STUDIES ON CHEMICAL AND CHEMOENZYMATIC TOTAL SYNTHESIS OF BIOACTIVE NATURAL PRODUCTS

THESIS

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By

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(Research Guide)

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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 Chemical and Chemoenzymatic Total Synthesis of Bioactive Natural Products***" which is being submitted to the ***Savitribai Phule Pune University*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Ramesh U. Batwal*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

December 2015
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Dr. N. P. Argade
(Research Guide)

Candidate's Declaration

I hereby declare that the research work incorporated in the thesis entitled "***Studies on Chemical and Chemoenzymatic Total Synthesis of Bioactive Natural Products***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***Savitribai Phule Pune University***, has been carried out by me at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India, from July 2009 to December 2015 under the supervision of Dr. Narshinha P. Argade. This work has not been submitted in part or full by me for a degree or diploma to this or any other University or Institution.

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

Ramesh

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General Remarks

1. All the solvents used were purified according to the literature procedures.
2. Petroleum ether used in the experiments was of 60-80 °C boiling range.
3. 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).
4. TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, phosphomolybdic acid (in ethanol), bromocresol green (in ethanol).
5. IR spectra were recorded on FTIR instrument, for solid either as nujol mull, neat or in chloroform solution (conc. 1 μM), in case of liquid compounds neat or in chloroform solution (conc. 1 μM).
6. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR, 500 MHz NMR and 700 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz), 500 NMR (125 MHz) and 700 MHz NMR (175 MHz) spectrometers.
7. Mass spectra were taken on MS-TOF mass spectrometer.
8. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer.
9. Microanalysis data were obtained using Flash EA 1112 series and Elementar Vario EL analyser.
10. All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
11. 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.
12. All the new experiments were repeated two or more times.
13. Starting materials were obtained from commercial sources or prepared using known procedures.
14. ***Independent referencing and numbering of compounds, schemes, tables & figures have been employed for Section A & B of both Chapter I and Chapter II***

Abbreviations

AIBN	2,2′-Azobisisobutyronitrile
Aq.	Aqueous
Ac	Acetyl
Bn	Benzyl
n-BuLi	*n*-Butyllithium
Bz	Benzoyl
Boc	*t*-Butoxycarbonyl
^{t}Bu	*tert*-Butyl
Cat.	Catalytic
Cbz	Carboxybenzyl
Conv.	Conversion
CSA	Camphorsulfonic acid
CNS	Central nervous system
DMAPP	Dimethylallyl pyrophosphate
dr	Diastereomeric ratio
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DIPE	Diisopropyl ether

EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EC	Enzyme Commission
ee	Enantiomeric excess
ESI	Electro spray ionisation
EI	Electron impact
equiv.	Equivalent(s)
h	Hour(s)
HRMS	High-resolution mass spectrometry
HMPA	Hexamethylphosphoramide
5-HT	5-hydroxytryptamine
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IDBA	Iodosobenzene diacetate
IPP	Isopentenyl pyrophosphate
IC	Inhibitory concentration
IR	Infra Red
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
m-CPBA	*m*-Chloroperbenzoic acid
min.	Minute(s)
mg	Milligram
ml	Millilitre(s)
MHz	Megahertz
mmol	Millimole(s)
μM	Micromole(s)
Mp	Melting point

MOM	Methoxymethyl
MeCN	Acetonitrile
MS	Mass spectrum
MsCl	Methanesulfonyl chloride
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
PPA	Polyphosphoric acid
Ph	Phenyl
PMB	*p*-Methoxybenzyl
p-TSA	*p*-Toluenesulfonic acid
p-TsCl	*p*-Toluenesulfonyl chloride
rt	Room temperature
rac	Racemic
TBAF	Tetrabutylammonium fluoride
TBDPSCl	*tert*-Butyl(chloro)diphenylsilane
TEOP	Triethylorthopropionate
TBME	*tert*-Butyl methyl ether
TBDMS / TBS	*t*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TPP	Triphenylphosphine
TEA	Triethylamine
TFAA	Trifluoroacetic anhydride
TTN	Thallium trinitrate

THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMSCl	Trimethylchlorosilane
VA	Vinyl acetate

Lipase Abbreviations

Amano PS	Commercially available preparation of lipase from *Burkholderia cepacia*
Amano PS-D	Lipase from *Pseudomonas cepacia* immobilized on diatomite
CAL	Lipase from *Candida antarctica*
CAL-A	Lipase from *Candida antartica* (A)
CAL-B	Lipase from *Candida antartica* (B)
CCL	Lipase from *Candida cylindracea*
CRL	Lipase from *Candida rugosa*
Lipase AK	Commercially available preparation of lipase from *Pseudomonas fluorescens*
Lipase PS-C	Lipase from *Pseudomonas cepacia* immobilized on ceramic particles
Lipozyme	Lipase from *Mucor miehei*
LPL	Lipoprotein lipase
Novozym 435	Lipase from *Candida antarctica*
PCL	Lipase from *Pseudomonas cepacia*
PLE	Pig liver esterase
PPL	Porcine pancreatic lipase
PFL	*Pseudomonas fluoresence* lipase
TLL	*Thermomyces lanuginosa* lipase

Abstract

The present dissertation is divided into two chapters. The section A of first chapter presents a brief introduction on enzymes. Section B of first chapter describes isolation, activity and reported synthesis of (±)/(–)-1,3,4,5-tetragalloylapiitol and putrescine bisamides. This section also describes our contribution towards the enzymatic resolution and total synthesis of bioactive natural products (+)-1,3,4,5-tetragalloylapiitol (antipode), putrescine bisamides, artabotriolcaffeate starting form cyclic anhydride and their derivatives.

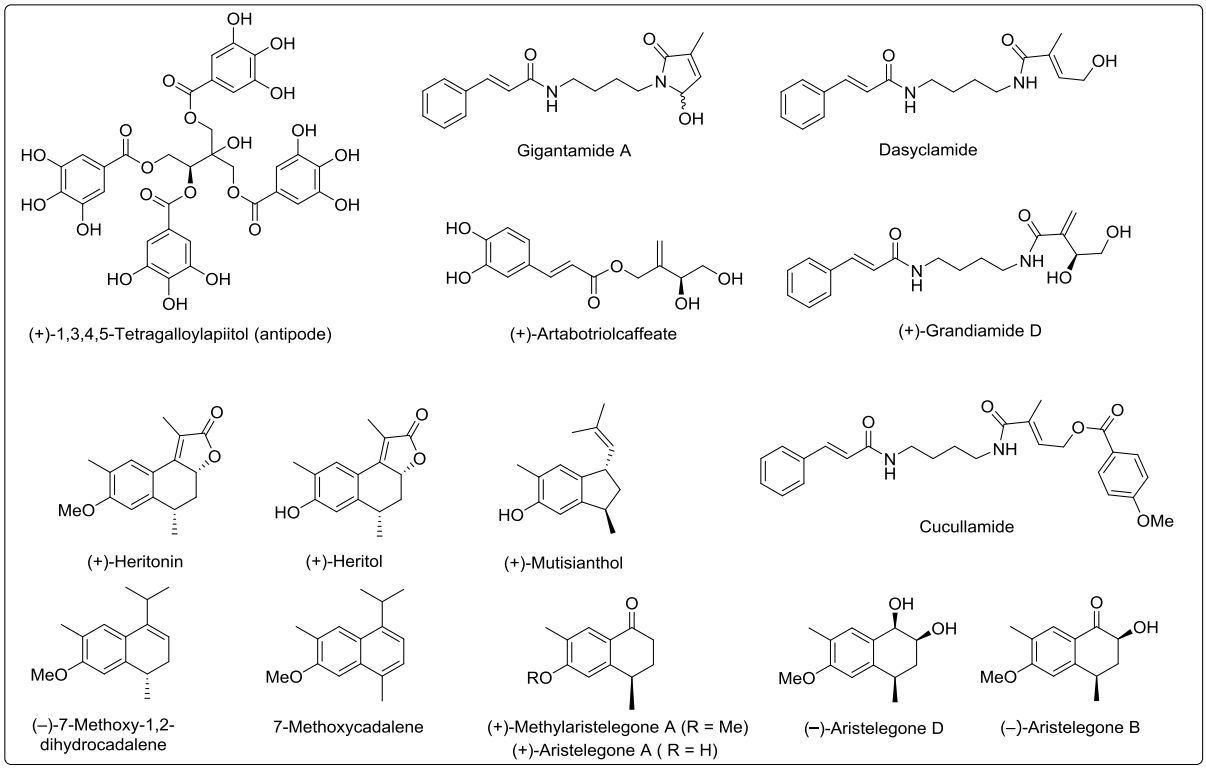


Figure 1. Natural products synthesized from cyclic anhydrides and their derivatives.

In second chapter, a concise account on the chemistry of methoxy(methyl)tetralone based natural products is presented in section A. Section B contains isolation, activity, reported synthesis and our chemoenzymatic synthesis of (–)-aristelegone B, (+)-methylaristelegone A, (+)-aristelegone A, (–)-aristelegone D, (+)-mutisianthol, (+)-heritonin, (–)-7-methoxy-1,2-dihydrocadalene, (–)-7-methoxycalamenene, 7-methoxycadalene and studies towards the total synthesis of (±)-vallapin.

Note: An independent figure, scheme & structure numbers have been used for both chapters.

Chapter One: Chemical and Chemoenzymatic Synthesis of Bioactive Natural Products

This chapter is divided into two sections. Section A presents brief introduction on enzymes in general and a concise account of the applications of lipases in resolution of racemic alcohols. The section B describes our contribution towards the synthesis of (+)-1,3,4,5-tetragalloylapiitol, putrescine bisamides, (+)-artabotriolcaffeate.

Section A: A Brief Introduction on Enzymes

In recent years, enzymes have emerged as powerful tools in organic synthesis for 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 provides a brief introduction on enzymes in general and a concise account of the applications of lipases in resolution of racemic alcohols.

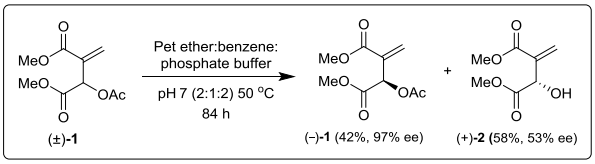
Section B: Total Synthesis of (+)-1,3,4,5-Tetragalloylapiitol, Putrescine Bisamides, Artabotriolcaffeate

This section describes isolation, activity, reported synthesis and our studies towards the synthesis of (+)-1,3,4,5-tetragalloylapiitol, putrescine bisamides gigantamide A, dasyclamide cucullamide, (+)-grandiamide D, (+)-artabotriolcaffeate and related natural products.

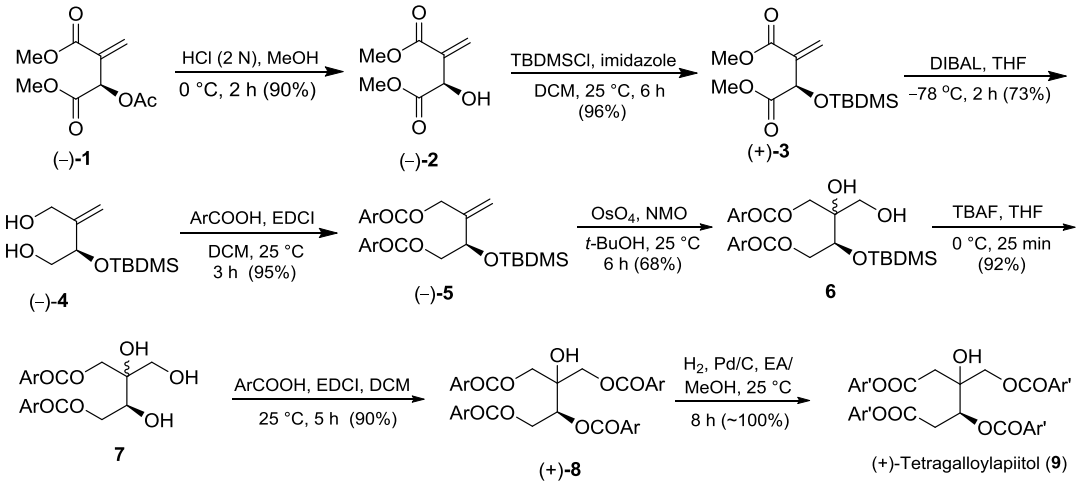
Section B.1 Chemoenzymatic Total Synthesis of (+)-1,3,4,5-Tetragalloylapiitol

Gustafson et al. isolated a new potent HIV RNase H inhibitor (–)-1,3,4,5-tetragalloylapiitol from an extract of the plant *Hylodendron gabunensis*. Two racemic and one stereoselective total synthesis of (–)-1,3,4,5-tetragalloylapiitol have been reported in the literature. A concise schematic summary of all syntheses is presented. In continuance of our studies on both cyclic anhydrides and derivatives to bioactive natural and unnatural products and efficient enzymatic resolutions we intended for the chemoenzymatic approach to our target compound.

Starting from racemic starting material (±)-dimethyl-2-acetoxy-3-methylenesuccinate (**1**), chemoenzymatic facile total synthesis of (+)-1,3,4,5-tetragalloylapiitol (**9**) has been demonstrated via an efficient lipase catalyzed resolution followed by the chemoselective DIBAL reductions-double gallyolation, osmium tetroxide dihydroxylation-double gallyolation and reductive global *O*-benzyl deprotection pathway (Schemes 1 and 2).



Scheme 1. Lipase Catalyzed Resolution of (±)-Dimethyl-2-Acetoxy-3-Methylenesuccinate

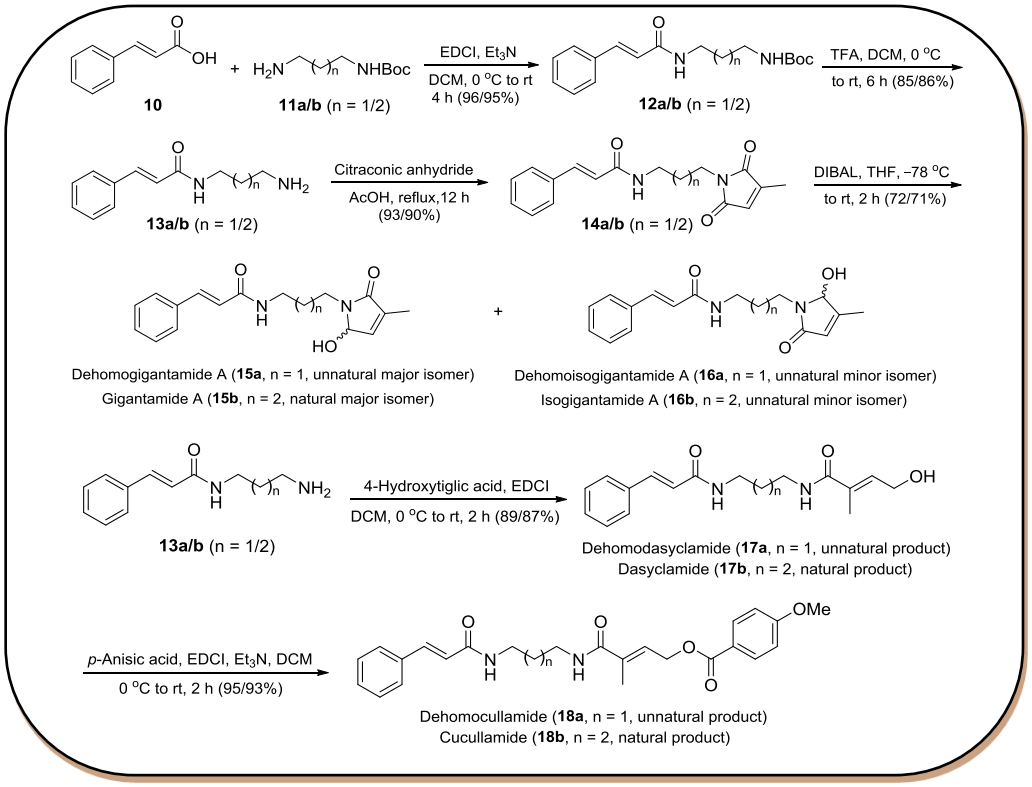


Ar = 3,4,5-Tribenzyloxyphenyl; Ar' = 3,4,5-Trihydroxyphenyl (**6**/**7** diastereomeric mixture with ~3:2 ratio)

Scheme 2. Total Synthesis of (+)-1,3,4,5-Tetragalloylapiitol from (*R*)-Dimethyl-2-Acetoxy-3-Methylenesuccinate

Section B.2 Synthesis of Putrescine Bisamides Gigantamide A, Dasyclamide and Cucullamide

The putrescine based natural products (±)-gigantamide A, dasyclamide and (+)-grandiamide D have been isolated from *Aglaia gigantea* and very recently the dasyclamide and cucullamide have been isolated from *Amoora cucullata*. Starting from putrescine and the

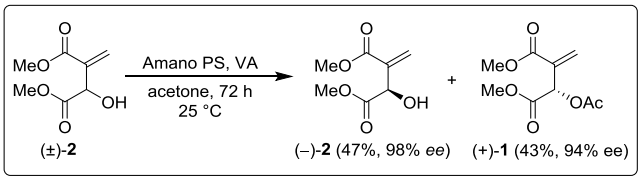


Scheme 3. Total Synthesis of Gigantamide A, Dasyclamide, Cucullamide and their Unnatural Dehomo-analogues

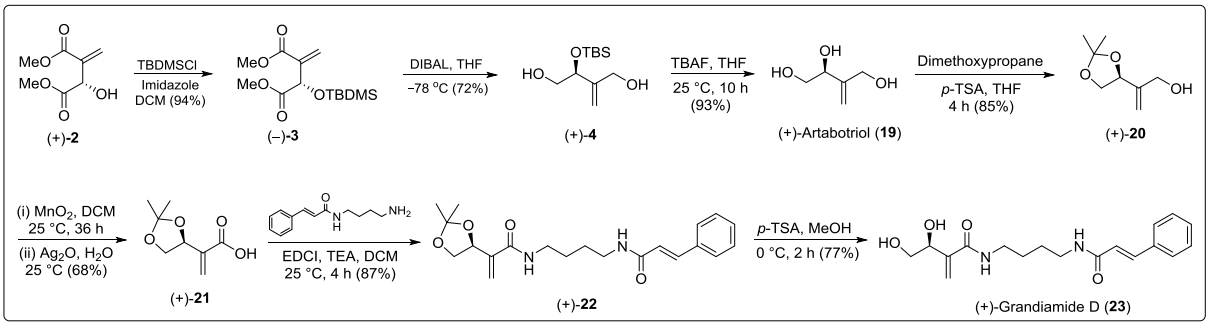
requisite carboxylic acids first synthesis of bioactive natural products gigantamide A (**15b**), dasyclamide (**17b**) and cucullamide (**18b**) have been accomplished in very good overall yields using an appropriate sequence of dehydrative coupling reactions (Scheme 3). Synthesis of corresponding dehomo-analogues of natural products has also been described. Regioselective DIBAL-reduction of an unhindered carbonyl group in citraconimide was the key step.

Section B.3 Chemoenzymatic Total Synthesis of (+)-Grandiamide D, (+)-**Artabotriolcaffeate and Related Natural Products**

Recently, the (+)-artabotriol derived natural product (+)-grandiamide D has been isolated from *Aglaia gigantean*; (–)-tulipalin B and (+)-spirathundiol have been isolated from *Tulipa gesneriana* and *Spiraea thunbergii* Sieb. respectively; whereas the (+)-artabotriolcaffeate, (–)-pubescenoside A (anti-platelet aggregation) and (–)-pubescenoside B (anti-platelet aggregation) have been isolated from *Ilex pubescens*. The absolute configuration of (+)-artabotriolcaffeate (**27**) has been established by using modified Mosher's method. The stereochemical assignment of artabotriolcaffeate part of (–)-pubescenoside A and B has not been fixed yet. Synthesis of (+)-grandiamide D (**23**) from racemic (±)-dimethyl-2-hydroxy-3-methylenesuccinate (**2**) has been accomplished in very good overall yields via an efficient lipase catalyzed resolution followed by the chemoselective DIBAL reductions, silyl deprotection, acetonoide protection of diol-oxidation, EDCI coupling followed by deprotection (Schemes 4 and 5).

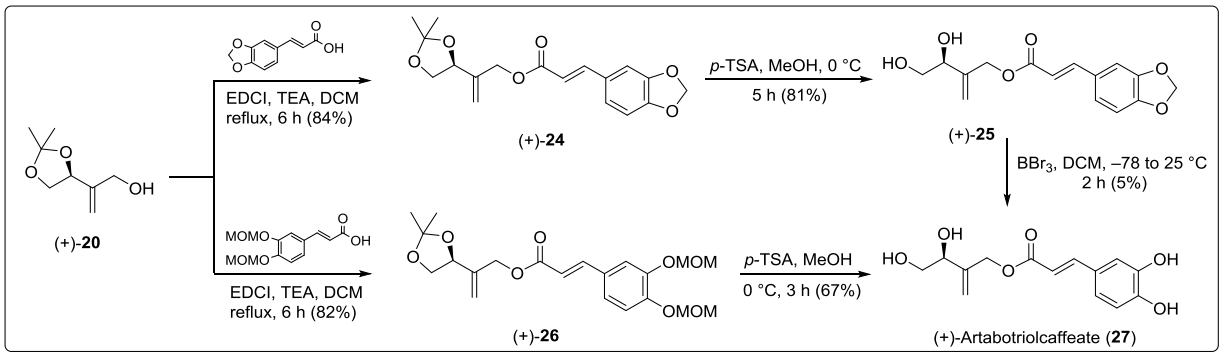


Scheme 4. Lipase Catalyzed Resolution of (±)-Dimethyl-2-Hydroxy-3-Methylenesuccinate



Scheme 5. Total Synthesis of (+)-Grandiamide (*S*)-Dimethyl-2-Hydroxy-3-Methylenesuccinate

Starting from racemic (±)-dimethyl-2-hydroxy-3-methylenesuccinate (**2**), chemoenzymatic facile total synthesis of (±)-artabotriolcaffeate (**27**) has also been demonstrated via an efficient lipase catalyzed resolution followed by the chemoselective DIBAL reductions, silyl deprotection, acetonoide protection of diol and EDCI induced coupling with an appropriately protected caffeic acid followed by deprotection (Scheme 6).



Scheme 6. Total Synthesis of (+)-Artabotriolcaffeate

Chapter 2: Chemoenzymatic Collective Synthesis of Bioactive Natural Products

This chapter is divided into two sections. Section A presents concise account on the chemistry methoxy(methyl)tetralone based natural products. The section B describes collective synthesis of optically active hydroxyl(methyl)tetrahydronaphthalene-based bioactive terpenoids.

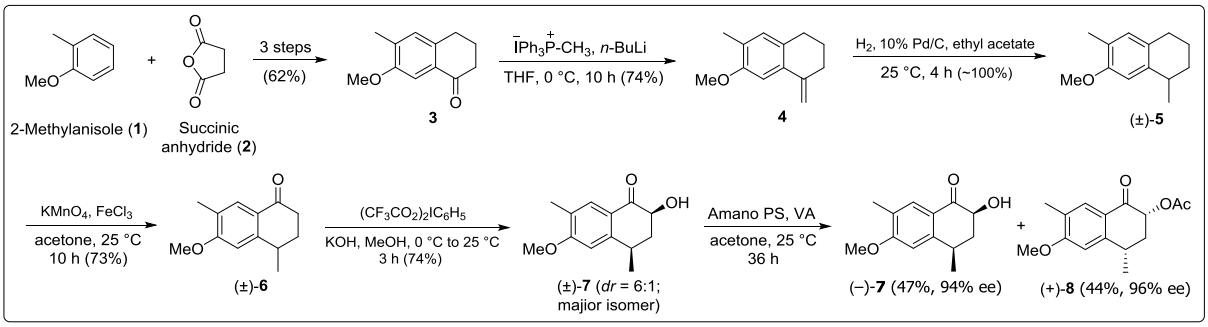
Section A: A Concise Account on the Chemistry of Methoxy(methyl)tetralone Based Natural Products

This section presents a short overview on the chemistry of the recently isolated important bioactive methoxy(methyl)tetralone based natural products.

Section B: Chemoenzymatic Collective Synthesis of Optically Active Hydroxyl(methyl) tetrahydronaphthalene-based Bioactive Terpenoids

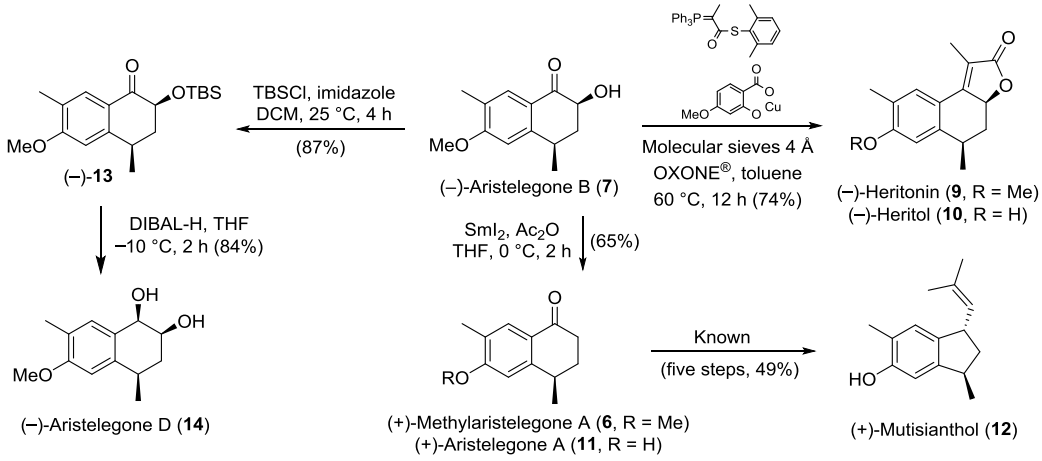
The (+)-aristelegone A, (–)-aristelegone B and (–)-aristelegone D have been isolated from *Aristolochia elegans*; while (+)-methylaristelegone A (antispasmodic) has been isolated from *Aristolochia constricta*. The (+)-heritonin (toxic to fish), (+)-heritol (toxic to fish) and (–)-vallapin (pesticide) have been isolated from *Heritiera littoralis* and (+)-mutisianthol (antitumor) has been isolated from *Mutisia homoeantha*. The (–)-7-methoxy-1,2-dihydrocadalene and (–)-7-methoxycalamenene have been isolated from *Heteroscyphus planus* culture. Several elegant product specific racemic as well as enantioselective total

synthesis of above specified natural products have been reported; except for the aristelegone D, 7-methoxy-1,2-dihydrocadalene and vallapin. Starting form 2-methylanisole (**1**) and succinic anhydride (**2**) the key intermediate (±)-**7** was synthesized in 7-steps with very good overall yield. The stereoselective introduction of hydroxyl group to form the hydroxyketone



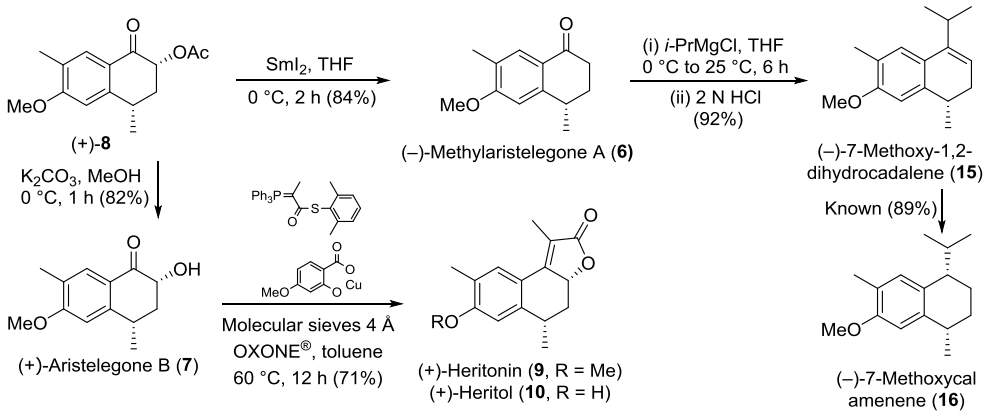
Scheme 1. Chemoenzymatic Total Synthesis of (–)-Aristelegone B

(±)-**7** was the key step. Synthesis of all those enantiomerically pure natural products have been achieved in very good overall yield via remarkable lipase catalyzed resolution of (±)-aristelegone B (**7**) (Scheme 1). The appropriately designed enantiomerically pure products (–)-**7** and (+)-**8** were then systematically used to accomplish the total synthesis of several novel natural products using selective chemical transformations (Schemes 2 to 3). The intramolecular Wittig reaction to form the enantiomerically pure (–)-heritonin (**9**) and the SmI_2 induced deoxygenation reaction were involved important steps. Our present studies describe noteworthy chemoenzymatic total synthesis of (**–**)-heritonin (**9**) and formal synthesis of (+)-mutisianthol (**12**). We have accomplished a total synthesis of (**–**)-aristelegone B (**7**),



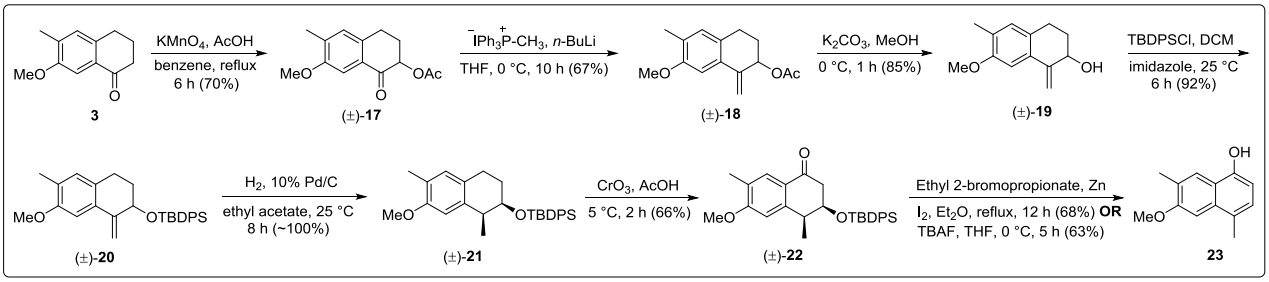
Scheme 2. Chemoenzymatic Total Synthesis of (–)-Heritonin, (–)-Aristelegone D, (+)-Aristelegone A

(+)-methylaristelegone A (**6**), (+)-aristelegone A (**11**), (–)-heritonin (**9**), (+)-heritonin (**9**), (**–**)-aristelegone D (**14**), (**–**)-7-methoxy-1,2-dihydrocadalene (**15**), 7-methoxycadalene and formal synthesis of (**–**)-heritol (**10**), (+)-mutisianthol (**12**) and (**–**)-7-methoxycalamenene (**16**) through this approach.

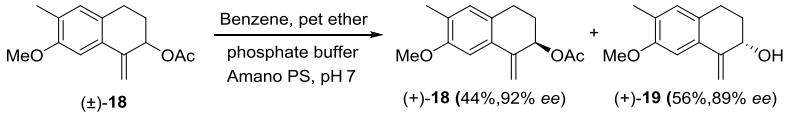


Scheme 3. Synthesis of (–)-7-Methoxy-1,2-dihydrocadalene and (+)-Heritonin

We initially prepared the product (±)-7-methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl acetate (**18**) and systematically performed the enzymatic resolution



Scheme 4. Attempted Diastereoselective Synthesis of (±)-Vallapin



Scheme 5. Amano PS Catalyzed Resolution of (±)-7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl Acetate

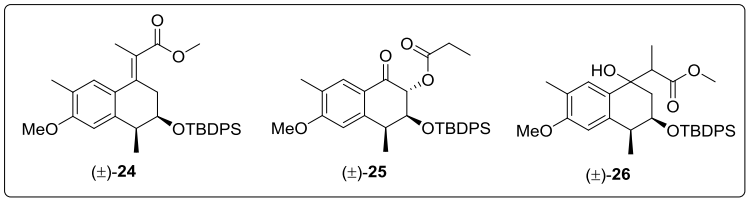


Figure 1. Expected products from tetralone (±)-**22**.

to obtain enantiomerically pure products (+)-**18** and (+)-**19**. We tentatively did the stereochemical assignment of (+)-**18** and (+)-**19** on the basis of known Amano PS selectivity. Anticipating the propensity of these tetrasubstituted systems to aromatise, we decided to first complete the racemic synthesis of our target compound. Hence starting from tetralone **3** we synthesized the advanced intermediate tetralone (±)-**22** in 8 steps with very good overall yield; via stereoselective reduction followed by selective benzylic oxidation pathway. We studied the Wittig reaction with tetralone (±)-**22** to obtain the product (±)-**24** and selective introduction of oxygen function to obtain (±)-**25**, but unfortunately both were not successful. An attempted Reformatsky reaction on carbonyl group of tetralone (±)-**22** met with failure and instead delivered the corresponding aromatized product **23** in 68% yield. An attempted desilylation also resulted into the formation of same aromatized product **23** with 63% yield (Schemes 4, 5 and Figure 1). We feel that much more soft reaction conditions will be required to transform tetralone (±)-**22** into the desired target compound (±)-Vallapin.

In summary present dissertation describes concise and efficient chemoenzymatic total/formal synthesis of natural products of (+)-1,3,4,5-tetragalloylapiitol (antipode), gigantamide A, dasyclamide, cucullamide, (+)-grandiamide D, (–)-tulipalin B, (+)-spirathundiol, (+)-artabotriolcaffeate, (–)-aristelegone B, (+)-methylaristelegone A, (+)-aristelegone A, (–)-aristelegone D, (–)-heritonin (antipode), (–)-heritol (antipode), (+)-mutisianthol, (+)-heritonin, (–)-7-methoxy-1,2-dihydrocadalene, 7-methoxycadalene, (–)-7-methoxycalamenene. An efficient enzymatic resolution also provides an access to the corresponding antipodes.

Chapter 1

Chemical and Chemoenzymatic Synthesis of Bioactive Natural Products

This chapter features the following sections:

Independent referencing and numbering of compounds, schemes, tables & figures have been employed for Section A & B of Chapter 1

1A. Section A

A Brief Introduction on Enzymes

This section features the following topics:

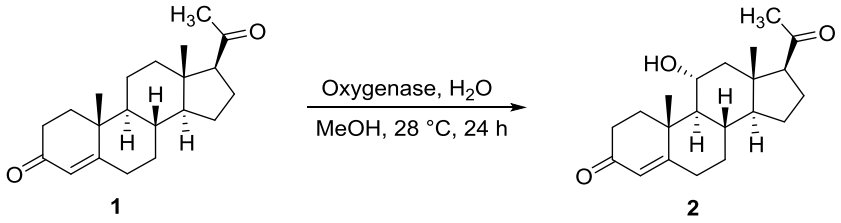
1A: A Brief Introduction on Enzymes

1A.1 Biotransformations

In 1876, German physiologist Wilhelm Kühne first used the term enzyme, which comes from Greek ἔνζυμον, "leavened" and experimentation on enzymes began in 1897. The existence of enzymes has been known for well over a century. Some of the earliest studies were performed in 1835 by the Swedish chemist Jon Jakob Berzelius who termed chemical action of enzymes as catalytic. In 1926, the first enzyme was obtained in pure form, a feat accomplished by James B. Sumner of Cornell University. Sumner was able to isolate and crystallize the enzyme urease from the jack bean.[1] His work was rewarded with 1946 Nobel Prize. He shared Nobel Prize with John H. Northrop and Wendell M. Stanley of the Rockefeller Institute for Medical Research for a complex procedure for isolating pepsin. The precipitation technique devised by them has been used to crystallize several enzymes.

An enzyme is born through repeated "trial & error" in Nature over an enormous length of time. 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. In biotransformations, enzymes are employed to consequent chemical changes on compounds that are not their natural substrates. This distinguishes biotransformation from biosynthesis, which involves action of biological systems in their normal habitat upon their natural substrates. In some biotransformations the synthetic substrate may resemble the natural substrates, while in some others it may be completely unrelated to the natural system. Whilst both may be used for synthetic purposes, the former can focus some light on structural and mechanistic features of biosynthesis. This type of study could be useful for the synthetic chemist in planning retrosynthetic approaches. In biotransformations, isolated enzyme systems or intact whole organisms may also be used. Many biotransformations are not only chemo- and regioselective but are also enantioselective allowing the production of chiral materials from racemic mixtures. The conditions for biotransformations are mild and in majority of cases do not require the protection of other functional groups. Furthermore the features governing their regioselectivity differ from those controlling the chemical specificity and indeed it is possible to obtain biotransformations at centres that are chemically non-reactive (e.g. in Scheme 1, compound **1** is transformed to **2** by hydroxylation at the chemically unreactive C-11 site by oxygenase enzyme).[2] From a commercial point of view some biotransformations can be cheaper and more direct than their

chemical analogues, whilst the transformations proceed under the conditions that are normally regarded as "environmentally friendly". There are many chemical reactions for which there are no equivalent biotransformation steps and the chemist should be versatile to use biotrans-



Scheme 1. Biotransformation Using Oxygenase

formations in combination with the conventional chemical reagents in a synthesis. The biocatalysis has emerged as such an important tool in organic synthesis considering the advantages of using enzymes such as easy availability, mild and simple reaction conditions, good economy, low environmental impact and recyclability. A number of comprehensive reviews[3-8] in the literature reiterate the importance of biotransformations. These reviews provide an elegant overview on diverse aspects of biotransformations in organic synthesis.

1A.2 Specificity of Enzymes

All known enzymes consists of proteins that are built up from 20 different amino acids. The activity of enzymes varies according to their three-dimensional architectures constituted of the L-amino acid sequence. Enzyme possesses active site, the region of an enzyme where substrate molecules bind and undergo a chemical reaction. Specificity of enzymes systematically explained by the three-point attachment rule.[9] In order for a substrate molecule to be held firmly in three-dimensional 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 and the groups are correctly aligned to fit into the active site pockets, while the opposite isomer turns out to be a misfit and does not react. A few enzymes exhibit absolute specificity and they catalyze only one particular reaction. Other enzymes will be specific for a particular type of chemical bond or functional group. In general, there are four distinct types of specificity:

1. Absolute specificity: The enzyme will catalyze only one reaction.

2. Group specificity: The enzyme will act only on molecules that have specific functional groups, such as amino, phosphate and methyl groups.

3. Linkage specificity: The enzyme will act on a particular type of chemical bond regardless of the rest of the molecular structure.

4. Stereochemical specificity: The enzyme will act on a particular optical isomer.

Though enzymes exhibit great degrees of specificity, cofactors may serve many apoenzymes. For example, nicotinamide adenine dinucleotide (NAD) is a coenzyme for a great number of dehydrogenase reactions in which it acts as a hydrogen acceptor. Among them are the alcohol dehydrogenase, malate dehydrogenase and lactate dehydrogenase reactions.

1A.3 Classification of Enzymes

Enzymes are classified by rules prescribed by the commission on Enzymes 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.

1A.4 Lipases: Introduction

1A.4.1 Occurrence and Role

Hydrolases form the most important class of enzymes[10,11] and among them, lipases have been the most popular and widely used. Lipases are ubiquitous enzymes that are found in bacteria/fungi,[12-15] plants[16-19] and animals.[20-22] They are triglycerol ester hydrolases defined in class EC 3.1.1.3 by enzyme nomenclature. Usually lipases are just one member of a "hydrolytic enzyme cocktail" elaborated by an organism with the objective to sustain its growth. 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).[8d,23] 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.

1A.4.2 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.[24,25] 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.[26] The molecular machinery of lipases is much like that of the serine protease's. The active site is generally characterized by the triad composed of the amino acids serine, 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.[27] The structural shape of the protein creates hydrophilic or lipophilic pockets within the enzyme active site, which leads to chemo-, regio- and enantio/diastereoselectivity.

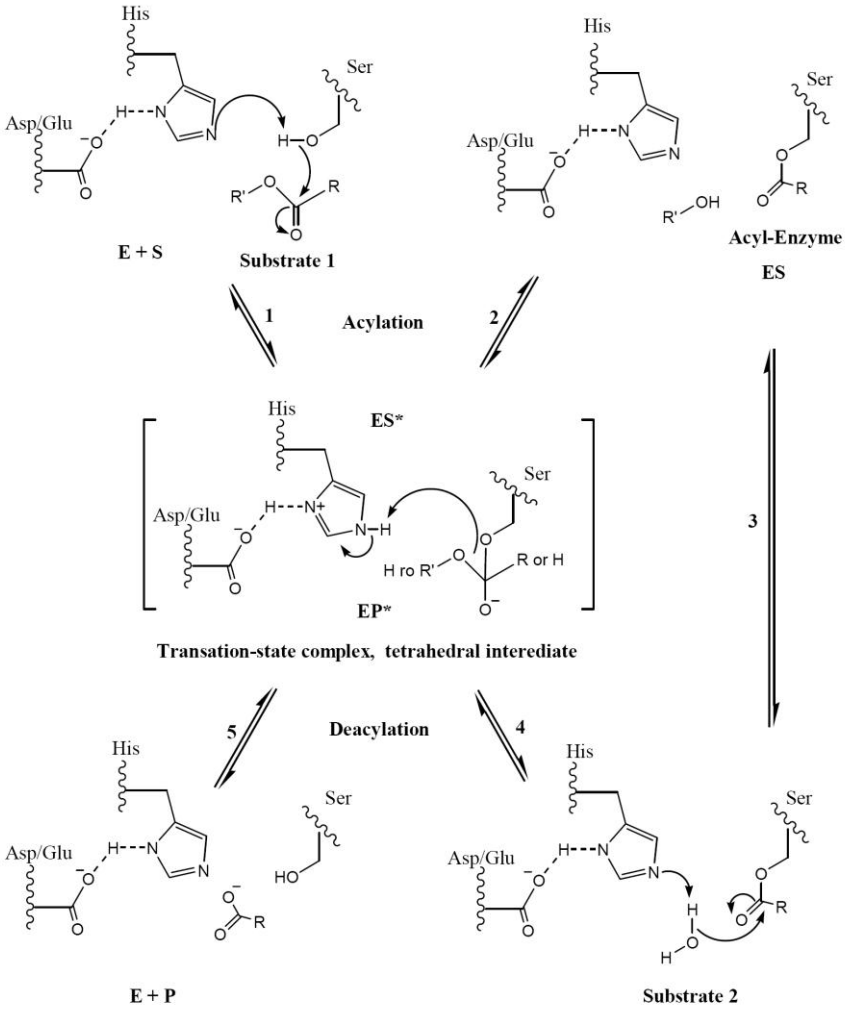


Figure 1. Catalytic mechanism of lipase action through procedures 1-5, where E is the enzyme, ES* & EP* are the substrate-enzyme and product-enzyme complexes respectively.

(*Structure numbers in the above figure are from the original reference*[27] *and do not correlate to the structure numbers in the present section*).

1A.4.3 Semiquantitative Predictions for Lipase Selectivity

Following a thorough survey of the literature on chiral resolutions with lipases from *Candida rugosa* (CRL) and *Pseudomonas cepacia* (PCL), Kazlauskas et al. put forward tentative rules for the enantiopreference of these two enzymes based on the spatial requirements of the substituents on the reagent. These rules are often dubbed "Kazlauskas rules".[28] Results have shown that the rules are highly predictive for lipase action on secondary alcohols, but less accurate for lipase-catalyzed transformations of primary alcohols and acids.

1A.5 Lipases as Biocatalysts in Organic Synthesis

1A.5.1 Foreword

The application fields of lipases are not only those in lipid-modification. Lipases are also very powerful tools for organic synthesis, where non-lipid substrates are reacted. One such application is kinetic resolution and asymmetric synthesis in which stereospecificity of lipases are employed. 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. Lipases also show chemo-, regio-, and stereoselectivity. Their high stability in organic solvents and at elevated temperatures,[8d,29,30] the reversibility of their mode of action,[8d,31] their non-toxic and environment friendly nature[6c] and finally their low cost are responsible for their huge number of applications in practice.

It must be mentioned here that the use of organic solvents for lipase-catalyzed reactions[30,32,33] has added a whole new perspective. In neat organic solvents enzymes retain the minimum amount of water which is necessary for their catalytic activity. Use of organic solvents increases substrate solubility, wider range of substrates can be implied, transformations of water-sensitive substrates become feasible. Moreover, the use of organic solvents is seen to enhance the enantioselectivity[34,35] and thermostability[34,36] of the enzymes, probably due to restricted conformational flexibility. Despite the advantages, enzymes nearly universally display low catalytic activities in non-aqueous conditions[37] 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 media and enzymes have a "pH memory": their catalytic activity reflects the pH of the last aqueous solution to which they were exposed.[30] 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 up to three to four orders of magnitude.[37,38] Hydrolysis of esters is generally carried out in a biphasic system of an aqueous buffer and an organic solvent while esterification is generally carried out in an organic solvent with an irreversible acyl donor[31] such as the enol ester vinyl acetate. The enzyme is conveniently removed by filtration during work-up.

It is not the intention of this review to comprehensively summarize all lipase-catalyzed transformations in the recent past. An excellent reviews on biocatalysis have appeared in recent years many of which have been exclusive lipase reports.[4b,8,39] The reviews by S. M. Roberts,[6d,6e,6f,6g] especially provide wonderful detailed descriptions. All the above literature would tell us, lipases can be used for a plethora of reactions, simple acylation and deacylation, synthesis of amides and peptides, regioselective reactions on polyfunctional compounds. To encompass everything is beyond the scope of this section, instead only alcohol substrates have been taken up since those are the substrates that have been extensively studied for lipase catalysis. Within this realm, interesting examples that have had significant impact over the last few years have been chosen and illustrated. Some of the useful transformations have been presented in a tabular form providing an appropriate reference alongside. The section also describes desymmetrization of prochiral & *meso*-substrates and dynamic kinetic resolution, wherein the chemical yield of the resolution can be remarkably improved.

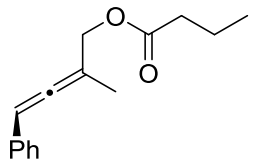
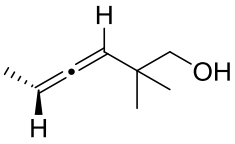
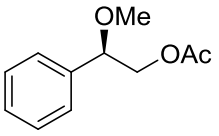
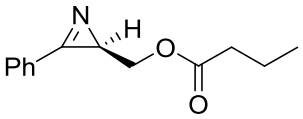
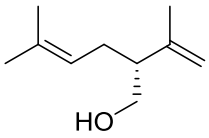
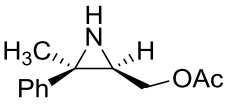
1A.5.2 Recent Applications of Lipase Catalysis in the Resolution of Alcohols

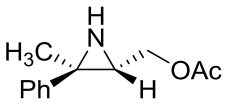
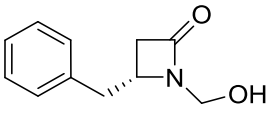
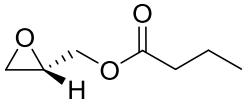
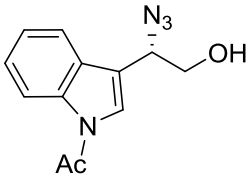
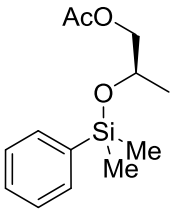
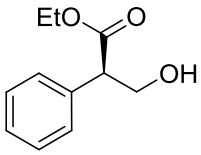
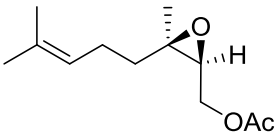
Alcohols are most extensively studied substrates for resolution by lipases. Lipases show extremely good selectivity when acting upon alcohols as well as the vast and diverse utilities of chiral alcohol substrates are known in research and industry. Some elegant reports of lipase-catalyzed hydrolysis as well as transesterification of 1°, 2° & 3° alcohols will be discussed in this section. 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" in parenthesis. Tables contain examples of both lipase-catalyzed hydrolysis as well as transesterification reactions.

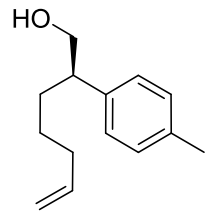
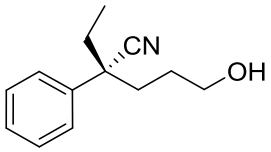
1A.5.2.1 Primary alcohols

Enantiomerically pure 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 stereoselectivities of lipases towards 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. Illustrations of a handful of other appealing reports are presented subsequently.

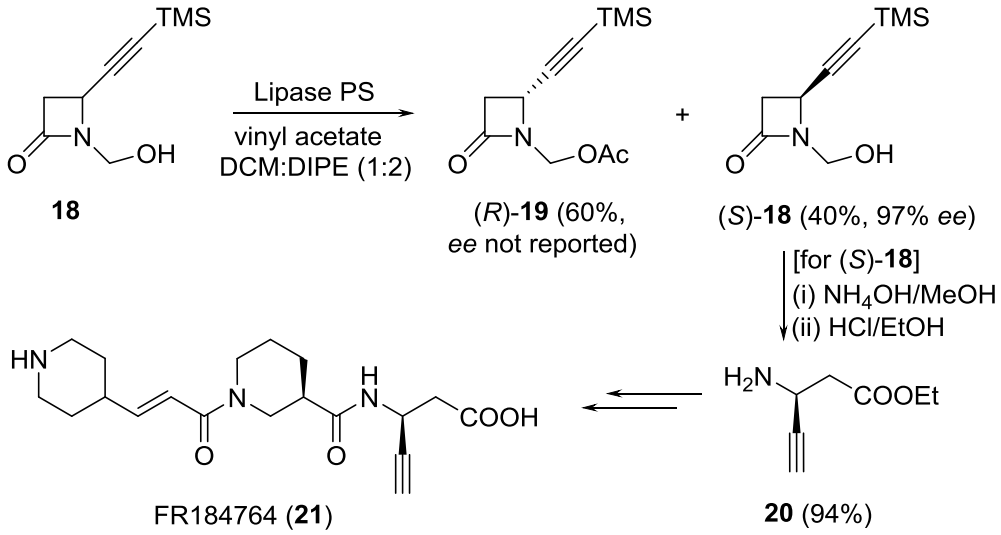
Table 1. Selected Examples Illustrating the Lipase-catalyzed Resolution of Primary Alcohols

Product	Lipase	% Yield	% Ee	Reference
 **3**	PPL	42	98	[40]
 **4**	CRL	36	99	[41]
 **5**	CAL-B	21	91	[42]
 **6**	PCL (on Toyonite)	35	97	[43]
 **7** (unreacted isomer)	*Hog pancreas*	55	95	[44]
 **8**	Lipase PS-C II	46	92	[45]

 **9**	Lipase PS-C II	30	96	[45]
 **10** (unreacted isomer)	Lipase PS	55	98	[46]
 **11** (unreacted isomer)	CAL-B	64	90	[47]
 **12**	Lipase PS	42	83	[48]
 **13**	Lipase PS-D	51	99	[49]
 **14**	Lipase PS	46	94	[50]
 **15**	Lipase PS	16	~99	[51]

 **16**	Lipase PS	40	>99	[52]
 **17** (unreacted isomer)	PCL	66	99	[53]

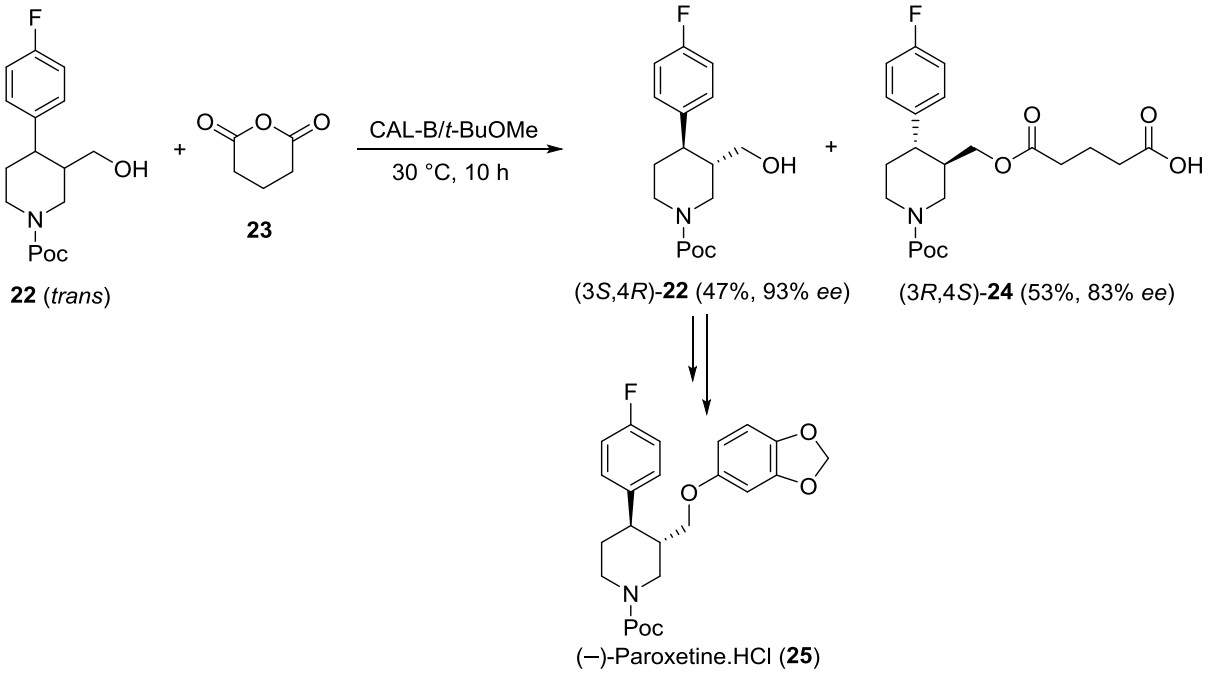
Apart from the above displayed examples there are some other interesting reports, where in the primary alcohols resolved have served as intermediates for the preparation of important active pharmaceutical ingredients and natural products.



Scheme 2. Synthesis of the Orally Active GpIIb/IIIa Antagonist FR184764

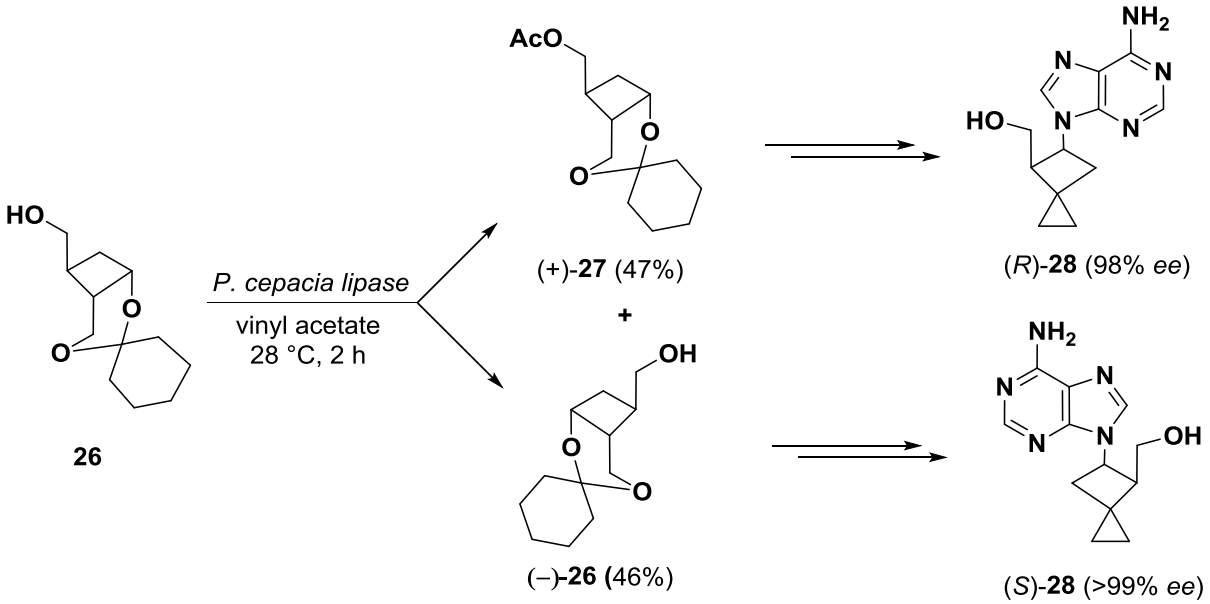
Yamanaka et al. achieved synthesis of the orally active GpIIb/IIIa antagonist FR184764 (**21**) from the key intermediate (*S*)-*β*-lactam **18,** which was prepared utilizing a lipase catalyzed resolution (Scheme 2).[54]

Gonzalo et al. achieved a chemoenzymatic synthesis of the potent and selective inhibitor of 5-hydroxytryptamine reuptake (–)-paroxetine, wherein the key intermediate, an optically active (3*S*,4*R*)-**22** was prepared utilizing a lipase catalyzed resolution (Scheme 3).[55]



Scheme 3. Chemoenzymatic Synthesis of the Potent and Selective Inhibitor of 5-Hydroxytryptamine Reuptake (−)-Paroxetine

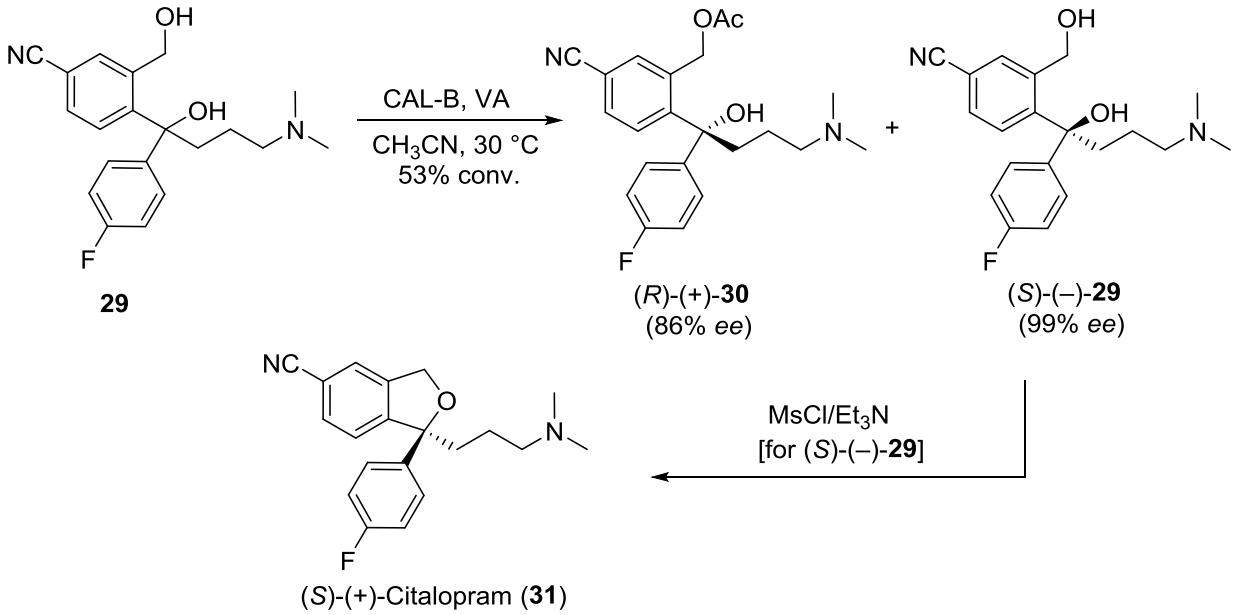
Nucleosides consisting of four-membered ring system have been studied continuously in the recent past to explore their chemistry and their antiviral activity. Chu et al. carried out lipase



Scheme 4. Synthesis of Novel Spiro[2.3]hexane Carbocyclic Nucleosides, *R*- & *S*-9-(6-Hydroxymethylspiro[2.3]hexane)-4-adenine

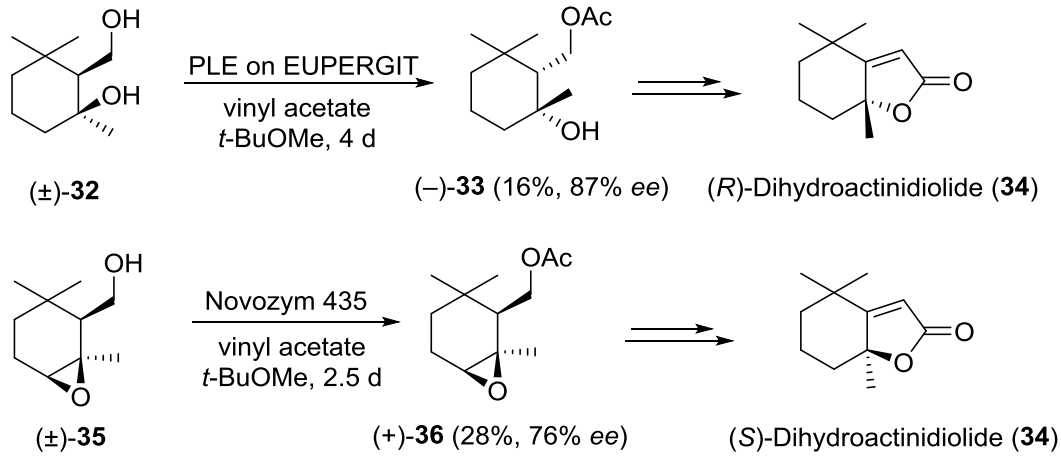
catalyzed resolution of racemic compound **26**, synthesized in 7-steps starting from diethoxyketene and diethyl fumarate to give the acetate (+)-**27** and the alcohol (–)-**26** (Scheme 4). The enantiomerically enriched compounds were separately transformed to novel spiro[2.3]hexane carbocyclic nucleosides, *R*- & *S*-9-(6-hydroxymethylspiro[2.3]hexane)-4-adenine, [(*R*)-**28** & (*S*)-**28**], possessing 98% & >99% *ee* respectively.[56] Both the compounds exhibited moderate antiviral activity.

(*S*)-(+)-Citalopram (**31**) is a very selective inhibitor of serotonin (5-HT) reuptake that has proved to be an efficient antidepressant. Solares et al. studied the enzymatic resolution of hydroxymethylbenzonitrile **29** having a quaternary stereo centre, a useful intermediate in the synthesis of enantiomerically pure citalopram. They reported that *Candida antartica* lipase B (CAL-B) catalyzes the enzymatic acetylation of the primary benzylic alcohol with high enantioselectivity at the quaternary stereogenic centre placed four bonds away from the reaction site (Scheme 5).[57]



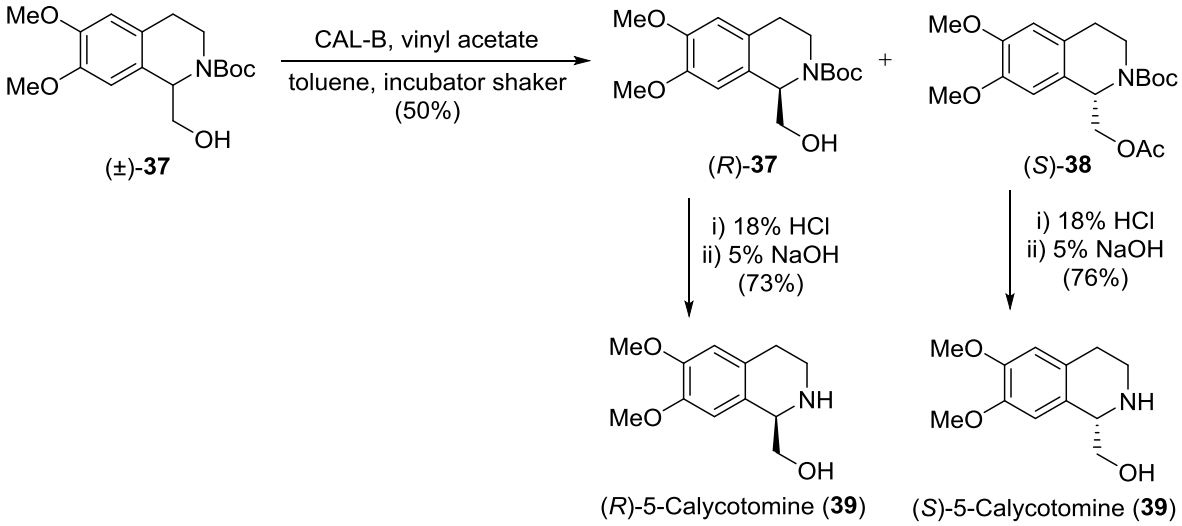
Scheme 5. Chemoenzymatic Synthesis of (+)-Citalopram

Serra & co-workers achieved a chemoenzymatic synthesis of the germination inhibitor tetrahydroactinidiolide and dihydroactinidiolide starting from ethyl-α- cyclogeraniate. Chiral intermediate acetates (–)-**33** and (+)-**36** were obtained from corresponding racemic alcohols by means of an optimized lipase-mediated resolution and fractional crystallization (Scheme 6).[58]



Scheme 6. Chemoenzymatic Synthesis of the Germinator Inhibitor Dihydroactinidiolide

Schönstein et al. used continuous-flow enzymatic resolution strategy for the acylation of amino alcohols with an adjacent stereogenic centre. Both enantiomers of calycotomine (*R*)-**39** and (*S*)-**39** were prepared through the CAL-B catalyzed asymmetric *O*-acylation of *N*-Boc-protected (6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol (±)-**37**. The optimum



Scheme 7. Preparation of Calycotomine Enantiomers

conditions for the enzymatic resolution were determined under continuous-flow conditions, while the preparative-scale resolution of (±)-**37** was performed as a batch reaction with high enantioselectivity (*E* >200). The resulting amino alcohol (*R*)-**37** and amino ester (*S*)-**38**, obtained with high enantiomeric excess (99% ee), were transformed into the desired calycotomine (*S*)-**39** and (*R*)-**39** (Scheme 7).[59]

A few other natural products synthesis involving lipase-mediated resolution as the key-step are (*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one (**40**, male-produced aggregation

pheromone of the Colorado potato beetle), (–)-rasfonin (**41**, apoptosis inducer), (+)-totarol (**42**, a diterpenoid antibacterial agent), (+)-ambrein (**43**, used for the production of expensive perfumes), (*R*)-(+)-aminoglutethimide (**44**, an aromatase inhibitory drug) and (+)-cystothiazole F (**45,** bithiazole-type antibiotic) (Figure 2).

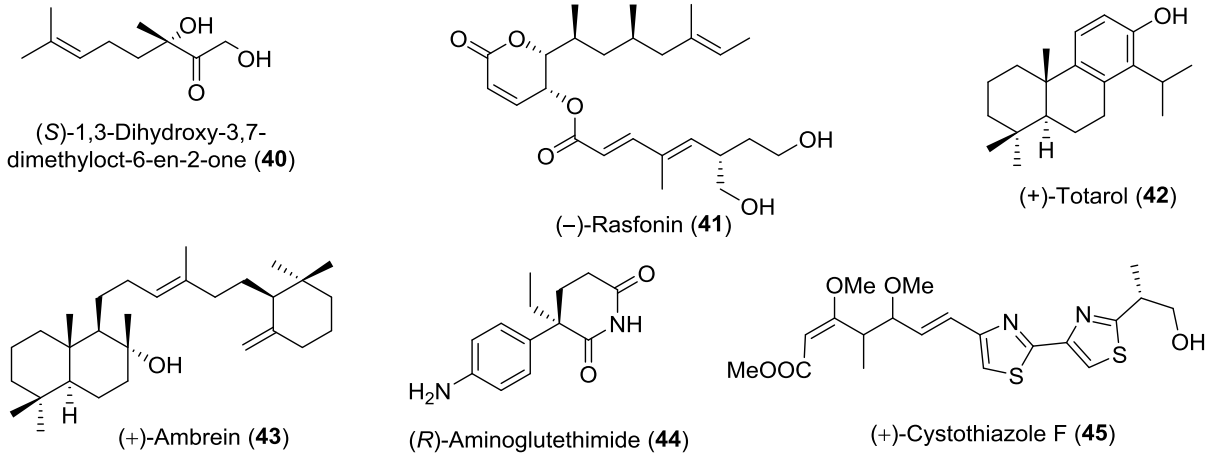


Figure 2. Bioactive natural products synthesized via lipase-mediated resolution.

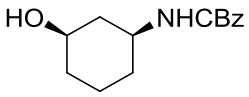
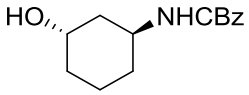
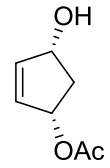
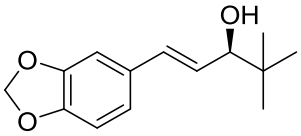
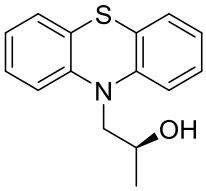
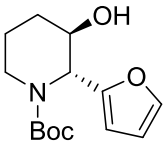
Lipase catalysis is also used in regioselective acylation reactions in the context of primary alcohols. Reports of regioselective transformations catalyzed by lipases can be found in the protection of α,α'-diols, α,ω-diols, including terpene diols,[60] naphthalene diols,[61] propanediols,[62] 3(*R*)-(+)-bis[hydroxymethyl]-1,1-dimethoxycyclobutanone[63] and also in the synthesis of steroids.[64]

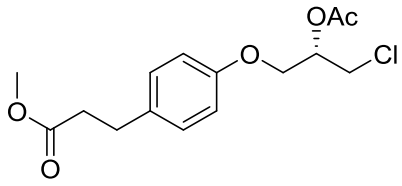
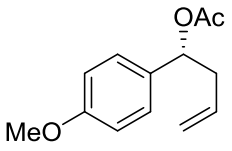
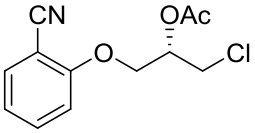
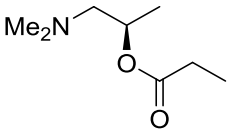
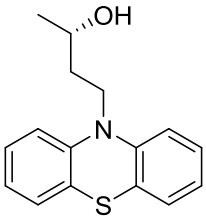
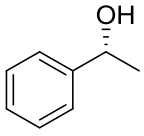
1A.5.2.2 Secondary Alcohols

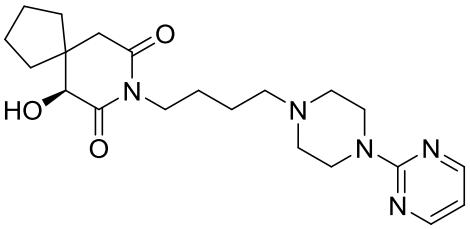
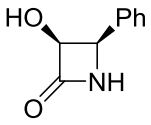
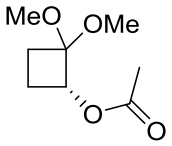
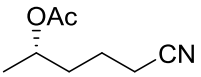
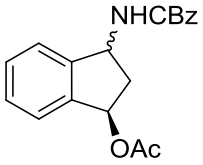
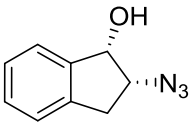
Secondary alcohols are the most widely explored substrates in lipase mediated resolutions. This is not only because of the importance of enantiopure secondary alcohols in organic synthesis (they constitute chiral drugs, intermediates for the synthesis of pharmaceuticals, industrially important flavour and aroma compounds) but also that lipases show much higher enantioselectivity in the resolution of secondary alcohols than primary or tertiary ones. A large number of examples with enormous structural diversity can be found in the literature. A few selected examples of lipase-catalyzed resolution have been presented in Table 2 along with the corresponding references.

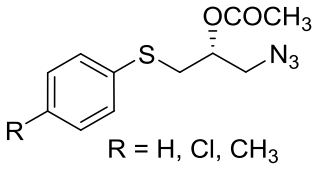
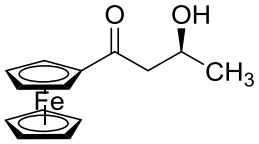
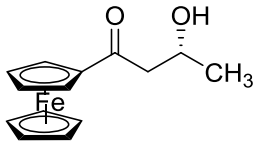
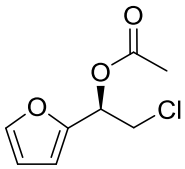
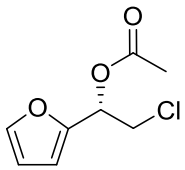
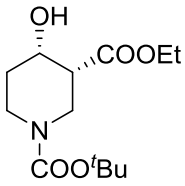
Subsequently, Table 3 presents some important natural products and drugs that have been synthesized employing lipase-mediated resolution (acylation of alcohols or hydrolysis of esters) of a secondary alcohol as the key step.

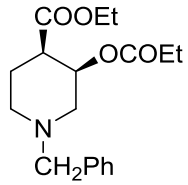
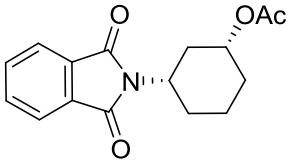
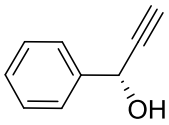
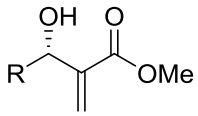
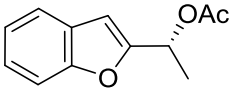
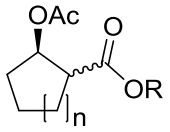
Table 2. Selected Examples of Lipase-catalyzed Resolution of Secondary Alcohols

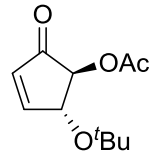
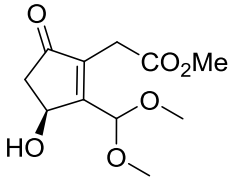
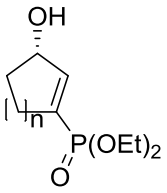
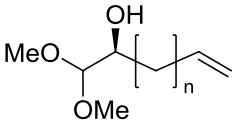
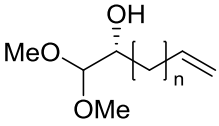
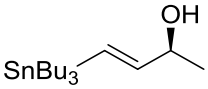
Product	Lipase	% Yield	% Ee	Ref.
 **46** (unreacted isomer)	*Thermomyces lanuginosus* (TLL)	50	~100	[65]
 **47** (unreacted isomer)	CAL-B	37	99	[65]
 **48**	PPL	56	99	[66]
 **49**	CAL	54	87	[67]
 **50**	CAL-B	52	99	[68]
 **51** (unreacted isomer)	CAL-B	42	99	[69]

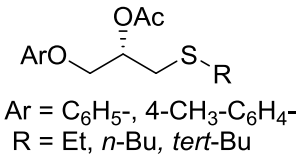
 **52**	CAL L4777	34	96	[70]
 **53**	Amano Lipase PS-C II	41	99	[71]
 **54**	Lipase PS-C	43	95	[72]
 **55**	Novozyme 435	45	95	[73]
 **56**	CAL-B	51	99	[74]
 **57**	Isoenzyme PLE 5	45	95	[75]

 **58**	Acylase from *Aspergillus melleus*	48	95	[76]
 **59**	Lipase from *Pseudomonas sp.*	56	99	[77]
 **60**	CAL-B	33	98	[78]
 **61** (unreacted isomer)	CAL-B	42	99	[79]
 (*syn* & *anti*) **62**	CAL-B	49/48	~99	[80]
 **63**	Amano AK	33	99	[81]

 **64**	CAL-B	35-42	92-96	[82]
 **65**	Lipozyme	49	>99	[83]
 **66**	Novozym 435	48	>99	[83]
 **67**	*C. antartica*	38	99	[84]
 **68**	*P. cepacia*	40	96	[84]
 **69**	Lipase AK	50	99	[85]

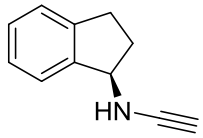
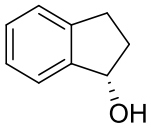
 **70**	CAL-A	27	96	[85]
 **71**	CAL-B	49	99	[86]
 **72**	Novozym 435	43	93	[87]
 R = Me, *n*-propyl **73** (unreacted isomer)	PSL in poly(ethylene oxide)	50/36	99/56	[88]
 **74**	Lipase AK	48	99	[89]
 (*cis* & *trans*) R = Me/Et; n = 1-3 **75**	CAL-B	~50	>99	[90]

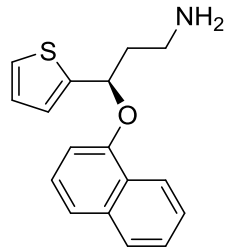
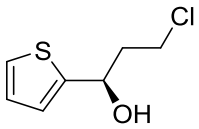
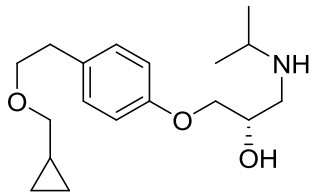
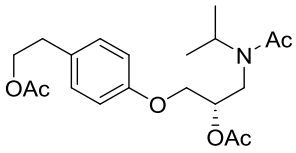
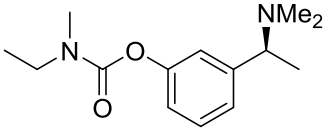
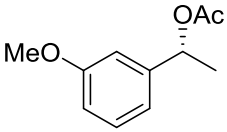
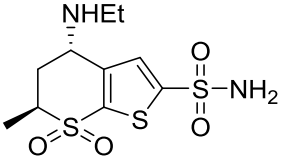
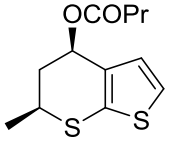
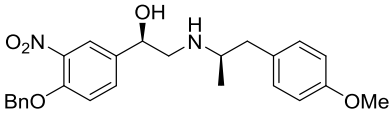
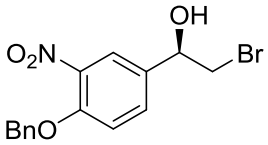
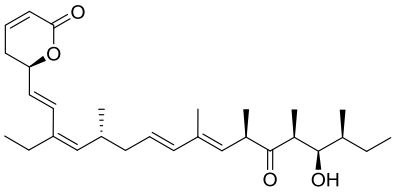
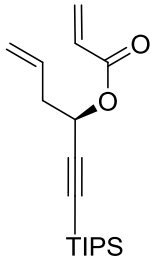
 **76**	Lipase PS	50	95	[91]
 **77**	CAL-B	48	94	[92]
 n = 1-3 **78**	Amano PS/AK	47-48	>99	[93]
 n = 0,1 **79**	CAL-B/PFL	50	93/92	[94]
 n = 0,1 **80**	CAL-B/LPL	50	94/98	[94]
 **81**	Lipozyme	48	99	[95]

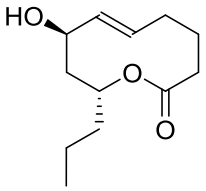
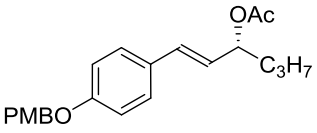
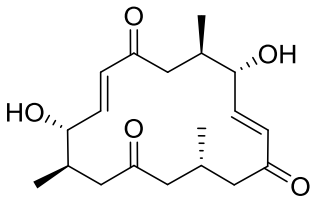
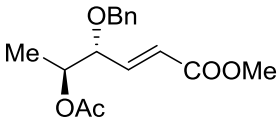
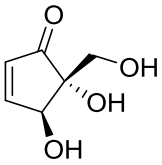
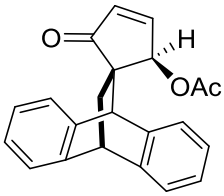
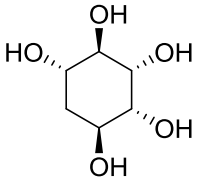
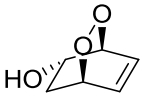
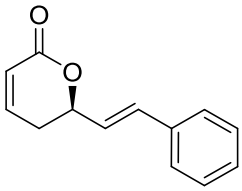
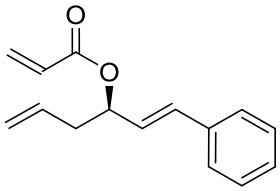
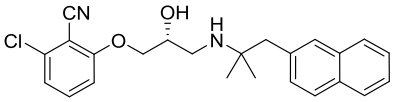
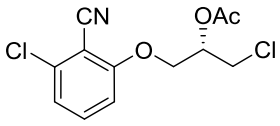
 Ar = C_6H_5-, 4-CH_3-C_6H_4- R = Et, *n*-Bu, *tert*-Bu **82**	Amano AK	21-62	24-86	[96]

Natural products have been a rich and best source of compounds for drug discovery point of view and their synthesis in enantiomerically pure form is of huge significance. From 1940s to date, 131 out of 175 small molecule anticancer drugs are natural product-based/inspired, with 85 being either natural products or derived therefrom. From 1981 to date, 79 out of 99 small molecule anticancer drugs are natural product-based/inspired, with 53 being either natural products or derived therefrom. One enantiomer of a drug may have a desired beneficial effect while the other may cause serious and undesired side effects, or sometimes even beneficial but entirely different effects.[97] Lipase-catalyzed resolution of secondary alcohols have served as key intermediates in the total synthesis of several important enantiopure natural products/drugs. In the case of multistep synthesis of natural products, such a resolution in the initial steps of the synthesis not only provides an easy and economic access to the important chiral intermediate in a highly enantioselective fashion but also sets the stage for the introduction of contiguous chiral centres in a stereoselective fashion. A handful of such examples have been enlisted in Table 3 with the intermediate involved in the synthesis depicted alongside.

Table 3. Examples of Natural Products/Drugs Synthesized and the Corresponding Chiral Secondary Alcohols Prepared by Lipase Catalyzed Resolution

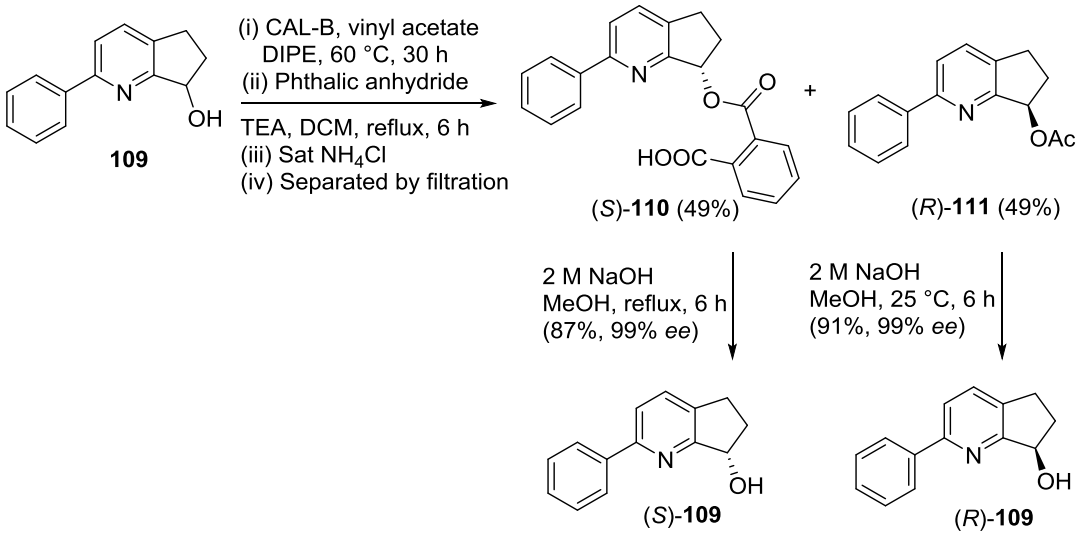
Natural product/Drug	**Intermediate**	**Lipase**	**% Ee**	**Ref.**
 (CH_3SO_3H salt) (−)-Rasagiline mesylate (Azilect®, **83**)	 **84**	*Pseudomonas fluorescens*	94	[98]

 (*R*)-Norduloxetine (**85**)	 **86**	CAL B	95	99
 (–)-Betaxolol (**87**)	 **88**	*Rhodotorula mucilaginosa*	95	100
 (–)-Rivastigmine (**89**)	 **90**	CAL-B	99	101
 Dorzolamide (**91**)	 **92**	Amano PS	97	102
 (*R*,*R*)-Formoterol (**93**)	 **94**	Amano PS	96	103
 (–)-Callystatin A (**95**)	 **96**	Lipase *P*. AK	>95	104

 (+)-Herabrumin III (**97**)	 **98**	CAL-B	98	[105]
 (+)-Macrosphelide (**99**)	 **100**	Amano PS	>99	[106]
 (–)-Epipentenomycin (**101**)	 **102**	Amano PS-D	>98	[107]
 (+)-*proto*-Quercitol (**103**)	 **104**	CCL	91	[108]
 (+)-Goniothalamin (**105**)	 **106**	CAL-B	93	[109]
 (+)-NPS-2143 (**107**)	 **108**	Lipase PS-D	99	[110]

The diversity of the compounds that have been resolved by lipases, especially taking in to account their miscellaneous applications is truly amazing. A few appealing reports have been illustrated below revealing the variety in the substrates employed and their significance.

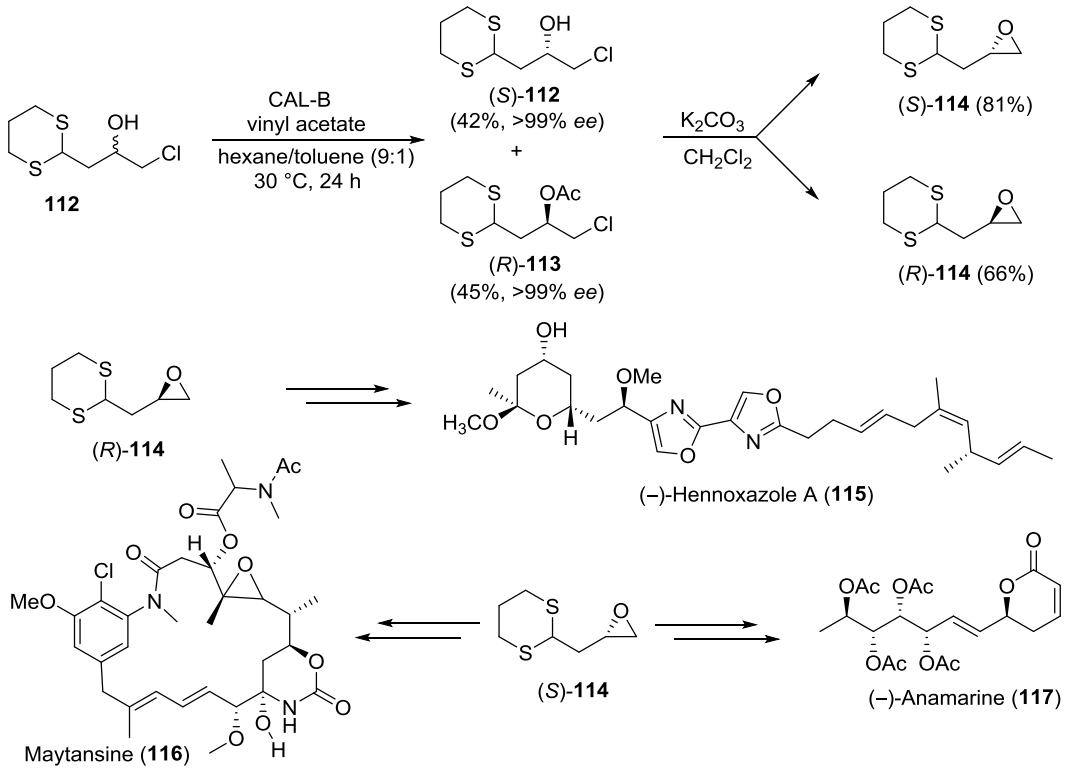
A drawback of the hydrolase-catalyzed enantioselective acylation of alcohols is the product isolation. Separation of the remaining alcohol from the ester is indeed often laborious, and column chromatography is frequently needed. Methods that avoid the purification step are therefore especially appreciated. One strategy was developed and applied by Pfaltz and co-workers for the kinetic resolution of pyridyl alcohols.[111] The method is based on the fact that many monoesters of phthalic acid are known to be crystalline solids (Scheme 8). The result is a two-step procedure in which enzymatic kinetic resolution of **109** is combined with derivatization of the unreacted alcohol with phthalic anhydride. Acetate **111** and phthalic acid



Scheme 8. Column Chromatography Free Kinetic Resolution of Pyridyl Alcohols

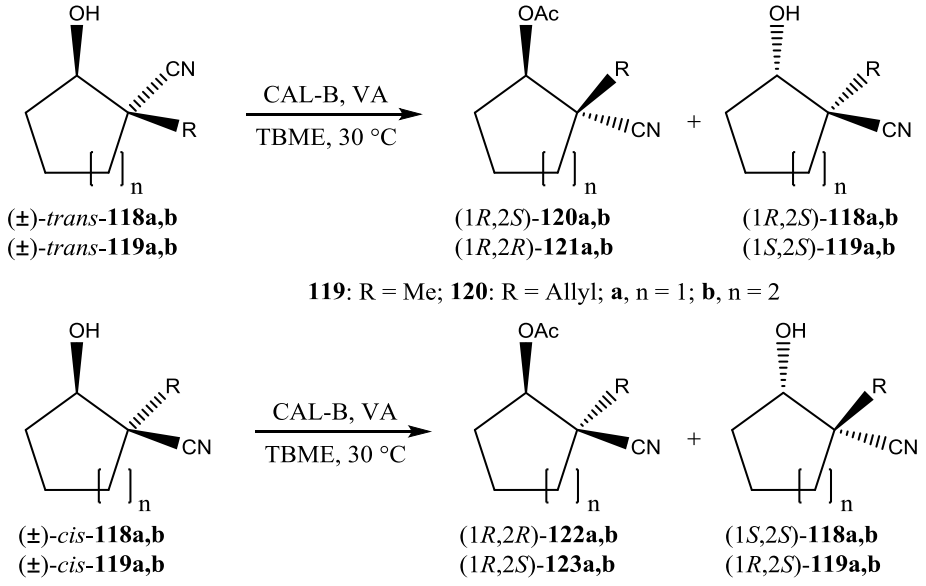
monoester **110** could be easily separated by filtration; hydrolysis of the esters with sodium hydroxide and subsequent recrystallization from cyclohexane afforded enantiopure alcohols (*S*)-**109** and (*R*)-**109**.

Enantiopure 2-(1,3-dithian-2-ylmethyl)oxirane have been used in synthesis of the polyhydroxy *δ*-pyranone natural product (−)-anamarine (**117**),[112] the antiviral agent hennoxazole A (**115**)[113] and derivatives of maytansine (**116**).[114] An efficient *Candida antartica* B lipase-catalyzed resolution of alcohol **112** carried out by Sundby et al.[115] for synthesis of both enantiomers, (*R*) & (*S*)-**114** (Scheme 9).



Scheme 9. Chemoenzymatic Synthesis of (2*S*)- and (2*R*)-2-(1,3-Dithian-2-ylmethyl)oxirane

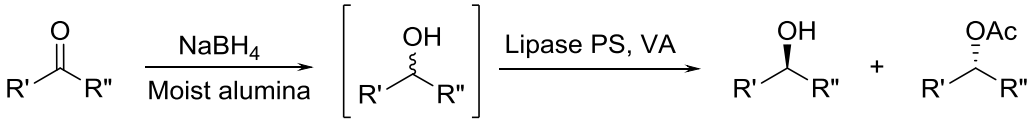
An asymmetric construction of quaternary carbon centres represents a challenging task in organic synthesis. On the other hand, the importance of optically active *β*-hydroxy nitriles as suitable synthons for the preparation of *γ*-amino alcohols (like the antidepressant fluoxetine



Scheme 10. General Representation of Lipase Catalyzed Resolution of *β*-Hydroxy Nitriles

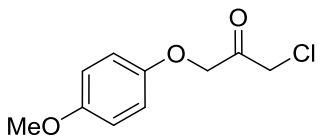
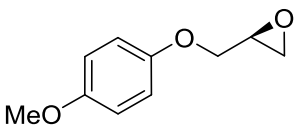
)[116] is steadily growing. Levy & Gotor combining both the above targets have reported an elegant kinetic resolution of racemic *cis*- and *trans*-1-alkyl-2-hydroxycycloalkane nitriles **118** and **119** via enzymatic transesterification. Both five and six-membered substrates were studied and excellent enantioselectivities were observed with *Candida antartica B* lipase (Scheme 10).[117] The conversion was 50% in all cases because of the extremely good *E*-values (enantiomeric ratio) and the enantiomeric excess were ≥ 99% for all the stereoisomers.

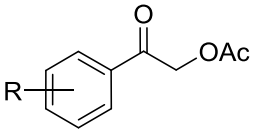
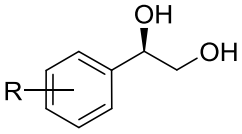
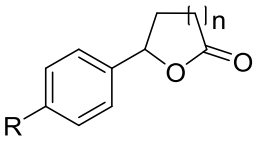
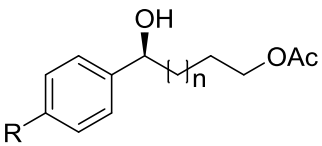
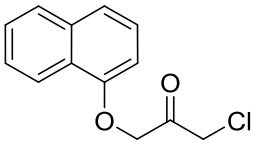
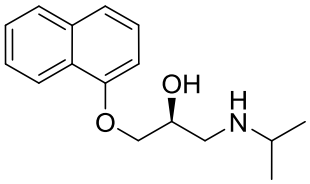
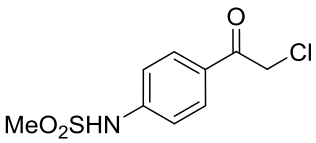
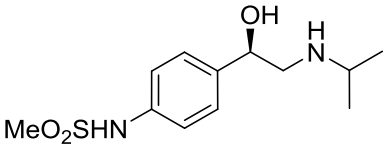
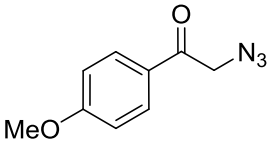
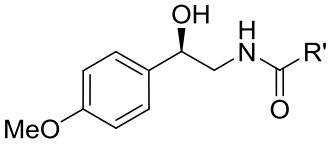
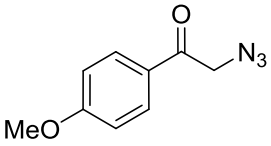
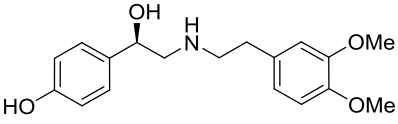
A new efficient enzymatic pathway has been developed by Kamal et al. for the synthesis of enantiopure alcohols. The method is not only cost effective but also offers reduced reaction times. An attractive protocol developed for the first time that lipase catalyzes a transesterification process in one-pot for the secondary alcohols after the reduction of the corresponding carbonyl compounds with alumina-assisted sodium borohydride. The faster reaction rates with high selectivity in organic media like hexane and environmentally acceptable reaction conditions provide a practical and mild in situ biocatalytic resolution process for secondary alcohols starting from their carbonyl precursors.[118] A general illustration is provided in Scheme 11 and they have applied this strategy for the synthesis of enantiopure secondary alcohols and also extrapolated a few of them to natural products. Some of the carbonyl substrates and the enantiopure end products including natural products are illustrated in Table 4.



Scheme 11. General Representation for Synthesis of Enantiopure Secondary Alcohols from their Carbonyl Precursors

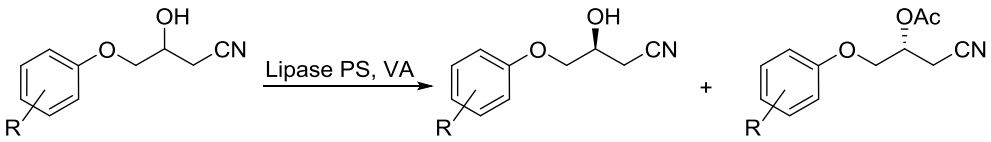
Table 4. Applications of One-pot Reduction-lipase-catalyzed Resolution of Carbonyl Compounds

Carbonyl Substrate	End Product	Lipase	Ref.
 **124**	 **125** (99% *ee*)	Lipase PS-C	[119]

 R = H, *p*-Me, *p*-OMe **126**	 **127** (>99% *ee*)	Lipase PS-C	[120]
 R = H, OCH_3, Cl; n = 1,2 **128**	 R = H, OCH_3, Cl; n = 1,2 **129** (>99% *ee*)	Lipase PS-C	[121]
 **130**	 (–)-(*S*)-Propranolol (**131**, 96% *ee*)	Lipase PS-C	[122]
 **132**	 (–)-(*R*)-Sotalol (**133**, 90% *ee*)	Lipase PS-C	[122]
 **134**	 (*R*)-Tembamide (**135**): R’ = Ph (*R*)-Aegeline (**136**): R’ = -CH=CH-Ph (both in 98% *ee*)	Lipase PS-C	[123]
		Lipase PS-C	[123]

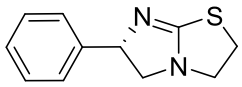
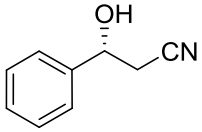
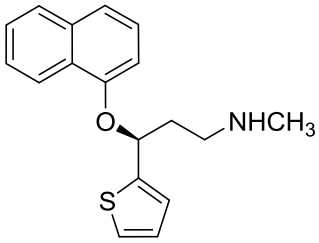
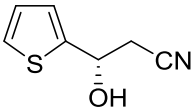
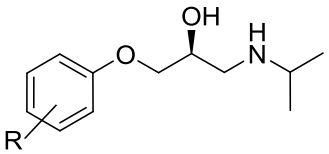
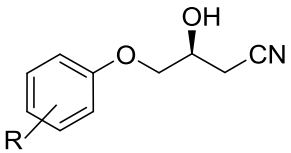
137	(*R*)-Denopamine (**138**, 99% *ee*)		

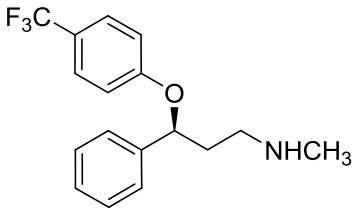
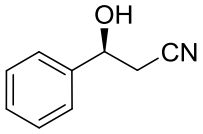
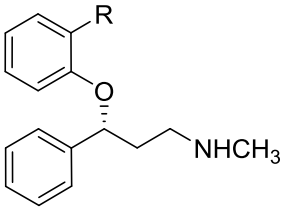
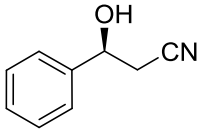
Kamal & Khanna have also synthesized optically pure β-hydroxy nitriles[124] employing lipase-catalyzed resolution (Scheme 12) and used them in the preparation of biologically important compounds or intermediates. The strategy has been applied for the synthesis of some natural products (Table 5).



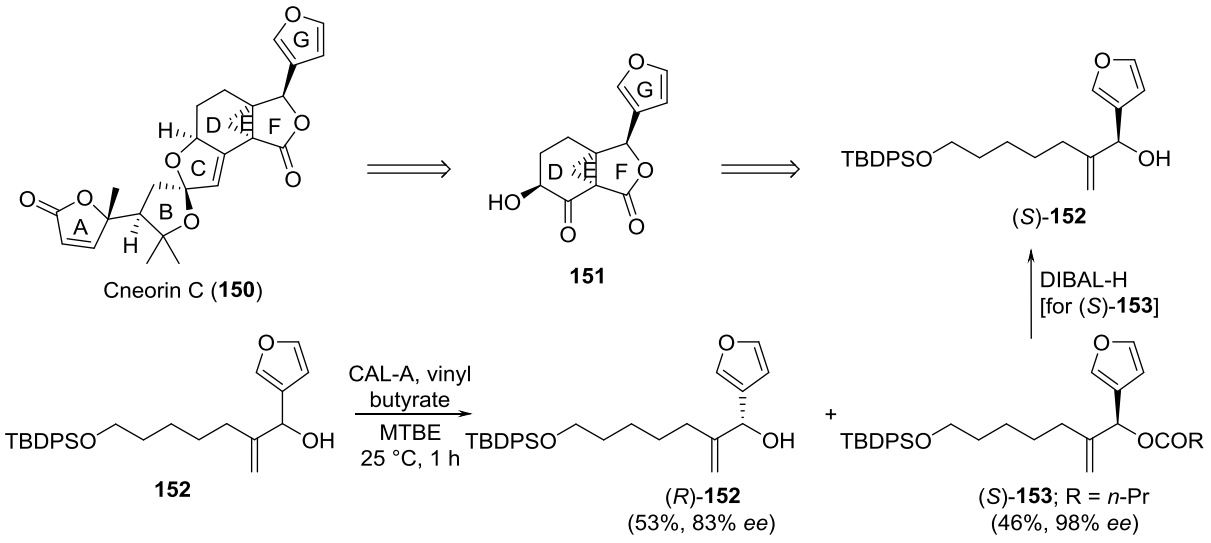
Scheme 12. Lipase Catalyzed Synthesis of Optically Pure β-Hydroxy Nitriles

Table 5 Examples of Natural Products Synthesized along with the Corresponding Optically Pure β-Hydroxy Nitrile Intermediates Prepared by Lipase-catalyzed Resolution

Natural Product	Intermediate	Lipase	Reference
 (−)-Levamisole (**139**)	 **140** (40%, >99% *ee*)	Lipase PS-C	125
 (+)-Duloxetine (**141**)	 **142** (42%, >99% *ee*)	Lipase PS-D	126
 R = 4-OCH_3, 2-(CH_2-CH=CH_2) β-Adrenergic blocking	 R = 4-OCH_3, 2-(CH_2-CH=CH_2) **144** (43-45%, 90-99% *ee*)	Lipase PS-D	127

agents **143**			
 (*S*)-Fluoxetine (**145**)	 **146** (46%, >99% *ee*)	Lipase PS-C	128
 R = CH_3: (*R*)-Tomoxetine (**147**) R = OCH_3: (*R*)-Nisoxetine (**148**)	 **149** (46%, >99% *ee*)	Lipase PS-C	128

Cneorin C (**150**) was originally isolated from the xerophytic shrub *Cneorum pulverulentum* native to the Canary Islands in the early 1970s. In the course of study towards the synthesis of



Scheme 13. Lipase-catalyzed Resolution of Allyl Alcohol **152** for Synthesis of Cneorin C

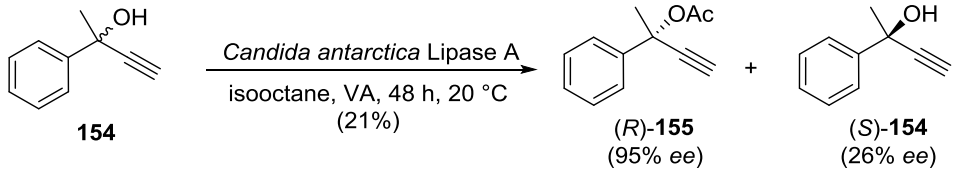
the DEFG ring system of the natural product, Koskinen and co-workers faced the task of preparing the furyl substituted allyl alcohol **152** enantioselectively. Interestingly, the authors

reported that the best method for achieving the above was by using a lipase-catalyzed resolution, whereas the results with three other asymmetric protocols adopted for the same were good.[129] The resolution of *rac*-**152** with CAL-A proved highly enantioselective (E >300) yielding the ester (*S*)-**153** with 98% *ee* and the alcohol (*R*)-**152** with 83% *ee* (Scheme 13). Subsequent reduction of the ester (*S*)-**153** provided the requisite intermediate (*S*)-**152** for the total synthesis of cneorin C.

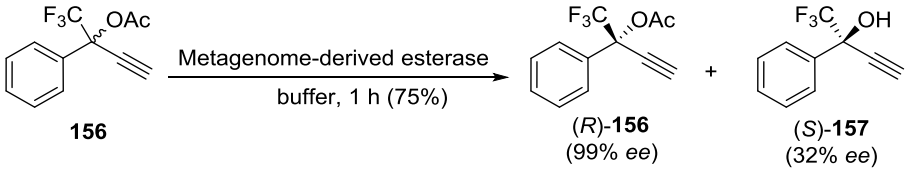
1A.5.2.3 Tertiary Alcohols

Tertiary alcohols and their esters are a group of important compounds, which can be found in many natural products (e. g., *α*-terpeneol, (*S*)-linalool and (*S*)-dihydrolinalool) and in intermediates for synthesis of them. The kinetic resolution of tertiary alcohols using lipases is limited. This is probably due to the adverse steric interactions caused by the bulk of 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 **154** using lipase A from *Candida antartica* (CAL-A).[130] This was the first example of a highly enantioselective enzyme-catalyzed resolution of a tertiary alcohol and the acetate (*R*)-**155** was obtained with 95% *ee* (Scheme 14). The % *ee* of the unreacted substrate was low due to very low conversion. They also studied several new metagenome-derived esterases with activity towards the hydrolysis of tertiary alcohol acetates. Most of the active esterases showed no significant enantioselectivity in the hydrolysis of the acetates of the tertiary alcohols terpinyl acetate, linalyl acetate and 3-methylpent-1-yn-3-yl acetate. However, esterase-34 demonstrated moderate preference for hydrolysis of the (+)-enantiomer of 1,1,1-trifluoro-2-phenylbut-3-yn-2-yl acetate (**156**) (Scheme 15).

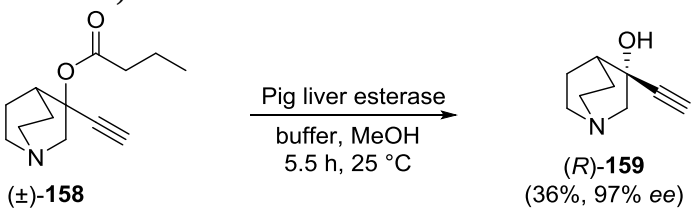


Scheme 14. Enantioselective Transesterification of a Tertiary Alcohol



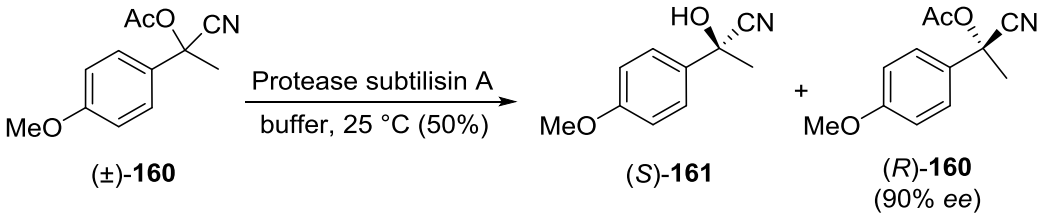
Scheme 15. Lipase-catalyzed Hydrolysis of Tertiary Alcohol Acetates

Resolution of quinuclidine ester **158** has been successfully accomplished by Coope and Main by means of a pig liver esterase leading to the corresponding alcohol (*R*)-**159** in 36% yield and with 97% *ee* (Scheme 16).[131]



Scheme 16. Lipase Catalyzed Resolution of Quinuclidine Ester

Hanefeld and co-workers reported the successful kinetic resolution of *α,α*-disubstituted cyanohydrin acetate, an interesting building block in organic synthesis. Subtilisin A catalyzed hydrolysis was (*S*)-selective, while Candida rugosa lipase was (*R*)-selective. These commercially available enzymes provided both enantiomers of the *α,α*-disubstituted cyanohydrin acetates (Scheme 17).[132]



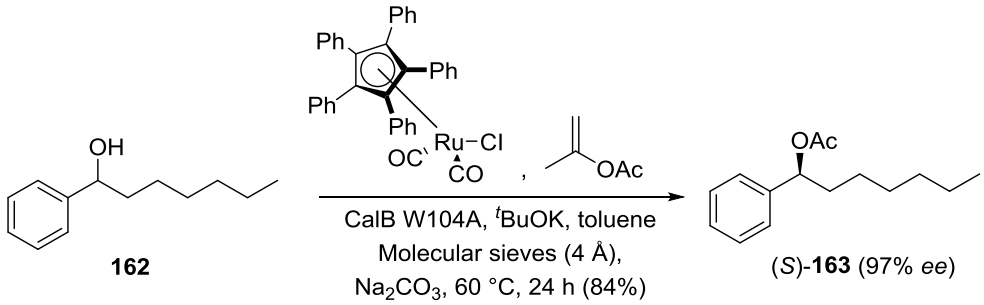
Scheme 17. Enzymatic Resolution of an *α,α*-Disubstituted Cyanohydrin Acetate

1A.5.3 Methods of Improving the Yield in Lipase Catalysis and Applications

The drawback with kinetic resolution is that a maximum of 50% of the starting material can be used to give product, poor 'atom economy'. 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) 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 conversion into one enantiomer and (ii) employing *meso* substrates ("the *meso* trick") or prochiral substrates, wherein all of the starting material can be utilized. The former is termed as dynamic kinetic resolution (DKR) whereas the latter involves desymmetrization of compounds possessing a plane of symmetry. A few examples of both these methods are illustrated below.

1A.5.3.1 Dynamic Kinetic Resolution

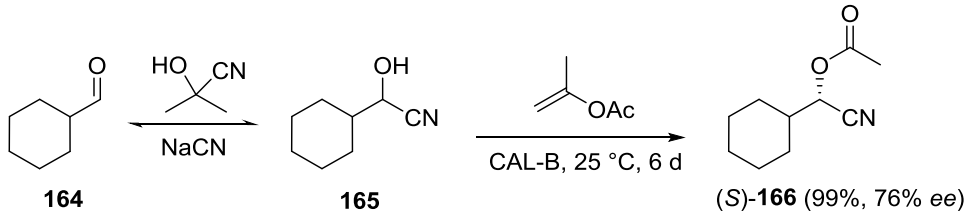
Dynamic Kinetic Resolution (DKR) is a methodology that has advanced most in recent years in improving enzyme catalysis.[133-135] Since enzymes offer a host of attractive advantages, the number of examples of chemoenzymatic DKR that combine the enzymatic resolution with an in situ racemization method has increased during the past few years. Classical racemization techniques include base-catalyzed (most common), Schiff's base mediated, thermal and even enzyme-catalyzed methods. A new concept that has emerged in recent years is the metal-catalyzed racemization, a technique that has provided a new dimension and added importance to DKR and its applications. Engström et al. developed (*S*)-selective dynamic kinetic resolution of secondary alcohols, employing a mutated variant of *Candida antarctica* lipase B



Scheme 18. (*S*)-Selective Dynamic Kinetic Resolution of 1-Phenylheptanol

(CalB) which gave products in 84–88% yield with 90–97% *ee*. 1-Phenylheptanol (**162)** was efficiently acylated at 60 °C to give the product with high yield (84%) and 97% *ee*. (Scheme 18).[136a]

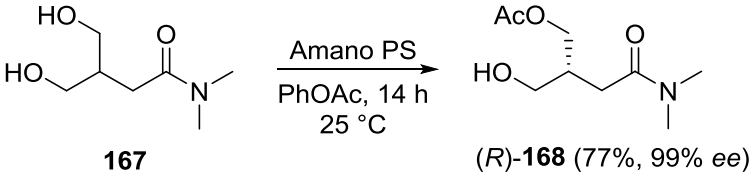
Amberlite (IRA-904 in -OH form) is commonly used as the racemizing agent in DKR but Hanefeld and co-workers observed that when it was used for the synthesis of aliphatic cyanohydrin acetates, only kinetic resolution took place with 46% yield and 90% *ee*. However upon exchanging the amberlite by NaCN, quantitative conversions with good enantioselectivity were obtained (Scheme 19).[136b]



Scheme 19. The Dynamic Kinetic Resolution of Aliphatic Cyanohydrins

1A.5.3.2 Enantioselective Enzymatic Desymmetrization

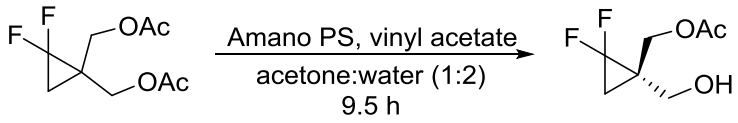
Desymmetrization of prochiral and meso substrates is another method that provides maximum yield of 100% and hence can be used for asymmetric synthesis. For this reason, enzymatic desymmetrizations constitute a very interesting alternative to kinetic resolution for the preparation of optically active compounds, reflected by the increasing applications in recent literature.[5b] A few examples useful from a synthetic point of view involving lipase-catalyzed desymmetrization are illustrated in this section. Takabe et al. studied enantioselective acetylation of 2-carbamoylmethyl-1,3-propanediol derivatives which was catalyzed effectively by lipase PS to give monoacetates with high enantioselectivity. The enantioselectivity was dependant on the 2-carbamoylmethyl groups. The reaction of propanediol **167** afforded the monoacetate **168** with the (*R*)-configuration (Scheme 20).[137]



167 (*R*)-**168** (77%, 99% *ee*)

Scheme 20. Lipase-catalyzed Desymmetrization of 2-Carbamoylmethyl-1,3-propanediol

Kirihara et al studied lipase-catalyzed asymmetric transesterification of prochiral diacetates to provide chiral monoacetates. Amano PS catalyzed asymmetric transesterification of prochiral diacetate **169** gave enantiopure monoacetate **170** (Scheme 21).[138]



169 (*S*)-**170** (86%, 92% *ee*)

Scheme 21. Amano PS Catalyzed Asymmetric Transesterification of Prochiral Diacetate

1A.6 Summary

The use of enzymes in organic synthesis is widely accepted since the past 4-decades. The selected examples illustrated in this section demonstrate a broad applicability of lipases in terms of substrate specificity and the ability to use wide range of structurally diverse compounds, alcohols, carboxylic acids, esters as substrates with good 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 dispelling any existing prejudice against enzymes as practical catalysts. The advent of new catalysts for dynamic kinetic resolution and the use of prochiral and meso substrates (enantioselective enzymatic desymmetrization) have, as we have seen, taken the field to another level by remarkable improvement of the chemical yield. A synthetically useful new variant of dynamic kinetic resolution has been published that is based on racemizing reversible Michael reactions in combination with lipase-catalyzed hydrolysis.[139] Moreover, novel developments such as additive effects, solvent optimization, the use of ionic liquids and immobilization techniques offer additional exciting opportunities leading to further practical applications of lipases in synthetic organic chemistry. Protein engineering has an exciting potential of altering the enzymatic properties at will, e.g., broadening substrate specificity, as well enhancing enzyme action in organic media. Rational design of new enzymatic catalysts to construct a protein with a designed catalytic activity and selectivity from a designed sequence of amino acids is very challenging. Thus, the concept of artificial enzymes offers an attractive alternative though whether they will be able to match their natural counterparts is debatable. Supercritical biocatalysis[7b,140] is another field of extensive research in the recent past though the advantages of replacing conventional organic solvents with supercritical fluids have not fully been demonstrated yet. More recently, modern molecular biology methods such as directed evolution[141-143] have given a further boost to the development of lipases for future applications. Considering their applications in the past, it can be therefore said with assurance, that the impact of enzymes, lipases in particular in organic synthesis has been enormous and their ever-increasing utilization is rather evident in the present scientific world. Recent developments demonstrate that more pathbreaking methods and processes brought about by the catalysts of Nature will be discovered in the future. We have tried our best to summarise the enzymatic resolution using selected relevent examples, however the pretension of completeness is not claimed.

In our group, over the past few years, we have successfully used enzymes in synthesis of important chiral intermediates and have also carried out studies relating to their selectivity pattern.[144] More recent work from our group utilizing lipases concerns a variety of applications[145] such as (i) preparation of enantiomerically pure allyl alcohols and allyl acetates and (ii) resolution of α-hydroxy ketones. The following section B discusses present work on enzymatic resolution and total synthesis.

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(145) We have also carried out an efficient lipase-catalyzed resolutions for synthesis of (i) enantiomerically pure allyl alcohols and allyl acetates and (ii) chiral *α*-hydroxy ketones which will be discussed in Section B of Chapter I and Chapter II of present dissertation.

1B.Section B

Total Synthesis of (+)-1,3,4,5-Tetragalloylapiitol, Putrescine Bisamides and Artabotriolcaffeate

This section features the following topics:

1B.1 Chemoenzymatic Total Synthesis of (+)-1,3,4,5-Tetragalloylapiitol

1B.1.1 Introduction

The polygalloylated sugars have been recently isolated as bioactive natural products and they possess anti-HIV, antiviral, antitumor and antidiabetic activities (Figure 1).[1-3] HIV-1 RNase H is an attractive molecular target for the development of new anti-HIV agents as potential chemotherapeutics.[4-6] Gustafson et al. isolated a new potent HIV RNase H inhibitor (–)-1,3,4,5-tetragalloylapiitol (**1a**) from an extract of the plant *Hylodendron gabunensis*.[1] The structure of **1a** was elucidated by NMR analysis and found to be an apiitol (**2**)[7] sugar moiety coupled with four gallic acid (**3**) residues (Figure 1). Optical rotation measurements of the free sugar obtained by basic hydrolysis of 1,3,4,5-tetragalloylapiitol (**1a**) indicated that the 3*S*-absolute configuration was the same as that of D-apiitol (**2**). Compound **1a** inhibits HIV-1, HIV-2 and human RNase H with IC_{50} values of 0.24, 0.13 and 1.5 μM, respectively, but it does not show inhibition of *E. coli* RNase H at 10 μM.[1]

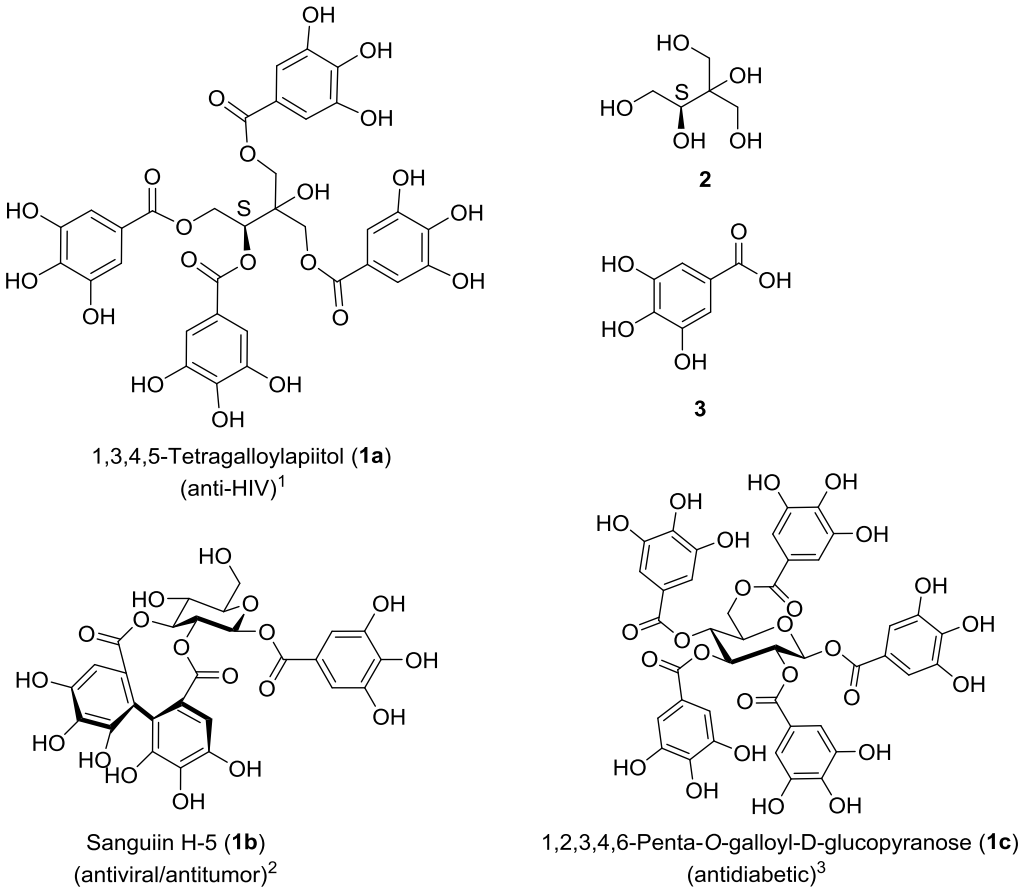
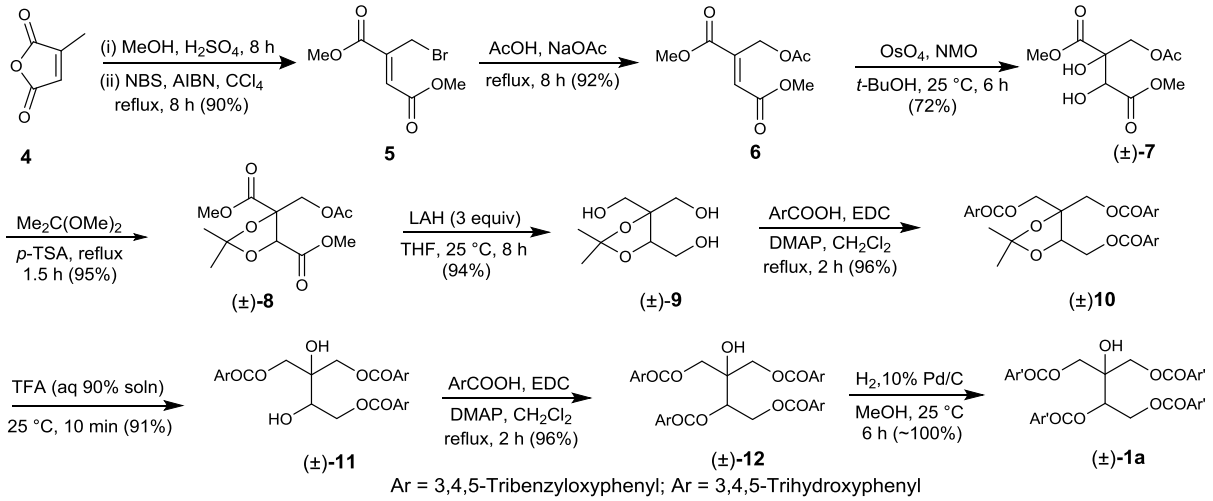


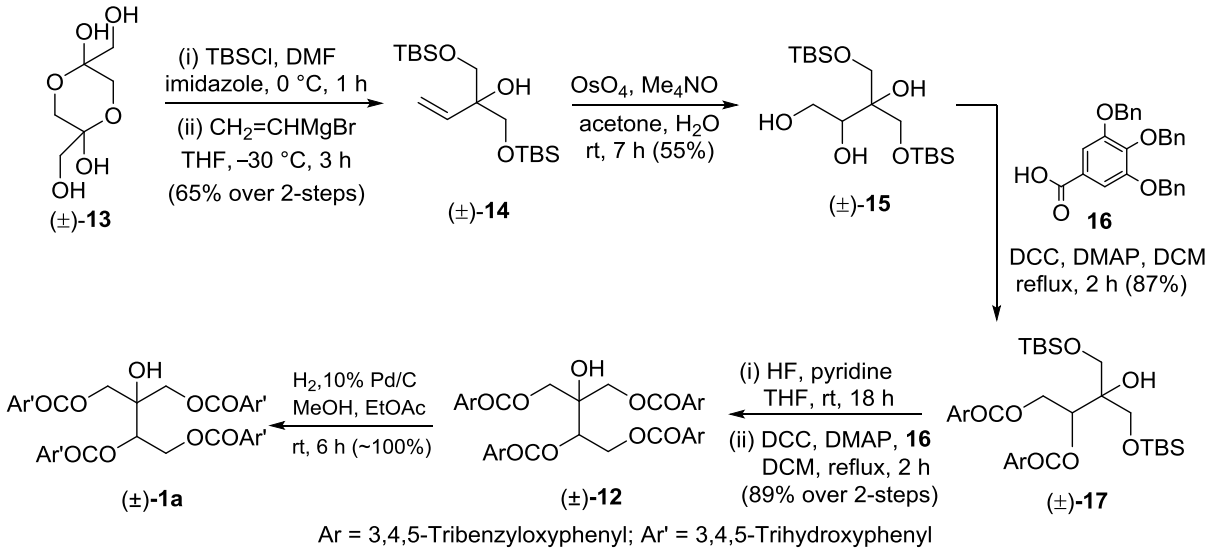
Figure 1. Recently isolated bioactive natural products with the polygalloylated sugar architectures and their biogenetic precursors.[1-3]

Patel and Argade reported the first total synthesis of (±)-1,3,4,5-tetragalloylapiitol (**1a**) starting from citraconic anhydride, they designed the pentahydroxy sugar, the apiitol and completed the synthesis of (±)-1,3,4,5-tetragalloylapiitol (**1a**) (Scheme 1).[8] The ten steps total synthesis of (±)-1,3,4,5-tetragalloylapiitol (**1a**) from citraconic anhydride is noteworthy and confirmed the structural assignment of natural product.



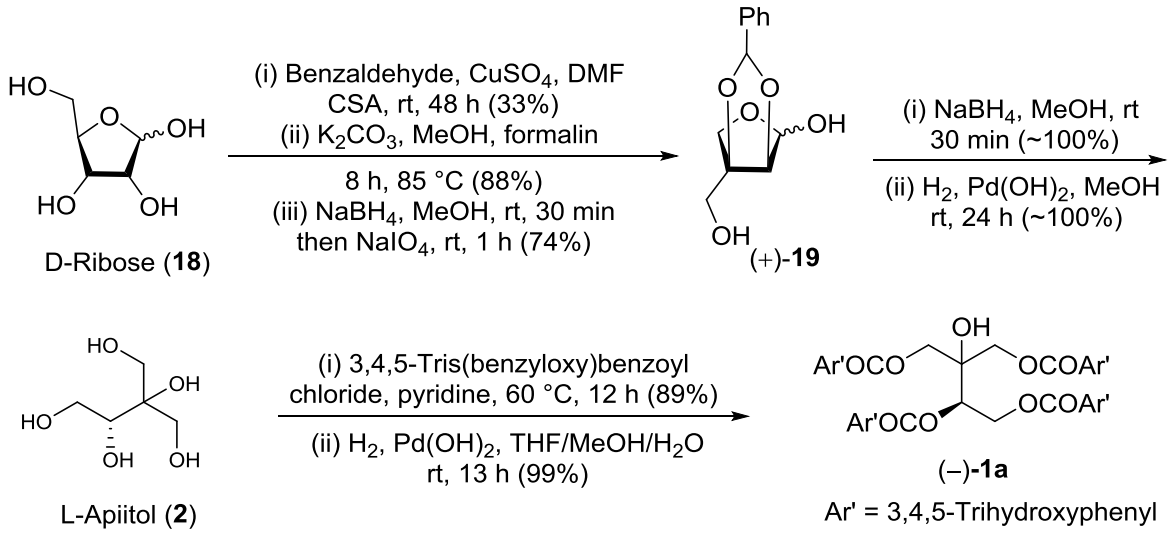
Scheme 1. First Total Synthesis of (±)-1,3,4,5-Tetragalloylapiitol

Kraus and Kempema have also accomplished the flexible racemic synthesis of (±)-1,3,4,5-tetragalloylapiitol (**1a**) starting from 1,3-dihydroxyacetone dimer (±)-**13** via Grignard reaction followed by the dihydroxylation-double gallyolation, silyl deprotection-double gallyolation and reductive global *O*-benzyl deprotection pathway.[9] Synthesis involves seven steps and provides (±)-**1a** in 28% overall yield (Scheme 2).



Scheme 2. Synthesis of (±)-1,3,4,5-Tetragalloylapiitol from 1,3-Dihydroxyacetone Dimer

Kojima et al. recently completed the total syntheses of both (–)- and (+)-1,3,4,5-tetragalloylapiitol in seven steps from D- and L-ribose respectively (Scheme 3). On the basis of comparison of the optical rotations of both enantiomers with that of the natural product, the absolute configuration at C-3 in the naturally occurring 1,3,4,5-tetragalloylapiitol has been revised to "*R*". The absolute configurations at C-3 in the synthetic (+)- and (–)-1,3,4,5-tetragalloylapiitol were further confirmed by the circular dichroism exciton chirality method.[10] The scheme 3 describes total synthesis of (–)-1,3,4,5-tetragalloylapiitol (**1a**) starting from D-ribose (**18**) and similarly total synthesis of (+)-1,3,4,5-tetragalloylapiitol (**1a**) was accomplished starting from L-ribose.



Scheme 3. Synthesis of (–)-1,3,4,5-Tetragalloylapiitol from D-Ribose

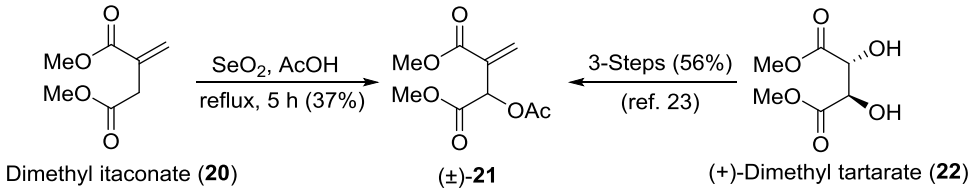
1B.1.2 Present Work

The chemoenzymatic synthesis provides a powerful approach and new opportunities for accessing chemical diversity.[11] In continuance of our studies on both cyclic anhydrides and derivatives to bioactive natural and unnatural products,[12-17] and an efficient enzymatic resolutions,[18-22] starting from (±)-dimethyl 2-acetoxy-3-methylenesuccinate (**21**) we intended for the chemoenzymatic approach to our target compound **1a**. In this context, we herein report our results on first total synthesis of enantiomerically pure (+)-**1a** (Schemes 4 and 5).

1B.1.2.1 Results and Discussions

We reasoned that (±)-dimethyl 2-acetoxy-3-methylenesuccinate (**21**) would be the potential precursor for the chemoenzymatic total synthesis of (+)-1,3,4,5-tetragalloylapiitol (**1a**) via the lipase catalyzed resolution followed by reduction of two ester units and the consequent

carbon–carbon double bond dihydroxylation route. We started our synthesis with selenium dioxide catalyzed allylic oxidation of dimethyl itaconate (**20**) and obtained the desired product



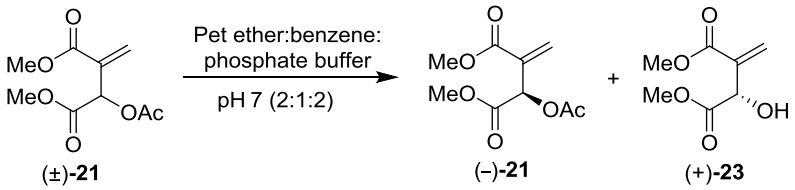
Scheme 4. Synthesis of (±)-Dimethyl 2-Acetoxy-3-methylenesuccinate (**21**)

(±)-**21**, but only in 37% yield (Scheme 4). All our attempts to further improve the yield were ineffective and under the forced reaction conditions we always ended up with the formation of decomposed materials and polymeric gums. Even the use of catalytic amount of SeO_2 and *t*-BuOOH at room temperature for the conversion of **20** to (±)-**21** was not effective and the starting material remained unreacted. Finally starting from (+)-dimethyl tartarate (**22**), the required precursor (±)-**21** was synthesized in three steps with very good overall yield by using the known Baylis-Hillman reaction between the methyl 2-oxoacetate and methyl acrylate, followed by the *O*-acylation step.[23]

On the basis of higher acidity of a methine proton in (–)-**21** and the anticipated propensity for racemization, an enzymatic resolution of (±)-**21** appeared more appropriate. Hence the systematic studies on biphasic hydrolytic enzymatic resolution of (±)-**21** using the promising enzymes *Pig pancreas* lipase (PPL), *Candida cylindracea* lipase (CCL) and *Pseudomonas cepacia* lipase (Amano PS) for the preparation of enantiomerically pure (–)-**21** were planned.[18-24] The enzyme PPL was ineffective in recognizing our racemic substrate **21**, while we obtained very low enantiomeric excess upon exercise of enzyme CCL (Table 1, entry 4). Fortunately, the readily available and relatively cheaper enzyme Amano PS, which is specific for the secondary alcohols, better recognized our starting material (±)-**21**. The Amano PS catalyzed resolutions of (±)-**21** at 25 °C and 35 °C were found to be slow (Table 1, entries 5 and 6). The same Amano PS catalyzed biphasic resolution of (±)-**21** at 50 °C furnished the desired unhydrolyzed enantiomerically pure (–)-**21** in 42% yield with 97% *ee* (by chiral HPLC) in 84 hours (Table 1, entry 7). In the above mentioned enzymatic resolution the hydrolyzed alcohol (+)-**23** was obtained in 58% yield, but with only 53% *ee*. The same reaction at about 40% conversion also provided the product (+)-**23** in very good yield with 87% *ee* (by chiral HPLC).[25] We infer that both the multifunctional enantiomerically pure

products (–)-**21** and (+)-**23** would serve as an important building blocks for the total synthesis of several desired bioactive natural and unnatural products.

Table 1. Lipase Catalyzed Resolution of (±)-**21**



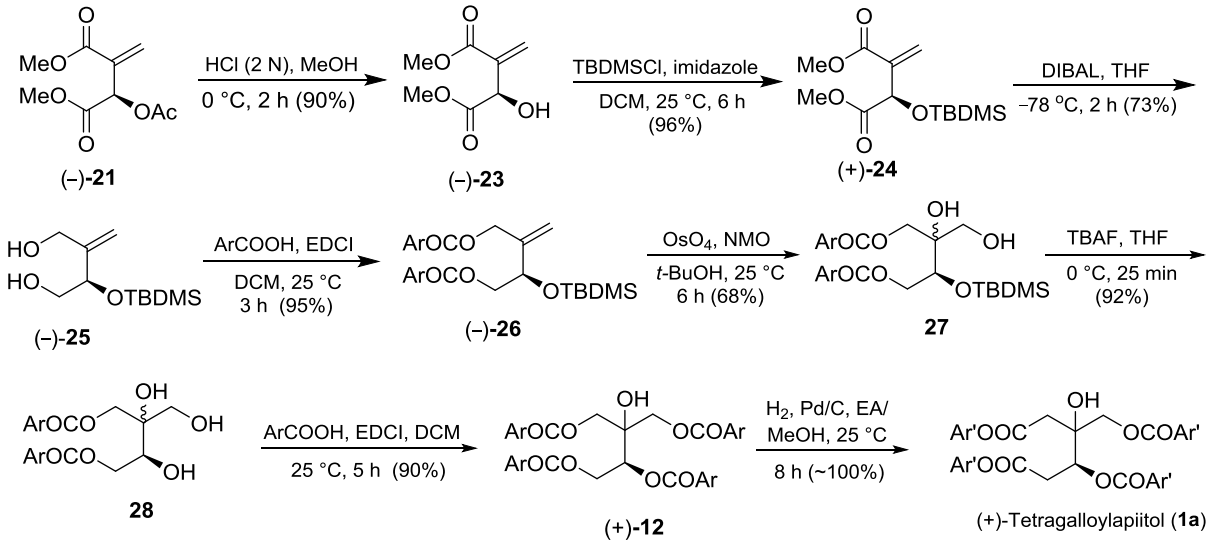
(±)-**21** (–)-**21** (+)-**23**

Entry	Enzyme	Temp/Time[a]	(–)-**21**: % Yield/*ee*
1	PPL	25 °C, 48 h	NR[b]
2	PPL	35 °C, 48 h	NR
3	CCL	25 °C, 48 h	NR
4	CCL	35 °C, 48 h	57/25
5	Amano PS	25 °C, 96 h	83/ND[c]
6	Amano PS	35 °C, 8 days	44/95[d]
7	Amano PS	50 °C, 84 h	42/97[d]

[a]Reactions were monitored by HPLC. [b]NR: no reaction. [c]ND: not determined. [d]Chiral HPLC, the (+)-**23** was obtained in 58% yield with only 53% *ee*.

The enantiomerically pure (–)-dimethyl 2-acetoxy-3-methylenesuccinate (**21**) on acid catalyzed methanolysis delivered the desired alcohol (–)-**23** in 90% yield with ~100% *ee* (by chiral HPLC), which on treatment with TBDMSCl gave the corresponding silyl ether (+)-**24** in 96% yield (Scheme 5). To avoid the foreseen difficulty of possible intramolecular cyclization upon dihydroxylation to form the γ-lactone, we first considered for the reduction of both the ester moieties in (+)-**24** to the corresponding primary alcohols. The DIBAL (6.00 equiv) reduction of diester (+)-**24** at –78 °C exclusively provided the expected diol (–)-**25** in 73% yield. At this stage we decided for the double gallyolation of diol (–)-**25** rather than the immediate dihydroxylation of the carbon–carbon double bond to form the corresponding tetrol for two obvious reasons viz. (i) to keep the polarity of our intermediate compounds under control for the convenient column chromatographic purifications and (ii) to avoid any plausible intramolecular shuffling of our protecting TBDMS group.[26-28] The *N*-ethyl *N*'-(3-dimethylpropyl)carbodiimide (EDCI) induced dehydrative double coupling of diol (–)-**25** with the triple benzyl protected gallic acid[29] furnished the required diester (–)-**26** in 95% yield. The osmium tetroxide induced dihydroxylation of carbon–carbon double bond in compound (–)-

26 in the presence of *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent yielded the diastereomeric mixture of desired diol **27** in 68% yield with ~3:2 ratio (by ^{1}H NMR). The TBAF-deprotection of silyl ether **27** provided the expected diastereomeric mixture of triol **28** in 92% yield. It is notable that the triol **28** contains free 1°, 2° and 3° alcohol units, but providentially we did not noticed any intramolecular acyl migration under our reaction conditions.[18] The second EDCI induced selective dehydrative double coupling of 1° and 2°



Scheme 5. Total Synthesis of (+)-1,3,4,5-Tetragalloylapiitol from (*R*)-Dimethyl 2-Hydroxy-3-methylenesuccinate

alcohol units in triol **28** with the tri-benzyl protected gallic acid yielded the required enantiomerically pure dodecabenzyl protected tetraester (+)-**12** in 90% yield. The final product **1a** is very polar in nature as it contains the free 12-phenolic groups and an alcoholic hydroxyl group. Hence we decided to check the enatiomeric purity of the penultimate step product (+)-**12**, alas all attempts to resolve the sample of (±)-**12** from our earlier racemic synthesis[8] on suitable chiral columns were futile. Finally, the hydrogenolysis using the palladium on charcoal was used for the global deprotection of benzyl groups in (+)-**12** to obtain the desired product (+)-**1a** in ~100% yield. The analytical and spectral data obtained for (+)-1,3,4,5-tetragalloylapiitol (**1a**) were in complete agreement with the reported data.[1,9] Starting from enantiomerically pure (–)-dimethyl 2-acetoxy-3-methylenesuccinate (**21**) the unnatural (+)-1,3,4,5-tetragalloylapiitol (**1a**) was obtained in 8-steps with 34% overall yield.

In summary, we have accomplished a straightforward chemoenzymatic total synthesis of the (+)-1,3,4,5-tetragalloylapiitol in very good overall yield. In the present synthesis an efficient

enzymatic resolution for the preparation of enantiomerically pure dimethyl acetoxysuccinate, DIBAL reduction of two different ester functions and very clean simultaneous deprotections of the twelve benzyl groups were the involved key steps. In our present synthesis the stepwise double gallyolation has demanded one step extra and was essential for the smooth handling of the intermediate compounds. We feel that the use of dimethyl itaconate/tartarate for the synthesis of a sugar moiety is noteworthy.

1B.2 Synthesis of Putrescine Bisamides Gigantamide A, Dasyclamide and Cucullamide

1B.2.1 Introduction

A large number of putrescine diamides have been isolated in the past two decades as bioactive natural products.[30-36] They exhibit broad range of biological activity's such as antileukemic, antiviral, antifungal, anti-inflammatory, antinociceptive, diuretic, CNS-depressant and insecticidal activities.[30-32,34-36] Moreover putrescine diamides are the potential biogenetic precursors of rocaglamides which possess strong insecticidal activity comparable to structurally altogether different azadirachtin.[37] They also have displayed pronounced antiproliferative activity against human cancer cells.[38] Recently the putrescine based natural products grandiamide D, (±)-gigantamide A and dasyclamide have been isolated from *Aglaia gigantea*[34] and very recently the dasyclamide and cucullamide have been isolated from *Amoora cucullata* (Figure 2).[35]

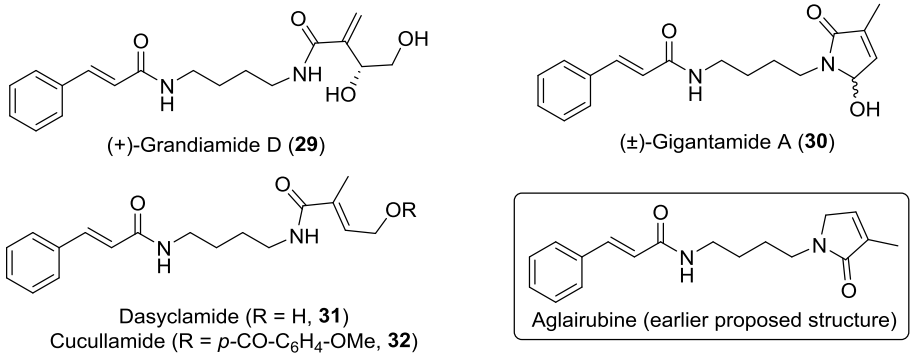
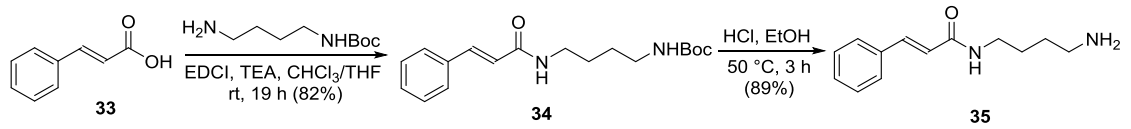


Figure 2. Naturally occurring bioactive putrescine bisamides.[34,35]

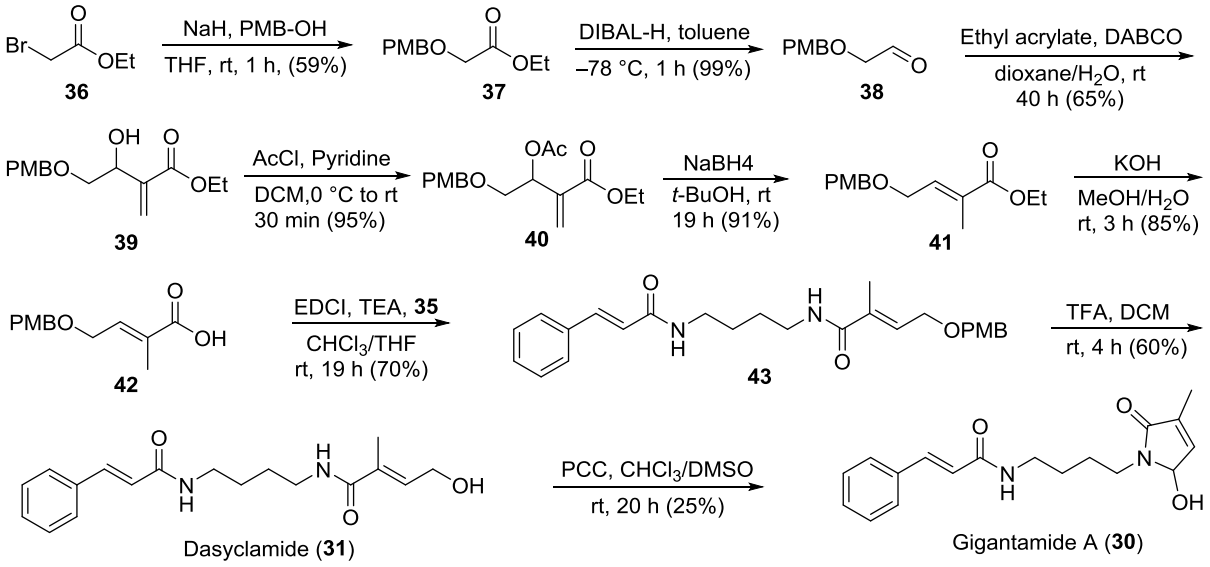
Dasyclamide, earlier known as aglairubine has also been previously isolated from several *Aglaia* species viz., *A. rubiginosa*, *A. australiensis*, *A. spectabilis*, *A. meridionalis*, *A. roburghiana* and *A. dasyclada.*[30,32-35] Its initial structural assignment was revised and re-established on the basis of extensive NMR studies and finally confirmed by using the X-ray crystallographic data.[30,33,34]

Recently Ilangovan & Saravanakumar reported synthesis of gigantamide A (**30**) and dasycla-



Scheme 6. Preparation of *N*-(4-Aminobutyl)cinnamamide

mide (**31**) by making use of a common synthetic intermediate prepared by the Baylis–Hillman reaction.[39] They synthesized putresine bisamide **35** starting form cinnamic acid in two steps (Scheme 6). Acid **42** was prepared from bromoester **36** utilizing Baylis–Hillman reaction as a key step. Putresine bisamide was then coupled with acid **42** to provide dasyclamide (**31**) with 12% overall yield in 8 steps. Dasyclamide on treatment with PCC in $CHCl_3$/DMSO provided gigantamide A (**30**) in one-step with 25% yield via oxidative intramolecular cyclization involving the *E*-isomer to *Z*-isomer transformation (Scheme 7).



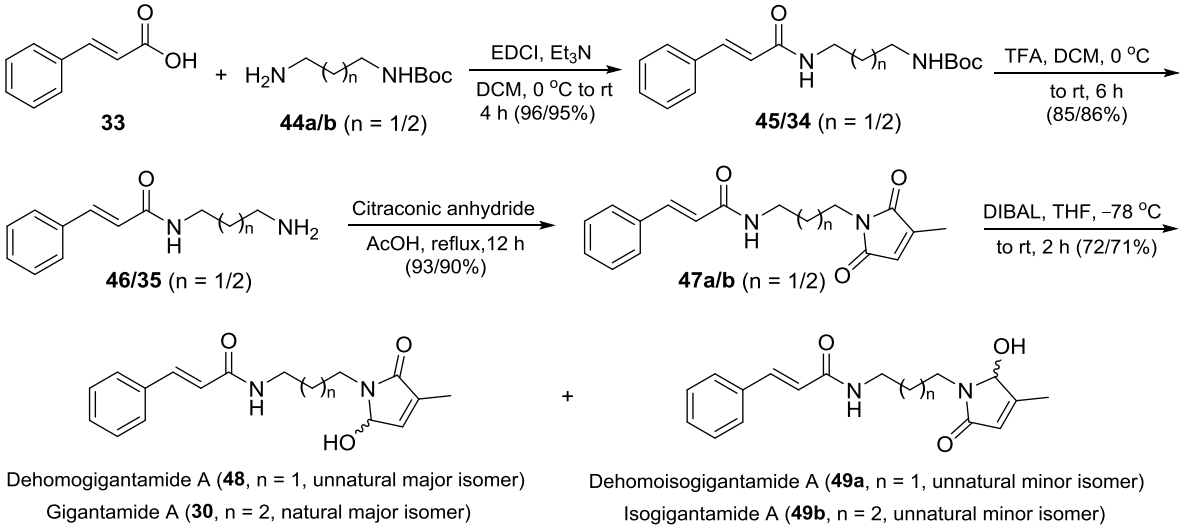
Scheme 7. Synthesis of Dasyclamide and Gigantamide A

1B.2.2 Present Work

On the basis of structural features and the plausible biogenetic pathway, we feel that the Nature might be designing them in a step wise fashion utilizing putrescine, cinnamic acid, citric acid (genesis of citraconic acid/4-hydroxytiglic acid) and the *p*-methoxybenzoic acid. In continuation of our studies on cyclic anhydrides/imides to bioactive natural product,[12-14,40,41] we herein report the concise synthesis of these linear natural products gigantamide A, dasyclamide, cucullamide and their unnatural dehomo-analogues (Schemes 8 & 9), however the synthesis of (+)-grandiamide D will be discussed in section 1B.3.

1B.2.2.1 Results and Discussions

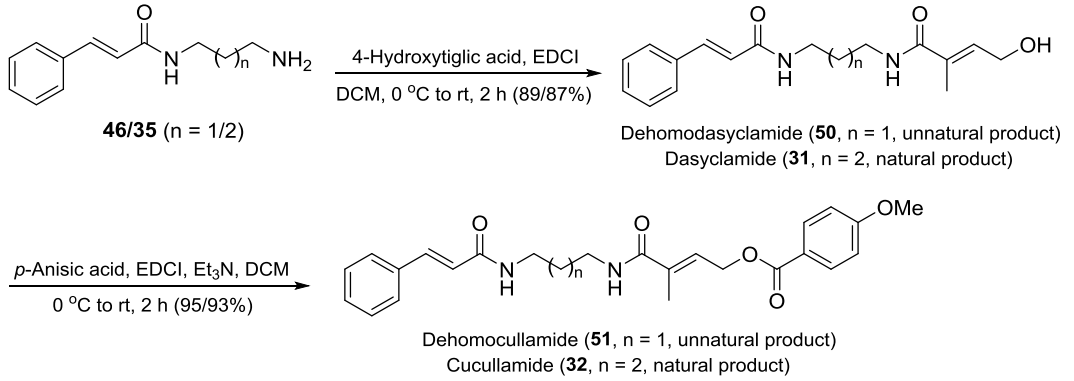
Synthesis of these linear target compounds demand an appropriate stepwise dehydrative coupling reactions of three/four essential building blocks. Maleimides obtained from the putrescine type diamine are prone for further intramolecular dehydrative cyclizations. Hence alternatively we planned synthesis of target compounds from the coupling reaction of cinnamic acid and mono-Boc-protected methylenediamines. EDCI-induced dehydrative coupling reaction of cinnamic acid (**33**) and amine **44a**/**b** gave the desired amide **45**/**34** in 96/95% yield (Scheme 8). The Boc-group in compound **45**/**34** was deprotected by using trifluoroacetic acid at room temperature to obtain the corresponding free amine **46**/**35** in 85/86% yield. Reaction of free amine **46**/**35** with an equivalent amount of citraconic anhydride in refluxing glacial acetic acid directly furnished the desired citraconimide **47a**/**b** in 93/90% yield via the dehydrative intramolecular cyclization of the corresponding intermediate



Scheme 8. Synthesis of Dehomogigantamide A (**48**), Gigantamide A (**30**), Dehomoisogigantamide A (**49a**) and Isogigantamide A (**49b**)

regioisomeric mixture of amic acids. The chemoselective $NaBH_4$ reduction of unsymmetrical citraconimide **47b** in methanol at 0 °C furnished a mixture of gigantamide A (**30**, natural) and a new compound isogigantamide A (**49b**, unnatural) in 91% yield but in desired:undesired = 15:85 ratio (by ^{1}H NMR). In the present reduction process the boron atom from $NaBH_4$ initially forms a complex with the unhindered maleimide carbonyl group and intramolecularly delivers the hydride to the hindered carbonyl group to form isogigantamide A (**49b**) as the major product. However the Luche reduction ($CeCl_3$/$NaBH_4$) of imide **47b** in methanol at 0 °C was partially regioselective and furnished the desired natural product as a major isomer (**30**:**49b** =75:25) in 93% yield. Under Luche reduction conditions[42] the unhindered maleimide

carbonyl group complexes with Ce^{3+} cation and undergoes relatively faster reduction reaction because of an enhancement in reactivity. Finally the DIBAL reduction reaction of imide **47b** in THF at lower temperature was highly regioselective for steric reasons and as expected majorly reduced an unhindered imide carbonyl group to form a mixture of products **30** and **49b** in 95:5 ratio with 71% yield. The above formed mixture of isomeric products **30** and **49b** was quantitatively separated by silica gel column chromatography to respectively obtain the isogigantamide A (**49b**) in 3% yield and the gigantamide A (**30**) in 67% yield. As expected the vinylic *β*-proton in the lactamol unit of gigantamide A (**30**) appeared at down field (*δ* 6.62) in comparison with the vinylic *α*-proton in the lactamol unit of isogigantamide A (**49b**) (*δ* 5.72) and confirmed the assigned regioisomeric structure of a natural product. The lactamols like gigantamide A exhibit ring–chain tautomerism and hence exist in the racemic form.[41,43,44] Similarly the DIBAL reduction reaction of imide **47a** furnished a mixture of products **48** and **49a** in 95:5 ratio with 72% yield. Theoretically, further reduction of masked



Scheme 9. Synthesis of Dehomodasyclamide (**51a**), Dasyclamide (**31**) Dehomocucullamide (**50**) and Cucullamide (**31**)

aldehyde unit in gigantamide A (**30**) to the corresponding *Z*-allylic alcohol followed by *Z*- to *E*- carbon–carbon double bond isomerization would constitute a biogenetic pathway to the yet another natural product dasyclamide (**31**). However to keep our synthesis concise and practical, we performed the EDCI induced direct dehydrative coupling reaction of amine **35** with a known 4-hydroxytiglic acid[45] and obtained the desired natural product **31** in 87% yield (Scheme 9). Finally, yet another similar dehydrative coupling reaction of an allylic alcohol unit in the natural product **31** with a *p*-methoxybenzoic acid was used to complete the synthesis of naturally occurring cucullamide (**32**) in 93% yield. The analytical and spectral data obtained for all three natural products gigantamide A (**30**) dasyclamide (**31**) and cucullamide (**32**) were in complete agreement with the reported data[34,35] and were

respectively obtained in 4/3/4 steps with 49/71/66% overall yields. The repetition of above mentioned sequence of reactions with amine **46** provided the corresponding unnatural products **50** and **51** in similar yields.

In summary, we have accomplished a concise and efficient first total synthesis of recently isolated bioactive natural products gigantamide A, dasyclamide, cucullamide and their unnatural dehomo-analogues. The involved selective dehydrative coupling reactions and a remarkable regioselective reduction of citraconimide unit were the key features in the described synthesis. Our present diversity-oriented practical approach to these natural/unnatural diamides will be useful to design several focused mini-libraries by appropriately varying all the three/four basic constituents and will lead to essential biological screening studies.

1B.3 Chemoenzymatic Total Synthesis of (+)-Grandiamide D, (+)-Artabotriolcaffeate and Related Natural Products

1B.3.1 Introduction

Nature derives large number of sugar monomers which rejoin with other natural products to form broad range of structurally interesting and biologically important secondary metabolites; in addition to the formation of prime essential complex carbohydrates.[46-50] More specifically the five carbon bearing sugar (–)-artabotriol has been isolated from *Artabostrys hexapetalus*.[51]

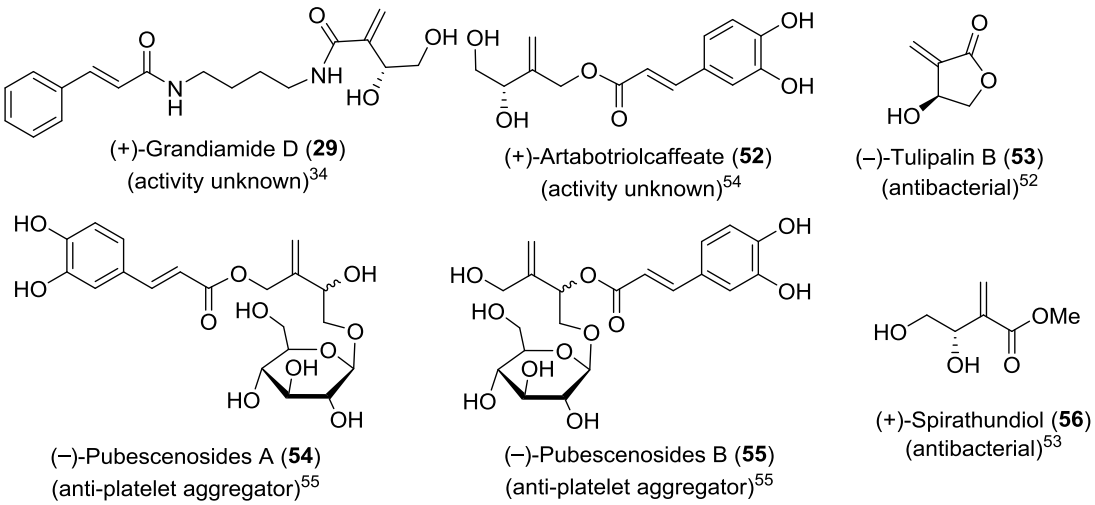
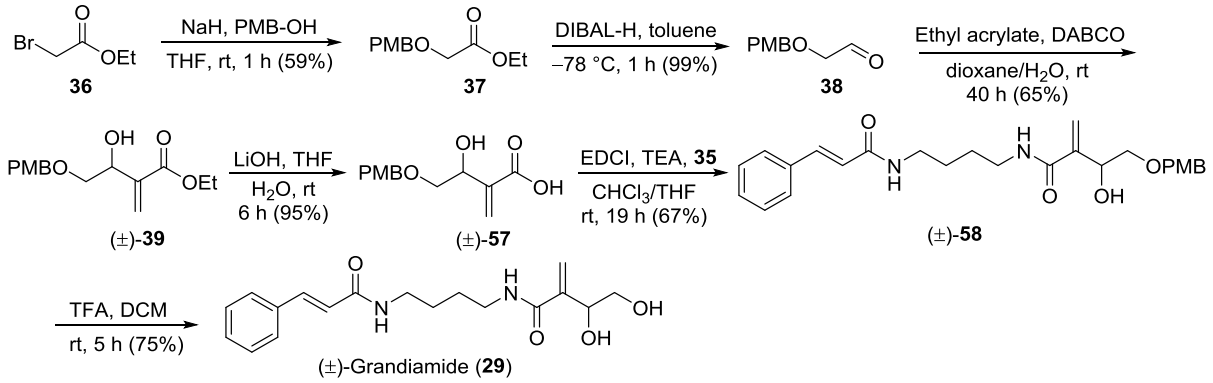


Figure 3. Artabotriol derived bioactive natural products.

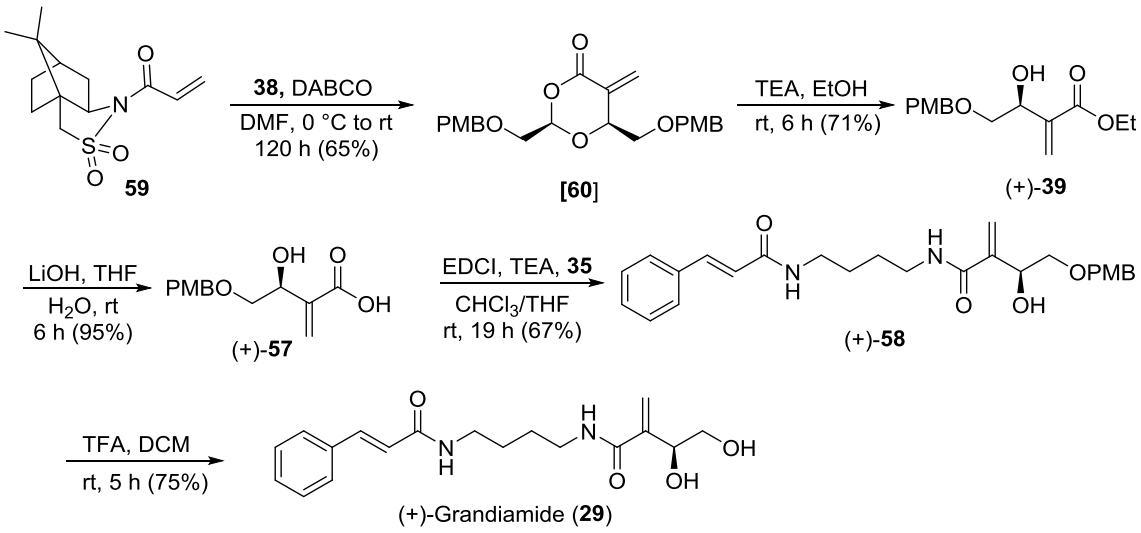
Recently, the (+)-artabotriol derived natural product (+)-grandiamide D (**29**) has been isolated from *Aglaia gigantean*;[34] (–)-tulipalin B (**53**) and (+)-spirathundiol (**56**) have been isolated from *Tulipa gesneriana* and *Spiraea thunbergii* Sieb. respectively;[52,53] whereas the (+)-

artabotriolcaffeate (**52**), (–)-pubescenoside A (**54**, anti-platelet aggregation) and (–)-pubescenoside B (**55**, anti-platelet aggregation) have been isolated from *Ilex pubescens* (Figure 3).[54,55] The absolute configuration of (+)-artabotriolcaffeate (**52**) has been established by using modified Mosher's method.[54] The stereochemical assignment of artabotriolcaffeate part of (–)-pubescenoside A and B has not been fixed yet; however on the basis of their genesis they are expected to be the same. First total synthesis of (±)-grandiamide D (**29**) and (+)-grandiamide D (**29**) have been recently reported by Ilangovan & Saravanakumar.[39] (±)-



Scheme 10. First Total Synthesis of (±)-Grandiamide D

Grandiamide D was synthesized starting from ethyl bromoacetate (**36**) involving Baylis-Hillman reaction as a key step, synthesis comprising of six steps with 18% overall yield (Scheme 10).

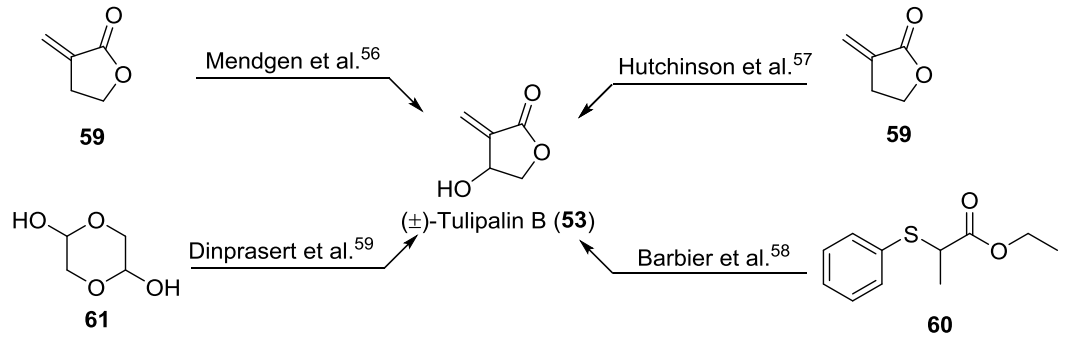


Scheme 11. First Total Synthesis of (+)-Grandiamide D

After completing the recemic synthesis of grandiamide D they also synthesized (+)-grandiamide D using asymmetric Baylis–Hillman reaction of acryloyl sultam **59** and aldehyde

38 as a key step. Chiral HPLC analysis of (+)-**39** showed that the *ee* was 99.5% in favour of the (+)-isomer while enantiomeric purity of (+)-grandiamide D (**29**) was found to be 98.6%. Synthesis was completed in five steps with 22% overall yield and they revised the stereochemistry of (+)-grandiamide D from "*R*" to "*S*" (Scheme 11).

Few synthesis of (±)-tulipalin B (**53**) have been reported in literature (Scheme 12). Mendgen et al. reported synthesis of (±)-tulipalin B (**53**) using selenium dioxide mediated allylic oxidation of tulipalin A (**59**) in one step with 84% yield.[56] Hutchinson also synthesized (±)-tulipalin B (**53**) using selenium dioxide mediated allylic oxidation tulipalin A (**59**) in one step with 43% yield.[57] Barbier & Benezra reported the synthesis of (±)-tulipalin B (**53**) from ethyl 2-(phenylthio)propionate (**60**) and α-acetoxyacetaldehyde in six steps.[58] Dinaprasert et al.

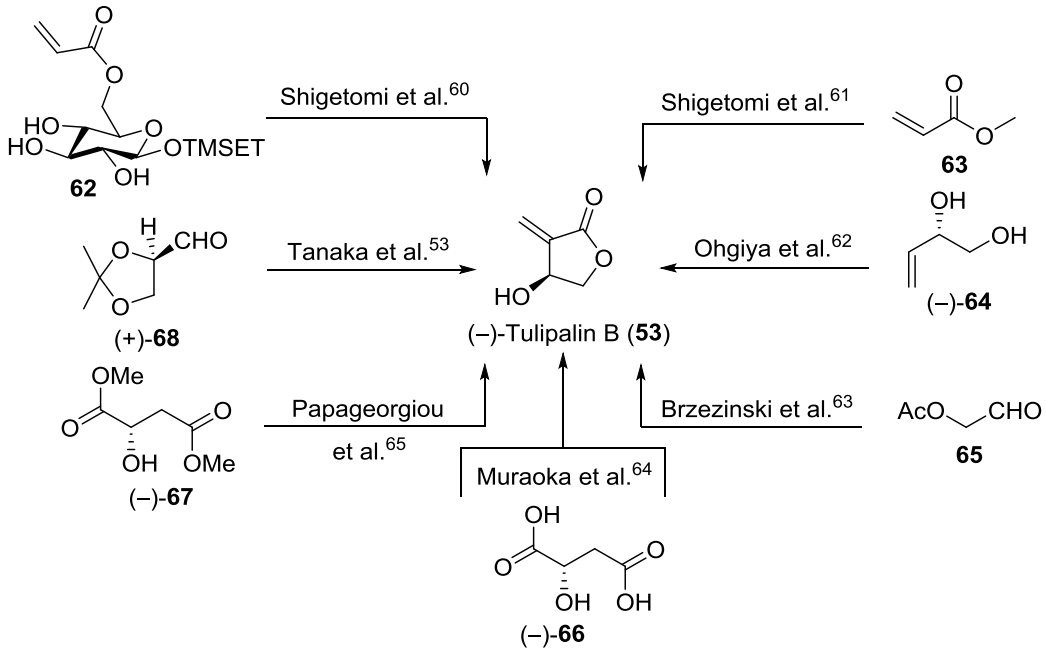


Scheme 12. Various Approaches for Synthesis of (±)-Tulipalin B

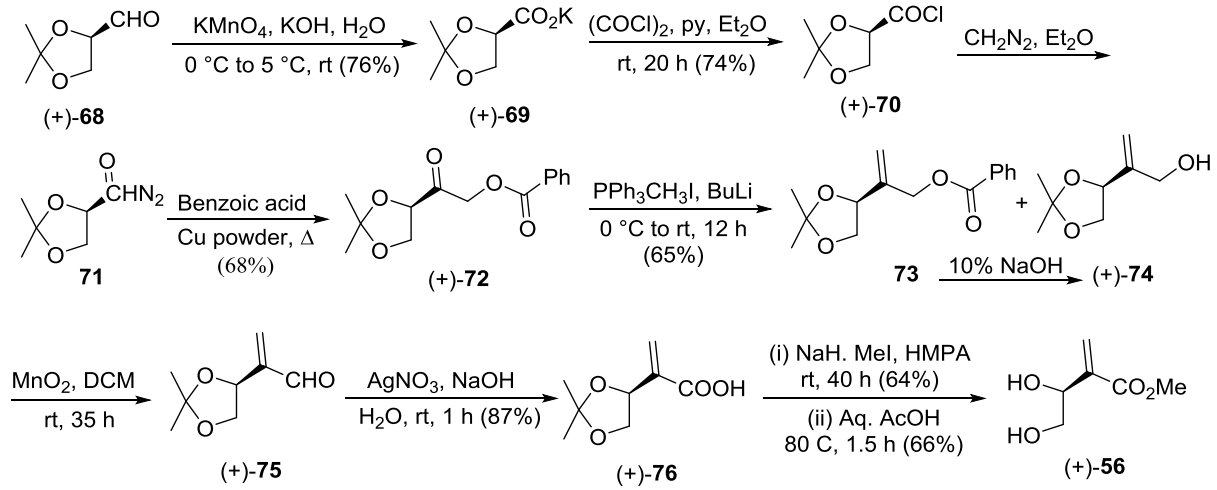
utilized glycolaldehyde dimer **61** as a starting material in two-step synthesis of (±)-tulipalin B (**53**) with 43% overall yield.[59]

A few literature reports are known for synthesis of (–)-tulipalin B (**53**) in very good yields (Scheme 13). Shigetomi et al. reported synthesis of (–)-tulipalin B (**53**) from 2-trimethylsilylethyl (TMSET) glucoside derivative **62**. Synthesis involves Baylis–Hillman reaction between 2-(*tert*-butyldimethylsilyloxy)-acetaldehyde and 2-trimethylsilylethyl (TMSET) glucoside derivative **62** to provide diastereomeric mixture of the Baylis–Hillman adduct, which was separated using a chiral HPLC column (CHIRALPAK® IA. DAICEL Co. Ltd, Japan) followed by deprotection using trifluro acetic acid. Overall yield of (–)-tulipalin B (**53**) was 19% in four steps.[60] Second synthesis reported by Shigetomi et al. also involves separation of diastereomeric mixture of the Baylis–Hillman adduct by chiral HPLC column with 15% overall yield in three steps.[61] Ohgiya & Nishiyama accomplished the synthesis of (–)-tulipalin B (**53**) from diol (–)-**64** involving regioselective HBr elimination as a key step.[62] Brzezinski et al. have demonstrated that Oppolzer's sultam can be used in the Baylis-Hillman

reaction to obtain products of very high enantiomeric purity. This methodology was used for synthesis of building blocks in organic synthesis, precursors to anti aldol adducts and for the total synthesis of (–)-tulipalin B (**53**) in three steps with 12% overall yield.[63] Muraoka et al. reported chiral pool synthesis of natural (–)-tulipalin B (**53**) starting from L-malic acid (–)-



Scheme 13. Various Approaches for Synthesis of (–)-Tulipalin B (**66**).[64] Papageorgiou & Benezra used Pig liver esterase (PLE) to hydrolyze the ester function –*α* to the hydroxyl group in dimethyl malate (–)-(**67**). The above regiospecific reaction was used to synthesize (+)- and (–)-tulipalin B.[65] Tanaka & Yamashita reported chiral pool synthesis of (–)-tulipalin B (**53**) starting from 2,3-*O*-isopropylidene-D-glyceraldehyde (+)-



Scheme 14. Synthesis of (+)-Spirathundiol

(**68**) in eight steps.[53]

Tanaka & Yamashita also reported chiral pool synthesis of (+)-spirathundiol (**56**) starting from 2,3-*O*-isopropylidene-D-glyceraldehyde (+)-**68** in eight steps with 9% overall yield (Scheme 14).[53]

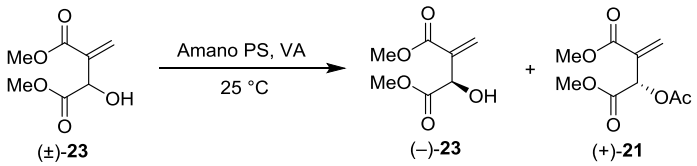
1B.3.2 Present Work

Synthesis of artabotriol and artabotriolcaffeate, pubescenoside A and pubescenoside B are still awaited. Simple retrosynthetic analysis revealed that nature constructs them starting from enantiomerically pure artabotriol in a stepwise fashion via an appropriate sequence of coupling reactions utilizing different combinations of the naturally occurring putrescine, cinnamic acid, caffeaic acid and D-glucose. The science of collective total synthesis of bioactive natural products is very important for structure activity relationship studies from lead optimization and drug discovery point of view.[66-73] In continuation with our studies on both cyclic anhydrides and derivatives to bioactive natural products[40,74-77] and an efficient enzymatic resolutions,[18-22,66,78] we herein report a facile chemoenzymatic synthesis of the (+)-artabotriol (**77**) and its application as a fundamental building block in collective formal/total synthesis of six other enantiomerically pure natural products (Schemes 15–17).

1B.3.2.1 Results and Discussions

A careful analysis of (+)/(–)-artabotriol structure specified that the (±)-dimethyl 2-hydroxy-3-methylenesuccinnate (**23**)[78] would be a potential precursor for their synthesis via enzymatic resolution followed by the reduction route (Scheme 15). Accordingly we systematically

Table 2. Lipase Catalyzed Resolution of (±)-Dimethyl 2-Hydroxy-3-methylenesuccinate

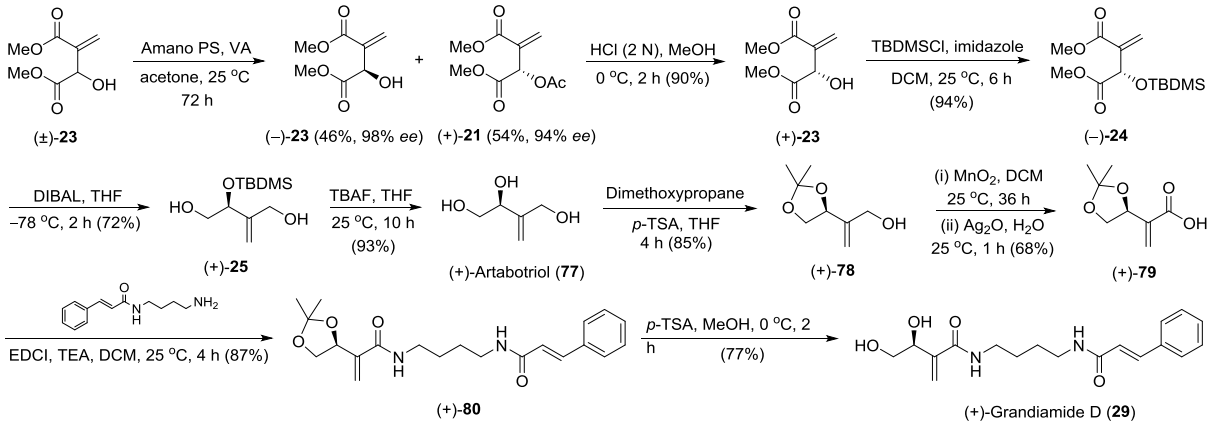


(±)-**23** (–)-**23** (+)-**21**

Entry	Solvent	Temp. (time)[a]	(–)-**23:** % Yield (*ee*)[b]	(+)-**21:** % Yield (*ee*)[b]
1	Benzene-PE	25 °C (24 h)	74 (ND)[c]	24 (ND)[c]
2	Benzene-PE	25 °C (48 h)	40 (72)	60 (51)
3	Acetone	25 °C (48 h)	72 (ND)[c]	28 (ND)[c]
4	Acetone	25 °C (72 h)	46 (98)	54 (94)
5	Acetone	25 °C (80 h)	44 (100)	56 (92)

[a]Reactions were monitored by HPLC; [b]Chiral HPLC; [c]ND: not determined.

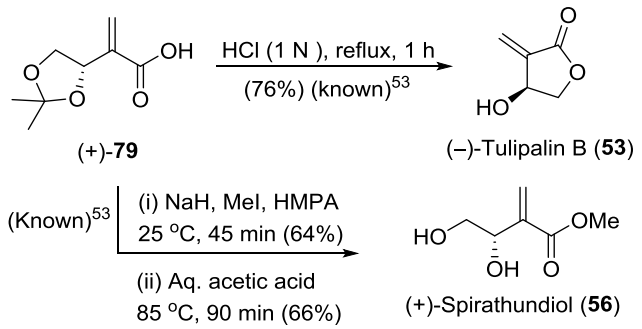
studied the Amano PS catalyzed stereoselective acylation of (±)-alcohol **23** using vinyl acetate (VA) as an acyl donor and obtained the enantiomerically pure (–)-alcohol **23** in 46% yield (98% *ee*, by chiral HPLC) and the corresponding (+)-acetate **21** in 54% yield (94% *ee*, by chiral HPLC) (Table 2). The obtained stereochemical outcome was further confirmed by



Scheme 15. Chemoenzymatic Total Synthesis of Putrescine Bisamide (+)-Grandiamide D

comparison with the reported analytical and spectral data for both the compounds (–)-**23** and (+)-**21**.[78] Acid catalyzed hydrolysis of (+)-acetate **21** to the corresponding (+)-alcohol **23** followed by TBDPS-protection provided (–)-silyl ether **24** in 85% yield over two steps. The DIBAL reduction of (–)-diester **24** to the corresponding (+)-diol **25** followed by TBAF induced desilylation supplied the desired enantiomerically pure (+)-artabotriol (**77**) in 67% yield over two steps. The analytical and spectral data obtained for synthetic (+)-artabotriol (**77**) was in complete agreement with the reported data for natural product (–)-artabotriol (**77**)[2] and the chemoenzymatic first synthesis of (+)-artabotriol (**77**) was accomplished in five steps with 31% overall yield. The selective protection of vicinal-diol moiety in compound (+)-**77** resulted in (+)-ketal **78** with 85% yield. The MnO_2 oxidation of (+)-allylic alcohol **78** to the corresponding *α*,*β*-unsaturated aldehyde followed by an immediate silver oxide induced oxidation delivered the known *α*,*β*-unsaturated (+)-carboxylic acid **79** in 68% yield. In the above mentioned reaction the formed intermediate *α*,*β*-unsaturated aldehyde was unstable and hence it was directly subjected to the next oxidation without any purification and characterization to obtain the corresponding (+)-carboxylic acid **79**. The (+)-acid **79** on EDCI induced dehydrative coupling reaction with the known requisite putrescine amide[79] formed the corresponding (+)-putrescine diamide **80** in 87% yield. Finally acid catalyzed deprotection of a ketal moiety in (+)-diamide **80** furnished the desired natural product (+)-grandiamide D (**29**) in 77% yield. The analytical and spectral data obtained for synthetic product was in

complete agreement with the reported data for natural product[34,39] and the chemoenzymatic synthesis of (+)-grandiamide D (2**9**) was accomplished in nine steps with 12% overall yield. As depicted in scheme 16; the acid catalyzed ketal deprotection in (+)-acid **79** followed by in situ regioselective dehydrative γ-lactonization to form the (–)-tulipalin B (**53**) in one step with

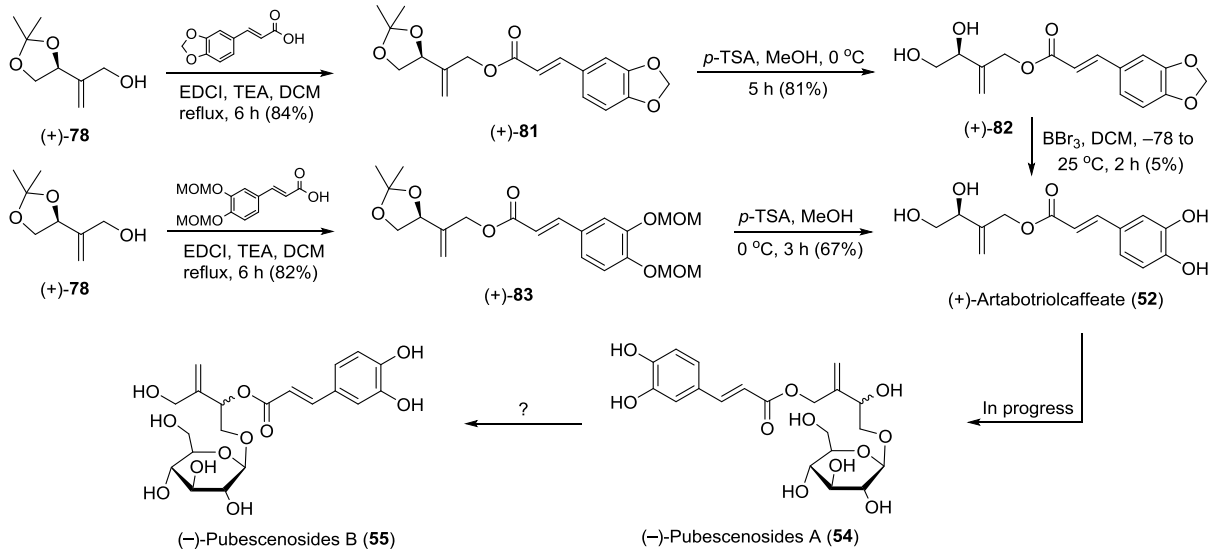


Scheme 16. Formal Synthesis of (–)-Tulipalin B and (+)-Spirathundiol

76% yield and the preparation of ester of (+)-acid **79** followed by the controlled ketal deprotection to form the (+)-spirathundiol (**56**) in two steps with 42% overall yield are known in the literature.[53]

In the next part of studies, it was envisioned to synthesize three important natural products (+)-artabotriolcaffeate, (–)-pubescenoside A and (–)-pubescenoside B starting from the (+)-artabotriol (**77**) (Scheme 17). Accordingly, the EDCI persuaded dehydrative coupling of (+)-allylic alcohol **78** with the methylenedioxy-protected caffeaic acid provided the corresponding (+)-ester 8**1** in 84% yield. Acid catalyzed deprotection of ketal moiety in compound (+)-**81** resulted into the essential product (+)-**82** in 81% yield. The final step BBr_3 promoted deprotection of methylenedioxy bridge in product (+)-**82** was not very clean and the desired natural product (+)-artabotriolcaffeate (**52**) was obtained only in ~5% yield. Plausibly the free vicinal-diol system in compound (+)-**82**/(+)-**52** was responsible for the noticed excessive decomposition. However the alternatively performed EDCI prompted dehydrative coupling of (+)-allylic alcohol **78** with the double –OMOM protected caffeaic acid delivered the corresponding (+)-ester **83** in 82% yield. The (+)-ester **83** on treatment with *p*-TSA in methanol directly furnished the desired natural product (+)-artabotriolcaffeate (**52**) in 67% yield. In the above specified reaction, fortunately both the deprotection of ketal moiety and the two –OMOM groups took place in one pot and the formed product with four free hydroxyl groups was quite stable under the set of our reaction conditions. The analytical and spectral data obtained for synthetic product was in complete agreement with the reported data for natural product[54] and the chemoenzymatic synthesis of (+)-artabotriolcaffeate (**52**) was

accomplished in eight steps with 14% overall yield. The systematic studies on direct regioselective coupling reaction of primary alcohol unit in (+)-artabotriolcaffeate (**52**) with D-glucose to obtain the natural product (–)-pubescenoside A (**54**) are in active progress. The enzyme catalyzed intramolecular shuffling on acyl functions has been reported earlier from



Scheme 17. Chemoenzymatic Total Synthesis (+)-Artabotriolcaffeate, (–)-Pubescenoside A and (–)-Pubescenoside B

our research group[21,22] and would hopefully deliver the yet another natural product (–)-pubescenoside B (**55**).

In summary, starting from itaconic anhydride we have completed the chemoenzymatic first synthesis of (+)-artabotriol sugar and used it as a potential starting material to accomplish the collective total synthesis of several enantiomerically pure bioactive natural products employing a chiral pool strategy. Total synthesis of those multifunctional natural products is noteworthy from their stability point of view. Application of enzymatic resolution pathway also provides an access to antipodes of all the synthesized natural products. The present approach on collective total synthesis of enantiomerically pure natural and unnatural products will be highly useful for the rational design of focused mini-libraries of their analogues and congeners for SAR-studies.

1B.4 Summary

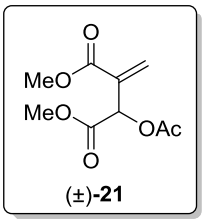
The importance and several utilities of lipases have been disscussed in this chapter. We have also utilized these remarkable natural catalysts for further important applications in organic synthesis. We have designed practical chemoenzymatic route to the potentially useful chiral

building blocks, dimethyl 2-acetoxy-3-methylenesuccinate/dimethyl 2-hydroxy-3-methylenesuccinate with excellent enatiomeric purity. We have also demonstrated use of these chiral building blocks in chemoenzymatic formal/total synthesis of enantiomerically pure (+)-1,3,4,5-tetragalloylapiitol, (+)-artabotriol, (+)-grandiamide D, (–)-tulipalin B, (+)-spirathundiol and (+)-artabotriolcaffeate. In the chemoenzymatic synthesis of (+)-1,3,4,5-tetragalloylapiitol, an efficient enzymatic resolution for the preparation of enantiomerically pure dimethyl acetoxysuccinate and DIBAL reduction of two different ester functions were the involved key steps. Chemoenzymatic synthesis of (+)-grandiamide D, (–)-tulipalin B, (+)-spirathundiol and (+)-artabotriolcaffeate have been described via the advanced level common precursor (+)-artabotriol with high enantiomeric purity, selective di-ester to diol reduction and requisite dehydrative coupling reactions. First synthesis of bioactive natural products gigantamide A, dasyclamide, and cucullamide have been demonstrated starting from putrescine and the requisite carboxylic acids in very good overall yields using an appropriate sequence of dehydrative coupling reactions with regioselective diisobutylaluminum hydride reduction of an unhindered carbonyl group in citraconimide as a key step. In summary, we have successfully utilized lipases for the resolution of advanced intermediates essential for total synthesis of bioactive natural products. Further research on lipases as catalysts in organic synthesis is our goal and efforts are in progress towards it. Enzymes have become a very important tool in academic and industrial research worldwide. This promising trend assures a very bright future to enzymology.

1B.5 Experimental Section

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR spectrometer, 400 MHz NMR spectrometer, 500 MHz NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz) and 500 NMR spectrometer (125 MHz). Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 mesh). Commercially available TBDMCl, DIBAL, EDCI, DMAP, aqueous solution of NMO (60%), OsO_4, TBAF solution in THF (1.0 M), dimethoxypropane, Pd on charcoal (10 wt%), citraconic anhydride, cinnamic acid, Boc-protected diamines, $CeCl_3$ and *p*-methoxybenzoic acid were used. Amano PS enzyme form Amano Enzyme Japan was used.

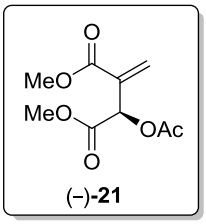
(±)-Dimethyl 2-acetoxy-3-methylenesuccinate (21).



(±)-**21**

To a stirred solution of dimethyl itaconate (2.00 g, 12.66 mmol) in glacial acetic acid (25 mL) was added SeO_2 (1.55 g, 13.92 mmol) and the reaction mixture was refluxed for 6 h. The deposited selenium metal was filtered off and the residue was washed with acetic acid (5 mL). The filtrate was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:11) as an eluent afforded pure product (±)-**21** as colorless oil (1.01 g, 37%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.00 (s, 1H), 6.02 (s, 1H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 52.3, 52.7, 70.2, 130.7, 134.6, 164.8, 168.3, 169.6; ESIMS (*m*/*z*) 217 $[M+H]^+$, 239 $[M+Na]^+$, 255 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1755, 1747, 1732, 1638 cm^{-1}.

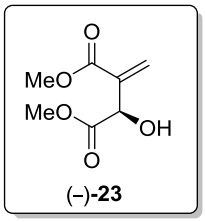
(*R*)-Dimethyl 2-acetoxy-3-methylenesuccinate (21).



(–)-**21**

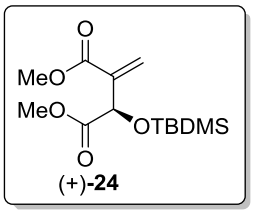
To a stirred solution of acetate (±)-**21** (1.00 g, 4.63 mmol) in a mixture of petroleum ether and benzene (15 mL, 1:2) were successively added the phosphate buffer (pH 7, 10 mL) and enzyme Amano PS (100 mg). The resulting reaction mixture was stirred at 50 °C for 84 h, with monitoring the reaction progress by chiral HPLC. The reaction mixture was filtered through Celite bed and washed with ethyl acetate (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:11) as an eluent afforded pure product (–)-**21** as colorless oil (421 mg, 42% yield, 97% *ee*). $[\alpha]^{25}_D = -49.9$ (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.00 (s, 1H), 6.02 (s, 1H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 52.3, 52.7, 70.2, 130.7, 134.6, 164.8, 168.3, 169.6; ESIMS (*m*/*z*) 217 $[M+H]^+$, 239 $[M+Na]^+$, 255 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1755, 1747, 1732, 1638 cm^{-1}. In the above mentioned enzymatic resolution the hydrolyzed opposite isomer (+)-**23** was obtained in 58% yield with only 53% *ee*. [*HPLC conditions:* column: Kromasil 5-CelluCoat (250 x 4.6 mm), wavelength: 220 nm, flow rate: 0.5 mL/min, retention time: 19.8 min (+)-isomer, 25.2 min (–)-isomer.]

(*R*)-Dimethyl 2-hydroxy-3-methylenesuccinate (23).



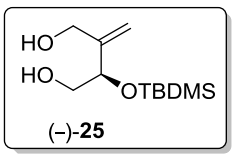
To a stirred solution of acetate (–)-**21** (400 mg, 1.85 mmol) in methanol (10 mL) at 0 °C was added 2 N HCl (10 mL) and the reaction mixture was further stirred for 2 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:3) as an eluent afforded pure product (–)-**23** as colorless oil (290 mg, 90%). $[\alpha]^{25}_D$ = –19.7 (*c* 0.68, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.58 (br s, 1H), 3.79 (s, 6H), 4.88 (br s, 1H), 5.97 (s, 1H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.1, 53.0, 71.2, 129.2, 137.8, 165.6, 172.7; ESIMS (*m*/*z*) 175 $[M+H]^+$, 197 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3503, 1746, 1726, 1636 cm^{-1}.

(*R*)-Dimethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-methylenesuccinate (24).



To a stirred solution of alcohol (–)-**23** (250 mg, 1.44 mmol) in dichloromethane (10 mL) at 0 °C were added imidazole (108 mg, 1.58 mmol) and TBDMSCl (239 mg, 1.58 mmol). The reaction mixture was allowed to attain room temperature and further stirred for 6 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:19) as an eluent afforded pure product (+)-**24** as colorless oil (397 mg, 96%). $[\alpha]^{25}_D$ = + 23.9 (*c* 0.60, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 3.72 (s, 3H), 3.78 (s, 3H), 5.08 (dd, *J* = 2 and 2 Hz, 1H), 6.07 (dd, *J* = 2 and 2 Hz, 1H), 6.38 (dd, *J* = 2 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ –5.4, –5.2, 18.3, 25.6, 52.0, 52.3, 70.9, 126.4, 138.7, 165.9, 171.2; ESIMS (*m*/*z*) 289 $[M+H]^+$, 311 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1759, 1736, 1686 cm^{-1}.

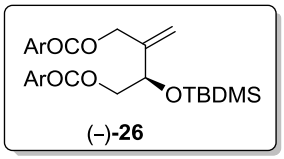
(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylenebutane-1,4-diol (25).



To a stirred solution of diester (+)-**24** (350 mg, 1.22 mmol) in THF (10 mL) at ⁻78 °C was dropwise added DIBAL solution in toluene (1 M, 7.30 mL, 7.30 mmol) and the reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated NH_4Cl solution and then concentrated

in vacuo. The obtained residue was diluted with ethyl acetate (20 mL) and washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:3) as an eluent afforded pure product (–)-**25** as colorless oil (206 mg, 73%). $[\alpha]^{25}_D$ = –7.0 (*c* 0.16, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 2.46 (br s, 2H), 3.54–3.70 (m, 2H), 4.10 (d, *J* = 12 Hz, 1H), 4.21 (d, *J* = 12 Hz, 1H), 4.34 (t, *J* = 6 Hz, 1H), 5.18 (br s, 1H), 5.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ –5.1, –4.8, 18.1, 25.7, 63.1, 66.5, 75.2, 114.2, 148.1; ESIMS (*m*/*z*) 255 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{24}O_3NaSi$ 255.1392, found 255.1383; IR ($CHCl_3$) ν_{max} 3456, 1652 cm^{-1}.

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylenebutane-1,4-diyl bis(3,4,5-tris(benzyloxy) benzoate) (26).



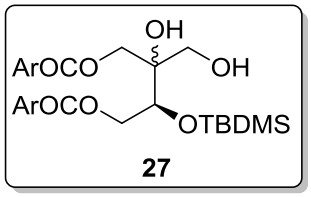
(–)-**26**

To a stirred solution of mixture of diol (–)-**25** (150 mg, 0.65 mmol), 3,4,5-tris(benzyloxy)benzoic acid (tribenzylgallic acid) (626 mg, 1.42 mmol) and catalytic amount of DMAP in dichloromethane (10 mL) at room temperature was dropwise added a solution of EDCI (371 mg, 1.94 mmol) in dichloromethane (3 mL). The reaction mixture was further stirred for 3 h and then quenched with water (10 mL). The reaction mixture was extracted with dichloromethane (2 × 25 mL) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:11) as an eluent afforded pure product (–)-**26** as a white solid (662 mg, 95%). Mp 59–61 °C; $[\alpha]^{25}_D$ = –4.2 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 4.38 (d, *J* = 6 Hz, 2H), 4.62 (t, *J* = 6 Hz, 1H), 4.80–5.00 (m, 2H), 5.05 (s, 4H), 5.09 (s, 8H), 5.34 (s, 1H), 5.40 (s, 1H), 7.15–7.45 (m, 34H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ –4.9, –4.8, 18.1, 25.7, 64.4, 68.2, 71.04, 71.06, 72.3, 75.1, 108.9, 117.1, 125.0, 127.46, 127.49, 127.86, 127.94, 128.1, 128.4, 128.5, 136.56, 136.62, 137.4, 142.36, 142.41, 143.4, 152.49, 152.53, 165.7, 165.9; ESIMS (*m*/*z*) 1100 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1716, 1590 cm^{-1}; Anal. Calcd for $C_{67}H_{68}O_{11}Si$: C, 74.70; H, 6.36. Found: C, 74.37; H, 5.84.

3-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-2-(hydroxymethyl)butane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) [diastereomeric mixture (3:2), **27].**

To a stirred solution of diester (–)-**26** (600 mg, 0.56 mmol) and aqueous solution of NMO (60%, 3 mL) in *t*-butanol (10 mL) at room temperature was added OsO_4 solution in *t*-butanol

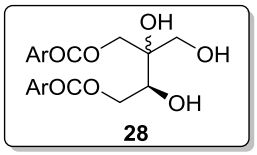
(0.22 mL, 1 M, 0.22 mmol) and the reaction mixture was further stirred for 6 h. The reaction was quenched with saturated solution of sodium sulfite and concentrated in vacuo. The



27

obtained residue was diluted with ethyl acetate (25 mL) and washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:2) as an eluent afforded product **27** as colorless oil (421 mg, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07–0.13 (m, 12H), 0.92 (s, 18H), 2.42 (br s, 4H), 3.65–3.83 (m, 4H), 4.05–4.10 (m, 2H), 4.35–4.70 (m, 8H), 5.02–5.15 (m, 24H), 7.20–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ –5.6, 18.2, 25.8, 64.1, 64.3, 64.9, 65.0, 65.4, 65.9, 71.06, 71.12, 72.5, 74.0, 74.3, 75.1, 108.96, 109.01, 109.07, 109.10, 124.3, 124.6, 124.68, 124.71, 127.4, 127.5, 127.9, 127.96, 127.98, 128.2, 128.5, 136.6, 137.32, 137.34, 142.4, 142.57, 142.62, 152.5, 152.6, 166.1, 166.25, 166.31, 166.6; ESIMS (*m*/*z*) 1134 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3463, 1716, 1590 cm^{-1}; Anal. Calcd for $C_{67}H_{70}O_{13}Si$: C, 72.41; H, 6.35. Found: C, 72.11; H, 6.78.

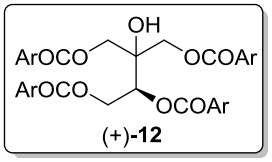
2,3-Dihydroxy-2-(hydroxymethyl)butane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate)



28

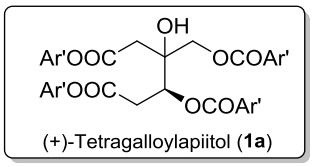
[diastereomeric mixture (3:2), **28].** To a stirred solution of diol **27** (400 mg, 0.36 mmol) in THF (10 mL) at 0 °C was added TBAF solution in THF (1 M, 0.43 mL, 0.43 mmol) and the reaction mixture was further stirred at the same temperature for 20 min. The reaction was then quenched with saturated solution of NH_4Cl and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:1) as an eluent afforded product **28** as colorless oil (330 mg, 92%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.22 (br s, 4H), 3.56–3.90 (m, 4H), 4.00–4.12 (m, 2H), 4.35–4.70 (m, 8H), 4.92–5.00 (m, 2H), 5.00–5.15 (m, 24H), 7.15–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 63.6, 64.1, 65.1, 65.3, 65.65, 65.69, 71.20, 71.24, 72.1, 72.2, 74.3, 74.8, 75.12, 75.14, 109.2, 109.25, 109.33, 109.4, 127.46, 127.48, 127.5, 127.6, 127.95, 127.97, 128.0, 128.1, 128.2, 128.3, 128.4, 128.46, 128.48, 128.50, 128.53, 136.56, 136.59, 137.31, 137.33, 152.58, 152.61, 166.5, 166.56, 166.58, 166.7; ESIMS (*m*/*z*) 1020 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3462, 1716, 1590 cm^{-1}; Anal. Calcd for $C_{61}H_{56}O_{13}$: C, 73.48; H, 5.66. Found: C, 73.08; H, 5.33.

(*S*)-3-Hydroxy-3-(((3,4,5-tris(benzyloxy)benzoyl)oxy)methyl)butane-1,2,4-triyl tris(3,4,5-tris(benzyloxy)benzoate) (12).



To a stirred solution of mixture of triol **28** (300 mg, 0.30 mmol), 3,4,5-tris(benzyloxy)benzoic acid (tribenzylgallic acid) (291 mg, 0.66 mmol) and DMAP (4 mg, 0.03 mmol) in dichloromethane (15 mL) was dropwise added a solution of EDCI (172 mg, 0.90 mmol) in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred for 5 h and then quenched with water (15 mL). The reaction mixture was extracted with dichloromethane (2 × 30 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:3) as an eluent afforded pure product (+)-**12** as a white solid (499 mg, 90%). Mp 130–131 °C; $[\alpha]^{25}_D$ = +26.5 (*c* 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.42 (br s, 1H), 4.46 (dd, *J* = 25 and 15 Hz, 2H), 4.58 (d, *J* = 10 Hz, 1H), 4.62–4.68 (m, 1H), 4.70 (d, *J* = 10 Hz,1H), 4.87–5.15 (m, 25H), 5.87–5.93 (m, 1H), 7.15–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.7, 65.4, 65.5, 70.9, 71.0, 71.1, 72.3, 74.3, 75.0, 75.1, 108.8, 109.1, 109.3, 123.9, 123.95, 124.03, 124.4, 127.4, 127.46, 127.52, 127.6, 127.8, 127.9, 127.96, 127.98, 128.09, 128.14, 128.3, 128.39, 128.40, 128.45, 128.47, 128.5, 136.3, 136.4, 136.5, 136.6, 137.3, 137.37, 137.38, 142.5, 142.8, 142.9, 143.1, 152.5, 152.56, 152.58, 152.61, 165.1, 165.7, 166.1, 166.2; ESIMS (*m*/*z*) 1859 $[M+NH_3]^+$, 1865 $[M+Na]^+$, 1881 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 3447, 1724, 1589, 1215 cm^{-1}.

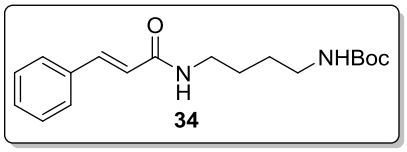
(*R*)-3-Hydroxy-3-(((3,4,5-trihydroxybenzoyl)oxy)methyl)-butane-1,2,4-triyl tris(3,4,5-trihydroxybenzoate) [(+)-tetragalloylapiitol, 1a].



To a stirred solution of (+)-**12** (450 mg, 0.24 mmol) in a mixture of ethyl acetate and methanol (20 mL, 1:1) at room temperature was added 10% Pd/C (50 mg) and the reaction mixture was subjected to hydrogenation at 65-psi hydrogen pressure for 8 h. The reaction mixture was filtered through Celite bed and washed with methanol. The concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the resulting residue using methanol–chloroform (3:1) as an eluent furnished pure product (+)-**1a** as a pale purple solid (185 mg, ~100%). The analytically pure sample was obtained by reversed-phase C_{18} HPLC (Grace Denali i.d. 4 x 250 mm) with a isocratic elution from 30% aqueous MeOH. Mp > 300 ^{o}C; $[\alpha]^{25}_D$ = +25.8 (*c* 0.10, MeOH); ^{1}H NMR (C_5D_5N, 400 MHz) δ 4.88 (d, *J* = 12 Hz, 1H),

4.92 (d, *J* = 12 Hz, 1H), 4.98 (d, *J* = 12 Hz, 1H), 5.06 (dd, *J* = 12 and 8 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 5.31 (br d, *J* = 12 Hz, 1H), 6.45 (dd, *J* = 8 and 4 Hz, 1H), 7.80 (s, 2H), 7.82 (s, 2H), 7.84 (s, 2H), 7.87 (s, 2H); ^{13}C NMR (C_5D_5N, 100 MHz) δ 63.8, 65.5, 72.7, 74.3, 110.3, 120.5, 120.66, 120.71, 141.1, 141.2, 147.4, 147.5, 166.4, 166.8, 166.9, 167.1; ESIMS (*m*/*z*) 759 $[M–H]^-$ (calcd for $C_{33}H_{27}O_{21}$); IR (Nujol) ν_{max} 3432, 1742, 1682 cm^{-1}.

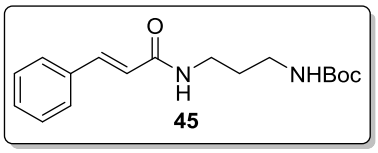
***tert*-Butyl (4-cinnamamidobutyl)carbamate (34).**



34

To a stirred solution of cinnamic acid (**33**, 2.00 g, 13.51 mmol) in dichloromethane (20 mL) were added *tert*-butyl(4-aminobutyl)carbamate (**44b**, 2.79 g, 14.86 mmol), EDCI (2.83 g, 14.86 mmol), triethylamine (2.06 mL, 14.86 mmol), catalytic amount of DMAP (5 mg) at 0 ^{o}C and the reaction mixture was stirred under argon atmosphere. The reaction mixture was allowed to gradually reach room temperature and it was stirred for 4 h. The reaction was quenched with water (20 mL) and the reaction mixture was extracted with dichloromethane (20 mL × 3). The combined organic layer was washed with brine (25 mL) and dried over Na_2SO_4. The concentration of the dried organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent afforded pure amide **34**[80] as a white solid (4.08 g, 95%); Mp 92–94 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.50–1.68 (m, 4H), 3.16 (q, *J* = 6 Hz, 2H), 3.41 (q, *J* = 6 Hz, 2H), 4.70 (br s, 1H), 6.28 (br s, 1H), 6.45 (d, *J* = 16 Hz, 1H), 7.30–7.40 (m, 3H), 7.43–7.53 (m, 2H), 7.62 (d, *J* = 16 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.7, 28.4, 39.3, 40.0, 79.2, 120.9, 127.7, 128.7, 129.5, 134.9, 140.6, 156.2, 166.0; ESIMS (*m*/*z*) 341 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3449, 3349, 1700, 1665, 1624 cm^{-1}.

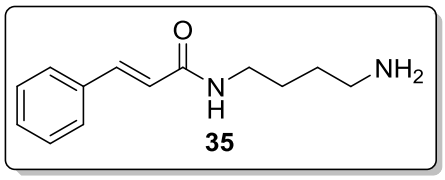
***tert*-Butyl (3-cinnamamidopropyl)carbamate (45).**[81]



45

It was similarly obtained from **44a** in 96% yield. Mp 103–105 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.67 (quintet, *J* = 6 Hz, 2H), 3.20 (q, *J* = 6 Hz, 2H), 3.43 (q, *J* = 6 Hz, 2H), 5.14 (br s, 1H), 6.47 (d, *J* = 16 Hz, 1H), 6.83 (br s, 1H), 7.27–7.40 (m, 3H), 7.42–7.55 (m, 2H), 7.61 (d, *J* = 16 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 30.2, 36.0, 37.0, 79.3, 121.0, 127.7, 128.7, 129.5, 134.8, 140.6, 156.8, 166.3; ESIMS (*m*/*z*) 327 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3451, 3328, 1691, 1663 cm^{-1}.

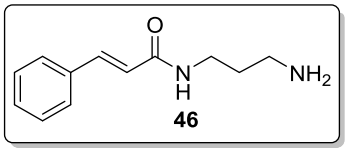
***N*-(4-Aminobutyl)cinnamamide (35).**



35

Trifluoroacetic acid (4.83 mL, 62.89 mmol) was added to a stirred solution of compound **34** (4.00 g, 12.57 mmol) in dichloromethane (25 mL) at 0 ^{o}C under argon atmosphere. The reaction mixture was allowed to gradually reach room temperature and it was stirred for 6 h. The reaction was quenched with water (10 mL) and the dichloromethane layer was separated. The aq. layer was saturated with NaCl and then neutralized with aq. NaOH (20%, 20 mL). The basified reaction mixture was extracted with dichloromethane (25 mL × 3) and the combined extract was dried over Na_2SO_4. The concentration of the dried organic layer in vacuo afforded amine **35**[80] as viscous yellow oil (2.35 g, 86%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 2H), 1.45–1.75 (m, 4H), 2.76 (t, J = 6 Hz, 2H), 3.41 (q, J = 6 Hz, 2H), 6.32 (br s, 1H), 6.39 (d, J = 16 Hz, 1H), 7.30–7.40 (m, 3H), 7.44–7.55 (m, 2H), 7.62 (d, J = 16 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 29.7, 39.4, 41.2, 120.9, 127.7, 128.8, 129.6, 134.9, 140.6, 166.1; ESIMS (*m*/*z*) 219 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 3500–3300, 1663, 1623 cm^{-1}.

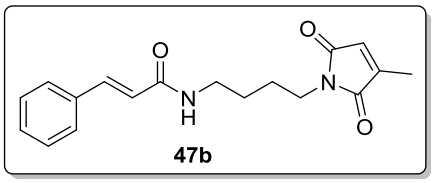
***N*-(3-Aminopropyl)cinnamamide (46).**[81]



46

It was similarly obtained from **45** as thick oil in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 2H), 1.70 (quintet, J = 8 Hz, 2H), 2.85 (t, J = 8 Hz, 2H), 3.51 (q, J = 8 Hz, 2H), 6.40 (d, J = 16 Hz, 1H), 6.80 (br s, 1H), 7.28–7.40 (m, 3H), 7.45–7.55 (m, 2H), 7.61 (d, J = 16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 38.4, 40.4, 121.0, 127.7, 128.8, 129.5, 134.9, 140.5, 165.9; ESIMS (*m*/*z*) 227 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3291, 2928, 2857, 1657, 1622 cm^{-1}.

***N*-(4-(3-Methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butyl)cinnamamide (47b).**

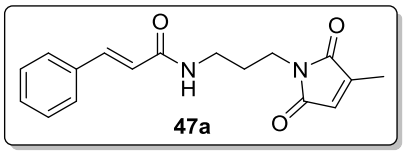


47b

A stirred solution of *N*-(4-aminobutyl)cinnamamide (**35**, 1.00 g, 4.58 mmol) and citraconic anhydride (565 mg, 5.04 mmol) in glacial acetic acid (10 mL) was refluxed for 12 h. Acetic acid was distilled off under vacuum and saturated sodium bicarbonate solution was slowly added to the reaction mass. The reaction mixture was extracted with ethyl acetate (20 mL × 3) and the combined organic layer was washed with brine (25 mL) and dried over Na_2SO_4. The concentration of the dried organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (9:1) afforded pure imide **47b** as a white solid (1.28 g, 90%). Mp 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50–1.75 (m, 4H), 2.07 (s,

3H), 3.35–3.65 (m, 4H), 6.07 (br s, 1H), 6.28–6.54 (m, 2H), 7.25–7.70 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 26.1, 26.6, 37.3, 39.1, 120.7, 127.2, 127.7, 128.7, 129.5, 134.8, 140.8, 145.6, 165.9, 170.9, 171.9; ESIMS (*m*/*z*) 313 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{21}O_3N_2$ 313.1547, found 313.1539; IR ($CHCl_3$) ν_{max} 3295, 1734, 1709, 1655, 1623 cm^{-1}.

***N*-(3-(3-Methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propyl)cinnamamide (47a).**



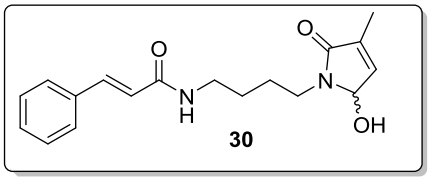
47a

It was similarly obtained from **46** as thick oil in 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (quintet, J = 10 Hz, 2H), 2.10 (s, 3H), 3.34 (q, J = 10 Hz, 2H), 3.61 (t, J = 10 Hz, 2H), 6.30–6.40 (br s, 1H), 6.36 (s, 1H), 6.46 (d, J = 15 Hz, 1H), 7.30–7.40 (m, 3H), 7.48–7.56 (m, 2H), 7.64 (d, J = 15 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 28.3, 34.8, 36.1, 120.8, 127.4, 127.8, 128.8, 129.6, 134.8, 140.9, 145.8, 165.9, 171.3, 172.2; ESIMS (*m*/*z*) 321 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_3$ 299.1390, found 299.1390; IR ($CHCl_3$) ν_{max} 3285, 1771, 1707, 1658, 1619 cm^{-1}.

***N*-(4-(5-Hydroxy-3-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)butyl)cinnamamide (Gigantamide A, 30) and *N*-(4-(2-Hydroxy-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)butyl)cinnamamide (Isogigantamide A, 49b).**

To a stirred solution of imide **47b** (500 mg, 1.60 mmol) in THF (10 mL) at –78 ^{o}C was dropwise added a DIBAL solution in toluene (1 M, 1.76 mL, 1.76 mmol) and the reaction mixture was stirred for 30 min under argon atmosphere. The reaction mixture was allowed to gradually reach the room temperature and further stirred for 1 h. The reaction was quenched with saturated NH_4Cl solution (5 mL) and then concentrated in vacuo. The obtained residue was diluted with ethyl acetate (25 mL) and the organic layer was washed with brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The obtained residue on silica gel column chromatographic purification using ethyl acetate–methanol (19:1) afforded pure product **49b** as thick oil (15 mg, 3%) and then pure product **30** as a white solid (337 mg, 67%).

Gigantamide A (30).

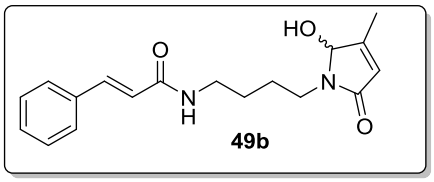


30

Mp 138–140 ^{o}C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.57 (sextet, J = 8 Hz, 2H), 1.66 (sextet, J = 8 Hz, 2H), 1.84 (s, 3H), 3.27–3.38 (m, 3H), 3.47–3.57 (m, 1H), 5.33 (s, 1H), 6.58 (d, J = 16 Hz, 1H), 6.62 (quintet, J = 4 Hz, 1H), 7.31–7.41 (m, 3H), 7.51 (d, J = 16 Hz, 1H), 7.51–7.56 (m, 2H); ^{13}C NMR (100 MHz,

CD_3OD) δ 10.9, 27.0, 27.9, 40.1, 40.2, 82.7, 121.9, 128.8, 130.0, 130.8, 136.3, 137.0, 140.9, 141.6, 168.6, 172.4; ESIMS (*m*/*z*) 337 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3296, 1687, 1655, 1615 cm^{-1}.

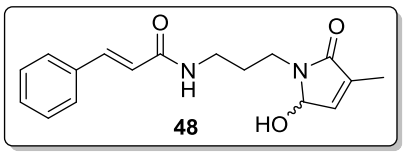
Isogigantamide A (49b).



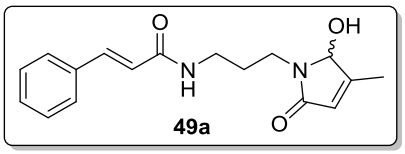
^1H NMR (200 MHz, CD_3OD) δ 1.40–1.70 (m, 4H), 1.99 (d, *J* = 2 Hz, 3H), 3.15–3.35 (m, 3H), 3.35–3.55 (m, 1H), 5.19 (s, 1H), 5.72 (q, *J* = 2 Hz, 1H), 6.54 (d, *J* = 16 Hz, 1H), 7.27–7.37 (m, 3H), 7.45–7.54 (m, 2H), 7.47 (d, *J* = 16 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 13.4, 27.1, 27.9, 39.9, 40.2, 86.1, 121.9, 122.5, 128.8, 130.0, 130.8, 136.3, 141.6, 161.0, 168.7, 172.4; ESIMS (*m*/*z*) 337 $[M + Na]^+$; HRMS (ESI) calcd for $C_{18}H_{22}O_3N_2Na$ 337.1523, found 337.1513; IR ($CHCl_3$) ν_{max} 3298, 1676, 1623 cm^{-1}.

***N*-(3-(5-Hydroxy-3-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)propyl)cinnamamide (Dehomogigantamide A, 48) and *N*-(3-(2-Hydroxy-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)propyl)cinnamamide (Dehomoisogigantamide A, 49a).**

They were similarly obtained from **47a** as thick oils in 68% and 3% yields respectively.

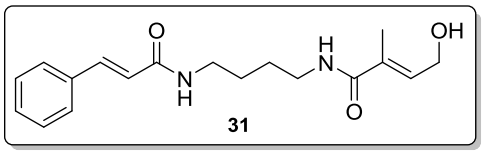


48: ^1H NMR (500 MHz, CD_3OD) δ 1.80–1.95 (m, 2H), 1.86 (s, 3H), 3.24–3.45 (m, 3H), 3.50–3.60 (m, 1H), 5.37 (s, 1H), 6.59 (s, 1H), 6.64 (d, *J* = 15 Hz, 1H), 7.32–7.45 (m, 3H), 7.52–7.60 (m, 2H), 7.53 (d, *J* = 15 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 10.8, 29.4, 38.2, 38.3, 82.9, 121.9, 128.8, 130.0, 130.8, 136.3, 137.0, 141.0, 141.7, 168.7, 172.6; ESIMS (*m*/*z*) 323 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366, found 323.1364; IR ($CHCl_3$) ν_{max} 3299, 1677, 1654, 1621 cm^{-1}.



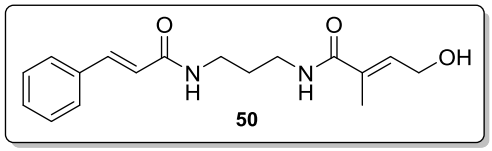
49a: ^1H NMR (500 MHz, CD_3OD) δ 1.80–1.90 (m, 2H), 2.05 (s, 3H), 3.25–3.43 (m, 3H), 3.48–3.57 (m, 1H), 5.27 (s, 1H), 5.79 (s, 1H), 6.61 (d, *J* = 15 Hz, 1H), 7.32–7.42 (m, 3H), 7.52–7.58 (m, 2H), 7.53 (d, *J* = 15 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 13.5, 29.5, 38.1, 38.2, 86.3, 121.9, 122.4, 128.8, 130.0, 130.8, 136.3, 141.7, 161.2, 168.7, 172.6; ESIMS (*m*/*z*) 323 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366, found 323.1365. IR ($CHCl_3$) ν_{max} 3289, 1668, 1553 cm^{-1}.

(*E*)-*N*-(4-Cinnamamidobutyl)-4-hydroxy-2-methylbut-2-enamide (Dasyclamide, 31).



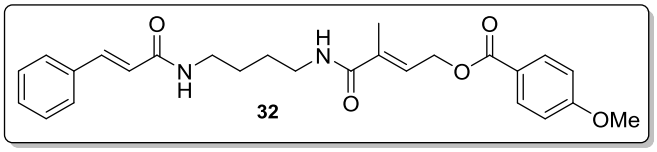
To a stirred solution of 4-hydroxytiglic acid[45] (50 mg, 0.43 mmol) in dichloromethane (10 mL) were added *tert*-butyl (4-aminobutyl)carbamate (**35**, 103 mg, 0.47 mmol), EDCI (90 mg, 0.47 mmol), triethylamine (0.07 mL, 0.47 mmol), catalytic amount of DMAP (1 mg) at 0 ^{o}C and the reaction mixture was stirred under argon atmosphere. The reaction mixture was allowed to gradually reach room temperature and it was stirred for 2 h. The reaction was quenched with water (10 mL) and the reaction mixture was extracted with dichloromethane (10 mL × 2). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The concentration of the organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue ethyl acetate–methanol (19:1) afforded pure product **31** as a white solid (110 mg, 87%). Mp 114–116 ^{o}C; ^{1}H NMR (500 MHz, CD_3OD) δ 1.59 (s, 4H), 1.82 (s, 3H), 3.23–3.35 (m, 4H), 4.23 (d, J = 5 Hz, 2H), 6.33 (t, J = 10 Hz, 1H), 6.59 (d, J = 15 Hz, 1H), 7.31–7.40 (m, 3H), 7.52 (d, J = 15 Hz, 1H), 7.50–7.55 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 13.0, 27.9 (2 carbons), 40.2, 40.3, 59.5, 122.2, 128.8, 129.9, 130.8, 133.1, 135.7, 136.3, 141.6, 168.6, 172.0; ESIMS (*m*/*z*) 339 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3286, 1655, 1622 cm^{-1}.

(*E*)-*N*-(3-Cinnamamidopropyl)-4-hydroxy-2-methylbut-2-enamide (50).



It was similarly obtained from **46** as thick oil in 89% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 1.74–1.82 (m, 2H), 1.86 (s, 3H), 3.25–3.37 (m, 4H), 4.25 (d, J = 5 Hz, 2H), 4.61 (br s, 1H) 6.39 (t, J = 10 Hz, 1H), 6.61 (d, J = 15 Hz, 1H), 7.32–7.42 (m, 3H), 7.54 (d, J = 15 Hz, 1H), 7.54–7.57 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 13.0, 13.3, 38.0, 38.1, 59.5, 121.8, 128.8, 130.0, 130.9, 132.8, 136.1, 136.3, 141.8, 168.8, 172.0; ESIMS (*m*/*z*) 325 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{22}N_2O_3Na$ 325.1523, found 325.1523; IR ($CHCl_3$) ν_{max} 3333, 1661, 1622 cm^{-1}.

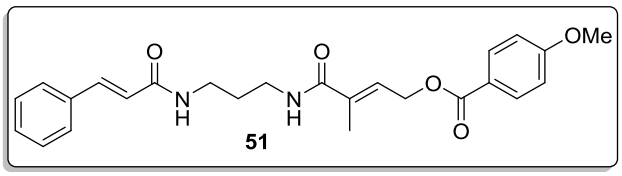
(*E*)-4-((4-Cinnamamidobutyl)amino)-3-methyl-4-oxobut-2-en-1-yl 4-methoxybenzoate (Cucullamide, 32).



To a stirred solution of *p*-methoxybenzoic acid (20 mg, 0.13 mmol) in dichloromethane (5 mL) were added dasyclamide (**31**, 45 mg, 0.14 mmol), EDCI (27 mg, 0.14 mmol), triethylamine (0.02 mL, 0.14 mmol) and a catalytic amount of DMAP at 0 ^{o}C under argon atmosphere. The

reaction mixture was allowed to gradually reach room temperature and further stirred for 2 h. The reaction was quenched with water (5 mL) and the reaction mixture was extracted with dichloromethane (10 mL × 2). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue ethyl acetate–petroleum ether (9:1) afforded pure product **32** as a white solid (55 mg, 93%). Mp 146–148 ^oC; ^1H NMR (200 MHz, CD_3OD) δ 1.60 (q, J = 4 Hz, 4H), 1.95 (s, 3H), 3.20–3.28 (m, 4H), 3.86 (s, 3H), 4.96 (d, J = 6 Hz, 2H), 6.40 (qt, J = 6 and 2 Hz, 1H), 6.59 (d, J = 16 Hz, 1H), 6.99 (d, J = 8 Hz, 2H), 7.33–7.45 (m, 3H), 7.51–7.58 (m, 2H), 7.52 (d, J = 16 Hz, 1H), 7.98 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 13.3, 27.8, 27.9, 40.2, 40.4, 56.0, 62.1, 114.9, 121.9, 123.3, 128.8, 130.0, 130.2, 130.8, 132.7, 136.1, 136.3, 141.6, 165.3, 167.6, 168.6, 171.6; ESIMS (m/z) 451$[M + H]^+$, 473 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3442, 3313, 1709, 1664, 1624, 1608 cm^{-1}.

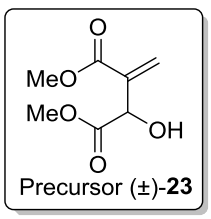
(*E*)-4-((3-Cinnamamidopropyl)amino)-3-methyl-4-oxobut-2-en-1-yl 4-methoxybenzoate (51).



51

It was similarly obtained from **50** in 95% yield. Mp 117–119 ^oC; ^1H NMR (500 MHz, CD_3OD) δ 1.73–1.83 (m, 2H), 1.97 (s, 3H), 3.27–3.38 (m, 4H), 3.85 (s, 3H), 4.96 (d, J = 10 Hz, 2H), 6.45 (t, J = 5 Hz, 1H), 6.60 (d, J = 15 Hz, 1H), 6.98 (d, J = 10 Hz, 2H), 7.30–7.40 (m, 3H), 7.50–7.57 (m, 2H), 7.53 (d, J = 15 Hz, 1H), 7.98 (d, J = 10 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 13.3, 30.3, 38.0, 38.2, 56.0, 62.1, 114.9, 121.8, 123.3, 128.8, 130.0, 130.5, 130.8, 132.7, 135.9, 136.2, 141.8, 165.3, 167.6, 168.8, 171.5; ESIMS (m/z) 459 $[M + Na]^+$; HRMS (ESI) calcd for $C_{25}H_{28}N_2O_5Na$ 459.1890, found 459.1890; IR ($CHCl_3$) ν_{max} 3309, 1709, 1663 cm^{-1}.

Amano PS Catalyzed Resolution of (±)-Dimethyl 2-hydroxy-3-methylenesuccinate (23).



Precursor (±)-**23**

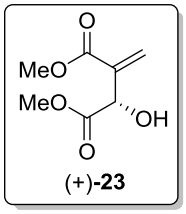
To a stirred solution of (±)-dimethyl 2-hydroxy-3-methylenesuccinate (**23**) (2.00 g, 9.25 mmol) and vinyl acetate (3.98 g, 46.25 mmol) in acetone (25 mL) was added the enzyme Amano PS (100 mg, Sigma-Aldrich). The resulting reaction mixture was stirred at 25 °C for 72 h with monitoring the reaction progress by HPLC. The reaction mixture was filtered through Celite bed and washed with ethyl acetate (30 mL). The concentration of organic layer in vacuo followed by silica gel

(60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–pet ether (1:3) as an eluent afforded pure product (–)-**23** as viscous oil (920 mg, 46%) and (+)-**21** as viscous oil (1.36 g, 54%).

(–)-**23:** $[\alpha]^{25}_{D}$ –18.5 (*c* 0.30 EtOH, 98% *ee*); the obtained spectroscopic data was identical with the data for (–)-**23**.

(+)-21: $[\alpha]^{25}_{D}$ +48.6 (*c* 0.19 EtOH, 94% *ee*); the obtained spectroscopic data was identical with the data for (–)-**21**.

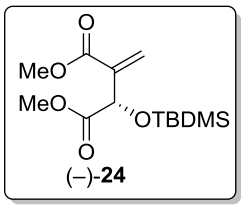
(+)-Dimethyl (*S*)-2-hydroxy-3-methylenesuccinate (23).



(+)-**23**

To a stirred solution of acetate (+)-**21** (1.20 g, 5.55 mmol) in methanol (10 mL) was added 2 N HCl (5 mL) at 0 °C and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:3) as an eluent afforded pure product (+)-**23** as viscous oil (760 mg, 90%). $[\alpha]^{25}_{D}$ +18.0 (*c* 0.28 EtOH); the obtained spectroscopic data was identical with the data for (–)-**23**.

(–)-Dimethyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3-methylenesuccinate (24).

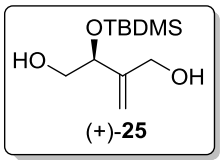


(–)-**24**

To a stirred solution of alcohol (+)-**23** (700 mg, 4.02 mmol) in dichloromethane (20 mL) were added imidazole (301 mg, 4.42 mmol) and TBDMSCl (666 mg, 4.42 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (40 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:19) as an eluent afforded pure product (–)-**24** as viscous oil (1.09 g, 94%). $[\alpha]^{25}_{D}$ –20.9 (*c* 0.40 EtOH); the obtained spectroscopic data was identical with the data for (+)-**24**.

(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylenebutane-1,4-diol (25).

To a stirred solution of diester (–)-**24** (1.00 g, 3.46 mmol) in THF (10 mL) was added DIBAL solution (0.16 mL, 0.16 mmol, 1 M in hexane) in dropwise fashion at –78 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The reaction was quenched with

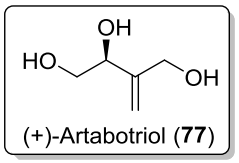


(+)-**25**

saturated NH_4Cl solution and reaction mass was concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:3) as an eluent afforded pure product (+)-**25** as viscous oil (580 mg, 72%). $[\alpha]^{25}_{D}$ +6.3 (*c* 0.50 EtOH); the obtained spectroscopic data was identical with the data for (–)-**25**.

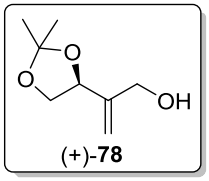
(*S*)-3-Methylenebutane-1,2,4-triol (77).

To a stirred solution of diol (+)-**25** (550 mg, 2.36 mmol) in anhydrous THF (10 mL) was added slowly a solution of tetrabutylammonium fluoride (2.60 mL, 2.60 mmol, 1 M in THF) at 0 °C and reaction mixture was stirred for 10 h at 25 °C. The reaction was quenched with saturated NH_4Cl solution and reaction mixture was concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using methanol–ethyl acetate (1:19) as an eluent afforded pure product (+)-**77** as viscous oil (260 mg, 93%). $[\alpha]^{25}_{D}$ +4.5 (*c* 0.28 MeOH); ^{1}H NMR (200 MHz, acetone-d_6) δ 3.40–4.35 (m, 8H), 5.13 (s, 2H); ^{13}C NMR (50 MHz, acetone-d_6) δ 64.2, 68.0, 75.7, 112.0, 152.2; IR ($CHCl_3$) ν_{max} 3355 cm^{-1}.



(+)-Artabotriol (**77**)

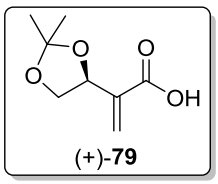
(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (78).



(+)-**78**

To a stirred solution of triol (+)-**77** (250 mg, 2.11 mmol) in anhydrous THF (5 mL) was added 2,2-dimethoxypropane (242 mg, 2.33 mmol) at 0 °C and reaction mixture was stirred for 4 h at 25 °C. Reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded pure product (+)-**78** as viscous oil (284 mg, 85%). $[\alpha]^{25}_{D}$ +35.9 (*c* 0.30 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.46 (s, 3H), 2.25 (br s, 1H), 3.72 (t, *J* = 8 Hz, 1H), 4.05–4.30 (m, 3H), 4.68 (t, *J* = 8 Hz, 1H), 5.21 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 26.3, 63.3, 68.9, 77.7, 109.4, 113.4, 145.7; IR ($CHCl_3$) ν_{max} 3419, 1656 cm^{-1}.

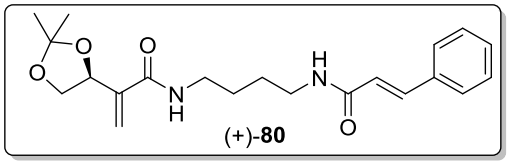
(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acrylic acid (79).



(+)-**79**

To a stirred solution of (+)-**78** (100 mg, 0.63 mmol) in DCM (2 mL) was added active MnO_2 (1.37 g, 15.75 mmol) at 25 °C and the reaction mixture was stirred for 36 h. The inorganic materials from reaction mixture were filtered off through Celite bed and thoroughly washed with DCM (10 mL). The combined filtrate was evaporated to give the crude *α*,*β*-unsaturated aldehyde which was used for next step without any purification. A suspension of Ag_2O prepared from $AgNO_3$ (115 mg, 0.69 mmol) and NaOH (100 mg, 2.52 mmol) in H_2O (3 mL) was added the above crude aldehyde at 0 °C and the reaction mixture was stirred at 25 °C for 1 h. Reaction mixture filtered through Celite bed and filtrate was acidified with sat. aq. oxalic acid followed by extraction with ethyl acetate. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:3) as an eluent afforded pure product (+)-**79** as a white solid (74 mg, 68%). Mp 60–62 ^{o}C; $[\alpha]^{25}_{D}$ +37.2 (*c* 0.60 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.47 (s, 3H), 3.65 (t, *J* = 10 Hz, 1H), 4.38 (t, *J* = 10 Hz, 1H), 4.87 (t, *J* = 10 Hz, 1H), 6.18 (s, 1H), 6.45 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 26.3, 70.1, 73.8, 109.6, 127.1, 138.7, 170.7; IR ($CHCl_3$) ν_{max} 3684, 3620, 1701, 1633 cm^{-1}.

(+)-(*S*)-*N*-(4-Cinnamamidobutyl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylamide (80).



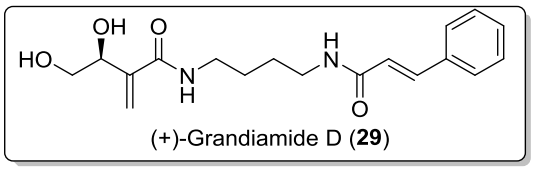
(+)-**80**

To a stirred solution of acid (+)-**79** (40 mg, 0.23 mmol) in dichloromethane (5 mL) were added amine **35** (56 mg, 0.25 mmol), EDCI (48 mg, 0.25 mmol), triethylamine (25 mg, 0.25 mmol) and a catalytic amount of DMAP at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and stirred for 4 h. The reaction was quenched with water (5 mL) and the reaction mixture was extracted with dichloromethane (10 mL × 2). The combined organic

layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate as an eluent afforded pure product (+)-**80** as a white solid (75 mg, 87%). Mp 110–112 ^{o}C; $[\alpha]^{25}_{D}$ +15.3 (*c* 0.20 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.48 (s, 3H), 1.63 (s, 2H), 1.80 (s, 2H), 3.37 (d, *J* = 5 Hz, 2H), 3.43 (d, *J* = 5 Hz, 2H), 3.75 (t, *J* = 10 Hz, 1H), 4.29 (t, *J* = 10 Hz, 1H), 4.86 (t, *J* = 10 Hz, 1H), 5.70 (s, 1H), 5.93 (s, 1H), 6.20 (br s, 1H), 6.43 (d, *J* = 20 Hz, 1H), 6.80 (br s, 1H), 7.36 (s, 3H), 7.50 (d, *J* = 5 Hz,

2H), 7.62 (d, J = 15 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 26.4, 26.8, 27.0, 39.0, 39.2, 69.4, 75.6, 109.6, 120.6, 120.7, 127.7, 128.8, 129.6, 134.8, 140.9, 141.8, 166.1, 166.6; ESIMS (m/z) 395 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{28}O_4N_2Na$ 395.1941, found 395.1933; IR ($CHCl_3$) ν_{max} 3688, 3621, 1732, 1663, 1623 cm^{-1}.

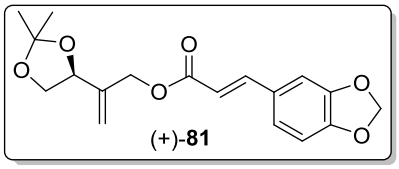
(+)-(*S*)-*N*-(4-Cinnamamidobutyl)-3,4-dihydroxy-2-methylenebutanamide (Grandiamide D, 29).



(+)-Grandiamide D (**29**)

To a stirred solution of (+)-**80** (50 mg, 0.13 mmol) in anhydrous MeOH (2 mL) was added catalytic amount of *p*-toluenesulfonic acid (5 mg) at 0 °C under argon atmosphere and the reaction mixture was stirred for 2 h. Reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (10 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using methanol—ethyl acetate (1:19) as an eluent afforded pure product (+)-2**9** as a white solid (34 mg, 77%). Mp 105–107 ^oC; $[\alpha]^{25}_D$ +2.7 (*c* 0.60 MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 1.61 (br s, 4H), 3.20–3-40 (m, 4H), 3.49 (dd, J = 11 and 8 Hz, 1H), 3.65 (dd, J = 10 and 4 Hz, 1H) 4.53 (t, J = 6 Hz, 1H), 5.63 (s, 1H), 5.80 (s, 1H), 6.61 (d, J = 16 Hz, 1H), 7.30–7.45 (m, 3H), 7.45–7.60 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.8, 27.9, 40.0, 40.2, 66.7, 73.3, 119.9, 121.9, 128.8, 129.9, 130.8, 136.3, 141.60, 146.3, 168.6, 170.4; ESIMS (m/z) 355 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3374, 1658, 1607 cm^{-1}.

(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)allyl (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)acrylate (81).

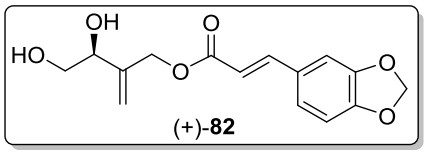


(+)-**81**

To a stirred solution of 3,4-(methylenedioxy)cinnamic acid (100 mg, 0.52 mmol) in dichloromethane (10 mL) were added alcohol (+)-**78** (74 mg, 0.47 mmol), EDCI (97 mg, 0.52 mmol), triethylamine (105 mg, 1.04 mmol) and a catalytic amount of DMAP at 0 °C under argon atmosphere. The reaction mixture was allowed to gradually reach to 25 °C and further refluxed for 6 h. The reaction was quenched with water (10 mL) and the reaction mixture was extracted with dichloromethane (10 mL × 2). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:3) as an eluent afforded pure product (+)-**81** as viscous

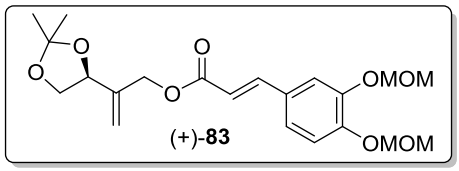
oil (176 mg, 84%). $[\alpha]^{25}_{D}$ +28.6 (*c* 0.64 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.46 (s, 3H), 3.77 (t, *J* = 8 Hz, 1H), 4.19 (t, *J* = 8 Hz, 1H), 4.64 (t, *J* = 8 Hz, 1H), 4.75 (dd, *J* = 20 and 16 Hz, 2H), 5.28 (s, 1H), 5.39 (s, 1H), 6.01 (s, 2H) 6.28 (d, *J* = 16 Hz, 1H), 6.82 (d, *J* = 12 Hz, 1H), 7.01 (d, *J* = 8 Hz, 1H), 7.04 (s, 1H), 7.61 (d, *J* = 16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 26.2, 64.0, 69.1, 77.1, 101.6, 106.5, 108.5, 109.4, 114.8, 115.4, 124.6, 128.6, 141.6, 145.0, 148.3, 149.7, 166.6; ESIMS (*m*/*z*) 355 $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{20}O_6Na$ 355.1152, found 355.1142; IR ($CHCl_3$) ν_{max} 1708, 1632, 1608 cm^{-1}.

(+)-(*S*)-3,4-Dihydroxy-2-methylenebutyl (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)acrylate (82).



To a stirred solution of (+)-**81** (50 mg, 0.15 mmol) in anhydrous MeOH (5 mL) was added catalytic amount of *p*-toluenesulfonic acid (5 mg) at 0 °C under argon atmosphere and the reaction mixture was stirred for 5 h. Reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (10 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:2) as an eluent afforded pure product (+)-**82** as viscous oil (36 mg, 81%). $[\alpha]^{25}_{D}$ +3.7 (*c* 0.90 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.47 (br s, 1H), 2.89 (br s, 1H), 3.67 (dd, *J* = 12 and 6 Hz, 1H), 3.79 (dd, *J* = 12 and 4 Hz, 1H), 4.36 (dd, *J* = 6 and 4 Hz, 1H), 4.75 (s, 2H), 5.32 (s, 1H), 5.36 (s, 1H), 6.01 (s, 2H), 6.28 (d, *J* = 16 Hz, 1H), 6.82 (d, *J* = 10 Hz, 1H), 7.01 (d, *J* = 8 Hz, 1H), 7.03 (s, 1H), 7.62 (d, *J* = 16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.3, 65.6, 73.2, 101.6, 106.5, 108.5, 115.2, 115.4, 124.7, 128.5, 143.3, 145.4, 148.3, 149.8, 167.0; ESIMS (*m*/*z*) 315 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{16}O_6Na$ 315.0839, found 315.0833; IR ($CHCl_3$) ν_{max} 3390, 1700, 1629, 1606 cm^{-1}.

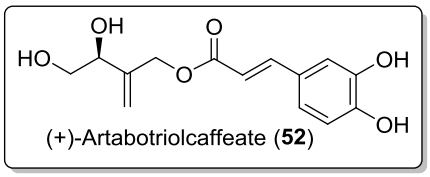
(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)allyl (*E*)-3-(3,4-bis(methoxymethoxy) phenyl)acrylate (83).



To a stirred solution of (*E*)-3-(3,4-bis(methoxymethoxy)phenyl)acrylic acid (100 mg, 0.37 mmol) in dichloromethane (10 mL) were added alcohol (+)-**78** (52 mg, 0.33 mmol), EDCI (71 mg, 0.37 mmol), triethylamine (75 mg, 0.74 mmol) and a catalytic amount of DMAP at 0 °C under argon atmosphere. The reaction mixture was allowed to reach to 25 °C and further refluxed for 6 h. The reaction was quenched with water (10 mL) and the reaction mixture was extracted with dichloromethane (10 mL × 2). The

combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (2:5) as an eluent afforded pure product (+)-**83** as viscous oil (176 mg, 84%). $[\alpha]^{25}_{D}$ +7.5 (*c* 0.52, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.46 (s, 3H), 3.52 (s, 3H), 3.53 (s, 3H), 3.77 (t, *J* = 8 Hz, 1H), 4.19 (t, *J* = 8 Hz, 1H), 4.65 (t, *J* = 8 Hz, 1H), 4.75 (s, 2H), 5.26 (s, 2H), 5.27 (s, 2H), 5.29 (s, 1H), 5.39 (s, 1H), 6.34 (d, *J* = 16 Hz, 1H), 7.16 (s, 2H), 7.37 (s, 1H) 7.63 (d, *J* = 16 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 26.3, 56.30, 56.32, 64.0, 69.1, 77.0, 95.1, 95.5, 109.5, 114.9, 115.7, 116.1, 116.2, 123.6, 128.8, 141.7, 144.9, 147.4, 149.3, 166.6; ESIMS (*m*/*z*) 431 $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{28}O_8Na$ 431.1676, found 431.1667; IR ($CHCl_3$) ν_{max} 3685, 3618, 1710, 1635, 1601 cm^{-1}.

(+)-(*S*)-3,4-Dihydroxy-2-methylenebutyl (*E*)-3-(3,4-dihydroxyphenyl)acrylate (Artabotriolcaffeate, 52).



(+)-Artabotriolcaffeate (**52**)

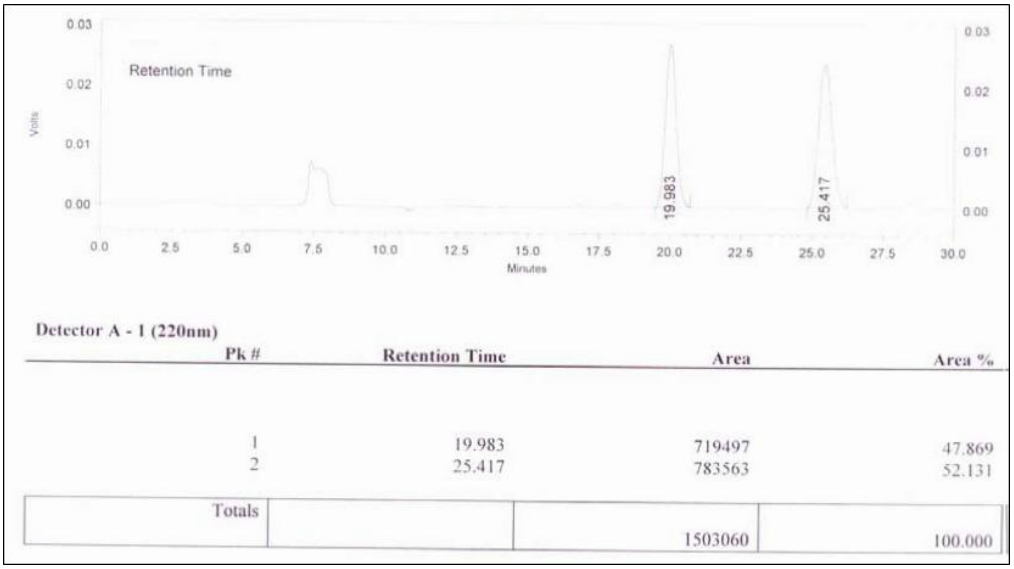
Method A: To a stirred solution of (+)-**82** (50 mg, 0.17 mmol) in DCM (5 mL) was added solution of a boron tribromide (0.68 mL, 0.68 mmol, 1 M in DCM) in dropwise fashion at –78 °C and the reaction mixture was stirred under argon atmosphere for 30 min. The reaction mixture was allowed to reach to 25 °C and stirred for 2 h. The reaction was quenched with ice cold water and the reaction mixture was extracted with DCM (7 mL × 2) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate as an eluent afforded pure product (+)-**52** as a white solid (2 mg, 5%).

Method B: To a stirred solution of (+)-**83** (100 mg, 0.24 mmol) in anhydrous MeOH (5 mL) were added catalytic amount of *p*-toluenesulfonic acid (5 mg) at 0 °C under argon atmosphere. The reaction mixture was stirred for 3 h. Reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (10 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate as an eluent afforded pure product (+)-**52** as a white solid (46 mg, 67%). Mp 168–169 °C; $[\alpha]^{25}_{D}$ +1.2 (*c* 0.80 MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.35–3.50 (m, 2H), 4.07 (q, *J* = 4 Hz, 1H), 4.64 (t, *J* = 4 Hz, 1H), 4.68 (s, 2H), 5.01 (d, *J* = 8 Hz, 1H),

5.11 (s, 1H), 5.18 (s, 1H), 6.30 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 7.02 (dd, J = 8 and 4 Hz, 1H), 7.07 (d, J = 4 Hz, 1H), 7.50 (d, J = 16 Hz, 1H), 9.15 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 63.6, 65.3, 72.8, 112.0, 113.8, 114.9, 115.8, 121.5, 125.5, 145.4, 145.5, 145.6, 148.5, 166.2; ESIMS (m/z) 303 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3383, 1690, 1602 cm^{-1}.

1B.6 Selected Spectra

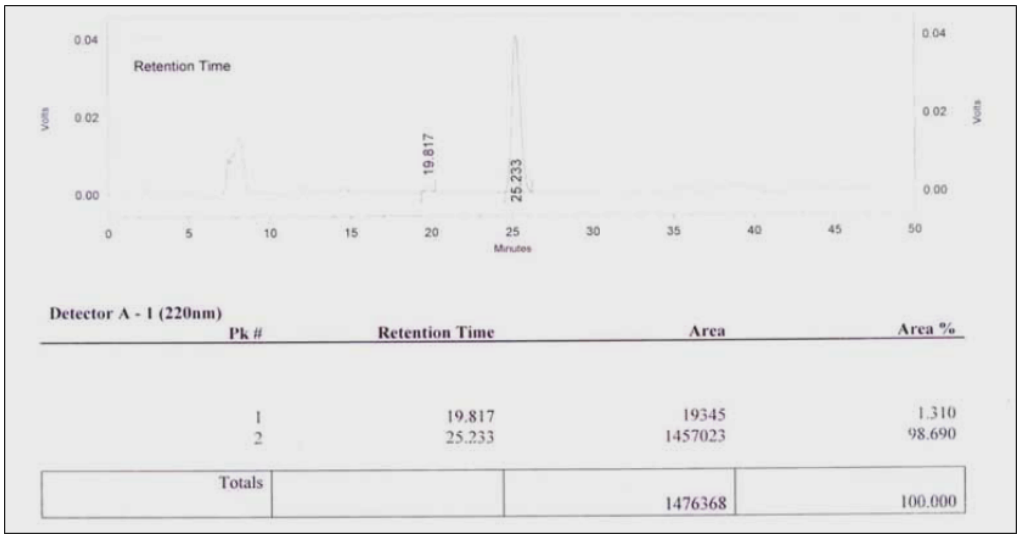
HPLC data of (±)-dimethyl 2-acetoxy-3-methylenesuccinate (21)



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	19.983	719497	47.869
2	25.417	783563	52.131
Totals		1503060	100.000

HPLC data of (–)-dimethyl 2-acetoxy-3-methylenesuccinate (21)



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	19.817	19345	1.310
2	25.233	1457023	98.690
Totals		1476368	100.000

Column: Kromasil 5-CelluCoat (250 mm × 4.6 mm)

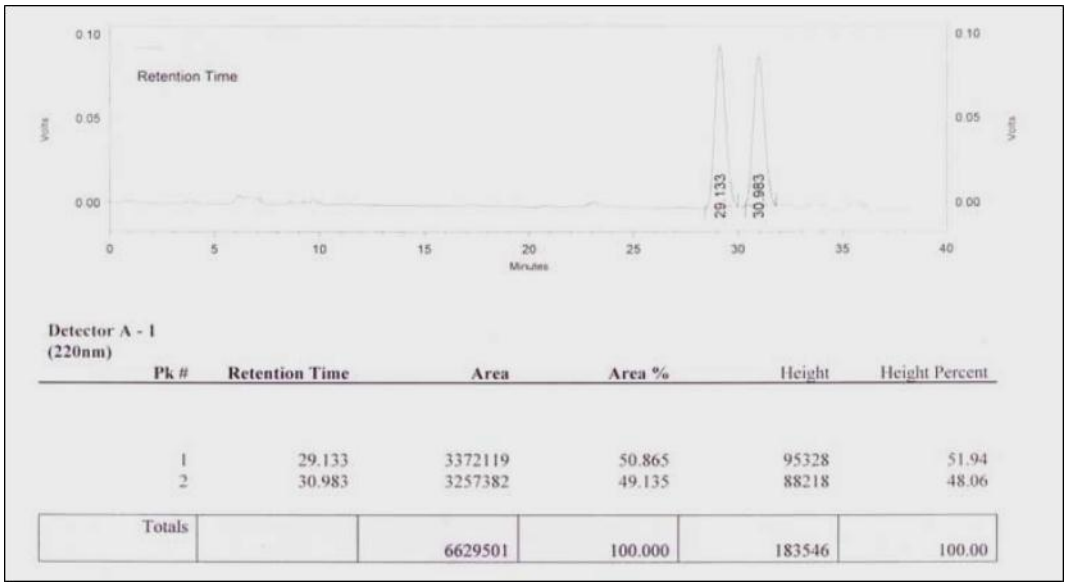
Mobile Phase: IPA:PE (05:95)

Wavelength: 220 nm

Flow Rate: 0.5 mL/min

Sample Conc.: 3 mg/mL

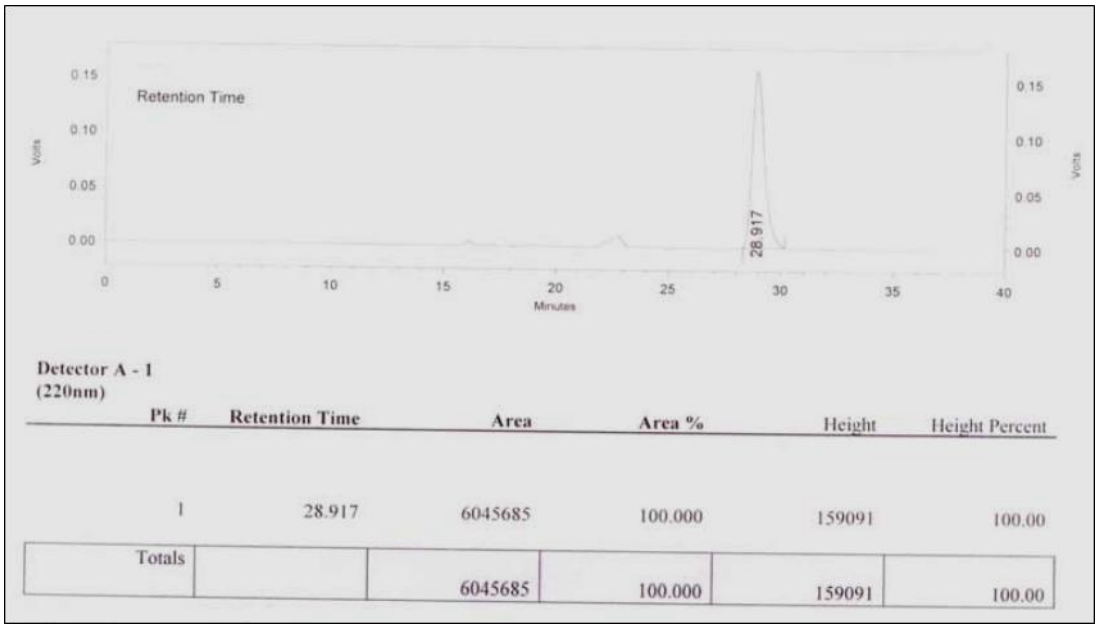
HPLC data of (±)-dimethyl 2-hydroxy-3-methylenesuccinate (23)



Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	29.133	3372119	50.865	95328	51.94
2	30.983	3257382	49.135	88218	48.06
Totals		6629501	100.000	183546	100.00

HPLC data of (–)-dimethyl 2-hydroxy-3-methylenesuccinate (23)



Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	28.917	6045685	100.000	159091	100.00
Totals		6045685	100.000	159091	100.00

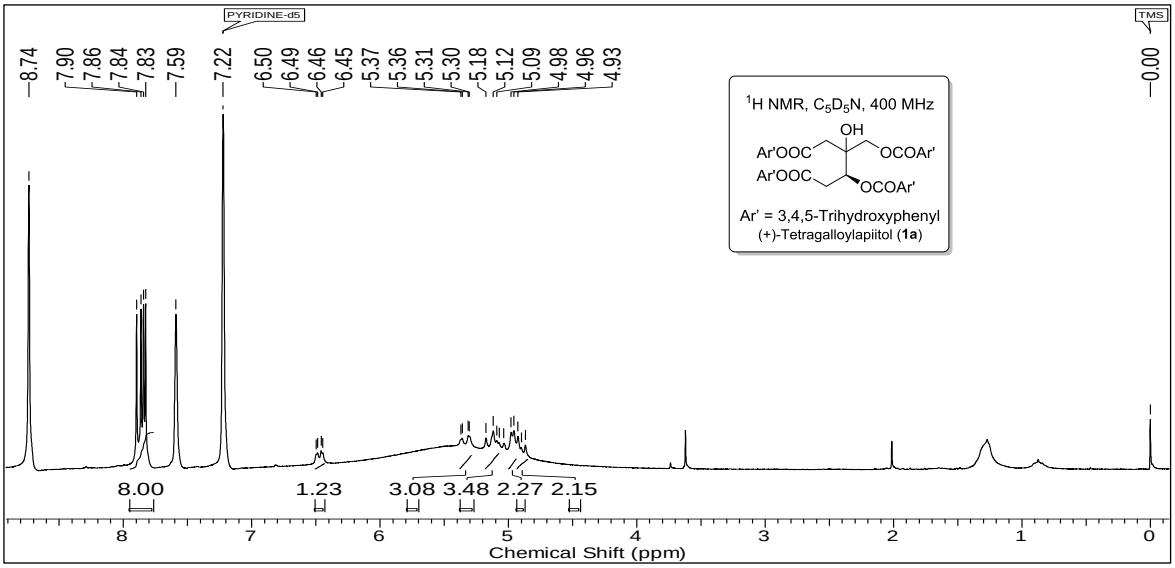
Column: Kromasil 5-CelluCoat (250 mm × 4.6 mm)

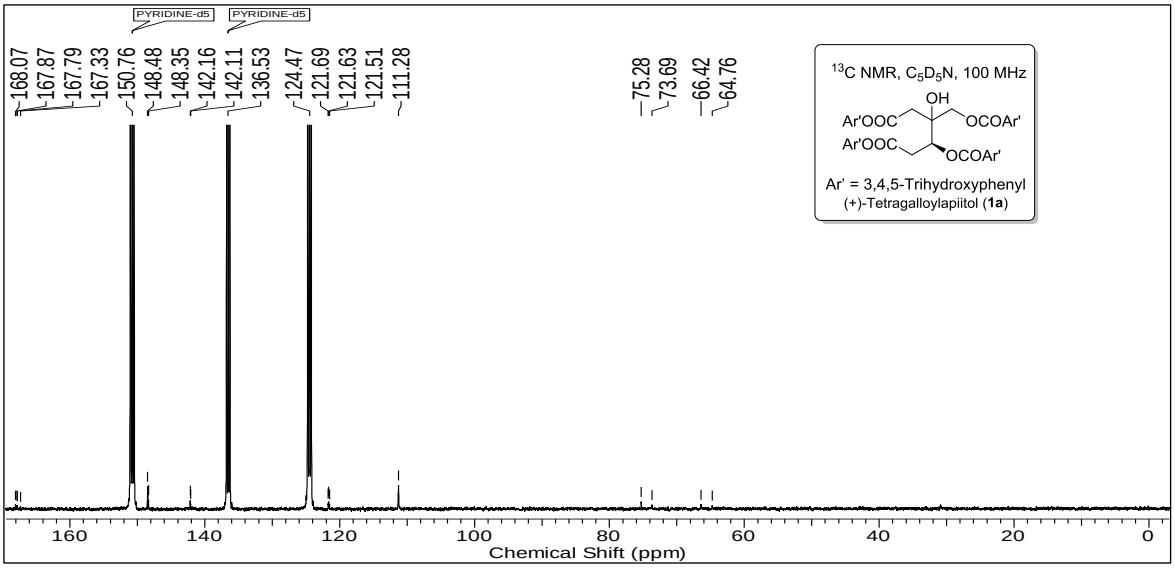
Mobile Phase: IPA:PE (05:95)

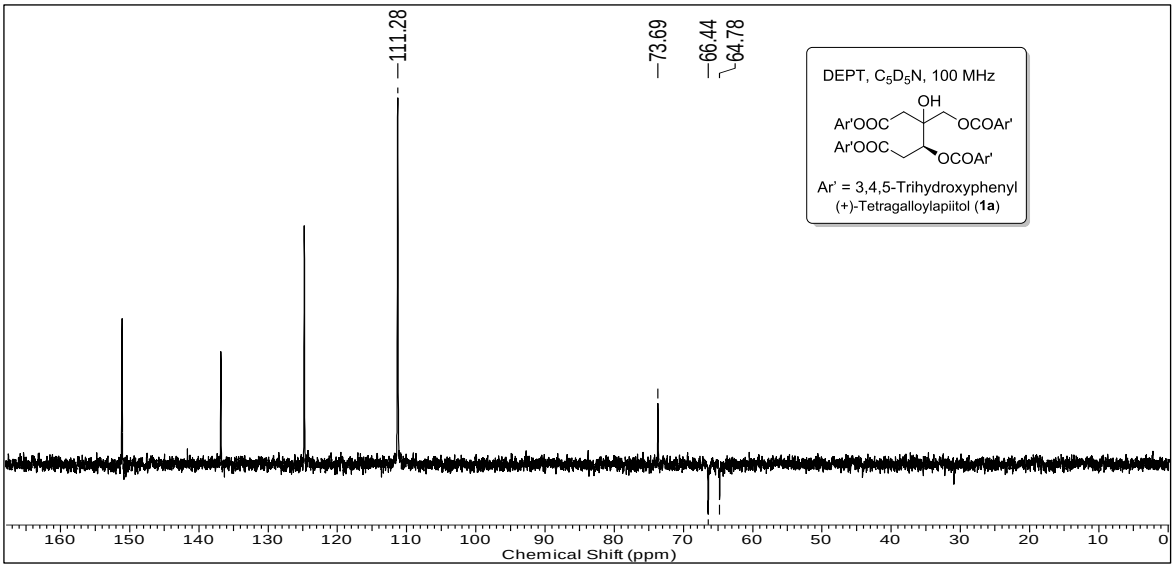
Wavelength: 220 nm

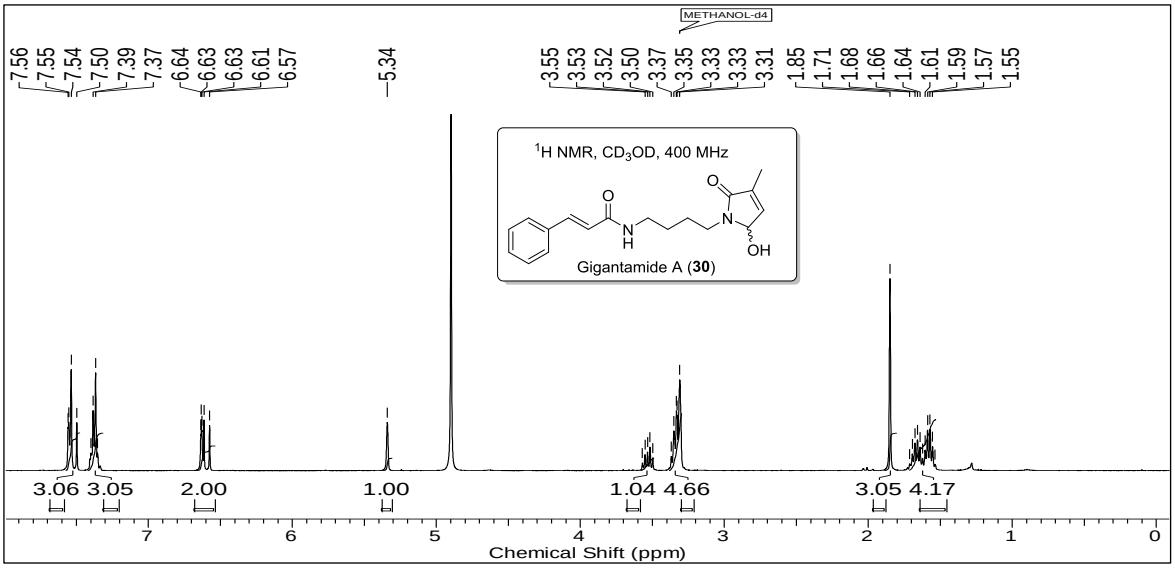
Flow Rate: 0.5 mL/min

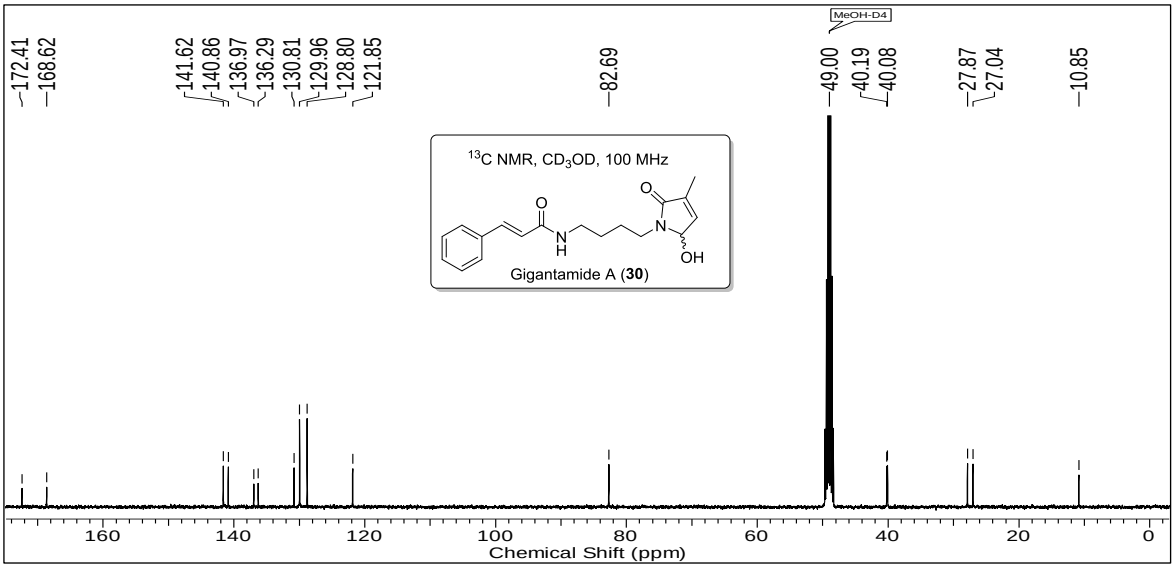
Sample Conc.: 2 mg/mL

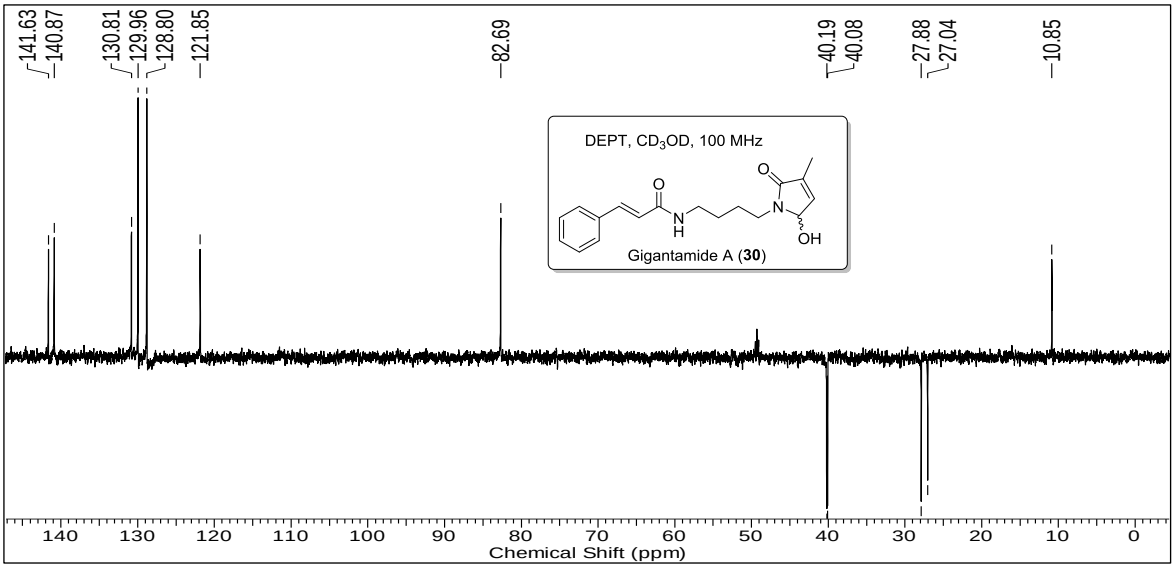

PYRIDINE-d5
TMS
8.74
7.90
7.86
7.84
7.83
7.59
7.22
6.50
6.49
6.46
6.45
5.37
5.36
5.31
5.30
5.18
5.12
5.09
4.98
4.96
4.93
0.00
^{1}H NMR, C_5D_5N, 400 MHz
OH
Ar'OOC
OCOAr'
Ar'OOC
OCOAr'
Ar' = 3,4,5-Trihydroxyphenyl
(+)-Tetragalloylapiitol (1a)
8.00
1.23
3.08 3.48 2.27 2.15
Chemical Shift (ppm)

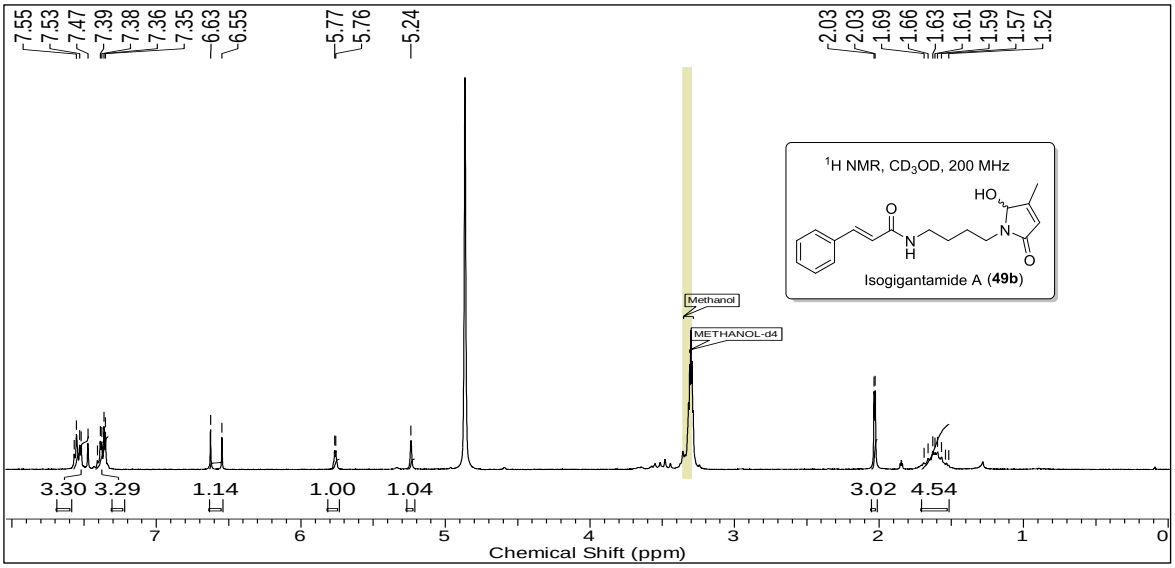

PYRIDINE-d5
PYRIDINE-d5
168.07
167.87
167.79
167.33
150.76
148.48
148.35
142.16
142.11
136.53
124.47
121.69
121.63
121.51
111.28
75.28
73.69
66.42
64.76
^{13}C NMR, C_5D_5N, 100 MHz
OH
Ar'OOC
OCOAr'
Ar'OOC
OCOAr'
Ar' = 3,4,5-Trihydroxyphenyl
(+)-Tetragalloylapiitol (1a)
Chemical Shift (ppm)

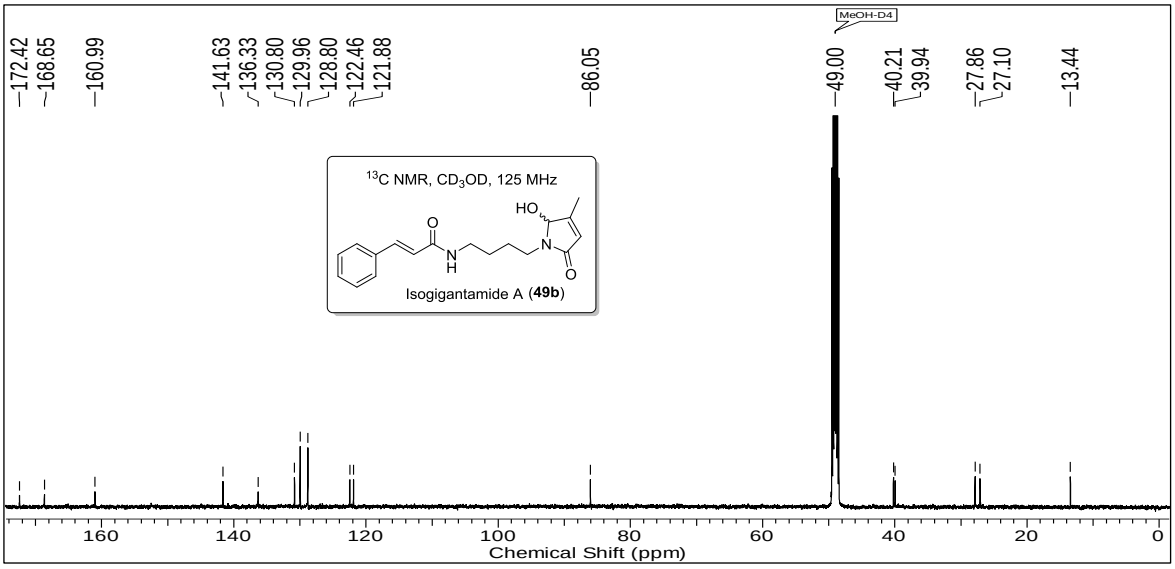

111.28
73.69
66.44
64.78
DEPT, C_5D_5N, 100 MHz
OH
Ar'OOC
OCOAr'
Ar'OOC
OCOAr'
Ar' = 3,4,5-Trihydroxyphenyl
(+)-Tetragalloylapiitol (1a)
Chemical Shift (ppm)

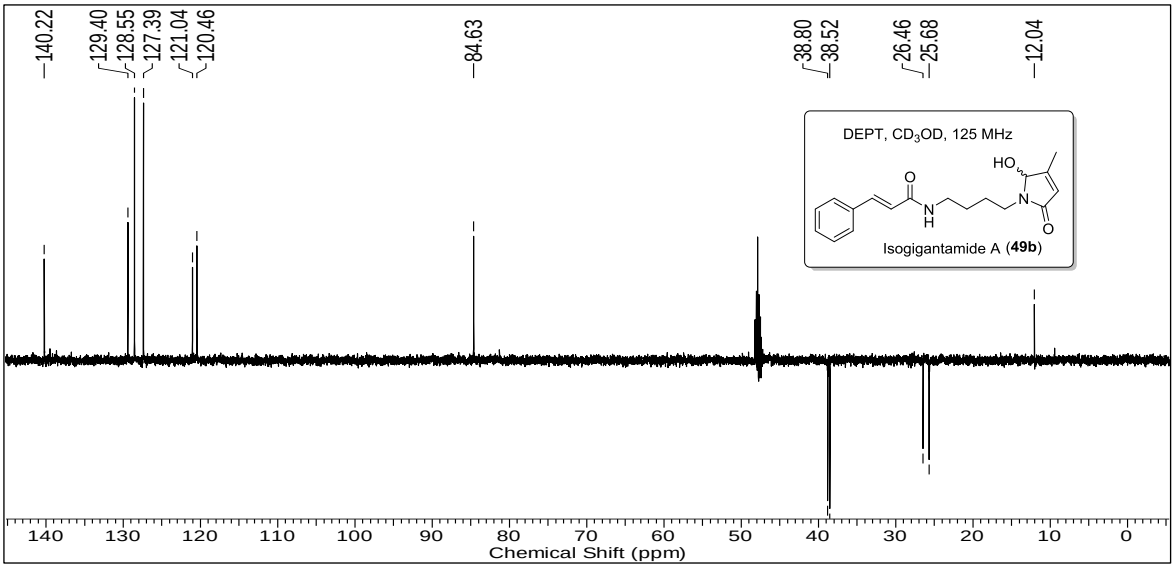

METHANOL-d4
7.56 7.55 7.54 7.50 7.39 7.37 6.64 6.63 6.63 6.61 6.57
5.34
3.55 3.53 3.52 3.50 3.37 3.35 3.33 3.33 3.31
1.85 1.71 1.68 1.66 1.64 1.61 1.59 1.57 1.55
^{1}H NMR, CD_3OD, 400 MHz
Gigantamide A (30)
3.06 3.05 2.00 1.00 1.04 4.66 3.05 4.17
Chemical Shift (ppm)

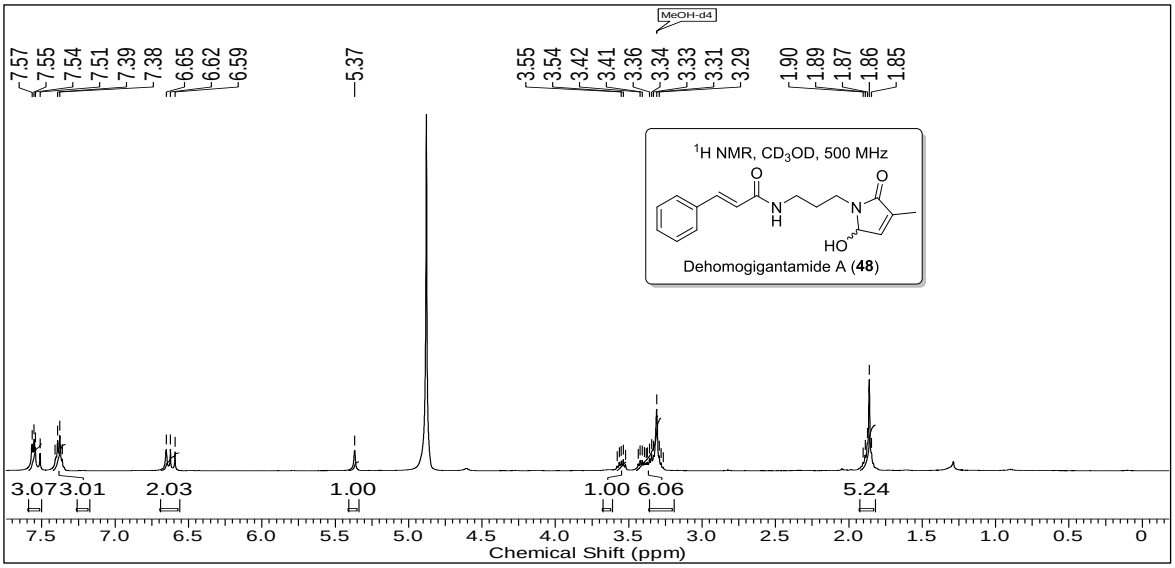

MeOH-D4
172.41 168.62 141.62 140.86 136.97 136.29 130.81 129.96 128.80 121.85
82.69
49.00 40.19 40.08 27.87 27.04 10.85
^{13}C NMR, CD_3OD, 100 MHz
Gigantamide A (30)
Chemical Shift (ppm)

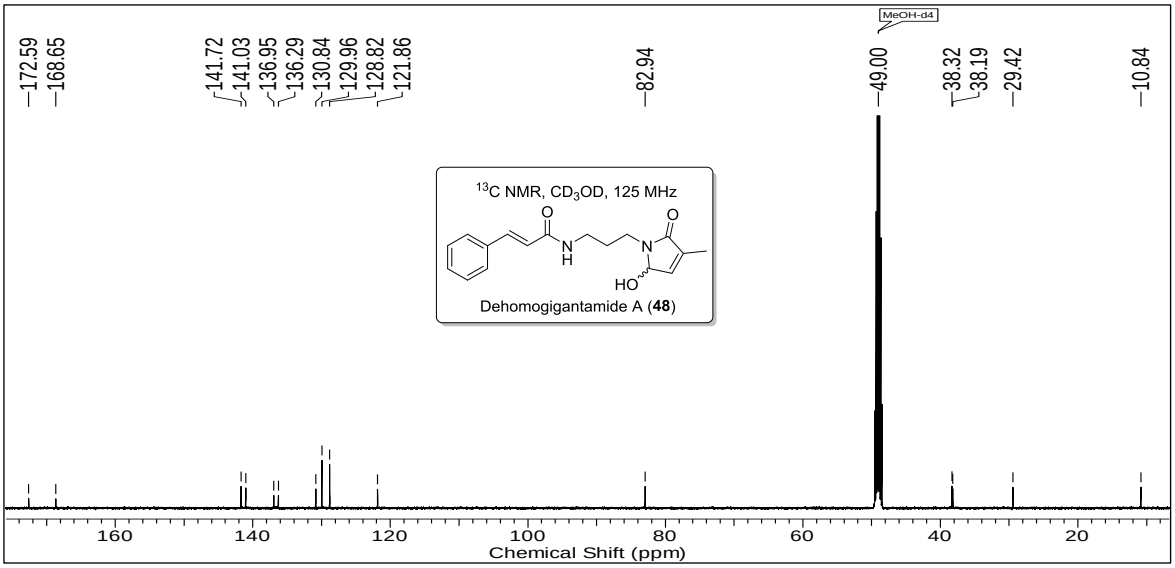

141.63 140.87 130.81 129.96 128.80 121.85
82.69
40.19 40.08 27.88 27.04 10.85
DEPT, CD_3OD, 100 MHz
Gigantamide A (30)
Chemical Shift (ppm)

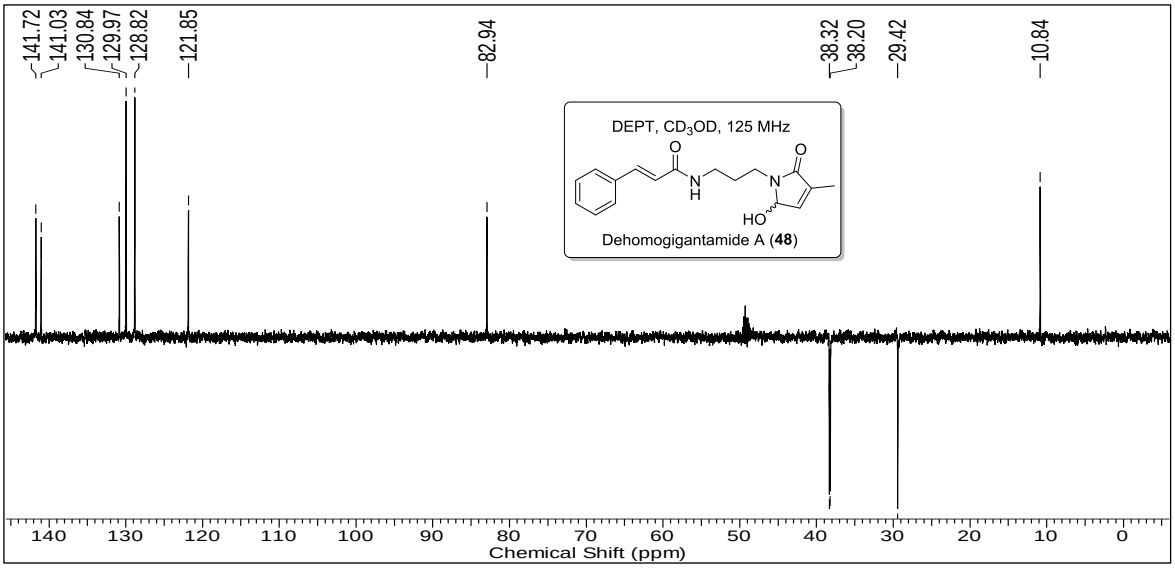

7.55
7.53
7.47
7.39
7.38
7.36
7.35
6.63
6.55
5.77
5.76
5.24
2.03
2.03
1.69
1.66
1.63
1.61
1.59
1.57
1.52
^{1}H NMR, CD$_3$OD, 200 MHz
Isogigantamide A (**49b**)
Methanol
METHANOL-d4
3.30 3.29
1.14
1.00
1.04
3.02
4.54
Chemical Shift (ppm)

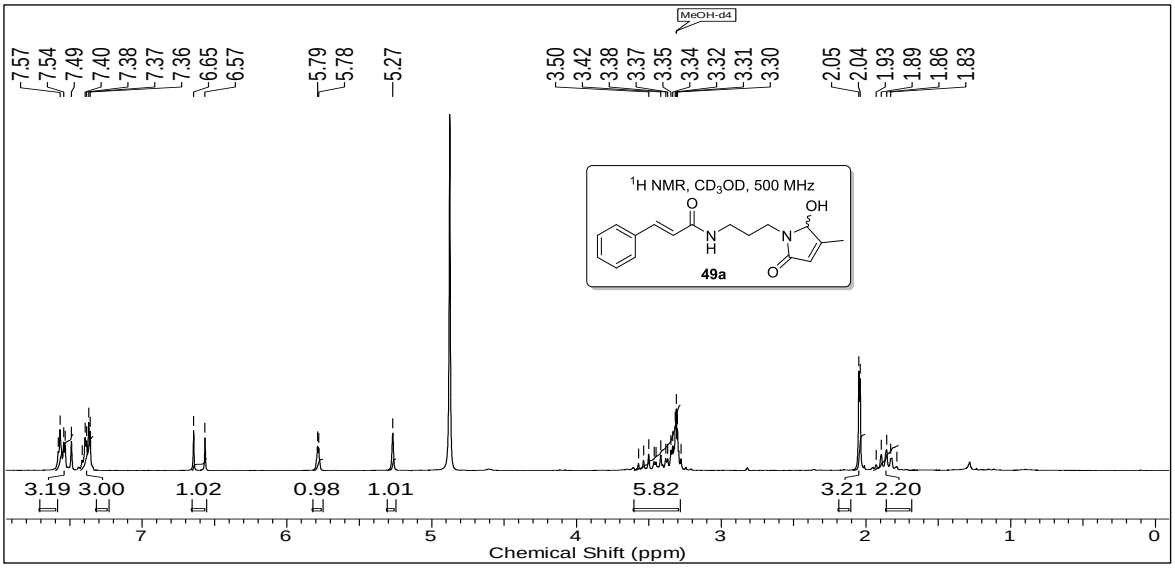

172.42
168.65
160.99
141.63
136.33
130.80
129.96
128.80
122.46
121.88
86.05
MeOH-D4
49.00
40.21
39.94
27.86
27.10
13.44
^{13}C NMR, CD$_3$OD, 125 MHz
Isogigantamide A (**49b**)
Chemical Shift (ppm)

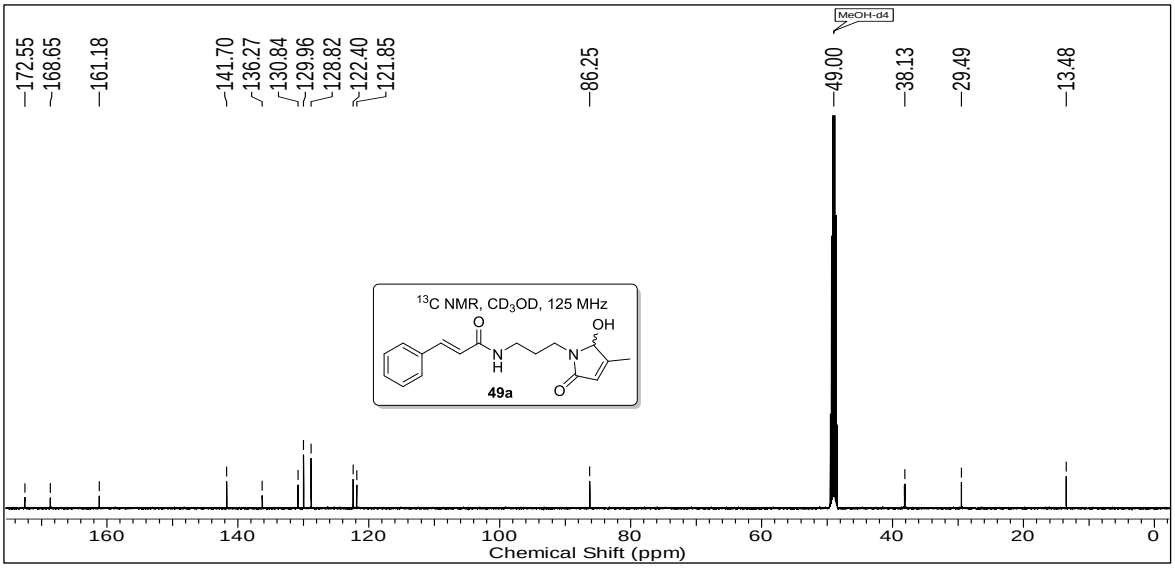

140.22
129.40
128.55
127.39
121.04
120.46
84.63
38.80
38.52
26.46
25.68
12.04
DEPT, CD$_3$OD, 125 MHz
Isogigantamide A (**49b**)
Chemical Shift (ppm)

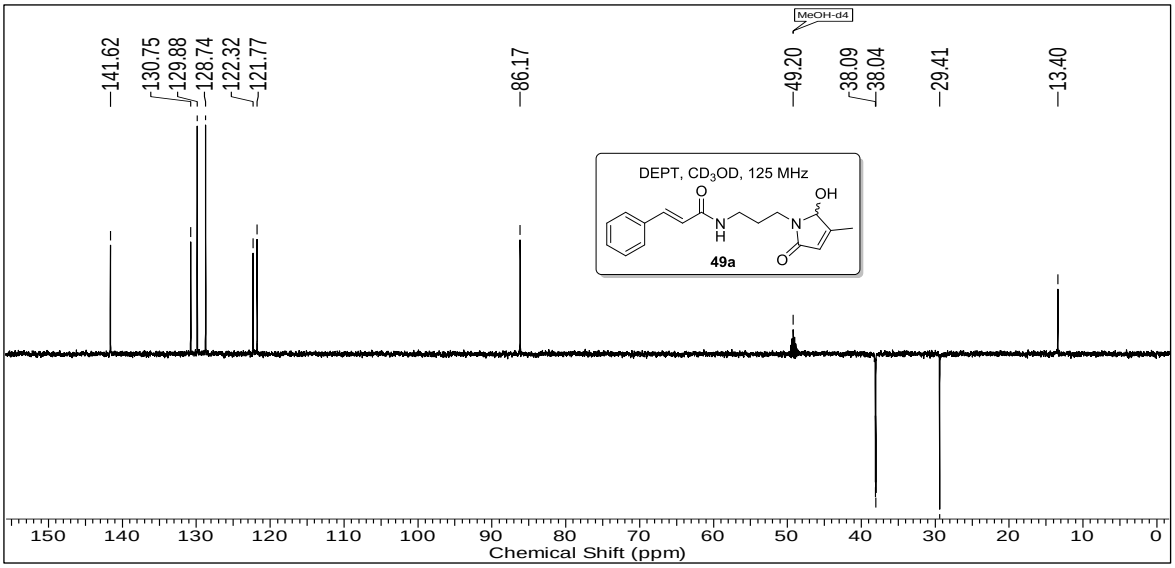

MeOH-d4
7.57
7.55
7.54
7.51
7.39
7.38
6.65
6.62
6.59
5.37
3.55
3.54
3.42
3.41
3.36
3.34
3.33
3.31
3.29
1.90
1.89
1.87
1.86
1.85
^{1}H NMR, CD$_3$OD, 500 MHz
Dehomogigantamide A (48)
3.07
3.01
2.03
1.00
1.00
6.06
5.24
Chemical Shift (ppm)

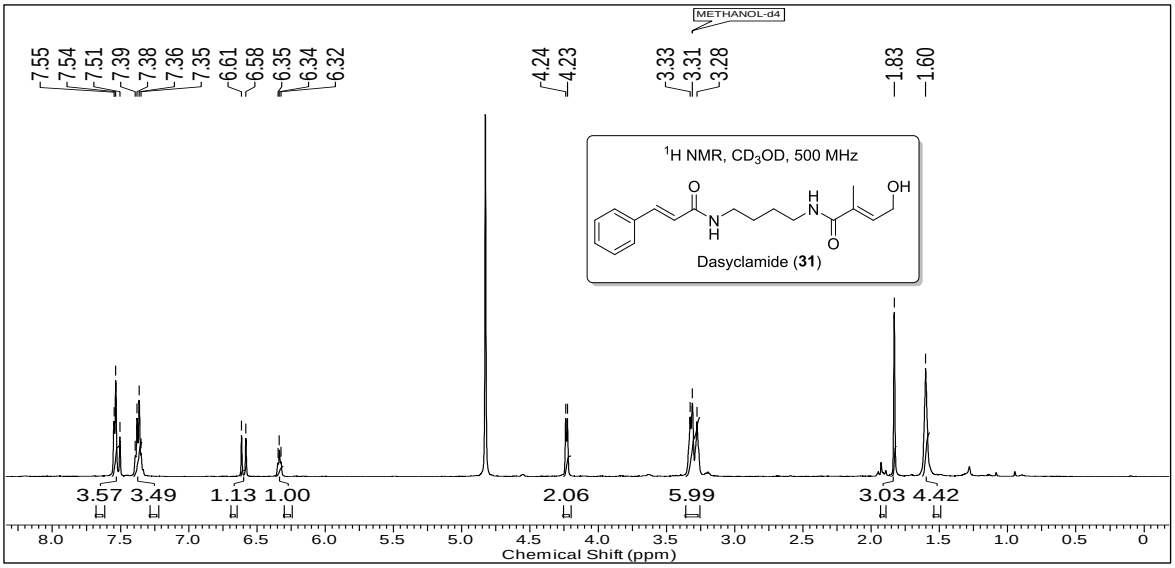

MeOH-d4
172.59
168.65
141.72
141.03
136.95
136.29
130.84
129.96
128.82
121.86
82.94
49.00
38.32
38.19
29.42
10.84
^{13}C NMR, CD$_3$OD, 125 MHz
Dehomogigantamide A (48)
Chemical Shift (ppm)

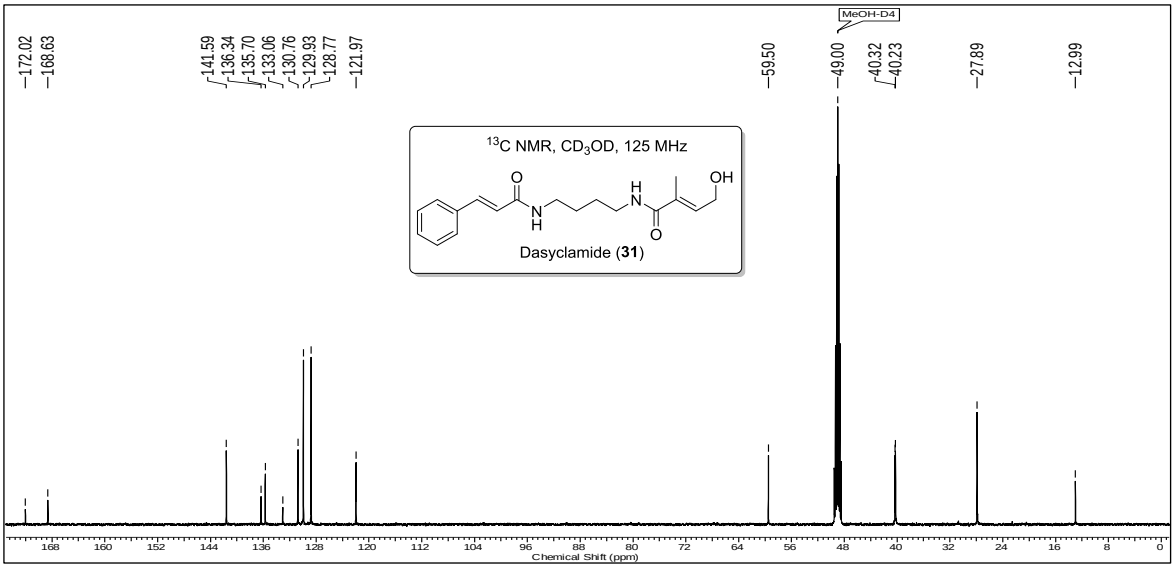

141.72
141.03
130.84
129.97
128.82
121.85
82.94
38.32
38.20
29.42
10.84
DEPT, CD$_3$OD, 125 MHz
Dehomogigantamide A (48)
Chemical Shift (ppm)

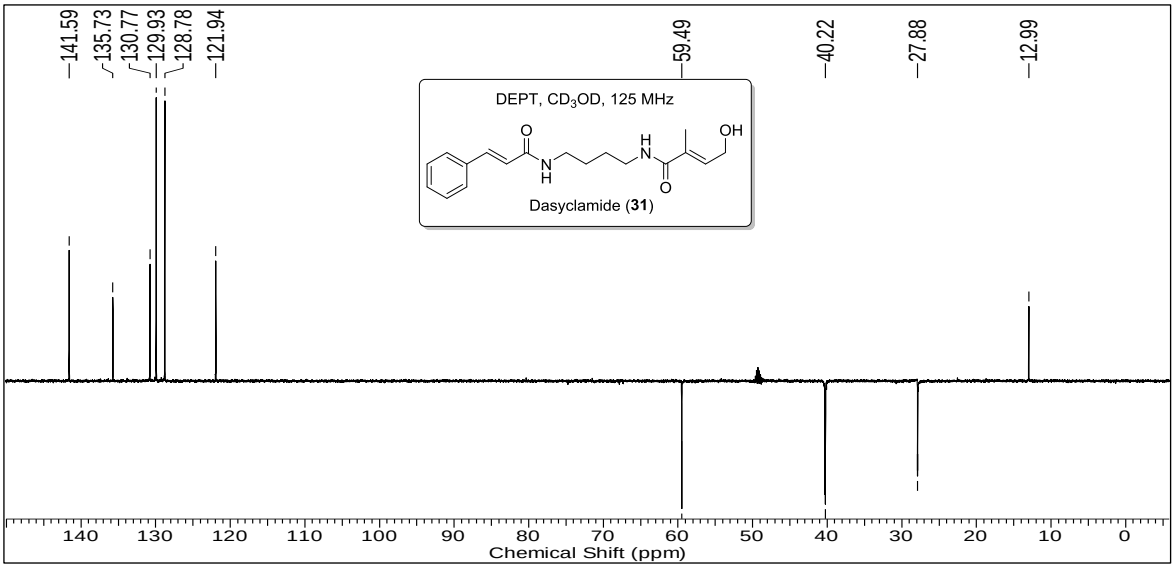

MeOH-d4
7.57
7.54
7.49
7.40
7.38
7.37
7.36
6.65
6.57
5.79
5.78
5.27
3.50
3.42
3.38
3.37
3.35
3.34
3.32
3.31
3.30
2.05
2.04
1.93
1.89
1.86
1.83
^{1}H NMR, CD$_3$OD, 500 MHz
49a
3.19
3.00
1.02
0.98
1.01
5.82
3.21
2.20
Chemical Shift (ppm)

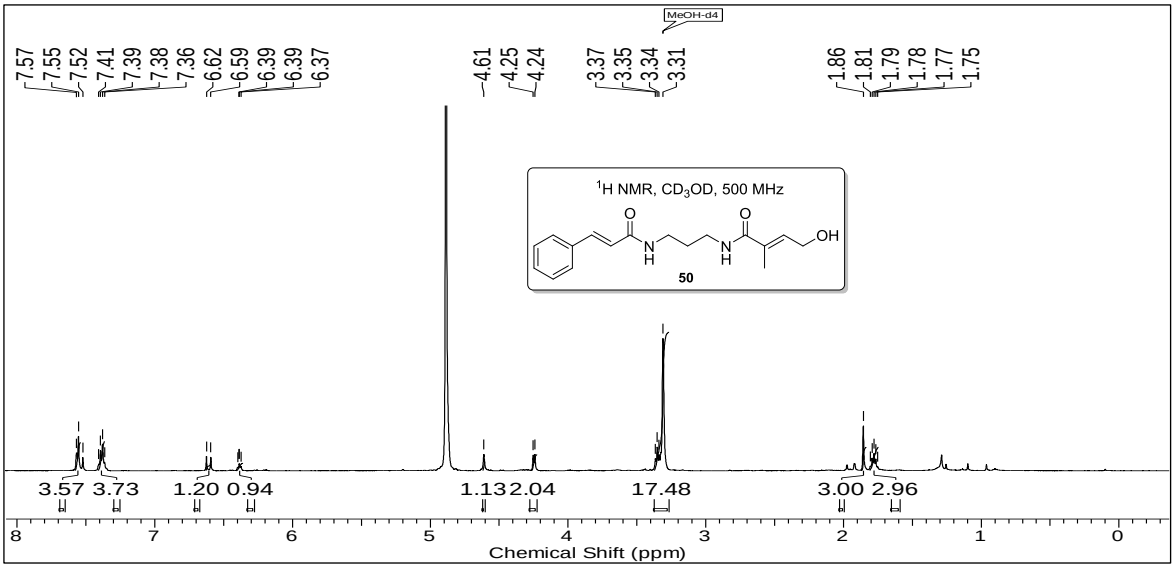

MeOH-d4
172.55
168.65
161.18
141.70
136.27
130.84
129.96
128.82
122.40
121.85
86.25
49.00
38.13
29.49
13.48
^{13}C NMR, CD$_3$OD, 125 MHz
49a
Chemical Shift (ppm)

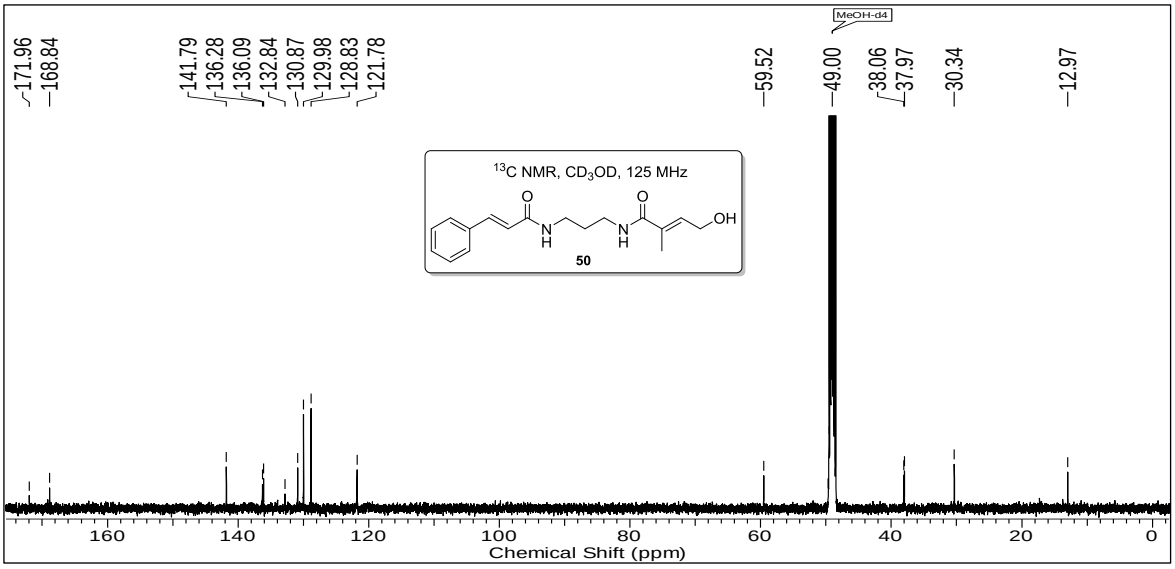

MeOH-d4
141.62
130.75
129.88
128.74
122.32
121.77
86.17
49.20
38.09
38.04
29.41
13.40
DEPT, CD$_3$OD, 125 MHz
49a
Chemical Shift (ppm)

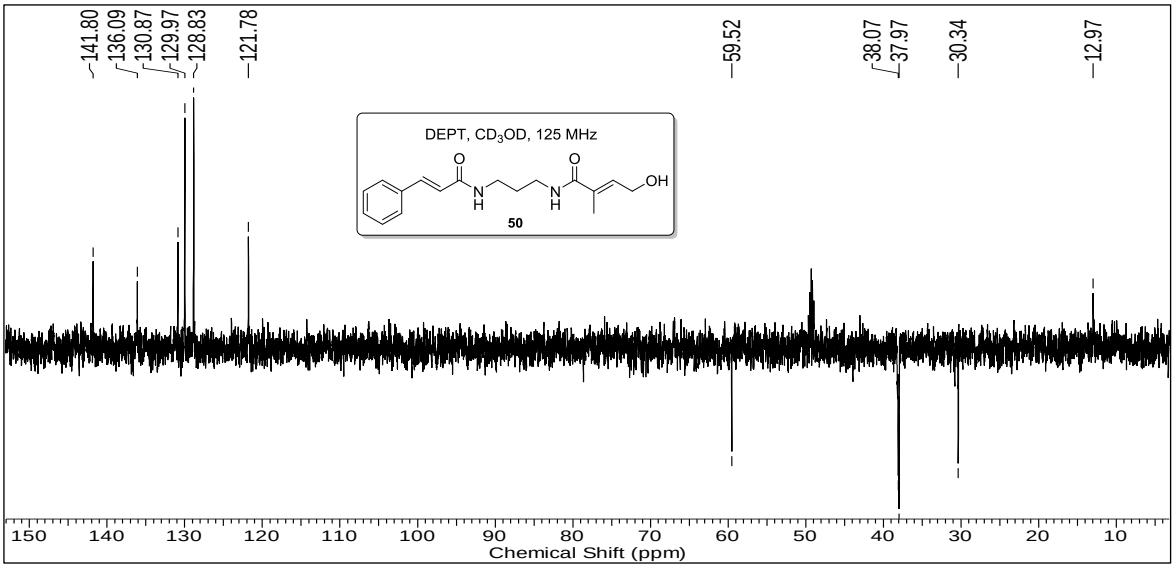

METHANOL-d4
7.55
7.54
7.51
7.39
7.38
7.36
7.35
6.61
6.58
6.35
6.34
6.32
4.24
4.23
3.33
3.31
3.28
1.83
1.60
^{1}H NMR, CD_3OD, 500 MHz
Dasyclamide (31)
3.57 3.49 1.13 1.00 2.06 5.99 3.03 4.42
Chemical Shift (ppm)

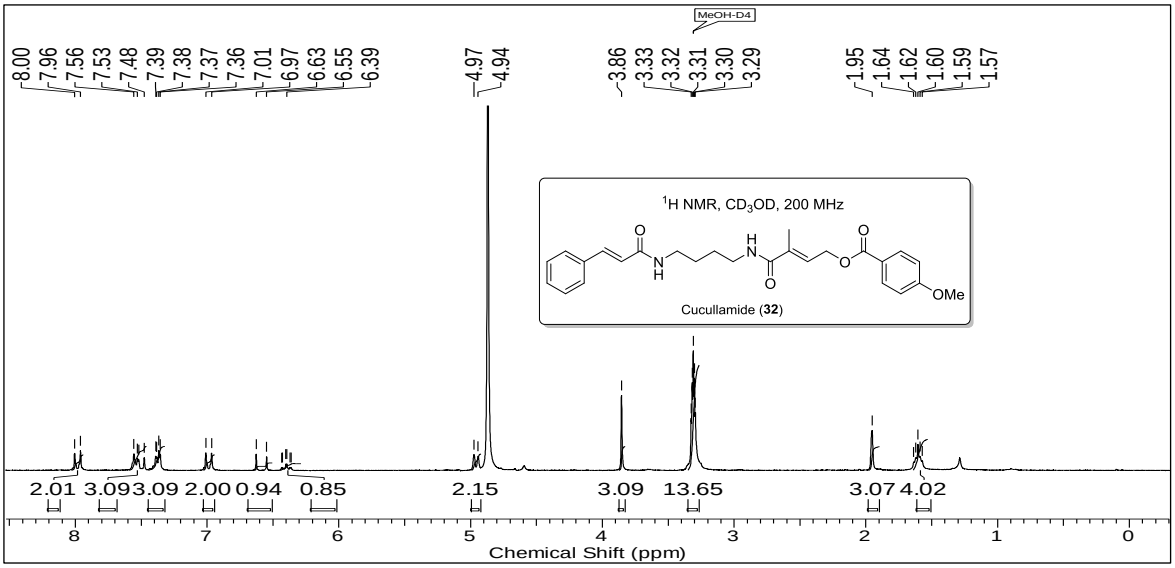

MeOH-D4
172.02
168.63
141.59
136.34
135.70
133.06
130.76
129.93
128.77
121.97
59.50
49.00
40.32
40.23
27.89
12.99
^{13}C NMR, CD_3OD, 125 MHz
Dasyclamide (31)
Chemical Shift (ppm)

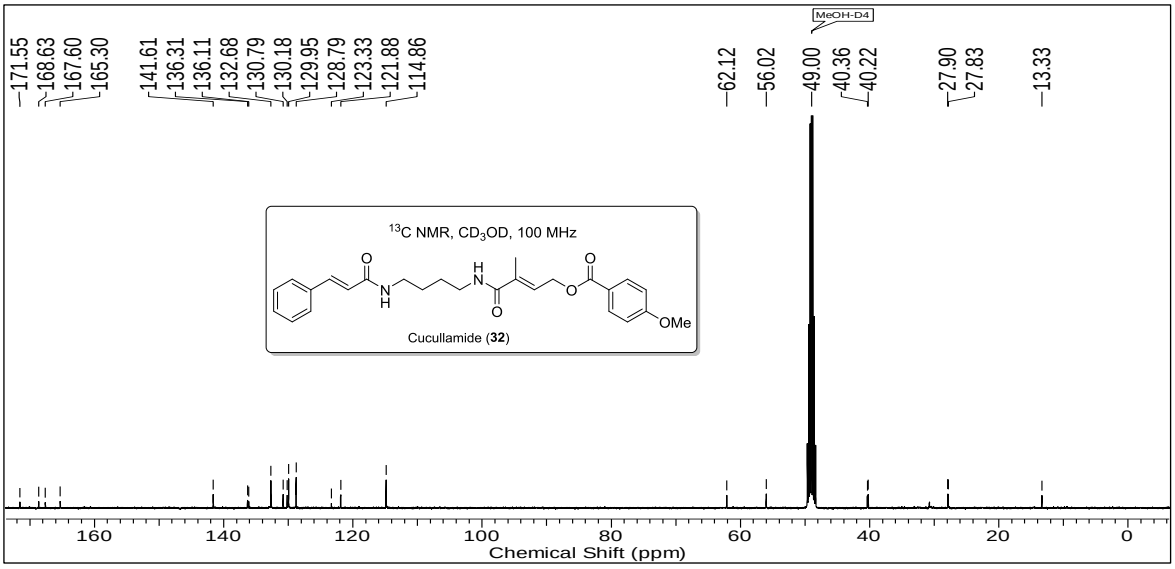

141.59
135.73
130.77
129.93
128.78
121.94
59.49
40.22
27.88
12.99
DEPT, CD_3OD, 125 MHz
Dasyclamide (31)
Chemical Shift (ppm)

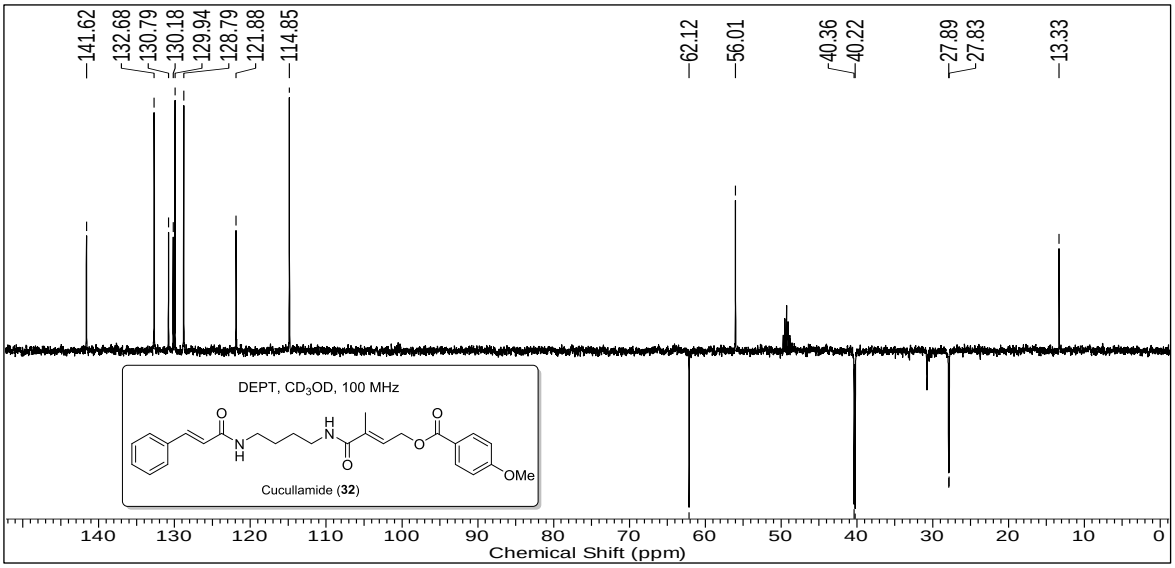

MeOH-d4
7.57
7.55
7.52
7.41
7.39
7.38
7.36
6.62
6.59
6.39
6.39
6.37
4.61
4.25
4.24
3.37
3.35
3.34
3.31
1.86
1.81
1.79
1.78
1.77
1.75
^{1}H NMR, CD_3OD, 500 MHz
50
3.57 3.73
1.20 0.94
1.13 2.04
17.48
3.00 2.96
Chemical Shift (ppm)

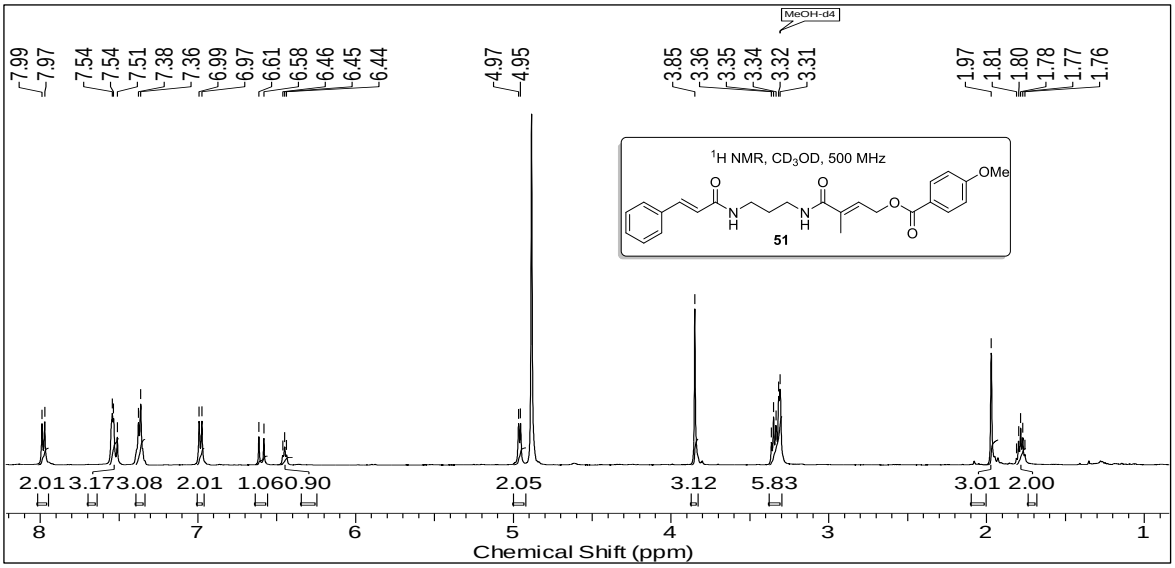

MeOH-d4
171.96
168.84
141.79
136.28
136.09
132.84
130.87
129.98
128.83
121.78
59.52
49.00
38.06
37.97
30.34
12.97
^{13}C NMR, CD_3OD, 125 MHz
50
Chemical Shift (ppm)

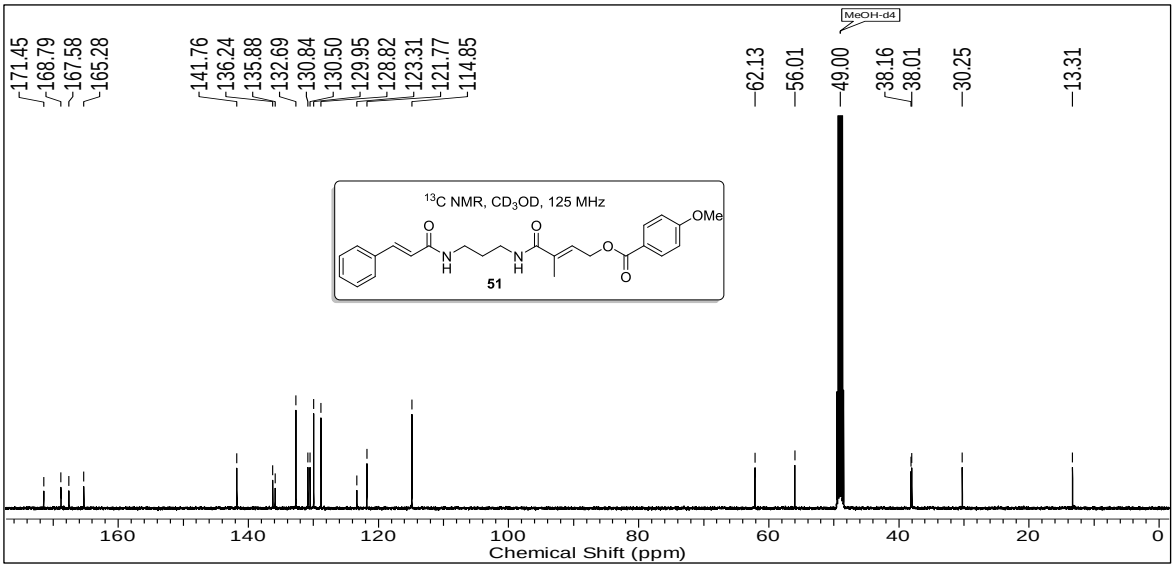

141.80
136.09
130.87
129.97
128.83
121.78
59.52
38.07
37.97
30.34
12.97
DEPT, CD_3OD, 125 MHz
50
Chemical Shift (ppm)

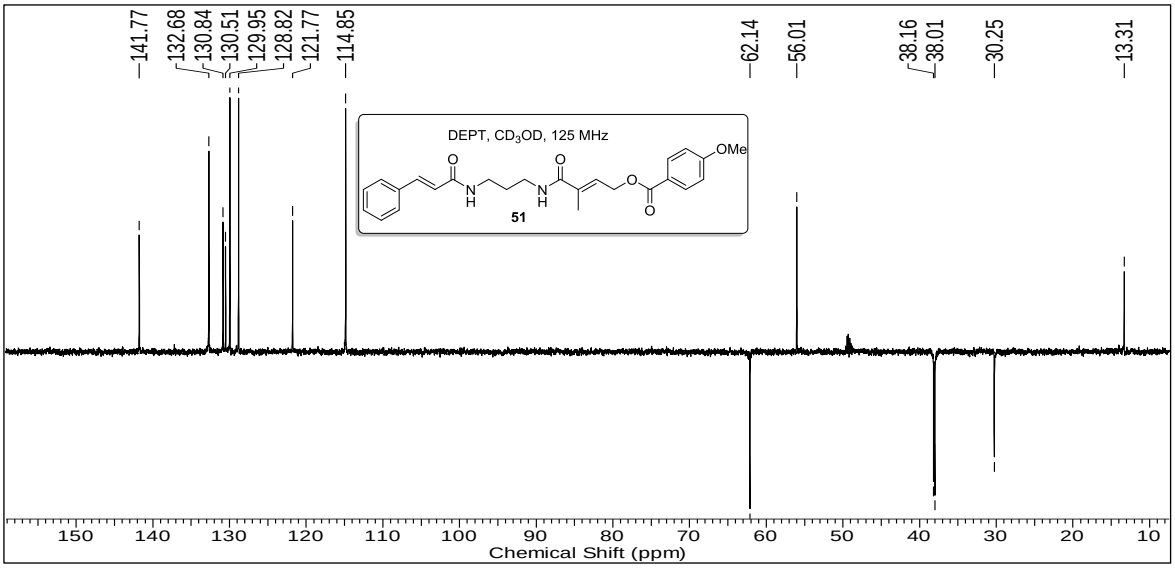

MeOH-D4
8.00 7.96 7.56 7.53 7.48 7.39 7.38 7.37 7.36 7.01 6.97 6.63 6.55 6.39
4.97 4.94
3.86 3.33 3.32 3.31 3.30 3.29
1.95 1.64 1.62 1.60 1.59 1.57
^{1}H NMR, CD_3OD, 200 MHz
Cucullamide (32)
2.01 3.09 3.09 2.00 0.94 0.85 2.15 3.09 13.65 3.07 4.02
Chemical Shift (ppm)


MeOH-D4
171.55 168.63 167.60 165.30 141.61 136.31 136.11 132.68 130.79 130.18 129.95 128.79 123.33 121.88 114.86
62.12 56.02 49.00 40.36 40.22 27.90 27.83 13.33
^{13}C NMR, CD_3OD, 100 MHz
Cucullamide (32)
Chemical Shift (ppm)

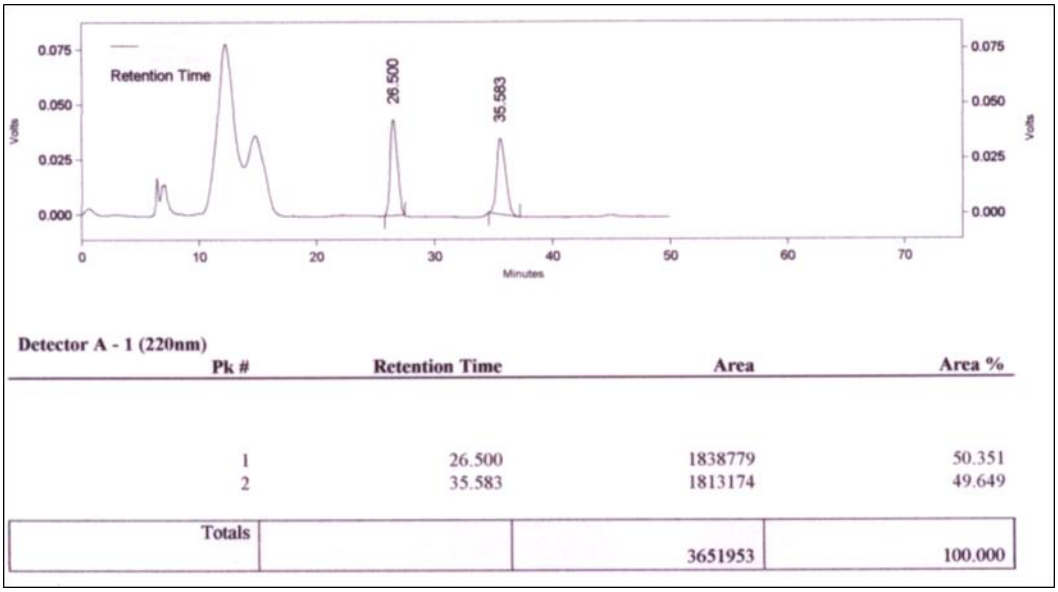

141.62 132.68 130.79 130.18 129.94 128.79 121.88 114.85
62.12 56.01 40.36 40.22 27.89 27.83 13.33
DEPT, CD_3OD, 100 MHz
Cucullamide (32)
Chemical Shift (ppm)


MeOH-d4
7.99
7.97
7.54
7.54
7.51
7.38
7.36
6.99
6.97
6.61
6.58
6.46
6.45
6.44
4.97
4.95
3.85
3.36
3.35
3.34
3.32
3.31
1.97
1.81
1.80
1.78
1.77
1.76
^{1}H NMR, CD_3OD, 500 MHz
OMe
51
2.01 3.17 3.08 2.01 1.06 0.90
2.05
3.12
5.83
3.01 2.00
Chemical Shift (ppm)


MeOH-d4
171.45
168.79
167.58
165.28
141.76
136.24
135.88
132.69
130.84
130.50
129.95
128.82
123.31
121.77
114.85
62.13
56.01
49.00
38.16
38.01
30.25
13.31
^{13}C NMR, CD_3OD, 125 MHz
OMe
51
Chemical Shift (ppm)


141.77
132.68
130.84
130.51
129.95
128.82
121.77
114.85
62.14
56.01
38.16
38.01
30.25
13.31
DEPT, CD_3OD, 125 MHz
OMe
51
Chemical Shift (ppm)

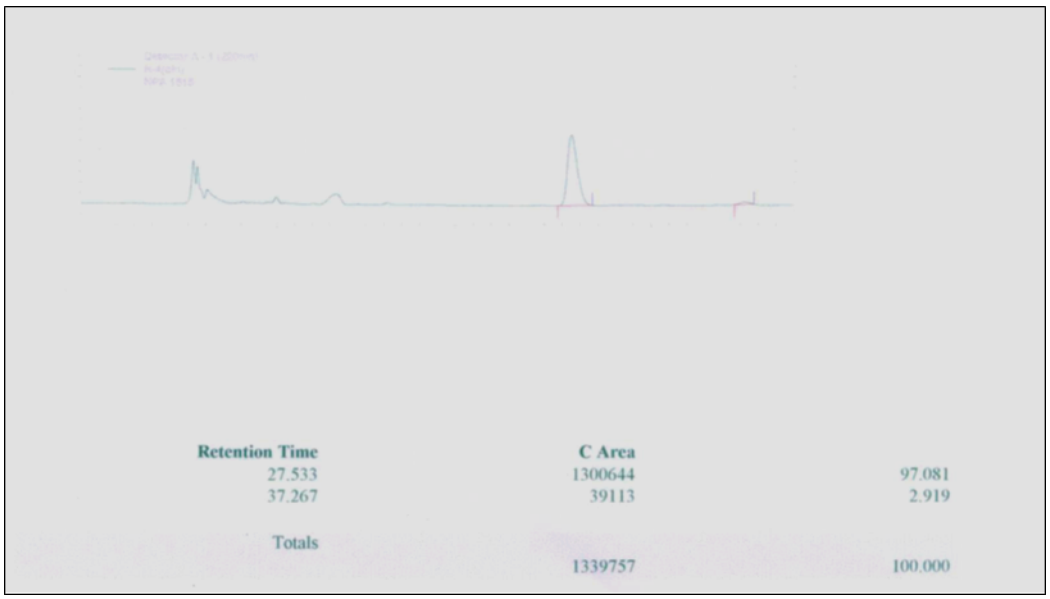
HPLC data of (±)-dimethyl 2-acetoxy-3-methylenesuccinate (21)



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	26.500	1838779	50.351
2	35.583	1813174	49.649
Totals		3651953	100.000

HPLC data of (+)-dimethyl 2-acetoxy-3-methylenesuccinate (21)



Retention Time	C Area	
27.533	1300644	97.081
37.267	39113	2.919
Totals	1339757	100.000

Column: Kromasil 5-CelluCoat (250 mm × 4.6 mm)

Mobile Phase: IPA:*n*-hexane (1.5:98.5)

Wavelength: 220 nm

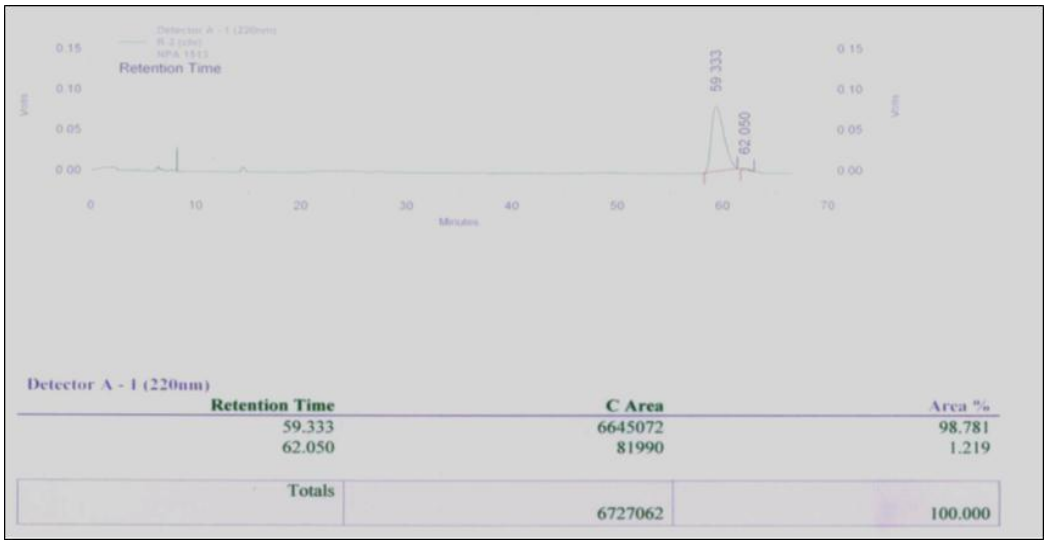
Flow Rate: 0.5 mL/min

Sample Conc.: 2 mg/mL

HPLC data of (±)-dimethyl 2-hydroxy-3-methylenesuccinate (23)

Retention Time	C Area	
59.067	2058106	44.499
60.867	2566931	55.501
Totals	4625037	100.000

HPLC data of (–)-dimethyl 2-hydroxy-3-methylenesuccinate (23)



Detector A - 1 (220nm)

Retention Time	C Area	Area %
59.333	6645072	98.781
62.050	81990	1.219
Totals	6727062	100.000

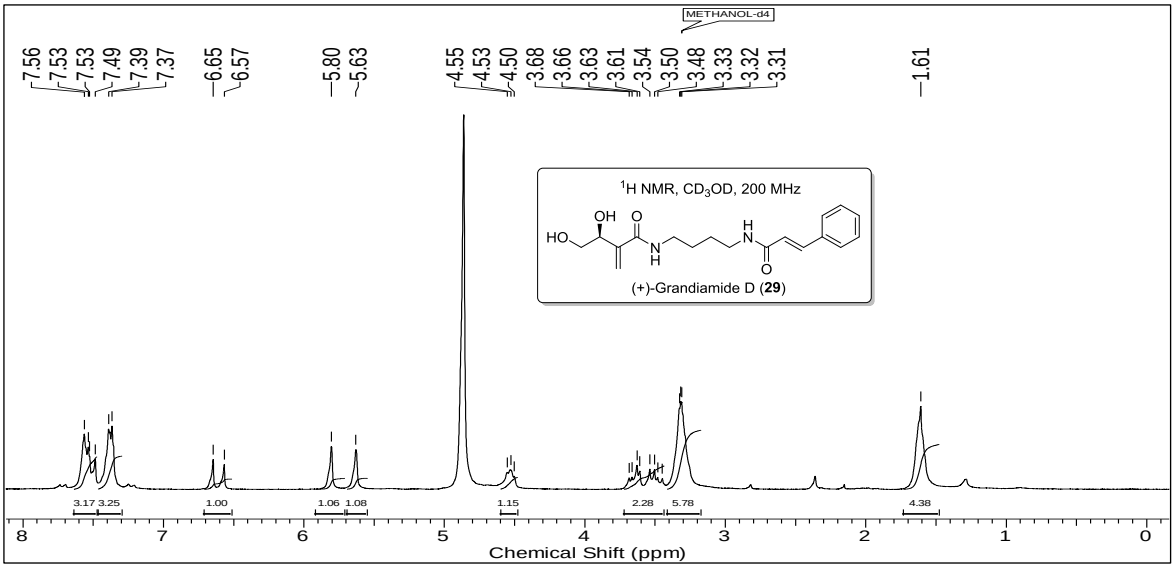
Column: Kromasil 5-CelluCoat (250 mm × 4.6 mm)

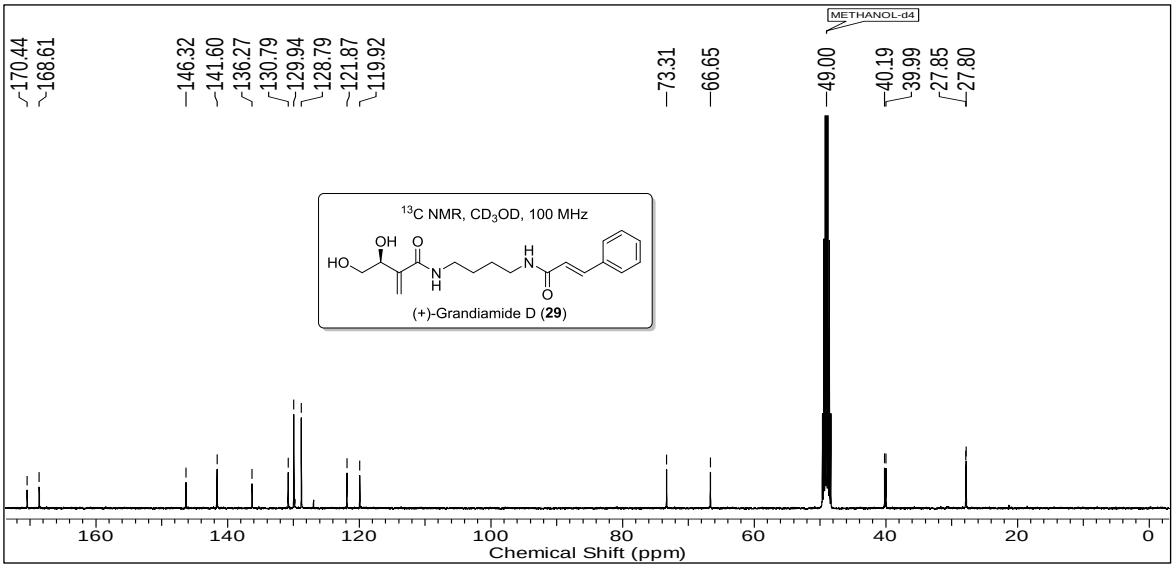
Mobile Phase: IPA:*n*-hexane (1.5:98.5)

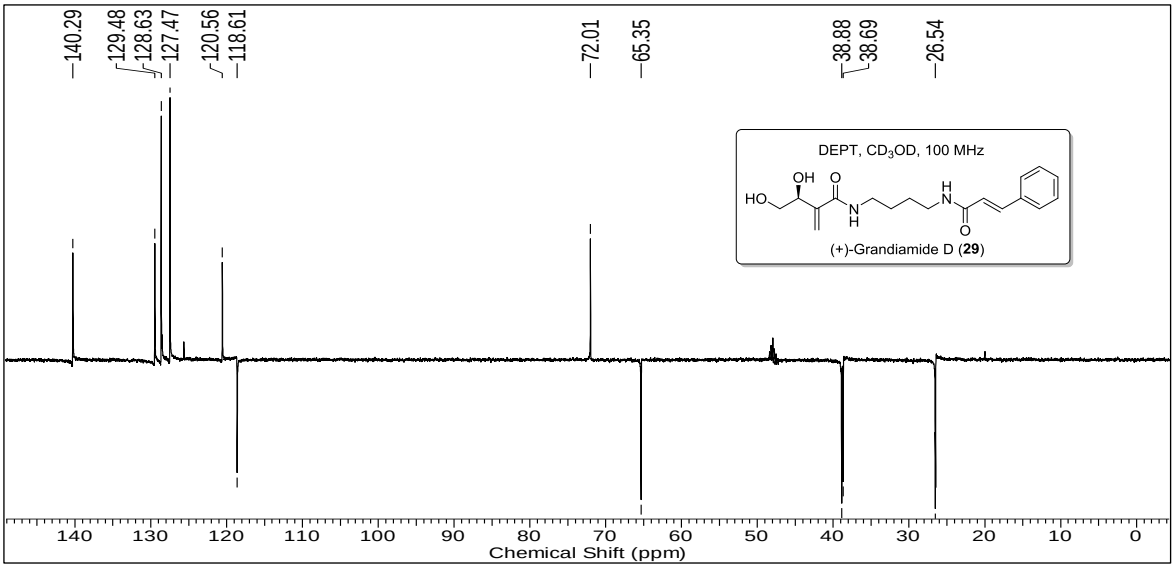
Wavelength: 220 nm

Flow Rate: 0.5 mL/min

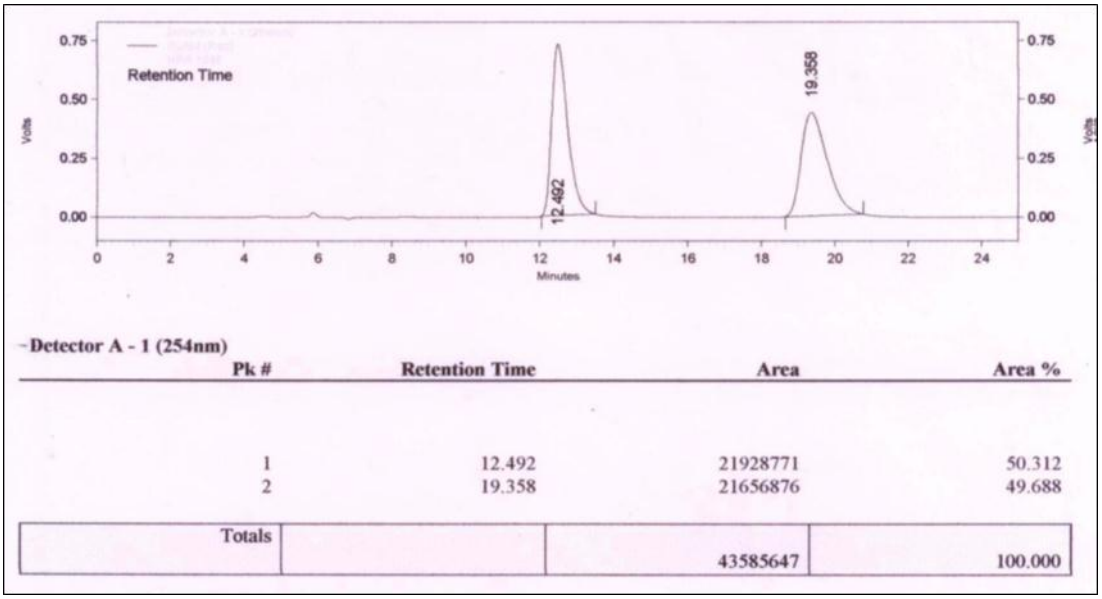
Sample Conc.: 2 mg/mL


METHANOL-d4
7.56
7.53
7.53
7.49
7.39
7.37
6.65
6.57
5.80
5.63
4.55
4.53
4.50
3.68
3.66
3.63
3.61
3.54
3.50
3.48
3.33
3.32
3.31
1.61
^{1}H NMR, CD_3OD, 200 MHz
(+)-Grandiamide D (**29**)
3.17 3.25
1.00
1.06 1.08
1.15
2.28
5.78
4.38
Chemical Shift (ppm)


METHANOL-d4
170.44
168.61
146.32
141.60
136.27
130.79
129.94
128.79
121.87
119.92
73.31
66.65
49.00
40.19
39.99
27.85
27.80
^{13}C NMR, CD_3OD, 100 MHz
(+)-Grandiamide D (**29**)
Chemical Shift (ppm)


140.29
129.48
128.63
127.47
120.56
118.61
72.01
65.35
38.88
38.69
26.54
DEPT, CD_3OD, 100 MHz
(+)-Grandiamide D (**29**)
Chemical Shift (ppm)

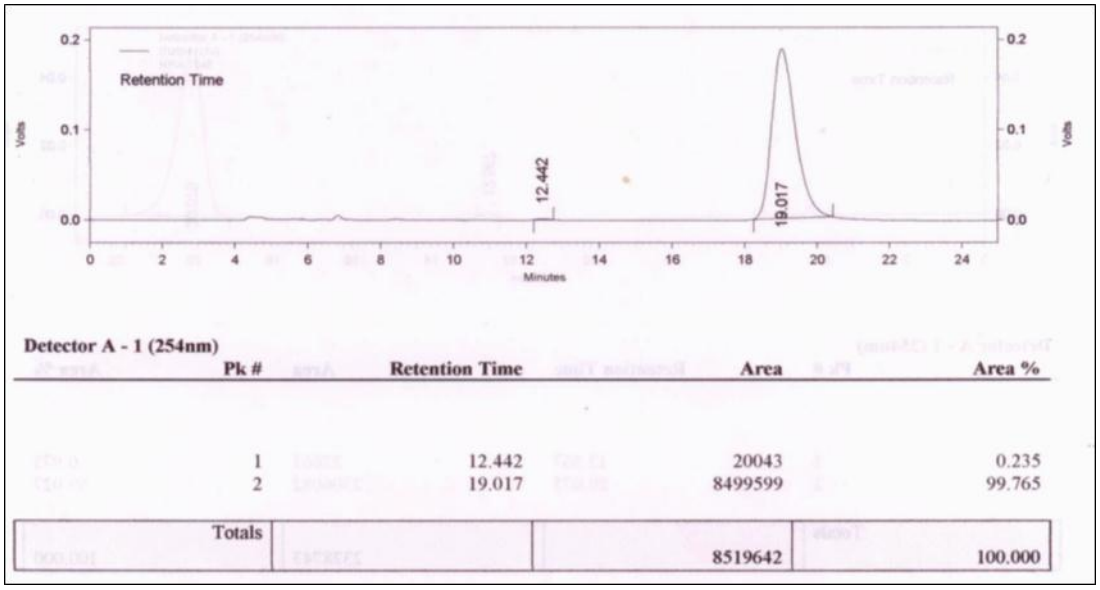
HPLC data of (±)-grandiamide D (29)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	12.492	21928771	50.312
2	19.358	21656876	49.688
Totals		43585647	100.000

HPLC data of (+)-grandiamide D (29)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	12.442	20043	0.235
2	19.017	8499599	99.765
Totals		8519642	100.000

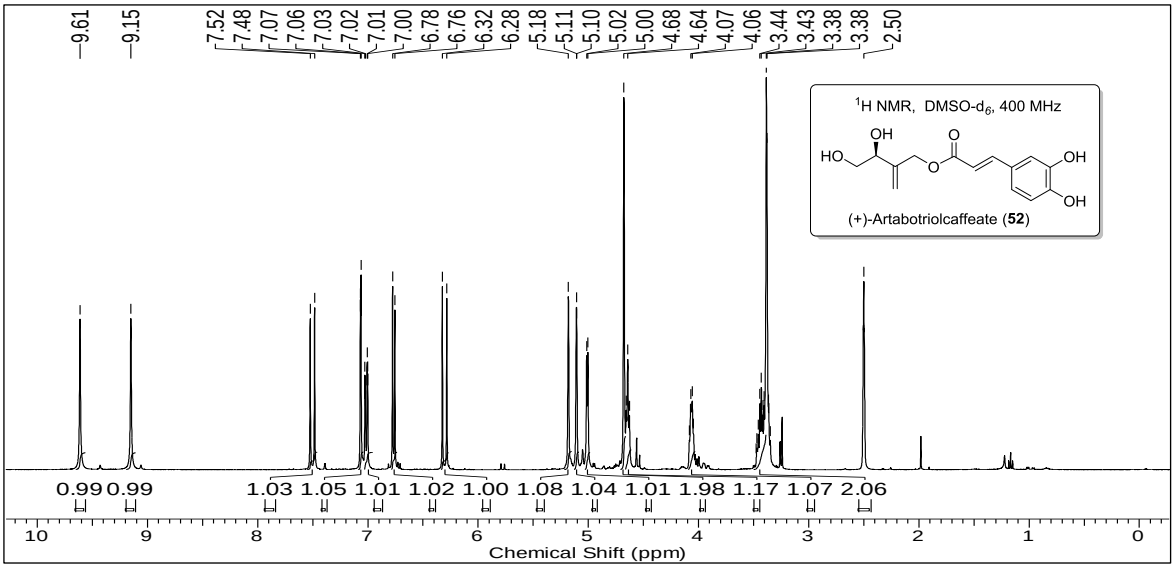
Column: Kromasil 5-AmyCoat (250 mm × 4.6 mm)

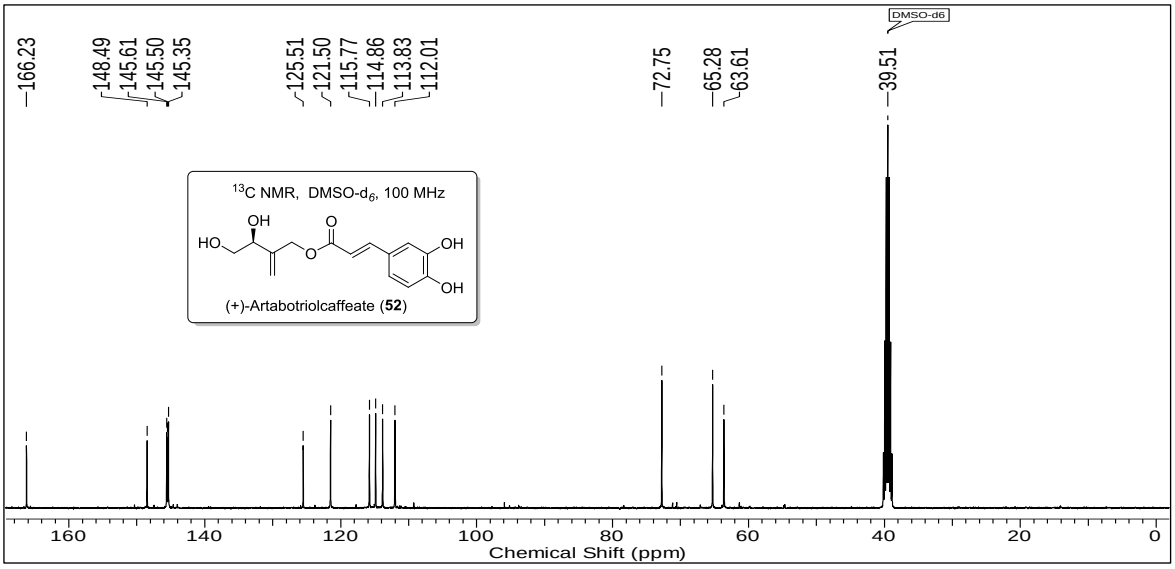
Mobile Phase: EtOH:PE (35:65)

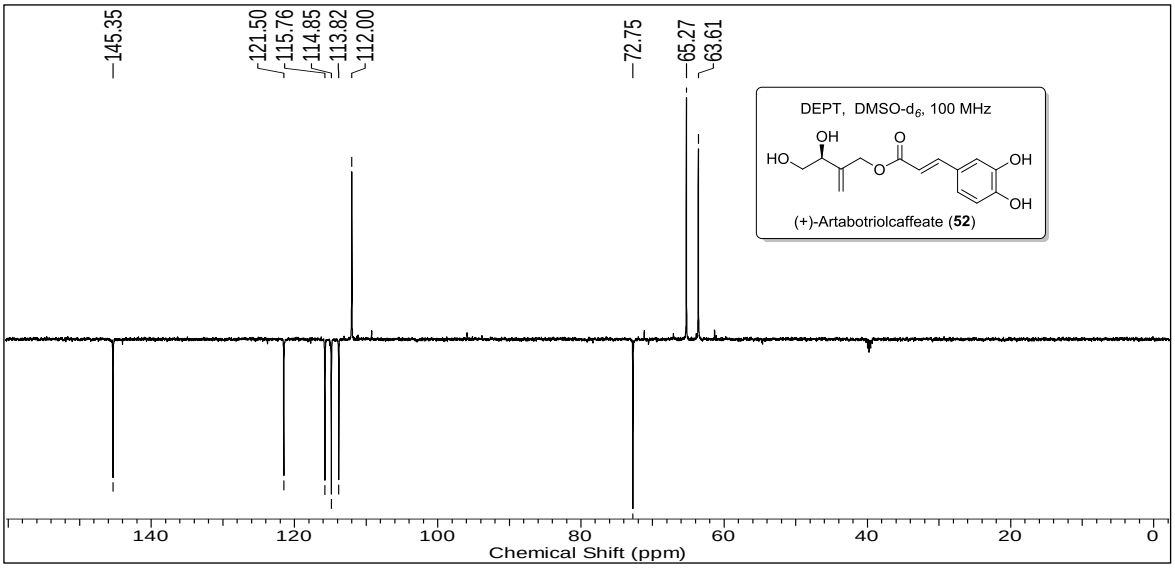
Wavelength: 254 nm

Flow Rate: 0.7 mL/min

Sample Conc.: 1 mg/mL


9.61
9.15
7.52
7.48
7.07
7.06
7.03
7.02
7.01
7.00
6.78
6.76
6.32
6.28
5.18
5.11
5.10
5.02
5.00
4.68
4.64
4.07
4.06
3.44
3.43
3.38
3.38
2.50
0.99 0.99
1.03 1.05 1.01 1.02 1.00 1.08 1.04 1.01 1.98 1.17 1.07 2.06
^{1}H NMR, DMSO-d$_6$, 400 MHz
(+)-Artabotriolcaffeate (52)
Chemical Shift (ppm)


166.23
148.49
145.61
145.50
145.35
125.51
121.50
115.77
114.86
113.83
112.01
72.75
65.28
63.61
39.51
DMSO-d6
^{13}C NMR, DMSO-d$_6$, 100 MHz
(+)-Artabotriolcaffeate (52)
Chemical Shift (ppm)


145.35
121.50
115.76
114.85
113.82
112.00
72.75
65.27
63.61
DEPT, DMSO-d$_6$, 100 MHz
(+)-Artabotriolcaffeate (52)
Chemical Shift (ppm)

1B.7 References

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Chapter 2

Chemoenzymatic Collective Synthesis of Bioactive Natural Products

This chapter features the following sections:

Independent referencing and numbering of compounds, schemes, tables & figures have been employed for Section A & B of Chapter 2

2A.Section A

A Concise Account on the Chemistry of Methoxy(methyl)tetralone Based Natural Products

This section features the following topics:

2A. A Concise Account on the Chemistry of Methoxy(methyl)tetralone Based Natural Products

The term terpenes originate from turpentine (*lat.* balsamum terebinthinae). Turpentine, the "resin of pine trees" is viscous pleasantly smelling balsam which flows upon cutting or carving the bark and the new wood of several pine tree species (Pinaceae). Turpentine contains the "resin acids" and some hydrocarbons, which were originally referred to as terpenes. Traditionally, all natural compounds built up from isoprene subunits and for the most part originating from plants are denoted as terpenes.[1]

Terpenes are predominantly responsible for pleasant smell, spicy taste, pharmacological activities of balm trees, conifer wood, coriander, citrus fruits, eucalyptus, lemon grass, lavender, lilies, caraway, carnation, peppermint species, rosemary, roses, sage, violet thyme, and large number of other plants or parts of those plants.

In order to enrich terpenes, the plants are carved for the production of incense or myrrh from balm trees. Generally terpenes are extracted or steam distilled. Precious oil of the blossoms of specific fragrant roses is recovered by extraction or steam distillation. These extracts and steam distillates, known as ethereal or essential oils "essence absolue" are used to create fine perfumes, to refine the flavor and the aroma of food and drinks and to produce medicines of plant origin (phytopharmaca).

2A.1 General Structure: The Isoprene Rule[2]

About 50000 terpenes are known at present in the literature.[3,4] Terpenes may be acyclic or cyclic, simple or complex, and of natural or synthetic origin. The cyclic terpenes have skeleton ranging from monocyclic to polycyclic. Their basic structure follows a general principle: 2-methylbutane residues, usually also referred as isoprene units, $(C_5)_n$, build up the carbon skeleton of terpenes; this is the isoprene rule.[1] In nature terpenes also denoted as *isoprenoids* occur predominantly as hydrocarbons, alcohols and their glycosides, ethers, aldehydes, ketones, carboxylic acids and esters. Depending on the number of 2-methylbutane (isoprene) subunits one differentiates between *hemi-* (C_5), *mono-* (C_{10}), *sesqui-* (C_{15}), *di-* (C_{20}), *sester-* (C_{25}), *tri-* (C_{30}), *tetraterpenes* (C_{40}) and *polyterpenes* $(C_5)_n$ with $n > 8$ according to Table 1. The isopropyl part of 2-methylbutane is defined as the *head*, and the ethyl residue as the *tail* (Table 1). In mono-, sesqui-, di- and sesterterpenes the isoprene units are linked to each other from *head-to-tail*; tri- and tetraterpenes contain one *tail-to-tail* connection in the center.

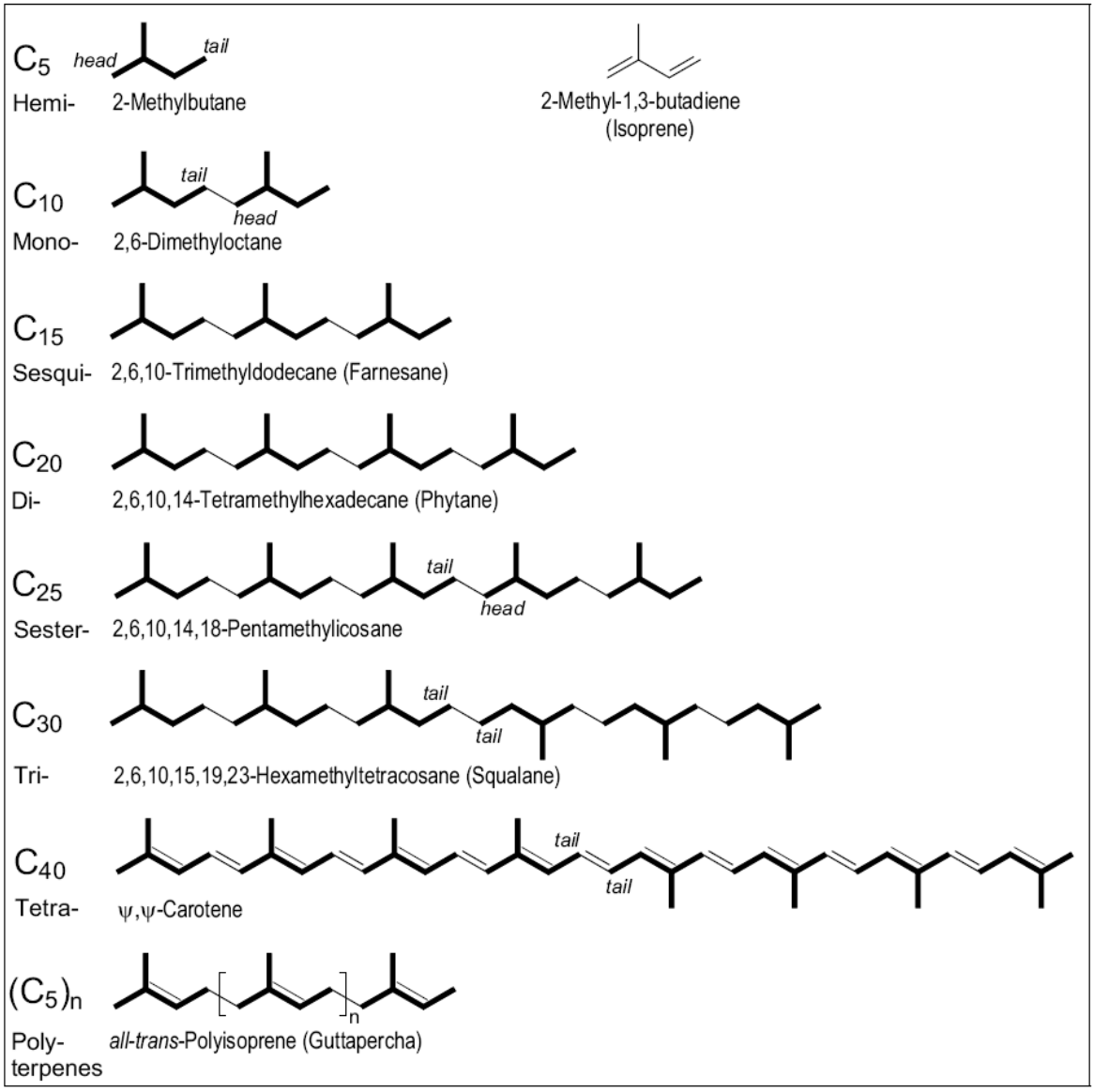


Table 1. Parent Hydrocarbons of Terpenes (Isoprenoids)[2]

(*Above figure is from the book: Terpenes; Wiley-VCH Verlag GmbH & Co. KGaA: Germany, 2006*).

2A.2 Biosynthesis[5]

To make terpenes, nature starts with the five-carbon building blocks isopentyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP).[5] These molecules are enzymatically joined to form longer chain diphosphates, which act as substrates for the terpene synthases. The terpene synthases catalyze reactions that increase the complexity of the linear molecules, effecting cyclizations thereby forming rings and stereocenters (Fig. 1).[6] From these cyclized structures, a large variety of compounds can be generated through further enzymatic conversions.[7]

Furthermore, terpenes generally function as secondary metabolites and terpene synthases produce a range of products.[8,9] With specialized metabolic enzymes, such as terpene

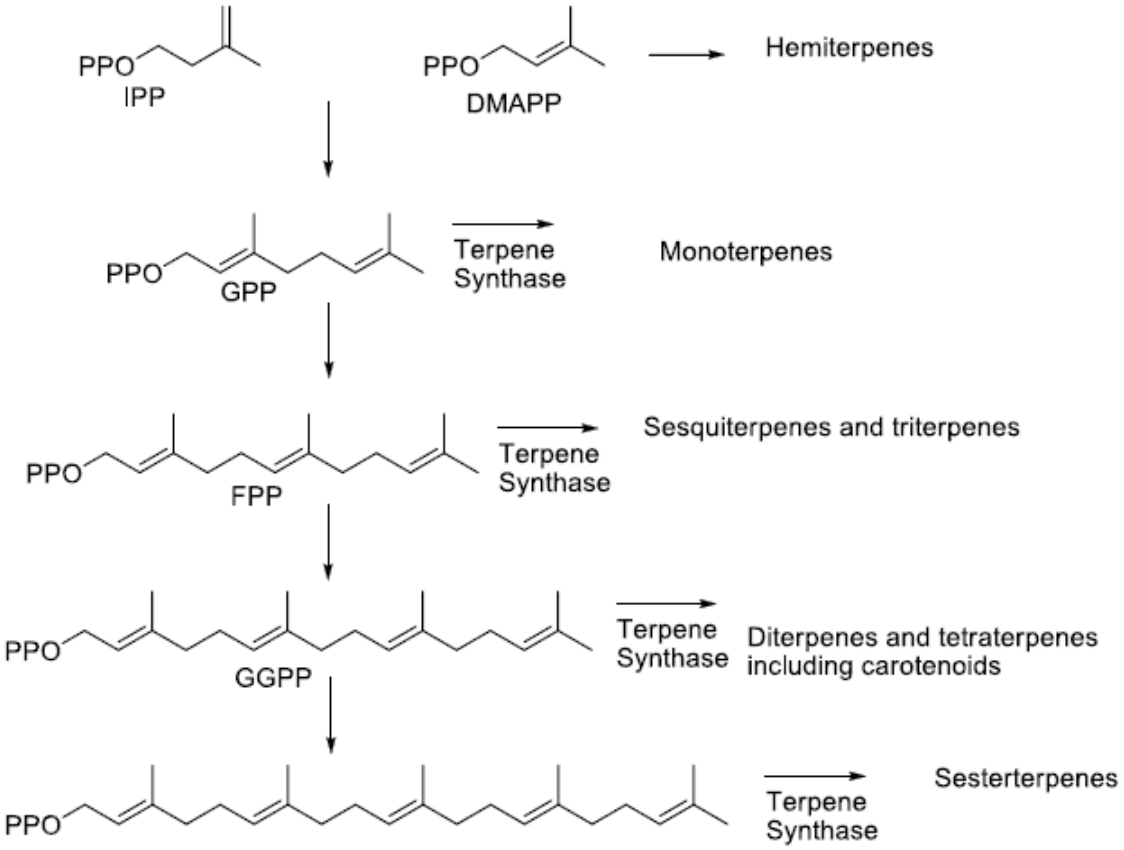


Figure 1. Terpene biosynthetic pathway.[5]

synthases, there exists a wider landscape of products that are produced with less specificity, however all synthases have a certain specificity to form some main products with greater probability.[10] Typically synthases are also stereospecific forming preferably certain stereoisomers.[10] With this diverse functionality, we believe that terpene synthases have the potential to be highly evolvable, with the ability to accept a wide range of non-natural compounds, and to evolve to have high product selectivity.[9,11-13] The C_{15} isoprenoid diphosphate, farnesyl diphosphate (FPP), serves as the precursor for about 300 distinct terpene synthase products, called sesquiterpenes.[7] Further diversity of products can be created through biosynthetic derivatization in the form of P450-mediated oxidations, enzymatic halogenations and esterifications.[14]

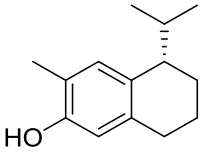
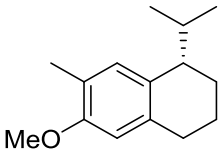
2A.3 Methoxy(methyl)tetralone Based Natural Products

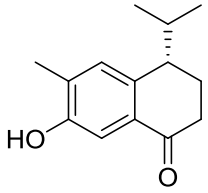
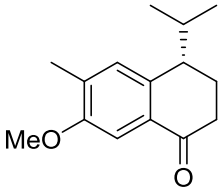
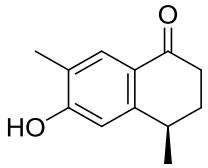
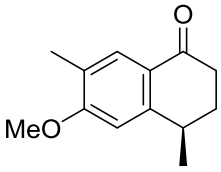
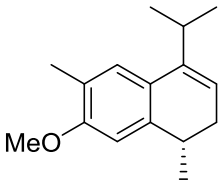
Large numbers of terpene natural products are known in literature bearing methoxy(methyl)tetralone moiety as a core structure or substructures have been isolated from

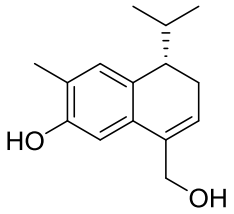
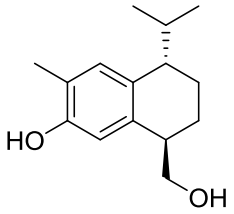
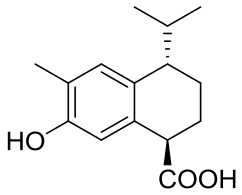
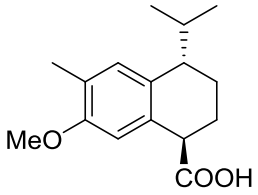
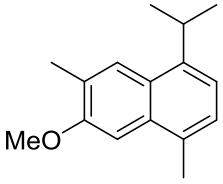
plants, animals, marine organisms, fungi and bacteria. Naturally occurring terpenes are generally bioactive and exhibit antitumor, antimicrobial, antifungal, antihyperglycemic, antiviral, antiparasitic, anti-inflammatory activities as well as a skin permeability effect.[15,16] There are few reports on the synthesis of especially methoxy(methyl)tetralones. Most of these approaches are target driven, aiming at a particular type of *terpene* natural products. However only in recent years, mainly through the advancements in organic synthesis have developed new routes to broadly functionalized methoxy(methyl)tetralones. The literature of terpene is very vast and hence only methoxy(methyl)tetralone based natural products form sesquiterpenes and norsesquiterpenes family have been summarized.

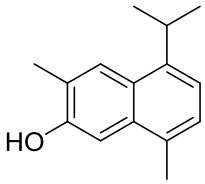
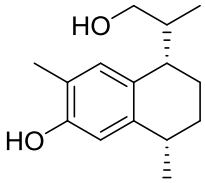
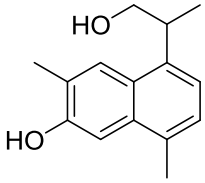
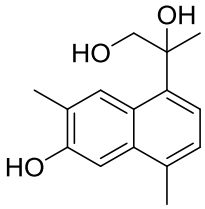
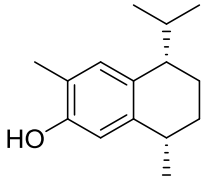
This chapter portrays a short overview on isolation, bioactivity and synthesis of important methoxy(methyl)tetralone based natural products with an emphasis on new general synthetic routes and strategies. A concise account of methoxy(methyl)tetralone based natural products is presented here and no pretension of completeness has been claimed. In order to simplify and understand the chemistry of methoxy(methyl)tetralone based natural products, they have been presented in tabular form (Table 2), which contains the natural product's structure, name, bioactivity, name of the species from which it was isolated and references pertaining to its isolation. The tables are followed by general synthetic strategies for methoxy(methyl)tetralones using different substrates and catalysts. However known synthesis of selected target compounds have been described in section B.

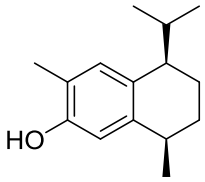
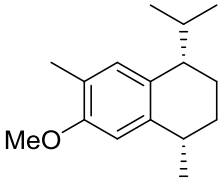
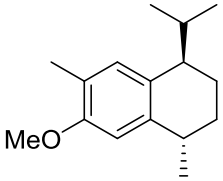
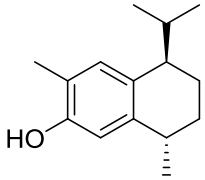
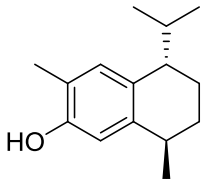
Table 2. Methoxy(methyl)tetralone Based Natural Products

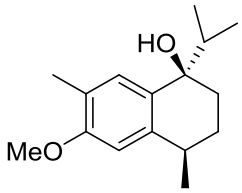
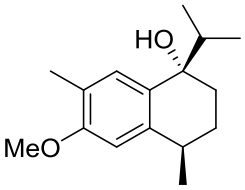
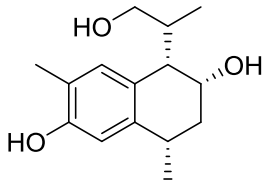
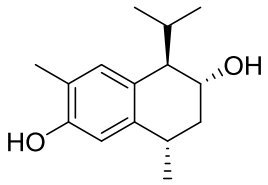
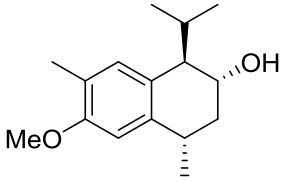
No.	Natural Product	Source	Activity	Ref.
1	 (*S*)-7-Desmethyl-2-hydroxycalamenene (**1**)	*Heterotheca grandijlora*	Not known	[17,18]
2	 (*S*)-7-Desmethyl-2-	*Heterotheca grandijlora*	Cytotoxic	[17]

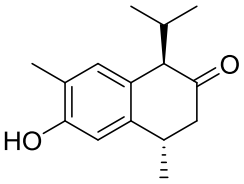
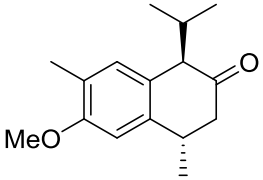
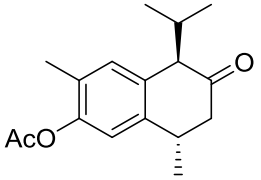
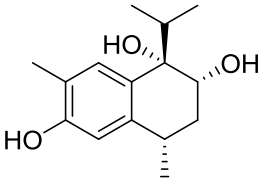
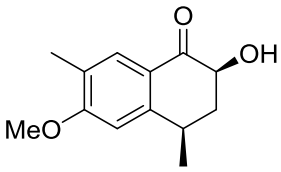
	methoxycalamenene (**2**)			
3	 (*S*)-7-Desmethyl-2-hydroxycalamenen-7-one (**3**)	*Heterotheca grandijlora, Heterotheca subaxillaris* (Lam.)	Phytotoxic	[17,19]
4	 (–)-7-Desmethyl-2-methoxycalamenen-7-one (**4**)	*Heterotheca grandijlora, Heterotheca subaxillaris* (Lam.)	Phytotoxic	[17,19]
5	 (+)-Aristelegone A (**5**)	*Phomopsis cassiae, Aristolochia elegans*	Antifungal	[20,21]
6	 (+)-Methylaristelegone-A (**6**)	*Aristolochia constricta*	Antispasmodic	[22]
7	 (–)-4-Isopropyl-7-methoxy-1,6-dimethyl-1,2-dihydronaphthalene (**7**)	*Heteroscyphus planus*	Not known	[23]

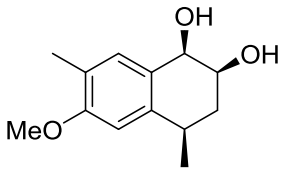
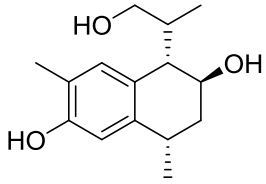
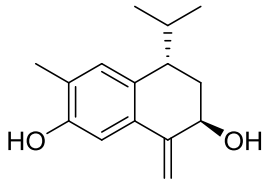
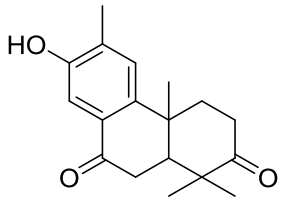
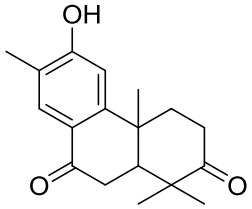
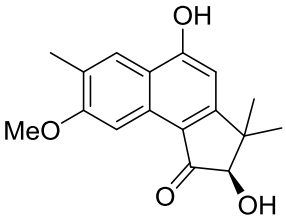
8	 (–)-7,8-Dehydro-2-hydroxy-calamenene-14-ol (**8**)	*Heterotheca subaxillaris*	Phytotoxic	[19]
9	 (+)-2-Hydroxy-calamenene-14-ol (**9**)	*Heterotheca subaxillaris*	Phytotoxic	[19]
10	 (+)-2-Hydroxy-calamenene-l4-carboxylic Acid (**10**)	*Heterotheca subaxillaris*	Phytotoxic	[19]
11	 (+)-2-Methoxy-calamenene-l4-carboxylic Acid (**11**)	*Heterotheca subaxillaris*	Phytotoxic	[19]
12	 7-Methoxycadalene (**12**)	*Heteroscyphus planus*	Not known	[23]

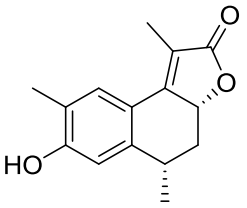
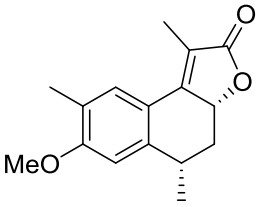
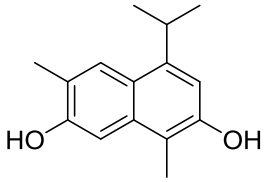
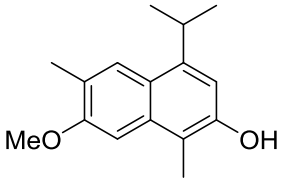
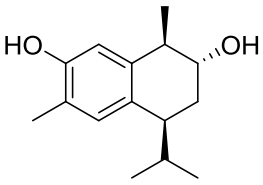
13	 7-Hydroxycadalene (**13**)	*Heterotheca inuloides, Ceiba pentandra*	Cytotoxic and antioxidative	24-26
14	 (+)-3,12-Dihydroxycalamenene (**14**)	*Phomopis cassiae*	Antifungal	27
15	 (–)-3,12-Dihydroxycadalene (**15**)	*Phomopis cassiae*	Antifungal	27
16	 (–)-3,11,12-Trihydroxycadalene (**16**)	*Phomopis cassiae*	Antifungal	27
17	 (–)-7-Hydroxycalamenene (**17**)	*Croton cajucara, Siparuna macrotepala, Tilia europea*	Antioxidant, antimicrobial and antifunagal	28-31

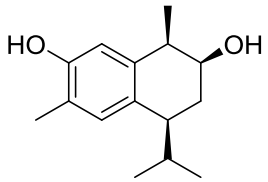
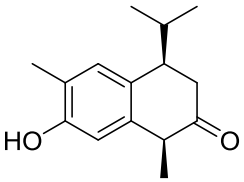
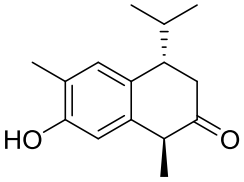
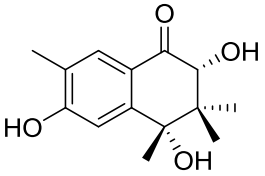
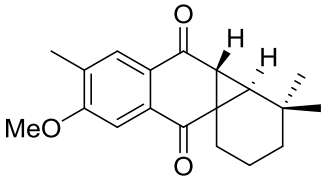
18	 (+)-7-Hydroxycalamenene (**18**)	*Bazzania trilobata, Osteospermum barberiae, Eremophila drummondii*	Not known	32-34
19	 (–)-(l*S*,4*S*)-7-Methoxycalamenene (**19**)	*Heteroscyphus planus*	Not known	23
20	 (+)-(l*S*,4*R*)-7-Methoxycalamenene (**20**)	*Heteroscyphus planus*	Not known	23
21	 (+)-(l*S*,4*R*)-7-Hydroxycalamenene (**21**)	*Tarenna madagascariensis, Heteroscyphus planus, Osteospermum barberiae*	Anti-inflammatory	23,33,35,36
22	 (–)-(7*S*,10*R*)-3-Hydroxycalamenene (**22**)	*Platycarya strobilacea, Pittosporum undulatum, Heterotheca grandijlora, Senecio tomentosus*	Anti-inflammatory	37-39

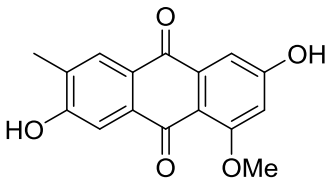
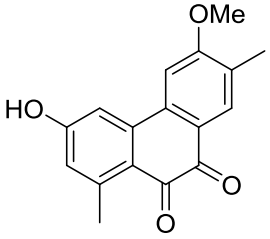
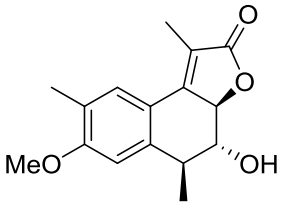
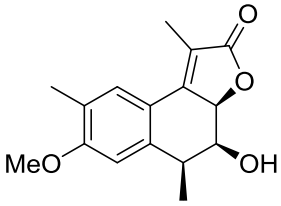
23	 (+)-(1*S*,4*S*)-7-Methoxycalamenen-3-ol (**23**)	*Lemnalia cervicornis*	Not known	[40]
24	 (–)-(1*S*,4*R*)-7-Methoxycalamenen-3-ol (**24**)	*Lemnalia cervicornis*	Not known	[40]
25	 (–)-3,9,12-Trihydroxycalamenene (**25**)	*Phomopis cassiae*	Antifungal	[27]
26	 (1*S*,3*R*,4*R*)-Calamene-3,7-diol (**26**)	*Lemnalia cervicornis*	Not known	[40]
27	 (1*S*,3*R*,4*R*)-7-Methoxycalamenen-3-ol (**27**)	*Lemnalia cervicornis*	Not known	[40]

28	 (+)-(1*S*,4*R*)-7-Hydroxycalamenen-3-one (**28**)	*Lemnalia cervicornis*	Not known	[40]
29	 (+)-(1*S*,4*R*)-7-Methoxycalamenen-3-one (**29**)	*Lemnalia cervicornis*	Not known	[40]
30	 (+)-(1*S*,4*R*)-7-Acetoxycalamenen-3-one (**30**)	*Lemnalia cervicornis*	Not known	[40]
31	 (+)-(1*S*,3*R*,4*S*)-Calamenene-3,4,7-triol (**31**)	*Lemnalia cervicornis*	Not known	[40]
32	 (–)-Aristelegone B (**32**)	*Aristolochia elegans*	Not known	[21]

33	 (–)-Aristelegone D (**33**)	*Aristolochia elegans*	Not known	21
34	 (+)-3,9,12-Trihydroxycalamenene (**34**)	*Phomopis cassiae*	Antifungal	27
35	 Inuloidin (**35**)	*Heterotheca inuloides*	Plant growth inhibitor	24,41
36	 Nimbione (**36**)	*Azadirachta indica*	Not known	42
37	 Nimbinone (**37**)	*Azadirachta indica*	Not known	42
38		*Trigonostemon xyphophylloides*	Not known	43

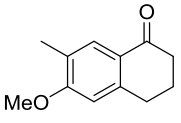
	Trigoxyphin M (**38**)			
39	 (+)-Heritol (**39**)	*Heritiera littoralis*	Toxic to fish	44
40	 (+)-Heritonin (**40**)	*Heritiera littoralis*	Toxic to fish	45
41	 2,7-Dihydroxycadalene (**41**)	*Alangium chinense, Gossypium hirsutum*	Antiviral, antibacterial	46-52
42	 2-Hydroxy-7-methoxycadalene (**42**)	*Gossypium hirsutum*	Antibacterial	49-52
43	 2-Hydroxy-8α-hydroxycalamene (**43**)	*Heterothecu subaxillaris, Phomopsis cassiae*	Antifungal, acetylcholineste-rase inhibitor	20,53,54

44	 2-Hydroxy-8*β*-hydroxycalamene (**44**)	*Phomopsis cassiae*	Antifungal, acetylcholinest-erase inhibitor	20
45	 *cis*-7-Hydroxycalamenen-2-one (**45**)	*Gossypium hirsutum*	Not known	52
46	 *trans*-7-Hydroxycalamenen-2-one (**46**)	*Gossypium hirsutum*	Not known	52
47	 (–)-Illinitone A (**47**)	*Limacella illinita*	Phytotoxic, nematocidal	55
48	 (+)-Favelanone (**48**)	*Cmdoscolus phyllacanthus*	Cytotoxic	56

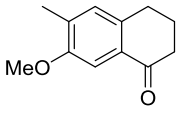
49	 Cajaquinone (**49**)	*Cajanus cajan*	Not known	57
50	 Manniorthoquinone (**50**)	*Neoboutonia mannii*	Not known	58
51	 Heritianin (**51**)	*Heritiera littoralis*	Toxic to fish	59
52	 (–)-Vallapin (**52**)	*Heritiera littoralis*	Active against boll weevils	60

2A.4 Reported Syntheses of Methoxy(methyl)tetralones

There are large numbers of natural products known in the literature having methoxy(methyl)tetralone moiety as a core structure or substructure. Because of their promising bioactivities, various synthetic methodologies applicable for the synthesis of meth-



6-Methoxy-7-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**53**)

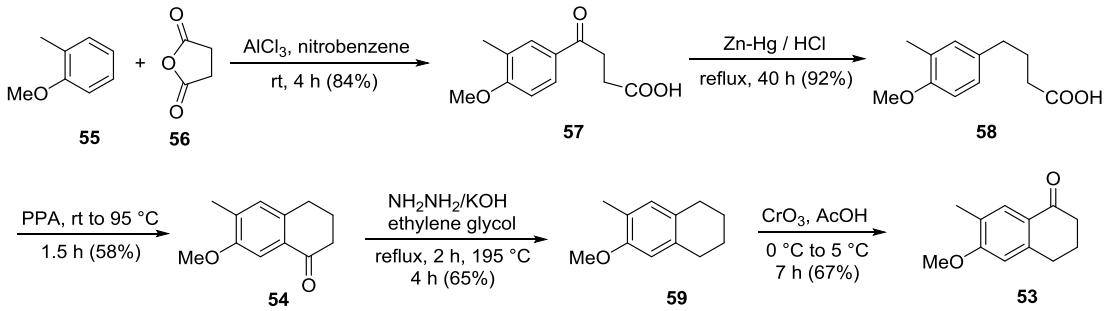


7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**)

Figure 2. Methoxy(methyl)tetralones.

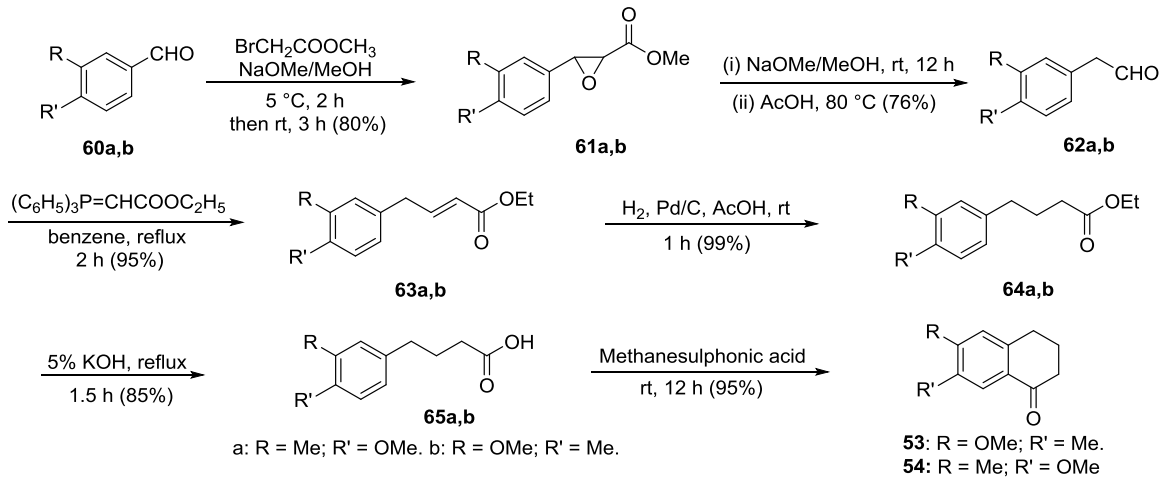
oxy(methyl)tetralone [6-methoxy-7-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**53**) and 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**)] have been reported in the literature. Some of the practical methodologies for the synthesis of methoxy(methyl)tetralone have been described here.

Mane and coworkers synthesized both 6-methoxy-7-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**53**) and 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**) utilizing Friedel-Crafts acylation of 2-methylanisole (**55**) with succinic anhydride (**56**) followed by reduction



Scheme 1. Synthesis of 6-Methoxy-7-methyl-3,4-dihydronaphthalen-1(2*H*)-one and 7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one

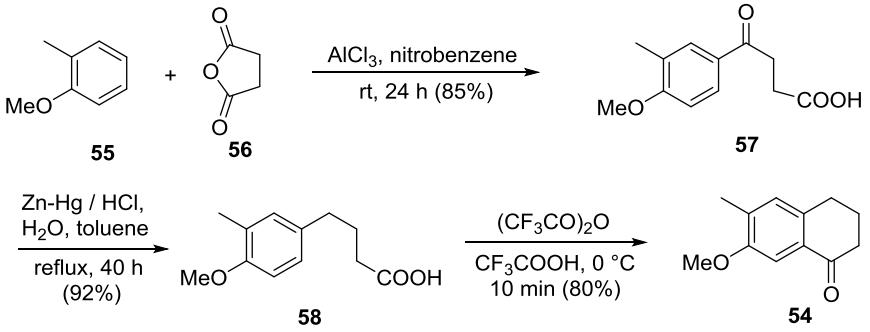
of ketone **57** and intramolecular Friedel-Crafts acylation to provide 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**). 7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**) was converted to 6-methoxy-7-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**53**) by reduction of ketone **54** and regioselective benzylic oxidation of corresponding tetrahydronaphthalene **59** at *para*-position to the electron donating methoxy group (Scheme 1).[61]



Scheme 2. Synthesis of 6-Methoxy-7-methyl-3,4-dihydronaphthalen-1(2*H*)-one and 7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one

Cannon et al. reported synthesis of 6-methoxy-7-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**53**) utilizing Darzens homologation methodology for the synthesis of aldehyde **62b**. Aldehyde **62b** on Wittig reaction, hydrogenation, ester hydrolysis followed by intramolecular cyclization provided tetralone **53**. They Similarly reported the synthesis 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**) from aldehyde **62a** using same sequence of reactions (Scheme 2).[62]

Bianco et al. reported synthesis of 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**) starting from 2-methylanisole (**55**) using Friedel–Crafts acylation, Clemmensen reduction and intramolecular cyclization (Scheme 3).[63] Few other approches reported by others for synthesis of 7-methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**54**) utilized nearly similar sequence of reactions.[64-69]



Scheme 3. Synthesis of 7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one Starting from 2-Methylanisole

Applications of above specified tetralones for the synthesis of target compounds has been described in section B.

2A.5 Summary

Large number of terpene natural products are known in the literature having methoxy(methyl)tetralone moiety as a core structure or substructure having simple to complex molecular architecture. They have varying range of biological activities as shown in the table with selected examples. The worldwide sales of terpene-based pharmaceuticals in 2002 were approximately US $12 billion. Among these pharmaceuticals, the anticancer drug “Taxol” and the antimalarial drug “Artemisinin” are two of the most renowned terpene-based drugs.[70,71] Many elegant substrate specific as well as general approaches are known in literature for terpene synthesis. Till toady there are many terpene based natural products for which synthesis are not known in the literature. Greater availability at a lower cost of terpene-based

drugs and availability of natural products for biological studies became feasible due to organic synthesis. Recent developments demonstrate that more pathbreaking methods and processes will be developed for natural product synthesis in the future.

In our group, over the past few years, we have successfully synthesized terpene based natural products.[72-74] The following section B discusses our present work on methoxy(methyl)tetralone based natural products synthesis along with their till date reported synthetic approaches.

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2B.Section B

Chemoenzymatic Collective Synthesis of Optically Active Hydroxyl(methyl)tetrahydronaphthalene-based Bioactive Terpenoids

This section features the following topics:

2B: Chemoenzymatic Collective Synthesis of Optically Active Hydroxyl(methyl) tetrahydronaphthalene-based Bioactive Terpenoids

2B.1 Introduction

A large number of hydroxyl(methyl)tetrahydronaphthalene and methoxy(methyl)tetrahydronaphthalene class of natural products with broad range of biological activities have been known (Fig. 1).[1-5] Nature designs them starting from either

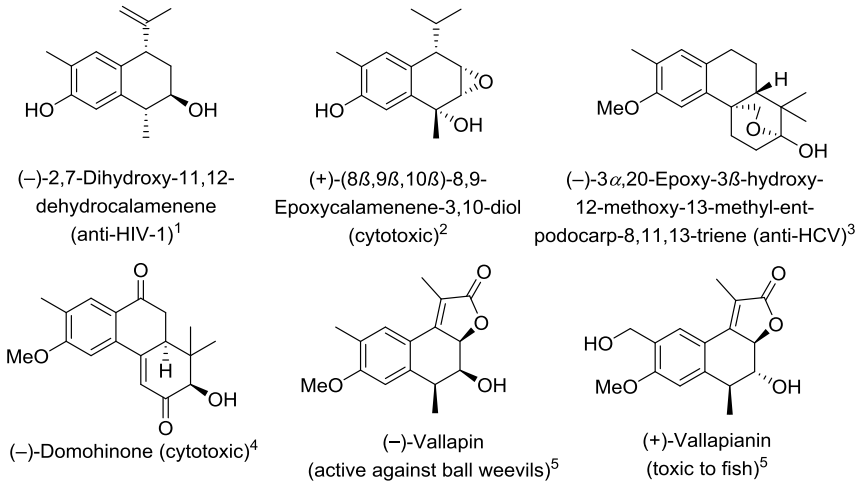
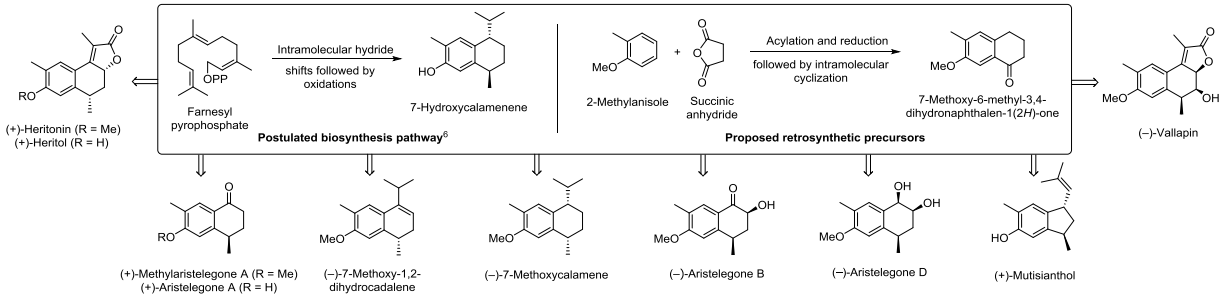


Figure 1. Hydroxyl/methoxy(methyl)tetrahydronaphthalene based bioactive natural products.

farnesyl pyrophosphate or geranyl pyrophosphate via intramolecular cyclizations involving 1,2- and 1,3-hydride shifts followed by a regioselective oxidation pathway.[6] A postulated biogenetic transformation of farnesyl pyrophosphate to the potential precursor 7-hydroxycalamene with an appropriate fixing of positions of both methyl and hydroxyl/methoxy groups has been depicted in scheme 1. In a biogenetic process the fifteen

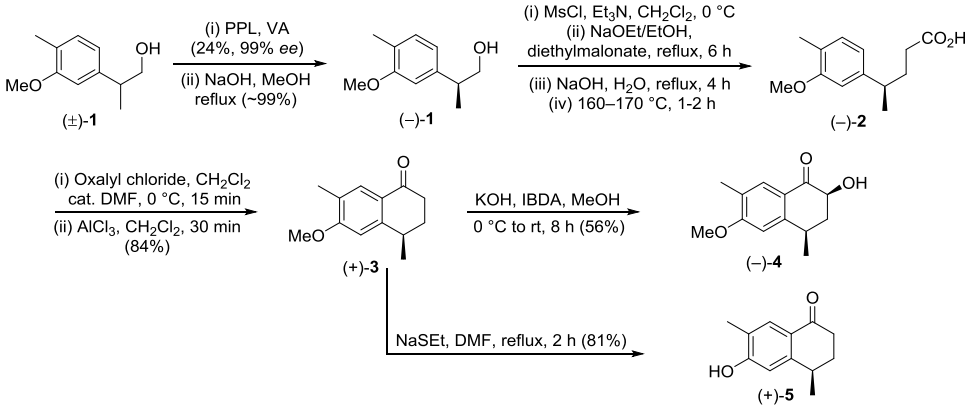


Scheme 1. Postulated Brief Biogenesis and Proposed Retrosynthetic Precursors of the Selected Bioactive Terpenoids

carbon bearing crucial intermediate 7-hydroxycalamene further undergoes several requisite functional group transformations in a stereoselective fashion with or without the loss of isopropyl group, thus delivering a variety of enantiomerically pure bioactive natural products

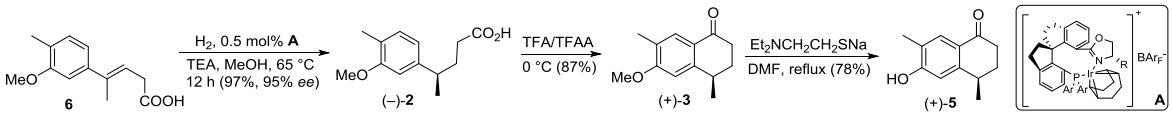
bearing twelve/fifteen carbon skeletons (Scheme 1). The (+)-aristelegone A, (–)-aristelegone B and (–)-aristelegone D have been isolated from *Aristolochia elegans*; while (+)-methylaristelegone A (antispasmodic) has been isolated from *Aristolochia constricta*.[7,8] The (+)-heritonin (toxic to fish), (+)-heritol (toxic to fish) and (–)-vallapin (pesticide) have been isolated from *Heritiera littoralis* and (+)-mutisianthol (antitumor) has been isolated from *Mutisia homoeantha*.[5,9-11] The (–)-7-methoxy-1,2-dihydrocadalene and (–)-7-methoxycalamenene have been isolated from *Heteroscyphus planus* culture.[12] Several elegant product specific racemic as well as enantioselective total synthesis of above specified natural products have been reported;[13-28] except for the aristelegone D, 7-methoxy-1,2-dihydrocadalene and vallapin.

Stefano Serra reported an elegant chemoenzymatic synthesis of (+)-methylaristelegone A (**3**), (+)-aristelegone A (**5**) and (–)-aristelegone B (**4**) starting from 2-arylpropanol (±)-**1**. Chiral building block was obtained through lipase-mediated resolution of racemic 2-arylpropanol (±)-**1**. Alcohol (**–**)-**1** was transformed into the corresponding homologated acid (**–**)-**2**, which on intramolecular Friedel-Crafts acylation provided (+)-methylaristelegone A (**3**); which on demethylation gave (+)-aristelegone A (**5**). (+)-Methylaristelegone A (**3**) on diastereoselective oxidation using iodobenzene diacetate provided (–)-aristelegone B (**4**) (Scheme 2).[13]



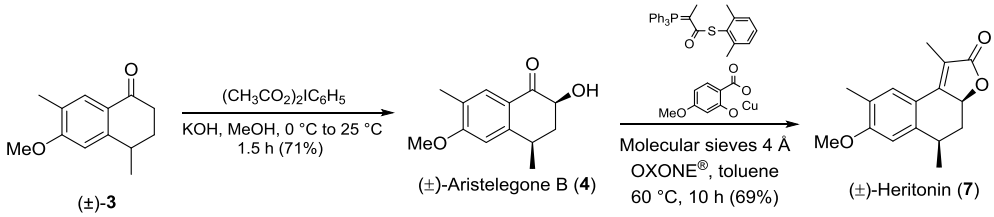
Scheme 2. Chemoenzymatic Synthesis of (+)-Methylaristelegone A, (+)-Aristelegone A and (–)-Aristelegone B

Zhou and co-workers reported the enatioseletive synthesis of (+)-methylaristelegone A (**3**) and (+)-aristelegone A (**5**) using enantioselective iridium-catalyzed hydrogenation of *α,β*-unsaturated carboxylic acid **6** as a key step. Acid (–)-**2** obtained by enantioselective iridium-catalyzed hydrogenation on treatment with TFA/TFAA provided (+)-methylaristelegone A (**3**); which on demethylation gave (+)-aristelegone A (**5**) (Scheme 3).[14]



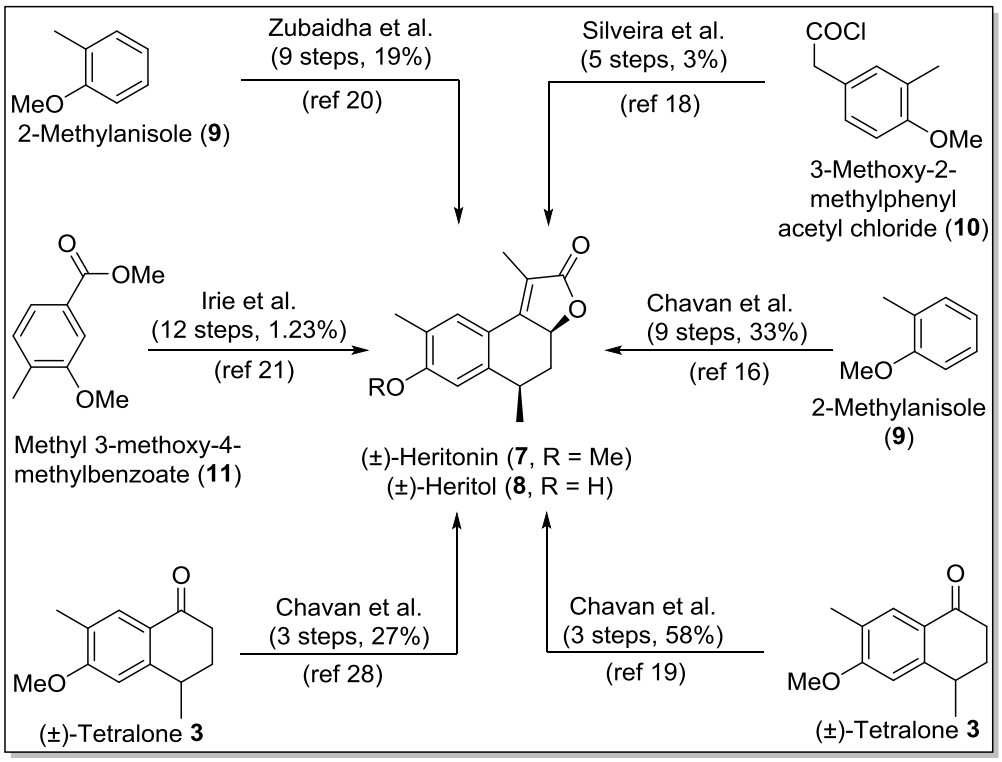
Scheme 3. Enatioseletive Synthesis of (+)-Methylaristelegone A and (+)-Aristelegone A

Matsuo and Shindo reported the synthesis of (±)-heritonin (**7**) in two steps from advanced tertalone intermediate (±)-**3** via oxidation using hypervalent iodine to provide (±)-aristelegone B (**4**). Acylation of (±)-aristelegone B (**4**) with a thiol ester present in Wittig reagents under neutral conditions catalyzed by the Cu(II) salt followed by the intramolecular Wittig reaction provided (±)-heritonin (**7**) (Scheme 4).[17]



Scheme 4. Synthesis of (±)-Heritonin via Intramolecular Wittig Reaction

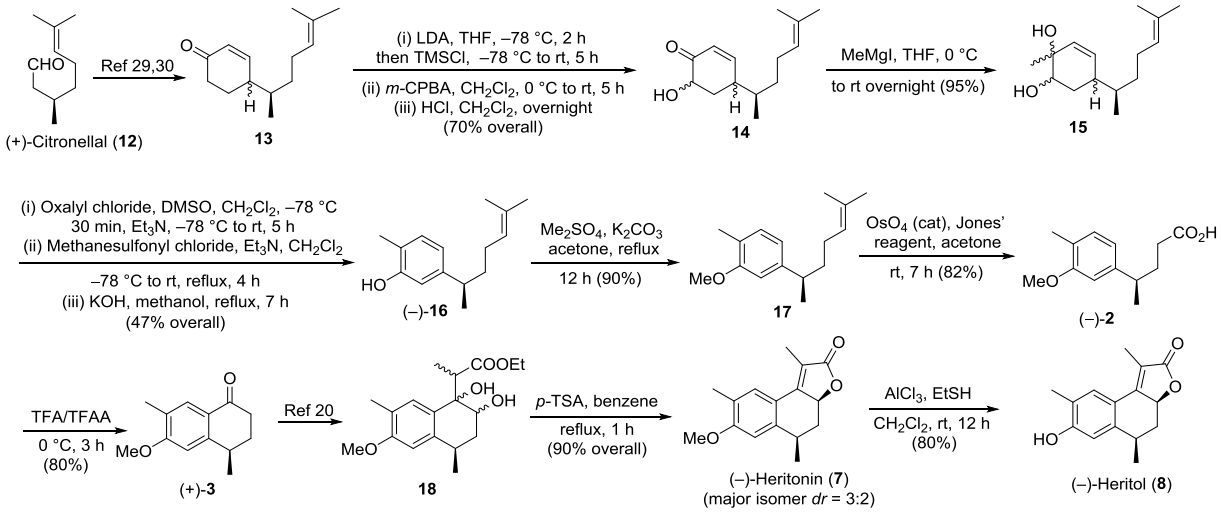
Few racemic syntheses of (±)-heritonin (**7**) and (±)-heritol (**8**) have been known, and are shown in a schematic form in scheme 5.



Scheme 5. Recemic Synthesis Reported for (±)-Heritonin and (±)-Heritol

Zubaidha et al. reported the synthesis of (±)-heritonin (**7**) and (±)-heritol (**8**) along with their epimers by osmylation of the unsaturated ester as the key step to construct the butenolide moiety of the title compound. Synthesis of (±)-heritol (**8**) was accomplished in 9 steps with 19% overall yield.[20] Silveira et al. accomplished the total synthesis of (±)-heritonin (**7**) and formal synthesis of (±)-heritol (**8**) via *β*-tetralone. The key step of this synthesis involved the selenocarbenium ion-mediated elaboration of the butenolide ring of the natural product. Synthesis of (±)-heritonin (**7**) was accomplished in 5 steps with 3% overall yield.[18] Chavan et al. achieved the highly diastereoselective total synthesis of (±)-heritonin (**7**) and (±)-heritol (**8**) from cheap and commercially available starting materials in eight and nine steps with 43% and 33% overall yield respectively, which is the highest overall yield reported so far.[16] Chavan et al. developed efficient methodology to generate butenolides by osmylation of *β*,*γ*-unsaturated esters and acid catalyzed cyclization of the resultant diol and applied it for synthesis of (±)-heritonin (**7**) and (±)-heritol (**8**). Synthesis of (±)-heritonin (**7**) was accomplished in 3 steps with 58% overall yield.[19] Chavan et al. also developed a novel strategy of converting *β*,*γ*-unsaturated esters to butenolides involving oxidative cyclization with ceric ammonium nitrate at room temperature and applied successfully for synthesis of (±)-heritonin (**7**) in 3 steps with 27% overall yield and to accomplish the formal synthesis of (±)-heritol (**8**).[28] Irie et al. reported the synthesis of (±)-heritol (**8**) and (±)-heritonin (**7**) starting from methyl 3-methoxy-4-methylbenzoate (**11**) using intramolecular Wittig reaction as a key step for constructing butenolide ring. Synthesis was completed in 12 steps with 1.23% overall yield.[21]

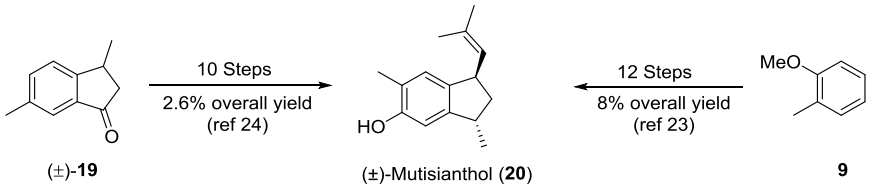
Chavan and co-workers reported the enantiospecific synthesis of (–)-heritonin (**7**) and (–)-heritol (**8**) starting from (*R*)-citronellal (**12**) as a key synthon which is abundantly available from both plants and also synthetically (Scheme 6). (*R*)-citronellal (**12**) was converted to enone **13** (1:1 diastereomeric mixture) as reported in the literature.[29,30] Enone **13** was converted to *α*-hydroxyenone **14** via epoxidation of silyl enol ether of enone. *α*-Hydroxy enone **14** was then subjected to 1,2-addition using MeMgI to give the corresponding diol **15** as a mixture of diastereomers, which were aromatized to give phenol (–)-**16**. The phenol was then converted to anisole derivative **17**, which was followed by conversion of double bond into the acid (–)-**2** using Weinreb's method.[31] Acid (–)-**2** on Friedel-Crafts acylation, reformatisky reaction and dihydroxylation furnished diol **18** using the previously reported conditions in good yields.[20]



Scheme 6. Enantiospecific Synthesis of (–)-Heritonin and (–)-Heritol

Diol **18** on treatment with *p*-toluenesulfonic acid in refluxing benzene gave a 3:2 diastereomeric mixture of heritonin (**7**) and its C8 epimer, which were separated by repeated crystallizations. Heritonin on demethylation gave (–)-heritol (**8**).[32]

Two racemic and one enantioselective synthesis are known for (+)-mutisianthol (**20**). Ho and

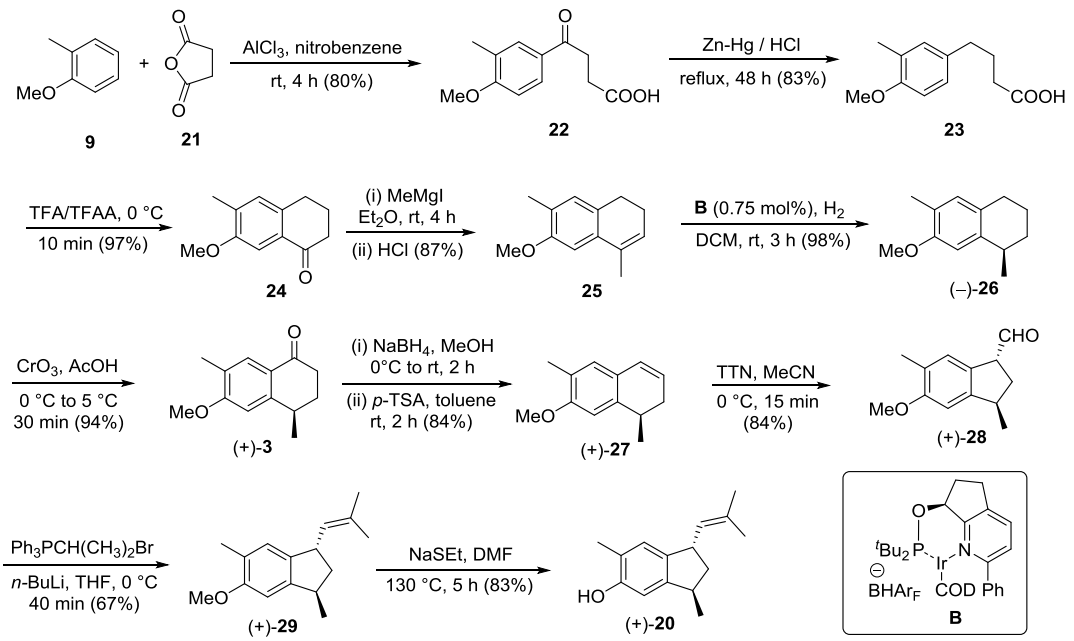


Scheme 7. Diasteroselective Synthesis of (±)-Mutisianthol

co-workers reported the synthesis of (±)-mutisianthol (**20**) starting from (±)-3,6-dimethyl-1-indanone (**19**) in 10 steps with 2.6% overall yield (Scheme 7). Synthesis involves tricarbonylchromium assisted stereoselective reduction leading to the desired *trans* intermediate. They also revised structure of mutisianthol from *cis*-1,3-dialkyl to the *trans*-1,3-dialkyl isomer.[24] Ferraz and co-workers completed the total synthesis of the phenolic sesquiterpene (±)-mutisianthol (**20**) in 12 steps from the readily available 2-methylanisole (**9**). The required *trans*-1,3-disubstituted indan intermediate was obtained through a diastereoselective thallium(III) mediated ring contraction of a 1-methyl-1,2-dihydronaphthalene derivative.[23]

Bianco et al. reported the first synthesis of the natural product (+)-mutisianthol (**20**), which was accomplished in 11 steps and in 21% overall yield from 2-methylanisole (**9**) (Scheme 8). The synthesis of its enantiomer was also performed in similar overall yield. The absolute configuration of the sesquiterpene (+)-mutisianthol (**20**) was assigned as (1*S*,3*R*). Key steps in

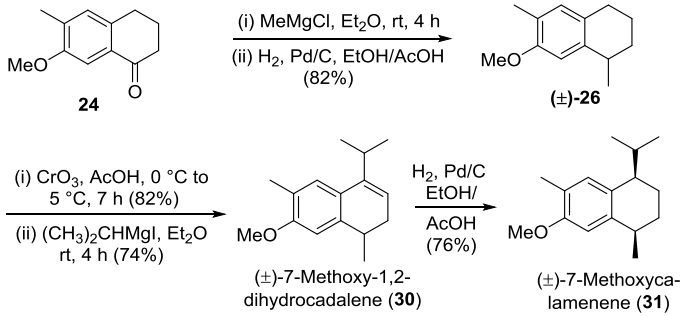
the route were the asymmetric hydrogenation of a nonfunctionalized olefin **25** using chiral



Scheme 8. Enantiospecific Synthesis of (+)-Mutisianthol

iridium catalysts and the ring contraction of 1,2-dihydronaphthalene (+)-**27** using thallium(III) or iodine(III).[22]

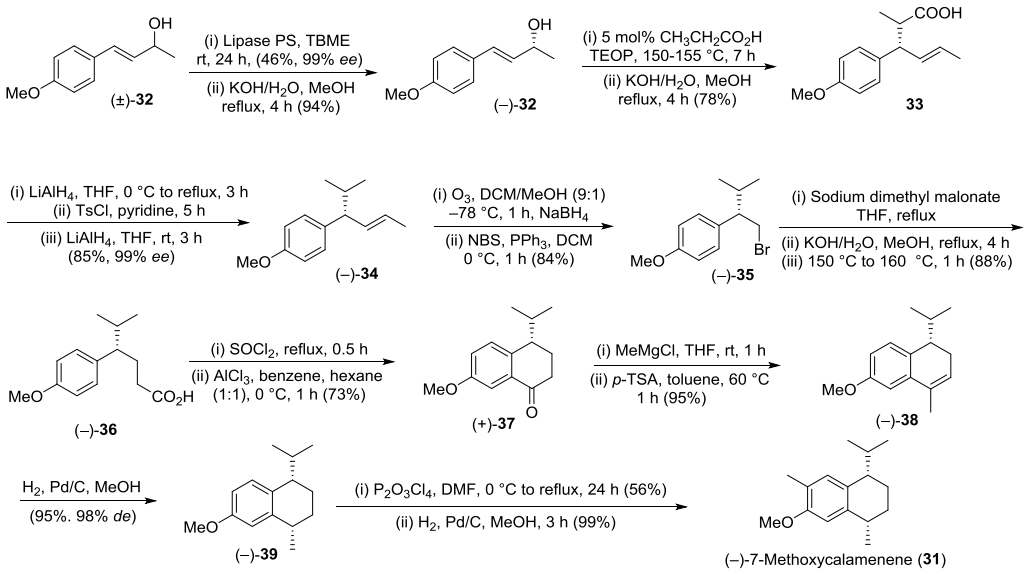
One racemic and two asymmetric syntheses are known for 7-methoxycalamenene (**31**). Kadam et al. reported the total synthesis of (±)-7-methoxycalamenene (**31**) via (±)-7-methoxy-1,2-dihydrocadalene (**30**). Synthesis involves various reductive and oxidative synthetic techniques along with diastereoselective hydrogenation of (±)-7-methoxy-1,2-dihydrocadalene (**30**) as a key step (Scheme 9).[33]



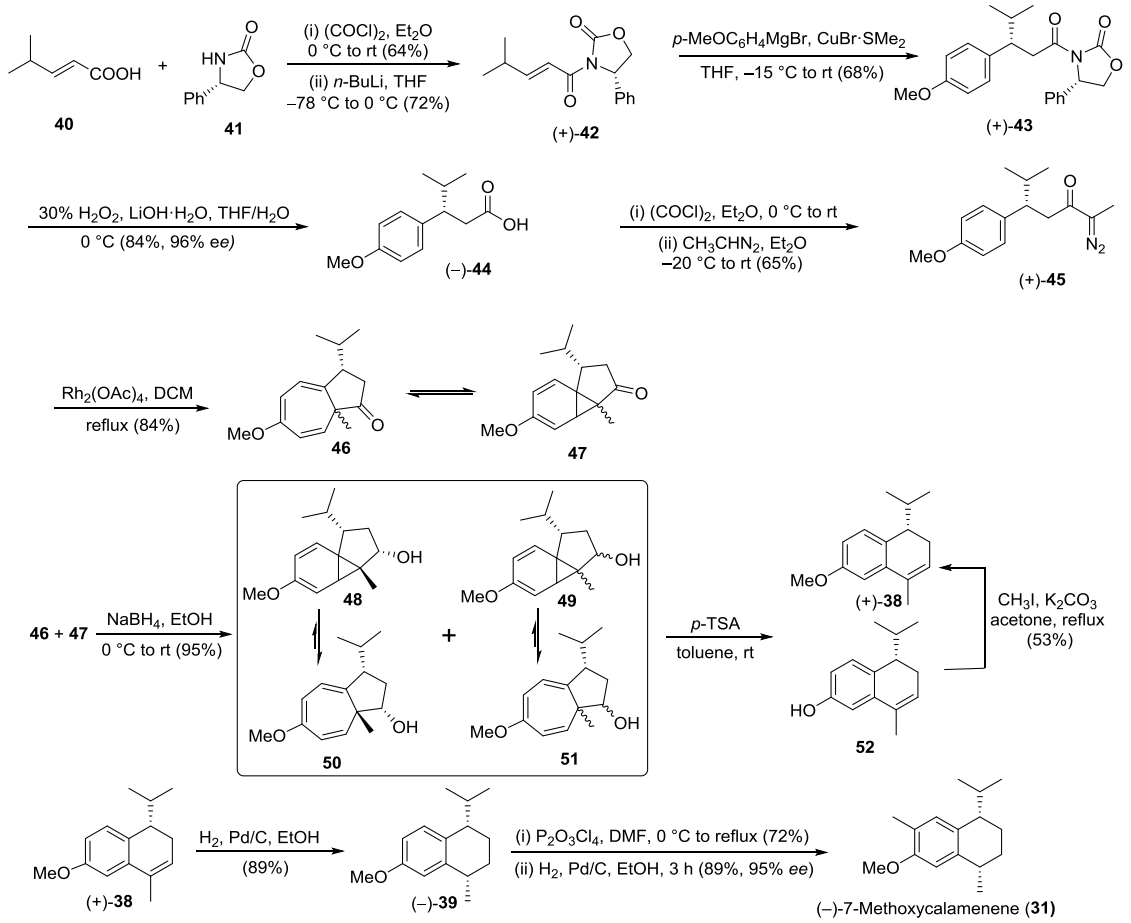
Scheme 9. Diastereoselective Synthesis of 7-Methoxycalamenene

Gatti and co-workers accomplished an elegant enantioselective synthesis of (–)-7-methoxy-calamenene (**31**) starting with enzymatic resolution of the racemic allyl alcohol (±)-**32**. Claisen-orthoester rearrangement of (–)-**32**, diastereoselective reduction of dihydronaphthalene derivative (–)-**38** and regioselective introduction of the formyl group by a

Vilsmeier reaction were the key steps in the synthesis. Synthesis of (–)-7-methoxycalamenene (**31**) was completed in 17 steps with 7.6% overall yield (Scheme 10).[26]



Scheme 10. Enantioselective Synthesis of (–)-7-Methoxycalamenene



Scheme 11. Enantioselective Synthesis of (–)-7-Methoxycalamenene

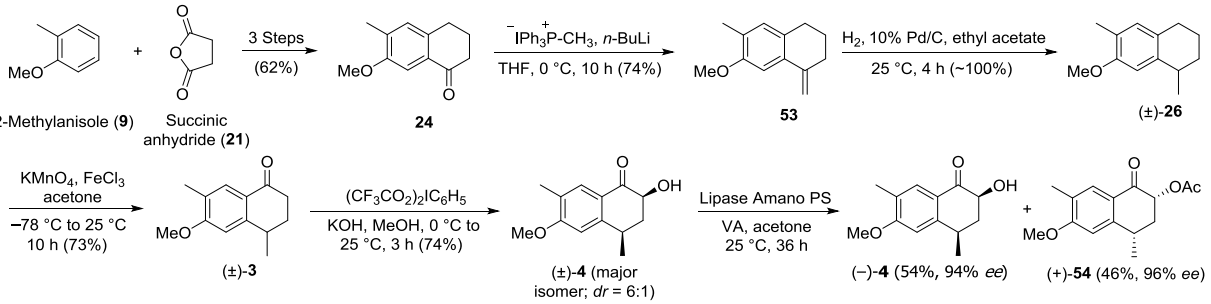
Maguire and co-workers have accomplished the asymmetric synthesis of (–)-7-methoxycalamenene (**31**) utilizing the intramolecular Buchner reaction of α-diazoketone (+)-**45** as key step. Upon reduction of the equilibrating azulenone structures (**46** and **47**), the resulting azulenols (**48**, **49**, **50** and **51**) rearrange to dihydronaphthalene (+)-**38** containing the 6,6-membered bicyclic ring system characteristic of methoxycalamenene, by means of an acid-catalyzed aromatization process. Transformation of (+)-**38** to (–)-**31** is accomplished through a three-step reaction sequence (Scheme 11**)**.[25]

2B.2 Present Work

The science of collective total synthesis of bioactive natural products is very important for structure activity relationship studies from lead optimization and drug discovery point of view.[34-40] The substituted methoxy(methyl)tetrahydronaphthalene based compounds have very high propensity towards instantaneous oxidation, elimination and enolization processes due to the facile stability driven aromatizations and hence synthesis of such type of target compounds is a challenging task.[41-44] A concise retrosynthetic analysis of natural products portrayed in scheme 1 revealed that the 7-methoxy-6-methyltetralone would be a potential precursor to accomplish both racemic and chemoenzymatic collective total synthesis of all selected target compounds. In continuation with our studies on both cyclic anhydrides and derivatives to bioactive natural products[45-49] and efficient enzymatic resolutions,[50-55] we herein present the collective formal/total synthesis of nine optically active natural products (Schemes 12–14) and an attempted diastereoselective synthesis of (±)-vallapin via alternatively designed β-hydroxytetralone intermediate (Scheme 15).[56]

2B.2.1 Results and Discussions

The 2-methylanisole (**9**) on Friedel-Crafts acylation with succinic anhydride (**21**) followed by



Scheme 12. Diastereoselective Synthesis of the Common Precursor (±)-Aristelegone B and its Efficient Enzymatic Resolution

Clemmensen reduction and acid-promoted intramolecular cyclization provided desired tetralone **24** in 62% yield over 3-steps as described earlier in scheme 8.[22] Tetralone **24** on

Wittig reaction exclusively formed the *exo*-methylene product **53** in 74% yield which on catalytic hydrogenation over palladium on charcoal delivered the reduced product (±)-**26** in quantitative yield. $KMnO_4/FeCl_3$ promoted regioselective benzylic oxidation of (±)-tetrahydronaphthalene **26** furnished the (±)-methylaristelegone A (**3**) in 73% yield.

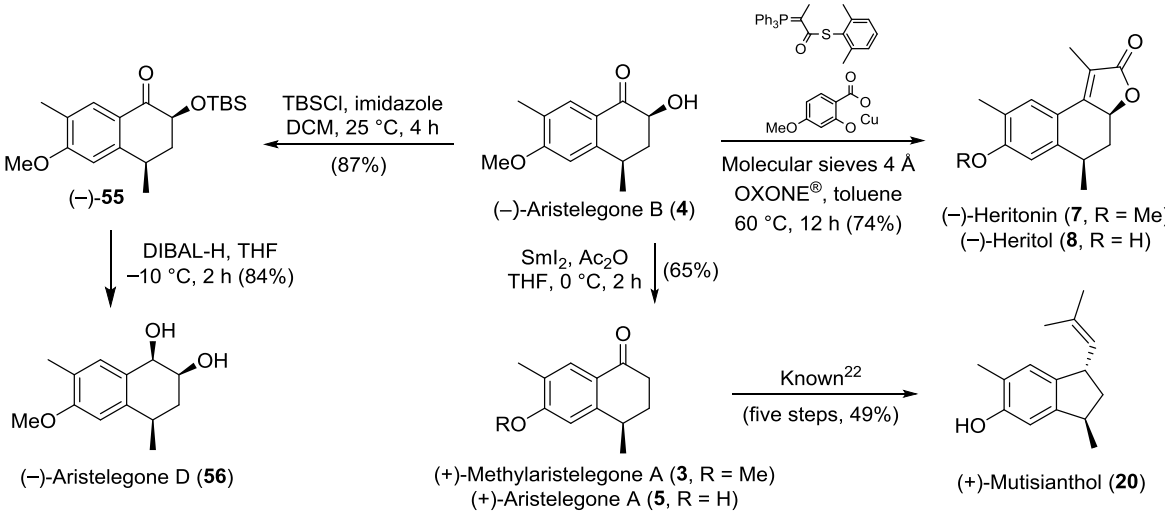
Table 1. Lipase Amano PS Catalyzed Resolution of (±)-Aristelegone B

Entry	Solvent	Temp. (Time)[a]	(–)-**4**: % Yield (*ee*)[b]	(+)-**54**: % Yield (*ee*)[b]	*E*
1	Benzene	25 ^oC (48 h)	42 (77)	48 (68)	12.0
2	Benzene-PE (1:1)	25 ^oC (48 h)	51 (67)	49 (50)	5.8
3	Acetone	25 ^oC (24 h)	67 (65)	33 (96)	96.7
4	Acetone	25 ^oC (36 h)	54 (94)	46 (96)	175.8
5	Acetone	25 ^oC (48 h)	49 (97)	51 (91)	89.0

[a] Reactions were monitored by HPLC; [b] chiral HPLC

Hypervalent iodine reagents are known to afford α-ketols with α-hydroxyl group attached to the more sterically hindered face of an enolate and mechanistically it takes place via the inversion of configuration.[15] Accordingly the base induced stereoselective α-hydroxylation of (±)-tetralone **3** with (bis(trifluoroacetoxy)iodo)benzene resulted into (±)-aristelegone B (**4**) as a desired major product (74%, *dr* = 6:1, by ^1H NMR). As represented in Table 1, we systematically studied the lipase Amano PS catalyzed stereoselective acylation of (±)-aristelegone B (**4**) using vinyl acetate (VA) as an acyl donor and obtained the optically active natural product (–)-aristelegone B (**4**) in 54% yield (94% *ee*, by HPLC) and (+)-acylaristelegone B (**54**) in 46% yield (96% *ee*, by HPLC) (Scheme 12). The obtained stereochemical outcome was further confirmed by comparison with reported analytical and spectral data for natural product (–)-**4**.[7] Typically, synthesis of a natural product starting from the natural product belonging to same genesis is more concise, efficient and involves minimum protection-deprotection steps. The twelve carbon skeleton of naturally occurring aristelegone B bears well placed substituents and essential functional groups; hence it was planned to use (±)/(+)/(–)-**4**/**54** as pivotal building blocks to accomplish racemic/chiral pool based/stereoselective collective synthesis of target compounds from scheme 1.

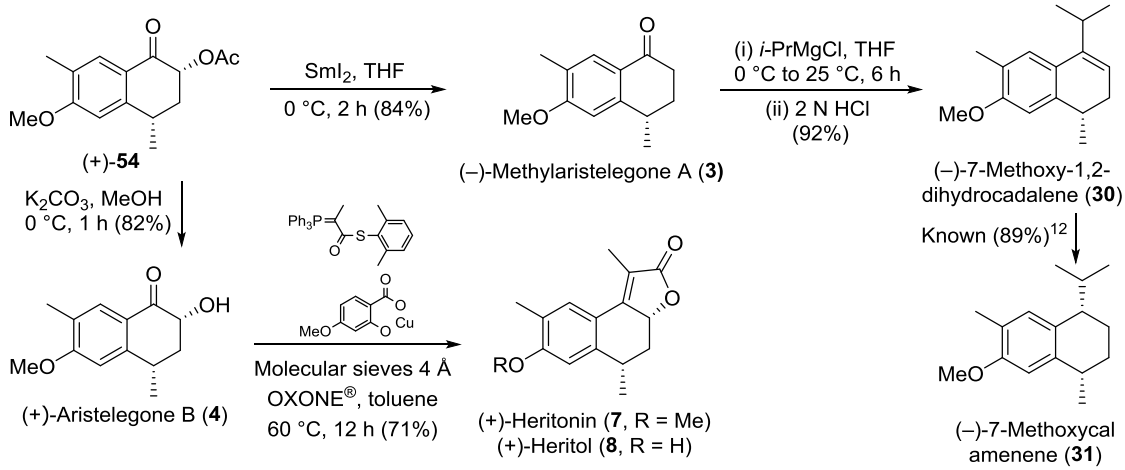
The free hydroxyl group in (–)-aristelegone B (**4**) was initially protected as –OTBS to avoid its direct interaction with aluminium from DIBAL-H and also to increase the steric bulk of *β*-face to favor a hydride attack from an anticipated less hindered *α*-face (Scheme 13). TBS-protected (–)-hydroxytetralone **55** on DIBAL-H reduction directly delivered the natural product (–)-aristelegone D (**56**) in 84% yield. TLC results of above reaction clearly indicated that *O*-desilylation takes place during the workup procedures. The analytical and spectral data obtained for synthetic product was in complete agreement with reported data for natural



Scheme 13. Collective Synthesis of Enantiomerically Pure Terpenoids from (–)-Aristelegone B

product[7] and the chemoenzymatic first synthesis of (–)-aristelegone D (**56**) was accomplished in ten steps with 8% overall yield. (–)-Aristelegone B (**4**) underwent a smooth tandem acylation-Wittig reaction under the recently reported Matsuo and Shindo conditions[17] and furnished an aimed product (–)-heritonin (**7**) in 74% yield (93% *ee*, by HPLC) via intramolecular cyclization. The above mentioned tandem acylation-Wittig reaction was moisture sensitive. Therefore freshly dried reagents were used under perfectly anhydrous reaction conditions to obtain the desired product in very good yield. It is noteworthy that starting material *α*-hydroxyketone, in situ formed corresponding *α*-acylated-ketone intermediate and the obtained product *γ*-lactone all three bear a sufficiently acidic methine proton; however the reaction was very clean and delivered the final product (–)-heritonin (**7**) without any racemization. The obtained analytical and spectral data for (–)-heritonin (**7**) was in complete agreement with reported data[16,32] and it was synthesized in nine steps with 8% overall yield. $AlCl_3$ induced transformation of (–)-heritonin (**7**) to (–)-heritol (**8**) in 80% yield

is known.[32] The α-hydroxyl group was diastereoselectively introduced on (±)-methylaristelegone A (**3**) to use it as a handle for efficient enzymatic resolution and also as an appropriate functional group. Samarium iodide persuaded post resolution detachment of hydroxyl group in (–)-aristelegone B (**4**) via the corresponding acetate formed (+)-methylaristelegone A (**3**) in 65% yield. (+)-Methylaristelegone A (**3**) on treatment with BBr_3 provided (+)-aristelegone A (**5**) in 74% yield. Starting from (+)-methylaristelegone A (**3**), three-step synthesis of (–)-heritonin (**7**) via Reformatsky reaction and five-step synthesis of (+)-mutisianthol (**20**) via thallium(III) trinitrate catalyzed ring contraction pathways are well known.[22,32]

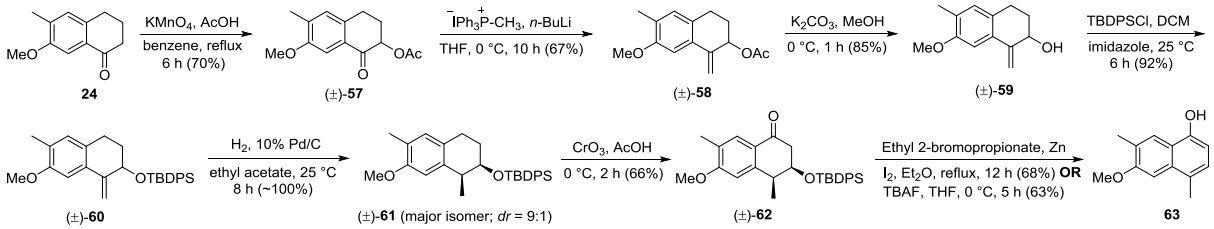


Scheme 14. Synthesis of (–)-7-Methoxy-1,2-dihydrocadalene and (+)-Heritonin

At this stage it was also decided to use the second enantiomerically pure building block (+)-**54** obtained in enzymatic resolution for synthesis of natural products. The samarium iodide influenced detachment of acetoxy group in compound (+)-**54** furnished (–)-methylaristelegone A (**3**) in 84% yield (Scheme 14). Reaction of isopropylmagnesium chloride with (–)-methylaristelegone A (**3**) followed by acid catalyzed in situ dehydration of the formed intermediate tertiary alcohol yielded another natural product (–)-7-methoxy-1,2-dihydrocadalene (**30**) in 92% yield. The analytical and spectral data obtained for synthetic product was in complete agreement with reported data for natural product[12] and the chemoenzymatic first synthesis of (–)-7-methoxy-1,2-dihydrocadalene (**30**) was accomplished in ten steps with 8% overall yield. (±)-7-Methoxy-1,2-dihydrocadalene (**30**) was aromatized to 7-methoxycadalene using palladium catalyst. An enantioselective reduction of the actually isolated natural product (–)-**30** to form yet another natural product (–)-7-methoxycalamenene (**31**) is known.[12] Base-induced de-acylation of compound (+)-**54** to form (+)-aristelegone B

(**4**) followed by its similarly performed tandem acylation-Wittig reaction provided the natural product (+)-heritonin (**7**) in 71% yield.

In the next part of study, chemoenzymatic total synthesis of (–)-vallapin (**67**) was initially planned again from same common precursor tetralone **24**. Tetralone **24** on treatment with $KMnO_4$/AcOH[57] in refluxing benzene furnished the required α-acetoxyketone (±)-**57** in 70% yield (Scheme 15). The ketone (±)-**57** on Wittig reaction exclusively formed yet another *exo*-



Scheme 15. Attempted Diastereoselective Synthesis of Vallapin

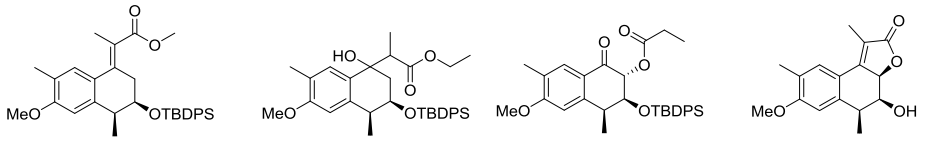
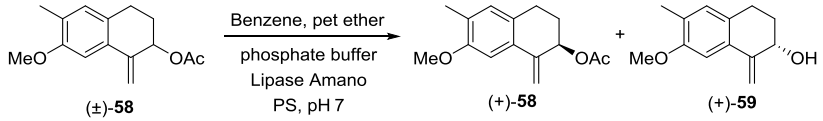


Figure 2. Expected products from tetralone (±)-**62** for the synthesis of vallapin (**67**).

methylene product (±)-**58** in 67% yield. As represented in Table 2, we also systematically studied the lipase Amano PS catalyzed stereoselective hydrolysis of acetate (±)-**58** and obtained the optically active products (+)-**58** in 44% yield (92% *ee*, by HPLC) and (+)-**59** in 56% yield (89% *ee*, by HPLC). Tentative stereochemical assignment of (+)-**58** and (+)-**59** was done on the basis of known Amano PS selectivity.[50-55] Anticipating high propensity of such type of substituted tetralone systems to aromatize and also from starting material availability point of view; it was essential to first standardize all reaction conditions and complete the diastereoselective synthesis of our target compound. Hydrolysis of acetate (±)-**58** to the corresponding alcohol (±)-**59** followed by TBDPS-protection provided silyl ether (±)-**60** in 78% yield over two steps. Diastereoselective reduction of exocyclic carbon–carbon double bond in compound (±)-6**0** delivered the *syn*-disubstituted tetrahydronaphthalene (±)-**61** in ~100% isolated yield (*dr* = 9:1, by ^{1}H NMR). The bulk of –OTBDPS group in (±)-**60** directs π-lobes adsorption on palladium catalyst from opposite face to form the desired *cis*-isomer as a major product. Regioselective CrO_3 oxidation of benzylic methylene group in tetrahydronaphthalene (±)-**61** furnished the expected tetralone (±)-**62** in 66% yield. Fortunately during the course of CrO_3 oxidation in acetic acid we did not notice any desilylation and concomitant aromatization. The studied Wittig reaction of tetralone (±)-**62** to

obtain product (±)-**64** and Reformatsky reaction of tetralone (±)-**62** to obtain (±)-**65** were unfortunately not successful (Fig. 2). An attempted Reformatsky reaction on (±)-**62**, instead formed the corresponding aromatized product **63** in 68% yield. An attempted desilylation of (±)-**62** also resulted in formation of same aromatized product **63** with 63% yield plausibly via

Table 2. Lipase Amano PS Catalyzed Resolution of (±)-Acetate **58**



Entry	Temp. (Time)[a]	(+)-**58:** % Yield (*ee*)[b]	(+)-**59:** % Yield (*ee*)[b]	*E*
1	35 ^{o}C (96 h)	55 (79)	45 (95)	94.6
2	40 ^{o}C (72 h)	55 (80)	45 (100)	497.0
3	45 ^{o}C (24 h)	54 (88)	46 (100)	590.3
4	45 ^{o}C (48 h)	44 (92)	56 (89)	56.2

[a] Reactions were monitored by HPLC; [b] chiral HPLC

the corresponding unstable *β*-hydroxyketone intermediate. Selective introduction of oxygen function on tetralone (±)-**62** by using $KMnO_4/CH_3CH_2COOH$ in refluxing benzene offered the expected product (±)-**66** but in less than 10% yield. The well functionalized product (±)-**66** was very unstable and hence we could cautiously characterize an isolated crude product only by using ^{1}H NMR and HRMS data (Fig. 2). We feel that much milder reaction conditions will be required to transform tetralone (±)-**62** or other similar type of intermediates to the desired target compound (±)-vallapin and it remains as a synthetic challenge.

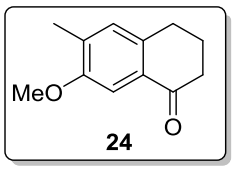
2B.3 Summary

In summary, we have described facile chemoenzymatic collective total/formal synthesis of several tetrahydronaphthalene based optically active terpenoids. The late stage efficient enzymatic resolution provides access to both (+)/(–)-isomers as potential building blocks. Remarkably stereoselective reactions were performed to accomplish the synthesis of several natural products from one single common precursor aristelegone B. Multistep total synthesis of both (+)-heritonin and (–)-heritonin have been accomplished and all synthetic pathways described herein will also be useful to mirror the total synthesis of their respective antipodes. Unfortunately all our attempts to complete first total synthesis of (±)-vallapin met with failure due to the inherent instability of advanced *β*-hydroxytetralone intermediate.

2B.4 Experimental Section

General Description: Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR, 500 MHz NMR and 700 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz), 500 NMR (125 MHz) and 700 MHz NMR (175 MHz) spectrometers. Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 mesh and 230–400 mesh). Commercially available 2-methylanisole, methyltriphenylphosphonium iodide, $PhI(OCOCF_3)_2$, vinyl acetate, TBSCl, DIBAL-H, molecular sieves 4 Å, OXONE®, samarium diiodide solution (0.10 M in THF), boron tribromide solution (1 M in DCM), acetic anhydride, TBDPSCl, ethyl 2-bromopropionate, tetrabutylammonium fluoride solution and Zn metal were used. Amano PS enzymes form Amano Enzyme Japan and Sigma-Aldrich were used.

7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(*2H*)-one (24).



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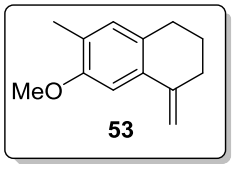
Mp 54–55 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10 (quintet, J = 6 Hz, 2H), 2.25 (s, 3H), 2.60 (d, J = 8 Hz, 1H), 2.64 (d, J = 6 Hz, 1H), 2.86 (t, J = 6 Hz, 2H), 3.86 (s, 3H), 7.02 (s, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 23.5, 28.7, 38.7, 55.3, 106.6, 130.7, 131.2, 133.6, 136.9, 156.5, 198.1; ESIMS (m/z) 191 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 1668, 1610 cm^{-1}.

7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalene (53).

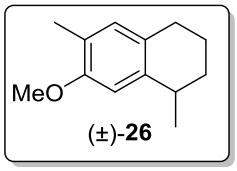


53

To a stirred solution of methyltriphenylphosphonium iodide (8.01 g, 19.72 mmol) in anhydrous THF (35 mL) was added a solution of *n*-BuLi (12.33 mL, 19.72 mmol, 1.60 M in hexane) in dropwise fashion at 0 °C under argon atmosphere and the reaction mixture was stirred for 30 min. A solution of compound **24** (2.50 g, 13.14 mmol) in THF (10 mL) was added to the above reaction mixture at 0 °C and it was further stirred for 10 h. The reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (100 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:19) as an eluent afforded product **53** as viscous oil (1.83 g, 74%). ^{1}H NMR ($CDCl_3$,

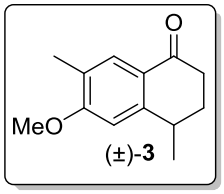
200 MHz) δ 1.79 (quintet, J = 6 Hz, 2H), 2.12 (s, 3H), 2.40–2.50 (m, 2H), 2.68 (t, J = 6 Hz, 2H), 3.77 (s, 3H), 4.85 (s, 1H), 5.35 (s, 1H), 6.81 (s, 1H), 7.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 24.1, 29.5, 33.3, 55.3, 105.0, 106.6, 126.9, 129.3, 131.2, 132.8, 143.8, 156.0; ESIMS (*m*/*z*) 189 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O$ 189.1274, found 189.1272; IR ($CHCl_3$) ν_{max} 1612 cm^{-1}.

(±)-7-Methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene (26).



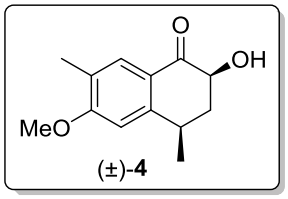
To a stirred solution of compound **53** (1.50 g, 7.97 mmol) in ethyl acetate (25 mL) was added 10% Pd/C (50 mg) at 25 °C and the reaction mixture was subjected to hydrogenation under balloon pressure for 4 h. The reaction mixture was filtered through Celite bed and washed with ethyl acetate. The concentration of the filtrate in vacuo furnished pure product (±)-**26** as viscous oil (1.51 g, ~100%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (d, J = 8 Hz, 3H), 1.40–2.00 (m, 4H), 2.18 (s, 3H), 2.68 (t, J = 6 Hz, 2H), 2.90 (sextet, J = 6 Hz, 1H), 3.83 (s, 3H), 6.68 (s, 1H), 6.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 20.6, 23.0, 29.0, 31.6, 32.6, 55.4, 109.6, 124.0, 128.3, 131.1, 140.3, 155.8; ESIMS (*m*/*z*) 213 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1615 cm^{-1}.

(±)-Methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (3).



To a stirred solution of (±)-**26** (1.50 g, 7.88 mmol) in acetone (30 mL) were added $KMnO_4$ (12.46 g, 78.80 mmol) and $FeCl_3$ (3.20 g, 19.70 mmol) and the reaction mixture stirred at –78 °C under argon atmosphere for 1 h. The reaction mixture was allowed to warm gradually to 25 °C and further stirred for 10 h. The resulting suspension was diluted with dichloromethane (30 mL), filtered and the residue was washed with dichloromethane (10 mL × 2). The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded product (±)-**3** as a white solid (1.17 g, 73%). Mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (d, J = 6 Hz, 3H), 1.75–2.00 (m, 1H), 2.10–2.35 (m, 1H), 2.20 (s, 3H), 2.40–2.85 (m, 2H), 2.95–3.15 (m, 1H), 3.90 (s, 3H), 6.68 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.7, 20.8, 30.7, 33.0, 35.8, 55.4, 107.6, 124.8, 125.4, 129.6, 149.4, 162.2, 197.4; ESIMS (*m*/*z*) 205 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ 205.1223, found 205.1224; IR ($CHCl_3$) ν_{max} 1667, 1599 cm^{-1}.

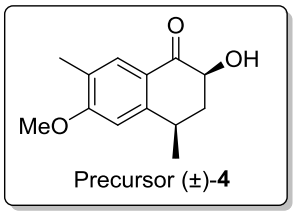
(±)-2-Hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Aristelegone B, 4).



(±)-**4**

A solution of the ketone (±)-**3** (1.10 g, 5.39 mmol) and KOH (3.02 g, 53.90 mmol) in MeOH (25 mL) was stirred at 0 °C under argon atmosphere for 10 min and $PhI(OCOCF_3)_2$ (2.78 g, 6.47 mmol) was added to the reaction mixture. It was stirred at the same temperature for 1 h and at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the obtained residue was dissolved in diethyl ether (50 mL). The organic layer was washed with sat. $NaHCO_3$, brine and dried over Na_2SO_4. The obtained product was purified by silica gel (230–400 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to afford the major product (±)-**4** as a white solid (0.75 g, 63%). Mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (d, J = 8 Hz, 3 H), 1.76 (dd, J = 26 and 14 Hz, 1H), 2.22 (s, 3H), 2.49 (ddd, J = 12, 4 and 4 Hz, 1H), 3.16 (septet, J = 6 Hz, 1H), 3.92 (s, 3H), 3.95 (d, J = 2 Hz, 1H), 4.34 (ddd, J = 14, 4 and 2 Hz, 1H), 6.78 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 20.5, 31.6, 40.8, 55.5, 72.9, 107.0, 121.7, 126.1, 129.7, 149.0, 162.9, 198.5; ESIMS (*m*/*z*) 243 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3466, 1674, 1606 cm $^{-1}$.

Amano PS Catalyzed Resolution of (±)-2-Hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (4).



Precursor (±)-**4**

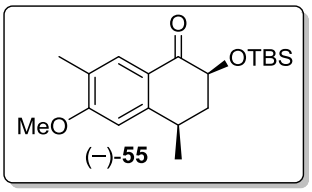
To a stirred solution of (±)-2-hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (**4**) (700 mg, 3.18 mmol) and vinyl acetate (1.35 g, 15.90 mmol) in acetone (20 mL) was added the enzyme Amano PS (50 mg, Sigma-Aldrich). The resulting reaction mixture was stirred at 25 °C for 36 h with monitoring the reaction progress by HPLC. The reaction mixture was filtered through Celite bed and washed with ethyl acetate (30 mL). The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–dichoromethane (1:99) as an eluent afforded pure product (+)-**54** as viscous oil (383 mg, 46%) and (–)-**4** as a white solid (378 mg, 54%).

(+)-54: $[\alpha]^{25}_D$ +30.6 (*c* 0.20 $CHCl_3$, 96% *ee*); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47 (d, J = 6 Hz, 3H), 2.00 (dd, J = 26 and 12 Hz, 1H), 2.21 (s, 3H), 2.23 (s, 3H), 2.37 (td, J = 12 and 8 Hz, 1H), 3.24 (septet, J = 6 Hz, 1H), 3.92 (s, 3H), 5.52 (dd, J = 12 and 8 Hz, 1H), 6.75 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 20.5, 20.9, 32.1, 38.0, 55.5, 74.0, 106.7,

124.0, 126.1, 130.0, 147.7, 162.7, 170.4, 192.2; ESIMS (*m*/*z*) 263 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ 263.1278, found 263.1273; IR ($CHCl_3$) ν_{max} 1741, 1688, 1607 cm^{-1}.

(–)-Aristelegone B (4): Mp 103–104 °C; $[\alpha]^{25}_D$ –28.9 (*c* 0.14 $CHCl_3$, 94% *ee*); the obtained spectroscopic data was identical with the data for (±)-**4**.

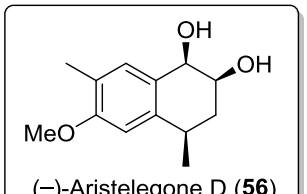
(–)-(2*S*,4*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (55).



(–)-**55**

To a stirred solution of alcohol (–)-**4** (50 mg, 0.22 mmol) in dichloromethane (5 mL) were added imidazole (18 mg, 0.26 mmol) and TBSCl (40 mg, 0.26 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and further stirred for 4 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:19) as an eluent afforded pure product **(–)-55** as viscous oil (66 mg, 87%). $[\alpha]^{25}_D$ –64.1 (*c* 0.10 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 3H), 0.23 (s, 3H), 0.95 (s, 9H), 1.44 (d, *J* = 8 Hz, 3H), 1.94 (q, *J* = 12 Hz, 1H), 2.19 (s, 3H), 2.29 (td, *J* = 12 and 8 Hz, 1H), 3.12 (septet, *J* = 8 Hz, 1H), 3.89 (s, 3H), 4.35 (dd, *J* = 12 and 4 Hz, 1H), 6.73 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ –5.4, –4.3, 15.7, 18.6, 20.7, 25.9, 32.4, 42.0, 55.4, 74.9, 106.7, 124.4, 125.8, 129.9, 147.9, 162.2, 197.0; ESIMS (*m*/*z*) 357 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{31}O_3Si$ 335.2037, found 335.2031; IR ($CHCl_3$) ν_{max} 1689, 1608 cm^{-1}.

(–)-(1*R*,2*S*,4*R*)-6-Methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene-1,2-diol (Aristelegone D, 56).

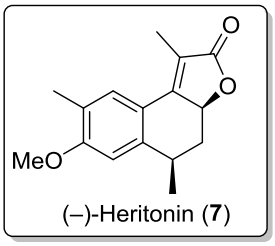


(–)-Aristelegone D (**56**)

To a stirred solution of **(–)-55** (50 mg, 0.15 mmol) in THF (4 mL) was added DIBAL solution (0.16 mL, 0.16 mmol, 1 M in hexane) in dropwise fashion at –10 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The reaction was quenched with saturated NH_4Cl solution and the reaction mixture was concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting

residue using ethyl acetate–petroleum ether (2:3) as an eluent afforded pure product (**–**)-**56** as a white solid (28 mg, 84%). Mp 124–125 °C; $[\alpha]^{25}_{D}$ –67.8 (*c* 0.27 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, *J* = 8 Hz, 3H), 1.72 (q, *J* = 12 Hz, 1H), 1.85–2.05 (m, 1H), 2.00–2.60 (br s, 2H), 2.20 (s, 3H), 2.90 (septet, *J* = 2 Hz, 1H), 3.84 (s, 3H), 3.89 (td, *J* = 12 and 4 Hz, 1H), 4.63 (d, *J* = 2 Hz, 1H), 6.75 (s, 1H), 7.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 21.4, 32.5, 35.0, 55.3, 69.7, 70.2, 107.7, 125.4, 127.8, 132.7, 139.9, 158.2; ESIMS (*m*/*z*) 245 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O_3$ 221.1172, found 221.1172; IR ($CHCl_3$) ν_{max} 3430, 1642 cm^{-1}.

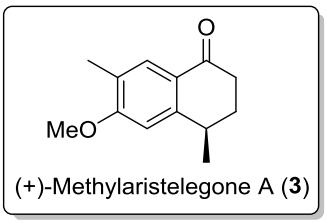
(–)-(3a*S*,5*R*)-7-Methoxy-1,5,8-trimethyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3a*H*)-one (Heritonin, 7).



(–)-Heritonin (**7**)

To a stirred solution of the (–)-aristelegone B (**4**) (88 mg, 0.40 mmol) in toluene (4 mL) was added Cu(II) catalyst (5 mol %), Wittig reagent (272 mg, 0.60 mmol), molecular sieves 4 Å (200 mg, 500 mg/mmol) and OXONE® (369 mg, 1.20 mmol) under argon atmosphere. The reaction mixture was stirred at 60 °C for 12 h until disappearance of the starting material, then xylene (6 mL) was added to the reaction mixture and the whole reaction mixture was stirred at 138 °C for 1 h. The reaction mixture was allowed to reach 25 °C, filtered through Celite bed and the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel (60–120) column chromatographic purification using ethyl acetate–petroleum ether (1:19) as an eluent to afford pure product (–)-**7** as a white solid (76 mg, 74%). Mp 110–112 °C; $[\alpha]^{25}_{D}$ –299.2 (*c* 0.25 $CHCl_3$, 93% *ee*); ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.46 (d, *J* = 7 Hz, 3H), 1.48 (q, *J* = 14 Hz, 1H), 2.14 (s, 3H), 2.25 (s, 3H), 2.64 (dt, *J* = 14 and 7 Hz, 1H), 3.14 (septet, *J* = 7 Hz, 1H), 3.89 (s, 3H), 4.92 (dd, *J* = 14 and 7 Hz, 1H), 6.86 (s, 1H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 9.9, 16.0, 21.7, 32.0, 38.7, 55.3, 78.1, 108.4, 115.9, 120.7, 125.7, 129.6, 142.2, 156.7, 159.6, 175.6; HRMS (ESI) calcd for $C_{16}H_{19}O_3$ 259.1329, found 259.1326; IR ($CHCl_3$) ν_{max} 1738, 1651, 1611 cm^{-1}.

(+)-(*R*)-6-Methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Methylaristelegone A, 3).

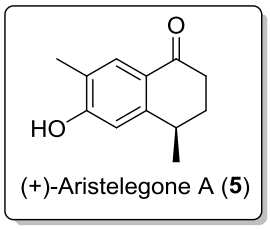


(+)-Methylaristelegone A (**3**)

To a stirred solution of (–)-aristelegone B (**4**) (50 mg, 0.22 mmol) in THF (2 mL) was added acetic anhydride (45 mg, 0.44 mmol) followed by a solution of samarium diiodide (8.80 mL, 0.88

mmol, 0.10 M in THF) in dropwise fashion at 0 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (10 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded pure product (+)-**3** as a white solid (30 mg, 65%). Mp 109–110 °C; $[\alpha]^{25}_{D}$ +21.3 (*c* 0.25 $CHCl_3$); the obtained spectroscopic data was identical with the data for (±)-**3**.

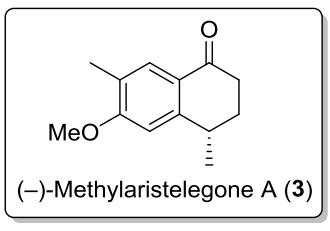
(+)-(*R*)-6-Hydroxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Aristelegone A, 5).



(+)-Aristelegone A (**5**)

To a stirred solution of (+)-methylaristelegone A (**3**) (25 mg, 0.12 mmol) in DCM (2 mL) was added solution of a boron tribromide (0.30 mL, 0.30 mmol, 1 M in DCM) in dropwise fashion at −78 °C and the reaction mixture was stirred under argon atmosphere for 1 h. The reaction mixture was allowed to reach 25 °C and stirred further for 12 h. The reaction was quenched with ice cold water and stirred for 30 min. The reaction mixture was extracted with DCM (7 mL × 2) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:2) as an eluent afforded pure product (+)-**5** as a white solid (17 mg, 74%). Mp 148–150 °C; $[\alpha]^{25}_{D}$ +13.6 (*c* 0.28 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36 (d, *J* = 5 Hz, 3H), 1.82–1.90 (m, 1H), 2.16–2.24 (m, 1H), 2.26 (s, 3H), 2.57 (ddd, *J* = 20, 10 and 5 Hz, 1H), 2.76 (ddd, *J* = 20, 10 and 5 Hz, 1H), 2.99 (sextet, *J* = 10 Hz, 1H), 6.64 (br s, 1H), 6.75 (s, 1H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 20.5, 30.8, 32.6, 36.2, 112.8, 123.0, 124.9, 130.6, 149.7, 159.5, 198.4; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ 191.1067, found 191.1070; IR ($CHCl_3$) ν_{max} 3218, 1651, 1585 cm^{-1}.

(–)-(*S*)-6-Methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Methylaristelegone A, 3).

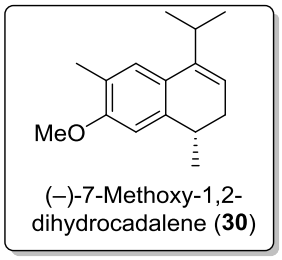


(–)-Methylaristelegone A (**3**)

To a stirred solution of acetoxy ketone (+)-**54** (100 mg, 0.38 mmol) in THF (4 mL) was added solution of samarium diiodide (7.60 mL, 0.76 mmol, 0.10 M in THF) in dropwise fashion at 0 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The

reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (10 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded pure product (–)-**3** as a white solid (65 mg, 84%). Mp 109–111 °C; $[\alpha]^{25}_{D}$ –22.4 (*c* 0.25 $CHCl_3$); the obtained spectroscopic data was identical with the data for (±)-**3**.

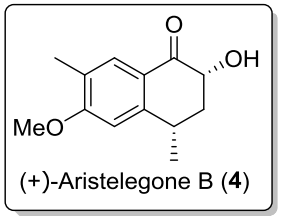
(–)-(*S*)-4-Isopropyl-7-methoxy-1,6-dimethyl-1,2-dihydronaphthalene (30).



(–)-7-Methoxy-1,2-dihydrocadalene (**30**)

To a stirred solution of (–)-methylaristelegone A (**3**) (50 mg, 0.24 mmol) in THF (4 mL) was added solution of isopropylmagnesium chloride (0.14 mL, 0.28 mmol, 2 M in THF) in dropwise fashion at 0 °C and the reaction mixture was stirred at the 25 °C under argon atmosphere for 6 h. The reaction was quenched with 2 N HCl and stirred for 30 min. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:49) as an eluent afforded pure product (–)-**30** as viscous oil (52 mg, 92%). $[\alpha]^{25}_{D}$ –57.8 (*c* 0.37 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, *J* = 8 Hz, 3H), 1.19 (d, *J* = 8 Hz, 3H), 1.22 (d, *J* = 8 Hz, 3H), 2.07 (dt, *J* = 16 and 8 Hz, 1H), 2.24 (s, 3H), 2.37–2.46 (m, 1H), 2.81 (sextet, *J* = 8 Hz, 1H), 2.95 (septet, *J* = 8 Hz, 1H), 3.87 (s, 3H), 5.67 (t, *J* = 4 Hz, 1H), 6.72 (s, 1H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 19.9, 22.0, 22.4, 28.1, 30.9, 32.6, 55.4, 108.6, 116.8, 123.4, 125.4, 126.5, 141.1, 141.5, 156.3; HRMS (ESI) calcd for $C_{16}H_{23}O$ 231.1743, found 231.1743; IR ($CHCl_3$) ν_{max} 1603 cm^{-1}.

(+)-(2*R*,4*S*)-2-Hydroxy-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (Aristelegone B, 4).

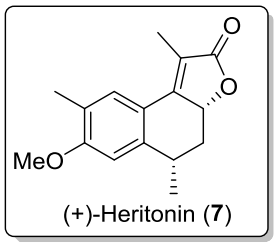


(+)-Aristelegone B (**4**)

To a stirred solution of acetoxy ketone (+)-**54** (200 mg, 0.76 mmol) in methanol (5 mL) was added K_2CO_3 (5 mg) at 0 °C and the reaction mixture was further stirred under argon atmosphere for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo

followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded pure product (+)-**4** as a white solid (137 mg, 82%). Mp 102–103 °C; $[\alpha]^{25}_{D}$ +29.2 (*c* 0.18 $CHCl_3$, 92% *ee*); the obtained spectroscopic data was identical with the data for (±)-**4**.

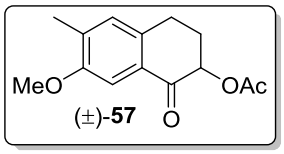
(+)-(3a*R*,5*S*)-7-Methoxy-1,5,8-trimethyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3a*H*)-one (Heritonin, 7).



(+)-Heritonin (**7**)

To a stirred solution of the (+)-aristelegone B (**4**) (88.0 mg, 0.40 mmol) in toluene (4 mL) was added Cu(II) catalyst (5 mol %), Wittig reagent (272 mg, 0.60 mmol), molecular sieves 4 Å (200 mg, 500 mg/mmol) and OXONE® (369 mg, 1.20 mmol) under argon atmosphere. The reaction mixture was stirred at 60 °C for 12 h until disappearance of the starting material, then xylene (6 mL) was added to the reaction mixture and the whole reaction mixture was stirred at 138 °C for 1 h. The reaction mixture was allowed to reach 25 °C, filtered through Celite bed and the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel (60–120) column chromatographic purification using ethyl acetate–petroleum ether (1:19) as an eluent to afford pure product (+)-**7** as a white solid (72 mg, 71%). Mp 111–113 °C; $[\alpha]^{25}_{D}$ +298.1 (*c* 0.32 $CHCl_3$); the obtained spectroscopic data was identical with the data for (–)-**7**.

(±)-7-Methoxy-6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl acetate (57).

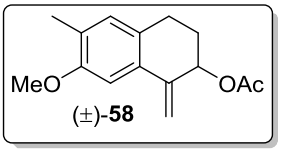


(±)-**57**

A solution of $KMnO_4$ (1.25 g, 78.84 mmol) in benzene–acetic acid (10:1, 250 mL) was stirred under reflux (Dean–Stark apparatus) until the purple color of $KMnO_4$ turned brown (30–45 min). To this solution was added compound **24** (5.00 g, 26.28 mmol) and reflux was continued. The reaction was monitored by TLC and after 6 h it was diluted with diethyl ether and neutralized with aq. $NaHCO_3$. The resulting organic phase was dried over Na_2SO_4 and concentrated under vacuo. The crude product was purified by silica gel (60–120) column chromatographic purification using ethyl acetate–petroleum ether (1:3) as an eluent to afford pure product (±)-**57** as viscous oil (4.56 g, 70%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10–2.42 (m, 2H), 2.21 (s, 3H), 2.23 (s, 3H), 2.86–3.18 (m, 2H), 3.83 (s, 3H), 5.49 (dd, J = 12 and 6 Hz, 1H), 7.00 (s, 1H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.5, 20.8, 27.0, 29.4, 55.4, 74.5, 107.0, 130.2, 130.6, 134.5, 135.6, 156.7, 170.2, 192.7; ESIMS (*m*/*z*) 271 $[M+Na]^+$;

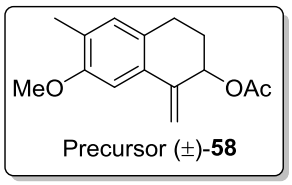
HRMS (ESI) calcd for $C_{14}H_{17}O_4$ 249.1121, found 249.1120; IR ($CHCl_3$) ν_{max} 1775, 1746, 1692, 1611 cm^{-1}.

(±)-7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl acetate (58).



To a stirred solution of methyltriphenylphosphonium iodide (8.10 g, 19.93 mmol) in anhydrous THF (40 mL) was added a solution of *n*-BuLi (12.45 mL, 19.93 mmol, 1.60 M in hexane) in dropwise fashion at 0 °C under argon atmosphere and the mixture was stirred for 30 min. A solution of compound (±)-**57** (4.50 g, 18.12 mmol in 20 ml THF) was added to the above reaction mixture at 0 °C and it was further stirred for 10 h. The reaction was quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (150 mL), washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60−120) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:4) as an eluent afforded product (±)-**58** as a white solid (2.99 g, 67%). Mp 52–54 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.95–2.18 (m, 2H), 2.09 (s, 3H), 2.21 (s, 3H), 2.70–3.05 (m, 2H), 3.86 (s, 3H), 5.25 (s, 1H), 5.61 (s, 1H), 5.66 (dd, J = 6 and 4 Hz, 1H), 6.92 (s, 1H), 7.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 21.4, 25.1, 28.7, 55.3, 72.8, 105.4, 109.9, 127.6, 127.8, 130.8, 130.9, 141.5, 156.3, 170.5; HRMS (ESI) calcd for $C_{15}H_{18}O_3Na$ 269.1148, found 269.1147; IR ($CHCl_3$) ν_{max} 1736, 1613 cm^{-1}.

Amano PS Catalyzed Resolution of (±)-7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl acetate (58).

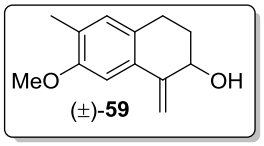


To a stirred solution of allyl acetate (±)-**58** (1.00 g, 4.05 mmol) in a mixture of petroleum ether and benzene (1:2, 30 mL) were successively added the phosphate buffer (pH 7, 20 mL) and enzyme Amano PS (50 mg, Amano Enzyme Japan). The resulting reaction mixture was stirred at 45 °C for 48 h with monitoring the reaction progress by HPLC. The reaction mixture was filtered through Celite bed and washed with ethyl acetate (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60−120) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:4) as an eluent afforded pure product (+)-**58** as a white solid (2.99 g, 44%) and (+)-**59** also as a white solid (329 mg, 56%).

(+)-58: $[\alpha]^{25}_{D}$ +2.8 (*c* 1.75 $CHCl_3$, 92% *ee*); the obtained spectroscopic data was identical with the data for (±)-**58**.

(+)-59: $[\alpha]^{25}_{D}$ +3.2 (*c* 0.40 $CHCl_3$, 89% *ee*); the obtained spectroscopic data was identical with the data for (±)-**59**.

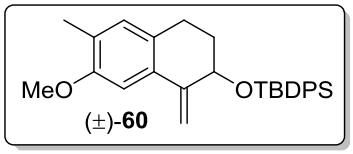
(±)-7-Methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-ol (59).



(±)-**59**

To a stirred solution of acetate (±)-**58** (1.50 g, 6.08 mmol) in methanol (10 mL) was added K_2CO_3 (20 mg) at 0 °C and the reaction mixture was further stirred under argon atmosphere for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:2) as an eluent afforded pure product (±)-**59** as a white solid (1.05 g, 85%). Mp 85–87 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.69 (br s, 1H), 1.85–2.15 (m, 2H), 2.20 (s, 3H), 2.68–3.07 (m, 2H), 3.86 (s, 3H), 4.51 (dd, *J* = 8 and 4 Hz, 1H), 5.27 (s, 1H), 5.55 (s, 1H), 6.91 (s, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 25.4, 31.7, 55.4, 70.9, 105.6, 107.2, 127.5, 128.1, 131.0 (2 C), 146.6, 156.3; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ 205.1223, found 205.1224; IR ($CHCl_3$) ν_{max} 3430, 1644, 1604 cm^{-1}.

(±)-*tert*-Butyl((7-methoxy-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalen-2-yl)oxy) diphenylsilane (60).

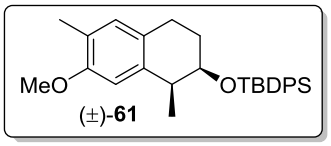


(±)-**60**

To a stirred solution of alcohol (±)-**59** (1.00 g, 4.89 mmol) in dichloromethane (20 mL) were added imidazole (366 mg, 5.38 mmol) and TBDPSCl (1.48 g, 5.38 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and further stirred for 6 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (40 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:49) as an eluent afforded pure product (±)-**60** as a white solid (1.99 g, 92%). Mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (s, 9H), 1.65–2.00 (m, 2H), 2.17 (s, 3H), 2.45–2.65 (m, 1H), 2.80–3.00 (m, 1H), 3.84 (s, 3H), 4.48 (dd, *J* = 8 and 4 Hz, 1H), 5.15 (s, 1H), 5.37 (s, 1H), 6.82 (s, 1H), 6.96 (s, 1H), 7.25–7.50 (m, 6H), 7.62 (dd, *J* = 8 and 2 Hz, 2H), 7.72 (dd, *J*

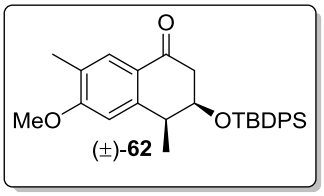
= 8 and 2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 19.4, 26.1, 27.0, 32.7, 55.4, 72.5, 105.9, 107.1, 126.9, 127.4, 127.6, 128.0, 129.5, 129.6, 130.8, 132.2, 134.0, 134.6, 135.9 (2 C), 146.4, 156.1; HRMS (ESI) calcd for $C_{29}H_{33}O_2Si$ 441.2244, found 441.2245; IR ($CHCl_3$) ν_{max} 1609 cm $^{-1}$.

(±)-*tert*-Butyl((7-methoxy-1,6-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)diphenylsilane (61).



To a stirred solution of compound (±)-**60** (1.50 g, 3.38 mmol) in ethyl acetate (25 mL) was added 10% Pd/C (25 mg) at 25 °C and the reaction mixture was subjected to hydrogenation under balloon pressure for 8 h. The reaction mixture was filtered through Celite bed and washed with ethyl acetate. The concentration of the filtrate in vacuo furnished diastereomeric mixture of compound (±)-**61** as a white solid with ~9:1 ratio (by ^{1}H NMR) (1.51 g, ~100%). Mp 110–113 °C; major isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 9H), 1.32 (d, J = 8 Hz, 3 H), 1.55–1.70 (m, 1H), 1.80–2.05 (m, 1H), 2.11 (s, 3H), 2.28–2.55 (m, 1H), 2.57–2.75 (m, 1H), 2.83–3.00 (m, 1H), 3.77 (s, 3H), 4.04–4.17 (m, 1H), 6.48 (s, 1H), 6.73 (s, 1H), 7.25–7.50 (m, 6H), 7.65–7.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 17.4, 19.4, 26.6, 27.0, 27.5, 39.6, 55.4, 71.8, 110.5, 124.5, 126.3, 127.47, 127.54, 129.5, 129.6, 130.5, 134.3, 134.8, 135.8, 139.9 (2 C), 155.9; ESIMS (*m*/*z*) 467 $[M+Na]^+$; HRMS (ESI) calcd for $C_{29}H_{36}O_2NaSi$ 467.2377, found 467.2371; IR ($CHCl_3$) ν_{max} 1602 cm $^{-1}$.

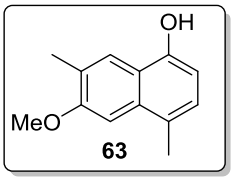
(±)-3-((*tert*-Butyldiphenylsilyl)oxy)-6-methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (62).



To a stirred solution of (±)-**61** (1.00 g, 2.24 mmol) in acetic acid (20 mL) was added a solution of CrO_3 (292 mg, 2.92 mmol) in AcOH plus H_2O (8:2, 8 mL) in dropwise fashion at 0 °C. The reaction mixture was further stirred for 2 h, diluted with water and carefully neutralized by addition of a saturated solution of $NaHCO_3$. The reaction mixture was extracted with diethyl ether (25 mL × 3) and the organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:9) as an eluent afforded product (±)-**62** as viscous oil (680 mg, 66%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09 (s, 9H), 1.37 (d, J = 8 Hz, 3 H), 2.15 (s, 3H), 2.59 (dd, J = 18 and 6 Hz, 1 H), 2.83 (dd, J = 18 and 12 Hz, 1 H), 3.03 (quintet, J = 6 Hz, 1H), 3.86 (s, 3H), 4.32 (td, J =

12 and 4 Hz, 1H), 6.53 (s, 1H), 7.30–7.50 (m, 6H), 7.60–7.80 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6, 19.2, 26.5, 26.9, 40.6, 42.7, 55.5, 69.8, 108.7, 124.1, 125.9, 127.7, 129.3, 129.6, 129.79, 129.83, 133.6, 133.7, 134.8, 135.7, 148.1, 162.5, 195.9; ESIMS (*m*/*z*) 481 $[M+Na]^+$; HRMS (ESI) calcd for $C_{29}H_{35}O_3Si$ 459.2350, found 459.2348; IR ($CHCl_3$) ν_{max} 1728, 1667, 1602 cm $^{-1}$.

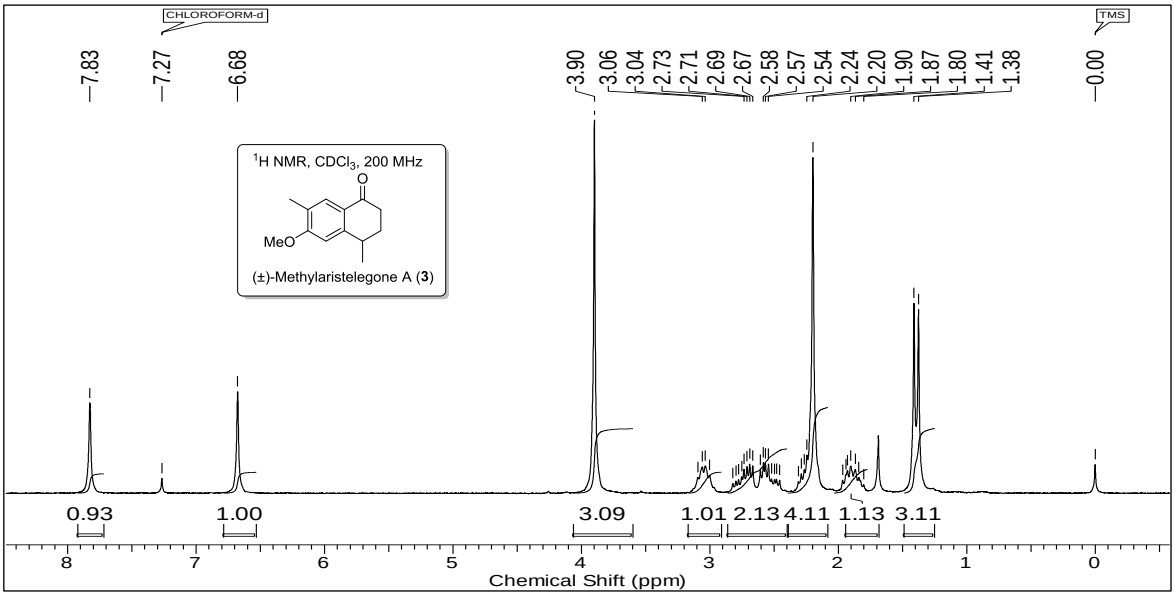
6-Methoxy-4,7-dimethylnaphthalen-1-ol (63).

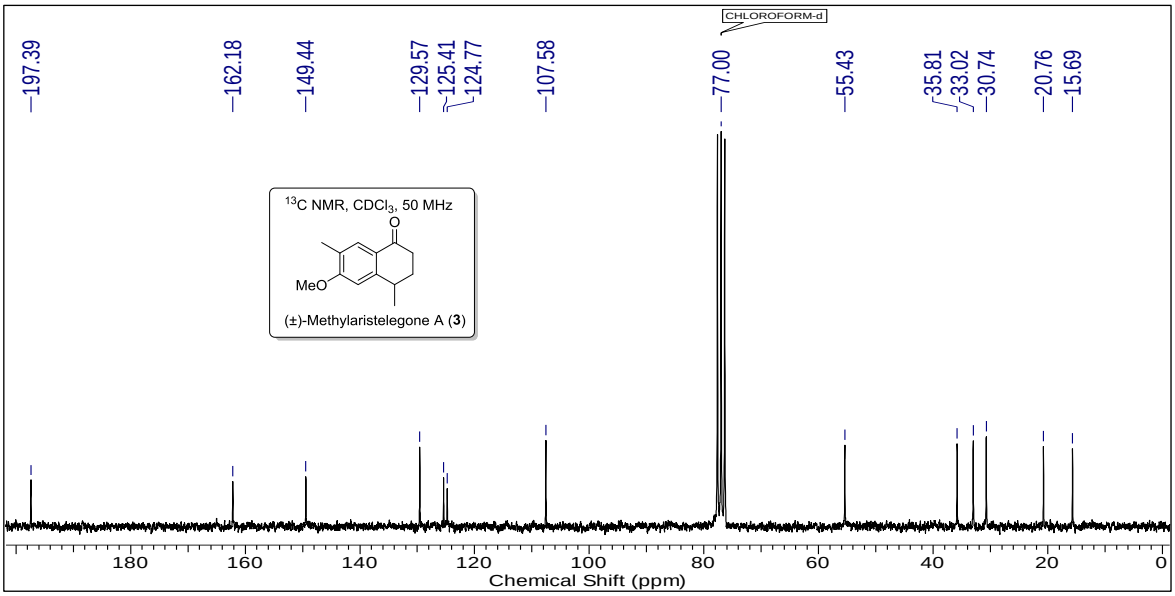


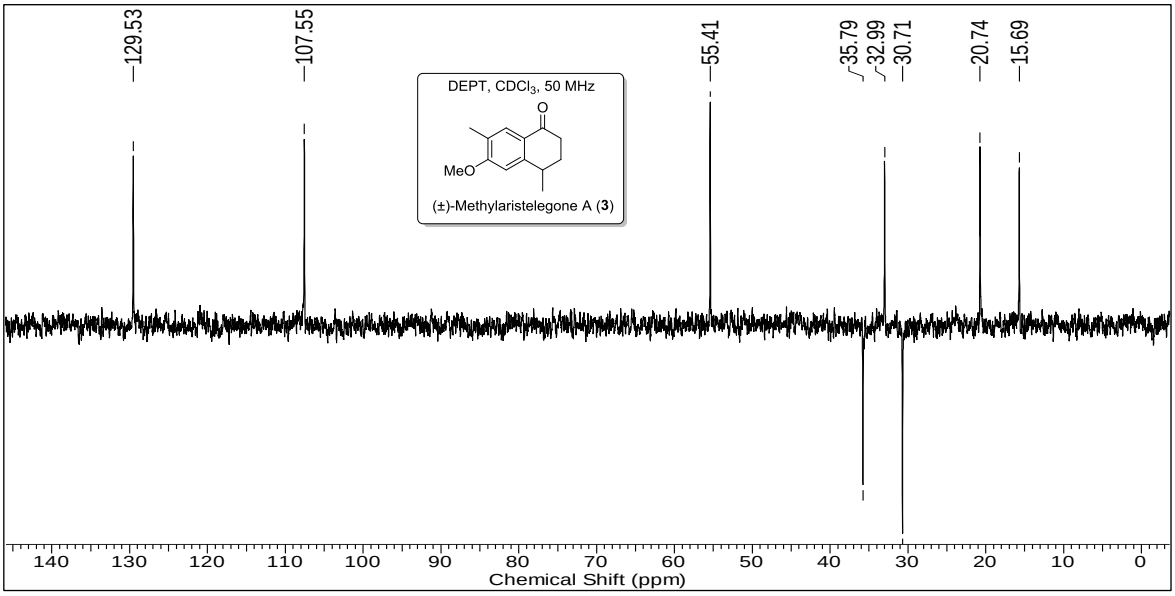
Method A: To a stirred slurry of keto compound (±)-**62** (100 mg, 0.21 mmol), activated Zn (27 mg, 0.42 mmol) and catalytic amount of iodine in anhydrous diethyl ether (10 mL) was slowly added a solution of ethyl 2-bromopropionate (76 mg, 0.42 mmol) in anhydrous diethyl ether (2 mL) at 25 °C under argon atmosphere. Reaction mixture further refluxed for 12 h, quenched with saturated NH_4Cl solution and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded pure product **63** as an orange oil (30 mg, 68%).

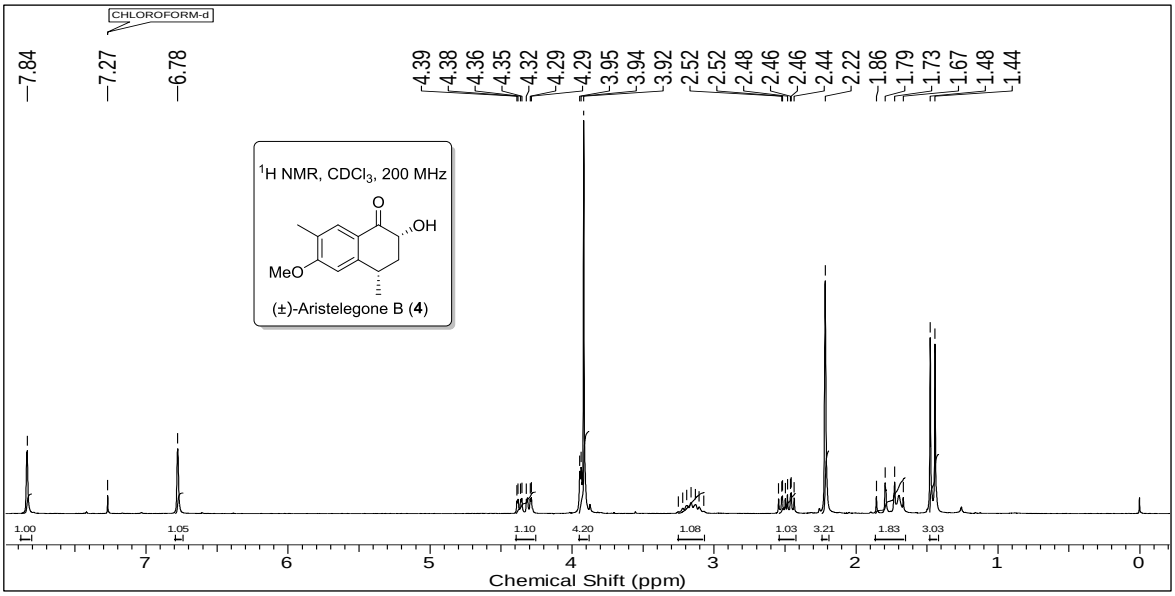
Method B: To a stirred solution of keto compound (±)-**62** (100 mg, 0.21 mmol) in anhydrous THF (10 mL) was slowly added a solution of tetrabutylammonium fluoride (0.23 mL, 0.23 mmol, 1 M in THF) at 0 °C. Reaction mixture was further stirred for 5 h at same temperature and quenched with saturated NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded pure product **63** as an orange oil (27 mg, 63%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 2.58 (s, 3H), 3.99 (s, 3H), 5.37 (br s, 1H), 6.59 (d, J = 8 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 7.11 (s, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.9, 19.1, 55.2, 101.3, 106.1, 119.3, 123.1, 125.0, 125.8, 127.2, 133.6, 149.5, 157.2; ESIMS (*m*/*z*) 203 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ 203.1067, found 203.1066; IR ($CHCl_3$) ν_{max} 3415, 1599 cm^{-1}.

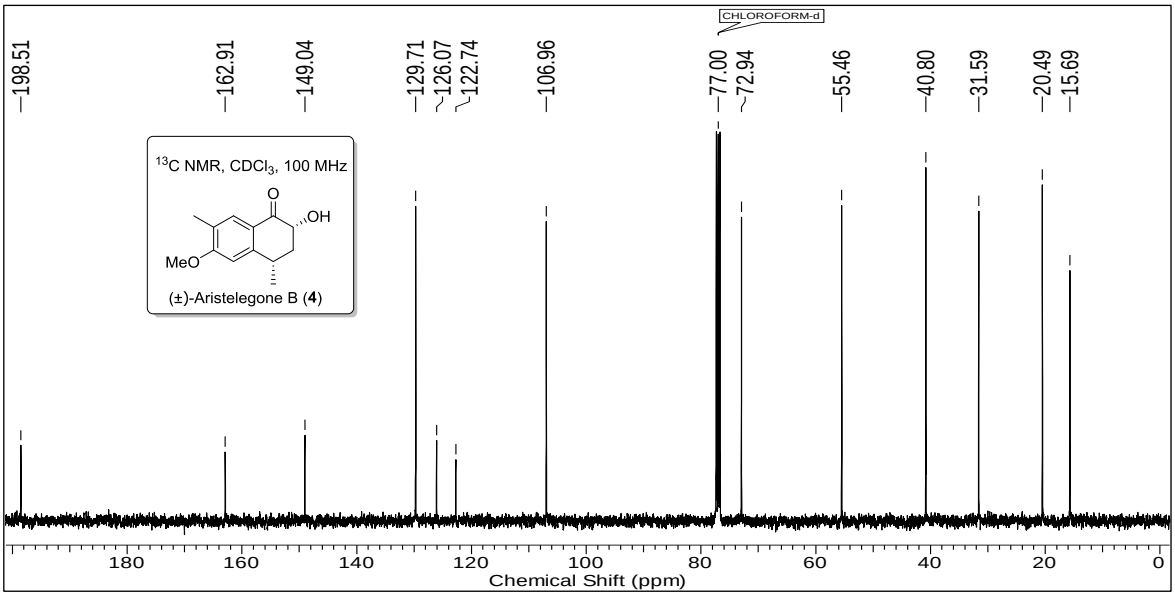
2B.5 Selected Spectra

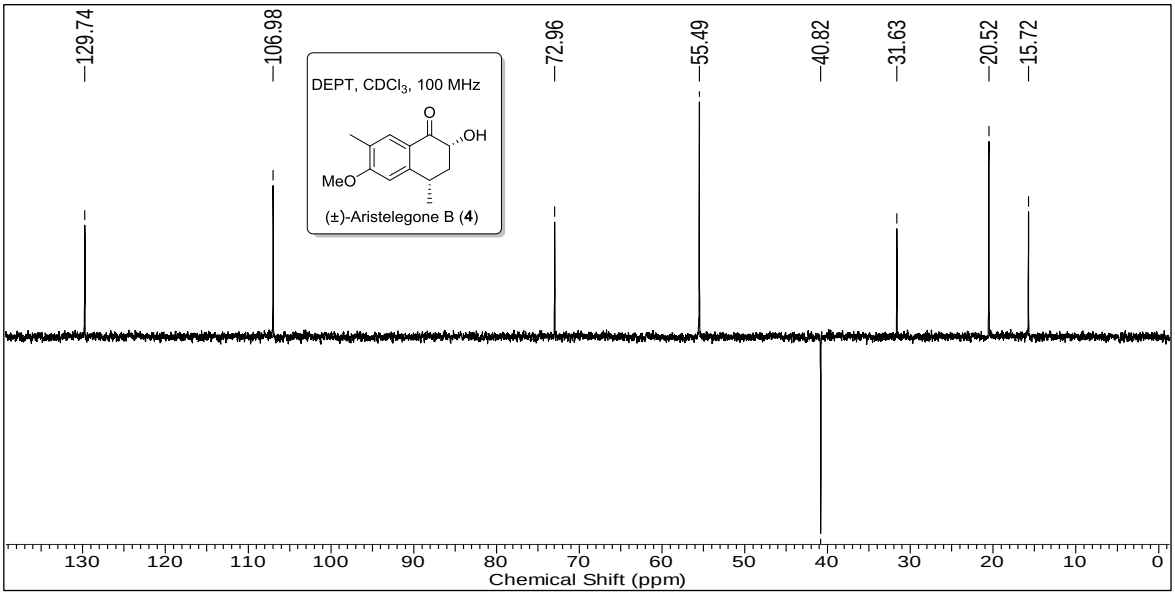

CHLOROFORM-d
TMS
7.83
7.27
6.68
3.90
3.06
3.04
2.73
2.71
2.69
2.67
2.58
2.57
2.54
2.24
2.20
1.90
1.87
1.80
1.41
1.38
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
MeO
(±)-Methylaristelegone A (3)
0.93
1.00
3.09
1.01
2.13
4.11
1.13
3.11
Chemical Shift (ppm)


CHLOROFORM-d
197.39
162.18
149.44
129.57
125.41
124.77
107.58
77.00
55.43
35.81
33.02
30.74
20.76
15.69
^{13}C NMR, CDCl$_3$, 50 MHz
MeO
(±)-Methylaristelegone A (3)
Chemical Shift (ppm)

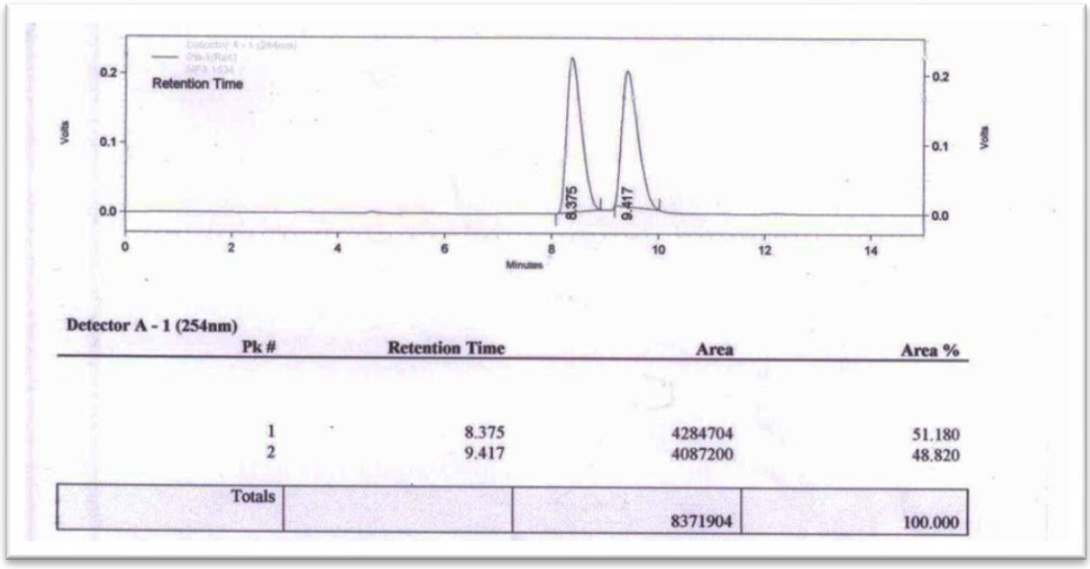

129.53
107.55
55.41
35.79
32.99
30.71
20.74
15.69
DEPT, CDCl$_3$, 50 MHz
MeO
(±)-Methylaristelegone A (3)
Chemical Shift (ppm)


CHLOROFORM-d
7.84
7.27
6.78
4.39
4.38
4.36
4.35
4.32
4.29
4.29
3.95
3.94
3.92
2.52
2.52
2.48
2.46
2.46
2.44
2.22
1.86
1.79
1.73
1.67
1.48
1.44
^{1}H NMR, CDCl$_3$, 200 MHz
OH
MeO
(±)-Aristelegone B (4)
1.00
1.05
1.10
4.20
1.08
1.03
3.21
1.83
3.03
Chemical Shift (ppm)


CHLOROFORM-d
198.51
162.91
149.04
129.71
126.07
122.74
106.96
77.00
72.94
55.46
40.80
31.59
20.49
15.69
^{13}C NMR, CDCl$_3$, 100 MHz
OH
MeO
(±)-Aristelegone B (4)
Chemical Shift (ppm)


129.74
106.98
72.96
55.49
40.82
31.63
20.52
15.72
DEPT, CDCl$_3$, 100 MHz
OH
MeO
(±)-Aristelegone B (4)
Chemical Shift (ppm)

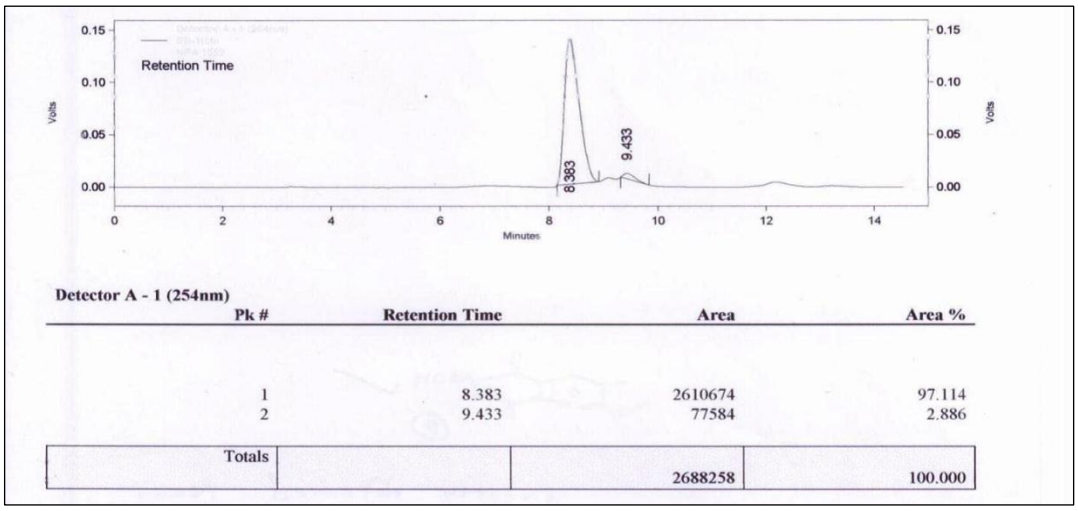
HPLC data of (±)-aristelegone B (4)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	8.375	4284704	51.180
2	9.417	4087200	48.820
Totals		8371904	100.000

HPLC data of (–)-aristelegone B (4)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	8.383	2610674	97.114
2	9.433	77584	2.886
Totals		2688258	100.000

Column: Chiralcel OJ-H (250 mm × 4.6 mm)

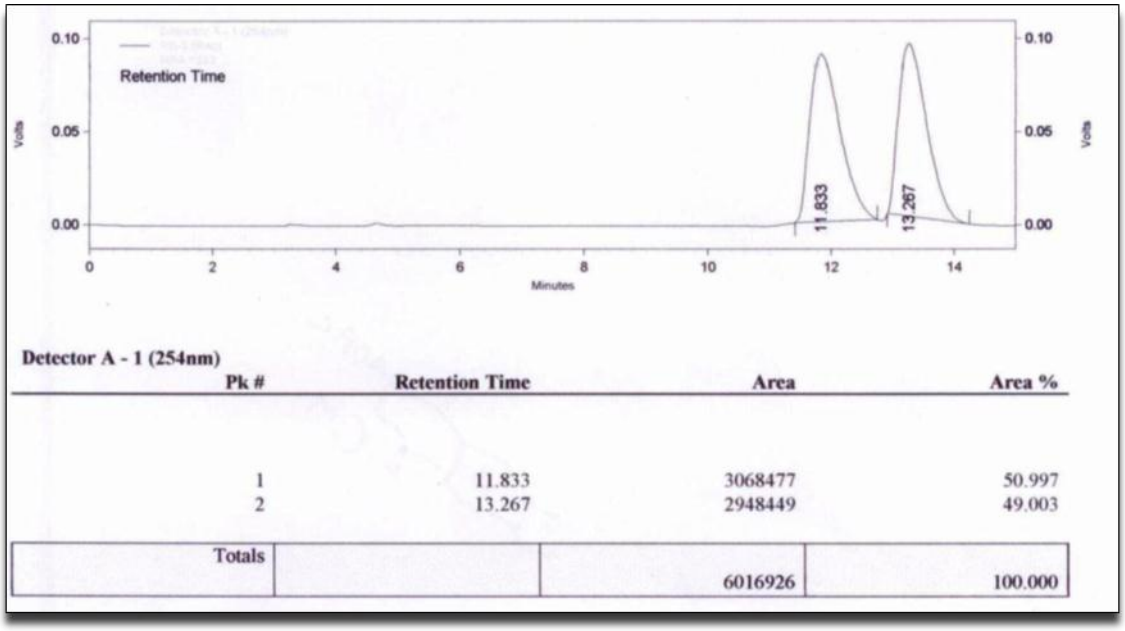
Mobile Phase: IPA:PE (10:90)

Wavelength: 254 nm

Flow Rate: 1 mL/min

Sample Conc.: 1 mg/mL

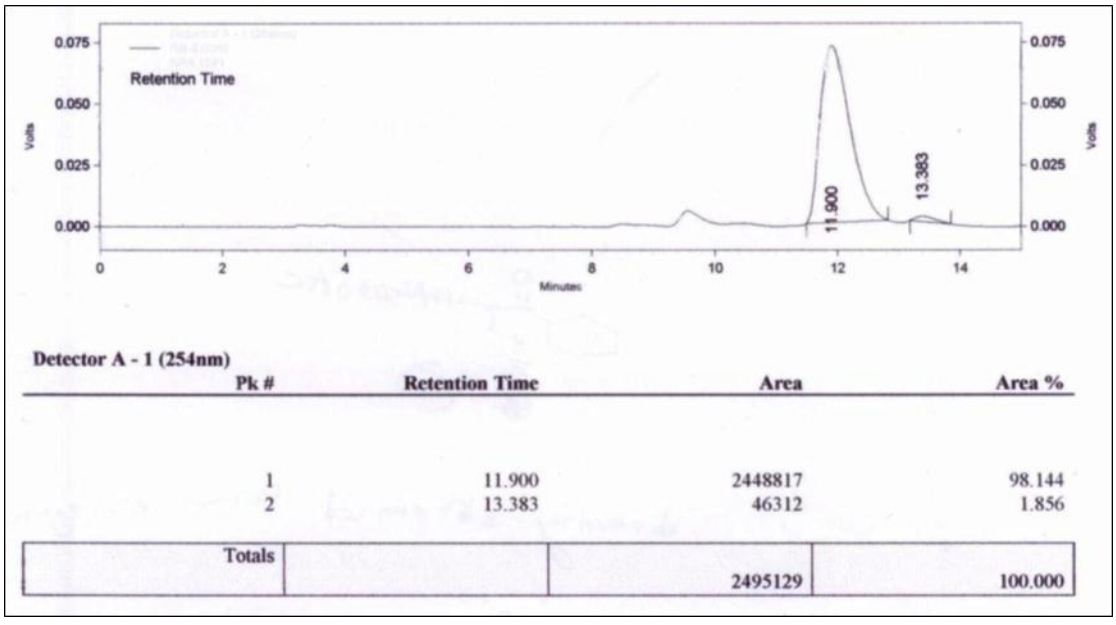
HPLC data of (±)-54



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	11.833	3068477	50.997
2	13.267	2948449	49.003
Totals		6016926	100.000

HPLC data of (+)-54



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	11.900	2448817	98.144
2	13.383	46312	1.856
Totals		2495129	100.000

Column: Chiralcel OJ-H (250 mm × 4.6 mm)

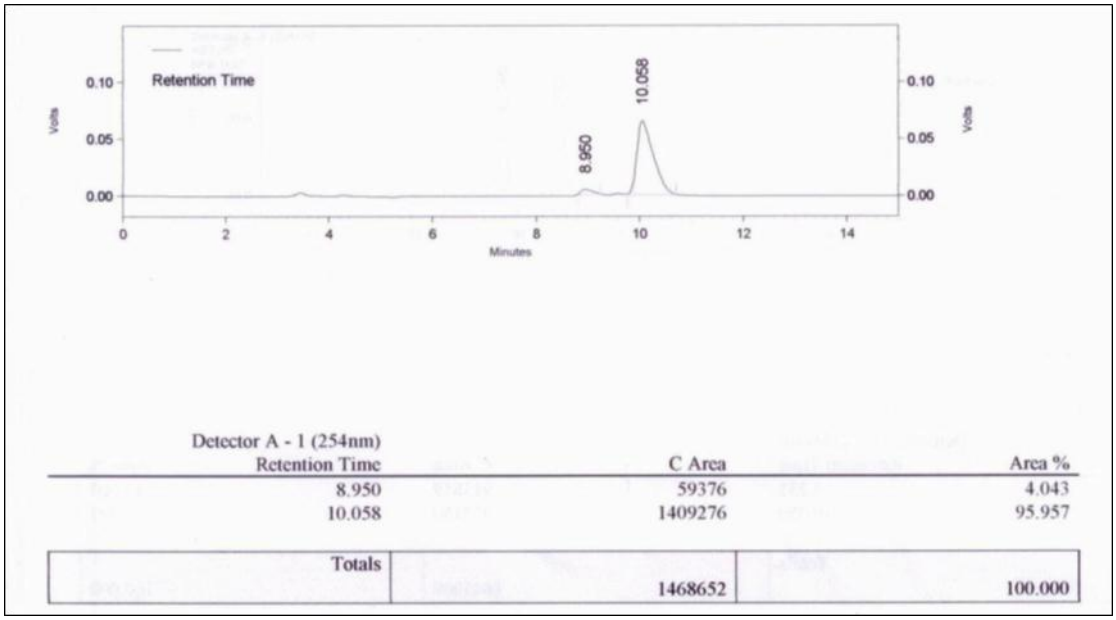
Mobile Phase: IPA:PE (10:90)

Wavelength: 254 nm

Flow Rate: 1 mL/min

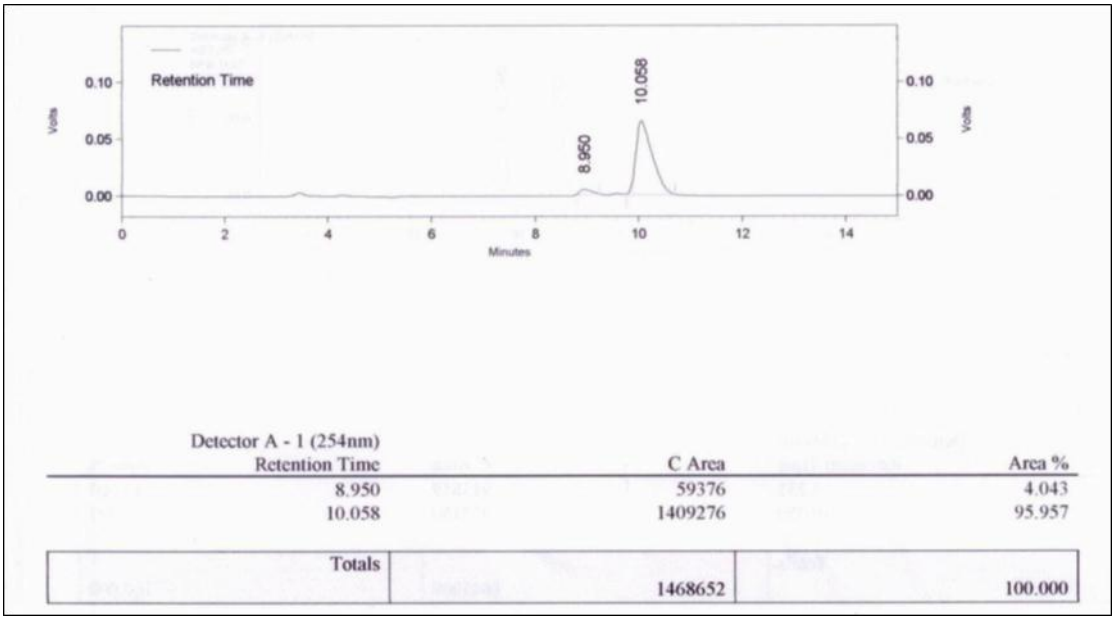
Sample Conc.: 1 mg/mL

HPLC data of (±)-aristelegone B (4)



Detector A - 1 (254nm) Retention Time	C Area	Area %
8.950	59376	4.043
10.058	1409276	95.957
Totals	1468652	100.000

HPLC data of (+)-aristelegone B (4)



Detector A - 1 (254nm) Retention Time	C Area	Area %
8.950	59376	4.043
10.058	1409276	95.957
Totals	1468652	100.000

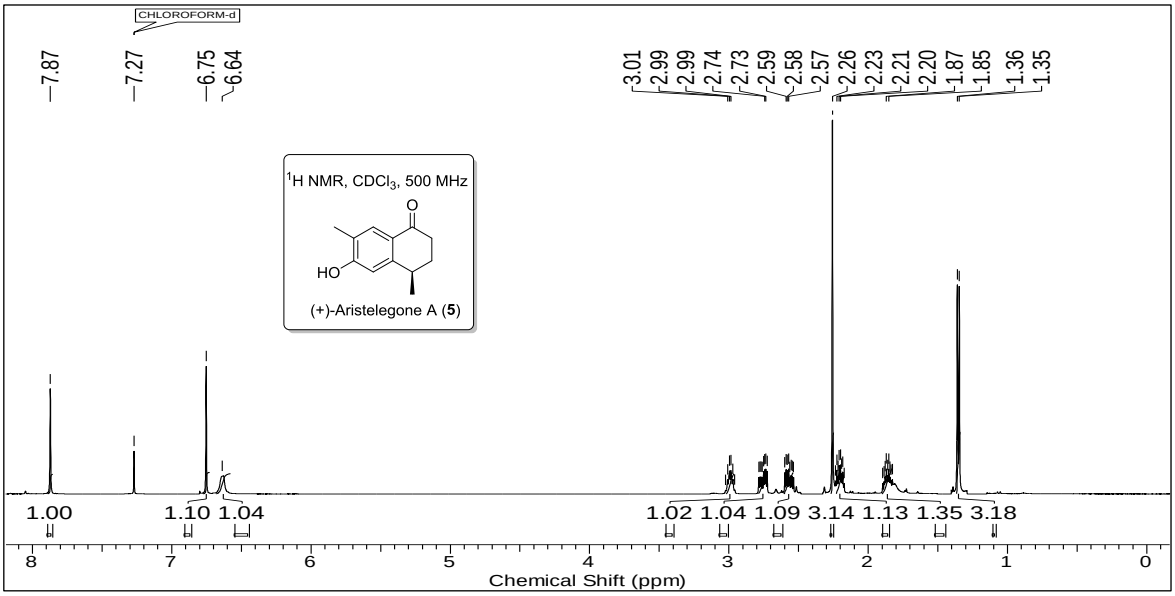
Column: Chiralcel OJ-H (250 mm × 4.6 mm)

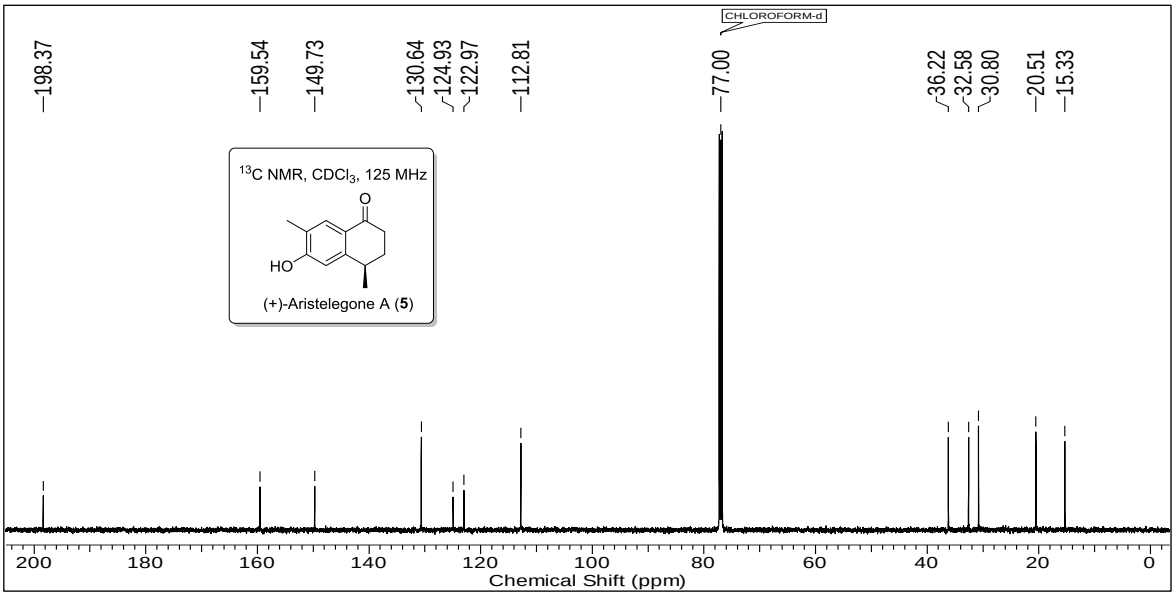
Mobile Phase: IPA:PE (10:90)

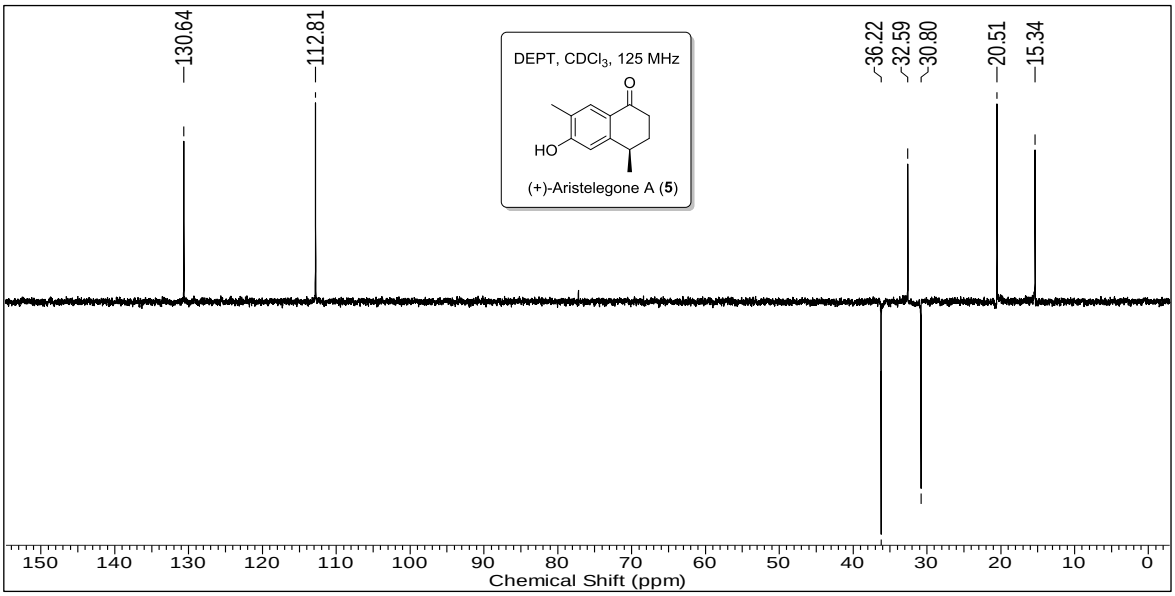
Wavelength: 254 nm

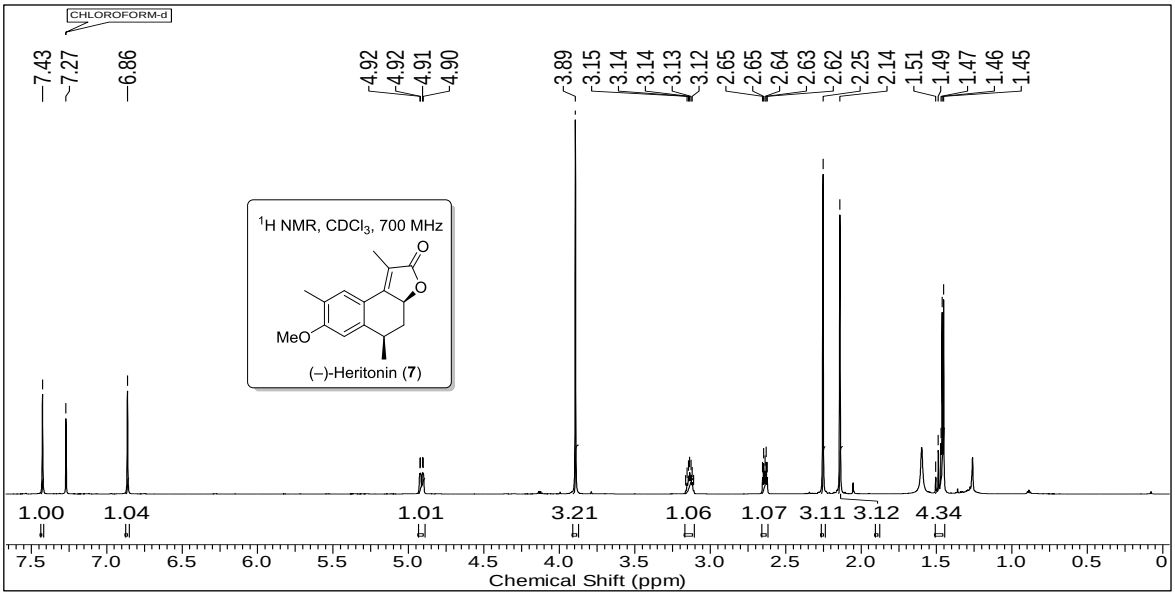
Flow Rate: 1 mL/min

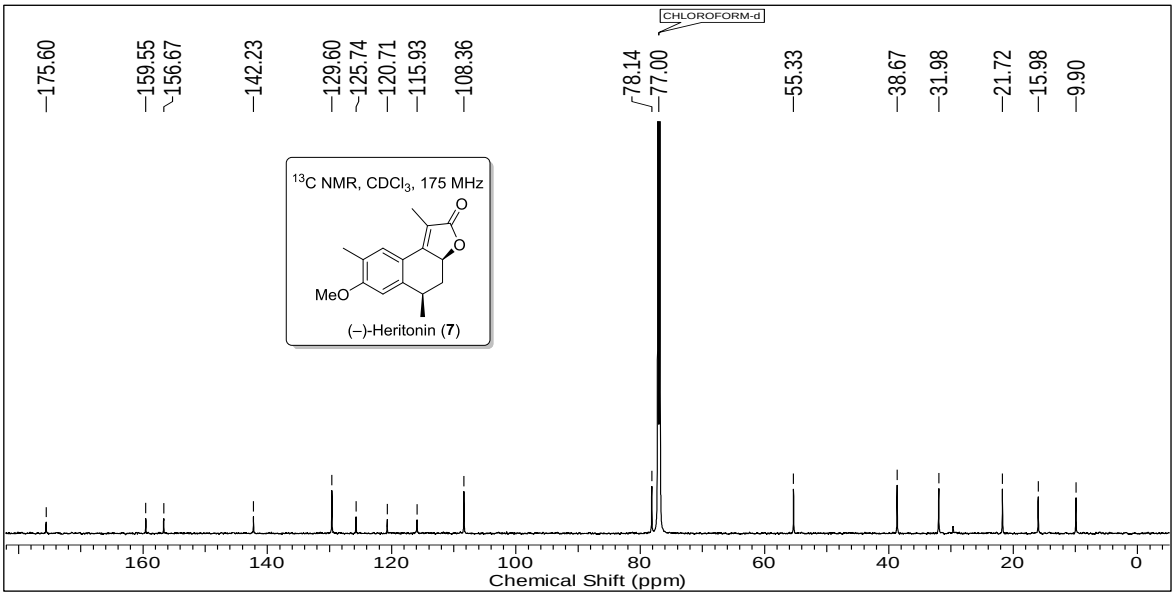
Sample Conc.: 1 mg/mL

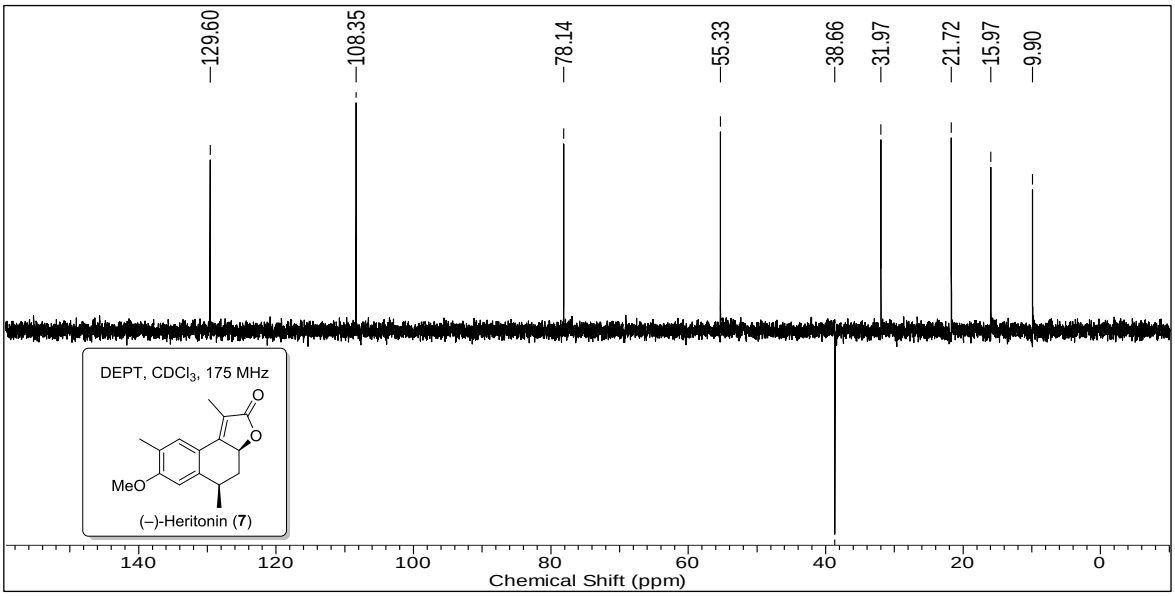

CHLOROFORM-d
7.87
7.27
6.75
6.64
3.01
2.99
2.99
2.74
2.73
2.59
2.58
2.57
2.26
2.23
2.21
2.20
1.87
1.85
1.36
1.35
^{1}H NMR, CDCl$_3$, 500 MHz
HO
O
(+)-Aristelegone A (5)
1.00
1.10
1.04
1.02
1.04
1.09
3.14
1.13
1.35
3.18
Chemical Shift (ppm)


CHLOROFORM-d
198.37
159.54
149.73
130.64
124.93
122.97
112.81
77.00
36.22
32.58
30.80
20.51
15.33
^{13}C NMR, CDCl$_3$, 125 MHz
HO
O
(+)-Aristelegone A (5)
Chemical Shift (ppm)

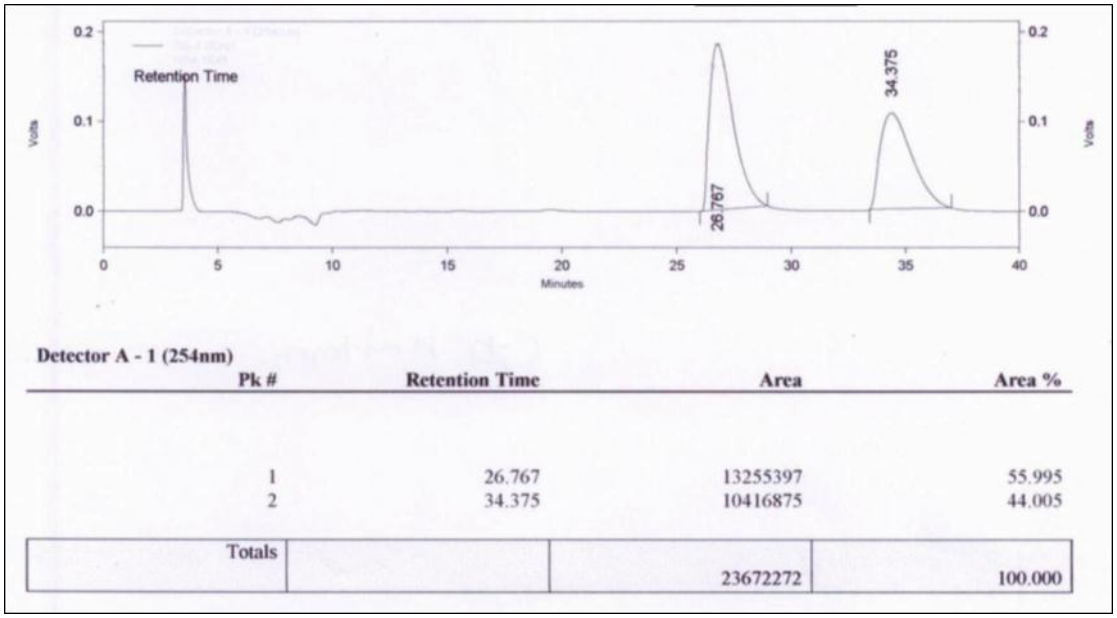

130.64
112.81
DEPT, CDCl$_3$, 125 MHz
HO
O
(+)-Aristelegone A (5)
36.22
32.59
30.80
20.51
15.34
Chemical Shift (ppm)


CHLOROFORM-d
7.43
7.27
6.86
4.92
4.92
4.91
4.90
3.89
3.15
3.14
3.14
3.13
3.12
2.65
2.65
2.64
2.63
2.62
2.25
2.14
1.51
1.49
1.47
1.46
1.45
^{1}H NMR, CDCl$_3$, 700 MHz
MeO
(–)-Heritonin (7)
1.00
1.04
1.01
3.21
1.06
1.07
3.11
3.12
4.34
Chemical Shift (ppm)


CHLOROFORM-d
175.60
159.55
156.67
142.23
129.60
125.74
120.71
115.93
108.36
78.14
77.00
55.33
38.67
31.98
21.72
15.98
9.90
^{13}C NMR, CDCl$_3$, 175 MHz
MeO
(–)-Heritonin (7)
Chemical Shift (ppm)


129.60
108.35
78.14
55.33
38.66
31.97
21.72
15.97
9.90
DEPT, CDCl$_3$, 175 MHz
MeO
(–)-Heritonin (7)
Chemical Shift (ppm)

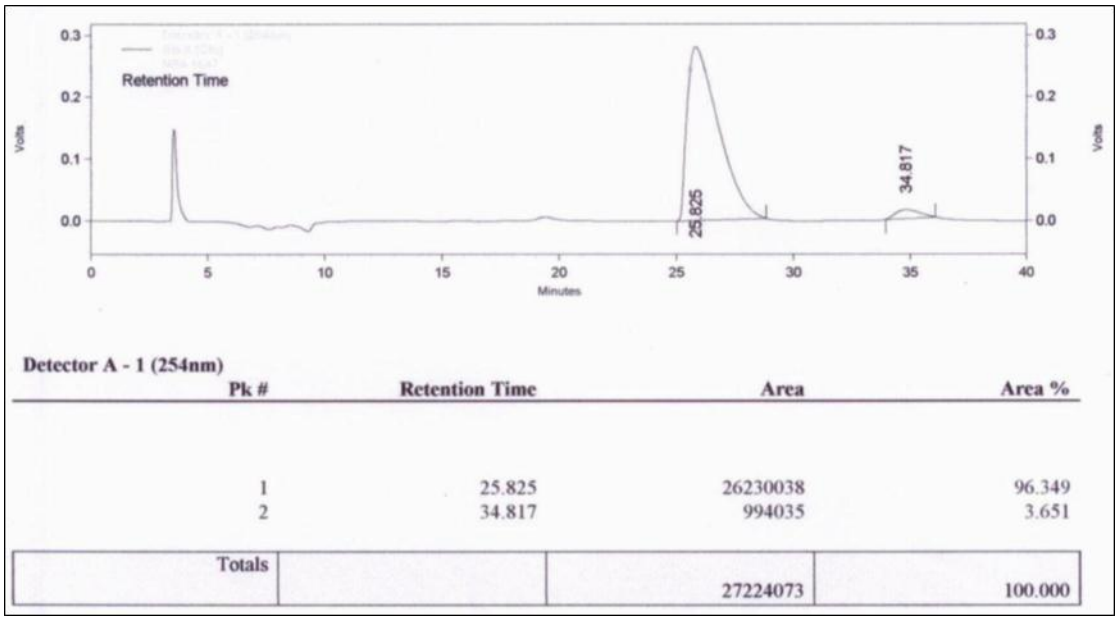
HPLC data of (±)-heritonin (7)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	26.767	13255397	55.995
2	34.375	10416875	44.005
Totals		23672272	100.000

HPLC data of (–)-heritonin (7)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	25.825	26230038	96.349
2	34.817	994035	3.651
Totals		27224073	100.000

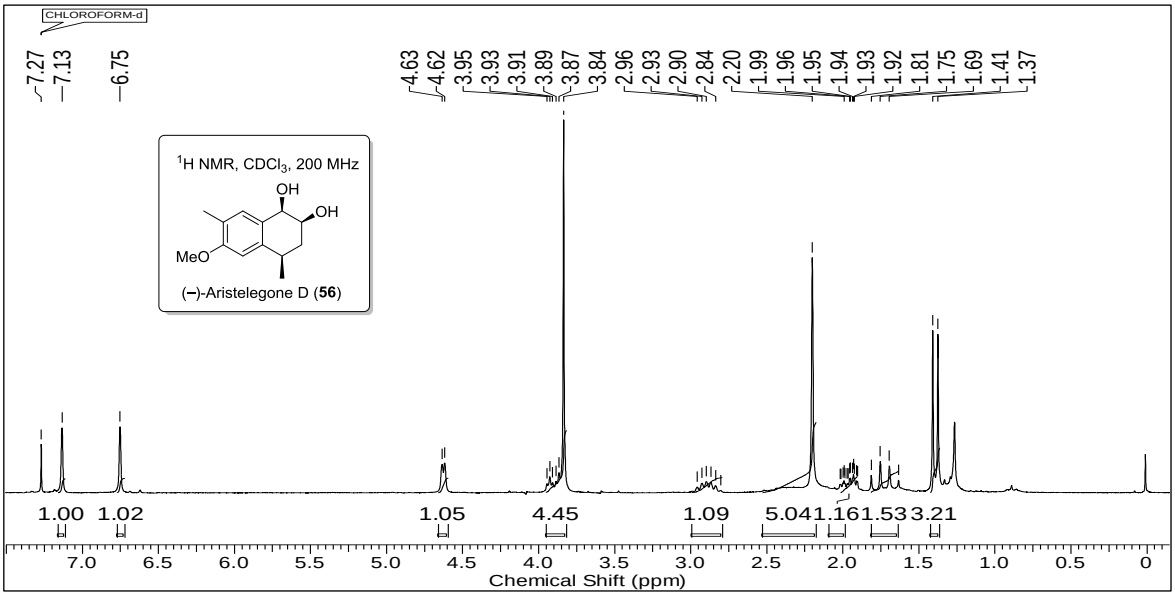
Column: Chiralcel OJ-H (250 mm × 4.6 mm)

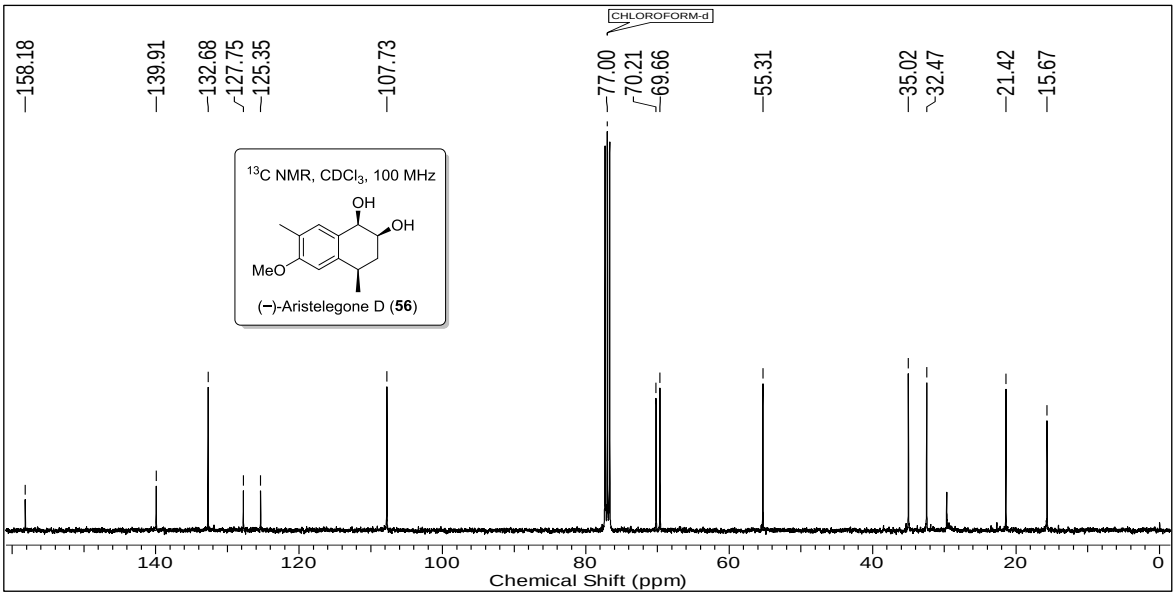
Mobile Phase: IPA:PE (02:98)

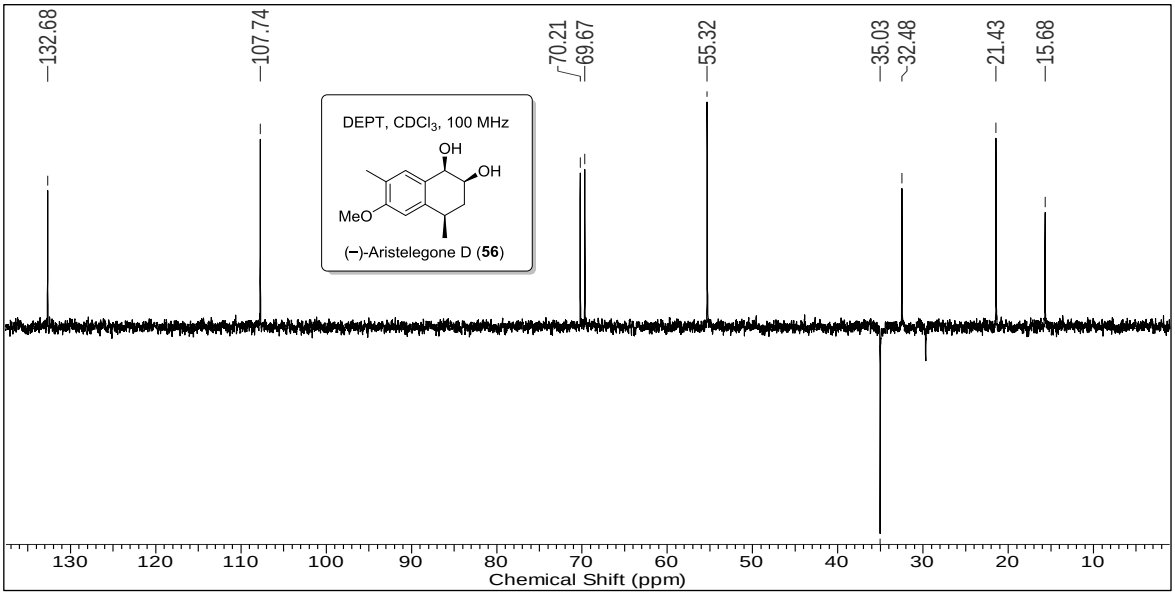
Wavelength: 254 nm

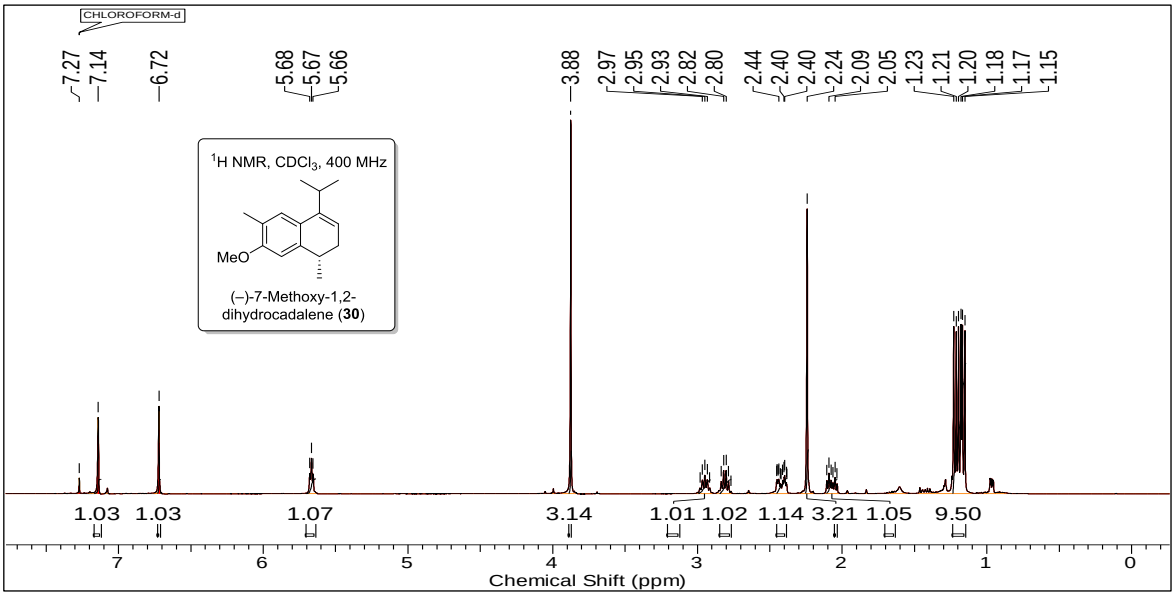
Flow Rate: 1 mL/min

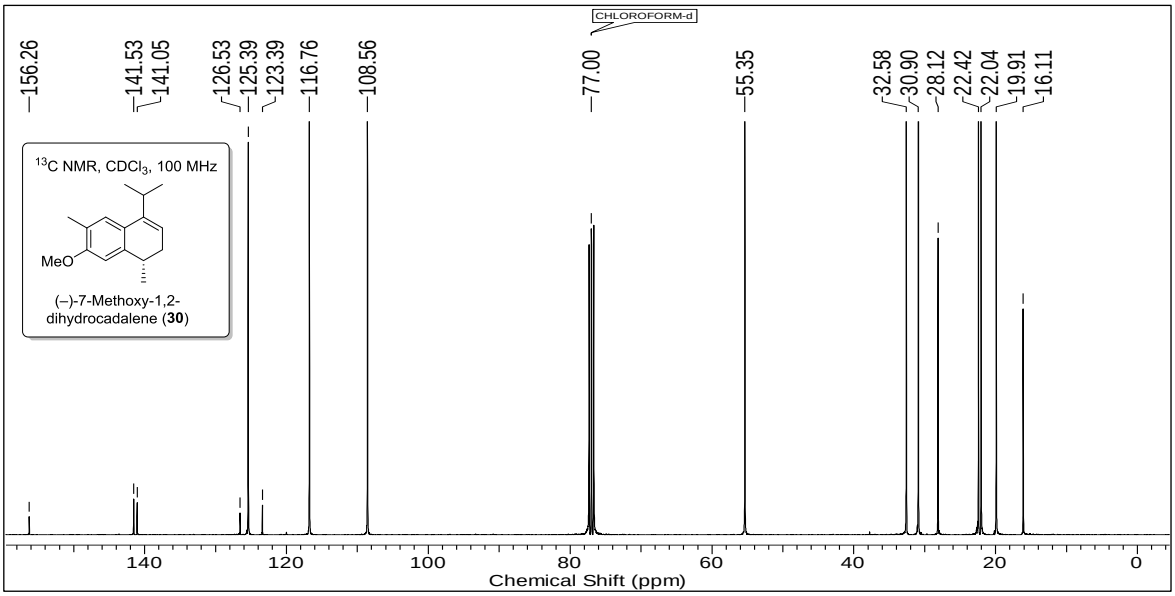
Sample Conc.: 1 mg/mL

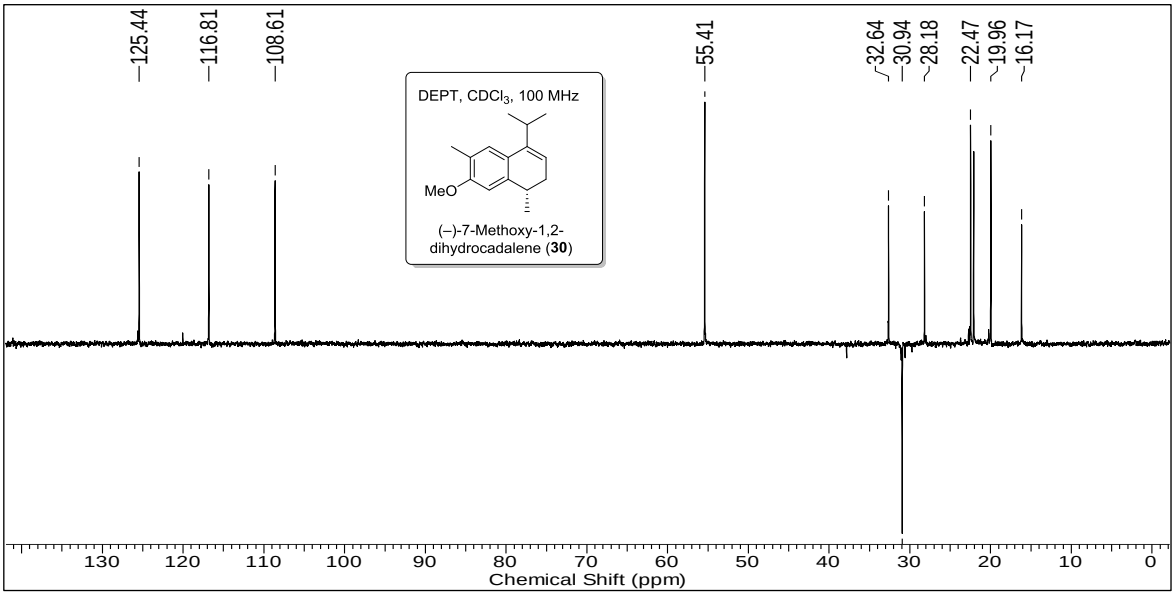

CHLOROFORM-d
7.27
7.13
6.75
4.63
4.62
3.95
3.93
3.91
3.89
3.87
3.84
2.96
2.93
2.90
2.84
2.20
1.99
1.96
1.95
1.94
1.93
1.92
1.81
1.75
1.69
1.41
1.37
^{1}H NMR, $CDCl_3$, 200 MHz
OH
OH
MeO
(−)-Aristelegone D (56)
1.00 1.02 1.05 4.45 1.09 5.04 1.16 1.53 3.21
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


CHLOROFORM-d
158.18
139.91
132.68
127.75
125.35
107.73
77.00
70.21
69.66
55.31
35.02
32.47
21.42
15.67
^{13}C NMR, $CDCl_3$, 100 MHz
OH
OH
MeO
(−)-Aristelegone D (56)
140 120 100 80 60 40 20 0
Chemical Shift (ppm)

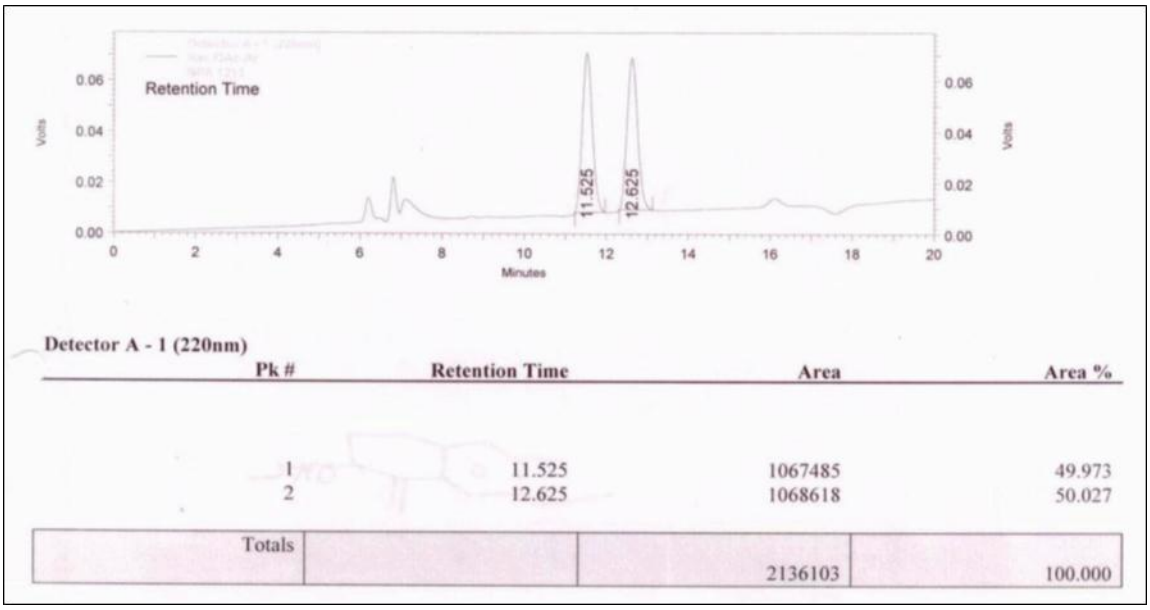

132.68
107.74
70.21
69.67
55.32
35.03
32.48
21.43
15.68
DEPT, $CDCl_3$, 100 MHz
OH
OH
MeO
(−)-Aristelegone D (56)
130 120 110 100 90 80 70 60 50 40 30 20 10
Chemical Shift (ppm)


CHLOROFORM-d
7.27
7.14
6.72
5.68
5.67
5.66
3.88
2.97
2.95
2.93
2.82
2.80
2.44
2.40
2.40
2.24
2.09
2.05
1.23
1.21
1.20
1.18
1.17
1.15
^{1}H NMR, CDCl$_3$, 400 MHz
MeO
(–)-7-Methoxy-1,2-dihydrocadalene (30)
1.03
1.03
1.07
3.14
1.01
1.02
1.14
3.21
1.05
9.50
Chemical Shift (ppm)


CHLOROFORM-d
156.26
141.53
141.05
126.53
125.39
123.39
116.76
108.56
77.00
55.35
32.58
30.90
28.12
22.42
22.04
19.91
16.11
^{13}C NMR, CDCl$_3$, 100 MHz
MeO
(–)-7-Methoxy-1,2-dihydrocadalene (30)
Chemical Shift (ppm)


125.44
116.81
108.61
55.41
32.64
30.94
28.18
22.47
19.96
16.17
DEPT, CDCl$_3$, 100 MHz
MeO
(–)-7-Methoxy-1,2-dihydrocadalene (30)
Chemical Shift (ppm)

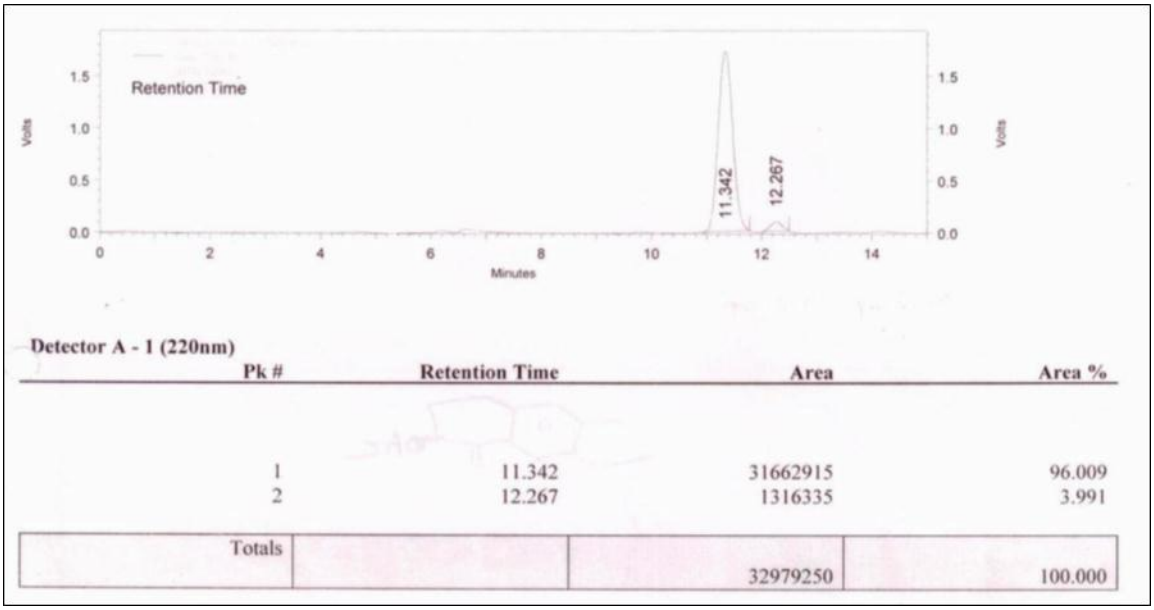
HPLC data of (±)-58



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	11.525	1067485	49.973
2	12.625	1068618	50.027
Totals		2136103	100.000

HPLC data of (+)-58



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	11.342	31662915	96.009
2	12.267	1316335	3.991
Totals		32979250	100.000

Column: Kromasil 5-AmyCoat (250 mm × 4.6 mm)

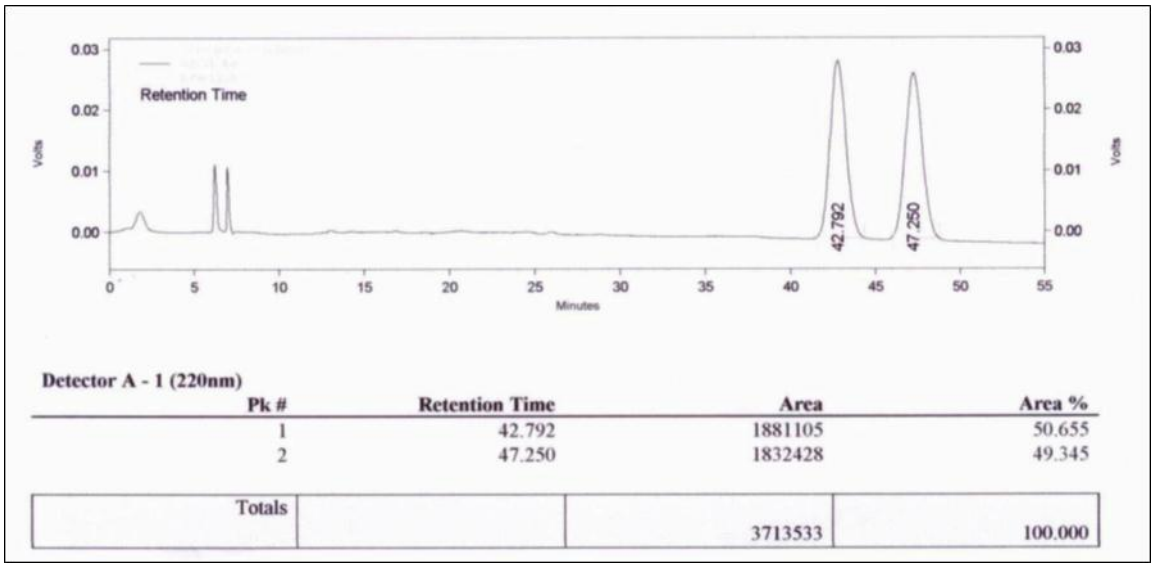
Mobile Phase: IPA:PE (02:98)

Wavelength: 220 nm

Flow Rate: 0.5 mL/min

Sample Conc.: 1 mg/mL

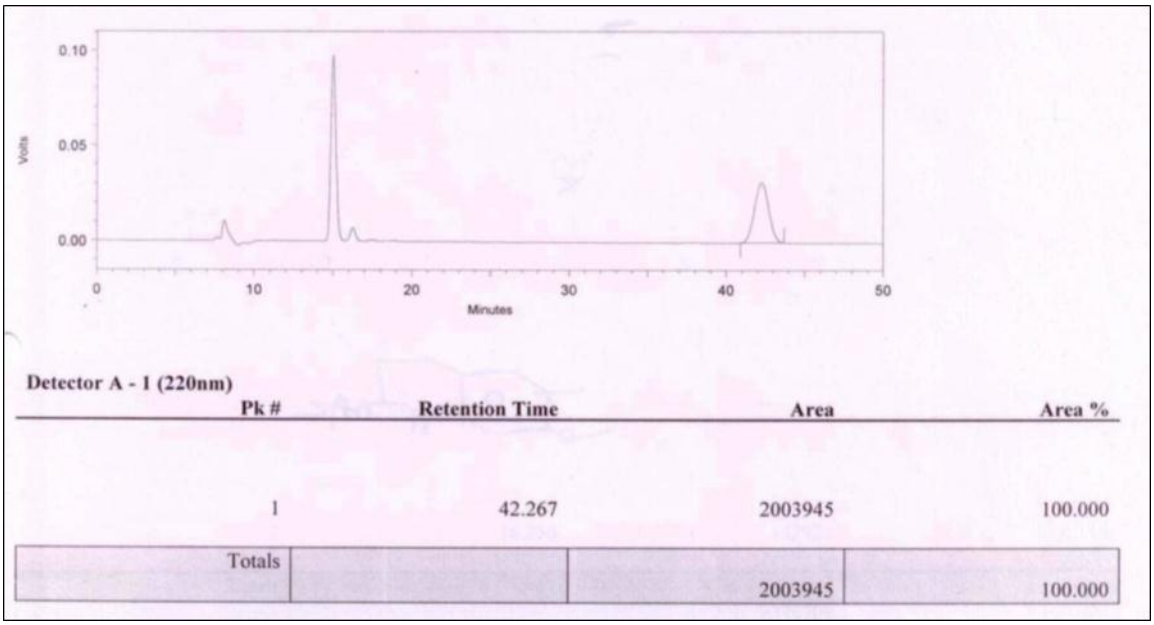
HPLC data of (±)-59



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	42.792	1881105	50.655
2	47.250	1832428	49.345
Totals		3713533	100.000

HPLC data of (+)-59



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	42.267	2003945	100.000
Totals		2003945	100.000

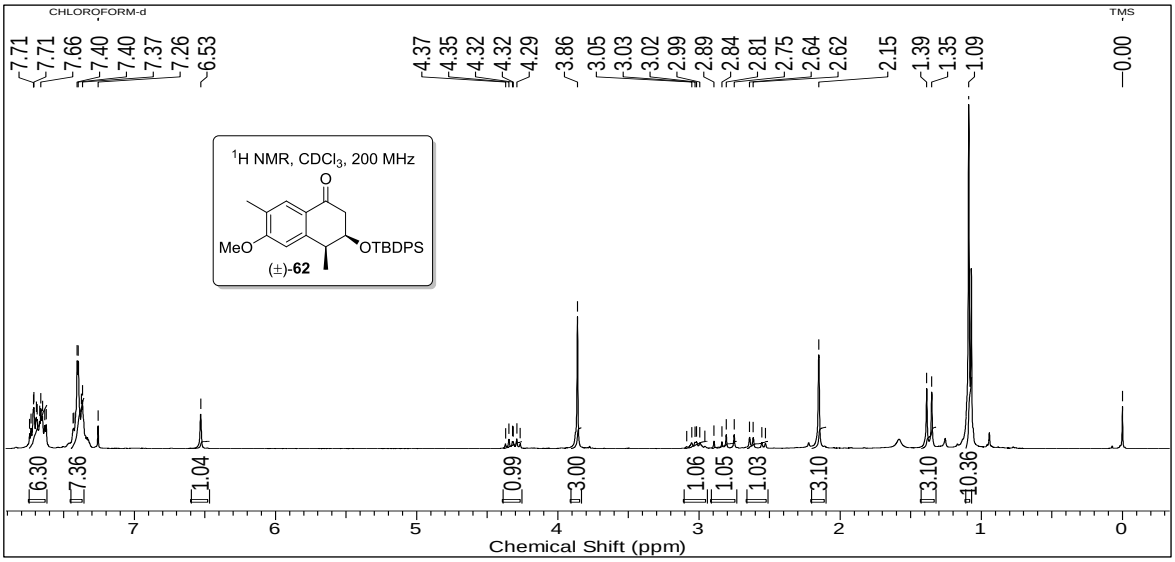
Column: Kromasil 5-AmyCoat (250 mm × 4.6 mm)

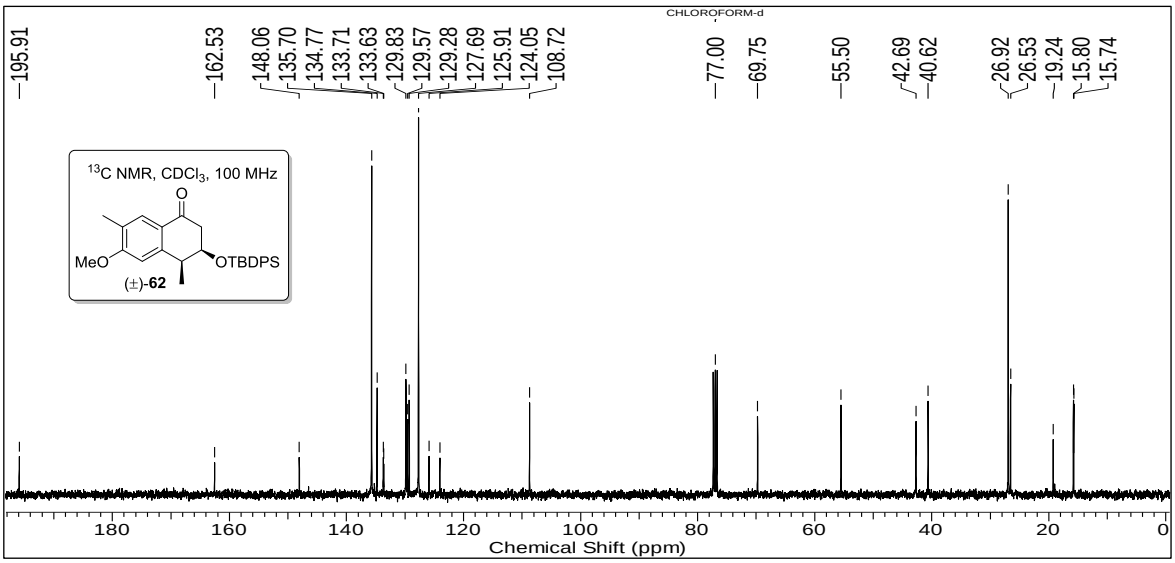
Mobile Phase: IPA:PE (02:98)

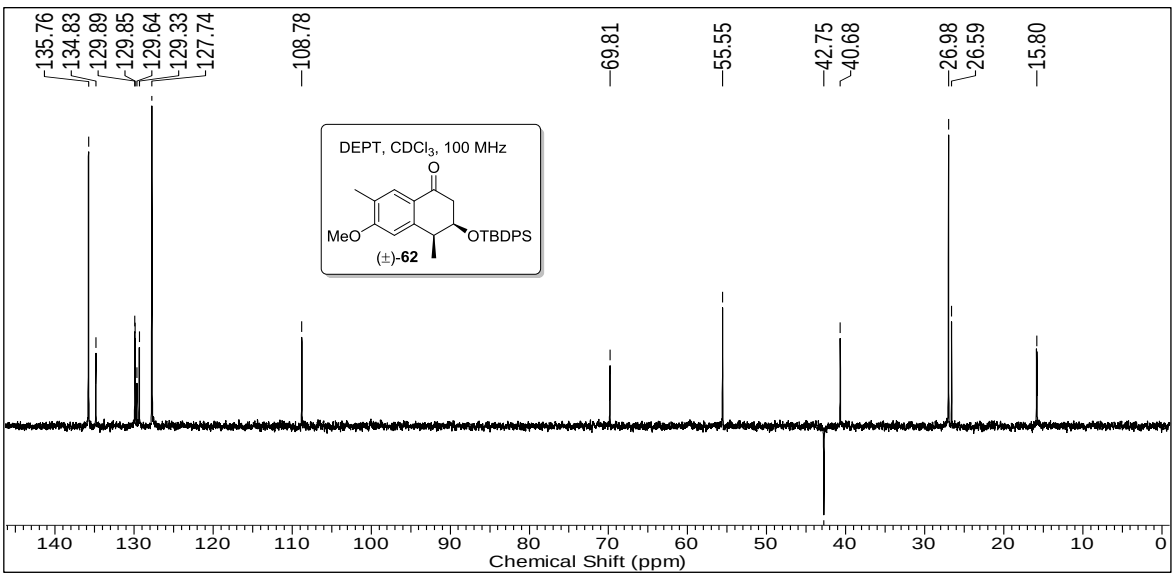
Wavelength: 220 nm

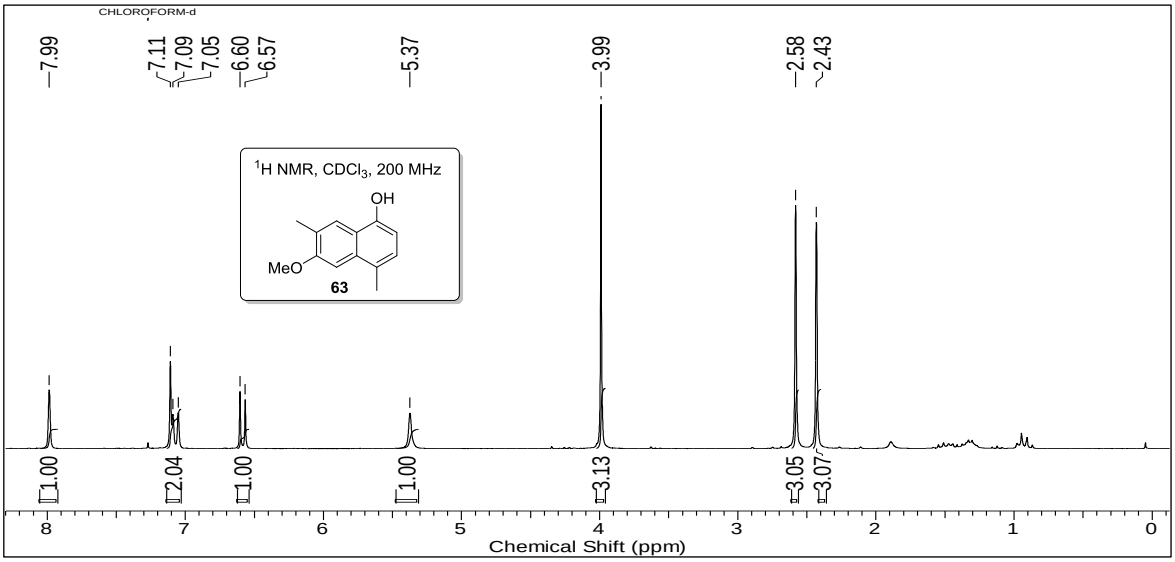
Flow Rate: 0.5 mL/min

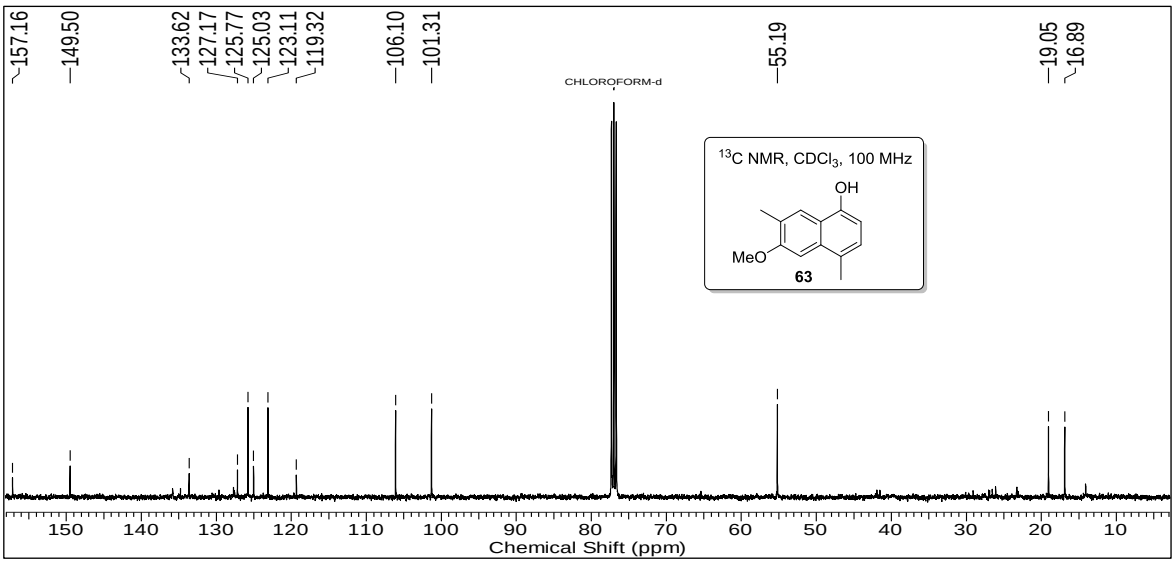
Sample Conc.: 1 mg/mL

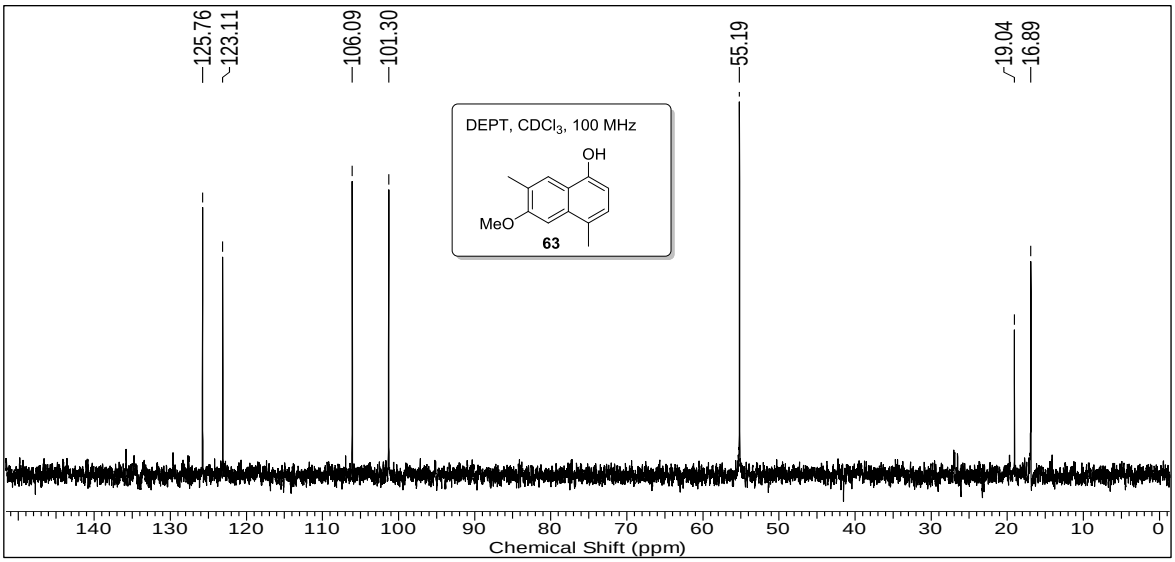

CHLOROFORM-d
TMS
7.71
7.71
7.66
7.40
7.40
7.37
7.26
6.53
4.37
4.35
4.32
4.32
4.29
3.86
3.05
3.03
3.02
2.99
2.89
2.84
2.81
2.75
2.64
2.62
2.15
1.39
1.35
1.09
0.00
^{1}H NMR, CDCl$_3$, 200 MHz
MeO
OTBDPS
(±)-62
6.30
7.36
1.04
0.99
3.00
1.06
1.05
1.03
3.10
3.10
10.36
Chemical Shift (ppm)


CHLOROFORM-d
195.91
162.53
148.06
135.70
134.77
133.71
133.63
129.83
129.57
129.28
127.69
125.91
124.05
108.72
77.00
69.75
55.50
42.69
40.62
26.92
26.53
19.24
15.80
15.74
^{13}C NMR, CDCl$_3$, 100 MHz
MeO
OTBDPS
(±)-62
Chemical Shift (ppm)


135.76
134.83
129.89
129.85
129.64
129.33
127.74
108.78
69.81
55.55
42.75
40.68
26.98
26.59
15.80
DEPT, CDCl$_3$, 100 MHz
MeO
OTBDPS
(±)-62
Chemical Shift (ppm)


CHLOROFORM-d
7.99
7.11
7.09
7.05
6.60
6.57
5.37
3.99
2.58
2.43
^{1}H NMR, CDCl$_3$, 200 MHz
OH
MeO
63
1.00
2.04
1.00
1.00
3.13
3.05
3.07
Chemical Shift (ppm)


157.16
149.50
133.62
127.17
125.77
125.03
123.11
119.32
106.10
101.31
CHLOROFORM-d
55.19
19.05
16.89
^{13}C NMR, CDCl$_3$, 100 MHz
OH
MeO
63
Chemical Shift (ppm)


125.76
123.11
106.09
101.30
55.19
19.04
16.89
DEPT, CDCl$_3$, 100 MHz
OH
MeO
63
Chemical Shift (ppm)

2B.6 References

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OVERALL CONCLUSION AND PERSPECTIVE

Present dissertation describes our concise and efficient approaches for the chemical and chemoenzymatic synthesis of various bioactive natural products and their analogues starting from cyclic anhydrides and their derivatives; along with a concise account on their chemistry, describing their isolation, bioactivity and various synthetic approaches. Various methodologies for lipase catalyzed resolution of recemic alcohols reported by different research groups have been also described.

Naturally occuring polygalloylated sugars possess bioactivities such as anti-HIV, antiviral, antitumor and antidiabetic. We have developed methodology for lipase catalyzed resolution of (±)-dimethyl-2-acetoxy-3-methylenesuccinate and (±)-dimethyl-2-hydroxy-3-methylenesuccinate and applied to accomplish the chemoenzymatic synthesis of polygalloylated sugar (+)-1,3,4,5-tetragalloylapiitol starting from enantiomerically pure (–)-dimethyl-2-acetoxy-3-methylenesuccinate. Using (+)-dimethyl-2-acetoxy-3-methylenesuccinate as the starting material, we have also completed the first synthesis of (+)-artabotriolcaffeate along with (+)-grandiamide D, (–)-tulipalin B and (+)-spirathundiol. We have also completed a concise and efficient first total synthesis of recently isolated putrescine bisamides gigantamide A, dasyclamide, cucullamide and their unnatural dehomo-analogues via selective dehydrative coupling reactions and a remarkable regioselective reduction of citraconimide unit. Large numbers of terpenoid natural products have been known in the literature having methoxy(methyl)tetralone moiety as a core structure or substructure exhibiting antitumor, antimicrobial, antifungal, antihyperglycemic, antiviral, antiparasitic and anti-inflammatory activities, as well as a skin permeability effect. We devloped methodology for lipase catalyzed resolution of acyloin (±)-aristelegone B and utilized for total synthesis of terpenoids (–)-aristelegone B, (+)-methylaristelegone A, (+)-aristelegone A, (–)-aristelegone D, (–)-heritonin, (+)-heritonin, (–)-7-methoxy-1,2-dihydrocadalene, 7-methoxycadalene and for formal synthesis of (–)-heritol, (+)-mutisianthol, (–)-7-methoxycalamenene. We have also attempted to complete first total synthesis of (±)-vallapin, which unfortunately met with failure due to the inherent instability of advanced β-hydroxytetralone intermediate.

In short, we have accomplished a concise and efficient total synthesis of (+)-1,3,4,5-tetragalloylapiitol, gigantamide A, dasyclamide, cucullamide, (+)-grandiamide D, (+)-artabotriolcaffeate, (–)-aristelegone B, (+)-methylaristelegone A, (+)-aristelegone A, (–)-aristelegone D, (–)-heritonin, (+)-heritonin, (–)-7-methoxy-1,2-dihydrocadalene, 7-methoxycadalene and formal synthesis of (–)-tulipalin B, (+)-spirathundiol , (–)-heritol, (+)-mutisianthol, (–)-7-methoxycalamenene using different routes and

strategies. All these studies provided us a nice opportunity for learning a lot of new basic and applied chemistry from both our present work and also from the vast literature in this field. We also feel that the approaches which we have developed are quite general in nature and would be useful in designing several important complex natural products and natural product hybrids for structure activity relationship studies. These studies on lipases and chemoenzymatic synthesis have left us with an experience that these are useful from both synthetic and pharmaceutical point of view. 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 putrescence bisamides and terpenoids with methoxy(methyl)teralone moiety will be discovered in the coming years with new properties and the chemistry of natural products synthesis will always have a bright future. Chemoenzymatic synthesis will spread wings wider over the field of organic and pharmaceutical chemistry providing this field of chemistry a brighter future.

LIST OF PUBLICATIONS

(1) Chemoenzymatic total synthesis of potent HIV RNase H inhibitor (–)-1,3,4,5-tetragalloylapiitol

R. U. Batwal and N. P. Argade, *Tetrahedron*: *Asymmetry* **2011**, *22*, 173.

(2) Biology-orientated synthesis of putrescine bisamides gigantamide A, dasyclamide and cucullamide

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(3) Synthesis of Yangjinhualine A

P. S. Deore, **R. U. Batwal** and N. P. Argade, *Synthesis* **2015**, *47*, 485.

(4) Chemoenzymatic collective synthesis of optically active hydroxyl(methyl) tetrahydronaphthalene-based bioactive terpenoids

R. U. Batwal and N. P. Argade, *Org. Biomol. Chem.* **2015**, *13*, 11331.

(5) Chemoenzymatic access to (+)-artabotriol and its application in collective synthesis of (+)-grandiamide D, (–)-tulipalin B, (+)-spirathundiol, (+)-artabotriolcaffeate, (–)-pubescenoside A and (–)-pubescenoside B: stereochemical assignment of (–)-pubescenoside A & B

R. U. Batwal and N. P. Argade, *manuscript under preparation*.

Erratum