Stereoselective Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions

A
Thesis
Submitted for the Degree of

Doctor of Philosophy

By

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SCHOOL OF CHEMISTRY
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Dedicated To

My Beloved Parents,
Teachers And Friends……

DEDICATED TO

MY BELOVED

PARENTS, TEACHERS

and FRIENDS……

DECLARATION

I hereby declare that the entire work embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the guidance of ***Prof. Dhevalapally B. Ramachary*** *and that it has not been submitted elsewhere for any degree or diploma and that all the sources I have used or quoted have been indicated and acknowledged as complete references.*

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CERTIFICATE

*Certified that the work contained in the thesis entitled "**Stereoselective Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions**" has been carried out by **Mr. R. Madhavachary** under my supervision and the same has not been submitted elsewhere for a degree.*

Prof. Dhevalapally B. Ramachary
(***Thesis Supervisor***)

Dean
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Stereoselective Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions

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Preface and Motivation

Over the last decade, organocatalysis has drawn remarkable attention and become a highly dynamic synthetic research area due to its wide applicability in organic synthesis. The well-defined organocatalysts allows the chemical transformations under mild reaction conditions in environmentally friendly and provides straightforward access to enantiopure products. Organocatalysts can act by coordination to the substrate to render it more reactive. This is often the case when amines are used as organocatalysts and is typified by enamine activation. Organocatalysts can also act through weak non-covalent interactions that are hydrogen bonding catalysis. The importance of weak interactions (non-covalent) in the transition state for high selectivity in asymmetric reactions are explored in recent days. And also a metal free C-C bond formation in one-pot mild reaction conditions are stimulating and challenging concepts in organocatalysis.

*The present thesis entitled "**Stereoselective Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions**"describes the total synthesis of natural products and drug-like molecules through organocatalytic reductive coupling and neighboring ortho-hydroxyl group participation in sequential reactions. In all sections, a brief introduction is provided to keep the present work in proper perspective. The compounds are sequentially numbered (bold) and references are marked sequentially as superscript and listed at the end of the thesis. All the figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA, and in some of them uninformative areas have been cut to save the space.*

The first chapter illustrates an organocatalytic reductive coupling (OrgRC) reaction in the synthesis of library of chiloglottone natural products and 2, 5-dialkylresorcinols. The OrgRC reaction is conducted in sequential two-pot manner by using a triple domino Michael addition/Claisen condensation/hydrolysis/decarboxylation sequence followed by metal-free reductive coupling of alkylideneacetones, diethyl malonate, aldehydes and Hantzsch ester catalyzed by L-proline yielded the products in an excellent manner.

The second chapter, extended the OrgRC reaction in total synthesis of butenolide (3-alkyl-5-methyl-2[5H] furanone) core natural products. Alkylation of chiral tetronic acid and deoxygenation reaction sequence from designed simple starting materials in mild reaction conditions allow to derive few butenolide natural products in reasonable overall yields.

The third chapter demonstrates a novel approach for the asymmetric synthesis of highly substituted spirodihydrocoumarins and chromenes through supramolecular-organocatalysis, where the neighboring ortho-hydroxyl group induced sequential Michael-lactonization reactions on 2-(2-nitrovinyl)phenols with alkyl cyclic/acyclic β-keto esters in the presence of a catalytic amount of quinine–NH–thiourea followed by p-TSA-catalysis. Several control experiments were conducted to express the asymmetric supramolecular catalysis and this catalysis has been confirmed through ESI-HRMS technique also.

In the fourth chapter, the neighboring group control in asymmetric Barbas–List aldol reaction was discussed and explored the various ortho-substituted benzaldehydes in BLA reaction to check the structure/activity relationship between proline and proline-like amino acid catalysts for achieving high asymmetric induction. Here we achieved high selectivity in BLA reaction by introducing the secondary interacting neighboring group to the aldehyde which is involved in transition state was observed.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
AcONa	sodium acetate
Ac_2O	acetic anhydride
Anal.	analysis
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	butyloxy carbonyl
Bp	boiling point
br	broad
Bu	butyl
*t*Bu or ^{t}Bu	*tertiary*-butyl
n-BuLi	*n*-butyl lithium
BLA	Barbas-List aldol
BzOH	benzoic acid
calcd.	Calculated
cat.	Catalytic
cm	centimeter
COSY	correlation spectroscopy
CSP	chiral stationary phase
dABq	doublet of AB quartet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
ddd	doublet of doublet of doublet
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPP	diphenyl prolinol
DPPP	1,3-Bis(diphenylphosphino)propane
DPP-OTMS	diphenyl prolinol trimethyl silyl ether
dr	diastereomeric ratio
dt	doublet of triplet
ee	enantiomeric excess
eq.	equation
equiv.	equivalent(s)
ESI-HRMS	Electrospray ionization-High resolution mass spectrometry
Et	ethyl
EWG	electron withdrawing group
Fg	functional group
Fig.	figure
gm	gram (s)
h	hour (s)
Hz	hertz

Hex	hexyl
HPLC	high-performance liquid chromatography
i-Pr	isopropyl
IR	infrared
lit.	literature
m	multiplet
m-CPBA	*m*-chloro perbenzoic acid
M	molarity
MCC	Multi-catalysis cascade
Mp.	melting point
Me	methyl
mg	milligram (s)
mL	milliliter
mmol	millimole
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
NSAIDs	non-steroidal anti-inflammatory drugs
PCC	pyridinium chlorochromate
Ph	phenyl
Pg	protecting group
PMHS	Polymethylhydrosiloxane
ppm	parts per million
pre-TS	*pre*-transition state
p-TSA	*p*-toluenesulfonic acid
py	pyridine
pr	propyl
q	quartet
rt	room temperature
s	singlet
sec	secondary
SMA	sequential Michael/acetalization
t	triplet
td	triplet of doublet
tert	tertiary
TBS	*tertiary* butyl dimethyl silyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thr	Threonine
TLC	thin layer chromatography
TMS	trimethylsilyl
TCRA	three component reductive alkylation
Trp	Tryptophan
TsCl	*p*-toluenesulphonyl chloride
Ts	Toluenesulphonyl
TS	Transition state
UV	ultraviolet

Stereoselective Synthesis of Bioactive Molecules through Organocatalytic Reductive Coupling, Michael and Aldol Reactions

1. ABSTRACT

In Part-A, biologically important, less-explored natural products of sexually deceptive chiloglottones, antimicrobial dialkylresorcinols and their many analogues were synthesized in very good yields in a sequential two-pot manner by using an "organocatalytic reductive coupling (OrgRC) reaction" as the key step. Herein, we describe the total synthesis of a library of chiloglottones, 2,5-dialkylresorcinols, and their many analogues from alkylideneacetones and diethyl malonate by using a triple domino Michael addition/Claisen condensation/hydrolysis/decarboxylation sequence followed by metal-free reductive coupling with aldehydes in a sequential two-pot manner. Chiloglottones and their analogues were transformed into 2, 5-dialkylresorcinols by using oxidative aromatization followed by metal-free demethylation in a sequential two-pot manner.[1e]

In continuation to the development of OrgRC reactions in total synthesis of natural products, we choose a small library of natural products containing butenolide (3-alkyl-5-methyl-2[5*H*] furanone) core as our synthetic target. In the second chapter, we have extended the OrgRC reaction for the synthesis of butenolide natural products *via* alkylation-deoxygenation reaction sequence from simple starting materials like chiral tetronic acid, different aldehydes, Hantzsch ester and proline as catalyst. This high yielding and chemo-selective alkylated products are potent precursor for synthesis of the butenolide natural products by following easily deoxygenating procedures was achieved.

In Part-B, a general approach was established for the asymmetric synthesis of highly substituted spirodihydrocoumarins and chromenes through supramolecular-organocatalysis, where the neighboring *ortho*-hydroxyl group induced sequential Michael-lactonization reactions on 2-(2-nitrovinyl)phenols with alkyl cyclic/acyclic β-keto esters in the presence of

a catalytic amount of quinine–N*H*–thiourea followed by *p*-TSA-catalysis. Our synthetic plan aims to prove that *pre*-TS supramolecular assembly through ESI-HRMS experiments and also for the synthesis of medicinally important spirocyclic dihydrocoumarins and chromenes. Quinine-N*H*-thiourea- and *p*-TSA-catalysed Michael-lactonization/Michael-dehydration reaction of β-keto ester and (*E*)-2-(2-nitrovinyl)phenols furnished the spirocyclic dihydrocoumarins and chromenes in good yields with high enantioselectivities. Further, the existence of supramolecular assembly in transition state was proved with experimental evidence by trapping the *pre*-TS intermediate through ESI-HRMS analysis.[1b]

In continuation, we studied the *ortho*-substitution effect in asymmetric Barbas-List aldol reactions, where the covalent and non-covalent interactions within substrates and catalysts are playing a key role in high asymmetric induction. Different *ortho*-substituted benzaldehydes were tested with ketones in the Barbas-List aldol reaction, interestingly donating groups (mostly nucleophilic in nature) presented *ortho* to the aldehyde group in aromatic rings producing the BLA products in good selectivity. This interesting neighboring group control in asymmetric BLA-reactions were studied in this chapter.

2. INTRODUCTION

2.1. Historical Background of Organocatalysis:

In modern organic chemistry, particularly in biological view, the use of metal containing catalysts are not suitable because of *environmental considerations* and their unsafe properties. Even the catalysts containing transition metals are very toxic, industrially not viable using in bulk, in many cases less stable under air and normally expensive, that means handling and utilization of transition metal catalysts has to be done attentively. In order to solve these problems, different new areas are coming up nowadays, but a complete discontinuance in the use of metal containing catalysts can be overcome by developing the organocatalysis due to their low cost and harmfulness to the environment. If once look into the literature, use of metal-free catalysts such as organocatalysis were already noticed in early 19th century. But in 19th and 20th centuries the "organocatalysis" term was not known. In this regard industrial scientists in the 1970's utilized L-proline successfully to catalyze an intramolecular aldol condensation of achiral tri-ketone to yield the bicyclic Wieland-Miescher and Hajos-Parrish ketones with excellent enantioselectivities,[2] this reaction is now known as the “Hajos-Parrish-Eder-Sauer-Wiechert” reaction. After that, early of 21st century the efforts from Barbas *et al.*[3] and MacMillan *et al.*[4] created a new era in research field into one of the main pillars of asymmetric catalysis. Prof. Barbas III published the first (*S*)-proline catalyzed asymmetric intermolecular aldol reaction of different aldehydes with acetone to produce the aldol products with excellent enantioselectivities *via* enamine activation. This discovery of L-proline induced chiral enamines from carbonyls initiated a new era in asymmetric catalysis and at the same time it has also given inspiration to develop many other new catalytic species *in-situ* from different carbonyl compounds. Shortly after, complementary activation mode of iminium activation was reported by MacMillan *et al.* this strategy was successfully applied in the enantioselective Diels-Alder reactions.

As the research work disclosed in this thesis deals with organocatalytic reductive coupling (*OrgRC*) reactions and neighboring *ortho*-hydroxyl group induced or control in organocatalytic asymmetric cascade reactions, a brief account of coupling reactions, their uses in total synthesis of natural products and asymmetric sequential reactions induced by neighboring group is presented below.

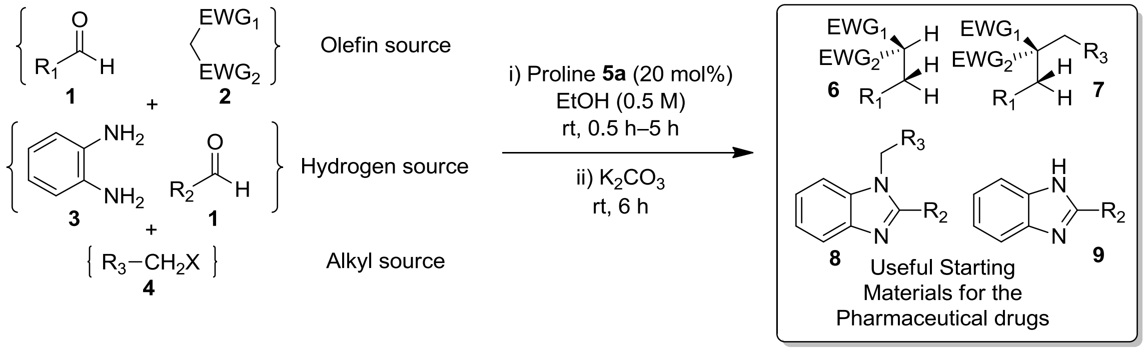
2.2. Brief Introduction to *OrgRC* Reactions and their Applications in Total Synthesis:

Some of the most fundamental transformations of organic chemistry involve the formation of carbon-carbon bonds. From carbon-carbon bond formation we can make a wide range of simple compounds to complex biological systems. In the 1970’s, reports from Miyaura, Yamada and Suzuki[5] laid the groundwork for what now is most important and useful transformations for construction of carbon-carbon bonds in organic synthesis. At the end of 20th century contributions from many research groups have led to a vast improvement on what now is known as the Suzuki-Miyaura cross-coupling reaction. Moreover, the coupling reactions like Stille coupling, Negishi coupling, Heck reaction and Sonogashira coupling reactions were reported based on palladium catalysis. In 2010, Heck, Negishi and Suzuki were recognized with a Nobel Prize for palladium-catalyzed cross coupling reactions in organic synthesis.

After such unlimited development witnessed in coupling reactions through organometallics, at one point we need to pay attention for the afore mentioned as early the transition metals in high toxicity does not allow the use of such catalysts in large amounts because it acts contrary to the principles of green chemistry to some extent. These coupling reactions are should be industrially viable, use of toxic metal catalysts has to be avoided. Keeping these facts in view, more attention has been devoted towards organocatalytic coupling reactions.[6]

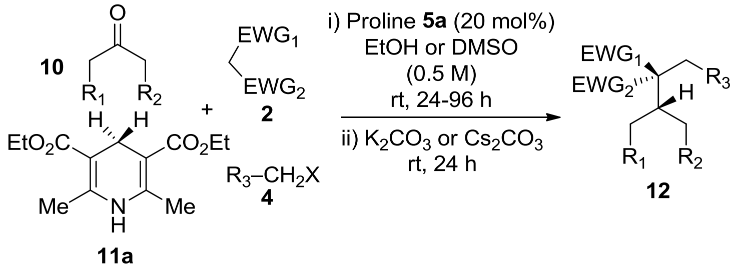
In early 2006, our group was inspired by *in vivo* reactions where the 5α-reductase [NADPH-Δ^4-3-oxosteroid-5α-oxidoreductase] is an NADPH-dependent enzyme that catalysze the *in vivo* reduction of testosterone to the more potent androgen dihydrotestosterone (DHT).[7] These kind of reductase enzymes can reduce the activated double bonds (homo or hetero double bonds). After thorough following of literature, in 2006 our group, for the first time discovered the mimicking of NADPH in the laboratory to get various *carbon-carbon* bond formations in chemo-selectively, what now is known as organocatalytic reductive coupling (*OrgRC*) reaction.

In 2006, our group introduced the bio-mimetic one-pot three and four-component Knoevenagel–hydrogenation (K–H), five-component Knoevenagel–hydrogenation–alkylation (K–H–A) reactions of aldehydes **1**, CH-acids **2**, *o*-phenylenediamine **3**, alkyl halides **4** using proline **5a** and proline–K_2CO_3 respectively. The reaction of aldehyde **1** with CH-acid **2** under proline **5a** catalysis leads to the C=C bond formation, which was *in-situ* reduced with available hydrogen source leads to C-C bond formation. In continuation, five-component Knoevenagel–hydrogenation–alkylation (K–H–A) reaction also reported in economically and environmental friendly manner (eq. 1).[8]



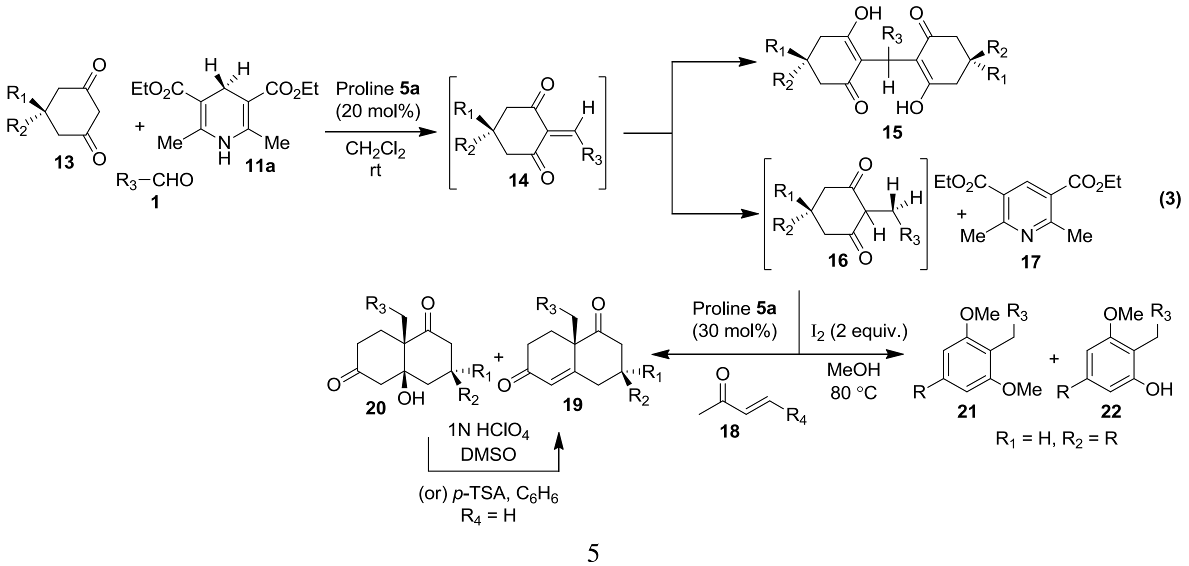
(1)

In simultaneous report from our group was demonstrated the less reactive ketone **10** and CH-acid **2** coupling reaction under proline **5a**-catalysis and Hantzsch ester **11a** as a hydrogen donor. Amino acid proline **5a** readily catalyzes the Knoevenagel condensation of less reactive ketones **10** with the CH-acid **2** afforded the active olefin, which was reduced *in-situ* by Hantzsch ester **11a** produced the hydrogenated product in sequential one-pot manner. Furthermore, extended the organocatalytic reductive coupling reactions into proline/K_2CO_3-catalyzed one-pot four-component K/H/A reaction of ketones **10**, CH-acids **2** and Hantzsch ester **11a** with various alkyl halides **4** produced the various 2,2-disubstituted ethyl cyanoacetates and malononitriles **12** in excellent yields (eq. 2).[9]



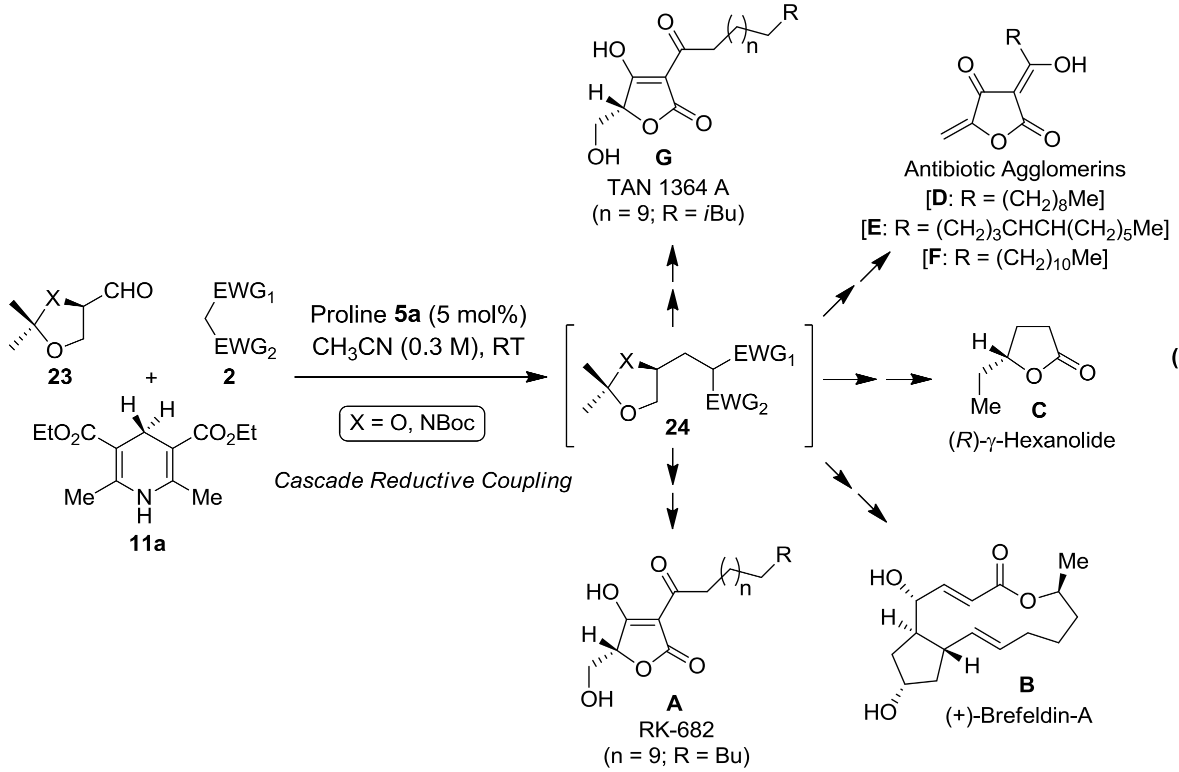
(2)

In 2007, our group utilized the OrgRC reaction and developed a practical and novel organocatalytic chemo- and enantioselective process for the cascade synthesis of highly substituted 2-alkyl-cyclohexane-1, 3-diones **16** and Wieland-Miescher (W-M) ketone **19** analogs *via* reductive coupling reaction as a key step. The direct combination of L-proline-catalyzed cascade Knoevenagel/hydrogenation and cascade Robinson annulation of 1, 3-cyclohexanedione **13a**, aldehydes **1**, Hantzsch ester **11a**, and α,β-unsaturated ketone **18** furnished the highly functionalized W-M ketone analogues **19** in high yields with excellent enantioselectivities (eq. 3).[10] This article shows and creates a path for utilizing the OrgRC reaction in total synthesis of natural products and bioactive molecules.



(3)

In 2010, high-yielding coupling reaction of a variety of CH-acids **2** with (*R*)-glyceraldehyde acetonide/(*S*)-Garner aldehyde **23** and Hantzsch ester **11a** through amino acid-catalysis was reported by our group, in this report alkylation reaction was performed without racemization at the α-position to carbonyl compounds. This organocatalytic single step approach to the asymmetric synthesis of functionalized chiral building blocks based on (*R*)-glyceraldehyde acetonide and (*S*)-Garner aldehydes are the important precursors for synthesizing biological active molecules (eq. 4, **A**-**G**).[11]

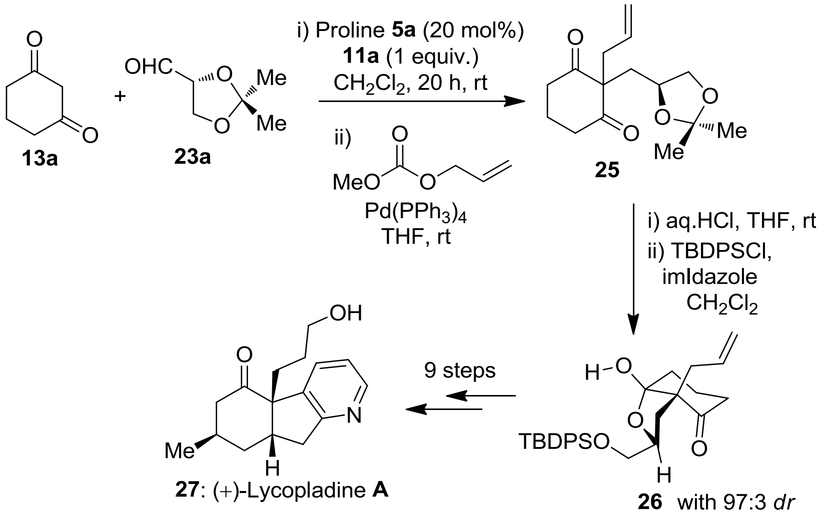


(4)

This emerging OrgRC reaction is explored by many other groups in total synthesis of natural products, pharmaceuticals and bio-active molecules, because one-pot multi-component OrgRC reaction is a high yielding process, who can operate these reactions in open air, environmental-friendly and economically useful manner in gram to kg scale.

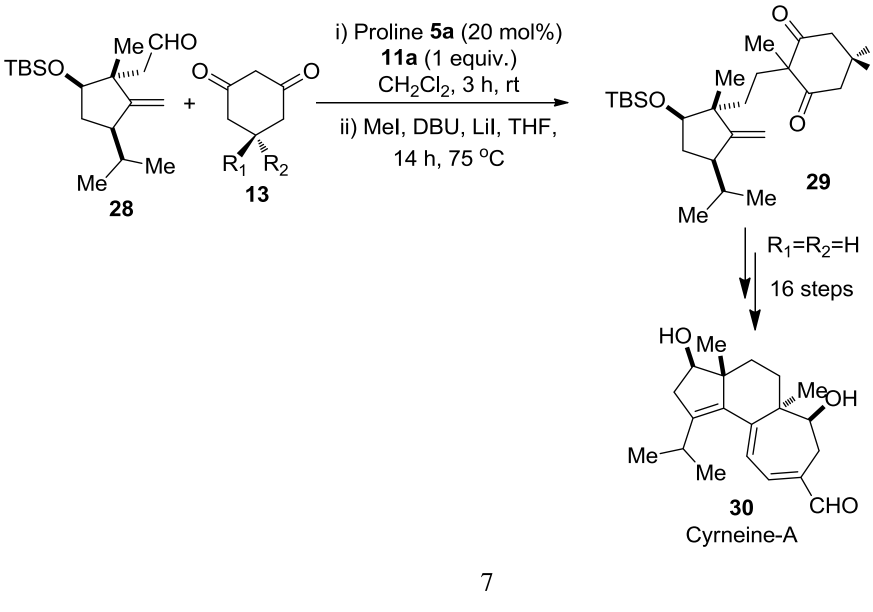
In 2011, Hiroya *et al.*[12] reported the total synthesis of natural product (+)-Lycopladine-A **27** as shown in eq. 5. In this report they constructed the asymmetric quaternary carbon center based on OrgRC/alkylation reaction sequence followed by hydrolysis of the acetal group of **25** and intramolecular hemiacetal formation then conversion of the primary alcohol to *tert*-butyldiphenylsilyl (TBDPS) ether briefly gave the hemiacetals

26 in more than 97:3 diastereomeric ratio. Further, within nine steps successfully synthesized (+) -lycopladine A **27** from the hemiacetal **26.** The title reaction (OrgRC) is utilized in one-pot manner without losing the yield and selectivity.



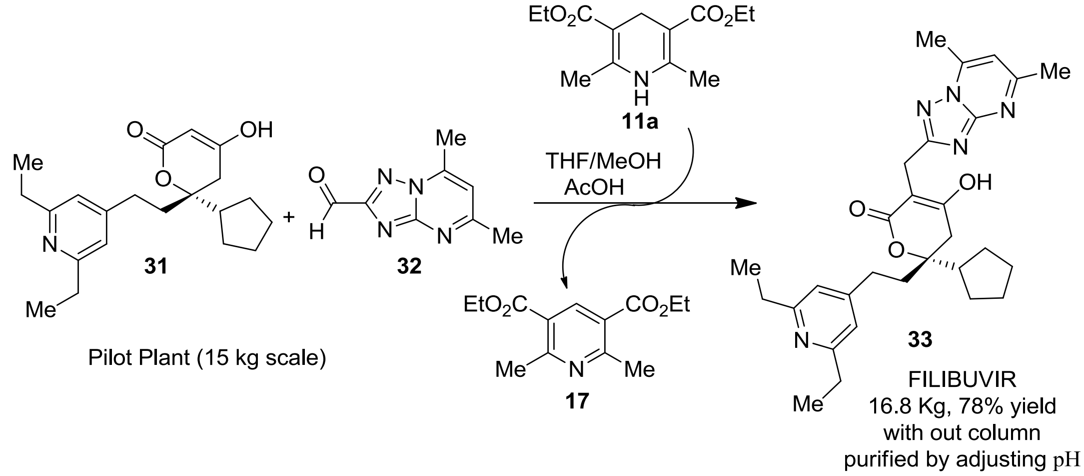
(5)

In 2012, Gademann *et al.*[13] reported the total synthesis of cyrneine-A **30,** featuring a hexatrienal unit was prepared synthetically for the first time by using OrgRC reaction, Heck reaction, a carbene ring expansion and a reductive carbonylation reactions are the key steps. Here designed aldehyde **28** was reacted with **13** in presence of proline as the catalyst, the unsaturated intermediate was reduced *in situ* by the Hantzsch ester to prevent multiple additions of the nucleophile in one-pot. Here the OrgRC technique is very useful to prevent the multiple side reactions and also it minimizes the number of steps for carbon-carbon bond formation.



(6)

Whereas in industrial chemistry, Nathan D. Ide *et al.*[14] (Pfizer worldwide research and development company) demonstrated the pilot plant (15 kg scale) synthesis of active pharmaceutical ingredient, Filibuvir (Hepatitis **C** virus polymerase inhibitor) by using our organocatalytic reductive coupling (OrgRC) reaction as key coupling protocol (eq. 7). Initially they used the borane-amine-mediated reductive coupling, β-keto-lactone/iminium condensation strategy and nucleophile-intercepted Knoevenagel akin strategy, but they are not superior to the OrgRC reaction for C-C coupling of **31** and **32**. This reaction expressed the importance of OrgRC reaction in "Kg-scale synthesis".



(7)

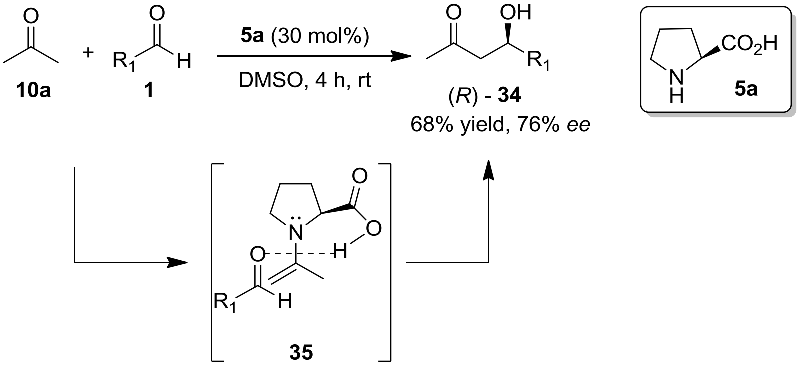
In continuation of synthesis of bio-active and natural products and their many analogues starting from the simple materials in one-pot, my research work has been carried out on the synthesis of sexually deceptive chiloglottones, antimicrobial dialkylresorcinols and butenolide natural products through organocatalytic reductive coupling (OrgRC) reaction and the results are presented in this thesis as part-A

2.3. Brief Introduction for Asymmetric Organocatalytic Supramolecular Catalysis:

The concept of chirality was recognized in the mid 1870's, this is a geometric property which describes all rigid objects that cannot be superimposed on their mirror images. Nowadays 70% of known drugs are single enantiomers, Hence, the synthesis of single-enantiomer compounds have become importance to the pharmaceutical and agrochemical industry.[15] Number of methods are existed in scientific literature to get enantiopure compounds, mainly kinetic resolution, enzymatic resolution and asymmetric synthesis. Asymmetric synthesis is one of the convenient method to create a new chiral center from achiral starting materials, which is mainly influenced by metals and metal-free (Organocatalysis) mediated enantioselective reactions.

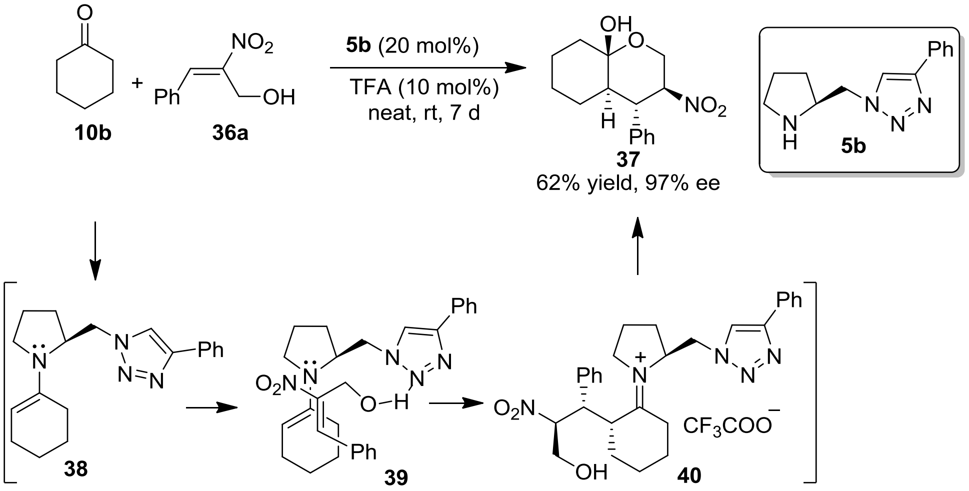
Organocatalysis born with the creation of many asymmetric reactions, in science today the organocatalysis is the most representative field for asymmetric reactions without using of any metal catalyst. As the number of chiral drugs are increasing, asymmetric synthesis and efficiency of catalysts gaining importance. Development of new chiral catalysts is based on the structural tuning of known catalysts especially organocatalysts are can readily prepare and easily modify, making it possible to synthesize large catalyst libraries in a reasonable time frame.[16] Therefore, considerable efforts have been made and one should concentrate on the development of efficient screening methods and optimizations, in this regard supramoleculer catalysis is newly developing and highly efficient technology for asymmetric reactions.[17]

The earliest example of asymmetric organocatalysis was reported by Barbas and List in 2000, L-proline catalyzes the reaction by activating the nucleophile through enamine formation and electrophile through the directed hydrogen bonding. Thus, the activation of both the substrates by the neighboring groups in catalyst initiates the bio-mimetic cellular type asymmetric reactions (eq. 8).[3]



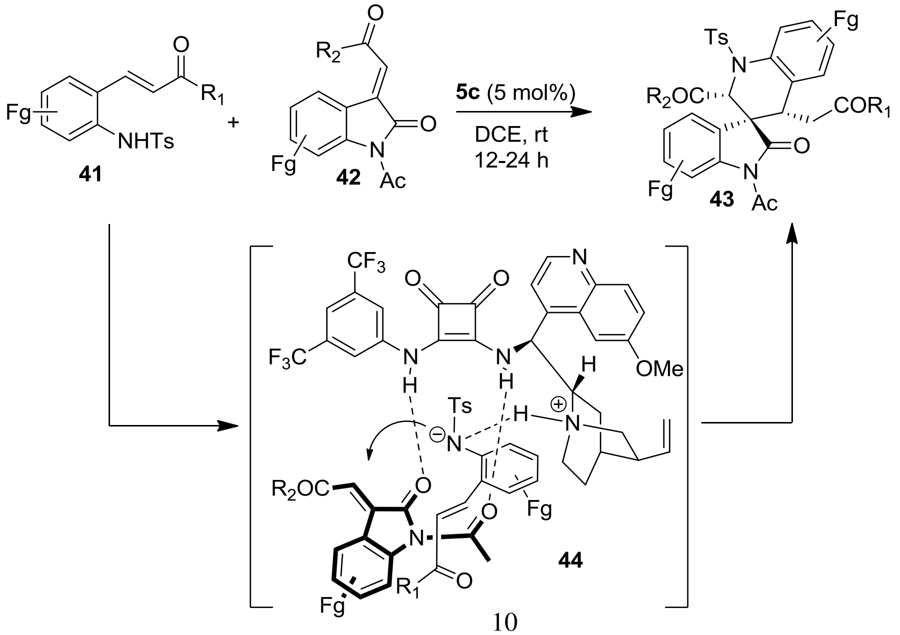
(8)

In 2009, Chandrasekhar *et al.* showed the hydrogen bonding between the catalyst and the allyl alcohol of the substrate is crucial for high asymmetric induction in domino Michael/ketalization reaction for the asymmetric synthesis of tetrahydropyrans **37**. Pyrrolidine-triazole catalyst **5b** catalyzed the Michael reaction of cyclohexanone **10b** and 2,3-disubstituted nitroolefin **36a** followed by intramolecular ketalization to result the cycloalkane fused tetrahydropyrans **37** with 62% yield and 97% *ee* as shown in eq. 9.[18] In this case, the absence of hydrogen bonding by changing catalyst the product yield and selectivity was very poor.



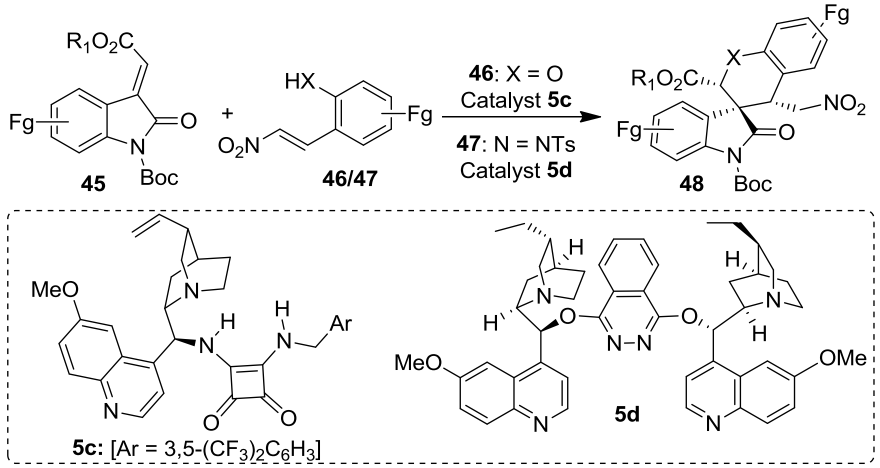
(9)

In 2013, Da-Ming Du *et at.* reported the cascade aza-Michael–Michael addition reaction of 2-tosylaminoenones **41** and 3-ylidenoxindoles **42** catalyzed by a chiral bifunctional tertiary amine-squaramide **5c** produced the spirooxindole tetrahydroquinolines **43** in excellent yields with excellent diastereoselectivities (>25 : 1 *dr*) and high enantioselectivities (up to 94% *ee*). In the transition state, *ortho*-tosyl-amine was activated by tertiary amine of catalyst and enophile was activated by squaramide through hydrogen bonding, together come closer and controls the selectivity and also initiated the subsequent cascade processes as shown in eq. 10.[19]



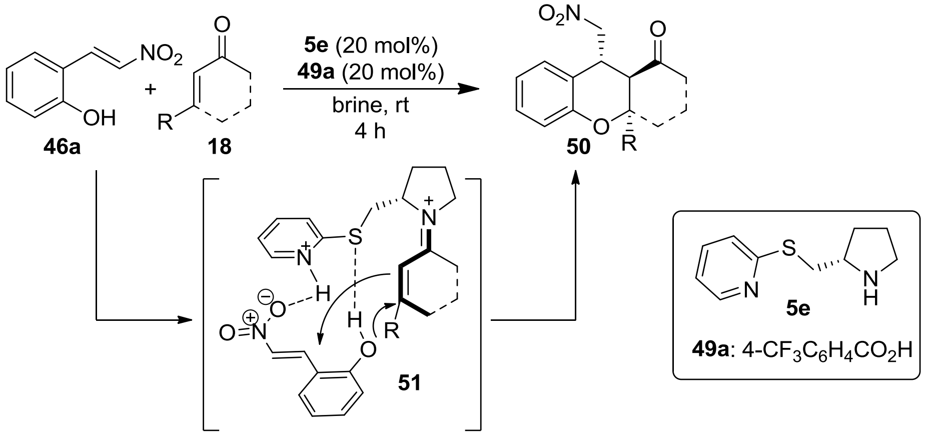
(10)

The simultaneous report from Chengjian Zhu *et al.* addressed the asymmetric synthesis of spiro [chroman/tetrahydro-quinoline-3,3'-oxindole] skeletons from *ortho*-OH/NHTs substituted nitrostyrenes and methyleneindolinones through hydrogen bonding catalysis. The oxa/aza-Michael-Michael reaction sequence catalyzed by a **5c/5d** proceeded well to furnish a series of spiro oxindole derivatives containing three contiguous stereocenters, including one spiro quaternary chiral center. This excellent stereocontrol (>20:1 dr and >99% ee) was achieved through rigid transition state controlled by ortho substitutions *via* hydrogen bonding (eq. 11).[20]



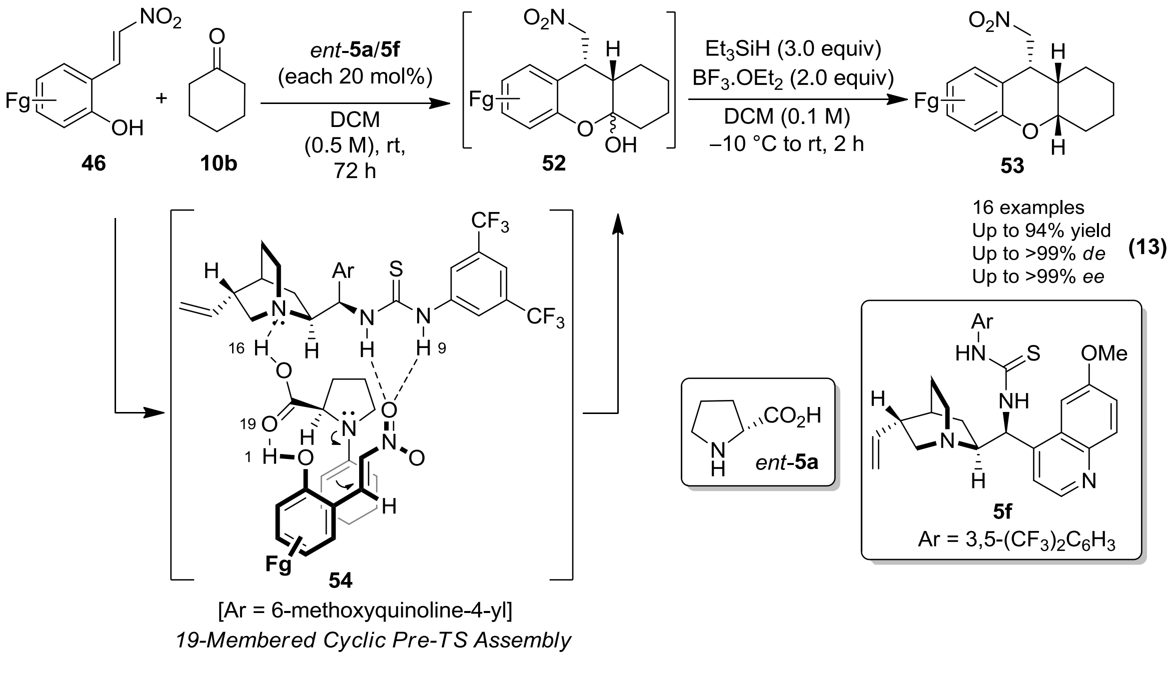
(11)

Zhen-Yuan Xu *et al.* in 2014, reported the cascade oxa-Michael–Michael reactions of 2-hydroxynitrostyrenes **46a** with enones **18** using a prolinol thioether catalyst **5e**. Reaction of 2-hydroxynitrostyrene **46a** with enones **18** under **5e,** constructed the functionalized tetrahydroxanthenones **50**. Preliminary understandings from catalyst screening explains that the initial asymmetric oxa-Michael reaction is made through hydrogen bonding between thioether of catalyst and 2-hydroxy nitrostyrene as shown in eq. 12.[21]

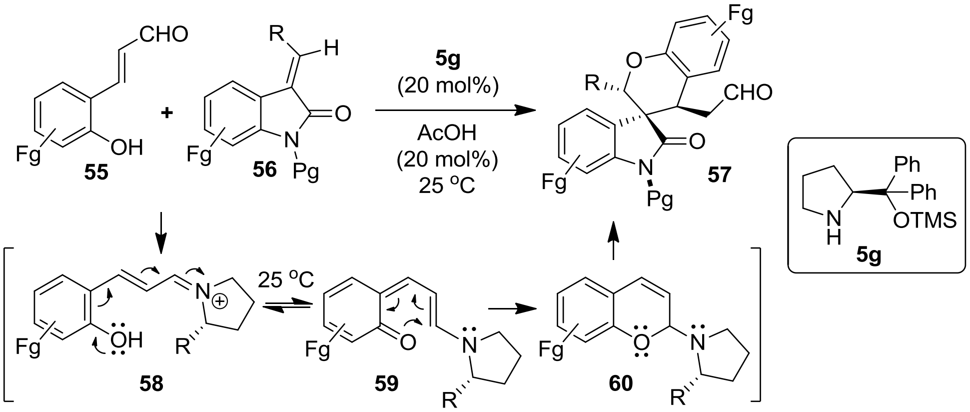


(12)

Our group also developed the original supramolecular organocatalysis in the synthesis of functionalized molecules, where the people did not realize the real importance of secondary interactions or neighboring group control in the transition state. First in 2012, utilization of large-size supramolecular rings in the *pre*-transition state (*pre*-TS) of enamine-based Michael reactions for high asymmetric induction was described. D-proline *ent*-**5a** and quinine-N*H*-thiourea **5f** catalyzed Michael reaction followed by intramolecular lactonization reaction between 2-(2-nitrovinyl)phenol **46a** and cyclohexanone **10b** resulted the corresponding hexahydroxanthenols **52** with high yield, *ee* and *de* values, which have showed further applications in the chiral synthesis of medicinally important compounds as shown in eq. 13. These fascinating results through the rigid transition state, where the covalent and weak interactions among the catalyst and substrates get involved and construct a *pre*-TS supramolecular assembly in this reaction is responsible for high asymmetric induction, thus this has proved to be the best example of showing the supramolecular assembly in the transition state with experimental evidence (ESI-HRMS).[22b]

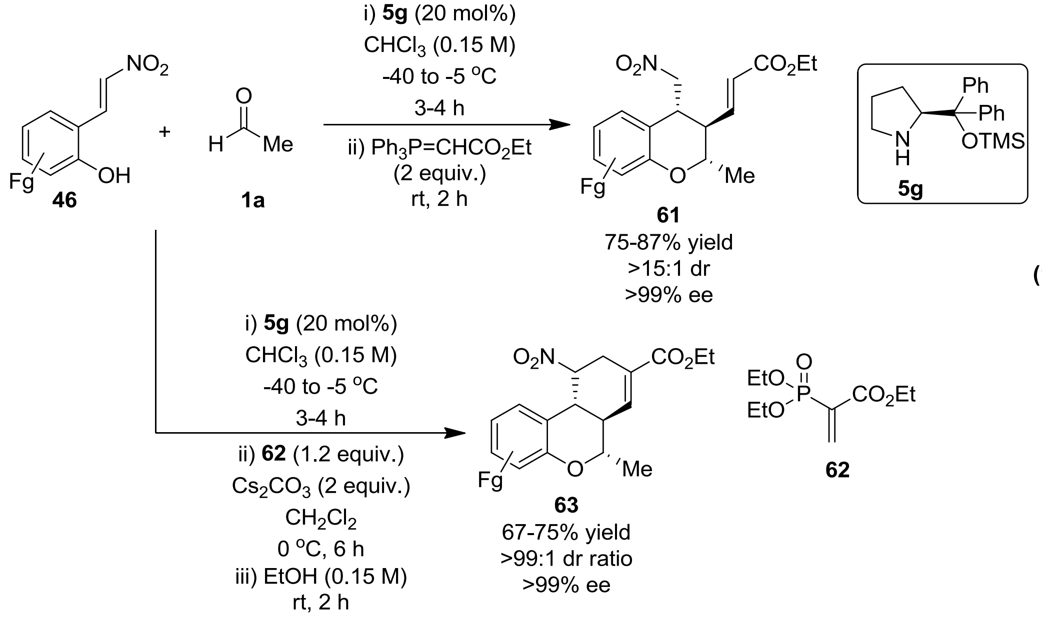


In 2014, our group reported a complementary active mode of catalyst known as aminol. In this report an important secondary catalytic species aminal activity was tested through spiro[chroman-3,3'-indolin]-2'-ones **57** synthesis. Hydroxyl group, *ortho* to the cinnamaldehyde is responsible to generate a secondary catalytic species of aminal from primary catalytic species iminium ion for high *ee* and *de*. This unusual activity of iminium ion was supported by NMR and ESI-HRMS experiments of an ongoing reaction between **55** and **5g** in $CDCl_3$.[22c]



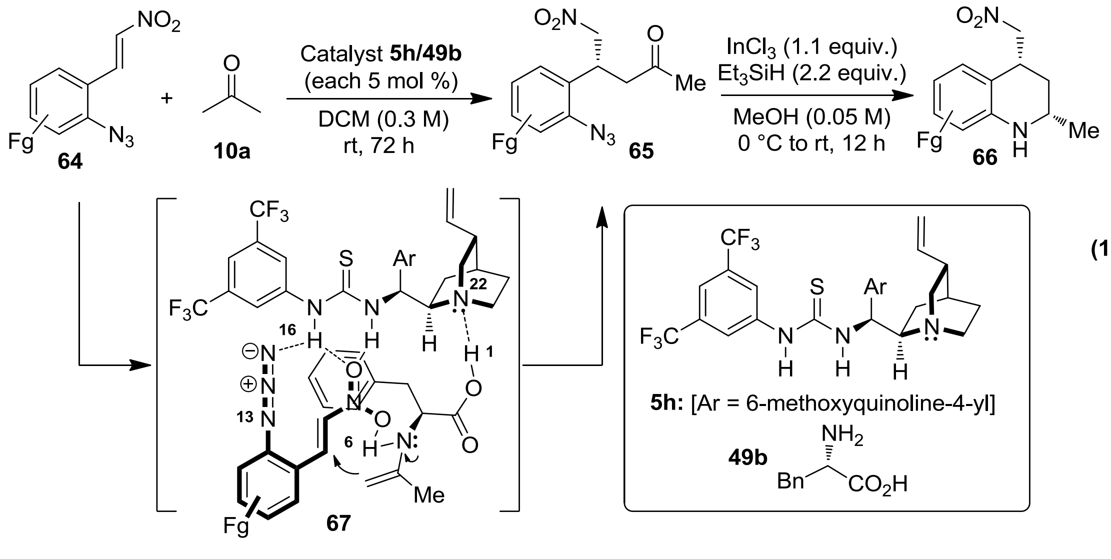
(14)

Simultaneous report from our group on supramolecular organocatalysis was demonstrated the Michael-aldol reaction sequence. This report shows the utilization of neighboring *ortho*-hydroxy group participation in the *pre*-transition state of enamine- and iminium-based triple domino reactions for high reaction rates and asymmetric induction for the synthesis of chromanes **61/63** from acetaldehyde **1a** and 2-(2-nitrovinyl)phenol **46** under **5g**-catalysis (eq. 15).[22d]



(15)

Very recently, our group demonstrated the asymmetric synthesis of tetrahydroquinolines through supramolecular organocatalysis. In this manuscript number of catalyst combinations were tested for Michael reaction though supramolecular organocatalysis, best and efficient yield and selectivity was achieved through combination of catalysts **5h** and **49b** (eq. 16). In the transition state, CO_2H group of **49b** undergoes hydrogen bonding with the *tert*-amine group of **5h**, which brings the two catalysts closer to the reaction centre; NH groups of **5h** involves the hydrogen-bonding with both N_3 and NO_2 groups of **64** to activate the electrophilic nature of olefin; the primary amino group of **49b** forms enamine with acetone **10a** to activate the nucleophilic nature and finally the NO_2 group of **64** undergoes hydrogen-bonding with enamine NH, thus closing the mobile 22-membered supramolecular cyclic *pre*-transition state to control the enantioselectivity and it was proved through several control experiments and ESI-HRMS analysis of ongoing reaction.[22e]



(16)

As our group is contributing novel asymmetric methods in the upcoming branch of organocatalysis, I am also achieved some biologically important optically pure molecules synthesis from supramolecular-catalysis and the results are presented in this thesis as part-B.

[33]

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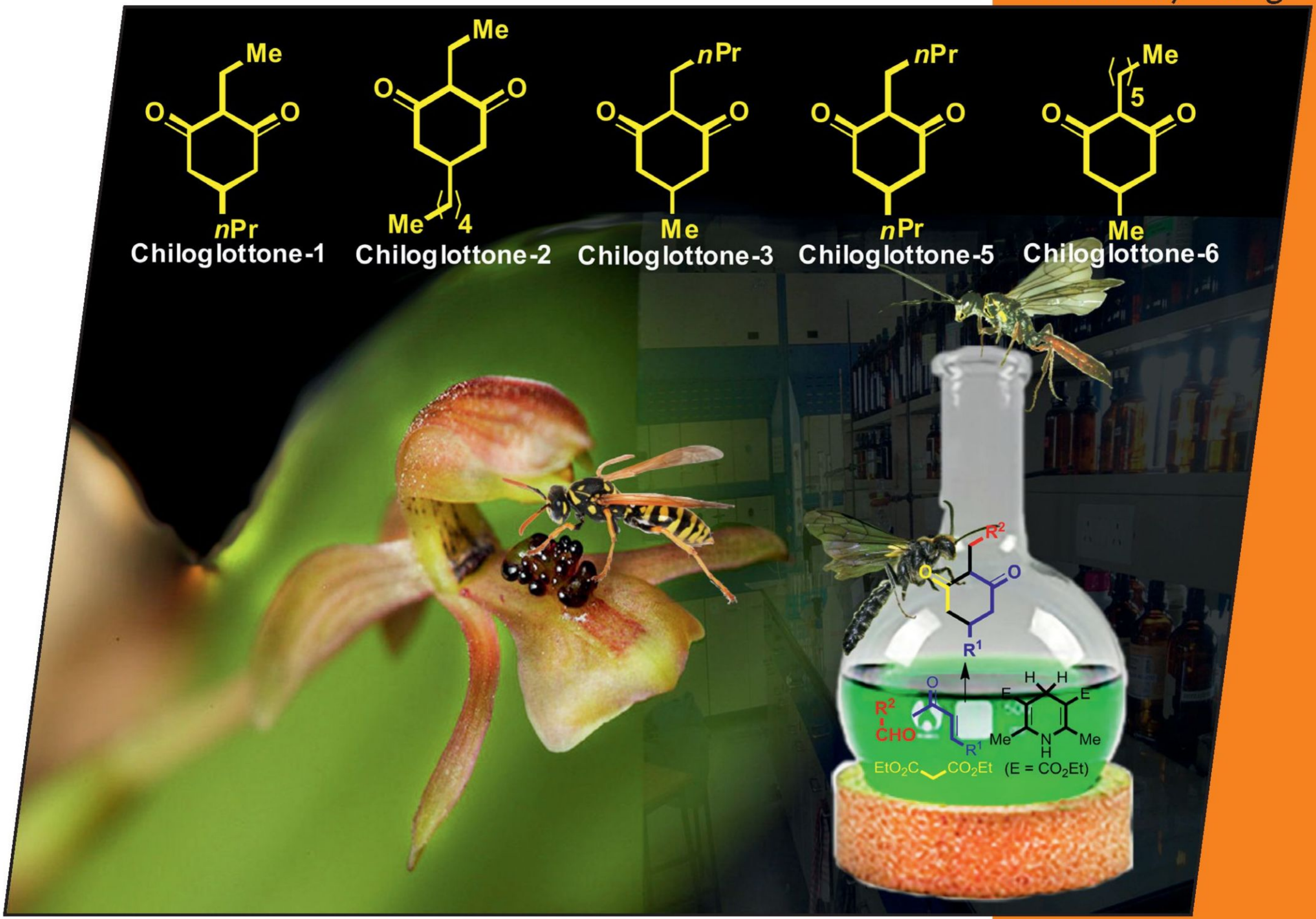

Cover Picture

Rudrakshula Madhavachary and Dhevalapally B. Ramachary
Total Synthesis of Chiloglottones and Dialkylresorcinols

Microreviews

Ana Maria Faísca Phillips
Carbohydrate-Based Organocatalysts in Enantioselective Synthesis

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Effective Molarities of Recognition-Mediated Bimolecular Reactions

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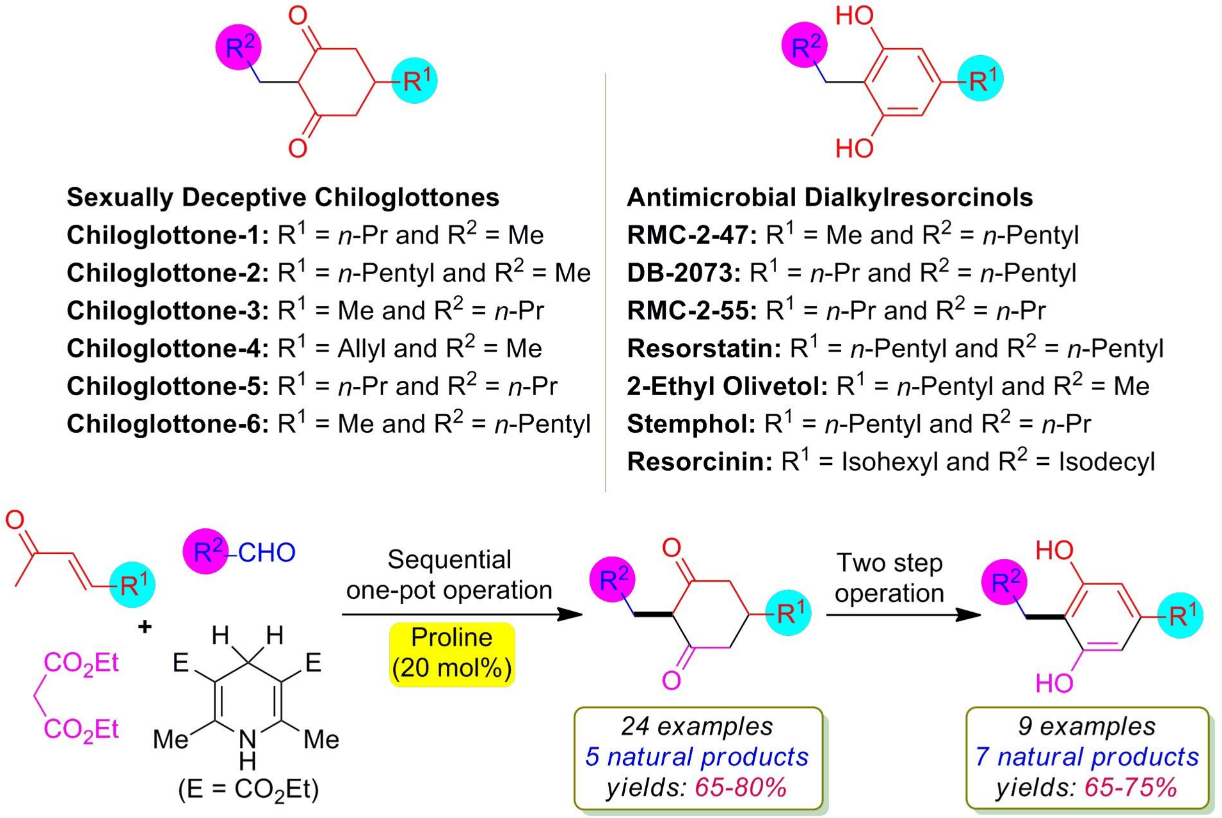
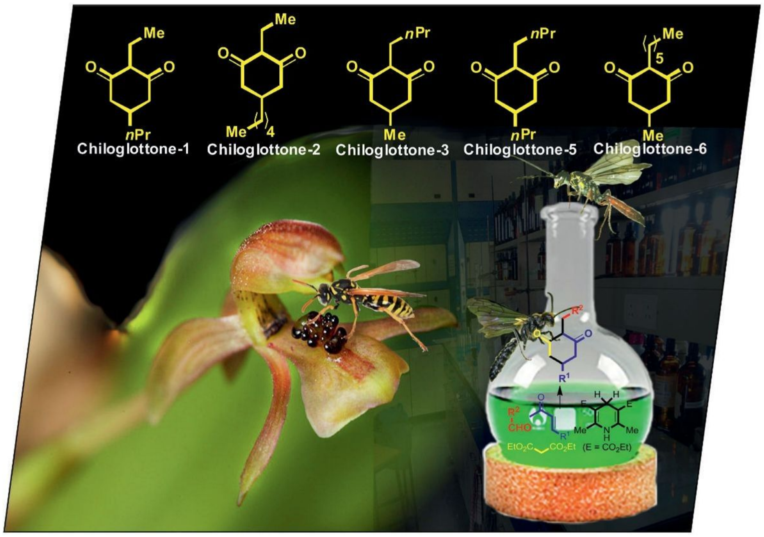

Sexually Deceptive Chiloglottones
Chiloglottone-1: R^1 = *n*-Pr and R^2 = Me
Chiloglottone-2: R^1 = *n*-Pentyl and R^2 = Me
Chiloglottone-3: R^1 = Me and R^2 = *n*-Pr
Chiloglottone-4: R^1 = Allyl and R^2 = Me
Chiloglottone-5: R^1 = *n*-Pr and R^2 = *n*-Pr
Chiloglottone-6: R^1 = Me and R^2 = *n*-Pentyl

Antimicrobial Dialkylresorcinols
RMC-2-47: R^1 = Me and R^2 = *n*-Pentyl
DB-2073: R^1 = *n*-Pr and R^2 = *n*-Pentyl
RMC-2-55: R^1 = *n*-Pr and R^2 = *n*-Pr
Resorstatin: R^1 = *n*-Pentyl and R^2 = *n*-Pentyl
2-Ethyl Olivetol: R^1 = *n*-Pentyl and R^2 = Me
Stemphol: R^1 = *n*-Pentyl and R^2 = *n*-Pr
Resorcinin: R^1 = Isohexyl and R^2 = Isodecyl

COVER PICTURE

The cover picture shows how an organocatalytic reductive coupling reaction became a key reaction for the high-yielding two-pot total synthesis of sexually deceptive chiloglottones, regarded as an unexplored class of natural products. Chiloglottones 1–6 were identified in orchids of the genus *Chiloglottis*, in which they act as pheromones to fool its pollinator, the male wasp *Neozeleboria cryptoides*. Details are discussed in the Short Communication by R. Madhavachary and D. B. Ramachary on p. 7317ff.



Part-A

3. High-yielding Total Synthesis of Sexually Deceptive Chiloglottones and Antimicrobial Dialkylresorcinols through an Organocatalytic Reductive Coupling Reaction

3.1 Introduction

Over the last two hundred years, efforts from the synthetic chemistry community must be appreciated for their intellectual design of the most complex molecules synthesis, but lengthy processing times, wasteful and expensive routes, environmental issues were often part of it. Thus, the objectives of the useful molecules, for example natural products, drugs, drug intermediates and ingredients can be challenging to synthesize even if they are only moderately complex. In this context, we believe that organic synthesis can be made perfect as similar to the cellular reactions by designing multi-domino processes in which multi-catalysts operate sequentially in one-pot with multi-components. Basically, this sequential one-pot combination of multi-domino processes should reduce the cost and waste associated with all kinds of molecules synthesis.

The increasing demands for economical and environmentally friendly synthetic processes promote the development of sequential one/two-pot combination of multi-domino processes to provide the desired products in most efficient ways.[23] The early discovery of amino acid- and/or amine-catalyzed double domino,[24] triple domino,[25] and quadruple domino[26] asymmetric reactions initiated a new era in the high-yielding total synthesis of natural products, drugs and drug-like molecules through a sequential one/two-pot combination of multi-domino processes.[27] There has been a considerable range of multi-domino processes effectively utilized by chemists for the high-yielding total synthesis of natural products/drugs from the last few years.[27] Although the sequential one/two-pot combination of multi-domino processes are evolving as better protocol,[27] whatever known of few domino processes are not enough for the vast library of natural products/drugs synthesis and we need to develop different better combination of multi-domino processes in one/two-pot manner. Herein, we have designed a new multi-domino process for the sequential two-pot high-yielding total synthesis of sexually deceptive chiloglottones **16**[28] and antimicrobial dialkylresorcinols **68** [Fig. 1].[29]

Figure-1: Structures of naturally known dialkylresorcinols and the chiloglottones.

16

Sexually Deceptive Chiloglottones
Chiloglottone-1: R^1 = *n*-Pr and R^2 = Me
Chiloglottone-2: R^1 = *n*-Pentyl and R^2 = Me
Chiloglottone-3: R^1 = Me and R^2 = *n*-Pr
Chiloglottone-4: R^1 = Allyl and R^2 = Me
Chiloglottone-5: R^1 = *n*-Pr and R^2 = *n*-Pr
Chiloglottone-6: R^1 = Me and R^2 = *n*-Pentyl

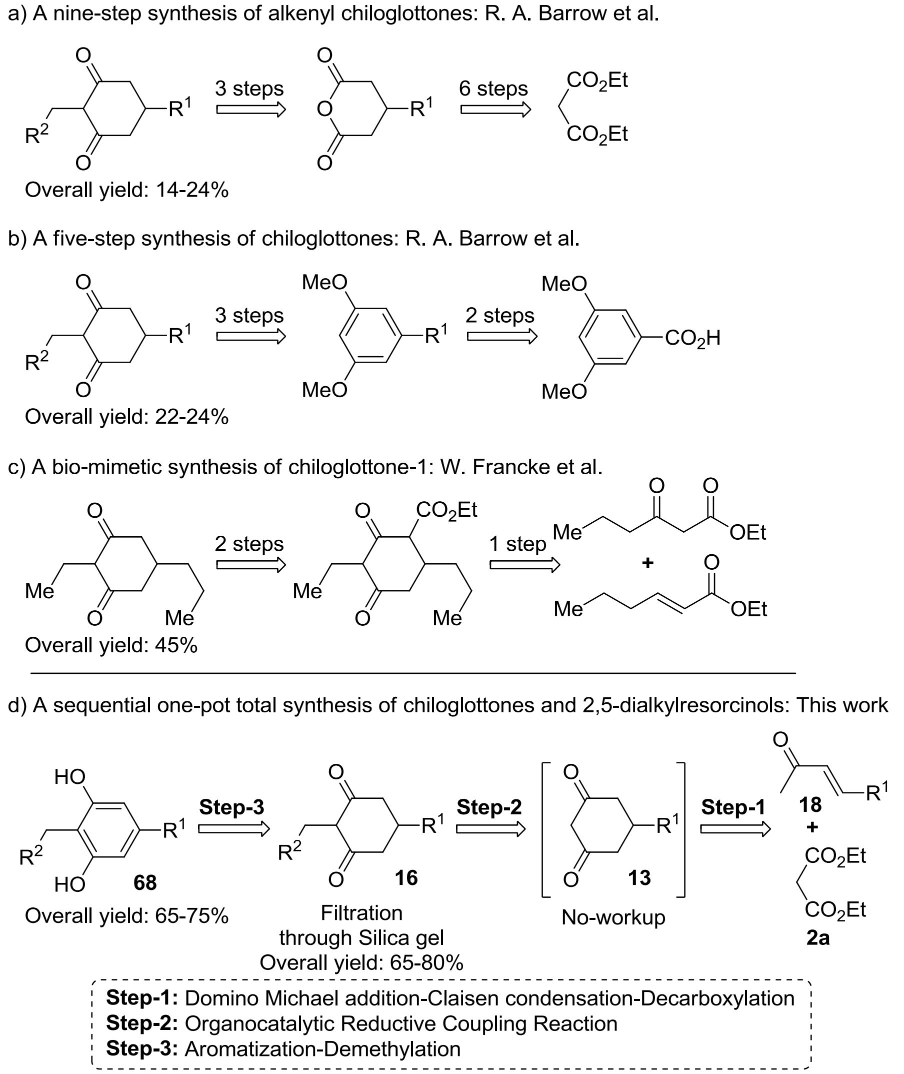
68

Antimicrobial Dialkylresorcinols
RMC-2-47: R^1 = Me and R^2 = *n*-Pentyl
DB-2073: R^1 = *n*-Pr and R^2 = *n*-Pentyl
RMC-2-55: R^1 = *n*-Pr and R^2 = *n*-Pr
Resorstatin: R^1 = *n*-Pentyl and R^2 = *n*-Pentyl
2-Ethyl Olivetol: R^1 = *n*-Pentyl and R^2 = Me
Stemphol: R^1 = *n*-Pentyl and R^2 = *n*-Pr
Resorcinin: R^1 = Isohexyl and R^2 = Isodecyl

Chiloglottones **16** and dialkylresorcinols **68** can be regarded as an unexplored class of natural products. Thus far, the only example of 2,5-dialkylcyclohexane-1,3-dione natural products are the chiloglottones 1-6 (**16**), which were identified in orchids of the genus *Chiloglottis*, where they act as pheromones to fool its pollinator, the male wasp *Neozeleboria cryptoides*.[28] Interestingly, chiloglottones 1-6 (**16**) can be easily transformed into another kind of natural products, 2,5-dialkylresorcinols **68** by an oxidative aromatization and the only known examples for dialkylresorcinols **68** are RMC-2-47 **68be**, RMC-2-55 **68cc**, DB-2073 **68ce**, 2-ethyl olivetol **68da**, stemphol **68dc**, resorstatin **68de**, resorcinin **68fj** and their analogues, which are showing very good antibacterial and anticancer activity.[29]

Based on their many applications, development of efficient and environmental friendly two-pot protocol from simple substrates to synthesize both the natural products **16** and **68** is a significantly challenging task. The first total synthesis of chiloglottone-1 was reported in 2008 by Barrow *et al.* by using nine steps in 14-24% overall yield (eq. a, Scheme 1).[30] In 2009, same group developed a five-step protocol for the total synthesis of chiloglottone-1 in 22-58% overall yield (eq. b, Scheme 1).[30]

Scheme 1: Previous multi-step approaches and present approach for the one-pot total synthesis of chiloglottones **16** and dialkylresorcinols **68**.



In 2009, Francke *et al.* developed a three-step protocol for the total synthesis of chiloglottone-1 in 45% overall yield (eq. c, Scheme 1).[31] In the above three methods, Barrow group utilized five to nine linear synthetic steps and longer reaction times to furnish the only one natural product chiloglottone-1 and their analogues in poor overall yields. Francke group used three steps to furnish chiloglottone-1 and their analogues in moderate overall yields from designed substrates, but using this method they also synthesized only one natural product (eq. a-c, Scheme 1). These three methods required harsh reaction conditions with each step purification or highly functionalized designed starting materials to furnish chiloglottone-1 out of six chiloglottones (Figure 1). With this limitations in mind, herein, we describe the total synthesis of library of natural products chiloglottones 1-6 (**16**), 2,5-dialkylresorcinols **68** and their many analogues from alkylideneacetones **18b-g** and diethyl malonate **2a** by using triple domino Michael addition/Claisen condensation/hydrolysis/decarboxylation[32] followed by metal-free reductive coupling[33-35] reaction in a sequential two-pot manner. Chiloglottones 1-6 (**16**) and their analogues were transformed into 2,5-dialkylresorcinols **68** by using oxidative aromatization followed by metal-free demethylation in a sequential two-pot manner (eq. d, Scheme 1).

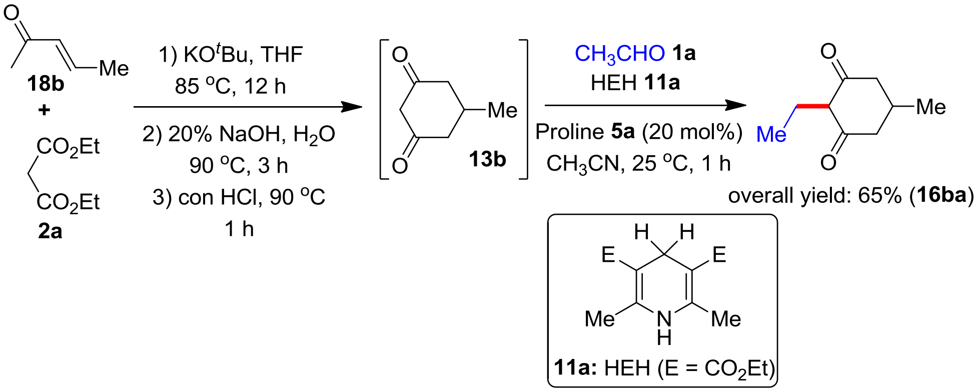
3.2 *Results and Discussions*

Our high-yielding two-pot strategy for the synthesis of chiloglottones **16** began with the facile *in situ* construction of 5-alkylcyclohexane-1,3-diones **13**, which is starting material for the reductive coupling with aldehydes **1** and **11a** under the proline **5a**-catalysis.[33] For this purpose, we have utilized domino Michael addition–Claisen condensation of alkylideneacetones **18** with diethyl malonate **2a** to furnish the β,δ-diketo ester, which on further one-pot hydrolysis-decarboxylation,[32] delivered the required 5-alkylcyclohexane-1,3-diones **13** in very good yields. Removal of the water layer from the reaction mixture and further treatment with aldehydes **1** and **11a** under the proline-catalysis delivered the chiloglottones **16** and their analogues in very good yields (Schemes 1 and 2).

Recently, we have developed a novel three-component reductive alkylation protocol for the selective *C*-alkylation of highly reactive cyclic-1,3-diones with a variety of aldehydes and Hantzsch ester (hydrogen source) through olefination followed by transfer hydrogenation under the proline-catalysis.[33] Soon after the discovery of this reductive coupling reaction in 2006, many chemists realized the importance of this reaction in the total synthesis of natural products, drugs and drug-like molecules.[34,35] Herein, we have utilized this three-component reductive coupling protocol as one of the main reaction in one-pot manner to synthesize chiloglottones through C-C bond formation.

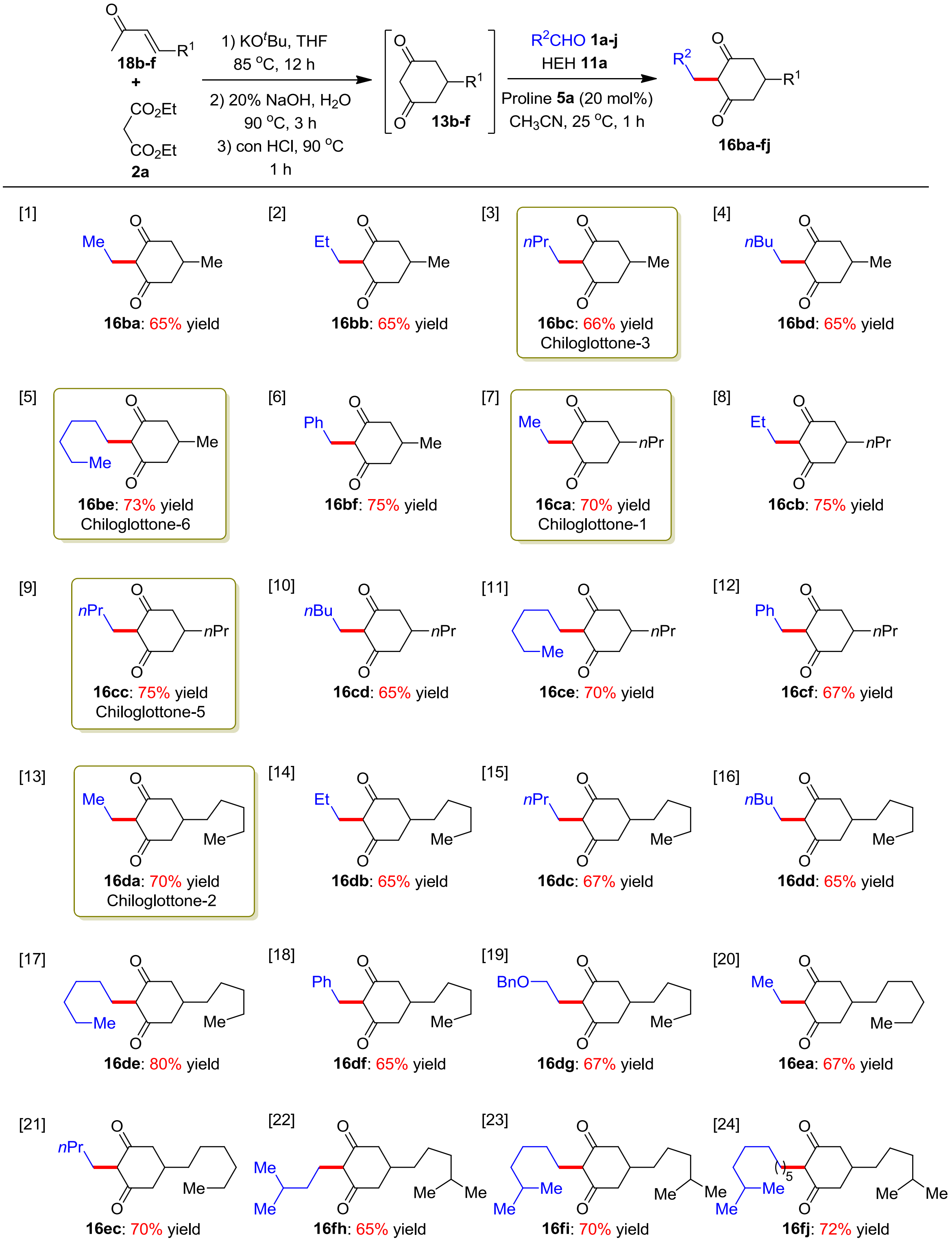
This design was first demonstrated with model substrates of **18b**, **2a**, **1a**, and **11a** under the proline-catalysis (Scheme 2). Base-induced domino Michael addition–Claisen condensation of **2a** with **18b** in THF under reflux for 12 h followed by one-pot hydrolysis with 20% aqueous NaOH at 90 °C for 3 h and *in situ* decarboxylation with con. HCl at 90 °C for 1 h furnished the basic skeleton with active functional group of 5-methylcyclohexane-1,3-dione **13b** in very good conversion. Quick removal of the aqueous layer from the reaction mixture followed by reductive coupling reaction of the crude product **13b** with acetaldehyde **1a** (5 equiv.) and Hantzsch ester **11a** (1 equiv.) under 20 mol% of proline in CH_3CN at 25 °C for 1 h furnished the analogue of chiloglottone-3 **16ba** in 65% yield (Scheme 2). Overall yield obtained from this two-pot method is very good compared to the previous multi-pot methods (Scheme 1).

Scheme 2: Model reaction for the one-pot total synthesis of chiloglottone-3 analogue **16ba**.



After the successful high-yielding synthesis of chiloglottone-3 analogue **16ba**, the principle of the "sequential two-pot reactions" was further extended by reacting a library of functionalized alkylideneacetones **18b-f** with diethyl malonate **2a** under the base and acid to make 5-alkylcyclohexane-1,3-diones **13b-f** followed by treatment with a variety of aldehydes **1a-j** and Hantzsch ester **11a** catalyzed by 20 mol% of proline **5a** at 25 °C in CH_3CN for 1 h (Table 1). All the substrates **18b-f**, **2a**, **1a-j** and **11a** furnished the huge library of expected 2,5-dialkylcyclohexane-1,3-diones **16ba-fj** in 65-80% overall yields, irrespective of the electronic and steric factors of the substituents present. From this two-pot method, for the first time we have synthesized the total family of sexually deceptive natural products of chiloglottone-3 **16bc**, chiloglottone-6 **16be**, chiloglottone-1 **16ca**, chiloglottone-5 **16cc**, and chiloglottone-2 **16da** in 66-75% overall yields (Table 1). Also, we have prepared nineteen molecules of chiloglottone family analogues **16** in 65-80% overall yields as shown in Table 1.

Table 1: Total Synthesis of chiloglottones and their analogues **16** through sequential one-pot operation.[a]



[1] **16ba**: 65% yield

[2] **16bb**: 65% yield

[3] **16bc**: 66% yield Chiloglottone-3

[4] **16bd**: 65% yield

[5] **16be**: 73% yield Chiloglottone-6

[6] **16bf**: 75% yield

[7] **16ca**: 70% yield Chiloglottone-1

[8] **16cb**: 75% yield

[9] **16cc**: 75% yield Chiloglottone-5

[10] **16cd**: 65% yield

[11] **16ce**: 70% yield

[12] **16cf**: 67% yield

[13] **16da**: 70% yield Chiloglottone-2

[14] **16db**: 65% yield

[15] **16dc**: 67% yield

[16] **16dd**: 65% yield

[17] **16de**: 80% yield

[18] **16df**: 65% yield

[19] **16dg**: 67% yield

[20] **16ea**: 67% yield

[21] **16ec**: 70% yield

[22] **16fh**: 65% yield

[23] **16fi**: 70% yield

[24] **16fj**: 72% yield

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[a] Yield refers to the column-purified product

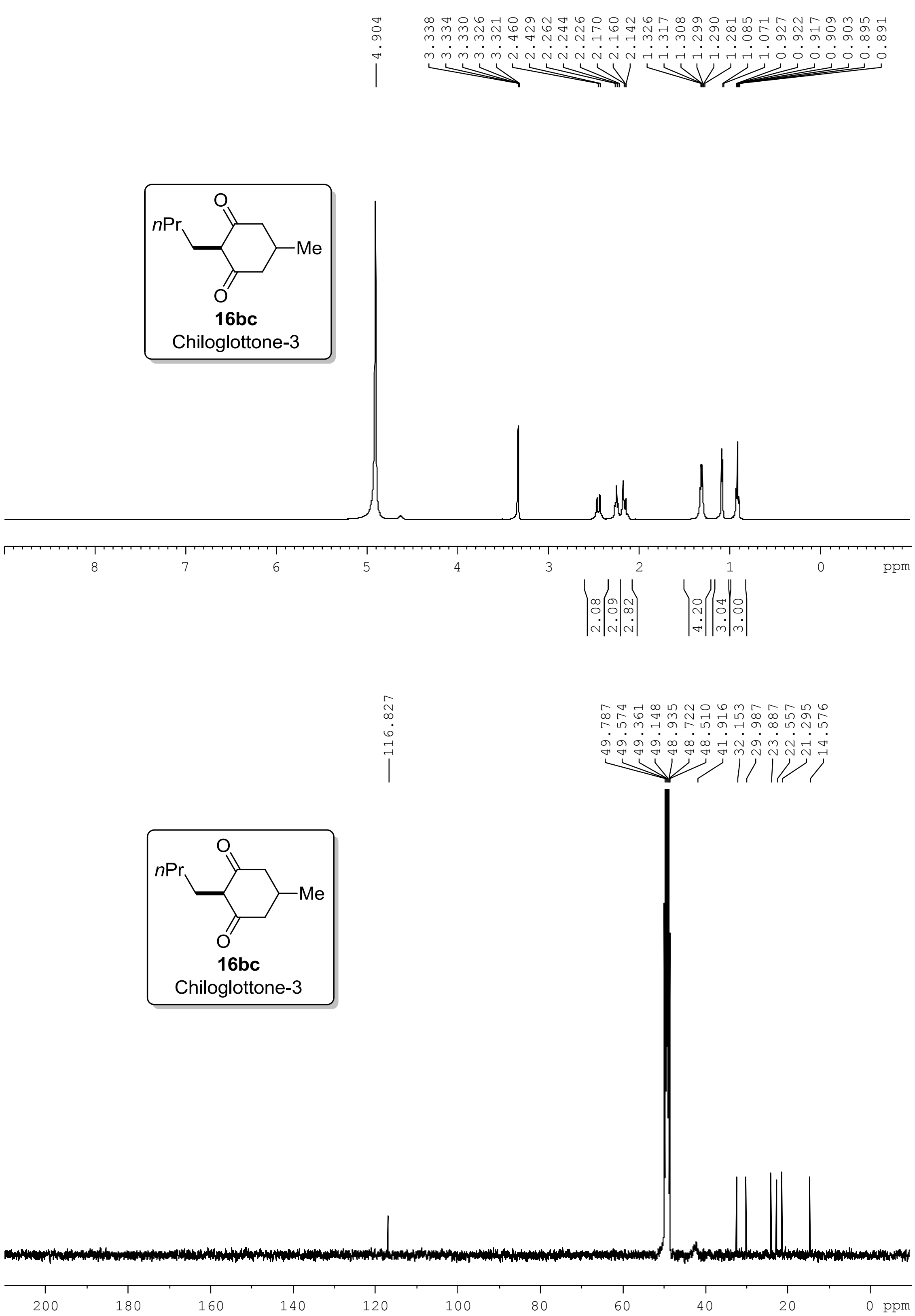


Figure-2: ^{1}H and ^{13}C NMR spectra of the product **16bc** (Chiloglottone-3).

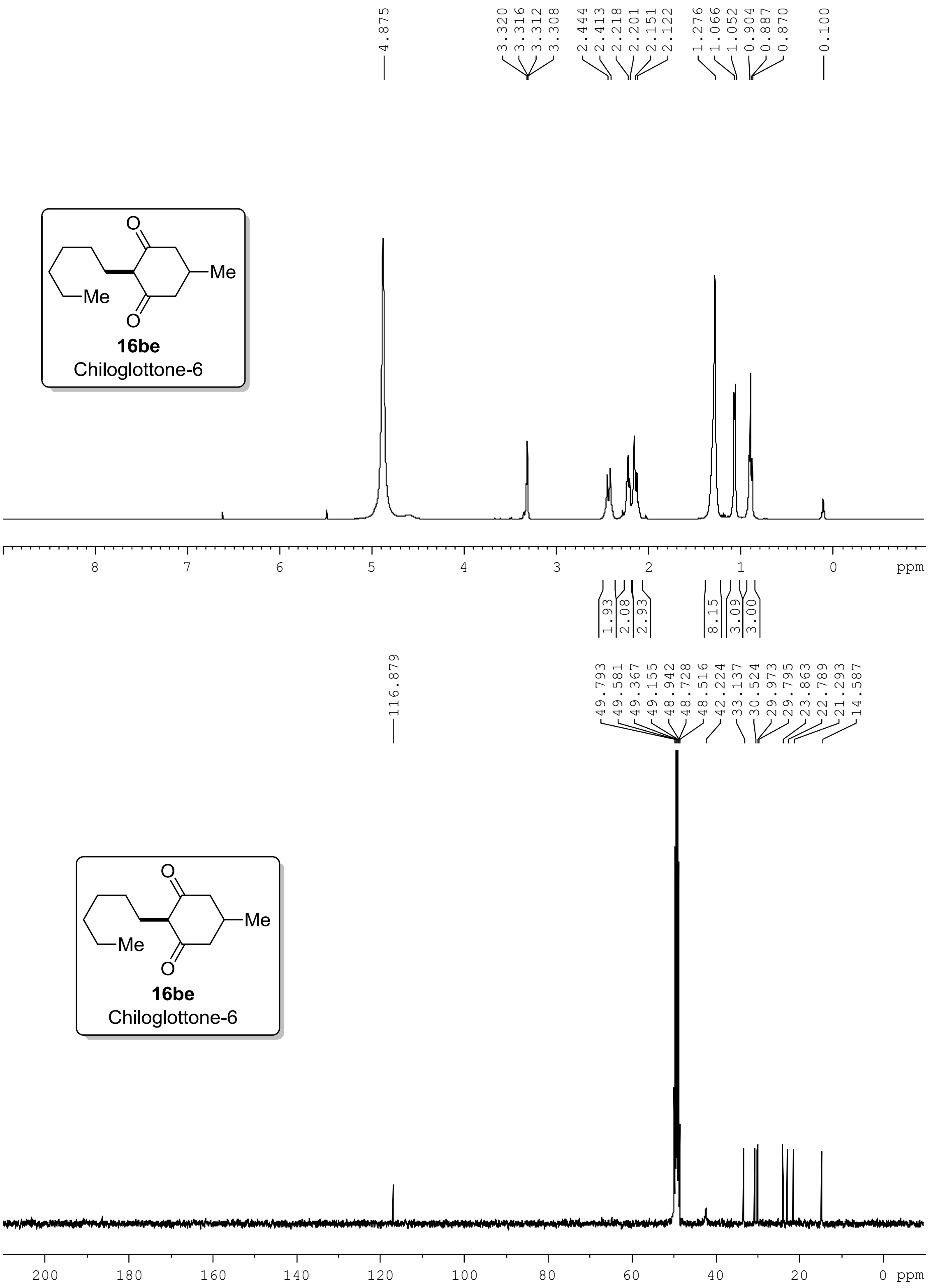


Figure-3: ^{1}H and ^{13}C NMR spectra of the product **16be** (Chiloglottone-6).

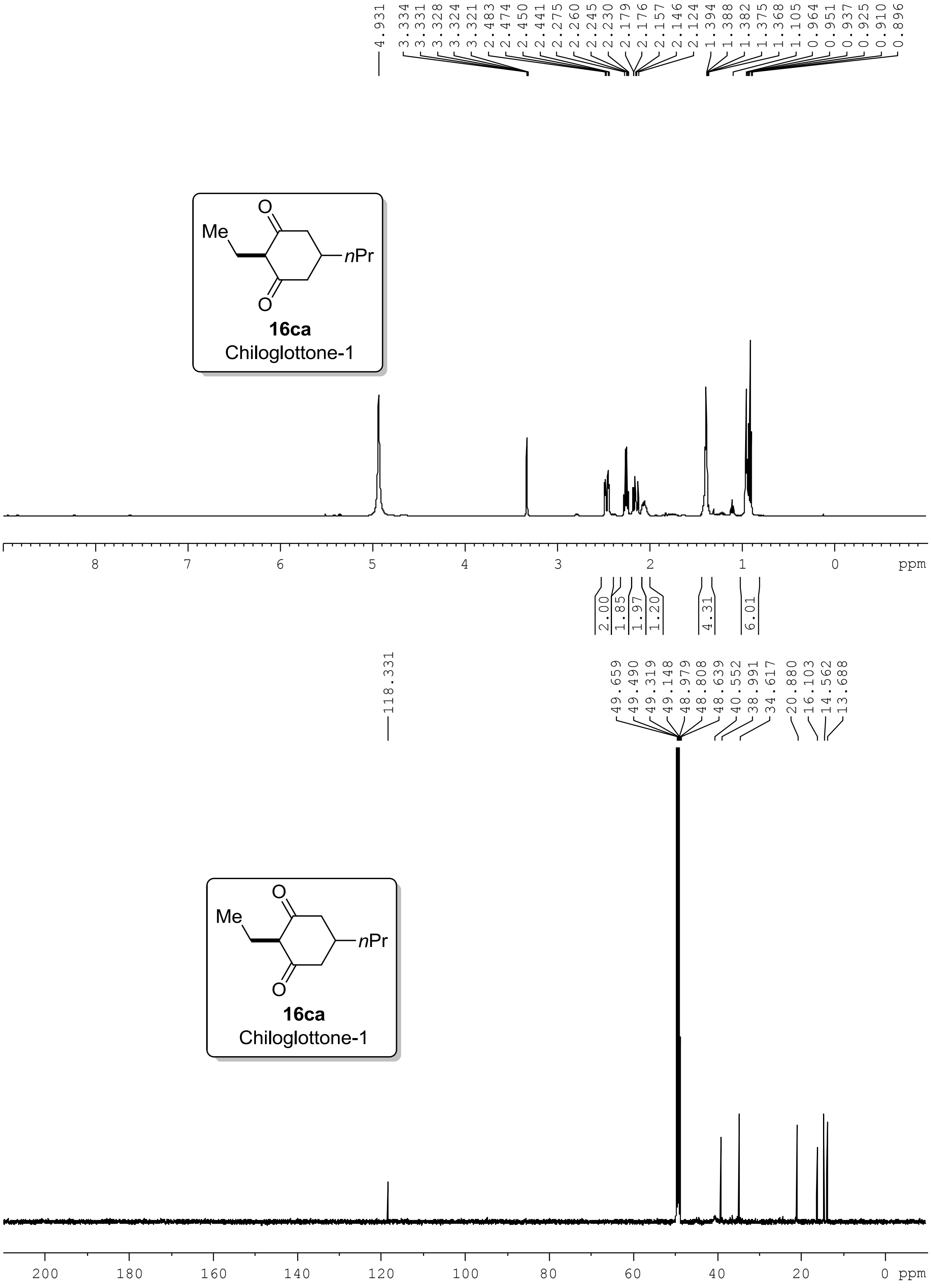


Figure-4: ^{1}H and ^{13}C NMR spectra of the product **16ca** (Chiloglottone-1).

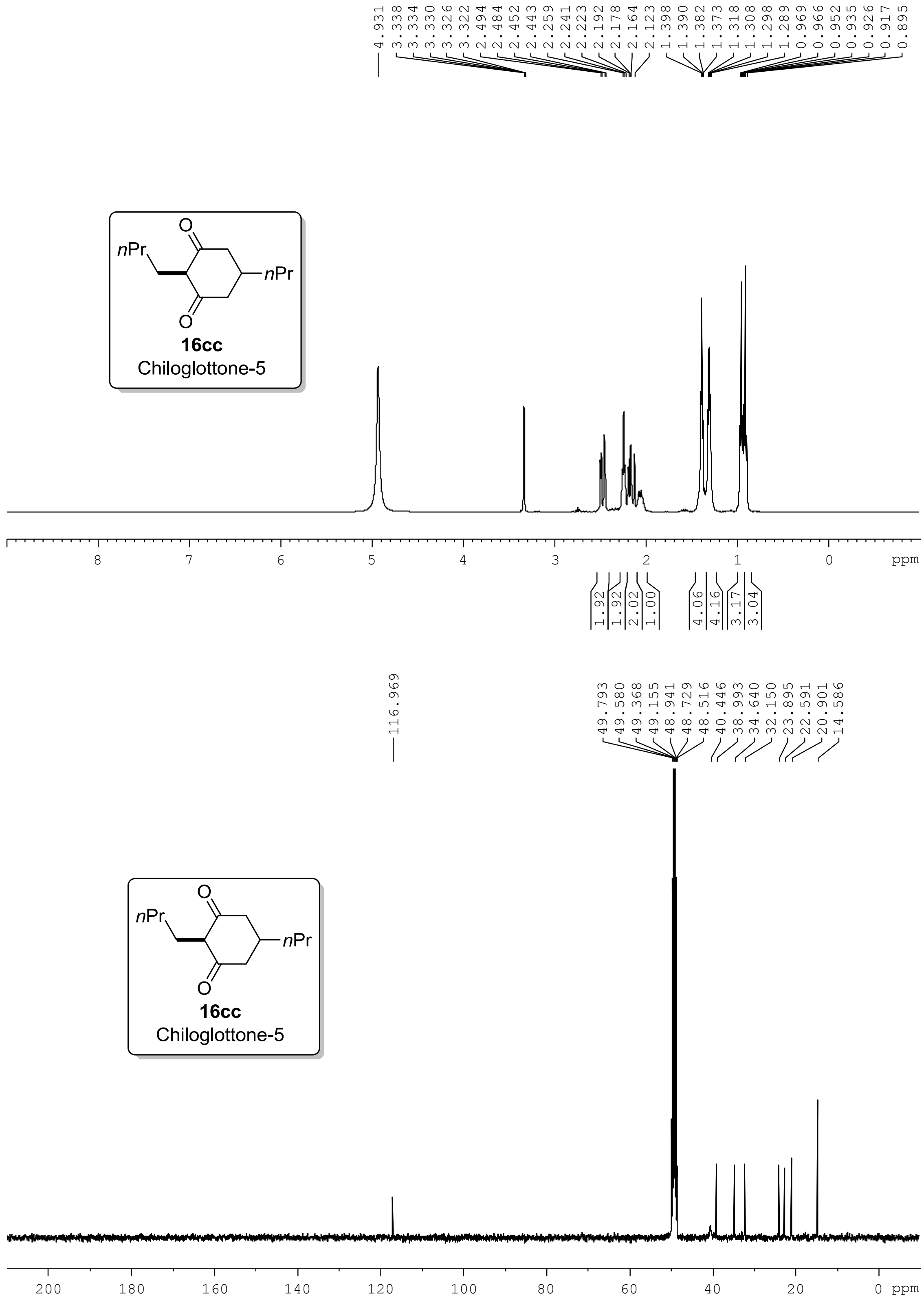


Figure-5: ^{1}H and ^{13}C NMR spectra of the product **16cc** (Chiloglottone-5).

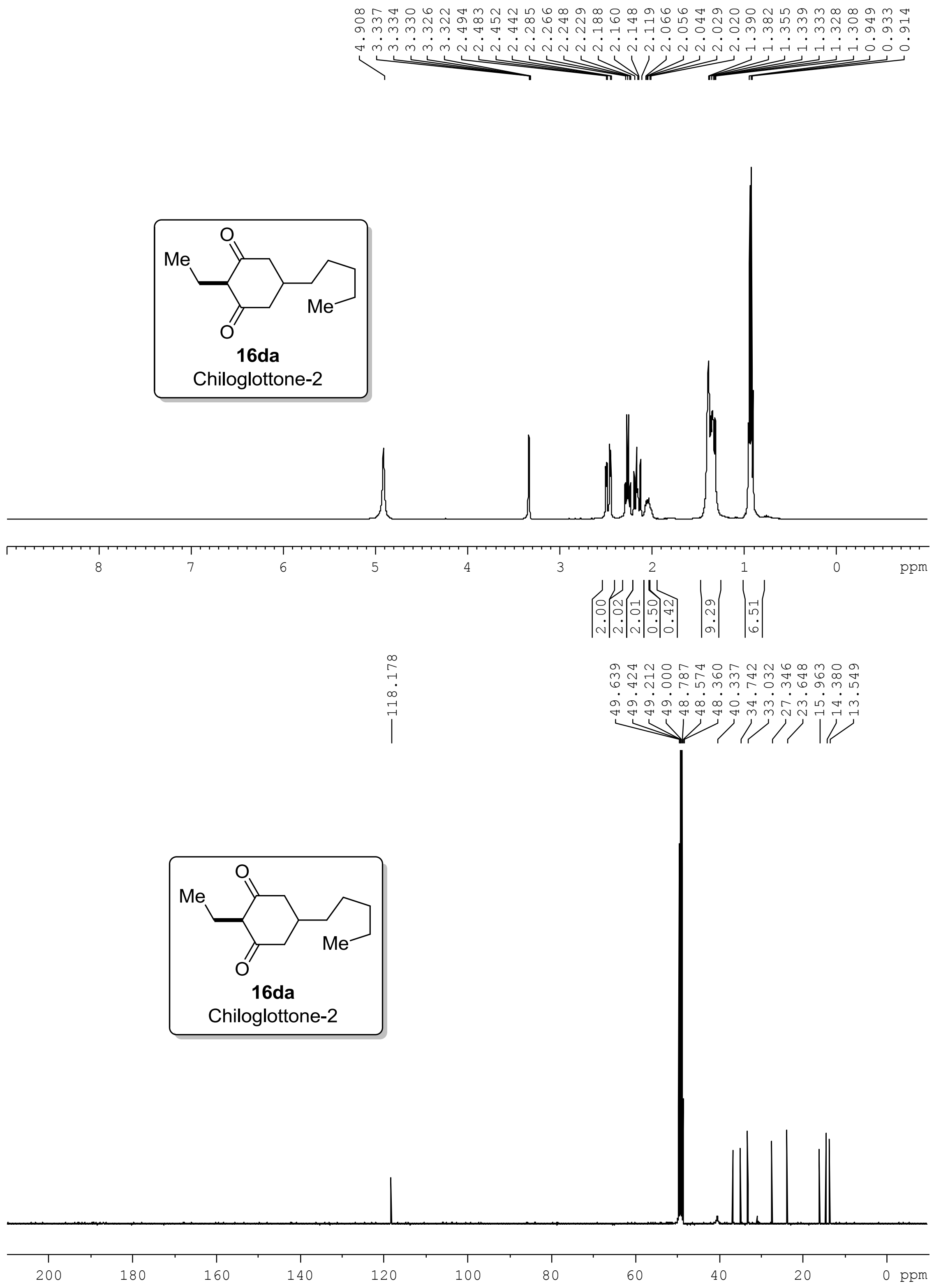
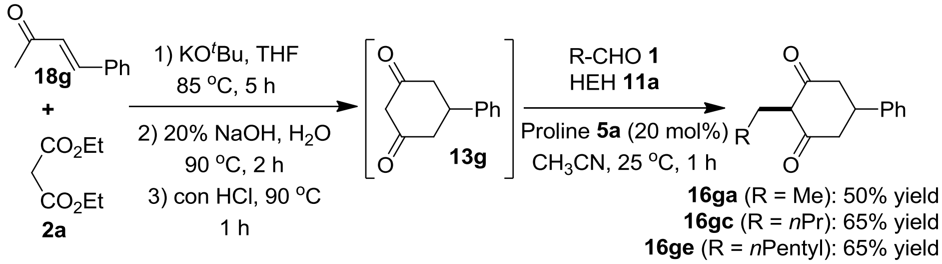


Figure-6: ^{1}H and ^{13}C NMR spectra of the product **16da** (Chiloglottone-2).

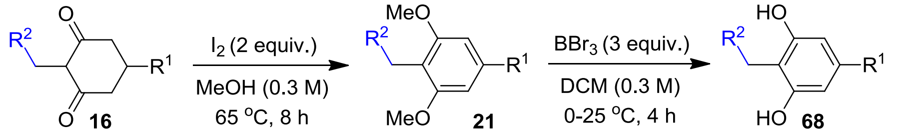
After demonstrating the two-pot high-yielding synthesis of chiloglottones and their analogues **16ba-fj**, the same protocol was further extended by reacting benzylidene acetone **18g** with diethyl malonate **2a** under the base/acid to make 5-phenylcyclohexane-1,3-dione **13g** followed by treatment with an aldehydes **1a,c,e** and **11a** catalyzed by 20 mol% of proline **5a** at 25 °C in CH_3CN for 1 h (Scheme 3). Surprisingly, all the expected 2-alkyl-5-phenylcyclohexane-1,3-diones **16** were furnished in 50-65% overall yields, irrespective of the electronic/steric factors (Scheme 3).

Scheme 3: Two-step total synthesis of chiloglottone analogues **16**.

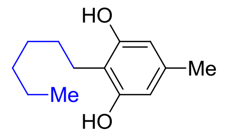


After synthesizing the library of chiloglottones **16** in a sequential two-pot manner, we further transformed them into medicinally important 2,5-dialkylresorcinols **68** through a two-step sequence of oxidative aromatization followed by demethylation.[36] Thorough investigation of **16**→**68** through two-step sequence of oxidative aromatization/demethylation proved that I_2/MeOH-BBr_3/DCM is the suitable condition to synthesize the 2,5-dialkylresorcinols **68** in good yields with high purity (Table 2).[36] Reaction of chiloglottone-6 **16be** with I_2 (2 equiv.) in MeOH at 65 °C for 8 h furnished the aromatized dimethoxy compound **21be** as the major isomer. Quick filtration of the dimethoxy compound **21be** through silica gel followed by demethylation with BBr_3 (3 equiv.) in DCM at 0-25 °C for 4 h furnished the natural product, 2-hexyl-5-methylbenzene-1,3-diol **68be** in 65% overall yield, which we named it as RMC-2-47 (Table 2, entry 1).[29] In a similar manner, the selective two-step sequential oxidative aromatization/demethylation strategy was demonstrated with eight more substrates of chiloglottones **16** containing different 2,5-dialkyl groups to furnish the medicinally important natural products of 2,5-dialkylresorcinols **68** in 65-76% overall yields with high purity (Table 2, entries 2-9). For the first time, we have prepared the seven natural products and two analogues of 2,5-dialkylresorcinols **68** in very good yields from a common protocol.

Table 2: Total synthesis of dialkylresorcinols **68** from chiloglottones **16** *via* two-step process.[a]

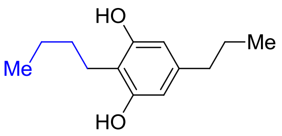


[1]



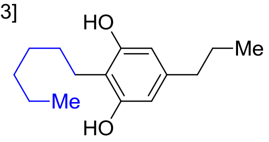
68be: 65% yield
RMC-2-47

[2]



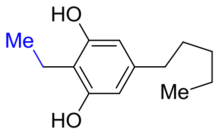
68cc: 72% yield
RMC-2-55

[3]



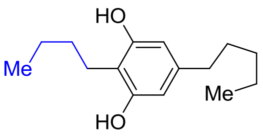
68ce: 73% yield
DB-2073

[4]



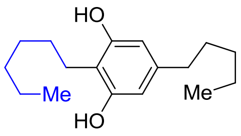
68da: 76% yield
2-Ethyl Olivetol

[5]



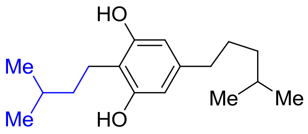
68dc: 65% yield
Stemphol

[6]



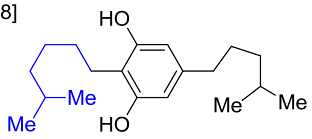
68de: 70% yield
Resorstatin

[7]



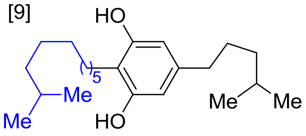
68fh: 75% yield
Resorcinin
analogue

[8]



68fi: 72% yield
Resorcinin
analogue

[9]



68fj: 75% yield
Resorcinin

[a]Yield refers to the column-purified product.

The structure and regiochemistry of the compounds **16** and **68** were confirmed by NMR analysis and also finally confirmed by correlation with literature data.

3.3 *Conclusions*

In conclusion, we have developed a common methodology for the high-yielding total synthesis of library of important natural products, chiloglottones 1-6 (**16**) and 2, 5-dialkylresorcinols **68** from readily available simple substrates through a sequential two-pot combination of domino Michael addition/Claisen condensation/hydrolysis/decarboxylation, organocatalytic reductive coupling reaction and oxidative aromatization/demethylation reactions respectively. This sequential two-pot protocol is an ideal method to synthesize the entire family of chiloglottone natural products.

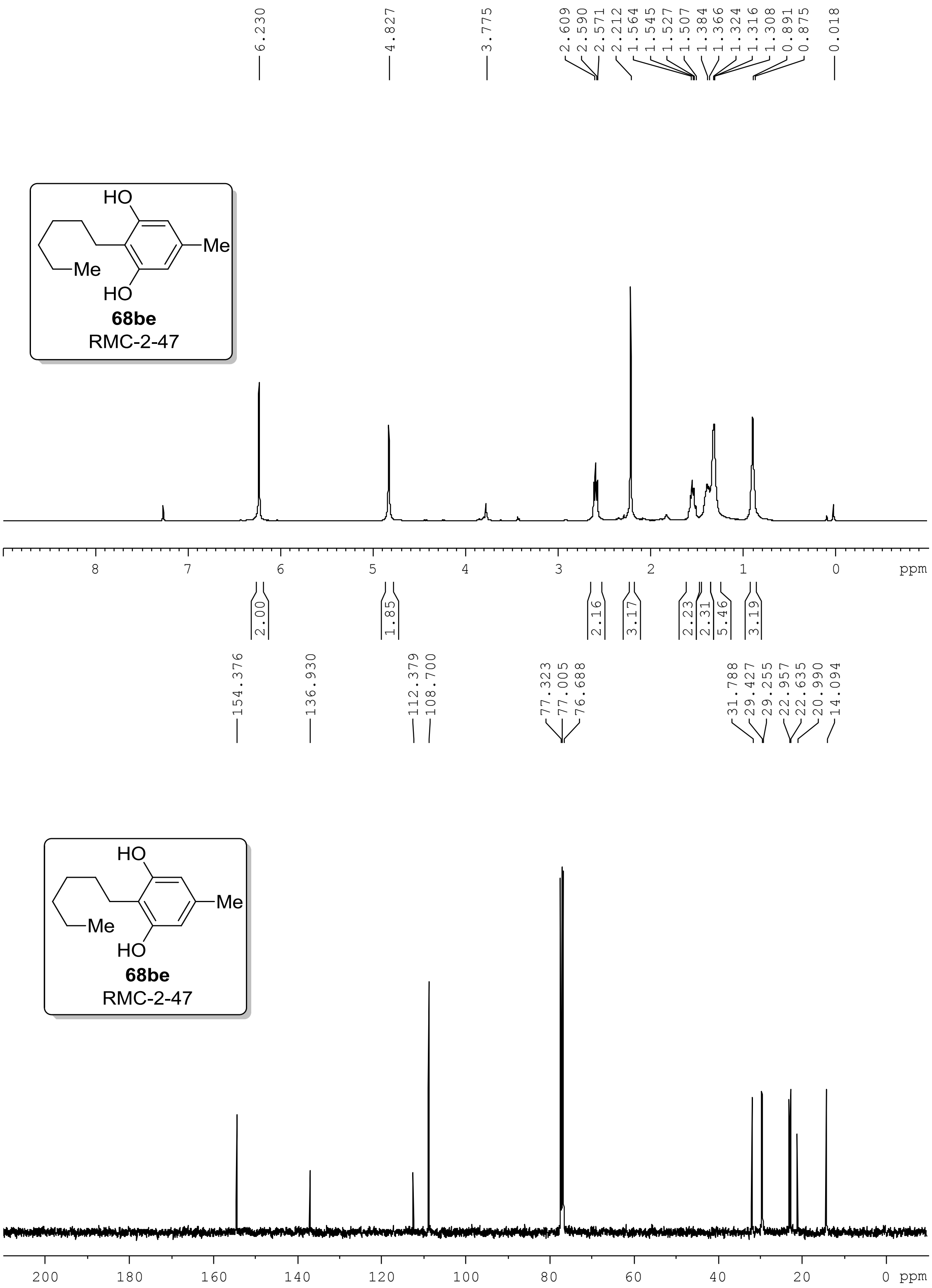


Figure-7: ^{1}H and ^{13}C NMR spectra of the product **68be (**RMC-2-47).

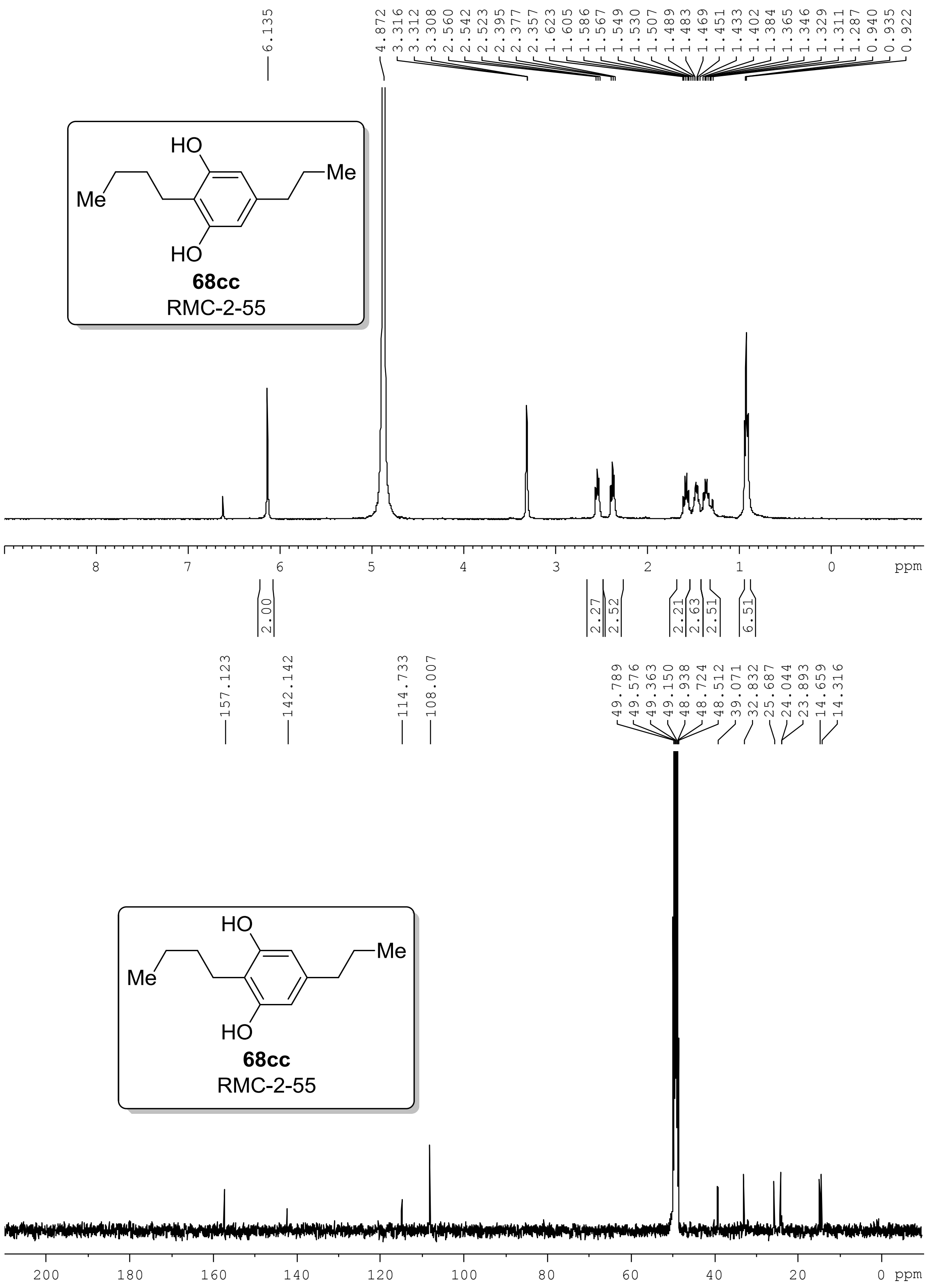


Figure-8: ^{1}H and ^{13}C NMR spectra of the product **68cc (**RMC-2-55).

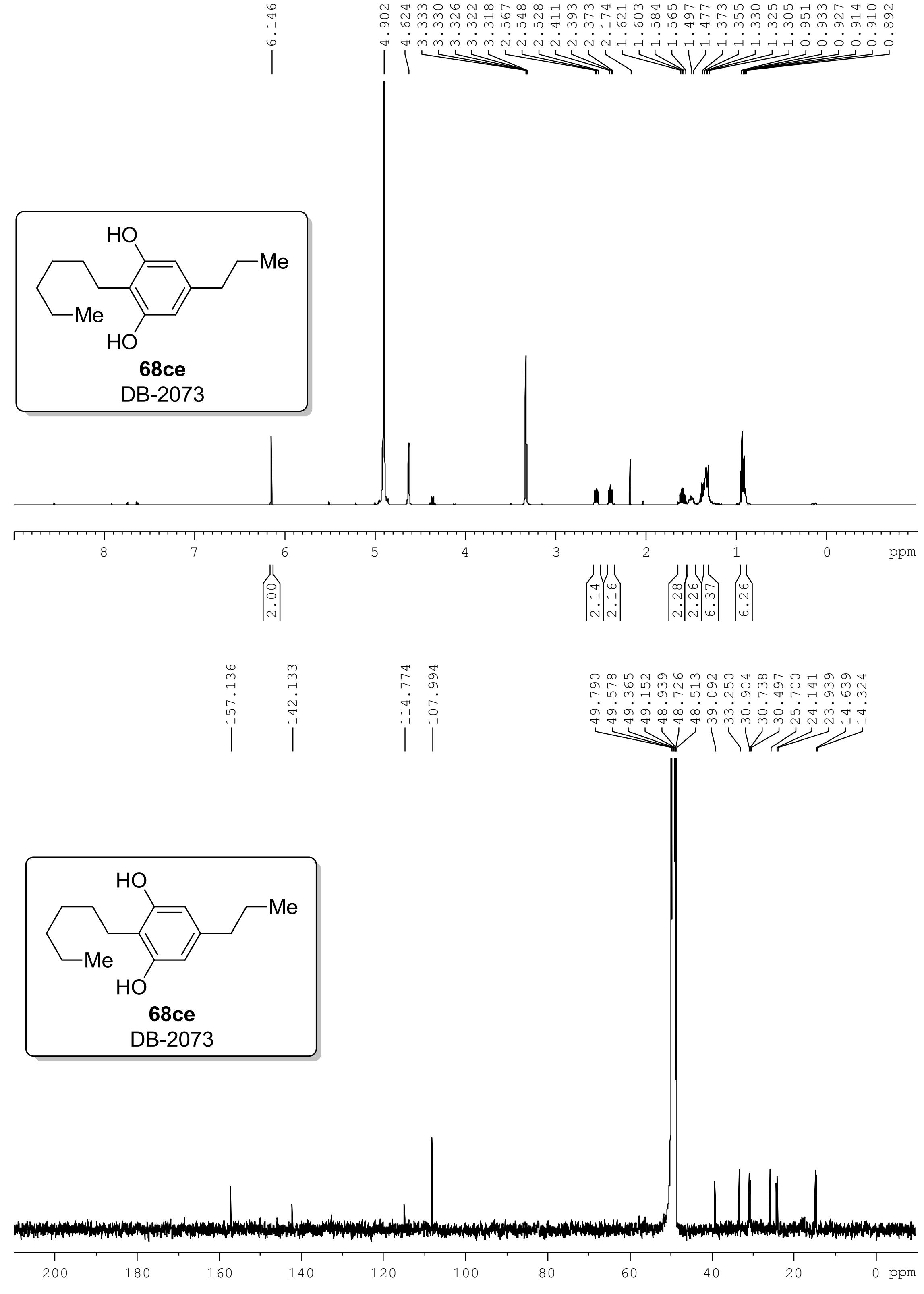


Figure-9: ^{1}H and ^{13}C NMR spectra of the product **68ce** (DB-2073).

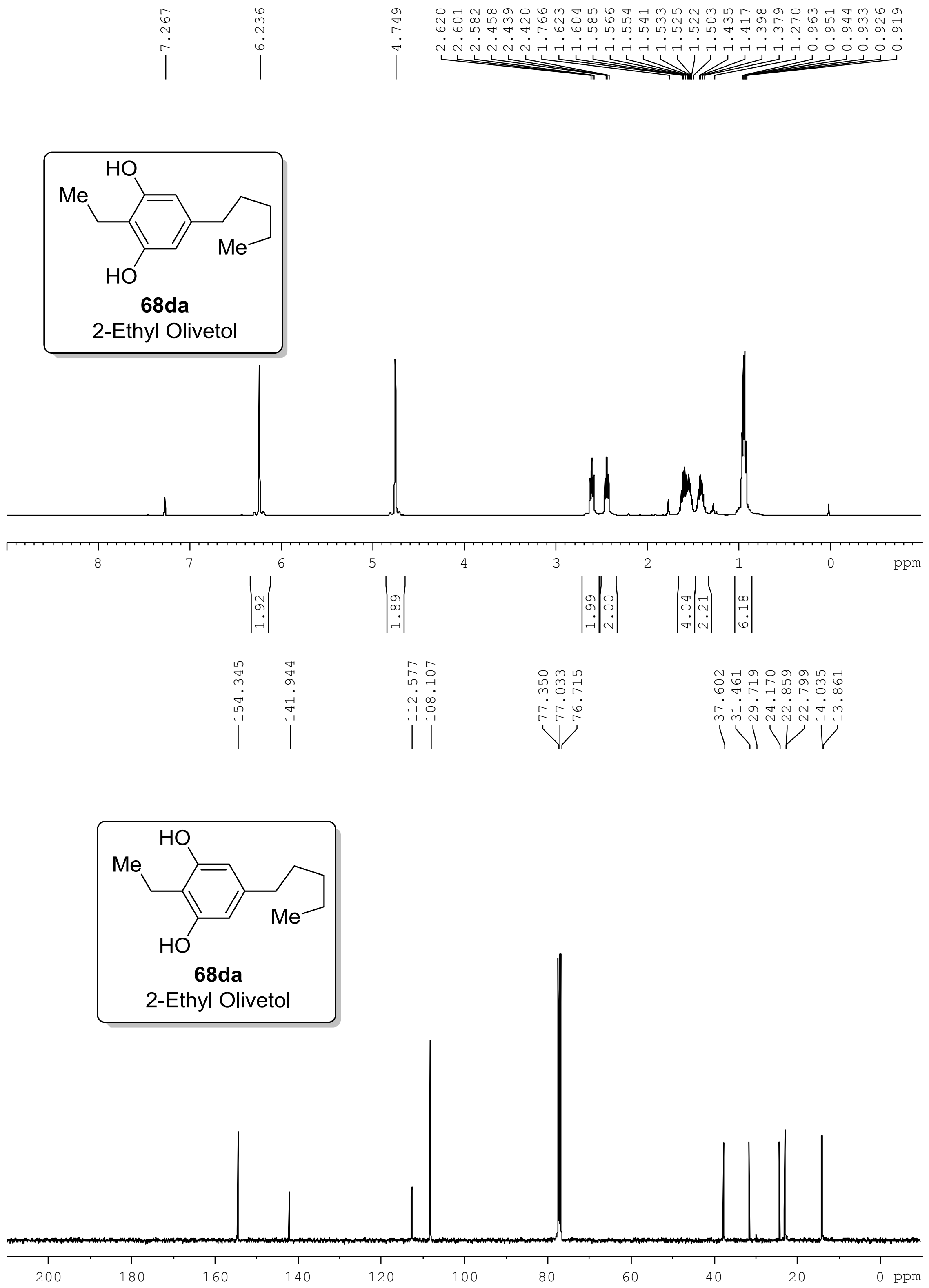


Figure-10: ^{1}H and ^{13}C NMR spectra of the product **68da** (2-Ethyl Olivetol).

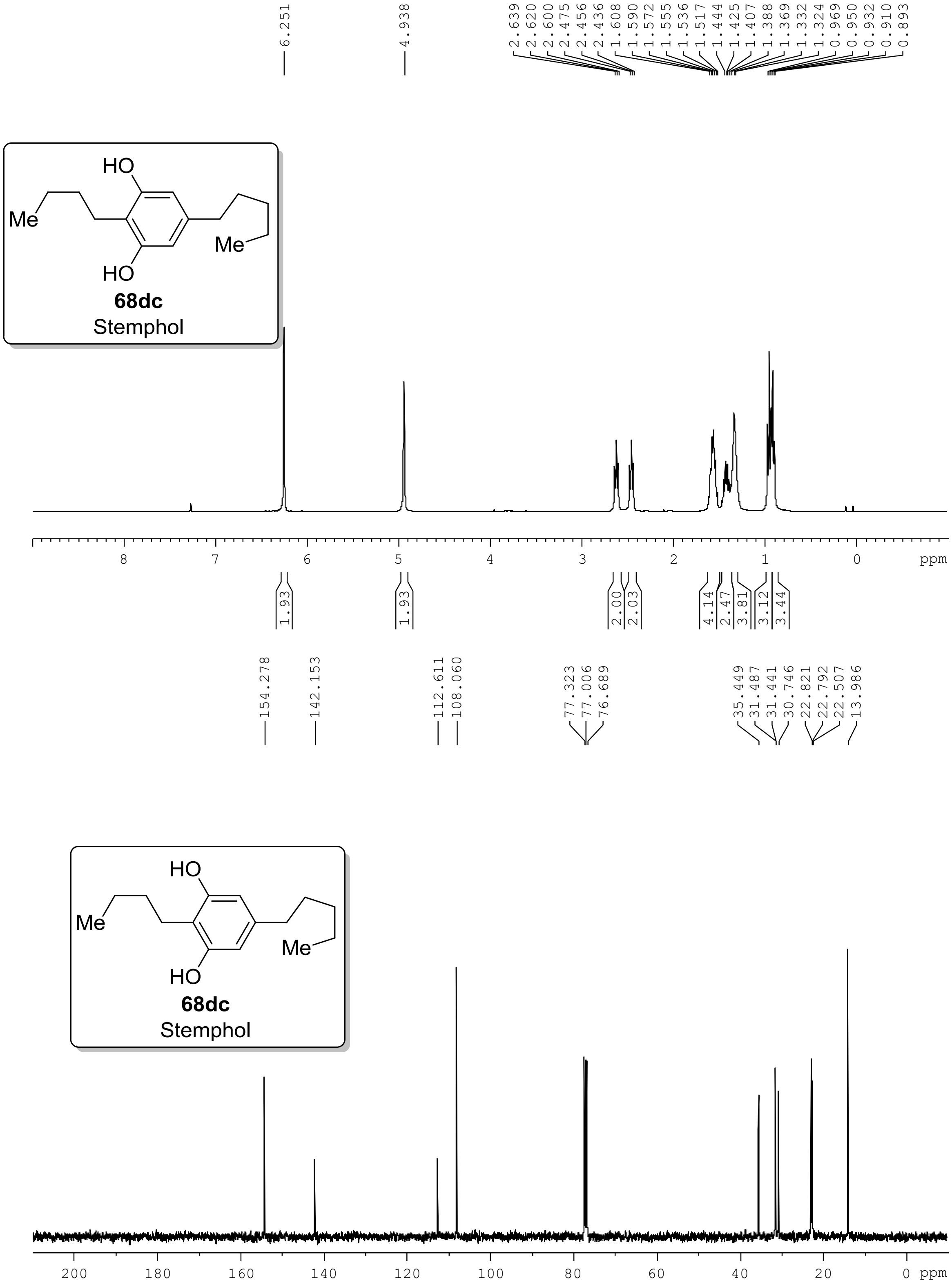


Figure-11: ^{1}H and ^{13}C NMR spectra of the product **68dc (**Stemphol).

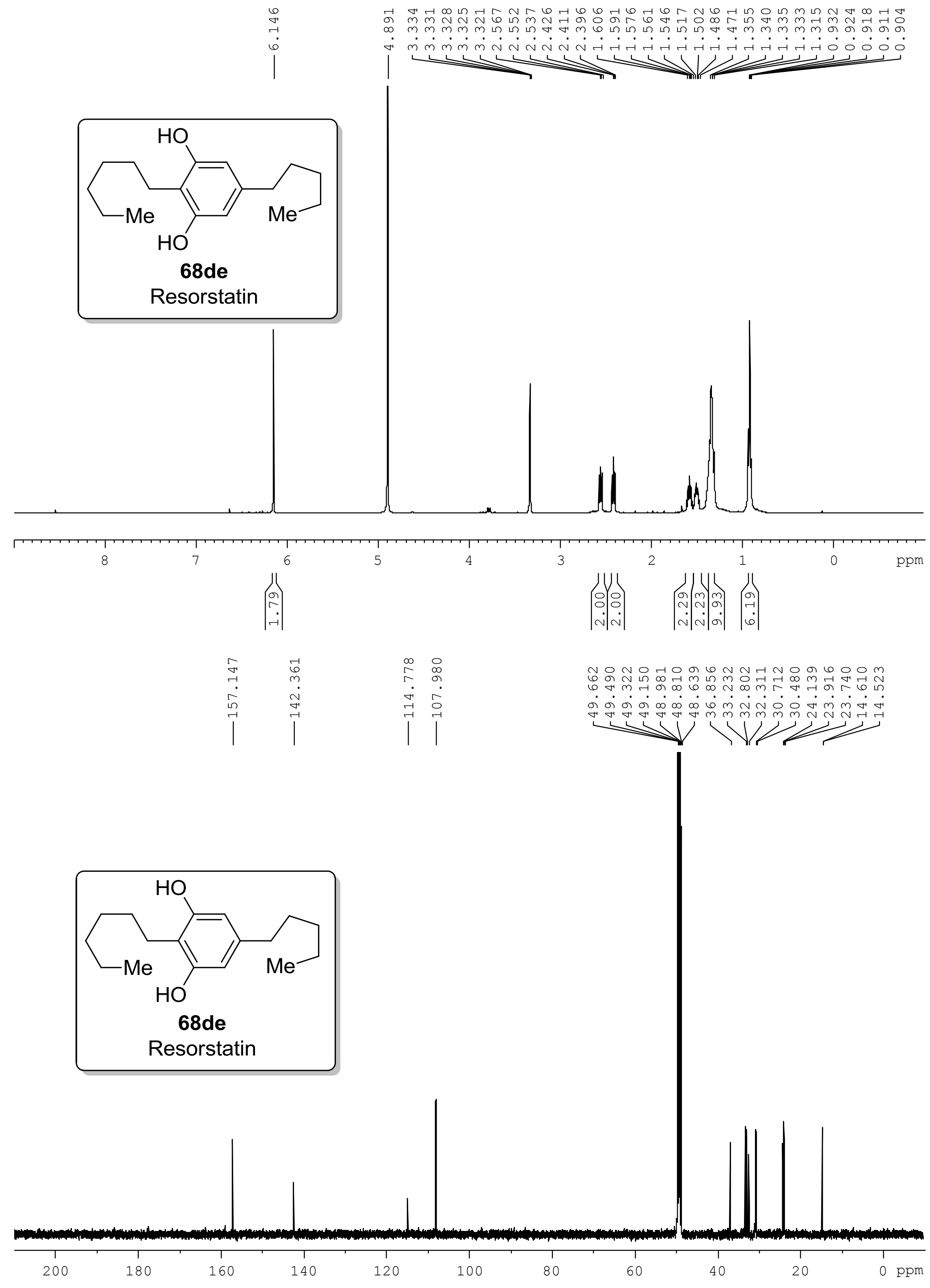


Figure-12: ^{1}H and ^{13}C NMR spectra of the product **68de** (Resorstatin).

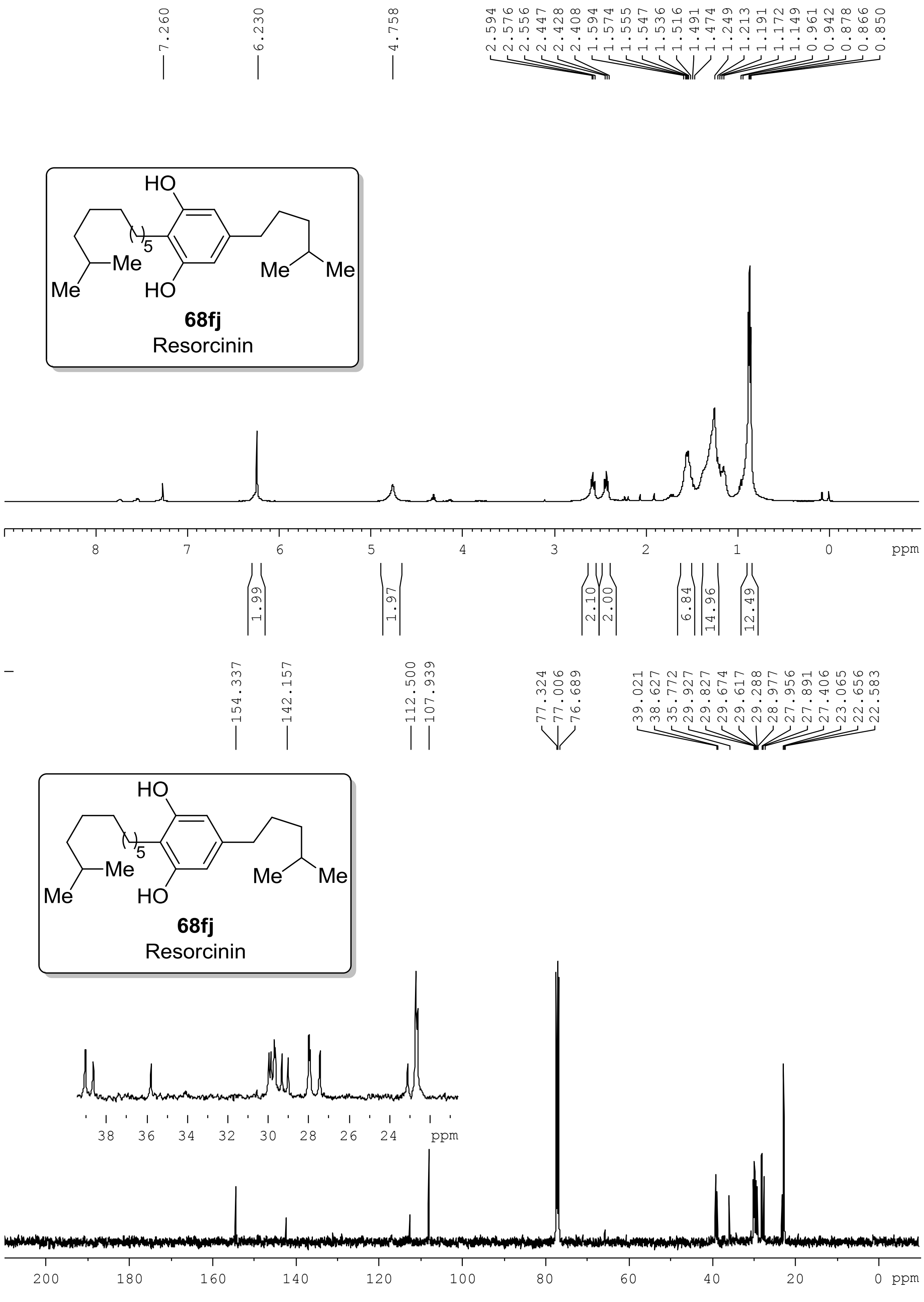


Figure-13: ^{1}H and ^{13}C NMR spectra of the product **68fj** (Resorcinin).

4. High-yielding Total Synthesis of Butenolide Natural Products and their Analogues through an Organocatalytic Reductive Coupling Reaction

4.1 Introduction

To develop a simple protocol by utilizing readily available starting materials and synthesizing a library of natural products, drugs and their analogues are challenging task for synthetic chemistry community.[37] The common drawbacks in the total synthesis of natural products and drugs are associated with multiple steps involving each step column purification, leading to increase in solvent consumption, harmful wastes and decrease in yield. Also for total synthesis of biologically important molecules to be industrially viable, use of toxic metal catalysts has to be avoided. Keeping these facts in mind, more attention has been devoted towards organocatalytic double domino, triple domino and quadruple domino sequential multi-step one-pot reactions. These sequential one-pot reactions can address the above cited problems by reducing the number of steps and thus minimizing the problems associated with it. That is why organocatalysis has been considered the green alternative route to the classical synthetic methods.[38] Even though there exist a considerable number of organo-catalytic asymmetric methods, only a few among them made their way into the total synthesis of natural products and their analogs.[39] Among the known organocatalytic reactions, Michael addition,[40] aldol,[41] Diels-Alder[42] and Friedel-Craft[43] reactions are the ones which have been repeatedly used in asymmetric total synthesis of natural products, drugs and drug intermediates.

Recently our laboratory discovered the organocatalytic reductive coupling (*OrgRC*) reaction is one of the recently developed organocatalytic selective *C*-alkylation protocol and it has been utilized by many other synthetic chemistry groups in total synthesis of natural products/drugs.[33-35] In our quest to develop organocatalytic methods and apply those methods in total synthesis, we choose a small library of natural products containing butenolide (3-

alkyl-5-methyl-2[5*H*] furanone) core as our synthetic target to synthesize through organocatalytic sequential one-pot manner.

Butenolides have attracted both isolation and synthetic chemists due to their broad range of bioactivities.[44] For example, butenolide **H** is a component in mushroom flavor,[44c] **I** show fungicidal activity,[44d] **J**, **K, M, N** and **O** are *Streptomyces griseus* metabolites,[44e] Ancepsenolide **X** has been known for its cytotoxicity and antimicrobial activity.[44b] Bullatacin **Q** is an effective cytotoxic acetogenin. (−)-Blastmycinolactol **R**, (+)-blastmycinone **S**, (−)-NFX-2 **T** and (+)-antimycinone **U** are polyketide metabolites and show antifungal and antitumor properties, **Z** and **Z'** are mosquito larvicides[44h] (Figure 14).

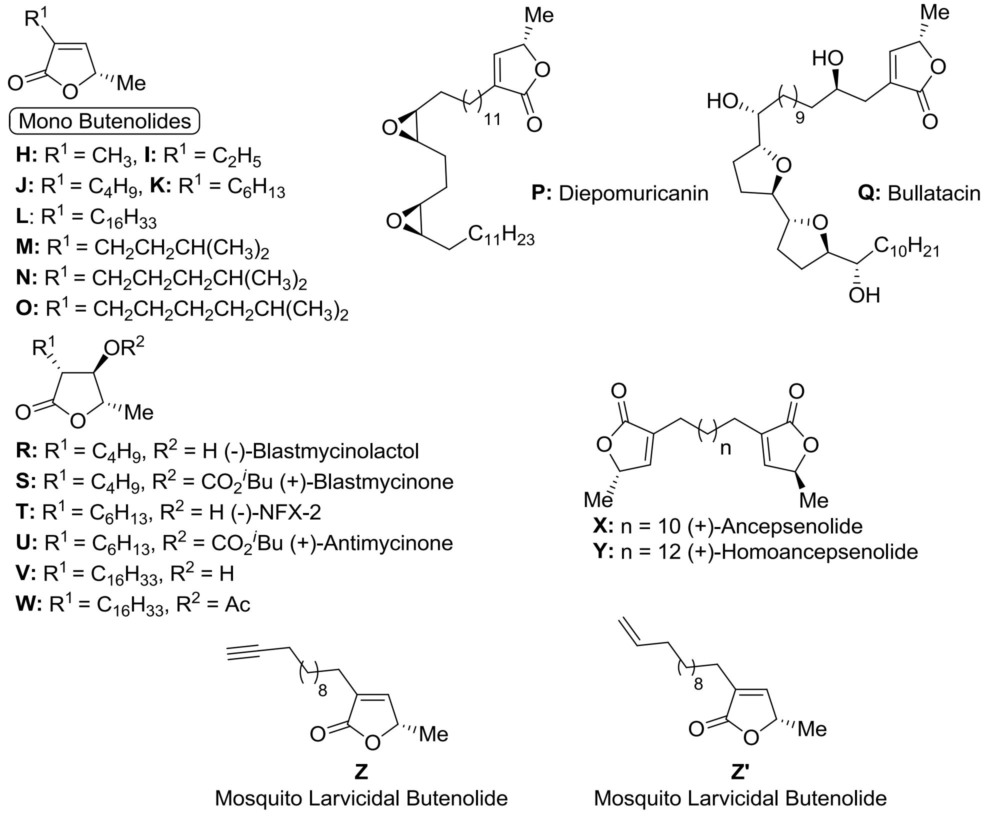
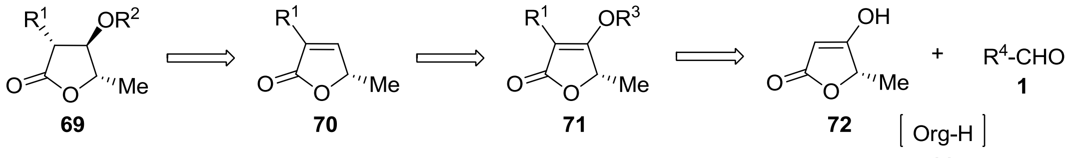


Figure 14. Examples of important butenolide natural products and their analogues.

4.2 Retrosynthetic Analysis

As outlined in Scheme 4, the alkylation at the 3-position of known chiral tetronic acid **72** can generate by using our organocatalytic reductive coupling (OrgRC) reaction, where an organic CH-acid **72** reacts with an aldehyde **1** to form olefin, which then reacts with an organic hydrogen donor such as Hantzsch ester **11a** in presence of proline **5a** as a catalyst (Scheme 4). The 3-alkylated chiral tetronic acid **71** is a potent precursor for synthesis of the butenolide natural products, followed by easily deoxygenating procedures.[45f,g]

Scheme 4. Retrosynthetic analysis.



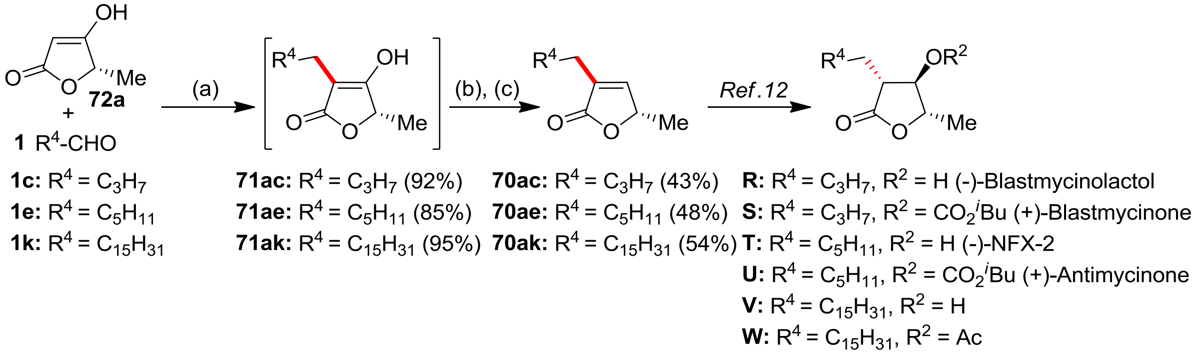
4.3 Results and discussion

α,β-unsaturated lactones are usually found in many natural products; in this context a family of δ-butenolide natural products have a broad spectrum of biological activities. Many groups already synthesized individual butenolide natural products using different methodologies in racemic and optically active form. [45] Herein, we synthesized six of natural products in butenolide family by using OrgRC reaction as the key step in the high yielding process through C-C bond formation.

Initially, we started the synthesis of monobutenolide natural products **J**, **K** and **L** from the chiral tetronic acid **72** and easily accessible alkyl aldehydes **1c**, **1e** and **1k**. The OrgRC reaction of tetronic acid **72** and aldehyde **1** in presence of Hantzsch ester **11a** and proline **5a**-catalyst afforded alkylated compounds **71** in excellent yields. Then, the enol hydroxyl group was activated by converting to the corresponding triflate followed by palladium catalyzed reduction for the preparation of monobutenolides **70** in excellent yields compared to the previous reports. [45]

To reduce the number of purification steps, we tried to carry out OrgRC followed by *O*-triflate reaction in one pot manner. Hence we preferred anhydrous CH_2Cl_2 as the solvent for OrgRC reaction which would also serve the purpose of the next step. The reaction of (*S*)-4-hydroxy-5-methylfuran-2(5H)-one **72a** with butyraldehyde **1c** and Hantzsch ester **11a** under 20 mol% of proline **5a** in anhydrous CH_2Cl_2 at 25 °C for 2-4 h furnished the (*S*)-3-alkyl-4-hydroxy-5-methylfuran-2(5H)-one **71ac** in very good conversion. After completion of OrgRC reaction, two equiv. of N,N-diisopropylethylamine (DIPEA) was added to the reaction mixture, followed by 1.5 equiv. of Tf_2O addition at -78 °C. After quenching the reaction with saturated NH_4Cl solution and work-up, the crude product was used directly for the deoxygenation reaction with $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP) and polymethylhydrosiloxane (PMHS) in DMF at 60 °C for 24 h to furnish desired monobutenolide **70ac** in 40% yield (overall three steps) (Scheme 5). The same reaction sequence was executed with two more different aldehydes **1e** and **1k**, the monobutenolides **70ae** and **70ak** were obtained in 41-52% overall yields. To our delight the reagents and by-products of OrgRC reaction did not affect the next reaction or the yield, but the final products **70ac** and **70ae** required careful column-chromatography to separate from Hantzsch ester pyridine.

Scheme 5. Synthesis of monobutenolides through sequential OrgRC/deoxygenation reactions.



Reagents and conditions: (a) **1** (1 equiv.), Hantzsch ester **11a** (1 equiv.) relative to the **72a**, Proline **5a** (20 mol%), DCM, rt, 2 to 4 h; (b) DIPEA (2 equiv.), Tf_2O (1.5 equiv.), DCM, −78 °C, 1 h, *aq*. workup; (c) $Pd(OAc)_2$ (10 mol%), DPPP (10 mol%), PMHS (2 equiv.), DMF, 60 °C, 8 to 24 h.

Monobutenolides **70ac**, **70ae** and **70ak** are itself having their own biological activity and also used as intermediates in the expeditious synthesis of antifungal and antitumor polyketide metabolites. (*S*)-3-butyl-4-hydroxy-5-methylfuran-2(5H)-one **70ac** is a potent precursor for synthesizing the (−)-blastmycinolactol **R** and (+)-blastmycinone **S** following the reported procedures.[45d] Following the same procedure (−)-NFX-2 **T** and (+)-antimycinone **U** can be obtained from butenolide **70ae** as shown in literature procedure. In a similar manner, natural products **V** and **W** were synthesized by using **70ak** as starting material. Overall, our method represents high-yielding formal total synthesis of these natural products **R**-**W** *via* OrgRC reaction as the key step.

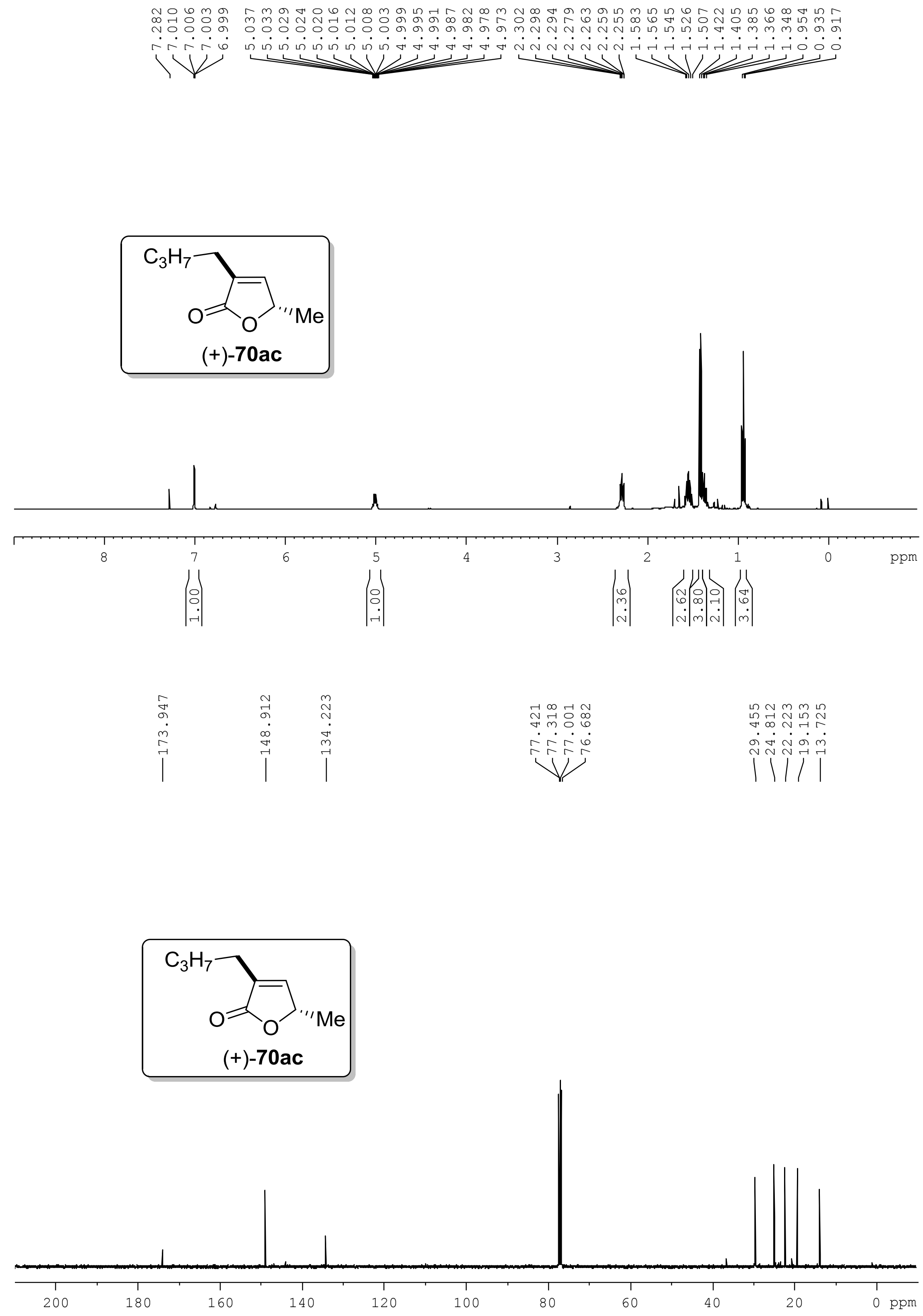


Figure-15. ^{1}H and ^{13}C NMR spectra of the product (+)-**70ac**.

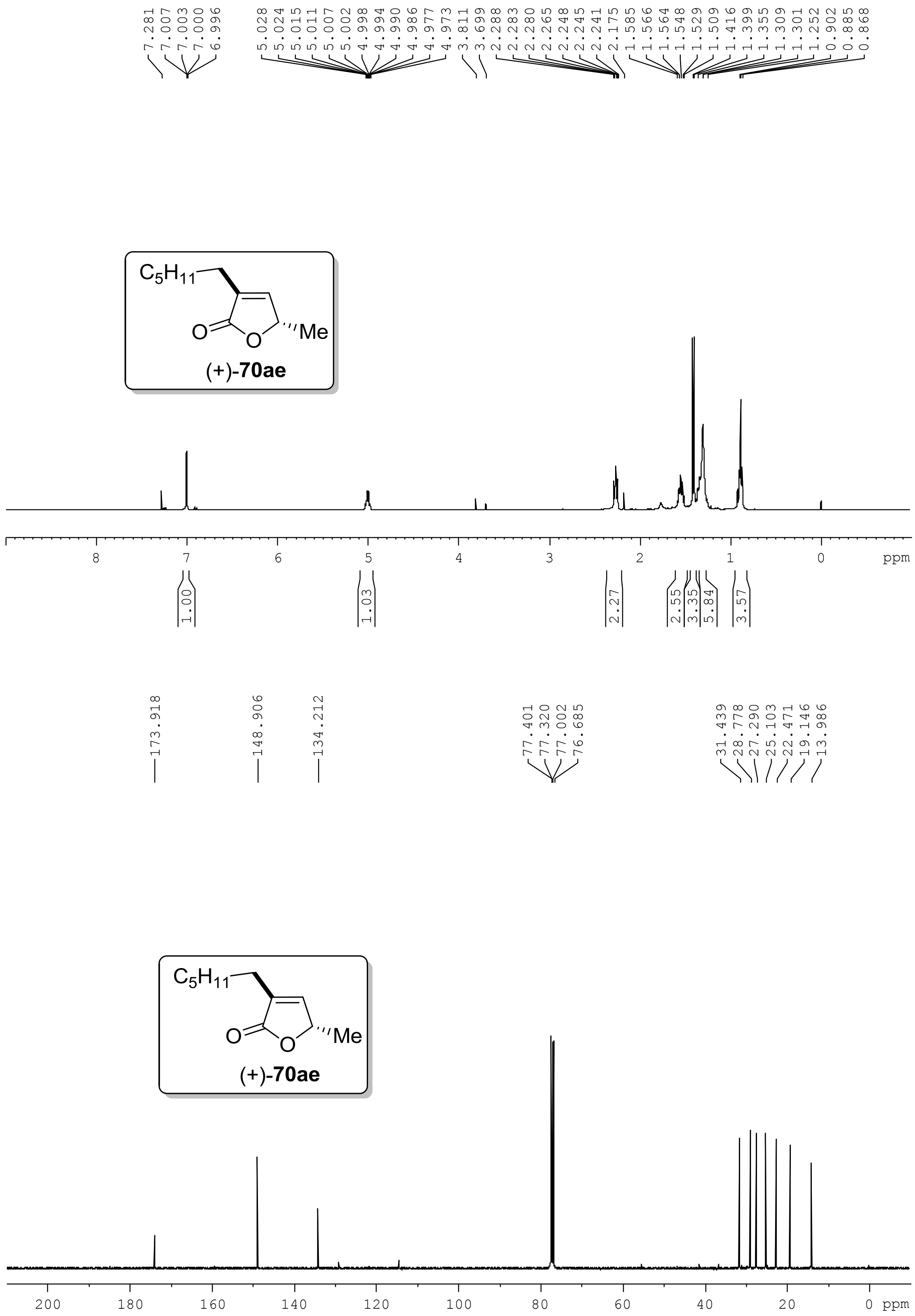


Figure-16. ^{1}H and ^{13}C NMR spectra of the product (+)-**70ae**.

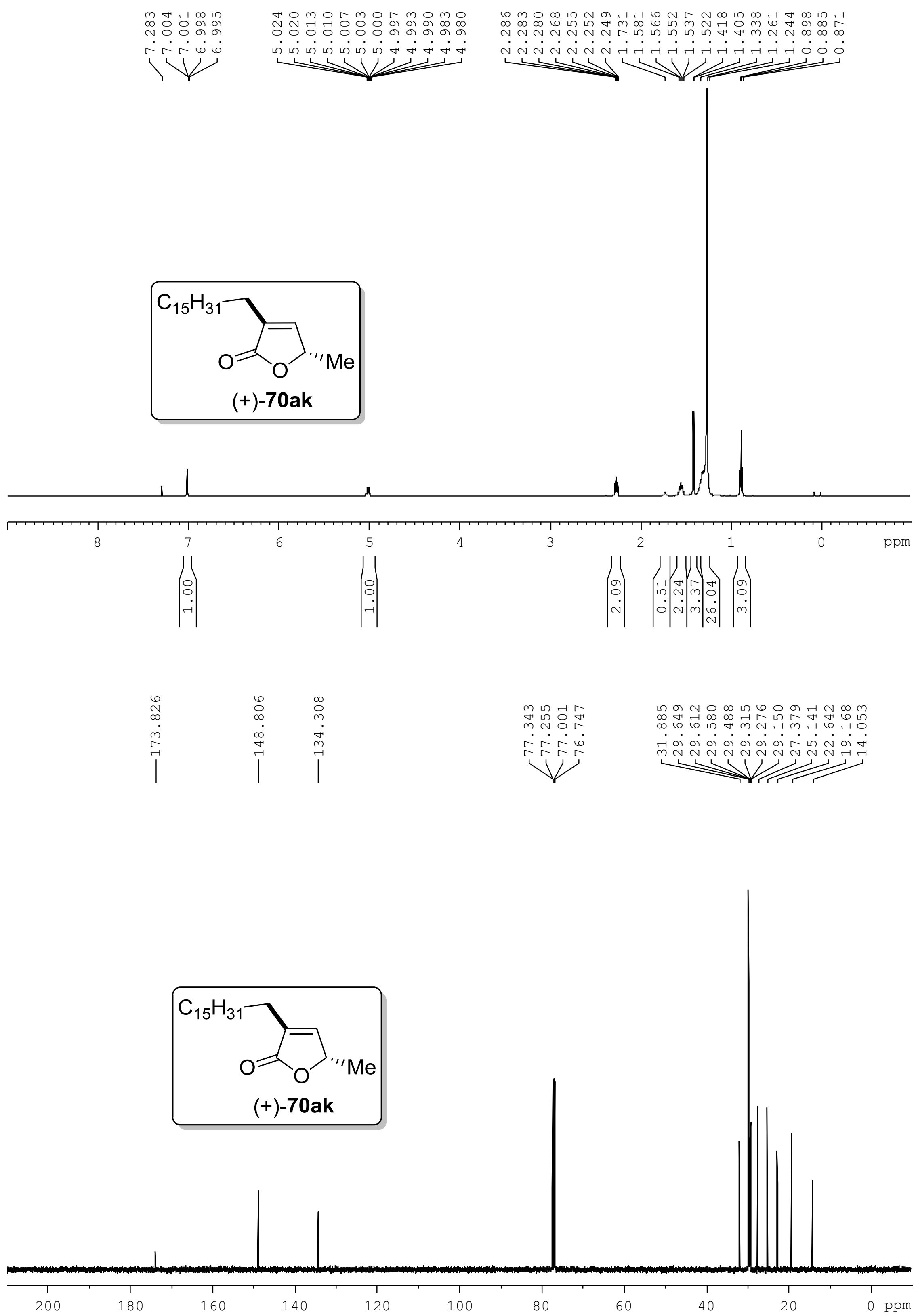
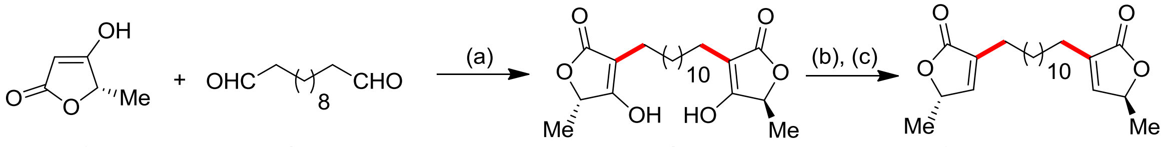


Figure-17. ^{1}H and ^{13}C NMR spectra of the product (+)-**70ak**.

Our next target was to synthesize (+)-ancepsenolide **X** (isolated from gorgonian *Pterogorgia anceps)*, an important *bis*-butenolide annonaceae acetogenin. The required 1, 12-dodecanal **1l** was obtained from 1, 12-dodecanol by PCC oxidation in quantitative yield. This was subjected to OrgRC reaction with chiral tetronic acid **72a**, Hantzsch ester **11a** and catalyst proline **5a**. The reaction of **1l** with 2 equivalents of tetronic acid **72a,** 2 equivalents of Hantzsch ester **11a** in anhydrous DCM under the proline **5a** (20mol %) catalysis furnished the *bis*-alkylated product **71al** in >99% conversion. Interestingly compound **71al** was highly polar and insoluble in the reaction solvent DCM. After completion of the reaction, the solvent was evaporated and the crude solid material was dried and used for the next step as such. Following similar deoxygenation reaction sequence as above, (+)-Ancepsenolide **70al** was obtained in a satisfactory yield of 55% in overall three steps (Scheme 6).

Scheme 6. Total synthesis of (+)-Ancepsenolide.



72a **1l** **71al** **70al:** (+)-Ancepsenolide

Reagents and conditions: (a) **72a** (2 equiv.), Hantzsch ester **11a** (2 equiv.) relative to the **1l**, Proline **5a** (20 mol%), DCM, rt, 6 h; (b) DIPEA (2 equiv.), Tf_2O (1.5 equiv.), DCM, –78 °C, 1 h, *aq*. workup; (c) $Pd(OAc)_2$ (10 mol%), DPPP (10 mol%), PMHS (2 equiv.), DMF, 60 °C, 8 to 24 h, 55% overal yield in three steps.

Further, we also accomplished the synthesis of the (+)-homoancepsenolide **Y** following the OrgRC/O-triflate and deoxygenation reactions in sequential manner, but unfortunately desired *bis*-butenolide **70am** was isolated in poor yield. Hence we followed Pashkovskii's[45f] approach to deoxygenated product, by converting **71am** into the corresponding enamine derivative followed by the cleavage of amine moiety to get required (+)-Homoancepsenolide **70am** in 39% with satisfactory overall yield (Scheme 7).

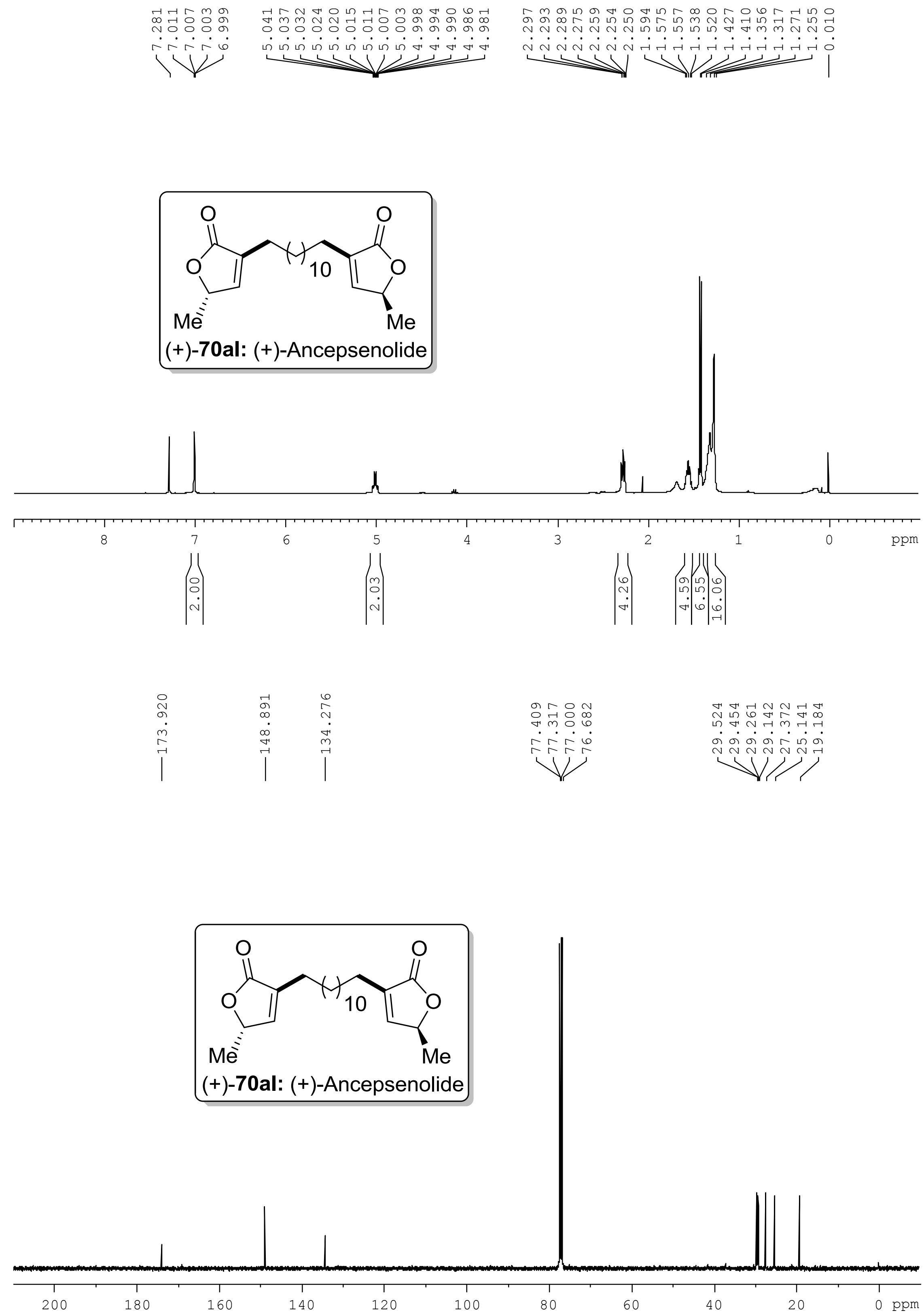


Figure-18. ^{1}H and ^{13}C NMR spectra of the product (+)-**70al** **[(+)**-Ancepsenolide].

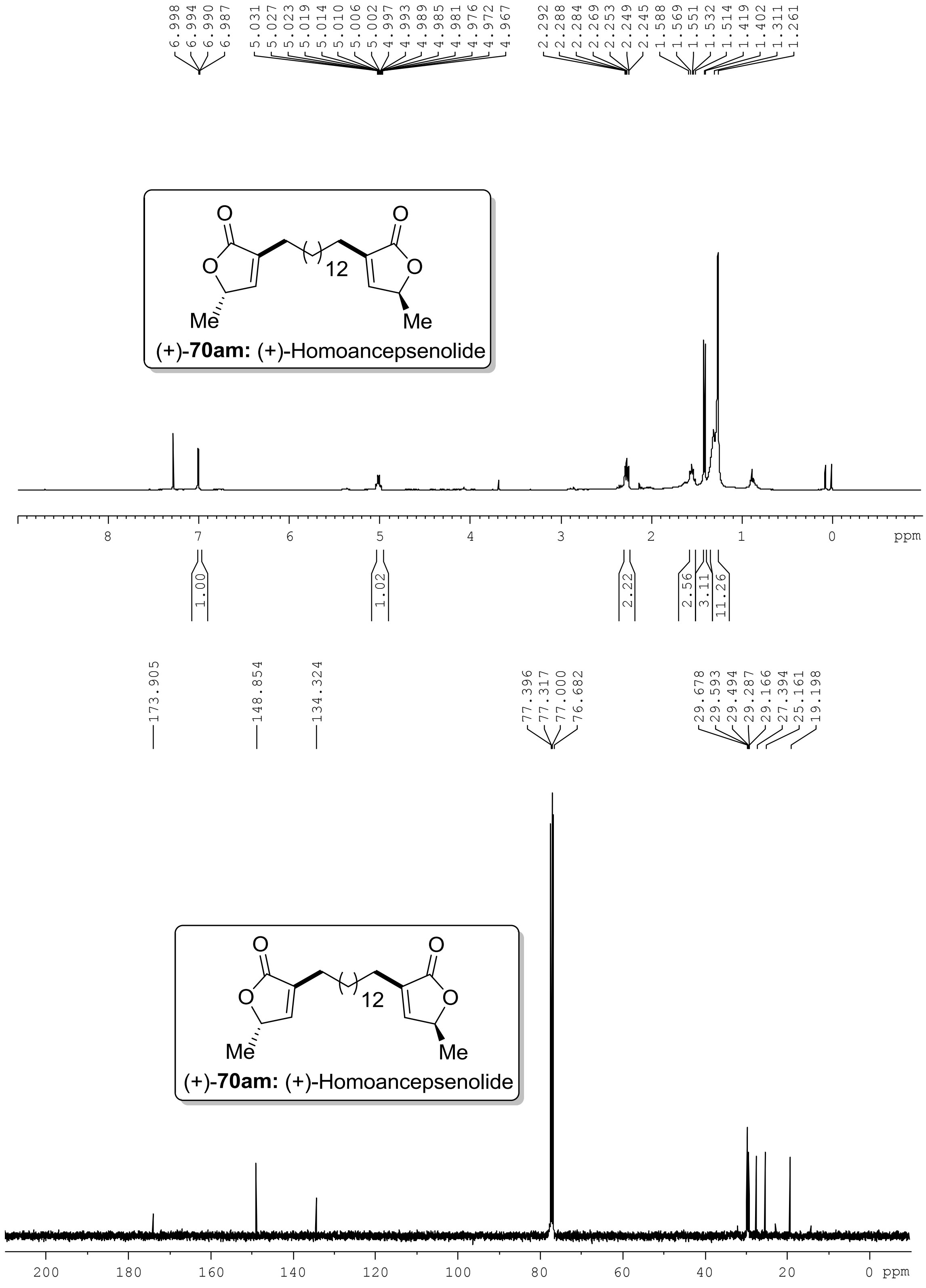
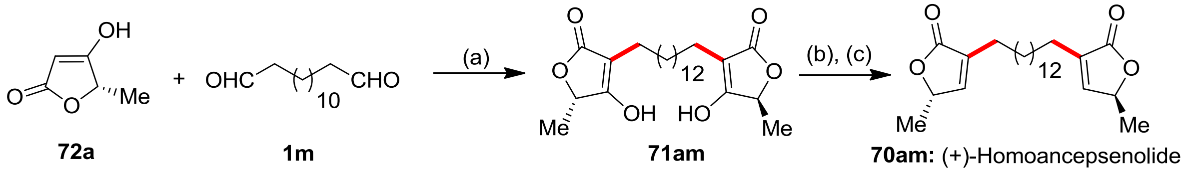


Figure-19. ^{1}H and ^{13}C NMR spectra of the product (+)-**70am** **[**(+)-Homoancepsenolide].

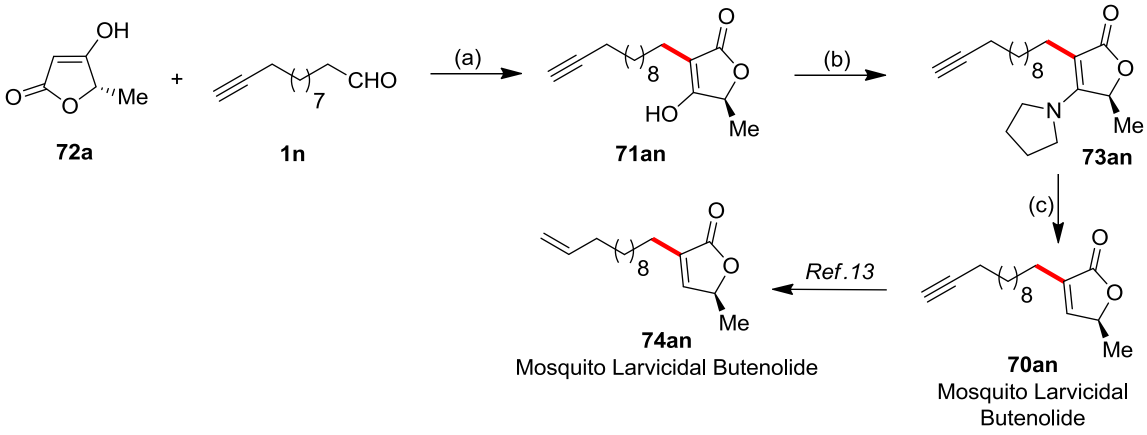
Scheme 7. Total synthesis of (+)-Homoancepsenolide.



Reagents and conditions: (a) **72a** (2 equiv.), Hantzsch ester **11a** (2 equiv.) relative to the **1m**, Proline **5a** (20 mol%), DCM, rt, 6 h, 76% yield; (b) Pyrrolidine (1.5 equiv.), *p*-TSA (20 mol%), Toluene, reflux, 15 h, 67% yield; (c) i. $NaBH_3CN$ (5 equiv.), MeOH, 2N HCl, rt, 15 h, *aq*. Work-up, ii. SiO_2 (2 equiv.), Toluene, reflux, 7 h, 76% yield in 2 steps.

The above results encouraged us to apply OrgRC reaction for the synthesis of Butenolide **Z**, an important natural product showing significant mosquito larvicidal property (LC_{50} = 0.41 ppm), along with its partially reduced counterpart **Z'** (LC_{50} 0.47 ppm).[44e] The required aldehyde **1n** was prepared from 1, 10-decanediol in five simple steps. Tetronic acid **72a** and aldehyde **1n** were subjected to an OrgRC reaction condition under the proline catalysis in DCM, and furnished the expected alkylated product **71an** in 90% yield. In our efforts to get the required deoxygenated product **70an**, we followed the Pashkovskii's approach, the desired OrgRC product **71an** was converted into the corresponding enamine derivative **73an** followed by reducing the conjugated double bond and the elimination of amine moiety to get required butenolide **70an** in 29% overall yield (Scheme 8). Another important mosquito larvicide natural product **74an** is the partially reduced counterpart of **70an** and can be obtained by simple functional group transformation.[46]

Scheme 8. Total Synthesis of Mosquito Larvicidal Butenolides.



Reagents and conditions: (a) **72a** (1 equiv.), Hantzsch ester **11a** (2 equiv.) relative to the **1n**, Proline **5a** (20 mol%), DCM, 12 h, rt, 90% yield; (b) Pyrrolidine (1.5 equiv.), *p*-TSA (20 mol%), Toluene, reflux, 16 h, 85% yield; (c) i. $NaBH_3CN$ (5 eq), MeOH, 2N HCl, 15 h, rt, *aq*. Work-up, ii. SiO_2 (2 equiv.), Toluene, reflux, 7 h, 38% yield in 2 steps.

4.4 Conclusions

In conclusion, we have developed a common methodology for the high-yielding total synthesis of important butenolide natural products, from readily available simple substrates through the organocatalytic reductive coupling reaction as the key step. This high yielding protocol is an ideal method to synthesize the entire family of butenolide natural products.

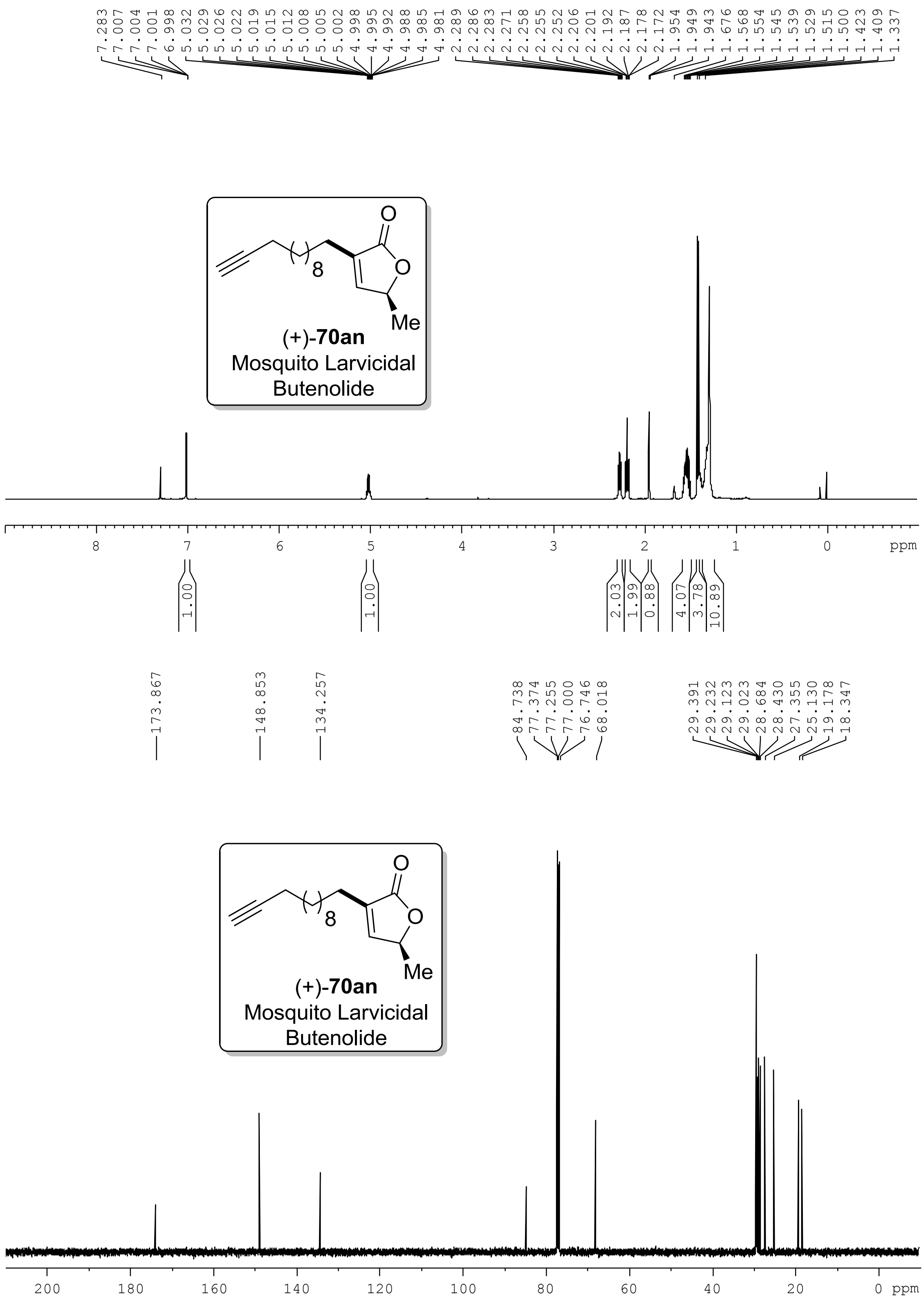
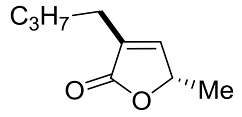


Figure-20. ^{1}H and ^{13}C NMR spectra of the product **(+)-70an** Mosquito Larvicidal Burenolide.

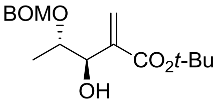
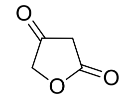
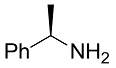
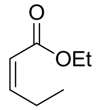
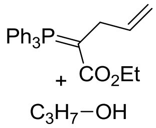
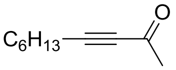
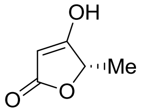
ANNEXURE-I: *Isolation and Yield Comparative Tables of Butenolide Natural Products.*

***Isolation of C-4 Butenolide*:**[44a]

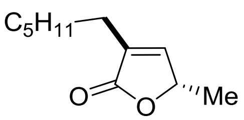


J

Butenolide, (*S*)-3-butylyl-5-methyl-2[5*H*]furanone is metabolite from *streptomyces griseus.*

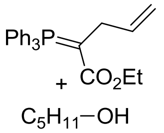
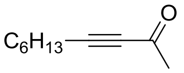
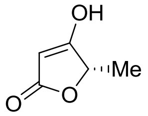
Reference	Starting material	Number of steps	Overall yield	α^D_{25}
Bernardi *et al*. J. Org. Chem, 1985		2 steps	Isolated yield unknown	+11.7 (c 0.16, $CHCl_3$)
Nishide *et al*. Tetrahedron 1994		4 steps	53%	+79.2 (c 1.18, $CHCl_3$)
Tsunoda *et al*. Tetrahedron Lett. 2000		7 steps	11%	Racemic
Yan-Tao He *et al.* Tetrahedron 2002		3 steps	69%	+44.3 (c 1.24, $CHCl_3$) with 82% ee
Amonkar *et al*. Synthesis 2005		3 steps	40%	Racemic
Ferrarini *et al*. Tetrahedron Lett. 2010		3 steps	51% 94% ee	–
Present OrgRC method		3 steps	40%	+ 36.1 (c 0.28, $CHCl_3$)

Isolation of C-6 Butenolide:

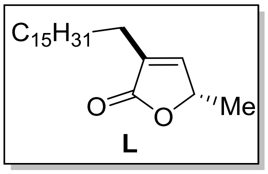


K

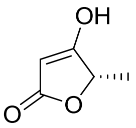
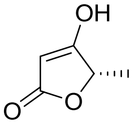
Butenolide, (*S*)-3-hexyl-5-methylfuran-2(5*H*)-one is metabolite from *streptomyces griseus*.

Reference	Starting material	Number of steps	Overall yield	α^{D}_{25}
Amonkar *et al*. Synthesis 2005		3 steps	49.6%	Racemic
Ferrarini *et al*. Tetrahedron Lett. 2010		3 steps	51.8% 96% ee	–
Present OrgRC method		3 steps	39.7%	+ 24.9 (c 0.28, $CHCl_3$)

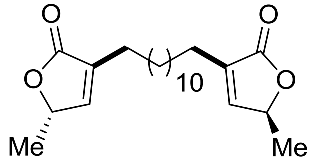
Isolation of C-16 Butenolide:[44i]


L

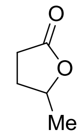
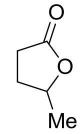
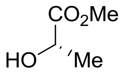
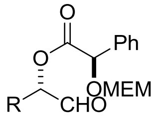
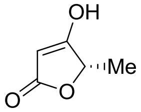
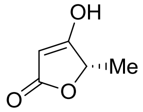
C-16 butenolide was first isolated from gorgonian *pterogorgia* spp. in 2006 by Lorenzo *et al.* and its enantiomer was isolated from gorgonian *pterogorgia anceps* in 1999 by Guo *et al.* Prior to its isolation C-16 butenolide was reported by Ortuno *et al.* who isolated it as an intermediate while attempting to synthesize 3,4,5-trisubstituted furanones.

Reference	Starting material	Number of steps	Overall yield	α^{D}_{25}
Ortuno *et al*. Tetrahedron, 1988		4 steps	25.4%	+ 26.7 (c 1.3, dioxane)
Present OrgRC method		3 steps	52.1%	+ 24.85 (c 0.5, $CHCl_3$)

Isolation of Ancepsenolide:[44b]

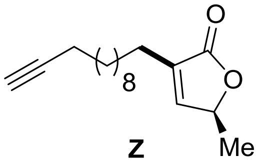

X (+)-Ancepsenolide

(+)-Ancepsenolide was isolated from gorgonian *pterogorgia anceps*, a marine organism in 1966. Later in 1971, Schimtz *et al.* isolated it from another gorgonion *pterogorgia* *guadalupensis* and in 1994 Rodriguez *et al*. reported its isolation from *pterogorgia citrina.*

Reference	Starting material	Number of steps	Overall yield	$\alpha^{D}{}_{25}$
Podraza, *et al.* J. Nat. Pro., 1985		4 steps	19%	Racemic
Larson, *et al*. J. Org. Chem., 1985		3 steps	77%	Racemic
Trost and Muller J. Am. Chem. Soc., 1994 J. Am. Chem. Soc., 1995		7 steps	31%	+39.6 (c 0.4, $CHCl_3$) +13.2 (c 2.8, $CHCl_3$)
Takai and Iriye Bio. Bio. Bio., 2001		3 steps	10%	+20.0 (c 0.1, $CHCl_3$)
Ghobril *et al*. Eur. J. Org. Chem., 2011		4 steps	12%	+45.53 (c 0.43, $CHCl_3$)
Present OrgRC method		3 steps	55%	+30.5 (c 0.12 , $CHCl_3$)

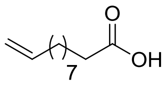
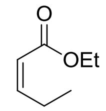
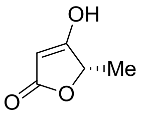
Isolation of Larvicidal Butenolides:[44h]

Butenolides **Z** was isolated by Ratnayake *et al.* in 2001 from three species of *Hortonia genus* and known to exhibit mosquito larvicidal activity.



Z

Mosquito Larvicidal Butenolide

Reference	Starting material	Number of steps	Overall yield	$\alpha^{D}{}_{25}$
Jiang *et al*. Chinese J. Chem, 2002		10 steps	7.6%	+ 30.6 (c 0.5, $CHCl_3$)
Yan-Tao He *et al*. Tetrahedron 2002		3 steps	46.4%	+ 30.3 (c 0.4, $CHCl_3$)
Present OrgRC method		4 steps	29%	+30.6 (c = 0.1, $CHCl_3$)

Part-B

5. Observation of Neighboring Group Participation in Organocatalytic Asymmetric Sequential Michael-lactonization/dehydration Reactions: Synthesis of Highly Substituted Chiral Spirodihydrocoumarins

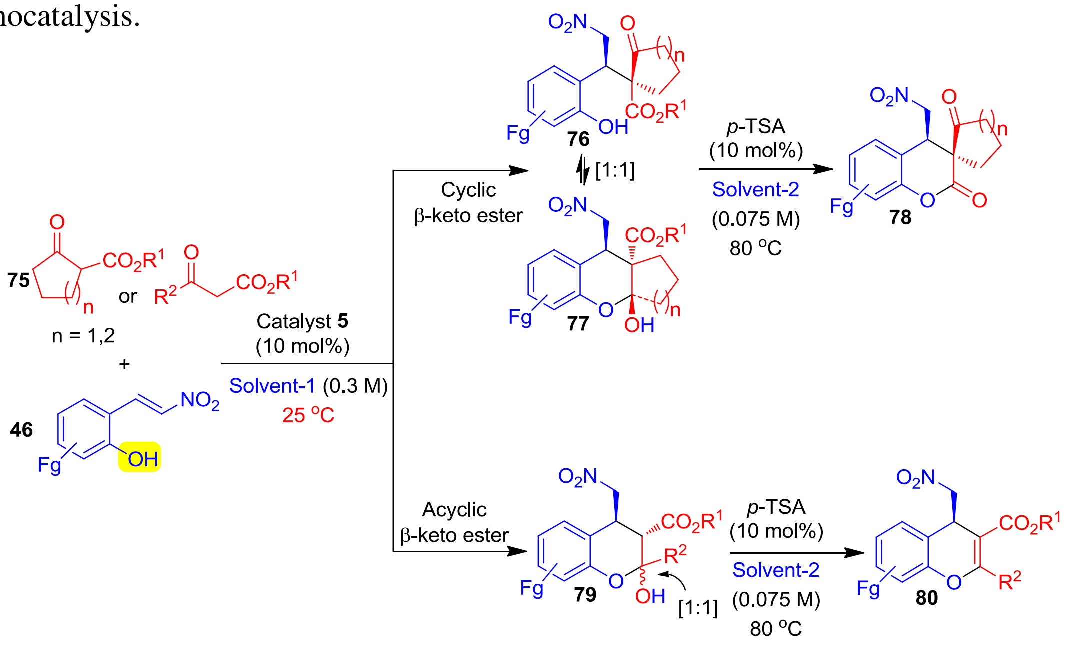
5.1 Introduction

Despite rapid progress in asymmetric organocatalytic sequential one-pot reactions,[47] mimicking cellular and highly efficient asymmetric sequential one-pot approaches remain in high demand. An ideal asymmetric sequential one-pot multi-catalysis reaction would be atom-economical, high substrate scope, rapid, performed under the mild conditions to yield quantitative and enantiomerically pure drug-like products with vast library of catalysts and substrates. Recently the organocatalytic aldol, Michael, Mannich or Diels-Alder reactions are become triggering reaction with a combination of other reactions like Michael, Henry, alkylation, amination, aldol, epimerization or acetalization in a sequential one-pot manner for the synthesis of complex chiral molecules.[48] Even though the development of new and highly efficient cellular-type organocatalytic sequential one-pot approaches based on the high-yielding asymmetric reactions to drug-like molecules is significant. Herein, we proposed a supramolecular organocatalysis from an unusual efficient neighboring group induced asymmetric organocatalytic sequential one-pot reaction for the synthesis of drug-like chiral spirodihydrocoumarins and chromenes from simple substrates and catalysts by using sequential Michael-lactonization/dehydration reactions.

The supramolecular organocatalysis is a new tool, where the covalent and weak interactions among the catalyst and substrates get involved to construct a stable *pre*-transition state (*pre*-TS) through the supramolecular assembly for high asymmetric induction. In this regard, we attempted sequential one-pot reactions for the synthesis of chromanes, creaminess and coumarins in a highly enantioselective manner through asymmetric supramolecular organocatalysis.

3,4-Dihydrocoumarins, chromanes and chromenes are important classes of heterocyclic cores found in many natural products and are widely used as drug intermediates and ingredients in pharmaceuticals.[49] Therefore, high-yielding asymmetric syntheses of these heterocycles have been extensively studied in recent years and provided many efficient methods.[50] Recently, our group, Enders *et al*., Gong *et al*., and Hong *et al*. have developed independently an organocatalytic Michael-acetalization-oxidation/reduction reaction sequence for the efficient synthesis of chromanes, chromenes and 3,4-dihydrocoumarins in a highly enantioselective manner.[51] However, there is no suitable asymmetric method to prepare spirodihydrocoumarins in enantiomerically pure form with more functional diversity. As a continuation of our research in this area and also utilizing the weak interactions between catalyst and substrates in the transition state, we envisaged (*E*)-2-(2-nitrovinyl)phenols and *β*-keto esters as the potential substrates for a newly designed Michael-lactonization (*M-L*) or Michael-dehydration (*M-D*) reaction under supramolecular organocatalysis (Scheme 9).[52]

Scheme 9. Design of sequential asymmetric M-L reaction through supramolecular organocatalysis.



As our group is working on the development of supramolecular organocatalysis for the synthesis of drug-like compounds,[53] herein we propose that medicinally important spirocyclic dihydrocoumarins **78** with a quaternary stereocenter and chromenes **80** could be constructed through newly designed neighboring group induced asymmetric sequential Michael-lactonization (*M-L*)/dehydration (*M-D*) reactions between *β*-keto esters **75** and (*E*)-2-(2-nitrovinyl)phenols **46** with suitable organocatalysts **5** followed by *p*-TSA-catalysis (Scheme 9).

As we were interested to investigate the role of weak interactions in the transition state called *pre*-TS supramolecular assembly in organocatalytic asymmetric reactions, we decided to explore the 2-(2-nitrovinyl)phenols **46** as Michael acceptor in an amine-catalyzed *M-L* reaction with *β*-keto-esters **75**.[54] Initially we started with cyclic *β*-keto esters, herein we expected that the reaction of 2-(2-nitrovinyl)phenol **46a** with *in situ* generated enolate from *β*-keto-ester **75a** under the standard reaction conditions would lead to Michael adduct **76aa** with high *ee*. However, Michael adduct **76aa** was not detected alone and instead it has shown the existence of fast dynamic equilibrium with lactol **77aa** with high *ee* under the modified conditions. This unexpected result represents a novel methodology for the preparation of **76/77** and a new reactivity for amine-catalysts. Herein, we report our findings regarding these new sequential reactions.

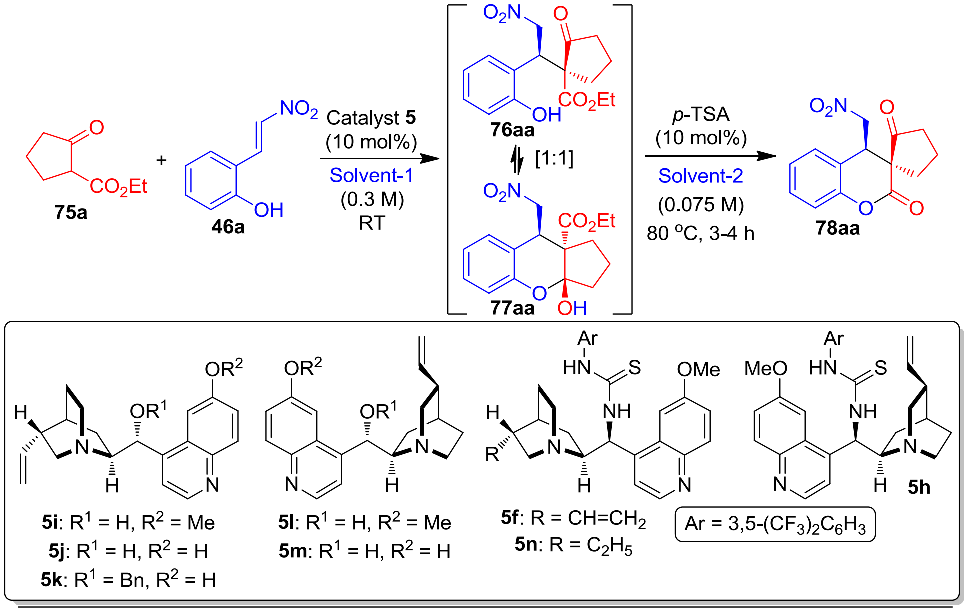
5.2 Results and Discussion

5.2.1 Reaction optimization for the cascade M-L reaction of 75a and 46a:

For the optimization of designed M-L reaction, we screened a number of organocatalysts for the reaction of 2-(2-nitrovinyl)phenol **46a** with 1.3 equiv. of *β*-keto-ester **75a** and some important results are shown in Table 1. Interestingly, reaction of **46a** with 1.3 equiv. of **75a** under 10 mol% of quinine **5i**-catalysis in toluene at 25 °C for 24 h furnished the 1:1 ratio of **76aa** and **77aa** in 90% yield with only 31% *ee* and >99% *de* (Table 3, entry 1). *For the clear understanding of diastereoselectivity and also for the clear HPLC separation, we transformed the quickly filtered products **76aa/77aa** into easily separable and also very important spirodihydrocoumarin cis-**78aa** with 70-76% yield via p-TSA-catalyzed lactonization in toluene or DCE at 80 °C for 3-4 h (Table 3).* In a further optimization, reaction of **75a** and **46a** in DCE under 10 mol% of quinine **5i**-catalysis at 25 °C for 24 h followed by *p*-TSA-catalyzed lactonization in DCE at 80 °C for 3-4 h furnished the product cis-**78aa** in 70% yield with only 51% *ee* and >99% *de* (Table 3, entry 3). Interestingly, reaction of **75a** with **46a** in DCE under 10 mol% of HO-Q-OH **5j**-catalysis at 25 °C for 8 h furnished the products **76aa/77aa** in 95% yield, which on further lactonization with *p*-TSA-catalysis furnished the product cis-(+)-**78aa** in 70% yield with 61% *ee* and >99% *de* (Table 1, entry 6). Same reaction under 10 mol% of HO-Q-OBn **5k**-catalysis in DCE for 14 h furnished the products **76aa/77aa** in 95% yield, which on further lactonization with *p*-TSA-catalysis furnished the spirodihydrocoumarin cis-(+)-**78aa** in 76% yield with 85% *ee* and >99% *de* (Table 3, entry 7). In a further optimization, sequential M-L reaction of **75a** with **46a** in DCE under 10 mol% of HO-QD-OH **5m**-catalysis at 25 °C for 8 h furnished the products **76aa/77aa** in 95% yield, which on further lactonization with *p*-TSA-catalysis in DCE furnished the product cis-(−)-**78aa** in 70% yield with 91% *ee* and >99% *de* (Table 3, entry 8). Correlation of these results with simple (2-nitrovinyl)benzene reveals that the outcome of product selectivity and reactivity is controlled by neighboring group (O-H) interaction in the transition state along with catalyst.[54b]

To further improve the asymmetric sequential M-L reaction, especially for decreasing the reaction time to <5 h and increasing the *ee*/*de* to >99%, for the first time we tested the M-L reaction of **75a** and **46a** catalyzed by quinine-NH-thiourea catalysts **5f/5n**[55] followed by *p*-TSA-catalysis. Interestingly, sequential M-L reaction of **75a** with **46a** in DCM under 10 mol% of quinine-N*H*-thiourea **5f**-catalysis at 25 °C for 3 h furnished the products **76aa/77aa** in 98% yield, which on further lactonization with *p*-TSA-catalysis furnished the cis-(−)-**78aa** in 75% yield with >99.9% *ee* and >99% *de* (Table 3, entry 9). After achieving the successful result with **5f** as catalyst, we further showed interest to screen alkaloid based primary amine thioureas like **5n** and **5h** as the catalysts for M-L reaction to monitor the outcome of reaction rate and selectivity (Table 3, entries 10-11). Results from sequential M-L reaction of **46a** with 1.3 equiv. of **75a** in DCM under 10 mol% of **5n**- or **5h**-catalysis followed by lactonization are not superior as compared to **5f**-catalysis (Table 3, entries 10 & 11). Then we proceeded to M-L reaction with **75b**, produced the desired product cis-(−)-**78aa** decreasing in yield to 62% with 98% *ee* and >99% *de* (Table 3, entry 12). Finally, we envisioned the optimized condition to be 25 °C in DCM under 10 mol% of quinine-N*H*-thiourea **5f**-catalysis followed by *p*-TSA induced lactonization to furnish the spirodihydrocoumarin cis-(−)-**78aa** in 75% yield with >99.9% *ee* and >99% *de* (Table 3, entry 9). With the optimal reaction conditions in hand, further M-L reaction was performed in cascade one-pot manner to furnish the product cis-(−)-**78aa** with reduced yield and *ee* as shown in entry 13, Table 3. Structure and absolute stereochemistry of M-L products **76aa/77aa** and **78aa** was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (−)-**78aa** as shown in Figure 22.[56]

Table 3. Optimization for the sequential M-L reactions with cyclic β-keto ester.



Entry	Catalyst 5 (10 mol%)	Solvent-1 (0.3 M)	Time (h)	Solvent-2 (0.075 M)	Yield (%)[a] **76aa/77aa**	Yield (%)[b] **78aa**	ee (%)[c] **78aa**	de (%)[c] **78aa**
1	**5i**	Toluene	24	Toluene	90	70	–31	>99
2	**5l**	Toluene	24	Toluene	90	73	38	>99
3	**5i**	DCE	24	DCE	95	70	–51	>99
4	**5l**	DCE	24	DCE	95	73	47	>99
5	**5i**	DCM	20	DCE	98	70	–49	>99
6	**5j**	DCE	8	DCE	95	70	–61	>99
7	**5k**	DCE	14	DCE	95	76	–85	>99
8	**5m**	DCE	8	DCE	95	70	91	>99
9	**5f**	**DCM**	**3**	**DCE**	**98**	**75**	**>99.9**	**>99**
10	**5n**	DCM	4	DCE	90	60	97	>99
11	**5h**	**DCM**	**3**	**DCE**	**98**	**75**	**–98**	**>99**
12[d]	**5f**	**DCM**	**10**	**DCE**	**99% conv.**	**62**	**98**	**>99**
13[e]	**5f**	**DCM**	**3**	**DCE**	**99% conv.**	**70**	**91**	**>99**

[a] Yield refers to the quickly filtered product. [b] Yield refers to the column-purified product. [c] ee and de determined by CSP HPLC analysis. [d] Reaction performed with methyl 2-oxocyclopentanecarboxylate **75b**. [e] Reaction performed in a cascade one-pot manner

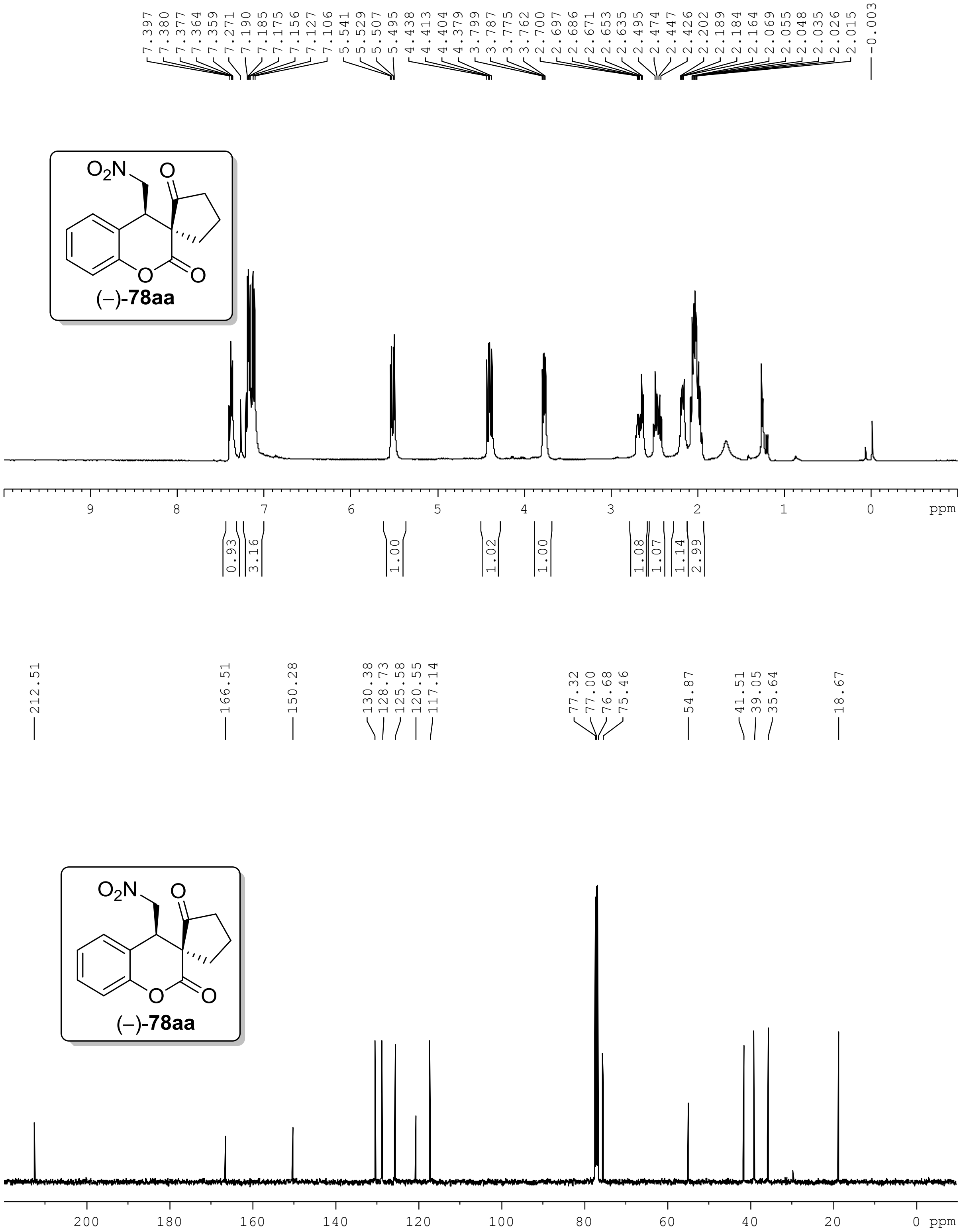
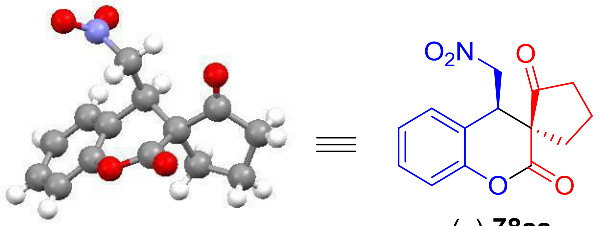


Figure-21. ^{1}H and ^{13}C NMR spectra of the product (−)-**78aa**.



(–)-**78aa**

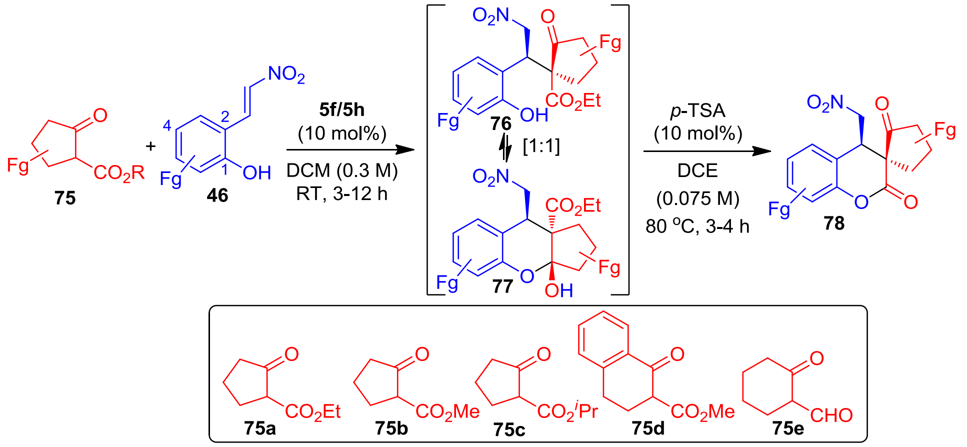
Figure 22. X-ray crystal structure of chiral product (–)-**78aa**.

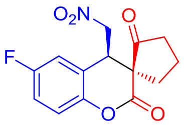
5.2.2 Scope of M-L reactions:

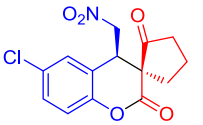
With the optimized reaction conditions in hand, the scope of the quinine-N*H*-thiourea/*p*-TSA-catalyzed asymmetric sequential *M-L* reactions were investigated.[57] A series of substituted 2-(2-nitrovinyl)phenols **46b-i** were reacted with 1.3 equiv. of keto-esters **75a-d** and keto-aldehyde **75e** catalyzed by 10 mol% of **5f** or **5h** at 25 °C in DCM for 3-12 h to furnish chiral products **76ab-ed/77ab-ed** with very good yields, *ee*'s and *de*'s, which on further lactonization with *p*-TSA-catalysis or oxidation with PCC furnished the chiral products **78ab-78ed** respectively (Table 4).[58] Without showing much effect of electronic factors; neutral, electron-withdrawing and electron-donating substituted 2-(2-nitrovinyl)phenols **46b-i** were generated the expected products **76ab-ed/77ab-ed** and **78ab-ed** with excellent yields, *ee*'s and *de*'s (Table 4). Surprisingly, reaction of (*E*)-3-(2-nitrovinyl)benzene-1,2-diol **46h** with keto-ester **75a** under **5h**-catalysis followed by lactonization furnished the *cis*-(+)-**78ah** as the major product in 70% yield with only 76% *ee* and >99% *de* (Table 4, entry 9). Observation of less *ee* in this reaction may be due to the involvement of second-*OH* group also in the transition state of the Michael reaction. Fascinatingly, 2-methoxy-6-(2-nitrovinyl)phenol **46i** was reacted with keto-esters **75a** and **75c** catalyzed by 10 mol% of **5f** at 25 °C in DCM for 3-4 h to furnish chiral Michael products (+)-**76ai** and (+)-**76ci** with very good yields, *ee*'s and *de*'s, which on further lactonization with *p*-TSA-catalysis in DCE for 5-6 h at 80 °C didn't furnish the cyclised products **78ai** and **78ci** respectively (Table 4). Reaction of (*E*)-2-(2-nitrovinyl)phenol **46a** with keto-ester **75d** under **5f-** or **5h**-catalysis followed by lactonization furnished the pure two enantiomers *cis*-(–)-**78da** and *cis*-(+)-**78da** in each 60% yield with >99.9/97% *ee* and >99% *de* respectively

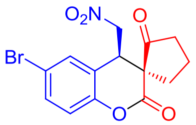
(Table 4). Interestingly, reaction of (*E*)-2-(2-nitrovinyl)phenol **46a** with methyl 2-oxocyclohexanecarboxylate under the **5f-** or **5h**-catalysis didn't furnish the expected Michael product but the same reaction with 2-oxocyclohexanecarbaldehyde **75e** in DCM for 2 h at 25 °C followed by PCC mediated oxidation furnished the functionalized spiro[chroman-3,1'-cyclohexane]-2,2'-dione *cis*-(–)-**78ea** in 65% yield with 99% *ee* and

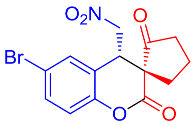
Table 4. Synthesis of chiral M-L products **78**.[a-c]

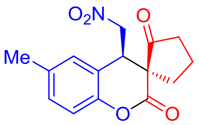


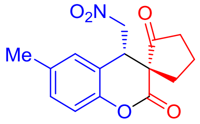

(–)-**78ab** (81%)
ee: 88%
de: >99%

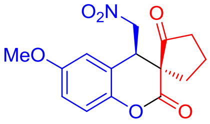

(–)-**78ac** (70%)
ee: 87%
de: >99%

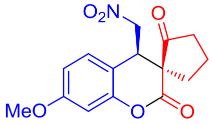

(+)-**78ad** (80%)
ee: >99.9%
de: >99%

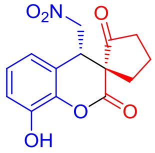

(–)-**78ad** (70%)[d]
ee: 96%
de: >99%

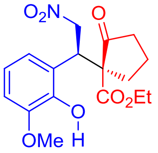

(–)-**78ae** (75%)
ee: 96%
de: >99%

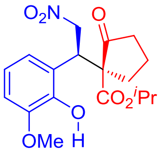

(+)-**78ae** (75%)[d]
ee: 99%
de: >99%

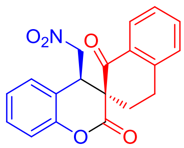

(–)-**78af** (65%)
ee: 84%
de: >99%

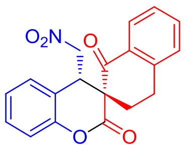

(–)-**78ag** (70%)
ee: 90%
de: >99%

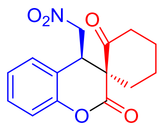

(+)-**78ah** (70%)[d]
ee: 76%
de: >99%

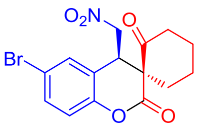

(+)-**76ai** (90%)
ee: 98%
de: >99%


(+)-**76ci** (90%)
ee: 99%
de: >99%


(–)-**78da** (60%)
ee: >99.9%
de: >99%


(+)-**78da** (60%)[d]
ee: 97%
de: >99%


(–)-**78ea** (65%)[e]
ee: 99%
de: >99%


(–)-**78ed** (70%)[e]
ee: 79%
de: >99%

---

[a] Reactions were carried out in DCM (0.3 M) with 1.3 equiv. of **75a-e** relative to the **46b-i** (0.3 mmol) in the presence of 10 mol% of catalyst **5f** or **5h** at 25 °C for 3-12 h. After one quick filtration, resulting prodcuts **76/77** were treated with 10 mol% of *p*-TSA in DCE (0.075 M) for 3-4 h at 80 °C. [b] Yield refers to the column-purified product. [c] Ee and de were determined by CSP HPLC analysis. [d] Reaction performed with 10 mol% of **5h** as catalyst. [e] PCC mediated oxidation was utilized for the cyclization reaction.

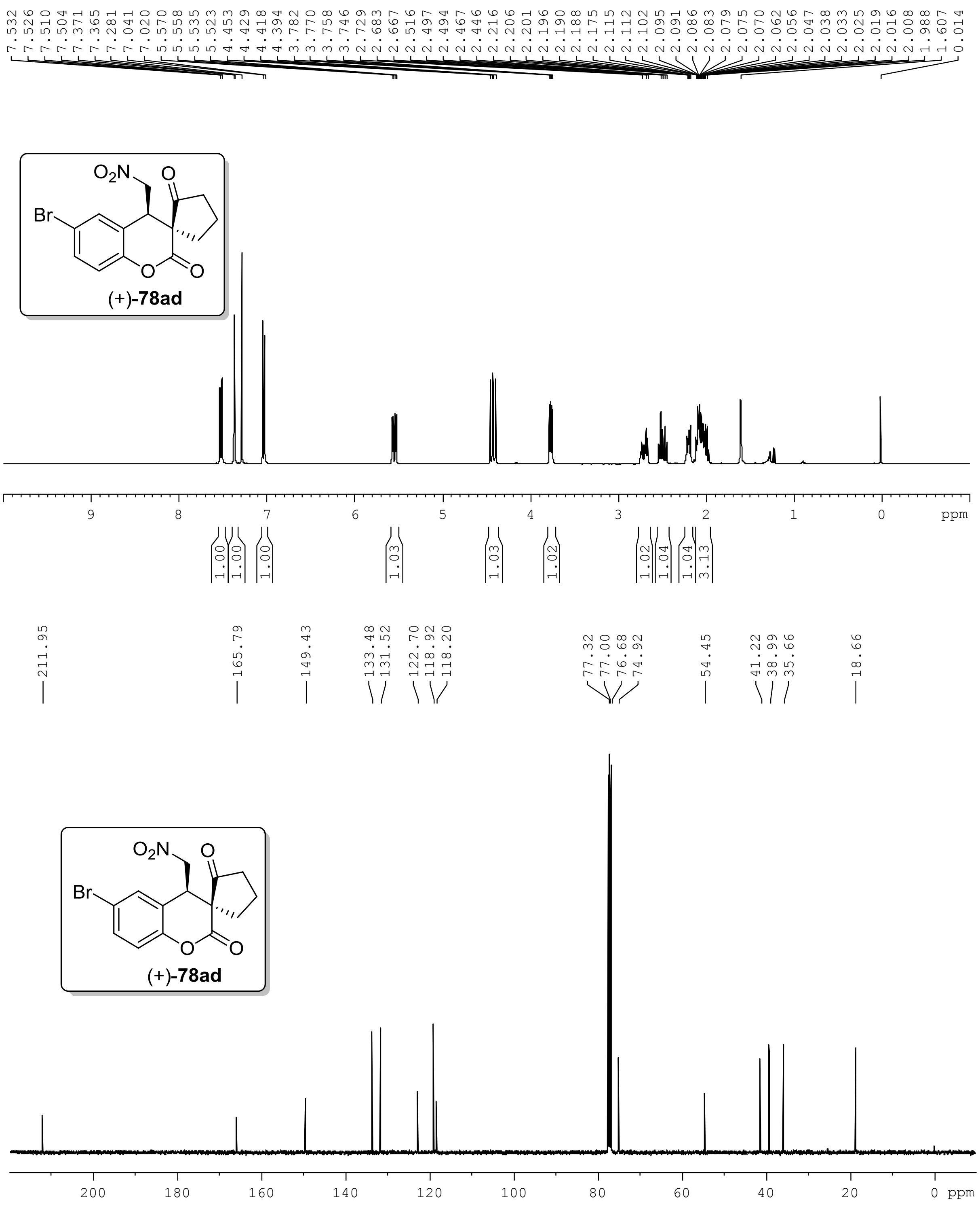


Figure-23. ^{1}H and ^{13}C NMR spectra of the product (+)-**78ad**.

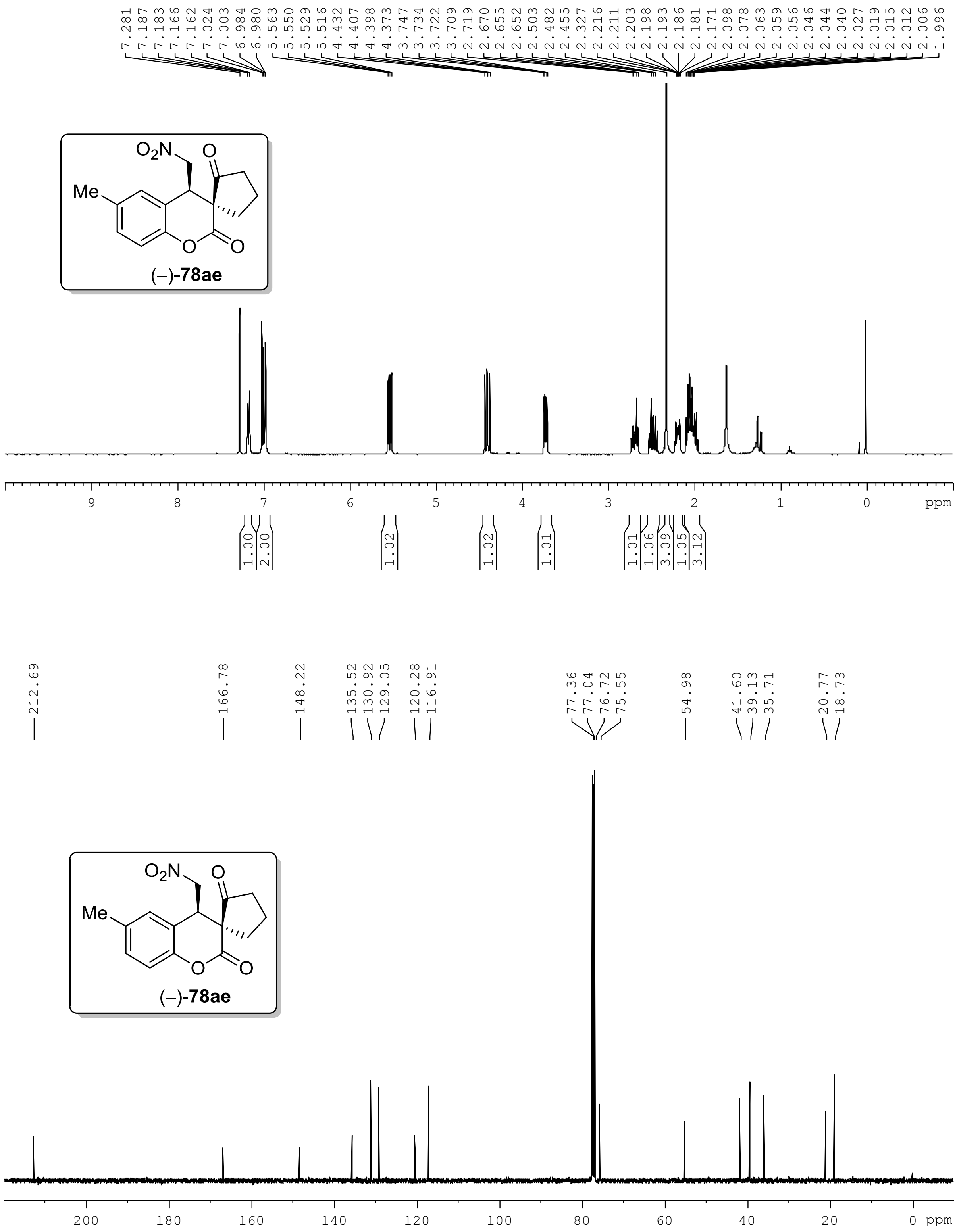


Figure-24. ^{1}H and ^{13}C NMR spectra of the product (−)-**78ae**.

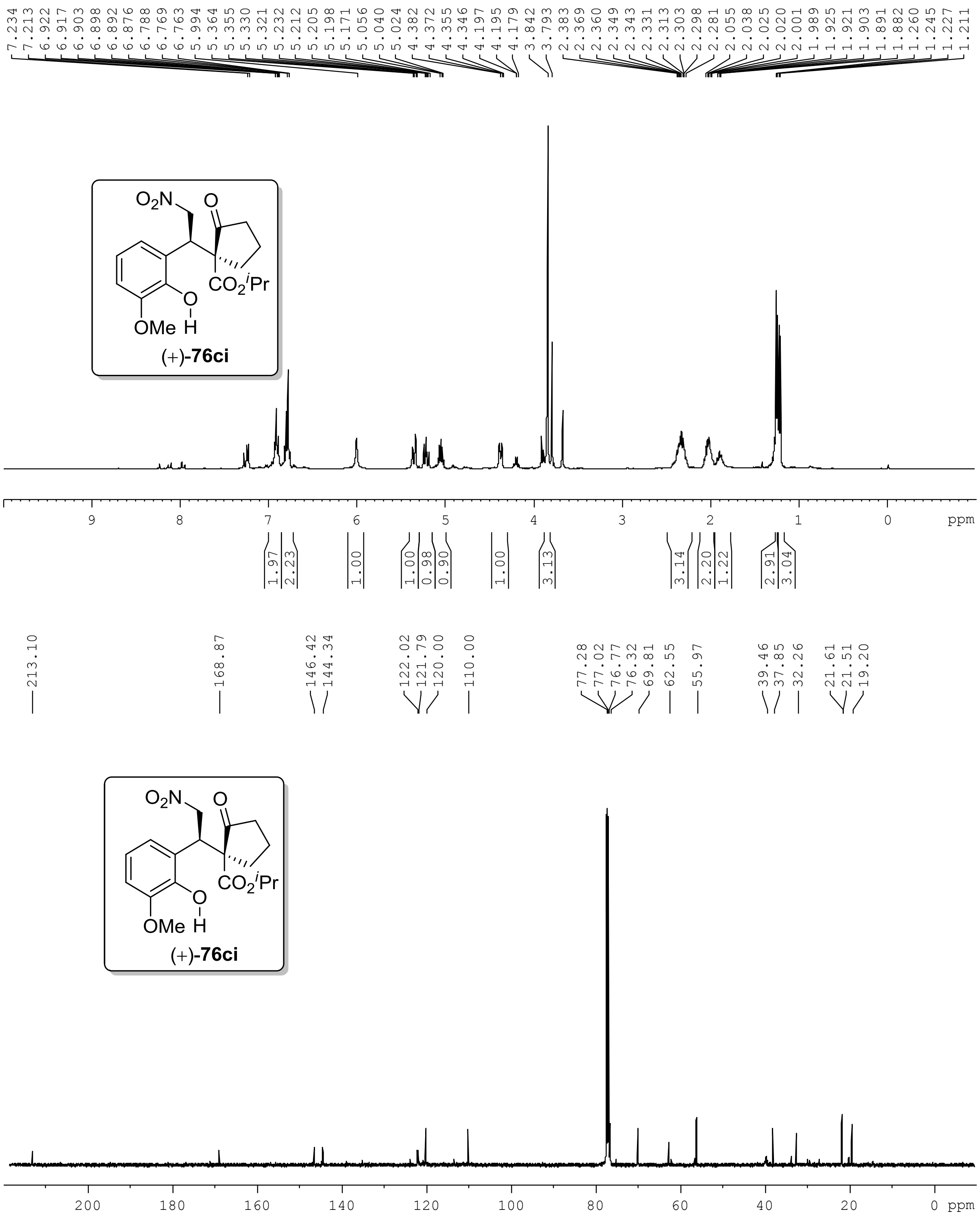


Figure-25. ^{1}H and ^{13}C NMR spectra of the product (+)-**76ci**.

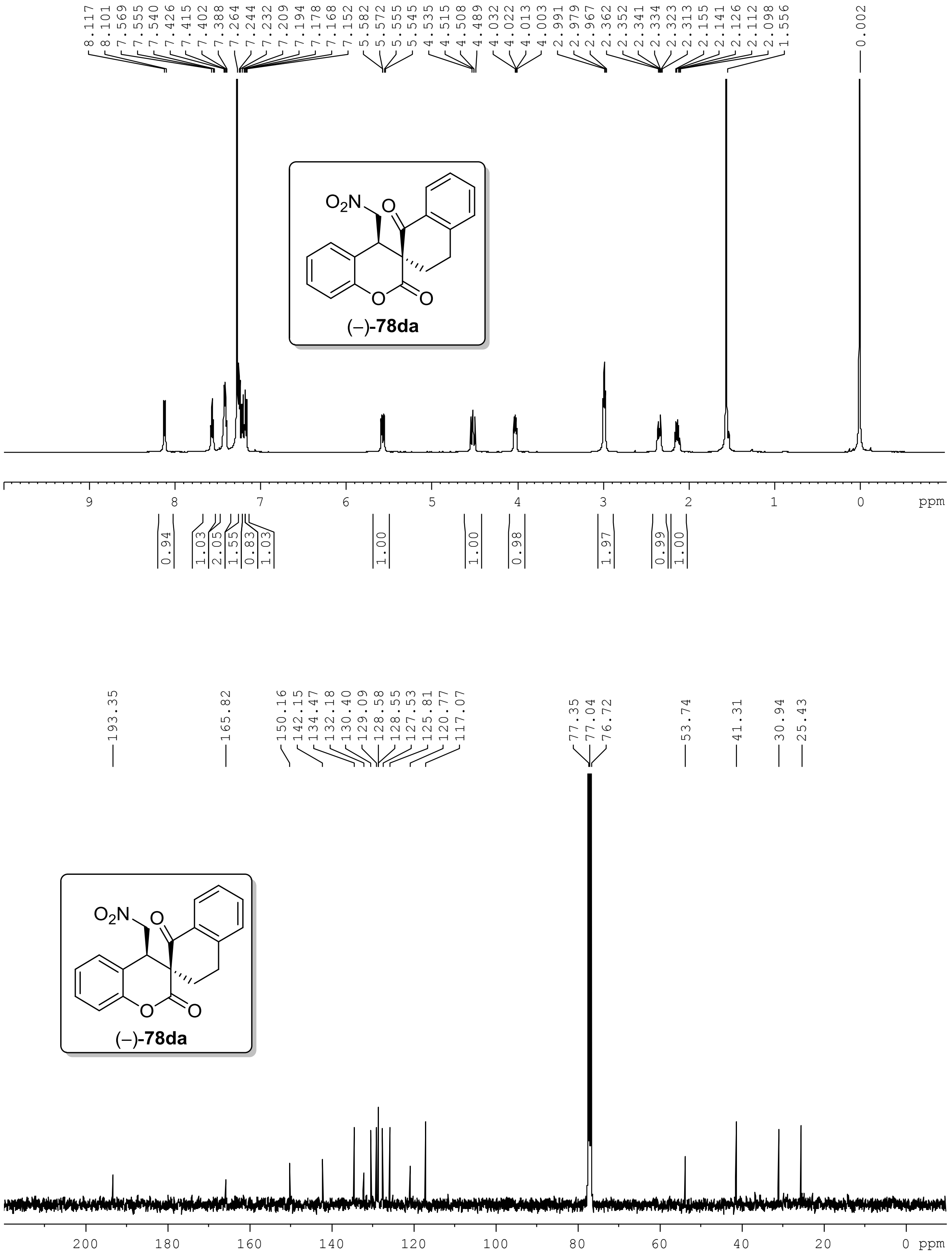


Figure-26. ^{1}H and ^{13}C NMR spectra of the product (–)-**78da**.

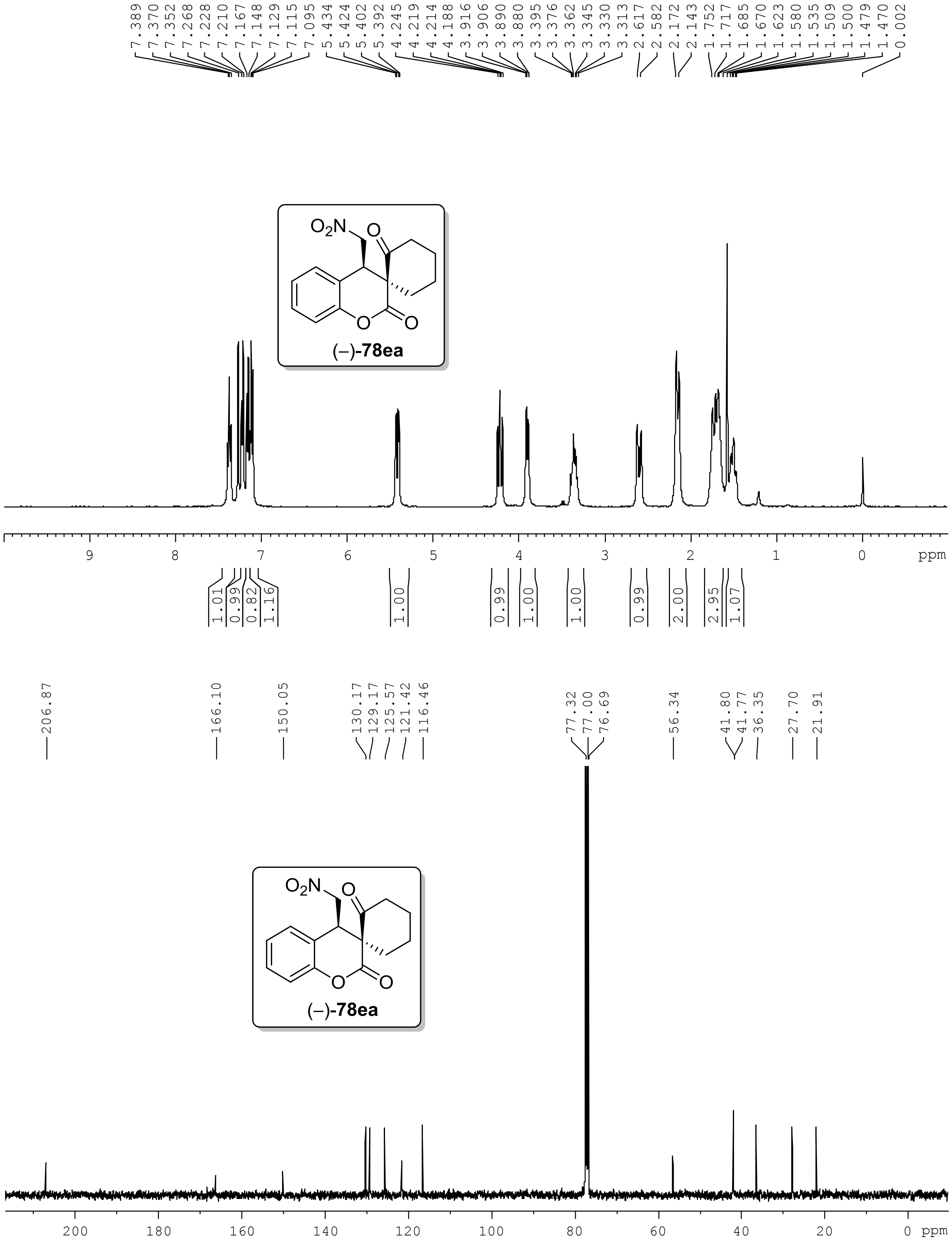
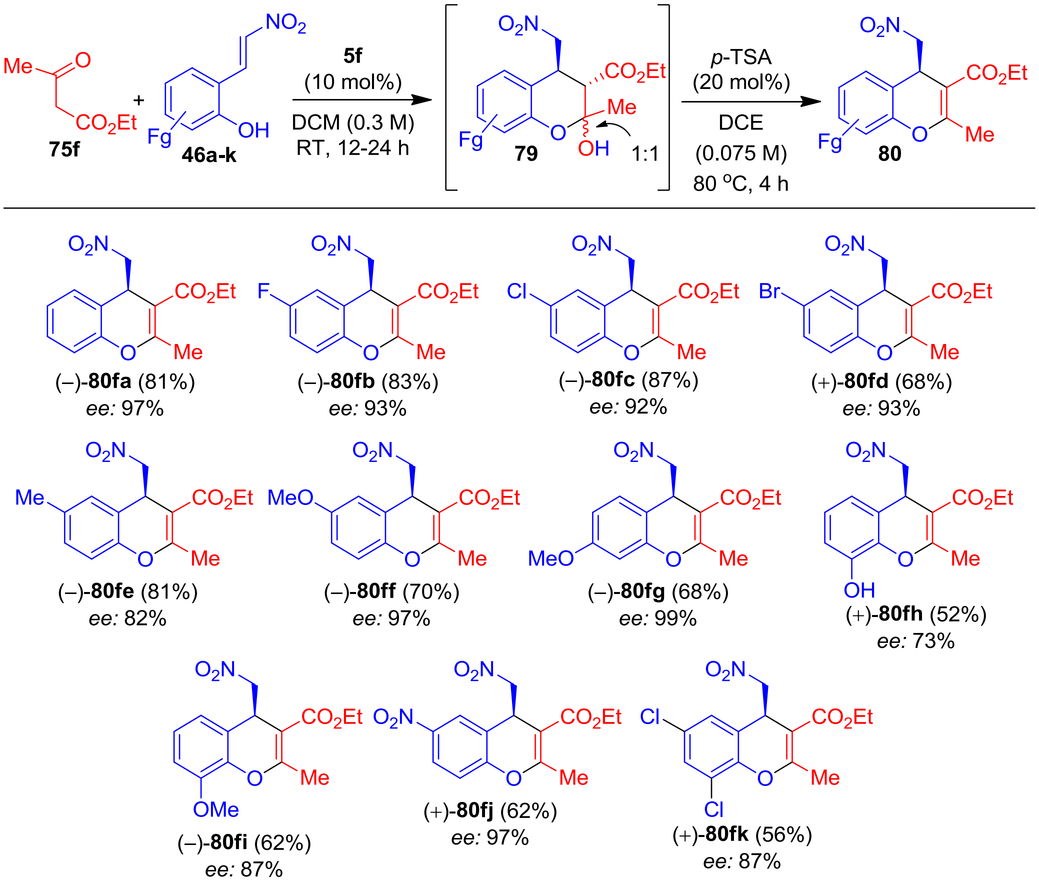


Figure-27. ^{1}H and ^{13}C NMR spectra of the product (−)-**78ea**.

>99% *de* (Table 4, entry 14). In a similar manner, another chiral spiro[chroman-3,1'-cyclohexane]-2,2'-dione *cis*-(−)-**78ed** was also furnished in 70% yield with 79% *ee* and >99% *de* from **75e** and **46d** (Table 4, entry 15). Structure and stereochemistry of *M-L* products **76ab-ed/77ab-ed** and **78ab-ed** were confirmed by NMR analysis.

After successful demonstration of *M-L* reaction with cyclic β-keto esters in spirodihydrocoumarin synthesis, we also interested in synthesis of chromenes, which are usually found in many natural products. Thus, we begin our studies with ethyl acetoacetate **75f** as a Michael donor with (*E*)-2-(2-nitrovinyl)phenols **46a-k** as shown in Table 5. (*E*)-2-(2-Nitrovinyl)phenol **46a** was reacted with ethyl acetoacetate **75f** under **5f**-catalysis in DCM at 25 °C for 12 h, surprisingly the reaction yielded 1:1 ratio of lactol products **79fa** in quantitative yield. The generated lactol products **79fa** was not clear enough for analyzing the selectivity of Michael reaction, so the yields and enantiomeric excesses were determined after the dehydration of **79fa** into chromene **80fa** *via* *p*-TSA-catalysis. This quickly filtered lactol **79fa** under *p*-TSA (20 mol%) in DCE at 80 °C for 4 h furnished the desired product (−)-**80fa** in 81% yield with 97% *ee*. Further, more functionalized (*E*)-2-(2-nitrovinyl)phenols **46b-k** were reacted with 1.3 equiv. of ethyl acetoacetate **75f** catalysed by 10 mol% of **5f** in DCM at room temperature for 12-24 h furnished the desired products **79fb-fk** in 1:1 diastereomeric ratio with good yield and excellent enantioselectivity, which on further treatment of these quickly filtered products **79fb-fk** with *p*-TSA (20 mol%) in DCE at 80 °C for 4 h furnished the chromenes **80fb-fk**. In general, Michael adducts with high enantiomeric excesses are obtained in good yields regardless of their electronic properties. Firstly, a wide variety of halogenated (**46b**, **46c**, **46d**), methylated (**46e**) and methoxy-substituted (**46f**, **46g**, **46i**) *o*-hydroxy nitrostyrenes with ethyl acetoacetate **75f** under **5f**-catalysis followed by *p*-TSA-catalysis furnished the desired chromene products **80fb-fg** and **80fi** in very good yield with high enantiomeric excesses (*ee*). Reaction of (*E*)-3-(2-nitrovinyl)benzene-1,2-diol **46h** with ethyl acetoacetate **75f** under **5f**-catalysis followed by *p*-TSA-catalysis furnished the (+)-**80fh** in 52% yield with only 73% *ee* (Table 5, entry 8), which is similar to the entry 9 in Table 4. Interestingly electron withdrawing groups on 2-(2-nitrovinyl)phenols for example (*E*)-4-nitro-2-(2-nitrovinyl)phenol **46j** and (*E*)-2,4-dichloro-6-(2-nitrovinyl)phenol **46k** with **75f** under **5f-** and *p*-TSA-catalysis furnished the products (+)-**80fj** and (+)-**80fk** in moderate yields with 97% *ee* and 87% *ee* respectively (Table 5, entry 10 & 11).

Table 5. Synthesis of chiral chromenes **80** through sequential M-D reactions.[a-c]



(–)-**80fa** (81%) *ee:* 97%

(–)-**80fb** (83%) *ee:* 93%

(–)-**80fc** (87%) *ee:* 92%

(+)-**80fd** (68%) *ee:* 93%

(–)-**80fe** (81%) *ee:* 82%

(–)-**80ff** (70%) *ee:* 97%

(–)-**80fg** (68%) *ee:* 99%

(+)-**80fh** (52%) *ee:* 73%

(–)-**80fi** (62%) *ee:* 87%

(+)-**80fj** (62%) *ee:* 97%

(+)-**80fk** (56%) *ee:* 87%

[a] Reactions were carried out in DCM (0.3 M) with 1.3 equiv. of **75f** relative to the **46a-k** (0.3 mmol) in the presence of 10 mol% of catalyst **5f** at 25 °C for 12-24 h. After one quick filtration, resulting mixture were treated with 20 mol% of *p*-TSA in DCE (0.075 M) for 3-4 h at 80 °C. [b] Yield refers to the column-purified product. [c] Ee and de were determined by CSP HPLC analysis.

To further demonstrate the generality of the **5f-** and *p*-TSA-catalyzed sequential Michael-dehydration reactions by developing diversity-oriented synthesis of optically pure chromenes **80,** we have utilized different acyclic *β*-keto esters in this study. Reaction of **46a** with **75g-m** catalyzed by **5f** in DCM at 25 °C for 12-24 h, which on further treatment with 20 mol% of *p*-TSA in DCE at 80 °C for 4 h furnished the chromenes **80ga-gj** in good yields with good *ee*'s (Table 6). Reaction between methyl acetoacetate **75g** and **46a** under standard reaction conditions furnished the expected chromene (–)-**80ga** only in 40% yield with 99% *ee*, in this reaction 3-acetyl-2H-chromen-2-one formed as by-product in 40% yield. Surprisingly the reaction of **75h** with **46a** under **5f** and *p*-TSA-catalysis produced desired product (-)-**80ha** in 66% yield with only 55% *ee*. Observation of this low enantioselectivity may be due to the bulky isopropyl group presented in the ester, which is not allowing to form

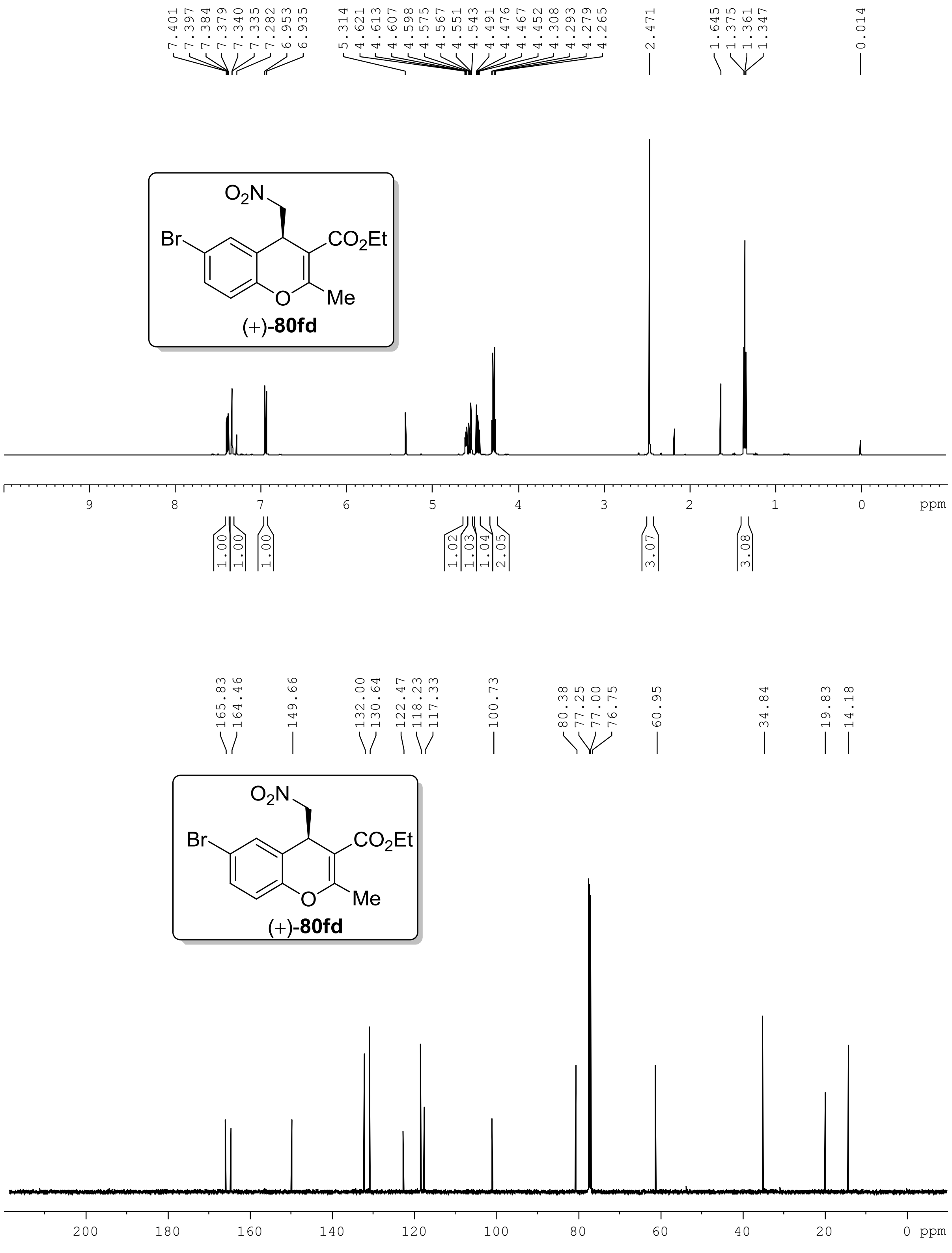


Figure-28. ^{1}H and ^{13}C NMR spectra of the product **80fd**.

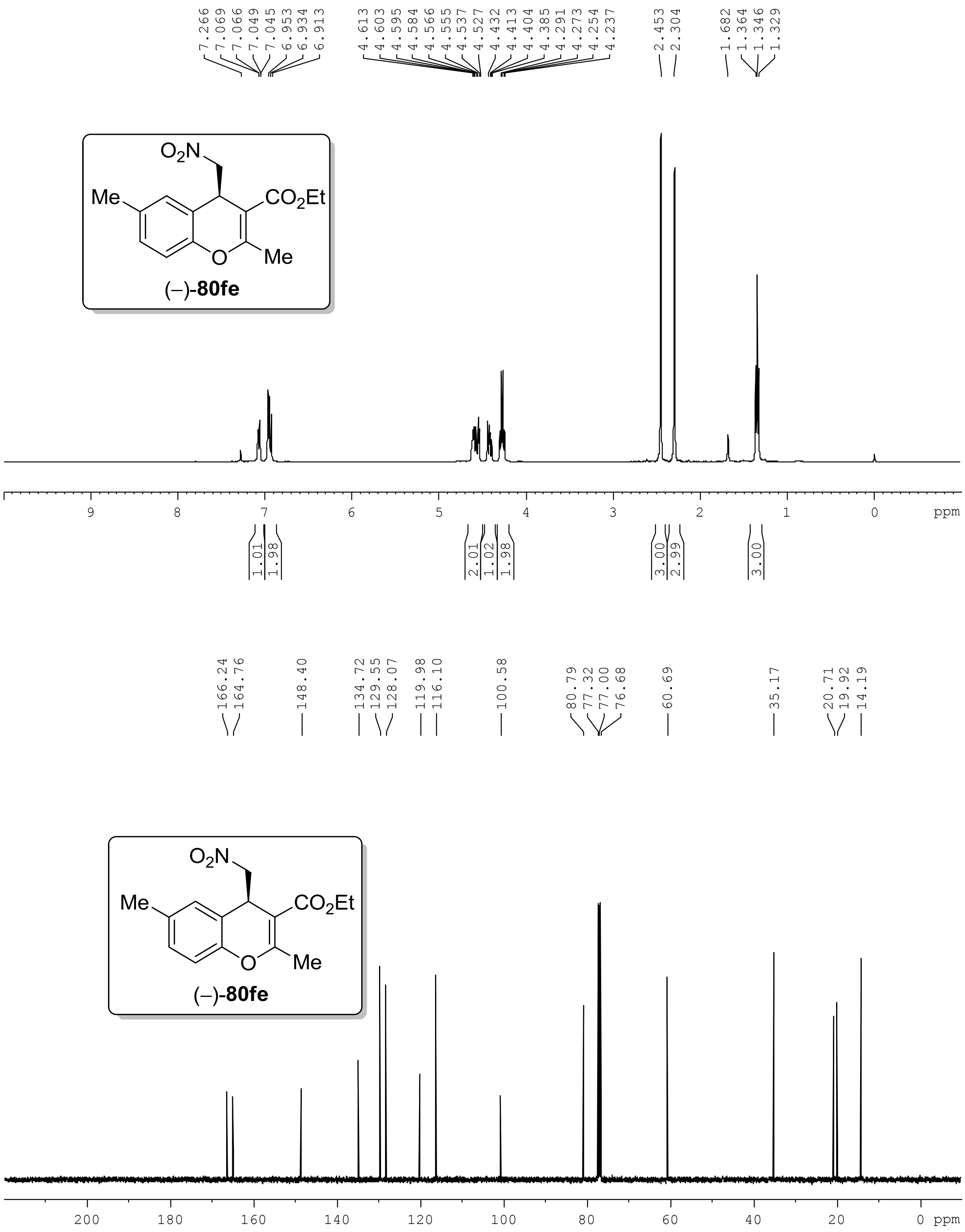


Figure-29. ^{1}H and ^{13}C NMR spectra of the product **80fe**.

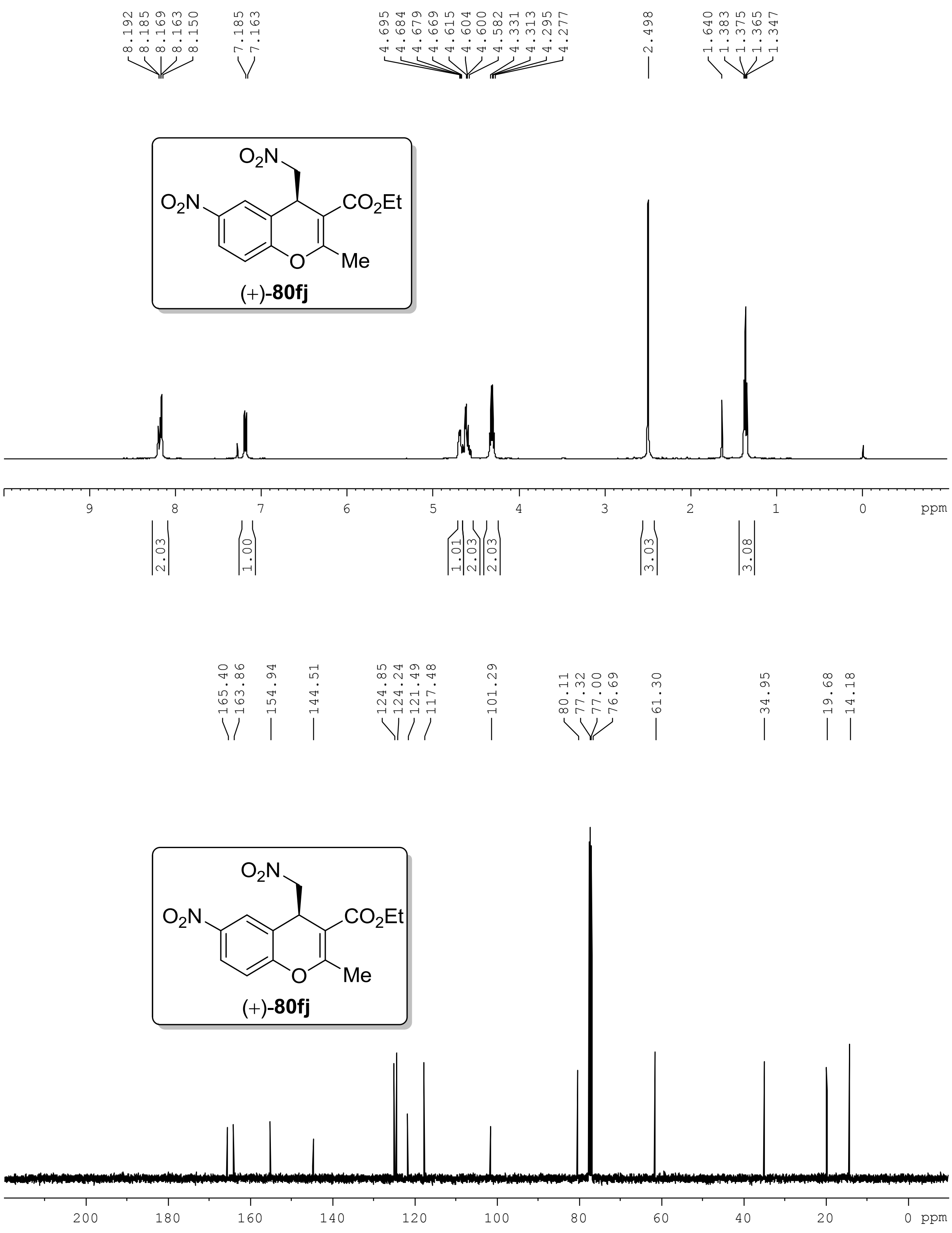
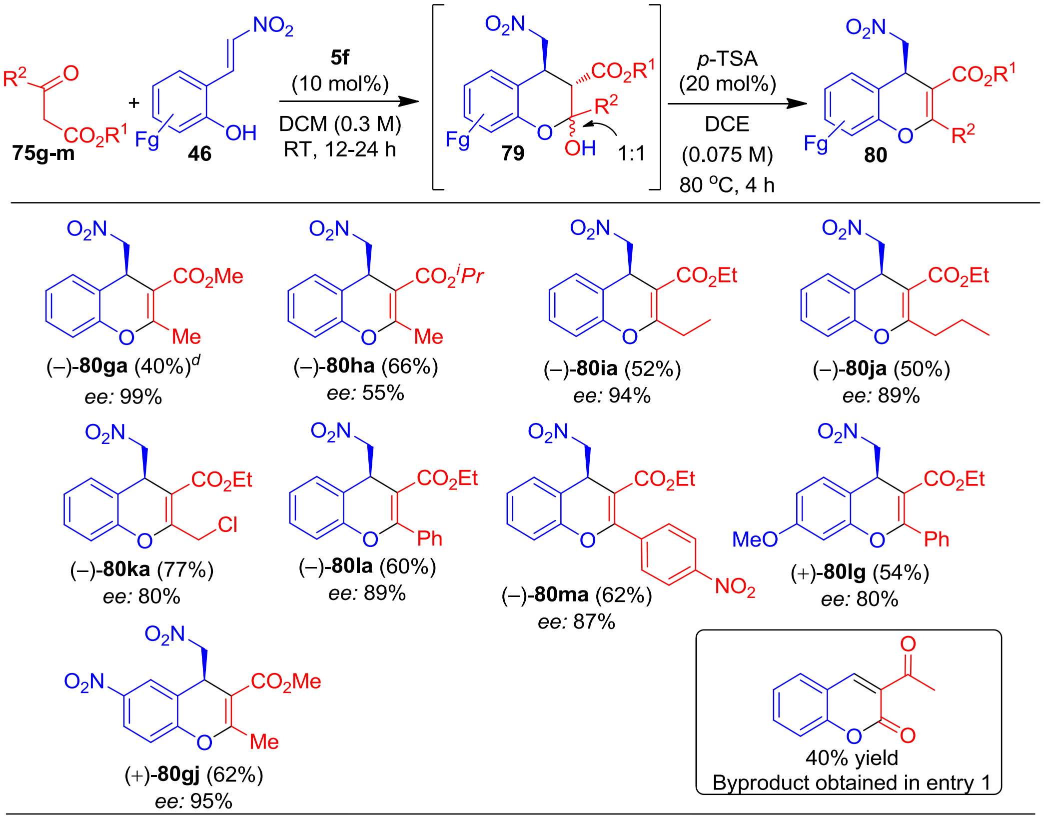


Figure-30. ^{1}H and ^{13}C NMR spectra of the product **80fj**.

the rigid transition state through supramolecular assembly. To our delight, 4-substituted ethyl acetoacetates and ethyl benzoylacetate also exhibited promising results. With ethyl 3-oxopentanoate **75i** as substrate, the product (−)-**80ia** was obtained in 52% yield with 94% *ee* (Table 6, entry 3). The other substrates such as ethyl 3-oxohexanoate **75j** and ethyl 4-chloro-3-oxobutanoate **75k** were also furnished the desired products (−)-**80ja** and (−)-**80ka** in 50% and 77% yields with 89% and 80% *ee*'s respectively (Table 6, entries 4 & 5). Substrates like **75l** and **75m** were furnished the expected chiral chromenes (−)-**80la** and **(−)-80ma** in good to excellent yields and *ee*'s respectively. In addition, the electronic factors of the substituent on the aromatic rings of **46** also showed without influence on the yields and enantioselectivities. The desired products (+)-**80lg** and (+)-**80gj** were afforded in 54% and 62% yields with 80% and 95% *ee*'s respectively (Table 6, entries 8 & 9).

Table 6. Synthesis of chiral chromenes **80** through sequential M-D reactions.[a-c]



(−)-**80ga** (40%)[d]
ee: 99%

(−)-**80ha** (66%)
ee: 55%

(−)-**80ia** (52%)
ee: 94%

(−)-**80ja** (50%)
ee: 89%

(−)-**80ka** (77%)
ee: 80%

(−)-**80la** (60%)
ee: 89%

(−)-**80ma** (62%)
ee: 87%

(+)-**80lg** (54%)
ee: 80%

(+)-**80gj** (62%)
ee: 95%

[a] Reactions were carried out in DCM (0.3 M) with 1.3 equiv. of **75g-m** relative to the **46** (0.3 mmol) in the presence of 10 mol% of catalyst **5f** at 25 °C for 12-24 h. After one quick filtration, resulting mixture were treated with 20 mol% of *p*-TSA in DCE (0.075 M) for 3-4 h at 80 °C. [b] Yield refers to the column-purified product. [c] Ee and de were determined by CSP HPLC analysis. [d] 3-Acetyl-2*H*-chromen-2-one formed as by-product in 40% yield.

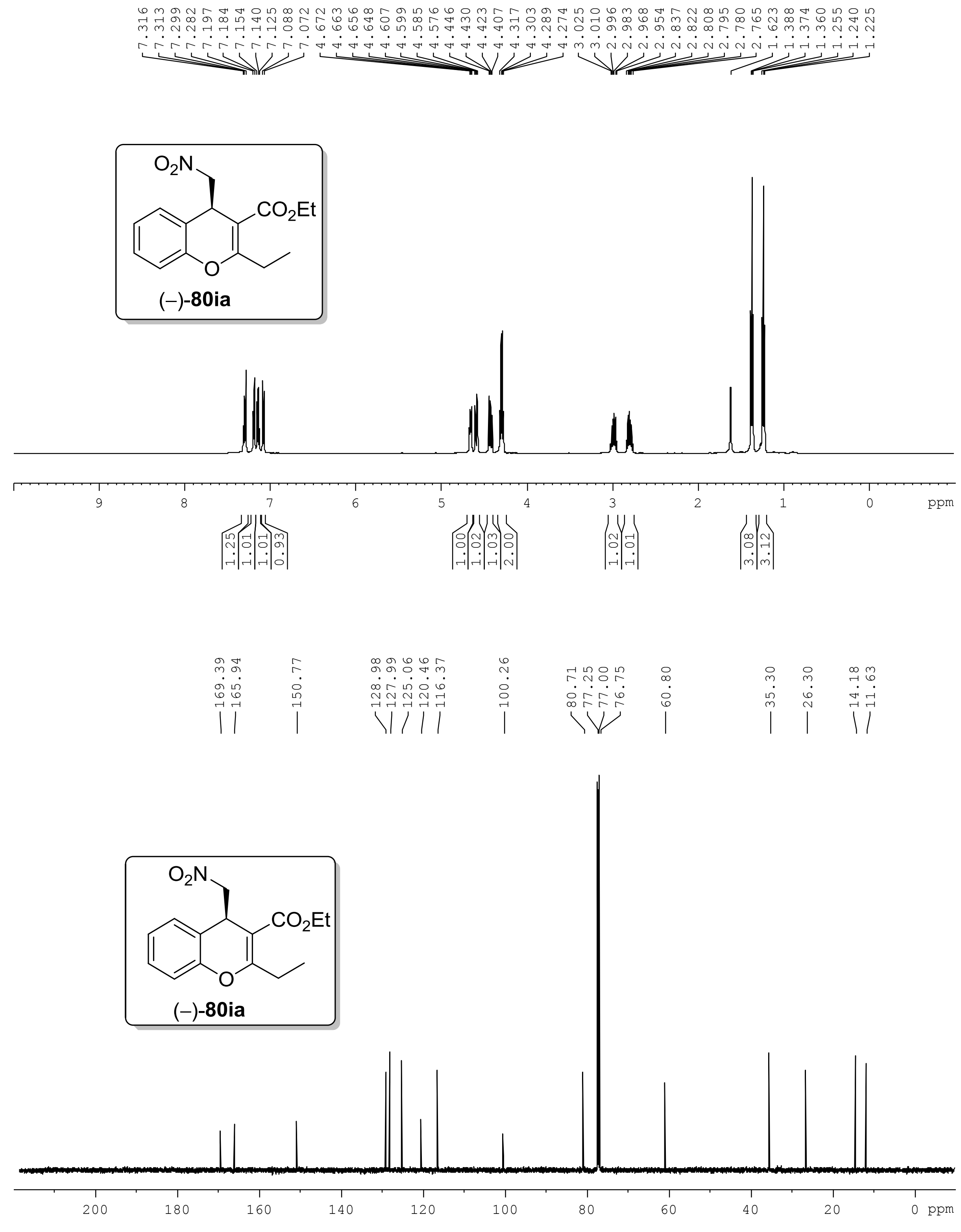


Figure-31. ^{1}H and ^{13}C NMR spectra of the product (−)-**80ia**.

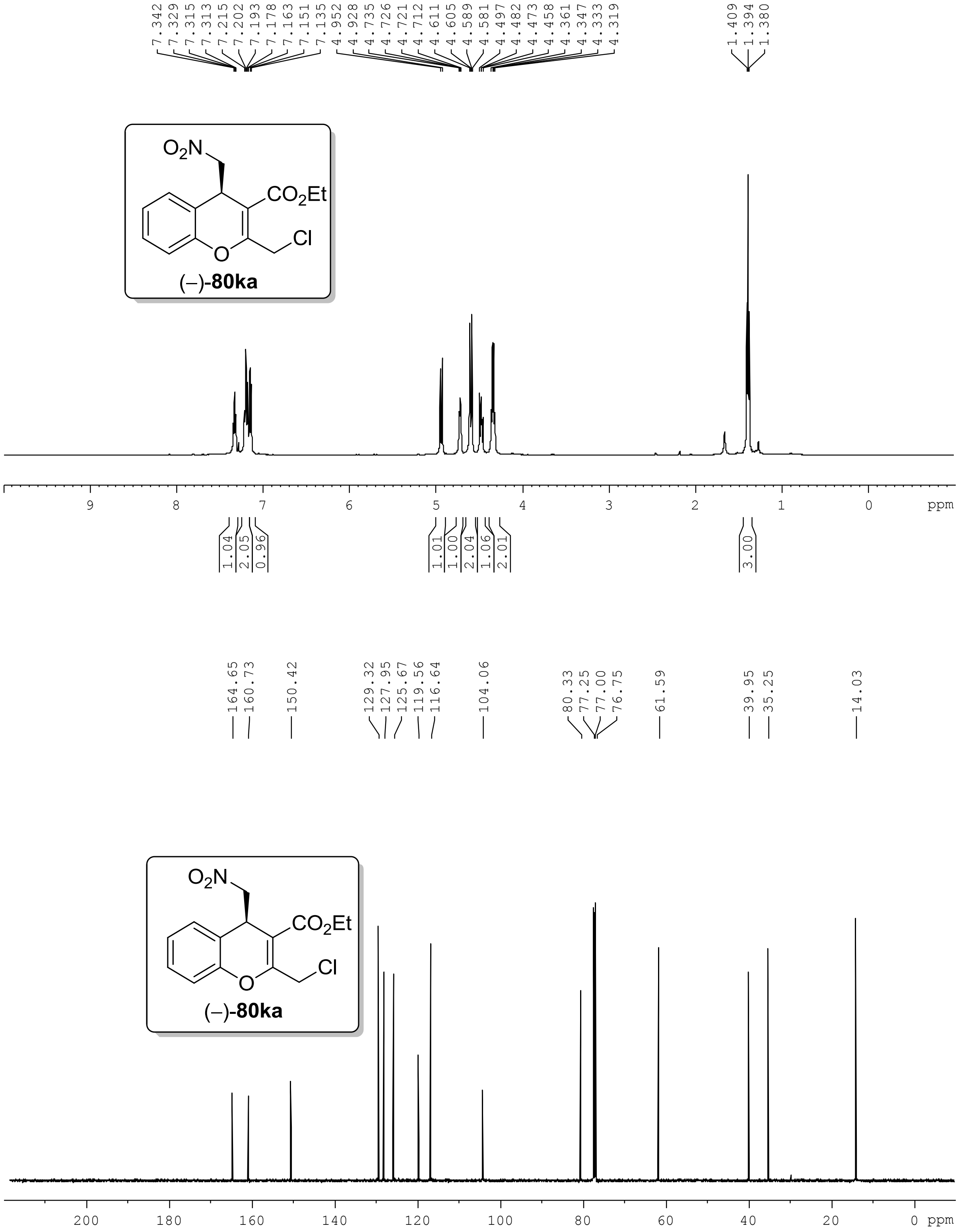


Figure-32. ^{1}H and ^{13}C NMR spectra of the product (−)-**80ka**.

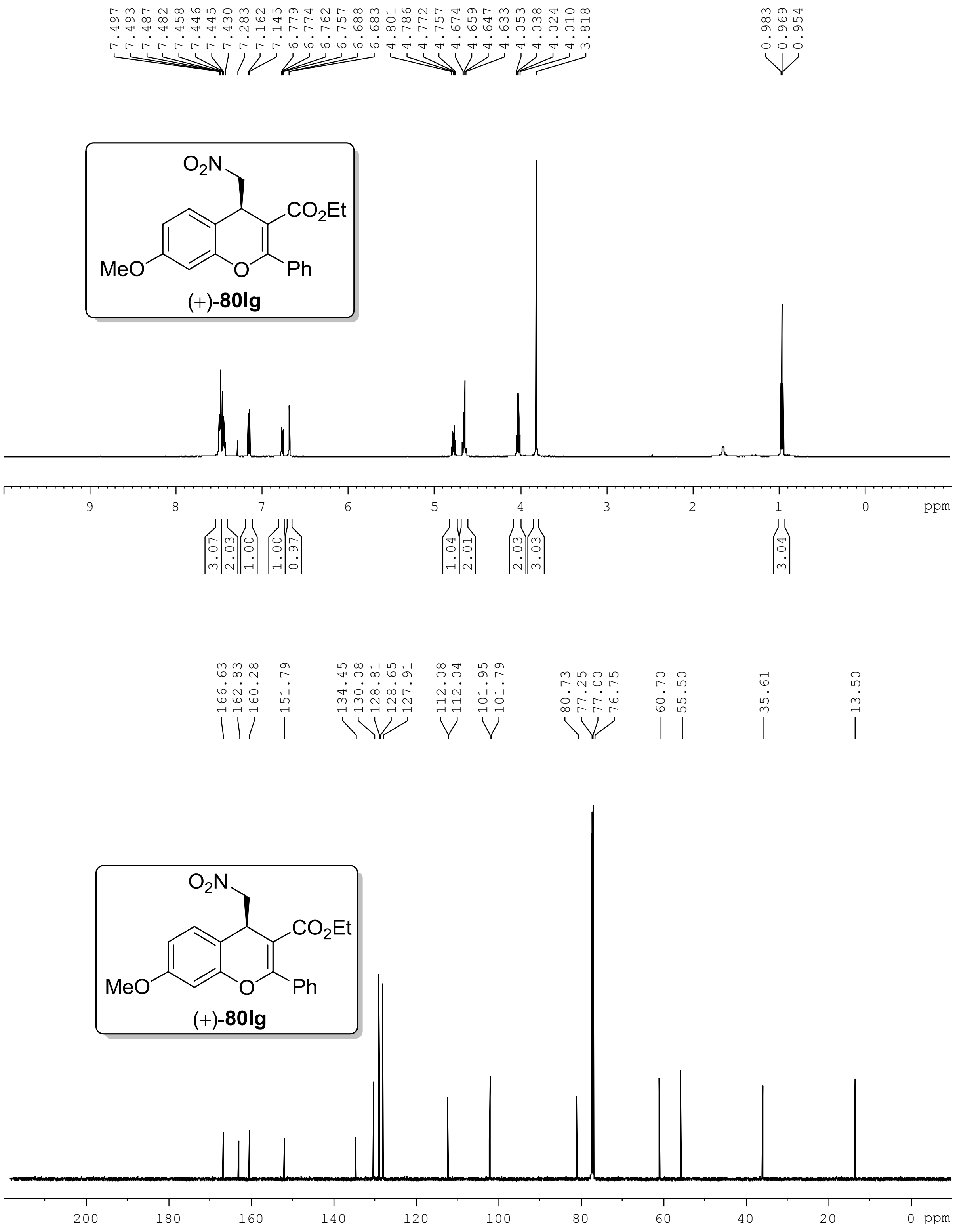
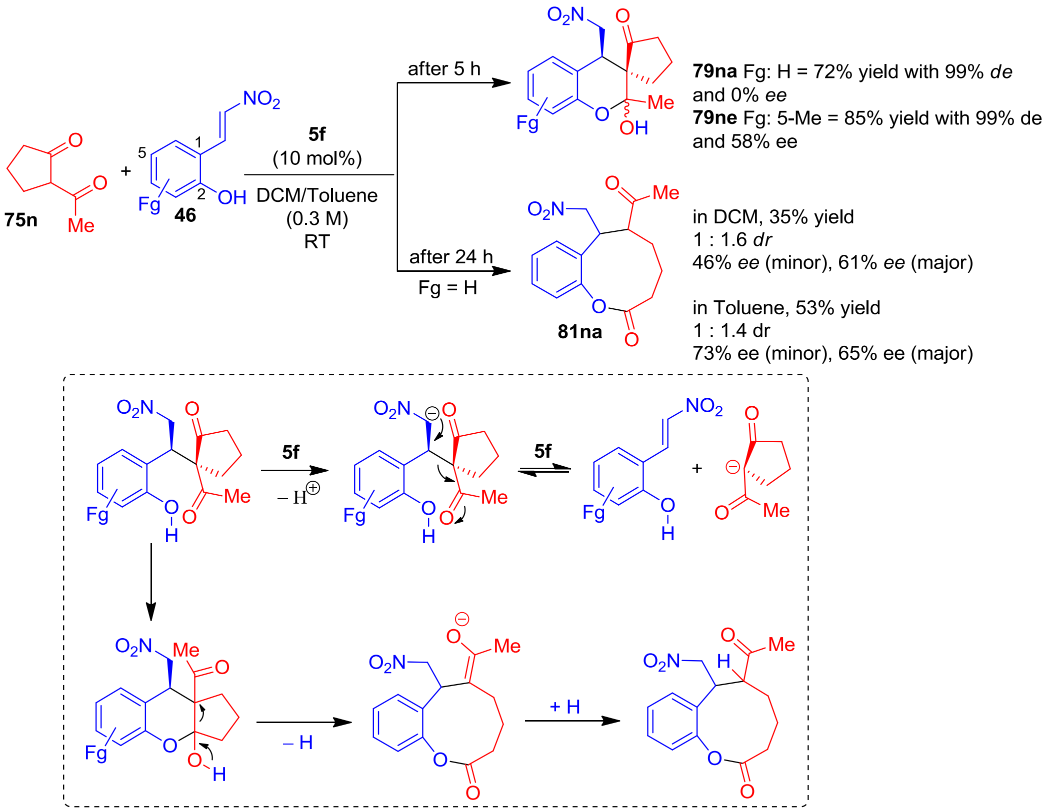


Figure-33. ^{1}H and ^{13}C NMR spectra of the product (+)-**80lg**.

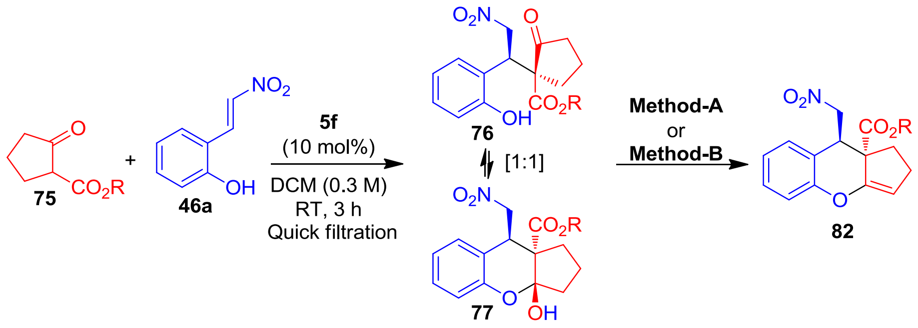
After several chiral spirodihydrocoumarins and chromenes were synthesized from *β*-keto esters and 2-(2-nitrovinyl)phenol, we used the 2-acetylcyclopentanone **75n** as a Michael donor with (*E*)-2-(2-nitrovinyl)phenol **46a** or (*E*)-4-methyl-2-(2-nitrovinyl)phenol **46e** under **5f**-catalysis. After 5 h of reaction afforded the expected Michael-hemiacetalized products, which on treatment with *p*-TSA didn't furnish the dehydrated product. Fortunately at Michael stage acetalized products **79na** and **79ne** were separated in HPLC, but the enantioselectivities were very poor. This may be due to the racemization of product through the base induced *retro*-Michael and Michael reaction. If prolonged the reaction time to 24 h**,** interestingly, ring expansion macromolecule **81na** was obtained in 35% with 1:1.6 diastereomeric ratio and 46% *ee* (minor), 61% *ee* (major) in DCM solvent. Even in toluene solvent **81na** was also obtained in 53% yield with 1:1.4 diastereomeric ratio and 73% *ee* (minor), 65% *ee's* (major). Products **79na**, **79ne** and **81na** were confirmed by NMR analysis and also finally confirmed by ESI-HRMS analysis.

Scheme 10. Time dependable M-L reaction of **75n** with **46a/46e**.



With synthetic applications in mind, we decided to explore the utilization of dynamic equilibrium products **76/77** in the synthesis of functionalized chiral chromanes and chromenes *via* Lewis acid-catalysis as shown in Table 7. Reaction of the pure chiral compounds (+)-**76aa/77aa** (99% *ee*) with 1.1 equiv. of $BF_3 \cdot OEt_2$ in DCM at 0-25 °C for 1.5 h furnished the cyclized ethyl 9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate *trans*-(−)-**82aa** in 52% yield with only 60% *ee* and unreacted products (+)-**76aa/77aa** recovered in 37% yield with 86% *ee* (Table 7, entry 1). Surprisingly, even with P_2O_5 induced dehydration of (+)-**76aa/77aa** produced the *trans*-(−)-**82aa** in 60% yield with only 72% *ee*. Formation of the low *ee* product in this reaction may be due to the decomposition or racemisation of **76aa/77aa** or **82aa** through *retro*-Michael and Michael reaction sequence under the Lewis acid-catalysis due to the steric hindrance. But surprisingly methyl cyclopentanone-2-carboxylate **75b** under Method-A and Method-B furnished the (−)-cyclized chromene **82ba** in good yields with 95-99% *ee* and 99% *de*.

Table 7. Synthesis of tetrahydrocyclopenta[b]chromenes **82** via Lewis acid-catalysis.[a,b]



Entry	R		Yield (%) **82**	ee (%) **82**	de (%) **82**
1[c]	Et (**75a**)	Method-A	52 (**82aa**)	60	>99
2	Et (**75a**)	Method-B	60 (**82aa**)	72	>99
3	Me (**75b**)	Method-A	60 (**82ba**)	99	>99
4	Me (**75b**)	Method-B	72 (**82ba**)	95	>99

[a] **Method-A**: $BF_3.OEt_2$ (1.1 equiv.), dry DCM (0.1 M) 0-25 °C, 1.5 h. [b] **Method-B**: P_2O_5 (3 equiv.),dry DCM (0.1 M), −25 °C, 48 h. [c] unreacted (+)-**76aa/77aa** were isolated in 37% yield with 86% ee

Treatment of dynamic equilibrium products (−)-**76aa/77aa** with AcCl under Et_3N in DCM at 0 °C→25 °C for 12 h furnished selectively the protected open product (−)-**83aa** in 85% yield with 98% *ee* and >99% *de* as shown in Scheme 11. Hydrogenation of (−)-**83aa** with 10% Pd/C in ethyl acetate at 25 °C for 24 h furnished the partially hydrogenated imine (+)-**84aa** in 90% yield with 98% *ee* and >99% *de*. Compounds **78, 80,** (−)-**81aa**, (−)-**82ba,** (−)- **83aa** and (+)-**84aa** are drug-like molecules; these types of molecules are used for the

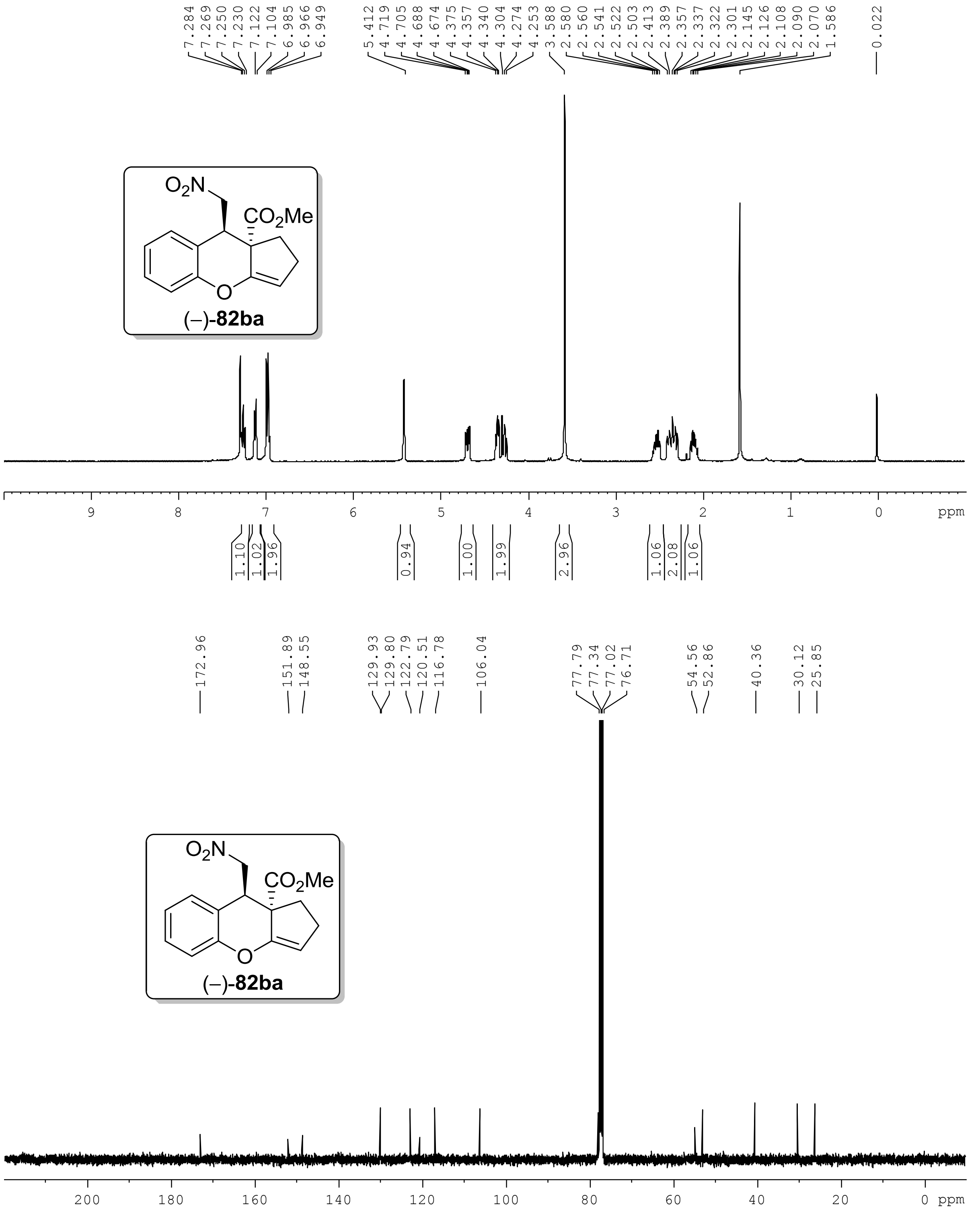


Figure-34. ^{1}H and ^{13}C NMR spectra of the product (−)-**82ba**.

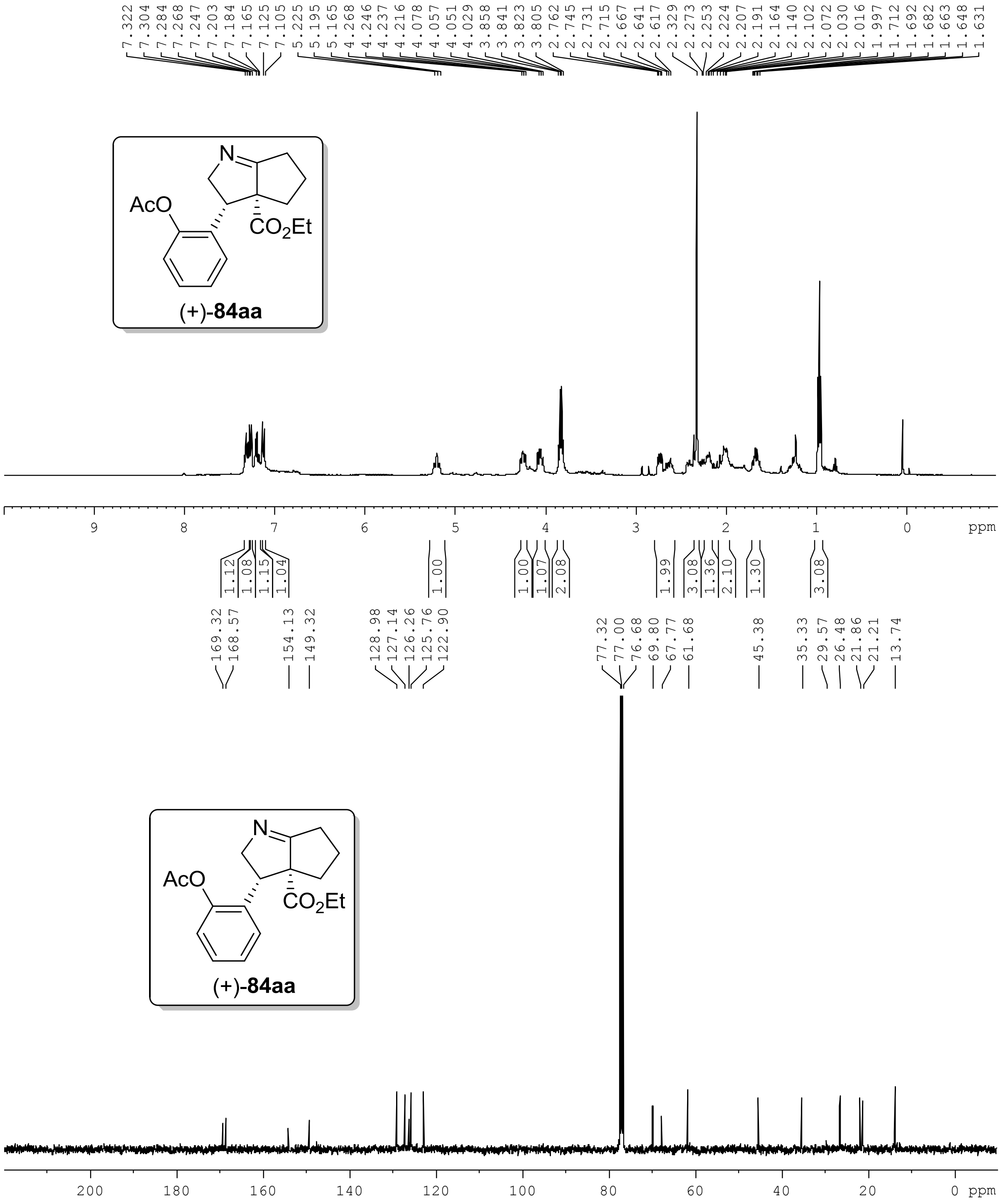
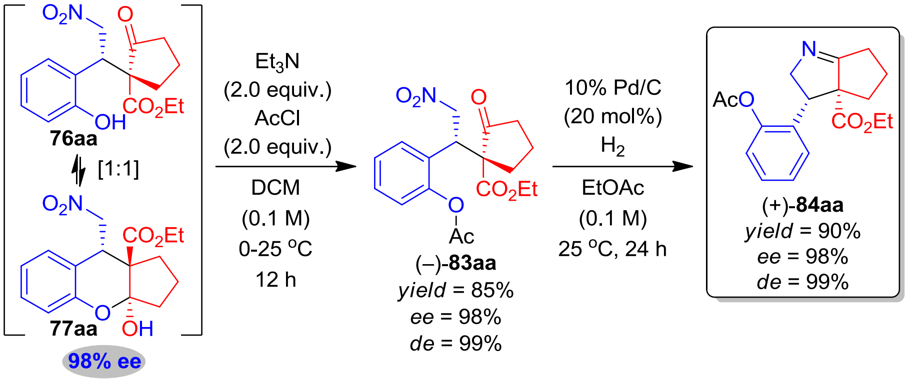


Figure-35. ^{1}H and ^{13}C NMR spectra of the product (+)-**84aa**.

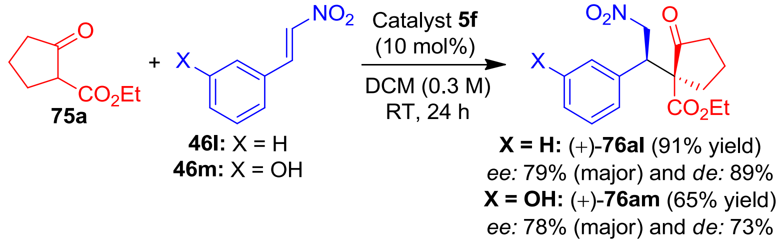
treatment of potent *anti*-ischemic property, *anti*-hypertensives, aldose reductase, spasmolytics for blood vessels, potassium channel blockers and also as HIV-1 reverse transcriptase, which is emphasizing the value of this *M-L/M-D* approach to the pharmaceuticals.[3] In addition, the presently discovered sequential *M-L/M-D* reaction will be suitable to develop substituted 3,4-dihydrocoumarins and chromene units, which is found in many natural products and designed drug molecules (Scheme 11).[49,50]

Scheme 11. Synthesis of functionalized chiral cyclic imine (+)-**84aa.**



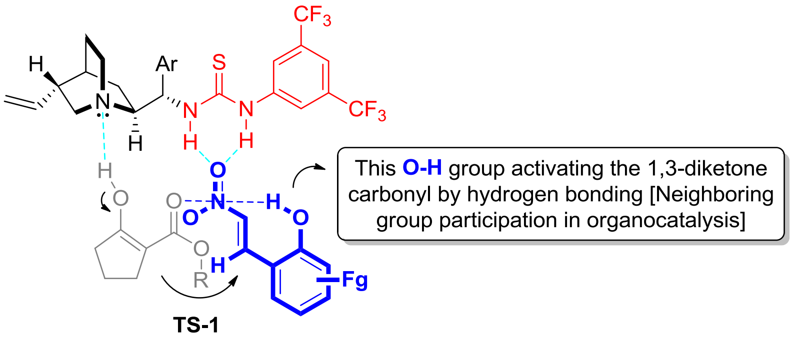
During our recent studies on 2-(2-nitrovinyl)phenol as Michael acceptor in enantioselective reactions, we observed that covalent and weak interactions among the catalyst and substrates may be utilized for the *in situ* supramolecular self-assembly. With this hypothesis, we conducted few controlled experiments under standard reaction conditions. The asymmetric Michael reaction between simple (*E*)-(2-nitrovinyl)benzene **46l** and (*E*)-3-(2-nitrovinyl)phenol **46m** with keto-ester **75a** *via* **5f**-catalysis in DCM, furnished the expected Michael products (+)-**76al** and (+)-**76am** with moderate yields, *ee*'s and *de*'s under longer reaction times as shown in Scheme 12. The observed moderate selectivity for the products (+)-**76al** and (+)-**76am** could be explained due to the lack of hydrogen bonding between phenolic-*OH* and ester carbonyl and also the catalyst quinine-N*H*-thiourea **5f** is only activating both the substrates in the transition state, which is not enough to control the selectivity as like in other substrates **46a-k**. This phenomenon was also observed in Table 6, entry 2, where the bulky isopropyl group, which is not allowing the hydrogen bonding due to steric hindrance.

Scheme 12. Controlled experiments to prove the involvement of supramolecular assembly for high-asymmetric induction.



With the controlled experimental data in hand, herein we firmly elucidate the mechanism of phenol group involvement in an asymmetric Michael reaction through **5f**-catalysis, the reaction most likely proceeds *via* 21-membered *pre*-transition state supramolecular assembly (Scheme 13). In case of the addition of keto-esters **75a-m** to substituted 2-(2-nitrovinyl)phenols **46a-k** *via* quinine-N*H*-thiourea **5f**-catalysis, we can rationalize the observed stereochemistries through a favored transition state where the less hindered *si*-face of **46a-k** approaches the *si*-face of *in situ* generated enol as shown in **TS-1**. This neighboring hydroxyl group induced *pre*-TS assembly, where the weak hydrogen bonding interactions among the catalyst and substrate-substrates get involved and construct a 21-membered-*pre*-TS supramolecular assembly could be explains the high asymmetric induction in this reaction.

Scheme 13. Proposed reaction mechanism through *pre*-TS supramolecular assembly.



This **O-H** group activating the 1,3-diketone carbonyl by hydrogen bonding [Neighboring group participation in organocatalysis]

TS Model for Neighboring Group Induced Michael Reaction *via* Thiourea Quinine-N*H*-Catalysis [***Si-Si-face Approach***]

To prove the involvement of hypothetical *pre*-transition state supramolecular assembly in this reaction, we examined careful ESI-HRMS experiments of the on-going reaction of **75a** and **46a** under the **5f**-catalysis. The ongoing reaction of **75a** (0.4 mmol) and

46a (0.3 mmol) in the presence of **5f** in DCM at 25 ° C, with in 30 minutes intervals recorded the ESI-HRMS spectrum. After 210 minutes, the ESI-HRMS spectrum shows the formation of the *pre*-transition state supramolecular assembly intermediate (**A** + Na) (m/z 938.2998) [Figure 36]. This identical peak was increasing by time intervals and confirmed by comparing with isotopic pattern of particular intermediate (**A** + Na) molecular formula. In a similar manner, ESI-HRMS spectrum of an ongoing reaction of **75f** and **46a** also confirmed the presence of *pre*-transition state supramolecular assembly in Michael reaction by showing the peak at 912.2841 (**B** + Na), which is confirmed by isotopic pattern of (**B** + Na) molecular formula as shown in Figure 37.

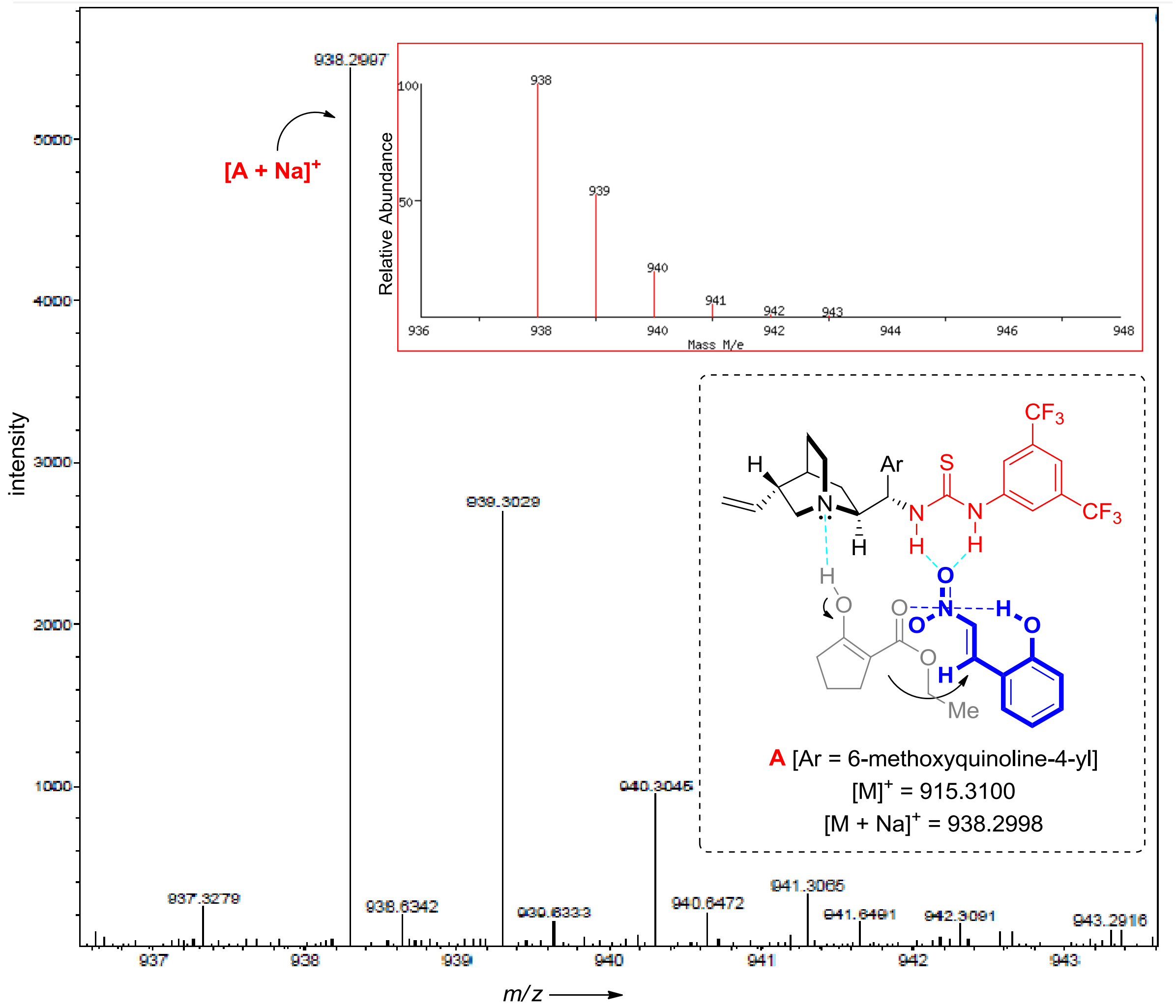


Figure-36. The ESI-HRMS (positive mode) spectrum of the reaction after 210 min of **75a** and **46a** catalyzed by **5f** in DCM at 25 °C.

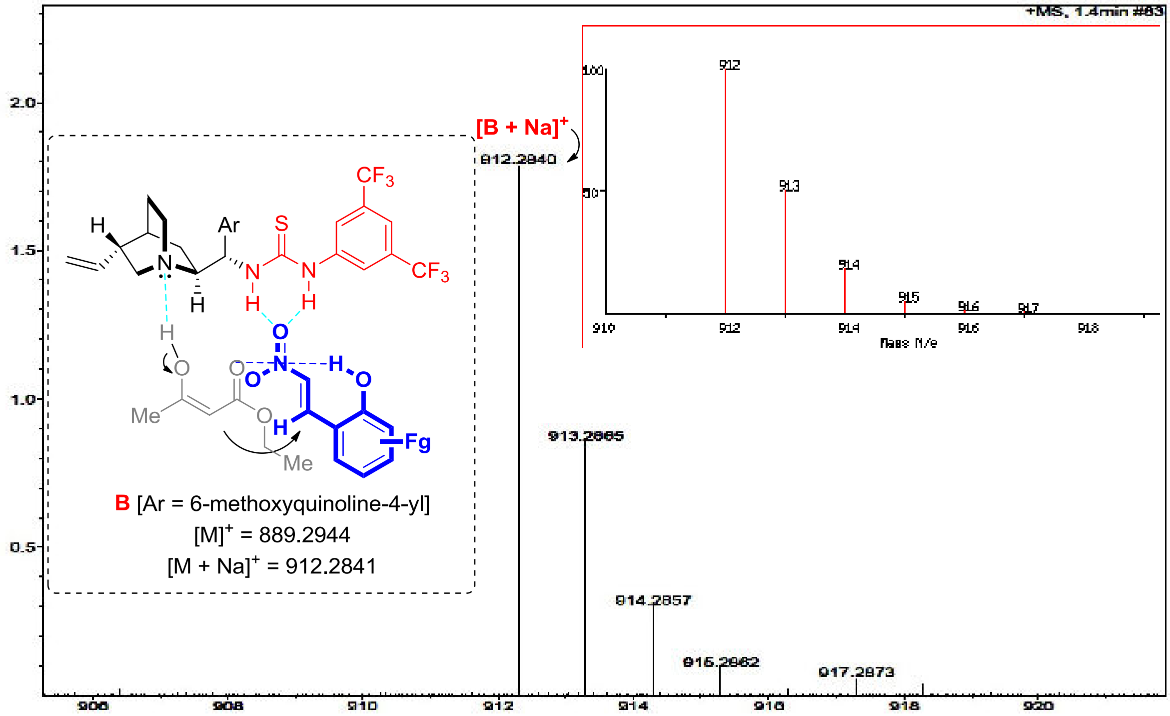
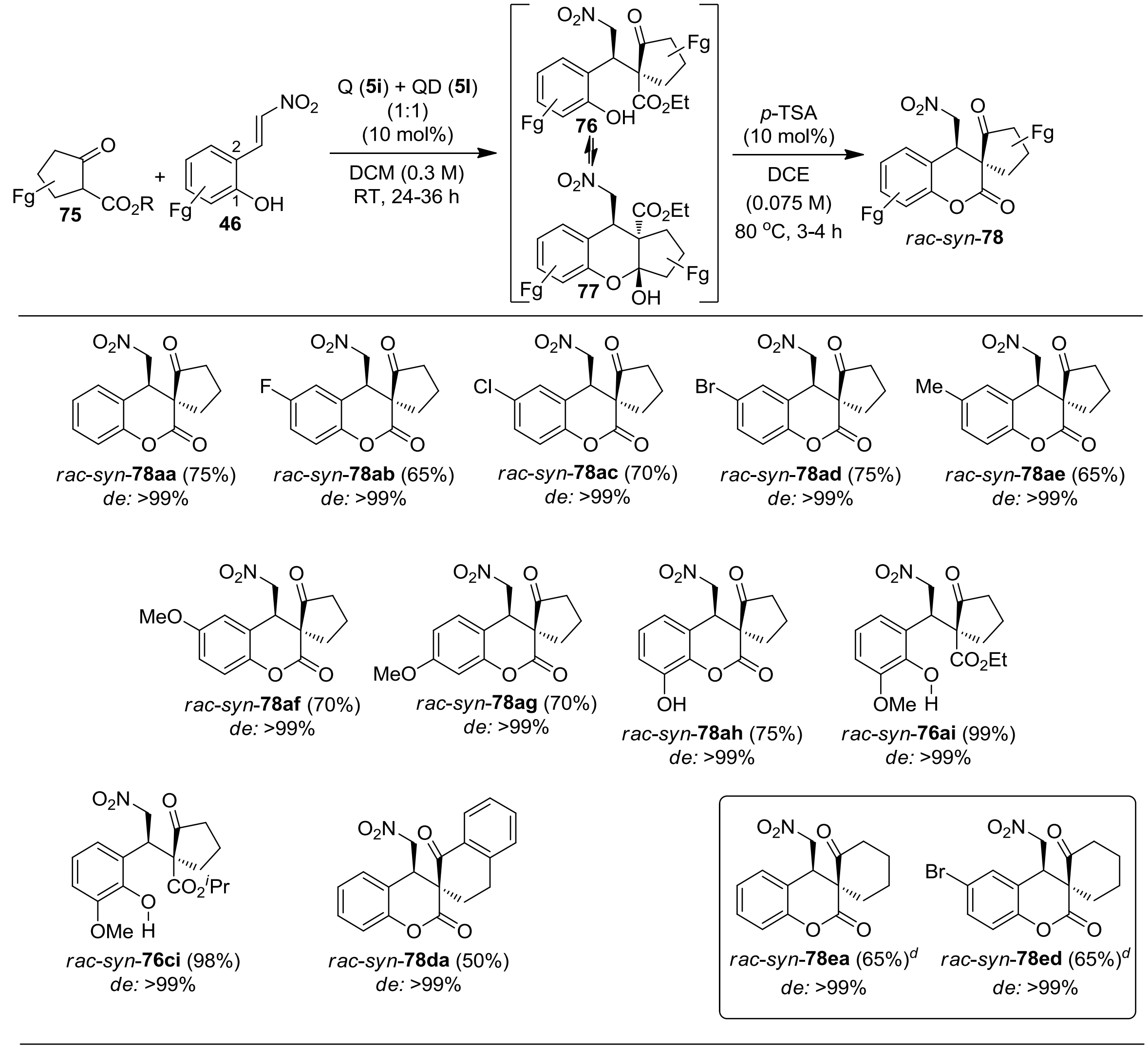


Figure-37. The ESI-HRMS (positive mode) spectrum of the reaction after 210 min of **75f** and **46a** catalyzed by **5f** in DCM at 25 °C.

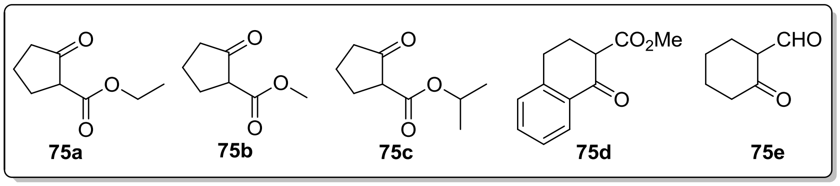
5.3 *Conclusions*

In summary, for the first time we have developed the quinine–N*H*–thiourea **5f** and *p*-TSA-catalyzed asymmetric sequential *M–L*/*M–D* reaction of keto-esters **75** with 2-(2-nitrovinyl)phenols **46**. The sequential asymmetric *M–L*/*M–D* reaction proceeds with very good yields and high selectivity through a favored 21-membered supramolecular transition state using **5f** followed by *p*-TSA as the catalyst. Furthermore, we have demonstrated the application of chiral products **76**/**77** in the synthesis of functionalized chiral spirochromans.

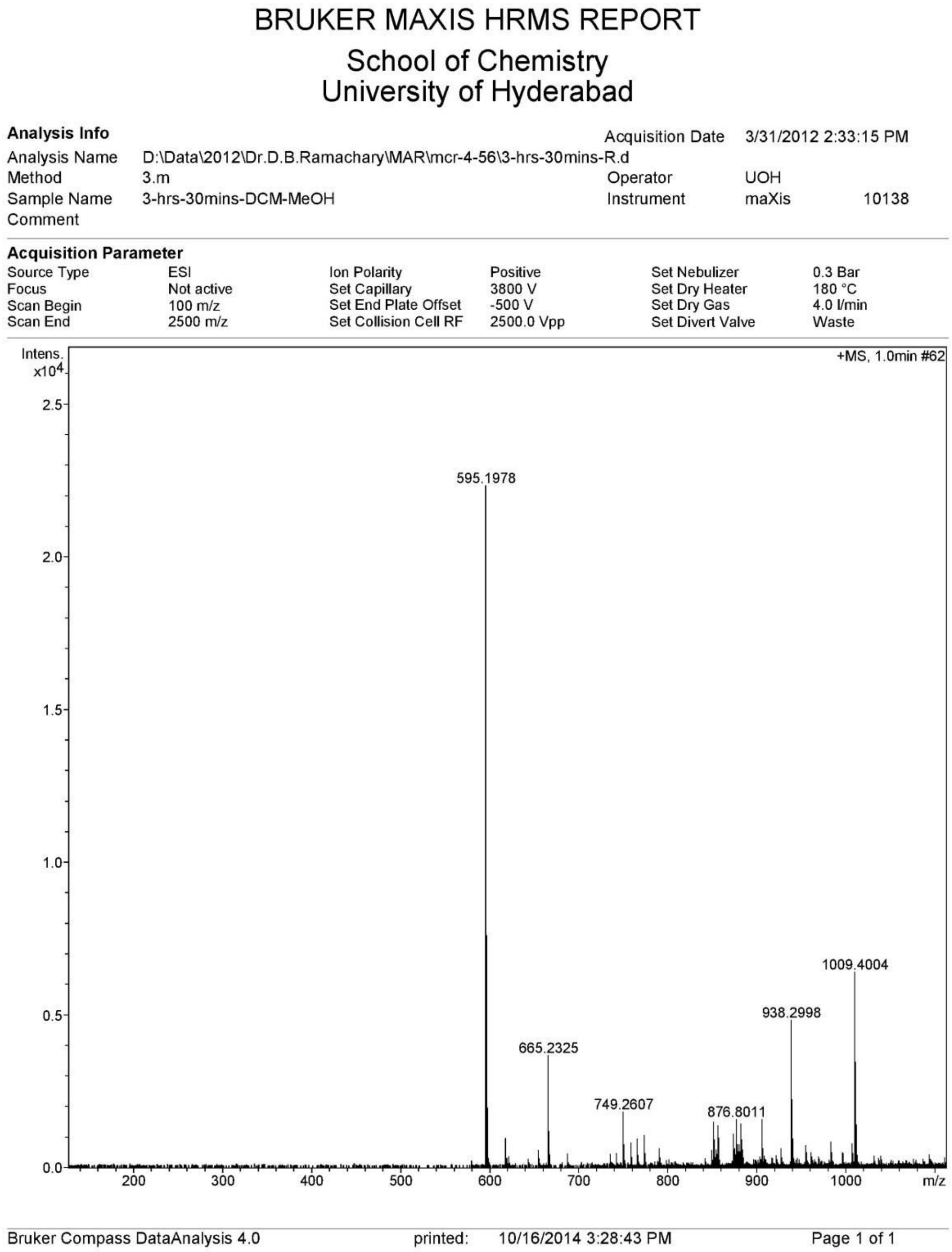
ANNEXURE-II: *Synthesis of racemic spirodihydrocoumarin products **78**.*[a-c].



[a] Reactions were carried out in DCM (0.3 M) with 1.3 equiv. of **75** relative to the **46a-i** (0.3 mmol) in the presence of 10-mol% of catalyst **5i** + **5l** [1:1]. After one quick filtration, resulting products **76/77** were treated with 10 mol% of *p*-TSA in DCE (0.075 M) for 3-4 h at 80 °C. [b] Yield refers to the column purified product. [c] Ratio or *de* is based on HPLC analysis. [d] 2-oxocyclohexanecarbaldehyde **1e** used as substrate and PCC mediated oxidation utilized for the cyclization reaction.



All high-yielding synthesis of racemic products **80** from **46** and **75** were done through [Q (**5i**) + QD (**5l**)]-catalysis followed by *p*-TSA-catalysis reactions.



BRUKER MAXIS HRMS REPORT
School of Chemistry
University of Hyderabad

Analysis Info

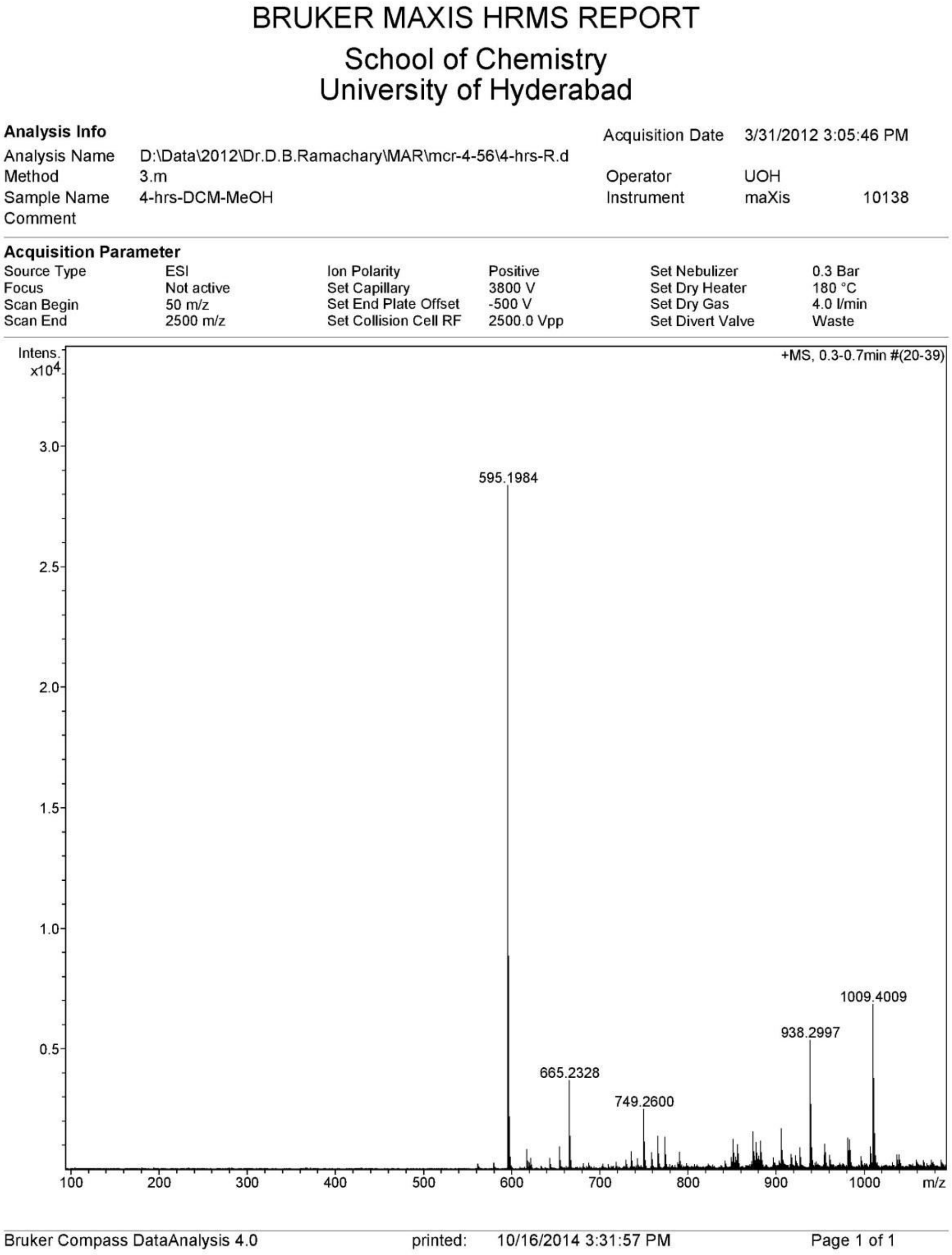
Analysis Name	D:\Data\2012\Dr.D.B.Ramachary\MAR\mcr-4-56\3-hrs-30mins-R.d	Acquisition Date	3/31/2012 2:33:15 PM
Method	3.m	Operator	UOH
Sample Name	3-hrs-30mins-DCM-MeOH	Instrument	maXis 10138
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	3800 V	Set Dry Heater	180 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	2500.0 Vpp	Set Divert Valve	Waste

Bruker Compass DataAnalysis 4.0 printed: 10/16/2014 3:28:43 PM Page 1 of 1

Figure-38. The ESI-HRMS (positive mode) spectrum of the reaction after 210 min of **75a** and **46a** catalyzed by **5f** in DCM at 25 °C.



BRUKER MAXIS HRMS REPORT
School of Chemistry
University of Hyderabad

Analysis Info

Analysis Name	D:\Data\2012\Dr.D.B.Ramachary\MAR\mcr-4-56\4-hrs-R.d	Acquisition Date	3/31/2012 3:05:46 PM
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Sample Name	4-hrs-DCM-MeOH	Instrument	maXis 10138
Comment			

Acquisition Parameter

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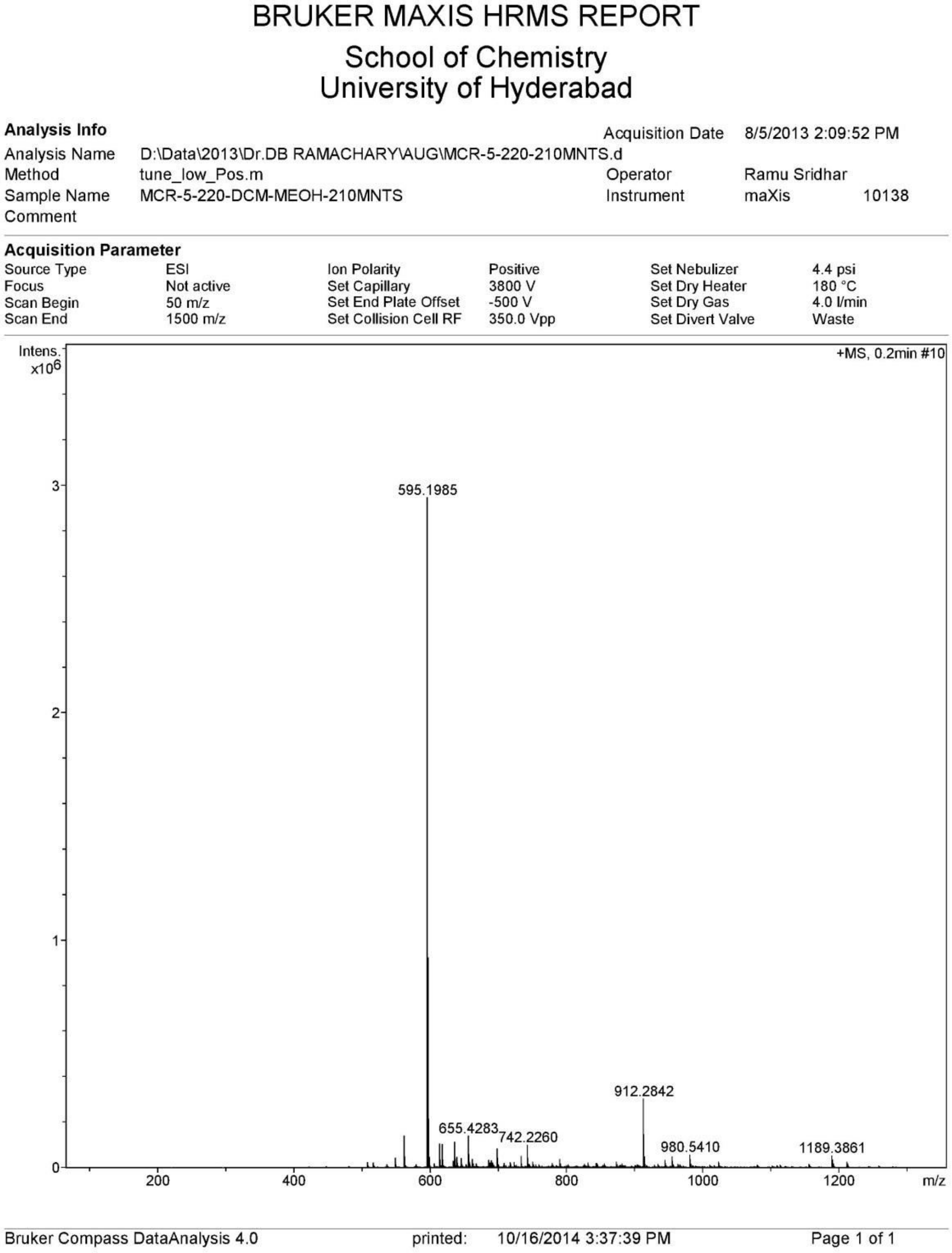
Scan End	2500 m/z	Set Collision Cell RF	2500.0 Vpp	Set Divert Valve	Waste

Bruker Compass DataAnalysis 4.0 printed: 10/16/2014 3:31:57 PM Page 1 of 1

Figure-39. The ESI-HRMS (positive mode) spectrum of the reaction after 240 min of **75a** and **46a** catalyzed by **5f** in DCM at 25 °C.



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School of Chemistry
University of Hyderabad

Analysis Info

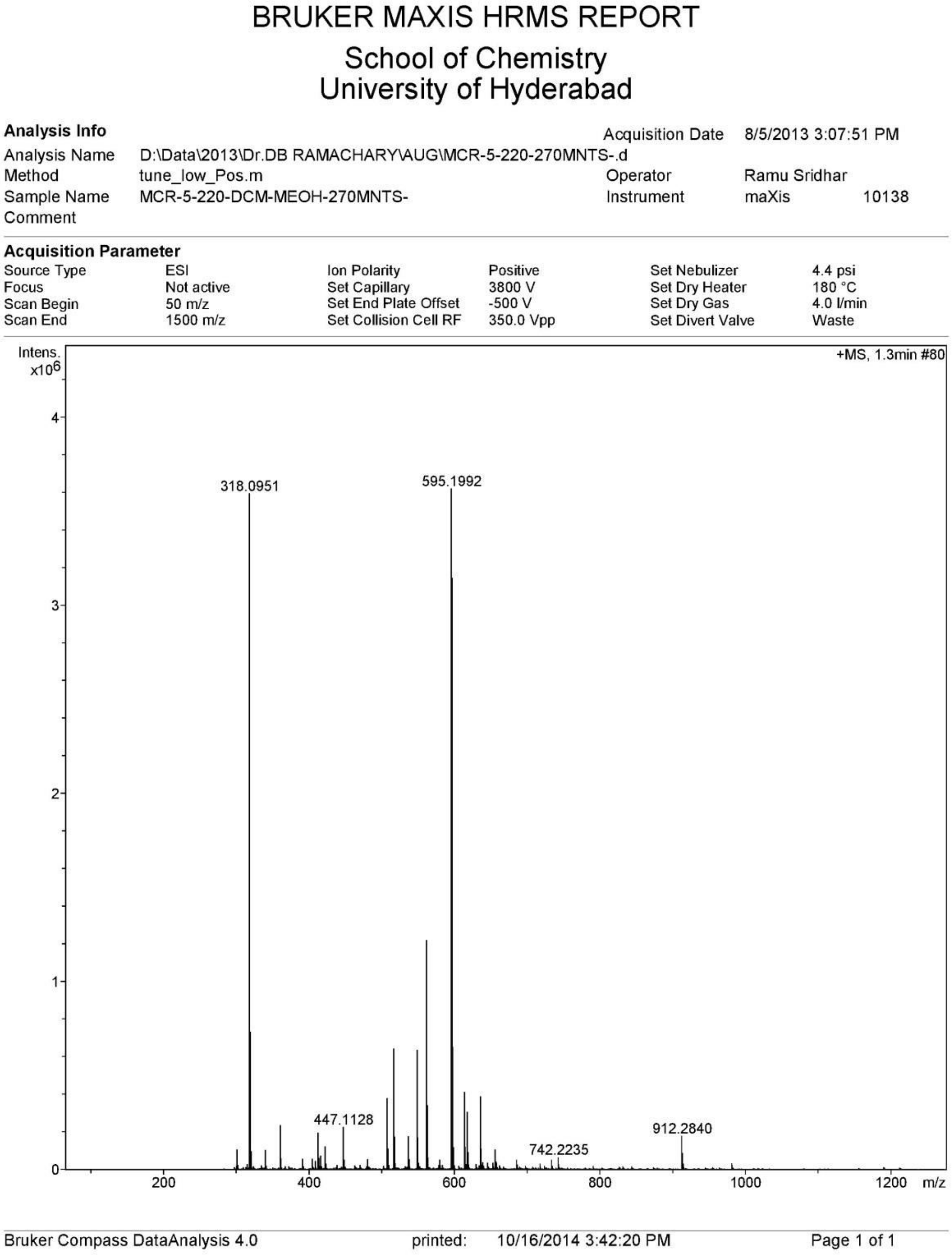
Acquisition Date 8/5/2013 2:09:52 PM
Analysis Name D:\Data\2013\Dr.DB RAMACHARY\AUG\MCR-5-220-210MNTS.d
Method tune_low_Pos.m
Operator Ramu Sridhar
Sample Name MCR-5-220-DCM-MEOH-210MNTS
Instrument maXis 10138
Comment

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	4.4 psi
Focus	Not active	Set Capillary	3800 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste

Bruker Compass DataAnalysis 4.0 printed: 10/16/2014 3:37:39 PM Page 1 of 1

Figure-40. The ESI-HRMS (positive mode) spectrum of the reaction after 210 min of **75f** and **46a** catalyzed by **5f** in DCM at 25 °C.



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Analysis Info

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Method	tune_low_Pos.m	Operator	Ramu Sridhar
Sample Name	MCR-5-220-DCM-MEOH-270MNTS-	Instrument	maXis 10138
Comment			

Acquisition Parameter

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Focus	Not active	Set Capillary	3800 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste

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Figure-41. The ESI-HRMS (positive mode) spectrum of the reaction after 270 min of **75f** and **46a** catalyzed by **5f** in DCM at 25 °C.

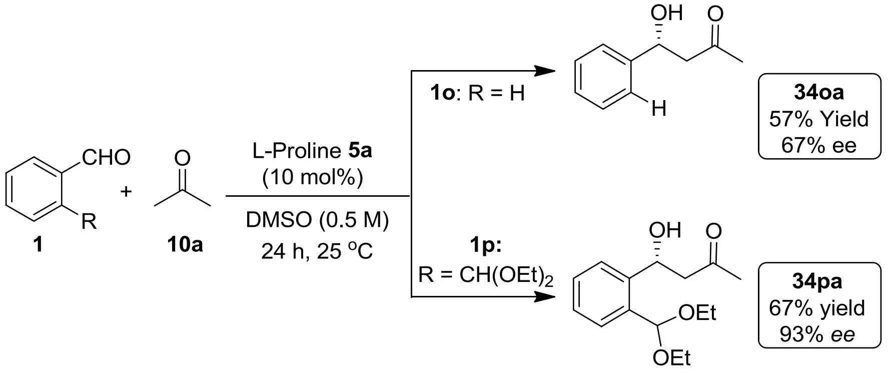
6. Observation of Neighboring Group Control in Asymmetric Barbas–List Aldol Reaction

6.1 Introduction

The asymmetric aldol reaction is one of the fundamental reaction in catalytic synthesis for C-C bond formation.[59] Barbas-List discovered the making use of small organic molecules as catalyst in asymmetric aldol reaction (BLA reaction) and the mechanistic path was observed by enamine formation from carbonyls had a strong influence which led to the establishment of different asymmetric routes for many other reaction types.[60] Moreover the tremendous development in BLA reactions since 2000, is mostly based on catalyst design, where the amine/amino acid derived catalysts were used extensively in both aqueous and organic media.[61] Although many strategies have been developed for the organocatalytic aldol reactions of aldehydes with ketones, it is still remains challenging for high asymmetric induction in sterically hindered and electronic constrain aldehydes.[62]

In asymmetric aldol methodology, main stereochemical controllers are the use of chiral auxiliaries, ligands, and catalysts, in this regard catalytic reactions are economically attractive. Most of organocatalytic asymmetric BLA-reactions are catalyst designed reactions, which will obey the aromatic and aliphatic aldehydes for high enantio- and diastereo-selectivity with different ketones. During the past few years, numerous enamine-type catalysts have been developed and successfully used for different aldehydes in BLA-reactions, the most of electron withdrawing groups contained benzaldehydes are successful, whereas donating groups (mostly nucleophilic in nature) introduced *ortho* to the aldehyde group on aromatic rings are still struggling to achieve high selectivity's. This may be due to the low reactivity or secondary interactions involvement in the transition state. But in 2012, our group reported the Michael reaction of (*E*)-(2-nitrovinyl)phenol with ketones, which is witnessed for the involvement of *ortho*-hydroxyl group in the transition state, to furnish the products with high selectivity's.[22] In 2000, Barbas reported aldol reaction, where the aldehyde carbonyl is activated by acid group of proline through hydrogen bonding which is responsible for high asymmetric induction. So this kind of small interactions involvement in the transition state and also study of the neighboring group involvement in controlling selectivity's are stimulating and interesting concepts in asymmetric synthesis. Thus, we investigated the BLA-reaction with appropriate neighboring groups presented on benzaldehydes with ketones by comparing the selectivity/reactivity of L-proline **5a**-, L-thioproline **5o**- and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) **5p**-catalyzed asymmetric BLA reactions (Scheme 14).

Scheme 14. Observation of neighboring group control in asymmetric Barbas–List aldol reaction.



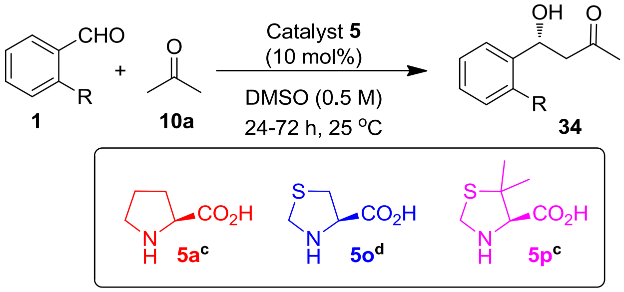
Initial studies on BLA-reaction were attempted with simple benzaldehyde **1o** as acceptor and acetone **10a** (28 equiv.) as donor under L-proline **5a**-catalysis in DMSO afford the aldol product (+)-**34oa** 57% yield with only 67% enantiomeric excess. Whereas *ortho* functionalized benzaldehyde like 2-(diethoxymethyl)benzaldehyde **1p** in same reaction conditions resulted the direct aldol product (+)-**34pa** in 67% yield with 93% ee as shown in Scheme 14. These results encouraged us to study the *ortho*-substituent effect in the asymmetric BLA-reaction.

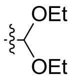
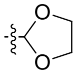
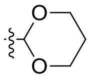
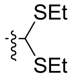
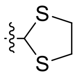
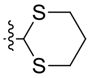
6.2 Results and Discussion

In 2001, Barbas *et al.* demonstrated the structure/activity relationship between proline and proline-like amino acid catalysts in BLA reaction,[60c] taking inspiration from this report we also investigated the three amino acid catalysts (**5a**, **5o**, **5p**) to show how the neighboring group controls the product enantio- and diastireo-selectivity's in BLA reactions.

Initial studies on simple benzaldehyde **1o** and 2-(diethoxymethyl)benzaldehyde **1p** with acetone **10a** in presence of 20 mol% of L-proline in DMSO (0.5 M) at 25 °C resulted the products (+)-**34oa** and (+)-**34pa** in large difference of selectivity's. Then we further moved the same reaction with L-thioproline **5o** and DMTC **5p** catalysis. When benzaldehyde **1o** reacted with 28 equiv. of acetone **10a** under L-thioproline **5o** and DMTC **5p** catalysts separately in DMSO for 48-72 h furnished the BLA product (+)-**34oa** in 56% and 64% yield with 71% ee and 85% ee respectively (Table 8, entry 1). Whereas interesting substrate 2-(diethoxymethyl)benzaldehyde **1p** with acetone in same reaction conditions, with L-thioproline **5o** yielded the (+)-**34pa** in 57% yield with 85% ee and with DMTC **5p** furnished the product (+)-**34pa** in 63% yield with enhanced selectivity 97% ee (Table 8, entry 2). These interesting results can explain through the secondary interacting neighboring group involvement in transition state. When BLA reaction performed with *ortho*-cyclic ether substituted benzaldehyde that is 2-(1,3-dioxolan-2-yl)benzaldehyde **1q** with acetone **10a** in DMSO at 25 °C, i. under **5a**-catalysis within 24 h, (+)-**34qa** furnished in 72% yield with 83% ee, ii. under **5o**-catalysis after 72 h furnished the BLA product (+)-**34qa** in 57% yield with 91% ee, iii. and with **5p**-catalysis after 48 h produced the (+)-**34qa** in 76% yield with 93% ee (Table 7, entry 3). The reaction of 2-(1,3-dioxan-2-yl)benzaldehyde **1r** with acetone **10a** in DMSO under **5a**-, **5o**- and **5p**-catalysis in separate vials within 24-72 h furnished the chiral BLA product (+)-**34ra** good yields with 91% ee, 96% ee and 94% ee, respectively. Other than oxygen containing *ortho*-substituents, we were used the sulphur containing neighboring group control in BLA reactions. When 2-(bis(ethylthio)methyl)benzaldehyde **1s** reacted with acetone **10a** in above same reaction conditions, under **5a**-catalysis 79% yield with 85% ee, in **5o**-catalysis 68% yield with 92% ee and under **5p**-catalysis 56% yield with 91% ee BLA product (+)-**34sa** was obtained. Interestingly, cyclic thioacetal substituted benzaldehydes (**1t**, **1u**) also reacted smoothly with acetone and furnished the desired products with good yields and selectivity's. After the observation of these six different kinds of *ortho*-substituted benzaldehydes under **5a**, **5o** and **5p** catalysis in BLA reactions, we can rationalize that, the control in selectivity was observed in *ortho*-substituent substrates compared to the simple benzaldehyde.

Table 8. Examination of various amino-acids in BLA reactions of acetone **10a** and *ortho*-substituted benzaldehydes.[e]



Entry	R 1o-w	Product 34	Yield (%)^a 34	ee (%)^b 34	Yield (%)^a 34	ee (%)^b 34	Yield (%)^a 34	ee (%)^b 34
			Catalyst **5a**		Catalyst **5o**		Catalyst **5p**	
1	-H	**34oa**	57	67	56	71	64	85
2		**34pa**	67	93	57	85	63	97
3		**34qa**	72	83	57	91	76	93
4		**34ra**	70	91	56	96	47	94
5		**34sa**	79	85	68	92	56	91
6		**34ta**	62	74	60	88	57	93
7		**34ua**	68	76	57	86	62	93
8	-OMe	**34va**	67	64	52	75	74	85
9	$-CH_3$	**34wa**	60	78	64	85	67	92

[a] Yield refers to the column-purified product. [b] ee determined by CSP HPLC analysis. [c] All L-proline **5a** and DMTC **5p**-catalysed reactions were took 24-36 h. [d] All L-thioproline **5o**-catalysed reactions were took 36-72 h. [e] Steriochemistry was assigned based on previous reports.

Later *ortho*-methoxy benzaldehyde **1v** was tested in BLA reaction condition, but selectivity was not superior then the previous substituents. But, in case of 2-methyl benzaldehyde **1w** under DMTC **5p**-catalysis desired product (+)-**34wa** was observed with 92% enantiomeric excess. This may be due to the steric factors between *ortho*-methyl and catalyst facilitated the high selectivity (TS-3, Figure 50).

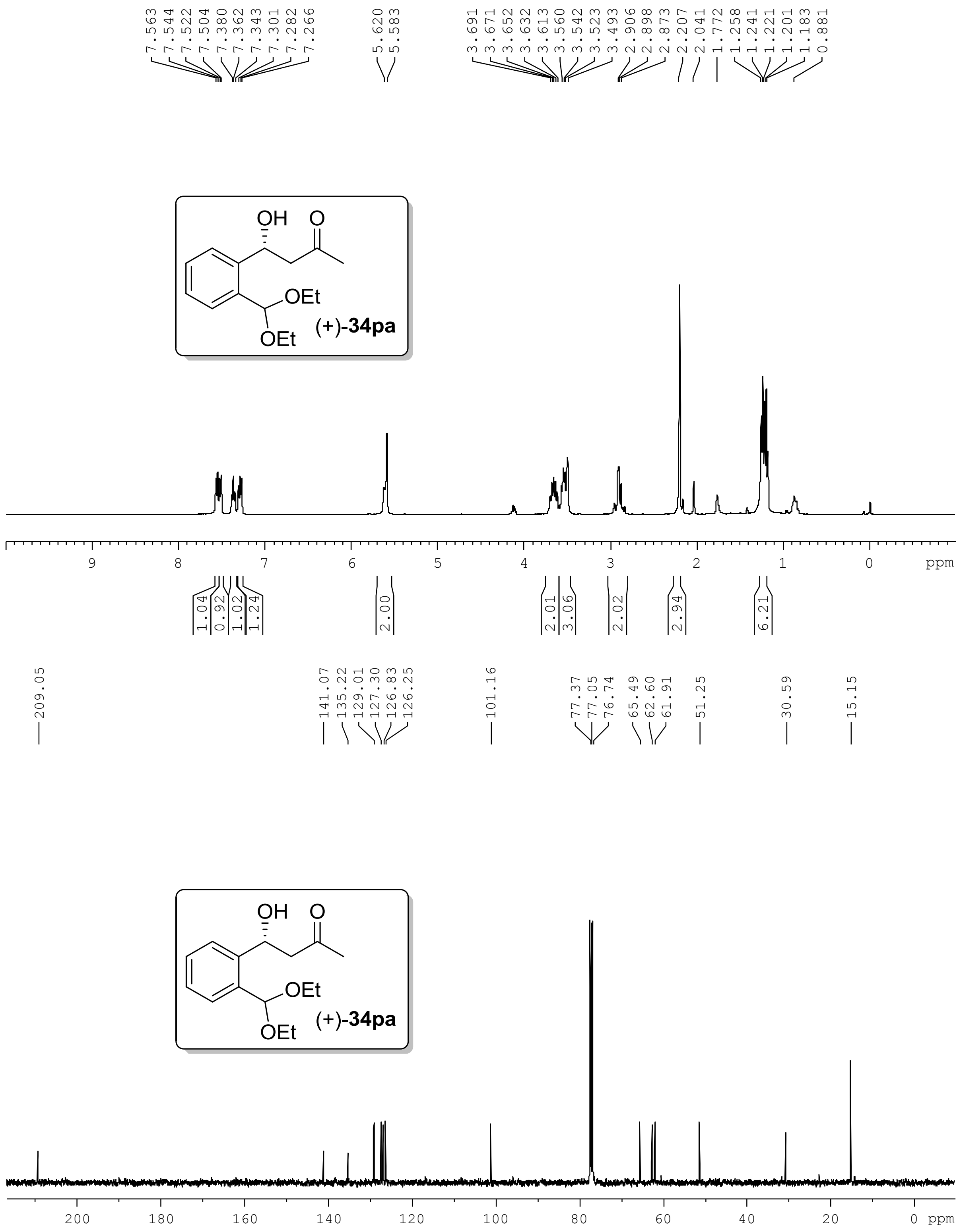


Figure-42. ^{1}H and ^{13}C NMR spectra of the product (+)-**34pa**.

Figure-43. ^{1}H and ^{13}C NMR spectra of the product (+)-**34qa**.

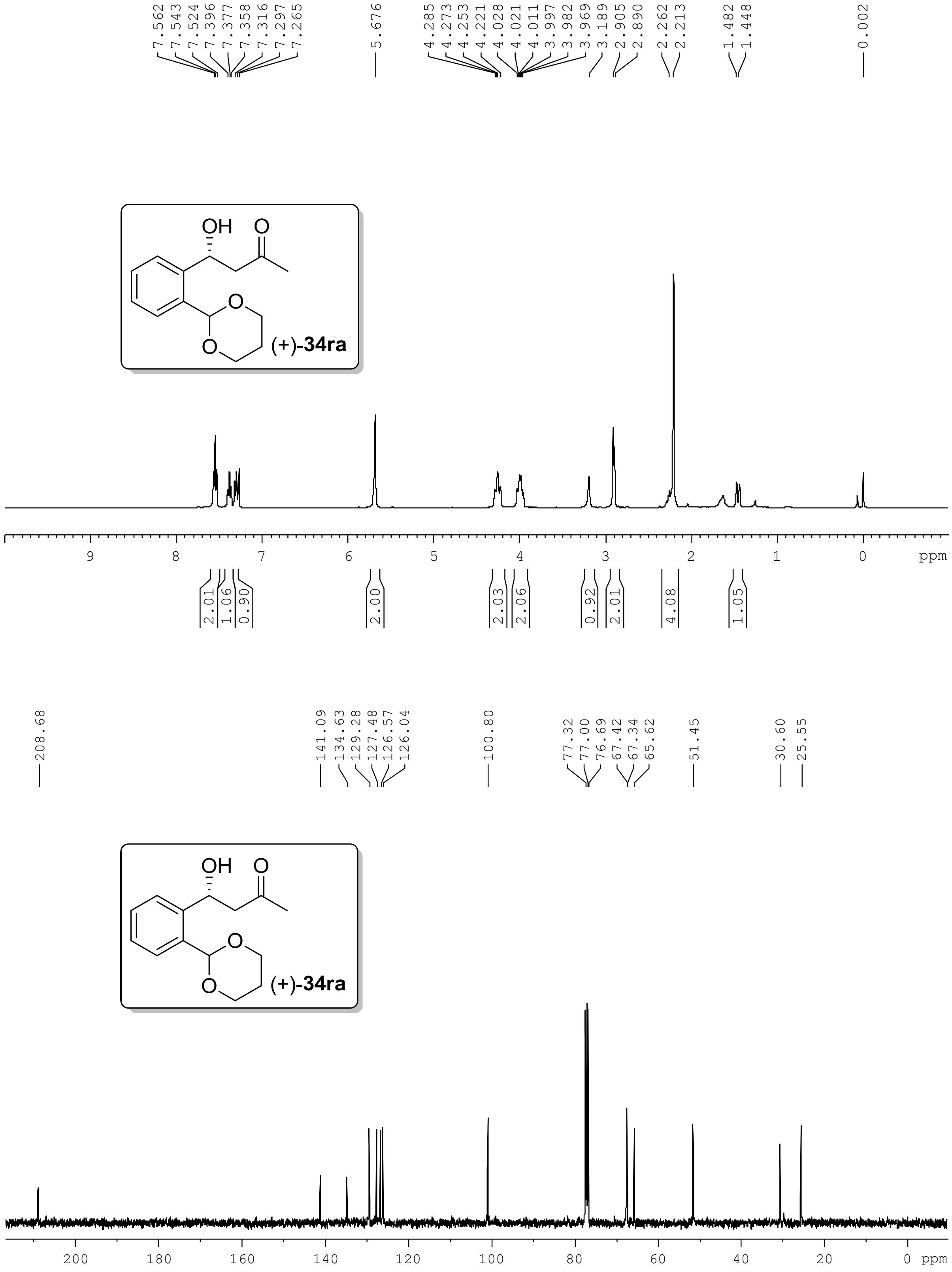


Figure-44. ^{1}H and ^{13}C NMR spectra of the product (+)-**34ra.**

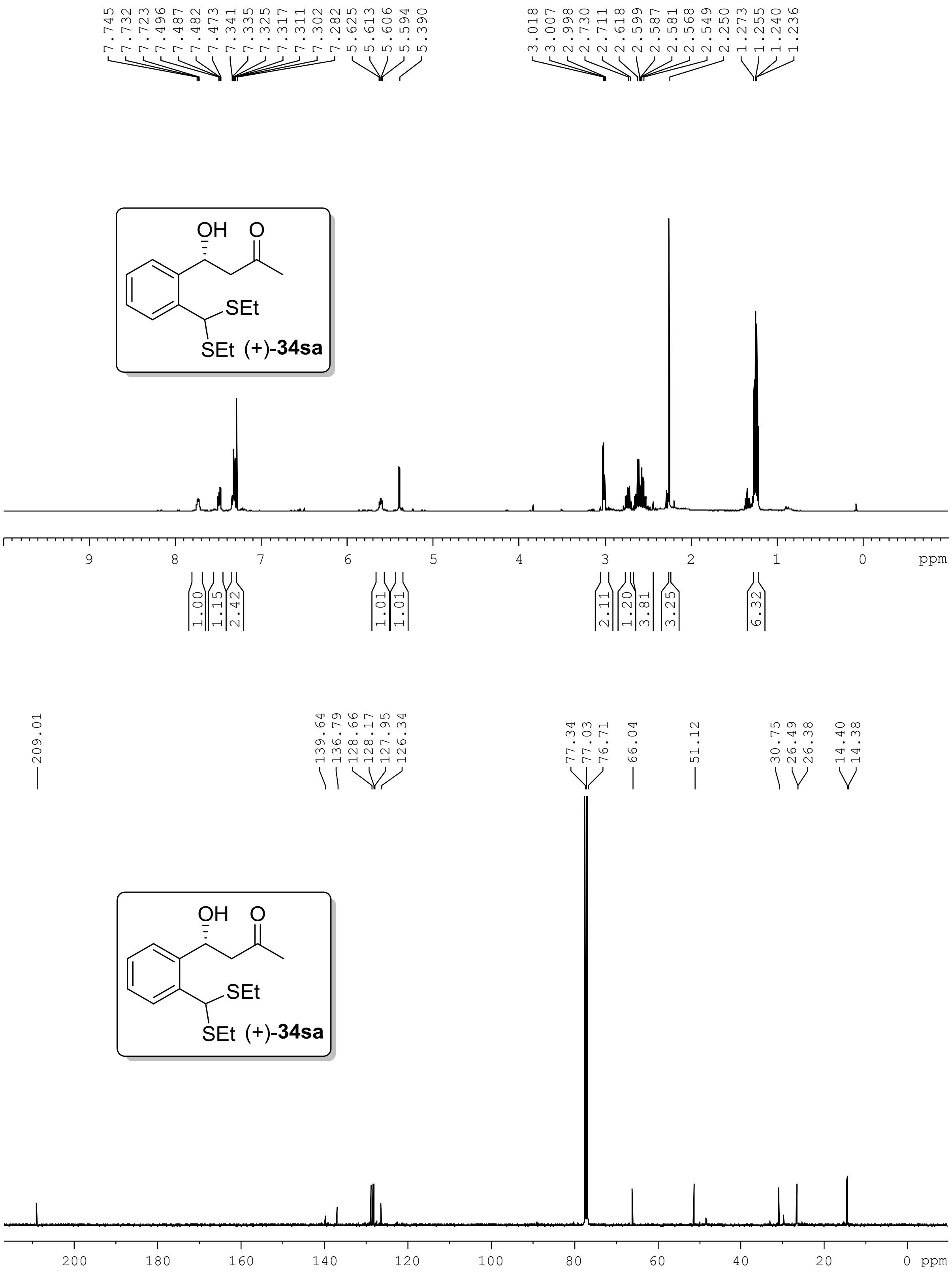


Figure-45. ^{1}H and ^{13}C NMR spectra of the product (+)-**34sa.**

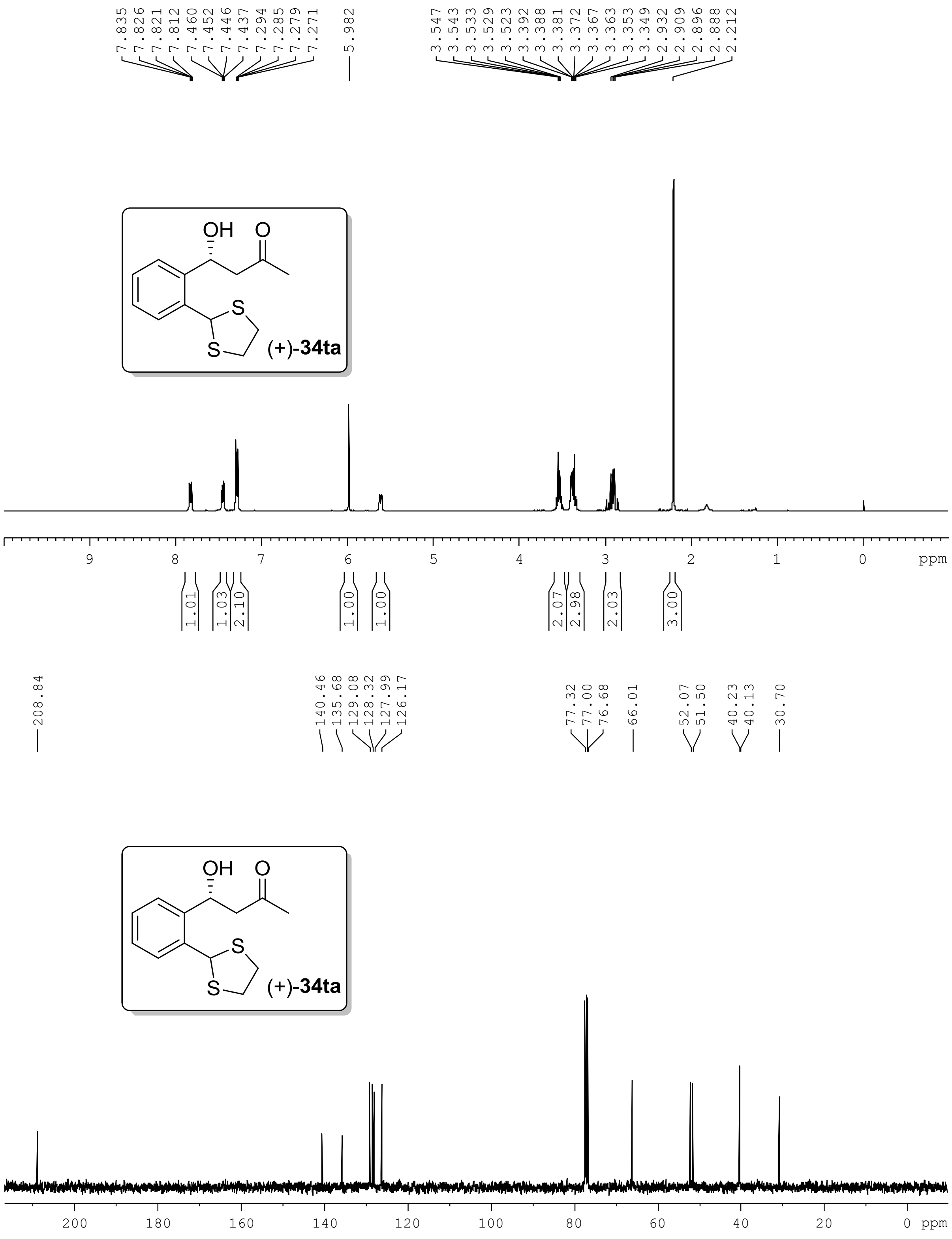


Figure-46. ^{1}H and ^{13}C NMR spectra of the product (+)-**34ta.**

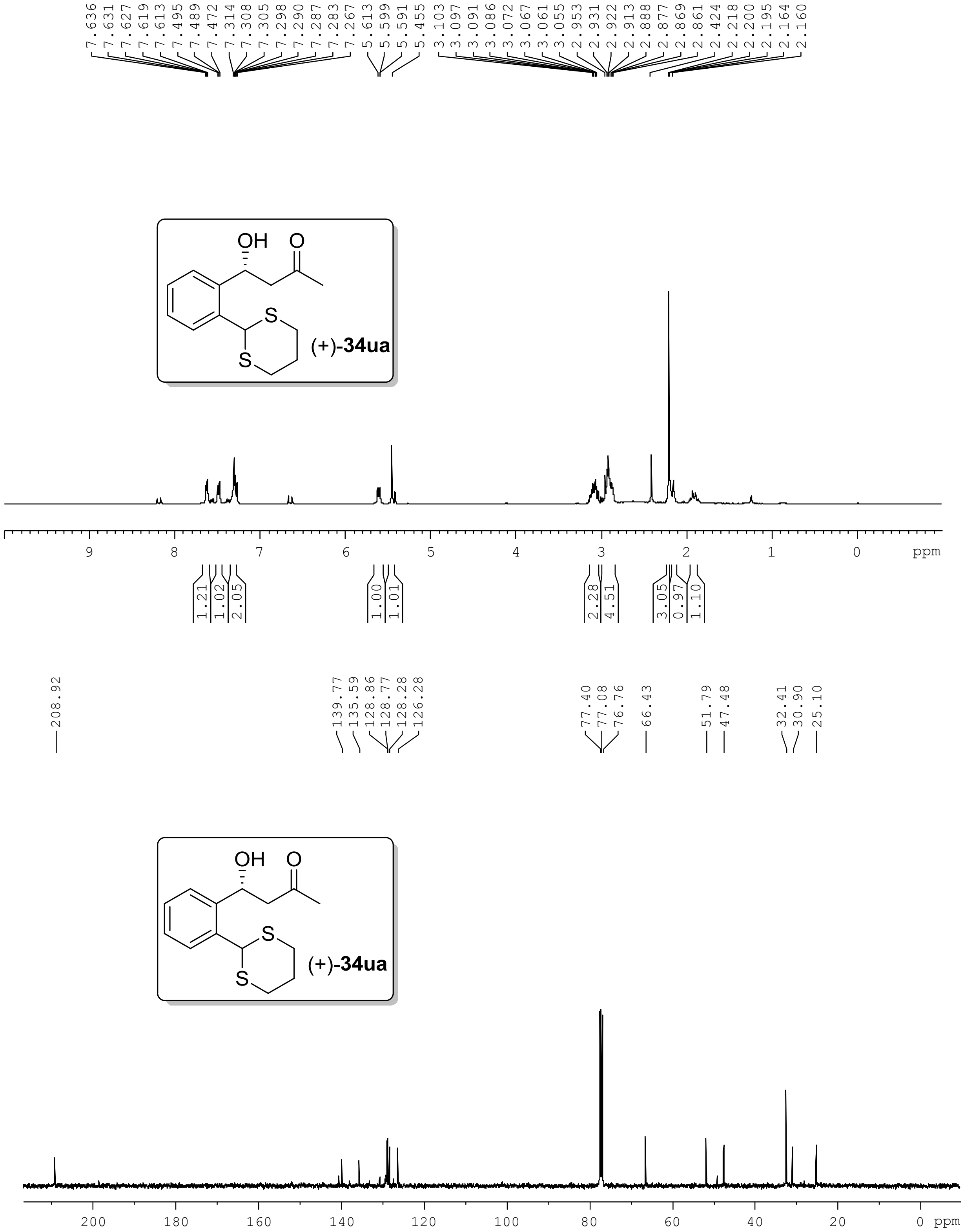
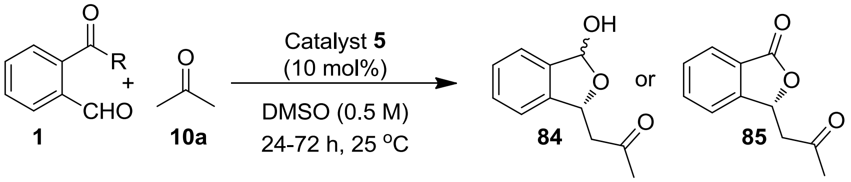
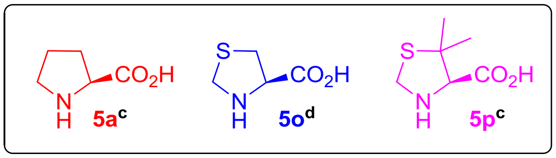


Figure-47. ^{1}H and ^{13}C NMR spectra of the product (+)-**34ua.**

On the other hand, if another competitive reacting functionality is there on the benzaldehyde, the outcome of the product selectivity/reactivity is interesting. When the *o*-phthalaldehyde **1x** reacted with acetone **10a** in DMSO under 20 mol% of L-proline for 24 h would lead to BLA product. However, BLA product was not detected in NMR instead it has shown the lactol formation of newly generated hydroxyl group with *ortho*-formyl substituent, the product dihydroisobenzofuranol (+)-**84xa** was obtained in 58% yield with 68% *ee*. Same substrate **1x** under **5o**-catalysis after 72 h furnished the dihydroisobenzofuranol (+)-**84xa** in 52% yield with 87% ee. In presence of DMTC, 70% yield 86% ee was obtained. Interestingly methyl 2-formylbenzoate **1y** with acetone **10a**, **5a** being a catalyst directly furnished the phthalide product (–)-**85ya** 74% yield with 41% ee only in DMSO. With other catalysts also furnished the phthalide (–)-**85ya** in very poor selectivity. This may be due to the *retro*-Michael-Michael addition reaction in DMSO solvent in presence of secondary amine as shown in ***ANNEXURE-III***, Figure **52**. Same thing happened with ethyl 2-formylbenzoate **1z** also as shown in entry 3, Table 9.

Table 9. Examination of various amino acids in BLA reactions of acetone **10a** and *ortho*-substituted benzaldehydes **1**.[e]





Entry	R	Product **84/85**	Yield (%)^a **84/85**	ee (%)^b **84/85**	Yield (%)^a **84/85**	ee (%)^b **84/85**	Yield (%)^a **84/85**	ee (%)^b **84/85**
			Catalyst **5a**		Catalyst **5o**		Catalyst **5p**	
1	**1x**: R=H	**84xa**	58	68	52	87	70	86
2	**1y**: R=OMe	**85ya**	74	41	68	13	75	10
3	**1z**: R=OEt	**85ya**	66	29	69	32	72	39

[a] Yield refers to the column-purified product. [b] ee determined by CSP HPLC analysis. [c] All L-proline **5a** and DMTC **5p**-catalysed reactions were took 24 h. [d] All L-thioproline **5o**-catalysed reactions were took 36 h. [e] Steriochemistry was assigned based on previous reports.

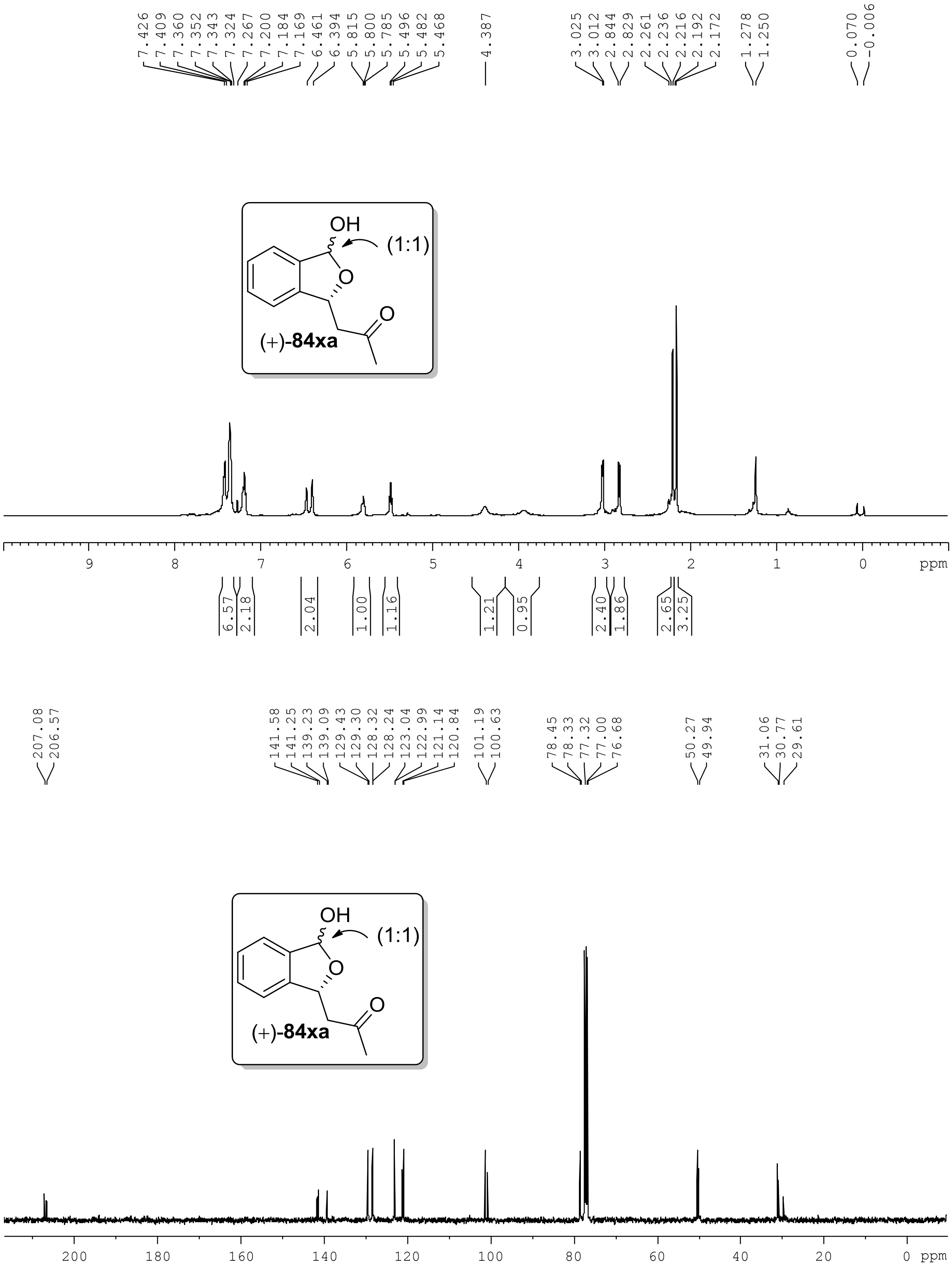


Figure-48. ^{1}H and ^{13}C NMR spectra of the product (+)-**84xa.**

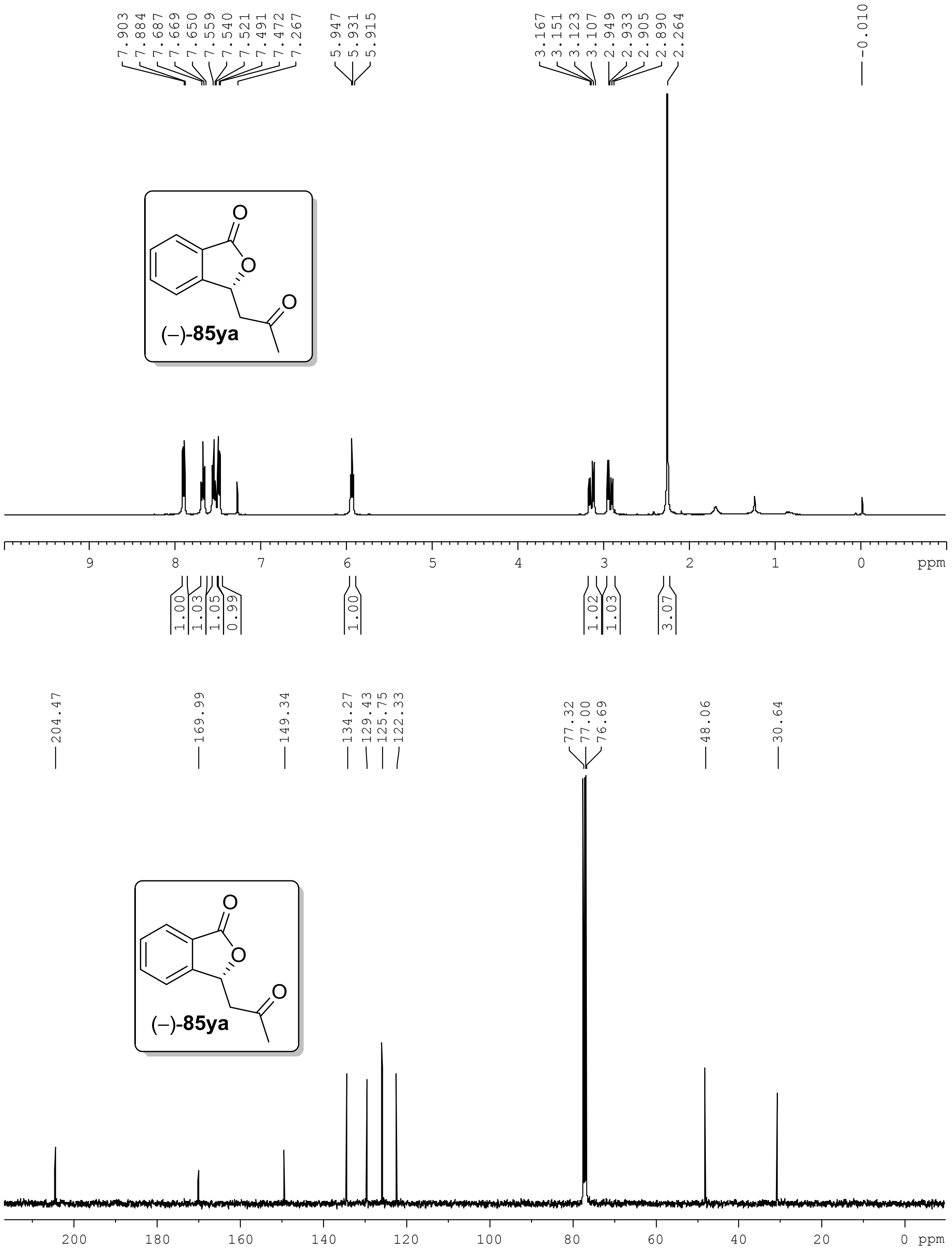
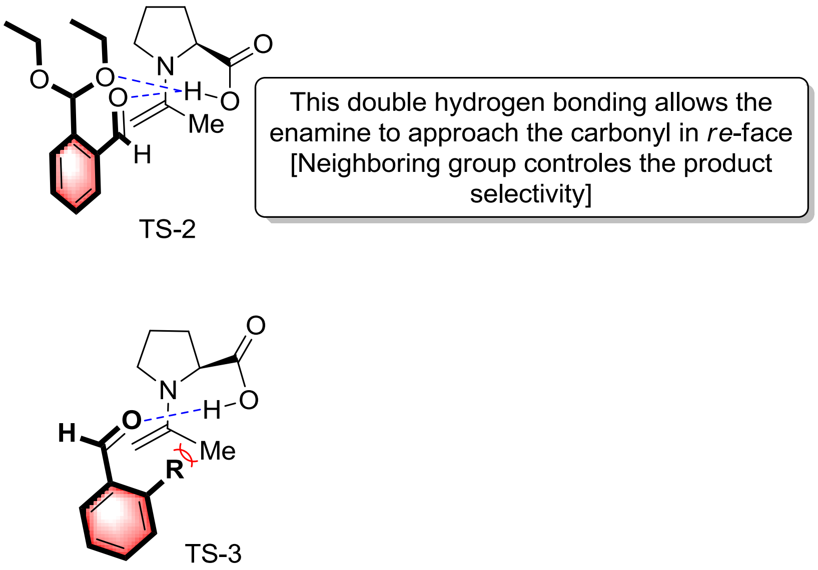


Figure-49. ^{1}H and ^{13}C NMR spectra of the product (–)-**85ya.**

6.3 Mechanistic Insights

The BLA reaction mainly proceeds through enamine formation and the hydrogen-bonding between aldehyde carbonyl and acid hydroxyl group of proline together plays a key role to achieve the high enantioselectivity's.[63] In-situ generated enamine approaches the *re*-face of aldehyde carbonyl. The outcome of high selectivity for the *ortho*-functionalized benzaldehydes with acetone could be explained by neighboring group participation through hydrogen bonding with the acid hydroxyl group (TS-2) and also because of steric hindrance (TS-3) in transition state as shown in Fig. 50.

Figure 50. Proposed reaction mechanism.



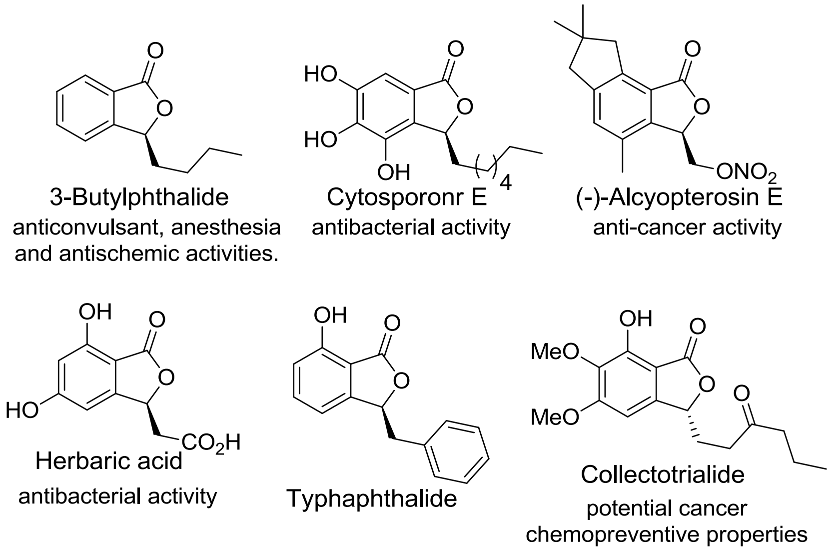
This double hydrogen bonding allows the enamine to approach the carbonyl in *re*-face [Neighboring group controles the product selectivity]

ANNEXURE-III:

AIII-1: Future utilization of BLA reaction in Phthalide Natural Products Synthesis.

Phthalides are five-membered lactones, which structural subunits are found in numerous natural products exhibiting a wide range of biological and pharmacological activities.[64] Phthalides are versatile building blocks for the synthesis of biologically active compounds and also useful in the treatment of circulatory and heart diseases. More than180 naturally occurring phthalide derivatives have been identified, among them nearly140 phthalides were isolated from a wide variety of plant species. Some of the biological active phthalides were charted in Figure 51.

Figure 51. Selected examples of naturally occurring chiral 3-substituted phthalides with reported biological activities.



3-Butylphthalide
anticonvulsant, anesthesia and antischemic activities.

Cytosporonr E
antibacterial activity

(-)-Alcyopterosin E
anti-cancer activity

Herbaric acid
antibacterial activity

Typhaphthalide

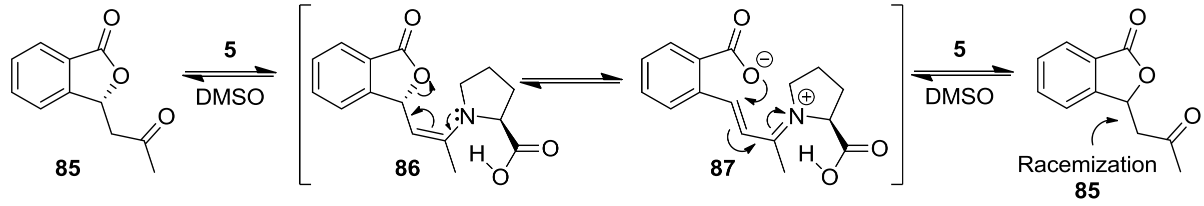
Collectotrialide
potential cancer chemopreventive properties

In recent years, many methodologies were employed for synthesis of phthalide natural products. Mainly Rh-, Pd- and Co-catalyzed cascade arylation, lactonization of phthalaldehyde [65] or iodo benzoates[66] using boron reagents and zinc are widely used for the phthalide synthesis. We are interested in organocatalytic synthesis of optically pure phthalides. As mentioned above, if we use phthalaldehyde in BLA reactions with appropriate ketones under modified conditions we can synthesize optically pure phthalides in high yields.

AIII-2: Explanation for decreasing selectivity in reaction of 1y/1z with 10a.

The BLA reaction of **1y/1z** with acetone **10a** in DMSO under amino-acid catalysis furnished the phthalides **85** in good yield with poor selectivity. This may be due to the formed phthalides in DMSO under amino-acid catalysis, *retro*-Michael fashion will generate the intermediate **87**, again that intermediate generate back phthalide **85** through Michael addition in racemic form as shown in Fig. 52.

Figure 52. Explanation for decreasing selectivity in BLA reaction of **1y/1z** with **10a**.



7. Experimental Section

7.1 General Methods:

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400/500 MHz and 100/125 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. *In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants J are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063-0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

7.2 General procedure for the synthesis of 5-alkylcyclohexane-1,3-dione 13:

To a stirred solution of potassium *tert*-butoxide (672 mg) in 40 mL of anhydrous THF, in an oven dried two neck round bottom flask equipped with a magnetic stirring bar and a refluxing condenser was added diethyl malonate (6.5 mmol) through septum at RT. After stirring for 0.5 h, alkylideneacetone **18** (6 mmol) was added. After stirring for 12 h at 85 °C, the solvent was removed under reduced pressure, then 20% aq. NaOH (50 equiv.) was added and stirred at 90 °C for 3 h. The reaction mixture was acidified with con. HCl up to pH = 2 and the whole mixture was refluxed at 90 °C for 1 h. The reaction mixture was cooled and the aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. Pure products 5-alkylcyclohexane-1,3-diones **13** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.3 General procedure for the synthesis of TCRA products 16:

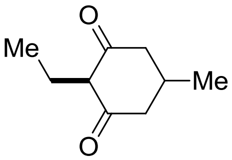
In an ordinary glass vial equipped with a magnetic stirring bar, containing 20 mol% of proline, 0.3 mmol of Hantzsch ester **11a** and 0.3 mmol of 5-alkylcyclohexane-1,3-dione **13** was added acetonitrile (1.0 mL) and stirred at 25 °C for 5 min and then 3 equiv. of aldehyde **1a-j** was added and the reaction mixture was stirred at ambient temperature for 1 h. The crude reaction mixture was treated with saturated aqueous ammonium chloride; the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure products **16** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.4 General procedure for the high-yielding synthesis of chiloglottones (16):

To a stirred solution of potassium *tert*-butoxide (112 mg) in 10 mL of anhydrous THF, in an oven dried two neck round bottom flask equipped with a magnetic stirring bar and refluxing condenser was added diethyl malonate **2** (1.5 mmol) through septum at RT. After stirring for 0.5 h, alkylideneacetone **18** (1 mmol) was added. After stirring for 12 h at 85 °C, the solvent was removed under reduced pressure, then 20% aq. NaOH (50 equiv.) was added and stirred at 90 °C for 3 h. Then reaction mixture was neutralized followed by acidified (pH = 2) with con. HCl, which was further refluxed at 90 °C for 1 h. Reaction mixture brought to room temperature and the aqueous layer, was extracted with THF (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuum. To this crude product **13**, 20 mol% of proline, 1 mmol of Hantzsch ester **11a** and acetonitrile (3.0 mL) were added and stirred at 25 °C for 5 min and then 3 equiv. of aldehyde **1a-j** was added and the reaction mixture was stirred at ambient temperature for 1 h. The crude reaction mixture was treated with saturated aqueous ammonium chloride solution; the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure products **16** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

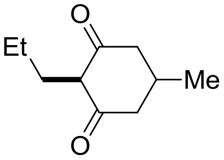
- Due to the keto-enol and enol-enol tautomerism in 2,5-dialkylcyclohexane-1,3-dione (**16**) compounds, ^{13}C NMR shows some of carbons (2 x CH_2 and 2 x C=O) are poor resolution even after more than 1000 scans in the solvent system of $CDCl_3$ or CD_3OD.[68]

2-Ethyl-5-methylcyclohexane-1,3-dione (16ba): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 150 °C. IR (neat): ν_{max} 2923, 1590 (*C=O*), 1389, 1253, 1000, 627, 613 and 606 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.42 (2H, d, *J* = 12.4 Hz), 2.24 (2H, q, *J* = 7.6 Hz), 2.20-2.12 (3H, m), 1.06 (3H, d, *J* = 5.6 Hz), 0.89 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 118.2 (C), 42.2 (br, 2 x CH_2), 30.0 (CH), 21.3 (CH_3), 16.1 (CH_2), 13.7 (CH_3); HRMS m/z 155.1072 (M + H), calcd for $C_9H_{15}O_2$ 155.1072.



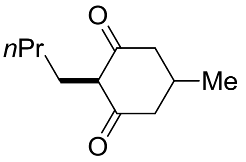
16ba

5-Methyl-2-propylcyclohexane-1,3-dione (16bb): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 126 °C. IR (neat): ν_{max} 2963, 1710 (*C=O*), 1602 (*C-O*), 1395, 1216, 913, 679, 650 and 610 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.45 (2H, d, *J* = 12.0 Hz), 2.22 (2H, t, *J* = 7.6 Hz), 2.17-2.14 (3H, m), 1.35 (2H, sextet, *J* = 7.2 Hz), 1.08 (3H, d, *J* = 5.6 Hz), 0.88 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 116.6 (C), 42.2 (br, 2 x CH_2), 30.0 (CH), 24.8 (CH_2), 22.9 (CH_2), 21.3 (CH_3), 14.5 (CH_3); LRMS m/z 169.10 (M+H$^+$), calcd $C_{10}H_{16}O_2$ 168.1150; Anal. calcd for $C_{10}H_{16}O_2$ (168.1150): C, 71.39; H, 9.59. Found: C, 71.52; H, 9.45%.



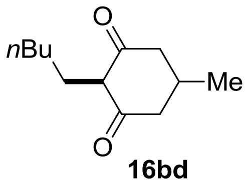
16bb

Chiloglottone-3 [2-butyl-5-methylcyclohexane-1,3-dione] (16bc):[69a] Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 108 °C. IR (neat): ν_{max} 2995, 1703 (*C=O*), 1416, 1217, 1170, 917, 648 and 615 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.44 (2H, d, *J* = 12.4 Hz), 2.24 (2H, t, *J* = 7.2 Hz), 2.19-2.13 (3H, m), 1.33-1.28 (4H, m), 1.08 (3H, d, *J* = 5.6 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 116.8 (C), 42.0 (br, 2 x CH_2), 32.1 (CH_2), 30.0 (CH), 23.9 (CH_2), 22.6 (CH_2), 21.3 (CH_3), 14.6 (CH_3); HRMS m/z 183.1383 (M + H), calcd for $C_{11}H_{19}O_2$ 183.1385.



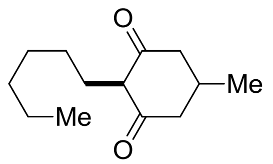
Chiloglottone-3 (**16bc**)

5-Methyl-2-pentylcyclohexane-1,3-dione (16bd): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 120 °C. IR (neat): ν_{max} 2963, 1710 (*C=O*), 1602 (*C-O*), 1395, 1145, 913, 679, 650 and 610 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 2.47 (2H, d, *J* = 12.4 Hz), 2.21 (2H, t, *J* = 6.8 Hz), 2.19-2.14 (3H, m), 1.32-1.26 (6H, m), 1.07 (3H, d, *J* = 5.6 Hz), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 116.8 (C), 42.2 (br, 2 x CH$_2$), 33.0 (CH$_2$), 29.8 (CH), 29.4 (CH$_2$), 23.7 (CH$_2$), 22.6 (CH$_2$), 21.2 (CH$_3$), 14.6 (CH$_3$); HRMS m/z 197.1540 (M + H), calcd for $C_{12}H_{21}O_2$ 197.1541.



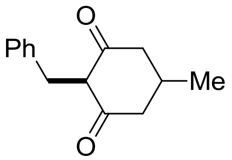
16bd

Chiloglottone-6 [2-hexyl-5-methylcyclohexane-1,3-dione] (16be): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 120 °C. IR (neat): ν_{max} 2963, 1710 (*C=O*), 1602 (*C-O*), 1395, 1216, 1145, 913, 679, 650 and 610 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 2.43 (2H, d, *J* = 12.4 Hz), 2.18 (2H, t, *J* = 7.2 Hz), 2.16-2.12 (3H, m), 1.31-1.26 (8H, m), 1.06 (3H, d, *J* = 5.6 Hz), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 116.9 (C), 42.2 (br, 2 x CH$_2$), 33.1 (CH$_2$), 30.5 (CH$_2$), 30.0 (CH), 29.8 (CH$_2$), 23.9 (CH$_2$), 22.8 (CH$_2$), 21.3 (CH$_3$), 14.6 (CH$_3$); HRMS m/z 233.1517 (M + Na), calcd for $C_{13}H_{22}O_2Na$ 233.1517.



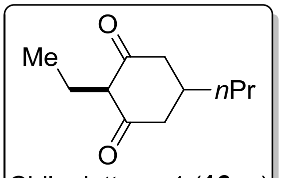
Chiloglottone-6 (**16be**)

2-Benzyl-5-methylcyclohexane-1,3-dione (16bf): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 131 °C. IR (neat): ν_{max} 2924, 1555, 1381, 1337, 1244, 1106, 680 and 652 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.19-7.13 (4H, m), 7.08-7.04 (1H, m), 3.56 (2H, s), 2.46 (2H, d, *J* = 12.4 Hz), 2.19-2.12 (3H, m), 1.06 (3H, d, *J* = 5.6 Hz); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 143.1 (C), 129.6 (2 x CH), 129.0 (2 x CH), 126.4 (CH), 116.2 (C), 42.1 (br, 2 x CH$_2$), 29.9 (CH), 28.5 (CH$_2$), 21.3 (CH$_3$); HRMS m/z 217.1228 (M + H), calcd for $C_{14}H_{17}O_2$ 217.1228.



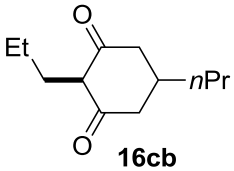
16bf

Chiloglottone-1 [2-ethyl-5-propylcyclohexane-1,3-dione] (16ca):[69b] Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 122 °C. IR (neat): ν_{max} 2945, 1721 (*C=O*), 1432, 1217, 1170, 918 and 657 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 2.46 (2H, dd, *J* = 15.0, 5.0 Hz), 2.26 (2H, q, *J* = 5.0 Hz), 2.16 (2H, dd, *J* = 15.0, 10.0 Hz), 2.08-2.04 (1H, m), 1.40-1.37 (4H, m), 0.95 (3H, t, *J* = 5.0 Hz), 0.91 (3H, t, *J* = 10.0 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 118.3 (C), 40.4 (br, 2 x CH_2), 39.0 (CH_2), 34.6 (CH), 20.9 (CH_2), 16.1 (CH_2), 14.6 (CH_3), 13.7 (CH_3); HRMS m/z 183.1384 (M + H), calcd for $C_{11}H_{19}O_2$ 183.1385.



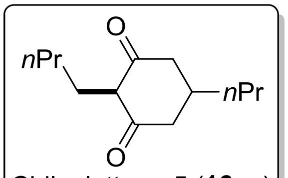
Chiloglottone-1 (**16ca**)

2,5-Dipropylcyclohexane-1,3-dione (16cb): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 126 °C. IR (neat): ν_{max} 2960, 1711 (*C=O*), 1568 (*C-O*), 1378, 1329, 1242, 1112, 652, 631 and 609 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.46 (2H, dd, *J* = 16.4, 4.4 Hz), 2.21 (2H, t, *J* = 7.6 Hz), 2.18-2.12 (2H, m), 2.08-2.01 (1H, m), 1.42-1.32 (6H, m), 0.95 (3H, t, *J* = 6.8 Hz), 0.88 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 116.7 (C), 40.4 (br, 2 x CH_2), 39.0 (CH_2), 34.6 (CH), 24.8 (CH_2), 22.9 (CH_2), 20.9 (CH_2), 14.6 (CH_3), 14.5 (CH_3); HRMS m/z 197.1539 (M + H), calcd for $C_{12}H_{21}O_2$ 197.1539.

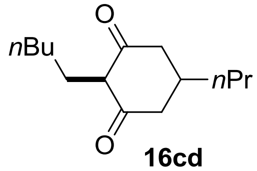


16cb

Chiloglottone-5 [2-butyl-5-propylcyclohexane-1,3-dione] (16cc):[69b] Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 137 °C. IR (neat): ν_{max} 2960, 1711 (*C=O*), 1568 (*C-O*), 1329, 1242, 1112, 671, 652, 631 and 609 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.46 (2H, dd, *J* = 16.8, 4.0 Hz), 2.24 (2H, t, *J* = 7.2 Hz), 2.19-2.12 (2H, m), 2.08-2.02 (1H, m), 1.40-1.37 (4H, m), 1.32-1.28 (4H, m), 0.95 (3H, t, *J* = 6.4 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 117.0 (C), 40.5 (br, 2 x CH_2), 39.0 (CH_2), 34.6 (CH), 32.1 (CH_2), 23.9 (CH_2), 22.6 (CH_2), 20.9 (CH_2), 14.6 (2 x CH_3); HRMS m/z 211.1698 (M + H), calcd for $C_{13}H_{23}O_2$ 211.1698.

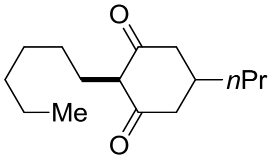


Chiloglottone-5 (**16cc**)



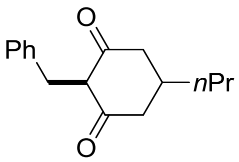
16cd

2-Pentyl-5-propylcyclohexane-1,3-dione (16cd): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 135 °C. IR (neat): ν_{max} 2960, 1711 (*C=O*), 1568 (*C-O*), 1378, 1242, 1112, 671, 652, 631 and 609 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.46 (2H, dd, *J* = 16.8, 4.0 Hz), 2.23 (2H, t, *J* = 6.8 Hz), 2.19-2.12 (2H, m), 2.08-2.02 (1H, m), 1.40-1.35 (4H, m), 1.34-1.26 (6H, m), 0.95 (3H, t, *J* = 6.8 Hz), 0.90 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 117.0 (C), 39.0 (CH_2), 34.6 (CH), 33.1 (CH_2), 29.5 (CH_2), 23.8 (CH_2), 22.8 (CH_2), 20.9 (CH_2), 14.6 (CH_3), 14.6 (CH_3); LRMS m/z 225.20 (M+H$^+$), calcd $C_{14}H_{24}O_2$ 224.1776; Anal. calcd for $C_{14}H_{24}O_2$ (224.1776): C, 74.95; H, 10.78. Found: C, 74.85; H, 10.66%.



16ce

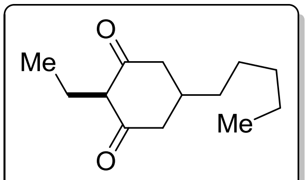
2-Hexyl-5-propylcyclohexane-1,3-dione (16ce): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 140 °C. IR (neat): ν_{max} 2958, 1548, 1367, 1322, 1241, 1189, 1073, 723, 690, 650 and 609 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.45 (2H, dd, *J* = 16.8, 4.0 Hz), 2.22 (2H, t, *J* = 6.8 Hz), 2.14 (2H, dd, *J* = 16.0, 11.4 Hz), 2.06-2.03 (1H, m), 1.40-1.35 (4H, m), 1.32-1.25 (8H, m), 0.93 (3H, t, *J* = 6.4 Hz), 0.89 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 117.0 (C), 40.4 (br, 2 x CH_2), 39.0 (CH_2), 34.6 (CH), 33.2 (CH_2), 30.5 (CH_2), 29.8 (CH_2), 23.9 (CH_2), 22.8 (CH_2), 20.9 (CH_2), 14.6 (2 x CH_3); HRMS m/z 239.2011 (M + H), calcd for $C_{15}H_{27}O_2$ 239.2011.



16cf

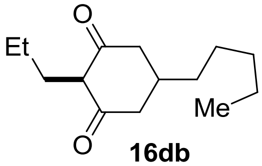
2-Benzyl-5-propylcyclohexane-1,3-dione (16cf): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 152 °C. IR (neat): ν_{max} 2960, 1547, 1366, 1322, 1241, 721, 692 and 609 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.21-7.15 (4H, m), 7.10-7.06 (1H, m), 3.58 (2H, s), 2.50 (2H, dd, *J* = 16.8, 4.0 Hz), 2.20 (2H, dd, *J* = 16.0, 11.2 Hz), 2.12-2.05 (1H, m), 1.41-1.37 (4H, m), 0.94 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 143.1 (C), 129.6 (2 x CH), 129.0 (2 x CH), 126.4 (CH), 116.4 (C), 40.5 (br, 2 x CH_2), 39.0 (CH_2), 34.6 (CH), 28.5 (CH_2), 20.9 (CH_2), 14.6 (CH_3); HRMS m/z 267.1366 (M + Na), calcd for $C_{16}H_{20}O_2Na$ 267.1361.

Chiloglottone-2 [2-ethyl-5-pentylcyclohexane-1,3-dione] (16da):[69a] Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 131 °C. IR (neat): ν_{max} 2927, 1719, 1565, 1384, 1106, 729, 638 and 611 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.46 (2H, dd, *J* = 16.8, 4.4 Hz), 2.25 (2H, q, *J* = 7.6 Hz), 2.15 (2H, dd, *J* = 16.4, 11.6 Hz), 2.06-2.01 (1H, m), 1.40-1.31 (8H, m), 0.93 (3H, t, *J* = 6.4 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 118.3 (C), 40.5 (br, 2 x CH_2), 36.7 (CH_2), 34.9 (CH), 33.2 (CH_2), 27.5 (CH_2), 23.8 (CH_2), 16.1 (CH_2), 14.5 (CH_3), 13.7 (CH_3); HRMS m/z 211.1698 (M + H), calcd for $C_{13}H_{23}O_2$ 211.1698.



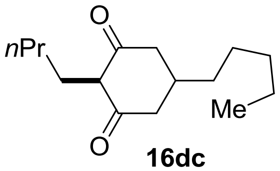
Chiloglottone-2 (**16da**)

5-Pentyl-2-propylcyclohexane-1,3-dione (16db): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 138 °C. IR (neat): ν_{max} 2927, 1720, 1565, 1384, 1241, 1106, 643, 620 and 605 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.47 (2H, dd, *J* = 16.4, 4.0 Hz), 2.22 (2H, t, *J* = 7.6 Hz), 2.16 (2H, dd, *J* = 16.4, 11.2 Hz), 2.06-2.00 (1H, m), 1.40-1.31 (10H, m), 0.93 (3H, t, *J* = 7.2 Hz), 0.88 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 116.8 (C), 40.4 (br, 2 x CH_2), 36.7 (CH_2), 34.9 (CH), 33.2 (CH_2), 27.5 (CH_2), 24.8 (CH_2), 23.8 (CH_2), 22.9 (CH_2), 14.5 (2 x CH_3); HRMS m/z 247.1674 (M + Na), calcd for $C_{14}H_{24}O_2Na$ 247.1674.



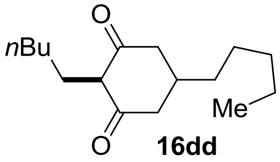
16db

2-Butyl-5-pentylcyclohexane-1,3-dione (16dc): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 140 °C. IR (neat): ν_{max} 2927, 1719, 1565, 1384, 1242, 1106, 729, 638 and 611 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.45 (2H, dd, *J* = 16.4, 4.0 Hz), 2.22 (2H, t, *J* = 7.2 Hz), 2.14 (2H, dd, *J* = 16.4, 11.2 Hz), 2.03-1.99 (1H, m), 1.37-1.23 (12H, m), 0.91 (3H, t, *J* = 6.8 Hz), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 117.0 (C), 40.5 (br, 2 x CH_2), 36.7 (CH_2), 34.9 (CH), 33.2 (CH_2), 32.1 (CH_2), 27.5 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 22.6 (CH_2), 14.6 (CH_3), 14.5 (CH_3); HRMS m/z 239.2011 (M + H), calcd for $C_{15}H_{27}O_2$ 239.2011.



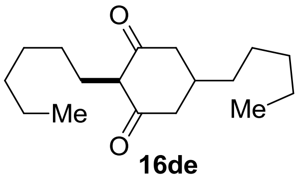
16dc

2,5-Dipentylcyclohexane-1,3-dione (16dd): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 147 °C. IR (neat): ν_{max} 2924, 1555, 1382, 1337, 1106, 655 and 611 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.47 (2H, dd, *J* = 16.8, 4.0 Hz), 2.23 (2H, t, *J* = 6.8 Hz), 2.16 (2H, dd, *J* = 16.4, 11.2 Hz), 2.06-2.00 (1H, m), 1.40-1.35 (4H, m), 1.34-1.27 (10H, m), 0.93 (3H, t, *J* = 6.8 Hz), 0.90 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 117.0 (C), 40.7 (br, 2 x CH_2), 36.7 (CH_2), 34.9 (CH), 33.2 (CH_2), 33.1 (CH_2), 29.5 (CH_2), 27.5 (CH_2), 23.82 (CH_2), 23.78 (CH_2), 22.8 (CH_2), 14.6 (CH_3), 14.5 (CH_3); LRMS m/z 253.50 (M + H$^+$), calcd $C_{16}H_{28}O_2$ 252.2089; Anal. calcd for $C_{16}H_{28}O_2$ (252.2089): C, 76.14; H, 11.18. Found: C, 76.25; H, 11.13%.



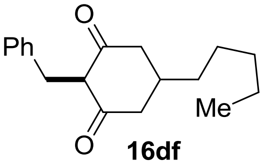
16dd

2-Hexyl-5-pentylcyclohexane-1,3-dione (16de): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 152 °C. IR (neat): ν_{max} 2927, 1720, 1565, 1384, 1106, 643, 620 and 605 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.45 (2H, dd, *J* = 16.4, 4.0 Hz), 2.22 (2H, t, *J* = 6.8 Hz), 2.14 (2H, dd, *J* = 16.0, 10.8 Hz), 2.04-2.01 (1H, m), 1.36-1.27 (16H, m), 0.91 (3H, t, *J* = 6.4 Hz), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 117.0 (C), 40.5 (br, 2 x CH_2), 36.7 (CH_2), 34.9 (CH), 33.2 (2 x CH_2), 30.5 (CH_2), 29.8 (CH_2), 27.5 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 22.8 (CH_2), 14.6 (CH_3), 14.5 (CH_3); LRMS m/z 265.43 (M - H$^+$), calcd $C_{17}H_{30}O_2$ 266.2246; Anal. calcd for $C_{17}H_{30}O_2$ (266.2246): C, 76.64; H, 11.35. Found: C, 76.58; H, 11.26%.



16de

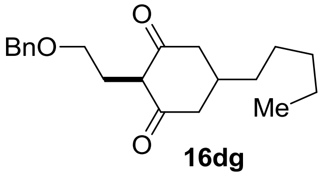
2-Benzyl-5-pentylcyclohexane-1,3-dione (16df): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp: 182 °C. IR (neat): ν_{max} 2960, 1548, 1366, 1322, 1241, 1189, 1073, 721, 692 and 609 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.19-7.13 (4H, m), 7.08-7.04 (1H, m), 3.56 (2H, s), 2.49 (2H, dd, *J* = 16.8, 4.4 Hz), 2.19 (2H, dd, *J* = 16.0, 11.2 Hz), 2.07-2.05 (1H, m), 1.36-1.30 (8H, m), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 143.1 (C), 129.6 (2 x CH), 129.0 (2 x CH), 126.4 (CH), 116.4 (C), 40.5 (br, 2 x CH_2), 36.7 (CH_2), 34.8 (CH), 33.2



16df

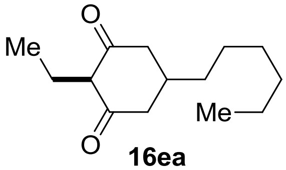
(CH$_2$), 28.5 (CH$_2$), 27.5 (CH$_2$), 23.8 (CH$_2$), 14.5 (CH$_3$); HRMS m/z 273.1854 (M + H), calcd for $C_{18}H_{25}O_2$ 273.1855.

2-(2-(Benzyloxy)ethyl)-5-pentylcyclohexane-1,3-dione (16dg): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as semi-solid. IR (neat): IR (neat): ν_{max} 2924, 1556, 1382, 1336, 1263, 1107, 754 and 655 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.36-7.33 (4H, m), 7.31-7.26 (1H, m), 4.52 (2H, s), 3.48 (2H, t, *J* = 7.2 Hz), 2.62 (2H, t, *J* = 7.2 Hz), 2.47 (2H, dd, *J* = 16.8, 4.0 Hz), 2.16 (2H, dd, *J* = 16.4, 11.2 Hz), 2.05-2.02 (1H, m), 1.40-1.28 (8H, m), 0.92 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 139.8 (C), 129.5 (2 x CH), 129.1 (2 x CH), 128.8 (CH), 113.0 (C), 73.8 (CH$_2$), 70.2 (CH$_2$), 40.3 (br, 2 x CH$_2$), 36.6 (CH$_2$), 34.7 (CH), 33.1 (CH$_2$), 27.5 (CH$_2$), 23.8 (CH$_2$), 23.3 (CH$_2$), 14.5 (CH$_3$); LRMS m/z 317.25 (M + H$^+$), calcd $C_{20}H_{28}O_3$ 316.2038; Anal. calcd for $C_{20}H_{28}O_3$ (316.2038): C, 75.91; H, 8.92. Found: C, 75.79; H, 8.84%.



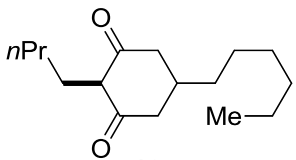
16dg

2-Ethyl-5-hexylcyclohexane-1,3-dione (16ea) : Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 143 °C. IR (neat): ν_{max} 2924, 1555, 1381, 1367, 1244, 1106, 680 and 652 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 2.45 (2H, dd, *J* = 16.8, 4.0 Hz), 2.24 (2H, q, *J* = 7.6 Hz), 2.14 (2H, dd, *J* = 15.6, 11.2 Hz), 2.03-2.01 (1H, m), 1.35-1.31 (10H, m), 0.90 (3H, t, *J* = 7.2 Hz), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 118.4 (C), 40.6 (br, 2 x CH$_2$), 36.7 (CH$_2$), 34.9 (CH), 33.1 (CH$_2$), 30.6 (CH$_2$), 27.8 (CH$_2$), 23.8 (CH$_2$), 16.1 (CH$_2$), 14.6 (CH$_3$), 13.7 (CH$_3$); LRMS m/z 225.30 (M + H$^+$), calcd $C_{14}H_{24}O_2$ 224.1776; Anal. calcd for $C_{14}H_{24}O_2$ (224.1776): C, 74.95; H, 10.78. Found: C, 74.78; H, 10.65%.



16ea

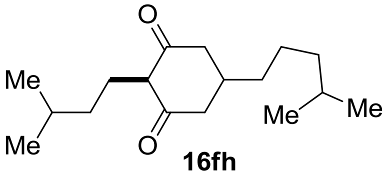
2-Butyl-5-hexylcyclohexane-1,3-dione (16ec): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 162 °C. IR (neat): ν_{max} 2920, 1586, 1138, 1082, 819, 678, 645 and 618 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 2.47 (2H, dd, *J* = 16.8, 4.4 Hz), 2.24 (2H, t, *J* = 7.2 Hz), 2.16 (2H, dd, *J* = 16.8, 11.6 Hz), 2.06-2.00 (1H, m), 1.38-1.29 (14H, m), 0.92 (3H, t, *J* = 6.4



16ec

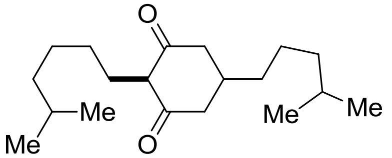
Hz), 0.90 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 117.0 (C), 40.9 (br, 2 x CH$_2$), 36.7 (CH$_2$), 34.9 (CH), 33.1 (CH$_2$), 32.1 (CH$_2$), 30.6 (CH$_2$), 27.8 (CH$_2$), 23.9 (CH$_2$), 23.8 (CH$_2$), 22.6 (CH$_2$), 14.6 (2 x CH$_3$); HRMS m/z 253.2167 (M + H), calcd for $C_{16}H_{29}O_2$ 253.2168.

2-Isopentyl-5-(4-methylpentyl)cyclohexane-1,3-dione (16fh): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 141 °C. IR (neat): ν_{max} 2954, 1560, 1381, 1330, 1245, 1120, 646 and 628 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 2.47 (2H, dd, J = 16.8, 4.4 Hz), 2.24 (2H, t, J = 8.0 Hz), 2.16 (2H, dd, J = 16.8, 11.2 Hz), 2.07-1.99 (1H, m), 1.60-1.47 (2H, m), 1.40-1.36 (4H, m), 1.22-1.17 (4H, m), 0.92 (6H, d, J = 6.8 Hz, 2 x CH$_3$), 0.90 (6H, d, J = 6.8 Hz, 2 x CH$_3$); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 117.2 (C), 40.3 (CH$_2$), 39.0 (CH$_2$), 36.9 (CH$_2$), 34.9 (CH), 29.5 (CH), 29.2 (CH), 25.6 (CH$_2$), 23.2 (2 x CH$_3$), 23.1 (2 x CH$_3$), 20.9 (CH$_2$); HRMS m/z 289.2148 (M + Na), calcd for $C_{17}H_{30}O_2Na$ 289.2143.



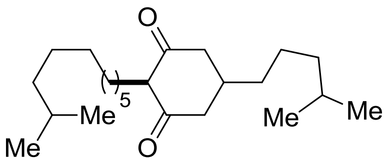
16fh

2-(5-Methylhexyl)-5-(4-methylpentyl)cyclohexane-1,3-dione (16fi): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 182 °C. IR (neat): ν_{max} 2958, 1798, 1753, 1376, 1276, 1208, 969, 668, 658 and 648 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 2.46 (2H, dd, J = 16.4, 3.6 Hz), 2.20 (2H, t, J = 7.2 Hz), 2.15 (2H, dd, J = 16.4, 10.8 Hz), 2.07-1.99 (1H, m), 1.58-1.46 (2H, m), 1.36-1.35 (4H, m), 1.28-1.27 (4H, m), 1.20-1.18 (4H, m), 0.89 (6H, d, J = 6.8 Hz, 2 x CH_3), 0.87 (6H, d, J = 6.4 Hz, 2 x CH_3); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 117.0 (C), 40.3 (2 x CH$_2$), 36.9 (CH$_2$), 34.9 (CH), 30.0 (CH$_2$), 29.3 (CH), 29.2 (CH), 28.6 (CH$_2$), 25.6 (CH$_2$), 23.2 (2 x CH$_3$), 23.1 (2 x CH$_3$), 22.8 (CH$_2$); HRMS m/z 295.2637 (M + H), calcd for $C_{19}H_{35}O_2$ 295.2637.



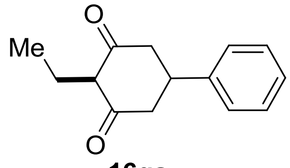
16fi

2-(9-Methyldecyl)-5-(4-methylpentyl)cyclohexane-1,3-dione (16fj): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 173 °C. IR (neat): ν_{max} 2927, 1719, 1565, 1384, 1106, 729, 638



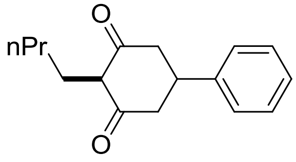
16fj

and 611 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.46 (2H, dd, *J* = 16.4, 4.0 Hz), 2.21 (2H, t, *J* = 6.8 Hz), 2.15 (2H, dd, *J* = 16.4, 10.8 Hz), 2.07-1.97 (1H, m), 1.60-1.48 (2H, m), 1.38-1.14 (20H, m), 0.89 (6H, d, *J* = 6.8 Hz, 2 x CH_3), 0.87 (6H, d, *J* = 6.8 Hz, 2 x CH_3); ^{13}C NMR (CD_3OD, DEPT-135) δ 117.0 (C), 40.4 (CH_2), 40.3 (CH_2), 36.9 (CH_2), 34.8 (CH), 31.2 (CH_2), 31.0 (CH_2), 30.8 (2 x CH_2), 29.8 (CH_2), 29.3 (CH), 29.2 (CH), 28.7 (CH_2), 25.6 (CH_2), 23.2 (2 x CH_3), 23.1 (2 x CH_3), 22.8 (CH_2); LRMS m/z 351.30 ($M+H^+$), calcd $C_{23}H_{42}O_2$ 350.3185.



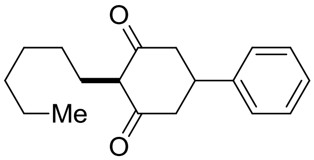
16ga

2-Ethyl-5-phenylcyclohexane-1,3-dione (16ga): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 156 °C. IR (neat): ν_{max} 2948, 1710 (*C=O*), 1567 (*C-O*), 1381, 1249, 1123 and 997 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.30 (4H, m), 7.26-7.22 (1H, m), 3.33-3.31 (1H, m), 2.71 (2H, dd, *J* = 16.8, 11.0 Hz), 2.61 (2H, dd, *J* = 16.8, 4.8 Hz), 2.31 (2H, q, *J* = 7.6 Hz), 0.96 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 144.7 (C), 129.9 (2 x CH), 128.1 (CH), 128.0 (2 x CH), 118.4 (C), 41.3 (2 x CH_2, br s), 40.7 (CH), 16.2 (CH_2), 13.7 (CH_3); HRMS m/z 217.1227 (M + H), calcd for $C_{14}H_{17}O_2$ 217.1229.



16gc

2-Butyl-5-phenylcyclohexane-1,3-dione (16gc): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 158 °C. IR (neat): ν_{max} 2959, 1710 (*C=O*), 1562 (*C-O*), 1381, 1238, 1112 and 608 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.36-7.30 (4H, m), 7.26-7.21 (1H, m), 3.33-3.27 (1H, m), 2.71 (2H, dd, *J* = 16.8, 11.6 Hz), 2.61 (2H, dd, *J* = 16.8, 4.8 Hz), 2.30 (2H, t, *J* = 6.8 Hz), 1.38-1.29 (4H, m), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 144.7 (C), 129.8 (2 x CH), 128.1 (CH), 128.0 (2 x CH), 117.1 (C), 41.4 (2 x CH_2, br s), 40.6 (CH), 32.1 (CH_2), 23.9 (CH_2), 22.6 (CH_2), 14.6 (CH_3); HRMS m/z 245.1542 (M + H), calcd for $C_{16}H_{21}O_2$ 245.1542.



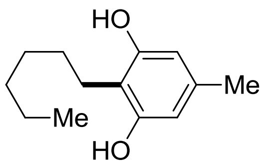
16ge

2-Hexyl-5-phenylcyclohexane-1,3-dione (16ge): Prepared by following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 162 °C. IR (neat): ν_{max} 2964, 1715 (*C=O*), 1567 (*C-O*), 1386, 1331, 1238, 1118 and 600 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.36-7.30 (4H, m), 7.26-7.21 (1H, m), 3.32-3.28 (1H, m), 2.71 (2H, dd, *J* = 16.8, 11.6 Hz), 2.62 (2H, dd, *J* = 16.4, 4.8 Hz), 2.29 (2H, t, *J* = 6.8 Hz), 1.40-1.31 (8H, m), 0.91 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (CD$_3$OD, DEPT-135) δ 144.7 (C), 129.8 (2 x CH), 128.1 (CH), 128.0 (2 x CH), 117.1 (C), 41.0 (2 x CH$_2$, br s), 40.6 (CH), 33.2 (CH$_2$), 30.6 (CH$_2$), 29.8 (CH$_2$), 23.9 (CH$_2$), 22.9 (CH$_2$), 14.6 (CH$_3$); HRMS m/z 295.1676 (M + Na), calcd for $C_{18}H_{24}O_2Na$ 295.1674.

7.5 General procedure for the synthesis of 2,5-dialkylresorcinols 68:

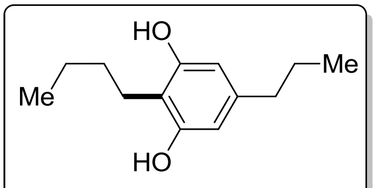
To a solution of 2,5-dialkylcyclohexane-1,3-dione **16** (0.3 mmol) in MeOH (1 ml) was added iodine (2 equiv.) and the reaction mixture was stirred for 6-8 h at 65 °C. After completion of the reaction, which is confirmed by TLC, the solvent was removed in vacuum, and quickly filtered through silica gel using 10% EtOAc/hexane, dried (Na$_2$SO$_4$) and concentrated in vacuum. To this product, 1 mL of dry DCM was added through septum, cooled to 0 °C, 3 equiv. of BBr$_3$ was added at 0 °C, and the temperature of the reaction was allowed to rise to 25 °C. The crude reaction mixture was diluted with DCM and treated with saturated aqueous ammonium chloride solution; the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were dried (Na$_2$SO$_4$), and concentrated. Pure products **68** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

RMC-2-47 [2-hexyl-5-methylbenzene-1,3-diol] (68be):[70c] Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp: 73 °C. IR (neat): ν_{max} 3309, 2959, 1627, 1594, 1457, 1435, 1101, 1003, 838 and 723 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.23 (2H, s, Ar-*H*), 4.82 (2H, s, Ar-*OH*), 2.59 (2H, t, *J* = 7.6 Hz), 2.21 (3H, s, Ar-C*H*$_3$), 1.56-1.50 (2H, m), 1.40-1.36 (2H, m), 1.32-1.30 (4H, m), 0.89 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 154.4 (2 x C), 136.9 (C), 112.4 (C), 108.7 (2 x CH), 31.8 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 23.0 (CH$_2$), 22.6 (CH$_2$), 21.0 (CH$_3$), 14.1 (CH$_3$); HRMS m/z 209.1541 (M + H), calcd for $C_{13}H_{21}O_2$ 209.1542.



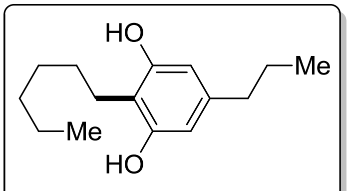
RMC-2-47 (**68be**)

RMC-2-55 [2-butyl-5-propylbenzene-1,3-diol] (68cc):[70c] Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp: 77 °C. IR (neat): ν_{max} 3397 (Ar-*OH*), 2956,1627, 1582, 1444, 1323, 1163, 1105, 994, 664, 637 and 605 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 6.13 (2H, s, Ar-*H*), 2.54 (2H, t, *J* = 7.6 Hz), 2.38 (2H, t, *J* = 8.0 Hz), 1.57 (2H, sextet, *J* = 7.2 Hz), 1.50-1.41 (2H, m), 1.40-1.28 (2H, m), 0.92 (3H, t, *J* = 7.2 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 157.1 (2 x C), 142.1 (C), 114.7 (C), 108.0 (2 x CH), 39.1 (CH_2), 32.8 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 14.7 (CH_3), 14.3 (CH_3); HRMS m/z 209.1536 (M + H), calcd for $C_{13}H_{21}O_2$ 209.1542.



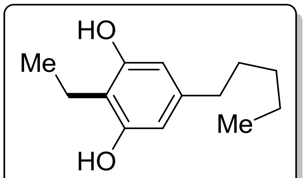
RMC-2-55 (**68cc**)

DB-2073 [2-hexyl-5-propylbenzene-1,3-diol] (68ce):[70c] Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp: 80 °C. IR (neat): ν_{max} 3315 (Ar-OH), 2957,1627, 1589, 1441, 1107, 997, 849 and 740 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 6.14 (2H, s), 2.55 (2H, t, *J* = 7.6 Hz), 2.39 (2H, t, *J* = 7.2 Hz), 1.59 (2H, sextet, *J* = 7.6 Hz), 1.53-1.45 (2H, m), 1.39-1.30 (6H, m), 0.93 (3H, t, *J* = 7.6 Hz), 0.91 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 157.1 (2 x C), 142.1 (C), 114.8 (C), 108.0 (2 x CH), 39.1 (CH_2), 33.2 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 25.7 (CH_2), 24.1 (CH_2), 23.9 (CH_2), 14.6 (CH_3), 14.3 (CH_3); HRMS m/z 237.1853 (M + H), calcd for $C_{15}H_{26}O_2$ 237.1855.



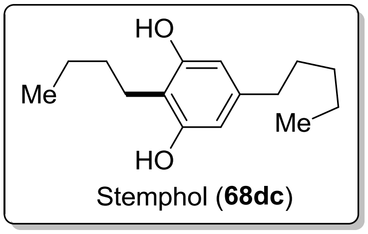
DB-2073 (**68ce**)

2-Ethyl Olivetol [2-ethyl-5-pentylbenzene-1,3-diol] (68da): Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp: 60 °C. IR (neat): ν_{max} 3315 (Ar-OH), 2959,1627, 1589, 1441, 1107, 997, 849 and 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (2H, s, Ar-*H*), 4.74 (2H, s, O*H*), 2.60 (2H, t, *J* = 7.6 Hz), 2.42 (2H, q, *J* = 6.4 Hz), 1.64-1.50 (4H, m), 1.45-1.36 (2H, m), 0.94 (3H, t, *J* = 7.2 Hz), 0.93 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 154.3 (2 x C), 141.9 (C), 112.6 (C), 108.1 (2 x CH), 37.6 (CH_2), 31.5 (CH_2), 24.2 (CH_2), 22.85 (CH_2), 22.79 (CH_2), 14.1 (CH_3), 13.8 (CH_3); LRMS m/z 209.10 (M



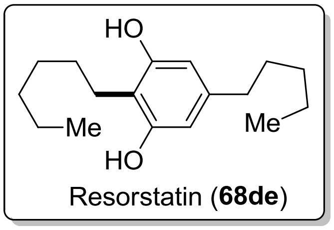
2-Ethyl Olivetol (**68da**)

+ H^+), calcd $C_{13}H_{20}O_2$ 208.1463; Anal. calcd for $C_{13}H_{20}O_2$ (208.1463): C, 74.96; H, 9.68. Found: C, 74.85; H, 9.62%.



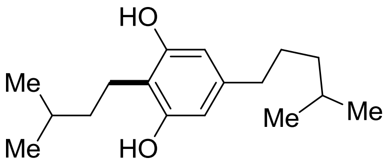
Stemphol (**68dc**)

Stemphol [2-butyl-5-pentylbenzene-1,3-diol] (68dc):[70a] Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp: 98 °C. IR (neat): ν_{max} 3419 (Ar-*OH*), 2959,1621, 1588, 1429, 1199, 1101, 1002, 827, and 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (2H, s, Ar-*H*), 4.94 (2H, s, Ar-*OH*), 2.62 (2H, t, *J* = 7.6 Hz), 2.45 (2H, t, *J* = 7.6 Hz), 1.60-1.51 (4H, m), 1.44-1.32 (6H, m), 0.95 (3H, t, *J* = 7.6 Hz), 0.91 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 154.3 (2 x C), 142.1 (C), 112.6 (C), 108.1 (2 x CH), 35.4 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 22.82 (CH_2), 22.79 (CH_2), 22.5 (CH_2), 14.0 (2 x CH_3); HRMS m/z 237.1854 (M + H), calcd for $C_{15}H_{25}O_2$ 237.1854.



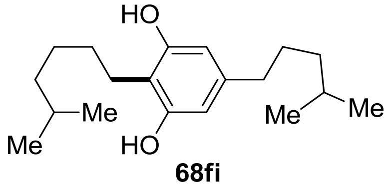
Resorstatin (**68de**)

Resorstatin [2-hexyl-5-pentylbenzene-1,3-diol] (68de):[70c] Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp: 93 °C. IR (neat): ν_{max} 3391 (Ar-*OH*), 2959,1627, 1588, 1429, 1271, 1101, 1007, 832, and 733 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.14 (2H, s), 2.55 (2H, t, *J* = 7.6 Hz), 2.41 (2H, t, *J* = 7.6 Hz), 1.57 (2H, quintet, *J* = 6.0 Hz), 1.50 (2H, quintet, *J* = 6.0 Hz), 1.40-1.30 (10H, m), 0.92 (3H, t, *J* = 7.2 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, DEPT-135) δ 157.1 (2 x C), 142.4 (C), 114.8 (C), 108.0 (2 x CH), 36.8 (CH_2), 33.2 (CH_2), 32.8 (CH_2), 32.3 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 24.1 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 14.6 (CH_3), 14.5 (CH_3); HRMS m/z 265.2167 (M + H), calcd for $C_{17}H_{29}O_2$ 265.2168.



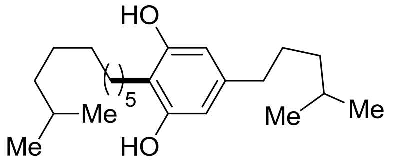
68fh

2-Isopentyl-5-(4-methylpentyl)benzene-1,3-diol (68fh): Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 75 °C. IR (neat): ν_{max} 3447 (Ar-*OH*), 2954, 1589, 1466, 1112, 830, 665, 647, 640 and 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (2H, s, Ar-*H*), 4.67 (2H, s, Ar-*OH*), 2.58 (2H, t, *J* = 7.6 Hz), 2.43 (2H, t, *J* = 7.6 Hz), 1.65-1.52 (4H, m), 1.45-1.39 (2H, m), 1.26-1.18 (2H, m), 0.96 (6H, d, *J* = 6.4 Hz, 2 x C*H*$_3$), 0.87 (6H, d, *J* = 6.8 Hz, 2 x C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 154.3 (2 x C), 142.1 (C), 112.7 (C), 108.0 (2 x CH), 38.6 (CH$_2$), 38.3 (CH$_2$), 35.8 (CH$_2$), 29.0 (CH$_2$), 28.3 (CH), 27.9 (CH), 22.6 (2 x CH$_3$), 22.5 (2 x CH$_3$), 20.9 (CH$_2$); HRMS m/z 265.2167 (M + H), calcd for $C_{17}H_{29}O_2$ 265.2167.



68fi

2-(5-Methylhexyl)-5-(4-methylpentyl)benzene-1,3-diol (68fi): Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 75 °C. IR (neat): ν$_{max}$ 3310 (Ar-*OH*), 2959, 1627, 1441, 1107, 997, 849 and 723 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.23 (2H, s, Ar-*H*), 4.72 (2H, s, Ar-O*H*), 2.58 (2H, t, *J* = 7.6 Hz), 2.43 (2H, t, *J* = 7.6 Hz), 1.58-1.51 (6H, m), 1.40-1.36 (2H, m), 1.26-1.18 (4H, m), 0.88 (6H, d, *J* = 6.8 Hz, 2 x C*H*$_3$), 0.86 (6H, d, *J* = 6.8 Hz, 2 x C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 154.3 (2 x C), 142.2 (C), 112.5 (C), 108.0 (2 x CH), 38.8 (CH$_2$), 38.6 (CH$_2$), 35.7 (CH$_2$), 29.5 (CH$_2$), 29.0 (CH$_2$), 28.0 (CH), 27.9 (CH), 27.6 (CH$_2$), 23.1 (CH$_2$), 22.65 (2 x CH$_3$) 22.57 (2 x CH$_3$); HRMS m/z 293.2481 (M + H), calcd for $C_{19}H_{33}O_2$ 293.2480.



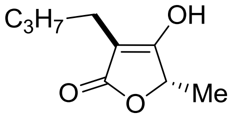
Resorcinin (**68fj**)

Resorcinin [2-(9-methyldecyl)-5-(4-methylpentyl)benzene-1,3-diol] (68fj):[70b] Prepared by following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 82 °C. IR (neat): ν$_{max}$ 3461 (Ar-*OH*), 2922, 1366, 1116, 830, 738, 680, 651 and 640 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.23 (2H, s, Ar-*H*), 4.76 (2H, brs, Ar-O*H*), 2.57 (2H, t, *J* = 7.6 Hz), 2.42 (2H, t, *J* = 8.0 Hz), 1.59-1.47 (6H, m), 1.32-1.14 (14H, m), 0.87 (6H, d, *J* = 6.8 Hz), 0.85 (6H, d, *J* = 6.8 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 154.3 (2 x C), 142.1 (C), 112.5 (C), 107.9 (2 x CH), 39.0 (CH$_2$), 38.6 (CH$_2$), 35.8 (CH$_2$), 29.9 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 29.0 (CH$_2$), 28.0 (CH), 27.9 (CH), 27.4 (CH$_2$), 23.1 (CH$_2$), 22.6 (2 x CH$_3$), 22.6 (2 x CH$_3$); HRMS m/z 349.3106 (M + H), calcd for $C_{23}H_{41}O_2$ 349.3106.

7.6 General procedure for the synthesis of TCRA products 71:

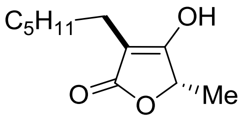
An vial equipped with a magnetic stirbar, containing proline (0.05 equiv), chiral tetronic acid **72** (1 equiv) and Hantzsch ester **11a** (1 equiv) was charged with DCM (0.2 M), followed by addition of aldehyde **1e-n** (1 equiv) and resulting mixture was stirred at room temperature till the completion of the reaction as monitored by TLC. After completion of TCRA reaction organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was used for the next step without purification.

(*S*)-3-butyl-4-hydroxy-5-methylfuran-2(5H)-one (**71ac**): Prepared by following the procedure **7.6** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.3 (30% Ethyl acetate in Hexanes), Mp: 156 °C. **$[\alpha]_D^{25}$ = +1.17° (*c* = 0.514 g/100 mL, $CHCl_3$)**; IR (neat): ν_{max} 3377, 2953, 1731, 1649, 1463, 1205, 1068 and 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, q, *J* = 6.4 Hz), 2.20 (2H, t, *J* = 7.2 Hz), 1.50 (3H, d, *J* = 6.8 Hz), 1.45 (2H, pentet, *J* = 7.2 Hz), 1.31 (2H, pentet, *J* = 7.2 Hz), 0.90 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 177.7 (C), 177.4 (C), 100.9 (C), 75.3 (CH), 30.1 (CH_2), 22.4 (CH_2), 20.8 (CH_2), 17.8 (CH_3), 13.8 (CH_3); HRMS m/z 171.1021 [M + H], Calcd for $C_9H_{15}O_3$ 171.1021.



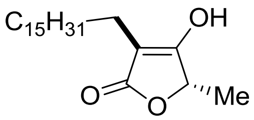
(+)-**71ac**

(*S*)-3-hexyl-4-hydroxy-5-methylfuran-2(5H)-one (**71ae**): Prepared by following the procedure **7.6** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.3 (40% Ethyl acetate in Hexanes), Mp: 156 °C. **$[\alpha]_D^{25}$ = +10.6° (*c* = 0.50 g/100 mL, $CHCl_3$)**; IR (neat): ν_{max} 2932, 2863, 2639, 1732, 1458, 1379, 1217, 1128, 1071, 926 and 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, q, *J* = 6.8 Hz), 2.20 (2H, t, *J* = 7.2 Hz), 1.50 (3H, d, *J* = 6.8 Hz), 1.48-1.42 (2H, m), 1.32-1.23 (6H, m), 0.86 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 178.0 (C), 177.8 (C), 100.7 (C), 75.4 (CH), 31.6 (CH_2), 29.0 (CH_2), 28.0 (CH_2), 22.6 (CH_2), 21.0 (CH_2), 17.8 (CH_3), 14.0 (CH_3); HRMS m/z 199.1334 [M + H]. Calcd for $C_{11}H_{19}O_3$ 199.1334.



(+)-**71ae**

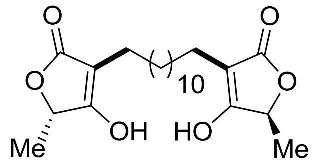
(*S*)-3-hexadecyl-4-hydroxy-5-methylfuran-2(5H)-one (**71ak**): Prepared by following the procedure **7.6** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.3 (40% Ethyl acetate in Hexanes), Mp: 66 °C. **$[\alpha]_D^{25}$ = +3.98° (*c* = 0.428 g/100 mL, $CHCl_3$)**; IR (neat): ν_{max} 2919, 2849, 2721, 1711, 1634, 1470, 1269,



(+)-**71ak**

1084 and 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (1H, q, *J* = 6.5 Hz), 2.20 (2H, t, *J* = 7.5 Hz), 1.51 (3H, d, *J* = 6.5 Hz), 1.49-1.43 (2H, m), 1.31-1.24 (26H, br m), 0.89 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 177.4 (C), 177.1 (C), 101.1 (C), 75.2 (CH), 31.9 (CH_2), 29.7 (4 x CH_2), 29.68 (2 x CH_2), 29.66 (2 x CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 21.1 (CH_2), 17.8 (CH_3), 14.1 (CH_3); HRMS m/z 361.2715 [M + Na], Calcd for $C_{21}H_{38}O_3Na$ 361.2719.

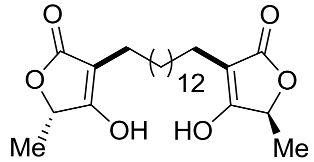
(5*S*,5'*S*)-3,3'-(dodecane-1,12-diyl)bis(4-hydroxy-5-methylfuran-2(5H)-one) (**71al**):



(+)-**71al**

Prepared by following the procedure **7.6** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.1 (Ethyl acetate), Mp: 138 °C. **[α]$_D$^{25} = +18.34°** (***c* = 0.142 g/100 mL, MeOH**); IR (neat): ν_{max} 2919, 2847, 2706, 1711, 1651, 1451, 1388, 1343, 1296, 1263, 1234, 1140, 1107, 1080, 1051, 918 and 789 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 4.77 (2H, q, *J* = 6.8 Hz), 2.15 (4H, t, *J* = 7.2 Hz), 1.50-1.44 (4H, m), 1.42 (6H, d, *J* = 6.8 Hz), 1.30 (16H, br s); ^{13}C NMR (CD_3OD) δ 178.4 (2 x C), 177.8 (2 x C), 101.0 (2 x C), 75.8 (2 x CH), 30.7 (4 x CH_2), 30.5 (2 x CH_2), 30.3 (2 x CH_2), 29.1 (2 x CH_2), 21.9 (2 x CH_2), 18.3 (2 x CH_3); HRMS m/z 417.2253 [M + Na], Calcd for $C_{22}H_{34}O_6Na$ 417.2253.

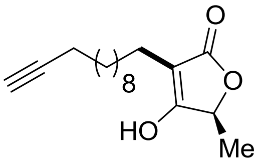
(5*S*,5'*S*)-3,3'-(tetradecane-1,14-diyl)bis(4-hydroxy-5-methylfuran-2(5H)-one) (**71am**):



(+)-**71am**

Prepared by following the procedure **7.6** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.1 (Ethyl acetate), Mp: 156 °C. **[α]$_D$^{25} = +1.17°** (***c* = 0.514 g/100 mL, $CHCl_3$**); IR (neat): ν_{max} 2918, 2847, 2702, 1711, 1647, 1452, 1386, 1342, 1284, 1255, 1140, 1107, 1080, 1051, 922. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ 4.51 (2H, q, *J* = 6.0 Hz), 2.00-1.96 (3H, m), 1.86-1.74 (1H, m), 1.31–1.14 (10H, m), 1.14–1.00 (20H, m); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 176.3 (2 x C), 176.2 (2 x C), 99.9 (2 x C), 74.1 (2 x CH), 29.2 (6 x CH_2), 29.0 (2 x CH_2), 28.9 (2 x CH_2), 27.6 (2 x CH_2), 20.6 (2 x CH_2), 17.3 (2 x CH_3). HRMS *m/z* Calcd for $C_{24}H_{38}O_6$: 422.2668; observed 423.2742 $[M + H]^+$, 445.2566 $[M + Na]^+$.

(S)-3-(dodec-11-yn-1-yl)-4-hydroxy-5-methylfuran-2(5H)-one (**71an**): Prepared by following the procedure **7.6** and purified by column chromatography using EtOAc/hexane and isolated as semisolid. Rf. = 0.2 (30% Ethyl acetate in Hexanes); **$[\alpha]_D^{25}$ = +8.08° (*c* = 0.57 g/100 mL, $CHCl_3$)**; IR (neat): ν_{max} 3299, 2919, 2849, 1711, 1626, 1466, 1261, 1082, 843 and 638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, q, *J* = 6.8 Hz), 2.21-2.15 (4H, m), 1.93 (1H, t, *J* = 2.4 Hz), 1.50 (3H, d, *J* = 6.8 Hz), 1.50-1.43 (4H, m), 1.39-1.36 (2H, m), 1.26 (10H, br s); ^{13}C NMR ($CDCl_3$) δ 178.0 (C), 177.8 (C), 100.7 (C), 84.7 (C), 75.4 (CH), 68.1 (CH), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.37 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 28.0 (CH_2), 21.0 (CH_2), 18.3 (CH_2), 17.8 (CH_3); HRMS m/z 301.1780 [M + Na], Calcd for $C_{17}H_{26}O_3Na$ 301.1780.



(+)-**71an**

7.7 General procedure for the synthesis of products 70:

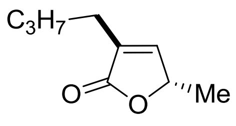
Step-1: A vial equipped with a magnetic stirbar, containing proline(0.05 equiv), chiral tetronic acid **72** (1 equiv) and Hantzsch ester **11a** (1 equiv) was charged with DCM (0.2 M), followed by addition of aldehyde **1** (1 equiv) and resulting mixture was stirred at room temperature till the completion of the reaction as monitored by TLC. After completion of TCRA reaction DIPEA (2 equiv) was added to it. The reaction mixture was cooled to –78 ºC and Tf_2O (1.5 equiv, freshly distilled over P_2O_5) was added to it drop wise. After 30 min. (or completion of the reaction), the reaction mixture was quenched with saturated NH_4Cl solution and partitioned between DCM (15 mL x 3) and water. Organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was used for the next step without purification.

Step-2: General procedure for the Palladium catalyzed reduction of enol-triflate: The enol-triflate was dissolved in dry DMF (0.2 M). $Pd(OAc)_2$ (0.01 mol%), DPPP (0.01 mol %) and PMHS (2 equiv) were added to the reaction mixture and heated at 60 ºC. After completion of the reaction, the reaction mixture was diluted with diethyl ether and extracted with diethyl ether (10 mL x 3). The organic layer was washed with water, brine and dried over Na_2SO_4. After evaporation under reduced pressure, the crude compound was purified by silica gel column chromatography.

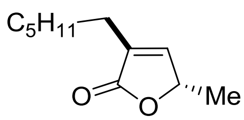
7.8 General procedure for the synthesis of products 70:

Step-1: Compound **71** (1 equiv) was taken in a dry R.B. equipped with a Dean-Stark apparatus and reflux condenser in dry toluene (20 mL). Pyrrolidine (1.5 equiv) was added to it followed by catalytic *p*-TSA. The mixture was refluxed at 130 °C. After completion of the reaction, the mixture was concentrated and purified by column chromatography (neutral alumina) to get **73**.

Step-2: Procedure for the reduction of enamino derivative: Compound **73** (1 equiv) was taken in MeOH and catalytic methyl orange was added to it. The mixture was acidified with a few drops of 2N HCl in MeOH so as to retain the deep red color of the indicator. NaBH$_3$CN (2.5 equiv) was added in portions with simultaneous addition of acid to maintain the pH. After completion of the reaction, MeOH was removed under reduced pressure. The residue was diluted with water, neutralized with 1 N NaOH and extracted with EtOAc (10 mL x 3). The combined organic layer was evaporated and crude diastereomeric mixture of aminolactones was refluxed in toluene (6 mL) with silica gel for 7 h to get the product **70**.

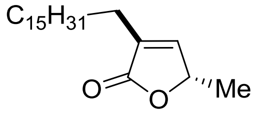

(+)-**70ac**

(*S*)-3-butyl-5-methylfuran-2(5H)-one (**70ac**): Prepared by following the procedure **7.7** and purified by column chromatography using EtOAc/hexane and isolated as colorless oil. Rf. = 0.3 (10% Ethyl acetate in Hexanes), **[α]$_D$^{25} = +36.09**° (***c* = 0.2 g/100 mL, CHCl$_3$**); IR (neat): ν$_{max}$ 3362, 2934, 2878, 1755, 1605, 1454, 1321, 1200, 1113, 1028 and 875 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.00 (1H, q, *J* = 2.0 Hz), 5.00 (1H, qq, *J* = 2.0, 8.5 Hz), 2.28 (2H, tt, *J* = 2.0, 9.5 Hz), 1.58-1.50 (2H, m), 1.41 (3H, d, *J* = 8.5 Hz), 1.38-1.32 (2H, m), 0.93 (3H, t, *J* = 9.5 Hz); ^{13}C NMR (CDCl$_3$) δ 173.9 (C), 148.9 (CH), 134.2 (C), 77.4 (CH), 29.5 (CH$_2$), 24.8 (CH$_2$), 22.2 (CH$_2$), 19.1 (CH$_3$), 13.7 (CH$_3$); HRMS m/z 155.1072 [M + H], Calcd for C$_9$H$_{15}$O$_2$ 155.1072.


(+)-**70ae**

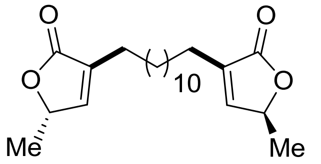
(*S*)-3-hexyl-5-methylfuran-2(5H)-one (**70ae**): Prepared by following the procedure **7.7** and purified by column chromatography using EtOAc/hexane and isolated as sticky solid. Rf. = 0.3 (10% Ethyl acetate in Hexanes), **[α]$_D$^{25} = +24.97**° (***c* = 0.285 g/100 mL, CHCl$_3$**); IR (neat): ν$_{max}$ 2926, 2855, 1759, 1655, 1463, 1381, 1320, 1118, 1074, 1025 and 866 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.00 (1H, q, *J* = 2.0 Hz), 5.00 (1H, qq, *J* = 8.5, 2.0 Hz), 2.26 (2H, tt, *J* = 9.0, 2.5 Hz), 1.58-1.51 (2H, m), 1.41 (3H, d, *J* = 8.5 Hz), 1.35-1.25 (6H, m), 0.88 (3H, t, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 173.9 (C), 148.9 (CH), 134.2 (C), 77.4 (CH), 31.4 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 19.1 (CH_3), 14.0 (CH_3); HRMS m/z 183.1385 [M + H], Calcd for $C_{11}H_{19}O_2$ 183.1385.

(*S*)-3-hexadecyl-5-methylfuran-2(5H)-one (**70ak**): Prepared by following the procedure **7.7** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.3 (5% Ethyl acetate in Hexanes), Mp: 59 °C. **$[\alpha]_D^{25}$ = +24.85° (*c* = 0.5 g/100 mL, $CHCl_3$)**; IR (neat): ν_{max} 3079, 2917, 2849, 1746, 1651, 1472, 1373, 1331, 1201, 1120, 1082, 1030, 883 and 638 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (1H, q, *J* = 1.5 Hz), 5.00 (1H, qq, *J* = 6.5, 1.5 Hz), 2.27 (2H, tt, *J* = 7.5, 1.5 Hz), 1.55 (2H, quintet, *J* = 7.5 Hz), 1.41 (3H, d, *J* = 6.5 Hz), 1.34-1.24 (26H, m), 0.88 (3H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 173.8 (C), 148.8 (CH), 134.3 (C), 77.3 (CH), 31.9 (CH_2), 29.65 (4 x CH_2), 29.61 (2 x CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.31 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 27.4 (CH_2), 25.1 (CH_2), 22.6 (CH_2), 19.2 (CH_3), 14.0 (CH_3); HRMS m/z 323.2950 [M + H], Calcd for $C_{21}H_{39}O_2$ 323.2950.



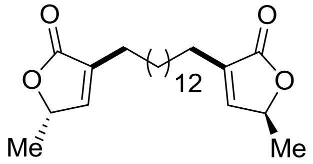
(+)-**70ak**

(5*S*,5'*S*)-3,3'-(dodecane-1,12-diyl)bis(5-methylfuran-2(5H)-one) (**70al**): Prepared by following the procedure **7.7** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.3 (10% Ethyl acetate in Hexanes), Mp: 97 °C. **$[\alpha]_D^{25}$ = +30.5° (*c* = 0.128 g/100 mL, $CHCl_3$)**; IR (neat): ν_{max} 2913, 2846, 1744, 1650, 1469, 1330, 1205, 1029 and 879 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (2H, q, *J* = 1.6 Hz), 5.00 (2H, qq, *J* = 6.8, 1.6 Hz), 2.27 (4H, tt, *J* = 7.2, 1.6 Hz), 1.55 (4H, quintet, *J* = 7.6 Hz), 1.42 (6H, d, *J* = 6.8 Hz), 1.35-1.26 (16H, m); ^{13}C NMR ($CDCl_3$) δ 173.9 (2 x C), 148.9 (2 x CH), 134.3 (2 x C), 77.4 (2 x CH), 29.5 (2 x CH_2), 29.4 (2 x CH_2), 29.3 (2 x CH_2), 29.1 (2 x CH_2), 27.4 (2 x CH_2), 25.1 (2 x CH_2), 19.2 (2 x CH_3); HRMS m/z 363.2535 [M + H], Calcd for $C_{22}H_{35}O_4$ 363.2535.



(+)-**70al:** (+)-Ancepsenolide

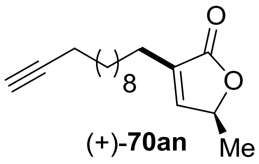
(5*S*,5'*S*)-3,3'-(tetradecane-1,14-diyl)bis(5-methylfuran-2(5H)-one) (**70am**): Prepared by following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Rf. = 0.3 (30% Ethyl acetate in Hexanes), Mp: 100 °C. **$[\alpha]_D^{25}$ = +11.4° (*c* = 0.114 g/100 mL, $CHCl_3$)**; IR (neat):



(+)-**70am:** (+)-Ancepsenolide

ν_{max} 2922, 2851, 1746, 1653, 1472, 1321, 1086, 1028 and 889 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (2H, q, *J* = 1.6 Hz), 5.00 (2H, qq, *J* = 6.8, 1.6 Hz), 2.27 (4H, tt, *J* = 9.2, 1.6 Hz), 1.55 (4H, quintet, *J* = 7.6 Hz), 1.41 (6H, d, *J* = 6.8 Hz), 1.36-1.21 (20H, m); ^{13}C NMR ($CDCl_3$) δ 173.9 (2 x C), 148.9 (2 x CH), 134.3 (2 x C), 77.4 (2 x CH), 29.7 (2 x CH_2), 29.6 (2 x CH_2), 29.5 (2 x CH_2), 29.3 (2 x CH_2), 29.2 (2 x CH_2), 27.4 (2 x CH_2), 25.2 (2 x CH_2), 19.2 (2 x CH_3); HRMS m/z 391.2848 [M + H], Calcd for $C_{24}H_{39}O_4$ 391.2848.

(*S*)-3-(dodec-11-yn-1-yl)-5-methylfuran-2(5H)-one (**70an**): Prepared by following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and isolated as oily liquid. Rf. = 0.2 (15% Ethyl acetate in Hexanes), **[α]$_D$^{25} = +30.6° (*c* = 0.114 g/100 mL, CHCl$_3$)**; IR (neat): ν_{max} 3308, 2928, 2855, 2116, 1755, 1655, 1462, 1373, 1319, 1200, 1076, 1026, 866 and 623 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (1H, q, *J* = 1.5 Hz), 5.00 (1H, qq, *J* = 6.5, 1.5 Hz), 2.27 (2H, tt, *J* = 7.5, 1.5 Hz), 2.19 (2H, td, *J* = 7.0, 2.5 Hz), 1.94 (1H, t, *J* = 2.5 Hz), 1.56-1.50 (4H, m), 1.42 (3H, d, *J* = 7.0 Hz), 1.41-1.36 (2H, m), 1.35-1.29 (10H, m); ^{13}C NMR ($CDCl_3$) δ 173.9 (C), 148.9 (CH), 134.3 (C), 84.7 (C), 77.4 (CH), 68.0 (CH), 29.4 (2 x CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 25.1 (CH_2), 19.2 (CH_3), 18.3 (CH_2); HRMS 285.1833 [M + Na], m/z Calcd for $C_{17}H_{26}O_2Na$ 285.1831.



(+)-**70an**

7.9 Preparation of *β*-keto esters*:*

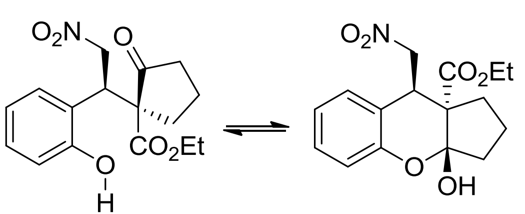
β-keto ester **75** is commercially available and **75c**, **75d** and **75e** were prepared according to literature procedures.[71-73]

7.10 General procedure for amine-catalyzed racemic Michael reaction of keto-esters 75 with 2-(2-nitrovinyl)phenols 46:

In an ordinary glass vial equipped with a magnetic stirring bar, to the 1:1 mixture of **5i/5l** (each 5 mol%) in DCM (1.0 mL), were added **75** (0.4 mmol, 1.33 equiv.) and 2-(2-nitrovinyl)phenols **46** (0.3 mmol). After stirring the reaction mixture at 25 °C, the crude reaction mixture was concentrated and pure racemic products **76/77** or **79** were obtained by quick filtration (silica gel, mixture of hexane/ethyl acetate).

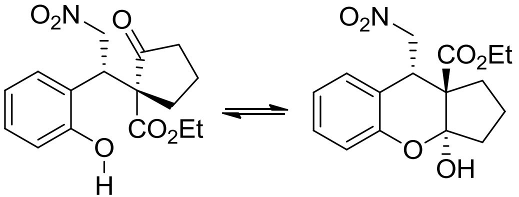
7.11 General procedure for quinine-NH-thiourea-catalyzed asymmetric Michael reaction of keto-esters 75 with 2-(2-nitrovinyl)phenols 46:

In an ordinary glass vial equipped with a magnetic stirring bar, to the **5f** or **5h** (10 mol%) in DCM (1.0 mL), were added **75** (0.4 mmol, 1.33 equiv.) and 2-(2-nitrovinyl)phenols **46** (0.3 mmol). After stirring the reaction mixture at 25 °C as shown in Tables 3-6, the crude reaction mixture was concentrated and pure chiral products **76/77** or **79** were obtained by quick filtration (silica gel, mixture of hexane/ethyl acetate).



76aa **77aa**

(*S*)-ethyl 1-[(*R*)-1-(2-hydroxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (76aa) and (3a*S*,9*R*,9a*S*)-ethyl 3a-hydroxy-9-(nitromethyl)-1,2,3,3a,9,9a-hexahydrocyclopenta[b]chromene-9a-carboxylate (77aa): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = +20.3° (*c* = 0.42 g/100 mL, $CHCl_3$, >99.9% *ee*)**. IR (Neat): ν_{max} 3449 (O-*H*), 2980, 2257, 1726 (C=O), 1555 (*NO_2*), 1379 (*NO_2*), 1231, 1015, 860, 733 and 648 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 ratio of **76aa** and **77aa**) δ 7.24-7.20 (2H, m), 7.15-7.09 (2H, m), 7.00 (1H, t, *J* = 7.6 Hz), 6.93 (1H, d, *J* = 8.0 Hz), 6.88 (1H, t, *J* = 7.6 Hz), 6.81 (1H, d, *J* = 8.0 Hz), 6.61 (1H, br s, OH), 5.22 (1H, dd, *J* = 13.6, 4.0 Hz), 5.11 (1H, dd, *J* = 13.6, 10.0 Hz), 4.76 (1H, dd, *J* = 13.6, 6.4 Hz), 4.59-4.54 (1H, m), 4.46-4.40 (2H, m), 4.31-4.17 (4H, m, 2 x OCH_2CH_3), 2.44-2.38 (2H, m), 2.29-2.22 (2H, m), 2.12-1.88 (6H, m), 1.82-1.71 (1H, m), 1.59-1.51 (1H, m), 1.33 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.27 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 ratio of **76aa** and **77aa**) δ 214.4 (C, C=O), 174.0 (C, O-C=O), 169.6 (C, O-C=O), 154.4 (C), 150.7 (C), 130.1 (CH), 129.4 (CH), 129.0 (CH), 126.3 (CH), 122.6 (C), 122.5 (CH), 121.1 (CH), 120.1 (C), 118.4 (CH), 117.3 (CH), 106.3 (C), 77.4 (CH_2), 76.2 (CH_2), 63.1 (C), 62.6 (CH_2), 62.4 (CH_2), 56.4 (C), 39.8 (CH), 37.8 (CH_2), 36.7 (CH_2), 36.4 (CH), 31.7 (CH_2), 27.6 (CH_2), 19.3 (CH_2), 19.1 (CH_2), 13.9 (CH_3), 13.8 (CH_3); LRMS m/z 322.15 (M + H^+), calcd for $C_{16}H_{19}NO_6$ 321.1212; Anal. calcd for $C_{16}H_{19}NO_6$ (321.1212): C, 59.81; H, 5.96; N, 4.36. Found: C, 59.75; H, 5.89; N, 4.41%.



76aa

77aa

(*R*)-ethyl 1-[(*S*)-1-(2-hydroxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (76aa) and (3a*R*,9*S*,9a*R*)-ethyl 3a-hydroxy-9-(nitromethyl)-1,2,3,3a,9,9a-hexahydrocyclopenta[b]chromene-9a-carboxylate (77aa): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –19.2° (*c* = 0.42 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): ν_{max} 3435 (O-*H*), 2966, 1720 (C=O), 1552 (*NO_2*), 1455, 1375 (*NO_2*), 1226, 1051, 1014 and 755 cm^{-1}.

7.12 General procedure for amine-/p-TSA-catalyzed racemic sequential Michael-lactonization/dehydration reaction of keto-esters 75 with 2-(2-nitrovinyl)phenols 46:

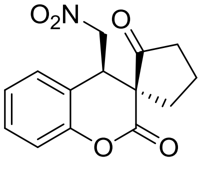
In an ordinary glass vial equipped with a magnetic stirring bar, to the 1:1 mixture of **5i/5l** (each 5 mol%) in DCM (1.0 mL), were added **75** (0.4 mmol, 1.33 equiv.) and 2-(2-nitrovinyl)phenols **46** (0.3 mmol). After stirring the reaction mixture at 25 °C, the crude reaction mixture was quickly filtered through silica gel, concentrated and taken into a oven dried round bottom flask equipped with a magnetic stirring bar, to this add dry DCE (4.0 mL) and *p*-TSA (0.03 mmol, 10 mol%). After stirring the reaction mixture at 80 °C for 3-4 h, the crude reaction mixture was worked up with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure racemic products **78** or **80** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.13 General procedure for quinine-NH-thiourea-/p-TSA-catalyzed asymmetric sequential Michael-lactonization/dehydration reactions of keto-esters 75 with 2-(2-nitrovinyl)phenols 46:

In an ordinary glass vial equipped with a magnetic stirring bar, to the **5f** or **5h** (10 mol%) in DCM (1.0 mL), were added **75** (0.4 mmol, 1.33 equiv.) and of 2-(2-nitrovinyl)phenols **46** (0.3 mmol). After stirring the reaction mixture at 25 °C, the crude reaction mixture was filtered through silica gel, concentrated and taken into a oven dried round bottom flask equipped with a magnetic stirring bar, to this add dry DCE (4.0 mL) and *p*-TSA (0.03 mmol, 10 mol%). After stirring the reaction mixture at 80 °C for 4 h, the crude reaction mixture was worked up with aqueous NaHCO$_3$ solution and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated. Pure chiral products **78** or **80** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.14 General procedure for quinine-NH-thiourea-/PCC-mediated asymmetric sequential Michael-oxidation reaction of keto-ester 75e with 2-(2-nitrovinyl)phenols 46:

In an ordinary glass vial equipped with a magnetic stirring bar, to the **5f** or **5h** (10 mol%) in DCM (1.0 mL), were added **75e** (0.4 mmol, 1.33 equiv.) and 2-(2-nitrovinyl)phenols **46a** or **46d** (0.3 mmol). After stirring the reaction mixture at 25 °C, the crude reaction mixture was filtered through silica gel, concentrated and taken into a oven dried round bottom flask equipped with a magnetic stirring bar, to this added dry DCM (3.0 mL), silica gel (3 equiv.) and PCC (0.9 mmol, 3 equiv.). After stirring the reaction mixture at room temperature for 24 h, the crude reaction mixture was passed through a pad of celite and concentrated to dryness. Pure chiral products **78ea** or **78ed** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

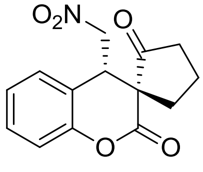


(–)-78aa

(1'*S*,4*R*)-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78aa): Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 142-145 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 20.99 min (major), t_R = 26.44 min (minor). **[α]$_D^{25}$ = –36.5° (*c* = 0.34 g/100 mL, CHCl$_3$, >99.9% *ee*);** IR (Neat): ν$_{max}$ 2954, 1762 (C=O), 1726, 1666 (*NO$_2$*), 1366 (*NO$_2$*), 1171, 1016, 911, 811 and 754 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.42-7.38 (1H, m), 7.22-7.17 (2H, m), 7.15-7.13 (1H, m), 5.56 (1H, dd, *J* = 10.8, 4.0 Hz), 4.42 (1H, dd, *J* = 10.8, 8.0 Hz), 3.78 (1H, dd, *J* = 8.0, 4.0 Hz), 2.73-2.67 (1H, m), 2.51-2.45 (1H, m), 2.22-

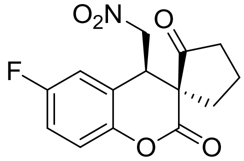
2.19 (1H, m), 2.10-1.99 (3H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 212.6 (C, C=O), 166.6 (C, O-C=O), 150.3 (C), 130.4 (CH), 128.8 (CH), 125.6 (CH), 120.6 (C), 117.2 (CH), 75.5 (CH$_2$), 54.9 (C), 41.6 (CH), 39.1 (CH$_2$), 35.7 (CH$_2$), 18.7 (CH$_2$); LRMS m/z 276.15 (M + H$^+$), calcd for $C_{14}H_{13}NO_5$ 275.0794; Anal. calcd for $C_{14}H_{13}NO_5$ (275.0794): C, 61.09; H, 4.76; N, 5.09. Found: C, 61.13; H, 4.68; N, 5.17%.

(1'*R*,4*S*)-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78aa): Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 143-145 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 20.52 min (minor), t_R = 25.46 min (major). **[α]$_D^{25}$ = +28.7° (*c* = 0.42 g/100 mL, CHCl$_3$, 98% *ee*);** IR (Neat): ν_{max} 2962, 1758 (C=O), 1736, 1546 (*NO$_2$*), 1375 (*NO$_2$*), 1258, 1087, 1011 and 793 cm^{-1}.



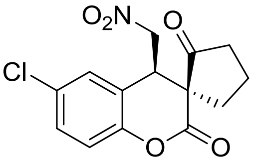
(+)-78aa

(1'*S*,4*R*)-6-fluoro-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ab): Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 125-127 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.46 min (major), t_R = 33.42 min (minor). **[α]$_D^{25}$ = –22.8° (*c* = 0.63 g/100 mL, CHCl$_3$, 88% *ee*);** IR (Neat): ν_{max} 2953, 1762 (C=O), 1725, 1552 (*NO$_2$*), 1366 (*NO$_2$*), 1191, 1016, 911, 811 and 754 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.12-7.10 (2H, m), 6.96 (1H, br dd, *J* = 7.6, 2.0 Hz), 5.58 (1H, dd, *J* = 13.6, 4.8 Hz), 4.42 (1H, dd, *J* = 13.6, 10.0 Hz), 3.77 (1H, dd, *J* = 10.0, 4.8 Hz), 2.74-2.67 (1H, m), 2.54-2.44 (1H, m), 2.22-2.18 (1H, m), 2.12-1.99 (3H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 212.1 (C, C=O), 166.1 (C, O-C=O), 159.3 (C, d, *J* = 245.6 Hz), 146.4 (C, d, *J* = 3.1 Hz), 122.3 (C, d, *J* = 8.0 Hz), 118.7 (CH, d, *J* = 8.3 Hz), 117.2 (CH, d, *J* = 23.4 Hz), 115.7 (CH, d, *J* = 24.5 Hz), 75.0 (CH$_2$), 54.4 (C), 41.5 (CH), 39.0 (CH$_2$), 35.6 (CH$_2$), 18.6 (CH$_2$); LRMS m/z 294.25 (M + H$^+$), calcd for $C_{14}H_{12}FNO_5$ 293.0700; Anal. calcd for $C_{14}H_{12}FNO_5$ (293.0700): C, 57.34; H, 4.12; N, 4.78. Found: C, 57.25; H, 4.19; N, 4.71%.



(–)-78ab

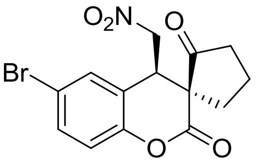
(1'*S*,4*R*)-6-chloro-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ac):



(–)-78ac

Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 116-118 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 24.85 min (major), t_R = 34.65 min (minor). **$[\alpha]_D^{25}$ = –12.1° (*c* = 0.28 g/100 mL, $CHCl_3$, 87% *ee*);** IR (Neat): ν_{max} 2957, 1767 (C=O), 1742, 1549 (*NO_2*), 1375 (*NO_2*), 1292, 1134, 826 and 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (1H, dd, *J* = 8.4, 2.4 Hz), 7.22 (1H, d, *J* = 2.4 Hz), 7.09 (1H, d, *J* = 8.8 Hz), 5.57 (1H, dd, *J* = 14.0, 4.8 Hz), 4.42 (1H, dd, *J* = 14.0, 10.0 Hz), 3.76 (1H, dd, *J* = 10.0, 4.8 Hz), 2.74-2.67 (1H, m), 2.54-2.44 (1H, m), 2.22-2.17 (1H, m), 2.10-1.98 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.0 (C, C=O), 165.9 (C, O-C=O), 148.9 (C), 130.8 (C), 130.6 (CH), 128.7 (CH), 122.3 (C), 118.6 (CH), 75.0 (CH_2), 54.5 (C), 41.4 (CH), 39.0 (CH_2), 35.7 (CH_2), 18.7 (CH_2); LRMS m/z 310.00 (M + H^+), calcd for $C_{14}H_{12}ClNO_5$ 309.0404; Anal. calcd for $C_{14}H_{12}ClNO_5$ (309.0404): C, 54.29; H, 3.91; N, 4.52. Found: C, 54.19; H, 3.96; N, 4.48%.

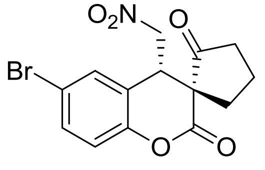
(1'*S*,4*R*)-6-bromo-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ad):



(+)-78ad

Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 120-122 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 27.45 min (major), t_R = 38.37 min (minor). **$[\alpha]_D^{25}$ = +14.0° (*c* = 0.27 g/100 mL, $CHCl_3$, >99.9% *ee*);** IR (Neat): ν_{max} 2921, 1759 (C=O), 1734, 1547 (*NO_2*), 1380 (*NO_2*), 1342, 1221, 1145, 941, 785 and 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (1H, dd, *J* = 8.8, 2.4 Hz), 7.37 (1H, d, *J* = 2.4 Hz), 7.03 (1H, d, *J* = 8.4 Hz), 5.54 (1H, dd, *J* = 14.0, 4.8 Hz), 4.42 (1H, dd, *J* = 14.0, 9.6 Hz), 3.76 (1H, dd, *J* = 9.6, 4.8 Hz), 2.75-2.67 (1H, m), 2.54-2.44 (1H, m), 2.22-2.17 (1H, m), 2.11-1.97 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 211.9 (C, C=O), 165.8 (C, O-C=O), 149.4 (C), 133.5 (CH), 131.5 (CH), 122.7 (C), 118.9 (CH), 118.2 (C), 74.9 (CH_2), 54.4 (C), 41.2 (CH), 39.0 (CH_2), 35.7 (CH_2), 18.7 (CH_2); LRMS m/z 353.20 (M + H^+), calcd for $C_{14}H_{12}BrNO_5$ 352.9899; calcd for $C_{14}H_{12}BrNO_5$ (352.9899): C, 47.48; H, 3.42; N, 3.95. Found: C, 47.56; H, 3.37; N, 3.89%.

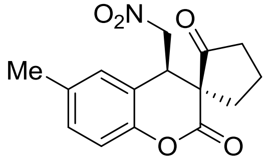
(1'*R*,4*S*)-6-bromo-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ad):



(–)-78ad

Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 118-119 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 28.22 min (minor), t_R = 38.36 min (major). **$[\alpha]_D^{25}$ = –12.9° (*c* = 0.28 g/100 mL, $CHCl_3$, 96% *ee*);** IR (Neat): ν_{max} 2924, 1761 (C=O), 1729, 1551 (*NO_2*), 1455, 1376 (*NO_2*), 1336, 1223, 1180, 1031 and 756 cm^{-1}.

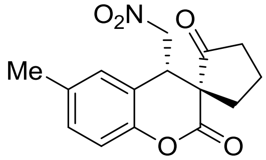
(1'*S*,4*R*)-6-methyl-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ae):



(–)-78ae

Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 130-133 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.14 min (major), t_R = 22.10 min (minor). **$[\alpha]_D^{25}$ = –18.3° (*c* = 0.28 g/100 mL, $CHCl_3$, 96% *ee*);** IR (Neat): ν_{max} 2921, 1758 (C=O), 1735, 1550 (*NO_2*), 1379 (*NO_2*), 1221, 1145, 897 and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17 (1H, d, *J* = 8.0 Hz), 7.01 (1H, d, *J* = 8.0 Hz), 6.98 (1H, br s), 5.54 (1H, dd, *J* = 13.6, 4.8 Hz), 4.40 (1H, dd, *J* = 13.2, 10.0 Hz), 3.73 (1H, dd, *J* = 9.6, 4.8 Hz), 2.72-2.65 (1H, m), 2.52-2.43 (1H, m), 2.33 (3H, s, C*H_3*), 2.21-2.17 (1H, m), 2.10-1.97 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.6 (C, C=O), 166.7 (C, O-C=O), 148.2 (C), 135.5 (C), 130.9 (CH), 129.0 (CH), 120.2 (C), 116.9 (CH), 75.5 (CH_2), 54.9 (C), 41.6 (CH), 39.1 (CH_2), 35.7 (CH_2), 20.7 (CH_3), 18.7 (CH_2); LRMS m/z 290.05 (M + H^+), calcd for $C_{15}H_{15}NO_5$ 289.0950; Anal. calcd for $C_{15}H_{15}NO_5$ (289.0950): C, 62.28; H, 5.23; N, 4.84. Found: C, 62.35; H, 5.28; N, 4.79%.

(1'*R*,4*S*)-6-methyl-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ae):

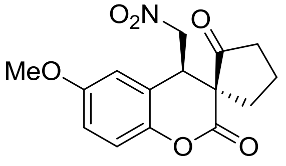


(+)-78ae

Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 126-128 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol =

80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.72 min (minor), t_R = 19.32 min (major). **$[\alpha]_D^{25}$ = +26.0° (*c* = 0.42 g/100 mL, CHCl$_3$, 99% *ee*);** IR (Neat): ν_{max} 2962, 1759 (C=O), 1736, 1546 (*NO_2*), 1375 (*NO_2*), 1258, 1086, 1011 and 793 cm^{-1}.

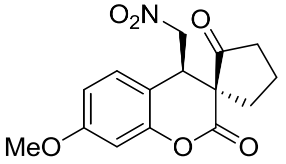
(1'*S*,4*R*)-6-methoxy-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78af):



(–)-78af

Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.94 min (major), t_R = 32.88 min (minor). **$[\alpha]_D^{25}$ = –35.2° (*c* = 0.30 g/100 mL, CHCl$_3$, 84% *ee*);** IR (Neat): ν_{max} 2924, 1762 (C=O), 1733, 1551 (*NO_2*), 1475, 1374 (*NO_2*), 1221, 1161 and 816 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.06 (1H, d, *J* = 9.2 Hz), 6.89 (1H, dd, *J* = 9.2, 3.2 Hz), 6.71 (1H, d, *J* = 2.8 Hz), 5.55 (1H, dd, *J* = 13.6, 4.8 Hz), 4.41 (1H, dd, *J* = 13.6, 10.0 Hz), 3.79 (3H, s, OC*H_3*), 3.73 (1H, dd, *J* = 10.0, 4.8 Hz), 2.72-2.65 (1H, m), 2.52-2.45 (1H, m), 2.22-2.18 (1H, m), 2.10-1.98 (3H, m); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 212.6 (C, C=O), 166.7 (C, O-C=O), 156.8 (C), 144.0 (C), 121.5 (C), 118.0 (CH), 115.4 (CH), 113.7 (CH), 75.4 (CH$_2$), 55.7 (CH$_3$, O*C*H$_3$), 54.8 (C), 41.8 (CH), 39.1 (CH$_2$), 35.6 (CH$_2$), 18.7 (CH$_2$); LRMS m/z 306.15 (M + H$^+$), calcd for $C_{15}H_{15}NO_6$ 305.0899; Anal. calcd for $C_{15}H_{15}NO_6$ (305.0899): C, 59.01; H, 4.95; N, 4.59. Found: C, 59.11; H, 5.03; N, 4.52%.

(1'*S*,4*R*)-7-methoxy-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ag):

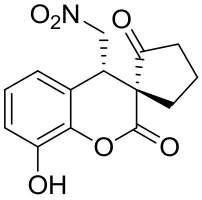


(–)-78ag

Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 13.50 min (major), t_R = 17.75 min (minor). **$[\alpha]_D^{25}$ = –41.1° (*c* = 0.29 g/100 mL, CHCl$_3$, 90% *ee*);** IR (Neat): ν_{max} 2953, 1764 (C=O), 1737, 1545 (*NO_2*), 1386 (*NO_2*), 1222, 1140, 893 and 816 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.08 (1H, d, *J* = 8.4 Hz), 6.69 (1H, dd, *J* = 8.4, 2.8 Hz), 6.66 (1H, d, *J* = 2.8 Hz) 5.46 (1H, dd, *J* = 13.2, 4.8 Hz), 4.39 (1H, dd, *J* = 13.6, 10.0 Hz), 3.81 (3H, s, OC*H_3*), 3.71 (1H, dd, *J* = 10.0, 5.2 Hz), 2.71-2.63 (1H, m), 2.52-2.43 (1H, m), 2.22-2.18 (1H, m), 2.09-1.99 (3H, m); ^{13}C NMR (CDCl$_3$, DEPT-

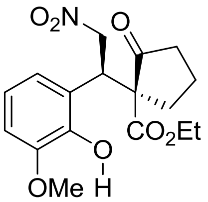
135) δ 212.6 (C, C=O), 166.5 (C, O-C=O), 161.1 (C), 151.1 (C), 129.3 (CH), 112.2 (C), 111.3 (CH), 102.9 (CH), 75.8 (CH_2), 55.6 (CH_3, O*C*H_3), 55.2 (C), 41.0 (CH), 39.1 (CH_2), 35.7 (CH_2), 18.7 (CH_2); LRMS m/z 306.15 (M + H^+), calcd for $C_{15}H_{15}NO_6$ 305.0899; Anal. calcd for $C_{15}H_{15}NO_6$ (305.0899): C, 59.01; H, 4.95; N, 4.59. Found: C, 59.11; H, 4.92; N, 4.51%.

(1'*R*,4*S*)-8-hydroxy-4-(nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (78ah):



(+)-78ah

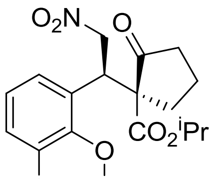
Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 66.89 min (minor), t_R = 76.20 min (major). **$[\alpha]_D^{25}$ = +15.4° (*c* = 0.143 g/100 mL, $CHCl_3$, 76% *ee*);** IR (Neat): ν_{max} 3419 (O-*H*), 2961, 1763 (C=O), 1736, 1555 (*NO_2*),1480, 1342 (*NO_2*), 1262, 1033, and 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08-7.00 (2H, m), 6.73 (1H, dd, *J* = 7.2, 1.6 Hz), 6.00 (1H, br s, OH), 5.46 (1H, dd, *J* = 13.6, 5.2 Hz), 4.44 (1H, dd, *J* = 13.6, 9.2 Hz), 3.80 (1H, dd, *J* = 9.6, 5.2 Hz), 2.72-2.65 (1H, m), 2.56-2.47 (1H, m), 2.26-2.22 (1H, m), 2.12-2.04 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.3 (C, C=O), 165.8 (C, O-C=O), 143.8 (C), 137.7 (C), 126.1 (CH), 121.0 (C), 119.7 (CH), 117.5 (CH), 75.4 (CH_2), 55.0 (C), 41.6 (CH), 39.1 (CH_2), 35.8 (CH_2), 18.8 (CH_2); LRMS m/z 292.10 (M + H^+), calcd for $C_{14}H_{13}NO_6$ 291.0743; Anal. calcd for $C_{14}H_{13}NO_6$ (291.0743): C, 57.73; H, 4.50; N, 4.81. Found: C, 57.62; H, 4.58; N, 4.76%.



(+)-76ai

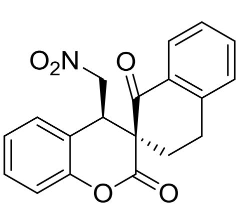
(*S*)-ethyl 1-[(*R*)-1-(2-hydroxy-3-methoxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (76ai): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 18.89 min (minor), t_R = 20.45 min (major). **$[\alpha]_D^{25}$ = +4.8° (*c* = 0.42 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): ν_{max} 3450 (O-*H*), 2961, 1740 (C=O), 1725, 1555 (*NO_2*), 1379 (*NO_2*), 1283, 1081, and 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90-6.88 (1H, m), 6.82-6.76 (2H, m), 5.94 (1H, br s, OH), 5.35 (1H, dd, *J* = 13.6, 3.6 Hz), 5.22 (1H, dd, *J* = 13.6, 10.4 Hz), 4.36 (1H, dd, *J* = 10.8, 4.0

Hz), 4.20 (2H, q, *J* = 7.2 Hz, O$CH_2$$CH_3$), 3.87 (3H, s, O$CH_3$), 2.40-2.32 (3H, m), 2.08-2.01 (2H, m), 1.95-1.89 (1H, m), 1.28 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.0 (C, C=O), 169.3 (C, O-C=O), 146.4 (C), 144.3 (C), 121.8 (CH), 121.7 (C), 120.0 (CH), 110.0 (CH), 76.2 (CH_2), 62.5 (C), 61.9 (CH_2, OCH_2CH_3), 55.9 (CH_3, OCH_3), 39.7 (CH), 37.9 (CH_2), 32.2 (CH_2), 19.2 (CH_2), 14.0 (CH_3, OCH_2CH_3); LRMS m/z 352.10 (M + H^+), calcd for $C_{17}H_{21}NO_7$ 351.1318; Anal. calcd for $C_{17}H_{21}NO_7$ (351.1318): C, 58.11; H, 6.02; N, 3.99. Found: C, 58.23; H, 5.96; N, 4.07%.



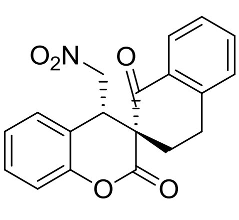
(+)-76ci

(*S*)-isopropyl 1-[(*R*)-1-(2-hydroxy-3-methoxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (76ci): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 23.07 min (minor), t_R = 26.96 min (major). **$[\alpha]_D^{25}$ = +5.6° (*c* = 0.143 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): ν_{max} 3468 (O-*H*), 2926, 1742 (C=O), 1723, 1615, 1555 (*NO_2*), 1377 (*NO_2*), 1254, 1101, and 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.92-6.88 (1H, m), 6.79-6.76 (2H, m), 5.99 (1H, br s, OH), 5.34 (1H, dd, *J* = 13.6, 3.6 Hz), 5.20 (1H, dd, *J* = 13.6, 10.8 Hz), 5.07-5.01 (1H, m, O$CH(CH_3)_2$), 4.36 (1H, dd, *J* = 10.8, 4.0 Hz), 3.84 (3H, s, OCH_3), 2.38-2.28 (3H, m), 2.07-1.97 (2H, m), 1.92-1.87 (1H, m), 1.25 (3H, d, *J* = 6.0 Hz, O$CH(CH_3)_2$), 1.22 (3H, d, *J* = 6.4 Hz, O$CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.1 (C, C=O), 168.9 (C, O-C=O), 146.4 (C), 144.3 (C), 122.0 (C), 121.8 (CH), 120.0 (CH), 110.0 (CH), 76.3 (CH_2), 69.8 (CH, O$CH(CH_3)_2$), 62.5 (C), 56.0 (CH_3, OCH_3), 39.6 (CH), 37.8 (CH_2), 32.3 (CH_2), 21.6 (CH_3), 21.5 (CH_3), 19.2 (CH_2); LRMS m/z 366.15 (M + H^+), calcd for $C_{18}H_{23}NO_7$ 365.1475; Anal. calcd for $C_{18}H_{23}NO_7$ (365.1475): C, 59.17; H, 6.34; N, 3.83. Found: C, 59.25; H, 6.41; N, 3.76%.



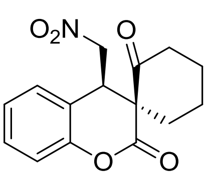
(–)-78da

(2'*S*,4*R*)-4-(nitromethyl)-3',4'-dihydro-1'*H*-spiro[chroman-3,2'-naphthalene]-1',2-dione (78da): Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 167-169 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 18.96 min (major), t_R = 26.08 min (minor). **$[\alpha]_D^{25}$ = –193.4° (*c* = 0.057 g/100 mL, $CHCl_3$, >99.9% *ee*);** IR (Neat): ν_{max} 2921, 1756 (C=O), 1734, 1550 (*NO_2*), 1456, 1377 (*NO_2*), 1340, 1221, 1146, and 759 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, d, *J* = 8.0 Hz), 7.55 (1H, t, *J* = 7.2 Hz), 7.43-7.38 (2H, m), 7.26-7.20 (2H, m), 7.22-7.10 (2H, m), 5.56 (1H, dd, *J* = 13.5, 5.0 Hz), 4.51 (1H, dd, *J* = 13.5, 10.0 Hz), 4.02 (1H, dd, *J* = 9.5, 5.0 Hz), 2.98 (2H, t, *J* = 6.0 Hz), 2.34 (1H, td, *J* = 14.0, 5.0 Hz), 2.12 (1H, td, *J* = 14.5, 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.3 (C, C=O), 165.8 (C, O-C=O), 150.2 (C), 142.1 (C), 134.5 (CH), 132.2 (C), 130.4 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 125.8 (CH), 120.8 (C), 117.1 (CH), 77.3 (CH_2), 53.7 (C), 41.3 (CH), 30.9 (CH_2), 25.4 (CH_2); LRMS m/z 338.25 (M + H$^+$), calcd for $C_{19}H_{15}NO_5$ 337.0950; Anal. calcd for $C_{19}H_{15}NO_5$ (337.0950): C, 67.65; H, 4.48; N, 4.15. Found: C, 67.56; H, 4.52; N, 4.21%.



(+)-78da

(2'*R*,4*S*)-4-(nitromethyl)-3',4'-dihydro-1'*H*-spiro[chroman-3,2'-naphthalene]-1',2-dione (78da): Prepared by procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 172-173 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 19.19 min (minor), t_R = 26.06 min (major). **$[\alpha]_D^{25}$ = +157.3° (*c* = 0.25 g/100 mL, $CHCl_3$, 97% *ee*);** IR (Neat): ν_{max} 2924, 1759 (C=O), 1734, 1547 (*NO_2*), 1493, 1375 (*NO_2*), 1257, 1011, and 815 cm^{-1}.

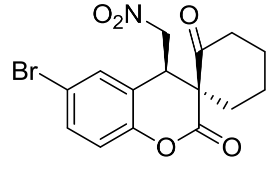


(–)-78ea

(1'*S*,4*R*)-4-(nitromethyl)spiro[chroman-3,1'-cyclohexane]-2,2'-dione (78ea): Prepared by procedure **7.14** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 142-145 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.04 min (major), t_R = 19.30 min (minor). **$[\alpha]_D^{25}$ = –43.7° (*c* = 0.128 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): ν_{max} 2931, 1759 (C=O), 1710, 1512 (*NO_2*), 1370 (*NO_2*), 1244, 1036, 811 and 767 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, t, *J* = 7.6 Hz), 7.22 (1H, d, *J* = 7.2 Hz), 7.15 (1H, t, *J* = 7.6 Hz), 7.10 (1H, d, *J* =

8.0 Hz), 5.41 (1H, dd, *J* = 12.8, 4.0 Hz), 4.21 (1H, dd, *J* = 12.4, 10.4 Hz), 3.90 (1H, dd, *J* = 10.4, 4.0 Hz), 3.39-3.31 (1H, m), 2.62-2.58 (1H, m), 2.17-2.14 (2H, m), 1.75-1.67 (3H, m), 1.50 (1H, td, *J* = 12.0, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.9 (C, C=O), 166.1 (C, O-C=O), 150.0 (C), 130.2 (CH), 129.2 (CH), 125.6 (CH), 121.4 (C), 116.5 (CH), 76.7 (CH_2), 56.3 (C), 41.8 (CH_2), 41.77 (CH), 36.3 (CH_2), 27.7 (CH_2), 21.9 (CH_2); LRMS m/z 290.05 (M + H^+), calcd for $C_{15}H_{15}NO_5$ 289.0950; Anal. calcd for $C_{15}H_{15}NO_5$ (289.0950): C, 62.28; H, 5.23; N, 4.84. Found: C, 62.14; H, 5.27; N, 4.75%.

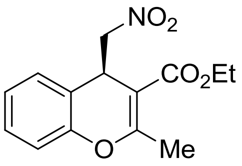
(1'*S*,4*R*)-6-bromo-4-(nitromethyl)spiro[chroman-3,1'-cyclohexane]-2,2'-dione (78ed):



(–)-78ed

Prepared by procedure **7.14** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 120 °C; The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 240 nm), t_R = 25.34 min (major), t_R = 30.76 min (minor). **[α]$_D^{25}$ = –4.2° (*c* = 0.21 g/100 mL, $CHCl_3$, 79% *ee*);** IR (Neat): ν_{max} 2918, 1764 (C=O), 1718, 1552 (*NO_2*), 1380 (*NO_2*), 1242, 1029 and 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (1H, dd, *J* = 8.4, 2.0 Hz), 7.38 (1H, d, *J* = 2.4 Hz), 7.00 (1H, d, *J* = 8.8 Hz), 5.37 (1H, dd, *J* = 13.2, 4.4 Hz), 4.22 (1H, dd, *J* = 13.2, 10.4 Hz), 3.87 (1H, dd, *J* = 10.4, 4.0 Hz), 3.38-3.29 (1H, m), 2.62-2.58 (1H, m), 2.20-2.11 (2H, m), 1.77-1.60 (3H, m), 1.52 (1H, td, *J* = 13.6, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.5 (C, C=O), 165.4 (C, O-C=O), 149.2 (C), 133.2 (CH), 131.9 (CH), 123.7 (C), 118.2 (C), 118.2 (CH), 76.3 (CH_2), 56.0 (C), 41.7 (CH_2), 41.4 (CH), 36.4 (CH_2), 27.7 (CH_2), 21.9 (CH_2); LRMS m/z 368.10 (M + H^+), calcd for $C_{15}H_{14}BrNO_5$ 367.0055; Anal. calcd for $C_{15}H_{14}BrNO_5$ (367.0055): C, 48.93; H, 3.83; N, 3.80. Found: C, 48.85; H, 3.76; N, 3.85%.

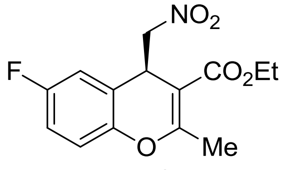
(*R*)-ethyl 2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fa): Prepared by



(–)-**80fa**

following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 87 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.89 min (major), t_R = 9.07 min (minor). **[α]$_D^{25}$ = –35.0° (*c* = 0.74 g/100 mL, $CHCl_3$, 97% *ee*);** IR (neat): ν_{max} 2977, 1686 (*C=O*), 1546 (*NO_2*), 1508, 1372 (NO_2), 1287, 1190, 1164, 1070 and 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (1H, m), 7.17 (1H, d, *J* = 6.4 Hz), 7.12 (1H, t, *J* = 7.2 Hz), 7.04 (1H, d, *J* = 8.0 Hz), 4.65 (1H, dd, *J* = 7.6, 4.4 Hz), 4.57 (1H, dd, *J* = 11.6, 4.4 Hz), 4.42 (1H, dd, *J* = 11.6, 8.0 Hz), 4.28 (2H, q, *J* = 6.8 Hz), 2.47 (3H, s), 1.35 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.1 (C), 164.7 (C), 150.5 (C), 129.0 (C), 128.0 (CH), 125.1 (CH), 120.3 (C), 116.4 (CH), 100.8 (C), 80.7 (CH_2), 60.8 (CH_2), 35.2 (CH), 19.9 (CH_3), 14.2 (CH_3); LRMS m/z 278.15 (M + H$^+$), calcd for $C_{14}H_{15}NO_5$ 277.10; Anal. calcd for $C_{14}H_{15}NO_5$ (277.10): C, 60.64; H, 5.45; N, 5.05. Found: C, 60.52; H, 5.38; N, 5.12%.

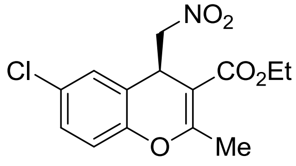
(*R*)-ethyl 6-fluoro-2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fb):



(–)-**80fb**

Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 76 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 11.06 min (major), t_R = 13.40 min (minor). **$[\alpha]_D^{25}$ = –81.4° (*c* = 0.32 g/100 mL, $CHCl_3$, 93% *ee*);** IR (neat): ν_{max} 2977, 1705 (*C=O*), 1542 (*NO_2*), 1499, 1375 (NO_2), 1336, 1241, 1209, 1146 and 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03-6.94 (2H, m), 6.89 (1H, dd, *J* = 8.4, 2.8 Hz), 4.62 (1H, dd, *J* = 7.6, 4.4 Hz), 4.56 (1H, dd, *J* = 11.6, 4.4 Hz), 4.44 (1H, dd, *J* = 11.6, 7.6 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 2.46 (3H, s), 1.35 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.0 (C), 164.7 (C), 159.3 (C, d, *J* = 242.6 Hz), 146.6 (C), 121.8 (C, d, *J* = 7.8 Hz), 117.8 (CH, d, *J* = 8.3 Hz), 115.9 (CH, d, *J* = 23.6 Hz), 114.2 (CH, d, *J* = 23.8), 100.0 (C), 80.3 (CH_2), 60.9 (CH_2), 35.2 (CH), 19.9 (CH_3), 14.2 (CH_3); HRMS m/z 318.0754 (M + Na), calcd for $C_{14}H_{14}FNNaO_5$ 318.0754.

(*R*)-ethyl 6-chloro-2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fc):

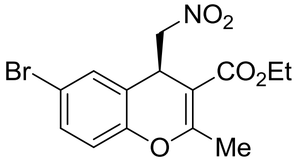


(–)-**80fc**

Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 76 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.83 min (major), t_R =

13.37 min (minor). **$[\alpha]_D^{25}$ = –63.7° (*c* = 0.24 g/100 mL, $CHCl_3$, 92% *ee*);** IR (neat): ν_{max} 2977, 1705 (*C=O*), 1631, 1541 (*NO_2*), 1486, 1375 (NO_2), 1219, 1088, 1063, 993 and 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 8.8, 2.4 Hz), 7.17 (1H, d, *J* = 2.4 Hz), 6.98 (1H, d, *J* = 8.8 Hz), 4.59 (H, dd, *J* = 6.8, 4.0 Hz), 4.55, (1H, dd, *J* = 11.6, 4.0 Hz), 4.45 (1H, dd, *J* = 12.0, 7.6 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 2.45 (3H, s), 1.34 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.8 (C), 164.5 (C), 149.1 (C), 129.9 (C), 129.1 (CH), 127.7 (CH), 122.0 (C), 117.8 (CH), 100.6 (C), 80.3 (CH_2), 60.9 (CH_2), 34.9 (CH), 19.8 (CH_3), 14.2 (CH_3); HRMS m/z 334.0459 (M + Na), calcd for $C_{14}H_{14}ClNNaO_5$ 334.0459.

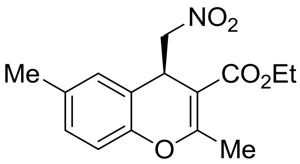
(*R*)-ethyl 6-bromo-2-methyl-4-(nitromethyl)-4H-chromene-3-arboxylate (80fd):



(+)-**80fd**

Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 110 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.43 min (major), t_R = 14.44 min (minor). **$[\alpha]_D^{25}$ = +54.2° (*c* = 0.21 g/100 mL, $CHCl_3$, 93% *ee*);** IR (neat): ν_{max} 2977, 1705 (*C=O*), 1535 (*NO_2*), 1483, 1377 (NO_2), 1329, 1202, 1066, 998 and 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (1H, dd, *J* = 2.5, 9.0 Hz), 7.33 (1H, d, *J* = 2.5 Hz), 6.94 (1H, d, *J* = 8.5 Hz), 4.61 (1H, dd, *J* = 7.5, 4.5 Hz), 4.56 (1H, dd, *J* = 11.5, 4.0 Hz), 4.47 (1H, dd, *J* = 12.0, 7.5 Hz), 4.28 (2H, q, *J* = 7.0 Hz), 2.47 (3H, s), 1.36 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.8 (C), 164.5 (C), 149.7 (C), 132.0 (CH), 130.6 (CH), 122.5 (C), 118.2 (CH), 117.3 (C), 100.7 (C), 80.4 (CH_2), 60.9 (CH_2), 34.8 (CH), 19.8 (CH_3), 14.2 (CH_3); LRMS m/z 357.95 ($M + H^+$), calcd for $C_{14}H_{14}BrNO_5$ 355.01; Anal. calcd for $C_{14}H_{14}BrNO_5$ (355.01): C, 47.21; H, 3.96; N, 3.93. Found: C, 47.36; H, 3.91; N, 3.85%.

(*R*)-ethyl 2,6-dimethyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fe): Prepared by

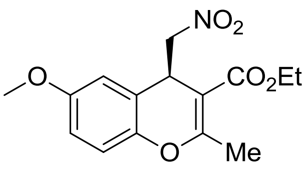


(–)-**80fe**

following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 83 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 16.16 min (major), t_R = 17.78 min (minor). **$[\alpha]_D^{25}$ = –11.0° (*c* = 0.57 g/100**

mL, $CHCl_3$, 81% *ee*); IR (neat): ν_{max} 2977, 1686 (*C=O*), 1546 (*NO_2*), 1508, 1372 (NO_2), 1287, 1190, 1164, 1070 and 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, dd, *J* = 8.0, 1.2 Hz), 6.96-6.91 (2H, m), 4.60 (1H, dd, *J* = 7.2, 4.0 Hz), 4.54 (1H, dd, *J* = 11.6, 4.4 Hz), 4.41 (1H, dd, *J* = 11.2, 7.6 Hz), 4.26 (2H, q, *J* = 7.2 Hz), 2.45 (3H, s), 2.30 (3H, s), 1.34 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.2 (C), 164.8 (C), 148.4 (C), 134.7 (C), 129.5 (CH), 128.1 (CH), 120.0 (C), 116.1 (CH), 100.6 (C), 80.8 (CH_2), 60.7 (CH_2), 35.2 (CH), 20.7 (CH_3), 19.9 (CH_3), 14.2 (CH_3); LRMS m/z 289.91 (M – H$^+$), calcd for $C_{15}H_{17}NO_5$ 291.11; Anal. calcd for $C_{15}H_{17}NO_5$ (291.11): C, 61.85; H, 5.88; N, 4.81. Found: C, 61.72; H, 5.81; N, 4.86%.

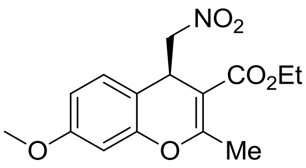
(*R*)-ethyl 6-methoxy-2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80ff):



(–)-**80ff**

Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 103 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.19 min (major), t_R = 10.05 min (minor). **$[\alpha]_D^{25}$ = –19.6° (*c* = 0.35 g/100 mL, $CHCl_3$, 97% *ee*);** IR (neat): ν_{max} 2977, 1705 (*C=O*), 1635, 1535 (*NO_2*), 1483, 1377 (NO_2), 1329, 1218, 1202, 1066 and 813 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 9.0 Hz), 6.83 (1H, dd, *J* = 9.0, 3.0 Hz), 6.68 (1H, d, *J* = 3.0 Hz), 4.64 (1H, dd, *J* = 8.0, 4.5 Hz), 4.58 (1H, dd, *J* = 11.5, 4.5 Hz), 4.44 (1H, dd, *J* = 12.0, 8.0 Hz), 4.28 (2H, q, *J* = 7.0 Hz), 3.78 (3H, s), 2.47 (3H, s), 1.36 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.3 (C), 164.9 (C), 156.6 (C), 144.5 (C), 121.1 (C), 117.3 (CH), 115.0 (CH), 111.8 (CH), 99.9 (C), 80.7 (CH_2), 60.7 (CH_2), 55.7 (CH_3), 35.5 (CH), 20.0 (CH_3), 14.2 (CH_3); LRMS m/z 306.30 (M – H$^+$), calcd for $C_{15}H_{17}NO_6$ 307.11; Anal. calcd for $C_{15}H_{17}NO_6$ (307.11): C, 58.63; H, 5.58; N, 4.56. Found: C, 58.72; H, 5.63; N, 4.57%.

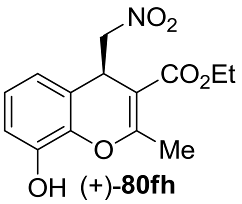
(*R*)-ethyl 7-methoxy-2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fg):



(–)-**80fg**

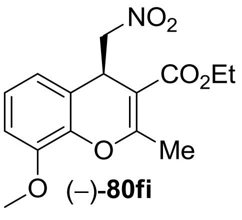
Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 116 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 23.66 min (major), t_R = 28.24 min (minor). **$[\alpha]_D^{25}$ = –63.0° (*c* = 0.10g/100 mL, $CHCl_3$, 99% *ee*);** IR (neat): ν_{max} 2977, 1727 (*C=O*), 1624, 1579 (*NO_2*), 1540, 1380 (NO_2), 1241, 1159, 1024, 852 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, d, *J* = 8.4 Hz), 6.70 (1H, d, *J* = 8.8 Hz), 6.59 (1H, s), 4.63-4.54 (2H, m), 4.39 (1H, dd, *J* = 9.6, 8.8 Hz), 4.28 (2H, q, *J* = 6.8 Hz), 3.80 (3H, s), 2.47 (3H, s), 1.37 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.2 (C), 164.4 (C), 160.1 (C), 151.2 (C), 128.5 (CH), 112.2 (C), 111.6 (CH), 101.6 (CH), 101.3 (C), 80.9 (CH_2), 60.7 (CH_2), 55.4 (CH_3), 34.7 (CH), 19.8 (CH_3), 14.2 (CH_3); HRMS m/z 330.0954 (M + Na), calcd for $C_{15}H_{17}NNaO_6$ 330.0954.

(*R*)-ethyl 8-hydroxy-2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fh):



(+)-**80fh**

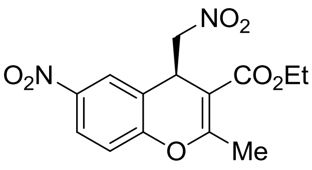
Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 126 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.82 min (major), t_R = 10.54 min (minor). **$[\alpha]_D^{25}$ = +5.6° (*c* = 0.28 g/100 mL, $CHCl_3$, 73% *ee*);** IR (neat): ν_{max} 3334 (O*H*), 2925, 1706 (*C=O*), 1541 (*NO_2*), 1477, 1378 (NO_2), 1269, 1198, 1087, 1010 and 901 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (1H, t, *J* = 8.0 Hz), 6.92 (1H, dd, *J* = 8.0, 1.5 Hz), 6.73 (1H, dd, *J* = 8.0, 1.5 Hz), 5.55 (1H, br s), 4.66 (1H, dd, *J* = 7.0, 4.0 Hz), 4.59 (1H, dd, *J* = 11.5, 4.5 Hz), 4.48 (1H, dd, *J* = 11.5, 7.5 Hz), 4.30 (2H, q, *J* = 7.0 Hz), 2.53 (3H, s), 1.37 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.0 (C), 163.6 (C), 143.8 (C), 138.3 (C), 125.5 (CH), 120.9 (C), 118.9 (CH), 115.3 (CH), 101.9 (C), 80.6 (CH_2), 61.0 (CH_2), 35.1 (CH), 19.8 (CH_3), 14.2 (CH_3); LRMS m/z 294.25 (M + H^+), calcd for $C_{14}H_{15}NO_6$ 293.09; Anal. calcd for $C_{14}H_{15}NO_6$ (293.09): C, 57.34; H, 5.16; N, 4.78. Found: C, 57.26; H, 5.23; N, 4.71%.



(–)-**80fi**

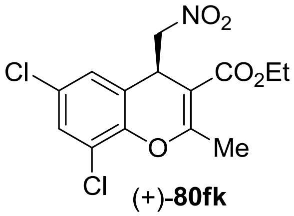
(*R*)-ethyl 8-methoxy-2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fi): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 106 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.20 min (major), t_R = 12.99 min (minor). **$[\alpha]_D^{25}$ = –72.3° (*c* = 0.11 g/100 mL, CHCl$_3$, 87% *ee*);** IR (neat): ν_{max} 2977, 1728 (*C=O*), 1626, 1542 (*NO$_2$*), 1396 (NO$_2$), 1275, 1174, 1160, 1024, 963 and 756 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.07 (1H, d, *J* = 8.5 Hz), 6.71 (1H, dd, *J* = 9.0, 2.5 Hz), 6.60 (1H, d, *J* = 2.5 Hz), 4.61 (1H, dd, *J* = 7.5, 4.5 Hz), 4.56 (1H, dd, *J* = 11.5, 4.5 Hz), 4.40 (1H, dd, *J* = 11.0, 7.5 Hz), 4.29 (2H, q, *J* = 7.0 Hz), 3.81 (3H, s), 2.47 (3H, s), 1.37 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.3 (C), 164.5 (C), 160.1 (C), 151.3 (C), 128.6 (CH), 112.2 (C), 111.7 (CH), 101.6 (CH), 101.3 (C), 80.9 (CH$_2$), 60.8 (CH$_2$), 55.5 (CH$_3$), 34.8 (CH), 19.9 (CH$_3$), 14.2 (CH$_3$); LRMS m/z 308.65 (M + H$^+$), calcd for $C_{15}H_{17}NO_6$ 307.11; Anal. calcd for $C_{15}H_{17}NO_6$ (307.11): C, 58.63; H, 5.58; N, 4.56. Found: C, 58.72; H, 5.63; N, 4.48%.

(*R*)-ethyl 2-methyl-6-nitro-4-(nitromethyl)-4H-chromene-3-carboxylate (80fj): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 156 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 36.24 min (major), t_R = 44.45 min (minor). **$[\alpha]_D^{25}$ = +33.2° (*c* = 0.07 g/100 mL, CHCl$_3$, 97% *ee*);** IR (neat): ν_{max} 2977, 1686 (*C=O*), 1546 (*NO$_2$*), 1508, 1373 (NO$_2$), 1287, 1190, 1164, 1120, 835 and 770 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.19-8.14 (2H, m), 7.17 (1H, d, *J* = 8.8 Hz), 4.68 (1H, dd, *J* = 6.4, 4.4 Hz), 4.64-4.55 (2H, m), 4.30 (2H, q, *J* = 7.2 Hz), 2.49 (3H, s), 1.36 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.4 (C), 163.9 (C), 154.9 (C), 144.5 (C), 124.8 (CH), 124.2 (CH), 121.5 (C), 117.5 (CH), 101.3 (C), 80.1 (CH$_2$), 61.3 (CH$_2$), 34.9 (CH), 19.7 (CH$_3$), 14.2 (CH$_3$); HRMS m/z 345.0701 (M + Na), calcd for $C_{14}H_{14}N_2NaO_7$ 345.0699.



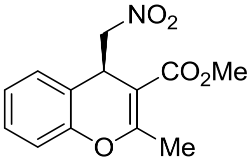
(+)-**80fj**

(*R*)-ethyl 6,8-dichloro-2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80fk): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and



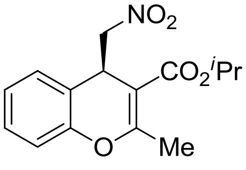
(+)-**80fk**

isolated as white powder. Mp: 113 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 16.84 min (major), t_R = 18.58 min (minor). **$[\alpha]_D^{25}$ = +30.8° (*c* = 0.21 g/100 mL, CHCl$_3$, 87% *ee*);** IR (neat): ν_{max} 2966, 1710 (*C=O*), 1637, 1547 (*NO$_2$*), 1498, 1381 (NO$_2$), 1280, 1206, 1158, 1067, 1030 and 871 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (1H, d, *J* = 2.5 Hz), 7.10 (1H, d, *J* = 2.5 Hz), 4.64 (1H, dd, *J* = 7.5, 4.0 Hz), 4.57 (1H, dd, *J* = 12.0, 4.0 Hz), 4.45 (1H, dd, *J* = 12.5, 8.0 Hz), 4.30 (2H, q, *J* = 7.0 Hz), 2.53 (3H, s), 1.37 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.5 (C), 164.3 (C), 145.5 (C), 129.8 (C), 129.5 (CH), 126.3 (CH), 123.3 (C), 122.8 (C), 101.4 (C), 80.0 (CH$_2$), 61.2 (CH$_2$), 35.2 (CH), 19.7 (CH$_3$), 14.2 (CH$_3$); LRMS m/z 345.85 (M + H$^+$), calcd for $C_{14}H_{13}Cl_2NO_5$ 345.02; Anal. calcd for $C_{14}H_{13}Cl_2NO_5$ (345.02): C, 48.58; H, 3.79; N, 4.05. Found: C, 48.51; H, 3.74; N, 4.12%.



(–)-**80ga**

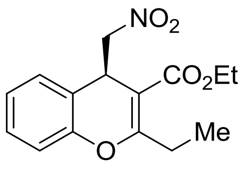
(*R*)-methyl 2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80ga): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 86 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.99 min (major), t_R = 11.65 min (minor). **$[\alpha]_D^{25}$ = –30.8° (*c* = 0.21 g/100 mL, CHCl$_3$, 99% *ee*);** IR (neat): ν_{max} 2966, 1710 (*C=O*), 1637, 1547 (*NO$_2$*), 1498, 1381 (NO$_2$), 1280, 1243, 1206, 1158, 1067, 1030, 813 and 771 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30-7.25 (1H, m), 7.18-7.10 (2H, m), 7.05 (1H, d, *J* = 8.0 Hz), 4.65 (1H, dd, *J* = 8.0, 4.4 Hz), 4.57 (1H, dd, *J* = 11.6, 4.4 Hz), 4.42 (1H, dd, *J* = 11.2, 7.6 Hz), 3.82 (3H, br s), 2.47 (3H, s); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.6 (C), 165.0 (C), 150.5 (C), 129.0 (CH), 128.0 (CH), 125.2 (CH), 120.3 (C), 116.5 (CH), 100.7 (C), 80.7 (CH$_2$), 51.8 (CH$_3$), 35.2 (CH), 19.9 (CH$_3$); LRMS m/z 263.95 (M + H$^+$), calcd for $C_{13}H_{13}NO_5$ 263.08; Anal. calcd for $C_{13}H_{13}NO_5$ (263.08): C, 59.31; H, 4.98; N, 5.32. Found: C, 59.26; H, 4.92; N, 5.41%.



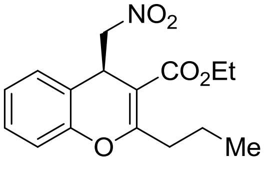
(–)-**80ha**

(*R*)-isopropyl 2-methyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80ha): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 78 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 11.68 min (major), t_R = 12.62 min (minor). **$[\alpha]_D^{25}$ = –10.8° (*c* = 0.31 g/100 mL, $CHCl_3$, 55% *ee*);** IR (neat): ν_{max} 2928, 1702 (*C=O*), 1633, 1536 (*NO_2*), 1434, 1376 (NO_2), 1290, 1209, 1155, 1069, 993 and 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, t, *J* = 6.8 Hz), 7.15 (1H, t, *J* = 7.2 Hz), 7.10 (1H, t, *J* = 7.2 Hz), 7.03 (1H, d, *J* = 8.4 Hz), 5.14 (1H, heptet, *J* = 6.4 Hz), 4.63 (1H, dd, *J* = 7.6, 4.0 Hz), 4.55 (1H, dd, *J* = 11.6, 4.4 Hz), 4.40 (1H, dd, *J* = 11.8, 8.0 Hz), 2.46 (3H, s), 1.34 (3H, d, *J* = 2.8 Hz), 1.32 (3H, d, *J* = 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.7 (C), 164.5 (C), 150.5 (C), 129.0 (CH), 128.0 (CH), 125.1 (CH), 120.4 (C), 116.4 (CH), 101.2 (C), 80.8 (CH_2), 68.4 (CH), 35.2 (CH), 22.0 (CH_3), 21.8 (CH_3), 19.9 (CH_3); HRMS m/z 314.1004 (M + Na), calcd for $C_{15}H_{17}NNaO_5$ 314.1005.

(*R*)-ethyl 2-ethyl-4-(nitromethyl)-4H-chromene-3-carboxylate (80ia): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 117 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.07 min (major), t_R = 11.75 min (minor). **$[\alpha]_D^{25}$ = –32.7° (*c* = 0.21 g/100 mL, $CHCl_3$, 94% *ee*);** IR (neat): ν_{max} 2958, 1712 (*C=O*), 1630, 1537 (*NO_2*), 1488, 1380 (NO_2), 1231, 1199, 1108, 1043, 771 and 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (1H, t, *J* = 8.5 Hz), 7.19 (1H, d, *J* = 6.5 Hz), 7.14 (1H, t, *J* = 7.0 Hz), 7.08 (1H, d, *J* = 8.0 Hz), 4.66 (1H, dd, *J* = 8.0, 4.5 Hz), 4.59 (1H, dd, *J* = 11.0, 4.0 Hz), 4.43 (1H, dd, *J* = 11.5, 8.0 Hz), 4.30 (2H, q, *J* = 7.0 Hz), 2.99 (1H, dq, *J* = 14.5, 7.5 Hz), 2.80 (1H, dq, *J* = 14.5, 7.5 Hz), 1.37 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.4 (C), 165.9 (C), 150.8 (C), 129.0 (CH), 128.0 (CH), 125.1 (CH), 120.5 (C), 116.4 (CH), 100.3 (C), 80.7 (CH_2), 60.8 (CH_2), 35.3 (CH), 26.3 (CH_2), 14.2 (CH_3), 11.6 (CH_3); HRMS m/z 314.1003 (M + Na), calcd for $C_{15}H_{17}NNaO_5$ 314.1005.

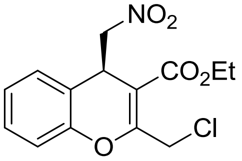


(–)-**80ia**



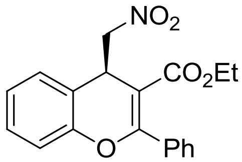
(–)-**80ja**

(*R*)-ethyl 4-(nitromethyl)-2-propyl-4H-chromene-3-carboxylate (80ja): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 108 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.72 min (major), t_R = 12.31 min (minor). **$[\alpha]_D^{25}$ = –22.7° (*c* = 0.14 g/100 mL, $CHCl_3$, 89% *ee*);** IR (neat): ν_{max} 2958, 1712 (*C=O*), 1630, 1537 (*NO_2*), 1489, 1457, 1380 (NO_2), 1231, 1199, 1108, 1084, 1043 and 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (1H, t, *J* = 7.5 Hz), 7.19 (1H, d, *J* = 7.0 Hz), 7.14 (1H, t, *J* = 7.0 Hz), 7.07 (1H, d, *J* = 8.5 Hz), 4.67 (1H, dd, *J* = 8.0, 4.5 Hz), 4.59 (1H, dd, *J* = 11.5, 4.5 Hz), 4.42 (1H, dd, *J* = 11.5, 8.0 Hz), 4.29 (2H, q, *J* = 7.0 Hz), 2.93 (1H, td, *J* = 13.5, 7.5 Hz), 2.78 (1H, td, *J* = 13.0, 7.5 Hz), 1.71 (2H, sestet, *J* = 7.5 Hz), 1.37 (3H, t, *J* = 7.5 Hz), 1.01 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.4 (C), 166.0 (C), 150.7 (C), 129.0 (CH), 128.0 (CH), 125.1 (CH), 120.5 (C), 116.4 (CH), 100.9 (C), 80.7 (CH_2), 60.8 (CH_2), 35.4 (CH), 34.5 (CH_2), 20.9 (CH_2), 14.2 (CH_3), 13.8 (CH_3); HRMS m/z 328.1161 (M + Na), calcd for $C_{16}H_{19}NNaO_5$ 328.1161.



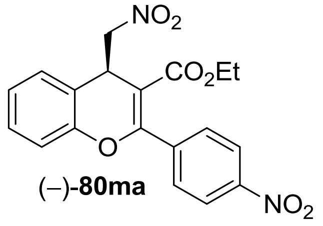
(–)-**80ka**

(*R*)-ethyl 2-(chloromethyl)-4-(nitromethyl)-4H-chromene-3-carboxylate (80ka): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 126 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = **8**0:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.03 min (major), t_R = 26.01 min (minor). **$[\alpha]_D^{25}$ = –20.4° (*c* = 0.34 g/100 mL, $CHCl_3$, 80% *ee*);** IR (neat): ν_{max} 2932, 1706 (*C=O*), 1635, 1540 (*NO_2*), 1376 (NO_2), 1269, 1199, 1088, 1010, 902 and 783 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, t, *J* = 6.5 Hz), 7.21-7.16 (2H, m), 7.14 (1H, d, *J* = 8.0 Hz), 4.94 (1H, d, *J* = 12.0 Hz), 4.72 (1H, dd, *J* = 7.0, 4.5 Hz), 4.61-4.58 (2H, m), 4.48 (1H, dd, *J* = 12.0, 7.5 Hz), 4.34 (2H, q, *J* = 7.0 Hz), 1.39 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.6 (C), 160.7 (C), 150.4 (C), 129.3 (CH), 128.0 (CH), 125.7 (CH), 119.6 (C), 116.6 (CH), 104.1 (C), 80.3 (CH_2), 61.6 (CH_2), 39.9 (CH_2), 35.2 (CH), 14.0 (CH_3); HRMS m/z 313.0705 (M + H), calcd for $C_{15}H_{16}NO_5$ 313.0705.



(–)-**80la**

(*R*)-ethyl 4-(nitromethyl)-2-phenyl-4H-chromene-3-carboxylate (80la): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.93 min (major), t_R = 13.61 min (minor). **[α]$_D^{25}$ = –37.4° (*c* = 0.17 g/100 mL, CHCl$_3$, 89% *ee*);** IR (neat): ν_{max} 2929, 1702 (*C=O*), 1633, 1536 (*NO$_2$*), 1434, 1376 (NO$_2$), 1290, 1209, 1155, 1069, 992 and 813 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.51-7.48 (3H, m), 7.46-7.43 (2H, m), 7.34 (1H, td, *J* = 9.0, 1.5 Hz), 7.27 (1H, d, *J* = 8.0 Hz), 7.20 (1H, td, *J* = 7.5, 1.0 Hz), 7.16 (1H, d, *J* = 8.0 Hz), 4.80 (1H, dd, *J* = 10.0, 3.0 Hz), 4.72-4.66 (2H, m), 4.04 (1H, q, *J* = 7.0 Hz), 0.98 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 166.5 (C), 163.0 (C), 151.0 (C), 134.4 (C), 130.1 (CH), 129.2 (CH), 128.9 (2 x CH), 128.1 (CH), 127.9 (2 x CH), 125.4 (CH), 120.2 (C), 116.7 (CH), 101.4 (C), 80.5 (CH$_2$), 60.7 (CH$_2$), 36.0 (CH), 13.5 (CH$_3$); LRMS m/z 340.85 (M + H$^+$), calcd for $C_{19}H_{17}NO_5$ 339.11; Anal. calcd for $C_{19}H_{17}NO_5$ (339.11): C, 67.25; H, 5.05; N, 4.13. Found: C, 67.15; H, 5. 21; N, 4.07%.

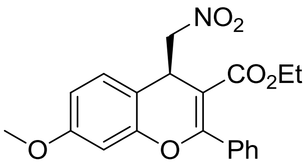


(–)-**80ma**

(*R*)-ethyl 4-(nitromethyl)-2-(4-nitrophenyl)-4H-chromene-3-carboxylate (80ma): Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 145 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 22.82 min (major), t_R = 25.72 min (minor). **[α]$_D^{25}$ = –11.2° (*c* = 0.71 g/100 mL, CHCl$_3$, 87% *ee*);** IR (neat): ν_{max} 2925, 1705 (*C=O*), 1601, 1555 (*NO$_2$*), 1520, 1346 (NO$_2$), 1254, 1217, 1077, 1038, 852 and 755 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.31 (2H, d, *J* = 8.5 Hz), 7.68 (2H, d, *J* = 8.5 Hz), 7.36 (1H, t, *J* = 7.0 Hz), 7.31 (1H, d, *J* = 7.0 Hz), 7.25 (1H, t, *J* = 7.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 4.77-4.72 (3H, m), 4.07 (1H, q, *J* = 7.0 Hz), 1.03 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 165.4 (C), 160.5 (C), 150.7 (C), 148.5 (C), 140.8 (C), 130.0 (2 x CH), 129.4 (CH), 128.1 (CH), 125.9 (CH), 123.1 (2 x CH), 119.5 (C), 116.8 (CH), 103.3 (C), 80.6 (CH$_2$), 61.1 (CH$_2$), 35.8 (CH), 13.6 (CH$_3$);

LRMS m/z 385.40 (M + H$^+$), calcd for $C_{19}H_{16}N_2O_7$ 384.10; Anal. calcd for $C_{19}H_{16}N_2O_7$ (384.10): C, 59.38; H, 4.20; N, 7.29. Found: C, 59.45; H, 4.26; N, 7.21%.

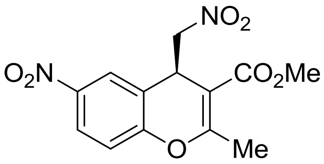
(*R*)-ethyl 7-methoxy-4-(nitromethyl)-2-phenyl-4H-chromene-3-carboxylate (80lg):



(+)-**80lg**

Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 9.55 min (major), t_R = 12.02 min (minor). **$[\alpha]_D^{25}$ = +10.8° (*c* = 0.85 g/100 mL, $CHCl_3$, 80% *ee*);** IR (neat): ν_{max} 2981, 1703 (*C=O*), 1601, 1555 (*NO_2*), 1519, 1346 (NO_2), 1254, 1217, 1077, 1038 and 1013 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (3H, m), 7.46-7.43 (2H, m), 7.15 (1H, d, *J* = 8.5 Hz), 6.77 (1H, dd, *J* = 8.5, 2.5 Hz), 6.68 (1H, d, *J* = 2.5 Hz), 4.78 (1H, dd, *J* = 14.5, 7.5 Hz), 4.67-4.63 (2H, m), 4.03 (1H, q, *J* = 7.0 Hz), 3.82 (3H, s), 0.97 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.6 (C), 162.8 (C), 160.3 (C), 151.8 (C), 134.4 (C), 130.1 (CH), 128.8 (2 x CH), 128.6 (CH), 127.9 (2 x CH), 112.1 (CH), 112.0 (C), 101.9 (C), 101.8 (CH), 80.7 (CH_2), 60.7 (CH_2), 55.5 (CH_3), 35.6 (CH), 13.5 (CH_3); LRMS m/z 368.20 (M – H$^+$), calcd for $C_{20}H_{19}NO_6$ 369.12; Anal. calcd for $C_{20}H_{19}NO_6$ (369.12): C, 65.03; H, 5.18; N, 3.79. Found: C, 65.13; H, 5.12; N, 3.86%.

(*R*)-methyl 2-methyl-6-nitro-4-(nitromethyl)-4H-chromene-3-carboxylate (80gj):

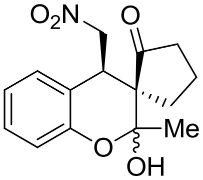


(+)-**80gj**

Prepared by following the procedure **7.13** and purified by column chromatography using EtOAc/hexane and isolated as white powder. Mp: 138 °C. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 26.45 min (major), t_R = 31.36 min (minor). **$[\alpha]_D^{25}$ = +92.3° (*c* = 0.28 g/100 mL, $CHCl_3$, 95% *ee*);** IR (neat): ν_{max} 2966, 1710 (*C=O*), 1637, 1547 (*NO_2*), 1498, 1381 (NO_2), 1280, 1206, 1158, 1067, 1030 and 871 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (1H, dd, *J* = 9.0, 2.5 Hz), 8.15 (1H, d, *J* = 3.0 Hz), 7.19 (1H, d, 9.0 Hz), 4.69 (1H, dd, *J* = 6.5, 4.0 Hz), 4.65-4.57 (2H, m), 3.86 (3H, br s), 2.51 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.8 (C), 164.1 (C), 154.9 (C), 144.5 (C), 124.9 (CH), 124.2 (CH), 121.4 (C), 117.5

(CH), 101.1 (C), 80.0 (CH_2), 52.1 (CH_3), 34.9 (CH), 19.7 (CH_3); LRMS m/z 307.15 (M – H^+), calcd for $C_{13}H_{12}N_2O_7$ 308.06; Anal. calcd for $C_{13}H_{12}N_2O_7$ (308.06): C, 50.65; H, 3.92; N, 9.09. Found: C, 50.72; H, 3.87; N, 9.18%.

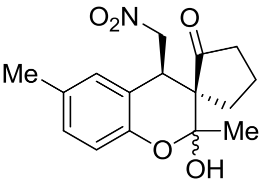
(1'*S*,4*R*)-2-hydroxy-2-methyl-4-(nitromethyl)spiro[chroman-3,1'-cyclopentan]-2'-one



(+)-**79na**

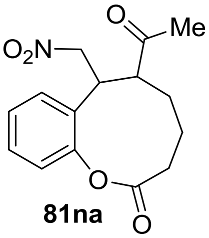
(79na): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.89 min (major), t_R = 25.62 min (minor). IR (Neat): ν_{max} 3449 (O-*H*), 2980, 1731 (C=O), 1556 (*NO_2*), 1380 (*NO_2*), 1276, 1200, 1106, 778 and 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, t, *J* = 8.0 Hz), 7.08 (1H, d, *J* = 7.6 Hz), 6.97 (1H, t, *J* = 7.2 Hz), 6.86 (1H, d, *J* = 8.0 Hz), 5.48 (1H, dd, *J* = 16.4, 7.2 Hz), 4.62 (1H, dd, *J* = 16.0, 4.4 Hz), 3.77 (1H, dd, *J* = 6.8, 4.4 Hz), 2.66-2.55 (1H, m), 2.39-2.27 (1H, m), 2.18-2.08 (2H, m), 2.08-1.99 (1H, m), 1.87-1.80 (1H, m), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 220.4 (C, C=O), 150.9 (C), 129.2 (CH), 129.0 (CH), 122.1 (CH), 119.7 (C), 117.8 (CH), 97.8 (C), 77.9 (CH_2), 54.3 (C), 40.1 (CH_2), 39.8 (CH), 33.7 (CH_2), 24.7 (CH_3), 18.2 (CH_2); HRMS m/z 314.1005 (M + Na), calcd for $C_{15}H_{17}NNaO_5$ 314.1004.

(1'*S*,4*R*)-2-hydroxy-2-methyl-4-(nitromethyl)spiro[chroman-3,1'-cyclopentan]-2'-one



(+)-**79ne**

(79ne): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.29 min (minor), t_R = 19.52 min (major). IR (Neat): ν_{max} 3449 (O-*H*), 2964, 1715 (C=O), 1643, 1594 (*NO_2*), 1518, 1380 (*NO_2*), 1331, 1005, 1068, 832 and 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, d, *J* = 8.0 Hz), 6.88 (1H, s), 6.76 (1H, d, *J* = 8.0 Hz), 5.48 (1H, dd, *J* = 16.0, 7.2 Hz), 4.62 (1H, dd, *J* = 16.4, 4.4 Hz), 3.73 (1H, dd, *J* = 7.0, 4.4 Hz), 2.65-2.56 (1H, m), 3.39-3.30 (1H, m), 2.27 (3H, s), 2.18-2.02 (3H, m), 1.87-1.82 (1H, m), 1.52 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 220.5 (C, C=O), 148.7 (C), 131.5 (C), 129.8 (CH), 129.4 (CH), 119.3 (C), 117.6 (CH), 97.8 (C), 77.9 (CH_2), 54.4 (C), 40.1 (CH_2), 39.8 (CH), 33.8 (CH_2), 24.8 (CH_3), 20.5 (CH_3), 18.2 (CH_2); LRMS m/z 306.20 ($M + H^+$), calcd for $C_{16}H_{19}NO_5$ 305.13; Anal. calcd for $C_{16}H_{19}NO_5$ (321.1212): C, 62.94; H, 6.27; N, 4.59. Found: C, 62.85; H, 6.32; N, 4.51%.



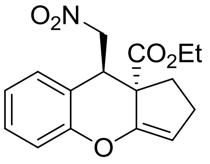
81na

6-acetyl-7-(nitromethyl)-4,5,6,7-tetrahydrobenzo[b]oxonin-2(3H)-one (81na): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 21.99 min, 23.05 min (minor), t_R = 29.12 min, 39.36 min (major). IR (Neat): ν_{max} 2964, 1709 (C=O), 1643, 1540 (NO_2), 1380 (NO_2), 1249, 1216, 1074, 1030 and 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (5H, m), 7.12-7.07 (1H, m), 5.31 (1H, dd, J = 13.2, 5.6 Hz), 4.97 (1H, dd, J = 13.2, 7.2 Hz), 4.83 (1H, dd, J = 13.2, 8.0 Hz), 4.72 (1H, dd, J = 13.2, 9.2 Hz), 4.22 (1H, td, J = 7.6, 4.0 Hz), 3.86 (1H, td, J = 9.2, 5.6 Hz), 2.49-2.40 (1H, m), 2.37 (3H, s), 2.34 (3H, s), 2.24-2.22 (1H, m), 1.96-1.87 (2H, m), 1.74-1.66 (2H, m), 1.49-1.37 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 218.8 (C, C=O), 218.5 (C, C=O), 169.5 (C, O-C=O), 169.2 (C, O-C=O), 148.8 (2 x C), 130.1 (2 x C), 128.8 (CH), 127.8 (CH), 126.6 (CH), 126.4 (CH), 123.4 (CH), 123.2 (CH), 77.5 (CH_2), 76.1 (CH_2), 51.2 (CH), 49.8 (CH), 38.8 (CH_2), 38.5 (CH_2), 38.2 (CH), 35.6 (CH), 28.9 (CH_2), 26.5 (CH_2), 21.1 (CH_3), 20.9 (CH), 20.5 (CH_2), 20.2 (CH_2); HRMS m/z 314.0997 (M + Na), calcd for $C_{15}H_{17}NNaO_5$ 314.1004.

7.15 Lewis acid-induced hydrolysis of cascade Michael products 76/77:

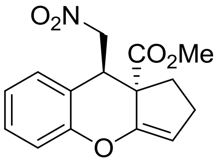
Method A: In an oven dried round bottomed flask, to the compound **76/77** (90 mg, 0.3 mmol), added dry DCM (0.1 M) under N_2 through syringe and $BF_3.Et_2O$ (1.1 equiv.) at 0 °C. This reaction mixture was stirred for 1.5 h at same temperature, brought the reaction to room temperature and worked up with H_2O and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **82** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Method B: In an oven dried round bottomed flask, to the compound **76/77** (90 mg, 0.3 mmol), added dry DCM (0.1 M) under N_2, P_2O_5 (3 equiv.) was added at −25 °C. This reaction mixture was stirred for 48 h at same temperature, brought the reaction to room temperature and worked up with H_2O and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **82** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



(–)-82aa

(9*R*,9a*S*)-ethyl 9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[b]chromene-9a-carboxylate (82aa): Prepared following the procedure **7.15** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 12.26 min (major), t_R = 13.12 min (minor). **$[\alpha]_D^{25}$ = –142.5° (*c* = 0.085 g/100 mL, $CHCl_3$, 60% *ee* and >99% *de*);** IR (Neat): ν_{max} 2926, 1736 (C=O), 1678, 1557 (*NO_2*), 1375 (*NO_2*), 1246, 862, 804 and 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22 (1H, dt, *J* = 8.8, 1.6 Hz), 7.08 (1H, dd, *J* = 7.2, 1.2 Hz), 6.96-6.91 (2H, m), 5.37 (1H, t, *J* = 2.4 Hz, olefinic-*H*), 4.68 (1H, dd, *J* = 11.2, 4.4 Hz), 4.32-4.23 (2H, m), 4.04-3.98 (2H, m, OCH_2CH_3), 2.56-2.47 (1H, m), 2.39-2.28 (2H, m), 2.13-2.07 (1H, m), 0.99 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.4 (C, O-C=O), 152.1 (C), 148.7 (C), 129.9 (CH), 129.8 (CH), 122.7 (CH), 120.6 (C), 116.7 (CH), 105.7 (CH), 77.8 (CH_2), 61.6 (CH_2, OCH_2CH_3), 54.6 (C), 40.5 (CH), 30.0 (CH_2), 25.9 (CH_2), 13.8 (CH_3, OCH_2CH_3); LRMS m/z 304.15 (M + H$^+$), calcd for $C_{16}H_{17}NO_5$ 303.1107; Anal. calcd for $C_{16}H_{17}NO_5$ (303.1107): C, 63.36; H, 5.65; N, 4.62. Found: C, 63.18; H, 5.71; N, 4.56%.



(–)-82ba

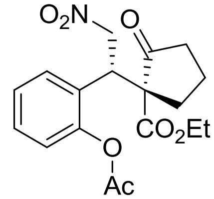
(9*R*,9a*S*)-methyl 9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[b]chromene-9a-carboxylate (82ba): Prepared following the procedure **7.15** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 98:02, flow rate 0.5 mL/min, λ = 254 nm), t_R = 26.82 min (major), t_R = 29.22 min (minor). IR

(Neat): ν_{max} 2980, 1709 (C=O), 1634, 1545 (*NO_2*), 1485, 1375 (*NO_2*), 1227, 1118, 1063, 811 and 761 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (1H, t, *J* = 7.6 Hz), 7.11 (1H, d, *J* = 7.2 Hz), 6.98-6.94 (2H, m), 5.41 (1H, s), 4.69 (1H, dd, *J* = 12.4, 5.6 Hz), 4.37-4.34 (1H, m), 4.04-4.25 (1H, m), 2.96 (3H, s), 2.58-2.50 (1H, m), 2.41-2.30 (2H, m), 2.14-2.07 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.9 (C, O-C=O), 151.9 (C), 148.5 (C), 129.9 (CH), 129.8 (CH), 122.8 (CH), 120.5 (C), 116.8 (CH), 106.0 (CH), 77.8 (CH_2), 54.5 (C), 52.8 (CH_3), 40.3 (CH), 30.1 (CH_2), 25.8 (CH_2).

7.16 Protection of Michael products 76/77:

In a dry oven dried round bottom flask, to the compound **76aa/77aa** (0.3 mmol) in dry DCM (3.0 mL) were added successively dry triethylamine (70 µL, 0.6 mmol) and acetyl chloride (0.6 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 12 h and then worked up with aqueous NH_4Cl and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure acetyl protected product **83aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(*R*)-ethyl 1-[(*S*)-1-(2-acetoxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (83aa):

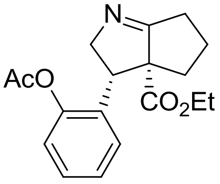


(–)-83aa

Prepared following the procedure **7.16** and purified by column chromatography using EtOAc/hexane and isolated as Liquid; **$[\alpha]_D^{25}$ = –16.7° (*c* = 1.32 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): ν_{max} 2931, 1764 (C=O), 1726, 1551 (*NO_2*), 1381 (*NO_2*), 1211, 1014, and 915 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (1H, d, *J* = 6.4 Hz), 7.32 (1H, t, *J* = 5.6 Hz), 7.22 (1H, t, *J* = 6.0 Hz), 7.14 (1H, d, *J* = 6.4 Hz), 5.34 (1H, dd, *J* = 11.2, 2.8 Hz), 4.95 (1H, dd, *J* = 11.2, 7.6 Hz), 4.33 (1H, dd, *J* = 7.6, 3.2 Hz), 4.21 (2H, q, *J* = 6.0 Hz, OCH_2CH$_3$), 2.50-2.40 (2H, m), 2.38 (3H, s, O=CCH$_3$), 2.33-2.23 (1H, m), 2.00-1.94 (2H, m), 1.92-1.86 (1H, m), 1.27 (3H, t, *J* = 6.0 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.4 (C, C=O), 169.6 (C, O-C=O), 168.9 (C, O-C=O), 149.2 (C), 129.0 (CH), 128.8 (CH), 128.7 (C), 126.4 (CH), 123.3 (CH), 77.0 (CH_2), 62.2 (C), 62.18 (CH_2, O*C*H$_2$CH$_3$), 38.1 (CH), 37.6 (CH_2), 32.6 (CH_3), 21.1 (CH_2), 19.2 (CH_2), 13.9 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 364.40 (M + H$^+$), calcd for $C_{18}H_{21}NO_7$ 363.1318; Anal. calcd for $C_{18}H_{21}NO_7$ (363.1318): C, 59.50; H, 5.83; N, 3.85. Found: C, 59.41; H, 5.87; N, 3.79%.

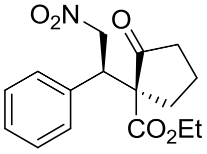
7.17 Hydrogenation of protected Michael products 83aa:

The product **83aa** was taken in an oven dried round bottom flask which contains activated 10% Pd/C (7 mg, 10 mol-%), and dry EtOAc (3.0 mL) were added and stirred under H_2 atmosphere at 25 °C for 24 h. The reaction mixture was passed through a pad of celite and concentrated to dryness. Pure product (+)-**84aa** was obtained by quick column chromatography (silica gel, mixture of hexane/ethyl acetate).



(+)-84aa

(3*S*,3a*R*)-ethyl 3-(2-acetoxyphenyl)-2,3,3a,4,5,6-hexahydrocyclopenta[b]pyrrole-3a-carboxylate (84aa): Prepared following the procedure **7.17** and purified by column chromatography using EtOAc/hexane and isolated as oil; **$[\alpha]_D^{25}$ = +160.2° (*c* = 1.21 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): ν_{max} 2930, 1761 (C=O), 1736, 1655 (*NO_2*), 1493, 1370 (*NO_2*), 1207, 1017, 912, 812 and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (1H, t, *J* = 8.0 Hz), 7.26 (1H, d, *J* = 8.4 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 7.11 (1H, d, *J* = 8.0 Hz), 5.19 (1H, t, *J* = 12.0 Hz), 4.24 (1H, dd, *J* = 12.4, 8.8 Hz), 4.05 (1H, dd, *J* = 10.8, 8.4 Hz), 3.83 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 2.76-2.61 (2H, m), 2.33 (3H, s, $O{=}CCH_3$), 2.27-2.16 (1H, m), 2.14-1.99 (2H, m), 1.71-1.63 (1H, m), 0.97 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.3 (C, O-C=O), 168.6 (C, O-C=O), 154.1 (C), 149.3 (C), 129.0 (CH), 127.1 (CH), 126.3 (C), 125.8 (CH), 122.9 (CH), 69.8 (CH_2), 67.8 (C), 61.7 (CH_2, OCH_2CH_3), 45.4 (CH), 35.3 (CH_2), 26.5 (CH_2), 21.9 (CH_2), 21.2 (CH_3, $O{=}CCH_3$), 13.7 (CH_3, OCH_2CH_3); LRMS m/z 316.10 (M + H^+), calcd for $C_{18}H_{21}NO_4$ 315.1471; Anal. calcd for $C_{18}H_{21}NO_4$ (315.1471): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.46; H, 6.67; N, 4.51%.



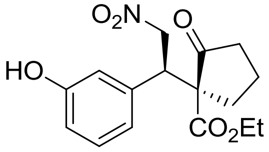
(+)-76al

(*S*)-ethyl 1-[(*R*)-2-nitro-1-phenylethyl]-2-oxocyclopentanecarboxylate (76al): Prepared by procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-

H column (hexane/2-propanol = 90:10, flow rate 0.7 mL/min, λ = 254 nm), t_R = 15.05 min (major), t_R = 22.10 min (minor). **$[\alpha]_D^{25}$ = +31.2° (*c* = 1.42 g/100 mL, $CHCl_3$, 79% *ee* and 89% *de*);** IR (Neat): ν_{max} 2979, 1748 (C=O), 1721, 1552 (*NO_2*), 1378 (*NO_2*), 1225, 1147, 1025 and 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, **89% *de*, major isomer**) δ 7.32-7.28 (3H, m), 7.27-7.24 (2H, m), 5.17 (1H, dd, *J* = 14.0, 4.0 Hz), 5.01 (1H, dd, *J* = 13.5, 11.0 Hz), 4.21 (2H, q, *J* = 8.0, 2.0 Hz, $\mathrm{OC}H_2\mathrm{CH}_3$), 4.07 (1H, dd, *J* = 11.5, 4.0 Hz), 2.40-2.31 (2H, m), 2.05-1.88 (3H, m), 1.84-1.77 (1H, m), 1.27 (3H, t, *J* = 7.0 Hz, $\mathrm{OCH_2C}H_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, **89% *de*, major isomer**) δ 212.3 (C, C=O), 169.3 (C, O-C=O), 135.4 (C), 129.3 (2 x CH), 128.8 (2 x CH), 128.2 (CH), 76.5 (CH_2), 62.4 (C), 62.2 (CH_2, $\mathrm{O}C\mathrm{H_2CH_3}$), 46.2 (CH), 37.9 ($CH_2$), 31.2 ($CH_2$), 19.3 ($CH_2$), 13.9 ($CH_3$, $\mathrm{OCH_2}C\mathrm{H_3}$); LRMS m/z 306.20 (M + H^+), calcd for $C_{16}H_{19}NO_5$ 305.1263; Anal. calcd for $C_{16}H_{19}NO_5$ (305.1263): C, 62.94; H, 6.27; N, 4.59. Found: C, 62.85; H, 6.32; N, 4.51%.

Configuration assignment: The absolute stereochemistry of (+)-**76al** was assigned as (*S*, *R*) by correlation with other examples and also by comparison of the retention time of HPLC with the literature data.[57a,d]

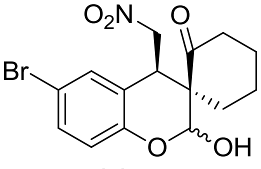
(*S*)-ethyl 1-[(*R*)-1-(3-hydroxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate (76am): Prepared by procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.42 min (major), t_R = 9.08 min (minor). **$[\alpha]_D^{25}$ = +26.1° (*c* = 1.35 g/100 mL, $CHCl_3$, 78% *ee* and 73% *de*);** IR (Neat): ν_{max} 3343 (O-*H*), 2977, 1716 (C=O), 1552 (*NO_2*), 1378 (*NO_2*), 1228, 1147, 1023 908, 785 and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, **73% *de*, major isomer**) δ 7.14 (1H, t, *J* = 7.5 Hz), 6.78-6.74 (3H, m), 6.29 (1H, br s, OH), 5.13 (1H, dd, *J* = 14.0, 4.0 Hz), 4.97 (1H, dd, *J* = 13.5, 11.0 Hz), 4.19 (2H, q, *J* = 7.5 Hz, $\mathrm{OC}H_2\mathrm{CH}_3$), 4.03 (1H, dd, *J* = 11.0, 4.0 Hz), 2.40-2.31 (2H, m), 2.04-1.97 (2H, m), 1.93-1.87 (1H, m), 1.83-1.79 (1H, m), 1.25 (3H, t, *J* = 7.0 Hz, $\mathrm{OCH_2C}H_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, **73% *de*, major isomer**) δ 213.0 (C, C=O), 169.4 (C, O-C=O), 156.1 (C), 136.9 (C), 129.9 (CH), 121.2 (CH), 116.5 (CH), 115.4 (CH), 76.4 (CH_2), 62.4 (C), 62.3 (CH_2, $\mathrm{O}C\mathrm{H_2CH_3}$), 46.0 (CH), 37.9 ($CH_2$), 31.0 ($CH_2$), 19.3 ($CH_2$), 13.9



(+)-76am

(CH_3, OCH_2CH_3); LRMS m/z 322.25 (M + H^+), calcd for $C_{16}H_{19}NO_6$ 321.1212; Anal. calcd for $C_{16}H_{19}NO_6$ (321.1212): C, 59.81; H, 5.96; N, 4.36. Found: C, 59.76; H, 5.91; N, 4.42%.

(1'*R*,4*R*)-6-bromo-2-hydroxy-4-(nitromethyl)spiro[chroman-3,1'-cyclohexan]-2'-one

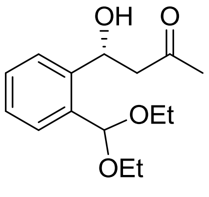


(–)-77ed

(77ed): Prepared by procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as liquid. **$[\alpha]_D^{25}$ = –9.9° (*c* = 0.38 g/100 mL, $CHCl_3$);** IR (Neat): ν_{max} 3427 (O-*H*), 2952, 1705 (C=O), 1552 (*NO_2*), 1481, 1377 (*NO_2*), 1223, 1018 and 904 cm^{-1}; ^1H NMR ($CDCl_3$, **3:1 ratio of isomers, major isomer**) δ 7.33 (1H, dd, *J* = 8.8, 2.4 Hz), 7.18 (1H, d, *J* = 2.0 Hz), 6.79 (1H, d, *J* = 8.8 Hz), 5.62 (1H, s, O-C*H*-O), 4.78 (1H, dd, *J* = 14.4, 8.4 Hz), 4.62 (1H, dd, *J* = 14.4, 2.4 Hz), 4.10-4.08 (1H, m), 3.94 (1H, br s, OH), 2.69-2.51 (2H, m), 2.18-2.09 (1H, m), 1.93-1.83 (2H, m), 1.81-1.73 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, **3:1 ratio of isomers, major isomer**) δ 212.8 (C, C=O), 148.1 (C), 132.6 (CH), 131.7 (CH), 122.7 (C), 119.4 (CH), 114.3 (C), 94.0 (CH, O-*C*H-O), 79.1 (CH_2), 53.0 (C), 40.1 (CH_2), 36.8 (CH), 34.8 (CH_2), 28.6 (CH_2), 20.4 (CH_2); LRMS m/z 370.15 (M + H^+), calcd for $C_{15}H_{16}BrNO_5$ 369.0212; Anal. calcd for $C_{15}H_{16}BrNO_5$ (369.0212): C, 48.67; H, 4.36; N, 3.78. Found: C, 48.56; H, 4.41; N, 3.73%.

7.18 General experimental procedures for the asymmetric BLA reactions:

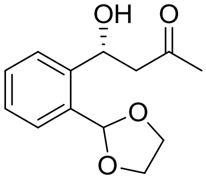
In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of benzaldehyde **1** was added 0.5M of solvent DMSO, followed by the addition of the catalyst **5a** or **5o** or **5p** (0.06 mmol, 20 mol%). After stirring the reaction mixture at 25 °C for 2–3 min, acetone **10a** was added and the reaction mixture was allowed to stir at the same temperature for 24–72 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethylacetate (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure BLA products **34** were obtained by column chromatography (silica gel, mixture of hexane/ethylacetate).



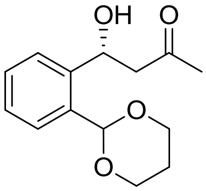
(+)-**34pa**

(*R*)-4-(2-(diethoxymethyl)phenyl)-4-hydroxybutan-2-one (34pa): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol **=** **9**0:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 11.14 min (minor), t_R = 12.41 min (major). **$[\alpha]_D^{25}$ = +45.0° (*c* = 0.28 g/100 mL, $CHCl_3$, 97% *ee*);** IR (Neat): ν_{max} 3387 (O-*H*), 1713, 1360, 1011, 965, 758, 651 and 616 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (1H, d, *J* = 7.6 Hz), 7.51 (1H, d, *J* = 7.6 Hz), 7.36 (1H, t, *J* = *7.2 Hz*), 7.28 (1H, t, *J* = 7.6 Hz), 5.61 (1H, br s), 5.58 (1H, s), 3.70-3.59 (2H, m), 3.55-3.49 (3H, m), 2.94-2.82 (2H, m), 2.20 (3H, s), 1.24 (3H, t, *J* = 6.8 Hz), 1.20 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.0 (C, *C*=O), 141.0 (C), 135.2 (C), 128.9 (CH), 127.2 (C), 126.8 (CH), 126.2 (CH), 101.1 (CH), 65.4 (CH), 62.5 (CH_2), 61.8 (CH_2), 51.2 (CH_2), 30.5 (CH_3), 15.1 (2 x CH_3); LRMS m/z 265.20 (M – H$^+$), calcd for $C_{15}H_{22}O_4$ 266.15; Anal. calcd for $C_{15}H_{22}O_4$ (265.20): C, 67.64; H, 8.33. Found: C, 67.55; H, 8.38.

(*R*)-4-(2-(1,3-dioxolan-2-yl)phenyl)-4-hydroxybutan-2-one (34qa): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol **=** **9**0:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.10 min (minor), t_R = 15.81 min (major). **$[\alpha]_D^{25}$ = +10.0° (*c* = 0.48 g/100 mL, $CHCl_3$, 93% *ee*);** IR (Neat): ν_{max} 3387 (O-*H*), 2892, 1709 (C=O), 1359, 1112, 1062, 945, 762 and 645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.59 (1H, d, *J* = 7.6 Hz), 7.55 (1H, d, *J* = 7.6 Hz), 7.40 (1H, t, *J* = 8.4 Hz), 7.30 (1H, t, *J* = 7.2 Hz), 5.99 (1H, s), 5.57 (1H, d, *J* = 6.8 Hz), 4.16-4.10 (2H, m), 4.08-4.00 (2H, m), 3.31 (1H, s), 2.95-2.85 (2H, m), 2.20 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, *C*=O), 141.7 (C), 133.5 (C), 129.6 (CH), 127.6 (C), 126.6 (CH), 126.2 (CH), 102.1 (CH), 65.5 (CH), 65.2 (2 x CH_2), 51.6 (CH_2), 30.6 (CH_3); LRMS m/z 237.05 (M + H$^+$), calcd for $C_{13}H_{16}O_4$ 236.10; Anal. calcd for $C_{13}H_{16}O_4$ (236.10): C, 66.09; H, 6.83. Found: C, 66.15; H, 6.76.



(+)-**34qa**

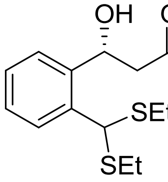


(+)-**34ra**

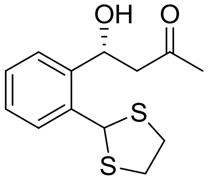
(*R*)-4-(2-(1,3-dioxan-2-yl)phenyl)-4-hydroxybutan-2-one (34ra): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel

OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.37 min (minor), t_R = 15.68 min (major). **$[\alpha]_D^{25}$ = +12.6° (*c* = 0.53 g/100 mL, CHCl$_3$, 94% *ee*);** IR (Neat): ν_{max} 3436 (O-*H*), 2878, 1714 (C=O), 1234, 1091, 998, 774 and 650 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.54 (2H, t, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.29 (1H, t, *J* = 7.6 Hz), 5.67 (2H, br s), 4.28-4.22 (2H, m), 4.02-3.96 (2H, m), 3.18 (1H, s), 2.90 (2H, d, *J* = 6.0 Hz), 2.30-2.24 (1H, s), 2.21 (3H, s), 1.46 (1H, d, *J* = 13.6 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 208.7 (C, *C*=O), 141.1 (C), 134.6 (C), 129.3 (CH), 127.5 (C), 126.6 (CH), 126.0 (CH), 100.8 (CH), 67.4 (CH), 67.3 (CH$_2$), 65.6 (CH), 51.4 (CH$_2$), 30.6 (CH$_3$), 25.5 (CH$_2$); LRMS m/z 251.12 (M + H$^+$), calcd for $C_{14}H_{18}O_4$ 250.12; Anal. calcd for $C_{14}H_{18}O_4$ (250.12): C, 67.18; H, 7.25. Found: C, 67.25; H, 7.18.

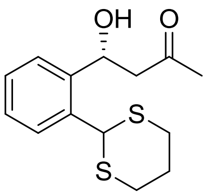
(*R*)-4-(2-(bis(ethylthio)methyl)phenyl)-4-hydroxybutan-2-one (34sa): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.20 min (major), t_R = 8.47 min (minor). **$[\alpha]_D^{25}$ = +29.3° (*c* = 0.45 g/100 mL, CHCl$_3$, 91% *ee*);** IR (Neat): ν_{max} 3436 (O-*H*), 2970, 1775, 1715, 1353, 1255, 1156, 997 and 756 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.76-7.70 (1H, m), 7.48 (1H, dd, *J* = 5.6, 3.6 Hz), 7.34-7.30 (2H, m), 5.62-5.59 (1H, m), 5.39 (1H, s), 3.01 (1H, s), 3.30 (1H, d, *J* = 3.6 Hz), 2.78-2.68 (1H, m), 2.64-2.50 (4H, m), 2.24 (3H, s), 1.25 (3H, t, *J* = 7.2 Hz), 1.24 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 209.0 (C, *C*=O), 139.6 (C), 136.8 (C), 128.7 (CH), 128.2 (CH), 127.9 (CH), 126.3 (CH), 66.0 (CH), 51.1 (CH$_2$), 30.7 (CH), 26.5 (CH$_2$), 26.4 (CH$_2$), 14.4 (CH$_3$), 14.4 (CH$_3$); LRMS m/z 299.20 (M + H$^+$), calcd for $C_{15}H_{22}O_2S_2$ 298.11; Anal. calcd for $C_{15}H_{22}O_2S_2$ (298.11): C, 67.64; H, 8.33. Found: C, 60.36; H, 7.43.


(+)-**34sa**

(*R*)-4-(2-(1,3-dithiolan-2-yl)phenyl)-4-hydroxybutan-2-one (34ta): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-amylose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 18.84 min

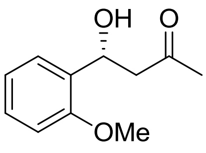

(+)-**34ta**

(major), t_R = 23.02 min (minor). **$[\alpha]_D^{25}$ = +32.4° (*c* = 0.28 g/100 mL, $CHCl_3$, 93% *ee*);** IR (Neat): ν_{max} 3436 (O-*H*), 2964, 1737, 1468, 1288, 1156, 1068 and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (1H, dd, *J* = 6.0, 3.6 Hz), 7.45 (1H, dd, *J* = 5.6, 3.6 Hz), 7.29 (1H, d, *J* =3.6 Hz), 7.27 (1H, d, *J* = 3.2 Hz), 5.98 (1H, s), 5.61 (1H, dd, *J* = 9.2, 2.0 Hz), 3.58-3.48 (2H, m), 3.40-3.32 (3H, m), 2.97-2.84 (2H, m), 2.21 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.8 (C, *C*=O), 140.5 (C), 135.7 (C), 129.1 (CH), 128.3 (CH), 128.0 (CH), 126.2 (CH), 66.0 (CH), 52.1 (CH), 51.5 (CH_2), 40.2 (CH_2), 40.1 (CH_2), 30.7 (CH_3); LRMS m/z 269.15 (M + H^+), calcd for $C_{13}H_{16}O_2S_2$ 268.06; Anal. calcd for $C_{13}H_{16}O_2S_2$ (268.06): C, 58.18; H, 6.01. Found: C, 58.26; H, 6.08.



(+)-**34ua**

(*R*)-4-(2-(1,3-dithian-2-yl)phenyl)-4-hydroxybutan-2-one (34ua): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-amylose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.17 min (major), t_R = 13.53 min (minor). **$[\alpha]_D^{25}$ = +32.4° (*c* = 0.28 g/100 mL, $CHCl_3$, 93% *ee*);** IR (Neat): ν_{max} 3309 (O-*H*), 2926, 1693, 1611, 1550, 1473, 1200, 1090 and 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63-7.60 (1H, m), 7.50-7.46 (1H, m), 7.32-7.28 (2H, m), 5.61 (1H, dd, *J* = 8.8, 3.2 Hz), 5.45 (1H, s), 3.15-3.02 (2H, m), 2.99-2.83 (4H, m), 2.21 (3H, s), 2.19-2.14 (1H, m), 1.98-1.86 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.9 (C, *C*=O), 139.8 (C), 135.6 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 126.3 (CH), 66.4 (CH), 51.8 (CH), 47.5 (CH_2), 32.4 (2 x CH_2), 30.9 (CH_3), 25.1 (CH_2); LRMS m/z 283.10 (M + H^+), calcd for $C_{14}H_{18}O_2S_2$ 282.07; Anal. calcd for $C_{14}H_{18}O_2S_2$ (282.07): C, 59.54; H, 6.432 Found: C, 59.63; H, 6.48.

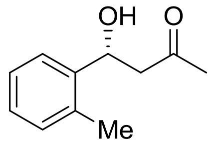


(+)-**34va**

(*R*)-4-hydroxy-4-(2-methoxyphenyl)butan-2-one (34va): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-amylose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.72 min (major), t_R = 16.38 min (minor). **$[\alpha]_D^{25}$ = +76.2° (*c* = 0.51 g/100 mL, $CHCl_3$, 85% *ee*);** IR (Neat): ν_{max} 3501 (O-*H*), 2920, 1758 (C=O), 1358, 1287, 1172, 953, 767 and 690 cm^{-1}; ^1H NMR ($CDCl_3$)

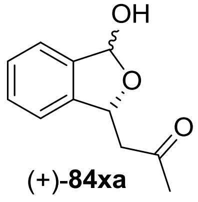
δ 7.4 (1H, dd, *J* = 6.0, 1.2 Hz), 7.27 (1H, dt, *J* = 6.4, 1.6 Hz), 7.00 (1H, dt, *J* = 6.4, 0.8 Hz), 6.89 (1H, d, *J* = 8.2 Hz), 5.43 (1H, td, *J* = 7.6, 2.8 Hz), 3.86 (3H, s), 3.43 (1H, d, *J* = 4.0 Hz), 2.95 (1H, dd, *J* = 17.0, 3.0 Hz), 2.81 (1H, dd, *J* = 17.5, 9.5 Hz), 2.21 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.3 (C, *C*=O), 155.8 (C), 130.9 (C), 128.4 (CH), 126.4 (CH), 120.9 (CH), 110.3 (CH), 65.6 (CH_3), 55.2 (CH), 50.4 (CH_2), 30.6 (CH_3);

(*R*)-4-hydroxy-4-(o-tolyl)butan-2-one (34wa): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.16 min (major), t_R = 7.08 min (minor). **[α]$_D^{25}$ = +76.2° (*c* = 0.51 g/100 mL, $CHCl_3$, 85% *ee*);** IR (Neat): ν_{max} 3364 (O-*H*), 2920, 1742 (C=O), 1611, 1474, 1238, 1019 and 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22-7.17 (1H, m), 6.97-6.80 (3H, m), 5.07 (1H, br d, *J* = 8.4 Hz), 3.26 (1H, br s), 2.59-2.38 (2H, m), 2.02 (3H, s), 1.90 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.0 (C, *C*=O), 140.7 (C), 133.9 (C), 130.2 (CH), 127.2 (CH), 126.2 (CH), 125.1 (CH), 66.2 (CH), 50.6 (CH_2), 30.5 (CH_3), 18.8 (CH_3);



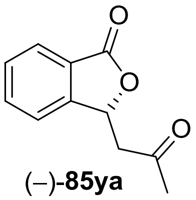
(+)-**34wa**

1-((1*R*)-3-hydroxy-1,3-dihydroisobenzofuran-1-yl)propan-2-one (84xa): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-amylose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.42 min (major), t_R = 29.13 min (minor). **[α]$_D^{25}$ = +21.3° (*c* = 0.08 g/100 mL, $CHCl_3$, 86% *ee*);** IR (Neat): ν_{max} 3387 (O-*H*), 1760, 1719, 1354, 1288, 1081, 1035, 752, 650 and 616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1:1 diasteriomeric ratio) δ 7.43-7.39 (2H, m), 7.37-7.32 (4H, m), 7.18 (2H, t, *J* = 6.8 Hz), 6.46 (1H, s), 6.39 (1H, s), 5.80 (1H, t, *J* = 6.0 Hz), 5.48 (1H, t, *J* = 6.0 Hz), 4.38 (1H, br s), 3.93 (1H, br s), 3.02 (2H, br d, *J* = 4.8 Hz), 2.83 (2H, d, *J* = 6.4 Hz), 2.21 (3H, s), 2.17 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.1 (C, *C*=O), 206.6 (), 141.6 (C), 141.2 (C), 139.2 (C), 139.1 (C), 129.4 (CH), 129.3 (CH), 128.3 (CH), 128.2 (CH), 123.0 (CH), 123.0 (CH), 121.1 (CH), 120.8 (CH), 101.2 (CH), 100.6 (CH), 78.4 (CH), 78.3 (CH), 50.3 (CH_2), 49.9 (CH_2), 31.1 (CH_3), 30.8 (CH_3); LRMS m/z 191.20 (M − H$^+$), calcd for



(+)-**84xa**

$C_{11}H_{12}O_3$ 192.08; Anal. calcd for $C_{11}H_{12}O_3$ (192.08): C, 68.74; H, 6.29. Found: C, 68.81; H, 6.19.


(–)-**85ya**

(*R*)-3-(2-oxopropyl)isobenzofuran-1(3H)-one (85ya): Prepared by procedure **7.18** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Lux-5u-amylose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.98 min (major), t_R = 20.85 min (minor). IR (Neat): ν_{max} 1760 (C=O), 1718, 1288, 1070, 1037 and 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.89 (1H, d, *J* = 8.0 Hz), 7.67 (1H, t, *J* = 8.0 Hz), 7.54 (1H, t, *J* = 8.0), 7.48 (1H, d, *J* = 8.0 Hz), 5.93 (1H, t, *J* = 8.0 Hz), 3.14 (1H, dd, *J* = 20.0, 8.3 Hz), 2.92 (1H, dd, *J* = 16.0, 8.0 Hz), 2.26 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.5 (C, C=O), 170.0 (C, O-*C*=O), 149.3 (C), 134.3 (CH), 129.4 (CH), 125.8 (CH), 122.3 (CH), 76.7 (CH), 48.1 (CH_2), 30.6 (CH_3); LRMS m/z 191.15 (M + H^+), calcd for $C_{11}H_{10}O_3$ 190.06; Anal. calcd for $C_{11}H_{11}O_3$ (190.06): C, 69. 64; H, 5.30. Found: C, 69.32; H, 5.38.

8. REFERENCES

1. (a) D. B. Ramachary, M. S. Prasad and R. Madhavachary, *Org. Biomol. Chem,* 2011, **9**, 2715; (b) D. B. Ramachary, R. Madhavachary and M. S. Prasad, *Org. Biomol. Chem,* 2012, **10**, 5825; (c) D. B. Ramachary, R. Mondal and R. Madhavachary, *Org. Biomol. Chem,* 2012, **10**, 5094; (d) D. B. Ramachary, Ch. Venkaiah and R. Madhavachary, *Org. Lett,* 2013, **15**, 3042; (e) R. Madhavachary and D. B. Ramachary, *Eur. J. Org. Chem.,* 2014, 7317; (f) A. B. Shashank, S. Karthik, R. Madhavachary and D. B. Ramachary *Chem.–Eur. J,* 2014, **20**, 16877.
2. (a) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem. Int. Ed.* 1971, **10**, 496; (b) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.* 1974, **39**, 1615.
3. B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.* 2000, **122**, 2395.
4. K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2000, **122**, 4243.
5. N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett*. 1979, **20**, 3437.
6. X. Song, A. Song, F. Zhang, H.-X. Li and W. Wang, *Nat. Commun.,* 2011, **2**, 524.
7. G. B. Herbert, G.-C. Margarita, A. Stefan, F. B. Walter, H. K. Chan, E. E. Dina, R. R. Miller, A. S. Ralph, K. B. Raman, H. R. Gary, L. T. Richard, W. M. Robert, W. K. John and G. S. Harris, *J. Am. Chem. Soc*., 1996, **118,** 2359.
8. D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, 2006, **47**, 651.
9. D. B. Ramachary, M. Kishor and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 1641.
10. D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056.
11. D. B. Ramachary and Y. V. Reddy, *J. Org. Chem.*, 2010, **75**, 74.
12. (a) K. Hiroya, Y. Suwa, Y. Ichihashi, K. Inamoto and T. Doi, *J. Org. Chem.*, 2011, **76**, 4522; (b) K. Hiroya, Y. Ichihashi, Y. Suwa, T. Ikai, K. Inamoto and T. Doi, *Tetrahedron Lett.*, 2010, **51**, 3728.
13. E. Elamparuthi, C. Fellay, M. Neuburger and K. Gademann, *Angew. Chem. Int. Ed.* 2012, **51**, 4071.
14. N. D. Ide, J. A. Ragan, G. Bellavance, S. J. Brenek, E. M. Cordi, G. O. Jensen, K. N. Jones, D. LaFrance, K. R. Leeman, L. J. Letendre, D. Place, C. L. Stanchina, G. W. Sluggett and H. Strohmeyer, *Org. Process. Res. Dev*, 2014, **18**, 45.

15. (a) I. Agranat, H. Caner and J. Caldwell, *Nat. Rev. Drug Discov.* 2002, **1**, 753. (b) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis: Targets, Strategies, Methods*, Wiley-VCH, Weinheim, 1996.
16. (a) N. Mase, F. Tanaka and C. F. Barbas III, *Angew. Chem. Int. Ed*. 2004, **43**, 2420; (b) M. H. Fonseca and B. List, *Curr. Opin. Chem. Biol*. 2004, **8**, 319; (c) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas III, *ACSCatal*. 2014, **4**, 743.
17. For early work on a self-assembly approach to asymmetric catalysis, see: (a) M. L. Clarke and J. A. Fuentes, *Angew. Chem. Int. Ed*., 2007, **46**, 930; (b) T. Mandal and C.-G. Zhao, *Angew. Chem., Int. Ed*., 2008, **47**, 7714; (c) D. Uraguchi,Y. Ueki and T. Ooi, *Science*, 2009, **326**, 120; (d) S. Perera, D. Sinha, N. K. Rana, V. Trieu-Do and J. C.-G. Zhao, J. Org. Chem., 2013, **78**, 10947; (e) S. Muramulla, J.-A. Ma and J. C.-G. Zhao, *Adv. Synth. Catal*., 2013, **355**, 1260; (f) D. Sinha, S. Pereraand J. C.-G. Zhao, *Chem.–Eur. J*., 2013, **19**, 6976.
18. S. Chandrasekhar, K. Mallikarjun, G. Pavankumarreddy, K. V. Rao, and B. Jagadeesh, *Chem. Commun.* 2009, 4985.
19. W. Yang and D.-M. Du, *Chem. Commun.,* 2013, **49**, 8842.
20. H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng and C. Zhu, *Org. Lett.,* 2013, **15**, 4062.
21. A.-B. Xia, C. Wu, T. Wang, Y.-P. Zhang, X.-H. Du, A.-G. Zhong, D.-Q. Xu and Z.-Y. Xu, *Adv. Synth. Catal*. 2014, **356**, 1753.
22. From my lab, self-assembly approach to asymmetric catalysis, see: (a) *ref.* 1b; b) D. B. Ramachary, R. Sakthidevi and K. S. Shruthi, *Chem.–Eur. J*., 2012, **18**, 8008; (c) D. B. Ramachary, M. S. Prasad, S. V. Laxmi and R. Madhavachary, *Org. Biomol. Chem*., 2014, **12**, 574; (d) D. B. Ramachary P. S. Reddy and M. S. Prasad, *Eur. J. Org. Chem.* 2014, 3076; (e) D. B. Ramachary and K. S. Shruthi, *Org. Biomol. Chem*., 2014, **12**, 4300.
23. For selected recent reviews on general domino and multi-component reactions, see: (a) L. F. Tietze, *Chem. Rev.* 1996, **96**, 115; (b) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.* 2003, 551; (c) L. F. Tietze amd F. Haunert, *Stimulating Concepts in Chemistry* (eds Vogtle, F.; Stoddart, J. F.; Shibasaki, M.) 39-64 (Wiley-VCH, Weinheim, 2000); (d) L. F. Tietze and A. Modi, *Med. Res. Rev.* 2000, **20**, 304; (e) J. –C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.* 2005, **105**, 1001; (f) D. J. Ramon and M. Yus, *Angew. Chem. Int. Ed.* 2005, **44**, 1602; For selected recent reviews on

organocatalytic sequential one-pot and domino reactions, see: (g) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.* 2007, **107**, 5416; (h) C. J. Chapman and C. G. Frost, *Synthesis* 2007, 1; (i) C. F. Barbas III, *Angew. Chem. Int. Ed.* 2008, **47**, 42; j) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.* 2010, **2**, 167; (k) D. B. Ramachary and Y. V. Reddy, *Eur. J. Org. Chem.* 2012, 865; (l) H. Jiang, L. Albrecht and K. A. Jørgensen, *Chem. Sci.* 2013, **4**, 2287.

24. For the selected organocatalytic double domino reactions, see: (a) D. B. Ramachary, N. S. Chowdari and C. F. Barbas III, *Angew. Chem. Int. Ed.* 2003, **42**, 4233; (b) N. Halland, P. S. Aburel and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2004, **43**, 1272; (c) J. W. Yang, M. T. H. Fonseca and B. List, *J. Am. Chem. Soc.* 2005, **127**, 15036; (d) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2005, **127**, 15051; (e) M. Marigo, T. Schulte, J. FranzQn and K. A. Jørgensen, *J. Am. Chem. Soc.* 2005, **127**, 15710; (f) W. Wang, H. Li, J. Wang and L. Zu, *J. Am. Chem. Soc.* 2006, **128**, 10354; (g) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem. Int. Ed.* 2006, **45**, 3683; (h) D. Enders, A. A. Narine, T. R. Benninghaus and G. Raabe, *Synlett* 2007, 1667; (i) Y. Hayashi, T. Okano, S. Aratake and D. Hazelard, *Angew. Chem. Int. Ed.* 2007, **46**, 4922; (j) J. L.Vicario, L. Reboredo, D. Badía and L. Carillo, *Angew. Chem. Int. Ed.* 2007, **46**, 5168; (k) D. Enders, C. Wang and J. W. Bats, *Angew. Chem. Int. Ed.* 2008, **47**, 7539; (l) G. –L. Zhao, R. Rios, J. Vesley, L. Eriksson and A. Córdova, *Angew. Chem. Int. Ed.* 2008, **47**, 8468; (m) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan and G. Zhong, *Angew. Chem. Int. Ed.* 2008, **47**, 10187; (n) J. Franzén and A. Fisher, *Angew. Chem. Int. Ed.* 2009, **48**, 787; (o) R. Imashiro, H. Uehara and C. F. Barbas III, *Org. Lett.* 2010, **12**, 5250; (p) K. Albertshofer, B. Tan and C. F. Barbas III, *Org. Lett.* 2012, **14**, 1834; (q) K. Albertshofer, K. E. Anderson and C. F. Barbas III, *Org. Lett.* 2012, **14**, 5968; (r) X. Jiang, B. Tan and C. F. Barbas III, *Angew. Chem. Int. Ed.* 2013, **52**, 9261; (s) B. –C. Hong, W. –K. Liao, N. S. Dange and J. –H. Liao, *Org. Lett.* 2013, **15**, 468; (t) B. –C. Hong, C. –W. Lin, W. –K. Liao and G. –H. Lee, *Org. Lett.* 2013, **15**, 6258; (u) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne and J. Rodriguez, *Synthesis* 2013, **45**, 1909.

25. For the selected organocatalytic triple domino reactions, see: (a) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature* 2006, **441**, 861; (b) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe and B. Wendt, *Angew. Chem. Int. Ed.* 2007, **46**, 467; (c) A. Carlone, S.

Cabrera, M. Marigo and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2007, **46**, 1101; (d) D. Enders, M. R. M. Hüttl, G. Raabe and J. W. Bats, *Adv. Synth. Catal.* 2008, **350**, 267; (e) D. Enders, M. Jeanty and J. W. Bats, *Synlett* 2009, 3175; (f) D. Enders, C. Joie and K. Deckers, *Chem. Eur. J.* 2013, **19**, 10818; (g) I. Chatterjee, D. Bastida and P. Melchiorre, *Adv. Synth. Catal.* 2013, **355**, 3124.

26. For the selected organocatalytic quadruple domino reactions, see: (a) F. –L. Zhang, A. –W. Xu, Y. –F. Gong, M. –H. Wei and X. –L. Yang, *Chem. Eur. J.* 2009, **15**, 6815; (b) D. Enders, C. Wang, M. Mukanova and A. Greb, *Chem. Commun.* 2010, **46**, 2447; (c) K. Jiang, Z. –J. Jia, X. Yin, L. Wu and Y. –C. Chen, *Org. Lett.* 2010, **12**, 2766; (d) M. Rueping, K. –L. Haack, W. Ieawsuwan, H. Sunden, M. Blanco and F. R. Schoepke, *Chem. Commun.* 2011, **47**, 3828; (e) D. Enders, A. Greb, K. Deckers, P. Selig and C. Merkens, *Chem. Eur. J.* 2012, **18**, 10226.
27. For the total synthesis of natural products and drugs from organocatalytic domino reactions, see: (a) J. –F. Austin, S. –G. Kim, C. J. Sinz, W. –J. Hiao and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* 2004, **101**, 5482; (b) Y. Hoashi, T. Yabuta and Y. Takemoto, *Tetrahedron Lett.* 2004, **45**, 9185; (c) B. –C. Hong, M. –F. Wu, H. –C. Tseng and J. –H. Liao, *Org. Lett.* 2006, **8**, 2217; (d) B. –C. Hong, M. –F. Wu, H. –C. Tseng, G. –F. Huang, C. –F. Su and J. –H. Liao, *J. Org. Chem.* 2007, **72**, 8459; (e) G. –S. Liu, Q. –L. Dong, Y. –S. Yao and Z. –J. Yao, *Org. Lett.* 2008, **10**, 5393; (f) B. Simmons, A. M. Walji and D. W. C. MacMillan, *Angew. Chem. Int. Ed.* 2009, **48**, 4349; (g) S. B. Jones, B. Simmons and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2009, **131**, 13606; (h) H. Ishikawa, T. Suzuki and Y. Hayashi, *Angew. Chem. Int. Ed.* 2009, **48**, 1304; (i) E. Marques-Lopez, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.* 2010, **27**, 1138; (j) M. Reiter, S. Torssell, S. Lee ans D. W. C. MacMillan, *Chem. Sci.* 2010, **1**, 37; (k) H. Ishikawa, M. Honma and Y. Hayashi, *Angew. Chem. Int. Ed.* 2011, **50**, 2824; (l) D. B. Ramachary, Ch. Venkaiah and P. M. Krishna, *Chem. Commun.* 2012, **48**, 2252; (m) Y. Hayashi and S. Umemiya, *Angew. Chem. Int. Ed.* 2013, **52**, 3450; (n) T. Mukaiyama, H. Ishikawa, H. Koshino and Y. Hayashi, *Chem. Eur. J.* 2013, **19**, 17789; (o) D. B. Ramachary, Y. V. Reddy, A. Banerjee and S. Banerjee, *Org. Biomol. Chem.* 2011, **9**, 7282; (p) R. Marcia de Figueiredo and M. Christmann, *Eur. J. Org. Chem.* 2007, 2575; (q) K. Liu, A. Chougnet and W. –D. Woggon, *Angew. Chem. Int. Ed.* 2008, **47**, 5827; (r)

G. Dickmeiss, K. L. Jensen, D. Worgull, P. T. Franke and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2011, **50**, 1580; (s) B. Bradshaw, C. Luque-Corredera and J. Bonjoch, *Chem. Commun.* 2014, **50**, 7099.

28. (a) H. Ledford, *Nature* 2007, **445**, 816; (b) R. Peakall, D. Ebert, J. Poldy, R. A. Barrow, W. Francke, C. C. Bower and F. P. Schiestl, *New Phytologist* 2010, **188**, 437; (c) S. W. Fuchs, K. A. J. Bozhuyuk, D. Kresovic, F. Grundmann, V. Dill, A. O. Brachmann, N. R. Waterfield and H. B. Bode, *Angew. Chem. Int. Ed.* 2013, **52**, 4108; (d) V. Falara, R. Amarasinghe, J. Poldy, E. Pichersky, R. A. Barrow and R. Peakall, *Annals of Botany*, 2013, **111**, 21; (e) R. Peakall and M. R. Whitehead, *Annals of Botany*, 2014, **113**, 341.
29. (a) A. Kozubek and J. H. P. Tyman, *Chem. Rev.* 1999, **99**, 1; (b) B. Nowak-Thompson, P. E. Hammer, D. S. Hill, J. Stafford, N. Torkewitz, T. D. Gaffney, S. T. Lam, I. Molna´r and J. M. Ligon, *J. Bacteriol.* 2003, **185**, 860; (c) A. Pohanka, J. Levenfors and A. Broberg, *J. Nat. Prod.* 2006, **69**, 654.
30. (a) J. Poldy, R. Peakall and R. A. Barrow, *Tetrahedron Lett.* 2008, **49**, 2446; (b) J. Poldy, R. Peakall and R. A. Barrow, *Org. Biomol. Chem.* 2009, **7**, 4296; (c) J. Poldy, R. Peakall and R. A. Barrow, *Eur. J. Org. Chem.* 2012, 5818.
31. (a) F. P. Schiestl, R. Peakall, J. G. Mant, F. Ibarra, C. Schulz, S. Franke and W. Francke, *Science* 2003, **302**, 437; (b) S. Franke, F. Ibarra, C. M. Schulz, R. Twele, J. Poldy, R. A. Barrow, R. Peakall, F. P. Schiestl and W. Francke, *Proc. Natl. Acad. Sci. USA* 2009, **106**, 8877.
32. (a) G. Mehta, T. Dhanbal and M. K. Bera, *Tetrahedron Lett.* 2010, **51**, 5302; (b) D. B. Duff, T. G. Abbe and B. C. Goess, *J. Chem. Educ.* 2012, **89**, 406.
33. For original papers on the development of organocatalytic reductive coupling reaction, see for review: (a) D. B. Ramachary and S. Jain, *Org. Biomol. Chem.* 2011, **9**, 1277; For the papers, see: (b) D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.* 2008, 975; (c) see *ref. No*. 8, 9, 10 and 11.
34. For the application of metal-free reductive coupling reaction in drugs/drug-like molecules synthesis, see: (a) *ref. No.* 14 (b) L. Li and W. K. S. Chua, *Tetrahedron Lett.* 2011, **52**, 1392; (c) C. Ballatore, J. H. Soper, F. Piscitelli, M. James, L. Huang, O. Atasoylu, D. M. Huryn, J. Q. Trojanowski, V. M. –Y. Lee, K. R. Brunden and A. B. Smith III, *J. Med. Chem.* 2011, **54**, 6969; (d) J. Tummatorn and G. B. Dudley, *Org. Lett.* 2011, **13**, 1572-

1575; (e) Y. –C. Wong, C. –T. Tseng, T. –T. Kao, Y. –C. Yeh and K. –S. Shia, *Org. Lett.* 2012, **14**, 6024.

35. For the application of metal-free reductive coupling reaction in total synthesis of natural products, see: (a) K. Hiroya, Y. Ichihashi, A. Furutono, K. Inamoto, T. Sakamoto and T. Doi, *J. Org. Chem.* 2009, **74**, 6623; (b) L. Miao, H. Shu, A. R. Noble, S. P. Fournet, E. D. Stevens and M. L. Trudell, *Arkivoc* 2010, **4**, 6; (c) *ref.* No. 12 and 13
36. J. M. Kim, K. Y. Lee and J. N. Kim, *Bull. Korean Chem. Soc.* 2003, **24**, 1057.
37. (a) A. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477; (b) P. Va, E. L. Campbell, W. M. Robertson and D. L. Boger, *J. Am. Chem. Soc.* 2010, **132**, 8489; (c) S. B. Jones1, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature,* 2011, **475**, 183.
38. For organocatalytic double domino, triple domino and quadruple domino sequential reactions; see *ref. 23-26.*
39. For the total synthesis of natural products and drugs from organocatalytic domino reactions, see *ref. 27* and (a) P. Winter, J. Swatschek, M. Willot, L. Radtke, T. Olbrisch, A. Schafer and M. Christmann, *Chem. Commun.* 2011, **47**, 12200; (b) R. R. Knowles, J. Carpenter, S. B. Blakey, A. Kayano, I. K. Mangion, C. J. Sinz and D. W. C. MacMillan, *Chem. Sci.,* 2011, **2**, 308; (c) S. R. Byeon, H. Park, H. Kim and J. Hong, *Org. Lett.* 2011, **13**, 5816; (d) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2011, **133**, 4260.
40. For examples of the Michael reaction cascade in natural product synthesis, see: (a) S. P. Brown, N. C. Goodwin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 1192; (b) O. Andrey, A. Vidonne and A. Alexakis, *Tetrahedron Lett.,* 2003, **44**, 7901; (c) Ian K. Mangion and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2005, **127**, 3696; (d) M. G. Banwell, D. A. S. Beck and A. C. Willis, *ARKIVOC*, 2006, (*iii*), 163; (e) T. Shibuguchi, H. Mihara, A. Kuramochi, S. Sakuraba, T. Ohshima and M. Shibasaki, *Angew. Chem. Int. Ed.* 2006, **45**, 4635; (f) S. Fustero, J, Moscardo, D. Jimenez, M. D. Pérez-Carrion, M. Sánchez-Rosello and C. D. Pozo, *Chem.–Eur. J.* 2008, **14**, 9868; (g) P. S. Hynes, P. A. Stupple and D. J. Dixon, *Org. Lett.* 2008, **10**, 1389; (h) K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe and D. R. Burton, *J. Am. Chem. Soc.* 2008, **130**, 11114; (i) P. Jakubec, D. M. Cockfield and D. J. Dixon, *J. Am. Chem. Soc.* 2009, **131**, 16632; (j) H. Yang and R. G. Carter, *J. Org. Chem.* 2010, **75**, 4929; (l) A. ElMarrouni, S. R. Joolakanti, A. Colon, M. Heras, S. Arseniyadis and J. Cossy, *Org. Lett.* 2010, **12**, 4074;

(m) K. L. Jensen, C. F. Weise, G. Dickmeiss, F. Morana, R. L. Davis and K. A. Jørgensen, *Chem. Eur. J.* 2012, **18**, 11913; (n) H. Ishikawa, T. Suzuki, H. Orita, T. Uchimaru and Y. Hayashi, *Chem. Eur. J.* 2010, **16**, 12616.

41. For examples of the Aldol reaction cascade in natural product synthesis, see: (a) P. M. Pihko and A. Erkkilä, *Tetrahedron Lett.* 2003, **44**, 7607; (b) N. A. B. Northrup and D. W. C. MacMillan, *Science* 2004, **305**, 1752; (c) O. Tokuda, T. Kano, W. –G. Gao, T. Ikemoto and K. Maruoka, *Org. Lett.* 2005, **7**, 5103; (d) S. Zhang, W. Duan and W. Wang, *Adv. Synth. Catal.* 2006, **348**, 1228; (e) N. Itagaki and Y. Iwabuchi, *Chem Commun.* 2007, 1175; (f) J. Carpenter, A. B. Northrup, D. –M. Chung, J. J. M. Wiener, S. –G. Kim and D. W. C. MacMillan, *Angew. Chem. Int. Ed.* 2008, **47**, 3568; (g) C. L. Chandler and B. List, *J. Am. Chem. Soc.,* 2008, **130**, 6737; (h) A. B. Smith III, C. Sfouggatakis, C. A. Risatti, J. B. Sperry, W. Zhu, V. A. Doughty, T. Tomioka, D. B. Gotchev, C. S. Bennett, S. Sakamoto, O. Atasoylu, S. Shirakami, D. Bauer, M. Takeuchi, J. Koyanagi and Y. Sakamoto, *Tetrahedron* 2009, **65**, 6489.
42. For examples of the cyclo-addition reaction cascade in natural product synthesis, see: (a) A. C. Kinsman and M. A. Kerr, *J. Am. Chem. Soc*. 2003, **125**, 14120; (b) R. M. Wilson, W. S. Jen and D. W. C. MacMillan, *J. Am. Chem. Soc*. 2005, **127**, 11616; (c) E. T. T. Kumpulainen, A. M. P. Koskinen and K. Rissanen, *Org. Lett.*, 2007, **9**, 5043; (d) B. D. Horning and D. W. C. MacMillan, *J. Am. Chem. Soc*. 2013, **135**, 6442; (e) B. N. Laforteza, M. Pickworth and D. W. C. MacMillan, *Angew. Chem., Int. Ed.* 2013, **52**, 11269.
43. (a) J. –F. Austin, S. –G. Kim, C. J. Sinz, W. –J. Hiao and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA,* 2004, **101**, 5482; (b) S. –G. Kim, J. Kim and H. Jung, *Tetrahedron Lett.* 2005, **46**, 2437; (c) K. C. Nicolaou, R. Reingruber, D. Sarlah and S. Brase, *J. Am. Chem. Soc*. 2009, **131**, 2086; (d) O. V. Maltsev, I. P. Beletskaya and S. G. Zlotin, *Russian Chemical Reviews* 2011, **80,** 1067.
44. For Reviews: (a) Y. S. Rao, *Chem. Rev.*, 1964, **64**, 353; (b) D. W. Knight, *Contemp. Org. Synth.*, 1994, **1**, 287. For papers see. (a) N. N. Gerber, *Tetrahedron Lett.* 1973, **10**, 771; (b) A. D. Rodrfguez and C. Ramfrez, *J. Nat. Prod.,* 1994, **57**, 339; (c) F.Y. Dijstra and T. O. Z. Wiken, *Lebensm. Unters. Forsch.* 1973, **160**, 263; (d) M. Mikayado, T. Kato, N. Ohno, H. Yoshioka, and H. Ohshio, *Agric. Biol. Chem.* 1977, **41**, 57; (e) J. Corbera, J.

Font, M. Monsalvatje, R. M. Ortuiio and F. Sanchez-Ferrando *J. Org. Chem.* 1988, **53**, 4393; (f) M. D. Esposti, A. Ghelli, M. Ratta, D. Cortes and E. Estornell, *Biochem. J.*, 1994, **301**, 161; (g) Y. –W. Guo, M. Gavagnin, E. Mollo, E. Trivellone and G. Cimino *J. Nat. Prod.* 1999, **62**, 1194; (h) R. Ratnayake, V. Karunaratne, B. M. R. Bandara, V. Kumar, J. K. MacLeod and P. Simmonds, *J. Nat. Prod.*, 2001, **64**, 376; (i) M. Lorenzo, I. Brito, M. Cueto, L. D'Croz and J. Darias, *Org. Lett.* 2006, **8**, 5001.

45. (a) G. L. Larson and R. M. Betancourt de Perez, *J. Org. Chem.* 1985, **50**, 5257; (b) K. F. Podraza and A. T. Snede, *J. Nat. Prod.* 1985, **48**, 792; (c) T. Berkenbusch and R. Bruckner, *Tetrahedron* 1998, **54**, 11461; (d) K. Nishide, A. Aramata, T. Kamanaka, T. Inoue and M. Node, *Tetrahedron* 1994, **50**, 8337; (e) M. –J. Chen, C. –Y. Lo, C. –C. Chin and R. –S. Liu, *J. Org. Chem.* 2000, **65**, 6362; (f) F. S. Pashkovsky, Y. M. Katok, T. S. Khlebnicova and F. A. Lakhvich, *Tetrahedron Lett.* 2001, **42**, 3657; (g) C. Ghobril, J. Kister and R. Baati, *Eur. J. Org. Chem.* 2011, 3416; (h) R. S. Ferrarini, A. A. Dos Santos and J. V. Comasseto, *Tetrahedron* 2012, **68**, 8431; (i) V. Pace, J. P. Rae, H. Y. Harb and D. J. Procter, *Chem. Commun.* 2013, **49**, 5150.
46. Y. –T. He, H. –N. Yang and Z. –J. Yao, *Tetrahedron* 2002, **58**, 8805.
47. For selected reviews on asymmetric organocatalytic sequential one-pot reactions, see: (a) D. Enders, C. Grondal and M. R. M. Huettl, *Angew. Chem. Int. Ed.,* 2007, **46**, 1570; (b) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.,* 2009, **38**, 2178; (c) M. Rueping, J. Dufour and F. R. Schoepke, *Green Chem.,* 2011, **13**, 1084; (d) J. Yu, F. Shi and L. –Z. Gong, *Acc. Chem. Res.,* 2011, **44**, 1156.
48. For selected papers on asymmetric organocatalytic sequential one-pot reactions, see *ref. 24* and (a) N. S. Chowdari, D. B. Ramachary and C. F. Barbas III, *Org. Lett.,* 2003, **5**, 1685; (b) D. B. Ramachary and C. F. Barbas III, *Chem. Eur. J.,* 2004, **10**, 5323; (c) M. Marigo, S. Bertelsen, A. Landa and K. A. Jorgensen, *J. Am. Chem. Soc.,* 2006, **128**, 5475; (d) J. Wang, H. Li, H. Xie, L. Zu, X. Shen and W. Wang, *Angew. Chem. Int. Ed.,* 2007, **46**, 9050; (e) J. Zhou and B. List, *J. Am. Chem. Soc.,* 2007, **129**, 7498; (f) O. Penon, A. Carlone, A. Mazzanti, M. Locatelli, L. Sambri, G. Bartoli and P. Melchiorre, *Chem. Eur. J.,* 2008, **14**, 4788; (g) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang and G. Zhong, *Org. Lett.,* 2008, **10**, 4585; (h) M. Rueping, A. Kuenkel, F. Tato and J. W. Bats, *Angew. Chem. Int. Ed.,* 2009, **48**, 3699.

49. (a) R. C. Neugebauer, U. Uchiechowska, R. Meier, H. Hruby, V. Valkov, E. Verdin, W. Sippl and M. Jung, *J. Med. Chem.*, 2008, **51**, 1203; (b) J. Posakony, M. Hirao, S. Stevens, J. A. Simon and A. Bedalov, *J. Med. Chem.,* 2004, **47**, 2635; (c) S. R. Trenor, A. R. Shultz, B. J. Love and T. E. Long, *Chem. Rev.,* 2004, **104**, 3059; (d) S. A. Buckner, I. Milicic, A. Daza, R. Davis-Taber, V. E. S. Scott, J. P. Sullivan and J. D. Brioni, *Eur. J. Pharmocol.*, 2000, **400**, 287; (e) A. Coi, A. M. Bianucci, V. Calderone, L. Testai, M. Digiacomo, S. Rapposelli and A. Balsamo, *Bioorg. Med. Chem.,* 2009, **17**, 5565; (f) M. C. Breschi, V. Calderone, A. Martelli, F. Minutolo, S. Rapposelli, L. Testai, F. Tonelli and A. Balsamo, *J. Med. Chem.,* 2006, **49**, 7600; (g) A. Widdig, H. J. Kabbe, A. Knorr and U. Benz, *Ger. Offen.*, 1984, **77**, DE 3300004 A1 19840712 [*Chem. Abstr.*, 1984, **102**, 6203], (patent written in German); (h) S. Khelili, X. Florence, M. Bouhadja, S. Abdelaziz, N. Mechouch, Y. Mohamed, P. D. Tullio, P. Lebrun and B. Pirotte, *Bioorg. Med. Chem.,* 2008, **16**, 6124; (i) R. Grandel, W. M. Braje, A. Haupt, S. C. Turner, U. Lange, K. Drescher, L. Unger and D. Plata, *PCT Int. Appl.,* 2007, **113**, WO 2007118899 A1 20071025 [*Chem. Abstr.*, 2007**,** **147**, 486320], (patent written in English).
50. (a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.,* 2000, **122**, 9939 and references therein; (b) B. Lesch and S. Braese, *Angew. Chem. Int. Ed.,* 2004, **43**, 115; (c) L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith and C. Große, *Chem. Eur. J.*, 2008, **14**, 8956; (d) H. C. Shen, *Tetrahedron* 2009, **65**, 3931; (e) J. F. Teichert and B. L. Feringa, *Chem. Commun.*, 2011, **47**, 2679.
51. For selected examples of organocatalytic asymmetric syntheses of chromans and 3,4-dihydrocoumarins, see: (a) P. Kotame, B. –C. Hong and J. –H. Liao, *Tetrahedron Lett.,* 2009, **50**, 704; (b) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.,* 2009, **11**, 1627; (c) A. E. Nibbs, A. –L. Baize, R. M. Herter and K. A. Scheidt, *Org. Lett.,* 2009, **11**, 4010; (d) H. Lv, L. You and S. Ye, *Adv. Synth. Catal.,* 2009, **351**, 2822; (e) D. B. Ramachary and R. Sakthidevi, *Chem. Eur. J.,* 2009, **15**, 4516; (f) B. –C. Hong, P. Kotame, C. –W. Tsai and J. –H. Liao, *Org. Lett.,* 2010, **12**, 776; (g) J. –L. Li, S. –L. Zhou, B. Han, L. Wu and Y. –C. Chen, *Chem. Commun.,* 2010, **46**, 2665; (h) K. –S. Choi and S. –G. Kim, *Tetrahedron Lett.,* 2010, **51**, 5203; (i) X. –F. Wang, Q. –L. Hua, Y. Cheng, A. –L. An, Q. –Q. Yang, J. –R. Chen and W. –J. Xiao, *Angew. Chem. Int. Ed.,* 2010, **49**, 8379; (j) D. Enders, C. Wang,

X. Yang and G. Raabe, *Adv. Synth. Catal.,* 2010, **352**, 2869; (k) D. Lu, Y. Li and Y. Gong, *J. Org. Chem.,* 2010, **75**, 6900; (l) Q. –L. Hua, C. Li, X. –F. Wang, L. –Q. Lu and J. –R. Chen, *ACS Catal.,* 2011, **1**, 221; (p) D. Enders, X. Yang, C. Wang, G. Raabe and J. Runsik, *Chem. Asian. J.,* 2011, **6**, 2255; (q) B. –C. Hong, P. Kotame and G. –H. Lee, *Org. Lett.,* 2011, **13**, 5758.

52. For recent papers on sequential Michael and lactonization reactions, see: (a) M. Belen Cid, S. Duce, S. Morales, E. Rodrigo and J. L. G. Ruano, *Org. Lett.,* 2010, **12**, 3586; (b) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.,* 2011, **133**, 2714.
53. For selected papers on asymmetric sequential one-pot reactions from our group, see *ref. 33* and (a) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.,* 2008, **6**, 2488; (b) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.,* 2010, **8**, 2859.
54. For recent papers on Michael addition of 1,3-diketones to simple nitrostyrenes, see: (a) S. H. McCooey and S. J. Connon, *Angew. Chem. Int. Ed*., 2005, **44**, 6367; (b) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman and L. Deng, *Angew. Chem. Int. Ed*., 2005, **44**, 105; (c) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc*., 2008, **130**, 14416; (d) Z. –H. Zhang, X. –Q. Dong, D. Chen and C. –J. Wang, *Chem. Eur. J*., 2008, **14**, 8780; (e) X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang and R. Wang, *J. Org. Chem.,* 2009, **74**, 5562; (f) Z. Yu, X. Liu, L. Zhou, L. Lin and X. Feng, *Angew. Chem. Int. Ed*., 2009, **48**, 5195; (g) J. Luo, L. –W. Xu, R. A. S. Hay and Y. Lu, *Org. Lett.,* 2009, **11**, 437; (g) D. Almasi, D. A. Alonso, E. Gomez-Bengoa and C. Najera, *J. Org. Chem.,* 2009, **74**, 6163; (h) H. Y. Bae, S. Some, J. S. Oh, Y. S. Lee and C. E. Song, *Chem. Commun*., 2011, **47**, 9621; (i) R. Manzano, J. M. Andres, M. D. Muruzabal and R. Pedrosa, *Adv. Synth. Catal*., 2010, **352**, 3364.
55. For selected papers on amine-thiourea catalyzed asymmetric reactions, see: (a) L. Zu, J. Wang, H. Li, H. Xie, W. Jiang and W. Wang, *J. Am. Chem. Soc.,* 2007, **129**, 1036; (b) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu and L. Deng, *J. Am. Chem. Soc.,* 2008, **130**, 2422; (c) H. Uehara and C. F. Barbas III, *Angew. Chem. Int. Ed.,* 2009, **48**, 9848; (d) Y. Wang, R. –G. Han, Y. –L. Zhao, S. Yang, P. –F. Xu and D. J. Dixon, *Angew. Chem. Int. Ed*., 2009, **48**, 9834; (e) T. Bui, S. Syed and C. F. Barbas III, *J. Am. Chem. Soc*., 2009, **131**, 8758; (f) B. Tan, Y. Lu, X. Zeng, P. J. Chua and G. Zhong, *Org. Lett.,* 2010, **12**,

2682; (g) H. Uehara, R. Imashiro, G. Hernandez-Torres and C. F. Barbas III, *Proc. Natl. Acad. Sci., USA,* 2010, **107**, 20672; (h) B. Tan, G. Hernandez-Torres and C. F. Barbas III, *J. Am. Chem. Soc*., 2011, **133**, 12354; (i) B. Tan, N. R. Candeias and C. F. Barbas III, *Nat. Chem.,* 2011, **3**, 473.

56. CCDC-856223 for (–)-**78aa** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or mailto:deposit@ccdc.cam.ac.uk. See supporting information for crystal structure.
57. For organocatalytic synthesis of substituted 2-(2-nitrovinyl)phenols **46a-m**, see: D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.,* 2010, **8**, 4259-4265.
58. For organocatalytic high-yielding synthesis of racemic products **78 or 80** from **75** and **46** through [Q (**5h**) + QD (**5k**)]-catalysis followed by *p*-TSA-catalysis, see *Annexure-II.*
59. (a) G. Pousse, F. L. Cavelier, L. Humphreys, J. Rouden and J. Blanchet, *Org. Lett*., 2010, **12**, 3582; (b) R. P. Singh, B. M. Foxman and L. Deng, *J. Am. Chem. Soc*., 2010, **132**, 9558.
60. (a) *ref. 3*; b) W. Notz and B. List, *J. Am. Chem. Soc*., 2000, **122**, 7386; (c) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc*., 2001, **123**, 5260.
61. (a) A. Córdova, W. Notz and C. F. Barbas III, *J. Org. Chem*., 2002, **67**, 301; (b) A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc*., 2002, **124**, 6798; (c) A. Bogevig, K. Juhl, N. Kumaragurubaran and K. A. Jorgensen, *Chem. Commun*., 2002, 620; (d) M. Nakadai, S. Saito and H. Yamamoto, *Tetrahedron*, 2002, **58**, 8167; (i) P. Kotrusz, I. Kmentova, B. Gotov, S. Toma and E. Solcaniova, *Chem. Commun*., 2002, 2510; (f) T. Darbre and M. Machuqueiro, *Chem. Commun*., 2003, 1090; (g) S. Bahmanyar, K. N. Houk, H. J. Martinand B. List, *J. Am. Chem. Soc*., 2003, **125**, 2475; (h) J. T. Suri, D. B. Ramachary and C. F. Barbas III, *Org. Lett*., 2005, **7**, 1383; (i) Y. Zhou and Z. Shan, *J. Org. Chem*., 2006, **71**, 9510; (j) J. Huang, X. Zhang and D. W. Armstrong, *Angew. Chem., Int. Ed*., 2007, **46**, 9073; (k) S. S. V. Ramasastry, H. Zhang, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc*., 2007, **129**, 288; (m) S. S. V. Ramasastry, K. Albertshofer, F. Tanaka and C. F. Barbas III, *Angew. Chem., Int. Ed*., 2007, **46**, 5572; (n) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi and C. F. Barbas III, *Org. Lett*., 2008, **10**, 1621;

(o) D. Enders and A. A. Narine, *J. Org. Chem.*, 2008, **73**, 7857; (p) J. N. Moorthy and S. Saha, *Eur. J. Org. Chem.*, 2009, 739; (q) S. Saha and J. N. Moorthy, *Tetrahedron Lett.*, 2010, **51**, 912; (r) R. Pedrosa, J. M. Andrés, R. Manzano, D. Román and S. Téllez, *Org. Biomol. Chem.*, 2011, **9**, 935; (s) J. Agarwal and R. K. Peddinti, *J. Org. Chem.*, 2011, **76**, 3502.

62. (a) S. G. Zlotin, A. S. Kucherenko and I. P. Beletskaya, *Russian Chemical Reviews*, 2009, **78**, 737; (b) M. M. Heravi and S. Asadi, *Tetrahedron: Asymmetry*, 2012, **23**, 1431.
63. (a) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 12911; (b) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 11273; (c) L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16; (d) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong and K. N. Houk, *Acc. Chem. Res.*, 2004, **37**, 558; (e) C. Marquez and J. O. Metzger, *Chem. Commun.*, 2006, 1539; (f) M. B. Schmid, K. Zeitler and R. M. Gschwind, *Angew. Chem., Int. Ed.*, 2010, **49**, 4997.
64. For recent reviews of synthesis and biological applications of phthalides, see: (a) D. H. R. Barton and J. X. de Vries, *Chem. Soc.* 1963, 1916; (b) S. Yu, S. You and H. Chen, *Yaoxue Xuebao*, 1984, **101**, 486. (c) H. Sato, H. Yorozu and S. Yamaoka, *Biomed. Res.* 1993, **14**, 385; (d) X. W. Wang, *Drugs Future* 2000, **25**, 16; (e) U. Holler, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.* 2002, **65**, 876; (f) J. Zhou, K. Gupta, J. Yao, K. Ye, D. Panda, P. Giannakakaou and H. C. Joshi, *J. Biol. Chem.* 2002, **277**, 39777; (g) K. Yoganathan, C. Rossant, S. Ng, Y. Huang, M. S. Butler and A. D. Buss, *J. Nat. Prod.* 2003, **66**, 1116; (h) P. Chatterjee and M. R. Franklin, *Drug Metab. Dispos.* 2003, **31**, 1391; (i) J. A. Palermo, B. Rodriguez, F. Maria, C. Spagnuolo and A. M. Seldes, *J. Org. Chem.* 2000, **65**, 4482; (j) Z. Xu, G. Y. Hu, G. S. Tan and J. Chin. *Modern Med.* 2004, 93; (h) G. Lin, S. S.-K. Chan, H.-S. Chung and S. L. Li, *Stud. Nat. Prod. Chem.* 2005, 611; (i) M. J. Xioang and Z. H. Li, *Curr. Org. Chem.* 2007, **11**, 833; (j) J. J. Beck and S.-C. Chou, *J. Nat. Prod.* 2007, **70**, 891.
65. M. Kuriyama, N. Ishiyama, R. Shimazawa, R. Shirai and O. Onomura, *J. Org. Chem.* 2009, **74**, 9210.
66. H. T. Chang, M. Jeganmohan and C. H. Cheng, *Chem.–Eur. J.* 2007, **13**, 4356.
67. K. Zumbansen, A. Dçhring and B. List, *Adv. Synth. Catal.* 2010, **352**, 1135.

68. a) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.,* 2008, **6**, 4176; b) D. B. Ramachary, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.,* 2008, **6**, 4188.
69. a) S. Franke, F. Ibarra, C. M. Schulz, R. Twele, J. Poldy, R. A. Barrow, R. Peakall, F. P. Schiestl and W. Francke*, Proc. Natl. Acad. Sci. USA,* 2009, **106**, 8877; b) J. Poldy, R. Peakallb and R. A. Barrow, *Org. Biomol. Chem.,* 2009, **7**, 4296.
70. a) S. Marumo, H. Hattori and M. Katayama, *J. Agric. Biol. Chem.,* 1985, **49**, 1521; b) C. Johnsonae, *The Journal of Antibiotics*, 1993, **46**, 1319; c) A. Pohanka, J. Levenfors and A. Broberg, *J. Nat. Prod.* 2006, **69***,* 654.
71. A. M. R. Smith, D. Billen and K. Kuok, *Chem. Commun*., 2009, 3925.
72. V. Justribo, S. C. Pellegrinet and M. I. Colombo, *J. Org. Chem.,* 2007, **72**, 3702.
73. D. A. May and T. D. Lash, *J. Org. Chem.,* 1992, **57**, 4820.

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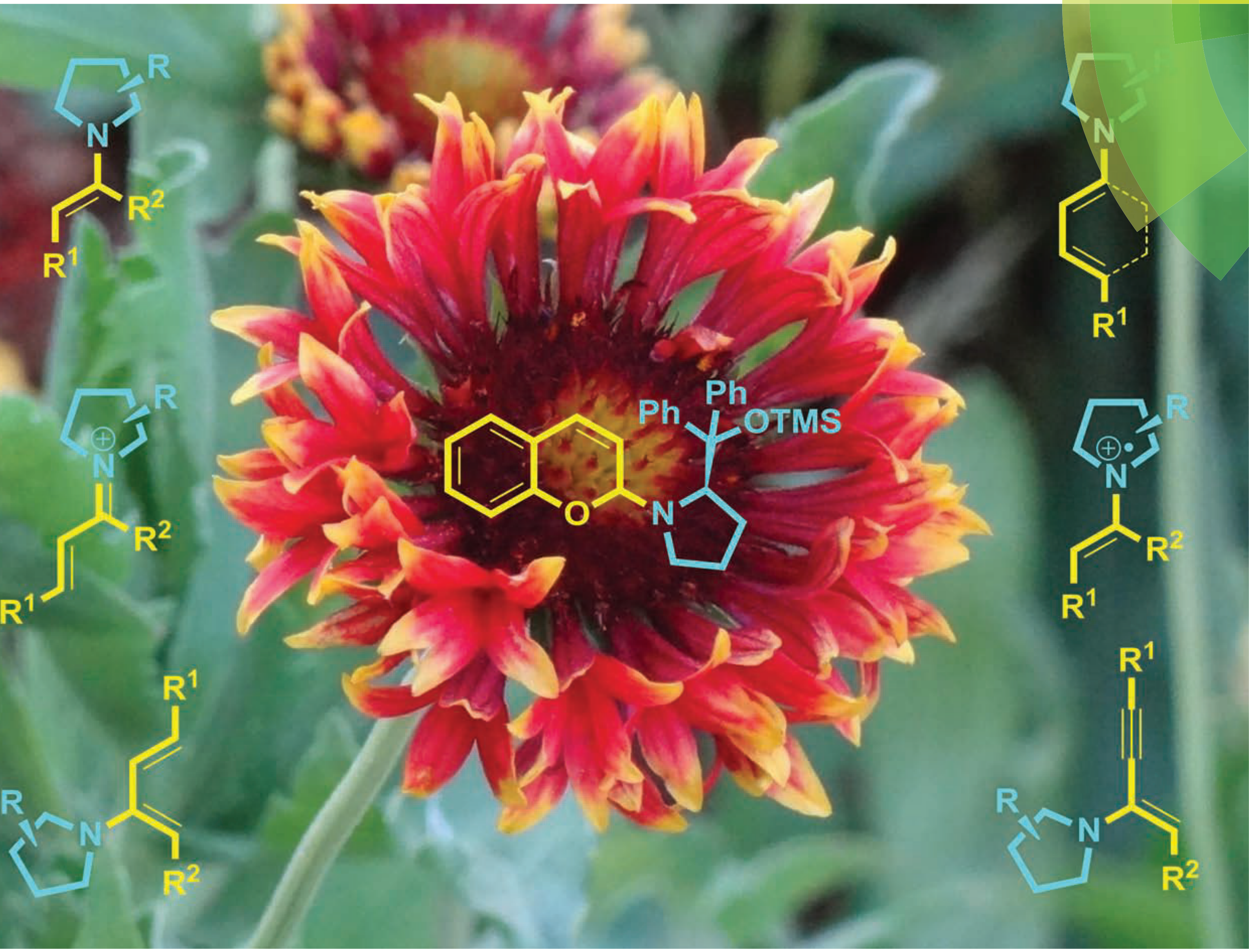

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PAPER
Dhevalapally B. Ramachary *et al.*
Asymmetric synthesis of drug-like spiro[chroman-3,3′-indolin]-2′-ones through *aminal*-catalysis

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The author, **Mr. R. Madhavachary** was born on 8th April 1986 in Khammam, Andhra Pradesh. After his initial schooling in Chinnakorukondi, he obtained his B.Sc. degree in 2006 from Susheela degree college, Madhira and he obtained his M.Sc. degree with organic chemistry specialization in 2008 from S. R. P. G. College, Kakatiya University, Warangal. He continued as a research scholar in the School of Chemistry, University of Hyderabad for the Ph. D. programme from July 2009 onwards.

LIST OF PUBLICATIONS

1. "A general approach to high-yielding asymmetric synthesis of chiral 3-alkyl-4-nitromethylchromans via cascade Barbas–Michael and acetalization reactions" D. B. Ramachary, M. Shiva Prasad and **R. Madhavachary**, *Org. Biomol. Chem*, 2011, **9**, 2715-2721.
2. "Observation of neighboring ortho-hydroxyl group participation in organocatalytic asymmetric sequential Michael-lactonization reactions: synthesis of highly substituted chiral spirodihydrocoumarins" D. B. Ramachary, **R. Madhavachary** and M. Shiva Prasad, *Org. Biomol. Chem*, 2012, **10**, 5825-5829.
3. "Direct catalytic asymmetric synthesis of highly functionalized (2-ethynylphenyl)alcohols via Barbas–List aldol reaction: scope and synthetic applications" D. B. Ramachary, R. Mondal and **R. Madhavachary**, *Org. Biomol. Chem*, 2012, **10**, 5094-5101.
4. "Asymmetric synthesis of druglike six-membered spirooxindoles through an amino enyne catalysis" D. B. Ramachary, Ch. Venkaiah and **R. Madhavachary**, *Org. Lett*, 2013, **15**, 3042-3045.
5. "Asymmetric synthesis of drug-like spiro[chroman-3,3′-indolin]-2′-ones through aminal-catalysis" D. B. Ramachary, M. Shiva Prasad, S. Vijaya Laxmi and **R. Madhavachary**, *Org. Biomol. Chem*, 2014, **12**, 574-580.
6. "High-yielding total synthesis of sexually deceptive chiloglottones and antimicrobial dialkylresorcinols through an organocatalytic reductive coupling reaction" **R. Madhavachary** and D. B. Ramachary, *Eur. J. Org. Chem.*, 2014, 7317-7323.

7. "An enolate-mediated organocatalytic azide–ketone [3+2]-cycloaddition reaction: regioselective high-yielding synthesis of fully decorated 1,2,3-triazoles" A. B. Shashank, S. Karthik, **R. Madhavachary** and D. B. Ramachary *Chem.–Eur J,* 2014, **20**, 16877-16881.
8. "High-yielding total synthesis of butenolide natural products and their analogues through an organocatalytic reductive coupling reaction" R. Mallik, **R. Madhavachary** and D. B. Ramachary (to be communicated).
9. "Asymmetric synthesis of spirodihydroquinolinones" A. Suresh, **R. Madhavachary,** T. Prabhakar and D. B. Ramachary (manuscript under preparation).
10. "Observation of neighboring group control in asymmetric Barbas–List aldol reactions: synthesis of phthalide natural products" **R. Madhavachary** and D. B. Ramachary (to be communicated).
11. "Construction of optically pure spiro[cyclohexanone-oxindole] backbone through Barbas cycloaddition reactions", P. Sreekanth reddy, **R. Madhavachary,** P. V. Govardhana reddy and D. B. Ramachary (manuscript under preparation).

Poster and Oral Presentations

1. **Poster Presentation**: 1st Indo-Taiwan Symposium on "Recent Trends in Chemical Sciences", November 2014, University of Hyderabad, INDIA.
   Organizer: Academica Sinica, Taiwan and School of Chemistry, University of Hyderabad.
2. **Poster Presentation**: Indo-German Conference on Bio-Inspired Chemistry, IGCBIC-2014, IISc-Bangalore, INDIA
   Organizer: IISc-Bangalore, INDIA.
3. **Oral Presentation**: "CHEM-FEST 2013", School of Chemistry, Hyderabad, India.
   Organizer: University of Hyderabad, INDIA.
4. **Poster Presentation**: National Symposium on Frontiers in Organic Chemistry NSFOC-2013, School of Chemistry, Hyderabad, India.
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5. **Oral Presentation**: "CHEM-FEST 2012", School of Chemistry, Hyderabad, India.
   Organizer: University of Hyderabad, INDIA.
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   Organizer: University of Hyderabad, INDIA.