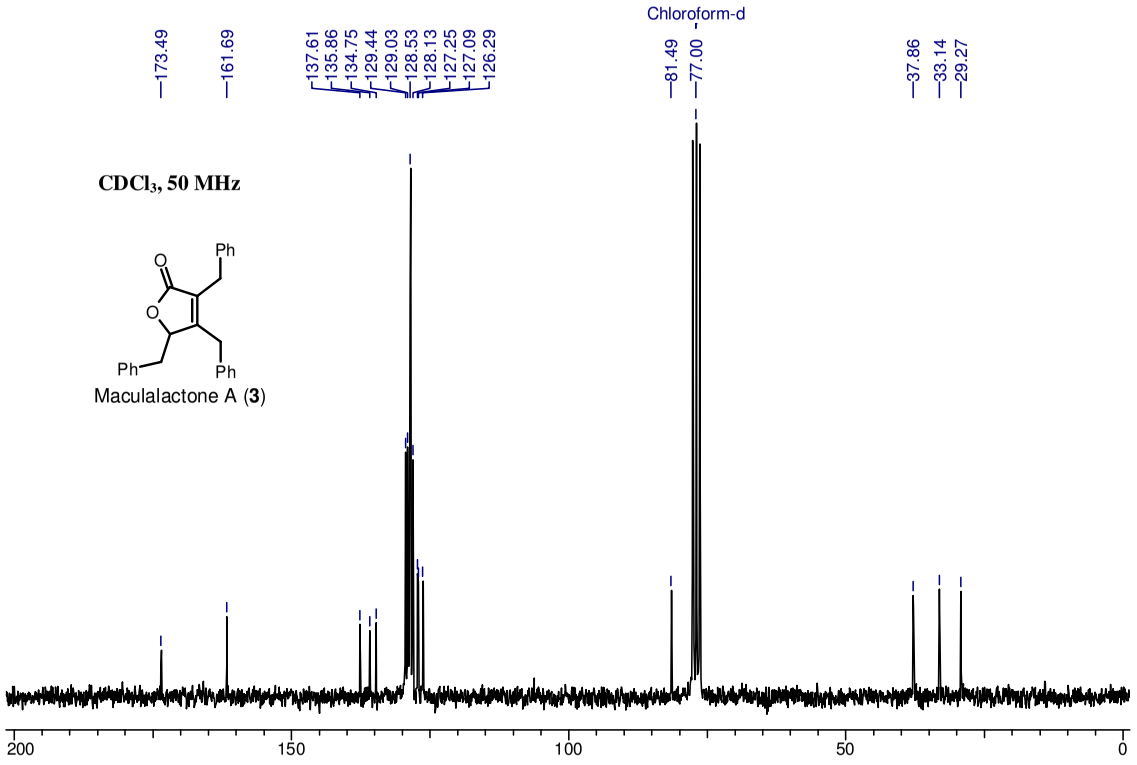
2A.5 Selected Spectra

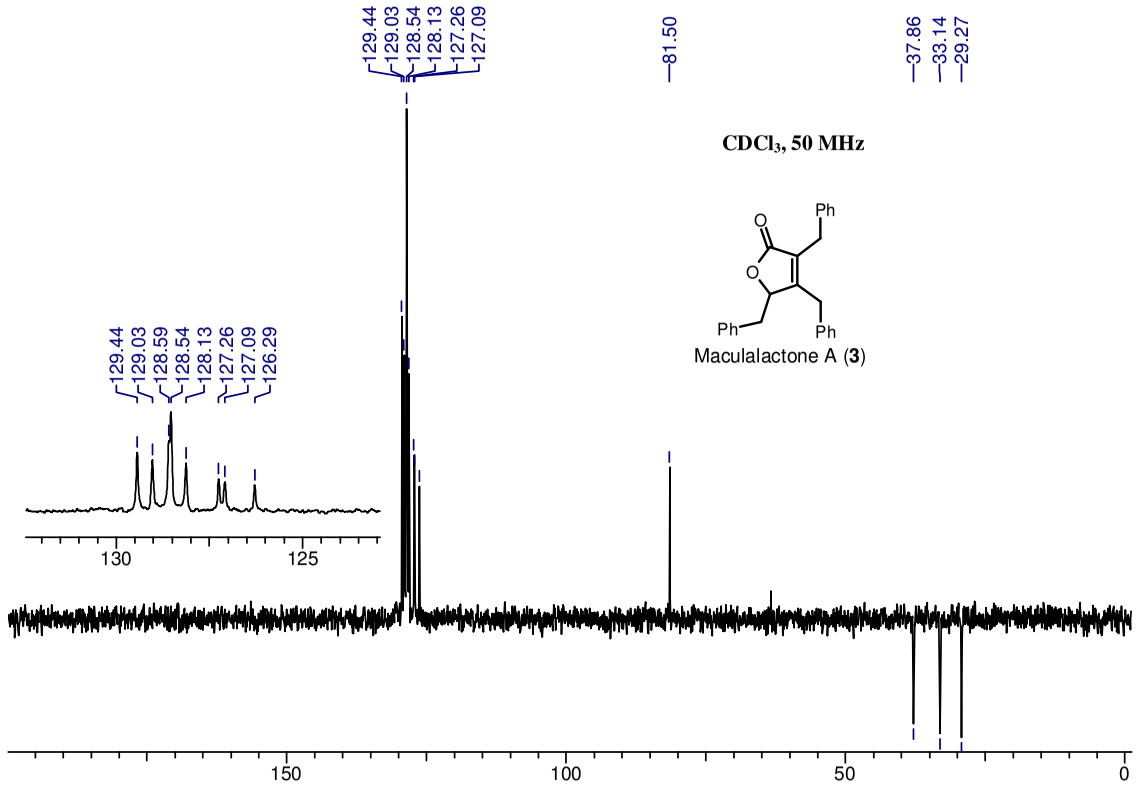

7.73
7.73
7.69
7.35
7.31
7.30
7.29
7.26
7.25
7.22
7.21
7.20
7.10
5.97
3.93
3.74
TMS
0.00
CDCl3, 200 MHz
Ph
O
O
Ph
Ph
H
Ph
Maculalactone B (1)
1.98
14.33
0.97
2.00
2.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

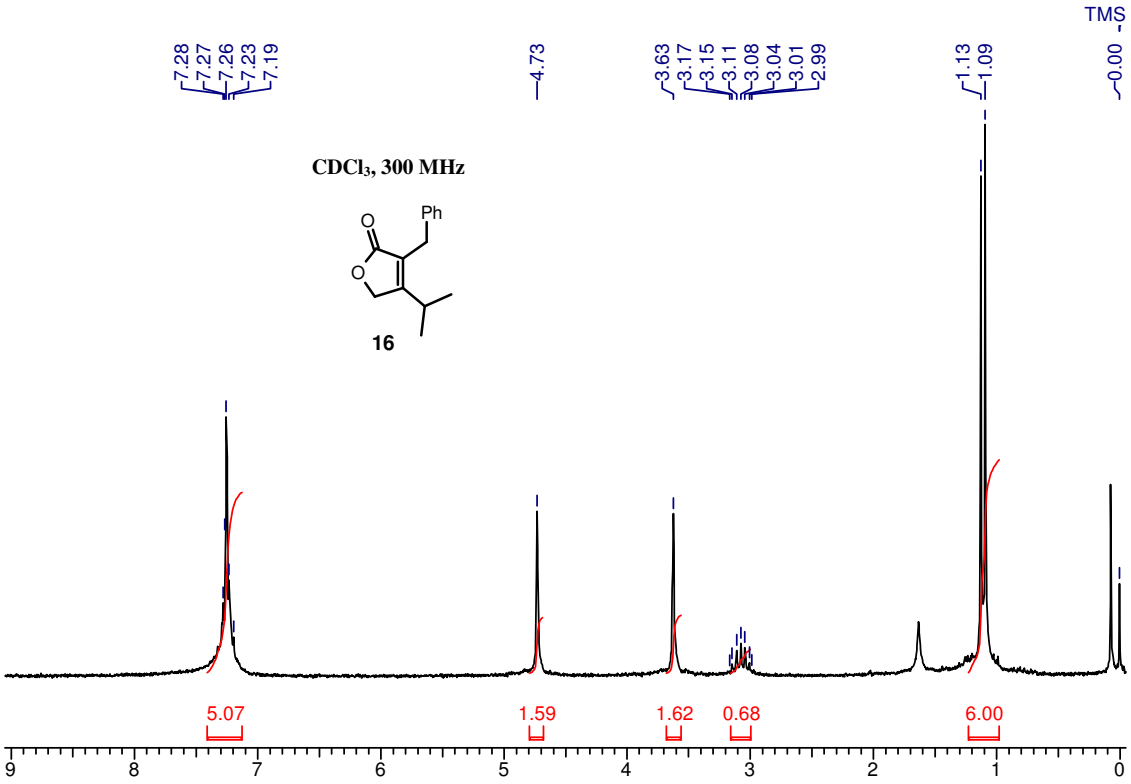

Chloroform-d
170.21
150.74
148.26
137.46
136.64
133.06
130.47
128.91
128.67
128.18
127.88
127.02
126.66
110.39
77.00
30.61
29.82
CDCl3, 75 MHz
Ph
O
O
Ph
Ph
H
Ph
Maculalactone B (1)
137.46
136.64
133.06
130.47
128.91
128.76
128.67
128.61
128.36
128.18
127.88
127.02
126.66
140
135
130
125
200
150
100
50
0

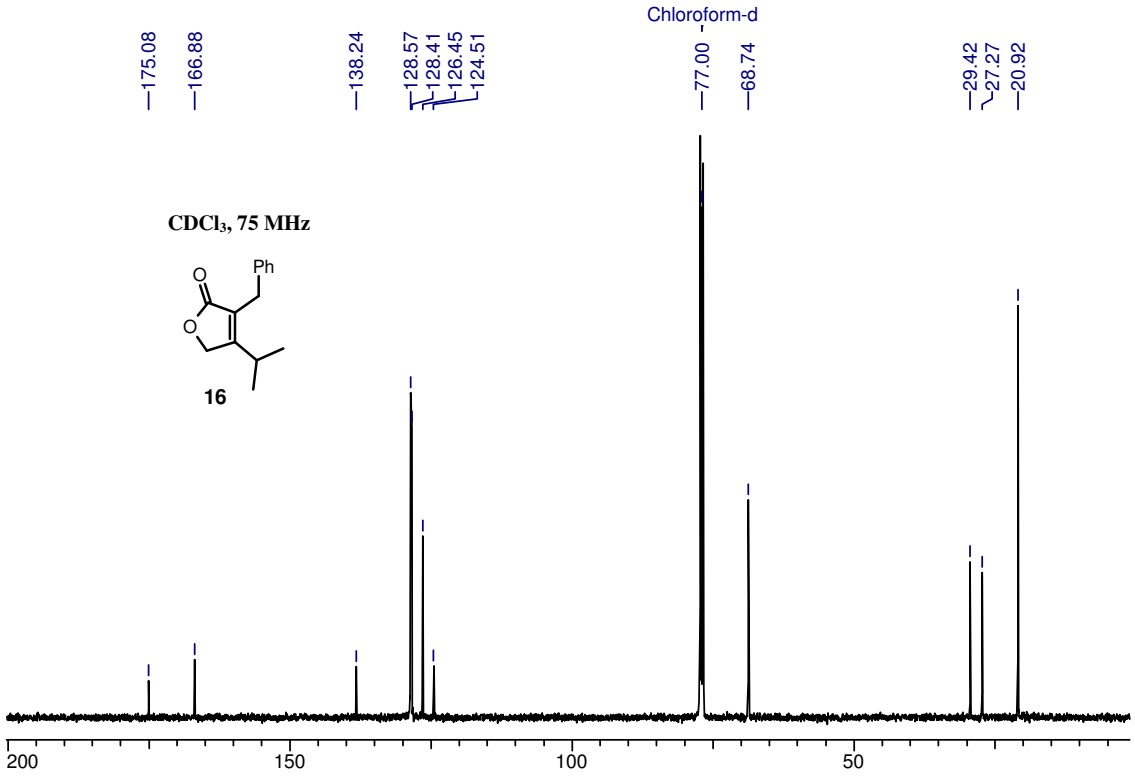

130.53
129.28
128.97
128.76
128.67
128.21
127.08
126.75
110.51
30.61
29.85
CDCl3, 75 MHz
Ph
O
O
Ph
Ph
H
Ph
Maculalactone B (1)
200
150
100
50
0

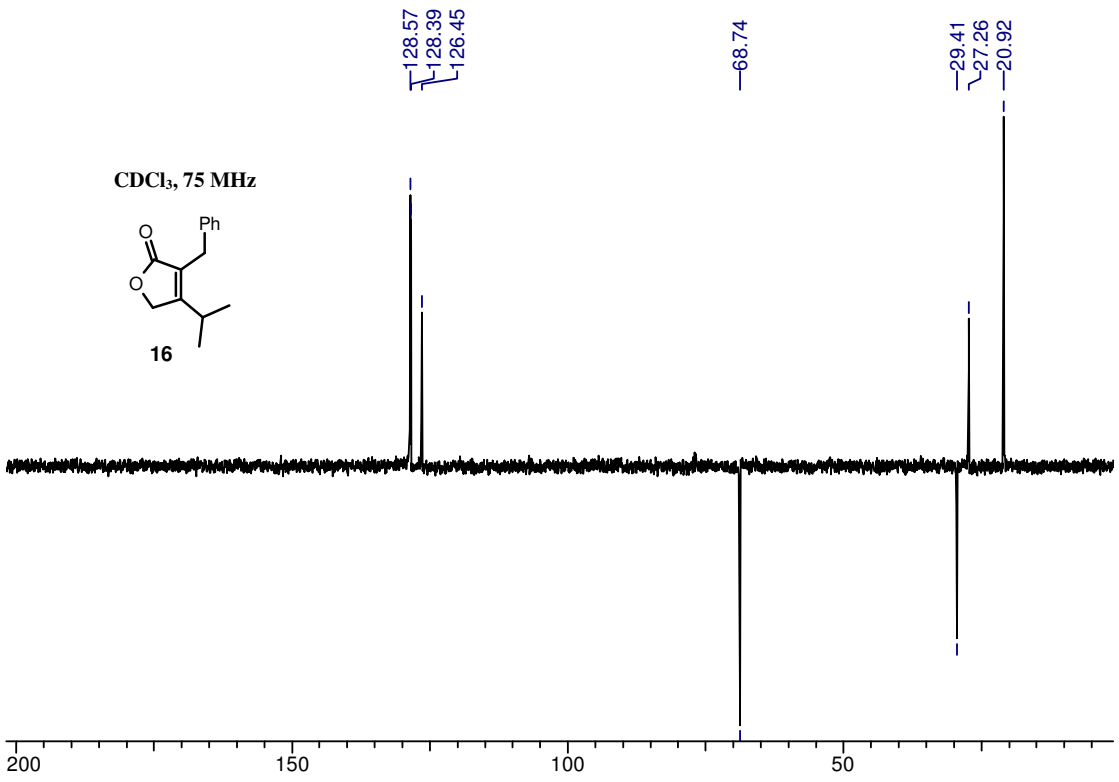

7.28
7.26
7.24
7.24
7.19
7.18
7.17
7.16
7.15
7.03
6.89
4.95
4.94
4.92
3.94
3.89
3.66
3.61
3.59
3.54
3.50
3.45
3.26
3.25
3.21
3.20
2.85
2.83
2.81
2.79
TMS
0.00
CDCl3, 300 MHz
O
Ph
O
Ph
Ph
Maculalactone A (3)
11.51
2.01
0.73
0.83
2.89
0.91
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
173.49
161.69
137.61
135.86
134.75
129.44
129.03
128.53
128.13
127.25
127.09
126.29
81.49
77.00
37.86
33.14
29.27
CDCl3, 50 MHz
Ph
O
O
Ph
Ph
Maculalactone A (3)
200
150
100
50
0


129.44
129.03
128.54
128.13
127.26
127.09
81.50
37.86
33.14
29.27
CDCl3, 50 MHz
129.44
129.03
128.59
128.54
128.13
127.26
127.09
126.29
130
125
Ph
O
O
Ph
Ph
Maculalactone A (3)
150
100
50
0


TMS
7.28
7.27
7.26
7.23
7.19
4.73
3.63
3.17
3.15
3.11
3.08
3.04
3.01
2.99
1.13
1.09
0.00
CDCl3, 300 MHz
Ph
O
O
16
5.07
1.59
1.62
0.68
6.00
9
8
7
6
5
4
3
2
1
0


Chloroform-d
175.08
166.88
138.24
128.57
128.41
126.45
124.51
77.00
68.74
29.42
27.27
20.92
CDCl3, 75 MHz
Ph
O
O
16
200
150
100
50


128.57
128.39
126.45
68.74
29.41
27.26
20.92
CDCl3, 75 MHz
O
Ph
O
16
200
150
100
50

2A.6 References

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2B. Section B

Synthesis of (±)-Norpandamarilactonines, (±)-Pandamarilactonines and Pandanamine

This section features the following topics:

2B Section B: Synthesis of (±)-Norpandamarilactonines, (±)-Pandamarilactonines and Pandanamine

2B.1 Background

The genus *Pandanus* comprises approximately 600 species that are widely distributed in tropical and subtropical regions. Several *Pandanus* species are used as a remedy for toothache, rheumatism and as a diuretic, cardiotonic, etc.[1] The plant *Pandanus amaryllifolius* is also known as fragrant screw pine, toei hom (Thiland), pandan mabango (Philipines), pandan wangi (Malay) and daun pandan (Indonesia). The leaves of this plant are used as food flavoring and in traditional medicine in the Philippines, Thailand, and Indonesia. Hot water extracts of the root of this plant show hypoglycemic activity. Takayama et al. isolated two new diastereomeric pyrrolidine alkaloids, pandamarilactonine A (**1**) and B (**2**) (Figure 1) having γ-alkylidene α,β-unsaturated γ-lactone from this plant species, whose structures were determined using high-resolution FABMS analysis, ^{1}H, ^{13}C NMR, UV, COSY, NOESY, HMQC, HMBC spectra and a new NMR technique, viz., PFG J-HMBC 2D spectroscopy and then confirmed the structures by biomimetic total synthesis.[2] Pandamarilactonine A (**1**) was obtained as an amorphous powder, exhibiting $[\alpha]^{23}_{D}$ = +35.0 (c 4.37, $CHCl_3$) and pandamarilactonine B (**2**) was also obtained as an amorphous powder, exhibiting $[\alpha]^{23}_{D}$ = 0 (c 0.20, $CHCl_3$). Again, same group of authors isolated two new pyrrolidine alkaloids, pandamarilactonine C (**3**) and D (**4**) from the same plant species.[3] Their structures were determined using FABMS analysis, ^{1}H, ^{13}C NMR, UV, COSY, NOESY, HMQC, HMBC and confirmed the structures and the relative stereochemistry at the C-14 and C-15 positions by total synthesis of pandamarilactonine C (**3**) and its related alkaloid pandamarilactonine A (**1**).[3] Based on the total synthesis of these alkaloids, the relative stereochemistry of pandamarilactonine A (**1**) and B (**2**), which was previously proposed by spectroscopic analysis,[2] was revised. A novel alkaloid having a symmetrical structure, which was anticipated to be a biogenetic precursor of pandamarilactonines was isolated by Talayama et al. from pandanus amaryllifolius[4] and its structure was determined using high resolution FABMS analysis, ^{1}H, ^{13}C NMR, UV, COSY, NOESY, HMQC, HMBC and this new alkaloid pandanamine (**5**) was identical with the synthetic compound,[2] which was previously prepared as a synthetic intermediate of pandamarilactonines. Two new diastereomeric alkaloids having a pyrrolidinyl-α,β-unsaturated γ-lactone skeleton were isolated as minor constituents by Takayama et al. from

the same plant species.[5] These interesting molecules norpandamarilactonine A (**6**) and norpandamarilactonine B (**7**), possessing the substructure of the known alkaloids pandamarilactonine A-D were first characterized by spectroscopic analysis and then the structures were confirmed by total synthesis.[5]

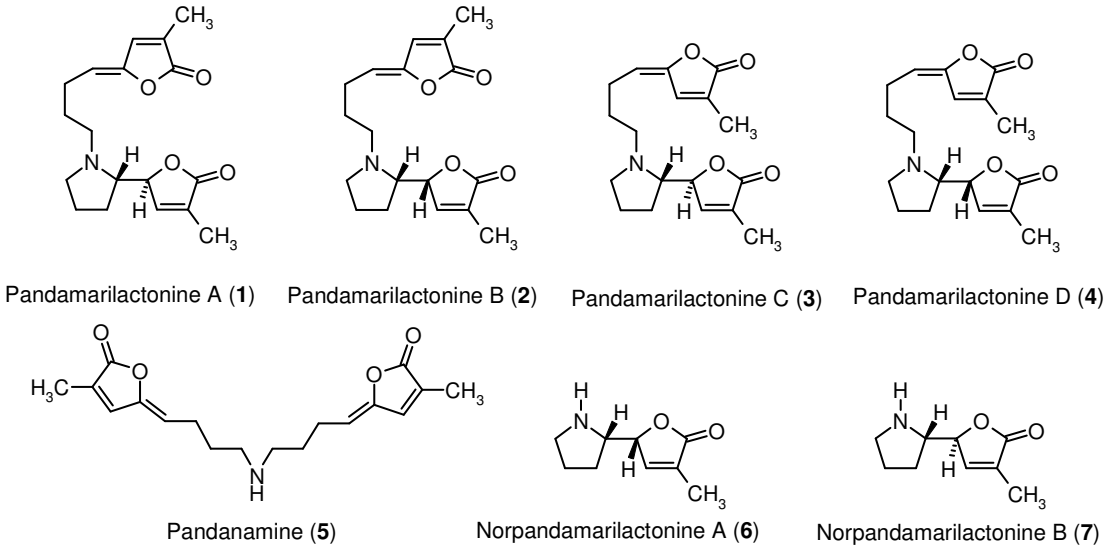


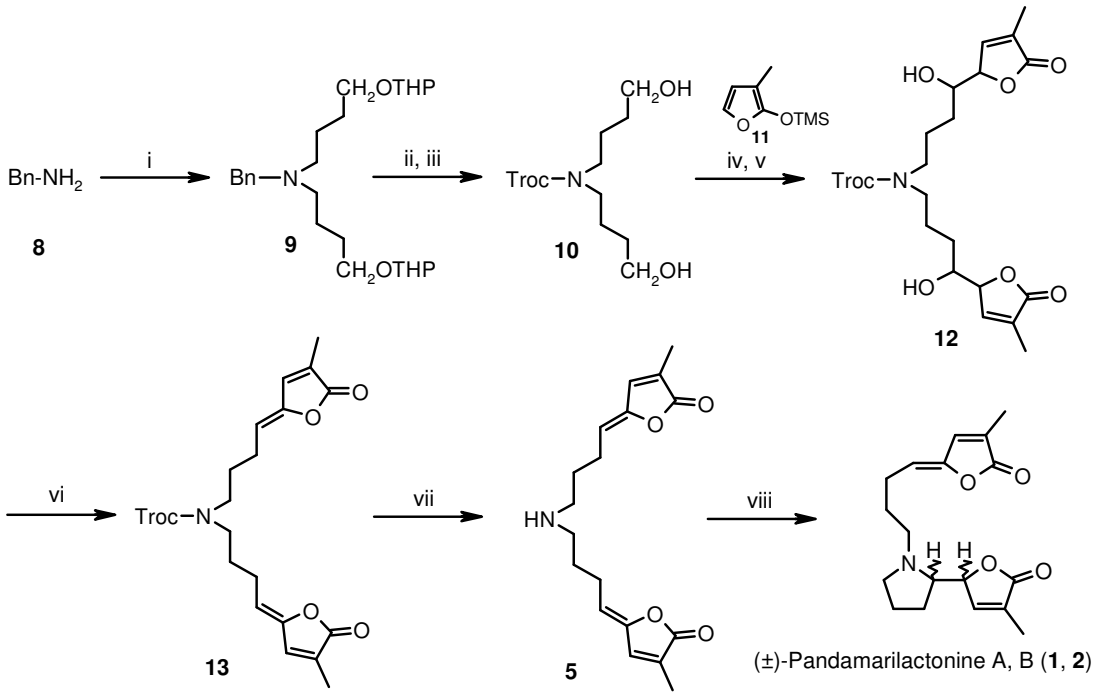
Figure 1. Pandanus alkaloids

2B.1.1 Synthetic Approaches Towards Norpandamarilactonines and Pandamarilactonines

Prior to our work,[6] number of total syntheses of norpandamarilactonines A-B and pandamarilactonines A-D were reported in the literature in racemic as well as in enantiomerically pure form which are discussed briefly below.

[A] Takayama's Synthetic Approach Towards (±)-Pandamarilactonine A and B

The first synthesis of (±)-pandamarilactonine A (**1**) and B (**2**) was reported by Takayama et al. (Scheme 1).[2] They started the synthesis from benzylamine (**8**), which on double alkylation with THP protected 4-chloro-1-butanol furnished tertiary amine **9**. Replacement of benzyl group by *β*,*β*,*β*-trichloroethoxycarbonyl group (Troc) followed by THP deprotection, swern oxidation of the resulting alcohol **10** to aldehyde and acid catalysed condensation of this aldehyde with silyloxyfuran **11** gave condensed product **12**. Next, hydroxyl group was converted to TMS-ether followed by base catalyzed elimination and Troc-deprotection of resulted amine **13** furnished pandanamine (**5**).



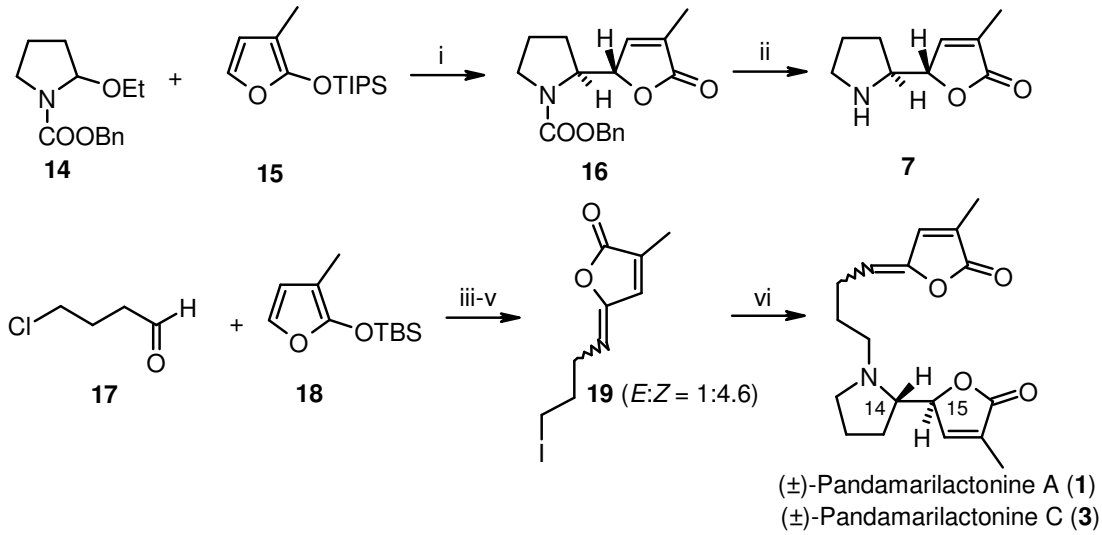
Scheme 1. *Reagents, conditions and yields*: (i) 2-(4-Chlorobutoxy)-tetrahydro-2*H*-pyran, K_2CO_3, NaI, CH_3CN, reflux, 18 h (61%); (ii) Troc-Cl, CH_3CN, rt, 1.5 h (76%); (iii) *p*-TSA, CH_3OH, 0 ^oC, 1.5 h (80%); (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 60 ^oC to rt (98%); (v) **11**, $BF_3.Et_2O$, CH_2Cl_2, -78 ^oC, 1 h (99%); (vi) TMSCl, DBU, $CHCl_3$, reflux, 1 h (41%); (vii) Zn, AcOH, rt, 4 h; (vii) Cat. CF_3COOH, CH_3CN, 80 ^oC, 5 h (**1** = 9%, **2** = 9%, 2-steps).

This amine **5** on acid catalyzed intramolecular cyclization gave (±)-pandamarilactonine A (**1**) and B (**2**) with 2.7% overall yield in 8-steps.

[B] Takayama's Synthetic Approach Towards (±)-Norpandamarilactonine B, (±)-Pandamarilactonine A and C

Takayama et al. reported the synthesis of (±)-pandamarilactonine A (**1**) and C (**3**) to confirm the structures and relative stereochemistry at C-14 and C-15 positions in these alkaloids.[3,5] Compound **16** whose stereochemistry at the vicinal positions was established to be *threo* by X-ray analysis was prepared by vinylogous Mannich coupling reaction[7] of carbamate **14** and silyloxyfuran **15**[7] (Scheme 2). The cbz-deprotection of amine **16** gave (±)-norpandamarilactonine B (**7**) in 69% overall yield (2-steps) and thus the relative stereochemistry was determined to be *threo* in this natural product **7**. Acid catalyzed condensation of aldehyde **17** with silyloxyfuran **18**[7] followed by dehydration of the resulting alcohol, halogen exchange furnished iodo compound **19** (*E*:*Z* = 1:4.6, 23%, 3-

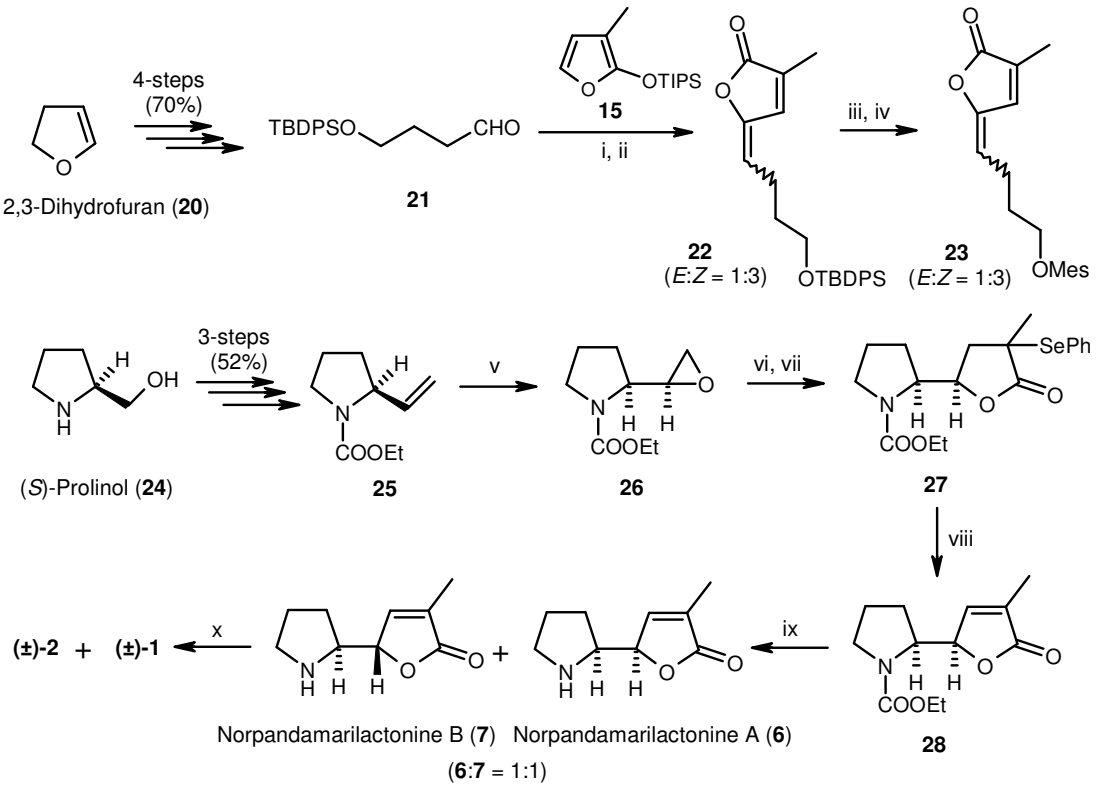
steps), which was subsequently condensed with amine **7** in presence of K_2CO_3 to obtain (±)-pandamarilactonine A (**1**, 33%) and B (**2**, 7%) having *threo* geometry at C-14 and C-15 positions.



Scheme 2. *Reagents, conditions and yields*: (i) (a) $BF_3.OEt_2$, CH_2Cl_2, -78 ^oC (*threo*:*erythro* = 4:1), (b) Separation of diastereomers (*threo* = 73%); (ii) TMSI, CH_3CN, rt (94%); (iii) $BF_3.OEt_2$, CH_2Cl_2; (iv) Tf_2O, pyridine, CH_2Cl_2 (48%, 2-steps); (v) NaI, acetone, rt (47%); (vi) **7**, K_2CO_3, CH_3CN, rt (**1** = 33%, **3** = 7%).

[C] Figueredo's Synthetic Approach Towards (±)-Norpandamarilactonine A-B and (±)-Pandamarilactonine A-B

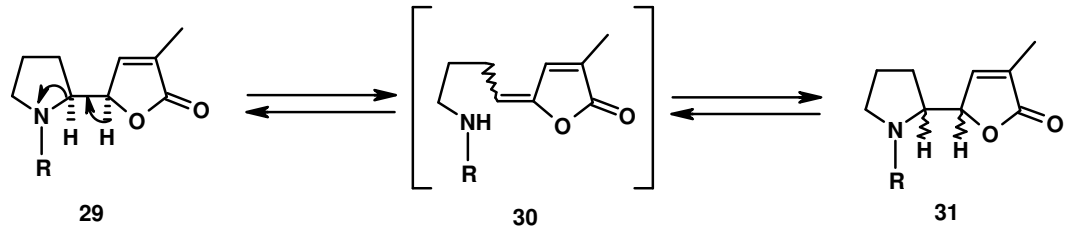
Figueredo and co-workers reported another synthesis of (±)-norpandamarilactonine A-B and (±)-pandamarilactonine A-B starting from (*S*)-prolinol.[8] Aldehyde **21** was synthesized from 2,3-dihydrofuran (**20**),[9] which after the vinylogous Mukaiyama reaction[10] with the silyloxy furan **15**, prepared by the Martin methodology[7] followed by treatment of the resulting alcohol with TMSCl/DBU furnished olefins **22** (Scheme 3). Desilylation of **22** followed by treatment with mesylchloride gave sulfonate **23** with 34% overall yield in 8-steps (*E*:*Z* = 1:3). The synthesis of the pyrrolidine fragment was accomplished starting from the carbamate **25**, which was prepared from (*S*)-prolinol (**24**).[11] Oxidation of **25** with *m*-CPBA produced both the *erythro* and *threo* oxiranes (*erythro*/*threo* =1.5:1). The oxiranes were separated and the major isomer **26** was converted into butyrolactone **27**, by a two-step protocol consisting in addition of the dianion of 2-phenylselenopropionic acid to **26** followed by acid induced lactonisation. The oxidation of the selenide function in **27** with consequent thermal elimination gave butenolide **28**. Cleavage of the carbamate in **28**



Scheme 3. *Reagents, conditions and yields*: (i) **15**, $BF_3.Et_2O$, CH_2Cl_2, -78 ^oC, 2 h (82%); (ii) TMSCl, DBU, $CHCl_3$, reflux, 1 h (94%); (iii) Bu_4NF, THF, rt, 3 h (86%); (iv) MesCl, pyridine, CH_2Cl_2, rt, 12 h (74%); (v) (a) *m*-CPBA, $CHCl_3$, 24 h, (b) Separation of diastereomers (77%); (vi) $CH_3CH(PhSe)COOH$ (2 equiv.), LDA, 0 ^oC to rt, 1.5 h; (vii) AcOH, THF, reflux, 16 h; (viii) H_2O_2, AcOH, 0 ^oC, 45 min. (61%, 3-steps); (ix) TMSI, $CHCl_3$, reflux, 5 h (84%); (x) **23**, pyridine, DMF, 60 ^oC, 3 days (44%).

$\{[\alpha]^{20}_D = -33$ (c 0.9, EtOH)$\}$ with partial concomitant epimerisation of the stereogenic centre of the lactone moiety, furnished a 1:1 mixture of the two norpandamarilactonine A (**6**) $\{[\alpha]^{20}_D = -7$ (c 1.5, $CHCl_3)\}$ and B (**7**) $\{[\alpha]^{20}_D = -3$ (c 2.6, $CHCl_3)\}$ in 9% overall yield (9-steps). They suspected that the reason for such low specific rotation could be that, besides partial epimerization, partial racemization had occurred to some extent during the carbamate deprotection process. They proposed a mechanism which causes configurational instability of these alkaloids, involving *β*-elimination-conjugate addition and operates in neutral or basic media (Scheme 4). They condensed **6**+**7** with mesylbutenolide **23** in presence of pyridine to obtain (±)-pandamarilactonine A (**1**) and B (**2**) in 44% yield (**1**:**2** = 1:1).

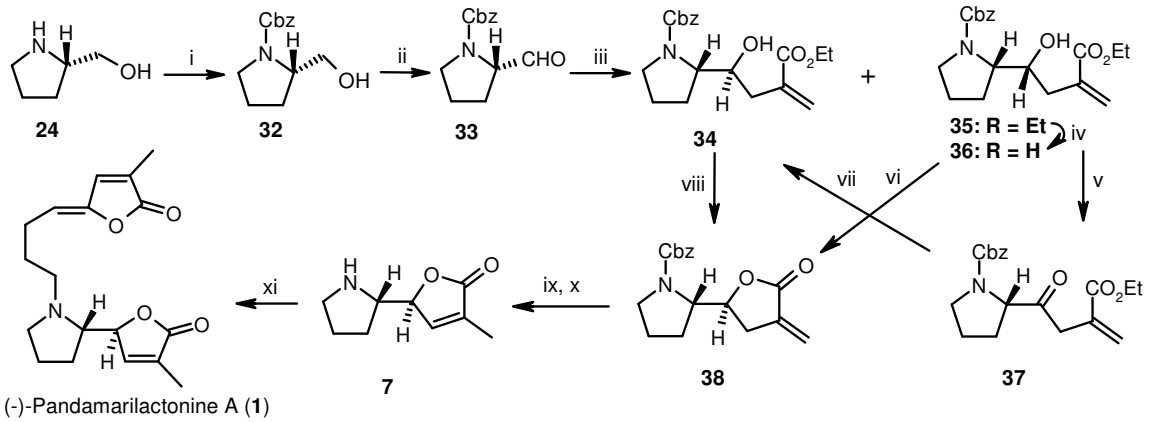
Scheme 4



29 **30** **31**

[D] Takayama's Synthetic Approach Towards (–)-Norpandamarilactonine B and (–)-Pandamarilactonine A

Takayama et al. reported the first asymmetric total synthesis of (–)-pandamarilactonine A starting from L-prolinol (**24**).[12] The -Cbz protection of amine and subsequent Swern oxidation of alcoholic group of L-prolinol (**24**) gave aldehyde **33**, which on Reformatsky-type condensation with ethyl 2-(bromomethyl)acrylate furnished hydroxyesters **34** and **35** (*erythro*:*threo* = 4:1) (Scheme 5). The *erythro* isomer **35** was transformed into the *threo* isomer **34** either by oxidation-reduction sequence or directly by the intramolecular Mitsunobo reaction of acid **36**, which was prepared by alkaline hydrolysis of **35**. The alcohol **34** on acid catalyzed lactonization followed by exocyclic to endocyclic double bond isomerization and carbamate deprotection gave (–)-norpandamarilactonine B (**7**), which on condensation with iodobutenolide **19**[3] gave (–)-pandamarilactonine A (**1**) in 24% overall yield (7-steps). Thus they determined the absolute stereochemistry in natural pandamarilactonine A (**1**) to be -14*R* and -15*R*.

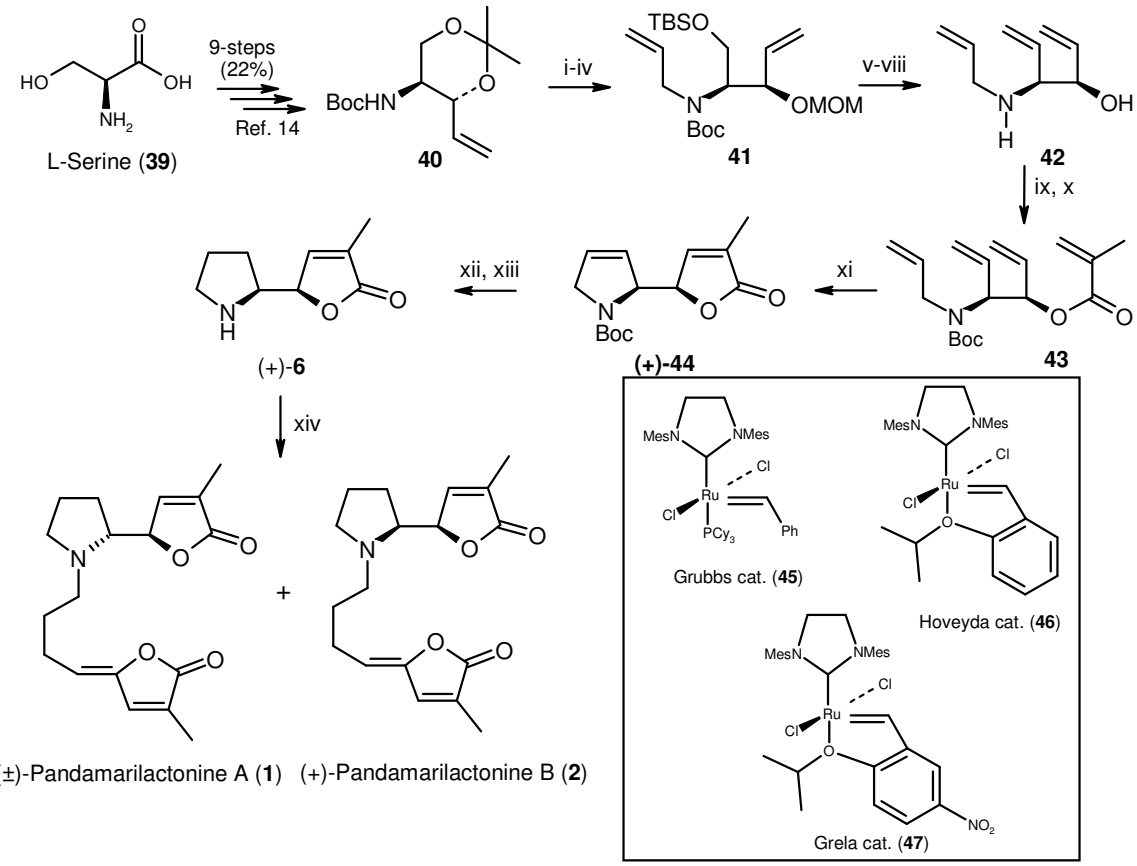


(-)-Pandamarilactonine A (**1**)

Scheme 5. *Reagents, conditions and yields*: (i) Cbz-Cl, K_2CO_3, CH_3CN; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 60 ^oC to rt (91%, 2-steps); (iii) Ethyl 2-(bromomethyl)acrylate, Zn, THF-aq. saturated NH_4Cl (52%); (iv) LiOH, aq. THF (~100%); (v) DMP, CH_2Cl_2, rt (~100%); (vi) DTAD, PPh_3, THF, rt (~100%); (vii) $NaBH_4$, MeOH, -20 ^oC (86%); (viii) TFA, CH_2Cl_2, rt (90%); (ix) 5 Mol% Et_3SiH, 10 mol% $Rh(PPh_3)_3Cl$, toluene, reflux (86%); (x) TMSI, CH_3CN, -15 ^oC (~100%); (xi) **19**, Ag_2CO_3, CH_3CN, rt (66%).

[E] Honda's Synthetic Approach Towards (+)-Norpandamarilactonine A, (+)-Pandamarilactonine B and (±)-Pandamarilactonine A

Very recently, Honda et al.[13] reported a synthesis of enantiomerically pure (+)-norpandamarilactonine A (**6**) by employing a double ring-closing metathesis of a tetraene derivative (**43**) as a key reaction, which was subsequently converted to (±)-pandamarilactonine A (**1**) and (+)-pandamarilactonine B (**2**) (Scheme 6). They prepared tetraene **43** starting from Boc-protected amine **40**, which was in turn prepared from L-serine,[14] via allylation, acetonide deprotection, protection of primary alcohol as TBDMS ether, protection of secondary alcohol as MOM ether, TBDMS deprotection, oxidation of the resulting alcohol to aldehyde, followed by methylenation of aldehyde, acid catalyzed

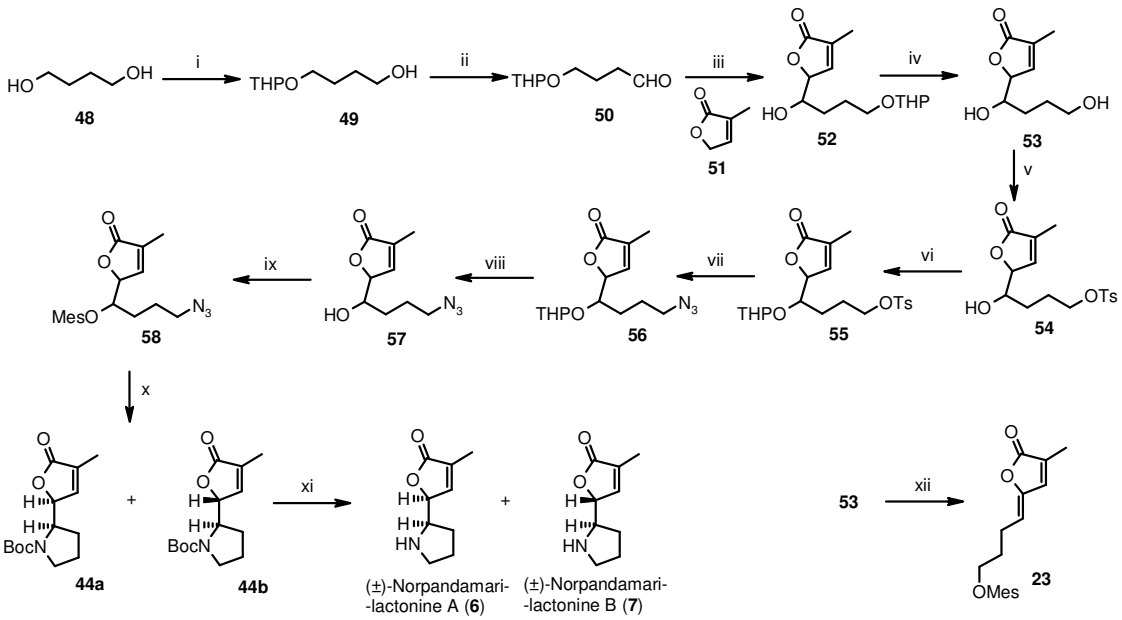


Scheme 6. *Reagents, conditions and yields*: (i) Allyl iodide, NaH, DMF, 0 ^{o}C to rt, 2 h (63%); (ii) *p*-TsOH, MeOH, rt, 3 h (92%); (iii) TBDMSCl, imidazole, DMF, rt, 3 h (93%); (iv) MOMCl, $^{i}Pr_2NEt$, DMAP, CH_2Cl_2, 0 ^{o}C to rt, 8 h (77%); (v) TBAF, THF, rt, 10 h (95%); (vi) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h (96%); (vii) $CH_3P^{+}Ph_3Br^{-}$, *n*-BuLi, THF, -78 ^{o}C, 2 h (85%); (viii) 10% HCl, MeOH, 70 ^{o}C, 2 h (73%); (ix) Boc_2O, Et_3N, THF, rt, 8 h (76%); (x) Methacrylic acid, DCC, DMAP, CH_2Cl_2, 0 ^{o}C to rt, 16 h (86%); (xi) Grela cat. (**47**), 60 ^{o}C, benzene, 20 h (76%); (xii) TMSOTf, 2,6-lutidine, CH_2Cl_2, -20 ^{o}C, 10 min. (43%); (xiii) Wilkinson cat., H_2, CH_2Cl_2, rt, 18 h (95%); (xiv) **19**, Ag_2CO_3, CH_3CN, rt, 24 h (**1** = 15%, **2** = 62%).

hydrolysis of MOM and Boc, reprotection of amino group as carbamate and esterification of secondary alcohol with methacrylic acid afforded tetraene derivative **43** in 15% overall yield (10-steps) as shown in scheme 6. They then tried the double RCM using different catalyst, such as Grubb's catalyst (**45**), Hoveyda catalyst (**46**) and Grela catalyst (**47**). The most effective catalyst was Grela catalyst (**47**) and using the same at 60 ^{o}C in 20 h they obtained highest yield (76%) of butenolide **44**, which on Boc-deprotection, regioselective reduction of double bond in pyrrol ring furnished (+)-norpandamarilactonine A (**6**) with 31% overall yield in 3-steps. Condensation of **1** with iodobutenolide **19**[3] in presence of Ag_2CO_3 furnished (+)-pandamarilactonine B (**2**, 62%) and epimerized and racemized product (±)-pandamarilactonine A (**1**, 15%).

2B.2 Present Work: Results and Discussion

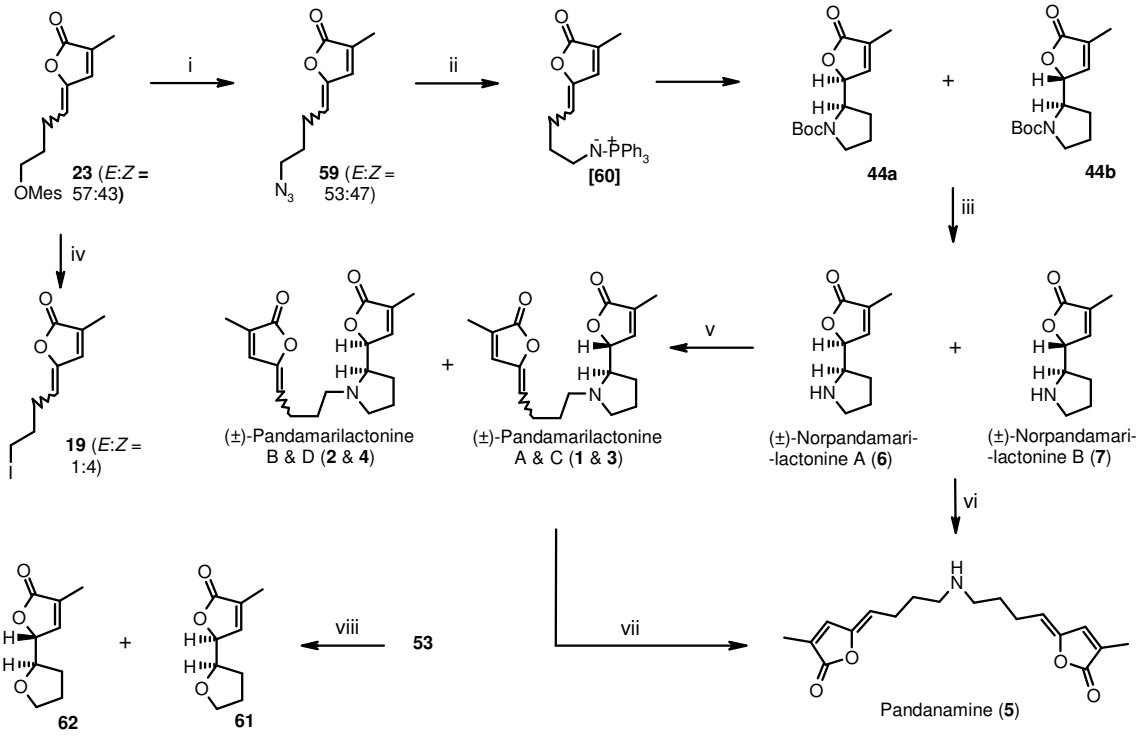
We envisaged the synthesis of norpandamarilactonines A & B (**1** & **2**) from the mesylazide **58** by chemoselective reduction of azide to amine followed by cyclization, would furnish natural products **6** and **7**, which on condensation with suitably substituted iodobutenolide **19** would furnish pandamarilactonines A-D (**1**-**4**). To synthesize the mesylazide **58**, we started from 1,4-butanediol (**48**), which on mono –OTHP protection with one equivalent of 3,4-dihydro-2*H*-pyran, followed by PCC oxidation of the resulting alcohol **49** in presence of NaOAc buffer gave the aldehyde **50** with 60% overall yield in 2-steps (Scheme 7). The base catalyzed condensation of 3-methyl-2(5*H*)-furanone (**51**) with the aldehyde **50** gave the condensed product **52** in 76% yield, which on –OTHP deprotection furnished lactone-diol **53** in 91% yield (*erythro*:*threo* = 64:36).[15] Using one equivalent of TsCl, diol **53** was converted regioselectively to monotosyl derivative **54** (*erythro*:*threo* = 64:36)[15] in presence of Et_3N as base with 85% yield. Then we made one attempt to synthesize directly hydroxyazide **57** from tosylate **54** by chemoselective substitution reaction with NaN_3, but this reaction furnished a mixture of azide **57** and cyclic compounds *α*-methyl-*γ*-tetrahydrofuranylbutyrolactones (**61**) and (**62**) (Scheme 8). The diol **53** on treatment with phosphorous pentoxide in refluxing toluene also gave the same column separable diastereomeric mixture of **61** and **62** in nearly 1:1 ratio with 88% yield, via the intramolecular dehydrative cyclization pathway.[15] Then we protected hydroxyl group of **54** as –OTHP, using 3,4-dihydro-2*H*-pyran and PPTS as catalyst to obtain tosylbutenolide **55,** which on chemoselective substitution reaction with



Scheme 7. *Reagents, conditions and yields*: (i) 3,4-Dihydro-2*H*-pyran, H^+/HCl, rt, 4 h (76%); (ii) Pyridinium chlorochromate, NaOAc, CH_2Cl_2, rt, 1 h (79%); (iii) 3-Methyl-2(5*H*)-furanone, LDA, THF, –78 ^oC to rt, 2 h (76%); (iv) PPTS, C_2H_5OH, 56 ^oC, 24 h (91%); (v) *p*-TsCl, Et_3N, DMAP, DCM, 0 ^oC to rt, 1.5 h (85%); (vi) 3,4-Dihydro-2*H*-pyran, PPTS, DCM, rt, 12 h (91%); (vii) NaN_3, DMF, rt, 12 h (88%); (viii) *p*-TSA, CH_3OH, rt, 1.5 h (95%); (ix) CH_3SO_2Cl, Et_3N, DCM, -10 ^oC, 2.5 h (91%); (x) (a) PPh_3, THF, rt, 0.5 h, (b) H_2O, rt, 12 h, (c) Boc_2O, DCM, Et_3N, 16 h (**44a**:**44b** = 3:7, 31%); (xi) TMSOTf, DCM, –20 ^oC to –5 ^oC, 2.5 h (**6**:**7** = 1:1, 99%); (xii) CH_3SO_2Cl, Et_3N, DCM, rt, 24 h (77%).

sodium azide yielded, the azidobutenolide **56** in 88% overall yield (2-steps). Acid catalyzed deprotection of –OTHP gave secondary alcohol **57** (*erythro*:*threo* = 55:45)[15] in 95% yield, which on mesylation at low temperature (–10 ^oC) furnished mesylazide **58** (*erythro*:*threo* = 61:39)[15] in 91% yield. Staudinger reduction[16] of azide **58** directly furnished **6** and **7** via reductive intramolecular cyclization pathway. Herein, the isolation of **6**+**7** mixture from the crude product by using column chromatographic separation was difficult. Hence an in situ, we converted the **6**+**7** mixture into their Boc-protected derivatives **44a**+**44b** and then isolated the mixture of **44a**+**44b** by using the silica-gel column chromatographic separation (**44a**:**44b** = 3:7, by ^1H NMR).[13,15] The Boc-deprotection of **44a**+**44b** mixture using TMSOTf at –20 ^oC furnished directly the mixture of desired natural products **6** and **7** (**6**:**7** = 1:1 ratio by ^1H NMR), but with low yield of 30% (2-steps) only.

Therefore we altered our strategy and decided to start the synthesis from mesylbutenolide **23**, which was easily obtained from the diol **53**. The diol **53** on treatment with methylsulfonyl chloride gave the desired mesylbutenolide **23** (*E*:*Z* = 57:43, by ^{1}H NMR) in 77% yield, following the double mesylation and an in situ mono elimination route. The mesylbutenolide **23** on chemo-selective substitution reaction with sodium azide yielded, the azidobutenolide **59** (*E*:*Z* = 53:47, by ^{1}H NMR) in 87% yield. The azidobutenolide **59** on triphenylphosphine induced reductive regioselective intramolecular aza-Michael type addition to the exocyclic activated carbon-carbon double bond yielded the desired mixture of lactones **6** and **7**. For the isolation of **6**+**7** mixture from the crude product by using column chromatographic separation, we in situ converted the **6**+**7** mixture into their Boc-protected derivatives **44a**+**44b** and then isolated the mixture of **44a**+**44b** by



Scheme 8. *Reagents, conditions and yields*: (i) NaN_3, DMF, rt, 16 h (87%); (ii) (a) PPh_3, THF, 42 ^oC, 0.5 h, (b) H_2O, 42 ^oC, 12 h, (c) Boc_2O, DCM, Et_3N, 16 h (**44a**:**44b** = 3:7, 77%); (iii) TMSOTf, DCM, –20 ^oC to –5 ^oC, 2.5 h (**6**:**7** = 1:1, 99%); (iv) LiI, THF, rt, 4 h (78%); (v) **19**, Ag_2CO_3, CH_3CN, rt, 24 h (**1**:**3**:**2**:**4** = 4:1:4:1, 64%); (vi) **19**, Ag_2CO_3, CH_3CN, rt, 48 h (66%); (vii) SiO_2, CH_2Cl_2, rt, 1 h (63%); (viii) P_2O_5, toluene, reflux, 1 h (**61** = 42%, **62** = 46%).

using the silica-gel column chromatographic separation (**44a**:**44b** = 3:7, by ^{1}H NMR, 77%).[13,15] The Boc-deprotection of **44a**+**44b** mixture furnished the mixture of desired natural products **6** and **7** in 99% yield with 1:1 ratio (by ^{1}H NMR). The column

chromatographic separation of diastereomeric norpandamarilactonines A & B is known in the literature.[5,8] At this stage, we avoided the separation of **6** and **7**, as **6** is known to epimerize to **7** probably via the β-elimination-conjugate addition mechanism.[8,13] The mesylbutenolide **23** (*E*:*Z* = 57:43) on reaction with lithium iodide gave the iodobutenolide **19** (*E*:*Z* = 1:4, by ^{1}H NMR) in 78% yield. We surmise that the change in ratio of *E*- and *Z*-isomers could be a result of addition of iodide to the carbon-carbon double bond followed by an instantaneous elimination. The reaction of mixture of lactones **6** & **7** with iodobutenolide **19** in the presence of Ag_2CO_3 as a coupling reagent was time dependent and in 24 h reaction time gave the desired mixture of natural products pandamarilactonines A-D (**1**-**4**) in 64% yield in a 4:4:1:1 ratio respectively, via the selective *N*-alkylation route. The same reaction in 48 h reaction time gave exclusively the pandanamine (**5**) in 66% yield via *N*-alkylation followed by pyrrole ring opening route. The pandamarilactonines A-D (**1**-**4**) mixture also on treatment with silica gel in CH_2Cl_2 at room temperature exclusively yielded the pandanamine (**5**) in 63% yield via the retro aza-Michael type reaction. The crucial column chromatographic separation of four isomeric pandamarilactonines A-D (**1**-**4**) is also well known in the literature.[2,8,12,13] The analytical and spectral data obtained for norpandamarilactonine A & B (**6** & **7**) mixture, pandamarilactonine A-D (**1**-**4**) mixture and pandanamine (**5**) were in complete agreement with the reported data.[2-5]

2B.3 Summary

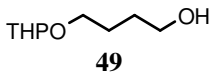
In this section we have demonstrated two simple and efficient methods to synthesize pandanus alkaloids (±)-norpandamarilactonine A and B. In the first approach we used Staudinger reduction of azide followed by intramolecular cyclization as the key reaction to obtain (±)-norpandamarilactonine A and B, while in the second approach we used reductive intramolecular aza-Michael type addition to activated double bond as the key reaction to obtain these natural products. These natural products were further elaborated to (±)-pandamarilactonines A-D and pandanamine via time dependent intermolecular coupling reaction with suitably substituted iodobutenolide in presence of a mild base. We obtained the two requisite building blocks to synthesize these pandanus alkaloids from the corresponding common precursors in one-step each. (±)-Pandamarilactonines A-D were also converted to pandanamine by treatment with silica gel. In the present approaches, the intramolecular aza-Michael type of addition reaction is noteworthy.

In conclusion, in the present two sections chapter we have described the relevant literature and our results with experimental and spectral data. We have presented an efficient synthesis of maculalactones A-C and nostoclide I using highly chemo- and regioselective S_N2' coupling reaction of appropriate Grignard reagents with dimethyl bromomethylfumarate as one of the key steps. This straightforward route gave maculalctones A-C, nostoclide I by simple conversion of corresponding anhydrides using regioselective reduction to lactones followed by Knoevenagel condensation reactions with appropriate aldehydes. The present approach is general in nature and will be useful to design diverse butyrolactone skeletons for the structure-activity relationship studies. We have also described two simple approaches to pandanus alkaloids (±)-norpandamarilactonines A-B, which were further converted to other pandanus alkaloids viz. (±)-pandamarilactonines A-D, pandanamine by intermolecular coupling reaction. Using reductive cyclization as the key reaction, in the first approach, we obtained norpandamarilactonines A-B in moderate yield (8%, 11-steps), which are precursors of other pandanus alkaloids. The second approach in which we obtained these precursors and pandamarilactonines A-D, pandanamine from the same common precursor was more efficient and the key aza-Michael type of addition reaction in this approach is noteworthy.

2B.4 Experimental Section

Column chromatographic separations were done on silica gel (60-120 mesh), flash silica (230-400 mesh) and neutral alumina. Commercially available 1,4-butanediol, 3,4-dihydro-2*H*-pyran, pyridinium chlorochromate, 3-methyl-2(5*H*)-furanone, *p*-toluenesulfonyl chloride, pyridine *p*-toluenesulfonate, phosphorous pentoxide, sodium azide, triphenylphosphine, Boc-anhydride, TMS triflate, lithium iodide and silver carbonate were used.

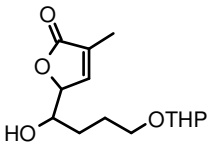
4-(Tetrahydropyran-2-yloxy)butan-1-ol (49). To a stirred solution of 1,4-butanediol (10.00 g, 110.96 mmol) and two drops of concentrated HCl was added 3,4-dihydro-2*H*-pyran (9.33 g, 110.96 mmol) in a drop wise fashion at room temperature. After 3 h of stirring at room temperature the reaction mixture was diluted with ethyl acetate (200 mL) and washed with saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (2:3) as an eluant gave compound **49** (14.69 g, 76%).

 **49** **$C_9H_{18}O_3$ (174)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3412, 1466, 1454, 1441 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.40-1.90 (m, 10H), 2.25 (bs, 1H), 3.35-3.60 (m, 2H), 3.66 (t, J = 6 Hz, 2H), 3.72-3.95 (m, 2H), 4.60 (t, J = 4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 19.4, 25.2, 25.3, 26.2, 26.4, 29.7, 30.4, 30.5, 62.0, 62.2, 67.1, 67.3, 98.6, 98.7 (some of the carbons showed splitting probably because of the two different possible intramolecular hydrogen bondings). **Anal. Calcd for $C_9H_{18}O_3$:** C, 62.04; H, 10.41. Found: C, 62.09; H, 10.37.

4-(Tetrahydropyran-2-yloxy)-butyraldehyde (50). To a stirred suspension of PCC 17.95 g, 83.27 mmol) and sodium acetate (2.04 g, 24.87 mmol) in 50 mL of DCM was added quickly a solution of alcohol **49** (14.50 g, 83.22 mmol) in DCM (50 mL). The reaction mixture immediately turned black and after 1 h of stirring, the reaction mixture was diluted with diethyl ether. The supernatant solution was filtered through basic alumina and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the residue using ethyl acetate-petroleum ether (1:9) as an eluant gave compound **50** (11.32 g, 79%).

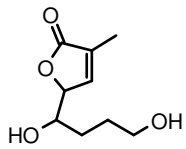
 **50** **$C_9H_{16}O_3$ (172)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 2945, 1726, 1468, 1441 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.40-1.83 (m, 6H), 1.92 (quintet, J = 6 Hz, 2H), 2.52 (t, J = 6 Hz, 2H), 3.32-3.55 (m, 2H), 3.67-3.90 (m, 2H), 4.54 (t, J = 2 Hz, 1H), 9.76 (t, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 19.3, 22.5, 25.3, 30.4, 41.0, 62.1, 66.3, 98.7, 202.3. **Anal. Calcd for $C_9H_{16}O_3$:** C, 62.76; H, 9.37. Found: C, 62.70; H, 9.42.

5-[1-Hydroxy-4(tetrahydropyran-2-yloxy)-butyl]-3-methyl-5*H*-furan-2-one (mixture of diastereomers, 52). To a stirred solution of 3-methyl-2(5*H*)-furanone (**51**, 5.00 g, 50.97 mmol) in THF (50 mL) at –78 °C was added the solution of freshly prepared LDA (5.99 g, 55.92 mmol) in THF (15 mL) in a drop wise fashion under argon atmosphere. The reaction mixture was stirred at –78 °C temperature for 30 min and a solution of aldehyde **50** (8.78 g, 50.98 mmol) in THF (10 mL) was added to it. Further stirring was continued for 2 h, allowing the reaction mixture to reach room temperature. THF was removed in vacuo at room temperature. The residue was then acidified with 2 N HCl and extracted with ethyl acetate (50 mL x 4). 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 **52** (10.47 g, 76%).

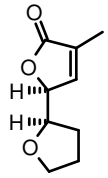
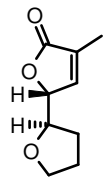
 **52** **$C_{14}H_{22}O_5$ (270)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3439, 1759, 1655, 1456 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.40-1.90 (m, 10H), 1.94 (bs, 3H), 3.35-3.60 (m, 2H), 3.60-4.00 (m, 3H), 4.50-4.65 (bs, 1H), 4.70-5.00 (m, 1H), 7.00-7.25 (m, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.6, 19.5, 19.6, 25.1, 25.2, 25.8, 26.0, 28.6, 30.1, 30.4, 30.5, 30.8, 30.9, 62.4, 62.6, 67.3, 67.4, 67.5, 71.6, 71.9, 72.0, 83.6, 83.8, 98.8, 99.0, 99.1, 130.6, 131.0, 145.4, 146.2, 146.8, 146.9, 174.2 (only prominent carbon signals are listed here). **Anal. Calcd for $C_{14}H_{22}O_5$:** C, 62.20; H, 8.20. Found: C, 62.25; H, 8.34.

***Erythro*- and *threo*- 5-(1,4-dihydroxybutyl)-3-methyl-5*H*-furan-2-one (53).** To a stirred solution of lactone **52** (10.00 g, 36.99 mmol) in ethanol (30 mL) was added

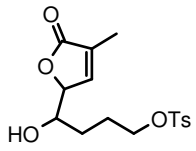
pyridinium toluene-4-sulfonate (900 mg, 3.58 mmol). The reaction mixture was heated at 56 ^{o}C for 24 h. The reaction mixture was then concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using ethyl acetate-petroleum ether (4:1) as an eluant to obtain compound **53** (*erythro*:*threo* = 64:36, 6.27 g, 91%).

 **53** **$C_9H_{14}O_4$ (186)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3390, 1751, 1655 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.50-1.88 (m, 4H), 1.94 (bs, 3H), 3.60-3.85 (m, 3H), 4.70-4.90 (m, 1H), 7.07 (quintet, J = 2 Hz, 0.36H), 7.20 (quintet, J = 2 Hz, 0.64H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.7, 28.6, 28.7, 30.1, 30.4, 62.39, 62.42, 71.7, 71.8, 83.8, 84.2, 130.9, 131.1, 146.4, 146.7, 173.3, 174.5 (except first signal, all other carbons showed diastereomeric splitting). **Anal. Calcd for $C_9H_{14}O_4$:** C, 58.05; H, 7.58. Found: C, 57.99; H, 7.63.

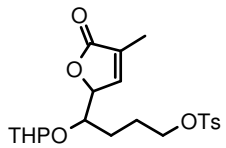
***Erythro*- & *threo*-3-methyl-5-(tetrahydrofuran-2-yl)furan-2(5*H*)-one (61 & 62).** To a stirred solution of diol **53** (200 mg, 1.07 mmol) in toluene (8 mL) was added P_2O_5 (305 mg, 2.15 mmol) and the reaction mixture was heated to reflux for 1 h. Toluene was removed in vacuo and the obtained residue was purified by flash column chromatography using ethyl acetate-petroleum ether (1:1) as an eluant to obtain compounds **61** (76 mg, 42%) and **62** (83 mg, 46%) as thick oils.

 **61** **$C_9H_{12}O_3$ (168)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1763, 1640, 1202 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.75-2.10 (m, 7H), 3.70-4.00 (m, 3H), 4.65-4.80 (m, 1H), 7.17 (quintet, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.7, 25.5, 28.0, 68.9, 79.4, 82.6, 130.8, 147.2, 174.1. **Anal. Calcd for $C_9H_{12}O_3$:** C, 64.27; H, 7.19. Found: C, 64.35; H, 7.09.
 **62** **$C_9H_{12}O_3$ (168)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1784, 1757, 1653 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.80-2.10 (m, 7H), 3.70-3.90 (m, 2H), 4.05-4.20 (m, 1H), 4.85-4.95 (m, 1H), 7.01 (quintet, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.8, 25.8, 27.4, 69.3, 77.6, 82.4, 131.4, 145.6, 174.1. **Anal. Calcd for $C_9H_{12}O_3$:** C, 64.27; H, 7.19. Found: C, 64.40; H, 7.13.

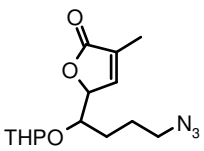
***Erythro*- & *threo*-toluene-4-sulfonic acid 4-hydroxy-4-(4-methyl-5-oxo-2,5-dihydro-furan-2-yl)-butyl ester (54).** To a stirred solution of diol **53** (1.5 g, 8.07 mmol) in DCM (20 mL) at 0 ^{o}C was added NEt_3 (1.12 mL, 8.07 mmol), *p*-toluenesulfonyl chloride (1.54 g, 8.07 mmol) and DMAP (252 mg, 2.42 mmol). The reaction mixture was allowed to reach room temperature and stirred for a further 2 h. It was then diluted with DCM (40 mL) and washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (2:3) as an eluant gave **54** (2.33 g, 85%).

 **54** **$C_{16}H_{20}O_6S$ (340)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3366, 1757, 1177 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.42-1.92 (m, 4H), 1.95 (s, 3H), 2.27 (bs, 1H), 2.46 (s, 3H), 3.56-3.85 (m, 1H), 4.01-4.19 (m, 2H), 4.71-4.83 (m, 1H), 7.01 (quintet, *J* = 2 Hz, 0.36H), 7.09 (quintet, *J* = 2 Hz, 0.64H), 7.36 (d, *J* = 8 Hz, 2H), 7.79 (d, *J* = 8 Hz, 2H). **Anal. Calcd for $C_{16}H_{20}O_6S$:** C, 56.46; H, 5.92; S, 9.42. Found: C, 56.60; H, 5.74; S, 9.69.

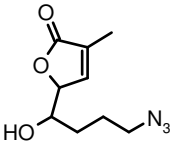
Toluene-4-sulfonic acid 4-(4-methyl-5-oxo-2,5-dihydro-furan-2-yl)-4-(tetrahydro-pyran-2-yloxy)-butyl ester (mixture of diastereomers, 55). To a stirred solution of hydroxy compound **54** (2.00 g, 5.88 mmol) in DCM (20 mL) was added *p*-toluenesulfonyl acid monohydrate (cat.) and 3,4-dihydro-2*H*-pyran (742 mg, 8.82 mmol) at room temperature and the reaction mixture was stirred for 16 h. The reaction mixture was then diluted with DCM (40 mL), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (3:7) as an eluant gave **55** (2.27 g, 91%).

 **55** **$C_{21}H_{28}O_7S$ (424)**	Thick oil. **IR** (Neat): ν_{max} 1759, 1358, 1177 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.35-2.10 (m, 13H), 2.46 (s, 3H), 3.30-4.20 (m, 5H), 4.45-5.25 (m, 2H), 6.94-7.21 (m, 1H), 7.36 (d, *J* = 8 Hz, 2H), 7.72-7.85 (m, 2H). **Anal. Calcd for $C_{21}H_{28}O_7S$:** C, 59.42; H, 6.65; S, 7.55. Found: C, 59.63; H, 6.32; S, 7.80.

5-[4-Azido-1-(tetrahydro-pyran-2-yloxy)-butyl]-3-methyl-5*H*-furan-2-one (mixture of diastereomers, 56). To a stirred solution of tosylate **55** (2.00 g, 4.71 mmol) in DMF (12 mL) was added NaN_3 (919 mg, 14.13 mmol) and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (3:7) as an eluant gave **56** (1.22 g, 88%).

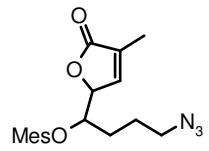
 **56** **$C_{14}H_{21}N_3O_4$ (295)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 2098, 1757, 1076, 910, 735 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.35-1.92 (m, 10H), 1.94 (bs, 3H), 3.20-4.00 (m, 5H), 4.52-5.00 (m, 2H), 7.05 (quintet, J = 2 Hz, 0.50H), 7.16 (quintet, J = 2 Hz, 0.20H), 7.22 (quintet, J = 2 Hz, 0.30H). **Anal. Calcd for $C_{14}H_{21}N_3O_4$:** C, 56.94; H, 7.17; N, 14.23. Found: C, 56.70; H, 7.01; N, 14.29.

***Erythro*- & *threo*-5-(4-azido-1-hydroxy-butyl)-3-methyl-5*H*-furan-2-one (57).** To a stirred solution of azide **56** (900 mg, 3.05 mmol) in CH_3OH (8 mL) was added *p*-toluenesulfonic acid monohydrate (cat.) at room temperature and the reaction mixture was stirred for 2 h. Methanol was removed in vacuo and the residue obtained was purified by silica gel column chromatography using ethyl acetate-petroleum ether (2:3) as an eluent to obtain compound **57** (614 mg, 95%).

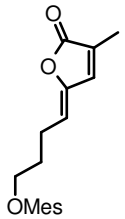
 **57** **$C_9H_{13}N_3O_3$ (211)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3032, 2098, 1757, 1751, 1059 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.40-2.00 (m, 7H), 2.41 (bs, 1H), 3.27-3.45 (m, 2H), 3.62-3.93 (m, 1H), 4.77-4.88 (m, 1H), 7.04 (quintet, J = 2 Hz, 0.45H), 7.13 (quintet, J = 2 Hz, 0.55H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.7, 10.8, 25.0, 25.2, 30.0, 30.1, 51.17, 51.2, 71.3, 71.8, 83.5, 84.0, 131.6, 131.7, 145.4, 145.44, 173.8, 173.9 (all carbons showed diastereomeric splitting). .**Anal. Calcd for $C_9H_{13}N_3O_3$:** C, 51.18; H, 6.20; N, 19.89. Found: C, 51.36; H, 6.27; N, 19.69.

***Erythro*- & *threo*-methanesulfonic acid 4-azido-1-(4-methyl-5-oxo-2,5-dihydro-furan-2-yl)-butyl ester (58).** To a stirred solution of hydroxy compound **57** (500 mg, 2.37 mmol) in DCM (8 mL) at –10 ^oC was added NEt_3 (0.36 mL, 2.60 mmol) and

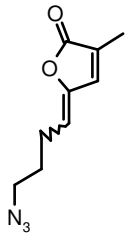
methanesulfonyl chloride (0.20 mL, 2.60 mmol). The reaction mixture was stirred further for 2 h at the same temperature and extracted in DCM (30 mL x 4), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (3:7) as an eluant gave **58** (623 mg, 91%).

 **58** **$C_{10}H_{15}N_3O_5S$ (289)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 2361, 2343, 2098, 1763, 1751, 1173 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.40-2.10 (m, 4H), 1.98 (s, 3H), 3.07 (s, 1.83H), 3.10 (s, 1.17H), 3.26-3.50 (m, 2H), 4.68-4.97 (m, 1H), 4.97-5.10 (m, 1H), 7.02-7.08 (m, 0.39H), 7.08-7.17 (m, 0.61H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.76, 10.82, 24.6, 27.9, 28.4, 29.6, 38.7, 38.8, 50.55, 50.59, 79.2, 79.7, 80.4, 80.7, 132.6, 132.7, 143.3, 143.8, 172.8, 172.9 (all carbons showed diastereomeric splitting). **Anal. Calcd for $C_{10}H_{15}N_3O_5S$:** C, 41.51; H, 5.23; N, 14.52. Found: C, 41.81; H, 5.09; N, 14.64.

(*E*,*Z*)-4-(4-Methyl-5-oxofuran-2(5*H*)-ylidene)butyl methanesulfonate (23). To a stirred solution of diol **53** (4.00 g, 21.48 mmol) in DCM (25 mL) was added NEt_3 (14.99 mL, 107.52 mmol) and methanesulfonyl chloride (3.49 mL, 45.13 mmol) at 0 ^oC. The reaction mixture was further stirred at room temperature for 24 h. The reaction mixture was diluted with DCM (50 mL), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using a mixture of ethyl acetate-petroleum ether (2:3) as an eluant gave **23** (*E*:*Z* = 57:43, 4.07 g, 77%).

 **23** **$C_{10}H_{14}O_5S$ (246)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1757 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.80-2.10 (m, 5H), 2.30-2.60 (m, 2H), 3.02 (s, 1.71H), 3.03 (s, 1.29H), 4.15-4.30 (m, 2H), 5.14 (t, *J* = 8 Hz, 0.43H), 5.57 (t, *J* = 8 Hz, 0.57H), 7.01 (d, *J* = 2 Hz, 0.43H), 7.32 (d, *J* = 2 Hz, 0.57H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.5, 10.8, 22.1, 22.3, 28.4, 29.1, 37.4, 68.6, 68.8, 110.8, 111.5, 129.7, 131.0, 133.5, 137.5, 149.2, 149.5, 170.7, 170.8 (except one, all other carbons showed *E*:*Z* splitting). **Anal. Calcd for $C_{10}H_{14}O_5S$:** C, 48.77; H, 5.73; S, 13.02. Found: C, 48.61; H, 5.69; S, 13.12.

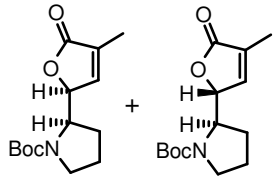
(*E*,*Z*)-5-(4-Azidobutylidene)-3-methylfuran-2(5*H*)-one (59). To a stirred solution of mesylate **23** (3.50 g, 14.21 mmol) in DMF (15 mL) was added NaN_3 (4.67 g, 71.84 mmol) and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using a mixture of ethyl acetate-petroleum ether (1:9) as an eluant gave **59** (*E*:*Z* = 53:47, 2.39 g, 87%).

 **59** **$C_9H_{11}N_3O_2$ (193)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 2097, 1769, 1763 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.60-1.85 (m, 2H), 2.00 (s, 1.41H), 2.03 (s, 1.59H), 2.35 (q, *J* = 8 Hz, 1.06H), 2.46 (q, *J* = 8 Hz, 0.94H), 3.25-3.40 (m, 2H), 5.13 (t, *J* = 8 Hz, 0.47H), 5.57 (t, *J* = 8 Hz, 0.53H), 7.00 (bs, 0.47H), 7.30 (bs, 0.53H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 10.5, 10.8, 23.3, 23.4, 28.3, 28.6, 50.2, 50.8, 111.4, 112.2, 129.5, 130.8, 133.4, 137.5, 149.0, 149.4, 170.8, 170.9 (all carbons showed diastereomeric splitting). **Anal. Calcd for $C_9H_{11}N_3O_2$:** C, 55.95; H, 5.74; N, 21.75. Found: C, 55.80; H, 5.70; N, 21.85.

(*E*,*Z*)-5-(4-Iodobutylidene)-3-methylfuran-2(5*H*)-one (19). To a stirred solution of mesylate **23** (280 mg, 1.14 mmol) in THF (10 mL) was added LiI (380 mg, 2.84 mmol) and the reaction mixture was stirred at room temperature for 4 h. THF was removed in vacuo at room temperature and the residue was stirred with DCM (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using ethyl acetate-petroleum ether (1:9) as an eluant gave **19** (*E*:*Z* = 1:4, 247 mg, 78%).

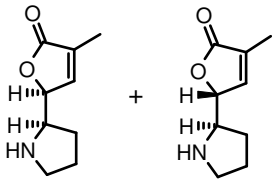
 **19** **$C_9H_{11}IO_2$ (278)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1767, 1676, 1620, 1443 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.90-2.10 (m, 5H), 2.25-2.55 (m, 2H), 3.10-3.25 (m, 2H), 5.12 (t, *J* = 8 Hz, 0.80H), 5.54 (t, *J* = 8 Hz, 0.20H), 6.99 (bs, 0.80H), 7.38 (bs, 0.20H). **^{13}C NMR** ($CDCl_3$, 50 MHz): *Z*-isomer (major): δ 5.3, 10.2, 26.8, 32.4, 111.4, 129.0, 137.4, 148.8, 170.5, *E*-isomer (minor): 5.9, 10.5, 26.5, 32.3, 110.8, 130.3, 133.7, 149.2, 170.4. **Anal. Calcd for $C_9H_{11}IO_2$:** C, 38.87; H, 3.99. Found: C, 38.71; H, 4.03.

***Threo*- & *erythro*- *tert*-butyl 2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (44a & 44b). *Method A*:** To a stirred solution of azide **58** (300 mg, 1.04 mmol) in THF (1 mL) at room temperature was added PPh_3 (272 mg, 1.04 mmol). The reaction mixture was stirred for 30 min and then H_2O (0.1 mL, 5.18 mmol) was added to it. After 12 h of stirring at room temperature, the reaction mixture was concentrated in vacuo. Then DCM (10 mL) was added to the reaction mixture followed by Boc-anhydride (272 mg, 1.25 mmol) and NEt_3 (0.44 mL, 3.11 mmol). The reaction mixture was stirred for 16 h at room temperature and diluted with DCM (30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (1:9) as an eluant gave mixture of **44a** and **44b** (**44a**:**44b** = 3:7, 86 mg, 31%). ***Method B*:** To a stirred solution of azide **59** (1.00 g, 5.18 mmol) in THF (5 mL) at 42 ^oC was added PPh_3 (1.36 g, 5.18 mmol). The reaction mixture was stirred for 30 min and then H_2O (0.47 mL, 25.89 mmol) was added to it. After 12 h of stirring at 42 ^oC, the reaction mixture was concentrated in vacuo. Then DCM (10 mL) was added to the reaction mixture followed by Boc-anhydride (1.36 g, 6.23 mmol) and NEt_3 (2.16 mL, 15.52 mmol). The reaction mixture was stirred for 16 h at room temperature and diluted with DCM (30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (1:9) as an eluant gave mixture of **44a** and **44b** as a thick oil (**44a**: **44b** = 7:3, 1.07 g, 77%).

 **44a+44b** **$C_{14}H_{21}NO_4$ (267)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 1755, 1682 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.42 (s, 2.70H), 1.47 (s, 6.30H), 1.60-2.10 (m, 7H), 3.20-3.50 (m, 2H), 3.90-4.30 (m, 1H), 5.00-5.40 (m, 1H), 7.03 (bs, 0.70H), 7.16 (bs, 0.30H). **Anal. Calcd for** $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.96; H, 8.01; N, 5.18.

Norpandamarilactonine A (6) and B (7). To a stirred solution of carbamates **44a** and **44b** (800 mg, 2.99 mmol) in DCM (10 mL) at −20 ^oC was added TMSOTf (0.54 mL, 2.99 mmol) in a drop wise fashion under argon atmosphere. The reaction mixture was stirred for 2.5 h allowing the temperature of the reaction mixture to rise to −5 ^oC, then 6 mL of 25%

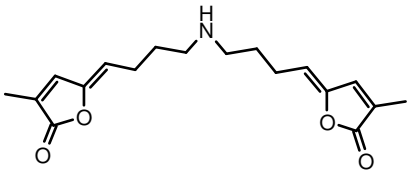
liquid NH_3 solution was added to it. The reaction mixture was then extracted with DCM (30 mL x 3), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo directly gave a mixture of pure norpandamarilactonine A and B (**6**:**7** **=** 1:1**,** 495 mg, 99%).

 **6+7** **$C_9H_{13}NO_2$ (167)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3402, 1759, 1655 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 1.50-1.90 (m, 4H), 1.93 (s, 3H), 2.10 (bs, 1H), 2.85-3.00 (m, 2H), 3.15-3.25 (m, 1H), 4.70-4.85 (m, 1H), 7.02 (s, 0.5H), 7.14 (s, 0.5H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 10.7, 25.1, 25.6, 26.9, 27.8, 46.5, 47.0, 60.2, 60.3, 83.7, 84.2, 130.7, 131.2, 146.6, 147.7, 174.2, 174.3 (except first signal, all other carbons showed diastereomeric splitting). **Anal. Calcd for $C_9H_{13}NO_2$:** C, 64.65; H, 7.83; N, 8.38. Found: C, 64.71; H, 7.74; N, 8.31.

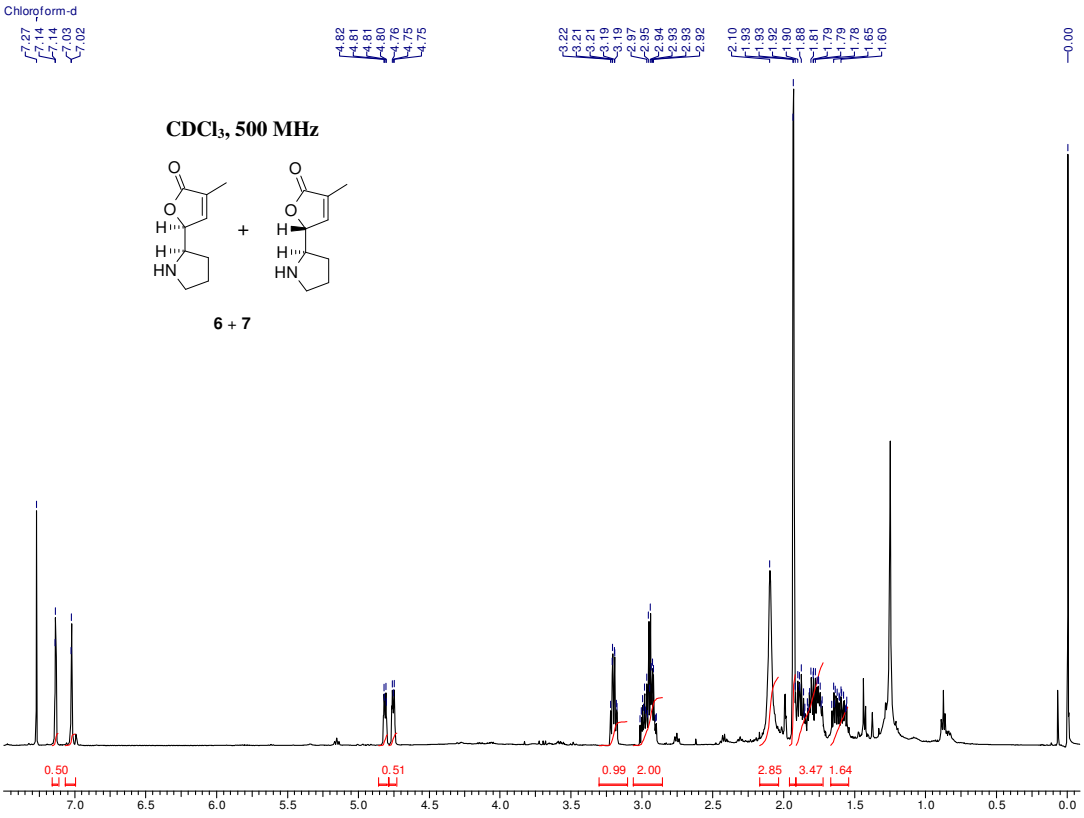
Pandamarilactonines A-D (1-4). To a stirred solution of 1:1 mixture of **6** and **7** (100 mg, 0.60 mmol) in CH_3CN (10 mL) was added freshly prepared iodo lactone **19** (166 mg, 0.60 mmol) and Ag_2CO_3 (181 mg, 0.66 mmol). The reaction mixture was stirred at room temperature for 24 h. Solvent was removed in vacuo and the crude product was dissolved in DCM (20 mL), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by neutral alumina column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (2:3) as an eluant gave a mixture of four pandamarilactonines as a thick oil (**1**:**2**:**3**:**4** = 4: 4:1:1, 121 mg, 64%). The column chromatographic separation of four isomeric pandamarilactonines A-D (**1**-**4**) is well known in the literature.[2,8,12,13]

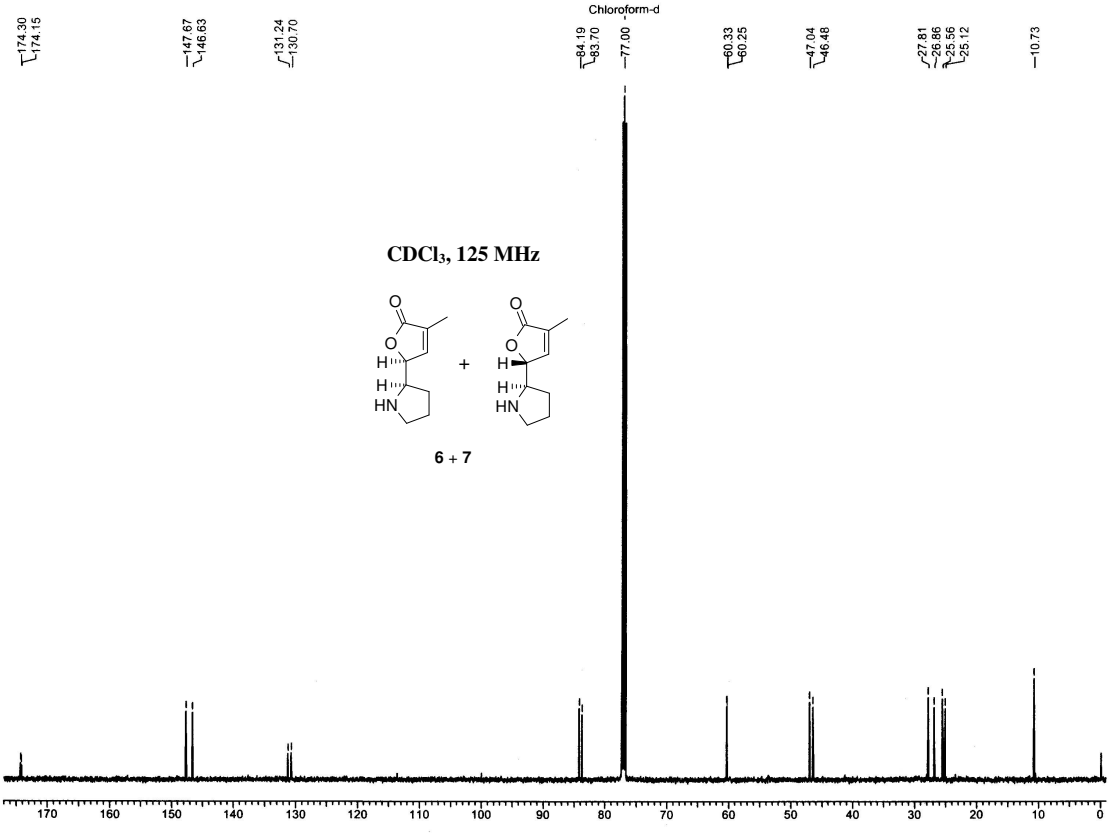
Pandanamine (5). ***Method A*:** To a stirred solution of 1:1 mixture of **6** and **7** (30 mg, 0.18 mmol) in CH_3CN (5 mL) was added freshly prepared iodo lactone **19** (50 mg, 0.18 mmol) and Ag_2CO_3 (54 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 48 h. Solvent was removed in vacuo and the crude product was dissolved in DCM (20 mL), washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by neutral alumina column chromatographic purification of the residue using a mixture of ethyl acetate-petroleum ether (1:1) as an eluant gave pandanamine (**5**) as a thick oil (38 mg, 66%). ***Method B*:** To a stirred solution of mixtures of **1-4** (30 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) and CH_3OH (2 mL) was added silica gel (1.00 g). The reaction mixture was stirred for 2 h. Solvent was removed in vacuo and the

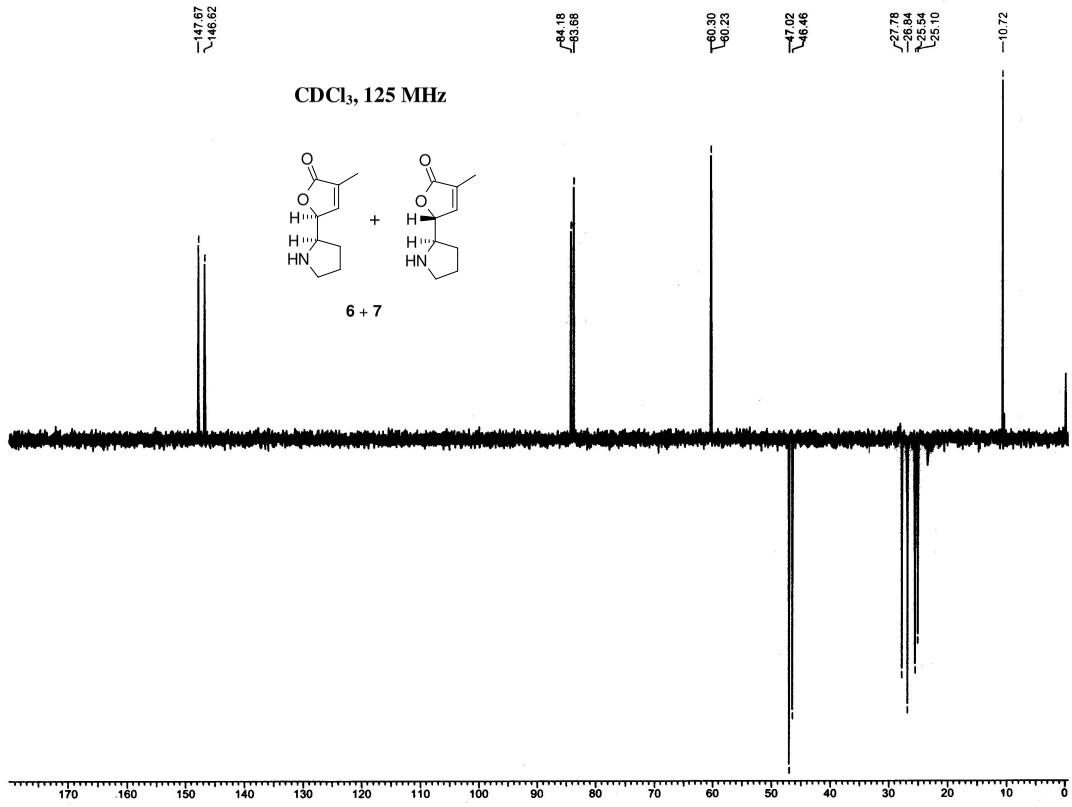
residue obtained was purified by silica gel column chromatography using DCM-methanol (9:1) as an eluant to furnish pandanamine (**5**) as a thick oil (19 mg, 63%).

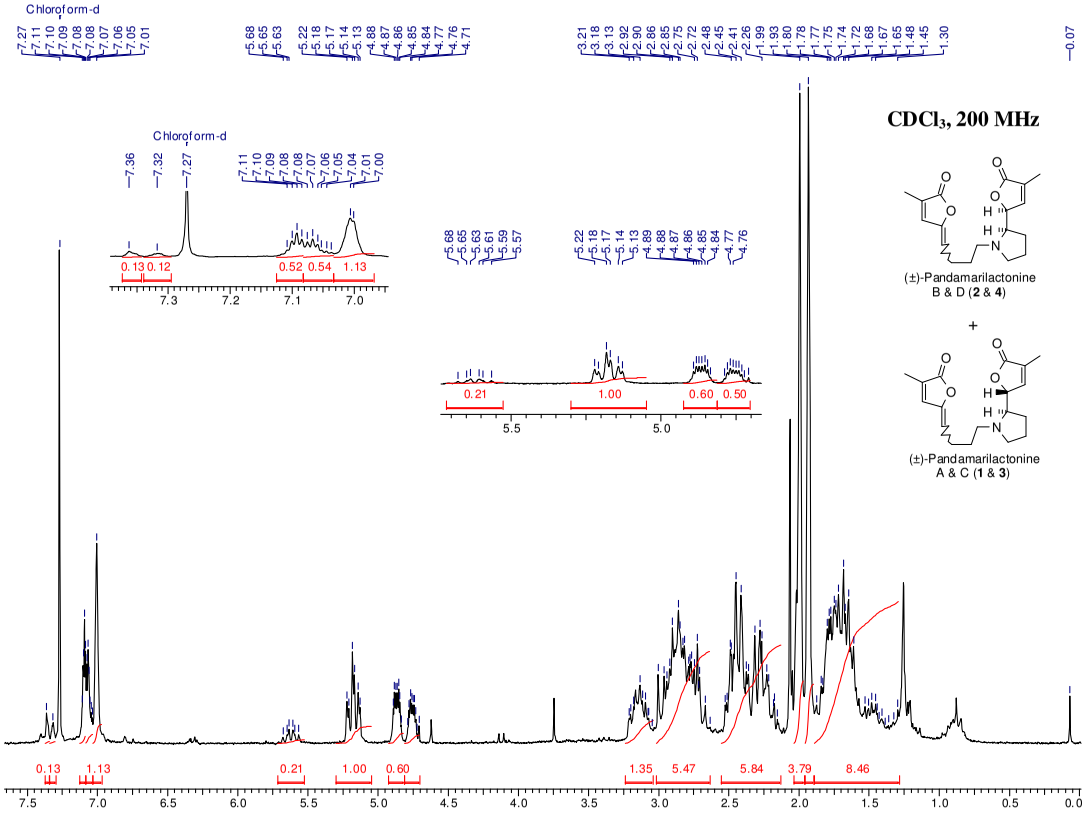
 **5** **$C_{18}H_{23}NO_4$ (317)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 3422, 1761, 1663 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.92-2.05 (m, 4H), 1.97 (bs, 6H), 2.30-2.55 (m, 4H), 2.96 (dd, J = 8 and 8 Hz, 4H), 5.17 (t, J = 8 Hz, 2H), 7.03 (bs, 2H). **MS** (m/z): 318, 264, 226, 148, 125, 116, 107. **Anal. Calcd for $C_{18}H_{23}NO_4$:** C, 68.12; H, 7.30; N, 4.41. Found: C, 67.98; H, 7.42; N, 4.53.

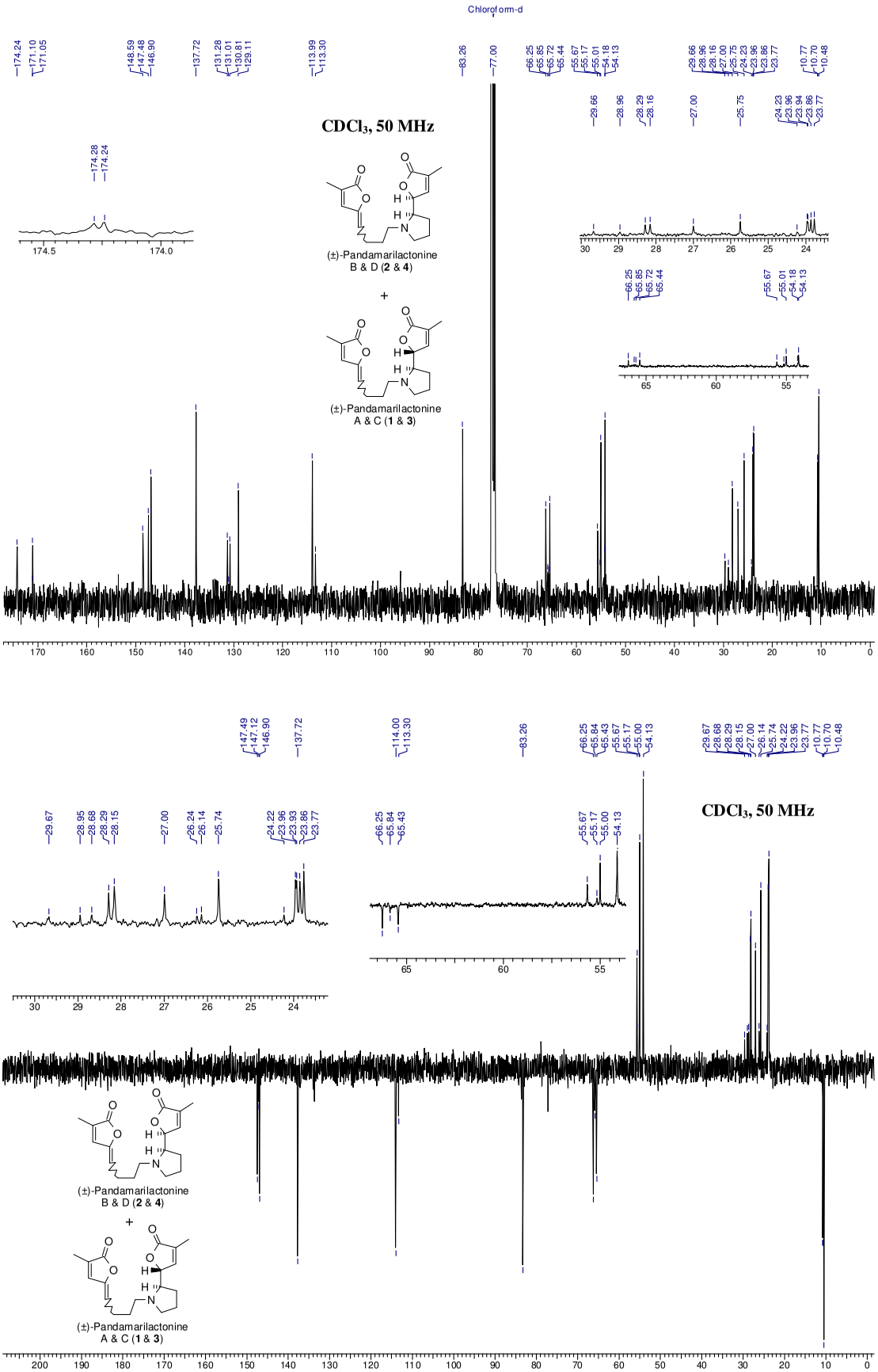
2B.5 Selected Spectra


Chloroform-d
7.27
7.14
7.14
7.03
7.02
4.82
4.81
4.81
4.80
4.76
4.75
4.75
3.22
3.21
3.21
3.19
3.19
2.97
2.95
2.94
2.93
2.93
2.92
2.10
1.93
1.93
1.92
1.90
1.88
1.81
1.79
1.79
1.78
1.65
1.60
0.00
CDCl3, 500 MHz
O
O
H
H
HN
+
O
O
H
H
HN
6 + 7
0.50
0.51
0.99
2.00
2.85
3.47
1.64
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


174.30
174.15
147.67
146.63
131.24
130.70
Chloroform-d
84.19
83.70
77.00
60.33
60.25
47.04
46.48
27.81
26.86
25.56
25.12
10.73
CDCl3, 125 MHz
O
O
H
H
HN
+
O
O
H
H
HN
6 + 7
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


147.67
146.62
84.18
83.68
60.30
60.23
47.02
46.46
27.78
26.84
25.54
25.10
10.72
CDCl3, 125 MHz
6 + 7


Chloroform-d
CDCl3, 200 MHz
(±)-Pandamarilactonine
B & D (2 & 4)
(±)-Pandamarilactonine
A & C (1 & 3)


Chloroform-d
CDCl3, 50 MHz
(±)-Pandamarilactonine
B & D (2 & 4)
+
(±)-Pandamarilactonine
A & C (1 & 3)
CDCl3, 50 MHz
(±)-Pandamarilactonine
B & D (2 & 4)
+
(±)-Pandamarilactonine
A & C (1 & 3)

2B.6 References and Footnote

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(15) The stereochemical assignments of compounds **53**, **54**, **57**, **58**, **44a**, **44b**, **61** and **62** are based on NMR parameters.[8b]

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Chapter 3

Chemoenzymatic Synthesis of Potassium (2R,3R)-2,3,4-Trihydroxy-2-methylbutanoate, Ellipsoidones and (+)-Erigeronic Acid

This chapter features the following sections:

3A. Section A

The Use of Lipases in Organic Synthesis

This section features the following topics:

3A. Section A: The Use of Lipases in Organic Synthesis

3A.1 Background

Enzymes are proteins that are built up in Nature from twenty different amino acids. The term enzyme was coined by Kanne in 1876 and experimentation on enzymes began in 1897. Active sites of enzymes evolved to allow the enzymes to mediate biological reactions under ambient conditions and thus they serve as excellent biological "catalysts", forming a bridge between chemistry and biology. Almost all processes in a biological cell need enzymes in order to occur at significant rates. Since enzymes are extremely selective for their substrates and speed up only a few reactions from among many possibilities, the set of enzymes made in a cell determines which metabolic pathways occur in that cell. In recent years, enzymes have emerged as powerful tools in organic synthesis for bringing about kinetic resolution of racemates as they are extremely specific in their action and offer a high degree of chemo-, regio- and stereoselectivity, which is of huge importance in organic synthesis. Like all catalysts, enzymes work by lowering the activation energy (E_a or $\Delta G^{\ddagger}$) for a reaction, thus dramatically accelerating the rate of the reaction. Most enzyme reaction rates are millions of times faster than those of comparable uncatalyzed reactions. As with all catalysts, enzymes are not consumed by the reactions they catalyze. The catalytic ability of enzymes depends upon their three-dimensional architectures, which are basically determined by the L-amino acid sequence. The 3-D structure of an enzyme often reveals that it possesses an active site, where the reaction takes place. In order for a substrate molecule to be held firmly in 3-D space, there must be at least three points of attachment of the substrate onto the active site. In a racemic substrate, only one isomer would possess a complementary structure, that is, the groups are correctly aligned and fit into the active site pockets, while the opposite isomer turns out to be a misfit and does not react. This section gives a brief introduction about enzymes in general and a concise account of the applications of lipases in synthetic organic chemistry. Earlier two Ph. D. dissertations from our group described details about the use of lipases, so to avoid repetition selected data are presented here.

3A.2 Classification of Enzymes

Enzymes are classified by rules prescribed by the Enzymes commission of the International Union of Biochemistry, according to which each enzyme is designated by

four numbers; the main class, the subclass, sub-subclass and the serial numbering in the sub-subclass. There are six main classes as shown:

1. **Oxidoreductases**: These enzymes mediate oxidation and reduction, including the insertion of oxygen to alkenes. This group also includes enzymes that are responsible for the addition or removal of hydrogen.
2. **Transferases**: These enzymes are involved in the transfer of one group, such as an acyl or a sugar unit from one substrate to another.
3. **Hydrolases**: This group includes the enzymes that mediate the hydrolysis or formation of amides, epoxides, esters and nitriles.
4. **Lyases**: These are group of enzymes that fragment larger molecules with the elimination of smaller units.
5. **Isomerases**: These enzymes are involved in epimerization, racemization and other isomerization reactions.
6. **Ligases**: This group includes the enzymes responsible for the formation of C-C, C-O, C-S and C-N bonds.

Units: The international unit (I.U.) of any enzyme activity is described as millimoles of substrate utilized per minute or millimoles of product formed per minute and the specific activity is defined as activity per milligram of enzyme.

3A.3 Lipases:

Hydrolases form the most important class of enzymes[1] and among them, lipases have been the most popular and widely used.

3A.3.1 Occurrence and Role

Lipases are ubiquitous enzymes that are found in bacteria/fungi,[2] plants[3] and animals.[4] They are triglycerol ester hydrolases defined in class EC 3.1.1.3 by enzyme nomenclature. In general, cells produce lipases to hydrolyze the extracellular fats and lipases are specially structured to act at water/organic interface (they undergo an interfacial activation leading to a large increase in hydrolytic activity).[5,6] For this reason lipases appear to have optimum property among the enzymes to operate in organic solvents, in this case the interface is between the insoluble enzyme with its essential water of hydration and the organic solvent containing the acylating agent.

3A.3.2 Structure and Mechanism

The first two lipase structures were solved in 1990 by X-ray crystallography, which revealed a unique mechanism, unlike that of any other enzyme. Their three dimensional structures suggested that interfacial activation is due to the presence of an amphiphilic peptidic loop covering the active site of the enzyme in solution, just like a lid or a flap.[7] From the X-ray structure of co-crystals between lipases and substrate analogue, there is a strong evidence that, upon contact with a lipid/water interface, the lid undergoes a conformational rearrangement which renders the activation site accessible to the substrate.[8] The active site is generally characterized by the triad composed of the amino acids serine,

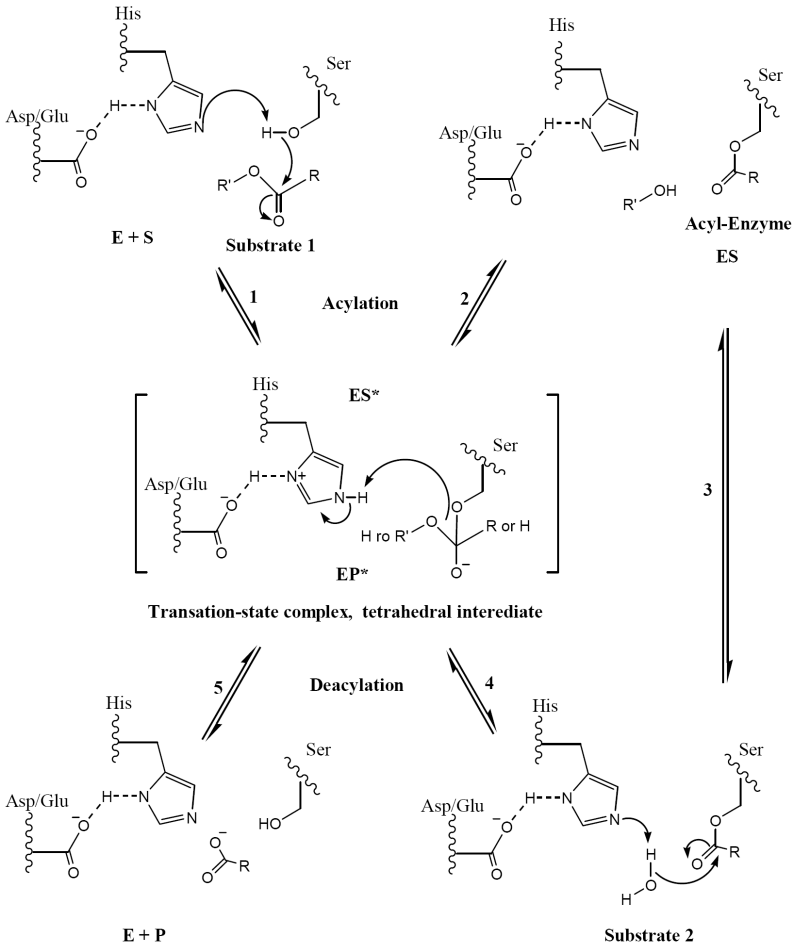


Figure 1. Catalytic mechanism of lipase action through procedure 1-5, where E is the enzyme, ES* & EP* are the substrate-enzyme and product-enzyme complexes respectively (*Structure numbers in the above figure are from the original reference and do not correlate to the structure numbers in the present section*).

histidine and aspartic/glutamic acid, acyl-enzyme complexes being the crucial intermediates in all lipase-catalyzed reactions. The system operates through a charge-relay system *via* hydrogen bonds as shown in figure 1. The mechanism has been termed as the ping-pong bi-bi mechanism.[9] The structural shape of the protein creates hydrophilic or lipophilic pockets within the enzyme active site, which leads to chemo-, regio- and enantio/diastereoselectivity.

3A.3.3 Lipases as Biocatalysts in Organic Synthesis

Considering their specific and limited function in metabolism, one should expect lipases to be of limited interest for the organic chemist. However, chemists have discovered lipases to be one of the most versatile classes of biocatalysts in organic synthesis. The versatility and popularity of lipases could be attributed to their high catalytic efficiency on a broad range of substrates (they can accommodate substrates other than triglycerides such as aliphatic, aromatic, alicyclic and bicyclic esters including the esters based on organometallic sandwich compounds), combined with high regioselectivity and chiral recognition,[5] their high stability in organic solvents and at elevated temperatures,[5,10] the reversibility of their mode of action,[5,11] their non-toxic and environment friendly nature[12] and finally their low cost. In practice, lipases are very easy to handle.

The use of organic solvents for lipase-catalyzed reactions has added a new perspective (in neat organic solvents enzymes retain the minimum amount of water which is necessary for their catalytic activity). This is because of the obvious advantages such as (i) increased substrate solubility and wider range of reactants, (ii) transformations of water-sensitive substrates, (iii) ease of operation and (iv) modified enzyme specificity. Moreover, the use of organic solvents is seen to enhance the enantioselectivity[13] and thermostability[14] of the enzymes, probably due to restricted conformational flexibility. Despite the advantages, enzymes nearly universally display low catalytic activities in non-aqueous conditions[15] compared to native aqueous solutions. One of the most influential parameters affecting enzymatic activity in aqueous solutions is pH. However, this does not operate in organic solvents since, in organic media, enzymes have a “pH memory”: their catalytic activity reflects the pH of the last aqueous solution to which they were exposed.[10] Consequently enzymatic activity in organic solvents can be enhanced if enzymes are lypophilized from aqueous solutions of pH optimal for their catalysis. Various other techniques and

approaches have been employed that have resulted in increasing enzymatic activities in organic solvents by up to three to four orders of magnitude.[15]

The free energy of fat hydrolysis is close to 0 kJ mol^{-1}.[16] As a result, thermodynamic equilibria are largely governed by the reactant concentrations and lipase catalyzed ester hydrolysis in water can easily be reversed, in non-aqueous media, into ester synthesis or transesterification. The acyl lipase formed in the first step of the enzymatic reaction can formally be considered as an acylating agent. The wide substrate specificity of this enzyme class allows acylation of nucleophiles other than those with hydroxyl groups, for example hydroperoxides, thiols and amines. Hydrolysis is usually performed in a biphasic system consisting of an aqueous buffer and an organic solvent while esterification is effected in an organic solvent with an irreversible acyl donor[11] such as the enol ester vinyl acetate. The enzyme is conveniently removed by filtration during work-up.

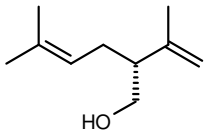
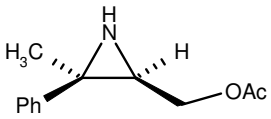
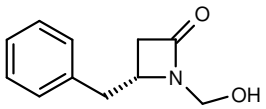
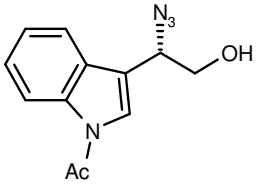
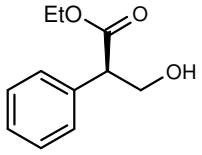
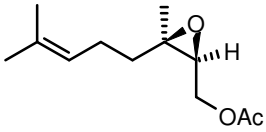
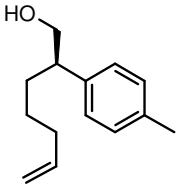
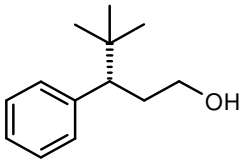
3A.4 Recent Applications of Lipase Catalysis in the Resolution of Alcohols

The most extensively studied substrates for lipase catalysis resolution are alcohols. This can be attributed to the extremely good selectivities shown by lipases when acting upon alcohols as well as the vast and diverse utilities of chiral alcohol substrates in research and industry. The present section will portray some elegant reports of lipase catalysis in 1°, 2° & 3° alcohol substrates. The "products" depicted in the tables in the following sections indicate the actual product formed from the recognized isomer in the lipase-catalyzed resolution. Entries wherein the non-recognized isomer of the substrate isomer is depicted have been indicated as "unreacted isomer" within brackets below the compound structure. Tables contain examples of both lipase-catalyzed hydrolysis as well as transesterification reactions.

3A.4.1 Primary alcohols

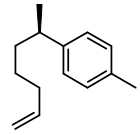
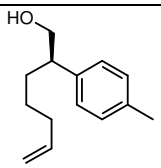
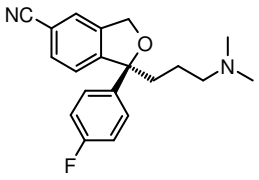
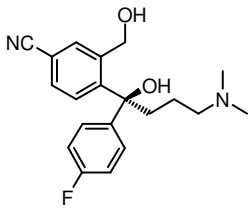
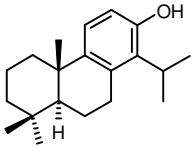
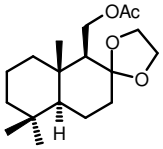
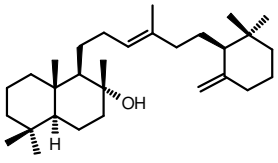
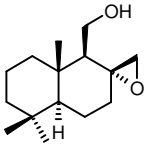
Homochiral primary alcohols are useful building blocks for the synthesis of a wide range of biologically active compounds. The kinetic resolution of racemates of primary alcohols by lipase-catalysis is more difficult to achieve due to lower enantioselectivities of lipases towards chiral primary alcohols. Lipase from *Pseudomonas cepacia* (PSL) has been most efficient, exhibiting high enantioselectivity towards a broad range of primary alcohols. Some primary alcohol substrates that have been successfully resolved using lipases are presented in table 1.

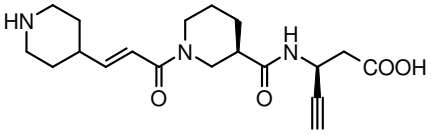
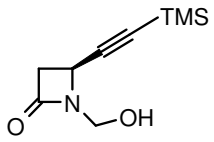
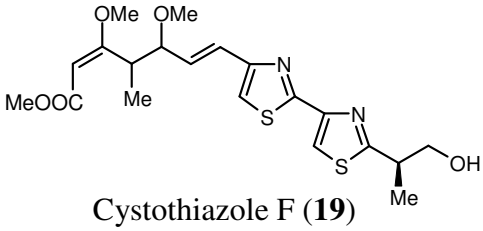
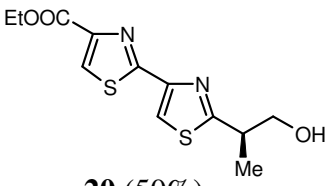
Table 1. Selected examples illustrating the lipase-catalyzed resolution of primary alcohols

Product	Lipase	% Yield	%Ee	Reference
 **1**(unreacted isomer)	*Hog pancreas*	85 (conv.)	90	17
 **2**	Lipase PS-C	46 (conv.)	92	18
 **3** (unreacted isomer)	Lipase PS	55 (conv.)	98	19
 **4**	Lipase PS	42	83	20
 **5**	Lipase PS	46	94	21
 **6**	Lipase PS	16	~99	22
 **7**	Lipase PS	40	>99	23
 **8**	PCL	52 (conv.)	66	24

Lipase-catalyzed resolution of primary alcohol intermediates have served as key steps in the total synthesis of several important natural products. In the case of complex natural products, resolution in the early phase of the synthesis not only provides an easy and economic access to the all-important chiral intermediate in a highly enantioselective fashion but also sets the stage for the introduction of contiguous chiral centres in a stereoselective fashion. Some examples of natural product synthesis are given in table 2 with the intermediate involved in the synthesis depicted alongside.

Table 2. Natural products synthesized with the corresponding chiral intermediate prepared by lipase catalyzed resolution

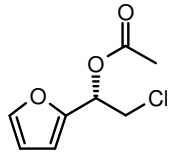
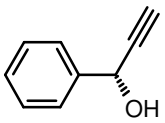
Natural product	**Intermediate (% yield)**	**Lipase used**	**% Ee**	**Ref.**
 (*R*)-5,6-Dehydrosenedigitalene (**9**)	 **10** (54%)	Amano PS	99%	23
 (*S*)-Citalopram (**11**)	 **12** (53%)	CAL-B	99%	25
 (+)-Totarol (**13**)	 **14** (49%)	Lipase PL-266	99%	26
 (+)-Ambrein (**15**)	 **16** (50%)	Lipase MY-30	91%	27

 FR 184764 (**17**)	 **18** (40%)	Amano PS	97%	28
 Cystothiazole F (**19**)	 **20** (50%)	lipase Godo E-1	74%	29

3A.4.2 Secondary Alcohols

Secondary alcohols are by far the most widely explored substrates in lipase-catalyzed resolutions. This is not only due to the importance of chiral secondary alcohols in organic synthesis but also that lipases usually show much higher enantioselectivity in the case of secondary alcohols as against primary and tertiary ones. A gamut of examples with tremendous structural diversity can be found in the literature in just the last 2-3 years. A few reports have been presented below in a tabular format with the corresponding reference alongside (Table 3). Subsequently, another table presents some important natural products that have been synthesized employing lipase-catalyzed resolution of a secondary alcohol as the key step (Table 4).

Table 3. Selected examples of lipase-catalyzed resolution of secondary alcohols

Product	**Lipase used**	**% Yield**	**% Ee**	**Reference**
 **21**	Amano PS	40	96	30
 **22**	Novozym 435	43	93	31

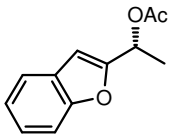
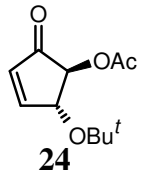
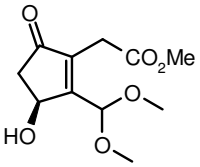
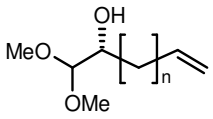
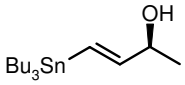
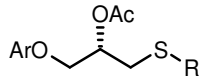
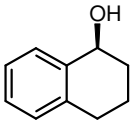
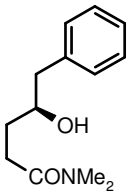
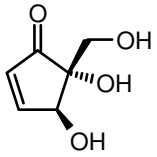
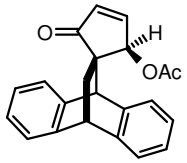
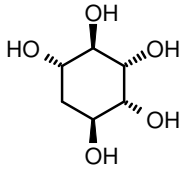
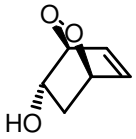
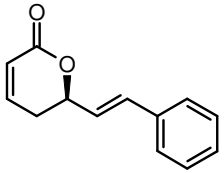
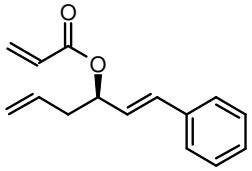
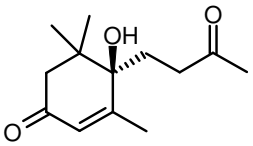
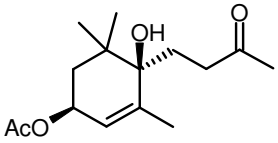
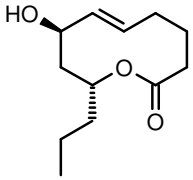
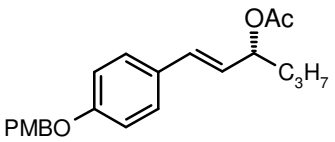
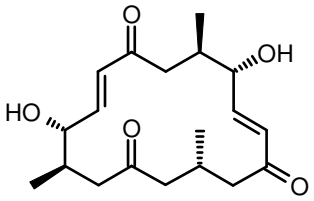
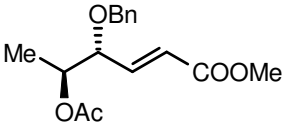
 **23**	Lipase AK	48	99	32
 **24**	Lipase PS	50	95	33
 **25**	CAL-B	48	94	34
 n = 0,1 **26**	CAL-B	50 (conv.)	94/98	35
 **27**	Lipozyme	48	99	36
 Ar = C_6H_5-, 4-CH_3-C_6H_4- R = Et, *n*-Bu, *tert*-Bu **28**	Amano AK	21-62 (conv.)	24-86	37
 **29**	CAL-B	50 (conv.)	>99	38
 **30**	Pseudomonas fluorescence lipase	40	99	39

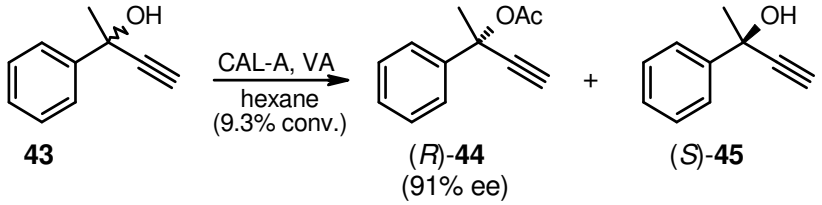
Table 4. Natural products synthesized with the corresponding chiral intermediate prepared by lipase catalyzed resolution

Natural product	Intermediate (yield, % ee)	Lipase used	Ref.
 (−)-Epipentenomycin (**31**)	 **32** (37%, >98)	Amano PS-D	40
 (+)-*proto*-Quercitol (**33**)	 **34** (47%, 91)	CCL	41
 (+)-Goniothalamin (**35**)	 **36** (38%, 93)	CAL-B	42
 (*R*)-Dehydrovomifoliol (**37**)	 **38** (50%, 90)	Lipase PS	43
 (+)-Herabrumin III (**39**)	 **40** (45%, 98)	CAL-B	44
 (+)-Macrosphelide (**41**)	 **42** (48%, >99)	Amano PS	45

3A.4.3 Tertiary alcohols

The kinetic resolution of tertiary alcohols using lipases is not that well documented in the literature. This is probably due to the adverse steric interactions caused by the tertiary alcohols and consequently the difficulty associated with the accommodation of these substrates into the active site of the lipases. Bornscheuer and co-workers reported the enantioselective transesterification of the tertiary alcohol **43** using lipase A from *Candida antartica* (CAL-A).[46] This was the first example of a highly enantioselective enzyme-catalyzed resolution of a tertiary alcohol and the acetate (*R*)-**44** was obtained with 91% ee (Scheme 1). The ee of the unreacted substrate was not determined due to very low conversion.

Scheme 1



The major drawback with kinetic resolution is that a maximum of 50% of the starting material can be used to give product. This has a huge impact in total synthesis of complex molecules involving several steps as it would drastically affect the overall yield. Yet, since kinetic resolution offers many other advantages, chemists sought ways of circumventing this problem. Two excellent methods which have grown in popularity of late are (i) employing *meso* substrates ("the *meso* trick") or prochiral substrates, wherein all of the starting material can be utilized and (ii) racemizing the nonreacting enantiomer in kinetic resolution continuously (in situ) during the enzymatic resolution so that all of the racemic starting material can be used for transformation into one enantiomer. The former involves desymmetrization of compounds possessing a plane of symmetry whereas the latter is termed as dynamic kinetic resolution (DKR).

3A.5 Summary

The use of enzymes in organic synthesis is widely accepted since the past 3-decades and the selected examples illustrated in this section demonstrate the broad applicability of lipases in terms of substrate structures and enantioselectivity. For their remarkable properties, enzymes were declared "Reagent of the Year" in 2000. As more and more synthetic research embraces the realization that enzymes are simply an alternative source of catalysis that may be as robust as others, sometimes more so, then their use will continue to flourish. Greater availability at a lower cost brought about by modern biotechnology will further assist in driving out any existing discrimination against enzymes as practical catalysts. Protein engineering has an exciting potential of altering the enzymatic properties at will, eg., broadening substrate specificity, as well enhancing enzyme action in organic media. Rational design of new enzymatic catalysts to construct a protein with designed catalytic activity selectivity from a designed sequence of amino acids is still very far from reality. Thus, the concept of artificial enzymes offers an attractive alternative though whether they will be able to match their natural counterparts is debatable. Considering their applications in the past, it can be therefore, said with assurance, that the impact that enzymes, lipases in particular, have had in organic synthesis has been enormous and their ever-increasing utilization is rather evident in the present scientific world. Recent developments only go to show that more pathbreaking methods and processes brought about by the catalysts of Nature lie in store for us in the future.

In our group, over the past few years, we have been successfully using the enzymes in preparation of important chiral intermediates and have also carried out studies relating to their selectivity pattern.[47] More recently, as a part of present dissertation, we have synthesized some naturally occurring bioactive γ-butyrolactones and γ-alkylidenebutenolides and their derivatives utilizing lipases for the resolution of key intermediate or in significant transformation, which will be discussed in detail in the following sections.

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3B. Section B

An Efficient Amano PS-Catalyzed Chemo-, Regio- and Enantioselective Hydrolysis of (±)-2,3-Di-O-acetyl-2-C-methyl-D-erythrono-1,4-lactone: A Facile Preparation of Bioactive Natural Products (–)-Saccharinic Acid Lactone and Potassium (2R,3R)-2,3,4-trihydroxy-2-methylbutanoate

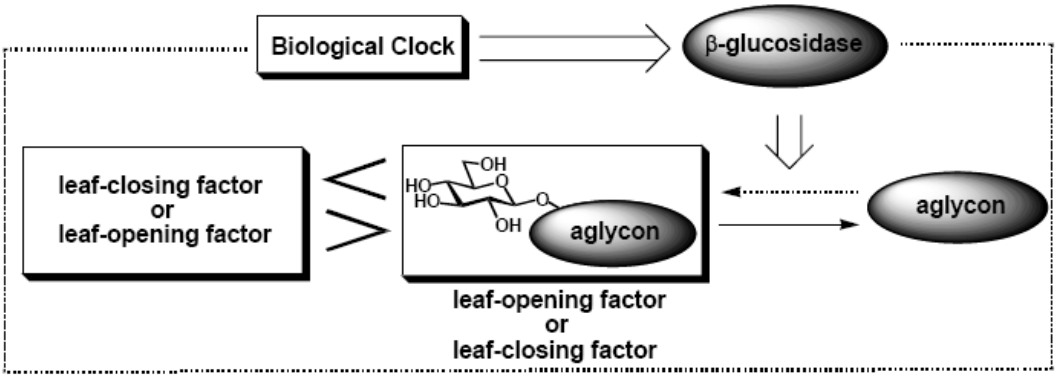
This section features the following topics:

3B. Section B: An Efficient Amano PS-Catalyzed Chemo-, Regio- and Enantioselective Hydrolysis of (±)-2,3-Di-*O*-acetyl-2-*C*-ethyl-D-erythrono-1,4-lactone: A Facile Preparation of Bioactive Natural Products (–)-Saccharinic Acid Lactone and Potassium (2*R*,3*R*)-2,3,4-Trihydroxy-2-methylbutanoate

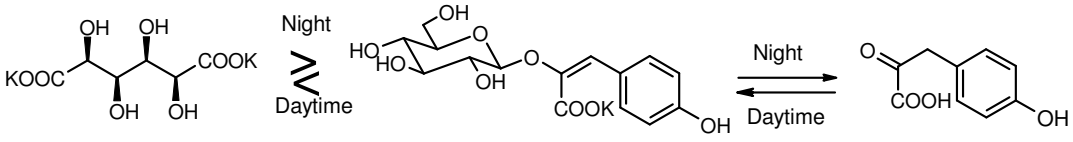
3B.1 Background

In general, plants are rooted and are unable to demonstrate mobility, however, a variety of plants are able to move in certain ways. Some plants are known to open their leaves in the daytime and close their leaves at night.[1] This circadian rhythmic leaf movement known as nyctinasty is widely observed in leguminous plants. This rhythm is regulated by a biological clock with a cycle of about 24 hours.[2] The phenomenon has been noted by scientists for centuries, with the oldest records dating from the time of Alexander the Great and a biological clock was discovered in 1729 from the careful observation of nyctinasty in *Mimosa pudica*. However, despite the advances that have been made in the interim, it has proven difficult to determine the detailed molecular mechanisms of these processes. Leaf-movement in nyctinastic plants has long been believed to be controlled by a common phytohormone. However, Yamamura and co-workers result contradict this theory.[3] Indeed, they developed a new theory of the chemical control of nyctinastic leaf movement; nyctinastic leaf-movement is controlled by the balance of concentration between two bioactive substances, leaf-opening and closing substances, which is inversed through the day according to the rhythm created by their biological clock. A biological clock regulates this balance through the control of the enzyme β-glucosidase activity.

Yamamura and co-workers have demonstrated that the regulation of all nyctinastic leaf movements can be explained by one mechanism, namely, that either the leaf-closing or leaf-opening substance is a glycoside and the glycoside is deactivated by a β-glucosidase, the activity of which is controlled by a biological clock.[4] Their model for the regulation of leaf movement is shown in figure 1. According to this model, there exist two types of plants, one has a glycoside-type leaf-opening substance which is formed in the morning from its aglycon and hydrolyzed to its aglycon in the evening by the activation of a β-glucosidase. The other has a glycoside-type leaf-closing substance which is formed in the evening from its aglycon and hydrolyzed to its aglycon in the morning by the activation



(1) Leaf-opening substance is glucoside (*Lespedeza cuneata* G. Don)



(2) Leaf-closinging substance is glucoside (*Phyllanthus urinaria*)

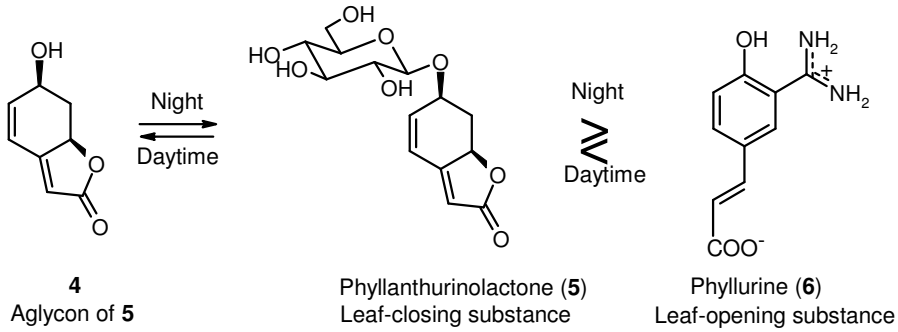


Figure 1. Universal mechanism of nyctinasty controlled by a biological clock

of *β*-glucosidase. The concentration of the nonglycoside leaf-opening/leaf-closing factor remains as it is in both day and night time.

Recently, Ueda et al. have authoritatively identified several bioactive substances that regulate this leaf-movement and they have demonstrated that these leaf movements are essential for the survival of legumes and they envisioned that the plant-specific leaf-movement factors could be useful as a herbicides.[3] *Leucaena leucocephalam* (gin-nemu in Japanese), a leguminous tropical plant is known for its rapid growth and secretion of

allelochemicals to inhibit the growth of other plants around them, which leads to a grove of that plant and elimination of vicinal plants.[5] Thus, the disruption of an ecosystem by *L. leucocephalam* is a serious problem. Very recently, Ueda et al. have isolated potassium 2,3,4-trihydroxy-2-methyl-butanoate (**9**) as a leaf-closing substance of *Leucaena leucocephalam*[6] and potassium aeshynomate (**10**) as a leaf-opening substance of *Aeshynomene indica* L. (Figure 2).[7] Their structural determination was done by means of FAB MS, ^{1}H NMR, HMQC and HMBC experiments. Compound **9** was effective for the leaf-closing of *L. leucocephalam* at 1×10^{-6} M.[6] Compound **10** was quite effective for the leaf-opening of *A. indica* L. at 1×10^{-3} M and it was found to be a new type of leaf-movement factor containing a novel γ-amino acid moiety.[7]

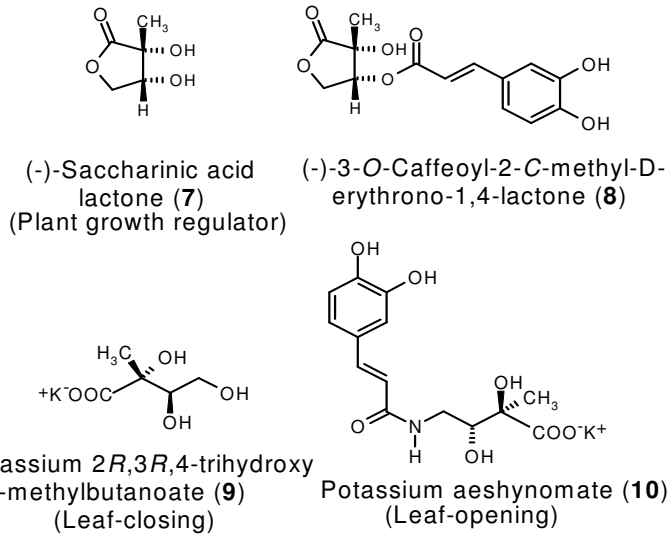


Figure 2. Naturally occruing bioactive α,β-dihydroxylactones/carboxylic acids

The saccharinic acid lactone [**7**, (2*R*,3*R*)-2,3-dihydroxy-2-methyl-γ-butyrolactone] is a potential precursor of leaf-closing substance **9** and it has been also earlier isolated as a natural product from *Astragalus lusitanicus* L.[8] and *Cicer arietinum* L.[9] The natural lactone (–)-**7** was thought to be a plant growth regulator involved in feedback inhibition in biosynthesis of valine.[10] In the recent years a number of natural products have been isolated which contain the saccharinic acid lactone [(–)-**7**] unit. Very recently, Ogawa et al. have isolated a new sugar lactone derivative, 3-*O*-caffeoyl-2-*C*-methyl-D-erythrono-1,4-lactone [(–)-**8**] from the leaves of *Bidens pilosa* (Figure 2).[11] Its structure was elucidated on the basis of chemical and spectral evidence. To date, four syntheses of *erythro*-saccharinic acid lactone are known starting from 2-methyl-D-erythrose,[12] D-mannitol,[10] methyl pyruvate (via asymmetric aldol reaction)[13] and D-arabinose.[14]

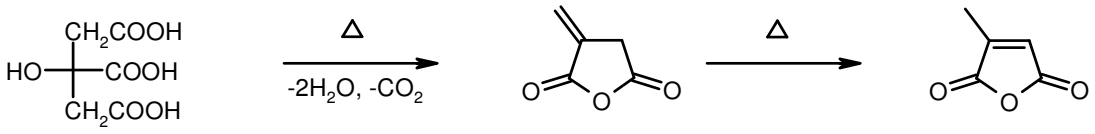
This section reports a facile 6-step synthesis of leaf closing substance (±)-*erythro* potassium 2,3,4-trihydroxy-2-methyl-butanoate (**9**) starting from citraconic anhydride (**13**) with 29% overall yield. In this section we also describe our studies on enantioselective Amano PS-catalyzed hydrolysis of diacetyl lactone (±)-**58** to obtain the enantiomerically pure lactones (+)-**7** and (–)-**7** in 45% yield (99% ee) (2-steps) and 46% yield (99% ee) respectively, followed by our studies on synthesis of natural products (–)-**8** and **10** (Schemes 9-13).

The utilities of the starting material methylmaleic anhydride (citraconic anhydride, **13**) have been well proved in laboratory as well as in industrial practice.[15] Methylmaleic anhydride has been used for the synthesis of important bioactive natural products,[16] heterocyclic systems,[17] as a potential dienophile in the Diels-Alder reaction[18] and as monomers in polymer chemistry.[19] A few representative examples of the application of citraconic anhydride as starting material in natural product synthesis are listed in table 1. To date, three nice methods are known for the synthesis of methylmaleic anhydride, which are discussed briefly below (Schemes 1-3). In our laboratory, one more method has been developed for methylmaleimide, which can be transformed to methylmaleic anhydride (Scheme 4)[20] (*for convenience the chemistry of methylmaleic anhydride has been summarized here*).

Synthesis of methylmaleic anhydride

Methylmaleic anhydride (citraconic anhydride, **13**) was prepared by Roll et al. from citric acid (**11**) in two-steps with 34% overall yield (Scheme 1).[21] Citric acid (**11**) was heated over a free flame and the fraction which distills around 175-190 °C was collected. On heating, **11** undergoes double dehydrative decarboxylation to furnish itaconic anhydride (**12**), which on further heating (210-215 °C) isomerizes and distills out as methylmaleic anhydride (**13**).

Scheme 1

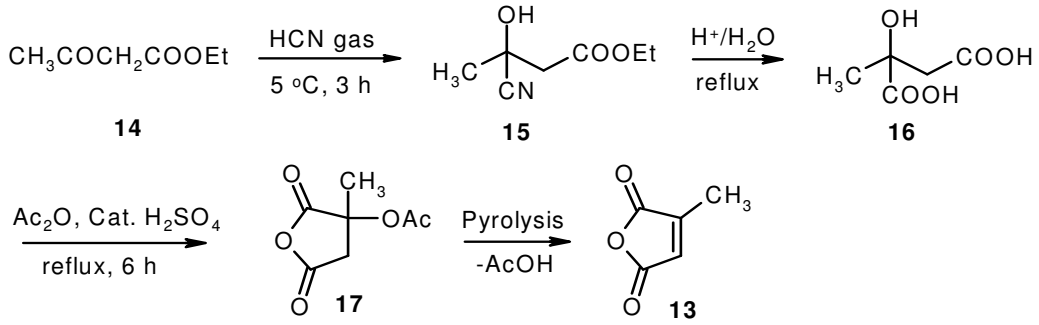


11 **12** **13**

The second approach was reported by Tanaka and co-workers. In this approach, ethyl acetoacetate (**14**) was quantitatively converted into the corresponding cyanohydrin **15**,

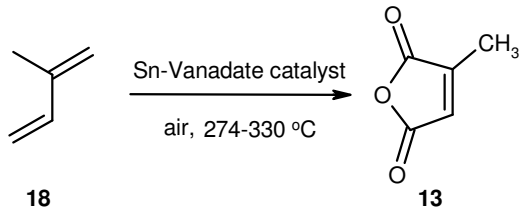
which on acid catalyzed hydrolysis followed by dehydrative cyclization and pyrolysis furnished methylmaleic anhydride (**13**) with 46% overall yield in 4-steps (Scheme 2).[22]

Scheme 2

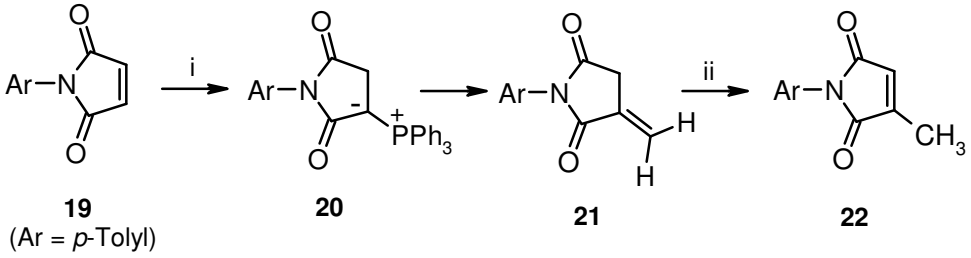


The third approach was reported by Pichler et al. by gas phase oxidation of isoprene (**18**) in presence of air using Sn-Vanadate catalyst at the temperature range of 274-330 °C to furnish methylmaleic anhydride (**13**) with 21% yield (Scheme 3).[23]

Scheme 3

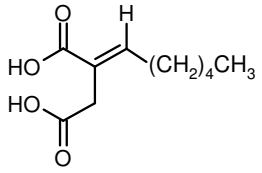
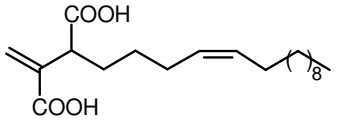
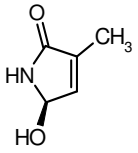
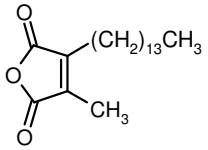
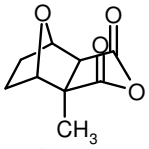
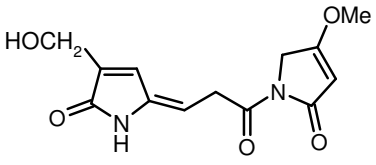
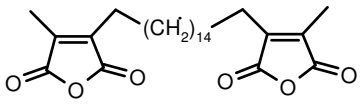


Recently, a two-step method has been developed in our group to synthesize **22** (Scheme 4) starting from maleimide **19**, using Wittig reaction (86% yield, 2-steps).[20]



Scheme 4. *Reagents, conditions and yields*: (i) PPh_3, $(CH_2O)_n$, AcOH, reflux, 1 h (92%); (ii) TEA, THF, reflux, 3 h (93%).

Table 1: Use of citraconic anhydride as starting material in natural product synthesis

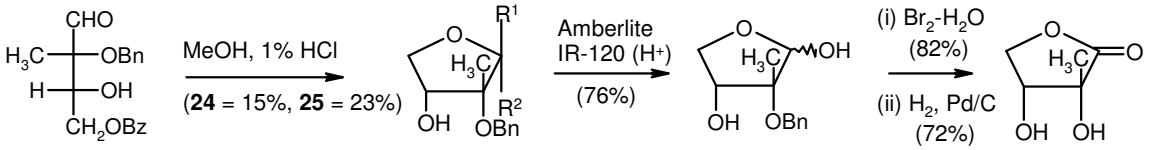
No.	Compound Synthesized	Source	Activity	Ref.
1	 (±)-Piliformic acid	*Hypoxylon deustum*	Anti-tumor	24a
2	 1,7(*Z*)-Nonadecadiene-2,3--dicarboxylic acid	*Ceriporiopsis subvermispora*	Not known	24b
3	 Jatropham	*Jatropha macrohiza*	Anti-tumor	25
4	 Chaetomellic anhydride A	*Chaetomella acutiseta*	Inhibitors of ras farnesyl-protein transferase	24b
5	 (-)-Palasonin	*Butea frondosa*	Cell proliferation inhibitors	26
6	 Pukilimide	*Lyngbya majuscula*	Not known	27
7	 Tyromycin A	*Tyromyces lacteus*	Aminopeptidase Inhibitor	28, 29

3B.1.1 Synthetic approaches towards (–)-saccharinic acid lactone and potassium 2,3,4-trihydroxy-2-methylbutanoate

[A] Yamaura's approach towards (–)-saccharinic acid lactone

Yamaura and co-workers reported[12] the synthesis of saccharinic acid lactone starting from 4-*O*-benzoyl-2-*O*-benzyl-2-*C*-methyl-D-erythrose[12a] (**23**), which on treatment with methanol containing 1% HCl followed by hydrolysis of methyl ether by cation-exchange resin, oxidation of the resulting lactol **26** to lactone and hydrogenolysis gave (**–**)-saccharinic acid lactone **7** with 17% yield over 4-steps (Scheme 5).

Scheme 5



23 (Bn = $PhCH_2$, Bz = PhCO)

24 (R^1 = OMe, R^2 = H)
25 (R^2 = OMe, R^1 = H)

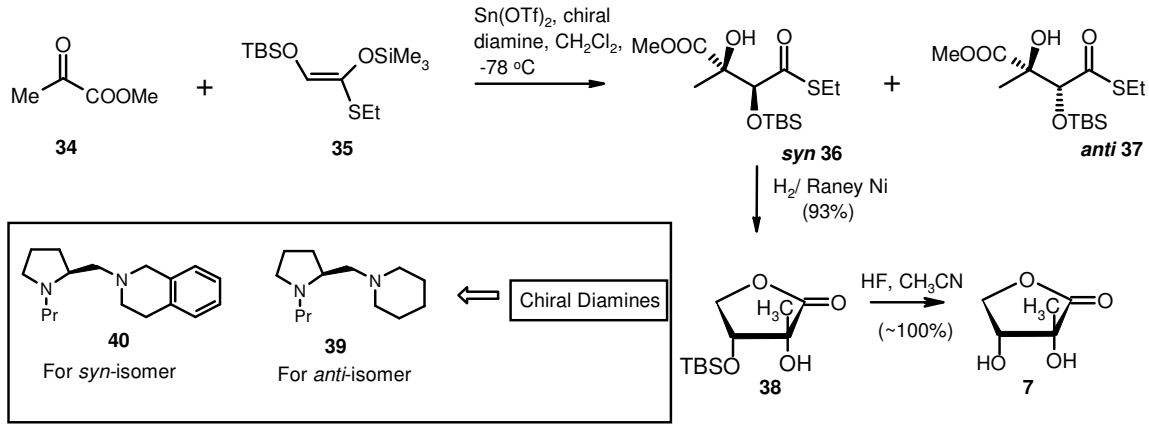
26

7

[B] Kobayashi's approach towards (–)-saccharinic acid lactone

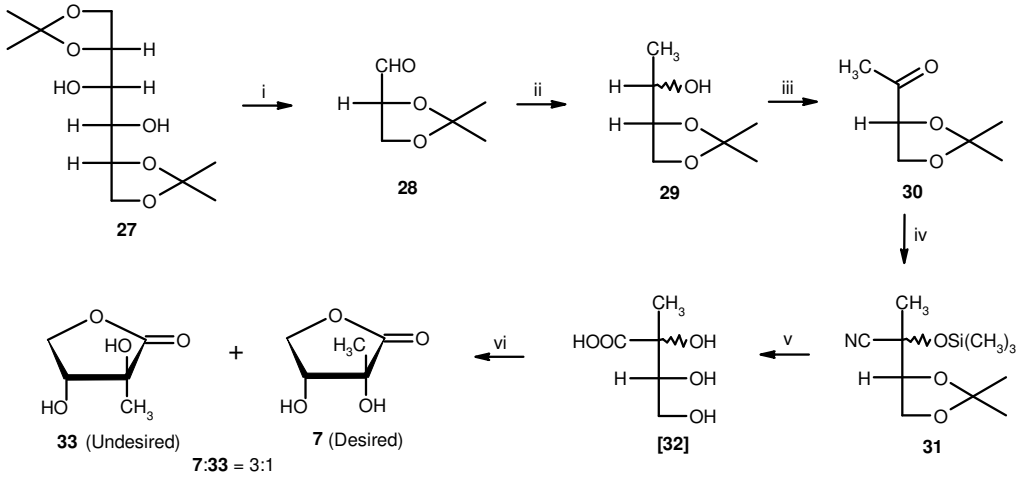
Kobayashi et al. accomplished the synthesis of (**–**)-saccharinic acid lactone (**7**) starting from methyl pyruvate, which on Lewis acid catalyzed aldol condensation with silyloxy enol **35** in presence of chiral amines **39** and **40** gave both the *syn*- and *anti*-alcohols.[13] Using chiral amines **39** and **40**, they obtained highest yield of *anti*-alcohol **37** (82%) and *syn*-alcohol **36** (94%) respectively. Regioselective reduction of thioester group of **36** followed by TBDMS deprotection gave (**–**)-saccharinic acid lactone (**7**) in 93% yield (two-steps) (Scheme 6).

Scheme 6



[C] Bacher's approach towards (–)-saccharinic acid lactone

Third synthesis of this lactone was performed by Bacher and co-workers.[10] They

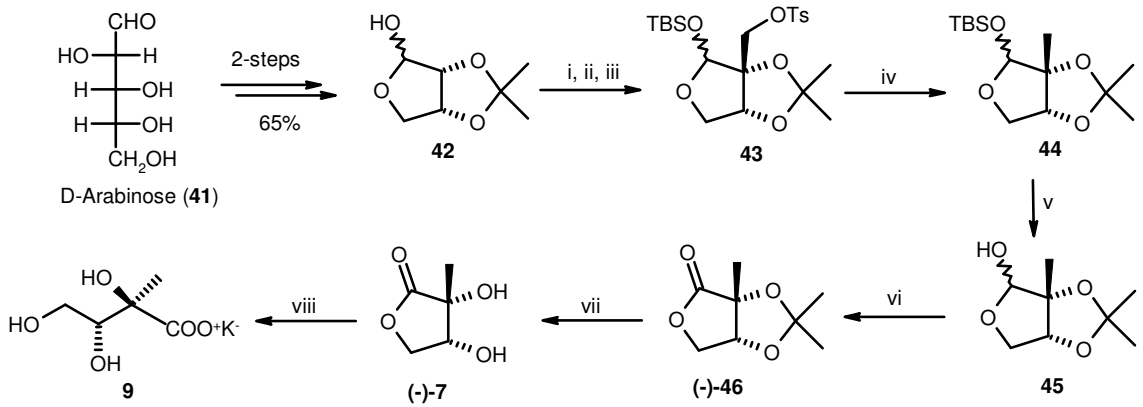


Scheme 7. *Reagents, conditions and yields*: (i) $Pb(OAc)_4$, CH_2Cl_2, 0 ^oC, 12 h (76%); (ii) MeMgI, Et_2O, 0 ^oC to 25 ^oC, 12 h (84%); (iii) RuO_2, $NaIO_4$, K_2CO_3, $CHCl_3/H_2O$, 25 ^oC (74%); (iv) Me_3SiCN, KCN, 18-crown-6, CH_2Cl_2, 0 ^oC to 25 ^oC, 30 min. (99%); (v) HCl (25%), EtOH, 40 ^oC to 0 ^oC, 3 h; (vi) HCOOH (60%), 80 ^oC, 2 h (91%, 2-steps).

started from acetonide protected mannitol (**27**), which on oxidative cleavage furnished aldehyde **28**. This aldehyde **28** on Grignard reaction with MeMgBr followed by RuO_4 catalyzed oxidation of secondary alcoholic group to ketone and nucleophilic attack of KCN on this carbonyl in presence of Me_3SiCN gave cyano compound **31**, which on acid catalyzed hydrolysis followed by lactonization furnished **(–)-**saccharinic acid lactone (**7**) with 32% yield in 6-steps (Scheme 7).

[D] Koumbis's approach towards (–)-saccharinic acid lactone and potassium 2,3,4-trihydroxy-2-methylbutanoate

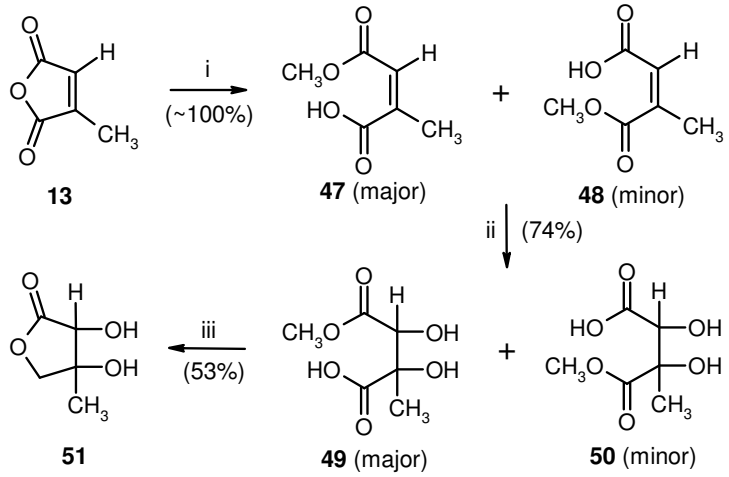
Recently, Koumbis and co-workers reported fourth synthesis of (–)-saccharinic acid lactone (**7**) and second synthesis of leaf closing compound potassium 2,3,4-trihydroxy-2-methylbutanoate (**9**) starting from D-arabinose (Scheme 8).[14a] They started the synthesis from lactol **42**, which was synthesized from D-arabinose.[14b] Lactol **42** on K_2CO_3 catalyzed alkylation with HCHO followed by regioselective tosylation of primary hydroxyl group, TBDMS protection of secondary hydroxyl group, $LiAlH_4$ reduction, TBDMS deprotection, oxidation of lactol to lactone and acetonide deprotection afforded (–)-saccharinic acid lactone (**7**) in 38% yield (9-steps). The lactone **7** on treatment with aqueous KOH gave the leaf closing compound **9** with 99% yield.



Scheme 8. *Reagents, conditions and yields*: (i) HCHO, K_2CO_3, MeOH, 65 ^oC, (82%); (ii) TsCl, pyridine, rt (90%); (iii) TBSCl, imidazole, CH_2Cl_2, rt (98%); (iv) $LiAlH_4$, THF, 60 ^oC (96%); (v) TBAF, AcOH, THF, 0 ^oC to rt (99%); (vi) CrO_3, pyridine, Ac_2O, CH_2Cl_2, rt (89%); (vii) TFA, H_2O, 0 ^oC to rt (95%); (viii) KOH, H_2O, 0 ^oC to rt (99%).

3B.2 Present work: Results and Discussion

The reaction of citraconic anhydride (**13**) with methanol at 0 ºC was fairly regioselective at the unhindered carbonyl[24a] and furnished the mixture of regioisomers of esters **47** and **48** in 86:14 ratio (by ^1H NMR) in nearly 100% yield (Scheme 9). In the above reaction the major isomer **47** is probably a kinetically controlled product as the ^1H

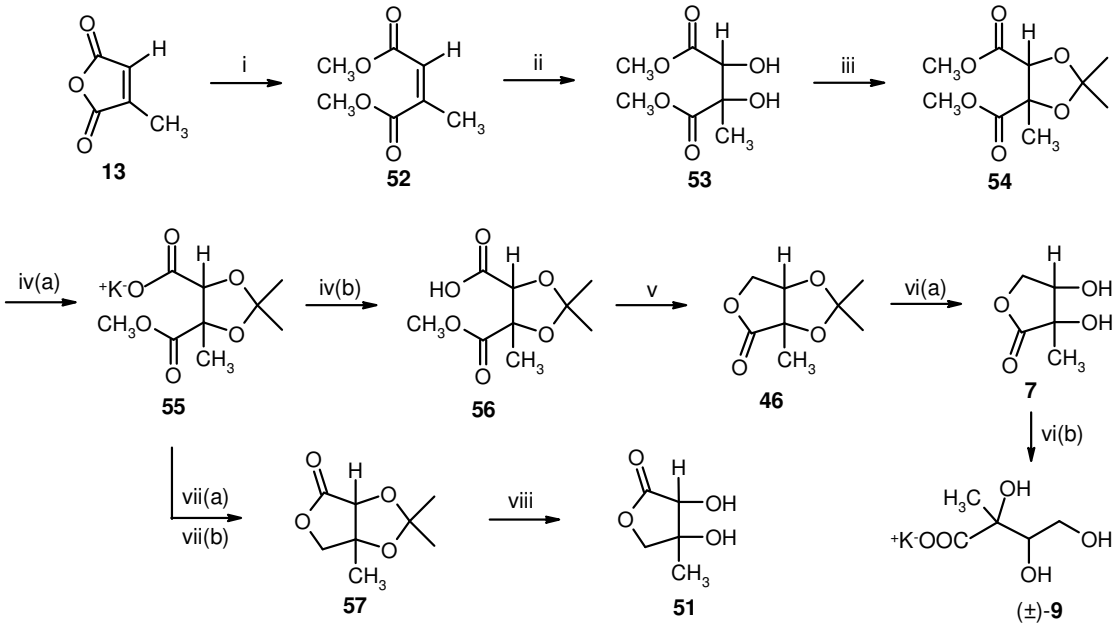


Scheme 9. *Reagents, conditions and yields*: (i) CH_3OH, 0 ºC, 60 h (~100%, **47**:**48** = 86:14); (ii) OsO_4, NMO, *t*-BuOH, CH_3COCH_3, rt, 72 h (74%, **49**:**50** = 85:15), (two recrystallizations of **49** plus **50** mixture with ethyl acetate furnished pure **49** in 50% yield); (iii) $NaBH_4$, CH_3OH, reflux, 12 h (53%).

NMR spectrum of above mixture after one-month time revealed the presence of **47** and **48** to be 1:1 and the migration of methoxy group might be taking place via the intermediate

cyclic anhydride **13**. The OsO_4-induced *cis*-dihydroxylation of above **47** plus **48** mixture (86:14) again furnished the mixture of diols **49** and **50** in 85:15 ratio (by ^1H NMR) in 74% yield. Two recrystallizations of mixture of diols **49** plus **50** with ethyl acetate gave the pure diol **49** in 50% yield. Surprisingly, the $NaBH_4$-reduction of mixture of **49** plus **50** or pure **49** in methanol, exclusively furnished the undesired lactone **51** in 53% yield. The structural assignment of lactone **51** was done on the basis of three clean singlets in the ^1H NMR spectrum and ^{13}C NMR spectra. Thus our first straightforward approach to obtain **9** met with failure and then we planned for synthesis of **9** using a different synthetic route as depicted in scheme 10.

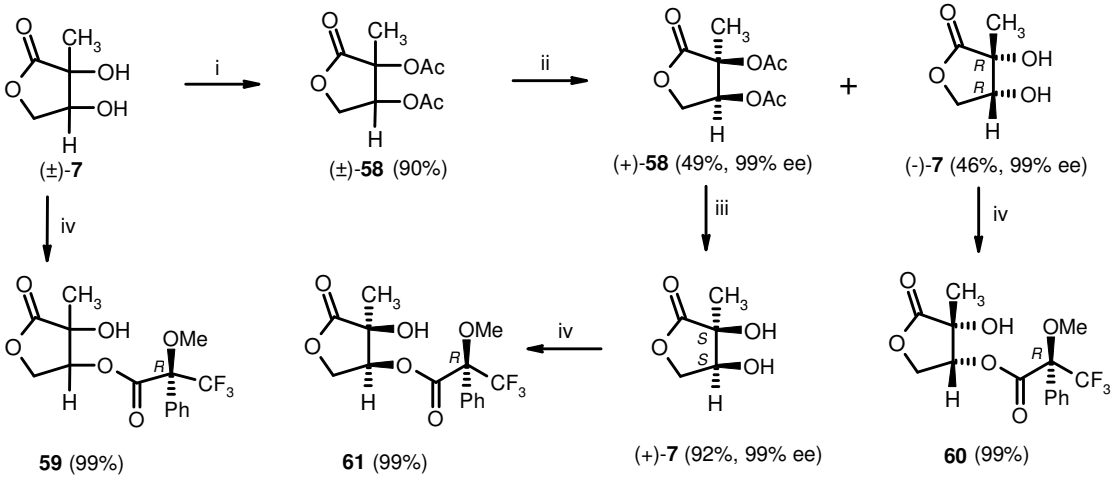
The citraconic anhydride (**13**) on treatment with methanol and catalytic amount of conc. H_2SO_4 under reflux, furnished the diester **52** in nearly 100% yield. The OsO_4-induced *cis*-dihydroxylation of **52** gave the diol **53** in 99% yield. The *cis*-diol moiety in compound **53** was protected as an acetonide using 2,2-dimethoxypropane and catalytic amount of *para*-toluenesulfonic acid (*p*-TSA) to obtain compound **54** in 92% yield. The highly regioselective hydrolysis of unhindered ester moiety in compound **54** using one equivalent of KOH in methanol at room temperature followed by acidification gave the desired



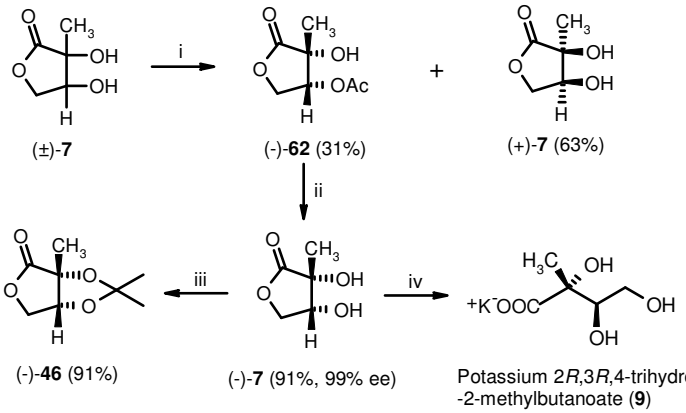
Scheme 10. *Reagents, conditions and yields*: (i) CH_3OH, H_2SO_4, reflux, 12 h (~100%); (ii) OsO_4, NMO, *t*-BuOH, CH_3COCH_3, rt, 60 h (99%); (iii) $(CH_3)_2C(OCH_3)_2$, *p*-TSA, benzene, reflux, 3 h (92%); (iv) (a) KOH, CH_3OH, rt, 2 h (~100%); (iv) (b) 2 N HCl, (66%); (v) $BH_3(CH_3)_2S$, THF, –8 ^oC to rt, 36 h (50%); (vi) (a) CF_3COOH, H_2O, 0 ^oC to rt, 24 h (97%); (vi) (b) KOH, rt, 10 min.; (vii) (a) $LiBH_4$, THF, 0 ^oC to rt, 6 h; (b) Dil. HCl (60%); (viii) CF_3COOH, THF, H_2O, 0 ^oC to rt, 3 h (78%).

monoacid **56** in 66% yield. The borane-dimethylsulfide complex induced chemoselective reduction of carboxylic group in compound **56** furnished the desired diol-protected lactone **46** in 50% yield.[30,31] The deprotection of the acetonide moiety using catalytic amount of TFA in water gave the desired lactone **7** in 97% yield. The treatment of lactone-diol **7** with aqueous KOH at room temperature gave the desired leaf-closing compound (±)-*erythro* potassium 2,3,4-trihydroxy-2-methylbutanoate (**9**).[32] The analytical and spectral data obtained for lactones **46** and **7** and leaf-closing compound **9** were in complete agreement with reported data.[6,10,13] As expected the $LiBH_4$-reduction of compound **55** gave the undesired diol-protected lactone **57** in 60% yield, which on deprotection of acetonide moiety gave the undesired lactone **51** in 78% yield.

Then we prepared a systematic plan to study the enzyme-catalyzed enantioselective hydrolysis of diacetyl lactone (±)-**58** and the enzyme-catalyzed enantioselective acylation of dihydroxy lactone (±)-**7**. The lactone (±)-**7** on treatment with Ac_2O in the presence of pyridine gave diacetyl lactone (±)-**58** in 90% yield (Scheme 11). The enzyme Amano PS did not recognize the substrate (±)-**58** at 25 °C, while we observed 26%, 30% and 33% hydrolysis of (±)-**58** to (–)-**7** at 30, 35 and 40 °C respectively, in 36 hours time. The Amano PS-catalyzed biphasic chemo-, regio- and enantioselective hydrolysis of the diacetyl lactone (±)-**58** at 45 °C directly furnished nearly 1:1 mixture (by ^1H NMR) of the dihydroxy lactone (–)-**7** with the recognition of secondary (*R*)-acetate in the presence of γ-lactone and tertiary acetate and the unrecognized diacetyl lactone (+)-**58** in 36 hours



Scheme 11. *Reagents, conditions and yields*: (i) Ac_2O, pyridine, rt, 12 h (90%); (ii) Amano PS, petroleum ether/benzene (2:1), sodium phosphate buffer (0.1 M, pH 7.0), 45 °C, 36 h, (+)-**58** (49%) and (–)-**7** (46%); (iii) K_2CO_3, CH_3OH, 0 °C to rt, 3 h (92%); (iv) (*R*)-Mosher's acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 8 h.

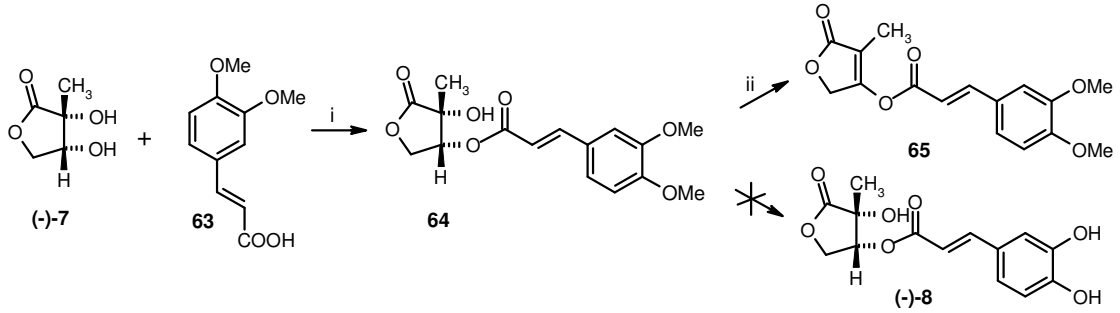


Scheme 12. *Reagents, conditions and yields*: (i) Amano PS, vinyl acetate, *n*-hexane/benzene (2:1), 45 °C, 96 h, (+)-**7** (63%) and (–)-**62** (31%); (ii) K_2CO_3, CH_3OH, 0 °C to rt, 3 h (91%); (iii) $(CH_3)_2C(OCH_3)_2$, *p*-TSA, rt, 10 h (91%); (iv) Aq. KOH (1 equiv.), rt, 10 min (~100%).

reaction time. The above formed mixture of (–)-**7** and (+)-**58** was easily separated by using silica gel column chromatography to obtain (–)-**7** in 46% yield and (+)-**58** in 49% yield. Herein, we propose[33] that the enzyme first recognizes the secondary acetate group to form the inisolable intermediate vicinal hydroxyacetate, which on in situ intramolecular hydroxy catalyzed further hydrolysis furnishes the (–)-**7**. The diacetyl lactone (+)-**58** on base catalyzed methanolysis gave (+)-**7** in 92% yield. The stereochemical assignments of the lactones (+)-**7** and (–)-**7** were done on the basis of comparison with literature data.[10,12] The ^{1}H NMR spectrum of diastereomeric mixture of Mosher's esters[34,35] obtained from dihydroxy lactone (±)-**7** and (*R*)-Mosher's acid showed a very clean resolution of the signals for methoxy and methylene group protons on the lactone moiety. The ^{1}H NMR spectrum of Mosher's esters of lactones (+)-**7** and (–)-**7** revealed that both of them possess plus 99% ee. Next we performed the Amano PS-catalyzed acylation of dihydroxy lactone (±)-**7** using vinyl acetate as an acyl donor at 45 °C and obtained the monoacetyl lactone (–)-**62** in 31% yield and the dihydroxy lactone (+)-**7** in 63% yield (Scheme 12). The present enzyme-catalyzed acylation was also highly regio- and enantioselective and as expected, exclusively furnished the secondary alcohol, acylated product, (–)-**62**. This monoacetyl lactone (–)-**62** on methanolysis in presence of K_2CO_3 as a catalyst furnished the dihydroxy lactone (–)-**7** in 91% yield with 99% ee. The dihydroxy lactone (–)-**7** on treatment with aqueous KOH at room temperature gave the enantiomerically pure naturally occurring leaf-closing compound, the potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate (**9**) in

quantitative yield.[32] This plant-specific leaf-movement factor **9** could be useful as herbicides.[6]

We then planned to synthesize natural products (–)-**8** and **10** from enantiomerically pure lactone (–)-**7**. The lactone (–)-**7** on treatment with 3,4-dimethoxycinnamic acid (**63**) in the presence of DCC and catalytic amount of DMAP at room temperature exclusively furnished the desired ester (–)-**64** in 85% yield (Scheme 13). Unfortunately, BBr_3-induced demethylation at –78 °C furnished the dehydrated product **65**. Herein the tertiary hydroxyl group got eliminated forming the α,β-unsaturated lactone **65** in preference to the deprotection of the two methyl ether units. However the synthesis of unnatural (+)-**8** using TBDMS protection of phenolic hydroxy groups is known in the literature.[36] The lactone (–)-**7** on reaction with 2,2-dimethoxypropane gave the protected lactone (–)-**46** in 91% yield (Scheme 12). In our hands, all our attempts to ring open the lactone (–)-**46** with sodium azide[37] by the nucleophilic attack of azide anion on a methylene carbon met with failure and hence we were unable to design naturally occurring **10**.



Scheme 13. *Reagents, conditions and yields*: (i) DCC, DMAP, CH_2Cl_2, rt, 10 h (85%); (ii) BBr_3, CH_2Cl_2, -78 ^oC, 0.5 h (64%).

3B.3 Summary

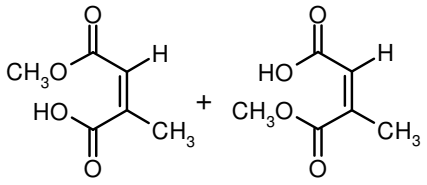
In summary, starting from citraconic anhydride (**13**), we have demonstrated a new six-step route to leaf-closing compound (±)-**9** with 29% overall yield.[38] In the present approach the regioselective hydrolysis of unhindered ester moiety in compound **54** and chemoselective reduction of carboxylic group in compound **56** are the key conversions. During the $NaBH_4$-reduction of **49** the migration of –OMe group from unhindered to hindered site followed by its reduction to generate the undesired regioisomer **51** is noteworthy. We have carried out an efficient practical chemo-, regio- and enantioselective

Amano PS-catalyzed hydrolysis of diacetyl lactone (±)-**58** to obtain the enantiomerically pure lactones (+)-**7** and (–)-**7** in 45% yield (99% ee) (2-steps) and 46% yield (99% ee) respectively.[39] We have also carried out Amano PS-catalyzed enantioselective acylation of (±)-**7** with vinyl acetate as an acyl donor, which was relatively less efficient and furnished (–)-**62** in 31% yield with 99% ee and (+)-**7** in 63% yield. This (–)-saccharinic acid lactone was then converted to leaf closing compound potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate with quantitative yield. We feel that the present highly efficient and selective enzymatic resolution of saccharinic acid lactone is noteworthy and these enantiomerically pure lactones will serve as potential building blocks for the synthesis of several natural and unnatural bioactive products.

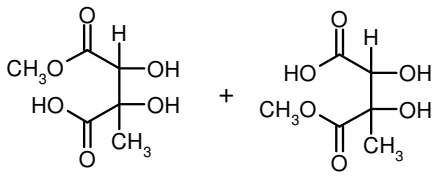
3B.4 Experimental Section

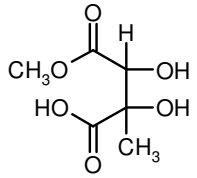
Melting points are uncorrected. Column chromatographic separations were carried out on silica gel (60-120 mesh). Commercially available citraconic anhydride, osmium tetraoxide, *N*-methylmorpholine *N*-oxide, sodium borohydride, 2,2-dimethoxypropane, *p*-toluenesulfonic acid, borane-methyl sulfide complex, trifluroacetic acid, acetic anhydride, DCC, DMAP, vinyl acetate, 3,4-dimethoxycinnamic acid, boron tribromide and (*R*)-Mosher's acid were used. Stereochemical assignments are based on the optical rotation of known compounds. Amano PS-1400 U from Amano Pharmaceuticals, Japan was used. The activity of the lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder.[40]

2-Methyl-but-2-enedioic acid 4-methyl ester & 2-methyl-but-2-enedioic acid 1-methyl ester (47 & 48). A solution of citraconic anhydride (**13**, 1.00 g, 8.93 mmol) in CH_3OH (6 mL) was stirred at 0 ^oC for 60 h under an argon atmosphere. The reaction mixture was then concentrated and dried in vacuo to obtain compounds **47** & **48** (1.28 g, ~100%) in the ratio 86:14 respectively. The obtained compounds **47** & **48** were used for the next step without any further purification.

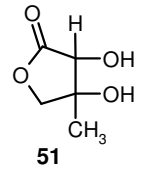
 **47** (major) **48** (minor) $C_6H_8O_4$ (144)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 500 MHz), major isomer: δ 2.09 (s, 3H), 3.82 (s, 3H), 5.90 (s, 1H), 9.43 (bs, 1H), minor isomer: δ 2.12 (s, 3H), 3.79 (s, 3H), 6.08 (s, 1H), 9.43 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz), major isomer: δ 20.8, 52.6, 121.0, 147.4, 169.1, 169.2, minor isomer: δ 21.3, 52.5, 122.6, 145.5, 166.1, 166.8. **IR** (Neat) ν_{max} 1771, 1728, 1651, 1448 cm^{-1}.

2,3-Dihydroxy-2-methyl-succinic acid 4-methyl ester & 2,3-dihydroxy-2-methyl-succinic acid 1-methyl ester (49 & 50). To a solution of olefins **47** & **48** (1.00 g, 6.94 mmol) in *t*-BuOH (12 mL) and acetone (3 mL) was added OsO_4 (0.5 mL, 0.08 mmol, 4% solution in *t*-BuOH) and NMO (7 mL, 60% aqueous solution) with constant stirring at room temperature. Reaction mixture was further stirred for 72 h and then quenched with addition of solid Na_2SO_3 (1.60 g). The reaction mixture was stirred for 1 h at room temperature and then concentrated and dried in vacuo. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (95:5) to furnish **49** & **50** (915 mg, 74%) as white crystalline solid. Analytically pure **49** (618 mg, 50%) was obtained by two recrystallizations from ethyl acetate.

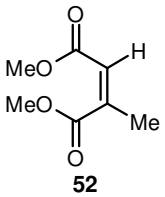
 **49** (major) **50** (minor) $C_6H_{10}O_6$ (178)	**Mp** 120-125 ^{o}C. **^{1}H NMR** (mixture), ($CDCl_3$ + CD_3COCD_3, 500 MHz), major isomer: δ 1.46 (s, 3H), 3.71 (s, 3H), 4.32 (s, 1H), 4.71 (bs, 2H), minor isomer: δ 1.48 (s, 3H), 3.66 (s, 3H), 4.38 (s, 1H), 4.71 (bs, 2H). **IR** (Nujol), mixture ν_{max} 3352, 1753, 1728, 1454 cm^{-1}.

 **49** (major) $C_6H_{10}O_6$ (178)	**Mp** 153-154 ^{o}C. **^{1}H NMR** ($CDCl_3$ + CD_3COCD_3, 500 MHz) δ 1.45 (s, 3H), 3.71 (s, 3H), 4.33 (s, 1H). **^{13}C NMR** ($CDCl_3$ + CD_3COCD_3, 125 MHz) δ 21.7, 51.4, 74.3, 75.6, 171.3, 173.7 **IR** (Nujol) ν_{max} 3389, 3340, 2700-2500, 1738, 1703, 1452 cm^{-1}. **Anal. Calcd for $C_6H_{10}O_6$:** C, 40.45; H, 5.66. Found: C, 40.51; H, 5.72.

3,4-Dihydroxy-4-methyl-dihydro-furan-2-one (51). To a solution of ester **49** (100 mg, 0.56 mmol) in CH_3OH (5 mL) was added $NaBH_4$ (85 mg, 2.25 mmol) and the reaction mixture was refluxed for 12 h. The reaction mixture was then concentrated and dried in vacuo. The residue was acidified with minimum amount of dilute HCl and then extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, concentrated and dried in vacuo to obtain pure **51** (39 mg, 53%).

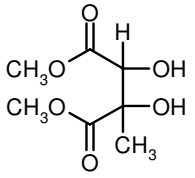
 **51** $C_5H_8O_4$ (132)	Faint yellow thick oil. **^{1}H NMR** (D_2O, 500 MHz) δ 1.34 (s, 3H), 4.22 (s, 2H), 4.38 (s, 1H). **^{13}C NMR** (D_2O, 125 MHz) δ 19.6, 73.3, 75.0, 76.0, 178.5. **IR** (Neat) ν_{max} 3415-3360, 1778, 1117, 1007 cm^{-1}. **Anal. Calcd for $C_5H_8O_4$:** C, 45.46; H, 6.10. Found: C, 45.63; H, 6.22.

Dimethyl methylmaleate (52). A solution of citraconic anhydride (4.48 g, 40 mmol) in methanol (40 mL) and H_2SO_4 (4 mL) mixture was refluxed for 12 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with aqueous solution of $NaHCO_3$, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo gave pure diester **52** (5.65 g, ~100%).

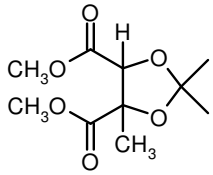
 **52** $C_7H_{10}O_4$ (158)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.04 (bs, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 5.84 (bs, 1H). **IR** (Neat) ν_{max} 1736, 1726, 1655 cm^{-1}.

2,3-Dihydroxy-2-methyl-succinic acid dimethyl ester (53). To a stirred solution of diester **52** (4.00 g, 28.17 mmol) in *t*-BuOH (16 mL) and acetone (4 mL) was added OsO_4 (1.5 mL, 0.24 mmol, 4% solution in *t*-BuOH) and NMO (14 mL, 60% aqueous solution) at room temperature. The reaction mixture was further stirred for 60 h and then quenched with solid Na_2SO_3 (3.0 g). After addition of Na_2SO_3 the reaction mixture was further stirred for 1 h at room temperature, and then concentrated and dried in vacuo. The crude

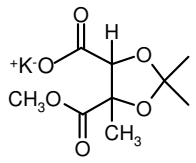
product was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:1) to furnish **53** (5.35 g, 99%) as white crystalline solid.

 **53** $C_7H_{12}O_6$ (192)	**Mp** 94-96 ^oC. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 3.24 (bs, 1H), 3.45 (bs, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 4.37 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 22.4, 52.5, 52.9, 75.5, 76.5, 171.7, 174.6. **IR** ($CHCl_3$) ν_{max} 3491, 3348, 1735, 1726 cm^{-1}. **Anal. Calcd for $C_7H_{12}O_6$:** C, 43.75; H, 6.29. Found: C, 43.69; H, 6.21.

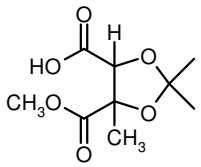
2,2,4-Trimethyl-[1,3]dioxolane-4,5-dicarboxylic acid dimethyl ester (54). To a solution of dihydroxy compound **53** (5.00 g, 26.05 mmol) in benzene (25 mL) was added 2,2-dimethoxypropane (5.42 g, 52.10 mmol) and *p*-toluenesulfonic acid monohydrate (4 mg, 0.02 mmol) and the reaction mixture was refluxed for 3 h using Dean and Stark apparatus containing freshly conditioned 4 Å molecular sieves (5.0 g). The reaction mixture was concentrated and dried in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **54** (5.55 g, 92%).

 **54** $C_{10}H_{16}O_6$ (232)	Faint yellow thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.55 (s, 3H), 1.66 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 4.40 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 22.2, 26.1 (2 *gem*-methyl carbons), 51.8, 51.9, 81.5, 82.9, 111.0, 167.2, 171.1. **IR** ($CHCl_3$) ν_{max} 1761, 1744 cm^{-1}. **Anal. Calcd for $C_{10}H_{16}O_6$:** C, 51.72; H, 6.95. Found: C, 51.66; H, 6.89.

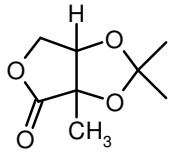
Potassium 2,2,4-trimethyl-[1,3]dioxolane-4-carbmethoxy-5-carboxylate (55). To a solution of diester **54** (4.00 g, 17.24 mmol) in methanol (30 mL) was added a solution of KOH (968 mg, 17.24 mmol) in methanol (15 mL) in a drop wise fashion with constant stirring at room temperature. The reaction mixture was stirred for 1 h and concentrated in vacuo. The residue obtained was washed with $CHCl_3$ (20 mL x 2) to obtain pure **55** (4.40 g, ~100%) as white solid.

 **55** $C_9H_{13}KO_6$ (256)	Mp 234-236 °C. **^{1}H NMR** (D_2O, 200 MHz) δ 1.33 (s, 3H), 1.46 (s, 3H), 1.55 (s, 3H), 3.59 (s, 3H), 4.33 (s, 1H). **^{13}C NMR** (D_2O, 50 MHz) δ 24.9, 28.2, 28.4, 55.3, 85.7, 86.6, 113.3, 175.7, 176.5. **IR** (KBr) ν_{max} 1736, 1628 cm^{-1}.

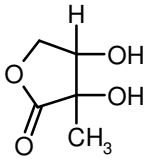
2,2,4-Trimethyl-[1,3]dioxolane-4,5-dicarboxylic acid 4-methyl ester (56). The salt **55** (4.00 g, 15.62 mmol) was acidified to pH 5 with minimum amount of 2 N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to obtain **56** (2.24 g, 66%).

 **56** $C_9H_{14}O_6$ (218)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.37 (s, 3H), 1.48 (s, 3H), 1.62 (s, 3H), 3.66 (s, 3H), 4.36 (s, 1H), 9.15 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 22.5, 26.5, 26.6, 52.3, 81.5, 83.5, 111.7, 171.3, 171.7. **IR** ($CHCl_3$) ν_{max} 1744, 1720 cm^{-1}. **Anal. Calcd for $C_9H_{14}O_6$:** C, 49.54; H, 6.47. Found: C, 49.39; H, 6.51.

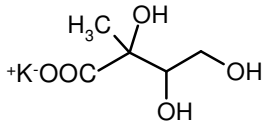
2,2,3*a*-Trimethyl-dihydro-furo[3,4-*d*][1,3]dioxol-4-one (46). To a solution of acid **56** (2.10 g, 9.66 mmol) in THF (25 mL) was added borane-dimethylsulfide complex (804 mg, 10.50 mmol) in THF (1 mL) in a drop wise fashion with constant stirring at ⁻8 °C. The reaction mixture was then allowed to warm up to room temperature and further stirred at room temperature for 36 h. The reaction was quenched with water (3 mL), and the reaction mixture was concentrated in vacuo. The obtained residue was stirred with diethyl ether (40 mL). The organic layer was washed with brine and dried over Na_2SO_4, concentrated and dried in vacuo. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **46** (819 mg, 50%).

 **46** $C_8H_{12}O_4$ (172)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.42 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 4.32 (dd, J = 10 & 4 Hz, 1H), 4.44 (dd, J = 10 & 0 Hz, 1H), 4.49 (dd, J = 4 & 0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 18.4, 26.6, 26.9, 68.9, 80.3, 81.4, 113.0, 176.7. **IR** ($CHCl_3$) ν_{max} 1788, 1379, 1105 cm^{-1}. **Anal. Calcd for $C_8H_{12}O_4$:** C, 55.81; H, 7.02. Found: C, 55.72; H, 6.97.

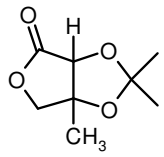
3,4-Dihydroxy-3-methyl-dihydro-furan-2-one (7). To a stirred solution of lactone **46** (790 mg, 4.74 mmol) in water (4 mL) was added trifluroacetic acid (0.04 mL) at 0 ^{o}C. The reaction mixture was allowed to warm up to room temperature and further stirred at room temperature for 24 h. The reaction mixture was then concentrated and dried in vacuo to obtain pure **7** (593 mg, 97%) as faint yellow thick oil.

 **7** $C_5H_8O_4$ (132)	Faint yellow thick oil. **^{1}H NMR** (CD_3OD, 200 MHz) δ 1.37 (s, 3H), 4.04 (dd, J = 4 & 2 Hz, 1H), 4.13 (dd, J = 10 & 2 Hz, 1H), 4.43 (dd, J = 10 & 4 Hz, 1H). **^{13}C NMR** (CD_3OD, 50 MHz) δ 21.6, 73.3, 74.4, 74.6, 180.4. **IR** ($CHCl_3$) 3421, 1778, 1215, 758 cm^{-1}. **Anal. Calcd for $C_5H_8O_4$:** C, 45.46; H, 6.10. Found: C, 45.45; H, 6.19.

Potassium 2,3,4-trihydroxy-2-methylbutanoate (9). To a solution of lactone **7** (10 mg, 0.08 mmol) in water (1 mL) was added KOH (4 mg, 0.08 mmol). The reaction mixture was stirred for 10 minutes and concentrated in vacuo to obtain **9**.

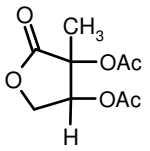
 (±)-**9** $C_5H_9KO_5$ (188)	**^{1}H NMR** (D_2O, 200 MHz) δ 1.34 (s, 3H), 3.57 (m, 2H), 3.80 (m, 1H). **^{13}C NMR** (D_2O, 50 MHz) δ 25.0, 64.9, 78.5, 79.5, 183.5.

2,2,6*a*-Trimethyl-dihydro-furo[3,4-*d*][1,3]dioxol-4-one (57). To the suspension of salt **55** (100 mg, 0.39 mmol) in THF (7 mL) was added $LiBH_4$ (34 mg, 1.56 mmol) at 0 ^{o}C. The reaction mixture was then stirred at room temperature for 6 h. The reaction was quenched with water and the reaction mixture was concentrated in vacuo. The aqueous layer was acidified with minimum amount of dilute HCl and extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, concentrated and dried in vacuo to obtain pure **57** (40 mg, 60%) as white crystalline solid.

 **57** $C_8H_{12}O_4$ (172)	**Mp** 42-44 °C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.49 (s, 3H), 1.54 (s, 3H), 4.15 (d, J = 12 Hz, 1H), 4.45 (d, J = 12 Hz, 1H), 4.46 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 21.9, 27.7, 28.5, 75.7, 79.6, 83.5, 114.1, 174.5. **IR** ($CHCl_3$) ν_{max} 1788, 1383, 1217 cm^{-1}. **Anal. Calcd for $C_8H_{12}O_4$:** C, 55.81; H, 7.02. Found: C, 56.01; H, 7.07.

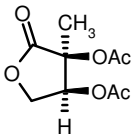
3,4-Dihydroxy-4-methyl-dihydro-furan-2-one (51). To a stirred solution of lactone **57** (20 mg, 0.12 mmol) in THF (2 mL) and water (0.5 mL) was added trifluroacetic acid (0.01 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and further stirred at room temperature for 3 h. The reaction mixture was then concentrated and dried in vacuo to obtain pure **51** in 78% yield. Analytical and spectral data matched with that of compound **51**, obtained from **49**.

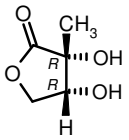
(±)-2,3-Di-*O*-acetyl-2-*C*-methyl-D-erythrono-1,4-lactone (58). To a stirred solution of dihydroxy lactone (±)-**7** (400 mg, 3.03 mmol) in pyridine (5 mL) were added acetic anhydride (0.9 mL, 9.09 mmol) and a catalytic amount of DMAP (10 mg). The reaction mixture was stirred at room temperature for 5 h and then concentrated in vacuo and diluted with water (15 mL). The aqueous layer was extracted with ethyl acetate (15 mL x 5) and the combined organic layer was washed with 5% $CuSO_4$ solution, water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) as an eluant gave diacetyl lactone (±)-**58** (589 mg, 90%) as colourless solid.

 (±)-**58** $C_9H_{12}O_6$ (216)	**Mp** 86-87 °C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.65 (s, 3H), 2.06 (s, 3H), 2.11 (s, 3H), 4.29 (dd, J = 10 and 4 Hz, 1H), 4.57 (dd, J = 10 and 6 Hz, 1H), 5.33 (dd, J = 6 and 4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 20.0, 20.1, 21.3, 69.8, 71.5, 74.7, 169.2, 169.3, 172.9. **IR** ($CHCl_3$) ν_{max} 1794, 1760, 1751, 1219, 1109 cm^{-1}. **Anal. Calcd for $C_9H_{12}O_6$:** C, 50.00; H, 5.59. Found: C, 50.08; H, 5.65.

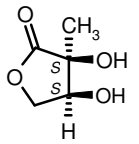
(–)-(3*R*,4*R*)-3,4-Dihydroxy-3-methyldihydrofuran-2-one (7) and (+)-(2*S*,3*S*)-2,3-di-*O*-acetyl-2-*C*-methyl-D-erythrono-1,4-lactone (58). A solution of diacetyl lactone (±)-

58 (400 mg, 1.85 mmol) in petroleum ether:benzene (2:1) mixture (12 mL) was added to a suspension of Amano PS lipase (40 mg) in aqueous sodium phosphate (0.01 M, 4 mL) at pH 7.0. The reaction mixture was stirred at 45 °C for 36 h. The reaction mixture was filtered through celite and the aqueous layer was extracted with ethyl acetate (15 mL x 5). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic separation using a mixture of ethyl acetate and petroleum ether (2:8) mixture as an eluant gave diacetyl lactone (+)-**58** (196 mg, 49%) and dihydroxy lactone (–)-**7** (112 mg, 46%) .

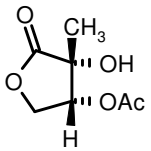
 (+)-**58** (99% ee) $C_9H_{12}O_6$ (216)	Colourless solid. $[\alpha]^{20}_D$ = +8.96 (c 1.6, $CHCl_3$). Analytical and spectral data obtained were identical with (±)-**58**.

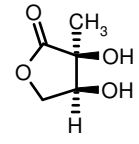
 (-)-**7** (99% ee) $C_5H_8O_4$ (132)	Colourless thick oil. $[\alpha]^{20}_D$ = –58.6 (c 0.50, H_2O). Analytical and spectral data obtained were identical with (±)-**7**.

(+)-(3*S*,4*S*)-3,4-Dihydroxy-3-methyldihydrofuran-2-one (7). To a stirred solution of diacetyl lactone (+)-**58** (60 mg, 0.28 mmol) in dry methanol (3 mL) was added anhydrous K_2CO_3 (10 mg, 0.07 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Methanol was removed in vacuo at room temperature and water (10 mL) was added to the reaction mixture, then acidified to pH 2 using 2 M HCl and extracted with ethyl acetate (15 mL x 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (2:8) as an eluant gave (+)-**7** (34 mg, 92%).

 (+)-**7** (99% ee) $C_5H_8O_4$ (132)	Colourless thick oil. $[\alpha]^{20}_D$ = +58.5 (c 0.50, H_2O). Analytical and spectral data obtained were identical with (±)-**7**.

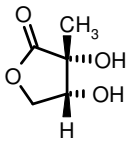
(–)-(3*R*,4*R*)-Acetic acid 4-hydroxy-4-methyl-5-oxotetrahydrofuran-3-yl ester (62). A solution of dihydroxy lactone (±)-**7** (200 mg, 1.52 mmol) in *n*-hexane/benzene (2:1) (12 mL) was added to Amano PS lipase (40 mg) and vinyl acetate (0.8 mL, 7.6 mmol). The reaction mixture was stirred at 45 °C for 96 h and then allowed to cool to room temperature. The enzyme was filtered off, washed with ethyl acetate and the organic layer was concentrated in vacuo. The residue was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (2.5:7.5) as an eluant to give acetyl lactone (–)-**62** (82 mg, 31%) and dihydroxy lactone (+)-**7** (126 mg, 63%), respectively.

 (-)-**62** $C_7H_{10}O_5$ (174)	Colourless oil. $[\alpha]^{20}_D$ = –44.0 (c 0.2, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.52 (s, 3H), 2.13 (s, 3H), 3.41 (bs, 1H), 4.29 (dd, *J* = 10 and 2 Hz, 1H), 4.47 (dd, *J* = 12 and 4 Hz, 1H), 5.16 (dd, *J* = 4 and 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 20.6, 21.7, 69.6, 72.3, 74.4, 170.1, 177.0. **IR** ($CHCl_3$) ν_{max} 3460, 1788, 1744, 1232, 1215 cm^{-1}. **Anal. Calcd for $C_7H_{10}O_5$:** C, 48.28; H, 5.79. Found: C, 48.35; H, 5.69.

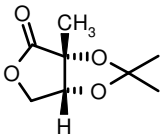
 (+)-**7** $C_5H_8O_4$ (132)	Colourless thick oil. $[\alpha]^{20}_D$ = +35.0 (c 0.40, H_2O). Analytical and spectral data obtained were identical with (±)-**7**.

(–)-(3*R*,4*R*)-3,4-Dihydroxy-3-methyldihydrofuran-2-one (7). To a stirred solution of acetyl lactone (–)-**62** (80 mg, 0.45 mmol) in dry methanol (6 mL) was added anhydrous K_2CO_3 (5 mg) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Methanol was removed in vacuo at room temperature and water (7 mL) was

added to the reaction mixture, then acidified to pH 2 using 2 M HCl and extracted with ethyl acetate (10 mL x 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (2.5:7.5) as an eluant gave (–)-**7** (55 mg, 91%).

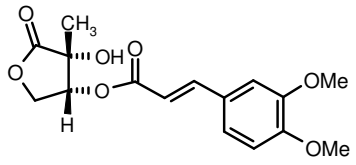
 (-)-**7** (99% ee) $C_5H_8O_4$ (132)	Colourless thick oil. $[\alpha]^{20}_D$ = –58.5 (c 0.50, H_2O). Analytical and spectral data obtained were identical with (±)-**7**.

(–)-(2*R*,3*R*)-2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythrono-1,4-lactone (46). To a stirred solution of lactone (–)-**7** (50 mg, 0.38 mmol) in 2,2-dimethoxypropane (5 mL) was added *p*-toluenesulfonic acid monohydrate (4 mg, 0.02 mmol). The reaction mixture was stirred at room temperature for 10 h and then concentrated in vacuo. The residue was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (0.5:9.5) as an eluant to give lactone (–)-**46** (59 mg, 91%) as colourless thick oil.

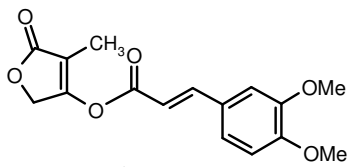
 (-)-**46** (91%) $C_8H_{12}O_4$ (172)	Colourless thick oil. $[\alpha]^{20}_D$ = –82.2 (c 2.0, acetone). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.42 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 4.32 (dd, J = 10 and 4 Hz, 1H), 4.44 (d, J = 10 Hz, 1H), 4.49 (d, J = 4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 18.4, 26.6, 26.9, 68.9, 80.3, 81.4, 113.0, 176.7. **IR** ($CHCl_3$) ν_{max} 1788, 1379, 1105 cm^{-1}. **Anal. Calcd for $C_8H_{12}O_4$:** C, 55.81; H, 7.02. Found: C, 55.72; H, 6.97.

(–)-(3*R*,4*R*)-*β*-(3,4-Dimethoxyphenyl)acrylic acid 4-hydroxy-4-methyl-5-oxotetrahydrofuran-3-yl ester (64). To a stirred solution of acid **63** (158 mg, 0.76 mmol), dihydroxy lactone (–)-**7** (100 mg, 0.76 mmol) and DMAP (cat.) in dry CH_2Cl_2 (7 mL) was added a solution of DCC (156 mg, 0.76 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 10 h. The formed urea

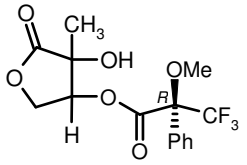
was filtered off and the organic layer was concentrated in vacuo. Silica gel column chromatographic purification of the residue using ethyl acetate and petroleum ether (2:8) as an eluent yielded ester (–)-**64** (208 mg, 85%) as yellow crystalline solid.

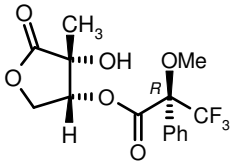
 (-)-**64** $C_{16}H_{18}O_7$ (322)	**Mp** 123-124 °C $[\alpha]^{20}_D$ = –70.0 (c 0.4, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.58 (s, 3H), 3.32 (bs, 1H), 3.90 (s, 6H), 4.38 (dd, *J* = 12 and 2 Hz, 1H), 4.54 (dd, *J* = 10 and 4 Hz, 1H), 5.30 (d, *J* = 4 Hz, 1H), 6.33 (d, *J* = 16 Hz, 1H), 6.85 (d, *J* = 8 Hz, 1H), 7.04-7.13 (m, 2H), 7.69 (d, *J* = 16 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 21.9, 55.8, 55.9, 69.9, 72.6, 74.5, 109.6, 111.0, 113.7, 123.1, 126.8, 147.0, 149.2, 151.6, 166.1, 177.0. **IR** ($CHCl_3$) ν_{max} 3477, 1786, 1719, 1632, 1599, 1512, 1263, 1215, 1140 cm^{-1}. **Anal. Calcd for $C_{16}H_{18}O_7$:** C, 59.62; H, 5.63. Found: C, 59.58; H, 5.68.

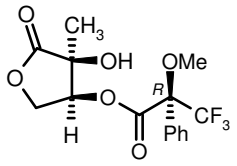
3-(3,4-Dimethoxyphenyl)acrylic acid 4-methyl-5-oxo-2,5-dihydrofuran-3-yl ester (65). To a stirred solution of lactone **64** (100 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) was added 1.0 M solution of boron tribromide (2.20 mL, 2.18 mmol) in CH_2Cl_2 at –78 °C in a drop wise fashion under argon atmosphere. The reaction mixture was stirred at –78 °C temperature for 30 minutes. The reaction was then slowly quenched with water and extracted with ethyl acetate (15 mL x 3) 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 ethyl acetate and petroleum ether (0.5:9.5) as an eluent gave **65** (60 mg, 64% yield) as yellow crystalline solid.

 **65** $C_{16}H_{16}O_6$ (304)	**Mp** 115-116 °C **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 5.30 (s, 2H), 6.60 (d, *J* = 16 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 7.00-7.11 (m, 2H), 7.62 (d, *J* = 16 Hz, 1H). **IR** ($CHCl_3$) ν_{max} 1779, 1733, 1640, 1602, 1260 cm^{-1}. **Anal. Calcd for $C_{16}H_{16}O_6$:** C, 63.15; H, 5.30. Found: C, 63.04; H, 5.36.

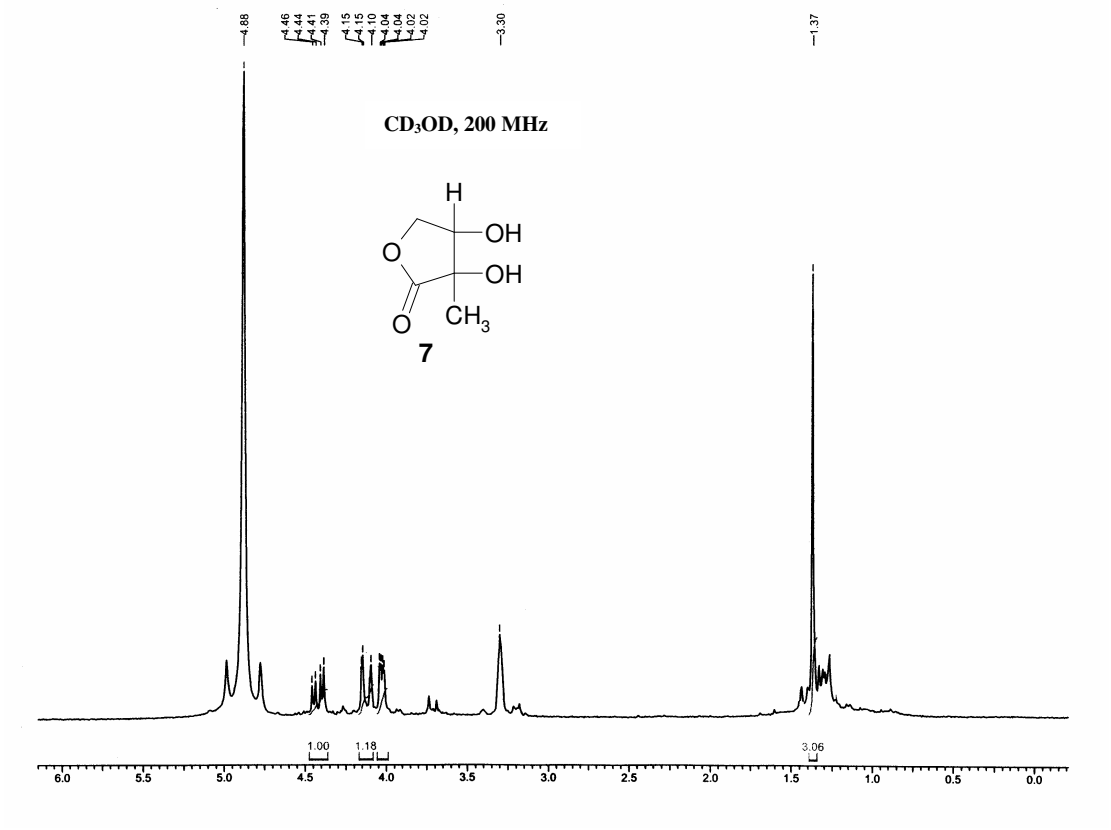
General procedure for MTPA-ester preparation. To a solution of (*R*)-Mosher's acid (27 mg, 0.11 mmol), dihydroxy alcohol (±)-**7** or (–)-**7** or (+)-**7** (15 mg, 0.11 mmol) and DMAP (cat.) in dry CH_2Cl_2 (3 mL) was added a solution of DCC (24 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) at 0 ^oC. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The formed urea was filtered off and the organic layer was concentrated in vacuo. Silica gel column chromatographic purification of the residue using ethyl acetate and petroleum ether mixture (1:9) gave the MTPA-esters **59** or **60** or **61** in quantitative yield.

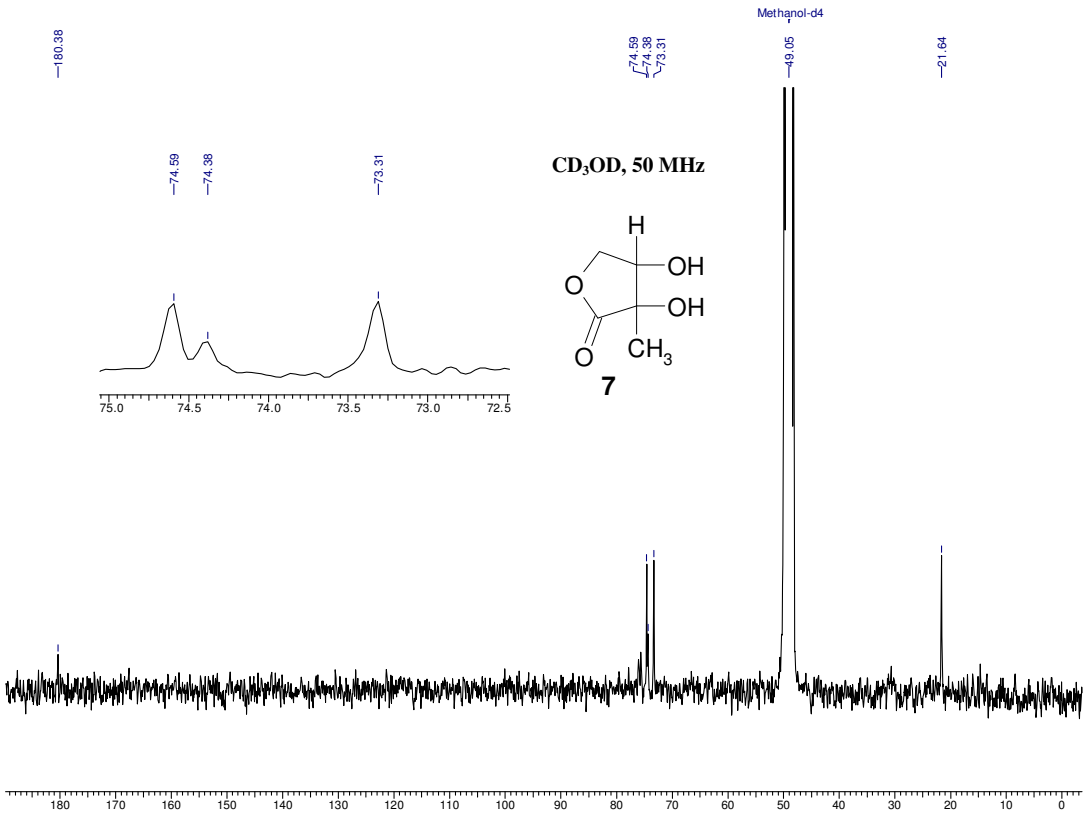
 **59** $C_{15}H_{15}F_3O_6$ (348)	Colourless thick oil . **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.59 (s, 3H), 2.70 (bs, 1H), 2.96 (bs, 1H), 3.53 (s, 3H), 3.57 (s, 3H), 4.27 (dd, *J* = 12 and 2 Hz, 1H), 4.40 (dd, *J* = 12 and 2 Hz, 1H), 4.50 (dd, *J* = 12 and 4 Hz, 1H), 4.56 (dd, *J* = 12 and 4 Hz, 1H), 5.41 (d, *J* = 4 Hz, 2H), 7.38-7.56 (m, 10H).

 **60** $C_{15}H_{15}F_3O_6$ (348)	Colourless thick oil . **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H), 2.82 (bs, 1H), 3.57 (s, 3H), 4.27 (dd, *J* = 12 and 2 Hz, 1H), 4.51 (dd, *J* = 12 and 4 Hz, 1H), 5.41 (d, *J* = 4 Hz, 1H), 7.41-7.57 (m, 5H).

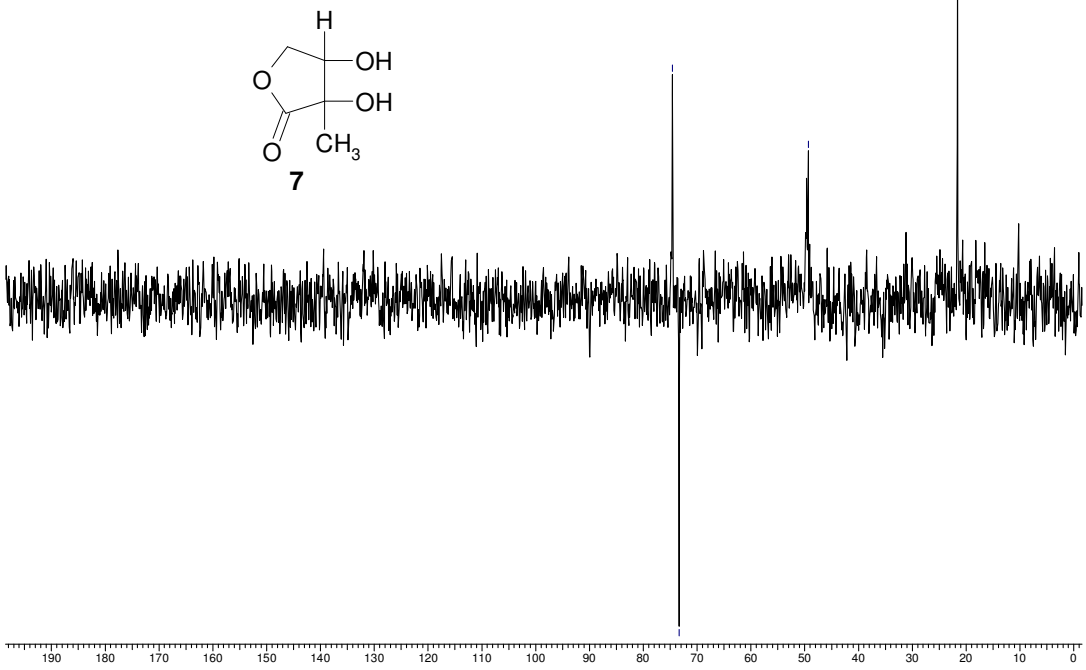
 **61** $C_{15}H_{15}F_3O_6$ (348)	Colourless thick oil . **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 2.57 (bs, 1H), 3.53 (s, 3H), 4.40 (dd, *J* = 12 and 2 Hz, 1H), 4.56 (dd, *J* = 12 and 4 Hz, 1H), 5.41 (d, *J* = 4 Hz, 1H), 7.41-7.57 (m, 5H).

3B.5 Selected spectra


4.88
4.46
4.44
4.41
4.39
4.15
4.15
4.10
4.04
4.04
4.02
4.02
3.30
1.37
CD3OD, 200 MHz
H
OH
O
OH
O
CH3
7
1.00
1.18
3.06
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

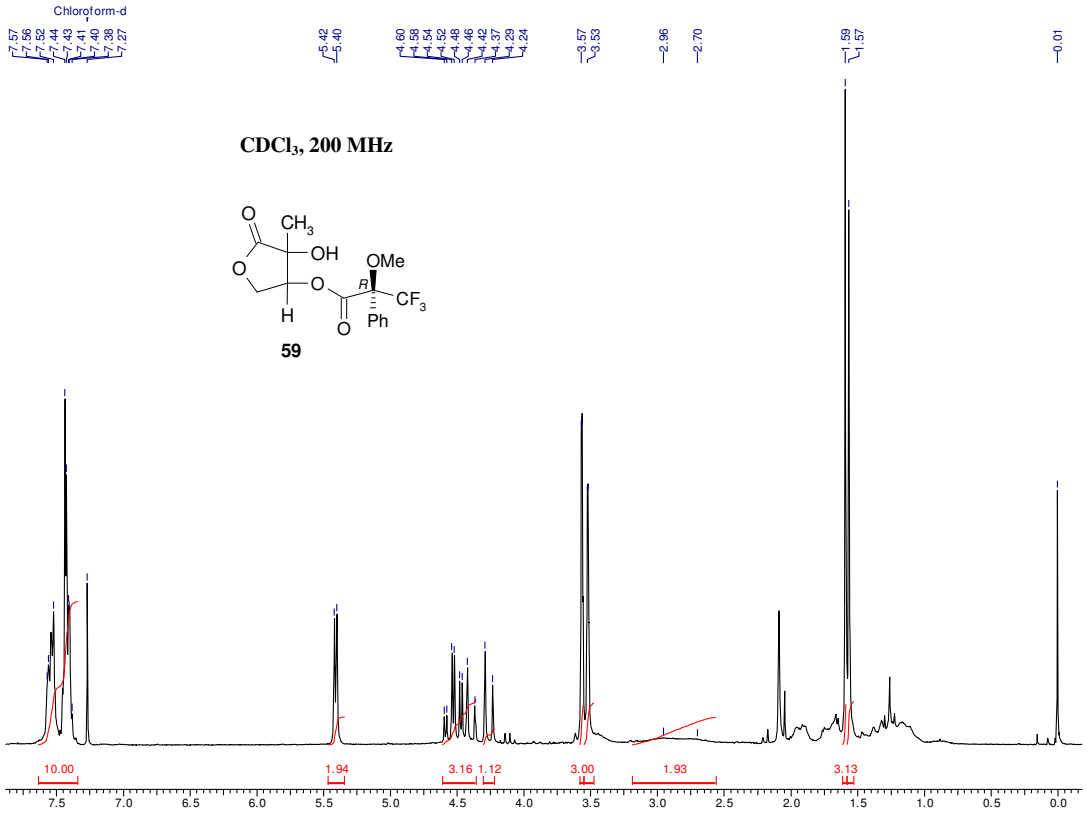

Methanol-d4
180.38
74.59
74.38
73.31
49.05
21.64
74.59
74.38
73.31
CD3OD, 50 MHz
H
OH
O
OH
O
CH3
7
75.0
74.5
74.0
73.5
73.0
72.5
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

CD_3OD, 50 MHz

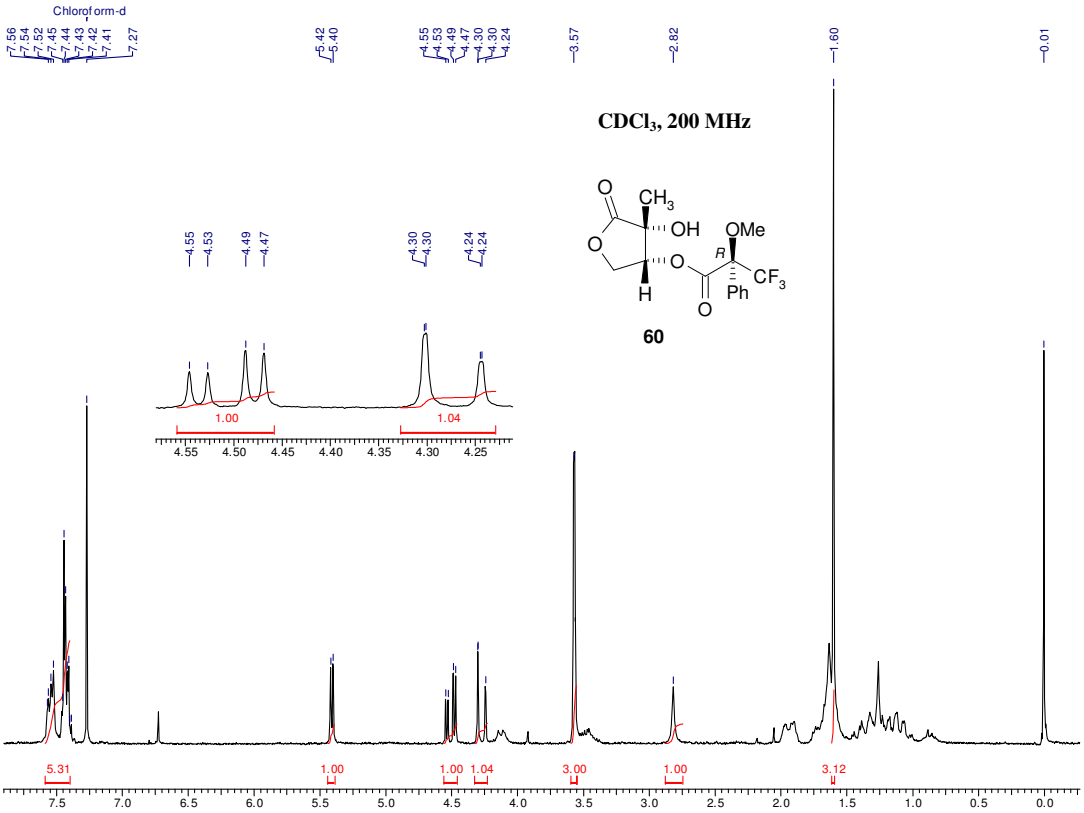


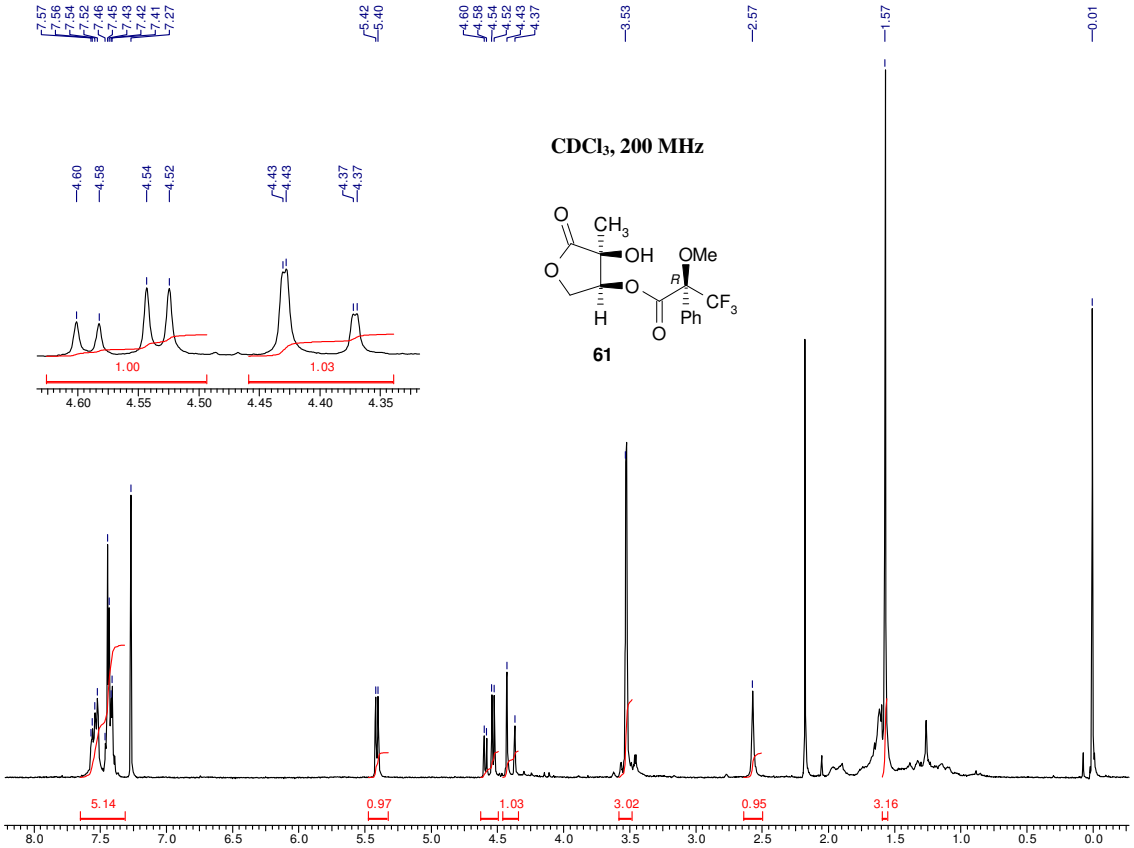
7

$CDCl_3$, 200 MHz



59


Chloroform-d
7.56
7.54
7.52
7.45
7.44
7.43
7.42
7.41
7.27
5.42
5.40
4.55
4.53
4.49
4.47
4.30
4.30
4.24
4.24
3.57
2.82
1.60
0.01
CDCl3, 200 MHz
CH3
OH
OMe
R
CF3
Ph
H
O
60
1.00
1.04
5.31
1.00
1.00
1.04
3.00
1.00
3.12


7.57
7.56
7.54
7.52
7.46
7.45
7.43
7.42
7.41
7.27
5.42
5.40
4.60
4.58
4.54
4.52
4.43
4.43
4.37
4.37
3.53
2.57
1.57
0.01
CDCl3, 200 MHz
CH3
OH
OMe
R
CF3
Ph
H
O
61
1.00
1.03
5.14
0.97
1.03
3.02
0.95
3.16

3B.6 References and footnote

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3C. Section C

A Facile Chemoenzymatic Approach to Natural Cytotoxic Ellipsoidone A and Natural Ellipsoidone B

This section features the following topics:

3C. Section C: A Facile Chemoenzymatic Approach to Natural Cytotoxic Ellipsoidone A and Natural Ellipsoidone B

3C.1 Background

Plants of the genus *Hemsleya* (Cucurbitaceae) are distributed throughout the southwest region of china. More than 30 species of the plants grow in the southwest region of china[1] and tubers of these pants have been used in Chinese folk medicinal system.[2] As a part of survey of Chinese folk medicinal resources, Normura et al. in collaboration with group of researchers from china, examined the components of the tubers of *Hemsleya ellipsoidea* and isolated the new compounds ellipsoidones A (**1**) and B (**2**) along with the known glucosidyl butenolide, siphonoside (Figure 1), which is as a cytotoxic compound against Walker-256-sarcoma cells.[3,4-6] One can easily imply that siphonoside is a biological precursor of **1** and **2**, which on losing three molecules of water generates **1** and **2** via an intramolecular condensation and dehydrative pathway. The structures of **1** and **2** were assigned on the basis of UV, ^{1}H NMR, ^{13}C NMR, 2D-NMR, NOE and HRFABMS data. The two acetogenins **1** and **2** are geometrical stereoisomers of each other and ellipsoidone A (**1**) has been reported as a cytotoxic compound against P-388 cells [IC_{50} 47 mg/mL].[3,4-6] Synthesis of these two geometric isomers **1** and **2** with two hydroxymethyl moieties is a challenging task as Nature derives them from the sugar, siphonodin 6-*O*-*β*-D-glycopyranoside.[4-6] This section portrays an efficient and 6-step first total synthesis of natural cytotoxic ellipsoidone A (**1**) and ellipsoidone B (**2**) using itaconic anhydride as the starting material.

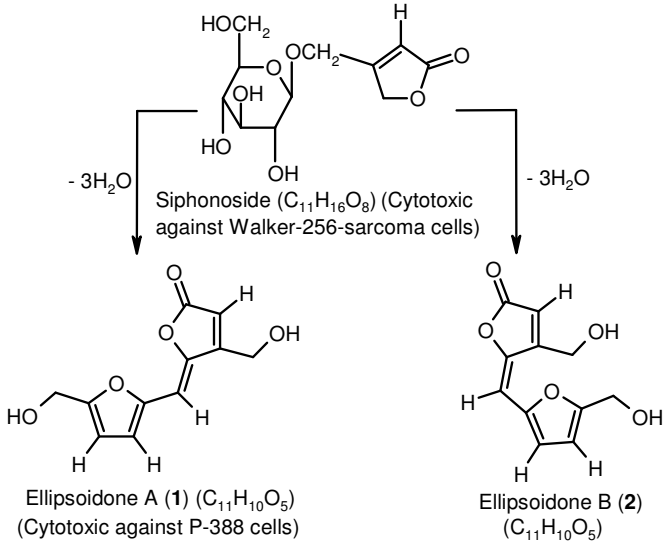
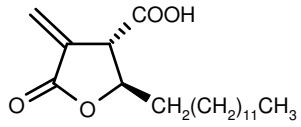
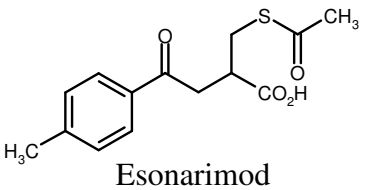


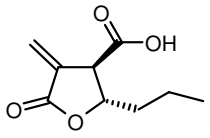
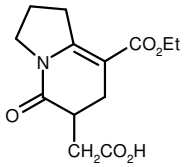
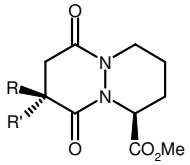
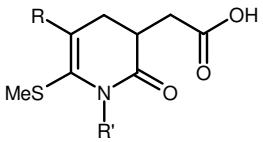
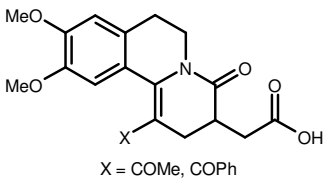
Figure 1. Bioactive natural products from *Hemsleya ellipsoidea*

Being a multifunctional entity, itaconic anhydride finds applications in nearly every field of both laboratory and industrial chemistry. The utmost interest has been centered in the use of itaconic anhydride as a building block in organic synthesis. It is a versatile synthon wherein all the sites are amenable for a variety of reactions and possesses exceptionally selective reactivity towards several nucleophiles. A vast array of nucleophilic reactions undergone by itaconic anhydride confers a high synthetic potential on them. Itaconic anhydride has been used for the synthesis of several unnatural and natural products, some of the representative examples are given in table 1.

This anhydride can be prepared by several routes. Gusev et al. synthesized itaconic anhydride by 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.[7] McCabe et al. have synthesized itaconic anhydride by the reaction of itaconic acid with Al_3^+-montmorillonite in refluxing toluene by the intramolecular cyclocondensation.[8] Kita et al. have used (trimethylsilyl)ethoxyacetylene as an excellent dehydrating agent for the synthesis of itaconic anhydride from itaconic acid.[9] Roll and co-workers have synthesized itaconic anhydride and citraconic anhydride by the double dehydrative decarboxylation of citric acid.[10]

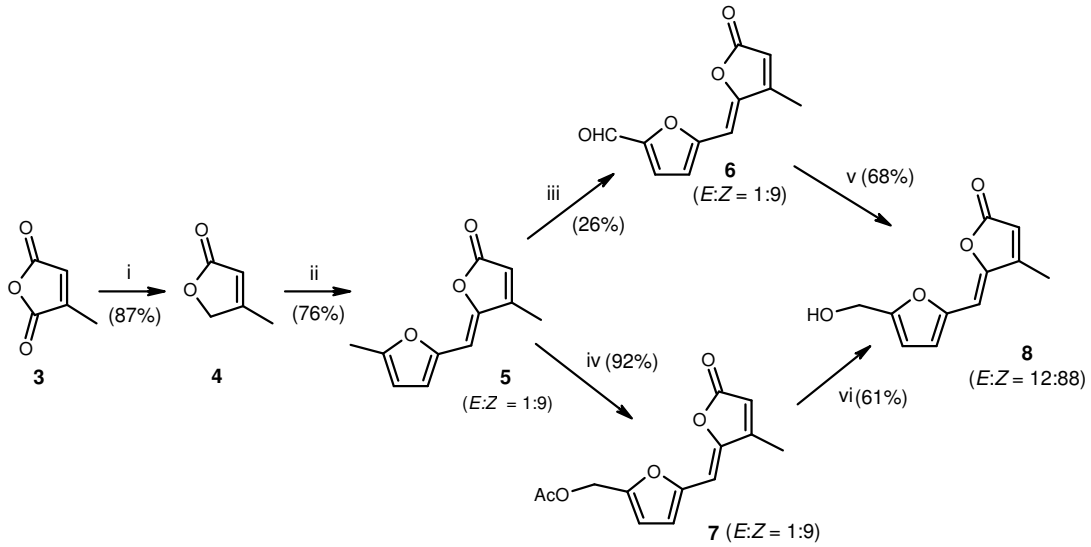
Table 1. Natural and unnatural compounds synthesized from itaconic anhydride (**9**)

No.	Compound synthesized	Source	Activity	Ref.
1	 Protolichesterinic acid	*Cetraria islandica* (L.)	Antibiotic activity	11
2	 Esonarimod	Synthetic compound	Antirheumatic activity	12

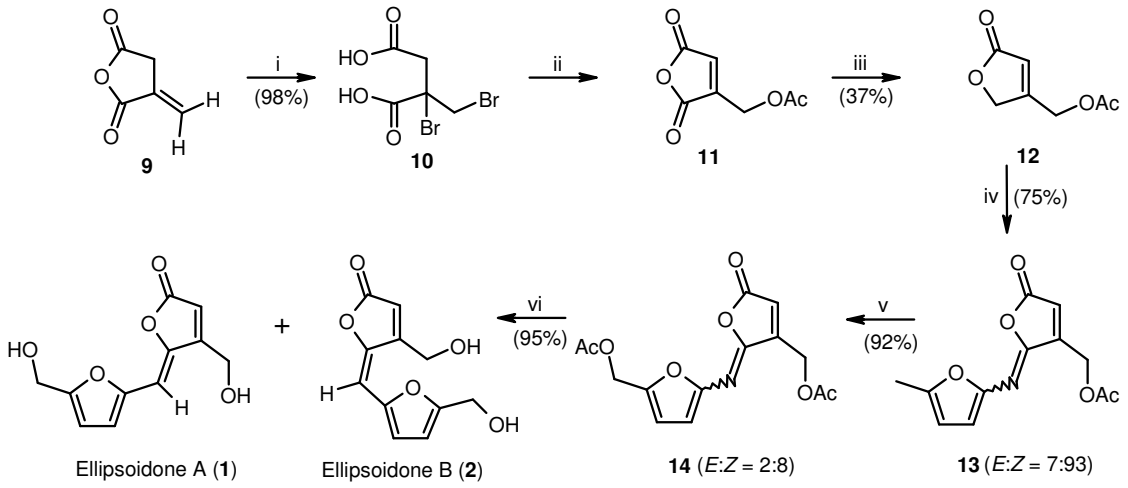
3	 (2*S*,3*R*)-4-Methylene-5-oxo-2-propyl-tetrahydrofuran-3-carboxylic acid	Synthetic compound	Inhibitor of the Histone Acetyltransferase Gcn 5	13
4	 2-[8-(Ethoxycarbonyl)-5-oxo-1,2,3,5,6,7-hexahydroindolizin-6-yl] acetic acid)	Synthetic compound	Not known	14
5	 R = H or CH_2SH; R' = H or CH_2SH. Octahydropyridazo[1,2-*a*]-pyridazinediones	Synthetic compound	Antihypertensive drug	15
6	 (R = COMe, COPh, NO_2; R^1 = *n*-Bu, Ph, $PhCH_2$, 4-MeO-$C_6H_4CH_2$) (1,2,3,4-tetrahydro-2-pyridones)	Synthetic compound (This scaffold is found in a wide variety of naturally occurring alkaloids)[16]	Compounds with these structural motifs have been shown to exhibit significant pharmacological properties.[17]	18
7	 X = COMe, COPh Benzo[*a*]quinolizinone-3-acetic acid derivatives	Synthetic compound	The benzo[*a*]quinolizinone derivatives such as Ro 41-3696 have been identified as promising nonsedative hypnotics.[19a,b]	20

3C.2 Present work: Results and Discussion

The selenium dioxide oxidation of β-methyl group of α,β-unsaturated esters and several types of allylic/benzylic methyl groups are known in the literature.[21] We felt that the butenolide **5** would be a potential starting material for the synthesis of ellipsoidones A (**1**) and B (**2**) and selenium dioxide oxidation of both the allylic methyl groups in **5** would provide a simple and efficient access to these natural products. In this context, for the preparation of **5**, we performed the sodium borohydride reduction of citraconic anhydride (**3**) and obtained the known[22] butyrolactone **4** in 87% yield (Scheme 1). Piperidine catalyzed Knoevenagel condensation of lactone **4** with 5-methylfurfural gave the desired butenolide **5** in 76% yield (*E*:*Z* = 1:9, by ^{1}H NMR). The butenolide **5** was strongly resistant to selenium dioxide oxidation in refluxing ethanol and 1,4-dioxane solutions and the starting material was recovered after twelve hours reflux time. The SeO_2 oxidation of **5** in 98% acetic acid directly furnished the aldehyde **6**, but only in 26% yield, wherein both the hydroxylation and further oxidation of the alcohol to the aldehyde took place in one pot. To arrest the SeO_2 oxidation of **5** at the alcohol stage, we performed the reaction in a freshly dried anhydrous acetic acid and exclusively obtained the monoacetoxymethylbutenolide **7** in 92% yield. The aldehyde **6** on $NaBH_4$ reduction as well as the monoacetate **7** on base catalyzed deacylation gave the deoxyellipsoidone **8** (*E*:*Z* =



Scheme 1. *Reagents, conditions and yields*: (i) (a) $NaBH_4$, THF, 0 °C, 2 h, (b) H^+/HCl (87%); (ii) 5-Methylfurfural, piperidine, CH_3OH, rt, 15 h (76%); (iii) SeO_2, CH_3COOH, reflux, 2 h (26%); (iv) SeO_2, CH_3COOH (anhydrous), reflux, 1.5 h (92%); (v) (a) $NaBH_4$, C_2H_5OH, rt, 1 h, (b) H^+/HCl (68%); (vi) K_2CO_3, CH_3OH, 0 °C to rt, 2 h (61%).



Scheme 2. *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%, **1**:**2** = 86:14).

12:88, by ^{1}H NMR) in 68% and 61% yields respectively. Most of the naturally occurring butenolides of such type exist as the thermodynamically more stable *Z*-isomer[23] and herein, we could assign the *Z*-geometry to the exocyclic carbon-carbon double bonds in compounds **5** to **8** on the basis of ^{1}H NMR data. As expected, in compounds **5** to **8** the lactone methyl group signals for the minor *E*-isomers in ^{1}H NMR spectra were more deshielded (ca. δ 2.51) than the corresponding major Z-isomer signals (ca. δ 2.22), due to the anisotropic effect of the furan ring. All our attempts to oxidize the allylic methyl group of the lactone moiety in **5** met with failure. We feel that, on the formation of new exocyclic carbon-carbon double bond in **5**, the allylic methyl group hydrogens lose the sacrificial hyperconjugation with the lactone carbonyl group and hence it becomes inactive to the SeO_2-oxidation. Therefore we altered our strategy and decided to start the synthesis of **1** and **2** from acetoxymethylbutenolide **12**.

We envisaged the preparation of acetoxymethyllactone **12** from itaconic anhydride (**9**). The bromination of itaconic anhydride (**9**) furnished the dibromodiacid **10**[11,24] in 98% yield (Scheme 2). The diacid **10** on treatment with Ac_2O/NaOAc mixture at room temperature for 6 h followed by removal of acetic anhydride in vacuo gave the crude acetoxymethylmaleic anhydride (**11**). Herein all the three steps, the ring closure of acid **10** to the intermediate succinic anhydride derivative, dehydrobromination to form the second

intermediate bromomethylmaleic anhydride and the allylic substitution of the bromide with the acetoxy group took place in one pot. The acetoxymethylmaleic anhydride (**11**) was very unstable and we were unable to purify it. The structure of the anhydride **11** was established on the basis of IR, ^{1}H NMR data of crude **11**. The direct regioselective $NaBH_4$ reduction of the crude anhydride **11** in THF furnished the desired lactone **12** in 37% yield (2-steps), without deacylation of the acetate moiety in **11/12**. Alternately, the desired lactone **12** can also be obtained from dihydroxy acetone in 4-steps with 38% overall yield.[25] The Knoevenagel condensation of lactone **12** with 5-methylfurfural gave the required monoacetoxymethylbutenolide **13** (*E*:*Z* = 7:93, by ^{1}H NMR) in 75% yield. Herein, the regioselective carbanion formation on an internal butyrolactone methylene group, rather than the external acetoxymethyl moiety is noteworthy and could be due to the generation of the stable oxyfurananion in the former case. As expected, here too the methylene proton signals from the $-CH_2OAc$ groups on lactone moieties for the minor *E*-isomers in compounds **13** and **14** appeared more downfield than the corresponding signals for their major *Z*-isomers. The SeO_2 oxidation of **13** in anhydrous acetic acid gave the desired diacetoxymethylbutenolide **14** in 92% yield. To obtain the natural products **1** and **2**, we systematically studied the deacylation of **14**, both under acidic and basic conditions and observed that the starting material **14** and formed products **1** & **2** are not very stable under these conditions. In our hands, we always got a complex mixture of products and this could be due to the intermolecular reactions of the two hydroxymethyl groups with the reactive enol-lactone. Finally, we carried out the Amano PS catalyzed double deacylation of **14** at pH 7 and obtained the mixture of desired products **1** and **2** (**1**:**2** = 86:14, by ^{1}H NMR) in 95% yield. All our attempts to obtain the pure major isomer **1** from the **1** plus **2** mixture by recrystallization were unsuccessful. Finally, we did the HPLC separation of **1** plus **2** mixture using the known procedure[3] and obtained pure **1** and **2** with quantitative recovery. The analytical and spectral data obtained for **1** and **2** were in complete agreement with the reported data.[3] In the present six-step synthesis, starting from itaconic anhydride (**9**), the overall yield of ellipsoidone A (**1**) and ellipsoidone B (**2**) were 20.4% and 3.3% respectively. The photochemical conversion of ellipsoidone B to ellipsoidone A is known.[3]

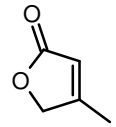
3C.3 Summary

In summary, we have demonstrated the first total synthesis of isomeric natural cytotoxic ellipsoidone A (**1**) and natural ellipsoidone B (**2**) using regioselective reduction of acetoxymethylmaleic anhydride (**11**), selenium dioxide hydroxylation of butenolide **13** and an enzymetic deacylation of diacetoxybutenolide **14** as key reactions.[26] In the present stepwise approaches, we could design the acetyl derivatives of both the unnatural deoxyellipsoidone regioisomers. In the present synthesis, the enzymatic hydrolysis of diacetate **14** to obtain the labile multifunctional ellipsoidones A and B in 95% yield is noteworthy. We feel that the present approach to **1** and **2** is general in nature and it would be useful to design the analogs and congeners of these bioactive natural products for the structure-activity relationship studies.

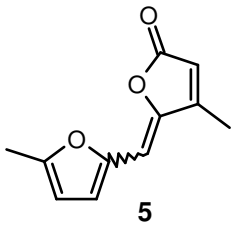
3C.4 Experimental Section

Column chromatographic separations were carried out on silica gel (60-120 mesh). Commercially available citraconic anhydride, sodium borohydride, 5-methylfurfural, piperidine, selenium dioxide, bromine, sodium acetate, and Amano PS-1310 U from Amano Pharmaceuticals, Japan were used. The activity of the lipase powder[27] used is expressed in terms of units,[27] one unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder. Dry acetic acid was obtained by refluxing it over active $CuSO_4$ for 12 h, followed by distillation.

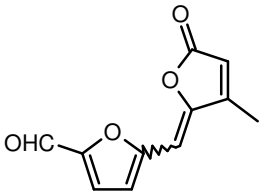
4-Methyl-5*H*-furan-2-one (4). To a stirred solution of citraconic anhydride (**3**, 800 mg, 7.14 mmol) in THF (15 mL), was added $NaBH_4$ (675 mg, 17.85 mmol) at 0 °C and the reaction mixture was further stirred at 0 °C for 2 h. The reaction was quenched with water, acidified with dilute HCl and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (3:7) furnished pure **4** (609 mg, 87%).

 **4** $C_5H_6O_2$ (98)	Thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H), 4.76 (s, 2H), 5.83 (q, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.5, 73.5, 115.5, 166.4, 173.8. **IR** ($CHCl_3$) ν_{max} 1782, 1751, 1647, 1215 cm^{-1}. **Anal. Calcd for $C_5H_6O_2$:** C, 61.22; H, 6.17. Found: C, 61.37; H, 6.21.

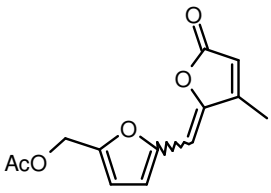
4-Methyl-5-(5-methyl-furan-2-ylmethylene)-5*H*-furan-2-one (5). To a stirred solution of lactone **4** (300 mg, 3.06 mmol) in methanol were added piperidine (0.21 mL, 2.14 mmol) and 5-methylfurfural (0.30 mL, 3.06 mmol) at room temperature and the reaction mixture was stirred for 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (0.5:9.5) furnished **5** (442 mg, 76%) as a yellow crystalline solid.

 **5** $C_{11}H_{10}O_3$ (190)	**Mp** 103-105 ^oC. **^{1}H NMR** ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.19 (d, J = 1 Hz, 3H), 2.35 (s, 2.7H), 5.91 (bs, 1H), 6.04 (s, 0.9H), 6.15 (d, J = 4 Hz, 0.9H), 6.94 (d, J = 4 Hz, 0.9H), [the following four signals for the minor *E*-isomer showed splitting and appeared at δ 2.49 (d, J = 1 Hz, 0.3H), 6.10 (d, J = 4 Hz, 0.1H), 6.44 (s, 0.1H), 6.49 (d, J = 4 Hz, 0.1H)]. **^{13}C NMR** ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.5, 13.7, 98.9, 109.6, 114.8, 116.6, 146.7, 147.5, 154.5, 154.7, 169.2. **IR** ($CHCl_3$) ν_{max} 1773, 1751, 1651, 1520, 1215 cm^{-1}. **Anal. Calcd for $C_{11}H_{10}O_3$:** C, 69.46; H, 5.30. Found: C, 69.22; H, 5.51.

5-(3-Methyl-5-oxo-5*H*-furan-2-ylidenemethyl)-furan-2-carbaldehyde (6). To a stirred solution of lactone **5** (100 mg, 0.53 mmol) in acetic acid (5 mL) was added SeO_2 (117 mg, 1.05 mmol) and the reaction mixture was refluxed for 2 h. The reaction mixture was filtered through celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **6** (28 mg, 26%) as a yellow crystalline solid.

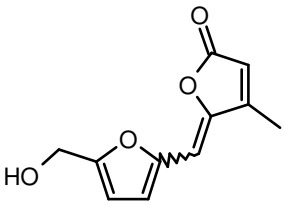
 **6** $C_{11}H_8O_4$ (204)	**Mp** 187-190 ^oC. **^{1}H NMR** ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.26 (s, 2.7H), 6.10 (s, 1H), 6.19 (s, 0.9H), 7.23 (d, J = 4 Hz, 1H), 7.34 (d, J = 4 Hz, 0.9H), 9.65 (s, 1H), [the following three signals for the minor *E*-isomer showed splitting and appeared at δ 2.58 (s, 0.3H), 6.53 (s, 0.1H), 6.71 (d, J = 4 Hz, 0.1H)]. **^{13}C NMR** ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 97.2, 116.1, 117.3, 123.5, 151.7, 152.0, 153.8, 154.9, 168.0, 177.3. **IR** ($CHCl_3$) ν_{max} 1782, 1676, 1215 cm^{-1}. **Anal. Calcd for $C_{11}H_8O_4$:** C, 64.71; H, 3.95. Found: C, 64.67; H, 4.04.

Acetic acid 5-(3-methyl-5-oxo-5*H*-furan-2-ylidene methyl)-furan-2-ylmethyl ester (7). To a stirred solution of lactone **5** (100 mg, 0.53 mmol) in dry acetic acid (5 mL) was added SeO_2 (117 mg, 1.05 mmol) and the reaction mixture was refluxed for 1.5 h. The reaction mixture was filtered through celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:9) to furnish **7** (120 mg, 92%) as a yellow crystalline solid.

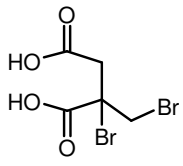
 **7** $C_{13}H_{12}O_5$ (248)	**Mp** 84-86 ^oC. **^{1}H NMR** ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.10 (s, 2.7H), 2.22 (d, J = 2 Hz, 3H), 5.08 (s, 2H), 5.97 (s, 1H), 6.09 (s, 1H), 6.55 (d, J = 4 Hz, 0.9H), 7.02 (d, J = 4 Hz, 1H), [the following two signals for the minor *E*-isomer showed splitting and appeared at δ 2.48 (s, 0.3H), 6.50 (d, J = 4 Hz, 0.1H)]. **^{13}C NMR** ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 20.8, 57.9, 98.4, 113.7, 115.6, 115.7, 148.1, 149.4, 150.6, 154.8, 168.9, 170.5. **IR** ($CHCl_3$) ν_{max} 1774, 1751, 1651, 1601, 1234 cm^{-1}. **Anal. Calcd for $C_{13}H_{12}O_5$:** C, 62.90; H, 4.87. Found: C, 63.03; H, 4.62.

5-(5-Hydroxymethyl-furan-2-ylmethylene)-4-methyl-5*H*-furan-2-one (8). ***Method A*:** To a stirred solution of lactone **7** (70 mg, 0.28 mmol) in methanol (5 mL) was added K_2CO_3 (5 mg, 0.04 mmol) and the reaction mixture was stirred at room temperature for 1 h. Methanol was removed in vacuo at room temperature and water (10 mL) was added to the reaction mixture. The reaction mixture was acidified to pH 4 using 2 N HCl and immediately extracted with ethyl acetate (15 mL x 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a

mixture of ethyl acetate and petroleum ether (2:8) as an eluant gave **8** (35 mg, 61%) as a yellow crystalline solid. ***Method B*:** Butenolide **6** (25 mg, 0.12 mmol) on $NaBH_4$ (5 mg, 0.14 mmol) reduction in EtOH (3 mL) at room temperature for 1 h followed by acidification with 2 N HCl gave **8** in 68% yield as a yellow crystalline solid.

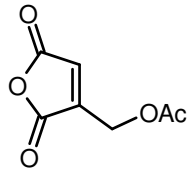
 **8** $C_{11}H_{10}O_4$ (206)	**Mp** 95-96 °C. **^{1}H NMR** ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.20 (s, 2.64H), 4.64 (s, 3H), 5.94 (s, 1H), 6.07 (s, 1H), 6.43 (d, J = 4 Hz, 0.88H), 6.95 (d, J = 4 Hz, 1H), [the following two signals for the minor *E*-isomer showed splitting and appeared at δ 2.49 (s, 0.36H), 6.53 (d, J = 4 Hz, 0.12H)]. **^{13}C NMR** ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 57.5, 98.6, 111.0, 115.4, 115.8, 147.7, 148.8, 154.9, 155.6, 169.1. **IR** ($CHCl_3$) ν_{max} 3449, 1780, 1755, 1649, 1599, 1217 cm^{-1}. **Anal. Calcd for $C_{11}H_{10}O_4$:** C, 64.07; H, 4.89. Found: C, 63.91; H, 4.99.

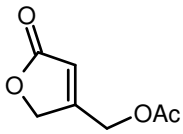
2-Bromo-2-(bromomethyl)succinic Acid (10). To a stirred solution of itaconic anhydride (**9,** 4.0 g, 35.70 mmol) in carbon tetrachloride (30 mL) was added a solution of bromine (3.60 mL, 71.40 mmol) in carbon tetrachloride (20 mL) at room temperature over a period of 20 minutes. The reaction mixture was further stirred for 24 h and then it was concentrated in vacuo. The obtained crude residue was recrystallized from petroleum ether plus ethyl acetate (1:1) mixture to obtain pure **10** (10.13 g, 98%) as a white crystalline solid.

 **10** $C_5H_6Br_2O_4$ (290)	**Mp** 163-165 °C [Petroleum ether + ethyl acetate (1:1)]. **^{1}H NMR** (D_2O, 200 MHz) δ 3.27 (dd, J = 18 & 4 Hz, 2H), 4.03 (s, 2H). **^{13}C NMR** (D_2O, 50 MHz) δ 40.0, 44.7, 59.5, 173.5, 174.8. **IR** (Nujol) ν_{max} 2700-2500, 1720, 1713, 1462 cm^{-1}.

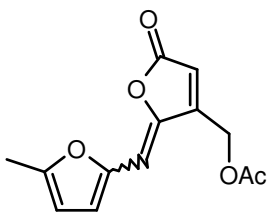
Acetic acid 5-oxo-2,5-dihydro-furan-3-ylmethyl ester (12). To a stirred solution of acid **10** (2.0 g, 6.90 mmol) in Ac_2O (15 mL) was added NaOAc (1.70 g, 20.70 mmol) and the reaction mixture was stirred at room temperature for 6 h. Acetic anhydride was removed in vacuo to obtain crude **11**. To the stirred solution of this residue in THF (20 mL) was added $NaBH_4$ (522 mg, 13.80 mmol) at 0 °C. The reaction mixture was further

stirred at 0 °C for 2 h and then quenched with water and acidified with dilute HCl and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by the silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (3:7) furnished **12** (400 mg, 37%).

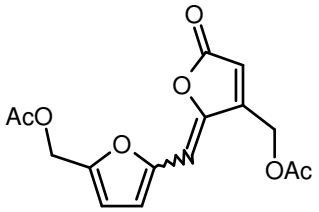
 **11** $C_7H_6O_5$ (170)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.19 (s, 3H), 5.05 (d, J = 2 Hz, 2H), 6.83 (t, J = 2 Hz, 1H). **IR** (Neat) ν_{max} 1771, 1738, 1730 cm^{-1}.

 **12** $C_7H_8O_4$ (156)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.11 (s, 3H), 4.81 (d, J = 2 Hz, 2H), 4.93 (d, J = 2 Hz, 2H), 6.01 (quintet, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 20.3, 59.2, 71.0, 116.6, 163.6, 170.0, 172.7. **IR** (Neat) ν_{max} 1782, 1747, 1651, 1229 cm^{-1}. **Anal. Calcd for $C_7H_8O_4$:** C, 53.85; H, 5.16. Found: C, 53.77; H, 5.04.

Acetic acid 2-(5-methyl-furan-2-ylmethylene)-5-oxo-2,5-dihydro-furan-3-ylmethyl ester (13). To a stirred solution of lactone **12** (300 mg, 1.92 mmol) in methanol was added piperidine (0.13 mL, 1.35 mmol) and 5-methylfurfural (0.19 mL, 1.92 mmol) at room temperature and the reaction mixture was stirred for 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) furnished **13** (358 mg, 75%) as a faint yellow solid.

 **13** $C_{13}H_{12}O_5$ (248)	**Mp** 83-85 ^{o}C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.16 (s, 2.79H), 2.23 (s, 0.21H), 2.35 (s, 2.79H), 2.43 (s, 0.21H), 5.06 (d, J = 2 Hz, 1.86H), 5.43 (d, J = 2 Hz, 0.14H), 6.08 (s, 0.93H), 6.11 (s, 0.93H), 6.17 (d, J = 4 Hz, 0.93H), 6.23 (s, 0.07H), 6.26-6.31 (m, 0.07H), 6.50 (bs, 0.07H), 6.53 (d, J = 4 Hz, 0.07H), 6.97 (d, J = 4 Hz, 0.93H). **^{13}C NMR** ($CDCl_3$, 50 MHz), major Z-isomer: δ 13.8, 20.6, 57.3, 100.3, 109.9, 114.8, 117.6, 143.1, 147.0, 152.5, 155.2, 168.4, 170.0 **IR** ($CHCl_3$) ν_{max} 1773, 1751, 1653, 1597, 1215 cm^{-1}. **Anal. Calcd for $C_{13}H_{12}O_5$:** C, 62.90; H, 4.87. Found: C, 63.02; H, 4.95.

Acetic acid 2-(5-acetoxymethyl-furan-2-ylmethylene)-5-oxo-2,5-dihydro-furan-3-ylmethyl ester (14). To a stirred solution of lactone **13** (300 mg, 1.21 mmol) in dry acetic acid (10 mL) was added SeO_2 (268 mg, 2.42 mmol) and the reaction mixture was refluxed for 6 h. The reaction mixture was filtered through celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (0.5:9.5) to furnish **14** (341 mg, 92%) as a faint yellow solid.



14

$C_{15}H_{14}O_7$ (306)

Mp 93-96 ^oC.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10 (s, 3H), 2.18 (s, 3H), 5.07 (d, J = 1 Hz, 1.6H), 5.08 (s, 1.6H), 5.11 (s, 0.4H), 5.42 (d, J = 1 Hz, 0.4H), 6.13 (s, 0.8H), 6.19 (d, J = 2 Hz, 0.8H), 6.30-6.35 (m, 0.2H), 6.50-6.60 (m, 0.6H), 6.56 (d, J = 4 Hz, 0.8H), 7.05 (d, J = 4 Hz, 0.8H).

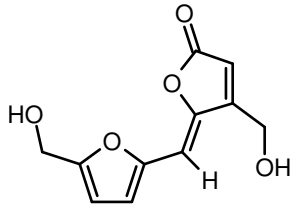
^{13}C NMR ($CDCl_3$, 125 MHz) (very clean two sets of ^{13}C carbon signals were obtained for the major and minor isomers), major isomer: δ 20.6, 20.8, 57.2, 57.9, 99.8, 113.8, 116.1, 116.6, 144.9, 149.0, 151.3, 152.7, 167.9, 170.0, 170.4, minor isomer: δ 20.6, 20.7, 57.7, 60.8, 103.5, 113.3, 117.2, 118.4, 145.4, 147.6, 152.0, 152.1, 167.6, 169.9, 170.5.

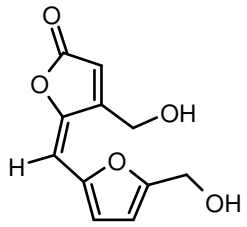
IR ($CHCl_3$) ν_{max} 1776, 1746, 1676, 1653, 1605, 1219 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}O_7$: C, 58.83; H, 4.61. Found: C, 58.72; H, 4.80.

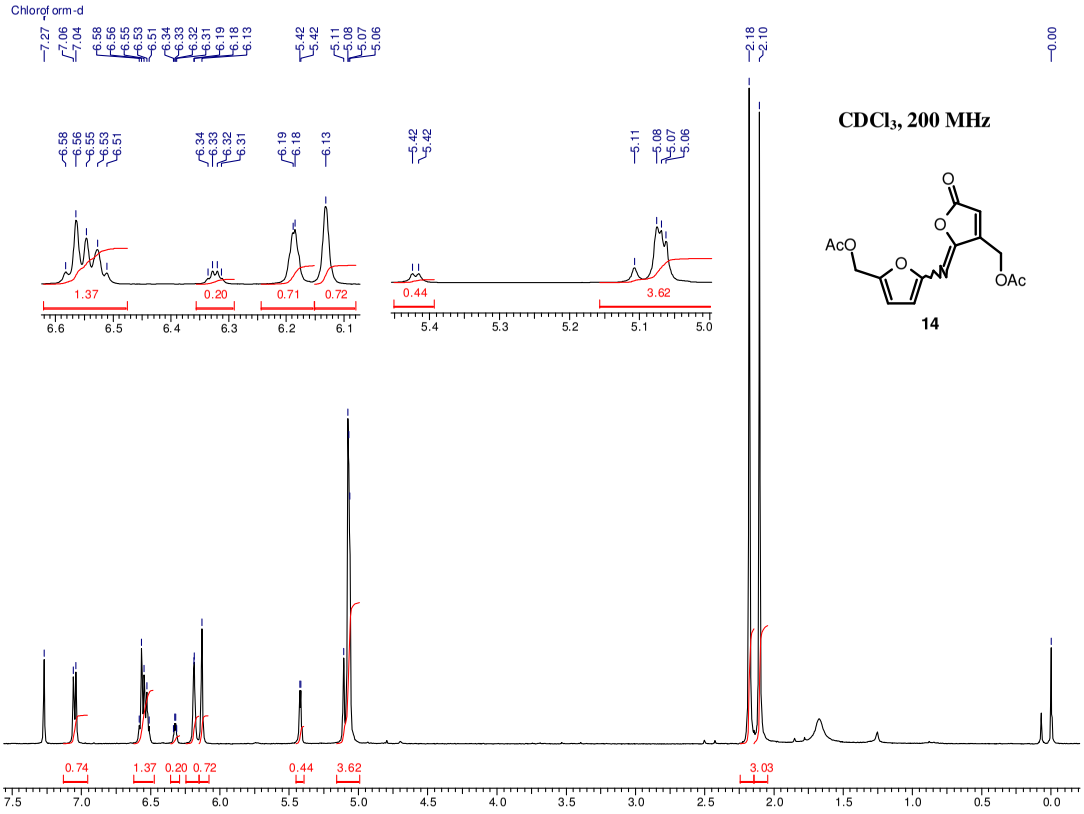
4-Hydroxymethyl-5-(5-hydroxymethyl-furan-2-ylmethylene)-5*H*-furan-2-one ellipsoidone A, 1 and ellipsoidone B, 2). A solution of diacetate **14** (100 mg, 0.33 mmol) in petroleum ether:benzene (2:1) mixture (12 mL) was added to a suspension of Amano PS lipase (40 mg) in aqueous sodium phosphate (0.01 M, 4 mL) at pH 7. The reaction mixture was stirred at room temperature for 40 h. The reaction mixture was filtered through celite and the aqueous layer was extracted with ethyl acetate (20 mL x 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:1) as an eluant to furnish ellipsoidone A (**1**) (59 mg, 81.4%) plus ellipsoidone B (**2**) (9.6 mg, 13.2%) in 95% yield as

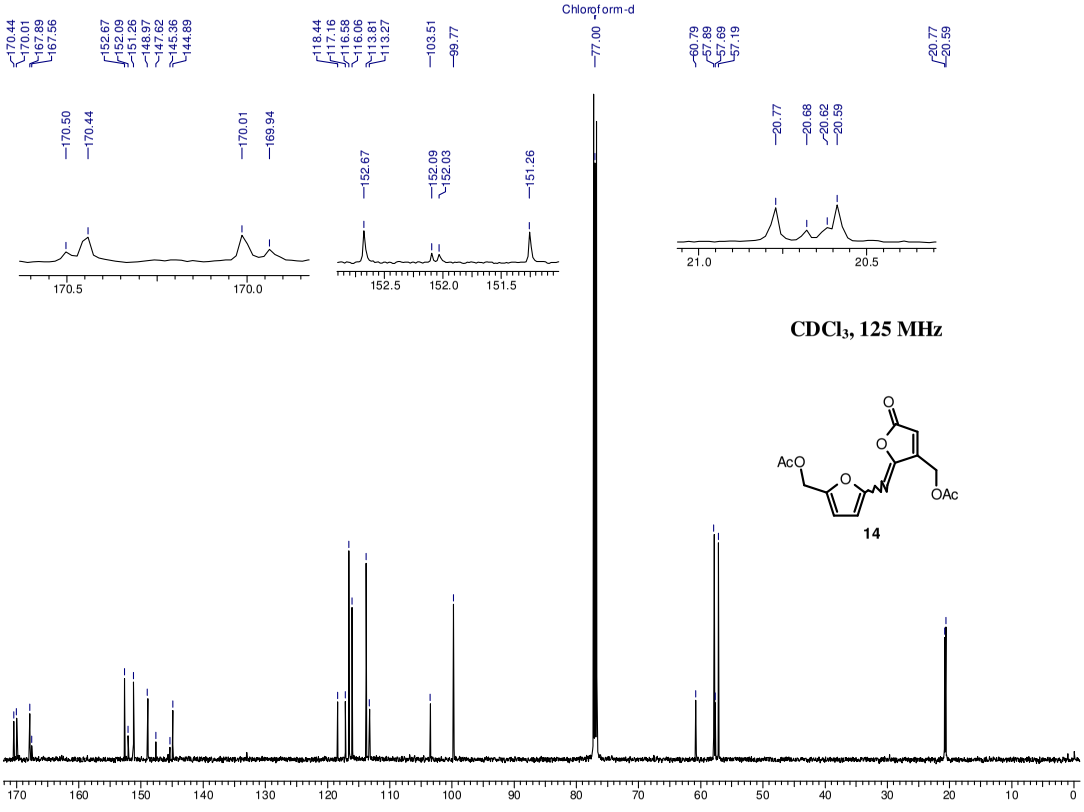
yellow crystalline solid. HPLC separation of **1** plus **2** mixture was done using the known literature procedure.[3]

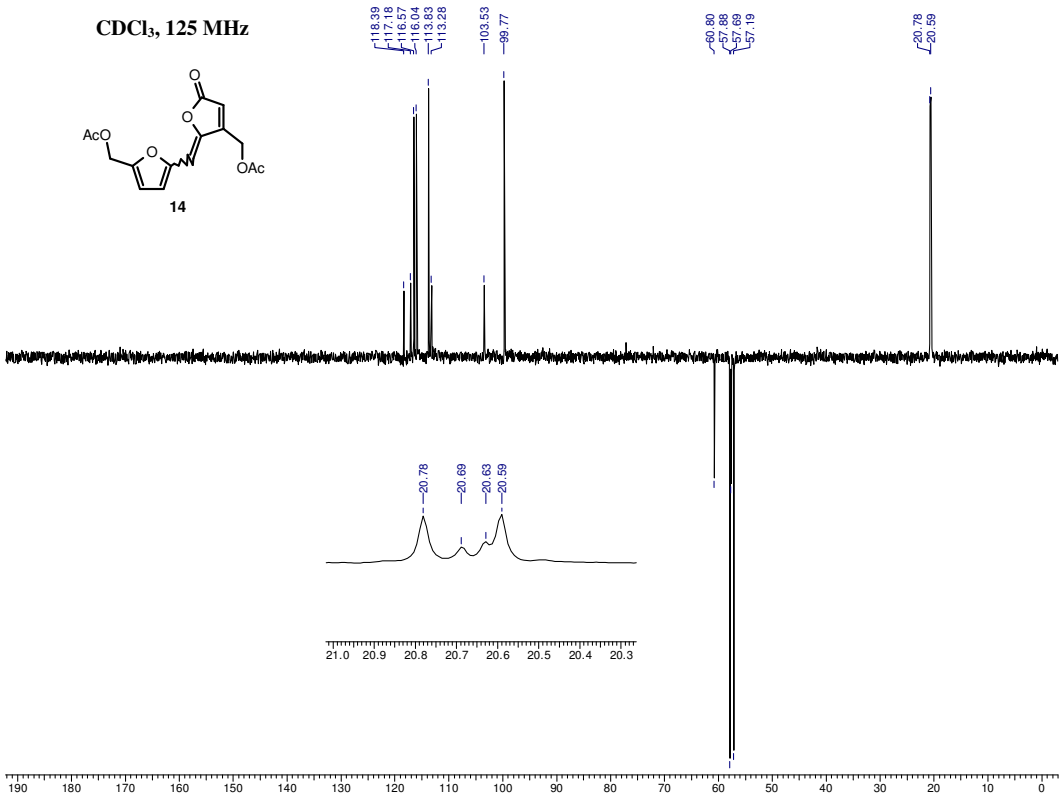
 **1** $C_{11}H_{10}O_5$ (222)	**Mp** 141-143 ^{o}C. **^{1}H NMR** (acetone-d_6, 500 MHz) δ 4.57 (s, 2H), 4.73 (s, 2H), 6.20 (s, 1H), 6.31 (s, 1H), 6.49 (d, J = 5 Hz, 1H), 6.90 (d, J = 5 Hz, 1H). **^{13}C NMR** (acetone-d_6, 125 MHz) δ 57.1, 57.3, 99.8, 111.0, 114.2, 116.4, 145.7, 149.3, 158.5, 161.5, 169.2. **IR** (Nujol) ν_{max} 3329, 3211, 1749, 1638, 1462 cm^{-1}. **Anal. Calcd for $C_{11}H_{10}O_5$:** C, 59.46; H, 4.54. Found: C, 59.52; H, 4.63.

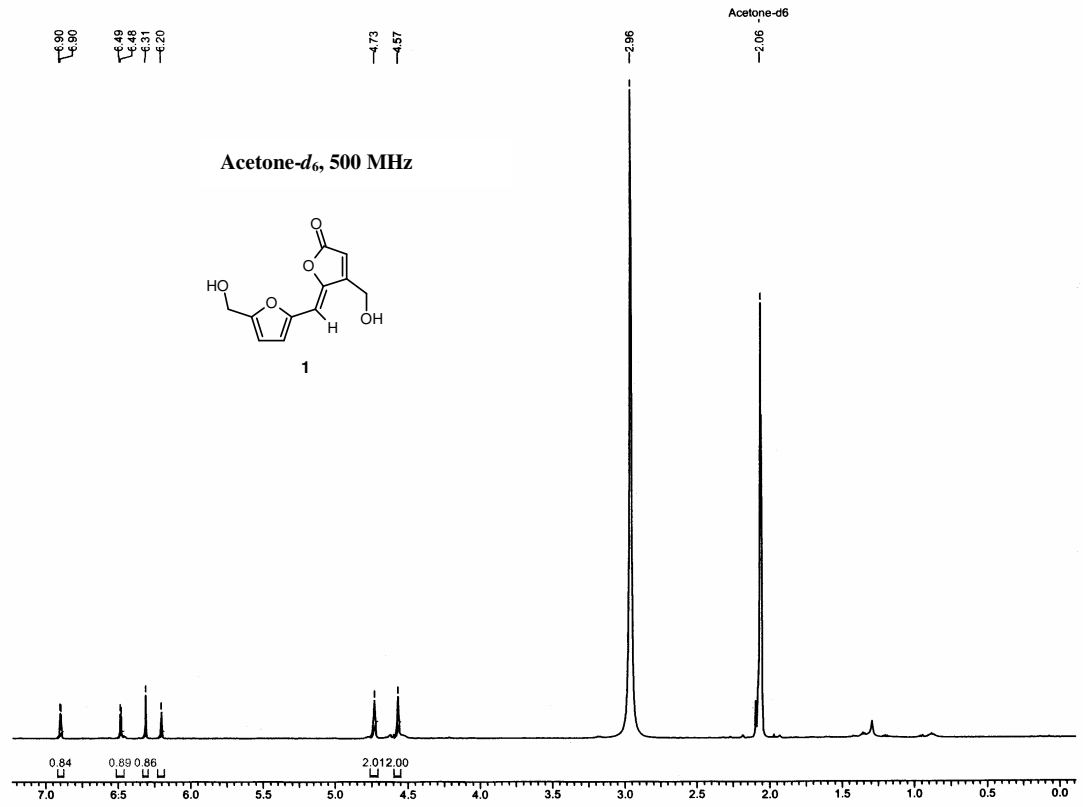
 **2** $C_{11}H_{10}O_5$ (222)	**Mp** 159-161 ^{o}C. **^{1}H NMR** (acetone-d_6, 500 MHz) δ 4.63 (s, 2H), 4.97 (d, J = 2 Hz, 2H), 6.41 (m, 1H), 6.46 (d, J = 1 Hz, 1H), 6.62 (s, 1H), 6.74 (d, J = 2 Hz, 1H). **^{13}C NMR** (acetone-d_6, 125 MHz) δ 57.3, 60.0, 103.6, 110.5, 117.8, 117.9, 146.1, 147.8, 159.0, 160.5, 168.4. **IR** (Nujol) ν_{max} 3331, 3302, 1736, 1638, 1460 cm^{-1}. **Anal. Calcd for $C_{11}H_{10}O_5$:** C, 59.46; H, 4.54. Found: C, 59.31; H, 4.60.

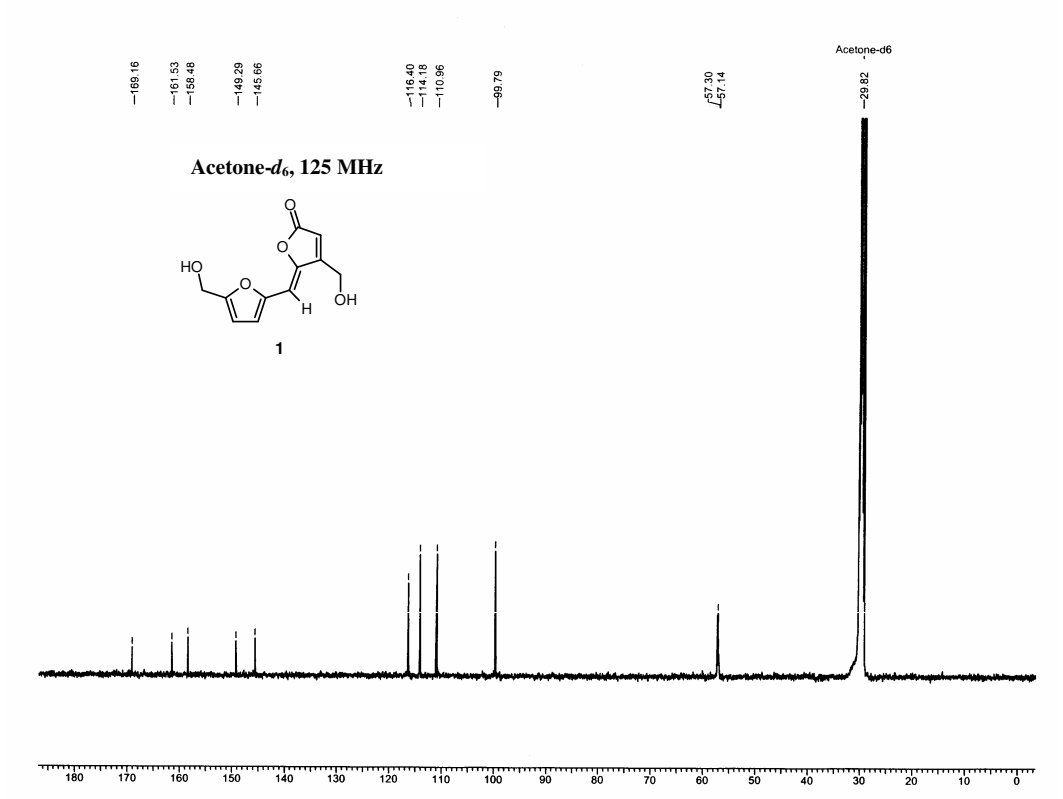
3C.5 Selected Spectra

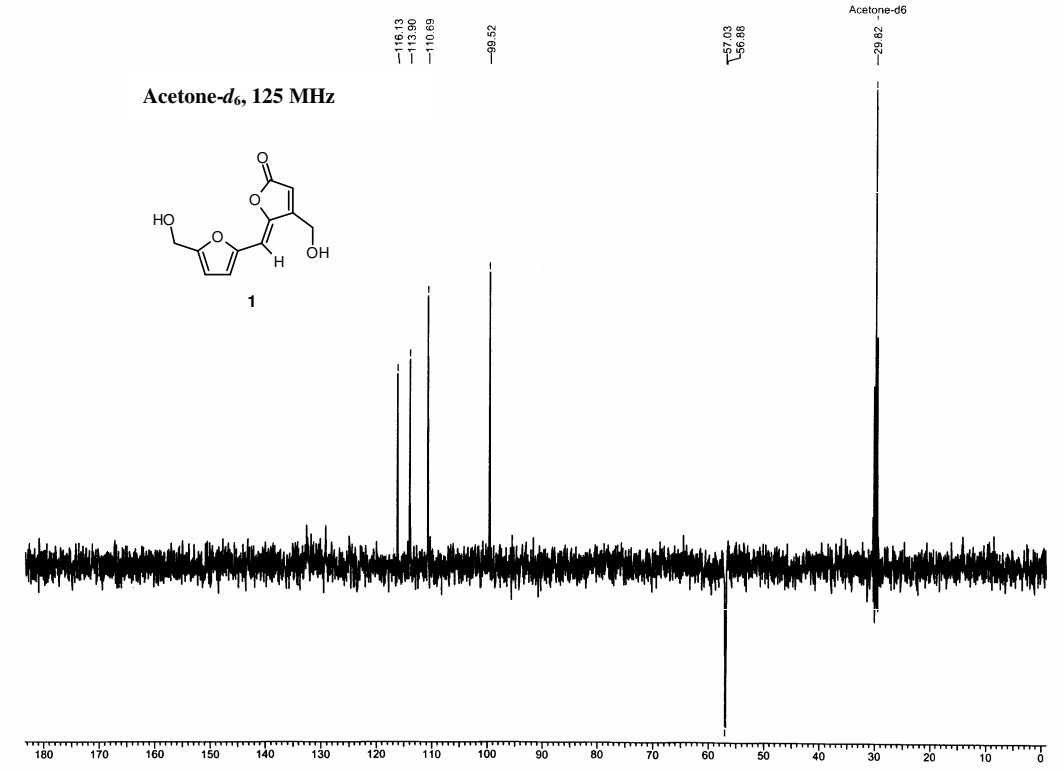

Chloroform-d
CDCl3, 200 MHz
AcO
OAc
14


Chloroform-d
CDCl3, 125 MHz
AcO
OAc
14


CDCl3, 125 MHz
AcO
OAc
14
118.39
117.18
116.57
116.04
113.83
113.28
103.53
99.77
60.80
57.88
57.69
57.19
20.78
20.59
20.78
20.69
20.63
20.59


Acetone-d6
6.90
6.90
6.49
6.48
6.31
6.20
4.73
4.57
2.96
2.06
Acetone-d6, 500 MHz
HO
OH
H
1
0.84
0.89
0.86
2.01
2.00


Acetone-d6
169.16
161.53
158.48
149.29
145.66
116.40
114.18
110.96
99.79
57.30
57.14
29.82
Acetone-d_6, 125 MHz
HO
O
O
H
OH
1
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Acetone-d6
116.13
113.90
110.69
99.52
57.03
56.88
29.82
Acetone-d_6, 125 MHz
HO
O
O
H
OH
1
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

3C.6 References

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3D. Section D

An Elegant Two-step Chemoenzymatic Access to Natural Germination Inhibitor (+)-Erigeronic Acid

This section features the following topics:

3D. Section D: An Elegant Two-step Chemoenzymatic Access to Natural Germination Inhibitor (+)-Erigeronic Acid

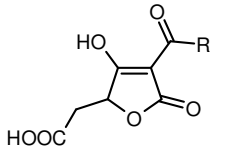
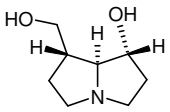
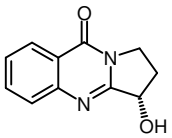
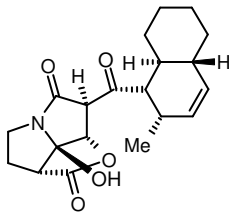
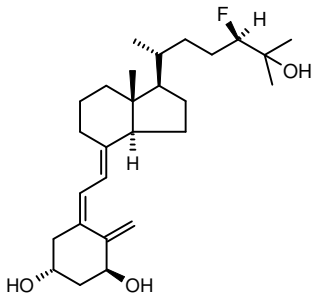
3D.1 Background

Plants are known to produce secondary metabolites that affect germination and growth of other plants. This is one of a variety of ways in which certain plants can reduce interspecies competition in their natural habitats. Allelopathy is the term used to describe such interactions.[1] In many cases, such allelochemicals are known to possess selective toxicity toward target species.[2] The genus *Erigeron* is a member of the Compositae (Asteraceae) family and contains more than 400 species. *Erigeron annuus*, commonly named as annual fleabane, is an indigenous weed from eastern North America. 5-Butyl-3-oxo-2,3-dihydrofuran-2-yl-acetic acid [Erigeronic acid A, **1**] was isolated by Kwon and co-workers[3] from the flowers of this *Erigeron annuus* and it possesses strong lettuce seed germination inhibitory activity [IC_{50} (mM) 2.13]. The structure of acid **1** was unambiguously deduced by analysis of 2D NMR spectroscopic data (COSY, HMQC and HMBC) but the configuration at the C-2 centre was not determined.[3] The structure of compound **1** represents a unique natural alkyl furanone possessing carboxylic acid and *n*-butyl substituents and it can be a agriculturally useful product. We envisaged (*R*)/(*S*)-acetoxysuccinic anhydride (**2**) as suitable building block for the synthesis and stereochemical assignment of acid **1**.

(*R/S*)-Acetoxysuccinic anhydrides (**2**) can be synthesized by acetylation–dehydration of (*R*/*S*)-malic acid with acetyl chloride at 45 °C over 4 hours, which gives quantitative yield of **2**.[4] (*R*/*S*)-Malic acids are important chiral building blocks which have found wide application in the enantioselective synthesis of chiral compounds. Manipulation of this polyfunctional synthon requires the selective protection of the different functionalities and the distinction of the two carboxyl groups present. The *O*-protected hydroxysuccinic anhydrides (**2**) derived from malic acid offer a unique way to achieve both these tasks. These anhydrides react regioselectively at the hindered, more electron deficient carbonyl with oxygen and nitrogen nucleophiles[5,6] and the stable carbanion from ethyl acetoacetate,[7] giving important chiral intermediates, which can be subsequently converted to bioactive natural products or their analogues. These acetoxysuccinic anhydrides (**2**) also have been used for enantioselective synthesis of novel optically active nucleoside analogues.[8]

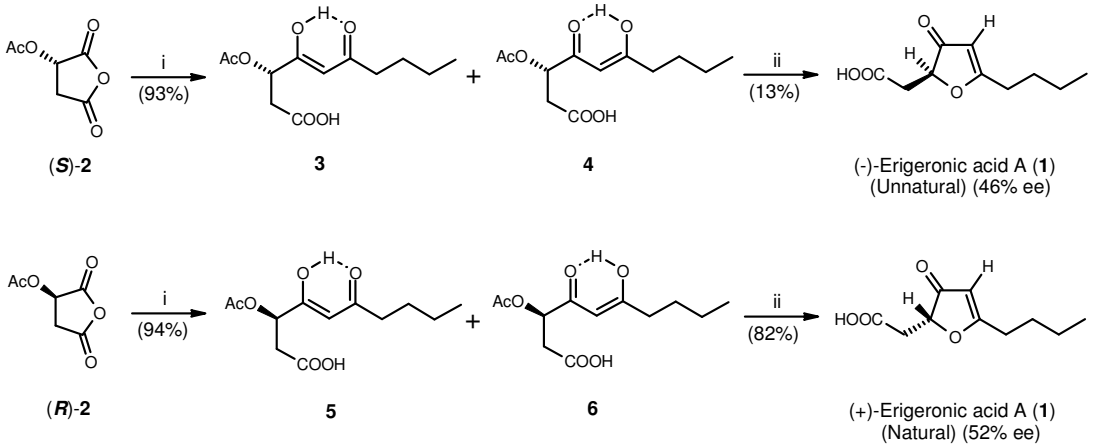
Synthesis of some representative examples of natural and unnatural products using (*R/S*)-acetoxysuccinic anhydrides are given in table 1.

Table 1. Natural and unnatural compounds synthesized from **2**

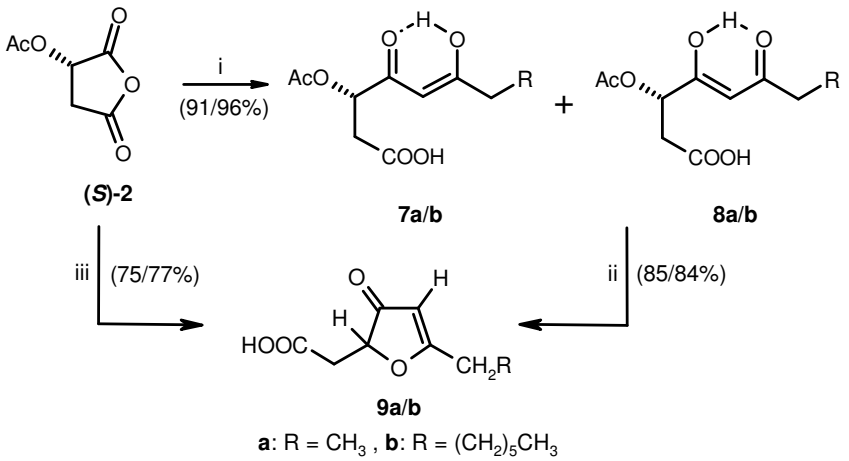
No.	Compound Synthesized	Source	Activity	Ref.
1	 Tetronic acids	A great number of tetronic acids and their metabolites are found as natural products, which exhibit a wide array of biological properties.[9,10]		7
2	 (–)-Hastanecine	*Cacalia hastata*	Anti-tumour activity	11
3	 (–)-Vasicinone	*Adhatoda vasica*	Anti-tumor, bronchodilating, hypotensive, anti-anaphylactic	5
4	 UCS1025A	*Acremonium sp.* KY4917	Telomerase inhibitor	12
5	 lα,25-Dihydroxy-24-(*R*)-fluorocholecalciferol	Analogue of vitamin D_3 metabolite lα,25-dihydroxycholecalciferol[13] with a longer half-life period.	Anti-rachitogenic activity	14

3D.2 Results and Discussion

This section reports a highly regioselective ring opening of (*R*)/(*S*)-acetoxysuccinic anhydrides with the kinetic enolates from alkyl methyl ketones, to design natural/unnatural **1** and its congeners (Schemes 1, 2). (*R*)/(*S*)-Malic acids on treatment with acetyl chloride furnished the corresponding (*R*)/(*S*)-acetoxysuccinic anhydrides (**2**) in 98% yield.[4] As expected, the (*S*)-acetoxysuccinic anhydride underwent a highly regioselective ring opening at the more reactive hindered carbonyl at –78 °C with the kinetic enolate generated from butyl methyl ketone using LDA as a base to exclusively provide the intermediate diketo compound in 93% yield, which was transformed in situ to a mixture of enantiomerically pure enols **3** and **4** in the ratio 80:20 (by ^{1}H NMR) (Scheme 1). The structural assignment of **3** and **4** was done on the basis of the presence of vinylic and enolic protons in the ^{1}H NMR spectrum. As expected the allylic methine proton in **3** was more deshielded than the corresponding methine proton in **4**, whereas the allylic methylene protons in **4** were more deshielded in comparison with the corresponding methylene protons in **3**. We feel that, due to the electron withdrawing influence of the acetoxy group, the enolization of an adjacent carbonyl occurs to a larger extent, forming **3** as a major isomer. The potassium carbonate catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture directly furnished the desired erigeronic acid in 89% yield via the intramolecular dehydrative cyclization pathway, but in a racemic form. The triethylamine/(–)-quinine catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture also directly furnished the erigeronic acid in 62-65% yield but with only 10-15% ee (by rotation). The acid catalyzed



Scheme 1. *Reagents, conditions and yields*: (i) (a) $CH_3COCH_2(CH_2)_2CH_3$, LDA, THF, –78 °C, 90 min, (b) H^+/HCl (**3**:**4**/**5**:**6** = 8:2); (ii) Amano PS, pet. ether/benzene (2:1), rt, 40 h, phosphate buffer pH 7.0.



Scheme 2. *Reagents, conditions and yields*: (i) (a) $CH_3COCH_2CH_3/CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, –78 °C, 90 min, (b) H^+/HCl (**a**: 91%, **b**: 96%; **7a/b**:**8a/b** = 8:2); (ii) (a) K_2CO_3, MeOH, 6 h, (b) H^+/HCl (**a**: 85%, **b**: 84%); (iii) (a) $CH_3COCH_2CH_3/CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, –78 °C, 90 min, (b) 10% Aq. LiOH, rt, 8 h, (c) H^+/HCl (**a**: 75%, **b**: 77%).

alcoholysis of the acetoxy group in **3** plus **4** mixture in methanol directly furnished the methyl ester of desired natural product in 95% yield, following the same pathway but again in racemic form. Under both acidic and basic conditions, we could isolate the erigeronic acid/ester in racemic form only and hence we planned for an enzymatic hydrolysis of **3** plus **4** mixture under neutral conditions at pH 7. The Amano PS catalyzed hydrolysis of **3** plus **4** mixture was very slow and gave the unnatural (–)-erigeronic acid only in 13% yield (46% ee, from the comparison with reported rotation value of the natural product). With the hope that the enzyme Amano PS will better recognize opposite isomer, we similarly obtained the mixture of **5** plus **6** from the corresponding (*R*)-acetoxysuccinic anhydride with 94% yield. The Amano PS catalyzed hydrolysis of **5** plus **6** mixture directly furnished the desired natural (+)-erigeronic acid A in 82% yield (52% ee, from the comparison with reported rotation value of the natural product). The analytical and spectral data obtained for (+)-erigeronic acid A was in agreement with the reported data[3] and thus we could assign the (*R*)-configuration to C-2 chiral centre in the natural acid using the present chiral pool strategy and chemoenzymetic pathway. During these studies we noticed that the (+)-erigeronic acid A in its neat form at room temperature undergoes a continuous racemization process and becomes completely racemic in 96 hours time. The present racemization of (+)-**1** could be attributed to the high acidity of the C-2 proton and the higher propensity for keto-enol tautomerism. We feel that alike the preparation of

enantiomerically pure α-hydroxycyclopentanone,[15] herein too, after the enzymatic hydrolysis of **5** plus **6** mixture, the formed product (+)-**1** undergoes a partial racemization process during the course of reaction and isolation procedures and hence, we could get only the 52% ee for (+)-**1**.

The present approach to 5-alkyl-3-oxo-dihydrofuranyl-2-acetic acids is general in nature and starting from **2** and ethyl methyl ketone/heptyl methyl ketone, we could synthesize **9a/b** in very good yields both in one pot and a stepwise fashion, with or without isolation of the intermediates **7a/b**+**8a/b** (Scheme 2). In the one pot synthesis, we quenched the anhydride **2** and ketone condensation reactions with 10% aqueous lithium hydroxide and then acidified the reaction mixture with 2 M hydrochloric acid to obtain **9a/b** in 75-77% yield.

3D.3 Summary

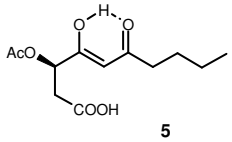
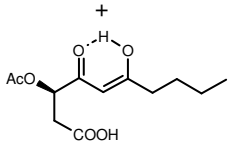
In summary, starting from (*R*)-acetoxysuccinic anhydride, an elegant first synthesis of natural germination inhibitor (+)-erigeronic acid has been demonstrated using chiral pool strategy and an enzymatic hydrolysis pathway, which helped us to assign (*R*)-configuration to the C-2 chiral centre in acid (+)-**1**.[16] In the present synthesis of (+)-**1**, the highly regioselective ring opening of anhydride (+)-**2** with the primary enolate of butyl methyl ketone and an enzymatic hydrolysis of **5** plus **6** mixture and subsequent in situ dehydrative cyclization to form (+)-**1** are noteworthy. The present approach is general in nature and can be used to design the analogs of **1**.

In conclusion, in the present four sections chapter we have described the relevant literature and our results with experimental and spectral data. Cyclic anhydrides are the multifunctional entity and have been extensively used for different reactions, at all the reactive sites, for the constructions of variety of bioactive natural products and unnatural compounds in the past century. In the present chapter, we have seen the utility of lipases for the enantiopure synthesis of important chiral intermediates and natural products. We used citraconic anhydride and Amano PS for the enantioselective synthesis of natural butyrolactone (–)-saccharinic acid lactone and leaf closing compound potassium (2R,3R)-2,3,4-trihydroxy-2-methylbutanoate. Using itaconic anhydride as the starting material and Amano PS, we have described first chemoenzymatic synthesis of γ-alkylidenebutenolides, cytotoxic ellipsoidone A and ellipsoidone B. We used (R)-acetoxysuccinic anhydride and Amano PS for 2-steps efficient synthesis of germination inhibitor (+)-erigeronic acid. In the synthesis of ellipsoidone A, ellipsoidone B and (+)-erigeronic acid A, we have seen that enzyme is the real reagent of choice as chemical approaches did not provide satisfactory results.

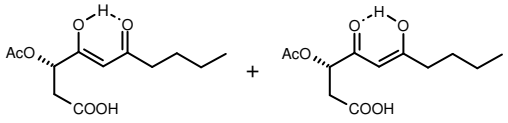
3D.4 Experimental Section

Column chromatographic separations were carried out on silica gel (60-120 mesh). Commercially available (*S*)-malic acid (97% ee), (*R*)-malic acid (98% ee), ethyl methyl ketone, butyl methyl ketone, heptyl methyl ketone, acetyl chloride and *n*-butyllithium were used. Amano PS-1360 U from Amano Pharmaceuticals, Japan was used. The activity of the lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder.[17]

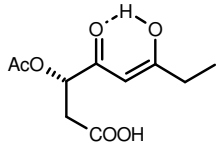
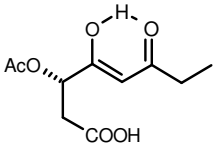
(*R*)-3-Acetoxy-4-hydroxy-6-oxo-dec-4-enoic acid (5) plus (*R*)-3-acetoxy-6-hydroxy-4-oxo-dec-5-enoic acid (6). To a stirred solution of butyl methyl ketone (253 mg, 2.53 mmol) in THF (8 mL) at –78 °C was added freshly prepared LDA (271 mg, 2.53 mmol) in THF (5 mL) in a drop wise fashion under argon atmosphere. The reaction mixture was stirred at –78 °C temperature for 30 minutes and the above reaction mixture was added to a stirred solution of the anhydride (*R*)-**2** (400 mg, 2.53 mmol) in THF (10 mL) at –78 °C under argon atmosphere in a drop wise fashion. Further stirring was continued for 90 minutes at the same temperature. The reaction was then quenched with water and acidified with 2 M HCl. The reaction mixture was then immediately 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 **5** plus **6** (**5**:**6** = 8:2, 614 mg, 94%).

 **5** +  **6** $C_{12}H_{18}O_6$ (258)	Colorless thick oil. $[\alpha]^{20}_D$ = +41 (c 1.0, CH_3OH). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.90 (t, *J* = 8 Hz, 0.6H), 0.91 (t, *J* = 8 Hz, 2.4H), 1.15-1.45 (m, 2H), 1.45-1.70 (m, 2H), 2.13 (s, 0.6H), 2.15 (s, 2.4H), 2.30 (t, *J* = 8 Hz, 1.6H), 2.51 (t, *J* = 8 Hz, 0.4H), 2.75-3.00 (m, 2H), 5.25-5.40 (m, 0.2H), 5.53 (dd, *J* = 8 & 6 Hz, 0.8H), 5.63 (s, 1H), 9.00 (bs, 1H), 15.02 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) (major enol isomer **5**) δ 13.7, 20.7, 22.2, 27.8, 36.2, 37.2, 71.1, 96.1, 169.8, 174.9, 191.7, 192.8. **MS** (*m*/*e*) 297, 281, 276, 259, 199, 144. **IR** ($CHCl_3$) ν_{max} 3207, 2700-2500, 1747, 1733, 1719, 1603 cm^{-1}. **Anal. Calcd for $C_{12}H_{18}O_6$:** C, 55.81; H, 7.02. Found: C, 55.73; H, 6.99.

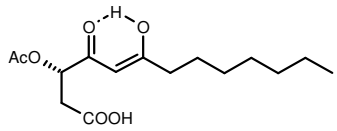
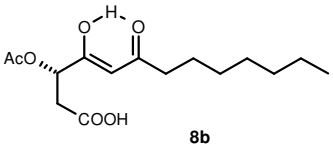
(*S*)-3-Acetoxy-4-hydroxy-6-oxo-dec-4-enoic acid (3) plus (*S*)-3-acetoxy-6-hydroxy-4-oxo-dec-5-enoic acid (4). Starting from (*S*)-**2** (400 mg, 2.53 mmol), the title compounds mixture was obtained (**3**:**4** = 8:2, 607 mg, 93%).

 **3** + **4** $C_{12}H_{18}O_6$ (258)	Colorless thick oil. $[\alpha]^{20}_D$ = –41 (c 1.4, CH_3OH). IR and ^{1}H NMR spectral data was identical with **5** + **6**.

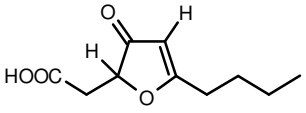
(*S*)-3-Acetoxy-6-hydroxy-4-oxo-oct-5-enoic acid (7a) plus (*S*)-3-acetoxy-4-hydroxy-6-oxo-oct-4-enoic acid (8a). Starting from (*S*)-**2** (400 mg, 2.53 mmol) and ethyl methyl ketone (183 mg, 2.53 mmol) the title compounds mixture was obtained (**7a**:**8a** = 8:2, 530 mg, 91%).

 **7a** +  **8a** $C_{10}H_{14}O_6$ (230)	Colorless thick oil. $[\alpha]^{20}_D$ = –42 (c 1.7, CH_3OH). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.07 (t, *J* = 8 Hz, 0.6H), 1.15 (t, *J* = 8 Hz, 2.4H), 2.14 (s, 0.6H), 2.15 (s, 2.4H), 2.36 (q, *J* = 8 Hz, 1.6H), 2.55 (q, *J* = 8 Hz, 0.4H), 2.75-3.02 (m, 2H), 5.25-5.40 (m, 0.2H), 5.54 (dd, *J* = 8 & 6 Hz, 0.8H), 5.64 (s, 1H), 7.80 (bs, 1H), 15.04 (bs, 1H). **MS** (*m*/*e*) 269, 253, 248, 231, 193, 171, 153. **IR** (Neat) ν_{max} 3225, 2700-2500, 1744, 1735, 1720, 1605 cm^{-1}. **Anal. Calcd for $C_{10}H_{14}O_6$:** C, 52.17; H, 6.13. Found: C, 52.31; H, 6.22.

(*S*)-3-Acetoxy-6-hydroxy-4-oxo-tridec-5-enoic acid (7b) plus (*S*)-3-acetoxy-4-hydroxy-6-oxo-tridec-4-enoic acid (8b). Starting from (*S*)-**2** (400 mg, 2.53 mmol) and heptyl methyl ketone (360 mg, 2.53 mmol) the title compounds mixture was obtained (**7b**:**8b** = 8:2, 729 mg, 96%).

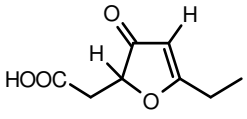
 **7b** +  **8b** $C_{15}H_{24}O_6$ (300)	Colorless thick oil. $[\alpha]^{20}_D = -35$ (c 1.4, CH_3OH). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.28 (bs, 8H), 1.50-1.70 (m, 2H), 2.14 (s, 0.6H), 2.16 (s, 2.4H), 2.31 (t, J = 6 Hz, 1.6H), 2.51 (t, J = 6 Hz, 0.4H), 2.75-3.05 (m, 2H), 5.30-5.45 (m, 0.2H), 5.54 (dd, J = 8 & 4 Hz, 0.8H), 5.63 (s, 1H), 9.00 (bs, 1H), 15.03 (bs, 1H). **MS** (*m/e*) 339, 323, 318, 301, 255, 241. **IR** (Neat) ν_{max} 3220, 2700-2500, 1751, 1730, 1720, 1597 cm^{-1}. **Anal. Calcd for $C_{15}H_{24}O_6$:** C, 59.98; H, 8.05. Found: C, 60.11; H, 7.86.

(±)-Erigeronic acid A [(±)-1]. To a stirred solution of enols **5** & **6** (60 mg, 0.23 mmol) in methanol (3 mL) was added K_2CO_3 (42 mg, 0.30 mmol) and the reaction mixture was stirred at room temperature for 4 h. Methanol was removed in vacuo at room temperature and water (10 mL) was added to the reaction mixture, then acidified to pH 2 using 2 N HCl and extracted with ethyl acetate (15 mL x 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (2:8) as an eluant gave (±)-**1** (41 mg, 89%).

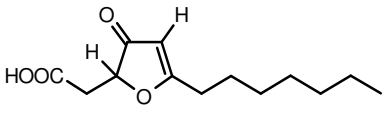
 Erigeronic acid A (**1**) $C_{10}H_{14}O_4$ (198)	Colorless thick oil. **^{1}H NMR** (CD_3OD, 200 MHz) δ 0.95 (t, J = 8 Hz, 3H), 1.41 (sextet, J = 8 Hz, 2H), 1.65 (quintet, J = 8 Hz, 2H), 2.57 (t, J = 8 Hz, 2H), 2.61 (d, J = 18 Hz, 1H), 2.91 (d, J = 18 Hz, 1H), 4.83 (m, 1H), 5.54 (s, 1H). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.94 (t, J = 8 Hz, 3H), 1.40 (sextet, J = 8 Hz, 2H), 1.65 (quintet, J = 8 Hz, 2H), 2.52 (t, J = 8 Hz, 2H), 2.65 (dd, J = 17 & 8 Hz, 1H), 3.04 (dd, J = 17 & 4 Hz, 1H), 4.84 (dd, J = 9 & 4 Hz, 1H), 5.51 (s, 1H), 7.50 (bs, 1H). **^{13}C NMR** (CD_3OD, 50 MHz) δ 14.1, 23.3, 29.3, 31.4, 36.4, 83.3, 104.1, 172.8, 197.3, 206.4. **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.6, 22.2, 28.0, 30.5, 35.7, 81.5, 103.2, 174.5, 195.3, 203.6. **IR** (Neat) ν_{max} 2700-2500, 1732, 1713, 1585 cm^{-1}. **Anal. Calcd for $C_{10}H_{14}O_4$:** C, 60.59; H, 7.12. Found: C, 60.60; H, 7.19.

The compounds **9a** and **9b** were similarly prepared using the above procedure.

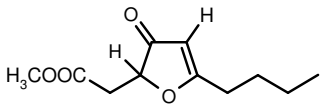
(5-Ethyl-3-oxo-2,3-dihydro-furan-2-yl)-acetic acid (9a). Starting from acids **7a** and **8a** (60 mg, 0.26 mmol) and K_2CO_3 (42 mg, 0.30 mmol) the title compound was obtained (38 mg, 85%).

 **9a** $C_8H_{10}O_4$ (170)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.24 (t, *J* = 8 Hz, 3H), 2.55 (q, *J* = 6 Hz, 2H), 2.65 (dd, *J* = 18 & 8 Hz, 1H), 3.04 (dd, *J* = 18 & 4 Hz, 1H), 4.85 (dd, *J* = 10 & 4 Hz, 1H), 5.53 (s, 1H), 8.77 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 10.1, 24.2, 35.7, 81.5, 102.6, 174.6, 196.2, 203.5. **IR** (Neat) ν_{max} 2700-2500, 1722, 1684, 1585 cm^{-1}. **Anal. Calcd for $C_8H_{10}O_4$:** C, 56.47; H, 5.92. Found: C, 56.33; H, 6.06.

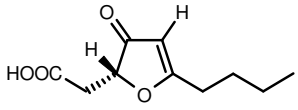
(5-Heptyl-3-oxo-2,3-dihydro-furan-2-yl)-acetic acid (9b). Starting from acids **7b** and **8b** (60 mg, 0.20 mmol) and K_2CO_3 (42 mg, 0.30 mmol) the title compound was obtained (40 mg, 84%).

 **9b** $C_{13}H_{20}O_4$ (240)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.88 (t, *J* = 8 Hz, 3H), 1.15-1.45 (bm, 8H), 1.64 (quintet, *J* = 8 Hz, 2H), 2.51 (t, *J* = 8 Hz, 2H), 2.63 (dd, *J* = 16 & 8 Hz, 1H), 3.04 (dd, *J* = 17 & 4 Hz, 1H), 4.85 (dd, *J* = 9 & 4 Hz, 1H), 5.52 (s, 1H), 9.78 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 25.9, 28.8, 29.0, 30.8, 31.5, 35.7, 81.5, 103.2, 174.5, 195.3, 203.7. **IR** (Neat) ν_{max} 2700-2500, 1734, 1707, 1584 cm^{-1}. **Anal. Calcd for $C_{13}H_{20}O_4$:** C, 64.98; H, 8.39. Found: C, 65.11; H, 8.23.

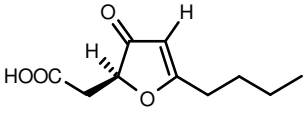
Methyl (5-butyl-3-oxo-2,3-dihydro-furan-2-yl)acetate. To a stirred solution of **5** plus **6** (60 mg, 0.23 mmol) in methanol was added conc. HCl (0.1 mL) and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was concentrated in vacuo and diluted with water (10 mL). The aqueous layer was extracted with ethyl actetate (15 mL x 4) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo gave the corresponding methyl ester (47 mg, 95%) of erigeronic acid **1**.

 Methyl ester of (±)-**1** $C_{11}H_{16}O_4$ (212)	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.93 (t, J = 8 Hz, 3H), 1.39 (sextet, J = 8 Hz, 2H), 1.63 (quintet, J = 8 Hz, 2H), 2.50 (t, J = 8 Hz, 2H), 2.59 (dd, J = 17 & 8 Hz, 1H), 2.97 (dd, J = 16 & 4 Hz, 1H), 3.74 (s, 3H), 4.81 (dd, J = 10 & 4 Hz, 1H), 5.47 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.6, 22.2, 28.0, 30.4, 35.7, 52.2, 81.6, 103.2, 170.0, 194.5, 203.1. **IR** (Neat) ν_{max} 1744, 1703, 1593 cm^{-1}. **Anal. Calcd for $C_{11}H_{16}O_4$:** C, 62.25; H, 7.60. Found: C, 62.37; H, 7.49.

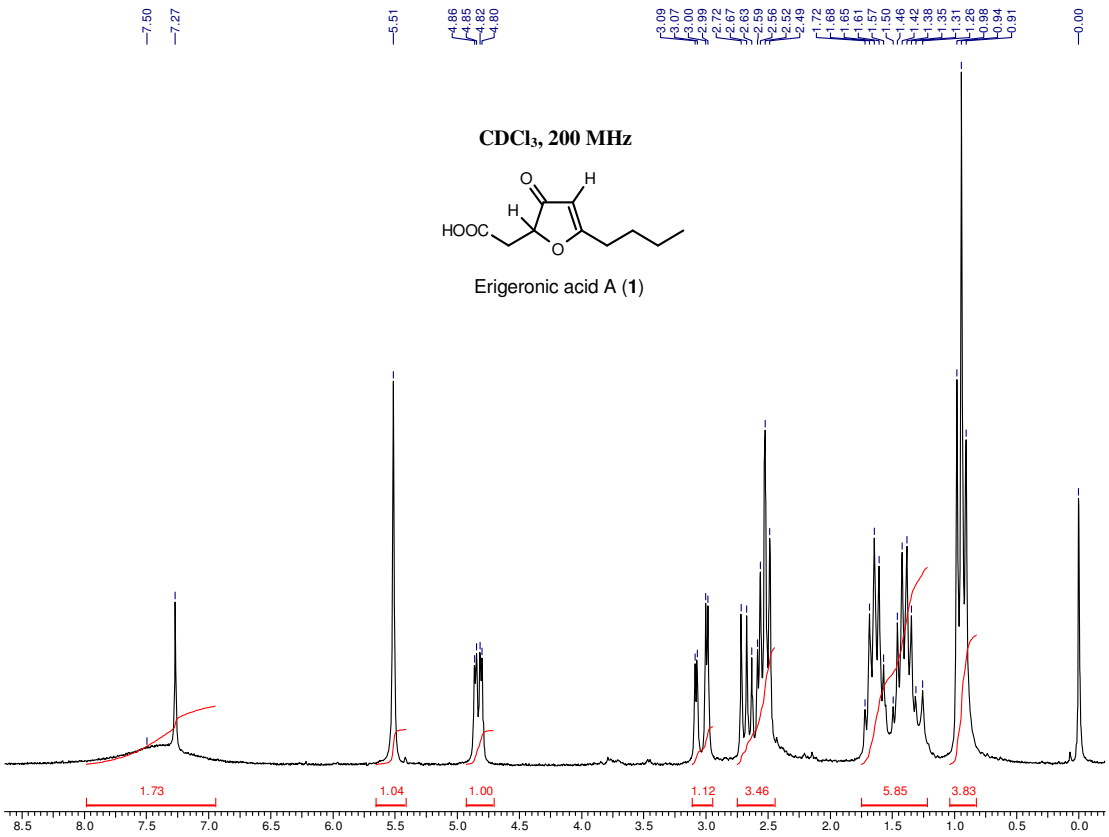
(+)-Erigeronic acid A (1). A solution of acids **5** and **6** (74 mg, 0.29 mmol) in petroleum ether:benzene (2:1) mixture (6 mL) was added to a suspension of Amano PS lipase (20 mg) in aqueous sodium phosphate (0.01 M, 2 mL) at pH 7. The reaction mixture was stirred at room temperature for 40 h. The reaction mixture was filtered through celite and the aqueous layer was extracted with ethyl acetate (15 mL x 4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic separation using a mixture of ethyl acetate/petroleum ether (2:8) as an eluent gave (+)-**1** (47 mg, 82%).

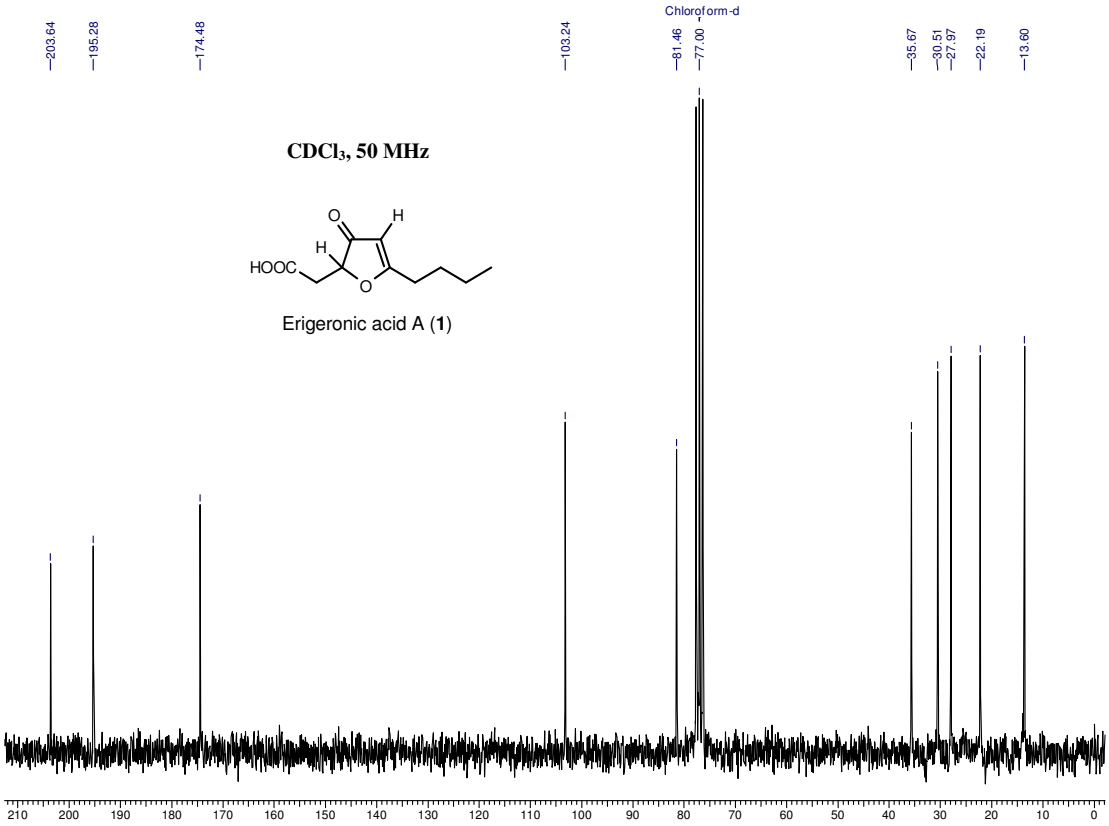
 (+)-Erigeronic acid A (**1**)	Colorless thick oil. $[\alpha]^{20}_D$ = +15.1 (c 1.0, CH_3OH), [Lit.[3] +29 (c 0.07, CH_3OH)]. **IR** and **^{1}H NMR** spectral data was identical with (±)**-1**.

(–)-Erigeronic acid A (1). Similarly starting from **3** & **4** (100 mg, 0.39 mmol) the title compound (–)**-1** was obtained (10 mg, 13%).

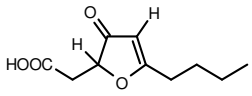
 (-)-Erigeronic acid A (**1**)	Colorless thick oil. $[\alpha]^{20}_D$ = –13.3 (c 0.3, CH_3OH). **IR** and **^{1}H NMR** spectral data was identical with (±)**-1**.

3D.5 Selected Spectra

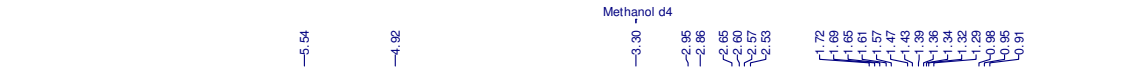

7.50
7.27
5.51
4.86
4.85
4.82
4.80
3.09
3.07
3.00
2.99
2.72
2.67
2.63
2.59
2.56
2.52
2.49
1.72
1.68
1.65
1.61
1.57
1.50
1.46
1.42
1.38
1.35
1.31
1.26
0.98
0.94
0.91
0.00
CDCl3, 200 MHz
O
H
H
HOOC
O
Erigeronic acid A (1)
1.73
1.04
1.00
1.12
3.46
5.85
3.83
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


203.64
195.28
174.48
103.24
Chloroform-d
81.46
77.00
35.67
30.51
27.97
22.19
13.60
CDCl3, 50 MHz
O
H
H
HOOC
O
Erigeronic acid A (1)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

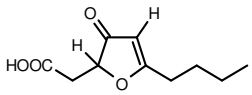
$CDCl_3$, 50 MHz



Erigeronic acid A (**1**)



CD_3OD, 200 MHz



Erigeronic acid A (**1**)

3D.6 References

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3E. Overall Conclusions and Perspectives

The present dissertation describes our studies on total synthesis of several naturally occuring bioactive γ-butyrolactone and γ-alkylidenebutenolide containing natural proucts and their derivatives along with a concise account on the chemistry of recently isolated bioactive γ-butyrolactone containing natural products, describing their isolation, bioactivity and various synthetic approaches.

We have completed the synthesis of γ-alkylidenebutenolides, maculalactones A-C and nostoclide I using highly chemo- and regioselective $S_N2´$ coupling reactions of appropriate Grignard reagents with dimethyl bromomethylfumarate as one of the key reaction. We have accomplished the synthesis of natural products norpandamarilactonines A-B using the reductive intramolecular aza-Michael type addition as the key reaction. These natural products were then further elaborated to natural products pandamarilactonines A-D and pandanamine via intermolecular coupling reaction with suitably substituted iodobutenolide unit in presence of a mild base. Using citraconic anhydride as the starting material, we have completed the first synthesis of leaf closing compound (±)-erythro potassium 2,3,4-trihydroxy-2-methylbutanoate in 6-steps with 29% overall yield. We have carried out lipase mediated resolution of (±)-saccharinic acid lactone and obtained the plant growth regulator (–)-saccharinic acid lactone with very good yield and enantiomeric excess. This (–)-saccharinic acid lactone was then converted to leaf closing compound potassium (2R,3R)-2,3,4-trihydroxy-2-methylbutanoate with quantitative yield. We have also completed an elegant 6-step first synthesis of cytotoxic ellipsoidone A and ellipsoidone B using itaconic anhydride as the starting material and lipase as key for double deacylation reaction with good overall yields. Finally, starting from (R)-acetoxysuccinic anhydride, an elegant first synthesis of natural germination inhibitor (+)-erigeronic acid has been completed using chiral pool strategy and an enzymatic hydrolysis pathway, which helped us to assign (R)-configuration to the C-2 chiral centre in natural (+)-erigeronic acid. We have also synthesized some analogs of this natural product via highly regioselective ring opening of (R/S)-acetoxysuccinic anhydride with appropriate primary enolate, followed by acid/base catalyzed alcoholysis and an in situ dehydrative cyclization pathway with good overall yields.

Our studies on γ-butyrolactone chemistry provided us a nice opportunity for learning lot of new chemistry not just from our work but also from the vast literature in this field,

practically all aspects in synthetic organic chemistry. These studies on γ-butyrolactone chemistry also have left us with an experience that these are the useful compounds from both synthetic and pharmaceutical point of view and several elegant methods have been developed to synthesize them. Still, it is challenging task to develop new methods to design these useful building blocks in high yields and enantiomeric purity. We feel that many more natural products with γ-butyrolactone moiety will be discovered in the coming years with new properties and chemistry of γ-butyrolactones will spread wings wider over the field of organic and pharmaceutical chemistry giving this field of chemistry a brighter future.

LIST OF PUBLICATIONS

1. Synthesis of potassium 2,3,4-trihydroxy-2-methylbutanoate: a leaf-closing substance of *Leucaena leucocephalam*

   Sanjib Gogoi and Narshinha P. Argade *Tetrahedron* **2004**, *60*, 9093.

2. Synthesis of naturally occurring bioactive butyrolactones: maculalactones A–C and nostoclide I

   Anirban Kar, **Sanjib Gogoi** and Narshinha P. Argade *Tetrahedron* **2005**, *61*, 5297.

3. A facile chemoenzymatic approach to natural cytotoxic ellipsoidone A and natural ellipsoidone B

   Sanjib Gogoi and Narshinha P. Argade *Tetrahedron* **2006**, *62*, 2715.

4. A facile two-step chemoenzymatic access to natural germination inhibitor (+)-erigeronic acid A

   Sanjib Gogoi and Narshinha P. Argade *Tetrahedron* **2006**, *62*, 2999.

5. An efficient Amano PS-catalyzed chemo-, regio- and enantioselective hydrolysis of (±)-2,3-di-*O*-acetyl-2-*C*-methyl-D-erythrono-1,4-lactone: a facile preparation of bioactive natural products (–)-saccharinic acid lactone and potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate

   Sanjib Gogoi and Narshinha P. Argade *Tetrahedron: Asymmetry* **2006**, *17*, 927.

6. Synthesis of norpandamarilactonines, pandamarilactonines and pandanamine

   Sanjib Gogoi and Narshinha P. Argade *Synthesis* **2008**, in press.

Erratum